The Pennsylvania State University

The Graduate School

Eberly College of Science

SYNTHETIC EFFORTS DIRECTED TOWARDS THE TOTAL SYNTHESIS OF THE POLYCYCLIC NATURAL PRODUCTS *N*-METHYLWELWISTATIN AND COMMUNESIN B

A Dissertation in

Chemistry

by

Seth L. Crawley

Submitted in Partial Fulfillment
of the Requirements
for the Degree of

Doctor of Philosophy

May 2009

The dissertation of Seth L. Crawley was reviewed and approved* by the following:

Raymond L. Funk
Professor of Chemistry
Dissertation Advisor
Chair of Committee

Ken S. Feldman
Professor of Chemistry

Steven. M. Weinreb
Russell and Mildred Marker Professor
of Natural Products Chemistry

Ming Tien
Professor of Biochemistry

Ayusman Sen
Professor of Chemistry
Head of the Department of Chemistry

*Signatures are on file in the Graduate School

ABSTRACT

Part 1 discusses the investigation of a novel strategy for the total synthesis of *N*-methylwelwistatin. The key transformation involves sequential stereoselective 5-*exo*-trig, 7-*endo*-trig radical cyclizations to provide the tricyclic core ring system of *N*-methylwelwistatin. Strategies that were investigated for the completion of the total synthesis from the radical cyclization product include: 1) an intramolecular alkylation strategy; 2) an intramolecular [3+2] nitrone-olefin cycloaddition strategy; 3) an intramolecular radical cyclization strategy.

Part 2 reviews the synthetic efforts directed towards the total synthesis of communesin B. The core ring systems of both nomofungin and communesin B were synthesized via intramolecular cycloadditions of an indole tethered to an *ortho*-quinone methide and an aza-*ortho*-xylylene respectively. This work provided definitive proof that the structure of nomofungin was published erroneously. Attempts to complete the total synthesis using a benzazepine-based approach were unsuccessful, but have inspired a strategy employing a tryptamine-derived indole/aza-*ortho* xylylene intramolecular cycloaddition. This approach has led to the development of two novel means of generating aza-*ortho*-xylylenes: 1) the acid or base catalyzed ring opening of aziridines; 2) retrocycloaddition of acyl-*N*-acyl-3,1-benzoxazin-2-ones. Also, successful extension of the acyl-*N*-acyl-3,1-bezoxazin-2-one route demonstrated that the vicinal quaternary centers of communesin B could be installed via an alkylation strategy.

TABLE OF CONTENTS

LIST OF SCHEMES

LIST OF FIGURES

LIST OF TABLES

ACKNOWLEDGEMENTS

First and foremost, I would like to thank my research advisor, Professor Raymond L. Funk for being my mentor during my graduate studies at Pennsylvania State University. The intensity with which he approaches organic chemistry has been an inspiration for me to continually strive for perfection. I look forward to using the skills that I have developed under his tutelage in a successful career in chemistry.

I would also like to sincerely thank my coworkers throughout the years in the Funk laboratory. They have all contributed to my personal development as a professional chemist and have helped to make my time at Penn State enjoyable. Specifically, I would like to thank Tom Greshock, Jim Fuchs, Ron Aungst, Ray Huntley, Yong He, and Johannes Belmar for helpful discussions.

I would like to thank my parents, Joyce and Larry Crawley for their unconditional love and support throughout my entire education. Everything I have accomplished has been derived from the values they taught me.

Finally, I would like to thank my fiancé (and soon to be wife), Manuella Barbosa. The sacrifices she has made for me are more than I could ever ask for. I will always be grateful for the support and encouragement she has given me.

PART 1

Synthetic Efforts Directed Towards the Total Synthesis Of *N*-Methylwelwistatin

CHAPTER 1

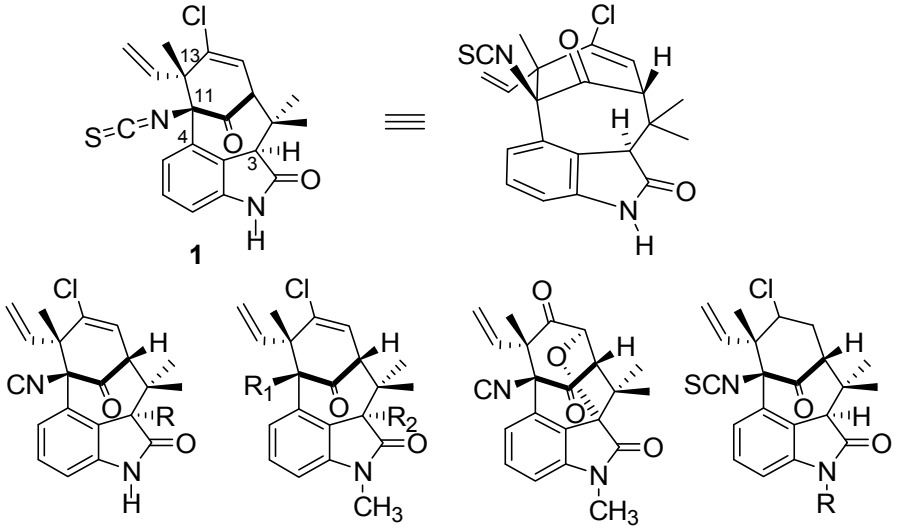
Investigation of a radical cyclization-based approach towards the total synthesis of *N*-methylwelwistatin

I. Introduction

A. Isolation of the welwitindolinones and related compounds

Increasingly, scientists are turning towards marine microorganisms as sources of structurally intriguing, biologically active natural products.[1] In 1994, Moore and coworkers[2] isolated the indole alkaloid welwitindolinone C isothiocyanate (later termed welwistatin)[3] from the lipophilic extracts of the blue-green algae *Hapalosiphon welwitschii* and *Westiella intricate* (Figure 1).[2] The key structural features of welwistatin (**1**) include a unique bicyclo[4.3.1]decananone about an oxindole, four stereocenters including two vicinal quaternary centers, vinyl chloride and bridgehead isothiocyanate functionalities, and a *gem*-dimethyl substituent.

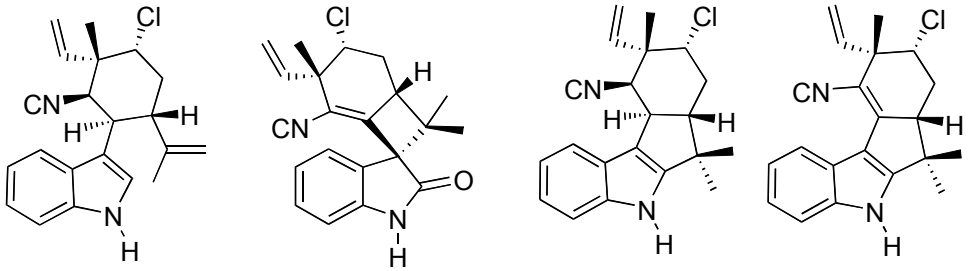
Figure 1. The welwitindolinone natural products.



Additional alkaloids, termed welwitindolinones, have also been isolated.[2,4] These include: welwitindolinone A isonitrile (**2**), 3-hydroxywelwitindolinone C isonitrile (**3**), *N*-methylwelwitindolinone C isothiocyanate (**4**), 3-hydroxy-*N*-methylwelwitindolinone C isothiocyanate (**5**), 3-hydroxy-*N*-methylwelwitindolinone C formamide (**6**), the oxidized compound, *N*-methylwelwitindolinone D isonitrile (**7**), and isothiocyanates **8** and **9** which possess a C(13) alkyl chloride substituent instead of a vinyl chloride that is present in almost of all of the welwitindolinones (Figure 1).[2,4] Compounds **3**, **5**, and **7** were isolated from a cyanobacteria (*Fischerella muscicola*)[4] but compound **6** was an artifact of isolation.[4] Most importantly, the absolute stereochemistry of the welwitindolinones has been confirmed by X-ray crystallographic analysis of **4**.[2]

Additional structurally related compounds that have been isolated from the same broth as that of the welwitindolinones include hapalindole E (**10**),[5] welwitindolinone A (**11**), fischerindole G (**12**),[6] and fischerindole I (**13**)[6] (Figure 2). Indeed, due to the structural similarity between these compounds and the welwitindolinones, Moore has proposed a biosynthetic pathway in which he postulates that the common intermediate for the chlorine containing alkaloids found in *H. welwitschii* (both the welwitindolinones and fischerindoles) is hapalindole E.[2]

Figure 2. Natural products isolated with welwistatin

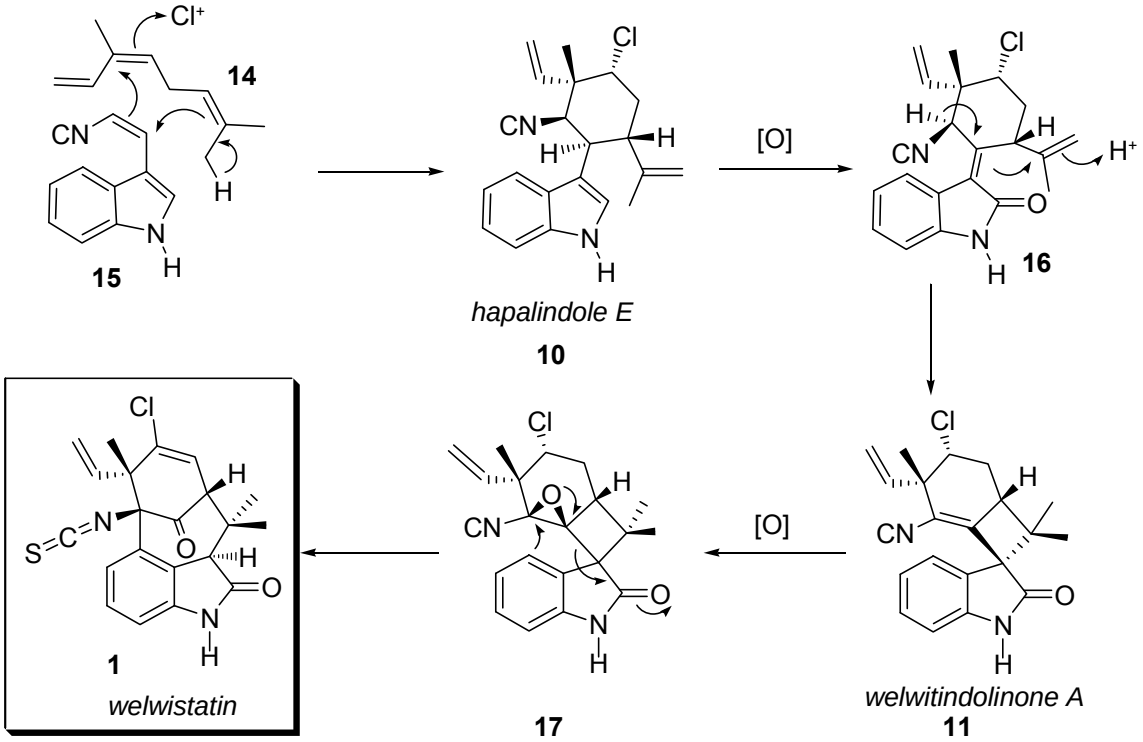


hapalindole E **10** | *welwitindolinone A* **11** | *fischerindole G* **12** | *fischerindole I* **13**

B. Biosynthetic Considerations

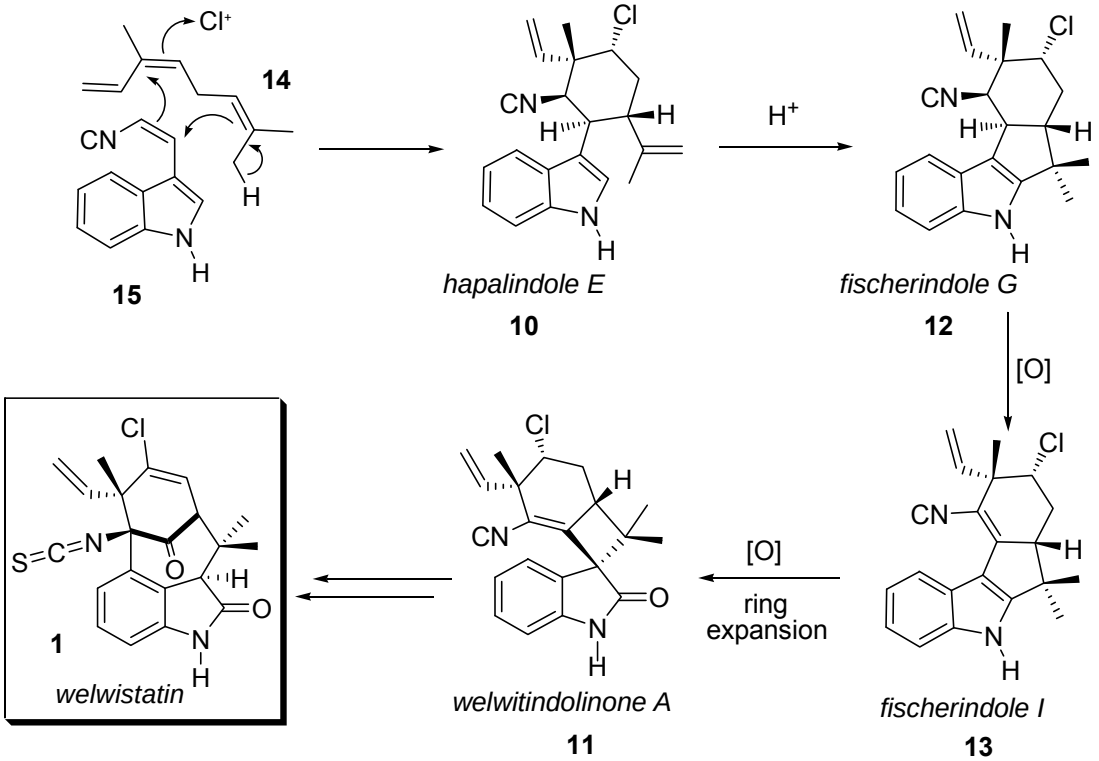
Moore postulates that the biosynthesis of the welwitindolinones could commence with intermediates **14** and **15**, ultimately derived from geranyl pyrophosphate and tryptophan[7], respectively (Scheme 1).[2] The origin of the isothiocyanate present in compounds **1, 4**, **5**, **8**, and **9** is not known, but could be introduced at any point via inorganic thiocyanate, or indirectly by introduction of a sulfur into an intermediate organic isonitrile.[2] Thus, chloronium-ion induced condensation of triene **14** with indole **15** would provide hapalindole E (**10**), a proposed intermediate in the biosynthesis of the fischerindoles as well.[6] Oxidation to the oxindole **16** (which was not isolated) followed by acid catalyzed cyclization could provide welwitindolinone A (**11**). Stereoselective epoxidation could provide intermediate **17**, followed by ring opening and cyclization at C(4) to give the complete ring system of all of the welwitindolinones.

Scheme 1. Moore's proposed biosynthesis of welwistatin



However, Baran contends that Moore's postulated biosynthesis, specifically the acid catalyzed ring closure from intermediate **16** to **11** (Scheme 1), is not favored thermodynamically. Therefore, Baran has proposed an alternate biosynthesis, which fully accounts for the formation of fischerindoles G and I, and which suggests that the actual precursor to welwitindolinone A (**11**) is in fact fischerindole I (**13**) (Scheme 2).[8] As in Moore's biosynthesis, Baran's biosynthetic hypothesis begins with a chloronium ion induced condensation of **14** and **15** to arrive at hapalindole E (**10**), but Baran proposes the next step is an acid catalyzed ring closure to fischerindole G (**12**). This step also helps to explain the isolation of fischerindole G from the same broth as that of the welwitindolinones. Subsequent oxidation to fischerindole I (**13**), followed by an oxidative ring expansion would then provide welwitindolinone A (**11**). It is believed that the stereoselective epoxidation, ring opening, and cyclization at C(4) as before would then provide the welwitindolinones.

Scheme 2. Baran's proposed biosynthesis of welwistatin



C. Biological activity

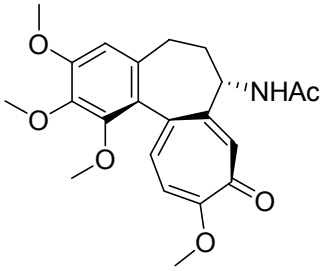
Cancer has become one of the most common causes of death throughout most countries, second only to heart disease. Therefore, chemists have been charged with designing and synthesizing new and more effective chemotherapeutic reagents to treat patients. Many pharmaceuticals target microtubules and their dynamics because they are critical for cellular signaling and transport, provide the cell's structure and shape, and most notably, they are necessary for the formation of the mitotic spindle, which is involved in cell replication.

Every nucleated cell in the human body contains two similar spherical proteins involved in cellular replication, α and β tubulin. These two proteins join to form $\alpha\beta$ heterodimers, which then combine in the presence of guanosine triphosphate (GTP) in a head-to-tail arrangement to give a protofilament. Protofilaments can group together to make a protein sheet, which coils around to form microtubules. However, microtubules are polymers that exist in an equilibrium, with dimers constantly adding to one end (the (+) end), and leaving at the other end (the (-) end).[9] It is this finely balanced equilibrium and the resulting control of the length of the microtubules (also called microtubule dynamics) that is vital for a number of their functions within a cell, the most important of which is mitosis, or the process by which cells replicate. Thus, if the microtubules can be prevented from assembling or disassembling properly (or in other words the microtubule dynamics are disrupted), the chromosomes cannot separate. A mitotic checkpoint in the cell is therefore not reached, which leads to apoptosis, or cell death.

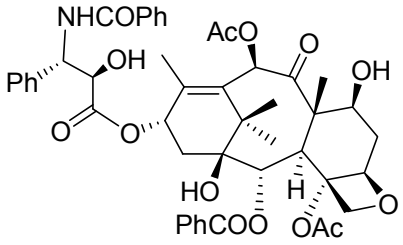
To date, many anti-microtubule agents have been discovered. Initial studies revealed that welwistatin reversed P-glycoprotein mediated multiple drug resistance. (MDR).[3] P-glycoprotein has been shown to reduce the intracellular accumulation of many pharmaceutical reagents, which therefore reduces their cytotoxicity.[10] Consequently, scientists touted the welwitindolinones as possible P-glycoprotein antagonists to be used in combination with anti-microtubule

reagents to make them more effective in treating cancer patients. Welwistatin was shown to attenuate the resistance of P-glycoprotein–overexpressing MCF-7/AdR cells to three compounds that are known to interfere with microtubule dynamics; colchicine (**18**),[11] taxol (**19**),[12] and vinblastine (**20**)[13] (Figure 3).

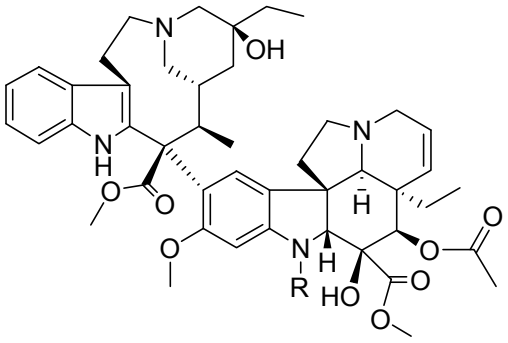
Figure 3. Established anti-microtubule drugs



18 *colchicine*



19 *taxol*



20 R = CH_3 *vinblastine*
21 R = CHO *vincristine*

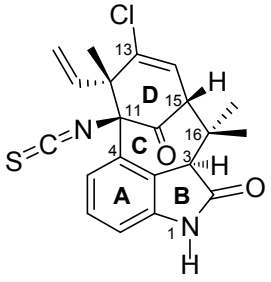
In contrast to these initial studies, subsequent studies have demonstrated that welwistatin is actually a cytotoxin itself.[14] Immunofluorescence studies indicated that welwistatin causes a dose-dependent disruption of microtubules in intact cells and has been shown to inhibit the proliferation of SK-OV-3 human ovarian carcinoma cells (IC_{50} = 72 nM) and A-10 vascular smooth muscle cells (IC_{50} = 900 nM). More importantly, it is also cytotoxic towards P-glycoprotein-overexpressing MCF-7/AdR cells (IC_{50} = 130 nM) in the G2 mitotic phase.[14] Additionally, these studies suggested that welwistatin may possess a unique binding site to microtubules, as the taxol and colchicine microtubule domains

were not affected in welwistatin-treated cells, suggesting that it does not bind to either the taxol or colchicine sites.[14] Thus, welwistatin may represent a new anti-microtubule drug that may be valuable for the treatment of drug resistant tumors.[15]

II. Previous synthetic efforts towards the welwitindolinones

To date, no completed total synthesis of welwistatin has been published. However, due to its intrinsic biological activity as well as its interesting tetracyclic ring system, several synthetic strategies have been published.[16] These efforts are summarized below and are classified according to the order of ring formation. For clarity, the rings have been lettered A-D and the ring system has been numbered in Figure 4 to be used during the following discussion.

Figure 4. Labeling of welwistatin for classification of syntheses



welwistatin

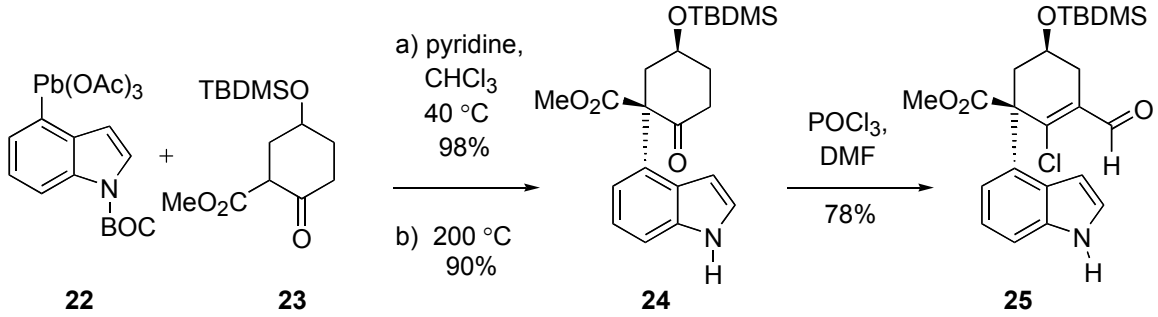
1

A. AB →ABD→ABDC

In 1998, Konopelski was the first to report synthetic work towards the welwitindolinone ring system.[17] He eventually reported formation of the C(11) quaternary center of *N*-methylwelwitindolinone C isothiocyanate via a stereoselective coupling of the 4-indolyllead(IV) acetate **22** with the anion of β-keto ester **23** followed by thermal cleavage of the *N*-BOC to lead to the indole **24**

(Scheme 3).[17] However, all attempts to use Vilsmeier conditions to formylate the indole for subsequent aldol closure of the C(15)-C(16) bond were unsuccessful, and instead provided the vinyl chloride **25**.

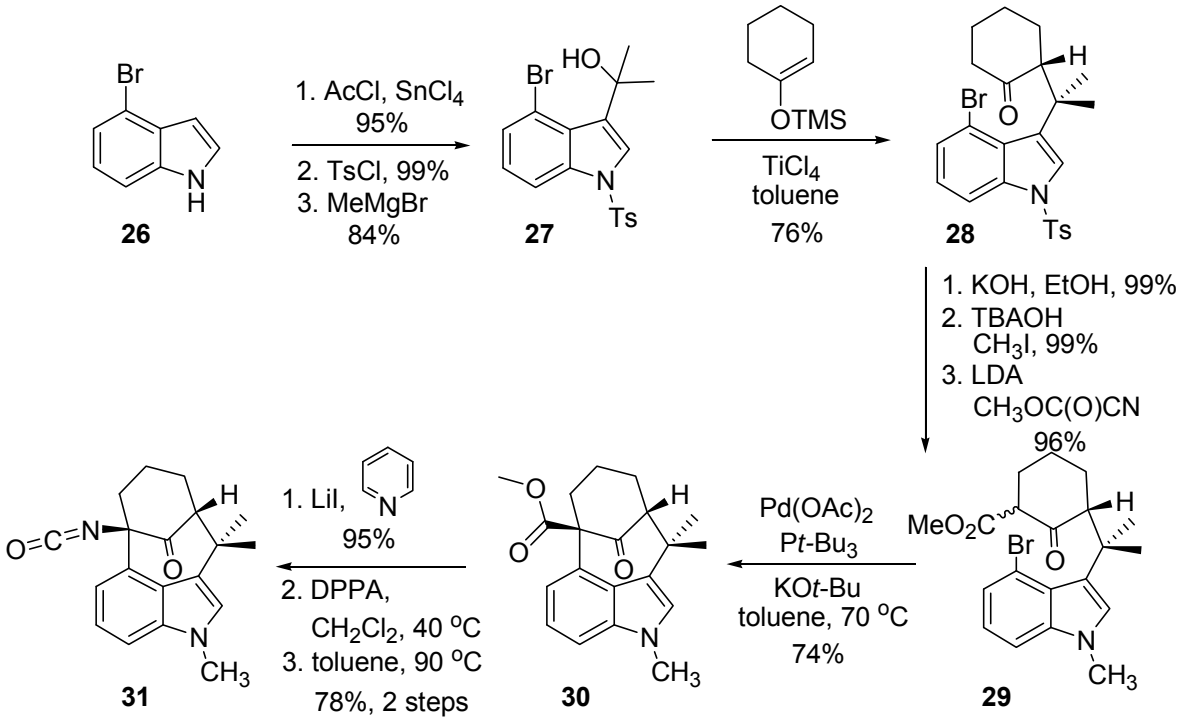
Scheme 3. Konopelski's construction of C(4)-C(11) bond.



22 **23** **24** **25**

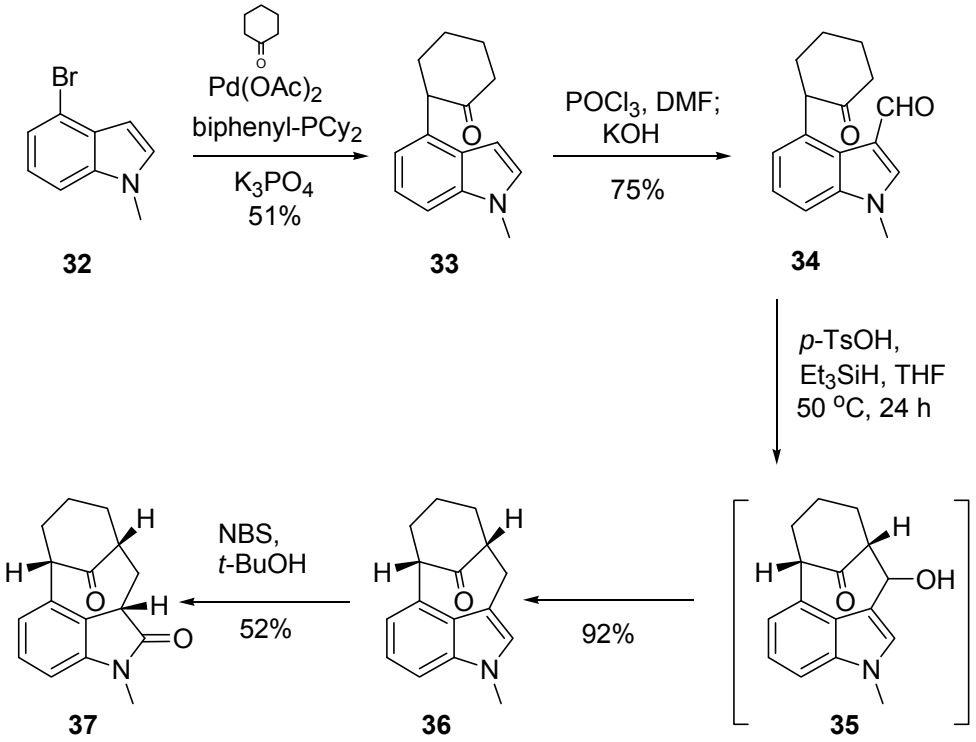
Rawal and coworkers have reported the construction of an advanced welwitindolinone model ring system using a related disconnection. Starting from the commercially available 4-bromoindole (**26**), Rawal arrived at the key β-keto ester **29** in eight straightforward steps (Scheme 4).[18] The key step involved an intramolecular palladium-mediated coupling of the anion derivative of β-keto ester **29** to furnish the tetracyclic ring system **30**. Subsequent hydrolysis of the ester, conversion to the acyl azide, and Curtius rearrangement afforded the bridgehead isocyanate **31**. It remains to be seen if Rawal can install the remaining functionality to complete the total synthesis, and most importantly introduce the vicinal quaternary centers via the palladium-catalyzed closure.

Scheme 4. Rawal's approach to the tetracyclic ring system.



Shortly after Rawal published his intramolecular palladium-mediated coupling approach, Simpkins and coworkers published an intermolecular palladium-mediated coupling of *N*-methyl–4-bromoindole (**32**) with cyclohexanone to arrive at ketone **33** (Scheme 5).[19] Subsequent Vilsmeier-Haack formylation, and acid mediated aldol-type ring closure in the presence of triethylsilane furnished the bridged indole **36** in good yield. This approach represents the first published C(15)-C(16) bond formation of the welwitindolinones. Simpkins noted that without the hydride donor triethylsilane, a 1 : 1 mixture of the bridged indole **36** with the diketone oxidation state of alcohol **35** was obtained. Also, if the key step was repeated in the presence of a hydride acceptor such as DDQ, only the diketone was isolated. Subsequent oxidation of the indole **36** afforded the oxindole **37**. It also remains to be seen if Simpkins can install the necessary functionality to complete the synthesis, and unfortunately, epimerization of the indolinone stereocenter has not been possible to date.

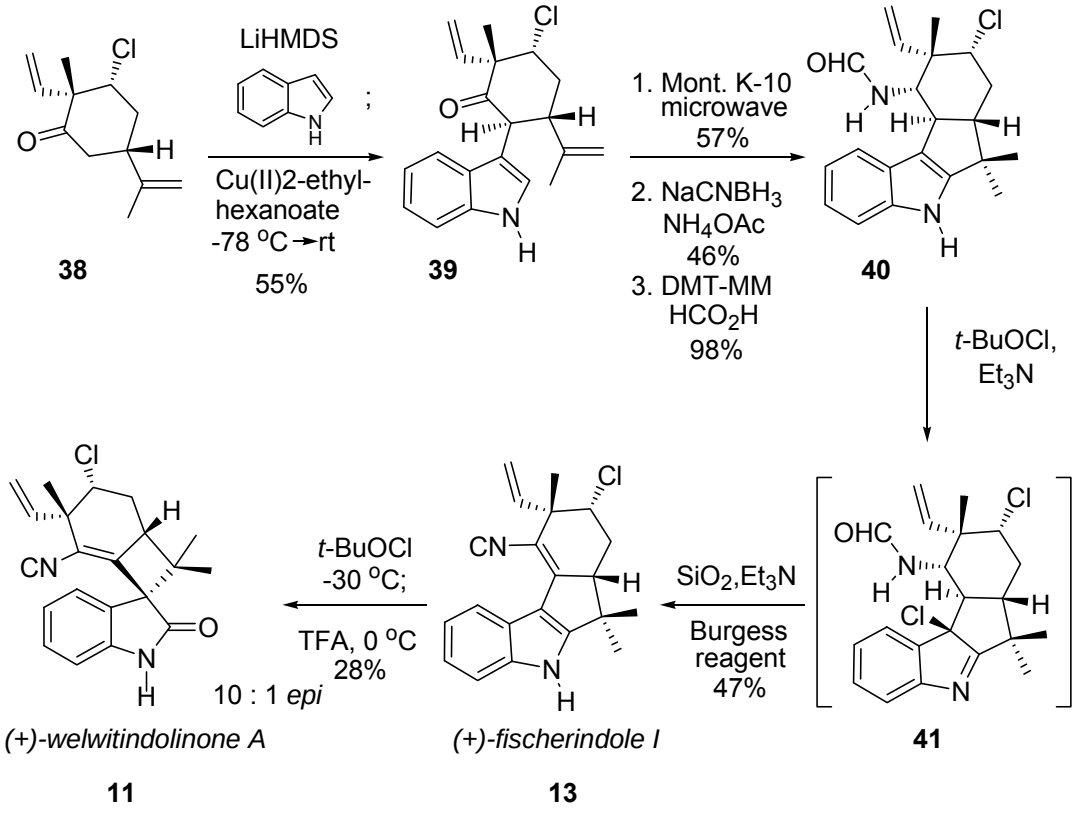
Scheme 5. Simpkins' approach to the tetracyclic ring system.



Recently, Baran and coworkers published a “biomimetic” route to welwistatin. Experimental evidence for his hypothesis for the biosynthesis of the welwitindolinones was obtained via the first enantioselective total syntheses of fischerindoles I, G, and welwitindolinone A (Scheme 6).[8] Thus, starting from *S*-carvone oxide, ketone **38** was formed in 2 steps and then coupled to indole using a recently developed protocol[20] to provide indole **39**, a compound that is very similar to hapalindole E. Friedel-Crafts cyclization gave the tetracycle, which was followed by stereoselective reductive amination and *N*-formylation to provide the amide **40**. Subjection of amide **40** to *t*-BuOCl presumably generated 3-chloroindolenine **41** via electrophilic attack from the opposite face of the amide. It is presumed that elimination of HCl generated a conjugated indolenine, which subsequently tautomerized to regenerate the indole and provide an enamide. Burgess reagent effected a dehydration of the incipient enamide to the isonitrile and furnish (-)-fischerindole I (**13**). To confirm his hypothesis that an oxidative ring expansion of fischerindole I generates welwitindolinone A, fischerindole I (**13**) was subjected to *t*-BuOCl at low temperature followed by addition of TFA to

provide (+)-welwitindolinone A (**11**). It remains to be determined if the completion of the welwistatin total synthesis can be accomplished via stereoselective epoxidation of the hindered tetrasubstituted olefin and concomitant cyclization.

Scheme 6. Baran's biosynthetic approach to welwistatin.

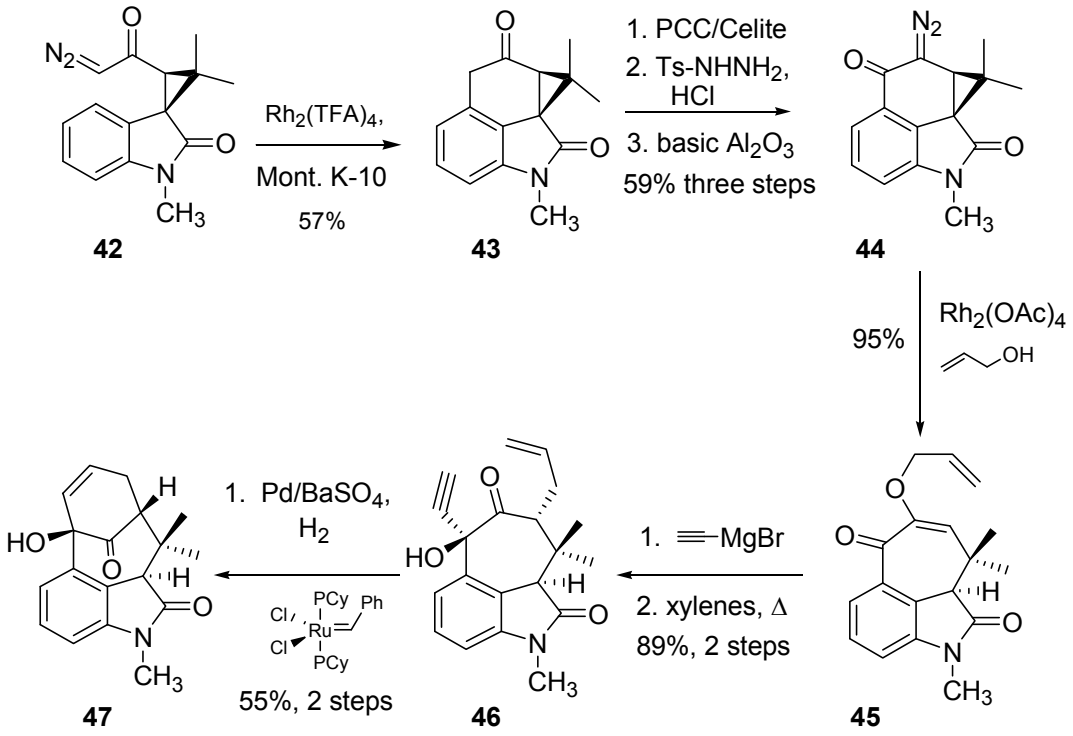


B. AB →ABC→ABCD

Wood and coworkers were the first group to report the construction of the complete carbon framework of welwistatin using a rhodium-mediated aryl C-H insertion strategy (Scheme 7). The key steps in his synthesis are an intramolecular aryl C-H insertion of α–diazo ketone **42** to provide cyclopropyl ketone **43**, followed by a rhodium carbenoid cyclopropane ring expansion of α-diazaketone **44** in the presence of allyl alcohol to provide the allyl vinyl ether **45**.[21] Grignard addition, Claisen rearrangement and subsequent olefin metathesis furnished the complete ring system of welwistatin, oxindole **47**.

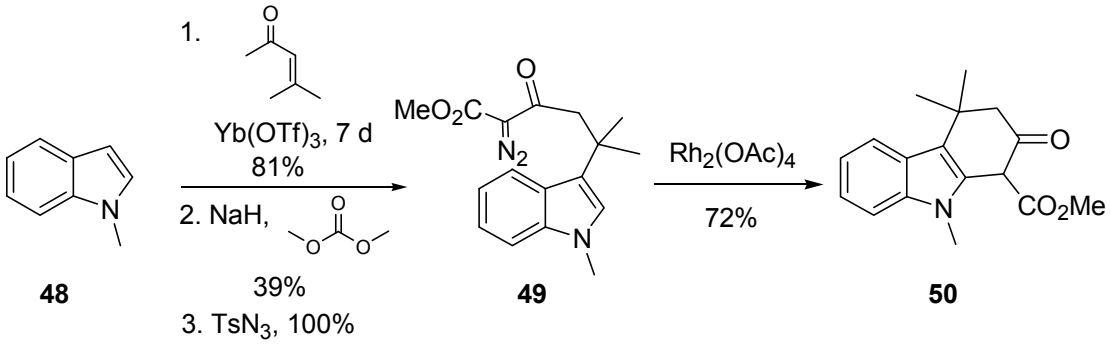
However, it remains to be determined whether the remaining functionality and, in particular the bridgehead nitrogen, can be introduced. This route has presumably been abandoned in favor of a total synthesis via welwitindolinone A, *vide infra*.

Scheme 7. Wood's first generation approach to welwistatin.



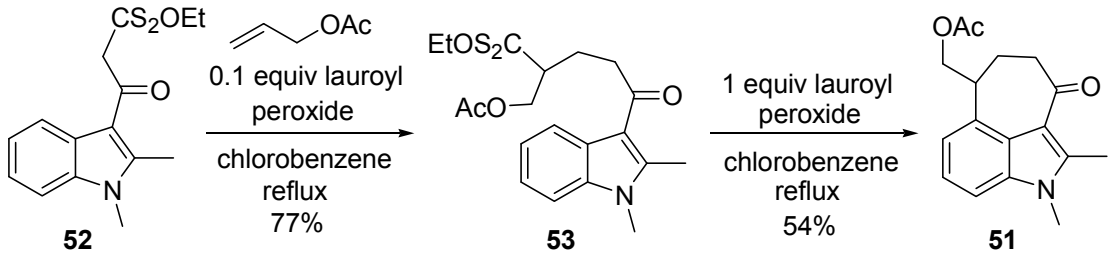
Jung has also published a metal mediated intramolecular aryl C-H insertion approach in an attempt to form an "ABC" tricyclic ring system (Scheme 8).[22] Unfortunately, subjection of the readily available α-diazo–β–ketoester **49** to $Rh_2(OAc)_4$ afforded a mixture of products, with the major product being the C(2) insertion adduct **50**.

Scheme 8. Jung's aryl C-H insertion approach.



Zard has disclosed a radical annulation strategy for the construction of a tricyclic compound **51** (Scheme 9).[23] The readily available xanthate **52** was formed via condensation of 2-methyl indole with chloroacetyl chloride and subsequent alkylation with the potassium *O*-ethylxanthilate. Alkylation of **52** with allyl acetate followed by radical mediated annelation, gave **51**. No further progress has been reported.

Scheme 9. Zard's intramolecular radical addition approach.

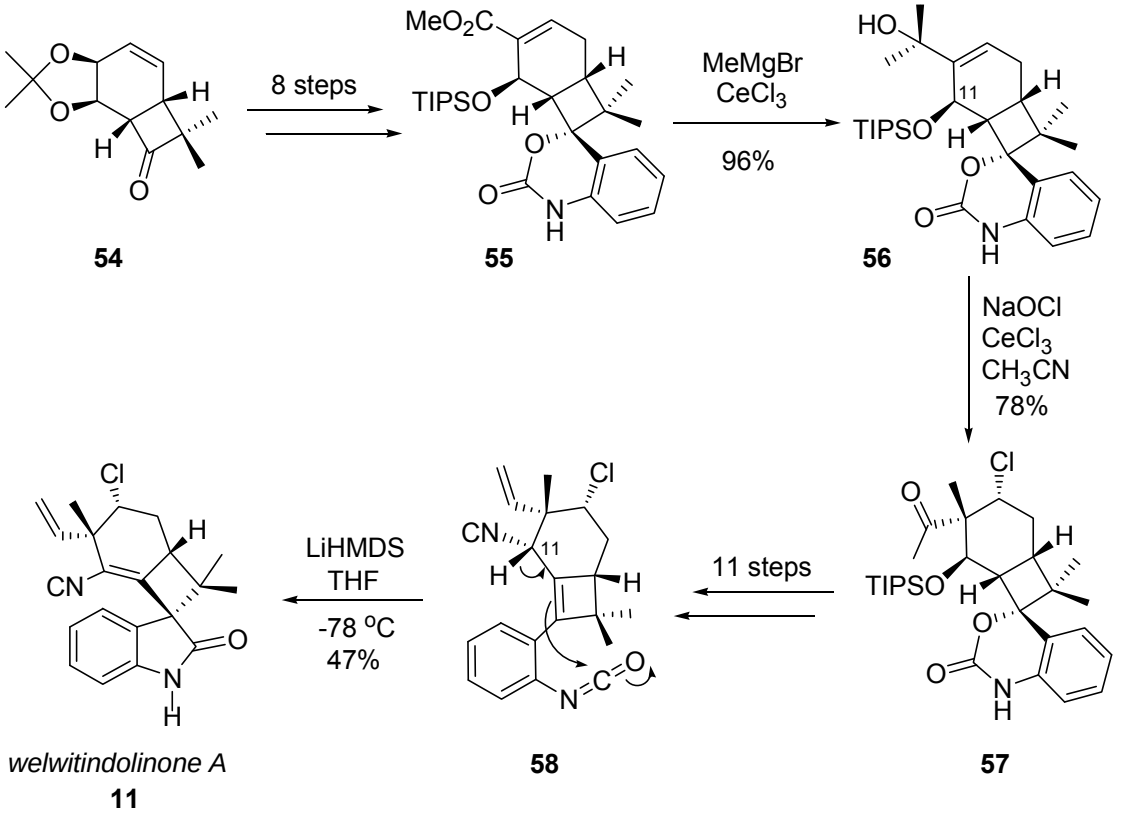


C. AD →ADB→ADBC

Wood and coworkers have also recently published an approach to welwitindolinone A / welwistatin. Treatment of a readily available cyclohexadiene acetonide with isobutyryl chloride effected a stereo- and regioselective [2+2] cycloaddition to furnish the cyclobutanone **54** in excellent yield (Scheme 10).[24] Subsequent steps then provided the conjugated ester **55**, which was converted to the tertiary alcohol **56**. Stereoselective chloronium ion induced semi-pinacol

rearrangement provided the ketone **57**. It is believed that the bulky C(11) silyloxy substituent forces chloronium ion formation from the opposite face, followed by methyl migration *anti* to the chloronium ion to provide the ketone. Several functional group manipulations subsequently provided the nitrile **58**, which was subjected to base induced intramolecular cyclization onto the aryl isocyanate to provide welwitindolinone A as a single diastereomer.

Scheme 10. Wood's approach to welwitindolinone A / welwistatin.

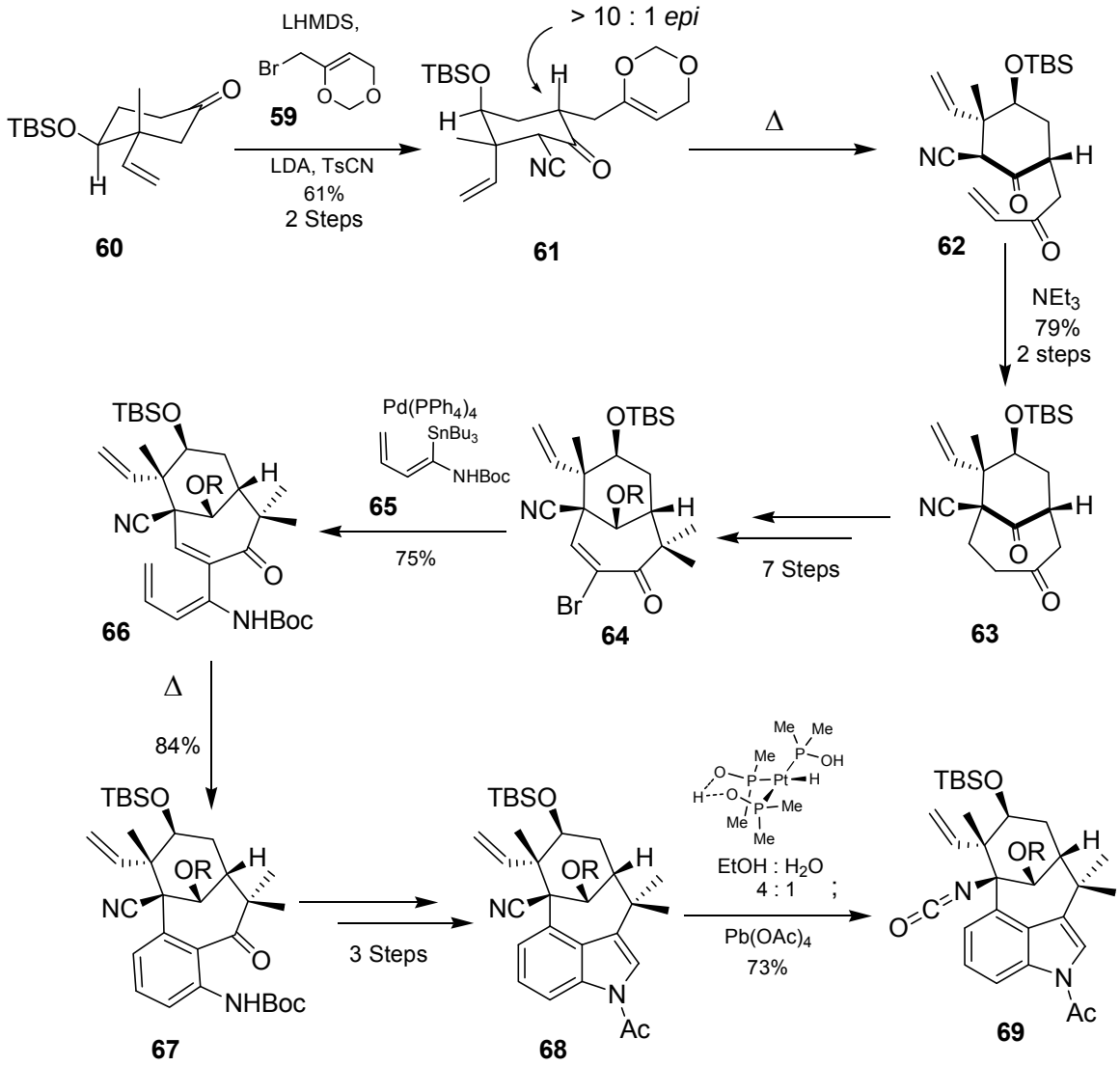


D. D→DC→DCA→DCAB

Our group has recently reported the synthesis of a fully functionalized welwitindolinone ring system via a novel strategy[25] which employed two methodologies previously reported by the Funk group, namely 1) the utilization of 6-

bromomethyl-4*H*-1,3-dioxin (**59**)[26] as a bromomethyl vinyl ketone equivalent and 2) annelation of an indole ring onto an α-haloenone.[27] Thus, stereoselective alkylation of the known ketone **60**[28] with the bromomethyldioxin **59** provided the dioxin **61** (Scheme 11). Thermolysis of dioxin **61** generated the enone **62** which was employed in a subsequent intramolecular Michael reaction to provide the functionalized bicyclo[4.3.1]decanone **63**. Several functional group manipulations provided the α-haloenone **64**, which underwent Stille coupling with the α–(tributylstannyl)-dienecarbamate **65** to arrive at the triene carbamate **66**. Subsequent electrocyclic ring closure and concomitant oxidation furnished the protected aniline **67**, which was converted to the *N*-acetyl indole **68** in three steps. Hydrogenolysis of the nitrile provided an amide that was converted to the isocyanate **69**, a fully functionalized ring system of the welwitindolinones. In order to complete this synthesis, several functional group manipulations must be performed, including installation of the isothiocyanate, vinyl chloride, and oxindole moieties.

Scheme 11. Funk and Greshock's approach to welwistatin.

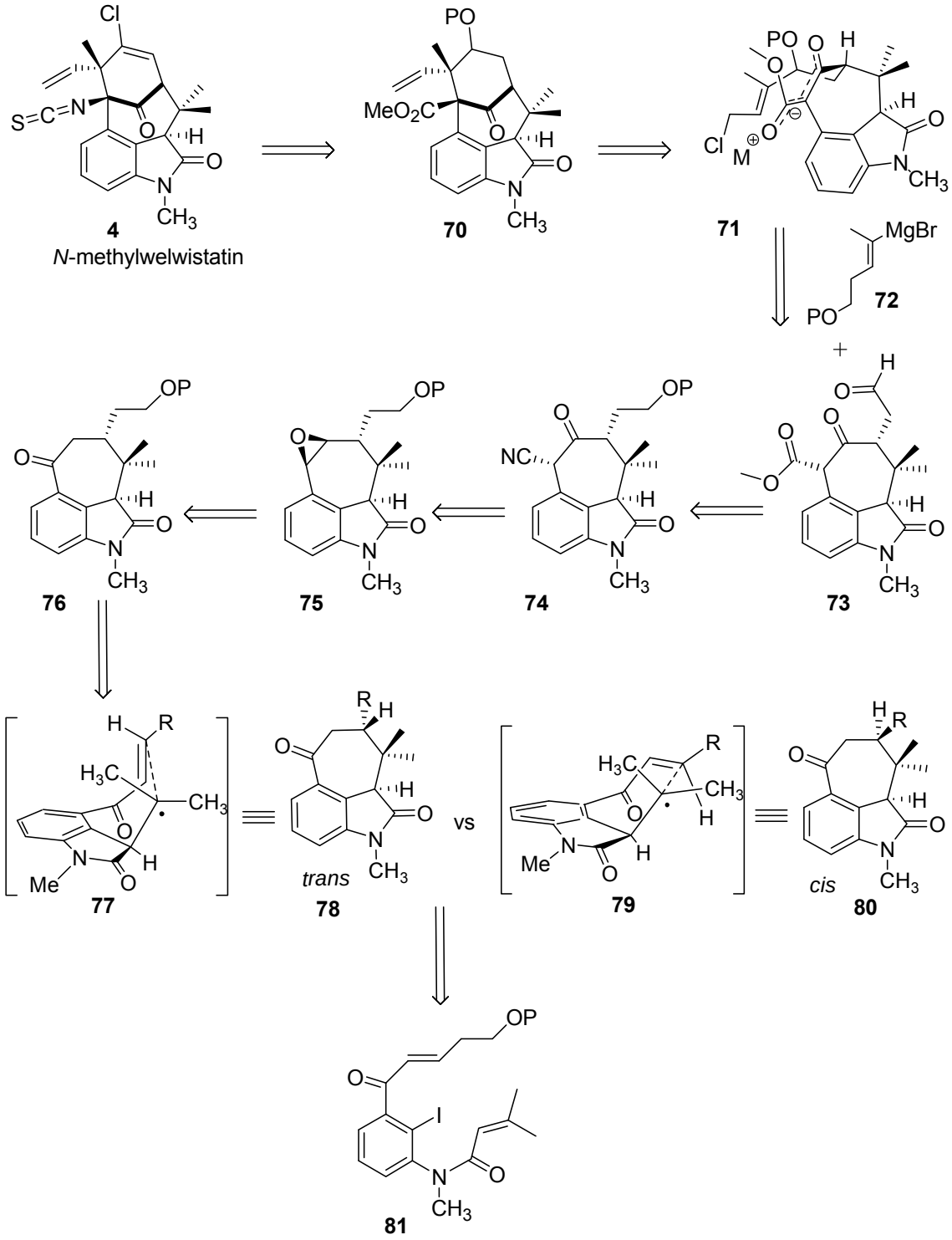


Thus, the total synthesis of welwistatin remains to be accomplished despite this intense synthetic effort. These syntheses focus on a single novel transformation for the construction of a single ring or stereocenter. The key step in most of these syntheses usually generates only one of the four stereogenic centers, and does not provide an easy way of introducing the remaining functionalities in order to complete the total synthesis. It is possible that a novel disconnection of the welwistatin ring system could provide an efficient synthesis of this intriguing natural product.

III. Retrosynthetic analysis for a radical cyclization-based approach to *N*-methylwelwistatin.

With the above considerations in mind, an alternative synthetic plan for the synthesis of *N*-methylwelwistatin was developed. Thus, it was believed that *N*-methylwelwitindolinone C isothiocyanate (**4**) (*N*-methylwelwistatin) could be made via deprotection of the alcohol **70**, oxidation to a ketone and transformation to the vinyl chloride.[29] Subsequent conversion of the bridgehead ester moiety to the corresponding bridgehead amine via Curtius rearrangement and reaction with thiophosgene would then provide *N*-methylwelwistatin (Scheme 12). The ester **70** could be accessed via the allylic chloride **71** via an S_N2' ring closure. The conformation shown might be preferred due to favorable ion pairing between the developing chloride ion and the counterion of the enolate to give rise to the stereochemistry shown. Allylic chloride **71** could be made via addition of the Grignard reagent[30] **72** to the aldehyde **73** followed by protection of the secondary alcohol. Standard allylic chloride[31] formation would then provide the desired substrate. The aldehyde **73** could be made from the β–ketonitrile **74** via hydrolysis of the nitrile and conversion to the ester, followed by deprotection and oxidation. β-Keto nitrile **74** could be made from epoxide **75** via ring opening[32] and oxidation. The epoxide might be available via reduction of ketone **76** to the alcohol, followed by elimination to the alkene, and stereoselective epoxidation. Finally, ketone **76** could be prepared via sequential stereoselective 5-*exo*-trig, 7-*endo*-trig radical cyclizations of enone **81.** The formation of two diastereomeric products is possible through the 7-*endo*-trig radical cyclization, the *trans* diastereomer **78**, and the *cis* diastereomer **80**. However, we expected the transition state conformation leading to the *trans* diastereomer to be preferred due to the fact that the alkene can maintain favorable overlap with the carbonyl group during bond formation. The alkene functionality in the conformation leading to the *cis* diastereomer is twisted out of plane with the carbonyl and therefore the developing oxoallylic radical is less stable.

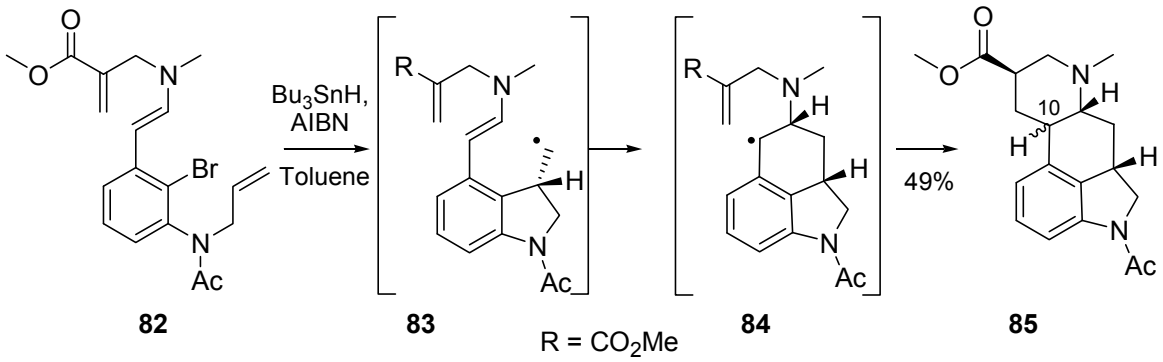
Scheme 12. Retrosynthetic analysis of *N*-methylwelwistatin.



A. Sequential radical cyclizations

Radical reactions are frequently used to create polycyclic compounds from structurally simple starting materials.[33] However, there are limited examples of sequential radical cyclizations that generate complex oxindole-, dihydroindole- or indole-based ring systems. One of the most notable examples of an aryl radical cascade reaction to create a complex 3,4-disubstituted dihydroindole based ring system was published by Parsons and coworkers in their studies of lysergic acid derivatives.[34] Enamine **82** underwent sequential 5-*exo*-trig, 6-*endo*-trig, 6-*endo*-trig radical cyclizations to provide the tertiary amine **85** in good yield (Scheme 13).

Scheme 13. Parsons' sequential radical cyclizations.



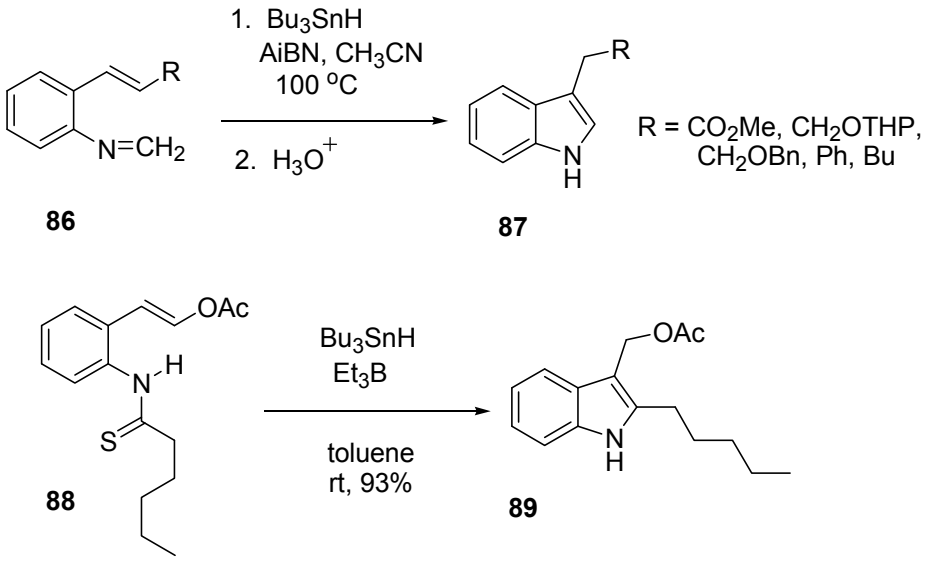
82 **83** **84** **85**

In this case, the kinetically preferred 5-*exo*-trig radical cyclization generates a methyl radical **83** which immediately undergoes 6-*endo*-trig radical cyclization with the enamine to arrive at the benzylic radical intermediate **84**. The methyl radical adds to the bottom face of the enamine in order to maximize orbital overlap during bond formation, which leads to the *cis* stereochemistry shown. Subsequent hydrogen atom abstraction provides the product as a mixture of C(10) diastereomers.

There are, however, many examples of radical cyclizations to generate indoles, oxindoles, and dihydroindoles, especially in the context of natural product synthesis. For example, 5-*exo-trig* radical cyclizations of a variety of

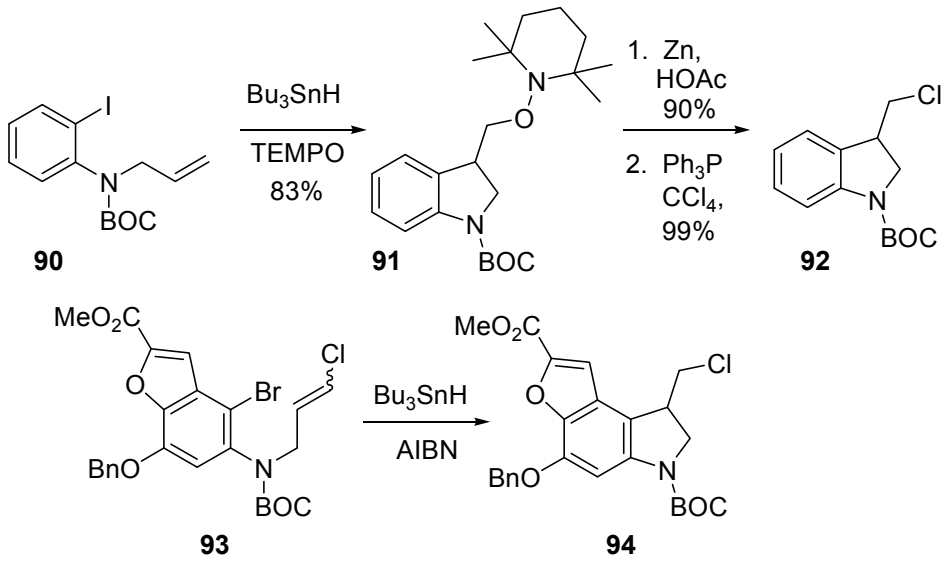
substrates, including *o*-isocyanostyrenes (**86**)[35] and *o*-alkenylthioanilides (**88**)[36] have been used to construct functionalized indoles (Scheme 14).

Scheme 14. Various radical cyclizations to make indoles.



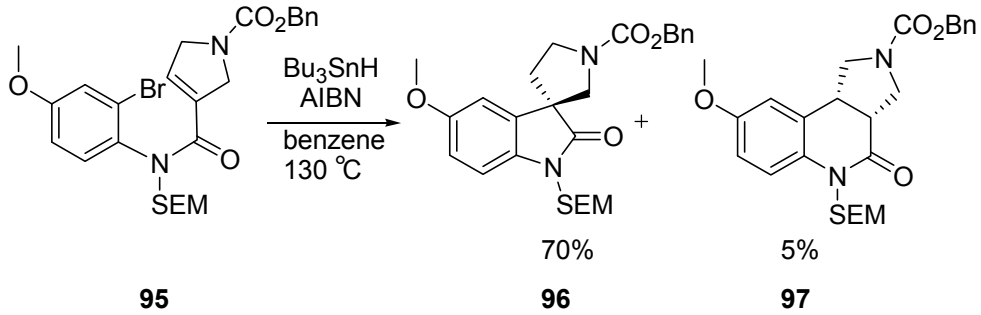
Boger has been one of the pioneers in the development of tin-mediated radical cyclizations to provide functionalized dihydroindoles. In his synthetic studies of both duocarmycin and CC-1065, a TEMPO radical trap was used to construct key subunits via a 5-*exo*-*trig* radical cyclization of a variety of protected 2-halo-anilides **90** (Scheme 15).[37] Later, Boger was able to streamline his synthesis by employing vinylic chloride substrates such as **93** in the 5-*exo*-*trig* radical cyclization to arrive at 3-chloromethyl dihydroindoles such as **94**.[38]

Scheme 15. Boger's radical cyclizations to dihydroindoles.



Jones has developed a methodology to synthesize oxindoles via radical cyclizations of protected enamides. Furthermore, he has applied this methodology to a total synthesis of the natural product horsfiline (Scheme 16).[39] Treatment of the aryl bromide **95** with tributyltin hydride and catalytic AIBN at high temperature provided the desired 5-*exo*-trig radical cyclization product, oxindole **96**, with a small amount of the 6-*endo*-trig radical cyclization product **97**.

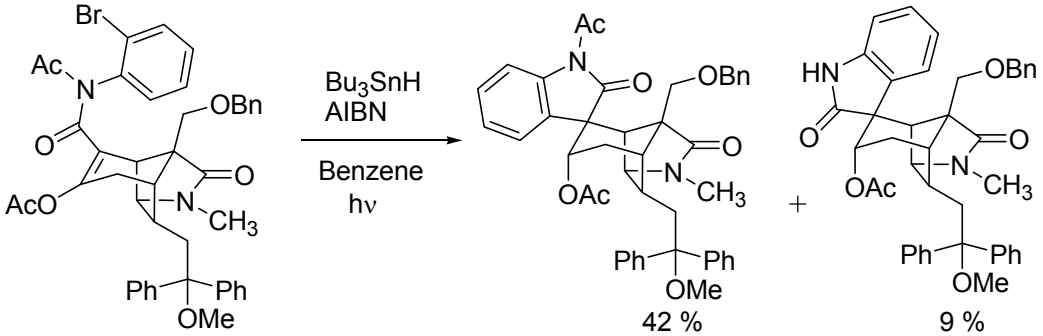
Scheme 16. Jones' synthesis of horsfiline.



Hart and coworkers generated an oxindole and thus completed a total synthesis of the natural product gelsemine via intramolecular 5-*exo*-trig radical cyclization of aryl bromide **98** onto a pendant olefin to provide the core ring

system **99** in good yield (Scheme 17).[40] In this case, Hart observed none of the 6-*endo*-trig radical cyclization product, but did isolate a small amount of the oxindole C-3 epimer **100**.

Scheme 17. Hart's radical cyclization for gelsemine.

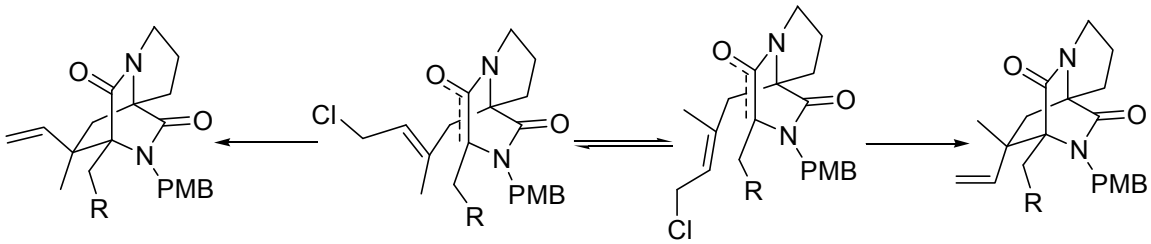


98 **99** **100**

B. S_N2' reaction to generate vicinal quaternary centers

The S_N2' reaction has been a useful method for forming carbon-carbon bonds in complex polycyclic natural products.[41] A notable example of a S_N2' ring closure can be found in Williams' brevianamide synthesis,[42] wherein vicinal quaternary centers were formed, and it was discovered that both solvent and steric interactions affected the stereochemical outcome (Scheme 18). It was

Scheme 18. Williams' S_N2' in his brevianamide synthesis.



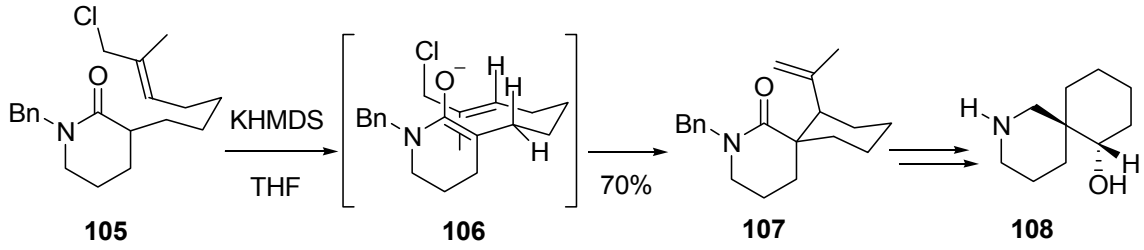
101 **102** **103** **104**

1	NaH, DMF	2
1	NaH, Benzene, 18-Crown-6	3.8
33	NaH, Benzene	1

speculated that polar, stabilizing solvents such as DMF form a solvent shell around the sodium cation. This creates a sterically demanding environment for the allylic chloride to fold over the enolate, and therefore achieve a proper transition-state geometry for cyclization. However, in benzene, the allylic chloride would be expected to fold over the enolate in order to bring the two developing ions closer, since solvation of the individual ions in a nonpolar environment would be less favorable.

Another example of an intramolecular S_N2' process can be found in Kim's isonitramine synthesis, which employed an S_N2' enolate alkylation to construct the core ring system **107** from allylic chloride **105** (Scheme 19). The chair-like transition state **106**, wherein the potassium ion is proximal to the developing chloride ion, helps to account for the high stereoselectivity observed in the product **107**.[43]

Scheme 19. Kim's S_N2' reaction in a synthesis of isonitramine.



105 **106** **107** **108**

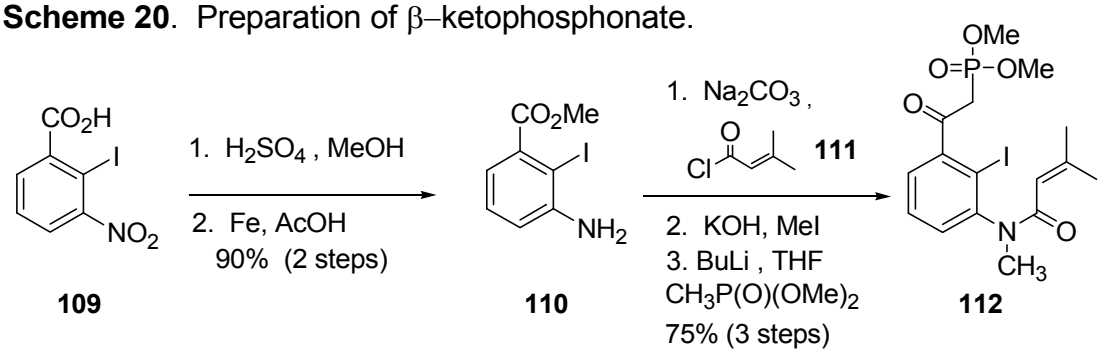
IV. Approach to the synthesis of *N*-methylwelwistatin

A. Radical cyclization of the enone

The projected synthesis of *N*-methylwelwistatin began with the preparation of the radical cyclization precursor enone **81** (Scheme 20). To that end, the iodide **109**[44] was esterified and the nitro group was reduced using iron powder to yield the iodoaniline **110**. Next, acylation of the aniline with 3,3-dimethylacryloyl chloride (**111**) and subsequent *N*-methylation with iodomethane gave the amide.

Finally, treatment of the ester with the anion of dimethyl methyl phosphonate provided the β-keto phosphonate **112**.

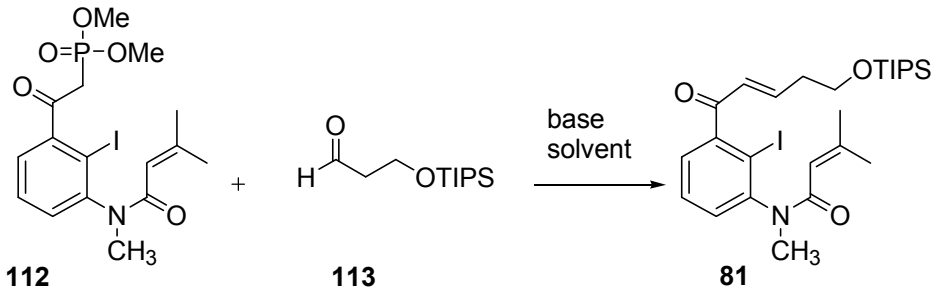
Scheme 20. Preparation of β–ketophosphonate.



109 **110** **112**

Extensive optimization of the Horner-Emmons reaction of phosphonate **112** with aldehyde **113** was required to synthesize the requisite enone **81** in satisfactory yields (Scheme 21). Poor yields were obtained if the conjugate base of **112** was prepared using strong bases such as NaH, NaHMDS, or KO*t*Bu, most likely due to decomposition (β-elimination) of the aldehyde. Furthermore, milder reagents, such as the Masamune-Roush conditions[45] also failed to produce satisfactory yields. Fortunately, we eventually discovered that by using the mild base tetramethylguanidine (TMG) in THF,[46] we were able to isolate the enone in good yield.

Scheme 21. Optimization of Horner Emmons Reaction.

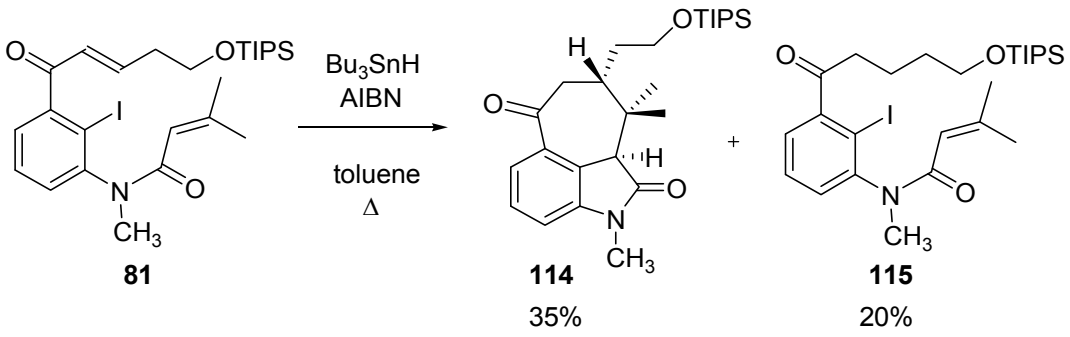


112 **113** **81**

Base	Solvent	Temp °C	Yield
Cs_2CO_3	THF	-78→rt 24 h	37%
Cs_2CO_3	THF	0→rt 24 h	58%
CsOH	THF	0→rt 24 h	10%
Cs_2CO_3	DMF	0→rt 4 h	NR
BuLi / H_2O	Et_2O / THF	0→rt 24 h	20%
NaH	THF	0→rt 10 h	61%
NaHMDS	DME	-30→rt 24 h	62%
NaHMDS	THF	-40→rt 8 h	42%
KO*t*Bu	THF	-10→rt 24 h	NR
Cs_2CO_3	CH_3CN	0→rt 24 h	38%
LiCl / DIPEA	CH_3CN	0→rt 24 h	40%
K_2CO_3	THF	0→rt 24 h	53%
LiCl / NEt_3	CH_3CN	0→rt 24 h	57%
LiCl / DBU	CH_3CN	0→rt 24 h	40%
LiCl / NEt_3	THF	0→rt 24 h	44%
LiCl / DIPEA	THF	0→rt 24 h	40%
LiCl / $HNEt_2$	CH_3CN	0→rt 24 h	41%
LiCl / NEt_3	CH_3CN	0→45 24 h	50%
TMG	THF	0→rt 24 h	74%

The enone **81** was subjected to radical cyclization conditions to afford the ketone **114** as a single stereoisomer. Initially, tributyltin hydride and AIBN in refluxing toluene was employed, but the desired product was accompanied by ketone **115**, the conjugate reduction product of the enone moiety of **81** (Scheme 22).

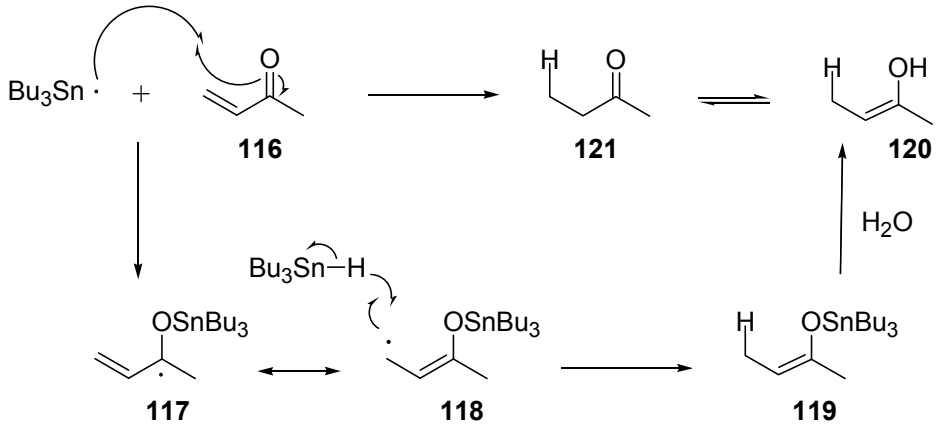
Scheme 22. Tributyltin hydride conjugate reduction of enone.



81 **114** 35% **115** 20%

This unwanted side reaction is well precedented[47] and has been further examined by Fu and coworkers.[48] A possible mechanism for this transformation is shown in Scheme 23. Tributyltin hydride adds to the ketone **116** to provide the stannyl ketyl intermediate **117** which then abstracts a hydrogen atom to arrive at the tin enolate **119.** Subsequent hydrolysis of the stannyl enol **119** generates an enol **120** which tautomerizes to the ketone **121**.

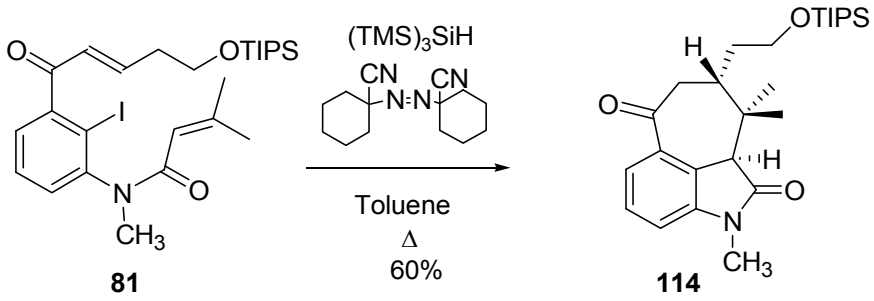
Scheme 23. A proposed catalytic cycle for conjugate reduction of enones by $SnBu_3H$



116 **121** **120** **117** **118** **119**

Subsequently it was discovered that tris(trimethylsilyl)silane (TTMSS) and azobis(cyclohexane)carbonitrile (ACN)[49] in toluene at 85 °C produced the desired ketone **114** more efficiently, and importantly, without conjugate reduction of the enone (Scheme 24). This could be due to the difference in bond dissociation energies between the Si-O vs Sn-O bond (148 ± kcal / mol vs 127 ± 2 kcal / mol, respectively).[50]

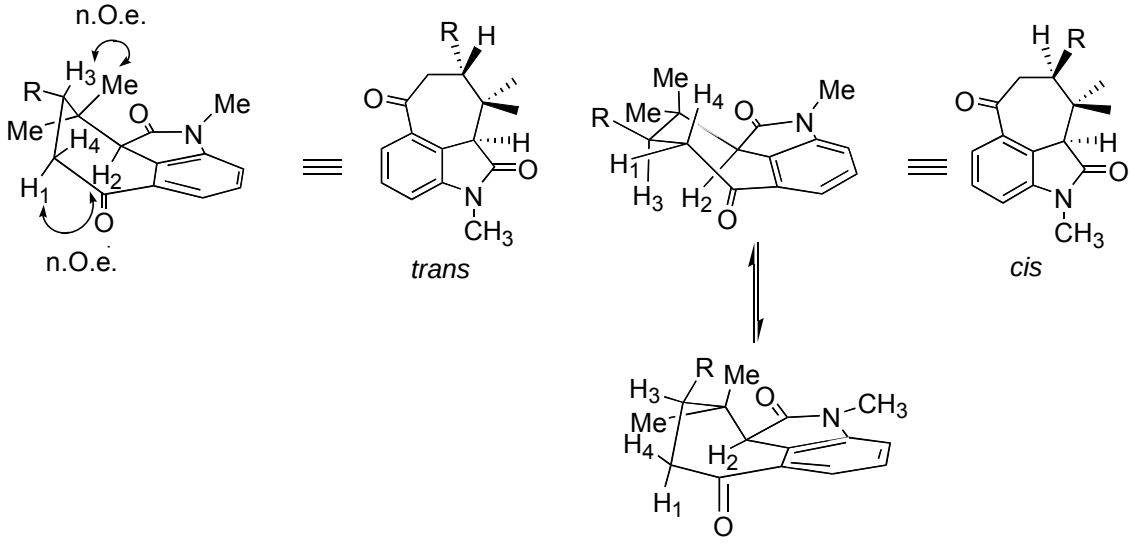
Scheme 24. Optimized radical cyclization of the enone.



Giese and Chatgilialoglu have postulated that because TTMSS is approximately 10 times less reactive than Bu_3SnH toward alkyl radicals,[51] most likely due to the slightly higher bond energy of the Si-H bond ($(TMS)_3Si$-H = 79 kcal / mol vs Bu_3Sn-H = 74 kcal / mol), the use of TTMSS in radical cyclization reactions could help to increase the yield of slow cyclization reactions.[51]

The stereochemical assignment of the radical cyclization product was based on both n.O.e. observations as well as the coupling constants of the diagnostic ^1H NMR resonances. As shown below (Figure 5), the key n.O.e. that was observed is between the pseudo-axial proton next to the ketone (H1) and the indolinone proton (H2). Additionally, as would be expected, a large coupling constant exists between (H1) and (H3) because the dihedral angle is approximately 180 degrees (J = 10.0 Hz). Another large coupling constant is observed for the geminal coupling between (H1) and (H4) (J = 16.8 Hz). If the opposite stereochemistry were obtained in the radical cyclization product, then an n.O.e. would have been expected between (H3) and (H2) for the preferred conformer. An n.O.e. between (H1) and (H2) would be possible in a higher energy conformer, but the coupling constant between (H1) and (H3) would be much smaller because the dihedral angle is approximately 90 degrees.

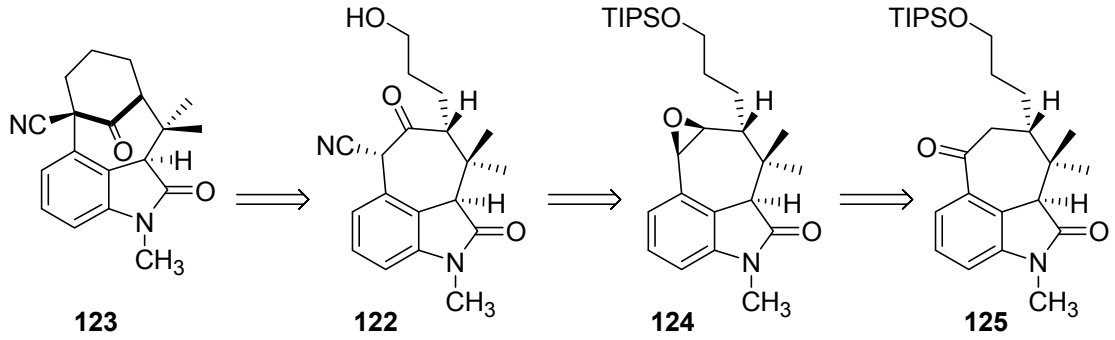
Figure 5. Explanation of the radical cyclization product's stereochemical assignment.



B. A possible alkylation strategy to complete the ring system

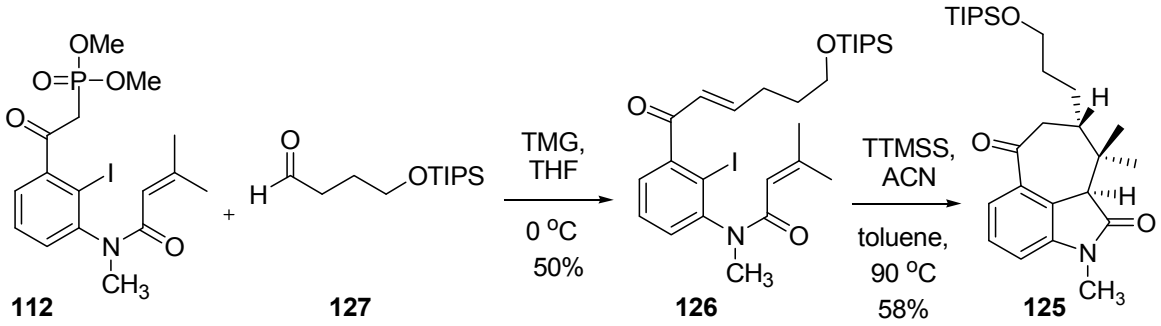
With the radical cyclization product in hand, our attention was now directed to annulation of the remaining six-membered ring onto the radical cyclization product **114**. However, we decided to investigate a model system before pursuing the total synthesis. It was believed that an intramolecular Mitsunobu reaction[52] of β–keto nitrile **122** would constitute a quick entry to the complete ring system, *e.g.* indolinone **123** (Scheme 25). The β-keto nitrile could be made from the epoxide **124** via ring opening with cyanide, followed by oxidation to the ketone and deprotection. The epoxide could be synthesized from the radical cyclization product, ketone **125**, via reduction to the alcohol, elimination, and epoxidation.

Scheme 25. Retrosynthetic analysis for a model system.



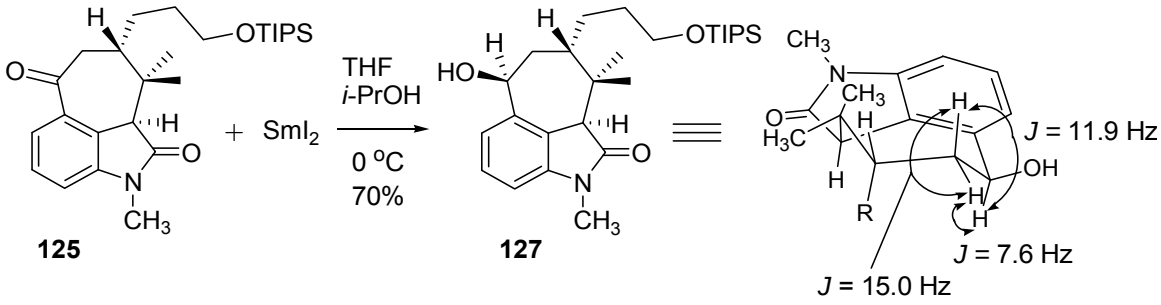
Thus, the enone **126** was synthesized from the phosphonate **112** and the aldehyde **127** as before. Subjection of the enone **126** to the optimized radical cyclization conditions effected transformation to the desired ketone **125** in good yield (Scheme 26).

Scheme 26. Synthesis of a radical cyclization product.



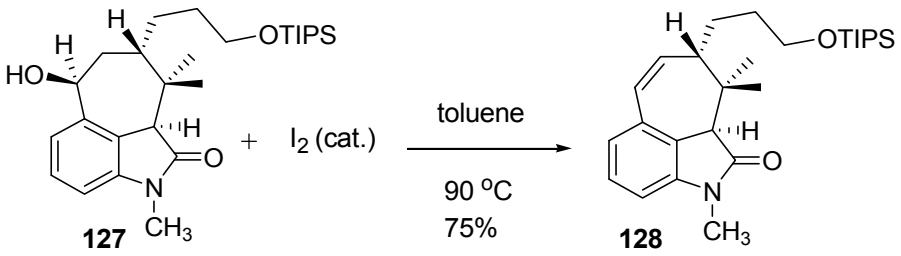
Unfortunately, reduction of the ketone **125** was not as easy as anticipated. Standard reduction protocols using aluminum or boron based reagents such as Red-Al, L-Selectride, $LiAl(O\text{-}tBu)_3H$, Luche conditions,[53] $NaBH_4$ in alcoholic solvents, or BH_3 gave poor yields with competing epimerization of the acidic (pKa ~ 20) indolinone benzylic proton.[54] However, reduction of ketone **125** with samarium(II) iodide in the presence of *i*-PrOH provided the alcohol **127** as a single diastereomer without epimerizing the indolinone stereocenter. The stereochemistry of the alcohol was tentatively assigned as shown based on coupling constants and conformational analysis (Scheme 27).

Scheme 27. Reduction of the radical cyclization product.



Dehydration of the benzylic alcohol proved to be troublesome, in part due to the reactive indolinone. Attempts to install the alkene via conversion to the benzylic halide and *in situ* elimination, or transformation to a suitable leaving group such as a tosylate or nosylate led to decomposition or recovery of unreacted starting material (Scheme 28). Direct conversion to the benzylic chloride[31] proceeded in poor yield, and even then this chloride could not be eliminated cleanly without epimerization of the indolinone benzylic proton. Additionally, elimination of the alcohol under acidic conditions was also unsuccessful due to competing epimerization of the indolinone benzylic proton. Finally, treatment of the alcohol **127** with a catalytic amount of iodine in refluxing toluene provided the alkene **128** in good yield, presumably via *in situ* generation of hydroiodic acid and subsequent acid catalyzed elimination.

Scheme 28. Elimination to the alkene.

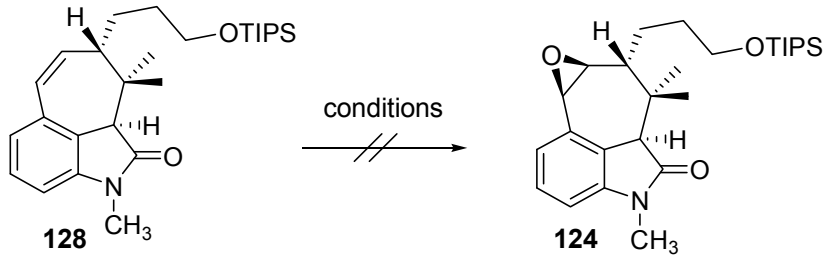


Elimination conditions attempted

1. $Et_3NSO_2NCO_2Me$, benzene
2. $SOCl_2$, Pyridine
3. PPh_3, I_2, imidazole, benzene
4. DMAP, TsCl, NEt_3, CH_2Cl_2
5. $POCl_3$, Pyridine
6. $POCl_3$, Pyridine, benzene
7. $SOCl_2$, HMPA
8. $SOCl_2$, Et_2O
9. $POCl_3$, DMF, $CHCl_3$
10. $POBr_3$, Pyridine
11. PBr_3, benzene
12. Tf_2O, Lutidine, $CHCl_3$
13. MsCl, NEt_3, CH_2Cl_2
14. NsCl, NEt_3, DMAP, CH_2Cl_2
15. MsCl, LiCl, Collidine, DMF
16. DIPEA, Tf_2O, CH_2Cl_2
17. MsCl, DBU, LiCl, CH_2Cl_2
18. TsCl, DMAP, NEt_3, CH_2Cl_2
19. P_2O_5, benzene
20. P_2O_5, hexanes
21. BF_3, CH_3CN
22. *p*-TsOH, benzene
23. CSA, $CHCl_3$

Thus, with the alkene in hand, we investigated the epoxidation to arrive at epoxide **124**. Unfortunately, all attempts to make the epoxide directly from the alkene using *m*CPBA,[55] DMDO,[56] or methyl(trifluoromethyl)dioxirane,[57] were unsuccessful and provided only unreacted starting material or decomposition (Scheme 29).

Scheme 29. Epoxidation attempts on the alkene.

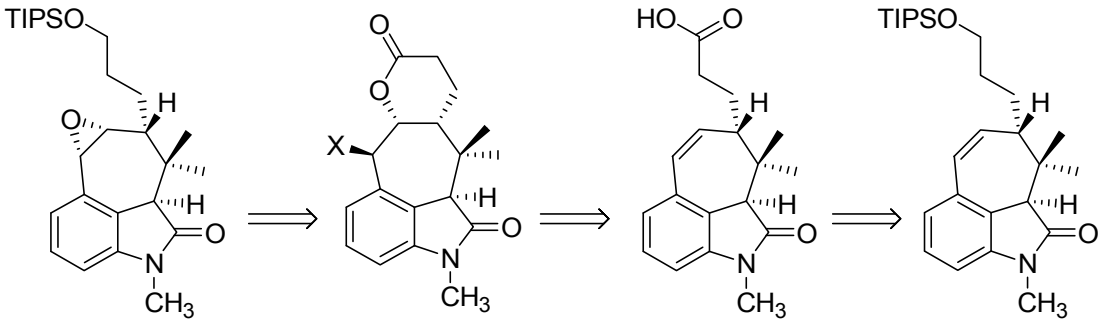


Epoxidation conditions attempted

1. *m*CPBA, CH_2Cl_2
2. DMDO, acetone
3. *m*CPBA,aq. $NaHCO_3$, CH_2Cl_2
4. *m*CPBA, K_2HPO_4, $CHCl_3$
5. $(CF_3CO_2)O$, H_2O_2, CH_2Cl_2
6. DMDO, CH_2Cl_2
7. methyl(trifluoromethyl)dioxirane, CH_2Cl_2
8. *m*CPBA,4,4'-thiobis-(6-*t*-butyl-3-methylphenol),CCl_4
9. *m*CPBA,4,4'-thiobis-(6-*t*-butyl-3-methylphenol),$C_2H_4Cl_2$
10. oxone, $NaHCO_3$, acetone / H_2O
11. trifluoroacetone, Na_2EDTA, $NaHCO_3$ Oxone, CH_3CN

As an alternative strategy for forming the epoxide, efforts were directed towards halolactonization[58] (Scheme 30). Thus, epoxide **124** would be derived from the halolactone **129** by methanolysis of the lactone and DIBAL-H reduction of the resultant ester. Halolactone **129** could be prepared from the acid **130**, which in turn could be synthesized from the alkene **128** via desilylation and oxidation to the acid.

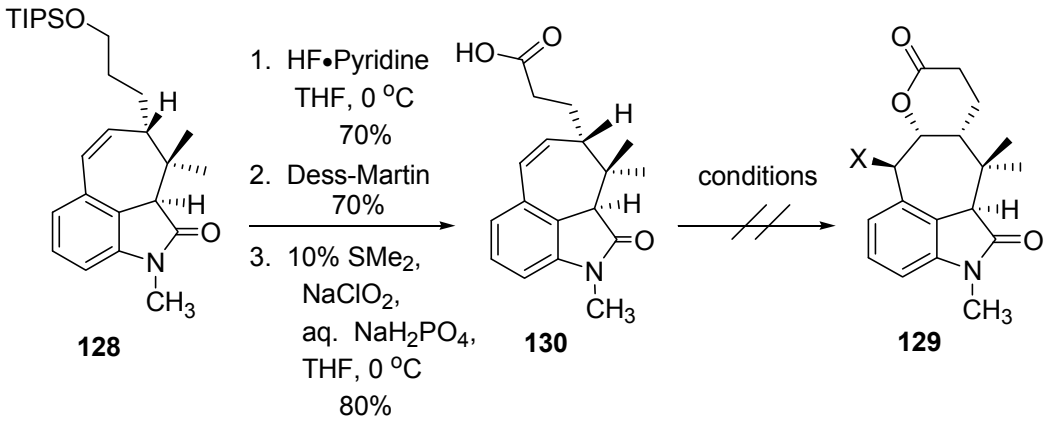
Scheme 30. Retrosynthetic analysis for a halolactonization strategy.



To that end, desilylation of alkene **128** with HF•pyridine followed by a two step oxidation protocol[59] provided the acid **130**. Unfortunately, the alkene was

extremely unreactive towards halolactonization conditions, providing only decomposition products or unreacted starting material once again. A disheartening indication of the low reactivity of the alkene was evident when both *N*-(phenyseleno)phthalimide[60] under acidic conditions, and treatment of the thallium carboxylate[61] with bromine failed to provide any halolactone (Scheme 31).

Scheme 31. Attempted halolactonization of the acid.

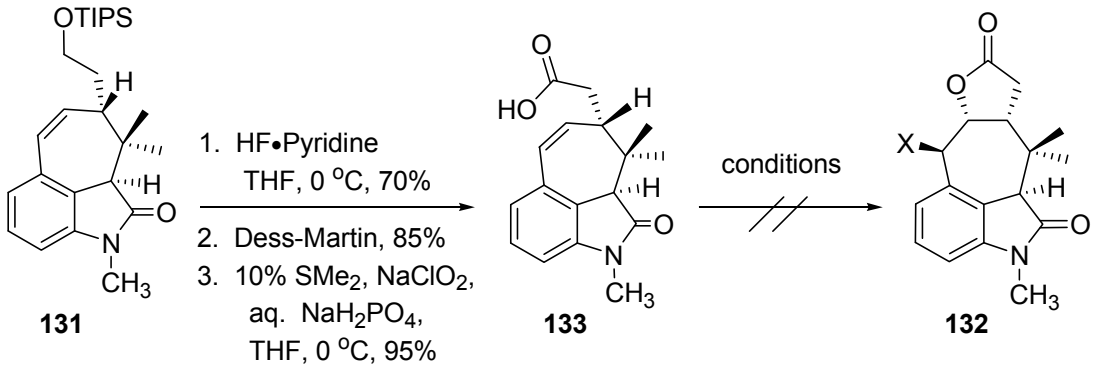


Halolactonization conditions attempted

1. I_2 , KI, aq $NaHCO_3$ CH_2Cl_2, 0 °C
2. NBS, DMF, 0 °C
3. KO*t*Bu, NBS, THF -40 °C→25 °C
4. *N*-(phenylseleno)-phthalimide, CH_2Cl_2 0 °C
5. *N*-(phenylseleno)-phthalimide, AcOH, CH_2Cl_2, 0 °C
6. PhSeBr, DIPEA, CH_2Cl_2, -78 °C→50 °C
7. Cs_2CO_3, NCS, CH_3CN
8. NBS, CH_2Cl_2, mol sieves, 25 °C
9. DIPEA, Br_2, CH_2Cl_2 -78 °C→25 °C
10. TlOEt, Br_2, CH_2Cl_2 -78°C→50°C

In addition, attempts to effect halolactonization to the butyrolactone **132** with the analogous acid **133** were unsuccessful (Scheme 32). These examples further demonstrated the relative (un)reactivity of the alkene. Even the lead(IV) acetate-metal halide complexes, which have been described as easily handled and highly reactive reagents for use in halolactonization,[62] provided unreacted starting material.

Scheme 32. Attempted halolactonization of the acid to provide a butyrolactone.

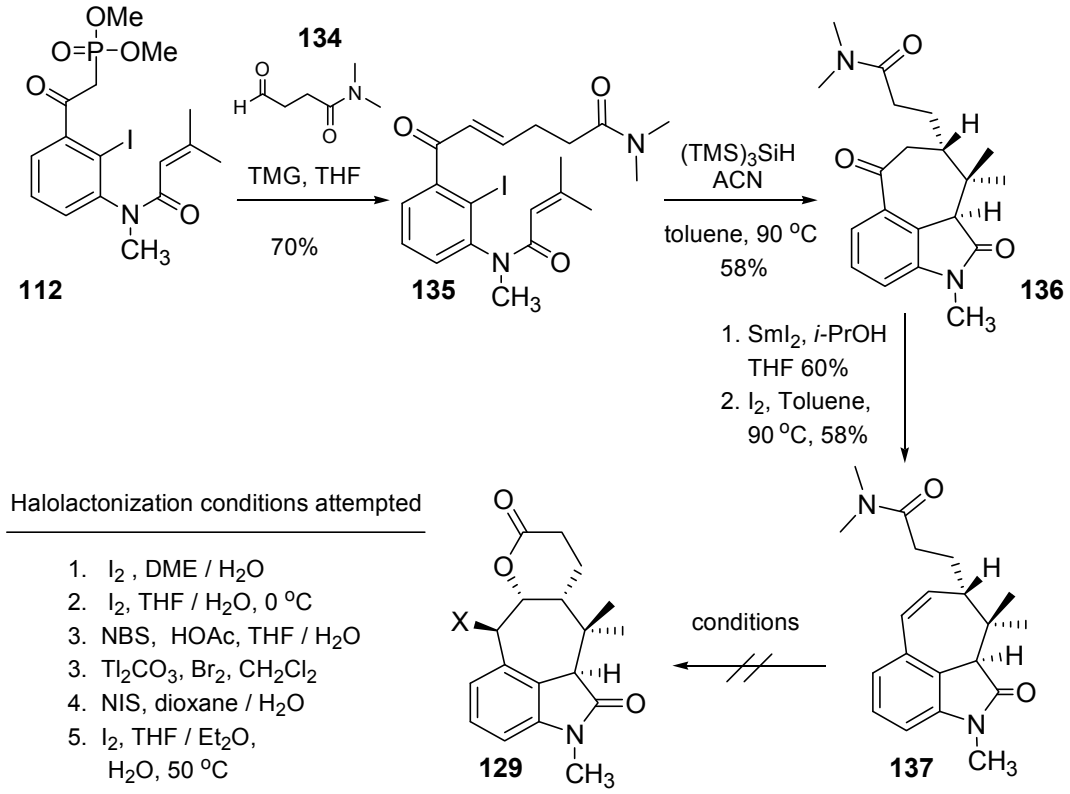


Halolactonization conditions attempted

1. I_2 , $NaHCO_3$ CH_3CN, 0 °C
2. $NaHCO_3$, Br_2, CH_2Cl_2
3. Tl_2CO_3, Br_2, CH_2Cl_2, 45 °C
4. DIPEA, Br_2, CH_2Cl_2 45 °C
5. NBS, THF, 0 °C
6. NBS, D_6-Acetone
7. $Pb(OAc)_4$, $ZnBr_4$, DME, 0 °C
8. $Pb(OAc)_4$, Bu_4NBr, DME, 0 °C
9. $Pb(OAc)_4$, NaI, DME, 0 °C
10. Br_2, NaOAc, AcOH
11. NBS, AcOH, THF, 0 °C
12. TMSBr, DMSO, DIPEA, $CHCl_3$, 60 °C
13. NBS, (aq) $NaHCO_3$, 0 °C
14. NCS, THF, 0 °C
15. NIS, D_6-Acetone
16. KI, I_2, $NaHCO_3$, H_2O, 0 °C

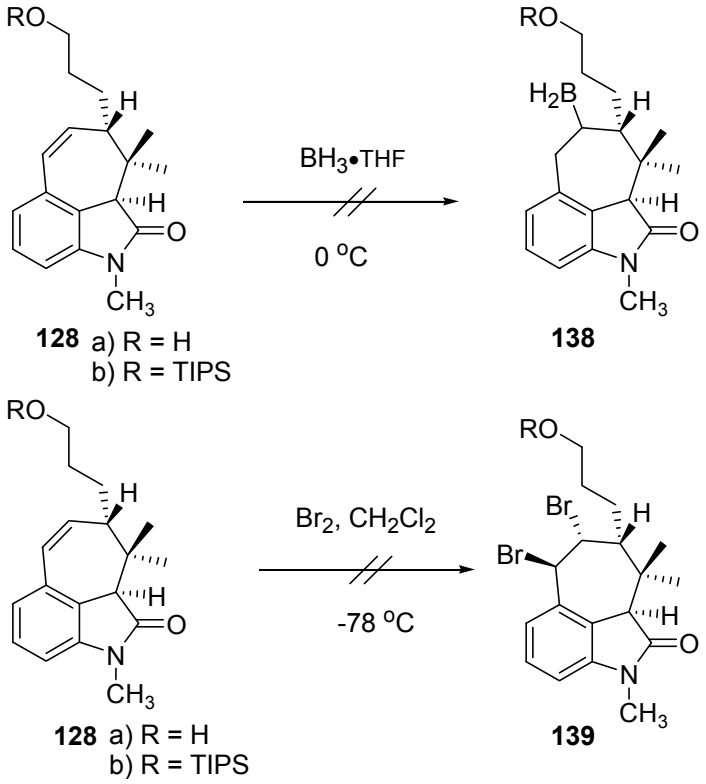
Alternately, we made the analogous *N,N*-dimethylamide derivatives. Horner-Emmons reaction of the phosphonate **112** with *N,N*-dimethyl-4-oxo-butryamide (**134**) provided the enone **135**. Subsequent radical cyclization, reduction, and elimination as before gave the alkene **137**. Unfortunately, repeated attempts to effect halolactonization with the amide were also unsuccessful (Scheme 33).

Scheme 33. Synthesis and attempted halolactonization of an amide.



The poor nucleophilicity of the alkene functionality became further evident upon the attempted hydroboration or bromination of alkene **128** (Scheme 34). It is difficult to rationalize the relative (un)reactivity of the alkene, since styrenes can be functionalized easily. There seems to be no real steric hindrance about the alkene so a possible explanation could be that the oxindole could be inductively withdrawing electron density from the conjugated alkene and thus affecting its reactivity. Some consideration was given to reducing the oxindole to the corresponding indole, which might be reactive to the epoxidations or halolactonization conditions. However, this would involve sacrificing a stereogenic center and was deemed unacceptable.

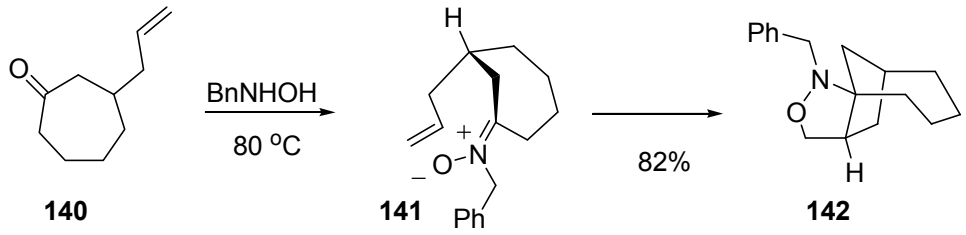
Scheme 34. Attempted functionalization of the alkene.



C. A possible intramolecular [3+2] nitrone-olefin cycloaddition to complete the ring system

In an effort to construct the complete ring system of welwistatin and avoid the unreactive alkene, a different strategy was explored. Efforts focused on closure of the final ring via an intramolecular [3+2] nitrone-olefin cycloaddition.[63] Exocyclic nitrones derived from ketones have been previously utilized to construct tricyclic ring systems like **142** by Funk and coworkers (Scheme 35).[64] A strategy such as this one seemed ideally suited to correct our problems because it could potentially introduce the bridgehead nitrogen functionality, close the remaining ring, and it could be tested quickly from the radical cyclization product, ketone **114**.

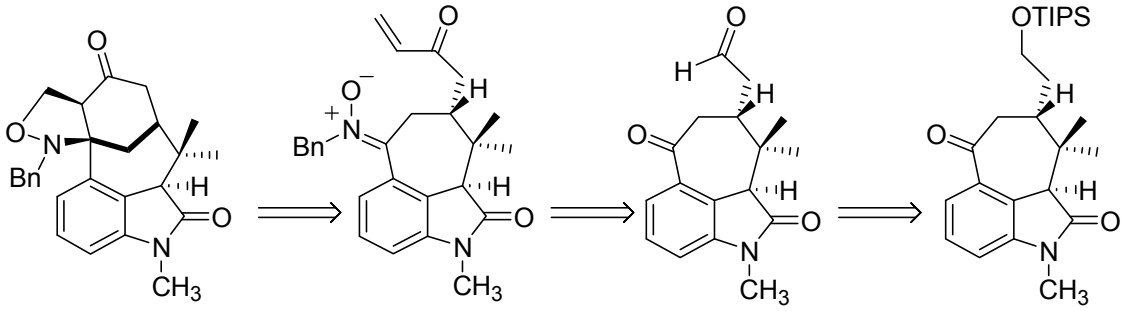
Scheme 35. Funk's intramolecular nitrone-olefin cycloaddition.



140 **141** **142**

Retrosynthetically, it was believed that the complete ring system **143** could be made via an intramolecular [3+2] cycloaddition of nitrone **144**. The nitrone **144** could be synthesized from the aldehyde **145** via vinylmagnesium bromide Grignard addition to the aldehyde, followed by nitrone formation and oxidation. Finally, the aldehyde **145** could be made from the previously prepared ketone **114** via deprotection and oxidation (Scheme 36).

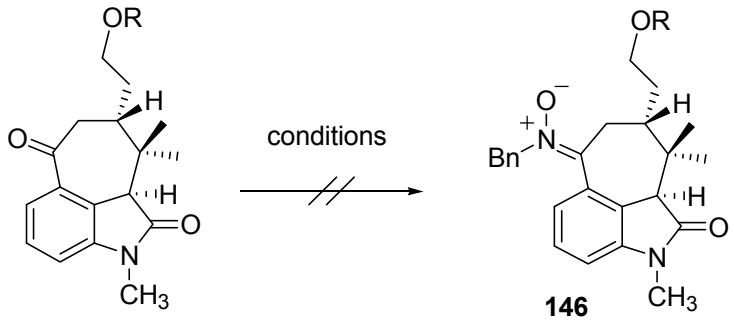
Scheme 36. Retrosynthetic analysis for a nitrone-olefin cycloaddition.



143 **144** **145** **114**

Unfortunately the formation of nitrone **146** from the ketones **114** or **147** (available via HF•pyridine deprotection of **114**) was unsuccessful under a variety of conditions (Scheme 37).

Scheme 37. Attempted *N*-benzyl nitrone formation from the ketone.



114 R = TIPS
147 R = H

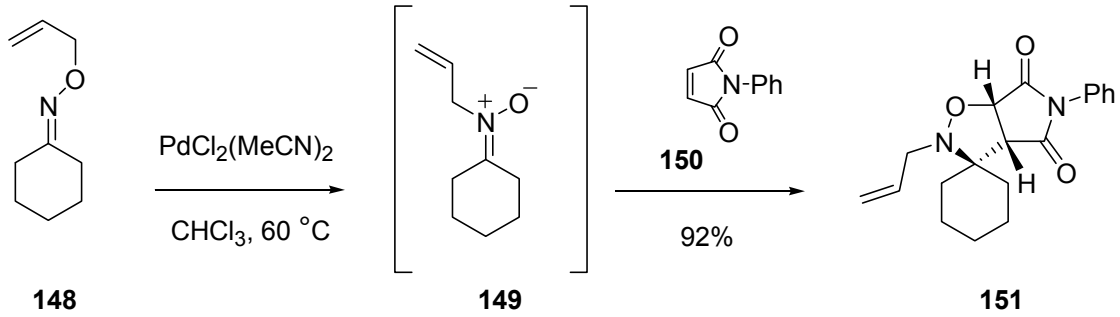
146

Attempted nitrone formation conditions

1. R = H $PhCH_2NHOH$, EtOH, mol. sieves, rt, 24 h
2. R = TIPS $PhCH_2NHOH$, EtOH, mol. sieves, rt, 24 h
3. R = TIPS $PhCH_2NHOH$, $ZnCl_2$, $MgSO_4$, CH_2Cl_2, rt, 48 h
4. R = TIPS $PhCH_2NHOH$, EtOH, mol. sieves, 50 ^oC, 48 h

As an alternative means of generating the nitrone, Grigg has established that *O*-allyl-oximes such as **148** can undergo a palladium-mediated rearrangement to afford the corresponding nitrone **149**, which was used in a [3+2] cycloaddition with *N*-phenylmaleimide (**150**) to give the heterocycle **151** (Scheme 38).[65]

Scheme 38. Grigg's palladium-mediated generation of a nitrone.

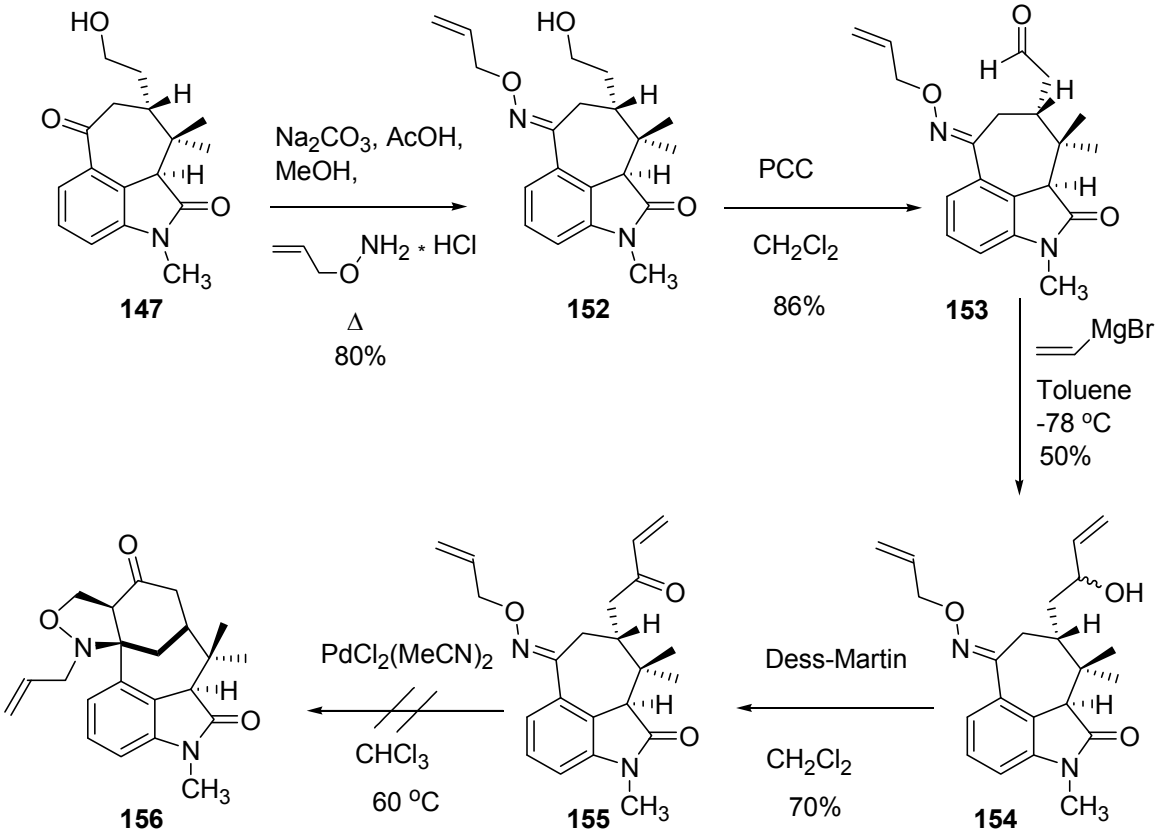


148 **149** **151**

To that end, *O*-allyl oxime **152** was generated from the corresponding ketone **147** (Scheme 39). Oxidation of **152** provided the aldehyde **153**, and subsequent Grignard addition gave the alcohol **154** as an inseparable mixture of diastereomers. Some epimerization of the indolinone benzylic carbon was also

observed. Vinyl zinc reagents,[66] vinyl chromium reagents (Takai)[67] as well as TMSCl-trapping of the incipient alkoxide were utilized in an attempt to circumvent this problem, but none of the conditions were successful in preventing epimerization. Subsequent Dess-Martin oxidation[68] of the allylic alcohol provided the enone **155**, but neither Grigg conditions, nor thermolysis (180 °C, toluene, sealed tube) provided the cycloadduct **156**. Additionally, in an effort to determine if enone reactivity was an issue, subjection of *O*-allyl oxime **153** to Grigg's conditions with *N*-phenylmaleimide in dicholoroethane at 80 °C failed to provide any cycloadduct.

Scheme 39. Attempted palladium-mediated generation of a nitrone.

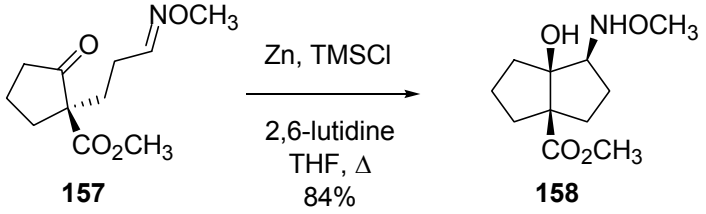


D. A possible intramolecular radical cyclization to complete the ring system

As an alternative to the nitrone-olefin cycloaddition strategy, efforts were directed towards annulation of the remaining six membered ring via a radical cyclization of an imine derivative of ketone **125**.

There are several examples in the literature of radical cyclizations of carbonyl-oxime ethers to afford the corresponding β-amino alcohols.[69] Corey was one of the first to report an aldoxime-ketone cyclization in his synthesis of functionalized cyclopentanols such as **158** mediated by zinc-trimethylchlorosilane (Scheme 40).[69a]

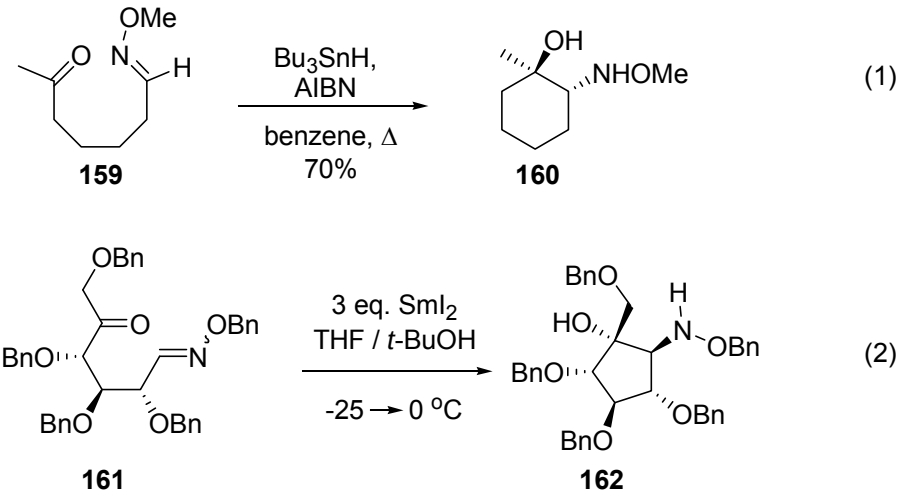
Scheme 40. Corey's aldoxime-ketone radical cyclization.



157 **158**

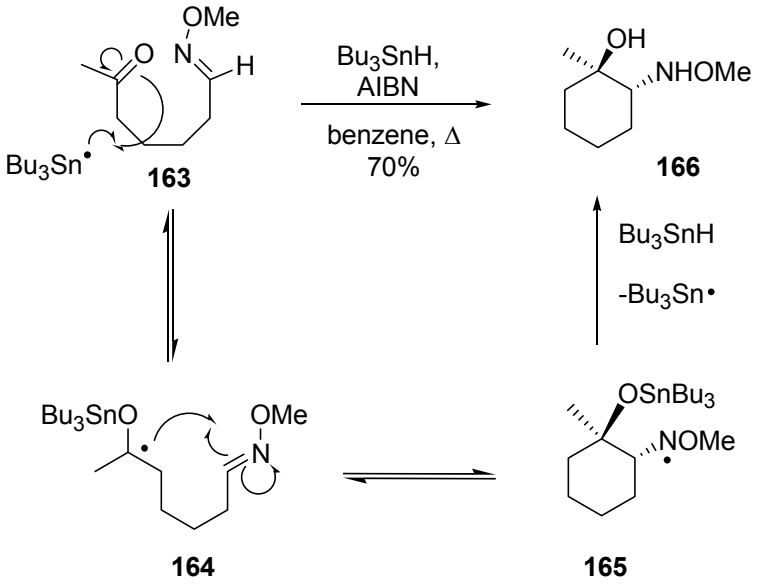
Subsequent studies have demonstrated that the reductive cyclization of carbonyl-oxime ethers to provide β-amino alcohols can also be accomplished with either tributyltin hydride and AIBN[69b] (eq 1) or SmI_2[69c] (eq 2) (Scheme 41).

Scheme 41. Radical cyclizations of carbonyl-oximes.



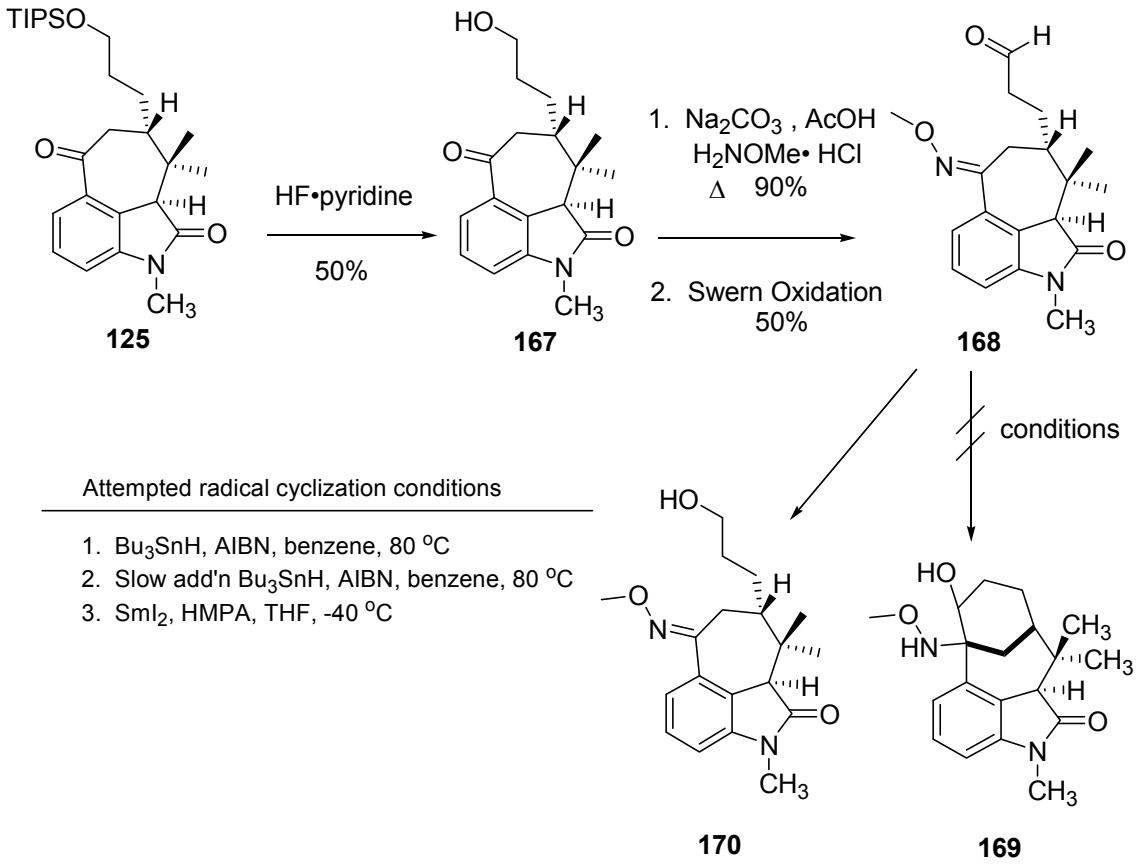
Mechanistically, Fu has proposed that tributylstannyl radical adds to the carbonyl group to generate a stannyl ketyl intermediate **164**. The ketyl then adds to the pendant oxime ether to produce the aminyl radical **165**. In the final irreversible step, the nitrogen radical abstracts a hydrogen atom from Bu_3SnH, providing the β–amino alcohol **166** and the chain-carrying tributylstannyl radical (Scheme 42).[69b] It has been postulated that the efficiency of these reactions is a result of the additional stabilization of the intermediate aminyl radical **165** by a lone pair on the adjacent heteroatom.[69f,70]

Scheme 42. Mechanism of Bu_3SnH-mediated radical cyclization of carbonyl-oximes.



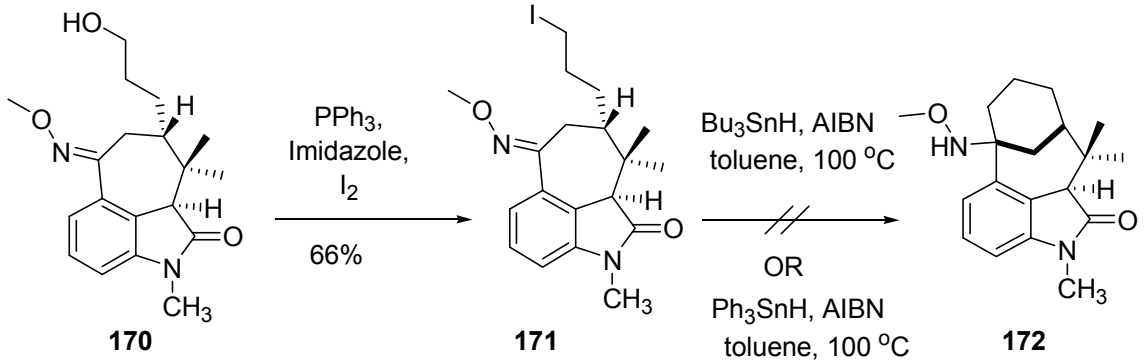
A similar strategy was examined in order to afford the complete ring system of welwistatin. To that end, ketone **125** was deprotected with HF•pyridine to provide the alcohol **167**. Oxime ether formation using standard conditions[69b] followed by Swern oxidation[71] of the primary alcohol provided aldehyde **168** (Scheme 43). However, ring closure to produce β–amino alcohol **169** using either the Fu protocol,[69b] slow addition of tributyltin hydride,[72] or SmI_2[69f] was unsuccessful and only provided the corresponding aldehyde reduction product **170**.

Scheme 43. Attempted radical cyclization of a carbonyl-oxime ether.



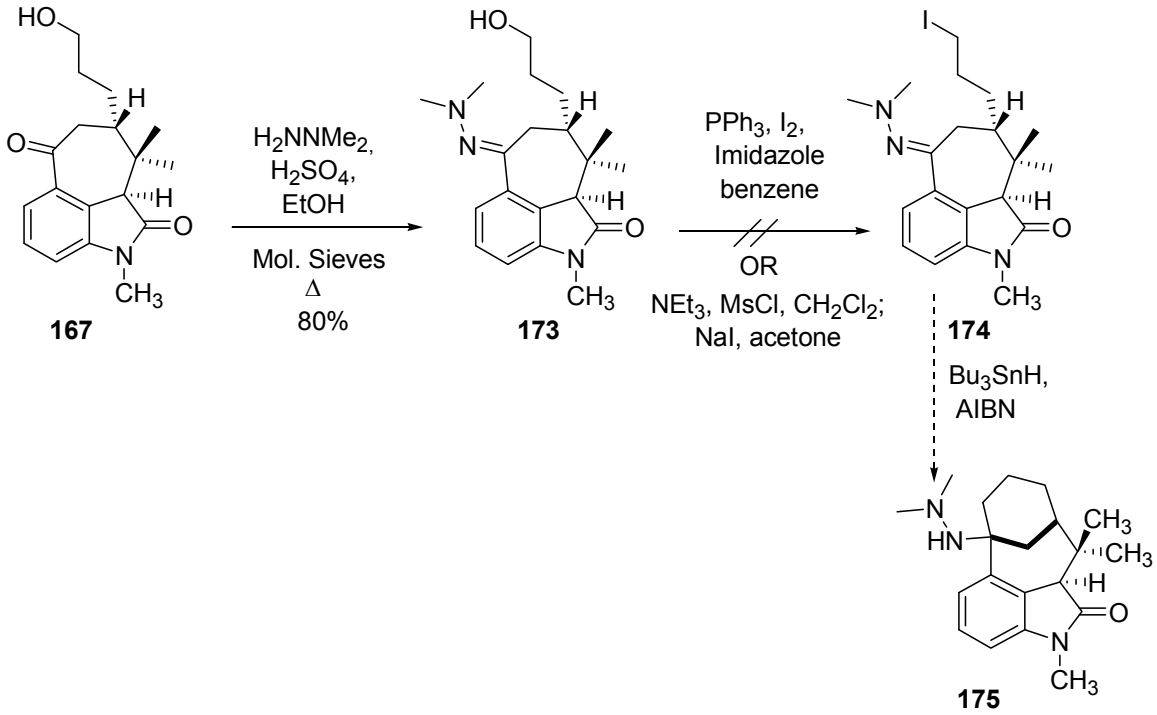
Additionally, conversion of alcohol **170** to the iodide **171** followed by attempted radical cyclization only gave the corresponding product of dehalogenation **172** (Scheme 44). Although there are examples of primary alkyl radicals participating in radical cyclizations with oximes,[73] in this case it is likely that the primary alkyl radical initially generated is not reactive enough to cyclize onto the oxime before being reduced by tributyltin hydride.[74]

Scheme 44. Attempted alkyl halide-oxime ether radical cyclization.



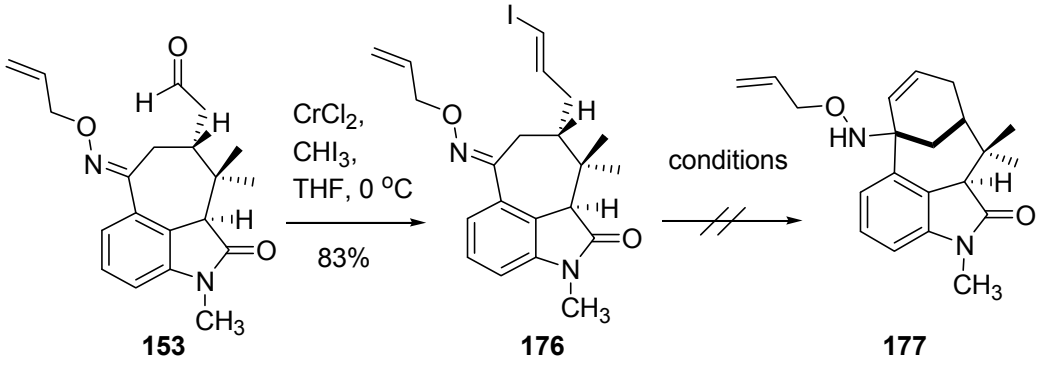
Hydrazones can also participate in intramolecular radical cyclizations with both alkyl halides and carbonyls.[75] Thus, *N*,*N*-dimethyl-hydrazone **173** was prepared from ketone **167** (Scheme 45). However, conversion of **173** to the iodide **174** or to the mesylate with subsequent S_N2 displacement by NaI was unsuccessful, due to instability of the hydrazone.

Scheme 45. Attempted formation of an alkyl halide / hydrazone.



Finally, in an effort to generate a more reactive radical in hopes of forcing the cyclization with the oxime to occur, the vinyl iodide **176** was synthesized from the aldehyde **153** using Takai's conditions[76] (Scheme 46). However, radical cyclization[77] with either tributyltinhydride or tris(trimethylsilyl)silane was unsuccessful, most likely due to premature quenching by tris(trimethylsilyl)silane of the unstable vinyl radical that was generated.

Scheme 46. Attempted radical cyclization of a vinyl iodide.



153 **176** **177**

Attempted radical cyclization conditions

1. Bu_3SnH, AIBN, benzene 80, °C
2. Bu_3SnH, ACN, toluene, 110 °C
3. $(TMS)_3SiH$, AIBN, toluene, 90 °C
4. $(TMS)_3SiH$, ACN, toluene 110 °C

V. Concluding Remarks

Although all of the strategies for "D" ring annulation were unsuccessful, the lessons learned from this failed synthesis have led to the realization that an approach that initiates with the six membered "D" ring might be advantageous. Indeed, a fellow member of the Funk group (Tom Greshock) recently accomplished a synthesis of the complete ring system of welwistatin via this conceptually distinct strategy (see Scheme 11).

PART II

Investigation of the Total Synthesis of Communesin B

CHAPTER 2

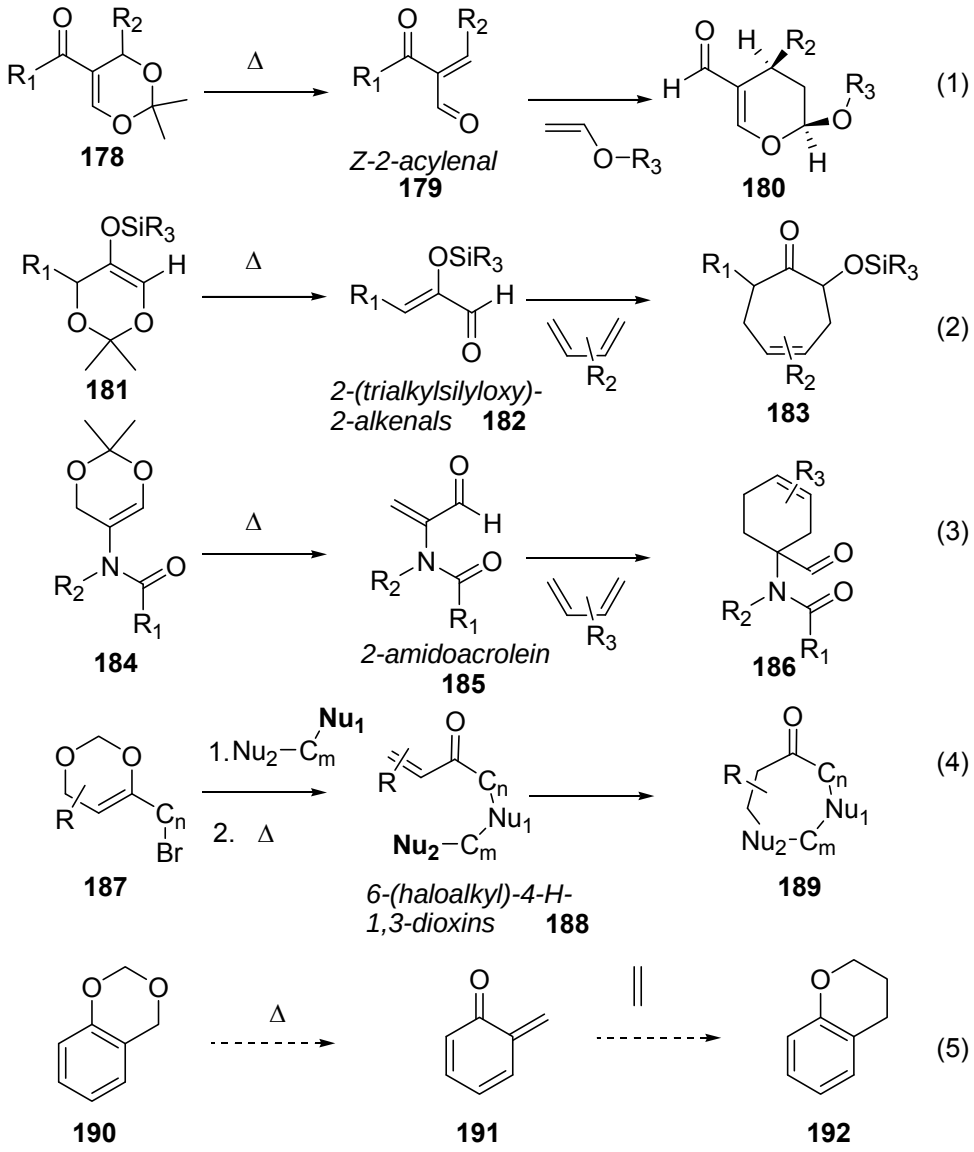
Synthetic efforts directed towards the total synthesis of communesin B. First generation approach: benzazepine-based routes

I. Introduction

The Funk group has had a long standing interest in the generation of novel 2-substituted acroleins prepared via retrocycloaddition of 5-substituted-4*H*-1,3-dioxins (Scheme 47).[78] For instance, 2-acylacroleins **179** have been generated and trapped with enol ethers to make 5-acyl-3,4-dihydro—2*H*-pyrans **180**, a ubiquitous substructure in several natural products (eq 1).[78b] We have demonstrated that 2-(trialkylsilyloxy)-2-alkenals **182** undergo catalyzed [4 + 3] cyclizations with dienes to provide 4-cyclohepten-1-ones **183** (eq 2).[78c] Additionally, a variety of alkaloids have been synthesized via either electrophilic aromatic substitution reactions or cycloaddition reactions of 2-amidoacroleins **185** (eq 3).[78d-h] Finally, alkylation of doubly nucleophilic compounds with 6-(haloalkyl)-4*H*-1,3-dioxins **187** followed by a retrocyloaddition, conjugate addition reaction sequence constitutes a new strategy for the construction of a variety of hetero-and carbocycles **189** (eq 4).[78i]

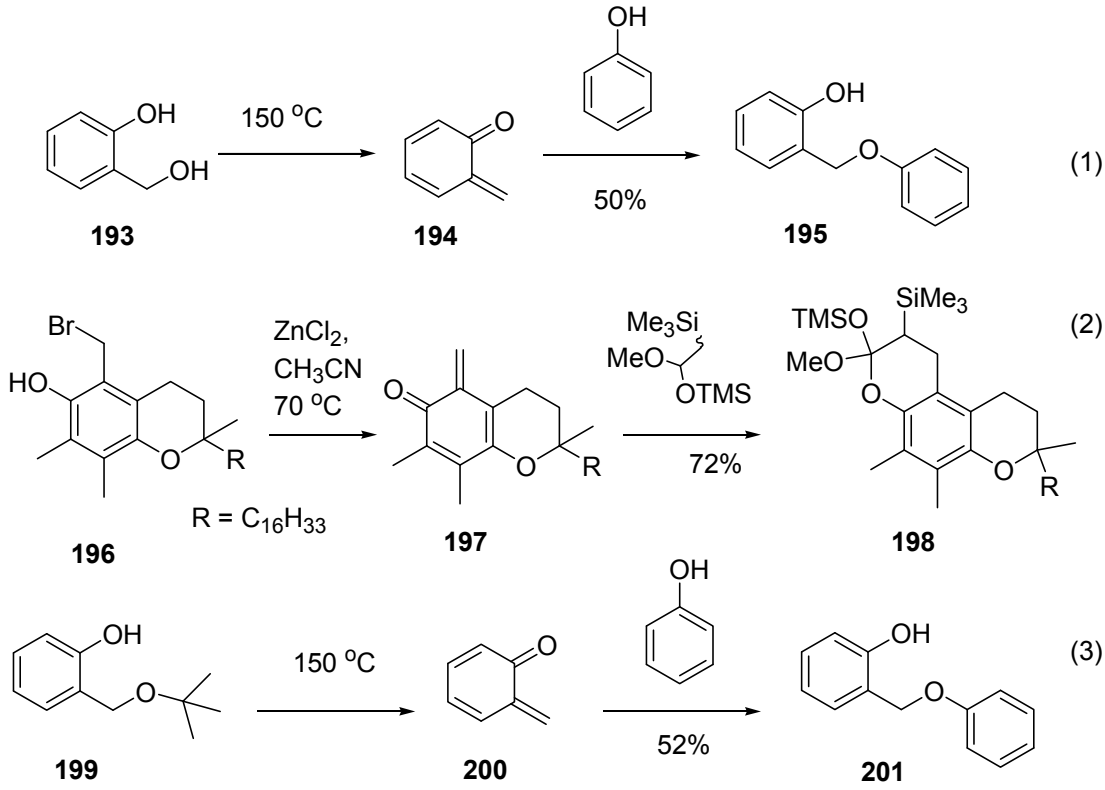
In view of the overall success of dioxin-based methodology, we contemplated an application of the related benzodioxin chemistry as a purely thermal way to generate *ortho*-quinone methides such as **191** (eq 5).

Scheme 47. Retrocycloaddition of substituted dioxins in the Funk lab.



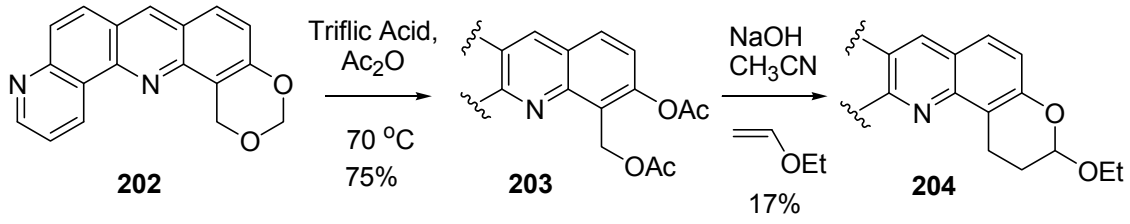
o-Quinone methides have been generated thermally from hydroxybenzyl alcohols **193**,[79a-c] hydroxybenzyl halides **196**,[79d-f] hydroxybenzyl ethers **199**,[79a,g,h] as well as other phenol-based compounds with a potential benzylic leaving group (Scheme 48).[79i] Nonetheless, the only example in the literature that has used a benzodioxin to generate an *o*-quinone methide was published by Lhomme and

Scheme 48. Generation of *o*-quinone methides.



coworkers, in which benzodioxin **202** was converted to the corresponding diacetate **203** and then base was used to generate an *o*-quinone methide (Scheme 49).[80]

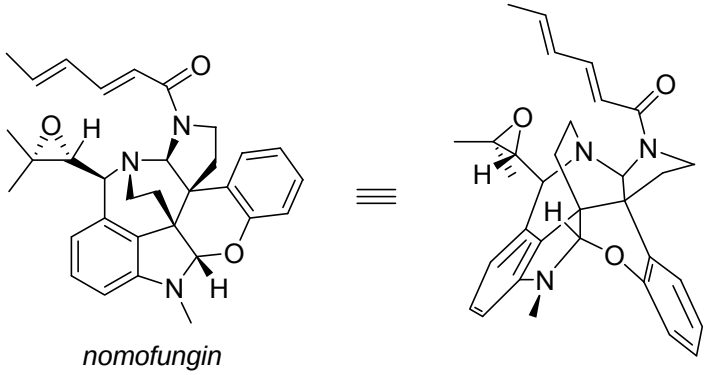
Scheme 49. Base generation of *o*-quinone methide from a benzodioxin.



The impetus to investigate the benzodioxin chemistry was provided by Heimscheidt and coworkers, who reported the isolation of the natural product nomofungin (**205**), which embodies a benzopyran substructure (Figure 6).[81]

Thus, we were fascinated by the possibility of constructing the core ring system of nomofungin by a cycloaddition reaction of an indole with an *ortho*-quinone methide, (*vide infra*). This structurally intriguing heptacyclic natural product was isolated from an endophytic fungus using a bioassay intended to identify anti-

Figure 6. The natural product nomofungin.



nomofungin

205

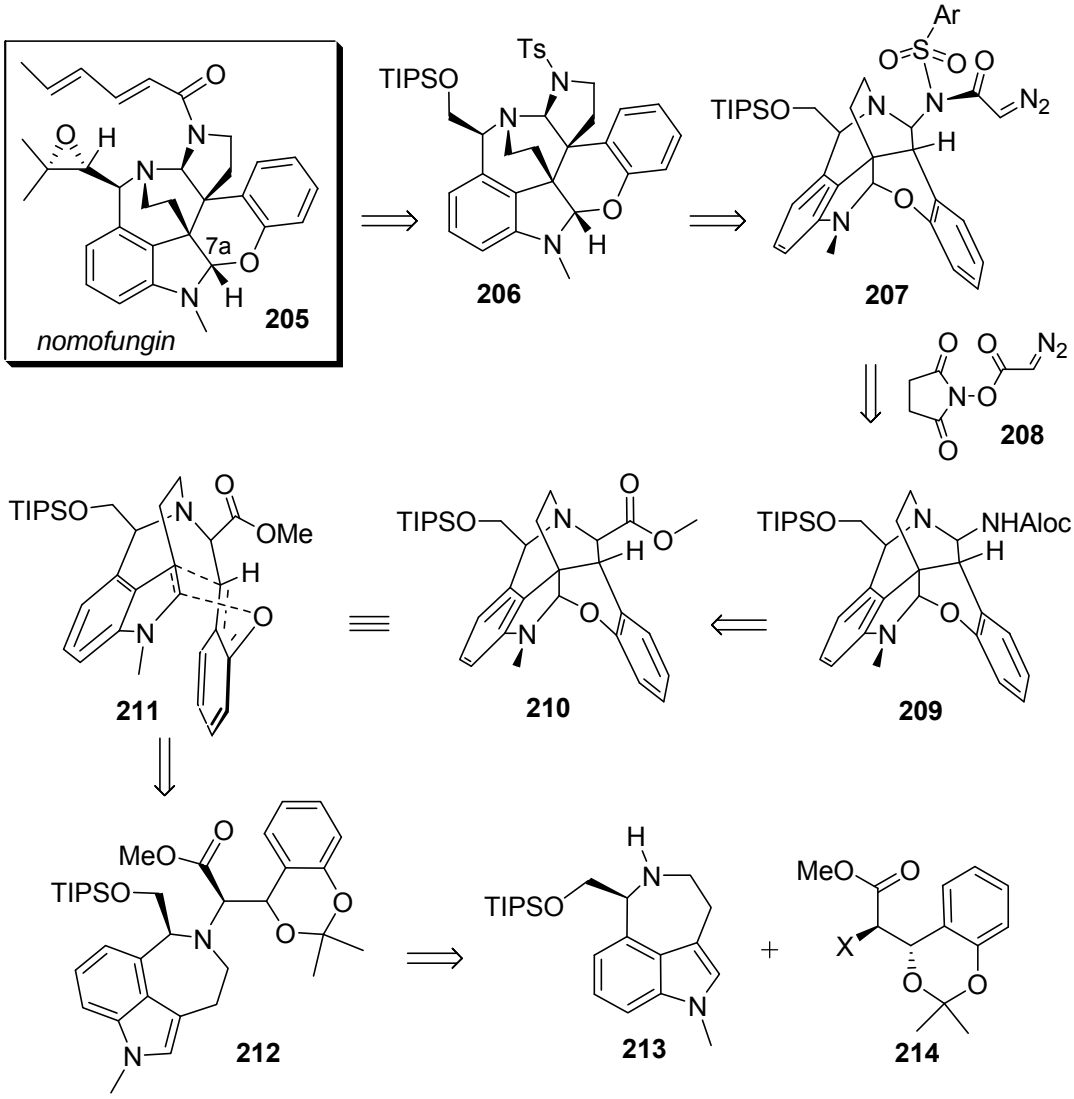
microtubule and anti-microfilament agents. The unidentified fungus was isolated from the bark of *Ficus microcarpa* L. but it was subsequently lost. Therefore, the natural product was labeled nomofungin.[81] Importantly, the structural assignment of nomofungin was based primarily on NMR spectroscopic measurements, and the absolute stereochemistry was determined using the exciton chirality method.[81] Preliminary studies have indicated that nomofungin disrupts microfilaments in P-388 cells (ED_{50} = 0.88 μM).[81]

A. Retrosynthetic analysis for the total synthesis of nomofungin

Our strategy for the synthesis of nomofungin is outlined in Scheme 50. It was believed that nomofungin (**205**) could be made from the tosylamide **206** via elaboration of the epoxide moiety,[82] deprotection, and acylation. The tosylamide **206** could be derived via the α–diazoimide **207** via metal-mediated insertion leading to a pyrrolidinone that would be reduced to a pyrrolidine.[83] The intramolecular C-H insertion of α-diazoamides has been well-precedented in

order to provide γ-lactams.[84] It was hoped that the *N*-tosyl group[85] would conformationally bias insertion into the aligned tertiary benzylic hydrogen, instead

Scheme 50. Retrosynthetic analysis of nomofungin.



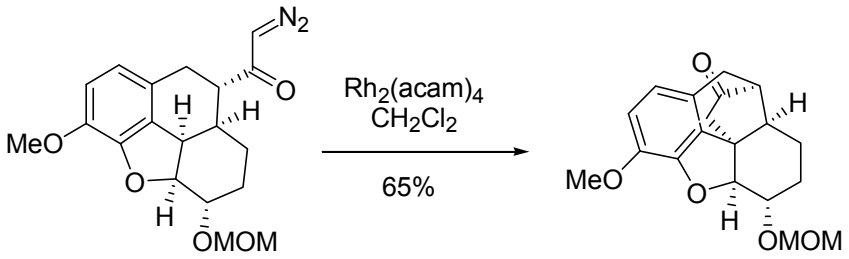
of competing aromatic C-H or secondary aliphatic C-H insertion.[86] The α-diazoimide **207** could be derived from the *N*-acylaminal **209** via sulfonylation, deprotection, and diazoacetylation using succinimidyl diazoacetate (**208**).[87] The aminal in turn, could be derived from the ester **210** by a Curtius rearrangement. This valuable transformation has been used in several natural product syntheses in order to introduce *N*-acylhemiaminals.[88] Ester **210** could be made via

thermolysis of the benzodioxin **212**. The benzodioxin should undergo smooth retrocycloaddition to generate an *ortho*-quinone methide intermediate **211**, which would then undergo a cycloaddition with the tethered indole[89] via the *endo* transition state to provide the desired product. It was expected that both the ester and silyloxy substituents should emerge on the convex face of ester **210**. Finally, the benzodioxin could be made via alkylation of the benzazepine **213** with the halide **214**.

1. Rhodium-mediated insertions to provide γ-lactams

Intramolecular metal-mediated C-H insertions have been a popular method for carbon-carbon bond formation, especially in polycyclic natural products. For example, in White's codeine synthesis, α-diazoketone **215** participated in a rhodium-mediated C-H insertion with the tertiary benzylic proton in preference to the other aliphatic protons to provide the cyclopentanone **216** (Scheme 51).[86a]

Scheme 51. White's rhodium mediated C-H insertion.

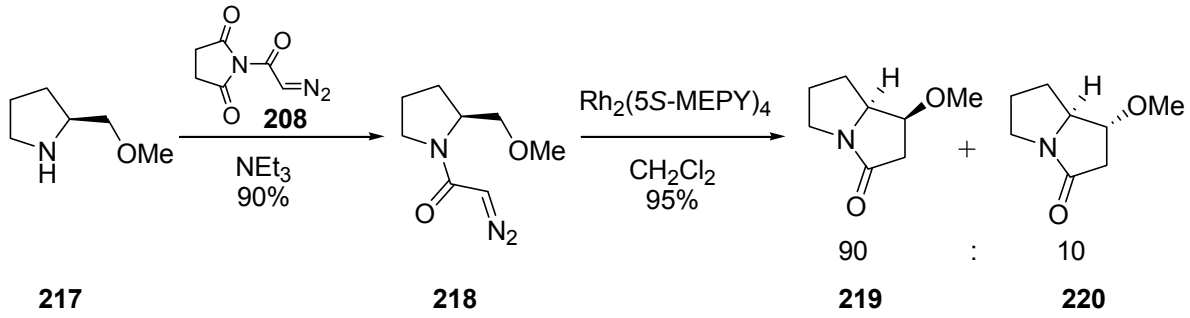


215 **216**

Additionally, this methodology has been applied to the rhodium-mediated insertion of α-diazoamides to provide γ-lactams. Doyle has published a synthesis of pyrrolizidines via rhodium-mediated insertions of α-diazoamides that are derived from the corresponding 2-substituted pyrrolidines (Scheme 52).[84a] For example, the methyl ether of (*S*)-2-pyrrolidinemethanol (**217**) was converted to the corresponding diazoacetamide **218** using succinimidyl diazoacetate

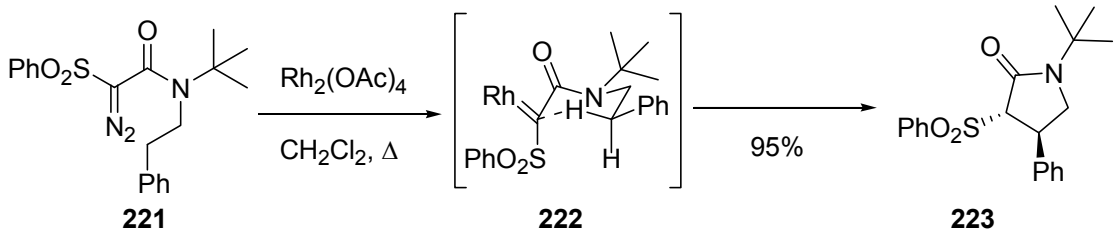
(**208**).[87] Subsequent diazo decomposition provided the γ-lactams **219** and **220** as a 90 : 10 mixture of diastereomers in good yield.

Scheme 52. Doyle's approach to g-lactams.



Jung has also published a synthesis of γ-lactams via rhodium insertion of α-diazo-α-(phenylsulfonyl)-acetamides.[84b] It is proposed that during the insertion reaction, the metallocarbenoid adopts a *s-cis* conformation **221** as a result of severe nonbonded interactions that would develop between the *t*-butyl group and the carbenoid in the opposing *s-trans* conformation (Scheme 53). The stereochemistry obtained was rationalized via the chair-like transition state **222**, wherein the C-Rh bond would be aligned with the benzylic C-H bond and the phenyl group would occupy a pseudoequatorial position. Interestingly, a β-lactam product could also be isolated, depending on the catalyst used.[90] Selectivity for γ-lactam formation was improved when a Rh catalyst with an electron-donating ligand was used. Presumably, the electron-donating ligand stabilizes the electrophilic carbenoid carbon, thereby causing the insertion reaction to proceed through a relatively late transition state with a resulting increase in selectivity.

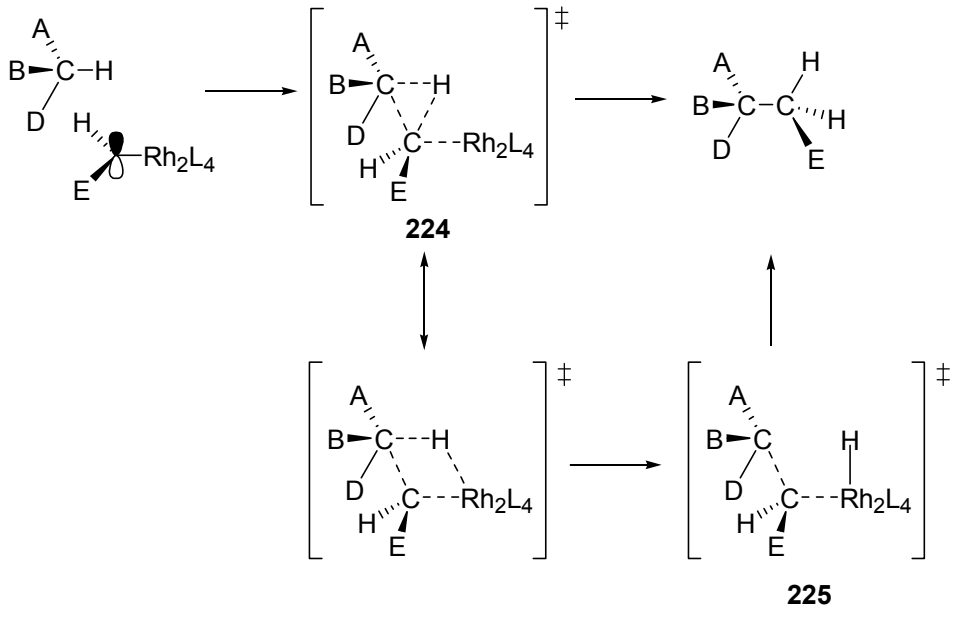
Scheme 53. Jung's synthesis of γ-lactams.



221 **222** **223**

Currently, there are several hypotheses concerning the mechanism of the transition metal catalyzed carbon-hydrogen insertion reactions of carbenes generated from diazo compounds. There is general agreement that the insertion occurs through an electrophilic metal carbene intermediate. One of the currently accepted mechanisms is depicted in Scheme 54. Overlap of the metal carbene *p* orbital with the σ-orbital of the reacting C-H bond initiates C-C and C-H bond formation with the carbene carbon as the ligated metal dissociates (transition state **224**).[91a] However, Taber has proposed a transition-state model wherein there is transfer of hydrogen to rhodium during the process to give an intermediate where the hydrogen has completely dissociated from the carbon (transition state **225**).[91b]

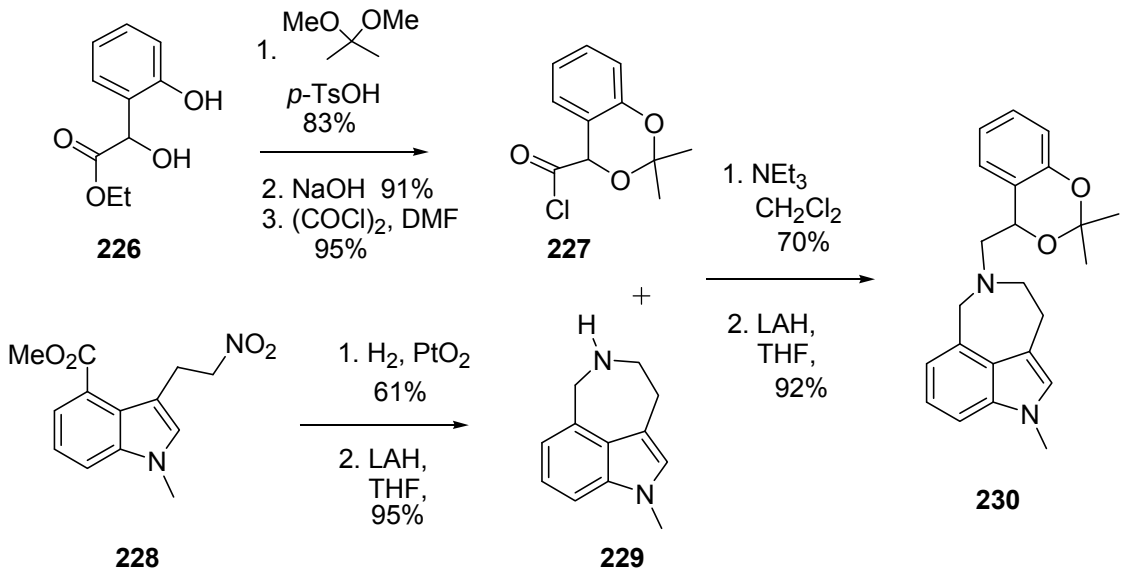
Scheme 54. Proposed mechanism of metal mediated C-H insertions.



2. Preparation of the core ring system of nomofungin

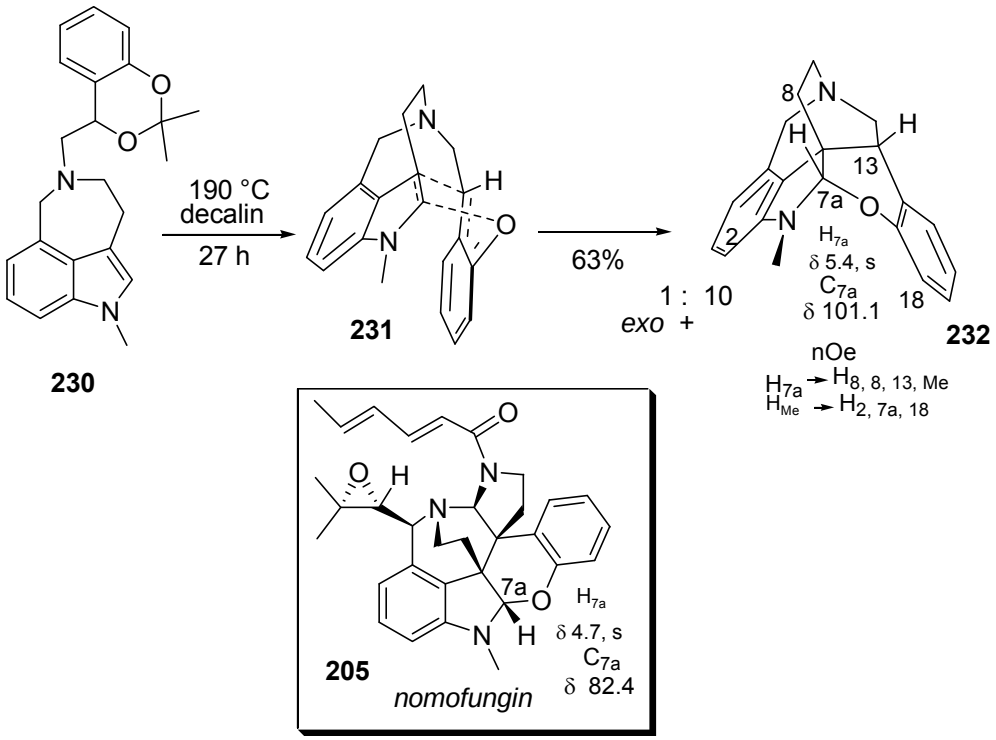
We decided to synthesize a model system for nomofungin in order to test the viability of our proposed method for thermally generating *o*-quinone methides from benzodioxins.[92] To that end, diol **226** was synthesized via the Lewis acid-catalyzed condensation of phenol with ethyl gloxylate[93] and was subsequently protected as the corresponding acetonide (Scheme 55). The ester functionality was saponified, and the resulting carboxylic acid was transformed to the acid chloride **227**. The indole **228** was synthesized by straightforward adaptation of the previously described synthesis of the analogous indole lacking the *N*-methyl substituent.[94] Hydrogenation of the nitro group led to concomitant cyclization of the intermediate amine to the corresponding lactam, which was subsequently reduced with lithium aluminum hydride to afford the benzazepine **229**. Finally, acylation of benzazepine **229** with acid chloride **227** followed by reduction of the resultant amide provided the key retrocycloaddition-cycloaddition substrate, benzodioxin **230**.

Scheme 55. Synthesis of the Aminomethylbenzodioxin.



We were pleased to discover that thermolysis of benzodioxin **230** provided the *N,O*-acetal **232** as a 10 : 1 mixture of stereoisomeric cycloadducts. The relative stereochemistry for the expected *endo* isomer was assigned on the basis of the observed nOe's, the most diagnostic of which are provided in Scheme 56**.** While at first glance, the high temperature seems harsh, it may actually be ideal because the reactive *o*-quinone methide intermediate, which is prone to undergo side reactions,[79i] is generated slowly and trapped immediately by a conformationally restricted and reactive heterodienophile to afford a stable product.

Scheme 56. Retrocycloaddition / cycloaddition of an aminomethylbenzodioxin.

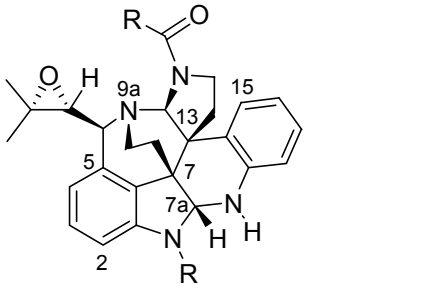


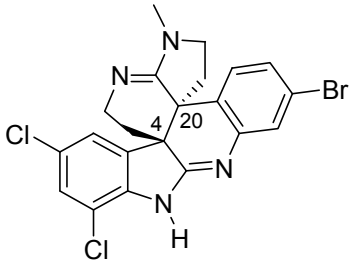
Unfortunately, there was a serious discrepancy between the chemical shifts of the *N,O*-acetal proton and carbon (δ 5.4, δ 101.1) of our model core ring system **232** and that reported for nomofungin (δ 4.7, δ 82.4).[81a] Moreover, it seemed highly unlikely that conformational effects were responsible for the

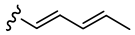
chemical shift differences because *N,O*-acetal **232** and nomofungin are in nearly identical conformations, despite the missing pyrrolidine ring in **232**.

A subsequent literature search for compounds that possess the lower tetracyclic substructure of nomofungin but have a nitrogen atom instead of the pyran oxygen was revealing and led to the communesins and perophoramidine. Thus, communesins A (**233**) and B (**234**), were previously reported by Numata and coworkers. They were isolated from the fungal strain *Penicillium* sp., which was attached to the marine alga *Enteromorpha intestinalis* (Figure 7).[95]

Figure 7. The structure of communesins A, B and perophoramidine.





233 communesin A R = CH_3
234 communesin B R = 

235 *perophoramidine*

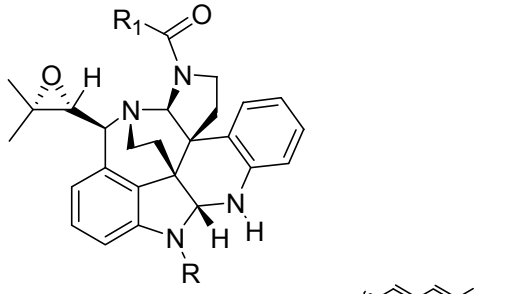
These natural products had gone relatively unnoticed by the synthetic community. Furthermore, and most alarming to us, was the fact that communesin B and nomofungin have identical ^{1}H and ^{13}C spectra. The structurally related alkaloid, perophoramidine (**235**), was recently isolated from the marine ascidian *Perophora namei*.[96] It possesses an indole derived ring system,[97] and lacks the benzazepine ring of the communesins. Other key structural differences include: it contains a bis-amidine rather than a bis-aminal functionality; it has halogenated aromatic rings;[98] and it has a *trans*- rather than a *cis*-relationship at the C(4) and C(20) vicinal quaternary centers.

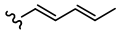
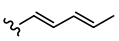
II. The Communesins

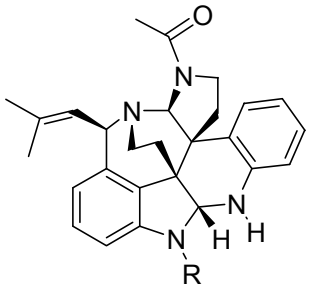
A. Isolation and biological activity

In addition to communesins A and B, other alkaloids from the communesin family have recently been isolated, including: communesin C (**236**),[99a,b] D (**237**),[99a,b] E (**238**),[99a,b] F (**239**),[99c] G (**240**),[99c] and H (**241**).[99c] These alkaloids have been isolated from various strains of *Penicillium* fungi (Figure 8).[99]

Figure 8. Additional communesin alkaloids isolated.



236 *communesin C*, R = H, R_1 = 
237 *communesin D*, R = CHO, R_1 = 
240 *communesin G*, R = CH_3, R_1 = CH_2CH_3
241 *communesin H*, R = CH_3, R_1 = $CH_2CH_2CH_3$



238 *communesin E,* R = H
239 *communesin F,* R = CH_3

Despite their structural similarities, communesin B and perophoramidine are significantly different in their biological activity. Perophoramidine has been demonstrated to be cytotoxic against the HCT-116 colon carcinoma cell line (IC_{50} = 60 μM) and to induce apoptosis (cell death) within 24 hours by cleaving PARP-1 (poly (ADP-ribose) polymerase-1).[96] Experimental evidence has indicated that cleavage of PARP-1 promotes apoptosis by preventing DNA repair-induced survival and by blocking energy depletion-induced necrosis.[100] On the other hand, communesins A and B were initially shown to exhibit moderate to potent cytotoxic activity against P-388 lymphocytic leukemia cells (ED_{50} = 7.6 and 0.88 μM respectively).[95] Communesins B, C and D have subsequently been shown to possess moderate cytotoxicity against a variety of leukemia cell lines (Table 1).[99a] Communesins G and H have exhibited no biological activity.[99c]

Table 1. Antiproliferative activity of the communesins.

	ED_{50} (μM)		
Cell line	communesin B	communesin C	communesin D
U-937	20.4	22.8	25.1
THP-1	22.4	26.5	30.9
NAMALWA	19.4	16.5	27.9
L-428	>39	inactive	inactive
MOLT-3	15.9	17.4	18.9
SUP-B15	14.1	21.8	17.2

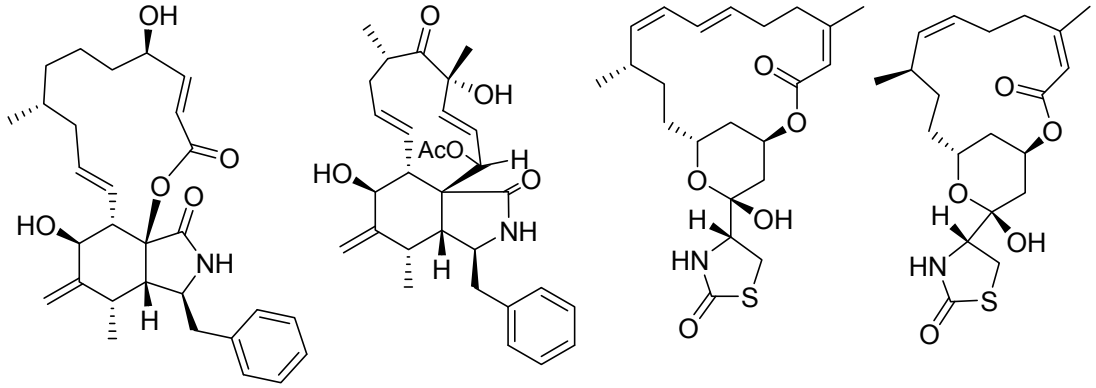
Furthermore, Heimscheidt and coworkers have demonstrated that communesin B / nomofungin was moderately cytotoxic (MICs of 3.9 μM and 8.8 μM against LoVo and KB cells, respectively) by disruption of microfilaments in cells.[81a]

Microfilaments are monomers of the protein actin, which polymerizes to form long, thin fibers. Actin, like tubulin, is a major component of the cytoskeleton, with important cellular functions such as determination of cell shape, cell motility, division, adhesion, and intracellular transportation.[101] Also, just like tubulin, actin structures are assembled and disassembled in a reversible process, with a dynamic polymerization / depolymerization equilibrium between monomeric soluble globular actin (G-actin) and helical filamentous actin (F-actin).[101a]

The fungal secondary metabolites, cytochalasins B (**242**) and cytochalasin D (**243**) were the first agents that were used as molecular probes to study the actin cytoskeleton (Figure 9).[102] Other examples of actin-binding natural products include latrunculins A (**244**) and B (**245**), which were the first marine macrolides that were identified to possess well defined actin-binding

properties.[103] These macrocycles form a 1 : 1 complex with G-actin, inhibiting its polymerization, as well as inducing F-actin depolymerization.[101a]

Figure 9. Other antimicrofilament agents.

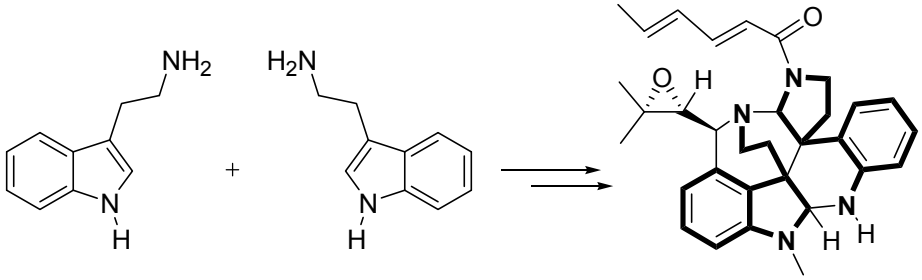


cytochalasin B **242** | cytochalasin D **243** | latrunculin A **244** | latrunculin B **245**

Actin also interacts with tubulin, although it seems that these two cytoskeleton systems more often operate independently.[101b] However, Gachet and Hyams discovered an actin-dependent cell cycle checkpoint that ensures the correct orientation of microtubule spindles during metaphase.[104] Therefore, as a possible alternative to the widely used pharmaceutical agents that interfere with microtubule dynamics such as colchicine (**18**),[11] taxol (**19**),[12] and vinblastine (**20**),[13] etc., compounds that interfere with actin dynamics or that bind to actin are currently being investigated.[101a,e]

B. Biosynthetic considerations for the communesins.

Scheme 57. Communesin is derived from 2 tryptamine subunits.

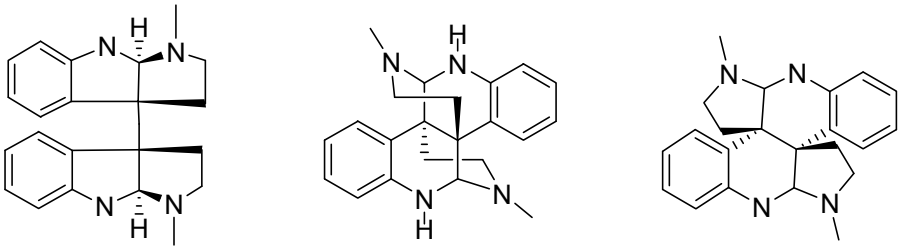


tryptamine
246

communesin B
234

It is believed that the communesins (as well as perophoramidine) are derived from the dimerization of two tryptamine (**246**) moieties. For example, the tryptamine subunits of communesin B have been outlined above in Scheme 57. Additional natural products that are believed to be derived from the dimerization of two tryptamine moieties include the *Calycanthus* alkaloids[105] chimonanthine (**247**), calycanthine (**248**), and isocalycanthine (**249**) (Figure 10).

Figure 10. Representative members of the *Calycanthus* alkaloids.



(+)-chimonanthine
247

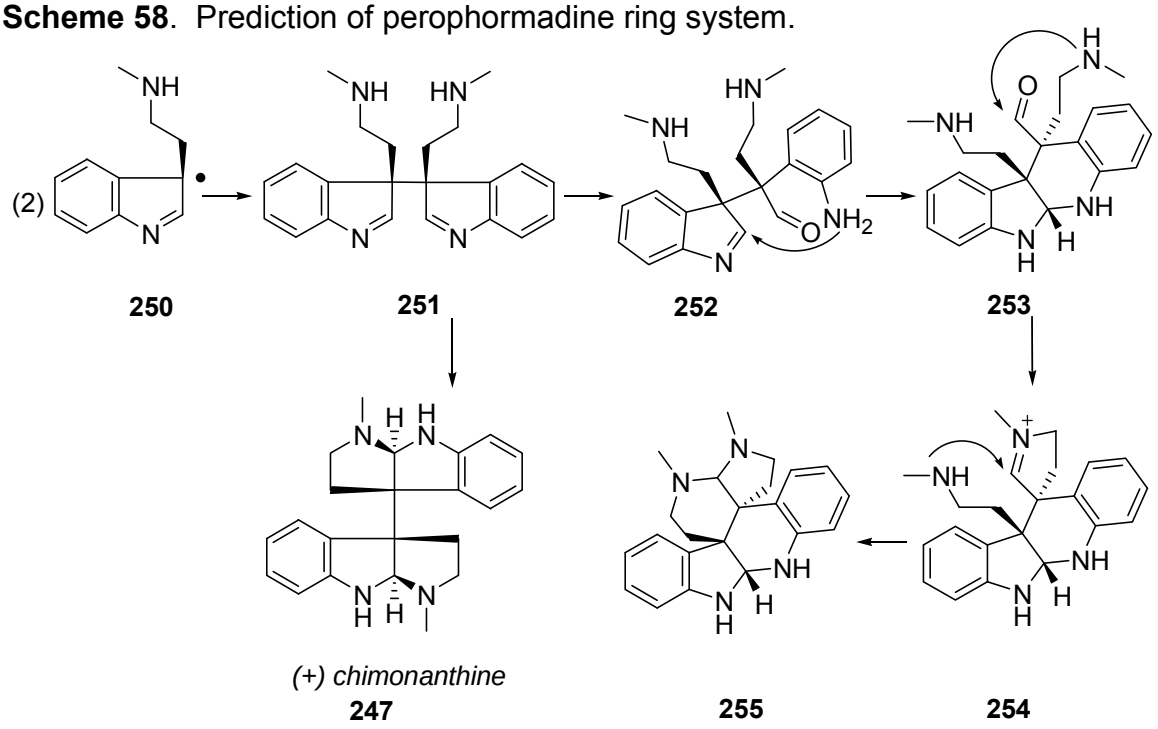
calycanthine
248

isocalcycanthine
249

Indeed, both Woodward and Robinson put forth biosynthetic proposals for the *Calycanthus* alkaloids.[106] For example, it was proposed that two indolenyl radicals **250** might dimerize to give the dimeric indolenine **251** (Scheme 58).[105] Closure of the methyl amine substituents of **251** onto the indolenines would provide (+) chimonanthine (**247**). Robinson and Woodward also proposed the

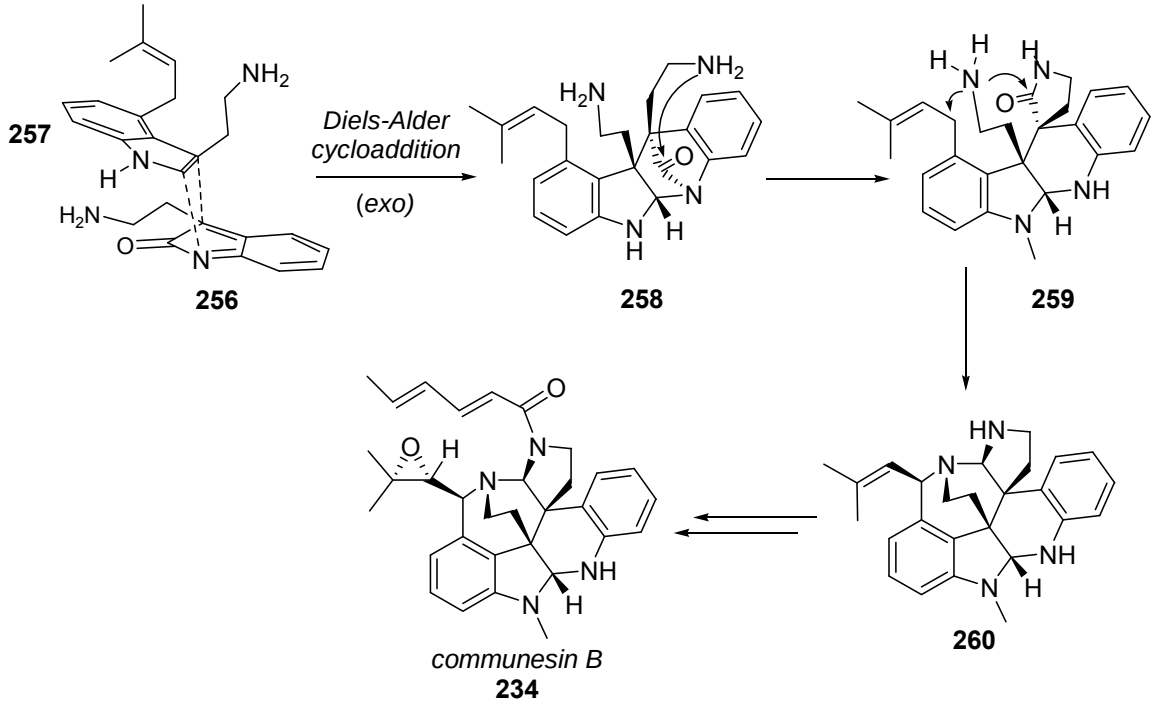
transamidation of indolenine **251** to form other compounds, one of which was bisaminal **255**, the complete ring system of perophoramidine![106] Thus, hydrolysis of one of the indolenines would give the aldehyde **252**. Subsequent closure of the aniline nitrogen onto the remaining indolenine could provide aminal **253**. Formation of a spirocyclic iminium ion intermediate **254**, followed by ring closure would furnish the perophoramidine ring system **255**.

Scheme 58. Prediction of perophormadine ring system.



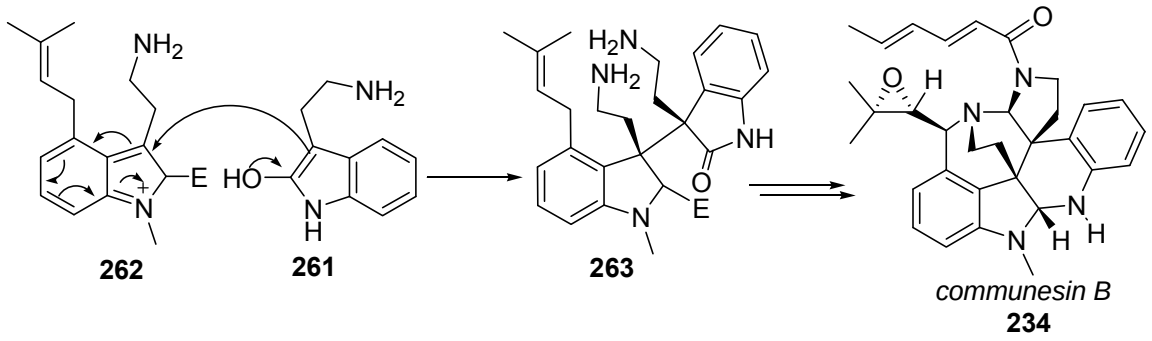
We have proposed that Nature might use a hetero Diels-Alder cycloaddition to effect dimerization of two tryptamines. Thus, it is conceivable that one tryptamine is oxidized to the indol-2-one[107] intermediate **256** that would then undergo a cycloaddition with a prenylated tryptamine **257** to arrive at the *exo*-cycloadduct **258** (Scheme 59). The resulting strained bridged bicyclic lactam would be expected to undergo a rapid transamidation reaction to afford the spirolactam **259**. Reduction of the lactam carbonyl and cyclizations with the primary amine nitrogen would then afford the complete ring system of communesin B **260**. Epoxidation and acylation would then provide the natural product. However, this proposed Diels-Alder reaction is highly speculative.

Scheme 59. Funk's proposed biosynthesis of communesin B.



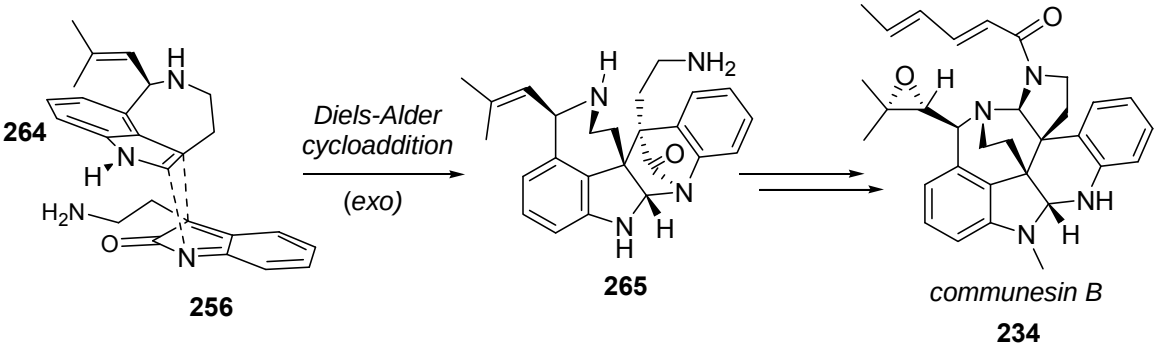
One could also imagine dimerization of the tryptamines by a stepwise process involving the condensation of an oxindole derivative **261** with an *ortho*-quininonoid iminium intermediate **262** generated by attack of an electrophile at C(2) of 1-methyltryptamine to provide the 2-substituted dihydroindole **263** (Scheme 60).

Scheme 60. An alternative biosynthetic pathway for the communesins.



Stoltz has proposed a similar biosynthetic pathway for the biogenesis of communesin B.[108] The major difference between the two proposed routes is that Stoltz proposes a Diels-Alder cycloaddition between indol-2-one **256** and the natural product aurantioclavine (**264**) to provide the bridged bicyclic lactam **265** with the benzazepine intact (Scheme 61). Subsequent steps analogous to those described above would then provide the natural product.

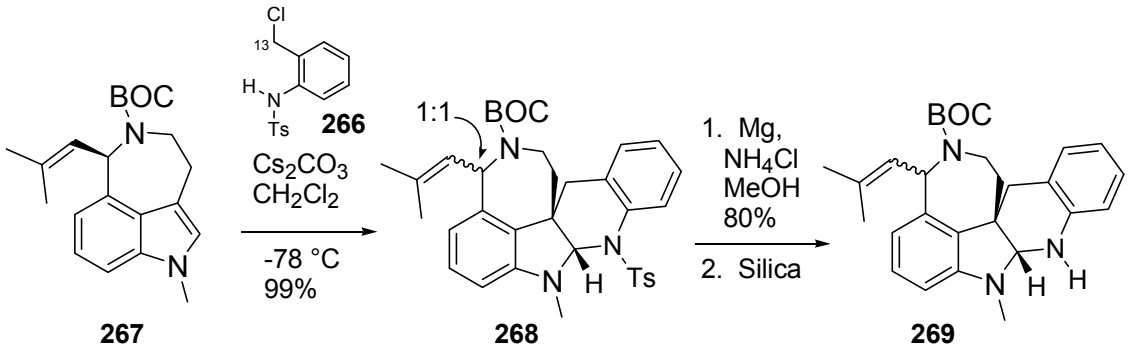
Scheme 61. Stoltz's proposed biosynthesis of communesin B.



C. Previous synthetic efforts directed towards the communesins and perophoramidine

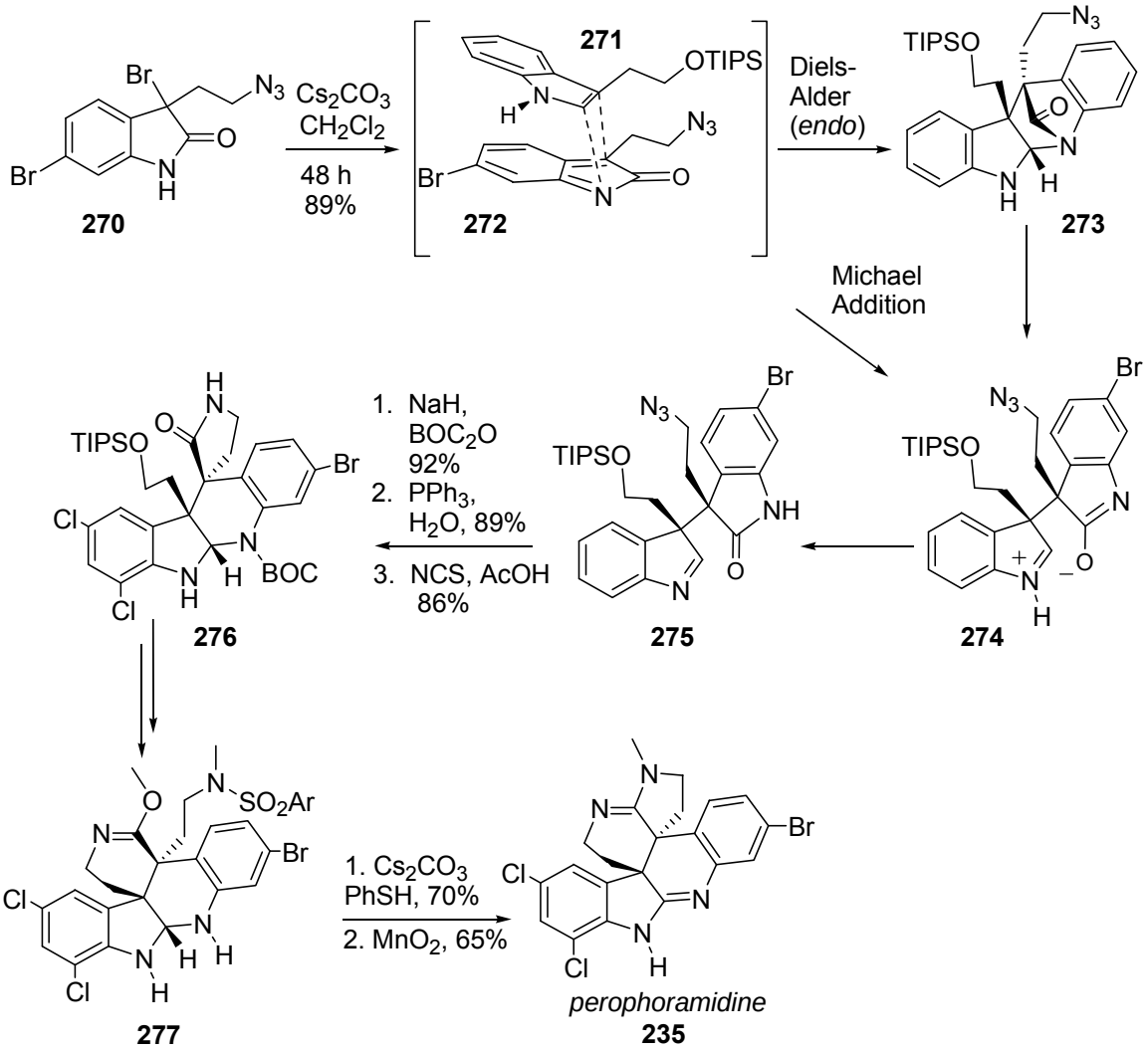
Although there is unquestionably considerable synthetic interest in the communesins and perophoramidine, limited examples of progress towards their total synthesis have been reported.[92,108,109] Stoltz has reported a "biomimetic" synthesis of the communesin B ring system via an intermolecular Diels-Alder cycloaddition of the aza-*ortho*-xylylene derived from chloroaniline **266** with the *N*-BOC-aurantioclavine derivative **267**.[108] This furnished the pentacyclic aminal **268** as a 1 : 1 mixture of diastereomers (Scheme 62). However, no further progress has been reported to date.

Scheme 62. Stoltz's approach to the communesin B ring system.



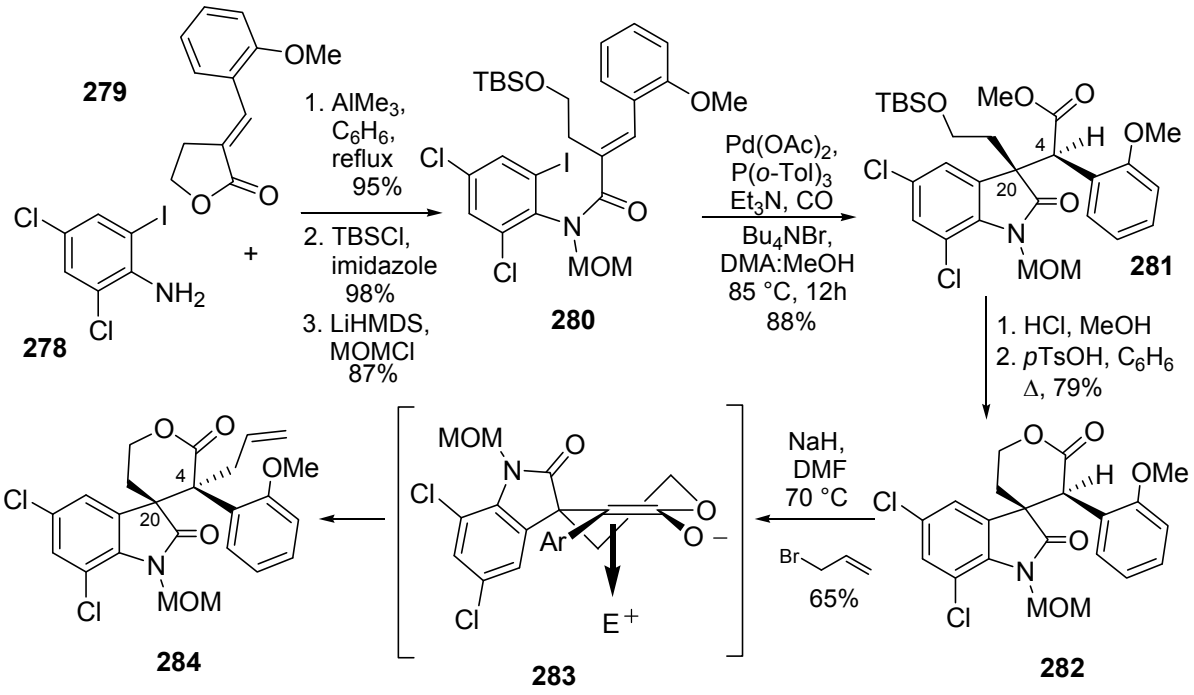
Funk and Fuchs were the first to publish a total synthesis of perophoramidine via a "biomimetic" approach.[109a] Treatment of the 3-alkyl-3-bromooxindole **270** with base in the presence of the indole **271** provided indolenine **275** (Scheme 63). This transformation proceeds via one of two pathways. The first pathway begins with the generation of the indol-2-one intermediate **272**[107] followed by subsequent cycloaddition proceeding via the *endo* transition state to provide the bridged bicyclic lactam **273**. Ring opening and proton transfer could then provide the indolenine **275**. Alternatively, the indol-2-one intermediate **272** could participate in a Michael addition reaction to arrive at intermediate **274**, which subsequently generates the indolenine in an analogous manner.[110] Other highlights of the synthesis include: conversion to the BOC-imide followed by closure to the spirocyclic lactam; electrophilic aromatic substitution to install two chloro substituents to provide the dihalide **276**; a transamidation and conversion to the cyclic imidate **277**; and finally, closure to the amidine and oxidation to provide perophoramidine (**235**). Most importantly, this concise and efficient synthesis has demonstrated that indol-2-ones are useful synthetic intermediates.

Scheme 63. Funk and Fuchs' synthesis of perophoramidine.



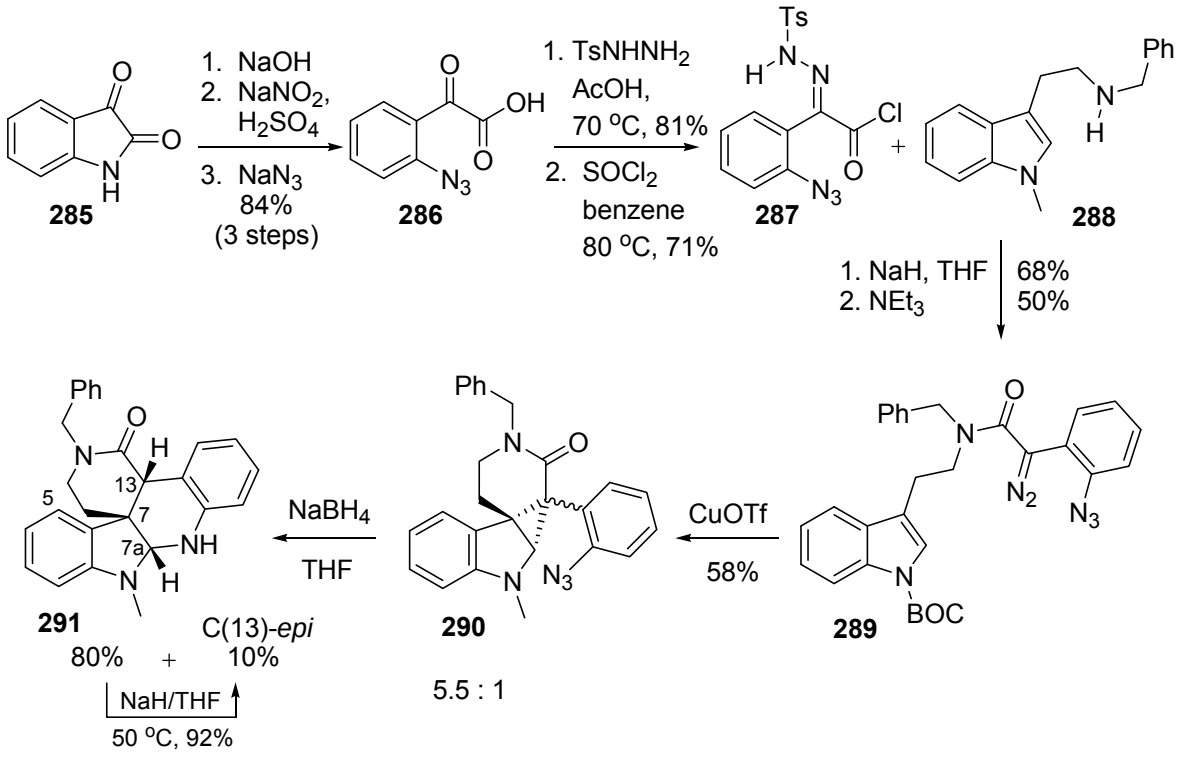
Weinreb has reported a halogen-selective tandem Heck/carbonylation sequence stating with iodoenone **280** to furnish oxindole **281** (Scheme 64).[109b] Subsequent formation of the lactone **282** and alkylation provided the lactone **284**. The stereochemical outcome of the alkylation was rationalized by a late transition state, favoring alkylation from the bottom face via the half chair conformation **283**. No further progress has been reported to date.

Scheme 64. Weinreb's approach to the perophoramidine ring system.



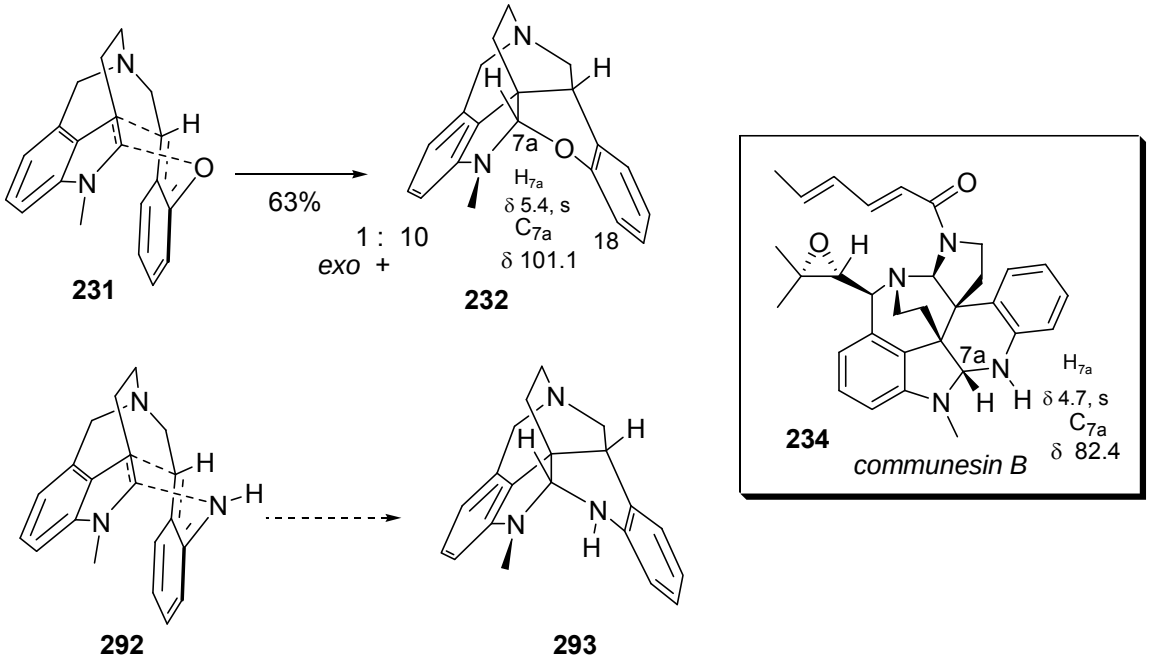
Qin has recently published an approach to both the communesins and perophoramidine via an intramolecular indole cyclopropanation approach.[109c] Thus, isatin (**285**) was converted in a straightforward manner to the acid **286** (Scheme 65). Subsequent conversion to the acid chloride **287**, acylation with the tryptamine **288**, and treatment of the resultant tosylhydrazone with triethylamine provided the α-diazo amide **289**. Decomposition of α-diazo amide **289** in the presence of a catalytic amount of copper(I) triflate provided the cyclopropane intermediate **290** as a 5.5 : 1 mixture of inseparable diastereomers. Finally, reduction of the aryl azide **290** followed by opening of the cyclopropane ring by the aniline then gave the pentacyclic lactam **291** in 81% yield along with 10% of the C(13) epimer. Additionally, the lactam **291** could be converted to the C(13) epimer by treatment with sodium hydride. Qin has yet to demonstrate that the cyclopropanation will tolerate a substituent at C(5) of the indole in order to elaborate the benzazepine ring.

Scheme 65. Qin's approach to communesins / perophoramidine.



Given that the cycloaddition of the *o*-quinone methide **231** furnished the core ring system of the erroneously assigned nomofungin **232**, we were intrigued by the possibility of using an intramolecular cycloaddition of an aza-*ortho*-xylylene **292** to construct the core ring system of communesin B **293** (Scheme 66). The preparation of compound **293** would provide unequivocal evidence that communesin B is the correct structure as well as initiate our total synthesis effort. To that end, we needed to adapt our synthesis such that an aza-*ortho*-xylylene[111] **292** would be generated for the key intramolecular cycloaddition.

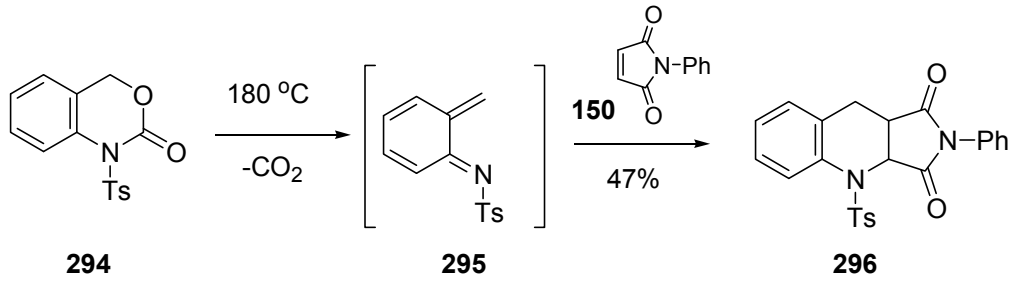
Scheme 66. Cycloaddition of an aza-*ortho*-xylylene to synthesize communesin B.



D. Generation of aza-*ortho*-xylylenes

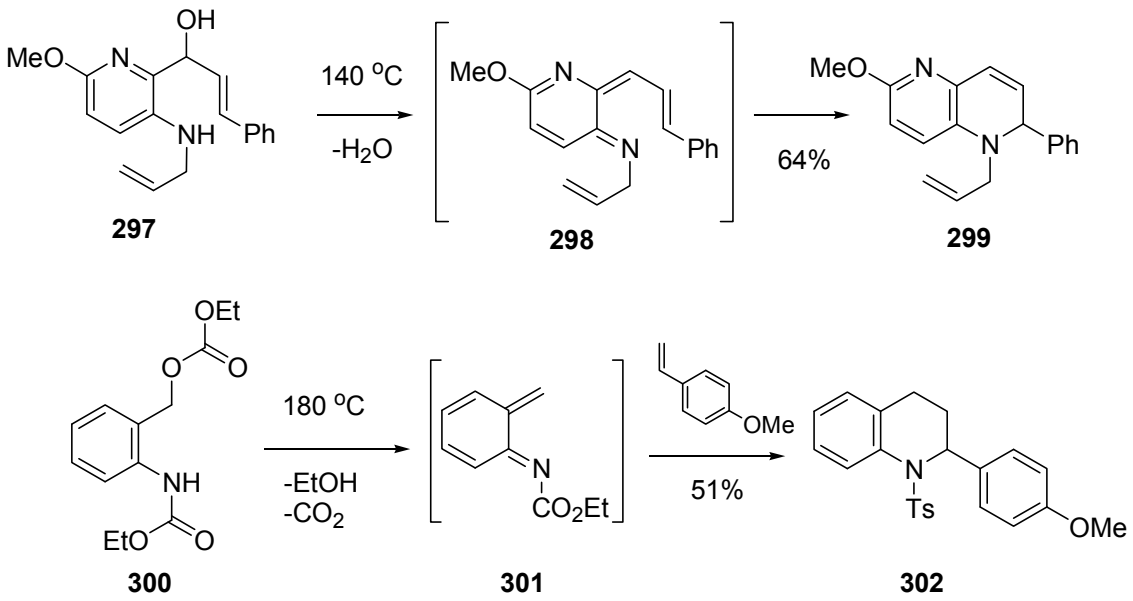
There are several different methods for generating aza-*ortho*-xylylenes, including the desired thermal protocol.[111] For example, *N*-sulfonyl-3,1-benzoxazin-2-one (**294**) underwent retro- [4+2] cycloaddition with loss of CO_2 to generate the *N*-sulfonyl-aza-*ortho*-xylylene **295**, and subsequent [4+2] cycloaddition with *N*-phenylmaleimide (**150**) provided the tricyclic compound **296** (Scheme 67).[112]

Scheme 67. Generation of aza-*ortho*-xylylenes from 3,1-benzoxazines.



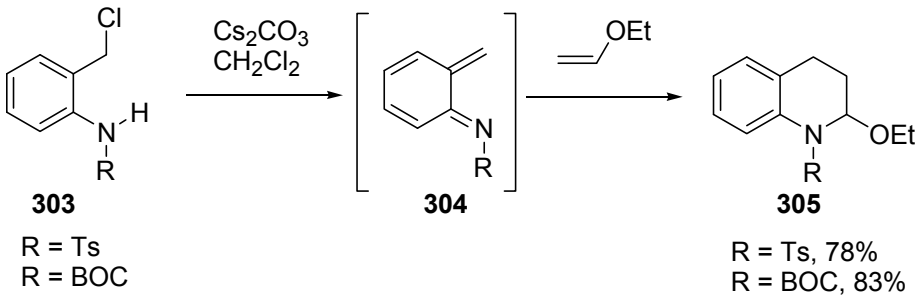
Additionally, the generation of aza-*ortho*-xylylenes **298** and **301** from 2-aminobenzyl alcohol **297**[113] and carbonate **300**[114] respectively proceeded smoothly (Scheme 68).

Scheme 68. Generation of aza-*ortho*-xylylenes via thermal elimination.



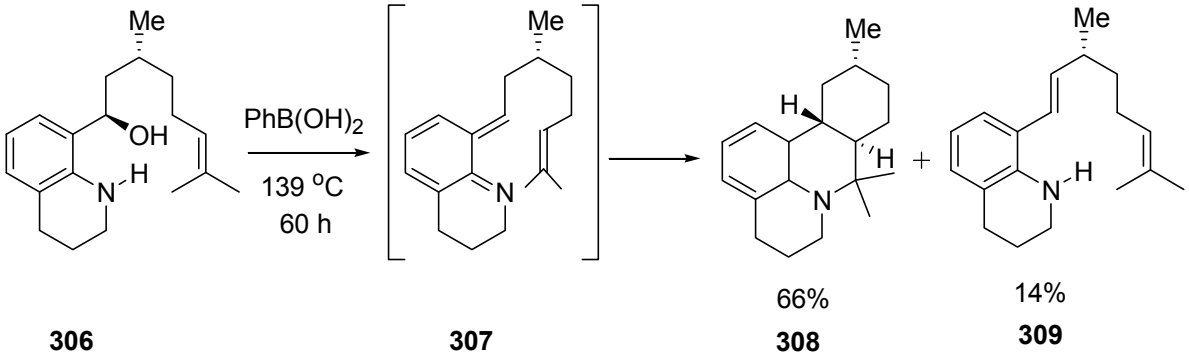
As an alternative to the standard thermolysis conditions, a very simple method for generating aza-*ortho*-xylylenes has recently been developed by Corey.[115] Readily available *ortho*-(chloromethyl)sulfonamide and related carbamate derivatives **303** have participated in cesium carbonate induced elimination of HCl to generate *N*-sulfonyl- and *N*-acyl-aza-*ortho*-xylylenes **304**, that are trapped *in situ* by a variety of dienophiles (Scheme 69).

Scheme 69. Corey's base-mediated generation of aza-*ortho*-xylylenes.



However, it is important to note that alkyl substituted aza-*ortho*-xylylenes can also undergo competing [1,5] sigmatropic hydrogen shifts, as in Scheme 70.[111, 113a]

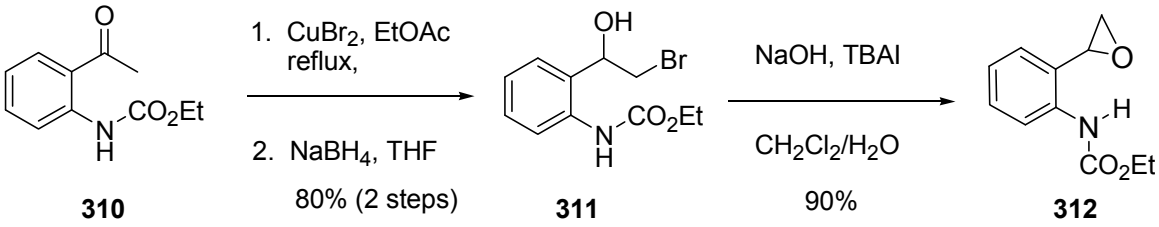
Scheme 70. Competing [1,5]-sigmatropic shift with aza-*ortho*-xylylene generation.



E. Synthesis of the core ring system of communesin B

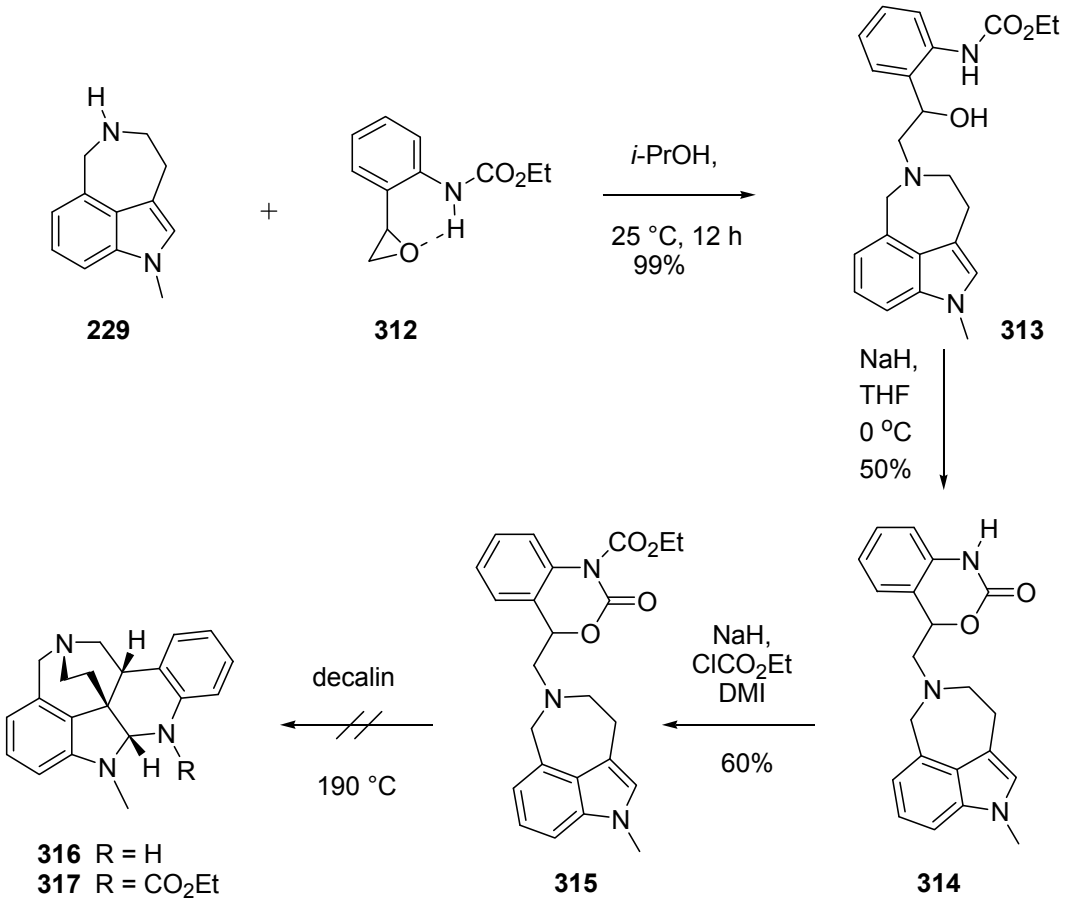
Fortunately, we were able to readily adapt our synthesis to generate an aza-*ortho*-xylylene in order to build the core ring system of communesin. Initially we decided to pursue the retrocycloaddition of 3,1-benzoxazines to generate the aza-*ortho*-xylylene. To that end, the epoxide **312** was prepared in three straightforward steps from the carbamate **310** following the published procedure (Scheme 71).[116]

Scheme 71. Synthesis of an epoxide.



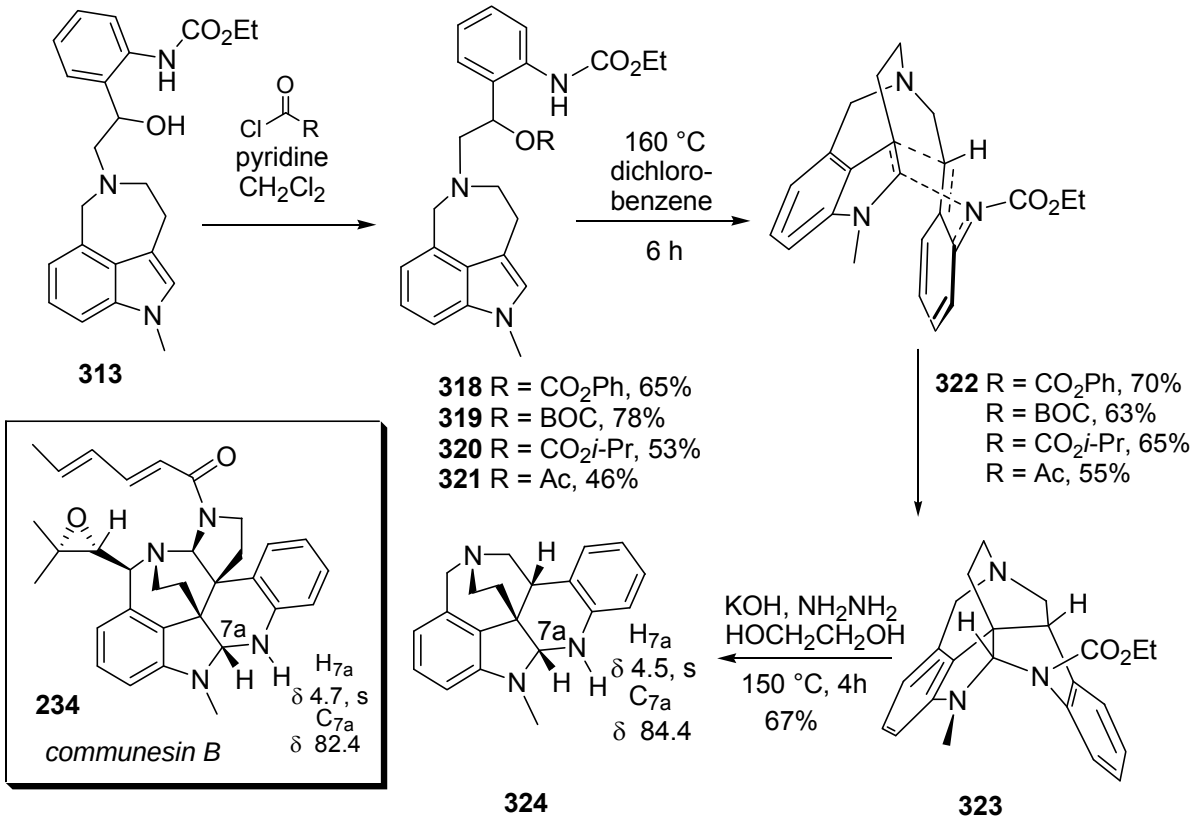
Ring opening of the epoxide **312** with the benzazepine **229** gave the alcohol **313** as a 9 : 1 mixture of regioisomers. This regioselectivity could be explained by an internal hydrogen bond between the carbamate N-H and epoxide. A conformation such as this one would be expected to encourage the benzazepine to attack the less substituted homobenzylic position. Subsequent treatment with base afforded the 3,1-benzoxazin-2-one **314** (Scheme 72). Unfortunately, thermolysis of **314** in decalin at 190 °C failed to generate the desired cycloadduct **316** and only led to decomposition of the starting material. Alternately, *N*-acylation[112d] of **314** provided the *N*-acyl-3,1-benzoxazin-2-one **315**. However, thermolysis of **315** failed to provide the desired cycloadduct **317**.

Scheme 72. Attempted generation of an aza-*ortho*-xylylene via retrocycloaddition of a 3,1-benzoxazin-2-one.



Therefore, alcohol **313** was converted to the corresponding phenylcarbonate **318** (Scheme 73). Other carbonates that were synthesized include the *t*-butyl carbonate **319**, isopropyl carbonate **320**, and the acetate **321**. However, upon thermolysis, the phenyl carbonate **318** was found to be the most efficient precursor to the presumed *N*-acyl-aza-*ortho*-xylylene **322**, as it gave rise to a single *endo* cycloadduct, aminal **323**. The stereochemical assignment was secured upon hydrolysis[117] of the carbamate moiety of **323** to the aminal **324**, which exhibited the analogous nOe's previously observed for the "nomofungin"

Scheme 73. Cycloaddition of a *N*-acyl-aza-*ortho*-xylylene.



core ring system **232** (Scheme 56). More importantly, the chemical shift of the key aminal proton and carbon resonances for **324** (δ 4.5 and 84.4 respectively) closely matched those reported for communesin B (δ 4.7 and 82.4). Thus, we provided definitive proof that the structure of nomofungin was assigned erroneously and that nomofungin is actually communesin B.

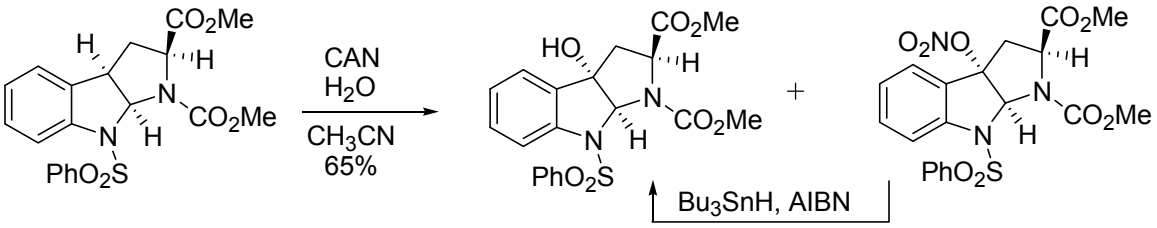
III. Benzazepine-based strategies for the elaboration of the pyrrolidine ring.

A. Attempted generation of a benzylic cation

With the core ring system of communesin in hand, we directed our attention towards elaboration of the remaining pyrrolidine ring. The first strategy

we investigated was the generation of a benzylic cation at C(13) which could then be intercepted by suitable nucleophiles. Oxidative transformations at benzylic positions induced by DDQ and cerium are well documented.[118] Crich used CAN on the aminal **325** to presumably generate a benzylic cation and thus isolated benzylic alcohol **326** (Scheme 74).[118g] The nitrate ester **327** was also isolated, which could be converted to the alcohol **326** with Bu_3SnH and AIBN.

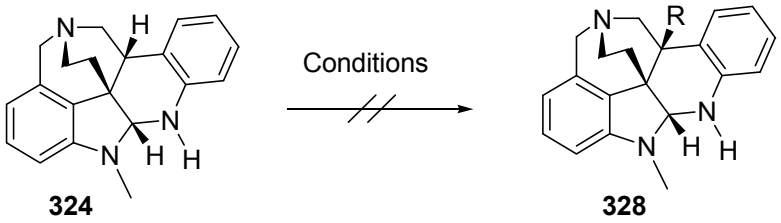
Scheme 74. Addition of a nucleophile to a benzylic position mediated by CAN.



325 **326** **327**

With this precedent in mind, **324** was subjected to either acetic acid,[118f] methanol, or allyltrimethylsilane[119] in the presence of either CAN, DDQ, and the DDQ alternative chloranil.[118h] Unfortunately, all attempts only provided unreacted starting material or decomposition. In addition, we investigated a benzylic bromination using NBS and various radical initiators,[118i-k] but only isolated products from bromination of the reactive aromatic rings (Scheme 75).

Scheme 75. Attempted benzylic functionalizations.



324 **328**

Benzylic functionalization conditions attempted

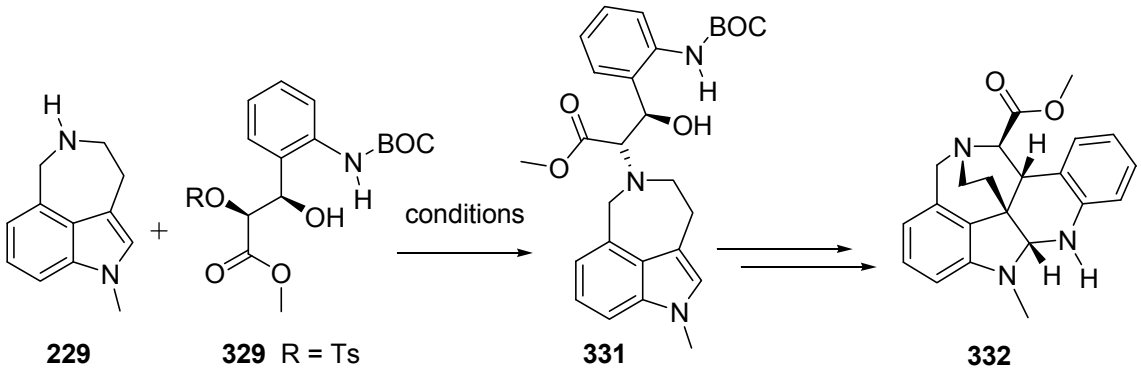
1. CAN, AcOH, CH_3CN / H_2O, rt
2. DDQ, MeOH, rt
3. DDQ, MeOH, CH_2Cl_2, -10 ^oC
4. DDQ, MeOH, CH_2Cl_2, 0 ^oC
5. DDQ, AcOH, 0 ^oC
6. DDQ, allyltrimethylsilane, CH_2Cl_2, 0 ^oC
7. DDQ, MeOH, dioxane, 50 ^oC
8. DDQ, MeOH, dioxane, 0 ^oC
9. DDQ, MeOH, benzene, rt
10. Chloranil, MeOH, 0 ^oC
11. Chloranil, MeOH, CH_2Cl_2, 0 ^oC
12. DDQ, K_2CO_3, toluene, 110 ^oC
13. NBS, AIBN, CCl_4, 77 ^oC
14. NBS, benzoyl peroxide, rt

B. Alkylation and epoxide aminolysis strategies

1. Alkylation strategy

We next investigated the alkylation of the benzazepine **229** with the tosylate **329** and the nosylate **330** (Scheme 76). If successful, this strategy would furnish alcohol **331**, which incorporates an ester substituent that could serve as a handle for introduction of the pyrrolidine ring.

Scheme 76. Attempted alkylations of the benzazepine.



229 **329** R = Ts **330** R = Ns **331** **332**

However, all attempts to directly displace the tosylate or nosylate with the benzazepine resulted in recovery of unreacted starting material (Table 2). On the other hand, when we used basic conditions, we were able to isolate the *cis* epoxide derivative of **330** in poor yield.[120]

Table 2. Unsuccessful alkylation conditions

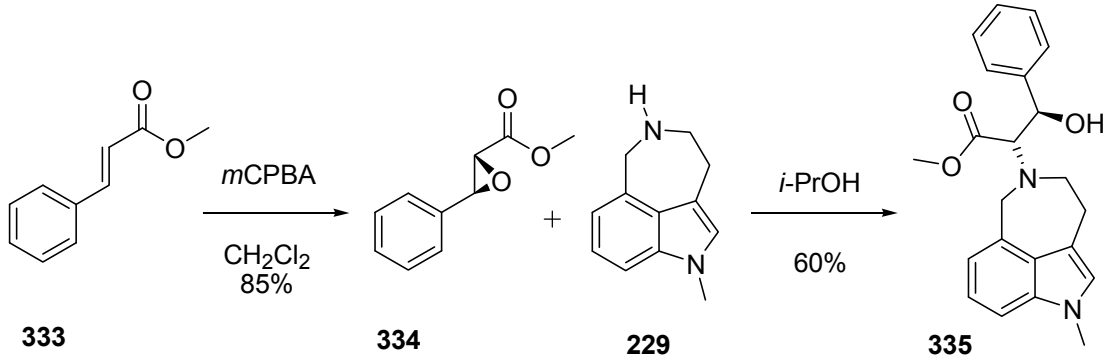
	attempted alkylation conditions
329 R = Ts	1. THF, rt, 12 h 2. CH_3CN, 60 ^oC, 12 h
330 R = Ns	3. CH_3CN, 60 ^oC, 12 h 4. DMF, 60 ^oC, 12 h 5. *i*-PrOH, 60 ^oC, 12 h 6. $NaHCO_3$, CH_3CN, 50 ^oC, 12 h 7. Cs_2CO_3, CH_3CN, rt, 2 h

2. Epoxide aminolysis strategies

This result led us to prepare epoxides analogous to epoxide **312** that possessed an ester substituent on the homobenzylic position in hopes that we could isolate alcohol **331** upon aminolysis with the benzazepine **229**. As a model system to evaluate this strategy, epoxide **334** was made via straightforward *m*CPBA epoxidation of the commercially available methyl *trans*-cinnamate (**333**).

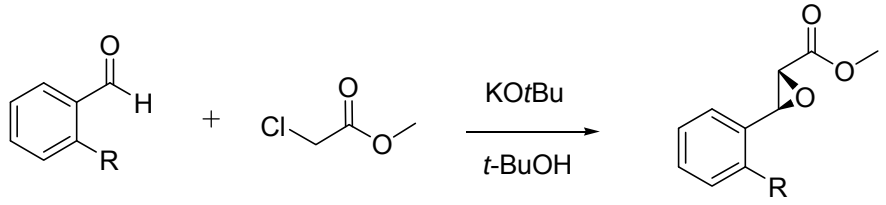
We were pleased to observe that subsequent aminolysis with the benzazepine **229** efficiently provided the alcohol **335** (Scheme 77).

Scheme 77. Aminolysis of an epoxide with an ester substituent.



Subsequently, epoxides **339**-**341** were prepared via Darzens condensation of the aldehydes **336** and **337** with methyl chloroacetate (**338**).[121] (Epoxide **341** was isolated by using an acidic workup for epoxide **340**) (Scheme 78).

Scheme 78. Preparation of *trans* epoxides.



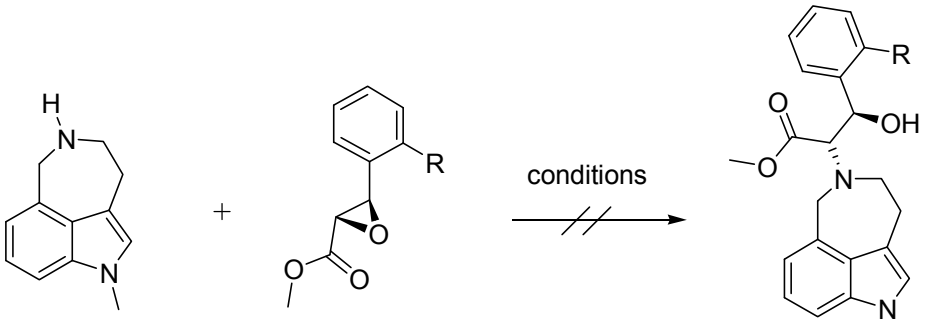
336 R = NO_2
337 R = N(BOC)TBS

338

339 R = NO_2 (45%)
340 R = N(BOC)TBS (60%)
341 R = NH(BOC) (50%)

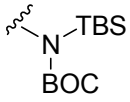
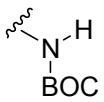
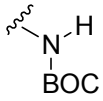
Further experimentation established that we could not repeat the aminolysis of the 2-substituted *trans*-benzylic epoxides **339-341** or the *cis* epoxide **342**[120] with the benzazepine **229**, despite using various solvents, Lewis acid catalysis,[122] or Lewis acid catalysis under high-pressure (Scheme 79).[122j,k] A possible explanation could be that the 2-substituted benzylic epoxides are in a congested steric environment that prohibits the benzazepine from opening the epoxide ring.[123]

Scheme 79. Attempted epoxide openings with the benzazepine.



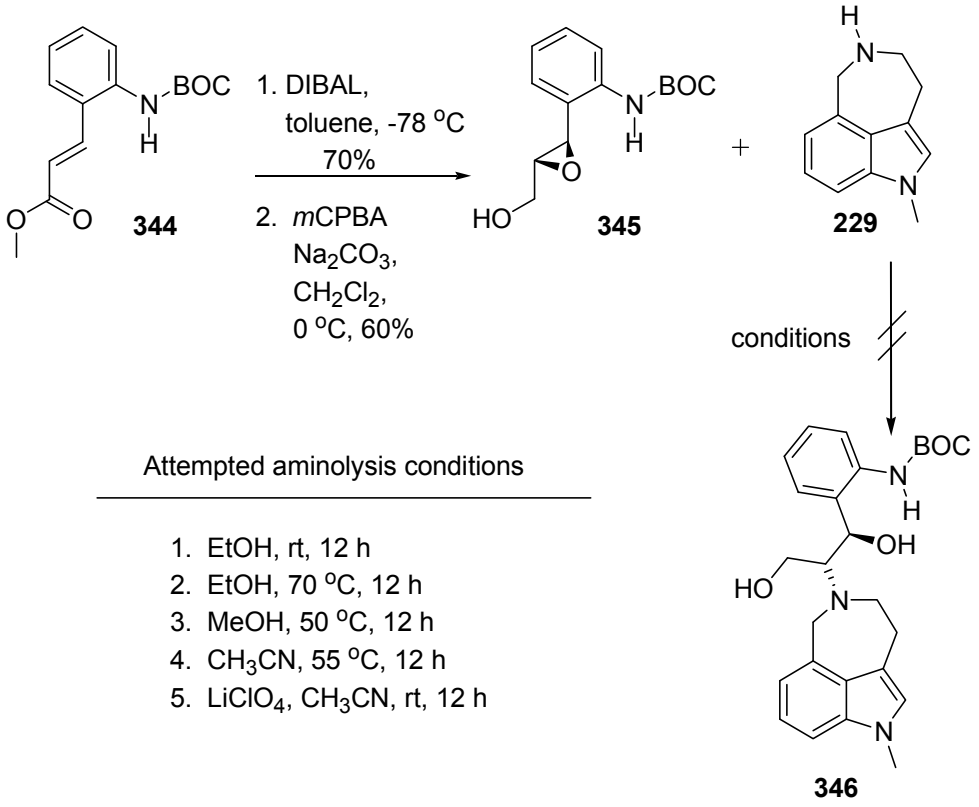
229 **339-341** **343**

Attempted conditions for epoxide aminolysis with the benzazepine

339 *trans* R = NO_2	1. EtOH, 50 °C, 24 h 2. *i*-PrOH, 60 °C, 12 h 3. *i*-PrOH, 80 °C, 12 h 4. MeOH, 80 °C, 24 h	
340 *trans* R = 	1. *i*-PrOH, rt, 12 h	
341 *trans* R = 	1. *i*-PrOH, rt, 12 h 2. EtOH, 65 °C, 12 h 3. MeOH, 60 °C, 12 h 4. CH_3CN, 70 °C, 12 h 5. DMF, 80 °C, 12 h 6. $InCl_3$, CH_2Cl_2, rt, 5 min 7. $LiClO_4$, CH_3CN, 40 °C, 12 h	8. $LiBF_4$, CH_3CN, rt, 1 h 9. $Yb(OTf)_3$, CH_3CN, 12 h 10.$Yb(OTf)_3$, CH_3CN, 10 kbar, 12 h 11. $Cu(OTf)_3$, CH_3CN, 50 °C, 12 h 12. $AlMe_3$, CH_2Cl_2, 12 h 13. $AlMe_3$, benzene, 12 h 14. Li(OTf) CH_3CN, 80 °C
342 *cis* R = 	1. *i*-PrOH, rt, 12 h, 2. EtOH, 65 °C, 12 h 3. toluene, 110 °C, 12 h 4. CH_3CN, 60 °C, 12 h	

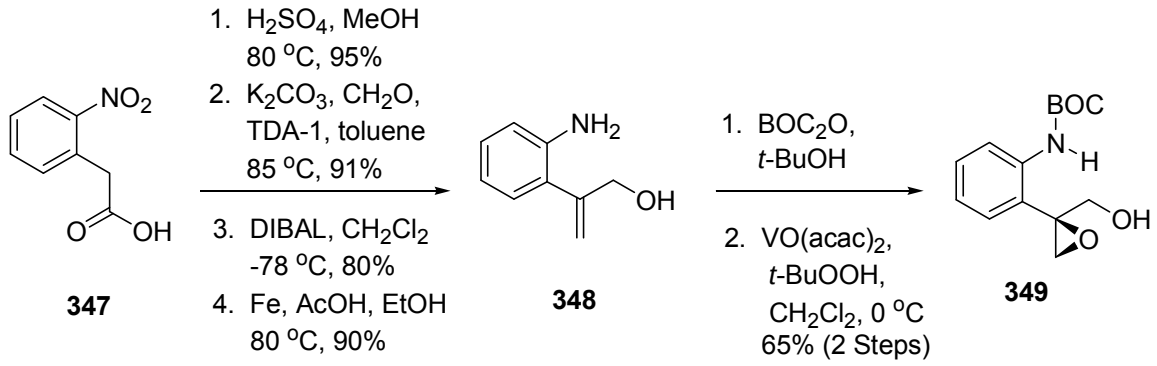
Thus, we synthesized epoxide **345** via DIBAL-H reduction of the ester **344**, followed by epoxidation.[124] It was hoped that the alcohol substituent would hydrogen bond with the amine, thereby facilitating aminolysis of the epoxide (Scheme 80).

Scheme 80. Synthesis and attempted aminolysis of an epoxy alcohol



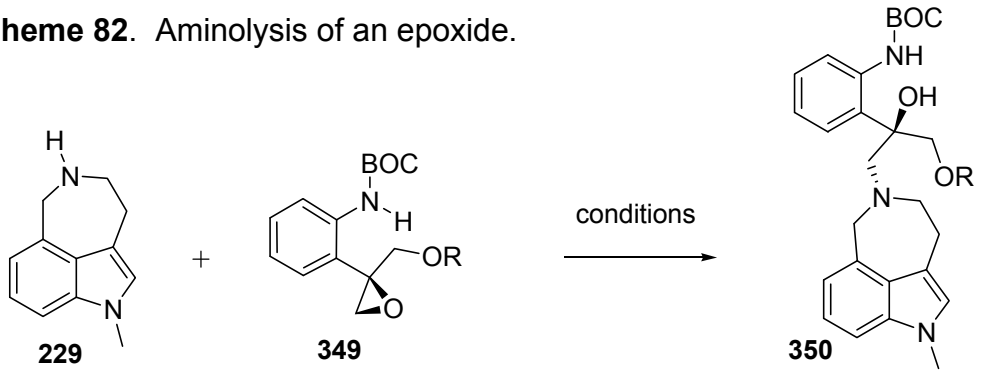
However, all attempts to prepare the diol **346** were unsuccessful. In an attempt to investigate the effects that substitution at the epoxide carbons was having on the aminolysis, the readily available aniline **348** was used to synthesize the epoxide **349** in anticipation that the benzazepine would favor aminolysis of an epoxide with an unsubstituted epoxide carbon (Scheme 81).

Scheme 81. Synthesis of a hydroxymethyl substituted epoxide.



Aminolysis of epoxide **349** was attempted in a variety of polar solvents at elevated temperatures, but only unreacted starting material was recovered. However, silylation of the primary hydroxyl group followed by aminolysis with the benzazepine **229** in the presence of Lewis acids did furnish the mono-protected alcohol **350**, albeit in poor yields (Scheme 82).

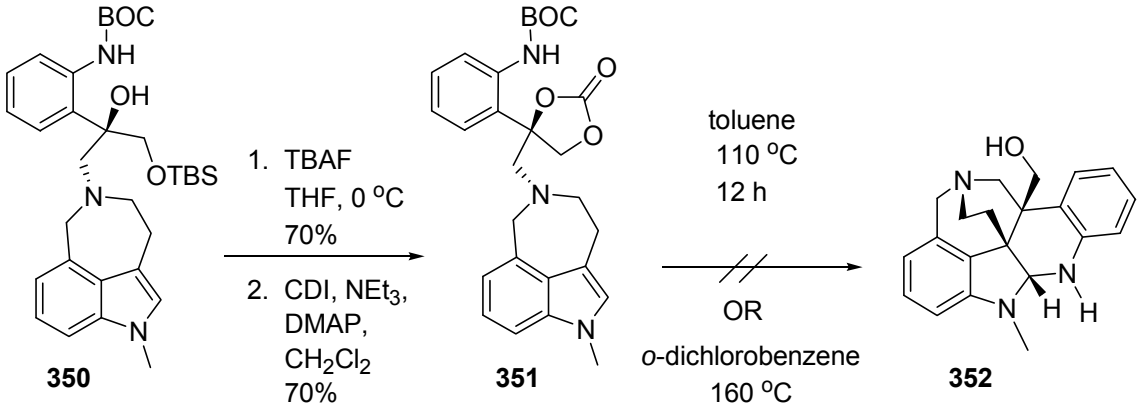
Scheme 82. Aminolysis of an epoxide.



	Attempted aminolysis conditions
349(a) R = H	1. H_2O / dioxane, 80 ^oC, NR
	2. DMF, 120 ^oC, 12 h, NR
	3. MeOH, 70 ^oC, 24 h, NR
349(b) R = TBS	4. H_2O / dioxane, 80 ^oC, NR
	5. DMF, 120 ^oC, 12 h, NR
	6. $Yb(OTf)_3$, CH_3CN, 80 ^oC, 24 h, 20%
	7. $Yb(OTf)_3$, $ClCH_2CH_2Cl$, 80 ^oC, 24 h, NR
	8. $LiClO_4$, CH_3CN, 80 ^oC, 12 h, 30%
	9. $LiClO_4$, $ClCH_2CH_2Cl$, 80 ^oC, 12 h, 30%
	10. $LiClO_4$, CH_3CN, 80 ^oC, 6 h, 20%
	11. LiOTf, CH_3CN, 80 ^oC, 6 h, NR

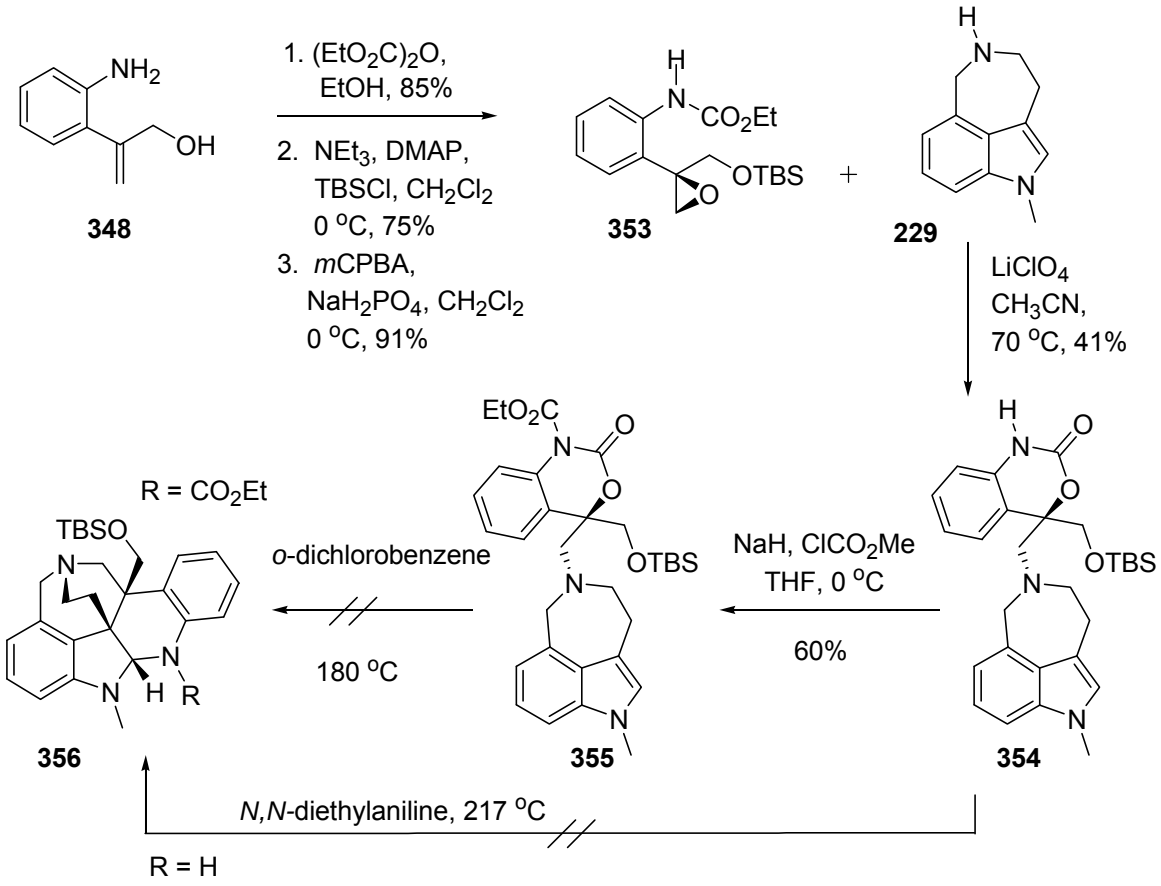
Subsequent desilylation and treatment of **350** with carbonyldiimidazole (CDI) furnished the 1,3-dioxolane-2-one **351** (Scheme 83). Thermolysis of **351** in toluene was ineffective, providing only unreacted starting material, whereas thermolysis at higher temperatures provided an inseparable mixture of products.

Scheme 83. Thermolysis of a 1,3-dioxolane-2-one.



Additionally, conversion of the aniline **348** to the ethyl carbamate, followed by protection and epoxidation provided the epoxide **353** (Scheme 84). Subsequent aminolysis of the epoxide generated an incipient alkoxide, which immediately closed onto the ethyl carbamate to furnish the 3-alkyl-3,1-benzoxazin-2-one **354**. *N*-acylation provided the *N*-acyl-3-alkyl-3,1-benzoxazin-2-one **355**. Unfortunately, thermolysis of either **354** in refluxing diethylaniline, or **355** in refluxing dichlorobenzene gave intractable material.

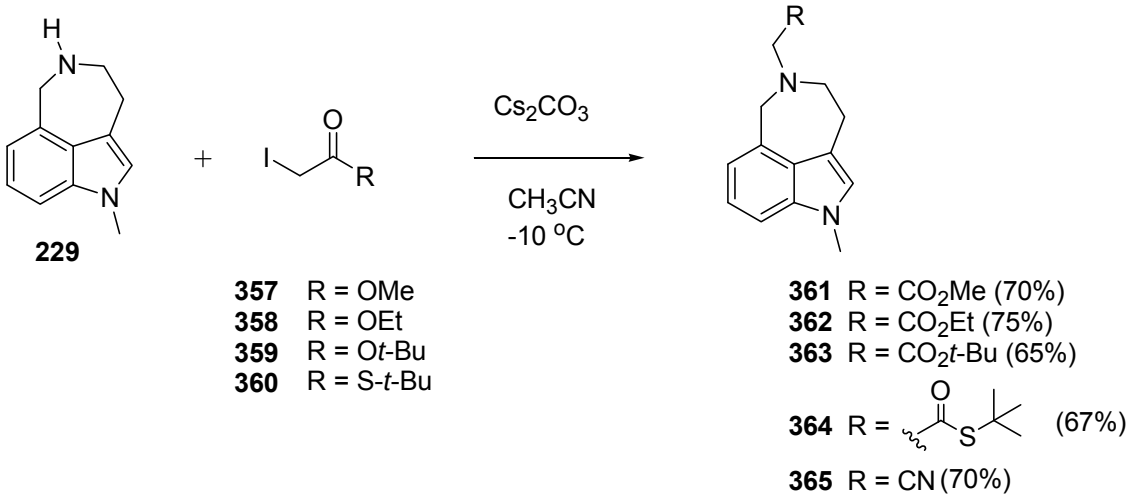
Scheme 84. Thermolysis of an *N*-acyl-3-alkyl-3,1-benzoxazin-2-one.



3. Alkylation strategy (revisited)

Next, our efforts focused on the alkylation strategy discussed above in Scheme 76. We were able to successfully alkylate the benzazepine **229** with α-iodoesters **357-360** to provide the benzazepines **361**-**364**, respectively. Additionally, iodoacetonitrile was alkylated to provide the analogous nitrile **365** (Scheme 85).

Scheme 85. Synthesis of β-aminoesters and a β-aminonitrile.

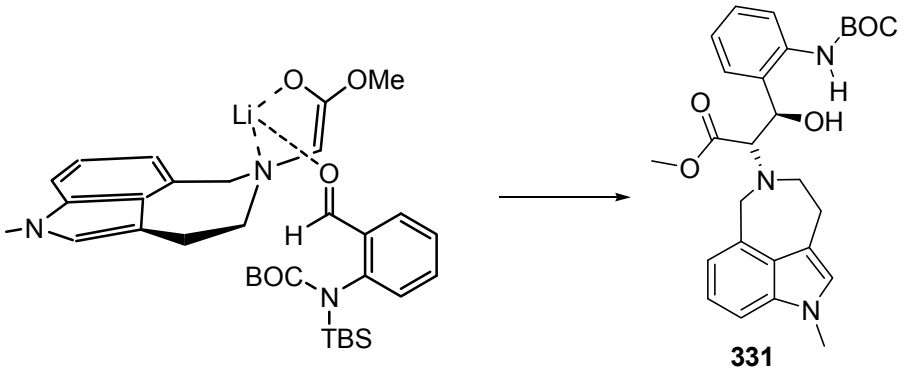


357 R = OMe
358 R = OEt
359 R = O*t*-Bu
360 R = S-*t*-Bu

361 R = CO_2Me (70%)
362 R = CO_2Et (75%)
363 R = CO_2t-Bu (65%)
364 R = (67%)
365 R = CN (70%)

It was anticipated that conditions might be found whereby a chelated enolate (such as that shown in Figure 11) could react with a suitably protected aldehyde to give the aldol adduct, alcohol **331**. Presumably, the aldehyde would approach from the β–face of the (*Z*)-enolate boat-like conformer shown.[125] However, the facial preference of the aldehyde is insignificant since the stereogenic center derived from the aldehyde carbon is lost during the generation of the *N*-acyl-aza-*ortho*-xylylene.

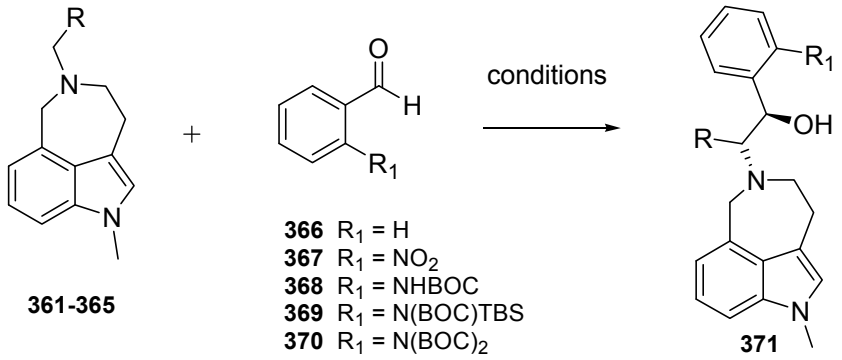
Figure 11. A possible chelated aldol transition state.

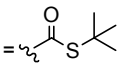


331

Despite repeated attempts, the enolate of the methyl ester **361** could not be formed, possibly due to competing elimination of methoxide to provide the corresponding ketene (Scheme 86). Compounds **362-365** could be cleanly deprotonated and methylated, but we were unable to add the respective enolates to aldehydes other than benzaldehyde (**366**) or 2-nitrobenzaldehyde (**367**).

Scheme 86. Attempted aldol reactions with the benzazepine.



benzazepine		aldehyde	conditions	result
361 R = CO_2Me	1.	MeI	NaH, THF, rt	NR
	2.	MeI	LDA, HMPA,THF, -78 °C → -40 °C	decomposition
	3.	MeI	LDA, THF, -78 °C → -40 °C	decomposition
	4.	MeI	LiHMDS, HMPA, -78 °C → -55°C	decomposition
	5.	**369** R_1 = N(BOC)TBS	LDA, THF, -78 °C → -10 °C	decomposition
	6.	**369** R_1 = N(BOC)TBS	LDA, THF, -78 °C	decomposition
	7.	**369** R_1 = N(BOC)TBS	LDA, THF, -78 °C → -20 °C	decomposition
	8.	**369** R_1 = N(BOC)TBS	LiHMDS, HMPA, THF, -78 °C → -55°C	decomposition
	9.	**366** R_1 = H	NaOMe / MeOH, rt	NR
362 R = CO_2Et	1.	MeI	LDA, THF, -78 °C → -20 °C	75%
	2.	MeI	LDA, Et_3B, THF, -78 °C → -20 °C	NR
	3.	**366** R_1 = H	LDA, Et_3B, THF, -78 °C → -20 °C	NR
	4.	**366** R_1 = H	LDA, THF, -78 °C → -20 °C	NR
	5.	**369** R_1 = N(BOC)TBS	LDA, THF, -78 °C → -20 °C	NR
	6.	**367** R_1 = NO_2	NaOEt / EtOH, rt	NR
	7.	**368** R_1 = NHBOC	K_2CO_3, EtOH, rt	NR
	8.	**368** R_1 = NHBOC	Cs_2CO_3, EtOH, rt	NR
	9.	**368** R_1 = NHBOC	NaOEt / EtOH	NR
	10.	**368** R_1 = NHBOC	NaOEt / EtOH, 60 °C	NR
363 R = CO_2t-Bu	1.	MeI	KHMDS, THF, -78 °C → -20 °C	80%
	2.	MeI	NaMDS, THF, -78 °C → -20 °C	NR
	3.	**367** R_1 = NO_2	KHMDS, THF, -78 °C → -20 °C	30%
	4.	**369** R_1 = N(BOC)TBS	KHMDS, THF, -78 °C → -20 °C	NR
	5.	**369** R_1 = N(BOC)TBS	KHMDS, THF, -78 °C → 0 °C	NR
	6.	**368** R_1 = NHBOC	KHMDS, THF, -78 °C → 0 °C	NR
364 R = 	1.	MeI	LDA, TMEDA, THF, -78 °C → -25°C	NR
	2.	MeI	LDA, HMPA, THF, -78 °C → -25°C	75%
	3.	**366** R_1 = H	LDA, HMPA, THF, -78 °C → -25°C	50%
	4.	**367** R_1 = NO_2	LDA, HMPA, THF, -78 °C → -25°C	30%
	5.	**368** R_1 = NHBOC	LDA, HMPA, THF, -78 °C → -25°C	NR
	6.	**368** R_1 = NHBOC	LDA, HMPA, THF, -78 °C → 0 °C	NR
	7.	**369** R_1 = N(BOC)TBS	LDA, HMPA, THF, -78 °C → -25°C	NR
	8.	**370** R_1 = $N(BOC)_2$	LDA, HMPA, THF, -78 °C → -25°C	NR
365 R = CN	1.	MeI	NaMDS, THF, -78 °C → -20 °C	75%
	2.	MeI	LDA, THF, -78 °C	NR
	3.	**366** R_1 = H	LDA, THF, -78 °C	NR
	4.	**367** R_1 = NO_2	NaMDS, THF, -78 °C	NR
	5.	**369** R_1 = N(BOC)TBS	NaMDS, THF, -78 °C → -20 °C	NR
	6.	**369** R_1 = N(BOC)TBS	NaMDS, THF, -78 °C	NR

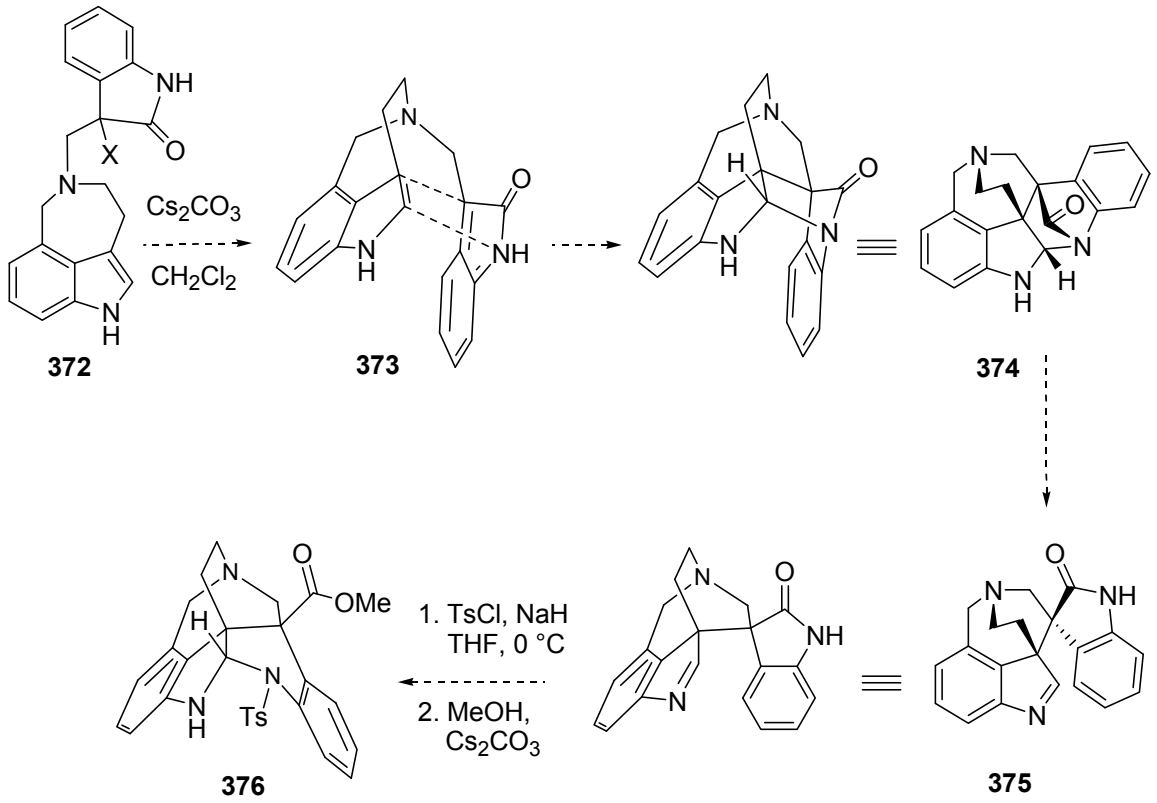
C. A potential application of indol-2-ones towards communesin B

1. Intramolecular approach

We now turned to an entirely different strategy for generating the aza-*ortho*-xylylene that drew upon the successful application of indol-2-one cycloadditions in the total synthesis of perophoramidine.[109a] We were intrigued by the possibility of using an intramolecular cyclization of an indol-2-one for the construction of communesin.

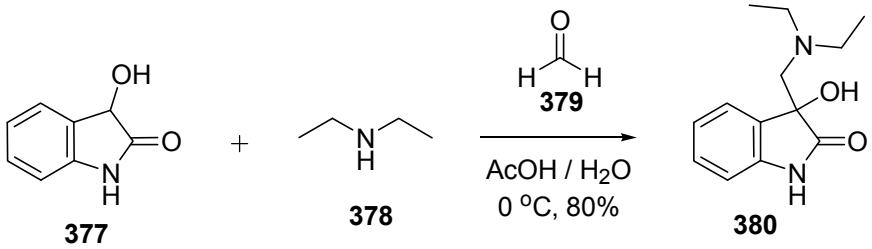
Thus, we believed that the indol-2-one intermediate **373**, generated from the oxindole **372**, could undergo an *endo* [4+2] cycloaddition with the pendant indole to provide the strained bridged bicyclic lactam **374**. Indolenine formation with concomitant ring opening could then provide the oxindole **375**. Subsequent transformation to a sulfonylimide, followed by methanolysis, could provide the ester **376** (Scheme 87).

Scheme 87. A possible application of intramolecular indol-2-one chemistry to communesin.



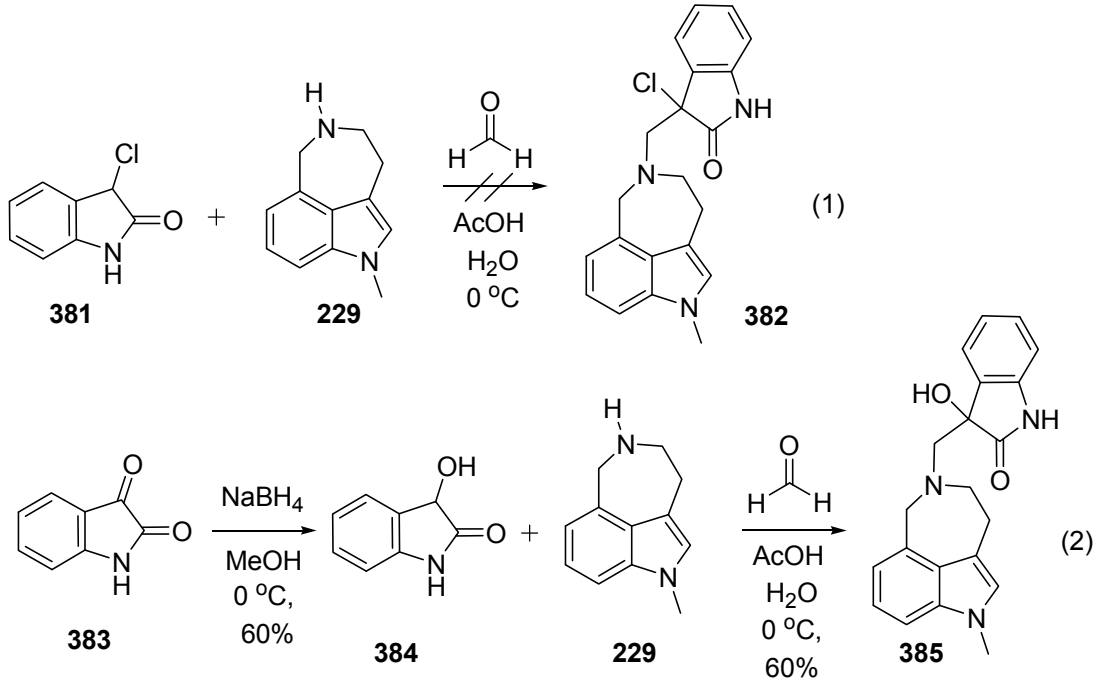
The preparation of oxindole **372** might take advantage of the observations of Hellmann and coworkers, who demonstrated that diethylamine (**378**) and formaldehyde (**379**) condensed with 3-hydroxyoxindole (**377**) to provide the Mannich[126] product, oxindole **380** (Scheme 88).[127a]

Scheme 88. A Mannich reaction of 3-hydroxyoxindole.



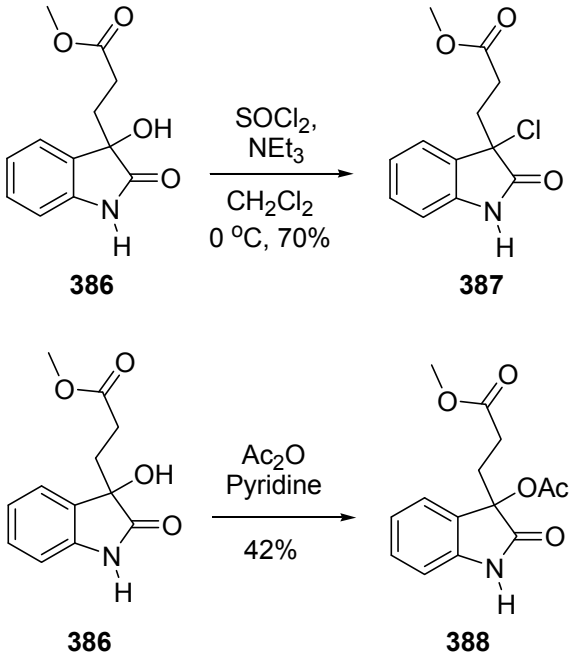
Subsequently, we discovered that although 3-chlorooxindole[128] (**381**) would not participate in the analogous Mannich reaction with benzazepine **229** (eq. 1, Scheme 89), alcohol **384**[129] underwent smooth conversion to the desired 3-alkyl-3-hydroxyoxindole **385** (eq. 2).

Scheme 89. Mannich reactions of 3-substituted oxindoles.



With the 3-alkyl-3-hydroxyoxindole **385** in hand, all that remained was conversion of the alcohol to a suitable leaving group, generation of the indolone, and cycloaddition. We anticipated this transformation to be relatively facile since there are numerous examples in the literature of functionalizations of 3-alkyl-3-hydoxyoxindoles.[130] For instance, Labroo has converted the alcohol **386** to both the corresponding chloride **387** and acetate **388** (Scheme 90).[107c]

Scheme 90. Labroo's functionalization of a 3-alkyl-3-hydroxyoxindole.

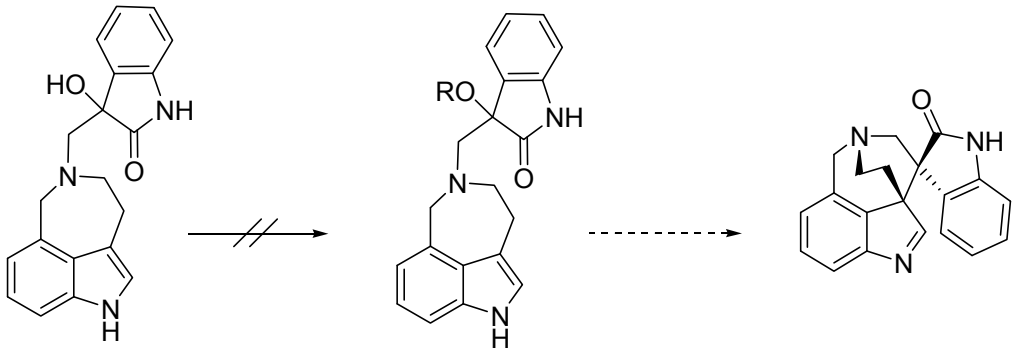


386 **387**

386 **388**

Regrettably, the conversion of the tertiary alcohol **385** to a suitable leaving group was more problematic than anticipated.[131] Despite numerous attempts, such as 1) acylation,[131a-g] 2) conversion to the chloride, mesylate or tosylate,[131h,i] 3) conversion to the carbonate,[131j,k] 4) conversion to the carbamate,[131l-o] 5) *O*-silylation, 6) thermolysis of the alcohol, or 7) subjection to acidic conditions, we were unable to functionalize the tertiary alcohol or isolate any of the cycloadduct. Instead we either recovered unreacted starting material or uncharacterized decomposition products were observed (Scheme 91).

Scheme 91. Attempted functionalization of a tertiary alcohol.



385 **389** **375**

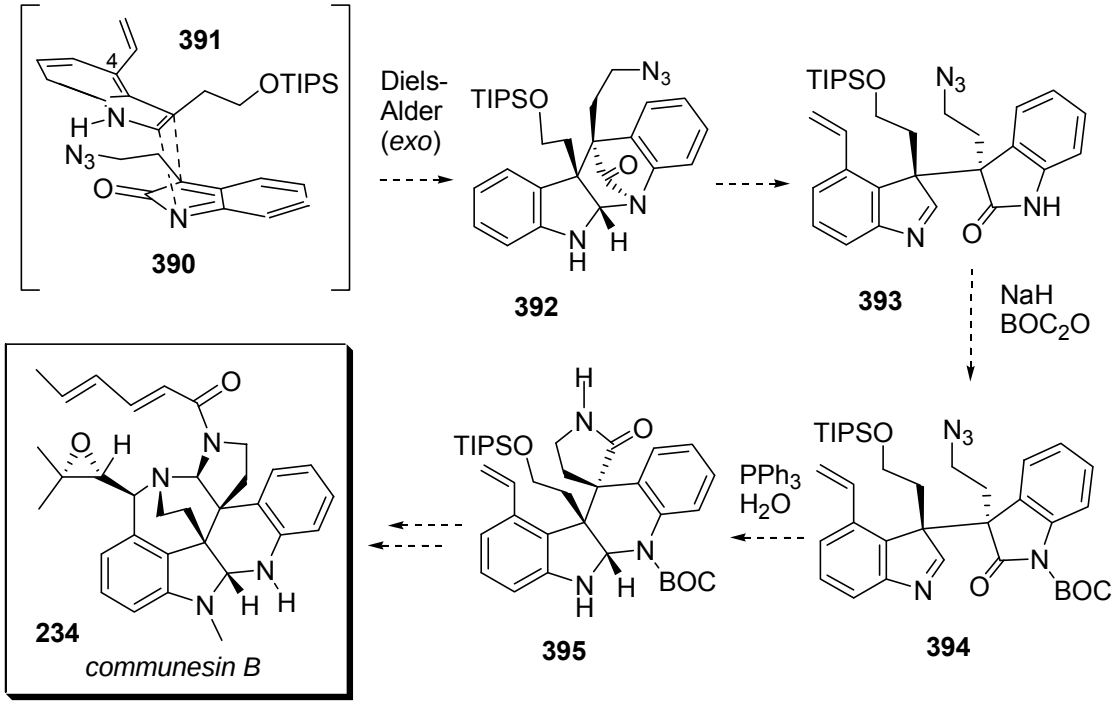
attempted tertiary alcohol functionalization conditions	
1. Ac_2O, NEt_3, DMAP, CH_2Cl_2, 0 °C ⟶ rt	decomposition
2. AcCl, NEt_3, CH_2Cl_2, 0 °C	*N*-acylated oxindole
3. Ac_2O, 80 °C	decomposition
4. $Sc(OTf)_3$, Ac_2O, 50 °C	decomposition
5. $SOCl_2$, imidazole, CH_2Cl_2 / THF, 0 °C	decomposition
6. $SOCl_2$, NEt_3, CH_2Cl_2, -78 °C ⟶ rt	decomposition
7. 2,6-lutidine, LiCl, $SOCl_2$, Cs_2CO_3, CH_2Cl_2 / THF, 0 °C	decomposition
8. 2,6-lutidine, LiCl, $SOCl_2$, Cs_2CO_3, CH_2Cl_2 / THF, -78 °C	decomposition
9. proton sponge, LiCl, $SOCl_2$, CH_2Cl_2 / THF, -78 °C ⟶ rt	decomposition
10. MsCl, NEt_3, CH_2Cl_2, -30 °C	decomposition
11. MsCl, DMAP, CH_2Cl_2, 0 °C	decomposition
12. MsCl, NEt_3, THF, 0 °C ⟶ 60 °C	decomposition
13. Ms_2O, 2,6-lutidine, CH_2Cl_2, -40 °C ⟶ rt	NR
14. MsCl, pyridine, rt	decomposition
15. MsCl, NEt_3, CH_2Cl_2, -78 °C	decomposition
16. TsCl, pyridine, rt	decomposition
17. BuLi, 4-nitrobenzoyl chloride, THF, -78 °C ⟶ 0 °C	NR
18. phenyl chloroformate, pyridine, CH_2Cl_2, 0 °C	decomposition
19. methyl chloroformate, pyridine, CH_2Cl_2, -5 °C ⟶ rt	decomposition
20. CDI, THF, 80 °C	NR
21. CDI, CH_2Cl_2, rt	NR
22. Ts-NCO, THF, 0 °C ⟶ rt	NR
23. Bu-NCO, THF, 90 °C	decomposition
24. Bu-NCO, toluene, 90 °C	decomposition
25. TESCl, imidazole, THF, 0 °C ⟶ rt	NR
26. TMSCl, pyridine, -30 °C ⟶ rt	NR
27. 1,1,1,3,3,3,-hexafluoro-2-propanol, 60 °C	NR
28. mesitylene, 160 °C	decomposition
29. $HNTf_2$, CH_3CN, 25 °C	decomposition
30. PPTs, CH_2Cl_2, 25 °C	decomposition
31. TFA, $SOCl_2$, NEt_3, CH_2Cl_2, 0 °C	decomposition

2. Intermolecular approach

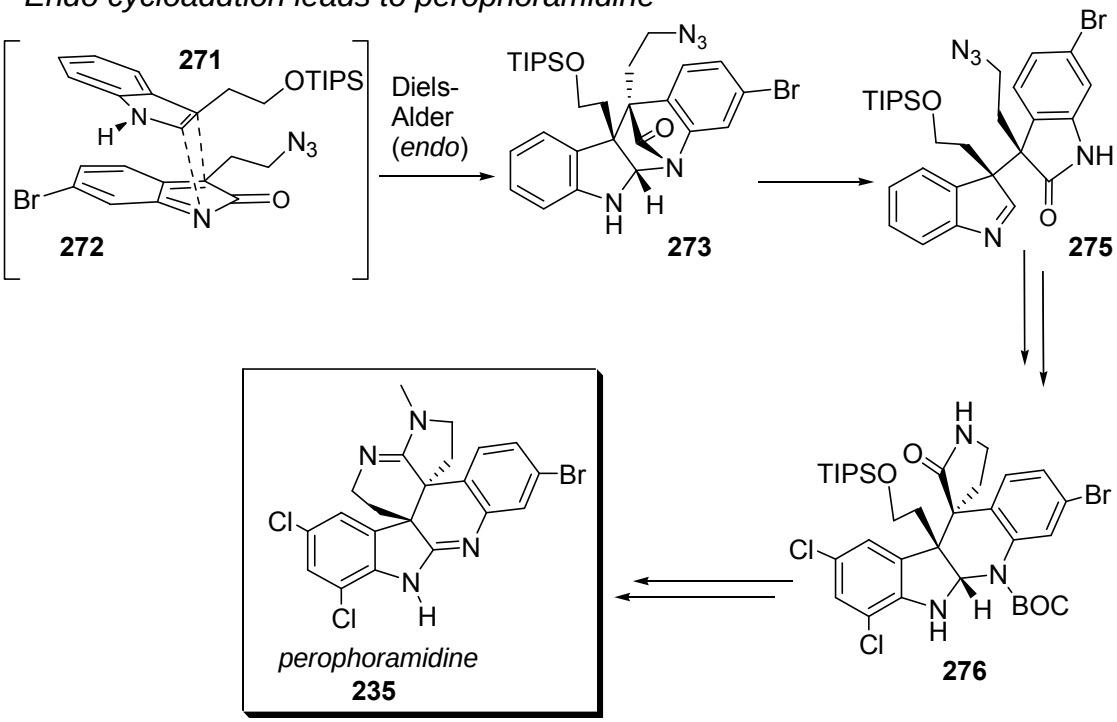
As an alternative to the unsuccessful intramolecular application of the indol-2-one methodology, we decided to investigate if a C(4) indole substituent could be used to disfavor the *endo* transition state of the intermolecular cycloaddition between the indol-2-one **390** and the indole **391** (Scheme 92). We had previously found out that the *endo* transition state is highly preferred in our

Scheme 92. Potential application of an indol-2-one cycloaddition to communesin B.

Exo cycloaddition



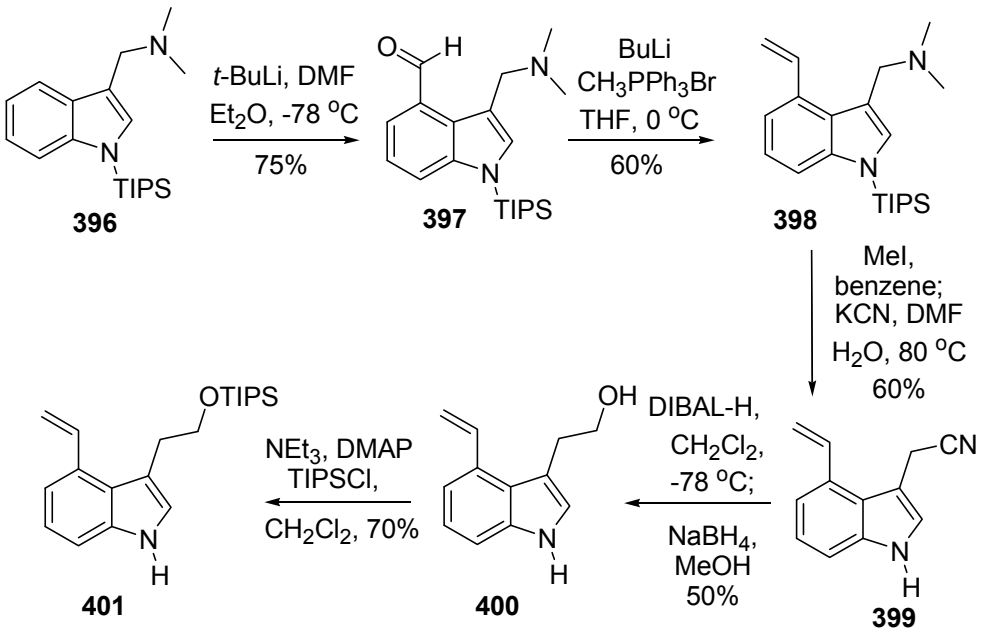
Endo cycloaddtion leads to perophoramidine



perophoramidine synthesis (see Scheme 63). If the cycloaddition now takes place through the *exo* transition state, then steps analogous to those used to complete the total synthesis of perophoramidine[109a] could then be applied to complete the total synthesis of communesin B.

Thus, the protected gramine derivative **396** was metallated and formylated to provide the aldehyde **397** (Scheme 93).[132] Subsequent Wittig olefination, conversion to the quaternary ammonium salt, and displacement with cyanide with concomitant desilylation provided the nitrile **399**. DIBAL-H reduction furnished the unstable aldehyde, which was reduced immediately to provide tryptophol **400**. Silylation then provided the necessary indole partner **401** for the proposed cycloaddition.

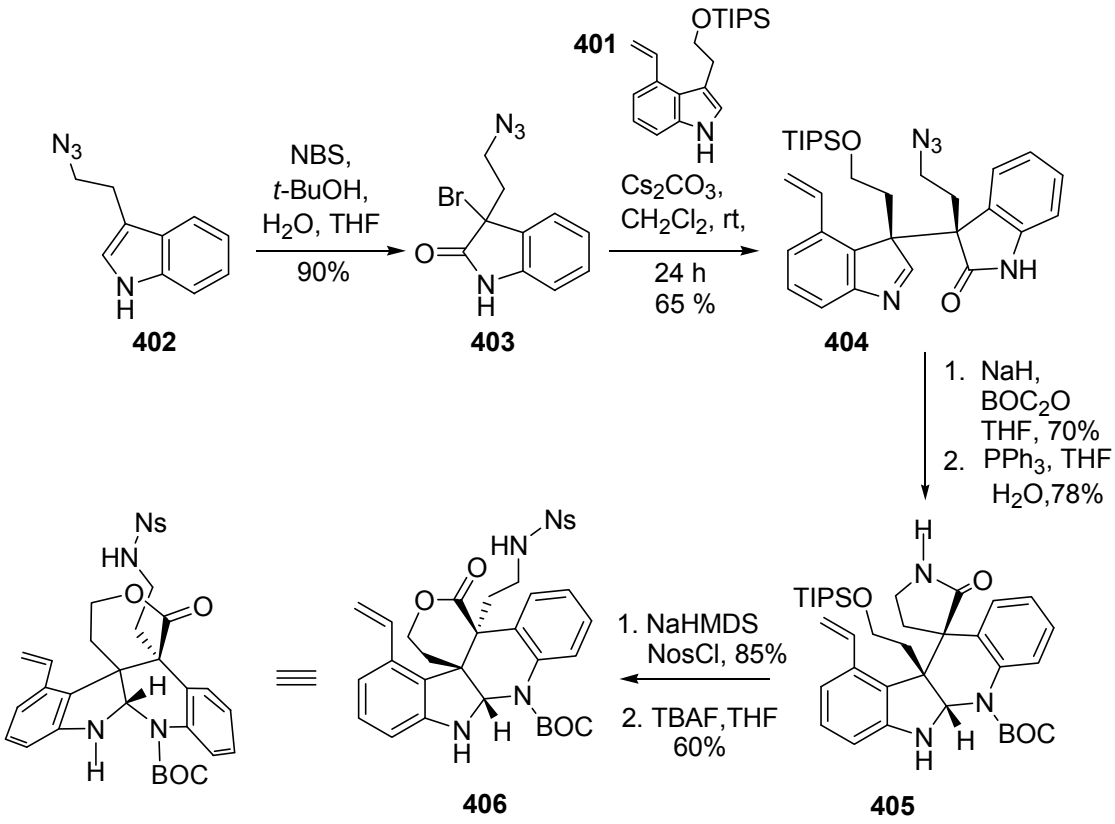
Scheme 93. Preparation of the tryptophol.



The indol-2-one precursor, bromooxindole **403** was made via the Hinman, Bauman oxidation[133] of the azide **402** (Scheme 94). Treatment of the bromooxindole with cesium carbonate in the presence of the indole **401** provided a single diastereomer of the indolenine **404**. The oxindole was *N*-acylated, followed by treatment of the azide moiety with triphenylphosphine, which effected

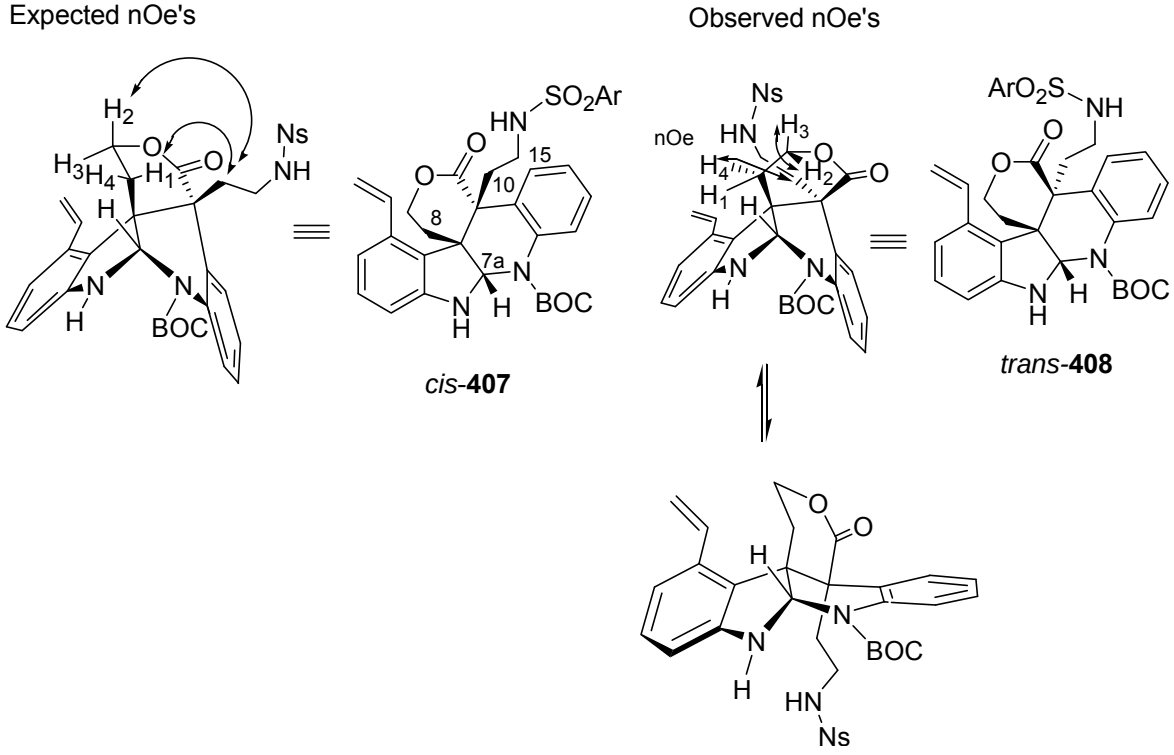
ring opening with concomitant spirocyclic lactam formation and subsequent closure of the aniline *in situ* onto the indolenine to provide the aminal **405**. *N*-Sulfonylation and deprotection of the alcohol provided the conformationally restricted lactone **406**.

Scheme 94. Application of indol-2-one chemistry towards communesin B.



The stereochemistry of the lactone **406** was assigned via nOe studies. Unfortunately, the nOe's we observed were inconsistent with the desired lactone *cis*-**407**. As shown below (Figure 12), diagnostic nOe's between H_4 and the C(10) methylene protons, as well as between H_3 and the C(10) methylene protons were observed. Moreover, the C(10) methylene protons exhibited nOe's with both the vinylic protons and the C(15) aromatic proton, which is not conceivable in **407**. On the other hand, these observations were consistent with the *trans* diastereomer **408**.

Figure 12. Confirmation of the lactone stereochemistry.



IV. Concluding remarks

In conclusion, we have been able to synthesize the core ring systems of the structures proposed for both nomofungin and communesin B and thereby show that nomofungin has been erroneously assigned. However, an inability to introduce functionality at C(13) or C(14) that could be used for the elaboration of the remaining pyrrolidine ring led us to abandon this approach and pursue a more biomimetic and successful one.

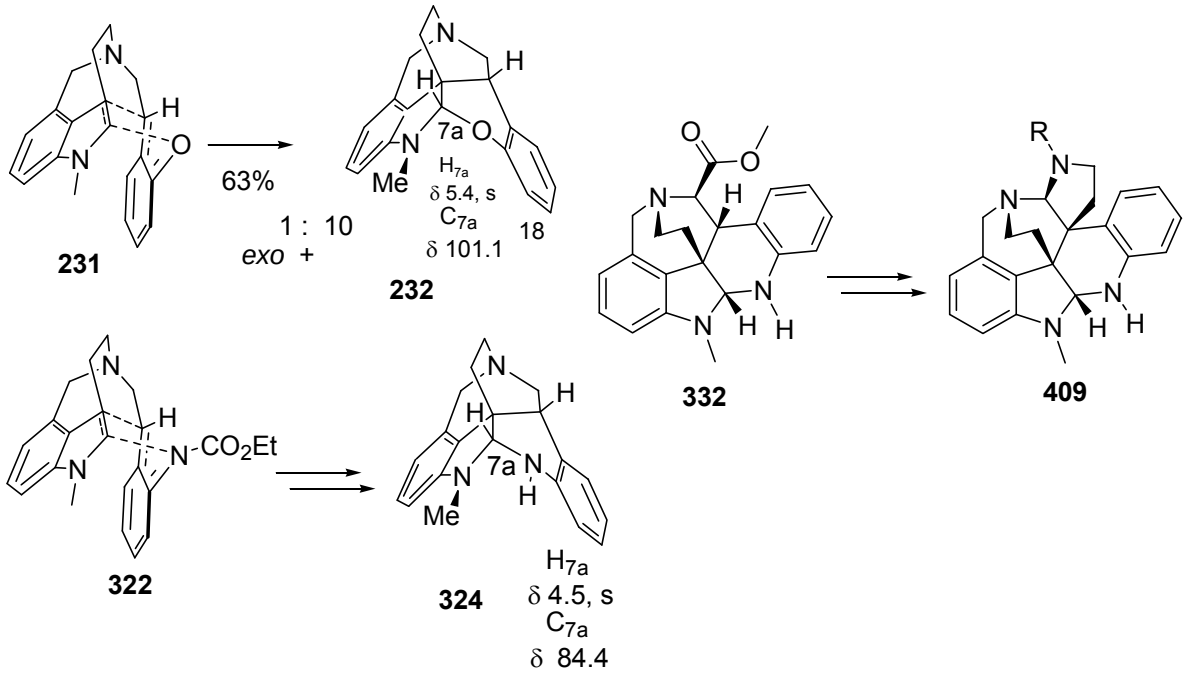
CHAPTER 3

Synthetic Efforts Directed Towards the Total Synthesis of Communesin B. Second Generation Approach: Tryptamine-Based Routes

I. An approach using aziridines derived from tryptamines

In the previous chapter, we described the intramolecular cycloadditions of an *ortho*-quinone methide **231** and an aza-*ortho*-xylylene **322** with a tethered indole to construct the core ring systems of nomofungin **232** and communesin B **324**, respectively (Scheme 95). This research helped to prove that nomofungin was actually communesin B. Subsequently, we investigated several unsuccessful strategies to construct compound **332**, which possesses an ester substituent that could be used for the elaboration of the pyrrolidine ring (compound **409**).

Scheme 95. Cycloaddition of an aza-*ortho*-xylylene to synthesize communesin B.



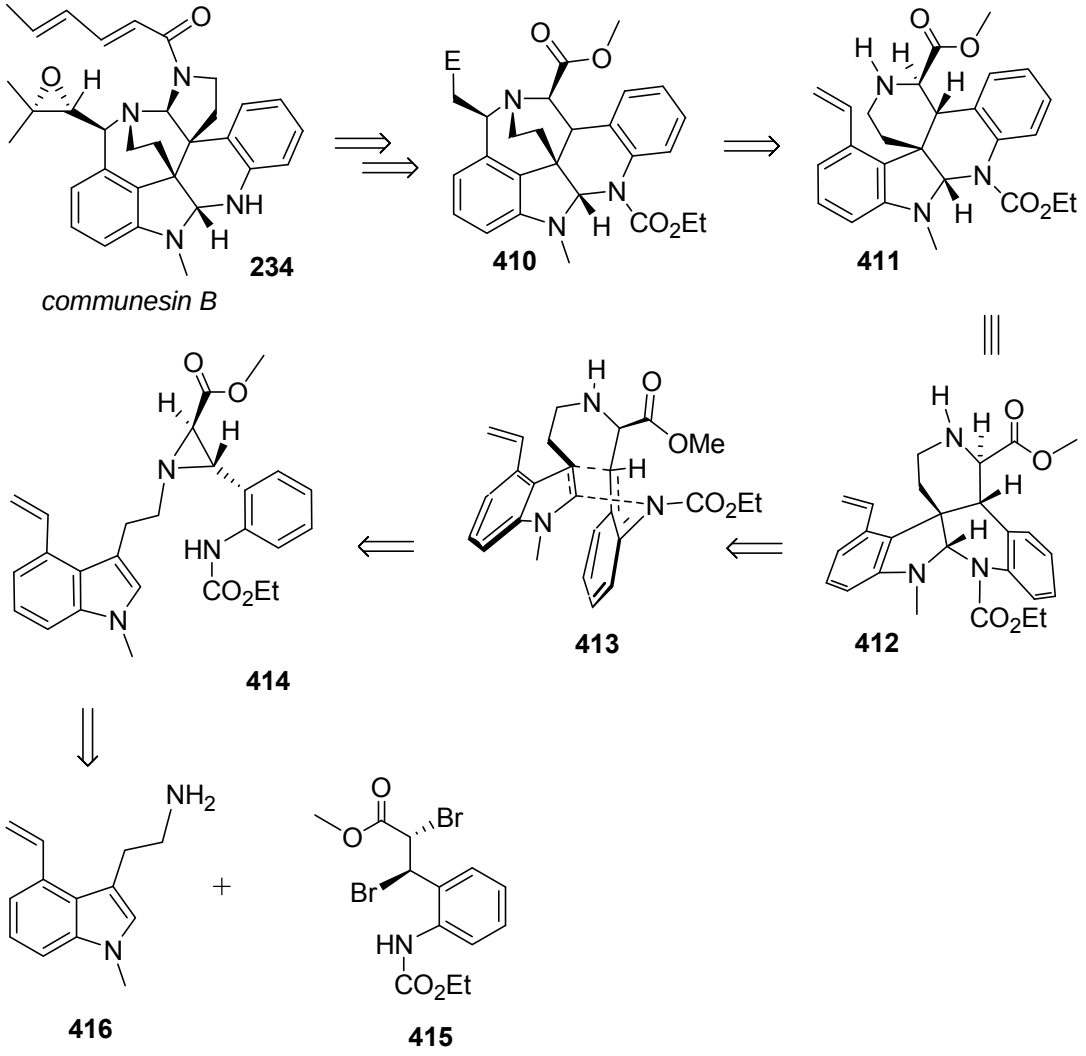
Consequently, an alternative strategy for the introduction of the ester substituent was considered that also suggested a new means of generating aza-

ortho-xylylenes. This new "biomimetic" strategy would initiate with a readily available tryptamine derivative[134] and still take advantage of an intramolecular cycloaddition of an aza-*ortho*-xylylene to construct the ring system of communesin B, but installation of the benzazepine would be deferred to a later stage.

A. Revised retrosynthetic analysis for communesin B.

A possible retrosynthetic analysis is shown in Scheme 96. It was believed that communesin B could be derived from ester **410** as discussed previously in Chapter 2. The ester in turn could be made from the alkene **411** via a cyclization of the alkene with the amine, promoted by an electrophile such as mercury triflate or NBS, etc.[135,136] If a halogen electrophile was employed, then a bridgehead aziridinium ion might be formed and should be opened by hydroxide at the less substituted carbon based on our recent synthetic efforts towards lepidiformine (*vide infra*).[78h,137] The alkene could be derived via an intramolecular *endo* cycloaddition of the aza-*ortho*-xylylene intermediate **413**, generated via acid catalyzed ring opening of the aziridine **414**. Although this is an unprecedented method for generating aza-*ortho*-xylylenes, the acid catalyzed ring opening of aziridines by nucleophiles is well precedented.[138] Finally, the aziridine could be prepared via alkylation of the vicinal dibromide **415** with the readily available tryptamine derivative **416**.[139k,l]

Scheme 96. Retrosynthetic Analysis for a Modified Route to Communesin B.

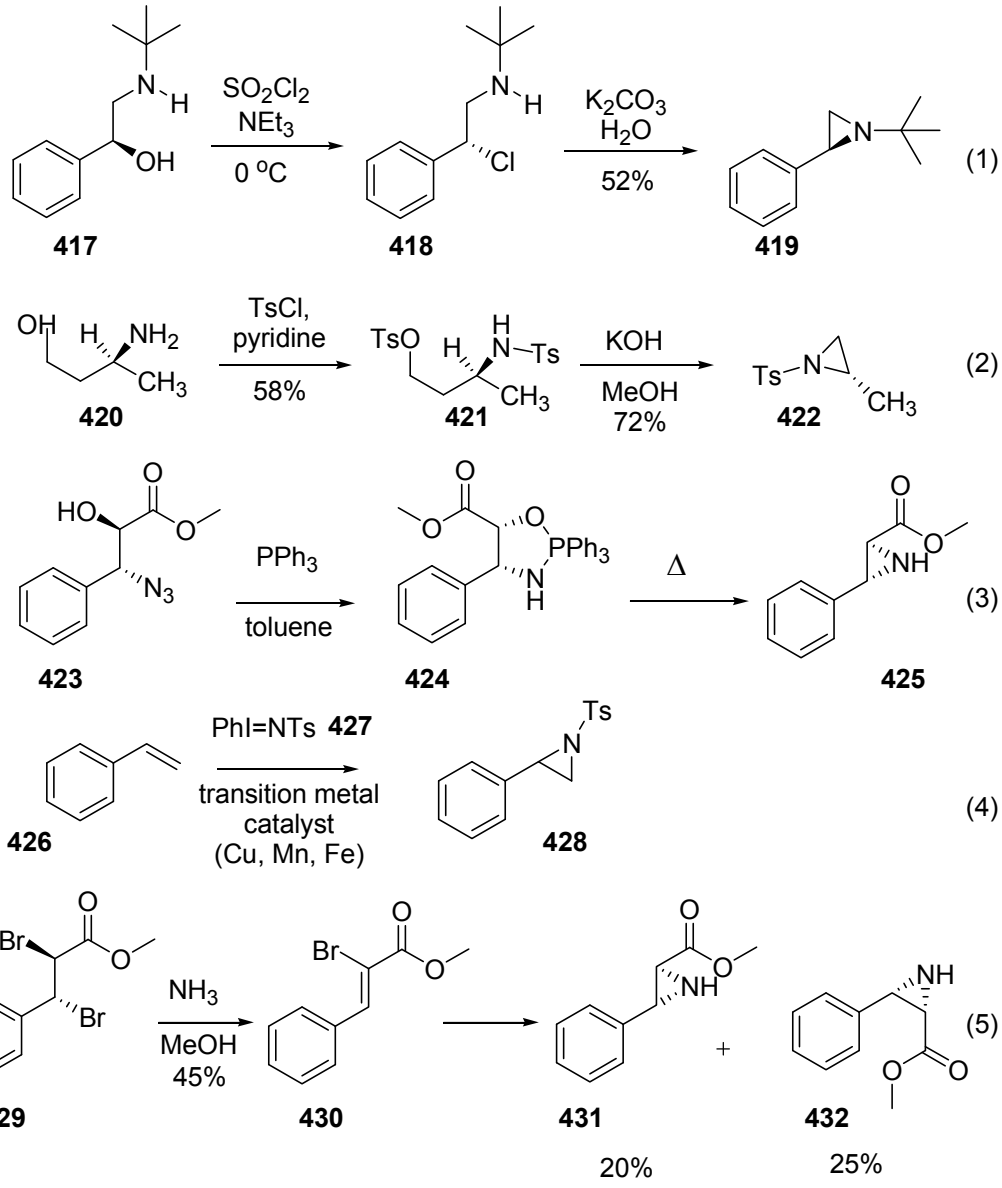


1. Synthesis of aziridines

There are currently a vast number of methods to make aziridines. Synthetic methodologies for the synthesis of aziridines include: cyclization of 1,2-amino alcohols **417** (via conversion of the alcohol to a 1,2-aminohalide **418** (eq 1)[139a] or other suitable leaving group (*i.e.* tosylate **421**[139b] (eq 2)).[139a-d] Additionally, 1,2-azidoalcohols **423** can form aziridines (via the oxazophospholidine **424**) (eq 3).[139e,f] Nitrene addition to olefins (via the nitrene precursor (*N*-(*p*-tolylsulfonyl)imino)phenyliodinane (**427**) has been demonstrated

to be a versatile method of aziridine synthesis (eq 4),[139g-k] as has 1,4-addition of ammonia or amines to electron-deficient olefins **430** followed by internal S_N2 displacement (eq 5)[139l,m] (Scheme 97).

Scheme 97. The synthesis of aziridines from various precursors.

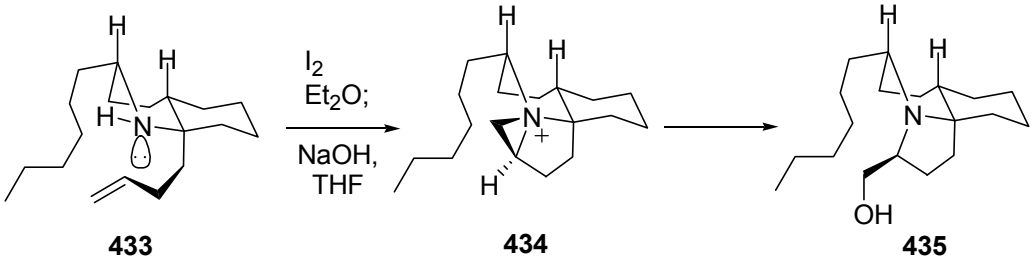


2. Aziridine and aziridinium ion openings

Due to their inherent reactivity, aziridinium ions have been utilized extensively to make substituted piperidine and pyrrolidine rings.[136] For example,

in our group's recent synthesis of lepidaformine, the bridgehead aziridinium ion **434** was opened with sodium hydroxide at the less substituted carbon to form the hydroxymethylated pyrrolidine ring **435** (Scheme 98).[78h]

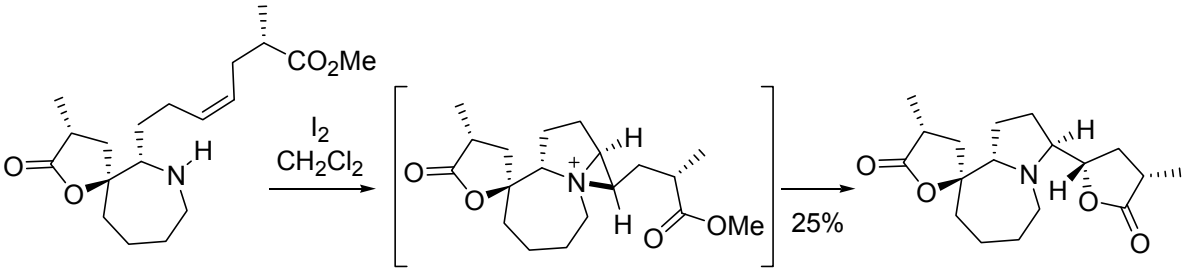
Scheme 98. A bridgehead aziridinium ion opened by sodium hydroxide.



433 **434** **435**

In Williams' total synthesis of (+)-croomine, the aziridinium ion **437** was generated via intramolecular closure of an amine moiety onto the alkene **436** (Scheme 99). Subsequent intramolecular nucleophilic ring opening of the aziridinium ion by the ester provided the natural product **438**.[136e]

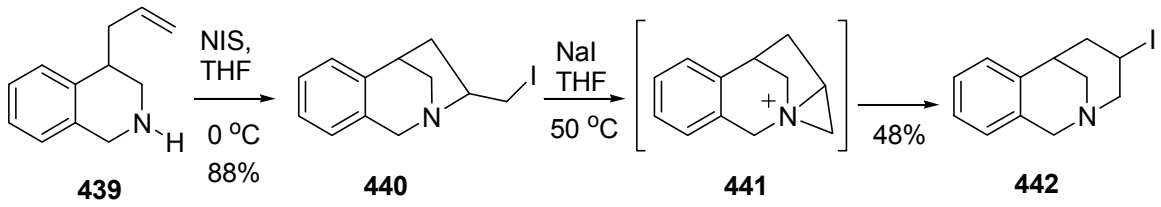
Scheme 99. Another nucleophilic aziridinium ion opening.



436 **437** **438**

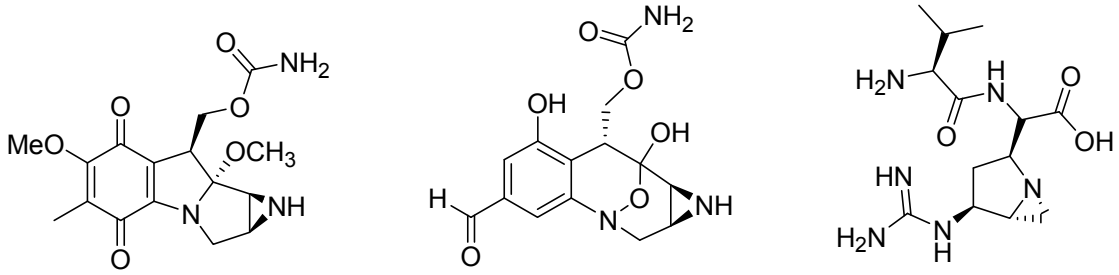
Additionally, starting from the tetrahydroisoquinoline **439**, Blough and coworkers isolated the kinetic product of intramolecular iodoamination, iodide **440** (Scheme 100).[136b] Resubjection of the iodide **440** to NaI and heat provided the thermodynamic product, the azabicyclo[3.3.1]octane **442**. Presumably, the transformation from iodide **440** to **442** proceeds via the bridgehead aziridinium ion **441**.

Scheme 100. Synthesis of a piperidine ring via a bridgehead aziridinium ion.



In fact, several natural products with potent biological activity contain aziridines,[140] such as the mitomycins (**443**),[141a-c] FR-900482 (**444**)[141d,e] and ficellomycin (**445**)[141f] (Figure 13). The biological activity is due, in part, to the reactive aziridine functionality.

Figure 13. Natural products containing aziridines.



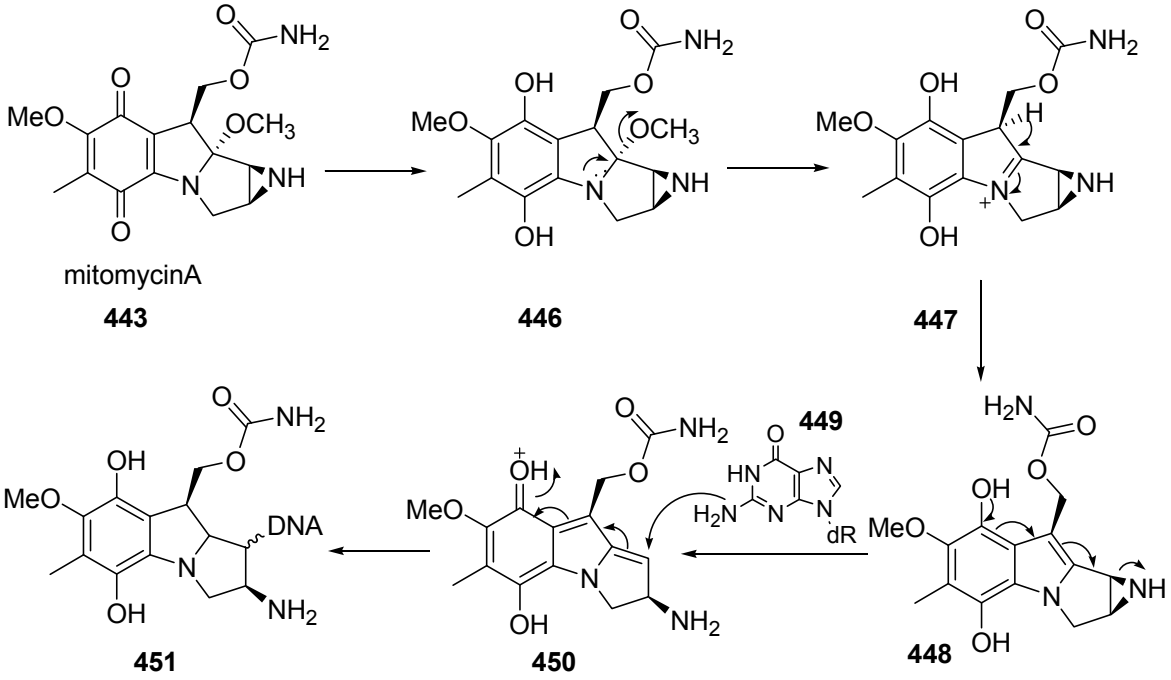
mitomycin A **443**

FR-900482 **444**

ficellomycin **445**

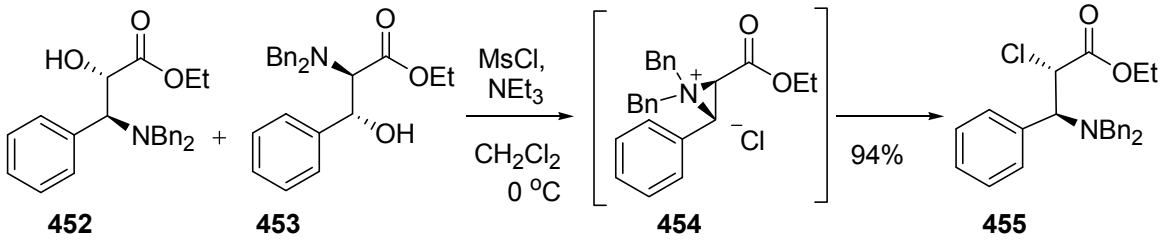
It has been demonstrated that the mitomycins and FR-900482 derive their antitumor properties via cross-linking DNA. Structure-activity relationships have identified the aziridine ring as being essential for this antitumor activity (Scheme 101).[141c,e] It is believed that isomerization, followed by aziridine ring opening generates an intermediate **450** with an electrophilic site that a DNA base **449** can attack, thus cross-linking the DNA strand.[141c,e]

Scheme 101. Aziridine ring opening of mitomycin cross-links DNA.



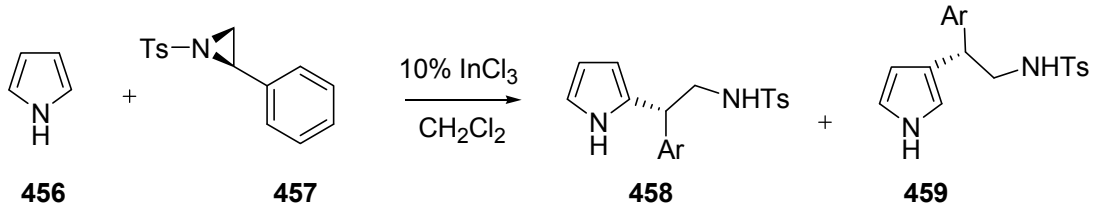
As a consequence of the inherent ring strain present in aziridines, ring-opening reactions are a dominant feature of their chemistry.[139] In this respect, aziridines can be divided into two groups. The first group, or "nonactivated" aziridines have either an alkyl or aryl group on the basic aziridine nitrogen. Ring-opening reactions with nonactivated aziridines usually only take place after protonation or quaternization. For example, Sharpless has recently described the ring opening of a "nonactivated" glycidic ester-derived aziridinium ion **454**, which was derived from a mixture of the aminoalcohols **452** and **453**, to furnish the chloroamine **455** (Scheme 102).[142a-c]

Scheme 102. Regioselective ring opening of "nonactivated" aziridinium ions.



The second group, or “activated” aziridines, has an electron withdrawing group on the aziridine nitrogen such as a carbonyl or sulfonyl group. These substituents help to stabilize a negative charge that may develop on the nitrogen atom in the transition state for ring opening by a nucleophile. Nucleophilic attack typically occurs via an S_N2-like mechanism with inversion. For instance, Yadov has reported the ring opening of the styrene-derived *N*-sulfonyl aziridine **457** by pyrrole (**456**), to afford a mixture of the 2- and 3- substituted pyrroles **458** and **459**. Importantly, ring opening occurred exclusively at the benzylic position (Scheme 103).[138b,c]

Scheme 103. Ring openings of "activated" aziridines by pyrrole.

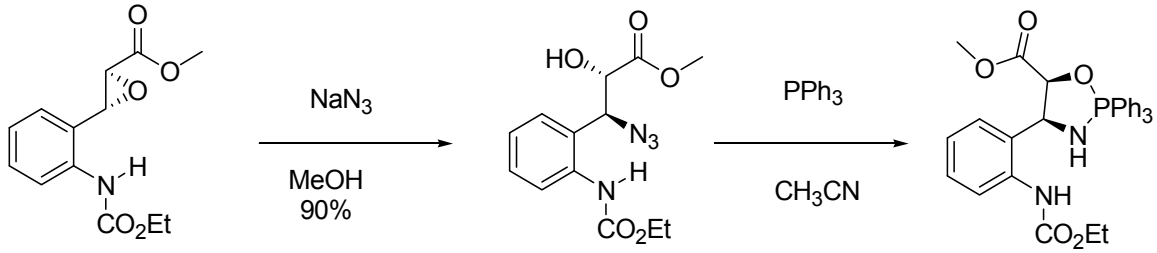


With the above precedents in mind, we were confident that we could make the desired aziridine **414**. However, this route is predicated on the idea that we could generate an aza-*ortho*-xylylene from an “unactivated” aziridine. We therefore decided to quickly investigate a model system to find suitable conditions to generate the necessary aza-*ortho*-xylylene.

B. Investigation of a model aziridine system. Acid-catalyzed ring opening of aziridines to generate aza-*ortho*-xylylenes

The first strategy we explored to make the aziridine was via a 1,2-azidoalcohol.[139e,f] Thus, ring opening of the epoxide **460** with sodium azide provided the azidoalcohol **461**. Treatment of the azide with triphenylphosphine provided the oxaphospholine, but we were unable to isolate any of the aziridine (Scheme 104).

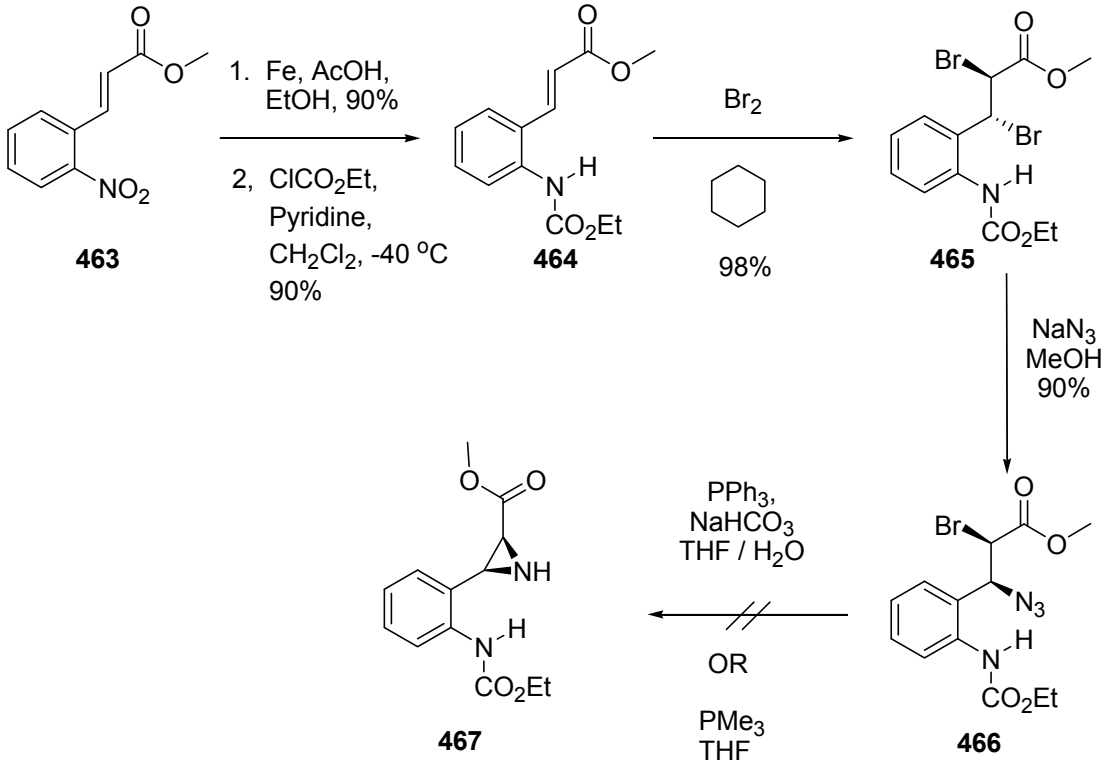
Scheme 104. Attempted synthesis of the azirdine from an azidoalcohol.



460 **461** **462**

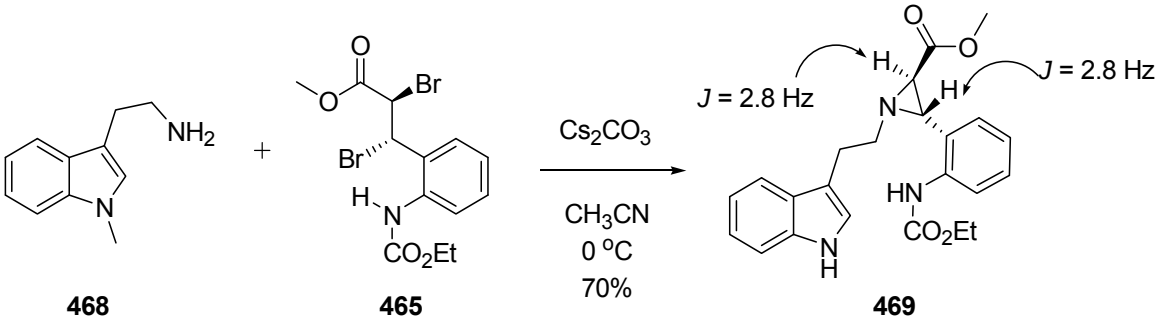
Alternately, starting from the readily available methyl 2-nitrocinnamate (**463**), we reduced the nitro group to the aniline and *N*-acylated to provide the carbamate **464**. Bromination in cyclohexane provided the dibromide **465** cleanly (Scheme 105). Subsequent treatment with sodium azide provided the 1,2-azidobromide **466**, but subjection to triphenylphosphine provided an inseparable mixture of products. On the other hand, the more reactive trimethylphosphine provided the alkene **464**.

Scheme 105. Attempted synthesis of the azirdine from an azidohalide.



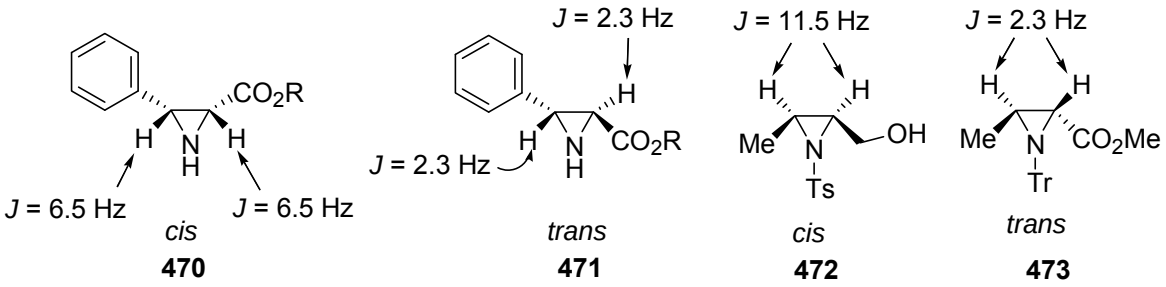
In a more direct approach, we modified the procedure of Prati[143a] and attempted an alkylation of 1-methyltryptamine (**468**) with the dibromide **465** to arrive at the *trans* aziridine **469** efficiently (Scheme 106).

Scheme 106. Aziridine formation via an amine alkylation.



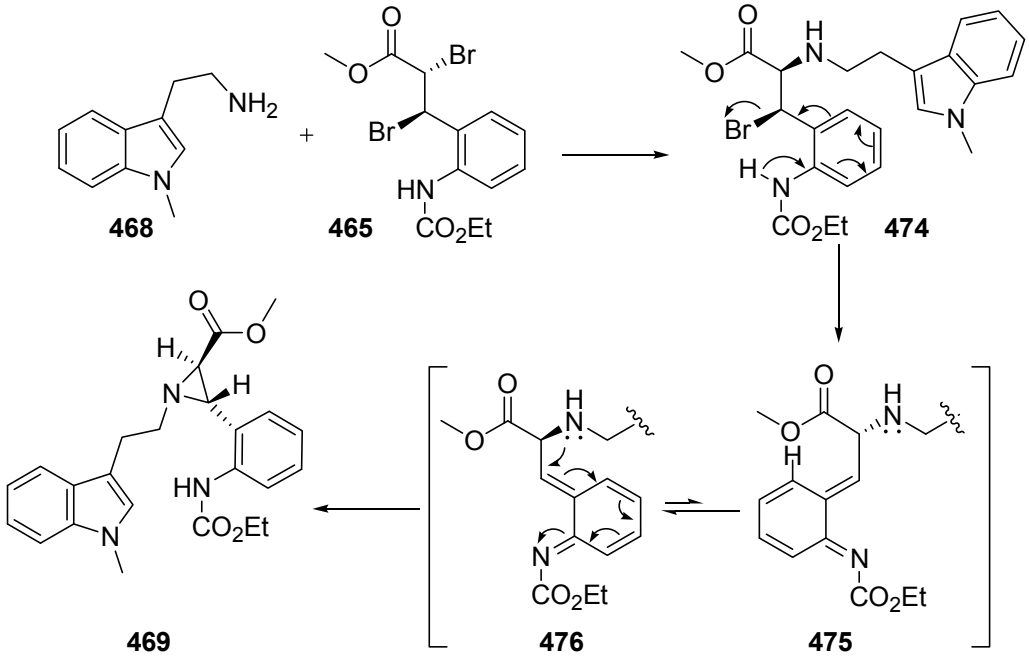
The stereochemistry of the aziridine was assigned as *trans* by comparing the coupling constants of the aziridine protons to published coupling constants of other *cis*- (**470**,[139l] **472**[144]) and *trans*- aziridines (**471**,[139l] **473**[144]) (Figure 14).

Figure 14. Coupling constants of other *cis*- and *trans*- aziridines.



The stereochemical outcome of this reaction cannot be explained by sequential S_N2 displacement reactions because the *cis* aziridine would be expected. Instead, a possible mechanism for this transformation involves alkylation of the tryptamine **468** with the dibromide **465** to provide the α amino ester **474** (Scheme 107). Subsequent aza-*ortho*-xylyene generation would provide intermediate **476** which could undergo internal conjugate addition to the aza-*ortho*-xylylene to provide the *trans* aziridine. The alternate conformation **475**, which would provide the *cis* aziridine, is most likely disfavored due to a *peri* interaction between the ester substituent and the proximal aromatic proton.

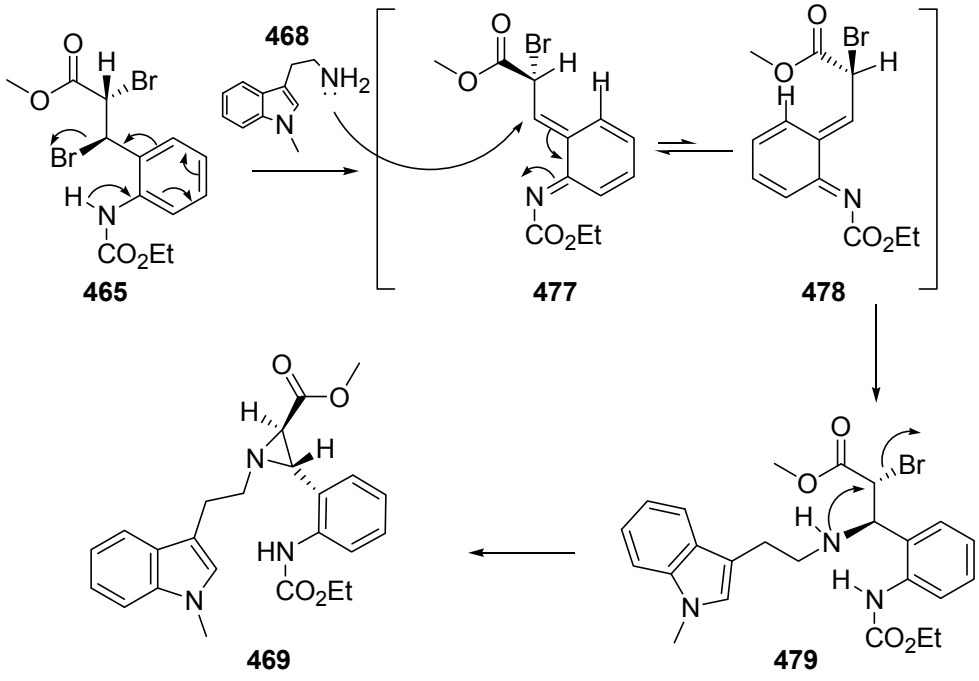
Scheme 107. A possible mechanism for aziridine formation.



Further experimental evidence for this mechanism was obtained when the ethyl carbamate substituent of **354** was replaced with an azide, and the analogous dibromide derivative was subjected to identical conditions and only the α-haloenone derivative was obtained.

However, another mechanistic possibility wherein aza-*ortho*-xylylene **477** is generated in the first step, followed by conjugate addition of the tryptamine **468** opposite to the bromine with subsequent internal S_N2 displacement can also account for the exclusive isolation of the *trans* aziridine. This pathway could be rationalized by invoking Felkin-Ahn overlap between the $\sigma^*_{C\text{-}Br}$ and π^*. In this case, the alternative aza-*ortho*-xylylene **478** would also be disfavored due to a *peri* interaction between the ester subtituent and the proximal aromatic proton (Scheme 108).

Scheme 108. An altenative mechanism for aziridine formation.



Next, we investigated triggering the aziridine in order to generate the aza-*ortho*-xylylene. Initially, we attempted to form the aziridinium ion with methyl

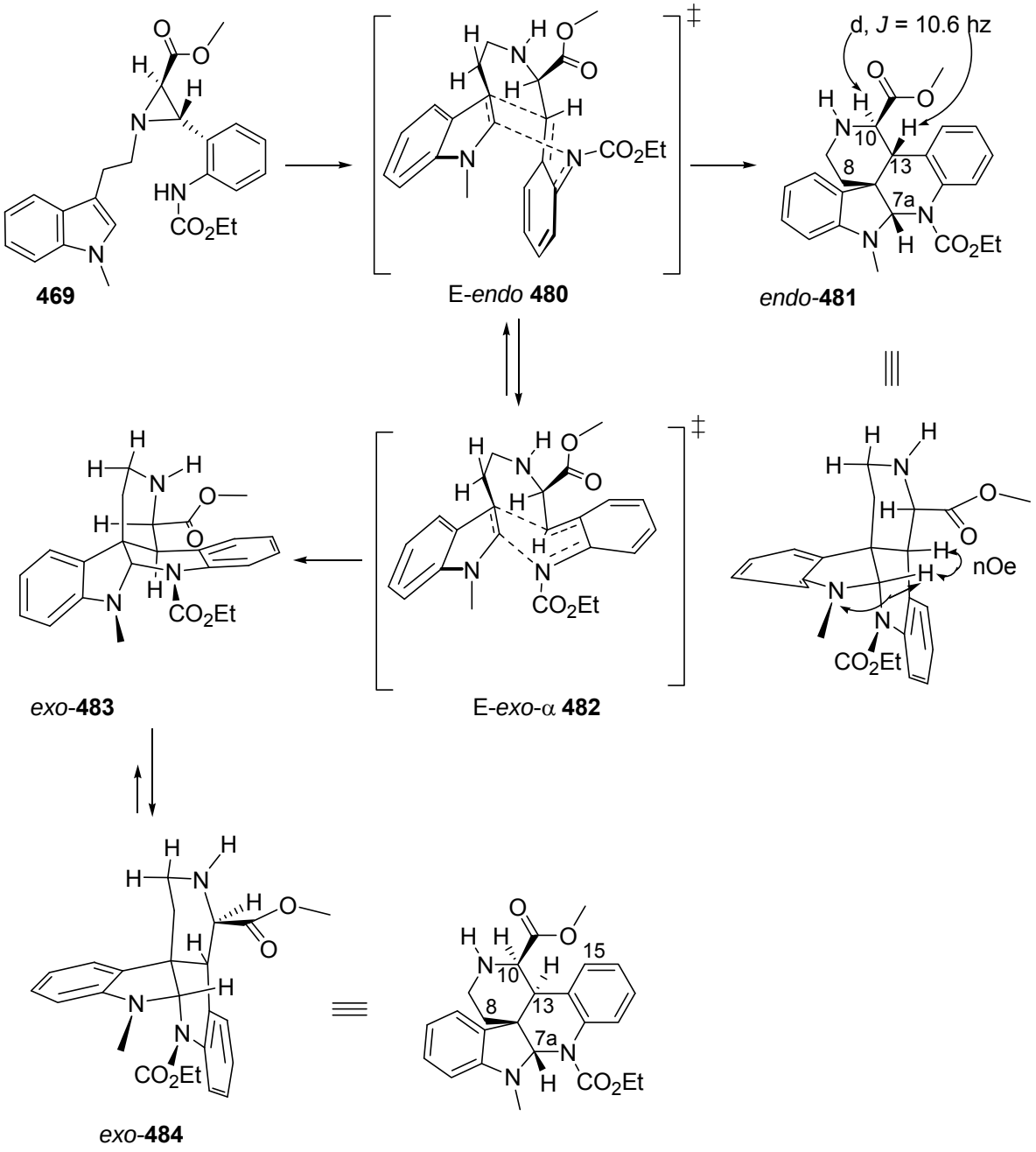
iodide or pyridinium tosylate (PPTS) in benzene at low temperature, but we only recovered unreacted starting material (Table 3). However, treatment of the

Table 3. Attempted conditions for triggering aziridine.

Attempted conditions for aza-*o*-xylylene generation
1. CH_3I, Et_2O, 0 ^oC, NR
2. toluene, 110 ^oC, decomposition
3. PPTS, benzene, 10 ^oC, decomposition
4. CSA, CH_3CN, rt, 20 %
5. PPTS, CH_2Cl_2, rt, 50%
6. $HN(SO_2CF_3)_2$, CH_3CN, 0 ^oC, 70%

aziridine **469** with PPTS at room temperature overnight provided a compound that we assigned to be cycloadduct **481**, presumably via the (*E*)-aza-*ortho*-xylylene **480** (Scheme 109). Conformational analysis predicted that if we isolated **481**, we should observe a large *trans* coupling constant between the C(10) and C(13) protons. The alternative products, *exo*-**483** and *exo*-**484**, would be expected to have a much smaller coupling constant between the C(10) and C(13) protons because the dihedral angle is much smaller. It was predicted that the *exo* product would prefer to exist in the ring-flipped conformer, *exo*-**484** to minimize a possible *peri* interaction between the ester substituent and the C(15) aromatic proton. Subsequently, we were able to optimize the yield for the cycloadduct by employing a more acidic catalyst (pKa ≈ 1.7),[145ab] that also possesses a non-nucleophilic counter ion bis(trifluoromethyl)sulfonyl)imide ($HNTf_2$).[145]

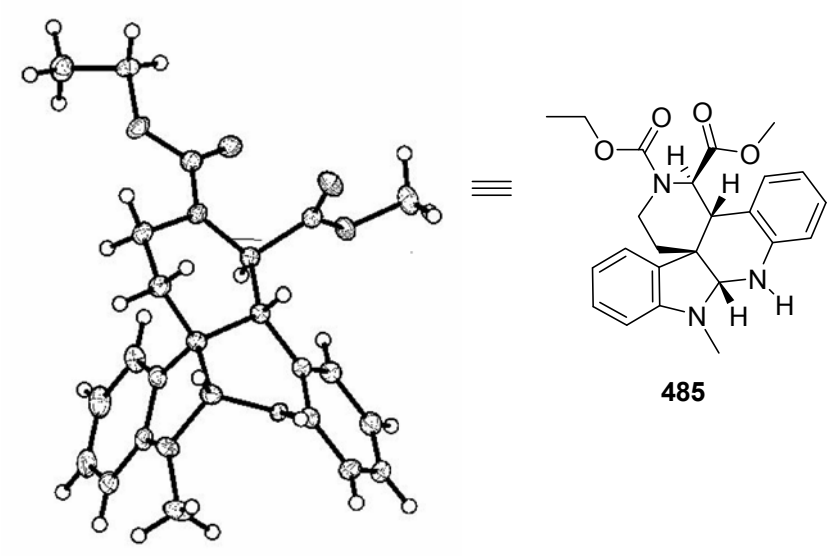
Scheme 109. Conformational analysis leading to a cycloadduct.



The stereochemistry of the cycloadduct thus obtained was confirmed by nOe studies. As shown above, the C(7a) aminal proton exhibited an nOe with the C(13) methine proton, as well as the C(8) methylene protons and the *N*-methyl. Moreover, we observed a large coupling constant between the C(10)

and C(13) protons, (d, *J* = 10.6 Hz). An X-ray crystal structure also proved to be very informative (Figure 15). Surprisingly, the X-ray crystal structure revealed that the ethyl carbamate had migrated to the piperidine nitrogen during the cycloaddition to provide the cycloadduct **485**.

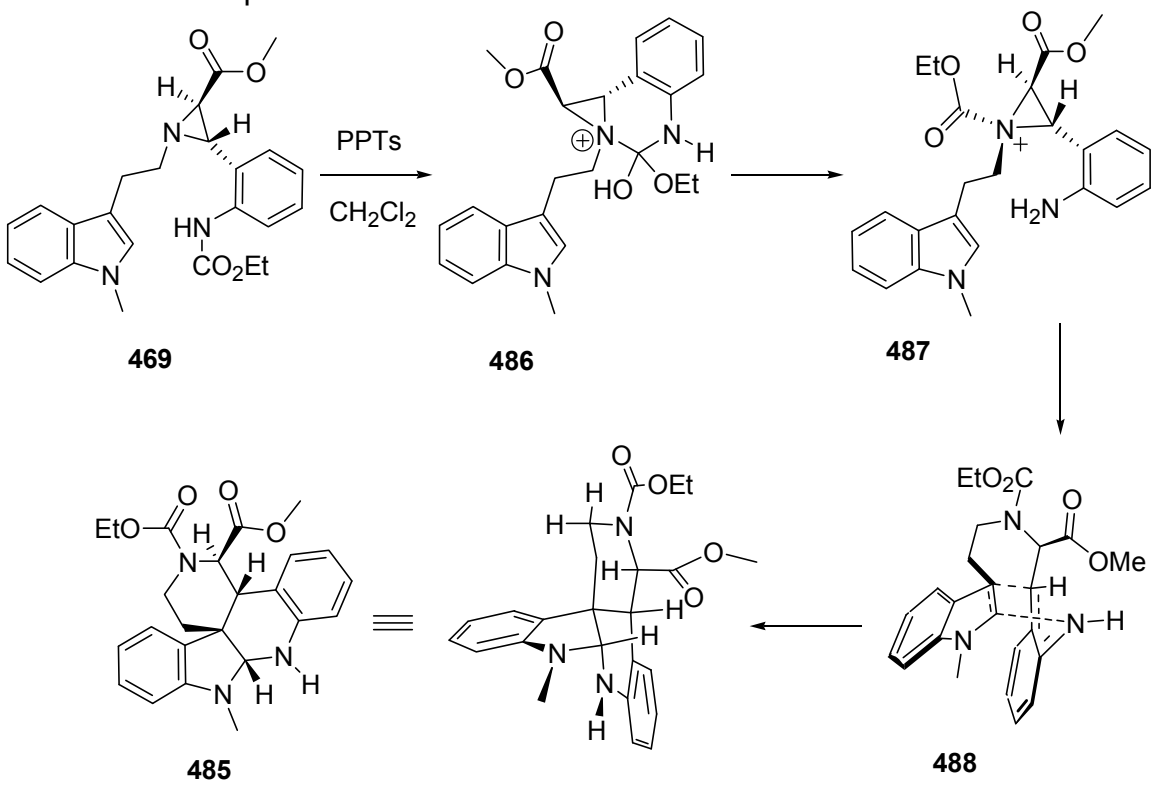
Figure 15. X-ray crystal structure of the cycloadduct.



485

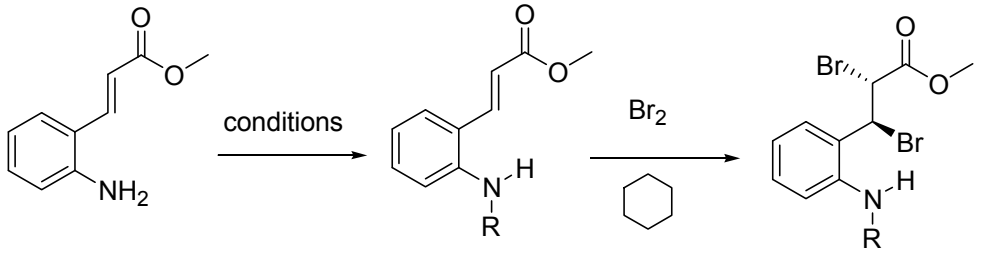
A possible mechanism for this transformation involves the aziridine nitrogen attacking the protonated carbamate to arrive at intermediate **486**. Acyl transfer generates an acylaziridinium ion that subsequently ring opens to afford the aza-*ortho*-xylylene **488**. A concomitant stereoselective cycloaddition then provides **485** (Scheme 110).

Scheme 110. A possible mechanism for the aziridine ring opening / cycloaddition sequence.



Next, we investigated *N*-acyl substituents for the aniline **489** in order to determine the scope of the proposed *N*-acyl aziridinium route to aza-*ortho*-xylylenes. Thus, the aniline **489** was acylated to provide the carbamates **490-496** (Scheme 111).[146] Subsequent bromination as before provided the bromides **497-503**.

Scheme 111. Synthesis of various dibromides.

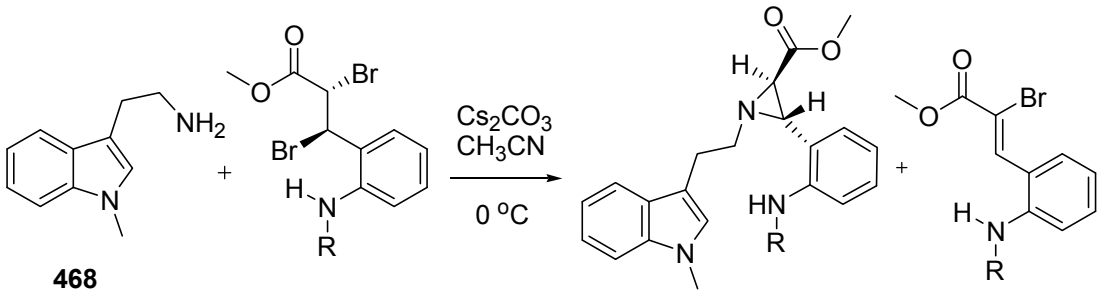


489 **490-496** **497-503**

	aniline acylation conditions	bromination yield	
490 R = $COCF_3$	$(CF_3CO)_2O$, NEt_3, CH_2Cl_2, 0 °C, 73%	99%	**497**
491 R = CO_2CH_3	$ClCO_2Me$, pyridine, -40 °C, 85%	95%	**498**
492 R = CO_2Bn	$ClCO_2Bn$, pyridine, -40 °C, 98%	95%	**499**
493 R = CO_2p-NO_2Bn	$ClCO_2p$-NO_2Bn, pyridine, -40 °C, 90%	99%	**500**
494 R = CHO	Ac_2O, formic acid, CH_2Cl_2, 5 °C, 75%	95%	**501**
495 R = TROC	$ClCO_2CH_2CCl_3$, pyridine, -40 °C, 85%	95%	**502**
496 R = TEOC	phosgene, 2-(trimethylsilyl)ethanol, pyridine CH_2Cl_2, -78 °C, 90%	91%	**503**

Aziridine formation as before with 1-methyltryptamine (**468**) provided aziridines **504-510**. The isolated yields of some of the aziridines were low due to competing formation of the corresponding α-haloenones **511**. Extended reaction times, or the use of other bases ($NaHCO_3$, DIPEA, NEt_3, K_2CO_3) failed to increase these yields (Scheme 112).

Scheme 112. Aziridine formation with different protecting groups.

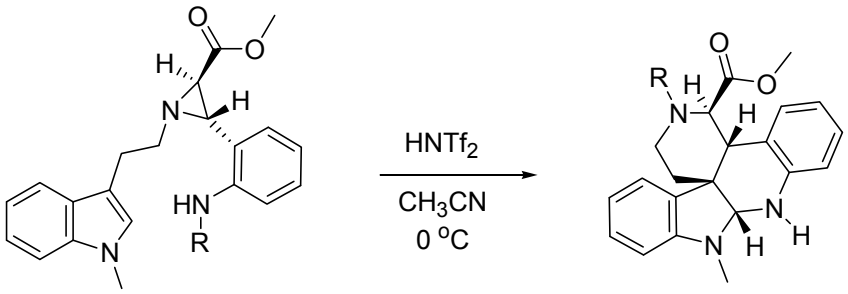


468

497 R = $COCF_3$	**504** R = $COCF_3$	40%	**511**
498 R = CO_2CH_3	**505** R = CO_2CH_3	70%	
499 R = CO_2Bn	**506** R = CO_2Bn	55%	
500 R = CO_2p-NO_2Bn	**507** R = CO_2p-NO_2Bn	50%	
501 R = CHO	**508** R = CHO	51%	
502 R = TROC	**509** R = TROC	40%	
503 R = TEOC	**510** R = TEOC	65%	

Interestingly, not all of the aziridines participated in the acyl transfer/ring-opening/cycloaddition transformation. Both the trifluoroacetamide **504** and the *N*-TEOC carbamate **510** provided unreacted starting material upon subjection to either PPTS or $HNTf_2$ in acetonitrile. However, compounds **505**-**509** provided the cycloadducts **512-516** in moderate yields (Scheme 113).

Scheme 113. Cycloaddition of different aziridines.

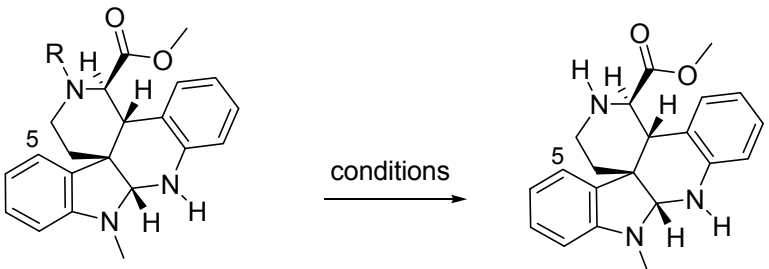


504 R = $COCF_3$
505 R = CO_2CH_3
506 R = CO_2Bn
507 R = CO_2*p*-NO_2Bn
508 R = CHO
509 R = TROC
510 R = TEOC

No Reaction
512 R = CO_2CH_3 68%
513 R = CO_2Bn 52%
514 R = CO_2*p*-NO_2Bn 55%
515 R = CHO 62%
516 R = TROC 30%
No Reaction

With cycloadducts **485** and **512-516** in hand, we next attempted to deprotect the piperidine nitrogen, which is necessary in order to perform the alkene-amine cyclization as discussed in the retrosynthetic analysis. However, deprotection required extensive optimization. Hydroxide-mediated hydrolysis of the ethyl carbamate **485**,[147] methyl carbamate **512**,[148] or formamide[149a] **515** provided either decomposition products or saponification of the methyl ester moiety. Additionally, transfer hydrogenation conditions[150] on **513** provided unreacted starting material. Subsequently, we discovered that treatment of the formamide **515** with HCl generated *in situ*[149b,c] cleanly provided the secondary amine **517** (Scheme 114).

Scheme 114. Deprotection of the piperidine nitrogen.



485, **513-515** **517**

	deprotection conditions	result
485 R = $CO_2CH_2CH_3$	1. KOH, MeOH / THF, 0 °C	ester saponification
	2. KOH, $HOCH_2CH_2OH$, NH_2NH_2, 40 °C	decomposition
	3. $Ba(OH)_2$, MeOH / H_2O, 80 °C	decomposition
512 R = CO_2CH_3	1. $HN(TMS)_2$, I_2, CH_2Cl_2	decomposition
	2. TMSI, $CDCl_3$	decomposition
	3. MeOH, K_2CO_3	No Reaction
513 R = CO_2Bn	1. Et_3SiH, $Pd(OAc)_2$, NEt_3, CH_2Cl_2	No Reaction
	2. $Pd(OH)_2$, H_2, MeOH	No Reaction
	3. Pd/C, NH_4CO_2H, Pd/C, MeOH	No Reaction
514 R = CO_2*p*-NO_2Bn	1. $Na_2S_2O_3$, NaOH, H_2O / CH_3CN	No Reaction
	2. Zn, $KHPO_4$, H_2O / THF	35%
515 R = CHO	1. Cs_2CO_3, MeOH, 0 °C	decomposition
	2. NaOMe, MeOH	decomposition
	3. AcCl, MeOH, THF, 0 °C	70%

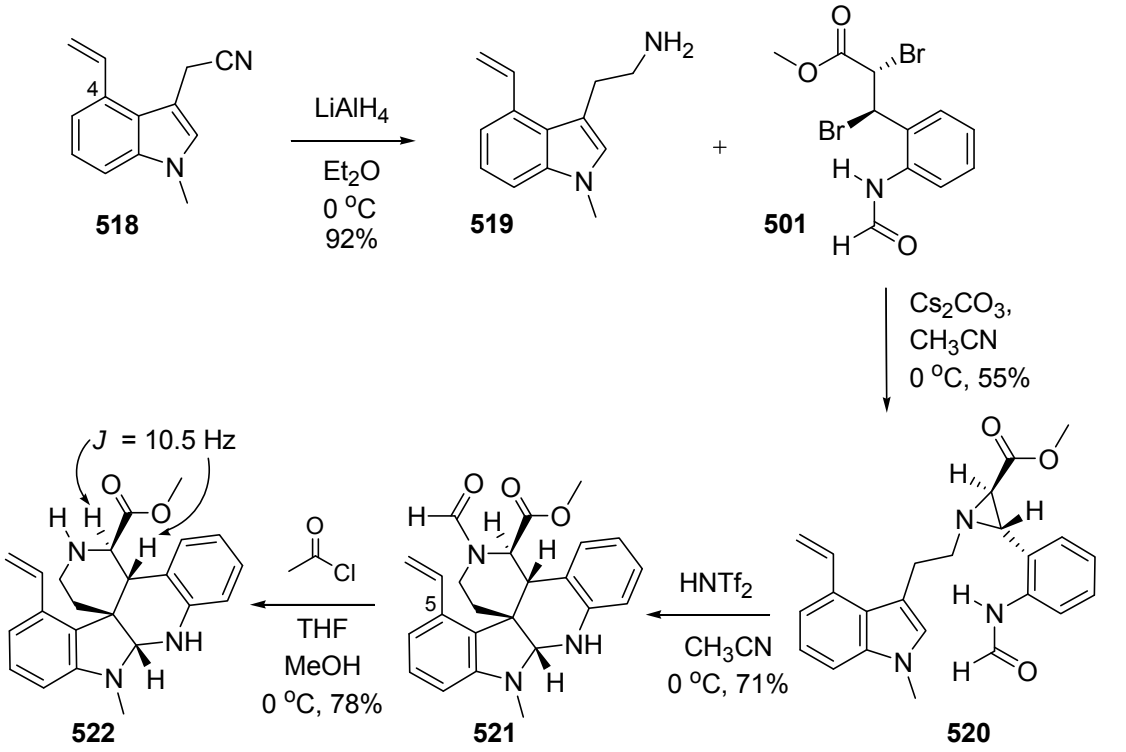
C. Intramolecular cycloaddition with a C(5) substituent

1. Investigation of a potential C(5) vinyl substituent

Now that we had demonstrated that we could deprotect the piperidine nitrogen, we directed our attention to the introduction of a substituent on the C(4) position of the tryptamine that could eventually be used to elaborate the benzazepine ring. Thus, the nitrile **518** (the preparation of which was discussed in Chapter 2) was reduced to the tryptamine **519** (Scheme 115). Formation of the aziridine **520** with the bromide **501**, followed by treatment with $HNTf_2$ provided a cycloadduct that we tentatively assigned to have the stereochemistry shown in **521**. Removal of the formamide was necessary to provide the secondary amine **522** which now had acceptable dispersion of the resonances in

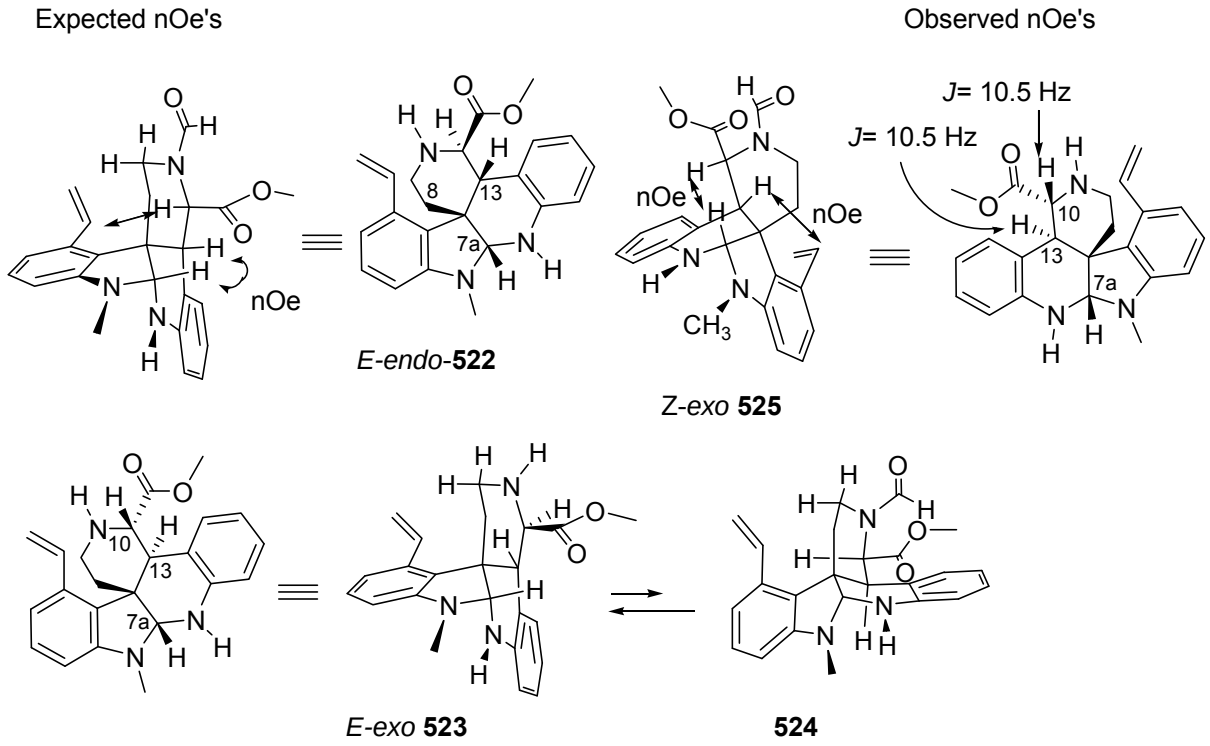
its ^{1}H NMR spectrum for an nOe experiment. The tentative stereochemical assignment was based upon the observation of another large coupling constant (d, *J* = 10.5 Hz) between the C(10) and C(13) protons that we had observed in the analogous *des*-vinyl cycloadduct **485**.

Scheme 115. Cycloaddition with a C(5) vinyl substituent.



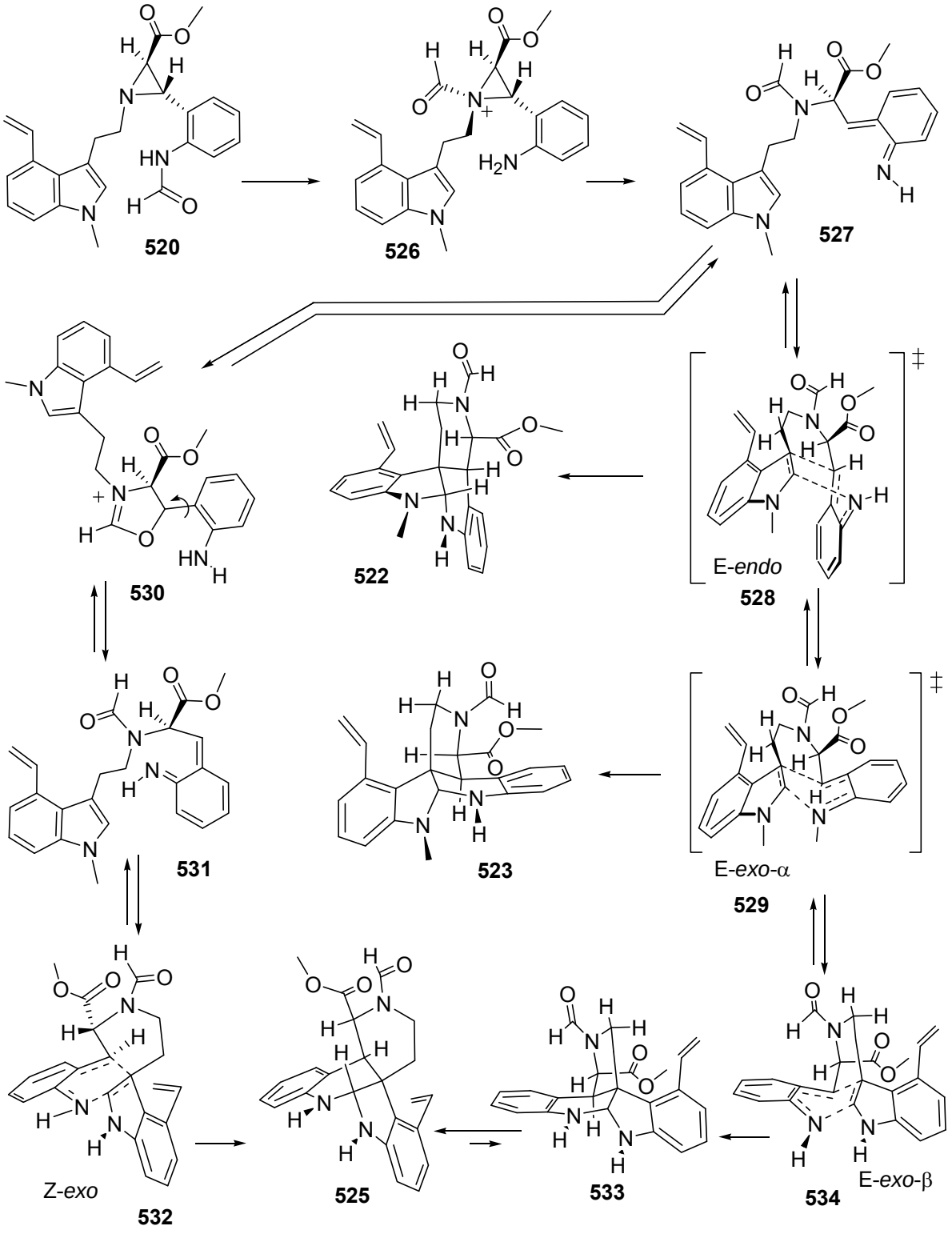
Unfortunately, the observed nOe's were inconsistent with the proposed structure *endo*-**522**. As shown below (Figure 16), although we still observed a large coupling constant between the protons on C(13) and C(10), we did not observe the diagnostic nOe between the C(7a) aminal proton and the C(13) methine proton. Additionally, we did not observe an nOe between H(10) and the vinylic protons. The observation of the large coupling constant for C(13) and C(10) ruled out the E-*exo* isomer **523** or the ring flipped conformer **524**. However, we did observe a nOe between H(13) and the vinylic proton, as well as a nOe between H(10) and H(7a) , which was conceivable in a structure such as *Z-exo* **525**.

Figure 16. Explanation of cycloadduct stereochemistry.



This proposal led us to analyze the transition states leading to the above structures. As shown below, aziridinium ion formation generates the aza-*ortho*-xylylene **527** as discussed previously (Scheme 116). However, the *E*-aza-*ortho*-xylylene leading to *E-endo* transition state **528** or the *E-exo*-α transition state **529** should be disfavored due to nonbonding interactions between the vinylic proton and the protons flanking the piperidine nitrogen. A situation such as this could force the formamide to close onto the aza-*ortho*-xylylene to generate intermediate **530**. Subsequent bond rotation could then allow the formation of *Z*-aza-*ortho*-xylylene **531**, with concomitant cyclization via the *Z-exo* transition state **532** to provide **525**. However, an alternative pathway proceeding via the *E-exo*-β transition state **534** that could also provide **525** cannot be ruled out.

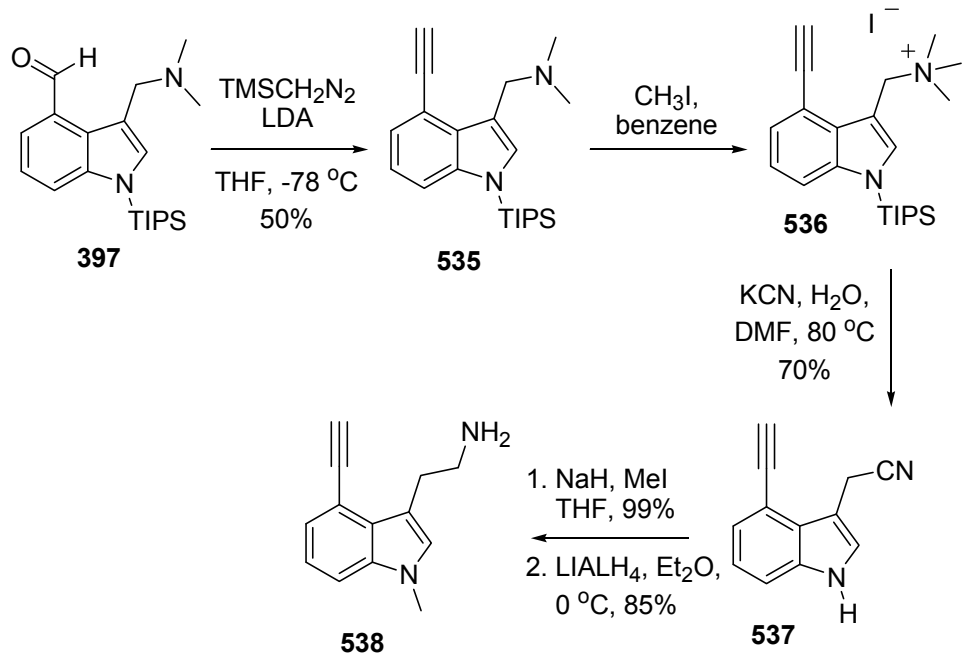
Scheme 116. Transition state analysis to explain the isolation of a *Z-exo* cycloadduct.



2. Investigation of a potential C(5) alkynyl substituent

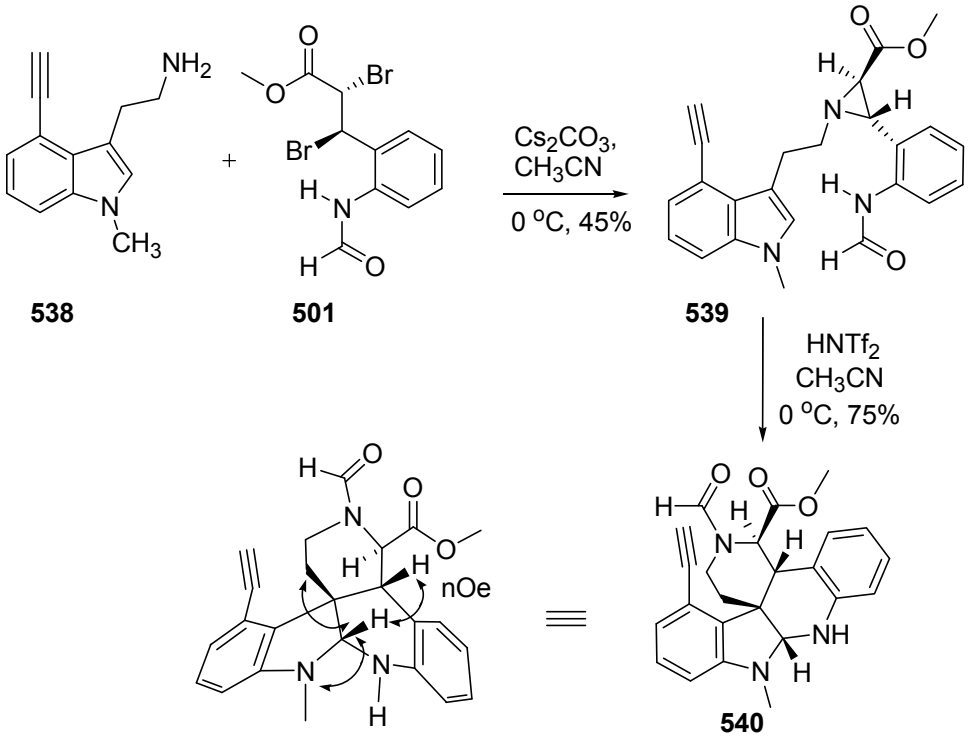
Thus, we expected that a small and linear group, such as an alkyne might be able to fit in between the protons flanking the piperidine nitrogen, which might help to favor the *endo* transition state over the *exo* transition state. To that end, aldehyde **397** was converted to the alkyne[151] **535** in one pot. Conversion of the tertiary amine to the quaternary salt, and displacement by cyanide with concomitant desilylation provided the indole **537** (Scheme 117). Subsequent *N*-methylation of the indole, followed by reduction of the nitrile provided the tryptamine **538**.

Scheme 117. Synthesis of an alkynyl substituted tryptamine.



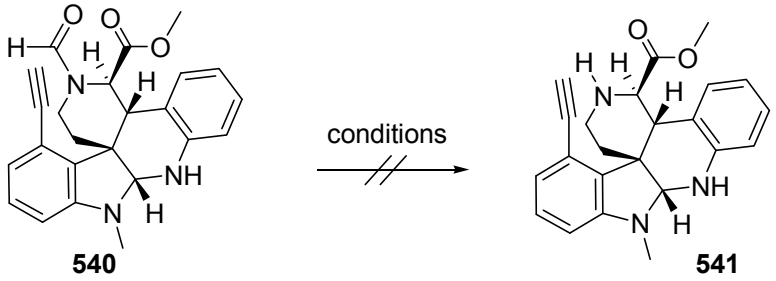
Aziridine **539** was then made from the tryptamine **538** and the dibromide **501** in the usual way (Scheme 118). Subsequent treatment of the aziridine with $HNTf_2$ provided the cycloadduct **540** uneventfully. The stereochemistry of the cycloadduct thus obtained was confirmed by n.O.e. studies, and we were pleased to discover that we had isolated the desired *endo* diastereomer after observing analogous diagnostic nOe's as with the model system **485**.

Scheme 118. Synthesis of the formamide protected alkynyl cycloadduct.



Our efforts now focused on the deprotection of the formamide **540**. Nonetheless, despite repeated attempts, both acidic and basic conditions provided an inseparable mixture of products (Scheme 119).

Scheme 119. Attempted deformylation of the cycloadduct.



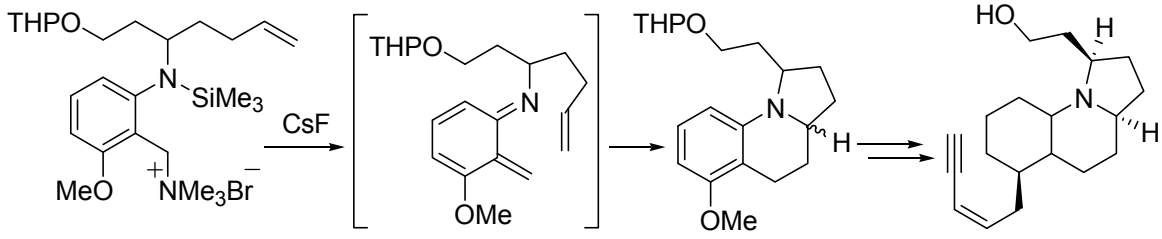
Attempted deformylation conditions

1. AcCl, THF / MeOH, 0 °C, NR
2. NaOH, MeOH, 50 °C, decomposition
3. $KHCO_3$, MeOH, H_2O, 0 °C, NR
4. KOH, THF / MeOH, 0 °C, decomposition
5. LiOH, THF / H_2O, 0 °C, decomposition
6. NaOH, EtOH / H_2O, 55 °C, decomposition
7. NH_2NH_2, EtOH / H_2O, 70 °C, NR
8. H_2O_2, H_2O, 80 °C, decomposition

D. Base-catalyzed decarboxylative generation of aza-*ortho*-xylylenes via ring opening of aziridines

In view of the success we had with the acid-catalyzed generation of aza-*ortho*-xylylenes via ring opening of aziridines, our attention now turned towards the investigation of a base-mediated decarboxylative generation of aza-*ortho*-xylylenes via ring opening of aziridines. The feasibility of this strategy was precedented, in part, by the method of Saegusa, who used fluoride to desilylate the aniline **542** with concomitant elimination of the quaternary ammonium salt to generate the aza-*ortho*-xylylene **543** in his studies of gephyrotoxin (**545**) (Scheme 120).[152]

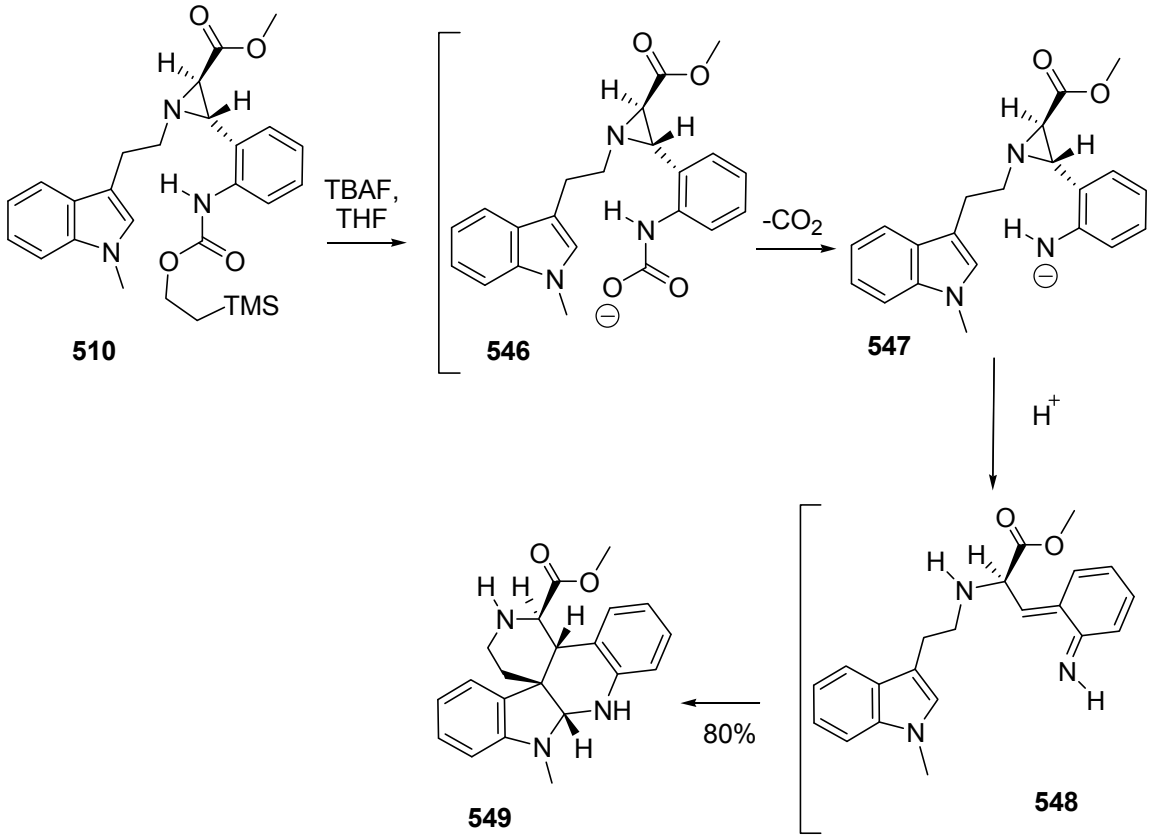
Scheme 120. An example of base-induced generation of aza-*ortho*-xylyene.



542 **543** **544** **545**

We decided to investigate a model system in order to evaluate our proposed method for base-mediated decarboxylative generation of aza-*ortho*-xylylenes. To that end, the previously made aziridine **510** was treated with TBAF to cleanly provide the desired deprotected *endo* cycloadduct **549** in one step (Scheme 121).

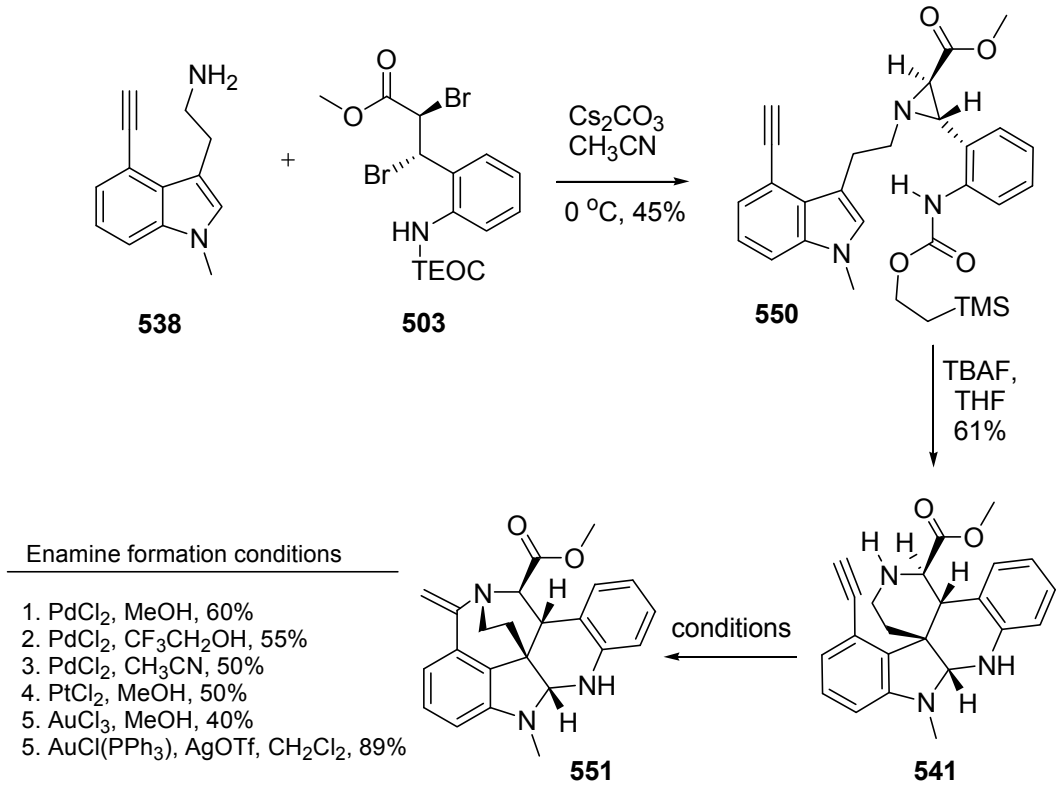
Scheme 121. A model system for base generation of an aza-*ortho*-xylylene.



A possible mechanism for this transformation involves desilylation to trigger decarboxylation of the (trimethylsilyl)ethoxycarbonyl group to afford a carboxylate **546**, which decomposes to a deprotonated aniline **547**. Generation of the aza-*ortho*-xylylene **548**, followed by cycloaddition provides the cycloadduct **549**.

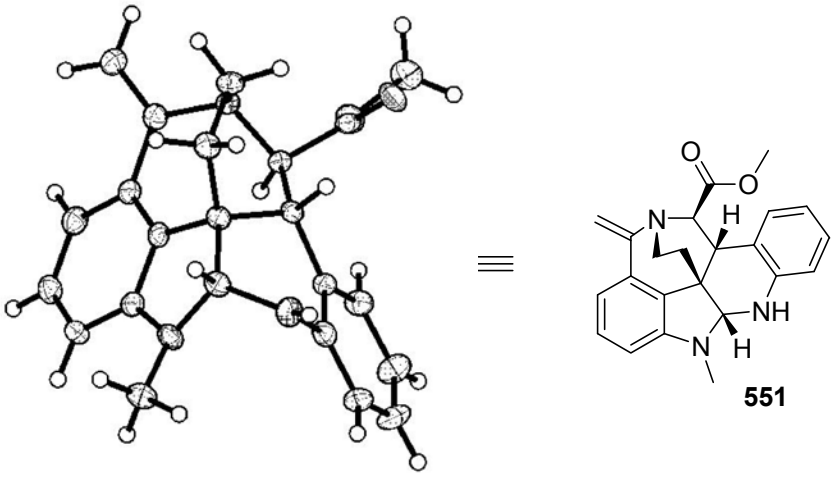
Next, the aziridine **550** was made from the tryptamine **538** and the dibromide **503** using the standard conditions (Scheme 122). Treatment of the aziridine furnished the desired *endo* cycloadduct **541** cleanly. However, slow transformation to an unidentified product was observed, even with storage at -20 ^{o}C. Thus, the alkyne was treated with various transition metal catalysts, in hopes

Scheme 122. Synthesis of the deprotected cycloadduct.



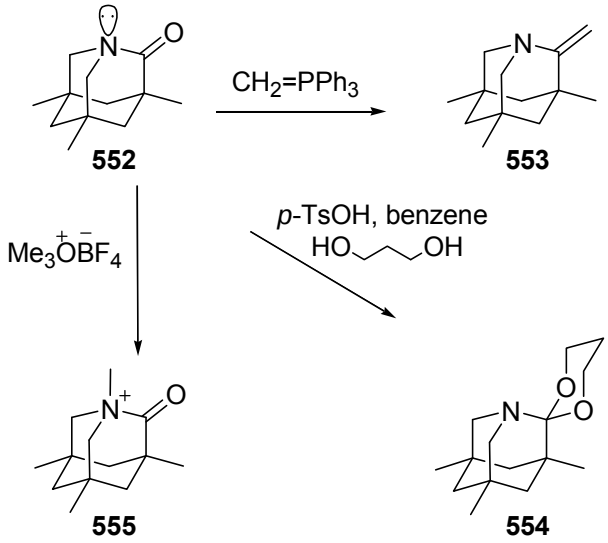
of effecting an intramolecular 7-*exo*-dig closure. We were pleased to discover that treatment of the alkyne **541** with gold or palladium catalysts[153] provided the bridgehead enamine[154] **551** efficiently. Close examination of the spectra of **541** showed that the unidentified product was in fact enamine **551**, indicating that the intramolecular 7-*exo*-dig closure proceeded spontaneously, albeit slowly, at room temperature. This spontaneous transformation clearly reflects the highly encumbered environment around the C(5) ethynyl substituent. Treatment of the cycloadduct **541** with base (NaOH or KOH in methanol) also effected the 7-*exo*-dig closure, although not as cleanly (~40%). Importantly, the stereochemistry of the enamine **551** was secured via X-ray crystal structural analysis (Figure 17).

Figure 17. X-ray crystal structure of the enamine.



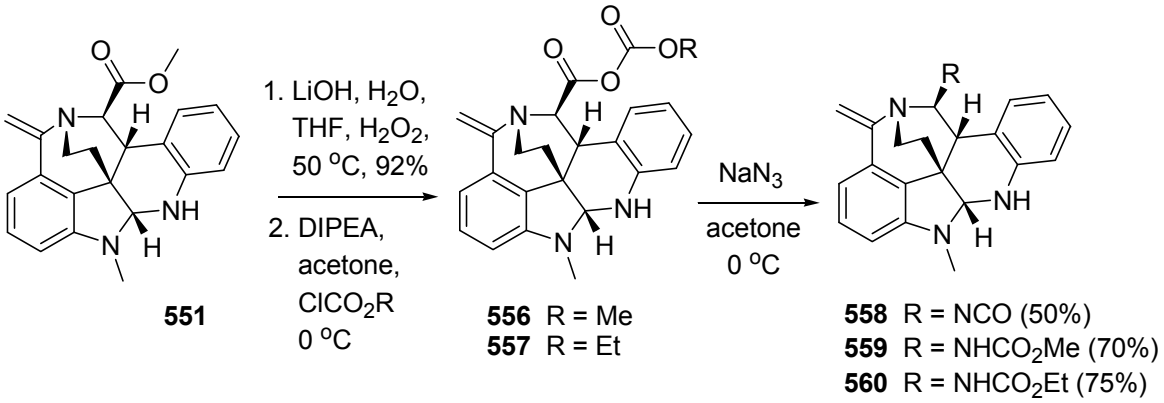
Not surprisingly, the bridgehead enamine **551** exhibited properties and stability similar to an alkene. The overlap of the lone pair on the nitrogen atom with the π system of the alkene group is prevented by the rigid structure of the hexacyclic system. A "twisted" amide was recently published by Kirby and co-workers in which the 1-aza-2-adamantanone **552** exhibited the properties and stability of a ketone.[155] For instance, it could be converted to the bridgehead "enamine" **553**, acetal **554**, or the quaternary salt **555** (Scheme 123).

Scheme 123. Reactions of a "twisted amide".



We next investigated the elaboration of the pyrrolidine ring via the rhodium-mediated C-H insertion discussed previously in the retrosynthetic analysis. To that end, the ester moiety of enamine **551** was hydrolyzed[156] and converted to the mixed anhydrides **556** or **557** (Scheme 124). Subsequent treatment of the anhydrides with sodium azide effected Curtius rearrangement to provide the isocyanate **558**. Alternatively, if the reaction was stirred longer, the carbamates **559** and **560**, respectively, could be isolated.

Scheme 124. Aminal formation from the bridgehead enamine.



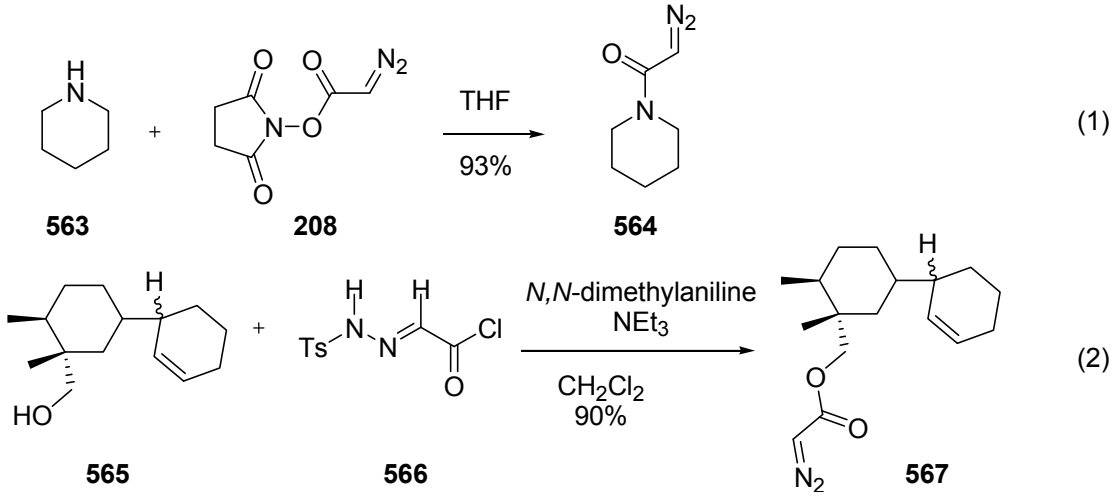
551

556 R = Me
557 R = Et

558 R = NCO (50%)
559 R = $NHCO_2Me$ (70%)
560 R = $NHCO_2Et$ (75%)

However, in order to evaluate the possibility of the unprecedented diazoacetylation of the carbamate, a model system was first investigated. Thus, cyclohexylamine was converted to the nosylamide- and methyl carbamate-derivatives (**561** and **562** respectively). We hoped that we could follow the example of Badet and coworkers, who reported the diazoacetylation of piperidine (**563**) using succinimidyl diazoacetate (**208**) (eq 1, Scheme 125).[87] Alternately, we could use Corey's conditions, wherein the alcohol **565** was treated with glyoxylic acid chloride *p*-toluenesulfonylhydrazone (**566**) to afford the diazoacetate **567** (eq 2).[157]

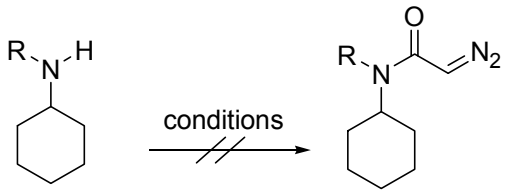
Scheme 125. Previous diazoacetylations.



Unfortunately, we could not diazoacetylate either **561** or **562**, or even cyclohexylamine (**568**) with either the succinimidyl diazoacetate reagent **208** or using Corey's conditions (Scheme 126).

In view of the results above, a different strategy for elaborating the pyrrolidine ring was devised. We believed that the natural product could be derived from the amide **569** via reduction of the lactam, elaboration of the epoxide moiety, and *N*-acylation. The amide in turn could be derived via a Beckman rearrangement[158] of the oxime **570**, which in turn would be made from the ketone **571**. Ketone **571** would be constructed from via an intramolecular rhodium-mediated C-H insertion of the diazo-ketone **572**. The intramolecular

Scheme 126. Diazoacetylation of a model system.

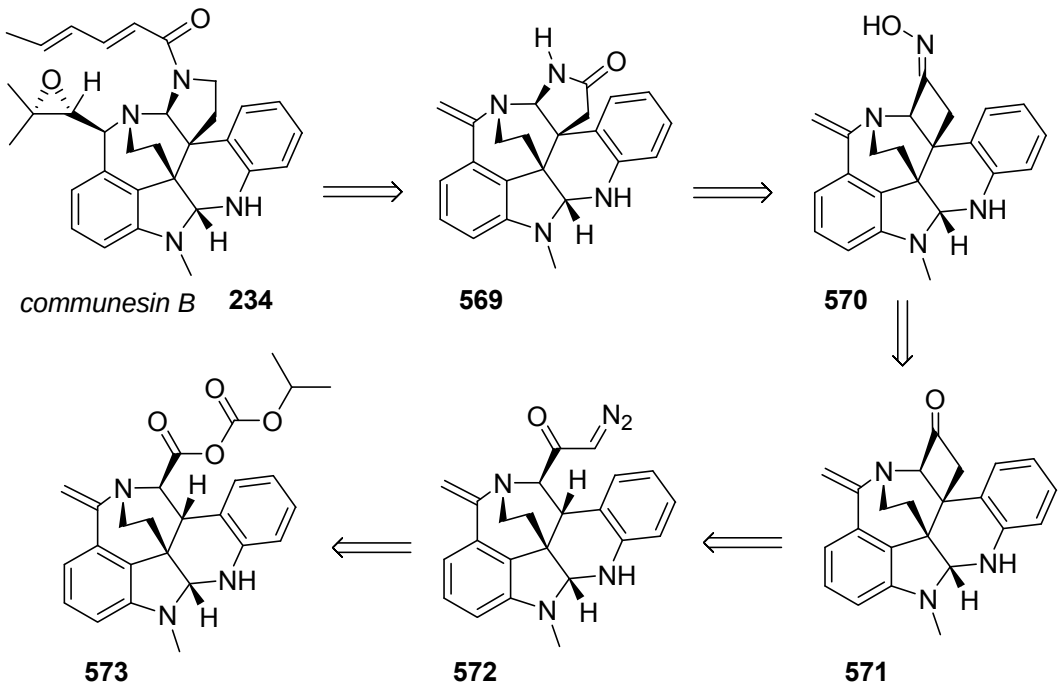


561 R = Ns
562 R = CO_2Me

	attempted diazoacetylation conditions
561 R = Ns	1. glyoxylic acid chloride *p*-toluenesulfonylhydrazone, diethylaniline, triethyamine, CH_2Cl_2, 0 ^oC, NR 2. glyoxylic acid chloride *p*-toluenesulfonylhydrazone, proton sponge, CH_2Cl_2, 0 ^oC, NR 3. glyoxylic acid chloride *p*-toluenesulfonylhydrazone, NaH, THF, 0 ^oC, decomposition 4. glyoxylic acid chloride *p*-toluenesulfonylhydrazone, NaH, THF, 65 ^oC, NR 5. glyoxylic acid chloride *p*-toluenesulfonylhydrazone, NaH, DMF, 25 ^oC, NR 6. succinimdyl diazoacetate, proton sponge, THF, 0 ^oC, NR 7. succinimdyl diazoacetate, proton sponge, DMF, 0 ^oC, NR
562 R = CO_2Me	1. NaH, succinimidyl diazoacetate, THF, 0 ^oC, NR 2. NaH, succinimidyl diazoacetate, THF, 80 ^oC, NR 3. NaH, succinimidyl diazoacetate, DMF, 50 ^oC, NR 4. BuLi, succinimidyl diazoacetate, THF, -78 ^oC, NR 5. glyoxylic acid chloride *p*-toluenesulfonylhydrazone, diethylaniline, triethyamine, CH_2Cl_2, 0 ^oC, NR
568 R = H	1. succinimidyl diazoacetate, THF, 0 ^oC, NR 2. succinimidyl diazoacetate, DMF, 25 ^oC, NR 3. succinimidyl diazoacetate, DMF, 60 ^oC, NR 4. glyoxylic acid chloride *p*-toluenesulfonylhydrazone, diethylaniline, triethyamine, CH_2Cl_2, 0 ^oC, NR 5. glyoxylic acid *p*-toluenesulfonylhydrazone, DCC, THF, 0 ^oC, NR

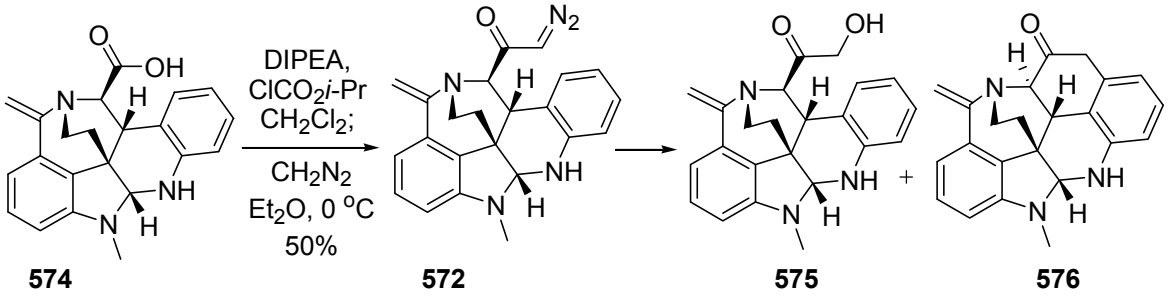
metal-mediated C-H insertion to provide β-lactams is also well precedented.[159] Finally, the diazo-ketone **572** could be made from the mixed anhydride **573** in a straightforward manner (Scheme 127).

Scheme 127. A revised synthetic strategy employing a rhodium-mediated C-H insertion.



Therefore, the acid **574** was converted to the mixed anhydride and treated with diazomethane to provide the diazoketone **572** (Scheme 128). Unfortunately, treatment of the diazoketone **572** with rhodium catalysts only provided decomposition products or a 1 : 1 mixture of the α-hydroxy ketone[160] **575** and the aryl C-H insertion product **576**.

Scheme 128. Attempted C-H insertions to the cyclobutanone.



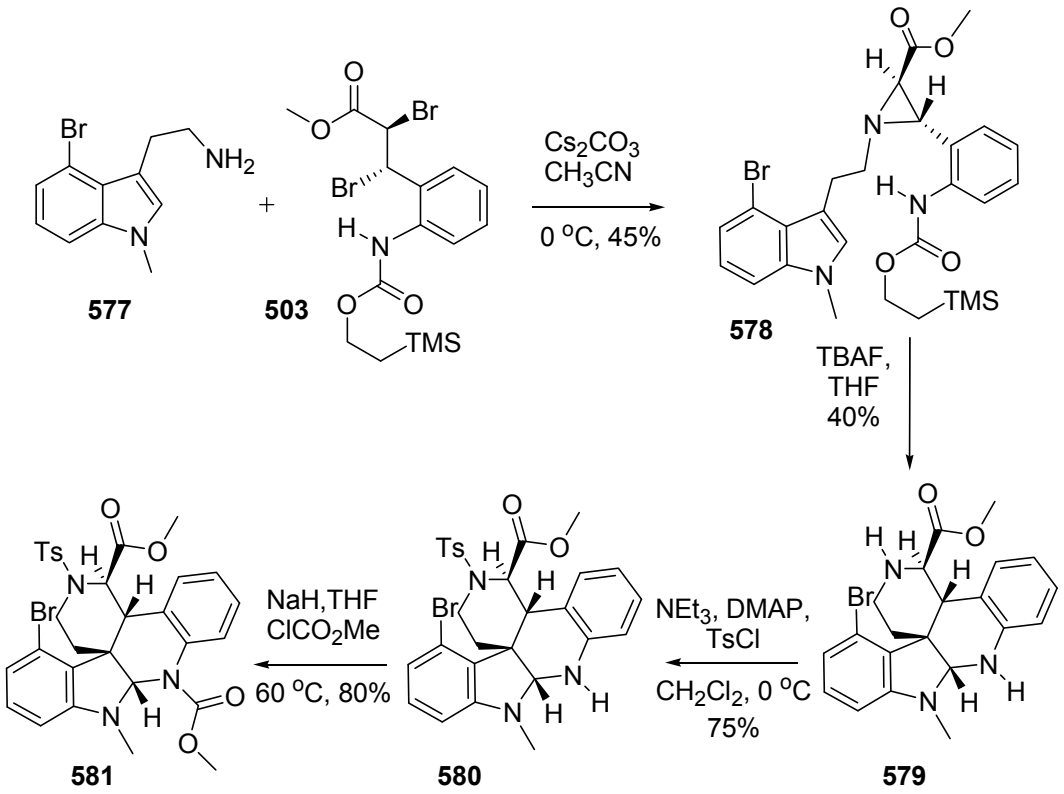
574 572 575 576

Attempted rhodium-mediated insertions

1. $Rh_2(OAc)_4$, benzene, 50 °C, decomposition
2. $Rh_2(OAc)_4$, benzene, 45 °C, slow add'n, 40%
3. $Rh_2(CF_3CO_2)_4$, benzene, 45 °C, slow add'n, 45%

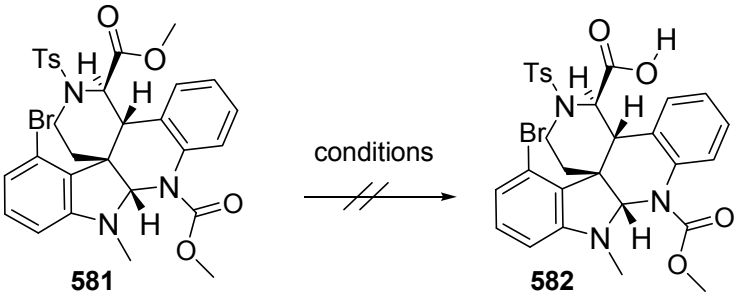
It was hoped that a less conformationally rigid structure, for instance a substrate without the bridgehead enamine, would allow the diazoketone to properly align with the tertiary benzylic C-H bond instead of the aromatic C-H bond. However, due to the instability of the cycloadduct **541**, we synthesized the corresponding bromine-substituted cycloadduct **579** starting from 4-bromotryptamine (**577**) and the dibromide **503** in the usual manner (Scheme 129). Tosylation of the piperidine nitrogen followed by *N*-acylation furnished the methyl carbamate **581**. The stereochemistry of the cycloadduct **579** was confirmed by the observation of nOe's analogous to those seen for the model system **485**.

Scheme 129. Synthesis of a bromine substituted cycloadduct.



Despite several attempts, saponification of the ester **581** only provided unreacted starting material or hydrolyzed both the ester and methyl carbamate (Scheme 130). Thus, we decided to investigate the readily available model system **517** instead to determine if a conformationally flexible substrate could solve the problem of aryl C-H insertion.

Scheme 130. Attempted saponification of the ester.

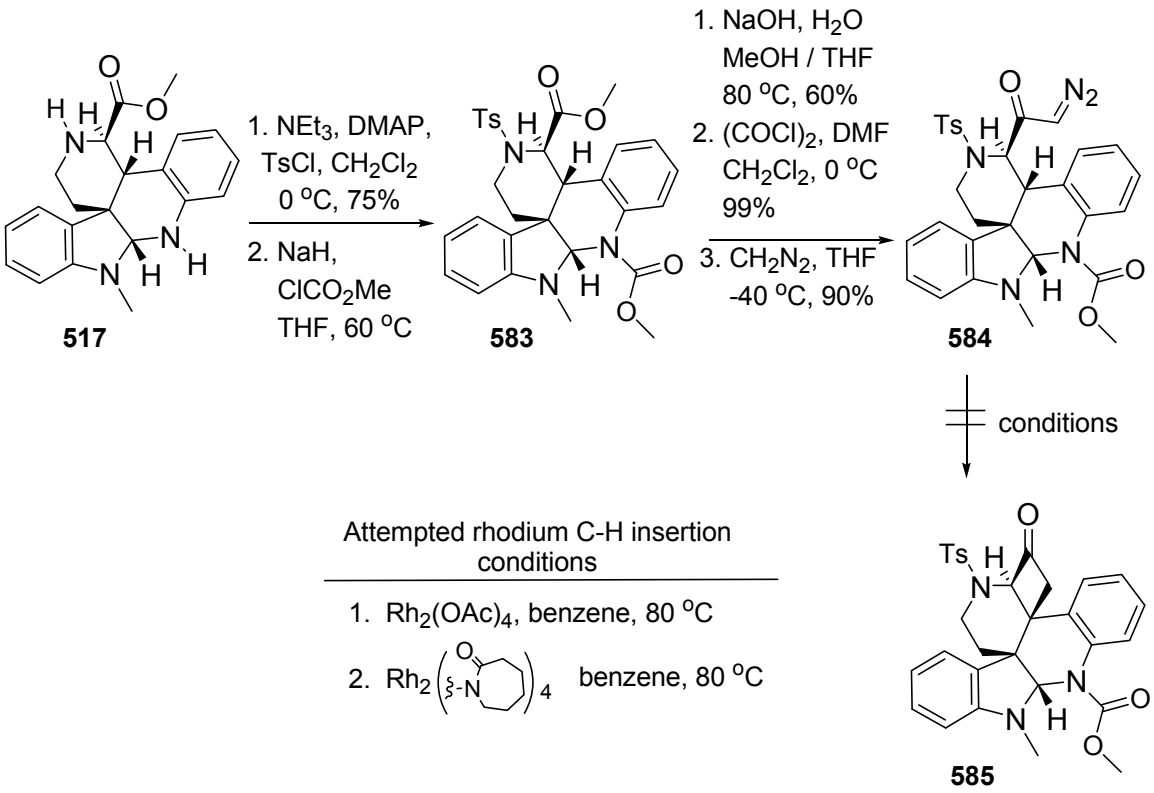


Attempted saponfication conditions

1. LiOH, THF / H_2O, 80 ^oC, NR
2. LiOH, H_2O / MeOH, rt, NR
3. KOH, THF / MeOH, 60 ^oC, hydrolyzed ester and carbamate
4. LiI, EtOAc, 80 ^oC, NR

To that end, tosylation and *N*-acylation of the cycloadduct **517** provided the carbamate **583** (Scheme 131). Saponification of the ester, conversion of the resultant acid to the acid chloride, and treatment of the acid chloride with diazomethane provided the diazoketone **584**. Unfortunately, treatment of the diazoketone **584** with either $Rh_2(OAc)_4$ or Rh_2(caprolactamate)$_4$ provided an unidentified mixture of products.

Scheme 131. Attempted rhodium-mediated C-H insertion on a model system.



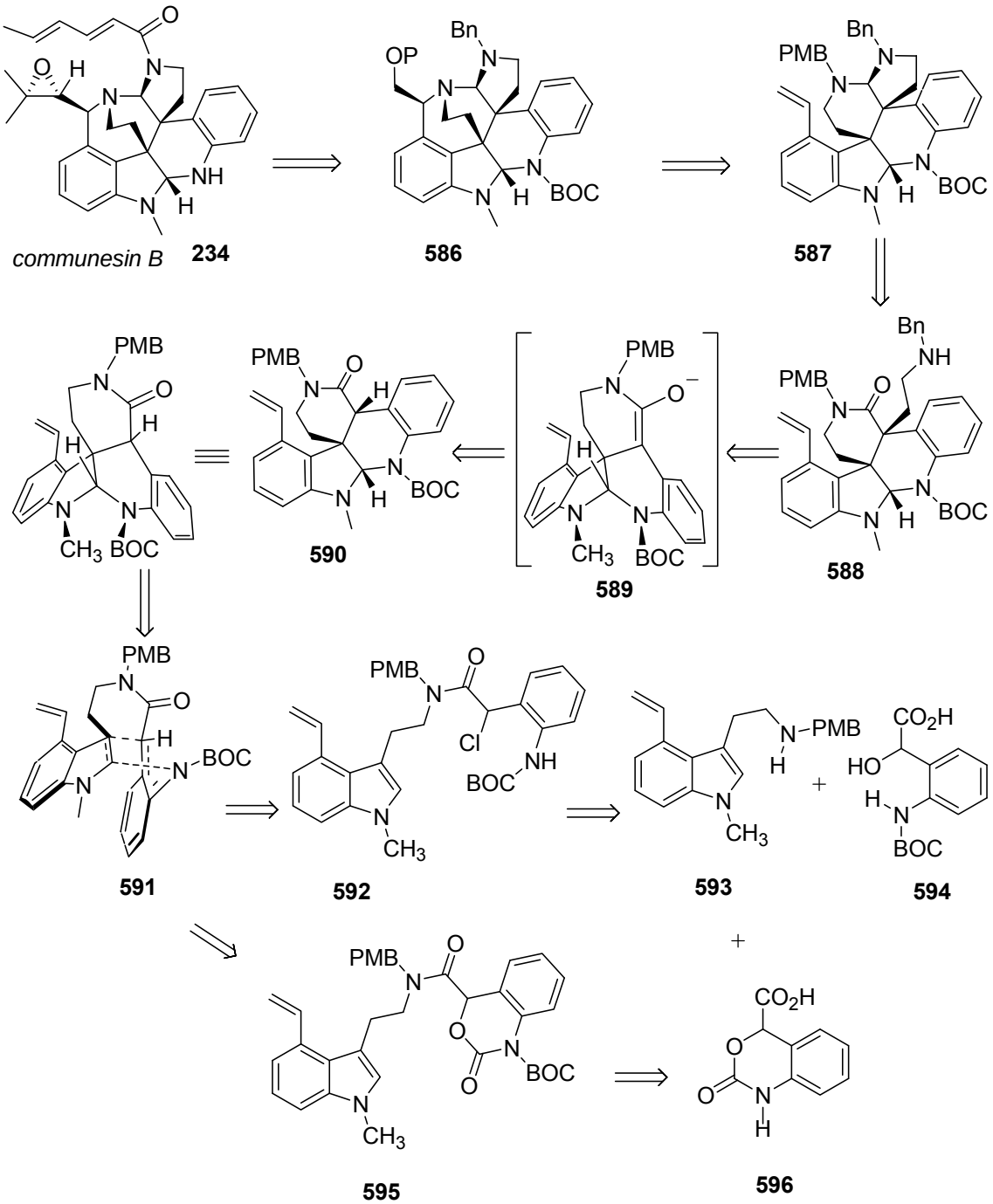
II. Intramolecular cycloaddition strategy of an acyl-substituted aza-*ortho*-xylylene

A. Revised retrosynthetic analysis

We now decided to revisit our initial strategy for generating aza-*ortho*-xylylenes via a retrocycloaddition that would also permit the introduction of the vicinal quaternary centers via enolate alkylation chemistry. Thus, it was believed that the natural product could be derived from the carbamate **586** via deprotection, *N*-acylation, and elaboration of the epoxide moiety as before. The carbamate in turn could be constructed from the alkene **587** via deprotection and cyclization with the proximate piperidine nitrogen as discussed previously in Scheme 96. The aminal **587** could be made from the amine **588** via reduction of the lactam with concomitant cyclization to provide the aminal (Scheme 132).[161]

Alternatively, the lactam could be deprotected, converted to the imide, and reduced to provide the hemiaminal. Intramolecular cyclization with the tethered benzylamine could then provide the aminal.[161h] The amine **588** could be

Scheme 132. A revised retrosynthetic analysis for an intramolecular cycloaddition.

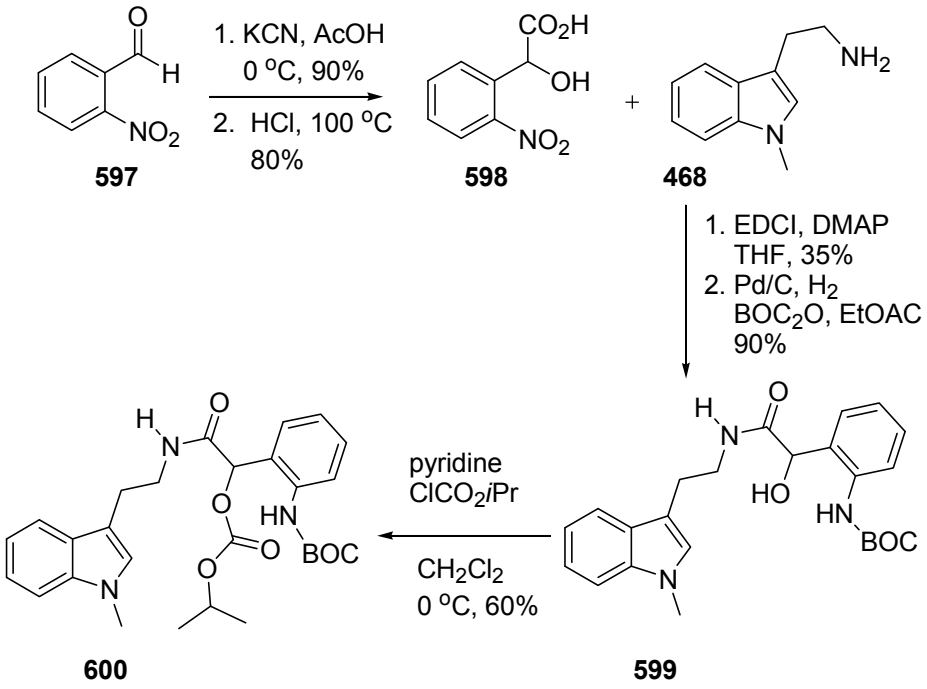


constructed from the lactam **590** via alkylation of the enolate **589** from the less hindered convex face with allyl iodide, followed by oxidative cleavage to the aldehyde,[162] and reductive amination. Lactam **590** could be made from the chloride **592** by treatment with base to generate the aza-*ortho*-xylylene **591** with concomitant intramolecular *endo* cycloaddition with the tethered indole. To the best of our knowledge, aza-*ortho*-xylylenes possessing a carbonyl at C(4) of the 1-azadiene have not been previously examined. Finally, the chloride **592** could be derived from the readily available tryptamine derivative **593** and the carboxylic acid **594** via amide formation and conversion to the chloride. Alternately, the aza-*ortho*-xylylene **591** could be generated from the *N*-acyl-3,1-benzoxazin-2-one **595**, which could made by amide formation of tryptamine **593** with the acid **596** followed by *N*-acylation.

B. Generation of the acyl-aza-*ortho*-xylylene via thermolysis

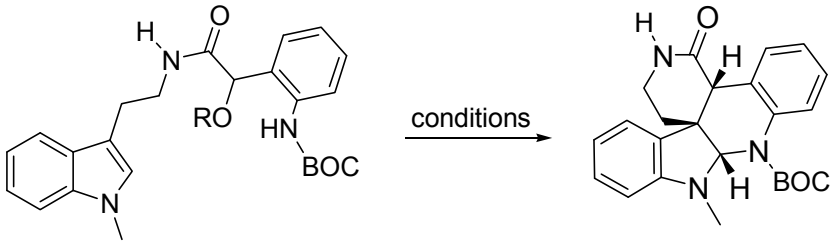
We decided to synthesize a model system for communesin B in order to test the viability of our proposed intramolecular cycloaddition of the novel acyl-aza-*ortho*-xylylene. To that end, commercially available 2-nitrobenzaldehyde (**597**) was converted to the cyanohydrin[163] and hydrolyzed[163] to provide the nitro compound **598**. Subsequent amide formation[164] with 1-methyltryptamine (**468**), and hydrogenolysis of the nitro group of the resultant amide in the presence of di-*t*-butyl dicarbonate provided the carbamate **599**. Finally, conversion of the alcohol to the carbonate derivative furnished the secondary amide **600** (Scheme 133).

Scheme 133. Synthesis of a cycloaddition precursor.



Gratifyingly, thermolysis of the carbonate **600** in dichlorobenzene at 150 °C provided cycloadduct **601**, even though it was accompanied by significant polymerization. Alternately, conversion of the alcohol **599** to the analogous chloride **602** using Corey's conditions,[115] followed by treatment with cesium carbonate only provided an inseparable mixture of products (Scheme 134). We believed that the low yield was due, in part, to the secondary amide which does not prefer to exist in the s-*cis* rotamer that is required for cycloaddition.

Scheme 134. Cycloaddition using a novel aza-*ortho*-xylylene.



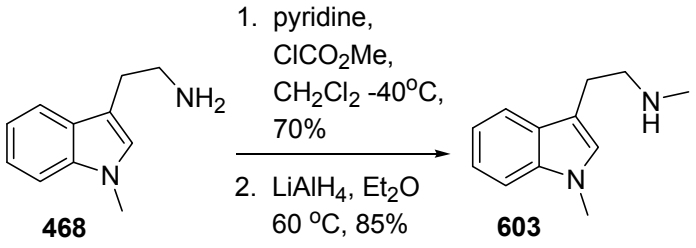
600 R = CO_2*i*Pr
602 R = Cl

601

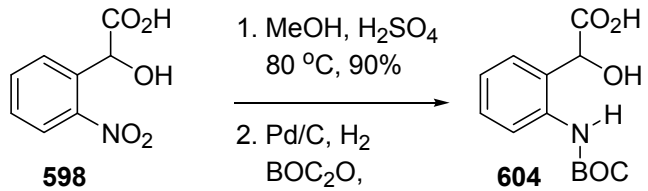
	conditions used
600 R = CO_2*i*Pr	1,2 dichlorobenzene, 150 ^oC, 30%
602 R = Cl	Cs_2CO_3, CH_2Cl_2, 0 ^oC, decomposition

To overcome this problem, we synthesized 1-methyl-*N*-ω-methyltryptamine (**603**) from 1-methyl tryptamine (**468**) in a straightforward manner (Scheme 135). Acid **598** was esterified, the nitro group was subjected to hydrogenolysis in the presence of di-*t*-butyl dicarbonate and the resultant ester was saponified to provide the acid **604**. Unfortunately, amide formation with acid **598** proceeded in poor yield to give **605**, and amide formation with **604** only

Scheme 135. Synthesis of amide coupling starting materials.



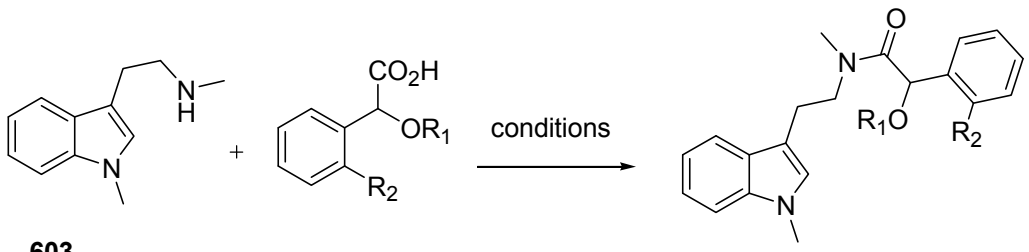
468 **603**



598 **604**

provided unreacted starting material. However, protection of the alcohol of **598** to give **606** and formation of the amide **607** via the corresponding mixed anhydride was successful (Scheme 136).

Scheme 136. Synthesis of the tertiary amide.



603

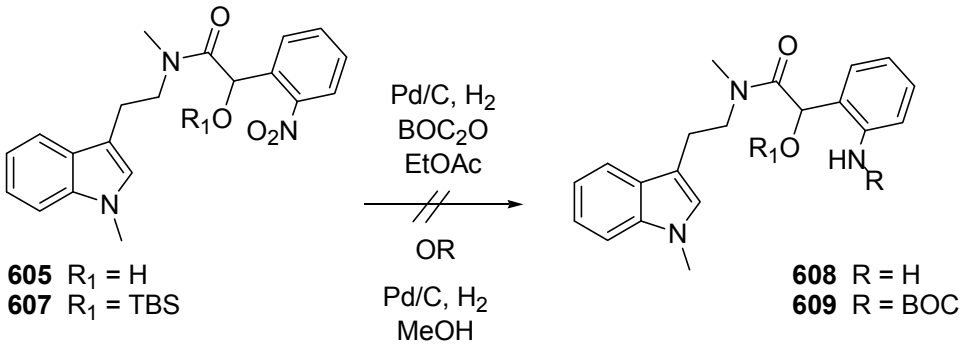
598 R_1 = H
R_2 = NO_2
604 R_1 = H
R_2 = NHBOC
606 R_1 = TBS
R_2 = NO_2

605 R_1 = H
R_2 = NO_2
607 R_1 = TBS
R_2 = NO_2

carboxylic acid	conditions
598 R_1 = H, R_2 = NO_2	1. EDCI, DMAP, THF, 14% 2. CDI, THF, decomposition 3. xylenes, reflux, decomposition 4. $SOCl_2$, NEt_3, THF, 0 ^oC, decomposition 5. HOBT, EDCI, NEt_3, CH_2Cl_2, DMF, decomposition 6. PYBOP, DIPEA, DMF, 0 ^oC, decomposition
604 R_1 = H, R_2 = NHBOC	1. DIPEA, $ClCO_2iPr$, CH_2Cl_2, 0 ^oC, NR 2. DIPEA, $ClCO_2iPr$, THF, 0 ^oC, NR 3. CDI, CH_2Cl_2,0 ^oC, NR
606 R_1 = TBS, R_2 = NO_2	1. DIPEA, $ClCO_2iPr$, CH_2Cl_2, 0 ^oC, 53%

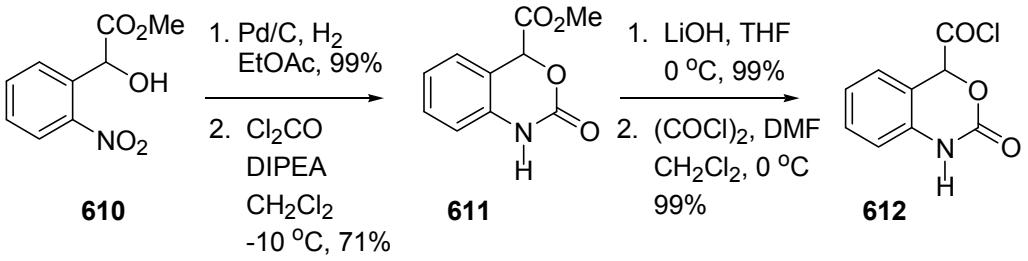
We were surprised to discover that despite the fact that the nitro group of **598** reduced quickly, the attempted hydrogenolysis of the analogous nitro groups of amides **605** and **607** only provided unreacted starting material (Scheme 137).

Scheme 137. Attempted reduction of the tertiary amide nitro group.



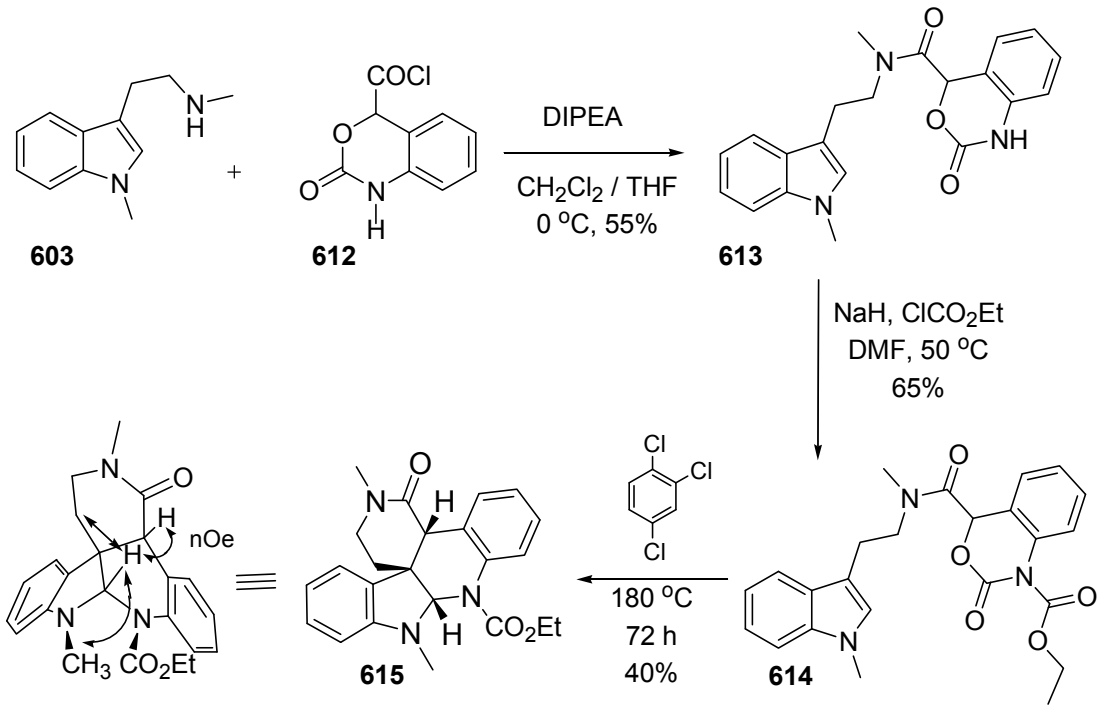
In view of the problems we were encountering forming and functionalizing the tertiary amide, we turned to generating the aza-*ortho*-xylylene via the *N*-acyl-3,1-benzoxazin-2-one **595**. Thus, the previously prepared nitro compound **610** was hydrogenated to the corresponding unstable aniline and immediately reacted with phosgene to provide the ester **611**. Subsequent saponification and acid chloride formation provided **612** (Scheme 138).

Scheme 138. Synthesis of a benzoxazin-2-one.



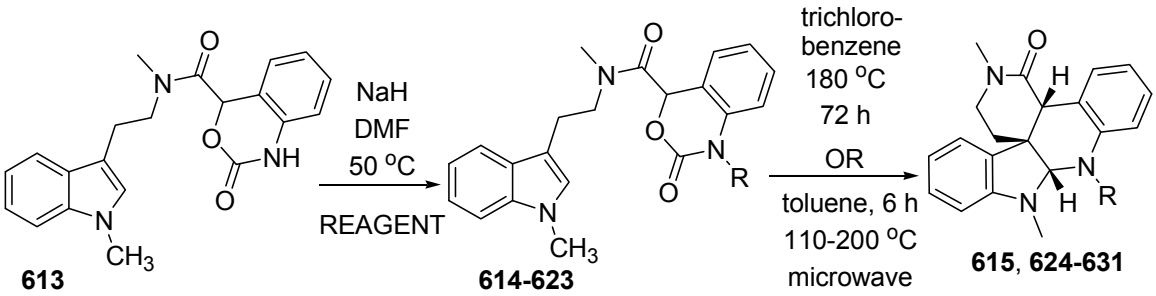
We were pleased to discover that by reacting the acid chloride **612** with the amine **603**, we could isolate the desired tertiary amide **613** in good yield. Furthermore, *N*-acylation of **613** followed by thermolysis of the resultant *N*-acyl-3,1-benzoxazin-2-one **614** provided the cycloadduct **615** in modest yield. The relative stereochemistry for the expected *endo* isomer was assigned on the basis of the observed nOe's, the most diagnostic of which are provided in Scheme 139.

Scheme 139. Synthesis of the cycloadduct via a *N*-acyl-3,1-benzoxazine-2-one.



However, in order for this strategy to be synthetically useful, we needed to improve the yield and diminish the reaction time of the cycloaddition. Consequently, the *N*-ethylcarbamate moiety of **614** was exchanged for the analogous *N*-tosyl **616**, *N*-nosyl **617**, *N*-BOC **618**, *N*-Cbz **619**, *N*-methylcarbamate **620**, *N*-acetyl **621**, *N*-trifluoroacetamide **622**, or *N*-formyl **623** derivatives. Subjection of any of these derivatives to identical conditions did not improve most yields or provided an inseparable mixture of products (Scheme 140). Furthermore, thermolysis of **614**, **616**, **617**, **619**, **620**, **621**, or **623** in toluene using microwave conditions at 110-200 °C (300 W) improved the reaction time to less than 6 hours, but the yield of the cycloadduct was not increased.

Scheme 140. Optimization of the thermal cycloaddition.



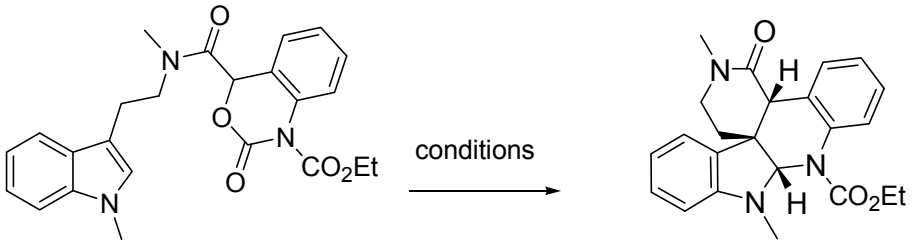
613 **614-623** **615**, **624-631**

Reagent		Yield	Yield	
$ClCO_2Et$	**614** R = CO_2Et	65%	40%	**615**
TsCl	**616** R = Ts	35%	decomposition	**624**
NsCl	**617** R = Ns	35%	16%	**625**
BOC_2O	**618** R = BOC	50%	<20%	**626**
Cbz-Cl	**619** R = Cbz	53%	33%	**627**
$ClCO_2Me$	**620** R = CO_2Me	45%	<35%	**628**
AcCl	**621** R = Ac	30%	decomposition	**629**
$(CF_3CO)_2O$	**622** R = CF_3CO	33%	decomposition	**630**
Formic Acetic Anhydride	**623** R = CHO	31%	30%	**631**

C. Lewis acid catalyzed generation of the acyl aza-*ortho*-xylylene

We next investigated Lewis acid catalysis of the retrocycloaddition-cycloaddition process in the hopes of activating one of the carbonyls so that we might decrease the temperature and thereby decrease the reaction time and increase the yield.[165] A variety of Lewis acids were screened on **614** and gratifyingly, ytterbium triflate in toluene gave the desired effect (Scheme 141).

Scheme 141. Lewis acid catalysis of the cycloaddition.

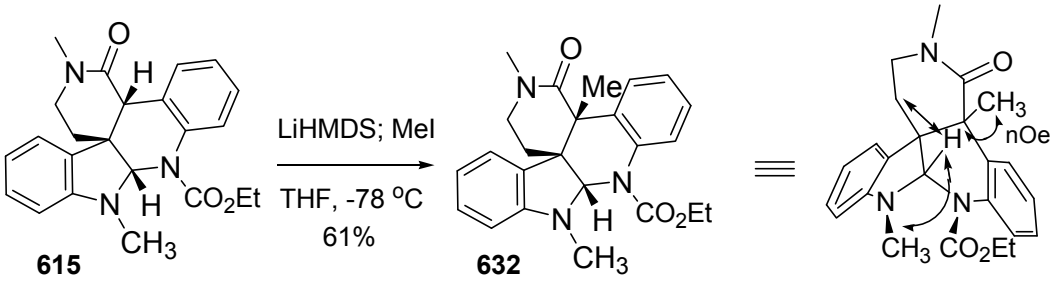


614 **615**

Catalyzed conditions
1. $BF_3 \cdot OEt_2$, CH_2Cl_2, 0 °C, NR
2. Me_2AlCl, toluene, 0 °C, NR
3. Me_2AlCl, toluene, 85 °C, NR
4. $EtAlCl_2$, CH_2Cl_2, 0 °C, NR
5. $ZnCl_2$, toluene, 50 °C, NR
6. $Sc(OTf)_3$, toluene, 50 °C, 48 h, 55%
7. $InCl_3$, CH_2Cl_2 / toluene, 50 °C, 72 h, 55%
8. $Yb(OTf)_3$, CH_2Cl_2 toluene, 50 °C,12 h, 75%

We now directed our attention to the elaboration of the pyrrolidine ring. We first needed to verify that the alkylation of the enolate generated from lactam **615** would proceed via the convex face. To that end, the enolate of amide **615** was generated with LiHMDS and alkylated with methyl iodide to give the methylated lactam **632**. The relative stereochemistry for the expected diastereomer **632** was assigned on the basis of subsequent nOe studies with the most diagnostic nOe's shown below in Scheme 142.

Scheme 142. Determination of the lactam alkylation stereochemistry.

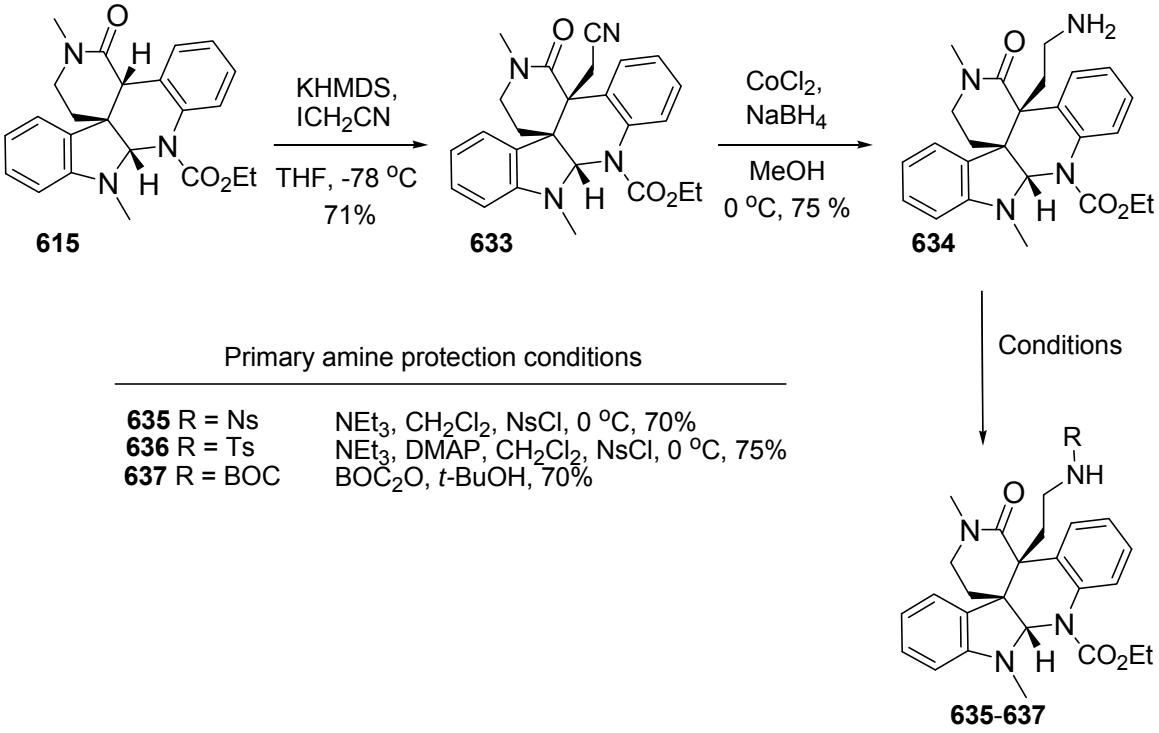


615 **632**

Next, alkylation of the amide **615** with iodoacetonitrile provided the nitrile **633**. Subsequent reduction of the nitrile using mild metal boride conditions[166]

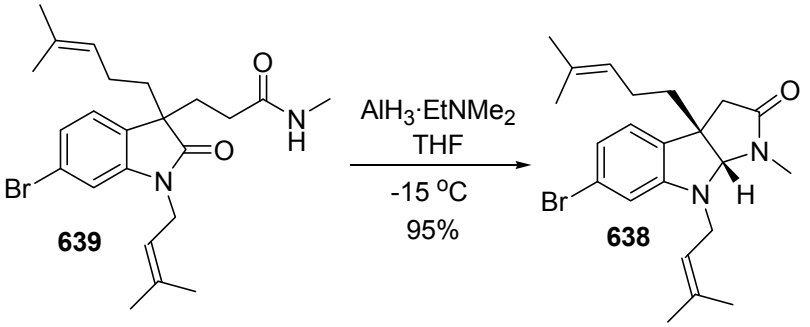
furnished the primary amine **634**. Finally, the amine was protected as the nosylamide **635**, tosylamide **636**, and *t*-butylcarbamate **637** (Scheme 143).

Scheme 143. Synthesis and protection of a primary amine substituent.



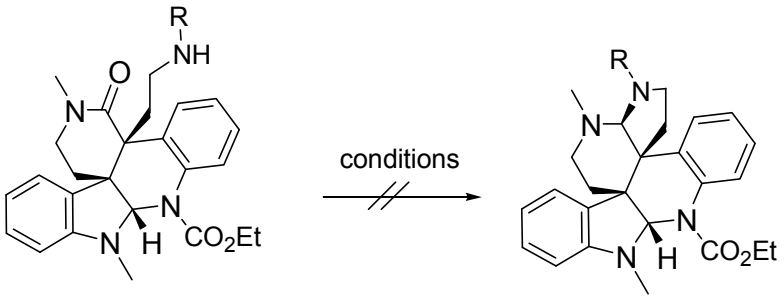
Given the many precedents for aminal closures,[161] we predicted that reduction of the amide with concomitant cyclization of one of the tethered amide derivatives **635-637** would form the desired aminal. A recent example of this type of closure was in the successful formation of aminal **638** from the amide **639** in a publication of a total synthesis of the flustramides (Scheme 144).[161h]

Scheme 144. Formation of an aminal from an amide.



Unfortunately, subjection of amides **635-637** to a variety of reducing agents only provided an inseparable mixture of products (Scheme 145). As an alternative strategy of forming the aminal, we drew upon a recent synthesis of

Scheme 145. Attempted aminal formation from various amides.



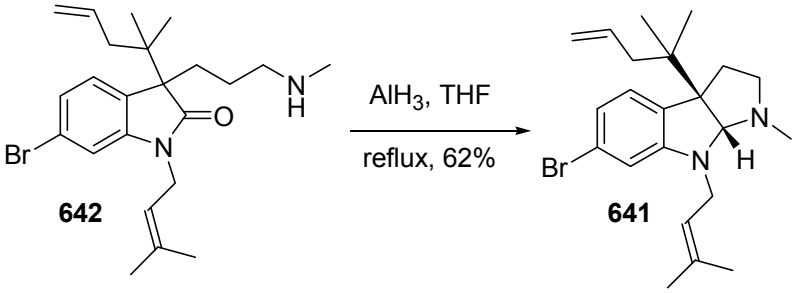
635 R = Ns
636 R = Ts
637 R = BOC

640

Attempted aminal formation conditions	
635 R = Ns	1. $AlH_3 \cdot EtNMe_2$, THF, -15 °C
636 R = Ts	2. Red-Al, THF, -78 °C
	3. Red-Al, THF, -78 °C→60 °C
	4. $AlH_3 \cdot EtNMe_2$, THF, 0 °C
	5. $LiEt_3BH$, THF, -78 °C→0 °C
	6. $NaBH_4$, MeOH, 80 °C
637 R = BOC	7. $AlH_3 \cdot EtNMe_2$, THF, -15 °C

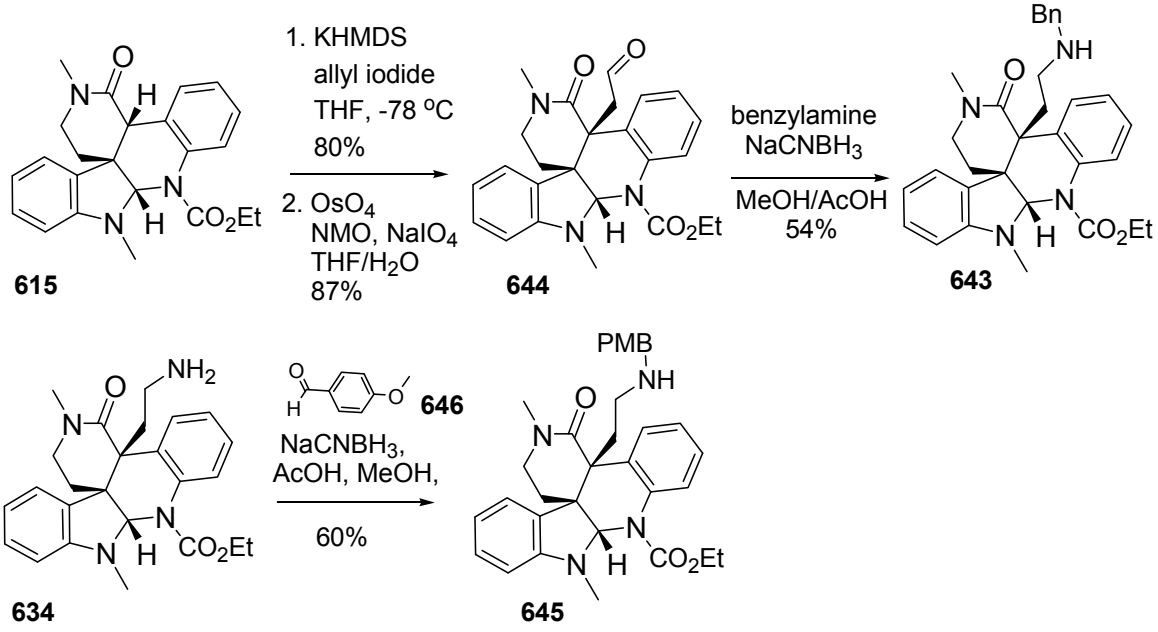
flustramine A, wherein the aminal **641** was prepared from the amide **642** (Scheme 146).[107] We hoped that an amine might be more likely to close on the intermediate hemiaminal than an amide or sulfonamide.

Scheme 146. Another synthesis of an aminal from an amide.



Consequently, the benzyl amine **643** was synthesized in three straightforward steps from the amide **615**. Additionally, the *p*-methoxybenzyl amine **645** was synthesized via reductive amination of the amine **634** with *p*-methoxybenzaldehyde (**646**) (Scheme 147).[167] Attempts to synthesize the amine **634** via reductive amination with the aldehyde **644** were unsuccessful.[168]

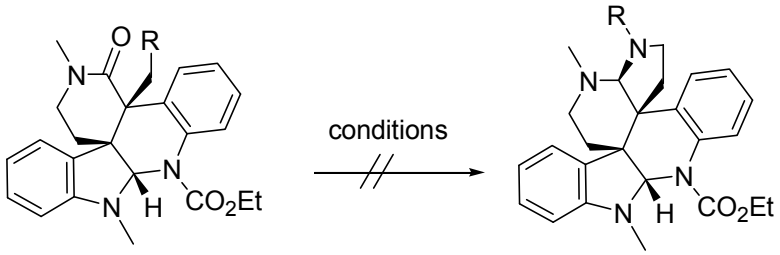
Scheme 147. Synthesis of secondary amines.



Thus, the nitrile **633**, and amines **634**, **643**, and **645** were subjected to various reducing agents. Unfortunately, the nitrile provided an inseparable mixture of products,[169] whereas the amine **634** only returned unreacted starting material when subjected to either borane-[170] or sodium-mediated reductions.[171]

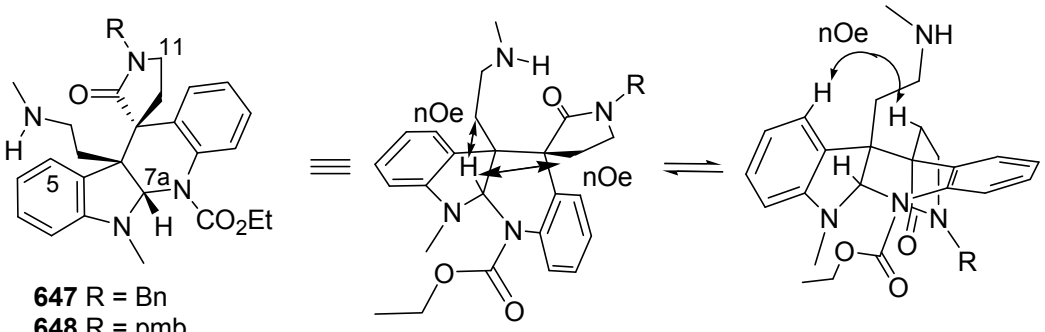
Surprisingly, amines **643** and **645** underwent transamidation[172] to the corresponding spirocyclic lactams **647** and **648**. The stereochemistry of the spirocyclic lactam **647** was confirmed by nOe studies, the most diagnostic of which are shown in Scheme 147. Importantly, the C(5) aromatic proton exhibited a nOe with the C(12) methylene proton, indicating that the ring-flipped conformer **649** was populated (Scheme 148).

Scheme 148. Attempted aminal formation.



633 R = CN
634 R = CH_2NH_2
643 R = CH_2NHBn
645 R = CH_2NHpmb

attempted aminal formation conditions	
633 R = CN	1. DIBAL, CH_2Cl_2, -78 ^oC, decomposition 2. $LiAlH_4$, THF, 0 ^oC, decomposition
634 R = CH_2NH_2	1. BH_3·THF, 25 ^oC, NR 2. BH_3·THF, 50 ^oC, NR 3. Na, EtOH, 0 ^oC, NR
643 R = CH_2NHBn	1. AlH_3·$EtNMe_2$, THF, 0 ^oC, **647** = 80%
645 R = CH_2NHpmb	1. AlH_3·$EtNMe_2$, THF, 0 ^oC, **648** = 82%

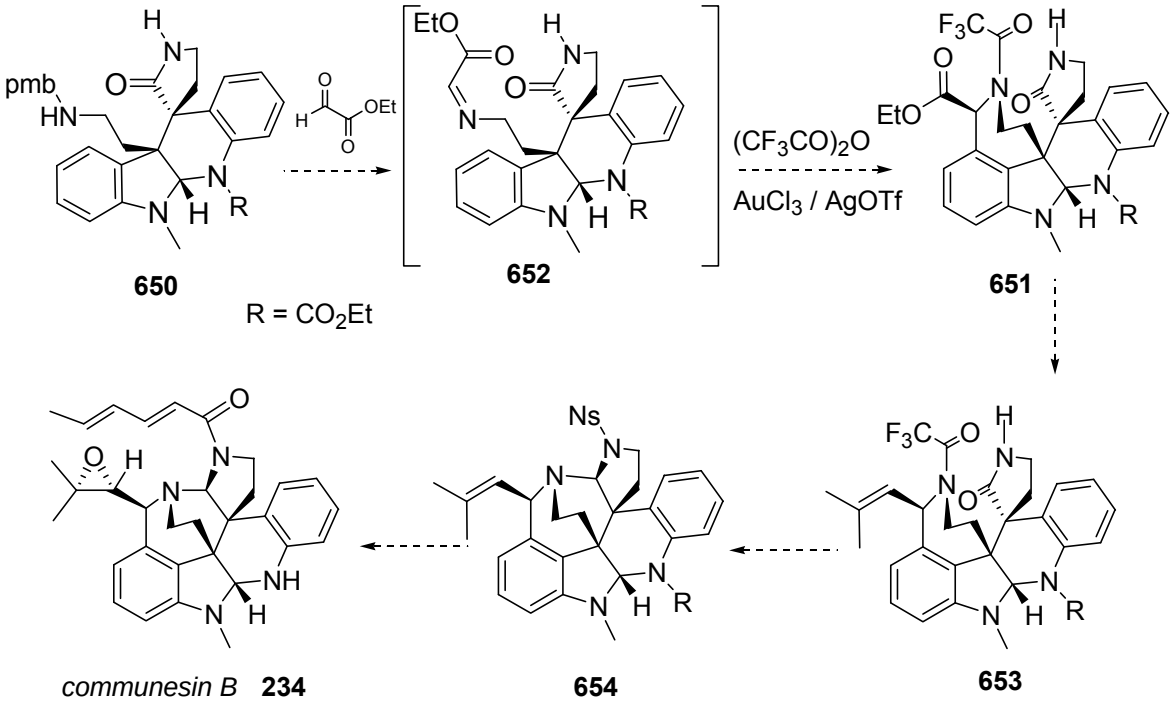


647 R = Bn
648 R = pmb

649

These results led us to contemplate a different strategy for elaboration of the benzazepine ring. Drawing upon a recent report of a gold-catalyzed Pictet-Spengler reaction of tryptamines to provide tetrahydroisoquinoline-acetamides,[173b] we believed that the spirocyclic lactam **650** could be used in an intramolecular Pictet-Spengler[173] reaction to provide the ester **651** via the acyl-imine **652** (alternatively an analogous, albeit inferior iminium ion, Bischler-Napieralski reaction could be used).[174] Grignard addition and elimination could provide the alkene **653**. Subsequent deprotection, conversion of the spirocyclic lactam to the imide, followed by aminal formation, and elaboration of the remaining functionalities could provide the natural product (Scheme 149).

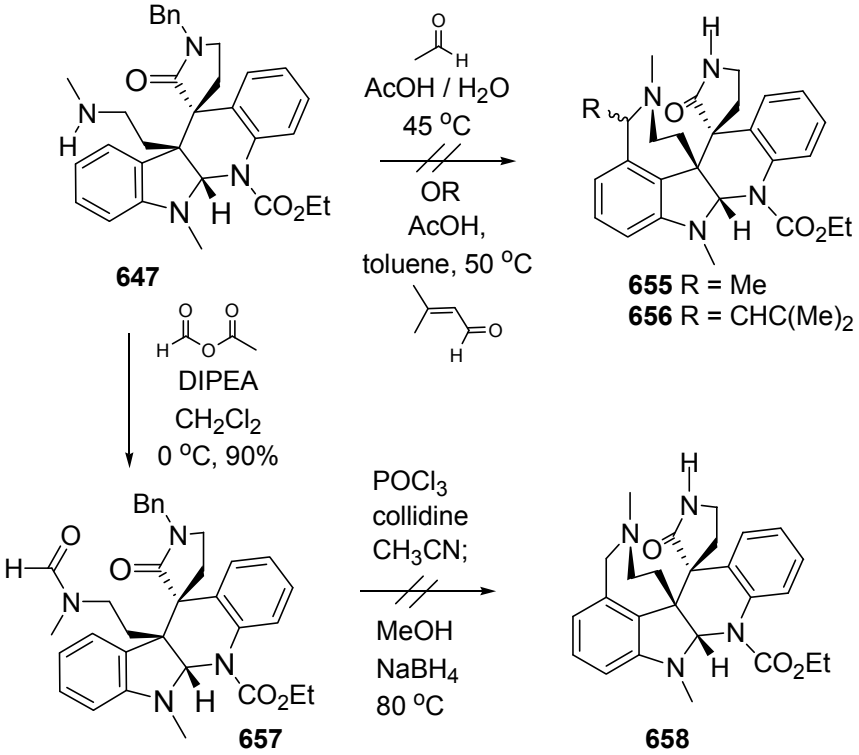
Scheme 149. A possible acyl-iminium based approach to communesin.



We briefly evaluated this ring closure strategy. Thus, the amine **647** was heated with acetaldehyde or 3-methylcrotonaldehyde in the presence of acetic acid in an effort to effect the Pictet-Spengler type closure (Scheme 150). Unfortunately, both reactions gave exclusively decomposition products. Alternately, the amine was converted to the formamide **657**. Subsequent

treatment of the formamide with $POCl_3$ and 2,4,6-collidine, followed by exposure to sodium borohydride also provided a complex mixture of products.

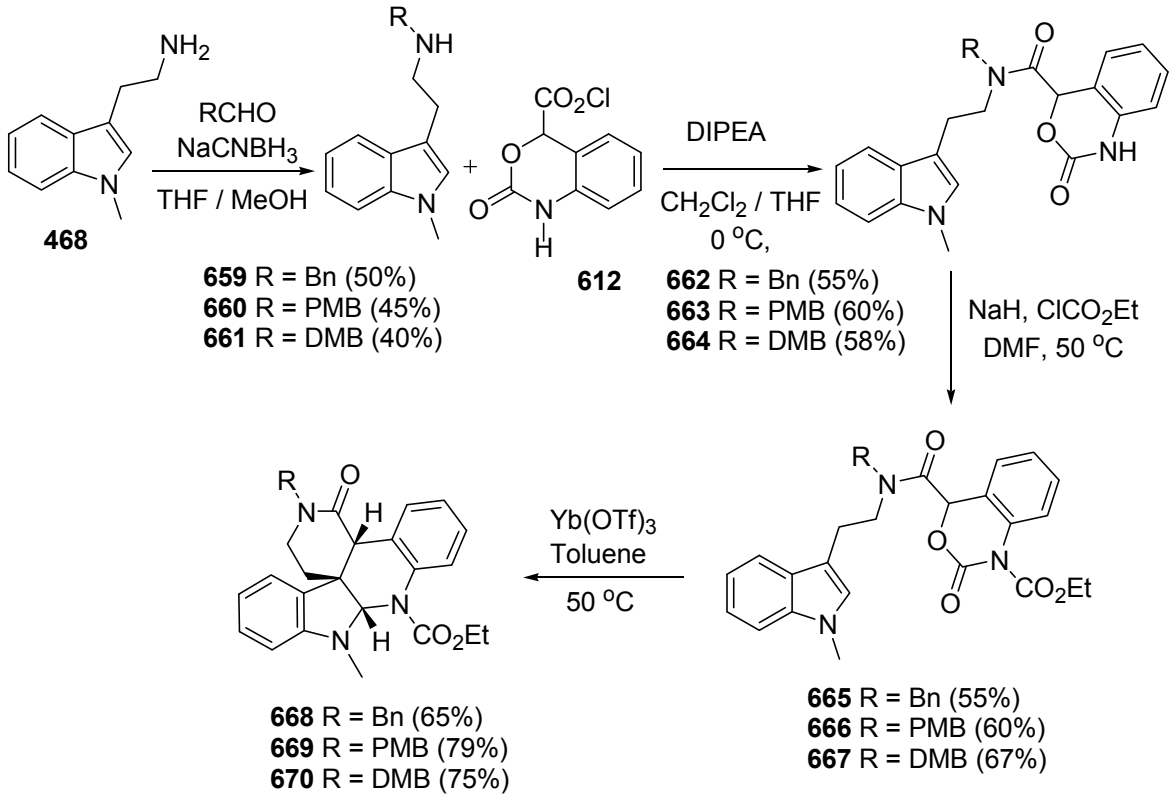
Scheme 150. Attempted cyclization to provide the benzazepine ring.



In view of the problems that we encountered with the reduction of the tertiary lactam in order to form the aminal, we explored the preparation of tertiary lactams that could be deprotected. It was hoped that this would allow transformation to an imide that could serve as a potential precursor to form the aminal.

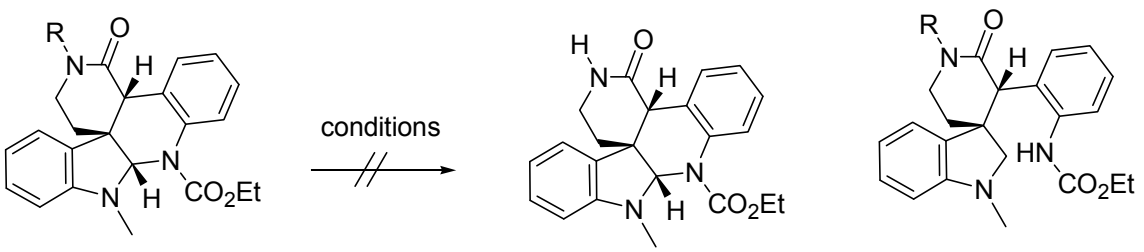
To that end, 1-methyltryptamine (**468**) was converted to the benzyl (**659**), *p*-methoxybenzyl (**660**) and 2,4-dimethoxybenzyl (**661**) tryptamine derivatives via reductive amination with the corresponding aldehydes (Scheme 151).[175] Amide formation with the acid chloride **612** followed by *N*-acylation as before provided the *N*-acyl-3,1-benzoxazin-2-ones **665-667**. Thermolysis of **665-667** subsequently furnished the desired tertiary lactams **668-670**, respectively, in good yield.

Scheme 151. Synthesis of protected tertiary amides via intramolecular cycloaddition.



However, deprotection of the tertiary lactams was much more problematic than anticipated. Hydrogenolysis of the benzyl- **668** or PMB- **669** lactam returned unreacted starting material.[176] Also, attempted removal of either the *N*-benzyl group in the presence of formic acid or removal of the *N*-PMB group in the presence of TFA / triethylsilane provided the indolines **671** and **672**, respectively (Scheme 152).[177]

Scheme 152. Attempted deprotection of tertiary amides.



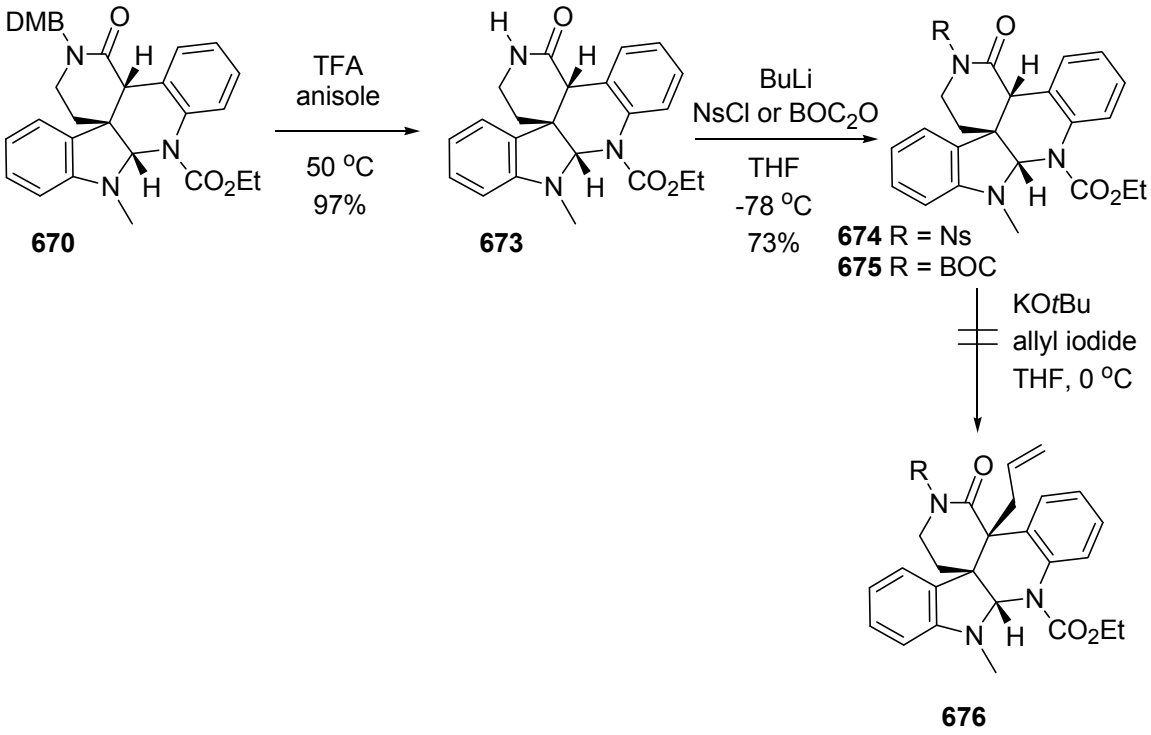
668 R = Bn
669 R = PMB

671 R = Bn
672 R = PMB

Attempted amide deprotection conditions	
668 R = Bn	1. $Pd(OH)_2$, AcOH, H_2, NR 2. HBr, THF / H_2O, NR 3. HCO_2H, 60 ^oC, **671** (70%)
669 R = PMB	1. $PdCl_2$, EtOAc, AcOH, H_2, NR 2. CAN, H_2O / CH_3CN, decomposition 3. TFA, anisole, 60 ^oC, decomposition 4. TFA, Et_3SiH, 60 ^oC, **672** (65%)

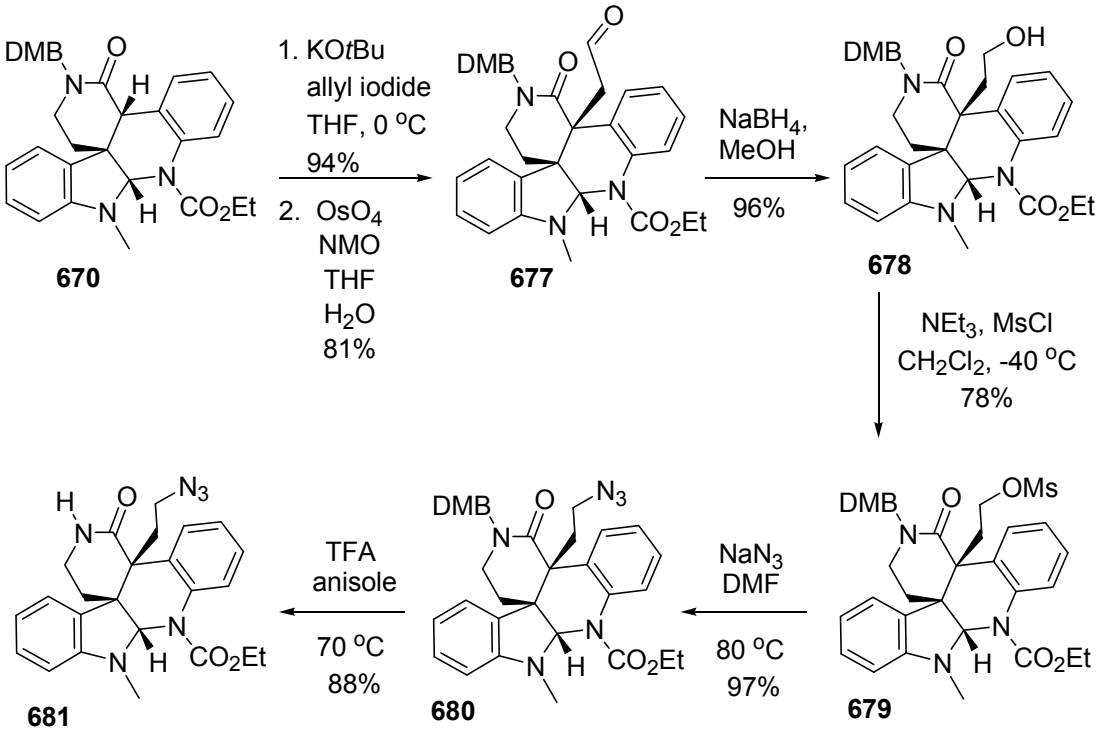
We were pleased to discover that subjection of the dimethoxybenzyl lactam **670** to TFA in anisole deprotected the lactam efficiently to provide **673** (Scheme 153).[178] Interestingly, treatment of **670** with CAN only provided decomposition. Next, we converted **673** to the nosylimide **674** and the BOC-imide **675**, but the attempted alkylation of both imides using KO*t*Bu and allyl iodide provided an inseparable mixture of products.

Scheme 153. Deprotection of the *N*-dmb amide.



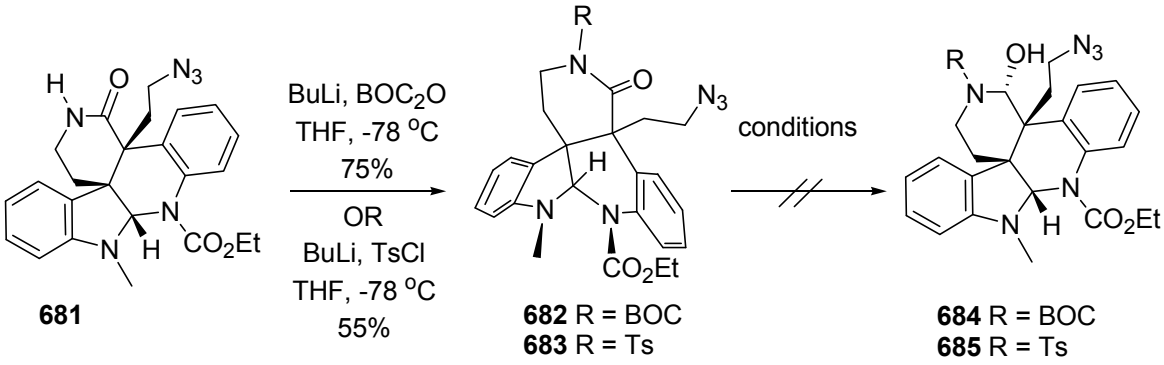
Alternately, alkylation of **670** with KO*t*Bu and allyl iodide, followed by oxidative cleavage provided the aldehyde **677**. Straightforward reduction with sodium borohydride provided the alcohol **678**. Initially we attempted to convert the alcohol **678** to the azide **680** in one step using Mitsunobu conditions (DPPA, PPh_3, DIAD), but we were unable to get clean conversion.[179] On the other hand, transformation to the mesylate **679** followed by S_N2 displacement furnished the azide **680** cleanly. Finally, deprotection of the lactam using TFA in anisole provided **681** in good yield (Scheme 154).

Scheme 154. Alkylation and deprotection of the tertiary amide.



With the secondary lactam in hand, our attention now turned towards elaboration of the aminal. Thus, **681** was converted to the BOC-imide **682** and the tosylimide **683** in a straightforward manner.[180] Unfortunately, reduction of the BOC-imide **682** provided exclusively **681** whereas the tosylimide **683** provided unreacted starting materials (Scheme 155).[181] We hypothesized that the azido-ethyl substituent in **682/683** create a sterically congested environment on the convex face, whereas the cup-shaped aromatic rings block attack on the concave face. This environment makes it difficult for the approaching reducing agent to attack the carbonyl.

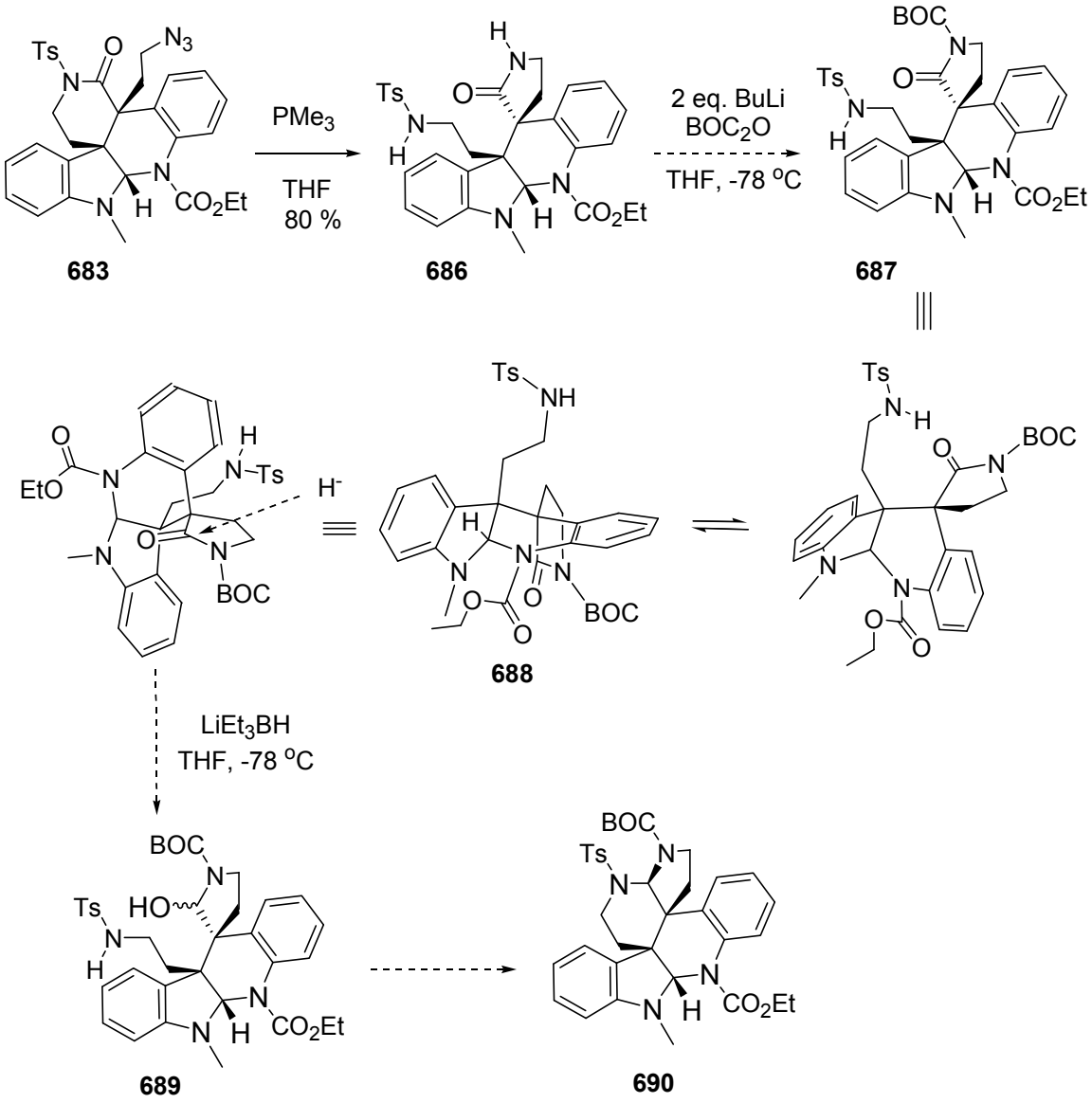
Scheme 155. Attempted reduction of imides to a hemiaminal.



Attempted reduction conditions	
682 R = BOC	1. DIBAL-H, CH_2Cl_2, -78 °C → -20 °C, **681** 2. $LiEt_3BH$, THF, -78 °C, **681** 3. $NaBH_4$, MeOH, -25 °C, **681**
683 R = Ts	1. DIBAL-H, CH_2Cl_2, -78 °C, NR 2. $NaBH_4$, EtOH, -30 °C → 25 °C, NR 3. $LiEt_3BH$, THF, -78 °C → 25 °C, NR

As a final alternative for forming the aminal, we reduced the azide **683** to the amine, which induced transamidation *in situ* to provide the spirocyclic lactam **686**. Future plans include acylating the spirocyclic lactam via the dianion to furnish the imide **687**. It is believed that a ring flip to conformer **688** could favor reduction of the carbonyl with an approach vector underneath the flat aromatic rings without steric interference as shown in Scheme 156. Subsequent closure of the tosylamide moiety onto the resultant hemiaminal **689** could then provide the desired bisaminal **690**.

Scheme 156. Transamidation revisited to make a more easily reduced carbonyl.

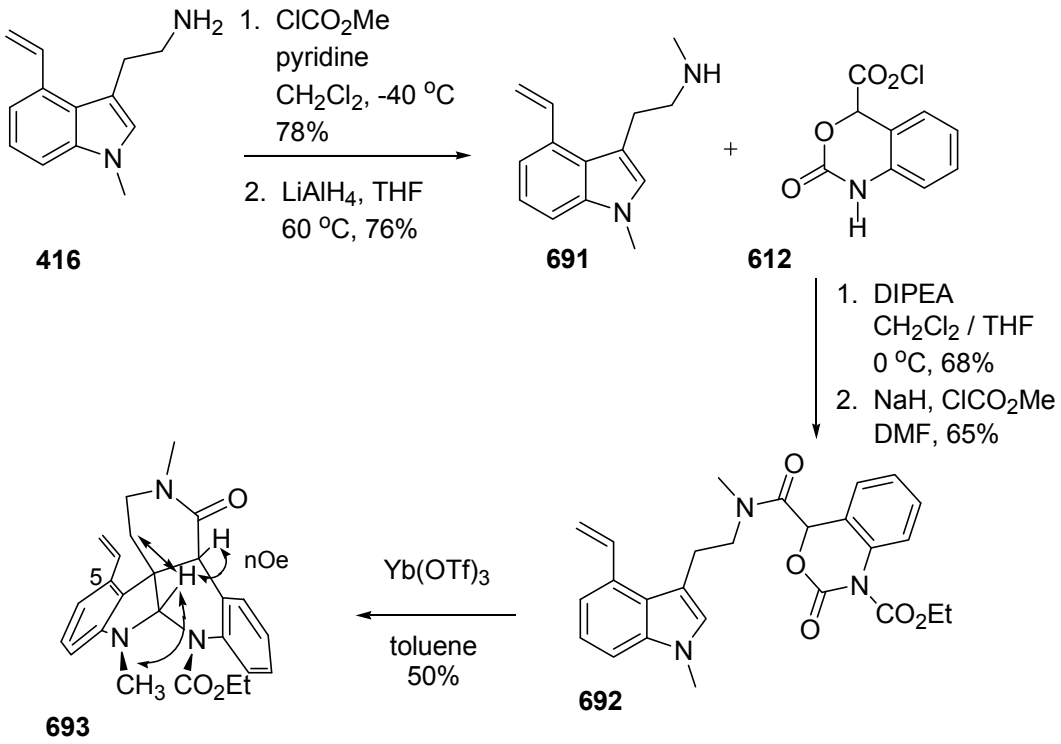


Should this route be successful, it will subsequently be applied towards the spirocyclic lactam analogous to **686** with a C(5) substituent. Concurrently, we have been investigating a synthesis of such a substrate.

D. Application of the Lewis acid catalyzed generation of an acyl-aza-*ortho*-xylylene towards the completion of the total synthesis of communesin B

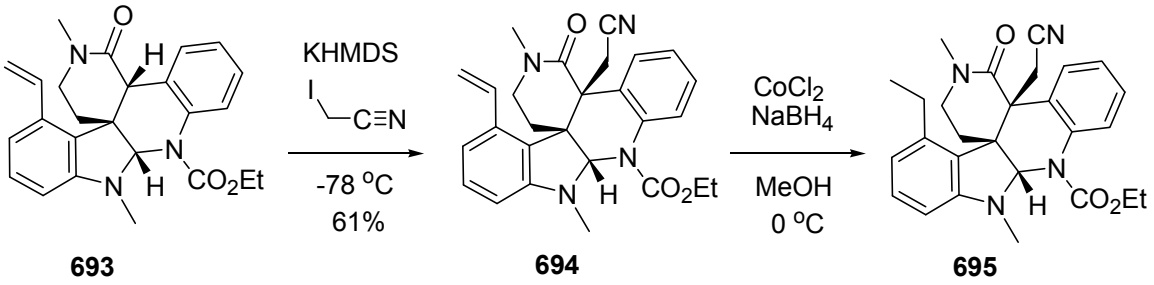
Our efforts now turned towards the incorporation of a C(5) substituent into a cycloadduct in order to have a means of elaborating the benzazepine ring. However, we first had to determine if we could incorporate a C(5) substituent into the cycloadduct. To that end, 4-vinyl-1-methyltryptamine (**416**) was *N*-acylated and reduced to provide the methylated tryptamine derivative **691**. Subsequent amide formation and *N*-acylation as before furnished the imide **692**. Most importantly, thermolysis of the imide **692** in the presence of $Yb(OTf)_3$ gave the expected *endo* isomer **693** in good yield. The relative stereochemistry of the cycloadduct **693** was determined using nOe studies, the most diagnostic of which are shown below in Scheme 157.

Scheme 157. Synthesis of a cycloadduct with a C(5) vinyl substituent.



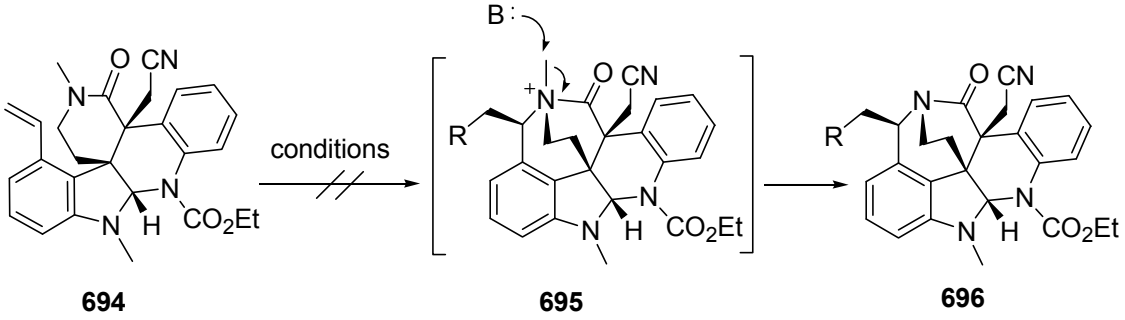
Alkylation of the cycloadduct **693** with iodoacetonitrile provided the nitrile **694**. Unfortunately, reduction using the metal boride conditions used earlier reduced the alkene in preference to the nitrile to give **695** (Scheme 158).[166h]

Scheme 158. Attempted reduction of a nitrile in the presence of an alkene.



In view of the spontaneous intramolecular 7-*exo*-dig closure we observed with the alkyne **541** discussed previously, we believed that the proximity of the nitrogen to the alkene might encourage a rather unusual intramolecular cyclization with the amide nitrogen. Thus, we briefly examined an amide-alkene cyclization by treating **694** with a variety of electrophiles (Scheme 159).[182] Unfortunately, subjection to iodine, NBS, PhSeBr, or mercury(II)trifluoroacetate all provided decomposition products, most likely due to the electron rich and reactive aromatic rings.

Scheme 159. Attempted intramolecular amide-alkene cyclization.

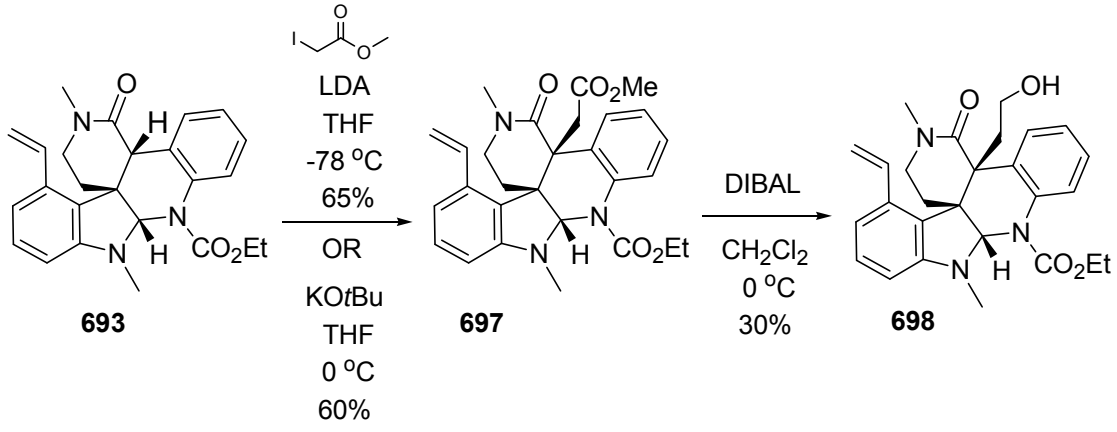


Attempted intramolecular cyclization conditions

1. I_2, CH_2Cl_2, 25 °C
2. I_2, pyridine, 25 °C
3. $(PhSe)_2$, Br_2, CH_3CN, 25 °C
4. PhSeBr, CH_3CN, 60 °C
5. mercury(II) trifluoracetate, K_2CO_3, THF, 50 °C

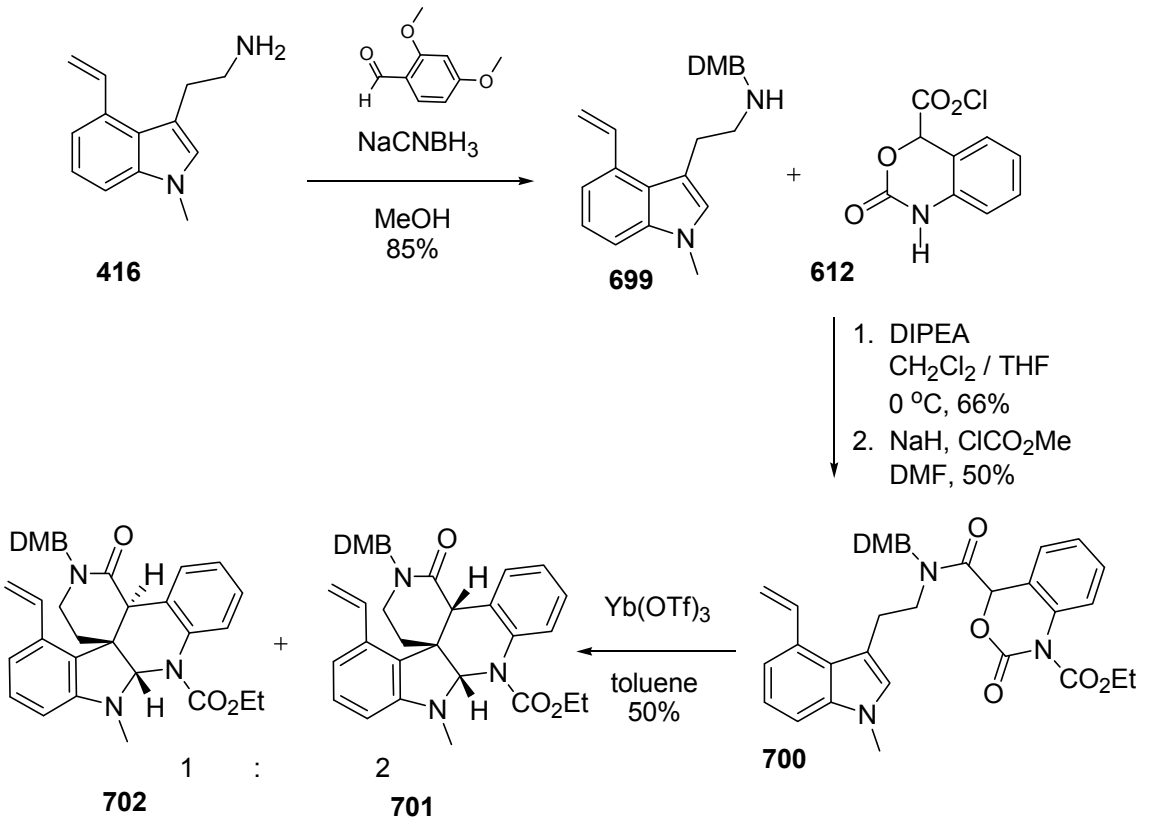
As an alternate means of installing the C(13) vicinal quaternary center, we have also explored the alkylation of **693** with methyl iodoacetate to furnish the ester **697**. Initial attempts to reduce the ester to provide alcohol **698** have proceeded in low yields. Therefore, optimization of this reduction is necessary if this strategy is to be employed (Scheme 160).

Scheme 160. Alkylation and reduction of an ester substituent.



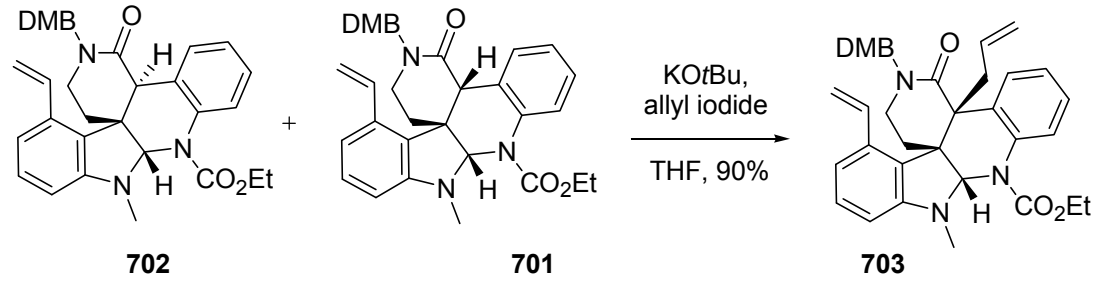
Finally, we have begun an investigation into the elaboration of the aminal via the analogous spirocyclic imide reduction discussed in Scheme 156. Thus, reductive amination of tryptamine **416** with 2,4-dimethoxybenzaldehyde furnished the amine **699**. Subsequent amide formation and *N*-acylation as before provided the imide **700**. Importantly, the ytterbium triflate catalyzed cycloaddition furnished the lactam **701** as an approximate 2:1 ratio of diastereomers (Scheme 161).

Scheme 161. Cycloaddition of the amide for the total synthesis of communesin.



An initial attempt to equilibrate the epimers of **701** was unsuccessful using potassium *t*-butoxide and *t*-BuOH at 0 °C, but alkylation of a mixture of the epimers as before provided the alkene **703** as a single diastereomer (Scheme 162).

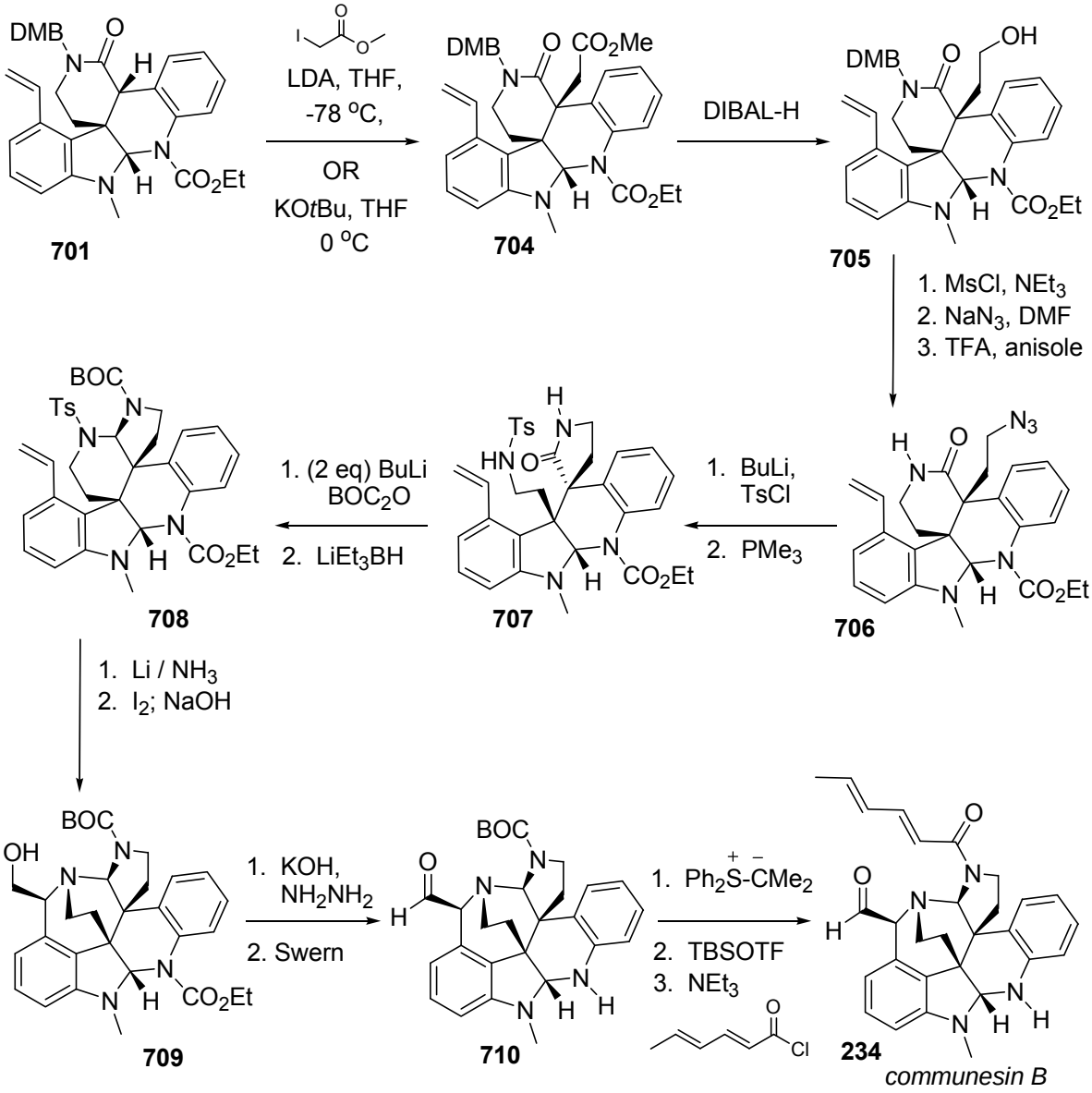
Scheme 162. Alkylation of a mixture of lactams provides one diastereomer.



It is hoped that the lessons learned between the aziridine-based generation of aza-*ortho*-xylylenes and the current route of acyl-aza-*ortho*-xylylenes generated from Lewis acid catalyzed retrocycloaddition/cycloaddition of

N-acyl-3,1-benzoxazin-2-ones with a tethered indole will lead to a successful total synthesis of communesin B. A possible synthetic strategy for the completion of communesin B from the lactam **701** is shown below in Scheme 163. Alkylation of methyl iodoacetate followed by reduction could provide the alcohol **705**. (Alternatively, alkylation of an electron rich olefin, followed by selective oxidative cleavage and reduction of the resultant aldehyde could also provide the alcohol). Subsequent two step conversion to the azide and deprotection would provide the secondary lactam **706**. Sulfonimide formation followed by transamidation could give the spirocyclic lactam **707**. It is hoped that BOC-imide formation followed by reduction of the resultant imide would furnish the aminal **708**. (Alternately, the tosylamide could be deprotected, cyclized onto the alkene via an aziridinium ion as discussed previously, and then closed on a spirocyclic BOC-imide. Also, we have not studied the reduction of the secondary lactam **706**. Potentially, we could make *des*-tosyl **708** via reduction of the azide **706** followed by acylation with BOC_2O of the resultant amine to provide a carbamate. Subsequent reduction of the lactam could then provide *des*-tosyl **708**). Deprotection of the tosylamide **708**, followed by ring closure via an aziridinium ion with subsequent hydroxide mediated ring opening as discussed earlier could provide the alcohol **709**. Deprotection of the aniline as in our initial model studies of communesin B,[92] followed by oxidation could furnish the aldehyde **710**. Sulfur ylid addition[82] to the aldehyde should generate the epoxide, and removal of the BOC protecting group using the Ohfune protocol[183] should leave the epoxide undisturbed. Finally, straightforward acylation could give the natural product.

Scheme 163. Proposed total synthesis of communesin B from a cycloadduct.

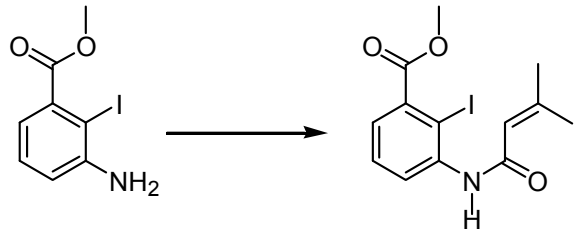


III. Concluding Remarks

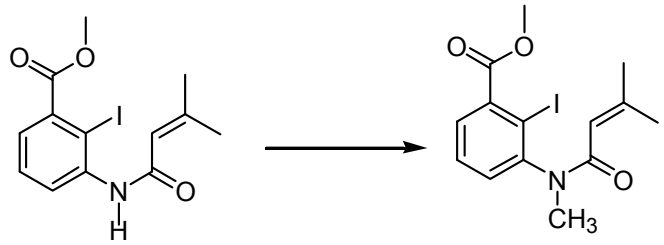
In conclusion, we have helped to correctly assign the structure of nomofungin/communesin B by synthesizing the core ring systems of both molecules employing an intramolecular cycloaddition of an *ortho*-quinone methide and an aza-*ortho*-xylylene with a tethered indole respectively. Initial

attempts to complete the total synthesis of communesin B using the initial benzazepine-based approach were unsuccessful.

Subsequently, a more biomimetic and successful strategy, which led to the development of two novel methods of generating aza-*ortho*-xylylenes via either the acid or base catalyzed ring opening of aziridines, or Lewis acid catalyzed retrocycloaddition of acyl-*N*-acyl-3,1-benzoxazin-2-ones, has been investigated. The latter strategy has also demonstrated that the vicinal quaternary centers of communesin B can be installed via alkylation. It is hoped that the installation of the bisaminal functionality on a model system can be subsequently applied to completion of the total synthesis. Finally, a promising substrate that could be used to complete the total synthesis of communesin B has been synthesized.

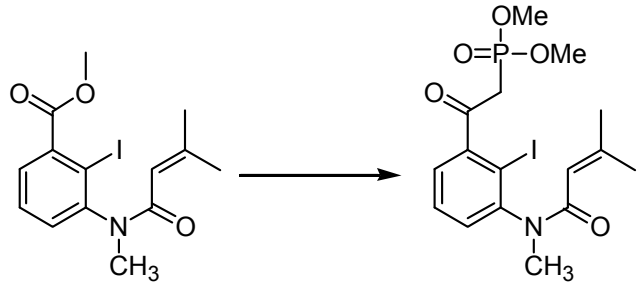


Methyl 3-(3',3'-dimethylacrylamido)-2-iodo-benzoate. To a solution of methyl 3-amino-2-iodo-benzoate (**110**) (6.57 g, 23.7 mmol) in benzene (21.2 mL) was added Na_2CO_3 (3.14 g, 29.6 mmol) and 3,3-dimethyl acroylchloride (**111**) (4.78 g, 40.3 mmol) in benzene (32.5 mL). The solution was stirred at rt 24 h, quenched with saturated aqueous sodium bicarbonate and extracted with Et_2O. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude liquid was purified by silica-gel chromatography (1 : 3 ethyl acetate : hexanes) to provide a yellow foam. (5.65 g, 86 %); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.89 (s, 3 H), 2.20 (s, 3 H), 3.88 (s, 3 H), 5.77 (s, 1 H), 7.26-7.40 (m, 2 H), 7.74 (br s, 1 H), 8.33 (dd, *J* = 1.7, 7.7 Hz, 1 H); ^{13}C (50 MHz, $CDCl_3$) δ 20.0, 27.3, 52.4, 90.5, 118.1, 124.3, 125.6, 128.4, 136.8, 139.6, 154.9, 164.5, 167.3; IR (neat) 3367, 3289, 2949, 1731, 1681, 1643, 1581, 1504, 1297 cm^{-1}; HRMS (M + H^+) calcd for $C_{13}H_{14}NO$ I 360.0096, found 360.0122.



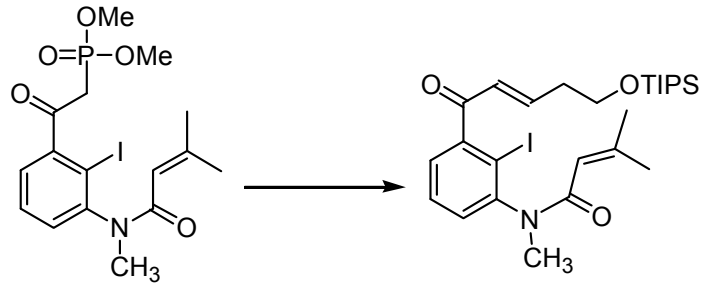
Methyl 3-(*N-methyl*-3',3'-dimethylacrylamido)-2-iodo-benzoate. To a solution of the methyl 3-(3',3'-dimethylacrylamido)-2-iodo-benzoate (5.53 g, 15.4 mmol) in CH_3CN (65 mL) at 0 °C was added KOH (2.59 g, 46.2 mmol) and MeI

(4.79 mL, 77.0 mmol). The solution was stirred at rt for 3 h, quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4), and concentrated. The crude liquid was purified by silica-gel chromatography (1 : 3 ethyl acetate : hexanes) to afford a white foam (4.45 g, 78 %); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.64 (d, *J* = 1.1 Hz, 3 H), 2.13 (d, *J* = 1.1 Hz, 3 H), 3.17 (s, 3 H), 3.95 (s, 3 H), 5.19 (t, *J* = 1.2 Hz, 1 H), 7.31 (dt, *J* = 1.8, 7.7 Hz, 1 H), 7.43 (t, *J* = 7.7 Hz, 1 H), 7.61 (dd, *J* = 1.8, 7.7 Hz, 1 H); ^{13}C (50 MHz, $CDCl_3$) δ 20.2, 27.2, 35.6, 52.7, 100.6, 116.7, 129.3, 129.3, 129.4, 131.5, 139.2, 147.9, 152.3, 166.7, 167.3; IR (neat) 2950, 1732, 1651, 1567, 1434, 1280 cm^{-1}; HRMS (M + H$^+$) calcd for $C_{14}H_{17}O_3NI$ 374.0210, found 374.0279.

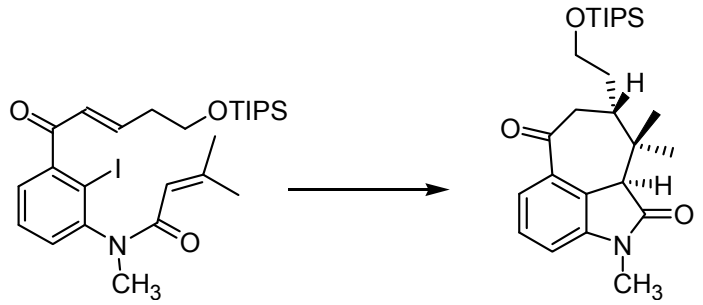


Phosphonate 112 . To a solution of methyl dimethyl phosphonate (1.82 mL, 16.8 mmol) in THF (16.8 mL) at –78 °C was added butyllithium (2.5M in THF, 6.31 mL, 15.8 mmol). The solution was stirred 30 min and cannulated into a –78 °C solution of the methyl ester (1.90 g, 5.09 mmol) in THF (5.0 mL). The solution was stirred at 0 °C over 2 h, quenched with saturated aqueous ammonium chloride, and extracted with Et_2O. The combined organic extracts were dried (Na_2SO_4), and concentrated. The crude liquid was purified by silica-gel chromatography (9 : 1 ethyl acetate : hexanes) to afford an orange oil (2.07 g, 77 %); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.57 (d, *J* = 1.1 Hz, 3 H), 2.05 (d, *J* = 1.1 Hz, 3 H), 3.08 (s, 3 H), 3.55 (d, *J* = 1. 4 Hz, 1 H), 3.67 (s, 3 H), 3.73 (s, 3 H), 5.12 (t, *J* = 1.3 Hz, 1 H), 7.23 (d, *J* = 2.8 Hz, 1 H), 7.26 (d, *J* = 2.8 Hz, 1 H), 7.20-7.40 (m, 2H); ^{13}C (50 MHz, $CDCl_3$) δ 20.0, 27.0, 35.4, 39.2, 41.8, 52.8, 53.0, 97.3,

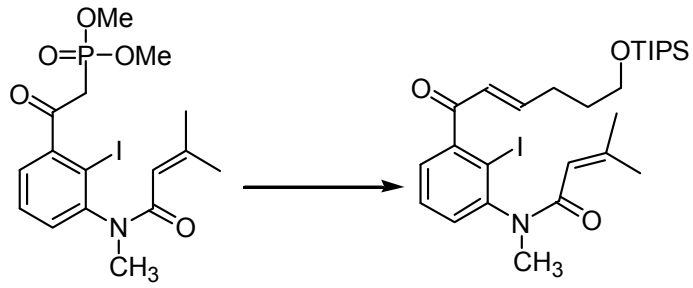
116.5, 127.5, 129.7, 130.9, 146.8, 147.3, 152.2, 166.4, 195.4, 195.5; IR (neat) 3481, 2954, 1698, 1650, 1566, 1453, 1259, 1030 cm^{-1}; HRMS (M + H^+) calcd for $C_{16}H_{21}O_5NPI$ 466.0280, found 466.0257.



Enone 81. To a solution of the phosphonate **112** (2.23 g, 4.23 mmol) in THF (85.0 mL) at -78 °C was added 3-(triisopropylsiloxy)propanal (**113**) (1.07 g, 4.65 mmol) and tetramethylguanidine (530 μL, 4.23 mmol). The solution was stirred at rt for 12 h, quenched with saturated aqueous ammonium chloride and extracted with Et_2O. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. The crude oil was purified by silica-gel chromatography (1 : 5 ethyl acetate : hexanes) to afford a yellow oil (1.24 g, 50 %); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.02 (s, 21 H), 1.66 (s, 3 H), 2.13 (s, 3 H), 2.49-2.52 (m, 3 H), 3.18 (s, 3 H), 3.81 (t, *J* = 6.1 Hz, 2 H), 5.24 (t, *J* = 1.2 Hz, 1 H), 6.49 (dd, *J* = 1.0, 16.0 Hz, 1 H), 6.68 (dt, *J* = 6.8, 15.9 Hz, 1 H), 7.15 (dd, *J* = 1.6, 7.4 Hz, 1 H), 7.26 (dd, *J* = 1.6, 7.9 Hz, 1 H), 7.42 (t, *J* = 7.6 Hz, 1 H); ^{13}C (50 MHz, $CDCl_3$) δ 11.6, 18.9, 20.2, 27.2, 29.1, 31.4, 35.8, 62.2, 98.1, 118.1, 126.8, 129.3, 146.8, 147.2, 152.1, 153.7, 166.6, 196.0; HRMS (M + H^+) calcd for $C_{27}H_{42}O_3NISi$ 582.2051, found 584.2041.

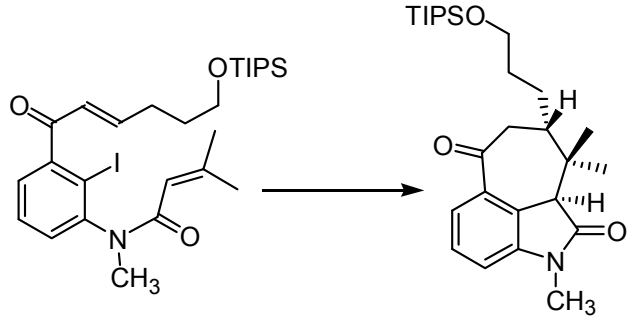


Ketone 114. To a refluxing solution of enone **81** (690 mg, 1.21 mmol) in toluene (12.1 mL) was added via syringe pump over 1 h a solution of ACN (14.8 mg, 0.061 mmol) and $(TMS)_3SiH$ (747 μL, 2.42 mmol) in toluene (9.1 mL). The solution was stirred for 3 h and concentrated. The crude oil was purified by silica-gel chromatography (1 : 7 ethyl acetate : hexanes) to afford a yellow foam (225 mg, 42 %); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.70 (s, 3 H), 1.00 (s, 21 H), 1.40 (s, 3 H), 1.53-1.74 (m, 2 H), 2.58 (d, *J* = 16.5 Hz, 1 H), 2.83 (dd, *J* = 9.3, 16.5 Hz, 1 H), 3.23 (s, 3 H), 3.43 (s, 1 H), 3.66 (t, *J* = 5.7 Hz, 2 H), 6.99 (d, *J* = 7.8 Hz, 1 H), 7.38 (t, *J* = 7.8 Hz, 1 H), 7.62 (dd, *J* = 0.9, 8.0 Hz, 1 H); ^{13}C (75 MHz, $CDCl_3$) δ 11.9, 12.6, 17.7, 17.9, 20.6, 22.0, 26.2, 26.8, 31.4, 38.3, 38.4, 43.7, 44.1, 54.2, 62.9, 111.5, 120.9, 128.1, 128.7, 132.9, 144.7; IR (neat) 2942, 2865, 1711, 1688, 1605, 1466 cm^{-1}.

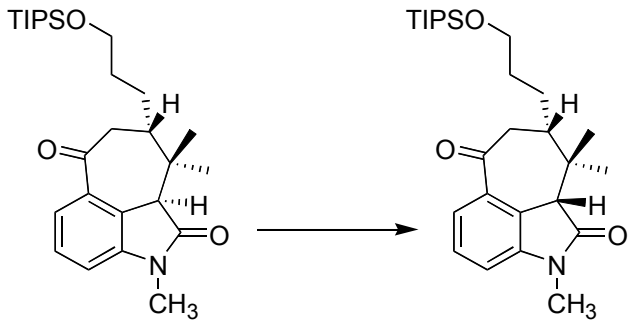


Enone 126. To a solution of the phosphonate **81** (2.25 g, 4.25 mmol) in THF (17.0 mL) at -78 °C was added 4-(triisopropylsiloxy)butanal (**127**) (1.04 g, 4.25 mmol) and tetramethylguanidine (587 μL, 4.67 mmol). The solution was stirred at rt 12 h, quenched with saturated aqueous ammonium chloride and extracted with Et_2O. The combined organic extracts were washed with brine,

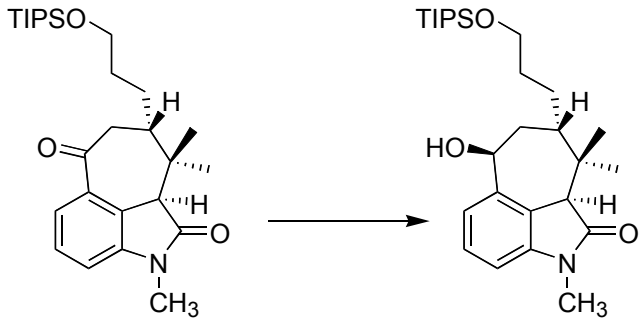
dried (Na_2SO_4), and concentrated. The crude oil was purified by silica-gel chromatography (1 : 5 ethyl acetate : hexanes) to afford a yellow oil (1.13 g, 45 %); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.05 (s, 21 H), 1.60 (s, 3 H), 1.60-1.78 (m, 2 H), 2.14 (s, 3 H), 2.34-2.15 (m, 2 H), 3.19 (s, 3 H), 3.71 (t, *J* = 6.1 Hz, 1 H), 5.24 (t, *J* = 1.2 Hz, 1 H), 6.46 (d, *J* = 15.8 Hz, 1 H), 6.65 (dt, *J* = 6.6, 15.8 Hz, 1 H), 7.19 (dd, *J* = 1.6, 7.3 Hz, 1 H), 7.29 (dd, *J* = 1.6, 7.9 Hz, 1 H), 7.45 (t, *J* = 7.7 Hz, 1 H); ^{13}C (50 MHz, $CDCl_3$) δ 11.8, 17.5, 20.6, 27.2, 35.8, 36.8, 61.4, 97.9, 116.8, 127.9, 129.3, 130.0, 131.0, 147.2, 147.7, 150.8, 152.1, 167.5, 196.0; IR (neat) 2941, 2865, 2360, 1659, 1454 cm^{-1}.



Ketone 125. To a refluxing solution of enone **126** (594 mg, 1.02 mmol) in toluene (12.7 mL) was added via syringe pump over 1 h a solution of ACN (12.4 mg, 0.05 mmol) and $(TMS)_3SiH$ (678 μL, 2.03 mmoL) in toluene (9.5 mL). The solution was stirred for 3 h and concentrated. The crude oil was purified by silica-gel chromatography (1 : 7 ethyl acetate : hexanes) to afford a white foam (270 mg, 58 %); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.80 (s, 3 H), 0.99-1.10 (m, 21 H), 1.39 (s, 3 H), 1.60-1.80 (m, 4 H), 2.62 (d, *J* = 16.4 Hz, 1 H), 2.87 (dd, *J* = 9.2, 16.7 Hz, 1 H), 3.23 (s, 3 H), 3.44 (s, 1 H), 3.63 (t, *J* = 5.8 Hz, 2 H), 7.02 (d, *J* = 7.6 Hz, 1 H), 7.42 (t, *J* = 7.7 Hz, 1 H), 7.65 (d, *J* = 8.0 Hz, 1 H).

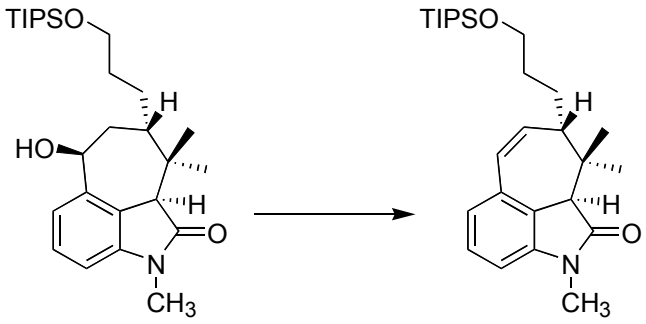


***Epi*-ketone 125.** To a solution of the ketone **125** (12 mg, 0.041 mmol) in MeOH (204 μL) at 0 °C was added K_2CO_3 (5.6 mg, 0.041 mmol). The solution was stirred for 3 h, quenched with saturated aqueous ammonium chloride and extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. The crude product was used without purification (10 mg, 83 %); ^{1}H NMR (200 MHz, d_6-benzene) δ 0.66 (s, 3 H), 0.80-1.1 (m, 4 H), 1.20 (s, 3 H), 2.46 (d, *J* = 16.4 Hz, 1 H), 2.49 (s, 3 H), 2.50 (s, 3 H), 3.12 (t, *J* = 5.8 Hz, 1 H), 4.83 (dd, *J* = 9.2, 16.7 Hz, 1 H), 6.15 (d, *J* = 7.4 Hz, 1 H), 6.96 (t, *J* = 7.7 Hz, 1 H), 7.81 (d, *J* = 8.0 Hz, 1 H).

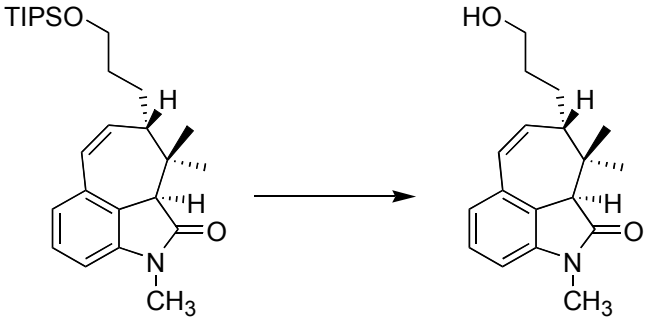


Alcohol 127. To a 0 °C solution of the ketone **125** (219 mg, 0.481 mmol) in THF (9.6 mL) and *i*-PrOH (463 μL) was added SmI_2 (77 μL, 2.6 mmol) dropwise. The solution was stirred at rt for 1 h, quenched with 0.1 M HCl and extracted with Et_2O. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. The crude oil was purified by silica-gel chromatography (1 : 5 ethyl acetate : hexanes) to afford a yellow oil (140 mg, 64 %); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.70 (s, 3 H), 1.02 (s, 21 H), 1.32 (s, 3 H), 1.48-

1.90 (m, 4 H), 3.20 (s, 3 H), 3.38 (br s, 1 H), 3.65-3.80 (br m, 2 H), 5.06 (br s, 1 H), 6.65-6.73 (m, 2 H), 7.20-7.28 (m, 1 H).

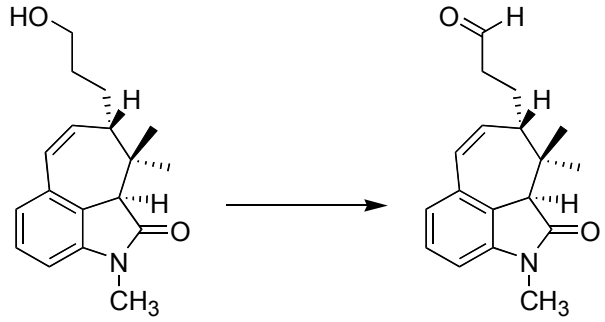


Alkene 128. To a solution of the alcohol **127** (57.5 mg, 0.125 mmol) in toluene (1.25 mL) was added a solution of iodine in toluene (265 μL of a 0.236 M solution). The solution was stirred for 1.5 h at 110 °C, quenched with 1 : 1 saturated aqueous sodium bicarbonate / 10 % $Na_2S_2O_3$, and extracted with Et_2O. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was used in the next reaction without purification (41.3 mg, 75 %); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.71 (s, 3 H), 0.99-1.10 (m, 21 H), 1.46 (s, 3 H), 1.70-1.95 (m, 4 H), 3.12 (s, 1 H), 3.21 (s, 3 H), 3.69 (t, *J* = 6.5 Hz, 2 H), 6.00 (dd, *J* = 6.2, 12.0 Hz, 1 H), 6.51 (d, *J* = 12.0 Hz, 1 H), 6.68 (d, *J* = 7.4 Hz, 1 H), 6.88 (d, *J* = 8.0 Hz, 1 H), 7.26 (t, *J* = 7.7 Hz, 1 H).

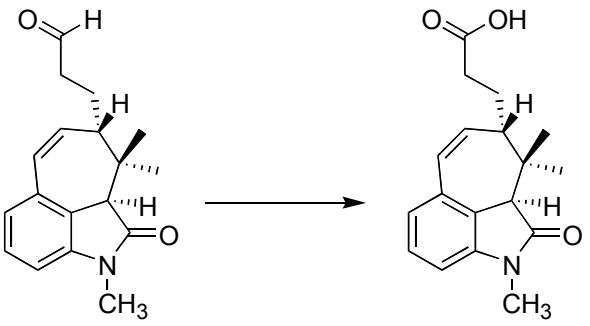


Alcohol 128a. To a solution of the alkene **128b** (129 mg, 0.292 mmol) in THF (2.9 mL) at 0 °C was added HF•pyridine (130 μL, 4.17 mmol). The solution was stirred for 12 h at 0 °C , quenched with saturated aqueous sodium

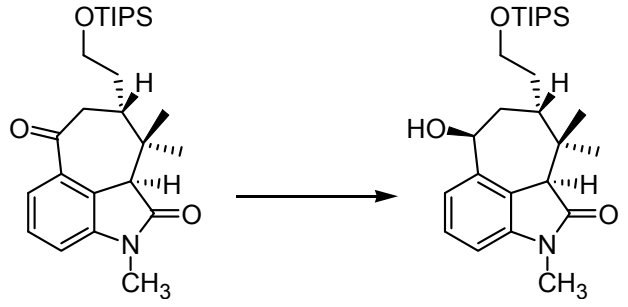
bicarbonate and extracted with Et_2O. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was used in the next reaction without purification (51 mg, 62 %); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.72 (s, 3 H), 1.41 (s, 3 H), 1.63-1.90 (m, 4 H), 3.05 (s, 1 H), 3.19 (s, 3 H), 3.63 (t, *J* = 6.5 Hz, 1 H), 5.98 (dd, *J* = 6.2, 12.0 Hz, 1 H), 6.52 (d, *J* = 12.0 Hz, 1 H), 6.71 (d, *J* = 7.4 Hz, 1 H), 6.37 (d, *J* = 8.0 Hz, 1 H), 7.26 (t, *J* = 7.7 Hz, 1 H).



3-(2,9,9-Trimethyl-1-oxo-2,8,9,9a-tetrahydro-1H-2-aza-benzo[cd]azulen-8-yl)-propionaldehyde. To a solution of the alcohol prepared in the previous experiment (15 mg, 0.053 mmol) in CH_2Cl_2 (180 μL) was added Dess-Martin reagent (33 mg, 0.080 mmol) and H_2O (1.0 μL, 0.058 mmol) in CH_2Cl_2 (100 μL). The solution was stirred for 15 min, then quenched with 1 : 1 $Na_2S_2O_3$ / saturated aqueous sodium bicarbonate, and extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was used in the next reaction without purification (11 mg, 73 %); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.83 (s, 3 H), 1.41 (s, 3 H), 1.40-2.10 (m, 2 H), 2.30-2.70 (m, 2 H), 3.06 (s, 1 H), 3.10 (s, 3 H), 5.90 (dd, *J* = 6.5, 12.0 Hz, 1 H), 6.55 (d, *J* = 12.0 Hz, 1 H), 6.70 (d, *J* = 7.4 Hz, 1 H), 6.86 (d, *J* = 8.0 Hz, 1 H), 7.26 (t, *J* = 7.7 Hz, 1 H), 9.75 (s, 1 H).

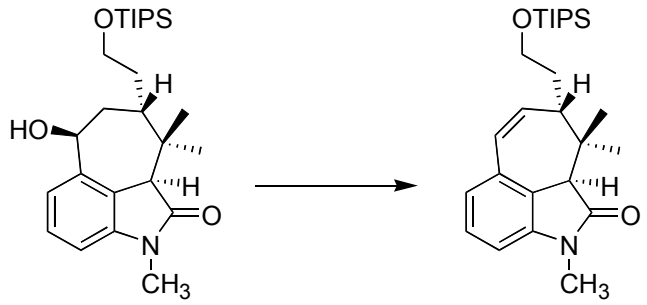


Acid 130. To a 0 °C solution of the aldehyde prepared in the previous experiment (11 mg, 0.039 mmol) in THF (215 μL) and 10 % aqueous NaH_2PO_4 (215 μL) was added a 10 % methyl sulfide in THF solution (72 μL, 1.1 mmol) and a 10 % aqueous $NaClO_2$ solution (42 μL, 0.46 mmol). The solution was stirred for 1 h at 0 °C, quenched with H_2O, and extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was used in the next reaction without purification (11 mg, 99 %); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.75 (s, 3 H), 1.40 (s, 3 H), 1.48-1.70 (m, 1 H), 1.81-2.00 (m, 1 H), 2.20-2.60 (m, 2 H), 3.08 (s, 1 H), 3.20 (s, 3 H), 5.93 (dd, *J* = 6.5, 12.0 Hz, 1 H), 6.56 (d, *J* = 12.0 Hz, 1 H), 6.70 (d, *J* = 7.4 Hz, 1 H), 6.86 (d, *J* = 8.0 Hz, 1 H), 7.26 (t, *J* = 7.7 Hz, 1 H).

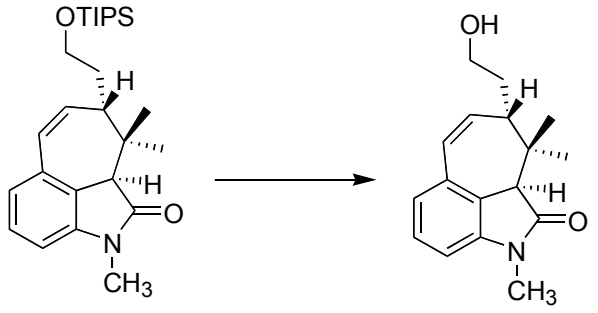


6-Hydroxy-2,9,9-trimethyl-8-(2-triisopropylsilanyloxy-ethyl)-2,6,7,8,9,9a-hexahydro-2-aza-benzo[cd]azulen-1-one. To a 0 °C solution of the ketone **114** (158 mg, 0.356 mmol) in THF (712 μL) and *i*-PrOH (344 μL) was added SmI_2 (19.6 μL, 1.96 mmol) dropwise. The solution was stirred at rt for 1 h, quenched with 0.1 M HCl and extracted with Et_2O. The combined organic

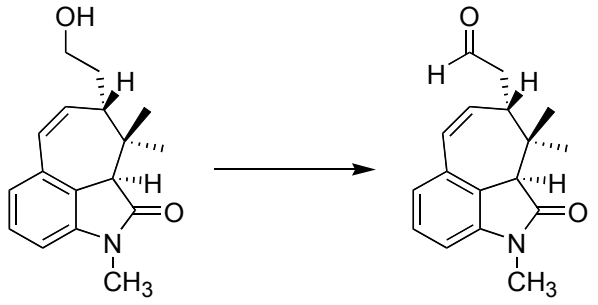
extracts were dried (Na_2SO_4) and concentrated. The crude oil was purified by silica-gel chromatography (1 : 5 ethyl acetate : hexanes) to afford a yellow oil (68 mg, 70 %); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.70 (s, 3 H), 1.00 (s, 21 H), 1.32 (s, 3 H), 1.60-1.99 (m, 2 H), 3.12 (s, 3 H), 3.38 (s, 1 H), 3.90 (dd, *J* = 4.1, 8.0 Hz, 2 H), 4.95 (br s, 1 H), 6.62-6.71 (m, 2 H), 7.20-7.28 (m, 2 H).



Alkene 131. To a solution of the alcohol prepared in the previous experiment (68 mg, 0.25 mmol) in toluene (1.25 mL) was added a solution of iodine in toluene (318 μL of a 0.395 M solution). The solution was stirred for 1.5 h at 110 °C, quenched with 1 : 1 saturated aqueous sodium bicarbonate / 10 % $Na_2S_2O_3$, and extracted with Et_2O. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product thus obtained was used in the next reaction without purification (60 mg, 88 %); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.71 (s, 3 H), 0.99-1.10 (m, 21 H), 1.41 (s, 3 H), 1.86-2.15 (m, 2 H), 3.11 (s, 1 H), 3.21 (s, 3 H), 3.70-3.90 (m, 2 H), 6.00 (dd, *J* = 6.2, 12.0 Hz, 1 H), 6.51 (d, *J* = 12.0 Hz, 1 H), 6.70 (d, *J* = 8.0 Hz, 1 H), 7.26 (t, *J* = 7.7 Hz, 1 H).

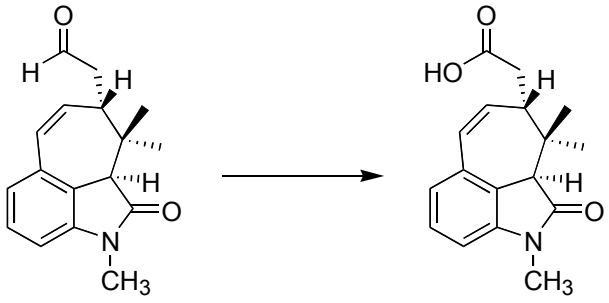


8-(2-Hydroxy-ethyl)-2,9,9-trimethyl-2,8,9,9a-tetrahydro-2-aza-benzo[cd]azulen-1-one. To a solution of alkene **131** (344 mg, 0.804 mmol) in THF (8.0 mL) at 0 °C was added HF•pyridine (358 μL, 11.5 mmol). The solution was stirred for 12 h at 0 °C, quenched with saturated aqueous sodium bicarbonate and extracted with Et_2O. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product thus obtained was used in the next reaction without purification (139 mg, 69 %); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.72 (s, 3 H), 1.42 (s, 3 H), 1.63-1.75 (m, 1 H), 1.78 (br s, 1 H), 1.75-2.10 (m, 1 H), 3.11 (s, 1 H), 3.21 (s, 1 H), 3.60-3.85 (m, 2 H), 6.00 (dd, *J* = 6.2, 12.0 Hz, 1 H), 6.55 (d, *J* = 12.0 Hz, 1 H), 6.70 (d, *J* = 7.4 Hz, 1 H), 6.86 (d, *J* = 8.0 Hz, 1 H), 7.26 (t, *J* = 7.7 Hz, 1 H).

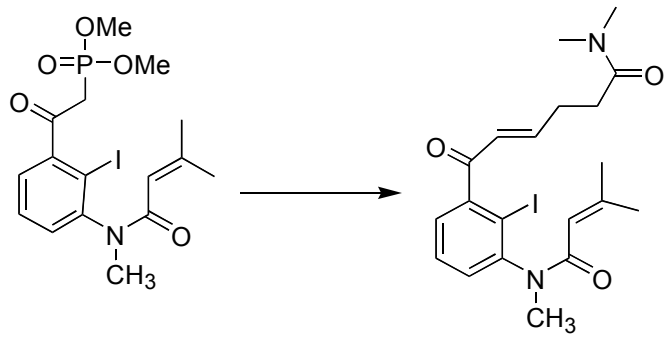


(2,9,9-Trimethyl-1-oxo-2,8,9,9a-tetrahydro-1H-2-aza-benzo[cd]azulen-8-yl)-acetaldehyde. To a solution of the alcohol prepared in the previous experiment (13 mg, 0.048 mmol) in CH_2Cl_2 (240 μL) was added Dess-Martin reagent (30 mg, 0.07 mmol) and H_2O (1.0 μL, 0.058 mmol) in CH_2Cl_2 (100 μL). The solution was stirred for 15 min, then quenched with 1 : 1 $Na_2S_2O_3$ / saturated

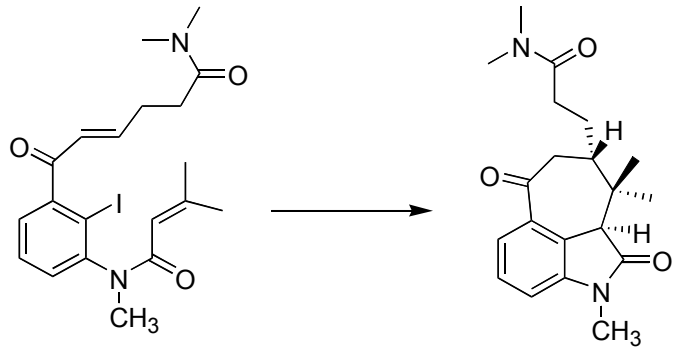
aqueous sodium bicarbonate, and extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product thus obtained was used in the next reaction without purification (11 mg, 85 %); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.73 (s, 3 H), 1.44 (s, 3 H), 2.42-2.83 (m, 2 H), 3.12 (s, 1 H), 3.20 (s, 3 H), 5.85 (dd, *J* = 6.5, 12.0 Hz, 1 H), 6.49 (d, *J* = 12.0 Hz, 1 H), 6.72 (d, *J* = 7.4 Hz, 1 H), 6.87 (d, *J* = 8.0 Hz, 1 H), 7.26 (t, *J* = 7.7 Hz, 1 H), 9.75 (s, 1 H).



Acid 133. To a 0 °C solution of the aldehyde prepared in the previous experiment (15 mg, 0.056 mmol) in THF (315 μL) and 10 % aqueous NaH_2PO_4 (315 μL) was added 10 % methyl sulfide solution in THF (123 μL, 1.67 mmol) and 10 % aqueous $NaClO_2$ (60 μL, 0.67 mmol). The solution was stirred for 1 h at 0 °C, quenched with H_2O, and extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product thus obtained was used in the next reaction without purification (15 mg, 95 %); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.83 (s, 3 H), 1.42 (s, 3 H), 2.30-2.75 (m, 2 H), 3.10 (s, 1 H), 3.20 (s, 3 H), 5.95 (dd, *J* = 6.5, 12.0 Hz, 1 H), 6.48 (d, *J* = 12.0 Hz, 1 H), 6.70 (d, *J* = 7.4 Hz, 1 H), 6.87 (d, *J* = 8.0 Hz, 1 H), 7.26 (t, *J* = 7.7 Hz, 1 H).

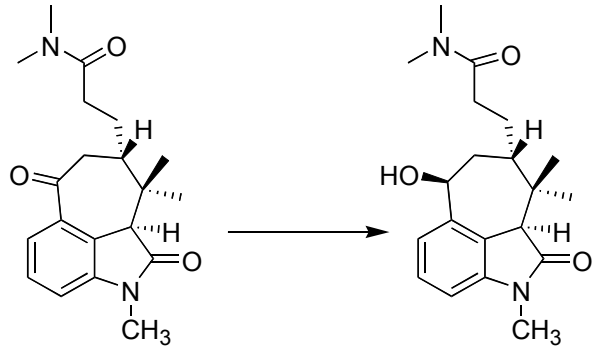


Amide 135. To a solution of the phosphonate **112** (156 mg, 0.295 mmol) in THF (5.91 mL) at -78 °C was added (42 mg, 0.32 mmol) and tetramethylguanidine (41 μL, 0.32 mmol). The solution was stirred to room temperature for 12 h, quenched with saturated aqueous ammonium chloride and extracted with Et_2O. The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. Purification by silica-gel chromatography (1 : 1 : 8 hexanes : *i*-PrOH : ethyl acetate) afforded a yellow oil (94 mg, 70 %); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.65 (s, 3 H), 2.12 (s, 3 H), 2.48 (t, *J* = 6.6 Hz, 2 H), 2.61 (t, *J* = 6.6 Hz, 2 H), 2.92 (s, 3 H), 2.99 (s, 3 H), 3.16 (s, 3 H), 5.23 (s, 1 H), 6.42 (d, *J* = 16.0 Hz, 1 H), 6.72 (dt, *J* = 6.1, 16.0 Hz, 1 H), 7.21 (dt, *J* = 1.7, 7.3 Hz, 1 H), 7.26 (d, *J* = 7.5 Hz, 1 H), 7.41 (t, *J* = 7.5 Hz, 1 H).

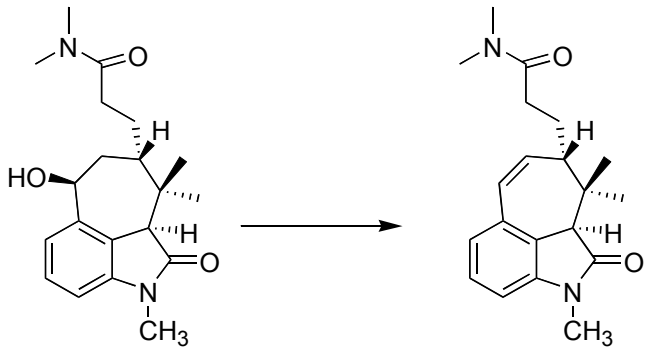


Ketone 136. To a solution of enone **135** (690 mg, 1.21 mmol) in toluene (12.1 mL) at 90 °C was added via syringe pump over 3 h, a solution of ACN (14.8 mg, 0.061 mmol) and $(TMS)_3SiH$ (747 μL, 2.42 mmoL) in toluene (9.1 mL). The solution was stirred for 3 h and concentrated. Purification by silica-gel

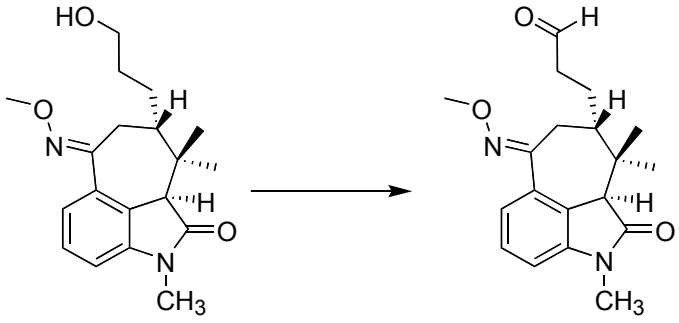
chromatography (1 : 1 : 8 hexanes : *i*-PrOH : ethyl acetate) afforded a yellow foam (40 mg, 58 %); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (s, 3 H), 1.41 (s, 3 H), 1.65 (br m, 2 H), 1.91-1.99 (m, 1 H), 2.19 (dd, *J* = 7.6, 15.8 Hz, 1 H), 2.39-2.49 (m, 1 H), 2.50 (d, *J* = 16.7 Hz, 1 H), 2.88 (dd, *J* = 5.6, 16.5 Hz, 1 H), 2.90 (s, 3 H), 2.97 (s, 3 H), 3.23 (s, 3 H), 3.44 (s, 1 H), 6.98 (dd, *J* = 0.6, 7.7 Hz, 1 H), 7.39 (dt, *J* = 0.7, 7.9 Hz, 1 H), 7.61 (dd, *J* = 0.9, 8.0 Hz, 1 H).



3-(6-Hydroxy-2,9,9-trimethyl-1-oxo-2,6,7,8,9,9a-hexahydro-1H-2-aza-benzo[cd]azulen-8-yl)-N,N-dimethyl-propionamide. To a 0 °C solution of the ketone **136** (38 mg, 0.11 mmol) in THF (2.2 mL) and *i*-PrOH (107 μL) was added SmI_2 (6.1 μL, 0.61 mmol) dropwise. The solution was stirred at room temperature for 1 h, quenched with 0.1M HCl and extracted with Et_2O. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude oil was purified by silica-gel chromatography (1 : 1 : 8 hexanes : *i*-PrOH : ethyl acetate) to afford an orange oil (23 mg, 60 %); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.65 (s, 3 H), 1.31 (s, 3 H), 1.40-1.82 (m, 2 H), 2.30-2.67 (m, 2 H), 2.85 (s, 3 H), 2.85-3.02 (m, 2 H), 3.02 (s, 3 H), 3.16 (s, 3 H), 3.33 (s, 1 H), 4.67 (br d, *J* = 9.0 Hz, 1 H), 4.99 (br m, 1 H), 6.67 (d, *J* = 7.7 Hz, 1 H), 7.30 (d, *J* = 8.0 Hz, 1 H), 7.35 (t, *J* = 7.9 Hz, 1 H).

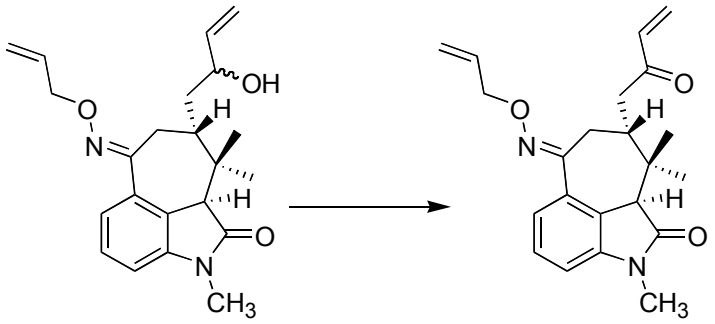


Alkene 137. To a solution of the alcohol prepared in the previous experiment (17 mg, 0.053 mmol) in toluene (510 μL) was added a solution of iodine in toluene (107 μL of a 0.236 M solution). The solution was stirred for 1.5 h at 110 °C, quenched with 1 : 1 saturated aqueous sodium bicarbonate / 10 % $Na_2S_2O_3$, and extracted with Et_2O. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product thus obtained was used in the next reaction without purification (10 mg, 58 %); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.84 (s, 3 H), 1.40 (s, 3 H), 1.84-2.60 (m, 4 H), 2.93 (s, 3 H), 2.98 (s, 3 H), 3.10 (s, 1 H), 3.19 (s, 3 H), 5.98 (dd, *J* = 6.5, 12.0 Hz, 1 H), 6.55 (d, *J* = 12.0 Hz, 1 H), 6.70 (d, *J* = 7.7 Hz, 1 H), 6.87 (d, *J* = 8.0 Hz, 1 H), 7.26 (t, *J* = 7.9 Hz, 1 H).

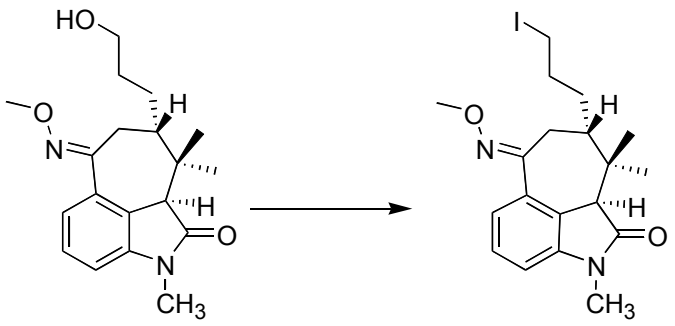


Aldehyde 153. To a solution of oxalyl chloride (35 μL, 0.40 mmol) in CH_2Cl_2 (3 mL) at -78 °C was added DMSO (109 μL, 1.54 mmol). The solution was stirred for 5 min, then a solution of the alcohol **152** (63 mg, 0.19 mmol) in CH_2Cl_2 (1.9 mL) was added. The solution was stirred 45 min at -78 °C and then triethylamine (657 μL, 4.72 mmol) was added. The solution was stirred at rt for 1

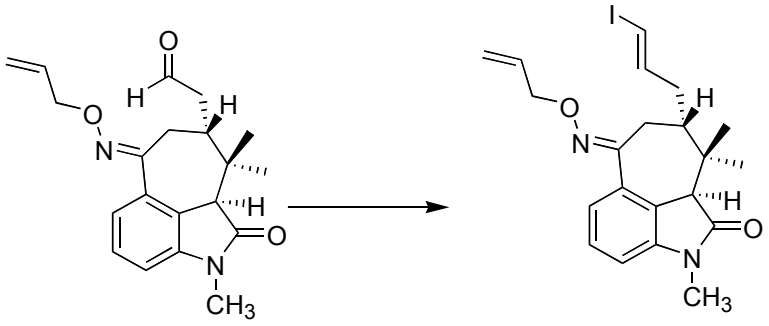
h, quenched with saturated aqueous sodium bicarbonate, and extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by silica-gel chromatography (4 : 1 hexanes : ethyl acetate) to afford a yellow oil (27 mg, 42%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.80(s, 3 H), 1.48 (s, 3 H), 1.82-1.96 (m, 1 H), 2.30-2.75 (m, 3 H), 3.00 (d, *J* = 16.7 Hz, 1 H), 3.20 (s, 3 H), 3.30 (s, 1 H), 4.00 (s, 3 H), 6.78 (d, *J* = 7.6 Hz, 1 H), 7.26 (t, *J* = 7.7 Hz, 1 H), 7.40 (d, *J* = 8.0 Hz, 1 H), 9.76 (s, 1 H).



Enone 155. To a solution of the alcohol **154** (10.1 mg, 0.027 mmol) in CH_2Cl_2 (270 μL) was added Dess-Martin reagent (17.3 mg, 0.041 mmol) and a solution of H_2O (522 μL) in CH_2Cl_2 (522 μL) over 5 min. The solution was stirred for 30 minutes, quenched with 1 : 1 saturated aqueous $NaHCO_3$ / $Na_2S_2O_3$ and extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by silica-gel chromatography (2 : 1 hexanes : ethyl acetate) to afford a yellow oil (9.04 mg, 92%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.80 (s, 3 H), 1.49 (s, 3 H), 2.15-2.30 (br m, 1 H), 2.50-2.80 (m, 5 H), 3.20 (s, 3 H), 3.30 (s, 1 H), 4.62 (d, *J* = 5.0 Hz, 2 H), 5.16-5.32 (m, 2 H), 5.70-6.45 (m, 3 H), 6.79 (d, *J* = 7.6 Hz, 1 H), 7.24-7.40 (m, 2 H).

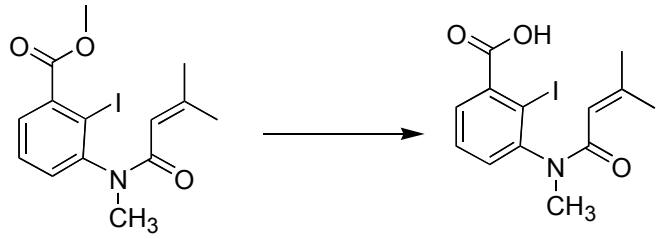


Iodide 171. To a solution of the alcohol **170** (15 mg, 0.045 mmol) in benzene (500 μL) was added imidazole (3.7 mg, 0.054 mmol), triphenylphosphine (14 mg, 0.054 mmol), and iodine (12 mg, 0.054 mmol). The solution was stirred for 2 h at room temperature, quenched with 1 : 1 saturated aqueous $NaHCO_3$ / $Na_2S_2O_3$, and extracted with hexanes. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by silica-gel chromatography (10 : 1 hexanes : ethyl acetate) to afford an orange oil (9.01 mg, 92%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.67 (s, 3 H), 1.34 (s, 3 H), 1.50-1.80 (m, 4 H), 2.50 (dd, *J* = 9.2, 16.7 Hz, 1 H), 3.02 (d, *J* = 16.7 Hz, 1 H), 3.10-3.25 (m, 2 H), 3.19 (s, 3 H), 3.30 (s, 1 H), 4.00 (s, 3 H), 6.78 (d, *J* = 7.6 Hz, 1 H), 7.26 (t, *J* = 7.7 Hz, 1 H), 7.40 (d, *J* = 8.0 Hz, 1 H).

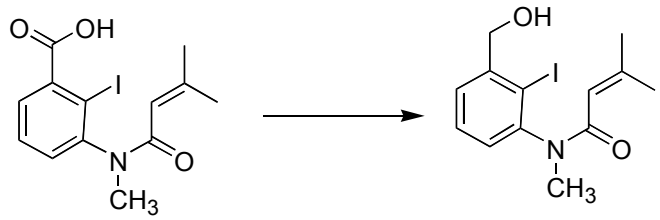


Iodide 176. To a solution of $CrCl_2$ (113 mg, 0.919 mmol) in THF (1.5 mL) at 0 °C was added a solution of the aldehyde **153** (40.0 mg, 0.118 mmol) and CHI_3 (92.5 mg, 0.235 mmol) in THF (587 μL). The solution was stirred for 4 h at 0 °C, quenched with H_2O, and extracted with ether. The crude product was purified by deactivated (NEt_3) silica-gel chromatography (5 : 1 hexanes : ethyl

acetate) to afford a yellow oil (45 mg, 83%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.76 (s, 3 H), 1.30 (s, 3 H), 1.80-1.99 (m, 1 H), 2.15-2.26 (m, 1 H), 2.43 (dd, *J* = 9.2, 16.7 Hz, 1 H), 3.05-3.20 (m, 1 H), 3.20 (s, 3 H), 3.21 (d, *J* = 16.7 Hz, 1 H), 3.30 (s, 1 H), 4.65-4.73 (m, 2 H), 5.20-5.40 (m, 2 H), 5.96-6.23 (m, 2 H), 6.38-6.50 (m, 1 H), 6.77 (d, *J* = 7.6 Hz, 1 H), 7.26 (t, *J* = 8.0 Hz, 1 H), 7.40 (t, *J* = 8.0 Hz, 1 H).

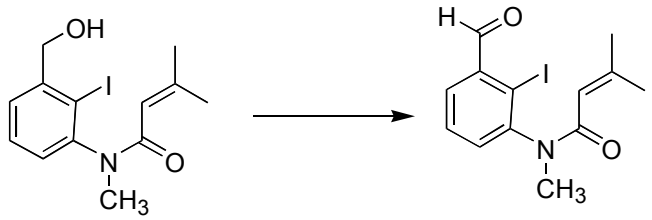


2-Iodo-3-[*N*-methyl-(3-methyl-but-2-enoyl)-amino]-benzoic acid. To a solution of methyl 2-Iodo-3-[*N*-methyl-(3-methyl-but-2-enoyl)-amino]-benzoate (539 mg, 1.44 mmol) in MeOH (1.44 mL) at 0 °C was added LiOH (481 μL, 1.44 mmol). The solution was stirred at rt 12 h, quenched with 10 % HCl, and extracted with ethyl acetate. The crude product thus obtained was used in the next step without purification. (272 mg, 55 %); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.66 (s, 3 H), 2.15 (s, 3 H), 3.23 (s, 3 H), 5.24 (s, 1 H), 7.38-7.51 (m, 2 H), 7.84 (d, *J* = 7.3 Hz, 1 H); ^{13}C (50 MHz, $CDCl_3$) δ 20.4, 27.3, 36.0, 100.8, 116.7, 129.5, 130.2, 131.9, 138.3, 147.9, 152.9, 167.5, 170.0.

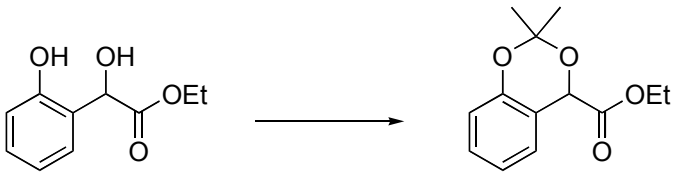


2-Iodo-3-[*N*-methyl-(3-methyl-but-2-enoyl)-amino]-benzyl alcohol. To a solution of 2-Iodo-3-[*N*-methyl-(3-methyl-but-2-enoyl)-amino]-benzoic acid (54 mg, 0.15 mmol) in THF (762 μL) at -10 °C was added morpholine (17 μL, 0.15 mmol) and ethyl chloroformate (15 μL, 0.15 mmol). The solution was stirred 10

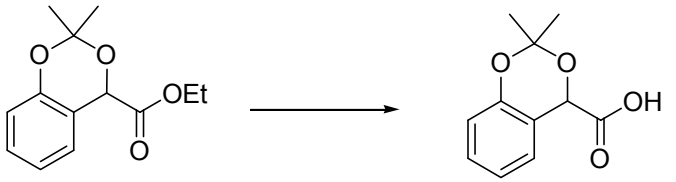
min, warming to 0 °C, then MeOH (1.5 mL, 32.5 mmol) and $NaBH_4$ (17 mg, 0.45 mmol) was added slowly. The solution was stirred for 5 min, quenched with 1 M HCl, and extracted with Et_2O. The combined organic extracts were dried (Na_2SO_4), filtered and concentrated. The crude product was purified by silica-gel chromatography (2 : 1 hexanes : ethyl acetate) to afford a white foam (40 mg, 76 %); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.57 (s, 3 H), 2.07 (s, 3 H), 3.11 (s, 3 H), 3.96 (t, *J* = 5.7 Hz, 1 H), 4.67 (d, *J* = 5.7 Hz, 2 H), 5.19 (s, 1 H), 7.07 (d, *J* = 7.6 Hz, 1 H), 7.35 (t, *J* = 7.6 Hz, 1 H), 7.57 (d, *J* = 7.6 Hz, 1 H).



2-Iodo-3-[*N*-methyl-(3-methyl-but-2-enoyl)-amino]-benzaldehyde. To a solution of 2-Iodo-3-[*N*-methyl-(3-methyl-but-2-enoyl)-amino]-benzyl alcohol (200 mg, 0.579 mmol) in CH_2Cl_2 (1.9 mL) was added molecular sieves (200 mg), NMO (97 mg, 0.86 mmol), and TPAP (10 mg, 0.029 mmol). The solution was stirred at rt overnight, filtered through a short silica plug, and concentrated. The crude product was purified by silica-gel chromatography (2 : 1 hexanes : ethyl acetate) to afford a yellow oil (40 mg, 76 %); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.65 (s, 3 H), 2.15 (s, 3 H), 3.21 (s, 3 H), 5.19 (s, 1 H), 7.48-7.51 (m, 2 H), 7.82-7.86 (m, 1 H), 10.15 (s, 1 H); ^{13}C (50 MHz, $CDCl_3$) δ 20.3, 27.3, 35.7, 107.4, 116.6, 129.3, 129.9, 134.7, 137.5, 147.8, 152.7, 195.7.

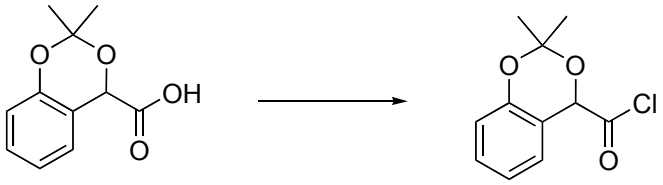


Ethyl 2,2-Dimethyl-4*H*-benzo[1,3]dioxine-4-carboxylate. To a solution of ethyl hydroxy(2-hydroxyphenyl)acetate (**226**) (2.00 g, 10.2 mmol) in acetone (4.4 mL) was added 2,2-dimethoxypropane (6.30 mL, 50.9 mmol) and (±)-camphorsulfonic acid (592 mg, 2.54 mmol). The solution was stirred at rt for 12 h, quenched with saturated aqueous sodium bicarbonate and extracted with ethyl acetate. The combined extracts were dried (Na_2SO_4) and concentrated to provide a yellow oil (2.00 g, 83%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.31 (t, *J* = 7.2 Hz, 3 H), 1.52 (s, 3 H), 1.63 (s, 3 H), 4.27 (q, *J* = 7.2 Hz, 2 H), 5.45 (s, 1 H), 6.81 (dd, *J* = 0.9, 8.4 Hz, 1 H), 6.91 (dt, *J* = 0.9, 8.4 Hz, 1 H), 7.16 (dt, *J* = 0.6, 7.5 Hz, 1 H), 7.29 (d, *J* = 7.5 Hz, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.0, 23.0, 26.9, 61.6, 70.3, 99.4, 116.7, 117.4, 120.6, 125.1, 129.1, 150.9, 169.4; IR (neat) 2993, 2941, 1759, 1732, 1612, 1587 cm^{-1}; HRMS (M + H$^+$) calcd for $C_{13}H_{17}O_4$ 237.1121, found 237.1134.

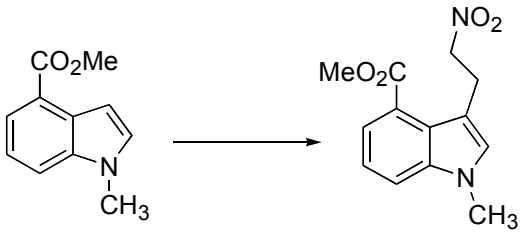


2,2-Dimethyl-4*H*-benzo[1,3]dioxine-4-carboxylic Acid. To a solution of ethyl 2,2-dimethyl-4*H*-benzo[1,3]dioxine-4-carboxylate (1.71 g, 7.23 mmol) in methanol (18.1 mL) at 0 °C was added 1M KOH (18.1 mL, 18.1 mmol) dropwise. The solution was stirred at 0 °C for 3 h, quenched with potassium phosphate buffer (pH =5) and extracted with Et_2O. The combined organic extracts were dried (Na_2SO_4) and concentrated to afford a white solid: mp 76-78 °C (1.37 g, 91%); ^{1}H NMR (200 MHz, $CDCl_3$) δ1.53 (s, 3 H), 1.65 (s, 3 H), 5.49 (s, 1 H), 6.83 (d, *J* = 8.0 Hz, 1 H), 6.95 (dt, *J* = 0.8, 7.6 Hz, 1 H), 7.24 (dt, *J* = 0.8, 8.0 Hz, 1 H),

7.47 (d, *J* = 7.6 Hz, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.6, 27.1, 69.7, 99.7, 115.5, 117.5, 121.1, 125.3, 129.5, 150.7, 173.7; IR (neat) 3044, 2996, 1731, 1610, 1587, 1488 cm^{-1}; HRMS (M + Na^+) calcd for $C_{11}H_{13}O_4$ 231.0627, found 231.0629.

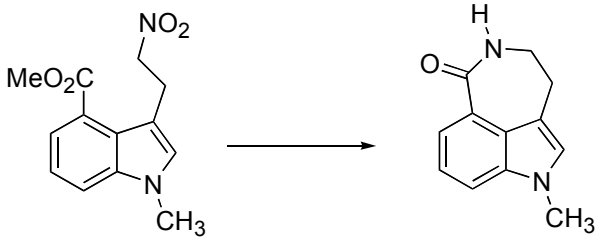


2,2-Dimethyl-4*H*-benzo[1,3]dioxine-4-carbonyl Chloride (**227**). To a solution of 2,2-dimethyl-4*H*-benzo[1,3]dioxine-4-carboxylic acid (93.0 mg, 0.447 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C was added oxalyl chloride (77.9 μL, 0.893 mmol) and DMF (3.5 μL, 0.045 mmol). The solution was stirred 5 min and concentrated *in vacuo* to provide a brown solid, which was used immediately without purification; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.54 (s, 3 H), 1.65 (s, 3 H), 5.54 (s, 1 H), 6.93 (d, *J* = 8.2 Hz, 1 H), 6.99 (dt, *J* = 1.0, 8.2 Hz, 1 H), 7.25 (d, *J* = 8.5 Hz, 1 H), 7.29 (t, *J* = 8.5 Hz, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.8, 26.4, 76.9, 100.1, 114.4, 117.9, 121.3, 125.6, 130.2, 151.0, 174.1.

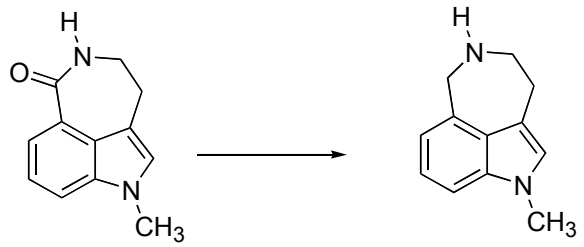


Methyl 1-methyl-3-(2-nitroethyl)-4-indolecarboxylate (**228**). To a solution of methyl 1-methyl-4-indolecarboxylate (1.02 g, 5.37 mmol) in xylenes (3.8 mL) was added 2-nitroethyl acetate (764 mg, 5.74 mmol), and 4-*tert*-butylcatechol (17.8 mg, 0.107 mmol). The solution was heated at 150 °C for 3 h. The mixture was concentrated and purified by silica-gel chromatography (1 : 3 ethyl acetate : hexanes) to afford a white solid : mp 86-88 °C (923 mg, 70%); ^{1}H

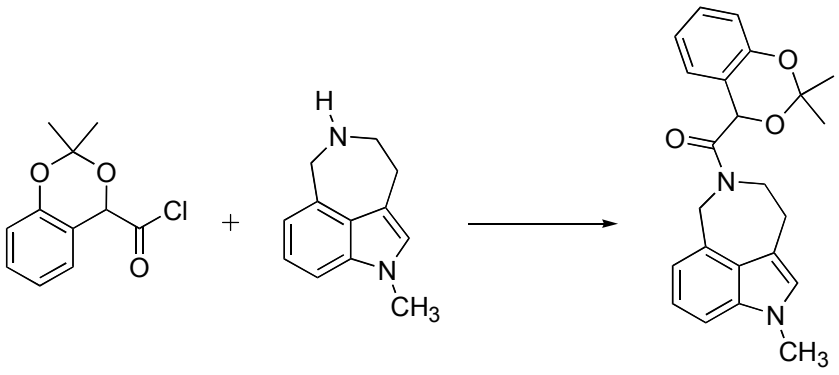
NMR (200 MHz, $CDCl_3$) δ 3.64 (t, *J* = 6.6 Hz, 2 H), 3.75 (s, 3 H), 3.95 (s, 3 H), 4.69 (t, *J* = 6.6 Hz, 2 H), 7.04 (s, 1 H), 7.24 (d, *J* = 7.9 Hz, 1 H), 7.5 (dd, *J* = 1.0, 7.9 Hz, 1 H), 7.82 (dd, *J* = 1.0, 7.9 Hz, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.8, 32.6, 51.9, 77.4, 109.2, 114.0, 120.6, 122.9, 123.3, 131.3, 138.3, 168.2 ; IR (neat) 2949, 1714, 1609, 1555, 1454 cm^{-1}; HRMS (M + H^+) calcd for $C_{13}H_{15}N_2O_4$ 263.1026, found 263.1038.



1-Methyl-1,3,4,5-tetrahydro-azepino[5,4,3-*cd*]indol-6-one. To a solution of methyl 1-methyl-3-(2-nitroethyl)-4-indolecarboxylate (923 mg, 3.72 mmol) in ethanol (12.4 mL) was added platinum oxide (21 mg, 0.093 mmol). The mixture was stirred at 70 °C under a hydrogen atmosphere for 4 d. The solution was filtered through celite and concentrated. Further purification by silica-gel chromatography (33 : 1 CH_2Cl_2 : MeOH) provided a light yellow solid: mp 179-180 °C (452 mg, 61%); ^1H NMR (200 MHz, $CDCl_3$) δ 3.03 (m, 2 H), 3.59 (dd, *J* = 5.6, 9.7 Hz, 2 H), 3.77 (s, 3 H), 6.92 (s, 1 H), 6.99 (br s, 1 H), 7.32 (d, *J* = 7.5 Hz, 1 H), 7.43 (d, *J* = 7.5 Hz, 1 H), 7.97 (d, *J* = 7.5 Hz, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 28.2, 32.6, 43.2, 112.9, 114.2, 121.3, 122.9, 124.3, 125.5, 126.5, 137.1,171.7; IR (neat) 3278, 2923, 1643, 1604, 1463 cm^{-1}; HRMS(M + H^+) calcd for $C_{12}H_{13}N_2O$ 201.1022, found 201.1037.

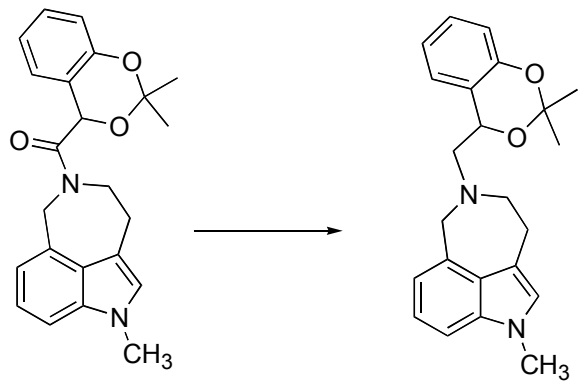


1-Methyl-3,4,5,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indole (**229**). To a refluxing solution of lithium aluminum hydride (135 mg, 3.57 mmol) in THF (5.9 mL) was added dropwise 1-methyl-1,3,4,5-tetrahydro-azepino[5,4,3-*cd*]indol-6-one (135 mg, 0.674 mmol) in THF (1.1 mL). The solution was stirred at reflux for 3 h. The mixture was quenched with water (135 μL), 10% NaOH (202 μL), and water (405 μL). The slurry was filtered and concentrated to give a light yellow solid: mp 64-66 °C (120 mg, 95%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.15 (br s, 1 H), 3.06 (m, 2 H), 3.21 (m, 2 H), 3.75 (s, 3 H), 4.35 (s, 2 H), 6.88 (m, 2 H), 7.17 (m, 2 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 31.1, 32.2, 50.5, 56.1, 106.6, 113.7, 115.4, 120.9, 125.5, 125.7, 136.7, 137.3; IR (neat) 2913, 1460, 1418 cm^{-1}; HRMS (M + H^+) calcd for $C_{12}H_{15}N_2$ 187.1229, found 187.1177.



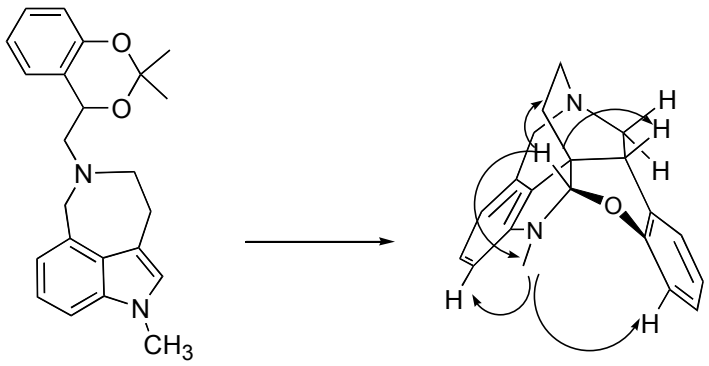
Amide. To a solution of the amine **229** (220 mg, 1.18mmol) and triethylamine (430 μL, 3.07 mmol) in CH_2Cl_2 (2.9 mL) at 0 °C was added dropwise the acid chloride **227** (401 mg, 1.77 mmol) in CH_2Cl_2 (500 μL). The solution was stirred 5 min, quenched with saturated aqueous sodium bicarbonate, and extracted with CH_2Cl_2. The combined organic extracts were

dried (Na_2SO_4) and concentrated. The crude product was purified by silica-gel chromatography (33 :1 CH_2Cl_2 : MeOH) to afford a colorless oil as a mixture of rotamers (300 mg, 70%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.41 (s, major, 3 H), 1.47 (s, major, 3 H), 1.54 (s, minor, 3 H), 1.69 (s, minor, 3 H), 3.21 (t, *J* = 5.0 Hz, 2 H), 3.74 (s, 3 H), 3.85 (m, 1 H), 4.03 (m, 1 H), 4.84 (m, minor, 2 H), 4.82 (d, major, *J* = 17.2 Hz, 1 H), 4.93 (d, major, *J* = 17.2 Hz, 1 H), 5.67 (s, major, 1 H), 5.78 (s, minor, 1 H), 6.67 (t, *J* = 7.9 Hz, 2 H), 6.86 (m, 2 H), 6.96 (d, *J* = 7.5 Hz, 1 H), 7.17 (m, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.1 (minor), 22.4 (major), 25.5 (major), 27.1 (major), 27.6 (minor), 27.9 (minor), 32.6 (major), 49.7 (minor), 50.5 (major), 53.3 (minor), 54.8 (major), 74.0 (minor), 74.1 (major), 100.0 (minor), 100.1 (major), 107.2 (major), 107.5 (minor), 112.7 (major), 115.8 (major), 116.8 (minor), 117.1 (major), 117.2 (major), 117.7 (minor), 117.9 (minor), 120.7 (major), 120.9 (major), 121.0 (minor), 121.4 (minor), 125.1 (major), 125.2 (minor), 125.7 (major), 126.0 (minor), 128.8 (minor), 128.9 (major), 131.5 (minor), 131.6 (major), 137.2 (minor), 137.3 (major), 150.4 (minor), 150.5 (major), 168.3 (major), 168.8 (minor); IR (neat) 2938, 2359, 1643 cm^{-1}; HRMS (M + H$^+$) calcd for $C_{23}H_{25}N_2O_3$ 377.1859, found 377.1850.



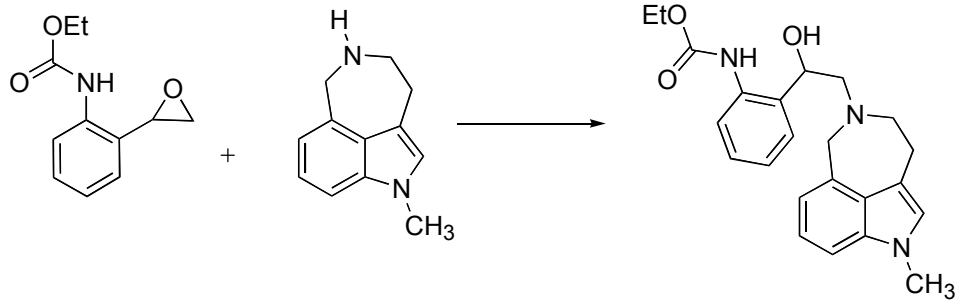
Dioxin 220. To a solution of lithium aluminum hydride (66.3 mg, 1.74 mmol) in THF (2.9 mL) was added dropwise the amide derived from the previous experimental procedure (124 mg, 0.329 mmol) in THF (3.3 mL). The solution was heated at 70 °C for 3 h. The mixture was quenched with water (66 μL), 10% NaOH (99 μL), and water (198 μL). The slurry was filtered and concentrated to

afford a colorless oil (119 mg, 92%); ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.51 (s, 3 H), 1.63 (s, 3 H), 3.06 (dd, *J* = 7.5 Hz, 13.8 Hz, 1 H), 3.15 (m, 3 H), 3.47 (t, *J* = 6.1 Hz, 2 H), 3.76 (s, 3 H), 4.44 (d, *J* = 16.8 Hz, 1 H), 4.49 (d, *J* = 16.8 Hz, 1 H), 5.13 (dd, *J* = 3.6, 7.5 Hz, 1 H), 6.79 (dt, *J* = 1.2, 7.5 Hz, 1 H), 6.87 (m, 3 H), 7.14 (m, 4 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.8, 25.8, 28.4, 32.6, 55.1, 56.9, 62.1, 68.7, 99.4, 107.1, 113.9, 116.8, 117.0, 120.3, 121.3, 122.6, 124.8, 125.7, 126.5, 127.9, 134.9, 137.1, 151.3; IR (neat) 2919, 1609, 1583, 1487, 1458 cm^{-1}; HRMS (M + H^+) calcd for $C_{23}H_{27}N_2O_2$ 363.2067, found 363.2057.



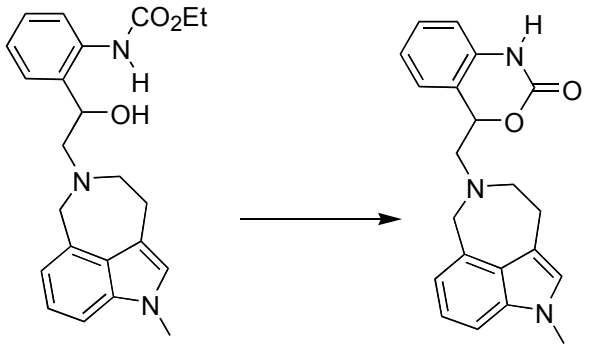
Cycloadduct 232. A solution of the amine **230** (161 mg, 0.444 mmol) in decahydronaphthalene (44.4 μL) was heated at 195 °C for 27 h. Removal of the solvent and purification of the crude product by silica-gel chromatography (2 : 3 acetone : hexanes) afforded two diastereomers (84.5 mg, 63%). Major diastereomer (79 mg, 59 %) : mp 153-154 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.26 (m, 2 H), 2.90 (s, 3 H), 3.20 (m, 2 H), 3.43 (m, 2 H), 3.78 (dd, *J* = 8.7, 13.7 Hz, 1 H), 4.15 (d, *J* = 17.6 Hz, 1 H), 4.34 (d, *J* = 17.6 Hz, 1 H), 5.40 (s, 1 H), 5.95 (d, *J* = 7.6 Hz, 1 H), 6.25 (d, *J* = 7.6 Hz, 1 H), 6.88 (t, *J* = 7.6 Hz, 1 H), 6.94 (m, 3 H), 7.09 (m, 1 H); ^{1}H NMR (400 MHz, d^6- benzene) δ 1.68 (ddd, *J* = 3.3, 9.3, 12.3 Hz, 1 H), 1.85 (ddd, *J* = 7.1, 9.3, 12.3 Hz, 1 H), 2.62 (s, 3 H) 2.86 (m, 1 H), 2.89 (t, *J* = 8.6 Hz, 1 H), 3.06 (ddd, *J* = 7.1, 9.3, 14.8 Hz, 1 H), 3.34 (ddd, *J* = 2.2, 8.6, 13.7 Hz, 1 H), 3.52 (dd, *J* = 8.6, 13.7, 1 H), 4.01 (d, *J* = 17.7 Hz, 1 H), 4.29 (d, *J* = 17.7 Hz, 1 H), 5.17 (s, 1 H), 5.79 (d, *J* = 7.7 Hz, 1 H), 6.23 (d, *J* = 7.7 Hz, 1 H), 6.71 (t, *J* = 7.5 Hz, 1 H), 6.75 (d, *J* = 7.5 Hz, 1 H), 6.82 (t, *J* = 7.7 Hz, 1 H), 6.94

(t, *J* = 7.2 Hz, 1 H), 7.03 (d, *J* = 7.2 Hz, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 30.0, 38.6, 39.0, 46.9, 48.6, 49.3, 62.0, 101.0, 101.3, 114.0, 118.3, 122.6, 123.9, 127.0, 128.3, 129.6, 130.9, 136.7, 149.6, 153.8; IR (neat) 3228, 1681, 1547, 1502, 1467, 1214, 1190, 1096 cm^{-1}; HRMS (M + H^+) calcd for $C_{20}H_{21}N_2O$ 305.1648, found 305.1633; Minor diastereomer (5.5 mg, 4 %); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.67 (m, 2 H), 3.01 (m, 1 H), 3.14 (s, 3 H), 3.28 (m, 1 H), 3.33 (t, *J* = 9.3 Hz, 1 H), 3.51 (dd, *J* = 9.3, 13.6 Hz, 1 H), 3.64 (br dd, *J* = 6.7, 13.6 Hz, 1 H), 4.25 (d, *J* = 17.6, 1 H), 4.35 (d, *J* = 17.6 Hz, 1 H), 4.74 (s, 1 H), 6.36 (d, *J* = 7.7 Hz, 1 H), 6.49 (d, *J* = 7.7 Hz, 1 H), 7.00 (dd, *J* = 1.1, 7.6 Hz, 1 H), 7.07 (dt, *J* = 1.1, 7.6 Hz, 1 H), 7.11 (t, *J* = 7.7 Hz, 1 H), 7.16 (d, *J* = 7.5 Hz, 1 H), 7.23 (t, *J* = 7.5 Hz, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ29.4, 30.7, 38.5, 46.4, 48.6, 49.9, 59.7, 100.8, 103.0, 115.5, 118.0, 122.7, 124.8, 127.6, 128.5, 130.9, 132.9, 153.8; IR (neat) 3228, 1681, 1547, 1502, 1467 cm^{-1}; HRMS (M + H^+) calcd for $C_{20}H_{21}N_2O$ 305.1648, found 305.1650.

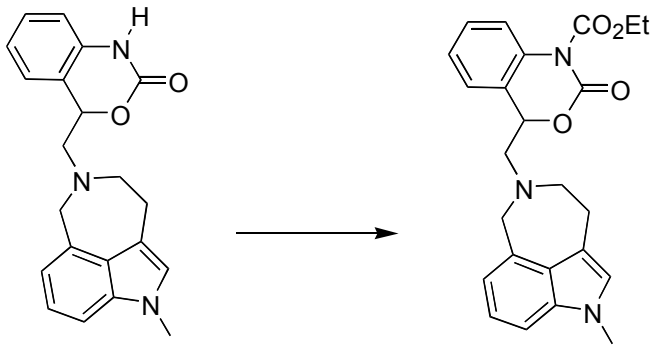


Benzylic alcohol 313. To a solution of the amine **229** (20.0 mg, 0.107 mmol) in isopropanol (110 μL) was added the epoxide **312** (22.2 mg, 0.107 mmol). The solution was stirred at 25 °C for 12 h and concentrated to afford a colorless oil as a 9 : 1 mixture of regioisomers, which was used in the next step (41 mg, 99%); ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.41 (t, *J* = 7.1 Hz, 3 H), 2.93 (dd, *J* = 10.9, 12.9 Hz, 1 H), 3.08 (dd, *J* = 3.7, 12.9 Hz, 1 H), 3.21 (q, *J* = 4.9 Hz, 2 H), 3.46 (t, *J* = 4.9, 2 H), 3.84 (s, 3 H), 4.30 (q, *J* = 7.1 Hz, 2 H), 4.43 (d, *J* = 16.6 Hz, 1 H), 4.50 (d, *J* = 16.6 Hz, 1 H), 4.90 (dd, *J* = 3.7, 10.8, 1 H), 6.96 (m, 2 H), 7.01 (t, *J* = 7.4 Hz, 1 H), 7.09 (dd, *J* = 1.5, 7.7 Hz, 1 H), 7.27 (m, 1 H), 7.30 (m, 1 H),

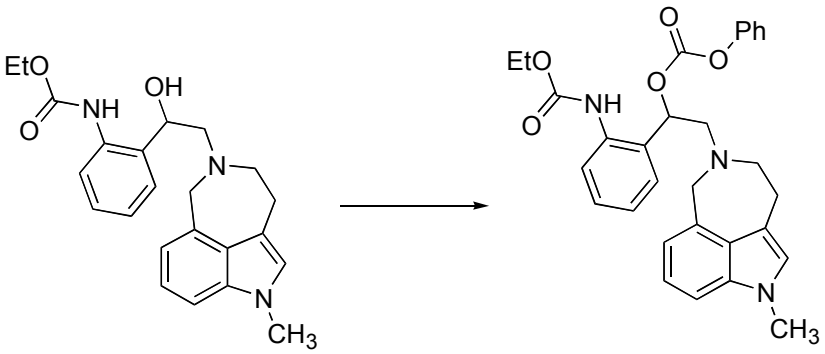
7.34 (m, 1 H), 8.11 (d, *J* = 7.9 Hz, 1 H), 9.04 (br s, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.6, 26.2, 32.6, 55.2, 57.3, 60.8, 61.5, 70.5, 107.5, 113.1, 116.9, 120.6, 121.3, 122.6, 126.0, 127.6, 127.9, 128.4, 133.2, 137.1, 137.6, 153.8; IR (neat) 3318, 2911, 1727, 1591 cm^{-1}; HRMS (M + H^+) calcd for $C_{23}H_{28}N_3O_3$ 394.2125, found 394.2111.



1,3-Benzoxaz-2-one 314. To a solution of the alcohol **313** (30 mg, 0.07 mmol) in THF (191 μL) at 0 ºC was added NaH (3 mg, 0.1 mmol). The solution was stirred 20 min at 0 ºC, then additional NaH (6 mg, 0.2 mmol) was added. The solution was stirred an additional 30 min at 0 ºC, quenched with saturated aqueous ammonium chloride, and extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by silica-gel chromatography (1 : 20 MeOH : CH_2Cl_2) to afford a yellow oil (14 mg, 50 %);^{1}H NMR (200 MHz, $CDCl_3$) δ 3.02-3.22 (m, 3 H), 3.34 (t, *J* = 5.4 Hz, 2 H), 3.73 (s, 3 H), 4.26 (s, 2 H), 5.49 (t, *J* = 6.0 Hz, 1 H), 6.70-6.76 (m, 2 H), 6.84 (s, 1 H), 6.95-7.26 (m, 5 H), 7.70 (br s, 1 H).

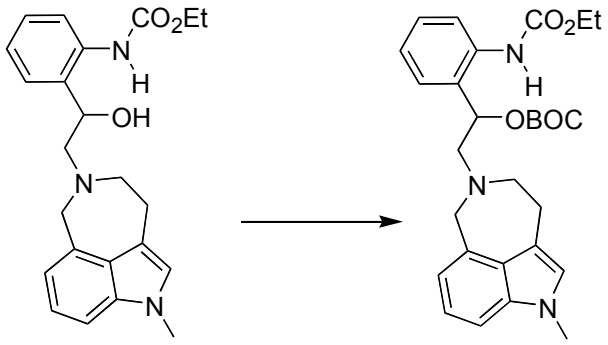


***N*-acyl-1,3-benzoxazin-2-one 315.** To a solution of the 1,3-benzoxazin-2-one **314** (11 mg, 0.029 mmol) in DMI (37 μL) at 0 ºC was added NaH (1.1 mg, 0.049 mmol). The solution was stirred 10 min at 0 ºC, then ethyl chloroformate (3.3 μL, 0.035 mmol) was added. The solution was stirred 30 min at 0 ºC, quenched with saturated aqueous ammonium chloride, and extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by silica-gel chromatography (1 : 3 ethyl acetate : hexanes) to afford a white foam (7.7 mg, 60%); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.37 (t, *J* = 7.1 Hz, 3 H), 3.03-3.13 (m, 2 H), 3.18-3.25 (m, 2 H), 3.28-3.33 (m, 2 H), 3.74 (s, 3 H), 4.26 (s, 2 H), 4.36 (q, *J* = 7.1, 14.2 Hz, 2 H), 5.33 (t, *J* = 6.0 Hz, 1 H), 6.78 (d, *J* = 6.0 Hz, 1 H), 6.83 (s, 1 H), 7.10-7.38 (m, 5 H), 7.61 (d, *J* = 8.0 Hz, 1 H).



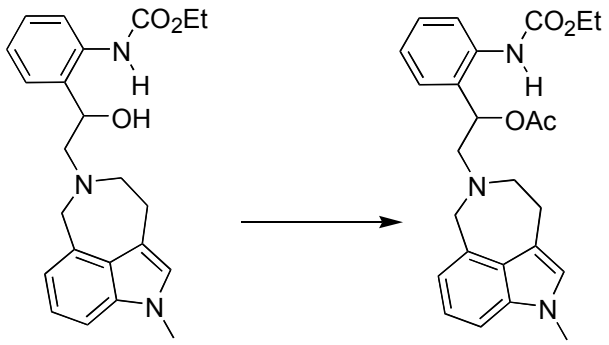
Phenyl carbonate 318. To a solution of the alcohol **313** (25.8 mg, 0.066 mmol) in CH_2Cl_2 (220 μL) at 0 °C was added pyridine (16.0 μL, 0.197 mmol) and phenyl chloroformate (12.3 μL, 0.098 mmol). The solution was warmed to rt over 1.5 h. The mixture was quenched with water and extracted with CH_2Cl_2. The

combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by silica-gel chromatography (1 : 3 ethyl acetate : hexanes) to provide a yellow oil (22 mg, 65%); ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.22 (t, *J* = 7.1 Hz, 3 H), 3.08 (dd, *J* = 7.6, 13.8 Hz, 1 H), 3.13 (t, *J* = 5.4 Hz, 2 H), 3.34 (m, 3 H), 3.75 (s, 3 H), 4.14 (dq, *J* = 1.6, 7.1 Hz, 2 H), 4.31 (d, *J* = 16.6 Hz, 1 H), 4.39 (d, *J* = 16.6 Hz, 1 H), 6.03 (dd, *J* = 4.5, 7.6 Hz, 1 H), 6.83 (d, *J* = 6.7 Hz, 1 H), 6.86 (m, 1 H), 7.13 (m, 4 H), 7.18 (d, *J* = 7.3 Hz, 1 H), 7.24 (br t, *J* = 7.5 Hz, 1 H), 7.36 (m, 3 H), 7.42 (dd, *J* = 1.5, 7.8 Hz, 1 H), 7.84 (d, *J* = 7.6 Hz, 1 H), 9.43 (br s, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.4, 25.1, 32.6, 55.0, 56.9, 60.8, 61.8, 74.9, 107.5, 113.2, 117.4, 120.9, 121.3, 122.8, 124.1, 125.9, 126.0, 126.2, 126.3, 128.8, 129.4, 130.2, 133.1, 136.0, 137.0, 151.0, 153.0, 154.4; IR (neat) 2910, 1759, 1727, 1251 cm^{-1}; HRMS (M + H$^+$) calcd for $C_{30}H_{32}N_3O_5$ 514.2336, found 514.2309.

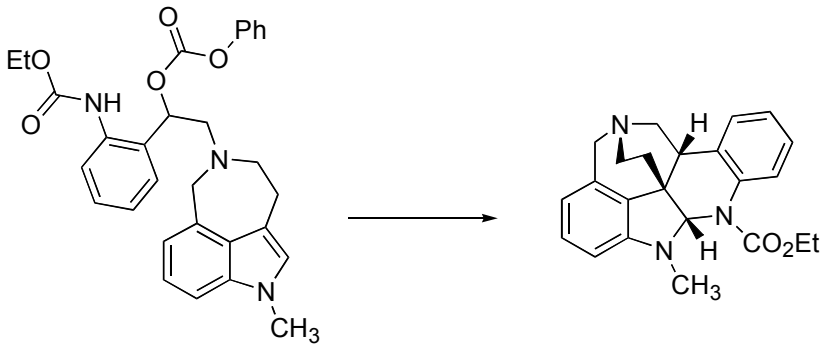


BOC-Carbonate 319. To a solution of the alcohol **313** (67 mg, 0.17 mmol) in toluene (1.7 mL) was added imidazole (13 mg, 0.17 mmol) and BOC_2O (56 mg, 0.25 mmol). The solution was stirred 24 h at rt, quenched with brine, and extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by silica-gel chromatography (1 : 4 ethyl acetate : hexanes) to afford a yellow oil (66 mg, 78 %); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.21 (t, *J* = 7.1 Hz, 3 H), 1.44 (s, 9 H), 2.93 (dd, *J* = 10.9, 12.9 Hz, 1 H), 3.13 (t, *J* = 5.4 Hz, 2 H), 3.20-3.40 (m, 3 H), 3.75 (s, 3 H), 4.14 (dq, *J* = 1.6, 7.1, 14.2 Hz, 2 H), 4.31 (d, *J* = 16.6 Hz, 1 H), 4.39 (d, *J* = 16.6 Hz, 1 H), 5.90 (dd,

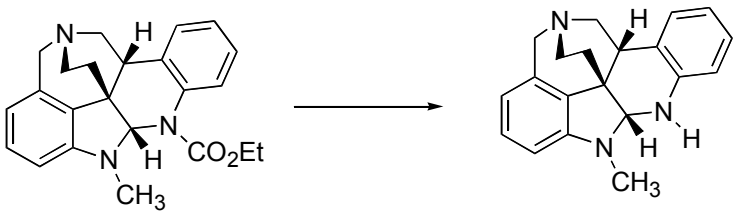
J = 4.5, 7.6 Hz, 1 H), 6.82 (d, *J* = 6.7 Hz, 1 H), 6.84 (s, 1 H), 7.00-7.20 (m, 3 H), 7.29-7.37 (m, 2 H), 7.80 (d, *J* = 7.6 Hz, 1 H), 9.64 (br s, 1 H).



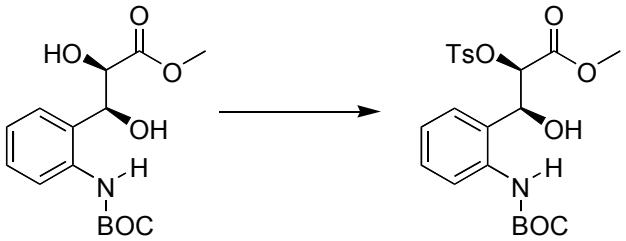
Acetate 321. To a solution of the alcohol **313** (39 mg, 0.09 mmol) in CH_2Cl_2 (330 μL) at 0 ºC was added NEt_3 (41 μL, 0.29 mmol), DMAP (2 mg, 0.02 mmol), and Ac_2O (14 μL, 0.15 mmol). The solution was stirred at 0 ºC 1 h, quenched with brine, and extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by silica-gel chromatography (1 : 3 ethyl acetate : hexanes) to afford a yellow oil (20 mg, 46 %); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.24 (t, *J* = 7.1 Hz, 3 H), 2.05 (s, 3 H), 3.00 (dd, *J* = 7.6, 13.8 Hz, 1 H), 3.13 (t, *J* = 5.4 Hz, 2 H), 3.17-3.50 (m, 3 H), 3.74 (s, 3 H), 4.15 (q, *J* = 1.6, 7.1, 14.2 Hz, 2 H), 4.24 (d, *J*= 16.6 Hz, 1 H), 4.40 (d, *J* = 16.6 Hz, 1 H), 6.10 (dd, *J* = 4.5, 7.6 Hz, 1 H), 6.82 (d, *J* = 6.7 Hz, 1 H), 6.84 (s, 1 H), 7.03-7.20 (m, 3 H), 7.82 (t, *J* = 7.6 Hz, 2 H), 7.85 (d, *J* = 7.6 Hz, 2 H), 9.73 (br s, 1 H).



Cycloadduct 323. A solution of the carbonate **318** (10.0 mg, 0.019 mmol) in 1,2-dichlorobenzene (1.9 mL) was heated at 160 °C for 6 h. Removal of the solvent and purification by silica-gel chromatography (1 : 19 MeOH : CH_2Cl_2) provided a yellow oil (5 mg, 70 %); ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.31 (m, 3 H), 2.19 (t, *J* = 10.7 Hz, 1 H), 2.42 (m, 1 H), 2.74 (s, 3 H), 3.02 (t, *J* = 8.5 Hz, 1 H), 3.17 (m, 1 H), 3.41 (m, 2 H), 3.71 (dd, *J* = 5.6, 14.0 Hz, 1 H), 4.14 (d, *J* = 17.8 Hz, 1 H), 4.31 (d, *J* = 17.8 Hz, 1 H), 4.34 (m, 2 H), 5.90 (d, *J* = 7.7 Hz, 1 H), 5.90 (br s, 1 H), 6.23 (d, *J* = 7.7 Hz, 1 H), 6.86 (t, *J* = 7.7 Hz, 1 H), 7.02 (d, *J* = 7.3 Hz, 1 H), 7.05 (t, *J* = 7.3 Hz, 1 H), 7.16 (t, *J* = 7.3 Hz, 1 H), 7.26 (v br s, 1 H); ^{1}H NMR (360 MHz, CD_3CN) δ 1.25 (br m, 3 H), 2.09 (m, 1 H), 2.28 (m, 1 H), 2.71 (s, 3 H), 3.01 (t, *J* = 8.7 Hz, 1 H), 3.08 (ddt, *J* = 2.5, 9.7, 14.3 Hz, 1 H), 3.25 (m, 1 H), 3.37 (ddd, *J* = 2.5, 8.7, 13.7 Hz, 1 H), 3.61 (dd, *J* = 8.7, 13.7 Hz, 1 H), 4.05 (d, *J* = 17.9 Hz, 1 H), 4.21 (d, *J* = 17.9 Hz, 1 H), 4.26 (br m, 2 H), 5.81 (br s, 1 H), 5.90 (d, *J* = 7.7 Hz, 1 H), 6.20 (d, *J* = 7.7 Hz, 1 H), 6.81 (t, *J* = 7.7 Hz, 1 H), 7.06 (m, 2 H), 7.17 (m, 1 H), 7.33 (br s, 1 H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 14.9, 30.1, 30.9, 40.4, 41.3, 47.5, 49.5, 51.5, 62.3, 62.4, 83.4, 102.1, 114.3, 124.1, 125.9, 126.1, 126.7, 128.9, 129.8, 134.9, 137.4, 137.7, 150.4; IR (neat) 2939, 1642, 1487, 1458 cm^{-1}; HRMS (M + H^+) calcd for $C_{23}H_{26}N_3O_2$ 376.2019, found 376.2022.

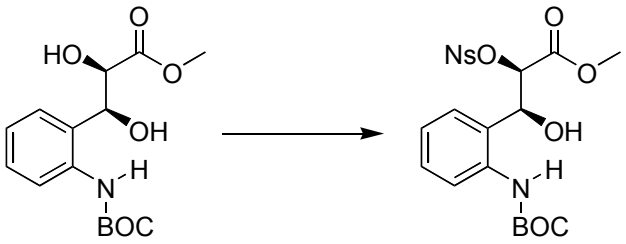


Aminal 324. To a solution of the carbamate **323** (14.6 mg, 0.039 mmol) in ethylene glycol (389 μL) was added KOH (56.0 mg, 1.01 mmol) and hydrazine (9.1 μL, 0.19 mmol). The solution was heated at 150 °C for 4 h. The mixture was quenched with H_2O and extracted with $CHCl_3$. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by silica-gel chromatography (1: 15 MeOH : CH_2Cl_2) to provide a yellow oil (8 mg, 67 %); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.19 (ddd, *J* = 2.1, 9.1, 11.5 Hz, 1 H), 2.35 (ddd, *J* = 9.1, 12.4, 17.7 Hz, 1 H), 2.72 (s, 3 H), 2.98 (br t, *J* = 9.1 Hz, 1 H), 3.17 (m, 1 H), 3.35 (t, *J* = 8.2 Hz, 1 H), 3.37 (m, 1 H), 3.75 (dd, *J* = 8.2, 13.3 Hz, 1 H), 4.15 (d, *J* = 17.7 Hz, 1 H), 4.35 (d, *J* = 17.7 Hz, 1 H), 4.53 (d, *J* = 2.1 Hz, 1 H), 4.63 (br s, 1 H), 5.95 (d, *J* = 7.7 Hz, 1 H), 6.26 (d, *J* = 7.7 Hz, 1 H), 6.71 (d, *J* =7.6 Hz, 1 H), 6.79 (t, *J* = 7.6 Hz, 1 H), 6.90 (br t, *J* = 7.7 Hz, 2 H), 7.04 (t, *J* = 7.6 Hz, 1 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 30.8, 40.5, 40.9, 47.2, 49.3, 50.0, 61.9, 84.4, 101.7, 113.9, 116.2, 120.5, 123.8, 126.6, 128.3, 130.0, 130.1, 137.1, 143.9, 150.7; IR (neat) 2851, 1597, 1492 cm^{-1}; HRMS (M + H$^+$) calcd for $C_{20}H_{22}N_3$ 304.1808, found 304.1829.

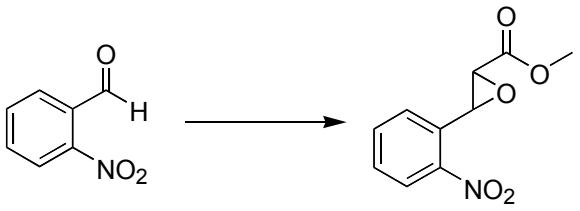


Tosylate 329. To a solution of methyl 3-(2'-*tert*-butoxycarbamate)-2,3-dihydroxypropionate (26 mg, 0.08 mmol) in CH_2Cl_2 (1.7 ml) at 0 ºC was added NEt_3 (24 μL, 0.17 mmol) and TsCl (16 mg, 0.08 mmol). The solution was stirred at rt 12 h, quenched with saturated aqueous sodium bicarbonate, and extracted

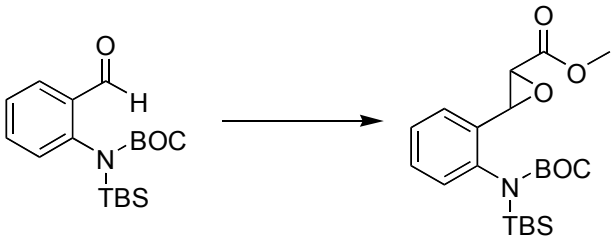
with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by silica-gel chromatography (1 : 2 ethyl acetate : hexanes) to afford a yellow foam (30 mg, 78 %); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.54 (s, 9 H), 2.42 (s, 3 H), 3.26 (br s, 1 H), 3.48 (s, 3 H), 5.13 (s, 2 H), 6.90-7.05 (m,2 H), 7.20-7.30 (m, 3 H), 7.70 (d, *J* = 8.0 Hz, 2 H), 7.81 (d, *J* = 8.0 Hz, 1 H).



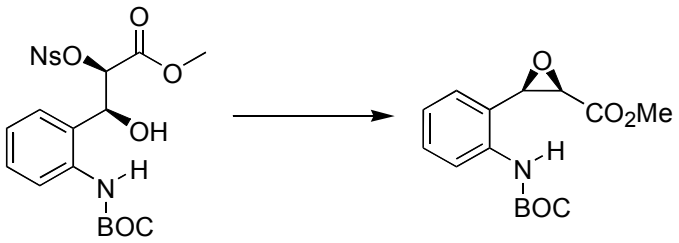
Nosylate 330. To a solution of methyl 3-(2'-*tert*-butoxycarbamate)-2,3-dihydroxypropionate (76 mg, 0.25 mmol) in CH_2Cl_2 (850 μl) at 0 ºC was added pyridine (56 μL, 0.25 mmol) and 4-nitrobenzenesulfonylchloride (56 mg, 0.25 mmol). The solution was stirred at 0 ºC 12 h, quenched with saturated aqueous ammonium chloride, and extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by silica-gel chromatography (1 : 2 ethyl acetate : hexanes) to afford a yellow foam (100 mg, 82 %); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.53 (s, 9 H), 3.12 (br s, 1 H), 3.70 (s, 3 H), 5.30 (br s, 2 H), 6.90 (t, *J* = 7.0 Hz, 1 H), 7.04 (d, *J* = 8.0 Hz, 1 H), 7.21 (t, *J* = 7.0 Hz, 1 H), 7.50 (br s, 1 H), 7.62 (d, *J* = 8.0 Hz, 1 H), 7.92 (d, *J* = 9.0 Hz, 2 H), 8.21 (d, *J* = 9.0 Hz, 2 H).



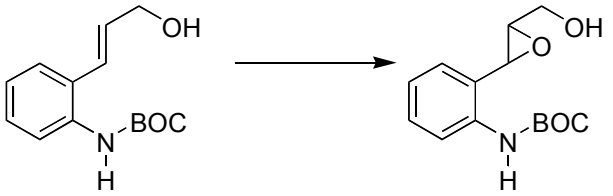
Epoxide 339. To a solution of 2-nitrobenzaldehyde (1.15 g, 7.66 mmol) in THF (7.6 mL) at 0 ºC was added methyl chloroacetate (672 μL, 7.66 mmol). To this solution was added K-O*t*Bu (7.60 mL, 7.60 mmol) dropwise via syringe pump over 30 min. The solution was stirred at 0 ºC 30 min, quenched with saturated aqueous ammonium chloride, and extracted with Et_2O. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by silica-gel chromatography (1 : 5 ethyl acetate : hexanes) to afford a yellow foam (721 mg, 45 %); ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.36 (d, *J* = 2.0 Hz, 1 H), 3.85 (s, 3 H), 4.67 (d, *J* = 2.0 Hz, 1 H), 7.50-7.75 (m, 3 H), 8.18 (d, *J* = 8.0 Hz, 1 H).



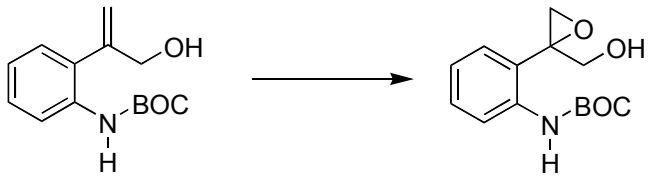
Epoxide 340. To a solution of the aldehyde **337** (125 mg, 0.386 mmol) in THF (772 μL) at 0 ºC was added methyl chloroacetate (40 μL, 0.46 mmol). To this solution was added K-O*t*Bu (464 μL,0.464 mmol) dropwise via syringe pump over 30 min. The solution was stirred at 0 ºC 30 min, quenched with saturated aqueous sodium bicarbonate, and extracted with Et_2O. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by silica-gel chromatography (NEt_3-deactivated) (1 : 20 ethyl acetate : hexanes) to afford a yellow foam (94 mg, 60 %); ^{1}H NMR (200 MHz, $CDCl_3$) δ -0.20 (s, 3 H), 0.40 (s, 3 H), 1.05 (s, 9 H), 1.40 (s, 9 H), 3.37 (dd, *J* = 2.0, 13.0 Hz, 1 H), 3.78 (s, 3 H), 4.14 (dd, *J* = 2.0, 6.0 Hz, 1 H), 7.10 (d, *J* = 7.0 Hz, 1 H), 7.20-7.34 (m, 3 H).



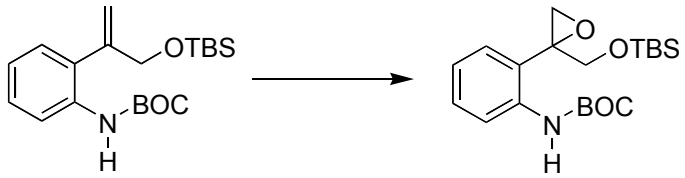
***Cis*-Epoxide 342**. To a solution of the nosylate **330** (26 mg, 0.05 mmol) in CH_2Cl_2 (540 μL) at rt was added DBU (10 μL, 0.06 mmol). The solution was stirred at rt for 12 h, quenched with saturated aqueous ammonium chloride, and extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated. The crude product was purified by silica-gel chromatography (1 : 3 ethyl acetate : hexanes) to afford a yellow oil (10 mg, 66 %); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.52 (s, 9 H), 3.55 (s, 3 H), 3.89 (d, *J* = 4.4 Hz, 1 H), 4.31 (d, *J* = 4.4 Hz, 1 H), 7.03 (t, *J* = 7.5 Hz, 1 H), 7.14-7.42 (m, 3 H), 7.80 (d, *J* = 8.0 Hz, 1 H).



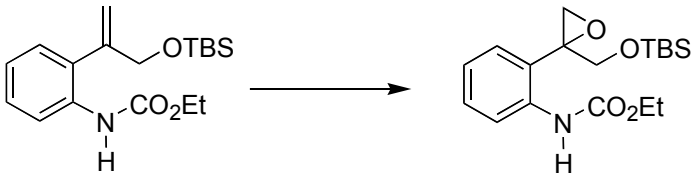
Epoxide 345. To a solution of the allylic alcohol **344** (70 mg, 0.29 mmol) in CH_2Cl_2 (1.5 mL) at 0 ºC was added Na_2CO_3 (75 mg, 0.71 mmol) and *m*-CPBA (102 mg, 0.589 mmol). The solution was stirred at rt overnight, quenched with saturated aqueous sodium bicarbonate, and extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by silica-gel chromatography (1 : 2 ethyl acetate : hexanes) to afford a yellow foam (47 mg, 63 %); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.50 (s, 9 H), 3.23-3.31 (m, 1 H), 3.85-3.96 (m, 3 H), 7.03-7.30 (m, 3 H), 7.62 (d, *J* = 8.0 Hz, 1 H).



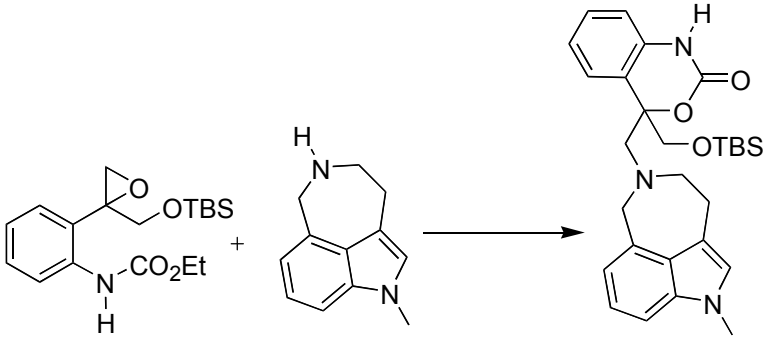
Epoxide 349(a). To a solution of the alkene **348** (28 mg, 0.11 mmol) in CH_2Cl_2 (1.1 ml) at 0 ºC was added molecular sieves (28 mg) and $VO(acac)_2$ (6 mg, 0.01 mmol). The solution was stirred 5 min, then *t*-BuOOH (100 μL, 0.49 mmol) was added dropwise. The solution was stirred 1 h at 0 ºC, quenched with 10 % aqueous $Na_2S_2O_3$ and extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by silica-gel chromatography (1 : 3 ethyl acetate : hexanes) to afford a yellow oil (20 mg, 70 %); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.52 (s, 9 H), 2.98 (d, *J* = 5.0 Hz, 1 H), 3.35 (d, *J* = 5.0 Hz, 1 H), 3.90 (br s, 2 H), 7.05 (t, *J* = 7.5 Hz, 1 H), 7.25-7.38 (m, 2 H), 7.53 (br s, 1 H), 8.00 (d, *J* = 8.0 Hz, 1 H).



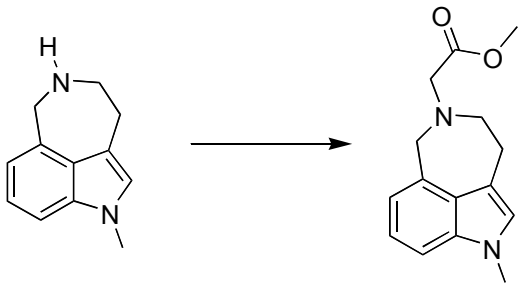
Epoxide 349(b). To a solution of the alkene (39 mg, 0.11 mmol) in CH_2Cl_2 (360 μL) at 0 ºC was added Na_2HPO_4 (38 mg, 0.27 mmol) and *m*-CPBA (39 mg, 0.22 mmol). The solution was stirred at rt for 12 h, quenched with saturated aqueous sodium bicarbonate, and extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by silica-gel chromatography (1 : 9 ethyl acetate : hexanes) to afford a yellow oil (30 mg, 75 %); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.01 (s, 6 H), 0.85 (s, 9 H), 1.12 (s, 9 H), 2.85 (d, *J* = 5.5 Hz, 1 H), 3.15 (d, *J* = 5.5 Hz, 1 H), 3.80 (d, *J* = 12 Hz, 1 H), 3.90 (d, *J* = 12.0 Hz, 1 H), 7.00 (t, *J* = 7.5 Hz, 1 H), 7.22-7.32 (m, 2 H), 7.84 (br s, 1 H), 7.96 (d, *J* = 8.0 Hz, 1 H).



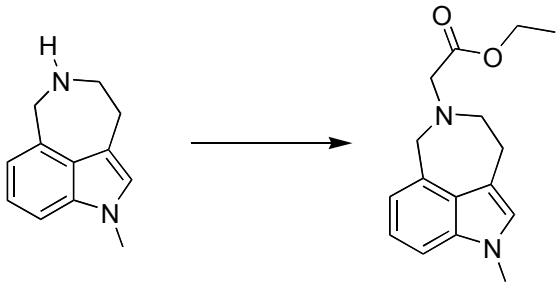
Epoxide 353. To a solution of the alkene (164 mg, 0.487 mmol) in CH_2Cl_2 (312 μL) at 0 ºC was added Na_2HPO_4 (707 mg, 0.1.46 mmol) and *m*-CPBA (185 mg, 0.1.07 mmol). The solution was stirred at rt for 12 h, quenched with saturated aqueous sodium bicarbonate, and extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by silica-gel chromatography (1 : 9 ethyl acetate : hexanes) to afford a yellow oil (157 mg, 91 %); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.31 (t, *J* = 7.0 Hz, 3 H), 2.30 (br s, 1 H), 2.92 (d, *J* = 5.0 Hz, 1 H), 3.30 (d, *J* = 5.0 Hz, 1 H), 3.89 (s, 2 H), 4.22 (q, *J* = 7.0, 14.0 Hz, 2 H), 7.05 (t, *J* = 7.5 Hz, 1 H), 7.24 (d, *J* = 7.0 Hz, 1 H), 7.32 (t, *J* = 8.0 Hz, 1 H), 7.80 (br s, 1 H), 7.99 (d, *J* = 8.0 Hz, 1 H).



1,3-Benzoxazin-2-one 354. To a solution of the epoxide **353** (33 mg, 0.09 mmol) in CH_3CN (312 μL) was added the benzazepine **229** (17 mg, 0.09 mmol) and $LiClO_4$ (10 mg, 0.09 mmol). The solution was stirred at 70 ºC for 12 h and concentrated. The crude product was purified by silica-gel chromatography (1 : 3 ethyl acetate : hexanes) to afford a yellow oil (20 mg, 41 %); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.34 (br t, *J* = 7.1 Hz, 3 H), 3.03 (s, 2 H), 3.13-3.18 (m, 2 H), 3.38-3.50 (m, 2 H), 3.76 (s, 3 H), 4.03 (br s, 1 H), 4.25 (br s, 2 H), 4.36 (d, *J* = d, *J* = 6.0 Hz, 2 H), 4.84 (s, 1 H), 6.82-6.90 (m, 2 H), 6.98 (t, *J* = 7.0 Hz, 1 H), 7.15-7.36 (m, 4 H), 7.62-7.70 (m, 1 H).

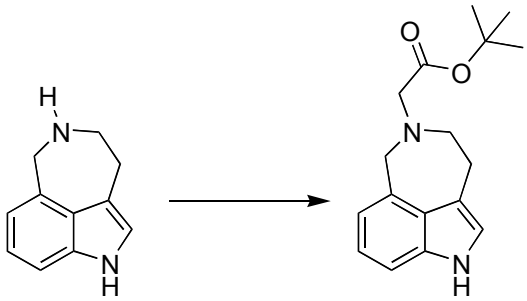


Methyl-(1-Methyl-3,4-dihydro-1H,6H-azepino[5,4,3-cd]indol-5-yl)-acetate (**361**). To a solution of the benzazepine **229** (44.5 mg, 0.239 mmol) in CH_3CN (796 μL) at 0 °C was added Cs_2CO_3 (85.6 mg, 0.263 mmol) and methyl iodo acetate (46.8 mg, 0.234 mmol). The solution was stirred for 3 h at 0 °C, quenched with saturated aqueous ammonium chloride, and extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by silica-gel chromatography (1 : 20 MeOH : CH_2Cl_2) to afford a yellow foam (77 mg, 70 %); ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.08 (t, *J* = 5.6 Hz, 2 H), 3.35-3.41 (m, 2 H), 3.58 (s, 2 H), 3.74 (s, 3 H), 3.75 (s, 3 H), 4.40 (s, 2 H), 6.81-6.86 (m, 2 H), 7.09-7.19 (m, 2 H).

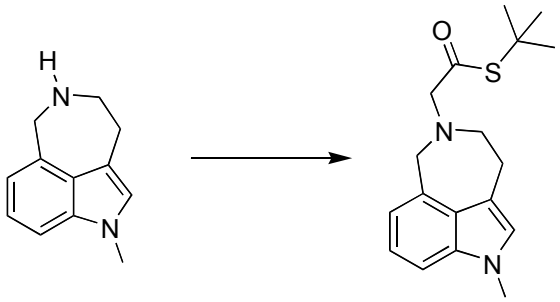


Ethyl-(1-Methyl-3,4-dihydro-1H,6H-azepino[5,4,3-cd]indol-5-yl)-acetate (**362**). To a solution of the benzazepine **229** (161 mg, 0.868 mmol) in CH_3CN (2.9 mL) at 0 °C was added Cs_2CO_3 (311 mg, 0.954 mmol) and ethyl iodo acetate (100 μL, 0.850 mmol). The solution was stirred for 3 h at 0 °C, quenched with saturated aqueous ammonium chloride, and extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by silica-gel chromatography (1 : 20 MeOH :

CH_2Cl_2) to afford a yellow foam (177 mg, 75 %); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.28 (t, *J* = 8.0 Hz, 3 H), 3.10 (t, *J* = 6.0 Hz, 2 H), 3.41 (t, *J* = 6.0 Hz, 2 H), 3.57 (s, 2 H), 3.75 (s, 3 H), 4.23 (q, *J* = 8.0, 14.0 Hz, 2 H), 4.41 (s, 2 H), 6.80-6.89 (m, 2 H), 7.14-7.20 (m, 2 H).

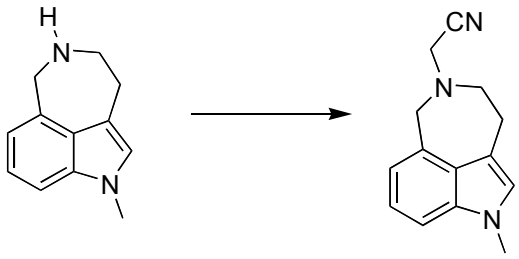


***Tert*-Butyl-(1-Methyl-3,4-dihydro-1H,6H-azepino[5,4,3-cd]indol-5-yl)-acetate** (**363**). To a solution of the benzazepine **229** (236 mg, 1.27 mmol) in CH_3CN (4.2 mL) at 0 °C was added Cs_2CO_3 (454 mg, 1.39 mmol) and *tert*-butyl iodo acetate (183 μL, 1.24 mmol). The solution was stirred for 3 h at 0 °C, quenched with saturated aqueous ammonium chloride, and extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by silica-gel chromatography (1 : 3 ethyl acetate : hexanes) to afford a yellow oil (247 mg, 65 %); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.48 (s, 9 H), 3.07 (t, *J* = 5.5 Hz, 2 H), 3.36 (t, *J* = 5.5 Hz, 2 H), 3.49 (s, 2 H), 3.74 (s, 3 H), 4.39 (s, 1 H), 6.79-6.88 (m, 2 H), 7.10-7.18 (m, 2 H); IR (neat) 2930, 1732, 1457, 1367, 1153 cm^{-1}.

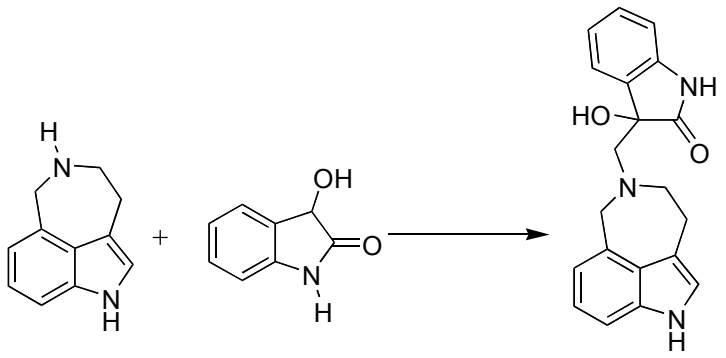


***Tert*-Butyl-(1-Methyl-3,4-dihydro-1H,6H-azepino[5,4,3-cd]indol-5-yl)-thioacetate** (**364**). To a solution of the benzazepine **229** (243 mg, 1.30 mmol) in

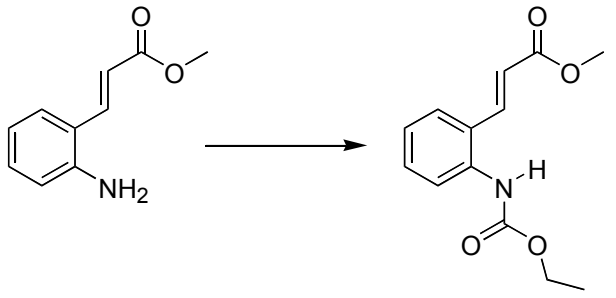
CH_3CN (4.3 mL) at 0 °C was added Cs_2CO_3 (468 mg, 1.44 mmol) and *t*-butyl bromo thioacetate (270 mg, 1.28 mmol) in CH_3CN (2.5 mL). The solution was stirred for 3 h at 0 °C, quenched with saturated aqueous ammonium chloride, and extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by silica-gel chromatography (1 : 20 MeOH : CH_2Cl_2) to afford a yellow oil (276 mg, 67 %); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.46 (s, 9 H), 3.07 (t, *J* = 6.0 Hz, 2 H), 3.36 (t, *J* = 6.0 Hz, 2 H), 3.49 (s, 2 H), 3.74 (s, 3 H), 4.40 (s, 2 H), 6.81 (m, 2 H), 7.14-7.18 (m, 2 H).



(1-Methyl-3,4-dihydro-1H,6H-azepino[5,4,3-cd]indol-5-yl)-acetonitrile (**365**)**.** To a solution of the benzazepine **229** (299 mg, 1.60 mmol) in CH_3CN (5.35 mL) at 0 °C was added Cs_2CO_3 (575 mg, 1.76 mmol) and bromo acetonitrile (160 μL, 1.52 mmol) in CH_3CN (3.2 mL). The solution was stirred for 3 h at 0 °C, quenched with saturated aqueous ammonium chloride, and extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by silica-gel chromatography (1 : 20 MeOH : CH_2Cl_2) to afford a yellow oil (360 mg, 70 %); ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.10 (t, *J* = 6.0 Hz, 2 H), 3.25 (t, *J* = 6.0 Hz, 2 H), 3.71 (s, 2 H), 3.74 (s, 3 H), 4.30 (s, 2 H), 6.15-6.90 (m, 2 H), 7.16-7.20 (m, 2 H).

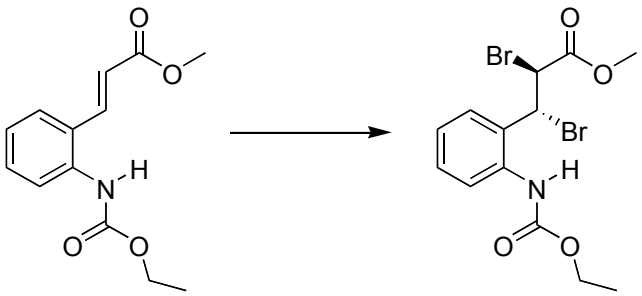


Mannich product 385. To a solution of the 3-hydroxyoxindole **384** (36 mg, 0.243 mmol) in 60 % AcOH (250 μL) at 0 °C was added formaldehyde (22 μL, 0.79 mmol) and the benzazepine **229** (42 mg, 0.24 mmol). The solution was stirred at rt for 12 h, quenched with saturated aqueous sodium bicarbonate, and extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by silica-gel chromatography (7 : 1 ethyl acetate : hexanes) to afford a yellow oil (43 mg, 56 %); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.79-2.82 (m, 1 H), 2.98-3.05 (m, 3 H), 3.13 (d, *J* = 13.7 Hz, 1 H), 3.20 (d, *J* = 13.7 Hz, 1 H), 3.97 (d, *J* = 16.3 Hz, 1 H), 4.06 (d, *J* = 16.3Hz, 1 H), 5.55 (br s, 2 H), 6.62 (dd, *J* = 0.9, 3.0 Hz, 1 H), 6.84 (dd, *J* = 0.7, 7.5 Hz, 1 H), 7.31 (dd, *J* = 0.7, 8.0 Hz, 1 H), 6.98-7.04 (m, 3 H), 7.22 (dt, *J* = 1.2, 7.6 Hz, 1 H), 7.37 (dt, 0.7, 7.3 Hz, 1 H), 9.16 (br s, 1 H); ^{13}C (50 MHz, $CDCl_3$) δ 57.2, 57.3, 59.5, 64.0, 64.1, 69.7, 76.9, 83.8, 108.6, 110.2, 115.3, 117.9, 121.8, 122.3, 125.3, 125.5, 128.1, 129.8, 135.5, 180.0; IR (neat) 3292, 2923, 1714, 1620, 1027 cm^{-1}.



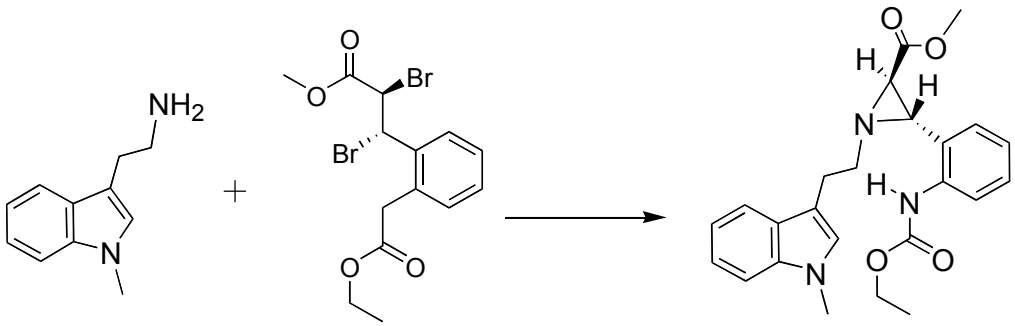
Methyl 2-*N*-(ethoxycarbonyl)cinnamate (464). To a solution of methyl 2-aminocinnamate (3.80 g, 21.4 mmol) in CH_2Cl_2 (71.4 mL) at –40 °C was added

pyridine (5.20 mL, 64.3 mmol) and ethyl chloroformate (2.25 mL, 23.5 mmol). The solution was stirred at rt 12 h, quenched with 10% HCl, and extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product thus obtained (4.26 g, 80%) was used in the next reaction without purification; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (t, *J* = 7.1 Hz, 1 H), 3.82 (s, 3 H), 4.23 (q, *J* = 7.1, 14.2 Hz, 2 H), 6.39 (d, *J* = 15.8 Hz, 1 H), 6.61 (br s, 1 H), 7.14 (dt, *J* = 0.5, 7.3 Hz, 1 H), 7.38 (dt, *J* = 1.5, 7.5 Hz, 1 H), 7.51 (dd, *J* = 1.5, 7.5 Hz, 1 H), 7.77 (br d, *J* = 7.8 Hz, 1 H), 7.83 (d, *J* = 15.8 Hz, 1 H); ^{13}C (50 MHz, $CDCl_3$) δ 14.2, 51.6, 61.4, 120.0, 123.0, 124.6, 126.2, 126.9, 130.6, 136.0, 139.2, 153.7, 165.9; IR (neat) 3291, 2982, 1715, 1632, 1529 cm^{-1}; HRMS (M + Na^+) calc for $C_{13}H_{15}NO_4Na$ 272.0889, found 272.0989.

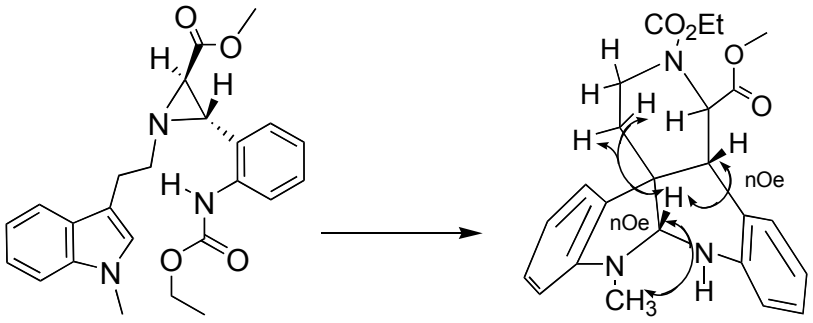


Vicinal dibromide 465. A solution of the alkene **464** (272 mg, 1.09 mmol) in cyclohexane (10.9 mL) was heated to reflux with a heatgun. Bromine (56 μL, 1.09 mmol) was added dropwise and the solution was stirred at rt for 10 min. The solution was quenched with 10 % aqueous sodium thiosulfate and extracted with Et_2O. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product thus obtained (440 mg, 99%) was used in the next reaction without purification; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (t, *J* = 7.1 Hz, 3 H), 3.85 (s, 3 H), 4.23 (q, *J* = 7.1, 14.2 Hz, 2 H), 4.93 (d, *J* = 11.7 Hz, 1 H), 5.62 (d, *J* = 11.7 Hz, 1 H), 6.82 (br s, 1 H), 7.18 (t, *J* = 7.4 Hz, 1 H), 7.32 (t, *J* = 7.6 Hz, 1 H), 7.38 (d, *J* = 7.7 Hz, 1 H), 7.61 (br d, *J* = 6.9 Hz, 1 H); ^{13}C (75 MHz, $CDCl_3$) δ 15.0, 45.8, 50.5, 53.8, 53.9, 62.1, 126.2, 128.5, 128.9, 130.5, 136.1, 154.6,

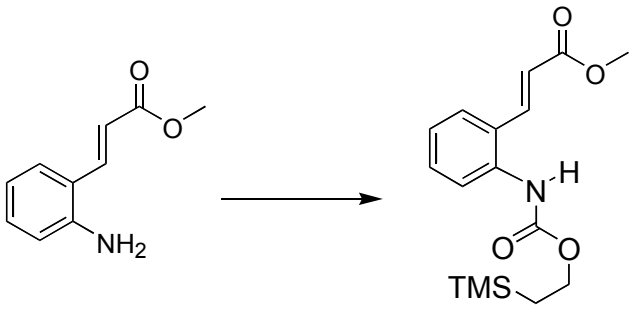
168.6; IR (neat) 3320, 2982, 1731, 1528, 1537 cm^{-1}; HRMS (M + Na^+) calc for $C_{13}H_{15}NO_4NaBr_2$ 429.9267, found 429.9266.



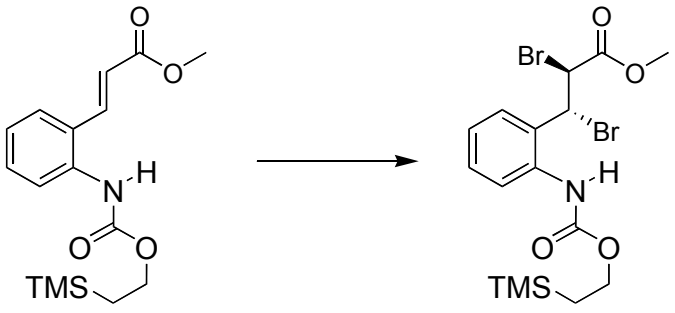
Aziridine 469. To a solution of the dibromide **465** (202 mg, 0.494 mmol) in CH_3CN (4.90 mL) at 0 °C was added the tryptamine **468** (86 mg, 0.494 mmol) in CH_3CN (1.6 mL) followed immediately by Cs_2CO_3 (563 mg, 1.73 mmol). The solution was stirred at rt 12 h, quenched with saturated aqueous ammonium chloride, and extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by silica-gel chromatography (1 : 7 ethyl acetate : hexanes) to afford a white foam (135 mg, 65 %); ^1H NMR (300 MHz, $CDCl_3$) δ 1.32 (t, *J* = 7.1 Hz, 3 H), 2.91 (d, *J* = 2.8 Hz, 1 H), 2.98 (d, *J* = 2.8 Hz, 1 H), 3.09 (t, *J* = 6.6 Hz, 2 H), 3.27-3.33 (m, 2 H), 3.55 (s, 3 H), 3.57 (s, 3 H), 4.20 (q, *J* = 7.0, 12.7 Hz, 2 H), 6.77 (s, 1 H), 6.89-6.93 (m, 2 H), 7.10-7.12 (m, 1 H), 7.20-7.24 (m, 3 H), 7.59 (d, *J* = 7.6 Hz, 1 H), 8.07 (d, *J* = 8.3 Hz, 1 H), 10.12 (br s, 1 H); ^{13}C (75 MHz, $CDCl_3$) δ 14.6, 25.7, 32.2, 40.1, 49.0, 51.2, 52.2, 60.7, 72.2, 109.0, 111.4, 118.6, 118.8, 119.3, 121.4, 122.1, 127.2, 127.5, 128.1, 129.3, 137.0, 137.5, 153.9, 168.8; IR (neat) 2950, 1729, 1592, 1530, 1224 cm^{-1}; HRMS (M + H^+) calc for $C_{24}H_{28}N_3O_4$ 422.2100, found 422.2080.



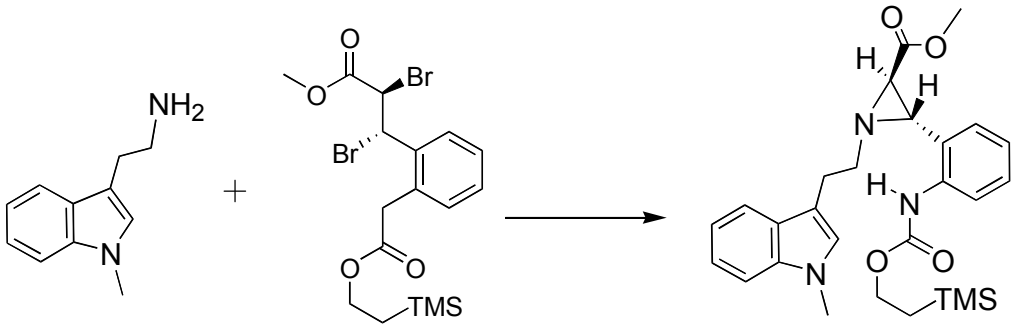
Cycloadduct 485. To a solution of the aziridine **469** (93 mg, 0.228 mmol) in CH_3CN (23 mL) was added bis(trifluoromethanesulfonimide (6.4 mg, 0.023 mmol). The solution was stirred 24 h at rt, quenched with saturated aqueous sodium bicarbonate, and extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by silica-gel chromatography (1 : 1 ethyl acetate : hexanes) to afford a yellow foam (64 mg, 70 %); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (dt, *J* = 0.5, 7.0 Hz, 2 H), 2.22 (t, *J* = 6.6 Hz, 2 H), 2.81 (s, 3 H), 3.43, (d, *J* = 10.4 Hz, 1 H), 3.72 (s, 3 H), 3.85-3.96 (m, 2 H), 4.19-4.35 (m, 2 H), 4.67 (s, 1 H), 5.23 (d, *J* = 10.6 Hz, 1 H), 6.12 (d, *J* = 7.8 Hz, 1 H), 6.43 (t, *J* = 7.4 Hz, 1 H), 6.53 (d, *J* = 8.1 Hz, 1 H), 6.67 (t, *J* = 7.5 Hz, 1 H), 6.76 (d, *J* = 7.4 Hz, 1 H), 6.91 (q, *J* = 7.9, 15.7 Hz, 2 H), 7.31 (d, *J* = 7.7 Hz, 1 H); ^{13}C (75 MHz, $CDCl_3$) δ 14.6, 30.0, 35.3, 38.8, 41.2, 50.5, 52.3, 55.1, 62.0, 85.9, 105.1, 115.4, 117.0, 119.8, 124.4, 124.5, 126.3, 126.8, 128.1, 129.8, 144.1, 150.8, 156.4, 173.3; IR (neat) 3358, 2950, 1741, 1692, 1607, 1496, 1253 cm^{-1}; HRMS (M + Na^+) calc for $C_{24}H_{27}N_3O_4Na$ 444.1917, found 444.1899.



Methyl *N*-[(2-trimethylsilyl)ethoxycarbonyl]cinnamate (496). To a solution of phosgene (29.4 mL, 297 mmol) at –40 °C was added a solution of 2-trimethylsilyl ethanol (2.98 mL, 20.8 mmol) in toluene (5.9 mL) over 30 min via syringe pump. The solution was warmed to 0 °C over 30 min, concentrated *in vacuo* to half volume, and added to a solution of methyl 2-amino-cinnamate **489** (3.51 g, 19.8 mmol) and pyridine (4.80 mL, 59.4 mmol) in CH_2Cl_2 (66.0 mL) at –78 °C. The solution was stirred at rt for 12 h, quenched with 10% HCl, and extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude material thus obtained (5.7 g, 90%) was used without further purification in the next reaction; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.2 (s, 9 H), 0.97-1.04 (m, 2 H), 3.75 (s, 3 H), 4.19-4.25 (m, 2 H), 6.34 (d, *J* = 15.8 Hz, 1 H), 6.96 (br s, 1 H), 7.10 (t, *J* = 7.3 Hz, 1 H), 7.32 (t, *J* = 7.6 Hz, 1 H), 7.47 (d, *J* = 7.8 Hz, 1 H), 7.68 (br d, *J* = 7.6 Hz, 1 H), 7.84 (d, *J* = 15.8 Hz, 1 H); ^{13}C (50 MHz, $CDCl_3$) δ –1.7, 17.6, 51.6, 63.7, 119.8, 123.6, 124.7, 126.1, 126.7, 130.6, 136.2, 139.5, 154.1 166.9; IR (neat) 3313, 2952, 2252, 1731, 1633, 1582 cm^{-1}; HRMS (M + Na^+) calc for $C_{16}H_{23}NO_4SiNa$ 344.1287, found 344.1294.

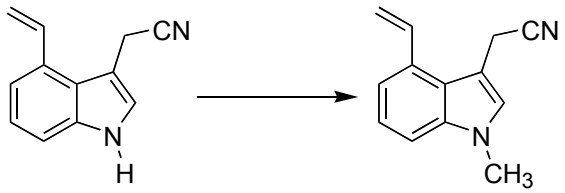


TEOC vicinal dibromide 503. A solution of methyl *N*-[(2-trimethylsilyl)ethoxycarbonyl]cinnamate (**496**) (1.20 g, 3.73 mmol) in cyclohexane (37 mL) was heated to reflux with a heatgun. Bromine (191 μL, 3.73 mmol) was added dropwise and the solution was stirred at rt for 10 min. The solution was quenched with 10 % aqueous sodium thiosulfate and extracted with Et_2O. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product thus obtained (1.65 g, 91%) was used in the next reaction without purification; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.06 (s, 9 H), 1.03-1.09 (m, 2 H), 3.90 (s, 3 H), 4.27-4.33 (m, 2 H), 4.95 (d, *J* = 11.7 Hz, 1 H), 5.59 (d, *J* = 11.7 Hz, 1 H), 6.64 (br s, 1 H), 7.25 (t, *J* = 2.7 Hz, 1 H), 7.33-7.41 (m, 2 H), 7.67 (br d, *J* = 7.9 Hz, 1 H); ^{13}C (75 MHz, $CDCl_3$) δ –1.5, 17.4, 17.6, 45.1, 53.4, 64.0, 65.9, 77.4, 125.8, 128.4, 130.0, 135.6, 154.1, 168.1; IR (neat) 3320, 2953, 1750, 1522 cm^{-1}; HRMS (M + Na^+) calc for $C_{16}H_{23}Br_2NO_4SiNa$ 501.9653, found 501.9661.

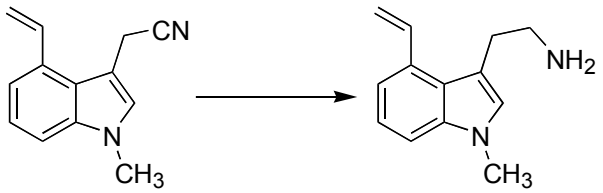


Aziridine 510. To a solution of the dibromide **503** (231 mg, 0.479 mmol) in CH_3CN (4.80 mL) at 0 °C was added the tryptamine **468** (83.6 mg, 0.479 mmol) in CH_3CN (1.60 mL) followed immediately by Cs_2CO_3 (470 mg, 1.44

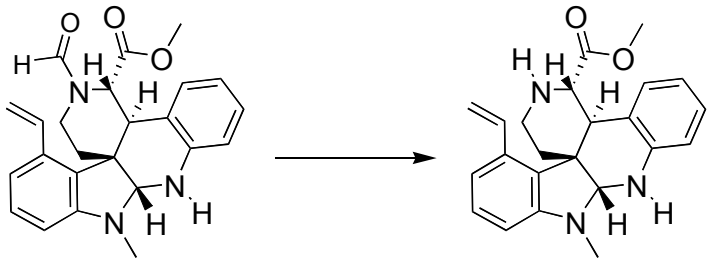
mmol). The solution was stirred at rt for 12 h, quenched with saturated aqueous ammonium chloride, and extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by silica-gel chromatography (1 : 3 ethyl acetate : hexanes) to afford a yellow foam (154 mg, 65 %); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.99 (s, 9 H), 1.03-1.09 (m, 2 H), 2.92 (d, *J* = 2.9 Hz, 1 H), 2.96 (d, *J* = 2.9 Hz, 1 H), 3.09 (t, *J* = 6.7 Hz, 2 H), 3.21-3.35 (m, 2 H), 3.53 (s, 3 H), 3.60 (s, 3 H), 4.22-4.28 (m, 2 H), 6.76 (s, 1 H), 6.88-6.92 (m, 2 H), 7.07-7.12 (m, 1 H), 7.16-7.28 (m, 3 H), 7.60 (d, *J* = 7.8 Hz, 1 H), 8.08 (d, *J* = 8.2 Hz, 1 H), 10.12 (br s, 1 H); ^{13}C (75 MHz, $CDCl_3$) δ –1.5, 1.4, 17.6, 25.7, 32.2, 39.9, 49.2, 51.3, 52.1, 62.9, 109.0, 111.4, 118.6, 119.3, 121.4, 122.0, 122.3, 127.2, 128.1, 129.3, 136.9, 137.6, 154.0, 168.8; IR (neat) 2951, 1729, 1593, 1531 cm^{-1} ; HRMS (M + Na^+) calc for $C_{27}H_{35}N_3O_4NaSi$ 516.2292, found 516.2295.



(1-Methyl-4-vinyl-1*H*-indol-3-yl)-acetonitrile (**518**). To a solution of the nitrile **399** (608 mg, 3.34 mmol) in CH_3CN (11.1 mL) at rt was added methyl iodide (1.1 mL, 16.7 mmol) and Cs_2CO_3 (1.3 g, 4.00 mmol). The reaction was stirred for 12 h at rt, filtered through celite, and concentrated to afford the nitrile as a yellow solid (650 mg, 99%). The crude product thus obtained was used in the next reaction without purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.78 (s, 3 H), 4.00 (s, 2 H), 5.43 (dd, *J* = 0.5, 10.8 Hz, 1 H), 5.73 (dd, *J* = 0.5 Hz, 17.1 Hz, 1 H), 7.15 (s, 1 H), 7.25-7.28 (m, 3 H), 7.32 (dd, *J* = 10.8, 17.1 Hz, 1 H); ^{13}C (50 MHz, $CDCl_3$) δ 16.8, 32.9, 103.3, 109.1, 116.9, 117.7, 118.5, 122.5, 123.7, 128.4, 131.8, 134.7, 137.1; IR (neat) 3054, 2944, 2247, 1603, 1553 cm^{-1}; HRMS (M + Na^+) calcd for $C_{13}H_{12}N_2Na$ 219.0901, found 219.0898.

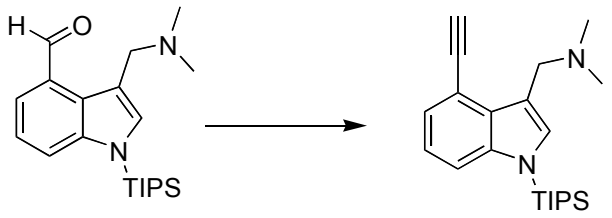


4-Vinyl-1-methyltryptamine (**519**). To a solution of the nitrile **518** (154 mg, 0.785 mmol) in Et_2O (3.9 mL) at 0 °C was added slowly $LiAlH_4$ (119 mg, 3.14 mmol). The solution was stirred for 20 min at 0 °C, and quenched with H_2O (119 μL), 10 % NaOH (178 μL), and H_2O (357 μL). The solids were filtered off, and the filtrate was concentrated to afford the tryptamine as a yellow oil (145 mg, 92 %). The crude product thus obtained was used in the next reaction without purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41 (br s, 2 H), 3.03 (br s, 4 H), 3.61 (s, 3 H), 5.44 (dd, *J* = 0.5, 10.8 Hz, 1 H), 5.85 (dd, *J* = 0.5, 17.3 Hz, 1 H), 6.80 (s, 1 H), 7.18-7.25 (m, 3 H), 7.36 (dd, *J* = 0.7, 7.0 Hz, 1 H), 7.56 (dd, *J* = 10.8, 17.3 Hz, 1 H); ^{13}C (75 MHz, $CDCl_3$) δ 31.2, 31.8, 42.1, 108.2, 111.9, 114.8, 116.5, 120.9, 124.3, 127.3, 131.6, 135.7, 137.3; IR (neat) 3361, 3051, 2922, 1623, 1602, 1563 cm^{-1}; HRMS (M + H$^+$) calc for $C_{13}H_{17}N_2$ 201.1391, found 201.1392.



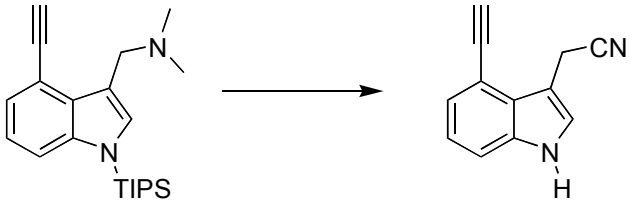
Vinyl-cycloadduct 522. To a solution of the formamide **521** (42 mg, 0.104 mmol) in methanol (1.5 mL) and THF (1.5 mL) at 0 °C was added acetyl chloride (37 μL, 0.520 mmol). The solution was stirred at rt for 12 h, quenched with saturated aqueous sodium bicarbonate, and extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by silica-gel chromatography (1 : 9 methanol : CH_2Cl_2) to afford a yellow oil (68 mg, 70 %); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.84 (d, *J* =

14.0 Hz, 1 H), 2.14 (dt, *J* = 4.9, 13.8 Hz, 1 H), 2.85 (s, 3 H), 3.13 (dt, *J* = 2.8, 12.9 Hz, 1 H), 3.24 (dd, *J* = 3.3, 13.8 Hz, 1 H), 3.44 (s, 3 H), 3.63 (d, *J* = 10.5 Hz, 1 H), 3.96 (d, *J* = 10.5 Hz, 1 H), 4.37 (br s, 1 H), 4.88 (s, 1 H), 5.36 (dd, *J* = 1.4, 10.8 Hz, 1 H), 5.49 (dd, *J* = 1.4, 17.1 Hz, 1 H), 6.11 (d, *J* = 12.1 Hz, 1 H), 6.45 (d, *J* = 12.1 Hz, 1 H), 6.50 (t, *J* = 12.2 Hz, 1 H), 6.56 (d, *J* = 7.7 Hz, 1 H), 6.67 (dd, *J* = 10.8, 17.1 Hz, 1 H), 6.87-6.96 (m, 2 H), 7.26 (dd, *J* = 10.8, 16.9 Hz, 1 H); ^{13}C (75 MHz, $CDCl_3$) δ 30.1, 34.2, 42.1, 45.8, 51.0, 51.4, 59.6, 79.0, 104.5, 114.2, 116.5, 119.0, 124.0, 127.7, 128.1, 128.3, 129.3, 134.1, 134.4, 142.8, 150.0, 173.2; IR (neat) 3300, 2947, 1733, 1577, 1495 cm^{-1}; HRMS (M + H$^+$) calc for $C_{23}H_{25}N_3O_2$ 376.2032, found 376.2025.

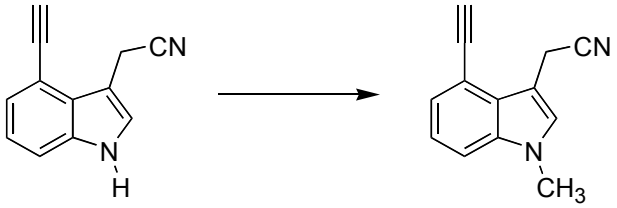


4-Ethynyl-1-(triisopropylsilyl)gramine (**535**). Butyllithium (1.97 mL, 4.94 mmol) was added dropwise to a solution of diisopropylamine (690 μL, 4.94 mmol) in THF (16.4 mL) at –78 °C. The solution was stirred for 30 min at –78 °C, and trimethylsilyldiazomethane (2.47 mL, 4.94 mmol) was added dropwise. The solution was stirred another 30 min at –78 °C, and then the aldehyde **397** (1.18 g, 3.29 mmol) was added dropwise. The solution was warmed to 0 °C over 3 h, quenched with saturated aqueous ammonium chloride and extracted with ether. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by silica-gel chromatography (1 : 9 methanol : CH_2Cl_2) to afford a yellow oil (589 mg, 50 %); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.60 (d, *J* = 2.6 Hz, 18 H), 2.23-2.38 (m, 3 H), 2.42 (s, 6 H), 3.35 (s, 1 H), 3.98 (s, 2 H), 7.10 (t, *J* = 8.2 Hz, 1 H), 7.36 (d, *J* = 7.2 Hz, 1 H), 7.53 (d, *J* = 8.3 Hz, 1 H); ^{13}C (100 MHz, $CDCl_3$) δ12.6, 17.8, 44.7, 53.9, 79.5, 83.8, 112.8, 114.7, 115.6, 120.7, 125.8, 130.1, 131.9, 141.3; IR (neat) 3308, 2946, 2813, 2787, 2097, 1892, 1877,

1698, 1632, 1593, 1358 cm^{-1}; HRMS (M + H^+) calc for $C_{22}H_{35}N_2Si$ 355.2562, found 355.2570.

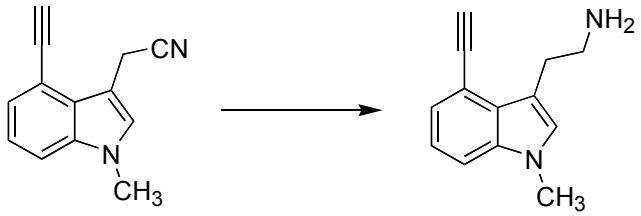


(4-Ethynyl-1*H*-indol-3-yl)acetonitrile (**537**)**.** To a solution of the gramine **535** (1.76 g, 4.96 mmol) in benzene (12.4 mL) at 0 °C was added iodomethane (1.55 mL, 24.8 mmol). The solution was stirred at rt for 12 h and concentrated. The crude ammonium salt was dissolved in DMF (7.1 mL), and a solution of KCN (1.29 g, 19.8 mmol) in H_2O (15.3 mL) was added. The solution was heated to 80 °C for 8 h, quenched with brine, and extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purifid by silica-gel chromatography (1 : 1 ethyl acetate : hexanes) to afford a white foam (615 mg, 70 %); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.34 (s, 1 H), 4.23 (s, 2 H), 7.18 (d, *J* = 7.5 Hz, 1 H), 7.31-7.34 (m, 2 H), 7.41 (dd, *J* = 0.9, 8.2 Hz, 1 H), 8.27 (br s, 1 H); ^{13}C (75 MHz, $CDCl_3$) δ 15.2, 77.4, 80.5, 82.5, 105.9, 112.7, 118.8, 122.5, 124.0, 125.6, 126.0, 136.3; IR (neat) 3334, 3290, 2918, 2254, 2102, 1651, 1609 cm^{-1}; HRMS (M + Na^+) calc for $C_{12}H_8N_2Na$ 203.0584, found 203.0585.

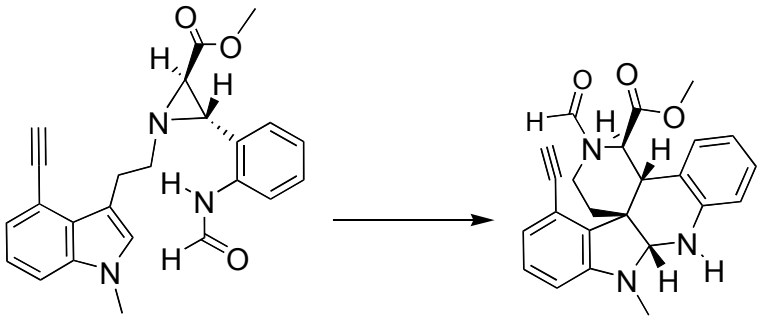


(4-Ethynyl-1-methyl-1*H*-indol-3-yl)acetonitrile. To a solution of the nitrile **537** (615mg, 3.41 mmol) in THF (11.4 mL) at 0 °C was added NaH (150

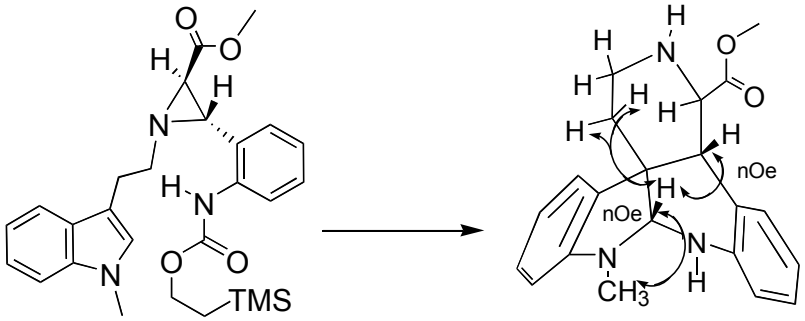
mg, 6.25 mmol). The solution was stirred for 15 min at 0 °C and methyl iodide (276 μL, 4.44 mmol) was added. The solution was stirred for 30 min at 0 °C, quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by silica-gel chromatography (1 : 1 ethyl acetate : hexanes) to afford a yellow foam (654 mg, 99 %); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.48 (s, 1 H), 3.69 (s, 3 H), 4.19 (d, *J* = 1.1 Hz, 2 H), 7.11 (s, 1 H), 7.24 (t, *J* = 8.3 Hz, 1 H), 7.32 (dd, *J* = 0.9, 8.3 Hz, 1 H), 7.39 (dd, *J* = 0.9, 7.1 Hz, 1 H); ^{13}C (100 MHz, $CDCl_3$) δ 14.4, 22.3, 80.3, 86.3, 103.9, 110.5, 112.2, 118.6, 121.4, 125.0, 125.5, 128.6, 136.6; IR (neat) 3282, 2942, 2249, 2047, 1552, 1454 cm^{-1}; HRMS (M + Na^+) calc for $C_{13}H_{10}N_2Na$ 217.0751, found 217.0742.



4-Ethynyl-1methyltryptamine (**538**). To a solution of (4-ethynyl-1-methyl-1*H*-indol-3-yl)acetonitrile (140 mg, 0.721 mmol) in Et_2O (2.40 mL) at 0 °C was added lithium aluminum hydride (109 mg, 2.8 8 mmol). The solution was stirred for 1 h at 0 °C, and quenched with H_2O (109 μL), 10 % NaOH (163 μL), and H_2O (327 μL). The solids were filtered off, and the filtrate was concentrated to provide the amine as a yellow foam (121 mg, 85%). The crude product thus obtained was used in the next reaction without purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.55 (br s, 2 H), 3.01 (t, *J* = 6.4 Hz, 2 H), 3.12 (t, *J* = 6.4 Hz, 2 H), 3.28 (s, 1 H), 3.67 (s, 3 H), 6.88 (s, 1 H), 7.10 (t, *J* = 7.6 Hz, 1 H), 7.26 (t, *J* = 7.5 Hz, 2 H); ^{13}C (75 MHz, $CDCl_3$) δ 29.4, 32.4, 43.5, 79.4, 83.5, 110.2, 112.9, 113.0, 120.8, 125.0, 127.1, 128.2, 137.0; IR (neat) 3280, 2935, 2097, 1453 cm^{-1}; HRMS (M + Na^+) calc for $C_{13}H_{14}N_2Na$ 221.1062, found 221.1055.

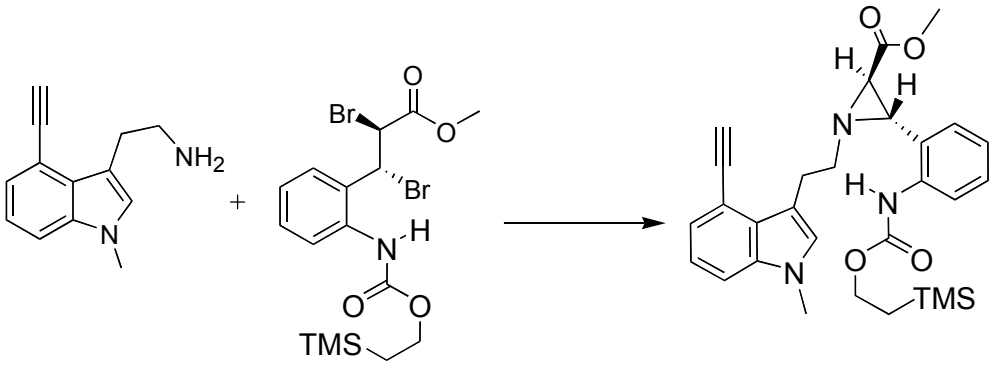


Cycloadduct 540. To a solution of the aziridine **539** (64 mg, 0.159 mmol) in CH_3CN (15.9 mL) was added bis(trifluoromethanesulfonimide (4.5 mg, 0.015 mmol). The solution was stirred 24 h at rt, quenched with saturated sodium bicarbonate, and extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by silica-gel chromatography (4 : 1 ethyl acetate : hexanes) to afford a yellow oil (48 mg, 75 %); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.15-2.34 (m, 2 H), 2.86 (s, 3 H), 3.60 (d, *J* = 16.3 Hz, 1 H), 3.71 (s, 3 H), 3.80-3.95 (m, 2 H), 4.46 (br s, 1 H), 4.74 (s, 1 H), 6.00 (d, *J* = 12.1 Hz, 1 H), 6.21 (d, *J* = 7.8 Hz, 1 H), 6.44 (d, *J* = 5.5 Hz, 1 H), 6.61-6.70 (m, 3 H), 6.83-6.96 (m, 3 H), 7.44 (d, *J* = 7.6 Hz, 1 H), 8.25 (s, 1 H); ^{13}C (75 MHz, $CDCl_3$) δ 30.3, 35.7, 39.7, 40.0, 51.5, 51.8, 55.0, 81.3, 84.1, 86.0, 106.6, 113.6, 117.4, 118.8, 124.1, 124.3, 124.5, 126.8, 128.0, 133.5, 144.4, 151.0, 162.9, 172.8; IR (neat) 3293, 2950, 2247, 1738, 1667, 1608, 1580, 1486 cm^{-1}; HRMS (M + H$^+$) calc for $C_{23}H_{25}N_3O_2$ found 402.1816.



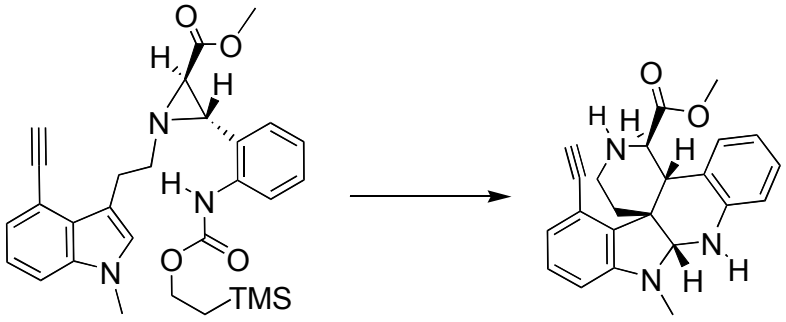
Cycloadduct 549. To a solution of the aziridine **510** (560 mg, 1.13 mmol) in THF (5.7 mL) was added tetrabutylammonium fluoride (4.53 mL, 4.53 mmol).

The solution was stirred 4 h at rt, quenched with saturated aqueous ammonium chloride, and extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by silica-gel chromatography (1 : 15 methanol : CH_2Cl_2) to afford a yellow oil (315 mg, 80 %); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.94-2.09 (m, 2 H), 2.86 (s, 3 H), 3.09-3.36 (m, 1 H), 3.25 (dt, *J* = 2.9, 13.4 Hz, 1 H), 3.33 (d, *J* = 11.4 Hz, 1 H), 3.77 (s, 3 H), 4.54 (d, *J* = 11.4 Hz, 1 H), 4.66 (s, 3 H), 6.21 (d, *J* = 7.7 Hz, 1 H), 6.43-6.59 (m, 2 H), 6.56 (t, *J* = 6.8 Hz, 1 H), 6.82 (d, *J* = 7.7 Hz, 1 H), 6.81-6.93 (m, 1 H), 6.91 (t, *J* = 7.7 Hz, 1 H), 7.10 (d, *J* = 7.3 Hz, 1 H); ^{13}C (75 MHz, $CDCl_3$) δ 30.3, 38.1, 41.3, 42.0, 50.7, 53.0, 58.1, 85.4, 106.1, 15.4, 117.8, 119.6, 123.7, 125.6, 126.9, 127.6, 127.9, 128.4, 131.8, 144.8, 151.2, 173.7; IR (neat) 3378, 2947, 1737, 1608, 1495 cm^{-1}; HRMS (M + H$^+$) calc for $C_{21}H_{24}N_3O_2$ 350.1877, found 350.1869.

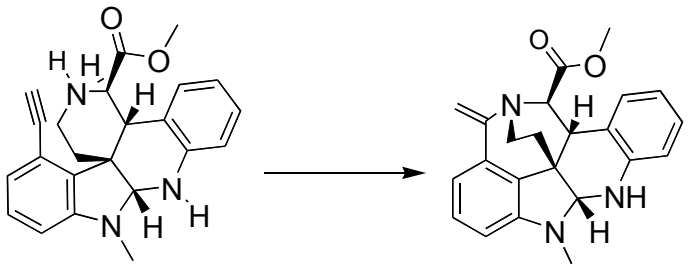


Alkynyl aziridine 550. To a solution of the tryptamine **538** (58 mg, 0.293 mmol) in CH_3CN (1.00 mL) at 0 °C was added sequentially Cs_2CO_3 (286 mg, 0.879 mmol) and the dibromide **503** (141 mg, 0.293 mmol) in CH_3CN (2.90 mL). The solution was stirred at rt for 12 h, quenched with saturated aqueous ammonium chloride, and extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by silica-gel chromatography (1 : 7 ethyl acetate : hexanes) to afford a yellow foam (68 mg, 45 %); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.08 (s, 9 H), 1.01-1.05 (m, 2 H), 2.94 (d, *J* = 2.8 Hz, 1 H), 2.98 (d, *J* = 2.8 Hz, 1 H), 3.31 (s, 1 H), 3.24-3.39 (m, 4 H), 3.49 (s, 3 H), 3.59 (s, 3 H), 4.17-4.28 (m, 2 H), 6.78 (s, 1 H), 6.89-6.98 (m, 2 H), 7.09-7.24 (m, 4 H), 8.11 (d, *J* = 8.3 Hz, 1 H), 10.31 (br s, 1 H); ^{13}C (100

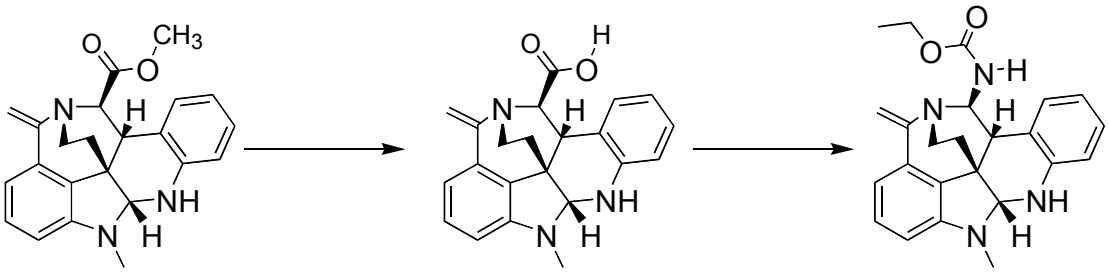
MHz, $CDCl_3$) δ -0.9, 18.1, 26.4, 32.7, 40.4, 49.7, 52.6, 53.1, 63.4, 80.0, 83.9, 110.7, 112.7, 113.5, 119.6, 121.3, 122.4, 122.7, 125.5, 127.5, 129.5, 129.5, 129.8, 137.6, 138.1, 154.4, 169.2; IR (neat) 3290, 2952, 2360, 1728, 1593 cm^{-1}; HRMS (M + H^+) calc for $C_{29}H_{36}N_3O_4Si$ 518.2488, found 518.2475.



Cycloadduct 541. To a solution of the aziridine **550** (611 mg, 1.18 mmol) in THF (11.8 mL) was added tetrabutylammonium fluoride (4.70 mL, 4.72 mmol). The solution was stirred for 4 h at rt, quenched with saturated aqueous ammonium chloride, and extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by silica-gel chromatography (1 : 15 methanol : CH_2Cl_2) to afford a yellow foam (270 mg, 61 %); ^1H NMR (300 MHz, $CDCl_3$) δ 1.89-2.08 (m, 2 H), 2.85 (s, 3 H), 3.08 (dq, *J* = 2.5, 3.9, 13.5, 16.2 Hz, 1 H), 3.31 (d, *J* = 11.6 Hz, 1 H), 3.38 (s, 1 H), 3.53 (dt, *J* = 2.7, 13.1 Hz, 1 H), 3.75 (s, 3 H), 4.39 (br s, 1 H), 4.67 (s, 1 H), 5.87 (d, *J* = 11.6 Hz, 1 H), 6.26 (dd, *J* = 0.9, 7.8 Hz, 1 H), 6.35 (dd, *J* = 0.9, 7.7 Hz, 1 H), 6.56 (dt, *J* = 1.0, 7.5 Hz, 1 H), 6.67 (dd, *J* = 1.0, 7.7 Hz, 1 H), 6.82 (t, *J* = 7.5 Hz, 1 H), 6.87 (t, *J* = 7.7 Hz, 1 H), 7.08 (d, *J* = 7.5 Hz, 1 H); IR (neat) 3389, 3291, 2949, 1732, 1576, 1484 cm^{-1}.

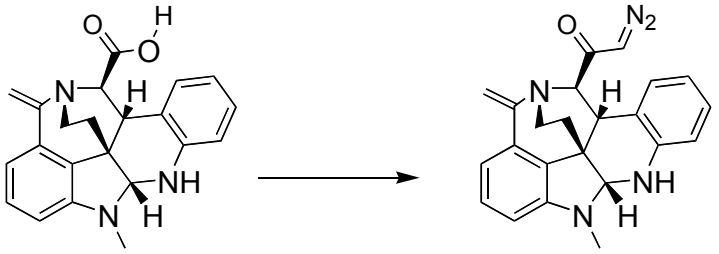


Enamine 551. To a solution of the alkene **541** (74 mg, 0.198 mmol) in CH_2Cl_2 (1.90 mL), was added Ph_3AuCl (1.00 mg, 0.0019 mmol) and AgOTf (0.5 mg, 0.0019 mmol). The solution was stirred for 12 h at 40 °C and concentrated. The crude product was purified by silica-gel chromatography (1 : 1 ethyl acetate : hexanes) to afford a white solid (66 mg, 89 %); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.18-3.05 (m, 2 H), 2.70 (s, 3 H), 3.16 (d, *J* = 8.5, 14.5 Hz, 1 H), 3.32 (d, *J* = 10.6 Hz, 1 H), 3.79 (s, 3 H), 3.74-3.85 (m, 1 H), 4.00 (d, *J* = 10.6 Hz, 1 H), 4.62 (s, 1 H), 4.65 (br s, 1 H), 5.16 (s, 1 H), 5.26 (s, 1 H), 6.02 (d, *J* = 7.7 Hz, 1 H), 6.73 (t, *J* = 8.2 Hz, 2 H), 6.76 (d, *J* = 5.3 Hz, 2 H), 6.95 (t, *J* = 7.8 Hz, 1 H), 7.04-7.07 (m, 1 H); ^{13}C (75 MHz, $CDCl_3$) δ 30.7, 39.4, 40.9, 47.8, 52.2, 52.3, 62.1, 84.2, 103.6, 108.0, 113.6, 116.5, 120.9, 124.0, 126.9, 128.5, 128.7, 130.0, 134.2, 144.0, 150.6, 156.7, 172.5; IR (neat) 1731, 1587, 1480, 1276, 1168 cm^{-1}; HRMS (M + H^+) calcd for $C_{23}H_{24}N_3O_2$ 374.1875, found 374.1869.

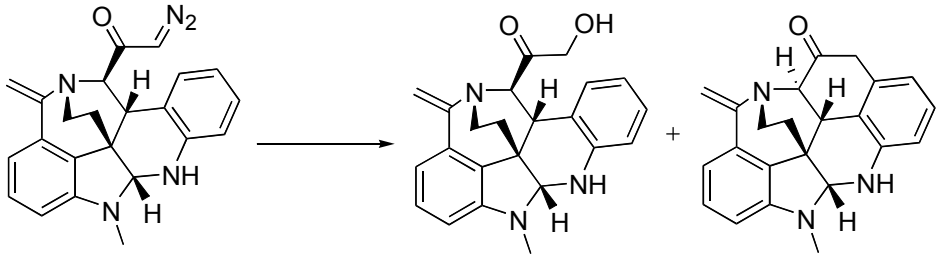


Acid 574. To a solution of the ester **551** (14 mg, 0.037 mmol) in THF (300 μL) and H_2O (75 μL) at rt was added a solution of LiOH (1.4 mg, 0.059 mmol) in H_2O (200 μL) and H_2O_2 (16.2 μL, 0.525 mmol). The solution was stirred for 12 h at 50 °C, quenched with 10 % HCl, and extracted with ethyl acetate. The

combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product thus obtained (12 mg, 92%) was used immediately in the next reaction without purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.23-2.28 (m, 2 H), 2.72 (s, 3 H), 3.16 (d, *J* = 10.1 Hz, 1 H), 3.25-3.33 (m, 1 H), 3.46 (dt, *J* = 8.8, 14.4 Hz, 1 H), 4.15 (dd, *J* = 1.5, 10.1 Hz, 1 H), 4.66 (s, 1 H), 5.25 (s, 1 H), 5.45 (s, 1 H), 6.01 (d, *J* = 7.7 Hz, 1 H), 6.70 (t, *J* = 5.2 Hz, 1 H), 6.73 (d, *J* = 13.1 Hz, 1 H), 6.92 (t, *J* = 7.4 Hz, 1 H), 6.95 (t, *J* = 7.8 Hz, 2 H), 7.06 (t, *J* = 7.5 Hz, 1 H); HRMS (M + Na^+) calc for $C_{22}H_{21}N_3O_2Na$ 382.1519, found 382.1531. **Carbamate 560**. To a solution of the crude acid prepared above (19 mg, 0.053 mmol) in acetone (530 μL) at 0 °C was added *N, N*-diisopropylethylamine (13.8 μL, 0.079 mmol) and ethyl chloroformate (5.6 μL, 0.058 mmol). The solution was stirred for 3 h at 0 °C, and then NaN_3 (12 mg, 0.185 mmol) was added. The solution was stirred at rt for 12 h, quenched with saturated aqueous sodium bicarbonate, and extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by silica-gel chromatography (1 : 1 ethyl acetate : hexanes) to afford a yellow foam (11 mg, 75 %); ^{1}H NMR (400 MHz, CD_3CN) δ 1.20 (t, *J* = 7.1 Hz, 3 H), 2.66 (s, 3 H), 2.67-2.69 (m, 1 H), 2.99-3.09 (m, 1 H), 3.47-3.67 (m, 2 H), 4.08 (q, *J* = 2.0, 14.3 Hz, 2 H), 4.61 (d, *J* = 2.5 Hz, 1 H), 4.81-4.84 (m, 1 H), 4.99 (br s, 1 H), 5.26 (s, 1 H), 5.43 (s, 1 H), 6.01 (d, *J* = 7.6 Hz, 1 H), 6.23 (br s, 1 H), 6.65-6.73 (m, 2 H), 6.77 (br s, 1 H), 6.81 (d, *J* = 6.8 Hz, 1 H), 6.91 (t, *J* = 7.8 Hz, 1 H), 7.03 (t, *J* = 7.4 Hz, 1 H); ^{13}C (75 MHz, $CDCl_3$) δ 14.5, 14.9, 30.1, 31.3, 40.1, 46.1, 46.3, 52.6, 61.4, 67.9, 84.6, 103.9, 109.1, 114.0, 117.0, 121.6, 125.3, 127.5, 127.8, 129.2, 129.8, 135.2, 144.2, 151.0, 155.8; IR (neat) 3333, 2927, 1704, 1587, 1480 cm^{-1}; HRMS (M + H^+) calcd for $C_{24}H_{27}N_4O_2$ 403.2128, found 403.2134.

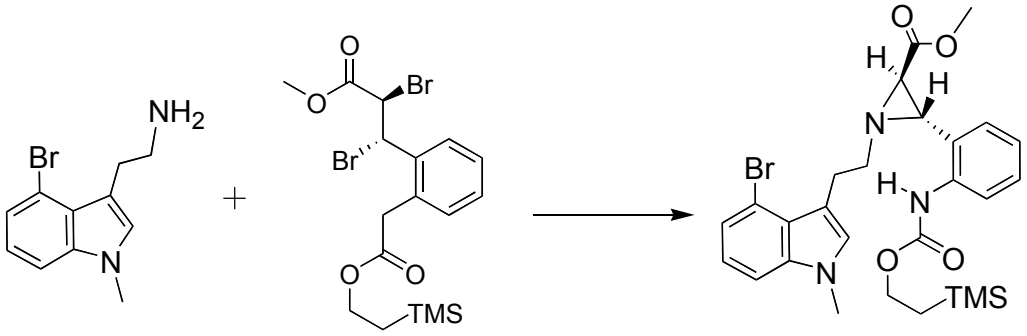


Diazoketone 572. To a solution of the acid **574** (73 mg, 0.20 mmol) in CH_2Cl_2 (2.0 mL) at 0 °C was added triethylamine (57 μL, 0.41 mmol) and isopropylchloroformate (410 μL, 0.41 mmol). The solution was stirred for 10 min at 0 °C, and then diazomethane (711 μL, 0.711 mmol) was added. The solution was stirred for 1 h at 10 °C, quenched with saturated aqueous sodium bicarbonate, and extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by silica-gel chromatography (1 : 3 ethyl acetate : hexanes) to afford a yellow foam (38 mg, 50 %); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (t, *J* = 7.1 Hz, 3 H), 2.13-2.26 (m, 2 H), 2.71 (s, 3 H), 3.14-3.22 (m, 1 H), 3.32-3.41 (m, 2 H), 3.85 (br d, *J* = 8.5 Hz, 1 H), 4.63 (s, 1 H), 5.15 (s, 1 H), 5.29 (s, 1 H), 5.99 (d, *J* = 7.7 Hz, 1 H), 6.10 (br s, 1 H), 6.67-6.76 (m, 4 H), 6.92 (t, *J* = 7.8 Hz, 1 H), 7.01 (t, *J* = 7.5 Hz, 1 H).



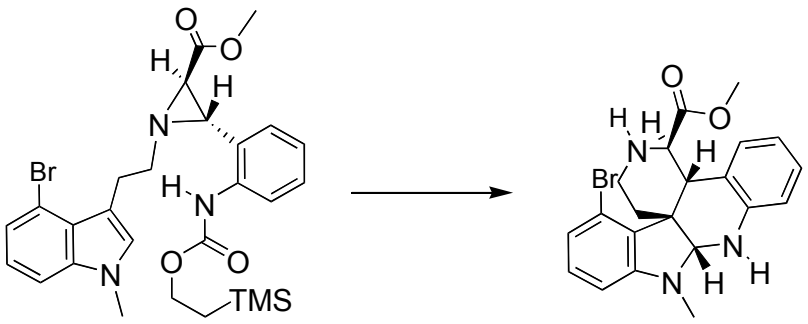
α-Hydroxy Ketone 575. To a solution of $Rh_2(OAc)_4$ (0.2 mg, 0.00003 mmol) in benzene (300 μL) at 45 °C was added a solution of the diazo ketone **572** (12 mg, 0.031 mmol) in benzene (300 μL) over 1 h via syringe pump. The solution was stirred for 2 h at that temperature, filtered through a short silica plug, and concentrated. The crude product was purified by silica-gel chromatography (1 : 10 Et_2O : CH_2Cl_2) to afford the α-hydroxy ketone **575** as a yellow oil (6 mg,

52%) and the cyclohexanone **576** as a yellow oil (3 mg, 30 %). **α-Hydroxy Ketone 575** ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.17 (m, 2 H), 2.60 (d, *J* = 9.9 Hz, 1 H), 2.69 (s, 3 H), 3.17 (dd, *J* = 10.1, 15.1 Hz, 1 H), 3.49 (m, 1 H), 4.62 (s, 1 H),5.19 (m, 2 H), 5.35 (s, 1 H), 5.66 (br d, *J* = 6.7 Hz, 1 H), 6.00 (d, *J* = 7.6 Hz, 1 H), 6.73 (d, *J* = 7.6 Hz, 1 H), 6.77 (d, *J* = 7. 3 Hz, 1 H), 6.81 (t, *J* = 7.4 Hz, 1 H), 6.92 (t, *J* = 9.8 Hz, 1 H), 6.97 (t, *J* = 9.8 Hz, 1 H), 7.08 (t, *J* = 7.4 Hz,1 H); IR (neat) 3483, 3360, 2921, 2852, 1731, 1587 cm^{-1}. **Cyclohexenone 576**. ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.11-2.32 (m, 2 H), 2.73 (s, 1 H), 3.55 (d, *J* = 6.0 Hz, 1 H), 3.73-3.89 (m, 1 H, 3.97 (d, *J* = 6.0 Hz, 1 H), 3.99 (d, *J* = 6.0 Hz, 1 H), 4.37 (d, *J* = 6.0 Hz, 1 H), 4.63 (s, 1 H), 5.14 (s, 1 H), 5.92 (d, *J* = 6.0 Hz, 1 H), 6.59-6.89 (m, 4 H), 6.98 (t, *J* = 6.2 Hz, 1 H).

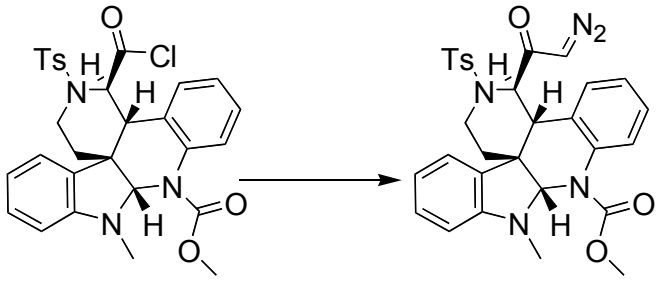


Aziridine 578. To a solution of the dibromide **503** (235 mg, 0.489 mmol) in CH_3CN (4.90 mL) at 0 °C was added the tryptamine **577** (62 mg, 0.244 mmol) in CH_3CN (820 μL) followed immediately by Cs_2CO_3 (240 mg, 0.735 mmol). The solution was stirred at rt for 12 h, quenched with saturated aqueous ammonium chloride, and extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by silica-gel chromatography (1 : 7 ethyl acetate : hexanes) to afford a yellow oil (50 mg, 40 %); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.07 (s, 9 H), 1.00-1.02 (m, 2 H), 2.92 (d, *J* = 2.9 Hz, 1 H), 2.95 (d, *J* = 2.9 Hz, 1 H), 3.30-3.32 (m, 4 H), 3.48 (s, 3 H), 3.58 (s, 3 H), 4.15-4.22 (m, 2 H), 6.77 (s, 1 H), 6.87-6.90 (m, 2 H), 6.99 (t, *J* = 7.6 Hz, 1 H), 7.14 (d, *J* = 7.4 Hz, 1 H), 7.15-7.24 (m, 2 H), 8.10 (d, *J* = 8.3 Hz, 1 H), 10.23 (br s, 1 H); ^{13}C (75 MHz, $CDCl_3$) δ –1.5, -1.4, 8.1, 17.6, 26.3, 32.4, 39.9, 49.2, 52.2,

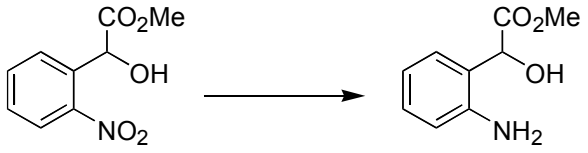
52.6, 62.9, 108.4, 112.1, 114.3, 119.1, 121.9, 122.1, 122.2, 123.2, 125.5, 128.1, 129.3, 129.5, 137.7, 138.2, 154.0, 168.8; IR (neat) 2951, 1729, 1592, 1530, 1454, 1223 cm^{-1}; HRMS (M + H^+) calcd for $C_{27}H_{35}N_3O_4SiBr$ 572.1587, found 572.1580.



Cycloadduct 579. To a solution of the aziridine **578** (50 mg, 0.087 mmol) in THF (871 μL) was added tetrabutylammonium fluoride (350 μL, 0.349 mmol). The solution was stirred for 4 h at rt, quenched with saturated aqueous ammonium chloride, and extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by silica-gel chromatography (1 : 15 methanol : CH_2Cl_2) to afford a yellow oil (33 mg, 90 %); ^1H NMR (300 MHz, $CDCl_3$) δ 1.97 (dt, *J* = 3.9, 12.5 Hz, 2 H), 2.87 (s, 3 H), 3.04-3.10 (m, 1 H), 3.39 (d, *J* = 11.6 Hz, 1 H), 3.44-3.53 (m, 1 H), 3.76 (s, 3 H), 4.27 (br s, 1 H), 4.69 (s, 1 H), 5.76 (d, *J* = 11.5 Hz, 1 H), 6.25 (dd, *J* = 0.9, 7.6 Hz, 1 H), 6.34 (dd, *J* = 0.9, 7.8 Hz, 1 H), 6.59 (dt, *J* = 0.9, 7.5 Hz, 1 H), 6.66 (dd, *J* = 1.0, 8.0 Hz, 1 H), 6.77 (t, *J* = 7.9 Hz, 1 H), 6.81 (t, *J* = 7.6 Hz, 1 H), 7.12 (d, *J* = 7.6 Hz, 1 H); ^{13}C (75 MHz, $CDCl_3$) δ 30.9, 39.1, 39.5, 41.4, 51.8, 52.4, 56.4, 86.9, 106.0, 112.4, 112.8, 117.5, 117.7, 123.8, 123.9, 124.1, 126.6, 129.2, 132.1, 145.2, 152.9, 174.2; IR (neat) 3391, 2948, 1734, 1607, 1593, 1488, 1446 cm^{-1}; HRMS (M + H^+) calcd for $C_{21}H_{23}N_3O_2Br$ 428.0961, found 428.0974.

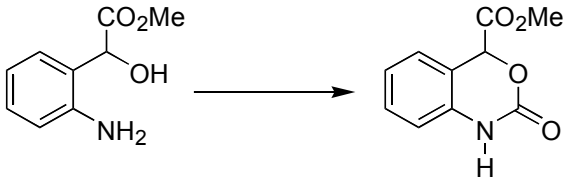


Diazoketone 584. To a solution of the acid chloride (8.1 mg, 0.014 mmol) in THF (150 μL) at 0 °C was added diazomethane (28 μL, 0.028 mmol). The solution was stirred for 30 min at 0 °C, and concentrated. The crude product was purified by silica-gel chromatography (1 : 1 ethyl acetate : hexanes) to afford a yellow foam (7.9 mg, 98 %); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.15 (dt, *J* = 4.1, 13.8 Hz, 1 H), 2.32-2.39 (m, 1 H), 2.54 (s, 3 H), 3.23 (dt, *J* = 4.2, 11.7 Hz, 1 H), 3.40 (d, *J* = 10.2 Hz, 1 H), 3.79 (br s, 3 H), 3.87-3.90 (m, 2 H), 4.85 (d, *J* = 10.8 Hz, 1 H), 5.51 (d, *J* = 8.2 Hz, 1 H), 5.85 (br s, 1 H), 5.89 (t, *J* = 7.5 Hz, 1 H), 6.02 (d, *J* = 7.3 Hz, 1 H), 6.76 (t, *J* = 7.6 Hz, 1 H), 6.96-7.09 (m, 4 H), 7.49 (d, *J* = 8.1 Hz, 2 H), 7.89 (d, *J* = 8.1 Hz, 2 H).

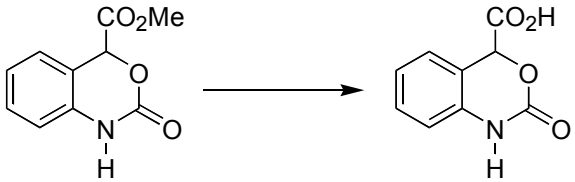


Methyl (2-aminophenyl)-hydroxy acetate. A solution of the nitro alcohol **610** (11.96 g, 56.6 mmol) in ethyl acetate (190 mL) and 5% palladium on carbon (1.2 g) was stirred in a Parr shaker apparatus under an atmosphere of hydrogen (200 psi) for 2 h. The solution was filtered through celite and concentrated *in vacuo*, to obtain a yellow oil (10.25 g, 99%). The crude material thus obtained was immediately used in the next reaction without purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.75 (s, 3 H), 3.92 (br s, 3 H), 5.20 (s, 1 H), 6.67 (dd, *J* = 0.8, 8.64 Hz, 1 H), 6.76 (dt, *J* = 1.06, 7.5 Hz, 1 H), 7.11-7.16 (m, 2 H); ^{13}C (50 MHz, $CDCl_3$) δ 52.8, 72.2, 117.1, 118.6, 122.6, 129.0, 129.5, 145.0, 174.0; IR (neat)

3373, 1736, 1624, 1496 cm^{-1}; HRMS (M + Na^+) calcd for $C_9H_{11}NO_3Na$ 204.0640, found 204.0637.

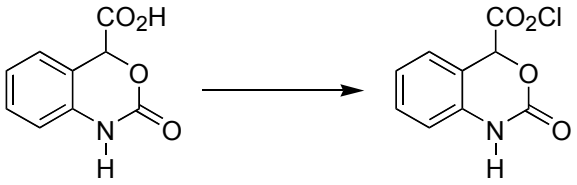


Methyl 1,4-dihydro-2*H*-benzoxazin-2-one-4-carboxylate (611). To a solution of methyl (2-aminophenyl)-hydroxy acetate (5.0 g, 28 mmol) in CH_2Cl_2 (140 mL) at -10 °C was added sequentially *N,N*-diisopropylethylamine (14.4 mL, 82.7 mmol) and phosgene (20% in toluene, 16.0 mL, 152 mmol). The solution was stirred at rt for 12 h, quenched with saturated aqueous ammonium chloride, and extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by silica-gel chromatography (1 : 1 ethyl acetate : hexanes) to afford a yellow solid (4.1 g, 71 %); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.78 (s, 3 H), 5.82 (s, 1 H), 6.90 (dd, *J* = 0.7, 8.0 Hz, 1 H), 7.07 (dt, *J* = 1.1, 6.2 Hz, 1 H), 7.25-7.32 (m, 2 H), 9.16 (br s, 1 H); ^{13}C (50 MHz, $CDCl_3$) δ 53.1, 114.7, 115.2, 123.5, 125.7, 130.2, 134.7, 151.3, 168.3; IR (neat) 3256, 1756, 1605, 1498 cm^{-1}; HRMS (M + Na^+) calcd for $C_{10}H_9NO_4Na$ 230.0429, found 230.0429.

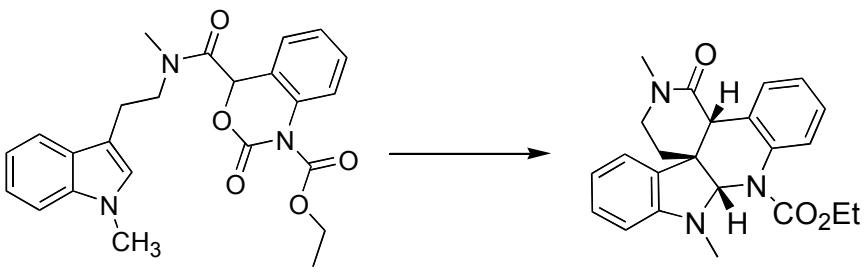


1,4-dihydro-2*H*-benzoxazin-2-one-4-carboxylic acid. To a solution of the carbamate **611** (1.46 g, 7.04 mmol) in THF (17.6 mL) at 0 °C was added dropwise 1 M LiOH (17.6 mL, 17.6 mmol). The solution was stirred at 0 °C for 1 h, quenched with 10 % HCl, and extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4) and concentrated to afford the acid as a

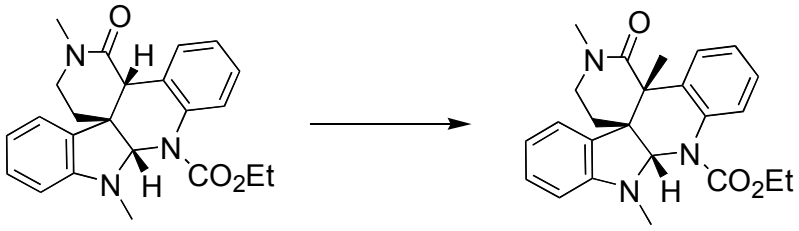
red solid (1.34 g, 99%). The crude material thus obtained was used in the next reaction without further purification. ^{1}H NMR (400 MHz, D_6-Acetone) δ 5.94 (s, 1 H), 6.30 (br s, 2 H), 6.99 (d, *J* = 7.9 Hz, 1 H), 7.07 (dt, *J* = 1.05, 6.5 Hz, 1 H), 7.28 (t, *J* = 7.7 Hz, 1 H), 7.40 (d, *J* = 7.5, 1 H), 9.32 (br s, 1 H); ^{13}C (50 MHz, D_6-Acetone) δ 77.1, 111.9, 117.3, 123.5, 127.0, 130.6, 136.7, 150.9, 169.8; IR (neat) 3257, 1729, 1603, 1499 cm^{-1} ; HRMS (M + Na^+) calcd for $C_9H_7NO_4Na$ 216.0278, found 216.0273.



1,4-dihydro-2*H*-benzoxazin-2-one-4-carbonyl chloride (**612**). To a solution of 1,4-dihydro-2*H*-benzoxazin-2-one-4-carboxylic acid (1.62 g, 8.39 mmol) in THF (27.9 mL) at 0 °C was added sequentially DMF (65 μL, 0.839 mmol) and oxalyl chloride (1.8 mL, 20.9 mmol). The solution was stirred at rt for 3 h and concentrated to afford the acid chloride as a red solid (1.77 g, 99%). The crude product thus obtained was used in the next reaction without purification. ^{1}H NMR (300 MHz, D_6-Acetone) δ 6.43 (s, 1 H), 7.07 (d, *J* = 8.0 Hz, 1 H), 7.19 (dt, *J* = 1.0, 7.6 Hz, 1 H), 7.43 (dt, *J* = 1.3, 7.8 Hz, 1 H), 7.60 (dd, *J* = 0.6, 6.9 Hz, 1 H); ^{13}C (50 MHz, CD_3CN) δ 83.4, 113.8, 118.2, 124.5, 127.2, 130.9, 132.1, 137.0, 171.7

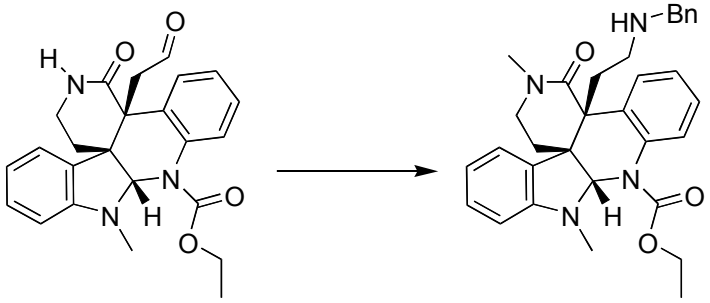


Cycloadduct 615. To a solution of the imide **614** (730 mg, 1.68 mmol) in toluene (16.8 mL) and CH_2Cl_2 (5.6 mL) was added $Yb(OTf)_3$ (208 mg, 0.335 mmol). The solution was stirred at 50 ºC for 12 h, and concentrated. The crude product was purified by silica-gel chromatography (1 : 1 hexanes : ethyl acetate) to afford a yellow oil (401 mg, 61 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (br m, 3 H), 1.47-1.51 (m, 1 H), 2.39 (dt, *J* = 2.4, 12.5 Hz, 1 H), 2.75 (s, 3 H), 2.82 (br s, 3 H), 2.96-3.10 (m, 1 H), 3.48 (s, 1 H), 4.01-4.32 (br m, 2 H), 6.00 (br s, 1 H), 6.03 (d, *J* = 7.7 Hz, 1 H), 6.42 (t, *J* = 7.4 Hz, 1 H), 6.63 (d, *J* = 7.3 Hz, 1 H), 6.75-6.88 (m, 3 H), 7.08 (br s, 1 H), 8.36-8.45 (m, 1 H); ^{13}C (50 MHz, $CDCl_3$) δ 14.4, 30.0, 31.6, 34.0, 45.3, 45.7, 53.9, 61.9, 84.1, 105.6, 117.5, 124.0, 125.7, 125.9, 126.2, 127.1, 127.6, 127.8, 127.9, 128.3, 128.4, 128.8, 132.9, 138.1, 151.6, 155.5, 166.5; IR (neat) 2932, 1698, 1644, 1606, 1488 cm^{-1}.



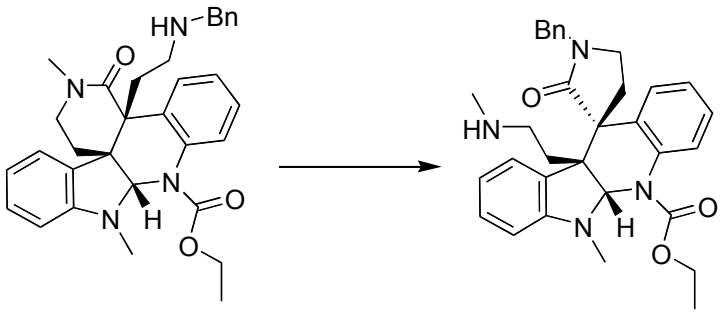
Methylated cycloadduct 632. To a solution of the cycloadduct **615** (16 mg, 0.043 mmol) in DME (220 μL) at -78 ºC was added LiHMDS (47 μL, 0.047 mmol). The solution was stirred for 1 h at -78 ºC, and MeI (3.5 μL, 0.055 mmol) was added. The solution was stirred an additional 30 min at -78 ºC, quenched with saturated aqueous ammonium chloride, and extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4) and concentrated. The

crude product was purified by silica-gel chromatography (1 : 1 hexanes : ethyl acetate) to afford a yellow oil (10 mg, 61 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (br m, 3 H), 1.55 (s, 3 H), 1.72 (s, 3 H), 1.97 (dt, *J* = 5.8, 14.4 Hz, 1 H), 2.63 (dt, *J* = 6.8, 13.4 Hz, 1 H), 2.91 (s, 3 H), 3.11 (s, 3 H), 3.32 (dd, *J* = 6.5, 12.4 Hz, 1 H), 3.44 (dt, *J* = 6.0, 12.7 Hz, 1 H), 4.17 (br m, 2 H), 5.74 (br s, 1 H), 6.23 (d, *J* = 7.1 Hz, 1 H), 6.37 (t, *J* = 7.5 Hz, 1 H), 6.45 (d, *J* = 7.3 Hz, 1 H), 6.84-6.91 (m, 4 H), 8.17-8.19 (m, 1 H); ^{13}C (50 MHz, $CDCl_3$) δ 23.5, 26.3, 30.4, 34.9, 46.2, 54.8, 62.1, 82.5, 106.0, 117.5, 123.5, 125.1, 126.0, 126.9, 128.1, 129.9, 136.4, 137.1, 150.5, 172.2.

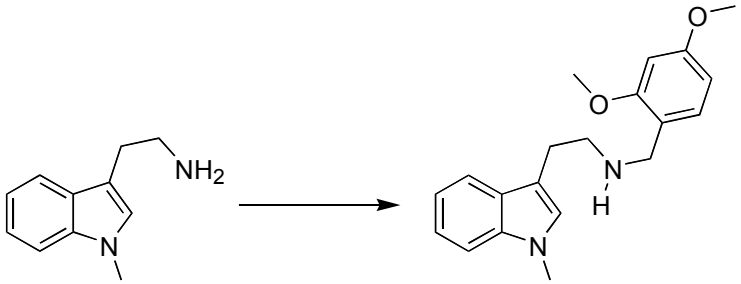


Benzylamine 643. To a solution of the aldehyde **644** (23 mg, 0.053 mmol) in methanol (530 μL) was added benzylamine (17 μL, 0.16 mmol) and AcOH (10 μL, 0.18 mmol). The solution was stirred for 5 min at rt and then $NaCNBH_3$ (1.6 mg, 0.026 mmol) was added. The solution was stirred for 3 h, quenched with saturated aqueous sodium bicarbonate, and extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by silica-gel chromatography (1 : 20 methanol : CH_2Cl_2) to afford a yellow oil (15 mg, 54 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.12 (br m, 3 H), 1.94 (dd, *J* = 4.9, 13.4 Hz, 1 H), 2.29 (br m, 2 H), 2.49 (br s, 1 H), 2.59-2.83 (m, 2 H), 2.89 (s, 3 H), 3.10 (s, 3 H), 3.33-3.49 (m,3 H), 3.51 (d, *J* = 13.2 Hz, 1 H), 3.60 (d, *J* = 13.2 Hz, 1 H), 4.20 (br m, 2 H), 5.74 (br s, 1 H), 6.19 (d, *J* = 7.7 Hz, 1 H), 6.35 (t, *J* = 7.4 Hz, 1 H), 6.86 (t, *J* = 7.6 Hz, 1 H), 6.88-6.95 (m, 3 H), 7.15-7.26 (m, 5 H), 8.24 (d, *J* = 7.5 Hz, 1 H);); ^{13}C (50 MHz, $CDCl_3$) δ 14.4, 26.4, 30.2, 35.0, 46.1, 48.3, 53.4, 56.1, 62.1, 82.3, 105.9, 117.4, 123.3,

125.2, 126.4, 126.9, 127.2, 128.1, 128.2, 128.4, 129.5, 133.7, 137.0, 150.5, 171.7; IR (neat) 3306, 2943, 2331, 2246, 1636, 1604, 1486 cm^{-1}.

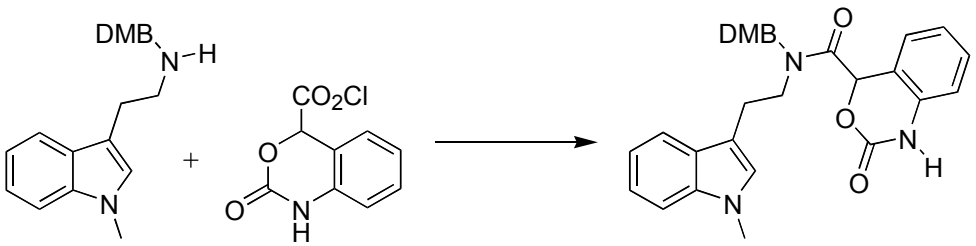


Spirocyclic lactam 647. To a solution of the benzylamine **643** (20 mg, 0.038 mmol) in THF (475 μL) at – 50 ºC was added AlH_3EtNMe_2 (26 μL, 0.013 mmol). The solution was stirred at rt for 1 h, quenched with 1 : 1 THF/ H_2O, and extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by silica-gel chromatography (1 : 20 methanol : CH_2Cl_2) to afford a yellow oil (16 mg, 80%). ^1H NMR (200 MHz, $CDCl_3$) δ 1.15-1.40 (br m, 3 H), 2.00-2.21 (m, 4 H), 2.26 (s, 3 H), 2.51-2.87 (m, 2 H), 2.84 (s, 3 H), 3.12-3.40 (m, 2 H), 4.05-4.32 (br m, 2 H), 4.50 (d, *J* = 13.5 Hz, 1 H), 4.82 (d, *J* = 13.5 Hz, 1 H), 5.84 (br s, 1 H), 6.10 (d, *J* = 7.7 Hz, 1 H), 6.43 (t, *J* = 7.3 Hz, 1 H), 6.82-7.11 (M, 4 H), 7.20 (br s, 1 H), 7.33 (br s, 5 H), 8.11 (br m, 1 H).



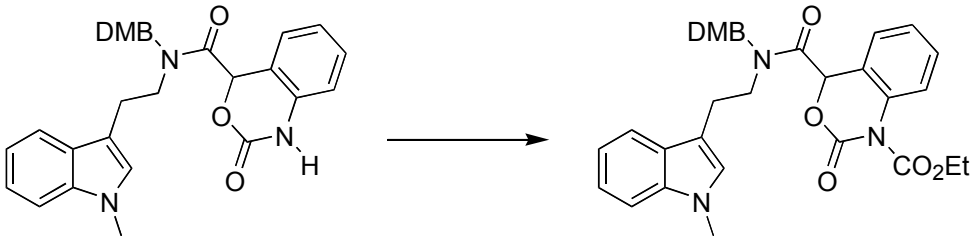
***N*-2,4-Dimethoxybenzyl-1-*N*-methyltryptamine** (**661**)**.** To a solution of the tryptamine **468** (4.46 g, 25.6 mmol) in MeOH (64 mL) was added 2,4-dimethoxy benzaldehyde (4.68 g, 28.1 mmol). The solution was stirred for 1 h at rt, then $NaBH_4$ (580 mg, 15.4 mmol) was added portionwise over 10 minutes.

The solution was stirred at rt for 12 h, quenched with saturated aqueous ammonium chloride, and extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by silica-gel chromatography (1 : 10 MeOH : CH_2Cl_2) to afford an orange foam (2.9 g, 35 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.02-3.09 (m, 5 H), 3.63 (s, 3 H), 3.70 (s, 3 H), 3.80 (s, 3 H), 3.86 (s, 2 H), 6.43-6.48 (m, 2 H), 6.88 (s, 1 H), 7.13-7.20 (m, 2 H), 7.25-7.33 (m, 2 H), 7.62 (d, *J* = 7.8 Hz, 1 H); ^{13}C (75 MHz, $CDCl_3$) δ 25.0, 32.0, 48.2, 48.6, 54.5, 54.9, 98.0, 103.3, 108.7,111.8, 118.3, 118.6, 119.6, 121.1, 126.4, 127.5, 130.1, 136.2, 136.7, 158.1; IR (neat) 3316, 2933, 2834, 1613, 1588, 1506 cm^{-1}; HRMS (M + H$^+$) calc for $C_{20}H_{25}N_2O_2$ 325.1898, found 325.1916.



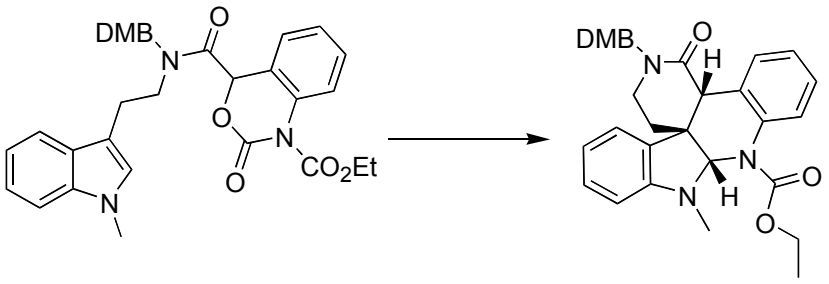
Amide 664. To a 0 °C solution of the tryptamine **661** (755 mg, 2.33 mmol) in CH_2Cl_2 (8.1 mL) was added sequentially *N, N*-diisopropylethylamine (1.21 mL, 6.98 mmol) and a solution of the acid chloride **612** (492 mg, 2.33 mmol) in THF (8.1 mL). The reaction was stirred at rt for 12 h, quenched with saturated aqueous sodium bicarbonate, and extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by silica-gel chromatography (1 : 20 MeOH : CH_2Cl_2) to afford a yellow oil (669 mg, 58 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.81-3.11 (m, 4 H), 3.46-3.59 (m, 2 H), 3.62-3.88 (m, 3 H), 3.66 (s, 3 H), 3.75 (s, 3 H), 3.76 (s, 3 H), 3.79 (s, 3 H), 3.81 (s, 3 H), 3.84 (s, 3), 4.29 (d, *J* = 15.9 Hz, 1 H), 4.63-4.68 (m, 2 H), 4.83 (d, *J* = 14.6 Hz, 1 H), 5.71 (s,1 H), 6.41-6.47 (m, 4), 6.59 (d, *J* = 7.8 Hz, 1 H), 6.64 (s, 1 H), 6.79 (d, *J* = 7.8 Hz, 1 H), 6.87-7.32 (m, 16 H), 7.52 (d, *J* = 7.7 Hz, 1 H), 8.46 (br s, 1 H), 8.66 (br s, 1 H); ^{13}C (75 MHz, $CDCl_3$) δ 22.7, 24.4, 32.5, 32.6, 42.9,

46.7, 47.4, 47.7, 55.2, 55.3, 55.4, 75.6, 76.5, 98.3, 98.7, 103.9, 104.2, 109.1, 111.1, 114.8, 116.0, 117.3, 118.6, 118.8, 119.1, 121.4, 122.9, 124.6, 127.0, 127.4, 127.6, 129.4, 129.5, 129.9, 135.7, 136.8, 151.9, 158.5, 158.6, 160.4, 161.0, 167.3, 167.6; IR (neat) 3260, 2935, 1725, 1650, 1613, 1504 cm^{-1}; HRMS ($M + H^+$) calc for $C_{29}H_{30}N_3O_5$ 500.2156, found 500.2185.

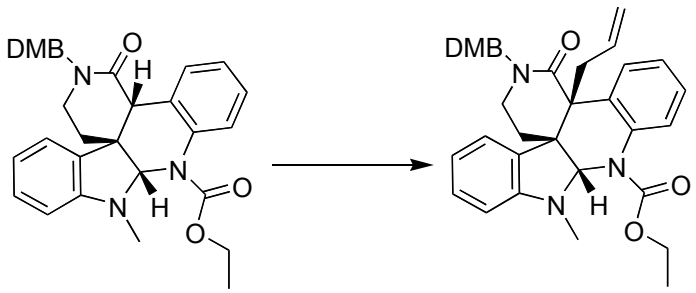


Imide 667. To a 0 °C solution of the carbamate **664** (2.40 g, 4.80 mmol) in DMF (16 mL) was added NaH (211 mg, 8.81 mmol). The reaction was stirred for 30 min at 0 °C, 30 min at 50 °C, and cooled to 0 °C. Ethyl chloroformate (690 μL, 7.21 mmol) was slowly added, the reaction was stirred for an additional 30 min, quenched with saturated aqueous ammonium chloride, and extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by silica-gel chromatography (1 : 1 ethyl acetate: hexanes) to afford a yellow foam (1.85 g, 67 %). ^1H NMR (300 MHz, $CDCl_3$) δ 1.39 (t, *J* = 7.1 Hz, 3 H), 1.44 (t, *J* = 7.1 Hz, 3 H), 2.75-2.81 (m, 1 H), 2.93-3.05 (m, 2 H), 3.35-3.39 (m, 1 H), 3.58 (s, 3 H), 3.61-3.75 (m, 4 H), 3.71 (s, 3 H), 3.76 (s, 3 H), 3.79 (s, 3 H), 3.81 (s, 3 H), 3.82 (s, 3 H), 4.39-4.52 (m, 5 H), 4.59 (d, *J* = 14.6 Hz, 1 H), 4.66 (d, *J* = 15.6 Hz, 1 H), 4.91 (d, *J* = 14.6 Hz, 1 H), 5.36 (s, 1 H), 6.29 (s,1 H), 6.41-6.49 (m, 4 H), 6.80 (d, *J* = 8.2 Hz, 1 H), 6.82 (s, 1 H), 6.86 (s, 1 H), 7.06-7.33 (m, 10 H), 7.41-7.58 (m, 4 H), 7.68 (d, *J* = 8.2 Hz, 1 H); ^{13}C (75 MHz, $CDCl_3$) δ 14.4, 14.5, 14.6, 23.0, 24.5, 32.9, 33.1, 43.5, 46.9, 47.4, 48.2, 55.6, 55.8, 55.9, 64.5, 64.6, 75.3, 76.2, 78.0, 98.7, 99.2, 104.5, 104.7, 109.6, 110.1, 110.3, 111.4, 116.0, 117.4, 118.5, 119.1, 119.2,119.6, 121.8,122.4, 122.7, 123.7, 124.7, 125.0, 125.5,125.6,125.9, 126.0,127.5, 127.6, 128.0, 129.5, 129.9, 130.7, 131.6, 135.4, 135.7, 137.3, 137.5, 149.2, 149.9,

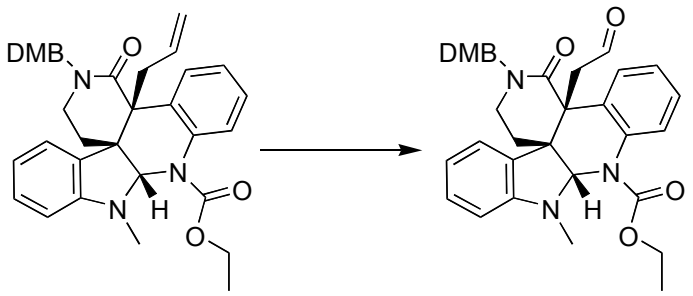
152.1, 152.5, 159.0, 159.1, 161.0, 161.6, 166.1, 166.4; IR (neat) 2938, 1769, 1650, 1613,1507 cm^{-1}; HRMS (M + H^+) calc for $C_{32}H_{34}N_3O_7$ 572.2437, found 572.2397.



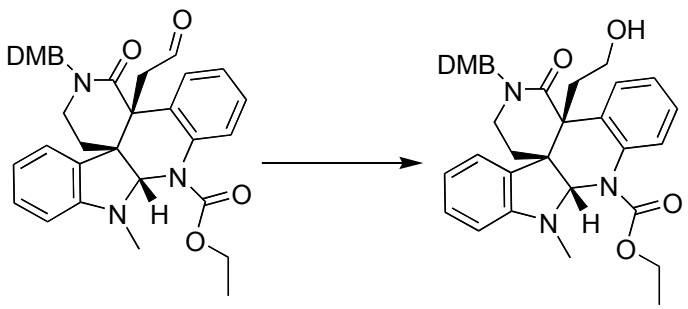
Cycloadduct 670. To a solution of the imide **667** (1.85 g, 3.23 mmol) in toluene (65 mL) and CH_2Cl_2 (22 mL) was added $Yb(OTf)_3$ (401 mg, 0.647 mmol). The solution was stirred for 12 h at 50 °C, cooled and concentrated. The crude product was purified by silica-gel chromatography (1 : 1 ethyl acetate: hexanes) to afford a white foam (1.2 g, 75 %). ^1H NMR (300 MHz, $CDCl_3$) δ 1.24-1.28 (br m, 3 H), 2.10 (dd, *J* = 3.4, 13.0 Hz, 1 H), 2.37 (dt, *J* = 6.0, 12.8 Hz, 1 H), 2.86 (s, 3 H), 3.38 (dd, *J* = 4.7, 13.0 Hz, 1 H), 3.50 (dt, *J* = 8.0, 12.8 Hz, 1 H), 3.82 (s, 3 H),3.85 (s, 3 H), 4.11-4.28 (m, 2 H), 4.61 (d, *J* = 14.1 Hz, 1 H), 5.06 (d, *J* = 14.1 Hz, 1 H), 5.87 (s, 1 H), 6.13 (d, *J* = 7.7 Hz, 1 H), 6.24 (dt, *J* = 0.7, 7.4 Hz, 1 H), 6.44-6.52 (m, 3 H), 6.82 (dt, *J* = 1.2, 7.7 Hz, 1 H), 6.92-7.03 (m, 3 H), 7.40 (d, *J* = 8.0 Hz, 1 H), 7.75-7.78 (m, 1 H); ^{13}C (75 MHz, $CDCl_3$) δ 14.3, 30.0, 31.7, 43.6, 44.4, 45.8, 53.6, 55.2, 55.3, 62.0, 83.6, 98.2, 104.2, 105.0, 116.8, 117.2, 124.0, 125.5, 125.7, 125.9, 126.9, 127.8, 128.1, 131.6, 132.3, 137.6, 151.0, 155.3, 158.7, 160.5, 166.8; IR (neat) 2979, 1698, 1638, 1608 cm^{-1} HRMS (M + H^+) calc for $C_{31}H_{34}N_3O_5$ 528.2514, found 528.2498.



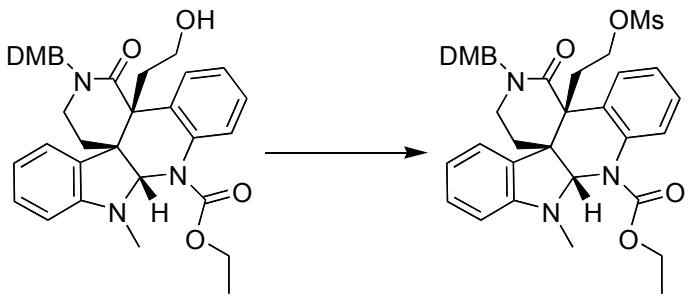
Alkene. To a solution of the amide **670** (240 mg, 0.454 mmol) in THF (1.5 mL) was added sequentially allyl iodide (208 μL, 2.27 mmol) and K-O*t*Bu (682 μL, 0.682 mmol) dropwise. The solution was stirred for 10 min, then additional allyl iodide (208 μL, 2.27 mmol) and K-O*t*Bu (682 μL, 0.682 mmol) were added. The solution was stirred for 15 min more, then quenched with saturated aqueous ammonium chloride, and extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by silica-gel chromatography (1 : 1 ethyl acetate: hexanes) to afford a yellow foam (242 mg, 95 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21-1.29 (br m, 3 H), 1.90 (d, *J* = 13.0 Hz, 1 H), 2.51-2.62 (m, 1 H), 2.76-2.81 (m, 2 H), 2.88 (s, 3 H), 3.32-3.35 (m, 2 H), 3.79 (s, 3 H), 3.81 (s, 3 H), 4.20-4.27 (br m, 2 H), 4.58 (d, *J* = 14.1 Hz, 1 H), 4.74-4.85 (m, 2 H), 4.94 (d, *J* = 14.1 Hz, 1 H), 5.71-5.81 (m, 2 H), 6.19 (d, *J* = 7.9 Hz, 1 H), 6.23 (t, *J* = 7.4 Hz, 1 H), 6.44-6.52 (m, 3 H), 6.81 (dt, *J* = 0.9, 7.4 Hz, 1 H), 6.88-6.96 (m, 3 H), 7.41 (d, *J* = 8.3 Hz, 1 H), 8.24-8.27 (m, 1 H); ^{13}C (75 MHz, $CDCl_3$) δ 14.4, 26.5, 30.2, 40.3, 43.5, 44.1, 49.7, 55.2, 55.3, 55.4, 61.9, 82.3, 98.2, 104.2, 105.6, 116.5, 117.2, 117.6, 123.8, 124.9, 125.9, 126.6, 127.9, 128.5, 130.0, 131.6, 134.4, 134.5, 136.8, 150.3, 158.7, 160.4, 164.6, 169.9; IR (neat) 2980, 1769, 1716, 1607, 1494 cm^{-1}; HRMS (M + H$^+$) calc for $C_{34}H_{38}N_3O_5$ 568.2804, found 568.2811.



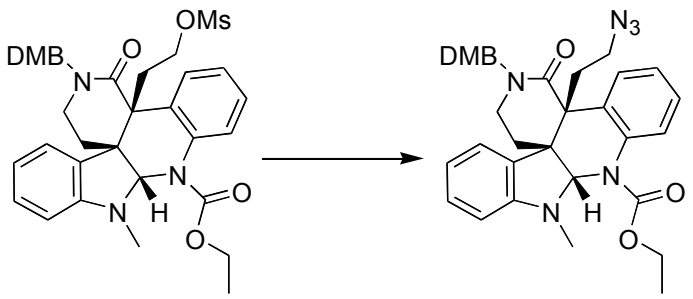
Aldehyde 677. To a solution of the alkene prepared in the previous experimental (98 mg, 0.173 mmol) in THF (3.5 mL) and H_2O (1.7 mL) was added NMO (40 mg, 0.345 mmol) and OsO_4 (21 μL, 0.0086 mmol). The solution was stirred for 12 h, then $NaIO_4$ (75 mg, 0.345 mmol) was added. The solution was stirred for an additional 7 h, quenched with 1 : 1 saturated aqueous sodium bicarbonate : 10 % $Na_2S_2O_3$, and extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4) and concentrated. The product was purified by silica-gel chromatography (1 : 1 ethyl acetate: hexanes) to afford a white foam (80 mg, 81 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21-1.29 (br m, 3 H), 1.93 (dd, *J* = 3.0, 13.2 Hz, 1 H), 2.34-2.44 (m, 1 H), 2.77-2.94 (m, 3 H), 2.89 (s, 3 H), 3.31-3.36 (m, 3 H), 3.79 (s, 3 H), 3.81 (s, 3 H), 4.20 (br s, 2 H), 4.75 (d, *J* = 1.7 Hz, 2 H), 5.69 (br s, 1 H), 6.18-6.25 (m, 2 H), 6.42 (d, *J* = 6.6 Hz, 1 H), 6.46-6.53 (m, 2 H), 6.82 (dt, *J* = 1.1, 7.6 Hz, 1 H), 6.94-7.00 (m, 3 H), 7.35 (d, *J* = 8.2 Hz, 1 H), 8.15-8.18 (m, 1 H), 9.56 (d, *J* = 7.5 Hz, 1 H); ^{13}C (75 MHz, $CDCl_3$) δ 14.3, 26.1, 30.4, 43.4, 44.6, 47.2, 47.8, 55.2, 55.2, 55.3, 62.3, 82.1, 98.3, 104.2, 106.0, 116.7, 116.8, 117.4, 123.9, 125.2, 126.8, 127.2, 128.1, 128.2, 128.8, 131.8, 133.0, 137.1, 150.3, 158.7, 160.7, 169.5; IR (neat) 2937, 1698, 1634, 1587 cm^{-1}.



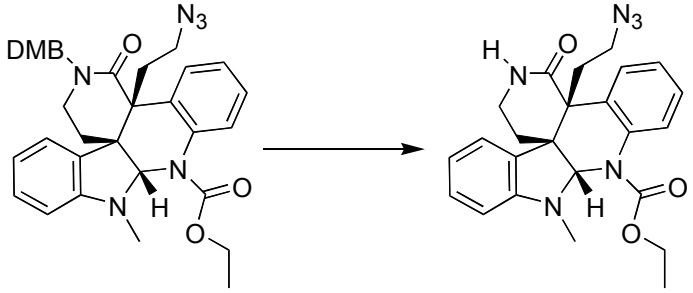
Alcohol 678. To a solution of aldehyde **677** (80 mg, 0.140 mmol) in MeOH (470 μL) and THF (470 μL) at 0 °C was added $NaBH_4$ (8 mg, 0.211 mmol). The solution was stirred for 1 h at 0 °C, quenched with saturated aqueous ammonium chloride, and extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by silica-gel chromatography (7 : 1 ethyl acetate: hexanes) to afford a yellow foam (77mg, 95 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.11-1.23 (br m, 3 H), 1.92 (d, *J* = 12.6 Hz, 1 H), 2.18-2.56 (m, 3 H), 2.87 (s, 3 H), 3.33-3.36 (m, 2 H), 3.46-3.48 (m, 1 H), 3.77-3.85 (m, 1 H), 3.81 (s, 6 H), 4.10-4.18 (br m, 2 H), 4.77 (d, *J* = 13.9 Hz, 1 H), 4.85 (d, *J* = 13.9 Hz, 1 H), 5.69 (br s, 1 H), 6.16-6.23 (m, 2 H), 6.40 (d, *J* = 7.3 Hz, 1 H), 6.46 (m, 2 H), 6.81 (dt, *J* = 0.9, 7.6 Hz, 1 H), 6.94-6.95 (m, 3 H), 7.41 (d, *J* = 8.2 Hz, 1 H), 8.17-8.19 (m, 1 H); ^{13}C (75 MHz, $CDCl_3$) δ 14.4, 26.1, 30.3, 37.9, 43.7, 44.7, 49.5, 55.3, 55.3, 56.1, 59.8, 62.1, 77.1, 82.2, 98.3, 104.3, 105.8, 116.8, 117.3, 123.8, 125.4, 126.4, 127.1, 128.0, 128.1, 129.8, 131.8, 133.7, 137.2, 150.5, 158.8, 160.7, 172.9; IR (neat) 3400, 2936, 1697, 1610 cm^{-1}.



Mesylate 679. To a solution of alcohol **678** (32 mg, 0.056 mmol) in CH_2Cl_2 (560 μL) at –78 °C was added NEt_3 (23 μL, 0.168 mmol) and MsCl (6.5 μL, 0.084 mmol). The solution was stirred for 30 min at –10 °C, quenched with saturated aqueous sodium bicarbonate, and extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by silica-gel chromatography (1 : 3 ethyl acetate: hexanes) to afford a yellow foam (30 mg, 78 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20-1.30 (br m, 3 H), 1.93 (d, *J* = 13.0 Hz, 1 H), 2.43-2.54 (m, 3 H), 2.73 (s, 3 H), 2.89 (s, 3 H), 3.32-3.35 (m, 2 H), 3.81 (s, 3 H), 3.82 (s, 3 H), 3.90-4.05 (br m, 1 H), 4.23-4.31 (m, 2 H), 4.42-4.49 (m, 1 H), 4.66 (d, *J* = 13.8 Hz, 1 H), 4.85 (d, *J* = 13.8 Hz, 1 H), 5.74 (br s, 1 H), 6.16-6.24 (m, 2 H), 6.42 (d, *J* = 7.1 Hz, 1 H), 6.47-6.53 (m, 2 H), 6.81 (t, *J* = 7.3 Hz, 1 H), 6.87-6.97 (m, 3 H), 7.36 (d, *J* = 8.2 Hz, 1 H), 8.17 (d, *J* = 7.3 Hz, 1 H); ^{13}C (75 MHz, $CDCl_3$) δ 14.7, 26.7, 30.7, 31.9, 35.1, 37.0, 44.0, 45.0, 48.0, 55.7, 55.8, 56.2, 62.9, 68.8, 82.6, 98.8, 104.7, 106.3, 117.5, 117.7, 124.2, 125.6, 127.1, 127.4, 128.6, 128.7, 129.5, 132.0, 133.2, 137.9, 150.8, 159.2, 161.0, 170.2; IR (neat) 2939, 1698, 1633, 1610 1508 cm^{-1}.

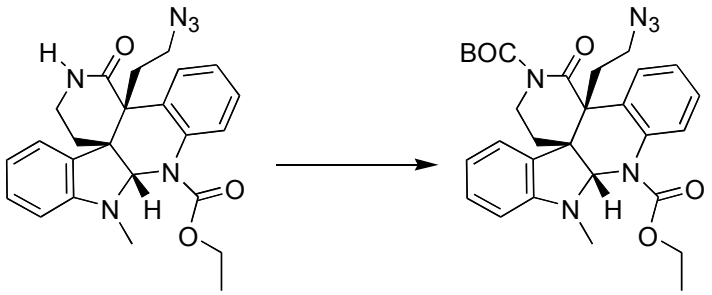


Azide 680. To a solution of mesylate **679** (85 mg, 0.121 mmol) in DMF (402 μL) was added NaN_3 (79 mg, 1.21 mmol). The solution was heated to 80 °C for 3 h, cooled, poured onto brine, and extracted with ethyl actetate. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by silica-gel chromatography (1 : 3 ethyl acetate: hexanes) to afford a white foam (242 mg, 95 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23-1.25 (br m, 3 H), 1.88-1.93 (m, 1 H), 2.22-2.28 (m, 2 H), 2.45-2.56 (m, 2 H), 2.80-2.95 (m, 1 H), 2.88 (s, 3 H), 3.32-3.35 (m, 2 H), 3.48-3.61 (m, 1 H), 3.81 (s, 3 H), 3.82 (s, 3 H), 4.15-4.31 (br m, 2 H), 4.62 (d, *J* = 14.0 Hz, 1 H), 4.91 (d, *J* = 14.0 Hz, 1 H), 5.72 (br s, 1 H), 6.16-6.25 (m, 2 H), 6.41-6.53 (m, 3 H), 6.81 (t, *J* = 7.7 Hz, 1 H), 6.91-6.93 (m, 3 H), 7.37 (d, *J* = 8.2 Hz, 1 H), 8.17-8.19 (m, 1 H); ^{13}C (75 MHz, $CDCl_3$) δ 14.8, 26.8, 30.1, 30.7, 35.1, 43.9, 44.9, 48.5, 49.4, 55.7, 55.8, 56.3, 62.7, 82.8, 98.8, 104.6, 106.2, 117.6, 117.7, 124.1, 125.7, 126.9, 127.3, 128.5, 128.7, 129.8, 132.0, 133.7, 137.5, 150.9, 159.2, 161.0, 170.3; IR (neat) 2938, 2097, 1698, 1634, 1608, 1588 cm^{-1}.



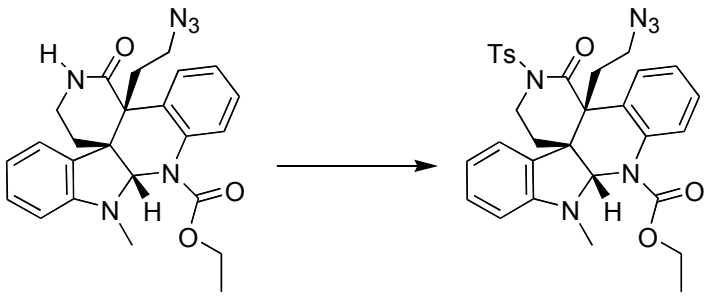
Lactam 681. To a solution of azide **680** (70 mg, 0.117 mmol) in anisole (590 μL) was added TFA (3.5 mL, 46.9 mmol). The solution was stirred at 70 °C for 12 h, diluted with H_2O, quenched carefully with sodium bicarbonate, and

extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by silica-gel chromatography (1 : 3 ethyl acetate: hexanes) to afford a white foam (28 mg, 64%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19-1.40 (br m, 3 H), 2.01 (dd, *J* = 5.0, 13.4 Hz, 1 H), 2.28-2.38 (m, 2 H), 2.57 (dt, *J* = 6.9, 13.4 Hz, 1 H), 2.87-2.91 (m, 1 H), 2.91 (s, 3 H), 3.40-3.56 (m, 3 H), 4.23-4.25 (br m, 2 H), 5.78 (br s, 1 H), 6.04 (br s, 1 H), 6.23 (d, *J* = 7.8 Hz, 1 H), 6.37 (t, *J* = 7.4 Hz, 1 H), 6.78 (d, *J* = 6.9 Hz, 1 H), 6.84-6.96 (m, 4 H), 8.14 (d, *J* = 7.6 Hz, 1 H); ^{13}C (75 MHz, $CDCl_3$) δ 14.8, 26.4, 30.7, 35.1, 39.2, 48.1, 49.2, 56.2, 62.8, 82.8, 106.4, 117.9, 124.1, 125.7, 127.1, 127.4, 128.3, 128.8, 129.4, 132.8, 137.5, 150.9, 155.6, 173.2; IR (neat) 2924, 2096, 1703, 1606, 1510 cm^{-1}.

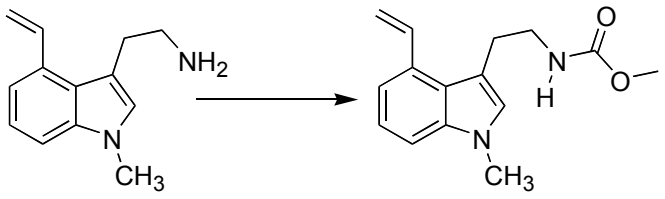


BOC-Imide 682. To a solution of lactam **681** (28 mg, 0.074 mmol) in THF (740 μL) at –78 °C was added BuLi (33 μL, 0.082 mmol). The solution was stirred at –78 °C for 45 min, then BOC_2O (19 mg, 0.089 mmol) was added. The solution was stirred for an additional 30 min, quenched with saturated aqueous ammonium chloride, and extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by silica-gel chromatography (1 : 5 ethyl acetate: hexanes) to afford a white foam (30 mg, 75%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.59 (s, 9H), 2.02 (dd, *J* = 3.3, 13.2 Hz, 1 H), 2.26-2.45 (m, 2 H), 2.61 (dt, *J* = 6.4, 13.2 Hz, 1 H), 2.83-2.93 (m, 1 H), 2.91 (s, 3 H), 3.39 (dt, *J* = 3.4, 11.7 Hz, 1 H), 3.64-3.86 (m, 2 H), 4.21-4.30 (br m, 2 H), 5.77 (br s, 1 H), 6.22 (d, *J* = 7.7 Hz, 1 H), 6.38 (dt, *J* = 0.9, 7.5 Hz, 1 H), 6.63 (dd, *J* = 0.7, 7.4 Hz, 1 H), 6.85-6.99 (m, 4 H), 8.24 (dt, *J* = 0.9, 7.9 Hz, 1 H);

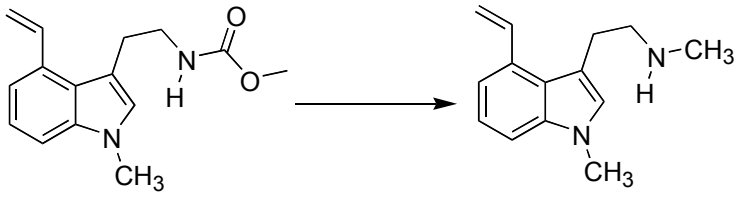
^{13}C (75 MHz, $CDCl_3$) δ 14.4, 26.9, 27.4, 27.9, 30.2, 33.8, 43.1, 48.3, 49.7, 56.0, 62.4, 82.3, 83.6, 106.0, 117.5, 123.5, 125.5, 126.9, 127.1, 128.5, 128.8, 132.5, 136.8, 146.6, 150.3, 153.7, 155.1, 171.8; IR (neat) 2979, 2097, 1766, 1701, 1605, 1486 cm^{-1}.



Tosylimide 683. To a solution of the lactam (21 mg, 0.056 mmol) in THF (560 μL) at –78 °C was added BuLi (24 μL, 0.061 mmol). The solution was stirred at –78 °C for 45 min, then TsCl (13 mg, 0.067 mmol) was added. The solution was stirred for an additional 30 min, quenched with saturated aqueous ammonium chloride, and extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by silica-gel chromatography (1 : 5 ethyl acetate: hexanes) to afford a white foam (30 mg, 71%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23-1.32 (br m, 3 H), 2.06-2.21 (m, 3 H), 2.49 (s, 3 H), 2.58-2.73 (m, 2 H), 2.88 (s, 3 H), 2.88-2.97 (m, 1 H), 3.78 (dt, *J* = 5.1, 12.5 Hz, 1 H), 4.72 (br m, 2 H), 4.38 (dd, *J* = 5.1, 12.5 Hz, 1 H), 5.74 (br s, 1 H), 6.17-6.25 (m, 3 H), 6.82-6.94 (m, 4 H), 7.43 (d, *J* = 8.5 Hz, 2 H), 7.92 (d, *J* = 7.9 Hz, 1 H), 8.03 (d, *J* = 8.5 Hz, 2 H); ^{13}C (75 MHz, $CDCl_3$) δ 14.1, 14.4, 21.7, 26.8, 29.3, 29.6, 30.1, 33.7, 43.1, 47.9, 49.8, 55.6, 62.5, 81.9, 106.1, 117.4, 123.0, 125.5, 127.1, 127.1, 127.4, 128.1, 128.7, 128.7, 129.4, 131.4, 135.4, 136.7, 145.3, 150.3; ; IR (neat) 2927, 2098, 1697, 1605, 1487 cm^{-1}.

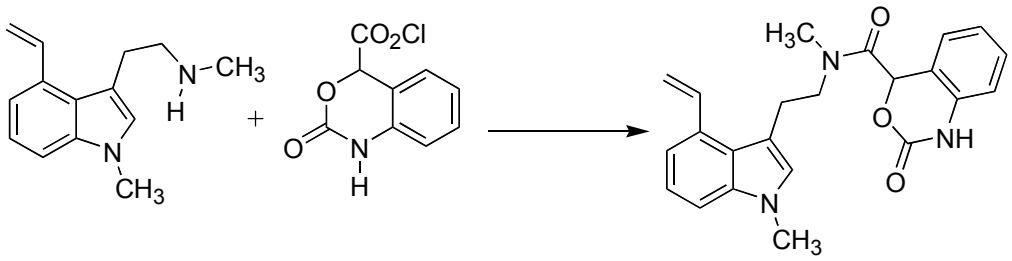


1-Methyl-4-vinyl tryptamine methyl carbamate. To a -78 °C solution of tryptamine **416** (145 mg, 0.724 mmol) in CH_2Cl_2 (2.6 mL) was added pyridine (88 μL, 1.09 mmol) and methyl chloroformate (61.5 μL, 0.796 mmol). The solution was stirred at rt for 6 h, quenched with 10 % HCl, and extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by silica-gel chromatography (1 : 1 hexanes : ethyl acetate) to afford a yellow solid (145 mg, 78 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.09 (t, *J* = 6.76 Hz, 2 H), 3.51-3.57 (br m, 2 H), 3.67 (br s, 3 H), 3.73 (s, 3 H), 4.80 (br s, 1 H), 5.35 (dd, *J* = 1.6, 10.8 Hz, 1 H), 5.72 (dd, *J* = 1.6, 17.2 Hz, 1 H), 6.87 (s, 1 H), 7.24-7.33 (m, 3 H), 7.44 (dd, *J* = 10.8, 17.2 Hz, 1 H); ^{13}C (50 MHz, $CDCl_3$) δ 27.8, 32.6, 41.8, 51.9, 106.3, 108.7, 115.4, 115.5, 116.8, 121.7, 122.5, 127.9, 132.1, 135.5, 137.8, 157.0; IR (neat) 3337, 2942, 2246, 1706, 1525 cm^{-1}; HRMS (M + Na^+) calc for $C_{15}H_{18}N_2O_2Na$ 281.1274, found 281.1266.

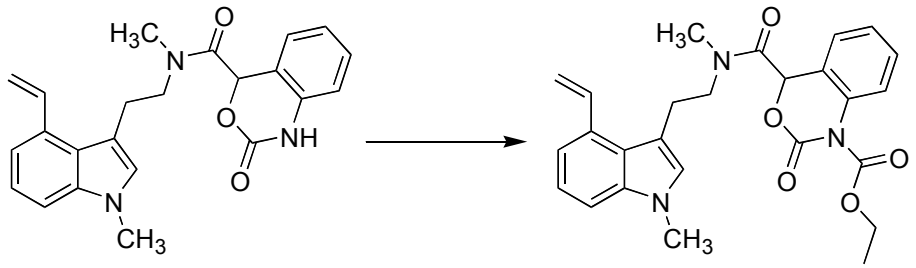


1-Methyl-4-vinyl-*N*-methyl-tryptamine (**691**). To a 0 °C solution of **1-**methyl-4-vinyl tryptamine methyl carbamate (1.00 g, 3.86 mmol) in THF (12.9 mL) was slowly added $LiAlH_4$ (586 mg, 15.5 mmol). The solution was stirred to rt over 30 min and heated to 55 °C for 3 h. The reaction was quenched with H_2O (586 μL), 10 % NaOH (879 μL), and H_2O (1.75 mL). The solids were filtered off, and the filtrate was concentrated to afford a yellow oil (620 mg, 76 %). The

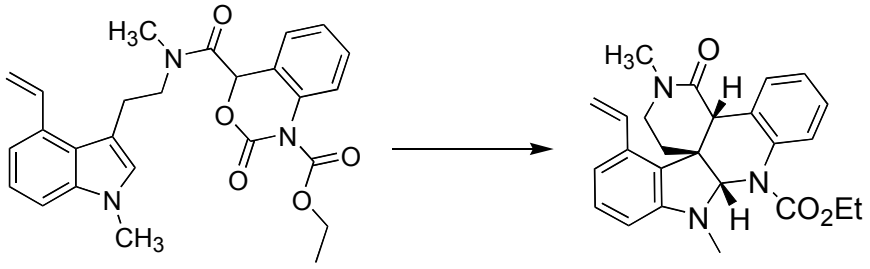
crude product thus obtained was used in the next reaction without purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.51 (s, 3 H), 2.95 (t, *J* = 6.7 Hz, 2 H), 3.14 (t, *J* = 6.7 Hz, 2 H), 3.74 (s, 3 H), 5.39 (dd, *J* = 1.6, 10.8 Hz, 1 H), 5.79 (dd, *J* = 1.6, 17.3 Hz,1 H), 6.92 (s, 1 H), 7.23-7.33 (m, 3 H), 7.54 (dd, *J* = 10.8, 17.3 Hz, 1 H); ^{13}C (75 MHz, $CDCl_3$) δ 27.6, 32.5, 36.3, 52.7, 108.6, 112.6, 115.0, 116.4, 121.5, 124.8, 127.7, 132.0, 135.6,137.7; IR (neat) 3304, 2934, 2243, 1624, 1550 cm^{-1}; HRMS (M + H^+) calc for $C_{14}H_{19}N_2$ 215.1536, found 215.1548.



Carbamate. To a 0 °C solution of tryptamine **691** (120 mg, 0.560 mmol) in CH_2Cl_2 (1.9 mL) was added sequentially *N, N*-diisopropylethylamine (293 μL, 1.68 mmol) and a solution of the acid chloride **612** (118 mg, 0.560 mmol) in THF (1.9 mL). The reaction was stirred at rt for 12 h, quenched with saturated aqueous ammonium chloride, and extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by silica-gel chromatography (1 : 26 MeOH : CH_2Cl_2) to afford a yellow oil (145 mg, 68 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.76-3.26 (m, 10 H), 3.49-3.72 (m, 10 H), 5.41 (d, *J* = 11.8 Hz, 2 H), 5.63 (s, 1 H), 5.73 (d, *J* = 16.5 Hz, 2 H), 6.52 (d, *J* = 4.96 Hz, 1 H), 6.75-7.03 (m, 6 H), 7.10-7.27 (m, 12 H), 7.46 (dd, *J* = 11.8, 16.5 Hz, 2 H), 6.13 (s, 1 H), 8.07 (br s, 1 H), 8.37 (br s, 1 H); IR (neat) 3270, 2929, 1728, 1651, 1604, 1498 cm^{-1}; HRMS (M + Na^+) calc for $C_{23}H_{23}N_3O_3Na$ 412.1642, found 412.1637.

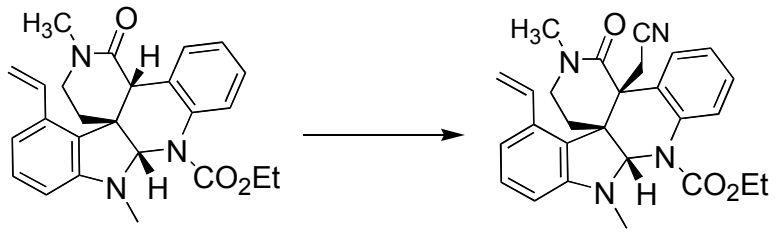


Imide 692. To a 0 °C solution of the carbamate prepared in the previous experimental (145 mg, 0.372 mmol) in DMF (1.2 mL) was added NaH (16 mg, 0.683 mmol). The reaction was stirred for 30 min at 0 °C, 30 min at 50 °C, and cooled to 0 °C. Ethyl chloroformate was slowly added, the reaction was stirred for an additional 30 min, quenched with saturated aqueous ammonium chloride, and extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by silica-gel chromatography (1 : 1 ethyl acetate: hexanes) to afford a yellow oil (110 mg, 65 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40 (t, *J* = 7.9 Hz, 3 H), 1.42 (t, *J* = 7.2 Hz, 3 H), 2.85 (s, 3 H), 3.02 (s, 3 H), 3.06-3.26 (m, 4 H), 3.54-3.85 (m, 4 H), 3.59 (s, 3 H), 3.74 (s, 3 H), 5.26 (s, 1 H), 5.36 (dd, *J* = 1.4, 10.8 Hz, 1 H), 5.43 (dd, *J* = 1.4, 10.8 Hz, 1 H), 5.72 (dd, *J* = 1.4, 17.2 Hz, 1 H), 5.77 (dd, *J* = 1.4, 17.2 Hz, 1 H), 5.88 (s, 1 H), 6.61 (s, 1 H), 6.79 (d, *J* = 7.0 Hz, 1 H), 6.85 (s, 1 H), 7.06 (t, *J* = 7.5 Hz, 1 H), 7.15-7.28 (m, 9 H), 7.39-7.53 (m, 4 H), 7.68 (d, *J* = 8.2 Hz, 1 H);); IR (neat) 2938, 1800, 1770, 1734, 1658 cm^{-1};HRMS (M + Na^+) calc for $C_{26}H_{27}N_3O_5Na$ 484.1825 found 484.1848 .



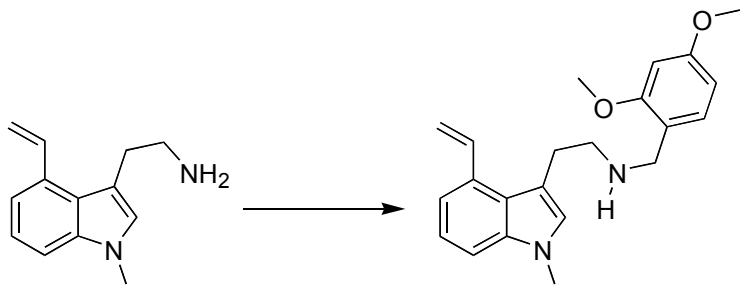
Cycloadduct 693. To a solution of imide **692** (37 mg, 0.80 mmol) in toluene (800 μL) and CH_2Cl_2 (300 μL) was added $Yb(OTf)_3$ (9.9 mg, 0.016 mmol).

The solution was stirred for 48 h at 50 °C, quenched with saturated aqueous sodium bicarbonate, and extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by silica-gel chromatography (5 : 1 ethyl acetate: hexanes) to afford a yellow foam (14 mg, 50 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22-1.27 (br m, 3 H), 2.20 (dq, *J* = 2.0, 3.9, 6.0, 13.2 Hz, 1 H), 2.41 (dt, *J* = 5.6, 13.1 Hz, 1 H), 2.96 (s, 3 H), 3.04 (s, 3 H), 3.19-3.26 (m, 1 H), 3.46 (dt, *J* = 4.1, 12.8 Hz, 1 H), 3.81 (br s, 1 H), 4.10 (br s, 1 H), 4.20-4.24 (m, 1 H), 5.17 (dd, *J* = 1.6, 10.8 Hz, 1 H), 5.41 (dd, *J* = 1.6, 17.1 Hz, 1 H), 5.76 (br s, 1 H), 6.19 (d, *J* = 7.2 Hz, 1 H), 6.44 (d, *J* = 7.68, 1 H), 6.64 (dd, *J* = 10.8, 17.1 Hz, 1 H),6.89 (t, *J* = 7.85 Hz, 1 H), 6.96-6.99 (m, 3 H), 7.95-7.98 (m, 1 H); ^{13}C (75 MHz, $CDCl_3$) δ 14.3, 30.8, 34.7, 43.7, 47.1, 47.1, 55.7, 55.8, 62.1, 76.5, 85.4, 105.1, 115.9, 117.3, 125.1, 125.7, 125.9, 126.1, 128.7, 131.3, 135.6, 135.9, 138.4, 151.4, 168.0; IR (neat) 2932, 2246, 1698, 1643, 1576 cm^{-1}; HRMS (M + Na^+) calc for $C_{25}H_{27}N_3O_3Na$ 440.1951, found 440.1950.

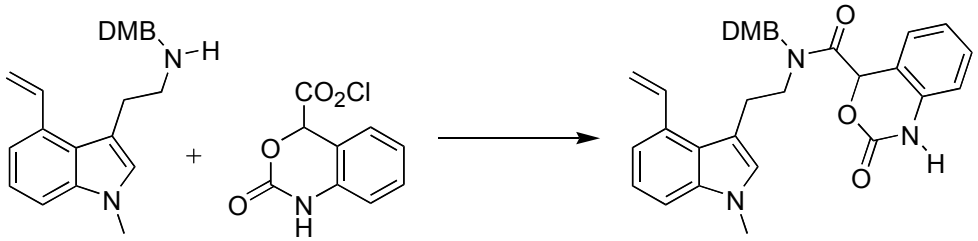


Nitrile 694. To a solution of lactam **693** (50 mg, 0.145 mmol), in THF (482 μL) at –78 °C was added KHMDS (320 μL, 0.159 mmol). After the solution was stirred for 1 h at –78 °C, iodoacetonitrile (21 μL, 0.289 mmol) was added dropwise. The solution was stirred for an additional 30 min at –78 °C, quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by silica-gel chromatography (1 : 1 ethyl acetate: hexanes) to afford a yellow foam (34 mg, 61 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (br s, 3 H), 1.99-2.04 (m, 1 H), 2.80 (dd, *J* = 10.3, 23.1 Hz, 1 H), 2.99 (s, 3

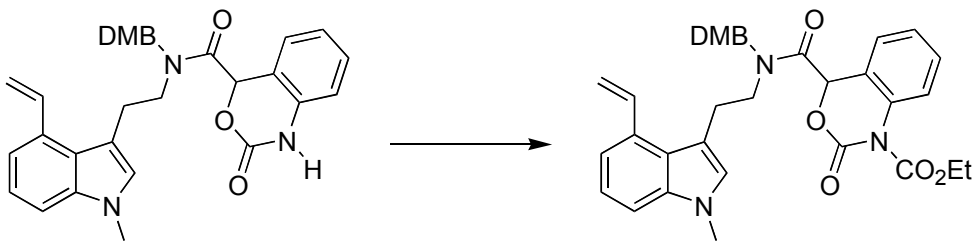
H), 3.13 (d, *J* = 3.7 Hz, 1 H), 3.40-3.55 (m, 2 H), 4.19-4.31 (m, 2 H), 5.15 (dd, *J* = 1.7, 10.7 Hz, 1 H), 5.31 (dd, *J* = 1.7, 16.9 Hz, 1 H), 5.66 (s, 1 H), 6.28 (d, *J* = 7.0 Hz, 1 H), 6.37 (d, *J* = 7.7 Hz, 1 H), 6.61 (dd, *J* = 10.7, 16.9 Hz, 1 H), 6.84-7.02 (m, 4 H), 8.16-8.22 (m, 1 H); IR (neat) 2934, 2361, 2247, 1698, 1641, 1574, 1481 cm^{-1}; HRMS (M + Na^+) calc for $C_{27}H_{28}N_4O_3Na$ 479.2069, found 479.2059.



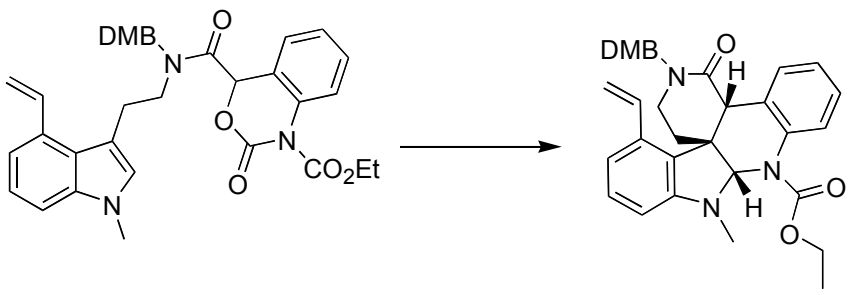
1-Methyl-4-vinyl-*N*-2,4-dimethoxybenzyl tryptamine (**699**)**.** To a solution of tryptamine **416** (754 mg, 3.76 mmol) in MeOH (9.4 mL) was added 2,4-dimethoxybenzaldehyde (481 mg, 4.14 mmol). The solution was stirred for 1 h at rt, then $NaBH_4$ (85 mg, 2.26 mmol) was added portionwise over 10 min. The solution was stirred at rt for 12 h, quenched with saturated aqueous ammonium chloride, and extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by silica-gel chromatography (1 : 10 MeOH : CH_2Cl_2) to afford an orange foam (1.04 g, 85 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.53 (br s,1 H), 2.98 (t, *J* = 6.8 Hz,2 H), 3.15 (t, *J* = 7.2 Hz, 2 H), 3.69 (s, 6 H), 3.79 (s, 3 H), 3.83 (s, 2 H), 5.35 (dd, *J* = 1.6, 10.8 Hz, 1 H), 5.75 (dd, *J* = 1.6, 17.2 Hz, 1 H), 6.44-6.47 (m, 2 H), 6.87 (s,1 H), 7.15-7.30 (m, 4H), 7.49 (dd, *J* = 10.8, 17.2 Hz, 1 H); ^{13}C (75 MHz, $CDCl_3$) δ 28.3, 33.0, 49.2, 50.1, 55.5, 55.7, 98.9, 104.1, 109.1, 113.2, 115.5, 116.9, 120.9, 122.0, 125.4, 128.3, 130.9, 132.6, 136.2,138.3, 159.0, 160.5; IR (neat) 3318, 2935, 2834, 1613, 1588, 1504 cm^{-1}; HRMS (M + H^+) calc for $C_{22}H_{27}N_2O_2$ 351.2055, found 351.2073.



Amide. To a 0 °C solution of tryptamine **699** (907 mg, 2.79 mmol) in CH_2Cl_2 (9.3 mL) was added sequentially *N, N*-diisopropylethylamine (1.46 mL, 8.39 mmol) and a solution of acid chloride **612** (592 mg, 2.79 mmol) in THF (9.3 mL). The reaction was stirred at rt for 12 h, quenched with saturated aqueous sodium bicarbonate, and extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by silica-gel chromatography (1 : 20 MeOH : CH_2Cl_2) to afford an orange oil (970 mg, 66 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.75-2.89 (m, 2 H), 2.83 (s, 3 H), 2.95-2.99 (m, 1 H), 3.25 (t, *J* = 7.1 Hz, 1 H), 3.37-3.41 (m, 1 H), 3.54-3.62 (m, 1 H), 3.69 (s, 3 H), 3.74-3.80 (m, 11 H), 3.86 (s, 3 H), 4.26 (d, *J* = 15.7 Hz, 1 H), 4.49 (d, *J* = 14.9 Hz, 1 H), 4.75 (d, *J* = 14.9 Hz, 1 H), 4.88 (d, *J* = 15.7 Hz, 1 H), 5.24 (dd, *J* = 1.7, 10.8 Hz, 1 H), 5.29 (dd, *J* = 1.3, 12.2 Hz, 1 H), 5.68 (dd, *J* = 1.7, 17.1 Hz, 2 H), 5.96 9s, 1 H), 6.41 (dd, *J* = 2.3, 8.4 Hz, 1 H), 6.47-6.52 (m, 2 H), 6.59-6.61 (m, 2 H), 6.72 (s, 1 H), 6.82-7.33 (m, 14 H), 7.42 (m, 2 H), 9.04 (br s, 1 H), 9.11 (br s, 1 H); ^{13}C (75 MHz, $CDCl_3$) δ 25.7, 27.3, 32.7, 47.7, 48.3, 48.9, 55.6, 55.9, 75.6, 75.8, 98.9, 99.3, 105.2, 109.8,110.1, 111.4,112.3, 114.8, 115.0, 115.1, 115.7, 116.9, 117.4, 117.5, 119.0, 122.1, 122.4, 123.0, 125.5, 125.9; IR (neat) 2930, 1724, 1651, 1611, 1507 cm^{-1}; HRMS (M + H$^+$) calc for $C_{31}H_{32}N_3O_5$ 526.2317, found 526.2342.



Imide 700. To a 0 °C solution of the carbamate prepared in the previous experimental (713 mg, 1.36 mmol) in DMF (4.5 mL) was added NaH (60 mg, 2.49 mmol). The reaction was stirred for 30 min at 0 °C, 30 min at 50 °C, and cooled to 0 °C. Ethyl chloroformate was slowly added, the reaction was stirred for an additional 30 min, quenched with saturated aqueous ammonium chloride, and extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4) and concentrated. The crude product was purified by silica-gel chromatography (1 : 1 ethyl acetate: hexanes) to afford a yellow foam (386 mg, 50 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39 (t, *J* = 7.1 Hz, 3 H), 1.44 (t, *J* = 7.1 Hz, 3 H), 2.91-3.16 (m, 3 H), 3.27-3.36 (m, 1 H), 3.51 (s, 3 H), 3.53-3.76 (m, 4 H), 3.66 (s, 3 H), 3.74 (s, 3 H), 3.78 (s, 3 H), 3.79 (s, 3 H), 3.80 (s, 3 H), 4.36-4.51 (m, 7 H), 4.93 (d, *J* = 14.6 Hz, 1 H), 5.26-5.35 (m, 2 H), 5.72 (dd, *J* = 1.4, 17.2 Hz, 1 h), 5.74 (dd, *J* = 1.6, 17.2 Hz, 1 H), 6.28 (s, 1 H), 6.33-6.44 (m, 6 H), 6.67 (d, *J* = 8.2 Hz, 1 H), 6.76 (d, *J* = 7.0 Hz, 1 H), 6.81 (s, 1 H), 7.04 (m, 1 H), 7.16-7.54 (m, 14 H), 7.69 (d, *J* = 8.1 Hz, 1 H); ^{13}C (75 MHz, $CDCl_3$) δ 13.9, 14.1, 24.4, 26.0, 32.5, 32.7, 43.0, 46.7, 47.3, 47.8, 55.0, 55.2, 55.2, 63.9, 64.0, 74.4, 75.7, 76.5, 77.1, 98.1, 98.5, 103.8, 104.0, 108.7, 109.3, 109.9, 110.9, 115.3, 115.3, 116.1, 116.3, 116.8, 117.1, 121.4, 122.0, 122.2, 123.4, 124.1, 124.4, 124.6, 125.1, 125.2, 125.5, 128.7, 128.8, 128.9, 129.0, 130.3, 130.8, 131.4, 131.7, 134.8, 135.3, 135.4, 137.6, 137.8, 148.7, 149.3, 151.6, 152.0, 158.4, 158.5, 160.3, 160.9, 165.5,166.0; IR (neat) 2938, 1803, 1773, 1734, 1654, 1612 cm^{-1}; HRMS (M + H$^+$) calc for $C_{34}H_{36}N_3O_7$ 598.2548, found 598.2553.



Cycloadduct 701. To a solution of imide **700** (243 mg, 0.407 mmol) in toluene (8.1 mL) and CH_2Cl_2 (2.7 mL) was added $Yb(OTf)_3$ (50 mg, 0.081 mmol). The solution was stirred for 12 h at 50 °C, cooled and concentrated. The crude product was purified by silica-gel chromatography (1 : 1 ethyl acetate: hexanes) to afford a white foam (100 mg, 5 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21-1.26 (br m, 3 H), 2.16 (dt, *J* = 3.0, 13.2 Hz, 1 H), 2.28-2.37 (m, 1 H), 2.95 (s, 3 H), 3.37-3.48 (m, 2 H), 3.79 (s, 3 H), 3.81 (s, 3 H), 3.86 (s, 1 H), 4.17 (d, *J* = 14.4 Hz, 1 H), 4.18-4.26 (m, 2 H), 5.03 (dd, *J* = 1.6, 10.8 Hz, 1 H), 5.14 (d, *J* = 14.4 Hz, 1 H), 5.42 (dd, *J* = 1.6, 17.0 Hz, 1 H), 5.76 (br s, 1 H), 6.18 (d, *J* = 7.2 Hz, 1 H), 6.45-6.52 (m, 3 H), 6.67 (dd, *J* = 10.8, 17.0 Hz, 1 H), 6.88 (t, *J* = 7.8 Hz, 1 H); ^{13}C (75 MHz, $CDCl_3$) δ 14.3, 30.8, 34.9, 43.9, 44.3, 44.7, 55.3, 55.4, 55.7, 62.0, 85.7, 98.3, 104.2, 105.0, 116.1, 116.8, 117.4, 125.1, 125.8, 125.8, 125.9, 126.4, 128.5, 131.3, 131.4, 135.4, 135.5, 138.3, 151.4, 155.6, 158.7, 160.3, 168.0; IR (neat) 2939, 2246, 1767, 1697, 1640, 1613, 1576, 1507 cm^{-1}; HRMS (M + H$^+$) calc for $C_{33}H_{36}N_3O_5$ 554.2645, found 554.2655.

REFERENCES

1. For recent reviews of marine natural products, see (a) Bugni, T. S.; Ireland, C. M. *Nat. Prod. Rep.* **2004**, *21*, 1. (b) Blunt, J. W.; Copp, B. R.; Munro, M. H. G.; Northcote, P. T.; Prinsep, M. R. *Nat. Prod. Rep.* **2004**, *21*, 1. (c) Hill, R. A. *Annu. Rep. Prog. Chem., Sect. B* **2003**, *99*, 183. (d) Patterson, G. M. L.; Larsen, L. K.; Moore, R. E. *J. Appl. Phycol.* **1994**, *6*, 151. (e) Burja, A. M.; Banaigs, B.; Abou-Mansour, E.; Burgess, J. G.; Wright, P. C. *Tetrahedron* **2001**, *57*, 9347. (f) Thajuddin, N.; Subramanian, G. *Curr. Sci. India* **2005**, *89*, 47. (g) Singh, S.; Kate, B. N.; Banerjee, U. C. *Crit. Rev. Biotechnol.* **2005**, *25*, 73.
2. Stratmann, K.; Moore, R. E.; Bonjouklian, R.; Deeter, J. B.; Patterson, G. M. L.; Shaffer, S.; Smith, C. D.; Smitka, T. A. *J. Am. Chem. Soc.* **1994**, *116*, 9935.
3. Smith, C. D.; Zilfou, J. T.; Stratmann, K.; Patterson, G. M. L.; Moore, R. E. *Mol. Pharm.* **1995**, *47*, 241.
4. Jimenez, J. L.; Huber, U.; Moore, R. E.; Patterson, G. M. L. *J. Nat. Prod.* **1999**, *62*, 940.
5. For related hapalindoles, see: Moore, R. E.; Cheuk, C.; Yang, X. G.; Patterson, G. M. L. *J. Org. Chem.* **1987**, *52*, 1036.
6. For related fischerindoles, see: Park, A.; Moore, R. E.; Patterson, G. M. L. *Tetrahedron Lett.* **1992**, *33*, 3257.
7. For the biosynthesis from tryptophan, see: (a) Brady, S. F.; Clardy, J. *Angew. Chem. Int. Ed.* **2005**, *44*, 7045. (b) Brady, S. F.; Clardy, J. *Angew. Chem. Int. Ed.* **2005**, *44*, 7063.
8. Baran, P. S.; Richter, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 15394.
9. (a) Jordan, M. A.; Wison, L. *Curr. Opin. Cell. Bio.* **1998**, *10*, 123. (b) Joran, A.; Hadfield, J. A.; Lawrence, N. J.; McGown, A. T. *Med. Res. Rev.* **1998**, *18*, 259.

10. For reviews on P-glycoprotein MDR, see: (a) Fojo, A.; Ueda, D. J.; Salman, D. G.; Poplack, M. M.; Pastan, I. *Proc. Natl. Acad. Sci. USA* **1987**, *84*, 265. (b) Gottesman, M. M.; Iastan, I. *Annu. Rev. Biochem*. **1993**, *62*, 385. (c) Moscow, J. A.; Cowan, K. H. *J. Natl. Cancer Inst.* **1988**, *80*, 14. (d) Endicott, J. A.; Ling, V. *Annu. Rev. Biochem.* **1989**, *58*, 137.

11. For the effects of colchicines on microtubules, see: (a) Taylor, E. W.; *J. Cell. Biol.* **1965**, *25*, 145. (b) Panda, D.; Daijo, J. E.; Jordan, M. A.; Wilson, L. *Biochemistry* **1995**, *34*, 9921. (c) Andreu, J. M.; Timasheff, S. N. *Proc. Natl. Acad. Sci. USA* **1982**, *79*, 6753.

12. For the effects of taxol on microtubules, see: (a) Schiff, P. B.; Horwitz, S. B. *Proc. Natl. Acad. Sci. USA* **1980**, *77*, 1561. (b) Jordan, M. A.; Toso, R. J.; Thrower, D.; Wilson, L. *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 9552. (c) Jordan, M. A.; Derry, W. B.; Wilson, L. *Biochemistry* **1995**, *34*, 2203. (d) Waters, J. C.; Mitchinson, T. J.; Rieder, C. L.; Salmon, E. D. *Mol. Biol. Cell.* **1996**, *7*, 1547.

13. For the effects of vinblastine on microtubules, see: (a) Toso, R. J.; Jordan, M. A.; Farrell, K. W.; Matsumoto, B.; Wilson, L. *Biochemistry* **1993**, *32*, 1285. (b) Panda, D.; Jordan, M. A.; Chin, K.; Wilson, L. *J. Biol. Chem.* **1996**, *271*, 29807. (c) Na, G. C.; Timasheff, S. N. *Biochemistry* **1980**, *19*, 1347.

14. Smith, C.D.; Zhang, X. *Mol. Pharm.* **1996**, *49*, 288.

15. For examples of compounds that are both toxic to P-glycoprotein-overexpressing cells as well as interfere with microtubule dynamics, for example, epothilones A and B or cryptophycin, see: (a) Höfle, G.; Bedorf, N.; Steinmetz, H.; Schumburg, D.; Gerth, K.; Reichenbach, H. *Angew. Chem. Int. Ed.* **1996**, *35*, 1567. (b) Gerth, K.; Bedorf, N.; Höfle, G.; Irschik, H.; Reichenbach, H. *J. Antibiot.* **1996**, *49*, 560. (c) Nicolaou, K. C.; Roschangar, F.; Vourloumis, D. *Angew. Chem. Int. Ed.* **1998**, *37*, 2014. (d) Smith, C. D.; Zhang, X.; Mooberry, S. L.; Patterson, G. M. L.; Moore, R. E. *Cancer Res.* **1994**, *54*, 3779.

16. For a review on approaches to the welwitindolinones, see: Avendaño, C.; Menéndez, J. C. *Curr. Org. Syn.* **2004**, *1*, 65.
17. (a) Konopelski, J. P., Deng, H.; Schiemann, K.; Keane, J. M.; Olmstead, M. M. *Synlett.* **1998**, 1105. (b) Elliot, G. I.; Konopelski, J. P.; Olmstead, M. M. *Org. Lett.* **1999**, *1*, 1867. (c) Deng, H.; Konopelski, J. P. *Org. Lett.* **2001**, *3*, 3001.
18. Mackay, J. A.; Bishop, R. L.; Rawal, V. H. *Org. Lett.* **2005**, *7*, 3421.
19. Baudoux, J.; Blake, A. J.; Simpkins, N. S. *Org. Lett.* **2005**, *7*, 4087.
20. (a) Baran, P. S.; Richter, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 7450. (b) Baran, P. S.; Richter, J. M.; Lin, D. W. *Angew. Chem. Int. Ed.* **2005**, *44*, 609.
21. Wood, J. L.; Holubec, A. A.; Stoltz, B. M.; Weiss, M. W.; Dixon, J. A.; Doan, B. D.; Shamji, M. F.; Chen, J. M.; Heffron, T. P. *J. Am. Chem. Soc.* **1999**, *121*, 6326.
22. Jung, M. E.; Slowinski, F. *Tetrahedron Lett.* **2001**, *42*, 6835.
23. Kaoudi, T.; Quiclet-Sire, B.; Seguin, S.; Zard, S. Z. *Angew. Chem. Int. Ed.* **2000**, *39*, 731.
24. (a) Ready, J. M.; Reisman, S. E.; Hirata, M.; Weiss, M. W.; Tamaki, K.; Ovaska, T. V.; Wood, J. L. *Angew. Chem. Int. Ed.* **2004**, *43*, 2170. (b) Reisman, S. E.; Ready, J. M.; Hasuoka, A.; Smith, C. J.; Wood, J. L. *J. Am. Chem. Soc.* **2006**, *128*, 1448.
25. Funk, R. L.; Greshock, T. J. *Org. Lett.* Submitted for publication.
26. Greshock, T. J.; Funk, R. L. *J. Am. Chem. Soc.* **2002**, *124*, 754.
27. Greshock, T. J.; Funk, R. L. *J. Am. Chem. Soc.* **2006**, *128*, 4946.
28. Frejd, T.; Polla, M. *Tetrahedron* **1991**, *47*, 5883.
29. Via either (1) treatment of the ketone with WCl_6, see: Jung, M. E.; Wasserman, J. I. *Tetrahedron Lett.* **2003**, *44*, 7273; (2) or via conversion of a vinyl triflate to the vinyl stannane and treatment with $CuCl_2$, see: (a) Simpkins, S. M. E.; Kariuki, B. M.; Arico, C. S.; Cox, L. R.; *Org. Lett.* **2003**, *5*, 3971. (b) Férézou, J.; Madec, D.; *Tetrahedron Lett.* **1997**, *38*, 6661. (c)

Takeda, T.; Kanamori, F.; Matsusita, H.; Fujiwara, T. *Tetrahedron Lett.* **1991**, *32*, 6563.

30. The halide to make the requisite Grignard reagent, (*E)*-4-bromo-3-methyl-but-2-en-1-ol is known, see: Van, T. N.; Kimpe, N. D.; *Tetrahedron* **2000**, *56*, 7969.

31. For leading publications on allylic and benzylic chlorides, see: (a) Hwang, C. K.; Li, W. S.; Nicolaou, K. C. *Tetrahedron Lett.* **1984**, *25*, 2295. (b) Collington, E. W.; Meyers, A. I. *J. Org. Chem.* **1971**, *36*, 3044.

32. For references pertaining to regioselective benzylic openings of epoxides to provide β-hydroxy nitriles, see: (a) Chini, M.; Crotti, P.; Favero, L.; Macchia, F. *Tetrahedron Lett.* **1991**, *32*, 4775. (b) Iranpoor, N.; Shekarriz, M. *Syn. Comm.* **1999**, *29*, 2249.

33. For reviews on radical cyclizations, radical cyclization cascades, and their use in natural product synthesis, see: (a) Curran, D. P. *Synthesis* **1988**, 417. (b) Curran, D. P. *Synthesis* **1988**, 489. (c) Srikanth, G. S. C.; Castle, S. L. *Tetrahedron* **2005**, *61*, 10377. (d) Bowman, W. R.; Bridge, C. F.; Brookes, P. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1. (e) Curran, D. P. *Synlett* **1991**, 63. (f) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237. (f) Rajanbabu, T. V. *Acc. Chem. Res.* **1991**, *24*, 139. (g) Giese, B. *Angew. Chem. Int. Ed.* **1985**, *24*, 553. (h) Giese, B. *Angew. Chem. Int. Ed.* **1983**, *22*, 753. (h) Chatgilialoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. *Chem. Rev.* **1999**, *99*, 1992. (i) Zhang, W. *Tetrahedron* **2001**, *57*, 7237. (j) Curran, D. P. *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon: London, 1991; Vol. 4 Chapters 4.1 and 4.2 (k) Giese, B.; Kopping, B.; Gobel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. *Org. React.* **1996**, *48*, 301.

34. (a) Cladingboel, D. E.; Parsons, P. *J. Chem. Soc., Chem. Commun.* **1990**, 1543. (b) Parsons, P; Ozlu, Y. *Tetrahedron* **1994**, *50,* 2183. For a radical cyclization cascade to provide a carbazole based ring system in the context of natural product synthesis, see: Jenkinson, J. J.; Parsons, P. J.; Eyley, S. C. *Synlett.* **1992**, 679.

35. (a) Fukuyama, T.; chen, X.; Peng, g. *J. Am. Chem. Soc.* **1994**, *116*, 3127. (b) Kobayashi, Y.; Fukuyama, T. *J. Heterocyc. Chem.* **1998**, *35*, 1043. (c) Kobayashi, S.; Peng, G.; Fukuyama, T. *Tetrahedron Lett.* **1999**, *40*, 1519.

36. Tokuyama, H.; Yamashita, T.; Kaburagi, Y.; Fukuyama, T. *J. Am. Chem. Soc.* **1999**, *121*, 3791.

37. Boger, D. L.; Mckie, J. A. *J. Org. Chem.* **1995**, *60*, 1271.

38. Boger, D. L.; Boyce, C. W.; Garbaccio, R. M.; Searcey, M. *Tetrahedron Lett.* **1998**, *39*, 2227. For radical cyclizations of *N*-allyl *o*-bromoacetanilides to provide dihydroindoles, see: Dittami, J.P.; Ramanathan, H. *Tetrahedron Lett*. **1988**, *29*, 45.

39. (a) Jones, K.; Brunton, S. A.; Gosain, R. *Tetrahedron Lett.* **1999**, *40*, 8935. (b) Jones, K.; Wilkinson, J. *J. Chem. Soc., Chem. Commun.* **1992**, 1767. For another radical cyclization to provide 3-substituted oxindoles, see: Bowman, W. R.; Heaney, H.; Jordan, B. M. *Tetrahedron Lett.* **1988**, *29*, 6657.

40. (a) Atarashi, S.; Choi, J.-K.; Ha, D.-C.; Hart, D. J.; Kuzmich, D.; Lee, C.-S.; Ramesh, S.; Wu, S. C. *J. Am. Chem. Soc.* **1997**, *119*, 6226. (b) Hart, D. J.; Wu, S. C. *Tetrahedron Lett.* **1991**, *32*, 4099.

41. For reviews on the S_N2' reaction, see (a) Paquette, L. A.; Stirling, C. J. M. *Tetrahedron* **1992**, *48*, 7383. (b) Magid, R. M. *Tetrahedron* **1980**, *36*, 1901. (c) Altenbach, H.-J. *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, **1991**; Vol 6. pp 830.

42. (a) Williams, R. M.; Glinka, T.; Kwast, E.; Coffman, H.; Stille, J. K. *J. Am. Chem. Soc.* **1990**, *112*, 808. For another S_N2' cyclization where the stereochemical outcome was based upon solvent and steric interactions, see: (b) Boeckman, R. K.; Zhang, J.; Reeder, M. R. *Org. Lett.* **2002**, *4*, 3891. (c) Boeckman, R. K.; Reeder, M. R. *J. Org. Chem.* **1997**, *62*, 6456.

43. Kim, D.; Choi, W. J.; Hong, J. Y.; Park, I. Y.; Kim, Y. B. *Tetrahedron Lett.* **1996**, *37*, 1433.

44. Whitmore, F. C.; Culhane, P. J.; Neher, H. *Organic Syntheses*; Wiley: New York, 1961; Collect. Vol. I, p 56, 125.

45. Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.

46. Barrow, R. A.; Hemscheidt, T.; Liang, J.; Paik, S.; Moore, R. E.; Tius, M. A. *J. Am. Chem. Soc.* **1995**, *117*, 2479.

47. The 1,4-addition of Bu_3SnH to an enone via a radical chain process was first reported by: (a) Pereyre, M.; Valade, J. *Compt. Rend.* **1965**, *260*, 581. (b) Pereyre, M.; Valade, J. *Bull. Soc. Chim. Fr.* **1967**, 1928. see also: (c) Wolf, H. R.; Zink, M. P. *Helv. Chim. Acta.* **1973**, *56*, 1062. (d) Laurent, H.; Esperling, P.; Baude, G. *Lieb. Ann. Chem.* **1983**, 1996.

48. (a) Hays, D. S.; Scholl, M.; Fu, G. C. *J. Org. Chem.* **1996**, *61*, 6751. For a review on tin-mediated reduction of enones, see: (b) Studer, A.; Amrein, S. *Synthesis* **2002**, *7*, 835.

49. For the use of ACN in natural product synthesis, see: (a) Inaba, T.; Umezawa, I.; Yuasa, M.; Inoue, T.; Mihashi, S.; Itokawa, H.; Ogura, K. *J. Org. Chem.* **1987**, *52*, 2958. (b) Nishida, A.; Miyoshi, I.; Ogasawara, Y.; Nagumo, S.; Kawahara, N.; Nishida, M.; Takayanagi, H. *Tetrahedron* **2000**, *56*, 9241. For the original publication on the use of ACN in radical cyclizations, see: Overberger, C. G.; Biletch, H.; Finestone, A. B.; Lilker, J.; Herbert, J. *J. Am. Chem. Soc.* **1953**, *75*, 2078.

50. For the Si-O bond dissociation energy, see: (a) Gingrich, K. A.; Finkbeiner, H. C. *Proc. Rare Earth Res. Conf.* **1971**, *2*, 795. For the Sn-O bond dissociation energy, see: (b) Brewer, L.; Brackett, E. *Chem. Rev.* **1961**, *61*, 425.

51. (a) Giese, B.; Kopping, B. *Tetrahedron Lett.* **1989**, *30*, 681. (b) Chatgilialoglu, C. *Acc. Chem. Res.* **1992**, *25*, 188. For a comparison of rate constants between TTMSS and Bu_3SnH for hydrogen abstraction by radicals, see, (b).

52. For seminal publications on the Mitsunobu reaction, see: (a) Mitsunobu, O.; Yamada, M. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380. (b) Mitsunobu, O.; Yamada, M.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 935. For reviews on the Mitsunobu reaction, see: (c) Mitsunobu, O. *Synthesis* **1981**,

1. (d) Castro, B. R. *Org. React.* **1983,** *29*, 1. (e) Hughes, D. L. *Org. React.* **1992**, *42*, 335. (f) Hughes, D. L. *Org. Prep. Proced. Intl.* **1996**, *28*, 127.

53. (a) Luche, J. L.; Gemal, A. L. *J. Am. Chem. Soc.* **1979**, *101*, 5848. (b) Gemal, A. L.; Luche, J. L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.

54. We have been able to epimerize ketone **114** with K_2CO_3 in MeOH quantitatively.

55. (a) For the use of *m*CPBA at elevated temperatures, see: Kishi, Y.; Aratani, H. T.; Fukuyama, T.; Goto, T. *J. Chem. Soc., Chem. Commun.* **1972**, 64. (b) Luong, T. M.; Lefort, D. *Bull. Soc. Chim. Fr.* **1962**, 827.

56. For references pertaining to *in situ* generation of DMDO, see (a) Frohn, M.; Wang, Z.-W.; Shi, Y. *J. Org. Chem.* **1998**, *63*, 6425. For a review of DMDO chemistry and properties, see: (b) Curci, R.; Dinoi, A.; Rubino, M. F. *Pure & Appl. Chem.* **1995**, *67*, 811. (c) Murray, R. W. *Chem. Rev.* **1989**, *89*, 1187.

57. (a) Mello, R.; Fiorentino, M.; Sciacovelli, O.; Curci, R. *J. Org. Chem.* **1988**, *53*, 3890. (b) Mello, R.; Fiorentino, M.; Fusco, C.; Curci, R. *J. Am. Chem. Soc.* **1989**, *111*, 6749. (c) Adam, W.; Curci, R.; Nuñez, M. E. G.; Mello, R. *J. Am. Chem. Soc.* **1991**, *113*, 7654. For *in situ* generation of methyl(trifluoromethyl)dioxirane, see: (d) Yang, D.; Wong, M.-K.; Yip, Y.-C. *J. Org. Chem.* **1995**, *60*, 3887. (e) Li, W.; Fuchs, P. L. *Org. Lett.* **2003**, *5*, 2853.

58. For a review of halolactonization, see: Bartlett, P. A.; Richardson, D. R.; Myerson, J. *Tetrahedron* **1984**, *40*, 2317.

59. Funk, R. L.; Fuchs, J. R. *Org. Lett.* **2001**, *3*, 3349.

60. For the use of *N*-(phenylseleno)phthalimide (N-PSP) , see: (a) Mihelich, E. D.; Hite, G. A. *J. Am. Chem. Soc.* **1992**, *114*, 7318. For the original publication concerning the synthesis and reactions of N-PSP, see: (b) Nicolaou, K. C.; Claremon, D. A.; Barnette, W. E.; Seitz, S. P. *J. Am. Chem. Soc.* **1979**, *101*, 3704. For a review of N-PSP, see: (c) Nicolaou, K. C.; Petasis, N. A.; Claremon, D. A. *Tetrahedron* **1985**, *41*, 4835.

61. Halolactonizations using thallium salts and bromine / iodine are postulated to be very effective, see: (a) Cambie, R. C.; Rutledge, P. S.; Somerville, R. F.; Woodgate, P. D. *Synthesis* **1988**, 1009. (b) Corey, E. J.; Hase, T. *Tetrahedron Lett.* **1979**, *37*, 355. (c) Cambie, R. C.; Ng, K. S.; Rutledge, P. S.; Woodgate, P. D. *Aust. J. Chem.* **1979**, *32*, 2793.

62. For references using $Pb(OAc)_4$ / metal halide complexes for halolactonization, see: (a) Motohashi, S.; Satomi, M.; Fujimoto, Y.; Tatsuno, T. *Chem. Pharm. Bull.* **1983**, *31*, 1788. (b) Motohashi, S.; Satomi, M. *Heterocycles* **1985**, *23*, 2035.

63. For fundamental reviews on intramolecular 1,3-dipolar additions, see: (a) Padwa, A. *Angew. Chem. Int. Ed.* **1976**, *15*, 123. (b) Oppolzer, W. *Angew. Chem. Int. Ed.* **1977**, *16*, 10. (c) Black, D. St. C.; Crozier, F.; Davis, V. C. *Synthesis* **1975**, 205. (d) Tufariello, J. J. *Acc. Chem. Res.* **1979**, *12*, 376. For reviews on synthetic applications of nitrones, see: (e) Balasubramanian, N. *Org. Prep. Proc. Intl.* **1985**, *17*, 23. (f) Banerji, A.; Sahu, A. *J. Sci. Ind. Res.***1986**, *45*, 355.

64. (a) Funk, R. L.; Horcher, L. H. M., II; Daggett, J. U.; Hansen, M. M. *J. Org. Chem.* **1983**, *48*, 2633. (b) Funk, R. L.; Bolton, G. L.; Daggett, J. U.; Hansen, M. M., Horcher, L. H. M. *Tetrahedron* **1985**, *41*, 3479. For the use of exocyclic nitrones in the synthesis of 1-azaspirocycles, see: (c) Funk, R. L.; Daggett, J. U. *Heterocycles* **1987**, *26*, 2175.

65. (a) Grigg, R.; Markandu, J. *Tetrahedron Lett.* **1991**, *32*, 279. Grigg does not comment on the mechanism of the Pd(II) catalyzed generation of nitrones, but implied that it does not proceed simply by a cyclization-fragmentation mechanism, see: (b) Constable, A. G.; McDonald, W. S.; Sawkins, L. C.; Shaw, B. L. *J. Chem. Soc., Dalton Trans.* **1980**, 1992. However, Pd(II) and Pd(0) complexes are known to catalyze [3,3]-sigmatropic shifts, see: (c) Overman, L. E.; Knoll, F. M. *J. Am. Chem. Soc.* **1980**, *102*, 865. For other metal-mediated generation of nitrones from oxime ethers, see: (d) Davies, S. G.; Fox, J. F.; Jones, S.; Price, A. J.; Sanz, M. A.; Sellers, T. G. R.; Smith, A. D.; Teixeira, F. C. *J. Chem. Soc.,*

Perkin Trans. 1 **2002**, 1757. For metal mediated generation of nitrones from oximes, see: (e) Miyabe, H.; Yoshida, K.; Reddy, V. K.; Matsumura, A.; Takemoto, Y. *J. Org. Chem.* **2005**, *70*, 5630. (f) Frederickson, M.; Grigg, R.; Markandu, J.; Thornton-Pett, M.; Redpath, J. *Tetrahedron* **1997**, *53*, 15051. (g) Frederickson, M.; Grigg, R.; Markandu, J.; Redpath, J. *J. Chem. Soc., Chem. Commun.* **1994**, 2225. (h) Grigg, R.; Hadjisoterou, M.; Kennewell, P.; Markandu, J.; Thornton-Pett, M. *J. Chem. Soc., Chem. Commun.* **1992**, 1388. (i) Grigg, R.; Markandu, J.; Perrior, T.; Surendrakumar, S.; Warnock, W. J. *Tetrahedron* **1992**, *48*, 6929. (j) Grigg, R.; Markandu, J.; Surendrakumar, S.; Thornton-Pett, M.; Warnock, W. J. *Tetrahedron* **1992,** *48*, 10399..

66. (a) Vinyl zinc reagents have been shown to give improved yields on enolizable substrates over vinyl Grignard reagents. For a specific example, see: Thompson, W. J.; Tucker, T. J.; Schwering, J. E.; Barnes, J. L. *Tetrahedron Lett.* **1990**, *31*, 6819. For a synthesis of vinylzinc chloride, see: (b) Coleman, R. S.; Carpenter, A. J. *Tetrahedron Lett.* **1992**, *33*, 1697.

67. Takai, K.; Kimura, K.; Kuroda, T.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett.* **1983**, *24*, 5281.

68. For the seminal publication on Dess-Martin oxidations, see: (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. For a modification, see (b) Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549.

69. For examples of carbonyl-oxime ether radical cyclizations, see: (a) Corey, E. J.; Pyne, S. G. *Tetrahedron Lett.* **1983**, *24*, 2821. (b) Tormo, J.; Hays, D. S.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 201. (c) Chiara, J. L.; Marco-Contelles, J.; Khiar, N.; Gallego, P.; Destabel, C.; Beranbé, M. *J. Org. Chem.* **1995**, *60*, 6010. (d) Egger, A.; Hunziker, J.; Rihs, G.; Leumann, C. *Helv. Chim. Act.* **1998**, *81*, 734. (e) Hart, D. J.; Seely, F. L. *J. Am. Chem. Soc.* **1988**, *110*, 1631. For the use of carbonyl-oxime radical cyclization in the context of natural product synthesis, see: (f) Marco-Contelles, J.; Gallego, P.; Rodriguez-Fernández, N.; Destabel, C.; Bernabé, M.;

Martínez-Grau, A.; Chiara, J. L. *J. Org. Chem.* **1997**, *62*, 7397. (g) Miyabe, H.; Torieda, M; Inoue, K.; Tajiri, K.; Kiguchi, T.; Naito, T. *J. Org. Chem.* **1998**, *63*, 4397. (h) Boiron, A.; Zillig, P.; Faber, D.; Giese, B. *J. Org. Chem.* **1998**, *63*, 5877.

70. The rate constant for alkyl radical additions to C=N bonds has been measured to be 6.7 X 10^5 s^{-1} at 80 ºC for 6-*exo* cyclization versus 5.0 X 10^3 s^{-1} for alkyl radical additions to C=C bonds in 6-*exo* cyclization, indicating that C=N bonds are better radical acceptors than C=C bonds, see Kim, S.; Yoon, K. S.; Kim, Y. S. *Tetrahedron* **1997**, *53*, 73.
71. For the seminal publications on the Swern oxidation, see: (a) Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 4537. (b) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.
72. The major side reaction of carbonyl-oxime ether reductive cyclization is 1,2-reduction of the carbonyl group, see 69 (b).
73. For radical cyclizations of oxime ethers with alkyl halides, see: (a) reference 69 b, and c. (b) Noya, B.; Paredes, M. D.; Ozores, L.; Alonso, R. *J. Org. Chem.* **2000**, *65*, 5960. For radical cyclizations of oxime ethers with phenyl thionocarbonates, see: (c) Bartlett, P. A.; McLaren, K. L.; Ting, P. C. *J. Am. Chem. Soc.* **1988**, *110*, 1633.
74. One way of measuring the relative inherent stability of free radicals is by comparison of the dissociation energies (*D* values) of R-H bonds. The higher the *D* value, the less stable the radical. For an ethyl radical, the *D* value is 100 kcal / mol, whereas for a benzyl radical, the *D* value is 88 kcal / mol. For a complete listing of *D* values, see: March, J.; Smith, M. B. *March's Advanced Organic Chemistry*, 5th ed.; Hoffman, T., Ed.; Wiley & Sons: New York, **2001**, 243.
75. Fallis, A. G.; Sturino, C. F. *J. Am. Chem. Soc.* **1994**, *116*, 7447.
76. Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408.
77. For examples of vinyl or aryl halide / oxime ether radical cyclizations, see: (a) Booth, S. E.; Jenkins, P. R.; Swain, C. J.; Sweeney, J. B. *J. Chem.*

Soc., Perkin Trans. 1 **1994**, 3499. (b) Booth, S. E.; Jenkins, P. R.; Swain, C. J. *J. Chem. Soc., Chem. Commun.* **1991**, 1248.

78. For references pertaining to the retrocycloaddition of 5-substituted-4*H*-1,3-dioxins, see: (a) Fearnley, S. P.; Funk, R. L.; Gregg, R. J. *Tetrahedron* **2000**, *56*, 10275. (b) Aungst, R. A.; Funk, R. L. *J. Am. Chem. Soc.* **2001**, *123*, 9455. (c) Aungst, R. A.; Funk, R. L. *Org. Lett.* **2001**, *3*, 3553-3555. (d) Maeng, J. H.; Funk, R. L. *Org. Lett.* **2002**, *4*, 331. (e) Maeng, J. H.; Funk, R. L. *Org. Lett.* **2001**, *3*, 1125. (f) Fuchs, J. R.; Funk, R. L. *Org. Lett.* **2001**, *3*, 3349. (g) Fuchs, J. R.; Funk, R. L. *Org. Lett.* **2001**, *3*, 3925. (h) Greshock, T. J.; Funk, R. L. *Org. Lett.* **2001**, *3*, 3511. (i) Greshock, T. J.; Funk, R. L. *J. Am. Chem. Soc.* **2001**, *124,* 754.

79. For *o*-quinone methide generation from *o*-hydroxy-benzylalcohols, see: (a) Kranenburg, M.; Ciriano, M. V.; Mulder, P. *J. Org. Chem.* **1999**, *64*, 3012. (b) Sprengling, G. R. *J. Am. Chem. Soc.* **1952**, *74*, 2937. (c) Dorrestijn, E.; Epema, O. J.; van Scheppingen, W. B.; Mulder, P. *J. Chem. Soc., Perkin Trans. 2* **1998**, 1173. For *o*-quinone methide generation from *o*-halo-benzylhalides, see: (d) Rosenau, T.; Habicher, W. D.; Potthast, A.; Kosma, P. *Synlett* **1998**, *3*, 291. (e) Rosenau, T.; Habicher, W. D.; *Tetrahedron* **1995**, *51*, 7919. (f) Rosenau, T.; Habicher, W. D. *Tetrahedron Lett.* **1997**, *45*, 1080. For *o*-quinone methide generation from *o*-halo-benzylethers, see: (g) Wakselman, M; Vilkas, M. C. R. *Hebd. Seaces Acd. Sci.* **1964**, *258*, 126. (h) Decodts, G.; Wakselman, M.; Vilkas, M. *Tetrahedron* **1970**, *26*, 3313. For a review on the generation and synthetic applications of *o*-quinone methides, see: (i) Van De Water, R. W.; Pettus, T. R. R. *Tetrahedron* **2002**, *58*, 5367.

80. Fixler, N.; Salez, H.; Demeunynck, M.; Lhomme, J. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1649.

81. (a) Ratnayake, A. S.; Yoshida, W. Y.; Mooberry, S. L.; Hemscheidt, T. K. *J. Org. Chem.* **2001**, *66*, 8717-8721. For the subsequent retraction of the structure of nomofungin, see: (b) Ratnayake, A. S.; Yoshida, W. Y. Mooberry, S. L.; Hemscheidt, T. K. *J. Org. Chem.* **2003**, *68*, 1640.

82. Via oxidation to the aldehyde with subsequent sulfur ylide addition. For related examples, see: (a) Corey, E. J.; de Monellano, P. R. *Tetrahedron Lett.* **1968**, *49*, 5113. (b) Faber, K.; Mischitz, M.; Mirtl, C.; Saf, R. *Tetrahedron: Asym.* **1996**, *7*, 2041.

83. The resultant tosylimide will be reduced to the corresponding alcohol and subjected to a Mitsunobu ring closure (see reference 52). For a related reduction, see: (a) Katagiri, N.; Muto, M.; Nomura, M.; Higashikawa, T.; Kaneko, C. *Chem. Pharm. Bull.* **1991**, *39*, 1112.

84. (a) Doyle, M. P.; Kalinin, A. V. *Tetrahedron Lett.* **1996**, *37*, 1371. (b) Yoon, C. H.; Zaworotko, M. J.; Moulton, B.; Jung, K. W. *Org. Lett.* **2001**, *3*, 3539. (c) Doyle, M. P.; Shanklin, M. S.; Oon, S. M.; Pho, H. Q.; Vanderheide, F. R.; Veal, W. R. *J. Org. Chem.* **1988**, *53*, 3384.

85. Metal-mediated intermolecular insertions of *N*-sulfonyldiazoamides into alkenes and alcohols have been reported, see: (a) Jiang, N.; Wang, J.; Chan, A. S. C. *Tetrahedron Lett.* **2001**, *42*, 8511. (b) Haddad, N.; Galili, N. *Tetrahedron: Asym.***1997**, *8*, 3367.

86. For a related insertion, see: (a) White, J. D.; Hrnciar, P.; Stappenbeck, F. *J. Org. Chem.* **1999**, *64*, 7871. Tertiary bridgehead C-H bonds of bridged bicyclic ring systems undergo insertion as well, see: (b) Sonawane, H. R.; Bellur, N. S.; Ahuja, J. R.; Kulkarni, D. G. *J. Org. Chem.* **1991**, *56*, 1434.

87. Ouihia, A.; Rene, L.; Guilhem, J.; Pascard, C.; Badet, B. *J. Org. Chem.* **1993**, *58*, 1641.

88. (a) Smith, A. B.; Safonov, I. G.; Corbett, R. M. *J. Am. Chem. Soc.* **2002**, *124*, 11102. (b) Roush, W. R.; Marron, T. G. *Tetrahedron Lett.* **1993**, *34*, 5421.

89. For examples of indoles participating in [4+2] cycloadditions, see: (a) Chrétien, A.; Chataigner, I.; L'Hélias, N.; Piettre, S. R.*J. Org. Chem.* **2003**, *68*, 7990. (b) Wenkert, E.; Moeller, P. D. R.; Piettre, S. R. *J. Am. Chem. Soc.* **1988**, *110*, 7188. (c) Bodwell, G. J. *Angew. Chem. Int. Ed.* **2002**, *41*, 3261. (d) Lynch, S. M.; Bur, S. K.; Padwa, A. *Org. Lett.* **2002**, *4*, 4643. (d) Biolatto, B.; Kneeteman, M.; Paredes, E.; Mancini, P. M. E. *J. Org. Chem.*

2001, *66*, 3906. For a review, see: (e) Lee, L.; Snyder, J. K. *Adv. Cycloaddit.* **1999**, *6*, 119.

90. For examples of the catalyst ligand affecting the regio- and stereochemical outcome, see: (a) West, F.; G.; Naidu, B. N.; Tester, R. W. *J. Org. Chem.* **1994**, *59*, 6892. (b) Paquette, L. A. *Encyclopedia of Reagents for Organic Synthesis*, Vol. 4; John Wiley & Sons: New York, **1995**, 2280-2294; and references cited therein. (c) see reference 86 (a).
91. (a) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*, John Wiley & Sons: New York, **1988**, 112-114. (b) Taber, D. F.; You, K. K.; Rheingold, A. L. *J. Am. Chem. Soc.* **1996**, *118*, 547.
92. Crawley, S. L.; Funk, R. L. *Org. Lett.* **2003**, *5*, 3169.
93. The procedure used for chiral glyoxylates was followed, see: Bigi, F.; Bocelli, G.; Maggi, R.; Sartori, G. *J. Org. Chem.* **1999**, *64*, 5004.
94. Clark, R. D.; Weinhardt, K. K.; Berger, J.; Fisher, L. E.; Brown, C. M.; Mackinnon, A. C.; Kilpatrick, A. T.; Spedding, M. *J. Med. Chem.* **1990**, *33*, 633.
95. For the isolation of communesins A and B, see: Numata, A.; Takahashi, C.; Ito, Y.; Takada, T.; Kawai, K.; Usami, Y.; Matsumura, E.; Imachi, M.; Ito, T.; Hasegawa, T. *Tetrahedron Lett.* **1993**, *34*, 2355.
96. Verbitski, S. M.; Mayne, C. L.; Davis, R. A.; Concepcion, G. P.; Ireland, C. M. *J. Org. Chem.* **2002**, *67*, 7124.
97. For a review of indole natural products, see: Somei, M.; Yamada, F.; *Nat. Prod. Rep.* **2004**, *21*, 278.
98. For a review of naturally occurring organobromine compounds, see: (a) Gribble, G. W. *Chem. Soc. Rev.* **1999**, *28*, 335. For a review of vanadium bromoperoxidase, the enzyme thought responsible for incorporation of halogens into natural products, see: (b) Butler, A.; Walker, J. *Chem. Rev.* **1993**, *93*, 1937.
99. For the isolation of communesins B, C, D and E see: (a) Jadulco, R.; Edrada, R. A.; Ebel, R.; Berg, A.; Schaumann, K.; Wray, V.; Steube, K.;

Proksch, P. *J. Nat. Prod.* **2004**, *67*, 78. (b) Hayashi, H.; Matsumoto, H.; Akiyama, K. *Biosci. Biotech. Biochem.* **2004**, *68*, 753. For the isolation of communesins G and H from psychrotolerant fungus *penicillium rivulum*, see: (c) Dalsgaard, P. W.; Blunt, J. W.; Munro, M. H. G.; Frisvad, J. C.; Christopherson, C. *J. Nat. Prod.* **2005**, *68*, 258. For the natural occurrence of *penicillium sp.* and detection of communesin B in fruit products, see: (d) Andersen, B.; Smedsgaard, J.; Frisvad, J. C. *J. Agric. Food Chem.* **2004**, *52*, 2421. (e) Andersen, B.; Frisvad, J. C. *J. Agric. Food Chem.* **2004**, *52,* 7507.

100. D'Amours, D.; Sallmann, F. R.; Dixit, V. M.; Poirier, G. G. *J. Cell. Sci.* **2001**, *114*, 3771.

101. For a review on actin-binding marine macrolides' biological implications and total synthesis, see: (a) Yeung, K.-S.; Paterson, I. *Angew. Chem. Int. Ed.* **2002**, *41*, 4632. For a review of small-molecule inhibitors of actin dynamics, see: (b) Fenteany, G.; Zhu, S. *Curr. Top. Med. Chem.* **2003**, *3*, 593. For other references pertaining to antimicrofilament agents, see: (c) Paterson, I.; Britton, R.; Ashton, K.; Knust, H.; Stafford, J. *Proc. Nat. Acad. Sci.* **2004**, *101*, 11986. (d) Klenchin, V. A.; Allingham, J. S.; King, R.; Tanaka, J.; Marriot, G.; Rayment, I. *Nat. Struct. Biol.* **2003**, *10*, 1058. For a reference pertaining to sphinxolides, natural products that are possible potent new antimicrofilament agents that circumvent multiple drug resistance mediated by overexpression of either P-glycoprotein or MRP, see: (e) Zhang, X.; Minale, L.; Zampella, A.; Smith, C. D. *Cancer Res.* **1997**, *57*, 3751.

102. For a review on the cytochalasins effect on actin, see; Cooper, J. A. *J. Cell. Biol.* **1987**, *105*, 1473.

103. Spector, I.; Shochet, N. R.; Kashman, Y.; Groweiss, A. *Science* **1983**, *219*, 493.

104. Gachet, Y.; Tournier, S.; Millar, J. B. A.; Hyams, J. S. *Nature* **2001**, *412*, 352.

105. (a) For the isolation of several members of the *calycanthus* family of natural products from the plant *Psychotria colorata*, see: (a) Verotta, L.; Pilati, T.; Tatò, M.; Elisabetsky, E.; Amador, T. A.; Nunes, D. S. *J. Nat. Prod.* **1998**, *61*, 392. For a review of their proposed biosynthesis, and the experimental evidence that the calycanthaceous alkaloids are derived from the rearrangement of a tryptamine dimerization product, see: (b) May, J. A.; Stoltz, B. *Tetrahedron* **2006**, 62, 5262. For further experimental evidence that the calycanthaceous alkaloids are derived from the rearrangement of the tryptamine dimerization product indolenine **191**, see: (c) Fang, C.-L.; Horne, S.; Taylor, N.; Rodrigo, R. *J. Am. Chem. Soc.* **1994**, *116*, 9480. (d) Scott, A. I.; McCapra, F.; Hall, E. S. *J. Am. Chem. Soc.* **1964**, *86*, 302. (e) Hendrickson, J. B.; Rees, R.; Göschke, R. *Proc. Chem. Soc.* **1962**, 383.

106. (a) Woodward, R. B.; Yang, N. C.; Katz, T. J. *Proc. Chem. Soc.* **1960**, 76. (b) Robinson, R.; Teuber, H. J. *Chem. Ind.* **1954**, 783.

107. For experimental evidence that suggests that transient indol-2-ones can be generated under mildly basic conditions, see: (a) Fuchs, J. R.; Funk, R. L. *Org. Lett.* **2005**, *7*, 677. For other examples in which indol-2-ones may have been generated, see: (b) Hinman, R. L.; Bauman, C. P. *J. Org. Chem.* **1964**, *29*, 2431. (c) Labroo, R. B.; Labroo, V. M.; King, M. M.; Cohen, L. A. *J. Org. Chem.* **1991**, *56*, 3637. (d) Rajeswaran, W. G.; Labroo, R. B.; Cohen, L. A.; King, M. M. *J. Org. Chem.* **1999**, *64*, 1369. (d) Kobayashi, M.; Aoki, S.; Gato, K.; Matsunami, K.; Kurosu, M.; Kitagawa, I. *Chem. Pharm. Bull.* **1994**, *42*, 2449.

108. For Stoltz's proposed biosynthetic pathway, and a synthesis of the communesin core ring system, see: (a) May, J. A.; Zeidan, R. K.; Stoltz, B. M. *Tetrahedron Lett.* **2003**, *44*, 1203. (b) reference 105 (b).

109. For our group's total synthesis of perophoramidine, see: (a) Fuchs, J. R.; Funk, R. L. *J. Am. Chem. Soc.* **2004**, *126*, 5068. For Weinreb's synthetic efforts directed towards perophoramidine, see: (b) Artman, G. D., III; Weinreb, S. M. *Org. Lett.* **2003**, *5*, 1523. For Qin's synthetic efforts

towards communesin B and perophoramidine, see: (c) Yang, J.; Xong, H.; Xiao, X.; Wang, J.; Qin, Y. *Org. Lett.* **2006**, *8*, 2187.

110. Additional alternative pathways for the formation of indolenine **275** include direct displacement and transfer alkylation. For respective examples of each, see: (a) Monde, K.; Taniguchi, T.; Miura, N.; Nishimura, S.-I.; Harada, N.; Dukor, R. K.; Nafie, L. A. *Tetrahedron Lett.* **2003**, *44*, 6017. (b) Melvin, L. S., Jr.; Trost, B. M. *J. Am. Chem. Soc.* **1972**, *94*, 1790.
111. For a review on the synthesis and applications of aza-*ortho*-xylylenes, see: Wojciechowski, K. *Eur. J. Org. Chem.* **2001**, 3587.
112. (a) Bowen, R. D.; Davies, D. E.; Fishwick, C. W. G.; Glasbey, T. O.; Noyce, S. J.; Storr, R. C. *Tetrahedron Lett.* **1982**, *23*, 4501. (b) Hodgetts, I.; Noyce, S. J.; Storr, R. C. *Tetrahedron Lett.* **1984**, *27*, 5435. (c) Fishwick, C. W. G.; Storr, R. C.; Manley, P. W. *J. Chem. Soc., Chem. Commun.* **1984**, 1304. (d) Consonni, R.; Dallacroce, R.; Ferraccioli, C.; LaRosa, C. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1809. (e) Ohno, M.; Sato, H.; Eguchi, S. *Synlett.* **1999**, 207.
113. (a) Wiebe, J. M.; Caille, A. S.; Trimble, L.; Lau, C. K. *Tetrahedron* **1996**, *52*, 11705. (b) Migneault, D.; Bernstein, M. A.; Lau, C. K. *Can. J. Chem.* **1995**, *73*, 1506.
114. Nishiyama, K.; Kubo, H.; Sato, T.; Higashiyama, K.; Ohmiya, S. *Heterocycles* **1998**, *48*, 1103.
115. (a) Steinhagen, H.; Corey, E. J. *Angew. Chem. Int. Ed.* **1999**, *111*, 2054. (b) Steinhagen, H.; Corey, E. J.; *Org. Lett.* **1999**, *1*, 823.
116. Ruano, J. L. G.; Pedrega, C.; Rodriguez, J. H. *Tetrahedron* **1989**, *45*, 203.
117. (a) Shono, T.; Matsumura, Y.; Uchida, K.; Tsubata, K.; Makino, A. *J. Org. Chem.* **1984**, *49*, 300. Other hydrolysis conditions that were examined include: (a) NaOH, H_2O, EtOH; (b) KOH, $HOCH_2CH_2OH$, 100 °C; (c) KOH, EtOH, 60 °C; (d) Red-Al, benzene, 60 °C; (e) BuLi, THF, -78 °C. However, none of these conditions were successful in hydrolyzing the ethyl carbamate cleanly.

118. For a review on the chemistry of cerium, see: (a) Ho, T.-L. *Synthesis* **1973**, 347. For a leading reference on the addition of nucleophiles to DDQ generated benzylic cations, see: (b) Xu, Y.-C.; Roy, C.; Lebeau, E. *Tetrahedron Lett.* **1993**, *51*, 8189. For recent synthetic applications of DDQ in this context, see: (c) Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S.; Jung, J.; Choi, H.-S.; Yoon, W. H. *J. Am. Chem. Soc.* **2002**, *124*, 2202. (d) Charmantray, F.; Demeunynck, M.; Wardani, A.; Lhomme, J. *Syn. Comm.* **2001**, *31*, 2001. For recent synthetic applications of cerium in this context, see: (e) Wood, J. L.; Porco, J. A., Jr.; Taunton, J.; Lee, A. Y.; Clardy, J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 5898. (f) Elbaum, D.; Porco, J. A., Jr.; Stout, T. J.; Clardy, J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1995**, *117*, 211. (g) Bruncko, M.; Crich, D.; Samy, R. *J. Org. Chem.* **1994**, *59*, 5543. For the application of the DDQ alternative chloranil, see: (h) Müller, A.; Maier, A.; Neumann, R.; Maas, G. *Eur. J. Org. Chem.* **1998**, 1177. For a recent benzylic bromination using NBS and radical initiators, see: (i) Hideg, K.; Sar, C. P., Jeko, J. *Synthesis* **1998**, 1497. (j) Mehta, G.; Sengupta, S. *Tetrahedron Lett.* **1996**, *37*, 8625. (k) Silva, A. M. S.; Silva, A. M. G.; Tome, A. C.; Cavaleiro, J. A. S. *Eur. J. Org. Chem.* **1999**, 135.

119. For references pertaining to the displacement of benzylic alcohols with allyltrimethylsilane, see: (a) Muratake, H.; Natsume, M. *Tetrahedron* **1990**, *40*, 6331.; (b) McCombie, S.; Cox, B.; Ganguly, A. K. *Tetrahedron Lett.* **1991**, *32*, 2087. (c) Hobbs-Mallyon, D.; Li, W.; Whiting, D. A. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1511. (d) Kaur, G.; Kaushik, M.; Trehan, S. *Tetrahedron Lett.* **1997**, *38*, 2521.

120. The *cis* epoxide **342** could be prepared efficiently from **330** using DBU in CH_2Cl_2 at room temperature (70%).

121. For a recent application of the Darzens reaction using phase transfer conditions to make the 4-nitro epoxide analogous to **257** see: (a) Arai, S.; Suzuki, Y.; Tokumaru, K.; Shioiri, T. *Tetrahedron Lett.* **2002**, *43*, 833. For the seminal publications on the Darzens glycidic ester condensation, see: (b) Erlenmeyer, E. *Lieb. Ann. Chem.* **1892**, *271*, 137. (c) Claisen, L. *Ber.*

1905, *38*, 693. (d) Darzens, G. *Compt. Rend.* **1911**, *151*, 883. For reviews on the Darzens reaction, see: (e) Newman, M. S.; Magerlein, B. J. *Org. React.* **1949**, *5*, 413. (f) Ballester, M. *Chem. Rev.* **1955**, *55*, 283.

122. For references pertaining to the Lewis Acid catalysis of epoxide aminolysis, see: (a) Chakraborti, A. K.; Kondaskar, A. *Tetrahedron Lett.* **2003**, *44*, 8315 and references therein. (b) Chini, M.; Crotti, P.; Macchia, F. *Tetrahedron Lett.* **1990**, *32*, 4661. (c) Chini, M.; Crotti, P.; Macchia, F. *J. Org. Chem.* **1991**, *56*, 5939. (d) Augé, J.; Leroy, F. *Tetrahedron Lett.* **1996**, *43*, 7715. (e) Sekar, G.; Singh, V. K. *J. Org. Chem.* **1999**, *64*, 287. (f) Fujiwara, M.; Imada, M.; Baba, A.; Matsuda, H. *Tetrahedron Lett.* **1989**, *30*, 739. (g) Chini, M.; Crotti, P.; Favero, L.; Macchia, F.; Pineschi, M. *Tetrahedron Lett.* **1994**, *35*, 433. (h) Harris, C. E.; Fisher, G. B.; Beardsley, D.; Lee, L.; Goralski, C. T.; Nicholson, L. W.; Singaram, B. *J. Org. Chem.* **1994**, *59*, 7746. For the use of aluminum amides for the aminolysis of epoxides, see: (i) Overman, L. E.; Flippin, L. A. *Tetrahedron Lett.* **1981**, *22*, 195. For high-pressure promoted aminolysis of epoxides, see: (j) Kotsuki, H.; Shimanouchi, T.; Teraguchi, M.; Kataoka, M.; Tatsukawa, A.; Nishizawa, H. *Chem. Lett.* **1994**, 2159. (k) Meguro, M.; Asao, N.; Yamamoto, Y. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2597.

123. For references pertaining to the difficulty of bulky amines participating in aminolysis of epoxides, see: (a) Freifelder, M.; Stone, M. *J. Org. Chem.* **1961**, *26*, 1477. (b) Sundaram, P. K.; Sharma, M. M. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 3141.

124. For a recent example of an epoxidation using *m*-CPBA in the presence of base, see: Pale, P.; Chuche, J. *Eur. J. Org. Chem.* **2000**, 1019.

125. For a similar *anti*-selective aldol reaction between an oxazolidine-based chiral glycine enolate and isobutyraldehyde, wherein an internal lithium-amine chelated (*Z*)-enolate was proposed, see: (a) Panek, J. S.; Masse, C. E. *J. Org. Chem.* **1998**, *63*, 2382. For another example of a diastereoselective aldol condensation of a glycine ester with aldehydes, see: (b) Shanzer, A.; Somekh, L.; Butina, D.; *J. Org. Chem.* **1979**, *44*,

3967. For the generation of another chelated (*Z*)-enolate, see: (c) Georg, G. I.; Akgün, E. *Tetrahedron Lett.* **1991**, *32*, 5521.

126. For the seminal publications on the Mannich reaction, see: (a) Mannich, C. *Arch. Pharm.* **1917**, *255*, 261. For reviews on the Mannich reaction, see: (b) Tramontini, M. *Synthesis* **1973**, 703. (c) Tramontini, M.; Angiolini, L. *Tetrahedron* **1990**, *46*, 1791. (d) Kleinman, E. F. *Comprehensive Organic Synthesis* Eds. Trost, B. M.; Fleming, I., Pergamon, Oxford: **1991**, *2*, 893. (e) Overman, L. E.; Ricca, D. J. *Comprehensive Organic Synthesis* Eds. Trost, B. M.; Fleming, I., Pergamon, Oxford: **1991**, *2*, 1007. (f) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem. Int. Ed.* **1998**, *37*, 1045.

127. (a) Hellman, H.; Hallman, G.; Lingens, F. *Chem. Ber.* **1953**, 1346. For other examples of 3-alkyl-3-hydroxyoxindole participating in Mannich reactions, see: (b) Horning, E. C.; Rutenberg, M. W. *J. Am. Chem. Soc.* **1950**, *72*, 3534.

128. For the preparation of 3-chlorooxindole, see: (a) Guillaumel, J.; Demerseman, P.; Clavel, J.-M.; Royer, R. *Tetrahedron* **1980**, *36*, 2459. (b) Guillaumel, J.; Demerseman, P.; Clavel, J. -M.; Royer, R. *J. Het. Chem.* **1980**, *17*, 1531. For the preparation of 3-bromooxindole, see: (c) Tacconi, G.; Righetti, P. P.; Desimoni, G. *J. Prakt. Chem.* **1980**, *322*, 679.

129. For an alternate reduction of isatin to 3-hydroxyoxindole using hydrogenation with Raney-Nickel, see: Porcs-Makkya, M.; Volk, B.; Kapiller-Dezsoefi, R.; Mezei, T.; Simig, G.; *Monatsh. Chem.* **2004**, *135*, 697.

130. For similar transformations of 3-hydroxyoxindoles, see: (a) Bell, S. E. V.; Brown, R. F. C.; Eastwood, F. W.; Horvath, J. M. *Aust. J. Chem.* **2000**, *53*, 183. (b) Miah, S.; Moody, C. J.; Richards, I. C.; Slawin, A. M. Z. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2405. (c) Akhmetova, G. Z.; Gurevich, P. A.; Moskva, V. V.; Arkhipov, V. P. *Russ. J. Gen. Chem.* **1999**, *69*, 155. (d) Ogata, M.; Matsumoto, H.; Tawara, K. *Eur. J. Med. Chem.* **1980**, *16*, 373. (e) Munusamy, R.; Dhathathreyan, K. S.; Balasubramanian, K. K.; Venkatachalam, C. S. *J. Chem. Soc., Perkin Trans. 2* **2001**, 1154. (f) Yu,

Q.-S.; Li, Y.-Q.; Luo, W.; Brossi, A. *Heterocycles* **1993**, *36*, 1791. (g) Fejes, I.; Toke, L.; Nyerges, M.; Pak, C. S. *Tetrahedron* **2000**, *56*, 639. (h) Garden, S. J.; da Silva, R. B.; Pinto, A. C. *Tetrahedron* **2002**, *58*, 8399. (i) Black, D. StC.; Ivory, A. J.; Kumar, N. *Tetrahedron* **1996**, *52*, 7003.

131. For references on the acylation of tertiary and tertiary benzylic alcohols, see: (a) Date, M.; Tamai, Y.; Hattori, T.; Takayama, H.; Kamikubo, Y.; Miyano, S. *J. Chem. Soc., Perkin Trans 1* **2001**, 645. (b) Vedejs, E.; Daugulis, O. *J. Org. Chem.* **1996**, *61*, 5702. (c) Ishihara, K.; Kubota, M.; Kurihara, H.; Yamamoto, H. *J. Org. Chem.* **1996**, *61*, 4560. (d) Orita, A.; Tanahashi, C.; Kakuda, A.; Otera, J. *Angew. Chem. Int. Ed.* **2000**, *39*, 2877. (e) Chakraborti, A. K.; Gulhane, R. *Tetrahedron Lett.* **2003**, *44*, 6749. (f) Saravanan, P.; Singh, V. K. *Tetrahedron Lett.* **1999**, *40*, 2611. (g) Kita, Y.; Sekihachi, J.; Hayshi, Y.; Da, Y. -Z.; Yamamoto, M.; Akai, S. *J. Org. Chem.* **1990**, *55*, 1108. For the conversion of tertiary alcohols to tosylates, see: (h) Hartung, J.; Hunig, S.; Kneuer, R.; Schwarz, M.; Wenner, H. *Synthesis*, **1997**, 1433. (i) Racouchot, S.; Sylvestre, I.; Ollivier, J.; Kozyrkov, Y. Y.; Pukin, A.; Kulinkovich, O. G.; Salaün, J. *Eur. J. Org. Chem.* **2002**, 2160. For the conversion of tertiary alcohols to carbonates, see: (j) Takeuchi, K.; Kurosaki, T.; Okamoto, K. *Tetrahedron* **1980**, *36*, 1557. (k) Fujio, M.; Ohe, M.; Nakata, K.; Tsuji, Y.; Mishima, M.; Tsuno, Y. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 929. For the conversion of tertiary alcohols to carbamates via reaction with isocyanates, see: (l) Francis, T.; Thorne, M. P. *Can. J. Chem.* **1976**, *54*, 24. (m) Grehn, L.; Almeida, L. S.; Ragnarsson, U. *Synthesis* **1988**, 992. (n) Kim, Y. H.; Park, H. S. *Synlett* **1998**, 261. (o) Ashimori, A.; Bachand, B.; Calter, M. A.; Govek, S. P.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6488. (p) For the functionalization of a tertiary alcohol β to a tertiary amine, see: Hodgson, D. M.; Maxwell, C. R.; Matthews, I. R. *Synlett* **1998**, 1349.

132. Perez-Serrano, L.; Casarrubios, L.; Dominguez, G.; Freire, G.; Perez-Castells, J. *Tetrahedron* **2002**, *58*, 5407.

133. Hinman, R. L.; Bauman, C. P. *J. Org. Chem.* **1964**, *29*, 2431.

134. The communesins are hypothesized to be biosynthetically derived from two tryptamine moieties, see chapter 2.

135. For reviews on alkene-amine cyclizations, see: (a) Frederickson, M.; Grigg, R. *Org. Prep. Proc. Int.* **1997**, *29*, 33. (b) Frederickson, M.; Grigg, R. *Org. Prep. Proc. Int.* **1997**, *29*, 63.

136. For a review on aziridinium ions used in the synthesis of piperidines, see: (a) Cossy, J.; Pardo, D. G. *Chemtracts* **2002**, *15*, 579. For related examples, see (b) Blough, B. E.; Macarella, S. W.; Rothman, R. B.; Carroll, F. I. *J. Chem. Soc., Chem. Commun.* **1993**, 758. (c) Bubnov, Y. N.; Misharin, M. A.; Ignatenko, A. V. *Tetrahedron Lett.* **1997**, *38*, 6259. For other recent examples of nucleophilic aziridinium ion openings in the context of natural product synthesis, see: (d) Dehmlow, H.; Mulzer, J.; Seilz, C.; Strecker, A. R.; Kohlmann, A. *Tetrahedron Lett.* **1992**, *33*, 3607. (e) Williams, D. R.; Brown, D. L.; Benbow, J. W. *J. Am. Chem. Soc.* **1989**, *111*, 1923. (f) Overman, L. E.; Sharp, M. J. *J. Org. Chem.* **1992**, *57*, 1035.

137. For a related example, see: Shi, Z.-C.; Zeng, C.-M.; Lin, G.-Q. *Heterocycles* **1995**, *41*, 277.

138. For the acetic acid catalyzed opening of *N*-ethoxycarbonyl benzylic aziridines, see: (a) Takeuchi, H.; Koyama, K. *J. Chem. Soc., Perkin Trans. 2* **1981**, 121. For the Lewis-acid catalyzed ring opening of *N*-sulfonyl benzylic aziridines by aromatic compounds, such as indole and pyrrole, see: (b) Yadov, J. S.; Reddy, B. V. S.; Abraham, S.; Sabitha, G.; *Tetrahedron Lett.* **2002**, *43*, 1565. (c) Yadov, J. S.; Reddy, B. V. S.; Parimala, G. *Synlett* **2002**, 1143.

139. For conversion of a 1,2-aminoalcohol to the 1,2-aminohalide with concomitant formation of the corresponding aziridine, see: (a) Deyrup, J. A.; Moyer, C. L. *J. Org. Chem.* **1969**, *34*, 175. For a related transformation, see: (b) Yeheskiely, E. K.; Lodder, M.; van der Marel, G. A.; van Bloom, J. H. *Tetrahedron Lett.* **1992**, *33*, 3013. For conversion of a 1,2-aminoalcohol to the corresponding aziridine via the tosylate, see: (c) Daub, G. W.; Heerding, D. A.; Overman, L. E. *Tetrahedron* **1988**, *13*,

3919. For an example of aziridine synthesis via the 1,2-alcohol via internal Mitsunobu reaction (treatment with phosphine) see: (d) Kelly, J. W.; Eskew, N. L.; Evans, S. A., Jr. *J. Org. Chem.* **1986**, *51*, 95. For recent examples of the synthesis of aziridines from azido-alcohols, see: (e) Legters, J.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* **1989**, *30*, 4881. (f) Tanner, D.; Somfai, P. *Tetrahedron* **1988**, *44*, 619. For recent examples of nitrene additions with **295** to make aziridines, see: (g) Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1994**, *116*, 2742. (h) Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Org. Chem.* **1991**, *56*, 6744. For reviews on nitrene-based aziridine synthesis, see: (i) Lwowski, W.; *Nitrenes*; Lwowski, W., Ed.; Interscience: New York, **1970**, pp 185-224. (j) Edwards, O. E. *Nitrenes*; Lwowski, W., Ed.; Interscience: New York, **1970**; pp 225-247. (k) Lwowski, W. *Azides and Nitrenes, Reactivity and Utility*; Scriven, E. F. V., Ed.; Academic: New York,**1984**; pp 205-246. For recent examples of the 1,4-addition of ammonia to an α-haloenone, see: (l) Ploux, O.; Caruso, M.; Chassaing, G.; Marquet, A. *J. Org. Chem.* **1988**, *53*, 3154. (m) Tokés, A.; Likei, G.; Janzsó, G. *Syn. Comm.* **1990**, *20*, 1905. For reviews on the synthesis and chemistry of aziridines, see: (n) Pearson, W. H.; Lian, B. W.; Bergmeier, S. C. *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R.; Reis, C. W.; Scriven, E. F.; Padwa, A. R., eds., Pergamon, New York: **1996**, vol 7, p. 61-97. (o) McCoull, W.; Davis, F. A. *Synthesis* **2000**, 1347. (p) Osborn, H. M. I.; Sweeney, J. *Tetrahedron: Asymm.* **1997**, *8*, 1693. (q) Tanner, D. *Angew. Chem. Int. Ed.* **1994**, *33*, 599. (r) Watson, I. D. G.; Yu, L.; Yudin, A. K. *Acc. Chem. Res.* **2006**, *39*, 194. (s) Hu, X. E. *Tetrahedron* **2004**, *60*, 2701.

140. For biological studies pertaining to aziridines and aziridinium ions, see: (a) Jones, G. B.; Mathews, J. E. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 93. (b) Rink, S. M.; Solomon, M. S.; Taylor, M. J.; Rajur, S. B.; McGlaughlin, L. W.; Hopkins, P. B. *J. Am. Chem. Soc.* **1993**, *115*, 2551 and references therein.

141. For the structural elucidation of Mitomycin B, see: (a) Yahashi, R.; Matsuhura, I. *J. Nat. Prod.* **1976**, *29*, 104. For the isolation of the Mitomycins, see: (b) Lefemine, D. V.; Dann, M.; Barbatschi, F.; Hausmann, W. K.; Zbinovsky, V.; Monnikendam, P.; Adam, J.; Bohnos, N. *J. Am. Chem. Soc.* **1962**, *34*, 3184. For a review on the biological activity and the structure-activity relationship of the mitomycins, see: (c) Kasai, M.; Kono, M. *Synlett* **1992**, 778. For the isolation of FR-900482, see: (d) Uchida, I.; Shigehiro, T.; Hiroshi, K.; Sumio, K.; Hashimoto, M.; Tada, T.; Shigetaka, K.; Morimoto, Y. *J. Am. Chem. Soc.* **1987**, *109*, 4108. For a review on the biological activity and its structure-activity relationship, see: (e) Williams, R. M.; Rajski, S. R. *Chem. Rev.* **1998**, *98*, 2723. For the isolation of ficellomycin, see: (f) Argoudelis, A. D.; Reusser, F.; Whaley, H. A.; Baczynsky, L.; Mizsak, S. A.; Wnuk, R. J. *J. Antibiot.* **1976**, *29*, 1001.

142. For the ring openings of aziridines derived from *trans*-glycidic esters, see: (a) Chuang, T.-H.; Sharpless, K. B. *Org. Lett.* **1999**, *1*, 1435. (b) Chuang, T.-H.; Sharpless, K. B. *Org. Lett.* **2000**, *2*, 3555. (c) Chuang, T.-H.; Sharpless, K. B. *Helv. Chim. Acta.* **2000**, *83*, 1734.

143. (a) Davoli, P.; Forni, A.; Moretti, I.; Prati, F.; Torre, G. *Tetrahedron* **2001**, *57*, 1801. For a related aziridine synthesis, see: (b) Comstock, L. R.; Rajski, S. R. *Tetrahedron* **2002**, *58*, 6019.

144. Fujii, N.; Nakai, K.; Habashita, H.; Hotta, Y.; Tamamura, H.; Otaka, A.; Ibuka, T. *Chem. Pharm. Bull.* **1994**, *42*, 2241.

145. For references pertaining to the pKa determination of $HNTf_2$, see: (a) Ruff, J. K. *Inorg. Chem.* **1965**, *4*, 1446. (b) Foropoulos, J., Jr.; DesMarteau, D. D. *Inorg. Chem.* **1990**, *29*, 2982. For literature concerning the synthesis and properties of $HNTF_2$ and related catalysts, see: (c) Vij, A.; Zheng, Y. Y.; Kirchmeier, R. L.; Shreeve, J. M. *Inorg. Chem.* **1994**, *33*, 3281. (d) Kaur, G.; Manju, K.; Trehan, S. *J. Chem. Soc., Chem. Commun.* **1996**, 581. (e) Desmarteau, D. D.; Witz, M. *J. Fluorine Chem.* **1991**, *52*, 7. For recent synthetic applications of $HNTf_2$, see: (f) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 10204. (g) Kuhnert, N.; Peverley, J.;

Robertson, J. *Tetrahedron Lett.* **1998**, *39*, 3215. (h) Ishihara, K.; Hiraiwa, Y.; Yamamoto, H. *Synlett* **2001**, 1851.

146. For an analogous transformation of an aniline to a formamide, see: (a) Sumi, S.; Matsumoto, K.; Tokuyama, H.; Fukuyama, T.; *Org. Lett.* **2003**, *5*, 1891. For an analogous *N*-acylation to provide a TEOC (2-tremethylsilyl)-ethoxy carbonyl), see: (b) Lundkvist, J. R. M.; Vargas, H. M.; Caldirola, P.; Ringdahl, B.; Hacksell, U. *J. Med. Chem.* **1990**, *33*, 3182.

147. For examples of hydroxide mediated hydrolysis of carbamates, see: (a) Wee, A. G. H.; Liu, B.; Zhang, L. *J. Org. Chem.* **1992**, *57*, 4404. (b) Wenkert, E.; Hudlicky, T.; Showalter, H. D. H. *J. Am. Chem. Soc.* **1978**, *100*, 4893. (c) Taylor, E. C.; Liu, B. *J. Org. Chem.* **2001**, *66*, 3726. Yamada, O.; Ogasawara, K. *Tetrahedron Lett.* **1998**, *39*, 7747. (d) Waserman, H. H.; Robinson, R. P.; Carter, C. G. *J. Am. Chem. Soc.* **1983**, *105*, 1697. (e) Holland, H. L.; Brown, F. M.; Lozada, D.; Mayne, B.; Szerminski, W. R.; van Vliet, A. J. *Can. J. Chem.* **2002**, *80*, 633. (f) Crich, D.; Lim, L. B. *Heterocycles* **1993**, *36*, 1199.

148. For examples of TMS-I mediated cleavage of methyl carbamates, see: (a) Jung, M. E.; Lyster, M. A. *J. Am. Chem. Soc.* **1977**, *99*, 968. (b) Jung, M. E.; Lyster, M. A. *J. Chem. Soc., Chem. Commun.* **1978**, 315. (c) Suga, S.; Watanabe, M.; Yoshida, J. *J. Am. Chem. Soc.* **2002**, *124*, 14824. (d) Kozmin, S. A.; Iwama, T.; Huang, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 4628. (e) Cooper, J.; Knight, D. W.; Gallagher, P. T. *J. Chem. Soc., Perkin Trans. 1* **1991**, 705. For the *in situ* generation of TMSI, see: (f) Kende, A. S.; Luzzio, M. J.; Mendoza, J. S. *J. Org. Chem.* **1990**, *55*, 918. (g) Brands, K. M. J.; Pandit, U. K. *Tetrahedron Lett.* **1989**, *30*, 1423.

149. For the hydroxide cleavage of formamides, see: (a) Lukács, A.; Szabó, L.; Hazai, L.; Szántay, C.; Mák, M.; Gorka, A.; Szántay, C. *Tetrahedron* **2001**, *57*, 5843. For the acid mediated deprotection of formamides, see: (b) Humber, L. G.; Ferdinandi, E.; Demerson, C. A.; Ahmed, S.; Shah, U.; Mobilio, D. Sabatucci, J.; De Lange, B.; Labbadia, F.; Hughes, P.; DeVergilio, J.; Newman, G.; Chau, T. T.; Weichman, B. M. *J. Med. Chem.*

1988, *31*, 1712. For the *in situ* generation of HCl to remove a formamide, see: (c) Keating, T. A.; Armstrong, R. W. *J. Am. Chem. Soc.* **1996**, *118*, 2574.

150. For examples of transfer hydrogenation to deprotect a Cbz-amide, see: (a) Coleman, R. S.; Carpenter, A. J. *J. Org. Chem.* **1992**, *57*, 5813. (b) Wipf, P.; Uto, Y. *J. Org. Chem.* **2000**, *65*, 1037. (c) Felix, A. M.; Heimer, E. P.; Lambros, T. J.; Tzougraki, C.; Meienhofer, J.; *J. Org. Chem.* **1978**, *43*, 4194. (d) Sakaitani, M.; Ohfune, Y. *J. Org. Chem.* **1990**, *55*, 870. (e) Kamatani, A.; Overman, L. E. *Org. Lett.* **2001**, *3*, 1230.
151. Feldman, K. S.; Cutarelli, T. D.; Di Florio, R. *J. Org. Chem.* **2002**, *67*, 8528.
152. Ito, Y.; Nakajo, E.; Nakatsuka, M.; Saegusa, T. *Tetrahedron Lett.* **1983**, *28*, 2881.
153. For other metal catalyzed intramolecular amine-alkyne cyclizations, see: (a) Li, Y.; Fu, P.-F.; Marks, T. J. *Organometallics* **1994**, *13*, 439. (b) Li, Y.; Marks, T. J. *J. Am. Chem. Soc.* **1996**, *118*, 707. (c) Li, Y.; Marks, T. J. *Organometallics* **1996**, *15*, 3770. (d) Li, Y.; Marks, T. J. *J. Am. Chem. Soc.* **1998**, *120*, 1757. (e) For an example of a Au / Ag co-catalyst system, see: (f) Kennedy-Smith, J. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 4526. For a review on gold catalysis, see: (g) Dyker, G.; *Angew. Chem. Int. Ed.* **2000**, *39*, 4327. (h) Arcadi, A.; Di Giuseppe, S. *Curr. Org. Chem.* **2004**, *8*, 795. (i) Hoffmann-Röder, A.; Krause, N. *Org. Biomol. Chem.* **2005**, *3*, 387.
154. For a gold-catalyzed bridgehead enamine synthesis, see: Kadzimirsz, D.; Hildebrandt, D.; Merz, K.; Dyker, G. *Chem. Commun.* **2006**, 661.
155. Kirby, A. J.; Komarov, I. V.; Wothers, P. D. ; Feeder, N. *Angew. Chem. Int. Ed.* **1998**, *37*, 785.
156. Amoroso, R.; Cardillo, G.; Sabatino, P.; Tomasini, C.; Trerè, A. *J. Org. Chem.* **1993**, *58*, 5615.
157. Corey, E. J.; Myers, A. G. *Tetrahedron Lett.* **1984**, *25*, 3559.

158. For the seminal publication on the Beckmann rearrangement, see: (a) Beckmann, E. *Ber. Dtsch. Chem. Ges.* **1886**, *19*, 988. For a review, see: (b) Donaruma, L. G.; Heldt, W. Z. *Org. React.* **1960**, *11*, 1.

159. For related examples of cyclobutanone formation via rhodium-mediated C-H insertion, see: (a) Ceccherelli, P.; Curini, M.; Marcotullio, M. C.; Pisani, E.; Rosati, O. *Tetrahedron* **1997**, *53*, 8501. (b) Mander, L. N.; Wells, A. P. *Tetrahedron Lett.* **1997**, *38*, 5709. (c) Padwa, A.; Austin, D. J.; Price, A. T.; Semones, M. A.; Doyle, M. P.; Protopopova, M. N.; Winchester, W. R.; Tran, A. *J. Am. Chem. Soc.* **1993**, *115*, 8669. (d) Doyle, M. P.; Shanklin, M. S.; Oon, S.-M.; Pho, H. Q.; van der Heide, F. R.; Veal, W. R. *J. Org. Chem.* **1988**, *53*, 3386. (e) For a review on rhodium mediated C-H insertions, see: (f) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091. (g) Davies, H. M. L. *Chem. Rev.* **2003**, *103*, 2861.

160. This unwanted side reaction is precedented, see: Padwa, A.; Hornbuckle, S. F.; Fryxell, G. E.; Stull, P. D. *J. Org. Chem.* **1989**, *54*, 517.

161. For aminal formation via reduction of amides, see: (a) Overman, L. E.; Paone, D. V. *J. Am. Chem. Soc.* **2001**, *123*, 9465. (b) Huang, A.; Kodanko, J. J.; Overman, L. E. *J. Am. Chem. Soc.* **2004**, *126*, 14043. (c) Matsuura, T.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6500. (d) Grieco, P. A.; Carroll, W. A. *Tetrahedron Lett.* **1992**, *33*, 4401. (e) reference 104a. (f) Meyers, A. I.; Hanreich, R.; Wanner, K. T. *J. Am. Chem. Soc.* **1985**, *107*, 7776. (g) Rege, P. D.; Johnon, F. *J. Org. Chem.* **2003**, *68*, 6133. (h) Kawasaki, T.; Shinada, M.; Kamimura, D.; Ohzono, M.; Ogawa, A. *J. Chem. Soc., Chem. Commun.* **2006**, 420. For aminal formation via reduction of imides, see: (h) Govek, S. P.; Overman, L. E. *J. Am. Chem. Soc.* **2001**, *123*, 9468.

162. For the seminal publication of the Lemieux-Johnson oxidation, see: Pappo, R.; Allen, D. S., Jr.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478.

163. Alford, E. J.; Schofield, K. *J. Chem. Soc.* **1952**, 2102.

164. For amide formation using EDCI, see: (a) Herpin, T. F.; Yu, G.; Carlson, K. E.; Morton, G. C.; Wu, X.; Kang, L.; Tuerdi, H.; Khanna, A.; Tokarski, J. S.; Lawrence, R. M.; Macor, J. E. *J. Med. Chem.* **2003**, *46*, 1123. We also explored making the amide via 1) HOBT / EDCI / NEt_3; 2) PYBOP / DIPEA; 3) DCC / DMAP; or 4) via the isopropyl mixed anhydride derivative of the acid, but all of the above conditions gave poor yields or decomposition. For other preparations of amides from carboxylic acids and amines, see: (b) Zask, A.; Birnberg, G.; Cheung, K.; Kaplan, J.; Chuan, N.; Norton, E.; Suayan, R.; Yamashita, A.; Cole, D.; Tang, Z.; Krishnamurthy, G.; Williamson, R.; Khafizova, G.; Musto, S.; Hernandez, R.; Annable, T.; Yang, X.; Discafani, C.; Beyer, C.; Greenberger, L. M.; Loganzo, F.; Kaloustian, S. A. *J. Med. Chem.* **2004**, *47*, 4774. (c) Boger, D. L.; Goldberg, J.; Satoh, S.; Ambroise, Y.; Cohen, S. B.; Vogt, P. K. *Helv. Chim. Acta.* **2000**, *83*, 1825.

165. It is well precedented that Lewis acid catalysis can greatly accelerate cycloadditions, see: Fringuelli, F.; Taticchi, A. *The Diels-Alder Reaction:Selected Practical Methods* Wiley, New York, NY, **2002**.

166. The *in situ* generation of Co_2B has been demonstrated to be a mild reducing agent. For another example of the reduction of nitriles in the presence of amides, see: (a) O'Brien, P. M.; Sliskovic, D. R.; Blankley, C. J.; Roth, B. D.; Wilson, M. W.; Hamelehle, K. L.; Krause, B. R.; Stanfield, R. L. *J. Med. Chem.* **1994**, *37*, 1810. For the seminal publications on the *in situ* generation and use of Co_2B, see: (b) Heinzman, S. W.; Ganem, B. *J. Am. Chem. Soc.* **1982**, *104*, 6801. (c) Osby, J. O.; Heinzman, S. W.; Ganem, B. *J. Am. Chem. Soc.* **1986**, *108*, 67. For other metal boride complexes, see: (d) Dhawan, D.; Grover, S. K. *Syn. Comm.* **1992**, *22*, 2405. (e) Adams, C. *Syn. Comm.* **1984**, *14*, 1349. (f) Itsuno, S.; Sakurai, Y.; Ito, K. *Synthesis* **1988**, 995. For a review on metal borides, see: (g) Ganem, B.; Osby, J. O. *Chem. Rev.* **1986**, *86*, 763. (h) For an example of the reduction of a nitrile in the presence of an alkene using metal borides, see: (b).

167. For a reductive amination with *p*-methoxybenzaldehyde, see: Cohen, S. B.; Halcomb, R. L. *J. Am. Chem. Soc.* **2002**, *124*, 2534.

168. For reductive amination of an aldehyde with NH_4Oac, see: (a) Zhou, P.; Berova, N.; Wiesler, W. T.; Nakanishi, K. *Tetrahedron* **1993**, *49*, 9343. (b) Collingnon, N.; Fabre, G.; Varlet, J. M.; Savignac, P. *Phosphorus Sulfur* **1981**, *18*, 81. (c) Sasaki, T.; Ohno, M.; Ito, E. *Bull. Chem. Soc. Jpn.* **1984**, 899.

169. For similar reactions to form an aminal, see: (a) Morales-Ríos, M. S.; Bucio, M. A.; Joseph-Nathan, P. *Tetrahedron* **1996**, *52*, 5339l. (b) Yu, Q.-S.; Luuo, W.; Holloway, H. W.; Utsuki, T.; Perry, T. A.; Lahiri, D. K.; Greig, N. H.; Brossi, A. *Heterocycles* **2003**, *61*, 529. (c) Pei, X.-F.; Greig, N. H.; Brossi, A. *Heterocycles* **1998**, *61*, 437. (d) Pei, X.-F.; Yu, Q.-S.; Lu, B.-Y.; Greig, N. H.; Brossi, A. *Heterocycles* **1996**, *61*, 229

170. For a similar reduction using borane, see: (a) Williams, S. J.; Hoos, R.; Withers, S. G. *J. Am. Chem. Soc.* **2000**, *122*, 2223. (b) van den Berg, R. J. B. H. N.; Noort, D.; Milder-Enacache, E. S.; van der Marel, G. A.; van Boom, J. H.; Benschop, H. P. *Eur. J. Org. Chem.* **1999**, 2593. (c) Ha, J. D.; Cha, J. K. *J. Am. Chem. Soc.* **1999**, *121*, 10012. (d) Pistia, G.; Hollingsworth, R. I. *Carb. Res.* **2000**, *328*, 467.

171. For a similar amide reduction using lithium or sodium, see: (a) Julian, P. L.; Pikl, J. *J. Am. Chem. Soc.* **1935**, *57*, 539 (b) Julian, P. L.; Pikl, J. *J. Am. Chem. Soc.* **1935**, *57*, 563.

172. For similar intramolecular transamidation reactions, see: (a) Langlois, N.; *Tetrahedron Lett.* **2002**, *43*, 9531. For other recent examples of transamidations, see: (b) Vasudevan, A.; Villamil, C. I.; Djuric, S. W. *Org. Lett.* **2004**, *6*, 3361. (c) Eldred, S. E.; Stone, D. A.; Gellman, S. H.; Stahl, S. S. *J. Am. Chem. Soc.* **2003**, *125*, 3422. (d) Kawasaki, T.; Kuoko, T.; Totsuka, H.; Hiramatsu, K.; *Tetrahedron Lett.* **2003**, *44*, 8849. (e) Lasri, J.; Gonzalez-Rosende, M. E.; Sepulveda-Arques, J. *Org. Lett.* **2003**, *5*, 3851.

173. For the seminal publication on the Pictet-Spengler reaction, see: (a) Pictet, A.; Spengler, T. *Chem. Ber.* **1911**, *44*, 2030. For a recent gold catalyzed

application, see: (b) Youn, S. W. *J. Org. Chem.* **2006**, *71*, 2521. For other recent applications, see: (c) Merriman, G. H.; Fink, D. M.; Freed, B. S.; Kurys, B. E.; Pavlek, S.; Varriano, J.; Paulus, E. F. *Synlett* **2000**, *1*, 137. (d) Katritzky, A. R.; Maimait, R.; Xu, Y.-J.; Akhmedova, R. G. *Synthesis* **2002**, 601. (e) Sanchez, I. H.; Larraza, M. I.; Flores, H. J.; Martell, E. A.; Linzaga, I.; Carter, A. A. *Heterocycles* **1985**, *23*, 251. Cesati, R. R., III; Katzenellenbogen, J. A. *Org. Lett.* **2000**, *2*, 3635. (f) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 10558. (g) Srinivasan, N.; Ganesan, A. *J. Chem. Soc., Chem. Commun.* **2003**, 916. For a review, see: (h) Hino, T.; Nakagawa, M. *Heterocycles* **1998**, *49*, 499.

174. For the seminal publication on the Bischler-Napieralski reaction, see: (a) Bischler, A.; Napieralski, B. *Chem. Ber.* **1893**, *26*, 1903. For an example of an indole participating in a similar reaction, see: (b) Lee, Y. S.; Min, B. J.; Park, Y. K.; Lee, J. L.; Lee, S. J.; Park, H. *Tetrahedron* **1999**, *55*, 12991. For recent examples, see: (c) Hoye, T. R.; Chen, M.; Hoang, B.; Mi, L.; Priest, O. P. *J. Org. Chem.* **1999**, *64*, 7184. (d) Bungar, C. J.; Morris, J. C. *Org. Lett.* **2002**, *4*, 631. (e) Alesso, E. N.; Ibañez, A. F.; Tombari, D. G.; Iglesias, G. Y. M. *J. Het. Chem.* **1989**, *26*, 25. (f) Ramesh, D.; Srinivasan, M. *Syn. Comm.* **1986**, *16*, 1523. (g) Nagubandi, S.; Fodor, G. *Heterocycles* **1981**, *15*, 165. (h) Pal, B.; Jaisankar, P.; Giri, V. S. *Syn. Comm.* **2003**, *33*, 2339. (h) Takano, S.; Akiyama, M.; Ogasawara, K. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2447. (i) Quirante, J.; Escolano, C.; Merino, A.; Bonjoch, J. *J. Org. Chem.* **1998**, *63*, 968. (j) Ishikawa, T.; Shimooka, K.; Narioka, T.; Noguchi, S.; Saito, T.; Ishikawa, A.; Yamazaki, E.; Harayama, T.; Seki, H.; Yamaguchi, K. *J. Org. Chem.* **2000**, *65*, 9143. For reviews, see: (k) Royer, J.; Bonin, M.; Micouin, L. *Chem Rev.* **2004**, *104*, 2311. (l) Fodor, G.; Nagubandi, S. *Tetrahedron* **1979**, *36*, 1300. (m) Chrzankowska, M.; Rozwadowska, M. D. *Chem. Rev.* **2004,** *104*, 3341.

175. Alternately, *N*-acylation with the respective benzoyl chlorides to give the amides, followed by reduction with lithium aluminum hydride was equally effective for the preparation of all three compounds.

176. For removal of a *N*-benzyl using hydrogenolysis, see: (a) Kozikowski, A. P.; Xia, Y.; Reddy, R.; Tückmantel, W.; Hanin, I.; Tang, X. C. *J. Org. Chem.* **1991**, *56*, 4639. (b) Gigg, R.; Conant, R. *Carbohydr. Res.* **1982**, *100*, C5. For removal of a *N*-PMB using hydrogenolysis, see: (c) Rigby, J. H.; Gupta, V. *Syn. Lett.* **1995**, 547.

177. For removal of a *N*-PMB using acidic conditions, see: (a) Baskaran, S.; Hanan, E.; Byun, D.; Shen, W. *Tetrahedron Lett.* **2004**, *45*, 2107. (b) Brooke, G. M.; Mohammed, S.; Whiting, M. C. *J. Chem. Soc., Chem. Commun.* **1997**, 1511. For removal of a *N*-benzyl using acidic conditions, see: (c) Semple, J. E.; Wang, P. C.; Lysenko, Z.; Joullie, M. M. *J. Am. Chem. Soc.* **1980**, *102*, 7505. (d) Baggiolini, E. G.; Lee, H. L.; Pizzolato, G.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1982**, *104*, 6460.

178. For the a similar deprotection of a *N*-DMB amide using TFA, see: Wood, J. L.; Stoltz, B. M.; Goodman, S. N. *J. Am. Chem. Soc.* **1996**, *118*, 10656.

179. For a similar transformation, see: reference 109 (a).

180. For a similar imide synthesis, see: Luker, T.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1997**, *62*, 8131.

181. For similar reductions of BOC-imides to hemiaminals, see: (a) Dieter, R. K.; Sharma, R. R. *J. Org. Chem.* **1996**, *61*, 4180. (b) Hanessian, S.; Tremblay, M.; Peteresen, J. F. W. *J. Am. Chem. Soc.* **2004**, *126*, 6064. (c) Fisher, M. J.; Overman, L. E. *J. Org. Chem.* **1990**, *55*, 1447. (d) Oliveira, D. F.; Miranda, P. C. M. L.; Correia, C. R. D. *J. Org. Chem.* **1999**, *64*, 6646. (e) Greico, P. A.; Kaufman, M. D. *J. Org. Chem.* **1999**, *64*, 6041. (f) Maligres, P. E.; Chartrain, M. M.; Upadhyay, V.; Cohen, D.; Reamer, R. A.; Askin, D.; Volante, R. P.; Reider, P. J. *J. Org. Chem.* **1998**, *63*, 9548. (g) Lerchner, A.; Carreira, E. M. *J. Am. Chem. Soc.* **2002**, *124*, 14826. (h) Marin, J.; Didierjean, C.; Aubry, A.; Casimir, J. R.; Briand, J.-P.; Guichard, G. *J. Org. Chem.* **2004**, *69*, 130. (i) Moeller, K. D.; Hanau, C. E. *Tetrahedron Lett.* **1992**, *33*, 6041. For similar reductions of *N*-tosylimides to hemiaminals, see: (j) Ahman, J.; Somfai, P. *Tetrahedron* **1992**, *48*, 9537. (k) Somfai, P.; Ahman, J. *Tetrahedron Lett.* **1992**, *33*, 3791.

182. For similar amide-alkene cyclizations, see: (a) Singh, O. V.; Han, H. *Org. Lett.* **2004**, *6*, 3067. (b) Toshimitsu, A.; Terao, K.; Uemura, S. *J. Org. Chem.* **1986**, *51*, 1724. (c) Kang, S. H.; Lee, J. H.; Lee, S. B. *Tetrahedron Lett.* **1998**, *39*, 59. (d) Danishefsky, S.; Berman, E. M.; Ciufolini, M.; Etheredge, S. J.; Segmuller, B. E. *J. Am. Chem. Soc.* **1985**, *107*, 3891. (e) de Koning, C. B.; van Otterlo, W. A. L.; Michael, J. P. *Tetrahedron* **2003**, *59*, 8337. (f) Khalaf, J. E.; Datta, A. *J. Org. Chem.* **2004**, *69*, 387.

183. Ohfune, Y.; Sakaitani, M. *Tetrahedron Lett.* **1985**, *26*, 5543.

VITA

Seth L. Crawley

Seth was born and raised in the northern suburbs of Detroit, Michigan. He attended Hope College, in Holland, MI. His undergraduate research efforts were directed towards the asymmetric synthesis of chiral epoxides using organometallic catalysts under the guidance of Professor Joanne Stewart. He graduated Summa Cum Laude in May 1999, and began his graduate studies in the laboratory of Professor Raymond L. Funk at the Pennsylvania State University. His Ph.D. studies have been directed towards the total syntheses of heterocyclic natural products. Following graduation, Seth will start as a research chemist with the Lubrizol corporation in Wickliffe, Ohio.