Total synthesis of (±)-isodihydrokoumine, (±)-(19Z)-taberpsychine, and (±)-isodihydroukoumine N4 oxide

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Abstract

We report the total synthesis of the natural products (±)-isodihydrokoumine, and (±)-(19Z)-taberpsychine in 11 steps each, and (±)-isodihydrokoumine N4-oxide in 12 steps from commercially available starting materials. The key reactions include an intramolecular [3+2] nitrone cycloaddition, and Lewis acid mediated cyclizations of a common intermediate to provide the core structures of either (19Z)-taberpsychine or isodihydrokoumine. Both failed and successful routes will be discussed.

Keywords

Geleganidine A, Geleganidine B, koumine, taberpsychine, (19Z)-taberpsychine, koumidine, isodihydrokoumine, total synthesis, natural product, nitrone cycloaddition, cyclization chemistry, convergent synthesis, divergent synthesis
Acknowledgments

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<th>Definition</th>
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<tr>
<td>(R)-DTBM-Segphos</td>
<td>(R)-(−)-5,5′-Bis[di(3,5-di-tert-butyl-4-methoxyphenyl)phosphino]-4,4′-bi-1,3-benzodioxole, [(4R)-(4,4′-bi-1,3-benzodioxole)-5,5′-diyl]bis[bis(3,5-di-tert-butyl-4-methoxyphenyl)phosphine]</td>
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<td>DIAD</td>
<td>diisopropyl azodicarboxylate</td>
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<td>DMAP</td>
<td>4-dimethylaminopyridine</td>
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<td>dimethylformamide</td>
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<td>LD50</td>
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Chapter 1

1 Introduction

Total synthesis, which in the context of this thesis is defined as the preparation of a naturally occurring compound from abiotically sourced precursors, has been a core discipline of organic chemistry since the Wohler synthesis of urea nearly 200 years ago.¹ The field experienced rapid growth and development during the Woodward era with chemists pushing the boundaries of synthesis by making ever increasingly complex molecules. The practice of making large molecules using a brute force approach started to decline in the 1990’s during which time molecules like taxol, rapamycin and brevetoxin were synthesized.²,³,⁴ These were undoubtedly major achievements; however, they were not a practical source of material for research. For example, the total synthesis of rapamycin by Nicolaou was completed in a total of 102 steps. While this provides extra support, or corrections for characterization, it is not a practical method to obtain ample quantities of the material for biological evaluation. During the 1990’s, a shift in the paradigm of total synthesis began to occur, with the focus changing from “can we make it?” to “how well we can make it?” This new philosophy in total synthesis has been adopted by many research groups today, and underlies the principles that govern the design and execution of the synthesis detailed in this thesis.

1.1 Aiming for the ideal synthesis

The first researcher to bring to light the idea of “how well can we make it?” was Hendrickson with the concept of an ideal synthesis. He claimed that an ideal synthesis is one which “…creates a complex skeleton from simpler starting materials…in a sequence of only construction reactions involving no intermediary refunctionalizations, and leads directly to the target, not only its skeleton but also its correctly placed functionality.”⁵ Baran and co-workers expanded on the ideas of Hendrickson by creating a simple numerical method to express ideality in total synthesis, and consistently use it to judge the quality of their synthesis. (Figure 1.1).⁶
\[
\% \text{ideality} = \left[ \frac{\text{\# of construction rxns} + \text{\# of strategic redox rxns}}{\text{total \# of steps}} \right] \times 100
\]

**Figure 1.1** Equation of ideality in total synthesis

In aiming for optimum ideality in synthesis, Baran outlines eight principles to follow which are: (1) redox reactions that do not form C-C bonds should be minimized, (2) the percentage of C-C bond forming reactions should be maximized, (3) disconnections should be made to maximize convergence, (4) the overall oxidation states of intermediates should follow a linear trend, (5) cascade and tandem reactions should be incorporated to maximize structural changes per step, (6) the innate reactivity of functional groups should be exploited, (7) new reactions should be discovered in order to develop new aspects of chemical reactivity, and (8) biomimetic pathways (known or proposed) should be incorporated into synthetic planning. When performing a retrosynthetic analysis of a target these principles should be kept in mind to help aid in developing the best possible way to synthesize a target.

Even with the concept of ideality being better established in recent years, poor efficiency, ideality, step counts, and overall yields still plague many syntheses in the field today. These examples can logically lead to two different viewpoints on total synthesis in the current era of chemistry which are: (1) total synthesis is a dead science as we have already made most of the interesting natural products out there, and this is not a practical way to obtain them, or (2) the inability for total synthesis to prepare ample quantities of any natural product in a highly efficient, and cost-effective way means the field is more akin to budding flower that has yet to bloom. The inadequacies of the field are evidenced by the fact that medicinal chemists are still mostly bound to the world of planar molecules, and easy to synthesize targets because we are not yet capable of producing complex molecules on an industrial scale in a meaningful way. Considering these circumstances, it is still important to study total synthesis, and methodology development in order to advance the field to a point where any chemist can rapidly make any molecule imaginable, on any scale, and in a cost-effective manner. Only once chemists can accomplish these goals, will total synthesis become a truly mature science. With these
goals in mind we set out to find synthetic targets that could potentially be medicinally useful. We applied these synthesis principles along with the use of key reactions in order to plan our retrosynthetic design.

1.2 The Genus *Gelsemium*

1.2.1 Ethnopharmacology and Folk Medicine

*Gelsemium* is a genus of flowering plants which comprises of three species: *Gelsemium elegans*, *Gelsemium rankii*, and *Gelsemium sempervirens*.⁸ *Gelsemium rankii* and *Gelsemium sempervirens* are both native to North America, while *Gelsemium elegans* is native to southeast Asia.⁹ All of these plants produce yellow flowers, but only *Gelsemium sempervirens* produces scented flowers, which has led to its use as a garden flower since the 17th century.⁹ All of these species are poisonous, and contain a rich variety of natural products including steroids, alkaloids, and iridoids.¹⁰ Due to the biological activity that these species possess, they have historically played a role in medicine. *Gelsemium elegans* has been used in traditional Chinese medicine to treat skin ulcers, eczema, tinea corporis/pedis, traumatic injury, fracture, hemorrhoids, leprosy, boils, pyodermas, ulcer, myiasis, scrofula, headaches, and cancer pain.¹¹,¹² *Gelsemium sempervirens* has been used for the treatment of neuralgias, malarial fever, cancer, inflammation of the spinal column, reducing spasmodic action, a blood purifier, and healing salve with varying degrees of efficacy.¹¹,¹³ Due to the relative rarity of *Gelsemium rankinii* there is a lack of information available about its use in traditional medicine.¹¹,¹⁴ To date there is no established clinical use for any species of *Gelsemium*, or compounds from *Gelsemium* with recent uses being more sinister such as a poison used for homicide.¹⁵ Due to the toxic properties of the plant, *Gelsemium* has made several appearances in popular media as a poison in such shows as House of Cards, and Outlander.¹⁶

1.2.2 Proposed biosynthesis of *Gelsemium* alkaloids

Alkaloids constitute the largest variety of natural products in *Gelsemium* comprising of 121 of the nearly 200 natural products isolated from this genus. These alkaloids are sorted into six general classes: humantenine, sarpagine, koumine,
gelsemine, gelsedine, and yohimbane (Figure 1.2).\textsuperscript{10}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{gelsemium_types.png}
\caption{Types of \textit{Gelsemium} alkaloids}
\end{figure}

These six classes of indole alkaloids are thought to originate from a single biogenetic route.\textsuperscript{17} It has been hypothesized that tryptamine (7) and secolganin (8) are condensed together via a Pictet-Spengler reaction to form strictosidine (9) which is the common intermediate for nearly every indole alkaloid (Scheme 1.1).\textsuperscript{18} Aldehyde 10 is the first intermediate where the biogenetic route is thought to diverge, and it is produced by hydrolysis of the glycosidic bond in 9. The biosynthesis of gelsedine type alkaloids is thought to occur by oxidation of C5 into an iminium followed by an enolate addition to form the bridged ring system in 11. A hydroamination reaction and loss of the C21 carbon yields the core framework for the gelsedine alkaloids. The last step in their proposed biosynthesis is the oxidation of the indole fragment into a spirocyclic oxindole. The other route that the biosynthesis follows is oxidation of the C5 nitrogen followed by attack of the enol present in 10. This yields structure 13 which is thought to be transformed into the sarpagine class of alkaloids through an alkene isomerization, an aldehyde-amine condensation, a decarboxylation, and an aldehyde reduction. It has been proposed that koumidine 2 of the sarpagine class of alkaloids is converted into (19Z)-taberpsychine (15) which is the next branching point for \textit{Gelsemium} alkaloid biosynthesis. The oxidation of C18 followed by an S\textsubscript{N}2′ attack from the indole is thought to lead to the koumine class of alkaloids, while the oxidation of C7 is thought to lead to both the humantenine, and gelsemine type alkaloids. The humantenine class of indole alkaloids is thought to arise when oxidized indole 17 is hydrated, followed by a 1,2-alkyl shift. Towards the gelsemine alkaloids it was proposed that instead of a hydration of oxidized indole 17, an elimination reaction occurs, followed by a conjugate addition from the exocyclic olefin to yield indole 20. Another oxidation of the indole followed by
hydration of the iminium, and subsequent 1,2 bond migration results in the gelsemine class of indole alkaloids.

Scheme 1.1. Proposed biosynthesis of *Gelsemium* alkaloids
Yohimbine type alkaloids are thought to arise from an internal enamine addition in 21 to an aldehyde forming the yohimbine core structure 22 (Scheme 1.2).\(^{19}\) The biosynthesis of *Gelsemium* alkaloids has been purely speculative to date, with semi-synthetic studies being conducted to determine if the proposed biosynthetic transformations are physically possible.

### 1.2.3 Project Motivation and Pharmacology of *Gelsemium* alkaloids

The biological effects of *Gelsemium* alkaloids are widely varied and include anti-tumor, anti-inflammatory, anti-anxiety, anti-stress, as well as analgesic and various immunoregulatory effects.\(^ {10,20}\) In recognition of the vast array of biological effects, as well as their intricate structures we developed an interest in this class of natural products.

**Figure 1.3: Gelegenidine B**

Gelegenidine B grabbed my initial attention because it was shown to have anti-cancer activity and contained unique structural features (Figure 1.3).\(^ {21}\) We noted that the natural product was a dimer linked via a diazo bond which represented the first example of such an alkaloid ever being isolated.\(^ {21}\) We thought that further study into its biological activity might uncover new pharmacological action. In planning a synthesis of this alkaloid we envisioned a route in which a single synthetic intermediate could be used to
prepare a variety of different alkaloids within *Gelsemium*. We sought to develop a synthetic intermediate that could be used to prepare the carbocyclic cores of koumidine (2), humantenine (1), and (19Z)-taberpsychine (15) on route to geleganidine B. We thought that this route could be used to develop analogues of several different classes of *Gelsemium* alkaloids. To date, no appreciable pharmacological activity of koumidine, taberpsychine, and humantenine has been discovered; however, our goal was to use these compounds as early synthetic checkpoints to show that our synthesis was working as designed. Another alkaloid that we found to be of interest was koumine (3), after we serendipitously discovered a synthesis of koumine analogues, which might display unique biological activity. Koumine itself has displayed numerous pharmacological effects including immunoregulatory effects, positive effects on psoriasis models, anti-stress activity, anti-anxiety activity, anti-inflammatory activity, analgesic effects, and antitumor activity. Unlike several other *Gelsemium* natural products with pharmacological activity koumine has a very low toxicity with an LD$_{50}$ of 99 mg/kg (i.p. injection) which makes it about as toxic as cocaine with an LD$_{50}$ at 96 mg/kg. The relatively low toxicity of koumine seems to have translated into low toxicity against cancer cell lines with typical IC$_{50}$ concentrations being close to the mmol/L level calling into question the effectiveness of koumine as a potential compound for cancer treatment.

1.2.4 Semi-Synthetic Studies

We were surprised to find that several key natural products in these classes of alkaloids have mainly been investigated by semi-synthetic studies, which in the context of this thesis is the preparation of a naturally occurring compounds from abiotically sourced precursors, with a relatively small amount of total synthesis work being completed. In addition, almost all of these semi-synthetic studies were conducted in the Sakai lab at Chiba University in Japan.

The original publication from the Sakai lab into the semi-synthesis of *Gelsemium* alkaloids initiated with a method to transform gardnerine (23) into 11-methoxytaberpsychine (25) (0% ideal) (Scheme 1.3). They found that by treating gardnerine with phenyl chloroformate they could cleave the C/D ring to yield the core
structure of taberpsychine (24). The carbamate was reduced with LiAlH₄ to a methyl group yielding 11-methoxytaberpsychine which has not yet been isolated as a natural product.³²

Scheme 1.3: Semi-synthesis of 11-methoxytaberpsychine

The first approach that was taken towards the semi-synthesis of koumidine was from ajmaline (26) (6% ideal) (Scheme 1.4).²⁵ A total of sixteen steps were required to perform this transformation, which was not a practical method to obtain koumidine. Initially they changed the hemi-aminal of ajmaline into a hydrazone using sulfuric acid, and N,N-dimethyl hydrazine. They cleaved the C/D ring with methyl chloroformate, and hydrolyzed the hydrazone to an aldehyde at a neutral pH in the presence of copper chloride. Protection of the alcohol as a MEM group followed by a two step sequence to install a bromine atom α to the aldehyde resulted in α-bromo aldehyde 27. They were able to treat 27 with DBU to form α,β-unsaturated aldehyde 28. From 28 they reduced the aldehyde with NaBH₄ locking in the alkene as the desired Z isomer. They deprotected the N₄ amine by hydrolyzing the carbamate with sodium hydroxide. Next, they mesylated the alcohol on C21 which was displaced via an S_N2 reaction to reform the C/D ring. At this point they switched the MEM protecting group for a TMS group to yield 29. Oxidation of 29 with lead tetraacetate yielded imine 30 with loss of the methyl group. Deprotection of the TMS group with TBAF followed by acidic ring fragmentation yielded aldehyde 31. Reduction of aldehyde 31 with sodium borohydride yielded koumidine. They synthesized (19Z)-taberpsychine by cleaving the C/D ring with methyl chloroformate, followed by reduction of the carbamate to a methyl group using LiAlH₄.
The Sakai group wanted to start exploring the chemistry of oxindole alkaloids which they had proposed are formed from koumidine via an oxidative rearrangement. In accordance with their proposal they needed to synthesize large amounts of koumidine to pioneer the required indole oxidation. Their previous 16 steps synthesis was not a practical source of koumidine which motivated them to find a more efficient route. Starting with gardnerine they protected the primary alcohol as an acetate ester, and the indole with a $p$-toluenesulfonyl group. They demethylated the phenol using $\text{AlCl}_3$, and ethanethiol. A palladium catalyzed hydrogenation reduced the phenol to a C-H bond to yield 32. They found that by treating 32 with a palladium catalyst in the presence of magnesium in methanol a global deprotection occurred, with simultaneous isomerization of the C19 olefin giving koumidine in a 48% yield (0% ideality), along with 34% of un-isomerized material.
Scheme 1.5: Semi-synthesis of koumidine from gardnerine

The Sakai group utilized their new route for the synthesis of koumidine to develop semi-synthetic work into several oxindole alkaloids that are found in Gelsemium. They first used trichloromethyl chloroformate to cleave the C/D ring cleavage of koumidine to yield 34. They found that by treating indole 34 with t-butyl hypochlorite, they obtained a spirocyclic oxindole with wrong stereochemistry at C7. The use of osmium tetroxide allowed them to transform indole 34 into an oxindole with the correct stereochemistry at C7, which took place concurrently with a dihydroxylation of the C19 alkene to yield 35. To reform the C19 alkene they first treated diol 35 with trimethyl orthoformate under mildly acidic conditions to form a 2-methoxy-1,3-dioxolane which upon treatment with acetic anhydride at reflux reformed the 19Z alkene in a stereoselective manner. The use of acetic anhydride acetylated the indoline Nα nitrogen which could be deprotected with sodium hydroxide in methanol. Zinc in acetic acid was used to deprotect the Nβ carbamate to form Nα-demethoxyrankinidine (17% ideal). Utilizing their osmium oxidation, they were also able to synthesize the oxindole alkaloids Nα-demethoxy-11-methoxy-19(R)-hydroxygelselegine, 28 20-hydroxydihydrorankinidine, 29 gelselegine, gelsenicine, and gelsedine. 30
Scheme 1.6: Semi-synthesis of N₃-demethoxyrankinidine 36

The Sakai group also performed the semi-synthesis of 11-methoxykoumine (20% ideal) based off of their methodology to cleave the C/D ring in koumidine and related structures (Scheme 1.7). They first treated 18-hydroxygarnderine with methyl chloroformate to yield 38. They acetylated the C18 alcohol and performed a palladium catalyzed S_N2′ alkylation to yield the carbon core of koumine. Reduction of the carbamate group with LiAlH₄ turned the carbamate into a methyl group, and reduced the imine to an amine to yield 39. Treatment of 39 with lead tetraacetate reformed the imine to produce 11-methoxykoumine which has not yet been isolated as a natural product to date.

Scheme 1.7: Semi-synthesis of 11-methoxykoumine
The first biomimetic semi-synthesis of koumine was not accomplished by the Sakai lab, but instead by the Yu lab. The Yu group was able to perform an allylic oxidation with SeO$_2$ on (19Z)-taberpsychine which underwent a simultaneous ring closure under acidic conditions to make koumine in a modest 25% yield, but with 100% ideality (Scheme 1.8).$^{33}$

![Scheme 1.8: Semi-synthesis of koumine from (19Z)-taberpsychine](image)

The second semi-synthesis of koumine was performed by the Sakai group starting from 18-hydroxygardnudidine (9% ideal) (Scheme 1.9).$^{34}$ They initially synthesized 18-hydroxykoumidine by performing a reductive ether cleavage on 37 with LiAlH$_4$. The resulting primary alcohol was protected as an acetate group, and the indole was protected with a p-toluenesulfonyl group. They demethylated the phenol using AlCl$_3$, and sodium ethanethiol. The resulting phenol was turned into a triflate ester, along with concurrent formation of a triflate ester at C18. Hydrolysis of the C18 triflate back to an alcohol followed by reduction of the aromatic triflate to a C-H bond yielded 18-hydroxykoumidine. Treating 18-hydroxykoumidine with methyl chloroformate, then LiAlH$_4$ yielded 18-hydroxytaberpsychine. Acetylation of the C18 alcohol followed by a palladium catalyzed Sn2’ reaction furnished koumine.
While there has been a significant amount of work directed towards the semi-synthesis of *Gelsemium* alkaloids from simpler alkaloids, only two total synthesis of koumine,\(^{35,36}\) two total synthesis of koumidine,\(^{36,37}\) no total synthesis of humantenine, and no total synthesis of (19Z)-taberpsychine have been published to date.

**Scheme 1.9: Semi-synthesis of koumine by the Sakai group**
1.2.5 Previous Total syntheses

In 1989 the Magnus group successfully performed the total synthesis of (+)-koumidine, (+)-taberpsychine, and (+)-koumine that are all the opposite enantiomer to the natural material (Scheme 1.10).36
Scheme 1.10: Magnus total syntheses of (+)-koumidine, (+)-taberpsychine, and (+)-koumine

Their route took a total of 16 steps for koumidine (25% ideal), 20 steps for taberpsychine (20% ideal) and 22 steps for koumine (23% ideal) from commercially
available starting materials. Starting from (S)-(-)-tryptophan (the natural enantiomer) they first protected the indole with a benzyl group, the carboxylic acid as a methyl ester, and the primary amine with a benzyl group to yield 44. Next, they performed a Pictet-Spengler reaction to yield 58% of 46 which led to the opposite enantiomers the natural material, and 25% of 45 which led to the natural enantiomers of the desired targets. The authors claim that they were able to use 45 to synthesize the (-) enantiomers of all three natural products, but they used 46 due to the greater availability of material. From 46 they performed a Dieckmann cyclization, followed by a decarboxylation, and a hydrogenation to remove the aliphatic benzyl amine to yield 47. Next, the secondary amine was alkylated with propargyl bromide, and the ketone was protected as a TBS enol ether. The alkyne was deprotonated with n-BuLi, and was reacted with methyl chloroformate to yield an α,β-unsaturated ester. The enol ether was hydrolyzed back into a ketone using lithium tetrafluoroborate under aqueous conditions to yield 48. Utilizing enamine chemistry they accomplished a conjugate addition into the α,β-unsaturated ester 48 which resulted in the formation of 49 in a 68% yield, and 50 in a 12% yield. The major alkene isomer was used to synthesize (+)-taberpsychine, and (+)-koumine, while the minor isomer was used to synthesize (+)-koumidine, and could also be transformed into (+)-koumine. The major isomer 49 was treated with Tebbe’s reagent to transform the ketone into an exocyclic olefin which underwent hydroboration oxidation to yield a primary alcohol. Next the ester was reduced with DIBAL-H to yield an alcohol at C18 which upon treatment with sodium in liquid ammonia at -78 °C formed 52 through removal of the benzyl protecting group. If the Bouveault-Blanc reduction was carried out at -30 °C it was found that the C18 alcohol was reduced to a methyl group to yield 53. Capitalizing on this discovery they were able to cleave the C/D ring in 53 with methyl carbamate followed by a LiAlH₄ reduction to yield (+)-taberpsychine. By treating 52 with methyl chloroformate, followed by LiAlH₄ they were able to form 18-hydroxytaberpsychine (57). Treatment of 57 with DEAD, PPh₃, imidazole, and NaH caused the indole anion to perform an S₈N₂’ alkylation on the activated C18 alcohol to produce (+)-koumine.

The other alkene isomer 50 could also be treated with Tebbe’s reagent, followed by hydroboration oxidation, and ester reduction to yield 55. Sodium in liquid ammonia at
-30 °C caused the C18 alcohol to be reduced to a methyl group along with removal of the benzyl group to yield (+)-koumidine. Treating 55 at -78 °C with sodium in liquid ammonia removed the benzyl group without reduction of the C18 alcohol. Subsequent treatment with methyl chloroformate, followed by LiAlH₄ resulted in the formation of 18-hydroxy-(19Z)-taberpsychine (56) which could be transformed into koumine by reacting it with DEAD, PPh₃, imidazole, and NaH albeit in lower yields compared to starting with 57.

Scheme 1.11: Takayama total synthesis of koumine

The second total synthesis of koumine was performed by Takayama (Scheme 1.11).³⁵ They were able to synthesize (-)-koumine (14% ideal) in a total of 22 steps from commercially available starting materials. They started their synthesis from bicyclic benzylamine 58 which had been previously reported as a four step synthesis in the literature.³⁸ First they performed a dual Swern oxidation, followed by a selective reduction to yield keto alcohol 59. The acetylation of the secondary alcohol in 59 was accomplished by treatment with acetic anhydride. Deprotection of the benzyl amine
under hydrogenolysis conditions, followed by alkylation with mesylated propargyl alcohol 61 gave rise to 62. A silyl enol ether was formed from the ketone in 62 using TIPSOTf, and triethylamine to yield 63. A gold catalyzed cyclization of 63 provided the non-indole fragment of koumidine (64). Olefination of the ketone in 64 was accomplished using Tebbe’s reagent, followed by an acetate deprotection, alcohol oxidation, and a trityl deprotection to yield 65. A Fischer indole synthesis was performed on 65 using benzyl protected phenyl hydrazine to yield 66. A hydroboration oxidation reaction followed by removal of the benzyl protecting group from the indole using sodium in liquid ammonia formed (-)-18-hydroxykoumidine. Upon treatment with methyl chloroformate, then LiAlH₄, they were able to form 18-hydroxytaberpsychine which they were able to acetylate to yield 68. The final step in their total synthesis was a palladium catalyzed S_N2' alkylation of the allylic acetate to yield (-)-koumine that is the natural enantiomer.

Scheme 1.12: Total synthesis of (-)-koumidine by Cook

The Cook group was able to perform the synthesis of (-)-koumidine in an impressive seven steps with an overall yield of 21% with 29% ideality (Scheme 1.12).³⁷
Initially they used an asymmetric Pictet-Spengler reaction that they had previously
developed to transform (S)-(−)-tryptophan methyl ester (69) into 70. They removed the
benzyl protecting group in 70 by hydrogenolysis to yield 71. Next they alkylated the
secondary amine with an allylic bromide to yield 72. A unique C-H activation reaction
was performed to couple the vinyl iodide functionality to C3 yielding 73. To finish their
synthesis they performed a Wittig reaction followed by a hydroboration oxidation
reaction to yield (-)-koumidine.

In addition to these completed total syntheses there has been a formal synthesis of
taberpsychine, koumidine, and koumine from the McLay group. They synthesized 47
which is an intermediate in the Magus synthesis, but the main difference in the work from
McLay is that 47 is the opposite enantiomer relative to the one in the Magus synthesis
which would give rise to the naturally occurring enantiomer of these natural products.
There is also a small body of work towards the total synthesis of these natural products
that has not yet been transformed into completed synthesis.  

1.2.6 Retrosynthetic Analysis

I presented a retrosynthesis plan that I had developed to Dr. Kerr upon my arrival
at the University of Western Ontario (Scheme 1.13). I thought that geleganidine B could
be synthesized through a late stage oxidative dimerization of aniline 76. At this point a
transamidation reaction could be conducted on geleganidine A (77) to yield intermediate
76, which has some literature precedence. It was surmised that geleganidine A could be
prepared via a C-H activation on methylated hydroxamic acid 78. To prepare
hydroxamic acid 78 it was thought that an aldol reaction from ester 79 to the aldehyde
followed by a subsequent S_N2 displacement of the formyl group might yield 78.
Literature precedence exists for transforming esters into hydroxamic acids which might
be applicable to transform ester 79 into hydroxamic acid 78. To prepare ester 79 it was
hypothesized that it could come from isoxazolidine 80 through cleavage of the N-O bond
followed by formylation of both the secondary amine, and the primary alcohol. I saw
that a potentially powerful way to generate isoxazolidine 80 would be through an
intramolecular [3+2] nitrene olefin cycloaddition that could be accomplished by heating
nitrene 81. The regioselectivity, and diastereoselectivity of nitrene olefin cycloadditions
can be hard to predict; however, previous research on similar systems gave me hope that the reaction would produce the desired product.\textsuperscript{47} The nitronone required for such a cycloaddition could come from a condensation reaction between aldehyde \textsuperscript{82}, and hydroxylamine \textsuperscript{83}. While aldehyde \textsuperscript{82} had been previously synthesized, hydroxylamine \textsuperscript{83} had not been reported in the literature.\textsuperscript{48} I saw that hydroxylamine \textsuperscript{83} could be prepared from alcohol \textsuperscript{84} through a Mitsunobu type alkylation of the allylic alcohol.\textsuperscript{49} The preparation of alcohol \textsuperscript{84} could result from the reduction of lactone \textsuperscript{85}. An enantioselective copper catalyzed conjugate addition of a vinyl nucleophile onto dihydropyranone \textsuperscript{86} could yield lactone \textsuperscript{85}.\textsuperscript{50} This would set the key stereocenter which all of the others are derived from in this synthesis. A recent methodology has demonstrated a concise way to generate dihydropyranones which I utilized as the starting point for my retrosynthetic plan.\textsuperscript{51}
In addition to my planned retrosynthesis, Dr. Kerr also added several ideas of his own that were valuable to this project (Scheme 1.14). The main idea that he included in the synthetic planning was the use of indole 93 such that after the nitrone olefin cycloaddition we would already have an indole in the molecule. After several functional group interconversions, we would be able to make intermediate 90 which mapped onto the core structures of taberpsychine, koumidine, and koumine. At first we had only planned to make koumidine, and taberpsychine while the synthesis of the core of
koumine was serendipitous. With a retrosynthesis plan finished, the synthetic studies commenced with finding a method to synthesize hydroxylamine 83.

Scheme 1.14: Dr. Kerr additional project ideas
Chapter 2

2 Results and Discussion

2.1 Synthesis of hydroxylamine 94

The planned route started off with the development of the chemistry to prepare large quantities of protected hydroxylamine 94 (Scheme 2.1).

\[
\text{Scheme 2.1: Optimized synthesis of hydroxylamine 94}
\]

2.1.1 Synthesis of dihydropyranone 86

Initially 2-butyn-1-ol (87) was hydrostannylated with tributyltin hydride using 2 mol% Pd(PPh₃)₄.⁵² The hydrostannylation reaction produced a mixture of alkene isomers in a ratio of 5.3:1 (Scheme 2.2). During initial attempts to optimize this reaction these isomers were isolated which allowed us to determine their relative ratio. It was found that benzene as a solvent gave the highest ratio of the desired isomer 95, compared to running the reaction in THF which resulted in a ratio of about 1.6 (95) to 1 (96).

\[
\text{Scheme 2.2: Hydrostannylation selectivity}
\]
Based upon a previous methodology, we found that it was unnecessary to isolate the vinyl stannane. In the next step of the reaction we added oxygen gas in order to oxidize the phosphine ligands to cause the palladium to precipitate which was the catalyst for the subsequent Stille coupling. We discovered that switching the solvent from benzene to THF before the oxygen was added increased the product yields by about 20%. It has been shown that if phosphine ligands are present for the Stille coupling a significant amount of the Tsuji-Trost reaction product (99) forms diminishing the yield of the desired product (Scheme 2.3).

Scheme 2.3: Proposed Tsuji-Trost mechanism for side product formation

Once vinyl iodide 88 had been cross coupled, a trans-esterification spontaneously took place to yield the desired dihydropyranone 86. We found that the reaction yield depended on two major factors, which were (1) the quality of the tributyltin hydride, and (2) how rigorously oxygen was excluded during the palladium catalyzed hydrostannylation step. We found that commercial samples of tributyltin hydride varied widely in purity. Several month-old samples provided diminished yields, and in order to achieve consistent yields purification before use was required.

Due to the toxicity of organotin reagents, we also attempted to find other conditions that could be used to synthesize dihydropyranone 86. The first alternate method that we tried was to use tetraphenylporphyrin (TPP) to generate singlet oxygen to perform an Alder-Ene reaction followed by a deprotonation of the intermediate hydroperoxide to generate lactone 102 (Scheme 2.4). Following this reaction, we planned to condense acetaldehyde with 102 to yield the desired dihydropyranone 86. This strategy was unsuccessful because the chemistry utilizing singlet oxygen was low yielding, and not amenable to scaling.
The second alternate approach that we tried was an Achmatowicz reaction on furfuryl alcohol to yield lactol 104, or acetate 106 (Scheme 2.5).\(^{55}\) We attempted to oxidize lactol 104 with CrO\(_3\); however, we were unable to isolate any product with mostly decomposition being observed.\(^{56}\) Utilizing acetate protected lactol 106, we attempted to perform a Wittig reaction to install the exocyclic olefin, but again a complex mixture of products was obtained from this reaction.

The final attempt to develop an alternate route was based around using a Hiyama-coupling (Scheme 2.6).

### Scheme 2.4: Singlet oxygen approach to dihydropyranone 86

### Scheme 2.5: Achmatowicz based route towards dihydropyranone 86

### Scheme 2.6: Hiyama coupling based approach towards dihydropyranone 86
We were able to protect 2-butyn-1-ol with a dimethylvinylsilyl protecting group yielding 107. Using Pt(dvds) (Figure 2.1) we attempted to hydrosilylate the alkyne with trimethoxysilane to yield 108.\textsuperscript{57} We hoped the vinyl group on the silicon could direct the regioselectivity of the hydrosilylation chemistry.\textsuperscript{57}

![Figure 2.1: Karstedt’s Catalyst, Pt(dvds)](image)

We opted to not isolate vinyl silane 108, and instead tried to couple it directly to acrylic iodide 88 using Pd(dba)\textsubscript{2}.\textsuperscript{58} The coupling reaction did not give us any of the desired product, which led us to abandon this route. We decided to continue to use the Stille coupling because it worked reliably even on 25-gram scales.

### 2.1.2 Development of the copper catalyzed conjugate addition

The next step of our planned route was the copper catalyzed conjugate vinyl Grignard addition to produce lactone 85. This reaction proved to be more challenging to optimize than anticipated. Typically, TMSCl and HMPA are necessary additives to produce high yields in these types of reactions.\textsuperscript{59} Due to the toxicity associated with HMPA, non-carcinogenic DMPU was employed instead.\textsuperscript{60} Our initial attempts towards optimizing this reaction utilized stoichiometric copper bromide dimethyl sulfide complex (CuBr•Me\textsubscript{2}S). It was imperative that the CuBr•Me\textsubscript{2}S be rigorously purified, otherwise the reaction yields dropped to 30% or below. When we attempted to scale up the reaction from ~200 mg to multigram scales the yields became erratic and unreproducible even when using freshly purified CuBr•Me\textsubscript{2}S. An interesting discovery that we made was that bidentate NHC ligand L1 in combination with copper (II) triflate resulted in higher yields, and superior reproducibility of the reaction even on decagram scales. We discovered this ligand when we were trying to screen various conditions to install the vinyl group asymmetrically to produce a single enantiomer of lactone 85. (Scheme 2.7).
If we could install the vinyl group enantioselectively we would have an asymmetric synthesis because all of the chiral centers later in the route are derived from the one present in lactone 85. We decided to screen a variety of ligands that had literature precedence for enantioselective conjugate addition reactions (Figure 2.2).\(^{61,50,62,63,64}\)

Unfortunately, we were unable to find any conditions that produced enantioenrichment of lactone 85. (Table 2.1) An interesting observation that we noted from this ligand screening was that while no enantiomeric excess was generated, chiral NHC ligand L2 was able to catalyze the reaction in reasonably high yields. We reasoned that by using a non-chiral NHC ligand we might be able circumvent the issues we had with scaling the reaction using stoichiometric CuBr•Me\(_2\)S. This led to the use of L1 which allowed us to run the reaction reliably on decagram scales using catalytic amounts of copper. The ligand optimization results also showed us that DCM was the best solvent, the temperature was best at -78 °C, the NHC ligand L1 worked at a 9 mol% loading, and the ideal copper source was Cu(OTf)\(_2\) at a 6 mol% loading (entry 15).
Table 2.1: Optimization of asymmetric copper catalyzed vinyl Grignard addition

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Solvent</th>
<th>Temperature (°C)</th>
<th>Copper Source</th>
<th>ee</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>L2</td>
<td>THF</td>
<td>-50</td>
<td>Cu(OTf)₂</td>
<td>0</td>
<td>29</td>
</tr>
<tr>
<td>2</td>
<td>L2</td>
<td>Et₂O</td>
<td>-50</td>
<td>Cu(OTf)₂</td>
<td>N/A</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>L2</td>
<td>DCM</td>
<td>-50</td>
<td>Cu(OTf)₂</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>4</td>
<td>L2</td>
<td>2-MeTHF</td>
<td>-50</td>
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<td>0</td>
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<td>CuBr•Me₂S</td>
<td>0</td>
<td>15&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Unless specified, the reaction was conducted on a 50 mg scale. <sup>a</sup> 200 mg scale <sup>b</sup> no DMPU <sup>c</sup> Divinyl zinc was used instead of vinylmagnesium bromide<sup>d</sup> No TMSCl <sup>e</sup> No DMPU or TMSCl <sup>f</sup> no NHC ligand was used <sup>g</sup> used vinyllithium<sup>h</sup> TMSOTf was used instead of TMSCl
When we attempted to use rhodium instead of copper for this reaction we discovered that the majority of the terminal alkene isomerized to yield ethylidene dihydropyranone 109 (Scheme 2.8).

![Scheme 2.8: Rhodium catalyzed 1,4-conjugate addition](image)

When we were running the reaction utilizing rhodium the rhodium catalyst, we noticed that a new spot was forming by TLC that was UV active. Lactone 85 does not absorb UV light, so we wondered what we were making. We decided to stop the reaction before all of the starting material was consumed in order to determine what was in the reaction mixture. Purification by column chromatography yielded an inseparable 90:10 mixture of isomerized to un-isomerized material. We submitted a sample for enantiomeric excess measurement and observed that we may have obtained >99% ee of the un-isomerized material; however, it was hard to tell due to the presence of a variety of impurities. We are currently investigating this reaction in more detail to determine if we can use it to generate a single enantiomer of lactone 85.

### 2.1.3 Preparation of hydroxylamine 94 via reduction and Mitsunobu reaction sequence

With lactone racemic lactone 85 a LiAlH₄ reduction was performed to yield diol 84. The reaction worked well with minimal by-product formation and was easy to conduct on decagram scales. The final step of making hydroxylamine 94 was the substitution of the allylic alcohol with hydroxylamine. Boc-NH-OBoc was used instead of free hydroxylamine because the N-H hydrogen could be deprotonated by DIAD which allowed us to use Mitsunobu chemistry to selectively substitute the allylic alcohol in the
presence of the primary alcohol. This reaction was reliably conducted on a 47 g scale (Scheme 2.9).

Scheme 2.9: Last two steps to synthesize hydroxylamine 94

2.1.4 Deprotection of hydroxylamine 94

Now that we had a method to prepare large quantities of hydroxylamine 94 we performed test reactions to see if we could isolate the unprotected hydroxylammonium salt 83 (Scheme 2.10).

Scheme 2.10: Synthesis of unprotected hydroxylamine 83

We attempted to deprotect the Boc groups using TFA, TMSCl, TMSOTf, NaI, aqueous TFA, MeMgBr, Sc(OTf)3, TMSI, and HCl, but none of them yielded the desired hydroxylamine 83. In several examples, a modest amount of an unexpected side product was formed, but at this point we were unable to characterize it due to difficulty in purification. We decided to try a separate approach towards hydroxylamine 83 to see if the issue was with the highly acidic conditions typically required for deprotection of Boc groups (Scheme 2.10). Starting from alcohol 84 we performed an allylic oxidation using MnO2. Next, we condensed aldehyde 110 with hydroxylamine to yield oxime 111. The last step towards hydroxylamine 83 was a reduction of the oxime to a hydroxylamine. We
used sodium cyanoborohydride under slightly acidic conditions (pH 3-4). This was accomplished by adding a small quantity of methyl orange to the reaction. Hydrochloric acid was slowly titrated into the reaction at such a rate as to keep the color either orange or yellow. This method prevented the pH from dropping below 3, but interestingly we obtained the exact same side product that we observed during the TFA deprotection. We hypothesized that in both cases hydroxylamine 83 was being formed, followed by an additional reaction to yield another product. Purification and analysis of the product from the reductive amination sequence showed that we had obtained pyrrolidine 112 which could only have arisen via a Cope type hydroamination reaction. There are several literature sources that support this hypothesis and show that it is quite a facile transformation. We found that the acidic conditions for deprotecting the Boc group in 94 produced the same result when using methyl carbamate 113. An interesting result we found when screening basic conditions was that NaSH in refluxing methanol cleaved the carbonate, but not the carbamate yielding compound 114. While this was an interesting result, we did not pursue it further because at this point we had discovered that we could trap hydroxylamine 83 in situ to generate nitrones and we wanted to focus our efforts towards developing the cycloaddition chemistry.

**Scheme 2.11:** Synthesis of methyl carbamate protected hydroxylamine 113

We found that the acidic conditions for deprotecting the Boc group in 94 produced the same result when using methyl carbamate 113. An interesting result we found when screening basic conditions was that NaSH in refluxing methanol cleaved the carbonate, but not the carbamate yielding compound 114. While this was an interesting result, we did not pursue it further because at this point we had discovered that we could trap hydroxylamine 83 in situ to generate nitrones and we wanted to focus our efforts towards developing the cycloaddition chemistry.
2.2 Development of the intramolecular nitrone cycloaddition

2.2.1 Model studies using 4-bromobenzaldehyde and 3-phenylpropanal

Starting with hydroxylamine 94, we performed a Boc deprotection in TFA, followed by concentrating the reaction under reduced pressure. The resulting brown oil was treated with 4-bromobenzaldehyde, triethylamine, and MgSO₄ and was allowed to stir at 21 °C. Much to our delight we were able to isolate nitrone 115 from this mixture by column chromatography in an 80% yield as a single isomer (Scheme 2.12). Upon heating the nitrone in refluxing toluene we were able to obtain isoxazolidine ring 116, but we were unable to assign the relative stereochemistry at this stage.

Scheme 2.12: Model study with 4-bromobenzaldehyde based nitrone

Our next model study used 3-phenylpropanal which was closer to the substrate that we proposed in our retrosynthesis. Treating 3-phenylpropanal with hydroxylamine 83 allowed us isolate nitrone 117 from this mixture by column chromatography in a 77% yield (Scheme 2.13).

Scheme 2.13: Isolation of nitrone 117

When we heated nitrone 117 in toluene we observed consumption of the nitrone by TLC, and the formation of several new spots. We were only able to purify one of the spots from the mixture which happened to be the desired all cis diastereomer 118 (Scheme 2.14).
Scheme 2.14: Model intramolecular [3+2] nitrone cycloaddition study

We were able to confirm the relative stereochemistry of isoxazolidine 118 through an X-ray structure of its hydrogen oxalate salt. (Figure 2.3). At this stage in our project we were unable to purify the other diastereomer to determine its identity. We also attempted to increase the yield of the nitrone cycloaddition by adding a 4-bromobenzoyl ester to the primary alcohol as a protecting group; however, we didn’t notice any difference in yield.

Figure 2.3: X-ray crystal structure of the hydrogen oxalate salt of isoxazolidine 118
2.2.2 First generation nitrone cycloaddition

With confidence from our model study that we could perform the desired cycloaddition, and isolate the all cis diastereomer, we moved onto using aldehyde 82 as planned in the retrosynthesis (Scheme 2.15).

Scheme 2.15: First generation isoxazolidine synthesis

We found that aldehyde condensation and subsequent nitrone cycloaddition reaction worked in a 53% yield over two steps giving us a mixture of diastereomers, but due to the α-stereocenter by the ester, the reaction mixture was much more complex than our model study. We were unable to separate any diastereomers at this stage, but we figured that it would not be a concern for two reasons. The first reason was that we were confident that the desired diastereomer was present based on our model study, and the second reason was that the chiral center beside the ester would be inconsequential because it would be destroyed during the upcoming aldol reaction. We decided to continue with the synthesis using a mixture of diastereomers in hopes that we could separate them at a later stage. Next, a Swern oxidation was performed on 120 to yield aldehyde 121 in a 95% yield (Scheme 2.16).
Scheme 2.16: Swern oxidation and N-O bond cleavage reactions

With aldehyde 121 we started to screen conditions that we thought could cleave the N-O bond. Treatment of 121 with either zinc in acetic acid, or zinc in trifluoroacetic acid resulted in new products that we were unable to purify by flash chromatography. The main difference between the product and the starting material from this reaction was that the products were much more polar than the starting materials. Based on this information we thought that we may have cleaved the N-O bond, so we attempted to perform an aldol reaction from the ester in 122 onto the lactol. After screening both basic, and acidic conditions without success we decided to re-evaluate our approach. The main issue that we were having was that the complex nature of the reaction prevented us from being able to diagnose problems. We essentially had no idea what we were forming in these reactions. We decided to try to revisit the nitrone cycloaddition using a substrate that didn’t contain an extra stereocenter to make the reaction mixture less complicated. We also tried to influence the diastereomeric ratio of the cycloaddition by running the reaction at different temperatures (reflux in DCM, CHCl₃, PhH, Toluene) and with different additives (Pt, Au, Ru, Sc, Yb, and Zn salts) all with no success.

2.2.3 Second generation nitrone cycloaddition

We knew that the nitrone cycloaddition worked, so we decided to try using an oxindole based nitrone which should undergo an aldol reaction under more mild conditions. We thought that this could help avoid issues associated with the previous route based on ester 120. Using this design, we wanted to synthesize aldehyde 125 and condense it with hydroxylamine 83, but unfortunately we found that it was unstable, and could not be isolated (Scheme 2.17).

Scheme 2.17: Attempted hydrolysis and isolation of aldehyde 125
We thought we might be able to trap aldehyde 125 *in situ* in a similar fashion to how we trapped hydroxylamine 83 *in situ* with an aldehyde. After screening several conditions in a model study we managed to isolate nitrone 126 in an 80% yield (Scheme 2.18).

![Scheme 2.18: Trapping of cyclopropane 124 as a nitrone](image)

Next, we attempted to deprotect hydroxylamine 94, then treat it with cyclopropane 124 in hopes that we could trap aldehyde 125 *in situ* to yield nitrone 127. Unfortunately, we were unable to isolate any product from this reaction (Scheme 2.19).

![Scheme 2.19: Attempted condensation of hydroxylamine 94 with cyclopropane 124](image)

We surmised that because both reagents were unstable, the reaction was only producing decomposition products, and none of the desired product. We were unable to optimize this reaction, so we decided to try another approach. It is worth mentioning that the methodology to synthesize nitrone 127 from cyclopropane 124 resulted in a Chem 4491 project that Ben Bridge undertook to synthesize Chanoclavine I, and lysergic acid diethylamide (LSD).

**2.2.4 Third generation nitrene cycloaddition**

The next plan that we tested was to use indole-3-acetaldehyde in order to generate isoxazolidine 129 which already contains an indole ring (Scheme 2.20). Previously reported studies have been able to oxidize indole into oxindole\textsuperscript{69} which could allow us to access several other indole alkaloids that are found in *Gelsemium*. 
Unfortunately, attempts to isolate nitrone 128, or isoxazolidine 129 by running the reaction in a single flask all failed. We attributed the failure of this route to the instability of indole-3-acetaldehyde. A simple modification that we devised was with the use of \( p \)-toluenesulfonyl protected indole-3-acetaldehyde (130) (Scheme 2.21).

By protecting indole-3-acetaldehyde with a \( p \)-toluenesulfonyl group we were able to successfully synthesize nitrone 131 and perform the cycloaddition to yield isoxazolidine 132. We found that nitrone 131 was much harder to isolate, with yields typically never reaching above 40%. We opted to run this reaction in a single flask to avoid the decreased yields associated with isolation of nitrone 131. The main observation that we made during attempts to optimize this reaction was that imidazole gave higher yields than triethylamine. We were unable to scale this reaction reliably, and the amount of material we managed to synthesize using this route was around 1 g. With limited material, we began to investigate the synthetic route using isoxazolidine 132.
2.3 Development of a synthetic route towards 134

2.3.1 First generation synthesis of 134

The next step we performed was a Swern oxidation, followed by an acetal protection to successfully yield acetal 133 (Scheme 2.22).

![Scheme 2.22: First generation synthesis of 134](image)

We were able to remove the \( p \)-toluenesulfonyl protecting group on the indole, and cleave the N-O bond in a single flask using SmI\(_2\) yielding 134.\(^{71} \) From this route we were able to generate enough acetal 134 to test out the final stages of our synthesis, but this was not a practical route to obtain more than 200 mg of 134.

2.3.2 Fourth generation nitrone cycloaddition

Based on our previous observation that the use of imidazole was higher yielding than triethylamine we hypothesized that enolization of nitrone 131 might have been our issue with the third-generation synthesis. We decided to use an indoline instead of an indole which would prevent the alpha anion from being stabilized like it is in 131 because it would no longer be conjugated into the aromatic system. We thought that we could transform the indoline into an indole following the cycloaddition which should eliminate issues associated with a complex mixture of diastereomers. Utilizing this strategy, we were successfully able to condense indole aldehyde 135 with hydroxylamine 94, and isolate nitrone 136 in yields of around 80%. We found that the key to scaling up this reaction to a decagram scale was to perform a workup on nitrone 136, and not a column. Using this procedure, we could generate decagram quantities of nitrone 136, and have it undergo a nitrone cycloaddition to yield isoxazolidine 137 in a 33% yield favouring the cis diastereomer 134 by 2:1 with an inconsequential 1:1 ratio of diastereomers about the indoline (Scheme 2.23).
We also attempted to use a Boc protected indoline for this process, but we found that yields were lower compared to using a p-toluenesulfonyl protecting group. Next, we attempted to screen oxidants that could transform the indoline into an indole so that we could remove the inconsequential chiral center (Scheme 2.24).

When screening reaction conditions we found that DDQ, MnO$_2$, and Mn(OAc)$_3$ were able to oxidize indoline 137 into indole 138, albeit with incomplete conversion in low yields. Different conditions such as solvents, temperatures, and mixtures of these oxidizing agents didn’t produce a yield above 40%. After trying these oxidations conditions we surmised that the N-protected indoline 137 was too electron poor to undergo a facile oxidation reaction. The next strategy that we attempted to employ was removal of the protecting group first, followed by oxidation.

We found that we were able to deprotect the p-toluenesulfonyl group with magnesium in methanol to yield the free indoline in an 85% yield (Scheme 2.25). Treatment of the indoline with a Swern oxidation oxidized both the alcohol to an aldehyde, and the indoline to an indole. A subsequent protection of aldehyde the as an acetal gave us 139 in reasonable yields. We found that the magnesium in methanol reduction did not reduce the N-O bond which turned out to be crucial to the success of this route because we found that the undesired diastereomer could be separated from 139.
only when the N-O bond remained intact.

Scheme 2.25: Second generation synthesis of indole 134

Based on NMR spectrum analysis of the purified undesired diastereomer we reasoned that it was 141 which was an epimer about the acetal sidechain (Figure 2.4). We did not observe coupling between H_b and H_c in a COSY spectrum of 141, and 134. When we modeled the dihedral angles between these hydrogens we saw that it was close to 80° which according to the Karplus equation would result in a coupling constant close to 0 Hz due to poor orbital overlap. In addition, 1D NOESY data backs up our assignment because in 141 H_a does not couple to H_c due to their distance apart in space, while we do observe coupling between H_a and H_c in 134. When we modeled the isoxazolidine system where H_b and H_c are trans to each other, we noticed that the dihedral angle was close to 50° which would allow for a significant coupling constant. Based on these observations we concluded that the undesired diastereomer could not have H_b and H_c in a trans relationship. We speculated that the six membered ring conformation of 136 can undergo a chair flip which would give rise to the undesired
diastereomer 141. We hypothesized that 134 is the major product because both substituents are equatorial, while in 141 the side chain is axial.

**Figure 2.4:** Diastereomers produced in this reaction, and their respective conformations

The final step of this sequence was an SmI₂ reduction which worked smoothly to yield acetal 134 in much higher yields than our first route. Using this fourth-generation route we were able to prepare 2.77 g of 134 in a single run (Figure 2.5). Using acetal 134 we were then able to investigate the end-game of our synthesis plan.

**Figure 2.5:** Flask containing acetal 134
2.4 Exploring cyclization chemistry of acetal 134

2.4.1 Reagent Screening for the Pictet-Spengler Reaction

Our next goal was to transform acetal 134 into the natural product koumidine which we thought could be accomplished by a Pictet Spengler reaction (Scheme 2.26). We knew that this reaction could be a bit of a challenge because intermediate 142 is a bridgehead iminium ion which violates Brett’s rule. If we could form 142 as an intermediate, then the subsequent alkyl shift to yield 144 and elimination to yield koumidine should proceed smoothly. We thought the existence of high energy intermediate 142 could be plausible therefore we screened reaction conditions hoping to find a way to make the Pictet Spengler reaction work.

Scheme 2.26: Mechanism of the Pictet Spengler reaction

A qualitative NMR reaction screening was undertaken of different conditions to develop a method to prepare koumidine (Table 2.2). From the screening, we produced three different compounds (Figure 2.6) in varying purity. The reactions were either conducted in NMR tubes, or transferred directly into NMR tubes following the reaction.

Table 2.2: Pictet-Spengler reagent screening for the synthesis of koumidine

<table>
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<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TFA, CD$_3$CN, 110 °C, 10 minutes, microwave reactor</td>
<td>No Reaction</td>
</tr>
<tr>
<td>2</td>
<td>TFA, H$_2$O, CD$_3$CN, 110 °C, 1 hour</td>
<td>145</td>
</tr>
<tr>
<td>3</td>
<td>(R)-DTBM-Segphos, [Ir(coe)Cl]$_2$, Toluene-$d_8$, 100 °C</td>
<td>Decomposition</td>
</tr>
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</table>
Figure 2.6: Structures obtained during reaction screening

Most of the reactions produced enamine 145, hemiaminal 146, or decomposition. We found that BF$_3$•OEt$_2$ unexpectedly produced the ring closed product 147. This was an exciting result because 147 only requires the methylation of the nitrogen atom to be transformed into the natural product (19Z)-taberpsychine which is also a component of
Gelsemium. We hypothesized that 147 is formed from a Friedel-Crafts type alkylation of the indole by cyclic oxonium ion 148 (Scheme 2.27).

Scheme 2.27: Mechanism of Friedel-Crafts reaction with cyclic oxonium ion 148

We surmised that BF$_3$•OEt$_2$ was probably coordinating to the nitrogen as well as the alcohol, facilitating the formation of the cyclic carboxonium ion, while preventing the nitrogen from participating in the reaction. We were able to obtain the ring closed product 147 as a single diastereomer in an isolated 64% yield on a 160 mg scale. In an attempt to use this methodology to synthesize koumidine, we tried to protect the primary alcohol in 134, followed by treatment with BF$_3$•OEt$_2$ (Scheme 2.28).

Scheme 2.28: Attempted synthesis of koumidine using TBDMS protected 134

Unfortunately, we only obtained a low yield of ring closed product 147 because under these conditions the TBDMSO group seemed to undergo a slow deprotection reaction. To finish off the synthesis we performed a reductive amination reaction using formaldehyde and sodium cyanoborohydride in methanol which gave us the natural product (19Z)-taberpsychine in a 73% yield (Scheme 2.29). The characterization matched
the literature, providing very strong evidence that we made the natural product with the correct diastereoselectivity.\textsuperscript{75}

Scheme 2.29: Final steps of the total synthesis of (19Z)-taberpsychine (15)

With the natural product in hand, we compared it with the literature spectra. The literature didn’t report several of the proton signals in the natural product, probably because they were using a 270 MHz spectrometer, while we were using a 600 MHz spectrometer. Multiplets that were clear in our spectra may not have been clear in their spectra. The information that they did report is in excellent agreement with our spectra (Table 2.3) leading us to conclude that we had successfully synthesized (19Z)-taberpsychine in 11 steps from commercially available starting materials. We obtained an ideality of 45\% and an overall yield of 2.2\%.

Figure 2.7: (19Z)-taberpsychine number scheme

Table 2.3: NMR Spectrum Comparison of synthetic (19Z)-taberpsychine to natural (19Z)-taberpsychine
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<td>–</td>
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<td>7.32 (dt, $J = 8.1, 0.9$ Hz)</td>
</tr>
<tr>
<td>13</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>14α</td>
<td>2.43 (dt, $J = 14.3, 9.8$ Hz)</td>
<td>2.43 (dt, $J = 14.4, 9.7$ Hz)</td>
</tr>
<tr>
<td>14β</td>
<td>2.12 (ddd, $J = 14.2, 10.7, 1.2$ Hz)</td>
<td>2.12 (ddd, $J = 14.4, 10.7, 1.4$ Hz)</td>
</tr>
<tr>
<td>15</td>
<td>2.82 (br td, $J = 10.0, 6.0$ Hz)</td>
<td>2.83 (td, $J = 10.0, 5.5$ Hz)</td>
</tr>
<tr>
<td>16</td>
<td>unreported</td>
<td>2.54 (dt, $J = 9.2, 4.4$ Hz)</td>
</tr>
<tr>
<td>17α</td>
<td>3.84 (ddd, $J = 11.6, 10.1$ Hz)</td>
<td>3.84 (dd, $J = 11.5, 10.3$ Hz)</td>
</tr>
<tr>
<td>17β</td>
<td>3.26 (d, $J = 11.6$ Hz)</td>
<td>3.26 (dd, $J = 11.5, 2.1$ Hz)</td>
</tr>
<tr>
<td>18</td>
<td>1.61 (br d, $J = 6.7$ Hz, 3H)</td>
<td>1.61 (dd, $J = 6.7, 1.4$ Hz, 3H)</td>
</tr>
<tr>
<td>19</td>
<td>5.43 (br q, $J = 6.7$ Hz)</td>
<td>5.42 (br q, $J = 6.8$ Hz)</td>
</tr>
<tr>
<td>20</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>21α</td>
<td>unreported</td>
<td>3.39 (d, $J = 14.9$ Hz)</td>
</tr>
<tr>
<td>21β</td>
<td>unreported</td>
<td>3.34 (d, $J = 14.9$ Hz)</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Position</th>
<th>$^{13}$C NMR Spectrum (δ) Natural Sample (67.8 MHz, CDCl$_3$)</th>
<th>$^{13}$C NMR Spectrum Synthetic Sample (151 MHz, CDCl$_3$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>136.2</td>
<td>136.4</td>
</tr>
<tr>
<td>3</td>
<td>67.6</td>
<td>67.8</td>
</tr>
<tr>
<td>4</td>
<td>43.0</td>
<td>43.2</td>
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<td>60.5</td>
<td>60.7</td>
</tr>
<tr>
<td>6</td>
<td>18.0</td>
<td>18.2</td>
</tr>
<tr>
<td>7</td>
<td>110.9</td>
<td>111.1</td>
</tr>
<tr>
<td>8</td>
<td>128.3</td>
<td>128.5</td>
</tr>
</tbody>
</table>
2.5 Serendipitous discovery of a synthesis for isodihydrokoumine

2.5.1 Koumidine reaction conditions screening

With structure 147 we wanted to try to find conditions that could activate the ether bond allowing the secondary amine to perform a substitution reaction that could yield koumidine. We screened several conditions in an attempt to get this reaction to work (Table 2.4).

Table 2.4: Reaction conditions screening to synthesize koumidine from 147

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AlCl₃, CD₃CN, 21 °C, 12 h</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>Sc(OTf)₃, D₂O, 21 °C, 12 h</td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
<td>TMSCl, NaI, CD₃CN, 21 °C, 0.5 h</td>
<td>150</td>
</tr>
<tr>
<td>4</td>
<td>p-TsOH•H₂O, D₂O, 21 °C, 12 h</td>
<td>No reaction</td>
</tr>
<tr>
<td>5</td>
<td>MgBr₂, D₂O, 21 °C, 12 h</td>
<td>No reaction</td>
</tr>
<tr>
<td>6</td>
<td>BBr₃, CD₃CN, 21 °C, 2 h</td>
<td>Decomposition</td>
</tr>
<tr>
<td>7</td>
<td>PPTS, DMSO-de, D₂O, 21 °C, 12 h</td>
<td>No reaction</td>
</tr>
<tr>
<td>8</td>
<td>BF₃•OEt₂, D₂O, 21 °C, 12 h</td>
<td>No reaction</td>
</tr>
<tr>
<td>9</td>
<td>ZnCl₂, CD₃CN, 21 °C, 12 h</td>
<td>No reaction</td>
</tr>
<tr>
<td>10</td>
<td>CD₃CO₂D, 21 °C, 12 h</td>
<td>No reaction</td>
</tr>
</tbody>
</table>
We found that all but one of the conditions that we tried yielded a product; however, upon isolation and purification it turned out to be the core of isodihydrokoumine (150), and not koumidine (Scheme 2.30). This discovery was completely serendipitous, but we were very excited by it.

Scheme 2.30: Accidental discovery of a synthesis of the core of isodihydrokoumine

We are still not quite sure exactly what mechanism this reaction proceeds by, but we have hypothesized that it might occur by a Conia-Ene type mechanism (Scheme 2.31).
Scheme 2.31: Proposed mechanism for the transformation of 147 into 150

We think the mechanism proceeds where the alkene is protonated by the indole N-H, and resulting charge on the indole forms a bond to C20. We are unsure what the role of TMSI is in this mechanism. During our screening of Lewis acids, we attempted to use a variety of different additives to ensure that the reaction was not mediated by HI, I₂, or any other source of acid. We were surprised to find that this reaction works well in the presence of base, and I₂ scavengers to yield the desired product. In addition, TMSCl, and TMSOTf do not facilitate this reaction. We wondered if this was a general reaction, and synthesized a test substrate to see if the reactivity was the same in a simpler system (Scheme 2.32).

Scheme 2.32: Synthesis and testing of model substrate 152

We first performed a reductive amination on tryptamine with crotonaldehyde to yield 152. We treated 152 with NaI, and TMSCl in CH₃CN which unfortunately just led to us isolating starting material. Based on this observation we hypothesized that the alkene is pre-arranged in 147 to have excellent orbital overlap with the indole. With some optimization this reaction might be able to work, but we have not pursued this chemistry any further to date.

At this point we wondered if we could transform acetal 134 in isodihydrokoumine, instead of going through des-N₄-methyl-(19Z)-taberpsychine (147). We decided to screen additional Lewis acids as well as the TMSCl/NaI reaction to see if we could unearth any new chemistry (Table 2.5).
We found that the TMSCl/NaI reaction worked to transform acetal 134 directly into des-N4-methylisodihydrokoumine 150 using a single set of reagents. Unlike the reaction of des-N4-methyl-(19Z)-taberspsychine 147 with TMSCl/NaI, we noted several differences when using acetal 134. When we tried to run the reaction with base present, the yields were significantly reduced. In addition, we found that the reaction gave the highest yield (52%) after running it for 8 hours. If we allowed the reaction to run for 18 hours the yields slowly started to decrease. Based on these results we found that the optimal conditions were 21 °C for around 8 hours. We speculated the TMSI mediated the same cyclization chemistry as BF3•OEt2, followed by the Conia-Ene type reaction.

### Table 2.5: Additional Lewis acid screening on acetal 134

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BF3•OEt2, CD3OD, 21 °C, 12 h</td>
<td>146</td>
</tr>
<tr>
<td>2</td>
<td>BBr3, CD3CN, 21 °C, 10 minutes</td>
<td>Decomposition</td>
</tr>
<tr>
<td>3</td>
<td>BBr3, pyridine, CD3CN, 21 °C, 10 minutes</td>
<td>Decomposition</td>
</tr>
<tr>
<td>4</td>
<td>BF3•OEt2, TMSCl, NaI, CD3CN</td>
<td>Decomposition</td>
</tr>
<tr>
<td>5</td>
<td>TiCl4, CD3CN</td>
<td>145</td>
</tr>
<tr>
<td>6</td>
<td>BF3•OEt2, CDCl3, 21 °C, 10 minutes</td>
<td>Decomposition</td>
</tr>
<tr>
<td>7</td>
<td>NaI, TMSCl, CD3CN, 21 °C, 2 h</td>
<td>150</td>
</tr>
<tr>
<td>8</td>
<td>NaI, TMSCl, Cs2CO3, CD3CN, 21 °C, 0.5 h</td>
<td>150 (41% yield)</td>
</tr>
<tr>
<td>9</td>
<td>NaI, TMSCl, CH3CN 21 °C, 0.5 h</td>
<td>150 (10% yield)</td>
</tr>
<tr>
<td>10</td>
<td>NaI, TMSCl, CH3CN 0 °C, 1.5 h</td>
<td>No reaction</td>
</tr>
<tr>
<td>11</td>
<td>NaI, TMSCl, CH3CN 0 °C (1 h) to 21 °C (1 h)</td>
<td>150 (13% yield)</td>
</tr>
<tr>
<td>12</td>
<td>NaI, TMSCl, CH3CN -5 °C, 36 h</td>
<td>150 (15% yield)</td>
</tr>
<tr>
<td>13</td>
<td>LiI, TMSCl, CDCl3, 21 °C, 0.5 h</td>
<td>Decomposition</td>
</tr>
<tr>
<td>14</td>
<td>NaI, TMSCl, CH3CN 0 °C (1 h) to 21 °C (1 h)</td>
<td>150 (13% yield)</td>
</tr>
<tr>
<td>15</td>
<td>NaI, TMSCl, CH3CN 40 °C, 0.5 h</td>
<td>150 (27% yield)</td>
</tr>
<tr>
<td>16</td>
<td>NaI, TMSCl, Cs2CO3, CH3CN, 21 °C, 12 h</td>
<td>150 (1% yield)</td>
</tr>
<tr>
<td>17</td>
<td>TMSBr, CH3CN, 21 °C, 3 h</td>
<td>150 (10% yield)</td>
</tr>
<tr>
<td>18</td>
<td>TMSI, BF3•OEt2, CH3CN, 21 °C, 10 minutes</td>
<td>Decomposition</td>
</tr>
<tr>
<td>19</td>
<td>NaI, TMSCl, 2,6-lutidine, CD3CN</td>
<td>No reaction</td>
</tr>
<tr>
<td>20</td>
<td>NaI, TMSCl, CH3CN, 21 °C, 8 h</td>
<td>150 (52% yield)</td>
</tr>
<tr>
<td>21</td>
<td>NaI, TMSCl, CH3CN, 21 °C, 18 h</td>
<td>150 (43% yield)a</td>
</tr>
</tbody>
</table>

*a performed on a 68 mg scale.*
2.5.2 Completion of isodihydrokoumine, and \((4R)\)-isodihydrokoumine \(N_4\)-oxide

Once we had established a method to produce des-\(N_4\)-methylisodihydrkoumine 150 we were successfully able to methylate the secondary amine to yield isodihydrokoumine (89) (Scheme 2.33).

Scheme 2.33: Completion of the synthesis of isodihydrokoumine, and isodihydrokoumine \(N_4\)-oxide

With isodihydrokoumine in hand we were able to oxidize the tertiary amine with \(m\)CPBA in excellent yields to give a 2:1 mixture of separable diastereomers 154 and 155. Unfortunately, the minor diastereomer 155 was a natural product, while the major diastereomer was not. Both isodihydrokoumine (Table 2.6), and \((4R)\)-isodihydrokoumine \(N_4\)-oxide (Table 2.7) matched the literature spectra providing very strong evidence that we had made both of these natural products. It took a total of 11 steps to synthesize isodihydrokoumine (45% ideal), and 12 steps to synthesize \((4R)\)-isodihydrokoumine \(N_4\)-oxide (50% ideal) from commercially available starting materials.

Figure 2.8: Isodihydrokoumine number scheme
**Table 2.6**: NMR Spectrum comparison of synthetic isodihydrokoumine to natural isodihydrokoumine

<table>
<thead>
<tr>
<th>Position</th>
<th>(^1\text{H NMR Spectrum Natural Sample (400 MHz, CDCl}_3)(^{76})</th>
<th>(^1\text{H NMR Spectrum Synthetic Sample (600 MHz, CDCl}_3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>4.97 (t, (J = 3.0) Hz)</td>
<td>4.99 (ddd, (J = 3.6, 2.4, 1.1) Hz)</td>
</tr>
<tr>
<td>4</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>2.77-2.66 (m)</td>
<td>2.76-2.71 (m)</td>
</tr>
<tr>
<td>6(\alpha)</td>
<td>2.38 (d, (J = 14.3) Hz)</td>
<td>2.40 (dt, (J = 14.4, 1.9) Hz)</td>
</tr>
<tr>
<td>6(\beta)</td>
<td>2.30 (dd, (J = 14.3, 3.2) Hz)</td>
<td>2.32 (dd, (J = 14.3, 3.2) Hz)</td>
</tr>
<tr>
<td>7</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>8</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>9</td>
<td>7.57 (d, (J = 7.7) Hz)</td>
<td>7.60 (dt, (J = 7.7, 0.8) Hz)</td>
</tr>
<tr>
<td>10</td>
<td>7.32 (t, (J = 7.5) Hz)</td>
<td>7.34 (td, (J = 7.6, 1.2) Hz)</td>
</tr>
<tr>
<td>11</td>
<td>7.21 (t, (J = 7.5) Hz)</td>
<td>7.24 (td, (J = 7.5, 1.1) Hz)</td>
</tr>
<tr>
<td>12</td>
<td>7.54 (d, (J = 7.4) Hz)</td>
<td>7.57 (dt, (J = 7.4, 0.9) Hz)</td>
</tr>
<tr>
<td>13</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>14(\alpha)</td>
<td>1.60 (dt, (J = 14.7, 2.3) Hz)</td>
<td>1.63 (dt, (J = 14.6, 2.3) Hz)</td>
</tr>
<tr>
<td>14(\beta)</td>
<td>2.59 (dt, (J = 15.2, 4.1) Hz)</td>
<td>2.62 (14.6, 3.8 Hz)</td>
</tr>
<tr>
<td>15</td>
<td>2.34-2.25 (m)</td>
<td>2.35-2.30 (m)</td>
</tr>
<tr>
<td>16</td>
<td>2.77-2.66 (m)</td>
<td>2.76-2.71 (m)</td>
</tr>
<tr>
<td>17(\alpha)</td>
<td>3.58 (d, (J = 12.0) Hz)</td>
<td>3.61 (d, (J = 11.9) Hz)</td>
</tr>
<tr>
<td>17(\beta)</td>
<td>4.22 (dd, (J = 11.9, 4.2) Hz)</td>
<td>4.25 (11.9, 4.4 Hz)</td>
</tr>
<tr>
<td>18</td>
<td>0.51 (t, (J = 7.2) Hz, 3H)</td>
<td>0.53 (t, (J = 7.4) Hz, 3H)</td>
</tr>
<tr>
<td>19</td>
<td>0.48-0.29 (m, 2H)</td>
<td>0.48-0.35 (m, 2H)</td>
</tr>
<tr>
<td>20</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>21(\alpha)</td>
<td>3.07 (d, (J = 11.3) Hz)</td>
<td>3.09 (d, (J = 11.3) Hz)</td>
</tr>
<tr>
<td>21(\beta)</td>
<td>2.85 (d, (J = 11.3) Hz)</td>
<td>2.87 (d, (J = 11.3) Hz)</td>
</tr>
<tr>
<td>22</td>
<td>2.55 (s, 3H)</td>
<td>2.58 (s, 3H)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Position</th>
<th>(^{13}\text{C NMR Spectrum (δ) Natural Sample (101 MHz, CDCl}_3)</th>
<th>(^{13}\text{C NMR Spectrum (δ) Synthetic Sample (151 MHz, CDCl}_3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>185.7</td>
<td>185.7</td>
</tr>
<tr>
<td>3</td>
<td>71.0</td>
<td>71.1</td>
</tr>
<tr>
<td>4</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Position</td>
<td>(^{1}H) NMR Spectrum (δ) Natural Sample (500 MHz, CD(_3)OD)</td>
<td>(^{1}H) NMR Spectrum (δ) Synthetic Sample (600 MHz, CD(_3)OD)</td>
</tr>
<tr>
<td>----------</td>
<td>---------------------------------------------------------------</td>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>1</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>4.94 (m,)</td>
<td>4.94 (ddd, (J = 3.5, 2.3, 1.0) Hz)</td>
</tr>
<tr>
<td>4</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

**Figure 2.9:** (4R)-isodihydrokoumine \(N_4\)-oxide number scheme

**Table 2.7:** Literature comparison of (4R)-isodihydrokoumine \(N_4\)-oxide
<table>
<thead>
<tr>
<th>Position</th>
<th>13C NMR Spectrum (δ) Natural Sample (125 MHz, CD$_3$OD)</th>
<th>13C NMR Spectrum (δ) Synthetic Sample (151 MHz, CD$_3$OD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>186.5</td>
<td>186.5</td>
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<tr>
<td>3</td>
<td>71.5</td>
<td>71.6</td>
</tr>
<tr>
<td>4</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>73.1</td>
<td>73.1</td>
</tr>
<tr>
<td>6</td>
<td>27.6</td>
<td>27.8</td>
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<td>58.0</td>
<td>58.1</td>
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<td>143.2</td>
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<td>124.9</td>
<td>124.9</td>
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<tr>
<td>10</td>
<td>127.9</td>
<td>127.9</td>
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<td>121.9</td>
</tr>
<tr>
<td>13</td>
<td>155.1</td>
<td>155.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>3.51 (m, 1H)</th>
<th>3.53-3.47 (m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6α</td>
<td>2.49 (dd, $J = 15.5$, 3.9 Hz)</td>
<td>2.48 (dd, $J = 15.4$, 3.9 Hz)</td>
</tr>
<tr>
<td>6β</td>
<td>3.49 (m)</td>
<td>3.53-3.47 (m)</td>
</tr>
<tr>
<td>7</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>8</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>9</td>
<td>7.70 (d, $J = 7.6$ Hz)</td>
<td>7.70 (d, $J = 7.5$ Hz)</td>
</tr>
<tr>
<td>10</td>
<td>7.36 (t, $J = 7.6$ Hz)</td>
<td>7.35 (td, $J = 7.5$, 1.2 Hz)</td>
</tr>
<tr>
<td>11</td>
<td>7.42 (t, $J = 7.6$ Hz)</td>
<td>7.42 (td, $J = 7.6$, 1.3 Hz)</td>
</tr>
<tr>
<td>12</td>
<td>7.57 (d, $J = 7.6$ Hz)</td>
<td>7.56 (d, $J = 7.5$ Hz)</td>
</tr>
<tr>
<td>13</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>14α</td>
<td>1.70 (m)</td>
<td>1.70 (dt, $J = 15.3$, 1.8 Hz)</td>
</tr>
<tr>
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<td>2.79 (dt, $J = 15.1$, 3.8 Hz)</td>
<td>2.78 (dt, $J = 15.1$, 3.8 Hz)</td>
</tr>
<tr>
<td>15</td>
<td>2.40 (m, 1H)</td>
<td>2.40 (dt, $J = 12.2$, 3.2 Hz)</td>
</tr>
<tr>
<td>16</td>
<td>3.09 (m, 1H)</td>
<td>3.09 (dt, $J = 12.2$, 4.1 Hz)</td>
</tr>
<tr>
<td>17α</td>
<td>3.72 (d, $J = 12.3$ Hz)</td>
<td>3.72 (d, $J = 12.4$ Hz)</td>
</tr>
<tr>
<td>17β</td>
<td>4.37 (dd, $J = 12.3$, 3.8 Hz)</td>
<td>4.37 (dd, $J = 12.4$, 5.0 Hz)</td>
</tr>
<tr>
<td>18</td>
<td>0.58 (t, $J = 7.5$ Hz, 3H)</td>
<td>0.58 (t, $J = 7.4$ Hz, 3H)</td>
</tr>
<tr>
<td>19</td>
<td>0.48 (q, $J = 7.5$ Hz, 2H)</td>
<td>0.50-0.44 (m, 2H)</td>
</tr>
<tr>
<td>20</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>21α</td>
<td>3.86 (d, $J = 13.8$ Hz)</td>
<td>3.87 (d, $J = 13.8$ Hz)</td>
</tr>
<tr>
<td>21β</td>
<td>3.82 (d, $J = 13.8$ Hz)</td>
<td>3.82 (d, $J = 13.8$ Hz)</td>
</tr>
<tr>
<td>22</td>
<td>3.42 (s, 3H)</td>
<td>3.42 (s, 3H)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Position</th>
<th>13C NMR Spectrum (δ) Natural Sample (125 MHz, CD$_3$OD)</th>
<th>13C NMR Spectrum (δ) Synthetic Sample (151 MHz, CD$_3$OD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>186.5</td>
<td>186.5</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>71.5</td>
<td>71.6</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>73.1</td>
<td>73.1</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>27.6</td>
<td>27.8</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>58.0</td>
<td>58.1</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>143.2</td>
<td>143.2</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>124.9</td>
<td>124.9</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>127.9</td>
<td>127.9</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>129.8</td>
<td>129.8</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>121.9</td>
<td>121.9</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>155.1</td>
<td>155.1</td>
<td></td>
</tr>
</tbody>
</table>
2.6 Synthesis of aldehydes for the nitrone cycloaddition reaction

During this project we needed several different aldehydes to condense with our hydroxylamine to prepare the nitrones needed for our cycloaddition chemistry. We found that the only aldehyde that had been reported in the literature was \textsuperscript{82}. Beyond aldehyde \textsuperscript{82} we needed to synthesize the \textsuperscript{125, 130, 135}. Some of the aldehyde syntheses that we undertook were modifications of chemistry reported in the literature, while some chemistry had to be invented to allow us to prepare these aldehydes, or aldehyde surrogates.

2.6.1 Attempted synthesis of nitrone \textsuperscript{127} for the second generation nitrone cycloaddition

The first aldehyde that we had to invent a synthesis for was aldehyde \textsuperscript{125} because it has not yet been reported in the literature. Initially we prepared oxindole \textsuperscript{158} which had been reported in the literature (Scheme 2.34).\textsuperscript{77}

\begin{center}
\begin{tabular}{|c|c|c|}
\hline
14 & 24.6 & 24.7 \\
15 & 26.6 & 26.6 \\
16 & 35.9 & 35.9 \\
17 & 61.0 & 61.0 \\
18 & 6.7 & 6.7 \\
19 & 22.2 & 22.2 \\
20 & 45.1 & 45.1 \\
21 & 73.9 & 73.9 \\
22 & 60.0 & 60.1 \\
\hline
\end{tabular}
\end{center}

\textbf{Scheme 2.34}: Synthesis of oxindole \textsuperscript{158}
From this oxindole we thought we could alkylate the alpha position with 2-bromoacetaldehyde diethylacetal to yield 159 (Scheme 2.35).

Scheme 2.35: Attempted alkylation of oxindole 158

Unfortunately, we were unable to get this reaction to work. We surmised that no reaction took place due to the poor reactivity of oxindole enolates. We decided to try to use a masked aldehyde in the form of a cyclopropanol. This led to the development of the synthesis of cyclopropane 124 through a one-pot diazo transfer, and then rhodium catalyzed cyclopropanation (Scheme 2.36).78,79

Scheme 2.36: Synthesis of cyclopropane 124

Table 2.8: Optimization of cyclopropane 124 synthesis on a 20 mg scale

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>TsN3 Eq.</th>
<th>DBU Eq.</th>
<th>Catalyst</th>
<th>Loading</th>
<th>Solvent</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>21</td>
<td>3</td>
<td>1.1</td>
<td>1.2</td>
<td>Rh2(esp)2</td>
<td>0.2 mol%</td>
<td>vinyl acetate</td>
<td>32%</td>
</tr>
<tr>
<td>2</td>
<td>21</td>
<td>0.5</td>
<td>1.3</td>
<td>1.3</td>
<td>Rh2(esp)2</td>
<td>5 mol%</td>
<td>vinyl acetate</td>
<td>29%</td>
</tr>
<tr>
<td>3</td>
<td>21</td>
<td>6</td>
<td>1.3</td>
<td>1.3</td>
<td>Rh2(OAc)4</td>
<td>5 mol%</td>
<td>vinyl acetate</td>
<td>16%</td>
</tr>
<tr>
<td>4</td>
<td>21</td>
<td>6</td>
<td>1.2</td>
<td>1.2</td>
<td>Rh2(esp)2</td>
<td>1 mol%</td>
<td>vinyl acetate</td>
<td>7%</td>
</tr>
<tr>
<td>5</td>
<td>21</td>
<td>0.5</td>
<td>1.2</td>
<td>1.2</td>
<td>Rh2(esp)2</td>
<td>1 mol%</td>
<td>3:1 ACN:VA</td>
<td>1%</td>
</tr>
<tr>
<td>6</td>
<td>21</td>
<td>0.25</td>
<td>10</td>
<td>10</td>
<td>Rh2(esp)2</td>
<td>1 mol%</td>
<td>vinyl acetate</td>
<td>51%</td>
</tr>
<tr>
<td>7</td>
<td>21</td>
<td>6</td>
<td>10</td>
<td>10</td>
<td>[Cp*IrCl]2</td>
<td>1 mol%</td>
<td>vinyl acetate</td>
<td>50%a</td>
</tr>
<tr>
<td>8</td>
<td>21</td>
<td>6</td>
<td>1.3</td>
<td>1.3</td>
<td>Cu(OTf)2-C6H6</td>
<td>5 mol%</td>
<td>vinyl acetate</td>
<td>51%a</td>
</tr>
</tbody>
</table>

a diazoamide 160 was obtained instead of cyclopropane 124
Table 2.9: Optimization of cyclopropane 124 synthesis on a 100 mg scale

<table>
<thead>
<tr>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>TsN3 Eq.</th>
<th>DBU Eq.</th>
<th>Catalyst</th>
<th>Loading</th>
<th>Solvent</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>21</td>
<td>0.5</td>
<td>8</td>
<td>4</td>
<td>Rh2.esp2</td>
<td>0.5 mol%</td>
<td>vinyl acetate</td>
<td>35%</td>
</tr>
<tr>
<td>0</td>
<td>0.5</td>
<td>10</td>
<td>10</td>
<td>Rh2.esp2</td>
<td>0.5 mol%</td>
<td>vinyl acetate</td>
<td>82%</td>
</tr>
</tbody>
</table>

Table 2.10: Optimization of cyclopropane 124 synthesis on a 400 mg scale

<table>
<thead>
<tr>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>TsN3 Eq.</th>
<th>DBU Eq.</th>
<th>Catalyst</th>
<th>Loading</th>
<th>Solvent</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.5</td>
<td>10a</td>
<td>10</td>
<td>Rh2.esp2</td>
<td>0.5 mol%</td>
<td>vinyl acetate</td>
<td>45%</td>
</tr>
<tr>
<td>0</td>
<td>0.5</td>
<td>5b</td>
<td>3</td>
<td>Rh2.esp2</td>
<td>0.5 mol%</td>
<td>vinyl acetate</td>
<td>75%</td>
</tr>
<tr>
<td>0</td>
<td>0.5</td>
<td>5c</td>
<td>3</td>
<td>Rh2.esp2</td>
<td>0.5 mol%</td>
<td>vinyl acetate</td>
<td>68%</td>
</tr>
<tr>
<td>0</td>
<td>0.5</td>
<td>5d</td>
<td>3</td>
<td>Rh2.esp2</td>
<td>0.5 mol%</td>
<td>vinyl acetate</td>
<td>40%</td>
</tr>
</tbody>
</table>

a 30 second addition time of TsN3 by hand
b 5 minute addition time of TsN3 from a syringe pump
c 10 minute addition time of TsN3 from a syringe pump
d 30 minute addition time of TsN3 from a syringe pump

This reaction took several optimization trials in order to achieve decent yields (Table 2.8; Table 2.9; Table 2.10). We found that the best result was when all the reagents were added except the tosyl azide, and were cooled to 0 °C. The addition of tosyl azide was found to give the highest, and most reproducible yields when added over 5 minutes by a syringe pump. We noticed that when we attempted to use iridium, or copper based catalysts we isolated diazoamide 160 instead of cyclopropane 124 (entry 7,8; Table 2.8), (Scheme 2.37).

Scheme 2.37: Isolation of diazoamide 160 when using copper or iridium catalysts

We were able to scale the cyclopropanation chemistry up to a 1.2 g scale using the 5 minute addition of tosyl azide, that resulted in a 74% yield of cyclopropane 124. With a
robust supply of cyclopropane 124 we wanted to synthesize aldehyde 125. Initial attempts to synthesize aldehyde 125 by hydrolysis of cyclopropane 124 resulted in a complex mixture of products (Scheme 2.38).

![Scheme 2.38: Attempted synthesis of aldehyde 125](image)

We were unsure if aldehyde 125 was stable to isolation, so we attempted to use the same trick that we tried when we were trying to deprotect hydroxylamine 94. Our goal was to try to react a hydroxylamine with cyclopropane 124 in hopes that it would directly open the cyclopropane to generate a nitro, or that it might react fast enough with the intermediate aldehyde 125 to trap it as a nitro. We screened conditions that we thought could open the cyclopropane slowly or activate it towards nucleophilic attack through coordination to a Lewis acid (Table 2.11).
Table 2.11: Synthesis of nitrone 161 optimization

<table>
<thead>
<tr>
<th>Entry</th>
<th>Hydroxylamine</th>
<th>Solvent</th>
<th>Additive(s)</th>
<th>Time</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph₂CH₂NHOH</td>
<td>Toluene</td>
<td>3Å MS</td>
<td>12 h</td>
<td>7%</td>
</tr>
<tr>
<td>2</td>
<td>Ph₂CH₂NHOH</td>
<td>DCM</td>
<td>Et₃NH⁺ TFA⁻</td>
<td>15 h</td>
<td>0%</td>
</tr>
<tr>
<td>3</td>
<td>Ph₂CH₂NHOH</td>
<td>DCM</td>
<td>ZnCl₂</td>
<td>15 h</td>
<td>0%</td>
</tr>
<tr>
<td>4</td>
<td>Ph₂CH₂NHOH</td>
<td>DCM</td>
<td>Yb(OTf)₃</td>
<td>15 h</td>
<td>0%</td>
</tr>
<tr>
<td>5</td>
<td>Ph₂CH₂NHOH</td>
<td>DCM</td>
<td>Sc(OTf)₃</td>
<td>48 h</td>
<td>0%</td>
</tr>
<tr>
<td>6</td>
<td>Ph₂CH₂NHOH</td>
<td>DCM</td>
<td>TFA</td>
<td>48 h</td>
<td>0%</td>
</tr>
<tr>
<td>7</td>
<td>Ph₂CH₂NHOH</td>
<td>DCM</td>
<td>MgI₂, Et₃N</td>
<td>24 h</td>
<td>0%</td>
</tr>
<tr>
<td>8</td>
<td>Ph₂CH₂NHOH</td>
<td>DCM</td>
<td>MgI₂</td>
<td>72 h</td>
<td>53%</td>
</tr>
<tr>
<td>9</td>
<td>Ph₂CH₂NHOH•TFA</td>
<td>DCM</td>
<td>MgI₂, pyridine</td>
<td>96 h</td>
<td>11%</td>
</tr>
<tr>
<td>10</td>
<td>Ph₂CH₂NHOH•TFA</td>
<td>CHCl₃</td>
<td>CeCl₃•7H₂O</td>
<td>72 h</td>
<td>0%</td>
</tr>
<tr>
<td>11</td>
<td>Ph₂CH₂NHOH•TFA</td>
<td>HFIP</td>
<td>Et₃N</td>
<td>72 h</td>
<td>0%</td>
</tr>
<tr>
<td>12</td>
<td>Ph₂CH₂NHOH•TFA</td>
<td>MeOH</td>
<td>Na₂CO₃, Sc(OTf)₃, 3Å</td>
<td>12 h</td>
<td>80%</td>
</tr>
<tr>
<td>13</td>
<td>Ph₂CH₂NHOH•TFA</td>
<td>MeOH</td>
<td>n-BuLi,</td>
<td>0.5 h</td>
<td>18%</td>
</tr>
<tr>
<td>14</td>
<td>Ph₂CH₂NHOH•TFA</td>
<td>MeOH</td>
<td>TMSOK, 3Å MS,</td>
<td>1.5 h</td>
<td>41%</td>
</tr>
<tr>
<td>15</td>
<td>Ph₂CH₂NHOH-TFA</td>
<td>MeOH</td>
<td>Li₂CO₃, 3Å MS,</td>
<td>1.5 h</td>
<td>77%</td>
</tr>
<tr>
<td>16</td>
<td>Ph₂CH₂NHOH•TFA</td>
<td>MeOH</td>
<td>DBU, Sc(OTf)₃, 3Å</td>
<td>1.5 h</td>
<td>0%</td>
</tr>
<tr>
<td>17</td>
<td>Ph₂CH₂NHOH•TFA</td>
<td>CF₃CH₂O</td>
<td>Na₂CO₃, 3Å MS,</td>
<td>1.5 h</td>
<td>0%</td>
</tr>
<tr>
<td>18</td>
<td>Ph₂CH₂NHOH•TFA</td>
<td>MeOH</td>
<td>3Å MS, Sc(OTf)₃</td>
<td>7 h</td>
<td>35%</td>
</tr>
</tbody>
</table>
Scheme 2.39: Optimized model synthesis of nitrone 161

From our screening we were very excited to find that we could trap cyclopropane 124 as nitrone 161 in an 80% yield. The best conditions utilized a hydroxylamine in the presence of either sodium or lithium carbonate in methanol, along with 3Å MS. The Lewis acid that worked the best in this reaction was found to be Sc(OTf)3. As discussed in section 2.2.3 when we applied our optimized conditions to the substrate required for the total synthesis we were unable to isolate any nitrone, or cycloaddition product.

2.6.2 Synthesis of aldehyde 130 for the third generation nitroine cycloaddition

The third generation route towards our nitroine cycloaddition required the use of indole-3-acetaldehyde. We followed a literature procedure to synthesize indole-3-acetaldehyde80, and developed modifications of a literature procedure to synthesize p-toluenesulfonyl protected indole-3-acetaldehyde 130 (Scheme 2.40).81

Scheme 2.40: Synthesis of indole aldehyde 130

Starting from indole we were able to perform a palladium catalyzed allylation using allyl alcohol activated by triethylborane to regioselectively allylate only the C3 carbon, with undetectable amounts of nitrogen allylation.82 The reaction worked well on scale up from 150 mg up to 12 g to yield alkene 163. The next step of the sequence was installation of the tosyl protecting group on the indole nitrogen. This reaction worked smoothly in high yields, and the product could be purified by recrystallization to reliably
give 164. The terminal alkene in 164 was dihydroxylated using an Upjohn dihydroxylation reaction. The crude diol from this reaction only required a workup, and was directly subject to sodium periodate diol cleavage to yield aldehyde 130. This two-step reaction sequence was clean enough that the final aldehyde did not require additional purification. Several attempts were made to perform this reaction sequence in a single flask, which included taking alkene 164 and treating it with OsO₄ using sodium periodate as the stoichiometric oxidant. These attempts produced complicated mixtures of products which we hypothesized arose from oxidation of the indole C2-C3 alkene. In addition, treatment of the NMO/OsO₄ dihydroxylation reaction with NaIO₄ after the alkene had been completely consumed also led to the formation of significant side products. It has been reported that 2,6-lutidine can often increase the yields of these types of reactions by limiting by-product formation, but this did not help in our case.⁸³ The only method that yielded clean material was to treat the diol with NaIO₄ in the absence of OsO₄ in a two step process.

While this reaction produced aldehyde 130 reliably, it consumed a large quantity of Pd(PPh₃)_4 due to its high molecular weight (1155.59 g/mol) relative to indole (117.15 g/mol). This led to the use of 1 g of palladium catalyst for every 2 g of indole in the reaction. The sheer volume of palladium that was required for scaling this chemistry was not cost effective⁸⁴, so we sought an alternate method to prepare aldehyde 130 using chemistry that we could afford to run on a larger scale.

### 2.6.3 Second generation synthesis of aldehyde 130

The second approach that we wanted to investigate towards the synthesis of aldehyde 130 was through a pinacol rearrangement (Scheme 2.41).

![Scheme 2.41: Proposed pinacol rearrangement to synthesize aldehyde 130](image-url)
In order to synthesize diol 165 we followed a literature procedure. The first step of this process was the reaction of indole with ethyl oxalyl chloride (Scheme 2.42).

Scheme 2.42: Synthesis of diol 165

The reaction worked quite well, and the crude indole 166 was isolated by vacuum filtration. Next, 166 was protected with a p-toluenesulfonyl protecting group to yield 167 which could be purified by recrystallization. The last step of this sequence was a sodium borohydride reduction which worked in a nearly quantitative yield to yield diol 165. We started to screen acids that we hoped could make the pinacol rearrangement work (Table 2.12).

Table 2.12: Acid screening for the pinacol reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid</th>
<th>Equiv.</th>
<th>Temp (°C)</th>
<th>Solvent</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H₂SO₄</td>
<td>0.1</td>
<td>21</td>
<td>CD₃OD</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>H₃PO₄</td>
<td>0.1</td>
<td>21</td>
<td>CD₃OD</td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
<td>TFA</td>
<td>0.1</td>
<td>21</td>
<td>CD₃OD</td>
<td>No reaction</td>
</tr>
<tr>
<td>4</td>
<td>CD₃CO₂D</td>
<td>-</td>
<td>21</td>
<td>CD₃CO₂D</td>
<td>No reaction</td>
</tr>
<tr>
<td>5</td>
<td>p-TsOH</td>
<td>0.1</td>
<td>21</td>
<td>CD₃OD</td>
<td>No reaction</td>
</tr>
<tr>
<td>6</td>
<td>p-TsOH</td>
<td>0.1</td>
<td>21</td>
<td>CD₃CN</td>
<td>No reaction</td>
</tr>
<tr>
<td>7</td>
<td>BF₃•OEt₂</td>
<td>0.1</td>
<td>21</td>
<td>CD₃CN</td>
<td>Traces of aldehyde</td>
</tr>
<tr>
<td>8</td>
<td>TFA</td>
<td>0.1</td>
<td>21</td>
<td>CD₃CN</td>
<td>No reaction</td>
</tr>
<tr>
<td>9</td>
<td>BF₃•OEt₂</td>
<td>0.1</td>
<td>21</td>
<td>CD₃OD</td>
<td>No reaction</td>
</tr>
<tr>
<td>10</td>
<td>HCl</td>
<td>10</td>
<td>Reflux</td>
<td>MeOH</td>
<td>Acetal 168 (99%)</td>
</tr>
</tbody>
</table>

We found that acetal 168 was produced when we treated diol 165 with an excess of HCl in methanol which we generated by the addition of acetyl chloride to methanol (Scheme 2.43).
Scheme 2.43: Pinacol reaction and simultaneous acetal protection

We were able to hydrolyze the acetal into an aldehyde under several different conditions, with the cleanest conditions utilizing Amberlyst® 15 in acetone and water. Unfortunately when we attempted to scale this reaction up from 100 mg to several grams the reaction length became much longer, and the reaction produced a variety of by-products. We were concurrently trying to find new conditions for the palladium catalyzed allylation of indole as a potential solution to the quantity of palladium catalyst required. A rather simple experiment that we performed with surprising success was to lower the quantity of Pd(PPh₃)₄ in the reaction. We found that by lowering the loading of palladium from 5 mol% to 0.03 mol% the yields didn’t change while the reaction time only increased by 8 hours. With this knowledge we stopped research towards the pinacol rearrangement and used the lower loading of palladium in this reaction because the reaction was now cost effective (Scheme 2.44).

Scheme 2.44: Improved allylation of indole conditions

2.6.4 Synthesis of aldehyde 135 for the fourth generation nitrone cycloaddition

In the fourth and final generation of our nitrone cycloaddition chemistry we needed to synthesize tosyl protected indoline aldehyde 135. We decided to start with the same indole allylation chemistry as the third generation aldehyde synthesis. Following the allylation, we reduced the indole to an indoline using sodium cyanoborohydride in
acetic acid. Next, we protected the nitrogen with a \( p \)-toluenesulfonyl group, and lastly performed a Lemieux–Johnson oxidation to yield aldehyde 130 (Scheme 2.45).

![Scheme 2.45: Synthesis of indoline aldehyde 135]

While this sequence of reactions worked quite well, there was a small side product from the sodium cyanoborohydride reduction (169). We found that around 10-20 mol\% of the alkene was hydrogenated to yield 169 possibly due to the presence of traces of palladium from the allylation chemistry. We decided that this was not a huge issue because the alkane was readily removed once the aldehyde had been formed by column chromatography. Using this procedure we could make over 60 g of aldehyde 135 in a single reaction sequence.
Chapter 3

3 Conclusions

The primary goal of this project was to create an asymmetric divergent synthesis of several natural products from a single set of starting materials. Towards this goal we have successfully synthesized the natural products \((\pm)-(19Z)\)-Taberpsychine (11 steps, 45% ideal, 2.0% overall yield), \((\pm)\)-isodihydrokoumine (11 steps, 45% ideal, 1.1% overall yield), and \((\pm)-(4R)\)-isodihydrokoumine N\(_4\)-oxide (12 steps, 50% ideal, 0.4% overall yield) from commercially available starting materials. Key aspects of this route are the convergent synthesis of aldehyde 135 and protected hydroxylamine 94 which can be condensed together to allow for a [3+2] nitrone cycloaddition reaction. This key cycloaddition establishes three of the four stereocenters, and the majority of the carbon framework contained in several of the natural products for this route. The use of BF\(_3\)•OEt\(_2\) and TMSI allowed us to convert our general acetal intermediate 134 into the cores of both \((19Z)\)-taberpsychine (147), and isodihydrokoumine (150). Continuation of work towards the synthesis of several other natural products, along with the development of an asymmetric synthetic route are currently being developed in the lab.
Chapter 4

4 Future Work

4.1 Development of chemistry to prepare enantiopure lactone 85

A problem that remains from this synthetic work is that we don’t have a method to enantioselectively synthesize lactone 85. We are currently investigating chemistry to add a B(pin) group enantioselectively to generate boronate 171 (Scheme 4.1).86

![Scheme 4.1: New strategy to synthesize enantiopure lactone 85](image)

If we are able to enantioselectively install the boronate group, then a Zweifel olefination may be able to yield the desired lactone because Zweifel olefinations are stereospecific (Scheme 4.1).87

4.2 Other alkaloids from this synthetic route

Using our optimized synthesis of acetal 134, our plan is to branch out to form a variety of other alkaloids in this class (Figure 4.1). The use of a common intermediate for a divergent synthesis to prepare multiple different targets represents a much more impactful synthesis than one that can only produce a single target.

![Figure 4.1: Natural products that are current targets](image)
The main modification to our current route that would allow us to synthesize geleganidine B, and other natural products containing a 6-methoxy group on the indole would be to start with 6-methoxyindole (Scheme 4.2).

**Scheme 4.2:** Proposed route changes required to synthesize geleganidine B

6-Methoxyindole is commercially available and will be used in place of indole in our synthesis towards the creation of several of these oxindole alkaloids. 

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5 Experimental Information

General Experimental Details

Unless otherwise stated all reactions were conducted in oven dried (120 °C for minimum 2 hours) flasks that were cooled under either high vacuum (0.4 torr) or a stream of argon. Benzene (PhH), tetrahydrofuran (THF), dichloromethane (DCM), 1,4-dioxane, and acetonitrile (ACN) that had been previously degassed were dried by passage through activated alumina columns before use. NMR experiments were performed on either a Bruker AvIII 400, Varian Inova 400 or Inova 600 instrument and samples were obtained in CDCl₃ (referenced to 7.26 ppm for ¹H and 77.2 ppm for ¹³C), acetone-d₆ (referenced to 2.05 ppm for ¹H and 29.8 ppm for ¹³C), CD₂OD (referenced to 3.31 ppm for ¹H and 49.0 ppm for ¹³C), CD₃CN (referenced to 1.94 ppm for ¹H and 118.3 ppm for ¹³C). Coupling constants (J) are in Hz. NMR spectra are reported using the following abbreviations: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). The multiplicity abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. IR spectra were recorded on a PerkinElmer Spectrum Two FT-IR on NaCl plates, or on a Bruker Alpha II Platinum ATR spectrometer and are reported in frequency of absorption (cm⁻¹). High resolution mass spectra (HRMS) were obtained on a Thermo Scientific DFS mass spectrometer using electron impact ionization. Reaction progress was followed by thin layer chromatography (TLC) (Merck, TLC Silica gel 60 F254) visualizing with UV light (254 nm), and the plates were developed using basic KMnO₄ or acidic anisaldehyde. Flash column chromatography was performed using SiliaFlash® P60 40-63 μm silica gel or SiliaFlash® R60 20-45 μm silica gel purchased from Silicycle Chemical Division Inc. IR spectra were acquired using a PerkinElmer Spectrum Two FT-IR. Melting points were obtained on a Digimelt MPA160 melting point apparatus from Stanford Research Systems (SRS). (Z)-methyl 3-iodoacrylate is commercially available but was prepared via a literature procedure. Unless otherwise stated, chemicals and reagents were used as received. 2-butyn-1-ol, tri-n-butyltin hydride, copper (II) trifluoromethane sulfonate, DMPU, DIAD, Boc₂O, and triphenylphosphine were purchased from Oakwood chemicals.
Scheme 5.1: Complete Route Towards Acetal 134

Scheme 5.2: Preparation of dihydropyranone 86

This procedure was adapted from the work of Pour and co-workers. An oven dried 5 L flask containing a stir bar was equipped with a Claisen adapter, rubber septum, 1 L addition funnel, and a gas inlet adapter (Figure 5.1 A). All joints were greased while hot and the apparatus was cooled under high vacuum (0.4 torr). The system was backfilled with argon, and was charged with Pd(PPh₃)₄ (8.32 g, 7.20 mmol, 2 mol%) through a paper funnel (Figure 5.1 B). The system was evacuated and backfilled with argon three times, then an argon balloon was added to the Claisen adapter, and the vacuum adapter was replaced by a rubber septum (Figure 5.1 C). The flask was placed into an empty bucket and was charged with benzene (2 L) via cannula along with 2-butyn-1-ol (43 mL, 575 mmol, 1.6 eq). The addition funnel was charged with benzene (800 mL) and tributyltin hydride (188 mL, 699 mmol, 2.0 eq) via cannula. The bucket
was filled with an ice slurry, and once the reaction solution began to freeze the tributyltin hydride solution was added over the course of 2 hours (ca. 8 mL/min). Towards the end of the addition minor amounts gas evolution was observed. After the tributyltin hydride solution had been added the reaction was stirred at 21 °C for 1.5 hours. The reaction was concentrated under reduced pressure, and to the resulting yellow slurry was added THF (1 L). The solution was purged with oxygen for 20 minutes, followed by stirring overnight (12 h) at 21 °C under an atmosphere of oxygen. The reaction was concentrated under reduced pressure during which point it changed from an orange solution to an opaque brown/black mixture. The flask was charged with DMF (750 mL), was purged with argon, and had a thermometer suspended into the solution (Figure 5.1D). The reaction was brought to 60 °C with a heat gun after which point heating was ceased. Iodoacrylate 88 (75.40 g, 357 mmol, 1.00 eq) was added at such a rate as to keep the temperature below 80 °C (ca. 15 minutes). Once the iodoacrylate addition was complete heat was applied to maintain the reaction temperature between 70-80 °C for 30 minutes followed by cooling the reaction with the aid of an ice bath. To the flask was added NaF (44 g, 1.05 mol, 2.9 eq), H$_2$O (700 mL), and EtOAc (1 L). The mixture was stirred vigorously for 10 minutes, followed by vacuum filtration over Celite®. The resulting biphasic filtrate had the organic layer separated, while the aqueous layer was extracted with EtOAc (3 x 300 mL). The combined organic layers were washed with water (5 x 500 mL), and sat. aq. NaF (1 x 750 mL). The formed precipitate was removed via vacuum filtration through a sintered glass funnel. The filtrate was returned to the separatory funnel and was washed with sat. aq. NaF (1 x 750 mL), and an 80:20 mixture of brine: sat. NH$_4$Cl (1 x 750 mL). The organic layer was dried over anhydrous MgSO$_4$, filtered, and concentrated under reduced pressure. The resulting dark brown oil was purified by SiO$_2$ flash chromatography [570 g SiO$_2$, 80 mm column diameter, 25% EtOAc/Hexanes (2 L) → 35% EtOAc (4 L), loaded as a solution in 200 mL of PhH] to yield the product 85 as an orange oil (26.72 g, 60%).

**Notes:** The product was slightly volatile, and it was found that leaving it overnight under high vacuum would result in the loss of some material. The quality of tri-$n$-butyltin hydride from Oakwood was found to be variable, and low purity samples diminished the reaction yield (purity established by NMR). Failure to rigorously exclude oxygen during...
the palladium catalyzed hydrostannylation reaction was also found to decrease the reaction yield.

**Physical state:** Orange oil, crystallized below -5 °C.

\(^1\text{H NMR}\) (600 MHz, CDCl\(_3\)): \(\delta = 6.89\) (d, \(J = 9.6\) Hz, 1H), 5.85 (qtt, \(J = 7.4, 2.2, 0.8\) Hz, 1H), 5.71 (dt, \(J = 9.6, 0.8\) Hz, 1H), 5.01 (dq, \(J = 2.8, 1.5\) Hz, 2H), 1.72 (dtt, \(J = 7.4, 1.4, 0.6\) Hz, 3H) ppm.

\(^{13}\text{C NMR}\) (151 MHz, CDCl\(_3\)): \(\delta = 163.8, 145.2, 131.9, 128.0, 115.9, 66.4, 13.8\) ppm.

**HRMS** (EI): \(m/z\): calculated for C\(_7\)H\(_8\)O\(_2\) [M]+ 124.0524, found 124.0526.

**IR** (thin film): 3440, 3074, 2985, 1725, 1643 cm\(^{-1}\).

**TLC** (30:70 EtOAc:Hexanes): \(R_f = 0.27\) (UV, KMnO\(_4\)).

**Figure 5.1:** Reaction setup for synthesis of dihydropyranone 86
Scheme 5.3: Preparation of lactone 85

An oven dried 5 L flask containing a stir bar was equipped with a Claisen adapter, rubber septum, 1 L addition funnel, and a vacuum adapter (Figure 5.2 A). All joints were greased while hot and the apparatus was cooled under high vacuum (0.4 torr). After backfilling with argon, the flask was charged with L1 (5.64 g, 14.9 mmol, 9 mol%), and anhydrous Cu(OTf)$_2$ (3.65 g, 10.1 mmol, 6 mol%) through a paper funnel (Figure 5.2 B). A thermometer suspended by a copper wire was added to the Claisen adapter. The system was evacuated and backfilled with argon three times, then an argon balloon was added to the Claisen adapter, and the vacuum adapter was replaced by a rubber septum (Figure 5.2 C). To the flask was added DCM (1.3 L) via cannula and anhydrous DMPU (44 mL, 365 mmol, 2.1 eq) yielding an apple green solution which was cooled to -78 °C. The addition funnel was charged with vinyl magnesium bromide (0.99 M in THF, 260 mL, 257 mmol, 1.5 eq). The Grignard reagent was added at such a rate as to keep the internal temperature below -70 °C (ca. 20 minutes), then the addition funnel was rinsed with THF (3 x 12 mL). The reaction initially turned into an opaque black mixture upon addition of the Grignard reagent. The reaction was stirred until it became a homogenous orange/yellow solution (ca. 1 hour). The additional funnel was charged with dihydropyranone 86 (20.60 g, 166 mmol, 1.0 eq), DCM (420 mL), and TMSCl (46 mL, 362 mmol, 2.1 eq). The dihydropyranone solution was added at such a rate as to keep in the internal temperature below -70 °C (ca. 35 minutes) during which time the reaction became lighter in colour. Once the addition was complete the reaction was stirred at -78 °C until complete consumption of the starting material was observed by TLC (ca. 2.5 hours). The reaction was quenched while cold with sat. aq. NH$_4$Cl (1 L), followed by warming the reaction using a warm water bath until the ice melted. The biphasic mixture was separated, and
the aqueous layer was extracted with DCM (2 x 300 mL). The combined organic layers were dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The resulting dark oil was purified by SiO₂ flash chromatography [570 g SiO₂, 80 mm column diameter, 15% EtOAc/hexanes (1.5 L) → 20% EtOAc (1 L) → 25% EtOAc (1 L) → 30% EtOAc (1 L), loaded as a solution in 100 mL of PhH] to yield the product 85 as an orange oil (21.46 g, 85%).

Notes: The product was slightly volatile, and it was found that leaving it overnight under high vacuum would result in the loss of some material. Failure to rigorously exclude oxygen and water during the reaction was also found to decrease the reaction yield. The purity of the DMPU was found to be crucial, so it was stored over 4A molecular sieves, and it was distilled from calcium hydride before use. The presence of water or alcohol containing impurities resulted in a dark brown to dark orange coloured reaction mixture once the Grignard reagent had been added, failing to reach a light orange/yellow colour.

Physical state: Orange oil.

¹H NMR (600 MHz, CDCl₃): δ = 5.72 (ddd, J = 16.8, 10.2, 7.3 Hz, 1H), 5.52 (qq, J = 7.0, 1.8 Hz, 1H), 5.14 (dt, J = 9.2, 1.1 Hz, 1H), 5.13 (dt, J = 16.1, 1.1 Hz, 1H), 4.87 (q, J = 14.2 Hz, 2H), 3.26 (br q, J = 6.9 Hz, 1H), 2.70 (dd, J = 15.8, 5.6 Hz, 1H), 2.55 (dd, J = 15.9, 8.5 Hz, 1H), 1.66 (dq, J = 7.0, 1.2 Hz, 3H) ppm.

¹³C NMR (151 MHz, CDCl₃): δ = 171.9, 138.4, 131.3, 123.4, 116.5, 66.8, 41.7, 35.9, 13.2 ppm.

HRMS (EI): m/z: calculated for C₉H₁₂O₂ [M]⁺ 152.0837, found 152.0837.

IR (thin film): 3479, 3081, 2980, 2922, 2252, 1750, 1638 cm⁻¹.

TLC (30:70 EtOAc:Hexanes): Rₜ = 0.45 (KMnO₄).
Figure 5.2: Reaction setup for synthesis of lactone 85

Scheme 5.4: Preparation of diol 84

A 2 L oven dried argon flushed flask was charged with lactone 85 (25.22 g, 166 mmol, 1.0 eq), and THF (800 mL). The solution was cooled to 0 °C, and LiAlH₄ (10.40 g, 274 mmol, 1.7 eq) was added in several portions over the course of 10 minutes. The reaction was allowed to stir at 0 °C until complete consumption of the starting material
was observed by TLC (ca. 1 h). To the grey suspension at 0 °C was added water (10 mL), 2 M NaOH (10 mL), water (30 ml), then anhydrous MgSO₄. The resulting suspension was vacuum filtered on a large sintered glass funnel (600 mL) to remove the voluminous alumina precipitate. The solids were washed with EtOAc (3 x 100 mL) then the filtrate was concentrated under reduced pressure. The crude yellow oil was purified by SiO₂ flash chromatography [490 g SiO₂, 80 mm column diameter, 50% EtOAc/hexanes (1 L) → 80% EtOAc (1 L) → 100% EtOAc (2 L), loaded as a solution in 100 mL PhH] to yield the product 84 as a pale-yellow oil (23.74 g, 92%).

**Physical state:** Pale yellow oil.

**¹H NMR** (600 MHz, CDCl₃): δ = 5.76 (ddd, J = 17.1, 10.2, 7.6 Hz, 1H), 5.50 (q, J = 6.9 Hz, 1H), 5.05 (dt, J = 17.2, 1.4 Hz, 1H), 5.00 (ddt, J = 10.2, 1.7, 0.9 Hz, 1H), 4.23 (d, J = 11.7 Hz, 1H), 4.08 (d, J = 11.7 Hz, 1H), 3.71 (dt, J = 10.8, 6.2 Hz, 1H), 3.65 (dt, J = 10.8, 6.0 Hz, 1H), 3.00 (q, J = 7.6 Hz, 1H), 1.99 (br s, 2H), 1.79 (qm, J = 6.4 Hz, 2H), 1.73 (d, J = 6.9 Hz, 3H) ppm.

**¹³C NMR** (151 MHz, CDCl₃): δ = 141.7, 140.1, 124.5, 114.2, 61.0, 59.2, 45.8, 35.7, 13.4 ppm.

**HRMS (EI):** m/z: calculated for C₉H₁₇O₂ [M+H]⁺ 157.1223, found 157.1230.

**IR (thin film):** 3413, 3065, 2938, 1645, 1635 cm⁻¹.

**TLC** (50:50 EtOAc:Hexanes): Rₚ = 0.18 (KMnO₄).

Scheme 5.5: Preparation of hydroxylamine 94

An argon flushed 2 L flask was charged with diol 84 (23.74 g, 152 mmol, 1.0 eq), triphenylphosphine (59.97 g, 229 mmol, 1.5 eq), Boc protected hydroxylamine 180 (54.44 g, 233 mmol, 1.5 eq), and THF (1 L), then the solution was cooled to 0 °C. To the
solution via syringe pump was added DIAD (39 mL, 198 mmol, 1.3 eq) at a rate of 0.25 mL/min. The reaction was monitored until complete consumption of starting material was observed by TLC (ca. 20 minutes once the addition of DIAD was complete). Once the reaction was complete methanol (50 mL) was added, and the reaction was stirred for 15 minutes at 21 °C. The reaction was concentrated under reduced pressure, followed by repeated concentration from hexanes (2-4 x 500 mL) until the triphenylphosphine oxide precipitated. The yellow cake was purified by SiO₂ flash chromatography [570 g SiO₂, 80 mm column diameter, 20% EtOAc/hexanes (2 L) → 25% EtOAc (5 L), loaded as a suspension in 150 mL of hexanes] to yield the product 94 as a thick pale yellow oil (46.91 g, 83%).

Notes: Due to O=PPh₃ overlapping with the diol 84 by TLC, conversion was judged by the disappearance of activity towards KMnO₄ staining. The product is soluble in CDCl₃; however, the spectra yielded broad proton and carbon signals which were found not to occur acetone.

Physical state: Pale yellow oil.

¹H NMR (600 MHz, acetone-d₆): δ = 5.66 (ddd, J = 17.1, 10.1, 8.2 Hz, 1H), 5.59 (qq, J = 6.9, 0.9 Hz, 1H), 5.03 (d, 17.2 Hz, 1H), 4.98 (d, J = 10.2 Hz, 1H), 4.26 (br s, 2H), 3.53 (m, 2H), 3.33 (br s, 1H), 2.96 (br q, J = 7.8 Hz, 1H), 1.77 (m, 1H), 1.67 (d, J = 6.9 Hz, 3H), 1.50 (s, 9H), 1.47 (s, 9H) ppm.

¹³C NMR (101 MHz, acetone-d₆): δ = 155.5, 153.4, 142.5, 136.9, 125.7, 115.1, 85.2, 82.5, 60.8, 47.8, 45.7, 36.7, 28.5, 27.9, 13.6 ppm.

HRMS (EI): m/z: calculated for C₁₉H₃₄NO₆ [M+H]⁺ 372.2381, found 372.2398.

IR (thin film): 3434, 3077, 2980, 2936, 1780, 1716, 1635 cm⁻¹.

TLC (50:50 EtOAc:Hexanes): Rf = 0.65 (KMnO₄).
Scheme 5.6: Preparation of isoxazolidine 137

To a 1 L flask was added trifluoroacetic acid (520 mL). A solution of hydroxylamine 94 (28.15 g, 75.8 mmol, 1.0 eq) in DCM (30 mL) was added over the course of two minutes to the trifluoroacetic acid. (Caution: Vigorous gas evolution occurred). The brown solution was stirred at 21 °C for 30 minutes, then the reaction was concentrated under reduced pressure. Toluene (130 mL) was added to the flask, and the reaction was concentrated under reduced pressure, followed by removal of residual solvents under high vacuum (0.4 torr) for 15 minutes. To the flask was added anhydrous sodium sulfate (43.57 g, 307 mmol, 4.1 eq), then the flask was evacuated/backfilled with argon three times. To the flask was added DCM (340 mL) via cannula, and once the oil had completely dissolved triethylamine (43 mL, 310 mmol, 4.1 eq), and a solution of aldehyde 135 (31.23 g, 99.0 mmol, 1.3 eq) in DCM (40 mL) were added simultaneously over the course of one minute. The resulting suspension was stirred at 21 °C for 6 hours, after which time the reaction mixture was diluted in EtOAc (1 L). The organic layer was washed with water (1 x 500 mL), brine (1 x 500 mL), dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. Toluene (100 mL) was added to the flask, and the solution was concentrated under reduced pressure to yield a brown oil. To a 3 L oven dried argon flushed flask equipped with a reflux condenser was added toluene (1.4 L) via cannula. The toluene was heated to reflux, then a solution of the crude nitrone in toluene (200 mL) was transferred via cannula into the refluxing toluene. Once all the nitrone had been transferred the reaction was refluxed until complete consumption of starting material was observed by TLC (ca. 45 minutes). The reaction was cooled to about 30 °C with the aid of an ice bath, then it was concentrated under reduced pressure.
The obtained thick brown semi-solid was purified by SiO$_2$ flash chromatography [570 g 20-45 µm SiO$_2$, 80 mm column diameter, 50% EtOAc/DCM, loaded as a solution in 100 mL DCM] to yield the product 137 and 141 as a tan foam (11.80 g, 33%, 2:2:1:1 d.r).

**Physical state:** Light tan foam.

$^1$H NMR (600 MHz, CDCl$_3$): $\delta = 7.73$-$7.67$ (m, 6H), 7.62 (t, $J = 8.0$ Hz, 3H), 7.27-7.16 (m, 9H), 7.08 (q, $J = 6.5$ Hz, 3H), 6.96 (td, $J = 7.5$, 3.2 Hz, 3H), 5.45 (q, $J = 7.1$ Hz, 2H), 5.41 (q, $J = 6.4$ Hz, 1H), 4.18 (d, $J = 15.8$ Hz, 1H), 4.14 (d, $J = 15.8$ Hz, 1H), 4.09 (d, $J = 16.2$ Hz, 1H), 4.07-3.96 (m, 3H), 3.84 (t, $J = 6.5$ Hz, 1H), 3.78-3.64 (m, 11H), 3.61 (dt, $J = 10.5$, 6.7 Hz, 1H), 3.54 (tt, $J = 9.9$, 4.8 Hz, 2H), 3.51-3.43 (m, 1H), 3.35-3.26 (m, 2H), 3.26-3.20 (m, 1H), 3.20-3.07 (m, 4H), 2.53-2.45 (m, 2H), 2.45-2.40 (m, 1H), 2.36 (s, 3H), 2.35 (s, 6H), 2.31 (dd, $J = 5.3$, 3.4 Hz, 1H), 2.28 (dd, $J = 5.3$, 1.9 Hz, 1H), 2.23 (dd, $J = 5.3$, 3.4 Hz, 1H), 2.06-1.97 (m, 2H), 1.74-1.55 (m, 15H), 1.52-1.46 (m, 1H), 1.46-1.36 (m, 2H), 1.31 (ddq, $J = 14.3$, 10.0, 5.4 Hz, 2H), 1.20-1.08 (m, 1H) ppm.

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta = 144.28$, 144.26, 144.10, 141.83, 141.74, 141.70, 135.61, 135.56, 135.24, 135.20, 135.07, 134.01, 133.89, 129.84, 129.82, 129.75, 128.22, 128.21, 128.13, 128.10, 127.55, 127.53, 127.44, 127.43, 125.44, 125.41, 124.92, 124.72, 124.62, 124.60, 123.89, 123.84, 123.55, 123.47, 120.93, 120.89, 114.87, 114.77, 114.71, 114.62, 77.37, 77.16, 76.95, 72.54, 72.52, 70.08, 69.32, 68.52, 68.47, 63.25, 62.45, 60.89, 60.83, 60.38, 60.35, 58.21, 58.00, 56.97, 56.83, 55.70, 55.50, 55.15, 55.09, 48.46, 47.82, 46.96, 46.67, 46.01, 45.98, 42.15, 38.02, 37.91, 37.35, 37.16, 37.12, 37.05, 36.90, 36.23, 33.01, 21.64, 13.12, 13.04, 13.03 ppm.

HRMS (EI): $m/z$: calculated for C$_{26}$H$_{32}$N$_2$O$_4$S [M]$^+$ 468.2083, found 468.2084.

FTIR (AT-IR): 3401, 2934, 2880, 1644, 1598 cm$^{-1}$.

TLC: (50:50 EtOAc:DCM): R$_f$ = 0.44 (UV, KMnO$_4$).
Scheme 5.7: Preparation of model isoxazolidine 118

To a 25 mL flask was added hydroxylamine 94 (0.2096 g, 0.564 mmol, 1.0 eq), followed by trifluoroacetic acid (4 mL). The resulting solution was stirred at 21 °C for 30 minutes after which point it was concentrated under reduced pressure, then high vacuum (0.4 torr) for 15 minutes. The flask was backfilled with argon, and to the flask was added DCM (4 mL), anhydrous MgSO$_4$ (0.2969 g, 2.47 mmol, 4.4 eq), 3-phenylpropanal (0.18 mL, 1.36 mmol, 2.4 eq), and lastly Et$_3$N (0.40 mL, 2.89 mmol, 5.1 eq). The reaction was stirred at 21 °C for 7 hours, followed by filtration through Celite® into a 100 mL flask. The solution was concentrated, then to the flask was added PhH (35 mL). The flask was equipped with a condenser, flushed with argon, and was refluxed until complete consumption of the starting material was observed by TLC (ca. 2 hours). The reaction was concentrated under reduced pressure, and the residue was purified by SiO$_2$ flash chromatography [110 g SiO$_2$, 40 mm column diameter, 50% EtOAc/hexanes (200 mL) → 55% EtOAc (200 mL) → 60% EtOAc (200 mL) → 65% EtOAc (200 mL), → 70% EtOAc (200 mL), loaded as a solution in 10 mL of PhH] to yield diastereomerically pure isoxazolidine 118 (0.0069 g, 4%), a mixture of 58% diastereomer 118 to 42% diastereomer 181 (0.0445 g, 27%), and a mixture of 21% diastereomer 118 to 79% diastereomer 181 (0.0414 g, 26%). A total of 0.0928 g of product was obtained in total corresponding to a 57% yield. A crystal was obtained by allowing a solution of its mono hydrogen oxalate salt in acetonitrile to slowly evaporate in an atmosphere of PhH.

Physical state: Cream coloured foam.
$^1$H NMR (600 MHz, CDCl$_3$): $\delta = 7.30$-$7.27$ (m, 2H), $7.23$-$7.17$ (m, 3H), $5.44$ (br q, $J = 6.9$ Hz, 1H), $4.20$ (d, $J = 15.8$ Hz, 1H), $3.78$ (d, $J = 6.8$ Hz, 1H), $3.74$ (ddd, $J = 10.4$, 6.8, 5.5 Hz, 1H), $3.70$ (ddd, $J = 10.5$, 7.6, 6.2 Hz, 1H), $3.63$ (t, $J = 6.0$ Hz, 1H), $3.17$ (dq, $J = 15.8$, 1.7 Hz, 1H), $3.11$ (dd, $J = 8.8$, 5.3 Hz, 1H), $2.86$ (ddd, $J = 14.2$, 8.9, 5.7 Hz, 1H), $2.73$ (ddd, $J = 13.8$, 8.8, 7.4 Hz, 1H), $2.47$ (br s, 1H), $2.42$ (dd, $J = 5.2$, 2.0 Hz, 1H), $2.01$ (dtd, $J = 14.2$, 7.2, 4.7 Hz, 1H), $1.80$ (ddt, $J = 13.6$, 8.8, 5.7 Hz, 1H), $1.64$ (ddd, $J = 6.9$, 2.2, 1.5 Hz, 3H), $1.59$ (dddd, $J = 14.1$, 8.9, 7.3, 5.3 Hz, 1H), $1.35$ (dddd, $J = 14.2$, 8.9, 6.3, 5.5 Hz, 1H) ppm.

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta = 142.1$, 135.5, 128.7, 128.6, 126.0, 120.7, 71.1, 68.5, 60.7, 58.3, 46.6, 42.2, 33.6, 33.2, 32.8, 13.1 ppm.

HRMS (EI): $m/z$: calculated for C$_{18}$H$_{25}$NO$_2$ [M]$^+$ 287.1885, found 287.1897.

FTIR (AT-IR): 3389, 3059, 3025, 2937, 2879, 1602 cm$^{-1}$.

TLC: (70% EtOAc: 30% Hexanes): $R_f = 0.33$ (UV, KMnO$_4$).

Scheme 5.8: Preparation of indoline 182 and 183

To an oven dried argon flushed 5 L flask was added isoxazolidine 137/141 (11.80 g, 25.2 mmol, 1.0 eq), magnesium powder (325 mesh, 4.25 g, 175 mmol, 6.9 eq), and anhydrous MeOH (1 L). The flask was cooled to 0 °C in a sonicator containing an ice slurry. After cooling for 15 minutes, sonication was initiated, which took about 4-8 minutes to activate the magnesium. Upon activation steady gas evolution occurred. After 50 minutes a second portion of magnesium (3.52 g, 145 mmol, 5.8 eq) was added, and
the reaction was sonicated for another 49 minutes. Reaction conversion was monitored by TLC, and more magnesium was added if any starting material remained. The flask was purged with argon, and water (50 mL) was added. The flask was shaken by hand to mix the resulting gel which vacuum filtered over Celite®. The resulting grey solids were suspended in DCM (5 x 300 mL), and vacuum filtered. The combined filtrate was concentrated under reduced pressure, and diluted with water (800 mL). The aqueous layer was extracted with DCM (3 x 400 mL). The combined organic layer was washed with brine (1 x 500 mL), dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The resulting crude product 182/183 was a cream colored foam and did not require addition purification (6.71 g, 85%).

**Notes:** Caution! The reaction was very exothermic, and it was important to ensure that there was adequate ice in the bath for cooling. A lot of gas evolution occurred, and the balloon needed to be vented frequently to prevent it from bursting. Depending on the quality of the magnesium powder between 14-25 equivalents was needed to ensure the reaction reached completion. The vacuum filtration process took a long time (typically 3-4 hours), so it was convenient to use a sintered glass funnel that can fit the entire reaction mixture so it can be left to filter without having to monitor it.

**Physical state:** Cream coloured foam.

**¹H NMR** (600 MHz, CDCl₃): δ = 7.13-7.06 (m, 3H), 7.07-6.99 (m, 3H), 6.71 (t, J = 7.4 Hz, 3H), 6.65-6.59 (m, 3H), 5.49-5.36 (m, 3H), 4.21 (d, J = 15.8 Hz, 1H), 4.18 (d, J = 15.9 Hz, 1H), 4.10 (t, J = 15.5 Hz, 1H), 3.92-3.81 (m, 3H), 3.81-3.51 (m, 17H), 3.49-3.39 (m, 3H), 3.37 (dd, J = 8.6, 4.8 Hz, 1H), 3.34-3.20 (m, 8H), 3.17 (d, J = 15.4 Hz, 1H), 2.55-2.47 (m, 2H), 2.48-2.41 (m, 3H), 2.39 (dd, J = 5.2, 1.9 Hz, 1H), 2.35 (dd, J = 5.2, 3.4 Hz, 1H), 2.00 (ddt, J = 14.3, 7.2, 4.7 Hz, 2H), 1.92 (dddd, J = 13.7, 8.8, 7.4, 4.5 Hz, 2H), 1.80-1.70 (m, 2H), 1.70-1.57 (m, 14H), 1.53 (dd, J = 14.2, 9.2, 5.2 Hz, 1H), 1.47 (dddd, J = 14.0, 9.2, 4.9 Hz, 1H), 1.31 (dtt, J = 14.5, 8.9, 5.8 Hz, 2H) ppm.

**¹³C NMR** (151 MHz, CDCl₃): δ = 151.51, 151.47, 151.37, 135.38, 135.33, 134.22, 134.19, 133.02, 132.94, 132.76, 132.71, 127.72, 127.70, 127.62, 127.60, 125.25, 125.18, 124.44, 124.12, 124.09, 124.02, 120.70, 120.66, 118.89, 118.68, 118.57, 109.86, 109.85,
109.70, 77.37, 77.16, 76.95, 72.63, 72.55, 70.31, 69.86, 68.61, 68.46, 63.45, 62.97, 60.82, 60.39, 60.29, 58.29, 58.08, 55.80, 54.65, 54.46, 53.01, 52.97, 48.39, 47.72, 46.75, 46.71, 45.95, 42.23, 42.15, 39.64, 39.56, 39.49, 39.22, 36.73, 36.49, 36.28, 36.25, 36.22, 33.05, 32.96, 13.09, 13.09, 13.01 ppm.

**HRMS** (EI): $m/z$: calculated for C$_{17}$H$_{15}$NO$_3$S [M]$^+$ 314.1994, found 314.2002.

**FTIR** (AT-IR): 3344, 2927, 2877, 1646, 1607 cm$^{-1}$.

**TLC**: (10% 7 N NH$_3$ in MeOH: 90% DCM): $R_f = 0.32$ (UV, KMnO$_4$, ninhydrin).

**Scheme 5.9: Preparation of indole 139 and 141**

To a 1 L oven dried argon flushed flask was added oxalyl chloride (3.9 mL, 45.6 mmol, 2.1 eq), and DCM (150 mL). The solution was cooled to -78 °C, then DMSO (6.1 mL, 85.9 mmol, 4.0 eq) was added dropwise over the course of two minutes. After the DMSO had been added the solution was allowed to stir at -78 °C for an additional 10 minutes. A solution of indoline 182/183 (6.71 g, 21.3 mmol, 1.0 eq, est. 4.29 g 183) in DCM (60 mL) was added dropwise over the course of 8 minutes. The reaction was stirred at -78 °C for 45 minutes, then Et$_3$N (24 mL, 173 mmol, 8.0 eq) was added dropwise over the course of 10 minutes. The reaction mixture was stirred at -78 °C for an additional 45 minutes, then at 0 °C for 45 minutes. The resulting tan suspension was concentrated under reduced pressure, then high vacuum (0.4 torr) for 30 minutes. To the flask was added PPTS (10.79 g, 42.9 mmol, 2.0 eq), then a condenser was added to the flask, and the entire system was evacuated/backfilled with argon three times.

Trimethylorthoformate (20 mL, 183 mmol, 8.6 eq) was added to the flask, followed by
MeOH (300 mL). The reaction was refluxed under argon until complete consumption of the starting material was observed by NMR (ca. 3-6 hours). The reaction solution was cooled to 21 °C, and was concentrated under reduced pressure. The residue was diluted in EtOAc (800 mL), and was washed with sat. Na₂CO₃, (1 x 300 mL), brine (1 x 300 mL), dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The crude brown oil was purified by SiO₂ flash chromatography [570 g 20-45 µm SiO₂, 80 mm column diameter, 50% EtOAc/DCM, loaded as a solution in 100 mL DCM, a second identical column was run to purify a small mixed fraction] to yield indole 139 as a white foam (2.8841 g, 59%).

Major Diastereomer 139

Physical state: White foam.

\(^{1}\text{H NMR}\) (600 MHz, CDCl₃): \(\delta = 8.38\) (br s, 1H), 7.64 (dd, \(J = 7.8, 1.0\) Hz, 1H), 7.36 (dt, \(J = 8.0, 0.9\) Hz, 1H), 7.19 (ddd, \(J = 8.1, 7.0, 1.2\) Hz, 1H), 7.13 (ddd, \(J = 7.9, 7.0, 1.0\) Hz, 1H), 7.01 (d, \(J = 2.3\) Hz, 1H), 5.43(q br t, \(J = 6.8, 1.3\) Hz, 1H), 4.36 (t, \(J = 5.6\) Hz, 1H), 4.22 (d, \(J = 15.8\) Hz, 1H), 3.88-3.81 (m, 2H), 3.57 (dd, \(J = 8.1, 6.5\) Hz, 1H), 3.23 (dd, \(J = 15.8, 1.2\) Hz, 1H), 3.23 (s, 3H), 3.17 (s, 3H), 3.01 (ddd, \(J = 14.8, 6.6, 1.0\) Hz, 1H), 2.77 (ddd, \(J = 14.9, 8.1, 0.7\) Hz, 1H), 2.62 (dd, \(J = 4.6, 1.6\) Hz, 1H), 2.44 (br s, 1H), 2.00 (dt, \(J = 14.2, 5.5\) Hz, 1H), 1.64 (dt, \(J = 6.8, 1.7\) Hz, 3H), 1.38 (ddd, \(J = 14.1, 8.6, 5.4\) Hz, 1H) ppm.

\(^{13}\text{C NMR}\) (151 MHz, CDCl₃): \(\delta = 136.5, 135.3, 127.7, 122.5, 122.0, 120.7, 119.4, 118.8, 113.2, 111.4, 103.2, 72.6, 68.5, 58.3, 53.4, 52.4, 46.2, 42.0, 33.5, 28.1, 13.1\) ppm.

HRMS (EI): \(m/z\): calculated for C₂₁H₂₈N₂O₃ [M]⁺ 356.2100, found 356.2108.

FTIR (AT-IR): 3326, 3056, 2932, 2882, 2832, 1646, 1619 cm⁻¹.

TLC: (50:50 EtOAc:DCM): \(R_f = 0.46\) (UV, KMnO₄).

Minor Diastereomer 141

Physical state: White foam.
\textbf{1H NMR (600 MHz, CDCl$_3$):} $\delta = 8.44$ (br s, 1H), 7.62 (d, $J = 7.8$ Hz, 1H), 7.35 (dt, $J = 8.1$, 0.9 Hz, 1H), 7.18 (ddd, $J = 8.2$, 7.0, 1.2 Hz, 1H), 7.12 (ddd, $J = 8.0$, 7.0, 1.0 Hz, 1H), 6.99 (d, $J = 2.3$ Hz, 1H), 5.41 (q, $J = 7.0$ Hz, 1H), 4.13 (d, $J = 16.1$ Hz, 1H), 4.02 (t, $J = 6.0$ Hz, 1H), 3.98 (t, $J = 6.0$ Hz, 1H), 3.94 (d, $J = 6.1$ Hz, 1H), 3.68 (dd, $J = 8.7$, 6.1 Hz, 1H), 3.31 (dt, $J = 16.1$, 2.2 Hz, 1H), 3.12 (s, 3H), 3.07 (s, 3H), 3.04 (ddd, $J = 14.6$, 6.1, 1.0 Hz, 1H), 2.73 (ddd, $J = 14.6$, 8.7, 0.7 Hz, 1H), 2.51 (dd, $J = 5.2$, 3.4 Hz, 1H), 2.41 (td, $J = 7.5$, 3.2 Hz, 1H), 1.63-1.61 (m, 2H), 1.60 (dd, $J = 6.9$, 1.6 Hz, 3H) ppm.

\textbf{13C NMR (151 MHz, CDCl$_3$):} $\delta = 136.6$, 134.3, 127.6, 125.1, 122.6, 122.1, 119.5, 118.7, 112.9, 111.4, 102.7, 72.4, 65.8, 55.8, 53.1, 52.5, 45.8, 45.0, 36.1, 27.9, 13.0 ppm.

\textbf{HRMS (EI):} $m/z$: calculated for C$_{21}$H$_{28}$N$_2$O$_3$ [M]$^+$ 356.2100, found 356.2089.

\textbf{FTIR (AT-IR):} 3321, 3055, 2832, 1599 cm$^{-1}$.

\textbf{TLC:} (50:50 EtOAc:DCM): $R_f = 0.38$ (UV, KMnO$_4$).

\textbf{Scheme 5.10:} Preparation of acetal 134

To a 1 L flask in a glovebox was added samarium chips (7.01 g, 46.6 mmol, 1.8 eq, 40 mesh), freshly purified diiodoethane (7.16 g, 25.4 mmol, 1.0 eq),$^{90}$ and THF (275 mL). The reaction was stirred for 12 hours at 21 °C, then it was allowed to sit for 30 minutes. The supernatant was decanted into a 1 L flask which was sealed and removed from the glovebox. The SmI$_2$ solution was cooled to 0 °C, then a solution of indole 139 (2.88 g, 8.08 mmol, 1.0 eq) in THF (50 mL) was added over the course of 5 minutes. The reaction was stirred at 0 °C until complete consumption of starting material was observed by TLC (ca. 10 minutes). The reaction was quenched with 28% aq. NH$_3$ (100 mL), and was exposed to air. The resulting suspension was stirred for 30 minutes at 21 °C yielding a creamy white slurry. The reaction mixture was vacuum filtered, and the solids were washed with DCM (3 x 100 mL). The filtrate was diluted in DCM (1 L), and was washed
with 10% tetrasodium EDTA (1 x 200 mL), 15% aq. NH₃ (1 x 400 mL), brine (1 x 400 mL), dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The resulting golden oil was purified by SiO₂ flash chromatography [150 g SiO₂, 50 mm column diameter, 7% 7 N NH₃ in MeOH/DCM, loaded as a solution in 15 mL DCM] to yield the product 134 as a white foam (2.77 g, 95%).

**Physical State:** White foam.

**¹H NMR** (600 MHz, CD₃OD): δ = 7.60 (dt, J = 7.9, 1.0 Hz, 1H), 7.34 (dt, J = 8.1, 0.9 Hz, 1H), 7.12 (s, 1H), 7.09 (ddd, J = 8.2, 7.0, 1.2 Hz, 1H), 7.02 (ddd, J = 8.0, 7.0, 1.2 Hz, 1H), 5.26 (br q, J = 6.9 Hz, 1H), 4.50 (t, J = 5.8 Hz, 1H), 3.84 (d, J = 12.6 Hz, 1H), 3.78 (dd, J = 11.5, 3.5 Hz, 1H), 3.65 (dd, J = 11.5, 5.0 Hz, 1H), 3.29 (s, 3H), 3.26 (s, 3H), 3.03 (ddd, J = 14.4, 6.0, 0.9 Hz, 1H), 2.96 (ddd, J = 14.3, 8.6, 0.8 Hz, 1H), 2.83 (dq, J = 12.5, 1.2 Hz, 1H), 2.32 (br s, 1H), 1.93 (ddd, J = 14.2, 6.9, 5.7 Hz, 1H), 1.86 (dq, J = 5.0, 3.7 Hz, 1H), 1.79 (ddd, J = 14.0, 7.7, 5.8 Hz, 1H), 1.65 (ddd, J = 6.8, 1.9, 1.2 Hz, 3H) ppm.

**¹³C NMR** (151 MHz, CD₃OD): δ = 138.3, 137.4, 128.8, 124.2, 122.4, 119.7, 119.4, 117.6, 112.8, 112.3, 104.8, 62.7, 59.3, 54.0, 53.0, 49.6, 45.7, 43.3, 33.5, 30.4, 13.0 ppm.

**HRMS** (EI): m/z: calculated for C₂₁H₃₀N₂O₃ [M]+ 358.2256, found 358.2256.

**IR** (CHCl₃): 3405, 3019, 2911, 1646, 1634 cm⁻¹.

**TLC:** (10% 7 N NH₃ MeOH: 90% DCM): Rₜ = 0.55 (UV, KMnO₄).
Scheme 5.11: Original Route to Prepare acetal 134

Scheme 5.12: Preparation of indole 132

To a 250 mL flask was added hydroxylamine 94 (3.45 g, 9.29 mmol, 1.0 eq.) and TFA (20 mL). The reaction was stirred for 30 minutes at 21 °C, then it was concentrated under reduced pressure. Toluene (20 mL) was added, and the flask was concentrated under reduced pressure. The flask was equipped with a reflux condenser, and was flushed with argon. To the flask was added aldehyde 130 (4.37 g, 14.0 mmol, 1.5 eq.), imidazole (2.62 g, 38.5 mmol, 4.1 eq.), 4Å molecular sieves (10 g), and 1,4-dioxane (100 mL). The reaction was stirred at 21 °C for 5 hours, after which point it was refluxed for 1 hour. The reaction was filtered, then concentrated under reduced pressure. The crude product was purified by SiO\textsubscript{2} flash chromatography (160 g SiO\textsubscript{2}, 50 mm column diameter, 70% EtOAc/Hexanes, loaded as a solution in 15 mL of PhH, re-purified mixed fractions using the same column conditions) to yield the desired diastereomer 132 as a light tan foam (0.39 g, 9%).
Physical State: Tan foam.

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ = 7.98 (dt $J$ = 8.3, 0.9 Hz, 1H), 7.76 (m, 2H), 7.53 (dt, $J$ = 7.5, 0.9 Hz, 1H), 7.45 (br t, $J$ = 1.1 Hz, 1H), 7.32 (ddd, $J$ = 8.4, 7.2, 1.3 Hz, 1H), 7.24 (ddd, $J$ = 8.1, 7.2, 1.0 Hz, 1H), 7.21 (m, 2H), 5.46 (br q, $J$ = 6.7 Hz, 1H), 4.20 (d, $J$ = 15.9 Hz, 1H), 3.85 (d, $J$ = 6.9 Hz, 1H), 3.75 (t, $J$ = 6.2 Hz, 1H), 3.66 (qdd, $J$ = 10.4, 7.2, 6.0 Hz, 2H), 3.48 (dd, $J$ = 7.9, 6.4 Hz, 1H), 3.20 (dq, $J$ = 15.9, 1.7 Hz, 1H), 2.89 (ddd, $J$ = 15.2, 7.9, 0.9 Hz, 1H), 2.65 (ddd, $J$ = 15.1, 7.9, 0.9 Hz, 1H), 2.56 (dd, $J$ = 5.2, 1.9 Hz, 1H), 2.47 (br s, 1H), 2.33 (s, 3H), 2.01 (dd, $J$ = 14.2, 7.2, 5.0 Hz, 1H), 1.65 (ddd, $J$ = 6.8, 2.2, 1.5 Hz, 3H), 1.34 (ddt, $J$ = 14.2, 8.5, 6.0 Hz, 1H) ppm.

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ = 145.0, 135.5, 135.3, 135.2, 131.2, 130.0, 126.9, 124.9, 123.7, 123.3, 121.0, 120.1, 119.7, 113.9, 71.7, 68.4, 60.5, 58.3, 46.0, 42.3, 33.1, 27.9, 21.7, 13.2 ppm.

HRMS (EI): $m/z$: calculated for C$_{26}$H$_{30}$N$_2$O$_4$S [M]$^+$ 466.1926, found 466.1926.

IR (CHCl$_3$): 3431, 3053, 2939, 1647, 1636 cm$^{-1}$.

TLC: (20:80 EtOAc:DCM): $R_f$ = 0.42 (KMnO$_4$, UV).

Scheme 5.13: Preparation of acetal 133

To a 25 mL oven dried argon flushed flask was added DCM (3 mL), and oxalyl chloride (120 μL, 1.40 mmol, 1.6 eq.). The solution was cooled to -78 °C, and DMSO (160 μL, 2.25 mmol, 2.6 eq.) was added dropwise. The solution was allowed to stir for 10 minutes, then the isoxadolidine 132 (0.407 g, 0.87 mmol, 1.0 eq.) was added as a solution in DCM (6 mL) dropwise over the course of 5 minutes. The reaction was stirred at -78 °C for one hour, then triethylamine (500 μL, 3.61 mmol, 4.1 eq.) was added. The reaction was warmed to 0 °C and was stirred for 45 minutes. The reaction mixture was diluted in
EtOAc (70 mL) and was washed with sat. aq. NaHCO₃ (1 x 50 mL), brine (1 x 50 mL), dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure to yield a brown foam.

The crude product was transferred into a 100 mL flask containing PPTS (0.269 g, 1.07 mmol, 1.2 eq.). The flask was equipped with a condenser and the system was flushed with argon. To the flask was added anhydrous MeOH (20 mL), and trimethyl orthoformate (400 μL, 3.66 mmol, 4.2 eq.). The reaction was refluxed until complete consumption of starting material was observed by TLC (ca. 1 hour). The reaction mixture was diluted in EtOAc (100 mL) and was washed with sat. aq. Na₂CO₃ (1 x 50 mL), brine (1 x 50 mL), dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The resulting brown semi-solid was purified by SiO₂ flash chromatography [90 g SiO₂, 40 mm column diameter, loaded as a solution in 10 mL of PhH] to yield the product 133 as a nearly white foam (0.350 g, 79% over 2 steps).

**Physical State:** Nearly white foam.

**¹H NMR** (600 MHz, CDCl₃): δ = 7.98 (dt, J = 8.3, 0.9 Hz, 1H), 7.76 (m, 2H), 7.54 (dt, J = 7.7, 1.0 Hz, 1H), 7.45 (br t, J = 1.2 Hz, 1H), 7.31 (dd, J = 8.4, 7.2, 1.3 Hz, 1H), 7.24 (ddd, J = 8.1, 7.3, 1.0 Hz, 1H), 7.21 (m, 2H), 5.43 (br q, J = 6.7 Hz, 1H), 4.35 (t, J = 5.7 Hz, 1H), 4.20 (d, J = 15.9 Hz, 1H), 3.85 (d, J = 7.0 Hz, 1H), 3.77 (ddd, J = 6.7, 5.4, 1.2 Hz, 1H), 3.49 (dd, J = 8.0, 6.4 Hz, 1H), 3.24 (s, 3H), 3.22 (d, J = 15.7 Hz, 1H), 3.19 (s, 3H), 2.89 (ddd, J = 15.1, 6.3, 1.3 Hz, 1H), 2.65 (ddd, J = 15.2, 8.0, 0.9 Hz, 1H), 2.57 (ddd, J = 5.1, 1.9 Hz, 1H), 2.44 (br s, 1H), 2.33 (s, 3H), 2.00 (dt, J = 14.2, 5.4 Hz, 1H), 1.65 (dd, J = 6.8, 2.2, 1.4 Hz, 3H), 1.37 (ddd, J = 14.2, 8.8, 5.4 Hz, 1H) ppm.

**¹³C NMR** (151 MHz, CDCl₃): δ = 144.9, 135.5, 135.3, 135.0, 131.2, 130.0, 127.0, 124.9, 123.7, 123.3, 121.0, 120.2, 119.7, 113.9, 103.1, 71.7, 68.5, 58.3, 53.5, 52.4, 46.2, 42.0, 33.4, 27.9, 21.7, 13.2 ppm.

**HRMS** (EI): m/z: calculated for C₂₈H₃₄N₂O₅S [M]⁺ 510.2188, found 510.2201.

**IR** (CHCl₃): 3446, 3045, 2947, 1652, 1609 cm⁻¹.
TLC: (50:50 EtOAc:Hexanes): R_f = 0.25 (UV, KMnO_4).

Scheme 5.14: Preparation of acetal 134

To an oven dried Ar flushed 25 mL flask was added 133 (40 mg, 0.08 mmol, 1.0 eq.), followed by freshly prepared SmI_2 (12 mL of a 0.07 M solution in THF, 0.84 mmol, 10.8 eq). The reaction was stirred at 21 °C for 12 h. Next, to the flask was added pyrrolidine (130 μL, 1.56 mmol, 20.0 eq.), then water (42 μL, 2.33 mmol, 30.0 eq.) and the reaction was stirred for an additional five minutes at 21 °C. The reaction was quenched with sat. aq. NH_3 (3 mL), and was stirred at 21 °C for 1 hour. The reaction mixture was diluted in Et_2O (25 mL) and was washed with water (1 x 50 mL), and aq. 2 M NaOH (2 x 50 mL). The aqueous layer was extracted with Et_2O (2 x 25 mL). The combined organic layers were washed with aq. 10% tetrasodium EDTA (2 x 50 mL), sat. aq. NH_3 (1 x 50 mL), brine (1 x 50 mL), dried over anhydrous MgSO_4, filtered, and concentrated under reduced pressure. The crude material was purified by SiO_2 flash chromatography (5% 7 N NH_3 in MeOH: 95% DCM, 20 mm column) to yield the product 134 as a white foam (24 mg, 84%).

Physical State: White foam.

^1H NMR (600 MHz, CD_3OD): δ = 7.60 (dt, J = 7.9, 1.0 Hz, 1H), 7.34 (dt, J = 8.1, 0.9 Hz, 1H), 7.12 (s, 1H), 7.09 (ddd, J = 8.2, 7.0, 1.2 Hz, 1H), 7.02 (ddd, J = 8.0, 7.0, 1.2 Hz, 1H), 5.26 (br q, J = 6.9 Hz, 1H), 4.50 (t, J = 5.8 Hz, 1H), 3.84 (d, J = 12.6 Hz, 1H), 3.78 (dd, J = 11.5, 3.5 Hz, 1H), 3.65 (dd, J = 11.5, 5.0 Hz, 1H), 3.29 (s, 3H), 3.26 (s, 3H), 3.03 (ddd, J = 14.4, 6.0, 0.9 Hz, 1H), 2.96 (ddd, J = 14.3, 8.6, 0.8 Hz, 1H), 2.83 (dq, J = 12.5, 1.2 Hz, 1H), 2.32 (br s, 1H), 1.93 (ddd, J = 14.2, 6.9, 5.7 Hz, 1H), 1.86 (dq, J = 5.0, 3.7 Hz, 1H), 1.79 (ddd, 14.0, 7.7, 5.8 Hz, 1H), 1.65 (ddd, J = 6.8, 1.9, 1.2 Hz, 3H) ppm.
$^{13}$C NMR (151 MHz, CD$_3$OD): $\delta = 138.3$, 137.4, 128.8, 124.2, 122.4, 119.7, 119.4, 117.6, 112.8, 112.3, 104.8, 62.7, 59.3, 54.0, 53.0, 49.6, 45.7, 43.3, 33.5, 30.4, 13.0 ppm.

HRMS (EI): $m/z$: calculated for C$_{21}$H$_{30}$N$_2$O$_3$ [M]$^+$ 358.2256, found 358.2256.

IR (CHCl$_3$): 3405, 3022, 2911, 1647, 1634, 1611 cm$^{-1}$.

TLC: (10% 7 N NH$_3$ MeOH: 90% DCM ): $R_f = 0.55$ (UV, KMnO$_4$)

Scheme 5.15: Preparation of des-N$_4$-methyl (19Z)-taberpsychine (147)

To an oven dried argon flushed 100 mL flask was added acetonitrile (10 mL), and BF$_3$OEt$_2$ (0.52 mL, 4.2 mmol, 4.9 eq.). To the resulting solution was added a solution of acetal 134 (0.308 g, 0.859 mmol, 1.0 eq.) as a solution in acetonitrile (10 mL) over the course of one minute. The reaction was stirred at 21 °C until complete consumption of the starting material was observed by TLC (ca. 20 minutes). The reaction was quenched with 2 M NaOH (10 mL), and was diluted in DCM (100 mL). The organic layer was washed with 2 M NaOH (1 x 80 mL), brine (1 x 80 mL), dried over anhydrous MgSO$_4$, filtered, and concentrated under reduced pressure. The crude product was purified by SiO$_2$ flash chromatography [90 g SiO$_2$, 40 mm column diameter, 5% 7 N NH$_3$ in MeOH/DCM, loaded as a solution in DCM] to yield the product 147 as a peach coloured foam (0.162 g, 64%), and enamine 145 as a yellow oil (0.0191 g, 8%).

Des-N$_4$-methyl (19Z)-taberpsychine 145

Physical state: Peach coloured foam.

$^1$H NMR (600 MHz, CDCl$_3$): $\delta = 8.22$ (br s, 1H), 7.63 (d, $J = 7.9$ Hz, 1H), 7.32 (dt, $J = 8.1, 1.0$ Hz, 1H), 7.19 (ddd, $J = 8.1, 7.0, 1.2$ Hz, 1H), 7.14 (ddd, $J = 8.0, 7.0, 1.1$ Hz, 1H), 5.37 (qdt, $J = 6.8, 1.0, 0.7$ Hz, 1H), 5.13 (dd, $J = 10.3, 1.3$ Hz, 1H), 3.80 (dd, $J = 11.4$, 1.1 Hz, 1H).
10.3 Hz, 1H), 3.73 (d, $J = 15.9$ Hz, 1H), 3.67 (d, $J = 15.8$ Hz, 1H), 3.46 (dd, $J = 14.9$, 10.3 Hz, 1H), 3.36-3.26 (m, 3H), 2.88 (td, $J = 10.2$, 5.0 Hz, 1H), 2.44 (dddd, $J = 14.5$, 10.5, 9.5, 1.3 Hz, 1H), 2.38 (m, 1H), 2.22 (ddd, $J = 14.3$, 11.1, 1.4 Hz, 1H), 1.69 (br s, 1H), 1.63 (dd, $J = 6.8$, 1.4 Hz, 3H) ppm.

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ = 137.9, 135.4, 131.8, 128.4, 122.5, 119.5, 118.9, 118.5, 111.5, 111.1, 67.7, 62.1, 54.2, 40.6, 37.8, 35.0, 30.3, 24.8, 12.8 ppm.

HRMS (EI): $m/z$: calculated for C$_{19}$H$_{22}$N$_2$O [M]$^+$ 294.1732, found 294.1728.

IR (CHCl$_3$): 3278, 3056, 2925, 1646, 1621 cm$^{-1}$.

TLC: (20:80 MeOH:DCM): $R_f$ = 0.50 (UV, KMnO$_4$)

Enamine 145

Physical state: Yellow Oil.

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ = 8.15 (s, 1H), 7.66 (dt, $J = 7.9$, 1.0 Hz, 1H), 7.38 (dt, $J$ =8.1, 0.9 Hz, 1H), 7.23 (ddd, $J$ = 8.2, 7.0, 1.2 Hz, 1H), 7.15 (ddd, $J$ = 8.0, 7.0, 1.1 Hz, 1H), 7.06 (d, $J$ = 2.3 Hz, 1H), 6.40 (d, $J$ = 6.1 Hz, 1H), 5.34 (q, $J$ = 6.8 Hz, 1H), 4.79 (t, $J$ = 5.9 Hz, 1H), 4.19 (dt, $J$ = 10.5, 2.3 Hz, 1H), 4.00 (dd, $J$ = 11.6, 10.2 Hz, 1H), 3.81 (d, $J$ = 12.2 Hz, 1H), 3.42 (dt, $J$ = 9.7, 4.0 Hz, 1H), 2.99 (dd, $J$ = 14.2, 4.5 Hz, 1H), 2.86 (d, $J$ = 13.5 Hz, 1H), 2.82 (dd, $J$ = 14.3, 9.9 Hz, 1H), 2.69 (s, 1H), 2.21 (dq, $J$ = 11.5, 3.7 Hz, 1H), 1.67 (d, $J$ = 6.9 Hz, 3H), 1.66 (br s, 1H) ppm.

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ = 143.8, 137.4, 136.7, 127.4, 122.7, 122.4, 122.3, 119.6, 119.1, 113.0, 111.4, 101.6, 62.8, 58.4, 47.0, 38.8, 38.7, 29.8, 13.3 ppm.

HRMS (EI): $m/z$: calculated for C$_{19}$H$_{22}$N$_2$O [M]$^+$ 294.1732, found 294.1728.

IR (CHCl$_3$): 3151, 3055, 2974, 2920, 1644, 1618 cm$^{-1}$.

TLC: (20:80 MeOH:DCM): $R_f$ = 0.73 (UV, KMnO$_4$).
Scheme 5.16: Preparation of (19Z)-Taberpsychine (15)

To an argon flushed 10 mL flask was added Des-N4-methyl (19Z)-taberpsychine 147 (12 mg, 0.04 mmol, 1.00 eq.), and MeOH (1 mL). To the flask was added formaldehyde (42 μL of a 37% aq. solution, 0.51 mmol, 12.8 eq.), then NaBH₃CN (26 mg, 0.41 mmol, 10.3 eq.). The reaction was stirred at 21 °C until complete consumption of starting material was observed by TLC (ca. 0.5 hours). Upon completion the reaction was quenched with aq. 2 M NaOH (1 mL), and was diluted in water (30 mL). The aqueous layer was extracted with DCM (3 x 25 mL). The combined organic layers were washed with aq. 2 M NaOH (1 x 50 mL), water (1 x 50 mL), brine (1 x 50 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The crude material was purified by SiO₂ flash chromatography [16 g SiO₂, 20 mm column diameter, 3% 7 N NH₃ in MeOH: 97% DCM, loaded as a solution in 2 mL of DCM] to yield the product 15 as a white solid (9 mg, 73%). In some instances, an impurity remained in the product. The product was dissolved in Et₂O (40 mL), and was extracted with 5% HCl (20 mL). The aqueous layer was washed with Et₂O (2 x 20 ml). Next, aq. 2 M NaOH (30 mL) was added, and the aqueous layer was extracted with Et₂O (3 x 25 mL). The combined organic layers were washed with sat. aq. NH₃ (50 ml), brine (1 x 50 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure to yield the product 15 as a white solid (9 mg, 73%).

Physical State: White solid.

¹H NMR (600 MHz, CDCl₃): δ = 7.98 (br s, 1H), 7.63 (dd, J = 7.9, 1.0 Hz, 1H), 7.32 (dt, J = 8.1, 0.9 Hz, 1H), 7.19 (ddd, J = 8.1, 7.0, 1.2 Hz, 1H), 7.14 (ddd, J = 8.0, 7.0, 1.1 Hz, 1H), 5.42 (br q, J = 6.8 Hz, 1H), 5.12 (dd, J = 10.1, 1.5 Hz, 1H), 3.84 (dd, J = 11.5, 10.3 Hz, 1H), 3.39 (d, J = 14.9 Hz, 1H), 3.34 (d, J = 14.9 Hz, 1H), 3.31 (dd, J = 15.4, 7.2 Hz,
1H), 3.26 (dd, $J = 11.5, 2.1$ Hz, 1H), 3.22 (dd, $J = 15.4, 10.1$ Hz, 1H), 3.10 (ddd, $J = 10.7, 7.1, 4.2$ Hz, 1H), 2.83 (td, $J = 10.0, 5.5$ Hz, 1H), 2.59 (s, 3H), 2.54 (dt, $J = 9.2, 4.4$ Hz, 1H), 2.43 (dt, $J = 14.4, 9.7$ Hz, 1H), 2.12 (ddd, $J = 14.4, 10.7, 1.4$ Hz, 1H), 1.61 (dd, $J = 6.7, 1.4$ Hz, 3H) ppm.

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta = 136.4, 135.5, 132.2, 128.5, 122.4, 119.9, 119.4, 118.3, 111.2, 111.1, 67.8, 62.1, 60.7, 46.1, 43.2, 37.7, 33.7, 30.6, 18.2, 12.9$ ppm.

HRMS (EI): $m/z$: calculated for C$_{20}$H$_{24}$N$_2$O [M]$^+$ 308.1889, found 308.1889.

IR (CHCl$_3$): 3020, 2964, 2400, 2361, 1521, 1216 cm$^{-1}$.

M.P. Charred between 160 – 250 °C, turned into a tar between 255.2 – 260.6 °C.

TLC: (20:80 MeOH:EtOAc): $R_f = 0.15$ (UV, KMnO$_4$).

**Scheme 5.17:** Preparation of des-$N_4$ methyl isodihydrokoumine (150)

To an oven dried flask was added the NaI (0.264 g, 1.76 mmol, 9.3 eq) while still hot, and was allowed to cool under a flow of argon. To the cooled flask was added acetal 134 (0.0682 g, 0.190 mmol, 1.0 eq), followed by anhydrous acetonitrile (10 mL). Next, TMSCl (130 $\mu$L, 1.0 mmol, 5.3 eq) was added in a single portion to the flask. The rubber septum was replaced with a glass gas inlet adapter containing an argon balloon, and the reaction was protected from light. After allowing the reaction to stir at 21 °C overnight it was quenched with 28% aq. NH$_3$ (3 mL), and 10% Na$_2$S$_2$O$_3$ (3 mL). The reaction was diluted in EtOAc (50 mL), washed with sat. Na$_2$CO$_3$ (1 x 40 mL), brine (1 x 40 mL), dried over anhydrous MgSO$_4$, filtered, and concentrated under reduced pressure. The crude product was purified by SiO$_2$ flash chromatography [16 g SiO$_2$, 20 mm column diameter, 10% 7 N NH$_3$ in MeOH/DCM, loaded as a solution in 3 mL of DCM] to yield des-$N_4$-methyl isodihydrokoumine 150 as a tan crystalline solid (24.3 mg, 43%).
Notes: These reaction conditions were found to rapidly attack metal needles causing metals salt to fall into the reaction. The starting material was consumed within minutes by TLC producing a variety of reaction intermediates which were partially transformed into the product. An NMR study was conducted, and it was found that the reaction needs to stir at 21 °C for at least 8 hours for the highest yields.

Physical state: Tan crystalline solid.

$^1$H NMR (600 MHz, CDCl$_3$): $\delta = 7.59$ (dt, $J = 7.6, 0.9$ Hz, 1H), 7.51 (dt, $J = 7.4, 0.9$ Hz, 1H), 7.33 (td, $J = 7.6, 1.2$ Hz, 1H), 7.23 (td, $J = 7.5, 1.1$ Hz, 1H), 4.99 (ddd, $J = 3.6, 2.4, 1.1$ Hz, 1H), 4.22 (dd, $J = 11.9, 4.5$ Hz, 1H), 3.61 (dd, $J = 11.9, 0.7$ Hz, 1H), 3.36 (d, $J = 12.2$ Hz, 1H), 3.17 (d, $J = 12.2$ Hz, 1H), 3.07 (td, $J = 4.0, 1.6$ Hz, 1H), 2.62 (dt, $J = 14.7, 3.8$ Hz, 1H), 2.58-2.54 (m, 1H), 2.55 (dd, $J = 14.2, 4.0$ Hz, 1H), 2.35 (ddt, $J = 11.3, 2.5, 1.3$ Hz, 1H), 2.30 (dt, $J = 14.0, 2.0$ Hz, 1H), 2.44-2.15 (br s, 1H), 1.64 (dt, $J = 14.0, 2.0$ Hz, 1H), 0.51 (t, $J = 7.4$ Hz, 3H), 0.48-0.37 (m, 2H) ppm.

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta = 185.6, 155.0, 143.4, 128.1, 126.0, 123.2, 121.2, 71.2, 61.2, 59.3, 49.6, 46.5, 41.3, 41.3, 34.3, 28.3, 24.8, 21.6, 6.8$ ppm.

HRMS (EI): $m/z$: calculated for C$_{19}$H$_{22}$N$_2$O [M]$^+$ 294.1732, found 294.1737.

FTIR (AT-IR): 3331, 3030, 2913, 2859, 1578, 1081 cm$^{-1}$.

TLC: (10% 7 N NH$_3$ in MeOH:90% DCM) $R_f = 0.35$ (UV, KMnO$_4$).

M.P. 192.4 – 195.4 °C.

Scheme 5.18: Preparation of isodihydrokoumine (89)

To a 20 mL flask was added des-$N_4$-methyl isodihydrokoumine 150 (52.9 mg, 0.180 mmol, 1.0 eq) followed by MeOH (4 mL), and DCM (1 mL). Next, sodium
cyanoborohydride (18.6 mg, 0.296 mmol, 1.6 eq), and 37% aqueous formaldehyde (30 μL, 0.359 mmol, 2.0 eq) were added simultaneously to the vial in air. The vial was stirred at 21 °C in air until complete consumption of starting material was observed by TLC (ca. 30 minutes). The reaction was diluted in EtOAc (40 mL), was washed with sat. NaHCO₃ (1 x 40 mL), brine (1 x 40 mL), dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The tan residue was purified by SiO₂ flash chromatography [16 g SiO₂, 20 mm column diameter, 8% 7 N NH₃ in MeOH/DCM, loaded as a solution in 3 mL of DCM] to yield the product 89 as a white crystalline solid (31.8 mg, 57% yield).

**Physical state:** White crystalline solid.

1H NMR (600 MHz, CDCl₃): δ = 7.60 (dt, J = 7.7, 0.8 Hz, 1H), 7.57 (dt, J = 7.4, 0.9 Hz, 1H), 7.34 (td, J = 7.6, 1.2 Hz, 1H), 7.24 (td, J = 7.5, 1.1 Hz, 1H), 4.99 (ddd, J = 3.6, 2.4, 1.1 Hz, 1H), 4.25 (dd, J = 11.9, 4.4 Hz, 1H), 3.61 (d, J = 11.9 Hz, 1H), 3.09 (d, J = 11.3 Hz, 1H), 2.87 (d, J = 11.3 Hz, 1H), 2.76-2.71 (m, 2H), 2.62 (dt, J = 14.6, 3.8 Hz, 1H), 2.58 (s, 3H), 2.40 (dt, J = 14.4, 1.9 Hz, 1H), 2.35-2.30 (m, 1H), 2.32 (dd, J = 14.3, 3.2 Hz, 1H), 1.63 (dt, J = 14.6, 2.3 Hz, 1H), 0.53 (t, J = 7.4 Hz, 3H), 0.48-0.42 (m, 1H), 0.42-0.35 (m, 1H) ppm.

13C NMR (151 MHz, CDCl₃): δ = 185.7, 155.1, 143.5, 128.1, 125.8, 123.2, 121.3, 71.1, 61.6, 59.5, 56.9, 56.2, 43.0, 42.8, 39.2, 28.5, 27.6, 24.8, 21.8, 6.8 ppm.

**HRMS (EI):** m/z: calculated for C₂₀H₂₄N₂O [M]⁺ 308.1889, found 308.1895.

**FTIR (AT-IR):** 3066, 2928, 2866, 1587, 1019 cm⁻¹.

**TLC:** (5% 7 N NH₃ in MeOH: 95% DCM) Rₜ = 0.29 (UV, KMnO₄).

**M.P.** 147.8 – 149.6 °C.

![Scheme 5.19](image)

**Scheme 5.19:** Preparation of isodihydrokoumine N₄-oxide 154 and 155
To a 20 mL oven dried argon flushed flask was added isodihydrokoumine 89 (31.8 mg, 0.103 mmol, 1.0 eq), and DCM (4 mL). The solution was cooled to 0 °C, followed by adding mCPBA (21.4 mg, 0.124 mmol, 1.2 eq) as a solution in DCM (1 mL). The reaction was allowed to stir at 0 °C until complete consumption of the starting material was observed by TLC (ca. 15 minutes). The reaction was purified by SiO$_2$ flash chromatography [16 g SiO$_2$, 20 mm column diameter, 20% 7 N NH$_3$ in MeOH/DCM, loaded the reaction directly onto the column] to yield (4S)-isodihydrokoumine N$_4$-oxide (154) (21.8 mg, 64%), and (4R)-isodihydrokoumine N$_4$-oxide (155) (12.8 mg, 35%) both as white semi-solids.

(4S)-isodihydrokoumine N$_4$-oxide (unnatural epimer, 154)

**Physical state:** White semi-solid.

$^1$H NMR (600 MHz, CD$_3$OD): $\delta = 7.56$ (t, $J = 7.5$ Hz, 2H), 7.43 (td, $J = 7.6$, 1.2 Hz, 1H), 7.36 (td, $J = 7.5$, 1.2 Hz, 1H), 4.94 (ddd, $J = 3.7$, 2.4, 1.1 Hz, 1H), 4.41 (dd, $J = 12.4$, 5.1 Hz, 1H), 3.99 (d, $J = 14.0$ Hz, 1H), 3.77-3.72 (m, 1H), 3.70 (d, $J = 12.4$ Hz, 1H), 3.61 (d, $J = 14.0$ Hz, 1H), 3.57 (br t, $J = 3.0$ Hz, 1H), 3.53 (s, 3H), 2.82 (dd, $J = 16.7$, 3.7 Hz, 1H), 2.80 (dt, $J = 15.1$, 3.8 Hz, 1H), 2.60 (d, $J = 9.1$ Hz, 1H), 2.55 (dt, $J = 16.6$, 2.0 Hz, 1H), 1.69 (dt, $J = 15.5$, 2.3 Hz, 1H), 0.61 (t, $J = 7.5$ Hz, 3H), 0.47 (q, $J = 7.4$ Hz, 2H) ppm.

$^{13}$C NMR (101 MHz, CD$_3$OD): $\delta = 186.0$, 155.2, 142.5, 130.1, 128.0, 124.4, 122.1, 72.1, 71.7, 71.7, 60.9, 58.3, 58.2, 45.3, 33.8, 31.0, 26.2, 24.7, 21.9, 6.8 ppm.

HRMS (EI): $m/z$: calculated for C$_{20}$H$_{24}$N$_2$O [M-H]$^+$ 322.1692, found 322.1683.

FTIR (AT-IR): 3044, 2692, 2880, 1651, 1614, 1591 cm$^{-1}$.

TLC: (20% 7 N NH$_3$ in MeOH: 80% DCM) $R_f = 0.45$ (UV, KMnO$_4$).

(4R)-isodihydrokoumine N$_4$-oxide (natural epimer, 155)

**Physical state:** White semi-solid.
\textbf{\textsuperscript{1}H NMR} (600 MHz, CD\textsubscript{3}OD): \(\delta = 7.70\) (d, \(J = 7.5\) Hz, 1H), 7.56 (d, \(J = 7.5\) Hz, 1H), 7.42 (td, \(J = 7.6, 1.3\) Hz, 1H), 7.35 (td, \(J = 7.5, 1.2\) Hz, 1H), 4.94 (ddd, \(J = 3.5, 2.3, 1.0\) Hz, 1H), 4.37 (dd, \(J = 12.4, 5.0\) Hz, 1H), 3.87 (d, \(J = 13.8\) Hz, 1H), 3.82 (d, \(J = 13.8\) Hz, 1H), 3.72 (d, \(J = 12.4\) Hz, 1H), 3.53-3.47 (m, 2H), 3.42 (s, 3H), 3.09 (dt, \(J = 12.2, 3.2\) Hz, 1H), 1.70 (dt, \(J = 15.3, 1.8\) Hz, 1H), 0.58 (t, \(J = 7.4\) Hz, 3H), 0.50-0.44 (m, 2H) ppm.

\textbf{\textsuperscript{13}C NMR} (151 MHz, CD\textsubscript{3}OD): \(\delta = 186.5, 155.1, 143.2, 129.8, 127.9, 124.9, 121.9, 73.9, 73.1, 71.6, 61.0, 60.1, 58.1, 45.1, 35.9, 27.8, 26.6, 24.7, 22.2, 6.7\) ppm.

\textbf{HRMS} (EI): \(m/z:\) calculated for C\textsubscript{20}H\textsubscript{24}N\textsubscript{2}O [M-H\textsubscript{2}]\textsuperscript{+} 322.1692, found 322.1683.

\textbf{FTIR} (AT-IR): 3010, 2926, 2489, 1650, 1594 cm\textsuperscript{-1}.

\textbf{TLC}: (20\% 7 N NH\textsubscript{3} in MeOH: 80\% DCM) \(R_f = 0.27\) (UV, KMnO\textsubscript{4}).

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{Scheme_5.20.png}
\caption{Scheme 5.20: Preparation of hemi-aminal ether 146}
\end{figure}

To an argon flushed NMR tube was added acetal 134 (23.0 mg, 0.064 mmol, 1.0 eq), Sc(OTf)\textsubscript{3} (48.4 mg, 0.098 mmol, 1.5 eq), D\textsubscript{2}O (0.5 mL), and CD\textsubscript{3}CN (0.2 mL). The NMR tube was sealed, and was heated to 50 \(^{\circ}\)C for five hours. The reaction was cooled to 21 \(^{\circ}\)C and was analyzed by NMR. The product 146 was unstable to isolation, and was characterized from the reaction mixture directly.

\textbf{\textsuperscript{1}H NMR} (600 MHz, CDCl\textsubscript{3}): \(\delta = 7.90\) (dt, \(J = 7.9, 1.0\) Hz, 1H), 7.75 (dt, \(J = 8.2, 1.0\) Hz, 1H), 7.54 (s, 1H), 7.49 (ddd, \(J = 8.2, 7.0, 1.2\) Hz, 1H), 7.40 (ddd, \(J = 7.9, 7.0, 1.0\) Hz, 1H), 6.04 (q, \(J = 6.9\) Hz, 1H), 5.27 (dd, \(J = 10.1, 2.1\) Hz, 1H), 4.44 (d, \(J = 13.9\) Hz, 1H), 4.27 (dd, \(J = 11.2, 3.8\) Hz, 1H), 4.02 (td, \(J = 7.9, 4.0\) Hz, 1H), 3.86 (t, \(J = 11.8\) Hz, 1H), 3.50 (d, \(J = 13.9\) Hz, 1H), 3.36 (dd, \(J = 14.9, 7.5\) Hz, 1H), 3.30 (dd, \(J = 14.9, 8.3\) Hz, 1H),
3.00 (s, 1H), 2.55-2.48 (m, 2H), 1.97 (dt, $J = 6.8, 2.2$ Hz, 3H), 1.81 (ddd, $J = 14.0, 10.0, 5.4$ Hz, 1H) ppm.

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta = 135.9, 126.6, 125.9, 125.0, 123.9, 121.5, 120.9, 118.8, 117.7, 117.6, 111.3, 106.8, 90.9, 59.4, 56.7, 48.3, 43.2, 36.6, 35.5, 32.5, 25.6, 11.8$ ppm.

HRMS (EI): $m/z$: calculated for C$_{19}$H$_{22}$N$_2$O [M]$^+$ 294.1732, found 294.1727.

IR (CHCl$_3$): 3356, 3010, 2946, 2989, 1645 cm$^{-1}$.

Scheme 5.21: Preparation of indole 163

This procedure was adapted from the work of Tamaru and co-workers.$^{82}$ A 3 L oven dried flask with a stir bar was equipped with a condenser. The joints were greased while hot and the apparatus was cooled under high vacuum (0.4 torr). The system was backfilled with argon, then the Pd(PPh$_3$)$_4$ (1.78 g, 1.54 mmol, 0.3 mol%), and indole (60.50 g, 516 mmol, 1.0 eq) was added. The system was evacuated, then backfilled with argon two more times. To the flask was added THF (1200 mL) via cannula, allyl alcohol (37 mL, 544 mmol, 1.05 eq), and triethylborane (160 mL of a 1.0 M solution in hexanes, 160 mmol, 0.3 eq). The reaction was refluxed until complete consumption of starting material was observed by TLC (ca. 20 hours). The reaction was cooled to 21 °C, and was quenched with a mixture of sat. NH$_4$Cl (150 mL), 5% HCl (40 mL), and AcOH (40 mL). The reaction was diluted in EtOAc (1 L), and was washed with sat. NH$_4$Cl (1 x 500 mL), brine (1 x 500 mL), dried over anhydrous MgSO$_4$, filtered, and concentrated under reduced pressure. The crude product was used without further purification. A pure sample could be obtained by SiO$_2$ flash chromatography [1 g crude sample, 150 g SiO$_2$, 40 mm column diameter, 8% EtOAc/hexanes (1 L), loaded in 10 mL of the eluent system] to yield the pure product 163 as a yellow oil.
Physical state: Yellow oil.

$^1$H NMR (600 MHz, CDCl$_3$): $\delta = 7.91$ (br s, 1H), 7.64 (dq, $J = 7.9$, 1.0 Hz, 1H), 7.37 (dt, $J = 8.2$, 0.9 Hz, 1H), 7.22 (ddd, $J = 8.2$, 7.0, 1.2 Hz, 1H), 7.15 (ddd, 8.0, 7.0, 1.0 Hz, 1H), 6.99 (dt, $J = 2.2$, 1.0 Hz, 1H), 6.11 (ddt, $J = 16.5$, 9.9, 6.4 Hz, 1H), 5.20 (dq, $J = 17.0$, 1.7 Hz, 1H), 5.11 (dq, $J = 10.0$, 1.6 Hz, 1H), 3.56 (dq, $J = 6.5$, 1.5 Hz, 2H) ppm.

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta = 137.4$, 136.5, 127.5, 122.1, 121.8, 119.4, 119.2, 115.3, 114.6, 111.2, 29.9 ppm.

HRMS (EI): $m/z$: calculated for C$_{11}$H$_{11}$N [M]$^+$ 157.089, found 157.0890.

IR (thin film): 3418, 3059, 3004, 2977, 2897, 2830, 2245, 1639, 1619 cm$^{-1}$.

TLC: (5:95 EtOAc:Hexanes): $R_f = 0.34$ (UV, KMnO$_4$).

Scheme 5.22: Preparation of indoline 169 and 170

To a 3 L flask was added the crude indole 163 (assumed 81.12 g, 516 mmol, 1.0 eq), and AcOH (600 mL). The solution was cooled on an ice slurry, and once it began to freeze NaBH$_3$CN (66.12 g, 1050 mmol, 2.0 eq) was added in portions over the course of 30 minutes. About halfway through the sodium cyanoborohydride addition the reaction mixture turned from a yellow slurry into a black slurry. Once the addition was complete the reaction was allowed to stir overnight at 21 °C. To the resulting black solution was added toluene (600 mL), then the mixture was concentrated under reduced pressure (in a fumehood) to yield a black slurry. The slurry was diluted in water (300 mL) and was cooled to 0 °C. To the mixture was added a precooled NaOH solution (300 g NaOH, 7.50 mol, 14.5 eq, in 600 mL of water) over the course of 15 minutes. The reaction mixture was diluted in water (600 mL), and was extracted with diethyl ether (3 x 600 mL). The combined organic layer was wash with brine (1 x 700 mL), dried over anhydrous MgSO$_4$,
filtered, and concentrated under reduced pressure. The crude product was purified by SiO$_2$ flash chromatography [500 g SiO$_2$, 80 mm column diameter, 20% EtOAc/hexanes (4 L), loaded as a suspension in 150 mL of PhH] to yield the product 170 as a pale yellow oil containing approximately 20 mol % of 169. (est. 55.05 g, 44.64 g alkene 180, 54% yield over 2 steps, 10.41 g alkane 169). The product was used in the next step as a mixture. A pure sample could be obtained by using a pure sample of indole 163 in the reaction.

**Physical state:** Pale yellow oil, darkens upon exposure to air.

$^1$H NMR (600 MHz, CDCl$_3$): $\delta = 7.15$ (dtd, $J = 7.3, 1.2, 0.6$ Hz, 1H), 7.07 (dddd, $J = 8.6, 7.6, 1.2, 0.7$ Hz, 1H), 6.75 (td, $J = 7.4, 1.0$ Hz, 1H), 6.67 (d, $J = 7.8$ Hz, 1H), 5.89 (ddt, $J = 17.1, 10.2, 6.9$ Hz, 1H), 5.14 (dq, $J = 17.1, 1.6$ Hz, 1H), 5.10 (ddt, $J = 10.1, 2.1, 1.2$ Hz, 1H), 3.72 (br s, 1H), 3.67 (t, $J = 8.8$ Hz, 1H), 3.41 (m, 1H), 3.27 (dd, 8.9, 7.2 Hz, 1H), 2.59 (dddt, $J = 14.7, 6.7, 5.4, 1.4$ Hz, 1H), 2.36 (dddt, $J = 14.2, 8.5, 7.1, 1.3$ Hz, 1H) ppm.

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta = 151.5, 136.5, 132.5, 127.6, 124.1, 118.6, 116.5, 109.6, 52.8, 41.5, 38.6$ ppm.

**HRMS (EI):** $m/z$: calculated for C$_{11}$H$_{11}$N [M]+ 159.1048, found 159.1048.

**IR (thin film):** 3380, 3074, 2974, 2923, 2855, 1640, 1608 cm$^{-1}$.

**TLC:** (20:80 EtOAc:Hexanes): $R_f = 0.37$ (UV, KMnO$_4$, ninhydrin).

**Scheme 5.23:** Preparation of tosyl protected indoline

To a 3 L oven dried argon flushed flask was added the indoline mixture of 169, and 170 (55.05 g, 345 mmol, 1.0 eq, est. 44.64 g alkene 170, 10.41 g alkane 169), DMAP (4.64 g, 38.0 mmol, 0.11 eq), $p$-TsCl (71.84 g, 377 mmol, 1.1 eq), and DCM (1 L). The
solution was cooled to 0 °C, then Et$_3$N (71 mL, 512 mmol, 1.5 eq) was added over the course of 10 minutes. Once the Et$_3$N had been added the reaction was stirred at 21 °C until complete consumption of starting material was observed by TLC (ca. 3 hours). The reaction mixture was washed with sat. NH$_4$Cl (1 x 500 mL), water (1 x 500 mL), 2 M NaOH (1 x 500 mL), brine (1 x 500 mL), dried over anhydrous MgSO$_4$, filtered, and concentrated under reduced pressure. The resulting pale brown oil slowly crystallized under high vacuum (0.4 torr) to yield a pale brown crystalline solid which did not require additional purification, and was used directly in the next step (107.15 g, 99%, est. 86.99 g alkene 184, 20.16 g alkane 185). A pure sample could be obtained by either using pure indoline 170, or by 10% AgNO$_3$ on SiO$_2$ flash chromatography [50 mg crude sample, 16 g 10% AgNO$_3$ on SiO$_2$, 20 mm column diameter, 10% EtOAc/hexanes, loaded in PhH].

**Alkene 184**

**Physical state:** White to tan crystalline solid.

**$^1$H NMR** (600 MHz, CDCl$_3$): $\delta$ = 7.69-7.67 (m, 2H), 7.65 (d, $J = 7.6$ Hz, 1H), 7.24-7.18 (m, 3H), 7.08 (dt, $J = 7.6$, 0.8 Hz, 1H), 6.98 (td, $J = 7.5$, 1.0 Hz, 1H), 5.63 (dddd, $J = 16.8$, 10.2, 7.3, 6.5 Hz, 1H), 5.01 (ddt, $J = 10.2$, 2.0, 1.2 Hz, 1H), 4.97 (dq, $J = 17.1$, 1.6 Hz, 1H), 3.97 (dd, $J = 10.8$, 9.2 Hz, 1H), 3.62 (dd, $J = 10.8$, 5.9 Hz, 1H), 3.21 (ddd, $J = 14.6$, 9.3, 5.4 Hz, 1H), 2.37 (s, 3H), 2.30 (dddt, $J = 14.3$, 8.7, 7.3, 1.3 Hz, 1H), 1.96 (dddt, $J = 14.3$, 8.7, 7.3, 1.3 Hz, 1H) ppm.

**$^{13}$C NMR** (151 MHz, CDCl$_3$): $\delta$ = 144.2, 141.9, 135.0, 134.9, 134.2, 129.7, 128.2, 127.4, 124.6, 123.7, 117.6, 115.0, 55.0, 39.4, 39.2, 21.6 ppm.

**HRMS** (EI): $m/z$: calculated for C$_{18}$H$_{19}$NO$_2$S [M]$^+$ 313.1137, found 313.1136.

**FTIR** (AT-IR): 3081, 2926, 1639, 1594 cm$^{-1}$.

**TLC:** (20:80 EtOAc:Hexanes): $R_f$ = 0.50 (UV, KMnO$_4$).

**M.P.** 59.9 – 60.8 °C.

**Alkane 185**
Physical state: White crystalline solid.

$^1$H NMR (600 MHz, CDCl$_3$): δ = 7.70-7.67 (m, 2H), 7.64 (d, $J = 8.2$ Hz, 1H), 7.24-7.21 (m, 2H), 7.19 (dddd, $J = 8.1$, 7.5, 1.4, 0.7 Hz, 1H), 7.05 (d, $J = 7.5$ Hz, 1H), 6.98 (td, $J = 7.4$, 1.0 Hz, 1H), 3.99 (dd, $J = 10.5$, 9.0 Hz, 1H), 3.56 (dd, $J = 10.5$, 6.1 Hz, 1H), 3.09 (tq, $J = 9.4$, 5.2 Hz, 1H), 2.37 (s, 3H), 1.55-1.48 (m, 1H), 1.31-1.23 (m, 2H), 1.19-1.11 (m, 1H), 0.86 (t, $J = 7.3$ Hz, 3H) ppm.

$^{13}$C NMR (151 MHz, CDCl$_3$): δ = 144.1, 141.8, 136.0, 134.2, 129.7, 128.0, 127.5, 124.5, 123.7, 115.0, 55.7, 40.0, 37.2, 21.7, 20.3, 14.1 ppm.

HRMS (EI): $m/z$: calculated for C$_{18}$H$_{21}$NO$_2$S [M]$^+$ 315.1293, found 315.1297.

FTIR (AT-IR): 3006, 2960, 2931, 1597, 1349 cm$^{-1}$.

TLC: (20:80 EtOAc:Hexanes): $R_f = 0.50$ (UV, KMnO$_4$).

M.P. 97.7 – 100.2 °C.

Scheme 5.24: Preparation of aldehyde 135

A 5 L 3 neck flask was equipped with a mechanical stirrer, rubber septa, and vacuum adapter. The flask was evacuated/backfilled with argon three times. To the flask was added tosyl protected indoline 184/185 (90.15 g, 288 mmol, 1.0 eq, est. 73.16 g alkene 184; 16.95 g alkane 185), 1,4-dioxane (1500 mL), 2,6-lutidine (70 mL, 603 mmol, 2.1 eq), and water (500 mL). Next, solid OsO$_4$ (0.783 g, 3.08 mmol, 0.011 eq) was added, then the reaction for stirred for 10 minutes. During this time the reaction turned from a light orange colour into a dark brown colour. Sodium periodate (248 g, 1160 mmol, 4.0 eq) was added in a single portion. The reaction was stirred at 21 °C under argon until complete consumption of starting material was observed by TLC ($ca.$ 3 hours). To the
reaction was added water (1 L). The reaction mixture was vacuum filtered, followed by
extracting the filtrate with EtOAc (2 x 1 L). The combined organic layers were washed
with water (1 x 1 L), 10% Na₂S₂O₃ (2 x 500 mL), 0.6 M HCl (1 x 1 L), brine, (1 x 1 L),
dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The
crude brown oil was purified by SiO₂ flash chromatography [550 g SiO₂, 80 mm column
diameter, 40% EtOAc/hexanes, loaded as a solution in 150 mL of benzene] to yield the
aldehyde 135 as a light pink oil which crystallized on cooling (64.78 g, 88% over 2 steps
based on alkene 170).

Notes: The reaction quickly warmed to 30-40 °C once the NaIO₄ had been added.

Physical state: White to pink crystalline Solid.

¹H NMR (600 MHz, CDCl₃): δ = 9.72 (s, 1H), 7.69-7.64 (m, 3H), 7.25-7.18 (m, 3H),
7.04 (d, J = 7.4 Hz, 1H), 6.99 (td, J = 7.5, 1.0 Hz, 1H), 4.11 (dd, J = 10.8, 8.9 Hz, 1H),
3.59 (tt, J = 9.0, 5.1 Hz, 1H), 3.54 (dd, J = 10.8, 5.7 Hz, 1H), 2.74 (ddd, J = 18.6, 4.8, 0.8
Hz, 1H), 2.44 (ddd, J = 18.7, 8.9, 0.7 Hz, 1H), 2.37 (s, 3H) ppm.

¹³C NMR (151 MHz, CDCl₃): δ = 199.8, 144.4, 141.8, 133.9, 133.9, 129.8, 128.6, 127.4,
124.5, 124.0, 115.2, 55.8, 49.4, 34.1, 21.7 ppm.

HRMS (EI): m/z: calculated for C₁₇H₁₇NO₃S [M]+ 315.0929, found 315.0942.

FTIR (AT-IR): 3024, 2816, 2720, 1723, 1600 cm⁻¹.

TLC: (40:60 EtOAc:Hexanes): Rₜ = 0.40 (UV, KMnO₄, anisaldehyde).

M.P. 97.5 – 100.7 ºC.

Scheme 5.25: Preparation of indole 164
Compound 164 was prepared via a modified literature procedure. To a 1 L flask was added indole 163 (12.91 g, 82.1 mmol, 1.0 eq.), tetrabutylammonium hydrogen sulfate (1.957 g, 5.76 mmol, 7 mol%), toluene (400 mL), and p-toluenesulfonyl chloride (17.24 g, 90.4 mmol, 1.1 eq). The solution was cooled to 0 °C, then a solution of KOH (58.07 g, 1034 mmol, 12.6 eq) in water (60 mL) was added in a single portion. The biphasic mixture was stirred rapidly until complete consumption of starting material was observed by TLC (ca. 1.5 hours). The reaction layers were separated, then the organic phase was washed with water (1 x 400 mL), brine (1 x 400 mL), dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The obtained solids were dissolved in refluxing MeOH (ca. 350 mL). The dark brown solution was allowed to cool to 21 °C, then 0 °C, then –10 °C. The obtained crystals were isolated by vacuum filtration, and were washed with MeOH (1 x 30 mL). The filtrate was concentrated, dissolved in refluxing MeOH (ca. 50 mL) and cooled to 21 °C, then 0 °C, then –10 °C to yield an additional crop of crystals. The product 164 was obtained as a light tan crystalline solid (21.25 g, 83%).

Physical state: Light tan crystalline solid.

**H NMR** (600 MHz, CDCl₃): δ = 7.98 (dt, J = 8.4, 0.9 Hz, 1H), 7.75 (m, 2H), 7.47 (dt, J = 7.9, 1.0 Hz, 1H), 7.33 (t, J = 1.2 Hz, 1H), 7.30 (ddd, J = 8.4, 7.2, 1.3 Hz, 1H), 7.22 (ddd, J = 7.9, 7.3, 1.0 Hz, 1H), 7.20 (m, 2H), 5.99 (ddt, J = 16.7, 10.1, 6.4 Hz, 1H), 5.13 (dq, 10.7, 1.6 Hz, 1H), 5.11 (m, 1H), 3.42 (dq, J = 6.4, 1.4 Hz, 2H), 2.33 (s, 3H) ppm.

**C NMR** (151 MHz, CDCl₃): δ = 144.8, 135.6, 135.4, 131.0, 129.9, 126.9, 124.8, 123.4, 123.1, 121.3, 119.8, 116.7, 113.9, 29.6, 21.7 ppm.

**HRMS** (EI): m/z: calculated for C₁₈H₁₇NO₂S [M⁺] 311.0980, found 311.0980.

**IR** (CHCl₃): 3020, 2955, 1641, 1599 cm⁻¹.

**M.P.** 102.8 – 104.2 °C.

**TLC:** (5:95 EtOAc:Hexanes): Rₜ = 0.28 (UV, KMnO₄).
Scheme 5.26: Preparation of aldehyde 130

To a 2 L argon flushed flask was added tosyl protected indole 164 (21.25 g, 68.3 mmol, 1.0 eq.), acetone (700 mL), water (250 mL), and 4-Methylmorpholine N-oxide (12.09 g, 103 mmol, 1.5 eq.). Once all the reagents had dissolved, solid OsO₄ (0.195 g, 0.767 mmol, 1.1 mol%) was added in a single portion. The reaction was stirred at 21 °C until complete consumption of starting material was observed by TLC (ca. 20 hours, 80:20 EtOAc:Hexanes). The reaction was diluted in brine (800 mL), and was extracted with EtOAc (3 x 400 mL). The organic layer was washed with 10% aq. Na₂SO₃ (1 x 600 mL), brine (1 x 500 mL), dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure to yield a brown foam.

The crude product was transferred into a 1 L flask argon flushed flask. To the flask was added THF (420 mL), water (130 mL), and NaIO₄ (58.37 g, 273 mmol, 4.0 eq.). The reaction was stirred at 21 °C until complete consumption of starting material was observed by TLC (ca. 1 hour). The reaction was diluted in EtOAc (800 mL) and was washed with water (2 x 500 mL), brine (1 x 500 mL), dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure to yield the product 130 as a light brown powder that was used without further purification (20.34 g, 95% over 2 steps). A pure sample was obtained by SiO₂ flash chromatography [1 g sample loading, 90 g SiO₂, 40 mm column diameter, 40% EtOAc/hexanes, loaded as a solution in 10 mL of PhH] to yield the product as a white crystalline solid.

Notes: The reaction became pleasantly warm to the touch after the NaIO₄ had been added.

Physical state: White crystalline solid to light brown powder.
1H NMR (600 MHz, CDCl3): δ = 9.75 (t, J = 2.1 Hz, 1H), 8.01 (dt, J = 8.3, 0.9 Hz, 1H), 7.78 (m, 2H), 7.57 (br t, J = 7.9, 1.0 Hz, 1H), 7.42 (dt, J = 7.9, 1.0 Hz, 1H), 7.35 (ddd, J = 8.0, 7.4, 1.0 Hz, 1H), 7.25 (ddd, J = 8.0, 7.4, 1.0 Hz, 1H), 7.23 (m, 2H), 3.75 (dd, J = 2.2, 1.0 Hz, 2H), 2.34 (s, 3H) ppm.

13C NMR (151 MHz, CDCl3): δ = 198.0, 145.2, 135.3, 135.2, 130.5, 130.1, 127.0, 125.3, 125.1, 123.5, 119.4, 113.9, 113.0, 40.0, 21.7 ppm.

HRMS (EI): m/z: calculated for C17H15NO3S [M]+ 313.0773, found 313.0784.

IR (CHCl3): 3020, 2400, 1729, 1601 cm⁻¹.

M.P. 120.0 – 121.5 °C.

TLC: 0.60 (50:50 EtOAc:Hexanes): Rf = 0.60 (UV, KMnO4).

Scheme 5.27: Preparation of iodoacrylate 88

Compound 88 was prepared via a modified literature procedure. To a 1 L flask was added sodium iodide (285 g, 1.90 mol, 1.6 eq.), then flask was heated under high vacuum (0.4 torr) for 1 hour at 100 °C, followed by cooling to 21 °C. The flask was backfilled with argon, then AcOH (450 mL) was added with vigorous shaking to prevent the NaI from clumping together. Methyl propiolate (186) (100 g, 1.19 mol, 1.0 eq.) was added, and the flask was immersed into an oil bath preheated to 115 °C. The reaction was stirred vigorously at 115 °C for 1 hour, then poured directly into ice slush (1.3 L) while hot. The resulting mixture was extracted with Et2O (3 x 400 mL). The combined organic layers were washed with aq. 2 M NaOH (3 x 200 mL), sat. NaHCO3 (1 x 500 mL), aq. 10% Na2SO3 (200 mL), brine (1 x 400 mL), dried over MgSO4, filtered, and concentrated under reduced pressure to yield the product 88 as a yellow oil (288 g of a 75% solution in Et2O, 216 g neat) Due to the volatility of the product it was not fully concentrated, but
instead used as a solution in Et$_2$O without further purification. The spectroscopic data was identical to the data reported in the literature.$^{89}$

\[
\begin{array}{c}
\text{NH}_2\text{OH}+\text{HCl} \\
\text{187} \quad \text{Boc}_2\text{O}, \text{Et}_3\text{N} \\
\text{H}_2\text{O}, \text{MTBE}, \text{Pentane} \\
\text{0}^\circ\text{C} - \text{21}^\circ\text{C} \\
\text{65% yield} \\
\text{180} \quad \text{BocNH-OBoc}
\end{array}
\]

**Scheme 5.28:** Preparation of protected hydroxylamine 180

Compound 180 was prepared via a modified literature procedure.$^{91}$ To a 3 L flask was added hydroxylamine hydrochloride (60 g, 863 mmol, 1.0 eq.), and water (600 mL). The solution was cooled to 0 $^\circ$C. In a 2 L Erlenmeyer flask was added Boc$_2$O (386 g, 1.77 mol, 2.1 eq.), Et$_3$N (251 mL, 1.81 mol, 2.1 eq.), methyl tert-butyl ether (MTBE) (120 mL), and pentane (600 mL). The Boc$_2$O solution was cooled to 0 $^\circ$C. The 3 L flask was equipped with a 1 L addition funnel, then the cold Boc$_2$O solution was added. The Boc$_2$O solution was added dropwise to the 0 $^\circ$C hydroxylamine solution over the course of 40 minutes. Once the addition was complete the reaction was stirred for 1 hour at 0 $^\circ$C, then at 21 $^\circ$C for 12 h. After 12 hours the two phases were separated, and the organic layer was washed with sat. aq. NH$_4$Cl (2 x 600 mL), brine (1 x 600 mL), dried over anhydrous MgSO$_4$, and concentrated under reduced pressure. The crude reaction was cooled to -78 $^\circ$C under high vacuum (0.4 torr) in a dry ice/acetone bath during which time the product made cracking noises as it froze into a glass. Once the solution had completely frozen, it was allowed to warm to 21 $^\circ$C during which point it began to crystallize. Once the reaction had warmed to 21 $^\circ$C it was allowed to completely crystallize under high vaccum (0.4 torr), then hexanes (400 mL) was added to the flask. The product was isolated by vacuum filtration, washed with hexanes (1 x 200 mL), dried by pulling air through, then additionally dried under high vacuum (0.4 torr) for 3 hours. The product 180 was obtained as a brilliant white free flowing crystalline solid. The spectroscopic data was identical to the data reported in the literature.$^{91}$

**Notes:** Vigorous stirring was required to ensure optimal mixing of the biphasic reaction mixture to consistently obtain high yields.
Scheme 5.29: Preparation of ligand L1

Compound L1 was prepared via a modified literature procedure.\textsuperscript{92} To a 1 L argon flushed oven dried flask was added 2,4,6-trimethylaniline (29 mL, 200 mmol, 1.0 eq.), pyridine (20 mL, 240 mmol, 1.2 eq.) and DCM (200 mL). The solution was cooled to 0 °C, then ethyl oxalyl chloride (27.5 mL, 240 mmol, 1.2 eq.) was added dropwise over the course of 10 minutes. The reaction was stirred for 10 minutes at 0 °C once the addition was complete, then at 21 °C for 12 h. The reaction was then diluted in EtOAc (1200 mL), and was washed with 5% HCl (2 x 300 mL), sat. aq. NaHCO\textsubscript{3} (1 x 500 mL), brine (1 x 500 mL), dried over anhydrous MgSO\textsubscript{4}, filtered, and concentrated under reduced pressure. The crude product 189 was obtained as a pale pink solid, and was used without further purification.

Crude oxalamide 189 was added to a 2 L flask, followed by ethanolamine (15.7 mL, 260 mmol, 1.3 eq.), and DCM (600 mL). The flask was equipped with a condenser, purged with argon, then refluxed for 12 hours. The reaction was diluted in EtOAc (800 mL), and was washed with 5% HCl (1 x 500 mL), brine (1 x 500 mL), dried over anhydrous MgSO\textsubscript{4}, filtered, and concentrated under reduced pressure. The crude product 190 was obtained as an off white solid, and was used without further purification.
A 2 L 5-neck flask was equipped with a reflux condenser, an addition funnel, and stopper. The apparatus was assembled while hot, and was allowed to cool under constant flow of argon. To the flask was added LiAlH₄ (31.3 g, 826 mmol, 4.0 eq.), and THF (700 mL). To the addition funnel was added the crude ethanolamide 190 in THF (700 mL). The LiAlH₄ solution was heated to reflux, then the solution of the crude ethanolamide 190 in THF was added dropwise over the course of an hour. Note: It was found that if the ethanolamide 190 was added at 0 °C, followed by warming the solution to reflux, a strong exotherm resulted that nearly overflowed the flask. Once the addition of ethanolamide 190 was complete, the suspension was refluxed for 20 hours. The reaction was cooled to 0 °C, followed by adding sat. Rochelles salt (400 mL) over the course of one hour. The chunky solids were removed by vacuum filtration, and the resulting solution was concentrated under reduced pressure. The mixture was diluted in EtOAc (1 L), and was washed with brine (1 x 500 mL), dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The crude product 191 was obtained as a yellow oil, and was used without further purification.

To a 2 L flask was added the crude diamine 191, Et₂O (1 L), and a solution of AcCl (14 mL, 196 mmol, 1.0 eq.) in MeOH (95 mL) at 0 °C (as a source of anhydrous HCl). The resulting suspension was stirred for 10 minutes at 0 °C, after which point it was concentrated under reduced pressure. To the flask was added trimethyl orthoformate (110 mL, 1.00 mol, 5.0 eq.), and toluene (700 mL). The reaction was heated to 90 °C for 12 h. The reaction was cooled to 21 °C, and was concentrated under reduced pressure. To the residue was added water (2.5 L). The aqueous solution was washed with EtOAc (3 x 1.2 L), and hexanes (1 x 1 L). To the aqueous layer was added potassium hexafluorophosphate (73 g, 397 mmol, 2.0 eq.), then the mixture was stirred for 3 hours at 21 °C. The resulting mixture was extracted with DCM (3 x 800 mL). The combined organic layers were washed with brine (1 x 1 L), dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure. The crude reaction mixture was dissolved in refluxing s-butanol (ca. 400 mL). The brown solution was allowed to cool to 21 °C, and sit undisturbed for 48 hours at -5 °C. The crystals were isolated by vacuum filtration, washed with s-butanol (1 x 100 mL), hexanes (2 x 200 mL), dried by pulling air through, and further dried under high vacuum (0.4 torr) for 12 hours to yield L1 as tan crystals (51
g, 63% over 4 steps). The spectroscopic data was identical to the data reported in the literature.\textsuperscript{92}

**X-ray Crystallography Data of the hydrogen oxalate salt of 118**

X-ray quality crystals were prepared by vapor diffusion of benzene into a solution of 118 in acetonitrile containing 1.05 eq. of oxalic acid. All X-ray measurements were made on a Bruker Kappa Axis Apex2 diffractometer at a temperature of 110 K. \textit{Data Collection and Processing}. The sample was submitted by Jeff Kerkovius of the Kerr research group at the University of Western Ontario. The sample was mounted on a Mitegen polyimide micromount with a small amount of Paratone N oil. All X-ray measurements were made on a Bruker-Nonius KappaCCD Apex2 diffractometer at a temperature of 110 K. The unit cell dimensions were determined from a symmetry constrained fit of 9906 reflections with $91^\circ < 2\theta < 129.06^\circ$. The data collection strategy was a number of $\omega$ and $\varphi$ scans which collected data up to $132.534^\circ$ (20). The frame integration was performed using SAINT.\textsuperscript{93} The resulting raw data was scaled and absorption corrected using a multi-scan averaging of symmetry equivalent data using SADABS.\textsuperscript{94}

\textit{Structure Solution and Refinement}. The structure was solved by using a dual space methodology using the SHELXT program.\textsuperscript{95} The molecule is disordered, but all non-hydrogen atoms from the dominant conformer were obtained from the initial solution. The distinct positions for the lesser disorder component were obtained from a subsequent difference Fourier map. The carbon bound hydrogen atoms were introduced at idealized positions and were allowed to ride on the parent carbon. The O and N bound hydrogen atom positions were obtained from a difference Fourier map and were allowed to refine isotropically. The structural model was fit to the data using full matrix least-squares based on $F^2$. The normalized occupancy for the predominant conformer refined to a value of 0.603(5). The calculated structure factors included corrections for anomalous dispersion from the usual tabulation. The structure was refined using the SHELXL program from the SHELX suite of crystallographic software.\textsuperscript{96} Graphic plots were produced using the NRCVAX program suite.\textsuperscript{97} Additional information and other relevant
literature references can be found in the reference section of this website (http://xray.chem.uwo.ca).

**Table 5.1: Summary of Crystal Data for hydrogen oxalate salt of 118**

<table>
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<th>Description</th>
<th>Value</th>
</tr>
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<td>Formula</td>
<td>$\text{C}<em>{20}\text{H}</em>{27}\text{NO}_6$</td>
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<tr>
<td>Formula Weight $(g/mol)$</td>
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<tr>
<td>Crystal Dimensions $(mm)$</td>
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<tr>
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<td>$b$,°</td>
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</tr>
<tr>
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</tr>
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<td>$V$, Å$^3$</td>
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<tr>
<td>Number of reflections to determine final unit cell</td>
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</tr>
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<td>Min and Max 2θ for cell determination, °</td>
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</tr>
<tr>
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<td>full matrix least-squares using $F^2$</td>
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<td>Weighting Scheme</td>
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Where:

- $R_1 = \frac{\sum |F_o| - |F_c|}{\sum F_o}$
- $wR_2 = \sqrt{\frac{\sum (w(F_o^2 - F_c^2))^2}{\sum (wF_o^4)}}$
- $\text{GOF} = \sqrt{\frac{\sum (w(F_o^2 - F_c^2))^2}{(\text{No. of reflns.} - \text{No. of params.})}}$
Figure 5.3: ORTEP drawing of the hydrogen oxalate salt of 118 showing naming and numbering scheme. Ellipsoids are at the 50% probability level and hydrogen atoms were omitted for clarity. The disordered portion of the molecule is depicted as “hollow” atoms and bonds.
Figure 5.4: ORTEP drawing of the hydrogen oxalate salt of 118. Ellipsoids are at the 50% probability level and hydrogen atoms were omitted for clarity. The disordered portion of the molecule is depicted as “hollow” atoms and bonds.
Figure 5.5: Stereoscopic ORTEP drawing of the hydrogen oxalate salt of 118. Ellipsoids are at the 50% probability level and hydrogen atoms were omitted for clarity. The disordered portion of the molecule is depicted as “hollow” atoms and bonds.
Appendix A – NMR Spectra
Compound 86

$^1$H NMR (600 MHz, CDCl$_3$)
Compound 86

$^{13}$C NMR (151 MHz, CDCl$_3$)
Compound 85
$^1$H NMR (600 MHz, CDCl$_3$)
Compound 85

$^{13}$C NMR (151 MHz, CDCl$_3$)
Compound 84

$^1$H NMR (600 MHz, CDCl$_3$)
Compound 84

$^{13}C$ NMR (151 MHz, CDCl$_3$)
Compound 94

$^1$H NMR (600 MHz, acetone-$d_6$)
Compound 94

$^{13}$C NMR (101 MHz, acetone-$d_6$)
Compound 141

Compound 137

$^1$H NMR (600 MHz, CDCl$_3$)
Compound 141

Compound 137

$^{13}$C NMR (151 MHz, CDCl$_3$)
Compound 182

Compound 183

$^1$H NMR (600 MHz, CDCl$_3$)
Compound 182

Compound 183

$^{13}$C NMR (151 MHz, CDCl$_3$)
Compound 139

$^1$H NMR (600 MHz, CDCl$_3$)
Compound 139

$^{13}$C NMR (151 MHz, CDCl$_3$)
Compound 141

$^1$H NMR (600 MHz, CDCl$_3$)
Compound 141

$^{13}$C NMR (151 MHz, CDCl$_3$)
Compound 134

$^1$H NMR (600 MHz, CD$_3$OD)
Compound 134

$^{13}$C NMR (151 MHz, CD$_3$OD)
Compound 132
$^1$H NMR (600 MHz, CDCl$_3$)
Compound 132

$^{13}$C NMR (151 MHz, CDCl$_3$)
Compound 133
$^1$H NMR (600 MHz, CDCl$_3$)
Compound 133

$^{13}$C NMR (151 MHz, CDCl$_3$)
Compound 147

$^1$H NMR (600 MHz, CDCl$_3$)
Compound 147

$^{13}$C NMR (151 MHz, CDCl$_3$)
Compound 145

$^1$H NMR (600 MHz, CDCl$_3$)
Compound 145

$^{13}$C NMR (151 MHz, CDCl$_3$)
(19Z)-taberpsychine (15)

$^1$H NMR (600 MHz, CDCl$_3$)
(19Z)-taberpsychine (15)
$^{13}$C NMR (151 MHz, CDCl$_3$)
Compound 150

$^1$H NMR (600 MHz, CDCl$_3$)
Compound 150

$^{13}$C NMR (151 MHz, CDCl$_3$)
Isodihydrokoumine (89)

$^1$H NMR (600 MHz, CDCl$_3$)
Isodihydrokoumine (89)

$^{13}$C NMR (151 MHz, CDCl$_3$)
Compound 154

$^{1}$H NMR (600 MHz, CD$_3$OD)
Compound 154

$^{13}$C NMR (151 MHz, CD$_3$OD)
(4R)-isodihydrokoumine $N_4$-oxide (155)

$^1$H NMR (600 MHz, CD$_3$OD)
(4R)-isodihydrokoumine $N_4$-oxide (155)

$^{13}$C NMR (151 MHz, CD$_3$OD)
Compound 146

$^1$H NMR (600 MHz, D$_2$O/CD$_3$CN)
Compound 146

$^{13}$C NMR (151 MHz, D$_2$O/CD$_3$CN)
Compound 163

$^1$H NMR (600 MHz, CDCl$_3$)
Compound 163

$^{13}$C NMR (151 MHz, CDCl$_3$)
Compound 170

$^1$H NMR (600 MHz, CDCl$_3$)
Compound 170

$^{13}$C NMR (151 MHz, CDCl$_3$)
Compound 184

$^1$H NMR (600 MHz, CDCl$_3$)
Compound 184

$^{13}$C NMR (151 MHz, CDCl$_3$)
Compound 185

$^1$H NMR (600 MHz, CDCl$_3$)
Compound 185

$^{13}$C NMR (151 MHz, CDCl$_3$)
Compound 135

$^1$H NMR (600 MHz, CDCl$_3$)
Compound 135

$^{13}$C NMR (151 MHz, CDCl$_3$)
Compound 164

$^1$H NMR (600 MHz, CDCl$_3$)
Compound 164

$^{13}$C NMR (151 MHz, CDCl$_3$)
Compound 130

$^1$H NMR (600 MHz, CDCl$_3$)
Compound 130

$^{13}$C NMR (151 MHz, CDCl$_3$)
Appendix B – References


32 11-methoxykoumine and 11-methoxytaberpsychine only appears as a product in their respective synthesis papers, and have not been found in any other references as searched by Sci-Finder® and Web of Science™.


Tetrakis(triphenylphosphine)palladium(0), (Product number: 216666) from sigma costs $143 CAD for 5 g. (Accessed April 24th, 2018).


Bruker-AXS, SAINT version 2013.8, 2013, Bruker-AXS, Madison, WI 53711, USA.

Bruker-AXS, SADABS version 2012.1, 2012, Bruker-AXS, Madison, WI 53711, USA.

Bruker-AXS, SADABS version 2012.1, 2012, Bruker-AXS, Madison, WI 53711, USA.


Appendix C – Curriculum Vitae

Education

University of Western Ontario September 2016-Present
M. Sc. Chemistry
Supervisor: Dr. Mike Kerr

University of British Columbia – Okanagan Campus September 2010-April 2016
Bachelor of Science, Honours Chemistry
Honours Degree Supervisor: Dr. Fred Menard

Awards

<table>
<thead>
<tr>
<th>Award</th>
<th>Amount</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipson-Baines Departmental Seminar Award</td>
<td>$1000</td>
<td>April 2018</td>
</tr>
<tr>
<td>NSERC Canada Graduate Scholarship-Masters Program (CGSM)</td>
<td>$17500</td>
<td>May 2017</td>
</tr>
<tr>
<td>UBC International Go Global Award</td>
<td>$1900</td>
<td>July 2016</td>
</tr>
<tr>
<td>99th Annual CSC Organic Poster Competition 2nd Place</td>
<td>$50</td>
<td>June 2016</td>
</tr>
<tr>
<td>UBC Student Union Special Travel Scholarship</td>
<td>$1600</td>
<td>May 2016</td>
</tr>
<tr>
<td>ECCU Conference Travel Award</td>
<td>$300</td>
<td>May 2016</td>
</tr>
</tbody>
</table>
2016 WCUCC Top Organic Oral Presentation — $125 May 2016
Western University Entrance Scholarship — $2500 April 2016
2015 WCUCC Oral Presentation Pedagogy Award — $500 May 2015
UBC Okanagan Provost Award for Teaching Assistants and Tutors — $500 May 2015
Irving K. Barber School Undergraduate Research Award — $8000 March 2015
UBC Okanagan Undergraduate Researcher of the Year Award — $1000 March 2015
UBC Okanagan Deans List Member — $0 April 2014
UBC Tuum Est Conference Travel Fund — $500 February 2014
British Columbia Government Scholarship — $1000 October 2011
Interior Savings Credit Union Bursary — $1000 September 2010
Special University of British Columbia Okanagan Award - X-Country Skiing — $100 September 2010

Publications

Research Experience

M.Sc. Research September 2016-Present
Developed novel cyclization chemistry allowing the synthesis of isodihydrokoumine, and isodihydrokoumine N4 oxide
Proposed a total synthesis project to Dr. Kerr, then completed the total synthesis of (±)-(19Z)-Taberpsychine in 11 steps based on that design
Working on the development of a divergent synthesis of the Humantenine class of alkaloids specifically aimed at Geleganidines A-C
Worked on the development of a novel azetidine synthesis methodology by ring expansion of donor-acceptor cyclopropanes
Supervisor: Dr. Mike Kerr

Worked towards developing a molecule for the traceless labeling of SERCA proteins in live cells
In charge of the development and synthesis of a sulfonium ion based lysine alkylation linker  
Supervisor: Dr. Frederic Menard

**Undergraduate Research Award (Barber School URA)  May 2015-August 2015**

Developed a second-generation approach to synthesize state-of-the-art labelling molecules for use in research into heart and Alzheimer’s disease  
Developed a bulk synthesis strategy for my calcium channel labels to allow for collaborative cell-imaging research using my molecule  
Supervisor: Dr. Frederic Menard

**Murch Lab Collaboration  May 2015-May 2016**

Synthesized an isomer of an un-natural amino acid for the Murch lab to analyze in mass spectrometry experiments  
Collaborated with a student from the Murch lab working towards developing the synthesis of four other un-natural amino acid isomers  
Supervisor: Dr. Frederic Menard, Dr. Susan Murch


Developed the synthesis for state-of-the-art fluorescent protein labelling molecules for use in heart and Alzheimer’s disease research  
Molecules are being used as proof-of-concept experiments in the development of next-generation protein-labeling techniques  
Supervisor: Dr. Frederic Menard

**Organic Chemistry Research Assistant  April 2014-September 2014**

Created a synthesis for and then synthesized novel fluorescent calcium channel labels with applications in neuroscience  
Developed a superior synthesis of the fluorescent dye Pacific Blue  
Purified the final product by preparatory HPLC  
Supervisor: Dr. Frederic Menard

**Organic Chemistry Research Volunteer  June 2013-September 2013**

Synthesized novel pyrazole based drugs, and characterized their biological activity in collaboration with a cell biology group  
Supervisor: Dr. Edward Neeland

**Hydrology Lab Research Assistant  May 2013-September 2013**

Collected soil, gas and moisture samples on grape and apple crops in the field  
Analyzed field samples in a Hydrology lab with the goal of figuring out how to lower greenhouse gas emissions for the Okanagan’s two biggest crops: apples and grapes  
Supervisor: Dr. Craig Nichol
Conference Presentations

8th BSOC (Banff Symposium on Organic Chemistry) Conference - Poster October 2017

100th Annual Canadian Society for Chemistry Conference - Poster June 2017
Kerkovius, J.K.; Kerr, M.A. “Studies Towards the Synthesis of Geleganidine B” 100th CSC Conference and Exhibition, Toronto, ON, June 2017, Abstract 02426.

QOMSBOC 2016 - Poster November 2016


99th Annual Canadian Society for Chemistry Conference - Poster June 2016

99th Annual Canadian Society for Chemistry Conference - Poster June 2016

30th Annual Western Canadian Undergraduate Chemistry Conference - Oral May 2016

Barber School Undergraduate Research Award Symposium - Oral September 2015

98th Annual Canadian Society for Chemistry Conference - Poster June 2015
29\textsuperscript{th} Annual Western Canadian Undergraduate Chemistry Conference (WCUCC) - Oral May 2015
Kerkovius, J.K.; Menard, F “Synthesis of an in vivo Traceless Affinity Label for the SERCA Protein” 29\textsuperscript{th} WCUCC, UBC Okanagan, Kelowna BC, May 2015.

Barber School Research Symposium – Poster April 2015
Kerkovius, J.K.; Menard, F. “Calcium Channel Imaging Tag for use in Fluorescence microscopy” 10\textsuperscript{th} Irving K. Barber School of Arts and Sciences Annual Undergraduate Research Conference, UBC Okanagan Kelowna BC, April 2015. Abstract 14.

UBC Student Leadership Conference (SLC) – Oral Nov 2014
Kerkovius, J.K.; Cloherty, A. “Supplemental Learning: Beyond everyday leadership” 8\textsuperscript{th} Annual Student Leadership Conference, UBC Okanagan, Kelowna BC, Nov 2014.

Service to the Chemistry Community

Mechanism Monday Organizer June 2017-Present
Founded a voluntary mechanism club for chemistry graduate students at the University of Western Ontario (UWO)
Conducted weekly meetings to discuss interesting or neat organic reaction mechanisms in a group setting, with the goal of improving problem solving, and teaching skills for the attendees

Chemistry Show Coordinator May 2017
Responsible for preparing demonstrations, including testing new experiments to showcase
Responsible for setup and takedown at an outdoor venue

Chemistry with a Bang Volunteer September 2016
Responsible for setting up demonstrations and cleaning up after the show was complete

Destination UBC Chemistry Show Volunteer May 2016
Responsible for developing new demonstrations, performing demonstrations in the show, and cleaning up after the show was complete

Western Canadian Undergraduate Chemistry Conference (WCUCC) May 2014-May 2015
Conference Chair: Coordinated, and directed the conference management committee of nine undergraduate students
Responsible for organizing all aspects of a three-day conference with attendance of 120 chemistry students and faculty

UBC Okanagan Chemistry Course Union (CCU) Executive September 2013-April 2016
Selected, managed, and trained team of 33 tutors for the CCU, offering > 70 hours of one-on-one tutoring assistance each week to students in the chemical sciences
Facilitated academic undergraduate chemistry student support on campus through the CCU. Personally tutored for two hours a week in all areas of chemistry.

**Meet the Deans Create Student Panel Member**  
*September 2015*

Responded to questions from the audience on what my experience was like at UBC Okanagan.

**Create Orientation Leader**  
*September 2014*

Responsible for giving a group of 15 first year students a tour of the campus with the goal of making the new students feel that they had made the right choice to come to UBC Okanagan.

### Teaching Experience

**Chemistry 2283 TA (UWO)**  
*January 2017-April 2017*

In charge of running two lab sections each week ensuring students complete their experiments in a timely and safe manner.

Marked student lab reports and exams.

**Western Resource Room TA (UWO)**  
*September 2016-December 2016*

In charge of running two tutorial sessions a week for a variable number of students.

Tutored and mentored students in second year organic chemistry (Chem 2213A).

Conducted group tutoring sessions for up to 50 people at a time.

**Supplemental Learning (SL) Student Mentor (UBCO)**  
*May 2014-April 2016*

In charge of mentoring a group of SL leaders to create top class SL leaders.

Organized an annual SL retreat for all SL leaders to create and share ideas to improve the program as a whole.

**Learning (SL) Program Leader (UBCO)**  
*May 2014-April 2016*

Attended the 8th annual international SL conference in Chicago IL, July 2014.

Developed and implemented Improvements to SL training and delivery.

Worked with another SL leader to train all new SL leaders and tutors.

**Supplemental Learning (SL) Student Leader (UBCO)**  
*September 2013-April 2014*

Ran two sessions a week for students that were each an hour and a half long.

Acquired skills to teach other students effectively.

Organized and prepared my own material for each session.

**Chemistry Tutor (UBCO and UWO)**  
*September 2010-Present*

Tutored high school, first year and second year university students in general and organic chemistry.

### Media

**Canadian Chemical News (ACCN) Showcase (UBCO)**  
*January 2016*

A showcase article about my research in a new column written on outstanding students featured in the Canadian Chemical News Journal.
It is located on the ACCN Website at: http://www.cheminst.ca/magazine/columns/king-synthesis

**Undergraduate Researcher of the Year Video (UBCO)** March 2015
Video summary about myself and my research for my research award
Can be found on the Irving K Barber School YouTube Channel or at: https://goo.gl/syFFFq

**Barber School Student Showcase (UBCO)** October 2015
Article written about excellent students in the Irving K Barber school of Arts and Science
It can be found at: https://ourstories.ok.ubc.ca/stories/jeff-kerkovius/

**UBCO Chemistry Department Student Profile (UBCO)** March 2015
My personal profile is featured on the home page of the UBCO chemistry department website
It is located on the UBCO Chemistry Homepage at: http://chem.ok.ubc.ca/profile.html

**Work Experience**

<table>
<thead>
<tr>
<th>Position</th>
<th>Dates</th>
<th>Responsibilities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exam Invigilator (UBCO)</td>
<td>September 2013-April 2014</td>
<td>Invigilated Exams for first- and second-year chemistry courses</td>
</tr>
<tr>
<td>Exam Marker (UBCO)</td>
<td>September 2013-April 2014</td>
<td>Marked first- and second-year chemistry exams alongside the professor</td>
</tr>
<tr>
<td>Assistant Teaching Assistant (UBCO)</td>
<td>September 2013-April 2014</td>
<td>Ensured labs were conducted in a safe and timely manner</td>
</tr>
<tr>
<td>SOKS Science Camp Coordinator (SOKS)</td>
<td>May 2012-August 2012</td>
<td>Designed and ran multiple experiments for camps throughout the summer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Counted inventory and created a detailed budget for the camp</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Created itineraries for each day</td>
</tr>
<tr>
<td>Assistant Coach (Telemark Ski Team)</td>
<td>October 2010-April 2014</td>
<td>Coached children ages 6 to 13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acquired basic medical training from St John’s Ambulance</td>
</tr>
</tbody>
</table>

**Personal Information**

Canadian Citizen
Callaghan Valley National Cross Country Skiing Training Center member in Whistler, BC in 2011-2012
UBCO Heat cross country running team member, 2012-2013
Attended 2012 cross country running national championships, Montreal, Quebec.
Second place in the 10 km classic race at the Canadian National Cross Country Skiing Championships, Mont St. Anne, Quebec