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Total Synthesis of (+)-nemorensic acid: En Route to (-)-callosine

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Graduate Program in Chemistry

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Abstract

An intramolecular oxime ether cyclopropane annulation developed in 2008 by Kerr has been shown to form 2,5-trans and 2,5-cis pyrrolidines in a stereodivergent fashion. When the oxime ether is functionalized with an enantioenhanced α-hydroxy substituent and a leaving group, the pyrrolizidine core of (-)-callosine can be accessed in short order. Callosine is a structurally unique pyrrolizidine alkaloid isolated from Mexican flowering plant Senecio callosus. In an effort to complete the total synthesis, the total synthesis of (+)-nemorensic acid, the necic acid component of the callosine, has been established. Attempts at appending the ansa bridge via esterification and macrolactonization are discussed.

Keywords

Cyclopropane, pyrrolizidine, annulation, callosine, nemorensic acid, necine base, necic acid, pyrrolidine, heterocycle, natural product, macrolactonization.
Co-Authorship Statement

The route to the pyrrolizidine core of callosine was established by previous graduate student Alex Driega. I have reproduced his work with identical yields and significantly shortened the route to the enantiopure cyclopropane starting material.

The majority of the experimental work for the alkylation of oximes with cyclopropyl halides followed by annulation (Section 1.2.5, Scheme 24) was performed by Meredith Allen. This manuscript is in preparation.
Acknowledgments

Firstly, I’d like to thank Dr. Michael Kerr for the opportunity to join the group. You have been a great supervisor – approachable, motivating, and intimidatingly clever, yet flexible, and always encouraging of creative side projects. Thank you for supporting my desire to attend conferences even if it interfered with lab time.

Dr. Huck Grover is the person responsible for the chemist I am today. I often wonder how different my life would be had you chosen James Stubbs to volunteer for you instead of me. You were the perfect teacher, and I proudly teach new chemists the things you taught me years ago. Except the way you ran columns. What was up with that? Good luck and see you at conferences in the future.

To my first volunteer, then 4491 student, current lab mate, and forever friend Lauren Irwin, it’s been wonderful watching you grow as a chemist. I’ll always remember how you added acetic acid to the wrong reaction on one of your first days. Contrast that with how you’re now two bonds away from tronocarpine. I would like take responsibility for the chemist you’ve become, but in reality you deserve every ounce of credit. Here’s an interesting thought: you’re going to get your PhD before me. What!? I will miss you dearly. Visit me often!

Meredith, it has been a treat to collaborate on a project with you. Mainly because I didn’t have to do any work. Your dedication to your thesis is inspiring and will soon be rewarded by a nice first authored publication. I am glad you decided not to pursue medicine, not because you wouldn’t make a great doctor, but because academia will
benefit from you more (sounds a bit biased, no?). Kill it in the Beauchemin group and keep in touch.

To the folks in 217: thanks for always having a place for me to come by when chemistry was not working well. Poly, I’ll never forget (mainly because it’s burned into my eyes) what you did after the kijiji deal. Matty, I’ll miss your winks. I promise we’ll go star-gazing before I leave. And Joanne – thanks for essentially organizing the whole Hawaii trip. It was an unforgettable adventure that I’m glad we had the chance to share together. Best of luck to all of you.

Thanks to Erin for the mandarin vodka, shampoo, and the trip to Canada’s Wonderland that you’ll never know about.

To my lovely pre-wife Natalie: are you ready for the adventure of a lifetime? We are about to go do what every couple dreams about doing together and that’s pretty special. Am I intentionally leaving that previous sentence ambiguous? Maybe. I am so thankful that I’m always able to come home to a stress-free and loving environment after long lab days. You are the reason I always have a positive attitude. I’m so excited to start the next chapter of our lives together.

Lastly, I’d like to thank my parents, who independently funded my entire undergraduate degree. None of this would have been possible without your unconditional love and support. I promise to repay you some day.
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<th>Full Form</th>
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<tbody>
<tr>
<td>1,2-DME</td>
<td>1,2-dimethoxyethane</td>
</tr>
<tr>
<td>Å</td>
<td>angstrom</td>
</tr>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>AD-mix</td>
<td>asymmetric dihydroxylation mixture</td>
</tr>
<tr>
<td>Ar</td>
<td>aromatic</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>BRSM</td>
<td>based on recovered starting material</td>
</tr>
<tr>
<td>Cbz</td>
<td>carboxybenzyl</td>
</tr>
<tr>
<td>CSA</td>
<td>camphor sulfonic acid</td>
</tr>
<tr>
<td>DA</td>
<td>donor-acceptor</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazabicycloundec-7-ene</td>
</tr>
<tr>
<td>DCC</td>
<td>dicyclohexylcarbodiimide</td>
</tr>
<tr>
<td>DCE</td>
<td>1,2-dichloroethane</td>
</tr>
<tr>
<td>DDQ</td>
<td>2,3-dichloro-5,6-dicyano-1,4-benzoquinone</td>
</tr>
<tr>
<td>DIPEA</td>
<td>diisopropyl ethyl amine (Hünig’s base)</td>
</tr>
<tr>
<td>DIPT</td>
<td>diisopropyl tartrate</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-(dimethylamino)pyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>dimethylformamide</td>
</tr>
<tr>
<td>DMP</td>
<td>dess martin periodinane</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethyl sulfoxide</td>
</tr>
<tr>
<td>E+</td>
<td>electrophile</td>
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<td>Abbreviation</td>
<td>Full Form</td>
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<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>EDG</td>
<td>electron donating group</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>EWG</td>
<td>electron withdrawing group</td>
</tr>
<tr>
<td>HATU</td>
<td>(1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate)</td>
</tr>
<tr>
<td>HBTU</td>
<td>N,N,N′,N′-Tetramethyl-O-(1H-benzotriazol-1-yl)uronium hexafluorophosphate</td>
</tr>
<tr>
<td>HMMC</td>
<td>homo-Michael addition Mannich closure</td>
</tr>
<tr>
<td>IBX</td>
<td>2-iodoxybenzoic acid</td>
</tr>
<tr>
<td>J</td>
<td>coupling constant</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropyl amide</td>
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<td>LG</td>
<td>leaving group</td>
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<tr>
<td>mCPBA</td>
<td>m-chloroperoxybenzoic acid</td>
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<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>MeCN</td>
<td>acetonitrile</td>
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<tr>
<td>Ms</td>
<td>methanesulfonyl</td>
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<tr>
<td>M.S.</td>
<td>molecular sieves</td>
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<td>MTM</td>
<td>methylthiomethyl</td>
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<tr>
<td>μW</td>
<td>microwave</td>
</tr>
<tr>
<td>NBS</td>
<td>N-bromosuccinimide</td>
</tr>
<tr>
<td>NIS</td>
<td>N-iodosuccinimide</td>
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<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>NOESY</td>
<td>Nuclear overhauser effect spectroscopy</td>
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<tr>
<td>Nu'</td>
<td>nucleophile</td>
</tr>
<tr>
<td>OAc</td>
<td>Acetate</td>
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<tr>
<td>PDC</td>
<td>pyridinium dichromate</td>
</tr>
<tr>
<td>Pg</td>
<td>protecting group</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
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<tr>
<td>Phth</td>
<td>phthalimide</td>
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<tr>
<td>Piv</td>
<td>pivaloyl</td>
</tr>
<tr>
<td>PMB</td>
<td>p-methoxybenzyl</td>
</tr>
<tr>
<td>PTSA</td>
<td>p-toluenesulfonic acid</td>
</tr>
<tr>
<td>Pyr</td>
<td>pyridine</td>
</tr>
<tr>
<td>RCM</td>
<td>ring closing metathesis</td>
</tr>
<tr>
<td>SAE</td>
<td>Sharpless asymmetric epoxidation</td>
</tr>
<tr>
<td>S_N1</td>
<td>unimolecular nucleophilic substitution</td>
</tr>
<tr>
<td>S_N2</td>
<td>bimolecular nucleophilic substitution</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetrabutylammonium fluoride</td>
</tr>
<tr>
<td>TBAI</td>
<td>tertbutylammonium iodide</td>
</tr>
<tr>
<td>TBDPS</td>
<td>tertbutyldiphenylsilyl</td>
</tr>
<tr>
<td>TBS</td>
<td>tertbutyldimethylsilyl</td>
</tr>
<tr>
<td>'Bu</td>
<td>tert-butyl</td>
</tr>
<tr>
<td>Tf</td>
<td>trifluoromethanesulfonyl</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
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<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
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<td>Abbreviation</td>
<td>Full Form</td>
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<td>-----------</td>
</tr>
<tr>
<td>THP</td>
<td>tetrahydropyran</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>Tr</td>
<td>triphenylmethyl</td>
</tr>
<tr>
<td>Ts</td>
<td>toluenesulphonyl</td>
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1 Introduction

1.1 Cyclopropanes

1.1.1 Bonding Model of Cyclopropanes

Over the past 20 years, the Kerr group has developed a fascination with the reactivity of cyclopropanes. While it may be convenient to visualize a planar cyclopropane as an equilateral triangle with 3 equivalent 60° bonds, this practice does not explain why it reacts differently than other cycloalkanes. The ring strain as per the deviance from ideal 109.5° bond angles also does not provide an accurate description of the behavior of this molecule. Cyclobutane, its four-carbon homologue, has a near identical ring strain energy but reacts quite differently. Several bonding modes have been proposed in order to explain why cyclopropanes react the way they do. The most accepted currently is the Förster model\textsuperscript{1}, which was later elaborated by Coulson and Moffitt\textsuperscript{2}. This theory states that the hybridized bonding orbitals adapted by cyclopropane are unequal. Relative to a typical sp\textsuperscript{3} hybrid, the internal C-C orbitals display a relatively high amount of p-character, and the external C-H orbitals are higher in s-character. This is validated by NMR evidence, as the \textsuperscript{1}J\textsubscript{C-H} coupling constant for cyclopropane is 160 Hz, which is approximately 40 Hz higher than the C-H bond in ethane. The value is indeed much closer to the coupling constant of an sp\textsuperscript{2} hybridized C-H bond, such as ethylene.
The lack of p character that the exterior hybridized orbitals portray is compensated by the interior C-C bonds, which are approximately sp$^5$ hybridized. This assignment in no way infers that 5 p-orbitals are utilized in this hybrid. It is merely a depiction stating the hybrid orbitals are 1/6 s in character and 5/6 p in character. This increased p-character within the C-C bonds helps alleviate ring strain. More of the electron density is situated away from the ring instead of directly between the carbon nuclei (Figure 1). The nucleophilicity of a cyclopropane is thus similar to an olefin, which have reactive π electrons perpendicular to the C-C center, and thus the reactivity of cyclopropanes is homologous to olefins.

Figure 1: Förster model of cyclopropane bonds

The reactivity of cyclopropane can be tuned by substituting a hydrogen for an electron donating group (EDG) or an electron withdrawing group (EWG). Cyclopropanes bearing EDGs tend to be better nucleophiles, whereas cyclopropanes bearing EWGs are good electrophiles (Scheme 1A). When an EWG and an EDG are substituted in a vicinal disposition within the cyclopropane, it is known as a donor-acceptor (DA) cyclopropane. Thermal or Lewis acid activation of these cyclopropanes results in ring opening, and the charges that result are stabilized by the donor and
acceptor groups (Scheme 1B). This double stabilization often allows for milder reaction conditions compared to mono-activated cyclopropanes.

1.1.2 Donor-Acceptor Cyclopropanes

DA cyclopropanes react analogously to zwitterionic intermediate 8. Nucleophilic additions into and annulations of cyclopropanes have been studied extensively under thermal, high pressure, and Lewis acidic conditions. Many reviews have been published in this area. The products of nucleophilic additions are homologous to the products seen in a traditional Michael addition. In addition to these nucleophilic ring openings, annulations are known to occur when nucleophiles bearing a pendant electrophile are used.
For example, the Kerr group reported the reaction between DA cyclopropanes and nitrones in 2003\textsuperscript{5} (Scheme 2).

\begin{align*}
A \ (n = 1) & \quad \begin{array}{c}
R^I_+ \quad O^- \\
\text{MeO}_2C \\
\text{CO}_2Me
\end{array}
\begin{array}{c}
\text{R}^\text{II} \\
\text{R}^\text{III}
\end{array}
\begin{array}{c}
11 \\
12
\end{array}
\begin{array}{c}
\text{Yb(O Tf)}_3 \ (5 \text{ mol\%}) \\
\text{via}
\end{array}
\begin{array}{c}
R^I_+ \quad O^- \\
\text{MeO}_2C \\
\text{CO}_2Me
\end{array}
\begin{array}{c}
\text{R}^\text{II} \\
\text{R}^\text{III}
\end{array}
\begin{array}{c}
14
\end{array}
\begin{array}{c}
\text{R}^\text{II} \\
\text{R}^\text{III}
\end{array}
\begin{array}{c}
\text{12}
\end{array}
\end{align*}

\begin{align*}
B \ (n = 0) & \quad \begin{array}{c}
R^I_+ \quad O^- \\
\text{R}^\text{II} \\
\text{R}^\text{III}
\end{array}
\begin{array}{c}
\text{EWG} \quad \text{EWG}
\end{array}
\begin{array}{c}
11 \\
15
\end{array}
\begin{array}{c}
\text{via}
\end{array}
\begin{array}{c}
R^I_+ \quad O^- \\
\text{R}^\text{II} \\
\text{R}^\text{III}
\end{array}
\begin{array}{c}
\text{EWG} \quad \text{EWG}
\end{array}
\begin{array}{c}
13 \quad 16
\end{array}
\end{align*}

Scheme 2: Nitrone annulations

In this process, the nucleophilic oxygen of the nitrone ring opens the cyclopropane, and the malonyl anion furnishes an oxazine ring \textit{via} a Mannich ring closure (Scheme 2A). This methodology is homologous to the same reaction with electron poor olefins (Scheme 2B), and will henceforth be referred to the homologous-Michael addition-Mannich ring closure (HMMC). This relationship is highly diastereoselective and results in a cis relationship between substituents $R^{\text{II}}$ and $R^{\text{III}}$ in the resulting tetrahydro-1,2-oxazines. Soon thereafter, it was demonstrated that the nitrones could be prepared in situ from hydroxylamines and aldehydes, creating a convergent system in which three variables are combined at once to produce the oxazines $14^6$. By using enantiopure cyclopropanes as starting materials, it was determined that the initial ring opening event occurred in an $S_{\text{N}2}$-type fashion, inverting the stereochemistry in the resulting oxazines\textsuperscript{7}. In the published literature, it is noted that when the nitrones contain
a hydrogen β to the nitrogen atom, reactions proceed with poor yields (*vide infra*).

Notably, the N-O bonds proved simple to reduce, and after mesylating the newly formed alcohol, 2,5-trans pyrrolidines can be isolated as a result of S_N2 inversion of the secondary alcohol. This extension to the nitrone HMMC was applied in the total synthesis of nakadomarin A^8.

**Scheme 3:** Application of nitrone cyclopropane HMMC – inversion of stereochemistry in the pyrrolidine motif of nakadomarin A
In 2005, the Kerr group realized that pyrrolidines could be formed directly through the cycloaddition reaction between cyclopropanes and imines under similar Lewis acid mediation (Scheme 4)⁹.

![Scheme 4: Imine cyclopropane HMMC cycloaddition](image)

This method notably favours 2,5-cis pyrrolidines, making this procedure complementary to the nitrone HMMC. An intramolecular variant of this transformation was utilized in the first total synthesis of FR901483 (Scheme 5)¹⁰. Treatment of cyclopropylamine 23 with an excess of formaldehyde followed by the imine annulation yielded tricyclic core 24 of the molecule in one step. Again, poor yields were often seen when imines bearing a β-hydrogen were used in the cycloaddition.

![Scheme 5: Application of imine cyclopropane HMMC - FR901483](image)
Continued success in this HMMC sequence and the suitability of the cyclopropane motif to form complex pyrrolidines prompted previous graduate students in the Kerr group to develop similar chemistry towards the synthesis of pyrrolidizine alkaloids.

1.2 Pyrrolizidine Alkaloids

Pyrrolizidine frameworks make up the core of several natural product alkaloids in the angiosperm and asteracae families\textsuperscript{11}. These natural products are often comprised of two components: a necine base (red), and a necic acid (blue) (Figure 2). The necine base portion contains a pyrrolizidine ring and usually bears hydroxy substituents either at position 1 or at positions 1 and 7. The necic acid piece contains either one or two carboxylic acids. Although they are often isolated as ester or macrolactonic combinations of each other, the necine base and necic acid components are all considered natural products. The disconnection can be seen at the bottom of Figure 2. The dilactonic pyrrolizidine alkaloids display a unique variety of biological activities, including hepatotoxicity, carcinogenicity, and anti-tumor properties\textsuperscript{11}. These traits as well as their intricate molecular architecture make them great synthetic targets.
1.2.1 Biosynthesis of Necine Bases

Target oriented synthesis is made easier by drawing inspiration from the way certain frameworks are synthesized naturally. In plants, necine bases are formed via enzymatic manipulation of putrescine, a diamine originating from the decarboxylation of arginine and ornithine (Scheme 6)\textsuperscript{12}.
Putrescine is dimerized into homospermidine by the enzyme homospermidine synthetase. Homospermidine is then transformed into iminium ion 25. Enzyme directed Mannich-type cyclization followed by conversion of the remaining primary amine to an oxygen affords common pyrrolizidine bases isoretronecanol, trachelanthamidine, and in subsequent steps several other necine bases. Even in nature, pyrrolizidines are made by iminium ring closure.

1.2.2 Synthesis of pyrrolizidines via iminium ring closure

Through logical and natural deconstructions of pyrrolizidines, many synthetic methodologies rely on the trapping of iminium ions with internal nucleophiles. For example, Stevens published a summary of his research into alkaloid chemistry, bravely tackling an impressive number of natural products with two enaminyl synthons derived from tetrahydropyridine and dihydropyrrole (Scheme 7)\textsuperscript{13}. These substrates are cleverly constructed from an intramolecular cyclopropane imine rearrangement.
Treatment of the dihydropyrroles with anhydrous mineral acids produced the desired pyrrolidine scaffolds via intramolecular trapping of iminium 28 with the in situ generated enol ether which collapses upon aqueous workup to the aldehyde. The resulting compound gave the group access to the isoretronecanol backbone.

Generating iminium ions by decarboxylating malonyl-tethered amino acids is another way to furnish pyrrolizidines (Scheme 8).
Proline-benzyl ester 30 was alkylated with electrophiles bearing a geminal diethyl ester substituent. Cyclopropane byproducts originating from an undesired Michael-addition-intramolecular S_N2 reaction were formed with unhindered allyl bromides (Scheme 8, Route A, R = H), so sterically bulky bromides such as 31 were used to prevent this. Reduction of the double bond and simultaneous deprotection of the benzyl ester yields carboxylic acid 33. Treating the carboxylic acid with POCl_3 allows for formation of iminium ion 34, which is trapped intramolecularly with the malonyl side chain, forming pyrrolizidine 35. Note that because sterically bulky bromides were used in the alkylation step, only substituted products could be isolated with this route. In order to synthesize the unsubstituted analogues, the alkylation step was performed with triester 36 (Scheme 8, Route B). Deprotection of the benzyl group followed by
decarbethoxylation with sodium benzoate provided the desired unsubstituted intermediate 38, which cyclized under similar reaction conditions.

Intramolecular iminium ion trapping with allyl silanes has also been demonstrated as a viable method of forming the pyrrolizidine skeleton (Scheme 9)\(^{15}\).

The cis relationship of the two new diastereomers is said to be a result of a chair-like transition state of a π complex formed between the olefin and positive charge in intermediate 40. The increased stability of this structure is a result of the β-silicon atom which lowers the energy of this charged complex \(\text{via}\) hyperconjugation. Interestingly, both E and Z olefins 39 form the same pyrrolizidine diastereomer 41. Unfortunately this strategy is limited to racemic derivatives.

In order to control the diastereoselectivity of the Mannich closure, Chamberlin reported on the chemistry of lactam 42, which was synthesized from commercially available (S)-malic acid\(^{16}\) (Scheme 10).

![Scheme 9: Speckamp's pyrrolizidine synthesis](image)
The enantioenriched protected alcohol controlled the facial selectivity of the Mannich-type ring closure, yielding diastereomerically and enantiomerically pure ketene dithioacetal 44. Through a series of chemical transformations, this intermediate was converted into seven enantiopure necic bases: heliotridine, dihydroxyheliotridane, hastunecine, dehydroheliotridine, turneforcidine, platynecine, and retronecine.

More recently, an organocatalytic approach to pyrrolizidines was studied using an asymmetric Mannich ring closure\(^\text{17}\) (Scheme 11). When acetal 45 is treated with a proton source and a chiral secondary amine, the corresponding optically active enamine forms \textit{in situ}, which directs the facial selectivity of the Mannich closure in intermediate 47. The optimized conditions are reasonably stereoselective, and the procedure also works for 5,6 and 6,6 ring systems. Treatment of the resulting enantioenriched lactam 48 with LiAlH\(_4\) provided the necine base trachelanthamidine in short order.
Noting that intramolecular trapping of iminium ions allows rapid access to pyrrolizidines, and recalling that DA cyclopropane annulations form 5-membered nitrogen heterocycles with high diastereoselectivity, we can hypothesize that pyrrolizidine formation from DA cyclopropane starting materials would be a facile process.

1.2.3 Synthesis of Pyrrolizidinones from intramolecular cyclopropane annulations

In a report from Danishefsky\textsuperscript{18}, phthalimide-bearing cyclopropanes 49 are converted to the corresponding pyrrolidizinone derivatives by treating the material with hot hydrazine (Scheme 12). The author notes that the reaction conditions required for these annulations were far less rigorous than analogous intermolecular cyclopropane annulations. The second ring-forming event occurs through lactamization as opposed to Mannich-type cyclization, but still demonstrates that pyrrolizidine backbones can be formed from cyclopropane starting materials.
1.2.4 Total Synthesis of Dilactonic Pyrrolizidine alkaloids

Although several papers report the total synthesis of many naturally occurring necine bases, there are relatively few total syntheses of the dilactonic alkaloids (middle of Figure 2). This is likely because of the increased complexity and difficulty associated with macrolactonization. All of the reported natural products are synthesized nearly identically: synthesis of the necine base (Scheme 13) and necic acid (Scheme 14) components separately, activation of the necic acid, esterification with one of the necine base alcohols, and subsequent lactonization (Scheme 15). As a result, total synthesis of these molecules is a rare case where the route to optically active material is simpler than a route to racemic material: the necine base and necic acid often both contain stereocenters, and convergence of the two pieces would yield a mixture of diastereomers if one or both components were made racemically. This section will discuss only the pioneering article; the first enantiopure synthesis of a dilactonic pyrrolizidine alkaloid.

The total synthesis of (-)-integerrimine was accomplished by Niwa in 1986\textsuperscript{19}. The necine base of (-)-integerrimine, (+)-retronecine, was synthesized in an enantiopure fashion from commercially available (S)-malic acid\textsuperscript{20} (Scheme 13).
Treatment of malic acid 52 with acetyl chloride in the presence of ethanolamine yields cyclic imide 53 after the acetates are removed in ethanolic HCl. Protection of the primary alcohol as the pivoylate followed by careful bromoacetylation of the secondary alcohol furnishes 54. Conversion of the primary halide into a Wittig reagent and treatment with base provides the lactone ring in 55. Reduction of the olefin is realized via hydrogenolysis. The lactam is reduced by conversion into the thiolactam with Lawesson’s reagent followed by sodium cyanoborohydride reduction of its ethyl oxonium salt. A phenylselenium group is appended α to the lactone as a placeholder for elimination to the allylic alcohol in retronecine, and the pivoylate group is removed with HCl. Tosylation of the alcohol and cyclization at the α position of the lactone yields
pyrrolizidine 58. Reduction of the lactone and oxidative elimination of the selenium group affords the allylic diol in (+)-retronecine.

The necic acid component, (+)-integerrinecic acid, was furnished via enantiopure epoxide 60, which was synthesized through Sharpless asymmetric epoxidation (SAE) (Scheme 14)\textsuperscript{21}.

Regioselective opening of the epoxide with trimethylaluminum followed by protection of the primary alcohol gave ester 62. Oxidative cleavage of the olefin followed by lactonization of the newly formed carboxylic acid provided 6-membered lactone 63. Deprotection of the primary alcohol with NaOMe also ring opened the lactone, and thus the crude mixture was treated with PTSA to reform it. Oxidation of the alcohol to the
acid was realized with RuO$_4$ generated in situ, and the acid was capped off as the methyl ester with TMSCHN$_2$. The ethylidene unit was installed via aldol condensation with acetaldehyde followed by elimination. Methanolysis of the lactone, protection of the tertiary alcohol as the MTM ether and hydrolysis of both methyl esters afforded MTM-protected (+)-integerriniecic acid which was suitable for coupling to the retronecine base.

Scheme 15: Niwa's (-)-integerrimine synthesis

The necine base was converted to the 7-membered cyclic stannoxane with dibutyl tin oxide in order to increase the nucleophilicity of the alcohol groups. When this was treated with the anhydride of diacid 66, a nearly quantitative yield of the coupled product was isolated. Macrolactonization with Mukayama’s reagent followed by deprotection of the MTM group yielded (-)-integerrimine. The same research group is credited with the
synthesis of another dilactonic pyrrolizidine alkaloid, monocrotaline\textsuperscript{22}, which was synthesized in a very similar fashion. Other groups have since made integerrimine racemically\textsuperscript{23}. Dicrotaline\textsuperscript{24}, usaramine\textsuperscript{25}, fulvine, and crispatine\textsuperscript{26} have all been synthesized, and two attempts at the molecule crobarbatine have been thwarted by the inability to perform a late stage deprotection\textsuperscript{27}. All of the strategies of these syntheses have involved coupling reactions between the acid components of the necic acid with the alcohols of the necine bases.

1.2.5 Kerr Group’s Attempts at Pyrrolizidine Formation

Having a solid understanding of a cyclopropane’s ability to form densely functionalized pyrrolidines, the synthesis of pyrrolizidines in a similar fashion seemed like a natural extension of this work. Thus, the synthesis of the necine base platynecine from an HMMC became the goal of a previous graduate student. Attempts at furnishing the pyrrolizidine ring via ring closing metathesis were explored (Scheme 16).

![Scheme 16: Attempted pyrrolizidine synthesis via imine cyclopropane HMMC and RCM](image-url)
Using the aforementioned imine chemistry (Scheme 4), pyrrolidine 73 was isolated in a low 14% yield. This is attributed to the reduced reactivity of cyclopropane 71 since it does not bear a donor substituent. Unfortunately this allyl amine did not undergo the desired cyclization under the attempted conditions.

The next undertaking was a similar reaction with nitrone 75, the imine analogue of 72 (Scheme 17).

Scheme 17: Attempted pyrrolizidine synthesis via nitrone cyclopropane HMMC and RCM

Again, after desired tetrahydro-1,2-oxazine 76 was isolated, no conditions screened provided bicycle 77, even under an ethylene atmosphere, and thus further elaboration to platynecine was not possible. With the problematic step being a ring closing reaction, it was hypothesized that executing the initial cyclopropane annulation intramolecularly would obviate the need for this step. With several successes in the literature mentioned in section 1.2.2, it seemed more feasible to form this bond through a Mannich-type ring closure. Tethering the cyclopropane unit to the dipolarophile would ultimately increase the effective concentration between the two reacting motifs, efficiently creating both rings in one pot with milder conditions (Scheme 18).
A cyclopropane was appended to alcohol group of Cbz-protected 3-hydroxyxpyrrolidine 78. The Cbz group was then removed, and the pyrrolidine was oxidized to the nitron. In this particular set of reactions, complexation of 81 with the Lewis acid converted the cyclopropane portion of the substrate into an excellent leaving group, and starting material 79 was isolated after chromatography. Tethering the dipolarophile through an ester linkage seemed to be a problem for intramolecular cyclizations for this reason. To demonstrate that the ester linkage is likely the problem, it was shown that an intramolecular nitron-cyclopropane annulation in an HMMC fashion yielded bicyclic oxazines as the established rules would predict\(^\text{38}\). The nitrones were tethered through the electron donating portion of the cyclopropane and the reactions proceeded without problems (Scheme 19).

Scheme 18: Attempted pyrrolizidine synthesis via intramolecular nitron cyclopropane HMMC
Results of intermolecular cycloadditions with both imines (Scheme 20 A) and nitrones (Scheme 20 B) has shown that competitive deprotonation of a β-hydrogen squanders this reaction’s potential. This is why transformations of this type are often limited to aromatic species. It is without question that a methodology that is limited to derivatives of benzaldehyde is less well received than one with a full scope. From the results of the intramolecular analogues, e.g. Scheme 19, it seems as though this is less of a problem, as substrates such as 83 contain said β-hydrogen and react without the formation of the elimination byproducts. To overcome this hurdle, the Kerr group looked at the intermediate in the nitrone cycloaddition, compound 90 in Scheme 20 B, and noted that a similar intermediate can be formed via N-alkylation of an oxime ether (Scheme 20 C, intermediate 93). The difference between the two is where the cyclopropane is tethered, through the N-C bond or the N-O bond.
The β hydrogen of an oximinium ion is less acidic than the carbon substituted analogues (intermediate 93, Scheme 20 C), and as a result it may not eliminate. This belief can be substantiated by the fact that when methoxylamine condenses with methyl acetoacetate, the oxime ether is formed quantitatively, whereas methylamine forms the enaminoate. It was also hypothesized that due to the electron donating nature of the oxygen substituent, reactions would proceed faster because the nitrogen atom would be more nucleophilic. However when reaction C in Scheme 20 was attempted, it was noted that yields were quite low and very substrate specific. The oxygen atom actually attenuated the nitrogen atom’s nucleophilicity and minor amounts of β elimination products were seen.

Recalling that the intramolecular nitrone-cyclopropane HMMC did not undergo β elimination, and noting the lack of success when the dipolarophile was appended via an
ester linkage, the group decided to attempt an intramolecular oxime ether-cyclopropane HMMC, hoping this would perform better than the intermolecular version. An alkoxyamine was synthesized as a component of the electron donating portion in DA cyclopropane 95 in the hopes that it would condense with an aldehyde to form an oxime ether (Scheme 21).

Scheme 21: Stereodivergent intramolecular oxime-ether cyclopropane annulation
When cyclopropane 95 is treated with an aldehyde in water-absorbing conditions, condensation to the oxime ether is observed. Treatment of these compounds with Yb(OTf)₃ catalyzes the desired HMMC, producing an intermediate analogous to the intermediate formed in the nitrone cycloaddition reaction. This procedure yields 2,5-trans pyrrolidines with exceptional diastereoselectivity. Interestingly, simply reversing the addition order of the aldehyde and the Lewis acid inverts the stereochemistry of the newly generated stereocenter. The final stereochemistry is dictated by the geometry of the intermediate oximinium ion as depicted in Scheme 21.

Scheme 22: Select examples of stereodivergent intramolecular oxime ether cyclopropane cycloaddition.

Note: yields are for step 2 only

Importantly, the method tolerated a broad range of functionality, including aldehydes bearing a β-hydrogen (Scheme 22, compound 109). As such, it served as an appropriate strategy for the pyrrolidine ring in allosecurinine; the total synthesis of which
was realized shortly after the reaction’s discovery\textsuperscript{32}. Both enantiomers of cyclopropane 95 have been isolated, improving the scope of possible naturally occurring pyrrolidines to be synthesized with this process. Further, if the aldehyde in question bears an enantioenhanced $\alpha$-hydroxy group (110), it could lactonize onto the proximal geminal diester after annulation, and be used to incorporate an aspect of stereocontrol (Scheme 23, compound 114). Finally, if a protected leaving group was furnished 4 carbons from the reacting nitrogen (LG in Scheme 23), a simple cyclization would yield the desired pyrrolizidine framework after cleavage of the N-O bond. Krapcho dealkoxycarbonylation and reduction of the lactone would furnish a necine diol. Notably, the resulting pyrrolizidine would contain an ethoxy sidechain at position 3. This strategy maps perfectly onto one of the known pyrrolizidine alkaloids, callosine (\textit{vide infra}).

Scheme 23: Proposed synthesis of (\textit{\textbf{-}})-callosine’s pyrrolizidine core from cyclopropane 95
Realizing the benefit of forming iminium intermediates such as 93 through alkylation, we also realized that cyclopropyl oxime ethers 119 could be formed via O-alkylation of oximes with cyclopropanes bearing alkyl halide sidechains. Thus we can form iminium intermediates like 93 through a two-step alkylation protocol.

Scheme 24: Homologous intramolecular cyclopropane oxime ether HMMC; * = NMR yield

Note that with a 3 carbon tether between the cyclopropane and the halide, the resulting adducts are fused oxazines. The N-O bonds can be reductively cleaved, and pyrrolizidines can be formed after displacement the primary alcohol, similar to the procedure used to form pyrrolidines from nitrone HMMC products (Scheme 3). The experimental work on this project was done by Meredith Allen, a 4491 student that I supervise.
1.2.6 Callosine

1.2.6.1 Isolation and Structure Determination

![Callosine structure](image)

Callosine was originally isolated from the methanolic extracts of the roots, stems, and leaves of Senecio callosus, a plant indigenous to Mexico, as a colourless oil\textsuperscript{34}. Note the 2,5-trans pyrrolidine moiety that perfectly matches the annulation reaction outlined in Scheme 21. The olefin geometry was assigned by NOESY correlation, and the relative stereochemistry of the vicinal methyl groups was assigned based on comparison to bulgarsenine, for which there exists an X-ray structure\textsuperscript{35}. To date, the effects of callosine on biological tissues are unknown.
1.2.6.2 Retrosynthesis

As outlined in Scheme 23, the pyrrolizidine core can be formed via HMMC of the condensation product between α-hydroxyaldehyde 133 and cyclopropane 95. In the reverse direction, the large bislactone macrocycle could be formed by late stage esterification chemistry between necine diol 130 and diacid 129 as seen in previous total syntheses. The synthesis of 129 will be discussed in section 2.4. Pyrrolizidine core 130 can be synthesized as described in Scheme 23: Using an enantioenriched α-hydroxyaldehyde, regiospecific lactonization will occur on the ester cis to the alcohol after the previously highlighted intramolecular HMMC reaction. Forming a bond between the nitrogen and the hydroxy-bearing carbon γ to the aldehyde will yield the second ring in the pyrrolizidine. Krapcho dealkoxycarbonylation of the remaining ester,
N-O bond cleavage, and lactone reduction would provide the pyrrolizidine core of callosine with the exact geometry needed. The synthesis of 130 became the priority of graduate student Alex Driega. Its synthesis, along with modifications we have made to synthesize the cyclopropane and aldehyde portions, will now be discussed.
2 Results and Discussion

2.1 Synthesis of Enantiopure Cyclopropane 95

2.1.1 First Generation Syntheses of Cyclopropane 95

Although the Kerr group has developed and published a route to cyclopropane 95, it was a tedious 10-step process, involving several protections and deprotections (Scheme 26).
The above scheme represents literature yields. Triol 134 is protected as acetal 135 with 3-pentanone. The remaining unprotected alcohol is then benzylated in a 93% yield, and the acetal is quantitatively deprotected. The resulting diol is converted into the cyclic sulfite and then oxidized to the cyclic sulfate in one pot. This crude material is then cyclopropanated with dimethyl malonate to yield benzyl cyclopropane 139 in a 60% yield over 3 steps. The benzyl group is deprotected with hydrogen in the presence of 10% palladium on carbon, and the newly generated alcohol is tosylated in an overall 93% yield. Nucleophilic displacement of the tosylate with N-hydroxyphthalimide produces phthalimido cyclopropane 141 in a 74% yield after recrystallization. The cyclopropane is stored in the freezer as the protected phthalimide because the alkoxyamine that forms after its deprotection tends to intramolecularly displace the cyclopropane shortly after its synthesis.

The other enantiomer is synthesized by a Sharpless asymmetric dihydroxylation of PMB ether 142 (Scheme 26)\textsuperscript{32}.

![Scheme 27: Formation of the other enantiomer of cyclopropane 140](image)

Upon conversion to the mesylate, cyclopropanation with dimethyl malonate and two equivalents of sodium hydride gave the PMB cyclopropane. Deprotection with DDQ provided the opposite enantiomer of intermediate 140, which was carried through to the alkoxyamine cyclopropane 95 as described previously. Note that both of the routes to optically pure cyclopropane 95, especially the one depicted in Scheme 26, require several
protecting group installations and deprotections. This raises the step count and lowers the atom efficiency, which in turn makes it more difficult and more expensive to push through several grams of material. A different approach was necessary.

2.1.2 Second Generation Synthesis of Cyclopropane 95

While this work was initially being performed in 2008, triol 134 was commercially available, but it no longer is. 134 was therefore synthesized by a borane reduction of (S)-malic acid. While repeating this chemistry, the initial protection of triol 134 at best yielded only 9% of acetal 135 even when taking care to distill the pentanone, drying the PTSA, and using freshly activated molecular sieves. Perhaps the reason behind this significant difference was the purity of the triol, although by all spectroscopic methods, the triol appeared pure. This problem was overcome initially by treating triol 134 instead with benzaldehyde dimethyl acetal to yield six-membered acetal 144 (Scheme 28). By use of a known procedure, this was reductively cleaved to yield benzyl protected triol 137 in a 78% yield. Compound 137 could then be taken to cyclopropane 95 as outlined in Scheme 26. This new route had the added benefit of being overall one step shorter to producing the desired cyclopropane as the benzyl protection was incorporated into the acetal protection strategy.
Unfortunately, this was not the only problem encountered in the synthesis of cyclopropane 95. Treatment of 137 with thionyl chloride generated the sulfite cleanly, however subsequent oxidation and cyclopropanation were troublesome as sulfate 138 decomposed readily in the presence of oxygen (Scheme 26). The deprotection of the benzyl group was also troublesome because only 2 grams of benzyl cyclopropane could be deprotected at once, increasing the tedium of this reaction sequence. With all of the problems encountered in this route, only small quantities of cyclopropane 95 were able to be carried through at one time.

2.1.3 Third Generation Synthesis of Cyclopropane 95

Fortunately, all of these problems were solved after a thorough literature search. Triol 134 has previously been converted to sulfate 145 in good yields, which has subsequently been cyclopropanated without affecting the chloride (Scheme 29).
Having this chloride leaving group already bound to the cyclopropane at this position would eliminate the need for any protecting groups to make cyclopropane 95.

Scheme 30: Third generation synthesis of cyclopropane 95

Treatment of triol 134 with 2.2 equivalents of thionyl chloride yields chlorosulfite 148, and after oxidation, sulfate 145 is isolated in a 79% yield over 2 steps after distillation (Scheme 30). As seen in the literature, cyclopropanation occurred cleanly with dimethyl malonate. A Finkelstein reaction substituted chloride 149 for iodide which
was easily converted to phthalimido protected cyclopropane 141. Shortly after, it was realized that the Finkelstein step of this reaction sequence caused minor racemization of the cyclopropane. Ultimately, the Finkelstein step proved to be unnecessary, as direct displacement of the chloride 149 with N-hydroxyphthalimide yields the desired enantiopure cyclopropane 141 in good yield after recrystallization from methanol. All of the steps of this new procedure could be done on multigram scales and none of the intermediates were air or moisture sensitive, allowing for expedient synthesis of the desired cyclopropane. The entire sequence is only four synthetic steps from triol 134 and only requires one chromatographic purification. This is five steps and two purifications shorter than the original procedure. It provides six grams of cyclopropane 141 at a time from eight grams of triol 134 in only five days.

2.2 Synthesis of the Aldehyde Required for the Desired HMMC

Scheme 31: Synthesis of aldehyde 133
After the route to cyclopropane 95 was optimized, the previous method towards the synthesis of desired enantiopure α-hydroxy aldehyde 133 was examined. Its synthesis is straightforward and had already been documented by a former group member (Scheme 31). The above reaction scheme represents my isolated yields. Initially, beginning with (L)-diethyl tartrate, a three-step sulfite formation, nucleophilic displacement, reduction protocol was executed in order to produce the commercially available but prohibitively expensive diethyl malate 152. Purification of this material was difficult as the reaction did not go to completion and the boiling point and Rf values of the starting material and product were similar, leading to mixtures of the two after both chromatography and distillation. This severely limited the amount of material to push forward to aldehyde 133. To circumvent this, (R)-malic acid (52-(R)), which is commercially available and inexpensive, can be quantitatively converted to diethyl ester 152 without purification. The remainder of the synthesis was realized by trityl protection of the secondary alcohol followed by reduction with LiAlH₄. Protection of the least hindered alcohol with TBDPSiCl occurred in a 50% yield after purifying the product from bissilylated material via chromatography. 50 grams of material was synthesized and stored as alcohol 154 to avoid epimerization. When material was needed, Swern oxidation produced desired aldehyde 133 in a 93% yield. Aldehyde 133 contains the α and γ hydroxy groups needed for the synthesis of the pyrrolizidine core of (-)-callosine as outlined in Scheme 23.
2.3 Synthesis of the Necine Base of Callosine

Condensation between aldehyde 133 and cyclopropane 95 afforded oxime ether 155 in a 90% yield over two steps (including the phthalimide deprotection) after purification (Scheme 32). The small amount of Z isomer seen was separable from the desired E product by chromatography. Treatment of 155 with 5 mol% Yb(OTf)$_3$ promoted the desired annulation and additionally the deprotection and lactonization of the trityl alcohol onto the ester cis to it. The yield for this process has been quantitative or nearly quantitative every time the reaction has been repeated. It is noteworthy to mention that at this point that the lactone moiety in molecule 158 will ultimately be
reduced to become the two alcohols requiring esterification in the necine base of (-)-callosine.

Krapcho dealkoxycarbonylation of methyl ester 158 proceeded cleanly to lactone 159 (Scheme 33). Deprotection of the TBDPS group followed by tosylation of the resulting primary alcohol yielded ammonium salt 161, the N-O bond of which was readily cleaved hydrogenolytically. The primary alcohol was protected as a TBDPS ether and the lactone was reduced with LiAlH₄ to form the pyrrolizidine core of callosine in six steps from intermediate 158 in an overall 58% yield. The chemistry was readily scalable, providing over 1 g of diol 130 each time pushing material through.

Scheme 33: Synthesis of the pyrrolizidine core of callosine
After bettering the synthesis of the cyclopropane and aldehyde subunits, large amounts of the core of callosine were easily carried through. Focus thus shifted towards the synthesis of the necic acid component.

2.4 Synthesis of the Necic Acid Unit

2.4.1 Setting the Absolute Geometry of the Methyl Groups in Diacid 129

A previous Kerr group member’s attempt at synthesizing the macrocycle of callosine focused on a molecule that in late stages would undergo a ring closing olefin metathesis (Scheme 34). Coupling carboxylic acid 164 to the primary alcohol of the callosine core and acylation of the secondary alcohol with acryloyl chloride would yield diene 163 which upon ring closing metathesis yield callosine’s macrocycle. Although this is an appealing method to finish the molecule, forming 1,1,2-trisubstituted alkenes from ring closing metathesis is often problematic. Additionally, the reaction would likely face E/Z selectivity issues due to the large ring size. There was also significant difficulty with the protecting group strategy among other steps towards the synthesis of acid 164, so this route was not explored further.

![Scheme 34: Previous retrosynthesis of (-)-callosine’s macrocycle](image-url)
A less risky method for macrocyclization would likely be realized through lactonization chemistry as it has proven to be effective in the syntheses of other pyrrolizidine alkaloids (see section 1.2.4 and references therein) (Scheme 35). The desired dicarboxylate species 129 was then targeted, and the vicinal methyl group geometry was set as it was en route to acid 164.

Scheme 35: Retrosynthesis of (-)-callosine’s macrocycle via lactonization

Reduction of methyl angelate 165 to the allyl alcohol followed by SAE\textsuperscript{39} and trityl protection yields epoxide 167 (Scheme 36). Grignard addition of 2-methallylmagnesium chloride occurs quantitatively and regioselectively for the less hindered site of the epoxide. This afforded the correct geometry of the two stereocenters and provided an olefin handle for further manipulation to the carboxylic acid.
2.4.2 Attempted Synthesis of Necic acid 129 via RCM

Although perhaps not immediately apparent, the most difficult part of synthesizing unit 129 proved to be the double bond geometry. We envisioned that we could exclusively form the Z isomer by hydrolyzing either 8-membered lactone 170, or 7-membered lactone 171, which could both be formed through RCM (Scheme 37).

This strategy does involve forming a 1,1,2-trisubstituted olefin via RCM, which is in part the reason why the route in Scheme 34 was avoided. However, this method does not involve such a late-stage intermediate and therefore involved less risk. Through some protecting group manipulations, either the primary or the tertiary alcohol in 174 could be
acylated with acryloyl chloride. Ring closing metathesis of the resulting dienes 172 or 173 would yield the lactones needed to install the desired Z-olefin geometry. Oxidation of the primary alcohol after lactone hydrolysis and deprotection would lead to desired diacid 129. Dienes 172 and 173 were thus targeted for synthesis (Scheme 38).

Scheme 38: Synthesis of dienes 177 and 179 and observation of furan byproducts 180 and 181

Acylating the tertiary alcohol of 168 would be the most step-economic method to get to diacid 129 because no protecting group modifications would be needed. When treating this compound with base and acryloyl chloride (Scheme 38 A), no acylation was observed, but a small amount furanyl byproduct 180 was isolated. The majority of the alcohol 168 remained unreacted. It is often difficult to acylate tertiary alcohols, and the additional steric bulk from the trityl group likely further impeded this transformation. Instead, we attempted to acylate the primary alcohol.
The initial deprotection of the trityl ether was done with formic acid and the resulting primary alcohol was formylated in the process (Scheme 38 B). The modest yield was attributed to the formation of furan 181. Although this was not the desired product, we figured the tertiary alcohol would be easier to acylate without the bulky trityl group. Indeed, using the same acylation conditions, we were able to isolate small quantities of diene 177.

In order to isolate free diol 178, trityl alcohol 168 was treated with PTSA (Scheme 38 C). This yielded diol 178 in a modest 54% yield, with the majority of the remaining yield attributed the production of furanyl alcohol 181. The importance and formation of these furanyl products will be discussed in section 2.4.4. Acylation of the primary alcohol in 178 yielded diene 179 in a 28% yield, the low yield being again attributed to the formation of the furanyl byproduct as noted by TLC. With dienes 177 and 179 in hand, we then attempted the ring closing metathesis.

Unfortunately, all attempts at ring closing metathesis of diene 177 with varying Grubbs catalysts in various solvents proved unsuccessful, with no significant quantities of the desired product and nearly complete recovery of starting material (Scheme 39 A). Small amounts of dimerization and metathesis with styrene were observed when utilizing alkene 179 (Scheme 39 B), indicating that the catalysts were indeed active, but the 2,2-disubstituted alkene would not participate in the metathesis cycle. Unfortunately, with these results, ring closing metathesis did not seem like a viable method of installing the correct olefin geometry, but it provided evidence that this strategy should not be used to form the macrocycle as depicted in Scheme 34.
2.4.3 Attempted Synthesis of Necic acid 129 via Cuprate Chemistry

It was at this time when we decided to search for alternative methods to produce diacid 129. As stated previously, the necessary geometry of the alkene made the synthesis difficult. A literature search revealed that cuprate additions into alkynyl carbonyl compounds are selective for the desired syn addition products at low temperatures (Scheme 40)\textsuperscript{40}.

We thus imagined building the alkenyl portion of the desired dicarboxylate 129 through cuprate chemistry. Manipulation of intermediate 185 to allylic chloride 186 would yield an intermediate that could be converted into a Grignard reagent to add into
epoxide 167, recalling that the previous epoxide opening with an allylic magnesium chloride was quantitative. Once the Grignard product 187 was isolated, protecting group manipulations and oxidations could yield the desired diester 129 (Scheme 41).

![Scheme 41: Retrosynthesis of dicarboxylate 129 via epoxide opening of allyl magnesium chloride 188](image)

Chloride 186 was then targeted for this strategy. Propargyl alcohol was protected as the tetrahydropyran acetal quantitatively (Scheme 42). Deprotonation of the terminal alkyne and subsequent quenching with ethyl chloroformate yielded ester 191 in 100% yield. 1,4–syn addition of methyl cuprate to 191 provided alkene 192 quantitatively without the need for purification. Treatment of 192 with excess LiAlH₄ yielded alcohol 193 in 76% yield. Note that this alcohol would ultimately become oxidized to an acid in the desired necic acid piece. An orthogonal protecting group capable of withstanding the upcoming Grignard reaction was thus required.
Protection of alcohol 193 as the TBS ether occurred in 85% yield (Scheme 42), however the THP group could not be removed without deprotecting the newly installed TBS group (Scheme 43). Instead, 193 was protected as the PMB ether in a 65% yield. Deprotection of the THP group was now chemoselective, yielding alcohol 196 quantitatively without purification. Appel conditions then afforded chloride 197 in a 79% yield.
This chemistry was simple and scalable, easily affording 2 grams of allyl chloride 197 each time through. Unfortunately, after efforts put into synthesizing 197, all attempts at opening epoxide 167 with 197 were unsuccessful (Scheme 44).

Scheme 44: Attempts at Grignard opening of epoxide 167 with allyl chloride 197

![Chemical structures](image)

The problem with this transformation was the formation of the active Grignard nucleophile, as no reaction was seen even when using the more reactive benzaldehyde as the electrophile. Recovery of starting materials, even the allyl chloride, was possible in all cases. Even when different methods of generating the active nucleophile were employed, for example Rieke magnesium, allyl chloride 197 was recovered. Other metals such as zinc and iridium that are commonly used to facilitate this process were also utilized without success. Epoxide opening through this route seemed impossible due to the inability to convert 197 into a nucleophile, and thus another strategy was needed to install the second carboxy domain. An idea came to us when analyzing the origin of furanyl byproducts 180 and 181.
2.4.4 Origin and Utilization of Furanyl Byproducts 180 and 181: Total synthesis of Nemorensic acid

As starting material was being pushed forward to both allyl chloride 197 and diene 179 from the previous route, we began to take a look at the origin of furan byproducts 180 and 181. The mechanism of their formation is simple: protonation of the alkene yields a stable tertiary carbocation which is intercepted by the tertiary alcohol. Trityl group deprotection also occurs under acidic conditions (Scheme 45).

![Scheme 45: Formation of byproducts 180 and 181](image)

Although initially undesired, it was through this byproduct that an alternative route to callosine’s necic acid was realized. Several pyrrolizidine alkaloids from Senecio callosus contain a furanyl moiety similar to 180, which are macrolactonic derivatives of the natural product (+)-nemorensic acid (Figure 4, Scheme 46). Further investigation revealed that (-)-callosine contains this subunit as well, although it exists as an uncyclized-retro-oxa-Michael addition analogue. If several other Senecio alkaloids contain this ring, it is proposed that callosine can equilibrate between a cyclized and uncyclized state.
If this hypothesis is true, we can also conclude that the forming an acid with a specific olefin geometry is unimportant because it will equilibrate back and forth until its energetic minimum is found. The cyclized furan corresponds to the natural product nemorensic acid. Nemorensic acid was isolated in 1976\textsuperscript{41} and its total synthesis has been documented a few times\textsuperscript{42}. We thus looked at this molecule as a synthetic target to be used in the macrocyclization of callosine and began to exploit the reactivity between the tertiary alcohol and the alkene in compound 168.
2.4.5 First Generation Total Synthesis of Nemorensic Acid

Although a proton source does not provide any beneficial functionality to expand upon, treatment with another electrophile could provide a handle which could be homologated to the carboxylic acid necessary for nemorensic acid (Scheme 47).

![Scheme 47: Proposed elaboration of 168 to (+)-nemorensic acid](image)

Treatment of 167 with an excess of mCPBA yielded furanyl alcohol 201-OH as a 1:1 mixture of separable diastereomers (Scheme 48). Realizing that the next step would involve converting the alcohol to a leaving group and homologating with a one carbon nucleophile, it was imagined that treatment of alkene 167 with an N-halo-succinimide would provide the necessary leaving group while saving one step. N-bromosuccinimide and N-iodosuccinimide both adequately produced the desired furanyl halides 201-Br and 201-I in 47% and 86% yields respectively, as an inseparable mixture of diastereomers in both cases.

![Scheme 48: Oxidative cyclization of trityl alcohol 168](image)
Because of the increased yield, better leaving group ability, and improved diastereoselectivity, N-iodosuccinimide was the obvious choice for further functionalization. At this point, the relative stereochemistry of the newly generated chiral center in either diastereomer was unknown. The transformations necessary to convert 201-I to (+)-nemorensic acid may epimerize the unknown stereocenter regardless, and it was thus not important to determine its configuration at this stage. Treatment of iodide 201-I with 5 equivalents of sodium cyanide in DMSO cleanly afforded nitrile 202 in 99% yield without the need for further purification and with no noteworthy epimerization (Scheme 49). Interestingly, performing the homologation at 90 °C instead of 80 °C scrambles the newest stereocenter, resulting in a 1:1 mixture of diastereomers.

![Scheme 49: Nucleophilic homologation of iodide 201-I](image)

Nitriles are notoriously difficult to hydrolyze. Although conditions exist for basic, acidic, and even enzymatic nitrile hydrolysis, these conditions are often impractical or require a harsh environment. Since the trityl group is quite acid sensitive, and nitrilases are expensive, basic hydrolysis seemed optimal. No hydrolysis was seen at room temperature or reflux, even when highly concentrated solutions of NaOH were used. Fortunately, heating nitrile 202 to 150 °C with excess NaOH in MeOH in the microwave for one hour resulted in fairly clean hydrolysis to acid 203. Because of the harsh conditions, complete epimerization occurred as was evident by ¹H NMR spectroscopy. Methylation of the crude carboxylic acid with trimethylsilyl diazomethane
followed by the addition of TFA yielded a separable 3:1 mixture of deprotected alcohols 204 and 205 in a 39% combined yield over the four steps: cyanide displacement, hydrolysis, methylation, and deprotection.

Scheme 50: Hydrolysis, methylation, and deprotection of nitrile 202

The geometries of the diastereomers was determined by conversion of each to the diacid and comparing the spectra with the natural product data after optimization of the oxidations (Scheme 51). With compounds 204 and 205 collected as separated diastereomers, we set off to oxidize the primary alcohol. Several oxidation conditions (IBX, DMP, PDC) did not promote the desired oxidation, but ultimately a Swern oxidation successfully provided aldehyde 206 in an 84% yield. Pinnick oxidation of aldehyde 206 provided acid 207 in a 90% yield after column chromatography. The yields were similar for the natural diastereomer. 207 and 210 are ideal substrates to couple to callosine core 130 as they possess a free carboxylic acid which will couple regioselectively to the primary alcohol in the stockpiled callosine core. The methyl ester would subsequently be deprotected and lactonized to form callosine’s macrocycle (Scheme 46). In order to isolate the natural product and assign the correct stereochemistry, the esters were saponified and diacids 208 and (+)-nemoresnic acid were
compared to literature data by a procedure described previously\textsuperscript{42B}. The minor product matched the natural product data identically.

Scheme 51: Oxidation of alcohols 204 and 205

2.5 Initial Convergence of Callosine Necine base and Necic acid

With the two ideal coupling partners in hand, we could attempt the first coupling between the necine base and necic acid components of callosine. Because of the relatively large step count associated with both pieces, scales as low as 10 μmol were necessary in order to be able to screen several coupling reagents. The ideal coupling strategy at this point also included the fewest number of reaction components and
transfers, as any exposure to atmospheric oxygen or moisture may have had deleterious effects on the reaction, especially on small scale.

The first coupling method attempted was converting acid 207 into the acid chloride by refluxing it for an hour with SOCl₂, and then adding it to a pre-stirred solution of alcohol 130 with triethylamine. No formation of the desired product was observed in the crude ¹H NMR spectrum. This method of making an active ester was likely too harsh, as decomposition of the necic acid component was evident in the crude ¹H NMR spectrum. HBTU and HATU were then screened, and fortunately both of these methods yielded what appeared to be coupled product 211. Note that at this stage, the coupling was only attempted with the major unnatural diastereomer of the mono-protected nemorensic acid unit because there was not enough of the natural isomer to be pushed through to this screening step. Notably, the excess diisopropylethylamine base appeared to have caused complete epimerization, yielding what looked like a 1:1 mixture of diastereomers in the ¹H NMR spectrum.

![Scheme 52: Coupling of acid 207 with callosine’s pyrrolizidine core 130](image)

However, at this point it was possible that the resulting mixture of diastereomers was either a result of epimerization of the indicated stereocenter or alternatively the acid
coupling partner being a racemic mixture of enantiomers. The enantiomeric purity of the necic acid portion had not been tested until this point.

Although we had to resolve the potential enantiomer problem, significant quantities of the coupled material were on hand, and so we investigated ways of deprotecting the methyl ester to furnish a molecule ready for the macrolactonization step.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(CH$_3$)$_3$SnOH (1.1 eq), DCE up to 150 °C</td>
<td>Recovered Starting Material</td>
</tr>
<tr>
<td>2</td>
<td>(CH$_3$)$_3$SnOH (10 eq), DCE, 170 °C</td>
<td>Recovered Starting Material</td>
</tr>
<tr>
<td>3</td>
<td>0.5M KOH (1.1 eq), THF/MeOH, RT</td>
<td>Deacylation, Recovery of 130</td>
</tr>
<tr>
<td>4</td>
<td>Ba(OH)$_2$ 8H$_2$O (1.5 eq), MeOH, RT</td>
<td>Deacylation, Recovery of 130</td>
</tr>
<tr>
<td>5</td>
<td>BBr$_3$ (1.1 eq), DCE, 0 °C</td>
<td>Recovered Starting Material</td>
</tr>
<tr>
<td>6</td>
<td>BBr$_3$ (7 eq), CH$_2$Cl$_2$, RT</td>
<td>Recovered Starting Material</td>
</tr>
<tr>
<td>7</td>
<td>(CH$_3$)$_3$SiOK (1.5 eq), THF, RT</td>
<td>Recovered Starting Material</td>
</tr>
<tr>
<td>8</td>
<td>LiI (10 eq), Pyridine, 110 °C</td>
<td>Recovered Starting Material</td>
</tr>
<tr>
<td>9</td>
<td>NaCN (3 eq), DMSO, 155 ºC, 20 min</td>
<td>TBDPS deprotection</td>
</tr>
<tr>
<td>10</td>
<td>LiCl (10 eq), DMSO, 155 ºC, 20 min</td>
<td>TBDPS deprotection</td>
</tr>
</tbody>
</table>
Following a procedure developed by Nicolaou\textsuperscript{43}, varying equivalents of (CH$_3$)$_3$SnOH at increasing temperatures (entries 1 and 2) showed no demethylation on this substrate, leading to recovered starting material. Basic aqueous hydrolysis proved to be selective for deacylation of the newly formed ester bond. This is likely a result of the enhanced electrophilicity of the carbonyl carbon by the inductive effect of the furan oxygen (entries 3 and 4). Varying equivalents of BBr$_3$ also lead to recovery of starting material (entries 5 and 6). Superstoichiometric amounts of (CH$_3$)$_3$SiOK failed to produce the desired carboxylic acid (entry 7). Krapcho-like conditions either lead to no reaction (entry 8) or, at higher temperatures, removal of the TBDPS group (entries 9 and 10). TMSI was equally ineffective at demethylating the ester (entry 11). Lastly, freshly made lithium propane thiolate seemed to decompose the starting material (entry 12). From these results, it was clear that a new protecting group strategy must be utilized.

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>11</strong></td>
<td>TMSI (7 eq), MeCN, 0 °C</td>
<td>Recovered Starting Material</td>
</tr>
<tr>
<td><strong>12</strong></td>
<td>LiS(CH$_2$)$_2$CH$_3$ (5 eq), HMPA, RT</td>
<td>Decomposition</td>
</tr>
</tbody>
</table>

Table 1: Attempts at demethylating coupled product 211
2.6 A New Protecting Group Strategy

Using the method in the previous route (Scheme 50), a new protecting group strategy was explored to avoid the ineffective demethylation of product 211.

![Chemical Reaction Diagram]

At this point, we decided on an allyl protecting group for the ester, as there are several methods to remove them, and there is a review article specifically for its use in complex molecule synthesis (Scheme 53)\textsuperscript{44}. As described previously, the nitrile was hydrolyzed with sodium hydroxide in the microwave, and the resulting carboxylic acid was protected as the allyl ester. Deprotection of the trityl group yielded an approximately 2:1 mixture of separable alcohols 213 and 214 in a 61% yield over 3 steps. Now that the protecting group strategy was altered, we decided to test the enantiopurity of this epoxide in order to determine whether the diastereomers observed in Scheme 52 are a result of epimerization or racemic furan.

2.6.1 Determination of Enantiopurity of 214

In order to determine the enantiopurity, we decided to append an enantiopure chiral auxiliary to the primary alcohol of the major diastereomer 214 and analyze the
resulting molecule by NMR spectroscopy (Scheme 54). Any indication of diastereomers in this product would suggest that the starting alcohol was not enantiopure. In order to have an accurate comparison, a racemic version of epoxide 167 was synthesized via Prilezhaev epoxidation of the requisite trityl alkene.

Scheme 54: Determination of ee via conversion of 214 to the camphorsulfonate

The $^1$H NMR spectrum of the racemic coupled adduct surprisingly showed no signs of diastereomers, likely because the two chiral portions of the molecule are too far away to influence each other. The $^{13}$C NMR spectrum of 216-rac, however, showed characteristic doubling of peaks, especially on carbons located at or near the stereogenic centers. When these data are compared to the $^{13}$C NMR spectrum of the adduct originating from the Sharpless epoxidation, we noticed a similar almost 1:1 mixture of
diastereomers, strongly suggesting that the starting alcohol 214 was racemic. The equal mixture of diastereomers from the coupling reaction (Scheme 52) were likely as a result of this, and not because of epimerization. This unfortunately prompted us to find a new route to enantiopure epoxide 167.

### 2.7 New Routes to Enantiopure Epoxide 167

#### 2.7.1 Formation of Epoxide 167 via Sharpless Asymmetric Dihydroxylation

When the SAE fails to provide adequate ee values, a way to isolate the desired enantiopure epoxide is to asymmetrically dihydroxylate the analogous olefin of opposite geometry, mesylating the secondary alcohol, and displacing the mesylate intramolecularly (Scheme 55).

![Scheme 55: Alternative asymmetric epoxidation technique via Sharpless asymmetric dihydroxylation](image)

We decided to utilize this strategy to synthesize the desired epoxide in this fashion. Tiglic acid was reduced to the allylic alcohol with LiAlH₄⁴⁵, and was then protected as
the trityl ether. Although the subsequent dihydroxylation did not go to completion, the diol was isolated in a 71% yield based on recovered starting material. The secondary alcohol was then selectively mesylated and subsequently displaced intramolecularly to yield epoxide 167 in an 84% yield over 2 steps.

Unfortunately, when converting the newly formed epoxide 167 into the camphor sulfonate 216, we observed results similar to what we did prior: the newly made epoxide is nearly racemic (Scheme 56). We rationalized that this was as a result of the poor solubility of trityl alcohol 220 in the Sharpless Asymmetric Dihydroxylation solvent system – the heterogeneous surface oxidation of 220 may not be enantioselective. This was also the cause of the sluggish reaction and the recovered starting material for this reaction. Clearly, this was not a viable route to the desired enantiopure epoxide 167.

Scheme 56: Ee determination of the new route to epoxide 167

Thankfully, just as this problem occurred, a new article was published in the European Journal of Organic Chemistry, depicting the Sharpless asymmetric dihydroxylation of different esters of tiglic and angelic acid. The article noted that
dihydroxylating these electron poor alkenes provided high ees when certain ester substituents were used.

![Chemical structure](image)

<table>
<thead>
<tr>
<th>X</th>
<th>Yield (%)</th>
<th>Ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-OMe</td>
<td>85</td>
<td>87</td>
</tr>
<tr>
<td>-OiBu</td>
<td>86</td>
<td>81</td>
</tr>
<tr>
<td>-OPMB</td>
<td>81</td>
<td>93</td>
</tr>
</tbody>
</table>

Table 2: Sharpless asymmetric dihydroxylation of tiglic acid esters. Ees were determined by chiral HPLC

We decided to use the PMB group as it provided the highest ee values. From this route, we realized that we could form the required epoxide by mesylating the resulting secondary alcohol and displacing the mesylate intramolecularly, yielding PMB-ester substituted epoxide 223 (Scheme 57 A). As substrate 223 is already in the acid oxidation
state, it would obviate the need for later oxidation of that position and reduce the overall step count. Thus Grignard additions into epoxide 223 were tested (Scheme 57 B).

Unfortunately, even after several conditions were screened, it seemed as though Grignard addition into the ester occurred faster than into the epoxide. In an attempt to avoid this, we reduced the electrophilicity of the ester by saponifying the PMB group. Ideally, one equivalent of the Grignard reagent would deprotonate the carboxylic acid of 225 first, and the resulting carboxylate anion would be significantly less electrophilic, leading to epoxide opening with another equivalent of the reagent. Again, after several conditions were screened, no desired product could be isolated.

Due to the difficulties experienced with having an ester group present in the Grignard step, we then simply converted PMB ester 222 into trityl epoxide 167 that we previously took forward to the desired coupling adduct. Reduction of ester 222 with BH₃ yielded triol 227 in an 82% yield (Scheme 58). The primary alcohol was trityl protected,
and the secondary alcohol could be then mesylated in the same pot. Intramolecular displacement of the crude mesylate yielded the desired epoxide in a 60% yield over the three steps. The process was scaled up to afford 9 grams of trityl epoxide 167.

![Scheme 58: Synthesis of enantiopure epoxide 167 from enantiopure triol 227](image)

### 2.7.2 Total synthesis of Nemorensic Acid

Now that trityl epoxide 167 has been synthesized via a method known to produce high ee values, it was converted to allyl esters 213 and 214 as described in Scheme 53. Separately, the alcohols were oxidized to the carboxylic acids in one step with the Jones reagent, yielding both enantiomers of the desired coupling adduct (Scheme 59). The natural product can be isolated by hydrolyzing crude product 228 obtained from the Jones reagent followed by an acid/base workup. The total synthesis of the natural isomer of nemorensic acid was thus completed in 14 steps in an overall 6% yield. Now that
sufficient quantities of the enantiopure coupling substrates 228 and 229 were on hand, coupling to the necine core could be attempted again.

Scheme 59: Synthesis of nemorensic acid and its allylated analogues

2.8 Second Convergence of Necine Base and Necic Acid Components

2.8.1 Coupling Enantiopure 228 and 229 to Pyrrolizidine Core 130

With this new route to nemorensic acid coupling unit, there was enough material to couple the core of callosine 130 to both diastereomers. Separately, acids 228 and 229
were treated with the same coupling conditions as used previously to couple the methyl ester analogue to the core (Scheme 60). After purifying the resulting compounds and analyzing the $^1\text{H}$ NMR spectrum, we noticed something unusual. It seemed like the natural diastereomer of nemorensic acid produced one single product as expected, however, in the $^1\text{H}$ NMR spectrum of the product resulting from the unnatural diastereomer (ie, the major product), there was evidence of two diastereomers.

From these two reactions, we can infer several things. First, the starting furan units are indeed enantiopure, as only one compound was seen in both the $^1\text{H}$ and $^{13}\text{C}$ NMR spectra of the coupled adduct when utilizing the naturally occurring diastereomeric coupling partner 228. Either before or after it is coupled to the callosine core, the presence of excess DIPEA causes the major unnatural nemorensic acid subunit to epimerize.
Because we are sure that epimerization is occurring even when only using a relatively mild base such as DIPEA, this bodes well for the hypothesis that callosine equilibrates between its ring opened and ring closed isomers. This also means that the experiment previously utilized to determine the enantiopurity of alcohol 214 using camphor sulfonyl chloride was ultimately useless (Scheme 54), as the product could easily epimerize under the basic reaction conditions.

### 2.8.2 Deprotection of allyl ester 230

The next step in the synthetic sequence is deprotection of the allyl ester. One of the problems we foresaw at this stage is the high polarity of the carboxylic acid resulting from this reaction. For instance, the allyl ester is purified in 10:89:1 MeOH/EtOAc/NH₄OH(aq), a solvent mixture which is basically the limit of methanol and water content before silica gel becomes soluble in the eluent system. Carboxylic acids are exceptionally more polar than their parent esters, and in this case, the molecule would likely exist as a zwitterion due to the alkaline nitrogen atom. The first several times that this reaction was performed, there was a disappearance in allyl protons in the crude ¹H NMR spectrum as the N-allyl morpholine byproduct was removed by an acidic workup (Scheme 61). However, several different solvent systems failed to move the very polar product off of the baseline. Finally, after everything else elutes from the column in the aforementioned eluent system, the column was flushed with 100% MeOH. The dissolved silica was removed by suspending the evaporated eluent in CH₂Cl₂, filtering through Celite, and reconcentrating the product *in vacuo*. 
Because the crude $^1$H NMR spectrum looked fairly clean, it is possible that the relatively low 45% yield was a result of NH$_4$OH$_{(aq)}$ decomposing the material. The ester bond is very sensitive to basic hydrolysis as outlined in Table 1. When this sequence is repeated, alternative eluent systems will be looked into.

2.8.3 Attempt at Macrolactonization of 231

As a result of the back-to-back low yields of the initial coupling and subsequent deprotection sequence, only 20 mg of pure material originating from the natural isomer of nemorensic acid was available for the macrolactonization step. This meant that only one credible attempt could be made at furnishing the second ester linkage. There are several methods for lactonization of medium-sized macrocycles, but there is no specific protocol that outlines which procedure works best in specific cases. In these scenarios, the method of choice depends primarily on the success of the most similar macrolactonizations in the literature. In Niwa’s synthesis of (-)-integerrimine (Scheme 15), the Mukayama reagent 69 was used to furnish the second ester bond. This is by far the most similar substrate to 231 in the literature and so their macrolactonization procedure was followed exactly (Scheme 62). Since large ring cyclizations are almost always performed at high dilution,
and because this starting material hardly leaves the baseline of a TLC plate, monitoring the completion of this reaction by TLC was futile. For this reason, the reaction time of Niwa’s lactonization was also replicated.

Scheme 62: Attempted macro lactonization of carboxylic acid 231

The reaction time was ultimately not long enough, as a TLC of the concentrated mixture showed some starting material remaining. Two purifications by flash column chromatography of the mixture yielded approximately 1 mg of what looked like the macrolactone by comparing the relevant peaks to the natural product data by $^1$H NMR spectroscopy, however with this little material, it was difficult to be confident about the formation of the product.
3 Conclusions

We have demonstrated the applicability of the intramolecular oxime ether cyclopropane HMMC reaction to the pyrrolizidine core of callosine 130. Though routes to the required enantiopure cyclopropane were known, a much shorter and less expensive sequence was developed. This allowed for the expedient synthesis of several grams of 130 in short order.

With an enantioselective route to trityl epoxide 167, we have developed a concise route to (+)-nemoresnic acid, the necie acid component of callosine. The key steps included a regioselective Grignard addition, an oxidative furanylization, and a microwave-assisted nitrile hydrolysis (Scheme 64).
With the necine base and necic acid on hand, attempts to furnish the macrocycle were made. Formation of the first ester bond was realized with HBTU, and the allyl ester was deprotected in order to attempt the macrolactonization with the corresponding acid. With limited time and material, this key bond formation has not been successful (Scheme 66).

Scheme 64: Total synthesis of (+)-nemoresnic acid
Scheme 65: Attempted synthesis of callosine
4 Future Work

As efficient routes to both coupling components have been established, the total synthesis can be realized in the near future. When sufficient material is pushed through to the deprotected carboxylic acid, longer reaction times for the macrolactonization should provide 232 in higher yields. With this compound in hand, deprotection of the TBDPS group and oxidation to the methyl ester will yield the oxa-Michael-addition analogue of callosine 199. Ideally, treatment of this product with base will open the furan to yield callosine (Scheme 66).
Appendix A – Experimental

General Information

IR spectra were obtained as thin films on NaCl plates on a Bruker Vector 33 FT-IR instrument. NMR spectra were obtained on Varian Mercury 400 MHz, Varian Inova 400 MHz, or Varian Inova 600 MHz instruments. Spectra obtained in CDCl₃ were referenced at 7.27 ppm for ¹H NMR and 77.0 ppm for ¹³C NMR, whereas spectra obtained in D₂O were referenced at 4.80 ppm for ¹H NMR spectra and unreferenced for ¹³C NMR spectra. CDCl₃ was kept over K₂CO₃. The coupling constants (J) are reported in Hz. Signal multiplicities are described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, AB = AB quartet. High resolution mass spectrometry was performed on a Finnigan MAT 8400 instrument and was ionized either via electron impact or chemical ionization on a solid sample probe. THF, ether, DMF, CH₂Cl₂, toluene, and acetonitrile were collected just prior to use from nitrogen-purged activated alumina columns. All other reaction solvents were glass distilled HPLC grade. All reagents were used as purchased without further purification. Reactions were performed in septa-capped round bottom flasks under a normal atmosphere unless otherwise indicated. Reactions were monitored by thin layer chromatography (TLC) on silica gel 60 F₂₅₄ aluminum backed plates and visualized with UV light, acidic anisaldehyde, basic potassium permanganate, or ceric ammonium molybdate. Flash column chromatography was performed using silica gel from Silicycle Chemical Division Inc. (230-400 mesh) via the Still method. The chromatography eluents indicated move the desired product to an R_f value between 0.3 and 0.4, except when simply passed through a plug of silica. When gradients of eluents were used during purification, the desired product had an R_f value between 0.3 and 0.4 in the final eluent system used.
(S)-dimethyl 2-(2-chloroethyl)cyclopropane-1,1-dicarboxylate: Dimethyl malonate (6.68 mL, 58.5 mmol) was added dropwise to a suspension of 60% NaH (4.68 g, 117 mmol) in anhydrous toluene (175 mL, 0.3 M) over a period of 10 minutes. The resulting viscous suspension was swirled manually periodically for 30 minutes. A solution of cyclic sulfate\textsuperscript{38} 145 (9.89 g, 53.2 mmol) in toluene (10 mL) was added and the reaction was stirred at room temperature for 18 hours. In order for the reaction to go to completion, additional dimethyl malonate (0.67 mL, 5.6 mmol) and NaH (0.85 g, 21 mmol) were added and the reaction was stirred for another 24 hours. 5% HCl was added and the layers were separated. The aqueous layer was extracted 3x with EtOAc and the combined organic layers were washed with brine, dried over MgSO\textsubscript{4}, and concentrated \textit{in vacuo}. Note: Washing with NaOH to remove excess dimethyl malonate at this stage results in significant product loss. The yellow oil was purified by column chromatography (15:85 EtOAc:Hexanes) to yield pure cyclopropane 149 (5.98 g, 51%) as a yellow oil.

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \( \delta = 3.78 \text{ (s, 3H)}, 3.74 \text{ (s, 3H)}, 3.60 \text{ (dd, } J = 6.6 \text{ Hz, 6.6 Hz, 2H)}, 2.07 \text{ (dddd, } J = 7.4 \text{ Hz, 7.4 Hz, 7.4 Hz, 7.4 Hz, 1H)}, 1.92 \text{ (dddd, } J = 6.3 \text{ Hz, 6.3Hz, 8.8 Hz, 12.6 Hz, 1H}), 1.73 \text{ (dddd, } J = 6.3 \text{ Hz, 6.3 Hz, 8.8 Hz, 12.6 Hz, 1H}) 1.50 \text{ (dd, } J = 4.7 \text{ Hz, 9.0 Hz, 1H)}), 1.44 \text{ (dd, } J = 4.7 \text{ Hz, 7.8 Hz, 1H}); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \( \delta = 170.32, 169.40, 52.72, 52.67, 43.34, 33.50, 31.84, 25.82, 20.68; \text{ FT-IR (thin film, cm}\textsuperscript{-1}) 3005.11, 2955.22, 2848.46, 1727.99, 1437.44, 1331.92, 1283.24, 1215.44, 1135.73, 988.97; \text{ HRMS calc. for } C_9H_{13}\text{ClO}_4^+ = 220.0502; \text{ exp.}= 220.0504.
(S)-dimethyl 2-((1,3-dioxoisindolin-2-yl)oxy)ethyl)cyclopropane-1,1-dicarboxylate: DBU (4.46 mL, 29.8 mmol) was added to a solution of N-hydroxyphthalimide (4.86 g, 29.8 mmol) in DMF (45 mL, 0.5 M). After stirring the reaction for 10 minutes, a solution of cyclopropane 149 (5.98 g, 27.1 mmol) in DMF (9 mL) was added to the reaction. The brown solution was stirred at room temperature for 2 days. Equal parts of EtOAc and H₂O were added to the reaction and the layers were separated. The aqueous layer was extracted 3x with EtOAc. The combined organic fractions were washed 5x with H₂O and once with brine, dried over MgSO₄, and concentrated in vacuo. The crude white solid was recrystallized from 100 mL of MeOH to yield enantiopure cyclopropane 141 (6.73 g, 72%) as a colourless solid. The obtained spectra, including those collected after the chiral shift reagent was added, matched the literature data³¹, indicating the obtained compound was enantiopure.

(E)-(((2-methylbut-2-en-1-yl)oxy)methanetriyl)tribenzene: TrCl (3.73 g, 13.4 mmol) was added to a solution of allylic alcohol 217 (1.00 g, 11.6 mmol) and DBU (2.60 mL, 17.4 mmol) in CH₂Cl₂ (40 mL, 0.3 M). The reaction was stirred at room temperature for
18 hours, after which it was quenched with NH₄Cl. The layers were separated and the organic layer was extracted 3x with CH₂Cl₂. The combined organic fractions were washed 1x with brine, dried over MgSO₄, and concentrated in vacuo. The residue was purified by flash column chromatography (5:95 EtOAc:Hexanes) to yield trityl alcohol 220 (2.874 g, 88%) as a yellow oil.

$^1$H NMR (400 MHz, CDCl₃) δ = 7.48 – 7.45 (m, 6H), 7.32 – 7.29 (m, 6H), 7.25 – 7.23 (m, 3H), 5.63 (qq, $J$ = 1.2 Hz, 6.5 Hz, 1H), 3.47 (s, 2H), 1.66 (dq, $J$ = 6.5 Hz, 1.2 Hz, 3H), 1.63 (br s, 3H).

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(Z)-((2-methylbut-2-en-1-yl)oxy)methanetriyl)tribenzene: TrCl (18.58 g, 66.8 mmol) was added to a solution of allylic alcohol 166 (5.00 g, 58.0 mmol) and NEt₃ (12.1 mL, 87.0 mmol) at 0 °C in CH₂Cl₂ (200 mL, 0.3 M). The reaction was allowed to warm to room temperature and stirred for 18 hours after which it was quenched with NH₄Cl. The layers were separated and the aqueous layer was extracted 3x with CH₂Cl₂. The combined organic fractions were dried over MgSO₄ and concentrated in vacuo. The resulting mixture was suspended in 100 mL of hexanes, and the solids were filtered. The filtrate was concentrated in vacuo to yield pure trityl alkene 215 (19.02 g, 86%) as a colourless solid.

$^1$H NMR (400 MHz, CDCl₃) δ = 7.51 – 7.49 (m, 6H), 7.33 – 7.30 (m, 6H), 7.26 – 7.23 (m, 3H), 5.36 (q, $J$ = 6.6 Hz, 1H), 3.61 (s, 2H), 1.87 (s, 3H), 1.44 (dd, $J$ = 6.6 Hz, 3H)
(2R,3R)-2-methyl-1-(trityloxy)butane-2,3-diol: Trityl alkene 220 (2.53 g, 7.70 mmol) was added to a suspension of AD-mix α (10.8 g) and methanesulphonamide (0.732 g, 7.70 mmol) in 1:1 tBuOH:H₂O (77 mL, 0.1 M) at 0 °C. After 24 hours, 11.6 g of Na₂SO₃ was added, and the reaction was stirred at room temperature for 2 hours. CH₂Cl₂ was added and the layers were separated. The aqueous layer was extracted 3x with CH₂Cl₂. The organic fractions were combined, washed 1x 2M NaOH, 1x brine, dried over MgSO₄, and concentrated in vacuo. The resulting material was purified by flash column chromatography (40:60 EtOAc:Hexanes) to yield diol 218 as a white solid (0.772 g) and recovered alkene 218 (1.384 g) (71% BRSM).

¹H NMR (400 MHz, CDCl₃) δ = 7.45 – 7.42 (m, 6H), 7.35 – 7.31 (m, 6H), 7.28 – 7.25 (m, 3H), 3.87 (dq, J = 2.7 Hz, 6.7 Hz, 1H), 3.25 (d, J = 9.4 Hz, 1H), 3.04 (d, J = 9.4 Hz, 1H), 2.83 (d, J = 2.7 Hz, 1H), 2.70 (s, 1H), 1.05 (s 3H), 1.04 (d, J = 6.7 Hz, 3H).

(2R,3R)-4-methoxybenzyl 2,3-dimethyloxirane-2-carboxylate: MsCl (0.335 mL, 4.32 mmol) was added dropwise to a solution of diol 222-PMB⁴⁶ (1.000 g, 3.93 mmol) and NEt₃ (1.10 mL, 7.86 mmol) in CH₂Cl₂ (20 mL, 0.2 M) at 0 °C. The solution was allowed to warm slowly to room temperature and stirred for an additional hour. The reaction was
quenched with NH$_4$Cl and the layers were separated. The aqueous layer was extracted 2x with CH$_2$Cl$_2$. The organic fractions were combined and washed with brine, dried over MgSO$_4$, and concentrated in vacuo. The crude mesylate was then dissolved in DMF (20 mL, 0.2 M) and 60% NaH (0.190 g, 4.72 mmol) was added. The solution was purged with argon and the reaction was stirred at room temperature for 18 hours. Equal portions of H$_2$O and Et$_2$O were added and the layers were separated. The aqueous layer was extracted 2x with Et$_2$O. The organic fractions were combined, washed 3x H$_2$O, 1x brine, dried over MgSO$_4$, and concentrated in vacuo. The resulting oil was purified by flash column chromatography (25:75 EtOAc:Hexanes) to yield epoxide 223 (0.517 g, 55%) as a colourless oil.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 7.32, 6.90 (AA’XX’, $J_{AA'} = 5.0$ Hz, $J_{XX'} = 0.1$ Hz, $J_{AX} = 8.33$ Hz, $J_{A'X} = 0.3$ Hz, 2H), 5.18, 5.15 (AB, $J = 12.1$ Hz, 2H), 3.82 (s, 3H), 3.04 (q, $J = 5.5$ Hz, 1H), 1.56 (s, 3H), 1.27 (d, $J = 5.5$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ = 169.97, 159.75, 130.30, 127.52, 113.92, 66.89, 60.03, 59.74, 55.26, 19.16, 13.59.

(2R,3R)-2,3-dimethyloxirane-2-carboxylic acid: 2 M NaOH (0.38 mL, 0.76 mmol) was added to a solution of PMB Epoxide 223 (0.150 g, 0.635 mmol) in 1:1 MeOH:THF (6 mL, 0.1 M) at 0 °C. After 45 minutes, the solution was concentrated in vacuo. Equal parts of H$_2$O and EtOAc were added and the layers were separated. The aqueous layer
was concentrated in vacuo to yield epoxy acid 225 as a colourless oil (42 mg, 57%) with a minor PMBOH impurity.

$^1$H NMR (600 MHz, D$_2$O) $\delta = 3.13$ (q, $J = 5.9$ Hz, 1H), 1.47 (s, 3H), 1.22 (d, $J = 5.9$ Hz, 3H).

(2R,3R)-2-methylbutane-1,2,3-triol: BH$_3\cdot$SMe$_2$ (12.7 mL, 127 mmol) was added dropwise to a solution of PMB ester 222-PMB$^{46}$ (14.60 g, 57.4 mmol) in THF (300 mL, 0.2 M) at room temperature. The resulting solution was stirred at room temperature for 3 hours and subsequently quenched slowly with MeOH. After concentrating in vacuo, the resulting oil was coevaporated with MeOH 3 additional times to remove volatile boron byproducts. The oil was purified by column chromatography (10:90 MeOH:EtOAc) yielding pure triol 227 (5.65 g, 82%) as a colourless oil.

$^1$H NMR (400 MHz, D$_2$O) $\delta = 3.76$ (q, $J = 6.6$ Hz, 1H), 3.49 (s, 2H), 1.11 (d, $J = 6.6$ Hz, 3H), 1.05 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta = 75.19, 70.45, 66.40, 17.69, 16.29$; FT-IR (thin film, cm$^{-1}$); 3388.20, 2978.73, 2939.63, 1652.30, 1381.82, 1047.45, 914.25, 867.15, 631.18; HRMS calc. for C$_{5}$H$_{12}$O$_{3}$ + H$^+$ = 121.0859; exp.= 121.0868.

(2S,3R)-2,3-dimethyl-2-((trityloxy)methyl)oxirane: DBU (3.81 mL, 27.0 mmol) was added to a solution of the requisite epoxy alcohol$^{39}$ (1.83 g, 17.9 mmol) in CH$_2$Cl$_2$ (120 mL, 0.15M) at 0 °C. After 10 minutes, trityl chloride (6.00 g, 21.5 mmol) was added and
the reaction was stirred overnight. The solution was concentrated on silica gel and purified by flash column chromatography (Ethyl acetate:hexanes 5:95). The resulting solid was recrystallized twice from hexanes to yield trityl epoxide 167 (3.06 g, 50%) as a colourless solid.

**Racemic version from trityl alkene 215:**

75% mCPBA (3.860 g, 16.8 mmol) was added to a solution of trityl alkene 215 (5.000 g, 15.2 mmol) in CH2Cl2 (61 mL, 0.25 M). The reaction was stirred at room temperature for 5 hours after which the reaction was quenched with NaHCO3 (sat). The layers were separated and the aqueous layer was extracted 3x with CH2Cl2. The combined organic fractions were washed 1x with brine, dried over MgSO4, and concentrated in vacuo. The solid material was recrystallized from hexanes to yield racemic trityl epoxide 167 (4.19 g, 80%) as a colourless solid.

**From trityl diol 218:**

MsCl (0.921 mL, 11.8 mmol) was added to a solution of trityl diol 218 (2.836 g, 7.88 mmol) and NEt3 (4.39 mL, 31.52 mmol) in CH2Cl2 (40 mL, 0.2 M) at 0 °C under argon. The solution was allowed to warm to room temperature overnight. The reaction was subsequently quenched with NH4Cl and the layers were separated. The aqueous layer was extracted 3x with CH2Cl2. The combined organic fractions were washed with brine, dried over MgSO4, and concentrated in vacuo. The resulting orange foam was dissolved in DMF (40 mL, 0.2 M) and 60% NaH (0.378 g, 9.46 mmol) was added. The reaction was stirred at room temperature for 16 hours, after which equal parts of Et2O and H2O were added. The layers were separated and the aqueous layer was extracted 3x with Et2O. The combined organic fractions were washed 5x with H2O, 1x with brine, dried
over MgSO₄, and concentrated \textit{in vacuo}. The resulting mixture was purified by flash column chromatography (7.5:92.5 EtOAc:Hexanes) to yield trityl epoxide \textbf{167} (2.266 g, 84\%) as a colourless solid.

\textbf{New procedure from enantiopure triol 227:}

To a solution of triol \textbf{227} (5.62 g, 46.8 mmol) in CH₂Cl₂ (150 mL, 0.3 M) at 0 °C was added NEt₃ (19.6 mL, 140.5 mmol) and trityl chloride (15.65 g, 56.2 mmol). After stirring the resulting solution for 18 hours at room temperature, MsCl (4.00 mL, 51.5 mmol) was added to the reaction, and the mixture was stirred at room temperature for another 24 hours. The solution was diluted with CH₂Cl₂, and then saturated NH₄Cl was added to the reaction. The layers were separated and the aqueous layer was extracted 1x with CH₂Cl₂. The organic layers were combined and washed once with brine, dried over MgSO₄, and concentrated \textit{in vacuo} to yield an orange foam. The crude trityl mesylate was dissolved in DMF (235 mL, 0.2 M), and NaH (3.75 g, 93.6 mmol) was added to the reaction. The suspension was stirred at room temperature for 18 hours. An equal volume of H₂O and Et₂O was added to the solution and the layers were separated. The aqueous layer was extracted 3x with Et₂O. The combined organic layers were washed 5x with H₂O and 1x with brine, dried over MgSO₄, and concentrated \textit{in vacuo} on 50 g of silica gel. The solid was purified by flash column chromatography (7.5:92.5 EtOAc:Hexanes) to yield 8.67 g of epoxide \textbf{167} as a white solid. To obtain a better yield, the combined aqueous phases were reextracted 2x with CH₂Cl₂. The combined organic phases were washed 1x with brine, dried over MgSO₄ and concentrated \textit{in vacuo}. The oily material was purified by flash column chromatography (7.5:92.5 EtOAc:Hexanes) to yield an additional 1.02 g of \textbf{167} (overall 9.69 g, 60\%). The combined solids were recrystallized
in 175 mL of hexanes to yield 6.33 g of 167 (65% recovery, 39% overall) as a colourless solid.

\(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta = 7.48-7.46\) (m, 6H), 7.32-7.29 (m, 6H), 7.25-7.23 (m, 3H), 3.27 (d, \(J = 9.8\) Hz, 1H), 2.97 (d, \(J = 9.8\) Hz, 1H), 2.90 (q, \(J = 5.6\) Hz, 1H), 1.48 (s, 3H), 1.10 (d, \(J = 5.8\) Hz, 3H); \(^1\)C NMR (150 MHz, CDCl\(_3\)) \(\delta = 143.81, 128.68, 127.91, 127.77, 127.01, 86.52, 64.69, 59.73, 20.91, 13.63\); FT-IR (thin film, cm\(^{-1}\)) 3057.89, 2964.82, 2927.12, 1490.27, 1448.32, 1072.74, 703.93; HRMS calc. for C\(_{24}\)H\(_{24}\)O\(_2\)\(^+\) = 344.1776; exp. = 344.1779

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\(168\)

(2R,3R)-2,3,5-trimethyl-1-(trityloxy)hex-5-en-2-ol: To a solution of trityl epoxide 167 (1.933 g, 5.61 mmol) in anhydrous THF (20 mL, 0.28 M) was added 1.1 M methallylmagnesium chloride (25 mL, 27.8 mmol). The solution was heated to reflux for 18 hours. The solution was then cooled to 0 °C and quenched with water. The solution was diluted with Et\(_2\)O and then washed once with brine. The organic layer was dried with MgSO\(_4\) and concentrated in vacuo. The residue was purified by flash column chromatography (5:95 EtOAc:hexanes) to yield alkene 168 (2.24 g, 100%).

\(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta = 7.45-7.43\) (m, 6H), 7.32-7.29 (m, 6H), 7.25-7.23 (m, 3H), 4.74 (s, 1H), 4.65 (s, 1H), 3.08, 3.05 (AB, \(J_{AB} = 8.8\) Hz, 2H), 2.40 (br d, \(J = 13.4\) Hz, 1H), 2.29 (br s, 1H), 1.98-1.93 (m, 1H), 1.71 (s, 3H), 1.65 (dd, \(J = 11.1\) Hz, 13.4 Hz, 1H), 1.05 (s, 3H), 0.61 (d, \(J = 6.8\) Hz, 3H); \(^1\)C NMR (150 MHz, CDCl\(_3\)) \(\delta = 145.04, 143.77, 128.70, 127.83, 127.09, 111.44, 86.49, 74.74, 68.73, 39.09,\)
37.39, 22.16, 19.98, 14.06; FT-IR (thin film, cm⁻¹) 3465.91, 3060.22, 2969.91, 2933.53, 1490.53, 144.27, 1071.75, 706.12, 632.53; HRMS calc. for C₂₈H₃₂O₂ + Na⁺ = 423.2300; exp. = 423.2311.

(2R,3R)-2-hydroxy-2,3,5-trimethylhex-5-en-1-yl formate: Crude alkene 168 (1.45 mmol theoretical) was dissolved in Et₂O (5 mL, 0.3 M). 88% of formic acid (5 mL, 117 mmol) was added and the reaction was stirred for 18 hours. An additional 5 mL Et₂O and 5 mL of formic acid were added to the reaction and it was stirred for an additional 1 hour. Et₂O was added and the solution was washed 2x with saturated NaHCO₃ and 1x with brine. The organic layer was dried over MgSO₄ and concentrated in vacuo. The oil was purified by flash column chromatography (gradient 10:90 – 20:80 EtOAc:Hexanes) yielding formyl alcohol 176 as a colourless oil (0.151 g, 66% over 2 steps).

¹H NMR (600 MHz, CDCl₃) δ = 8.16 (s, 1H), 4.80 (s, 1H), 4.73 (s, 1H), 4.17, 4.11 (AB, 2H, JAB = 11.2 Hz, 2.44 (br d, 1H, J = 14.1 Hz), 1.88 (ddq, J = 2.9 Hz, 6.5 Hz, 10.0 Hz, 1H), 1.79 (dd, J = 10.0, 14.1 Hz, 1H), 1.73 (s, 3H), 1.16 (s, 3H), 0.86 (d, J = 6.5 Hz, 3H).
(2R,3R)-1-(formyloxy)-2,3,5-trimethylhex-5-en-2-yl acrylate: DMAP (12 mg, 0.1 mmol) and NEt₃ (0.200 mL, 1.41 mmol) were added to a solution of formyl alcohol 176 (0.148 g, 0.94 mmol) in CH₂Cl₂ (3 mL, 0.3 M) at room temperature under argon. Acryloyl chloride (92 μL, 1.13 mmol) was added *via* syringe and the solution was stirred at room temperature for 18 hours. The reaction was quenched with H₂O and the layers were separated. The aqueous layer was extracted 2x with CHCl₃. The combined organic layers were washed with brine, dried over MgSO₄ and concentrated *in vacuo*. The oily substance was purified by column chromatography (gradient 5:95 – 25:75 EtOAc:Hexanes) to yield acrylate 177 as a colourless oil (0.026 g, 19% based on 40 mg recovered starting material).

¹H NMR (600 MHz, CDCl₃) δ = 8.10 (s, 1H), 6.36 (dd, *J* = 1.8 Hz, 17.0 Hz, 1H), 6.08 (dd, *J* = 10.6 Hz, 17.0 Hz, 1H), 5.81 (dd, *J* = 1.8 Hz, 10.6 Hz, 1H), 4.80 (s, 1H), 4.72 (s, 1H), 4.70 (d, *J* = 11.1 Hz, 1H), 4.54 (d, *J* = 11.7 Hz, 1H), 2.51 (ddq, *J* = 2.9 Hz, 6.5 Hz, 10.0 Hz, 1H), 2.30 (d, *J* = 12.9 Hz, 1H), 1.81 (dd, *J* = 11.1 Hz, 12.9 Hz, 1H), 1.71 (s, 3H), 1.45 (s, 3H), 0.87 (d, *J* = 6.5 Hz, 3H).

(2R,3R)-2,3,5-trimethylhex-5-ene-1,2-diol, ((2R,3R)-2,3,5,5-tetramethyltetrahydrofuran-2-yl)methanol: PTSA (152 mg, 0.80 mmol) was added to a solution of alkene 168 (2.46 g, 6.14 mmol) in a 3.5:1 mixture of CH₂Cl₂:MeOH (60 mL total, 0.1 M). After the reaction was stirred for 18 hours, it was concentrated *in vacuo*.
and saturated NaHCO₃ was subsequently added. The aqueous layer was extracted 3x with EtOAc. The combined organic fractions were dried over MgSO₄ and concentrated \textit{in vacuo}. The mixture was purified via flash column chromatography to yield furan 181 and diol 178 as a colourless oil (0.517 g, 54%).

Furan 181: $^1$H NMR (600 MHz, CDCl₃) $\delta = 3.42$ (d, $J = 11.2$ Hz, 1H), 3.33 (d, $J = 11.7$ Hz, 1H), 2.53 (ddq, $J = 7.0$ Hz, 7.0 Hz, 12.3 Hz, 1H), 1.92 (dd, $J = 7.0$ Hz, 12.3 Hz, 1H), 1.67 (dd, $J = 12.3$ Hz, 12.3 Hz, 1H), 1.33 (s, 3H), 1.22 (s, 3H), 0.97 (s, 3H), 0.93 (d, $J = 7.0$ Hz, 3H).

Diol 178: $^1$H NMR (600 MHz, CDCl₃) $\delta = 4.80$ (s, 1H), 4.73 (s, 1H), 3.58 (d, $J = 10.6$ Hz, 1H), 3.45 (d, $J = 10.6$ Hz, 1H), 2.43 (dd, $J = 3.5$ Hz, 13.5 Hz, 1H), 1.90 (ddq, $J = 3.5$ Hz, 7.0 Hz, 10.0 Hz, 1H), 1.80 (dd, $J = 10.0$ Hz, 11.1 Hz, 1H), 1.74 (s, 3H), 1.10 (s, 3H), 0.83 (d, $J = 7.0$ Hz, 3H).

(2R,3R)-2-hydroxy-2,3,5-trimethylhex-5-en-1-yl acrylate: DMAP (0.008 g, 0.064 mmol) and NEt₃ (133 μL, 0.955 mmol) were added to a solution of diol 178 (0.100 g, 0.637 mmol) in CH₂Cl₂ (2 mL) at 0 °C. Acryloyl chloride (62 μL, 0.76 mmol) was added dropwise via syringe and the resulting solution was stirred for 3 hours, allowing slow warming to room temperature. Additional acryloyl chloride (30 μL, 0.37 mmol) was added and after 1 hour the reaction was quenched with H₂O. NH₄Cl was added to the reaction and the layers were separated. The aqueous layer was extracted 2x with CHCl₃.
and the combined organic fractions were dried over MgSO₄ and concentrated in vacuo. The residue was purified by flash column chromatography (10:90 EtOAc:Hexanes), yielding acrylate 179 as a colourless oil (0.038 g, 28%).

$$^1$$H NMR (600 MHz, CDCl₃) δ = 6.46 (dd, J = 1.8 Hz, 17.0 Hz, 1H), 6.20 (dd, J = 10.6 Hz, 17.0 Hz, 1H), 5.89 (dd, J = 1.8 Hz, 10.6 Hz, 1H), 4.80 (s, 1H), 4.73 (s, 1H), 4.18, 4.12 (AB, J_AB = 11.7 Hz, 2H), 2.45 (d, J = 12.9 Hz, 1H), 1.89 – 1.85 (m, 1H), 1.79 (dd, J = 10.0 Hz, 12.3 Hz, 1H), 1.73 (s, 3H), 1.16 (s, 3H), 0.87 (d, J = 7.0 Hz, 3H); $$^{13}$$C NMR (150 MHz, CDCl₃) δ = 166.2, 144.5, 131.3, 128.1, 112.0, 74.1, 70.3, 39.3, 37.6, 22.1, 19.9, 14.3.

![Structure of compound 182](image)

(2R,3R)-2-hydroxy-2,3,5-trimethylhex-5-en-1-yl cinnamate: Grubb’s 2nd generation catalyst (0.006 g, 0.007 mmol) was added to a solution of acrylate 179 (0.031 g, 0.146 mmol) in CH₂Cl₂ (5 mL, 0.03 M) and the flask was purged several times with argon. The solution was stirred at room temperature for 16 hours, after which, additional Grubb’s 2nd generation catalyst (0.006 g, 0.007 mmol) was added. The reaction was subsequently heated to reflux for 18 hours. The solution was concentrated in vacuo and purified by flash column chromatography (gradient 5:95 – 15:85 EtOAc:Hexanes) to yield a small quantity (< 0.002 g) of alkene 182 as a colourless oil.
$^1$H NMR (600 MHz, CDCl$_3$) $\delta = 7.74$ (d, $J = 16.4$ Hz, 1H), 7.56 – 7.55 (m, 2H), 7.42 – 7.41 (m, 3H), 6.51 (d, $J = 16.4$ Hz, 1H), 4.80 (s, 1H), 4.74 (s, 1H), 4.23, 4.17 (AB, $J_{AB} = 11.7$ Hz, 2H), 2.48 (d, $J = 13.5$ Hz, 1H), 2.06 (br s, 1H), 1.91 (m, 1H), 1.81 (dd, $J = 10.6$ Hz, 13.5 Hz, 1H), 1.75 (s, 3H), 1.19 (s, 3H), 0.90 (d, $J = 7.1$ Hz, 3H).

**bis((2R,3R)-2-hydroxy-2,3,5-trimethylhex-5-en-1-yl) fumarate:** Grubb’s-Hoveyda 2$^{nd}$ generation catalyst (0.008, 0.012 mmol) was added to a solution of diene 179 (0.013 g, 0.061 mmol) in toluene (12 mL) and the resulting solution was heated to 75 °C for 24 hours and was subsequently stirred for 24 hours at room temperature. The solution was concentrated *in vacuo* and purified by flash column chromatography (gradient 10:90 – 40:60 EtOAc:Hexanes) yielding dimer 183 (0.003 g, 23%) as a colourless oil.

$^1$H NMR (600 MHz, CDCl$_3$) $\delta = 6.96$ (s, 2H), 4.81 (s, 2H), 4.73 (s, 2H), 4.22, 4.17 (AB, $J_{AB} = 11.2$ Hz, 4H), 2.45 (br d, $J = 12.9$ Hz, 2H), 1.89 – 1.86 (m, 4H), 1.80 (dd, $J = 10.6$ Hz, 12.9 Hz, 2H), 1.73 (s, 6H), 1.18 (s, 6H), 0.88 (d, $J = 6.5$ Hz, 6H).

**(Z)-ethyl 3-methyl-4-((tetrahydro-2H-pyran-2-yl)oxy)but-2-enoate:** CuI (2.013 g, 10.57 mmol) was added to THF (55 mL, 0.2 M) and the resulting suspension was purged
with argon and cooled to 0 °C. 1.6 M MeLi (13.15 mL, 21.01 mmol) was added dropwise. The solution was stirred for 30 minutes at 0 °C, then cooled to -78 °C. Alkyne 191 (2.000 g, 9.35 mmol) dissolved in 20 mL THF was added dropwise to the solution, and the reaction temperature was maintained at -78 °C for 4 hours. The reaction was quenched with saturated NH₄Cl and allowed to warm to room temperature. The blue solution was filtered and extracted 3x with EtOAc. The organic fractions were combined, washed with brine, dried over MgSO₄ and concentrated in vacuo yielding 2.18 g (100% yield) of alkene 192 as a thin brown oil which required no further purification.

^1^H NMR (600 MHz, CDCl₃) δ = 5.74 (q, J = 1.8 Hz, 1H), 4.75, 4.69 (AB, J_AB = 14.1 Hz, 2H), 4.63 (t, J = 3.8 Hz, 1H), 4.14 (q, J = 7.0 Hz, 2H), 3.88 (ddd, J = 2.9 Hz, 8.2 Hz, 11.2 Hz, 1H), 3.55-3.51 (m, 1H), 2.00 (d, J = 1.8 Hz, 3H), 1.90-1.83 (m, 1H), 1.75-1.72 (m, 1H), 1.63-1.53 (m, 4H), 1.27 (t, J = 7.0 Hz, 3H).

(Z)-3-methyl-4-((tetrahydro-2H-pyran-2-yl)oxy)but-2-en-1-ol: LiAlH₄ (1.05 g, 27.6 mmol) was suspended in anhydrous Et₂O (15 mL) at 0 °C. Alkene 192 (4.20 g, 18.4 mmol) dissolved in Et₂O (5 mL, 1.4 M total) was added to the LiAlH₄ suspension dropwise. The reaction was allowed to warm to room temperature slowly and was then stirred for an additional 3.25 hours. The solution was then cooled to 0 °C and H₂O was added to the reaction until it stopped bubbling, diluting with Et₂O as needed to break up the salts forming. The quenched mixture was stirred for an additional 2 hours at 0 °C, sonicated for 15 minutes, and filtered over celite. The filter cake was washed with
EtOAc and the filtrate was concentrated in vacuo, yielding alcohol 193 as a colourless oil (2.61 g, 76%).

$^1$H NMR (600 MHz, CDCl$_3$) $\delta = 5.73$ (t, $J = 7.0$ Hz, 1H), 4.66 (t, $J = 3.5$ Hz, 1H), 4.20 – 4.07 (m, 4H), 3.86 (ddd, $J = 2.9$ Hz, 8.8 Hz, 11.7 Hz, 1H), 3.57 – 3.54 (m, 1H), 1.82 – 1.80 (m, 4H), 1.74 – 1.70 (m, 1H), 1.64 – 1.53 (m, 4H).

(Z)-tert-butyldimethyl((3-methyl-4-((tetrahydro-2H-pyran-2-yl)oxy)but-2-en-1-yl)oxy)silane: Alcohol 193 (1.096 g, 5.89 mmol) was dissolved in CH$_2$Cl$_2$ (20 mL, 0.3 M) and the solution was cooled to 0 °C. Imidazole (0.522 g, 7.66 mmol) was added and once fully dissolved, TBSCl (1.16 g, 7.66 mmol) was added in one portion. The reaction was allowed to warm to room temperature and was then stirred for 6.5 hours. The reaction was quenched with NH$_4$Cl and the layers were separated. The aqueous layer was extracted 2x with CH$_2$Cl$_2$. The combined organic fractions were washed with brine, dried over MgSO$_4$, and concentrated in vacuo. Excess TBSOH was removed via azeotropic distillation with toluene to yield pure 194 as a colourless oil (1.500 g, 85%)

$^1$H NMR (600 MHz, CDCl$_3$) $\delta = 5.52$ (t, $J = 5.9$ Hz, 1H), 4.58 (t, $J = 3.5$ Hz, 1H), 4.25 (d, $J = 5.9$ Hz, 2H), 4.12, 4.05 (AB, $J_{AB} = 11.7$ Hz, 2H), 3.88 (ddd, $J = 2.9$ Hz, 8.2, 11.2, 1H), 3.54-3.51 (m, 1H), 1.87-1.80 (m, 4H), 1.76-1.69 (m, 1H), 1.62-1.52 (m, 4H), 0.91 (s, 9H), 0.08 (s, 6H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta = 133.59$, 128.96, 97.59, 65.46, 62.13, 59.58, 30.61, 25.99, 25.48, 21.65, 19.45, 18.40.
(Z)-2-((4-((4-methoxybenzyl)oxy)-2-methylbut-2-en-1-yl)oxy)tetrahydro-2H-pyran:
60% NaH (1.667 g, 41.7 mmol) was suspended in DMF (46 mL, 0.3 M) and cooled to 0 °C. Alcohol 193 (2.588 g, 13.9 mmol) was added and the reaction was stirred for 1 hour at 0 °C. PMBCl (2.83 mL, 20.9 mmol) and TBAI (0.513 g, 1.39 mmol) were added and the resulting solution was purged with argon. The solution was stirred for 1 hour at 0 °C and then at room temperature for 4 hours. The reaction was quenched with brine and extracted 3x with Et₂O. The combined organic layers were dried over MgSO₄ and concentrated in vacuo. The oily residue was preadsorbed onto 15 g of silica and purified by column chromatography (gradient 5:95 – 8:92 EtOAc:Hexanes) yielding PMB alcohol 195 as a colourless oil (2.76 g, 65%).

1H NMR (400 MHz, CDCl₃) δ = 7.27, 6.88 (AA’XX’, Jₐₐ=Jₓₓ‘ = 5.1 Hz, Jₐₓ = 4.5 Hz, Jₓ’ₓ = 4.5 Hz, 4H) 5.60 (t, J = 5.5 Hz, 1H), 4.57 (t, J = 2.7 Hz, 1H), 4.44 (s, 2H) 4.15 - 4.05 (m, 4H), 3.85 (ddd, J = 2.7 Hz, 7.8 Hz, 10.9 Hz, 1H), 3.81 (s, 3H), 3.52-3.47 (m, 1H), 1.82 – 1.79 (m, 4H), 1.72-1.68 (m, 1H), 1.60-1.51 (m, 4H).

(Z)-4-((4-methoxybenzyl)oxy)-2-methylbut-2-en-1-ol: PPTS (0.022 g, 0.082 mmol) was added to a solution of PMB alcohol 196 (0.162 g, 0.529 mmol) in MeOH (5 mL, 0.1 M). The reaction was stirred at room temperature for 1.25 hours and then heated to
reflux for 3 hours. The reaction was cooled to room temperature and concentrated in vacuo. The residue was dissolved in EtOAc, washed once with 1.7 M NaOH and once with brine. The organic layer was dried over MgSO₄ and concentrated in vacuo, yielding alcohol 196 as a colourless oil (0.117 g, 100%)

\(^1\)H NMR (400 MHz, CDCl₃) δ = 7.27, 6.89 (AA’XX’, \(J_{AA}=J_{XX}=4.8\) Hz, \(J_{AX}=J_{A’X’}=4.5\) Hz, 2H) 5.58 (qtt, \(J = 1.2\) Hz, 1.6 Hz, 6.8 Hz, 1H), 4.46 (s, 2H), 4.11 (s, 2H), 4.02 (dq, \(J = 6.8\) Hz, 1.2 Hz, 2H), 3.81 (s, 3H), 1.85 (td, \(J = 1.2\) Hz, 1.2 Hz, 3H).

\(\text{(Z)}\)-1-(((4-chloro-3-methylbut-2-en-1-yl)oxy)methyl)-4-methoxybenzene: PPh₃ (2.62 g, 10 mmol) was added to a solution of alcohol 196 (1.710 g, 7.69 mmol) in CCl₄ (8 mL, 1 M) and the resulting solution was heated to reflux for 2 hours. The reaction was cooled to room temperature, concentrated onto 15 g of silica gel, and purified by flash column chromatography (gradient 3:97 – 5:95 EtOAc:Hexanes) to yield allyl chloride 197 as a pale yellow oil (1.46 g, 79%).

\(^1\)H NMR (400 MHz, CDCl₃) δ = 7.28, 6.89 (AA’XX’, \(J_{AA}=J_{XX}=4.8\) Hz, \(J_{AX}=4.3\), \(J_{A’X’}=4.3\) Hz) 5.61 (qt, 1 H, \(J = 1.2\) Hz, 6.6 Hz), 4.46 (s, 2H), 4.06 (s, 2H) 4.05 (dq, \(J = 6.6\) Hz, 1.2 Hz, 2H), 3.82 (s, 3H), 1.85 (td, \(J = 1.2\) Hz, 1.2 Hz, 3H).

\(\text{(2R,3R)}\)-5-(iodomethyl)-2,3,5-trimethyl-2-((trityloxy)methyl)tetrahydrofuran:
Alkene 168 (3.71 g, 9.28 mmol) was dissolved in CH₂Cl₂ (37 mL, 0.25 M) and wrapped in aluminum foil to avoid contact with light. N-iodosuccinimide (2.23 g, 10.2 mmol) was added to the solution and the mixture was stirred for 1 hour. The mixture was concentrated in vacuo on 17 g of silica gel and purified by flash column chromatography (5.95 EtOAc:Hexanes) to yield iodide 201-I (4.20 g, 86%).

1H NMR (600 MHz, CDCl₃) δ = 7.48-7.45 (m, 6H), 7.30-7.27 (m, 6H), 7.23-7.20 (m, 3H), 3.31 (d, J = 9.9 Hz, 1H), 3.24 (d, J = 9.9 Hz, 1H), 3.04 (d, J = 9.3 Hz, 1H), 2.94 (d, J = 9.3 Hz, 1H), 2.53-2.46 (m, 1H), 1.99 (dd, J = 6.8 Hz, 12.4 Hz, 1H), 1.74 (dd, J = 12.5 Hz, 12.5 Hz, 1H), 1.40 (s, 3H), 1.04 (s, 3H), 0.90 (d, J = 7.0 Hz, 3H); 13C NMR (150 MHz, CDCl₃) δ = 144.14, 128.85, 127.74, 126.85, 86.47, 85.74, 79.73, 69.70, 56.60, 45.46, 38.41, 26.68, 20.42, 14.30; FT-IR (thin film, cm⁻¹) 3058.03, 2969.30, 2929.40, 2871.08, 1490.44, 1448.26, 1373.07, 1149.52, 1077.23, 705.93, 632.77; HRMS calc. for C₂₈H₃₁IO₂ + Na⁺ = 549.1261; exp. = 549.1280.

2-((4R,5R)-2,4,5-trimethyl-5-((trityloxy)methyl)tetrahydrofuran-2-yl)acetonitrile:
Sodium cyanide (1.96 g, 40.0 mmol) was added to a solution of iodide 201-I (4.20 g, 7.97 mmol) in DMSO (80 mL, 0.1 M) and the mixture was heated to 90 °C for 18 hours. The solution was cooled to 0 °C and water was added. The mixture was extracted 4x with Et₂O, and the combined organic extracts were washed 5x with water and 1x with brine. The organic layer was dried over MgSO₄ and concentrated in vacuo to yield crude nitrile 202 (3.36 g, 99%) as a yellow oil as a 3:1 mixture of diastereomers.
**1H NMR** (600 MHz, CDCl$_3$) $\delta = 7.48$-7.41 (m, 6H), 7.34-7.26 (m, 6H), 7.24-7.21 (m, 3H), 3.07 (d, $J = 9.6$ Hz, 1H), 2.95 (d, $J = 9.6$ Hz, = 1H), 2.60, 2.58 (AB, $J = 16.4$ Hz, 2H), 257 – 2.51 (m, 1H), 1.97 (dd, $J = 6.9$ Hz, 12.3 Hz, 1H), 1.82 (dd, $J = 12.3$ Hz, 12.3 Hz, 1H), 1.33 (s, 3H), 1.05 (s, 3H), 0.90 (d, $J = 6.8$ Hz, 3H); **13C NMR** (150 MHz, CDCl$_3$) $\delta = 144.06, 128.81, 127.70, 126.89, 117.96, 86.52, 85.80, 78.22, 69.23, 44.15, 37.58, 31.75, 27.92, 20.14, 14.13;$ FT-IR (thin film, cm$^{-1}$) 3058.66, 2970.84, 2931.45, 2872.74, 2251.38, 1490.54, 1378.34, 1077.10, 986.23, 706.99, 632.74; HRMS calc. for C$_{29}$H$_{31}$NO$_2$ = 425.2355; exp. = 425.2351.

**methyl 2-((2R,4R,5R)-5-(hydroxymethyl)-2,4,5-trimethyltetrahydrofuran-2-yl)acetate:** Crude nitrile 202 (3.36g, ~7.97 mmol) was dissolved in methanol (80 mL, 0.1 M) and separated into 8 x 20 mL microwave vials. 2M NaOH (8 mL, 160 mmol) was added to each vial and they were each heated to 150 °C for one hour. The combined contents of each vial were neutralized with concentrated H$_2$SO$_4$. The mixture was filtered over celite and the methanol was removed *in vacuo*. The remaining aqueous layer was extracted 3x with ethyl acetate. The combined organic extracts were washed with brine, dried over MgSO$_4$ and concentrated *in vacuo*. The resulting white foam was dissolved in a 7:1 mixture of toluene:methanol (80 mL) and wrapped in aluminum foil. Trimethylsilyl diazomethane (6 mL, 2M in hexanes, 12 mmol) was added dropwise and the solution was stirred for 18 hours. Trifluoroacetic acid was added dropwise until the yellow solution
turned colourless. Once colourless, excess trifluoroacetic acid (6.1 mL, 79.7 mmol) was added and the solution was stirred for one hour. Saturated sodium bicarbonate was added to quench the excess acid and the solution was extracted 3x with Et₂O. The organic extracts were washed with brine, dried with MgSO₄, and concentrated in vacuo. The resulting mixture was purified by flash column chromatography (EtOAc:hexanes 40:60) to yield separable diastereomers 204 (0.503 g) and 205 (0.175 g) (0.678 g total, 39% over 4 steps).

Major Diastereomer 204: ¹H NMR (600 MHz, CDCl₃) δ = 3.66 (s, 3H), 3.42 (d, J = 11.7 Hz, 1H), 3.32 (d, J = 11.7 Hz, 1H), 2.62, 2.56 (AB, J_AB = 14.1 Hz, 2H), 2.57-2.50 (X of ABXY₃, m, 1H), 1.97, 1.98 (AB of ABXY₃, J AX = 6.6 Hz, J BX = 12.7 Hz, J_AB = 12.3 Hz, 2H), 1.29 (s, 3H), 0.92 (d, J = 6.8 Hz, 3H), 0.91 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ = 171.35, 85.79, 79.37, 66.21, 51.50, 47.74, 44.14, 35.09, 28.09, 19.18, 13.54; HRMS calc. for C₁₁H₂₀O₄ + H⁺ = 217.1434; exp. = 217.1416.

Minor Diastereomer 205: ¹H NMR (600 MHz, CDCl₃) δ = 3.73 (s, 3H), 3.51 (d, J = 11.7 Hz, 1H), 3.32 (d, J = 11.7 Hz, 1H), 2.72 (ddq, J = 7.0 Hz, 7.0 Hz, 12.9 Hz, 1H) 2.61 (d, J = 12.3 Hz, 1H), 2.38 (d, J = 12.3 Hz, 1H), 2.04 (dd, J = 7.0 Hz, 12.3 Hz, 1H), 1.71 (dd, J = 12.9 Hz, 12.9 Hz, 1H), 1.42 (s, 3H), 0.95 (s, 3H), 0.94 (d, J = 7.0 Hz, 3H).

methyl 2-((2R,4R,5R)-5-formyl-2,4,5-trimethyltetrahydrofuran-2-yl)acetate: To a solution of oxalyl chloride (192 μL, 2.20 mmol) in CH₂Cl₂ (10 mL) at -78 °C was added
DMSO (275 μL, 3.88 mmol). After stirring for 10 minutes at this temperature, alcohol 204 was added (400 mg, 1.85 mmol) in CH₂Cl₂ (9 mL). After stirring for 45 minutes, NEt₃ (1.29 mL, 9.24 mmol) was added, and the solution was allowed to warm slowly to room temperature. After stirring for 2 hours, the solution was quenched with saturated sodium bicarbonate. The mixture was extracted 4x with CH₂Cl₂, and the combined organic layers were washed 1x with brine, dried over MgSO₄, and concentrated in vacuo. The residue was purified by flash column chromatography (20:80 EtOAc:hexanes) to yield aldehyde 206 (331 mg, 84%). The minor isomer 209 was synthesized from 205 in the same manner with nearly identical yields.

Major Diastereomer 206: ¹H NMR (400 MHz, CDCl₃) δ = 9.45 (s, 1H), 3.67 (s, 3H), 2.67, 2.56 (AB, J = 14.3 Hz, 2H), 2.46 (ddq, J = 7.0 Hz, 7.0 Hz, 12.1 Hz, 1H), 2.08 (dd, J = 7.0 Hz, 12.5 Hz, 1H), 1.92 (dd, J = 12.5 Hz, 12.5 Hz, 1H), 1.33 (s, 3H), 1.07 (s, 3H), 0.96 (d, J = 7.0 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ = 202.73, 171.08, 88.22, 81.69, 51.57, 47.13, 43.76, 36.68, 27.71, 16.34, 12.94; HRMS calc. for C₁₁H₁₈O₄ + H⁺ = 215.1278; exp.= 215.1278.

Minor Diastereomer 209: ¹H NMR (400 MHz, CDCl₃) δ = 9.47 (s, 1H), 3.69 (s, 3H), 2.55, 2.53 (AB, J = 13.7 Hz, 2H), 2.46 – 2.36 (m, 2H), 1.65 (dd, J = 10.9 Hz, 10.9 Hz, 1H), 1.49 (s, 3H), 1.14 (s, 3H), 0.97 (d, J = 6.6 Hz, 3H).

(2R,3R,5R)-5-(2-methoxy-2-oxoethyl)-2,3,5-trimethyltetrahydrofuran-2-carboxylic
acid: To a solution of aldehyde 206 (200 mg, 0.94 mmol) in THF (4 mL), \( \text{^tBuOH} \) (1.5 mL), and water (0.5 mL) at 0 °C was added 2-methyl-2-butene (792 μL, 7.48 mmol), potassium dihydrogen phosphate (336 mg, 2.80 mmol), and sodium chlorite (253 mg, 2.80 mmol) sequentially. After 1 hour, 5% HCl was added to the reaction and the aqueous layer was extracted 3x with CH₂Cl₂. The combined organic fractions were washed with brine, dried over MgSO₄, and concentrated in vacuo. The residue was purified by flash column chromatography (50:49:1 EtOAc:hexanes:Acetic acid) and the remaining acetic acid was coevaporated with benzene 3 times to yield carboxylic acid 207 (194 mg, 90%). The minor diastereomer 210 was synthesized from aldehyde 209 following the same procedure in nearly identical yields.

Major Diastereomer 207: \(^1\)H NMR (400 MHz, CDCl₃) \( \delta = 10.71 \) (br s, 1H), 3.76 (s, 3H), 2.57, 2.47 (AB, \( J_{AB} = 12.9 \) Hz, 2H), 2.57-2.47 (m, 1H), 2.10 (dd, \( J = 6.9 \) Hz, 12.8 Hz, 1H), 1.73 (dd, \( J = 12.8 \) Hz, 12.8 Hz, 1H), 1.39 (s, 3H), 1.33 (s, 3H), 1.14 (d, \( J = 6.8 \) Hz, 3H); \(^1\)C NMR (100 MHz, CDCl₃) \( \delta = 175.27, 170.61, 85.60, 82.05, 51.65, 46.91, 44.17, 40.05, 27.21, 19.41, 13.73; HRMS calc. for C₁₃H₂₂O₄ + H⁺ = 231.1227; exp. = 231.1230.

Minor Diastereomer 210: \(^1\)H NMR (400 MHz, CDCl₃) \( \delta = 3.70 \) (s, 3H), 2.69, 2.62 (AB, \( J = 14.7 \) Hz, 2H), 2.64 – 2.56 (m, 1H), 2.12 (dd, \( J = 7.0 \) Hz, 12.9 Hz, 1H), 1.98 (dd, \( J = 12.9 \) Hz, 12.9 Hz, 1H), 1.42 (s, 3H), 1.30 (s, 3H), 1.17 (d, \( J = 7.0 \) Hz, 3H).
((1S,3R,7R,7aR)-3-(2-((tert-butyl diphenylsilyl)oxy)ethyl)-7-hydroxyhexahydro-1H-pyrrolizin-1-yl)methyl 5-(2-methoxy-2-oxoethyl)-2,3,5-trimethyltetrahydrofuran-2-carboxylate: HBTU (0.576 g, 1.52 mmol) was added to a solution of acid 207 (0.100 g, 0.434 mmol), diol 130 (0.286 mg, 0.651 mmol), and DIPEA (266 μL, 1.52 mmol) in DMF (2 mL, 0.2 M) at room temperature and the resulting solution was stirred under an argon atmosphere for 8 hours. Equal parts of H₂O and Et₂O were added and the two phases were separated. The aqueous layer was extracted 3x with Et₂O and the combined organic layers were washed once with brine, dried over MgSO₄, and concentrated in vacuo. The orange oil was purified by flash column chromatography (1:15:84 NEt₃:MeOH:EtOAc) to yield the coupled adduct 211 as a brown oil (162 mg, 57%). The compound was only approximately 90% pure by mass, with the majority of the impurities being attributed to tetramethylurea and DMF as identified by ¹H NMR.

Note that this data is not completely accurate as there is a 1:1 mixture of diastereomers, making it challenging to determine which diastereomer each set of peaks represents.

¹H NMR (400 MHz, CDCl₃) δ = 7.68 - 7.65 (m, 4H), 7.43 – 7.41 (m, 2H), 7.39 – 7.36 (m, 4H), 4.50 (dd, J = 6.5 Hz, 11.3 Hz, 1H), 4.36 (dd, J = 5.3 Hz, 10.6 Hz, 1H), 4.22 (br s, 1H), 3.82 – 3.78 (m, 1H), 3.76 – 3.72 (m, 1H), 3.67 (s, 3H), 3.35 – 3.20 (br m, 3H), 2.98 (br m, 1H), 2.82 – 2.77 (br m, 1H), 2.71 (d, J = 14.1 Hz, 1H), 2.69 – 2.63 (m, 1H),
2.57 (d, $J = 14.1$ Hz, 1H), 2.16 – 2.10 (m, 1H), 2.07 (dd, $J = 6.9$ Hz, $12.9$ Hz, 1H), 1.97 – 1.87 (m, 3H), 1.82 – 1.73 (m, 1H), 1.70 – 1.64 (m, 1H), 1.57 – 1.47 (m, 1H), 1.32 (s, 3H), 1.26 (s, 3H), 1.10 (d, $J = 7.0$ Hz, 3H), 1.05 (s, 9H).

\[ \text{allyl } 2-((2R,4R,5R)-5-(hydroxymethyl)-2,4,5-trimethyltetrahydrofuran-2-yl)acetate:}\]

Nitrile 202 (1.529 g, 3.6 mmol) was dissolved in MeOH (36 mL, 0.1 M). 9 mL of the resulting solution and 2M NaOH (9 mL, 180 mmol) were added to a large microwave vial. The white suspension was heated to 150 °C for 1 hour in the microwave. This procedure was repeated 3 times with the remaining original methanol solution. The MeOH/NaOH solutions were combined and saturated with NaCl. The pH was then adjusted to pH 7 using 5% HCl. This mixture was extracted 4x with CH$_2$Cl$_2$. The combined organic phases were washed with brine, dried over MgSO$_4$, and concentrated \textit{in vacuo}. The crude carboxylic acid was dissolved in DMF (36 mL, 0.1 M). Cs$_2$CO$_3$ (3.52 g, 10.8 mmol) was added and the solution was stirred for 15 minutes at room temperature. Allyl bromide (1.31 g, 10.8 mmol) was added, and the solution was purged with argon and stirred at room temperature for 18 hours. Equal volumes of H$_2$O and Et$_2$O were added and the phases were separated. The aqueous layer was extracted 4x with Et$_2$O. The combined organic layers were washed 5x with H$_2$O and once with brine. The organic layer was dried over MgSO$_4$ and concentrated \textit{in vacuo}. CH$_2$Cl$_2$ (36 mL, 0.1
M) was added to the resulting oil, and TFA (2.76 mL, 36 mmol) was subsequently added over 5 minutes. The brown solution was stirred at room temperature for one hour. The solution was neutralized with sat NaHCO$_3$ and the resulting layers were separated. The aqueous layer was extracted 3x with CH$_2$Cl$_2$, and the combined organic layers were washed once with brine, dried over MgSO$_4$, and concentrated in vacuo. The solid residue was purified by flash column chromatography (40:60 EtOAc:Hexanes) to yield diastereomeric alcohols 213 (0.153 g), 214 (0.329 g) along with a mixture of both diastereomers (0.046 g) (overall 61% yield over 3 steps) as colourless oils.

**Major Diastereomer 214:** $^1$H NMR (400 MHz, CDCl$_3$) $\delta = 5.93$ (dddd, $J = 5.9$ Hz, 5.9 Hz, 11.8 Hz, 16.0 Hz, 1H), 5.34 (dddd, $J = 1.6$ Hz, 1.6 Hz, 1.6 Hz, 17.2 Hz, 1H), 5.25 (dddd, $J = 1.2$ Hz, 1.2 Hz, 1.2 Hz, 10.6 Hz, 1H), 4.63 – 4.53 (m, 2H), 3.43, 3.33 (AB of ABXY$_3$, $J_{AX} = 2.9$ Hz, $J_{BX} = 10.0$ Hz, $J_{AB} = 11.3$ Hz, 2H), 2.60, 2.66 (AB, $J_{AB} = 14.1$ Hz, 2H), 2.60 – 2.49 (X of ABXY$_3$, $J_{AX} = 2.9$ Hz, $J = 10.0$ Hz, $J_{XY} = 6.6$ Hz, 1H), 2.04-1.94 (m, 3H), 1.32 (s, 3H), 0.94 (s, 3H), 0.94 (Y of ABXY$_3$, d, $J = 6.6$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta = 170.54$, 132.08, 118.43, 86.76, 79.35, 66.22, 65.11, 47.99, 44.36, 35.11, 27.97, 19.19, 13.56; FT-IR (thin film, cm$^{-1}$) 3453.44, 2969.35, 2934.71, 2875.60, 1735.85, 1453.64, 1374.59, 1218.27, 1046.91, 990.98, 927.29; HRMS calc. for C$_{13}$H$_{22}$O$_4$ + H$^+$ = 243.1596; exp.= 243.1594.

**Minor Diastereomer 213:** $^1$H NMR (400 MHz, CDCl$_3$) $\delta = 5.94$ (dddd, $J = 5.9$ Hz, 5.9 Hz, 11.8 Hz, 16.0 Hz, 1H), 5.34 (dddd, $J = 1.6$ Hz, 1.6 Hz, 1.6 Hz, 17.2 Hz, 1H), 5.25 (dddd, $J = 1.2$ Hz, 1.2 Hz, 1.2 Hz, 10.6 Hz, 1H), 4.68 – 4.57 (m, 2H), 3.51 – 3.25 (ABC system, 3H), 2.71 (ddq, $J = 7.0$ Hz, 7.0 Hz, 12.9 Hz, 1H), 2.62 (d, $J = 12.1$ Hz, 1H), 2.40
(d, \( J = 12.1 \) Hz, 1H), 2.05 (dd, \( J = 7.0 \) Hz, 12.5 Hz, 1H), 1.71 (dd, \( J = 12.5 \) Hz, 12.5 Hz, 1H), 1.43 (s, 3H), 0.94 (s, 3H), 0.94 (d, \( J = 7.4 \) Hz, 3H).

allyl 2-((2R,4R,5R)-5-(((1R,4R)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)methyl)sulfonyl)oxy)methyl)-2,4,5-trimethyltetrahydrofuran-2-yl)acetate: (S)-camphorsulfonyl chloride (0.120 g, 0.477 mmol) was added to a solution of alcohol 214 (0.077 g, 0.318 mmol), NEt\(_3\) (221 \( \mu \)L, 1.59 mmol), and DMAP (0.012 g, 0.100 mmol) in CH\(_2\)Cl\(_2\) (3 mL, 0.1 M) at room temperature under argon. The solution was stirred for 5 hours at room temperature, after which it was concentrated \textit{in vacuo}. The residue was purified by column chromatography (40:60 EtOAc:Hexanes) to yield title compound 216-rac as a colourless oil (0.121 g, 83%).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta = 5.91 \) (dddd, \( J = 5.9 \) Hz, 5.9 Hz, 10.5 Hz, 16.4 Hz, 1H), 5.32 (dddd, \( J = 1.2 \) Hz, 1.2 Hz, 1.2 Hz, 17.2 Hz, 1H), 5.23 (ddddd, \( J = 1.2 \) Hz, 1.2 Hz, 1.2 Hz, 10.5 Hz, 1H), 4.60 – 4.52 (m, 2H), 4.14 – 4.08 (m, 2H), 3.65 (dd, \( J = 14.8 \) Hz, 14.8 Hz, 1H), 3.06 (dd, \( J = 9.4 \) Hz, 14.8 Hz, 1H), 2.66 – 2.54 (m, 2H), 2.50 – 2.35 (m, 4H), 2.13 – 1.90 (m, 4H), 1.89 – 1.87 (m, 1H), 1.69 (dddd, \( J = 4.7 \) Hz, 9.4 Hz, 14.0 Hz, 1H), 1.44 (dddd, \( J = 3.9 \) Hz, 9.4 Hz, 12.5 Hz, 1H), 1.30 (s, 3H), 1.12 (s, 3H), 1.04 (s, 3H), 0.99 (d, \( J = 6.6 \) Hz, 3H), 0.88 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\), one diastereomer
shown) δ = 214.28, 170.40, 132.03, 118.35, 83.06, 79.86, 74.86, 65.02, 57.89, 47.88, 47.65, 46.97, 44.04, 42.74, 42.45, 37.36, 27.79, 26.83, 24.87, 19.78, 19.64, 19.20, 13.94.

(2R,3R,5R)-5-(2-(allyloxy)-2-oxoethyl)-2,3,5-trimethyltetrahydrofuran-2-carboxylic acid: Alcohol 214 (0.244 g, 1.00 mmol) was dissolved in glass distilled acetone (20 ml, 0.05 M) and the resolution solution was cooled to 0 °C and purged with argon. 2M Jones’ reagent (1.50 mL, 3.00 mmol) was added to the cooled reaction mixture dropwise over 5 minutes and the red-brown solution was stirred at 0 °C for 2.5 hours. 2-propanol was added to quench the excess Jones’ reagent until the reaction mixture turned blue. The solution was concentrated in vacuo. EtOAc was added to the blue sludge and the suspension was triturated. The blue mixture was passed through a short pad of celite and silica, and the filter cake was washed with 200 mL of EtOAc. The eluted carboxylic acid solution 229 was concentrated in vacuo and often needed no further purification (0.249 g, 97%). 228 was synthesized from alcohol 213 following the same procedure in nearly identical yields.

Major diastereomer 229: $^1$H NMR (400 MHz, CDCl$_3$) δ = 5.92 (dddd, $J = 5.5$ Hz, 5.5 Hz, 10.2 Hz, 16.4 Hz, 1H), 5.35 (dddd, $J = 1.6$ Hz, 1.6 Hz, 1.6 Hz, 17.2 Hz, 1H), 5.27 (dd, $J = 1.2$ Hz, 10.2 Hz, 1H), 4.59 (dd, $J = 1.6$ Hz, 5.9 Hz, 2H), 2.71, 2.64 (AB, $J = 14.5$ Hz, 2H), 2.64 – 2.58 (m, 1H), 2.15 (dd, $J = 6.6$ Hz, 12.1 Hz, 1H), 1.97 (dd, 12.7 Hz, 12.7 Hz,
1H), 1.42 (s, 3H), 1.30 (s, 3H), 1.16 (d, $J = 6.6$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta =$ 169.84 (2 carbons), 131.82, 118.72, 85.54, 82.01, 65.31, 47.09, 44.24, 40.04, 27.15, 19.47, 13.76; FT-IR (thin film, cm$^{-1}$) 2975.87, 1735.84, 1452.34, 1378.89, 1219.37, 1117.37, 772.21; HRMS calc. for C$_{13}$H$_{21}$O$_5$ + H$^+$ = 257.1389; exp. = 257.1389

Minor diastereomer 228: $^1$H NMR (400 MHz, CDCl$_3$) $\delta =$ 10.63 (br s, 1H), 5.94 (dddd, $J = 5.9$ Hz, 5.9 Hz, 10.2 Hz, 17.2 Hz, 1H), 5.37 (dddd, $J = 1.2$ Hz, 1.2 Hz, 1.2 Hz, 17.2 Hz, 1H), 5.30 (dddd, $J = 1.2$ Hz, 1.2 Hz, 1.2 Hz, 10.5 Hz, 1H), 4.70 – 4.64 (m, 2H), 2.58, 2.48 (AB, $J_{AB} = 12.9$ Hz, 2H), 2.57 – 2.48 (m, 1H), 2.12 (dd, $J = 7.0$ Hz, 12.9 Hz, 1H), 1.75 (dd, $J = 12.5$ Hz, 12.5 Hz, 1H), 1.42 (s, 3H), 1.34 (s, 3H), 1.15 (d, $J = 6.6$ Hz, 3H)

![Chemical Structure](image)

(2R,3R,5S)-((1S,3R,7R,7aR)-3-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-7-hydroxyhexahydro-1H-pyrrolizin-1-yl)methyl 5-(2-(allyloxy)-2-oxoethyl)-2,3,5-trimethyltetrahydrofuran-2-carboxylate: HBTU (0.400 g, 1.05 mmol) was added to a solution of acid 228 (0.077 g, 0.300 mmol), diol 130 (0.145 mg, 0.330 mmol) and DIPEA (0.183 mL, 1.05 mmol) in DMF (1.5 mL, 0.2 M) at room temperature and the resulting solution was stirred under an argon atmosphere for 18 hours. Equal parts of H$_2$O and Et$_2$O were added and the two phases were separated. The aqueous layer was extracted 3x with Et$_2$O and the combined organic layers were washed once with brine, dried over
MgSO$_4$, and concentrated in vacuo. The orange oil was purified by flash column chromatography (1:8:91 NH$_4$OH:MeOH:CH$_2$Cl$_2$) to yield the coupled adduct 230 as a brown oil (0.078 mg, 35%).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta = 7.68 – 7.64$ (m, 4H), 7.45 – 7.36 (m, 6H), 5.97 – 5.87 (m, 1H), 5.33 (dddd, $J = 1.6$ Hz, 1.6 Hz, 1.6 Hz, 16.0 Hz, 1H), 5.25 (ddddd, $J = 1.2$ Hz, 1.2 Hz, 1.2 Hz, 10.6 Hz, 1H), 4.60 – 4.58 (m, 3H), 4.33 – 4.17 (m, 2H), 3.87 – 3.68 (m, 3H), 3.60 – 3.38 (br m, 1H), 3.20 – 3.02 (br m, 1H), 2.91 – 2.78 (m, 1H), 2.75, 2.60 (AB, $J_{AB} = 14.5$ Hz, 2H), 2.67 (m, 1H), 2.25 – 2.15 (m, 1H), 2.12 – 1.78 (m, 8H), 1.68 – 1.50 (m, 1H), 1.35 (s, 3H), 1.27 (s, 3H), 1.10 (d, $J = 6.6$ Hz, 3H), 1.05 (s, 9H); FT-IR (thin film, cm$^{-1}$) 3070.61, 2932.30, 2857.67, 1734.28, 1471.29, 1427.86, 1380.78, 1272.36, 1234.67, 1111.60, 990.08, 505.33; HRMS calc. for C$_{39}$H$_{55}$O$_7$Si + H$^+$ = 678.3826; exp.= 678.3838.

2-((2S,4R,5R)-5-(((1S,3R,7R,7aR)-3-((tert-butyldiphenylsilyl)oxy)ethyl)-7-hydroxyhexahydro-1H-pyrrolizin-1-yl)methoxy)carbonyl)-2,4,5-trimethyltetrahydrofuran-2-yl)acetic acid: Morpholine (18 $\mu$L, 0.21 mmol) was added to a solution of allyl ester 230 (0.071 g, 0.105 mmol) and Pd(PPh$_3$)$_4$ (11 mg, 0.010 mmol) in anhydrous CH$_2$Cl$_2$ (3.5 mL, 0.03 M) and the reaction was stirred for 19 hours at room temperature. The solution was diluted with CH$_2$Cl$_2$, washed with NH$_4$Cl and brine, dried
over MgSO₄ and concentrated in vacuo. The material was purified by flash column chromatography (2:10:78 NH₄OH:MeOH:EtOAc, then 6:20:74 NH₄OH:MeOH:EtOAc, followed by 100% MeOH). Note: The Rᵣ of this compound is ~ 0.1 in 100% MeOH. The latter fractions were concentrated, dissolved in CH₂Cl₂ and passed through a small pad of Celite to remove the dissolved silica. The filtrate was concentrated to yield carboxylic acid 231 as a colourless oil (30 mg, 45%).

$^1$H NMR (600 MHz, CDCl₃, after D₂O wash) δ = 7.63 – 7.61 (m, 4H), 7.44 – 7.42 (m, 2H), 7.40 – 7.37 (m, 4H), 4.64 (br s, 1H), 4.59 (dd, $J = 10.3$ Hz, $10.3$ Hz, 1H), 4.27 (dd, $J = 6.5$ Hz, 10.0 Hz, 1H), 4.20 (d, $J = 5.3$ Hz, 1H), 3.87 – 3.77 (m, 3H), 3.70 (dddd, $J = 4.6$ Hz, 4.6 Hz, 4.6 Hz, 4.6 Hz, 1H), 3.26 – 3.19 (m, 1H), 3.02 (dddd, $J = 10.0$ Hz, 10.0 Hz, 10.0 Hz, 18.8 Hz, 1H), 2.70 – 2.65 (m, 1H), 2.55, 2.47 (AB, $J_{AB} = 14.7$ Hz, 2H), 2.36 (dd, $J = 6.5$ Hz, 12.3 Hz, 1H), 2.28 – 2.17 (m, 3H), 2.12 – 2.09 (m, 1H), 1.88 – 1.83 (m, 1H), 1.79 (dddd, $J = 4.7$ Hz, 9.4 Hz, 13.5 Hz, 1H), 1.51 (dd, $J = 12.3$ Hz, 12.3 Hz, 1H), 1.45 (s, 3H), 1.26 (s, 3H), 1.05 – 1.03 (m, 12 H); $^{13}$C NMR (100 MHz, CDCl₃) δ = 175.43, 175.13, 135.46, 133.13, 133.09, 127.81, 85.15, 82.20, 71.99, 70.99, 67.49, 63.64, 60.37, 52.66, 46.71, 44.41, 40.08, 36.94, 36.62, 35.29, 33.41, 28.23, 26.87, 20.62, 19.14, 14.14.
Figure 5: $^1$H NMR Spectrum of 141 in CDCl$_3$ at 400 MHz
Figure 6: $^{13}$C NMR Spectrum of 141 in CDCl$_3$ at 100 MHz
Figure 7: $^1$H NMR Spectrum of 220 in CDCl$_3$ at 400 MHz
Figure 8: $^1$H NMR Spectrum of 215 in CDCl$_3$ at 400 MHz
Figure 9: $^1$H NMR Spectrum of 218 in CDCl$_3$ at 400 MHz
Figure 10: $^1$H NMR Spectrum of 223 in CDCl$_3$ at 400 MHz
Figure 11: $^{13}$C NMR Spectrum of 223 in CDCl$_3$ at 100 MHz
Figure 12: $^1$H NMR Spectrum of 225 in D$_2$O at 600 MHz
Figure 13: $^1$H NMR Spectrum of 227 in D$_2$O at 400 MHz
Figure 13: $^{13}$C NMR Spectrum of 227 in D$_2$O at 100 MHz
Figure 14: $^1$H NMR Spectrum of 167 in CDCl$_3$ at 600 MHz
Figure 15: $^{13}$C NMR Spectrum of 167 in CDCl$_3$ at 150 MHz
Figure 16: $^1$H NMR Spectrum of 168 in CDCl$_3$ at 600 MHz
Figure 17: $^{13}$C NMR Spectrum of 168 in CDCl$_3$ at 150 MHz
Figure 18: $^1$H NMR Spectrum of **176** in CDCl$_3$ at 600 MHz
Figure 19: $^1$H NMR Spectrum of 177 in CDCl$_3$ at 600 MHz
Figure 20: $^1$H NMR Spectrum of 181 in CDCl$_3$ at 600 MHz
Figure 21: $^1$H NMR Spectrum of 178 in CDCl$_3$ at 600 MHz
Figure 22: $^1$H NMR Spectrum of 179 in CDCl$_3$ at 600 MHz
Figure 22: $^{13}$C NMR Spectrum of 179 in CDCl$_3$ at 150 MHz
Figure 23: $^1$H NMR Spectrum of 182 in CDCl$_3$ at 600 MHz
Figure 24: $^1$H NMR Spectrum of 183 in CDCl$_3$ at 600 MHz
Figure 25: $^1$H NMR Spectrum of 192 in CDCl$_3$ at 600 MHz
Figure 26: $^1$H NMR Spectrum of 193 in CDCl$_3$ at 600 MHz
Figure 27: $^1$H NMR Spectrum of 194 in CDCl$_3$ at 600 MHz
Figure 28: $^{13}$C NMR Spectrum of 194 in CDCl$_3$ at 150 MHz
Figure 29: $^1$H NMR Spectrum of 195 in CDCl$_3$ at 400 MHz
Figure 30: $^1$H NMR Spectrum of 196 in CDCl$_3$ at 400 MHz
Figure 31: $^1$H NMR Spectrum of 197 in CDCl$_3$ at 400 MHz
Figure 32: $^1$H NMR Spectrum of 201-I in CDCl$_3$ at 600 MHz
Figure 33: $^{13}$C NMR Spectrum of 201-I in CDCl$_3$ at 150 MHz
Figure 34: $^1$H NMR Spectrum of 202 in CDCl$_3$ at 600 MHz
Figure 35: $^{13}$C NMR Spectrum of \textbf{202} in CDCl$_3$ at 150 MHz
Figure 36: $^1$H NMR Spectrum of 205 in CDCl$_3$ at 600 MHz
Figure 37: $^1$H NMR Spectrum of 204 in CDCl$_3$ at 600 MHz
Figure 38: $^{13}$C NMR Spectrum of $^{204}$ in CDCl$_3$ at 150 MHz
Figure 39: $^1$H NMR Spectrum of 209 in CDCl$_3$ at 400 MHz
Figure 40: $^1$H NMR Spectrum of 206 in CDCl$_3$ at 400 MHz
Figure 41: $^{13}$C NMR Spectrum of 206 in CDCl$_3$ at 100 MHz
Figure 42: $^1$H NMR Spectrum of 210 in CDCl$_3$ at 400 MHz
Figure 43: \(^1\)H NMR Spectrum of 207 in CDCl\(_3\) at 400 MHz
Figure 44: $^{13}$C NMR Spectrum of 207 in CDCl$_3$ at 100 MHz
Figure 45: $^1$H NMR Spectrum of 211 in CDCl$_3$ at 400 MHz
Figure 46: $^1$H NMR Spectrum of 213 in CDCl$_3$ at 400 MHz
Figure 47: $^1$H NMR Spectrum of 214 in CDCl$_3$ at 400 MHz
Figure 48: $^{13}$C NMR Spectrum of 214 in CDCl$_3$ at 100 MHz
Figure 49: $^1$H NMR Spectrum of 216-rac in CDCl$_3$ at 400 MHz
Figure 50: $^{13}$C NMR Spectrum of 216-rac in CDCl$_3$ at 100 MHz
Figure 51: $^1$H NMR Spectrum of 228 in CDCl$_3$ at 400 MHz
Figure 52: $^1$H NMR Spectrum of 229 in CDCl$_3$ at 400 MHz
Figure 53: $^{13}$C NMR Spectrum of 229 in CDCl$_3$ at 100 MHz
Figure 54: $^1$H NMR Spectrum of 230-epi in CDCl$_3$ at 400 MHz
Figure 55: $^1$H NMR Spectrum of 231 in CDCl$_3$ at 600 MHz
Figure 56: $^{13}$C NMR Spectrum of 231 in CDCl$_3$ at 100 MHz
Appendix C - References

1 Förster, T.; Phys. Chem. 1939, 43, 58.


EDUCATION AND ACADEMIC ACHIEVEMENTS

M. Sc. Organic Chemistry  
Western University, Ontario  
May 2014 – Present

B. Sc. (Honours Specialization) Chemistry  
Western University, Ontario  
September 2010 – April 2014

Awards and Scholarships
- NSERC CGSD Award, September 2016 – September 2019 (declined);
- NSERC PGSD Award, September 2016 – September 2019;
- Ontario Graduate Scholarship, May 2015 – May 2016;
- NSERC CGSM Award, May 2014 – May 2015;
- Ontario Graduate Scholarship, May 2014 – May 2015 (declined);
- Academic Gold Medal – awarded to the student with the highest graduating average, June 2014;
- Dean's Honour List, Western University, 2011-2014;
- NSERC USRA, Summer 2013;
- 1st prize in Western University’s annual Analytical Poster Presentation Day, 2013;
- Western University Entrance Scholarship, 2010.

Publications

Poster presentations

Additional Languages
Intermediate German

ACADEMIC AND RESEARCH EXPERIENCE

Masters in Organic Chemistry  
Department of Chemistry, Western University, London, Ontario  
May 2014 – Present

Supervisor: Dr. Michael A Kerr
Research focus: The total synthesis of callosine
• Responsible for all aspects of maintaining a functional organic chemistry laboratory
• Consistently train and advise new students coming into the Kerr group
• Head graduate teaching assistant for a third year organic class

**Undergraduate Honours Thesis Research Project**  September 2013 – Present
Department of Chemistry, Western University, London, Ontario
Supervisor: Dr. Michael A Kerr
Research focus: Total alkaloid syntheses from a common intermediate
  • Became familiar with finding and referencing scientific literature

**NSERC USRA**  May – August 2013
Department of Chemistry, Western University, London, Ontario
Supervisors: Dr. Michael A Kerr, Dr. Paul J Ragogna
Research focus: Developing an inexpensive high-yielding Conia-ene catalyst
  • Gained experience with air-sensitive chemistry using a glove-box and Schlenk line
  • Furthered my knowledge of organic and inorganic synthesis

**Volunteer Research Assistant**  February – April 2013
Department of Chemistry, Western University, London, Ontario
Supervisor: Dr. Michael A Kerr
Research focus: Advancing the reactivity of dimethylcyclopropane-1,1-dicarboxylates via cross metathesis
  • Was exposed to manuscript submission and scientific writing
  • Became familiar with aspects of methodology such as optimization and reaction scope

**Summer Research Assistant**  May – August 2012
Department of Chemistry, University of Windsor, Windsor, Ontario
Supervisor: Dr. Stephen J. Loeb
Research focus: Scaled up synthesis of organic rotaxane ligands.
  • Worked under a post-doctorate applicant to prepare interlocked molecules to be used in Metal Organic Rotaxane Frameworks (MORFs)
  • Learned how to accurately follow previously documented procedures

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**WORK EXPERIENCE**

**Canadian Census Enumerator**  May – August 2011
Statistics Canada, Windsor, Ontario
  • Met census quotas in assigned areas
  • Was selected based on efficiency to help meet tolerance levels in Northern Alberta

**Kitchen Operations Staff**  November 2007 – September 2009
Seasons Bistro restaurant, LaSalle, Ontario
  • Responsible for maintaining kitchen sanitation

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**VOLUNTEER EXPERIENCE**

**President of the Western Chemistry Club**  September 2013 – May 2014
Western University, London, Ontario
Supervisor: Professor Kay Calvin
• Managed a team of 18 executives
• Held executive and club meetings
• Intrigued over 140 active chemistry club members to participate in meetings and events

**VP Outreach of the Western Chemistry Club**

September 2012 – April 2013

Western University, London, Ontario

Supervisor: Professor Kay Calvin

• Organized the Chemistry Club’s display during National Chemistry Week at White Oaks Mall
• Helped organize Fall Preview Day and March Break Open House for the chemistry department
• Taught first year chemistry material in tutorial sessions held by the Chemistry Club