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Exploring The Reactivity Of Donor-Acceptor Cyclopropanes And The Synthesis Of (+/-)-Quebrachamine

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Graduate Program in Chemistry

A thesis submitted in partial fulfillment of the requirements for the degree in Doctor of Philosophy

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Exploring The Reactivity Of Donor-Acceptor Cyclopropanes And The Synthesis Of (±)-Quebrachamine

(Thesis format: Monograph)

by

Huck Grover

Graduate Program in Chemistry

A thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy

The School of Graduate and Postdoctoral Studies
The University of Western Ontario
London, Ontario, Canada

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Abstract

The development and utility of cyclopropanes is an ever-growing field within organic chemistry. In particular, donor-acceptor cyclopropanes have been used in a vast array of methods to access a variety of different hetero and carbocyclic molecular scaffolds. Recently, we have developed a Zn(NTf₂)₂ catalyzed tandem reaction consisting of a nucleophilic ring-opening of 1,1-cyclopropanediesters by 2-alkynyl indoles followed by a Conia-ene ring closure, resulting in the efficient one-step synthesis of tetrahydrocarbazoles. These adducts may be further elaborated to carbazoles. The scope and limitations of this method were determined along with a mechanistic study into the function of the zinc catalyst.

In an expansion of our work with 1,1-cyclopropanediesters, we have explored the reactivity and utilization of hemimalonate cyclopropanes. To this end, we have developed two unique methods exploring the self-activating nature of these cyclopropanes under catalyst free conditions. Cyclopropane hemimalonates, when treated with sodium azide, undergo a tandem ring-opening decarboxylation to produce γ-azidobutyric acids in good yields. These adducts were hydrogenated to form γ-aminobutyric acid (GABA) methyl esters. Additionally, cyclopropane hemimalonates have led to the facile synthesis of γ-substituted butanolides. Under microwave irradiation, cyclopropane hemimalonates undergo rapid conversion to butanolides in the presence of inorganic salts with an unprecedented retention of stereochemistry. This unique process, in conjunction with a newly developed cross-metathesis method, has been applied to the total synthesis of the naturally occurring, (R)-dodecan-4-olide.

Finally, recent efforts to develop a unified approach to piperidine-containing indole natural products have shown great promise. A preliminary investigation into the prospect of a common synthetic intermediate for the synthesis of a variety of indole alkaloids has led to a synthesis of substituted piperidinones and the corresponding piperidines. These common natural product cores are accessed via a reductive amination/lactamization sequence of dimethyl 3-ethyl-3-formylpimelate. The synthetic utility of this initial study has been displayed in the formal synthesis of (±)-quebrachamine.
Keywords

Co-Authorship Statement

Chapter 1 – The project presented in this chapter was co-authored in collaboration with Dr. Terry Lebold. Dr. Lebold was responsible for the majority of the optimization as well as a few substrate scope examples.

Chapter 2 – The projects presented in this chapter were co-authored in collaboration with Dr. Michael Emmett (hemimalonate cyclopropane work) and Matthew Vriesen (cross-metathesis work). In section 2.4.1, Dr. Emmett was responsible for the majority of the optimization and selected substrate scope examples (as indicated within the chapter) in the synthesis of γ-azidobutyric acids. In section 2.4.2, Dr. Emmett was responsible for selected substrate scope examples (electron withdrawing aromatics) in the synthesis of γ-Substituted Butanolides. In section 2.4.6, an equal division of work was completed by me and Mr. Vriesen.
Acknowledgments

My time at Western has gone by so fast; it’s hard to believe it has already been five years. While here, I have had the opportunity to meet new people, make many new friends, develop new skill sets as a synthetic chemist, and share my research findings at both national and international conferences. None of this would have been possible without the guidance and support of my supervisor, Dr. Michael Kerr. I would like to thank Dr. Kerr for being an amazing inspiration to me, for pushing me to achieve my best, and for guiding me to ensure that I do so. All of my successes and accomplishments in this field so far, and all the accomplishments I will achieve in the future are owed to his significant contribution in my life as a chemist, mentor, and friend.

Next, I would like to thank all the Kerr group members, both past and present, for all of their help over the last five years. I am very thankful to both Terry Lebold and Mike Johansen for their invaluable guidance and advice that set me on the correct path when I started graduate studies. Additionally, I would never have been able to make it through the long journey of grad school without the help of my more recent lab mates: Mike Emmett, Poly Kyriacou, Byran Landschoot, and Matt Vriesen, who not only assisted me countless times in the lab but have made my overall experience at Western enjoyable and have become lifelong friends. In particular, I have to thank Mike Emmett whose passion for chemistry has driven both our successes and provided me with a daily source of inspiration. To the newer lab members: Erin Armstrong, Joanne Curiel-Tejeda and Matt Vriesen, I am thankful for your friendship and support and can move on from the group knowing that your efforts and ambition will certainly help propel the group’s research in promising directions.

Of course I have to thank the Pagenkopf group (past and present), whose significant input during group meeting and general chemistry discussions have helped me in many areas of my research. I also owe a great deal of thanks to Dr. Brian Pagenkopf, who has been a great supporter and friend, and was always available to help me with both chemistry and non-chemistry related questions and has undoubtedly enriched my time here.

I would also like to take this opportunity to thank some other people at Western who have helped me in completing this thesis. The support staff at Western including Dr. Mathew Willans
(NMR), Doug Hairsine (mass spectrometry), Darlene McDonald (graduate secretary), and Marylou Hart and Sherry McPhee (ChemBiostores), have been excellent assets throughout my time at Western and I certainly would not be where I am today without their help and assistance.

Additionally, I would like to acknowledge my family as without their continual support and love, I would have never achieved the multitude of successes I have achieved today. Both of my parents have been instrumental in every step of my education. They have bestowed me with the courage and confidence to attain my dreams and the will to never give up, regardless of the obstacles. I am extremely grateful to my brother, his family (including little Everett), my aunts, uncles, cousins and grandparents who I’m sure didn’t understand anything I was doing but were always excited to hear about my recent research exploits and continued to give me support under any circumstance. Most importantly, I would like to thank my loving and understanding wife, Melissa. She has always been there for me, to help me with assignments, to listen to me rant about chemistry, and help me in all aspects of my life. There is not much I can say other than that I could not imagine having completed this chapter of my life without her by my side.

Finally, I would like to thank my grandmother and dedicate this collective work to her as she has always motivated me to achieve more than I thought was possible. I would like to thank her for her love and support and for being such a strong role model in my life. In conclusion, it is clear that there have been many wonderful and talented individuals who have helped me reach this point and I can only hope that one day I will be in such a position to aid others in achieving their academic goals as well.
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<td>Å</td>
<td>Angstrom</td>
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<td>A</td>
<td>Acceptor Group</td>
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<td>Ac</td>
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<td>Boc</td>
<td>tert-butoxycarbonyl</td>
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<td>Broad</td>
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<td>cm</td>
<td>Centimeter</td>
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<td>FT</td>
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<td>g</td>
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<td>Term</td>
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<tr>
<td>GABA</td>
<td>Gamma-aminobutyric acid</td>
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<td>succ</td>
<td>Succinimide</td>
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<td>Abbreviation</td>
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Chapter 1: Synthesis of Tetrahydrocarbazoles from Donor-Acceptor Cyclopropanes

1 Kerr Group Introduction and Thesis Overview

Organic chemistry is a wide and ever-growing field that is comprised of several different areas. Within the Kerr group, research is focused on two specific areas: the total synthesis of complex natural products and the development of new synthetic methods. Natural products are the driving force for many different aspects of organic synthesis as these molecules and their derivatives are the base components in a variety of industrial, pharmaceutical, and biologically active compounds. Due to the importance of these target molecules much research has been devoted to the development of synthetic routes that would allow access to natural products and their derivatives in order to study their unique properties. Developing routes to these molecules gives chemists the opportunity to discover new and innovative techniques and synthetic methods. One of the largest contributions the Kerr group has made in this area is through the ongoing research toward the reactivity of donor-acceptor cyclopropanes. To this end, chapter 1 and the beginning of chapter 2 of this thesis will focus on the development of donor-acceptor cyclopropane chemistry. This will be followed up in the end of chapter 2 and chapter 3 by the efforts toward total synthesis of dodecanolide, a butanolide natural product and the indole alkaloids aspidospermidine and quebrachamine.

1.1 Donor-Acceptor (DA) Cyclopropanes

The toolbox of the synthetic organic chemist benefits greatly from the development of new reactive molecular entities for the construction of complex architectures. In this light, donor-acceptor cyclopropanes have emerged to have a prominent role. The reactivity of these compounds and their use in the total synthesis of natural and unnatural targets continue to be extensively studied and have resulted in numerous reviews.1 Useful reactions of these molecules I include both nucleophilic ring-opening as well as cycloaddition (or annulation) processes to yield III or V respectively (Figure 1-1). Both types of transformations require an acceptor moiety and a donor moiety vicinally.
disposed. The “donor” group can be any functional group capable of stabilizing a developing positive charge in the transition states (II or IV) in the ring opening event.

Figure 1-1: The Reactivity of DA Cyclopropanes

The vast majority of this latter class of reactions (annulations) involves the formation of heterocycles. This development is not surprising since the initial ring opening event may be more facile with heteroatom based nucleophilic entities. Such reactive partners are often dipolar in nature. In some cases however, the reaction may involve a partner that is all-carbon resulting in a carbocycle. This area of research is currently expanding and many elegant methods utilizing Lewis acid, protic acid, base, or thermal activation (among others) have been developed.

1.2 Carbocycles from [3+2] Annulations of DA Cyclopropanes

The cyclopentane and cyclopentene moieties are common to a wide variety of terpene and alkaloid natural products (Figure 1-2A).² Due to the prevalence and importance of these carbocyclic structures, many strategies have been developed for their construction.³ For over 50 years, DA cyclopropanes have been synthetically useful 1-3 carbon dipolarophile starting materials for the synthesis of highly substituted 5-membered carbocycles via annulation reactions with alkenes, alkynes, and allenes (Figure 1-2B). Although much of the seminal research in this area has been developed with the previously mentioned dipoles, herein, we discuss the most recent syntheses of
cyclopentane and cyclopentene compounds via the annulation of enol ethers and enamines with DA cyclopropanes.

Figure 1-2: Cyclopentane and Cylopentene Containing Target Molecules

1.2.1 Reactions with Enol Ethers

Over the last 25 years, there has been significant interest in the use of enol ethers and ketene acetals as dipoles for the annulation reaction with cyclopropanes. Studies have revealed successful reactivity with a large array of different DA cyclopropanes, and both diastereoselective and enantioselective methods have been developed. One of the first reports in this field was presented in 1990, showcasing the use of 2,2-dialkoxy cyclopropanes 1-2 with a series of silyl ketene acetals to access the desired cyclopentenone 1-3 or 1-4 depending on the cyclopropane used (Scheme 1-1). While TiCl₄ mediated conditions allowed for practical conversion to the desired products, the reaction conditions proved to be non-selective, typically leading to a mixture of four diastereomers. In some cases, when excess ketene acetal was used, addition product 1-5 was also observed in small quantities.
Scheme 1-1: Preliminary Investigations into the Reaction of DA Cyclopropanes and Silyl Enol Ethers

Shortly after this seminal work, Kuwajima and co-workers published two papers on the exploration of the use of alkoxy and phenylsulfide activated cyclopropanes as reaction partners with silyl enol ethers (Scheme 1-2A/B). In the case of alkoxy-cyclopropane esters 1-6, product formation (1-9) could be attained in good overall yields as a mixture of stereoisomers with stoichiometric amounts of SnCl₄ (Scheme 1-2A).⁵ These conditions were accepting of a wide range of silyl enol ethers including disubstituted and cyclic examples (from cyclohexanone etc.); however, trisubstituted enol ethers proved unreactive. In the same report, it was determined that alkoxy-cyclopropane ketones 1-7 were too reactive for the use of stoichiometric amounts of SnCl₄ leading to dimerization of the starting material. To overcome this issue, catalytic amounts of the Lewis acid were used allowing for low to moderate product conversion with silyl enol ethers. While this report did show the first Lewis acid catalysed addition of enol ethers and DA cyclopropanes, the selectivity of the reaction was poor leading to complex mixtures of stereoisomers.
Scheme 1-2: Reactions of Alkoxy- and Phenylsulfide-substituted Cyclopropanes with Silyl Enol Ethers

Kuwajima next showed a diastereoselective process using 2-phenylthiocyclopropane 1-11 (Scheme 1-2B). It was determined that increasing the steric bulk of the silyl group (TIPS or TBDPS) led to diastereoselective product formation (1-13) up to 99:1. Additionally, the rate of starting material dimerization could be minimized using aluminum reagents instead of tin, leading to overall higher yields and larger substrate scopes than previously reported.

Scheme 1-3: Triflimide Catalysed Reactivity of Cyclopropylketones
In a similar manner to the work of Kuwajima, the Ihara group showed the triflic imide catalysed annulation of silyl enol ethers and p-methoxyphenyl (PMP) activated cyclopropanes 1-15 to access cyclopentanes 1-16 (Scheme 1-3).\(^7\) The conditions were favourable for cyclic silyl enol ethers (cyclohexanone derived) and diminished yields were seen for acetophenone derived enol ethers. These results paralleled those of Kuwajima’s first report, showing little to no diastereoselectivity under these reaction conditions. To showcase the diversity of their catalytic conditions, the group applied them to a multi-component sequential Diels-Alder/[3+2] annulation reaction to produce highly substituted 1-20 in a modest overall yield (Scheme 1-4).

Scheme 1-4: Multi-component Sequential Diels-Alder/[3+2] Annulation Reaction

In 1999, Sugita et al. highlighted the use of catalytic TMSOTf conditions in the synthesis of bridged[4.2.1]bicyclic products. This catalytic method allowed a range of silyl enol ethers to react with fused cyclopropane 1-22 to give low to serviceable isolated yields of the desired product 1-23 with usable cis/trans ratios up to 18:1 (Scheme 1-5).\(^8\) The report gave a small substrate scope indicating that substitution on the cyclopropane greatly decreased the yield of the desired product and increased yields of the ring-opened product.

Scheme 1-5: TMSOTf Catalysed Reaction of 1-21 and 1-22

Near the end of 2008, investigations by Wang\(^9\) showed the annulation of 1,1-cyclopropanediesters 1-25 with silyl enol ethers to be rather difficult, as the cyclic
products 1-26 readily underwent retro-aldol reactions to produce high yields of the acyclic product 1-27 under Lewis acid conditions (Scheme 1-6). Under optimal conditions, only a few cyclic products could be isolated and in very low yields.

The Tang group began investigations on the reactivity of 1,1-cyclopropanediesters in the hopes of developing a highly enantioselective process for the [3+2] annulation reaction with silyl enol ethers. Their initial exploration into this field required finding ideal conditions for the suppression of acyclic by-product 1-27 (Scheme 1-6). It was quickly discovered that the acyclic by-product of the annulation process could be minimized by modifying two simple aspects of the reaction: 1) by changing the Lewis acid, and 2) by increasing the steric bulk of the silyl group. Making both of these modifications showed a significant increase in yield and the selectivity now favoured the desired cyclopentane ring over the acyclic product. Finally, they discovered that if both changes were made along with the addition of a bulky bisoxazoline dimer ligand (A), not only was the acyclic product suppressed completely but the desired products 1-30 were isolated with good to excellent diastereomeric ratios (Scheme 1-7). The reaction conditions were compatible with a variety of aromatic substituted cyclopropanes with lower yields observed for the less stable vinyl and heteroaromatic substituted cyclopropanes. The silyl enol ether could also be changed; however, when cyclic examples were employed (cyclohexanone derived), a decrease in yield and loss of diastereoselectivity was observed.
Scheme 1-7: Tang’s Work Toward the Enantioselective Reaction of Cyclopropanes and Silyl Enol Ethers

In hopes of overcoming this selectivity problem and gaining access to fused bicyclic cyclopentane derivatives, the Tang group needed to develop a new set of reaction conditions.\textsuperscript{11} Once again, they exploited the idea of steric bulk. By surveying an assortment of different ester-substituted cyclopropanes, they found that when sterically bulky 2-adamantyl diester cyclopropanes 1-28 were employed with silyl enol ethers containing large silyl groups (TDBPS), smooth annulation occurred with excellent diastereoselectivity (Scheme 1-7). Again, by utilizing a bisoxazoline ligand (B), the bicyclic products 1-31 could be isolated in high yields and near perfect diastereoselectivity. The conditions were tolerant of a range of aromatic cyclopropanes with lower yields again being observed for the less stable vinyl and heteroaromatic substituted cyclopropanes. A variety of different ring sized silyl enol ethers could also be used with the trend that the smaller ring sizes gave higher product yields.
The most recent stage of Tang’s research focused on enantioselective conditions for the synthesis of cyclopentanes from cyclopropanes and silyl enol ethers. In 2013, such enantioselective conditions for the dynamic kinetic asymmetric transformation (DYKAT) were discovered (Scheme 1-7). The conditions worked well for highly activated electron rich aromatic cyclopropanes (almost exclusively) allowing access to cyclopentanes 1-32 in good to excellent yields with moderate to excellent diastereoselectivity and overall excellent enantiomeric excess. Again, a similar trend was shown for the cyclic silyl enol ethers, where the smaller ring sizes gave overall higher yields and greater diastereoselectivity. Additionally, the conditions that were developed worked for less electron rich aromatic cyclopropanes (1-34); however, they proceeded in a kinetic resolution fashion and typically required increased reaction times (Scheme 1-8). Further exploration into this process is currently underway.

Scheme 1-8: Kinetic Resolution of Less Activated DA Cyclopropanes with Silyl Enol Ethers (for ligand C see Scheme 1-7)

Recently, Waser became engaged in investigating the reactivity of amino activated cyclopropanediesters toward the same [3+2] reaction process with enol ethers. In 2011, the first of two papers in this area were published showing the first catalytic [3+2] annulation of aminocyclopropanes (Scheme 1-9). The appropriate phthalimidecyclopropane 1-37 was discovered to be the ideal cyclopropane starting material for this transformation. Unlike previous reports by Kuwajima and Ihara, it was found that the mono-carbonyl cyclopropanes were unreactive to a variety of reaction conditions. Initial Lewis acid screening proved very important to find a suitable catalyst that would minimize the formation of any unwanted acyclic products. SnCl₄ was selected as the best catalyst allowing for great conversion to the corresponding cyclopentanes 1-38 in excellent yields with modest to great diastereoselectivity up to 20:1. The reaction conditions were tolerant of many different substituted silyl enol and alkyl enol ethers, and
in contrast to Tang’s work, the size of the silyl group had little to no effect on the selectivity of the reaction. Although a large substrate scope was evaluated, a few examples resulted in diminished yields and selectivities, including trisubstituted, aliphatic substituted, and cyclic silyl enol ethers, as well as 3,4-dihydropyran enol ethers. It was also shown that when optically enriched phthalimidecyclopropane \(1-37\) was subjected to the reaction conditions with a series of silyl enol ethers, little to no erosion of enantiomeric purity was observed.

![Scheme 1-9: Diastereoselective Annulation of Enol Ethers and Aminocyclopropanes](image)

Waser next explored a DYKAT method for the synthesis of amino-substituted cyclopentanes. The result of this exploration was realized in early 2014 by utilizing a succinimidocyclopropane \(1-40\), a bulky bisoxazoline ligand (\(D\)), and by replacing the silyl group on the enol ether with an alkyl group (Scheme 1-10).\(^{14}\) Parallel to Tang’s result, the overall \([3+2]\) annulation worked well with a variety of different enol ethers, giving high yields, moderate to excellent diastereomeric ratios, and excellent enantiomeric excess in most cases. The reaction could be performed on gram scale without significant loss of yield or stereocontrol. Further experiments are underway to establish the origin of asymmetric induction.
Scheme 1-10: DYKAT Reaction of Aminoactivated Cyclopropanes and Enol Ethers

Finally, 2,5-dimethylfuran had also been shown to be a suitable dipole for the [3+2] annulation of cyclopropanes, although only a limited substrate scope had been displayed (Scheme 1-11A). In fact, only 2-thienyl and phenyl substituted cyclopropanes 1-42 underwent cyclization with furan 1-43 to give the desired cycloadduct 1-44 under Yb(OTf)₃ or SnCl₄ conditions, respectively. Additionally, it was shown that when thienyl cyclopropane 1-45 was subjected to SnCl₄ conditions, the desired cycloadduct underwent a subsequent electrophilic aromatic substitution reaction with the dihydrofuran ring to give 1-46 (Scheme 1-11B).
1.2.2 Reactions with Enamines

Since the historical discovery of the thermal enamine annulation with cyclopropanes reported by Dolfini (Scheme 1-12), this field of research has been dominated by one type of enamine: the highly reactive indole.

![Scheme 1-12: Seminal Reaction of Enamines with Cyclopropanes](image)

During the development of a follow up project on the alkylation of indoles with α,β-unsaturated ketones, Kerr and co-workers explored the use of DA cyclopropanes as a homologous evolution of this work. Their preliminary results showed that when using catalytic Yb(OTf)3 under high pressure conditions, indole 1-50 could open cyclopropane 1-51 (Scheme 1-13A), however, a trace amount of the 1-53 was formed as well, presumably through nucleophilic ring-opening followed by Mannich type trapping by the corresponding malonic enolate (Scheme 1-13B).

![Scheme 1-13: Preliminary Investigation into the Annulation of Indoles with Cyclopropanes](image)

Encouraged by the formation of 1-53, the Kerr group next set out to optimize this [3+2] annihilation process. It was discovered that placing a substituent on the three position of
the indole allowed for direct conversion to the annulated 1-57 product using both thermal and hyperbaric conditions (Scheme 1-14A). Although the reaction proceeded well with 2- and 3-substituted indoles and various substituted cyclopropanes to access the cyclic 1-57 as the major product, when high temperature conditions were utilized, the formation of migration product 1-60 became a competing and sometimes major product (Scheme 1-14B). It was later determined that when cyclic product 1-57 was heated under Lewis acid conditions, conversion to 1-60 was observed providing evidence for the reversibility of this process. 

![Scheme 1-14: Annulation of DA Cyclopropanes with 3-substituted Indoles](image)

When less activated cyclopropanes were used (R⁴ = Me or H), hyperbaric conditions resulted in the highest yields. When more activated cyclopropanes were used (R⁴ = phenyl, vinyl, or styrenyl), ambient pressure conditions resulted in higher yields. To display the utility of this transformation, the key tetracyclic subunit of the kopsane alkaloid 1-64 was synthesized by the reaction of cyclopropane 1-62 with tetrahydrocarbazole 1-61 (Scheme 1-15).
Scheme 1-15: Synthesis of Kopsane’s Core

The groups of Ila and Pagenkopf then showed expansions of this chemistry with different DA cyclopropanes. In 2006, Ila showed that trans cyclopropylketones 1-66 could undergo annulations with indoles to give high diastereoselective products 1-67 under BF$_3$•Et$_2$O mediated conditions (Scheme 1-16).$^{21}$ Electron rich aromatic substituents on the cyclopropane led to isolated products as a single diastereomer, while electron neutral (Ar = phenyl) cyclopropanes led to diastereomeric mixtures, similar to the results seen by Kerr. When highly activated (Ar = 3,4-dimethoxyphenyl) cyclopropanes were used, modified TiCl$_4$ conditions were required. To expand the scope of their study, the reaction conditions were applied to the 1,1-cyclopropanediester starting material and similar results to those of Kerr were observed. It is noteworthy that under these reaction conditions, little to no migration product was observed as in the case with Yb(OTf)$_3$. This result can presumably be attributed to the low reaction temperatures employed.
Scheme 1-16: Reactivity of Cyclopropylketones with Indoles

In 2007, Pagenkopf showed that alkoxy-activated cyclopropanes could undergo annihilation reactions with indoles in the presence of TMSOTf. In contrast to previous reports, the annihilation of cyclopropanes 1-69 was achieved in high yields using 2,3-unsubstituted and 2-substituted indoles 1-68 (Scheme 1-17); in fact, when 3-substituted indoles were employed under these reaction conditions, only the migration and elimination products were observed. The reaction conditions were suitable for a series of alkoxy-activated cyclopropanes with highest diastereoselectivities (single diastereomer) coming from conformationally restricted cyclopropanes (e.g. 1-70a). In general, the unfused cyclopropanes resulted in the lowest yields (e.g. 1-70c) while the fused cyclopropanes gave good to excellent yields of the product. Additionally, the reaction conditions were tolerant of many different substituents on the benzenoid ring of the indole.
Scheme 1-17: Reactivity of Alkoxycyclopropanes with Indoles

The next progression in this vein was the development of asymmetric reaction conditions for the synthesis of enantioenriched cyclopentan[b]indoles. While continuing their work on dynamic kinetic asymmetric transformation reactions of DA cyclopropanes, Johnson reported the first asymmetric synthesis of indole homo-Michael adducts via cyclopropanes. This DYKAT method using pybox ligand (E) and catalytic MgI₂ was very efficient for the alkylation of indoles with cyclopropanes (er up to 97:3). While not the focus of this work, Johnson did show that this process could be applied to the annulation process when 3-methyl indole was employed (Scheme 1-18).

Scheme 1-18: Preliminary Results for the Asymmetric Reaction of Indoles and Cyclopropanes
In 2013, the Tang group was able to develop a highly enantioselective cyclopentannulation reaction of indoles and DA cyclopropanes (Scheme 1-19).\textsuperscript{25} Much like their work with enol ethers, this process worked well with activated (p-methoxyphenyl) cyclopropanes 1-75 in almost all cases giving good diastereoselectivity and high enantioselectivity of 1-76. Lower yields and selectivities were observed when less activated cyclopropanes were utilized (e.g. 2-furyl, vinyl, p-iodophenyl). To showcase this method, Tang devised a short synthesis to the core of Borreverine, in very high yield and as a single diastereomer.

Scheme 1-19: Synthesis of 1-76 via a DYKAT Reaction of Cyclopropanes and Indoles

In a recent expansion of this work, Tang has developed a highly switchable diastereoselective intramolecular [3+2] annulation of cyclopropanes and indoles.\textsuperscript{26} Extensive optimization led to the use of diimine ligand (G) and catalytic copper, which provided modest diastereoselectivity of the products 1-78 (83:17 dr). Upon further optimization, when the esters were changed from methyl to isopropyl, an increase in diastereoselectivity was observed (90:10). Additionally, when larger adamantyl groups were used, the selectivity reversed to the other diastereomer 1-79. Both esters were tested.
with a variety of benzenoid substitutions, leading to high yields and excellent selectivities of both isomers of the unique pentacyclic structure (Scheme 1-20).

Scheme 1-20: Diastereoselective Intramolecular Annulations of Indole

1.3 Carbocycles from [3+3] Annulations of DA Cyclopropanes

Much like their five membered counterparts, the cyclohexane ring is an important structural moiety in natural products. Its structure is ubiquitous in a variety of naturally, pharmaceutically, and historically relevant molecules (Figure 1-3) and thus synthetic methods devoted to the synthesis of cyclohexanes are of high interest and value. In contrast to cyclopentanes, less research has been devoted to the [3+3] annulation of cyclopropanes to access cyclohexanes.
Yadav reported the addition of two equivalents of alkynes with cyclopropane 1-84 to access spirocyclic compounds 1-90 (Scheme 1-21).\textsuperscript{28} Ring-opening of cyclopropane 1-84 with SnCl\textsubscript{4} led to silicon stabilized cation 1-85 which could react with an alkyne to give arylvinyl cation 1-87 followed by trapping with the newly formed olefin. Styrenyl cation 1-88 could then be attacked by another equivalent of alkyne to give arylvinyl cation 1-89, which in turn could then be trapped by the aromatic ring (from the cyclopropane) to give the observed product.

Scheme 1-21: Mechanism for the Formation of Spirocycle 1-90
The conditions worked well for electron neutral aromatic cyclopropanes reacting with a series of electron neutral alkynes giving diastereomerically pure products 1-90 in reasonable yields (Scheme 1-22A). The stability of the vinyl cation intermediates was presumably the reason electron poor alkynes were ineffective. When TMS phenyl alkyne 1-91 was used under the standard reaction conditions, cyclohexadiene 1-92 was formed in a modest yield (Scheme 1-22B). It is proposed that 1-92 was formed through the elimination of a 1-88 type intermediate followed by a subsequent reaction with another equivalent of alkyne.

Scheme 1-22: Reactivity of Cyclopropane 1-84

In 2009, Kerr and co-workers reported the reaction of 1,1-cyclopropanediesters 1-94 with 2-(chloromethyl)-3-trimethylsilyl-1-propene 1-93 as a trimethylenemethane (TMM)29 equivalent in the synthesis of exo-methylene cyclohexanes 1-95 (Scheme 1-23).30 After various attempts to promote this reaction via one-step palladium catalysis had proven unsuccessful, a sequential two-step Lewis acid mediated ring-opening followed by a base mediated ring closure was invoked to access the cyclohexane 1-95.
Scheme 1-23: Reactions with 2-(chloromethyl)-3-trimethylsilyl-1-propane (1-93)

Ring-opening worked in modest yields with a variety of aromatic and vinyl cyclopropanes, while ring closure worked in excellent yields for almost all substrates. Lower yields were seen for the ring-opening of 2-thienyl cyclopropane presumably due to the stability of the cyclopropane under TiCl₄ conditions. Alkyl substituted cyclopropanes did not undergo ring-opening/allylation due to the lack of stability of the putative ring-opened intermediate. In the same paper, the utility of this reaction was displayed in the rapid synthesis of tronocarpine’s core 1-98 (Scheme 1-24).

Scheme 1-24: Synthesis of Tronocarpine’s Core
Recently, a highly diastereoselective tandem ring-opening/Michael addition has been reported by Ghorai.\textsuperscript{32} Reaction of indole 1-100 with 1,1-cyclopropanediester 1-101 under Yb(OTf)\textsubscript{3} catalysis yielded the corresponding tetrahydrocarbazole 1-102 in average to excellent yields with good diastereoselectivity (in most cases as a single diastereomer) (Scheme 1-25). It was proposed that the selectivity was achieved after ring-opening in which the Michael acceptor favoured the pseudoaxial half-chair conformation leading to the \textit{cis} isomer. Overall, the reaction conditions were efficient for a variety of aromatic cyclopropanes with lower yields and selectivity when styrenyl substituted cyclopropanes were used. In general, the malonate acceptor groups gave higher yields than the corresponding nitro acceptors.

![Scheme 1-25: Highly Diastereoselective Tandem Ring-opening/Michael additions](image)

1.4 Indoles and Carbazoles

It is unarguable that indoles rank among the most important heterocyclic compounds. They remain prime scaffolds for pharmaceutical drug discovery and their prominence in natural products is prodigious; as such, there continues to be a large degree of activity devoted to the efficient chemical elaboration of the benzopyrrole ring system.\textsuperscript{33} A subset of the indoles are the carbazoles and their hydro-derivatives. The preparations of these

![Selected Examples](image)
structures has seen significant interest among the chemical community due in part to the
carbazoles and the presence of their hydro-derivatives in naturally occurring and
bioactive compounds.\textsuperscript{34} Of additional interest, the carbazole structure has been shown to
exhibit material properties as optoelectronic materials,\textsuperscript{35} conducting polymers,\textsuperscript{36} and
synthetic dyes.\textsuperscript{37} Figure 1-4, for example, shows a sampling of carbazole natural products
isolated in recent years.\textsuperscript{38}

![Image of carbazole natural products]

**Figure 1-4: Representative Carbazole Natural Products**

1.4.1 Selected Recent Syntheses of Carbazoles

In 2013 Samanta and co-workers showed the facile synthesis of substituted carbazoles
through a one pot Henry reaction/aerial oxidation (Scheme 1-26).\textsuperscript{39} Michael acceptor
1-103 underwent smooth conversion to carbazole 1-104 in the presence of nitromethane,
catalytic DBU, and air. The transformation was successful with a range of substituted
Michael acceptors resulting in good to excellent yields of the product, with the highest
yields observed when R=alkyl (e.g. 1-104c). From a synthetic standpoint, this method is
particularly interesting as it excludes the use of acids, toxic reagents, metals, or strong
oxidants.
In a similar search for mild conditions capable for the synthesis of carbazoles, Xu and Shi have shown the unique conversion of alkynylcyclopropane 1-105 to the corresponding carbazole 1-106 via mild gold catalysis in dichloromethane (Scheme 1-27). Nucleophilic addition of indole onto the activated alkyne could give spirocyclic intermediate 1-108 which could undergo a migration to give stabilized cation 1-109. Aromatization and protonation followed by elimination of H2O would lead to gold carbene intermediate 1-111. Intermediate 1-111 could then undergo cyclopropane ring expansion and subsequent elimination to produce carbazole 1-106. The reaction conditions were suitable for an array of alkyne substituted starting materials (including aromatic and alkyl) leading to the desired product in low to modest yields. Interestingly, when alcohol solvents were employed, cyclopropane ring-opening of intermediate 1-111 with the alcohol was observed leading to high yields of the corresponding ether substituted carbazole product.

Scheme 1-26: Synthesis of Carbazoles via a Henry/aerial Oxidation Process
Scheme 1-27: Carbazole Formation from Cyclopropane 1-105

With the ever growing development and interest in C-H activation methods, Hirano and Miura have displayed an intramolecular C-H/N-H coupling of substituted anilines (1-113) to produce carbazoles.\(^{41}\) This recently reported method allowed for efficient access to a variety of substituted carbazoles 1-114 in moderate to excellent isolated yields (Scheme 1-28). Overall, the reaction worked well for electron donating aromatic substituents (\(R^1\) and \(R^2 = \text{EDG}\)) while electron withdrawing substituents gave lower yields.

Scheme 1-28: Carbazoles from Cu-Catalyzed C-H Amination Reaction
While only a few synthetic methods were discussed within this section, the overwhelming development of new synthetic methods for the synthesis of carbazoles is a testament to the overall importance of these molecules.\textsuperscript{42}

1.5 The Conia-ene Reaction

Developed in the mid-1970s, the Conia-ene reaction is a powerful intramolecular carbon-carbon bond forming reaction between an enol and a tethered “ene” system. Early work in this area favored thermal conditions for the cyclization of unsaturated carbonyl compounds (Scheme 1-29).\textsuperscript{43} Although this seminal work provided a functional route to carbocycles, the method suffered from major limitations. The reaction conditions typically employed high temperatures, which severely limited the synthetic utility of the approach and also resulted in only low to modest yields of the product. Additionally, the transformation was biased toward the formation of smaller ring systems (five-membered rings being the most common) with larger ring systems being formed in only small amounts.

Since the initial discovery of this transformation, the literature has overflowed with new and improved reaction conditions for this cyclization.\textsuperscript{44} These new methods utilizing alkyne substituted carbonyl starting materials have allowed for lower temperatures to be used when transition metals are employed. Also these methods produce overall increases in yield, and allow for the formation of larger ring systems. Most recently asymmetric variations of this chemistry have been explored and have shown great promise.
1.5.1 Selected Recent Advances in Conia-ene Chemistry

Although there has been much effort toward finding the ideal catalyst system to promote the Conia-ene reaction, it was not until recently that boronic acid was found to be an efficient catalyst for this cyclization. Building from the seminal work of Dixon, Shibata and co-workers have shown the use of a new organocatalyst \textbf{1-119} in the cyclization of 1,3-dicarbonyl compounds (Scheme 1-30). In contrast to the more common transition metal mediated approach which activates the alkyne toward cyclization, it is proposed that the boronic acid catalyst has little effect on activation of the alkyne and is simply used to promote enolization. These results will undoubtedly promote subsequent research into the development of mild reaction conditions predominately focused on the activation of the carbonyl species rather than the activation of the alkyne.

![Scheme 1-30: Boronic Acid Catalyzed Conia-ene](image)

Recent advances in this area have reported the enantioselective Conia-ene reaction by the use of optically enriched ligands and pre-catalysts. Dixon has recently shown a cooperative catalyst system between a cinchona-derived amino-urea pre-catalyst (\textbf{1-123}) and copper salts which has led to very high yields and enantioselectivities of cyclized product \textbf{1-122} (up to 93% ee) (Scheme 1-31A). The use of these two catalysts together not only led to high yields, but they allowed for significantly decreased reaction temperatures for most all keto-ester explored substrates. Following Dixon’s report, the White group has displayed the enantioselective cyclization of keto-substituted starting...
materials 1-121 utilizing an iron-salen catalyst system (Scheme 1-31B). This method was effective for a variety of substituted keto-esters leading to excellent enantioselectivities. Interestingly, this method could be expanded to include different electron withdrawing groups, including R² = NO₂, PO(OMe)₂, Tosyl, and CN; however, reaction times were typically increased for the non keto-ester starting materials.

Scheme 1-31: Enantioselective Conia-ene Reactions

1.5.2 Tandem Reactions Involving the Conia-ene Cyclization

During the long sought-after search for optimal conditions to increase yields, minimize byproducts, decrease reaction times, and allow for asymmetric conversion of the Conia-ene cyclization, another promising area of research utilizing this powerful reaction began to appear: one-pot tandem reactions incorporating the Conia-ene cyclization. The first work reported to display a tandem reaction utilizing the Conia-ene cyclization was reported by Malacria in 1996 using the previously established cobalt mediated cyclization method. This seminal work displayed the cobalt catalyzed Conia-ene/[2+2+2]/[4+2] cascade of triyne 1-125 and bis(trimethylsilyl)acetylene (BTMSA) (Scheme 1-32). This unique reaction led to tetracyclic carbocycle 1-126 in a serviceable 42% yield. These remarkable initial results certainly would have left an impression on this research field, while at the same time opening the door for many others to utilize the facile Conia-ene cyclization in tandem fashion to access unique and complex scaffolding.
Not too long after Malacria’s preliminary report, Balme and co-workers described two different conditions for the synthesis of tetrahydrofurans via a tandem oxy-Michael addition/Conia-ene reaction (Scheme 1-33A).\textsuperscript{50} Initial results showed that catalytic butyl lithium and palladium could not only mediate the Michael addition between propargyl alcohol 1\textsuperscript{-127} and 1\textsuperscript{-128}, but also catalyzed the Conia-ene cyclization to give a range of substituted tetrahydrofurans (THF) in excellent yields. It was later determined that copper iodide could be used in place of palladium and the THF products could be isolated in an overall higher yield. In a follow up to this work, Balme was able expand this method to the synthesis of pyrrolidines, via the tandem reaction of propargyl amines and Michael acceptors (Scheme 1-33B).\textsuperscript{51} Interestingly, although the pyrrolidines could be isolated (intermediate 1\textsuperscript{-132}), they were subjected, in the same pot, to an additional palladium catalyzed phenol coupling reaction to give highly functionalized pyrrolidine 1\textsuperscript{-133}. This three-step one-pot process lead to modest overall yields of the product; however, in most cases the products were isolated as a mixture of double bond isomers (1\textsuperscript{-133} and 1\textsuperscript{-134}). The development of these unique tandem heteroatom-Michael addition/Conia-ene processes (synthesis of tetrahydrofurans and pyrrolidines) have since been improved to allow for single catalyst conditions, as well as diastereoselective product formation.\textsuperscript{52}
In the same theme of research, utilizing the Conia-ene transformation, Zhang disclosed the synthesis of polycyclic scaffold 1-136 via the one-pot tandem Navarov cyclization/Conia-ene reaction of alkyne 1-135 (Scheme 1-34A).\textsuperscript{53} In(OTf)\textsubscript{3} and DBU conditions provided rapid access to an array of polycyclic products in great yields; however, it was shown that electron withdrawing phenyl ketones did not undergo the transformation with much success. It is noteworthy that the Conia-ene reaction can be performed on disubstituted alkynes, a task not regularly observed with this type of reaction. Furthermore, Zhang has displayed the reliability of this reaction by applying it to the three step one-pot reaction of aldehyde 1-138 and 1,3-dicarbonyl 1-137 (Scheme 1-34B).
In a similar manner to the three step one-pot reaction of Zhang, Ramachary was able to show a one-pot sequential multicatalysis cascade condensation/reduction/Conia-ene method for the synthesis of indenes (Scheme 1-35). Initial proline catalyzed condensation followed by an in situ Hantzsch ester hydrogenation gave 1-142, which, in the same pot, could be cyclized providing 1-143 in the presence of catalytic copper. This method allowed quick access to indenes in excellent yields; however, due to the specificity of the starting material, only a small scope varying the EWG was presented.

Scheme 1-34: Tandem Nazarov/Conia-ene Reactions

Scheme 1-35: Ramachary's Tandem Conia-ene Reaction
With the ever-growing success in the field of tandem reactions involving the Conia-ene reaction, Lee next entered the field showcasing a Michael/Conia-ene cascade reaction in the synthesis of natural product targets.\(^5\) This new reaction was first displayed in the formal synthesis of (±)-Clavukerin A (1-146) starting from readily available alkyne 1-144 (Scheme 1-36A). Amine-induced Michael addition was readily achieved in the presence of diethylamine and the corresponding enol formed initiated the Conia-ene reaction in the presence of a zinc catalyst to give carbocycle 1-145. Lee was further able to display this method in the total synthesis of a more complex natural product (-)-teucvidin (1-149) (Scheme 1-36B).

\[
\text{Scheme 1-36: Tandem Michael Addition/Conia-ene Reactions in Total Synthesis}
\]

In 2011, extending their tandem reaction approach to total synthesis, Lee was also able to showcase the one-pot Prins/Conia-ene reaction in the synthesis of the core skeleton of Phomactin A.\(^5\) Indium mediated intermolecular reaction between aldehyde 1-151 and 1,3-ketoester 1-150 led to oxonium intermediate 1-152 that underwent a subsequent Prins type reaction. In the same pot, indium mediated the conversion to 1-153 via the Conia-ene cyclization (Scheme 1-37A). The reaction conditions were well accepted for different substitutions on the ketoester and chain lengths of the aldehyde, allowing for this process to be employed in target oriented synthesis (Scheme 1-37B).
Finally, one of the most recent explorations into this area of research was reported by Hatakeyama in 2014 who showed the multi-catalyst tandem O-H insertion/Conia-ene cyclization reaction to access formal [4+1] cycloadducts 1-161 (Scheme 1-38).57 This unique reaction showed the facile rhodium catalyzed insertion of diazomalonate 1-159 with homo-propargyl alcohols to give acyclic intermediate 1-160. Insertion product 1-160 then underwent a Conia-ene cyclization in the presence of catalytic ZnCl₂. Interestingly, tetrahydrofurans 1-161 could be accessed using only a rhodium catalyst; however, increased reaction times were required and significantly lower yields of the product were observed. These preliminary results will certainly have a profound effect on this area of research giving leeway to develop new and improved methods for tandem insertion/Conia-ene reactions with a variety of different tethered alkynyl starting materials.
1.5.3 Previous Tandem Cyclopropane Ring-Opening/Conia-ene Reactions Developed by the Kerr Group

With interest building in the area of tandem reactions involving the Conia-ene reaction, the Kerr group entered the field in hopes of utilizing the reactivity of donor-acceptor cyclopropanes in conjunction with the Conia-ene cyclization. It was envisioned that any nucleophilic moiety (1-162) with a tethered alkynyl group could, in principle, participate in a two-step sequence involving a nucleophilic cyclopropane ring-opening reaction to yield a pendent malonate 1-164 and a subsequent Conia-ene reaction could proceed with the malonate and the acetylenic group to give cyclic compounds 1-165 (Scheme 1-39).

Scheme 1-39: General Nucleophilic Cyclopropane Ring-Opening/Conia-ene Cyclization

In 2009, this concept was realized when propargyl amines 1-166 and 1,1-cyclopropanediesters 1-163 were reacted in the presence of a zinc catalyst to give the corresponding piperidine 1-167 (Scheme 1-40A). This process was efficient for a variety of substituted cyclopropanes resulting in excellent yields of the desired product.
This tandem process was once again achieved later in 2009 by the use of propargyl alcohols 1-168 to access tetrahydropyrans 1-170 (Scheme 1-40B).\textsuperscript{59} In contrast to the previous method with propargyl amines, the tandem cyclopropane ring-opening/Conia-ene reaction with propargyl alcohols required a sequential dual catalyst system. This interesting result is presumably due the ability of the nucleophile to open the cyclopropane ring thus requiring a stronger Lewis acid to efficiently activate the cyclopropane. The use of In(OTf)\textsubscript{3} allowed for ring opening to give intermediate 1-169 which then underwent cyclization upon the addition of a zinc catalyst furnishing 1-170. The development of these two methods has demonstrated the generality of this tandem process and has sparked the interest of the Kerr group to expand this process to different systems.

\begin{center}
\textbf{Scheme 1-40: Tandem Cyclopropane Ring-Opening/Conia-ene Reactions with Propargyl Amines and Alcohols}
\end{center}

1.6 The Synthesis of Tetrahydrocarbazoles via a Tandem Cyclopropane Ring-opening/Conia-ene Reaction

With the Kerr group’s interest in the ongoing development and utility of donor-acceptor cyclopropanes along with the initial progress in the area of ring-opening/Conia-ene reactions, we next looked to probe other nucleophiles for use in the tandem process. Having already established the superior cyclopropane ring-opening capabilities of indole (see section 1.2.2) we envisioned this to be an appropriate nucleophile to combine with
the Conia-ene process. It was hypothesized having an alkyne tethered to the indole (1-171) could allow for nucleophilic ring-opening (1-173) followed by a subsequent Conia-ene reaction to give tetrahydrocarbazoles (Scheme 1-41). The results of this project are discussed herein.60

Scheme 1-41: Hypothesized General One Pot Tetrahydrocarbazole Synthesis

1.6.1 Results and Discussion – Synthesis of Starting Materials

With a library of cyclopropanes available through traditional methods, the initial focus of this project was directed toward the synthesis of the substituted 2-alkynyl indole starting materials. The synthesis of 1-171a was first attempted by employing standard Corey-Fuchs conditions (Scheme 1-42A).61 Ramirez type product 1-17562 was isolated in good yield from the commercially available aldehyde 1-174; however, treatment of this compound led to quick decomposition of the starting material. Gratifyingly, when aldehyde 1-174 was subjected to trimethylsilyldiazomethane and lithium diisopropylamide (LDA) alkyne was isolated in a 76% yield (Scheme 1-42B). While this method proved successful, the use of explosive reagents along with the expensive cost of starting material (TMSCHN₂) caused us to abandon this route in search for a cheaper, more scalable method.
To this end, a gram scale synthesis of \( \text{1-171a} \) was achieved utilizing an Ohira-Bestmann\(^{63} \) protocol in an excellent 89\% yield (Scheme 1-43A). While this procedure worked well with several N-substituted indoles, the availability of benzenoid-substituted indole-2-carbaldehydes was limited; in order to obtain a series of 2-alkynyl indoles, another procedure was required. A series of benzenoid-substituted alkynes \( \text{1-171d-f} \) were efficiently prepared following a procedure developed by Lautens (Scheme 1-43B).\(^{64} \) Finally, disubstituted alkynes could be prepared via 1) Sonogashira cross coupling (\( \text{1-171g} \)) or 2) base mediated alkylation and acylation (\( \text{1-171h,j} \)) with 2-alkynyl indole \( \text{1-171a} \) (Scheme 1-43C/D).
1.6.2 Optimization and Scope

Readily accessible indole starting material \textbf{1-171a} was chosen as the nucleophilic partner for the initial investigation into the tetrahydrocarbazole synthesis via a tandem Conia-ene process. The main challenges for the implementation of the strategy are twofold: i) The nucleophiles’ reactivity must be orthogonal to that of the acetylenic group (i.e., they must not react with each other), and ii) a Lewis acid must be found which can activate the cyclopropane toward ring-opening and also activate the acetylene in the Conia-ene process. This last issue is somewhat complicated by the fact that it is the harder, oxophilic Lewis acids which are usually required for chelation with the geminal diester moiety on the cyclopropane, while softer metals are usually most successful in the Conia-ene reaction. In this vein, phenyl substituted cyclopropane \textbf{1-163a}, chosen for its well-known reactivity in nucleophilic ring-opening chemistry, was subjected with \textbf{1-171a} and a variety of different reaction conditions in order to determine the ideal conditions required to access the tetrahydrocarbazole \textbf{1-173a} (Table 1-1).
Table 1-1: Optimization of the Synthesis of Tetrahydrocarbazoles

<table>
<thead>
<tr>
<th>entry</th>
<th>indole (equiv)</th>
<th>catalyst</th>
<th>solvent</th>
<th>time (h)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.1</td>
<td>Sc(OTf)$_3$ (10 mol %) then ZnBr$_2$ (3 equiv), NEt$_3$ (1 equiv)</td>
<td>Benzene</td>
<td>1.5</td>
<td>63</td>
</tr>
<tr>
<td>2</td>
<td>1.1</td>
<td>Zn(NTf)$_2$ (20 mol %)</td>
<td>Benzene</td>
<td>2.0</td>
<td>84</td>
</tr>
<tr>
<td>3</td>
<td>1.4</td>
<td>Zn(NTf)$_2$ (10 mol %)</td>
<td>Benzene</td>
<td>2.0</td>
<td>87</td>
</tr>
<tr>
<td>4</td>
<td>1.4</td>
<td>Zn(NTf)$_2$ (5 mol %)</td>
<td>Benzene</td>
<td>4.0</td>
<td>88</td>
</tr>
<tr>
<td>5</td>
<td>1.4</td>
<td>Zn(NTf)$_2$ (5 mol %)</td>
<td>Toluene</td>
<td>24.0</td>
<td>decomp.</td>
</tr>
<tr>
<td>6</td>
<td>1.4</td>
<td>Zn(NTf)$_2$ (5 mol %)</td>
<td>CH$_2$Cl$_2$</td>
<td>23.0</td>
<td>84</td>
</tr>
<tr>
<td>7</td>
<td>1.4</td>
<td>Zn(NTf)$_2$ (5 mol %)</td>
<td>Cl(CH$_2$)$_2$Cl</td>
<td>1.5</td>
<td>84</td>
</tr>
</tbody>
</table>

Initial observations using Sc(OTf)$_3$ (an oxophilic catalyst) proved efficient for ring-opening; however as predicted, sequential ring closure was not achieved. To invoke the Conia-ene cyclization, a sequential dual catalyst system was explored in a similar manner to that of the tetrahydropyran synthesis. The addition of ZnBr$_2$ and NEt$_3$ after the cyclopropane ring-opening event allowed for smooth cyclization in a one-pot to give the desired tetrahydrocarbazole **1-173a** in 63% yield (Table 1-1, entry 1). Building on knowledge gained from our previous work allowed us to arrive quickly at optimal reaction conditions; in fact, Zn(NTf)$_2$ at a loading of 5 mol % in dichloroethane at reflux emerged as the reaction conditions of choice, giving tetrahydrocarbazole **1-173a** in an 84% isolated yield (entry 7). It should be noted that benzene (entry 4) and dichloromethane (entry 6) were also effective media for the reaction; however, starting materials were only sparingly soluble in benzene, while dichloromethane required extended reaction times.

With optimal conditions in hand, we set out to investigate the substrate scope. Gratifyingly, a variety of cyclopropanes underwent the desired cyclization in excellent yields. Table 1-2 shows the results of several indoles (varying in the N-substitution) with a variety of 1,1-cyclopropanediesters. As seen from the table, there was a wide tolerance
for the substituents on the cyclopropanediester. Both electron-rich (1-173b, c, n) and electron-poor (1-173e, f, o) aryl substituents performed with equal efficiency. Heterocycles were also well tolerated, although the furan substituted adduct 1-173g decomposed somewhat under the reaction conditions. This result is common when using nucleophilic aromatic substituted cyclopropanes as they are very reactive and can participate in unwanted side reactions.65 Both styrenyl and vinyl cyclopropanediesters gave good yields of products (1-173j, k, q). As expected, the parent cyclopropane (no substituent) produced 1-173l in greatly diminished yield, due to the absence of a π-donor group vicinal to the geminal diester moiety. Typically, harder Lewis acids, not compatible with Conia-ene chemistry, are required to activate this cyclopropane successfully. If the cyclopropane used was optically enriched, this was transferred with stereochemical fidelity to the adducts (1-173a and 1-173k).
In an expansion of the substrate scope, a short array of products using benzenoid-substituted indoles were explored (Table 1-3). The purpose of this study was to see whether electron withdrawing groups on the benzenoid ring would attenuate the indoles’ nucleophilicity. We were happy to observe that the presence of a trifluoromethyl or carbomethoxy moiety were not only tolerated, but produced these adducts in superb yields (1-173s, t).
We next investigated the effects of substitution on the 2-alkynyl moiety in the hopes of furthering functional group inclusion for application to the synthesis of complex target molecules. To our disappointment, we found that internal alkynes (Table 1-4) produced solely the acyclic products (1-172b-c), despite an exhaustive study of reaction conditions. In addition to the formation of 1-172d, an additional 25% of 1-173a was isolated, presumably via in situ desilylation. To overcome this drawback in reaction scope, a methyl ester was used as the alkyne substituent. With the ester present, we obtained product 1-173v in a 95% yield. Tetrahydrocarbazole 1-173v was most likely the product of a conjugate addition reaction rather than a Conia-ene cyclization. However, the ability to form 1-173v allowed a strategy for further structural elaboration. We believed the geometry of the alkene in 1-173v to be as shown based on the absence of an nOe correlation, which is always apparent between the indole N-methyl group and a proximal vinyl hydrogen. Further exploration of the tandem cyclopropane ring-opening/Michael additions has recently been reported by Ghoria.32
1.6.3 Short Mechanistic Study

A plausible mechanistic description is shown in Scheme 1-44 where initial coordination of diesters allows nucleophilic ring-opening of the cyclopropanediester. Following the ring opening, it is postulated that the Conia-ene ring closure could occur through one of two mechanistic paths. Pathway \( a \) occurs by having the Zn species coordinate to not only the alkyne, but to the oxygen of the ester (1-179) as well. This arrangement sets the alkynyl hydrogen of the starting material cis to the N-methyl group of the indole in the intermediate product (1-180). Alternatively, pathway \( b \) has the Zn species coordinate specifically to the alkyne (1-181) and has the malonic nucleophile perform an attack on the activated alkyne anti to the zinc. The end result would see the alkenylzinc moiety cis to the N-methyl group of the indole in the penultimate intermediate (1-182). It should be noted that the nature of the Conia-ene ring closure (specifically the role of the metal) is somewhat ambiguous. Our depiction in Scheme 65 is reminiscent of that shown by Toste in 2004 in which the role of the gold catalyst in a Conia-ene ring closure was probed.\textsuperscript{44g}
In Toste’s case, the two options put forth are gold activation similar to pathway \( b \) in Scheme 44 and a carbometalation similar to pathway \( a \).

Scheme 1-44: Proposed Mechanistic Pathways

In hopes to shed some light on the mechanistic possibilities of this reaction, a deuterium labelling study was performed (Scheme 1-45). The hydrogen on the alkyne compound 1-171a was replaced with a deuterium (1-171k) by deprotonation and quenching with D\(_2\)O. A standard reaction with compound 1-163a was performed, leading to product 1-173w, the identity of which was determined by comparison to the nOe spectra of the fully protonated species. In 1-173w, the relevant nOe observed in the protio species 1-173a was absent, leading us to assign the olefin geometry as shown. Since the deuterium was determined to be cis to the N-methyl group on the indole, the results support pathway \( a \) as the operational process.
1.6.4 Carbazole Synthesis

Finally, to show that the tetrahydrocarbazole adducts could be elaborated, 1-173a was subjected to Krapcho dealkoxy carbonylation to yield the mono-ester 1-183. Unsurprisingly, conjugation of the alkenyl moiety occurred under these conditions, leading to a mixture of products. Treatment of this mixture (1-183) with catalytic palladium on charcoal in refluxing mesitylene resulted in dehydrogenation to the carbazole (1-184) (Scheme 1-46). This expedient method as a whole (starting from readily available cyclopropanes) should be useful, given the ubiquity of carbazole natural products.

1.7 Summary and Future Outlook

The reactivity and utilization of donor-acceptor cyclopropanes and Conia-ene cyclization is a highly valuable and growing approach toward the synthesis of carbocyclic compounds. The use of cyclopropanes together with the Conia-ene reaction has allowed access to a variety of interesting and useful scaffolds. We have successfully developed an
efficient method for producing substituted tetrahydrocarbazoles using a tandem nucleophilic ring-opening/Conia-ene reaction.

It is envisioned that future development of this area of chemistry (cyclopropane ring-opening/Conia-ene) could follow three different paths. First, in a direct expansion of the above discussed research, optimal conditions should be developed for the cyclization of disubstituted alkynes or additional methods should be explored to access these functionalized products. An example method could be the exploration of an additional sequential third cross-coupling step, similar to that displayed by Blame (Scheme 1-47A). The second avenue this research area could follow is simply in the search for different orthogonal nucleophilic alkynes capable of undergoing both cyclopropane ring-opening and the Conia-ene cyclization. Finally, the third path this research area could follow is switching the location of the alkyne from nucleophile to cyclopropane, thus allowing access to new exo methylene products (Scheme 1-47B).

Scheme 1-47: Possible Future Directions of this Research
1.8 Experimental

General Considerations

Infrared spectra were obtained as thin films on NaCl plates using a Bruker Vector 33 FT-IR instrument. NMR experiments were performed on Varian Mercury 400, Varian Inova 600 and Inova 400 instruments, and samples were obtained in CDCl$_3$ (referenced to 7.26 ppm for $^1$H and 77.0 ppm for $^{13}$C). $^{19}$F spectra were externally referenced to neat trifluorotoluene (referenced to -63.9 ppm). Coupling constants (J) are in Hz. The multiplicities of the signals are described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, sept = septuplet, m = multiplet, br = broad. High resolution mass spectra (HRMS) were obtained on a Finnigan MAT 8200 spectrometer at 70 eV. Optical rotations were recorded in cells of 10 cm path length using a Perkin-Elmer 241 digital polarimeter.

All reagents and solvents were used as purchased from Aldrich, Strem, Caledon or VWR. Reaction progress was followed by thin layer chromatography (TLC) (EM Science, silica gel 60 F$_{254}$) visualizing with UV light, and the plates developed using acidic anisaldehyde. Flash chromatography was performed using silica gel purchased from Silicycle Chemical Division Inc. (230-400 mesh).

General Experimental Procedure for the Synthesis of Tetrahydrocarbazoles: 1,1-cyclopropane diester (1 equivalent) and 2-ethynyl-N-methylindole (1.4 equivalent) were dissolved in dichloroethane. Zinc(II) bistriflamide (0.05 equivalent) was then added and a reflux condenser was attached. The reaction vessel was then purged with argon and the reaction brought to reflux. Upon completion by TLC analysis, the reaction mixture was purified by flash chromatography (EtOAc/Hexanes) to yield the desired tetrahydrocarbazoles.

THC **1-173a** was prepared using general experimental procedure. Reagents employed: dimethyl (R)-2-phenylcyclopropane-1,1-dicarboxylate **1-163a** (82 mg, 0.35 mmol, 91% ee), 2-ethynyl-N-methylindole **1-171a** (77 mg, 0.50 mmol), zinc(II) bistriflamide (11
mg, 0.018 mmol), and DCE (4.0 mL). Yielded THC 1-173a as a pale yellow foam, 84% (115 mg, 0.29 mmol, 93% ee). R_f = 0.25, 10% EtOAc in hexanes; ¹H-NMR (400 MHz, CDCl₃): δ = 7.32-7.56 (m, 6H), 6.84 (ddd, J = 8.0, 6.8, 0.8 Hz, 2H), 6.72 (d, J = 8.0 Hz, 1H), 5.57 (s, 1H), 5.17 (s, 1H), 4.28 (dd, J = 10.4, 5.6 Hz, 1H), 3.91 (s, 3H), 3.77 (s, 3H), 3.70 (s, 3H), 2.98 (dd, J = 13.2, 5.8 Hz, 1H), 2.56 (dd, J = 13.2, 10.4 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ = 170.4, 170.3, 144.4, 140.0, 135.4, 134.6, 128.5, 128.2, 126.6, 125.6, 122.8, 120.6, 119.3, 114.7, 111.3, 109.4, 62.8, 53.0, 52.8, 41.8, 38.4, 32.1; IR (thin film): 3027, 2951, 1734, 1669, 1630, 1503, 1467, 1436, 1369, 1343, 1240, 1175, 1105, 1081, 1060, 1025, 968, 939, 895, 735, 702; HRMS calc’d for C₂₄H₂₃NO₄ = 389.1627, found = 389.1621. The enantiomeric excess was determined to be 93% by chiral HPLC, Chiralcel OD-H, 250 x 4.6 mm², Diacel Chemical Industries; 9:1 Hexanes / iPrOH at 1 mL/min; 220 nm the retention time for the enantiomers were r₁ (+) = 11.86 mins, r₁ (-) = 15.00 mins

THC 1-173b was prepared using general experimental procedure. Reagents employed: 2-piperonylcyclopropane-1,1-dicarboxylate 1-163b (98 mg, 0.35 mmol), 2-ethynyl-N-methylindole 1-171a (77 mg, 0.50 mmol), zinc(II) bistriflamide (12 mg, 0.019 mmol), and DCE (4.0 ml). Yielded THC 1-173b as a yellow foam, 68% (104 mg, 0.24 mmol). R_f = 0.23, 30% EtOAc in hexanes; ¹H-NMR (600 MHz, CDCl₃): δ = 7.31 (d, J = 8.4 Hz, 1H), 7.20 (ddd, J = 8.3, 6.8, 1.8 Hz, 1H), 6.89 (ddd, J = 8.4, 8.4, 1.2 Hz, 1H), 6.84 (d, J = 8.4 Hz, 1H), 6.76-6.73 (m, 2H), 6.65 (s, 1H), 5.92 (d, J = 1.2 Hz, 1H), 5.91 (d, J = 1.2 Hz, 1H), 5.56 (s, 1H), 5.16 (s, 1H), 4.21 (dd, J = 10.5, 5.7 Hz, 1H), 3.90 (s, 3H), 3.80 (s, 3H), 3.69 (s, 3H), 2.95 (dd, J = 13.8, 5.4 Hz, 1H), 2.52 (dd, J = 13.5, 10.5 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ = 170.4, 170.2, 147.7, 146.2, 139.9, 138.5, 135.3, 134.5, 125.6, 122.8, 121.2, 120.6, 119.3, 114.7, 111.3, 109.4, 108.4, 100.8, 62.9, 53.0, 52.8, 41.93, 41.90, 38.2, 32.0; IR (thin film): 3053, 3003, 2952, 2903, 735, 1668, 1630, 1609, 1503, 1486, 1440, 1364, 1245, 1097, 1079, 1039, 935, 812, 736; HRMS calc’d for C₂₅H₂₅NO₆ = 433.1525, found = 433.1530.
THC 1-173c was prepared using general experimental procedure. Reagents employed: 2-p-methoxycyclopropane-1,1-dicarboxylate 1-163c (94 mg, 0.36 mmol), 2-ethynyl-N-methylindole 1-171a (78 mg, 0.50 mmol), zinc(II) bistriflamide (12 mg, 0.019 mmol), and DCE (4.0 mL). Yielded THC 1-173c as a yellow oil, 74% (111 mg, 0.27 mmol). Rf = 0.26, 30% EtOAc in hexanes; 1H-NMR (400 MHz, CDCl3): δ = 7.32 (d, J = 8.0 Hz, 1H), 7.20 (ddd, J = 8.0, 8.0, 1.0 Hz, 1H), 7.17 (d, J = 8.4 Hz, 2H), 6.90-6.84 (m, 3H), 6.79 (d, J = 7.6 Hz, 1H), 5.59 (s, 1H), 5.19 (s, 1H), 4.26 (dd, J = 10.6, 5.8 Hz, 1H), 3.92 (s, 3H), 3.81 (s, 3H), 3.80 (s, 3H), 3.72 (s, 3H), 2.98 (dd, J = 13.6, 5.8 Hz, 1H), 2.57 (dd, J = 13.6, 10.4 Hz, 1H); 13C NMR (100 MHz, CDCl3) δ = 170.5, 170.3, 158.3, 140.0, 136.5, 135.5, 134.5, 129.1, 125.6, 122.7, 120.7, 119.3, 115.1, 113.8, 111.2, 109.4, 62.9, 55.2, 53.0, 52.8, 42.0, 37.6, 32.1; IR (thin film): 3053, 3029, 2999, 2952, 2837, 1735, 1669, 1610, 1585, 1511, 1467, 1437, 1367, 1339, 1319, 1277, 1246, 1211, 1175, 1134.9, 1109, 1079, 1064, 1033, 1016, 968, 940, 895, 832, 784, 748, 736, 702, 658; HRMS calc’d for C25H25NO5 = 419.1733, found = 419.1730.

THC 1-173d was prepared using general experimental procedure. Reagents employed: 2-p-chlorocyclopropane-1,1-dicarboxylate 1-163d (97 mg, 0.36 mmol), 2-ethynyl-N-methylindole 1-171a (78 mg, 0.50 mmol), zinc(II) bistriflamide (12 mg, 0.019 mmol), and DCE (4.0 mL). Yielded THC 1-173d as a yellow foam, 89% (135 mg, 0.32 mmol). Rf = 0.21, 15% EtOAc in hexanes; 1H-NMR (400 MHz, CDCl3): δ = 7.32 (d, J = 8.0 Hz, 1H), 7.26-7.24 and 7.17-7.14 (2m, AA’BB’, 4H), 7.20 (ddd, J = 8.4, 7.2, 1.2 Hz, 1H), 6.88 (ddd, J = 8.0, 7, 1 Hz, 1H), 6.73 (d, J = 8.0 Hz, 1H), 5.58 (s, 1H), 5.18 (s, 1H), 4.27 (dd, J = 10.6, 5.8 Hz, 1H), 3.91 (s, 3H), 3.78 (s, 3H), 3.70 (s, 3H), 2.96 (dd, J = 13.6, 6.0 Hz, 1H), 2.50 (dd, J = 13.8, 10.6 Hz, 1H); 13C NMR (100 MHz, CDCl3) δ = 170.3, 170.1, 143.0, 139.9, 135.2, 134.6, 132.2, 129.5, 128.6, 125.4, 122.9, 120.4, 119.5, 114.0, 111.6, 109.5, 62.7, 53.1, 52.8, 41.6, 37.8, 32.1; IR (thin film): 3053, 3027, 3002, 2952, 2879, 2844, 1900, 1739, 1631, 1608, 1535, 1489, 1467, 1436, 1410, 1369, 1338, 1305, 1271,
THC 1-173e was prepared using general experimental procedure. Reagents employed: 2-\textit{p}-methylestercyclopropane-1,1-dicarboxylate 1-163e (103 mg, 0.350 mmol), 2-ethynyl-N-methylindole 1-171a (78 mg, 0.50 mmol), Zinc(II) bistriflamide (12 mg, 0.019 mmol), and DCE (4.0 mL). Yielded THC 1-173e as a yellow film, 90% (141 mg, 0.32 mmol). R\textsubscript{f} = 0.24, 30% EtOAc in hexanes; \textsuperscript{1}H-NMR (400 MHz, CDCl\textsubscript{3}): \(\delta = 7.98\) (d, \(J = 9.2\) Hz, 2H), 7.34-7.31 (m, 3H), 7.20 (ddd, \(J = 8.0, 8.0, 0.8\) Hz, 1H), 6.86 (t, \(J = 7.4\) Hz, 1H), 6.69 (d, \(J = 7.6\) Hz, 1H), 5.61 (s, 1H), 5.21 (s, 1H), 4.39 (dd, \(J = 10.2, 5.8\) Hz, 1H), 3.93 (s, 3H), 3.78 (s, 3H), 3.70 (s, 3H), 3.02 (dd, \(J = 14.6, 7.0\) Hz, 1H); 13C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta = 170.2, 170.1, 167.0, 149.9, 139.9, 135.1, 134.6, 129.9, 128.5, 128.2, 125.3, 122.9, 120.3, 119.5, 113.6, 111.6, 109.5, 62.6, 53.0, 52.8, 51.9, 41.3, 38.4, 32.0; IR (thin film): 3053, 3030, 2999, 2951, 1724, 1610, 1467, 1436, 1368, 1281, 1224, 1177, 1111, 1078, 1065, 1018, 967, 939, 896, 855, 778, 736, 704; HRMS calc’d for C\textsubscript{26}H\textsubscript{25}NO\textsubscript{6} = 447.1682, found = 447.1685.

THC 1-173f was prepared using general experimental procedure. Reagents employed: 2-\textit{p}-cyanocyclopropane-1,1-dicarboxylate 1-163f (91 mg, 0.35 mmol), 2-ethynyl-N-methylindole 1-171a (77 mg, 0.50 mmol), Zinc(II) bistriflamide (12 mg, 0.019 mmol), and DCE (4.0 mL). Yielded THC 1-173f as a yellow oil, 84% (122 mg, 0.30 mmol). R\textsubscript{f} = 0.25, 30% EtOAc in hexanes; \textsuperscript{1}H-NMR (400 MHz, CDCl\textsubscript{3}): \(\delta = 7.59\) (d, \(J = 6.4\) Hz, 2H), 7.34 (d, \(J = 8.4\) Hz, 3H), 7.22 (ddd, \(J = 8.0, 8.0, 0.6\) Hz, 1H), 6.89 (t, \(J = 7.6\) Hz, 1H), 6.65 (d, \(J = 8.0\) Hz, 1H), 5.61 (s, 1H), 5.21 (s, 1H), 4.38 (dd, \(J = 10.2, 5.8\) Hz, 1H), 3.93 (s, 3H), 3.78 (s, 3H), 3.70 (s, 3H), 3.00 (dd, \(J = 14.6, 7.0\) Hz, 1H), 2.50 (dd, \(J = 13.4, 10.6\) Hz, 1H); 13C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta = 170.0, 169.9, 150.1, 139.8, 134.8, 134.76, 132.3,\)
THC 1-173g was prepared using general experimental procedure. Reagents employed: 2-p-furanocyclopropane-1,1-dicarboxylate 1-163g (85 mg, 0.35 mmol), 2-ethynyl-N-methylindole 1-171a (77 mg, 0.50 mmol), Zinc(II) bistriflamide (12 mg, 0.019 mmol), and DCE (4.0 mL). Yielded THC 1-173g as a yellow oil, 49% (65 mg, 0.17 mmol). \( R_f = 0.25, 30\% \) EtOAc in hexanes; \(^1\)H-NMR (400 MHz, CDCl\(_3\)): \( \delta = 7.34-7.30 \) (m, 2H), 7.22 (ddd, \( J = 8.2, 7.0, 1.2 \) Hz, 1H), 7.12 (d, \( J = 7.6 \) Hz, 1H), 6.98 (ddd, \( J = 7.6, 7.6, 0.8 \) Hz, 1H), 6.28 (dd, \( J = 2.8, 2.0 \) Hz, 1H), 6.01 (d, \( J = 3.2 \) Hz, 1H), 5.56 (s, 1H), 5.17 (s, 1H), 4.48 (dd, \( J = 8.4, 6.0 \) Hz, 1H), 3.90 (s, 3H), 3.72 (s, 3H), 3.69 (s, 3H), 2.97 (dd, \( J = 13.8, 6.2 \) Hz, 1H), 2.86 (dd, \( J = 13.6, 8.4 \) Hz, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta = 170.2, 156.2, 143.4, 141.4, 139.8, 135.0, 134.1, 125.5, 122.9, 119.9, 119.5, 111.9, 111.7, 110.1, 109.5, 106.6, 62.1, 53.0, 52.8, 37.4, 32.1, 31.4; IR (thin film): 2949, 1735, 1605, 1468, 1365, 1245, 1073, 1007, 902, 737; HRMS calc’d for C\(_{22}\)H\(_{21}\)NO\(_5\) = 379.1420, found = 379.1446.

THC 1-173h was prepared using general experimental procedure. Reagents employed: dimethyl 2-(1-tosyl-1H-indol-3-yl)cyclopropane-1,1-dicarboxylate 1-163h (136 mg, 0.320 mmol), 2-ethynyl-N-methylindole 1-171a (70 mg, 0.45 mmol), Zinc(II) bistriflamide (10 mg, 0.016 mmol), and DCE (4.0 mL). Yielded THC 1-173h as a yellow foam, 67% (125 mg, 0.21 mmol). \( R_f = 0.35, 40\% \) EtOAc in hexanes; \(^1\)H-NMR (400 MHz, CDCl\(_3\)): \( \delta = 8.02 \) (d, \( J = 8.2 \) Hz, 1H), 7.68 (d, \( J = 8.6 \) Hz, 2H), 7.40 (bs, 1H), 7.31-7.27 (m, 1H), 7.23 (d, \( J = 7.8 \) Hz, 3H), 7.21-7.14 (m, 2H), 6.77
(d, J = 3.5 Hz, 2H), 5.62 (s, 1H), 5.20 (dd, J = 9.0, 6.2 Hz, 1H), 3.94 (s, 3H), 3.72 (s, 3H), 3.64 (s, 3H), 3.06 (dd, J = 13.4, 5.8 Hz, 1H), 2.72 (dd, J = 13.2, 9.2 Hz, 1H), 2.38 (s, 3H); 13C NMR (100 MHz, CDCl3) δ = 179.2, 170.1, 144.7, 143.3, 139.8, 135.9, 135.0, 134.8, 134.2, 129.7, 126.8, 125.2, 125.0, 124.6, 124.0, 123.1, 122.8, 120.2, 119.7, 119.1, 113.8, 112.4, 111.8, 109.6, 62.1, 53.1, 52.7, 38.4, 32.1, 28.9, 21.6; IR (thin film): 3053, 2952, 1736, 1670, 1597, 1448, 1369, 1267, 1122, 1019, 972, 908, 813, 733, 704; HRMS calc’d for C33H30N2O6S = 582.1825, found = 582.1807.

THC 1-173i was prepared using general experimental procedure. Reagents employed: 2-thiocyclopropane-1,1-dicarboxylate 1-163i (51 mg, 0.21 mmol), 2-ethynyl-N-methylindole 1-171a (48 mg, 0.31 mmol), Zinc(II) bistriflamide (6.0 mg, 0.010 mmol), and DCE (3.0 mL). Yielded THC 1-173i as a yellow foam, 74% (62 mg, 0.16 mmol). Rf = 0.13, 15% EtOAc in hexanes; 1H-NMR (400 MHz, CDCl3): δ = 7.32 (d, J = 5.2 Hz, 1H), 7.21 (ddd, J = 5.6, 4.8, 0.8 Hz, 1H), 7.18 (dd, J = 3.6, 0.8 Hz, 1H), 6.99 (d, J = 5.2 Hz, 1H), 6.94-6.91 (m, 3H), 5.58 (s, 1H), 5.19 (s, 1H), 4.66 (dd, J = 6.4, 4.0 Hz, 1H), 3.91 (s, 3H), 3.77 (s, 3H), 3.71 (s, 3H), 3.07 (dd, J = 9.0, 3.8 Hz, 1H), 2.71 (dd, J = 8.8, 6.8 Hz, 1H); 13C NMR (100 MHz, CDCl3) δ = 170.2, 170.1, 148.4, 139.8, 135.1, 134.0, 126.3, 125.6, 125.0, 123.9, 122.9, 120.4, 119.5, 114.2, 111.7, 109.5, 62.6, 53.0, 52.8, 42.2, 33.5, 32.1; IR (thin film): 3105, 3055, 3002, 2952, 2850, 1735, 1667, 1613, 1529, 1469, 1435, 1361, 1303, 1267, 1245, 1178, 1132, 1103, 1078, 1065, 1023, 968, 927, 907, 831, 784, 736, 702; HRMS calc’d for C22H21NO4S = 395.1191, found = 395.1192.

THC 1-173j was prepared using general experimental procedure. Reagents employed: 2-styrenycyclopropane-1,1-dicarboxylate 1-163j (81 mg, 0.31 mmol), 2-ethynyl-N-methylindole 1-171a (68 mg, 0.44 mmol), Zinc(II) bistriflamide (10 mg, 0.016 mmol), and DCE (4.0 mL). Yielded THC 1-173j as a yellow foam, 70% (91 mg, 0.22 mmol). Rf = 0.33, 30% EtOAc in hexanes; 1H-NMR (400 MHz, CDCl3): δ = 7.57 (d, J = 8.4 1H), 7.37-7.18 (m, 7H), 6.98
(ddd, J = 8.0, 8.0, 1 Hz, 1H), 6.66 (d, J = 15.6 Hz, 1H), 6.25 (dd, J = 15.6, 8.4 Hz, 1H), 5.52 (s, 1H), 5.13 (s, 1H), 3.95-3.89 (m, 1H), 3.87 (s, 3H), 3.78 (s, 3H), 3.67 (s, 3H), 2.83 (dd, J = 13.6, 6.0 Hz, 1H), 2.51 (dd, J = 13.6, 9.4 Hz, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta = 170.5, 170.3, 139.9, 137.3, 135.3, 133.5, 133.1, 130.9, 128.5, 127.2, 126.2, 126.1, 122.9, 120.6, 119.5, 113.7, 111.3, 109.5, 60.3, 53.0, 52.9, 38.6, 35.7, 32.1; IR (thin film): 3056, 3026, 2952, 2845, 1736, 1666, 1612, 1468, 1434, 1397, 1246, 1175, 1099, 1072, 1024, 968, 748, 698; HRMS calc’d for C\(_{26}\)H\(_{25}\)NO\(_4\) = 415.1784, found = 415.1796.

THC 1-173k was prepared using general experimental procedure. Reagents employed: (R)-2-vinylcyclopropane-1,1-dicarboxylate 1-163k (61 mg, 0.33 mmol, 100% ee), 2-ethynyl-N-methylindole 1-171a (71 mg, 0.46 mmol), Zinc(II) bistriflamide (10 mg, 0.017 mmol), and DCE (4.0 mL). Yielded THC 1-173k as a yellow foam, 77% (87 mg, 0.26 mmol, 99% ee). \(R_f = 0.17, 20\% \) EtOAc in hexanes; \(^1\)H-NMR (600 MHz, CDCl\(_3\)): \(\delta = 6.62 (d, J = 7.2 \text{ Hz}, 1\text{H}), 7.31 (d, J = 8.4 \text{ Hz}, 1\text{H}), 7.25 (\text{ddd partially obscured by solvent peak at 7.26 ppm, } J = 9.0, 7.8, 1.5 \text{ Hz}, 1\text{H}), 7.06 (\text{ddd, } J = 8.4, 1.2 \text{ Hz}, 1\text{H}), 5.86 (\text{ddd, } J = 16.8, 10.2, 8.4 \text{ Hz}, 1\text{H}), 5.50 (s, 1\text{H}), 5.31 (dd, J = 17.1, 1.2 \text{ Hz}, 1\text{H}), 5.19 (dd, J = 10.2, 1.8 \text{ Hz}, 1\text{H}), 5.12 (s, 1\text{H}), 3.87 (s, 3\text{H}), 3.83 (s, 3\text{H}), 3.79-3.73 (m, 1\text{H}), 3.67 (s, 3\text{H}), 2.78 (dd, J = 13.5, 6.3 \text{ Hz}, 1\text{H}), 2.43 (dd, J = 13.5, 9.9 \text{ Hz}, 1\text{H}); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta = 170.5, 170.3, 141.1, 139.8, 135.3, 133.5, 126.0, 122.8, 120.5, 119.3, 115.7, 113.3, 111.2, 109.4, 62.2, 52.9, 52.7, 38.3, 36.4, 32.0; IR (thin film): 3055, 3001, 2953, 2846, 1735, 1668, 1613, 1469, 1435, 1369, 1267, 1245, 1161, 1132, 1072, 1016, 917, 737, 702; HRMS calc’d for C\(_{20}\)H\(_{21}\)NO\(_4\) = 339.1471, found = 339.1460. The enantiomeric excess was determined to be 99% by chiral HPLC, Chiralcel OD-H, 250 x 4.6 mm\(^2\), Diacel Chemical Industries; 92:8 Hexanes / iPrOH at 10 mL/min; 220 nm the retention time for the enantiomers were \(\eta_1 (+) = 11.95 \text{ mins.} \)
THC 1-173l was prepared using general experimental procedure. Reagents employed: cyclopropane-1,1-dicarboxylate 1-163l (62 mg, 0.39 mmol), 2-ethynyl-N-methylindole 1-171a (85 mg, 0.55 mmol), Zinc(II) bistriflamide (12 mg, 0.019 mmol), and DCE (4.0 mL). Yielded THC 1-173l as a yellow foam, 14% (18 mg, 0.056 mmol). \( R_f = 0.10 \), 10% EtOAc in hexanes; \(^1\)H-NMR (400 MHz, CDCl\(_3\)): \( \delta = 7.48 \) (d, \( J = 7.6 \) Hz, 1H), 7.30 (ddd, \( J = 7.8, 7.8, 1.2 \) Hz, 1H), 7.25 (dd, \( J = 8.4, 2.8 \) Hz, 1H), 7.10 (ddd, \( J = 7.8, 6.6, 1.2 \) Hz, 1H), 5.51 (s, 1H), 5.09 (s, 1H), 3.87 (s, 3H), 3.76 (s, 6H), 2.89 (t, \( J = 6.4 \) Hz, 2H), 2.67 (t, \( J = 6.4 \) Hz, 2H); \(^1^3\)C NMR (100 MHz, CDCl\(_3\)) \( \delta = 170.7, 139.7, 135.6, 126.0, 123.0, 121.4, 119.3, 119.0, 112.8, 110.5, 109.4, 62.6, 52.8, 41.8, 31.2, 18.5; IR (thin film): 2951, 2848, 1734, 1668, 1615, 1468, 1436, 1373, 1313, 1246, 1169, 1076, 929, 887, 775; HRMS calc’d for C\(_{18}\)H\(_{19}\)NO\(_4\) = 313.1314, found = 313.1311.

THC 1-173m was prepared using general experimental procedure. Reagents employed: 2-phenylcyclopropane-1,1-dicarboxylate 1-163a (25 mg, 0.11 mmol), 2-ethynylindole 1-171b (21 mg, 0.15 mmol), Zinc(II) bistriflamide (4.0 mg, 0.0060 mmol), and DCE (2.0 mL). Yielded THC 1-173m as a yellow foam, 76% (31 mg, 0.083 mmol). \( R_f = 0.18 \), 20% EtOAc in hexanes; \(^1\)H-NMR (600 MHz, CDCl\(_3\)): \( \delta = 8.35 \) (bs, 1H), 7.31-7.21 (m, 6H), 7.11 (t, \( J = 7.5 \) Hz, 1H), 6.81 (t, \( J = 7.2 \) Hz, 1H), 6.65 (d, \( J = 7.8 \) Hz, 1H), 5.52 (s, 1H), 5.06 (s, 1H), 4.21 (dd, \( J = 10.5, 5.1 \) Hz, 1H), 3.78 (s, 3H), 3.70 (s, 3H), 2.92 (dd, \( J = 13.8, 5.4 \) Hz, 1H), 2.59 (dd, \( J = 13.5, 10.5 \) Hz, 1H); \(^1^3\)C NMR (100 MHz, CDCl\(_3\)) \( \delta = 170.6, 170.4, 143.4, 137.3, 133.9, 132.4, 128.4, 128.3, 126.7, 123.2, 120.6, 119.5, 115.4, 110.9, 108.3, 98.3, 60.9, 53.1, 52.8, 41.3, 38.2; IR (thin film): 3388, 3058, 3028, 3003, 2951, 2853, 1732, 1633, 1612, 1493, 1453, 1436, 1328, 1277, 1241, 1201, 1196, 1065, 1045, 901, 738, 701; HRMS calc’d for C\(_{23}\)H\(_{21}\)NO\(_4\) = 375.1471, found = 375.1466.
THC 1-173n was prepared using general experimental procedure.
Reagents employed: 2-phenylcyclopropane-1,1-dicarboxylate 1-163c (103 mg, 0.390 mmol), 2-ethynylindole 1-171b (77 mg, 0.55 mmol), zinc(II) bistriflamide (12 mg, 0.020 mmol), and DCE (4.0 mL). Yielded THC 1-173n as a yellow foam, 71% (112 mg, 0.28 mmol). Rf = 0.06, 20% EtOAc in hexanes; 1H-NMR (600 MHz, CDCl3): δ = 8.68 (bs, 1H), 7.26 (d, J = 8.4 Hz, 1H), 7.16 (d, J = 7.8 Hz, 2H), 7.11 (ddd, J = 8.1, 8.1, 1.2 Hz, 1H), 6.86 (d, J = 8.4 Hz, 2H), 6.84 (t, J = 7.8 Hz, 1H), 6.72 (dd, J = 8.4 Hz, 1H), 5.51 (s, 1H), 5.02 (s, 1H), 4.21 (dd, J = 10.2, 3.6 Hz, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.74 (s, 3H), 2.93 (dd, J = 13.8, 5.4 Hz, 1H), 2.60 (dd, J = 13.5, 9.9 Hz, 1H); 13C NMR (100 MHz, CDCl3) δ = 170.7, 170.5, 158.3, 137.3, 135.7, 133.9, 132.4, 129.3, 126.7, 123.1, 120.7, 119.4, 115.7, 113.8, 110.9, 108.3, 61.0, 55.2, 53.1, 52.8, 41.5, 37.4; IR (thin film): 3387, 3057, 3032, 3001, 2952, 2837, 1732, 1611, 1511, 1452, 1438, 1326, 1279, 1246, 1176, 1071, 1037, 902, 832, 738; HRMS calc’d for C24H23NO5 = 405.1576, found = 405.1569.

THC 1-173o was prepared using general experimental procedure.
Reagents employed: 2-p-methylestercyclopropane-1,1-dicarboxylate 1-163e (86 mg, 0.29 mmol), 2-ethynylindole 1-171b (64 mg, 0.45 mmol), zinc(II) bistriflamide (10 mg, 0.016 mmol), and DCE (4.0 mL). Yielded THC 1-173o as a yellow foam, 61% (78 mg, 0.18 mmol). Rf = 0.10, 20% EtOAc in hexanes; 1H-NMR (400 MHz, CDCl3): δ = 8.47 (bs, 1H), 7.98 (d, J = 8.4 Hz, 2H), 7.30 (dd, J = 8.2, 3.0 Hz, 3H), 7.12 (ddd, J = 8.0, 8.0, 0.8 Hz, 1H), 6.81 (t, J = 7.6 Hz, 1H), 6.61 (d, J = 7.6 Hz, 1H), 5.55 (s, 1H), 5.08 (s, 1H), 4.29 (dd, J = 10.2, 5.0 Hz, 1H), 3.91 (s, 3H), 3.79 (s, 3H), 3.70 (s, 3H), 2.93 (dd, J = 13.4, 5.0 Hz, 1H), 2.56 (dd, J = 13.6, 10.4 Hz, 1H); 13C NMR (100 MHz, CDCl3) δ = 170.4, 170.2, 167.0, 149.0, 137.3, 133.7, 132.6, 129.8, 128.7, 128.4, 126.4, 123.3, 120.4, 119.7, 114.4, 111.0, 108.7, 60.8, 53.2, 52.8, 52.0, 40.9, 38.2; IR (thin film): 3375, 3032, 3002, 2952, 2846, 1723, 1610, 1452, 1436, 1326, 1280, 1242, 1198, 1178, 1113, 1070, 1045,
THC 1-173p was prepared using general experimental procedure. Reagents employed: 2-thiocyclopropane-1,1-dicarboxylate 1-163i (77 mg, 0.32 mmol), 2-ethynylindole 1-171b (64 mg, 0.45 mmol), zinc(II) bistriflamide (10 mg, 0.016 mmol), and DCE (4.0 mL). Yielded THC 1-173p as an orange foam, 86% (105 mg, 0.28 mmol). \( R_f = 0.13, 20\% \) EtOAc in hexanes; \(^1\)H-NMR (400 MHz, CDCl\(_3\)): \( \delta = 8.42 \) (bs, 1H), 7.28 (d, \( J = 8.0 \) Hz, 1H), 7.20 (dd, \( J = 4.8, 1.2 \) Hz, 1H), 7.14 (ddd, \( J = 8.2, 5.8, 2.2 \) Hz, 1H), 6.94 (dd, \( J = 5.0, 3.4 \) Hz, 1H), 6.91-6.87 (m, 3H), 5.51 (s, 1H), 5.06 (s, 1H), 4.60 (dd, \( J = 9.4, 5.0 \) Hz, 1H), 3.79 (s, 3H), 3.70 (s, 3H), 3.01 (dd, \( J = 13.4, 5.0 \) Hz, 1H), 2.72 (dd, \( J = 13.4, 9.4 \) Hz, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta = 170.5, 170.3, 147.4, 137.2, 133.5, 131.9, 126.6, 126.4, 125.3, 124.0, 123.3, 120.3, 119.7, 115.0, 111.0, 108.7, 60.7, 53.1, 52.8, 41.6, 33.3; IR (thin film): 3392, 3056, 3002, 2952, 2852, 1732, 1633, 1614, 1453, 1436, 1324, 1266, 1173, 1072, 1044, 900, 853, 831, 738, 702; HRMS calc’d for C\textsubscript{25}H\textsubscript{23}NO\textsubscript{6} = 433.1525, found = 433.1517.

THC 1-173q was prepared using general experimental procedure. Reagents employed: 2-vinylcyclopropane-1,1-dicarboxylate 1-163k (59 mg, 0.32 mmol), 2-ethynylindole 1-171b (64 mg, 0.45 mmol), zinc(II) bistriflamide (10 mg, 0.016 mmol), and DCE (4.0 mL). Yielded THC 1-173q as a yellow foam, 59% (61 mg, 0.19 mmol). \( R_f = 0.17, 20\% \) EtOAc in hexanes; \(^1\)H-NMR (400 MHz, CDCl\(_3\)): \( \delta = 8.43 \) (bs, 1H), 7.60 (d, \( J = 8.0 \) Hz, 1H), 7.28 (d partially obscured by solvent peak at 7.26 ppm, \( J = 8.0 \) Hz, 1H) 7.17 (ddd, \( J = 8.4, 7.2, 1.2 \) Hz, 1H), 7.03 (ddd, \( J = 8.0, 8.0, 1.2 \) Hz, 1H), 5.91 (ddd, \( J = 17.2, 10, 8.0 \) Hz, 1H), 5.43 (s, 1H), 5.29 (dd, \( J = 17.0, 1.4 \) Hz, 1H), 5.21 (dd, \( J = 10.2, 1.0 \) Hz, 1H), 4.99 (s, 1H), 3.81 (s, 3H), 3.77 (s, 3H), 3.75-3.69 (m, 1H), 2.73 (dd, \( J = 13.4, 5.0 \) Hz, 1H), 2.46 (dd, \( J = 13.6, 9.2 \) Hz, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta = 170.8, 170.6, 140.5, 137.2, 133.8, 131.5, 1178, 1164, 1143, 1134, 1124, 1104, 1095, 1087, 1072, 1053, 1031, 1018, 967, 854, 738, 703; HRMS calc’d for C\textsubscript{21}H\textsubscript{19}NO\textsubscript{4}S = 381.1035, found = 381.1039.
THC 1-173r was prepared using general experimental procedure. Reagents employed: 2-phenylcyclopropane-1,1-dicarboxylate 1-163a (50 mg, 0.21 mmol), 2-ethynyl-N-benzylindole 1-171c (68 mg, 0.29 mmol), zinc(II) bistriflamine (7.0 mg, 0.010 mmol), and DCE (3.0 mL). Yielded THC 1-173r as a yellow foam, 76% (76 mg, 0.16 mmol). R\textsubscript{f} = 0.23, 20% EtOAc in hexanes; \textsuperscript{1}H-NMR (600 MHz, CDCl\textsubscript{3}): \(\delta = 7.37 (t, J = 7.5 \text{ Hz}, 2\text{H}), 7.35-7.27 (m, 6\text{H}), 7.21 (d, J = 7.8 \text{ Hz}, 2\text{H}), 7.18 (d, J = 8.4 \text{ Hz}, 1\text{H}), 7.13 (t, J = 7.8 \text{ Hz}, 1\text{H}), 6.89 (t, J = 7.5 \text{ Hz}, 1\text{H}), 6.80 (d, J = 7.8 \text{ Hz}, 1\text{H}), 5.63 (d, J = 17.7 \text{ Hz}, 1\text{H}), 5.49 (d, J = 17.7 \text{ Hz}, 1\text{H}), 5.28 (s, 1\text{H}), 4.36 (dd, J = 10.5, 5.7 \text{ Hz}, 1\text{H}), 3.74 (s, 3\text{H}), 3.72 (s, 3\text{H}), 3.03 (dd, J = 14.1, 5.7 \text{ Hz}, 1\text{H}), 2.62 (dd, J = 13.2, 10.8 \text{ Hz}, 1\text{H}); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta = 170.4, 170.3, 144.4, 140.2, 138.1, 134.8, 134.6, 128.9, 128.5, 128.2, 127.2, 126.6, 125.9, 125.8, 123.1, 120.7, 119.8, 115.1, 111.4, 110.0, 62.9, 53.0, 52.7, 48.1, 41.8, 38.5; IR (thin film): 3060, 3029, 3004, 2952, 2855, 1735, 1670, 1605, 1495, 1453, 1436, 1346, 1323, 1265, 1237, 1202, 1175, 1082, 1074, 1062, 1029, 910, 736, 701; HRMS calc’d for C\textsubscript{19}H\textsubscript{19}NO\textsubscript{4} = 325.1314, found = 325.1309.

THC 1-173s was prepared using general experimental procedure. Reagents employed: 2-phenylcyclopropane-1,1-dicarboxylate 1-163a (33 mg, 0.14 mmol), 2-ethynyl-6-trifluoromethylindole 1-171d (40 mg, 0.19 mmol), zinc(II) bistriflamine (5.0 mg, 0.0070 mmol), and DCE (2.0 mL). Yielded THC 1-173s as a yellow oil, 93% (58 mg, 0.13 mmol). R\textsubscript{f} = 0.2, 20% EtOAc in hexanes; \textsuperscript{1}H-NMR (400 MHz, CDCl\textsubscript{3}): \(\delta = 9.01 (bs, 1\text{H}), 7.33-7.27 (m, 4\text{H}), 7.19 (d, J = 0.017 \text{ Hz}, 2\text{H}), 6.85 (dd, J = 8.8, 1.2 \text{ Hz}, 1\text{H}), 6.51 (d, J = 8.4 \text{ Hz}, 1\text{H}), 5.62 (s, 1\text{H}), 5.13 (s, 1 \text{H}), 4.15 (dd, J = 10.8, 4.8 \text{ Hz}, 1\text{H}), 3.92 (s, 3\text{H}), 3.77 (s, 3\text{H}), 2.93 (dd, J = 13.6, 4.8 \text{ Hz}, 1\text{H}), 2.62 (dd, J = 13.8, 10.6 \text{ Hz}, 1\text{H}); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta = 171.2, 170.4, 143.0, 136.0, 134.6,
133.3, 128.6, 128.2, 127.0, 120.6, 115.9, 115.8, 115.1, 110.1, 108.04, 108.01, 61.0, 53.4, 52.9, 41.2, 38.3 (Note: one carbon missing presumably due to overlap); IR (thin film): 3369, 3029, 2954, 2854, 1726, 1511, 1444, 1338, 1280, 1229, 1202, 1164, 1141, 1115, 1083, 1065, 1052, 925, 815, 701; HRMS calc’d for C_{24}H_{20}F_{3}NO_{4} = 443.1344, found = 443.1339.

THC 1-173t was prepared using general experimental procedure. Reagents employed: 2-phenylcyclopropane-1,1-dicarboxylate 1-163a (59 mg, 0.25 mmol), 2-ethynyl-6-methylester indole 1-171e (70 mg, 0.35 mmol), zinc(II) bistriflamide (8.0 mg, 0.013 mmol), and DCE (3.5 mL). Yielded THC 1-173t as a yellow film, 92% (99 mg, 0.23 mmol). R_f = 0.11, 20% EtOAc in hexanes; ^1H-NMR (400 MHz, CDCl_3): δ = 9.00 (bs, 1H), 8.00 (s, 1H), 7.43 (d, J = 8.8 Hz, 1H), 7.32-7.25 (m, 3H), 7.20 (d, J = 6.8 Hz, 2H), 6.56 (d, J = 8.8 Hz, 1H), 5.71 (s, 1H), 5.18 (s, 1H), 4.20 (dd, J = 10.4, 4.8 Hz, 1H), 3.91 (s, 3H), 3.86 (s, 3H), 3.74 (s, 3H), 2.93 (dd, J = 13.4, 5.0 Hz, 1H), 2.61 (dd, J = 13.2, 10.4 Hz, 1H); ^13C NMR (100 MHz, CDCl_3) δ = 170.6, 170.4, 168.0, 143.1, 136.5, 135.4, 133.5, 130.1, 128.5, 128.2, 126.9, 124.3, 120.4, 120.0, 115.4, 113.1, 110.2, 60.8, 53.3, 51.9, 41.8, 41.1, 38.1; IR (thin film): 3355, 2952, 1718, 1603, 1486, 1436, 1276, 1222, 1089, 1050, 871, 774, 692; HRMS calc’d for C_{25}H_{23}NO_{6} = 433.1525, found = 433.1517.

THC 1-173u was prepared using general experimental procedure. Reagents employed: 2-phenylcyclopropane-1,1-dicarboxylate 1-163a (38 mg, 0.16 mmol), 2-ethynyl-1,5-dimethyl-1H-indole 1-171f (38 mg, 0.22 mmol), zinc(II) bistriflamide (5.0 mg, 0.0080 mmol), and DCE (2.0 mL). Yielded THC 1-173u as a yellow foam, 70% (46 mg, 0.11 mmol). R_f = 0.23, 20% EtOAc in hexanes; ^1H-NMR (600 MHz, CDCl_3): δ = 7.30-7.19 (m, 6H), 7.01 (dd, J = 12.0, 6.0 Hz, 1H), 6.51 (s, 1H), 5.54 (s, 1H), 5.14 (s, 1H), 4.26 (dd, J = 10.0 5.8 Hz, 1H), 3.88 (s, 3H), 3.75 (s, 3H), 3.69 (s, 3H), 2.98 (dd, J = 14.0, 5.8 Hz,
1H), 2.55 (dd, $J = 13.5, 10.0$ Hz, 1H), 2.21 (s, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta = 170.1, 170.5, 144.6, 138.7, 135.7, 134.9, 128.7, 128.6, 128.3, 126.6, 126.0, 124.6, 120.3, 114.3, 111.2, 109.3, 63.0, 53.2, 52.9, 42.0, 38.5, 36.8, 32.3; IR (thin film): 3026, 2951, 2857, 1736, 1668, 1629, 1488, 1436, 1370, 1265, 1241, 1174, 1074, 1060, 1027, 900, 793, 736, 702; C$_{25}$H$_{25}$NO$_4$ = 403.1784, found = 403.1758.

Acyclic adduct 1-172b was prepared using general experimental procedure. Reagents employed: 2-phenylcyclopropane-1,1-dicarboxylate 1-163a (58 mg, 0.25 mmol), 2-ethynyl-2-phenylethynylindole 1-171g (80 mg, 0.35 mmol), zinc(II) bistriflamide (8.0 mg, 0.012 mmol), and DCE (4.0 mL). Yielded acyclic adduct 1-172b as an orange oil, 84% (98 mg, 0.21 mmol). $R_f = 0.26$, 15% EtOAc in hexanes; $^1$H-NMR (400 MHz, CDCl$_3$): $\delta = 7.49$-$7.46$ (m, 2H), 7.44 (s, 1H), 7.36 (d, $J = 7.4$ Hz, 2H), 7.30-7.24 (m, 3H), 7.17-7.11 (m, 4H), 6.95 (ddd, $J = 8.0, 5.9, 2.0$ Hz, 1H), 4.47 (dd, $J = 10.5, 6.2$ Hz, 1H), 3.73 (s, 3H), 3.52 (s, 3H), 3.47 (s, 3H), 3.32 (dd, $J = 9.8, 5.5$ Hz, 1H), 3.0-2.84 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta = 169.8, 169.7, 143.7, 137.5, 131.2, 128.6, 128.5, 128.3, 127.6, 126.2, 125.8, 123.2, 122.7, 121.1, 120.5, 119.9, 119.7, 109.4, 98.2, 80.7, 52.4, 52.3, 50.2, 40.6, 33.2, 30.7; IR (thin film): 3057, 2951, 2202, 1734, 1599, 1490, 1435, 1405, 1359, 1227, 1152, 1028, 910, 848, 755, 742, 691; HRMS calc’d for C$_{30}$H$_{27}$NO$_4$ = 465.1940, found = 465.1918.

Acyclic adduct 1-172c was prepared using general experimental procedure. Reagents employed: 2-phenylcyclopropane-1,1-dicarboxylate 1-163a (120 mg, 0.510 mmol), 1-methyl-2-prop1-ynylindole 1-171h (120 mg, 0.710 mmol), zinc(II) bistriflamide (16 mg, 0.026mmol), and DCE (6.0 mL). Yielded acyclic adduct 1-172c as a yellow foam, 97% (199 mg, 0.49 mmol). $R_f = 0.16$, 25% EtOAc in hexanes; $^1$H-NMR (600 MHz, CDCl$_3$): $\delta = 7.56$ (d, $J = 8.2$ Hz, 1H), 7.5 (d, $J = 7.6$ Hz, 2H), 7.34 (t, $J = 7.5$ Hz, 2H), 7.29 (t, $J = 9.0$ Hz, 2H), 7.23 (t, $J = 7.0$ Hz, 1H), 7.11 (ddd, $J = 8.2, 6.2, 1.8$ Hz, 1H), 4.56
(dd, $J = 10.8, 5.6$ Hz, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.66 (s, 3H), 3.49 (dd, $J = 10.0, 5.3$ Hz, 1H), 3.12-3.07 (m, 1H), 3.02-2.97 (m, 1H), 2.26 (s, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) δ = 169.91, 169.90, 144.0, 137.0, 128.3, 127.6, 126.1, 125.8, 122.7, 121.5, 119.8, 119.5, 119.4, 109.3, 94.7, 71.1, 52.44, 52.40, 50.3, 40.5, 33.3, 30.6, 4.8; IR (thin film): 3027, 2950, 1734, 1606, 1265, 1370, 1232, 1156, 1019, 743, 704; HRMS calc’d for C$_{25}$H$_{25}$NO$_4$ = 403.1784, found = 403.1438.

Acyclic adduct 1-172d was prepared using general experimental procedure. Reagents employed: 2-phenylcyclopropane-1,1-dicarboxylate 1-163a (78 mg, 0.33 mmol), 2-(trimethylsilyl)ethynylindole 1-171i (100 mg, 0.47 mmol), zinc(II) bistriflamide (10 mg, 0.017 mmol), and DCE (4.0 mL). Yielded acyclic adduct 1-172d as a yellow oil, 72% (106 mg, 0.24 mmol). R$_f$ = 0.29, 30% EtOAc in hexane; $^1$H-NMR (600 MHz, CDCl$_3$): δ = 8.16 (bs, 1H), 7.6 (d, $J = 8.2$ Hz, 1H), 7.47 (d, $J = 7.0$ Hz, 2H), 7.29 (m, 3H), 7.23 (dd, $J = 7.0, 1.2$ Hz, 1H), 7.20 (d, $J = 8.2$ Hz, 1H), 7.09 (ddd, $J = 8.2, 8.2, 1.2$ Hz, 1H), 4.49 (dd, $J = 10.5, 6.4$ Hz, 1H), 3.73 (s, 3H), 3.65 (s, 3H), 3.41 (dd, $J = 9.4, 5.9$ Hz, 1H), 3.10-3.05 (m, 1H), 2.98-2.93 (m, 1H), 0.32 (s, 9H); $^{13}$C NMR (150 MHz, CDCl$_3$) δ = 169.70, 169.66, 143.6, 135.8, 128.3, 127.7, 126.2, 126.1, 123.8, 123.1 120.2, 119.8, 116.8, 110.9, 101.7, 96.7, 72.4, 52.3, 50.2, 40.4, 33.0, 0.3; IR (thin film): 3053, 2953, 2929, 2855, 1736, 1668, 1614, 1468, 1435, 1375, 1266, 1244, 1166, 1075, 745; HRMS calc’d for C$_{26}$H$_{29}$NO$_4$Si = 447.1866, found = 447.1858.

THC 1-173v was prepared using general experimental procedure. Reagents employed: 2-phenylcyclopropane-1,1-dicarboxylate 1-163a (59 mg, 0.25 mmol), methyl 3-(1-methylindol-2-yl)propionate 1-171j (74 mg, 0.35 mmol), zinc(II) bistriflamide (8.0 mg, 0.013 mmol), and DCE (2.5 mL). Yielded THC 1-173v as an orange foam, 95% (106 mg, 0.24 mmol). R$_f$ = 0.33, 20% EtOAc in hexanes; $^1$H-NMR (600 MHz, CDCl$_3$): δ = 7.33-7.27 (m, 7H), 6.93-6.88 (m, 2H), 5.78 (s, 1H), 4.51 (dd, $J = 10.0, 6.4$ Hz, 1H), 3.84 (s, 3H),
3.78 (s, 3H) 3.60 (s, 3H), 3.59 (s, 3H), 3.15 (dd, $J = 14.0, 6.4$ Hz 1H), 2.59 (dd, $J = 10.0, 14.0$ Hz 1H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta = 169.3, 169.2, 166.1, 144.4, 141.9, 141.0, 134.0, 128.6, 127.9, 126.7, 125.4, 123.8, 120.7, 119.6, 117.2, 114.5, 110.2, 64.5, 53.2, 53.1, 51.8, 42.2, 38.3, 31.7; IR (thin film): 2925, 2854, 1733, 1627, 1464, 1436, 1334, 1276, 1230, 1177, 1082, 1020, 747, 701; HRMS calc’d for C$_{26}$H$_{25}$NO$_6$ = 447.1682, found = 447.1676.

2-ethynyl-N-methylindole 1-171a was prepared using the following procedure. Commercially available 1-methylindole-2-carboxaldehyde (1.0 g, 6.3 mmol) was dissolved in a MeOH:THF solution (8.0 mL : 5.0 mL), and cooled to zero for 10 min. K$_2$CO$_3$ (2.6 g, 19 mmol) was then added to the solution, directly followed by the drop wise addition of dimethyl(1-diazo-2-oxopropyl)phosphonate in a 1:1 solution of MeOH:THF (2.0 mL). The yellow mixture was stirred at room temperature until completion which was determined by TLC (5 hours). The mixture was worked up using EtOAc and water; the organic was washed with brine and dried with MgSO$_4$. The compound was purified by flash chromatography in 5% EtOAc/Hexanes to yield a yellow solid, 89% (860 mg, 5.6 mmol); The data for this compound matched that of the commercially available material.

2-((TMS)ethynyl)-1H-indole 1-171i was prepared according to the procedure of Lautens. The data for this compound matched the previously reported.

2-ethynyl-1H-indole 1-171b was prepared using the following procedure: 2-((TMS)ethynyl)-1H-indole (840 mg, 3.90 mmol) was dissolved in THF (30 mL) under a balloon of argon, and cooled to zero for 10 min. 1.0 M TBAF (5.9 mL, 5.9 mmol) in THF was then added drop wise to the solution. The dark solution was stirred at room temperature until completion which was determined by TLC (20 min).
The mixture was worked up using EtOAc and water. The compound was purified by flash chromatography in a gradient solvent (0 %, 10 %, 20 %) EtOAc/Hexanes to yield a brown solid, 95% (520 mg, 3.7 mmol). The data for this compound matched that of the commercially available material.

Methyl 2-ethynyl-1H-indole-6-carboxylate **1-171d** was prepared in a two-step fashion. Methyl 2-((TMS)ethynyl)-1H-indole-6-carboxylate was first prepared according to the procedure of Lautens. Crude methyl 2-((TMS)ethynyl)-1H-indole-6-carboxylate (290 mg, 1.10 mmol) was dissolved in THF (10 mL) under a balloon of argon, and cooled to zero for 10 min. 1.0 M TBAF (1.6 mL, 1.6 mmol) in THF was then added drop wise to the solution. The dark solution was stirred at room temperature until completion which was determined by TLC (30 min). The mixture was worked up using EtOAc and water. The compound was purified by flash chromatography in 20 % EtOAc/Hexanes to yield the product as a yellow film, 73% (159 mg, 0.80 mmol). \( R_f = 0.29 \), 25% EtOAc in hexanes; \(^1\)H-NMR (600 MHz, CDCl\(_3\)): \( \delta = 8.70 \) (bs, 1H), 8.11 (s, 1H), 7.82 (d, \( J = 8.8 \) Hz, 1H), 7.61 (d, \( J = 8.2 \) Hz, 1H), 6.84 (s, 1H), 3.95 (s, 3H), 3.37 (s, 1H); \(^1^3\)C NMR (150 MHz, CDCl\(_3\)) \( \delta = 168.0, 135.2, 130.9, 125.2, 121.4, 120.8, 120.6, 113.2, 109.6, 81.9, 75.6, 52.1 \); IR (thin film): 3368, 3257, 3033, 2998, 2950, 1691, 1618, 1515, 1434, 1386, 1322, 1307, 1272, 1220, 1090, 992, 882, 835, 801, 760, 742, 716, 639; HRMS calc’d for C\(_{12}\)H\(_9\)NO\(_2\) = 199.0633, found = 199.0635

1-methyl-2-(phenylethynyl)-1H-indole **1-171g** was prepared using the following procedure: 2-ethynyl-N-methylindole **1-171a** (155 mg, 1.0 mmol) and iodobenzene (1.3 mL, 1.2 mmol) were dissolved in NEt\(_3\) (5.0 mL) and purged with argon. Pd(PPh\(_3\))\(_4\) (27 mg, 0.020 mmol) and Cul (10 mg, 0.050 mmol) were added and the solution was heated to reflux. The solution stirred at reflux until completion which was determined by TLC (3 h). The mixture was worked up using ether and water. The compound was purified by flash chromatography in 20 % EtOAc/Hexanes to yield
an orange solid, 95% (220 mg, 0.95 mmol); The data for this compound matched that of the commercially available material.

Methyl 3-(1-methyl-1H-indol-2-yl)propionate 1-171j was prepared using the following procedure: 2-ethynyl-N-methylindole 1-171a (100 mg, 0.640 mmol) was dissolved in ether (2.0 mL) and cooled to -30°C. 2.5 M n-BuLi (0.5 mL, 1.3 mmol) in hexanes was added drop wise and the solution mixed at zero for 30 min. The solution was then re-cooled to -30°C and methyl chloroformate (0.2 mL, 2.6 mmol) was added and the mixture was stirred at room temperature for 1.5 hours. The mixture was then quenched with NH₄Cl and worked up with EtOAc and water. The compound was purified by flash chromatography in 20 % EtOAc/Hexanes to yield an orange film, 63% (85 mg, 0.40 mmol). Rₚ = 0.36, 20% EtOAc in hexanes; ¹H-NMR (400 MHz, CDCl₃): δ = 7.73 (d, J = 8.2 Hz, 1H), 7.31 (ddd, J = 8.0, 6.7, 1 Hz, 1H), 7.26 (dd, J = 8.2, 0.8 Hz, 1H), 7.13 (ddd, J = 8.0, 6.8, 1.2 Hz, 1H) 7.03 (d, J = 0.8 Hz, 1H), 3.84 (s, 3H), 3.80 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ = 154.2, 138.0, 126.6, 124.8, 121.7, 120.7, 118.2, 112.5, 109.7, 87.1, 79.1, 52.7, 30.7; IR (thin film): 3118, 2996, 2212, 1700, 1459, 1436, 1381, 1363, 1254, 1146, 806, 736;

Deuterated 2-ethynyl-N-methylindole 1-171k was prepared using the following procedure: 2-ethynyl-N-methylindole 1-171a (60 mg, 0.39 mmol) was dissolved in THF (3.0 mL), purged with argon and cooled to zero in an ice bath for 10 mins. 2.0 M BuLi (0.40 mL, 0.70 mmol) was added and the solution mixed at zero for 1.5 h. D₂O (approx. 1 mL) was then added and the solution mixed at zero for an additional 2 h. The mixture was then quenched with NH₄Cl and worked up with EtOAc and water. The organic layer was dried using magnesium sulfate, filtered, and concentrated to yield the product as a brown film, 92% (56 mg, 0.36 mmol). Rₚ = 0.55, 20% EtOAc in hexanes; ¹H-NMR (600 MHz, CDCl₃): δ = 7.64 (d, J = 8.2 Hz, 1H), 7.33-7.30 (m, 2H), 7.17 (ddd, J = 7.9, 5.9, 2.1 Hz, 1H), 6.88 (s, 1H), 3.84 (s, 3H); ¹³C NMR
Carbazole 1-184 was prepared in a two-step procedure from THC 1-173a. THC 1-173a (110 mg, 0.280 mmol), LiCl (24 mg, 0.56 mmol), and NEt₃-HCl (27 mg, 0.28 mmol) were dissolved in DMF (2.0 mL) and placed in microwave reactor at 120°C for 1.5 h. The solution was added to water and extracted with ether three times and concentrated. The mixture was purified by flash chromatography in 10% EtOAc/Hexanes to yield the crude monoester as a mixture of endo and exo methylene products (68 mg, 0.21 mmol). The monoester mixture (48 mg, 0.14 mmol) was then dissolved in mesitylene (4.5 mL) with 10% activated carbon (5.0 mg). The solution was heated to reflux (180°C) for 1 h. The solution was cooled and applied directly to a column and was purified in 20% EtOAc/Hexanes to yield the product as a yellow film, 95% (65 mg, 0.20 mmol). Rf = 0.55, 20% EtOAc in hexanes;

\[^1\text{H}-\text{NMR}(600 \text{ MHz, CDCl}_3): \delta = 7.56 (\text{dd, } J = 7.9, 1.5 \text{ Hz, 2H}), 7.52 (d, J = 7.0 \text{ Hz, 2H}) 7.50-7.48 (m, 2H), 7.42 (ddd, J = 8.2, 7.0, 1.2 \text{ Hz, 1H}), 7.4 (d, J = 8.2 \text{ Hz, 1H}), 7.33 (d, J = 8.2 \text{ Hz, 1H}), 6.96 (ddd, J = 8.0, 8.0, 1.2 \text{ Hz, 1H}), 4.19 (s, 3H), 3.94 (s, 3H), 3.07 (s, 3H); \[^{13}\text{C NMR}(100 \text{ MHz, CDCl}_3) \delta = 169.3, 143.6, 141.0, 140.6, 134.9, 129.2, 128.7, 128.4, 127.6, 123.7, 122.8, 122.7, 121.9, 121.5, 119.1, 108.9, 52.0, 33.8, 17.1; IR (thin film): 3055, 2948, 2836, 1717, 1613, 1489, 1464, 1434, 1375, 1322, 1242, 1200, 1111, 1060, 1023, 972, 933, 875, 749, 704, 662; HRMS calc’ed for C₂₂H₁₉NO₂ = 329.1416, found = 329.1405.\)

Deuterated THC 1-173w was prepared using general experimental procedure. Reagents employed: 2-phenylcyclopropane-1,1-dicarboxylate 1-163a (50 mg, 0.21 mmol), deuterated 2-ethynyl-N-methylindole 1-171k (68 mg, 0.29 mmol), Zinc(II) bistriflamide (7.0 mg, 0.010 mmol), and DCE (3.0 mL). Yielded deuterated THC 1-173w as a yellow foam, 76% (76 mg, 0.16 mmol). Rf = 0.23, 20% EtOAc in hexanes. Data for this
compound was consistent with that of THC 1-173a with the exception of the
disappearance of the alkene singlet at 5.58, thus indicating that the substitution on the
alkyne will end up syn to the methyl group on the nitrogen. The overall conformation
can once again be confirmed by referring to the nOe experiments.
1.9 References


19 Similar results have been reported in recent indole alkylation with cyclopropane papers; Dulin, C.; Murphy, K.; Nolin, K. *Tetrahedron Lett.* **2014**, *55*, 5280.


Chapter 2: γ-Aminobutyric Acids and γ-Butanolides from Cyclopropane Hemimalonates

2 Introduction and Overview

The study of donor-acceptor cyclopropanes within the Kerr group has focused on the development and reactivity of vicinally substituted 1,1-cyclopropanediesters. Recent exploits have discovered a new type of cyclopropane which displays a unique mode of reactivity: donor-acceptor hemimalonate cyclopropanes. This chapter will focus on the preliminary work directed toward the development and use of hemimalonate cyclopropanes in the synthesis of unique molecular scaffolds. In particular, a brief discussion on the synthesis of γ-aminobutyric acid derivatives will be presented, along with a detailed account of the synthesis of butanolides from donor-acceptor hemimalonate cyclopropanes.

In addition, this chapter will discuss the development of a new synthetic method for the functionalization of donor-acceptor cyclopropanes. The synthetic usefulness of these cyclopropanes will be explored, specifically in the access of cycloaddition products containing substitution patterns that were previously inaccessible with prior cyclopropane annulation methods. Finally, the instrumental utility of this method will be exploited in the total synthesis of (R)-dodecan-4-olide in conjunction with previous methods.

2.1 Butanolides and Butenolides

The butanolide and butenolide cores have been isolated from a variety of natural sources (Figure 2-1) and are common compounds in flavourings and insect pheromones. Due to their broad spectrum of bioactivities, these molecules and their derivatives have been ideal candidates for drug development. Their abundance in nature and potent bioactivities leave no question; these molecules are highly desirable and have attracted considerable synthetic attention. While a vast array of new elegant methods for the synthesis of these small molecules have been developed, only a few methods have been reported utilizing cyclopropanes as a core starting material.
2.1.1 Selected Synthesis of Butanolides from Cyclopropanes

One of the earlier entries in the field of butanolide synthesis from cyclopropanes was developed by Theodorakis in 2004 while investigating strategies for the formation of fused bicyclic systems. Highly activated alkoxy cyclopropanes 2-1 underwent smooth ring expansion to the desired bicyclic lactone 2-2 in the presence of methanesulfonic acid in moderate yields (Scheme 2-1).\(^5\) While a small scope was developed for this unique transformation, the reaction suffered from several drawbacks including minimal functional group (R and \(R^1\)) variation due to the required meticulous synthesis of the starting materials. Nonetheless, this method was instrumental in showcasing rather mild conditions for the synthesis of substituted butanolides.

\[ \text{Scheme 2-1: Alkoxy Cyclopropane Ring Expansion} \]

In a similar manner, Reiser et al. showed that alkoxy cyclopropane 2-4 could be made from simple furan starting materials 2-3 and could undergo the same ring expansion with HCl at room temperature to give the fused lactone 2-5a (Scheme 2-2A).\(^6\) This method allowed for great diversity in substitution patterns of the product based on the ease of the
cyclopropane synthesis. Interestingly, when these reactions were heated to reflux, the opposite diastereomer was observed. The utility of this method was applied to the total synthesis of (-)-paeonilide (Scheme 2-2B).³

Scheme 2-2: Synthesis of (-)-paeonilide

In 2007, Chandrasekaran displayed a variation of this reaction utilizing 1,2-cyclopropanated sugar derivatives 2-9 (Scheme 2-3). This two-step synthesis was efficient for the conversion of several different substituted cyclopropanes giving excellent yields and perfect diastereoselectivity of the products 2-10.⁴ Interestingly, in contrast to the previous reports, initial LiOH hydrolysis of the ester was required to get good conversion of the NIS mediated ring opening. The advantage to this method as opposed to the previous acid catalyzed rearrangement strategies was the incorporation of a new functionalized chiral center.
Scheme 2-3: Butanolides from 1,2-Cyclopropanated Sugar Derivatives

Shortly after Chandrasekaran’s NIS conditions were developed, Mead showed it was possible to perform this transformation using catalytic Lewis acid. The transformation of cyclopropane 2-11 to tricyclic butanolides 2-12 was achieved utilizing a variety of Lewis acid catalysts (BF₃·OEt₂, Sn(OTf)₂, and Cu(OTf)₂) with the tin catalyst giving the highest yields (72%) and copper giving the lowest yields overall (Scheme 2-4). Although this method only gave low to modest yields over a small substrate scope, it was a significant advancement in this research area because it showed that non alkoxy activated cyclopropanes (albeit high strained and fused) could undergo the one-pot transformation to butanolides.

Scheme 2-4: Lewis Acid Catalyzed Synthesis of Butanolides
More recently, Boysen and co-workers showed the two-step synthesis of butanolides \(2-16\) from indole derived cyclopropane \(2-14\) (Scheme 2-5). Similar to the seminal work in this area, acid mediated conditions were employed allowing for cyclopropane ring-opening of amine activated cyclopropane \(2-14\) to give imine \(2-15\) which was then subjected to saponification conditions to give butanolide \(2-16\). Boysen was able to show the usefulness of this reaction by applying it to the synthesis of \((-\text{-desoxyeseroline 2-17})\).

![Scheme 2-5: Butanolides from Indole Derived Cyclopropanes](image)

Reissig, a well-known and common contributor to the development of cyclopropane chemistry, recently revisited a previously developed method for the synthesis of perfluoroalkyl-substituted butanolides \(2-20\). Reissig’s interest in the synthesis of these molecules stemmed from high biological activity of butanolides paired with the remarkable changes in bioactivity that can be brought about by the introduction of a fluorinated substitution; accessing molecules of these types would be of great interest to the pharmacological industry. First, protic solvent ring-opening of silyl cyclopropane \(2-18\) liberated the corresponding \(\gamma\)-oxo ester \(2-19\). \(2-19\) then underwent lactonization, following an in situ reduction and then acid cyclization to give butanolides \(2-20\) (Scheme 2-6). The reducing conditions allowed access to several different fluoroalkyl substituted butanolides in modest overall yields.
Scheme 2-6: Synthesis of Fluoroalkyl Substituted Butanolides

The most recent effort in this field came from the Corey group in 2013. In hopes of developing routes to unique structural moieties of natural and biologically active compounds, the group directed a focus toward the synthesis of butanolides due to their ability to serve as versatile intermediates in synthesis. They first showed the TMSOTf mediated transformation of conformationally restricted cyclopropanes 2-21 to give complex fused bicyclic butanolides 2-22 (Scheme 2-7A).\textsuperscript{14} While these skeletal rearrangements produced interesting molecular scaffolds, this method required large excesses of reagents and led to modest yields of the desired product. However, in the same paper, Corey was able to perform a skeletal rearrangement of fused carbonyl cyclopropanes 2-23 to butanolides 2-24 which were achieved in higher yields, although excess TMSOTf was still required (Scheme 2-7B). With the quick access to complex molecular framework, it is surely just a matter of time until this method is utilized in target oriented synthesis.
Scheme 2-7: TMSOTf Mediated Skeletal Rearrangement of Cyclopropanes

In contrast to the synthesis of butanolides from fused cyclopropanes, little recent work has been reported on the synthesis of butanolides from monocyclic cyclopropanes. In fact, most of the recent reports in this area record the butanolide compound as a minor byproduct in the synthesis of different structural motifs (Scheme 2-8). Such examples can be seen in the work of Yang\textsuperscript{15} in the synthesis of diastereomerically pure tetrahydrofurans 2-27 (Scheme 2-8A), Tomilov\textsuperscript{16} in the synthesis of cyclopropane dimer 2-30 (Scheme 2-8B), and Melnikov\textsuperscript{17} in the synthesis of ring opened adduct 2-32 (Scheme 2-8C).
Scheme 2-8: Synthesis of Fused Butanolides from Cyclopropanes

2.2 Naturally Occurring (R)-Dodecan-4-olide

Among the vast array of butanolide-containing natural products, (R)-dodecan-4-olide (dodecanolide) displays a simple mono-lactone core perfect for showcasing developing methodologies (Figure 2-2).\textsuperscript{18} Isolated from an array of natural sources including the pygidial glands of rove beetles,\textsuperscript{19} fruits,\textsuperscript{20} butterfat,\textsuperscript{21} and the territorial marking fluid of the Bengal tiger,\textsuperscript{22} dodecanolide is a small natural product which plays a role in many different biological processes.\textsuperscript{23} Many of the recent syntheses of this molecule have focused on enzymatic resolutions, optically enriched epoxide openings, and optically enriched reductive lactonizations.

Figure 2-2: (R)-Dodecan-4-olide
2.2.1 Selected Previous Syntheses of Dodecanolide

A prime example of an enzymatic type approach to dodecanolide was displayed by Utaka in 1987. The enantioselective baker’s yeast reduction of a variety of δ-keto acids \textbf{2-34} gave intermediate alcohol \textbf{2-35} in moderate yields and high ee (Scheme 2-9). Alcohol intermediate \textbf{2-35} was then subjected to acid catalyzed cyclization during work-up to furnish butanolide \textbf{2-33}. This process worked with a variety of different chain lengths in excellent selectivities and gave dodecanolide \textbf{2-33} in a 71% yield. This method allowed for quick access to the natural product and an array of substituted derivatives, and has since spurred forward several different enzymatic approaches to this product.

Scheme 2-9: Baker's Yeast Reduction Approach to Dodecanolide

Another generalized approach to dodecanolide can be illustrated by the work of Boland, utilizing epoxides. Optically enriched epoxide \textbf{2-36} (synthesized through a Jacobson hydrolytic kinetic resolution) underwent ring opening with allyl Grignard to give alcohol \textbf{2-37} as the penultimate intermediate (Scheme 2-10). The opening of the epoxide was achieved with stereochemical transfer resulting in no erosion of enantiomeric excess. Oxidative cleavage of the terminal olefin of \textbf{2-37} was achieved with OsO₄ to give the corresponding acyclic hydroxyl acid which, readily cyclized upon acidic workup to give \textbf{2-33}. Starting from a readily available epoxide, dodecanolide was synthesized in a two-step 75% overall yield in 99% ee.

Scheme 2-10: Epoxide Opening Approach to Dodecanolide
In early 2013, Matsumoto reported a combination of the previous two methods in the synthesis of dodecanolide. The first step employed an enzymatic hydrolysis to access optically enriched starting materials; the second step involved an epoxide opening allowing the synthesis to be finished in a similar manner to that of Boland. The synthesis of optically enriched epoxide 2-36 was achieved via a lipase hydrolysis to give a mixture of (S)-2-39 and 2-40 (Scheme 2-11). The mixture was then subjected to a polymer supported Mitsunobu reaction to convert 2-40 to the desired enantiomer giving (S)-2-39 in an isolated 81% yield and 97% ee. This approach was interesting as kinetic resolution methods can give a theoretical maximum of 50% of each enantiomer, but by applying a simple second inversion step to one enantiomer, the authors have, in principle, increased their total theoretical yield from 50% to 100% of one enantiomer. The unfortunate drawback of this approach toward (R)-dodecan-4-olide is that the wrong enantiomer ((S)-2-39) was given. Thus a second inversion had to be performed via a DIBAL reduction of the acetate followed by another Mitsunobu inversion of the secondary alcohol and finally an acetate cleavage to give 2-40. 2-40 was then converted in epoxide 2-36 which could be carried forward using a two-step sequence similar to that of Boland, giving (R)-dodecan-4-olide in a 44% yield over the two steps. Matsumoto also showed the synthesis of (S)-dodecan-4-olide using (S)-2-39 and following a similar epoxide forming and opening route.

Scheme 2-11: Matsumoto's Approach to Dodecanolide

While the two-step epoxide opening approach to butanolides allowed quick access to dodecanolide, Jacobsen showed that butanolides could be accessed directly through a
one-step reaction of ynamines 2-42 and epoxides 2-41 (Scheme 2-12).\textsuperscript{27} The strategy utilized an electron rich alkyne to invoke epoxide ring-opening followed by an intramolecular oxy-Mannich type reaction to give cyclic ketenaminal 2-43. The cyclic intermediate then underwent a subsequent hydrolysis and protodesilylation in the presence of KHF\textsubscript{2} to give the corresponding butanolide 2-44. In the exploration of the substrate scope of this reaction, it was determined that the use of optically enriched epoxides allowed for efficient stereotransfer throughout the transformation, giving optically enriched butanolides without the loss of enantiomeric excess (eg. 2-44a, 2-44b). Finally, to display the utility of this transformation, Jacobsen applied it to the one-pot synthesis of (±)-dodecan-4-olide using the appropriate racemic epoxide and ynamine 2-42 in an 86% isolated yield. Future advancements of this chemistry to include different substituted ynamines would allow access to highly substituted butanolides which would certainly find significant use in target oriented synthesis.

Moving away from the many epoxide opening methods developed for the synthesis of dodecanolide, Snyder showed the use of cycloaddition chemistry to access the target molecule.\textsuperscript{28} First, the asymmetric cycloaddition between 2-46 and anthracene gave 2-47 plus a small amount of the regioisomer (Scheme 2-13). The desired stereochemistry was obtained presumably through the steric effects of the trifluoromethyl handle. Subsequent testing with other anthracenes proved that 2-45 gave the highest yields and best selectivities. Treatment of 2-47 with octyl magnesium bromide gave the desired

\textbf{Scheme 2-12: Butanolide Synthesis from Ynamines and Epoxides}
substituted butanolide 2-48 in excellent yield presumably through nucleophilic addition to an oxonium intermediate in a stereoselective fashion. Cycloreversion of 2-48 at high temperatures led to a moderate yield of butenolide 2-49 which could then be reduced to the natural product following known procedures. This method displayed the unique capabilities of a chiral diene to produce an enantiomerically enriched product through a cycloaddition/retro-cycloaddition sequence.

Scheme 2-13: Cycloaddition Approach to Dodecanolide

Finally, in another interesting approach to this molecule, Fukumoto showed the use of an advanced cyclopropane intermediate in the synthesis of dodecanolide via two ring expansion reactions. Cyclopropane 2-50, prepared from commercially available starting materials, was subjected to a two-step ring expansion via sequential mesylation and desilylation to give cyclobutanone 2-51 (Scheme 2-14). NaBH₄ reduction and protection of the corresponding secondary alcohol followed by oxidative solvolysis furnished cyclobutane 2-52 in 84% yield over three steps. The desired octyl chain was installed via a three-step reduction, tosylation, displacement sequence to give 2-53. Reinstallation of the ketone of the cyclobutanone was achieved through a two-step procedure followed by a ring expanding Baeyer-Villiger oxidation to give dodecanolide 2-33 in a 65% yield over three steps. Although lengthy, this synthesis displayed the overall utility of cyclopropanes in butanolide target oriented synthesis.
Scheme 2-14: The use of Cyclopropanes in the Synthesis of Dodecanolide

2.3 Cyclopropane Hemimalonates (Seminal Investigations)

In 2010, while continuing to explore the reactivity of 1,1-cyclopropanediesters 2-54, the Kerr group also looked into modified donor-acceptor cyclopropanes, in hopes of discovering a new mode of reactivity (Figure 2-3). The synthesis of these cyclopropanes comes from the mild saponification of the readily available cyclopropanediester in a highly diastereoselective manner.

Inspired by the boronic acid mediated Diels-Alder results of Hall,\textsuperscript{31} it was envisioned that the donor-acceptor hemimalonate cyclopropanes could be activated under similar conditions (Scheme 2-15A). Coordination of boronic acid with the acid moiety (2-59) could potentially polarize the cyclopropane C-C bond thus allowing for nucleophilic ring-opening ultimately to give ring opened adduct 2-60 (Scheme 2-15B).
Scheme 2-15: Boronic Acid Activation of Cyclopropanes Hypothesis

Initial investigations utilizing indoles as nucleophiles under hyperbaric conditions (for previously successful conditions see 1.2.2) with cyclopropane hemimalonate 2-55a and 2-bromophenyl boronic acid 2-62 showed great promise giving ring opened adduct 2-63a a 52% yield (Scheme 16A). While these primary results indicated that the boronic acid was activating the cyclopropane toward ring-opening, it was later determined when running a control experiment that the boronic acid was not required in the reaction (Scheme 16B).32 In fact, in the absence of boronic acid, a higher yield of the isolated product 2-63a was observed.

Scheme 2-16: Initial Investigation into the Ring-Opening of Cyclopropane Hemimalonates
Based on our previous knowledge in the area of activating 1,1-cyclopropanediesters 2-54, it was unusual to see a cyclopropane be opened without the addition of a catalyst. It was proposed that the hemimalonate cyclopropane could be self-activating. In particular, under the hyperbaric conditions, a potential high pressure induced hydrogen bonding effect (2-55) could take place activating the cyclopropane toward ring-opening (Figure 2-4). This result is particularly interesting as it could allow a more atom economical approach to cyclopropane chemistry where no catalysts are required.

![Lewis Acid Activation vs Hydrogen Bonding Activation](image)

**Figure 2-4: Postulated Cyclopropane Hemimalonate Activation**

The scope of these high pressure reaction conditions was investigated varying substitution on the indole 2-64 and on the cyclopropane 2-55 (Scheme 2-17). The conditions were suitable for a variety of different substituted indoles with trends indicating higher yields when R² = H. Cyclopropane substitution was also well tolerated for aromatic substituted cyclopropanes while alkyl substituted cyclopropanes showed no reactivity under these conditions. Interestingly, vinyl cyclopropane 2-55b was extremely reactive under the high pressure conditions leading only to cyclopropane polymerization. Overall, the results were very comparable to previously developed methods utilizing 1,1-cyclopropanediesters and a Lewis acid catalyst.
2.4 The Synthesis of \( \gamma \)-Aminobutyric Acids and \( \gamma \)-Butanolides from Hemimalonate Cyclopropanes

Based on the initial success displayed for the opening of cyclopropane hemimalonates with indoles, we were encouraged to continue studying these interesting molecules in hopes of accessing different molecular scaffolds. While determining which direction to explore with these cyclopropanes, it occurred to us that an ideal starting point may be investigating different nucleophiles and dipoles that proved to be incompatible or efficient when reacted with our standard 1,1-cyclopropanediesters. To this end, we set out to first explore the reactivity of the cyclopropane hemimalonates with azides, as this reaction with the cyclopropanediesters 2-54 provided pyrrolidines 2-66 via a desirable fragmentation pathway (Scheme 2-18). We envisioned the unique activation of the hemimalonate cyclopropanes may give the desired ring opened product which could be used to make derivatives of \( \gamma \)-aminobutyric acid (GABA), an inhibitory neurotransmitter in the central nervous system.\(^{33}\)
2.4.1 Results and Discussion – Aminobutyric Acid Synthesis

(Note this project was initiated by Michael Emmett and the majority of the optimization was performed by him. The remainder of the project was completed with joint contributions from Dr. Emmett and myself. Division of labor has been indicated in the following schemes and tables.)

The primary investigation into this reaction employed sodium azide, cyclopropane 2-55a, and ammonium chloride in a solvent mixture of 2-methoxyethanol and water. These conditions were chosen due to their previous success in the azido epoxide opening reported by Bäckvall (Scheme 2-19A).34 The results from the initial reaction with cyclopropane hemimalonates were rather interesting for several distinct reasons. First, not only was the desired ring opened product isolated, but in contrast to the reaction with indoles, a tandem decarboxylation occurred in situ giving azidobutyric acid ester derivative 2-69a (Scheme 2-19B).35 In the current case, the decarboxylation is presumably due to the elevated reaction temperatures whereas the opening with indoles was performed at lower temperatures, thus suppressing the decarboxylation pathway. The second interesting finding from this initial reaction was that the reaction proceeded in an aqueous medium, a result not very commonly seen in cyclopropane chemistry. Finally, a third interesting finding was that the ring-opening proceeded once again without the use of a catalyst. A quick optimization of solvent/co-solvent ratios and reagent stoichiometry revealed the optimal conditions for the tandem ring-opening/decarboxylation to be 1.2 equivalents of sodium azide and 1.4 equivalents of ammonium chloride in a refluxing 10:1 mixture of a 2-methoxyethanol:water solution leading to an isolated 78% yield of 2-69a.

\[ R \text{CO}_2\text{Me} + \text{Na}_2\text{N}_3 \rightarrow R\text{N} = \text{C}(\text{H})\text{CO}_2\text{Me} \]
Scheme 2-19: Initial Reaction Between Hemimalonate Cyclopropane 2-55a and Sodium Azide

With optimal conditions in hand along with a variety of readily available cyclopropane hemimalonates, we next set out to determine generality of this method with different substituted cyclopropanes (Table 2-1). In general, the reaction proceeded effectively with aromatic or heteroaromatic substituents on the cyclopropane. Note, that electron withdrawing groups on the phenyl ring attenuated the reactivity and resulted in lower yields (adducts 2-69g and 2-69h). Electron donating groups had the opposite effect, producing adducts in excellent yields (adducts 2-69c and 2-69d). While a styrenyl substituent was well tolerated (adduct 2-69i), cyclopropanes where R = alkyl or R = H were unreactive under these conditions and starting material was recovered intact. It is of note that the optically enriched phenyl cyclopropane (S)-2-55a (90% ee) underwent this transformation with full retention of enantiopurity to give (S)-2-69a.
Interestingly, when vinyl cyclopropane hemimalonates were subjected to the reaction conditions, polymerization was not observed as in the previous indole opening method. However, instead of direct ring-opening, the use of vinyl cyclopropane resulted in an inseparable mixture of 2-69m and 2-70 (Scheme 2-20). 2-69m was achieved through the standard ring-opening method while 2-70 was formed via a $S_N'$ type opening event, a result that has never before been observed in previous reaction of dimethyl 2-vinylcyclopropane-1,1-dicarboxylate. All attempts to increase the formation of either product always resulted in equal amounts of the inseparable mixture.

Scheme 2-20: Vinyl Cyclopropane Opening with Azide

Finally, as proof that the azidoesters 2-69 could be viable precursors to GABA esters, a representative example (2-69a) was subjected to reduction under a balloon of hydrogen gas with catalysis by palladium on carbon. GABA ester 2-71 was produced in 93% yield
(Scheme 2-21). In addition to directed reduction with palladium on carbon, more mild Staudinger reduction conditions could be employed albeit a lower yield of the desired product was obtained.

Scheme 2-21: Synthesis of GABA Derivatives via an Azide Reduction

In summary, we have reported a technically simple and catalyst free method for the nucleophilic ring-opening of cyclopropane hemimalonates with azides. The products underwent concomitant decarboxylation to yield 4-azido carboxylic acid esters. Simple reduction yields γ-aminobutyric acid (GABA) methyl esters.

2.4.2 Synthesis of γ-Butanolides via Cyclopropane Hemimalonates

While trying to expand the substrate scope of our previously developed methodology to include substituted azides, we encountered an interesting result. When benzyl azide was used instead of sodium azide, a skeletal rearrangement of the cyclopropane hemimalonates was observed, giving butanolide 2-72a as the major product (Scheme 2-22). Due to the modest isolated yield of butanolide 2-73a and the lack of current methods to access simple butanolides in high yields from non-structurally biased cyclopropanes, we decided to explore this transformation fully.36

Scheme 2-22: Initial Synthesis of Butanolides

2.4.3 Results and Discussion - Optimization

The optimization process was initially directed to the formation of butanolide 2-72a. Attempts to optimize this cyclopropane reorganization proved quite fruitful allowing
access to butanolide 2-72a in an 82% yield upon heating in 2-methoxyethanol in the presence of a slight excess of ammonium chloride (Table 2-2 entry 1). Although the use of ammonium chloride gave a high yield of 2-72a, it also led to a trace amount of inseparable butanolide 2-73a, a product of a dealkoxycarbonylation. In hopes of preventing the formation of 2-73a, lower temperatures were evaluated; however, no reaction was observed (entry 2). While changing the solvent to 2-MeO(CH₂)₂OH, polar DMSO, and DMF resulted in slightly higher yields, inseparable 2-73a was still formed (entry 3, 4, and 6). In the absence of the salt, the reaction failed to proceed (entry 5). Less polar and non-polar solvent proved to be ineffective, recovering only starting material from the reaction (entry 7 and 8). Next, different additives were investigated. While a variety of salts promoted the reaction (entry 9-12), ammonium chloride salts seemed to be superior. It was never possible to obtain 2-72a as the sole product in our hands.

Table 2-2: Optimization for Butanolide 2-72a

<table>
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<tr>
<th>entry</th>
<th>additive (1.4 equiv)</th>
<th>solvent</th>
<th>temp (°C)</th>
<th>time (h)</th>
<th>product (%)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>NH₄Cl</td>
<td>2-MeO(CH₂)₂OH/H₂O</td>
<td>reflux</td>
<td>2</td>
<td>82% 2-72a, trace 2-73a</td>
</tr>
<tr>
<td>2</td>
<td>NH₄Cl</td>
<td>2-MeO(CH₂)₂OH/H₂O</td>
<td>rt</td>
<td>24</td>
<td>no rxn</td>
</tr>
<tr>
<td>3</td>
<td>NH₄Cl</td>
<td>2-MeO(CH₂)₂OH</td>
<td>reflux</td>
<td>2</td>
<td>84% 2-72a, trace 2-73b</td>
</tr>
<tr>
<td>4</td>
<td>NH₄Cl</td>
<td>DMSO</td>
<td>135</td>
<td>1</td>
<td>87% 2-72a, trace 2-72b</td>
</tr>
<tr>
<td>5</td>
<td>NH₄Cl</td>
<td>DMF</td>
<td>135</td>
<td>16</td>
<td>no rxn</td>
</tr>
<tr>
<td>6</td>
<td>NH₄Cl</td>
<td>DMSO</td>
<td>135</td>
<td>2</td>
<td>mixture a</td>
</tr>
<tr>
<td>7</td>
<td>NH₄Cl</td>
<td>Cl(CH₂)₂Cl</td>
<td>reflux</td>
<td>16</td>
<td>no rxn</td>
</tr>
<tr>
<td>8</td>
<td>NH₄Cl</td>
<td>Toluene</td>
<td>reflux</td>
<td>16</td>
<td>no rxn</td>
</tr>
<tr>
<td>9</td>
<td>NaCl</td>
<td>DMSO</td>
<td>135</td>
<td>1</td>
<td>mixture a</td>
</tr>
<tr>
<td>10</td>
<td>KCl</td>
<td>DMSO</td>
<td>135</td>
<td>1</td>
<td>mixture a</td>
</tr>
<tr>
<td>11</td>
<td>LiCl</td>
<td>DMSO</td>
<td>135</td>
<td>24</td>
<td>mixture a</td>
</tr>
<tr>
<td>12</td>
<td>Me₃N.HCl</td>
<td>DMSO</td>
<td>135</td>
<td>24</td>
<td>mixture a</td>
</tr>
</tbody>
</table>

a1:1 mixture of compounds 2-72a and 2-73a

Frustrated with the inability to form 2-72a cleanly, it was decided to focus on pushing the reaction toward the formation of 2-73a. (Table 2-3). Reaction conditions were modified
by using DMSO and H$_2$O, a solvent mixture commonly used in Krapcho
dealkoxycarbonylation reactions. The use of ammonium chloride in DMSO (entry 2)
yielded both 6 and 7 as an inseparable 1:1 mixture. The reaction temperature was
increased to reflux in DMSO/H$_2$O; however, this led to slow decomposition of the
starting material (entry 3). We next turned our attention to the use of sodium cyanide as
an additive due to its common use in Krapcho dealkoxycarbonylation reactions.
Unfortunately, when sodium cyanide was employed, no reaction occurred (entry 4). It
was at this point that a one-pot, two-step process was engaged, using ammonium chloride
to promote initial butanolide formation followed by the addition of sodium cyanide to
facilitate the dealkoxycarbonylation (entry 5). We were pleased to find that the two step
process worked, giving 2-73a in a 65% yield as the sole product. Interestingly, when
ammonium chloride and sodium cyanide were used in a non-sequential fashion, only
slow conversion to a mixture of 2-72a and 2-73a was observed (entry 6).

Spurred by this success (entry 5), we next examined the use of standard
dealkoxycarbonylation salt systems, which could also promote the butanolide formation.
The use of lithium chloride and trimethyl ammonium chloride together at 135 °C and
reflux both unfortunately led to a 1:1 mixture of 2-72a and 2-73a even after extended
reaction times (entry 7 and 8). In order to circumvent the problem with incomplete
conversion, microwave irradiation was employed. Gratifyingly, the reaction proceeded
well at 150 °C in both DMSO and DMF giving rise to adduct 2-73a in excellent yields at
71% and 82% respectively (entry 9 and 10). Finally, the cyclopropanediester was
subjected to the optimized reaction conditions of lithium chloride, and trimethyl
ammonium chloride in DMF at 150 °C. However, only a small amount of the desired
product could be isolated, along with a significant amount of starting material
decomposition (entry 11).
Table 2-3: Optimization for Butanolide 2-73a

<table>
<thead>
<tr>
<th>entry</th>
<th>additive (1.4 equiv)</th>
<th>solvent</th>
<th>temp (°C)</th>
<th>time (h)</th>
<th>product (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NH₄Cl</td>
<td>DMSO</td>
<td>135</td>
<td>1</td>
<td>87% 2-72a, trace 2-73a</td>
</tr>
<tr>
<td>2</td>
<td>NH₄Cl</td>
<td>DMSO/H₂O</td>
<td>135</td>
<td>1</td>
<td>mixture⁵</td>
</tr>
<tr>
<td>3</td>
<td>NH₄Cl</td>
<td>DMSO/H₂O</td>
<td>reflux</td>
<td>3</td>
<td>Slow decomp.</td>
</tr>
<tr>
<td>4</td>
<td>NaCN</td>
<td>DMSO</td>
<td>135</td>
<td>24</td>
<td>no rxn</td>
</tr>
<tr>
<td>5</td>
<td>NH₄Cl then NaCN</td>
<td>DMSO</td>
<td>135</td>
<td>1/6</td>
<td>65% 2-73a</td>
</tr>
<tr>
<td>6⁵</td>
<td>NH₄Cl/NaCN</td>
<td>DMSO</td>
<td>135</td>
<td>24</td>
<td>mixture⁵</td>
</tr>
<tr>
<td>7</td>
<td>LiCl/Me₃NCl</td>
<td>DMSO</td>
<td>135</td>
<td>24</td>
<td>mixture⁵</td>
</tr>
<tr>
<td>8</td>
<td>LiCl/Me₃NCl</td>
<td>DMSO</td>
<td>reflux</td>
<td>24</td>
<td>mixture⁵</td>
</tr>
<tr>
<td>9⁶</td>
<td>LiCl/Me₃NCl</td>
<td>DMSO</td>
<td>150</td>
<td>40</td>
<td>71% 2-73a</td>
</tr>
<tr>
<td>10⁷</td>
<td>LiCl/Me₃NCl</td>
<td>DMF</td>
<td>150</td>
<td>40</td>
<td>82% 2-73a</td>
</tr>
<tr>
<td>11⁷</td>
<td>LiCl/Me₃NCl</td>
<td>DMF</td>
<td>150</td>
<td>40</td>
<td>45% 2-73a</td>
</tr>
</tbody>
</table>

¹:1 mixture of compounds 2-72a and 2-73a. ²:reaction conditions gave a low yield of the mixture. ³:performed in microwave reactor. ⁴:the corresponding methyl diester was used.

2.4.4 Substrate Scope

With successful reaction conditions determined and a variety of cyclopropane hemimalonates readily available, we set forth to determine the scope of this transformation (Table 2-4). Both electron-donating and halogen substituted phenyl cyclopropanes effectively underwent the butanolide conversion in moderate to excellent yields (adducts 2-73b-e). In contrast, electron-withdrawing phenyl cyclopropanes decreased the reactivity of butanolide production, resulting in lower isolated yields (adducts 2-73f-g), a trend common to donor-acceptor cyclopropane reactivity. The heteroaromatic substituted cyclopropanes (3-N-tosylindolyl and 2-thienyl) underwent the transformation with great success leading to isolated yields of 85% and 74% of butanolides 2-73h, and 2-73i, respectively. Alkenyl substituted cyclopropanes were able to withstand the reaction conditions allowing access to the β-styrenyl substituted adduct 2-73j in 80% yield. Interestingly, when the vinyl cyclopropane hemimalonate was subjected to the reaction conditions, vinyl adduct 2-73k was isolated in 60% yield. The
lower yield of \(2-73k\) can be attributed to the highly reactive nature of this cyclopropane toward polymerization. Finally, alkyl substituted cyclopropanes were subjected to the reaction conditions (not in table); however, no product formation was achieved.

**Table 2-4: Butanolide Substrate Scope**

<table>
<thead>
<tr>
<th>2-73a 82%</th>
<th>2-73b 91%</th>
<th>2-73c 90%</th>
<th>2-73d 81%</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Structure" /></td>
<td><img src="image2.png" alt="Structure" /></td>
<td><img src="image3.png" alt="Structure" /></td>
<td><img src="image4.png" alt="Structure" /></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2-73e 74%</th>
<th>2-73f 52%</th>
<th>2-73g 39%</th>
<th>2-73h 85%</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image5.png" alt="Structure" /></td>
<td><img src="image6.png" alt="Structure" /></td>
<td><img src="image7.png" alt="Structure" /></td>
<td><img src="image8.png" alt="Structure" /></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2-73i 73%</th>
<th>2-73j 80%</th>
<th>2-73k 60%</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image9.png" alt="Structure" /></td>
<td><img src="image10.png" alt="Structure" /></td>
<td><img src="image11.png" alt="Structure" /></td>
</tr>
</tbody>
</table>

### 2.4.5 Reaction Mechanism

To shed light onto the mechanism, optically enriched phenyl cyclopropane \((-)-2-55a\) was subjected to the reaction conditions (Scheme 2-23). Smooth transformation led to an isolated 82% yield of enriched butanolide \((-)-2-73a\), with only slight erosion of enantiomeric excess (determined by a Mosher’s ester sequence). Optical rotation analyses of the product support the (S) isomer butanolide being isolated (when compared to the literature compound).\(^{37}\) This outcome suggests that the reaction occurs with *retention of*
stereochemistry, a result unusual in donor-acceptor cyclopropane chemistry. A proposed mechanism for this transformation can be seen in Scheme 24.

Scheme 2-23: Optically Enriched Example

There appeared to be two possible mechanistic explanations for this transformation (Scheme 2-24). First, solvolytic cleavage of the cyclopropane bond in 2-55a may occur to produce a benzylic carbocation and a malonate ion in an intimate ion pair 2-74. The cation moiety would undergo attack by the malonate in an O-alkylation event to produce the lactone 2-72a as the observed mixture of diastereomers. Subsequent Krapcho dealkoxycarbonylation would yield 2-73a. Alternatively, the cyclopropane 2-55a may undergo nucleophilic attack by chloride with inversion of configuration to yield the benzylic chloride 2-75. O-Alkylation of the putative malonic anion with a second inversion would yield lactone 2-72a, again as a mixture of diastereomers. Any small erosion of stereochemistry could be rationalized in the first case by bond rotation of the cationic moiety in 2-74 or a Finkelstein inversion of the chloride in 2-75. We are unsure at this time of the most likely scenario.
We next envisioned applying this method to the total synthesis of a commonly targeted butanolide natural product, (R)-dodecan-4-olide. Attempts to access the target molecule directly from cyclopropane proved unsuccessful due to the lack of reactivity typically displayed by alkyl substituted cyclopropanes (Scheme 2-25A). In our experience, the substrates which behave the best toward nucleophilic ring-opening (or annulations) are those bearing an aryl or vinyl group vicinal to the geminal diester (Scheme 2-25B). While simple alkyl moieties at this position are sometimes tolerated, the reaction times are longer and the yields are typically lower. Thus, in order to synthesize (R)-dodecan-4-olide, a new method to access alkyl substituted products from cyclopropane reactions was required.
2.4.6 Advancing the Reactivity of Dimethylcyclopropane-1,1-dicarboxylates via Cross Metathesis

One strategy to circumvent the lack of reactivity of cyclopropanes bearing a simple alkyl substituent is to employ the corresponding alkenyl cyclopropane 2-79 (Scheme 2-26) and to saturate the double bond in 2-80 after the cycloaddition to yield 2-81. This procedure would obviate the use of the less reactive cyclopropane 2-82. Cyclopropanes 2-79 bearing a variety of alkenyl groups may be difficult to prepare using typical cyclopropanation methods (Corey-Chaykovsky\(^40\) or carbenoid insertion\(^41\)). The simple parent 2-vinyl cyclopropane-1,1-dicarboxylate (R = H) is, on the other hand, very readily available in large quantities and in racemic\(^42\) or enantioenriched\(^43\) form. Herein, we present a divergent strategy involving cross-metathesis for the synthesis of a wide variety of dimethyl 2-alkenylcyclopropane-1,1-dicarboxylates from simple starting materials and their use in circumventing difficulties in cycloaddition chemistry.\(^44\)
Quick optimization of the cross metathesis reaction varying solvent, temperature, catalyst, and stoichiometry led to ideal conditions of 1 equivalent of cyclopropane 2-83, 1.4 equivalents of alkene 2-84, and 1 mol % Grubbs 2nd Generation Catalyst in refluxing dichloromethane. It should be noted that when lower temperatures were employed in hopes of increasing $E:Z$ selectivity, incomplete conversion was observed. With our best conditions in hand, we examined the scope of olefins that would undergo metathesis with dimethyl 2-vinylcyclopropane-1,1-dicarboxylate 2-83 (Table 2-5).

**Table 2-5: Cross Methathesis Scope**

We first studied the use of readily available alkyl substituted olefins (Table 2-5). Gratifyingly, 1-hexene, 1-octene, and 1-dodecene underwent the cross metathesis smoothly giving vinyl cyclopropanes 2-79a, 2-79b, and 2-79c in 67%, 74%, and 69%
yields respectively, with little or no observed dimerization products isolated. It is noteworthy to mention that with a much longer alkyl chain (product 2-79c), the E:Z ratio was reduced to 3:1. More functionalized olefins also underwent the metathesis efficiently, allowing access to 2-79d and 2-79e in good yields. In the case of 2-79e, a higher catalyst loading was required to drive the reaction to completion. Disubstituted alkyl olefins, including 2,4,4-trimethylpent-1-ene, were also subjected to the reaction conditions; however, only cyclopropane dimer was isolated.

We next examined the effects of styrenes as participants in the cross metathesis reaction. The reaction of dimethyl 2-vinylcyclopropane-1,1-dicarboxylate 2-83 and styrene proved to be difficult due to the increased reactivity of styrene toward dimerization as well as polymerization. After several attempts at modifying the reaction conditions, it was determined that the required metathesis product 2-79f could be isolated in good yield (75%) when 3 equivalents of styrene and 2.5 mol % of catalyst were used. The reaction had to be monitored scrupulously by TLC until the cyclopropane starting material was consumed, as styrene dimer would form rapidly, making purification extremely difficult. When p-methoxy styrene was subjected to the reaction conditions, the styrene dimer proved to be the major product allowing for isolation of 2-79g in 29% yield. Many modifications were made to increase the yield of 2-79g; however, the p-methoxy styrene proved to be too reactive and in all cases the dimer was the major isolated product. Finally, electron withdrawing p-nitro styrene underwent the metathesis with success giving 2-79h in 60% yield, a result that could be attributed to the lowered reactivity of the olefin toward dimerization under these conditions.

A variety of electron deficient α,β-unsaturated olefins were explored as cross-metathesis partners. The initial metathesis between 283 and acrolein led to the desired product 2-79i; however, the process occurred in a low yield of 33% with significant decomposition of acrolein. To avoid the decomposition of acrolein, (E)-but-2-enal was used as a substitute and 2-79i was isolated in 69% yield. Interestingly, methyl vinyl ketone underwent the reaction giving 2-79j as the sole product in 82% yield with no sign of starting material decomposition. Methyl acrylate also showed great success toward the metathesis allowing access to 2-79k in 92% yield.
With adducts such as 2-79 in hand, we set forth to compare the reactivity of these cyclopropanes against their saturated counterparts. In order to secure the corresponding alkyl substituted cyclopropanes 2-85a and 2-85b (Table 2-6), vinyl cyclopropanes 2-79a and 2-79f were reduced using mild hydrazine transfer hydrogenation conditions. To test the reactivity of each cyclopropane, a fundamental and well-studied nitrone cycloaddition reaction was performed (Table 2-6). Each cyclopropane was subjected to nitrone 2-86 and catalytic Yb(OTf)₃ in CH₂Cl₂ for an extended reaction period of 18 hours. Both alkenyl substituted cyclopropanes 2-79a and 2-79f gave excellent conversions to the corresponding tetrahydro-1,2-oxazines (2-87a and 2-87b) in 96% and 92% yields respectively. In contrast, saturated cyclopropane 2-85a produced tetrahydro-1,2-oxazines 2-87c in a 34% yield (based on recovered starting material) as an inseparable mixture of product and starting cyclopropane. Saturated cyclopropane 2-85b did not react under the standard reaction conditions and only starting material was recovered.

### Table 2-6: Comparative Nitrone Cycloaddition Reactions

<table>
<thead>
<tr>
<th>R</th>
<th>2-79 or 2-85</th>
<th>2-79a: R = Ph</th>
<th>2-79f: R = Ph</th>
<th>2-85a: R = Ph&lt;sub&gt;3&lt;/sub&gt;</th>
<th>2-85b: R = Ph&lt;sub&gt;3&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeO₂C⁺CO₂Me</td>
<td>2-86</td>
<td>2-87a-d</td>
<td>Tol·N·O</td>
<td>Tol·N·O</td>
<td>Tol·N·O</td>
</tr>
<tr>
<td>Ph Ph Ph</td>
<td></td>
<td>2-87a: 95% (6:1 E:Z)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ph Ph Ph</td>
<td>2-87c: 34%&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ph Ph Ph</td>
<td>2-87b: 92% (E only)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ph Ph Ph</td>
<td>2-87d: no nm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated as an inseparable mixture of product and cyclopropane starting material.

Finally, the tetrahydro-1,2-oxazines were reduced in order to access the alkyl substituted derivative. Due to the sensitivity of the tetrahydro-1,2-oxazines N-O bond, a mild
tosylhydrazine/sodium acetate reduction was utilized (Scheme 2-27). The reductions of 2-87a and 2-87b were successful, leading to isolations of tetrahydro-1,2-oxazines 2-87c and 2-87d in 91% and 98% yields respectively. Due to the observed success of this study, in theory, this method could allow access to a range of alkyl substituted substrates which would be more difficult to access via other means.

Scheme 2-27: Vinyl-tetrahydro-1,2-oxazine reduction

2.4.7 Synthesis of (R)-Dodecan-4-olide

To test the generality of the cross metathesis method and the utility of the butanolide synthesis, the natural lactone (R)-dodecan-4-olide was targeted for total synthesis (Scheme 2-28). Readily available dimethyl ester vinyl cyclopropane (-)-2-83 was subjected to cross metathesis conditions with oct-1-ene in the presence of Grubbs 2nd generation ruthenium catalyst (5 mol %) to access the crude octenyl cyclopropane. Following monosaponification, cyclopropane hemimalonate 2-55m was isolated in an 87% yield over two steps. Hemimalonate 2-55m was then exposed to the standard butanolide synthesis conditions and alkenyl butanolide 2-88 was isolated in 78% yield. Reduction of the π-system proved to be the most difficult step in the synthesis, resulting in over reduction of the lactone ring under standard conditions including hydrogenation over Pd on carbon or PtO₂. The π-system reduction of butanolide 2-88 was finally achieved using tosylhydrazide as a diimide source allowing access to (R)-dodecan-4-olide 2-33 in 98% yield and 94% ee (determined by a Mosher’s ester sequence).
Scheme 2-28: Total Synthesis of Dodecanolide

2.5 Summary and Future Outlook

In summary, we have developed two new methods for the synthesis of \( \gamma \)-aminobutyric ester and \( \gamma \)-butanolides from the unique reactivity of cyclopropane hemimalonates. Both methods are catalyst free and work well with a variety of substituted cyclopropanes. Additionally, the application of the \( \gamma \)-butanolides method in conjunction with a new cross metathesis method has resulted in the 4 step 67% overall yield synthesis of naturally occurring (R)-dodecan-4-olide.

It is envisioned that the future direction of the cyclopropane hemimalonates will focus on tandem annulation/decarboxylation reactions (Scheme 2-29). This focus will allow quick access to hetero and carbocyclic compounds with a functional ester handle 2-89; this would be an invaluable result as many previous routes to target molecules utilizing the 1,1-cyclopropanediester require a subsequent decarboxylation step.

Scheme 2-29: Possible Future Direction of this Chemistry
2.6 Experimental

General Considerations

Infrared spectra were obtained as thin films on NaCl plates using a Bruker Vector 33 FT-IR instrument. NMR experiments were performed on Varian Mercury 400, Varian Inova 600 and Inova 400 instruments and samples were obtained in CDCl₃ (referenced to 7.26 ppm for ¹H and 77.0 ppm for ¹³C). ¹⁹F spectra were externally referenced to neat trifluorotoluene (referenced to -63.9 ppm). Coupling constants (J) are in Hz. The multiplicities of the signals are described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, sept = septuplet, m = multiplet, br = broad. High resolution mass spectra (HRMS) were obtained on a Finnigan MAT 8200 spectrometer at 70 eV. Optical rotations were recorded in cells of 10 cm path length using a Perkin-Elmer 241 digital polarimeter.

All reagents and solvents were used as purchased from Aldrich, Strem, Caledon or VWR. Reaction progress was followed by thin layer chromatography (TLC) (EM Science, silica gel 60 F₂₅₄) visualizing with UV light, and the plates developed using acidic anisaldehyde. Flash chromatography was performed using silica gel purchased from Silicycle Chemical Division Inc. (230-400 mesh).

General Experimental Procedure for the synthesis of γ-aminobutyric esters: Sodium azide (0.55 mmol, 1.2 equiv.) and ammonium chloride (1.4 equiv.) were added to a solution of cyclopropane hemimalonate (1.0 equiv.) in 2-methoxyethanol:water (5.0 mL:0.5 mL). The mixture was stirred at reflux (125 °C) until the reaction was complete (as determined by TLC analysis). The reaction was then quenched with H₂O extracted 3 times with ether. The organic was dried and the solvent was removed. The residue was purified by flash chromatography (EtOAc:Hexanes) to yield the desired product 2-69a-l.

γ-Aminobutyric ester 2-69c was prepared using general experimental procedure. Reagents employed: 2-
(benzo[d][1,3]dioxol-5-yl)-1-(methoxycarbonyl)cyclopropanecarboxylic acid (2-55c) (97 mg, 0.37 mmol), sodium azide (29 mg, 0.44 mmol), ammonium chloride (27 mg, 0.51 mmol), and 2-methoxyethanol:water (5.0 mL:0.5 mL). Yielded 2-69c as a clear oil, 87% (84 mg, 0.32 mmol). R_f = 0.58, 30% EtOAc in hexanes; ^1H-NMR (400 MHz, CDCl3): δ = 6.80 (d, J = 1.6 Hz, 1H), 6.78 (s, 1H) 6.76 (d, J = 1.6 Hz, 1H) 5.97 (s, 2H), 4.44 (dd, J = 7.8, 6.25 Hz, 1H), 3.66 (s, 3H), 3.76 (t, J = 7.4, 2H), 2.11-1.94 (m, 2H); ^13C NMR (100 MHz, CDCl3) δ = 173.1, 148.2, 147.7, 132.7, 120.7, 108.3, 106.9, 101.2, 65.1, 51.7, 31.3, 30.5; IR (thin film): 3459, 3323, 2953, 2101, 1739, 1505, 1490, 1443, 1342, 1328, 1252, 1170, 1102, 1042, 933, 863, 813, 661; HRMS calc’d for C_{12}H_{13}N_{3}O_{4} = 263.0906, found = 263.0905.

γ-Aminobutyric ester 2-69d was prepared using general experimental procedure. Reagents employed: 1-(methoxycarbonyl)-2-(4-methoxyphenyl)cyclopropanecarboxylic acid (2-55d) (100 mg, 0.400 mmol), sodium azide (31 mg, 0.48 mmol), ammonium chloride (30 mg, 0.56 mmol), and 2-methoxyethanol:water (5.0 mL:0.5 mL). Yielded 2-69d as a clear oil, 95% (95 mg, 0.38 mmol). R_f = 0.54, 30% EtOAc in hexanes; ^1H-NMR (400 MHz, CDCl3): δ = 7.25-7.21 and 6.92-6.89 (m, AA’BB’, 4H), 4.47 (dd, J = 7.8, 6.3 Hz, 1H), 3.80 (s, 3H), 3.66 (s, 3H), 2.36 (t, J = 7.4, 2H), 2.15-1.98 (m, 2H); ^13C NMR (100 MHz, CDCl3) δ = 173.1, 159.6, 130.8, 128.1, 114.2, 64.8, 55.2, 51.6, 31.2, 30.5; IR (thin film): 3451, 3319, 2953, 2839, 2482, 2101, 1739, 1611, 1529, 1438, 1245, 1174, 1034, 832, 545; HRMS (M-N_{2}) calc’d for C_{12}H_{15}N_{3}O_{3} = 221.1052, found = 221.1050.

γ-Aminobutyric ester 2-69e was prepared using general experimental procedure. Reagents employed: 2-(4-bromophenyl)-1-(methoxycarbonyl)cyclopropanecarboxylic acid (2-55e) (95 mg, 0.32 mmol), sodium azide (25 mg, 0.38 mmol), ammonium chloride (24 mg, 0.45 mmol), and 2-methoxyethanol:water (4.0 mL:0.4 mL). Yielded 2-69e as a clear oil, 62% (51 mg, 0.20
mmol). Rf = 0.53, 30% EtOAc in hexanes; $^1$H-NMR (400 MHz, CDCl3): δ = 7.53-7.50 and 7.20-7.17 (m, AA’BB’, 4H), 4.52 (dd, J = 8.2, 6.3 Hz, 1H), 3.66 (s, 3H), 2.44-2.31 (m, 2H), 2.12-1.97 (m, 2H); $^{13}$C NMR (100 MHz, CDCl3) δ = 173.0, 183.0, 132.0, 128.5, 122.4, 64.6, 51.7, 31.3, 30.3; IR (thin film): 3455, 3319, 2951, 2101, 1737, 1489, 1437, 1250, 1201, 1171, 1044, 1011, 822, 532; HRMS (M+1) calc’d for C$_{11}$H$_{12}$BrN$_3$O$_2$ = 298.0186, found = 298.0185.

\[ \gamma \text{-Aminobutyric ester 2-69f was prepared using general experimental procedure. Reagents employed: 2-}(4\text{-chlorophenyl})-1-\text{(methoxycarbonyl)cyclopropanecarboxylic acid (2-55f)} (105 mg, 0.410 mmol), sodium azide (32 mg, 0.50 mmol), ammonium chloride (30 mg, 0.58 mmol), and 2-methoxyethanol:water (5.0 mL:0.5 mL). Yielded 2-69f as a clear oil, 60% (62 mg, 0.25 mmol). Rf = 0.56, 30% EtOAc in hexanes; $^1$H-NMR (400 MHz, CDCl3): δ = 7.38-7.35 and 7.26-7.23 (m, AA’BB’, 4H), 4.53 (dd, J = 7.8, 6.3 Hz, 1H), 3.67 (s, 3H), 2.44-2.32 (m, 2H), 2.13-1.98 (m, 2H); $^{13}$C NMR (100 MHz, CDCl3) δ = 173.0, 137.5, 134.2, 129.1, 128.2, 64.5, 51.7, 31.3, 30.3; IR (thin film): 2952, 2101, 1739, 1493, 1437, 1325, 1249, 1202, 1171, 1092, 1015, 826, 534; HRMS (M+1) calc’d for C$_{11}$H$_{12}$ClN$_3$O$_2$ = 254.0691, found = 254.0710.

\[ \gamma \text{-Aminobutyric ester 2-69i was prepared using general experimental procedure. Reagents employed: (E)-1-}(\text{methoxycarbonyl})-2-\text{(4-styrylphenyl)cyclopropanecarboxylic acid (2-55i)} (101 mg, 0.410 mmol), sodium azide (32 mg, 0.49 mmol), ammonium chloride (30 mg, 0.57 mmol), and 2-methoxyethanol:water (5.0 mL:0.5 mL). Yielded 2-69i as a clear oil, 78% (78 mg, 0.32 mmol). Rf = 0.50, 30% EtOAc in hexanes; $^1$H-NMR (400 MHz, CDCl3): δ = 7.37 (d, J = 7.4 Hz, 2H), 7.31 (t, J = 7.4 Hz, 2H), 7.26-7.22 (m, 1H), 6.60 (d, J = 15.6 Hz, 1H), 6.06 (dd, J = 16.0, 8.2 Hz, 1H) 4.08 (dd, J = 14.9, 7.4 Hz, 1H), 3.64 (s, 3H), 2.41 (t, J = 7.4 Hz, 2H), 1.94-1.88 (m, 2H); $^{13}$C NMR (100 MHz, CDCl3) δ = 173.2, 135.7, 534; IR (thin film): 2952, 2101, 1739, 1493, 1437, 1325, 1249, 1202, 1171, 1092, 1015, 826, 534; HRMS (M+1) calc’d for C$_{11}$H$_{12}$ClN$_3$O$_2$ = 254.0691, found = 254.0710.
\( \gamma \)-Aminobutyric ester 2-69l was prepared using general experimental procedure. Reagents employed: 2-(4-(furan-3-yl)phenyl)-1-(methoxycarbonyl)cyclopropanecarboxylic acid (2-55l) (126 mg, 0.600 mmol), sodium azide (47 mg, 0.72 mmol), ammonium chloride (45 mg, 0.84 mmol), and 2-methoxyethanol:water (5.0 mL:0.5 mL). Yielded 2-69l as a clear oil, 63% (79 mg, 0.38 mmol). \( R_f = 0.54, 30\% \text{ EtOAc in hexanes; } \) \( ^1\)H-NMR (400 MHz, CDCl₃): \( \delta = 7.42 (d, J = 1 \text{ Hz}, 1H), 6.36 (dd, J = 3.1, 1.8 \text{ Hz}, 1H), 6.33 (d, J = 3.1 \text{ Hz}, 1H), 4.53 (dd, 7.2, 7.2 Hz, 1H), 3.68 (s, 3H), 2.45-2.41 (m, 2H), 2.25-3.12 (m, 2H); \( ^{13}C\) NMR (100 MHz, CDCl₃) \( \delta = 172.9, 151.5, 143.0, 110.2, 108.1, 57.9, 51.7, 30.2, 27.8; \) IR (thin film): 2954, 2102, 1736, 1438, 1338, 1239, 1210, 1173, 1013, 745; HRMS (M-N₂) calc’d for \( \text{C}_{9}\text{H}_{11}\text{N}_3\text{O}_3 = 181.0739, \) found = 181.0739.

**General Experimental Procedure for the Synthesis of \( \gamma \)-Substituted Butanolides:**
Cyclopropane hemimalonates (1 equivalent), LiCl (2 equivalent), and Me₃NHCl (1.4 equivalent) were added to a microwave vial and dissolved in DMF. The vial was sealed and heated for 40 minutes at 150 °C. After the required reaction time the reaction was quenched with H₂O and extracted 3 times with ether. The organic layer was dried and the solvent was removed. The residue was purified by flash chromatography (EtOAc/Hexanes) to yield the desired butanolide 2-73a-k.

Lactone 2-73a was prepared using general experimental procedure. Reagents employed: (2S)-1-(methoxycarbonyl)-2-phenylcyclopropanecarboxylic acid 2-55a (75 mg, 0.34 mmol), LiCl (29 mg, 0.68 mmol), Me₃NHCl (46 mg, 0.48 mmol), and DMF (4 mL). Yielded 2-73a as a clear oil, 82% (45 mg, 0.28 mmol). Spectral properties are identical to those previously reported. 48 80% ee calculated from a
Mosher’s ester via the following procedure: Lactone **2-73a** was reduced with excess LiAlH₄ in THF giving the the crude diol. The crude diol was dissolved in dichloromethane and TBSCl (approx. 1 equiv) and NEt₃ (approx. 1 equiv) were added. Upon completion water was added and the organic was extracted with dichloromethane. The crude protected material was subjected to a DCC coupling with Mosher’s acid to give the desired Mosher’s ester upon purification by flash chromatography. ¹⁹F-NMR (376 MHz, CDCl₃): δ = -71.31 (s, 90), -71.59 (s, 10).

Lactone **2-73b** was prepared using general experimental procedure. Reagents employed: 1-(methoxycarbonyl)-2-(4-methoxyphenyl)cyclopropanecarboxylic acid **2-55b** (77 mg, 0.31 mmol), LiCl (26 mg, 0.61 mmol), Me₃N.HCl (41 mg, 0.43 mmol), and DMF (4 mL). Yielded **2-73b** as a yellow oil, 91% (54 mg, 0.28 mmol). Rₓ = 0.25, 30% EtOAc/hexanes; ¹H-NMR (400 MHz, CDCl₃): δ = 7.26 (d, J = 9.0 Hz, 2H), 6.90 (d, J = 8.6 Hz, 2H), 5.45 (dd, J = 8.6, 6.2 Hz, 1H), 3.80 (s, 3H), 2.68-2.56 (m, 3H), 2.26-2.14 (m, 1H). ¹³C-NMR (100 MHz, CDCl₃): δ = 176.9, 159.7, 131.1, 126.9, 114.0, 81.3, 55.3, 30.8, 29.2. IR (thin film, cm⁻¹): 3129, 1771, 1517, 1400, 1250, 1175, 1141, 1112, 1032. HRMS calc’d for C₁₁H₁₂O₃ = 192.0786, found = 192.0783.

Lactone **2-73c** was prepared using general experimental procedure. Reagents employed: 2-(benzo[d][1,3]dioxol-5-yl)-1-(methoxycarbonyl)cyclopropanecarboxylic acid **2-55c** (78 mg, 0.30 mmol), LiCl (25 mg, 0.59 mmol), Me₃N.HCl (40 mg, 0.42 mmol), and DMF (4 mL). Yielded **2-73c** as a brown oil, 90% (55 mg, 0.27 mmol). Rₓ = 0.22, 30% EtOAc/hexanes; ¹H-NMR (400 MHz, CDCl₃): δ = 6.81-6.78 (m, 3H), 5.96 (s, 2H), 5.40 (dd, J = 8.6, 6.2 Hz, 1H), 2.66-2.54 (m, 3H), 2.22-2.09 (m, 1H). ¹³C-NMR (100 MHz, CDCl₃): δ = 176.7, 148.0, 147.7, 133.0, 119.1, 108.2, 105.9, 101.2, 81.2, 30.9, 29.0. IR (thin film, cm⁻¹): 3135, 2992, 1771, 1505, 1446, 1400, 1245, 1141, 1037. HRMS calc’d for C₁₁H₁₀O₄ = 206.0579, found = 206.0575.
Lactone **2-73d** was prepared using general experimental procedure. Reagents employed: 2-(4-chlorophenyl)-1-(methoxycarbonyl)cyclopropanecarboxylic acid **2-55d** (75 mg, 0.29 mmol), LiCl (25 mg, 0.59 mmol), Me₃N·HCl (39 mg, 0.41 mmol), and DMF (4 mL). Yielded **2-73d** as a yellow oil, 81% (47 mg, 0.24 mmol). Rf = 0.16, 30% EtOAc/hexanes; ¹H-NMR (400 MHz, CDCl₃): δ = 7.36 (d, J = 8.6 Hz, 2H), 7.27 (d, J = 8.2 Hz, 2H), 5.48 (dd, J = 8.6, 6.2 Hz, 1H), 2.70-2.61 (m, 3H), 2.20-2.07 (m, 1H). ¹³C-NMR (100 MHz, CDCl₃): δ = 176.5, 137.8, 134.2, 128.9, 126.6, 80.4, 30.9, 28.8. IR (thin film, cm⁻¹): 3135, 2924, 1773, 1402, 1173, 1138, 1091, 1035. HRMS calc’d for C₁₀H₉ClO₂ = 196.0291, found = 196.0299.

Lactone **2-73e** was prepared using general experimental procedure. Reagents employed: 2-(4-bromophenyl)-1-(methoxycarbonyl)cyclopropanecarboxylic acid **2-55e** (76 mg, 0.25 mmol), LiCl (22 mg, 0.52 mmol), Me₃N·HCl (35 mg, 0.37 mmol), and DMF (4 mL). Yielded **2-73e** as a yellow oil, 74% (45 mg, 0.19 mmol). Rf = 0.29, 30% EtOAc/hexanes; ¹H-NMR (400 MHz, CDCl₃): δ = 7.51 (d, J = 8.6 Hz, 2H), 7.20 (d, J = 8.6 Hz, 2H), 5.46 (dd, J = 8.2, 6.2 Hz, 1H), 2.71-2.61 (m, 3H), 2.21-2.07 (m, 1H). ¹³C-NMR (100 MHz, CDCl₃): δ = 176.5, 138.4, 131.9, 126.9, 122.3, 80.4, 30.9, 28.8. IR (thin film, cm⁻¹): 3136, 2923, 1781, 1402, 1173, 1140, 1035, 1010. HRMS calc’d for C₁₀H₉BrO₂ = 239.9786, found = 239.9794.

Lactone **2-73f** was prepared using general experimental procedure. Reagents employed: 2-(4-cyanophenyl)-1-(methoxycarbonyl)cyclopropanecarboxylic acid **2-55f** (75 mg, 0.31 mmol), LiCl (26 mg, 0.61 mmol), Me₃N·HCl (41 mg, 0.43 mmol), and DMF (4 mL). Yielded **2-73f** as a clear oil, 52% (30 g, 0.16
mmol). \( R_f = 0.11 \), 30\% EtOAc/hexanes; \(^1\)H-NMR (600 MHz, CDCl\(_3\)): \( \delta = 7.69 \) (d, \( J = 8.8 \) Hz, 2H), 7.45 (d, \( J = 8.2 \) Hz, 2H), 5.55-5.51 (m, 1H), 2.76-2.60 (m, 3H), 2.16-2.07 (m, 1H). \(^{13}\)C-NMR (150 MHz, CDCl\(_3\)): \( \delta = 176.0, 144.7, 132.6, 125.8, 118.3, 112.3, 79.8, 30.8, 28.6 \). IR (thin film, cm\(^{-1}\)): 2954, 2924, 1772, 1657, 1174, 1019, 525. HRMS calc’d for C\(_{11}\)H\(_9\)NO\(_2\) = 187.0633, found = 187.0639.

Lactone 2-73\(g\) was prepared using general experimental procedure. Reagents employed: 1-(methoxycarbonyl)-2-(4-(methoxycarbonyl)phenyl)cyclopropanecarboxylic acid 2-55\(g\) (75 mg, 0.27 mmol), LiCl (23 mg, 0.54 mmol), Me\(_3\)N.HCl (36 mg, 0.38 mmol), and DMF (4 mL). Yielded 2-73\(g\) as a clear oil, 39\% (23 mg, 0.10 mmol). \( R_f = 0.16 \), 30\% EtOAc/hexanes; \(^1\)H-NMR (400 MHz, CDCl\(_3\)): \( \delta = 8.06 \) (d, \( J = 8.6 \) Hz, 2H), 7.40 (d, \( J = 8.2 \) Hz, 2H), 5.59-5.53 (m, 1H), 3.92 (s, 3H), 2.76-2.63 (m, 3H), 2.21-2.12 (m, 1H). \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)): \( \delta = 176.5, 166.5, 144.4, 130.2, 130.1, 125.0, 80.4, 52.2, 30.9, 28.7 \). IR (thin film, cm\(^{-1}\)): 2998, 1785, 1721, 1613, 1436, 1283, 1178, 1142, 1113, 1019, 940, 768, 706. HRMS calc’d for C\(_{12}\)H\(_{12}\)O\(_4\) = 220.0736, found = 220.0720.

Lactone 2-73\(h\) was prepared using general experimental procedure. Reagents employed: 1-(methoxycarbonyl)-2-(1-tosylindol-3-yl)cyclopropanecarboxylic acid 2-55\(h\) (82 mg, 0.20 mmol), LiCl (17 mg, 0.40 mmol), Me\(_3\)N.HCl (27 mg, 0.28 mmol), and DMF (4 mL). Yielded 2-73\(h\) as a yellow oil, 85\% (60 mg, 0.17 mmol). \( R_f = 0.24 \), 30\% EtOAc/hexanes; \(^1\)H-NMR (400 MHz, CDCl\(_3\)): \( \delta = 7.99 \) (d, \( J = 8.2 \) Hz, 1H), 7.77 (d, \( J = 8.6 \) Hz, 2H), 7.59 (s, 1H), 7.52 (d, \( J = 7.8 \) Hz, 1H), 7.35 (dt, \( J = 8.6, 1.2 \) Hz, 1H), 7.28-7.20 (m, 3H), 5.75-5.69 (m, 1H), 2.72-2.64 (m, 3H), 2.47-2.35 (m, 1H), 2.33 (s, 3H). \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)): \( \delta = 176.4, 145.3, 135.3, 134.9, 130.0, 128.0, 126.8, 125.3, 123.4, 123.0, 120.5, 119.8, 113.7, 75.4, 28.5, 28.2, 21.5 \). IR (thin film, cm\(^{-1}\)): 3115, 1775, 1447, 1400, 1371, 1174, 1124, 1100, 1036. HRMS calc’d for C\(_{19}\)H\(_{17}\)NO\(_4\)S = 355.0878, found = 355.0879.
Lactone 2-73i was prepared using general experimental procedure. Reagents employed: 1-(methoxycarbonyl)-2-(thiophene-2-yl)cyclopropanecarboxylic acid 2-55i (68 mg, 0.30 mmol), LiCl (25 mg, 0.59 mmol), Me₃N.HCl (40 mg, 0.42 mmol), and DMF (4 mL). Yielded 2-73i as an orange oil, 74% (37 mg, 0.22 mmol). R_f = 0.24, 30% EtOAc/hexanes; ¹H-NMR (400 MHz, CDCl₃): δ = 7.34 (dd, J = 5.1, 1.6 Hz, 1H), 7.09 (d, J = 3.5 Hz, 1H), 7.00 (dd, J = 4.7, 3.5 Hz, 1H), 5.76-5.69 (m, 1H), 2.74-2.60 (m, 3H), 2.45-2.31 (m, 1H). ¹³C-NMR (100 MHz, CDCl₃): δ = 176.1, 141.7, 126.9, 126.2, 125.9, 77.3, 30.7, 28.9. IR (thin film, cm⁻¹): 3108, 2923, 2851, 1777, 1401, 1172, 1135, 1015, 921. HRMS calc’d for C₈H₈O₂S = 168.0245, found = 168.0243.

Lactone 2-73j was prepared using general experimental procedure. Reagents employed: (E)-1-(methoxycarbonyl)-2-styrylcyclopropanecarboxylic acid 2-55j (98 mg, 0.40 mmol), LiCl (34 mg, 0.80 mmol), Me₃N.HCl (53 mg, 0.56 mmol), and DMF (4 mL). Yielded 2-73j as a clear oil, 80% (60 mg, 0.32 mmol). R_f = 0.28, 30% EtOAc/hexanes; ¹H-NMR (600 MHz, CDCl₃): δ = 7.39 (d, J = 7.6 Hz, 2H), 7.34 (t, J = 7.6 Hz, 2H), 7.29 (d, J = 7.0 Hz, 1H), 6.68 (d, J = 15.8 Hz, 1H), 6.20 (dd, J = 15.8, 7.0 Hz, 1H), 5.13-5.09 (m, 1H), 2.62-2.57 (m, 2H), 2.51-2.44 (m, 1H), 2.13-2.06 (m, 1H). ¹³C-NMR (100 MHz, CDCl₃): δ = 176.8, 135.6, 132.8, 128.6, 128.3, 126.7, 126.4, 80.6, 28.8, 28.5. IR (thin film, cm⁻¹): 2924, 1768, 1073, 1032, 974, 758. HRMS calc’d for C₁₂H₁₂O₂ = 188.0837, found = 188.0837.

Lactone 2-73k was prepared using general experimental procedure. Reagents employed: 1-(methoxycarbonyl)-2-vinylcyclopropanecarboxylic acid 2-55k (86 mg, 0.51 mmol), LiCl (43 mg, 1.01 mmol), Me₃N.HCl (68 mg, 0.71 mmol), and DMF (4 mL). Yielded 2-73k as a clear oil, 60% (34 mg, 0.30 mmol). R_f = 0.33, 30% EtOAc/hexanes; ¹H-NMR (400 MHz, CDCl₃): δ = 5.87 (ddd, J = 16.8, 10.5 Hz, 5.9 Hz, 1H), 5.36 (dt, J = 17.2, 1.2 Hz, 1H), 5.25 (dt, J = 10.5, 1.2 Hz, 1H), 4.96-4.90 (m, 1H),
2.56-2.50 (m, 2H), 2.41 (dt, J = 12.5, 6.6 Hz, 1H), 2.04-1.94 (m, 1H). $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ = 176.9, 135.5, 117.4, 80.4, 28.2, 28.2. IR (thin film, cm$^{-1}$): 2957, 2921, 2851, 1772, 1734, 1558, 1457. HRMS calc’d for C$_6$H$_8$O$_2$ = 112.0524, found = 112.0520

**Synthesis of Cyclopropane Hemimalonate 2-55m for Dodecanolide:** Vinyl cyclopropane (−)-2-83 (250 mg, 1.36 mmol) and 1-octene (0.26 mL, 1.6 mmol) were dissolved in DCM (20 mL) and the reaction vessel was purged with argon. Grubbs II (56 mg, 0.068 mmol) was added as one portion. The purple solution was heated to reflux for 3 hours. Florisil® was added and the mixture was stirred for another 20 minutes. The reaction mixture was filtered, concentrated and flushed through a plug of silica. The crude octenyl cyclopropane was taken up in MeOH (5 mL) and treated with 1.7 M NaOH (1.6 mL, 2.7 mmol). The reaction was stirred at room temperature for 2.5 hours, and then H$_2$O was added. The organic was extracted with EtOAc, and the aqueous layer was acidified with 5% HCl. The aqueous was extracted 3 times with EtOAc to obtain the product. The organic was dried with MgSO$_4$, filtered and concentrated to obtain 2-55m (300 mg, 1.18 mmol) in an 87% yield over the two steps. $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ = 5.82 (dt, J = 15.2, 7.0 Hz, 1H), 5.25 (dd, 15.2, 8.6 Hz, 1H), 3.81 (s, 3H), 2.73 (q, 8.6 Hz, 1H), 2.20-1.90 (m, 4H), 1.36-1.21 (m, 9H), 0.87 (t, 7.0 Hz, 3H). $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ = 174.2, 170.5, 138.3, 123.4, 53.0, 40.3, 33.2, 32.6, 31.6, 29.7, 28.9, 28.7, 23.8, 22.6. IR (thin film, cm$^{-1}$): 2925, 2855, 1772, 1734, 1456, 1436, 1338, 1262, 1162, 967. HRMS calc’d for C$_{14}$H$_{22}$O$_4$ = 254.1518, found = 254.1524. (Isolated in 7:1 cis:trans)

**Synthesis of Lactone 2-88 for Dodecanolide:** Lactone 2-88 was prepared using general experimental procedure. Reagents employed: 2-55m (130 mg, 0.510 mmol), LiCl (43 mg, 1.02 mmol), Me$_3$N.HCl (68 mg, 0.71 mmol), and DMF (4 mL). Yielded 2-88 as a clear oil, 78% (78 mg, 0.40 mmol). $R_f$ = 0.48, 30% EtOAc/hexanes; $^1$H-NMR
(400 MHz, CDCl₃): δ = 5.80 (dt, J = 15.3, 7.0 Hz, 1H), 5.48 (dd, J = 15.3, 7.0 Hz, 1H), 4.88 (dd, J = 7.6, 7.0 Hz, 1H), 2.55-2.50 (m, 2H), 2.39-2.31 (m, 1H), 2.08-2.03 (m, 2H), 2.01-1.92 (m, 1H), 1.41-1.34 (m, 2H), 1.32-1.22 (m, 6H), 0.87 (t, J = 7.0 Hz, 3H). ¹³C-NMR (100 MHz, CDCl₃): δ = 177.0, 135.8, 127.3, 110.0, 81.1, 32.1, 31.6, 28.8, 28.8, 28.7, 22.6, 14.1. IR (thin film, cm⁻¹): 2926, 2855, 1773, 1734, 1457, 1176, 969. HRMS calc’d for C₁₂H₂₀O₂ = 196.1463, found = 196.1460. (Isolated in 7:1 cis:trans)

Reduction of Olefin 2-33 for Dodecanolide: Lactone 2-88 (175 mg, 0.892 mmol) was dissolved in THF:H₂O (8mL:8mL). Tosylhydrazine (1660 mg, 8.910 mmol) and sodium acetate (951 mg, 11.6 mmol) were added and the reaction mixture was heated to reflux for 24 hours. Water was added to quench the reaction and the aqueous was extracted with ether 4 times. The organic was dried with MgSO₄, filtered and subjected to column chromatography. The product 2-33 (173 mg, 0.867 mmol) was isolated in a 98 % yield. Rf = 0.49, 30% EtOAc/hexanes; ¹H-NMR (600 MHz, CDCl₃): δ = 4.51-4.44 (m, 1H), 2.56-2.48 (m, 2H), 2.35-2.26 (m, 1H), 1.77-1.70 (m, 1H), 1.62-1.55 (m, 1H), 1.49-1.41 (m, 1H), 1.40-1.22 (m, 12H), 0.88 (t, 7.0 Hz, 3H). ¹³C-NMR (150 MHz, CDCl₃): δ = 177.3, 81.0, 35.6, 31.8, 29.4, 29.3, 29.2, 28.9, 28.0, 25.2, 22.6, 14.1. IR (thin film, cm⁻¹): 2926, 2855, 1773, 1458, 1352, 1179, 1017, 914. HRMS calc’d for C₁₂H₂₂O₂ = 199.1698, found = 199.1703 (M + H). 94% ee calculated from Mosher’s ester. ¹⁹F-NMR (376 MHz, CDCl₃): δ = -71.29 (s, 97), -71.36 (s, 3).

General Experimental Procedure for the Cross-Metathesis Synthesis of Substituted Vinyl Cyclopropane: Dimethyl 2-vinylcyclopropane-1,1-dicarboxylate (1 equivalent) and olefin (1.4 - 5 equivalent) were dissolved in anhydrous dichloromethane. Grubbs 2nd generation catalyst (G2) (0.01 equivalent) was then added and a reflux condenser was attached. The reaction vessel was then purged with argon and the reaction brought to reflux. Upon completion by TLC analysis the solvent was removed and the residue was purified by flash chromatography (EtOAc/Hexanes) to yield the desired cyclopropanes 2-79a-k.
Cyclopropane 2-79a was prepared using general experimental procedure. Reagents employed: dimethyl 2-vinylcyclopropane-1,1-dicarboxylate 2-83 (147 mg, 0.798 mmol), hex-1-ene (99 mg, 1.18 mmol), G2 (7 mg, 8.24 x 10⁻³ mmol), and anhydrous CH₂Cl₂ (15 mL). Yielded 2-79a as a yellow oil, 67% (128 mg, 0.533 mmol). Rᵣ = 0.63, 30% EtOAc in hexanes; ¹H NMR (400 MHz, CDCl₃) δ = 5.71 (dt, J = 15.3, 7.0 Hz, 1H), 5.35 (ddt, J = 15.2, 8.2, 1.2 Hz, 1H), 3.72 (s, 6H), 2.54 (q, J = 8.2 Hz, 1H), 1.99 (q, J = 7.0 Hz, 2H), 1.68 (dd, J = 7.4, 4.7 Hz, 1H), 1.55 (dd, J = 9.4, 4.7 Hz, 1H) 1.31 – 1.25 (m, 4H), 0.86 (t, J = 7.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ = 170.2, 168.0, 135.6, 124.2, 52.6, 35.6, 32.1, 31.2, 27.5, 27.0, 22.0, 20.8, 13.9; IR (thin film) 3000, 2955, 2929, 2857, 1730, 1437, 1332, 1280, 1210, 1131; HRMS calc’d for C₁₃H₂₀O₄ = 240.1362, found = 240.1368. (6:1 Trans to Cis)

Cyclopropane 2-79b was prepared using general experimental procedure. Reagents employed: dimethyl 2-vinylcyclopropane-1,1-dicarboxylate 2-83 (151 mg, 0.820 mmol), oct-1-ene (133 mg, 1.185 mmol), G2 (7 mg, 8.24 x 10⁻³ mmol), and anhydrous CH₂Cl₂ (15 mL). Yielded 2-79b as a yellow oil, 74% (162 mg, 0.604 mmol). Rᵣ = 0.63, 30% EtOAc in hexanes; ¹H NMR (400 MHz, CDCl₃) δ = 5.71 (dt, J = 15.2, 7.0 Hz, 1H), 5.03 (ddt, J = 15.2, 8.2, 1.6 Hz, 1H), 3.72 (s, 6H), 2.54 (q, J = 8.2 Hz, 1H), 1.97 (q, J = 6.6 Hz, 2H), 1.68 (dd, J = 7.4, 4.7 Hz, 1H), 1.55 (dd, J = 9.0, 4.7 Hz, 1H), 1.32 – 1.20 (m, 8H), 0.86 (t, J = 6.6 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ = 170.2, 168.0, 135.7, 124.2, 52.6, 52.4, 35.6, 32.5, 31.7, 31.2, 29.1, 28.7, 22.6, 20.8, 14.1; IR (thin film) 3000, 2955, 2927, 2855, 1729, 1437, 1330, 1280, 1210, 1131, 965; HRMS calc’d for C₁₅H₂₄O₄ = 268.1675, found = 268.1682. (6:1 Trans to Cis)

Cyclopropane 2-79c was prepared using general experimental procedure. Reagents employed: dimethyl 2-vinylcyclopropane-
1,1-dicarboxylate 2-83 (150 mg, 0.814 mmol), dec-1-ene (274 mg, 1.628 mmol), G2 (7 mg, 8.24 x 10^{-3} mmol), and anhydrous CH₂Cl₂ (15 mL). Yielded 2-79c as a brown oil, 69% (182 mg, 0.561 mmol). R_f = 0.61, 30% EtOAc in hexanes; ¹H NMR (600 MHz, CDCl₃) δ = 5.71 (dt, J = 15.3, 7.0 Hz, 1H), 5.05 (ddt, J = 15.3, 8.2, 1.2 Hz, 1H), 3.73 (s, 6H), 2.53 (q, J = 8.2 Hz, 1H), 1.98 (q, J = 7.0 Hz, 2H), 1.69 (dd, J = 7.6, 5.3 Hz, 1H), 1.55 (dd, J = 8.8, 4.7 Hz, 1H), 1.33 – 1.21 (m, 16H), 0.87 (t, J = 7.0 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ = 170.2, 168.0, 135.7, 124.2, 52.6, 52.5, 35.6, 32.5, 31.9, 31.2, 29.62, 29.60, 29.5, 29.3, 29.2, 29.0, 22.7, 20.8, 14.1; IR (thin film) 3004, 2953, 2854, 1731, 1437, 1330, 1280, 1131, 965; HRMS calc’d for C₁₉H₃₂O₄ = 324.2301, found = 324.2308. (3:1 Trans to Cis)

Cyclopropane 2-79d was prepared using general experimental procedure. Reagents employed: dimethyl 2-vinylcyclopropane-1,1-dicarboxylate 2-83 (151 mg, 0.820 mmol), 4-bromobut-1-ene (275 mg, 2.037 mmol), G2 (7 mg, 8.24 x 10^{-3} mmol), and anhydrous CH₂Cl₂ (15 mL). Yielded 2-79d as a brown oil, 78% (185 mg, 0.635 mmol). R_f = 0.58, 30% EtOAc in hexanes; ¹H NMR (600 MHz, CDCl₃) δ = 5.71 (dt, J = 15.3, 7.0 Hz, 1H), 5.19 (ddt, J = 15.3, 8.2, 1.2 Hz, 1H), 3.74 (s, 3H), 3.73 (s, 3H), 3.34 (dt, J = 7.0, 1.2 Hz, 2H), 2.56 (dq, J = 7.0, 1.2 Hz, 3H), 1.70 (dd, J = 7.6, 4.7 Hz, 1H), 1.58 (dd, J = 8.8, 4.7 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ = 170.0, 167.8, 131.3, 127.9, 52.7, 52.65, 35.7, 35.6, 32.0, 30.7, 20.8; IR (thin film) 3004, 2953, 2848, 1728, 1437, 1331, 1271, 1211, 1131; HRMS calc’d for C₁₁H₁₅BrO₄ = 290.0154, found = 290.0155. (4:1 Trans to Cis)

Cyclopropane 2-79e was prepared using general experimental procedure. Reagents employed: dimethyl 2-vinylcyclopropane-1,1-dicarboxylate 2-83 (107 mg, 0.581 mmol), tert-butyl(hex-5-enyloxy)dimethylsilane (175 mg, 0.816 mmol), G2 (12 mg, 1.41 x 10^{-2} mmol), and anhydrous CH₂Cl₂ (11 mL). Yielded 2-79e as a brown oil, 73% (156 mg, 0.421 mmol). R_f = 0.71, 30% EtOAc in hexanes; ¹H NMR (600 MHz, CDCl₃) δ = 5.71 (dt, J = 15.3, 7.0
Cyclopropane 2-79f was prepared using general experimental procedure. Reagents employed: dimethyl 2-vinylcyclopropane-1,1-dicarboxylate 2-83 (350 mg, 1.900 mmol), styrene (591 mg, 5.675 mmol), G2 (40 mg, 4.71 x 10^{-2} mmol), and anhydrous CH$_2$Cl$_2$ (22 mL). Yielded 2-79f as a yellow oil, 75% (373 mg, 1.433 mmol). R$_f = 0.56$, 30% EtOAc in hexanes; $^1$H NMR (400 MHz, CDCl$_3$) $\delta =$ 7.32 – 7.28 (m, 4H), 7.26 – 7.20 (m, 1H), 6.65 (d, $J = 16.0$ Hz, 1H), 5.81 (dd, $J = 16.0, 9.0$ Hz, 1H), 3.77 (s, 3H), 3.73 (s, 3H), 2.76 (q, $J = 8.2$ Hz, 1H), 1.85 (dd, $J = 7.8, 5.1$ Hz, 1H), 1.70 (dd, $J = 9.0, 5.1$ Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta =$ 169.9, 167.9, 136.7, 133.9, 128.6, 127.6, 126.1, 124.5, 52.8, 52.7, 36.0, 31.7, 21.3; IR (thin film) 3027, 2953, 2847, 1731, 1494, 1437, 1283, 1252, 1207, 1128, 964, 770, 744, 694; HRMS calc’d for C$_{15}$H$_{16}$O$_4$ = 260.1049, found = 260.1049. (only E olefin observed by $^1$H NMR)

Cyclopropane 2-79g was prepared using general experimental procedure. Reagents employed: dimethyl 2-vinylcyclopropane-1,1-dicarboxylate 2-83 (147 mg, 0.798 mmol), 1-methoxy-4-vinylbenzene (197 mg, 1.468 mmol), G2 (7 mg, 8.24 x 10^{-3} mmol), and anhydrous CH$_2$Cl$_2$ (15 mL). Yielded 2-79g as a yellow oil, 29% (67 mg, 0.231 mmol). R$_f = 0.50$, 30% EtOAc in hexanes; (column purified in CH$_2$Cl$_2$): $^1$H NMR (400 MHz, CDCl$_3$) $\delta =$ 7.23 (d, $J = 8.6$ Hz, 2H), 6.82 (d, $J = 9.0$ Hz, 2H), 6.58 (d, $J = 15.6$ Hz, 1H), 5.67 (dd, $J =
15.6, 8.6 Hz, 1H), 3.79 (s, 3H), 3.75 (s, 3H), 3.72 (s, 3H), 2.73 (q, $J = 8.6$ Hz, 1H), 1.84 (dd, $J = 7.4$, 4.7 Hz, 1H), 1.68 (dd, $J = 9.0$, 4.7 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl3) $\delta$ = 170.0, 168.0, 159.2, 133.3, 129.5, 127.3, 122.1, 114.0, 55.3, 52.7, 52.6, 36.0, 31.9, 21.3; IR (thin film) 3003, 2953, 2838, 1728, 1608, 1512, 1437, 1286, 1255, 1208, 1176, 1130, 1033, 964, 821; HRMS calc’d for C$_{16}$H$_{18}$O$_5$ = 290.1154, found = 290.1148. (only E olefin observed by $^1$H NMR)

Cyclopropane 2-79h was prepared using general experimental procedure. Reagents employed: dimethyl 2-vinylcyclopropane-1,1-dicarboxylate 2-83 (119 mg, 0.646 mmol), 1-nitro-4-vinylbenzene (135 mg, 0.905 mmol), G2 (6 mg, 7.07 $\times$ 10$^{-3}$ mmol), and anhydrous CH$_2$Cl$_2$ (12 mL). Yielded 2-79h as a brown oil, 60% (119 mg, 0.390 mmol). R$_f$ = 0.40, 30% EtOAc in hexanes; $^1$H NMR (400 MHz, CDCl3) $\delta$ = 7.85 (d, $J = 9.0$ Hz, 2H), 7.42 (d, $J = 8.6$ Hz, 2H), 6.71 (d, $J = 15.6$ Hz, 1H), 6.00 (dd, $J = 15.6$, 9.0 Hz, 1H), 3.77 (s, 3H), 3.75 (s, 3H), 2.77 (q, $J = 8.6$ Hz, 1H), 1.87 (dd, $J = 7.8$, 5.1 Hz, 1H), 1.75 (dd, $J = 9.0$, 5.1 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl3) $\delta$ = 169.5, 167.8, 146.9, 142.9, 131.7, 130.0, 126.6, 124.0, 52.9, 52.8, 36.2, 31.3, 21.5; IR (thin film) 3105, 3027, 2959, 2926, 2844, 1729, 1593, 1511, 1436, 1342, 1288, 1253, 1205, 1133; HRMS calc’d for C$_{15}$H$_{15}$NO$_6$ = 305.0899, found = 305.0900. (only E olefin observed by $^1$H NMR)

Cyclopropane 2-79i was prepared using general experimental procedure. Reagents employed: dimethyl 2-vinylcyclopropane-1,1-dicarboxylate 2-83 (100 mg, 0.543 mmol), acrolein (151 mg, 2.694 mmol), G2 (4 mg, 4.71 $\times$ 10$^{-3}$ mmol), and anhydrous CH$_2$Cl$_2$ (10 mL). Yielded 2-79i as a yellow oil, 33% (38 mg, 0.179 mmol). R$_f$ = 0.23, 30% EtOAc in hexanes; $^1$H NMR (600 MHz, CDCl3) $\delta$ = 9.43 (d, $J = 6.5$ Hz, 1H), 6.38 – 6.29 (m, 2H), 3.76 (s, 3H), 3.75 (s, 3H), 2.76 (q, $J = 8.2$ Hz, 1H), 1.86 (dd, $J = 7.4$, 5.3 Hz, 1H), 1.81 (dd, $J = 8.8$, 4.7 Hz, 1H); $^{13}$C NMR (150 MHz, CDCl3) $\delta$ = 192.7, 168.8, 167.2, 152.1, 134.9, 53.1, 53.0, 29.9, 21.9, 20.8; IR (thin
Cyclopropane 2-79i was prepared using general experimental procedure. Reagents employed: dimethyl 2-vinylcyclopropane-1,1-dicarboxylate 2-83 (100 mg, 0.543 mmol), (E)-but-2-enal (186 mg, 2.655 mmol), G2 (5 mg, 5.89 x 10^{-3} mmol), and anhydrous CH2Cl2 (10 mL). Yielded 2-79i as a yellow oil, 69% (80 mg, 0.377 mmol): data matched that previously reported above.

Cyclopropane 2-79j was prepared using general experimental procedure. Reagents employed: dimethyl 2-vinylcyclopropane-1,1-dicarboxylate 2-83 (100 mg, 0.543 mmol), but-3-en-2-one (193 mg, 2.754 mmol), G2 (4 mg, 4.71 x 10^{-3} mmol), and anhydrous CH2Cl2 (10 mL). Yielded 2-79j as a brown oil, 82% (101 mg, 0.446 mmol). R_f = 0.19, 30% EtOAc in hexanes; 1H NMR (600 MHz, CDCl3) δ =6.30 – 6.23 (m, 2H), 3.71 (s, 6H), 2.65 – 2.56 (m, 1H), 2.15 (s, 3H), 1.78 (dd, J = 7.6, 5.3 Hz, 1H), 1.72 (dd, J = 8.8, 4.7 Hz, 1H); 13C NMR (150 MHz, CDCl3) δ =197.0, 169.0, 167.2, 142.1, 133.3, 52.9, 52.8, 36.5, 29.8, 27.0, 21.5; IR (thin film) 3007, 2956, 2856, 1731, 1674, 1625, 1438, 1333, 1291, 1253, 1212, 1131, 983; HRMS calc’d for C11H14O5 = 226.0841, found = 226.0831. (only E olefin observed by 1H NMR)

Cyclopropane 2-79k was prepared using general experimental procedure. Reagents employed: dimethyl 2-vinylcyclopropane-1,1-dicarboxylate 2-83 (100 mg, 0.543 mmol), methyl acrylate (116 mg, 1.347 mmol), G2 (4 mg, 4.71 x 10^{-3} mmol), and anhydrous CH2Cl2 (10 mL). Yielded 2-79k as a brown oil, 92% (121 mg, 0.500 mmol). R_f = 0.35, 30% EtOAc in hexanes; 1H NMR (600 MHz, CDCl3) δ = 6.42 (dd, J = 15.8, 10.0 Hz, 1H), 6.02 (d, J = 15.8 Hz, 1H), 3.72 (m, 6H), 3.67 (s, 3H), 2.63 (q, J = 7.6 Hz, 1H), 1.77 (dd, J = 7.0, 4.7 Hz, 1H), 1.68 (dd, J = 8.8, 5.3 Hz, 1H).
General Experimental Procedure for Olefin Reduction to Cyclopropane 2-79a,f:

Vinyl Cyclopropane (2-79a,f) (1 equivalent) was dissolved in (1:1) THF:H₂O. Tosylhydrazine (10 equivalent) and sodium acetate (13 equivalent) were added and the reaction mixture was heated to reflux for 24 hours. Water was added to the reaction and the aqueous was extracted with ether 4 times. The organic phase were combined and dried with MgSO₄, filtered, and the solvent was removed. The residue was purified by flash chromatography (EtOAc/Hexanes) to yield the desired cyclopropane (2-85a,b).

Cyclopropane 2-85a was prepared using general experimental procedure. Reagents employed: dimethyl 2-(hex-1-enyl)cyclopropane-1,1-dicarboxylate 2-79a (400 mg, 1.665 mmol), tosylhydrazine (3.100 g, 16.646 mmol), sodium acetate (1.780 g, 21.699 mmol), and THF:H₂O (16:16 mL). Yielded 2-85a as a yellow oil, 90% (364 mg, 1.499 mmol). Rf = 0.63, 30% EtOAc in hexanes; ¹H NMR (600 MHz, CDCl₃) δ = 3.71 (s, 3H), 3.67 (s, 3H), 1.89 – 1.82 (m, 1H), 1.45 – 1.30 (m, 5H), 1.29 – 1.16 (m, 6H), 1.15 – 1.08 (m, 1H), 0.83 (t, J = 7.0 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ = 170.9, 168.7, 52.5, 52.3, 33.9, 31.6, 28.9, 28.8, 28.7, 28.6, 22.5, 21.3, 14.0; IR (thin film) 3007, 2955, 2927, 2858, 1731, 1437, 1331, 1286, 1212, 1132; HRMS calc’d for C₁₃H₂₂O₄ = 243.1591, found = 243.1603 (M+1).

Cyclopropane 2-85b was prepared using general experimental procedure. Reagents employed: dimethyl 2-styrylcyclopropane-1,1-dicarboxylate 2-79f (150 mg, 0.576 mmol), tosylhydrazine (1.070 g,
5.746 mmol), sodium acetate (0.615 g, 7.497 mmol), and THF:H₂O (6:6 mL). Yielded 2-85b as an orange oil, 82% (124 mg, 0.472 mmol). Rₚ = 0.56, 30% EtOAc in hexanes; ¹H NMR (400 MHz, CDCl₃) δ = 7.31 – 7.25 (m, 2H), 7.21 – 7.14 (m, 3H), 3.76 (s, 3H), 3.72 (s, 3H), 2.79 – 2.66 (m, 2H), 1.99 – 1.90 (m, 1H), 1.81 – 1.71 (m, 1H), 1.58 – 1.47 (m, 1H), 1.44 – 1.36 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ = 170.8, 168.6, 141.3, 128.4, 126.0, 110.0, 52.6, 52.5, 35.1, 33.3, 30.8, 28.2, 21.2; IR (thin film) 3085, 3027, 2952, 2862, 1719, 1652, 1436, 1330, 1289, 1212, 1133, 750, 700; HRMS calc’d for C₁₅H₁₈O₄ = 262.1205, found = 262.1198.

**General Experimental Procedure for the Synthesis of Tetrahydro-1,2-oxazines 2-87a-d:** Yb(OTf)₃•ₓH₂O (5 - 20 mol %) was added to a solution of cyclopropane (2-79a,f and 2-85a-b) (1 equivalent) and nitrone 2-86 (1.2 equivalent) in methylene chloride at room temperature for 18 hours. The reaction mixture was wet loaded and purified by flash chromatography (EtOAc/Hexanes) to yield the desired tetrahydro-1,2-oxazine (2-87a-c).

Cyclopropane 2-87a was prepared using general experimental procedure. Reagents employed: dimethyl 2-(hex-1-enyl)cyclopropane-1,1-dicarboxylate 2-79a (100 mg, 0.416 mmol), nitrone 2-86 (106 mg, 0.502 mmol), Yb(OTf)₃•ₓH₂O (13 mg, 2.10 x 10⁻² mmol), and methylene chloride (3.5 mL). Yielded 2-87a as a yellow oil, 96% (181 mg, 0.401 mmol). Rₚ = 0.63, 30% EtOAc in hexanes; ¹H NMR (600 MHz, CDCl₃) δ = 7.56 – 7.49 (m, 2H), 7.21 – 7.14 (m, 3H), 6.98 – 6.91 (m, 4H), 5.97 – 5.88 (m, 1H), 5.76 – 5.64 (m, 1H), 5.62 (s, 1H), 4.47 – 4.40 (m, 1H), 3.88 (s, 3H), 3.45 (s, 3H), 2.61 – 2.44 (m, 2H), 2.11 – 2.05 (m, 5H), 1.49 – 1.33 (m, 4H), 0.95 (t, J = 7.4 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ = 170.1, 168.4, 146.3, 135.2, 135.0, 130.8, 130.5, 129.0, 127.9, 127.8, 127.7, 116.0, 77.2, 65.9, 59.2, 53.3, 52.5, 32.2, 30.8, 22.3, 22.2, 20.5, 13.9; IR (thin film) 3028, 2954, 2927, 2859, 1742, 1509, 1453, 1434, 1330, 1289, 1212, 1133, 750, 700; HRMS calc’d for C₂₇H₃₃NO₅ = 451.2359, found = 451.2354. (6:1 Trans to Cis)
Cyclopropane 2-87b was prepared using general experimental procedure. Reagents employed: dimethyl 2-styrylcyclopropane-1,1-dicarboxylate 2-79f (100 mg, 0.384 mmol), nitrone 2-83 (97 mg, 0.46 mmol), Yb(OTf)₃•xH₂O (12 mg, 1.93 x 10⁻² mmol), and methylene chloride (3 mL). Yielded 2-87b as a white foam 92% (166 mg, 0.352 mmol). Rₓ = 0.56, 30% EtOAc in hexanes; Data matched that previously reported.⁴⁷

Cyclopropane 2-87c was prepared using general experimental procedure. Reagents employed: dimethyl 2-hexylcyclopropane-1,1-dicarboxylate 2-85a (100 mg, 0.413 mmol), nitrone 2-86 (106 mg, 0.502 mmol), Yb(OTf)₃•xH₂O (51 mg, 8.2 x 10⁻² mmol), and DCE (4 mL). Yielded 2-87c as a brown oil, 44% (83 mg, 0.183 mmol). Rₓ = 0.63, 30% EtOAc in hexanes; ¹H NMR (600 MHz, CDCl₃) δ = 7.54 – 7.50 (m, 2H), 7.20 – 7.14 (m, 3H), 6.96 – 6.90 (m, 4H), 5.64 (s, 1H), 3.99 – 3.90 (m, 1H), 3.86 (s, 3H), 3.45 (s, 3H), 2.47 – 2.36 (m, 2H), 2.17 (s, 3H), 1.87 – 1.77 (m, 1H), 1.70 – 1.59 (m, 2H), 1.55 – 1.45 (m, 1H), 1.43 – 1.36 (m, 2H), 1.35 – 1.29 (m, 4H), 0.91 (t, J = 7.0 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ = 170.3, 168.5, 146.4, 135.3, 130.52, 130.50, 129.0, 127.9, 127.8, 115.6, 77.04, 65.6, 59.2, 53.3, 52.5, 34.7, 31.8, 31.0, 29.3, 25.5, 22.6, 20.5, 14.1; IR (thin film) 3028, 2952, 2927, 2858, 1743, 1452, 1435, 1234, 1174, 1081, 820, 702; HRMS calc’d for C₂₇H₃₅NO₅ = 453.2515, found = 453.2512.

General Experimental Procedure for Olefin Reduction to Tetrahydro-1,2-oxazines 2-87c-d: Vinyl tetrahydro-1,2-oxazines (2-87a-b) (1 equivalent) were dissolved in (1:1) THF:H₂O. Tosylhydrazine (10 equivalent) and sodium acetate (13 equivalent) were added and the reaction mixture was heated to reflux for 24 hours. Water was added to the reaction and the aqueous was extracted with ether 4 times. The organic phases were combined and dried with MgSO₄, filtered, and the solvent was removed. The residue was purified by flash chromatography (EtOAc/Hexanes) to yield the desired tetrahydro-1,2-oxazines (2-87c-d).
Cyclopropane 2-87c was prepared using general experimental procedure. Reagents employed: dimethyl 6-(hex-1-enyl)-2-phenyl-3-p-tolylmorpholine-4,4-dicarboxylate 2-87a (70 mg, 0.155 mmol), tosylhydrazine (289 mg, 1.552 mmol), sodium acetate (165 mg, 2.011 mmol), and THF:H₂O (2:2 mL). Yielded 2-87c as an yellow oil, 91% (64 mg, 0.141 mmol). R = 0.63, 30% EtOAc in hexanes; data matched that previously reported above.

Cyclopropane 2-87d was prepared using general experimental procedure. Reagents employed: dimethyl 2-phenyl-6-styryl-3-p-tolylmorpholine-4,4-dicarboxylate 2-87b (70 mg, 0.148 mmol), tosylhydrazine (277 mg, 1.487 mmol), sodium acetate (158 mg, 1.926 mmol), and THF:H₂O (1.5:1.5 mL). Yielded 2-87d as a yellow foam, 98% (69 mg, 0.146 mmol). R = 0.56, 30% EtOAc in hexanes; ¹H NMR (600 MHz, CDCl₃) δ = 7.56 – 7.52 (m, 2H), 7.34 – 7.30 (m, 2H), 7.29 – 7.26 (m, 2H), 7.24 – 7.17 (m, 4H), 7.00 – 6.94 (m, 4H), 5.67 (s, 1H), 4.07 – 3.98 (m, 1H) 3.85 (s, 3H), 3.46 (s, 3H), 3.04 – 2.96 (m, 1H), 2.91 – 2.83 (m, 1H), 2.52 – 2.46 (m, 2H), 2.23 – 2.13 (m, 4H), 2.06 – 1.97 (m, 1H); ¹³C NMR (150 MHz, CDCl₃) δ = 170.2, 168.5, 146.4, 141.6, 135.2, 130.7, 130.5, 129.1, 128.4, 128.0, 127.9, 126.0, 115.7, 76.5, 66.0, 59.2, 53.3, 52.5, 36.4, 31.9, 31.0, 20.6 (one carbon missing presumably due to overlap in the aromatic region); IR (thin film) 3027, 2951, 2924, 2857, 1741, 1509, 1453, 1434, 1236, 1166, 1090, 820, 753, 701; HRMS calc’d for C₂₉H₃₁NO₅ = 473.2202, found = 473.2191.
2.7 Reference


Chapter 3 : Progress Toward Aspidospermidine and the Formal Synthesis of Quebrachamine

3 Introduction and Overview

Our group has had long standing interest in the Aspidosperma family of indole alkaloids. Due to the presence of the piperidine/pyrrolidine core of these alkaloids, we have recently begun synthetic efforts toward the synthesis of the parent compounds: aspidospermidine and quebrachamine. This chapter will focus on the ongoing progress toward indole alkaloid aspidospermidine via an intramolecular [3+2] annulation between an imine and cyclopropane. Additionally, a discussion on the formal synthesis of quebrachamine will be displayed. The latter will also include the current efforts toward completing the total synthesis of quebrachamine through a new 9-membered ring closing method.

3.1 Aspidosperma Alkaloids

With over 250 different compounds isolated from a variety of different biological sources, the aspidosperma alkaloids represent one of the largest classes of indole alkaloids (Figure 3-1). Among the vast array of these compounds, the parent compound aspidospermidine and its structural analogue quebrachamine have been the focused synthetic target for many different research groups. The lack of functionality, partnered with the quaternary center presented by these molecules, makes them ideal candidates for the development of new synthetic methods. Isolated over a century ago from the bark of the Aspidosperma quebracho-blanco tree, these alkaloids, along with several other structurally similar alkaloids, exhibit a large array of biological activity. While the parent compound aspidospermidine, is not pharmacologically active, quebrachamine, the less structurally complex compound, does display biological activity. In 1994, studies by Madsen showed the potent α-adrenergic blocking activity of quebrachamine in urogenital tissue. The study found that the alkaloid reduced muscle contractions in human prostatic tissues, rabbit corpus spongiosum, and guinea pig vas deferens making quebrachamine a possible drug candidate for the treatment of erectile dysfunction and benign prostatic hyperplasia. Although much of the biological research into the aspidosperma family of alkaloids has been focused on quebrachamine, recent reports have shown the potential for
aspidospermine and N-formyl-aspidospermidine to treat malaria, due to the synergic antiplasmodial activity displayed by these compounds.⁴

![Figure 3-1: Select Aspidosperma Alkaloids](image)

### 3.2 Total Synthesis of Aspidospermidine

Since isolation, aspidospermidine has been synthesized by over 40 different research groups utilizing a plethora of different methods.⁵ To date, one of the most useful and unique methods stems from the seminal work in this area by Harley-Mason. In 1967, Harley-Mason reported the first racemic total synthesis of aspidospermidine starting from substituted aldehyde 3-1 (Scheme 3-1).⁶ Aldehyde 3-1 was efficiently converted into acetal 3-3 through a three step protection, ozonolysis, and reduction sequence. In acetic acid the acetal (3-3) was deprotected in situ followed by a Pictet-Spengler reaction with tryptamine to furnish indoloquinolizidine intermediate 3-4. This unique intermediate (3-4) contained not only the desired quaternary center of the target molecule, but also contained all the necessary carbons required to build the natural product. Indoloquinolizidine 3-4 then underwent a skeletal rearrangement in the presence of BF₃•OEt₂ to give penultimate intermediate 3-5. Final reduction of both the imine and the lactam with LiAlH₄ gave the desired product, (±)-aspidospermidine 3-6. Among the varying approaches to aspidospermidine, the indoloquinolizidine rearrangement approach developed by Harley-Mason and co-workers has been a fundamental late stage method utilized by several researchers in the synthesis of this natural product.
3.2.1 First Asymmetric Synthesis of Aspidospermidine

It wasn’t until many years after the seminal work by Harley-Mason, that the first asymmetric synthesis of (-)-aspidospermidine 3-6 was completed (Scheme 3-2).\(^7\) Readily available optically enriched lactone 3-7\(^8\) was converted to hemiacetal 3-8 via a McMurry modification of the Nef reaction.\(^9\) The hemiacetal 3-8 was then reduced followed by subsequent acid catalyzed cyclization to give lactone 3-9 in good overall yield (75% over three steps) with the desired stereocenter set for the natural product. Transformation of 3-9 to acetal 3-10 was achieved through a three step procedure involving a Jones oxidation of the primary alcohol, DIBAL-H reduction of the lactone, followed by treatment with acidic methanol to secure the acetal product. Acetal 3-10 was then subjected to a Pictet-Spengler reaction followed by lactamization to give tetracyclic intermediate (S)-3-4. In a similar manner to Harley-Mason’s work, this intermediate was rearranged and reduced in an overall 81% yield to give optically enriched (-)-aspidospermidine 3-6. Since this report by Fuji, many other researchers have exploited the use of enantioenriched starting materials, catalysts, and auxiliaries to synthesize effectively both (+) and (-)-3-6.\(^10\)
Scheme 3-2: First Asymmetric Synthesis of Aspidospermidine

3.2.2 Recent Syntheses of Aspidospermidine

In 2013, Shao and co-workers reported a novel enantioselective palladium-catalyzed decarboxylative allylation approach to (-)-aspidospermidine.\(^\text{11}\) While there have been many recent advances in the area of asymmetric decarboxylative allylation reactions,\(^\text{12}\) the use of carbazolones (not previously studied) would allow access to optically active allyl carbazolones featuring the \(\alpha\)-quaternary carbon center common to many of the aspidosperma alkaloids. The authors explored this concept by showing that allyl ester 3-11 could undergo a palladium-catalyzed decarboxylative allylation in the presence of chiral ligand 3-16 to give 3-12 in an excellent yield and very high enantioselectivity (Scheme 3-3). With the quaternary center installed, the remainder of the synthesis focused on the formation of the last two ring systems. Mild hydrolysis of nitrile 3-12 followed by a tandem chemoselective reduction of the ketone and a cyclization furnished the 6-membered nitrogen containing ring (3-13) of the natural product. Next, the allyl group was converted into the desired ethyl group by first creating cyclic dithiane 3-14 and then subjecting 3-14 to a Raney nickel reduction. Lactam reduction and benzyl group deprotection gave tetracyclic intermediate 3-15. Finally, the synthesis was completed following a three step procedure developed by Heathcock for the installation of the
remaining pyrrolidine ring system.\textsuperscript{5m} The success of this method was also displayed in the synthesis of a related alkaloid (+)-kopsihainanine A.

![Scheme 3-3: Shao's Approach to (-)-Aspidospermidine](image)

Most recently, the Zhu group developed a unified approach to a series of indole alkaloids including aspidospermidine via a unique palladium-catalyzed decarboxylative vinylation followed by an integrated oxidation/reduction/cyclization (iORC) sequence.\textsuperscript{13} Coupling between potassium butanoate 3-17 and vinyl triflate 3-18 followed by work up with TBAF afforded primary alcohol 3-19 (Scheme 3-4). Two consecutive Mitsunobu reactions under Walker’s conditions\textsuperscript{14} gave access to macrocycle 3-20 setting up for iORC sequence. Oxidative cleavage of the cyclopentene ring gave dialdehyde 3-21, followed by deprotection of the secondary amine to give intermediate 3-22. Nitro reduction and cyclization then led to the pentacyclic core (3-25) of the target molecule. Final imine reduction gave aspidospermidine 3-6 in a 50% yield over the 4 sequential transformations. In the same paper, the overall utility of this iORC method displayed access to several other indole alkaloids including goniomitine and vincadifformine.
3.3 Total Synthesis of Quebrachamine

Unlike aspidospermidine, quebrachamine has attracted significantly less synthetic efforts than aspidospermidine, presumably due to the difficulty in creating the medium sized 9-membered ring.\(^\text{15}\) Although this alkaloid has seen less synthetic efforts, the first total synthesis of (±)-quebrachamine was reported 4 years prior to the synthesis of aspidospermidine. In 1963, Stork and Dolfini developed a ring-expansion route (a now common approach to the 9-membered ring) toward the synthesis of quebrachamine.\(^\text{16}\) The synthesis began with pyrroloenamine (of 3-26) alkylation to give to enone 3-27 (Scheme 3-5). Bicycle 3-28, furnished through a 4 step sequence from 3-27, was acylated with 2-chloroacetyl chloride giving 3-29. Base mediated ring-closure followed by selective lactam reduction provided tricyclic ketone 3-31. Fischer indolization with phenylhydrazine led to pentacyclic 3-25, which then underwent ring-expansion with KBH\(_4\) to give (±)-quebrachamine 3-32.
Scheme 3-5: First Total Synthesis of Quebrachamine

3.3.1 Asymmetric Syntheses of Quebrachamine

Over 15 years after the first total synthesis of (±)-quebrachamine, Takano and co-workers displayed the first asymmetric total synthesis of (+)-quebrachamine.\(^1\) Exploiting the chiral pool, L-glutamic acid was converted into lactone 3-34 (Scheme 3-6).\(^1\) Following trityl protection of the primary alcohol, two substrate controlled selective alkylations gave quaternary lactone 3-36. Trityl deprotection, base hydrolysis of the lactone, and periodate cleavage led to the formation of 3-37 as an inconsequential 1:1 mixture of diastereomers. Pictet-Spengler reaction of 3-37 with tryptamine followed by hydroboration/oxidation of the allyl group and lactam reduction furnished tetracyclic intermediate 3-39 in an overall 34% yield. The tetracyclic intermediate 3-39 was then converted into (+)-3-32 via alcohol mesylation and N-alkylation to give the resulting iminium ion which then underwent a dissolving metal reductive ring expansion in 65% yield over the three steps. One year later, Takano was able to complete the synthesis of (-)-3-32, utilizing a similar approach from another optically enriched starting material.\(^1\)

---

1. Takano and co-workers
2. L-glutamic acid was converted into lactone 3-34
3. Trityl protection of the primary alcohol
4. Two substrate controlled selective alkylations gave quaternary lactone 3-36
5. Trityl deprotection, base hydrolysis of the lactone, and periodate cleavage led to the formation of 3-37
6. Pictet-Spengler reaction of 3-37 with tryptamine
7. Hydroboration/oxidation of the allyl group
8. Lactam reduction furnished tetracyclic intermediate 3-39
9. Conversion into (+)-3-32 via alcohol mesylation and N-alkylation
10. Dissolving metal reductive ring expansion in 65% yield
11. One year later, Takano completed the synthesis of (-)-3-32
With advances in both cross metathesis and ring-closing metathesis being developed at an increasing rate, Schrock and Hoveyda displayed an elegant enantioselective synthesis of (-)-quebrachamine via a stereoselective olefin metathesis.\textsuperscript{20} Weinreb amide 3-42, secured in a 6 step process from keto-lactone 3-40, was subjected to a Pictet-Spengler reaction with tryptamine followed by LAH reduction to give tetracyclic indole 3-43 in a modest overall yield (Scheme 3-7). Indole 3-43 was then subjected to an N-acylation/reductive ring-expansion, installing the 9-membered ring core (3-44) of the natural product. Next, a palladium-catalyzed decarboxylative allylation reaction occurred, giving ring-closing precursor 3-45 in an excellent yield. With the olefin systems in place, the synthesis of the piperidine ring of this natural product became the focus. After scanning several different chiral molybdenum catalysts, it was shown that 3-47 could effectively catalyze the enantioselective ring-closing metathesis, providing 3-46 in great yield and excellent enantioselectivity. Global reduction of the remaining olefins in 3-46 gave (+)-3-32 in a high yield. Certainly, the unique ring-closing metathesis shown in this synthesis will have a profound effect on current research directed toward asymmetric synthesis of piperidine-containing target molecules.
3.3.2 Recent Total Syntheses of Quebrachamine

In 2009, Pagenkopf and Bajtos showcased their cyclopropane/nitrile [3+2] annulation reaction in the synthesis of (±)-quebrachamine. Additionally, this synthesis focused on a unique 9-membered ring-closing reaction, in contrast to the many ring-expansion methods. The synthesis began with the TMSOTf mediated annulation reaction between nitrile 3-48 and donor-acceptor cyclopropane 3-49 to give the corresponding pyrrole which then underwent an oxidation with catalytic palladium on carbon to afford indole 3-50 (Scheme 3-8). Microwave-assisted decarboxylation followed by benzyl deprotection and lactam reduction secured the formation of piperidine 3-52. Early attempts to close the large ring system with N-alkylation, acylation, and Friedel–Crafts methods were met with no success. Interestingly, a chloroacetamide Witkop photocyclization of acylated piperidine 3-53 proceeded in an excellent yield to give the desired 9-membered ring product. Lactam reduction gave quebrachamine 3-32 in an overall 17.8% yield in 13 steps from commercially available starting materials.
Scheme 3-8: 9-Membered Ring-Closing Approach to Quebrachamine

One of the most recent syntheses of quebrachamine reported in 2013 by the Prasad group utilized a common quaternary center intermediate in the unified approach to several aspidosperma natural products.\textsuperscript{23} This approach is becoming increasingly popular due to the structural similarities not only in aspidosperma alkaloids, but other indole alkaloids as well. The synthesis of common intermediate 3-57 began with a two-step procedure involving an ester reduction followed by a Wittig reaction of readily available 3-54 to access olefin 3-55 (Scheme 3-9). Next, DIBAL-H reduction and MOM protection of the resulting primary alcohol was completed followed by desilylation revealed 3-56. The desired quaternary center was created via a [3,3]-sigmatropic Johnson-Claisen rearrangement giving common intermediate 3-57 in 79% yield. The intermediate 3-57 was then continued to quebrachamine via an ester reduction and Pictet-Spengler reaction to afford tricyclic 3-59 in modest yield. N-allylation of piperidine 3-59 followed by ring-closing metathesis and olefin reduction gave intermediate 3-61. Finally, deprotection of the primary alcohol and mesylation allowed formation of a quaternary salt which could then undergo a reductive ring expansion to give (+)-quebrachamine 3-32 in 13% yield over the 4 steps.
3.4 Pyrrolidine Synthesis from Donor-Acceptor Cyclopropanes

In a follow up study on the successful formal cycloaddition between nitrones and DA cyclopropanes, the Kerr group explored the reactivity of imines in a similar fashion. In 2005 the Kerr group reported the successful synthesis of substituted pyrrolidines from the three-component reaction of DA cyclopropanes, primary amines, and aldehydes (Scheme 3-10). Initial condensation between a primary amine and aldehyde 3-62 gave intermediate imine 3-63, which was then reacted with cyclopropane 3-64 in the presence of Yb(OTf)3 to give zwitter-ionic intermediate 3-65, followed by a Mannich type ring-closure to give the desired pyrrolidine 3-66. The reaction conditions were tolerant of a variety of different substitutions on the cyclopropane and aldehyde giving good to excellent yields of the pyrrolidine products with great diastereoselectivity.
Scheme 3-10: Synthesis of Pyrrolidines from DA Cyclopropanes

The success of this method led to its application in the total synthesis of FR901483 (Scheme 3-11).\(^{26}\) Readily available cyclopropane \(3-67\) was converted in a six step sequence to the corresponding amine cyclopropane \(3-68\). At this point, two of the required functionalities (primary amine and cyclopropane) were in place and intramolecularly connected. Cyclopropane \(3-68\) was subjected to paraformaldehyde and Lewis acid to give bicyclic pyrrolidine \(3-71\) via sequential imine formation (\(3-69\)), intramolecular cyclopropane ring-opening (\(3-70\)), and Mannich type ring-closure. With pyrrolidine \(3-71\) in hand, the synthesis was completed following another six step procedure furnishing the natural product \(3-72\).
3.5 Progress Toward Aspidospermidine

3.5.1 Retrosynthesis of Aspidospermidine

The utility of the pyrrolidine forming reaction in the total synthesis of FR901483, coupled with our interest in aspidosperma alkaloids, inspired us to continue exploring this method in the synthesis of aspidospermidine. It was envisioned that the indole system of aspidospermidine could come from a late stage Fischer indolization of 3-73 (after decarboxylation), a common intermediate in several approaches to aspidospermidine (Scheme 3-12). Tricyclic keto-ester 3-73 could come from an intramolecular pyrrolidine forming reaction between the tethered cyclopropane and cyclic imine 3-74, which could be formed in situ via a mild acid deprotection of amino-aldehyde cyclopropane 3-75. It is believed that the synthesis of key cyclization precursor 3-75 could be achieved through selective oxidation and homologation reactions of commercially available triol 3-76.
3.5.2 Synthesis of Key Cyclization Precursor 3-75

The synthesis of advanced intermediate 3-77 (reported synthesis from a previous Kerr group member) was achieved in an 8 step sequence from commercially available triol 3-76 (Scheme 3-13). Smooth protection of the desired aldehyde with 1,3-propanediol in toluene with catalytic TsOH gave cyclic acetal 3-78 in near quantitative yields. With the protected aldehyde in hand, focus was next directed to installing the required amine functionality of the cyclization precursor.

Scheme 3-13: Aldehyde Protection

Selective base hydrolysis of the benzoyl (Bz) protecting group was achieved using a slight excess of sodium hydroxide in methanol (Scheme 3-14). The selectivity of this hydrolysis can presumably be attributed to the steric hindrance near the other ester, which
occupies a neopentyl position. The unprotected primary alcohol was converted into a
leaving group in excellent yield. Mesylated alcohol 3-79 was then subjected to potassium
phthalimide in DMF to yield the desired protected amine 3-80 albeit in modest yield. It
should be noted that the direct Mitsunobu reaction of the unprotected alcohol with
phthalimide did give product; however, due to the low yield and cost of the reagents, we
decided to search for more scalable conditions. All attempts to increase the yield of the
phthalimide displacement proved unsuccessful and thus use of sodium azide was
attempted. Gratifyingly, the displacement with sodium azide gave a 95% yield of the
desired product 3-81 and could efficiently be performed on gram scale with little loss in
yield. Finally, the Boc-protected amine 3-82 was furnished through a two-step azide
reduction Boc protection in an overall 84% yield.

Scheme 3-14: Synthesis of the Protected Amine

With both the aldehyde and amine functionalities of the desired cyclization precursor
installed, we next moved to appending the cyclopropane moiety. Initially, we believed
the cyclopropane could be installed through direct enolate alkylation of a geminally
substituted keto-ester cyclopropane. To this end, saponification of the PMP benzoyl
group (3-81) with sodium hydroxide in refluxing methanol followed by mesylation gave
3-83 in 90% yield (Scheme 3-15A). While optimizing the conditions for the synthesis of
3-83, a model study of the alkylation was performed using cyclopropane 3-84 and
neopentyl bromide 3-85 (Scheme 3-15B). Unfortunately, under all conditions attempted
(varying solvent and temperature), no alkylation product was formed and the reaction
resulted solely in decomposition of the cyclopropane starting material. Similar results were obtained when 3-83 was used in place of neopentyl bromide, leading only to recovery of 3-83 (Scheme 3-15C). Due to the decomposition of the nucleophilic cyclopropane and the recovery of the electrophile, these results suggest that the bulky quaternary center of 3-83 may hinder the alkylation process; thus, we set out to determine another method for installing the cyclopropane moiety.

Scheme 3-15: Cyclopropane Alkylation Attempts

Based on previous success utilizing homologation methods to synthesize intermediate 3-77, we envisioned the cyclopropane moiety could be installed through a Horner-Wadsworth-Emmons reaction. This approach required the synthesis of a unique phosphonate cyclopropane 3-89 (Scheme 3-16A). Our original approach to this molecule applied a three-step sequence from cyclopropane 3-88; however, the yields were irreproducible and did not fare well with scale up. A second generation approach was developed using a one-step acylation method of dimethyl methylphosphonate and cyclopropane 3-88 to give phosphonate cyclopropane 3-89 in modest yield (Scheme 3-16B).
Scheme 3-16: Synthesis of Phosphonate Cyclopropane 3-89

With phosphonate cyclopropane 3-89 in hand, we performed a model study with pivaldehyde to determine the reactivity of the cyclopropane with a sterically contested aldehyde (Scheme 3-17A). In contrast to the previous attempts at alkylating the cyclopropane, homologation was successful giving 3-91 in an excellent 94% yield. Pleased with these results, we set out to install the cyclopropane on the appropriate scaffold to furnish the desired cyclization precursor. In this vein, aldehyde 3-92 was synthesized through a two-step procedure involving a saponification followed by a Swern oxidation in an overall 90% yield from 3-81 (Scheme 3-17B).

Scheme 3-17: Reactivity Study of Cyclopropane 3-89 and the Synthesis of 3-92

Initial investigations into the synthesis of 3-93 employed the identical conditions used in the model study (Table 3-1, entry 1). Unfortunately, these conditions failed to provide any desired product 3-93 and only the recovery of both starting materials was observed.
We next examined the effect of temperature (entry 2-3); however, both room temperature and heating showed no sign of product formation. Similarly, when different solvents were explored, only recovery of starting materials (entry 4) or complete decomposition of the starting material (entry 5) was observed. High pressure and microwave conditions also led to quick decomposition of the starting materials (entry 6-7). The use of different bases had little effect on the outcome of the reaction, showing no indication of product formation (entry 8-9). In hopes of activating both the phosphate cyclopropane and aldehyde, a Masamune-Roush modification was attempted (entry 10); however, once again, no reaction was observed.28 Finally, the initial conditions from the model study (entry 1) were employed with a variety of sterically hindered aldehydes in hopes of installing the cyclopropane moiety at an earlier stage in the synthesis of 3-75 (Figure 3-2). To our displeasure, the conditions employed resulted only in recovery of starting material with each aldehyde tested. With difficulties installing the desired cyclopropane functionality, presumably due to the steric bulk of aldehyde 3-92, we were intrigued to determine if the cycloaddition reaction could be performed on such a sterically demanding substrate.

**Table 3-1: Investigation into the Synthesis of 3-93**

<table>
<thead>
<tr>
<th>entry</th>
<th>additive</th>
<th>solvent</th>
<th>temp (°C)</th>
<th>time (h)</th>
<th>result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>KOtBu</td>
<td>THF</td>
<td>zero</td>
<td>5</td>
<td>No rxn</td>
</tr>
<tr>
<td>2</td>
<td>KOtBu</td>
<td>THF</td>
<td>rt</td>
<td>O/N</td>
<td>No rxn</td>
</tr>
<tr>
<td>3</td>
<td>KOtBu</td>
<td>THF</td>
<td>reflux</td>
<td>O/N</td>
<td>cyclopropane decomp.</td>
</tr>
<tr>
<td>4</td>
<td>KOtBu</td>
<td>ether</td>
<td>rt</td>
<td>O/N</td>
<td>No rxn</td>
</tr>
<tr>
<td>5</td>
<td>KOtBu</td>
<td>toluene</td>
<td>rt-reflux</td>
<td>O/N</td>
<td>decomp.</td>
</tr>
<tr>
<td>6&lt;sup&gt;b&lt;/sup&gt;</td>
<td>KOtBu</td>
<td>THF</td>
<td>rt</td>
<td>3</td>
<td>decomp.</td>
</tr>
<tr>
<td>7&lt;sup&gt;c&lt;/sup&gt;</td>
<td>KOtBu</td>
<td>THF</td>
<td>140</td>
<td>2</td>
<td>decomp.</td>
</tr>
<tr>
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<td>5</td>
<td>No rxn</td>
</tr>
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<td>THF</td>
<td>zero</td>
<td>5</td>
<td>decomp.</td>
</tr>
<tr>
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<td>THF</td>
<td>rt</td>
<td>O/N&lt;sup&gt;a&lt;/sup&gt;</td>
<td>No rxn</td>
</tr>
</tbody>
</table>

<sup>a</sup>O/N = overnight. <sup>b</sup>reaction performed in a high pressure reactor. <sup>c</sup>reaction performed in microwave
3.5.3 Retrosynthesis of Aspidospermidine Revisited

To determine if our pyrrolidine synthesis could work with a sterically demanding aldehyde starting material, we revised our synthetic path to aspidospermidine 3-6 to include an intermolecular [3+2] annulation reaction between a protected amine, cyclopropane 3-88, and aldehyde 3-99 (Scheme 3-18). In a similar fashion to the original approach, it was envisioned that the indole moiety could come from a late stage Fischer indolization reaction of ketone 3-31, which could be furnished via a lactam reduction and double decarboxylation of 3-96. Tricyclic intermediate 3-96 could be achieved through sequential lactamization and Dieckmann condensation reactions from the corresponding pyrrolidine 3-97. Pyrrolidine 3-97 could be achieved via the three component reaction of cyclopropane 3-88, amine 3-98, and aldehyde 3-99.

Scheme 3-18: Retrosynthesis Revisited

To test this route, aldehyde 3-99 was synthesized via exhaustive alkylation of the pyrrolidine enamine of butyraldehyde\(^2\) and subjected to the three component reaction
with a variety of different amines (Table 3-2). The first conditions explored followed the general procedure outlined in our 2005 paper utilizing reactive p-methoxy aniline. While imine formation did go to completion (determined by NMR), the ring-opening annulation event did not take place leaving only recovered starting material upon aqueous workup. The use of microwave conditions also failed to produce any of the cycloadduct $3\text{-101}$ (entry 2). Varying the amine and Lewis acid also proved unsuccessful, leading to recovery of starting materials (entry 3-8). We next explored the use of an activated cyclopropane ($R = \text{Ph}$) to determine if the reactivity of the cyclopropane species was at fault. Once again however, the cyclopropane ring-opening annulation event did not take place (entry 9). Having ruled out the reactivity of the cyclopropane, we next looked at the nucleophilic partner by employing the more reactive nitrone species (entry 10). Unfortunately, these conditions resulted only in recovery of starting material.

### Table 3-2: Investigating the Synthesis of $3\text{-101}$

<table>
<thead>
<tr>
<th>entry</th>
<th>$R$</th>
<th>amine$^a$</th>
<th>Lewis acid</th>
<th>temperature</th>
<th>time (h)</th>
<th>result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>PMP</td>
<td>Yb(OTf)$_3$</td>
<td>reflux</td>
<td>O/N$^b$</td>
<td>Imine formation$^d$ then no rxn</td>
</tr>
<tr>
<td>2$^c$</td>
<td>H</td>
<td>PMP</td>
<td>Yb(OTf)$_3$</td>
<td>150</td>
<td>4</td>
<td>Imine formation$^d$ then no rxn</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>Bn</td>
<td>Yb(OTf)$_3$</td>
<td>reflux</td>
<td>O/N$^b$</td>
<td>Imine formation$^d$ then no rxn</td>
</tr>
<tr>
<td>4$^c$</td>
<td>H</td>
<td>Bn</td>
<td>Yb(OTf)$_3$</td>
<td>150</td>
<td>4</td>
<td>Imine formation$^d$ then no rxn</td>
</tr>
<tr>
<td>5</td>
<td>H</td>
<td>PMP</td>
<td>Sc(OTf)$_3$</td>
<td>reflux</td>
<td>O/N$^b$</td>
<td>Imine formation$^d$ then no rxn</td>
</tr>
<tr>
<td>6$^c$</td>
<td>H</td>
<td>Bn</td>
<td>Sc(OTf)$_3$</td>
<td>150</td>
<td>4</td>
<td>Imine formation$^d$ then no rxn</td>
</tr>
<tr>
<td>7</td>
<td>H</td>
<td>PMP</td>
<td>Sc(OTf)$_3$</td>
<td>reflux</td>
<td>O/N$^b$</td>
<td>Imine formation$^d$ then no rxn</td>
</tr>
<tr>
<td>8$^c$</td>
<td>H</td>
<td>Bn</td>
<td>Sc(OTf)$_3$</td>
<td>150</td>
<td>4</td>
<td>Imine formation$^d$ then no rxn</td>
</tr>
<tr>
<td>9</td>
<td>H</td>
<td>PMP</td>
<td>In(OTf)$_3$</td>
<td>reflux</td>
<td>O/N$^b$</td>
<td>Imine formation$^d$ then no rxn</td>
</tr>
<tr>
<td>10</td>
<td>H</td>
<td>BnNHOH</td>
<td>Yb(OTf)$_3$</td>
<td>reflux</td>
<td>O/N$^b$</td>
<td>No rxn</td>
</tr>
</tbody>
</table>

$^a$PMP = p-methoxyphenyl, Bn = Benzyl. $^b$O/N = overnight. $^c$reaction performed in microwave. $^d$Imine formation determined by NMR (aliquot test).
At this point, it was clear to us that steric bulk around the aldehyde was too large to promote a three component intermolecular reaction to produce the desired pyrrolidine. Thus, we decided to explore an intramolecular imine formation followed by an intermolecular cyclopropane annulation (Scheme 3-19A). It was envisioned that cyclic imine 3-103 may be slightly more accessible for the annulation event. To this end, we started to develop a scalable route to amine 3-102. While attempting to selectively convert one of the esters of 3-99 to the corresponding amine, we noticed an interesting reductive lactonization process that gave lactone 3-105 in near quantitative yield (Scheme 3-19B). The potential utility of this transformation sparked our interest and ultimately shifted our focus to a different ring system and a different target molecule.

Scheme 3-19: Inspiring Lactone Forming Reaction

3.6 Progress Toward Quebrachamine

3.6.1 The Synthesis of 5,5-disubstituted Piperidinones

Intrigued by the lactone formation, we hypothesized that if an imine was used in place of the aldehyde, we would have quick access to quaternary substituted piperidines upon lactam reduction 3-107 (Figure 3-3A). Similar to pyrrolidine (previously shown), the quaternary substituted piperidine core is not only prevalent in the aspidosperma alkaloids, but also a variety of kopsia, vinca, and leuconotis alkaloids (Figure 3-3A). Due to the reoccurring nature of the 3,3-substituted piperidine core in target molecules, it occurred to us that compound 3-99 may be useful as a common intermediate in the synthesis of a
series of piperidine containing natural products. Herein, we report our initial findings on
the utility of intermediate 3-99 and the formal synthesis of quebrachamine.

A quick optimization varying solvent, temperature, and reducing agents led to facile
synthesis of piperidinone 3-108 in excellent overall yield via a one pot scandium triflate
catalyzed imine condensation followed by a sodium borohydride induced reductive
amination/lactamization sequence (Table 3-3). Although it was found that imine
formation was possible in the absence of the catalytic Lewis acid, the reaction times were
significantly increased and yields decreased when no catalytic additive was used.
Standard reductive amination conditions using sodium cyanoborohydride, proved to be
less efficient than sodium borohydride resulting in large amounts of recovered starting
materials. With ideal conditions in hand, we set out to determine the scope of amines
suitable for this transformation.

Tryptamine derivatives were quite compatible with the reaction conditions leading to
3-108a and 3-108b in good to excellent yields (Table 3-3). These results were
particularly interesting as they allowed quick access to the indole skeleton prevalent in
several target alkaloid molecules. Protected ethanolamine underwent the transformation
giving access to 3-108c in 76% yield while 2-(phenylthio)ethanol led to 3-108d in a
moderate 64% yield. The future utility of these two compounds (3-108c,d) was
noteworthy as their functional handles allowed for easy manipulation to more complex
scaffolding, as seen in several previous alkaloid syntheses.\textsuperscript{31} Additionally, benzyl amine was suitable as a starting material, giving $3\text{-}108e$ as protected piperidinone in an excellent yield. This particular reaction was amenable to scale up.

Table 3-3: Piperidine Synthesis Reaction Scope

<table>
<thead>
<tr>
<th>Reaction Scope</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Butyl amine</td>
<td>96%</td>
</tr>
<tr>
<td>Cyclohexanamine</td>
<td>64%</td>
</tr>
<tr>
<td>$3\text{-}108g$</td>
<td>31%\textsuperscript{b}</td>
</tr>
<tr>
<td>$3\text{-}108i$</td>
<td>31%</td>
</tr>
<tr>
<td>TBSO</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a} Reaction Conditions: Amine (1 equiv), 3-99 (1 equiv), $\text{Sc(OTf)}_3$ (2.5 mol%), $\text{NaBH}_4$ (1.25 equiv)\textsuperscript{b} Reaction gave $3\text{-}108g$ plus reductive amination product as the major product

Butyl amine worked well, giving high yields of the desired product $3\text{-}108f$; however, when cyclohexanamine was employed, lower yields of the desired product $3\text{-}108i$ were isolated. This result was presumably due to steric effects between the bulky amine and the neopentyl aldehyde, resulting in lower formation of the requisite imine. This hypothesis was further supported when tertbutylamine proved unreactive toward imine condensation with 3-99 under the reaction conditions. P-Methoxyaniline was shown to undergo the reaction with $3\text{-}108g$; however, in the best case, only 31% yield of $3\text{-}108g$
could be isolated. This low yield could be attributed to the slow lactam formation step of the reaction process since significant amounts of the simple reductive amination product were also isolated. Attempts to modify the reaction conditions (including variations in temperature) proved unsuccessful in increasing the overall yield for anilines. Finally, allylamine successfully led to 3-108h in an 83% yield, providing another useful handle for future manipulations.

In addition to amine substitution, the ester moiety of the product can also be manipulated in a one pot sequence (Scheme 3-20). When the reaction conditions were adjusted to use excess sodium borohydride in refluxing methanol, the corresponding (3-hydroxypropyl)piperidinones were isolated as the sole product. Interestingly, when compared to the initial reaction conditions (see Table 3-3), there was little to no effect on the overall yield of product even though an additional reduction event was added to the sequence (see Scheme 3-20 3-109a,b,c). This result allowed quick access to ideal functional handles on the three position of the piperidine core without loss of yield or extraneous purification.

![Scheme 3-20: One-pot Reductive Lactamization Ester Reduction](image)

If necessary, a two-step piperidinone ring formation ester reduction protocol could be applied, allowing access to the corresponding (3-hydroxypropyl)piperidinone in excellent yields (Scheme 3-21). Finally, the piperidine ring system can be accessed through a Red-Al® mediated lactam/ester reduction (Scheme 3-21). Piperidinone 3-108c containing the TBS ether gave piperidine 3-110a in 72% yield while benzyl protected 3-108e gave 3-110b in a nearly quantitative yield. The decrease in yield seen for 3-110a can be attributed to the in situ desilylation of the product under the reaction conditions.
3.6.2 Formal Synthesis of Quebrachamine

To display the utility of this transformation, the indole alkaloid (±)-quebrachamine (3-32) was targeted for synthesis. Starting from readily available dimethyl 3-ethyl-3-formylpimelate, a one-pot global reductive amination/lactamization protocol was employed with benzyl amine leading to piperidinone 3-109c in an 81% yield (Scheme 3-22). Oxidation of the corresponding primary alcohol with IBX gave aldehyde 3-111 without purification. Homologation of 3-111 with the Bestmann-Ohira reagent led to alkyne 3-112 in an excellent yield. Again, these conditions gave clean product upon workup. Next, the alkyne was subjected to a two-step cross coupling hydroamination protocol to furnish 3-113 in an overall 93% yield. It is noteworthy that all attempts at a one-pot Larock type indole synthesis resulted in lower yields of the desired product. With the indole core in hand, all that remained was lactam reduction and deprotection to give intermediate 3-52 that would merge with Pagenkopf’s synthesis in 2009.²¹

Scheme 3-22: Synthesis of Indole 3-113
Identifying the ideal conditions for the last two steps of the formal synthesis was not trivial. Initially, a dissolving metal reduction with sodium metal in ammonia was performed to remove the benzyl group (Scheme 3-23A). These results were promising by crude $^1$H-NMR; however, purification proved difficult. Attempts to take the crude deprotected product $3$-$114$ forward through the reduction process only resulted in decomposition. It was at this point that we focused on first reducing the lactam and then deprotecting the piperidine in hopes that these products would be easier to purify. Gratifyingly, reduction of the lactam with Red-Al® supplied the benzyl protected piperidine $3$-$115$ in an exceptional 97% yield (Scheme 3-23B). After several unsuccessful attempts to deprotect the benzyl group using standard hydrogenation conditions ($H_2$ with Pd/C or PtO$_2$) and dissolving metal conditions, it was found that transfer hydrogenation provided piperidine $3$-$52$, thus constituting a formal total synthesis of quebrachamine.

Scheme 3-23: Formal Synthesis of Quebrachamine

3.6.3 Progress Toward the Total Synthesis of Quebrachamine

With application of our piperidinone method successfully applied to the formal synthesis of quebrachamine, we were interested to see if we could complete the total synthesis utilizing a new 9-membered ring closing method. Two separate approaches were taken to close the 9-membered ring of quebrachamine and complete the total synthesis. The first approach involved finding a two carbon unit that could be attached directly to the indole 3-position and the nitrogen of the piperidine ring (Scheme 3-24A). The second approach
required synthesizing intermediate \(3-117\), thus allowing us to explore direct indole alkylation methods to close the 9-membered ring (Scheme 3-24B).

### Scheme 3-24: Total Synthesis Approaches

#### 3.6.3.1 Ring-Closing Approach 1

The first attempt at ring-closing involved the intramolecular attack of the indole onto an alkyne \((3-120)\) (Scheme 3-25B). Precedent for this transformation was supported by the work of Fujii and Ohno who showed the synthesis of fused indoles via a cascade cyclization of diynes (Scheme 2-25A).34 While their method worked well for the formation of smaller 5 and 6-membered ring systems, in our hands, the 9-member ring would not close, leading to slow decomposition of \(3-120\).

### Scheme 3-25: Alkyne Ring-Closing Attempted
Our next effort to close the ring using intermediate 3-52 paralleled the work of Diez, who showed the 6-membered ring closure of intermediate 3-122 with glyoxal (Scheme 3-26A). All attempts to utilize Diez’s conditions were met with decomposition of starting material 3-52 (Scheme 3-26B). While several other attempts utilizing a variety of different methods were made to attach the required two carbon unit to 3-52, no promising results were observed. Although there was ample precedence for the formation of smaller 5, 6, and 7-membered rings, the difficulty we observed in forming the 9-membered ring under the same conditions compelled us to pursue an alternative approach to closing the ring system.

Scheme 3-26: Glyoxal Approach

3.6.3.2 Ring-Closing Approach 2

To attempt our second approach at ring-closing, intermediates 3-125 and 3-126 were synthesized following the same procedure (see Scheme 3-22) used to make intermediate 3-113 (Scheme 3-27). 3-125 and 3-126 were furnished in overall 55% and 35% yields respectively over the 5 step procedure. TBAF deprotection of 3-125 gave the free primary alcohol which we initially envisioned could be converted into a leaving group, allowing for a direct indole alkylation approach to close the 9-membered ring.
Following procedures developed by Bach in the synthesis of aspidospermidine (Scheme 3-28A),\textsuperscript{36} we attempted a one pot mesylation/displacement method. Alcohol 3-128 was subjected to MsCl in dichloromethane at -20 °C followed by the addition of excess tBuOK (Scheme 3-28B). Interestingly, the chloro intermediate 3-129 was isolated instead of the ring-closed adduct. This result can be explained by simple displacement of the mesylate with the resulting chloride anion. Attempts to close the ring of 3-129 directly using forcing conditions (e.g. excess base, microwave heating) resulted in slow decomposition of the starting material. Additionally, Friedel-Crafts alkylation\textsuperscript{37} conditions of 3-129 also resulted in decomposition of the starting material (Scheme 3-28C).
With both direct alkylation and Friedel-Crafts approaches proving inadequate for closing the 9-membered ring, we next directed our focus to a reductive alkylation approach, utilizing aldehyde 3-130 (Scheme 3-29A). This method proved difficult due to the instability of 3-128 toward oxidative conditions, leading to decomposition under all oxidations attempted, including Swern, Parikh-Doering, IBX, DMP, and PCC oxidation methods. In addition to the oxidation attempts, direct Mitsunobu displacement of 3-128 also proved insufficient at closing the ring system, leading only to small amounts of recovered starting material (Scheme 3-29B).

Scheme 3-29: Reductive Alkylation and Mitsunobu Attempts

In a final attempt to close the 9-membered ring of quebrachamine, we explored the use of a Pummerer type reaction of 3-126 due to its previous success in this area in creating smaller membered rings.\(^{31}\) It was envisioned that oxidation of sulfide 3-126 to the corresponding sulfoxide 3-132, followed by treatment with TFAA and a final reduction would furnish the target molecule 3-32 (Scheme 3-30). Unfortunately, once again, 3-126 proved to be unstable to oxidation conditions leading to undesired byproducts and decomposition. Due to the instability of intermediates 3-128 and 3-126 toward oxidation chemistry, it is unclear at this point whether the ring-closing process (Scheme 3-29A and 3-30) would be effective in the synthesis of quebrachamine. Thus, future work in this area should involve the protection of the indole nitrogen to limit any unwanted side reactions during both oxidation steps.
3.7 Summary and Future Outlook

In conclusion, synthetic attempts have been explored into the synthesis of aspidospermidine, albeit conditions have yet to be determined to promote the [3+2] pyrrolidine forming reaction of sterically restricted aldehydes. Additionally, we have developed a method utilizing common starting material 3-99 in the synthesis of a variety of N-substituted piperidinone scaffolds via a reductive amination/lactamization sequence, and this process has been applied to the short formal synthesis of indole alkaloid (±)-quebrachamine. Although advancing this method to the total synthesis of quebrachamine has yet to be achieved, several alternative methods to close the last 9-membered ring have been left unexplored due to time constraints. The preliminary results using common intermediate 3-99 show great promise for the use of a common intermediate in the synthesis of a series of nitrogen containing natural products.

It is envisioned that future efforts in this area of research can be directed toward two different areas. First, in the total synthesis of quebrachamine, additional efforts should be explored for the ring closing event, including the protection of the indole moiety followed by reevaluation of all the oxidation methods, as previously described. Additionally, due to the recent advancements in both cross-coupling reactions and C-H activation methods, it would be useful to explore this chemistry to close the last ring of quebrachamine (Scheme 3-31).
The second area of future research should focus on exploiting the common structural features of the aspidosperma, kopsia, vinca, and leuconotis alkaloids. The similarity of these compounds would allow for a unified approach from a common intermediate. While the use of 3-99 was successful in the formal synthesis of quebrachamine, it possesses structural drawbacks which will ultimately limit the utility of this intermediate in the synthesis of other target molecules. In this vein, attention should be directed toward a suitable amine intermediate such as 3-135 (Figure 3-4) as a potential ideal starting material for the synthesis of a series of alkaloid natural products.

Scheme 3-32: Potential Intermediate for the Synthesis of Alkaloid Natural Products
3.8 Experimental

General Considerations

Infrared spectra were obtained as thin films on NaCl plates using a Bruker Vector 33 FT-IR instrument. NMR experiments were performed on Varian Mercury 400, Varian Inova 600 and Inova 400 instruments and samples were obtained in CDCl₃ (referenced to 7.26 ppm for "H and 77.0 ppm for [13C]). [19F] spectra were externally referenced to neat trifluorotoluene (referenced to -63.9 ppm). Coupling constants (J) are in Hz. The multiplicities of the signals are described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, sept = septuplet, m = multiplet, br = broad. High resolution mass spectra (HRMS) were obtained on a Finnigan MAT 8200 spectrometer at 70 eV. Optical rotations were recorded in cells of 10 cm path length using a Perkin-Elmer 241 digital polarimeter.

All reagents and solvents were used as purchased from Aldrich, Strem, Caledon or VWR. Reaction progress was followed by thin layer chromatography (TLC) (EM Science, silica gel 60 F₂₅₄) visualizing with UV light, and the plates developed using acidic anisaldehyde. Flash chromatography was performed using silica gel purchased from Silicycle Chemical Division Inc. (230-400 mesh).

Dimethyl 3-ethyl-3-formylpimelate 3-99 was prepared using the following procedure: Pyrrolidine (50.0 mL, 609 mmol) and K₂CO₃ (21.0 g, 150 mmol) were stirred at 0°C. Butyraldehyde (36.4 mL, 406 mmol) was added dropwise to the solution. The solution was mixed for 20 h then filtered through Celite, and the volatiles were removed. The cured 1-(but-1-enyl)pyrrolidine was dissolved in methanol (391 mL). Methyl acrylate (118.0 mL, 1302 mmol) was added and the solution was heated to reflux for 21 h. The reaction mixture was then cooled and acetic acid (24.0 mL) and H₂O (156.0 mL) was added and the mixture was heated to reflux for an additional 7 hours. The volatiles were then removed and H₂O (820.0 mL) was added, and the solution was extracted four times with DCM. The organics were then
washed with aqueous sodium bicarbonate and brine sequentially. The organic layer was dried and the solvent removed. The crude product was purified by fractional distillation (140-142°C at 1 mmhg) to yield pure 3-99 as a yellow oil, 54% (54 g, 221 mmol). \(^1\)H-NMR (600 MHz, CDCl\(_3\)): \(\delta = 9.37\) (s, 1H), 3.62 (s, 6H), 2.17 (ddd, \(J = 7.6, 7.6, 3.5\) Hz, 4H), 1.81 (ddd, \(J = 8.2, 7.1, 1.8\) Hz, 4H), 1.51 (q, \(J = 7.6\) Hz, 2H), 0.79 (t, \(J = 7.0\) Hz, 3H); \(^1\)C NMR (150 MHz, CDCl\(_3\)) \(\delta = 205.0, 173.4, 51.9, 51.0, 28.2, 26.0, 24.3, 7.6\); IR (thin film): 2954, 2708, 1732, 1438, 1377, 1377, 1120, 991, 886, 784; HRMS (M+1) calc’d for C\(_{12}\)H\(_{20}\)O\(_5\) = 245.1384, found = 245.1397.

**General Experimental Procedure for the Synthesis of Piperidinones 3-108a-i:** dimethyl 3-ethyl-3-formylpimelate (1 equivalent) and primary amine (1 equivalent) were dissolved in methanol. Sc(OTf)_3 (0.025 equivalent) was then added and the mixture was stirred for 1-2 hours, followed by the addition of NaBH\(_4\) (1.25 equivalent). Upon completion by TLC analysis water was added to the reaction mixture and extracted 3 times with ethyl acetate. The organic layer was dried and the solvent was removed. The residue was purified by flash chromatography (EtOAc/Hexanes) to yield the desired piperidinones 3-108a-i.

Piperidine 3-108a was prepared using general experimental procedure. Reagents employed: dimethyl 3-ethyl-3-formylpimelate 3-99 (200 mg, 0.820 mmol), 2-(1H-indol-3-yl)ethanamine (144 mg, 0.90 mmol), Sc(OTf)_3 (20 mg, 0.041 mmol), NaBH\(_4\) (37 mg, 0.98 mmol), and methanol (2 mL). Yielded piperidine 3-108a as a light yellow oil, 96% (280 mg, 0.79 mmol). \(R_f = 0.33, 100\%\) EtOAc in hexanes; \(^1\)H-NMR (600 MHz, CDCl\(_3\)): \(\delta = 8.22\) (brs, 1H), 7.65 (d, \(J = 7.6\) Hz, 1H), 7.35 (d, \(J = 8.2\) Hz, 1H), 7.18 (t, \(J = 8.2\) Hz, 1H), 7.12 (t, \(J = 7.6\) Hz, 1H), 7.04 (d, \(J = 2.4\) Hz, 1H), 3.70-3.59 (m, 5H), 3.03 (dd, \(J = 12.3, 7.4\) Hz, 2H), 2.92 (AB system, \(J = 12.3\) Hz, 2H), 2.37 (dd, \(J = 7.0, 7.0\) Hz, 2H), 2.19-2.07 (m, 2H), 1.66-1.60 (m, 1H), 1.59-1.51 (m, 3H), 1.34-1.27 (m 1H), 1.27-1.20 (m, 1H), 0.74 (t, \(J = 7.6\) Hz, 3H); \(^1\)C NMR (150 MHz, CDCl\(_3\)) \(\delta = 173.9, 169.5, 136.3, 127.5, 122.1,\)
Piperidinone 3-108b was prepared using general experimental procedure. Reagents employed: dimethyl 3-ethyl-3-formylpimelate 3-99 (200 mg, 0.82 mmol), tert-butyl 3-(2-aminoethyl)-1H-indole-1-carboxylate (234 mg, 0.90 mmol), Sc(OTf)\(_3\) (20 mg, 0.041 mmol), NaBH\(_4\) (37 mg, 0.98 mmol), and methanol (2 mL). Yielded piperidinone 3-108b as a light yellow oil, 76% (285 mg, 0.62 mmol). R\(\text{f}\) = 0.43, 100% EtOAc in hexanes; \(^1\)H-NMR (600 MHz, CDCl\(_3\)): \(\delta = 8.12\) (brs, 1H), 7.62 (d, \(J = 7.6\) Hz, 1H), 7.41 (brs, 1H), 7.31 (t, \(J = 7.6\) Hz, 1H), 7.26-7.23 (m, 1H), 3.70-3.63 (m, 4H), 3.59-3.53 (m, 1H), 3.02-2.91 (m, 4H), 2.38 (dd, \(J = 7.0, 7.0\) Hz, 2H), 2.23-2.13 (m, 2H), 1.70-1.51 (m, 13H), 1.40-1.32 (m, 1H), 1.31-1.23 (m, 1H), 0.79 (t, \(J = 7.6\) Hz, 3H); \(^{13}\)C NMR (150 MHz, CDCl\(_3\)) \(\delta = 173.6, 169.4, 149.5, 135.4, 130.3, 124.3, 123.0, 122.4, 118.9, 117.6, 115.1, 82.3, 57.2, 51.6, 47.9, 34.3, 29.5, 29.1, 28.4, 28.12, 28.08, 26.5, 22.8, 7.2; IR (thin film): 2969, 2936, 2879, 1735, 1640, 1618, 1454, 1371, 1256, 1157, 1093, 751; HRMS calc’d for C\(_{26}\)H\(_{36}\)N\(_2\)O\(_5\) = 456.2624, found = 456.2629.

Piperidinone 3-108c was prepared using general experimental procedure. Reagents employed: dimethyl 3-ethyl-3-formylpimelate 3-99 (300 mg, 1.23 mmol), 2-(tert-butyldimethylsilyloxy)ethanamine (237 mg, 1.35 mmol), Sc(OTf)\(_3\) (30 mg, 0.061 mmol), NaBH\(_4\) (56 mg, 1.48 mmol), and methanol (3 mL). Yielded piperidinone 3-108c as a yellow oil, 76% (346 mg, 0.93 mmol). R\(\text{f}\) = 0.27, 100% EtOAc in hexanes; \(^1\)H-NMR (600 MHz, CDCl\(_3\)): \(\delta = 3.76\) (dd, \(J = 5.9, 5.9\) Hz, 2H), 3.67 (s, 3H), 3.49-3.40 (m, 2H), 3.18 (Br s, 2H), 2.35 (dd, \(J = 7.0, 7.0\) Hz, 2H), 2.25-2.22 (m, 2H), 1.75-1.66 (m, 2H), 1.63-1.55 (m, 2H), 1.44-1.38 (m, 1H), 1.36-1.30 (m, 1H), 0.89 (s, 9H), 0.84 (t, \(J = 7.3\) Hz, 3H), 0.05 (s, 6H); \(^{13}\)C NMR (150 MHz, CDCl\(_3\)) \(\delta = 173.6, 169.4, 149.5, 135.4, 130.3, 124.3, 123.0, 122.4, 118.9, 117.6, 115.1, 82.3, 57.2, 51.6, 47.9, 34.3, 29.5, 29.1, 28.4, 28.12, 28.08, 26.5, 22.8, 7.2; IR (thin film): 2969, 2936, 2879, 1735, 1640, 1618, 1454, 1371, 1256, 1157, 1093, 751; HRMS calc’d for C\(_{26}\)H\(_{36}\)N\(_2\)O\(_5\) = 456.2624, found = 456.2629.
MHz, CDCl₃) δ = 173.8, 169.6, 61.6, 58.9, 51.7, 50.5, 34.5, 29.7, 28.9, 28.5, 28.3, 26.9, 25.8, 18.1, 7.4, -5.5; IR (thin film): 2930, 2858, 1740, 1646, 1493, 1470, 1436, 1363, 1256, 1105, 1054, 1006, 921, 837, 778; HRMS (M+1) calc’d for C₁₀H₁₇NO₄Si = 372.2565, found = 372.2565.

Piperidinone 3-108d was prepared using general experimental procedure. Reagents employed: dimethyl 3-ethyl-3-formylpimelate 3-99 (726 mg, 2.97 mmol), 2-(phenylthio)ethanamine (500 mg, 3.26 mmol), Sc(OTf)₃ (36 mg, 0.073 mmol), NaBH₄ (135 mg, 3.57 mmol), and methanol (7 mL). Yielded piperidinone 3-108d as a red oil, 64% (660 mg, 1.89 mmol). Rₙ = 0.23, 100% EtOAc in hexanes; ¹H-NMR (600 MHz, CDCl₃): δ = 7.38 (d, J = 7.0 Hz, 2H), 7.30 (t, J = 7.6 Hz, 2H), 7.18 (t, J = 7.0 Hz, 1H), 3.67 (s, 3H), 3.57-3.49 (m, 2H), 3.14 (dd, J = 7.0, 7.0 Hz, 2H), 3.05 (Br s, 2H), 2.33 (dd, J = 7.0, 7.0 Hz, 2H), 2.24-2.21 (m, 2H), 1.70-1.66 (m, 2H), 1.58-1.50 (m, 2H), 1.41-1.30 (m, 2H), 0.83 (t, J = 7.6 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ = 173.7, 169.8, 129.0, 128.9, 126.0, 58.1, 51.8, 48.1, 34.6, 30.5, 29.7, 29.1, 28.4, 28.3, 26.7, 7.4 (missing 1 carbon presumably due to overlap); IR (thin film): 2932, 2876, 1736, 1642, 1492, 1438, 1363, 1295, 1229, 1168, 1025, 741, 693; HRMS calc’d for C₁₉H₂₇NO₃S = 349.1712, found = 349.1719.

Piperidinone 3-108e was prepared using general experimental procedure. Reagents employed: dimethyl 3-ethyl-3-formylpimelate 3-99 (200 mg, 0.82 mmol), phenylmethanamine (88 mg, 0.82 mmol), Sc(OTf)₃ (10 mg, 0.020 mmol), NaBH₄ (39 mg, 1.031 mmol), and methanol (2 mL). Yielded piperidinone 3-108e as an orange oil, 81% (202 mg, 0.67 mmol). Rₙ = 0.28, 100% EtOAc in hexanes; ¹H-NMR (600 MHz, CDCl₃): δ = 7.32-7.30 (m, 2H), 7.27-7.24 (m, 3H), 4.57 (AB system, J = 14.7 Hz, 2H), 3.65 (s, 3H), 2.91 (s, 2H), 2.46 (dd, J = 7.0, 1.2 Hz, 2H), 2.18-2.12 (m, 1H), 2.04-1.98 (m, 1H), 1.63-1.59 (m, 4H), 1.33-1.22 (m, 2H), 0.71 (t, J = 7.6 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ = 173.7, 169.5, 137.1, 128.6, 128.3, 127.5,
Piperidinone 3-108f was prepared using general experimental procedure. Reagents employed: dimethyl 3-ethyl-3-formylpimelate 3-99 (200 mg, 0.82 mmol), butan-1-amine (60 mg, 0.82 mmol), Sc(OTf)_3 (10 mg, 0.020 mmol), NaBH_4 (39 mg, 1.031 mmol), and methanol (2 mL). Yielded piperidinone 3-108f as a yellow oil, 86% (190 mg, 0.71 mmol). R_f = 0.38, 100% EtOAc in hexanes; ^1H-NMR (600 MHz, CDCl_3): δ = 3.67 (s, 3), 3.36-3.26 (m, 2H), 2.99 (s, 2H), 2.33 (dd, J = 7.0, 7.0 Hz, 2H), 2.27-2.19 (m, 2H), 1.73-1.64 (m, 2H), 1.63-1.54 (m, 2H), 1.50-1.45 (m, 2H), 1.42-1.27 (m, 4H), 0.91 (t, J = 7.0 Hz, 3H), 0.84 (t, J = 7.6 Hz, 3H); ^13C NMR (150 MHz, CDCl_3) δ = 173.8, 169.2, 56.5, 51.8, 47.1, 34.4, 29.9, 29.2, 29.1, 28.5, 28.3, 26.7, 20.1, 13.9, 7.4; IR (thin film): 2957, 2872, 1739, 1644, 1435, 1366, 1317, 1229, 1167, 1000; HRMS calc’d for C_{15}H_{27}NO_3 = 269.1991, found = 269.1986.

Piperidinone 3-108g was prepared using general experimental procedure. Reagents employed: dimethyl 3-ethyl-3-formylpimelate 3-99 (200 mg, 0.82 mmol), 4-methoxyaniline (101 mg, 0.82 mmol), Sc(OTf)_3 (10 mg, 0.020 mmol), NaBH_4 (39 mg, 1.031 mmol), and methanol (2 mL). Yielded piperidinone 3-108g as a brown oil, 31% (82 mg, 0.26 mmol). R_f = 0.32, 100% EtOAc in hexanes; ^1H-NMR (600 MHz, CDCl_3): δ = 7.12 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 3.79 (s, 3H), 3.67 (s, 3H), 3.34 (s, 2H), 2.59 (dd, J = 7.0, 7.0 Hz, 2H), 2.31-2.21 (m, 2H), 1.84-1.76 (m, 2H), 1.75-1.71 (m, 2H), 1.53-1.41 (m, 2H), 0.87 (t, J = 7.6 Hz, 3H); ^13C NMR (150 MHz, CDCl_3) δ = 173.7, 170.0, 158.1, 136.2, 127.2, 114.5, 60.4, 55.4, 51.7, 34.9, 30.0, 29.0, 28.9, 28.3, 28.8, 7.4; IR (thin film):
Piperidinone 3-108h was prepared using general experimental procedure. Reagents employed: dimethyl 3-ethyl-3-formylpimelate 3-99 (200 mg, 0.82 mmol), prop-2-en-1-amine (47 mg, 0.82 mmol), Sc(OTf)₃ (10 mg, 0.02 mmol), NaBH₄ (39 mg, 1.031 mmol), and methanol (2 mL). Yielded piperidinone 3-108h as a yellow oil, 83% (171 mg, 0.68 mmol). R_f = 0.30, 100% EtOAc in hexanes; ¹H-NMR (600 MHz, CDCl₃): δ = 5.76-5.69 (m, 1H), 5.17 (ddd, J = 10.0, 7.0, 1.2 Hz, 2H), 4.08-3.92 (m, 2H), 3.67 (s, 3H), 2.96 (s, 2H), 2.38 (dd, J = 7.0, 7.0 Hz, 2H), 2.27-2.18 (m, 2H), 1.69 (ddd, J = 10.6, 7.0, 3.5 Hz, 2H), 1.64-1.57 (m, 2H), 1.40-1.32 (m, 2H), 0.84 (t, J = 7.6 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ = 173.8, 169.3, 132.9, 117.9, 55.7, 51.8, 49.6, 34.4, 29.9, 29.1, 28.4, 28.3, 26.7, 7.4; IR (thin film): 3079, 2949, 2878, 1740, 1636, 1493, 1436, 1364, 1314, 1270, 1228, 1195, 996, 926, 853, 726; HRMS calc’d for C₁₅H₂₃NO₃ = 253.1678, found = 253.1678.

Piperidinone 3-108i was prepared using general experimental procedure. Reagents employed: dimethyl 3-ethyl-3-formylpimelate 3-99 (200 mg, 0.82 mmol), cyclohexanamine (81 mg, 0.82 mmol), Sc(OTf)₃ (10 mg, 0.020 mmol), NaBH₄ (39 mg, 1.031 mmol), and methanol (2 mL). Yielded piperidinone 3-108i as a pale yellow oil, 40% (98 mg, 0.33 mmol). R_f = 0.29, 100% EtOAc in hexanes; ¹H-NMR (600 MHz, CDCl₃): δ = 4.50-4.44 (m, 1H), 3.66 (s, 3H), 2.88 (s, 2H), 2.34 (dd, J = 7.0, 7.0 Hz, 2H), 2.22 (dd, J = 14.7, 7.0 Hz, 2H), 1.77-1.75 (m, 2H), 1.65-1.63 (m, 3H), 1.61-1.57 (m, 2H), 1.55-1.50 (m, 2H), 1.41-1.23 (m, 6H), 1.08-1.01 (m, 1H), 0.83 (t, J = 7.6 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ = 173.8, 169.0, 51.7, 51.6, 50.1, 34.1, 29.54, 29.50, 29.4, 29.1, 28.8, 28.2, 26.5, 25.51, 25.48, 25.46, 7.3; IR (thin film): 2929, 2856, 1739, 1637, 1451, 1296, 1254, 1228, 1196, 1168, 1069; HRMS calc’d for C₁₇H₂₉NO₃ = 295.2147, found = 295.2151.
General Experimental Procedure 1 for the Synthesis of 5-(3-hydroxypropyl)piperidin-2-one 3-109a-c: Piperidinone 3-108c-e (1 equivalent) was dissolved in methanol, followed by the addition of NaBH₄ (5 equivalents). The mixture was heated to reflux for 10 min, and then cooled to room temperature. Then additional NaBH₄ (5 equivalents) was added followed by a 10 min reflux period, this process was continued until a total of 40 equivalents NaBH₄ was added. Upon complete addition of NaBH₄, water was slowly added to the reaction mixture and extracted 3 times with ethyl acetate. The organic layer was dried and the solvent was removed. The residue was purified by flash chromatography (EtOAc/Hexanes) to yield the desired piperidinones 3-109a-c.

5-(3-Hydroxypropyl)piperidin-2-one 3-109a was prepared using general experimental procedure 1. Reagents employed: piperidinone 3-108c (677 mg, 1.82 mmol), NaBH₄ (2750 mg, 72.88 mmol), and methanol (30 mL). Yielded 3-109a as a thick yellow oil, 99% (630 mg, 1.81 mmol). Rf = 0.14, 100% EtOAc in hexanes; ¹H-NMR (600 MHz, CDCl₃): δ = 3.71 (dd, J = 5.3, 5.3 Hz, 2H), 3.56 (dd, J = 5.9, 5.9 Hz, 2H), 3.46-3.42 (m, 1H), 3.37-3.33 (m, 1H), 3.14 (AB system, J = 12.3 Hz, 2H), 2.47 (brs, 1H), 2.29 (dd, J = 7.0, 7.0 Hz, 2H), 1.55 (dd, J = 7.0, 7.0 Hz, 2H).

General Experimental Procedure 2 for the Synthesis of 5-(3-hydroxypropyl)piperidin-2-one 3-109a-c: Dimethyl 3-ethyl-3-formylpimelate (1 equivalent) and primary amine (1 equivalent) were dissolved in methanol. Sc(OTf)₃ (0.025 equivalent) was then added and the mixture was stirred for 1-2 hours, followed by the addition of NaBH₄ (5 equivalents). The mixture was heated to reflux for 10 min, and then cooled to room temperature. Then additional NaBH₄ (5 equivalents) was added followed by a 10 min reflux period, this process was continued until a total of 40 equivalents NaBH₄ was added. Upon complete addition of NaBH₄, water was slowly added to the reaction mixture and extracted 3 times with ethyl acetate. The organic layer was dried and the solvent was removed. The residue was purified by flash chromatography (EtOAc/Hexanes) to yield the desired piperidinones 3-109a-c.
7.0 Hz, 2H), 1.46-1.34 (m, 4), 1.33-1.26 (m, 2H), 0.84 (s, 9H), 0.79 (t, J = 7.6 Hz, 3H), 0.00 (s, 6H); \(^{13}\)C NMR (150 MHz, CDCl\(_3\)) \(\delta = 170.1, 62.9, 61.4, 59.3, 50.5, 34.5, 30.0, 29.8, 28.5, 27.1, 26.2, 25.8, 18.1, 7.4, -5.5\); IR (thin film): 2930, 2858, 1626, 1497, 1464, 1418, 1362, 1255, 1101, 1058, 837, 778; HRMS (M+1) calc’d for C\(_{18}\)H\(_{37}\)NO\(_3\)Si = 344.2622, found = 344.2615.

5-(3-Hydroxypropyl)piperidin-2-one \textit{3-109b} was prepared using general experimental procedure 1. Reagents employed: piperidinone \textit{3-108d} (540 mg, 1.55 mmol), NaBH\(_4\) (2340 mg, 61.80 mmol), and methanol (30 mL). Yielded \textit{3-109b} as an orange oil, 100% (498 mg, 1.55 mmol). R\(_f\) = 0.22, 100% EtOAc in hexanes; \(^1\)H-NMR (600 MHz, CDCl\(_3\)): \(\delta = 7.39\) (d, J = 7.0 Hz, 2H), 7.30 (t, J = 7.6 Hz, 2H), 7.18 (t, J = 7.6 Hz, 1H), 3.63 (dd, J = 6.5 Hz, 2H), 3.53 (dd, J = 8.2, 6.5, 2H), 3.31 (dd, J = 7.0, 7.0 Hz, 2H), 3.06 (Br s, 2H), 2.33 (dd, J = 7.0, 7.0 Hz, 2H), 1.55 (dd, J = 7.0, 7.0 Hz, 2H), 1.51-1.43 (m, 4H), 1.42-1.33 (m, 2H), 0.83 (t, J = 7.6 Hz, 3H); \(^{13}\)C NMR (150 MHz, CDCl\(_3\)) \(\delta = 170.1, 129.0, 128.7, 126.0, 63.2, 58.4, 48.0, 34.6, 30.4, 30.0, 29.9, 28.6, 27.1, 26.3, 7.5\) (missing 1 carbon presumably due to overlap); IR (thin film): 2938, 2866, 1623, 1496, 1438, 1418, 1363, 1297, 1229, 1066, 741, 692; HRMS calc’d for C\(_{18}\)H\(_{27}\)NO\(_2\)S = 321.1762, found = 321.1769.

5-(3-Hydroxypropyl)piperidin-2-one \textit{3-109c} was prepared using general experimental procedure 1. Reagents employed: piperidinone \textit{3-108e} (1600 mg, 5.30 mmol), NaBH\(_4\) (10 \(\times\) 10\(^4\) mg, 264.00 mmol), and methanol (79 mL). Yielded \textit{3-109c} as a dark yellow oil, 100% (1459 mg, 5.30 mmol). R\(_f\) = 0.14, 100% EtOAc in hexanes; \(^1\)H-NMR (600 MHz, CDCl\(_3\)): \(\delta = 7.32-7.30\) (m, 2H), 7.27-7.24 (m, 3H), 4.55 (AB system, J = 14.6 Hz, 2H), 3.51 (dd, J = 5.9, 5.9 Hz, 2H), 2.92 (Br s, 2H), 2.43 (dd, J = 7.0, 7.0 Hz, 2H), 1.62 (m, 3H), 1.43-1.35 (m, 1H), 1.34-1.16 (m, 5H), 0.71 (t, J = 7.0 Hz, 3H); \(^{13}\)C NMR (150 MHz, CDCl\(_3\)) \(\delta = 169.8, 137.3, 128.5, 128.3, 127.4, 63.1, 55.7, 50.3, 34.3, 30.2, 29.9, 28.5, 26.9, 26.2, 7.3\); IR (thin film): 3395, 2939, 2866,
5-(3-Hydroxypropyl)piperidin-2-one 3-109a was prepared using general experimental procedure 2. Reagents employed: dimethyl 3-ethyl-3-formylpimelate 3-99 (633 mg, 2.59 mmol), 2-(tert-butyldimethylsilyloxy)ethanamine (500 mg, 2.85 mmol), Sc(OTf)₃ (32 mg, 0.65 mmol), NaBH₄ (3920 mg, 103.62 mmol), and methanol (65 mL). Yielded 3-109a as a thick yellow oil, 72% (640 mg, 1.86 mmol).

5-(3-Hydroxypropyl)piperidin-2-one 3-109b was prepared using general experimental procedure 1. Reagents employed: dimethyl 3-ethyl-3-formylpimelate 3-99 (1880 mg, 7.70 mmol), 2-(phenylthio)ethanamine (1300 mg, 8.48 mmol), Sc(OTf)₃ (94 mg, 0.19 mmol), NaBH₄ (11650 mg, 308.00 mmol), and methanol (98 mL). Yielded 3-109b as an orange oil, 60% (1485 mg, 4.62 mmol).

5-(3-Hydroxypropyl)piperidin-2-one 3-109b was prepared using general experimental procedure 1. Reagents employed: dimethyl 3-ethyl-3-formylpimelate 3-99 (4560 mg, 18.67 mmol), phenylmethanamine (2000 mg, 18.67 mmol), Sc(OTf)₃ (231 mg, 0.47 mmol), NaBH₄ (35300 mg, 933.12 mmol), and methanol (250 mL). Yielded 3-109c as a dark yellow oil, 81% (4160 mg, 15.11 mmol).

Piperidine 3-110a was prepared using the following procedure: Piperidinone 3-108c (250 mg, 0.67 mmol) was dissolved in THF (25 mL) followed by the addition of Red-Al® (65% by weight) (0.82 mL, 2.69 mmol). Upon completion by TLC analysis water was added to the reaction mixture and extracted 3
times with EtOAc. The organic layer was dried and the solvent was removed. The residue was purified by flash chromatography (EtOAc/Hexanes) to yield the desired product 3-110a as an orange oil, 72% (160 mg, 0.49 mmol). Rf = 0.11, 100% EtOAc in hexanes; 1H-NMR (600 MHz, CDCl3): δ = 3.71 (dd, J = 6.5, 6.5 Hz, 2H), 3.61 (ddd, J = 6.5, 6.5, 2.3 Hz, 2H), 2.51-2.39 (m, 3H), 2.31-2.19 (m, 2H), 2.08-2.04 (m, 1H), 1.61-1.50 (m, 2H), 1.49-1.37 (m, 3H), 1.36-1.25 (m, 4H), 1.20-1.16 (m, 1H), 0.88 (s, 9H), 0.77 (t, J = 7.0 Hz, 3H), 0.05 (s, 6H); 13C NMR (150 MHz, CDCl3) δ = 63.8, 63.6, 61.3, 61.2, 55.4, 35.3, 33.6, 28.3, 25.9, 21.9, 18.3, 7.3, 5.3 (missing 2 carbon presumably due to overlap); IR (thin film): 2933, 2857, 1463, 1255, 1103, 1068, 836, 776; HRMS calc’d for C18H39NO2Si = 329.2750, found = 329.2754.

Piperidine 3-110b was prepared using the following procedure: Piperidinone 3-108e (131 mg, 0.43 mmol) was dissolved in THF (10 mL) followed by the addition of Red-Al® (65% by weight) (0.53 mL, 1.74 mmol). Upon completion by TLC analysis water was added to the reaction mixture and extracted 3 times with EtOAc. The organic layer was dried and the solvent was removed. The residue was purified by flash chromatography (EtOAc/Hexanes) to yield the desired product 3-110b as brown oil, 98% (110 mg, 0.42 mmol). Rf = 0.23, 100% EtOAc in hexanes; 1H-NMR (600 MHz, CDCl3): δ = 7.34-7.28 (m, 4H), 7.24-7.22 (m, 1H), 3.60 (dd, J = 5.9, 5.9 Hz, 2H), 3.46-3.38 (m, 2H), 2.45-2.36 (m, 1H), 2.31-2.22 (m, 1H), 2.17-2.10 (m, 1H), 2.03-1.94 (m, 1H), 1.65-1.51 (m, 2H), 1.47-1.14 (m, 2H), 1.38-1.23 (m, 6H), 0.73 (t, J = 7.6 Hz, 3H); 13C NMR (150 MHz, CDCl3) δ = 128.9, 128.0, 126.8, 63.8, 63.5, 62.5, 54.8, 35.4, 33.8, 26.2, 21.8, 18.4, 7.2 (missing 2 carbon presumably due to overlap); IR (thin film): 2936, 2858, 2793, 2754, 1453, 1350, 1059, 739, 698; HRMS calc’d for C17H27NO = 261.2093, found = 261.2097.

**General Experimental Procedure for Alcohol 3-109a-c Oxidation to Aldehyde 3-111a-c:** Alcohol 3-109a-c (1 equivalent) was dissolved in EtOAc, followed by the addition of IBX (3 equivalents). The mixture was heated to reflux with rapid stirring until consumption of starting material as determined by TLC analysis. The reaction mixture
was filter through Celite® with EtOAc and the solvent was removed to yield the desired aldehyde 3-111a-c.

Aldehyde 3-111a was prepared using general experimental procedure. Reagents employed: piperidinone 3-109a (200 mg, 0.58 mmol), IBX (489 mg, 1.75 mmol), and EtOAc (10 mL). Yielded 3-111a as a pale yellow oil, 91% (180 mg, 0.53 mmol). R<sub>f</sub> = 0.26, 100% EtOAc in hexanes; <sup>1</sup>H-NMR (600 MHz, CDCl<sub>3</sub>): δ = 9.79 (t, J = 1.8 Hz, 1H), 3.77 (dd, J = 5.3 Hz, 2H), 3.49-3.41 (m, 2H), 3.20 (AB system, J = 12.9 Hz, 2H), 2.39-2.35 (m, 4H), 1.72-1.55 (m, 4H), 1.45-1.39 (m, 1H), 1.37-1.31 (m, 1H), 0.89 (s, 9H), 0.84 (t, J = 7.0 Hz, 3H), 0.05 (s, 6H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ = 201.4, 169.6, 61.8, 59.0, 50.6, 38.1, 34.4, 29.8, 28.5, 26.9, 25.92, 25.88, 18.2, 7.4, -5.4; IR (thin film): 2931, 2858, 1724, 1617, 1471, 1419, 1256, 1103, 1055, 837, 778; HRMS (M+1) calc’d for C<sub>18</sub>H<sub>35</sub>NO<sub>3</sub>Si = 342.2459, found = 342.2460.

Aldehyde 3-111b was prepared using general experimental procedure. Reagents employed: piperidinone 3-109b (440 mg, 1.37 mmol), IBX (1200 mg, 4.29 mmol), and EtOAc (24 mL). Yielded 3-111b as a red oil, 64% (280 mg, 0.88 mmol). R<sub>f</sub> = 0.30, 64% EtOAc in hexanes; <sup>1</sup>H-NMR (600 MHz, CDCl<sub>3</sub>): δ = 9.78 (s, 1H), 7.38 (d, J = 9.4 Hz, 2H), 7.30 (t, J = 7.6 Hz, 2H), 7.18 (t, J = 7.0 Hz, 1H), 3.54 (dd, J = 8.2, 8.2, 1.2 Hz, 2H), 3.18-3.11 (m, 2H), 3.06 (s, 2H), 2.39-2.35 (m, 2H), 2.33 (dd, J = 7.6, 7.6 Hz, 2H), 1.86 (dd, J = 9.4, 7.0 Hz, 2H), 1.60-1.50 (m, 2H), 1.42-1.31 (m, 2H), 0.83 (t, J = 7.0 Hz, 3H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ = 201.2, 165.2, 129.0, 128.7, 126.1, 58.1, 48.0, 38.0, 34.5, 30.5, 29.7, 28.4, 28.8, 25.9, 7.4 (missing 1 carbon presumably due to overlap); IR (thin film): 2931, 2877, 1722, 1640, 1492, 1438, 1363, 1295, 1230, 1088, 1025, 742, 693; HRMS calc’d for C<sub>18</sub>H<sub>25</sub>NO<sub>2</sub>S = 319.1606, found = 319.1603.
Aldehyde 3-111c was prepared using general experimental procedure. Reagents employed: piperidinone 3-109c (580 mg, 2.11 mmol), IBX (1770 mg, 6.32 mmol), and EtOAc (40 mL). Yielded 3-111d as a dark yellow oil, 82% (475 mg, 1.74 mmol). R$_f$ =0.31, 100% EtOAc in hexanes; $^1$H-NMR (600 MHz, CDCl$_3$): $\delta$ = 9.65 (s, 1H), 7.33-7.30 (m, 2H), 7.28-7.24 (m, 3H), 4.55 (AB system, $J$ = 14.7 Hz, 2H), 2.92 (AB system, $J$ = 12.3 Hz, 2H), 2.46 (dd, $J$ = 7.0, 7.0 Hz, 2H), 2.27-2.21 (m, 1H), 2.07-2.01 (m, 1H), 1.67-1.59 (m, 2H), 1.58-1.52 (m, 2H), 1.30-1.22 (m, 2H), 0.70 (t, $J$ = 7.6 Hz, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ = 201.2, 169.5, 137.1, 128.6, 128.3, 127.5, 55.1, 50.1, 37.8, 34.1, 30.1, 28.4, 26.7, 25.5, 7.2; IR (thin film): 2936, 1722, 1603, 1496, 1454, 1420, 1364, 1309, 1265, 1232, 703; HRMS calc’d for C$_{17}$H$_{23}$NO$_2$ = 273.1729, found = 273.1728.

**General Experimental Procedure for the Synthesis of Alkyne 3-112a-c:** Aldehyde 3-111a-c (1 equivalent) was dissolved in MeOH, followed by the addition of K$_2$CO$_3$ (4.7 equivalents). Dimethyl 1-diazo-2-oxopropylphosphonate (2.5 equivalents) as added drop wise in MeOH and the mixture was stirred rapidly until consumption of starting material as determined by TLC analysis. Brine was added to the reaction mixture and extracted 3 times with ethyl acetate. The combined organic layer was washed thoroughly 2 times with water, and once with brine. The organic layer was dried and the solvent was removed to yield alkynes 3-112a-c.

Alkyne 3-112a was prepared using general experimental procedure. Reagents employed: piperidinone 3-111a (580 mg, 1.70 mmol), K$_2$CO$_3$ (1104 mg, 7.99 mmol), dimethyl 1-diazo-2-oxopropylphosphonate (816 mg, 4.25 mmol), and MeOH (17 mL). Yielded 3-112a as a pale yellow foam, 100% (572 mg, 1.69 mmol). R$_f$ = 0.18, 50% EtOAc in hexanes; $^1$H-NMR (600 MHz, CDCl$_3$): $\delta$ = 3.77 (dd, $J$ = 5.3, 5.3 Hz, 2H), 3.48-3.42 (m, 2H), 2.39-2.33 (m, 2H), 2.13 (ddd, $J$ = 6.5, 6.5, 1.2 Hz, 2H), 1.95 (t, $J$ = 2.9 Hz, 1H), 1.70-1.59 (m, 4H), 1.46-1.39 (m, 1H), 1.38-1.31 (m, 1H), 0.89 (s, 9H), 0.84 (t, $J$ = 7.6 Hz, 3H), 0.05 (s, 6H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ = 169.6,
Alkyne 3-112b was prepared using general experimental procedure. Reagents employed: piperidinone 3-111b (232 mg, 0.73 mmol), K$_2$CO$_3$ (471 mg, 3.41 mmol), dimethyl 1-diazo-2-oxopropylphosphonate (349 mg, 1.82 mmol), and MeOH (7.3 mL). Yielded 3-112b as a dark yellow foam, 95% (218 mg, 0.69 mmol). R$_f$ = 0.5, 100% EtOAc in hexanes; $^1$H-NMR (600 MHz, CDCl$_3$): δ = 7.39 (d, $J$ = 7.6 Hz, 2H), 7.29 (t, $J$ = 7.6 Hz, 2H), 7.18 (t, $J$ = 7.6 Hz, 1H), 3.57-3.49 (m, 2H), 3.14 (dd, $J$ = 7.0 Hz, 2H), 3.08 (AB system, $J$ = 12.3 Hz, 2H), 2.38-2.28 (m, 2H), 2.15-2.09 (m, 2H), 1.95 (t, $J$ = 2.9 Hz, 1H), 1.66-1.58 (m, 2H), 1.55 (dd, $J$ = 7.0, 7.0 Hz, 2H), 1.43-1.32 (m, 2H), 0.83 (t, 7.6 Hz, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) δ = 169.8, 135.7, 129.0, 128.8, 126.0, 84.0, 68.7, 58.1, 48.0, 35.0, 33.0, 30.4, 29.7, 28.5, 26.7, 12.8, 7.5; IR (thin film): 3373, 3293, 3056, 2927, 1639, 1482, 1439, 1361, 1252, 1100, 1026, 925, 741, 692; HRMS calc’d for C$_{19}$H$_{25}$NOS = 315.1657, found = 315.1662.

Alkyne 3-112c was prepared using general experimental procedure. Reagents employed: piperidinone 3-111c (430 mg, 1.57 mmol), K$_2$CO$_3$ (1020 mg, 7.38 mmol), dimethyl 1-diazo-2-oxopropylphosphonate (755 mg, 3.93 mmol), and MeOH (16 mL). Yielded 3-112c as a pale yellow foam, 97% (410 mg, 1.52 mmol). R$_f$ = 0.52, 100% EtOAc in hexanes; $^1$H-NMR (600 MHz, CDCl$_3$): δ = 7.33-7.30 (m, 2H), 7.27-7.23 (m, 3H), 4.56 (AB system, $J$ = 14.1 Hz, 2H), 2.93 (AB system, $J$ = 12.3 Hz, 2H), 2.50-2.40 (m, 2H), 2.06-2.00 (m, 1H), 1.94-1.88 (m, 2H), 1.62 (dd, $J$ = 7.6, 7.6 Hz, 2H), 1.58-1.52 (m, 2H), 1.35-1.23 (m, 2H), 0.72 (t, $J$ = 7.0 Hz, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) δ = 169.5, 137.1, 128.6, 128.2, 127.4, 84.0, 68.5, 55.4, 50.2, 34.6, 32.6, 29.9, 28.4, 26.5, 12.7, 7.3; IR (thin film): 3290, 3230, 2940, 2877, 1641,
General Experimental Procedure for the Sonogashira Cross Coupling: Aniline (1.2 equivalents) was dissolved in THF and the flask was purged with argon. Alkyne 3-112a-c (1 equivalent) was then added drop wise in THF and the flask was purged with argon. CuI (0.05 equivalent) and PdCl2(PPh3)2 (0.025 equivalent) were then added to the reaction mixture and the flask was purged with argon. Diisopropylamine was then added to the reaction mixture and the solution was stirred in the absence of light for 12 hours. The reaction mixture was then diluted with DCM and water. The aqueous was extracted 2 times with DCM. The organic layer was dried and the solvent was removed. The residue was purified by flash chromatography (EtOAc/Hexanes) to yield the desired piperidinones.

The piperidinone was prepared using general experimental procedure. Reagents employed: alkyne 3-112a (650 mg, 1.93 mmol), aniline (506 mg, 2.31 mmol), PdCl2(PPh3)2 (34 mg, 0.048 mmol), CuI (18 mg, 0.96 mmol), diisopropylamine (1.7 mL), and THF (4.5 mL). Yielded the product as a brown oil, 91% (753 mg, 1.76 mmol). Rf = 0.17, 75% EtOAc in hexanes; 1H-NMR (600 MHz, CDCl3): δ = 7.22 (d, J = 6.5 Hz, 1H), 7.10-7.07 (m, 1H), 6.69-6.65 (m, 2H), 3.78 (dd, J = 5.3, 5.3 Hz, 2H), 3.52-3.48 (m, 1H), 3.24 (s, 2H), 2.43-2.37 (m, 4H), 1.80-1.63 (m, 4H), 1.53-1.45 (m, 1H), 1.43-1.37 (m, 1H), 0.90-0.87 (m, 12H), 0.06 (s, 3H), 0.05 (s, 3H); 13C NMR (150 MHz, CDCl3) δ = 169.6, 132.1, 129.0, 117.9, 114.2, 94.9, 61.7, 59.1, 50.6, 35.0, 33.5, 29.8, 28.6, 27.0, 25.9, 25.6, 18.2, 14.1, 7.6, -5.4 (missing 2 carbon presumably due to overlap); IR (thin film): 3329, 2927, 2856, 1620, 1495, 1457, 1418, 1311, 1052, 748; HRMS calc’d for C25H40N2O2Si = 428.2859, found = 428.2866.
The piperidinone was prepared using general experimental procedure. Reagents employed: alkyne 3-112b (505 mg, 1.60 mmol), aniline (421 mg, 1.92 mmol), PdCl$_2$(PPh$_3$)$_2$ (28 mg, 0.040 mmol), CuI (15 mg, 0.079 mmol), diisopropylamine (1.4 mL), and THF (3.8 mL). Yielded the product as a yellow oil, 81% (528 mg, 1.30 mmol). R$_f$ = 0.43, 100% EtOAc in hexanes; $^1$H-NMR (600 MHz, CDCl$_3$): $\delta$ = 7.38 (d, $J$ = 7.0 Hz, 2H), 7.28 (t, $J$ = 7.6 Hz, 2H), 7.21 (d, $J$ = 7.6 Hz, 1H), 7.16 (t, $J$ = 7.0 Hz, 1H), 7.07 (t, $J$ = 7.0 Hz, 1H), 6.67-6.63 (m, 2H), 4.16 (brs, 2H), 3.57-3.49 (m, 2H), 3.16-3.07 (m, 4H), 2.41-2.31 (m, 4H), 1.74-1.68 (m, 2H), 1.58 (ddd, $J$ = 7.0, 7.0, 1.8 Hz, 2H), 1.47-1.35 (m, 2H), 0.85 (t, $J$ = 7.6 Hz, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ = 169.7, 147.6, 135.6, 131.9, 128.9, 128.6, 125.9, 117.7, 114.1, 108.3, 94.7, 77.4, 58.0, 47.9, 34.9, 33.4, 30.3, 29.6, 28.4, 26.7, 14.0, 7.4 (missing 1 carbon presumably due to overlap); IR (thin film): 3447, 3370, 3055, 2933, 1633, 1493, 1456, 1362, 1312, 1101, 1025, 925, 745, 692; HRMS calc’d for C$_{25}$H$_{30}$N$_2$OS = 406.2079, found = 406.2070.

The piperidinone was prepared using general experimental procedure. Reagents employed: alkyne 3-112c (330 mg, 1.23 mmol), aniline (322 mg, 1.47 mmol), PdCl$_2$(PPh$_3$)$_2$ (22 mg, 0.031 mmol), CuI (12 mg, 0.063 mmol), diisopropylamine (1.1 mL), and THF (3 mL). Yielded the product as a dark yellow oil, 93% (413 mg, 1.15 mmol). R$_f$ = 0.33, 100% EtOAc in hexanes; $^1$H-NMR (600 MHz, CDCl$_3$): $\delta$ = 7.33-7.30 (m, 2H), 7.27-7.24 (m, 3H), 7.20 (d, $J$ = 7.6 Hz, 1H), 7.08 (t, $J$ = 7.0 Hz, 1H), 6.68-6.65 (m, 2H), 4.58 (AB system, $J$ = 14.7 Hz, 2H), 4.11 (brs, 2H), 2.99 (AB system, $J$ = 12.3 Hz, 2H), 2.52-2.45 (m, 2H), 2.36-2.30 (m, 1H), 2.24-2.18 (m, 1H), 1.70-1.60 (m, 4H), 1.41-1.30 (m, 2H), 0.76 (t, $J$ = 7.6 Hz, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ = 169.5, 147.6, 137.1, 132.0, 129.0, 128.6, 128.2, 127.4, 117.9, 114.2, 108.5, 94.8, 77.3, 55.6, 50.3, 34.8, 33.5, 30.1, 28.5, 26.5, 13.9, 7.4; IR (thin film): 3458, 3335, 3029, 2936, 1632, 1493, 1454, 1311, 1263, 1157, 1029, 748, 702; HRMS calc’d for C$_{24}$H$_{28}$N$_2$O = 360.2202, found = 360.2218.
General Experimental Procedure for the Synthesis of Indoles 3-113a-c: The cross coupled piperidinone (1 equivalent) was dissolved in toluene. ZnBr$_2$ (1-1.2 equivalent) was then added to the reaction mixture and the solution was heated to reflux for 12 hours. Water was added and the reaction mixture was extracted 3 times with EtOAc. The combined organic layer was washed 2 times with water. The organic layer was dried and the solvent was removed to yield the desired indoles 3-113a-c.

Indole 3-113a was prepared using general experimental procedure. Reagents employed: piperidinone (60 mg, 0.14 mmol), ZnBr$_2$ (32 mg, 0.14 mmol), and toluene (0.60 mL). Yielded 3-113a as a yellow foam, 90% (54 mg, 0.13 mmol). R$_f$ = 0.30, 75% EtOAc in hexanes; $^1$H-NMR (600 MHz, CDCl$_3$): $\delta$ = 8.36 (brs, 1H), 7.53 (d, $J$ = 7.6 Hz, 1H), 7.29 (d, $J$ = 8.2 Hz, 1H), 7.11 (t, $J$ = 7.0 Hz, 1H), 7.07 (t, $J$ = 7.6 Hz, 1H), 6.24 (s, 1H), 3.82-3.76 (m, 2H), 3.53 (ddd, $J$ = 13.5, 5.3, 5.3 Hz, 1H), 3.41 (ddd, $J$ = 13.5, 5.3, 5.3 Hz, 1H), 3.26 (AB system, $J$ = 12.3 Hz, 2H), 2.72-2.86 (m, 2H), 2.42 (ddd, $J$ = 7.6, 7.6, 3.5 Hz, 2H), 1.86-1.74 (m, 2H), 1.70-1.65 (m, 2H), 1.55-1.43 (m, 2H), 0.92-0.89 (m, 12H), 0.05 (s, 3H), 0.04 (s, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ = 169.8, 139.2, 136.0, 128.7, 121.0, 119.7, 119.6, 110.3, 99.3, 61.7, 59.2, 50.6, 34.9, 33.4, 29.9, 28.6, 27.3, 25.9, 22.2, 18.2, 7.6, -5.4; IR (thin film): 3270, 2928, 2857, 1623, 1461, 1418, 1362, 1255, 1102, 836, 777, 748; HRMS calc’d for C$_{25}$H$_{40}$N$_2$O$_2$Si = 428.2859, found = 428.2852.

Indole 3-113b was prepared using general experimental procedure. Reagents employed: piperidinone (72 mg, 0.18 mmol), ZnBr$_2$ (44 mg, 0.20 mmol), and toluene (1.5 mL). Yielded 3-113b as a white foam, 83% (60 mg, 0.15 mmol). R$_f$ = 0.43, 100% EtOAc in hexanes; $^1$H-NMR (600 MHz, CDCl$_3$): $\delta$ = 8.27 (brs, 1H), 7.53 (d, $J$ = 7.6 Hz, 1H), 7.37 (d, $J$ = 7.0 Hz, 2H), 7.29-7.26 (m, 3H), 7.17 (t, $J$ = 7.6 Hz, 1H), 7.11 (t, $J$ = 7.0 Hz, 1H), 7.07 (t, $J$ = 7.6 Hz, 1H), 6.24 (s, 1H), 3.82-3.76 (m, 2H), 3.53 (ddd, $J$ = 13.5, 5.3, 5.3 Hz, 1H), 3.41 (ddd, $J$ = 13.5, 5.3, 5.3 Hz, 1H), 3.26 (AB system, $J$ = 12.3 Hz, 2H), 2.72-2.86 (m, 2H), 2.42 (ddd, $J$ = 7.6, 7.6, 3.5 Hz, 2H), 1.86-1.74 (m, 2H), 1.70-1.65 (m, 2H), 1.55-1.43 (m, 2H), 0.92-0.89 (m, 12H), 0.05 (s, 3H), 0.04 (s, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ = 169.8, 139.2, 136.0, 128.7, 121.0, 119.7, 119.6, 110.3, 99.3, 61.7, 59.2, 50.6, 34.9, 33.4, 29.9, 28.6, 27.3, 25.9, 22.2, 18.2, 7.6, -5.4; IR (thin film): 3270, 2928, 2857, 1623, 1461, 1418, 1362, 1255, 1102, 836, 777, 748; HRMS calc’d for C$_{25}$H$_{40}$N$_2$O$_2$Si = 428.2859, found = 428.2852.
Indole 3-113c was prepared using general experimental procedure. Reagents employed: piperidinone (375 mg, 1.04 mmol), ZnBr₂ (281 mg, 1.25 mmol), and toluene (8.6 mL). Yielded 3-113c as a yellow foam, 100% (375 mg, 1.04 mmol). R_f = 0.39, 100% EtOAc in hexanes; ¹H-NMR (600 MHz, CDCl₃): δ = 7.69 (brs, 1H), 7.51 (d, J = 7.6 Hz, 1H), 7.34-7.27 (m, 6H), 7.12 (t, J = 7.0 Hz, 1H), 7.06 (t, J = 7.0, 1H), 6.16 (s, 1H), 4.56 (AB system, J = 14.7 Hz, 2H), 3.01 (AB system, J = 12.3 Hz, 2H), 2.62-2.57 (m, 1H), 2.48 (dd, J = 7.0 Hz, 2H), 2.39-2.34 (m, 1H), 1.71-1.85 (m, 4H), 1.42-1.37 (m, 2H), 0.80 (t, J = 7.6, 3H); ¹³C NMR (150 MHz, CDCl₃) δ = 169.7, 139.1, 137.3, 135.9, 128.8, 128.6, 128.4, 127.5, 121.0, 119.7, 119.6, 110.3, 99.2, 55.4, 50.3, 34.6, 33.0, 30.3, 28.5, 27.1, 22.1, 7.3; IR (thin film): 3266, 3058, 2930, 1624, 1495, 1455, 1419, 1363, 1288, 1229, 736, 701; HRMS calc’d for C₂₄H₂₈N₂O = 360.2202, found = 360.2207.

Piperidide 3-115 was prepared using the following procedure: Piperidinone 3-113c (99 mg, 0.27 mmol) was dissolved in THF (12 mL) and cooled to 0°C. Red-Al® (65% by weight) (0.52 mL, 1.71 mmol) was added drop wise and the solution was mixed for 3.5 hours at 0°C. Upon completion by TLC analysis water was added to the reaction mixture and extracted 3 times with ether. The organic layers were combined and washed 2 times with water. The organic was dried and the solvent was removed to yield desired product 3-115 as an orange oil, 97% (91 mg, 0.26 mmol). R_f = 0.60, 100% EtOAc in hexanes; ¹H-NMR (600
MHz, CDCl₃): δ = 8.04 (brs, 1H), 7.53 (d, J = 8.2 Hz, 1H), 7.36-7.31 (m, 4H), 7.28-7.25 (m, 2H), 7.11 (t, J = 7.0 Hz, 1H), 7.07 (t, J = 7.6 Hz, 1H), 6.23 (s, 1H), 3.46 (AB system, J = 13.5 Hz, 2H), 2.62-2.56 (m, 1H), 2.52-2.46 (m, 1H), 2.31-2.21 (m, 2H), 2.02-1.87 (m, 2H), 1.71-1.65 (m, 2H), 1.63-1.56 (m, 1H), 1.46-1.40 (m, 2H), 1.37-1.31 (m, 1H), 1.28-1.24 (m, 2H), 0.81 (t, J = 7.6 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ = 140.7, 135.9, 128.92, 128.85, 128.1, 126.9, 120.8, 119.6, 119.5, 110.2, 99.0, 63.4, 62.1, 55.0, 35.8, 33.9, 29.7, 22.0, 21.9, 7.3 (missing 2 carbon presumably due to overlap); IR (thin film): 3408, 2931, 2856, 1457, 12.88, 779, 745, 699; HRMS calc’d for C₂₄H₃₀NO₂ = 346.2409, found = 346.2408.

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3-52 was prepared using the following procedure: Piperidine 3-115 (290 mg, 0.84 mmol) was dissolved in Methanol (9.5 mL) followed by the addition of Pd/C (10% Pd on C) (290 mg). To the slurry was then added ammonium formate (264 mg, 4.19 mmol) and the reaction was heated to reflux for 3 hours. Upon completion by TLC analysis the reaction mixture was filtered through celite washing with chloroform. The volatiles were removed to yield the desired product 3-52 as an orange oil, 97% (208 mg, 0.81 mmol). Rf = 0.12, 10% MeOH in EtOAc; (Note that based washed CDCl₃ was used to suppress in situ solvent protonation)

¹H-NMR (600 MHz, CDCl₃): δ = 9.31 (brs, 1H), 7.53 (d, J = 7.6 Hz, 1H), 7.32 (d, J = 7.6 Hz, 1H), 7.11-7.05 (m, 2H), 6.23 (s, 1H), 4.76 (brs, 1H), 2.97-2.95 (m, 1H), 2.78 (d, J = 12.9 Hz, 1H), 2.69-2.63 (m, 3H), 2.47 (d, J = 12.32 Hz, 1H), 2.02 (ddd, J = 14.7, 8.2, 8.2 Hz, 1H), 1.70-1.61 (m, 2H), 1.54-1.49 (m, 2H), 1.46-1.39 (m, 1H), 1.34-1.25 (m, 2H), 0.86 (t, J = 7.6 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ = 140.11, 136.1, 128.6, 120.6, 119.47, 119.2, 110.5, 98.9, 53.3, 46.1, 34.5, 33.6, 32.8, 28.4, 21.9, 21.0, 7.0; IR (thin film): 3400, 3275, 2930, 2856, 1458, 1419, 1287, 781, 740; HRMS calc’d for C₁₇H₂₄N = 256.1939, found = 256.1936.
3.9 References


27 Unpublished work by Dr. Gibe a previous Kerr group member. Replication of the eight step route has been achieved in similar overall yields.
32 Sequential additions of sodium borohydride in between reflux periods are required to ensure complete conversion. See experimental for details.
33 Excess sodium borohydride is used. See experimental for details.
Appendices – Selected Data from Compounds from Chapter 1-3
### nOe Study

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### NMRS Spectra

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*Note: The images show detailed NMRS spectra for both protons and carbon, with specific peaks and assignments marked.*

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*Further analysis and interpretation of these spectra would require additional context and expertise in NMRS spectroscopy.*
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Pulse Sequence: PROTON (2pul)
Solvent: cdcl3
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Temp. 25.0 C / 298.1 K
Sample #17, Operator: Kerr
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DATA PROCESSING
FT size 20268
Total time 0 min 31 sec

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Pulsefile: CARBON
Pulse Sequence: CARBON (2pul)
Solvent: cdcl3
Data collected on: Oct 24 2012
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Sample #17, Operator: Kerr
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2-73g

CO₂Me
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Sample directory: HG-9-46-1_Oct22_12_01
Fidfile: PROTON

Pulse Sequence: PROTON (s2pu1)
Solvent: cdcl3
Data collected on: Oct 22 2012

Temp. 25.0 °C / 298.1 K
Sample #12, Operator: Kerr

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DATA PROCESSING
FT size 32768
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Sample Name: Huck
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Fidfile: CARBON

Pulse Sequence: CARBON (s2pu1)
Solvent: cdcl3
Data collected on: Oct 22 2012

Temp. 25.0 °C / 298.1 K
Sample #12, Operator: Kerr

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Pulse 45.0 degrees
Acq. time 1.384 sec
Width 25125.6 Hz
356 repetitions

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Pulse Sequence: PROTON (a2pal)
Solvent: cdcl3
Data collected on Jul 25 2013

Temp. 25.0 C / 298.1 K
Operator: Farr
Relax. delay 1.000 sec
Pulse 90.0 degrees
Avg. time 7.705 sec
MLD 9311.9 Hz
8 repetitions
OBSERVE H1 539.4468502 MHz
DATA PROCESSING
FT size 12756
Total time 3 min 31 sec

Sample Name: NMR
Data Collected on: nmr-660.chen.sce.ca-ionsf64
Archive directory: /home/data/Farr/Rock
Sample directory: NMR/11-34-1.2013.07.25.92
File: CARBON_NO-11-34-1.01
Pulse Sequence: CARBON (a2pal)
Solvent: cdcl3
Data collected on Jul 25 2013

Temp. 25.0 C / 298.1 K
Operator: Farr
Relax. delay 1.000 sec
Pulse 90.0 degrees
Avg. time 5.650 sec
Width 17750.8 Hz
512 repetitions
OBSERVE H1 350.7393226 MHz
DRSCF H1 699.4470617 MHz
Power 45 Hz
continuously on
MULTI-16 modulated
DATA PROCESSING
Line broadening 8.5 Hz
FT size 65536
Total time 16 min
RD 9-110-1

Sample Name: Nuch
Data Collected on: smart650, chem.uwo.ca-inova600
Archive directory: /home/data/ferr/Nuch
Sample directory: 9_9.110-1_9.0_1_2012_01
Pulse: 90°
Solvent: CDCl3
Data collected on Dec 5 2012

Temp. 25.0 °C / 298.1 K
Operator: Ferr

*Relax. Delay 1.000 sec
Pulse 45.0 degrees
Acq. Time 1.705 sec
Width 1011.9 Hz
6 repetitions

OBSERVED CHL 593.4743350 MHz
DATA PROCESSED
PT size 32768
Total time 6 min 31 sec

RD 9-110-1

Sample Name: Nuch
Data Collected on: smart650, chem.uwo.ca-inova600
Archive directory: /home/data/ferr/Nuch
Sample directory: 9_9.110-1_9.0_2_2012_01
Pulse Sequence: CHEMB (2xpol)
Solvent: CDCl3
Data collected on Dec 5 2012

Temp. 25.0 °C / 298.1 K
Operator: Ferr

*Relax. Delay 1.000 sec
Pulse 45.0 degrees
Acq. Time 0.862 sec
Width 37735.0 Hz
512 repetitions

OBSERVED CI2, 518.7395016 MHz
DCOUPPE 81, 599.4731765 MHz
Power 42 W
Continuously on
WALTZ-16 modulated
DATA PROCESSED
Line shimming 0.5 Hz
PT size 55534
Total time 16 min
PhSN=C
\[ \text{NH}_2 \]
Curriculum Vitae

A) ACADEMIC INFORMATION

Doctor of Philosophy in Chemistry
The University of Western Ontario, London, ON
Research Advisor: Professor Michael A. Kerr
Jan. 2010 – Present

Bachelor of Science in Chemistry (Honors Specialization)
Wilfrid Laurier University, Waterloo, ON
Thesis Title: Studies Toward the Synthesis of Helical Molecules via a Tandem Sonogashira Cross-Coupling – Cyclization Strategy
Research Supervisor: Associate Professor Stephen MacNeil
Completed: Dec. 2009

B) RESEARCH EXPERIENCE

Research Assistant
Chemistry Dept., Kerr Lab, The University of Western Ontario, London, ON
Research conducted under Professor Michael A. Kerr
Jan. 2010 – Present

Teaching Assistant, The University of Western Ontario
Chemistry Dept., The University of Western Ontario, London, ON
Jan. 2010 – Present

Research Assistant
Chemistry Dept., MacNeil Lab, Wilfrid Laurier University, Waterloo, ON
Research conducted under Associate Professor Stephen MacNeil

Teaching Assistant, Wilfrid Laurier University
Chemistry Dept., Wilfrid Laurier University, Waterloo, ON

C) Publications


**D) Presentations**


E) Awards

<table>
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<tr>
<th>Award</th>
<th>Value</th>
<th>Location of Tenure</th>
<th>Period Held</th>
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<tbody>
<tr>
<td>Ontario Graduate Scholarship</td>
<td>$15,000/yr</td>
<td>U. Western Ontario</td>
<td>May 2013 – April 2014</td>
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<tr>
<td>2nd place CSC Organic Chemistry Poster Award</td>
<td>$100</td>
<td>U. Western Ontario</td>
<td>2014</td>
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<td>NSERC Postgraduate Scholarship, Doctoral (waitlisted 2013)</td>
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<td>Community Service Award</td>
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<td>City of Hamilton</td>
<td>2013</td>
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<td>Nominated for (2012-2013) UWO Teaching Assistant Award</td>
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<tr>
<td>Nominated for (2011-2012) UWO Teaching Assistant Award</td>
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<tr>
<td>Western Graduate Research Scholarship</td>
<td>$7,000/yr</td>
<td>U. Western Ontario</td>
<td>Sept. 2011 – April 2013</td>
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<tr>
<td>3rd place CSC Organic Chemistry Poster Award</td>
<td>$50</td>
<td>U. Western Ontario</td>
<td>2011</td>
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<tr>
<td>Science and Technology Endowment Program Grant</td>
<td>$1,000</td>
<td>WLU</td>
<td>Nov. 2008</td>
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