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Studies Towards the Total Synthesis of Condylocarpine and Studies Towards the Enantioselective Synthesis of (+)-Methyl Lysergate

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Studies Towards the Total Synthesis of Condylocarpine and Studies Towards the Enantioselective Synthesis of (+)-Methyl Lysergate

by

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Studies Towards the Total Synthesis of Condylocarpine and Studies Towards the Enantioselective Synthesis of (+)-Methyl Lysergate

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An iminium ion cascade sequence was designed and its implementation attempted to form the pentacyclic core structure of the natural product condylocarpine. Trapping of the transient Pictet-Spengler-type spiroindolenium ion with a latent nucleophile would form two of the five rings of condylocarpine in a regioselective manner.

Progress towards the first fully stereocontrolled synthesis of a lysergic acid derivative has been described. The route utilizes intermediates with the appropriate oxidation state for the target, and the two stereocenters are installed *via* asymmetric catalysis. The ***d*** ring and second stereocenter were simultaneously formed *via* an unprecedented microwave heated asymmetric ring closing metathesis (ARCM).

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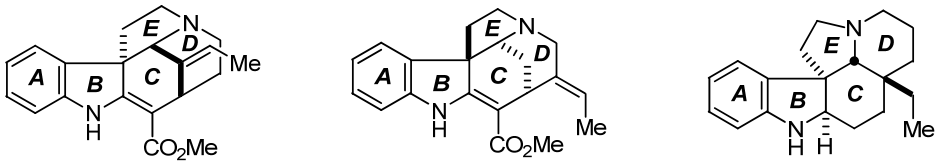
Chapter 1: Condylocarpine Alkaloids

1.1 INTRODUCTION

The condylocarpine group of alkaloids is represented by their unique pentacyclic, cage-like structures (**1.1**, Figure 1). They vary from other similar pentacyclic indole alkaloid families such as strychnos (**1.2**) and aspidosperma (**1.3**) by the skeletal connectivities of the ***C***, ***D***, and ***E*** rings (Figure 1.1). The first condylocarpine type compound, aspidospermatine, was isolated from the bark of *Aspidosperma quebracho-blanco* in 1882 by Hesse during his search for the source of the activity of "quebracho".[1] However, aspidospermatine, as well as all of the compounds within the condylocarpine family, shows no noteworthy biological activity. Condylocarpine itself was not isolated until 1961, and its structure was proven both by spectroscopic means and synthesis from stemmadenine.[2,3] The absolute stereochemistry of **1.1** was deduced *via* chemical relation with strychnine and later proven by X-ray analysis.[4]

Figure 1.1



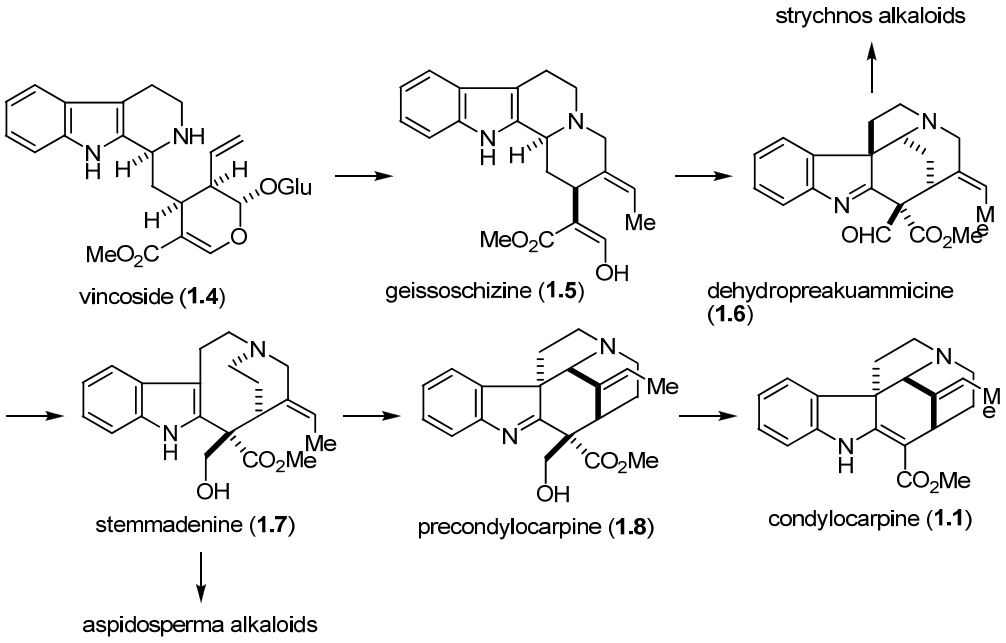
condylocarpine (**1.1**) akuammicine (strychnos) (**1.2**) aspidospermidine (**1.3**)

1.2 BIOGENESIS

The proposed biogenesis of condylocarpine, put forth by Heimberger and Scott in their discussion of the biosynthesis of strychnine, is delineated in Scheme 1.1.[5,6] The condylocarpine family is derived from geissoschizine (**1.5**) *via* two separate skeletal

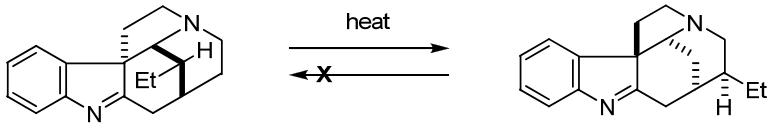
rearrangements. Initially, the extended tetracycle reforms to give dehydropreakuammicine (**1.6**), which has the strychnos skeleton, and then in a separate step the eastern ***C***, ***D***, ***E*** tricycle opens to give stemmadenine (**1.7**). Rotation of the piperidine ring and reformation of a bond between the ***B*** and ***D*** rings gives the condylocarpine skeleton. A potential reason for the route to proceed through dehydropreakuammicine instead of directly to condylocarpine may be due to mild steric repulsion of the ethylidene side group. A similar case is the isomerization of condyfoline (**1.9**) to tubifoline (**1.10**) (Scheme 1.2). Simply heating condyfoline provides, among other isomers, tubifoline, but heating tubifoline yields no condyfoline.[7] There are no published values, but simple molecular modeling (MM2 level) indicates that tubifoline is more stable by ~4 kcal/mol over condifoline.[8]

Scheme 1.1



The favoritism of the tubifoline isomer over the condyfoline isomer has played a pivotal role in the syntheses of compounds in these families. In the syntheses of tubifoline and skeletally similar compounds, the preference was beneficial, but for condyfoline and skeletally similar compounds the preference was detrimental. How different research groups have approached this issue is interesting.

Scheme 1.2



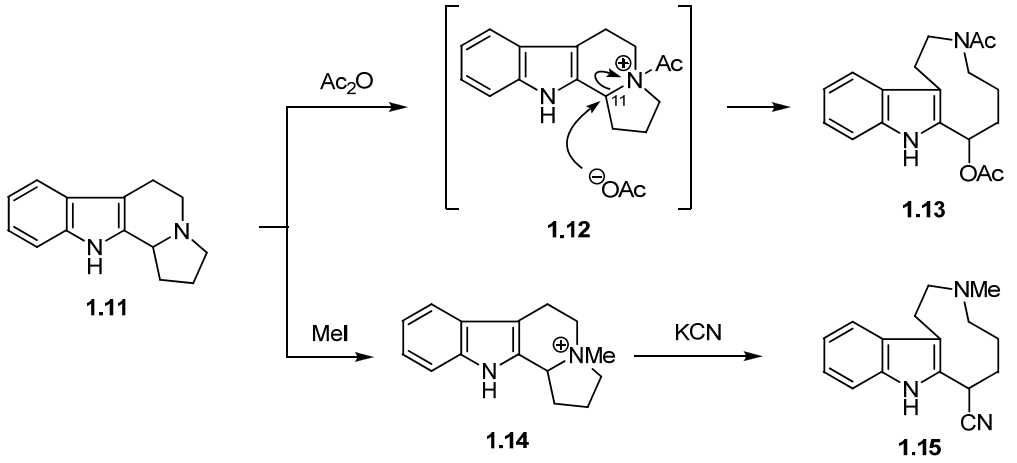
condyfoline (**1.9**) tubifoline (**1.10**)

1.3 SYNTHESIS OF CONDYLOCARPINE ALKALOIDS – CONDYFOLINE AND TUBIFOLINE

1.3.1 Synthesis of Condyfoline and Tubifoline by Harley-Mason

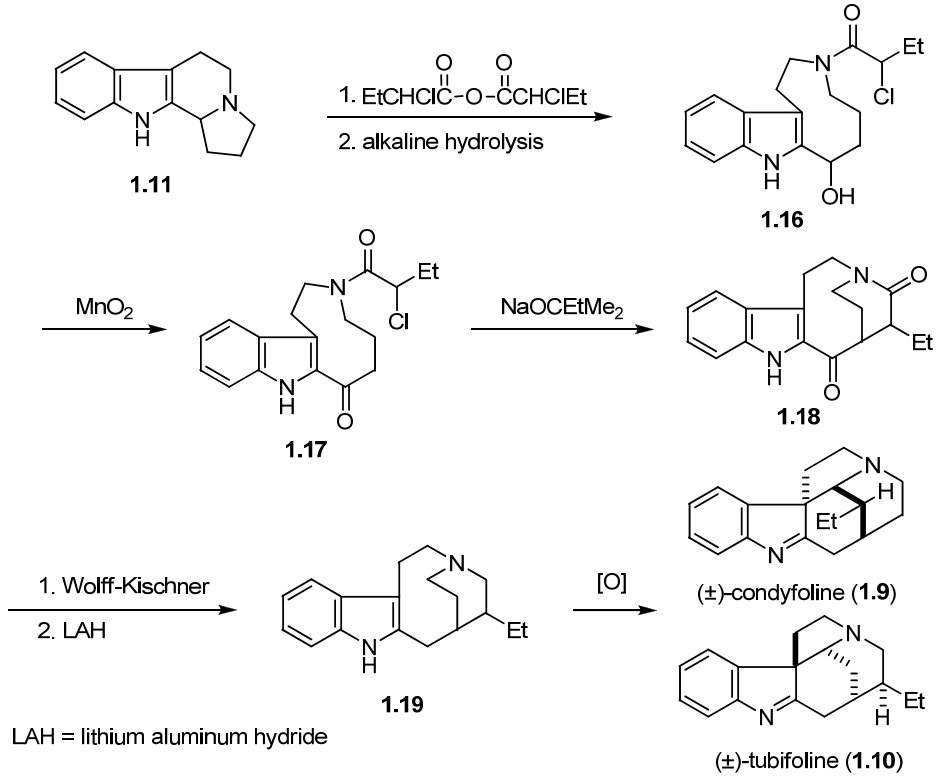
The first synthesis of a condylocarpine alkaloid was performed by Harley-Mason when he synthesized both condyfoline and tubifoline in 1968.[9] When readily available **1.11** was treated with acetic anhydride, the intermediate acyl ammonium ion underwent a nucleophilic ring opening to **1.13**, and the addition of potassium cyanide to tetraalkylammonium **1.14** proceeded in a similar fashion to **1.15** (Scheme 1.3).[10] Presumably the acyl ammonium ion is opened selectively due to the greater partial positive charge at the stabilized α-aryl position C(11).

Scheme 1.3



Realizing the potential of the newly functionalized indole, **1.11** was opened with a functionalized anhydride and, after careful hydrolysis of the ester, all of the necessary carbons for several frameworks had been installed in **1.16** without any yield data given (Scheme 1.4).[9] Oxidation of the alcohol gave ketone **1.17**, that cyclized upon exposure to strong base to form the ***D*** ring of **1.18**. Exhaustive carbonyl reduction created the skeleton of stemmadinine (**1.19**). Oxidation of the amine to an iminium and subsequent cyclization gave both condyfoline (**1.9**) and tubifoline (**1.10**). Benefiting from both the simplicity and the flexibility of this method, Harley-Mason used the approach to make a small library of condylocarpine and strychnos type alkaloids.

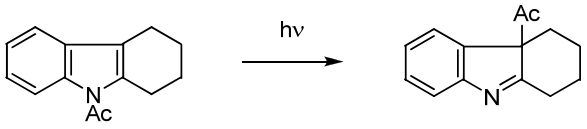
Scheme 1.4



1.3.2 Synthesis of Condyfoline and Tubifoline by Ban

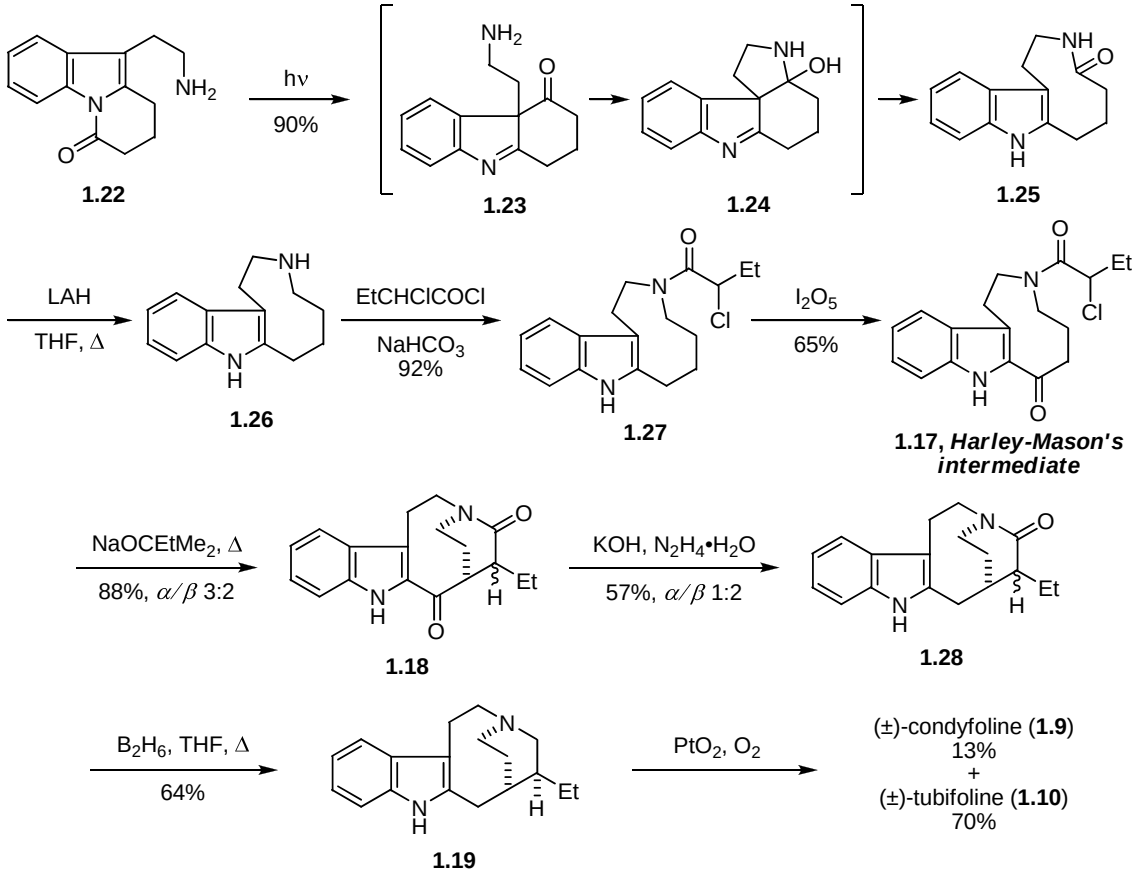
Capitalizing on a novel photocyclization adapted from a Fries type rearrangement that converted **1.20** to **1.21** (Scheme 1.5), Ban subjected tryptamine derivative **1.22** to the same conditions (Scheme 1.6).[11] In all cases, the initially formed products **1.23** were unstable, but the addition of a tethered nucleophile trapped the product, and through a subsequent rearrangement macrolactam **1.25**, which is reminiscent of Harley-Mason's intermediate **1.16**, was formed. Reduction of **1.26**, amine functionalization to provide **1.27**, and regioselective oxidation intercepted the Harley-Mason intermediate **1.17**. Ban continued to make a variety of natural products, including condyfoline (**1.9**) and tubifoline (**1.10**) in a similar manner to Harley-Mason.

Scheme 1.5



1.20 **1.21**

Scheme 1.6



1.22 **1.23** **1.24** **1.25**

1.26 **1.27** **1.17, *Harley-Mason's intermediate***

1.18 **1.28**

1.19

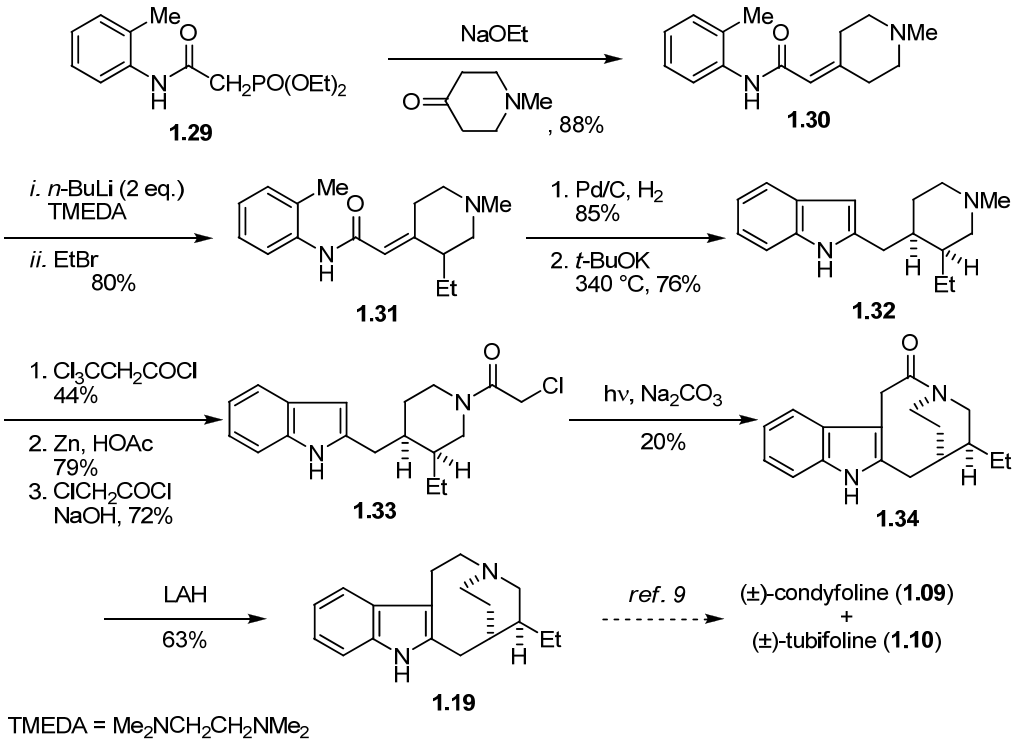
1.3.3 Formal Synthesis of Condyfoline and Tubifoline by Snieckus

Snieckus approached the synthesis of the stemmadenine system differently (Scheme 1.7). The piperidine ***D*** ring was incorporated *via* a Horner-Wadsworth-Emmons (HWE) process to give **1.30** prior to formation of the indole nucleus.[12,13] The ethyl

substituent of **1.31** was appended to the ***D*** ring *via* regioselective alkylation of the dienolate. The regioselective alkylation of amide dianions had been known, but this was the first example with an unsaturated substrate.[14,15]

When the HWE was performed on a piperidine with the ethyl group already in place there was a significant reduction in yield making the two step process more efficient even though it was longer. Reduction of the double bond followed by Madelung cyclization gave indole **1.32**. Demethylation of the amine and exchange of the trichloromethylacetamide for a monochloroacetamide provided the macrocyclization precursor **1.33**. Photocyclization of **1.33** gave **1.34** that was reduced to provide the stemmadenine skeleton **1.19** which had previously been used to synthesize condyfoline and tubifoline.[9]

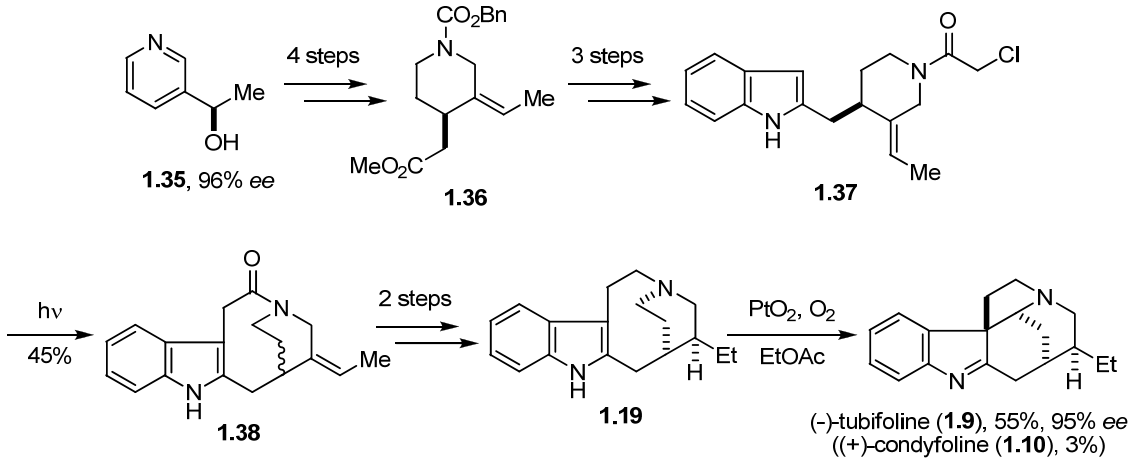
Scheme 1.7



1.3.4 Asymmetric Synthesis of Condyfoline and Tubifoline by Bosch

An asymmetric synthesis of **1.9** and **1.10** heavily based upon the approach of Snieckus was performed two decades later by Bosch *et al*. Enzymatic resolution of a racemic mixture of pyridyl ethanol **1.35** provided enriched alcohol in 96% enantiomeric excess (Scheme 1.8).[16] After reduction of the benzylated pyridinium ion to the corresponding tetrahydropyridine, the protecting group was changed to benzoyl, and a Johnson-Claisen rearrangement set the lynchpin chiral center in **1.36**. Indole synthesis and functional handle substitution gave the Witkop cyclization precursor **1.37**. Compound **1.37** only differed from precursor **1.34** of Snieckus by containing an olefin and optical enrichment. Cyclization furnished **1.38**, reduction of both the amide and double bond to **1.19** and oxidative cyclization gave (-)-tubifoline (**1.9**) with a trace of (+)-condyfoline (**1.10**).

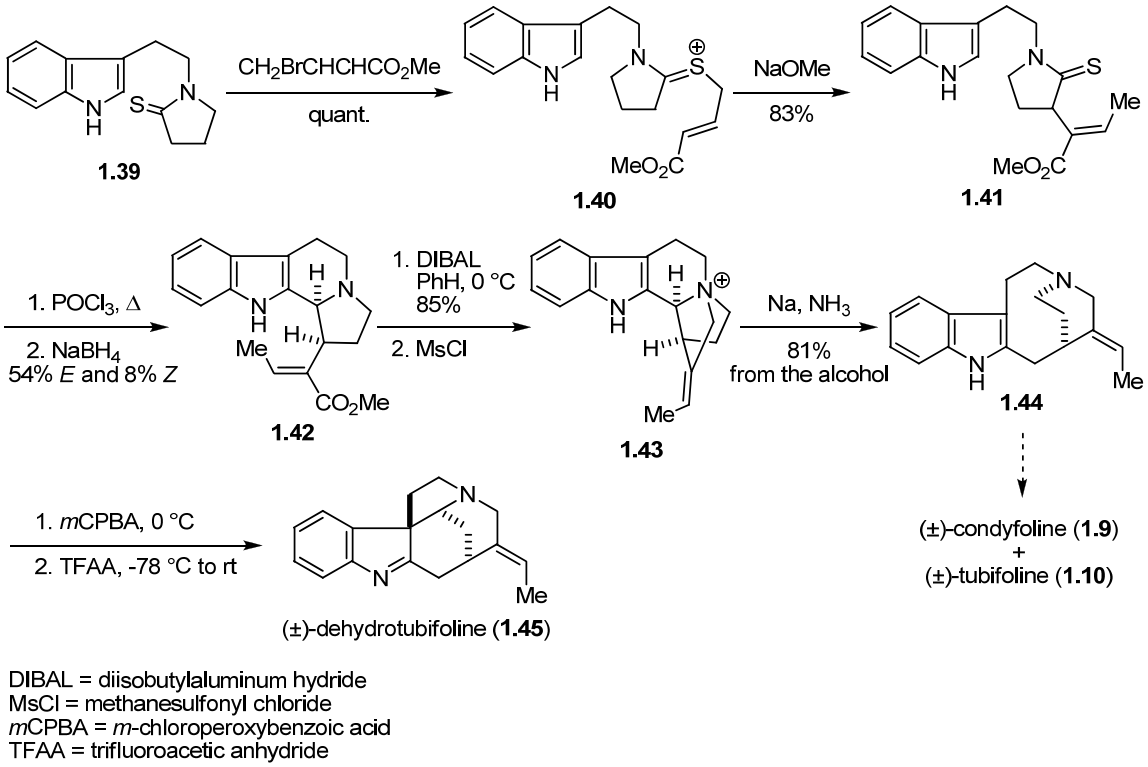
Scheme 1.8



1.3.5 Formal Synthesis of Condyfoline and Tubifoline, and Synthesis of Dehydrotubifoline by Takano

Takano synthesized Harley-Mason-type intermediates through a different approach. Alkylation of thioamide **1.39** with methylbromocrotonate gave sulfonium salt **1.40**, which underwent a remarkable cascade of reactions upon treatment with base (Scheme 1.9).[17] Tautomerization of the sulfonium ion **1.40** to the thioamino ketene acetal was followed by Claisen rearrangement. Isomerization of the resultant vinyl double bond brought it into conjugation with the ester, and stereoselectively generated **1.41** with the *E*-ethylidene required for the final product. Bischler-Napieralski-type cyclization garnered tetracycle **1.42**; the ester was reduced to the alcohol, and subsequent cyclization formed **1.43**. Cleavage *via* dissolving metal reduction generated **1.44** containing the stemmadinine skeleton. Macrocycle **1.44** was a formal precursor to both condyfoline (**1.9**) and tubifoline (**1.10**), and it also contained the unsaturated side chain with the proper stereochemistry for the strychnos class of alkaloids. Interestingly, Polonovski-Potier cyclization only provided dehydrotubifoline (**1.45**); no isomeric dehydrocondyfoline was detected. Dehydrostemmadinine **1.44** may cyclize preferentially to dehydrotubifoline (**1.45**) for the same reasons stemmadinine cyclizes to tubifoline (*vide supra*).

Scheme 1.9



DIBAL = diisobutylaluminum hydride
MsCl = methanesulfonyl chloride
*m*CPBA = *m*-chloroperoxybenzoic acid
TFAA = trifluoroacetic anhydride

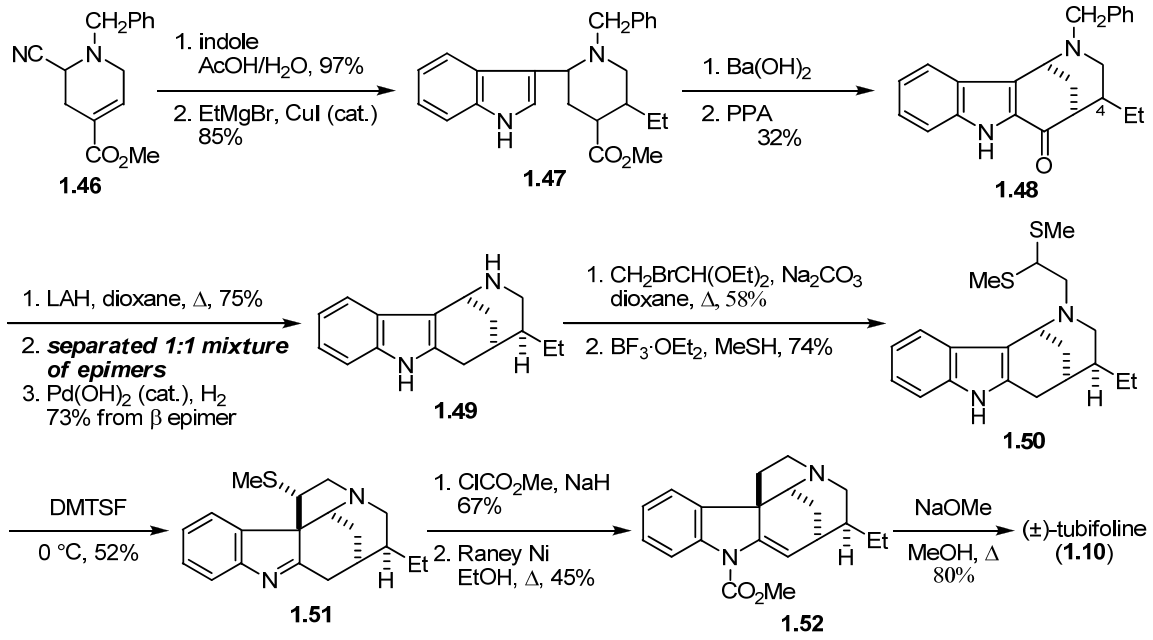
1.3.6 Synthesis of Tubifoline by Bosch

All of the approaches discussed thus far share the stemmadinine type skeleton as either the target or the penultimate compound. In a somewhat different approach, Bosch developed routes to tetracyclic uleine (*cf.* **1.48**, Scheme 1.10) type alkaloids and then used these scaffolds as common intermediates containing the ***A***, ***B***, ***C***, and ***D*** rings of the strychnos alkaloids.

Starting from **1.46**, made in two steps from isonicotinate, an iminium ion was generated *in situ* with acid, and indole was added. The ethyl substituent was added, generating **1.47** as a mixture of diastereomers that were cyclized in a Friedel-Crafts fashion giving the dasycarpidan type structure **1.48** as an inseparable mixture of C(4)

epimers (Scheme 1.10).[18-20] Lithium aluminum hydride reduction of the ketone followed by epimer separation and deprotection provided **1.49**. Alkylation of amine **1.49** with bromoacetaldehyde diethylacetal provided a functional handle for the introduction of the next ring. The ethyl acetal was exchanged for a thiomethyl acetal generating **1.50**, and upon exposure to dimethyl(methylthio)sulfonium fluoroborate (DMTSF) cyclized to form the ***E*** ring of **1.51**. Reduction of the thiomethyl group of **1.51** with Raney nickel concomitantly reduced the indolenine providing tubofolidine (not shown); however, acylation of the indolenine moiety of **1.51** proceeded with tautomerization of the double bond, and was followed by desulfurization to give **1.52**. Deprotection of the reduced compound **1.52** under basic conditions furnished tubifoline (**1.10**).

Scheme 1.10

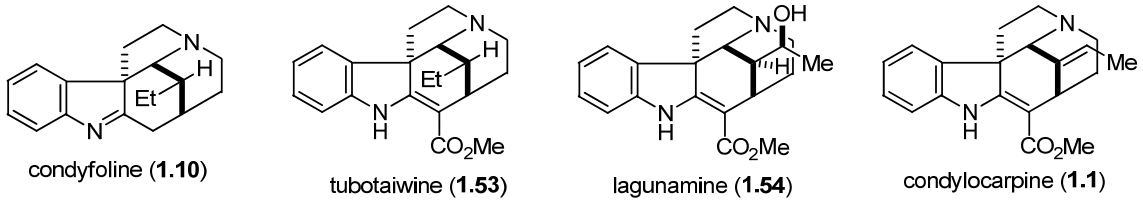


DMTSF = dimethyl(methylthio)sulfonium fluoroborate
DME = 1,2-dimethoxyethane

1.4 Synthesis of Condylocarpine Alkaloids – Tubotaiwine and Lagunamine

Among the interesting natural products of the condylocarpine family are tubotaiwine (**1.53**) and lagunamine (19-hydroxytubotaiwine, **1.54**) (Figure 1.2). More complex than condyfoline (**1.10**) and similar in complexity to condylocarpine (**1.1**), both of these alkaloids have an α,β-unsaturated ester appended adjacent to the indoline. Instead of the ethylidene moiety present in condylocarpine (**1.1**), they contain an ethyl and an ethyl carbinol respectively.

Figure 1.2



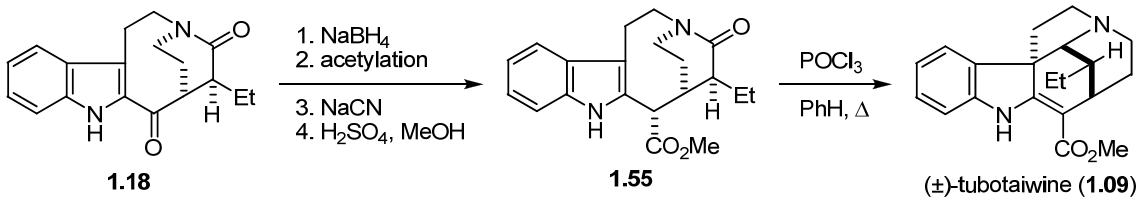
1.4.1 Synthesis of Tubotaiwine by Harley-Mason

Utilizing the dicarbonyl compound **1.18** from his synthesis of condyfoline and tubifoline, Harley-Mason added functionality to the α-aryl ketone instead of removing it, and expanded the series of alkaloids he could make from a single intermediate.[21,22] Upon homologation of **1.18** to the methyl ester **1.55**, subsequent treatment of the amide with phosphorous oxychloride made tubotaiwine (**1.09**) directly with no discussion of chemical efficiency (Scheme 1.11). This unusual transformation presumably proceeded *via* a Vilsmeier-type salt, but the starting material and product are of differing oxidation states. Giving no insight into the nature of the oxidation transfer Harley-Mason stated:

> … transannular cyclisation followed by disproportionation. As would be expected, the yield is low.[22]

One of the most important features of this synthesis was the use of the amide to control the regioselectivity of the cyclization forming the ***C*** and ***E*** rings. Although the yield was poor, the attempt to favor the tubotaiwine skeleton over the generally preferred dihydroakuamacine was successful.

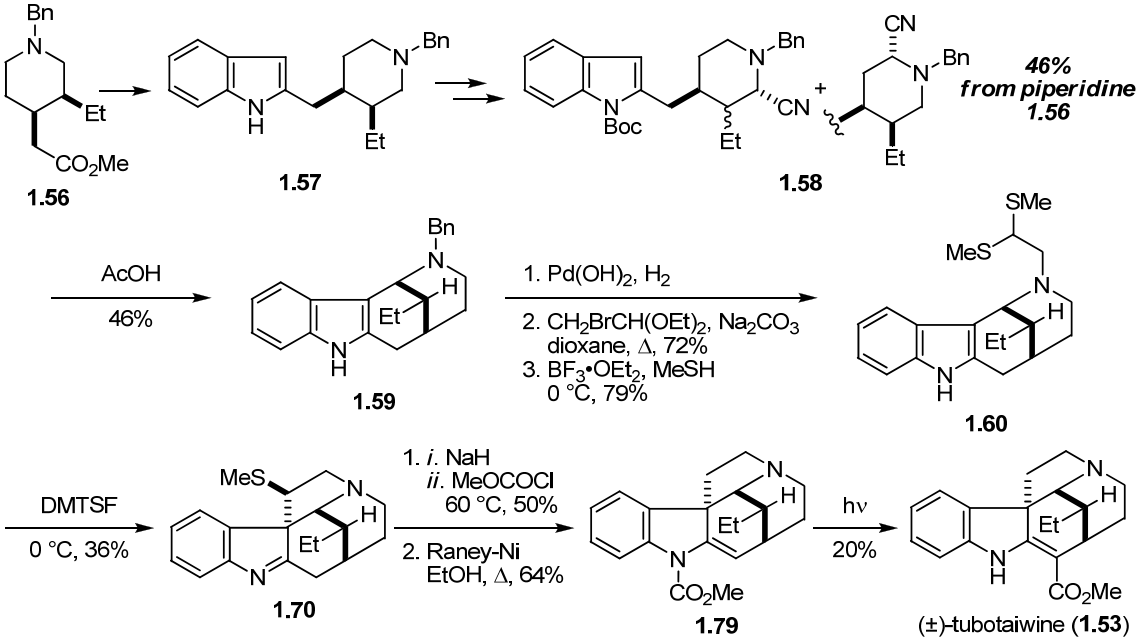
Scheme 1.11



1.4.2 Synthesis of Tubotaiwine by Bosch

Using a modification of his general approach to *strychnos* alkaloids Bosch made piperidinyl indole **1.56** (Scheme 1.12).[23] While the indole synthesis of **1.57** and the installation of the cyano group providing **1.58** *via* Polonovski-Potier chemistry showed poor regio- and stereocontrol, almost all of the isomers are useful for different targets. Acidic ionization of the cyano amine **1.58** generated the desired iminium ion for cyclization of the ***c*** ring, and after extended reaction times the indole was conveniently deprotected yielding **1.59**. Attachment of the acetal, exchange for the thio-acetal analog **1.60**, and cyclization proceeded to **1.70** as in the tubifoline synthesis. Protection of the indole and desulfurization gave **1.79**, a regioisomer of tubotaiwine (**1.53**). Subsequent rearrangement, rather than deprotection, provided tubotaiwine (**1.53**) by utilizing the carbomethoxy group already present.

Scheme 1.12

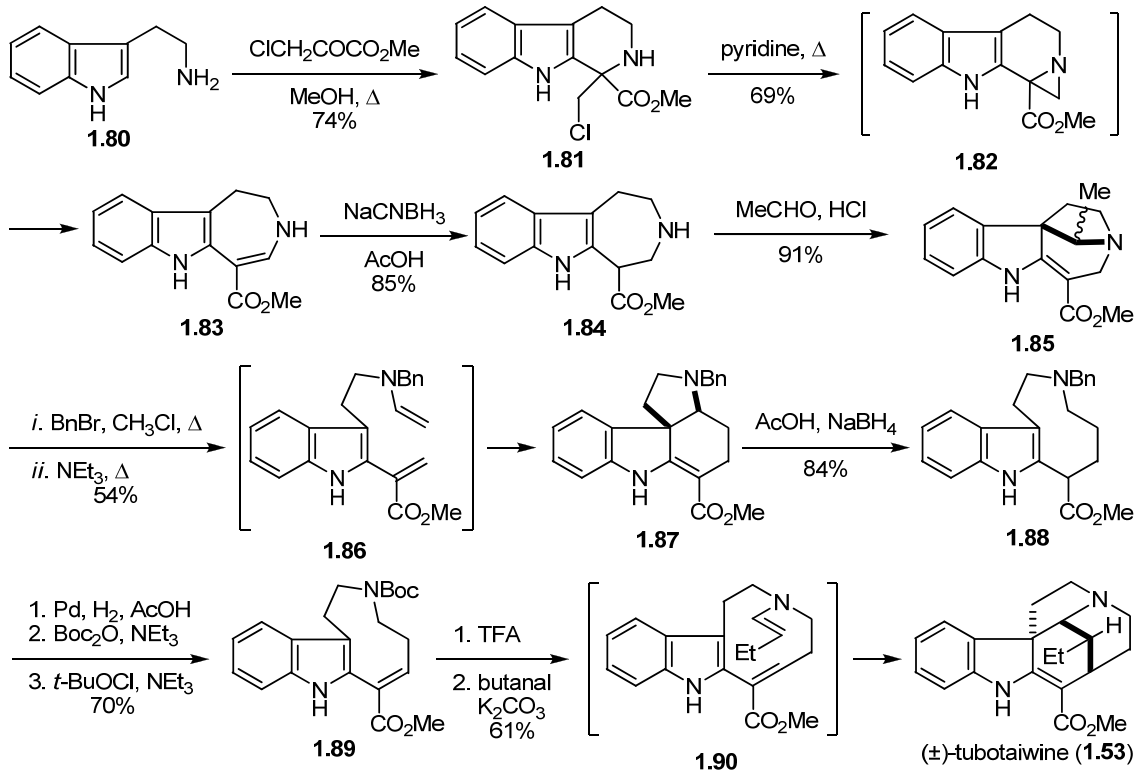


1.4.3 Synthesis of Tubotaiwine by Kuehne

Indoloazepines have been extensively studied and utilized by Kuehne as central precursors to many families of indole alkaloids.[24-54] Pictet-Spengler condensation of tryptamine (**1.80**) with methyl chloropyruvate and treatment of the product (**1.81**) with pyridine provided the ring expanded azepine **1.83** *via* the aziridylcarboline **1.82** (Scheme 1.13).[32] This intermediate has been used by Kuehne to make members of the *iboga*, *aspidosperma*, and *strychnos* families as well as the condylocarpine alkaloids. After reduction, condensation of **1.84** with acetaldehyde, ring opening, and Diels-Alder cyclization built tetracycle **1.87**. Treatment of **1.87** with acidic borohydride gave the indole **1.88**.[31] Protecting group manipulation, oxidation of the ester back to the α,β-unsaturated ester **1.89**, and deprotection provided the free amine.[41] Addition of butanal initiated a cascade wherein the aldehyde condensed with the amine, which then

tautomerized to the enamine **1.90**, and underwent another Diels-Alder to give tubotaiwine (**1.53**).

Scheme 1.13

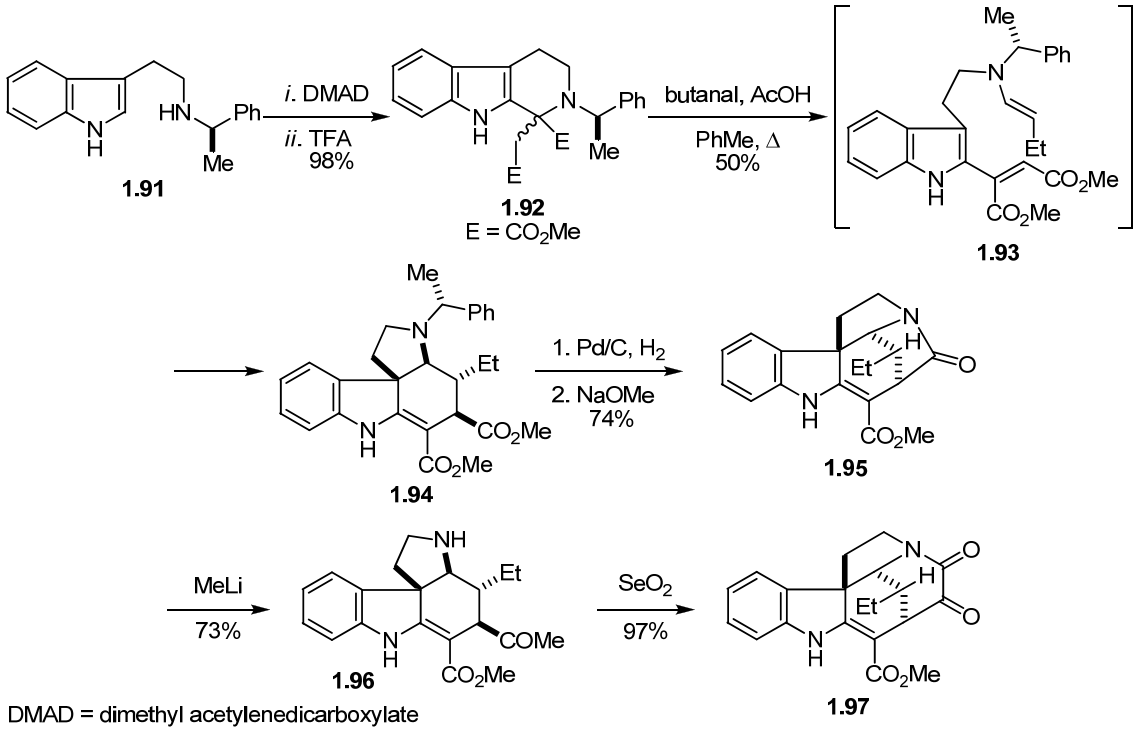


Note that the initial seven steps were devoted to installing five carbons and making a Harley-Mason type intermediate **1.88** modified with an ester, and then immediately followed by three steps, **1.88** → **1.89**, to reinstall a double bond that had been removed earlier. To be fair, the relative simplicity of this inelegant synthesis does not show the strengths of Kuehne's general approach based on indole azepines.

1.4.4 Synthesis of the (-)-Tubotaiwine Skeleton by Vercauteren

Vercauteren developed an intriguing Pictet-Spengler analogue using activated alkynes in place of aldehydes (*cf.* **1.91** → **1.92**, Scheme 1.14) and then applied his method to the syntheses of indole alkaloids.[55] The amino nitrogen of tryptamine derivative **1.91** added in a 1,4-manner to dimethyl acetylenedicarboxylate (DMAD), and addition of acid tautomerized the newly formed enamine into a reactive iminium ion that cyclized to give **1.92**. Combining this methodology with a rearrangement through intermediate **1.93**, similar to Kuehne's **1.81**, and a chiral auxiliary very rapidly provided all of the carbons atoms for tubotaiwine (**1.53**) and set four contiguous stereocenters in **1.94** (Scheme 1.14).[56] The absolute configuration of **1.94** is opposite the configuration of the natural product, but Vercauteren claimed the rationale for the synthesis of the antipodal compound was based on the disparity of cost between the starting materials for either enantiomer of the chiral auxiliary. Hydrogenolysis of the auxiliary and base-induced cyclization gave the lactam **1.95** to which methyllithium was added forming ketone **1.96**. Oxidation of the **1.96** with selenium dioxide directly provided the lactam **1.97**, which had all of the structural components of (-)-tubotaiwine (**1.53**).

Scheme 1.14

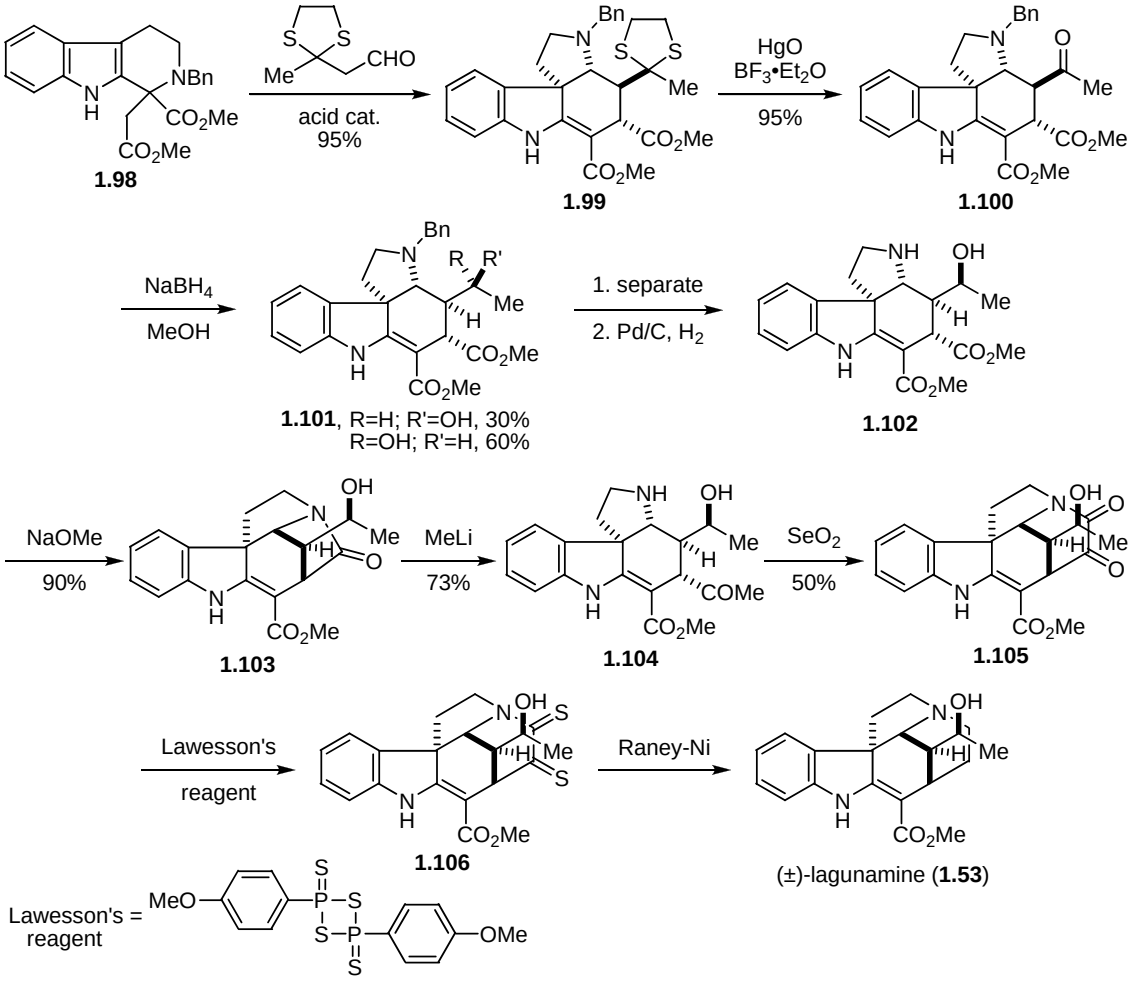


1.4.5 Synthesis of the Lagunamine by Vercauteren

In addition to tubotaiwine, Vercauteren utilized his surrogate Pictet-Spengler to synthesize other compounds in the family of condylocarpine alkaloids. The synthesis of lagunamine (19-hydroxytubotaiwine, **1.54**) not only showcased the method but also led to the elucidation of the stereochemistry of the natural product. By performing the initial rearrangement with an aldehyde that contained a masked ketone, four contiguous stereocenter relative configurations were again set, and the product, **1.99**, contained accessory functionality vs. **1.94** (Scheme 1.15).[57] After revealing the ketone **1.100**, it was reduced without regard to stereoselection to give **1.101** as a stereoisomeric pair, both of which were separated and independently carried forward. After nitrogen deprotection gave **1.102**, the three step ring formation/expansion was performed giving the skeleton of

lagunamine **1.105**. Upon exposure to Lawesson's reagent, the pyruvamide **1.105** was transformed into the thio analog **1.106**, and subsequently desulfurized with Raney nickel yielding **1.53**. Comparison of the spectral and chromatographic properties of the two alcohol epimers and of the natural products defined the previously unknown stereochemistry of the ethyl carbinol side chain of the natural product.

Scheme 1.15



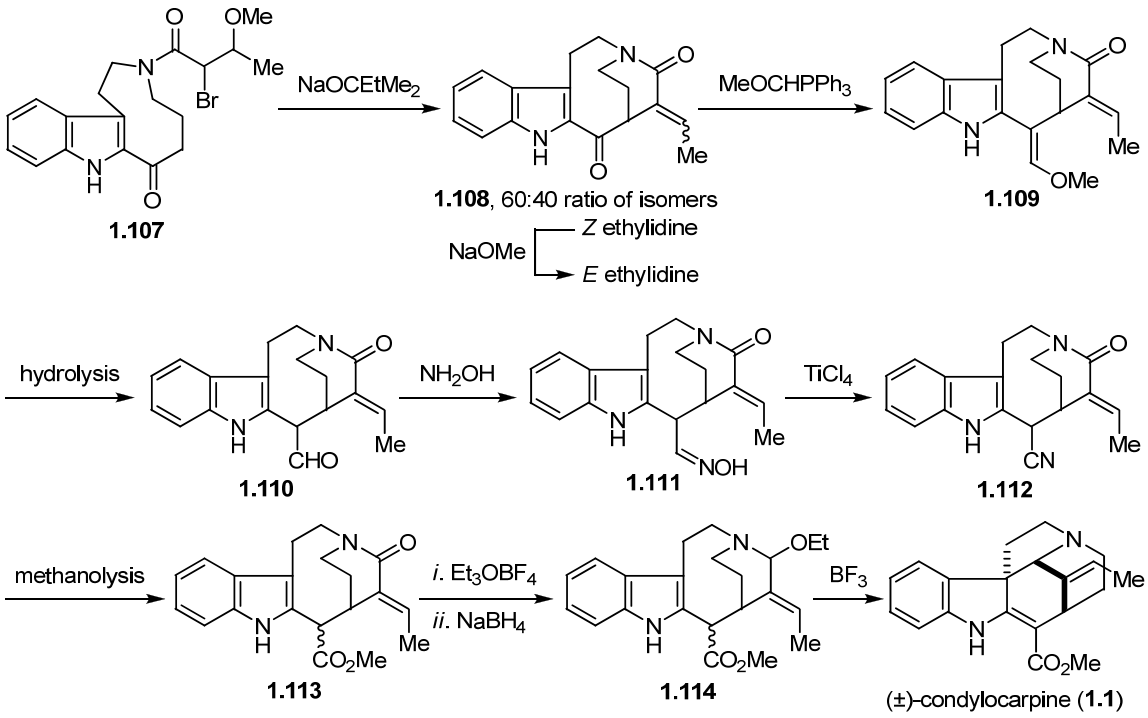
1.5 Synthesis of Condylocarpine Alkaloids – Condylocarpine

1.5.1 Synthesis of Condylocarpine by Harley-Mason

The first total synthesis of condylocarpine was performed, appropriately enough, by Harley-Mason. In a concise paper he described, with minimal detail, the general synthesis of five natural products all arising from the single precursor **1.108** (Scheme 1.16).[58] Opening the tricycle **1.11** (Scheme 1.3) in this case with 2-bromo-3-methoxybutanoic acid anhydride provided α,β-disubstituted amide **1.107** (Scheme 1.16). Treatment of **1.107** with sodium *tert*-pentoxide caused cyclization to form the ***D*** ring and eliminated methanol to form the ethylidene **1.108**. The ethylidene was formed as an easily separable pair of double bond isomers, and the isomer with unnatural geometry could be equilibrated to the natural isomer with sodium methoxide presumably *via* an addition/elimination sequence. Wittig olefination gave **1.109**, which upon hydrolysis had homologated the ketone to aldehyde **1.110**. Condensation of **1.110** with hydroxylamine to give **1.111** and subsequent dehydration produced a net oxidation of the aldehyde **1.110** to nitrile **1.112**. Methanolysis of **1.112** revealed ester **1.113** as a pair of stereoisomers.

Harley-Mason's original intent was to completely reduce the amide of **1.113** to the amine providing the stemmadenine skeleton, but the *N,O*-acetal **1.114** was unusually stable. More vigorous reaction conditions only served to reduce the ester moiety. Presumably the recalcitrance of the functional group is due to the anti-Bredt iminium ion that would necessarily form as the reduction intermediate. Taking this stable *N,O*-acetal and using it to his advantage Harley-Mason, cyclized **1.114** under Lewis acidic conditions, that had no adverse effect on the ester, to provide condylocarpine (**1.1**).

Scheme 1.16



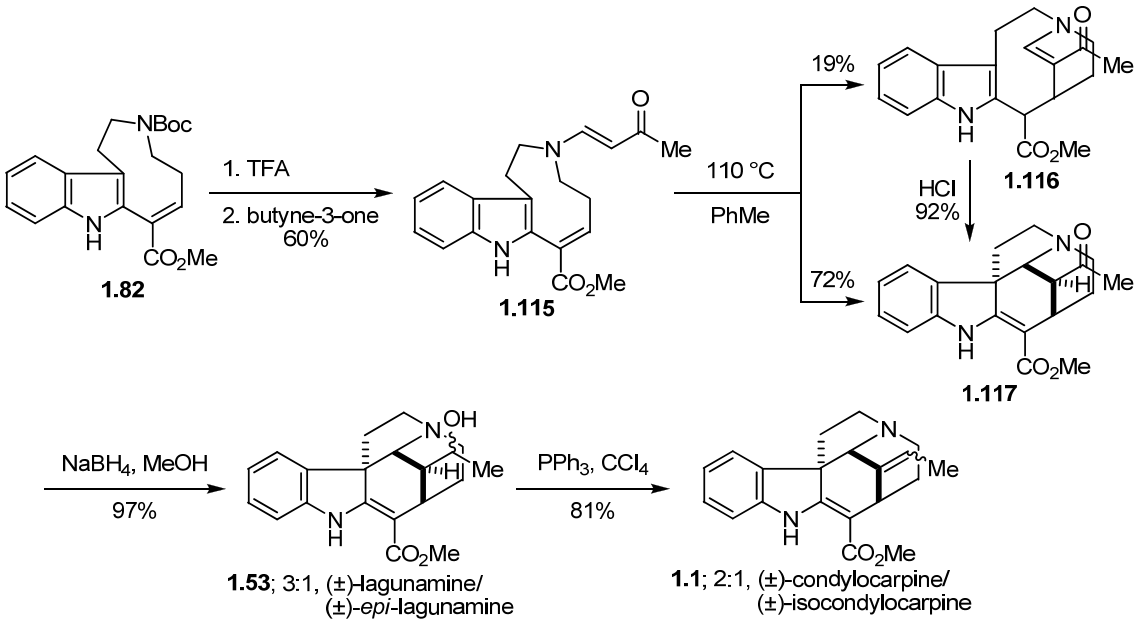
Harley-Mason's synthesis of tubotaiwine and condylocarpine are interesting and stand out among the others because of the directed cyclization to form the ***C*** and ***E*** rings. While cyclizations of stemmadenine-like structures are not unusual, the majority of these proceed with little to no regiocontrol with regard to forming the carbon-carbon bond between the indoline and the piperidine ring. In all other, non-directed, cases the *strychnos* skeleton is favored, and in examples with ethylidene side chains only the *strychnos* is seen.[17,59]

1.5.2 Synthesis of Condylocarpine by Kuehne

For Kuehne, accessing condylocarpine was relatively simple after his synthesis of tubotaiwine.[41] Beginning from the same advanced intermediate **1.82**, he deprotected and

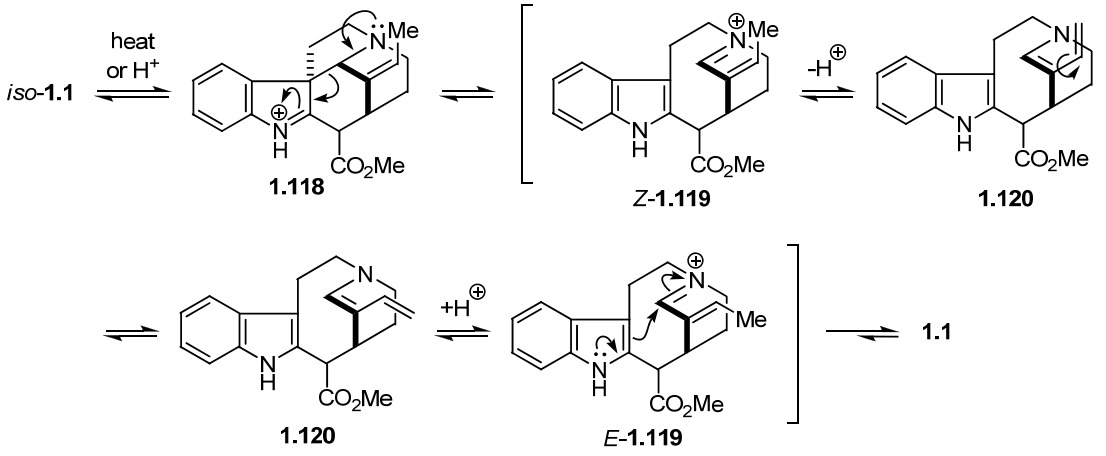
then added the free amine to an ynoate in a 1,4-sense to make the vinylogous amide **1.115** (Scheme 1.17).[45] The amide **1.115** was isolated and in a separate step heated to effect the cyclization giving the ***C***, ***D***, ***E*** ring system **1.117**. In addition to the desired product **1.117**, a moderate amount of side product **1.116** was formed. This side product was most likely formed from **1.117**, perhaps due to the stability of the vinylogous amide versus the keto-amine. Support for this hypothesis was found when **1.117** was heated, whereupon it cleanly opened to **1.116**. Treatment of side product **1.116** with acid reclosed the tetracycle in good yield. Reduction of the ketone moiety provided a mixture of lagunamine and *epi*-lagunamine (**1.53**). The lack of stereocontrol is unimportant because both isomers undergo elimination under the same conditions to provide a mixture (2:1) of condylocarpine and isocondylocarpine (**1.1**). Either of the two isomers may be readily equilibrated to the same ratio of isomers upon treatment with acid or heat. Subsequent to this study it was discovered that a natural sample of condylocarpine had isomerized upon standing yielding a ratio (3.7:1) of condylocarpine to isocondylocarpine.

Scheme 1.17



Kuehne proposed that the equilibrium took place *via* iminium ion formation and ring opening which reestablishes aromaticity (Scheme 1.18). Elimination of a proton to satisfy the iminium ion led to dienamine **1.120** that underwent σ-bond rotation. Recyclization favors the slightly more stable condylocarpine.

Scheme 1.18



1.6 Conclusions

When viewing the condylocarpine alkaloids, the eye is drawn to the tricyclic eastern portion. Immediately, as the quaternary spirocycle is noticed, methods of construction are contemplated. The most intriguing aspects of synthetic design lay within the formation of these elements and how to achieve their control.

While the approaches discussed have achieved the syntheses of several condylocarpine-type alkaloids, they often lacked control in the installation of the spirocyclic center of the indoline. Almost all lacked power over the regiocontrol of the ethyl/ethylidene moiety. In fact, all of the syntheses of both condyfoline and tubifoline took advantage of the substrates' cyclization preferences; therefore, the product mixtures heavily favored tubifoline.

The syntheses of tubotaiwine were formulated in such a way that the spirocycle was formed in a controlled fashion. Harley-Mason's approach relied on an unexpected, fortuitous transformation, but proceeded in low yield. Bosch built the spirocyclic center in several individual steps with only moderate control and yield. Kuehne showed excellent control in his cyclization, but setting the stage for the transformation was long and convoluted.

Vercauteren's syntheses of the tubotaiwine skeleton and lagunamine are interesting applications of novel chemistry and introduce asymmetry as well. Several poor yields and the need for the late stage disposal of functionality lacks the elegance promised in the outset.

Building upon the methodological development of their respective processes, Harley-Mason's and Kuehne's syntheses of condylocarpine are similar in overall

approach to their syntheses of tubotaiwine. Again they are effective, but also seemingly unnecessarily complex.

While condylocarpine type alkaloids have been synthesized, there is still ample space for further development. The difficulty in synthesizing condylocarpine and similar alkaloids illustrates the continued need for methods to make multicyclic/spirocyclic alkaloids. An efficient method to synthesize such spirocycles that was not at the mercy of substrate control would be very valuable. Moreover it should be sufficiently general that the method could be applied to the synthesis of other multicycles/spirocycles.

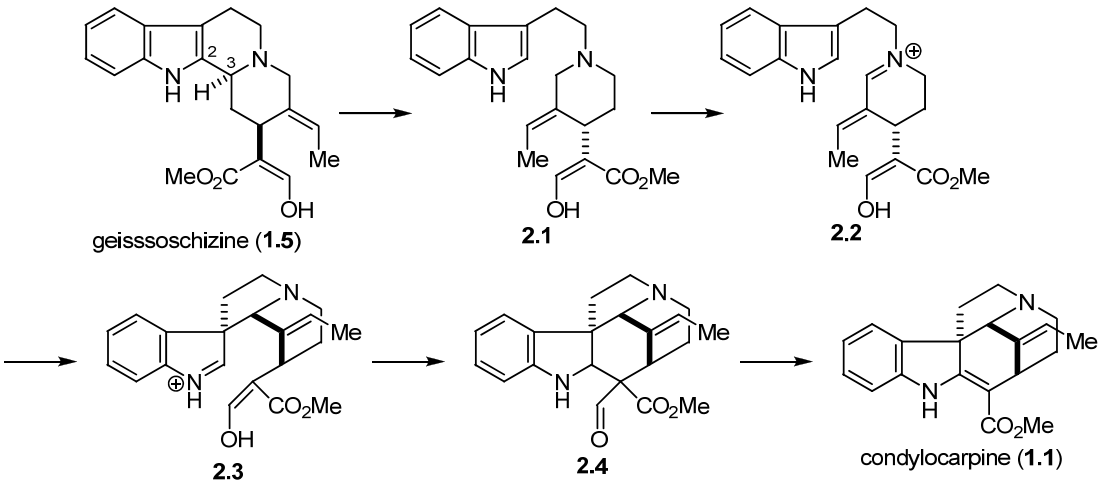
Chapter 2: Studies Towards the Total Synthesis of Condylocarpine

2.1 Prior Art from Within the Martin Group

The Martin group has a long standing tradition in the total synthesis of alkaloid natural products, and as part of our ongoing efforts to develop general strategies for the efficient synthesis of members of the various subgroups of alkaloids, we have completed the total syntheses of a number of structurally diverse indole alkaloids. In designing approaches to several of these syntheses, the key steps for skeletal construction were inspired by proposals for their biogenesis.

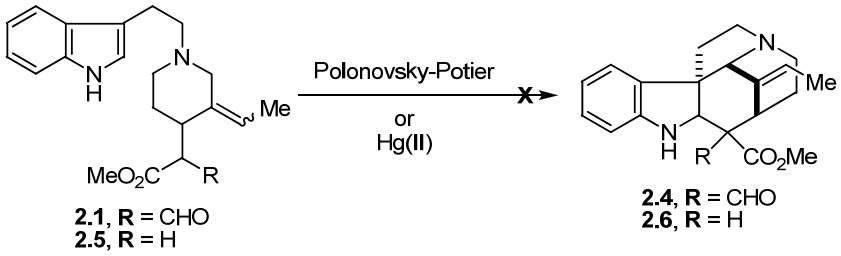
Having recently completed a concise enantioselective total synthesis of (+)-geissoschizine (**1.5**, Scheme 2.1), attention was turned towards its use as a precursor for other indole alkaloids.[60,61] The ideal biomimetic precursor of a natural product would be its biogenic precursor, and based upon this premise the desired path of construction of condylocarpine (**1.1**) from geissoschizine (**1.5**) was outlined as shown in Scheme 2.1. Reductive cleavage of the bond connecting indole-C(2) to the piperidine ring followed by regioselective reoxidation would create a suitable precursor like **2.1** for a cascade of cyclizations creating the entire eastern portion of the structure of condylocarpine (**1.1**) in one sequence. Deformylation of the pentacycle **2.4** and oxidation to the α,β-unsaturated ester would provide **1.1**.

Scheme 2.1



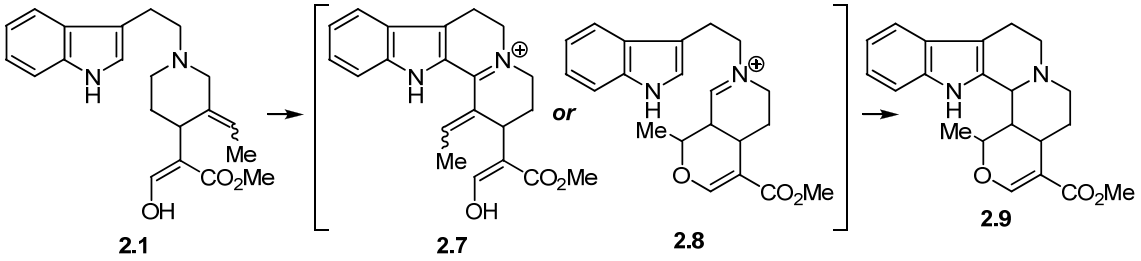
All of the attempts to cleave the C(2)-C(3) bond of geissoschizine (**1.5**) or similar analogs by Drs. Chen and Eary were unsuccessful, so this was revised. [62] The most interesting aspect of the synthesis was the proposed cyclization cascade starting with **2.1** or **2.2**. To access the cascade, the racemic compounds **2.1** and **2.5** were synthesized and subjected to a variety of Polonovski-Potier and mercury acetate oxidation conditions (Scheme 2.2). None of the reactions generated identifiable cascade products leaving instead starting materials, carbolines from simple iminium ion cyclizations, or complex mixtures of undesired materials.

Scheme 2.2



The carboline side product **2.9** arose from formation of the iminium ion, but the pendant nucleophile of **2.1** was ineffective in trapping the indolenium ion intermediate (Scheme 2.3). A possible mechanistic rational for the side product **2.9** was iminium ion formation from **2.1** followed by cyclization and subsequent iminium ion formation generating **2.7** or **2.8**. A second cyclization took place to provide product **2.9**, wherein the enol, appended to the bottom of the molecules as drawn, attacked the intermediary iminium ion with the oxygen as opposed to the desired carbon atom. Because both **2.7** and **2.8** were potential precursors for **2.9**, it was not possible to determine which was the actual precursor. The desired spirocenter was not formed, and the dihydropyran was formed from undesired attack of the oxygen of the latent nucleophile.

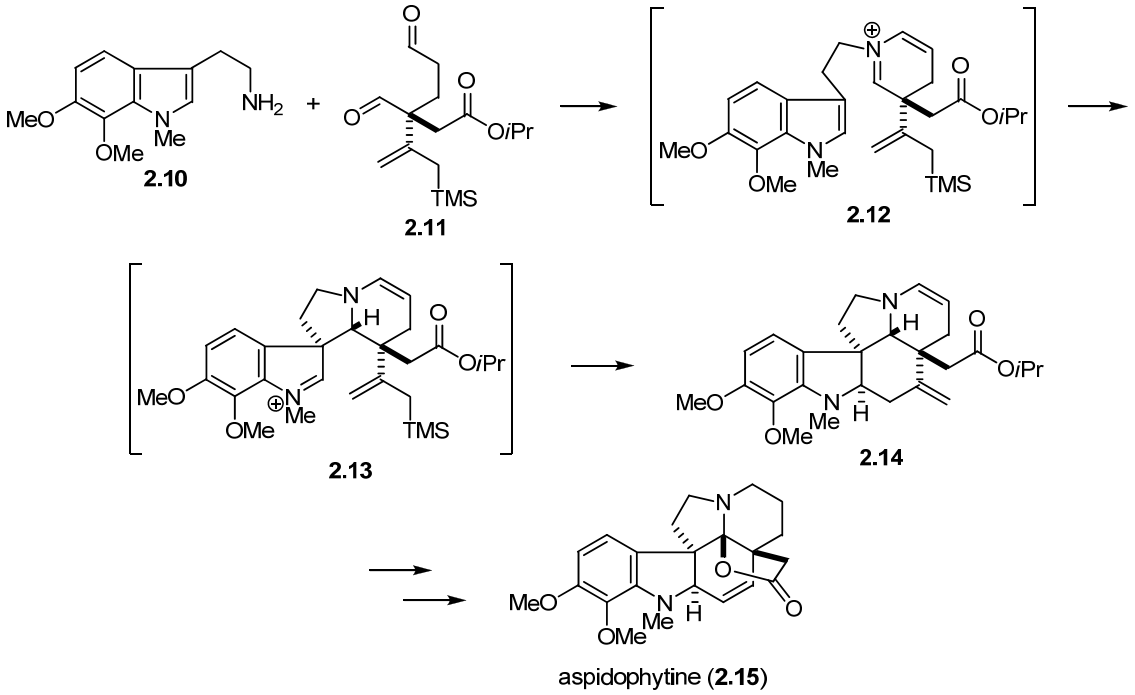
Scheme 2.3



We hypothesized that if the method of formation of the initial iminium ion was more controllable and the latent nucleophile was more directed, i.e., monodentate, the cascade should be successful. If the iminium ion formation was more controlled the issue of over oxidation of the reaction intermediates and/or products would be avoided (*i.e.* **2.7**, **2.8**). A nucleophile with a single mode of attack would suppress undesired side reactions such as the attack of the oxygen in the prior attempt (*i.e.* **2.8**, **2.9**). An example of this type of reaction sequence was exhibited by Corey in his elegant synthesis of

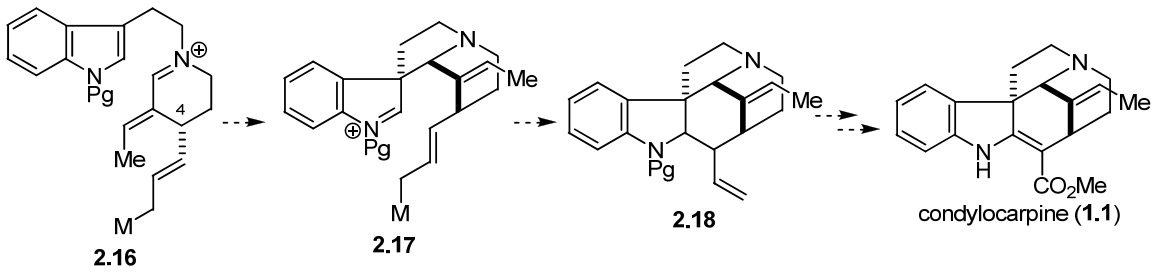
aspidophytine (**2.15**) (Scheme 2.4).[63] The use of the allylsilane in **2.11** as the latent nucleophile ensures only a single mode of reactivity under the reaction conditions.

Scheme 2.4



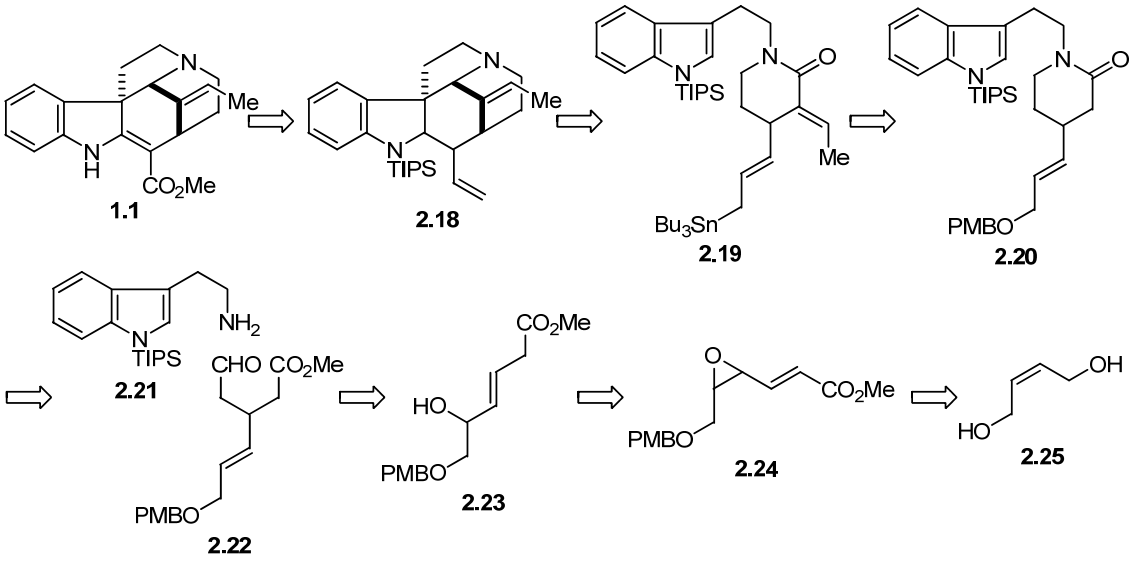
Modification and application of this concept to developing a synthetic approach to condylocarpine was straightforward. Formation of the iminium ion **2.16** would initiate a Pictet-Spengler reaction, and the spirocycle would be trapped *via* allylation of **2.17**, leading to **2.18** (Scheme 2.5). The pendant vinyl group left in **2.18** would then be transformed into the requisite carbonyl group by oxidative cleavage followed by installation of the olefin providing condylocarpine (**1.1**) (Scheme 2.5). Defining the chirality at C(4) of the piperidine ring in **2.16** would direct the formation of the rest of the chiral centers in the target.

Scheme 2.5



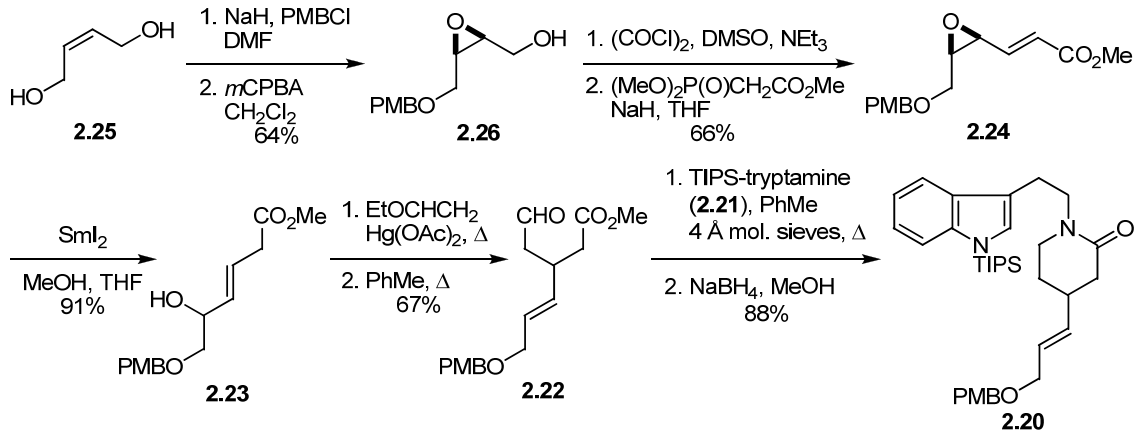
With this in mind, Dr. Eary redesigned the precursor. He envisioned the iminium ion of **2.16** arising from a lactam and the pendant nucleophile as an allyl stannane (M = $SnBu_3$). In this way condylocarpine (**1.1**) could be made from **2.19** *via* **2.18** *vide supra* (Scheme 2.6) The iminium ion precursor (**2.16**) to the cascade sequence would be a product of partial reduction and subsequent ionization of lactam **2.19**. The ethylidene would be available *via* aldol chemistry, and the stannane moiety would arise from displacement of an appropriate leaving group generated from protected alcohol **2.20**. Formation of the lactam in **2.20** would result from the combination of **2.21** and **2.22**, then reductive amination, and amidation. Compound **2.22** would be the product of vinyl ether formation and Claisen rearrangement of allylic alcohol **2.23**. The alcohol **2.23** would be formed *via* deconjugative epoxide opening of **2.24**, which would be made in straightforward fashion from *cis*-1,4-butenediol (**2.25**).

Scheme 2.6



Dr. Eary began with inexpensive, readily available *cis*-1,4-butenediol (**2.25**), and following literature protocol, monoprotected **2.25** with a paramethoxybenzyl group, and epoxidized with peracid to give **2.26** (Scheme 2.7).[64] While the initial foray into the total synthesis was racemic, it could easily be made asymmetric with the known enantioenriched version of **2.26** that has been made both with Sharpless methodology and from the chiral pool.[65,66] Swern oxidation of the primary alcohol in **2.26** and subsequent olefination of the crude product mixture with triethylphosphonoacetate provided **2.24**. Initially **2.24** was opened to provide **2.23** with magnesium metal in methanol,[67] but higher yields and greater reproducibility were found using samarium diiodide.[68] Vinyl etherification of **2.23** with ethyl vinyl ether and Claisen rearrangement provided **2.22** in good combined yield, and piperidone formation to give **2.20** proceeded in high yield.

Scheme 2.7

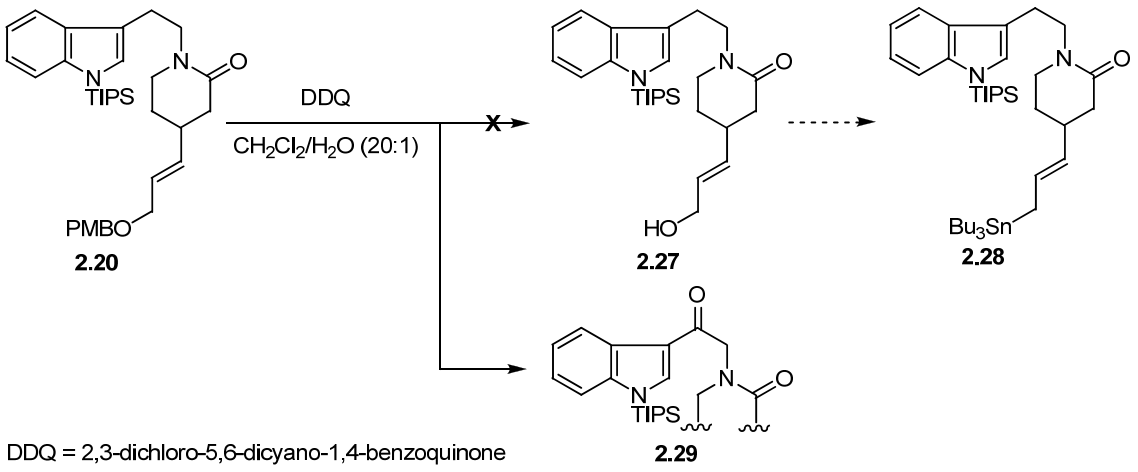


2.2 CURRENT WORK

2.2.1 First Generation Approach

Immediately prior to the completion of his postdoctoral appointment within the Martin group, Dr. Eary synthesized several grams of **2.20** and performed initial experiments exploring the transformation of the protected alcohol to the allyl metal. The allylic alcohol **2.20** was deprotected using dichlorodicyanoquinone (DDQ) in wet methylene chloride (Scheme 2.8). Unfortunately, the conditions most commonly used to remove the paramethoxy benzyl ether protecting group are also conditions that efficiently oxidize the α-position of C(3) alkylated indoles.[69] Thus, reaction produced a mixture of deprotected material **2.27** and deprotected oxidized material **2.29** in varying ratios. The chromatographic and spectroscopic (^{1}H-NMR) properties of the two compounds were so similar that Dr. Eary did not realize that there were two separate compounds in the product mixture. Once this issue was discovered, it was also realized that selective deprotection using DDQ was not possible. With the amounts of advanced material **2.20** graciously provided by Dr. Eary, alternate deprotection methods were explored.

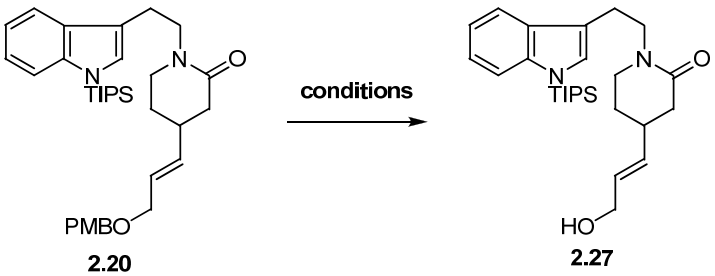
Scheme 2.8



Of the available methods for removal of activated benzylic alcohols, the additional functionality of substrate **2.20** significantly limited the possibilities. The presence of the indole nucleus rendered oxidizing techniques problematic, as was the case with DDQ. Refluxing **2.20** in a 1% w/v solution of molecular iodine (I_2) in methanol did effect the deprotection in moderate yield, but the reaction was accompanied by overoxidation of the primary alcohol to an aldehyde and a variety of polar side products that were not identified (Scheme 2.9).[70] The isolated olefin made selective reduction difficult, and when **2.20** was exposed to mild catalytic hydrogenolysis conditions with palladium on carbon and 1,4-cyclohexadiene a product whose R_f did not match that of the desired compound was provided. Heating **2.20** with chromium (II) chloride and lithium iodide in wet ethyl acetate appeared to react 'spot to spot' by TLC analysis, but the isolated yield of **2.27** was remarkably poor (11%).[71] It is possible that the product adhered to the chromium salts and was not recovered; however, repetition of the procedure with more stringent extraction and recovery techniques did not improve the yield. Strong acids, both Lewis and Brønsted-Lowry, removed the triisopropylsilyl

(TIPS) protecting group on the indole. To circumvent this issue, a hard acid/soft nucleophile combination was used in the deprotection step. Namely the mild Lewis acid cerium chloride hydrate and the nucleophile sodium iodide were used.[72,73] The combination worked well providing the alcohol **2.27** in 63% yield. When the protected alcohol **2.20** was refluxed in methanol with a catalytic amount of carbon tetrabromide, [74] **2.27** was obtained in up to 70% yield accompanied by 13% recovered starting material **2.20**.

Scheme 2.9



2.20 **2.27**

conditions	yield
DDQ, CH_2Cl_2/H_2O	inseparable mixture of **2.27** & **2.29**
I_2 (cat.), MeOH, Δ	45%, 6% rsm, & 27% aldehyde
Pd/C (cat.), cyclohexene	no product formation
$CrCl_2$, LiI	11% **2.27**
$CeCl_3 \cdot 7H_2O$, NaI	63% **2.27**
CBr_4 (cat.), MeOH, Δ	70% **2.27** & 13% **2.20**
CBr_4 (cat.), MeOH[a]	63% **2.27** & 12% **2.20**
CBr_4 (cat.), MeOH[b]	49% **2.27** & 21% **2.20**

[a] sublimed CBr_4 (0.5 eq.), sealed vial, 80-85 °C, 5.75 h

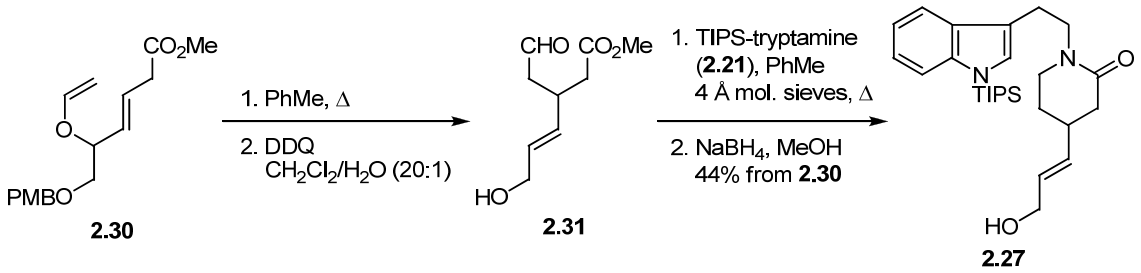
[b] sublimed CBr_4 (0.25 eq.), sealed vial, 95-100 °C, 1.5 h

While deprotection of **2.20** with catalytic carbon tetrabromide in refluxing methanol was the most successful method, the reaction suffered from variable yields and the product mixture was difficult to purify. A series of experiments determined that raising the temperature of the deprotection reaction of **2.20** increased the rate of production of **2.27** at least as much as it increased the rate of decomposition of **2.20**

and/or **2.27**. The most practical method for the temperature insensitive reaction was to perform it at elevated temperatures for insufficient time to reach completion (Scheme 2.9 final two entries). In this way **2.27** was obtained in the highest reproducible yields based upon the recovered starting material, reaction times were reduced, and background reaction(s) that consumed the product were minimized. Sublimation of the carbon tetrabromide immediately prior to use improved the yield slightly.

The optimized deprotection process provided enough **2.27** for further investigations, but in the event that the deprotection would need to be revisited on a larger scale, a simple alternative was examined. To avoid the difficulties associated with the transformation of **2.20** into **2.27**, the PMP protecting group was removed at an earlier stage. Thus precursor **2.30** underwent the Claisen rearrangement, and the crude product mixture was deprotected with DDQ to give **2.31**, which was cyclized to provide **2.27** directly (Scheme 2.10). Although this initial foray was performed rapidly as a proof of concept with little care for ultimate yield, it still provided 44% over four steps (three pots), which compares favorably with the prior route.

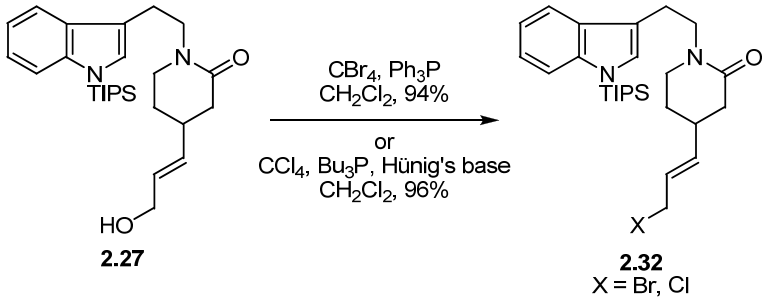
Scheme 2.10



Preparation of the alcohol **2.27** for stannane displacement was straightforward. While mesylation of **2.27** worked poorly and was not reproducible, halogenation of **2.27**

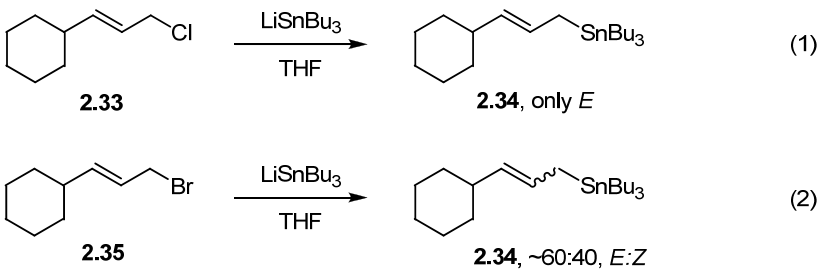
under Appel type conditions to generate allyl chloride **2.32** worked exceptionally well (Scheme 2.11).[75,76] During chlorination of **2.27**, the addition of Hünig's base to buffer the reaction was necessary. Both of the allylic halides **2.32**, X = Br, Cl, were stable and isolable as pure compounds facilitating the forthcoming displacement.

Scheme 2.11



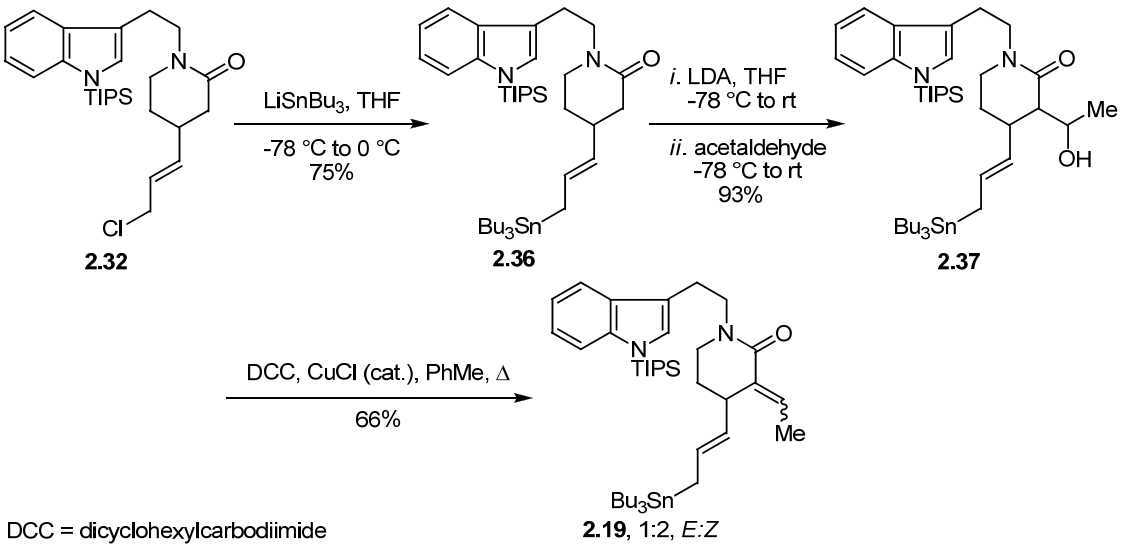
Hünig's base = *N,N*-diisopropylethylamine

Initial difficulties in stannylation prompted a model study, which was performed on a simple allylic system (Scheme 2.12). These studies showed that, in our hands, the quality of the tin hydride was of the utmost importance. The tributyltin hydride (TBTH) was distilled prior to each use to ensure its purity and stored under nitrogen below 10 °C. Assays of the TBTH treated in this fashion always indicated greater than 97% purity.[77] Whether the allyl halide was chloride **2.33** or bromide **2.35** did not appear to influence yield, which was estimated from the ^{1}H-NMR of the inseparable reaction mixture. Interestingly, the use of bromide **2.35** as a leaving group adversely affected the stereochemical purity of the double bond of **2.34**, while chloride **2.33** did not (Equations 1 and 2).[78]



The allyl chloride **2.32** was then found to react smoothly with lithium tributylstannane to give **2.36** in good yield. Addition of the enolate **2.36** to acetaldehyde installed the ethyl carbinol, providing **2.37** as a mixture of diastereomers (Scheme 2.12). Elimination of the alcohol from **2.37** by treatment with mild acid, base, or mesylation/elimination worked poorly or not at all. Stereospecific syn-elimination of **2.37** *via* the dicyclohexylcarbodiimide (DCC) imidate gave the ethylidene derivative **2.19** as an easily separable mixture of *E* and *Z* isomers.[79,80] The efficiency of the elimination was high, but the lack of stereocontrol in the aldol led to favoritism of the undesired *Z*-double bond isomer of **2.19**. The ratio may have been inconsequential, however, because Kuehne had shown that the *Z*-ethylidene of isocondylocarpine (iso **1.1**) was isomerizable to the *E*-ethylidene of condylocarpine (**1.1**) (*vide supra*).

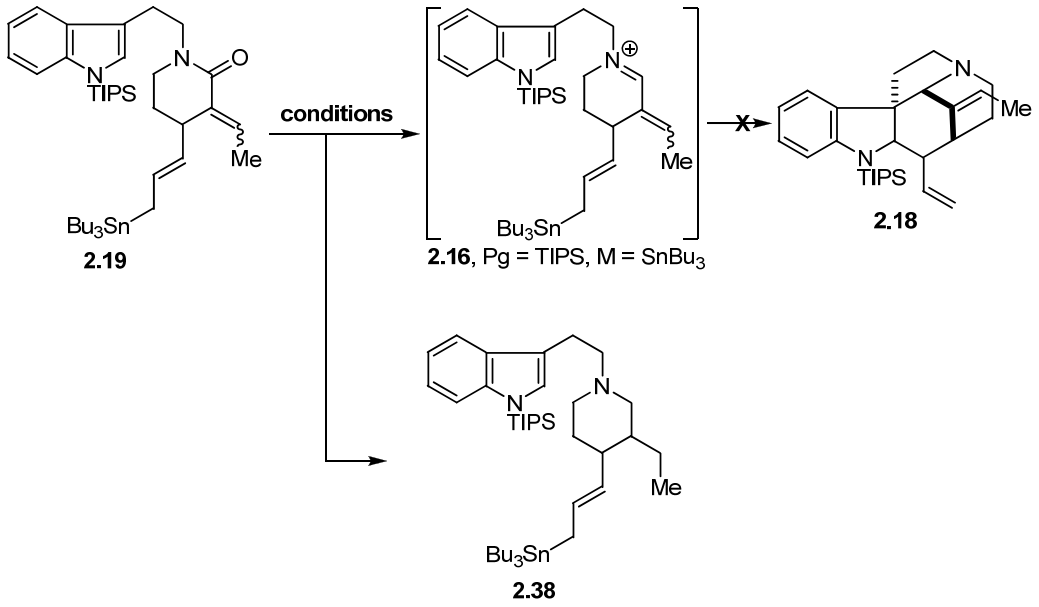
Scheme 2.12



With **2.19** in hand attempts were initiated to invoke the cyclization sequence. The desired pathway to access the cascade was reduction of the amide moiety in **2.19** to the hemiaminal, ionization of which would give the iminium ion **2.16** eliciting the Pictet-Spengler reaction and the subsequent cascade (Scheme 2.13). To attempt to control the reduction rate, diisobutylaluminum hydride (DIBAL) was slowly added to a solution of the substrate **2.19** at -78 °C. The amount of reducing agent was carefully controlled to minimize the undesired reduction of the iminium ion **2.16** to the corresponding amine. Unexpectedly, there was no reaction at all, and addition of more DIBAL made no difference. Employing stoichiometric or excess DIBAL in methylene chloride did not consume starting material **2.19**. Exposure of **2.19** to excess DIBAL in toluene at reduced, ambient, or elevated temperatures similarly appeared to do nothing. The more active lithium aluminum hydride (LAH) provided minimal reaction with **2.19**, providing unreacted starting material and over reduced piperidine **2.38**. Alane reduction of **2.19** provided a product mixture that resembled the LAH reaction. Apparently reduction of

2.19 to the hemiaminal was difficult, and the subsequent cyclization slower than the second, presumably more facile, reduction to give **2.38**.

Scheme 2.13



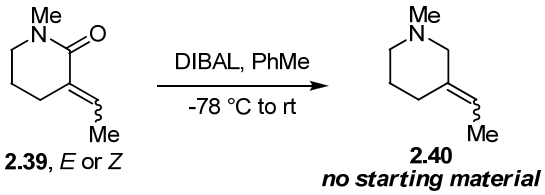
SM	conditions	temp.	product(s)
E	DIBAL-H (CH_2Cl_2)	-78 °C to rt	RSM
Z	DIBAL-H (CH_2Cl_2)	-78 °C to rt	RSM
E	DIBAL-H (toluene)	-78 °C to rt	RSM
Z	DIBAL-H (toluene)	-78 °C to rt	RSM
Z	DIBAL-H (toluene)	rt to 70 °C	RSM
Z	LAH	-78 °C to rt	RSM, **2.38**
Z	AlH_3	-78 °C to rt	RSM, **2.38**

RSM = recovered starting material

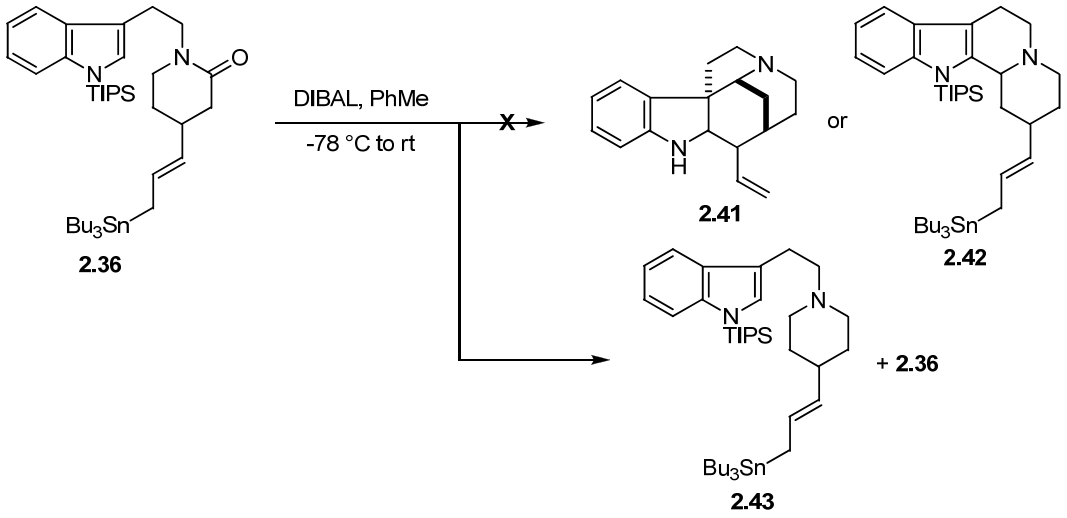
Reduction of similarly functionalized piperidones **2.39**, to give **2.40**, was rapid and near quantitative upon inspection (^{1}H-NMR) of the crude product mixture (Scheme 2.14). Lactam **2.39** was a very simple model, so a small amount of the stannane **2.36** was subjected to the same conditions in hopes of forming either the desired pentacycle skeleton **2.41**, or if the latent nucleophile was insufficiently reactive, the Pictet-Spengler reaction product **2.42** (Scheme 2.15). The amide function in **2.36** was reduced slowly,

but with significantly greater facility than that in **2.19**. Unfortunately, neither of the expected cyclization products **2.41** or **2.42** was seen; only reduced product **2.43** was isolated. Apparently the interception of the iminium ion was significantly slower than completion of the reduction.

Scheme 2.14



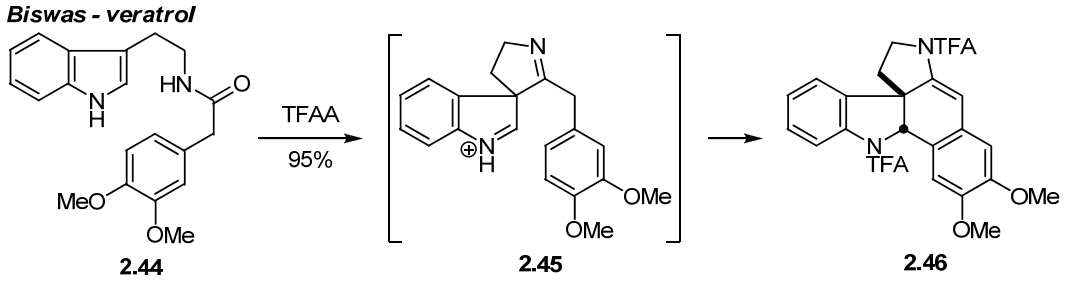
Scheme 2.15



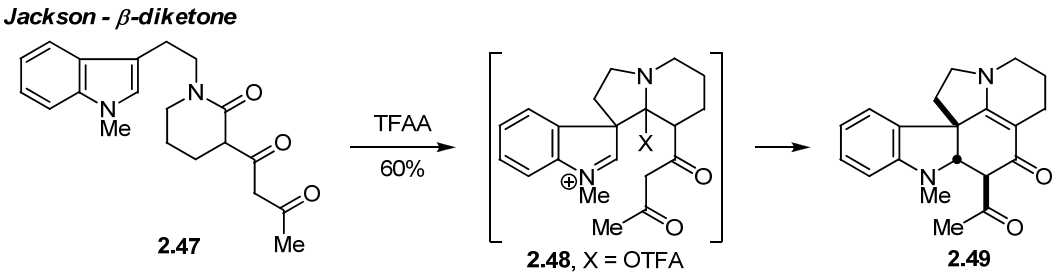
Another method to synthesize spirocyclic indolenines is the Bischler-Napieralski reaction. Spiro intermediates from the Bischler-Napieralski reaction have been trapped with pendant latent nucleophiles independently by both Biswas and Jackson.[81,82] Both research teams found that trifluoroacetic anhydride (TFAA) was effective in forming

imidate ions such as **2.45** and **2.48** from tryptamine-derived amides to initiate cyclization (Schemes 2.16 and 2.17). As their traps, Biswas used veratrol **2.44** and Jackson used β-diketone **2.47**, illustrating good flexibility of nucleophiles able to trap the indolenium ions.

Scheme 2.16



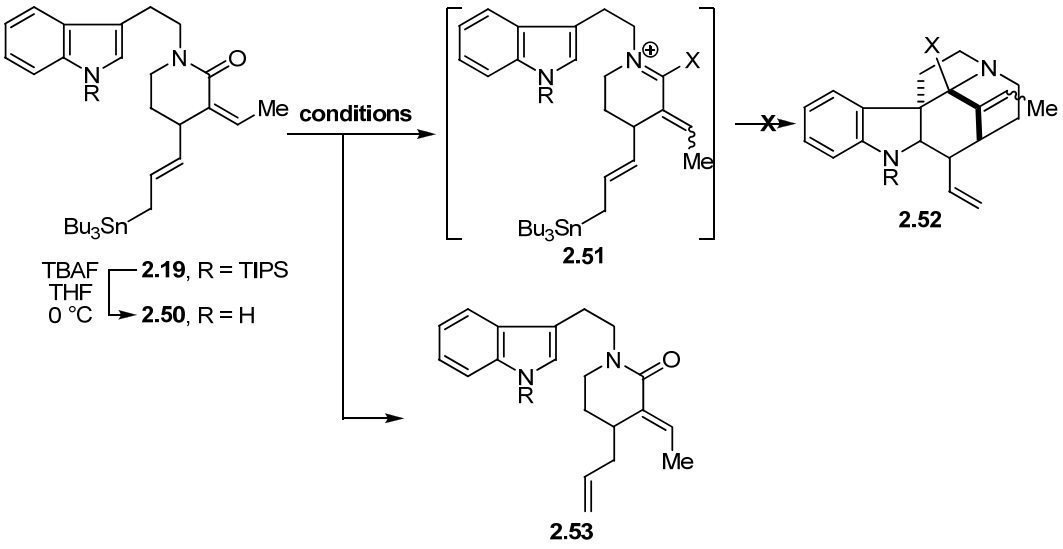
Scheme 2.17



Bischler-Napieralski processes begin at the same oxidation level as **2.19**, so instead of trying to partially reduce and intercept the transient intermediate **2.16**, the formation of an imidate ion would be more facile. Attempted mild formation of the imidate ion **2.51** (**X** = OMe) from **2.19** with Meerwein's salt in the presence of 2,6-di-*tert*-butylpyridine, caused no discernable reaction. However, exposure of **2.19** to

trifluoroacetic anhydride resulted in compound **2.53**. The desired cyclization to **2.52** was again not seen, but the geometry of the ethylidene group in **2.53** had changed from *Z* to *E*. This could have been a secondary result of the formation of the long sought cation **2.51**. If **2.51** were formed, tautomerization could lead to the energetically favored *Z*-isomer. Additionally, the stannane was lost, and to rule out adventitious acid as the culprit, the reaction was repeated in the presence of 2,6-di-*tert*-butylpyridine, but **2.53** was obtained again. The data suggest the iminium ion may have been formed, but the cyclization was not taking place.

Scheme 2.18



R =	conditions	X =	temp.	product(s)
TIPS	$(CH_3)_3OBF_4$, di-*t* Bu-pyridine	OCH_3	rt	RSM
TIPS	TFAA	$OCOCF_3$	0 °C to rt	**2.53**
TIPS	TFAA, di-*t* Bu-pyridine	$OCOCF_3$	0 °C to rt	**2.53**
H	$(CH_3)_3OBF_4$, di-*t* Bu-pyridine	OCH_3	rt	RSM

RSM = recovered starting material

The adverse result could have stemmed from deactivation of the indole as a nucleophile, or the inability of the nucleophilic indole C(3) and electrophilic iminium ion

to achieve sufficient proximity to react. There are examples of silylated indoles undergoing the Pictet-Spengler reaction, and there is an isolated example from Nishida in which it was found that *tert*-butyldimethylsilyl protection was beneficial.[83] However, this did not appear to be true of **2.19**, and the bulk of the triisopropylsilyl group may have impeded the approach of the electrophile.

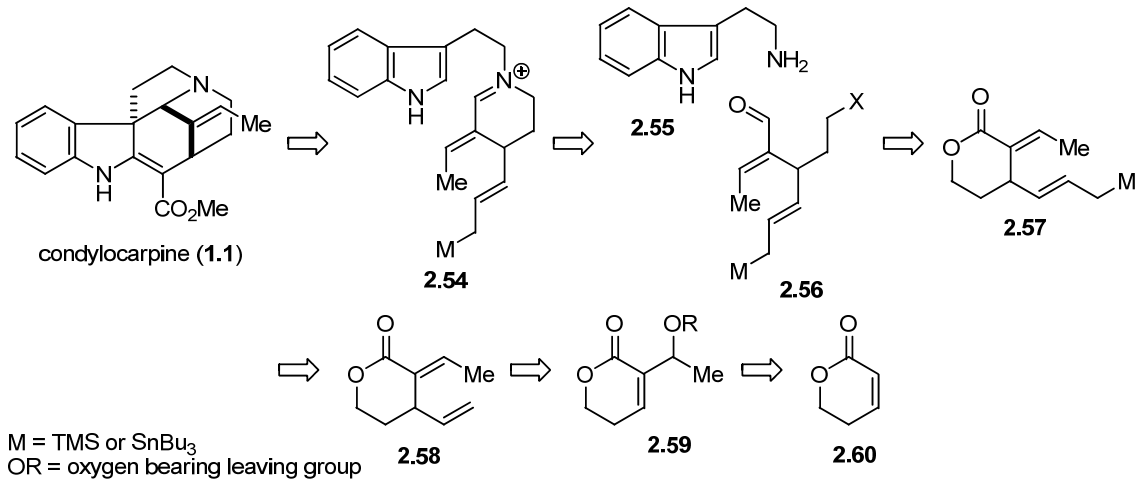
Removal of the TIPS protecting group from **2.19** with fluoride ion proceeded smoothly to give **2.50**, but upon exposure to Meerwein's salt in the presence of 2,6-di-*tert*-butylpyridine cyclization still did not take place. The reluctance of **2.19** to undergo reaction prompted reexamination of it as the penultimate compound to the cascade initiator **2.16**. Concomitantly we aspired to make the approach to the putative cascade compound more expedient than the prior 14 step pathway.

1.6.2 Second Generation Approach

The iminium ion cascade sequence stemming from **2.16** was still very attractive as a key transformation, but the approach to this intermediate needed to be modified. The typical Pictet-Spengler reaction is initiated by the condensation of an amine and an aldehyde. Using that disconnect made it apparent that the necessary iminium ion **2.54** could be a product of the reaction of tryptamine (**2.55**) and **2.56** (Scheme 2.19). Such a process would not only allow formation of two carbon-carbon bonds and two rings, it would also form the two carbon-nitrogen bonds of the piperidine ring all in one cascade. Although more was being demanded from the conversion **2.56** $\rightarrow$ **2.54** than **2.19** $\rightarrow$ **2.18**, the novel route had the possibility of isolable useable intermediates (i.e., imine formation or amine displacement of the leaving group) if the reaction did not proceed all of the way to **2.54**. In the event of partial completion of the cascade sequence the intermediates would act as direct evidence of desired transformations as well as being useful for

conversion to **2.54**. Like the first generation approach, the addition of the latent nucleophile was flexible, allowing for the introduction of different metals (M) should it prove necessary. Overall, the transformation from **2.60** to **2.56** should be stepwise efficient as well.

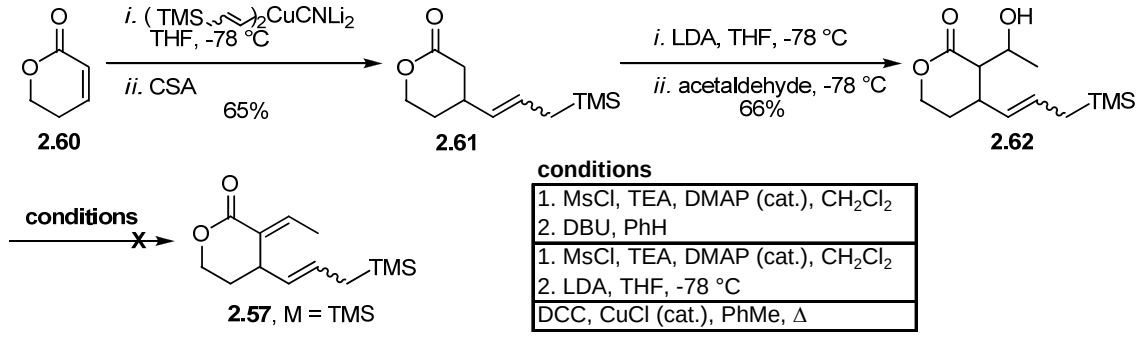
Scheme 2.19



The diene **2.58** was envisioned as the product of an addition/elimination sequence, where a vinyl cuprate would be added to an appropriately modified Baylis-Hillman reaction adduct **2.59**. Unfortunately, the Baylis-Hillman reaction works notoriously poorly on α,β-unsaturated carbonyl compounds with substitution at the β-position.[84] To avoid this issue entirely, a modified approach was adopted wherein the allyl nucleophile was added to dihydropyrone **2.60** first to give **2.61**. Although the aldol reaction of **2.61** with acetaldehyde provided **2.62**, the elimination to give **2.57** was unsuccessful, negating the benefit of the route as a quick and simple access to the key step precursor (Scheme 2.20). Mesylation of **2.62** with methanesulfonyl chloride and triethylamine provided a mixture of sulfonylated alcohol diastereomers that were used

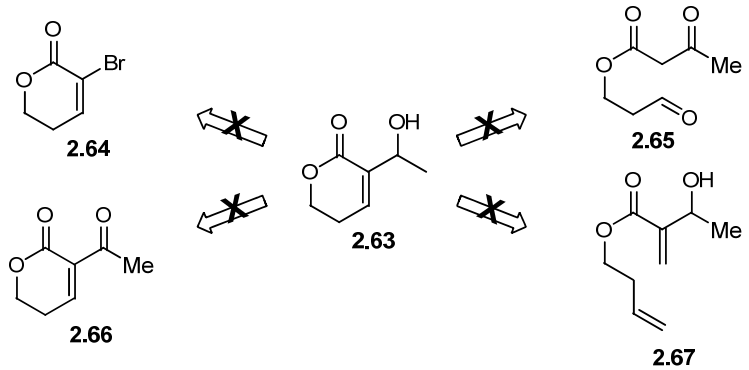
without purification. Elimination of the mesylate mixture with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) provided a complex mixture of compounds containing no **2.57**. Elimination of the mixture of mesylates with lithium diisopropylamide, *via* an $E1_{cb}$ mechanism, also produced a complex mixture of compounds, and no **2.57** was detected. The DCC imidate elimination protocol that was successful in the first generation approach (**2.17** → **2.19**) failed to transform **2.62** to **2.57**.

Scheme 2.20



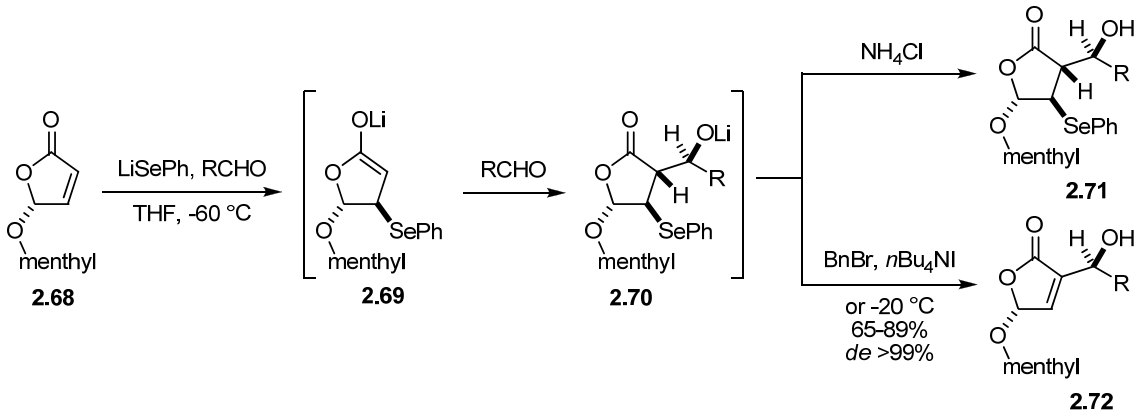
Several alternate methods for the synthesis of Baylis-Hillman-type adduct **2.63** were attempted (Scheme 2.21). Intermediate **2.63** was more difficult to acquire than expected and could not be made easily from retrons **2.64**-**2.67**.

Scheme 2.21



Recently, Jauch developed a novel selenation-elimination protocol to give a net Baylis-Hillman reaction of substrates not normally amenable to either standard or forcing conditions.[84,85] For example enantioenriched γ-substituted butenolides such as **2.68** did not undergo Baylis-Hillman reaction under typical conditions, and when harsh conditions, i.e., stronger bases and/or higher temperatures, were used to promote the reactions, the enantiomeric excess of the epimerization prone butenolides was degraded. Jauch replaced the more common amine bases with a phenyl selenyl anion, apparently forming **2.70** from **2.69**. If the reaction was quenched with ammonium chloride at -78 °C compound **2.71** was isolated, supporting the hypothesis of **2.69** and **2.70** as intermediates. Elimination of phenyl selenol from **2.70** was promoted by either *O*-alkylating **2.70** with benzyl bromide, or by warming the reaction mixture containing **2.70**, producing **2.72** in good to excellent yields accompanied by excellent diastereomeric excess (Scheme 2.22).

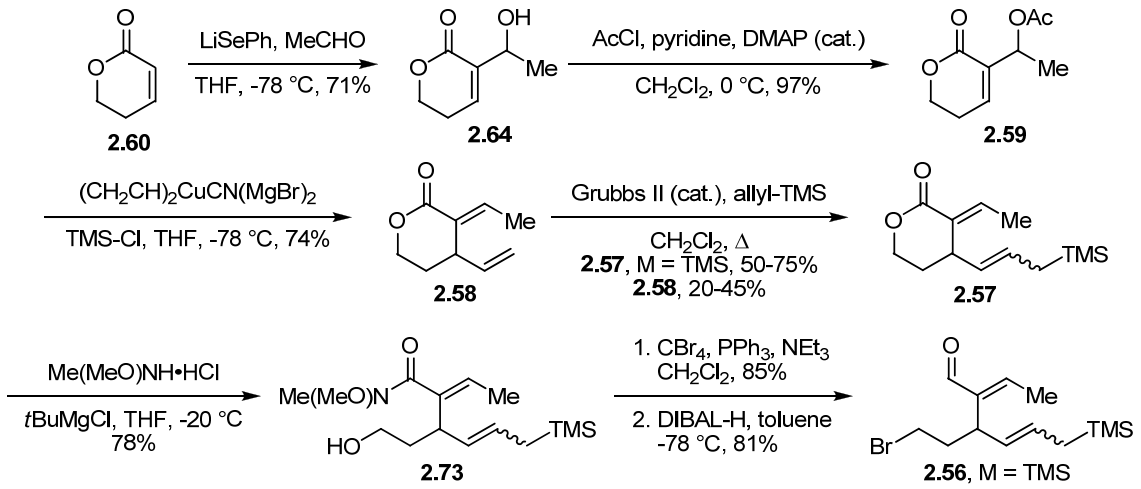
Scheme 2.22



Applying Jauch's technology to dihydropyrone **2.60** proved immediately successful, and alcohol **2.64** was thus obtained in good yield (Scheme 2.23). The product

mixture contained selenated compounds which gave additional amounts of **2.64** upon exposure to hydrogen peroxide. Acetylation of **2.64** followed by vinyl cuprate addition provided diene **2.58** and a small amount of the diene corresponding to the direct displacement of the acetoxy group.

Scheme 2.23



Olefin metathesis is finding more and more use as a standard olefination technique.[86-89] The benefits include the ready availability of olefin containing starting materials and the ability of olefins to tolerate a wide variety of reaction conditions, allowing them to be carried through many steps without the need for protection. In addition to the preeminent ring closing metathesis (RCM), cross metathesis (CM) is becoming progressively more commonplace.[90,91]

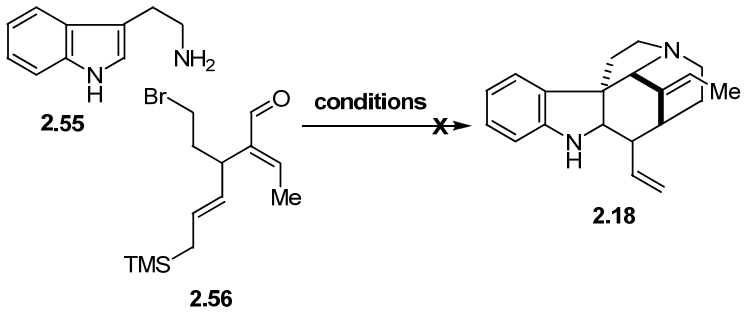
Using CM for incorporation of the allyl nucleophile greatly simplified introduction of the pendant nucleophile, and removed the multistep production of allylsilane cuprates previously needed (i.e., **2.60** → **2.61**, Scheme 2.20). The late stage CM also allowed different nucleophiles such as allyl stannane or allyl halide, for

conversion to an allyl metal, to be appended based on need. The percent conversion of **2.58** to **2.57** by CM with allyltrimethylsilane was somewhat variable, but the yield of **2.57** was always good based on conversion (Scheme 2.23). If allyltrimethylsilane were inadequately nucleophilic allyltributylstannane could be introduced in the same fashion using Schrock's metathesis catalyst.[92] It was necessary to open the lactone **2.57** in such a fashion as to be able to differentiate between the two oxygen bearing termini. This goal was achieved *via* the formation of the so-called Weinreb's amide **2.73**. Using Weinreb's own aluminoamidation conditions proved inferior to the more reactive magnesioamide.[93] The magnesioamide must be made in situ via due to instability, so a common side reaction is addition of the Grignard reagent used to form the magnesioamide to the substrate and product. Use of *tert*-butylmagnesium chloride instead of the more common isopropylmagnesium chloride reduced the amounts of undesired addition of the Grignard reagent to the starting **2.57** and **2.73**. Appel type halogenation of **2.73** and partial reduction of the Weinreb amide to the aldehyde gave the cascade precursor **2.56**.

Exposure of aldehyde **2.56** to tryptamine (**2.55**) did not provide the cascade product **2.18** or any of the possible intervening intermediates, and the aldehyde was recovered in excellent yield (Scheme 2.23). Increasing the temperature and/or time of reaction, and adding 4 Å molecular sieves did not give **2.18**. Activation of the aldehyde with trifluoroacetic acid or activation of the bromide with silver trifluoromethanesulfonate also did not give **2.18**. Performing the reaction in an NMR tube and monitoring progress by ^{1}H-NMR indicated that the aldehyde **2.56** was untouched, and after extended periods (many days to several weeks) it would slowly degrade. In many cases, the tryptamine degraded more rapidly than the aldehyde. Using conditions that did consume **2.56** in a timely fashion, i.e., not multiple weeks, produced complex mixtures without key ^{1}H-NMR resonances or low resolution mass spectra

(LRMS) peaks characteristic of any desirable products or intermediates. Spectra were also examined for intermediary and possible side products of interest, but none were visible.

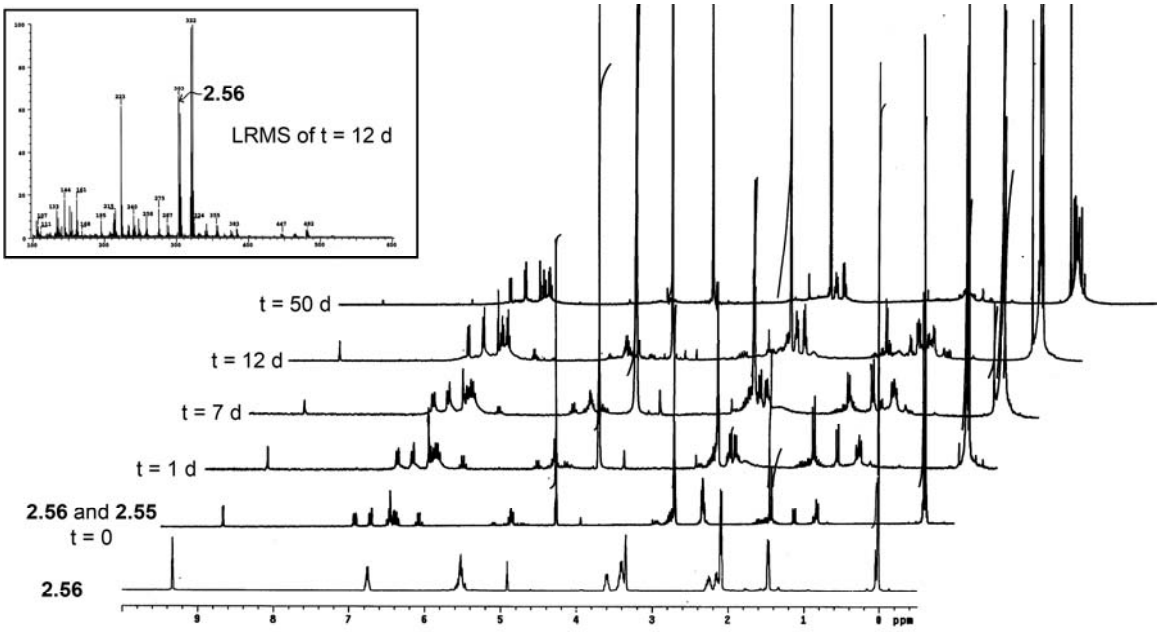
Scheme 2.24



conditions			
X =	**solvent**	**additives**	**temp.**
Br	PhMe	4 Å sieves	rt to 90 °C
Br	EtOH	-	rt to 55 °C
Br	CD_3COD	-	60 °C
Br	toluene-d_8	4 Å sieves	rt to 60 °C
Br	CD_3CN	TFA	rt to 60 °C
Br	PhMe	AgOTf 4 Å sieves	rt

An example of a ^{1}H-NMR reaction of **2.56** and **2.55** is shown in Figure 1. The bottom spectrum is **2.56** in methanol-d_4, the second from bottom is the same solution of **2.56** with **2.55** added. The rest of the spectra are of the mixture after heating at 35 °C for the specified times. The aldehyde peak (ca 9.4 ppm) and the alkenyl proton β to the aldehyde (ca 6.8 ppm) never totally vanish, and are still visible at 50 elapsed days. The inset is the low resolution mass spectrum (LRMS) of the reaction mixture taken at day 12. While **2.56** is not the base peak it is still quite significant.

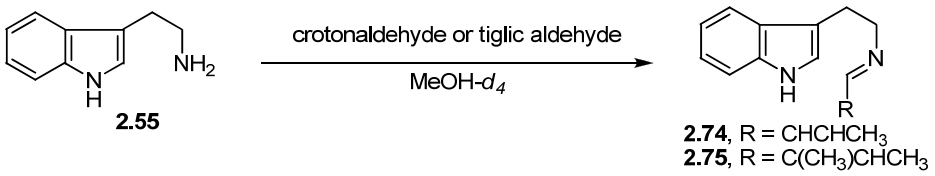
Figure 2.1



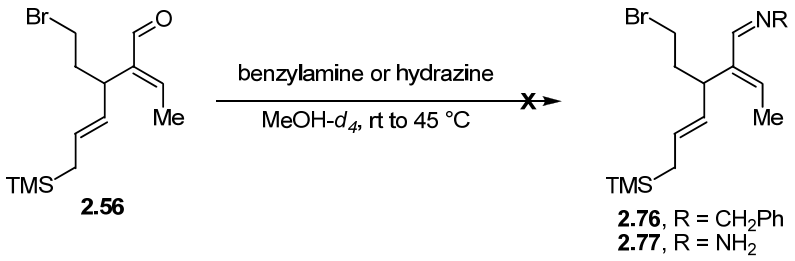
Although aldehyde **2.56** should have readily reacted with tryptamine (**2.55**) it did not. Anecdotal information about aldehyde to imine condensations, especially of α,β-unsaturated aldehydes, indicates that the rate can vary widely from aldehyde to aldehyde and amine to amine without an obvious trend. To probe the issue of severely moderated activity a simple cross comparison was performed. A quick determination of the requisite reaction time of tryptamine (**2.55**) with crotonaldehyde and tiglic aldehyde did show that the α-substitution retarded the reaction, but both were still quite rapid and were essentially complete within 12 hours (Scheme 2.25). Combination of **2.56** with benzylamine or hydrazine provided, again, only slow decomposition of the aldehyde (Scheme 2.26). The series of ^{1}H-NMR spectra of the reaction mixture containing benzylamine and **2.56** showed characteristic deshielding of the benzylic protons over time typical of falling pH, which would suggest that the bromide was being eliminated

from **2.56**. There was an excess of the amine to act as a base, so the hydrobromic acid should not have caused any undesirable reactions or effects.

Scheme 2.25

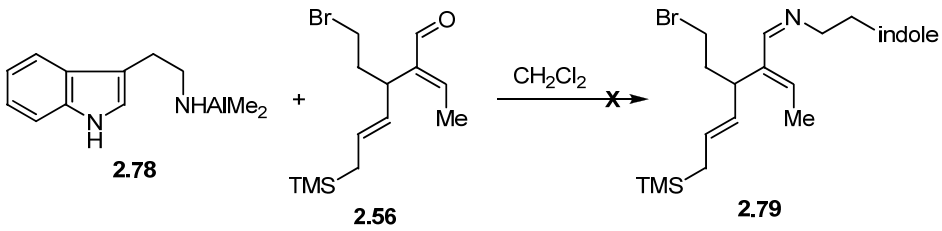


Scheme 2.26



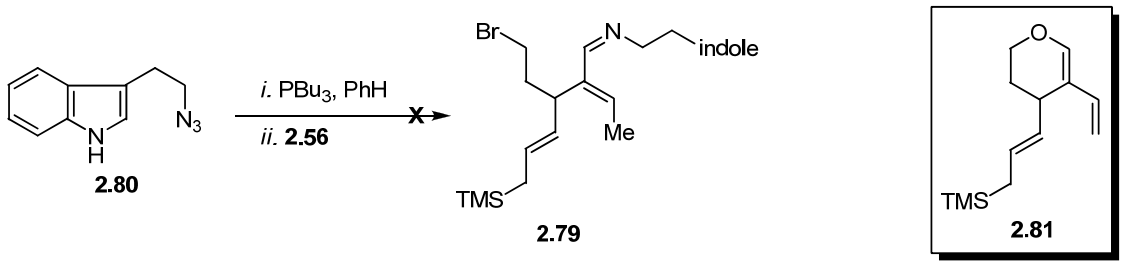
After the lack of success in activating either the aldehyde or bromide of **2.56**, the nucleophilicity of tryptamine (**2.55**) was examined. The use of aluminoamides as enhanced nucleophiles for esters is common, so they might also be useful for unreactive aldehydes.[94,95] The known aluminoamide of tryptamine, **2.78**,[96] was combined with **2.56**, but this reaction only provided decomposed material, albeit significantly faster than previously (Scheme 2.27).

Scheme 2.27

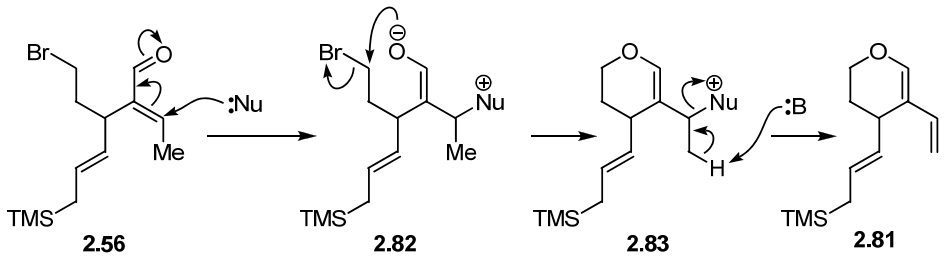


The known azide of tryptamine **2.80** was prepared and transformed into its aza-Wittig reagent *via* a Staudinger reaction (Scheme 2.28).[97] Addition of **2.56** to this mixture did not provide **2.79**, but it did produce **2.81** in excellent yield. This interesting side product may have arisen from 1,4-nucleophilic attack engendering **2.82**, cyclization to **2.83**, and subsequent elimination to **2.81** (Scheme 2.29).

Scheme 2.28



Scheme 2.29



2.3 OUTLOOK AND CONCLUSIONS

The unusual stability of the key step precursors has made the total synthesis of condylocarpine (**1.1**) very challenging. However, the greater the challenge the greater the reward. A third generation approach designed upon the scaffold of the two unsuccessful routes is currently in the very preliminary stages of chemical exploration.

While the total synthesis of condylocarpine (**1.1**) has yet to be achieved a number of interesting transformations have been utilized in the attempt. The application of Jauch's selenol-Baylis-Hillman reaction to a novel substrate exemplifies the substrate flexibility of the little-used transformation. While the use of organoselenium compounds is generally avoided, the transformation of **2.60** to **2.64** was rapid, facile, and high yielding. The addition of hydrogen peroxide (30%) to the work up procedure ensured that all of the selenium by-products were water soluble, and easily separated from the organic products. The reaction can be an excellent alternative to some of the less reactive Baylis-Hillman reaction variants, in the transformation of sluggish activated alkenes.

The vinyl cuprate addition/elimination sequence coupled with the cross metathesis proved to be an effective way to rapidly form substituted skip-dienes. The CM reactions to install allyl trimethylsilane were performed in 2003, and since then the field has exploded with examples illustrating the diversity of CM as an olefination reaction surrogate.

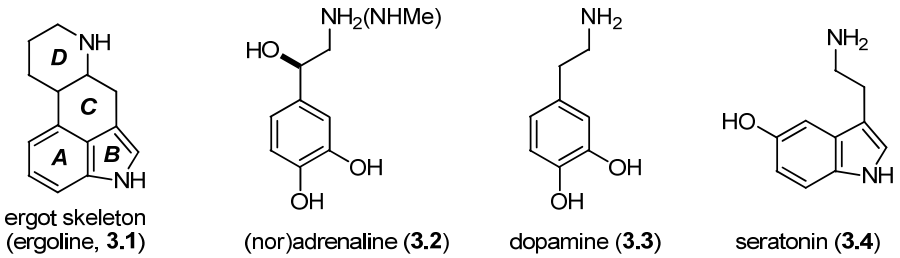
Chapter 3: Methyl Lysergate

3.1 INTRODUCTION

The ergot family of alkaloids possesses the widest spectrum of biological activity found in any family of natural products. Throughout its history, the fungi that produce the ergot alkaloids have been both boon and bane to those who come into contact with them. Historically, people and livestock who inadvertently consumed grain tainted with ergot became ill or died, and recently ergotism (vomiting, diarrhea, hallucinations, and possible gangrene) has been proposed as the cause of perceived witchcraft leading to the Salem witch trials.[98]

Today, ergot alkaloids have found widespread clinical use, and more than 50 formulations contain natural or semisynthetic ergot alkaloids.[99] They are used in the treatment of an immense array of diverse conditions including uterine atonia, postpartum bleeding, migraine, orthostatic circulatory disturbances, senile cerebral insufficiency, hypertension, acromegaly ('giantism', a pituitary disorder), and Parkinsonism. New therapeutic applications are continually emerging such as those based on antibacterial and cytostatic effects, as well as immunomodulatory and hypolipemic activity. The broad physiological effects of ergot alkaloids are based mostly on their interactions with neurotransmitter receptors on cells. The presence of pharmacophores resembling some important neurochemical mediators (e.g., noradrenaline (**3.2**), serotonin (**3.3**), dopamine (**3.4**)) in ergot alkaloids (*cf.* **3.1**) could explain their interactions with these receptors (Figure 3.1).[100]

Figure 3.1

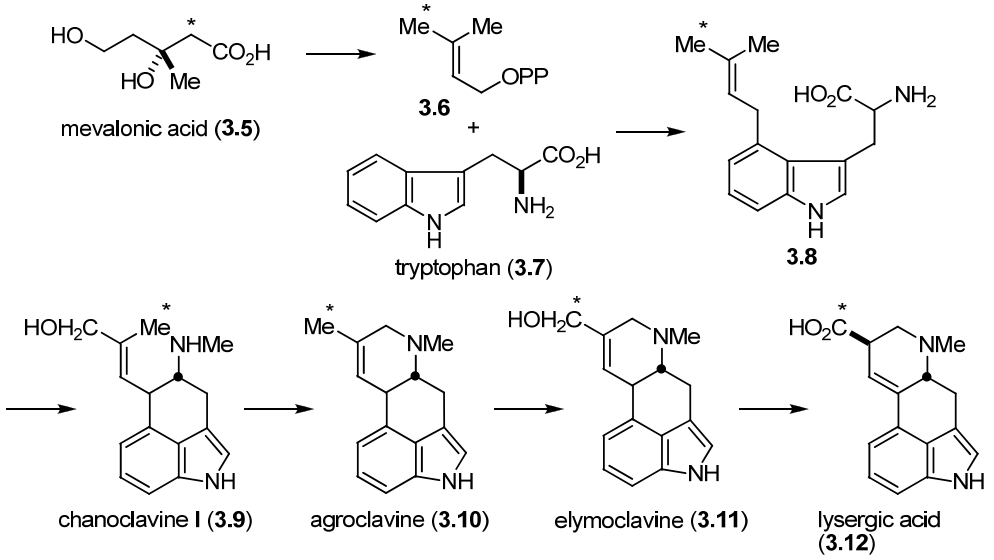


ergot skeleton (ergoline, **3.1**) (nor)adrenaline (**3.2**) dopamine (**3.3**) seratonin (**3.4**)

3.2 BIOGENESIS OF THE LYSERGATES

The indole ring contained within the ergot framework implies tryptophan (**3.7**) as a precursor in its biosynthesis. Through feeding experiments with ^{14}C-labelled tryptophan, Mothes showed that this was in fact the case for ergometrine and ergopeptine (not shown).[101] In similar fashion, several groups found that the incorporated isoprenyl unit was formed from mevalonate, parallel to terpene biosynthesis.[101-107] The biogenic proposal involved mevalonic acid (**3.5**) being reduced to isoprene unit **3.6** and appended to tryptophan (**3.7**) to give 4-(γ,γ-dimethylallyl)tryptophan (DMAT, **3.8**) (Scheme 3.1). An interesting facet of the biogenesis was realized with terminally ^{14}C-labelled DMAT (**3.8**). The DMAT (**3.8**) cyclized to form chanoclavine I (**3.9**) with the labeled carbon proximally disposed to the amine as drawn. In the cyclization to agroclavine (**3.10**), the labeled carbon was ultimately positioned distally to the amine. Terminal oxidation of **3.10** to elymoclavine (**3.11**) and migration of the double bond provided lysergic acid (**3.12**).

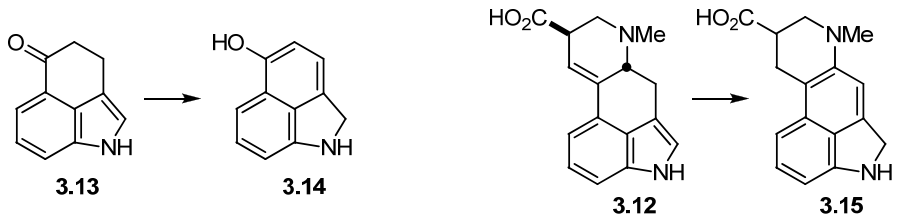
Scheme 3.1



3.3 SYNTHESIS OF LYSERGATES

Due to their historical importance and medicinal utility, the ergot alkaloids have been extensively studied. From the time when the first total synthesis of lysergic acid (**3.12**) was completed in 1954 by Woodward, it has remained a favorite target of synthetic chemists to showcase both novel methodologies and technical acumen.[108] The intricacies of the biogenesis, i.e., the reorganization of the terminal methyl group location, and the migration of the double bond, add interest, but make a true biomimetic synthesis impractical. The fact that indole containing tricycles such as Uhle's ketone (**3.13**) are known to isomerize to the favored naphthol **3.14** represents an additional synthetic challenge; lysergic acid (**3.12**) itself has undergone the analogous isomerization to **3.15** (Scheme 3.2).[109]

Scheme 3.2



3.13 3.14 3.12 3.15

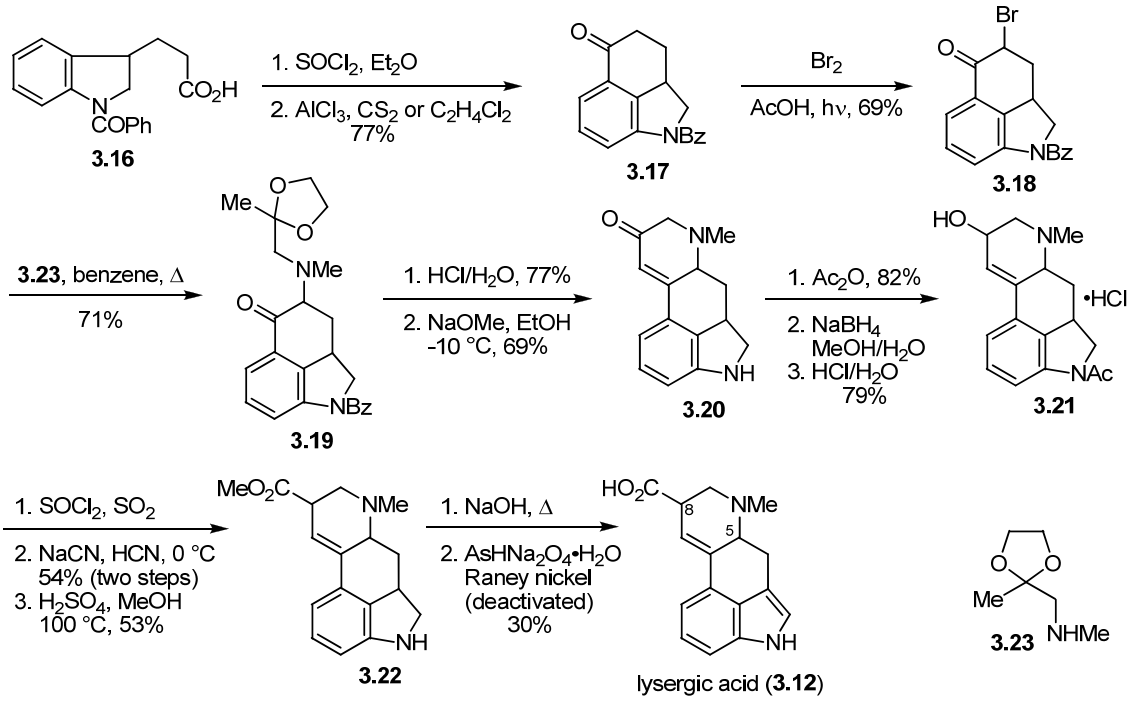
3.3.1 Synthesis of Lysergic Acid by Woodward

While the synthetic approach undertaken by Woodward and his research group was fraught with difficulties, they made some important decisions at the outset to minimize problems.[108,109] To avoid the possibility of the indole C(2)-C(3) double bond migrating, it was omitted, a tactic adopted by other research groups in several later total syntheses of lysergates. The reduced indole compound **3.16** was cyclized under Friedel-Crafts conditions to give Kornfeld's ketone (**3.17**), a reduced version of Uhle's ketone (**3.13**) (Scheme 3.3). The ketone **3.17** was α-brominated to give **3.18**, and aminated to **3.19** with functionalized amine **3.23**. At that stage, all of the skeletal carbons were in place save one, the ester carbon attached to C(8).

Prior attempts to displace the bromide of **3.18** had failed, and an extensive study was performed to find a solution. The solution that was found was laborious and, stepwise, quite lengthy. Eventually it was discovered that if the amination of **3.18** was carried out in non-polar solvent it was successful, removing ten stages from the alternate route. Hydrolysis of the ketal moiety in **3.19** followed by aldol cyclization and cleavage of the benzamide furnished **3.20**. The secondary amino group in **3.20** was acetylated, the ketone was reduced, and the product was made into the amine salt **3.21**. The alcohol in **3.21** was homologated to the methyl ester **3.22** utilizing standard procedures. Hydrolysis of the ester and oxidation of the indoline to the indole completed the first synthesis of

lysergic acid (**3.12**). While the stereochemistry at C(5) and C(8) were not explicitly given, presumably it was *trans* as in the natural isomer. Later when Ramage performed a formal synthesis of lysergic acid (*vide infra*), he intercepted the Woodward penultimate carboxylic acid (not shown). Ramage used spectroscopic techniques unavailable to Woodward to show that Woodward's carboxylic acid, and presumably **3.12**, was a mixture of both α and β at the carboxylic acid.[110]

Scheme 3.3



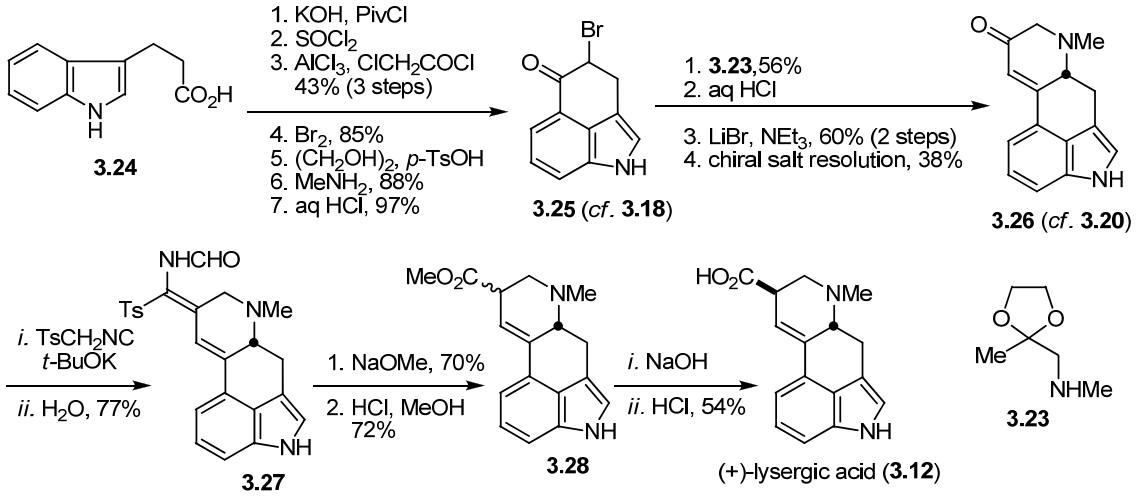
3.3.2 Synthesis of (+)-Lysergic Acid by Szántay

One of the more important contributions to the synthetic arena of the lysergates was the first enantioselective synthesis of lysergic acid by Szántay.[111,112] The foremost goal was to develop an asymmetric and scaleable route to (+)-lysergic acid. If the criteria were met, it would be an exceptionally valuable entry into the production of

enantiomerically enriched lysergate analogs. To achieve the latter goal, simple and effective chemistry needed to be used, so a route heavily based on that of Woodward was used.

Beginning with a modification of the modern method of Goto, a derivative of Uhle's ketone was synthesized from **3.24** (Scheme 3.4).[113] Bromination of **3.24**, followed by a series of protecting group manipulations, provided **3.25**, which was an oxidized, deprotected version of Woodward's intermediate **3.18**. Condensation of **3.25** with **3.23** followed by enantiomeric resolution provided **3.26**, which was an oxidized version of Woodward's tetracycle **3.20**. The use of *p*-toluenesulfonylmethyl isocyanide (TOSMIC) allowed Szántay to homologate the carbonyl group of **3.26** *via* **3.27** in only three steps, as opposed to Woodward's six, providing **3.28** as a mixture of diastereomers. According to Szántay, the hydrolysis of the methyl ester **3.28** concomitantly epimerized the mixture of diastereomers to (+)-lysergic acid (**3.12**). It is worth noting that all other reported syntheses of lysergic acid, or advanced intermediates containing either an acid or ester function, have provided mixtures of diastereomers when treated with base, acid, or heat. (±)-Lysergic acid (**3.12**) was carried on to make α-ergocryptine and α-ergocryptinine.

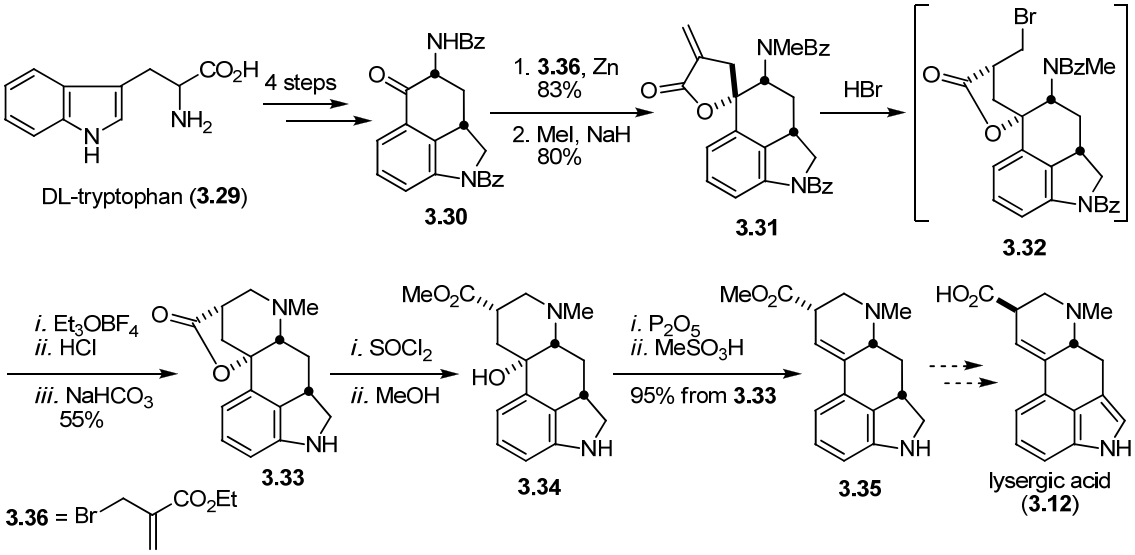
Scheme 3.4



3.3.3 Formal Synthesis of Lysergic Acid by Rebek

Another approach, starting from tryptophan (**3.29**), provided potential for an enantioselective synthesis.[114] Racemic tryptophan (**3.29**), possibly used due to the higher cost of the unnatural isomer that has the requisite stereochemistry for (+)-lysergic acid, was first transformed into ketone **3.30** (Scheme 3.5). Reaction of **3.30** with **3.36** in the presence of zinc led to **3.33**. At that point all of the skeletal elements and the appropriate overall oxidation state were in place; all that was required was reorganization of the lactone to the ***D*** ring. Hydrobromination of **3.31** gave **3.32**, which cyclized to **3.33** upon deprotection of the amine. The lactone in **3.33** was opened giving **3.34**. Elimination of the tertiary hydroxyl group provided reduced methyl isolysergate (**3.35**), thereby completing the formal synthesis.

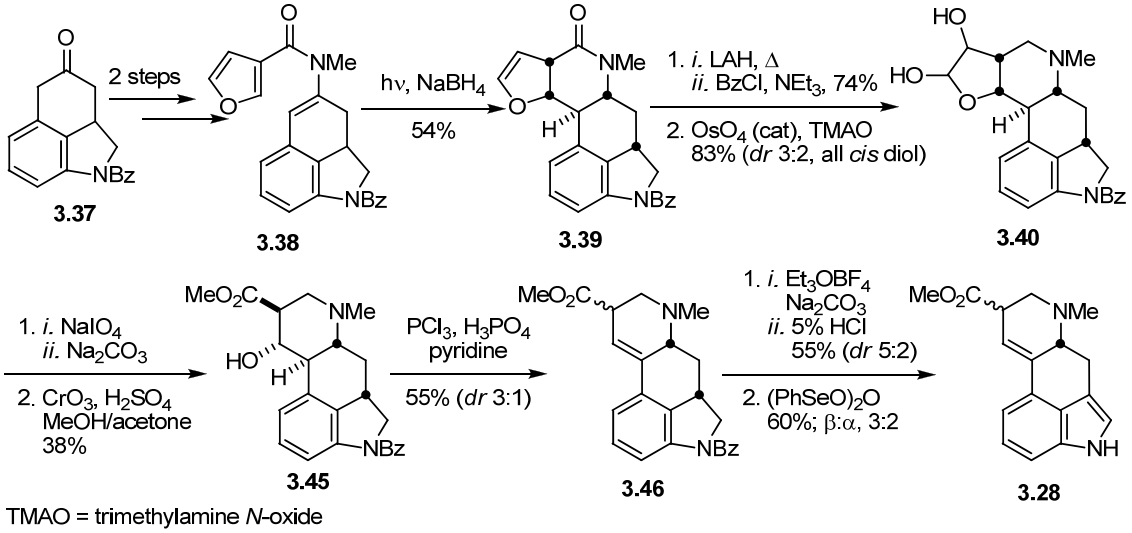
Scheme 3.5



3.3.4 Formal Synthesis of Lysergic Acid by Ninomiya

In an approach similar to that of Rebek, Ninomiya capitalized upon a reductive photocyclization to form the ***D*** ring as the final ring. A furan amide was appended to ketone **3.37**, an isomer of Kornfeld's ketone (**3.17**), to give cyclization precursor **3.38** (Scheme 3.6).[115] Exposure of **3.38** to light in the presence of sodium borohydride gave **3.39** as one of three diastereomers. All of the skeletal elements and the appropriate overall oxidation state were present. Reduction of the amide **3.39** and osmylation of the dihydrofuran afforded **3.40**. Both diastereomers of diol **3.40** were cleaved removing the superfluous ring. Oxidation of the formyl group in the presence of methanol afforded ester **3.45**, which is an epimeric diastereomer of Rebek's **3.34**. Elimination of the alcohol, deprotection, and oxidation to the indole provided methyl- and methyl isolysergate (**3.28**).

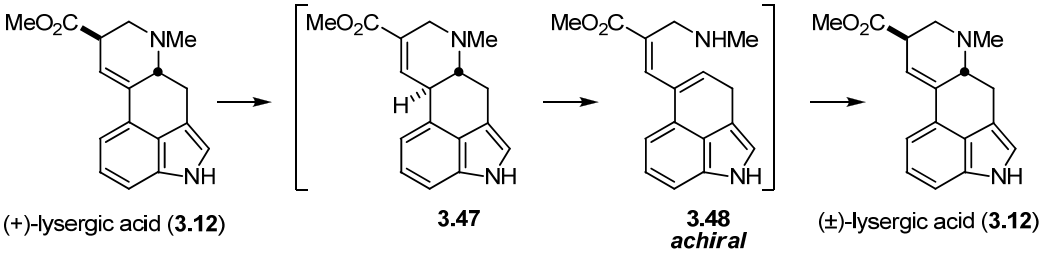
Scheme 3.6



3.3.5 Formal Synthesis of Lysergic Acid by Ramage

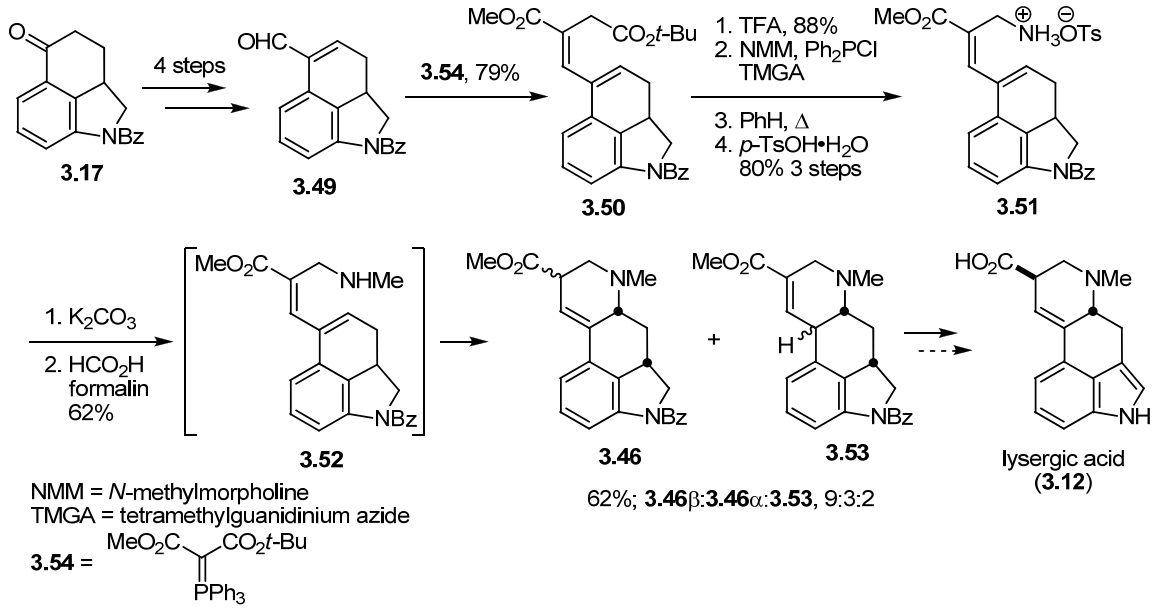
It has long been known that (+)-lysergic acid and some of its derivatives could be racemized by treatment with hot, aqueous barium hydroxide.[116] In a personal communication with Ramage, Woodward proposed that the racemization of (+)-lysergic acid (**3.12**) proceeded *via* the fragmentation of the ***D*** ring, possibly through **3.47**, to the achiral tricycle **3.48** (Scheme 3.7).[110] Addition of the amine in a 1,6-sense returned the lysergic acid structure, but without any memory of stereochemical purity.

Scheme 3.7



Based on the proposed mechanism of racemization of **3.12**, Ramage wanted to make **3.48**, or an appropriate analog, which would spontaneously generate lysergic acid (**3.12**). Taking Kornfeld's ketone **3.17** and transforming the carbonyl group into the α,β-unsaturated moiety in aldehyde **3.49** gave Ramage a functional handle to attach the necessary elements of the ***D*** ring (Scheme 3.8).[110] The Wittig reagent **3.54** provided the remaining skeletal carbons in **3.50** with exclusively the required double bond geometry for the key cyclization. The *tert*-butyl ester was transformed into amine salt **3.51**, the free base of which was 'exceedingly reluctant' to cyclize. Methylation of the amine using the Eschwieler-Clark reaction gave, presumably *via* **3.52**, a mixture of **3.46** and **3.53**. The secondary amine **3.52** cyclized sufficiently rapidly that it was not methylated a second time to give the dimethylamino analog. The mixture of **3.46** diastereomers was carried on to **3.22** (Scheme 3.3) to complete the formal total synthesis.[109]

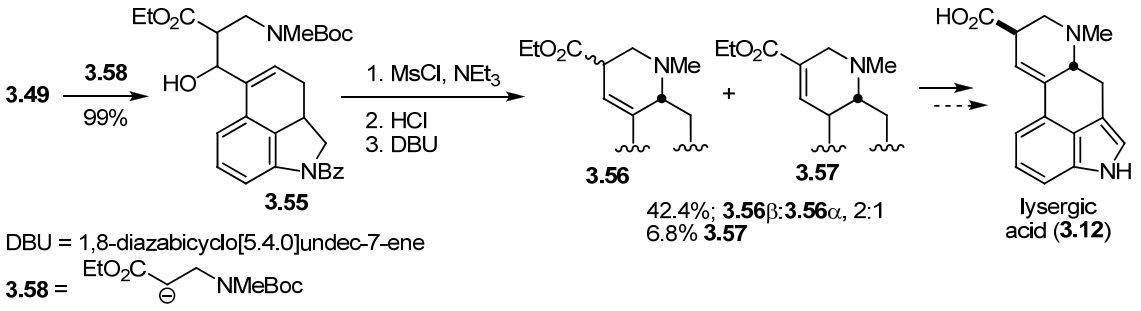
Scheme 3.8



3.3.6 Formal Synthesis of Lysergic acid by Kurihara

Following the same retrosynthetic approach as Ramage, Kurihara synthesized **3.55**, an analog of **3.48**.[117] Using aldehyde **3.49**, all of the remaining elements of lysergic acid were appended by means of anion **3.58** (Scheme 3.9). Deprotection of the amine and elimination of the alcohol from **3.55** provided a mixture of products **3.56** and **3.57** in similar ratio to **3.46** and **3.53** of Ramage, again presumably *via* the intermediacy of an α,β,γ,δ-unsaturated ester related to **3.52**. To complete the formal synthesis of lysergic acid (**3.12**), the ethyl ester of **3.56** was exchanged for a methyl ester, and the indoline amine was reprotected to intercept **3.46** a known compound in the formal synthesis of lysergic acid (**3.12**) by Ninomiya.[115]

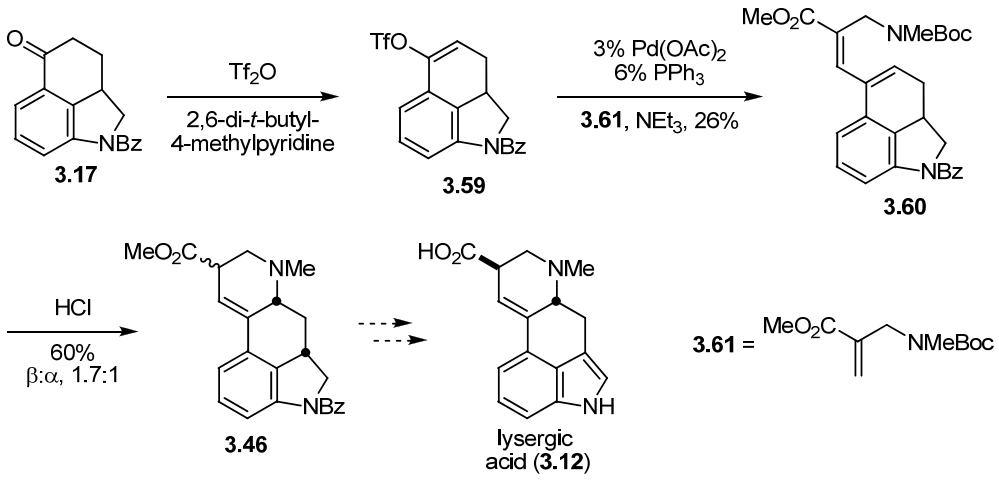
Scheme 3.9



3.3.7 Formal Synthesis of Lysergic Acid by Ortar

Expanding on the approach of Ramage and Kurihara, Ortar made the enol-triflate **3.59** from Kornfeld's ketone (**3.17**) and performed a Heck coupling with **3.61** to give **3.60** (Scheme 3.10).[118] Deprotection provided the cyclization product **3.46**.

Scheme 3.10

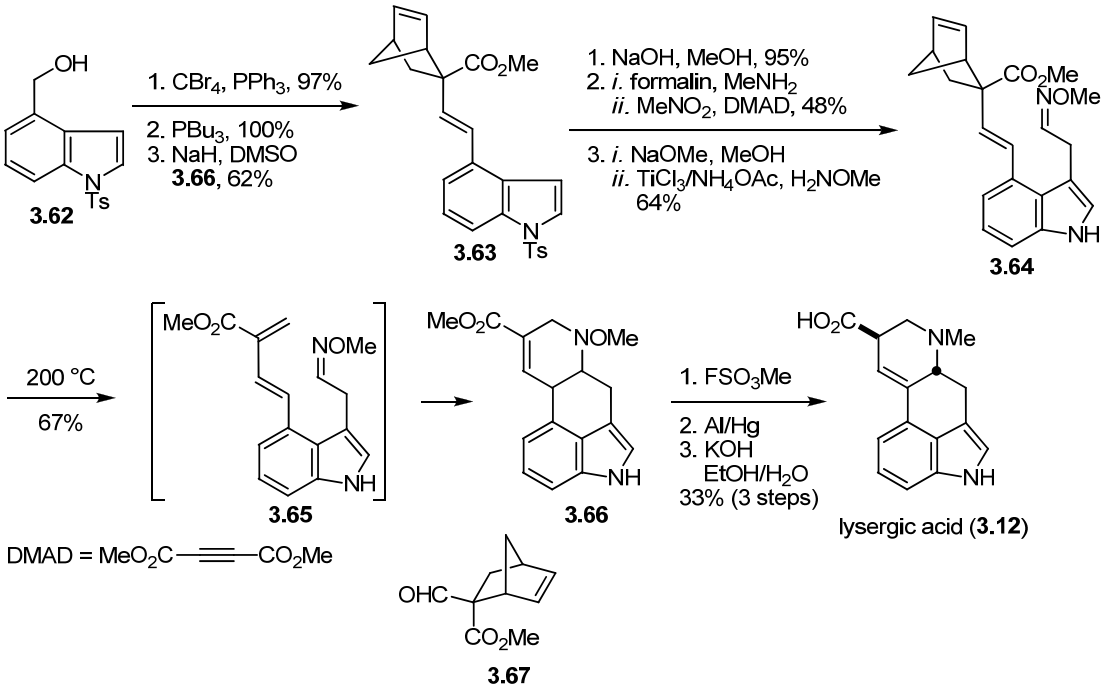


The yield of the palladium coupling of **3.59** and **3.61** to give **3.60** was moderate, but the direct use of ketone **3.17** versus aldehyde **3.49** removed six steps. That in addition to the increased efficiency with which the upper portion of the molecule was installed nets a significant improvement over the previous two routes.

3.3.8 Synthesis of Lysergic Acid by Oppolzer

Oppolzer developed an entirely different approach to lysergic acid. Instead of forming the ***c*** ring and then appending the ***D*** ring sequentially, the ***C*** and ***D*** rings were formed simultaneously. Beginning with indole carbinol **3.62**, a masked diene, which would later be used in an inverse demand Diels-Alder reaction, was installed giving **3.63** (Scheme 3.11).[119] An oxime ether was introduced at C93) of the indole affording **3.64**. Upon heating, retro [4+2] to deliver **3.65** that then cyclized by a Diels-Alder reaction to give tricycle **3.66**. Methylation of the amine of **3.66**, reduction of the resulting methoxyammonium ion, and hydrolysis of the ester and concomitant migration of the double bond, efficiently provided lysergic acid (**3.12**).

Scheme 3.11



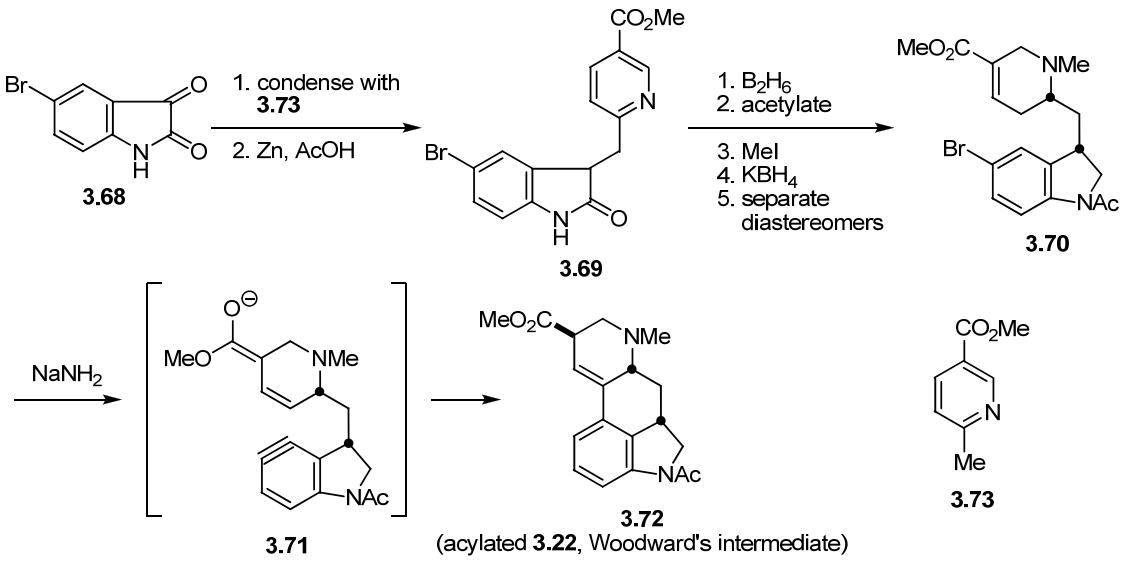
In what is probably the most biomimetic synthesis of a member of the lysergates, Oppolzer pioneered a route that would be mimicked several times in the syntheses of ergot alkaloids outside the lysergate family.[120]

3.3.9 Formal Synthesis of Lysergic Acid by Julia

In an alternate and unique approach, Julia reported an interesting formal synthesis of lysergic acid. Although the synthetic plan was comparable with many of the other syntheses, the ***D*** ring was introduced prior to the ***C*** ring. Methyl nicotinate (**3.73**) was condensed with 5-bromoisatin (**3.68**) to give **3.69** which contains almost all of the heavy atoms present for lysergic acid (Scheme 3.12).[121] After reduction of the amide group in **3.69** the resulting aniline was protected. *N*-Methylation and reduction of the pyridine ring provided a mixture of isomers that were separated, giving **3.70**. Treatment of **3.70**

with sodium amide cyclized the ***c*** ring, presumably *via* the intermediacy of the dienolate-benzyne **3.71**. The product **3.72** was claimed to be the same as the Woodward penultimate indoline **3.22** (Scheme 3.3) if it were acetylated. Because no yields were given it is impossible to judge the efficiency of this approach.

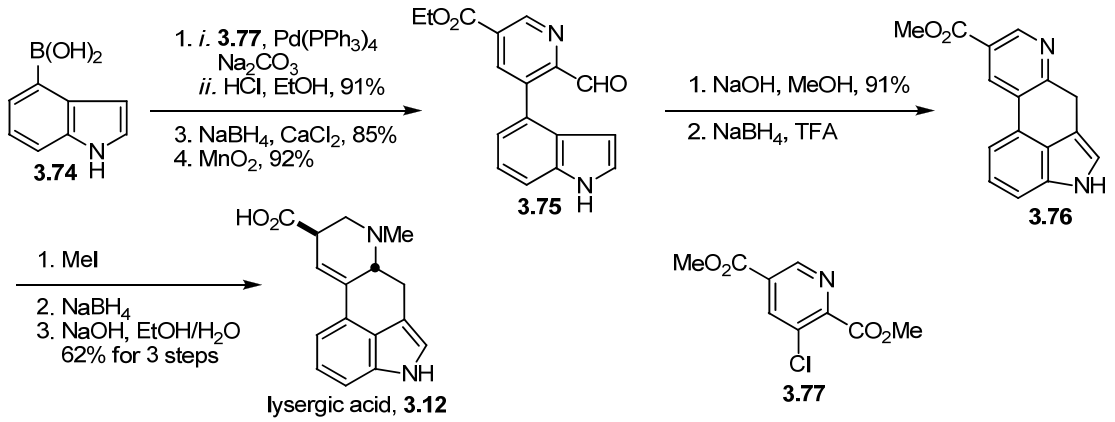
Scheme 3.12



3.3.10 Synthesis of Lysergic Acid by Hendrickson

Hendrickson also developed a unique approach to lysergic acid, in which the ***c*** ring was formed last; however, the bond formed that closes the ring is on the opposite side of the ***C*** ring from the closure by Julia. Coupling of indole-4-boronic acid (**3.74**) with chloropyridine dimethylester **3.77**, regioselective reduction of one of the, now ethyl, esters to an alcohol, and oxidation of the alcohol to an aldehyde gave **3.75** (Scheme 3.13).[122] Base-promoted cyclization of **3.75**, followed by reduction, provided tetracyclic methyl ester **3.76**. *N*-Methylation of the pyridine moiety, reduction of the ensuing pyridinium ion, and saponification furnished lysergic acid (**3.12**) *via* its methyl ester.

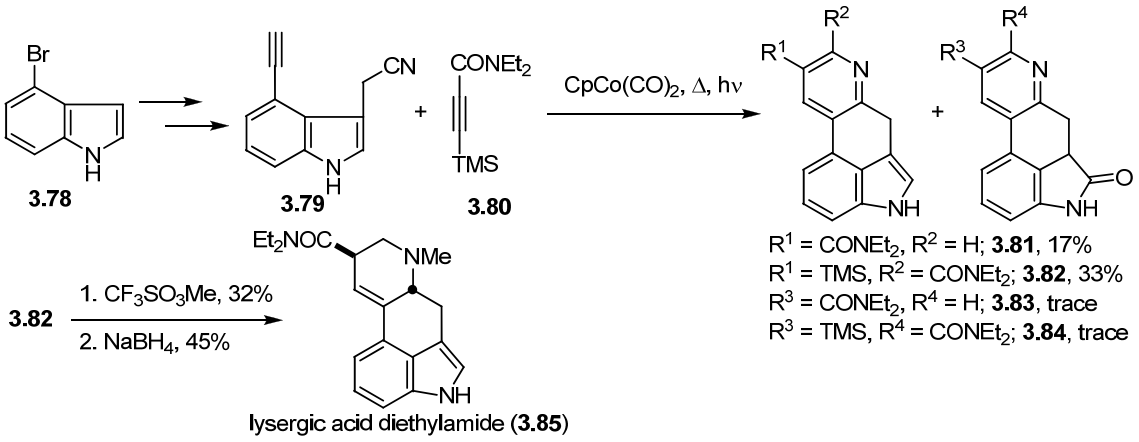
Scheme 3.13



3.3.11 Synthesis of Lysergic Acid Diethylamide by Vollhardt

Perhaps the most rapid synthesis of a lysergic acid derivative was performed by Vollhardt. As an example of the utility of his [2+2+2] cyclotrimerization, 4-bromoindole (**3.78**) was transformed into **3.79** (Scheme 3.14).[123] Exposure of **3.79** to alkyne **3.80** in the presence of catalyst, heat, and light gave a mixture of four compounds **3.81** - **3.84**. The desired compound **3.81** was isolated in only 17% yield, but the expedient route somewhat offsets the poor yield. After *N*-methylation and reduction of the pyridinium ion under standard conditions, lysergic acid diethylamide (**3.85**) was obtained in only seven steps.

Scheme 3.14



3.4 CONCLUSIONS

From the time of the original synthesis of lysergic acid (**3.12**) by Woodward there have been a number of improvements in the approach to lysergates, and some exciting methods have been showcased. Lysergic acid has been made enantioselectively by Szántay, and the formal synthesis by Ortar could potentially provide lysergic acid in as few as ten steps. Vollhardt's synthesis does not contribute greatly to the arena of lysergate total synthesis, but the exposition of his method is unparalleled in its stepwise efficiency. While individuals have addressed specific problems, no one synthesis has addressed all of them. In many of the syntheses, the indole C(2)-C(3) bond had to be reduced to preclude migration. Szántay and Vollhardt found ways to work around the indole without reducing it, while Oppolzer and Hendrickson used the inherent nucleophilicity of indole in their syntheses.

The C(9)-C(10) double bond has provided some difficulties to researchers either regarding its installation, or in the effect it has had on the C(8) stereocenter. Woodward and Szántay installed the C(9)-C(10) double bond directly, but in such a fashion that the

C(8) chiral center was introduced later and without control. Rebek and Ninomiya installed this double bond in the late stages of the synthesis by elimination, almost as an afterthought. Ramage, Kurihara, and Ortar all installed the olefin during the key steps of their respective routes, albeit from an achiral precursor with no possibility for stereochemical control of the stereo centers. Oppolzer, Julia, Hendrickson, and Vollhardt all had sp^2 centers at C(8) of their penultimate compounds. All of the syntheses contained some sort of equilibrating step late in the route that would give ratios of lysergates and isolysergates while the C(9)-C(10) double bond was migrated into place.

To take full advantage of any synthetic natural product or natural product analog as a pharmaceutical, access to both enantiomers is necessary. In some cases enantiomeric resolution is adequate, but enantioselective production of a compound is preferred once the desired configuration is known. The synthesis of Szántay provided an enantioenriched product and was scaleable, but the chiral centers were resolved and equilibrated, not controlled during installation.

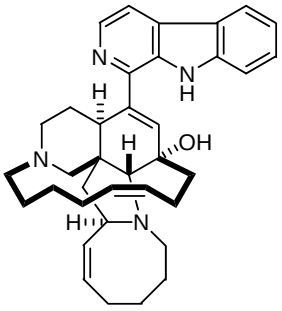
The optimum route to the lysergates would address all of the prior issues, not just one or two of them. The synthesis should be enantioselective, while maintaining expediency. The installation of the stereo centers should be controlled, so that there is no C(8) epimeric mixture. The oxidation states of the skeletal atoms should be modified as little as possible, i.e., the C(2)-C(3) double bond should be included for the entire time C(2) and C(3) are connected, not oxidized as a late stage transformation. Similarly the C(9)-C(10) double bond should be installed as a double bond, not a masked equivalent of a double bond.

Chapter 4: Studies Towards the Stereocontrolled Synthesis of (+)-Methyl Lysergate

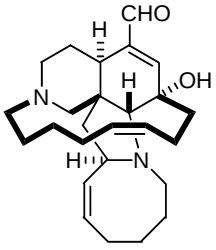
4.1 Prior Art from Within the Martin Group

The development of new and general strategies for the synthesis of biologically important natural and unnatural substances constitutes an area of considerable interest in organic chemistry. In this context, we were attracted some years ago to the potential of using ring closing metathesis (RCM) reactions as key constructions for alkaloid synthesis.[124-126] We have reported the application of such reactions to the syntheses of manzamine A (**4.1**), ircinal A (**4.2**), (+)-anatoxin-α (**4.3**), and (+)-8-*epi*-xanthatin (**4.4**), among others (Figure 1).[127-132] As part of an ongoing program in developing the utility of RCM reactions, we were intrigued by the possibility of exploiting such a construction in formulating a novel synthetic approach to the tetracyclic ergot alkaloid methyl lysergate (**3.28**) *via* cyclization of a precursor diene.

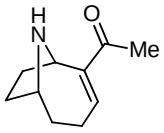
Figure 4.1



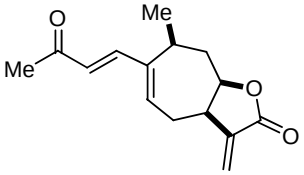
manzamine A (**4.1**)



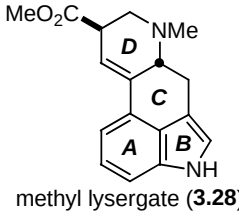
ircinal A (**4.2**)



(+)-anatoxin-α (**4.3**)



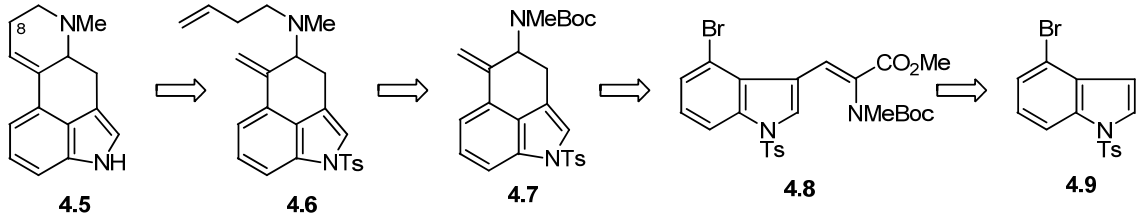
(+)-8-*epi*-xanthatin (**4.4**)



methyl lysergate (**3.28**)

Prior to the current work, a synthesis of the C(8) unsubstituted analog **4.5** was examined. The retrosynthetic analysis depended upon a late-stage RCM to provide **4.5** (Scheme 4.1).[133] The precursor of **4.5**, diene **4.6**, was seen as arising from deprotection and alkylation of amine **4.7**. The ***A***, ***B***, ***C*** tricycle **4.7** could arise from a derivative of a dehydrotryptophan such as **4.8**, which should be accessible from the 4-bromoindole **4.9**.

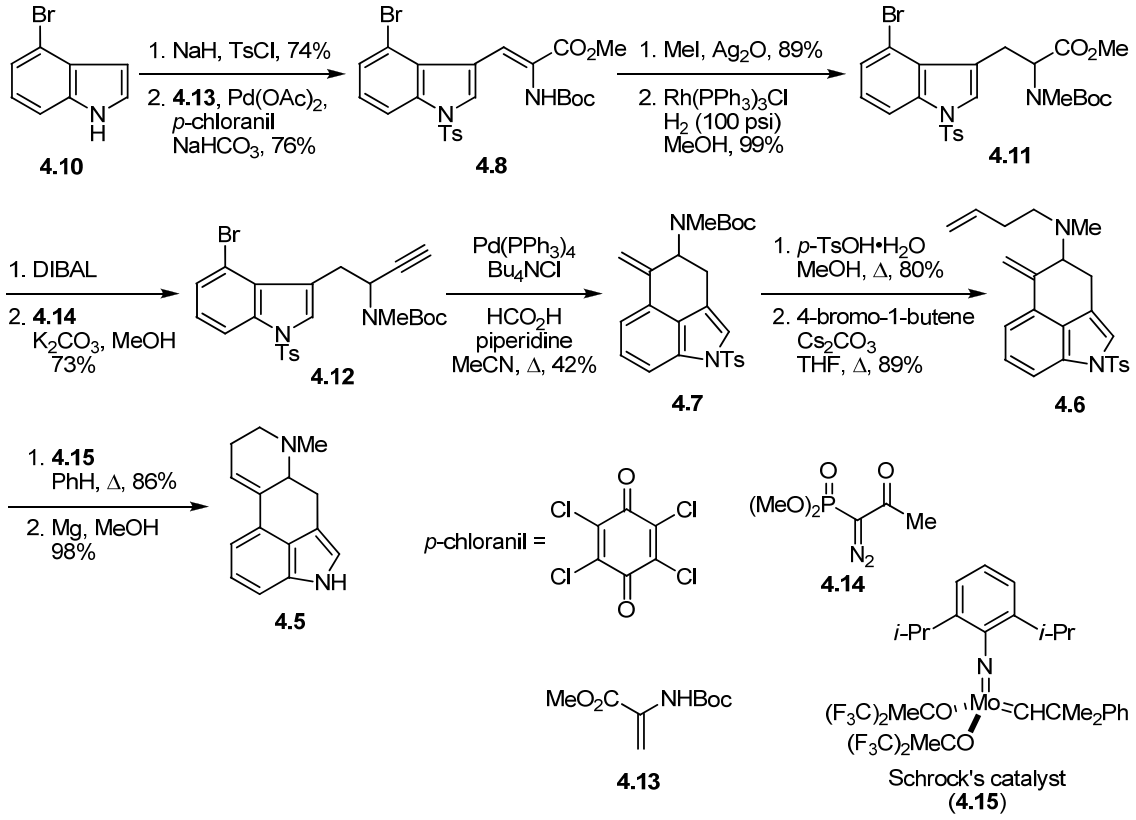
Scheme 4.1



Application of this route was straightforward. Tosylation of 4-bromoindole (**4.10**) followed by coupling of the indole with dehydroalanine **4.13** provided the known dehydrotryptophan **4.8** (Scheme 4.2).[134] Transformation of **4.8** by methylation and reduction gave the protected, racemic tryptophan **4.11**. Conversion of ester **4.11** to alkyne **4.12** was realized through a two step reduction/alkynylation protocol using the Ohira-Bestmann reagent.[135,136] The cyclization to form the ***C*** ring was originally envisioned as arising from a radical process, but only traces of the desired **4.7** could be detected. After different approaches were studied, the reductive Heck reaction was found to be the most successful. Extensive optimization to minimize the formation of the undesired seven membered ring regioisomer made **4.7** available in reasonable yields. Deprotection of the amine in **4.7** followed by alkylation with 4-bromo-1-butene generated the key cyclization precursor **4.6**. Exposure of **4.6** to the first generation Grubbs catalyst

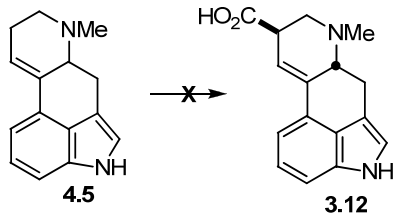
offered no reaction at all, but the ***D*** ring cyclization proceeded smoothly when the more reactive Schrock's catalyst (**4.15**) was used. Removal of the *p*-toluenesulfonyl group from the indole gave the lysergate derivative **4.5** in excellent yield.

Scheme 4.2

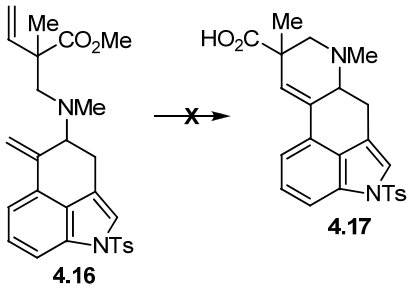


The success of the RCM was very exciting, and it was envisioned that a new route to a variety of ergot alkaloids had been developed. The RCM substrate **4.6** was thought of as potentially recalcitrant because there are few examples of exocyclic olefins as RCM substrates, and in particular, both 1,1-disubstituted and α-aryl olefins are poor substrates for Schrock's catalyst.[91] While the RCM did work, further elaboration of **4.5** did not. Attempts to install functionality at C(8) uniformly failed (e.g., Equation 1). The creation

of analogs of **4.6** that contained an ester was difficult, and when successful would not cyclize to give the ***D*** ring (e.g., Equation 2).



(1)



(2)

4.2 CURRENT WORK

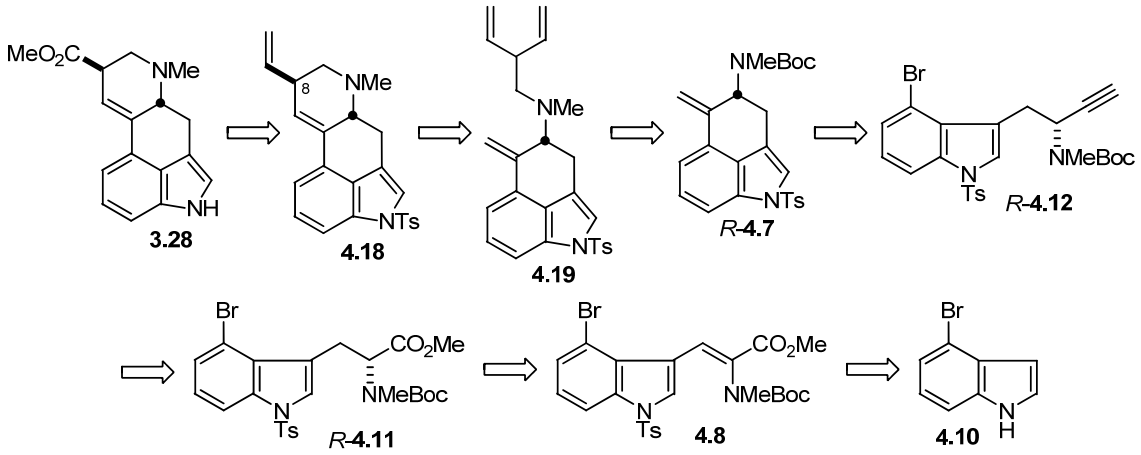
We envisaged that the ideal synthetic route to the lysergates would be enantiocontrolled, and have a minimum of oxidation adjustments. There has yet to be an enantioselective synthesis of any of the lysergates that does not rely on a resolution, and, perhaps more importantly, both antipodes of both diastereomers should be available for pharmacological testing. The chiral centers would be installed with chiral catalysts, to facilitate the construction of all stereoisomers using the same general synthetic sequence. The oxidation states of the skeletal atoms should be modified a minimum number of times for both the sake of asthetics and synthetic efficiency. The indole core should be introduced as the fully aromatic system and preserve aromaticity for the entire synthesis. Similarly the C(9)-C(10) double bond should be in place as soon as C(9) and C(10) become connected and remain for the entire synthesis.

After completion of the synthesis of **4.5**, the project lay dormant for a short while until RCM technology progressed to the point that it could be used for the synthesis of the lysergates. The addition of a functional handle for later conversion to the ester moiety would circumvent the difficulties encountered in both appending a carbonyl to **4.5**, and performing a RCM on **4.16**. The elegant work of Schrock and Hoveyda in developing new asymmetric ring closing metathesis (ARCM) catalysts rekindled interest as a possible solution to these problems.[137]

The desymmetrization of prochiral trienes with ARCM makes an intriguing approach to the ***D*** ring of the lysergates possible. Whereas previously the C(8) position could not be functionalized before or after the metathesis, the cyclization of a triene to form the ***D*** ring would leave an olefin appended to C(8) as the requisite functional handle. Additionally, an asymmetric catalyst would provide an entry to a controlled enantioselective synthesis, as opposed to a resolution based enantioselective synthesis such as that of Szántay.

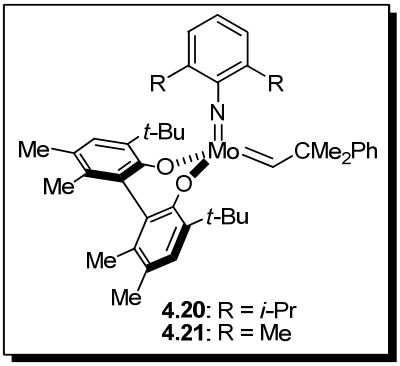
Using the prior art from within the Martin group as a starting platform, the use of an ARCM to form the ***D*** ring fits seamlessly. The carbonyl group of methyl lysergate (**3.28**) would arise from the olefin **4.18** by a series of oxidations (Scheme 4.4). ARCM of **4.19** would form the ***D*** ring and set the requisite stereochemistry at C(8). Installation of the pentadienyl subunit on to *R*-**4.7** should proceed analogously to the addition of the homoallyl side chain of **4.6** (Scheme 4.2). The synthesis of compounds *R*-**4.7**, *R*-**4.12**, and *R*-**4.11** would be similar to their racemic counterparts, with the absolute stereochemistry in *R*-**4.11** being installed by asymmetric reduction of **4.8**.

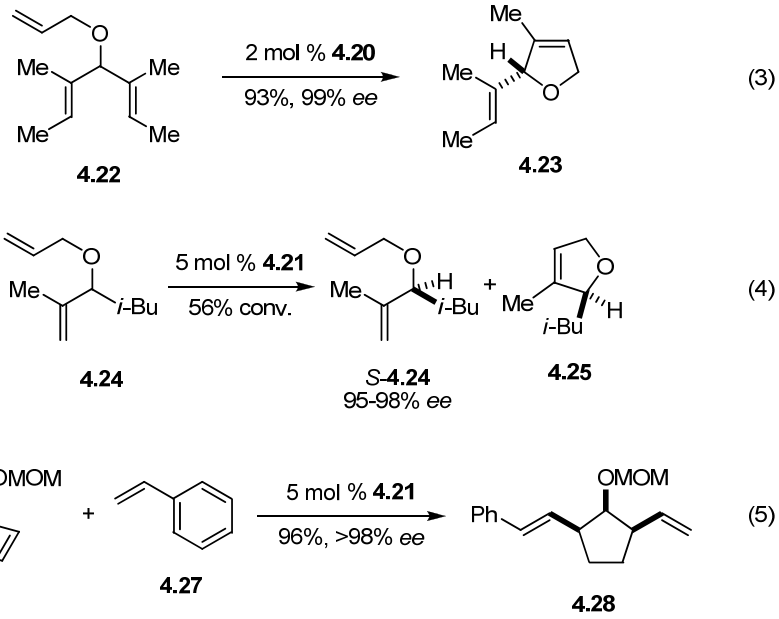
Scheme 4.4



The advent of chirally modified metathesis catalysts has extended the toolkit of the synthetic chemist. The molybdenum based chiral catalysts **4.20** and **4.21** (Figure 4.3) among many others, have been used for creating chiral cyclic alkenes such as **4.23** from prochiral trienes like **4.22** (Equation 3), kinetic resolution of racemic dienes such as **4.24** (Equation 4) and asymmetric ring opening metathesis-cross metathesis (AROM/CM) of substituted norbornenes such as **4.26** (Equation 5).[138,139]

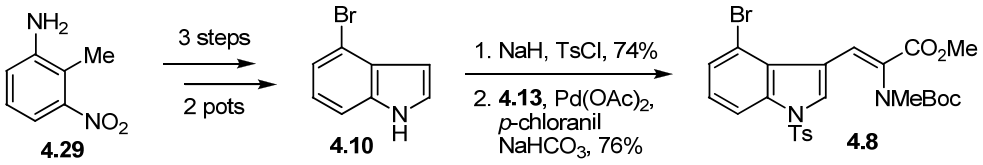
Figure 4.3





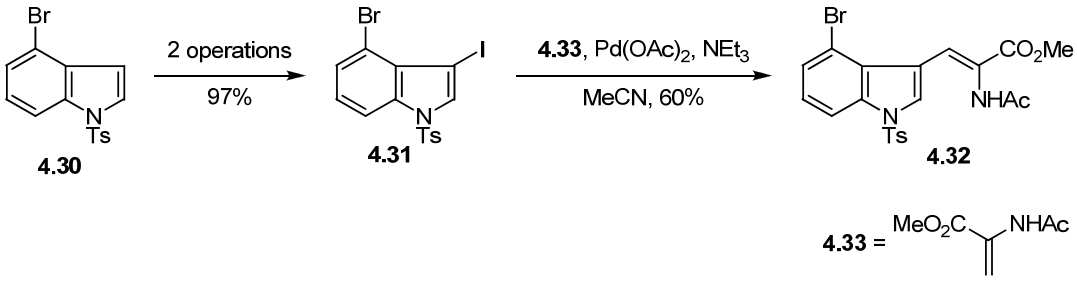
4-Bromoindole (**4.10**) is commercially available, but somewhat expensive ($182.00 for 5 mL[140]), so it was synthesized in three simple steps from 2-methyl-3-nitro-aniline (**4.29**, $88.30 for 100 g[140]). *N*-Tosylation of **4.10** followed by coupling with dehydroalanine **4.13** gave **4.8** (Scheme 4.6).[133,134] The use of stoichiometric palladium in the coupling step was undesirable, but studies performed by Yokoyama showed that poor yields of product resulted from use of sub-stoichiometric amounts.[134]

Scheme 4.5



The coupling was an opportunity to improve the existing synthesis, but it would need to be at least as rapid, and at least as efficient to be valuable. Hegedus has reported some success in performing Heck couplings with the 4-bromo-3-iodoindole **4.31**, complementing his palladium catalyzed indole synthesis (Scheme 4.6).[141-144] While the dehydrotryptophan **4.32** that Hegedus made was similar in disposition to the desired **4.8**, it was synthesized in three steps, versus only one to make **4.8** from **4.30**, and was overall less efficient. The salient feature of the Hegedus coupling was the selectivity between the two halides. If a more advanced coupling partner were used to form the eastern portion of the amino acid with the same selectivity witnessed by Hegedus it would potentially offset the drawbacks.

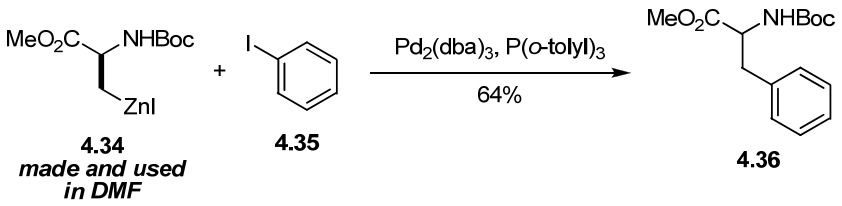
Scheme 4.6



Jackson has contributed greatly to synthesizing non-natural amino acids *via* Negishi couplings between zinc amino acid derivatives such as **4.34** and aryl halides, but he has never made tryptophan derivatives (*cf.* **4.11**) (Scheme 4.7).[145] If this chemistry

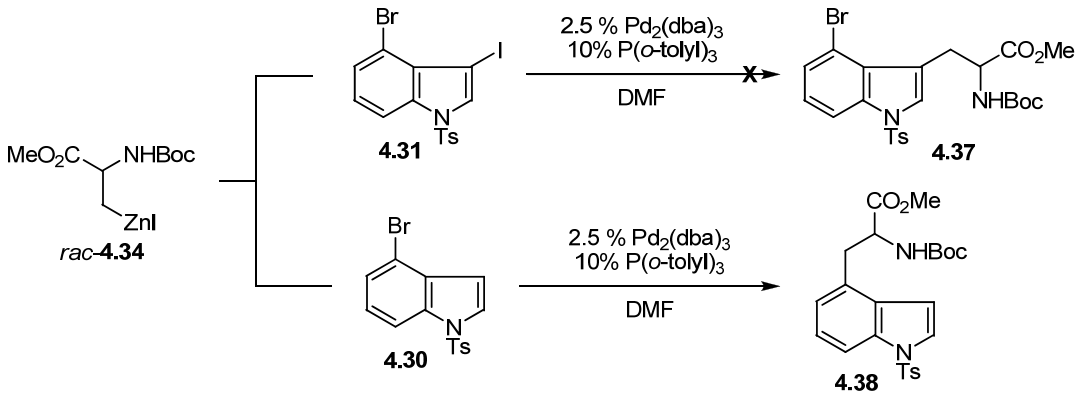
could be successfully applied to **4.31**, the unnatural tryptophan **4.11** could be made directly without the intermediacy of the dehydro-analog **4.8**. While the yields from the coupling of both Jackson and Hegedus were moderate, that may have no bearing on the possibility of optimization of a different system.

Scheme 4.7



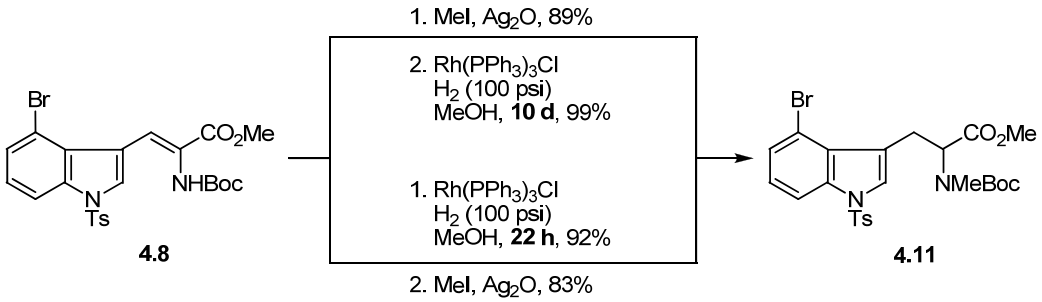
A few cursory experiments were performed to determine if a combination of the Hegedus and Jackson protocols was viable. The organozinc *rac*-**4.34** was formed following the Jackson protocol, and attempts to couple it with iodo-bromoindole **4.31** were undertaken (Scheme 4.8). There was no reaction, and **4.31** was recovered. The organozinc reagent *rac*-**4.34** was also coupled with 4-bromoindole **4.30** to give **4.38** (yield not determined). While the experiments were preliminary, the complete lack of success discouraged us from investigating the Negishi coupling further.

Scheme 4.8



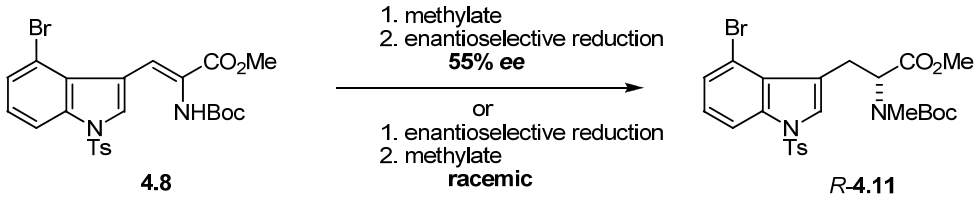
In the previous route the highest yield in transforming **4.8** to **4.11** was realized when the amide nitrogen atom was methylated prior to reduction of the double bond (Scheme 4.9). While the reduction was very efficient, it was also quite slow, taking ten days to go to completion. If the steps were reversed, the yield suffered only slightly, and the required time was reduced significantly.

Scheme 4.9



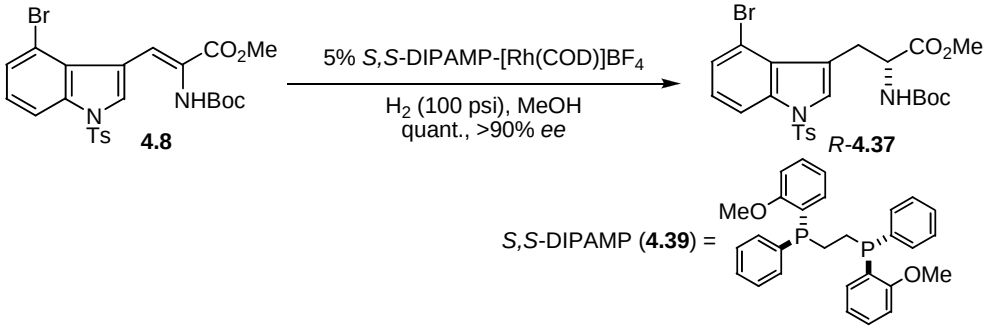
This situation has different implications for the enantioselective application. The enantioselective reduction of enamides requires strong coordination of the amide/carbamate to optimize both yield and enantiomeric excess.[146] If the amide/carbamate is tertiary, like **4.8**, the coordination is not strong enough, and poor yields and enantiomeric excesses are observed.[147] Yokoyama showed that not only did the enantioselective reduction of the *N*-methylated carbamate of **4.8** proceed with poor enantiomeric excess, but also the methylation after reduction of **4.8** completely racemized the material (Scheme 4.10).

Scheme 4.10



We had envisioned utilizing, in essence, the same route as Yokoyama, but wanted to have an enantiomeric excess higher than 55%. To overcome the low enantioselectivity/racemization issue, the methylation was delayed until the chiral center was no longer labile. The reduction of **4.8** was performed identically to a known example from Yokoyama, except the antipodal catalyst was used.[134] Excellent yield and enantiomeric excess were realized when **4.8** was reduced with (1*S*,2*S*)-(+)-bis[(2-methoxyphenyl)phenylphosphino]ethane (*S*,*S*-DIPAMP, **4.39**) modified rhodium (Scheme 4.11).[148] The absolute configuration of *R*-**4.37** was confirmed by comparison of the optical rotation versus the literature value for the enantiomer; *S*-**4.37**: $[\alpha]_D$=-34 ° (>99% *ee*), *R*-**4.37**: $[\alpha]_D$=+29 ° (>90% *ee*).

Scheme 4.11



The ester function in *R*-**4.37** was transformed into an alkyne by employing a diisobutylaluminum hydride (DIBAL) reduction followed by the Ohira-Bestmann protocol as for the synthesis of **4.12** (Scheme 4.2), but there was degradation of the enantiomeric excess of **4.40**, from greater than 90% enantiomeric excess for **4.12** to less than 70% enantiomeric excess for **4.40**. Conditions were screened to optimize enantiomeric excess without sacrificing chemical yield. After DIBAL reduction, the resultant aldehyde was exposed to different reagent/condition combinations, and the enantiomeric excess was measured. Selected examples are presented in Scheme 4.12.

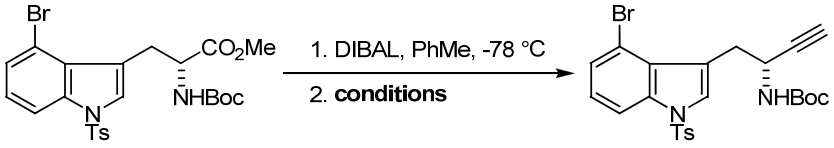
Ohira's reagent (**4.14**) provided the best ratio when the reduction and alkynylation were performed sequentially in the same reaction vessel without any isolation of the intermediate aldehyde (entry 3). Upon completion of the DIBAL reduction, while still at -78 °C, the reaction was flooded with methanol, warmed to room temperature, and Ohira's reagent and potassium carbonate were added in one portion.[149] Lower temperatures tended to decrease the enantioselection and increase the reaction time (entries 1 and 2).

Gilbert's reagent (dimethyl(diazomethyl)phosphonate) provided good retention of enantiomeric excess, but the yields of **4.40** were consistently lower (in general, less than 50%) than the Ohira's reagent examples. Practically speaking, Ohira's reagent is both easier to make and use than Gilbert's reagent, and was used in all subsequent alkynylations.[135,150]

In addition to Gilbert's and Ohira's reagents the anion of trimethysilyldiazomethane ($TMSCH_2N_2$) was examined. The addition of the $TMSCH_2N_2$ anion provided **4.40** with good enantiomeric excess, but the mass recovery of the crude product was quite poor (<50% possible yield), so it was not investigated further. The Corey-Fuchs reaction was not attempted due to potential selectivity issues between the

gem-dibromoalkene intermediate and the bromine on the benzenoid ring during the metallation.

Scheme 4.12



R-**4.37**
>90% *ee*

4.40
70%, 80% *ee*
(entry 3)

conditions

entry	reagent	solvent	base	temperature	*ee* [a]
1	Ohira's	MeOH	K_2CO_3	-10 °C	70%
2	Ohira's	MeOH	K_2CO_3	0 °C to rt	72%
3[b]	Ohira's	MeOH	K_2CO_3	rt	80%
4	Ohira's	iPrOH	K_2CO_3	0 °C to rt	50%
5	Ohira's	iPrOH	Cs_2CO_3	0 °C to rt	52%
6	Ohira's	MeOH	NaOMe	-78 °C to rt	71%
7	Ohira's	THF	KOtBu	-78 °C to rt	81%
8	Gilbert's	THF	KOtBu	-78 °C to rt	87%
9	Gilbert's	THF	NaHMDS	-78 °C to rt	84%
10	Gilbert's	THF	BuLi	-78 °C to rt	83%
11	Gilbert's	THF	NaH	-78 °C to rt	85%
12	$TMSCH_2N_2$	THF	LDA	-78 °C to rt	82%

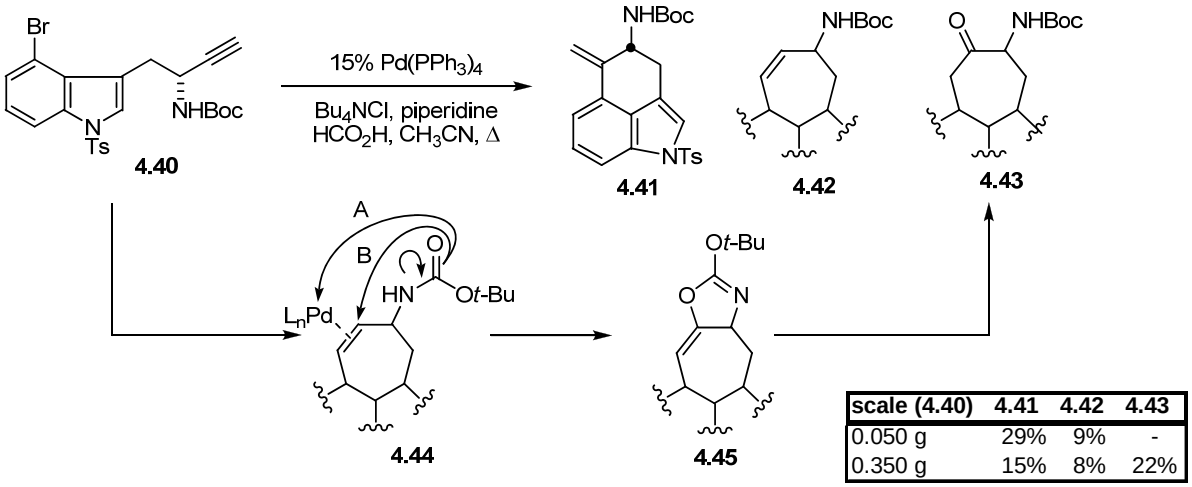
[a] Determined by chiral HPLC.

[b] Reduction and alkynylation performed in one pot.

Performing the reductive Heck reaction on **4.40** provided the desired **4.41** along with some of the undesired, although not unexpected, regioisomer **4.42** (Scheme 4.13). The formation of the seven membered ring had been an issue in the similar conversion of **4.12** to **4.7** in the synthesis of the lysergate skeleton (Scheme 4.2).[133] Inexplicably, when the reaction was scaled up not only did the ratio of **4.41** to **4.42** degrade, but ketone **4.43** was formed as the major product. A possible mechanism for the formation of the ketone would involve one of two reasonable mechanistic hypotheses. The interception of an alkenyl palladium species **4.44** *via* attack of the *tert*-butoxycarbonyl group oxygen on an

η^1 palladium center, path A, followed by reductive elimination would provide **4.45** which would hydrolyze to **4.43**. Alternatively attack of the *tert*-butoxycarbonyl group oxygen on a carbon activated as an η^2 palladium complex, followed by β-hydride elimination would provide **4.45**.

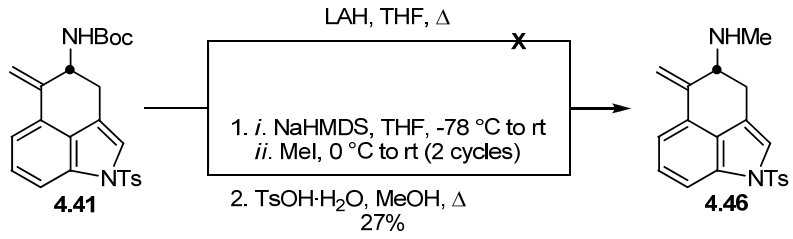
Scheme 4.13



scale (4.40)	4.41	4.42	4.43
0.050 g	29%	9%	-
0.350 g	15%	8%	22%

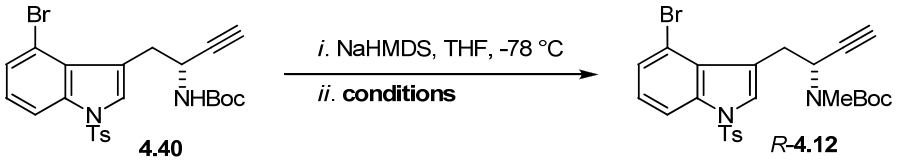
The small amounts of **4.41** thus generated were carried forward. The requisite N-methyl group could be installed *via* reduction of the *tert*-butoxycarbonyl protecting group to improve the stepwise efficiency of the synthetic route. In the event, reduction of **4.41** with lithium aluminum hydride did not convert the *tert*-butoxycarbonyl group into the needed methylamino group (Scheme 4.14). Methylation of **4.41** followed by deprotection supplied **4.46** in a moderate, unoptimized yield.

Scheme 4.14



Simultaneous with exploring the cyclization/methylation approach, the alternate sequence of methylation/cyclization was being investigated. *N*-Methylation of carbamate **4.40** proceeded in good yield, but was difficult to reproduce (Scheme 4.15). The yields of *R*-**4.12** varied between near quantitative to less than 40%, with varying amounts of indole-deprotected starting material. Eventually it was discovered that the reaction was temperature sensitive and required warming over a relatively short period of time. If it was kept cold for too long or warmed too rapidly, the reaction did not go to completion. Fortunately, the rate of warming had some flexibility, and warming from -78 °C to room temperature over the course of 20 to 45 min was adequate. If there was remnant starting material, the reaction mixture could be re-submitted to the reaction conditions. Because the base sensitive ester functional group was no longer present, the issues Yokoyama faced were totally circumvented during the installation of the methyl group.

Scheme 4.15

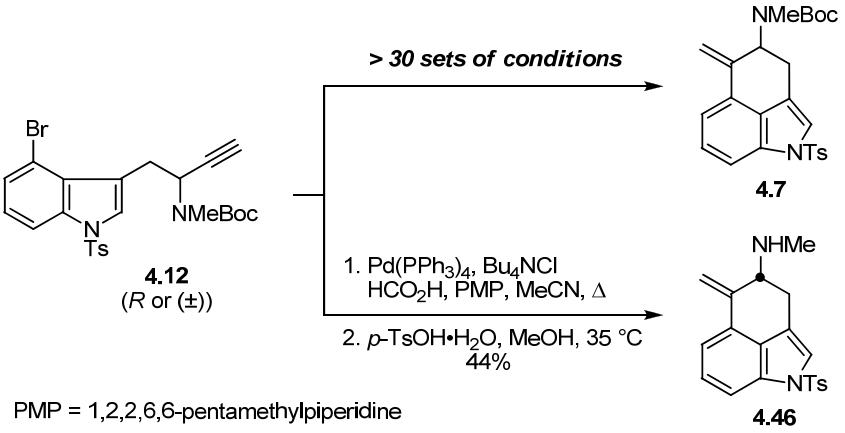


conditions

alkylating agent	warming rate	*R*-4.12	4.40
MeI	slow (overnight)	39%	26%
MeI	normal (hours)	76%	18%
MeI, xs	normal (hours)	84%	10%
Me_2SO_4	normal (hours)	93%	0%
Me_2SO_4	normal (hours)	68%	12%
Me_2SO_4	fast (< 1 hour)	93%	trace

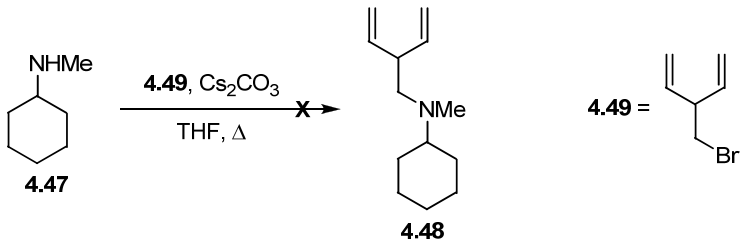
With the enantioenriched *R*-**4.12** in hand for the reductive Heck reaction to provide **4.7**, conditions were screened to attempt to improve on the prior 42% yield (Scheme 4.16).[133] However, the prior work had explored a large array of reaction systems, and after several failed attempts it seemed as though there would be no improvement in yield of tricycle **4.7**. Eventually, it was discovered that the use of 1,2,2,6,6-pentamethylpiperidine improved the yield of *R*-**4.7** (not shown) in a reproducible fashion. In providing **4.7**, racemic or enriched, the product mixture was a complex mixture of inseparable compounds including **4.7**. Much of the prior work optimizing this transformation was aimed at reducing the side products to improve the recovery of pure **4.7**. Fortuitously it was found that the next reaction in the sequence, deprotection of the amine in **4.7** to give **4.46**, was unaffected by impurities, and provided a much more easily separated mixture of products. With these two improvements the yield of **4.46** from *R*-**4.12** was improved, and the sequence was expedited as well.

Scheme 4.16



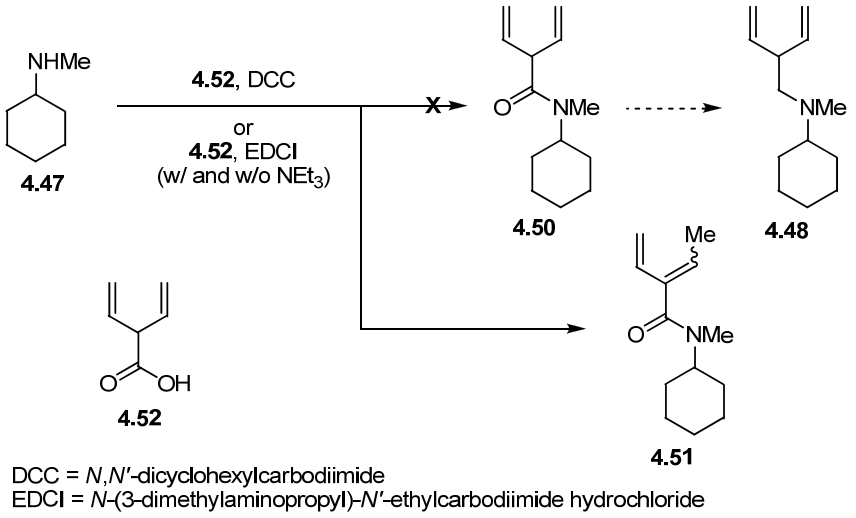
The installation of the pentadienyl subunit onto **4.46** in anticipation of the ARCM was an issue of some concern. While branched pentadienyl-containing molecules were not unknown, they were far from common and there were few general methods for putting them in place.[151] Model studies were performed to determine what method or methods would best be applied to the precious **4.46**. Attempted alkylation of **4.47** with **4.49**[152] using cesium carbonate in refluxing THF, as in the alkylation of the deprotected amine of **4.6**, failed (Scheme 4.17). The amine **4.47** was unreacted and the bromide **4.49** degraded.

Scheme 4.17



Coupling of the amine **4.47** with acid **4.52**[152] worked, but the reaction gave the conjugated products **4.51**, not the desired **4.50** (Scheme 4.18). It was likely possible to deconjugate **4.51** to provide **4.50**, but this procedure would have made for inefficient access to **4.48**.

Scheme 4.18

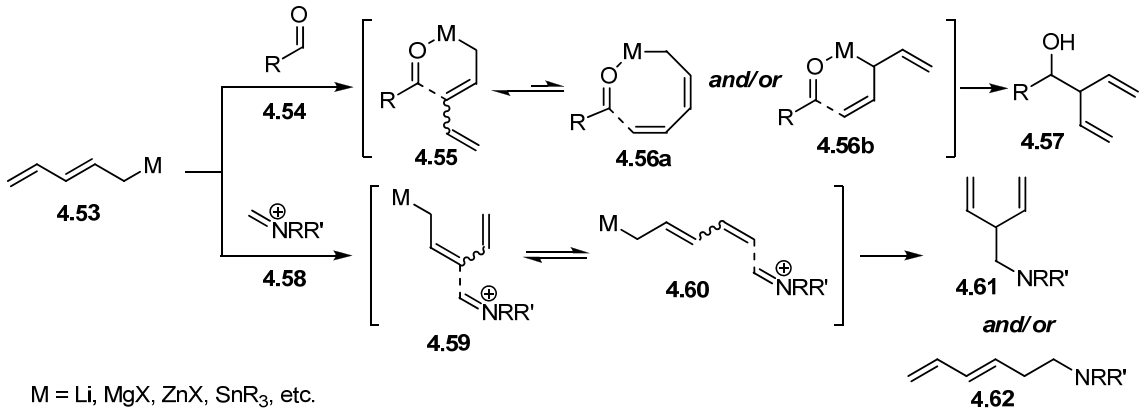


DCC = *N*,*N*′-dicyclohexylcarbodiimide
EDCI = *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride

One of the more general methods of installing pentadienes was by use of a pentadienyl metal reagent **4.53** (Scheme 4.19). For example the addition of a coordinating pentadienyl metal to an aldehyde **4.54** undergoes an allylation type reaction *via* a Zimmerman-Traxler transition state **4.55**.[151,153,154] The alternative pentadienylation, giving the linear product, has to go through an unfavored eight membered transition state **4.56a** or allylate *via* the unfavored branched **4.56b**, and is generally not seen. However, the organometal **4.53** cannot add to an iminium ion **4.58** *via* the same coordinated transition state. There are no coordinating sites on the nitrogen atom, so it must pentadienylate through an open transition state like **4.59** or **4.60**. Unfortunately, this generally leads to mixtures of both **4.61** and **4.62** with no real recourse to control the

isomer ratio. While it is difficult to make a prediction of the outcome of the pentadienylation of an iminium ion, Miginiac has contributed an abundance of empirical data to the pentadienylation regime with general trends of reactivity.[152,155-160]

Scheme 4.19



Several electrophile surrogates were synthesized and tested to determine what protocol would provide the best yield of branched pentadiene with the greatest reproducibility. An abbreviated version of these experiments is presented in Scheme 4.20. The salient points learned from the study were: organozinc reagents and tetrahydrofuran as solvent gave the best yields and ratios of **4.48** to **4.67**; the *N,S*- and *N,O*-acetals were both more effective as electrophile precursors than the cyanoamine, but the *N,O*-acetal was easier to synthesize and handle. Bis-pentadienylzinc provided higher yields and greater reproducibility than pentadienylzinc bromide. A possible explanation for the greater efficacy is that the reduced Lewis acidity of the diorganozinc may ionize the *N,O*-acetal to a lesser extent in the transition state, allowing more opportunity for coordination (Figure 4.4).

Scheme 4.20

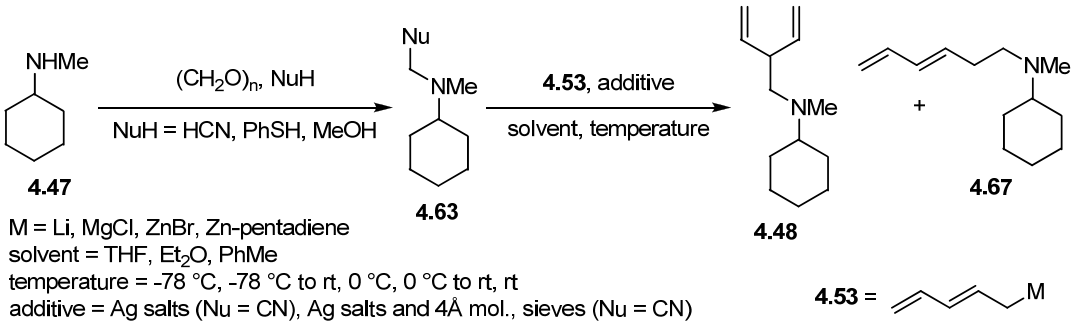
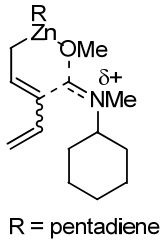
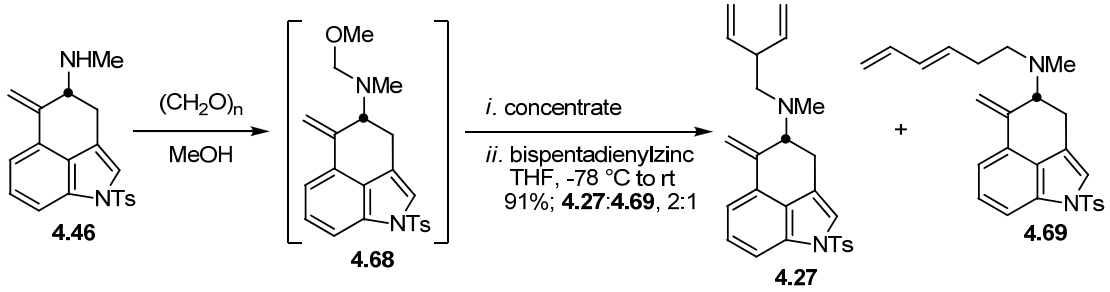


Figure 4.4



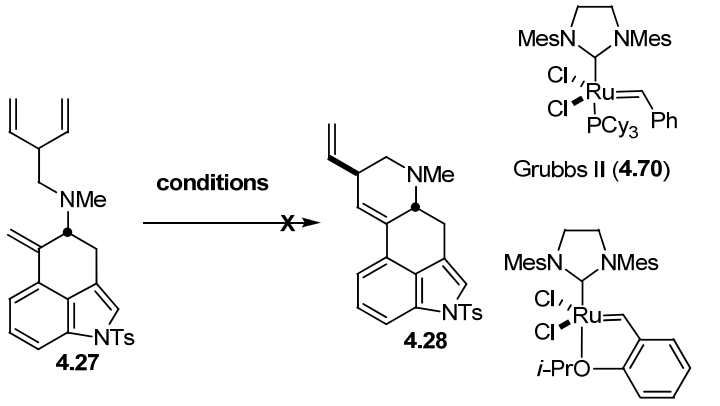
Compound **4.63** (Nu = OMe) could be purified *via* distillation to remove excess solvent while maintaining the integrity of the *N,O*-acetal. However, the *N,O*-acetal **4.68** derived from **4.46** could not be distilled, so the solvent was removed rapidly *in vacuo*, before being replaced with tetrahydrofuran (Scheme 4.21). Bispentadienylzinc addition to **4.68** provided **4.27** in similar yields to the best examples from the addition of pentadienylzinc bromide to **4.68**. Additionally the use of bispentadienylzinc proved more reliable than pentadienylzinc bromide at producing **4.27**.

Scheme 4.21



With **4.27** in hand, the RCM experiment was performed with the achiral Schrock's catalyst **4.15**. In an unexpected result, exposure of **4.27** to **4.15** produced no reaction at all, returning **4.27** quantitatively (Scheme 4.22). The use of a large excess of catalyst, and heat offered no change. Subjecting **4.27** to **4.15** in toluene and heating to 100 °C also returned starting material. Grubbs' second generation metathesis catalyst **4.70** was similarly unreactive with **4.27**. The addition of titanium isopropoxide to **4.27** prior to exposure to **4.70** gave the same result.[161] The Grubbs-Hoveyda second generation catalyst **4.71** consumed some **4.27**, but there was no detectable **4.28** in the product mixture. The racemic Schrock-Hoveyda catalyst **4.20** did not react with **4.27** in benzene at reflux temperature.

Scheme 4.22



conditions

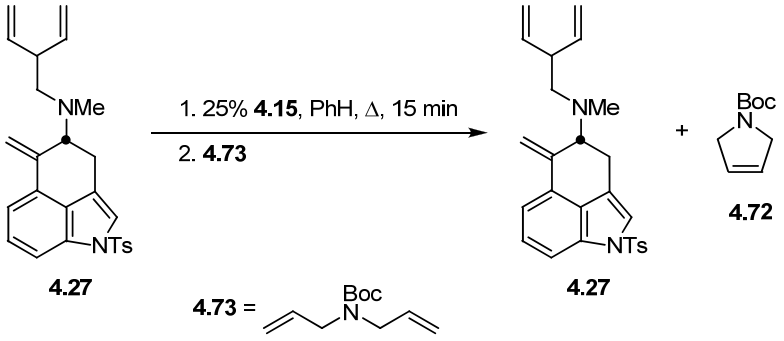
catalyst	solvent	temp.	product
25% **4.15**	PhH	rt	**4.27**
50% **4.15**	PhH	Δ	**4.27**
50% **4.15**	PhMe	100 °C	**4.27**
500% **4.15**	PhH	Δ	**4.27**
300% **4.15**	PhMe	100 °C	**4.27**
20% **4.70**	CH_2Cl_2	Δ	**4.27**
50% **4.70**	CH_2Cl_2	Δ	**4.27**
50% **4.71**	CH_2Cl_3	Δ	**4.27**[a]
20% **4.70**, Ti(O*i*-Pr)$_4$	CH_2Cl_2	Δ	**4.27**[a]
20% (±)-**4.23**	PhH	Δ	**4.27**

[a] Slight decomposition of **4.27**

The surprising lack of reaction between **4.27** and **4.15** may have been due to **4.27** coordinating with catalyst **4.15** in a non-productive fashion. If that were the case the catalyst should be deactivated towards alternate substrates as well. To explore this possibility **4.15** was incubated with **4.27** in benzene at reflux temperature for 15 minutes followed by the addition of **4.73**, a known substrate for **4.15** (Scheme 4.23).[162] The diallylamine **4.73** was completely consumed, and **4.27** did not react at all. The implication of that reaction was that if **4.27** was coordinating **4.15** it must have been a reversible process. It was interesting to note that the subtle difference between **4.27** and

4.6 (Scheme 4.2), i.e., a vinyl group, was sufficient to shut down the RCM of **4.27** with what is generally held to be the most active commercially available metathesis catalyst.[137]

Scheme 4.23

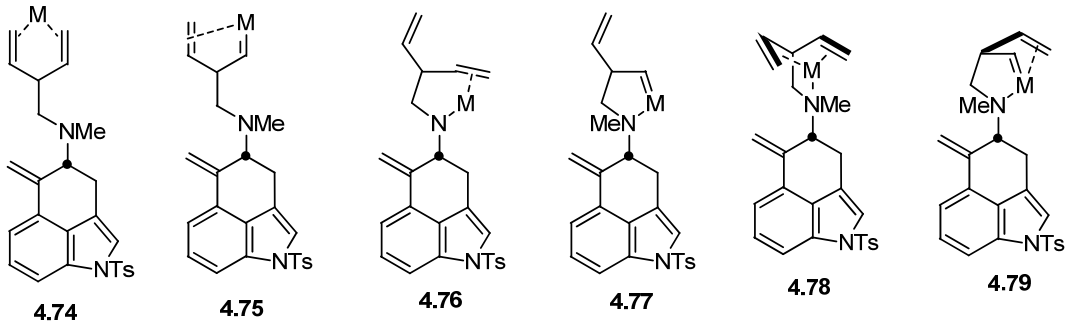


The substrate **4.27** was completely recalcitrant, but did not deactivate the Schrock's catalyst (**4.15**). Diene **4.6** (Scheme 4.2), which only differed from **4.27** by the extra vinyl group had been a good substrate for RCM with catalyst **4.15**. Because of this it was proposed that the cause, at least in part, of the reticence of **4.27** to undergo RCM somehow hinged upon the additional vinyl group. The catalyst **4.15** and the triene **4.27** may have formed some sort of non-productive coordination complex such as those shown in Figure 4.2.

The pentadiene moiety has been used successfully for stereoselective RCM reactions, so it seems unlikely that a coordination complex such as **4.74** or **4.75** could be the unreactive culprit.[138,163] The fruitful RCM of **4.6**, which contained a homoallylamine, counters either **4.76** or **4.77** as the inhospitable complex. There was no way of gathering direct evidence to support or refute **4.78** or **4.79** as possibilities, but they were the only reasonable complexes unique to this system. Both of the alkenes of the gem-divinyl

group were necessary for the ARCM, so the nitrogen was investigated as a possible site for modification.

Figure 4.2



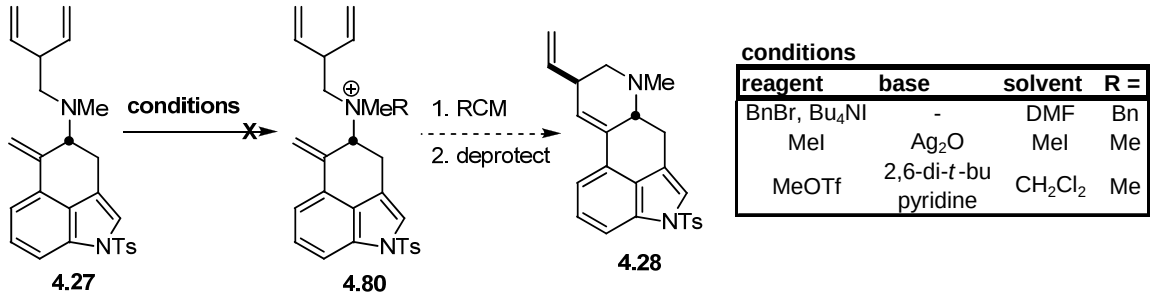
M = metal center of catalyst, ligands not shown for clarity

Because **4.27** was already available, the initial amine modifications were performed on this substrate. A generalization about the ruthenium based metathesis catalysts, such as the Grubbs type catalysts **4.70**, is that they sometimes work poorly on substrates with Lewis basic sites such as amines. A common method to alleviate this problem is to protonate the amine.[88] Molybdenum based metathesis catalysts, such as the Schrock catalyst **4.15**, are incompatible with protic acids, so if a Lewis basic site needs to be engaged it must be done another way.

To remove the Lewis basic site, the amine was subjected to quaternization to completely occupy the lone pair. Adding a large excess of benzyl bromide to **4.27** in dimethylformamide in the presence of tetrabutylammonium iodide led to no reaction (Scheme 4.24). Methylation of **4.27** in neat iodomethane with silver oxide also failed. Methylation of **4.27** with methyl triflate in the presence of 2,6-di-*tert*-butylpyridine, however, did provide a small amount of product that may have been **4.80**. The product mixture decomposed during chromatography, the ^{1}H-NMR was difficult to de-convolute,

and exposure of the mixture to Schrock's catalyst **4.15** did not provide RCM product. The difficulty in formation and characterization of ammonium ion **4.80** made it a less than desirable intermediate, and other tactics for the functionalization of the amine lone pairs in **4.27** were investigated.

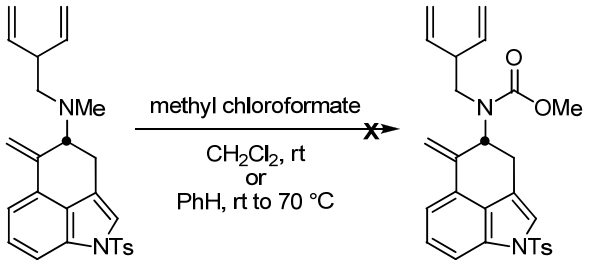
Scheme 4.24



An alternate method of functionalizing the amine was to append a protecting group to the amine. The concomitant *N*-methyl cleavage and carbamate protection of **4.27** by treatment with a chloroformate was undertaken (Figure McKlusky).[164] Unfortunately the desired cleavage did not take place providing recovered **4.27** and degradation. The route to the pentadiene was modified to retain the *tert*-butoxycarbonyl protecting group. To accomplish this a different method of installing the pentadiene moiety was used. With the carbamate protecting group on the nitrogen, any iminium ion formed would be an *N*-acyliminium ion. *N*-Acyliminium ions follow the reactivity trends for pentadienylation of iminium ions and tend to give excellent regioselectivity for the linear isomer (*cf.* **4.69**), not the branched isomer (*cf.* **4.27**). While *N*-acyliminium ions are poor electrophiles for pentadienylation to the branched product, they can be excellent electrophiles for allylation. If the *N*-acyliminium ion was allylated with an allylating

agent containing a masked alkene then the desired nitrogen-protected pentadiene could be made in a slightly longer, but straightforward fashion.

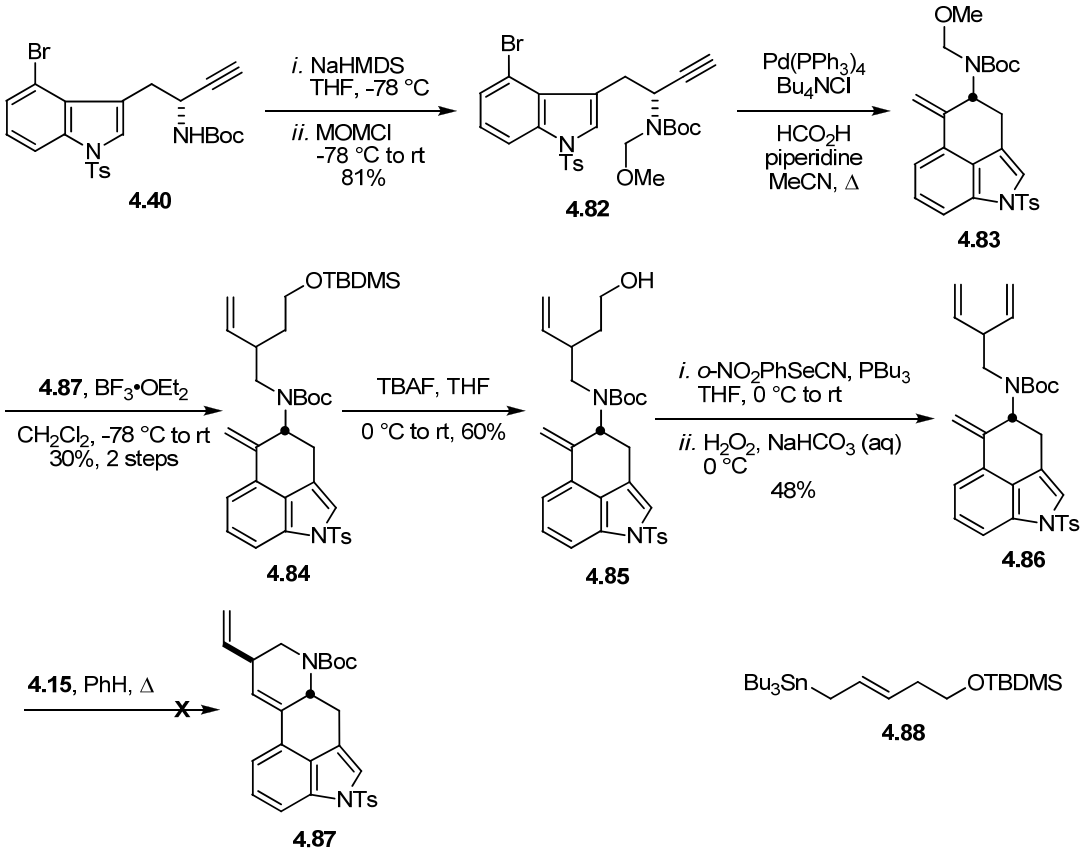
Scheme 4.25



4.27 **4.81**

An ionizable group was necessary in the place of the previous *N*-methyl group. To this end compound **4.40** was alkylated with chloromethyl methyl ether, so that, in conjunction with the *tert*-butoxycarbonyl group, the *N,O*-acetal could be used as an *N*-acyl iminium ion precursor (Scheme 4.26). The *N*-alkyl group assisted in the reductive Heck cyclization of **4.82** to give **4.83** in that it had been found that tertiary carbamates are more successful than secondary carbamates (*vide supra*). The cyclization of **4.82** to **4.83** followed by allylation of the *N*-acyl iminium ion of **4.83** generated *in situ* with **4.88,** gave **4.84**.[165] Treatment of **4.84** with tetrabutylammonium fluoride revealed alcohol **4.85**, which, upon elimination, gave triene **4.86**, the *N*-Boc analog of **4.27**.[166,167] When *tert*-butoxycarbonyl protected **4.86** was treated with **4.15** in benzene under reflux, **4.87** could not be detected.

Scheme 4.26



The complete lack of success of the key RCM of **4.27** and **4.87** prompted a reevaluation of the route. While methods for realizing the key metathesis were being considered, the Martin research group made an important and serendipitous acquisition. A CEM Discover microwave reactor was procured. It is well known that microwave heating can accelerate, and improve the efficiency of transition metal mediated processes.[168] That fact notwithstanding, there is no record of molybdenum based metathesis catalysts ever having been used in conjunction with microwave heating.

In the event, a solution **4.27** and 50 mol % **4.15** in benzene was heated in the microwave reactor at full power (300 W) for 10 min, and **4.27** was completely consumed

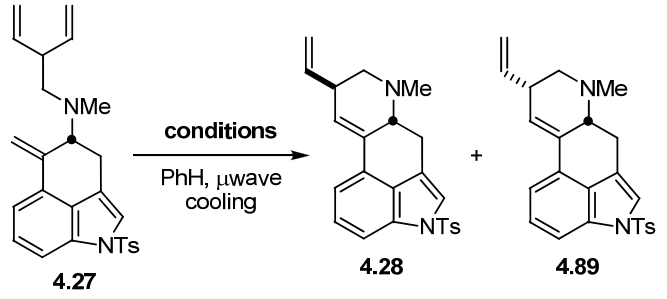
(Scheme 4.27). Gratifyingly, the long sought ***ABCD*** tetracycle **4.89** was isolated in a modest 25% yield along with a small amount of the separable epimer **4.28**. The chemical shifts of the protons were assigned with the aid of the COSY spectra of **4.28** and **4.89**, and the relative configurations were subsequently assigned based upon the nOesy spectra. The configuration of the C(5)-H was known, so it was used to determine the relative configuration of the newly formed stereocenter by using nOe data to 'walk' around the ***D*** ring (Figure 4.5). Although the goal had been to synthesize methyl lysergate with the β absolute stereochemistry at C(8), there is variety of natural products with α stereochemistry at C(8) so the RCM was still a valuable step. When mixtures of methyl lysergate and methyl isolysergate were treated with base the mixture equilibrates favoring the so called normal stereochemistry. The formation of the iso stereochemistry is disfavored, so the favoritism of **4.89** over **4.28** was in reality a quite an accomplishment.

Reduced catalyst loads of 10 mol % or 30 mol % were insufficient for complete consumption of **4.27**. After some experimentation the use of catalyst **4.15** and 300 W of irradiation was optimized to 36% **4.89** and 8% **4.28**. After this exhilarating success, the next logical extension was to determine if the chiral catalyst **4.20** would be an improvement versus the achiral catalyst **4.15**.

The literature covering the chiral metathesis catalysts does not contain any pneumonic for determining which enantiomer should be used for a given substrate.[137] Regardless, no substrates of the complexity of **4.27** have ever been subjected to enantioselective metathesis reactions. Inspection of published reactions (*cf.* **4.16** → **4.17**) suggested that *S*-**4.20** (Scheme 4.3) would provide **4.28** in preference to **4.88**.[138,169] This was not found to be the case, but *S*-**4.20** catalyzed the ARCM of **4.27** with an improved 47% yield of **4.89** and 18% yield of **4.28** versus the 36% yield of **4.88** and ca 8% yield of **4.28** when the achiral **4.15** was used. When **4.27** was exposed to *R*-**4.20** under identical

conditions as the *S*-**4.20** catalyst reaction, ~55% of **4.27** was consumed but only trace amounts of **4.28** and **4.89** were isolated. In addition to the reduced amounts of desired products there was a significant increase in the amount of a side product that was most likely the $\Delta^{8,9}$ double bond regioisomer of **4.28**/**4.89**. The $\Delta^{8,9}$ regiochemistry was determined by ^{1}H-NMR and LRMS data, and by the fact that treatment of the **4.89** with catalyst **4.15** also provided the isomer. Reduced loads of catalyst *S*-**4.20** provided **4.89** in higher yield than reduced loads of **4.15** had, but likewise did not completely consume the starting material. Reducing the microwave power transferred to the reaction vessel to 50 watts and extending the reaction times to 30 minutes improved the yield of **4.89** to a reproducible 55% with 20% **4.28**.

Scheme 4.27



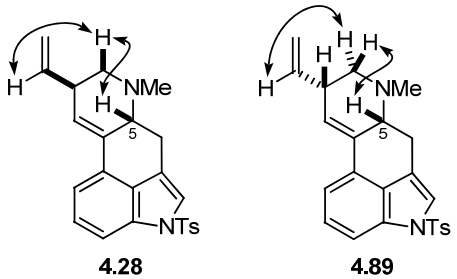
4.27 **4.28** **4.89**

conditions

catalyst	power	time	4.89	4.28
10% **4.15**	300 W	10 min	-	-
30% **4.15**	300 W	30 min	trace	-
50% **4.15**	300 W	10 min	36%	~8%
50% *S*-**4.23**	300 W	10 min	47%	18%
50% *R*-**4.23**	300 W	10 min	see text	
30% *S*-**4.23**	300 W	10 min	39%[a]	*na*
50% *S*-**4.23**	50 W	30 min	55%	20%

[a] 24% rsm

Figure 4.5

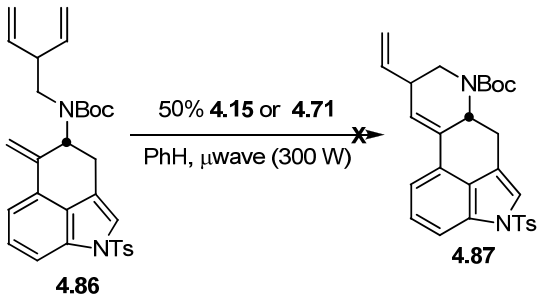


4.28 **4.89**

arrows represent significant nOe interactions

After it was discovered that the microwave heating promoted the RCM from the amine substrate **4.27**, carbamate **4.86** was subjected to the same conditions as for the initial RCM of **4.27**. Exposure of a benzene solution of **4.86** to microwave heating (300 W) in the presence of 50 mol % of either **4.15** or **4.72** did not provide **4.87** (Scheme 4.27). It appeared that carbamate **4.86** was actually a worse substrate for the RCM than the parent amine **4.27**.

Scheme 4.28



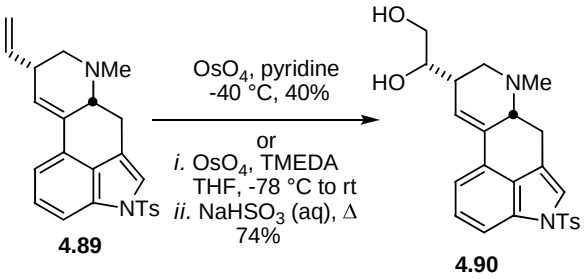
4.86 **4.87**

Although the original synthetic goal had been to synthesize methyl lysergate (**3.28**), the predominance of the epimeric metathesis product **4.89** was not seen as a negative result. A large number of lysergate natural products have the iso absolute configuration of **4.89** at C(8) and the material was moved forward to synthesize methyl-isolysergate.

With the long sought tetracycle **4.89** in hand, conditions to cleave the vinyl olefin to the ester were explored. To selectively functionalize one of the two double bonds in **4.89**, our initial approach was through the cleavage of an appropriate diol. Dihydroxylations are a useful method of selectively functionalizing one olefin in the presence of another based on steric differences between the two, and one of the most

successful reagents for steric discrimination between olefins is the asymmetric dihydroxylation (AD) mix.[170] Unfortunately, the use of the commercial AD-mix β was unsuccessful, and **4.89** was recovered quantitatively. Osmylation of **4.89** with stoichiometric amounts of osmium tetroxide in pyridine provided the diol **4.90** in 40% yield (Scheme 4.29).[170,171] When the *N,N,N',N'*-tetramethylethylenediamine (TMEDA) ligated osmium tetroxide protocol of Donohoe,[172] or the triethylamine variant,[131] was used the diol **4.90** was obtained in 74% yield. The ligation of the osmium tetroxide by the amine gave the dihydroxylating agent additional steric bulk and accordingly provides discrimination between the vinyl group and the less sterically accessible, but more electron rich, C(9)-C(10) double bond.

Scheme 4.29



4.89 **4.90**

TMEDA = *N,N,N',N'*-tetramethylethylenediamine

With **4.90** available, the oxidative cleavage of the diol to the aldehyde **4.91** was explored. Reaction of **4.89** with sodium periodate in either tetrahydrofuran/water or methanol/water provided a complex mixture (entries 1 and 2, Scheme 4.30). The ^{1}H-NMR spectrum of the mixture contained several very minor peaks that may have corresponded to aldehydes. The mass spectra did not have peaks that corresponded to the mass of **4.91**. To ensure that the product was not present, but not visible in either of the aforementioned spectra, the product mixtures were subjected to Pinnick oxidation

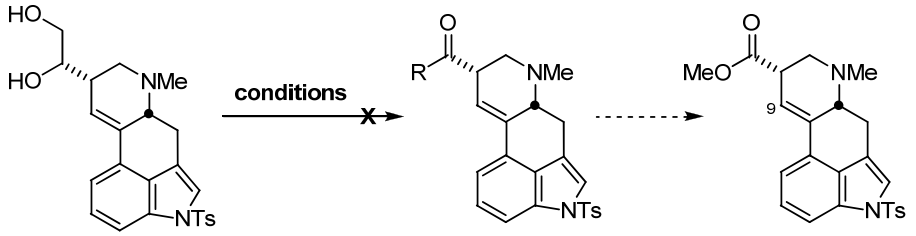
($NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, not shown).[173] The product mixtures from the Pinnick oxidation also lacked key signals for **4.92** in both the ^{1}H-NMR spectrum, such as the alkenyl proton at C(9), and mass spectra. Oxidation of **4.90** with lead tetraacetate also provided a complex mixture (entry 3).

Immobilizing sodium periodate on silica significantly increases the surface area, and thereby the reactivity of sodium periodate in non-aqueous solvent systems.[174] The combination of sodium periodate and 2,6-di-*tert*-butylpyridine as a buffer in organic solvent is known to cleave simple diols rapidly and cleanly to their corresponding aldehydes.[175] However, exposure of **4.90** to the $NaIO_4/SiO_2$ and buffer system provided a complex mixture of compounds (entry 4).

It appeared as though the cleavage of diol **4.90** occurred, but the product **4.91** appeared to be unstable to the reaction conditions. In an attempt to prevent this, the periodate cleavage of **4.90** was performed in the presence of sodium bicarbonate, and a Pinnick oxidation was performed immediately in the same reaction vessel (entry 5). A complex mixture of products was again produced. To further minimize the exposure time of **4.91** to the reaction conditions, **4.90** was subjected to both sodium periodate and the Pinnick reaction conditions at the same time, but the result was the same as sequential reaction (entry 6).

After the repeated failures to isolate any **4.91**, **4.92**, or **4.93** from the attempted oxidation of **4.90**, the compatibility of the substrate with sodium periodate came into question. To determine if there were any deleterious reactions other than the diol cleavage taking place, the diene **4.28** was subjected to sodium periodate cleavage conditions. Because **4.28** was recovered in quantitative yield, it seemed likely that the aldehyde **4.91** was unstable and hence not a viable intermediate on the path to **4.92** or **4.95**.

Scheme 4.30



4.90

4.91, R = H
4.92, R = OH
4.93, R = CH_2OH
4.94, R = CHO

4.95

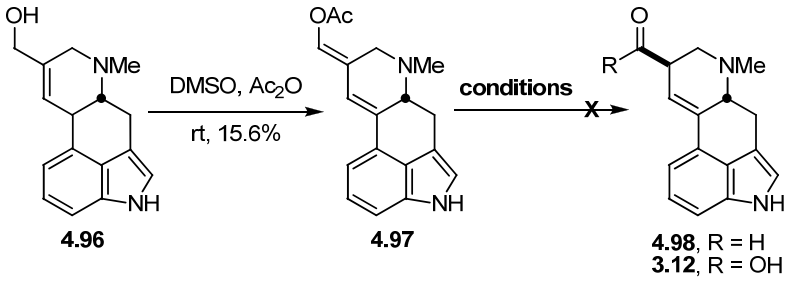
conditions

entry	reagents	solvent	temp.	R	product
1	$NaIO_4$	THF/H_2O	0 °C	H	complex mix.
2	$NaIO_4$	MeOH/H_2O	0 °C	H	complex mix.
3	$Pb(Oc)_4$	PhH	rt	H	complex mix.
4	$NaIO_4/SiO_2$, 2,6-di-*t*-Bu-pyridine	THF	rt	H	complex mix.
5	*i*. $NaIO_4$, $NaHCO_3$ *ii*. $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene	THF/H_2O	0 °C	OH	complex mix.
6	$NaIO_4$, $NaClO_2$ NaH_2PO_4, 2-methyl-2-butene	MeOH/H_2O	0 °C	OH	complex mix.
7	IBX	DMSO	rt	CH_2OH	no reaction
8	IBX, β-cyclodextrin	acetone/H_2O	rt	CH_2OH	no reaction
9	1. Bu_2SnO, 4 Å mol. Sieves 2. NBS	1. PhH 2. PhH/CH_2Cl_2	1. Δ 2. 0 °C	CH_2OH	complex mix.
10	PDC	CH_2Cl_2	rt	CH_2OH	complex mix.
11	SO_3·pyridine, NEt_3, DMSO	CH_2Cl_2	0 °C to rt	CHO	complex mix.

There is very little discussion of lysergaldehyde (**4.97**), and no reports of its synthesis. This absence is conspicuous due to the wealth of chemistry performed in the area of ergot alkaloids. One of the few reports of chemistry dealing directly with a lysergaldehyde derivative was reported by Floss, who attempted to make lysergaldehyde (**4.97**) and $\Delta^{8,9}$-lysergaldehyde from elymoclavine (**4.95**) for biosynthetic studies.[176] He found that oxidation of elymoclavine (**4.96**) was surprisingly difficult, and in a personal communication Hofmann disclosed to Floss that extensive research into oxidizing elymoclavine to lysergic acid had failed. Floss's best result was treatment of elymoclavine with acetic anhydride in dimethyl sulfoxide (Scheme 4.31). The acetyl-

enol ether of lysergaldehyde **4.96** was isolated in low yield. All attempts to hydrolyze or oxidize the enol acetate of **4.97** failed, yielding only decomposition or complex mixtures.

Scheme 4.31



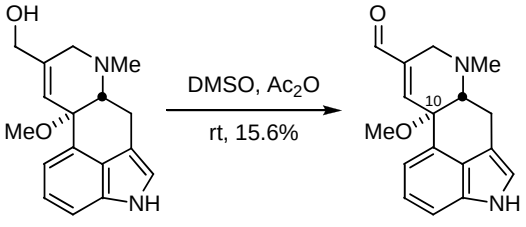
4.96 **4.97** **4.98**, R = H **3.12**, R = OH

conditions

reagent	R =
dil. AcOH	H
NH_4OH	H
MeLi	H
AgO (acidic or basic)	OH
OH^-, O_2	OH

Shough reported in a paper documenting synthetic studies towards lysergaldehydes that he was never able to synthesize either lysergaldehyde or $\Delta^{8,9}$-lysergaldehyde. Shough was able to transform **4.99** to aldehyde **4.100** in low yield, with C(10) tetrasubstituted to prevent enolization of α,β-unsaturated aldehyde **4.100** (Scheme 4.32). Neither Floss nor Shough shed any light on the pathway(s) of decomposition, but it is likely that lysergaldehydes were too unstable to be isolated and may have been too unstable to be synthesized at all.

Scheme 4.32



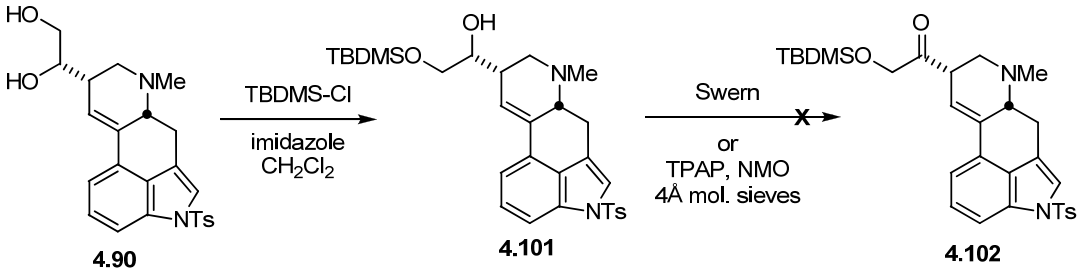
4.99 **4.100**

To avoid the intermediacy of aldehyde **4.91**, the syntheses of the hydroxy ketone **4.93** and the glyoxal **4.94** were undertaken (Scheme 4.30). Both hydroxy ketones and

glyoxals can be cleaved directly to the carboxylic acid without the intermediacy of an aldehyde. When diol **4.90** was subjected to oxidation with *o*-iodoxybenzoic acid (IBX) in the presence of β-cyclodextrin, conditions shown by Rao to be effective at oxidizing 1,2-diols selectively to hydroxy ketones, there was no visible reaction to afford **4.93** (entry 8).[177] Concomitantly, **4.90** was oxidized with IBX in the absence of β-cyclodextrin (entry 7). Unfortunately, neither oxidation appeared to consume **4.90**, returning it untouched. Oxidations with chromium-based reagents tends to oxidize secondary alcohols faster than primary alcohols, but pyridinium dichromate only decomposed **4.90** (entry 10).[178] Another method of selectively oxidizing diols to hydroxy ketones was taken from sugar chemistry. Initial formation of the stannylidene acetal of **4.90**, followed by treatment with *N*-bromosuccinimide should have provided **4.93** (entry 9),[179] but again only an intractable mixture was obtained. The conditions of the Parikh-Doering oxidation likewise destroyed **4.90** (entry 11).[180]

The hydroxy ketone **4.93** was still an attractive intermediate, but it was approached in a different fashion. For example, diol **4.90** was mono-protected as the *tert*-butyldimethylsilyl ether **4.101** (Scheme 4.33). The crude product mixture was deemed sufficiently pure, so **4.101** was subjected to a Swern oxidation as well as oxidation with tetrapropylammonium perruthenate. These reactions did not generate any **4.102**; only complex mixtures of products and recovered **4.101** were obtained.

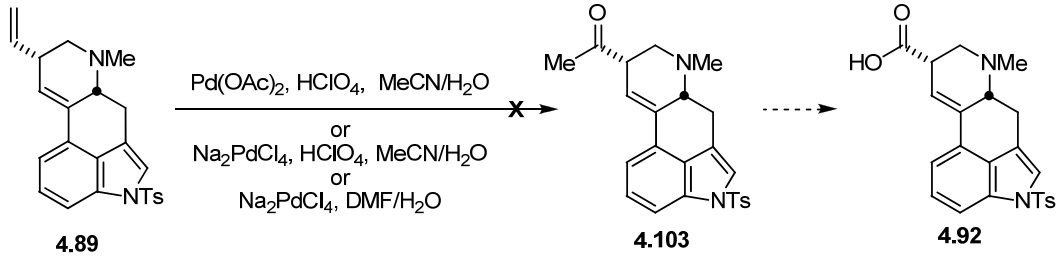
Scheme 4.33



TPAP = tetrapropylammonium perruthenate
NMO = *N*-methylmorpholine *N*-oxide

The Wacker oxidation is known for excellent selectivity in transforming terminal olefins into methyl ketones without oxidizing internal olefins in the same substrate. However, oxidation of diene **4.89** under a variety of conditions with stoichiometric palladium salts provided the same complex mixture of products and recovered **4.89** (Scheme 4.34). Presumably, like the aldehyde **4.91**, the ketone **4.103** was unstable to the reaction conditions.

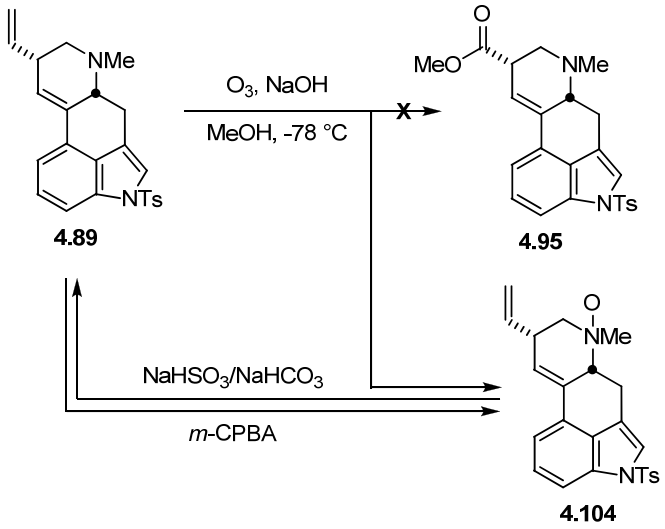
Scheme 4.34



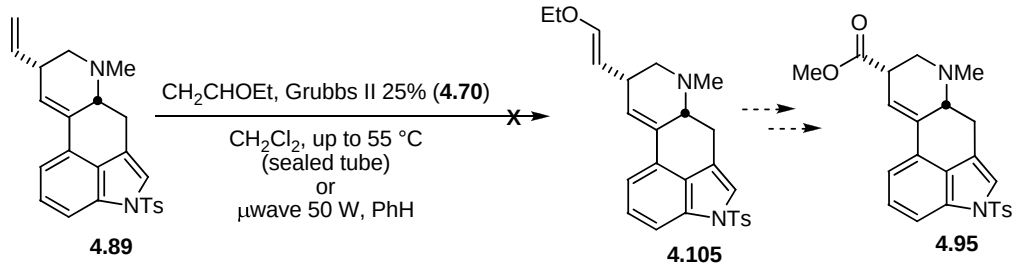
The most well known method for the oxidation of an olefin to a carboxylic acid derivative without the intermediacy of an isolable aldehyde is ozonolysis, and there are several useful methods for converting an olefin directly to an ester. Ozonolysis of **4.89** using the conditions of Marshall did not provide **4.95** or any other methyl ester (Scheme

4.35). [181] The only recognizable product was the *N*-oxide **4.104**, whose identity was confirmed by both reduction to provide **4.89**, and independent synthesis by oxidation of **4.89** with 4-chloroperoxybenzoic acid (*m*-CPBA). It is well known that more electron rich olefins react more readily with ozone while in solution.[182] In an endeavor to make the vinyl substituent of **4.89** significantly more nucleophilic a cross metathesis with ethyl vinyl ether was attempted. Molybdenum catalysts have worked poorly for cross metathesis with simple alkyl or aryl vinyl ethers, instead forming relatively unreactive Fischer carbene complexes upon metathesis with the vinyl ether.[183] The very reactive second generation Grubbs catalyst was utilized for the metathesis, but only unreacted **4.89** was recovered from the reaction (Scheme 4.35).

Scheme 4.35

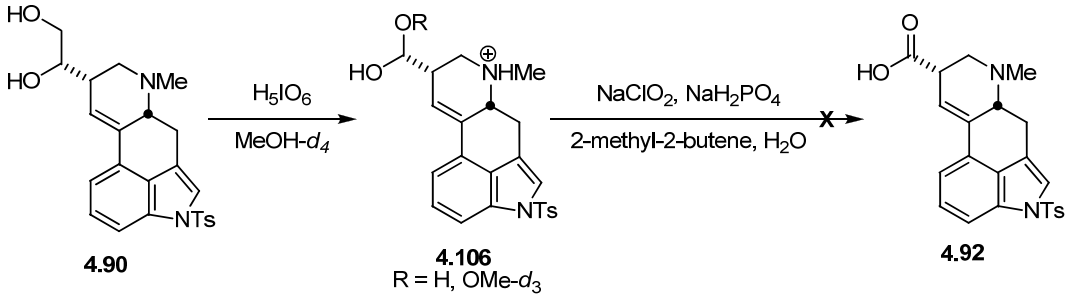


Scheme 4.36



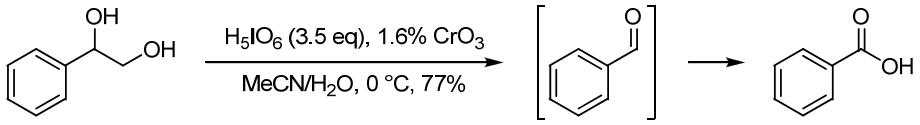
When **4.90** was exposed to periodic acid in deuterated methanol, the result was interesting. The reaction progress was monitored by ^{1}H-NMR spectroscopy, and **4.90** appeared to be consumed and form primarily one product (Scheme 4.37). The ^{1}H-NMR spectrum of the reaction mixture was consistent with the presence of **4.106**. When the reaction mixture was subjected directly to a Pinnick oxidation, it decomposed in an all too familiar fashion. The low pH of the periodic acid cleavage must have been necessary to form the aldehyde hydrate, presumably the source of the stabilization of **4.106**. The buffered Pinnick oxidation was not sufficiently acidic, and as the pH increased the aldehyde hydrate may have reverted to the unstable aldehyde **4.91** and suffered degradation.

Scheme 4.37



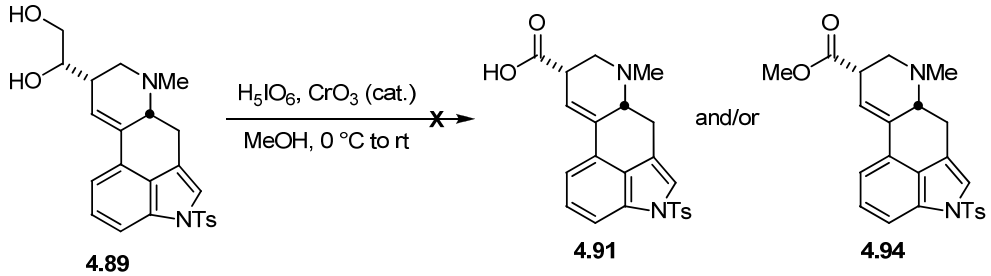
The periodic acid cleavage of **4.90** was very exciting for two reasons. It was the first evidence of a possible success in creating a carbonyl group or carbonyl surrogate from the diol. The second reason was the convenient overlap with an interesting method for the oxidation of alcohols to acids developed recently by some researchers at Merck. They found that chromium trioxide could be used in catalytic amounts in the presence of stoichiometric amounts of periodic acid to oxidize primary alcohols to carboxylic acids and secondary alcohols to ketones.[184] An artifact of using periodic acid as the stoichiometric oxidant was the preliminary cleavage of vicinal diols followed by the oxidation of the subsequent aldehyde to a carboxylic acid. As an example they converted styrene glycol, directly to benzoic acid in good yield (Scheme 4.38).

Scheme 4.38



The reaction between **4.90** and the periodic acid/chromium trioxide system was conducted in methanol to try to take advantage of possible Fischer esterification, hopefully providing **4.95** *via* **4.92** (Scheme 4.39). Unfortunately neither of the desired products were isolated.

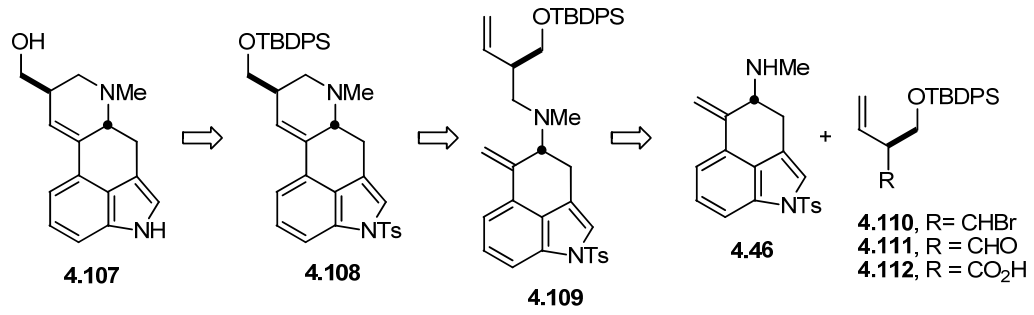
Scheme 4.39



4.89 **4.91** **4.94**

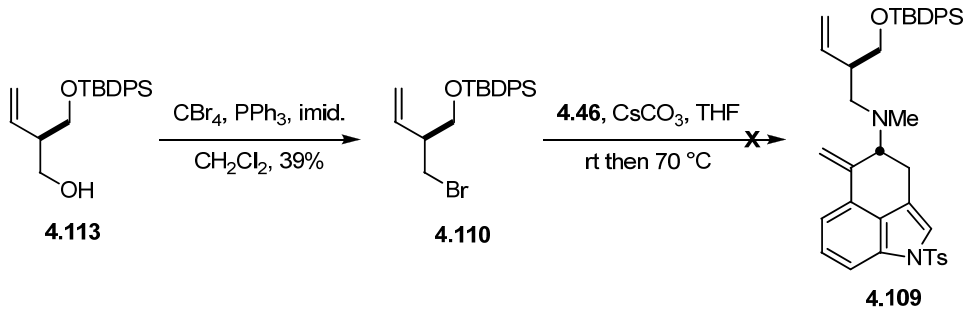
To avoid the intermediacy of unstable aldehyde **4.91**, the late stages of the synthesis were modified. The target lysergol (**4.107**) would be completed with late stage formation of the ***D*** ring *via* RCM (**4.109** → **4.108**, Scheme 4.40). Diene **4.109** would come from the coupling of amine **4.46** with an electrophile already containing a protected carbinol with requisite stereochemistry. If successful, the same approach would be applicable to the synthesis of methyl lysergate (**4.95**).

Scheme 4.40



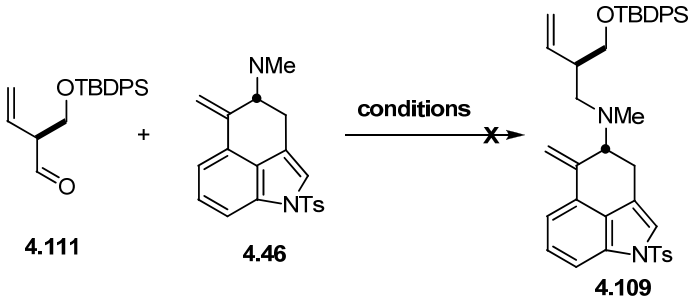
The alcohol **4.113** was made in the same manner as its known enantiomer, and transformed into bromide **4.110** (Scheme 4.41).[185] Addition of the amine **4.46** to the bromide under the conditions that proved optimal for the homoallylation of **4.46** (**4.7** → **4.2**, Scheme 4.2) at room temperature provided no reaction. Elevating the temperature decomposed **4.110** without any trace of **4.109**.

Scheme 4.41



Reductive amination of the aldehyde **4.111**, which was a precursor of **4.113**, and **4.46** under several sets of conditions provided complex mixtures of products (Scheme 4.42). There was no **4.109**, but there were inseparable mixtures of compounds that may have been alkene regioisomers of **4.109**.

Scheme 4.42



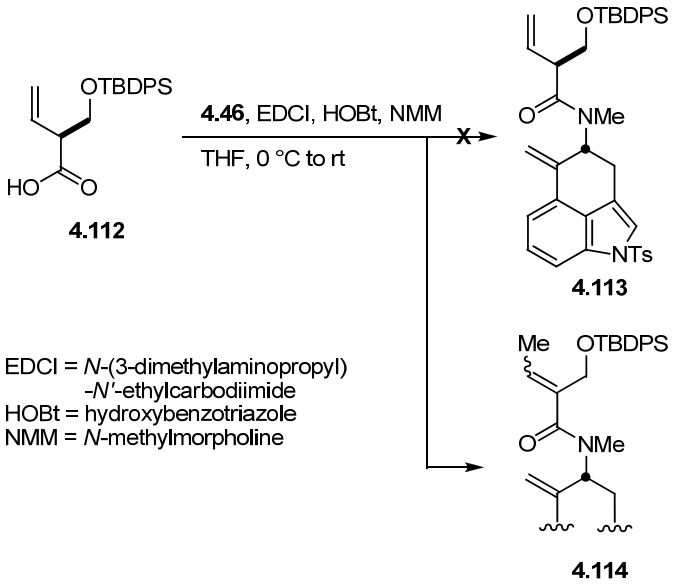
conditions

reductant	solvent	additive
$NaBH(OAc)_3$	1,2-dichloroethane	4Å mol. sieves
$NaBH(OAc)_3$	acetonitrile	4Å mol. sieves
$NaBH(OAc)_3$	acetonitrile	4Å mol. sieves, AcOH
$NaCNBH_3$	acetonitrile	4Å mol. sieves
$NaCNBH_3$	acetonitrile	4Å mol. sieves, AcOH

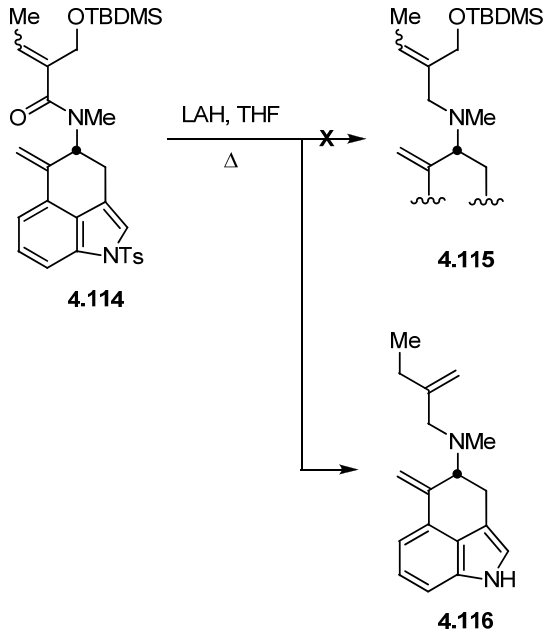
Oxidation of aldehyde **4.111** to the acid **4.112** went smoothly in quantitative yield. Peptide coupling of the amine **4.46** with the acid **4.112** did not give **4.113**, instead generating **4.114** (Scheme 4.43). Interestingly when **4.114** was exposed to lithium

aluminum hydride in an effort to selectively reduce the amide, a number of changes took place. Instead of solely reducing the amide, the allylic silanol was completely removed, and the toluenesulfonyl protecting group of the indole was cleaved creating **4.116** (Scheme 4.44). While the allylic reduction would not have been an issue with **4.109**, the deprotection of the indole would have necessitated a reprotection step.

Scheme 4.43

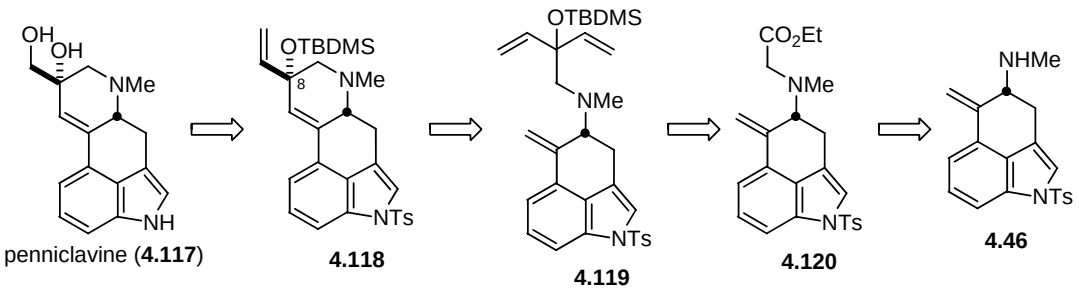


Scheme 4.44



The appending of a fully developed portion of the ***D*** ring appeared untenable. In an effort to return to the original goals of the synthesis while mediating potential problems the target penniclavine (**4.117**) was considered. Penniclavine (**4.117**) could be made from **4.118** in the same fashion as was proposed for lysergol (**4.107**, Scheme 4.40). The problems encountered when attempting to synthesize aldehyde **4.91** would be minimized through the isolation of the aldehyde functionality by the tetrasubstituted center at C(8). The ***D*** ring would be formed *via* asymmetric ring closing metathesis of **4.119**, which would be produced in uncomplicated fashion from **4.46**.

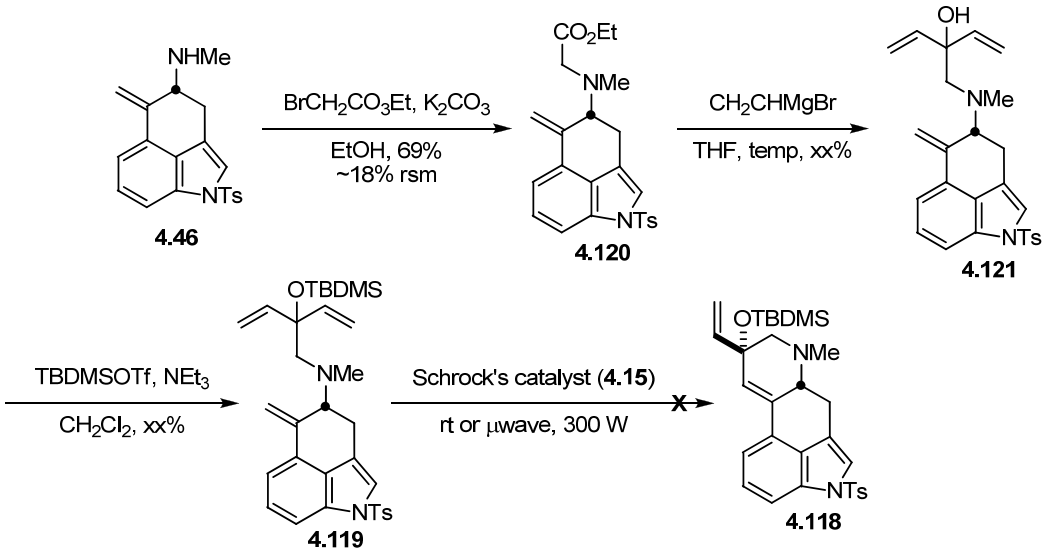
Scheme 4.45



Amine **4.46** underwent facile monoalkylation with ethylbromoacetate to give **4.120** (Scheme 4.46). Vinyl magnesium bromide added twice to the ester of **4.120**, placing all of the needed elements to complete the synthesis. Protection of the tertiary alcohol with *tert*-butyldimethylsilyl trifluoromethanesulfonate gave the ring closing metathesis precursor **4.119**. Remarkably **4.119** was completely inert to Schrock's catalyst (**4.15**). The most forcing conditions available, namely 300 watts of microwave irradiation in nonabsorbing solvent, yielded only recovered starting material.

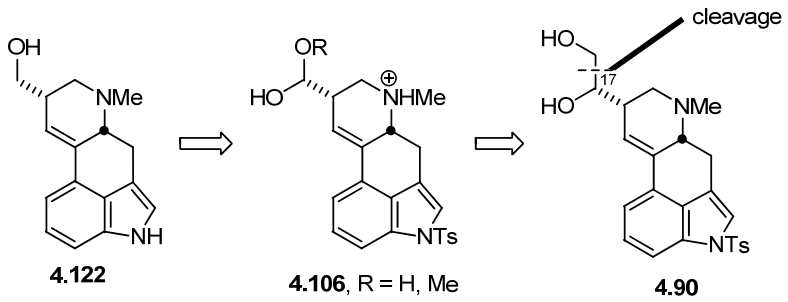
Substrate **4.27** would not undergo RCM using any prior technology, but the addition of microwave irradiation vastly improved the conversion of **4.27** to **4.28**. The addition of another substituent near the reaction center, namely the vinyl group of **4.119**, halted even the microwave enhanced process. It appeared as though the substrate **4.27** was right at the limit of what was a usable substrate for ring closing metathesis.

Scheme 4.46



An expedient one carbon cleavage of **4.90** would greatly assist a total synthesis effort. If the terminal carbon of the diol could be excised without the intermediacy of a carbonyl at the internal position, C(17), perhaps the total synthesis could be achieved. The most successful method for the removal of the terminal carbon was with periodic acid in methanol (Scheme 4.37). The ^{1}H-NMR of the reaction mixture illustrated that the carbinol was removed to provide a single compound, which was presumed to be **4.106**, that was stable under the reaction conditions. Oxidation of **4.103** failed, but reduction, if successful would provide isolysergol (**4.122**) (Scheme 4.47).

Scheme 4.47

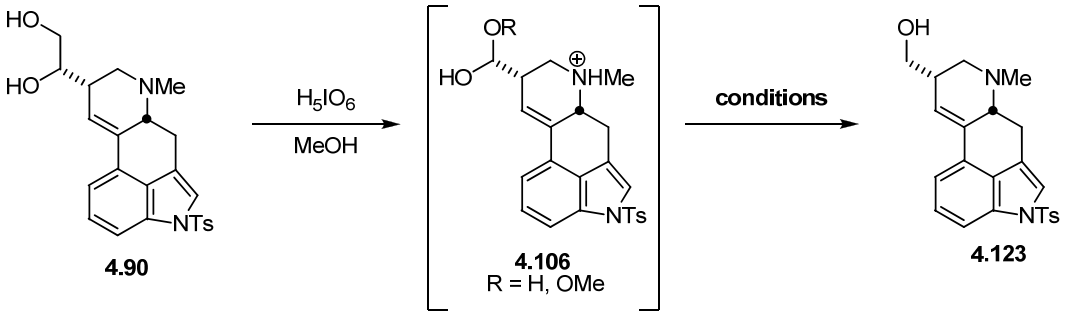


Keeping the pH sufficiently low in the presence of a nucleophile, such as water or methanol, seemed to stabilize **4.106**. For the subsequent reduction, a reductant was needed that was both compatible with the acidic medium, and would maintain the necessary low pH. The use of borohydrides in carboxylic acids for aldehyde reductions, has been studied and reviewed by Gribble.[186] There are examples of diol cleavage followed by reduction of the aldehyde generated *in situ* with borohydrides, but none under acidic conditions.[187] Gribble's work showed that borohydride reductants were effective under acidic reaction conditions, so we reasoned that perhaps the combination of periodic acid and methanol, followed by borohydride would be effective.

A general screen of cleavage and reduction conditions was performed on simple models, and periodic/acid borohydride combinations did indeed prove to be the best reagents for the transformation. Application of the optimal reagent combinations to **4.90** was performed on micro scale followed by examination of the ^{1}H-NMR spectrum of the crude product mixture for key resonances H(9) and CH_2OH (Scheme 4.48). Treatment of **4.90** with periodic acid followed by the addition of a large excess of sodium borohydride provided a complex mixture of compounds without any sign of **4.123**. The sodium borohydride may have neutralized the acid present in the mixture, leading to the large number of undesired compounds. Addition of acetic acid as cosolvent and use of the

more acid tolerant sodium cyanoborohydride did provide a small amount of **4.123**, in addition to several other compounds. Unfortunately the reaction was difficult to reproduce and failed more often than it was successful. Exchanging acetic acid (pKa_{water} 4.76) for the stronger trifluoroacetic acid (pKa_{water} -0.25) provided the desired **4.123**, and the crude product mixture was cleaner than the most successful attempt with acetic acid. Interestingly the use of trichloroacetic acid (pKa_{water} 0.65) or methanesulfonic acid (pKa_{water} -0.6), which are slightly less and slightly more acidic than trifluoroacetic acid respectively, failed to provide any significant amount of **4.123**. It is more likely that the failure of these alternate acids to provide **4.123** is due to the variability of the reaction itself than the pKa difference.

Scheme 4.48



conditions

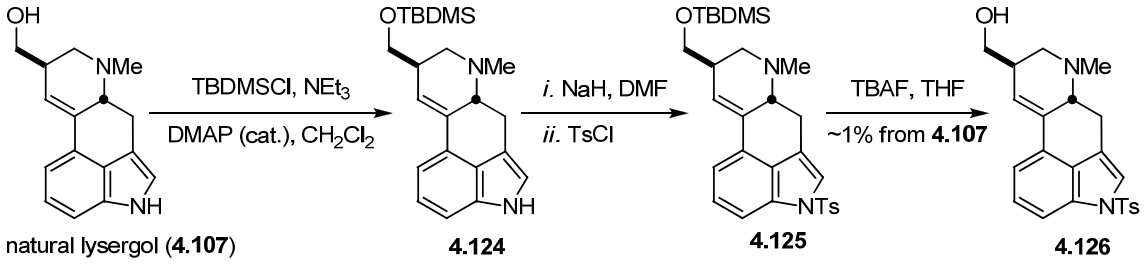
reductant	solvent	target present?
$NaBH_4$	MeOH	no
$NaCNBH_3$	AcOH, MeOH	0 to ~20%
$NaBH_4$	MeOH, TFA	yes
$NaCNBH_3$	MeOH, TFA	54%
$NaCNBH_3$	MeOH, TCA	trace
$NaCNBH_3$	MeOH, $MeSO_3H$	no

TFA = trifluoroacetic acid
TCA = trichloroacetic acid

For comparison to the synthetic material, an appropriately protected compound had been made from natural lysergol (**4.107**). The straightforward synthesis was carried

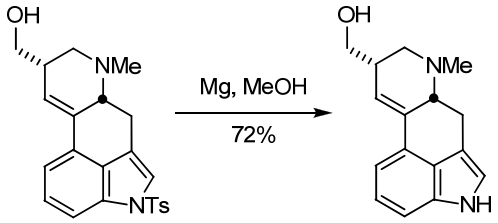
out rapidly and without optimization with the sole purpose of providing *N*-tosyl lysergol **4.126** from natural **4.107** expediently (Scheme 4.49).

Scheme 4.49



When the ^{1}H-NMR spectrum of **4.126** from natural lysergol was compared to that of the synthetic **4.123**, they did not match. Both contained resonances characteristic of the lysergate family, but they were obviously different compounds. Deprotection of synthetic **4.123** went smoothly to provide **4.122** again differing from lysergol (**4.107**), but including lysergate resonances. Comparison with literature spectra and thin layer chromatography data showed **4.122** to be in fact isolysergol (Scheme 4.50).[188-190]

Scheme 4.50



4.123
(synthetic)

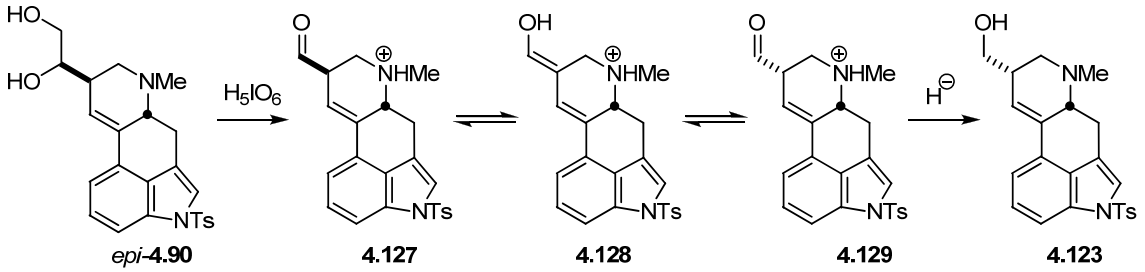
4.122
matches literature data for isolysergol

4.122 (this work)			**4.122 (lit. value)**		**4.107 (lit. value)**	
H	**δ**	**J (Hz)**	**δ**	**J (Hz)**	**δ**	**J**
NH			7.94			
14	7.17	5.1, 3.7	7.2[a]		7.36-7.10[a]	
12-13	7.09-7.06					
2	6.89	1.60	6.9	2	7	1.5
9	6.40	4.7 (br)	6.5	6	6.47	br s
CH_2OH	3.82	10.3, 4.2	4.02	10, 3	3.66	
	3.71	10.3, 5.5, 0.7	3.86	10, 3, 2		
4 beta	3.48	14.4, 5.5	3.54	15, 5.5	3.59	14, 6
5 beta	3.17	11.5, 5.5, 2.2	3.18		3.3	
7 alpha	2.98	11.4, 1.8	3.07	11	3.2	11, 5
7 beta	2.77	11.4, 3.8	2.87	11, 3.5, 2	2.39	11, 11
4 alpha	2.63	14.4, 11.5, 1.7	2.68	15, 12, 2	2.74	14, 12, 1.5
NMe	2.53		2.56		2.64	
8	2.5-2.45		2.46		2.92	

[a] C(12-14)H

The isolysergol stereochemistry was expected due to the nOe data gathered from **4.28** and **4.89**. If the stereochemical assignment of **4.28** and **4.89** had been incorrect, however, we may still have seen iso geometry in the product if C(8) epimerized during the cleavage sequence. If the product of the cleavage **4.127** had enolized, it could have epimerized to **4.129** and then been reduced to provide **4.125** (Scheme 4.51).

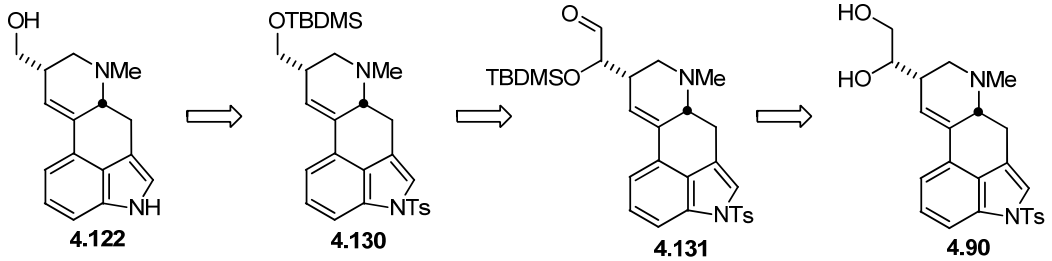
Scheme 4.51



epi-**4.90** **4.127** **4.128** **4.129** **4.123**

It was unlikely that enolization was taking place to any great extent. If enolization was taking place both epimers **4.123** and **4.126,** and/or the $\Delta^{8,9}$ analogs should have been formed analogous to the equilibrium mixtures seen in all of the methyl lysergate and lysergic acid analogs (*vide supra*). To prove that this was not taking place another method was used to remove the extra carbon of **4.90**. Cleaving of the carbon *via* deformylation would remove the possibility of epimerization at C(8), and could be useful both as a mechanistic probe of the oxidative cleavage/reduction of **4.90** and as a structural proof of the product of the asymmetric ring closing metathesis **4.28**.[191] Isolysergol (**4.107**) could be obtained from protected **4.130**, which would be the deformylation product of **4.131** (Scheme 4.52).

Scheme 4.52

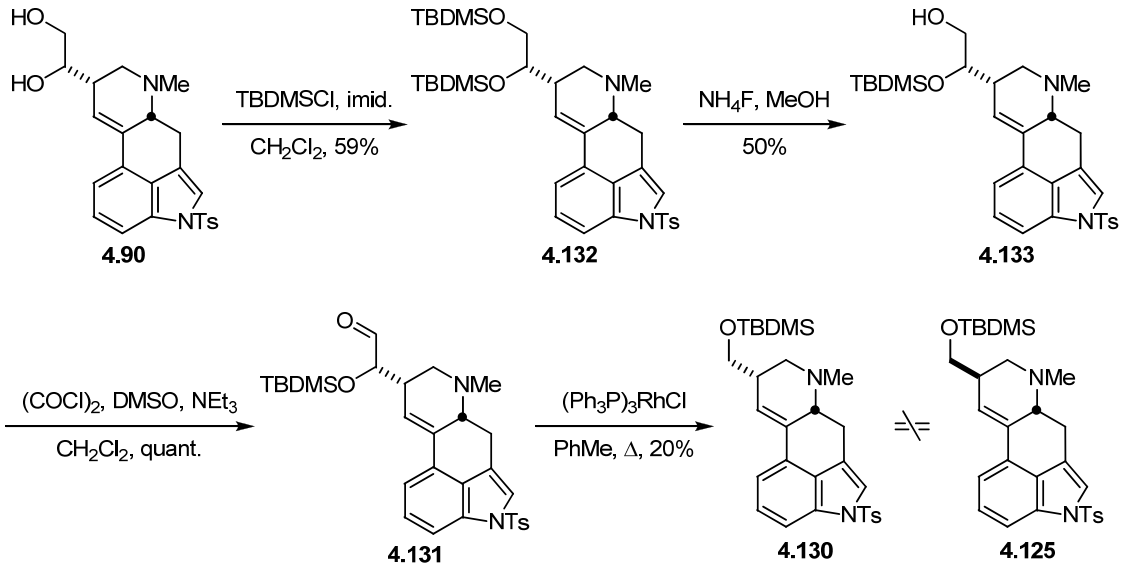


4.122 **4.130** **4.131** **4.90**

The installation of both silyl ethers on **4.90** was sluggish, but selective removal of the terminal protecting group was quite facile (Scheme 4.53). Swern oxidation of **4.133**

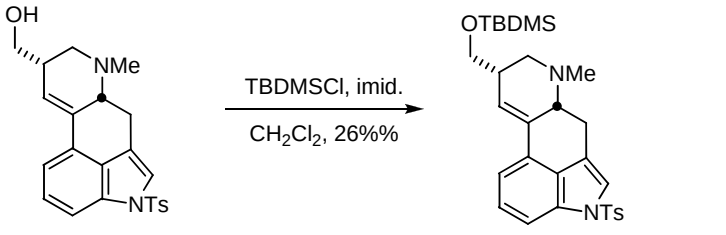
proceeded well to give **4.131**, which was carried on with minimal purification. Deformylation of **4.131** was performed with a stoichiometric quantity of Wilkinson's catalyst, yielding a small amount of **4.130**. Upon comparison of the ^{1}H-NMR spectra it was confirmed that **4.130** was not **4.125** synthesized from natural lysergol.

Scheme 4.53



When **4.133** was compared to the silyl ether of **4.123**, however, they were found to be identical (Scheme 4.54). Therefore the original stereochemical assignment of **4.28** was correct, and additional support was gained for the *lack* of the enolization process shown in Scheme 4.51.

Scheme 4.54



4.122

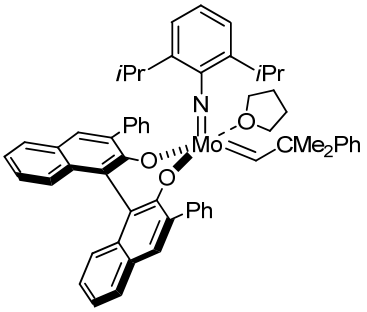
4.133
matched deformylation product

Based upon the available information, there is no reasonable way to determine the cause of the formation of the diastereomer **4.28** during the RCM of **4.27**. Different catalysts (**4.15**, *R/S*-**4.23**) all favored the isolysergate stereochemistry, which would imply substrate control was in effect. Without any isolable intermediates or spectral evidence, only supposition based on the observed products and the slight preference for iso geometry was available.

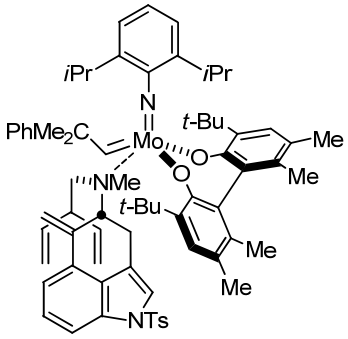
Catalysts such as **4.134** are Lewis acidic enough at the molybdenum center that they are isolated as their tetrahydrofuran or pyridine adducts (Figure 4.6). A potential reason for the apparent substrate control of the RCM may be that the basic amine of **4.27** is coordinating the RCM catalyst to generate a complex such as **4.135**. If this were the case the large, sterically demanding, catalyst would likely be disposed towards the most open area in the vicinity of the amine, the top of the tricycle as drawn. This positioning of the spatially demanding catalyst might force the pentadienyl moiety down and away from the catalyst, perhaps as drawn. Regardless of the specifics of the positioning of the catalyst and pentadiene, they would be sufficiently far away from each other to react with any facility. If this were the case the complex could not only impede the formation of the alkylidene leading to one or the other stereoisomer, it would explain the need for large catalyst loads and forcing conditions to produce any reaction. However **4.135** is

sufficiently complicated that it was unreasonable to make any stereochemical predictions based upon it.

Figure 4.6



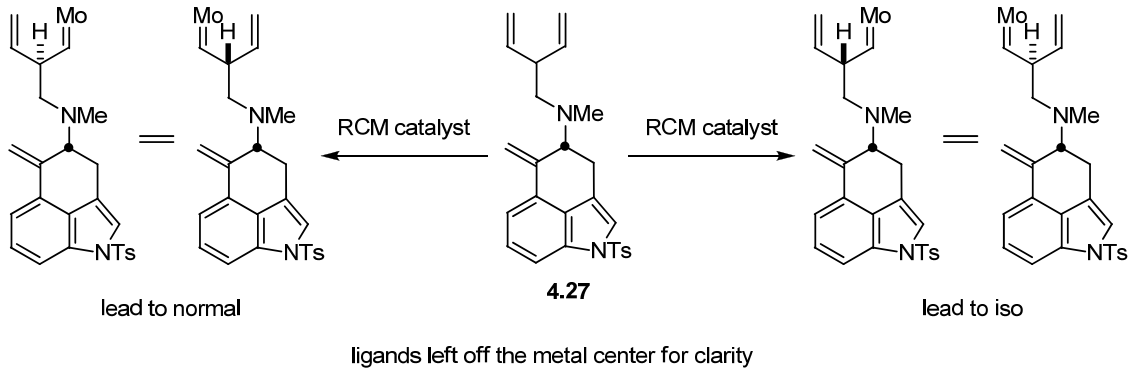
4.134



4.135

Another rationale for the preference of **4.89** over **4.28** would be the loading of the catalyst on the 1,1-disubstituted olefin of **4.27**, rather than either of the two vinyl groups. Another proposition for the RCM was that the catalyst loaded on the 1,1-disubstituted olefin of **4.27**, rather than either of the two vinyl groups. If the catalyst were to load on one of the vinyl substituents first, the event would be the stereo determining step. There is quite a bit of flexibility in the σ-bonds between the diastereomeric vinyl groups of **4.27** and the tricyclic core. It is not immediately apparent whether there would be a preference for loading of the catalyst on one versus the other (Figure 4.7). Once the catalyst has loaded on to an olefin only one of the two possible diastereomers can form. The preference shown between **4.28** and **4.89** was slight, but there seems to be little reason to believe there would be any preference at all between the loading of one vinyl substituent over the other.

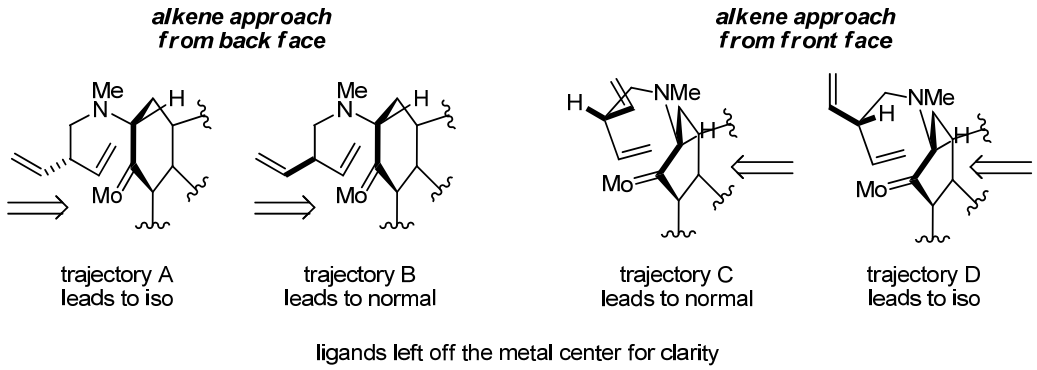
Figure 4.7



Conversely, if the catalyst were to load on the 1,1-disubstituted olefin the stereochemical determining step would be the approach of one of the vinyl groups to the molybdenum-substrate carbene. Some possible approach trajectories are shown in Figure 4.8. This mode of reactivity and stereoselection is what has been proposed as the source of the high enantioselectivities in ARCM reactions of substrates such as **4.22** (Equation 3).

The two approaches A and B appear to be slightly favored versus C or D. Of the two more favored trajectories A, with the extra vinyl group disposed down as drawn, would have more clearance between the alkene and the ligands on the molybdenum than B with the vinyl group up as drawn. Again this is only supposition, and the trajectories are too complicated to model with any real confidence.

Figure 4.8


alkene approach
from back face
alkene approach
from front face
Me
N
H
Mo
NMe
trajectory A
leads to iso
trajectory B
leads to normal
trajectory C
leads to normal
trajectory D
leads to iso
ligands left off the metal center for clarity

4.3 CONCLUSIONS

Isolysergol has been synthesized in an enantiocontrolled fashion in 12 operations from commercially available starting materials. Both of the chiral centers were installed by employing chiral catalysts, and there were relatively few oxidation state modifications throughout the molecule

Prior to the current work only Szántay had synthesized an enantiomerically enriched lysergate, and a lysergate containing both a C(2)-C(3) double bond for the entire synthesis and unambiguous installation of the C(9)-C(10) double bond, as opposed to an equilibrating/isomerizing method of moving the bond into final position. In fact only Woodward and Szántay installed the C(9)-C(10) double bond with specificity, both using essentially the same method.

The indole core of the present work was present from the commercially available starting material and remained intact the completion of the synthesis without the need to reduce or otherwise protect the C(2)-C(3) π-bond. The C(9)-C(10) olefin was installed in a discrete fashion using RCM and, likewise, remained until the completion of the synthesis.

Not only did the RCM form the ***D*** ring and install the olefin in analogous fashion to Szántay and Woodward, but use of olefins for the installation removed potential issues with the carbonyl groups used by Woodward and Szántay. Without the carbonyl present the C(5) chiral center could be set and maintained without fear of racemization during the condensation to form the ***D*** ring. This set the stage for an enantioselective formation of *R*-**4.37** instead of the inherently less efficient resolution employed by Szántay.

While the key ARCM was not able to produce both the normal and the iso stereochemistry, it was still a triumph of RCM technology. The surprising difficulty encountered in performing the RCM on **4.27** provoked the development of a novel combination of molybdenum metathesis catalysis and microwave heating. This new combination may find use in other RCM reactions. Reports of similarly difficult RCM transformations are conspicuously absent from the literature, but that may be due to solely to the lack of publications covering failed chemistry. Furthermore the ring closure of **4.27** to **4.28** with the chiral catalyst *S*-**4.20** represents the first use of a chiral metathesis catalyst on an advanced substrate. Although **4.28** was of the unplanned diastereomeric configuration this example shows some of the potential of the relatively young field of catalytic asymmetric ring closing metathesis in that it is indeed applicable to late stage transformations on advanced, functionality laden, compounds. Additionally this work represents the first example of any significant favoritism for the iso stereochemistry in the synthesis of a lysergate, an outcome that may, one day, find use in synthesizing analogs for pharmaceutical testing.

The excision of the terminal carbinol of **4.90** *via* the exceedingly sensitive presumed intermediate **4.106** avoiding the completely intractable **4.91** was accomplished. After many false starts success came *via* the coupling of very dissimilar methodologies, namely oxidation and reduction in strong acid, to provide a technically very simple method to rapidly cleave a terminal diol to an alcohol in one pot. These extreme conditions won't be useful for the same transformation on a wide array of substrates, but may prove invaluable for similarly sensitive aldehydes.

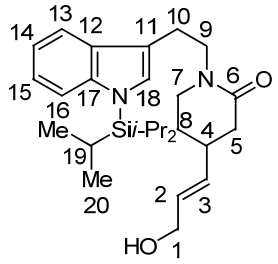
Chapter 5: Experimental Procedures

5.1 General methods

Unless otherwise indicated, all starting materials were obtained from commercial suppliers and used without further purification. The (*S*)-Schrock-Hoveyda catalyst (**4.20**) was stored below -30 °C in a nitrogen filled glove box, and weighed into septum sealed vials before removal from the glove box. Methanol (MeOH), acetonitrile (CH_3CN), and *N*,*N*-dimethylformamide (DMF) were dried by passage through two columns of activated molecular sieves. Toluene was dried by passage through a column of activated neutral alumina followed by passage through a column of Q5 reactant. Tetrahydrofuran (THF) was dried by passage through two columns of activated neutral alumina. Benzene (PhH) was distilled from sodium and benzophenone under an atmosphere of nitrogen immediately prior to use. Triethylamine (NEt_3) was distilled from CaH_2 under an atmosphere of nitrogen immediately prior to use. Methylene chloride (CH_2Cl_2) was distilled from CaH_2 under an atmosphere of nitrogen immediately prior to use. Reactions involving air or moisture sensitive reagents or intermediates were carried out under an inert atmosphere of nitrogen or argon in glassware that had been oven dried, flame dried, or dried *via* repeated evacuation (<0.2 mm Hg) followed by nitrogen purge. Reaction temperatures are reported as the temperature of the bath surrounding the vessel. Microwave reactions were carried out in a CEM Discovery single mode microwave reactor with stirring *via* magnetic stir bar. Flash chromatography was conducted according to the established Still protocol using ICN Biomedicals ICN-SILITech 32-63d silica gel with the indicated solvents.[192] All NMR spectra were taken on a Bruker AC 250, General Electric QE-300, Varian Mercury 400, or Varian INOVA 500 instrument in deuterated chloroform ($CDCl_3$) unless otherwise noted. Chemical shifts (δ) are

expressed as ppm referenced to the residual solvent (i.e. chloroform, 7.24 ppm). Splitting patterns are expressed as s, singlet; d, doublet; t, triplet; q, quartet; p, pentet; m, multiplet; comp, complex multiplet; br, broad; app, apparent. High resolution mass spectra were taken on VG Analytical ZAB2-E instrument.

5.2 CONDYLOCARPINE EXPERIMENTAL PROCEDURES



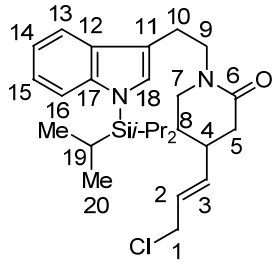
4-(3-Hydroxypropenyl)-1-[2-(1-triisopropylsilanyl-1*H*-indol-3-yl)ethyl]piperidin-2-one (2.27).

Method A: (JD 1-166). Carbon tetrabromide (42 mg, 0.13 mmol) was sublimed at 100 °C (<1 mmHg) to the sides of a borosilicate glass vial. The vessel was flushed with N_2, and **2.20** (290 mg, 0.504 mmol) in dry MeOH (1.75 mL) was added *via* cannula. The vessel was sealed and heated to 100 °C with stirring for 1.5 h. The mixture was cooled to room temperature, concentrated under reduced pressure, and the residue purified *via* flash chromatography eluting with MeOH/CH_2Cl_2 (1-4%) to yield 112 mg (49%) of **2.27** and 60 mg (21%) of **2.20**.

Method B: (JD 1-179, 1-184, 1-185). A solution of **2.30** (44 mg, 0.14 mmol) in dry toluene (15 mL) was heated at 115 °C for 26 h. The solution was concentrated under reduced pressure and the residue dissolved in CH_2Cl_2/H_2O (20:1, 1.6 mL). 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (28 mg, 0.12 mmol) was carefully added portionwise with stirring over the course of 1 h until no starting material remained. Saturated aqueous $NaHCO_3$ (1 mL) and EtOAc (2 mL) were added, and the layers were separated. The aqueous layer was washed with EtOAc (3 X 2 mL), and the combined organic layers were dried (Na_2SO_4). The solution was filtered through a pad of silica (deactivated with triethylamine) washing with EtOAc, concentrated under reduced

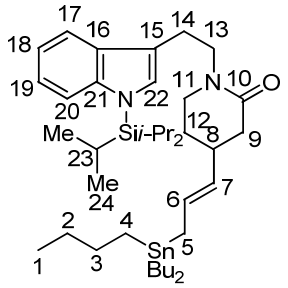
pressure, and the residue was dissolved in dry toluene (0.5 mL). TIPS protected tryptamine **2.21** (21 mg, 0.066 mmol) and 4 Å molecular sieves were added, and the mixture was heated at 115 °C for 4 h. The mixture was cooled, and MeOH (0.5 mL) and $NaBH_4$ (5 mg, 0.13 mmol) were added. The mixture was stirred for 24 h whereupon saturated aqueous $NaHCO_3$ (0.5 mL) and EtOAc (0.5 mL) were added, the layers were separated, the aqueous layer was washed with EtOAc (3 X 0.5 mL), and the combined organic layers were dried (Na_2SO_4). The solution was concentrated under reduced pressure, and the residue purified *via* flash chromatography eluting with MeOH/CH_2Cl_2 (2-3%) to yield 13 mg (20%) of **2.27**. ^{1}H NMR δ 7.60-7.57 (m, 1 H), 7.47-7.43 (m, 1 H), 7.15-7.06 (comp, 2 H), 7.05 (s, 1 H), 6.00-5.55 (comp, 2 H), 4.07 (br d, *J* = 3.5 Hz, 2 H), 3.64 (t, *J* = 7.3 Hz, 2 H), 3.15-2.95 (comp, 4 H), 2.55-2.30 (comp, 2 H), 2.15 (dd, *J* = 10.0, 16.4 Hz, 1 H), 1.77-1.59 (comp, 4 H), 1.50-1.30 (m, 1 H), 1.11 (d, *J* = 7.5 Hz, 18 H); ^{13}C NMR δ 168.9, 141.2, 133.6, 131.0, 129.0, 128.7, 121.4, 119.3, 118.5, 115.0, 113.9, 63.1, 48.1, 47.6, 38.0, 35.3, 28.9, 23.0, 18.1, 12.7; IR (neat) 3382, 3046, 2946, 2867, 1621; MS CI+ *m/z* 455.3090 [$C_{27}H_{43}N_2O_2Si$ (M+1) requires 455.3094] (base), 437, 411.

NMR Assignments. ^{1}H NMR δ 7.60-7.57 (m, 1 H, C13-H or C16-H), 7.47-7.43 (m, 1 H, C13-H or C16-H), 7.15-7.06 (comp, 2 H, C14-H, C15-H), 7.05 (s, 1 H, C18-H), 6.00-5.55 (comp, 2 H, C2-H, C3-H), 4.07 (br d, *J* = 3.5 Hz, 2 H, C1-H), 3.64 (t, *J* = 7.3 Hz, 2 H, C9-H), 3.15-2.95 (comp, 4 H, C7-H, C10-H), 2.55-2.30 (comp, 2 H, C4-H, C5-Ha), 2.15 (dd, *J* = 10.0, 16.4 Hz, 1 H, C5-Hb), 1.77-1.59 (comp, 4 H, C8-Ha, C19-H), 1.50-1.30 (m, 1 H, C8-Hb), 1.11 (d, *J* = 7.5 Hz, 18 H, C20-H); ^{13}C NMR δ 168.9 (C6), 141.2 (C17), 133.6 (C3), 131.0 (C12), 129.0 (C2), 128.7 (C18), 121.4 (C14), 119.3 (C15), 118.5 (C13), 115.0 (C11), 113.9 (C16), 63.1 (C1), 48.1 (C9), 47.6 (C7), 38.0 (C5), 35.3 (C8), 28.9 (C4), 23.0 (C10), 18.1 (20), 12.7 (C19).



4-(3-Chloropropenyl)-1-[2-(1-triisopropylsilanyl-1*H*-indol-3-yl)ethyl]piperidin-2-one (2.32). (JD 1-133). Tributylphosphine (0.070 mL, 0.28 mmol) was added to a stirred solution of *i*-Pr_2NEt (ca 0.025 mL, 0.14 mmol) in dry CCl_4 (1 mL) and an exotherm was observed. After 30 s the solution was added *via* cannula to a stirred solution of **2.27** (33 mg, 0.073mmol) in dry CH_2Cl_2 (1 mL). The reaction was stirred for 5 min whereupon saturated aqueous $NaHCO_3$ (1 mL) was added, and the layers were separated. The aqueous layer was washed with CH_2Cl_2 (3 X 1 mL), and the combined organic layers were dried (Na_2SO_4). The solution was concentrated under reduced pressure, and the residue was filtered through a pad of silica washing with EtOAc to remove tributylphosphine oxide. The solution was again concentrated under reduced pressure, and the residue was purified *via* flash chromatography eluting with MeOH/CH_2Cl_2 (1%) to yield 33 mg (96%) of **2.32**. ^{1}H NMR δ 7.60-7.57 (m, 1 H), 7.47-7.43 (m, 1 H), 7.15-7.06 (comp, 2 H), 7.05 (s, 1 H), 5.61-5.57 (comp, 2 H), 3.98 (d, *J* = 5.8 Hz, 2 H), 3.65 (t, *J* = 6.5 Hz, 2 H), 3.12-2.95 (comp, 4 H), 2.55-2.30 (comp, 2 H), 2.16 (dd, *J* = 9.6, 16.2 Hz, 1 H), 1.67 (comp, 4 H), 1.43 (m, 1 H), 1.11 (d, *J* = 7.5 Hz, 18 H); ^{13}C NMR δ 169, 141.2, 136.9, 131.0, 128.7, 125.8, 121, 119.4, 118.6, 115, 114.0, 48.2, 47.4, 44.8, 37.7, 35.2, 28.6, 23.0, 18.1, 12.8; IR (neat) 2950, 2925, 2867, 1625.4; MS CI+ *m/z* 473.2743 [$C_{27}H_{42}N_2OSiCl$ (M+1) requires 473.2755] (base), 437.

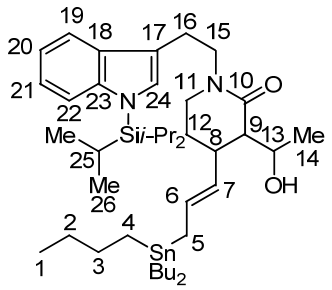
NMR Assignments. ^{1}H NMR δ 7.60-7.57 (m, 1 H, C13-H or C16-H), 7.47-7.43 (m, 1 H, C13-H or C16-H), 7.15-7.06 (comp, 2 H, C14-H, C15-H), 7.05 (s, 1 H, C18-H), 5.66-5.60 (comp, 2 H, C2-H, C3-H), 3.88 (d, *J* = 6.5 Hz, 2 H, C1-H), 3.65 (dd, *J* = 7.0, 3.3 Hz, 2 H, C9-H), 3.15-2.95 (comp, 4 H, C7-H, C10-H), 2.55-2.30 (comp, 2 H, C4-H, C5-Ha), 2.16 (dd, *J* = 9.3, 16.0 Hz, 1 H, C5-Hb), 1.80-1.55 (comp, 4 H, C8-Ha, C19-H), 1.43 (m, 1 H, C8-Hb), 1.11 (d, *J* = 7.5 Hz, 18 H, C20-H); ^{13}C NMR δ 169(C6), 141.2 (C17), 136.9 (C3), 131.0 (C12), 128.7 (C18), 125.8 (C2), 121 (C14), 119.4 (C15), 118.6 (C13), 115 (C11), 114.0 (C16), 48.2 (C9), 47.4 (C7), 44.8 (C1), 37.7 (C5), 35.2 (C8), 28.6 (C4), 23.0 (C10), 18.1 (C20), 12.8 (C19).



4-(3-Tributylstannanylpropenyl)-1-[2-(1-triisopropylsilanyl-1*H*-indol-3-yl)ethyl]piperidin-2-one (2.36). (JD 1-113). $LiSnBu_3$ was formed using the method of Still[193] [*n*-BuLi (0.69 mL of 1.47 M in hexane, 1.0 mmol) was added to a stirred solution of diisopropylamine (0.17 mL, 1.2 mmol) in THF (3.88 mL) at 0 °C under N_2 in a flame dried vial, and stirred for 30 min. Freshly distilled tributyltin hydride (0.27 mL, 0.10 mmol) was added to the LDA. The solution was stirred for 15 min to form 5 mL of 0.2 M $LiSnBu_3$.] $LiSnBu_3$ (ca 1.8 mL of 0.2 M in THF, 0.3 mmol) was added *via* cannula to a solution of **2.32** (77 mg, 0.16 mmol) in dry THF (1 mL) at –78 °C under N_2. After 5 min the reaction was warmed to 0 °C, H_2O (1 mL) and EtOAc (1 mL) were added, and

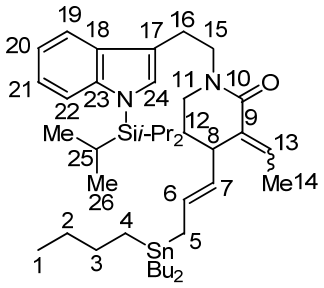
the layers were separated. The aqueous layer was washed with EtOAc (3 X 1 mL) and the combined organic layers were dried (Na_2SO_4). The mixture was concentrated under reduced pressure, dissolved in EtOAc and filtered through a pad of silica gel washing with EtOAc. The mixture was again concentrated under reduced pressure and the residue held at low pressure (<1 mm Hg) for 14 h. The residue was purified *via* flash chromatography eluting with EtOAc/hexanes (5-10%) to yield 89 mg (75%) of **2.36**. ^{1}H NMR δ 7.61-7.52 (m, 1 H), 7.47-7.43 (m, 1 H), 7.15-7.08 (comp, 2 H), 7.04 (s, 1 H), 5.52 (dt, *J* = 15.3, 7.5 Hz, 2 H), 5.05 (dd, *J* = 6.5, 15.3 Hz, 1 H), 3.64 (m, 2 H), 3.15-2.95 (comp, 4 H), 2.55-2.40 (m, 1 H), 2.40-2.20 (m, 1 H), 2.17 (dd, *J* = 10.5, 16.4 Hz, 1 H), 1.80-1.20 (comp, 20 H), 1.11 (d, *J* = 7.5 Hz, 18 H), 1.00-0.75 (m, 15 H); ^{13}C NMR δ 169.4, 141.3, 131.0, 129.3, 128.8, 127.4, 121.4, 119.3, 118.6, 115.1, 114.0, 48.0, 47.8, 38.9, 36.0, 29.7, 29.1, 27.3, 23.1, 18.1, 14.2, 13.7, 12.8, 9.1; IR (neat) 2952, 2924, 2868, 1643; MS CI+ *m/z* 729.4206 [$C_{39}H_{69}N_2OSi^{120}Sn$ (M+1) requires 729.4201] 727, 439, 291 (base), 287.

NMR Assignments. ^{1}H NMR δ 7.61-7.52 (m, 1 H, C17-H or C20-H), 7.47-7.43 (m, 1 H, C17-H or C20-H), 7.15-7.08 (comp, 2 H, C18-H, C19-H), 7.04 (s, 1 H, C22-H), 5.52 (dt, *J* = 15.3, 7.5 Hz, 2 H, C6-H), 5.05 (dd, *J* = 6.5, 15.3 Hz, 1 H, C7-H), 3.64 (m, 2 H, C13-H), 3.15-2.95 (comp, 4 H, C11-H, C14-H), 2.55-2.40 (m, 1 H, C9-Ha), 2.40-2.20 (m, C8-H, 1 H), 2.17 (dd, *J* = 10.5, 16.4 Hz, 1 H, C9-Hb), 1.80-1.20 (comp, 20 H, C2-H, C3-H, C8-H, C9-H, C12-H, C23-H), 1.11 (d, *J* = 7.5 Hz, 18 H, C24-H), 1.00-0.75 (m, 15 H, C1-H, C4-H); ^{13}C NMR δ 169.4 (C10), 141.3 (C21), 131.0 (C16), 129.3 (C7), 128.8 (C27), 127.4 (C6), 121.4 (C18), 119.3 (C19), 118.6 (C17), 115.1 (C15), 114.0 (C20), 48.0 (C13), 47.8 (C11), 38.9 (C9), 36.0 (12), 29.7 (C8), 29.1 (C3), 27.3 (C2), 23.1 (C14), 18.1 (C24), 14.2 (C5), 13.7 (C1), 12.8 (C23), 9.1 (C4).



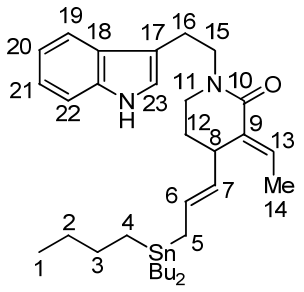
3-(1-Hydroxyethyl)-4-(3-tributylstannanylpropenyl)-1-[2-(1-triisopropylsilanyl-1*H*-indol-3-yl)ethyl]piperidin-2-one (2.37). (JD-171). A 0.48 M solution of LDA (0.93 mL, 0.45 mmol) in a flame dried vial was cooled to –78 °C, and a –78 °C solution of **2.36** in THF (1 mL) was added *via* cannula. After ca 1.5 h excess freshly distilled acetaldehyde was added *via* cannula, and the solution was stirred for 15 min. The solution was warmed to rt for 15 min and then recooled to 0 °C whereupon 0.5 M H_2SO_4 (2 mL) and EtOAc (2 mL) were added. The layers were separated, and the organic layer was washed with EtOAc (3 X 2 mL). The combined organic layers were washed with saturated $NaHCO_3$ (2 mL) and dried ($NaSO_4$). The mixture was concentrated under reduced pressure, dissolved in EtOAc, and filtered through a pad of silica gel washing with EtOAc. The mixture was again concentrated under reduced pressure and held at low pressure (<1 mm Hg) for 14 h. The residue was purified *via* flash chromatography eluting with EtOAc/hexanes (5-20%) to yield 140 mg (81%) of **2.37**. ^{1}H NMR δ 7.65-7.55 (m, 1 H), 7.47-7.43 (m, 1 H), 7.15-7.08 (comp, 2 H), 7.05 (s, 1 H), 5.58 (dt, *J* = 14.8, 7.9 Hz, 1 H), 5.04 (dd, *J* = 8.0, 15.1 Hz, 1 H), 4.04 (d, *J* = 5.9 Hz, 1 H), 3.92 (q, *J* = 5.9 Hz, 1H), 3.70-3.55 (m, 2 H), 3.12-2.97 (comp, 4 H), 2.45-2.25 (m, 1 H), 2.11-2.02 (m, 1 H), 1.80-1.55 (comp, 7 H), 1.55-1.35 (comp, 7 H), 1.35-1.20 (comp, 10 H), 1.11 (d, *J* = 7.5 Hz, 18 H), 1.00-0.75 (m, 15 H); ^{13}C NMR δ 171.5, 141.3, 131.1, 130.9, 128.8,

127.6, 121.5, 119.4, 118.5, 114.9, 114.0, 68.72, 53.0, 48.6, 46.8, 38.8, 36.0, 29.1, 27.3, 23.2, 23.1, 18.2, 14.3, 13.7, 12.8, 9.2



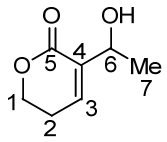
3-Ethylidene-4-(3-tributylstannanylpropenyl)-1-[2-(1-triisopropylsilanyl-1*H*-indol-3-yl)ethyl]piperidin-2-one (2.19). (JD 1-172). Copper chloride (3 mg, 0.03 mmol) and **2.37** (23 mg, 0.030 mmol) were suspended in a stock solution of DCC in toluene (0.15 mL, 0.25 M, 0.038 mmol). The mixture was heated with stirring to 100 °C for 3 h., cooled to rt and saturated aqueous $NaHCO_3$ (1 mL) was added. The layers were separated, the aqueous layer was washed with EtOAc (3 X 1 mL), and the combined organic layers were dried (Na_2SO_4). The mixture was concentrated under reduced pressure, and the residue was purified *via* flash chromatography eluting with EtOAc/hexanes (5-20%) to yield 5 mg (22%) of *E*-**2.19**, 10 mg (44%) of *Z*-**2.19**, and 2 mg (9%) of **2.37**. *E*-**2.19** ^{1}H NMR δ 7.62-7.57 (m, 1 H), 7.47-7.43 (m, 1 H), 7.15-7.06 (comp, 3 H), 5.85 (dq, *J* = 6.0, 1.3 Hz, 1 H), 5.51 (dt, *J* = 15.1, 8.5 Hz, 1 H), 5.10 (dd, *J* = 15.1, 6.9 Hz, 1 H), 3.86-3.70 (m, 1 H), 3.61-3.45 (m, 1 H), 3.30-2.86 (comp, 5 H), 2.17 (dd, *J* = 6.0, 1.1 Hz, 3 H), 1.82-1.16 (comp, 19 H), 1.10 (d, *J* = 7.5 Hz, 18 H), 0.97-0.68 (comp, 15 H). *Z*-**5** ^{1}H NMR δ 7.64-7.60 (m, 1 H), 7.47-7.42 (m, 1 H), 7.14-7.00 (comp, 3 H), 5.45 (dt, *J* = 16.5, 8.5 Hz, 1 H), 5.10 (dd, *J* = 15.1, 5.2 Hz, 1 H), 3.92-3.80 (m, 1 H),

3.64-3.42 (comp, 3 H), 3.08-2.89 (comp, 3 H), 1.85-1.16 (comp, 21 H), 1.10 (d, *J* = 7.5 Hz, 18 H) 0.97-0.65 (comp, 15 H).



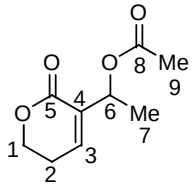
3-Ethylidene-1-[2-(1*H*-indol-3-yl)-ethyl]-4-(3-tributylstannanylpropenyl)piperidin-2-one (2.50). (JD 1-221). Tetrabutylammonium fluoride (TBAF) (0.036 mL, 0.037 mmol, 1 M in THF) was added to a stirred solution of **2.19** (23 mg, 0.031 mmol) in THF (0.35 mL) cooled to 0° C *via* syringe. The reaction was stirred 5 min whereupon saturated aqueous $NaHCO_3$ (0.5 mL) was added, the mixture was warmed to rt, and the layers were separated. The aqueous layer was washed with EtOAc (3 X 1 mL), and the combined organic layers were dried (Na_2SO_4). The solution was filtered through a pad of silica washing with EtOAc, concentrated under reduced pressure, and the residue was purified *via* flash chromatography eluting with EtOAc/hexanes (40%) to yield 18 mg (99%) of **2.50**. ^{1}H NMR (250 MHz) δ 8.09 (s br, 1 H), 7.65 (d, 1 H), 7.34 (d, 1 H), 7.20-7.03 (comp, 3 H), 5.86 (q, *J* = 7.3 Hz, 1 H), 5.53 (dt, *J* = 15.0, 8.5 Hz, 1 H), 5.11 (dd, *J* = 15.0, 6.8 Hz, 1 H), 3.71-3.69 (m, 2 H), 3.35-2.90 (m, 5 H), 2.17 (d, *J* = 6.9 Hz, 3 H), 1.95-1.17 (comp, 16 H), 0.97-0.68 (comp, 15 H); ^{13}C NMR (250 MHz) δ 165.3, 136.3, 136.1, 132.5, 131.3, 127.5, 126.0, 122.0, 121.9, 119.3, 118.9, 113.6, 111.1, 48.3, 46.2, 44.4, 29.6, 29.2, 27.3, 23.1, 17.7, 16.0, 14.4, 13.7, 12.3, 9.2

NMR Assignments. 1H NMR (250 MHz) δ 8.09 (s br, 1 H, N-H), 7.65 (d, 1 H, C19-H or C22-H), 7.34 (d, 1 H, C19-H or C22-H), 7.20-7.03 (comp, 3 H, C20-H, C21-H, C23-H), 5.86 (q, *J* = 7.3 Hz, 1 H, C13-H), 5.53 (dt, *J* = 15.0, 8.5 Hz, 1 H, C6-H), 5.11 (dd, *J* = 15.0, 6.8 Hz, 1 H, C7-H), 3.71-3.69 (m, 2 H, C15-H), 3.35-2.90 (m, 5 H, C8-H, C11-H, C16-H), 2.17 (d, *J* = 6.9 Hz, 3 H, C14-H), 1.95-1.17 (comp, 16 H, C2-H, C3-H, C5-H, C12-H), 0.97-0.68 (comp, 15 H, C1-H, C4-H).



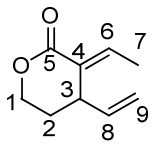
3-(1-Hydroxyethyl)-5,6-dihydropyran-2-one (2.64). (JD 2-203). A mixture of 5,6-dihydropyran-2-one (**2.60**, 1.00 g, 10.2 mmol) and freshly distilled acetaldehyde (0.859 mL, 15.3 mmol) in THF (35 mL) was added slowly dropwise *via* syringe over 30 min to a stirred solution of lithium phenylselenide (6.22 mmol).[85] After 1 h the mixture was warmed to –20 °C for 2 h whereupon saturated aqueous $NaHCO_3$ (50 mL) and EtOAc (50 mL) were added. The layers were separated, the aqueous layer was washed with EtOAc (3 X 50 mL), and the combined organic layers were dried (Na_2SO_4). The mixture was concentrated under reduced pressure and the residue was purified *via* flash chromatography eluting with EtOAc/hexanes (50-75%) to yield 1.029 g (71%) **2.64** and 58 mg (6%) of impure 5,6-dihydropyran-2-one. ^{1}H-NMR (250 MHz) δ 6.83 (t, *J* = 4.2 Hz, 1 H), 4.60-4.50 (m, 1 H), 4.34 (t, *J* = 6.3, 2 H), 3.10-3.05 (m, 1 H), 2.49-2.40 (m, 2 H), 1.34 (d, *J* = 6.5 Hz, 3 H); ^{13}C-NMR δ 164.8, 138.7, 135.7, 66.3 (66.326), 66.3 (66.260), 23.9, 21.6; MS CI+ *m/z* 143.0713 [$C_7H_{11}O_3$ (M+1) requires 143.0708] (base), 125, 157, 285.

NMR Assignments. ^{1}H-NMR (250 MHz) δ 6.80 (t, 1 H, C3-H), 4.60-4.50 (m, 1 H, C6-H), 4.34 (t, 2 H, C1-H), 3.10-3.05 (m, 1 H, OH), 2.49-2.40 (m, 2 H, C2-H), 1.34 (d, 3 H, C7-H); ^{13}C-NMR δ 164.8 (C5), 138.7 (C3), 135.7 (C4), 66.3 (66.326) (C1), 66.3 (66.260) (C6), 23.9 (C2), 21.6 (C7).



1-(2-Oxo-5,6-dihydro-2*H*-pyran-3-yl)ethyl acetate (2.59). (JD 2-297). Pyridine (1.14 mL, 14.1 mmol) was added to a solution of **2.64** (1.00 g, 7.05 mmol) and 4-dimethyaminopyradine (86 mg, 0.71 mmol) in dry CH_2Cl_2 (35 mL) cooled to 0 °C. Acetyl chloride (0.752 mL, 10.6 mmol) was added dropwise *via* syringe; and the mixture immediately became flocculent. The mixture was stirred for 75 min whereupon 1 M HCl (50 mL) was added. The layers were separated and the aqueous layer was washed with CH_2Cl_2 (3 X 50 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (50 mL) and dried (Na_2SO_4). The solution was concentrated under reduced pressure and the residue was purified *via* flash chromatography eluting with EtOAc/hexanes (50-66%) to yield 1.26 g (97%) of **2.59**. ^{1}H-NMR (250 MHz) δ 6.83 (t, *J* = 4.2 Hz, 1 H), 5.61 (qd, *J* = 6.5, 1.1 Hz, 1H), 4.29 (t, *J* = 6.3, 2 H), 2.42 (q, *J* = 6.25, 1 H), 1.99 (s, 3 H), 1.33 (d, *J* = 6.5 Hz, 3 H).

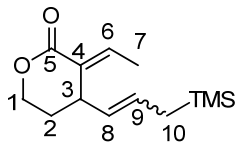
NMR assignments. ^{1}H-NMR (250 MHz) δ 6.83 (t, *J* = 4.2 Hz, 1 H, C3-H), 5.61 (qd, *J* = 6.5, 1.1 Hz, 1H, C6-H), 4.29 (t, *J* = 6.3, 2 H, C1-H), 2.42 (q, *J* = 6.25, 1 H, C2-H), 1.99 (s, 3 H, C9H), 1.33 (d, *J* = 6.5 Hz, 3 H, C7-H).



3-Ethylidene-4-vinyltetrahydropyran-2-one (2.58). (JD 3-78). CuCN (103 mg, 1.15 mmol) was dried *via* alternating evacuation/N_2 purge (two cycles), THF (50 mL) was added *via* syringe, the slurry was cooled to –78 °C, and a stock solution of vinylmagnesium bromide (7.34 mL, 1.57 M, 11.5 mmol) was added dropwise *via* syringe with stirring. The mixture was stirred for 1 h, the -78 °C bath was exchanged for a 0 °C bath for 10 min, and the dark solution was then re-cooled to –78 °C. A portion of the solution of divinyl cuprate thus made (35 mL, ~1.2 eq) was added dropwise to **2.59** (1.062 g, 5.77 mmol) in dry THF (50 mL) cooled to -78 °C. The mixture was stirred for 45 min and then poured into saturated aqueous NH_4Cl (100 mL). The resulting mixture was stirred for 30 min, whereupon EtOAc (50 mL) and enough H_2O to dissolve the formed white precipitate were added. The layers were separated, the aqueous layer was washed with EtOAc (3 X 50 mL), the combined organic layers were dried (Na_2SO_4), concentrated under reduced pressure, and the residue was purified *via* flash chromatography eluting with EtOAc/hexanes (20%) to yield 737 mg (73%) of **2.58**. ^{1}H NMR (400 MHz) δ 7.30 (qd, *J* = 7.7 & 1.3, overlaps with $CHCl_3$), 5.76 (ddd, *J* = 17.2 & 10.3 & 5.2, 1 H), 5.19 (dd, *J* = 9.6 & 1.4, 1 H), 5.00 (dt, *J* = 17.2 & 1.5, 1 H), 4.32 (td, *J* = 11.0 & 2.7, 1 H), 4.25-4.19 (m, 1 H), 3.60-3.48 (m, 1 H), 2.22-2.0 (m, 1 H), 1.84-1.73 (comp, 4 H); ^{13}C-NMR δ 166.3, 143.8, 136.7, 127.2, 117.0, 64.9, 36.5, 28.4, 14.3; MS CI+ *m/z* 153.0909 [$C_9H_{13}O_2$ (M+1) requires 153.0916] (base), 97, 154, 305.

NMR assignments. ^{1}H NMR (400 MHz) δ 7.30 (qd, overlaps with $CHCl_3$, C6-H), 5.76 (ddd, 1 H, C8-H), 5.19 (dd, 1 H, C9-H *E*), 5.00 (dt, 1 H, C9-H *Z*), 4.32 (td, 1 H, C1-H),

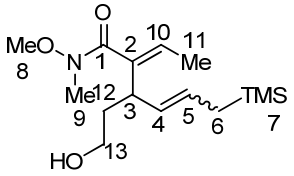
4.25-4.19 (m, 1 H, C1-H), 3.60-3.48 (m, 1 H, C3-H), 2.22-2.0 (m, 1 H, C2-H), 1.84-1.73 (comp, 4 H, C2-H &C-7H); ^{3}C-NMR δ 166.3 (C5), 143.8 (C8), 136.7 (C6), 127.2 (C4), 117.0 (C9), 64.9 (C1), 36.5 (C3), 28.4 (C2), 14.3 (C7).



3-Ethylidene-4-(3-trimethylsilanylpropenyl)tetrahydropyran-2-one (2.57). JD 2-268. Freshly distilled allyl trimethylsilane (0.223 mL, 160 mg, 1.41 mmol) was added to a solution of **2.58** (107 mg, 0.703 mmol) in degassed (sparged with Ar for >30 min) CH_2Cl_2 (3 mL) *via* syringe. The solution was heated to reflux, Grubbs's second generation catalyst (29 mg, 0.035 mmol) was added in one portion, and the golden brown solution was heated under reflux for 7 h by which time it had become dark. The reaction mixture was cooled to rt, DMSO (0.121 mL, 133 mg, 1.76 mmol) was added, and the mixture was stirred overnight. The mixture was concentrated under reduced pressure, and the residue was purified *via* flash chromatography eluting with EtOAc/hexanes (20-30%) to yield 104 mg (62%) of **2.57** and 31 mg of **2.58** (28%). ^{1}H NMR (400 MHz) δ 7.22 (qt, *J* = 7.3 & 1.2 Hz, overlaps with $CHCl_3$), 5.35 (dtd, *J* = 15.2 & 8.1 & 1.7 Hz, 1 H), 5.17 (ddt, *J* = 15.2 & 5.4 & 1.2 Hz, 1 H), 4.33 (td, *J* = 11.1 & 2.7 Hz, 1 H), 4.19 (dtd, *J* = 11.1 & 3.9 & 1.3 Hz, 1 H), 3.52-3.45 (m, 1 H), 2.12-2.02 (m, 1 H), 1.78-1.68 (comp, 4 H), 1.43 (d, *J* = 8 Hz, 2 H), -0.64 (s, 9 H). ^{13}C-NMR (63 MHz) δ 166.4, 142.7, 129.1, 128.4, 126.7, 65.0, 35.61, 29.1, 22.7, 14.1, -2.0.

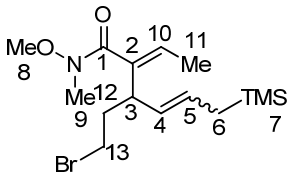
NMR assignments. ^{1}H NMR (400 MHz) δ 7.22 (qt, overlaps with $CHCl_3$, C6-H), 5.35 (dtd, 1 H, C9-H), 5.17 (ddt, 1 H, C8-H), 4.33 (td, 1 H, C1-H), 4.19 (dtd, 1 H, C1-H),

3.52-3.45 (m, 1 H, C3-H), 2.12-2.02 (m, 1 H, C2-H), 1.78-1.68 (comp, 4 H, C2-H & C7-H), 1.43 (d, 2 H, C10-H), -0.64 (s, 9 H, TMS). ^{13}C-NMR (63 MHz) δ 166.4 (C5), 142.7 (C6), 129.1 (C8 or C9), 128.4 (C4), 126.7 (C8 or C9), 65.0 (C1), 35.61 (C3), 29.1 (C2), 22.7 (C10), 14.1 (C7), -2.0 (TMS).



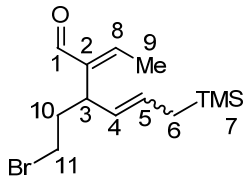
2-Ethylidene-3-(2-hydroxy-ethyl)-6-trimethylsilanylhex-4-enoic acid methoxy-methylamide (2.73). JD 2-279. *t*-Butylmagnesium bromide (0.80 mL, 1.4 mmol) was added slowly dropwise to a vigorously stirred mixture of *N,O*-dimethylhydroxylamine hydrochloride (71 mg, 0.73 mmol) and **2.57** (108 mg, 0.453 mmol) slurried in dry THF (5 mL) at –20 °C. The reaction was stirred for 30 min at -20 °C, slowly warmed to rt, and 0.5 M aqueous H_2SO_4 (1 mL) and EtOAc (1 mL) were added. The layers were separated, and the organic layer was washed with EtOAc (3 X 1 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (5 mL), dried (Na_2SO_4), concentrated under reduced pressure, and the residue was purified *via* flash chromatography eluting with EtOAc/hexanes (50-75%) to yield 120 mg (78%) of **2.73** and 10 mg of **2.57** (9%). ^{1}H-NMR (250 MHz) δ 5.76 (q, 1 H), 5.48 (dt, *J* = 15.2, 7.5 Hz, 1 H), 5.37 (dd, *J* = 15.2, 7.9 Hz, 1 H), 3.70-3.57 (comp, 5 H), 3.32 (q, *J* = 7.9 Hz, 1 H), 3.21 (s, 3 H), 3.01 (br s, 1 H), 1.88-1.74 (comp, 5 H), 1.40 (d, *J* = 7.5, 2 H), -0.04 (s, 9 H); ^{13}C-NMR (250 MHz) 172.1, 137.1, 129.1, 128.1, 127.5, 80.8, 60.5, 40.1, 37.2, 34.7, 22.7, 13.7, -2.0; MS CI+ m/z 300.199374 [$C_{15}H_{30}NO_3Si$ (M+1) requires 300.199498] 239, 270, 284, 300 (base).

NMR assignments. ^{1}H-NMR (250 MHz) δ 5.76 (q, 1 H, C10-H), 5.48 (dt, *J* = 15.2, 7.5 Hz, 1 H, C5-H), 5.37 (dd, *J* = 15.2, 7.9 Hz, 1 H, C4-H), 3.70-3.57 (comp, 5 H, C8-H, C13-H), 3.32 (q, *J* = 7.9 Hz, 1 H, C3-H), 3.21 (s, 3 H, C9-H), 3.01 (br s, 1 H, -OH), 1.88-1.74 (comp, 5 H, C11-H, C12-H), 1.40 (d, *J* = 7.5, 2 H, C6-H), -0.04 (s, 9 H, TMS); ^{13}C-NMR (250 MHz) 172.1 (C1), 137.1 (C2), 129.1 (C4, 5, or 10), 128.1 (C4, 5, or 10), 127.5 (C4, 5, or 10), 80.8 (C8), 60.5 (C13), 40.1 (C9), 37.2 (C11), 34.7 (C3), 22.7 (C12), 13.7 (C6), -2.0 (C7).



3-(2-Bromoethyl)-2-ethylidene-6-trimethylsilanylhex-4-enoic acid methoxymethylamide. JD 2-274. Triphenyl phosphine (142 mg, 0.551 mmol) was added in one potion to a stirred solution of **2.73** (81 mg, 0.27 mmol), carbon tetrabromide (170 mg, 0.541 mmol), and triethylamine (0.113 mL, 0.811 mmol) in dry CH_2Cl_2 (2.7 mL). The mixture was stirred for 10 min whereupon H_2O (5 mL) was added, the layers were separated, and the aqueous layer was washed with CH_2Cl_2 (4 X 5 mL). The combined organic layers were dried (Na_2SO_4), concentrated under reduced pressure, and the residue was purified *via* flash chromatography eluting with EtOAc/hexanes (20%) to yield 83 mg (85%) of the bromide. ^{1}H-NMR (250 MHz) δ 5.69 (q, *J* = 7.0 Hz, 1 H), 5.53 (dt, *J* = 15.2, 7.8 Hz, 1 H), 5.18 (dd, *J* = 15.2, 9.0 Hz, 1 H), 3.86 (s, 3 H), 3.65-3.30 (comp, 3 H), 3.15 (s, 3 H), 2.18-1.98 (m, 2 H), 1.75 (d, *J* = 7.0 Hz, 3 H), 1.40 (d, *J* = 7.8, 2 H), -0.05 (s, 9 H); ^{13}C-NMR (250 MHz) δ 170.9, 137.4, 129.3, 127.3, 127.1, 60.7, 41.1, 36.6, 34.4, 32.8, 22.8, 13.2, -2.0.

NMR assignments. ^{1}H-NMR (250 MHz) δ 5.69 (q, *J* = 7.0 Hz, 1 H, C10-H), 5.53 (dt, *J* = 15.2, 7.8 Hz, 1 H, C5-H), 5.18 (dd, *J* = 15.2, 9.0 Hz, 1 H, C4-H), 3.86 (s, 3 H, C8-H), 3.65-3.30 (comp, 3 H, C13-H, C3-H), 3.15 (s, 3 H, C9-H), 2.18-1.98 (m, 2 H, C12-H), 1.75 (d, *J* = 7.0 Hz, 3 H, C11-H), 1.40 (d, *J* = 7.8, 2 H, C6-H), -0.05 (s, 9 H, C7-H); ^{13}C-NMR (250 MHz) δ 170.9 (C1), 137.4, 129.3 (C4, 5, or 10), 127.3 (C4, 5, or 10), 127.1 (C4, 5, or 10), 60.7 (C8), 41.1 (C9), 36.6 (C11), 34.4 (C3), 32.8 (C13), 22.8 (C12), 13.2 (C6), -2.0 (C7).

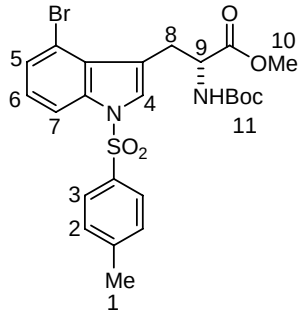


3-(2-Bromoethyl)-2-ethylidene-6-trimethylsilanylhex-4-enal (2.56). JD 2-282. Diisobutylaluminum hydride (0.44 mL, 1 M in hexanes, 0.44 mmol) was added dropwise to a solution of the bromide from the previous step (97 mg, 0.27 mmol) in toluene (2.7 mL) at –78 °C. The mixture was stirred for 20 min, whereupon MeOH (0.22 mL, 5.4 mmol) was added. The mixture was stirred for 5 min, warmed to rt, and saturated aqueous Rochelle's salt (5 mL) was added. The heterogeneous mixture was stirred vigorously for 30 min, the layers were separated, and the aqueous layer was washed with EtOAc (2 X 5 mL). The combined organic layers were dried (Na_2SO_4), concentrated under reduced pressure, and the residue was purified *via* flash chromatography eluting with EtOAc/hexanes (20%) to yield 90 mg (quant.) of **2.56**. ^{1}H-NMR (500 MHz) δ 9.30 (d, *J* = 1.6 Hz, 1 H), 6.56 (q, *J* = 7.1 Hz, 1 H), 5.50-5.40 (comp, 2 H), 3.49 (qd, *J* = 7.4, 1.6 Hz, 1 H), 3.35 (ddd, *J* = 9.5, 7.1, 5.5 Hz, 1 H), 3.28 (ddd, *J* = 9.6, 6.6, 5.6 Hz, 1 H), 2.27-2.2 (m, 1 H), 2.14-2.07 (m, 1 H), 2.03 (d, *J* = 7.1 Hz, 3 H), 1.42-1.35 (m, 2 H), -0.06

(s, 9 H); ^{13}C-NMR (500 MHz) δ 194.8, 151.2, 145.4, 128.7, 127.2, 39.1, 35.1, 32.7, 22.7, 15.0, –2.0; MS CI+ m/z 303.077213 [$C_{13}H_{24}OSiBr$ (M+1) requires 303.07798] 223, 303 (base), 305.

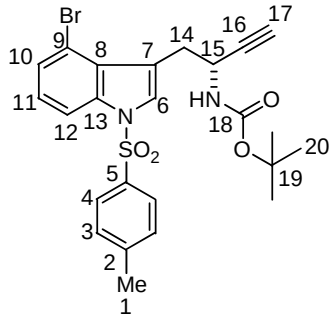
NMR assignments. ^{1}H-NMR (500 MHz) δ 9.30 (d, *J* = 1.6 Hz, 1 H, C1-H), 6.56 (q, *J* = 7.1 Hz, 1 H, C8-H), 5.50-5.40 (comp, 2 H, C4-H, C5-H), 3.49 (qd, *J* = 7.4, 1.6 Hz, 1 H, C3-H), 3.35 (ddd, *J* = 9.5, 7.1, 5.5 Hz, 1 H, C11a-H), 3.28 (ddd, *J* = 9.6, 6.6, 5.6 Hz, 1 H, C11b-H), 2.27-2.2 (m, 1 H, C10a-H), 2.14-2.07 (m, 1 H, C10b-H), 2.03 (d, *J* = 7.1 Hz, 3 H, C9-H), 1.42-1.35 (m, 2 H, C6-H), -0.06 (s, 9 H, C7-H); ^{13}C-NMR (500 MHz) δ 194.8 (C1), 151.2 (C8), 145.4 (C2), 128.7 (C4 or C5), 127.2 (C4 or C5), 39.1 (C3), 35.1 (C10), 32.7 (C11), 22.7 (C6), 15.0 (C9), –2.0 (C7).

5.3 METHYL LYSERGATE EXPERIMENTAL PROCEDURES



4-Bromo-1-tosyl-*N*-(*tert*-butoxycarbonyl)tryptophan methyl ester (*R*-4.37). JD 3-220. In a round bottom flask fitted with a rubber septum 4-bromo-1-tosyl-*N*-(*tert*-butoxycarbonyl)dehydrotryptophan methyl ester (**4.8**, 3.00 g, 5.46 mmol)[134] was dried *via* alternating evacuation/N_2 purge. Dry MeOH (150 mL) which had been sparged with a stream of Ar while being sonicated was added *via* syringe, and the mixture was heated to dissolve **4.8**. The solution was cooled, and [Rh(cod)*S,S*-DIPAMP]BF_4 (120 mg, 0.158 mmol), which was synthesized by the method of Knowles,[148] in dry MeOH was added *via* syringe. The flask was placed in a high pressure stainless steel bomb, the septum was removed, the bomb was evacuated and backfilled with Ar. The bomb was then evacuated again and backfilled with H_2 (5 cycles, 100 psi). The reaction mixture was then stirred 5 d. The reaction progress was checked periodically *via* no D ^{1}H-NMR; TLC is not viable due to the similar R_f values of the starting material and the product.[150] The mixture was concentrated under reduced pressure, the residue was dissolved in EtOAc, and the mixture was filtered through a pad of silica washing with EtOAc. The combined filtrate and washings were concentrated under reduced pressure, and the residue was purified *via*

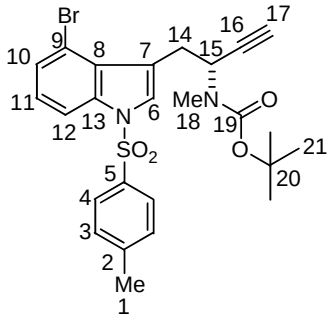
flash chromatography eluting with EtOAc/hexanes (30%) to yield 2.90 g (96%) of *R*-**4.37**. ^{1}H-NMR spectral characteristics matched those for *S*- **4.37**.[134] HPLC: Chiracel-OD column eluting with 98:2 hexanes/isopropanol at 1 mL/min, t_R = 30.04 min (***R***), t_R = 44.89 min (***S***), *er* = 27:1.



tert*-Butyl (*R*)-1-(4-bromo-1-tosyl-1*H*-indol-3-yl)but-3-yn-2-ylcarbamate (4.40). JD 4-250.** A solution of *R*-**4.37** (1 g, 1.82 mmol) in dry toluene (20 mL) was cooled to -78 °C, and DIBAL (5.44 mL, 1 M in hexanes, 5.44 mmol) was added dropwise *via* syringe with vigorous stirring. The mixture was stirred for 1 h, whereupon the excess DIBAL was destroyed *via* dropwise addition of dry MeOH (20 mL). The cooling bath was removed and the mixture was warmed to rt. Ohira's reagent (**4.14**, 1.05 g, 5.44 mmol) and K_2CO_3 (752 mg, 5.55 mmol) were added sequentially in one portion each. The mixture was stirred overnight whereupon saturated aqueous Rochelle's salt and EtOAc were added. The mixture was stirred vigorously for 15 min, and the layers were separated. The aqueous layer was washed with EtOAc, the combined organic layers were dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified *via* flash chromatography eluting with EtOAc/hexanes (30%) to yield 616 mg (70%) of **4.40**. HPLC (JD 4-202): Chiracel-OD column eluting with 98:2 hexanes/isopropanol at 1 mL/min, t_R = 18.74 min (R***), t_R = 28.38 min (***S***), *er* = 8.5:1. ^{1}H-NMR (250 MHz) δ 7.91

(d, *J* = 8.2 Hz, 1 H), 7.71 (d, *J* = 8.2 Hz, 2 H), 7.54 (s, 1 H), 7.35 (d, *J* = 8.2 Hz, 1 H), 7.20 (d, *J* = 8.2 Hz, 2 H), 7.09 (t, *J* = 8.2 Hz, 1 H), 4.80 (comp, 2 H), 3.37 (m, 2 H), 2.32 (s, 3 H), 2.27 (s, 1 H), 1.34 (br s, 9 H); ^{13}C-NMR (63 MHz) δ 154.5, 145.2, 136.2, 134.8, 129.9, 128.7, 127.9, 126.9, 126.6, 125.4, 117.8, 114.4, 112.8, 83.0, 80.1, 71.8, 43.5, 32.5, 28.2, 21.6; MS CI+ *m/z* 516.071374 [$C_{24}H_{25}BrN_2O_4S$ (M+) requires 516.071840] 417, 419, 461 (base), 463.

NMR Assignments. ^{1}H-NMR (250 MHz) δ 7.91 (d, *J* = 8.2 Hz, 1 H, C10-H or C12-H), 7.71 (d, *J* = 8.2 Hz, 2H, C4-H), 7.54 (s, 1 H, C6-H), 7.35 (d, *J* = 8.2 Hz, 1 H, C10-H or C12-H), 7.20 (d, *J* = 8.2 Hz, 2 H, C3-H), 7.09 (t, *J* = 8.2 Hz, 1 H, C11-H), 4.80 (comp, 2 H, C15-H, *N*H), 3.37 (m, 2 H, C14-H), 2.32 (s, 3 H, C1-H), 2.27 (s, 1 H, C17-H), 1.34 (br s, 9 H, C20-H); ^{13}C-NMR (63 MHz) δ 154.5 (C18), 145.2 C(13), 136.2 (C2), 134.8 (C8), 129.9 (C5), 128.7 (C3), 127.9 (C4), 126.9 (C10), 126.6 (C11), 125.4 (C6), 117.8 (C12), 114.4 (C9), 112.8 (C7), 83.0 (C16), 80.1 (C19), 71.8 (C17), 43.5 (C15), 32.5 (C14), 28.2 (C20), 21.6 (C1).

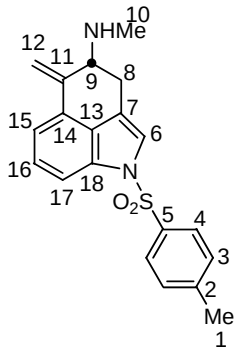


(*R*)-*tert*-Butyl 1-(4-bromo-1-tosyl-1*H*-indol-3-yl)but-3-yn-2-yl(methyl)carbamate (*R*-4.12). (JD 4-253). A stock solution of NaHMDS (1.2 mL, 1.17 M, 1.4 mmol) was added dropwise to a solution of **4.40** (616 mg, 1.19 mmol) in dry THF (2 mL) cooled to -78 °C. The mixture was stirred for 1h 15 min and then freshly distilled dimethyl sulfate (0.17

mL, 1.8 mmol) was added dropwise. The mixture was stirred 10 min and the cooling bath was removed. The reaction vessel warmed to rt over 10-20 min, and after 20 additional min saturated aqueous NH_4Cl was added. The layers were separated. The aqueous layer was washed with EtOAc, the combined organic layers were dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified *via* flash chromatography eluting with EtOAc/hexanes (10-30%) to yield 601 mg (95%) of *R*-**4.12**. ^{1}H-NMR spectral characteristics matched those for racemic **4.12**.[194] ^{1}H NMR (500 MHz, DMSO-d_6, 90 °C) δ 7.92 (dd, *J* = 8.1, 0.7 Hz, 1 H), 7.77 (dt, *J* = 8.4, 1.2 Hz, 2 H), 7.68 (s, 1 H), 7.45 (dd, *J* = 8.1, 0.7 Hz, 1 H), 7.37 (dd, *J* = 8.4, 1.2 Hz, 2 H), 7.22 (t, *J* = 8.1 Hz, 1 H), 5.34 (ddd, *J* = 9.9, 5.2, 2.4 Hz, 1 H), 3.37 (ddd, *J* = 14.5, 5.2, 1.0 Hz, 1 H), 3.20 (d, *J* = 2.4 Hz, 1 H), 3.17 (dd, *J* = 14.5, 9.9 Hz, 1 H), 2.84 (s, 3 H), 2.33 (s, 3 H), 1.04 (s, 9 H); ^{13}C NMR (125 MHz, DMSO-d_6, 90 °C) δ 153.4, 145.0, 135.5, 133.8, 129.7, 127.6, 127.2, 126.7, 126.1, 125.2, 116.9, 113.2, 112.2, 81.0, 78.6, 74.7, 47.7, 29.1, 28.3, 27.0, 20.4; IR (CHCl3) 3306, 3014, 2980, 2632, 1915, 1685, 1598, 1556, 1369 cm^{-1}; MS CI+ *m/z* 530.0873 [$C_{25}H_{27}N_2O_4SBr$ (M+1) requires 530.0875], 517, 505, 475, 431 (base), 402, 364, 321, 275, 187.

NMR Assignments. ^{1}H NMR (500 MHz, DMSO-d_6, 90 °C) δ 7.92 (dd, *J* = 8.1, 0.7 Hz, 1 H, C12-H), 7.77 (dt, *J* = 8.4, 1.2 Hz, 1 H, C4-H), 7.68 (s, 1 H, C6-H), 7.45 (dd, *J* = 8.1, 0.7 Hz, 1H, C10-H), 7.37 (dd, *J* = 8.4, 1.2 Hz, 2 H, C3-H), 7.22 (t, *J* = 8.1 Hz, 1 H, C11-H), 5.34 (ddd, *J* = 9.9, 5.2, 2.4 Hz, 1 H, C15-H), 3.37 (ddd, *J* = 14.5, 5.2, 1.0 Hz, 1 H, C14-H), 3.20 (d, *J* = 2.4 Hz, 1 H, C17-H), 3.17 (dd, *J* = 14.5, 9.9 Hz, 1 H, C14-H), 2.84 (s, 3 H, C18-H), 2.33 (s, 3 H, C1-H), 1.04 (s, 9 H, C21-H); ^{13}C NMR (125 MHz, DMSO-d_6, 90 °C) δ 153.4 (C19), 145.0 (C13), 135.5 (C2), 133.8 (C8), 129.7 (C5), 127.6 (C3), 127.2 (C4), 126.7 (C10), 126.1 (C11), 125.2 (C6), 116.9 (C12), 113.2 (C9), 112.2 (C7),

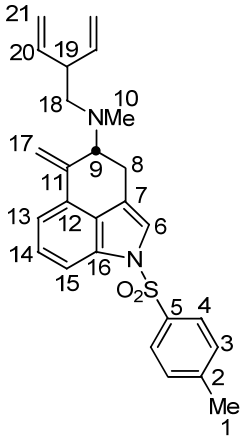
81.0 (C16), 78.6 (C20), 74.7 (C17), 47.7 (C15), 29.1 (C14), 28.3 (C18), 27.0 (C21), 20.4 (C1).



(*R*)-*N*-Methyl-6-methylene-2-tosyl-2,6,7,8-tetrahydrobenzo[*cd*]indol-7-amine (4.46). JD 5-118, 5-119. Dry, degassed (sparged with Ar under sonication for >30 min) CH_3CN (94 mL) was added *via* syringe to a mixture of the alkyne *R*-**4.12** (500 mg, 0.941 mmol), $Pd(PPh_3)_4$ (163 mg, 0.141 mmol), and Bu_4NCl (392 mg, 1.41 mmol) under Ar, and 1,2,2,6,6-pentamethylpiperidine (510 μL, 2.82 mmol) was then added *via* syringe. The mixture was heated to 80 °C, and HCO_2H (71 μL, 1.9 mmol) was added *via* syringe. The reaction was stirred for 2 h at 80 °C, and then cooled to rt. The solvent was removed under reduced pressure, and the residue was partially purified *via* flash chromatography eluting with EtOAc/hexanes (15-50%). The solvent was concentrated under reduced pressure, the residue was dissolved in MeOH (8.5 mL), p-TsOH·H_2O (328 mg, 1.73 mmol) was added in one portion, and the reaction was warmed to 35 °C. The mixture was stirred overnight, cooled to rt, and saturated aqueous $NaHCO_3$ (25 mL) and CH_2Cl_2 (25 mL) were added. The layers were separated, the aqueous layer was washed with CH_2Cl_2 (3 X 25 mL), the combined organic layers were dried (Na_2SO_4), the solvent was removed under reduced pressure, and the residue was purified *via* flash chromatography

eluting with EtOH/CH_2Cl_2 (5-10%) to yield 148 mg (44%) of **4.46**. ^{1}H NMR (300 MHz) δ 7.81-7.75 (comp, 3 H), 7.37-7.20 (comp, 5 H), 5.70 (s, 1 H), 5.22 (s, 1 H), 3.57 (app t, *J* = 4.0 Hz, 1 H), 3.09-2.95 (comp, 2 H), 2.34 (s, 3 H), 2.30 (s, 3 H); ^{13}C NMR (75 MHz) δ 145.0, 141.9, 136.1, 134.0, 130.2, 129.0 (2), 127.2, 126.3, 121.5, 118.1, 117.5, 113.4, 112.3, 61.7, 34.2, 29.2, 21.9; IR (neat) cm-1 3334, 2925, 1360, 1175; MS (FAB) m/z 353.1324 [$C_{20}H_{21}N_2O_2S$ (M+1) requires 353.7324], 353(base).

NMR Assignments. ^{1}H NMR (300 MHz) δ 7.81-7.75 (comp, 3 H, C16-H & C10-H), 7.37-7.20 (comp, 5 H, C17-H & C9-H & C8-H & C2-H), 5.70 (s, 1 H, C13-H), 5.22 (s, 1 H, C13-H), 3.57 (app t, *J* = 4.0 Hz, 1 H, C5-H), 3.09-2.95 (comp, 2 H, C4-H), 2.34 (s, 3 H, C14-H), 2.30 (s, 3 H, C19-H); ^{13}C NMR (75 MHz) δ 145.0 (C11), 141.9 (C2), 136.1 (C18), 134.0 (C5), 130.2 (3), 129.0 (C4, C14), 127.2 (C13), 126.3 (C16), 121.5 (C6), 118.1 (C12 or C17), 117.5 (C12 or C17), 113.4 (C15), 112.3 (C7), 61.7 (C9), 34.2 (C10), 29.2 (C8), 21.9 (C1)

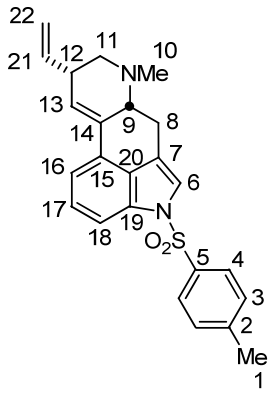


(*R*)-2,6,7,8-Tetrahydro-*N*-methyl-6-methylene-2-tosyl-*N*-(2-vinylbut-3-enyl)benzo[*cd*]indol-7-amine (4.27). JD 5-52. Paraformaldehyde (6 mg, 0.2 mmol) was added to a solution of **4.46** (25 mg, 0.071 mmol) in MeOH (1 mL) in one portion,

and the mixture was stirred overnight. The solvent was remove under reduced pressure, the residue was dissolved in THF (1 mL). Bispentadienyl zinc was made by adding a solution of *n*-BuLi (284 μL, 2.5 M, 0.709 mmol) to a solution of 1,4-pentadiene (73 μL, 0.71 mmol) in THF (0.4 mL) cooled to 0 °C. After 15 min a stock solution of $ZnBr_2$ (355 μL, 1 M, 0.355 mmol) was added, and the solution was warmed to rt and stirred for 15 min. The solution of pentadienyl zinc thus made was added to the solution of the *N,O*-acetal **4.68** cooled to -78 °C. The mixture was stirred and warmed to rt overnight whereupon H_2O (2 mL)) was added, and saturated aqueous NH_4Cl was added until all formed solids dissolved. CH_2Cl_2 (5 mL) was added, the layers were separated, and the aqueous layer was washed with CH_2Cl_2 (3 X 5 mL). The combined organic layers were dried (Na_2SO_4), concentrated under reduced pressure, and the residue was purified *via* flash chromatography eluting with EtOAc/hexanes (10-100%) then EtOH/EtOAc (0-100%) to yield 18 mg (61%) of **4.27**, 9 mg (30%) of **4.69**, and a trace of **4.46**. ^{1}H-NMR (400 MHz) δ 7.76-7.70 (comp, 3 H), 7.32 (d, *J* = 7.6 Hz, 1 H), 7.26 (t, *J* = 7.5 Hz, 1 H), 7.19-7.14 (comp, 3 H), 5.75 (s, 1 H), 5.69-5.54 (comp, 2 H), 5.40 (s, 1 H), 4.96-4.89 (comp, 4 H), 3.57 (t, *J* = 6.2 Hz, 1 H), 2.96-2.91 (comp, 2 H), 2.85 (m, 1 H), 2.50 (d, *J* = 7.6 Hz, 2 H), 2.31 (s, 3 H), 2.21 (s, 3 H); ^{13}C-NMR (100 MHz) 144.6, 141.0, 139.5, 135.5, 133.6, 130.4, 129.8, 129.1, 126.7, 125.7, 119.7, 119.1, 117.0, 114.9, 114.8, 112.6, 112.3, 64.4, 59.1, 46.4, 38.2, 23.1, 21.5; MS CI+ *m/z* 433.195247 [$C_{26}H_{29}N_2O_2S$ (M+1) requires 433.194975] 365, 433 (base).

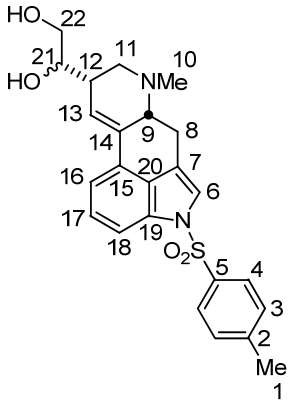
NMR Assignments. ^{1}H-NMR (400 MHz) δ 7.76-7.70 (comp, 3 H, C4-H, C15-H), 7.32 (d, *J* = 7.6 Hz, 1 H, C13-H), 7.26 (t, *J* = 7.5 Hz, 1 H, C14-H), 7.19-7.14 (comp, 3 H, C3-H, C6-H), 5.75 (s, 1 H, C17a-H), 5.69-5.54 (comp, 2 H, C20-H), 5.40 (s, 1 H, C17b-H), 4.96-4.89 (comp, 4 H, C21-H), 3.57 (t, *J* = 6.2 Hz, 1 H, C9-H), 2.96-2.91 (comp, 2 H,

C8-H), 2.85 (m, 1 H, C19-H), 2.50 (d, *J* = 7.6 Hz, 2 H, C18-H), 2.31 (s, 3 H, C1-H), 2.21 (s, 3 H, C10-H).



(6a*R*,9*S*)-7-Methyl-4-tosyl-9-vinyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline (4.89). JD 5-69. A solution of (*S*)-Schrock-Hoveyda catalyst (*S*-**4.23**, 22 mg, 0.029 mmol) in dry benzene (0.75 mL) was added *via* syringe to a solution of **4.27** (25 mg, 0.058 mmol) in dry benzene (5 mL) in a CEM 8 mL reactor equipped with a stir bar and septum. The vessel was irradiated with microwaves (50 W) while being externally cooled with compressed air for 30 min. The crude reaction mixture was concentrated under reduced pressure and the residue was purified *via* flash chromatography eluting with EtOAc/hexanes (20-75%) to yield 13 mg (54%) of **4.89**. ^{1}H NMR (500 MHz, C_6D_6) δ 8.07 (dd, *J* = 7.8, 1 Hz, 1 H), 7.72-7.70 (comp, 2 H), 7.13-7.10 (comp, 3 H), 6.51-6.49 (m, 2 H), 6.20 (app d, *J* = 3.7 Hz, 1 H), 6.06 (ddd, *J* = 17.4, 10.0, 7.6 Hz, 1 H), 5.05-4.99 (comp, 2 H), 2.99 (dd, *J* = 15.1, 5.3 Hz, 1 H), 2.73-2.63 (comp, 2 H), 2.53 (ddd, *J* = 11.3, 2.6, 0.8 Hz, 1 H), 2.40 (dd, *J* = 11.3, 4.0 Hz, 1 H), 2.34 (ddd, *J* = 15.1, 11.6, 2.2 Hz, 1 H), 2.12 (s, 3 H), 1.63 (s, 3 H); MS CI+ *m/z* 405.1637 [$C_{24}H_{25}N_2O2S$ (M+1) requires 405.1637] (base), 121, 251, 300.

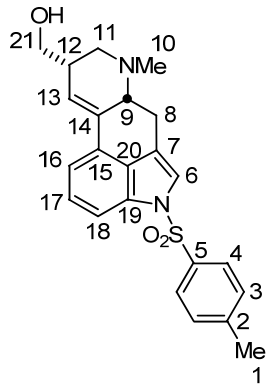
NMR assignments. ^{1}H NMR (500 MHz, C_6D_6) δ 8.07 (dd, *J* = 7.8, 1 Hz, 1 H, C18-H), 7.72-7.70 (comp, 2 H, C4-H), 7.13-7.10 (comp, 3 H, C6-H, C16-H, C17-H), 6.51-6.49 (m, 2 H, C3-H), 6.20 (app d, *J* = 3.7 Hz, 1 H, C13-H), 6.06 (ddd, *J* = 17.4, 10.0, 7.6 Hz, 1 H, C21-H), 5.05-4.99 (comp, 2 H, C22-H), 2.99 (dd, *J* = 15.1, 5.3 Hz, 1 H, C8α-H), 2.73-2.63 (comp, 2 H, C9-H, C12-H), 2.53 (ddd, *J* = 11.3, 2.6, 0.8 Hz, 1 H, C11α-H), 2.40 (dd, *J* = 11.3, 4.0 Hz, 1 H, C11β-H), 2.34 (ddd, *J* = 15.1, 11.6, 2.2 Hz, 1 H, C8β-H), 2.12 (s, 3 H, C10 H), 1.63 (s, 3 H, C1-H)



1-((6a*R*,9*S*)-7-Methyl-4-tosyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinolin-9-yl)ethane-1,2-diol (4.90). JD 4-135. This representative example was performed on racemic **4.89**. A solution of osmium tetroxide (6 mg, 0.03 mmol) in THF (0.1 mL) was added to a stirred solution of **4.89** and *N*,*N*,*N*',*N*'-tetramethylethylenediamine (TMEDA, 5 μL, 0.03 mmol) in THF (0.4 mL) cooled to -78 °C. The orange/brown mixture was stirred and allowed to warm to room temperature overnight in the dark, whereupon saturated aqueous sodium bisulfite was added. The mixture was heated to 70 °C for 3.5 h, cooled to room temperature, diluted with CH_2Cl_2 (2 mL), and filtered through a cotton pad. The layers were separated, and the aqueous layer was washed with CH_2Cl_2 (5 X 2

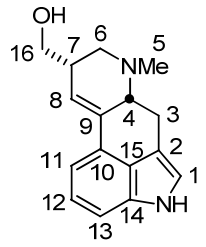
mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure, and the residue was purified *via* flash chromatography eluting with EtOH/EtOAc (20-100%) to yield 8 mg (72%) **4.90** as a 6.5:1 ratio of diastereomers. ^{1}H NMR major diastereomer (500 MHz, C_6D_6) δ 8.07 (dd, *J* = 8.0, 0.6 Hz, 1 H), 7.74-7.70 (m, 2 H), 7.12-7.08 (comp, 3H), 6.54-6.50 (m, 2 H), 6.27 (d, *J* = 5.6 Hz, 1 H), 3.77 (td, *J* = 6.3, 3.0 Hz, 1 H), 3.50 (d, *J* = 6.3 Hz, 2 H), 2.84 (dd, *J* = 15.1, 5.2 Hz, 1 H), 2.68 (d, *J* = 11.6 Hz, 1 H), 2.46 (ddt, *J* = 11.6, 5.2, 2.4 Hz, 1 H), 2.20 (ddd, *J* = 15.1, 11.6, 2.1 Hz, 1 H), 2.17-2.13 (m, 1 H), 2.11 (dd, *J* = 11.6, 4.3, 1 H), 1.89 (s, 3 H), 1.64 (s, 3 H); ^{13}C-NMR (125 MHz) 144.4, 136.5, 135.1, 134.2, 129.8, 129.6, 129.0, 128.5, 126.9, 126.2, 123.2, 120.4, 117.7, 116.9, 112.9, 74.5, 65.1, 61.9, 54.3, 42.8, 38.9, 27.1, 21.0

NMR assignments. ^{1}H NMR (500 MHz, C_6D_6) δ 8.07 (dd, *J* = 8.0, 0.6 Hz, 1 H, C18-H), 7.74-7.70 (m, 2 H, C4-H), 7.12-7.08 (comp, 3H, C6-H, C16-H, C17-H), 6.54-6.50 (m, 2 H, C3-H), 6.27 (d, *J* = 5.6 Hz, 1 H, C13-H), 3.77 (td, *J* = 6.3, 3.0 Hz, 1 H, C21-H), 3.50 (d, *J* = 6.3 Hz, 2 H, C22-H), 2.84 (dd, *J* = 15.1, 5.2 Hz, 1 H, C8-H), 2.68 (d, *J* = 11.6 Hz, 1 H, C11-H), 2.46 (ddt, *J* = 11.6, 5.2, 2.4 Hz, 1 H, C9-H), 2.20 (ddd, *J* = 15.1, 11.6, 2.1 Hz, 1 H, C8-H), 2.17-2.13 (m, 1 H, C12-H), 2.11 (dd, *J* = 11.6, 4.3, 1 H, C11-H), 1.89 (s, 3 H, C10-H), 1.64 (s, 3 H, C1-H); ^{13}C-NMR partial assignment (125 MHz) 144.4 (C5), 136.5 (C2), 135.1, 134.2 (C19), 129.8 (C3), 129.6, 129.0, 128.5, 126.9 (C4), 126.2 (C16 or C17), 123.2 (C13), 120.4 (C20), 117.7 (C6), 116.9, 112.9 (C18), 74.5 (C21), 65.1 (C22), 61.9 (C9), 54.3 (C11), 42.8 (C10), 38.9 (C12), 27.1 (C8), 21.0 (C1).



((6a*R*,9*S*)-7-Methyl-4-tosyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinolin-9-yl)methanol (*N*-tosyl isolysergol, 4.123). JD 6-232. To two stirred solutions of **4.90** (4 mg, 0.009 mmol each) in MeOH (0.2 mL each) was added H_5IO_6 (6 mg, 0.03 mmol each). The mixtures were stirred for 45 min, one was cooled to 0 °C, one was cooled to -20 °C, TFA (0.1 mL each) was added dropwise, and $NaCNBH_3$ (57 mg, 0.91 mmol each) was added portionwise. The reactions momentarily darkened, then lightened, and gas was evolved while the reaction mixtures were allowed to stir and warm to rt. The reaction mixtures, were made basic (pH > 10) with aqueous NaOH (3 M, ca 2 mL each), CH_2Cl_2 (2 mL each) was added, H_2O (2 mL each) was added, the layers were separated, and the aqueous layer was washed with CH_2Cl_2 (4 X 2 mL each). The combined organic layers were dried (Na_2SO_4), concentrated under reduced pressure, and the residue from each reaction was analyzed *via* ^{1}H-NMR. The samples were very similar, so they were combined and purified *via* flash chromatography eluting with MeOH/$CHCl_3$ (5-10%) to yield 4 mg (54%) of **4.123**. ^{1}H NMR (500 MHz, CD_3OD) δ 7.74 (d, *J* = 4.4 Hz, 1 H), 7.69 (d, *J* = 8.5 Hz, 2 H), 7.27 (comp, 2 H), 7.21-7.14 (comp, 3 H), 6.43 (d, *J* = 6.07 Hz, 1 H), 3.97 (dd, *J* = 10.3, 3.0, 1 H), 3.77 (dt, *J* = 10.3, 2.4 Hz, 1 H), 3.42 (dd, *J* = 15.2, 5.6 Hz, 1 H), 3.03-2.96 (comp, 2 H), 2.79 (ddd, *J* = 11.3, 3.7, 2.1 Hz, 1 H), 2.53-2.45 (comp, 4 H), 2.41 (br s, 1 H), 2.31 (s, 3 H); ^{13}C-NMR (125 MHz) δ 144.7, 135.4, 135.3, 133.6,

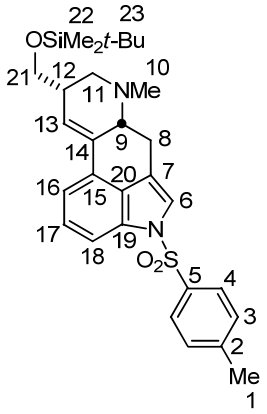
129.8, 129.1, 128.6, 126.6, 125.9, 123.2, 120.0, 117.7, 116.5, 112.5, 66.6, 62.1, 58.1, 43.5, 36.5, 27.2, 21.5; IR (PhH) 3378, 2993, 2852, 1724, 1666, 1597 cm^{-1}; MS CI+ *m/z* 409.1583 [$C_{23}H_{25}N_2O_3S$ (M+1) requires 409.1586] (base), 255, 438.



((6a*R*,9*S*)-7-Methyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinolin-9-yl)methanol (isolysergol, 4.122). JD 6-238. Magnesium turnings (ca 10 mg) were added to a vigorously stirred solution of **4.123** (4 mg, 0.01) in MeOH (0.5 mL). The reaction was stirred 5 h, filtered through a pad of celite, and the filtrate washed with $CHCl_3$. The mixture was concentrated and the residue was filtered through a pad of silica washing with MeOH/$CHCl_3$ (50%). The mixture was concentrated under reduced pressure and the residue was purified *via* flash chromatography eluting with MeOH/$CHCl_3$ (10-30%) to yield 2 mg of **4.122** (72%). ^{1}H NMR (500 MHz, CD_3OD/$CDCl_3$, 1:1) δ 7.17 (dd, *J* = 5.1, 3.7 Hz, 1 H), 7.09-7.06 (comp, 2 H), 6.89 (d, *J* = 1.6 Hz, 1 H), 6.40 (app d, *J* = 4.7, 1 H), 3.82 (dd, *J* = 10.3, 4.2 Hz, 1 H), 3.71 (ddd, *J* = 10.3, 5.5, 0.7 Hz, 1 H), 3.48 (dd, *J* = 14.4, 5.5 Hz, 1 H), 3.17 (ddt, *J* = 11.5, 5.5, 2.2 Hz, 1 H), 2.98 (dd, *J* = 11.4, 1.8 Hz, 1 H), 2.77 (dd, *J* = 11.4, 3.8 Hz, 1 H), 2.63 (ddd, *J* = 14.4, 11.5, 1.6 Hz, 1 H), 2.53 (s, 3 H), 2.5-2.45 (m, 1 H); ^{13}C-NMR (125 MHz) δ 137.5, 134.8, 128.7, 126.8, 123.3, 121.2, 119.3, 111.9, 110.3, 110.2, 65.9, 63.8, 56.4, 43.7, 37.6, 27.8.

NMR assignments. ^{1}H NMR (500 MHz) δ 7.17 (dd, *J* = 5.1, 3.7 Hz, 1 H, C13-H), 7.09-7.06 (comp, 2 H, C11-H, C12-H), 6.89 (d, *J* = 1.6 Hz, 1 H, C1-H), 6.40 (app d, *J* = 4.7, 1 H, C8-H), 3.82 (dd, *J* = 10.3, 4.2 Hz, 1 H, C16-H), 3.71 (ddd, *J* = 10.3, 5.5, 0.7 Hz, 1 H,

C16-H), 3.48 (dd, *J* = 14.4, 5.5 Hz, 1 H, C3α-H), 3.17 (ddt, *J* = 11.5, 5.5, 2.2 Hz, 1 H, C4-H), 2.98 (dd, *J* = 11.4, 1.8 Hz, 1 H, C6α-H), 2.77 (dd, *J* = 11.4, 3.8 Hz, 1 H, C6β-H), 2.63 (ddd, *J* = 14.4, 11.5, 1.6 Hz, 1 H, C3α-H), 2.53 (s, 3 H, C5-H), 2.5-2.45 (m, 1 H, C7-H); ^{13}C-NMR (125 MHz) δ 137.5, 134.8, 128.7, 126.8, 123.3, 121.2, 119.3, 111.9, 110.3, 110.2, 65.9, 63.8, 56.4, 43.7, 37.6, 27.8.



(6a*R*,9*S*)-9-((*tert*-Butyldimethylsilyloxy)methyl)-7-methyl-4-tosyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinoline (4.130). Method 1: JD-6-234. *N*-Ts-isolysergol (**4.123**, ca 3mg, 0.00734 mmol) from a diol cleavage reaction was used without purification. Imidazole (5 mg, 0.0734 mmol) and *tert*-butyldimethylsilyl chloride (11 mg, 0.0734 mmol) were added to the solution of **4.123** in CH_2Cl_2 (0.25 mL). The reaction progress was monitored by TLC, and when **4.123** had been consumed H_2O (2 mL) was added, the layers were separated, and the aqueous layer was washed with CH_2Cl_2 (4 X 2 mL). The combined organic layers were dried (Na_2SO_4), concentrated under reduced pressure, and purified *via* flash chromatography eluting with EtOAc/hexanes (20-100%) to yield 1 mg (26%) of **4.130**.

Method 2: JD 6-144, 6-181, 6-187, 6-189. Imidazole (31 mg, 0.456 mmol) and *tert*-butyldimethylsilyl chloride (34 mg, 0.228 mmol) were added to a solution of **4.90** (20

mg, 0.0456 mmol) in CH_2Cl_2 (0.5 mL). The reaction was stirred overnight whereupon H_2O (2 mL) was added, the layers were separated, and the aqueous layer was washed with CH_2Cl_2 (4 X 2 mL). The combined organic layers were dried (Na_2SO_4), concentrated under reduced pressure, and purified *via* flash chromatography eluting with EtOAc/hexanes (20-100%) the EtOH/EtOAc (0-100%) to yield 18 mg (59%) of **4.132**. Solid NH_4F (3 mg, 0.0810) was added in one portion to a solution of **4.132** (12 mg, 0.0178 mmol) in MeOH (1 mL) in a plastic vessel (Eppendorf type tube) and stirred for 6 h whereupon saturated aqueous $NaHCO_3$ (2 mL) and CH_2Cl_2 (2 mL) were added. The layers were separated and the aqueous layer was washed with CH_2Cl_2 (4 X 2 mL), the combined organic layers were dried (Na_2SO_4), the solvent was removed under reduced pressure, and the residue was purified via flash chromatography to yield 5 mg (50%) of **4.133**. DMSO (26 μL, 0.362 mmol) was added dropwise to a stirred solution of oxalyl chloride (16 μL, 0.180 mmol) in CH_2Cl_2 (0.25 mL) cooled to -78 °C. After 15 min, **4.133** (5 mg, 0.00904 mmol) dissolved in CH_2Cl_2 (0.5, 2 X 0.25 mL) was added dropwise, the mixture was stirred 15 min, and NEt3 (80 μL, 0.271 mmol) was added dropwise. The mixture was stirred and allowed to warm to rt over ca 45 min whereupon several drops of EtOH was added, and the reaction mixture was filtered through a pad of silica washing with EtOAc. The mixture was concentrated under reduced pressure, the residue was dissolved in EtOAc, the mixture was filtered through a pad of silica washing with EtOAc, and the mixture was concentrated under reduced pressure to yield 5 mg (quant.) of **4.131**, which was used directly in the next step. A solution of **4.131** in PhMe (1 mL) was degassed (freeze, pump, thaw 3 cycles), Wilkinson's catalyst (tris(triphenylphosphine)rhodium(I) chloride, 17 mg, 0.0181 mmol) was added, the mixture was degassed (freeze, pump, thaw 3 cycles), and the mixture was heated to 120 °C for 30 min. The mixture was concentrated under reduced pressure, and the residue

was purified *via* flash chromatography eluting with EtOAc/hexanes (20-100%) to yield 1 mg (21%) of **4.130**. ^{1}H NMR (400 MHz) δ 7.76-7.68 (comp, 3 H), 7.28-7.14 (comp, 4H), 6.34 (app d, *J* = 3.2 Hz, 1 H), 3.72-3.58 (comp, 2 H), 3.36 (dd, *J* = 15.4, 5.4 Hz, 1 H), 3.02-2.94 (mult, 1 H), 2.89 (d, *J* = 12.0 Hz, 1 H), 2.52-2.38 (comp, 6 H), 2.32 (s, 3 H), 0.88 (s, 9 H), 0.03 (s, 6 H).

NMR assignments. ^{1}H NMR (400 MHz) δ 7.76-7.68 (comp, 3 H, C4-H, C18-H), 7.28-7.14 (comp, 4H, C3-H, C6-H, C16-H, C17-H), 6.34 (app d, *J* = 3.2 Hz, 1 H, C13-H), 3.72-3.58 (comp, 2 H, C21-H), 3.36 (dd, *J* = 15.4, 5.4 Hz, 1 H, C8-H), 3.02-2.94 (mult, 1 H, C9-H), 2.89 (d, *J* = 12.0 Hz, 1 H, C11-H), 2.52-2.38 (comp, 6 H, C8-H, C10-H, C11-H, C12-H), 2.32 (s, 3 H, C1-H), 0.88 (s, 9 H, C23-H), 0.03 (s, 6 H, C22-H).

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