Title

Stereoselective Synthesis of Isochromans and Isochroman-Based Natural Products by C—H Insertion with Donor/Donor Carbenes

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Stereoselective Synthesis of Isochromans and Isochroman-Based Natural Products By C–H Insertion with Donor/Donor Carbenes

by

BENJAMIN DAVID BERGSTROM
DISSERTATION

Submitted in partial satisfaction of the requirements for the degree of

DOCTOR OF PHILOSOPHY

in

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in the

OFFICE OF GRADUATE STUDIES

of the

UNIVERSITY OF CALIFORNIA

DAVIS

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Mark J. Kurth

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Dean J. Tantillo

Committee in Charge

2022

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ABSTRACT OF DISSERTATION

Described herein are three projects in the field of organic chemistry pertaining to the asymmetric synthesis of isochromans and isochroman-based natural products by C–H insertion reactions with donor/donor carbenes. The first chapter details the development of a methodology to stereoselectively synthesize isochromans. This work expands on our previous reports by accommodating six-membered ring substrates, notably with perfect diastereoselectivity in all cases and without observation of Stevens rearrangement byproducts. The second chapter employs this methodology towards the asymmetric total synthesis of panowamycin A, panowamycin B, TM-135, and veramycin F. The synthesis of the proposed structure of panowamycin A revealed a stereochemical misassignment. Computational NMR was used to predict the isomer most likely to be the natural substance; the synthesis of this compound was completed and the spectral data were consistent with the reported natural product, therefore confirming the structure to be correct. The third chapter involves the synthesis of tetrasubstituted geminal acyl/alkoxy allenes, which was incidentally discovered while exploring the substrate scope for isochroman formation. With support from byproduct identification and control experiments, the mechanism of formation for these novel compounds is proposed. This new class of allenes was then explored as a reagent in subsequent transformations, where they demonstrated unique reactivity.

Acknowledgments

I have no one more to thank than my parents, Dave and Gina. You never pressured me to go to college or to do well in school. You simply laid a foundation of love and hard work that would carry me along any path. I thank you for bearing with me in my most difficult years. You embody integrity, earnestness, and persistence, and you are my biggest inspirations. I owe you more than I can express with words.

To my sister, Ellie, you have always been a role model to me. You blazed the trail before me, teaching me the importance of discovery and adventure. You are a refreshing point of view and a friend for life. To Grandma Bergstrom, Aunt Ann, and Aunt Gay: your support never ceases to bring a smile to my face and a warmth to my heart.

I thank my girlfriend, Colleen, for always showing me the light. You have put up with my stubbornness, but more importantly you have gifted me new ways of living. You inspire me to be a better person, with more joy in every moment. I can't wait to experience new things with you and to see our love grow.

I would like to thank my best friends Erik, Nick, Paul, and Marty. From the first grade until now, you have always motivated me to become more creative, sincere, and fun-loving. You have made me a better person and your unending friendship has gotten me through many tough days. I would also like to acknowledge my friends from the University of Minnesota. To Bryce, Eric, James, and Matt: you continue to be a big influence in my life and you have taught me so much about honesty and community.

To JJ and Vanessa, how can I begin to say thank you? "*I'm having the best time with my best friends.*" You have been an integral part to my time at UC Davis and I cannot imagine doing this without your love, friendship, and support. Our quarantine together was truly a joy and I will always remember the laughs we shared. I wish the best for you two and I look forward to more trips together.

It would take far too long to thank all of the educators and mentors who have helped me get to this point, so I will simply give a list with some additional commentary. Thank you: Mrs. Grosskopf; Mr.

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model during our time in 303. You are an inspiring scientist with a titanic capacity for hard work, empathy, and intellect. It would be hard to imagine my last few years in the lab without your friendship and it will be a joy to see where you end up. DAG: it has been incredible to see you chase your dreams and achieve so much. I remember the recruitment weekend at *El Burrito* like it was yesterday. You are extremely competent and equally as funny. You are a great friend and you will bring your authenticity with you wherever you go. JS: you have a deep reservoir of chemical knowledge and an even deeper reservoir of good-nature and optimism. You have taught me so much and have given me so many good ideas. You are truly one of the finest chemists to come out of the Shaw lab and I look forward to hearing about your future successes. JMR: you are a tremendous chemist with an incredible modesty and work ethic; these traits will take you very far. You are a friendly face in lab and I wish you the best. GTW, AH, MWD: you are wonderful additions to the Shaw lab and I know you will be future leaders in the group. You are smart, capable, and I look forward seeing you succeed. Although they are not Shaw lab members, Austin, Jake, and Angel have been fantastic lab-mates, mentors, and friends. Our time together in Davis is something I remember fondly. Thanks to Room 303, Department of Chemistry. You were sort of gross looking/smelling and I hated all of the dirt and pollen you spewed out of your ventilation. Your pressure differential with the rest of the building never ceased to give me a headache. Despite your faults, you were my home for 5 years. Long may you live.

I also thank James Hetfield, Lars Ulrich, Kirk Hammett, and Cliff Burton of Metallica for creating *Ride the Lightning*. Listening to this album has been my good luck charm since high school and has never failed.

Finally, thank you to my dissertation committee: thank you Prof. Dean Tantillo for your creative-thinking and scientific rigor. Thank you Prof. Mark Kurth for always having a thoughtful piece of advice and a good story to tell. Last but not least, thank you Prof. Jared Shaw for being my mentor throughout these last 5 years. I was overjoyed to join your lab and I consider myself fortunate to have received your

guidance and learned from you. I will miss running over to your office to discuss a fun, new, and potentially stupid idea I have. You instilled in me your passion for organic chemistry and your zeal for problem-solving. You have trusted me, perhaps more than I deserve, and given me the space and opportunity to pursue my ambitions. In my new endeavors, I will look deeply into any problem and come out with a good strategy thanks to you.

Epigraph

"There is no royal road to science, and only those who do not dread the fatiguing climb of its steep paths have a chance of gaining its luminous summits."

Karl Marx, 1872, Capital Vol. 1, preface to the French edition

"Therefore let us be happy while we are happy. Let us be kind, generous, affectionate and good. It is necessary and not at all shameful to take pleasure in the little world."

Gustav Ekdahl, in *Fanny och Alexander* (1982), dir. Ingmar Bergman

Chapter 1.0

Stereoselective Synthesis of Isochromans by Dirhodium Catalyzed C–H Insertion Reactions with Donor/Donor Carbenes[1,2]

1.1 Introduction

The activation and functionalization of carbon–hydrogen bonds has long been a 'holy grail' in organic chemistry.[3] With miraculous effort and ingenuity over several decades, the goal of viewing the C–H bond as a functional group has been achieved in many contexts using a multitude of different methods. These methods have allowed for new retrosynthetic analyses and have opened the door to the novel and efficient construction of natural products and other molecules of interest to the broader scientific community.[4–8]

One such method is the use of metal carbenes to insert into C–H bonds, making a new carbon–carbon bond.[9–14] Although several metals are capable of forming a metal-carbene (Figure 1), dirhodium tetracarboxylate complexes have been demonstrated as a privileged class of catalysts for C–H insertion reactions, often using chiral ligands to provide stereoselectivity.[9,14–16] The design and development of new catalysts/ligands for use in rhodium-carbene catalysis has advanced significantly over the decades, where many complexes are also commercially available.[17]

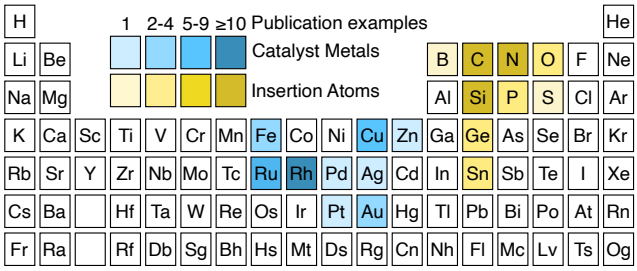


Figure 1. Publication heat map of metals and insertion atoms used in insertion reactions with donor/donor carbenes

The properties and synthetic applications of metal carbenes depend heavily on the substituents appended to the carbene (Figure 2). C–H insertion reactions have been well-documented for carbenes with two electron withdrawing substituents (CO_2R, COR, CN, SO_2R, acceptor/acceptor),[15] and with one electron donating substituent (aryl, alkenyl, alkyl) and one electron withdrawing substituent (donor/acceptor).[18] Asymmetric variants of these reactions have also been developed with significant success and larger impact in the field. Acceptor-substituted carbenes are typically derived from diazo-compounds in a facile manner using diazo-transfer reagents; although these reagents and the resulting diazo-species are potentially explosive, they are stable to purification by column chromatography and short periods of storage.[19] On the other hand, once the acceptor and acceptor/acceptor diazo-species are decomposed to the metal carbene, they are usually very reactive and may react indiscriminately with other functionalities on the molecule.[15,20,21] Later developments showed that donor/acceptor carbenes are less electrophilic and less reactive due to the donating substituent, increasing chemoselectivity for C–H insertion.[11,13,18] Over the last decade, the Shaw lab has investigated donor/donor rhodium

carbenes, which have two electron-donating groups and, as a result, are highly selective for C–H insertion while also tolerating functional groups present in complex substrates.[2,22,23]

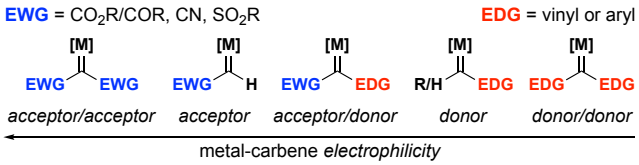


Figure 2. Metal carbene electrophilicity scaling

Our research in this field has demonstrated the utility of donor/donor carbenes in chemo-, regio-, and stereo-selective C–H insertion reactions in the synthesis of a wide variety of five-membered ring (1,5-C–H insertion) heterocycles.[9,15,20,24] However, there are few examples of six-membered ring (1,6-C–H insertion) formation in the literature.[25–31] Accessing 1,6-C–H insertion is difficult due to the kinetic favorability of 1,5-C–H insertion and the potential for rearrangement products when heteroatoms are present (Figure 3, **2** and **3**). Previous work to synthesize 1,6-C–H insertion products with accessible 1,5-insertion sites consistently produced mixtures of five- and six-membered ring products.[32–36] Installing a heteroatom at the 5-position can eliminate 1,5-C–H insertion, however this introduces the possibility of nucleophilic attack on the carbene by the heteroatom.[25,27,31] This reaction forms an ylide that undergoes the Stevens rearrangement (or a Stevens-type rearrangement when the heteroatom is oxygen), forming an alternative five-membered ring product (**6**) (see section 1.1.4 for more details on Stevens-Type rearrangements).[31,37] There are several reports of forming tetrahydropyran, chroman, and chromanone cores through 1,6-C–H insertion using donor/acceptor or acceptor carbenes, but all of these examples are prone to Stevens-type side reactions.[27–29,31,38–41] In 2012, Cossy and coworkers demonstrated the use of donor carbenes generated from cyclopropenes in the synthesis

of tetrahydropyrans by C–H insertion,[29,41] further expanding the diazo-free insertion work demonstrated by Zhu.[42,43] In the cases where chiral catalysts were used, enantioselectivity was often moderate;[27,28] it wasn't until 2015 when Hashimoto and coworkers achieved higher levels of enantioselectivity using Rh_2(*S*-PTTL)$_4$ (up to 97:3 er).[31] We hypothesized that using our donor/donor system would reduce the potential for Stevens rearrangements due to its reduced relative electrophilicity, allowing for C–H insertion reactions to proceed chemoselectively to form isochromans.

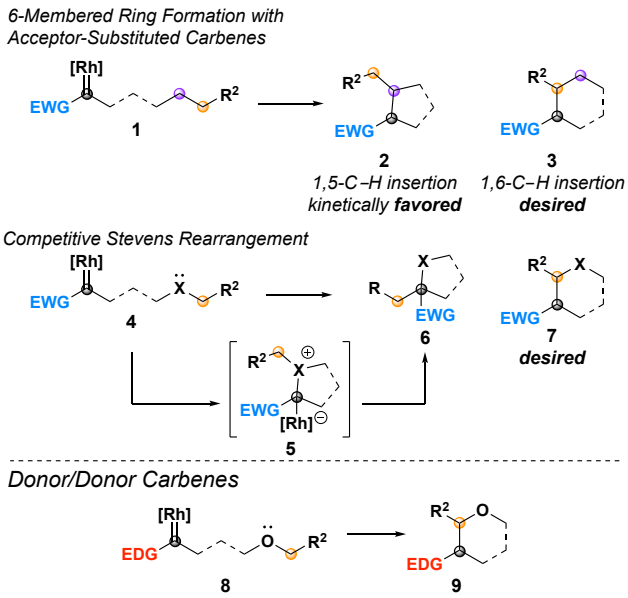


Figure 3. Synthetic strategy for generating isochromans by C–H insertion reactions with donor/donor carbenes, and the competing Stevens-type rearrangement

The stereoselective generation of isochromans is of importance to the broader scientific community in that they are found as key structures and sub-structures featured in many natural products and biologically relevant molecules (Figure 4).[44,45] Isochromans are observed to have CNS activity as dopamine receptor modulators, 5-HT_{1D} receptor agonists, NOP receptor inhibitors, kappa opoid receptor antagonists, NPY Y5 antagonists, NK_1 receptor antagonists, sigma receptor modulators, NMDA receptor

antagonists, and AChE inhibitors.[45] Additionally, isochromans have shown activity as antioxidant, antimicrobial, antihypertensive, antitumor, and anti-inflammatory agents.[45] Having new methods to synthesize these natural products is essential to the study of their biological and medicinal properties (see section 1.1.1). Furthermore, having new methods to construct substituted isochromans with high degrees of diastereoselectivity and enantioselectivity is vital to screening biological activity, as it is frequently observed that one enantiomer or diastereomer can have drastically higher targeted activity, better selectivity, or, on the other hand, drastically higher toxicity, off target effects, etc.

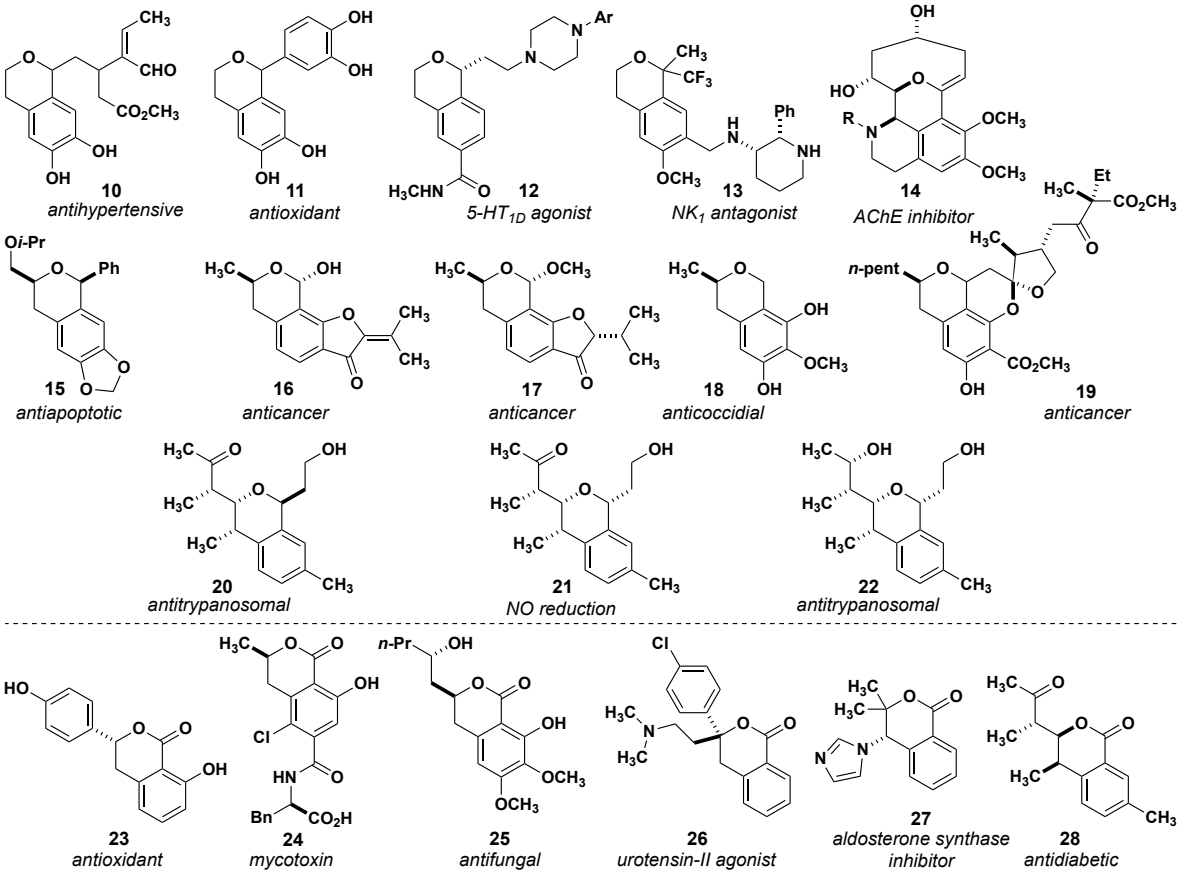


Figure 4. Natural products and biologically relevant molecules with isochromans or isochromanones as the key structural feature.

As evidence of the importance of stereoselectivity in isochroman synthesis, **29** was tested for antihypertensive activity in assays for diastolic arterial pressure (DAP) and systolic arterial pressure (SAP)

modulation in spontaneously hypertensive rats and renal hypertensive rats, showing good activity when compared to captopril as the positive control (Figure 5).[46,47] When the enantiomers were separated by chiral chromatography, it was shown that (-)-**29** had significantly more antihypertensive activity than (+)-**29**. While the authors devised a synthesis for producing the compounds as single enantiomers, the source of chirality in this procedure is derived from the chiral pool (i.e. the Roche ester). Therefore, developing a method which stereoselectively and catalytically constructs isochromans without the need for chiral resolution, separation, or stoichiometric chiral pool derivatives greatly improves the state of the art in this field.

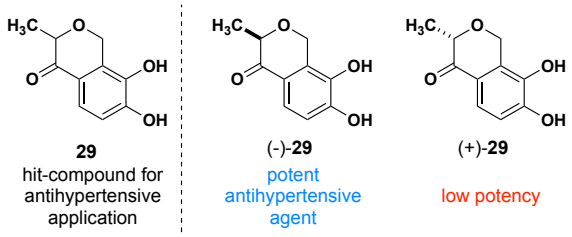


Figure 5. Antihypertensive drug-like molecules synthesized and tested by Jinyi Xu and coworkers.

In this chapter, the synthesis of isochromans, intramolecular C–H insertion reactions with donor/donor carbenes, and the Stevens rearrangement will be discussed as introductory information. The novel methodology developed to asymmetrically synthesize isochromans using donor/donor carbenes will then be discussed as a contribution to this field of research.

1.1.1 The synthesis of isochromans

The desire to expand our previously reported C–H insertion methodology to the synthesis of isochromans was motivated not only by a will to expand the chemical space accessible by the method, but also by the limitations of current methods to synthesize isochromans. Methods for generating these scaffolds are, generally, as follows: oxa-Pictet Spengler cyclizations at the 1-position, modifications at the

3 and 4-positions of 1*H*-isochromenes, intramolecular Heck reactions, intramolecular Friedel-Crafts reactions, oxa-Michael cyclizations, and other various cyclization strategies (Figure 6).

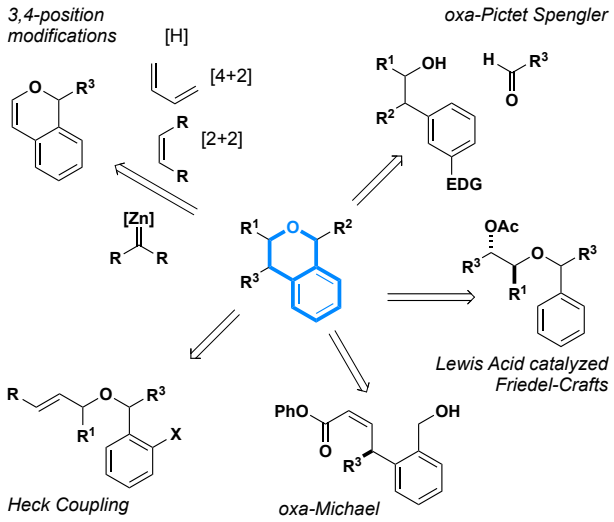


Figure 6. General strategies for synthesizing isochromans

One of the most well-known methods of synthesizing isochromans is the oxa-Pictet Spengler (Figure 7) and as such has been the subject of two thoughtful reviews by Kaufman and Larghi.[48,49] This variant of the Pictet Spengler reaction is particularly useful in the modular construction of isochromans from homobenzylic alcohols and ketones or aldehydes. Mechanistically, however, there are a few features that limit the broad application of this method. The 1-position on the isochroman is the site of the C–C bond formation; cyclization occurs by an electrophilic aromatic substitution mechanism. This reaction typically necessitates the presence of some electron donating substituent on the ring. Additionally, this reaction is also usually acid-catalyzed, occasionally involving harsh reaction conditions. Therefore, the oxa-Pictet Spengler suffers from substrate specificity (EDG requirement), reaction selectivity (variable only at 1-position), and harsh reaction conditions. Anecdotally, the Rosenmund–von Braun reaction has been used in a similar manner to the oxa-Pictet Spengler to form isochromanone **39** *via* an aryl nitrile intermediate that then cyclizes with the pendant alcohol.[50,51] Also anecdotally, a report from Manabe and coworkers

has been used to generate an aryl ester which can then transesterify with the pendent alcohol to form isochromanone **39**.[52]

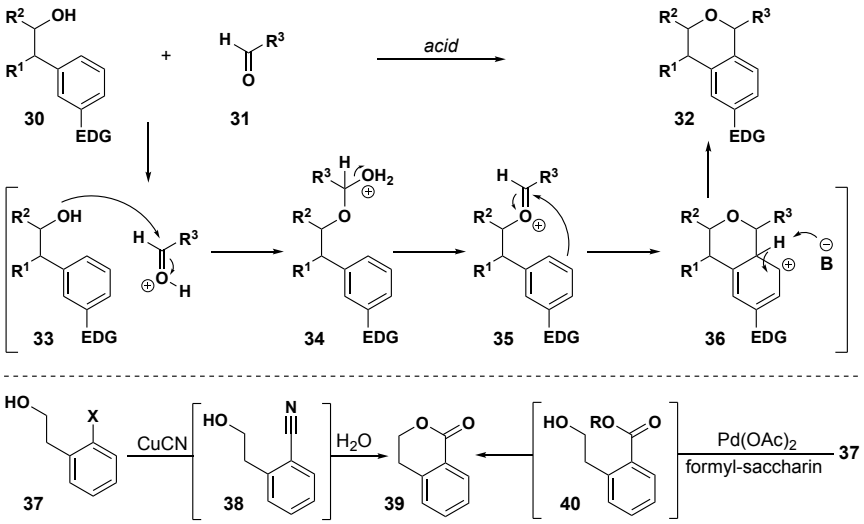


Figure 7. Mechanism for acid catalyzed oxa-Pictet Spengler cyclization to form isochromans and the Rosenmund–von Braun/Manabe protocols for isochromanone formation

Reactions at the 3 and 4-position of 1*H*-isochromenes generate interesting and valuable chemical scaffolds, usually in a *cis* configuration (Figure 8). These methods have the benefit of modularity in the transformation of the 1*H*-isochromene unsaturation. However, they require the benzopyran core to be created prior to the reaction, necessitating the use of other methods to create the heterocycle, limiting the efficiency and utility of such sequences. For these reasons, 3,4-modifcations will not be discussed at length here, but only to note that these reactions are the primary way of access 3,4-*cis* configurations on the isochroman, where most other methods generate 3,4-*trans* products. With that, reductions of 1*H*-isochromenes may proceed stereoselectively with a pre-existing stereogenic center at the 1 position using H_2, Pd/C, or non-selectively using $NaBH_4$.[53,54] [2+2] Cycloadditions also generate complex polycyclic products (**47** and **49**) with pharmacological interest.[55,56] Similarly, Simmons-Smith reactions with 1*H*-isochromenes produce unique [6.6.3] polycyclic scaffolds (**45**).[57]

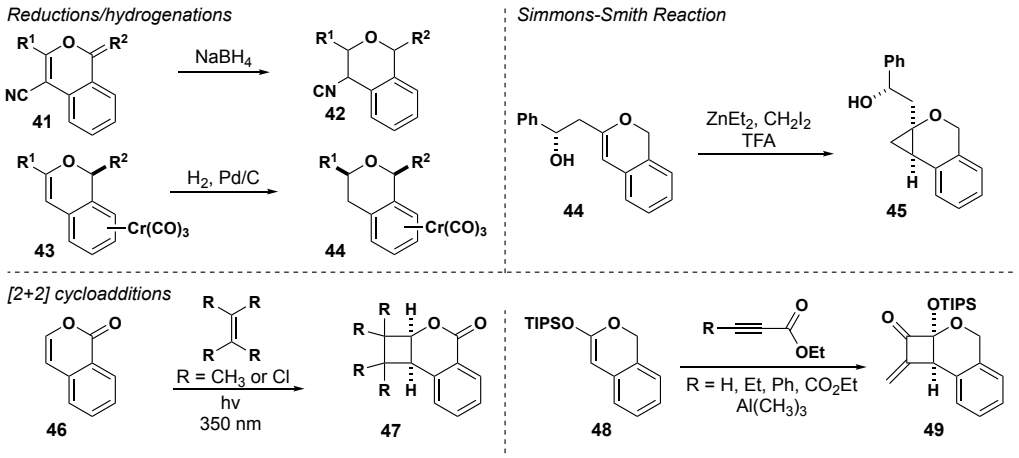


Figure 8. Modifications of the 1*H*-isochromene to afford primarily 3,4-*cis* substituted products.

Other useful strategies for the synthesis of isochromans are transition metal catalyzed cyclizations, namely carbonylative Sonogashira couplings, Heck couplings, and palladium catalyzed domino reactions (Figure 9).[58–60] Aronica and coworkers show the utility of carbonylative Sonogashira reactions in constructing 1-alkenyl isochromans; a propargyl ketone is generated *in situ*, which, in the presence of the palladium catalyst and base, are suitable electrophiles for intramolecular hydroalkoxylation by the pendant hydroxyl to form the isochroman scaffold **52**. Tietze and coworkers demonstrated the facile synthesis of isochromans by intramolecular Heck coupling (Figure 9B). A shortcoming of this approach was the propensity of the beta-hydride elimination to occur reversibly and unselectively resulting in a non-diastereoselective process to generate **54**. Most interestingly, Werz and coworkers were successful in using carbohydrates as starting materials for an efficient domino cascade reaction to generate valuable [6.5.6.5]-ring fusions (**57**) in a single step with good selectivity. While the yields for this protocol were less satisfactory compared to their five-membered analogues, the efficiency and novelty of the approach is noteworthy.

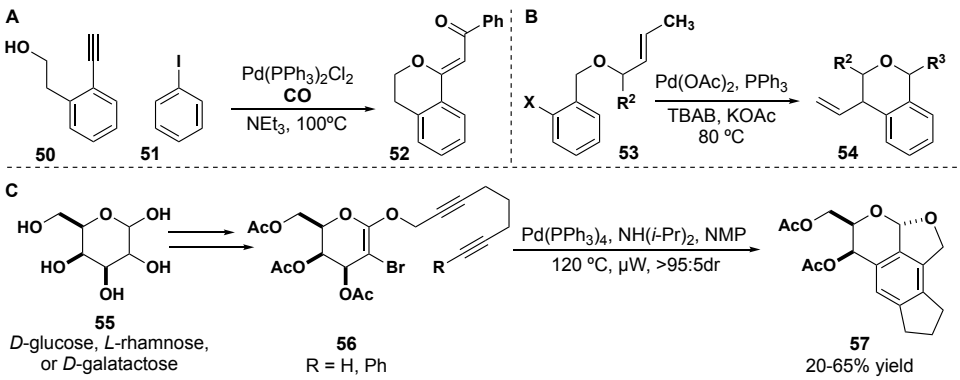


Figure 9. Isochroman formation by A) Carbonylative Sonogashira coupling and hydroalkoxylation cascade; B) Intramolecular Heck coupling; C) palladium-catalyzed domino reaction with carbohydrates-derived substrates

In another interesting example of transition metal catalyzed isochroman formation, Zhou, Qu, and coworkers demonstrate the synthesis of (–)-berkelic acid (**63**) using a modified Catellani reaction to construct the isochroman core in a single step (Figure 10).[61] As a multi-component reaction, this palladium catalyzed sequence is highly efficient and amenable to varied substitution around the isochroman core. However, the stereoselectivity is governed by the configuration of the epoxide started material and despite having a chiral center pre-installed in epoxide **58**, the reaction was marginally stereoselective (55:45dr).

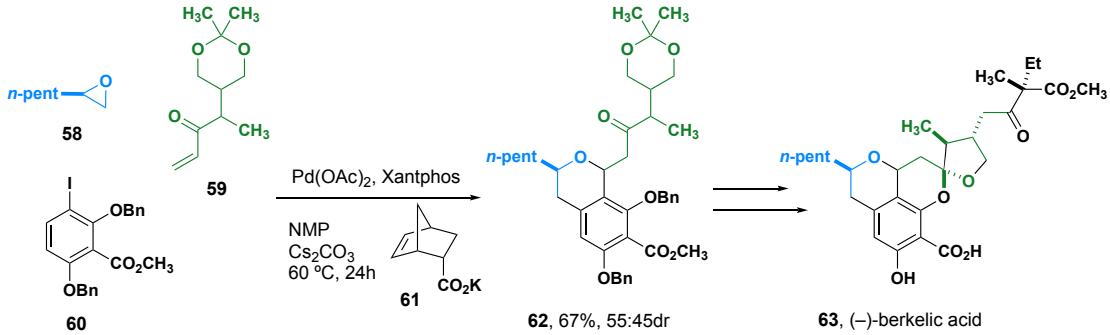


Figure 10. Catellani reaction/oxa-Michael cascade reaction to form an isochroman leading to (–)-berkelic acid

Another potential synthetic approach to the construction of isochromans is the use of oxa-Michael additions to cyclize benzyl alcohols or benzaldehyde-derived nucleophiles with homobenzylic alkenes (**64** and **65**), or inversely, to cyclize homobenzylic alcohols with styrenes (**67**) (Figure 11).[62,63] However, attention to this method has remained limited with one of the only reported methods being enantioselective *via* Lewis acid organocatalysis: most of the scope of this reaction is covered in section 1.1.2. The lack of reports for this transformation is likely derived from the lack of reactivity for oxygen nucleophiles in 1,4-addition.

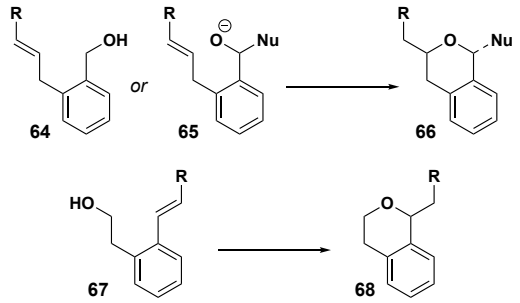


Figure 11. Oxa-Michael cyclization strategies to produce isochromans

Another useful technique for the construction of isochromans is via intramolecular Friedel-Crafts cyclizations (Figure 12). Common Lewis acids bismuth triflate, scandium triflate, and tin tetrachloride were effective in generating propargylic, allylic, and secondary cation electrophiles, respectively, followed by participation in electrophilic aromatic substitutions.[64–66] Of note, all of these reactions proceed with some degree of selectivity for the 3,4-*trans* configuration about the isochroman ring.

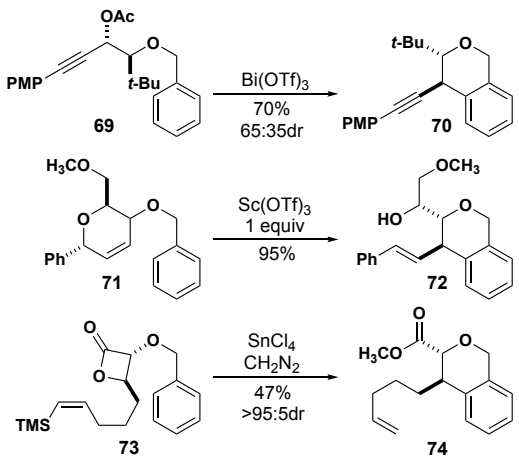


Figure 12. Lewis acid catalyzed Friedel-Crafts cyclizations to form isochromans

Finally, there are several reports that do not necessarily fall into the above general categories for the synthesis of isochromans (Figure 13). Nucleophilic additions of aryl Grignard reagents to Lewis acid-activated epoxides resulted in alkoxide intermediates that then rapidly cyclized to form 3,4-*trans* substituted isochroman **77** in good diastereoselectivity (Figure 13A).[67] Benzophenone benzaldehydes, when treated with acid and ethylene glycol, formed interesting polycyclic acetal **79** which could be reduced to the corresponding isochroman **80**, again, with good diastereoselectivity for the 3,4-*trans* configuration (Figure 13B).[68] Most interestingly is a report from Molander and Ryu involving the diastereoselective assembly of vicinal bis trifluoromethyl isochromans **87** from cyclic arylboroxines and trifluorodiazoethane **82** in a novel insertion and *alpha*-transfer mechanism sequence (Figure 13C).[69]

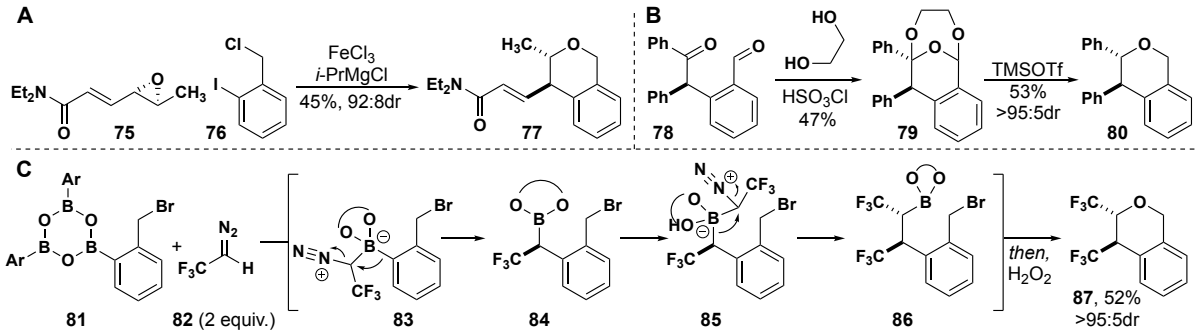


Figure 13. Diastereoselective access to *trans*-substituted isochromans: A) iron-catalyzed Grignard addition to epoxides, B) acetal formation/cleavage, C) *alpha*-transfer of trifluordiazoethanes to boroxines

1.1.2 Enantioselective synthesis of isochromans

As isochromans have three carbons on which a stereogenic center can be made, these scaffolds have been attractive candidates in enantioselective synthetic method development. As mentioned above, several methods of constructing isochromans may be modified to be enantioselective. This topic has been thoroughly reviewed by Chauhan and coworkers, detailing the asymmetric synthesis of isochromans. This section will highlight some of the examples they give, in addition to several others.[44] For simplicity and brevity, only examples derived from acyclic racemic or achiral starting materials will be shown; figure 14 shows a summary of strategies to accomplish this transformation that have been made enantioselective. Because of the thoroughness of the Chauhan review, this section will not cover these reactions in excessive detail.

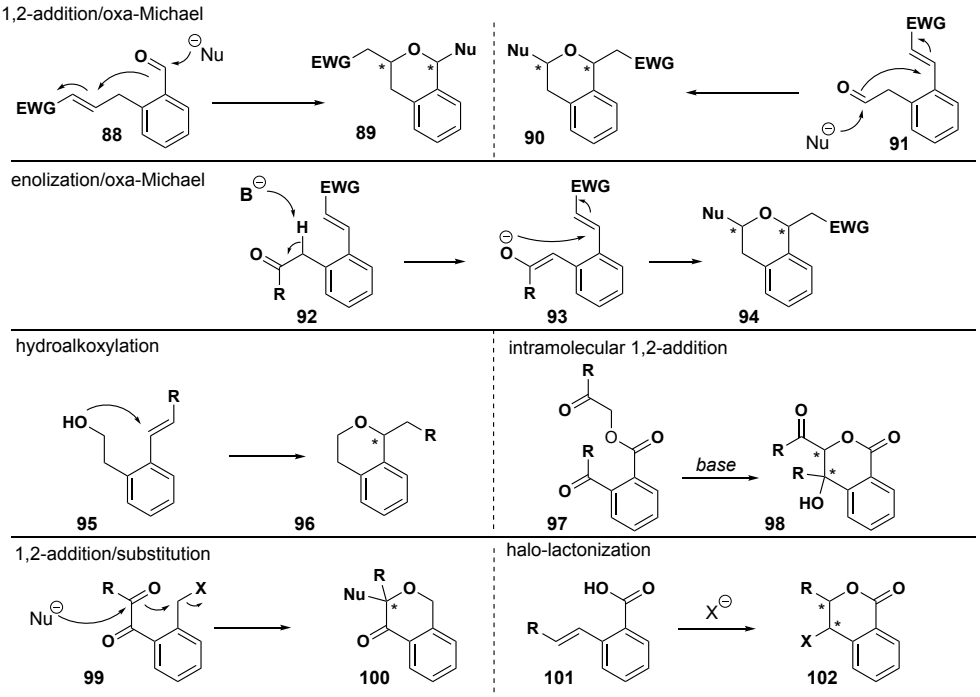


Figure 14. Stereoselective isochroman syntheses from acyclic starting materials

One generalized strategy that is amenable to enantioselectivity in the synthesis of isochromans is organocatalytic variants of oxa-Pictet Spengler reactions and oxa-Michael additions (Figure 15). Seminal work by Benjamin List demonstrates the use of an asymmetrically substituted BINOL imidodiphosphate **106** to catalytically generate isochromans **105** from homobenzylic alcohols and aldehydes with high degrees enantioselectivity at the isochroman 1-position.[70] Ghorai and coworkers report a squaramide catalyzed reductive oxa-Michael addition protocol that imparts enantioselectivity through the bifunctional organocatalyst **111** with high fidelity at the 1-position or 3-position based on the construction of the substrate (**107** or **108**, Figure 15).[71] As an interesting modification to this protocol, a peroxy-nucleophile was added in lieu of a reductant, allowing for simultaneous 1- and 3-position functionalization for form **112** with excellent diastereoselectivity and enantioselectivity.[72]

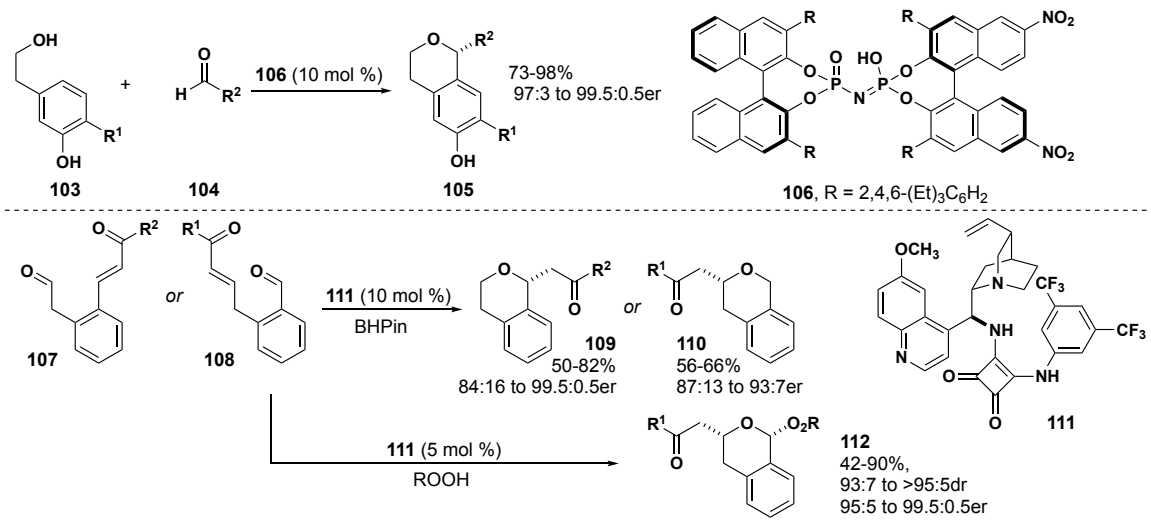


Figure 15. Enantioselective isochroman synthesis by organocatalytic oxa-Pictet Spengler reaction and oxa-Michael addition

Transition metal-catalyzed reactions are also fruitful routes to enantioselectivity in isochroman synthesis (Figure 16). Kitamura and coworkers, over two publications, report a ruthenium catalyzed dehydrative alkylation/cyclization sequence that allows for the enantioselective construction of isochroman scaffolds **114** and **115**. Notably, these substrates resemble oxa-Pictet Spengler reaction products that may be difficult to achieve under typical conditions (i.e. from unsaturated aldehyde starting materials and without electron rich arenes).[73,74] In another example, a palladium and norbornene-derived bisphosphine ligand (**118**) system catalyzes the hydroalkoxylation of an allene generated *in situ* from a propargylic subunit.[75] Due to the reversible Trost-type isomerization of the propargyl group to an axially chiral allene, the chiral ligands on the palladium species are able to invoke a good degree enantioselectivity in the generation of isochroman **119**. White and coworkers also report a palladium catalyzed cyclization through a C–H oxidation pathway.[76] Utilizing a sulfoxide/oxazoline mixed donor ligand **122**, they find considerable success in the synthesis of 1-vinyl-isochroman **121** with excellent enantioselectivity.

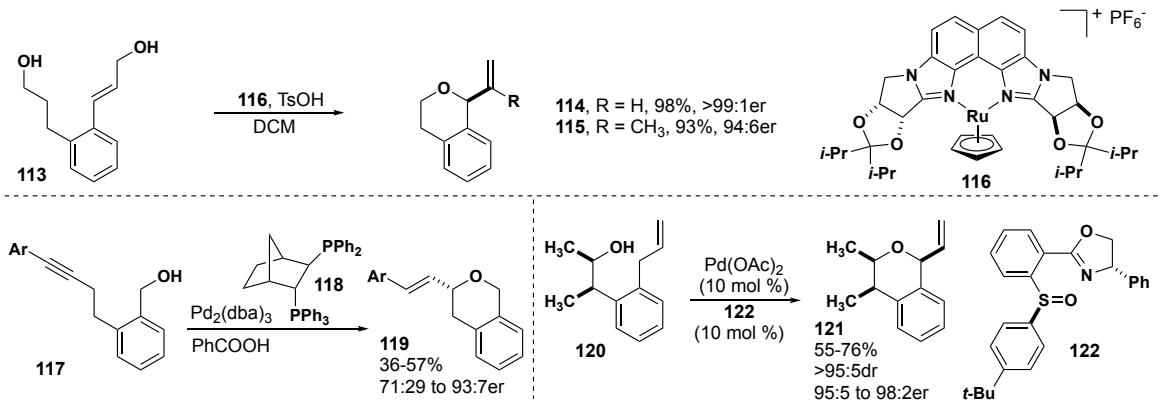


Figure 16. Transition metal-catalyzed enantioselective dehydrative alkylation/cyclization, hydroalkoxylation, and C–H oxidation

As the singular example of a Diels-Alder reaction to produce an isochroman, Li, Liu, and coworkers report a diastereo- and enantioselective *ortho*-quinone methide and isochromene [4+2] cyclization to form the densely functionalized natural product scaffold **125** (Figure 17).[77] This complex bimetallic system makes use of $Sc(OTf)_3$ to generate the hetero-diene **126** in a dehydrative process, while the JohnPhos-gold complex activates the alkyne **124** to form the aurated isochromene. This aurated isochromene then undergoes proto-deauration to form **127** before participating in the hetero Diels-Alder reaction, as evidenced by mechanistic studies in the report. Enantioselectivity in the cyclization then is derived by a proposed **128** ligation of the scandium Lewis acid activation of the *ortho*-quinone methide, with no involvement of the JohnPhos ligand/gold complex.

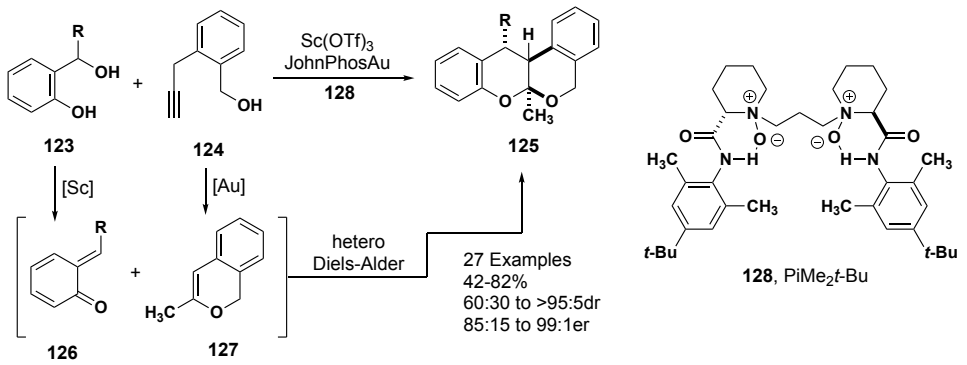


Figure 17. Hetero Diels-Alder reaction to form isochromans form *ortho*-quinone methide and isochromene generated *in situ*

Finally, there are a few reports of isochroman synthesis by transition-metal catalyzed insertion reactions. Zhou make use of donor/acceptor copper carbenes to achieve enantioselective intramolecular O–H insertions to generate 3-substituted isochromans **130** (Figure 18).[78] In these reactions, it is generally accepted that the alcohol oxygen stereoselectively attacks the highly electrophilic copper carbene, then undergoes a hydride shift to expel the copper catalyst.[2] When O–H insertion reactions are not the desired outcome, this propensity of acceptor substituted metal carbenes to be attacked by heteroatoms can generate undesired byproducts. For example, Hashimoto and coworkers report C–H insertion reactions to form isochroman **133** with donor/acceptor rhodium carbenes with high degrees of diastereo and enantioselectivity, but they also observe a competing side-reaction.[79] They are able to establish stereogenic centers at both the 3-position *and* the 4-position, a transformation not before seen in the literature. However, due to the electrophilicity associated with the acceptor substituted carbene, the competing Stevens-type rearrangement forms byproduct **134** (see section 1.1.4). The degree to which the electrophilicity of the metal carbene impacts the occurrence of the Stevens rearrangement was studied by McKervey and coworkers over a decade earlier.[80] In this report, they explore the product distributions between acceptor/acceptor carbene derived from diazos **135a** and **135b**. When the carbene has more

donating character (i.e. **135a**), the reaction favors C–H insertion product (**136**) with high stereoselectivity. On the other hand, when the carbene is highly withdrawing (i.e. **135b**), the Stevens rearrangement product **137** is the sole outcome of the reaction and is sparingly stereoselective.

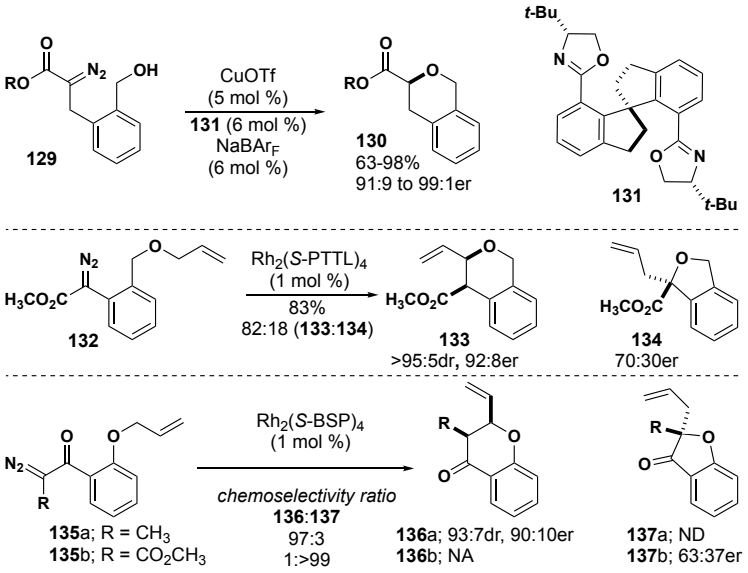


Figure 18. C–H insertion reactions to form isochromans, competing Stevens-type rearrangement, and comparisons with acceptor substituted carbenes

In conclusion, many methods to synthesize isochromans and isochromanones have been discussed above. Oxa-Michael additions, carbonylative Heck couplings, C–H insertion reactions, and the oxa-Pictet Spengler, among others, have been shown to efficiently construct isochromans and many of these methods have been modified to be asymmetric. The construction of these chemical scaffolds is of importance to the field in that isochromans and chromanones are featured in natural product structures, many of which are found as single enantiomers. As such, development in the state of the art in this field facilitates the further exploration of isochromans as structures and substructures in pharmaceuticals.

1.1.3 Intramolecular C–H insertion reactions with donor/donor metal carbenes

Metal carbenes are reactive intermediates that are capable of undergoing a wide variety of reactions. Selective insertion into both C–H and X–H bonds by these intermediates forms the basis for many useful

transformations. Foundational work in these fields by Taber, Doyle, Davies, and Hashimoto, to name only a few, have brought the chemistry of metal carbenes into common and convenient use.[10,15,81–83] As mentioned above (Figure 2), variations in the electronic character of metal carbenes have been found to drastically change the chemo-, regio-, and stereo-selective outcome of a given reaction and have been well studied with carbenes appended with electron-withdrawing substituents (Figure 3). This section focuses on metal-catalyzed intramolecular insertion reactions with carbenes *lacking* electron-withdrawing substituents. Most donor/donor carbenes have two aromatic rings; the corresponding metal carbenes exhibit unique reactivity and, importantly, much wider functional group tolerance when compared to the more reactive acceptor-substituted carbenes. In some cases, the dihedral angle between one of the aryl rings and the carbene center reduces the donor character, wherein the term 'diaryl' carbene has been used.[84–86] Although the first example of a 'donor/donor' carbene was in 1913, their use has been infrequent and underdeveloped;[87] a recent review of donor-substituted carbenes by Zhu and co-workers highlights the appeal of this upcoming field and discusses the subject as a whole.[88] This section summarizes the catalytic mechanisms and comparitive reactivity of these carbenes toward C–H insertion reactions. N–H and Si–H insertion reactions have also seen prominent development, while carbene insertions into other X–H bonds remain a nascent field. Many transition metal catalysts have been demonstrated to be effective in C–H insertion reactions, and dirhodium paddlewheel complexes have been established as a privileged class of catalysts (Figure 19).[89–94] The functionalization of un-activated C–H bonds, namely C_{sp3}–H bonds, has been an attractive target in synthetic organic chemistry for decades.[3,95] The ubiquity of the moiety in all organic molecules and the potential for dramatic increases in the chemical and stereochemical diversity of simple starting materials have placed C–H activation/insertion methodology at the forefront of transition metal catalysis. While efforts towards

intermolecular C–H insertion with acceptor-substituted metal carbenes have seen success, examples with donor/donor carbenes are still limited.

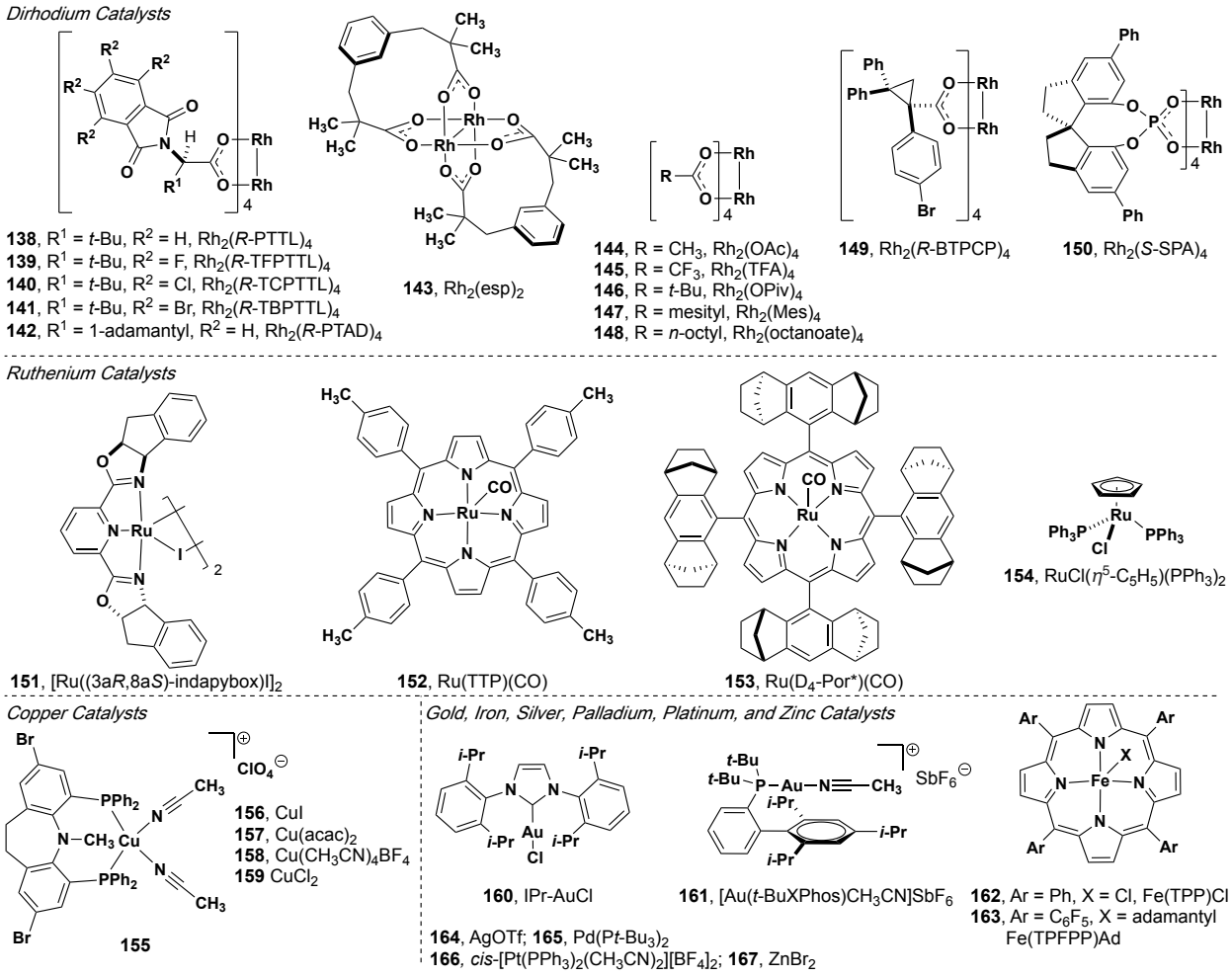


Figure 19. Collation of transition metal complexes used in catalytic C–H insertion reactions with donor/donor carbenes

Catalytic reactions *via* carbene intermediates often employ diazo compounds as precursors to metal carbenes. These intermediates can be isolated in some cases or generated *in situ*; when exposed to a catalyst, nitrogen gas is extruded and the metal carbene is formed. In most cases of acceptor-substituted carbenes, diazo transfer to a stabilized anion affords the carbene precursor.[19] For donor-substituted carbenes, diazo compounds are typically generated from hydrazone precursors (Figure 20).

Tosylhydrazones **168** require base to form diazo compounds, often with heating. This method avoids the use of neat hydrazine, which is toxic and unstable, and can be performed as a one-pot procedure from the requisite ketones. As an alternative to tosylhydrazones, unsubstituted hydrazones **170** can be chemoselectively oxidized with manganese dioxide to form diazo compounds. Although this method requires special handling of hydrazine, it benefits from the use of a heterogenous and chemoselective oxidant which operates without base or elevated temperature. In some cases, the oxidation can be carried out in the presence of a metal catalyst (e.g. rhodium), enabling facile, one-pot conversion of hydrazones to carbene insertion products.[96]

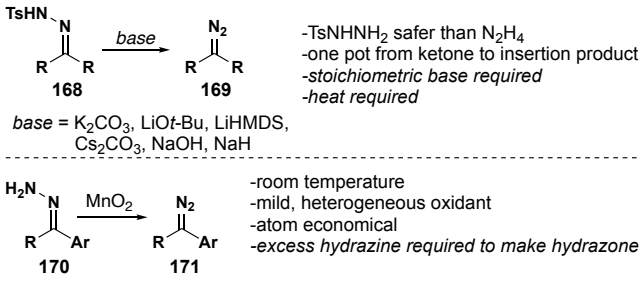


Figure 20. Hydrazone decomposition to form diazo-compounds

Due to the reactive nature of metal carbenes and their requisite precursors, a variety of byproducts may be observed (Figure 21). Tosylhydrazone **173** is known to degrade to sulfone **174** at the elevated temperatures required to form the diazo compound **175**. Once formed, diazo intermediates themselves are potentially explosive and are often used on small scale and/or at low concentrations (e.g. dilute solutions and/or inverse addition). Donor/donor diazo compounds readily form metal carbenes; the process is nearly instantaneous at ambient and lower (e.g. -20 °C) temperatures. For hydrazone precursor **172**, when oxidation is slower than carbene formation, metal carbene **179** can react with hydrazone **172** to form imine **178**. This process can be avoided by filtering off the oxidant after diazo formation is complete, then adding the catalyst. If the insertion reaction is slow, then the diazo **175** can react with the

metal carbene to form azine **177**. Although most intramolecular insertions are fast enough to avoid this process, azine formation can be suppressed using inverse addition of the diazo compound to a solution of catalyst. Another byproduct of slow insertion reactions is O–H insertion if the reaction is not kept sufficiently anhydrous. If MnO_2 is present, benzylic alcohol **182** may be oxidized to ketone **183**. When the carbene is substituted with an alkyl group, β-hydride elimination can occur, forming alkene **176** or other degradation products; this byproduct can occasionally be suppressed based on the choice of catalyst/ligand and the character of the β-hydride.[97] Under certain reaction conditions for N–H insertion, imine **181** is observed as the byproduct of β-hydride elimination.[98]. Finally, donor/donor carbenes can occasionally dimerize to form an alkene **180**.

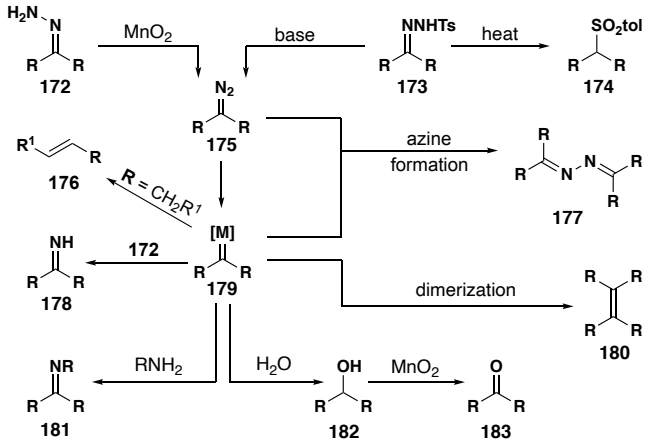


Figure 21. Byproduct formation in association with diazo and hydrazone-based metal carbene generation

While relatively little is known about the exact mechanism(s) of insertion reactions with donor/donor carbenes, they can potentially undergo C–H and X–H insertion by several proposed pathways. Although both singlet and triplet carbenes are considered for reactions involving free carbenes, transition metals are known to stabilize the singlet carbene to be the energetic ground state.[99–102] As such, transition metal catalyzed carbene reactions for C–H and X–H are typically considered in the singlet state, supported by experimental selectivity and computational data.[103–105] A notable exception to this notion is in the field of

metalloradical catalysis, where triplet-type metal carbenes can undergo a variety of single electron processes. While significant work has been completed in reactions with donor-substituted triplet-type metal carbenes, such reports fall outside of the scope of this review as we are primarily concerned with transition metal-catalyzed insertion reactions that involve singlet carbene, two electron processes.[106–110] Some efforts have also been made to characterize the steric and electronic factors that influence donor/donor carbene stereoselectivity and reactivity, but these examples have primarily been within the context of intermolecular cyclopropanation reactions.[84–86,111]

Metal-catalyzed insertions into non-C–H bonds (i.e. X–H bonds) are generally believed to proceed by a stepwise mechanism.[112] Interestingly, C–H insertion reactions have been postulated to proceed by both concerted and stepwise reactions. A concerted mechanism is proposed in analogy to significant previous computational work supporting this pathway for acceptor-substituted carbenes.[101,113,114] On the other hand, experimental data for reactions with acceptor-substituted carbenes have also suggested a potential step-wise mechanism.[115] DFT computations support a stepwise mechanism for a singular donor/donor carbene system.[116] Furthermore, more recent reports by Dishman and coworkers experimentally establish the stepwise mechanism by showing the ability of intramolecular insertion substrates to undergo bond rotations after C–H activated hydride transfer (*vide infra*).[117]

Mechanistic insight into C–H insertion reactions with donor-substituted metal carbenes is currently limited to intramolecular reactions. For this process, two mechanistic pathways have been proposed (Figure 22). The concerted pathway involves a three-centered transition state **187**, while the stepwise pathway produces a zwitterionic intermediate **188**. In support of the mechanism first proposed by Doyle,[101] Nakamura and co-workers performed DFT calculations for acceptor-substituted rhodium carbenes, demonstrating a three-center concerted transition state.[114] This mechanism is corroborated implicitly or explicitly in several investigations into various donor-substituted carbene insertions.[41,82,118–

[120] In previous work in our lab, the calculated reaction coordinate for a benzodihydrofuran substrate (e.g. Table 1) showed two discrete local maxima: one for hydride transfer and one for C–C bond formation, indicating the brief existence of a zwitterion, i.e. a *stepwise mechanism* (Figure 22, **188**).[116]

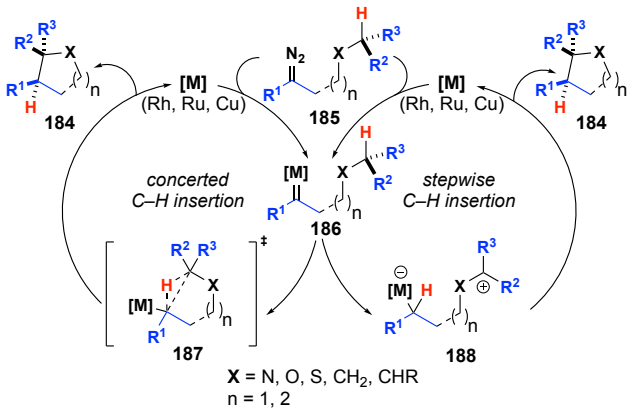


Figure 22. Stepwise and concerted C–H insertion mechanism with metal carbenes

Later efforts on this topic were concerned with C–H insertion reactions into chiral centers; experimental observations of diastereoselectivity and enantioselectivity insinuated the transfer of a hydride species, therefore establishing the enantioselectivity of the reaction (i.e. **188**, Figure 22), followed by bond rotation to form the more favored diastereomer (Figure 23, **191** to **192**).[117] These conclusions were explored computationally by graduate student Croix Laconsay of the Tantillo group, solidifying these mechanistic claims. This system was studied further, to explore the ability for substrate and/or catalyst control. The authors determined that reaction diastereoselectivity can be determined by substrate control with sterically bulky substrates, exhibiting high diastereoselectivity regardless of catalyst. Reaction enantioselectivity for these hindered substrates is always governed by substrate per the stepwise mechanism above (i.e. enantiopure substrates generate enantiopure products). Catalyst control over reaction diastereoselectivity was observed with less bulky substrates (e.g. **189**), where enantioselectivity was also observed to be high, but still dictated by the initial substrate configuration. These conclusions allow for the reliable prediction of stereochemical outcomes for an insertion reaction based on substrate

bulk and catalyst, enabling the synthesis of several complex natural products with benzofuran substructures. Furthermore, with this report, the existence of the stepwise C–H insertion mechanism was substantiated, and therefore can be a plausible explanation for observed phenomena in future efforts in the field.

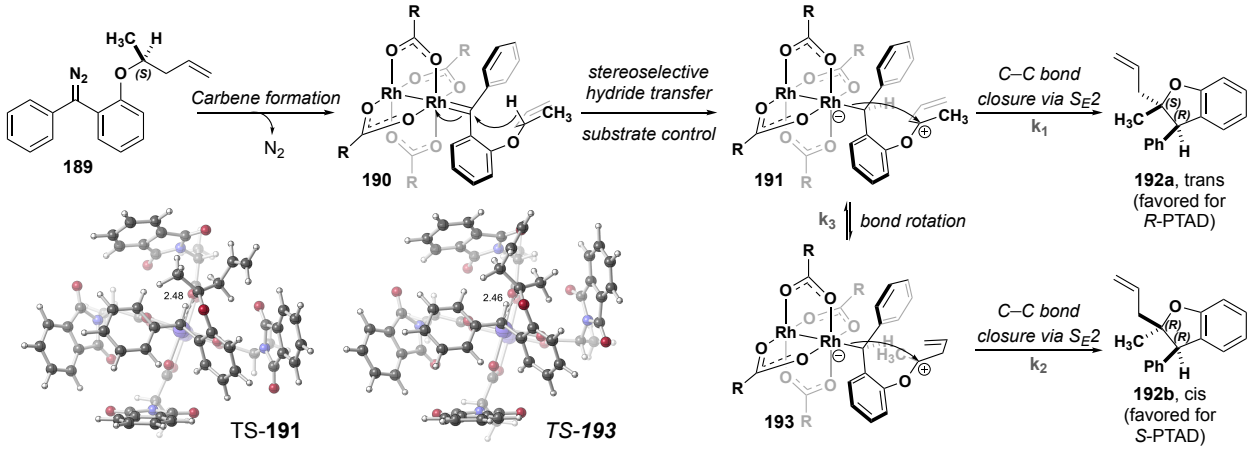


Figure 23. Experimental and computationally supported stepwise C–H insertion mechanism

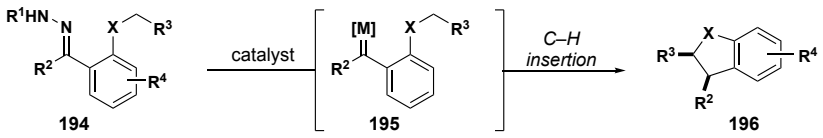
Given the breadth of intramolecular insertion substrates to date, it is also likely that changes to the substrate (e.g. substituents at the inserting carbon, the steric and electronic character of the carbene, and/or the size of the ring that is formed) can shift the pathway from stepwise to concerted. Moreover, changes to these substrate/catalyst interactions can alter the observed stereochemical outcome. As donor/donor carbenes continue to be studied, additional experimental and computational mechanistic data will shed light on the factors that favor one pathway or the other.

The most common C–H insertion products are benzene-fused 5-membered ring products, frequently generated with excellent stereoselectivity (Table 1). Che and co-workers first demonstrated this bond-construction using ruthenium porphyrin catalyst **152**.[121,122] Using carbenes generated from tosylhydrazones they achieved the synthesis of benzodihydrofurans and one example of an indoline (Table 1, entries 1-2). Notably, no β-hydride elimination products were reported for acetophenone-

derived carbenes, however the elevated temperatures that were required resulted in variable reaction yields and diastereoselectivities. Our lab subsequently showed that carbene formation occurred rapidly at ambient or reduced temperatures in the presence of dirhodium tetracarboxylates (occasionally referred to as paddlewheel complexes).[123] Although initial reactions with achiral rhodium complexes showed nominal reactivity and diastereoselectivity, the use of catalyst **142** improved both the yield and diastereoselectivity while also enabling high degrees of enantioselectivity (Table 1, entry 3). This method was used as the key bond construction for our synthesis of *E*-δ-viniferin, representing the first enantioselective synthesis of an oligoresveratrol natural product.[123,124] Subsequent studies elucidated the origins of byproducts and computed transition state structures that explain the catalyst control of stereochemistry.[116] Solvent screens for these systems also demonstrated the reduced electrophilicity of these donor/donor carbene systems, showing tolerance of Lewis basic solvents, isopropanol, and even wet acetonitrile.

Intramolecular insertion reactions with donor/donor carbenes have also lead to the stereoselective formation of indanes, benzodihydrothiophenes, and indolines (Table 1, entry 5).[125] Substrates for indane formation lack the activating heteroatom adjacent to the insertion site, reducing reactivity to the point where insertion at a tertiary carbon provided the widest substrate scope. Replacement of oxygen with sulfur resulted in comparable reactivity and, in some cases, higher stereoselectivity. The expansion of the indoline substrate scope from previous studies demonstrated excellent stereocontrol with N–alkyl and N–H substrates.

Table 1. Synthesis of benzene-fused five-membered rings by C–H insertion



194 195 196

entry	R^1	R^2	R^3	X	catalyst	examples	yield (%)	dr[a]	er
1[121]	Ts	CH_3	PMP	O	152	1	77	>98:2	NA
2[122]	Ts	CH_3, Ph	Ar, alkyl, CO_2CH_3	O, NCH_2R^3	152	8	62-89	34:66 to 99:1	98:2
3[96,126]	H	Ar, alkyl	Ar, alkyl, H, allyl	O, NTs, CH_2	142	19	66-99	88:12 to 99:1	68:32 to 99:1
4[124]	H	Ar	PMP	O	139	1	87	>95:5	98:2
5[127]	H	Ar	Ar, alkyl	NR^5, CH_2, S	142	22	65-99	80:20 to >95:5	75:25 to 99.5:0.5

[a] cis:trans ratio

Driver and co-workers reported several examples of polycyclic indanes, indolines, and benzodihydrofurans using Du Bois's $Rh_2(esp)_2$ catalyst **143** from acetophenone-derived tosylhydrazones (Figure 24).[128] This work highlights catalyst control of carbene reactivity: while copper (I)-based aryl/alkyl carbenes were previously found to undergo cyclization/alkyl migrations,[129] rhodium carbenes in this work cleanly furnish allylic insertion products **198** while avoiding cyclopropanation reactions. Interestingly, when the available bond for C_{sp3}–H insertion is at a bridgehead, the preferred pathway is the vinyl C_{sp2}–H insertion reaction to afford **202**. It is also notable that in all cases where the carbene is appended with a methyl group, the potential Bamford-Stevens elimination product is not observed.[130]

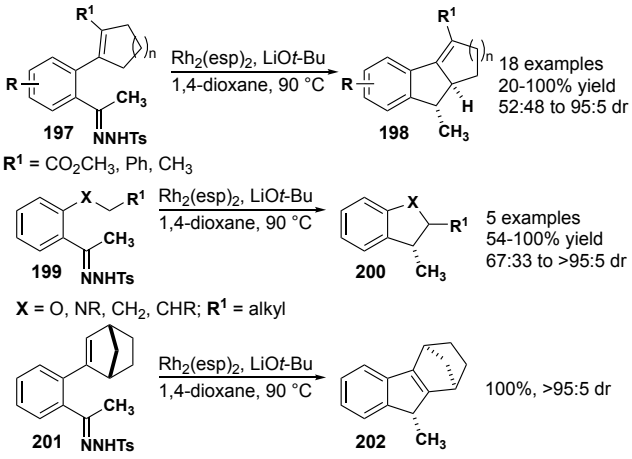


Figure 24. C–H insertion reactions with donor/donor rhodium carbenes to form indanes

The synthesis of saturated monocyclic 5-membered heterocycles is also enabled using ruthenium porphyrin catalyst **143** (Figure 25). Che and co-workers demonstrated that substituted tetrahydrofurans and pyrrolidines were formed in good yield and, in many cases, high diastereoselectivity.[131] Pyrrolidines with a variety of nitrogen substituents (CH_3, Ph, CBz) were also tolerated, demonstrating the robustness of the catalyst and carbene intermediates to Lewis bases. This report further displayed the attenuated reactivity of the system (i.e. catalyst and reaction conditions), given that β-hydride elimination products were not observed despite having two potential elimination sites on the dialkyl carbenes.

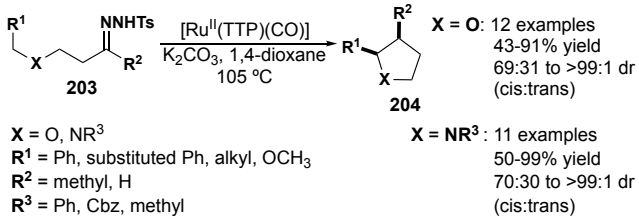
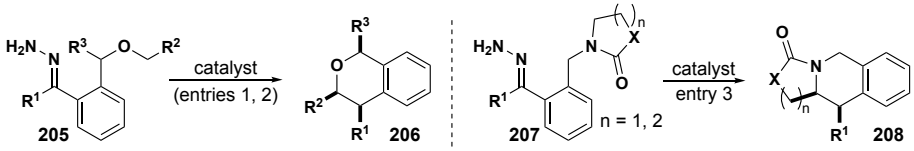


Figure 25. Ruthenium porphyrin catalyzed C–H insertion with alkyl/alkyl carbenes

Although the formation of five-membered rings by intramolecular C–H insertion is most common due to kinetic favorability, the formation of six-membered rings is also possible using rhodium catalysts. Hashimoto reported a study of acceptor-substituted carbenes undergoing 1,6-insertion, where a Stevens-type rearrangement was a competing reaction.[132] 1,5-Nucleophilic attack on the metal carbene by a

heteroatom (i.e. oxygen in this case) and subsequent [2,3]-sigmatropic shift, reduced the yield of the insertion product in many cases. In contrast, the reduced electrophilicity of donor/donor carbenes enables the formation of isochromans in high yield, as a single diastereomer with excellent enantioselectivity, and without any Stevens-type rearrangement products (Table 2, entry 1).[1] This work will be discussed in further detail in section 1.3 of this dissertation. 1,3-Diaxial interactions were also investigated, demonstrating that the reaction will produce a single diastereomer (with three stereocenters in the *cis* configuration) from racemic starting materials where R^3 is a phenyl or methyl substituent (Table 2, entry 2). Moreover, the first examples of donor/donor C–H insertion to form nitrogen-based six-membered heterocycles were shown to proceed with similarly high levels of stereoselectivity (Table 2, entry 3). Under harsher reaction conditions (i.e. electron deficient catalyst **145**, elevated temperatures), a Stevens rearrangement was observed, and the computed transition state demonstrated a polar mechanism involving the dissociation of the rhodium catalyst prior to rearrangement (see section 1.3.6 for further details).

Table 2. Synthesis of benzene-fused six-membered rings by C–H insertion



entry	R^1	R^2	R^3	X	catalyst	examples	yield (%)	dr[a]	er
1[1]	Ar, CH_3	Ar, alkyl, allyl, propargyl	H	NA	142	18	54-98	>95:5	63:37 to >99.5:0.5
2[1]	Ph	PMP, vinyl	Ph, CH_3	NA	140	3	60-70	>95:5	NA
3[1]	Ph	H	H	O, CH_2	142	3	54-83	>95:5	94:6 to 99:1

[a] cis:trans ratio

Access to donor/donor carbenes without the use of diazo precurors offers an alternative method for accessing these useful intermediates. Although most donor/donor carbenes are derived from diazo

compounds, there are implicit risks involved in the generation and handling of these potentially explosive molecules, especially at larger scales. Several methods have been developed to generate donor-substituted metal carbenes; most prominently, enynones, retro-Büchner ring expansion intermediates, and cyclopropenes can be manipulated in the presence of a transition metal catalyst to form the reactive carbene intermediate (Figure 26). Coordination of the alkyne moiety of an enynone (**210**) by a suitable rhodium or gold catalyst allows for the rearrangement of the structure to form a furyl-substituted metal carbene (**211**).[133] Similarly, the alkene moiety of a strained cyclopropene (**213**) can be activated by a rhodium or zinc catalyst, opening the ring and forming a vinyl carbene (**214**). Additionally, when the retro-Büchner ring expansion intermediate (**216**) is exposed to a rhodium or gold catalyst, the norcaradiene is decomposed to form a metal carbene (**217**) and benzene. These metal carbene species may then be used in further intra- or intermolecular insertion reactions.

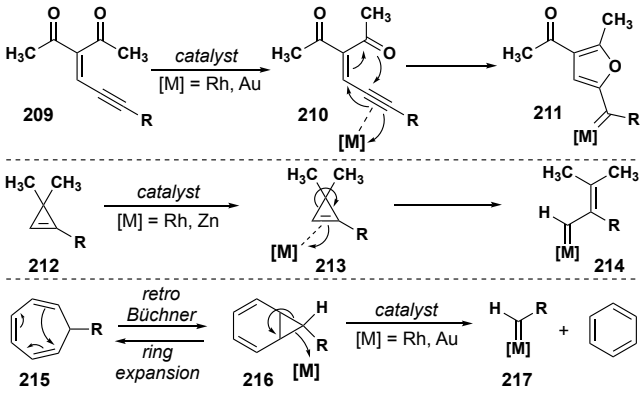
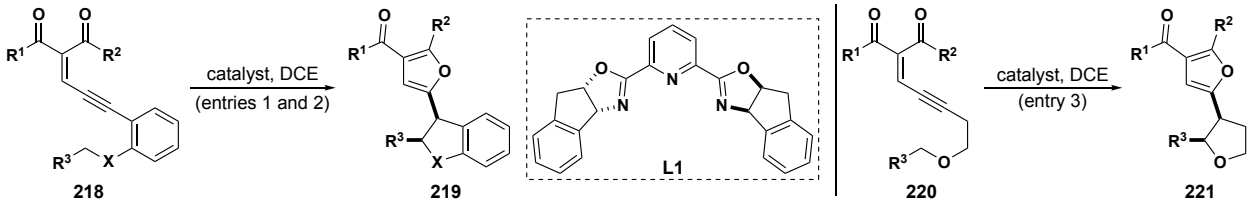


Figure 26. Diazo-free donor-substituted metal carbene formation

Recent work by Zhu (South China University of Technology) circumvents potential safety issues through a novel *diazo-free* generation of donor/donor metal carbenes from the cyclization of enynones.[42] These metal carbenes then undergo diastereoselective and enantioselective C–H insertion to form furyl-substituted dihydroindole and dihydrobenzofuran structural cores (Table 3). Entry 1 demonstrates the utility of the methodology with a broad variety of both oxygen and *N*-acyl substrates; nearly all examples

gave excellent diastereo- and enantio-selectivity at low catalyst loadings (**142**, 1-5 mol %). Entry 3 describes the application of this methodology with a furyl/alkyl carbene, affording excellent yields of the tetrahydrofuran product but with diminished stereoselectivity compared to entry 1. C–H insertion substrates with allylic or propargylic insertion sites often suffer from competing cyclopropanation (and cyclopropenation) reactions. Zhu and co-workers expanded upon their diazo-free methodology to include chemoselective reactions with allylic and alkyl substrates by using an alternative catalyst: the dirhodium carboxylate catalyst used in entries 1 and 3, when applied to allylic insertion sites for *N*-acyl substrates, was found to give tetrahydroquinoline cyclopropanation products with excellent stereoselectivity.[43] However, when a ruthenium precatalyst is used with inda-pybox as the ligand (Figure 19, **151**, Table 3, L1), the C–H insertion reaction predominates, giving good yields of dihydroindolines with excellent stereoselectivity (Table 3, entry 2).

Table 3. Diazo-free C–H insertion reactions with donor/donor and donor carbenes from enynones



entry	X	R^1	R^2	R^3	catalyst	examples	yield (%)	dr[a]	er
1[42]	O, NAc	alkyl, alkoxy	alkyl	alkyl, allyl, Ar, CO2Et	142	29[b]	65-99	50:50 to >99:1	82:12 to 99.5:0.5
2[134]	NAc	alkyl, alkoxy, Ph	alkyl, Ph	alkyl, allyl, Ar	151	34[c]	43-97	91:9 to >99:1	98:2 to >99.5:0.5
3[42]	NA	CH_3	CH_3	allyl, Ph	142	3[b]	99	77:23 to 95:5	80:20 to 87:13

[a] cis:trans ratio, [b] reactions run at -20 to -30 °C, [c] reactions run 80-120 °C

Echavarren and co-workers were able to generate diazo-free donor carbenes through a retro-Büchner ring expansion (Figure 27). With gold phosphine catalyst **161**, intramolecular C–H insertion to form an

indane was achieved as the minor product, affording mostly cyclopropanation products.[135] In more recent efforts, the Echavarren group used dirhodium paddlewheel complex $Rh_2(TFA)_4$ (**145**) to better effect, generating numerous intermolecular Si–H insertion products (Figure 27).[136]

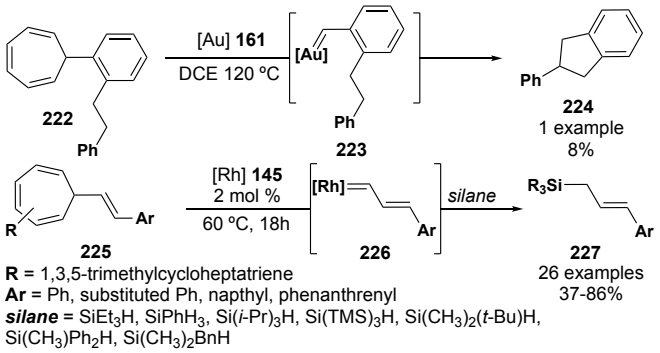


Figure 27. Retro-Büchner ring expansion derived donor carbene insertion reactions

Another robust method for generating diazo-free donor metal carbenes is by the ring opening of substituted cyclopropenes. Early efforts by Cossy and co-workers demonstrated an impressive substrate scope using this method for intramolecular C–H insertion (Figure 28). With $Rh_2(OAc)_4$ as the catalyst, substituted pyrans (**230**) were achieved with excellent diastereoselectivity at low catalyst loadings (0.5 mol %); a desymmetrization experiment furthermore demonstrated excellent stereoselectivity, affording **230** (where R^2 = CH_2CH_2OR) as a single diastereomer. The authors also offered intriguing stereoselectivity models for these novel substrates and produced convincing evidence for a concerted mechanism for these insertion substrates *via* stereospecific deuterium labeling experiments.[41] While these researchers have had considerable success with these diazo-free methodologies, there are still many opportunities to expand substrate scope, further develop enantioselective variants, and introduce new, orthogonal, and safer diazo-free methods.

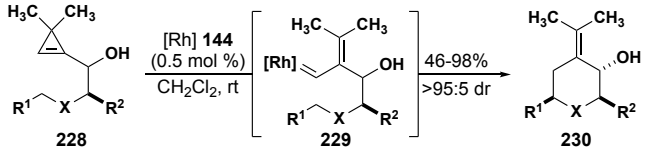


Figure 28. Cyclopropene-derived donor carbene insertion reactions

In conclusion, donor/donor carbenes exhibit reduced electrophilicity compared to their acceptor-substituted equivalents; in C–H and X–H insertion reactions, this attenuated reactivity provides excellent chemoselectivity, functional group tolerance, and insensitivity to adventitious moisture. Traditionally delicate insertion reactions are accessible without rigorous drying procedures and can even tolerate Lewis basic or other X–H moieties on the substrate without diminished reactivity and/or significant side reactions. In many cases, this difference in reactivity can also produce enhanced stereoselective outcomes. While dirhodium carboxylate catalysts remain a privileged class of catalysts for C–H and some X–H insertion reactions, there are many reports of ruthenium and copper-catalyzed reactions (among others) that demonstrate equivalent selectivity and orthogonal reactivity to allow reactions deemed infeasible with rhodium paddlewheel complexes. Mechanistic proposals have suggested that C–H insertion reactions may proceed by several different pathways depending on the type of catalyst, the accompanying metal-carbene, and the steric and electronic properties of the insertion site.

Significant work with dirhodium paddlewheel complexes has shown that intramolecular C–H insertion reactions with donor/donor carbenes can achieve high degrees of chemo-, regio-, and stereo-selectivity. While these insertion reactions remain a hot topic, the field of donor-substituted carbene insertion chemistry has been expanded in recent years to include N–H, B–H, O–H, Si–H, Ge–H, Sn–H and P–H moieties. However, whereas C–H insertion reactions have been made stereoselective for many substrate classes, diastereo- and/or enantio-selective, X–H insertion reactions remain limited and there remains open methodological territory for creating stereoselective variants of X–H moieties in insertion

chemistry. Concerns over the safety of diazo compounds have spawned novel diazo-free procedures that generate unique substrates; these methods have been successfully applied not only in C–H insertion reactions, but also with N–H, O–H, and Si–H bonds. The volume of work in the field of donor-substituted carbene chemistry, while still small compared to acceptor-substituted carbenes, is growing and will continue to offer up unique chemical disconnections, opportunities for stereoselective transformations, and superb chemoselectivity in complex substrates. With these considerations in mind, there is a great outlook for the application of these methods in natural product syntheses, which have remained rare in the literature.

1.1.4 Stevens-type rearrangements

As mentioned in sections 1.1 and 1.1.2, the use of metal carbenes in the synthesis of isochromans can be interrupted by a competing side-reaction: a Stevens-type Rearrangement (Figure 29). In the original report by Stevens and coworkers, they demonstrate the decomposition of quaternary ammonium salts with base to afford Stevens rearrangement products.[137] The precise mechanism of this reaction lacks concensus, but generally relies upon the formation of an ylide species (e.g. **233**) that is aided by the presence of an electron-withdrawing group.[138] While there are several modes claimed for the mechanics of the rearrangement, the reaction is highly unlikely to be a concerted process as the migrating group is observed to have retention of configuration and the mechanism would have to be antarafacial. Alternative explanations for this phenomenon are the homolytic cleavage of the N–C bond to form a diradical, or the heterolytic cleavage of the N–C bond with significant ion-pairing in the solvent cage to promote retention of configuration.

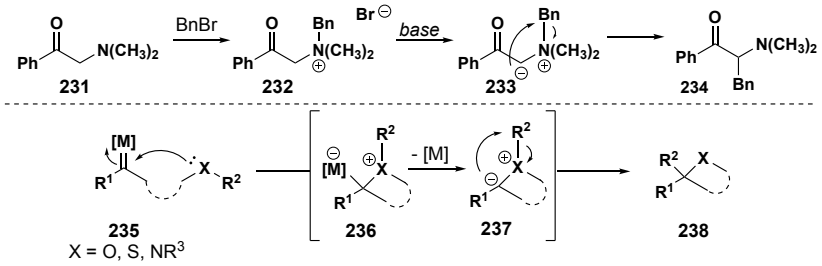


Figure 29. First reported Stevens rearrangement and a general reaction pathway for Stevens rearrangements involving metal carbenes

Stevens-type rearrangements have been invoked in the presence of metal-carbenes to generate a wide variety of products in a stereoselective manner (Figure 30). It is known that once the metal decomposes the diazo species to extrude nitrogen and afford the metal carbene, the metal can disassociate from the ylide species after the attack of the heteroatom lone-pair (**236** and **237**, Figure 29). Therefore, stereoselectivity in metal-carbene-derived Stevens-type rearrangements is often governed by substrate control and thermodynamic stability (i.e. if the rearrangement is reversible). In some circumstances, sigmatropic rearrangements can command stereoselectivity. Figures 30A-F all show the propensity of these acceptor substituted carbenes to undergo 1,6-nucleophilic attack, rather than C–H insertion reactions on other accessible and electronically favorable sites.[139–144] Nitrogen-based substrates are observed to have greater degrees of stereoselectivity in these examples than sulfur-based substrates, though the increased nucleophilicity and location at the 6-position dictate the regioselectivity for S-attack over N-attack on the electrophilic metal carbene (i.e. Figures 30, E and F). These examples also highlight the relevance of copper and rhodium catalysts in these reactions. Also of note is the presence of electron withdrawing substituents on all of these examples (i.e. acceptor/acceptor and acceptor carbenes); the synthesis of acceptor substituted diazo compounds is prevalent because of their kinetic stability, but upon formation of the metal-carbene, they are quite reactive. Therefore, due to the high reactivity of the acceptor metal-carbenes, Stevens-type rearrangements are the predominant product. Figure 30G

demonstrates the ability of allylic heteroatoms to facilitate [2,3]-sigmatropic shifts once the ylide is formed.[145] **259** will orient itself in a conformation that gains secondary orbital effect stabilization. This phenomenon allows for the observed >95:5dr for the rearrangement product, affording a functionally dense pyrrolidine **260**.

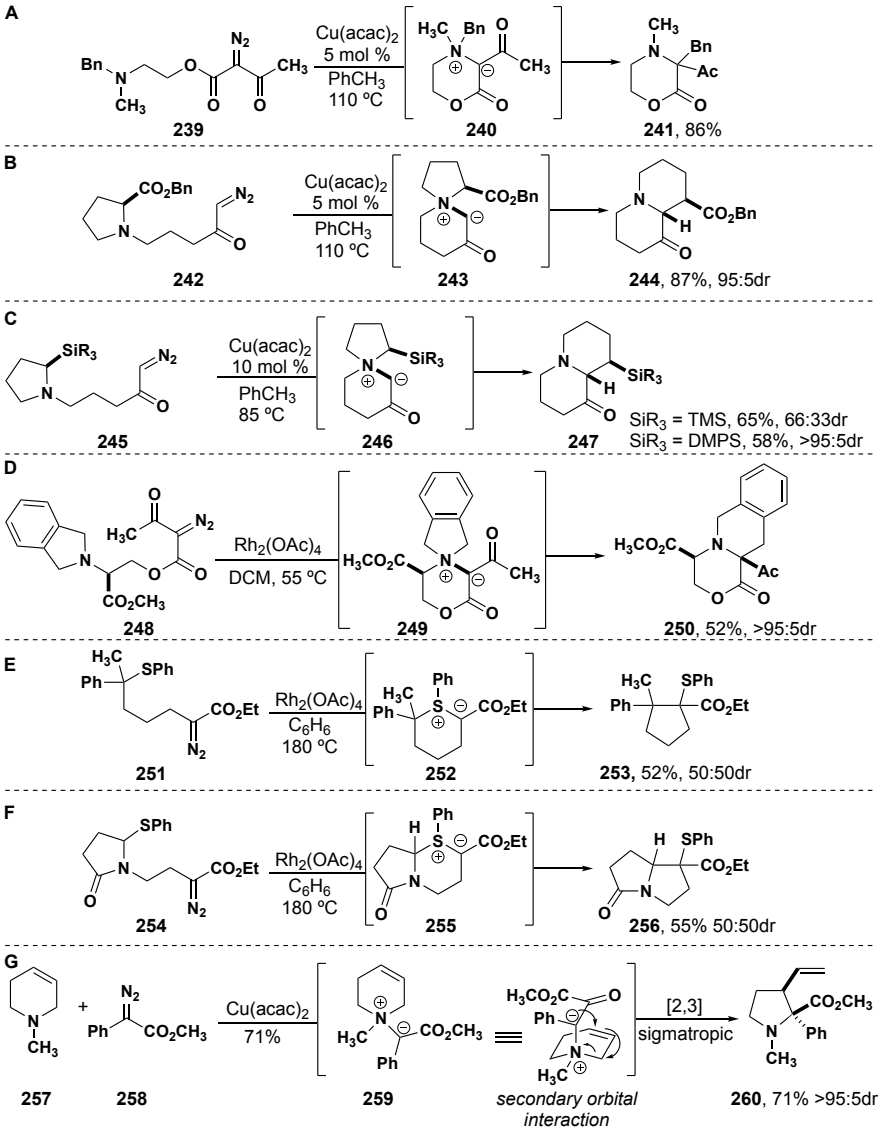


Figure 30. Examples of Stevens-type rearrangements with metal-carbenes

Generally, oxa-variants of metal-carbene-derived Stevens-type rearrangements are uncommon in the literature and still entirely represented by acceptor substituted metal carbenes.[146] Figure 18 (section

1.1.2) details the examples by McKervey and Hashimoto, wherein chemoselectivity between C–H insertion and Stevens-type rearrangement is dependent on the donating capacity of the carbene substituents (donor = phenyl by Hashimoto and donor = CH_3 by McKervey).[80,132] Doyle and coworkers report a fascinating example of desymmetrization by oxa-Stevens rearrangement with predominating C–H insertion as another product (Figure 31).[37] Using Doyle's oxazolidinone-based rhodium catalyst MEOX, the authors explored the possibility for desymmetrization of a 1,3 dioxanyl-substrate **263** to undergo a Stevens-type rearrangement: interestingly, the chiral catalyst mediates the stabilization of ylides **261** and **266**, giving good selectivity between **262a** and **262b** (82:18er). C–H insertion, however, was shown to be highly enantioselective (99:1er) and was isolated as the major product of the reaction in low yield (25%).

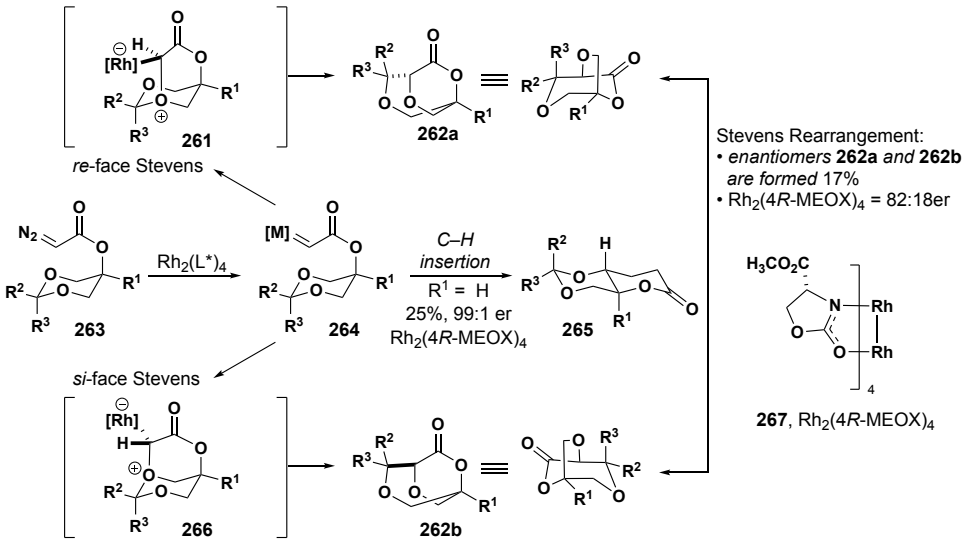


Figure 31. Intramolecular desymmetrization via oxa-Stevens-type rearrangement and competing C–H insertion by Doyle and coworkers

In conclusion, the Stevens rearrangement is a competing reaction with C–H insertion reactions when the heteroatom is in suitable proximity to attack a metal carbene, namely at the 5- or 6-position. This reaction results in an ylide intermediate that is stabilized by electron withdrawing substituents (i.e.

acceptors) that facilitate this byproduct formation. Stevens rearrangements can be stereoselectively achieved, usually in the case of nitrogen ylides that with internal chirality to influence rearrangement selectivity. As shown by McKervey and Hashimoto, acceptor/acceptor, and acceptor/donor metal carbenes exhibit drastic differences in chemoselectivity between C–H insertion and Stevens rearrangement. Therefore, as proposed above, the donor/donor carbene should have the benefit of minimal Stevens rearrangement byproducts as a result of their reduced electrophilicity.

1.2 Substrate Synthesis

The synthetic route to substrates that allows entry into this new chemical space often involves the manipulation of established chemistry in order to afford key intermediates, which, in and of themselves, are novel structures. For the synthesis of isochromans by C–H insertion with donor/donor carbenes, a retrosynthesis from the desired 3,4-substituted isochromans was conceived (Figure 32). Through the established donor/donor carbene and C–H insertion methodology the benzophenone hydrazone was identified as a potential key intermediate. Based on prior work in the lab, oxidation of a benzophenone hydrazone **269** with manganese dioxide is a fruitful and facile method to afford the carbene precursor diazo species and usually does not need to be optimized. The formation of the hydrazone intermediate by condensation onto benzophenone **270** can be difficult due to the relatively low electrophilicity of the ketone and the relatively large amount of steric hindrance adjacent to it (i.e. diaryl ketone with one *ortho*-substituent). However, microwave reactions at very high temperatures (e.g. 170 °C) were often sufficient to achieve synthetically useful quantities of the hydrazones (i.e. ~40-60% yields). Therefore, the primary synthetic step that needed to be route-scouted was the formation of the benzophenone. While there are many ways to generate diaryl ketones, there are few methods which tolerate or operate robustly with *ortho*-substituted substrates. Figure 32 gives a general map of the strategies attempted to produce the benzophenones. Prior efforts in the lab had indicated that the oxidative coupling between aryl iodides **272**

and benzaldehydes developed by Suchand and coworkers was a working method to afford benzophenones.[147] An ideal step-economic synthesis was also conceived, involving the addition of an aryl lithiate **274** or Grignard to phthalide **276** with added electrophile for *in situ* alkylation. A simple protocol involving aryl lithiate or Grignard additions to Weinreb benzamides **271**, benzaldehydes, and/or benzonitriles was also conceived; inversion of the electrophile/nucleophile pair gives an alternative approach to this synthesis as well (**277** and **274**).

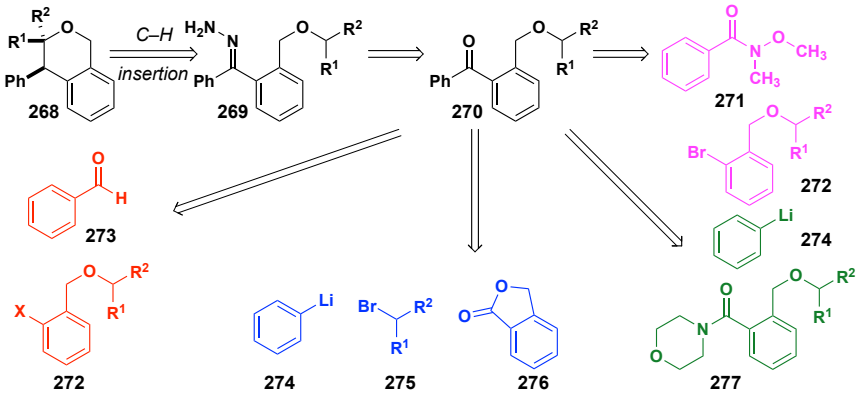
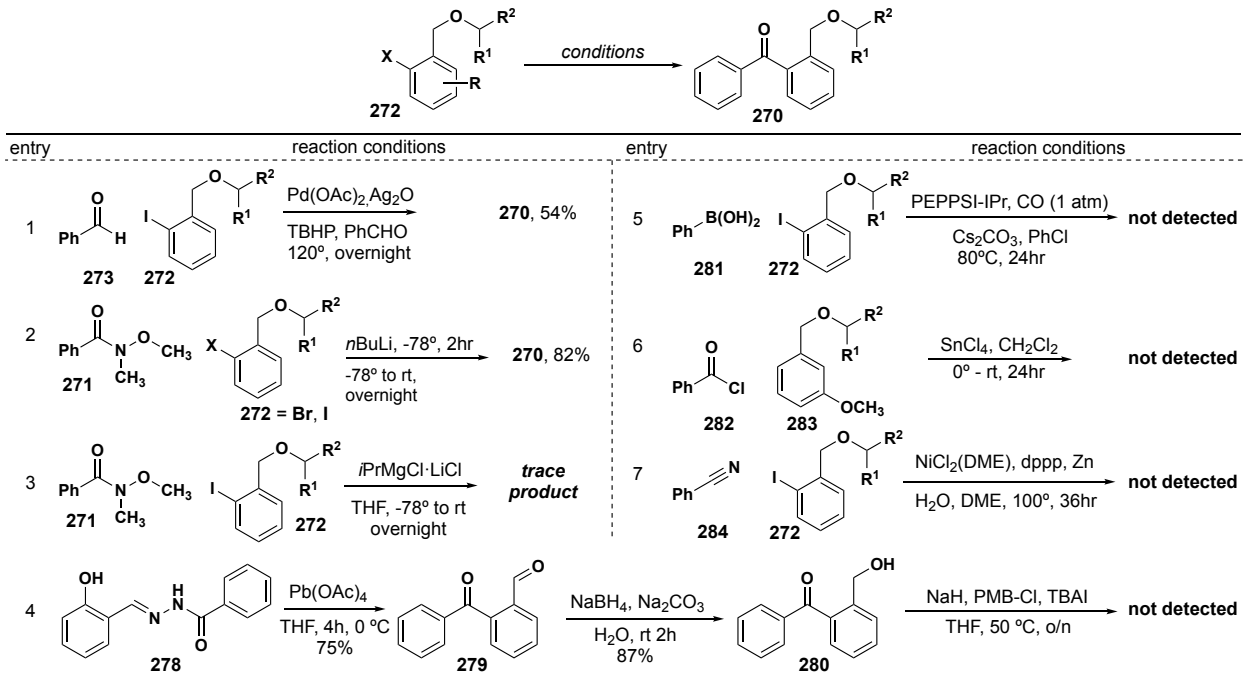


Figure 32: Retrosynthetic map detailing various routes to benzophenone intermediates

1.2.2 Ketone Synthesis Optimization

The protocol reported by Suchand and coworkers appeared to be a robust method to achieve the benzophenone from iodo-arenes, but due to the required excess of benzaldehyde, the strategy suffered from inefficient purification involving co-elution between aldehyde and benzophenone (Table 4, entry 1).[147] Another common method was attempted, involving aryl lithiate or Grignard additions to Weinreb benzamides (entry 2).[148] This strategy proved to be the most reliable and robust method for most substrates discussed in this work. For substrates that were not amenable to this Weinreb-amide protocol, several other conditions were attempted.

Table 4: Benzophenone Synthesis Condition Screen

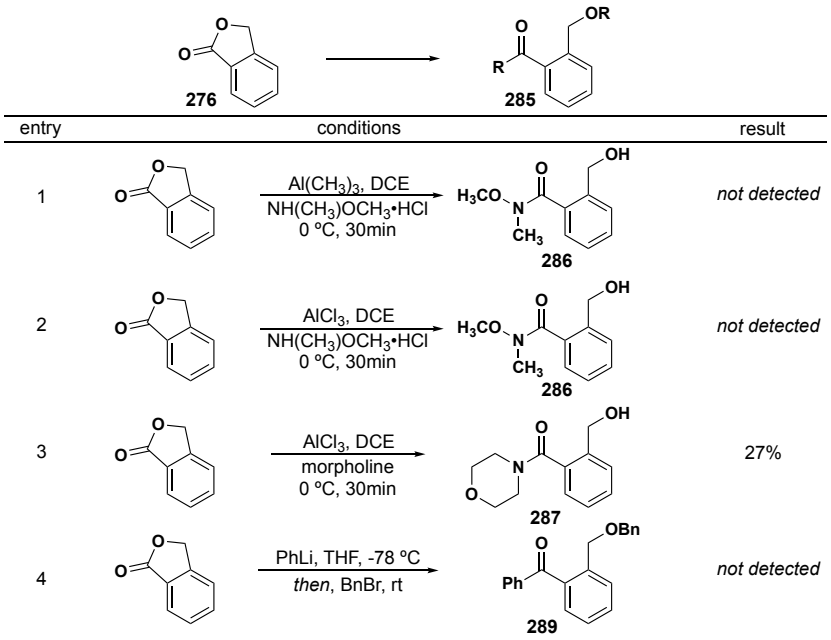


When low yields were obtained with lithium halogen exchange and addition to a Weinreb amide, preparations to increase the nucleophilicity of the aryl lithiate were explored. Magnesium halogen exchange with isopropylmagnesium chloride and lithium chloride conditions (i.e. *turbo*-Grignard conditions) were employed, but magnesium halogen exchange was sluggish and only trace addition to the Weinreb amide was observed (Table 4, entry 3).[149,150] Acylhydrazone **278** can be subjected to lead tetraacetate to undergo the Kotali rearrangement, affording ketone-aldehyde **279** in good yield (Table 4, entry 4).[151,152] Subsequent reduction of the aldehyde with sodium borohydride affords benzyl alcohol **280**; alkylation conditions were attempted with this intermediate, but only trace product was observed by TLC and the unpurified NMR spectrum was complex. Similarly, when **280** was brominated with phosphorous tribromide, the resulting S_N2 reaction with benzyl alcohol was unsuccessful and showed a complex NMR spectrum (not shown). It is noteworthy that this Kotali-derived strategy was quite useful in the synthesis of nitrogen analogues via reductive amination of **279**. Another protocol was reported that

showed particularly good tolerance of hindered and electron-rich substrates using the *N*-heterocyclic carbene palladium complex PEPPSI-*i*Pr in a carbonylative Suzuki coupling (Table 4, entry 5);[153] this procedure failed to produce any of the desired ketone. Tin tetrachloride mediated Friedel Crafts acylation appeared to give some conversion to the desired ketone by TLC, but generated an intractable mixture and complex NMR spectrum that was unable to be purified (Table 4, entry 6). Similarly, simple nucleophilic additions to benzonitriles **284** were unsuccessful (not shown); an orthogonal reaction condition, nickel catalyzed Negishi additions to benzonitriles were also unsuccessful (Table 5, entry 7).

Finally, in attempts to create an efficient sequence to produce the desired benzophenones **270**, transformations from a phthalide starting material and subsequent alkylation were explored (Table 5). Entries 1 and 2 involve the trimethylaluminum and aluminum trichloride mediated amidation of the phthalide lactone functionality to afford benzamide benzyl alcohol **286**.[154,155] No conversion was observed from the Weinreb amine salt and phthalide, so the amine nucleophile was changed to morpholine. This modification gave much better conversion to the morpholine amide (a Weinreb amide surrogate in nucleophilic additions), but was still only yielding **287** in 27% (Table 5, entry 3). Furthermore, alkylations of **287** with 2-iodopropane and benzyl bromide with sodium hydride were not fruitful, primarily affording phthalide via intramolecular esterification (not shown). Finally, a one-pot sequence where phthalide was nucleophilically attacked with phenyllithium, followed by *in situ* alkylation of the resultant benzylic alkoxide with benzyl bromide was attempted (entry 4). Similar to the results of alkylation attempts with **287**, consumption of starting material was observed, but alkylation was unsuccessful: after protic reaction quench, mostly starting material was observed. Because efforts to optimize other reactions were gaining more traction, attempts to create a method derived from phthalide were no longer pursued.

Table 5. Attempted phthalide-derived benzophenone synthetic strategy



While the aryl lithiate additions to Weinreb amides were effective in synthesizing benzophenones, we wished to create a diversity-oriented synthesis by reversing the nucleophile/electrophile pairing between **271** and **272** (Table 4, entry 2) to that of **274** and **277** (Figure 32). This would cut out a step of synthesizing the Weinreb amides, and would allow for the exploration of a variety of commercially available aryl bromides and/or lithiates. Buchwald and coworkers report a carbonylative amidation protocol utilizing the hindered Xantphos ligand under carbon monoxide gas.[156] Their method appeared to be tolerant to *ortho*-substitution and could furnish the Weinreb benzamide directly from an aryl bromide. When applying this method to an isopropyl substrate (i.e. $R^2 = R^3 = CH_3$), formation of **293** was observed in 23% yield. Various elements of the catalytic sequence were investigated (i.e. solvent, higher CO pressures, choice of base, reaction temperature, source of amine), and it was determined that it was necessary to obtain potassium phosphate tribasic in a very anhydrous and finely powdered state. Additionally, the method benefitted from changing the solvent to *m*-xylenes which, in turn, facilitated higher reaction temperatures (i.e. 120 °C) to increase conversion. Running this protocol with a model

substrate (**292**, i.e. R^2 = R^3 = H) to repeat results from the original work, we were only successful in achieving a 23% yield (Buchwald and coworkers report 81%). With help from the original authors (many thanks to Joe Martinelli and Steve Buchwald) it was then determined that the source of amine salt could be the issue and the modified protocol was subjected to conditions to form the morpholine amide **287**. It is known in the literature that morpholine amides can function similarly to the Weinreb amide in nucleophilic additions (Figure 33, **294**). When morpholine was filtered through basic alumina immediately prior to conducting the reaction, synthesis of morpholine amide **285** was achieved in 84%. Successive additions of alkyl/aryl/heteroaryl nucleophiles were achieved as well to afford benzophenones in high yields. It is noteworthy that this modified sequence offered orthogonal electrophile/nucleophile pairing to that in Figure 32, entry 3, however, it does suffer from incompatibility with distal olefins or alkynes, resulting in complex NMR spectra and trace yields of morpholine amide.

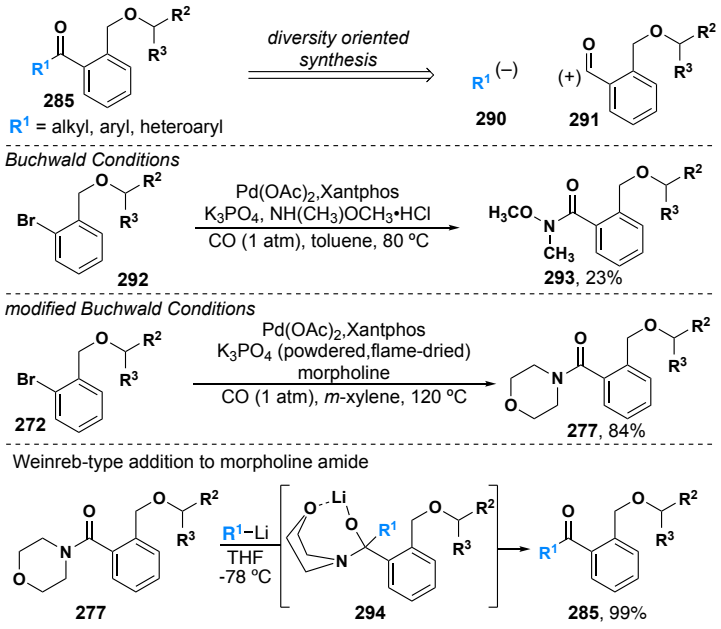


Figure 33. Modified Buchwald procedure to achieve a reversal of nucleophile/electrophile pairing from Figure 32, entry 3

From here, benzophenone substrates were readily converted to their hydrazone analogues and sent forward into our one-pot C–H insertion reaction protocols (see section 1.5 for experimental procedures). Lessons learned from this exploration of reaction conditions would continue to assist in future efforts to generate ketones. Namely, the carbonylative amidation reaction optimized in this work has been reliable in creating benzophenones for particularly hindered substrates in other research efforts in the lab. Much time has transpired since the exploration of these procedures and new methods have been developed that may benefit future work in this area with these types of substrates; for example, a review by Das and Hajra on the subject of carbonylative Suzuki couplings may offer superior results.[157] Additionally, the efficiency of the phthalide-derived substrates is very attractive and could further be explored if the synthesis of a large variety of benzophenone-benzylic ethers was needed in future methodological work.

1.3 Insertion reactions and substrate scope

After the initial discovery of the C–H insertion reaction to synthesize isochromans, we wanted to explore the limits of the methodology and a substrate scope was devised. It was important to assess substrates with varied activation at the insertion site to test the limits of reactivity and stereoselectivity in C–H insertion reactions with donor/donor carbenes. Based on the successes of the previous efforts in the lab regarding the synthesis of five-membered rings by intramolecular C–H insertion (i.e. benzodihydrofurans, benzodihydrothiophenes, dihydroindoles, and dihydroindanes), benzylic, alkyl, allylic, propargylic, acetalyl, and various other insertion sites were chosen.

1.3.1 Benzylic C–H insertion sites to form isochromans

The first result for six-membered ring C–H insertion reactions was achieved by Prof. Leslie Nickerson during a period of preliminary result farming for an upcoming grant submission. After synthesizing the requisite hydrazone, Leslie subjected the substrate to the *one-pot sequential*

reaction conditions (see section 1.5 for experimental details): the benzophenone hydrazone is dissolved in solvent and fine powder manganese dioxide is added with stirring at room temperature (Figure 34). This chemoselective oxidation occurs under mild conditions and is monitored by TLC to confirm complete conversion of hydrazone to diazo. The heterogeneous solution is then cooled to 0 °C in an ice bath and the rhodium catalyst is added, stirring to room temperature overnight. This method is operationally simple and the one-pot oxidation and insertion sequence does not require removal of the oxidant. Much to everyone's satisfaction, this first reaction proceeded cleanly to form 3,4-*cis*-diphenylisochroman **297** in good yield and as a single diastereomer (>95:5 dr). After performing the reaction with a racemic catalyst (i.e. $Rh_2(mes)_4$) the chiral HPLC trace revealed that the reaction was very nicely enantioselective as well with 97:3 er. $Rh_2(R\text{-PTAD})_4$ was established as a highly efficient and stereoselective selective catalyst in this work and was used thereafter. With this excellent preliminary result, we were encouraged to expand the scope of benzylic insertions to form isochroman substrates. Adding electronic density to the insertion site (i.e. increasing the hydridic character of the C–H bonds), we saw a modest increase in yield and enantioselectivity when a methoxy group was installed *para* on the phenyl ring adjacent to the insertion site (Figure 34, **298**). We then wanted to explore electronic effects at the carbene center and interestingly found no discernible effect on reactivity or stereoselectivity when there was an electron-withdrawing nitrile group (**300**) or an electron-donating methoxy group para to the carbene (**299**). These two reactions were also optimized and modified by Jack Shiue to include the use of acetonitrile as a reaction solvent, increasing the yield and enantioselectivity. Highly unusual for the reactive intermediates involved in carbene chemistry, it is significant that the donor/donor metal carbene system is highly tolerant to Lewis

basic solvent functionalities (i.e. acetonitrile, tetrahydrofuran, etc.; see section 1.3.4). Furthermore, heterocycles with a Lewis basic moiety were also well-tolerated as substituents adjacent to the carbene (**301**). Encouraged by these results, we wanted to explore the effect of alkyl substituents on the carbene in combination with an aryl substituent (**302**). The yield was slightly lower, and most noticeably, we saw a significant decrease in enantioselectivity (60:40er), suggesting that the other aryl ring plays a large role in fitting the substrate into the chiral catalyst pocket in a way that promotes stereoselectivity.

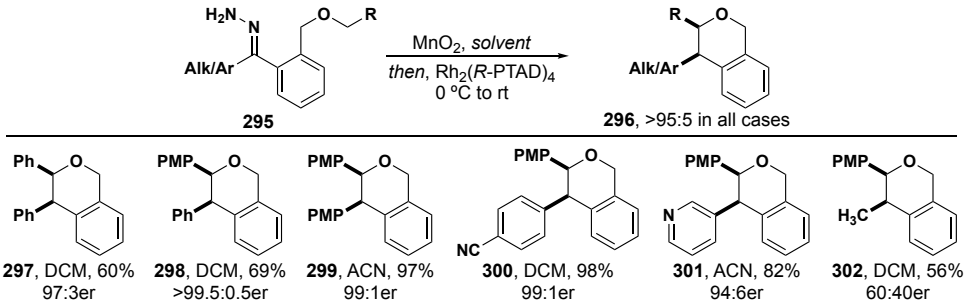


Figure 34. Benzylic insertion site substrates and variations in carbene

1.3.2 Aliphatic C–H insertion sites to form isochromans

Aliphatic substrates also reacted with high diastereo- and enantioselectivity (Figure 35). There is a clear trend of decreasing yield from substrates with tertiary vs secondary substitution at the insertion site. Isochromans **303**, **304**, and **305** were synthesized in excellent yield with insertion into a carbon with two alkyl substituents. When inserting into a carbon with one alkyl substituent, the yields decreased significantly (**306** and **307**, 54-62%) indicating a preference for inserting into more highly substituted carbons, likely due to hydridic character via hyperconjugation. Importantly, throughout the isochroman examples, all products were formed as a single diastereomer and no Stevens-type rearrangement products were observed.

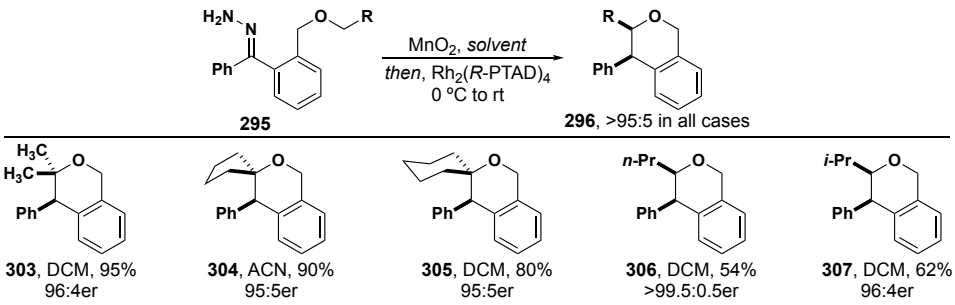


Figure 35. Aliphatic insertion site substrates

1.3.3 Allylic and Propargylic C–H insertion sites to form isochromans

Allylic and propargylic ethers were excellent substrates for C–H insertion (Figure 36). Although the analogous substrates for the synthesis of benzodihydrofurans can suffer from competing dipolar cycloaddition reactions,[126,158] this side reaction was not observed in the reactions leading to isochromans. Most notably, metal carbenes can undergo cyclopropanation or cyclopropenation reactions in the presence of alkenes and alkynes, respectively, and none of these competing products were observed. Stevens-type rearrangement products were also not observed for unsaturated substrates. Notably, **308** did not undergo any Stevens-type rearrangement under reaction conditions via [2,3]-sigmatropic rearrangement or otherwise, in contrast to a similar substrate derived from a donor/acceptor carbene in work by Hashimoto and co-workers.[31] These results appear to support our hypothesis that the reduced electrophilicity of the donor/donor carbene prevents the competing rearrangement reaction. Additionally, while an unsubstituted allyl group underwent insertion with modest yield, the addition of a single substituent resulted in yields of 90% or greater. The crystal structure of **310** was obtained, confirming that the absolute configuration produced with Rh_2(*R*-PTAD)$_4$ is the same for isochromans as was observed with benzodihydrofurans and related heterocycles.[22,159] Trans and cis alkene products **311** and **312** were afforded with no detectable isomerization as well. A propargyl substituted insertion site

proved to be the lowest yielding isochroman (**313**). Although the yield was comparatively lower than the other unsaturated substrates, no evidence of dipolar cycloaddition was observed. We hypothesize that a larger ring size helps to limit the dipolar cycloaddition pathway.[126,158] Also of note for **313** was the observed reduction in enantioselectivity compared to other substrates (92:8 er). It is hypothesize that substrates that have more linear steric volume and fewer degrees of rotation incur more energy penalties when interacting with the catalyst pocket. In turn, this substrate reacts poorly and with less stereoselectivity. Again, acetonitrile was not only tolerated for these substrates, but favorable; reactions with acetonitrile gave cleaner, higher-yielding reactions.

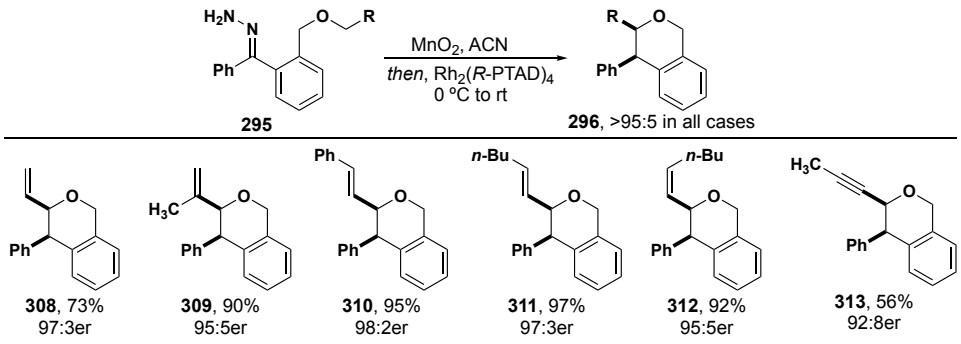


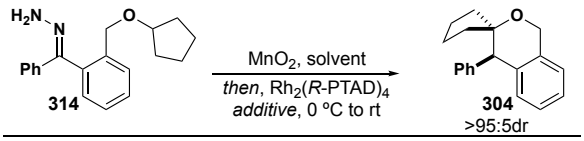
Figure 36. Allylic and propargylic insertion site substrates

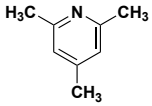
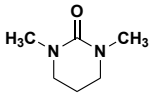
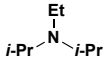
1.3.4 Lewis Base Additive Screen

Based on the surprising observations that reactions to form six-membered rings were typically optimized with acetonitrile as the solvent, it was hypothesized that the Lewis basic nitrogen of acetonitrile was modulating the reactivity of the dirhodium catalyst. When the rhodium carbene is formed with the dirhodium carboxylate catalyst, it is accepted that only one of the rhodium atoms is active in a catalytic transformation as a Lewis acid; more specifically, with the class of catalysts we use, the phthalimidated ligands form the catalyst pocket where the carbene forms, while the distal rhodium site is blocked by bulky

tert-butyl or adamantyl groups (Figure 19). However, if a Lewis base in the reaction mixture was small or flexible enough (e.g. acetonitrile), then it could have the potential to modulate the reactivity of the active rhodium carbene once formed. To test this hypothesis, several Lewis basic solvents and additives with screened. Between dichloromethane, tetrahydrofuran, and acetonitrile, acetonitrile was the highest yielding, tetrahydrofuran also affording isochroman **304** in good yield, while dichloromethane was much lower (Table 6, entries 1-3). Based on the relative Lewis basicity of these solvents ($-\Delta H^o$ of complexation with BF_3 at rt: DCM = 10kJ/mol, ACN = 60kJ/mol, THF = 90 kJ/mol), no clear trend is observed; that is, tetrahydrofuran is significantly more Lewis basic than acetonitrile, but was not higher yielding.[160] One explanation for this observed phenomenon is that while tetrahydrofuran is more Lewis basic, it incurs steric repulsion from the catalyst ligands where acetonitrile is more linear and with fewer degrees of conformational freedom. This would limit the amount of distal complexation with the catalyst and would temper any potential modulation of the catalyst performance. A second explanation is that *because* tetrahydrofuran is more Lewis basic, it competes with the substrate for the active catalytic site and therefore impedes carbene formation and catalyst turnover. Lewis base additives pyridine, 2,4,5-trimethylpyridine, *N,N*-dimethylpropyleneurea, and Hünig's base were all investigated (Table 6, entries 4-7): pyridine and Hünig's base almost entirely shut down the reaction, while more sterically encumbered Lewis bases showed similar reactivity compared to entry 3. These data would lead to a similar conclusion to the solvent screen, in that the effect on modulating the distal rhodium atom is possible for nitrogen-based Lewis acids, but due to the steric hindrance of the additive, the primary effect is to compete with the substrate for catalyst complexation. Still, the effect is pronounced when comparing entries 5 and 6 to entry 1, where a reproducible increase in yield is observed. To investigate the specific mechanism of this effect would require further study.

Table 6. Lewis base additive and solvent screen for insertion reactions with dirhodium catalyst



entry	solvent	additive	result
1	DCM	NA	54%
2	ACN	NA	90%
3	THF	NA	76%
4	DCM		trace product
5	DCM		69%
6	DCM		71%
7	DCM		*no reaction*

Given the molecular orbitals calculated by Fürstner and coworkers, it appears that the LUMO of the dirhodium catalysts are primarily of metal-based d_z^{2*} character, while the HOMO is the ligand-based d_{xy}, and the next level is ligand-based $d_{x^2-y^2}$.[102] This would suggest that if the catalyst was precomplexed with a Lewis basic moiety (i.e. two electron donor), the molecular orbital energies would be changed and the new LUMO would likely be a ligand based orbital, perhaps impeding reactivity. On the other hand, it has recently been reported that these systems may be more nuanced, where a distal coordination event can have a *push-pull* effect to have a dynamic effect on modulation of reactivity.[161–163] Berry and Darko have studied the effect of Lewis bases in with dirhodium carboxylate complexes and have even synthesized a class of catalysts with a tethered thioether proximal to the distal rhodium atom. These complexes show superior chemoselectivity in cyclopropanation reactions and molecular orbitals were also calculated to show that the HOMO/LUMO gap was increased by ~1kcal/mol. Therefore, while the effects of Lewis bases did not positively affect the selectivity or reactivity of our intramolecular C–H insertion reactions with donor/donor carbenes, the field is in active study.

1.3.5 Acetalyl C–H insertion sites to form isochromans and attempted derivatization

In attempts to diversify the products accessible by our C–H insertion method, we explored the possibility of post-insertion transformations. An acetalyl insertion substrate **316** was synthesized that would potentially allow for the formation of oxocarbenium upon exposure to a Lewis acid per literature precedent for similar substrates (Figure 37).[164–166] This would enable further functionalization at the 3-position by adding various nucleophiles to **316**. Hydrazone **315** was constructed in a straightforward manner *via* lithium halogen exchange and addition to a Weinreb amide. Upon subjection to one-pot sequential insertion conditions (see section 1.5 experimental details), the substrate was observed to undergo oxidation and subsequent C–H insertion with excellent conversion. After workup, the unpurified reaction mixture showed good conversion to the insertion product **316** in >95:5dr. However, upon purification on silica gel and neutral alumina, the acetal **316** was observed to degrade to an unidentifiable mixture of products. As the compound could not be suitably purified for accurate chiral HPLC analysis, a conservative estimate of the enantiomer ratio is 90:10, based on integrations of peaks with some overlapping with adjacent signals. Understanding that any purification would only introduce more impurities to the reaction, it was determined that the further functionalization of **316** would benefit from a 1-pot sequence without purification of the acetalyl isochroman. Therefore, the reaction sequence was modified to the two-pot procedure and upon completion of the insertion reaction (monitored by TLC), allyl and silyl enol ether nucleophiles were added to the reaction mixture alongside Lewis acid boron trifluoride diethyl etherate at 0 °C. Upon addition of the Lewis acid to the reaction mixture, the clear solution was observed to turn a persistent bright yellow color and by TLC several new spots appeared. In all cases, the substrate was fully consumed and the unpurified NMR spectrum indicated a complex mixture. Exploring other transformations, a reduction to form **320** was attempted using trifluoroacetic acid and triethylsilane conditions seen in the literature for similar substrates with acetals at the 1-position,

but unfortunately no conversion was observed.[167] Analogous conditions with boron trifluoride were attempted affording **320** in 55% yield on a small scale;[168] this result, however was not repeatable and was not able to be fully characterized. After these attempts, no further efforts were made to functionalize the isochroman scaffold post-insertion for the purposes of this methodology publication.

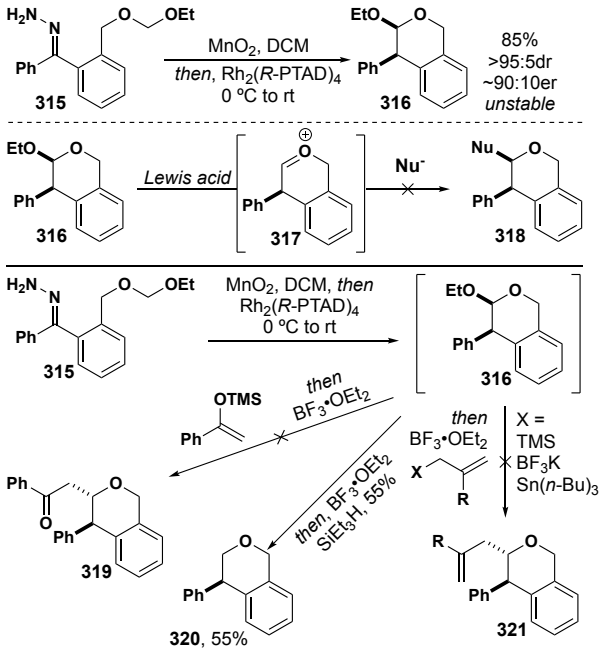


Figure 37. Insertion into an acyclic acetal C–H bond to form cyclic acetal and attempts at nucleophilic additions to an oxocarbenium ion

1.3.6 Other attempted substrates and tetrahydroisoquinolines

Several other substrates were attempted that were not successful in the formation of isochromans, but were informative and interesting insofar that they tested the limits of the insertion methodology to form six-membered rings by C–H insertion with donor/donor carbenes. Firstly, a benzaldehyde-derived hydrazone **322** was synthesized and subjected to our usual one-pot sequential conditions. For this substrate, no oxidation of the hydrazone to the diazo was observed with MnO_2; the reaction was pursued no further but it is possible that other oxidation methods would proceed smoothly. Next, for thioether **324**, oxidation of the hydrazone was complete, but no insertion product was observed. This is likely due

to the relative unfavorability of the alkyl insertion site, and the ability of the electron-rich sulfur atom to occupy a coordination site on the rhodium catalyst (similarly to Darko's work)[163] and interfere with catalyst turnover. Finally, insertion into a methyl ether to form **327** was unsuccessful, showing no consumption of the diazo species. This substrate would later be effective in the formation of *ortho*-quinone dimethides for use in Diels-Alder reactions optimized by Jose Ruiz. While these attempted substrates were not fruitful, they did highlight the limits of the insertion method: aldehyde-derived hydrazones would require more optimization of the oxidation, thioethers suffer from poor catalyst turnover, and insertion into a methyl group is not possible with 6-membered ring substrates to form isochromans.

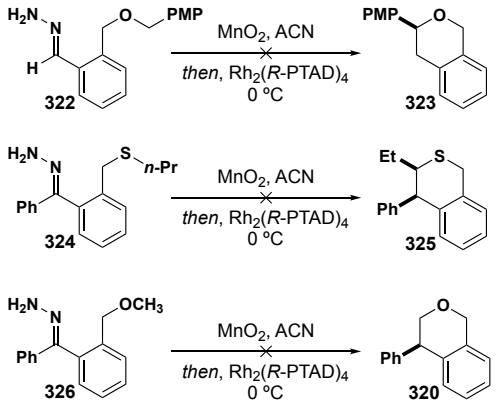


Figure 38. Attempted C–H insertion substrates

Our success in synthesizing isochromans motivated our attempts to synthesize their nitrogen analogues; this work was completed by Prof. Leslie Nickerson and is included for completeness. To the best of the authors' knowledge, 1,6-C–H insertion on aliphatic systems has never been done to synthesize nitrogen-containing heterocycles. Substrates featuring lactams were tolerated, affording tetrahydroisoquinolines **330** and **331** as single diastereomers and with high stereoselectivity (Figure 39). The carbamate derived **332** was also synthesized in moderate yield and with excellent stereoselectivity. X-ray crystallography of **332** showed the same absolute

stereochemistry as is observed with isochromans. In analogy to our work with indolines, in which insertion into methyl C–H bonds was possible,[159] we attempted to synthesize **334**. However, the sole identifiable product of the reaction was isoindoline **335**, resulting from an apparent Stevens [1,2]-rearrangement (Figure 39).[169,170] Although previous studies propose a stepwise diradical mechanism for the Stevens rearrangement,[170] density functional theory (DFT) studies support *N*-attack to the metal carbene, followed by a concerted free ylide Stevens rearrangement (Figure 39). This model suggests that the metal catalyst is not essential in the Stevens rearrangement step.[171]

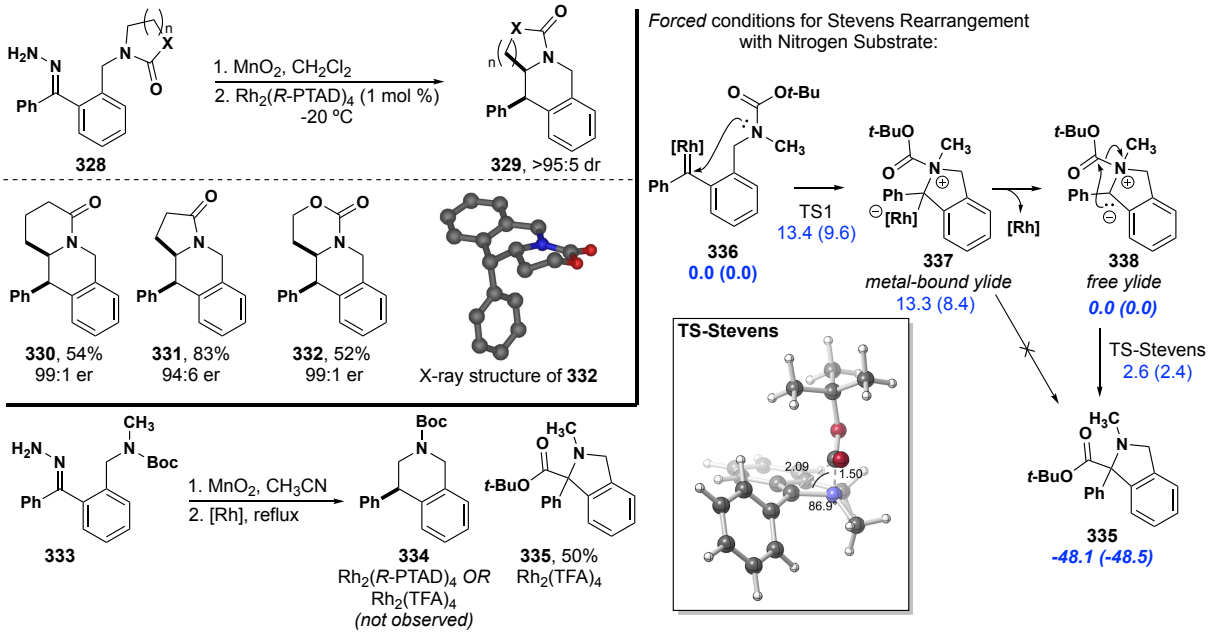


Figure 39. Tetrahydroisoquinoline substrate scope and investigation of Stevens rearrangement product

1.3.7 Three-Center Diastereoselective C–H Insertion Reactions

With the formation of six-membered rings comes the opportunity to explore the influence of 1,3-diaxial interactions in the diastereoselective formation of the stereogenic centers that form during insertion (Figure 40). A single diastereomer (**341**) was observed from hydrazone **339** using $Rh_2(mes)_4$ as

the catalyst, the conformation of which was determined by a nuclear Overhauser effect (NOE) NMR experiment. This indicates that the C–H insertion step occurs in a diastereoselective manner despite having a bulky group close to the rhodium carbene. Furthermore, 1,3,4-substituted isochromans **342** and **343** were also isolated in good yields with excellent diastereoselectivity when Rh_2(*R*-TCPTTL)$_4$ was used as the catalyst to accelerate the rate of C–H insertion. The chiral phthalimido catalysts generally exhibit higher activity than any of the achiral catalysts used with donor/donor carbenes. The structure of compound **343** was also determined by X-ray diffraction.

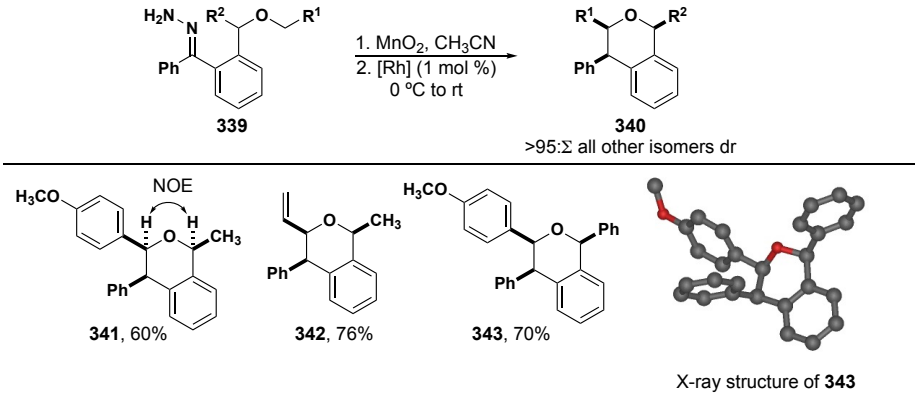


Figure 40. Three-center diastereoselective C–H insertion reactions to form isochromans

1.4 Conclusions

In conclusion, this chapter demonstrates the development of a new chemical reaction methodology to produce isochromans through C–H insertion reactions with donor/donor carbenes. Isochromans are prevalent in many natural products and drug-like substances, but methods to synthesize them are limited in breadth and further limited in stereoselective variation. This work appeals to the broader scientific in that it creates a new synthetic tool for synthetic chemists to use towards their efforts in natural products synthesis and medicinal chemistry. Our method enables the chemo-, diastereo-, and enantioselective formation of 3,4-substituted isochromans in a thereto unreported manner which is facile and accessible to the general community. Aryl, alkyl, allyl, propargylic, and acetalyl insertion sites were well tolerated, as

well as variations in the electronic character of the arenes adjacent to the carbene. Finally, donor/donor carbene insertions reactions are an emerging field and this work continues to push the boundaries of reactivity and selectivity; no Stevens-type rearrangement products were observed and furthermore, we also explored the synthesis of isochromans in a diastereoselective fashion by installing a substituent on the benzylic carbon alpha to oxygen and were gratified to see a single diastereomer formed. Additionally, we synthesized the first six-membered rings containing nitrogen through 1,6-C(sp^3)–H insertion in moderate yields and with excellent stereoselectivity. A Stevens-type rearrangement product was isolated from one substrate using increased temperature and computational evidence suggests that isoindoline formation occurs *via* a free ylide not bound to rhodium.

1.5 Experimental Section

1.5.1 General Procedures

General Procedure A (alkylation of alcohols)

Following a modified literature procedure,[172] NaH (60% suspension in mineral oil, 1.5-3.0 equiv) and anhydrous THF (0.56 M with NaH) were added to a flame-dried round bottom flask. The suspension of NaH in THF was stirred and cooled to 0 °C. To the flask was added a solution of the desired alcohol (1.0 equiv) in anhydrous THF (0.78 M) dropwise and stirred for 2 h. The respective bromide (1.1-1.7 equiv) was added dropwise and the reaction was warmed to rt and stirred for 2-16 hours. Upon completion by TLC, the reaction was quenched at 0 °C with sat. aq. NH_4Cl or H_2O (20 mL) dropwise. The crude mixture was extracted with EtOAc (3 X 40 mL) and the combined organic layers were washed with brine (1 X 30 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude reaction mixture was purified by flash column chromatography to yield the desired ether.

General Procedure C (alkylation of alcohols)

To a flame-dried round bottom flask was added NaH (60% suspension in mineral oil, 3.0 equiv) and anhydrous THF (1.2 M with NaH). The suspension of NaH in THF was stirred for 15 min and cooled to 0 °C. To the flask was added a solution of the respective alcohol (2.5 equiv) in anhydrous THF (6.0 M) and stirred for 1 h. To the flask was added a solution of the desired alkyl/aryl halide (1.0 equiv) in THF (0.8 M) followed by tetrabutyl ammonium iodide (0.14 equiv). The reaction was allowed to warm to rt overnight. Upon completion by TLC, the reaction was quenched with sat. aq. NH_4Cl (20-50 mL) and the crude mixture was extracted with EtOAc (3 X 40 mL). The combined organic layers were washed with H_2O (1 X 30 mL) and brine (1 X 30 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude reaction mixture was purified by flash column chromatography to yield the desired ether.

General Procedure D (synthesis of morpholine amide)

Following a modified literature procedure,[173] $Pd(OAc)_2$ (0.025 equiv), Xantphos (0.05 equiv), and potassium phosphate tribasic (K_3PO_4, 3 equiv) were added to a dry 20 mL μW tube or a 25 mL round bottom flask under argon and the tube was sealed. A solution of the relevant aryl halide (1 equiv) in toluene (0.5 M) was added to the tube followed by morpholine (1.5 equiv) which had been freshly filtered through basic alumina. A vent needle was placed in the septum of the μW tube and the headspace was purged with CO (g) from a balloon for 30 sec. The vent needle was removed and the reaction was kept under an atmosphere of CO with the balloon in the headspace. The reaction was heated to 100 °C overnight. Upon completion by TLC, the reaction was diluted with EtOAc (10 mL) and filtered through Celite. The crude reaction mixture was purified by flash column chromatography to yield the desired

morpholine amide. *Morpholine amides often showed significant rotamer distortion in the ^{1}H and ^{13}C NMR.*

General Procedure E (addition to morpholine amide)

To a flame-dried round bottom flask was added the desired morpholine amide (1.0 equiv) in THF (0.1-0.17 M) and the solution was cooled to -78 °C. The respective aryl/alkyl lithium reagent (2 equiv) was added dropwise and the reaction was allowed to warm to rt overnight. The reaction was quenched at -78 °C with sat. NH_4Cl in CH_3OH (10 mL) and the mixture was allowed to warm to rt. H_2O (10 mL) was added and the crude mixture was extracted with EtOAc (3 X 30 mL) and the combined organic layers were washed with brine (1 X 20 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude reaction mixture was purified by flash column chromatography to yield the desired ketone.

General Procedure F (addition to morpholine amide)

To a flame-dried round bottom flask was added the desired morpholine amide (1.0 equiv) in THF (0.1 M) and the solution was cooled to -78 °C. The respective aryl lithium (2 equiv) was added dropwise and reacted for 10 min. Then the reaction was allowed to warm to rt for 1 h. The reaction was quenched at -78 °C with sat. aq. NH_4Cl (10 mL) and the crude mixture was extracted with EtOAc (3 X 30 mL) and the combined organic layers were washed with brine (1 X 20 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude reaction mixture was purified by flash column chromatography to yield the desired ketone.

General Procedure G (addition to morpholine amide)

To a flame-dried round bottom flask was added the desired aryl halide (1.5 equiv) in THF (0.26 M) and the solution was cooled to -78 °C. To the solution was added *n*-butyllithium (1.6 equiv) dropwise and the solution was stirred for 2 h at -78 °C. The respective morpholine amide (1.0 equiv) in THF (0.44 M) was added to the solution and the reaction was allowed to warm to rt overnight. The reaction was quenched at -78 °C with sat. NH_4Cl in CH_3OH (10 mL) and the mixture was allowed to warm to rt. H_2O (10 mL) was added and the crude mixture was extracted with EtOAc (3 X 30 mL) and the combined organic layers were washed with brine (1 X 20 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude reaction mixture was purified by flash column chromatography to yield the desired ketone.

General Procedure H (synthesis of Weinreb amide)

Following a modified literature procedure,[174] the desired benzoic acid (1.0 equiv) in CH_2Cl_2 (0.5 M) was added to a flame-dried round bottom flask under argon and equipped with a vent needle. Oxalyl chloride (2.0 equiv) was added dropwise to the solution followed by addition of *N, N*-dimethylformamide (1.3 equiv) and the solution was stirred at rt for 1 h. The mixture was concentrated *in vacuo* and the resulting acid chloride was diluted with CH_2Cl_2 (0.1 M) and Et_3N (3.0 equiv) and *N,O*-dimethylhydroxylamine hydrochloride (1.5 equiv) were added. After stirring for 2.5 h the reaction was quenched with sat. aq. $NaHCO_3$ (175 mL) and the mixture was extracted with CH_2Cl_2 (3 X 175 mL) and the combined organic layers were washed with $NaHCO_3$ (2 X 175 mL) and brine (175 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude reaction mixture was purified by flash column chromatography to yield the desired Weinreb amide.

General Procedure I (synthesis of Weinreb amide)

Following a modified literature procedure, to a flame-dried round bottom flask were added *N,O*-dimethylhydroxylamine hydrochloride (1.0 equiv) and CH_2Cl_2 (0.4 M). Et_3N (3.0 equiv) was added slowly at 0 °C. Benzoyl chloride (1.0 equiv) was then added dropwise into the mixture the solution was stirred at rt overnight. Upon completion, the reaction was quenched with sat. aq. $NaHCO_3$ (10 mL) and the mixture was extracted with CH_2Cl_2 (3 X 30 mL) and the combined organic layers were washed with H_2O (20 mL) and brine (20 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude reaction mixture was purified by flash column chromatography to yield the desired Weinreb amide.

General Procedure J (addition to Weinreb amide)

Following a modified literature procedure, the desired aryl halide (1.0 equiv) in anhydrous THF (0.1 M) was added to a flame-dried round bottom flask under argon and cooled to -78 °C. To the solution was added *n*-butyllithium in hexanes (1.1 equiv) dropwise and the resulting mixture was stirred at -78 °C for 1-2 h. The relevant Weinreb amide (1.5 equiv) in THF (0.2-1 M) was added to the mixture and the reaction was allowed to warm to rt overnight. The reaction was quenched at -78 °C with sat. aq. NH_4Cl and was extracted with EtOAc (3 X 20 mL). The combined organic layers were washed with H_2O (1 X 20 mL) and brine (1 X 20 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude reaction mixture was purified by flash column chromatography to yield the desired ketone.

General Procedure K (Reduction of Ketone)

To a flame-dried round bottom flask were added 1-(2-bromophenyl)ethan-1-one (1.0 equiv) and anhydrous EtOH (0.25 M with ketone). The solution was cooled to 0 °C. To the flask was added $NaBH_4$

(4.0 equiv) in one portion and stirred for 10 min. The reaction was allowed to warm to rt overnight. Upon completion by TLC, the reaction was quenched with sat. aq. NH_4Cl (20 mL) and the crude mixture was extracted with EtOAc (3 X 40 mL). The combined organic layers were washed with H_2O (1 X 30 mL) and brine (1 X 30 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude reaction mixture was purified by flash column chromatography to yield the desired alcohol.

General Procedure L (Alkylation of Alcohol)

To a flame-dried round bottom flask were added 1-(2-bromophenyl)ethan-1-ol (1.0 equiv) and anhydrous THF/DMF (91:9 v/v, 0.18 M with alcohol). NaH (60% suspension in mineral oil, 2.5 equiv) was added portion-wise at 0 °C and the mixture was stirred for 10 min. The respective chloride (1.1 equiv) and TBAI (0.1 equiv) were added to the flask. The reaction was allowed to warm to rt overnight. Upon completion by TLC, the reaction was quenched with H_2O (20 mL) and the crude mixture was extracted with EtOAc (3 X 40 mL). The combined organic layers were washed with brine (1 X 30 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude reaction mixture was purified by flash column chromatography to yield the desired ether.

General Procedure M (addition to Weinreb amide)

Following a modified literature procedure,[175] the desired aryl halide (1.0 equiv) in anhydrous THF (0.31 M) was added to a flame-dried round bottom flask under argon and cooled to -78 °C. To the solution was added *n*-butyllithium in hexanes (1.3 equiv) dropwise and the resulting mixture was stirred at -78 °C for 2 h. The relevant Weinreb amide (1.2 equiv) in THF (1.2 M) was added to the mixture and the reaction was allowed to warm to rt overnight. The reaction was quenched with sat. NH_4Cl in CH_3OH at -78 °C and upon warming to rt the reaction was extracted with diethyl ether (3 X 20 mL). The combined organic

layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude reaction mixture was purified by flash column chromatography to yield the desired ketone.

General Procedure N (carbonylation with benzaldehyde)

Following a modified literature procedure,[176] the desired aryl halide (1.0 equiv), palladium (II) acetate (0.05 equiv), silver (I) oxide (1.2 equiv), benzaldehyde (8.0 equiv), and 70% *tert*-butyl hydroperoxide in H_2O (5.0 equiv) were added to a microwave vial with a stir bar and the microwave vial was sealed. An argon line (or balloon) was added to the vial and the system was heated to 118 °C. When the temperature was reached the argon line/balloon was removed and the mixture was heated overnight. The reaction mixture was cooled to rt, diluted with EtOAc, filtered through Celite with a small pad of silica, and concentrated *in vacuo*. The crude product was purified using flash column chromatography to yield the desired ketone.

General Procedure O (microwave hydrazone formation)

Following a modified literature procedure,[125] the respective ketone (1.0 equiv) in anhydrous EtOH (0.1 M) was added to a flame-dried 5-25 mL argon-backfilled microwave vial. The solution was sparged with argon for 10-30 min after which AcOH (1.0-1.3 equiv) and anhydrous hydrazine (6-13 equiv) were added and the solution was sparged for an additional 1 min. The vial was heated in a microwave reactor at 150-170 °C for 2-10 hours. The reaction mixture was then concentrated *in vacuo,* dissolved in Et_2O (50 mL), and washed with H_2O (3 X 30 mL). The organic layer was dried over Na_2SO_4, filtered, concentrated *in vacuo*, and purified by flash column chromatography to yield the desired hydrazone. *Hydrazones were often isolated as a mixture of E/Z isomers and were used without further purification. As such ^{1}H NMR peaks have been reported only for selected examples. Due to restricted rotation, the hydrazone NMRs often indicated diastereotopic protons.*

General Procedure P (hydrazone formation)

Following literature precedent,[123] the desired ketone (1 equiv) in anhydrous EtOH (0.06 M) was added to a flame-dried round bottom flask under argon. To the flask was added anhydrous hydrazine (10 equiv.) and glacial acetic acid (0.5 to 2.0 equiv). The reaction was heated to 80 °C for 18-120 h. Upon completion by TLC, the reaction was allowed to cool and EtOH was removed *in vacuo*. The residue was dissolved in diethyl ether (30 mL) and washed with H_2O (2 X 20 mL) and brine (1 X 20 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*, and purified by flash column chromatography to yield the desired hydrazone. *Hydrazones were often isolated as a mixture of E/Z isomers or were used without further purification. As such ^{1}H NMR peaks have been reported only for selected examples. Due to restricted rotation, the hydrazone NMRs often indicated diastereotopic protons.*

General Procedure Q (one-pot insertion)

Following literature precedent,[125] the desired hydrazone (1.0 equiv) was added to a flame-dried scintillation vial under argon followed by anhydrous CH_2Cl_2 or CH_3CN (0.015 M). The vial was cooled to 0 °C and manganese (IV) oxide (MnO_2, 8.0 equiv) and the desired rhodium catalyst (0.01 equiv) were added. The resulting dark suspension was warmed to room temperature and allowed to stir from 10 min to 12 h. The crude reaction mixture was filtered over Celite, concentrated *in vacuo*, and purified by flash column chromatography to yield the desired insertion product.

General Procedure R (sequential one-pot insertion)

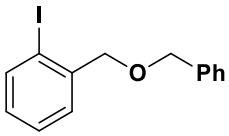
Following literature precedent,[125] the desired hydrazone (1.0 equiv) was added to a flame-dried scintillation vial under argon followed by anhydrous CH_2Cl_2 or CH_3CN (0.015-0.017 M). To the vial was added manganese (IV) oxide (MnO_2, 8.0 equiv) and the resulting dark suspension was stirred until full

conversion of the starting material was observed by TLC. Upon pausing stirring, a color change from clear to magenta was observed from formation of the diazo. The vial was then cooled to 0 °C and the desired rhodium catalyst was added (0.01 equiv). The reaction mixture was allowed to warm to rt for 10 min to 24 h. The crude reaction mixture was filtered over Celite to remove MnO_2, concentrated *in vacuo*, and purified by flash column chromatography to yield the desired insertion product.

General Procedure S (two-pot insertion)

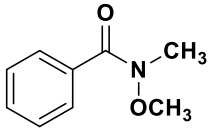
Following literature precedent,[125] the desired hydrazone (1.0 equiv) was added to a flame-dried scintillation vial under argon followed by anhydrous CH_2Cl_2 or CH_3CN (0.015 M). To the vial was added manganese (IV) oxide (MnO_2, 8.0 equiv) and the resulting dark suspension was stirred until full conversion of the starting material was observed by TLC. The reaction mixture was filtered over Celite into a new flame-dried, argon backfilled 20 mL scintillation vial using the same solvent. The magenta solution was cooled to 0 °C and the desired rhodium catalyst was added (0.01 equiv). The reaction mixture was allowed to warm to rt for 10 min to 16 h. The crude reaction mixture was concentrated *in vacuo* and purified by flash column chromatography to yield the desired insertion product.

1.5.2 Experimental procedures

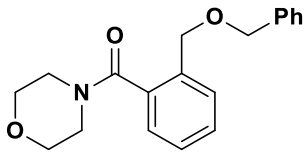


1-((benzyloxy)methyl)-2-iodobenzene (344) was synthesized according to General Procedure A using 2-iodobenzyl alcohol (1.000 g, 4.273 mmol) in THF (5.5 mL), NaH (0.292 g, 7.30 mmol) in THF (13 mL), and benzyl bromide (0.87 mL, 7.3 mmol).The crude product was extracted from NH_4Cl (20 mL) with EtOAc (2 X 40 mL) and washed with brine (1 X 20 mL). The crude material was purified by flash

column chromatography (99:1 to 90:10, hexanes:EtOAc) affording **344** as a yellow oil (1.320 g, 95%).^{1}H NMR (600 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.49 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.43 – 7.39 (m, 2H), 7.39 – 7.33 (m, 3H), 7.33 – 7.29 (m, 1H), 7.02 – 6.96 (m, 1H), 4.64 (s, 2H), 4.55 (s, 2H).. ^{1}H NMR data was consistent with reported literature values.[177]

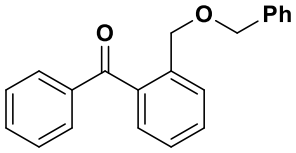


***N*-methoxy-*N*-methylbenzamide (271)** was synthesized according to General Procedure H using benzoic acid (2.000 g, 16.37 mmol) in CH_2Cl_2 (3.3 mL), oxalyl chloride (2.8 mL, 33 mmol), *N, N*-dimethylformamide (1.64 mL, 21.3 mmol), Et_3N (6.3 mL, 49 mmol), and *N,O*-dimethylhydroxylamine hydrochloride (2.400 g, 24.60 mmol) in CH_2Cl_2 (164 mL). The crude product was extracted from $NaHCO_3$ (100 mL) with CH_2Cl_2 (3 X 60 mL) and washed with $NaHCO_3$ (2 X 70 mL) and brine (1 X 70 mL). The crude product was purified by flash column chromatography (90:10 to 70:30, hexanes:EtOAc) affording **271** as a clear oil (1.937 g, 71%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.3 Hz, 2H), 7.47 – 7.43 (m, 1H), 7.42 – 7.38 (m, 2H), 3.55 (s, 3H), 3.36 (s, 3H). ^{1}H NMR data was consistent with literature values.[178]

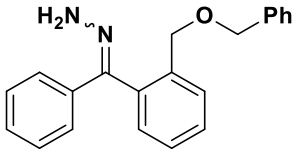


(2-((benzyloxy)methyl)phenyl)(morpholino)methanone (345) was synthesized according to General Procedure D using ether **344** (0.500 g, 1.54 mmol), morpholine (0.20 mL, 2.3 mmol), palladium (II) acetate (0.008 g, 0.02 mmol), Xantphos (0.045 g, 0.077 mmol), potassium phosphate tribasic (0.981 g, 4.62 mmol), CO (1 balloon), in toluene (3 mL). The crude product was purified using flash column chromatography (40:60, hexanes:EtOAc) affording **345** as a yellow oil (0.403 g, 84%). ^{1}H NMR (400

MHz, $CDCl_3$) δ 7.46 (d, *J* = 7.6 Hz, 1H), 7.41 – 7.28 (m, 7H), 7.19 (d, *J* = 7.4 Hz, 1H), 4.73 – 4.39 (m, 4H), 3.79 – 3.58 (m, 4H), 3.47 (s, 2H), 3.31 – 3.09 (m, 2H). ^{1}H NMR was taken at rt and shows a mixture of rotamers.

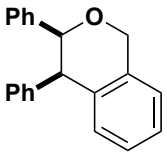


(2-((benzyloxy)methyl)phenyl)(phenyl)methanone (289). To a flame-dried vial was added bromobenzene (0.30 mL, 2.8 mmol) in THF (3 mL) and the solution was cooled to -78 °C. A 1.7 M solution of *tert*-butyllithium (3.3 mL, 5.68 mmol) was added dropwise to the solution and the mixture was stirred at -78 °C for 1 h. A solution of morpholine amide **345** (0.295 g, 0.947 mmol) in THF (5.6 mL) was added dropwise to the solution and the reaction was allowed to warm to rt overnight. The reaction was quenched with sat. NH_4Cl in MeOH (6 mL) at -78 °C. The quenched solution was warmed to rt and diluted with water (20 mL). The resulting mixture was extracted with EtOAc (3 X 30 mL), washed with brine (1 X 30 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified using flash column chromatography (90:10, hexanes:EtOAc) affording **289** as a yellow oil (0.144 g, 50%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.8 Hz, 2H), 7.60 – 7.51 (m, 2H), 7.49 – 7.43 (m, 1H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.37 – 7.29 (m, 2H), 7.23 – 7.17 (m, 3H), 7.17 – 7.11 (m, 2H), 4.65 (s, 2H), 4.39 (s, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 197.91, 137.98, 137.92, 137.89, 137.60, 133.09, 130.45, 130.17, 128.79, 128.65, 128.40, 128.26, 127.66, 127.52, 127.04, 72.82, 70.00; AMM (ESI-TOF) *m/z* calcd for $C_{21}H_{18}NaO_2^+$ $[M+Na]^+$ 325.1205, found 325.1200.

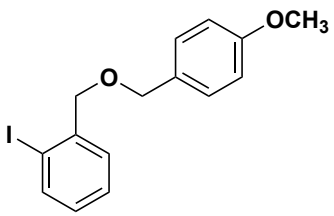


((2-((benzyloxy)methyl)phenyl)(phenyl)methylene)hydrazine (346) was synthesized according to General Procedure O using ketone **289** (0.280 g, 0.926 mmol), hydrazine (0.29 mL, 9.3 mmol), acetic acid (0.06 mL, 1 mmol), and EtOH (9.3 mL) at 150 °C for 2 h. The crude product was purified by flash column chromatography (100:0 to 70:30, hexanes:EtOAc) affording **346** as a white foam (0.172 g, 58%). *Major stereoisomer* **346***:* ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69 (d, *J* = 7.6 Hz, 1H), 7.51 – 7.41 (m, 4H), 7.30 – 7.20 (m, 8H), 7.18 (d, *J* = 7.3 Hz, 1H), 5.34 (s, 2H), 4.46 (d, *J* = 11.8 Hz, 1H), 4.43 (d, *J* = 11.7 Hz, 1H), 4.40 (d, *J* = 11.9 Hz, 1H), 4.35 (d, *J* = 12.0 Hz, 1H).

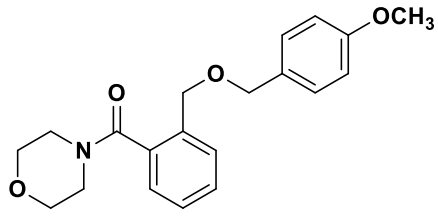
Minor stereoisomer **346***:* (0.028 g, 9%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.7 Hz, 1H), 7.48 – 7.41 (m, 2H), 7.40 – 7.24 (m, 9H), 7.21 (t, *J* = 7.5 Hz, 1H), 7.14 (d, *J* = 7.7 Hz, 1H), 5.53 (s, 2H), 4.67 (s, 2H), 4.50 (s, 2H).



(3*S*,4*R*)-3,4-diphenylisochromane (297) was synthesized according to General Procedure R using hydrazone **346** (0.050 g, 0.16 mmol), MnO_2 (0.111 g, 1.28 mmol), and Rh_2(*R*-PTAD)$_4$ (0.002 mg, 0.002 mmol) in CH_2Cl_2 (11 mL). The crude product was purified by flash column chromatography (100:0 to 97:3, hexanes: EtOAc) affording **297** as white crystals (0.028 g, 61%, >95:5 dr, 97:3 er). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.27 – 7.22 (m, 1H), 7.21 – 7.10 (m, 5H), 7.08 – 6.99 (m, 4H), 6.99 – 6.93 (m, 2H), 6.78 – 6.73 (m, 2H), 5.24 (d, *J* = 15.2 Hz, 1H), 5.12 (d, *J* = 15.3 Hz, 1H), 5.10 (d, *J* = 3.3 Hz, 1H), 4.13 (d, *J* = 3.2 Hz, 1H).; ^{13}C NMR (151 MHz, $CDCl_3$) δ 140.8, 140.3, 137.3, 134.3, 130.4, 130.2, 127.8, 127.4, 127.0, 127.0, 126.8, 126.2, 126.0, 124.2, 80.1, 69.2, 50.4; AMM (CI-TOF) *m/z* calcd for $C_{21}H_{22}NO^+$ $[M+H]^+$ 304.1696, found 304.1690; $[\alpha]_D^{22} = -33.4$ (c = 0.086, $CHCl_3$).

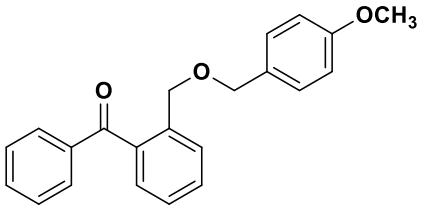


2-(4-methoxybenzyloxymethyl)iodobenzene (347) was synthesized according to General Procedure C, using sodium hydride (0.352 g, 8.55 mmol) in THF (10.7 mL), iodobenzyl alcohol (1.001 g, 4.273 mmol) in THF (5.3 mL), tetrabutylammonium iodide (0.224 g, 0.607 mmol), and 4-methoxybenzyl chloride (0.64 mL, 4.7 mmol), reacting for 2 h at 50 °C. The crude product was purified using flash column chromatography (60:40, hexanes:CH_2Cl_2), affording **347** as a yellow oil (1.344 g, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 7.9 Hz, 1H), 7.47 (d, *J* = 7.1 Hz, 1H), 7.38 – 7.30 (m, 3H), 6.98 (t, *J* = 7.6 Hz, 1H), 6.93 – 6.86 (m, 2H), 4.57 (s, 2H), 4.52 (s, 2H), 3.81 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0, 140.4, 138.8, 129.8, 129.1, 128.9, 128.6, 127.9, 113.5, 97.7, 75.5, 72.1, 54.9; AMM (ESI-TOF) *m/z* calcd for $C_{15}H_{15}INaO_2^+$ $[M+Na]^+$ 377.0009, found 377.0015.

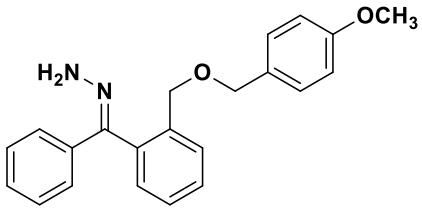


((4-methoxybenzyl)oxymethyl-phenyl)-morpholin-4-yl-methanone (348) was synthesized according to General Procedure D, using $Pd(OAc)_2$ (0.012 g, 0.052 mmol), Xantphos (0.058 g, 0.10 mmol), and potassium phosphate tribasic (1.280 g, 6.031 mmol), morpholine (0.26 mL, 3.0 mmol), and **347** (0.711 g, 2.00 mmol) in toluene (4.0 mL), reacting at 100 °C for 6.5 h. The crude product was purified using flash column chromatography (20:80, hexanes:EtOAc), affording **348** as a clear oil (0.572 g, 84%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.6 Hz, 1H), 7.37 (t, *J* = 7.5 Hz, 1H), 7.32 (t, *J* = 7.5 Hz, 1H), 7.30 – 7.27 (m, 2H), 7.19 (d, *J* = 7.4 Hz, 1H), 6.91 – 6.89 (m, 1H), 6.89 – 6.87 (m, 1H), 4.64

(br s, 1H), 4.51 (s, 2H), 4.44 (br s, 1H), 3.81 (s, 3H), 3.77 – 3.73 (m, 2H), 3.73 – 3.60 (m, 2H), 3.48 (br s, 2H), 3.29 – 3.08 (m, 2H); AMM (ESI) *m/z* calcd for $C_{20}H_{24}NO_4^+$ $[M+H]^+$ 342.1700, found 342.1704; IR (neat): 2855, 1635, 1514, 1429, 1114 cm^{-1}. ^1H NMR was taken at rt and shows a mixture of rotamers.

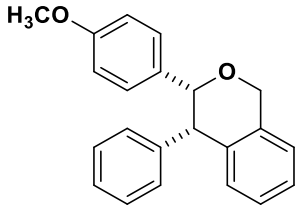


2-(4-methoxybenzyloxymethyl)benzophenone (349) was synthesized according to General Procedure E, using **348** (0.406 g, 1.19 mmol) in THF (11.7 mL), and 1.9 M phenyllithium in dibutyl ether (1.25 mL, 2.38 mmol), reacting for 2 h. The crude product was purified using flash column chromatography (90:10, hexanes:EtOAc), affording **349** as a yellow oil (0.330 g, 84%). ^1H NMR (600 MHz, $CDCl_3$) δ 7.80 (d, *J*= 7.2 Hz, 2H), 7.59 – 7.55 (m, 2H), 7.48 (t, *J*= 7.3 Hz, 1H), 7.44 (t, *J*= 7.8 Hz, 2H), 7.38 – 7.32 (m, 2H), 7.08 (d, *J*= 8.6 Hz, 2H), 6.76 (d, *J*= 8.6 Hz, 2H), 4.62 (s, 2H), 4.33 (s, 2H), 3.77 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 198.1, 159.2, 138.2, 138.0, 137.7, 133.1, 130.5, 130.3, 130.1, 129.4, 128.8, 128.8, 128.5, 127.1, 113.7, 72.6, 69.8, 55.4; AMM (ESI) *m/z* calcd for $C_{22}H_{21}O_3^+$ $[M+H]^+$ 333.1485, found 333.1484; IR (neat): 2930, 2855, 1665, 1514, 1271 cm^{-1}.

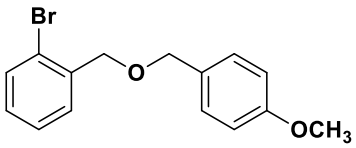


((2-(((4-methoxy)benzyloxy)methyl)phenyl)(phenyl)methylene)hydrazine (350) was synthesized according to General Procedure O, using **349** (0.124 g, 0.372 mmol) in EtOH (3.7 mL), glacial acetic acid (0.03 mL, 0.5 mmol), and hydrazine (0.15 mL, 4.8 mmol), reacting for 3 h at 170 °C. The crude product was purified using flash column chromatography (70:30, hexanes:EtOAc), affording **350** as a

yellow oil (0.079 g, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.1 Hz, 1H), 7.51 – 7.40 (m, 4H), 7.27 (dd, *J* = 5.1, 1.9 Hz, 3H), 7.19 – 7.11 (m, 3H), 6.81 (d, *J* = 8.6 Hz, 2H), 5.34 (s, 2H), 4.39 – 4.29 (m, 4H), 3.78 (s, 3H); AMM (ESI) *m/z* calcd for $C_{22}H_{23}N_2O_2^+$ $[M+H]^+$ 347.1754, found 347.1750.

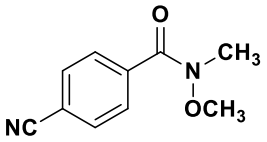


(3*R*,4*S*)-3-(4-methoxy)phenyl-4-phenylisochromane (298) was synthesized according to General Procedure R, using MnO_2 (0.021 g, 0.24 mmol) and **350** (0.027 g, 0.078 mmol) in CH_2Cl_2 (5.2 mL), reacting for 20 min. Rh_2(*S*-PTAD)$_4$ (0.001 g, 0.7 μmol) was added, reacting for 30 h. The crude product was purified using flash column chromatography (90:10, hexanes:EtOAc), affording **298** as a white crystalline solid (0.016 g, >95:5 dr, >99.5:0.5 er, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.21 (m, 1H), 7.19 – 7.11 (m, 2H), 7.08 – 6.98 (m, 4H), 6.85 (d, *J* = 8.5 Hz, 2H), 6.80 – 6.72 (m, 2H), 6.71 – 6.62 (m, 2H), 5.22 (d, *J* = 15.3 Hz, 1H), 5.10 (d, *J* = 15.3 Hz, 1H), 5.04 (d, *J* = 3.2 Hz, 1H), 4.07 (d, *J* = 2.8 Hz, 1H), 3.72 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.6, 141.0, 137.4, 134.4, 132.6, 130.4, 130.3, 127.4, 127.3, 126.9, 126.7, 126.2, 124.2, 113.2, 79.9, 69.3, 55.3, 50.5; AMM (CI-TOF) *m/z* calcd for $C_{22}H_{20}O_2^+$ $[M]^+$ 316.1463, found 316.1455; m.p. 167-168 °C; $[\alpha]_D^{21} = 523.9$ (c = 0.19, $CHCl_3$).

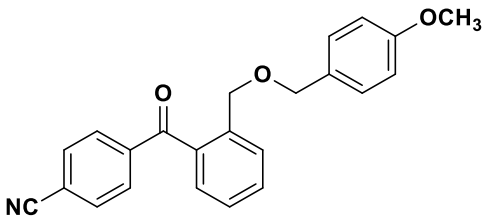


1-bromo-2-(((4-methoxybenzyl)oxy)methyl)benzene (351) was synthesized according to General Procedure C using 2-bromobenzyl bromide (3.000 g, 12.00 mmol) in THF (15 mL), *p*-methoxybenzyl alcohol (3.7 mL, 30 mmol) in THF (5 mL), NaH (1.440 g, 36.00 mmol) in THF (30 mL), and tetrabutylammonium iodide (0.621 g, 1.68 mmol). The crude product was quenched with sat. aq. NH_4Cl

(50 mL) and extracted with EtOAc (3 X 40 mL), the combined organic layers were washed with H_2O (1 X 40 mL) and brine (1 X 40 mL). The crude product was purified by flash column chromatography (90:10, hexanes:EtOAc) affording **351** as a clear oil (3.424 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (t, *J* = 8.0 Hz, 2H), 7.36 – 7.28 (m, 3H), 7.14 (t, *J* = 7.7 Hz, 1H), 6.90 (d, *J* = 8.1 Hz, 2H), 4.60 (s, 2H), 4.57 (s, 2H), 3.81 (s, 3H). ^{1}H NMR data was consistent with literature values.[179]

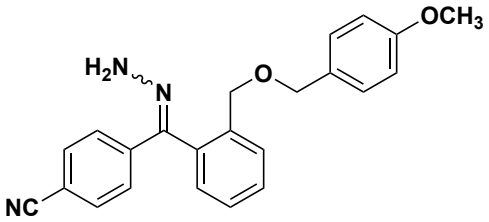


4-cyano-*N*-methoxy-*N*-methylbenzamide (352) was synthesized according to General Procedure H using 4-cyanobenzoic acid (1.863 g, 12.66 mmol) in CH_2Cl_2 (25 mL), oxalyl chloride (12.66 mL, 25.32 mmol), DMF (1.3 mL, 16 mmol), Et_3N (5.3 mL, 28 mmol), and *N,O*-dimethylhydroxylamine hydrochloride (1.852 g, 18.99 mmol) in CH_2Cl_2 (164 mL). The crude product was extracted from $NaHCO_3$ (100 mL) with CH_2Cl_2 (3 X 60 mL) and the combined organic layers were washed with $NaHCO_3$ (2 X 70 mL) and brine (1 X 70 mL). The crude product was purified by flash column chromatography (90:10, hexanes:EtOAc) affording **352** as a clear oil (1.858 g, 77%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.1 Hz, 2H), 7.71 (d, *J* = 8.1 Hz, 2H), 3.53 (s, 3H), 3.39 (s, 3H). ^{1}H NMR data was consistent with literature values.[180]

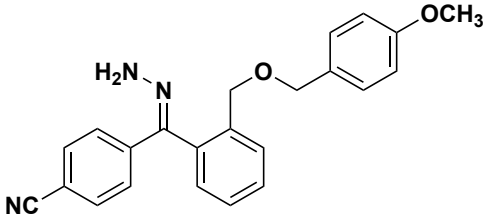


4-(2-(((4-methoxybenzyl)oxy)methyl)benzoyl)benzonitrile (353) was synthesized according to General Procedure J using **351** (0.538 g, 1.75 mmol), 2.5 M *n*-butyllithium in hexanes (0.85 mL, 2.1 mmol), **352** (0.500 g, 2.63 mmol), and THF (10.0 mL). The crude product was purified using flash

column chromatography (80:20, hexanes:EtOAc), affording **353** as a white solid (0.455 g, 73%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.4 Hz, 2H), 7.70 (d, *J* = 8.3 Hz, 2H), 7.57 – 7.48 (m, 2H), 7.41 – 7.36 (m, 1H), 7.31 (d, *J* = 7.2 Hz, 1H), 7.03 (d, *J* = 8.6 Hz, 2H), 6.75 (d, *J* = 8.6 Hz, 2H), 4.60 (s, 2H), 4.30 (s, 2H), 3.79 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.4, 159.2, 140.9, 138.2, 136.9, 132.1, 130.9, 130.2, 129.6, 129.3, 128.8, 128.5, 127.3, 118.0, 116.0, 113.6, 72.6, 69.7, 55.2; AMM (ESI-TOF) *m/z* calcd for $C_{23}H_{19}NaNO_3^+$ $[M+Na]^+$ 380.1263, found 380.1262.

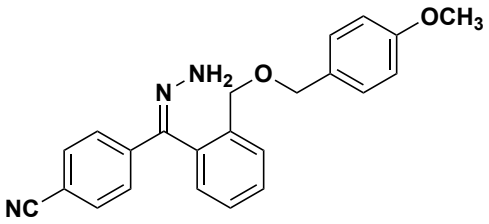


(*E/Z*)-4-(hydrazineylidene(2-(((4-methoxybenzyl)oxy)methyl)phenyl)methyl)benzonitrile (354) was synthesized according to General Procedure P using **353** (0.357 g, 1.00 mmol), hydrazine (0.31 mL, 10 mmol), acetic acid (0.07 mL, 1 mmol), and EtOH (6.7 mL). The reaction was heated at 90 °C for 2 days. The crude product was purified using flash column chromatography (80:20, hexanes:EtOAc), affording **354***trans* as a colorless liquid (0.040 g, 11%), and **354***cis* as a colorless liquid (0.181 g, 49%)

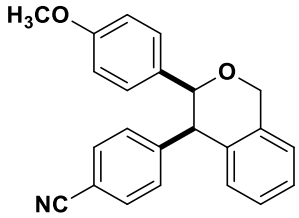


(*E*)-4-(hydrazineylidene(2-(((4-methoxybenzyl)oxy)methyl)phenyl)methyl)benzonitrile (354*trans*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 7.8 Hz, 2H), 7.57 – 7.50 (m, 1H), 7.47 (d, *J* = 7.9 Hz, 2H), 7.32 (t, *J* = 7.5 Hz, 1H), 7.26 – 7.19 (m, 3H), 7.07 (d, *J* = 7.6 Hz, 1H), 6.86 (d, *J* = 8.1 Hz, 2H), 5.55 (s, 2H), 4.57 (s, 2H), 4.41 (s, 2H), 3.80 (s, 3H);^{13}C NMR (151 MHz, $CDCl_3$) δ 159.2, 146.5, 138.3,

137.2, 137.2, 132.7, 130.3, 129.9, 129.7, 129.5, 129.0, 128.4, 127.4, 118.3, 113.7, 112.5, 72.1, 70.1, 55.3; AMM (ESI) *m/z* calcd for $C_{23}H_{22}N_3O_2^+$ $[M+H]^+$ 372.1707, found 372.1703.

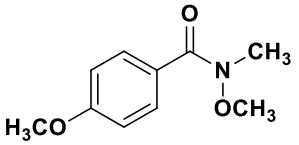


(*Z*)-4-(hydrazineylidene(2-(((4-methoxybenzyl)oxy)methyl)phenyl)methyl)benzonitrile (354*cis*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.3 Hz, 1H), 7.59 – 7.42 (m, 6H), 7.13 (d, *J* = 7.1 Hz, 1H), 7.08 (d, *J* = 8.1 Hz, 2H), 6.80 (d, *J* = 8.0 Hz, 2H), 5.58 (s, 2H), 4.35 – 4.30 (m, 2H), 4.29 – 4.23 (m, 2H), 3.79 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.2, 145.6, 142.3, 137.4, 132.0, 131.1, 129.9, 129.8, 129.7, 129.3, 129.2, 128.9, 126.2, 119.1, 113.7, 110.8, 72.7, 69.7, 55.3; AMM (ESI) *m/z* calcd for $C_{23}H_{22}N_3O_2^+$ $[M+H]^+$ 372.1707, found 372.1701.

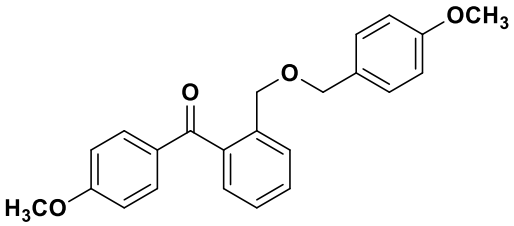


4-((3*S*,4*R*)-3-(4-methoxyphenyl)isochroman-4-yl)benzonitrile (300) was synthesized according to General Procedure R using hydrazone **354***trans* (0.025 g, 0.067 mmol), MnO_2 (0.047 g, 0.54 mmol), and Rh_2(*R*-PTAD)$_4$ (0.001 g, 0.0007 mmol) in CH_3CN (4.5 mL). The crude product was purified by flash column chromatography (83:17, hexanes:EtOAc), affording **300** as white crystals (0.0223 g, 97%, >95:5 dr, 99:1 er). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.2 Hz, 2H), 7.29 (t, *J* = 7.5 Hz, 1H), 7.21 – 7.17 (m, 2H), 6.99 (d, *J* = 7.8 Hz, 1H), 6.89 – 6.83 (m, 4H), 6.70 (d, *J* = 8.8 Hz, 2H), 5.23 (d, *J* = 15.4 Hz, 1H), 5.12 (d, *J* = 15.4 Hz, 1H), 5.08 (d, *J* = 3.4 Hz, 1H), 4.14 (d, *J* = 3.4 Hz, 1H), 3.75 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.6, 146.5, 135.7, 134.2, 131.7, 131.1, 130.8, 130.1, 127.2, 127.1, 126.8, 124.4, 119.1,

113.3, 109.9, 79.3, 69.1, 55.2, 50.5; AMM (ESI-TOF) *m/z* calcd for $C_{23}H_{19}NaNO_2^+$ $[M+Na]^+$ 364.1313, found 364.1318; m.p. 163-164 °C; $[\alpha]_D^{22} = -487$ (c = 0.11, $CHCl_3$).

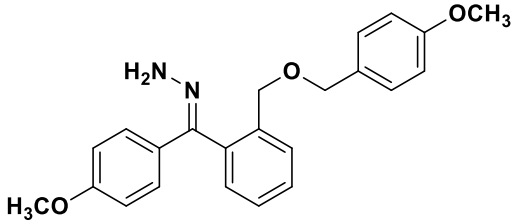


N,4-dimethoxy-N-methylbenzamide (355) was synthesized according to General Procedure H using 4-methoxybenzoic acid (3.041 g, 20.00 mmol) in CH_2Cl_2 (40 mL), 2 M oxalyl chloride in CH_2Cl_2 (20.0 mL, 40.0 mmol), DMF (2.0 mL, 26 mmol), Et_3N (8.4 mL, 60 mmol), and *N,O*-dimethylhydroxylamine hydrochloride (2.926 g, 30.00 mmol) in CH_2Cl_2 (200.0 mL). The crude product was extracted from $NaHCO_3$ (200 mL) with CH_2Cl_2 (3 X 120 mL) and the combined organic layers were washed with $NaHCO_3$ (2 X 70 mL) and brine (1 X 70 mL). The crude product was purified by flash column chromatography (90:10, hexanes:EtOAc) affording **355** as a clear oil (3.360, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.4 Hz, 2H), 6.90 (d, *J* = 8.5 Hz, 2H), 3.85 (s, 3H), 3.56 (s, 3H), 3.36 (s, 3H). ^{1}H NMR data was consistent with literature values.[180]

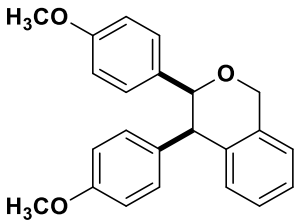


(2-(((4-methoxybenzyl)oxy)methyl)phenyl)(4-methoxyphenyl)methanone (356) was synthesized according to General Procedure J using **351** (1.536 g, 5.000 mmol), 2.5 M *n*-BuLi in hexanes (2.4 mL, 6.0 mmol), **355** (1.464 g, 7.500 mmol), and THF (30 mL). The crude product was purified using flash column chromatography (80:20, hexanes:EtOAc), affording **356** as a white solid (1.464 g, 84%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.2 Hz, 2H), 7.56 (d, *J* = 7.7 Hz, 1H), 7.49 – 7.43 (m, 1H), 7.36 – 7.32

(m, 2H), 7.08 (d, J = 8.1 Hz, 2H), 6.91 (d, J = 8.2 Hz, 2H), 6.76 (d, J = 8.1 Hz, 2H), 4.60 (s, 2H), 4.34 (s, 2H), 3.87 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 196.6, 163.6, 159.0, 138.5, 137.5, 132.5, 130.5, 130.1, 130.0, 129.5, 129.3, 128.6, 128.2, 126.9, 113.6, 72.4, 69.6, 55.5, 55.2; AMM (ESI) *m/z* calcd for $C_{23}H_{23}O_4^+$ $[M+H]^+$ 363.1591, found 363.1586.

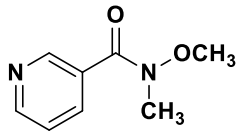


((2-(((4-methoxybenzyl)oxy)methyl)phenyl)(4-methoxyphenyl)methylene)hydrazine (357) was synthesized according to General Procedure P using **356** (0.500 g, 1.38 mmol), hydrazine (0.45 mL, 14 mmol), acetic acid (0.14 mL, 2.8 mmol), and ethanol (9.2 mL). The reaction was heated at 90 °C for 4 days. The crude product was purified using flash column chromatography (80:20, hexanes:EtOAc), affording **357** as a colorless liquid (0.421 g, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 7.2 Hz, 1H), 7.45 (p, J = 7.5 Hz, 2H), 7.37 (d, J = 8.3 Hz, 2H), 7.15 (m, 3H), 6.88 – 6.73 (m, 4H) 5.21 (s, 2H), 4.50 – 4.27 (m, 4H), 3.79 (s, 3H), 3.78 (s, 3H) ;^{13}C NMR (151 MHz, $CDCl_3$) δ 159.8, 159.1, 148.5, 137.2, 132.4, 130.8, 130.2, 129.4, 129.2, 129.2, 128.8, 128.7, 127.3, 113.7, 113.6, 72.6, 69.7, 55.3, 55.2; AMM (ESI) *m/z* calcd for $C_{23}H_{25}N_2O_3^+$ $[M+H]^+$ 377.1860, found 377.1855.

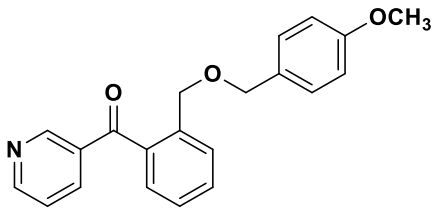


(3*S*,4*R*)-3,4-bis(4-methoxyphenyl)isochromane (299) was synthesized according to General Procedure R using **357** (0.025 g, 0.066 mmol), MnO_2 (0.046 g, 0.53 mmol), and Rh_2(*R*-PTAD)$_4$ (0.001 g, 0.0007 mmol) in CH_2Cl_2 (4.5 mL). The crude product was purified by flash column chromatography

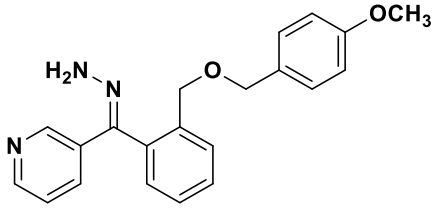
(83:17, hexanes:EtOAc), affording **299** as white crystals (0.023 g, 98%, >95:5 dr, 99:1 er). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.27 – 7.21 (m, 1H), 7.19 – 7.13 (m, 2H), 7.04 (d, *J* = 7.5 Hz, 1H), 6.85 (d, *J* = 8.3 Hz, 2H), 6.70 (d, *J* = 8.3 Hz, 2H), 6.67 (d, *J* = 8.3 Hz, 2H), 6.59 (d, *J* = 8.3 Hz, 2H), 5.21 (d, *J* = 15.3 Hz, 1H), 5.10 (d, *J* = 15.2 Hz, 1H), 5.01 (d, *J* = 3.3 Hz, 1H), 4.03 (d, *J* = 3.2 Hz, 1H), 3.75 (s, 3H), 3.70 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.4, 157.8, 137.6, 134.2, 133.1, 132.6, 131.0, 130.2, 127.2, 126.8, 126.5, 124.0, 113.0, 112.7, 79.8, 69.1, 55.2, 55.1, 49.5; m.p. 159-160 °C ; AMM (ESI) *m/z* calcd for $[M+Na]^+$ $C_{23}H_{22}NaO_3^+$ 369.1467, found 369.1464; $[\alpha]_D^{22} = -352$ (c = 0.12, $CHCl_3$).



_N_-methoxy-_N_-methyl-3-nicotinamide (358) was synthesized by preparing a suspension of *N*-methoxy-*N*-methylamine•HCl (1.317 g, 13.50 mmol, 1.2 equiv.) in CH_2Cl_2 (45.0 mL), following a modified literature procedure.[180] This suspension was cooled to 0 °C and triethylamine (6.25 mL, 44.8 mmol, 3.9 equiv) was added slowly over 20 minutes, the resulting solution was cooled to 0 °C. To the solution was added nicotinoyl chloride•HCl (2.032 g, 11.41 mmol, 1.0 equiv) and the mixture was allowed to warm to rt and stirred for 23 h, The reaction mixture was quenched with sat. aq. $NaHCO_3$ (10 mL), and the organic layer was separated. The aqueous layer was then neutralized with 1 M HCl and extracted with CH_2Cl_2 (3 X 50 mL); the combined organic layers were washed with brine (2 X 100 mL) and dried over Na_2SO_4. The resulting solution was concentrated *in vacuo* and the crude product was purified using flash column chromatography (95:5, CH_2Cl_2:CH_3OH), affording **358** as a yellow oil (1.511 g, 80%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.96 (s, 1H), 8.69 (d, *J* = 4.7 Hz, 1H), 8.03 (d, *J* = 7.8 Hz, 1H), 7.37 (dd, *J* = 7.8, 4.9 Hz, 1H), 3.56 (s, 3H), 3.40 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 167.4, 151.4, 149.3, 136.1, 129.8, 123.0, 61.3, 33.1. ^{1}H NMR and ^{13}C NMR data were consistent with literature values.[180]

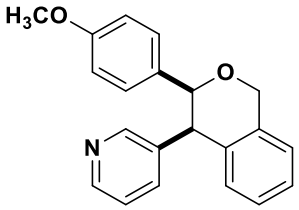


(2-(((4-methoxybenzyl)oxy)methyl)phenyl)(pyridin-3-yl)methanone (359) was synthesized according to General Procedure J, using **351** (1.008 g, 3.282 mmol) in THF (12.2 mL), 2.13 M *n*-butyllithium in hexanes (2.0 mL, 4.3 mmol), and **358** (0.649 g, 3.91 mmol) in THF (4.9 mL), reacting for 16 h. The crude product was purified using flash column chromatography (60:40, Et_2O:hexanes), affording **359** as a white oil (0.974 g, 89%). ^1H NMR (600 MHz, $CDCl_3$) δ 8.94 (s, 1H), 8.77 (d, J = 4.7 Hz, 1H), 8.07 (d, J = 7.9 Hz, 1H), 7.57 (d, J = 7.6 Hz, 1H), 7.52 (t, J = 7.2 Hz, 1H), 7.42 – 7.33 (m, 3H), 7.08 (d, J = 8.4 Hz, 2H), 6.77 (d, J = 8.4 Hz, 2H), 4.64 (s, 2H), 4.33 (s, 2H), 3.77 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 196.6, 159.2, 153.3, 151.5, 138.5, 137.2, 137.0, 133.2, 131.1, 129.9, 129.5, 129.0, 128.9, 127.4, 123.4, 113.8, 72.7, 69.8, 55.4; AMM (ESI) *m/z* calcd for $C_{21}H_{20}NO_3^+$ $[M+H]^+$ 334.1438, found 334.1443.

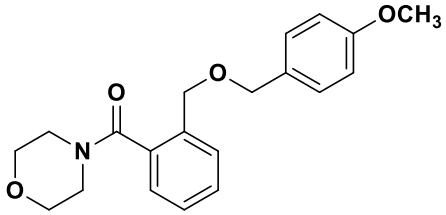


((2-(((4-methoxybenzyl)oxy)methyl)phenyl)(pyridin-3-yl)methylene)hydrazine (360) was synthesized according to General Procedure O, using **359** (0.321 g, 0.963 mmol) in anhydrous EtOH (9.6 mL), hydrazine (0.17 mL, 5.4 mmol), and glacial acetic acid (0.06 mL, 1 mmol), reacting for 4.5 h at 155 °C. The crude product was purified using flash column chromatography (40:60, hexanes:EtOAc), affording **360** as a dense yellow oil (0.204 g, 61%). ^1H NMR (600 MHz, $CDCl_3$) δ 8.63 (s, 1H), 8.49 (d, J = 4.7 Hz, 1H), 7.74 (d, J = 8.1 Hz, 1H), 7.66 (d, J = 7.5 Hz, 1H), 7.53 – 7.44 (m, 2H), 7.19 (dd, J = 8.0,

4.8 Hz, 1H), 7.17 (d, *J* = 7.2 Hz, 1H), 7.14 (d, *J* = 8.5 Hz, 2H), 6.82 (d, *J* = 8.6 Hz, 2H), 5.48 (s, 2H), 4.40 – 4.35 (m, 2H), 4.35 – 4.29 (m, 2H), 3.79 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 159.3, 149.0, 147.7, 145.5, 137.4, 133.8, 133.0, 131.2, 130.0, 129.8, 129.5, 129.2, 129.0, 123.2, 113.9, 72.8, 69.9, 55.4, 14.3.

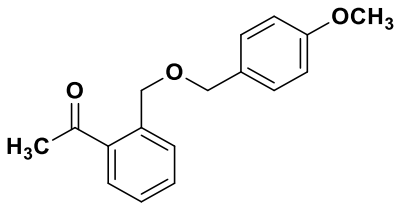


(3*S*,4*S*)-3-(4-methoxy)phenyl-4-(pyridin-3-yl)lisochromane (301) was synthesized according to General Procedure R, using MnO_2 (0.050 g, 0.58 mmol), **360** (0.025 g, 0.072 mmol) in CH_3CN (4.8 mL), reacting for 1 h. Rh_2(*R*-PTAD)$_4$ (0.001 g, 0.8 μmol) was added, reacting for 38 h. The crude product was purified using flash column chromatography (40:60, hexanes:EtOAc), affording **301** as a white solid (0.019 g, >95:5 dr, 94:6 er, 82%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.29 (d, *J* = 4.5 Hz, 1H), 7.95 (s, 1H), 7.30 – 7.25 (m, 1H), 7.21 – 7.16 (m, 2H), 7.13 (d, *J* = 7.7 Hz, 1H), 7.06 – 6.96 (m, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 6.70 (d, *J* = 8.5 Hz, 2H), 5.23 (d, *J* = 15.3 Hz, 1H), 5.12 (d, *J* = 15.3 Hz, 1H), 5.09 (d, *J* = 2.9 Hz, 1H), 4.10 (d, *J* = 2.3 Hz, 1H), 3.73 (s, 3H); ^{13}C NMR (151 MHz, CD_2Cl_2) δ 158.5, 150.7, 147.3, 137.1, 136.7, 136.1, 134.4, 132.1, 129.9, 126.9, 126.9, 126.8, 124.2, 122.4, 113.0, 78.9, 69.0, 55.0, 47.7; AMM (CI-TOF) *m/z* calcd $C_{21}H_{20}NO_2^+$ $[M+H]^+$ 318.1494, found 318.1490; m.p. 181-183 °C; $[\alpha]_D^{20} = -217.1$ (c = 0.57, $CHCl_3$).

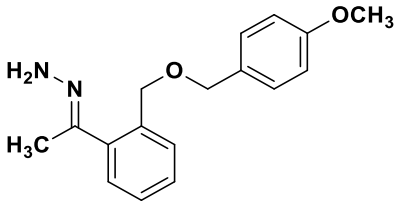


(2-(((4-methoxybenzyl)oxy)methyl)phenyl)(morpholino)methanone (361) was synthesized using General Procedure D using ether **351** (1.000 g, 3.255 mmol), morpholine (0.43 mL, 4.9 mmol),

palladium (II) acetate (0.018 g, 0.081 mmol), Xantphos (0.094 g, 0.16 mmol), potassium phosphate tribasic (2.073 g, 9.765 mmol), CO (1 balloon), in toluene (6.5 mL). The crude product was purified using flash column chromatography (40:60, hexanes:EtOAc) affording **361** as a pale yellow oil (0.800 g, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.6 Hz, 1H), 7.40 – 7.26 (m, 4H), 7.18 (d, *J* = 7.1 Hz, 1H), 6.94 – 6.85 (m, 2H), 4.51 (s, 2H), 3.81 (s, 3H), 3.78 – 3.61 (m, 4H), 3.55 – 3.41 (m, 2H), 3.19 (s, 2H), 1.62 (s, 2H). ^{1}H NMR was taken at rt and shows a mixture of rotamers.

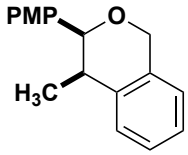


1-(2-(((4-methoxybenzyl)oxy)methyl)phenyl)ethan-1-one (362) was synthesized according to General Procedure E using morpholine amide **361** (0.552 g, 1.62 mmol) and methyllithium (1.52 M in diethyl ether, 1.28 mL, 1.94 mmol) in THF (9.5 mL). The crude product was purified using flash column chromatography (80:20 hexanes: EtOAc) affording **362** as a yellow oil (0.267 g, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 7.9 Hz, 2H), 7.50 (t, *J* = 7.6 Hz, 1H), 7.39 – 7.28 (m, 3H), 6.92 – 6.85 (m, 2H), 4.85 (s, 2H), 4.55 (s, 2H), 3.80 (s, 3H), 2.57 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.7, 159.3, 139.7, 136.6, 132.0, 130.6, 129.5, 129.4, 128.1, 127.0, 113.9, 72.8, 70.4, 55.4, 29.3; AMM (ESI-TOF) *m/z* calcd for $C_{17}H_{18}NaO_3^+$ $[M+Na]^+$ 293.1157, found 293.1157.

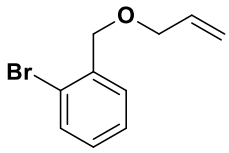


(1-(2-(((4-methoxybenzyl)oxy)methyl)phenyl)ethylidene)hydrazine (363) was synthesized according to General Procedure O using ketone **362** (0.267 g, 0.988 mmol), hydrazine (0.31 mL, 9.8

mmol), acetic acid (0.07 mL, 1 mmol) and ethanol (6.6 mL). The crude product was purified using flash column chromatography (100:0 to 60:40 hexanes:EtOAc) affording **363** as a yellow oil (0.0447 g, 16%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.50 (m, 1H), 7.42 – 7.33 (m, 2H), 7.32 – 7.23 (m, 2H), 7.13 – 7.03 (m, 1H), 6.88 (d, *J*= 8.0 Hz, 2H), 4.88 (s, 2H), 4.50 (s, 2H), 4.42 (s, 2H), 3.80 (s, 3H), 2.14 (s, 3H).

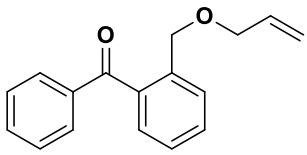


(3*S*,4*R*)-3-(4-methoxyphenyl)-4-methylisochromane (302) was synthesized according to General Procedure R using **363** (0.022 g, 0.077 mmol), MnO_2 (0.054 g, 0.62 mmol), Rh_2(*R*-PTAD)$_4$ (0.001 g, 0.0008 mmol) and CH_2Cl_2 (5 mL). The crude product was purified using flash column chromatography (90:10 to 80:20 hexanes:EtOAc) affording **302** as a clear oil (0.011 g, 56%, >95:5 dr, 60:40 er). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J*= 8.2 Hz, 2H), 7.23 – 7.14 (m, 3H), 7.08 – 7.02 (m, 1H), 6.92 (d, *J*= 8.3 Hz, 2H), 5.05 (d, *J*= 15.1 Hz, 1H), 4.98 (d, *J*= 15.2 Hz, 1H), 4.86 (d, *J*= 2.8 Hz, 1H), 3.82 (s, 3H), 3.03 – 2.91 (m, 1H), 0.97 (d, *J*= 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.6, 140.5, 134.0, 133.3, 129.0, 126.9, 126.6, 126.3, 124.2, 113.7, 78.4, 69.0, 55.4, 38.1, 17.2; AMM (CI-TOF) *m/z* calcd for $C_{17}H_{18}O_2^+$ $[M]^+$ 254.1307, found 253.1304; $[\alpha]_D^{22} = -3.4$ (c = 0.07, $CHCl_3$).

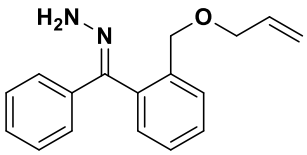


2-((allyloxy)methyl)bromobenzene (364) was synthesized according to General Procedure A, using NaH (1.216 g, 30.31 mmol) in THF (37.9 mL), 2-bromobenzyl bromide (3.003 g, 12.02 mmol) in THF (15.0 mL), and allyl alcohol (1.03 mL, 14.7 mmol), reacting for 47 h at 60 °C. The crude product was purified using flash column chromatography (95:5, hexanes:EtOAc), affording **364** as a clear oil (2.251 g,

82%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.9 Hz, 1H), 7.50 (d, *J* = 7.3 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.14 (t, *J* = 7.6 Hz, 1H), 5.98 (ddt, *J* = 16.3, 10.6, 5.5 Hz, 1H), 5.39 – 5.31 (m, 1H), 5.23 (d, *J* = 10.4 Hz, 1H), 4.58 (s, 2H), 4.11 (d, *J* = 5.5 Hz, 2H).; ^{13}C NMR (151 MHz, $CDCl_3$) δ 137.8, 134.6, 132.6, 129.0, 128.9, 127.5, 122.7, 117.4, 71.8, 71.5; AMM (CI-TOF) *m/z* calcd for $C_{10}H_{11}BrO^+$ $[M]^+$ 225.9993, found 225.9993.

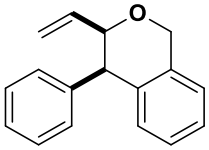


2-((allyloxy)methyl)benzophenone (365) was synthesized according to General Procedure J, using **364** (0.501 g, 2.21 mmol) in THF (8.2 mL), 2.13 M *n*-butyllithium in hexanes (1.34 mL, 2.86 mmol), and **271** (0.436 g, 2.64 mmol) in THF (3.3 mL), were combined and allowed to react for 20 h. The crude product was purified using flash column chromatography (90:10, hexanes:EtOAc), affording **365** as a clear oil (0.482 g, 87%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.3 Hz, 2H), 7.57 (t, *J* = 6.6 Hz, 2H), 7.49 (t, *J* = 7.3 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 2H), 7.38 – 7.33 (m, 2H), 5.74 (ddt, *J* = 16.1, 10.8, 5.4 Hz, 1H), 5.18 – 5.11 (m, 1H), 5.10 – 5.03 (m, 1H), 4.60 (s, 2H), 3.87 (d, *J* = 5.5 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 198.0, 138.2, 137.8, 137.7, 134.4, 133.1, 130.5, 130.2, 128.9, 128.5, 128.4, 127.0, 117.1, 71.7, 69.8; AMM (ESI) *m/z* calcd for $C_{17}H_{17}O_2^+$ $[M+H]^+$ 253.1223, found 252.1226.

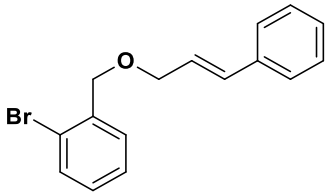


((2-((allyloxy)methyl)phenyl)(phenyl)methylene)hydrazine (366) was synthesized according to General Procedure P in a sealed microwave vial, using ketone **365** (0.251 g, 0.996 mmol) in anhydrous EtOH (10.0 mL), hydrazine (0.19 mL, 6.0 mmol), and glacial acetic acid (0.07 mL, 1 mmol) reacting for

5 d at 90 °C. The crude product was purified using flash column chromatography (80:20, hexanes:EtOAc), affording **366** as a yellow oil (0.132 g, 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J*= 7.4 Hz, 1H), 7.53 – 7.40 (m, 4H), 7.32 – 7.23 (m, 3H), 7.17 (d, *J*= 7.2 Hz, 1H), 5.82 (ddt, *J*= 16.7, 10.6, 5.5 Hz, 1H), 5.36 (s, 2H), 5.19 (d, *J*= 17.3 Hz, 1H), 5.11 (d, *J*= 10.4 Hz, 1H), 4.39 – 4.25 (m, 2H), 3.92 (d, *J*= 5.5 Hz, 2H).

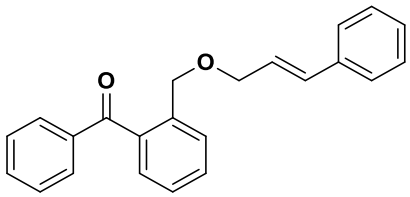


(3*R*,4*R*)-4-phenyl-3-vinylisochromane (308) was synthesized according to General Procedure R, using MnO_2 (0.065 g, 0.75 mmol) and **366** (0.026 g, 0.099 mmol) in CH_3CN (6.6 mL), reacting for 0.25 h. Rh_2(*R*-PTAD)$_4$ (0.002 g, 1 μmol) was added, reacting for 3 h. The crude product was purified using flash column chromatography (90:10, hexanes:EtOAc), affording **366** as a white crystalline solid (0.017 g, >95:5 dr, 97:3 er, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.16 (m, 4H), 7.16 – 7.07 (m, 4H), 7.02 (d, *J*= 7.5 Hz, 1H), 5.57 – 5.44 (m, 1H), 5.24 (d, *J*= 17.3 Hz, 1H), 5.13 – 5.03 (m, 2H), 4.99 (d, *J*= 15.2 Hz, 1H), 4.50 – 4.40 (m, 1H), 3.96 – 3.89 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.7, 137.1, 137.0, 134.1, 130.3, 130.1, 128.0, 127.0, 126.6, 126.5, 124.2, 116.4, 79.3, 68.5, 48.7; AMM (CI-TOF) *m/z* calcd for $C_{17}H_{20}NO^+$ $[M+NH_4]^+$ 254.1545, found 254.1554; m.p. 83-86 °C; $[\alpha]_D^{22} = -207.6$ (c = 0.26, $CHCl_3$).

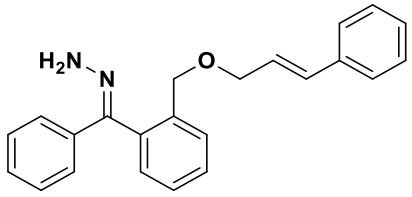


2-((cinnamyloxy)methyl)bromobenzene (367) was synthesized according to General Procedure A, using NaH (0.961 g, 24.0 mmol) in THF (30 mL), 2-bromobenzyl bromide (2.011 g, 8.047 mmol) in

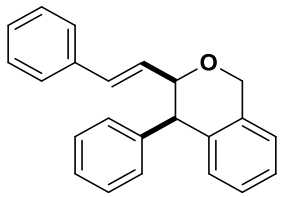
THF (10.1 mL), *trans*-cinnamyl alcohol (1.623 g, 12.09 mmol), reacting for 20 h. The crude product was purified using flash column chromatography (95:5, hexanes:EtOAc), affording **367** as a clear oil (1.793 g, 74%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57 – 7.50 (m, 2H), 7.41 (d, J = 7.4 Hz, 2H), 7.32 (t, J = 7.6 Hz, 3H), 7.25 (t, J = 7.3 Hz, 1H), 7.15 (t, J = 8.2 Hz, 1H), 6.67 (d, J = 15.9 Hz, 1H), 6.36 (dt, J = 15.9, 6.0 Hz, 1H), 4.64 (s, 2H), 4.28 (d, J = 6.0 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.8, 136.8, 132.8, 132.7, 129.3, 129.1, 128.7, 127.9, 127.6, 126.7, 126.0, 122.9, 71.6, 71.5; AMM (CI-TOF) *m/z* calcd for $C_{16}H_{15}BrO^+$ $[M]^+$ 302.0306, found 302.0291.



2-((cinnamyloxy)methyl)benzophenone (368) was synthesized according to General Procedure J, using **367** (1.005 g, 3.30 mmol) in THF (12.2 mL), 2.13 M *n*-butyllithium in hexanes (2.01 mL, 4.29 mmol), and **271** (0.654 g, 3.96 mmol) in THF (5.0 mL), reacting for 36 h. The crude product was purified using flash column chromatography (80:20, hexanes:EtOAc), affording **368** as a yellow oil (0.530 g, 49%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 7.7 Hz, 2H), 7.57 (t, J = 7.7 Hz, 2H), 7.53 – 7.46 (m, 1H), 7.43 (t, J = 7.5 Hz, 2H), 7.40 – 7.31 (m, 2H), 7.32 – 7.17 (m, 5H), 6.44 (d, J = 15.9 Hz, 1H), 6.08 (dt, J = 15.8, 5.9 Hz, 1H), 4.65 (s, 2H), 4.03 (d, J = 5.9 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 198.1, 138.1, 138.0, 137.7, 136.8, 133.2, 132.4, 130.5, 130.2, 128.8, 128.7, 128.6, 128.5, 127.7, 127.2, 126.6, 125.7, 71.4, 70.0; AMM (ESI) *m/z* calcd for $C_{23}H_{21}O_2^+$ $[M+H]^+$ 329.1536, found 329.1533. NOTE: compound was found to degrade over several days and should be used immediately.

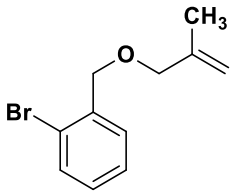


((2-((cinnamyloxy)methyl)phenyl)(phenyl)methylene)hydrazine (369) was synthesized according to General Procedure P using a sealed microwave vial, using **368** (0.309 g, 0.939 mmol) in anhydrous EtOH (9.4 mL), hydrazine (0.19 mL, 6.0 mmol), and glacial acetic acid (0.07 mL, 1 mmol), reacting for 3d at 100 °C. The crude product was purified using flash column chromatography (80:20, hexanes:EtOAc), affording **369** as a yellow amorphous solid (0.224 g, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 7.3 Hz, 1H), 7.56 – 7.39 (m, 4H), 7.34 – 7.22 (m, 8H), 7.18 (d, *J* = 7.2 Hz, 1H), 6.50 (d, *J* = 16.0 Hz, 1H), 6.16 (dt, *J* = 15.8, 6.0 Hz, 1H), 5.37 (s, 2H), 4.46 – 4.27 (m, 2H), 4.07 (d, *J* = 5.9 Hz, 2H); AMM (ESI) *m/z* calcd for $C_{24}H_{25}N_2O^+$ $[M+H]^+$ 343.1805, found 343.1814.

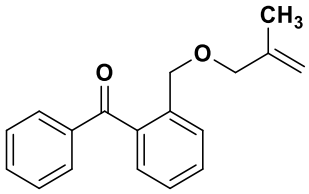


(3*R*,4*R*)-4-phenyl-3-((*E*)-styryl)isochromane (310) was synthesized according to General Procedure R, using MnO_2 (0.051 g, 0.58 mmol) and **369** (0.022 g, 0.065 mmol) in CH_3CN (4.3 mL), reacting for 3 h. Rh_2(*R*-PTAD)$_4$ (0.001 g, 0.7 μmol) was added, reacting for 14 h. The crude product was purified using flash column chromatography (90:10, hexanes:EtOAc), affording **310** as a white crystalline solid (0.019 g, >95:5 dr, 98:2 er, 95%). **310** was crystallized out of hexanes:*i*-PrOH (90:10) with a small amount of CH_2Cl_2 to dissolve fully followed by slow evaporation over 24 h. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.16 (m, 9H), 7.16 – 7.10 (m, 4H), 7.04 (d, *J* = 7.5 Hz, 1H), 6.57 (d, *J* = 16.0 Hz, 1H), 5.81 (dd, *J* = 15.9, 6.9 Hz, 1H), 5.13 (d, *J* = 15.2 Hz, 1H), 5.04 (d, *J* = 15.2 Hz, 1H), 4.61 (dd, *J* = 6.4, 2.9 Hz, 1H), 4.02 (d, *J*

= 2.6 Hz, 1H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.6, 137.0, 137.0, 134.2, 131.6, 130.3, 130.1, 128.6, 128.6, 128.0, 127.7, 127.0, 126.7, 126.7, 126.6, 124.2, 79.1, 68.6, 49.2; AMM (CI-TOF) *m/z* calcd for $C_{23}H_{20}O^+$ $[M]^+$ 312.1514, found 312.1526; m.p. 106-107 °C; $[\alpha]_D^{21} = -431.0$ (c = 0.22, $CHCl_3$).

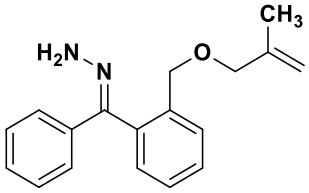


2-(((2-methylallyl)oxy)methyl)bromobenzene (370) was synthesized according to General Procedure A, using NaH (0.960 g, 24.0 mmol) in THF (30 mL), 2-bromobenzyl bromide (2.008 g, 8.033 mmol) in THF (10.0 mL), and 2-methallyl alcohol (1.01 mL, 12.0 mmol), reacting for 48 h at 60 °C. The crude product was purified using flash column chromatography (80:20, hexanes:CH_2Cl_2), affording **370** as a clear oil (1.438 g, 75%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.0 Hz, 1H), 7.51 (d, *J* = 7.8 Hz, 1H), 7.32 (t, *J* = 7.5 Hz, 1H), 7.14 (t, *J* = 7.6 Hz, 1H), 5.04 (s, 1H), 4.95 (s, 1H), 4.56 (s, 2H), 4.02 (s, 2H), 1.79 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 142.2, 138.0, 132.6, 129.1, 128.9, 127.5, 122.7, 112.6, 74.8, 71.3, 19.7; AMM (CI-TOF) *m/z* calcd for $C_{11}H_{14}BrO^+$ $[M+H]^+$ 241.0228, found 241.0224.

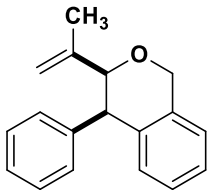


2-(((2-methylallyl)oxy)methyl)benzophenone (371) was synthesized according to General Procedure J, using **370** (1.913 g, 4.200 mmol) in THF (15.6 mL), 2.13 M *n*-butyllithium in hexanes (2.53 mL, 5.33 mmol), and **271** (0.822 g, 4.98 mmol) in THF (6.2 mL) were combined and allowed to react for 18 h. The crude product was purified using flash column chromatography (95:5, hexanes:EtOAc), affording **371** as a clear oil (0.844 g, 75%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.5 Hz, 2H), 7.61

– 7.54 (m, 2H), 7.49 (t, J = 7.9 Hz, 1H), 7.45 (t, J = 7.7 Hz, 2H), 7.39 – 7.32 (m, 2H), 4.84 (s, 1H), 4.80 (s, 1H), 4.59 (s, 2H), 3.79 (s, 2H), 1.61 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 198.0, 142.0, 138.3, 137.8, 137.7, 133.1, 130.6, 130.2, 128.9, 128.5, 128.4, 127.0, 112.3, 74.8, 69.7, 19.5; AMM (ESI) *m/z* calcd for $C_{18}H_{19}O_2^+$ $[M+H]^+$ 267.1380, found 267.1380.

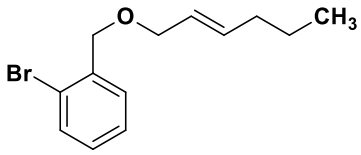


((2-(((2-methallyl)oxy)methyl)phenyl)(phenyl)methylene)hydrazine (372) was synthesized according to General Procedure P in a sealed microwave vial, using **371** (0.308 g, 1.16 mmol) in anhydrous EtOH (11.6 mL), hydrazine (0.21 mL, 6.8 mmol), and glacial acetic acid (0.08 mL, 1 mmol), reacting for 3.5 d at 100 °C. The crude product was purified using flash column chromatography (80:20, hexanes:EtOAc), affording **372** as a yellow oil (0.251 g, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 7.4 Hz, 1H), 7.53 – 7.40 (m, 4H), 7.32 – 7.23 (m, 3H), 7.16 (d, J = 7.2 Hz, 1H), 5.36 (s, 2H), 4.89 (s, 1H), 4.83 (s, 1H), 4.32 (d, J = 12.2 Hz, 1H), 4.26 (d, J = 12.2 Hz, 1H), 3.83 (s, 2H), 1.67 (s, 3H); AMM (ESI) *m/z* calcd for $C_{18}H_{21}N_2O^+$ $[M+H]^+$ 281.1648, found 281.1646.

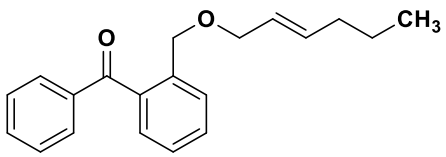


(3*S*,4*R*)-4-phenyl-3-((1-methyl)vinyl)isochromane (309) was synthesized according to General Procedure R, using MnO_2 (0.064 g, 0.71 mmol) and **372** (0.022 g, 0.078 mmol) in CH_3CN (5.2 mL), reacting for 1.5 h. Rh_2(*R*-PTAD)$_4$ (0.001 g, 0.9 μmol) was added, reacting for 16 h. The crude product was purified using flash column chromatography (90:10, hexanes:EtOAc), affording **309** as a white solid

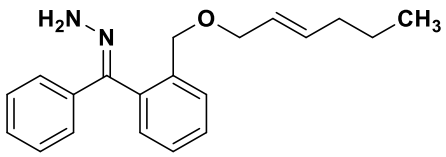
(0.018 g, >95:5 dr, 95:5 er, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 – 7.13 (m, 6H), 7.13 – 7.07 (m, 2H), 7.03 (d, *J* = 7.5 Hz, 1H), 5.13 (d, *J* = 15.2 Hz, 1H), 4.98 (d, *J* = 15.2 Hz, 1H), 4.81 (s, 1H), 4.72 (s, 1H), 4.39 (s, 1H), 4.06 – 3.97 (m, 1H), 1.55 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.3, 141.9, 137.4, 134.1, 130.4, 129.8, 127.8, 126.9, 126.6, 126.5, 124.2, 111.4, 80.8, 68.9, 47.5, 19.7; AMM (CI-TOF) *m/z* calcd for $C_{18}H_{22}NO^+$ $[M+NH_4]^+$ 268.1701, found 268.1702; m.p. 88-90 °C; $[\alpha]_D^{22} = -225.1$ (c = 0.46, $CHCl_3$).



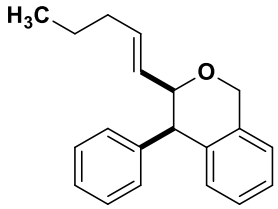
2-((*E*-hex-2-en-1-yloxy)methyl)bromobenzene (373) was synthesized according to General Procedure A, using NaH (1.616 g, 40.40 mmol) in THF (50.5 mL), 2-bromobenzyl bromide (2.017 g, 8.071 mmol) in THF (10.1 mL), and *E*-hexen-1-ol (1.42 mL, 12.0 mmol), reacting for 20 h at rt. The crude product was purified using flash column chromatography (90:10, hexanes:EtOAc), affording **373** as a yellow oil (2.057 g, 95%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.0 Hz, 1H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.14 (t, *J* = 7.7 Hz, 1H), 5.75 (dt, *J* = 14.5, 6.7 Hz, 1H), 5.66 – 5.59 (m, 1H), 4.56 (s, 2H), 4.05 (d, *J* = 6.2 Hz, 2H), 2.05 (app. q, *J* = 14.6, 7.2 Hz, 2H), 1.43 (sextet, *J* = 7.4 Hz, 2H), 0.92 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 138.0, 135.2, 132.6, 129.2, 128.9, 127.5, 126.3, 122.8, 71.7, 71.2, 34.6, 22.4, 13.9; AMM (CI-TOF) *m/z* calcd for $C_{13}H_{17}BrO^+$ $[M]^+$ 268.0463, found 268.0468.



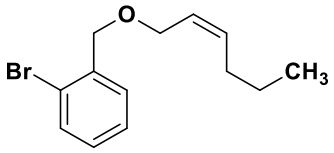
2-((*E*-hex-2-en-1-yloxy)methyl)benzophenone (374) was synthesized according to General Procedure J, using **273** (1.002 g, 3.723 mmol) in THF (13.8 mL), 2.13 M *n*-butyllithium in hexanes (2.27 mL, 4.83 mmol), and **271** (0.736 g, 4.46 mmol) in THF (5.6 mL), reacting for 18 h. The crude product was purified using flash column chromatography (95:5, hexanes:EtOAc), affording **374** as a clear oil (0.756 g, 71%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.6 Hz, 2H), 7.60 – 7.54 (m, 2H), 7.51 – 7.42 (m, 3H), 7.38 – 7.32 (m, 2H), 5.54 (dt, *J* = 14.1, 6.7 Hz, 1H), 5.36 (dt, *J* = 14.6, 6.2 Hz, 1H), 4.56 (s, 2H), 3.81 (d, *J* = 6.2 Hz, 2H), 1.92 (app. q, *J* = 14.2, 7.1 Hz, 2H), 1.31 (sextet, *J* = 7.4 Hz, 2H), 0.84 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 198.1, 138.3, 138.0, 137.8, 134.8, 133.1, 130.5, 130.2, 128.8, 128.6, 128.5, 127.0, 126.0, 71.5, 69.5, 34.5, 22.3, 13.8; AMM (ESI) *m/z* calcd for $C_{20}H_{23}O_2^+$ $[M+H]^+$ 295.1693, found 295.1694.



((2-((*E*-hex-2-en-1-yloxy)methyl)phenyl)(phenyl)methylene)hydrazine (375) was synthesized according to General Procedure O, using **374** (0.301 g, 1.02 mmol) in anhydrous EtOH (10.2 mL), hydrazine (0.20 mL, 6.1 mmol), and glacial acetic acid (0.07 mL, 1 mmol) reacting for 5 h at 160 °C. The crude product was purified using flash column chromatography (80 hexanes :20 EtOAc), affording **375** as a white solid (0.244 g, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.2 Hz, 1H), 7.51 – 7.40 (m, 4H), 7.29 – 7.25 (m, 3H), 7.16 (dd, *J* = 7.3, 1.4 Hz, 1H), 5.65 – 5.54 (m, 1H), 5.49 – 5.40 (m, 1H), 5.36 (s, 2H), 4.35 – 4.21 (m, 2H), 3.86 (d, *J* = 6.1 Hz, 2H), 1.95 (app. q, *J* = 7.5, 7.2 Hz, 2H), 1.34 (sextet, *J* = 7.3 Hz, 2H), 0.86 (t, *J* = 7.4 Hz, 3H).

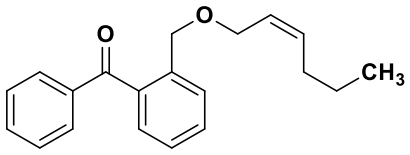


(3*R*,4*R*)-3-(*E*-pent-1-en-1-yl)-4-phenylisochromane (311) was synthesized according to General Procedure R, using MnO_2 (0.059 g, 0.68 mmol) and **375** (0.020 g, 0.069 mmol) in CH_3CN (4.6 mL), reacting for 1.5 h. Rh_2(*R*-PTAD)$_4$ (0.001 g, 0.8 μmol) was added, reacting for 16 h. The crude product was purified using flash column chromatography (90:10, hexanes:EtOAc), affording **311** as a clear oil (0.019 g, >95:5 dr, 97:3 er, 97%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.24 – 7.20 (m, 2H), 7.20 – 7.14 (m, 2H), 7.14 – 7.07 (m, 4H), 7.01 (d, *J* = 7.6 Hz, 1H), 5.68 (dt, *J* = 14.4, 6.8 Hz, 1H), 5.11 – 5.04 (m, 2H), 4.98 (d, *J* = 15.2 Hz, 1H), 4.40 (dd, *J* = 7.1, 3.2 Hz, 1H), 3.89 (d, *J* = 2.7 Hz, 1H), 1.91 (app. q, *J* = 14.2, 7.1 Hz, 2H), 1.29 (sextet, *J* = 14.6, 7.6 Hz, 2H), 0.80 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 141.9, 137.3, 134.2, 133.6, 130.3, 130.2, 128.9, 127.9, 126.9, 126.5, 126.4, 124.1, 79.2, 68.5, 49.1, 34.5, 22.3, 13.8; AMM (CI-TOF) *m/z* calcd for $C_{20}H_{26}NO^+$ $[M+NH_4]^+$ 296.2014, found 296.2002; $[\alpha]_D^{23} = -88.3$ (c = 0.52, $CHCl_3$).

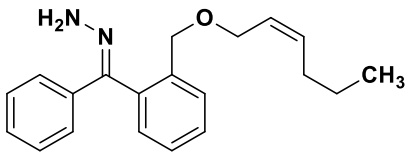


2-((*Z*-hex-2-en-1-yloxy)methyl)bromobenzene (376) was synthesized according to General Procedure A, using NaH (1.611 g, 40.28 mmol) in THF (50.4), 2-bromobenzyl bromide (2.009 g, 8.036 mmol) in THF (10.0 mL), and *Z*-hexen-1-ol (1.42 mL, 12.0 mmol), reacting for 27 h at room temperature. The crude product was purified using flash column chromatography (95:5, hexanes:EtOAc), affording **376** as a clear oil (1.826g, 84%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.0 Hz, 1H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.14 (t, *J* = 7.6 Hz, 1H), 5.68 – 5.58 (m,

2H), 4.57 (s, 2H), 4.16 (d, *J* = 4.9 Hz, 2H), 2.06 (m, 2H), 1.41 (sextet, *J* = 7.3 Hz, 2H), 0.91 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 138.0, 134.1, 132.6, 129.2, 128.9, 127.5, 126.0, 122.8, 71.5, 66.5, 29.8, 22.8, 13.9; AMM (CI-TOF) *m/z* calcd for $C_{13}H_{17}BrO^+$ $[M]^+$ 268.0463, found 268.0475.

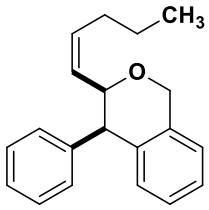


2-((*Z*-hex-2-en-1-yloxy)methyl)benzophenone (377) was synthesized according to General Procedure J, using **376** (1.002 g, 3.721 mmol) in THF (13.8 mL), 2.13 M *n*-butyllithium in hexanes (2.3 mL, 3.0 mmol), and **271** (0.737 g, 4.46 mmol) in THF (5.6 mL), reacting for 21 h. The crude product was purified using flash column chromatography (95:5, hexanes:EtOAc), affording **377** as a clear oil (0.826 g, 75%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.9 Hz, 2H), 7.60 – 7.54 (m, 2H), 7.48 (t, *J* = 7.2 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.38 – 7.32 (m, 2H), 5.52 – 5.45 (m, 1H), 5.41 – 5.35 (m, 1H), 4.58 (s, 2H), 3.93 (d, *J* = 6.5 Hz, 2H), 1.93 (app. q, *J* = 14.7, 7.3 Hz, 2H), 1.31 (sextet, *J* = 7.3 Hz, 2H), 0.85 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 198.0, 138.3, 137.9, 137.8, 133.6, 133.1, 130.5, 130.2, 128.9, 128.6, 128.5, 127.0, 125.9, 69.8, 66.5, 29.7, 22.8, 13.8; AMM (ESI-TOF) *m/z* calcd for $C_{20}H_{23}O_2^+$ $[M+H]^+$ 295.1693, found 295.1689.

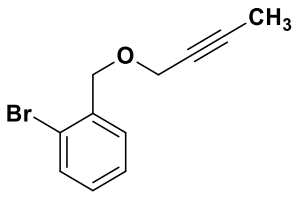


((2-((*Z*-hex-2-en-1-yloxy)methyl)phenyl)(phenyl)methylene)hydrazine (378) was synthesized according to General Procedure O, using **377** (0.302 g, 1.03 mmol) in anhydrous EtOH (10.3 mL), hydrazine (0.22 mL, 7.0 mmol), and glacial acetic acid (0.08 mL, 1 mmol) reacting for 5.5h at 150 °C. The crude product was purified using flash column chromatography (80:20, hexanes:EtOAc), affording

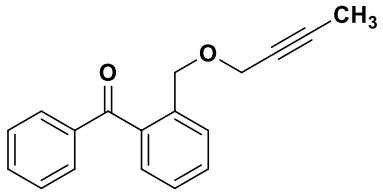
378 as a clear oil (0.245 g, 77%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.6 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 1H), 7.46 – 7.38 (m, 3H), 7.31 – 7.22 (m, 3H), 7.15 (d, *J* = 7.3 Hz, 1H), 5.55 – 5.41 (m, 2H), 5.36 (s, 2H), 4.36 – 4.22 (m, 2H), 4.01 – 3.90 (m, 2H), 1.93 (app. q, *J* = 14.5, 7.3 Hz, 2H), 1.32 (sextet, *J* = 7.4 Hz, 2H), 0.84 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 148.3, 137.9, 137.4, 133.5, 131.9, 129.3, 129.0, 128.7, 128.6, 128.2, 128.1, 125.9, 125.9, 69.7, 66.5, 29.5, 22.6, 13.7.



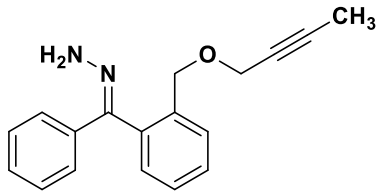
(3*R*,4*R*)-3-(*Z*-pent-1-en-1-yl)-4-phenylisochromane (312) was synthesized according to General Procedure R, using MnO_2 (0.056 g, 0.65 mmol), **378** (0.021 g, 0.068 mmol) in CH_3CN (4.5 mL), reacting for 0.5 h. Rh_2(*R*-PTAD)$_4$ (0.001 g, 0.8 μmol) was added, reacting for 2.5 h. The crude product was purified using flash column chromatography (90:10, hexanes:EtOAc), affording **312** as a clear oil (0.017 g, >95:5 dr, 95:5 er, 92%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.25 – 7.16 (m, 4H), 7.16 – 7.08 (m, 4H), 7.02 (d, *J* = 7.6 Hz, 1H), 5.53 – 5.41 (m, 1H), 5.07 (d, *J* = 15.2 Hz, 1H), 5.01 (d, *J* = 15.2 Hz, 1H), 4.96 (dd, *J* = 9.6, 8.6 Hz, 1H), 4.76 (dd, *J* = 8.3, 3.0 Hz, 1H), 3.85 (d, *J* = 2.7 Hz, 1H), 2.16 – 2.06 (m, 2H), 1.44 (sextet, *J* = 7.1 Hz, 2H), 0.94 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 141.8, 137.3, 134.2, 132.4, 130.3, 130.2, 128.7, 127.9, 126.9, 126.6, 126.5, 124.2, 74.3, 68.4, 48.4, 30.4, 22.9, 14.0; AMM (CI-TOF) *m/z* calcd for $C_{20}H_{26}NO^+$ $[M+NH_4]^+$ 296.2014, found 296.2024; $[\alpha]_D^{22} = -146.2$ (c = 0.45, $CHCl_3$).



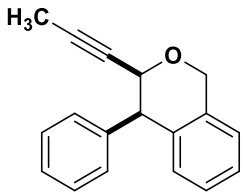
2-((but-2-yn-1-yloxy)methyl)bromobenzene (379) was synthesized according to General Procedure A, using NaH (1.216 g, 30.40 mmol) in THF (38.0 mL), 2-bromobenzyl bromide (3.001 g, 12.01 mmol) in THF (15.0 mL), and but-2-yn-1-ol (1.14 mL, 15.2 mmol), reacting for 15 h at 65 °C. The crude product was purified using flash column chromatography (95:5, hexanes:EtOAc), affording **379** as a clear oil (2.473 g, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.9 Hz, 1H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.14 (t, *J* = 7.6 Hz, 1H), 4.65 (s, 2H), 4.22 (s, 2H), 1.88 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 137.3, 132.6, 129.4, 129.1, 127.5, 123.0, 83.1, 75.0, 71.0, 58.6, 3.8; AMM (CI-TOF) *m/z* calcd for $C_{11}H_{15}BrNO^+$ $[M+NH_4]^+$ 256.0332, found 256.0327.



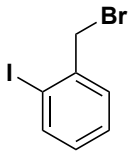
2-((but-2-yn-1-yloxy)methyl)benzophenone (380) was synthesized according to General Procedure J, using **379** (0.202 g, 0.846 mmol) in THF (3.1 mL), 2.13 M *n*-butyllithium in hexanes (0.51 mL, 1.1 mmol), and **271** (0.166 g, 1.01 mmol) in THF (1.3 mL), reacting for 21 h. The crude product was purified using flash column chromatography (90:10, hexanes:EtOAc), affording **380** as a clear oil (0.132 g, 59%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.9 Hz, 2H), 7.63 – 7.54 (m, 2H), 7.54 – 7.42 (m, 3H), 7.39 – 7.31 (m, 2H), 4.67 (s, 2H), 4.00 (s, 2H), 1.76 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.0, 138.0, 137.8, 137.8, 133.1, 130.7, 130.3, 129.0, 128.8, 128.5, 127.1, 82.9, 74.9, 69.1, 58.4, 3.7; AMM (ESI) *m/z* calcd for $C_{18}H_{17}O_2^+$ $[M+H]^+$ 265.1223, found 265.1235.



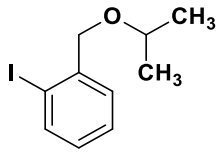
((2-((but-2-yn-1-yloxy)methyl)phenyl)(phenyl)methylene)hydrazine (381) was synthesized according to General Procedure P, using **380** (0.132 g, 0.501 mmol) in anhydrous EtOH (5.0 mL), hydrazine (0.10 mL, 3.2 mmol), and glacial acetic acid (0.03 mL, 0.6 mmol) reacting for 3d at 90 °C. The crude product was purified using flash column chromatography (80:20, hexanes:EtOAc), affording **381** as a yellow oil (0.108 g, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 7.3 Hz, 1H), 7.51 – 7.41 (m, 4H), 7.31 – 7.24 (m, 3H), 7.17 (d, J = 7.2 Hz, 1H), 5.37 (s, 2H), 4.44 – 4.30 (m, 2H), 4.04 (s, 2H), 1.76 (s, 3H).



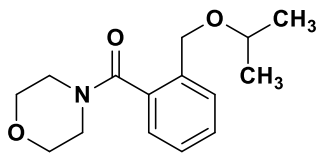
(3*S*,4*R*)-4-phenyl-3-(prop-1-yn-1-yl)isochromane (313) was synthesized according to General Procedure R, using MnO_2 (0.063 g, 0.72 mmol), **381** (0.025 g, 0.090 mmol) in CH_3CN (6.0 mL), reacting for 0.75 h. Rh_2(*R*-PTAD)$_4$ (0.001 g, 0.9 μmol) was added, reacting for 4 h. The crude product was purified using flash column chromatography (90:10, hexanes:EtOAc), affording **313** as a clear oil (0.014 g, >95:5 dr, 92:8 er, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.17 (m, 6H), 7.13 (t, J = 7.4 Hz, 1H), 7.07 (d, J = 7.5 Hz, 1H), 6.99 (d, J = 7.6 Hz, 1H), 5.12 (d, J = 15.2 Hz, 1H), 4.91 (d, J = 15.2 Hz, 1H), 4.77 (br s, 1H), 4.13 (d, J = 3.5 Hz, 1H), 1.70 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.9, 135.8, 134.0, 130.4, 129.9, 127.8, 126.9, 126.9, 126.7, 124.1, 85.2, 75.9, 69.8, 67.4, 48.6, 3.7; AMM (ESI) *m/z* calcd for $C_{18}H_{17}O^+$ $[M+H]^+$ 249.1274, found 249.1275; $[\alpha]_D^{20} = -46.7$ (c = 0.69, $CHCl_3$).



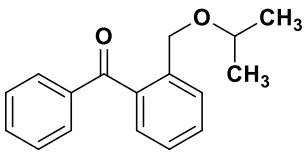
1-(bromomethyl)-2-iodobenzene (382). Following a literature procedure,[181] phosphorus tribromide (0.72 mL, 7.7 mmol) was added to a solution of 2-iodobenzyl alcohol (3.000 g, 12.82 mmol) in THF (64 mL) at 0 °C under argon. The reaction was stirred for one hour at 0 °C and then was concentrated *in vacuo* (NOTE: concentration *in vacuo* should be performed in a fume hood). The crude product was purified using flash column chromatography (85:15, hexanes:EtOAc) affording **382** as white crystals (3.685 g, 97%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.86 (d, J = 8.0 Hz, 1H), 7.48 (d, J = 7.6 Hz, 1H), 7.34 (t, J = 7.5 Hz, 1H), 6.98 (t, J = 7.7 Hz, 1H), 4.60 (s, 2H). ^{1}H NMR data matched literature values.[181]



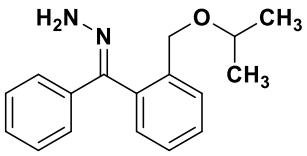
2-((isopropoxy)methyl)iodobenzene (383) was synthesized according to General Procedure A, using NaH (0.410 g, 17.1 mmol) in THF (21.4 mL), **382** (1.005 g, 3.385 mmol) in THF (4.2 mL), and *i*-PrOH (0.64 mL, 11 mmol, previously dried over activated 3 Å molecular sieves for a minimum of 24 h), reacting at 50 °C for 24 h. The crude product was purified using flash column chromatography (50:50, hexanes:CH_2Cl_2), affording **383** as a yellow oil (0.617 g, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 7.9 Hz, 1H), 7.46 (d, J = 7.4 Hz, 1H), 7.34 (t, J = 7.5 Hz, 1H), 6.96 (t, J = 8.2 Hz, 1H), 4.47 (s, 2H), 3.75 (hept, J = 6.1 Hz, 1H), 1.26 (d, J = 6.1 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.3, 139.1, 129.0, 128.8, 128.3, 97.8, 74.2, 71.8, 22.3; AMM (CI-TOF) *m/z* calcd for $C_{10}H_{13}IO^+$ $[M]^+$ 276.0011, found 276.0015.



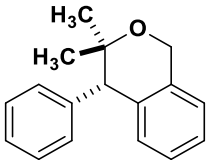
(isopropoxymethyl-phenyl)-morpholin-4-yl-methanone (384) was synthesized according to General Procedure D, using $Pd(OAc)_2$ (0.012 g, 0.052 mmol), Xantphos (0.058 g, 0.10 mmol), and potassium phosphate tribasic (1.271 g, 5.989 mmol), morpholine (0.26 mL, 3.0 mmol), and **383** (0.557 g, 2.00 mmol) in *m*-xylene (4.0 mL), reacting at 100 °C for 6.5 h. The crude product was purified using flash column chromatography (40:60, hexanes:EtOAc), affording **384** as a yellow oil (0.439 g, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.5 Hz, 1H), 7.36 (t, *J* = 7.4 Hz, 1H), 7.30 (t, *J* = 7.4 Hz, 1H), 7.18 (d, *J* = 7.4 Hz, 1H), 4.61 (br s, 1H), 4.42 (s, 1H), 3.97 – 3.64 (m, 5H), 3.59 (s, 2H), 3.26 (s, 2H), 1.21 (d, *J* = 6.1 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9, 136.2, 135.1, 129.4, 129.2, 127.7, 126.0, 71.9, 67.9, 66.8, 47.7, 42.0, 22.2; AMM (ESI) *m/z* calcd for $C_{15}H_{22}NO_3^+$ $[M+H]^+$ 264.1594, found 264.1594 . ^{1}H NMR and ^{13}C NMR were taken at rt and show a mixture of rotamers.



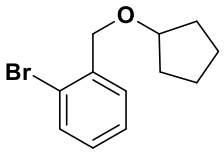
2-(isopropoxymethyl)benzophenone (385) was synthesized according to General Procedure E, using **384** (0.552 g, 2.10 mmol) in THF (21.0 mL), and 1.9 M phenyllithium in dibutyl ether (2.21 mL, 4.20 mmol), reacting for 2 h. The crude product was purified using flash column chromatography (90:10 to 80:20, hexanes:EtOAc), affording **385** as a yellow oil (0.385 g, 72%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.0 Hz, 2H), 7.60 – 7.53 (m, 2H), 7.50 – 7.42 (m, 3H), 7.33 (d, *J* = 3.8 Hz, 2H), 4.58 (s, 2H), 3.50 (hept, *J* = 6.1 Hz, 1H), 1.00 (d, *J* = 6.1 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 198.1, 138.7, 138.1, 137.8, 133.1, 130.4, 130.3, 128.6, 128.6, 128.4, 126.9, 71.9, 67.9, 21.9; AMM (ESI) *m/z* calcd for $C_{17}H_{19}O_2^+$ $[M+H]^+$ 255.1380, found 255.1378.



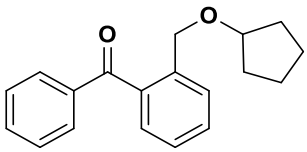
((2-((isopropyloxy)methyl)phenyl)(phenyl)methylene)hydrazine (386) was synthesized according to General Procedure O, using **385** (0.385 g, 1.51 mmol) in anhydrous EtOH (15.1 mL), glacial acetic acid (0.10 mL, 1.8 mmol), and hydrazine (0.62 mL, 20 mmol), reacting at 170 °C for 3h. The crude product was purified using flash column chromatography (80:20, hexanes:EtOAc), affording **386** as a yellow oil (0.308 g, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.4 Hz, 1H), 7.51 – 7.39 (m, 4H), 7.32 – 7.22 (m, 3H), 7.16 (d, *J* = 7.2 Hz, 1H), 5.36 (s, 2H), 4.31 (d, *J* = 11.8 Hz, 1H), 4.26 (d, *J* = 11.8 Hz, 1H), 3.53 (hept, *J* = 6.1 Hz, 1H), 1.09 (d, *J* = 6.1 Hz, 3H), 1.04 (d, *J* = 6.1 Hz, 3H); AMM (ESI) *m/z* calcd for $C_{17}H_{21}N_2O^+$ $[M+H]^+$ 269.1648, found 269.1657; IR (neat): 3400, 2971, 2930, 1126, 1068 cm^{-1}.



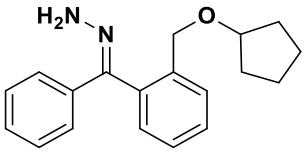
(*S*)-3,3-dimethyl-4-phenylisochromane (303) was synthesized according to General Procedure R, using MnO_2 (0.130 g, 1.49 mmol) and **386** (0.055 g, 0.19 mmol) in CH_3CN (12.7 mL), reacting for 30 min. Rh_2(*S*-PTAD)$_4$ (0.003 g, 2 μmol) was added, reacting for 4 h. The crude product was purified using flash column chromatography (50:50, hexanes:CH_2Cl_2), affording **303** as a white crystalline solid (0.046 g, 96:4 er, 95%). ^{1}H NMR (600 MHz, CD_2Cl_2) δ 7.26 (s, 2H), 7.21 – 7.13 (m, 4H), 7.10 (t, *J* = 7.0 Hz, 2H), 6.95 (d, *J* = 7.8 Hz, 1H), 4.97 (d, *J* = 15.9 Hz, 1H), 4.90 (d, *J* = 15.9 Hz, 1H), 3.74 (s, 1H), 1.32 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (101 MHz, CD_3CN) δ 143.7, 137.0, 133.6, 130.2, 129.6, 127.8, 126.4, 126.2, 126.0, 123.9, 73.0, 62.5, 52.7, 26.3, 24.6; AMM (CI-TOF) *m/z* calcd for $C_{17}H_{22}NO^+$ $[M+NH_4]^+$ 256.1701, found 256.1706; m.p. 105-106 °C; $[\alpha]_D^{22} = 119.2$ (c = 0.29, $CHCl_3$).



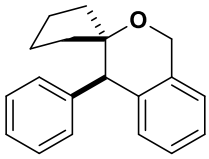
2-((cyclopentyloxy)methyl)bromobenzene (387) was synthesized according to General Procedure A, using NaH (0.960 g, 24.0 mmol) in THF (30.0 mL), 2-bromobenzyl bromide (2.002 g, 8.010 mmol) in THF (10.0 mL), and cyclopentanol (1.09 mL, 12.0 mmol, previously dried over activated 3 Å molecular sieves for a minimum of 24 h), reacting for 53 h. The crude product was purified using flash column chromatography (95:5, hexanes:EtOAc), affording **387** as a yellow oil (1.903 g, 93%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.0 Hz, 1H), 7.49 (d, *J* = 7.5 Hz, 1H), 7.30 (t, *J* = 7.5 Hz, 1H), 7.12 (t, *J* = 7.6 Hz, 1H), 4.52 (s, 2H), 4.09 – 4.02 (m, 1H), 1.81 – 1.68 (m, 6H), 1.61 – 1.50 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 138.5, 132.5, 129.1, 128.7, 127.5, 122.6, 81.7, 70.2, 32.5, 23.8; AMM (CI-TOF) *m/z* calcd for $C_{12}H_{15}BrO^+$ $[M]^+$ 254.0306, found 254.0305.



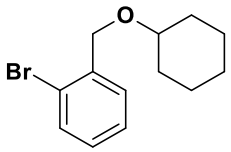
2-(cylopentyloxymethyl)benzophenone (388) was synthesized according to General Procedure J, using **387** (0.376 g, 1.25 mmol) in THF (4.6 mL), 1.68 M *n*-butyllithium in hexanes (0.96 mL, 1.7 mmol), and **271** (0.247 g, 1.50 mmol) in THF (1.9 mL), reacting for 20h. The crude product was purified using flash column chromatography (90:10, hexanes:EtOAc), affording **388** as a clear oil (0.248 g, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.7 Hz, 2H), 7.62 – 7.50 (m, 2H), 7.50 – 7.39 (m, 3H), 7.33 (d, *J* = 4.0 Hz, 2H), 4.53 (s, 2H), 3.85 – 3.75 (m, 1H), 1.63 – 1.30 (m, 8H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 198.1, 138.6, 138.1, 137.7, 133.1, 130.3, 130.2, 128.6, 128.5, 128.4, 126.9, 81.7, 68.5, 32.0, 23.6; AMM (ESI-TOF) *m/z* calcd for $C_{19}H_{21}O_2^+$ $[M+H]^+$ 281.1536, found 281.1552.



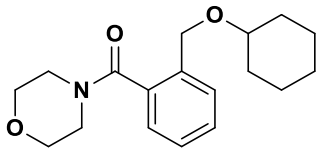
((2-((cyclopropyloxy)methyl)phenyl)(phenyl)methylene)hydrazine (314) was synthesized according to General Procedure O, using **388** (0.303 g, 1.08 mmol) in anhydrous EtOH (10.8 mL), hydrazine (0.20 mL, 6.4 mmol), and glacial acetic acid (0.07 mL, 1 mmol), reacting for 8 hr at 170 °C. The crude product was purified using flash column chromatography (80:20, hexanes:EtOAc), affording **314** as a clear oil (0.318 g, 100%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7.3 Hz, 1H), 7.49 – 7.40 (m, 4H), 7.31 – 7.23 (m, 3H), 7.15 (d, *J* = 8.1 Hz, 1H), 5.36 (s, 2H), 4.24 (q, *J* = 11.9 Hz, 2H), 3.90 – 3.80 (m, 1H), 1.66 – 1.50 (m, 6H), 1.49 – 1.38 (m, 2H).



(4*R*)-spiro[cyclopentane-1,3'-(4-phenyl)isochromane] (304) was synthesized according to General Procedure R, using MnO_2 (0.060 g, 0.69 mmol) and **314** (0.023 g, 0.077 mmol) in CH_3CN (5.1 mL), reacting for 1 h. Rh_2(*R*-PTAD)$_4$ (0.001 g, 0.8 μmol) was added, reacting for 2 h. The crude product was purified using flash column chromatography (80:20, hexanes:EtOAc), affording **304** as a clear oil (0.018 g, 97:3 er, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.12 (m, 6H), 7.08 (t, *J* = 8.2 Hz, 2H), 6.99 (d, *J* = 7.5 Hz, 1H), 4.99 (d, *J* = 16.0 Hz, 1H), 4.91 (d, *J* = 16.0 Hz, 1H), 3.72 (s, 1H), 2.10 – 1.97 (m, 1H), 1.88 – 1.55 (m, 4H), 1.55 – 1.36 (m, 2H), 1.36 – 1.20 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.9, 137.2, 133.6, 130.3, 129.5, 128.1, 126.6, 126.4, 126.3, 124.0, 85.4, 63.1, 52.2, 37.3, 34.4, 23.9, 23.1; Low-resolution MS (Advion ASAP-APCI) *m/z* calcd for $C_{19}H_{21}O^+$ $[M+H]^+$ 265.1587, found 265.0; $[\alpha]_D^{22} = -34.9$ (c = 0.20, $CHCl_3$).

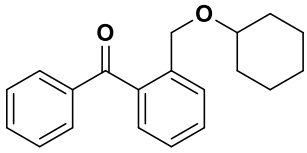


2-((cyclohexyloxy)methyl)bromobenzene (389) was synthesized according to General Procedure A, using NaH (0.480 g, 12.0 mmol) in THF (15.0 mL), **382** (1.034 g, 3.139 mmol) in THF (3.9 mL), and cyclohexanol (0.53 mL, 5.1 mmol, previously dried over activated 3 Å molecular sieves for a minimum of 24 h), reacting at 50 °C for 14 h. The crude product was purified using flash column chromatography (80:20, hexanes:EtOAc), affording **389** as a clear oil (0.832 g, 87%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.55 – 7.49 (m, 2H), 7.30 (t, *J* = 7.5 Hz, 1H), 7.11 (t, *J* = 7.7 Hz, 1H), 4.59 (s, 2H), 3.44 – 3.35 (m, 1H), 2.03 – 1.94 (m, 2H), 1.81 – 1.73 (m, 2H), 1.58 – 1.50 (m, 1H), 1.45 – 1.36 (m, 2H), 1.32 – 1.18 (m, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 138.7, 132.5, 129.0, 128.7, 127.4, 122.6, 77.8, 69.3, 32.4, 26.0, 24.2; AMM (CI-TOF) *m/z* calcd for $C_{13}H_{17}BrO^+$ $[M]^+$ 268.0463, found 268.0463.

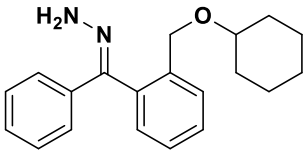


(cyclohexyloxymethyl-phenyl)-morpholin-4-yl-methanone (390) was synthesized according to General Procedure D, using $Pd(OAc)_2$ (0.010 g, 0.043 mmol), Xantphos (0.046 g, 0.080 mmol), and potassium phosphate tribasic (1.015 g, 4.780 mmol), morpholine (0.21 mL, 2.4 mmol), and **389** (0.430 g, 1.60 mmol) in *m*-xylene (3.2 mL), reacting at 100 °C for 17 h. The crude product was purified using flash column chromatography (30:70, hexanes:EtOAc), affording **390** as a clear oil (0.411 g, 47%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.6 Hz, 1H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.30 (t, *J* = 7.5 Hz, 1H), 7.18 (d, *J* = 7.5 Hz, 1H), 4.65 (br s, 1H), 4.46 (br s, 1H), 3.97 – 3.65 (m, 4H), 3.60 (br d, *J* = 14.5 Hz, 2H), 3.42 – 3.33 (m, 1H), 3.27 (br d, *J* = 13.6 Hz, 2H), 1.98 (d, *J* = 9.6 Hz, 2H), 1.81 – 1.71 (m, 2H), 1.60 –

1.52 (m, 1H), 1.37 – 1.15 (m, 5H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.1, 136.4, 135.2, 129.5, 127.7, 126.1, 78.1, 67.7, 66.9, 47.8, 42.1, 32.5, 25.9, 24.3; AMM (ESI) *m/z* calcd for $C_{18}H_{26}NO_3^+$ $[M+H]^+$ 304.1907, found 304.1902; IR (neat): 2930, 2855, 1639, 1428, 1115 cm^{-1}. ^{1}H NMR and ^{13}C NMR were taken at rt and show a mixture of rotamers.

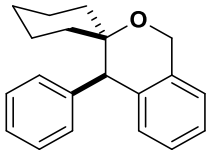


2-(cylohexyloxymethyl)benzophenone (391) was synthesized according to General Procedure E, using **390** (0.427 g, 1.41 mmol) in THF (14.1 mL), and 1.9 M phenyllithium in dibutyl ether (1.48 mL, 2.82 mmol), reacting for 2 h. The crude product was purified using flash column chromatography (90:10, hexanes:EtOAc), affording **391** as a yellow oil (0.339 g, 82%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.84 – 7.78 (m, 2H), 7.60 – 7.54 (m, 2H), 7.49 – 7.42 (m, 3H), 7.33 (d, *J* = 4.4 Hz, 2H), 4.61 (s, 2H), 3.22 – 3.14 (m, 1H), 1.76 – 1.67 (m, 2H), 1.65 – 1.55 (m, 2H), 1.48 – 1.40 (m, 1H), 1.19 – 1.06 (m, 5H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 198.1, 138.9, 138.1, 137.8, 133.1, 130.4, 130.3, 128.6, 128.6, 128.4, 126.8, 77.8, 67.6, 31.9, 25.9, 24.1; AMM (ESI) *m/z* calcd for $C_{20}H_{23}O_2^+$ $[M+H]^+$ 295.1693, found 295.1690; IR (neat): 2932, 2856, 1667, 1449, 1272 cm^{-1}.

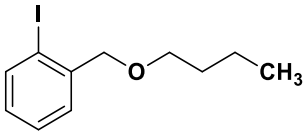


((2-((cyclohexyloxy)methyl)phenyl)(phenyl)methylene)hydrazine (392) was synthesized according to General Procedure O, using **391** (0.306 g, 1.04 mmol) in anhydrous EtOH (10.4 mL), glacial acetic acid (0.07 mL, 1 mmol), and hydrazine (0.19 mL, 6.1 mmol), reacting for 6 h at 170 °C. The crude product was purified using flash column chromatography (80:20, hexanes:EtOAc), affording **392** as a

yellow oil (0.312 g, 97%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.6 Hz, 1H), 7.49 – 7.40 (m, 4H), 7.31 – 7.22 (m, 3H), 7.15 (d, *J* = 7.3 Hz, 1H), 5.37 (s, 2H), 4.38 – 4.26 (m, 2H), 3.23 – 3.14 (m, 1H), 1.85 – 1.78 (m, 1H), 1.78 – 1.73 (m, 1H), 1.70 – 1.61 (m, 2H), 1.48 (s, 1H), 1.27 – 1.11 (m, 5H); AMM (ESI) *m/z* calcd for $C_{20}H_{25}N_2O^+$ $[M+H]^+$ 309.1961, found 309.1957.

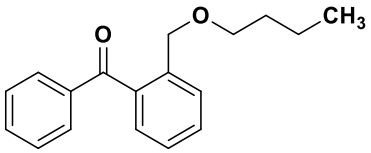


(*R*)-spiro[cyclohexane-1,3'-(4-phenyl)isochromane] (305) was synthesized according to General Procedure S, using MnO_2 (0.056 g, 0.73 mmol) and **392** (0.026 g, 0.08 mmol) in CH_2Cl_2 (5.3 mL), reacting for 2.5 h. Rh_2(*R*-PTAD)$_4$ (0.001 g, 1 μmol) was added, reacting for 1.5 h. The crude product was purified using flash column chromatography (90:10, hexanes:EtOAc), affording **305** as a white solid (0.019 g, 95:5 er, 80%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.26 – 7.20 (m, 2H), 7.19 – 7.10 (m, 4H), 7.10 – 7.04 (m, 2H), 6.95 (d, *J* = 7.6 Hz, 1H), 4.95 (d, *J* = 15.9 Hz, 1H), 4.87 (d, *J* = 15.9 Hz, 1H), 3.69 (s, 1H), 1.97 (d, *J* = 13.1 Hz, 1H), 1.62 – 1.51 (m, 4H), 1.47 – 1.40 (m, 1H), 1.35 (t, *J* = 11.1 Hz, 1H), 1.26 – 1.16 (m, 3H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 143.10, 136.77, 133.71, 130.46, 129.76, 127.76, 126.42, 126.12, 125.89, 123.79, 73.73, 62.01, 53.01, 34.96, 33.07, 25.83, 22.29, 21.57.; AMM (CI-TOF) *m/z* calcd for $C_{20}H_{26}NO^+$ $[M+NH_4]^+$ 296.2014, found 296.2029; m.p. 109-112 °C; $[\alpha]_D^{22} = -48.3$ (c = 0.20, $CHCl_3$). Note: compound appears to degrade rapidly on silica gel during purification, a very small silica gel plug was used to remove the catalyst from the reaction mixture.

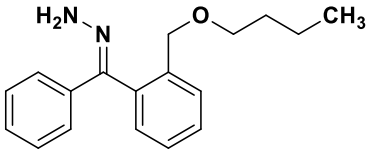


1-(butoxymethyl)-2-iodobenzene (393) was synthesized according to General Procedure C using 2-iodobenzyl alcohol (2.000 g, 8.546 mmol) in THF (4 mL), NaH (1.712 g, 42.80 mmol) in THF (10 mL),

n-butyl bromide (4.58 mL, 42.8 mmol), and tetrabutylammonium iodide (0.380 g, 10.3 mmol). The crude product was purified using flash column chromatography (95:5 hexanes:EtOAc) affording **393** as a clear oil (2.257 g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.8 Hz, 1H), 7.42 (d, *J* = 7.5 Hz, 1H), 7.29 (t, *J* = 7.5 Hz, 1H), 6.95 – 6.87 (m, 1H), 4.43 (s, 2H), 3.52 (t, *J* = 6.5 Hz, 2H), 1.67 – 1.57 (m, 2H), 1.48 – 1.35 (m, 2H), 0.92 (t, *J* = 7.4 Hz, 3H). ^{1}H NMR data was consistent with literature values.[182]

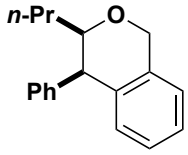


(2-(butoxymethyl)phenyl)(phenyl)methanone (394) was synthesized according to General Procedure N using **393** (0.300 g, 1.03 mmol), palladium (II) acetate (0.012 g, 0.052 mmol), silver (I) oxide (0.288 g, 1.24 mmol), benzaldehyde (0.84 mL, 8.3 mmol), and 70% *tert*-butyl hydroperoxide in H_2O (0.73 mL, 5.3 mmol). The crude product was purified using flash column chromatography (90:10 to 0:100 hexanes:CH_2Cl_2) affording **394** as a yellow oil (0.133 g, 48%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.77 (m, 2H), 7.60 – 7.52 (m, 2H), 7.51 – 7.41 (m, 3H), 7.38 – 7.31 (m, 2H), 4.57 (s, 2H), 3.32 (t, *J* = 6.6 Hz, 2H), 1.44 – 1.33 (m, 2H), 1.27 – 1.15 (m, 2H), 0.79 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.0, 138.5, 137.9, 137.8, 133.1, 130.4, 130.2, 128.7, 128.5, 128.4, 126.9, 70.9, 70.6, 31.7, 19.3, 14.0; AMM (ESI) *m/z* calcd for $C_{18}H_{21}O_2^+$ $[M+H]^+$ 269.1536, found 269.1535; IR (neat): ν_{max} 2957, 1667, 1270 cm^{-1}.

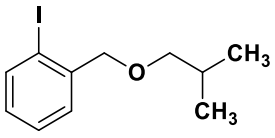


((2-(butoxymethyl)phenyl)(phenyl)methylene)hydrazine (395) was synthesized according to General Procedure O using **394** (0.120 g, 0.447 mmol), hydrazine (0.14 mL, 4.5 mmol), acetic acid (0.03

mL, 0.5 mmol) and anhydrous ethanol (4.5 mL). The crude product was purified using flash column chromatography (95:5 to 80:20 hexanes:EtOAc) affording **395** as a yellow oil (0.114 g, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.3 Hz, 1H), 7.52 – 7.40 (m, 4H), 7.31 – 7.26 (m, 3H), 7.16 (dd, *J* = 7.3, 1.6 Hz, 1H), 5.36 (s, 2H), 4.32 (d, *J* = 12.2 Hz, 1H), 4.26 (d, *J* = 12.2 Hz, 1H), 3.36 (t, *J* = 6.6 Hz, 2H), 1.53 – 1.41 (m, 2H), 1.37 – 1.22 (m, 2H), 0.86 (t, *J* = 7.4 Hz, 3H).

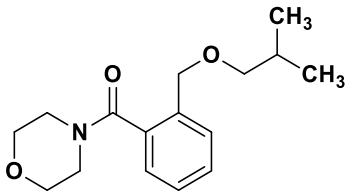


(3*R*,4*R*)-4-phenyl-3-propylisochromane (306) was synthesized according to General Procedure R using **395** (0.050 g, 0.18 mmol), manganese (IV) oxide (0.123 g, 0.708 mmol), Rh_2(*R*-PTAD)$_4$ (0.003 g, 0.01 mmol), and CH_2Cl_2 (12 mL). The crude product was purified using flash column chromatography (97:3 hexanes:EtOAc) affording **306** as a clear oil (0.024 g, 54%, >95:5 dr, >99.5:0.5 er). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.20 (m, 2H), 7.20 – 7.13 (m, 4H), 7.13 – 7.05 (m, 2H), 7.00 (d, *J* = 7.6 Hz, 1H), 5.04 (d, *J* = 15.1 Hz, 1H), 4.91 (d, *J* = 15.1 Hz, 1H), 3.91 – 3.82 (m, 1H), 3.81 (d, *J* = 3.2 Hz, 1H), 1.58 – 1.31 (m, 2H), 1.31 – 1.20 (m, 1H), 1.20 – 1.08 (m, 1H), 0.86 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.3, 137.8, 134.4, 130.4, 129.9, 128.1, 126.8, 126.4, 126.4, 124.2, 78.0, 68.9, 48.1, 35.8, 19.3, 14.2; AMM (CI-TOF) *m/z* calcd for $C_{18}H_{24}NO^+$ $[M+NH_4]^+$ 270.1852, found 270.1866; IR (neat): ν_{max} 3024, 2958, 1493, 742 cm^{-1}; $[\alpha]_D^{21} = -21.4$ (c = 2.4, $CHCl_3$).

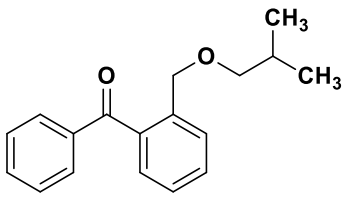


1-iodo-2-(isobutoxymethyl)benzene (396) was synthesized according to General Procedure C using 2-iodobenzyl alcohol (1.000 g, 4.273 mmol) in THF (2 mL), NaH (0.855 g, 21.4 mmol) in THF (1.5 mL), 1-bromo-2-methylpropane (2.32 mL, 21.4 mmol), and tetrabutylammonium iodide (0.221 g, 0.598

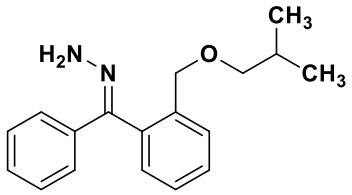
mmol). The crude product was purified using flash column chromatography (99:1 to 98:2, hexanes:CH_2Cl_2) affording **396** as a clear oil (0.493 g, 40%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.9 Hz, 1H), 7.45 (d, *J* = 7.4 Hz, 1H), 7.34 (t, *J* = 7.5 Hz, 1H), 7.01 – 6.93 (m, 1H), 4.47 (s, 2H), 3.32 (d, *J* = 6.7 Hz, 2H), 2.02 – 1.90 (m, 1H), 0.96 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (151 MHz, $(CD_3)_2CO$) δ 141.9, 139.8, 130.0, 129.5, 129.0, 97.9, 78.1, 77.1, 29.3, 19.7.; AMM (CI-TOF) *m/z* calcd for $C_{11}H_{15}IO^+$ $[M]^+$ 290.0168, found 290.0178.



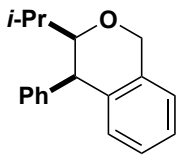
(2-(isobutoxymethyl)phenyl)(morpholino)methanone (397) was synthesized according to General Procedure D using **396** (0.290 g, 0.999 mmol), palladium (II) acetate (0.006 g, 0.02 mmol), morpholine (0.13 mL, 1.5 mmol), Xantphos (0.029 g, 0.050 mmol), potassium phosphate tribasic (0.637 g, 3.00 mmol), and toluene (2 mL). The crude product was purified using flash column chromatography (90:10 to 50:50, hexanes:EtOAc) affording **397** as a red oil (0.259 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 7.7 Hz, 1H), 7.37 (t, *J* = 7.5 Hz, 1H), 7.30 (t, *J* = 7.5 Hz, 1H), 7.18 (d, *J* = 7.4 Hz, 1H), 4.71 – 4.31 (m, 2H), 3.90 – 3.67 (m, 4H), 3.64 – 3.53 (m, 2H), 3.35 – 3.17 (m, 4H), 1.96 – 1.85 (m, 1H), 0.92 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9, 136.0, 135.0, 129.3, 129.1, 127.7, 126.1, 78.3, 70.6, 67.0, 47.8, 42.1, 28.6, 19.6. ^{1}H NMR was taken at rt and shows a mixture of rotamers.



(2-(isobutoxymethyl)phenyl)(phenyl)methanone (398) was synthesized according to General Procedure E using **397** (0.250 g, 0.901 mmol), 1.9 M phenyllithium solution in dibutyl ether (0.95 mL, 1.8 mmol), and THF (9 mL). The crude product was purified using flash column chromatography (99:1 to 98:2, hexanes:EtOAc) affording **398** as a yellow oil (0.200 g, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.9 Hz, 2H), 7.60 – 7.53 (m, 2H), 7.52 – 7.41 (m, 3H), 7.39 – 7.30 (m, 2H), 4.58 (s, 2H), 3.11 (d, *J* = 6.6 Hz, 2H), 1.77 – 1.65 (m, 1H), 0.77 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.0, 138.6, 137.8, 137.8, 133.1, 130.5, 130.3, 128.8, 128.5, 128.4, 126.9, 78.0, 70.7, 28.5, 19.4; AMM (ESI) *m/z* calcd for $C_{18}H_{21}O_2^+$ $[M+H]^+$ 269.1536, found 269.1532.

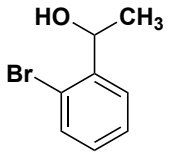


((2-(isobutoxymethyl)phenyl)(phenyl)methylene)hydrazine (399) was synthesized according to General Procedure O using **398** (0.184 g, 0.684 mmol), hydrazine (0.22 mL, 6.8 mmol), acetic acid (0.05 mL, 0.8 mmol), and anhydrous ethanol (6.8 mL). The crude product was purified using flash column chromatography (99:1 to 90:10, hexanes:EtOAc) affording **399** as an orange oil (0.145 g, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.7 Hz, 1H), 7.53 – 7.39 (m, 4H), 7.32 – 7.26 (m, 3H), 7.16 (d, *J* = 7.3 Hz, 1H), 5.36 (s, 2H), 4.32 (d, *J* = 12.4 Hz, 1H), 4.25 (d, *J* = 12.4 Hz, 1H), 3.14 (d, *J* = 6.6 Hz, 2H), 1.85 – 1.72 (m, 1H), 0.85 (d, *J* = 6.6 Hz, 6H).

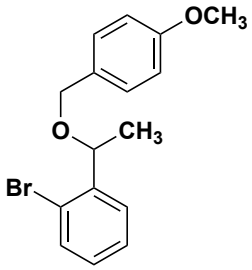


(3*R*,4*R*)-3-isopropyl-4-phenylisochromane (307) was synthesized according to General Procedure R using **399** (0.050 g, 0.18 mmol), manganese (IV) oxide (0.123 g, 1.42 mmol), Rh_2(*R*-PTAD)$_4$ (0.003 g,

0.002 mmol), and CH_3CN (12 mL). The crude product was purified using flash column chromatography (80:20 to 70:30, hexanes:CH_2Cl_2) affording **307** as white crystals (0.027 g, 62%, >95:5 dr, 96:4 er). ^1H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J = 7.1 Hz, 2H), 7.27 – 7.19 (m, 2H), 7.20 – 7.10 (m, 2H), 7.07 (t, J = 6.7 Hz, 2H), 7.02 (d, J = 7.5 Hz, 1H), 5.07 (d, J = 15.1 Hz, 1H), 4.89 (d, J = 15.2 Hz, 1H), 3.96 (d, J = 2.6 Hz, 1H), 3.37 (dd, J = 9.9, 2.9 Hz, 1H), 1.45 – 1.31 (m, 1H), 0.98 (d, J = 6.5 Hz, 3H), 0.92 (d, J = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.5, 138.2, 134.2, 130.3, 129.9, 128.2, 126.8, 126.4, 126.3, 124.2, 84.6, 69.2, 46.0, 30.2, 19.8, 18.8; AMM (CI-TOF) m/z calcd for $C_{18}H_{24}NO^+$ $[M+NH_4]^+$ 270.1852, found 270.1852; m.p. 100-104 °C; $[\alpha]_D^{22} = -36.3$ (c = 0.2, $CHCl_3$).

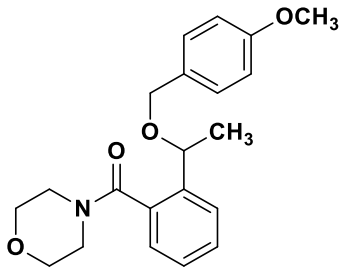


1-(2-bromophenyl)ethan-1-ol (400) was synthesized according to the General Procedure K using 1-(2-bromophenyl)ethan-1-one (0.995 g, 5.00 mmol), $NaBH_4$ (0.757 g, 20.0 mmol) in EtOH (20 mL, 0.25 M). The crude product was purified by flash column chromatography (91:9, hexanes:EtOAc) affording **400** as a clear oil (0.924 g, 92%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 7.7 Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.39 – 7.30 (m, 1H), 7.17 – 7.08 (m, 1H), 5.25 (q, J = 6.4 Hz, 1H), 1.97 (s, 1H), 1.49 (d, J = 6.4 Hz, 3H). ^1H NMR data of the crude material was consistent with the reported literature values.[183]



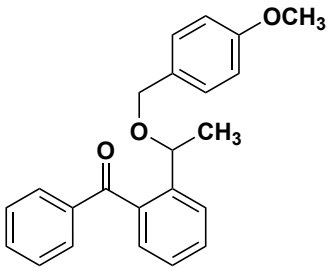
1-bromo-2-(1-((4-methoxybenzyl)oxy)ethyl)benzene (401) was synthesized according to the General Procedure L using **400** (0.608 g, 3.02 mmol), 1-(chloromethyl)-4-methoxybenzene (0.45 mL,

3.3 mmol), 60% NaH in mineral oil (0.300 g, 7.50 mmol), TBAI (0.111 g, 0.301 mmol) in THF (20 mL) and DMF (2 mL). The crude product was purified by flash column chromatography (91:9, hexanes:EtOAc) affording **401** as a clear oil (1.000 g, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.7 Hz, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.41 – 7.32 (m, 1H), 7.25 (d, *J* = 8.3 Hz, 2H), 7.19 – 7.10 (m, 1H), 6.88 (d, *J* = 8.3 Hz, 2H), 4.90 (q, *J* = 6.4 Hz, 1H), 4.38 (d, *J* = 11.2 Hz, 1H), 4.25 (d, *J* = 11.2 Hz, 1H), 3.81 (s, 3H), 1.42 (d, *J* = 6.4 Hz, 3H). ^{1}H NMR data of the crude material was consistent with the reported literature values.[184]

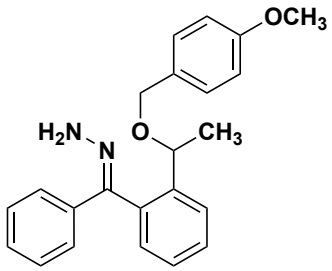


(2-(1-((4-methoxybenzyl)oxy)ethyl)phenyl)(morpholino)methanone (402) was synthesized according to General Procedure D using **401** (0.964 mg, 3.00 mmol), morpholine (0.39 mL, 4.5 mmol), $Pd(OAc)_2$ (0.017 g, 0.0757 mmol), Xantphos (0.087 g, 0.15 mmol) and potassium phosphate tribasic (1.91 g, 9.00 mmol) in toluene (6 mL, 0.5 M). The crude product was purified by flash column chromatography (67:33, hexanes:EtOAc) affording **402** as a pale yellow oil (0.769 g, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 – 7.62 (m, 1H), 7.49 – 7.40 (m, 1H), 7.34 – 7.27 (m, 1H), 7.24 (d, *J* = 8.2 Hz, 2H), 7.15 (d, *J* = 7.6 Hz, 1H), 6.86 (d, *J* = 7.9 Hz, 2H), 4.84 – 4.50 (m, 1H), 4.38 – 4.24 (m, 2H), 3.92 – 3.40 (m, 9H), 3.37 – 3.06 (m, 2H), 1.56 – 1.34 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.5, 159.2, 159.1, 141.4, 134.5, 134.2, 130.8, 130.3, 129.7, 129.4, 129.1, 127.4, 126.7, 126.4, 125.7, 113.9, 113.7, 77.3, 74.4, 73.5, 70.4, 66.9, 66.8, 55.3, 47.6, 42.0, 24.0, 23.4. AMM (ESI) *m/z* calcd for $C_{21}H_{26}NO_4^+$ $[M+H]^+$

356.1856, found 356.1861. ^{1}H NMR was taken at rt and shows a mixture of rotamers. IR (neat): ν_{max} 1633, 1514, 1250, 1114 cm^{-1}.

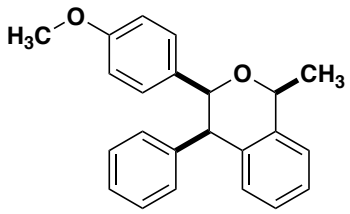


(2-(1-((4-methoxybenzyl)oxy)ethyl)phenyl)(phenyl)methanone (403) was synthesized according to General Procedure F using **402** (0.340 g, 0.957 mmol), phenyllithium (1.9 M in Bu_2O, 1.0 mL, 1.9 mmol) in THF (10 mL, 0.1 M). The crude product was purified by flash column chromatography (91:9, hexanes:EtOAc) affording **403** as a clear oil (0.294 g, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.7 Hz, 2H), 7.75 (d, *J* = 7.9 Hz, 1H), 7.63 – 7.52 (m, 2H), 7.50 – 7.41 (m, 2H), 7.37 – 7.28 (m, 2H), 7.10 (d, *J* = 8.3 Hz, 2H), 6.76 (d, *J* = 8.5 Hz, 2H), 4.73 (q, *J* = 6.4 Hz, 1H), 4.28 (d, *J* = 11.1 Hz, 1H), 4.15 (d, *J* = 11.1 Hz, 1H), 3.76 (s, 3H), 1.46 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.0, 159.0, 143.6, 137.9, 137.7, 133.3, 130.7, 130.4, 130.3, 129.3, 128.4, 128.0, 126.6, 126.5, 113.7, 73.6, 70.4, 55.2, 24.0. AMM (ESI) *m/z* calcd for $C_{23}H_{22}NaO_3^+$ $[M+Na]^+$ 369.1467, found 369.1469.

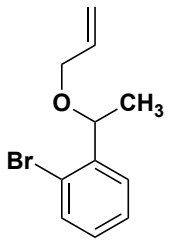


((2-(1-((4-methoxybenzyl)oxy)ethyl)phenyl)(phenyl)methylene)hydrazine (**404**) was synthesized according to General Procedure O using **403** (0.144 g, 0.415 mmol), hydrazine (0.17 mL, 5.4 mmol), acetic acid (0.03 mL, 0.5 mmol), and EtOH (3 mL) at 160 °C for 3 h. The crude product was purified by

flash column chromatography (91:9 to 84:16, hexanes:EtOAc) affording **404** as a clear oil (0.106 g, 71%). Compound was isolated as a mixture of isomers; ^{1}HNMR spectral data for this mixture is complex and the mixture was carried on to the next step.

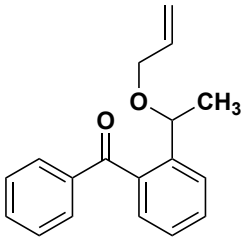


3-(4-methoxyphenyl)-1-methyl-4-phenylisochromane (341) was synthesized according to General Procedure R using **404** (0.031 g, 0.085 mmol), MnO_2 (0.059 g, 0.68 mmol), and $Rh_2(mes)_4$ (0.001 g, 0.0008 mmol) in CH_3CN (5 mL, 0.017 M). The crude product was purified by flash column chromatography (97:3, hexanes:EtOAc) affording **341** as a clear oil (0.017 g, 60%, >95:5:Σ other isomers dr). ^{1}H NMR (599 MHz, $CDCl_3$) δ 7.21 – 7.17 (m, 3H), 7.12 – 7.06 (m, 1H), 7.00 – 6.94 (m, 4H), 6.81 (d, *J* = 8.3 Hz, 2H), 6.72 – 6.67 (m, 2H), 6.61 (d, *J* = 8.5 Hz, 2H), 5.09 (q, *J* = 6.5 Hz, 1H), 5.00 (d, *J* = 3.1 Hz, 1H), 4.01 (d, *J* = 3.2 Hz, 1H), 3.66 (s, 3H), 1.71 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.6, 140.9, 139.4, 137.4, 132.9, 130.5, 130.3, 127.4, 127.4, 126.90, 126.87, 126.1, 124.6, 113.1, 79.2, 74.4, 55.3, 51.2, 22.4. Low-resolution MS (Advion ASAP-APCI) *m/z* calcd for $C_{23}H_{23}O_2^+$ $[M+H]^+$ 331.1693, found 331.0.

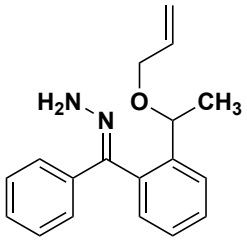


1-(1-(allyloxy)ethyl)-2-bromobenzene (405) was synthesized according to the General Procedure L using **400** (0.468 g, 2.33 mmol), 3-bromoprop-1-ene (0.3 mL, 3 mmol), 60% NaH in mineral oil (0.23 g,

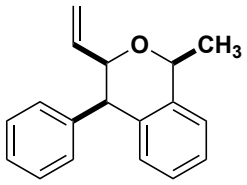
5.8 mmol) in THF (10 mL) and DMF (1 mL). The crude product was purified using flash column chromatography (91:9, hexanes:EtOAc) affording **405** as a clear oil (0.481 g, 87%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.56 – 7.48 (m, 2H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.16 – 7.09 (m, 1H), 5.97 – 5.87 (m, 1H), 5.27 (d, *J* = 17.2 Hz, 1H), 5.18 (d, *J* = 10.4 Hz, 1H), 4.87 (q, *J* = 6.4 Hz, 1H), 3.91 (dd, *J* = 12.7, 5.2 Hz, 1H), 3.82 (dd, *J* = 12.7, 5.9 Hz, 1H), 1.42 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 143.0, 134.8, 132.7, 128.8, 128.0, 127.3, 122.6, 117.1, 76.0, 69.9, 22.9; Low-resolution MS (Advion ASAP-APCI) *m/z* calcd for $C_{11}H_{14}BrO^+$ $[M+H]^+$ 241.0223, found 240.9.



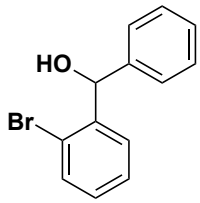
(2-(1-(allyloxy)ethyl)phenyl)(phenyl)methanone (406) was synthesized according to the General Procedure J using **405** (0.241 g, 1.00 mmol), **271** (0.165 g, 1.00 mmol), 2.13 M *n*-butyllithium in hexanes (0.52 mL, 1.1 mmol) and THF (20 mL). The crude product was purified using flash column chromatography (95:5, hexanes:EtOAc) affording **406** as a clear oil (0.109 g, 41%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.6 Hz, 2H), 7.69 (d, *J* = 7.9 Hz, 1H), 7.60 (t, *J* = 7.7 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.33 (t, *J* = 7.4 Hz, 1H), 7.29 (d, *J* = 7.8 Hz, 1H), 5.81 – 5.71 (m, 1H), 5.12 (d, *J* = 17.2 Hz, 1H), 5.04 (d, *J* = 10.4 Hz, 1H), 4.68 (q, *J* = 6.4 Hz, 1H), 3.81 (dd, *J* = 12.7, 5.0 Hz, 1H), 3.73 (dd, *J* = 13.1, 6.2 Hz, 1H), 1.46 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.2, 143.7, 137.9, 137.8, 134.8, 133.4, 130.8, 130.4, 128.6, 128.1, 126.7, 126.6, 116.9, 73.8, 69.9, 24.0; AMM (ESI) *m/z* calcd for $C_{18}H_{19}O_2^+$ $[M+H]^+$ 267.1385, found 267.1374.



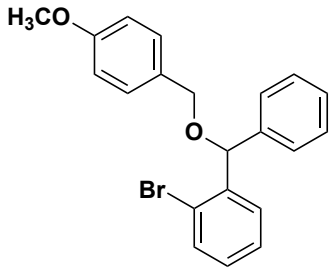
((2-(1-(allyloxy)ethyl)phenyl)(phenyl)methylene)hydrazine (**407**) was synthesized according to General Procedure O using **406** (0.053 g, 0.20 mmol), hydrazine (0.080 mL, 2.6 mmol), acetic acid (0.014 mL, 0.24 mmol), and EtOH (2 mL) at 160 °C for 3 h. The crude product was purified by flash column chromatography (91:9 to 84:16, hexanes:EtOAc) affording **407** as a clear oil (0.029 g, 51%). Compound was isolated as a mixture of isomers; ^{1}HNMR spectral data for this mixture is complex and the mixture was carried on to the next step.



(1*S*,3*R*,4*R*)-1-methyl-4-phenyl-3-vinylisochromane (342) was synthesized according to General Procedure R using **407** (0.037 g, 0.13 mmol), MnO_2 (0.091 g, 1.0 mmol), and Rh_2(*R*-TCPTTL)$_4$ (0.003 g, 0.001 mmol) in CH_3CN (7.7 mL). The crude product was purified using flash column chromatography (99:1, hexanes:EtOAc) affording **342** as a clear oil (0.025 g, 76%, >95:Σ other isomers dr). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 – 7.12 (m, 8H), 7.01 (d, *J* = 7.7 Hz, 1H), 5.56 – 5.45 (m, 1H), 5.25 (d, *J* = 17.3 Hz, 1H), 5.10 – 5.00 (m, 2H), 4.51 – 4.45 (m, 1H), 3.95 – 3.89 (m, 1H), 1.72 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 141.6, 139.0, 137.3, 137.1, 130.3, 130.2, 127.9, 126.9, 126.8, 126.5, 124.5, 116.4, 78.8, 73.6, 49.5, 22.2; AMM (CI) *m/z* calcd for $C_{18}H_{18}O^+$ [M+H]$^+$ 250.1358, found 250.1359; IR (neat): ν_{max} 1490, 1451, 1098, 722, 698 cm^{-1}.

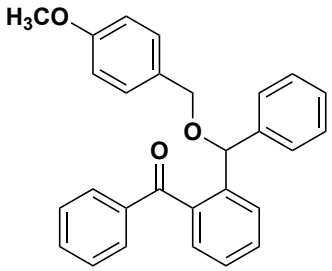


(2-bromophenyl)(phenyl)methanol (408) To a flame-dried flask was added 2-bromobenzaldehyde (0.92 g, 5.0 mmol) and Et_2O (15 mL). Phenylmagnesium bromide (1.0 M in THF) (7.5 mL, 7.5 mmol) was then added dropwise at 0 °C. The reaction was allowed to warm to rt overnight. Upon completion by TLC, the reaction was quenched with sat. aq. NH_4Cl (10 mL) and the crude mixture was extracted with Et_2O (3 X 10 mL). The combined organic layers were washed with H_2O (1 X 10 mL) and brine (1 X 10 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude reaction mixture was purified using flash column chromatography (91:9, hexanes:EtOAc), affording **408** as a clear oil (1.3 g, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J = 7.7 Hz, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.41 (d, J = 7.5 Hz, 2H), 7.34 (t, J = 7.3 Hz, 3H), 7.29 (d, J = 7.3 Hz, 1H), 7.15 (t, J = 7.6 Hz, 1H), 6.21 (d, J = 3.5 Hz, 1H), 2.35 (d, J = 3.8 Hz, 1H). ^{1}H NMR data of the crude material was consistent with the reported literature values.[185]

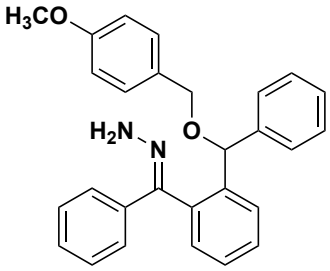


1-bromo-2-(((4-methoxybenzyl)oxy)(phenyl)methyl)benzene (409) was synthesized according to the General Procedure L using **408** (0.789 g, 3.00 mmol), 1-(chloromethyl)-4-methoxybenzene (0.45 mL, 3.3 mmol), 60% NaH in mineral oil (0.300 g, 7.50 mmol), TBAI (0.111 g, 0.301 mmol) in THF (20 mL) and DMF (2 mL). The crude product was purified using flash column chromatography (95:5,

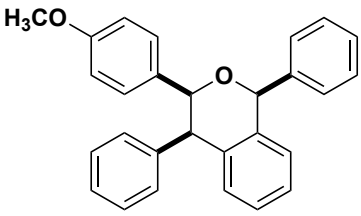
hexanes:EtOAc) affording **409** as a clear oil (1.17 g, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.40 (d, *J* = 7.6 Hz, 2H), 7.36 – 7.20 (m, 6H), 7.12 (td, *J* = 7.7, 1.7 Hz, 1H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.86 (s, 1H), 4.51 (d, *J* = 11.3 Hz, 1H), 4.43 (d, *J* = 11.2 Hz, 1H), 3.79 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.4, 141.3, 140.9, 132.9, 130.3, 129.7, 129.1, 129.0, 128.4, 127.9, 127.7, 127.6, 123.8, 113.9, 80.8, 70.8, 55.4; AMM (CI) *m/z* calcd for $C_{21}H_{19}BrO_2^+$ $[M]^+$ 382.0569, found 382.0564.



(2-(1-((4-methoxybenzyl)oxy)ethyl)phenyl)(phenyl)methanone (410) was synthesized according to the General Procedure J using **409** (0.387 g, 1.01 mmol), **271** (0.165 g, 1.00 mmol), 2.13 M *n*-butyllithium in hexane (0.52 mL, 1.1 mmol) and THF (15 mL). The crude product was purified using flash column chromatography (95:5, hexanes:EtOAc) affording **410** as a clear oil (0.23 g, 56%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.7 Hz, 2H), 7.54 (t, *J* = 7.5 Hz, 1H), 7.43 – 7.20 (m, 11H), 6.96 (d, *J* = 8.5 Hz, 2H), 6.68 (d, *J* = 8.6 Hz, 2H), 5.86 (s, 1H), 4.29 (d, *J* = 10.8 Hz, 1H), 4.23 (d, *J* = 10.8 Hz, 1H), 3.74 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.3, 159.1, 141.7, 141.0, 138.7, 137.8, 133.2, 130.4, 130.2, 130.2, 129.5, 128.5, 128.4, 128.1, 128.0, 128.0, 127.7, 126.8, 113.6, 79.0, 71.0, 55.4; Low-resolution MS (Advion ASAP-APCI) *m/z* calcd for $C_{28}H_{25}O_3^+$ $[M+H]^+$ 409.1798, found 409.0.



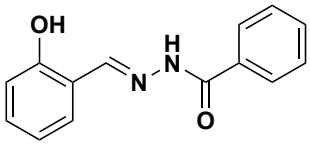
((2-(((4-methoxybenzyl)oxy)(phenyl)methyl)phenyl)(phenyl)methylene)hydrazine (**411**) was synthesized according to General Procedure O **410** (0.123 g, 0.300 mmol), hydrazine (0.12 mL, 3.9 mmol), acetic acid (0.021 mL, 0.36 mmol), and anhydrous EtOH (3 mL) were heated in a microwave reactor at 160 °C for 3 h. After cooling down to room temperature, hydrazine (0.12 mL, 3.9 mmol) and acetic acid (0.021 mL, 0.36 mmol) were added again and the mixture was heated in a microwave reactor at 160 °C for another 3 hours. The crude product was purified by flash column chromatography (91:9 to 84:16, hexanes:EtOAc) affording **411** as a clear oil (0.088 g, 69%). Compound was isolated as a mixture of isomers; ^{1}HNMR spectral data for this mixture is complex and the mixture was carried on to the next step.



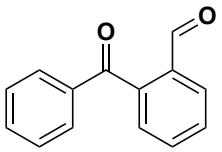
(1*S*,3*S*,4*R*)-3-(4-methoxyphenyl)-1,4-diphenylisochromane (343) was synthesized according to General Procedure R using **411** (0.037 g, 0.087 mmol), MnO_2 (0.060 g, 0.69 mmol), and Rh_2(*R*-TCPTTL)$_4$ (0.002 g, 0.0009 mmol) in CH_3CN (5.1 mL). The crude product was purified using flash column chromatography (99:1, hexanes:EtOAc), affording **343** as a white solid (0.024 g, 70%, >95:Σ other isomers). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.6 Hz, 2H), 7.47 – 7.41 (m, 2H), 7.41 – 7.35 (m, 1H), 7.18 – 7.11 (m, 2H), 7.10 – 7.01 (m, 4H), 6.96 – 6.83 (m, 5H), 6.66 (d, *J* = 8.7 Hz, 2H), 5.98 (s,

1H), 5.31 (d, J = 3.6 Hz, 1H), 4.24 (d, J = 3.6 Hz, 1H), 3.72 (s, 3H); ^{13}C NMR (201 MHz, $CDCl_3$) δ 158.6, 141.8, 141.3, 137.8, 137.5, 132.7, 130.5, 130.5, 129.1, 128.7, 128.4, 127.5, 127.4, 127.2, 126.7, 126.5, 126.2, 113.1, 82.4, 80.3, 55.3, 50.8; m.p. 157-158 °C; AMM (ESI) *m/z* calcd for $C_{28}H_{25}O_2^+$ $[M+Na]^+$ 415.1674, found 415.1676; IR (neat): ν_{max} 1516, 1252, 1033, 706 cm^{-1}.

Note: for all tetrahydroisoquinole substrates (section 1.3.6) see the dissertation of Prof. Leslie Nickerson

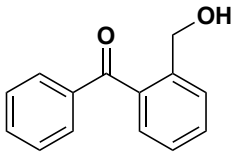


(E)-N'-(2-hydroxybenzylidene)benzohydrazide (278). To solution of benzhydrazide (2.70 g, 19.8 mmol) in EtOH (10 mL) was added a solution of salicylaldehyde (2.13 mL, 20.0 mmol) in EtOH (20 mL). The reaction was stirred at rt for 16 h during which time a precipitate formed. The solid was filtered off and washed with EtOH. The filtrate was concentrated in vacuo, affording 84 as an off-white powder (4.785 g, 99%) with no purification necessary. 1H NMR (400 MHz, DMSO- d6) δ 12.11 (s, 1H), 11.30 (s, 1H), 8.65 (s, 1H), 7.95 (d, J = 7.4 Hz, 2H), 7.65 – 7.50 (m, 4H), 7.31 (t, J = 7.7 Hz, 1H), 6.97 – 6.89 (m, 2H).278

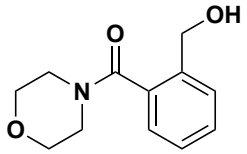


2-benzoylbenzaldehyde (**279**). Following a literature procedure,104 a solution of hydrazone 84 (2.350 g, 9.781 mmol) in THF (58 mL) was added to a flame-dried flask under argon. To the solution was added Pb(OAc)4 (4.345 g, 9.800 mmol) gradually. The solution was stirred for 2h at rt. The solution was concentrated in vacuo in a hood and the crude residue was purified using flash column chromatography (95:5 to 80:20, hexanes:EtOAc), affording 85 as a clear oil (1.710 g, 83%). ^{1}H NMR (400 MHz, CDCl3)

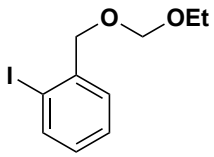
δ 10.02 (s, 1H), 8.06 – 7.98 (m, 1H), 7.83 – 7.77 (m,2H), 7.73 – 7.63 (m, 2H), 7.63 – 7.55 (m, 1H), 7.54 – 7.41 (m, 3H).



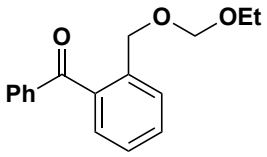
2-benzoylbenzyl alcohol (280) was synthesized following a modified literature procedure,[186] by preparing a solution of **279** (0.107 g, 0.5 mmol, 1 equiv), sodium carbonate (0.102 g, 1 mmol, 2 equiv), and $NaBH_4$ (0.022 g, 0.6 mmol, 1.2 equiv) in EtOH (0.25 M). The reaction was quenched after two hours with sat. aq. ammonium chloride (5 mL), extracted with diethyl ether (10 mL x 2), washed with brine (20 mL), dried over sodium sulfate, and concentrated *in vacuo* to afford **280** (0.090 g, 87%) as a clear oil. BDB-I-059.



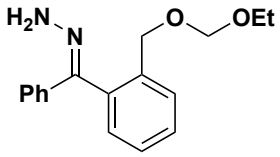
2-(hydroxymethyl)morpholine benzamide (287) was synthesized according to a modified literature procedure,[155] by charging a flask with aluminum trichloride (0.348 g, 2.6 mmol, 1.3 mmol) and 1,2-dichloroethane (2 M) and cooled to 0 °C. Morpholine (0.43 mL, 5 mmol, 2.5 equiv) was then added as solution in DCE (6 M), allowing to stir for 30 minutes before adding phthalide (0.269 g, 2 mmol, 1 equiv) portionwise. After stirring for 1 hour, the reaction was quenched with ice, filtered through celite, extracted with DCE (10 mL x3), washed with water (10 mL x2), washed with brine (20 mL), dried over sodium sulfate, concentrated *in vacuo*, and purified by flash column chromatography (95$CHCl_3$:5MeOH) to afford **287** (0.141 g, 27%) as a white solid. BDB-I-077



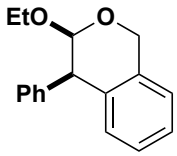
1-iodo-2-((ethoxymethoxy)methyl)benzene (412) was synthesized according to General Procedure A, using NaH (1.029 g, 25.637 mmol, 3 equiv.) in 25 mL THF, 2-iodobenzyl alcohol (2.002g, 8.546 mmol, 1 equiv.) in 10 mL THF, and ethoxymethyl chloride (1.19 mL, 10.25mmol 1.5 equiv.) to afford **412** (2.414 g, 97%) as a clear oil after purification with flash column chromatography (100% hexanes to 90hexanes:10EtOAc). BDB-II-071



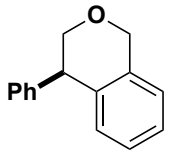
2-((ethoxymethoxy)methylbenzophenone (413) was synthesized according to General Procedure J, using **412** (1.001 g, 3.42 mmol, 1 equiv.) in THF (13mL), 2.13 M *n*-butyllithium in hexanes (2.09 mL, 4.45 mmol, 1.3 equiv.), and **271** (0.678g, 4.11 mmol, 1.2 equiv.) in THF (5 mL), reacting overnight. The crude product was purified using flash column chromatography (90hexanes:10EtOAc), affording **413** as a yellow oil (0.440 g, 47%). BDB-II-076



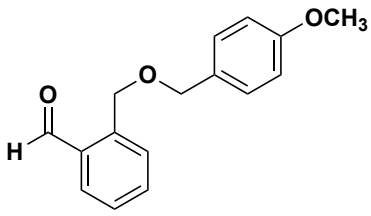
2-((ethoxymethoxy)methylbenzophenone hydrazone (315) was synthesized according to General Procedure O, using **416** (0.290 g, 1.110 mmol, 1 equiv.) in EtOH (11 mL), and hydrazine (0.21 mL, 6.66 mmol, 6 equiv.), reacting for 10h at 160 °C in the microwave reactor. The crude product was purified using flash column chromatography (70:30, hexanes:EtOAc), affording **315** as a yellow oil (0.252 g, 82%). BDB-II-082



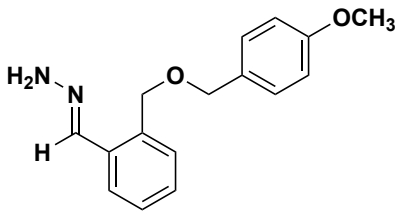
(3*S*,4*R*)-3-ethoxy-4-phenylisochromane 316 was synthesized according to General Procedure S, using **315** (0.049 g, 0.176 mmol, 1 equiv), MnO (0.123 g, 1.407 mmol, 8 equiv.), and Rh2(*R*-PTAD)4 (0.003 g, 0.002 mmol, 1 mol %) in acetonitrile (12 mL), affording **316** (0.0XX g, XX%) as a clear oil without purification. BDB-II-090



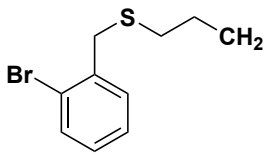
(*R*)-4-phenylisochromane 320 was synthesized according to a modified literature procedure,[168] by preparing a solution of **316** (0.0784 mmol, 1 equiv.) and triethyl silane (0.05 mL, 0.314 mmol, 4 equiv.) in DCM (0.2 M). The solution was cooled to -10 °C and boron trifluoride diethyl etherate (0.02 mL, 0.196 mmol, 2.5 equiv.) was then added dropwise, allowing to stir for 2 hours at 0 °C. The reaction mixture was then poured into a 0 °C solution of potassium carbonate (2.5 equiv) in H_2O (0.24 M) and diethyl ether (0.12 M). This mixture was stirred for 10 minutes and then extracted with diethyl ether (5 mL x3), washed with brine (10 mL), dried over sodium sulfate, concentrated *in vacuo*, and purified by flash column chromatography to afford **320** (0.0091 g, ~55%) as a clear oil. The isolated compound was not able to be further purified. BDB-II-136



2-(((4-methoxybenzyl)oxy)methyl)benzaldehyde (414) was synthesized according to a modified literature procedure,[187] by preparing a solution of **351** (0.503g 1.628 mmol, 1 equiv.) in diethyl ether (0.25 M) which was cooled to -78 °C. *n*-Butyllithium (1.15 mL, 2.44 mmol, 1.5 equiv.) was then added and the mixture was allowed to stir for 2 hours. Dimethylformamide (1.26 mL, 16.28 mmol, 10 equiv.) was then added at -78 °C and the solution was stirred to room temperature overnight. The reaction was quenched with sat. aq. ammonium chloride (5 mL), washed with H_2O (15 mL), washed with brine (10 mL), dried over sodium sulfate, and concentrated *in vacuo* to afford **414** (0.291 g, 69%) as a clear oil. BDB-II-046.

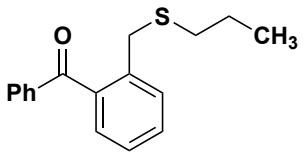


(2-(((4-methoxybenzyl)oxy)methyl)benzylidene)hydrazine (322) was synthesized according to general procedure P, using **414** (0.283 g, 1.105 mmol, 1 equiv.) in EtOH (11 mL), glacial acetic acid (0.08 mL, 1.33 mmol), and hydrazine (0.21 mL, 6.63 mmol, 6 equiv.), reacting for 1 h at room temperature. The crude product was purified using flash column chromatography (70:30, hexanes:EtOAc), affording **322** as a yellow oil (0.202 g, 68%). BDB-II-048

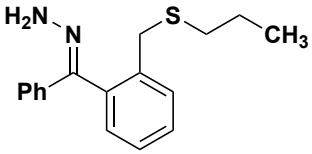


2-bromobenzyl propyl thioether (415) was synthesized according to a modified literature procedure,[188] by preparing a solution of 2-bromobenzylbromide (1.007g 4.0 mmol, 1 equiv.), *n*-propanethiol (0.37 mL, 4.0 mmol, 1 equiv.), and potassium carbonate (0.829 g, 6 mmol, 1.5 equiv.) in dimethylformamide (0.25 M). This mixture was stirred for 7 hours and then quenched with H_2O (5 mL),

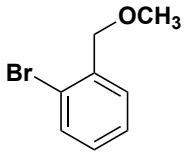
extracted with diethyl ether (10 mL x3), washed with H_2O (5 mL x2), and dried over sodium sulfate for afford **415** (0.950 g, 96%) as a clear oil. BDB-II-041



2-benzoylbenzyl propyl thioether (416) was synthesized according to general procedure J, using **415** (0.504 g, 2.039 mmol, 1 equiv.) in THF (8 mL), 2.13 M *n*-butyllithium in hexanes (1.24 mL, 2.651 mmol, 1.3 equiv.), and **271** (0.438 g, 2.447 mmol, 1.2 equiv.) in THF (3 mL), reacting overnight. The crude product was purified using flash column chromatography (95hexanes:5EtOAc), affording **416** as a clear oil (0.352 g, 63%). BDB-II-042

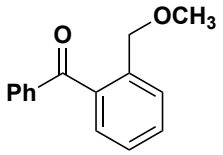


2-(thiopropyloxy)methylbenzophenone hydrazone (324) was synthesized according to general procedure P, using **416** (0.305 g, 1.110 mmol, 1 equiv.) in EtOH (11 mL), glacial acetic acid (0.08 mL, 1.33 mmol), and hydrazine (0.21 mL, 6.66 mmol, 6 equiv.), reacting for 3 h at 90 °C. The crude product was purified using flash column chromatography (90:10, hexanes:EtOAc), affording **324** as a clear oil (0.270 g, 84%). BDB-II-043

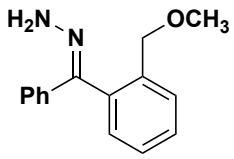


2-bromobenzyl methyl ether (417) was synthesized according to General Procedure A, using NaH (1.610 g, 40.000 mmol) in THF (25 mL), 2-bromobenzyl bromide (2.082 g, 8.002 mmol) in THF (10 mL), and methanol (0.50 mL, 12 mmol, previously dried over activated 3 Å molecular sieves for a

minimum of 24 h), reacting at room temperature for 24 h. The crude product was purified using flash column chromatography (100% hexanes to 90hexanes:10ethyl acetate), affording **417** as a clear oil (1.079g, 64%). BDB-II-024



2-benzoylbenzyl methyl ether (418) was synthesized according to general procedure J, using **417** (1.079 g, 4.974 mmol) in THF (19 mL), 2.13 M *n*-butyllithium in hexanes (3 mL, 6.5 mmol), and **271** (0.988 g, 5.968 mmol) in THF (7.5 mL), reacting for 21 h. The crude product was purified using flash column chromatography (90hexanes:10EtOAc to 80hexanes:20EtOAc), affording **417** as a clear oil (0.874 g, 78%). BDB-II-033



2-(methoxy)methylbenzophenone hydrazone (326) was synthesized according to general procedure P, using **417** (0.304 g, 1.326 mmol) in EtOH (12 mL), glacial acetic acid (0.09 mL, 1.59 mmol), and hydrazine (0.25 mL, 7.95 mmol), reacting for 3 h at 90 °C. The crude poduct was purified using flash column chromatography (70:30, hexanes:EtOAc), affording **326** as a yellow oil (0.271 g, 84%). BDB-II-034

1.6 References

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Chapter 2.0

Divergent Asymmetric Synthesis of Panowamycins, TM-135, and Veramycin F using C–H Insertion with Donor/Donor Carbenes[1]

Foreword:

> "When a stone is thrown into a pond, several waves are produced in succession, gradually spreading until they finally cover the whole pond. The first total synthesis of bioactive natural products is a stone thrown into the pond of the chemistry of natural products. In particular, the first total syntheses require the creation of original concepts and synthetic methodologies, and include the assignment of the absolute structure of bioactive natural products as well as verification of their biological activities."
>
> - Prof. Dr. Kuniaki Tatsuta, **2006**[2]

2.1 Introduction

The field of natural product synthesis has served four main purposes: to provide feedstocks of raw chemicals that are not abundant in nature,[3–5] corroborate or refute proposed structures,[6,7] use as a basis for drug development,[8–10] and finally, for the love of the game. Natural product syntheses have always presented a unique challenge to synthetic organic chemists: the development of novel methods to transform complex and sensitive intermediates can be a rewarding process. It is also a joy to simply "climb the unclimbed mountain" by being the first human to recreate the handiwork of nature. Ever since Friedrich Wöhler broke chemistry out of the myth of *vitalism* it's been off to the races,[3] though natural product synthesis has come quite a way since the days of synthesizing urea. Rare and exotic natural products have been sought out by isolation chemists in harsh and unique environments.[11] Organic chemists have attempted to synthesize these natural products and derivatize them into pharmaceuticals. Natural products and natural product derived substances represent 25% of all new approved drugs between 1981 and 2016, whereas fully synthetic drugs composed 27%.[12–14] It is within this framework that the importance of total synthesis reveals itself; continued efforts in this field spur on new and exciting

chemistries while also providing structural confirmations and biologically relevant quantities of material for further pharmaceutical investigation.

Following the development of our method to stereoselectively synthesize 3,4-*cis* isochromans by C–H insertion reactions with donor/donor carbenes (see chapter 1 of this dissertation), it was desirable to apply this method towards a natural product synthesis. Isochromans are found as the core structure of several natural products and biologically relevant molecules (see chapter 1 of this dissertation, section 1.1).[15–23] In 2012, Ōmura and coworkers, as part of their program for discovering treatments for infectious tropical diseases, isolated panowamycin A (**1**) and B (**2**), containing a novel, polyketide-derived isochroman scaffold from a culture of *Streptomyces* sp. K07-0010 (Figure 1).[24] It was decided that these natural products would be suitable synthetic targets using our C–H insertion methodology to construct the isochroman core. Known *Streptomyces* metabolite NFAT-133 (**6**) was also isolated in this work and appeared to be closely related to the panowamycins and benwamycins.[25,26] NFAT-133 has been the subject of several publications resulting in the unambiguous determination of its relative and absolute configuration, supporting the original stereochemical assignment for **1** and **2** at C10, C11 and C12.[26,27] Mahmud and coworkers also isolated NFAT-133 from their fermentation of *Streptomyces pactum* ATCC 27456 in a 2020 publication; in this work they determine the biosynthetic pathway to NFAT-133 (Figure 1).[28] In a subsequent report, they isolate panowamycin A (**3**) (from the same microorganism), alongside the related TM-135 (**4**). Based on an updated NMR spectral analysis and CD spectroscopy, they proposed a revised relative and absolute structure for panowamycin A (**3**).[29] In their report, they also posit that an intramolecular alkoxylation of the styrene of NFAT-133 from either the *si* or *re* face can proceed to form **3** or **4**, respectively. Shortly thereafter, Schäberle and Bauer published the isolation of veramycins A–G, further expanding the class of NFAT-133 related polyketide natural products (Figure 1).[22] The narrative around the stereochemical identity of these natural products was continually evolving

during the synthesis described in this chapter. The structural revisions of panowamycin A by Mahmud and coworkers and the subsequent report of veramycin F isolation were contemporaneous with active efforts towards the synthesis of **3** and **4** (the project began in early 2019). As such, the (retro)synthetic approach to these molecules will be presented in chronological order in this chapter.

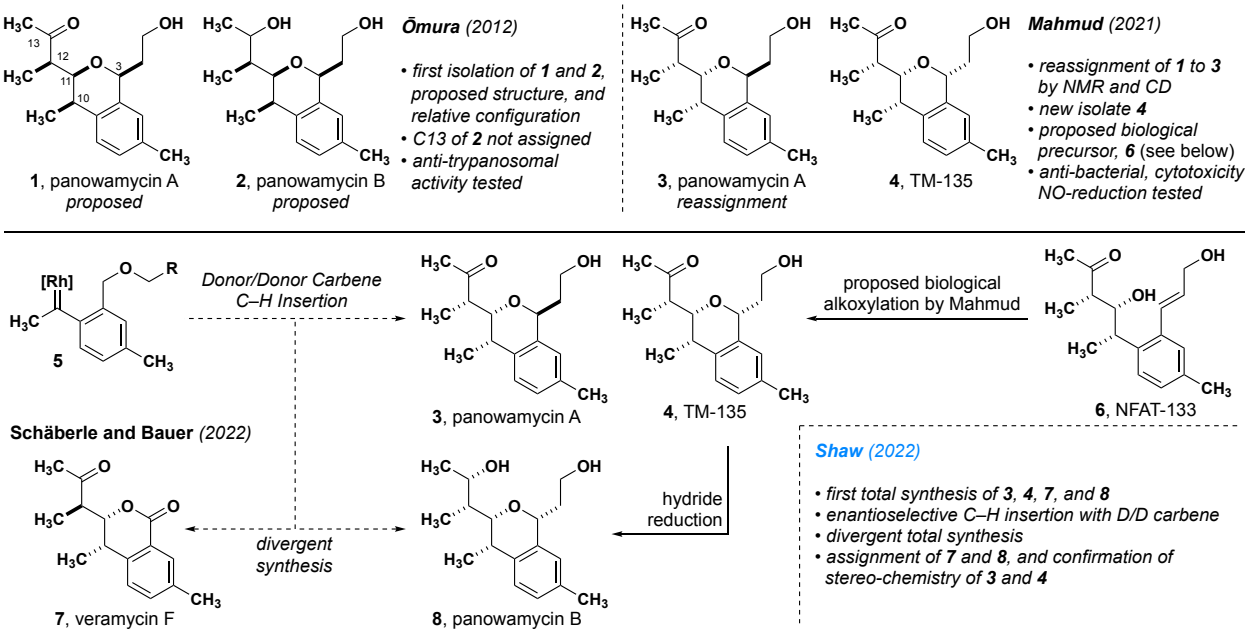


Figure 1. Isochroman natural products synthesized by C–H insertion with donor/donor carbenes

In this chapter, the isolation, biosynthesis, and biological activity of NFAT-133-based polyketide natural products will be briefly discussed as introductory information. Then, the asymmetric first synthesis of panowamycin A, panowamycin B, TM-135, and veramycin F is reported. After synthesizing the originally reported structure of panowamycin A (Ōmura, 2012) and identifying a stereochemical misassignment, computational NMR was utilized to predict the configuration of the natural substance. The use of donor/donor carbenes to asymmetrically generate the isochroman core and development of a robust, divergent synthesis to produce these natural products and unambiguously assign their stereochemistry will then be discussed in this dissertation as a contribution to this field of research.

2.1.1 Proposed biosynthesis of NFAT-133 and related natural products

With multiple sources in nature (e.g. bacteria, fungi, plants, invertebrates), polyketide natural products are commonly isolated, studied, and synthesized.[2,30–32] They are derived from a serial combination of acyl functionalities, most commonly acetyl and propionyl CoA bound carboxylic acids.[33,34] Based on the specific microorganism, these building blocks can be added to each other, modified by other enzymes (e.g. cytochrome P450, Figure 2), oligomerized, and cyclized to form a broad variety of unique polyketide natural products.[28] These natural products have been indicated in a swath of medicinally important areas and continue to be of interest to medicinal chemists.[10,35] For example, anguinomycins have been studied by Gademann and coworkers in anti-cancer contexts and extensively modified to improve their IC50's and on-target selectivities.[36] Macrocyclic polyketide natural products have been synthesized effectively using Prins cyclizations, facilitating the synthesis of anti-cancer drug rapamycin (trade names: Sirolimus, Rapamune, Fyarro) and anti-cancer drug candidate bryostatin 1.[37] As this work is primarily concerned with the panowamycin natural products, the relevant biosynthesis to consider is that of precursor NFAT-133 (Figure 2) and further discussion about the biological activity of this family of natural products will be given in section 2.1.3.

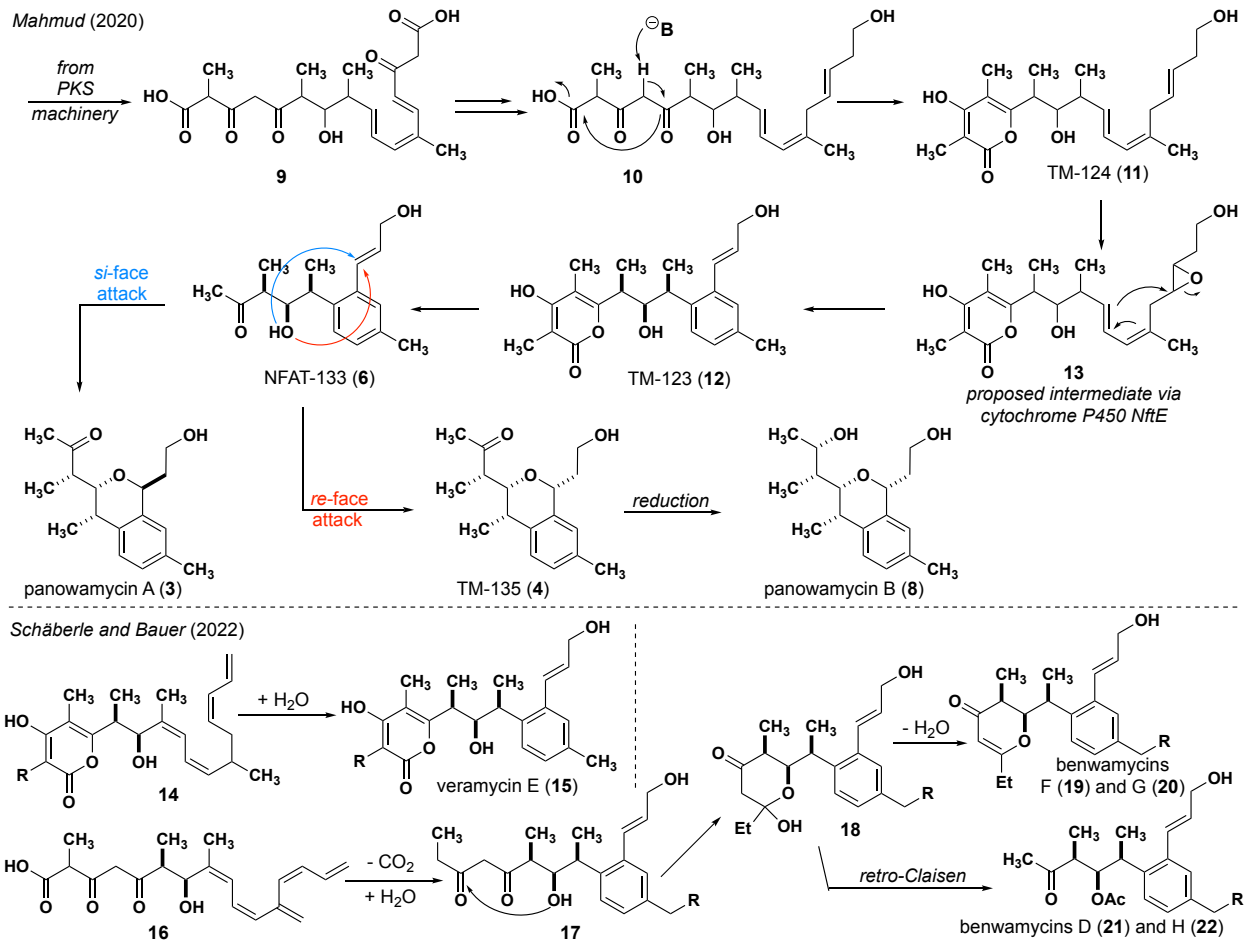


Figure 2. Biosynthesis of NFAT-133 and panowamycin A *via* polyketide synthase (PKS), modified from Mahmud and coworkers and Schäberle and Bauer et al.[22,28]

In 2020 Mahmud and coworkers sequenced the genome of *streptomyces pactum* ATCC 27456 and identified the biosynthetic gene cluster of NFAT-133.[28] This gene cluster contains a noncanonical, highly disordered collection of type I modular polyketide synthase (PKS) genes which are responsible for the assembly of the aromatic substructure of NFAT-133 and related products. Per this report, NFAT-133 is synthesized *via* PKS machinery going through intermediate **9** (Figure 2). After several biochemical transformations, **10** is thought to be deprotonated and the corresponding enolate undergoes 1,6-nucleophilic attack with the carbonyl oxygen as nucleophile. This intermediate is then oxidized to form the more conjugated TM-124 (**11**). Mahmud posits that this substrate is epoxidized by cytochrome P450

to afford **12**, which then cyclizes and is oxidized to TM-123 (**13**), featuring the cinnamyl substructure found in many of the natural products in this family. Octaketide **13** (TM-123) is then degraded to heptaketide NFAT-133 by losing the 4-hydroxypyran-2-one substructure found in the benwamycins and veramycin natural products. In their later work, Mahmud and coworkers isolate panowamycin A (**3**) and TM-135 (**4**).[29] These epimeric structures differ only at C3, and therefore it is posited that they are formed by an unselective alkoxylation across the styrene alkene under biological conditions, but the involvement of enzymes cannot be ruled out. Stereoselective reduction of **4** to panowamycin B (**8**) is typically governed by ketoreductase domains within the PKS machinery.[28]

The biosynthesis of the veramycin and benwamycin natural products was also studied by Schäberle and Bauer in 2022, where they propose that **14**, a dehydrated form of TM-124, is hydrated and cyclizes to form veramycin E (**15**). Biosynthetic intermediate **16** is also suggested as the precursor to the benwamycins *via* a decarboxylative pathway to **17**. A 1,6-cyclization produces **18** which can then dehydrate to form benwamycins F (**19**) and G (**20**) or undergo a retro-Claisen reaction to form benwamycins D (**21**) and H (**22**) (Figure 2). In addition to their in depth studies of the biosynthesis of these natural products, Schäberle and Bauer et al. also suggest that some of the isolated natural products in the NFAT-133 family may be generated non-enzymatically as a result of the conditions used in isolation and purification. For example, the posited retro-Claisen can occur under only slightly acidic conditions (i.e. slightly acidic silanols found in silica-based purification).

2.1.2 Isolation and structural elucidation of NFAT-133 and relevant *Streptomyces* metabolite polyketide natural products

The family of polyketide natural products associated with NFAT-133 is an actively growing field (Figure 3). Since its original isolation and elucidation in 1995 by Burres and coworkers,[38] NFAT-133 (**6**) has been isolated several times, alongside new and interesting natural products such as the panowamycins

(2012),[24] the benwamycins (2020),[25] the Mahmud "TM" isolates (2020 and 2021),[28,29] and the most recent veramycins (2022).[22] All members of this family contain an aromatic substructure unique among polyketide natural products and feature a stereotriad stemming from the aryl ring, with the exception of veramycin G (**40**), where an apparent dehydration has ablated two of the stereocenters.

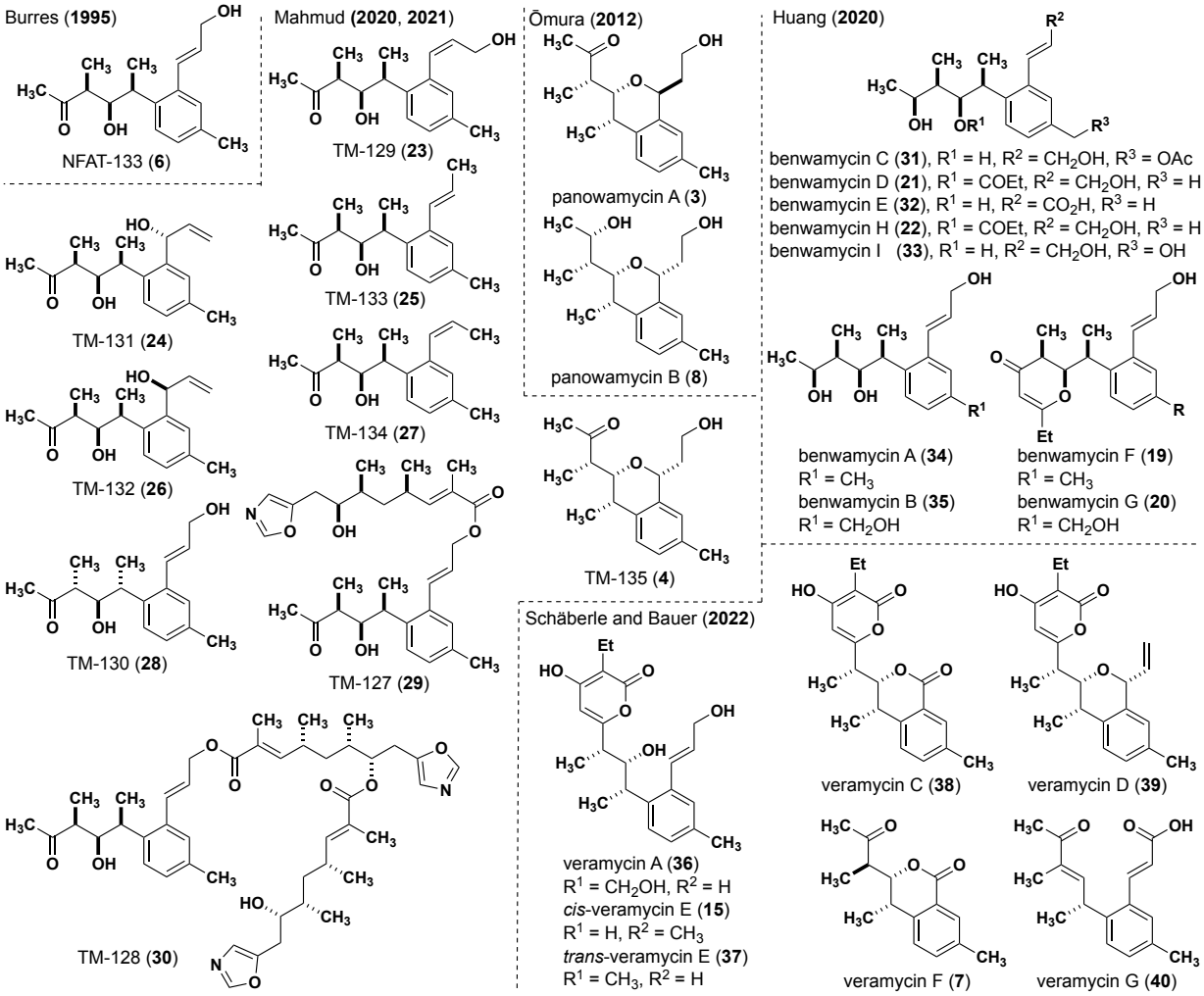


Figure 3. Polyketide natural products related to NFAT-133

For all of these natural products, traditional methods of isolation and structural elucidation have been employed. Fermentation of each respective microbial strain was performed, organic extracts were analyzed, and each component was separated by sequential chromatographic methods. Purified compounds were then subjected to infrared spectroscopy (IR), mass spectrometry (MS) and several

nuclear magnetic resonance (NMR) experiments (NOESY, ROESY, HMBC, HSQC, etc.). In one case, circular dichroism (CD) measurements were paired with predictive computational CD to propose absolute stereochemistry.[29] In another case, Mosher's acid was employed to suggest relative stereochemistry through chiral anisotropy.[27,39] Prior to the subject matter reported in our 2022 publication and this dissertation chapter, the only examples of total synthesis as a stereochemical and structural elucidation method were for NFAT-133, TM-123, and veramycin A.[22,26]

NFAT-133 was the first isolated, is the most frequently observed from *streptomyces* fermentations, and has been proposed as the biological precursor for many of these compounds. Therefore it was of high importance to establish the relative and absolute stereochemistry of **6** to better understand and predict the other natural products in the family (Figure 4A). Burres and coworkers employed HMBC and HMQC NMR experiments to determine the structure of NFAT-133, reporting a *E*-styrene and the characteristic stereotriad (unassigned relative configuration). Another isolation and structural assignment was published by Kulkarni and coworkers in 2011, still leaving the stereotriad unconfigured, but reassigning the *E*-styrene to the *Z*-styrene.[40] Over a decade after the original isolation in 2016, Igarashi and coworkers took to the challenge of identifying the relative configuration by esterifying Mosher's acid with **42** and assigning the natural product's stereotriad as 10*R*, 11*R*, 12*S* with additional evidence provided by NOESY experiments and *J*-coupling analysis.[27] They also reaffirmed Burres' original assignment of the *E*-styrene. This stereochemical assignment opened the door for a total synthesis of the molecule, which was completed by Ogura and coworkers in 2019.[26] In this publication, they synthesize the reported structure by asymmetric aldol reaction and determine by NMR spectroscopy that the relative configuration was misassigned. They then synthesized an alternate epimer at C10 which matched the ^{1}H and ^{13}C NMR spectra as well as the optical rotation measurements; with this total synthesis, NFAT-133 was reassigned to 10*S*, 11*R*, 12*S* (**6**). Notably, due to the matching optical rotation value obtained by this synthesis, it is

likely that the other members of the NFAT-133 derived natural product family would also contain that relative and absolute configuration barring any epimerizations.

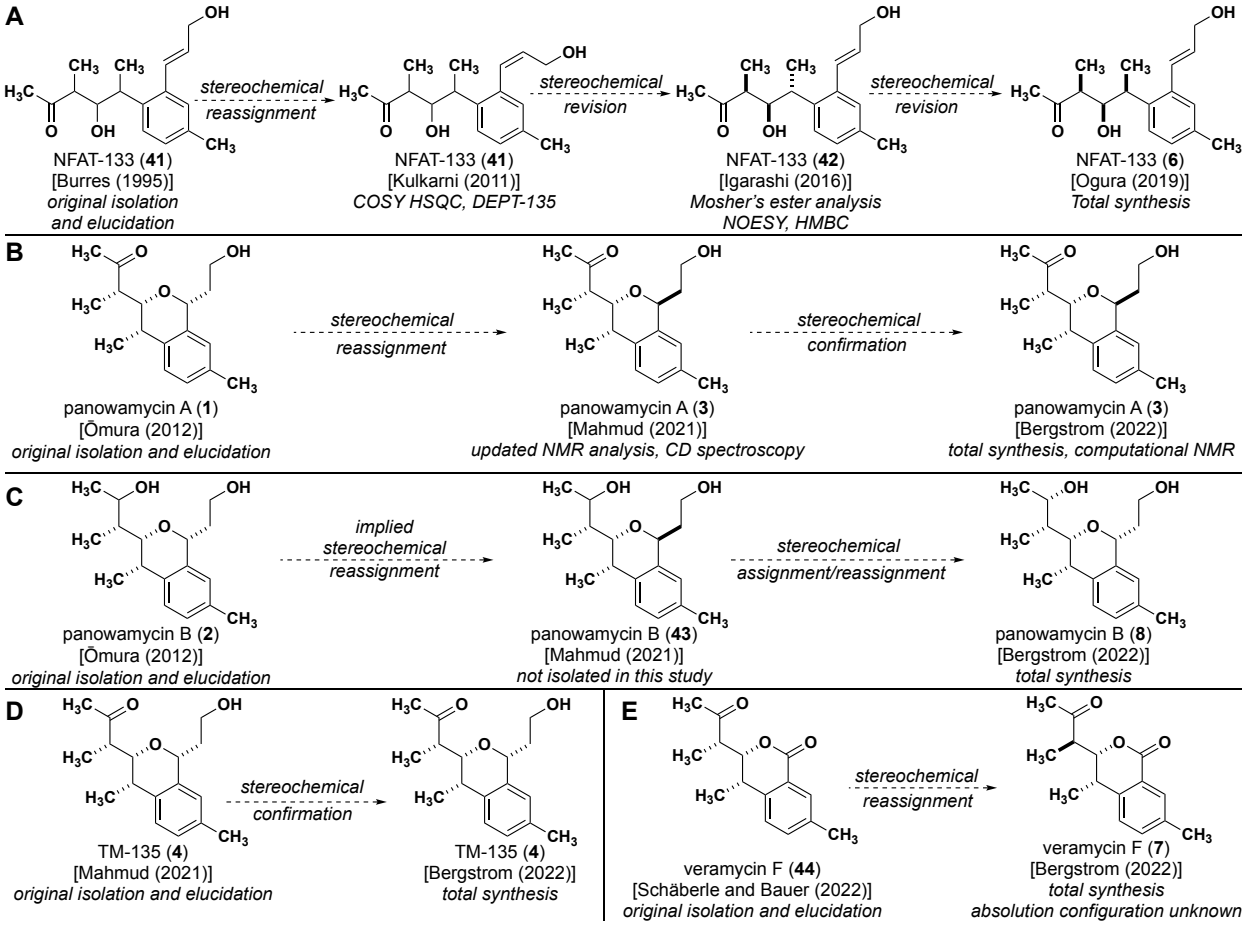


Figure 4. Chronology of isolation and structural/stereochemical assignment/reassignment of NFAT-133 and related natural products

Prior to the reports by Igarashi and Ogura, Ōmura and coworkers isolated a new group of NFAT-133 related natural products. Panowamycin A and B were isolated from *streptomyces sp.* K07-0010 and structurally elucidated using ROESY and HMBC experiments to propose the relative stereochemistry of these heterocycles, although configuration C13 of panowamycin B (**2**) was not determined in this work (Figure 4, B and C). Mahmud would later isolate panowamycin A (alongside NFAT-133); measuring NMR spectra in a different deuterated solvent (i.e. MeOD) made the splitting patterns more clear and

allowed the authors to make a more definitive assessment of relative stereochemistry (Figure 4B). With this updated analysis, the structure of panowamycin A was reassigned to **3**, featuring the alkyl sidechain in the 3*S* configuration. In this work, although panowamycin B was not isolated, they implicitly draw the structure of panowamycin B as having the same 3*S* alkyl sidechain as **43** (Figure 4C). The closely related natural product TM-135 (**4**) was also isolated in this study and by the same NMR spectroscopic techniques was elucidated to be the originally proposed structure of panowamycin A with a 3*R* configuration (Figure 4D). When the total syntheses of panowamcyin A, B, and TM-135 were completed (discussed in section 2.8 in this dissertation), it was confirmed that Mahmud's reassigned structure for panowamycin A **3** and assigned structure for TM-135 (**4**) were correct. Computational NMR was used to suggest the configuration of panowamycin A reaching the same conclusion as Mahmud's updated NMR spectral analysis (these studies were contemporaneous with each other). Furthermore, the absolute and relative configuration of panowamycin B (**8**) was also assigned in this work, discovering that **8** is derived from TM-135 rather than panowamycin A, contrary to Mahmud's implied assignment. Finally, in 2022 Schäberle and Bauer reported the discovery of the natural product veramycin F, which closely resembles the panowamycins but lacks the alkyl C3 sidechain (Figure 4E). This compound was synthesized (reported in section 2.8.4 of this dissertation) and it was observed that the NMR spectra were incongruent, suggesting a misassignment. As such, related isomer **7** was synthesized, which proved to be incongruent with the NMR spectra for the natural material, reassigning the structure of veramycin F.

2.1.3 Biological activity of NFAT-133 and relevant natural products

The primary focus of natural product isolation and structure elucidation is to determine the biological activity of these isolates for applications in human health and medicine. Microbial secondary metabolites (e.g. polyketide natural products) are often created by an organism in response to exogenous stress. While the exact biological purpose of a given metabolite may not be known, it is generally understood that nature

produces structurally complex and biologically active substances as a response to these external circumstances as a survival mechanism for the organism. Therefore, many of these compounds and/or derivatives thereof are also suitable for addressing stressors in human biology as well.

The natural product family related to NFAT-133 has not seen extensive study. Only 8 publications from 7 different investigators report any evaluation of biological properties for these compounds (Table 1). Burres' original isolation, as the name suggests, was primarily concerned with testing microbial metabolites for activity in inhibiting the Nuclear Factor of Activated T-Cells (NFAT) transcription factor.[38] This application leads to increased understanding in the signaling pathways that are involved with immune response, leading to better treatments of transplant rejection and autoimmune diseases. In their 1995 publication, Burres and coworkers produced NFAT-68 and NFAT-133 through fermentation of streptomyces strains *sp.* AB 2199J-103 and *sp.* AB 2184C-502, respectively. They then sent these compounds into an NFAT assay, calcineurin phosphatase activity assay, mixed lymphocyte reaction assay, and β-galactosidase assay, determining that NFAT-133 was effective in inhibiting NFAT-dependent transcription at 0.70±0.05μg/mL concentration, without toxicity to cells. Similarly, they observed inhibition of mixed lymphocyte reaction at 12±5 μg/mL concentration, which is an effective correlate for graft rejection and immunosuppression activity.

In 2011, Kulkarni-Almeida and coworkers isolated NFAT-133 from *sp.* PM0324667 and tested for antidiabetic activity.[40] The compound was screened in an assay to determine glucose uptake induction in insulin stimulated differentiated L6 myotubes, demonstrating increased glucose uptake activity at 3μg/mL, comparable to the current antidiabetic medication rosiglitazone (10.75μg/mL) in the same experiment. Furthermore, NFAT-133 did not significantly affect PPAR- γ activity (a key mechanism in glucose uptake) in a PPAR- γ luciferase assay at concentrations as high as 100μM, whereas rosiglitazone

is a full agonist at 1μM. This demonstrates that the antidiabetic activity of NFAT-133 is the result of a distinct mechanism from that of a current medication.

Ōmura and coworkers were next to isolate NFAT-133 (**6**) in 2012, employing it in an anti-trypanosomal activity assay as part of their campaign to discover new treatments for tropical diseases.[24] NFAT-133 was evaluated using *Trypanosoma brucei brucei* GUTat 3.1 strain, showing activity at 2.78μg/mL, which is comparable to current clinical treatments for trypanosomiasis. However, against MRC-5 cell lines, **6** exhibited significant cytotoxicity (21 μg/mL).

Mahmud and coworkers isolated NFAT-133 (**6**) in 2020; in this work they were primarily concerned with identifying its biological synthesis (*vide supra*).[28] One year later, the authors published further efforts with this system, isolating **6** in addition to many other related polyketide natural products.[29] In this follow-up publication, Mahmud and coworkers tested NFAT-133 (**6**), TM-132 (**26**), and TM-135 (**4**) for anti-bacterial activity, demonstrating no effect with *Staphylococcus aureus* ATCC 12600, *Bacillus subtilis* ATCC 6051, *Escherichia coli* ATCC 11775, and *Pseudomonas aeruginosa* ATCC 9721. Cytotoxicity was also assessed, showing that **6**, **26**, **4**, and panowamycin A are not toxic to cancer cell lines (i.e. RAW264.7, HeLa, NCI- H460, and MCF-7) up to 50μM. Nitric oxide production in the RAW264.7 cell line was weakly reduced when exposed to **6**, **26**, **4**, and **3** in a dose-dependent manner.

Panowamycin A (**3**) and B (**8**) were first isolated in 2012 by Ōmura and coworkers as part of their program for discovering new treatments for tropical diseases.[24] In this work they were concerned with Human African Trypanosomiasis (i.e. sleeping sickness) and tested **3**, and **8** against *Trypanosoma brucei brucei* GUTat 3.1, observing good activity at low IC_{50} 0.4 and 3.3 μg/mL, respectively. While this activity is comparable or better than current medications for sleeping sickness (i.e. eflornithine and suramin), **3** and **8** were also tested for cytotoxicity against the MRC-5 cell line, demonstrating fairly potent cytotoxicity

and therefore giving the compounds a poor selectivity index. Mahmud was next to isolate panowamycin A and, as mentioned above, the experiments for biological activity did not exhibit favorable properties.

Expanding the class of NFAT-133 related polyketide natural products, the benwamycin A-G were isolated by Huang and coworkers in 2020 from a fermentation of *Streptomyces sp.* KIB-H1471.[25] These new natural products feature the same stereotriad and styrene functionalities present in NFAT-133 and the authors were interested in comparing the biological activity of these new structures to **6**. Hence, with the previously described T-cell production inhibition and glucose uptake increase assays, Huang and coworkers tested benwamycins A-G for T-cell proliferation *via* flow cytometry with carboxyfluorescein diacetate succinimidyl ester (CFSE) labeling, finding that benwamycins **35** and **19** were effective inhibitors at 14.3 and 12.5 μM concentration without obvious cytotoxicity for naïve human T-cells. In their adipocyte-based glucose uptake assay, benwamycins **31** and **19** weakly increased glucose uptake in mature 3T3-L1 adipocytes. Other benwamycin natural products did not show significant activity, but it is noted by Huang that there are potential discrepancies between mouse and human assays for T-cell proliferation for NFAT-133, suggesting a selective activity in human cells.

Veramycins A-G were isolated Schäberle and Bauer in 2022 as part of Sanofi's profiling program for potentially anti-diabetic microbial metabolites.[22] These compounds share many of the same features as the other natural products in this family (Figure 3), and therefore they were studied in a similar manner to Kulkarni-Almeida and coworkers. Cellular glucose uptake was measured in an assay using rat skeletal muscle cell line (L6 GLUT4 AS160) that were modified to have a higher insulin sensitivity compared to Kulkarni-Almeida's work (5nM *versus* 200nM). TM-123 was isolated in this work and had no effect on insulin uptake, while NFAT-133 and veramycin A (**36**) both demonstrate a concentration-dependent increase deoxyglucose uptake.

Table 1. Isolation and Biological activity assessed for NFAT-133 related natural products

natural product	isolation	microorganism (*streptomyces*)	biological activity
NFAT-133 (**6**)	Burres (1995)[38]	*sp.* AB 2184C-502	blocks nuclear factor of activated T-cells (NFAT)-dependent transcription, suppresses interleukin-2 expression and T-cell proliferation
	Kulkarni-Almeida (2011)[40]	*sp.* PM0324667	anti-diabetic, increases glucose uptake in L6 myotubes
	Ōmura (2012)[24]	*sp.* K07-0010	anti-trypanosomiasis
	Igarashi (2016)[27]	*karnatakensis* NBRC 13051	NA
	Mahmud (2020, 2021)[28,29]	*pactum* ATCC 27456	nitric oxide reduction in RAW246.7 cells
panowamycin A (**3**)	Ōmura (2012)[24]	*sp.* K07-0010	anti-trypanosomiasis
	Mahmud (2020, 2021)[28,29]	*pactum* ATCC 27456	nitric oxide reduction in RAW246.7 cells
panowamycin B (**8**)	Ōmura (2012)[24]	*sp.* K07-0010	anti-trypanosomiasis
benwamycins	Huang (2020)[25]	*sp.* KIB-H1471	inhibits T-cell proliferation, enhanced insulin-stimulated glucose uptake
veramycins	Schäberle (2022)[22]	*sp.* ST157608	anti-diabetic
TM-132 (**26**) and 135 (**4**)	Mahmud (2020, 2021)[28,29]	*pactum* ATCC 27456	nitric oxide reduction in RAW246.7 cells

As evidenced by the relatively limited exploration of the biological activity of these natural products, despite their presence across several different strains of *streptomyces*, it is important to establish efficient and modular syntheses of these natural products in order to determine their role in human biology. Robust, adaptable, and scalable synthetic protocols to create these scaffolds enable structural modifications to be made for structure activity relationships to be tested. Often, the limited quantity of a given natural product (frequently less than 5 mg) limits the extent to which one or more biological tests can be performed. Total synthesis offers a consistent way to generate a functional quantity of the natural

substance, in addition to structural analogues. In this way, the route to new pharmaceutical compounds and new eras in human health is paved with natural product synthesis.

2.1.4 Retrosynthetic strategies for panowamycins

To date, very few methods exist to construct isochromans stereoselectively (see chapter 1 of this dissertation, section 1.1.1).[23,41,42] Asymmetric variants of the oxa-Pictet Spengler reaction have achieved high levels of enantioselectivity at the isochroman C3.[43,44] Carbene insertion reactions into ether C–H bonds have been shown to be powerful tools in constructing complex chiral molecules, with foundational intramolecular work by Doyle and Davies,[45–47] and intermolecular work by Davies.[48,49] Previous work to construct chroman scaffolds with acceptor-substituted carbenes have the liability of competing Stevens rearrangement.[50,51] Recently, our lab has demonstrated that donor/donor rhodium carbenes offer excellent reactivity, chemo-, regio-, diastereo-, and enantioselectivity when applied to the synthesis of isochromans by intramolecular C–H insertion reactions.[52] Specifically, our method provides a single *cis*-diastereomer at C10 and C11 in all cases with high enantioselectivity and without competing Stevens rearrangement. As such, this method provides an excellent strategy for synthesizing the panowamycins and offers some benefits over traditional approaches in polyketide natural products synthesis; most notably, it avoids the use of chiral auxiliaries (Figure 5).

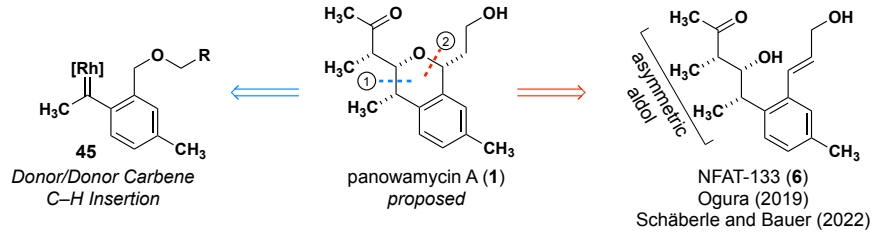


Figure 5. Donor/donor carbene C–H insertion strategy to form panowamycins *versus* chiral auxiliary strategy

Based on the substrate scope of our previous work synthesizing isochromans, two strategies were initially apparent (Figure 6). By using the three-center diastereoselective C–H insertion reaction developed by Prof. Mingchun Gao (see section 1.3.7 of this dissertation), the construction of the isochroman ring of **47** would be complete in a single step and feature all of the cyclic stereogenic centers. With regards to step-economy and novelty, this was the most attractive strategy. However, for an enantioselective synthesis, the stereochemistry at C3 would have to be set prior to the insertion step, which would require an asymmetric aldol or a stereoselective reduction to accomplish. Additionally, there could be some match/mismatch complications in the insertion step if the enantiomer of catalyst required for the proposed structure of panowamycin A or B was less stereochemically compatible with the enantiomer of starting material.

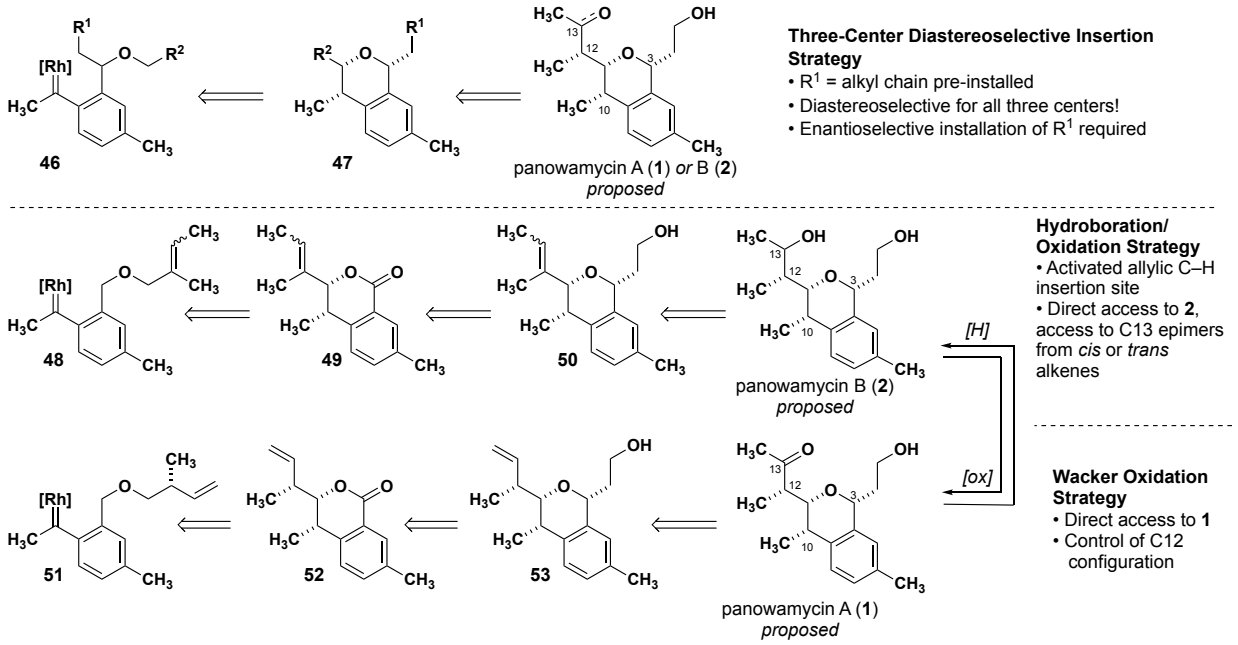


Figure 6. Retrosynthetic strategies for C–H insertion with methyl/aryl rhodium carbenes

The second strategy was to use the two-center diastereoselective strategy and install the C3 alkyl chain at a later point. Allylic insertion sites were successful substrates in our previous work, often giving good reactivity, clean reactions, and high degrees of enantioselectivity. A vinyl substituted isochroman **50**

would also serve as a useful functional group handle for further transformations to achieve the secondary alcohol of **2** via hydroboration/oxidation. Furthermore, because the relative configuration of the this secondary alcohol at C13 was unknown in the original isolation publication, we would be able to access either epimer at C13 by changing the isomer of alkene. With the number of available borane reagents with varying steric and stereochemical environments, we were confident that we would be able to control the diastereoselectivity of the hydroboration/oxidation to achieve the desired C12 isomer. As a second strategy for the two-center diastereoselective C–H insertion method, it would also be possible to insert into a homoallylic site (**51**). If we were unable to control the stereoselectivity in the hydroboration/oxidation-based strategy, this substrate would allow for control of the absolute configuration at C12. After construction of the isochroman by C–H insertion, the C3 alkyl sidechain would be installed and the pendant terminal olefin would undergo a Wacker oxidation to afford the ketone for panowamycin A (**1**). Similar to the three-center diastereoselective strategy, however, there is the possibility of match/mismatch interactions between the substrate and the chiral catalyst. Additionally, C–H insertion into relatively unactivated alkyl centers with adjacent branching is not precedented for having high reactivity nor selectivity, making this the more challenging strategy. For both of these two-center diastereoselective strategies, oxidation of the benzylic position would provide an isochromanone (**49** or **52**) that could be further functionalized to install the C3 sidechain (**50** or **53**). Interconversion between **1** and **2** could be achieved in a straightforward manner by changing the oxidation state of the secondary alcohol at C13. Stereoselective reduction of **1** would afford either isomer of **2**, and a protection/oxidation/deprotection sequence would give **1** from **2**.

Notably, all three of these retrosynthetic approaches make use of aryl/methyl carbenes. Previous work in our lab with this type of carbene showed poor enantioselectivity when C–H insertion occurred at a benzylic site (i.e. 60:40er, see section 1.3.1 of this dissertation), therefore posing a unique challenge in the

synthesis.[52] While aryl/alkyl carbenes have been used in other C–H insertion reactions, to date there have been no reports that are enantioselective.[53] The three-center diastereoselective route appeared to be the most interesting and step-economic, the two-center stereoselective hydroboration/oxidation route the second most attractive, and finally the Wacker oxidation route presented the most challenges. In the following section, the exploration of these routes will be discussed. The synthetic target was originally the proposed structure of panowamycin A (**1**) and B (**2**), but as was discussed in section 2.1.2, it was discovered that panowamycin A was misassigned. As the narrative surrounding these natural products changed, the synthesis adapted, demonstrating the robustness of the methodology and the synthetic strategy.

2.2 Three-center diastereoselective C–H insertion route

Construction of the substrate required for the three-center diastereoselective C–H insertion route was attempted starting from commercially available benzoic acid **54**, which would also serve as the starting material for all other routes (Figure 7). This material was reduced with borane dimethyl sulfide complex; reduction of this acid with excess lithium aluminum hydride (2 equiv.) was found to produce a sizable quantity of the debrominated benzyl alcohol, which was inseparable from the desired 2-bromo-5-methylbenzyl alcohol. This side reaction is in accordance with the literature for similar substrates.[54,55] Oxidation of the benzyl alcohol was performed with Dess-Martin periodinane, affording aldehyde **55** in 92% yield over two steps. An aldol reaction with ethyl acetate and lithium diisopropylamide proceeded in 68% yield to the racemic beta-hydroxy ester, which was then reduced to diol **57** with lithium aluminum hydride in 95% yield. This reaction could be adapted to the asymmetric variation at a later time, if the route was successful, by using Evans aldol conditions.[56] Selective protection of the primary alcohol with TBDPS-chloride then afforded **58**, which could be sent into the typical alkylation conditions optimized

for the methodology used in section 1.2 of this dissertation (i.e. NaH in THF at room temperature with an alkyl bromide electrophile).

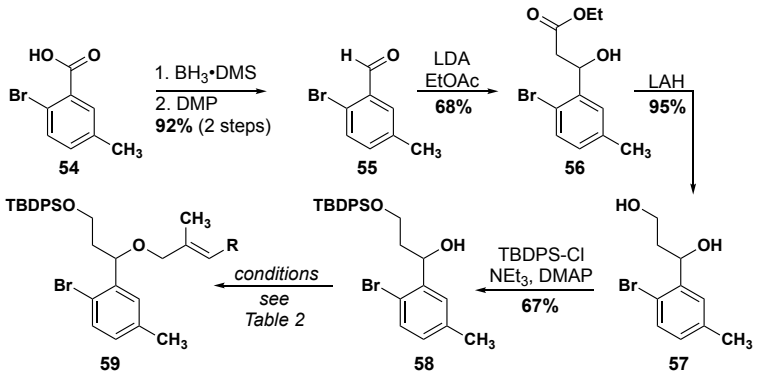


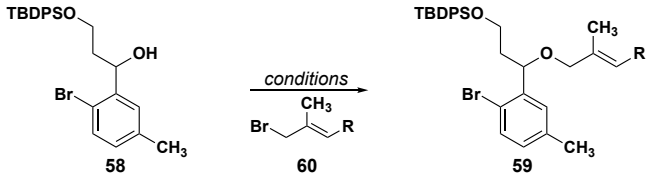
Figure 7. Synthesis of benzylic-substituted allylic/benzylic ether

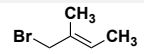
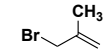
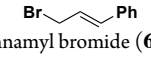
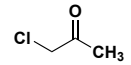
2.2.1 Alkylation optimization

Alkylation reactions with hindered secondary alcohol **58** were difficult to achieve. Previously optimized conditions produced only trace product and were unable to be separated from unidentified byproducts in the reaction mixture (Table 2, entry 1). Importantly, the next step in the synthesis is water sensitive lithium-halogen exchange, so it was vital to obtain ether **61** in high purity. It is also worthwhile to note that reactions with tiglyl bromide (**61**) contained significantly more unidentifiable byproducts than with methallyl (**62**) and cinnamyl bromides (**63**). **61** was synthesized by lithium aluminum hydride reduction of methyl tiglate and then brominated with phosphorous tribromide. Due to the relative instability of this allyl electrophile it was used without further purification, which may have produced unwanted byproducts in this alkylation. Entry 2 shows conversion similar to that of entry 1 and entry three shows no reaction with **63**. Increasing the temperature of the reaction (entry 4) and adding sodium chelator 15-crown-5 (entry 5) had no comparative benefit over entry 1 and changing the solvent to dimethylformamide (entry 6) gave no conversion of starting material. Screening for a more effective base in this reaction, potassium hexamethyldisilazane (KHMDS) and potassium *tert*-butoxide were explored.

At cryogenic temperatures, KHMDS with **61** produced an appreciable amount of the desired ether **59**, but unfortunately the mixture was not sufficiently purifiable (entry 7). Meanwhile the reaction with **62** and KHMDS cleanly afforded **59** in 75% yield. The reaction conditions with potassium *tert*-butoxide in THF at room temperature produced comparable results with tiglyl and methallyl electrophiles while having the added benefit of being operationally much more simple and affordable (entries 9-10).

Table 2. Alkylation optimization



entry	base/condition/additive	electrophile	result
1	NaH/THF/rt	 tiglyl bromide (**61**)	trace product, unable to purify
2	NaH/THF/rt	 methallyl bromide (**62**)	trace product, unable to purify
3	NaH/THF/rt	 cinnamyl bromide (**63**)	no reaction
4	NaH/THF/66 °C	**61**	trace product, intractable mixture
5	NaH/THF/rt/15-crown-5	**61**	trace product, intractable mixture
6	NaH/DMF/rt	**61**	no reaction
7	KHMDS/THF/-78 °C to rt	**61**	~72% yield, unable to purify
8	KHMDS/THF/-78 °C to rt	**62**	75% yield
9	*t*-BuOK/THF/rt	**61**	some product, unable to purify
10	*t*-BuOK/THF/rt	**62**	69% yield
11	*t*-BuOK/THF/rt	 chloroacetone (**64**)	no reaction

While **62** was used primarily to screen conditions with a pure and commercially available allyl bromide reagent, the resultant substrate would not directly furnish the desired intermediate for hydroboration oxidation. It was conceived, however, that the hydroboration/oxidation product **67** could be oxidized to aldehyde **68** and attacked with methyllithium in a stereoselective manner to product panowamycin B (Figure 8). Alkylation with **64** was also attempted, which could be later converted to the desired alkene

via Wittig reaction, but no reaction was observed (Table 2, entry 11, and Figure 8). With efficient and facile access to **59** using potassium *tert*-butoxide and **62** alkylation conditions, the substrate was carried further into the synthesis to screen ketone formation conditions.

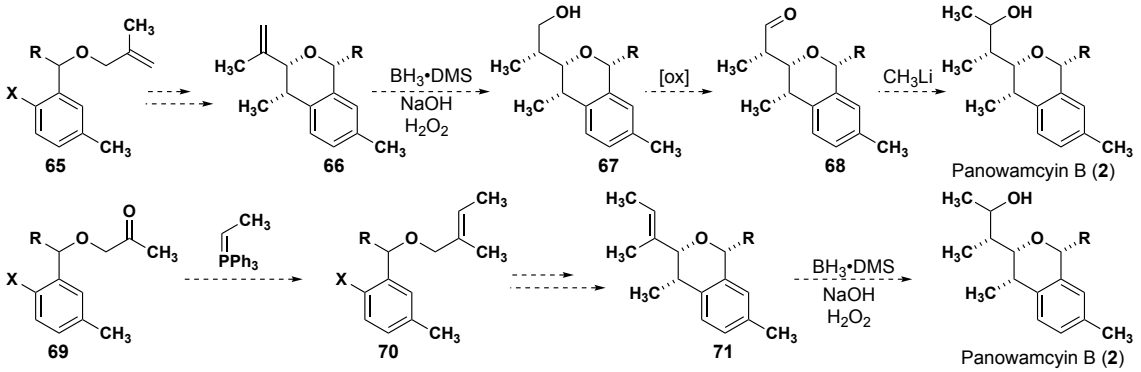


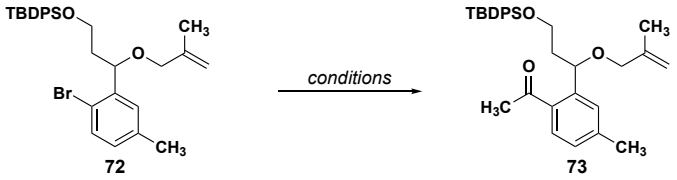
Figure 8. Potential post-alkylation conversion of methallyl and chloroacetyl derivatives to useful intermediates for panowamycin synthesis

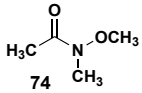
2.2.2 Ketone synthesis optimization

As detailed in section 1.2.2 of this dissertation, ketone formation can be difficult with *ortho*-substituted arenes; this proved to be true as well for this di-substituted benzylic ether. Previously optimized conditions for lithium halogen exchange and attack by the aryllithium nucleophile on a Weinreb amide electrophile were attempted, observing no consumption of the aryl bromide **59** (Table 3, entry 1). Magnesium-halogen exchange was similarly unsuccessful (entry 2). *tert*-Butyllithium was employed in hopes of higher reactivity in lithium halogen exchange (entries 3-5). In these cases, full consumption of **59** was observed (as evidenced by recovery of the proto-debrominated product), but this hindered nucleophile was not suitable for additions to Weinreb amides (entry 3) even at elevated temperature (entry 4), nor with acyl chloride electrophile **75** (entry 5). Another reasonable explanation for the lack of ketone formation is that the aryl lithiate, once formed, will only go on to deprotonate the suitably acidic *alpha*-proton of the acyl electrophile, generating only proto-debrominated product. As will

be discussed later in this chapter, this phenomenon will continue to be an inconvenience in the synthesis, resulting in low yields for the requisite acetophenone intermediates.

Table 3. Ketone synthesis optimization



entry	condition	electrophile	result
1	*n*-BuLi/THF/-78 °C to rt	 **74**	lithium-halogen exchange unsuccessful
2	Mg°/Et_2O/-78 °C to rt	**74**	magnesium-halogen exchange unsuccessful
3	*t*-BuLi/THF/-78 °C to rt	**74**	complete lithiation, no addition
4	*t*-BuLi/THF/-78 to 60 °C	**74**	complete lithiation, no addition
5	*t*-BuLi/THF/-78 °C to rt	 **75**	complete lithiation, no addition

The significant issues encountered with the three-center diastereoselective route highlight the difficulties associated with synthesizing sterically congested substrates such as these. After the above optimization attempts, it was therefore decided that subsequent transformations would be similarly fraught with issues related to the steric encumbrance at the benzylic position. Contemporaneously, the synthetic efforts associated with the two-center diastereoselective route were gaining momentum and the three-center strategy was abandoned. Any future work with synthesizing similar substrates for methodology or total synthesis will require new methods and different synthetic strategies to circumvent these issues.

2.3 Hydroboration/Oxidation Strategy: Tiglyl/Angelyl Route

Construction of the tiglyl and angelyl-derived substrates for the hydroboration/oxidation strategy was a much more straightforward process. Starting material **54** was reduced in quantitative yield with borane

dimethyl sulfide complex and the resulting benzyl alcohol was brominated with phosphorous tribromide in 99% yield. Tiglyl and angelyl alcohols (*E* and *Z*-**77**) were synthesized from their corresponding methyl tiglate or angelate in excellent yields. Luche conditions were also attempted, but because of the volatility of the allyl alcohols, purification was difficult.[57] A simple lithium aluminum hydride reduction of the esters, followed by the Fieser workup,[58] proved to be a facile protocol and the volatile allyl alcohols were afforded in near quantitative yields, isolated as a solution in diethyl ether. This solution could then be gently concentrated *in vacuo* without heating and not below 160 torr, producing 20-50% by weight solutions of *E* and *Z*-**77** in diethyl ether (measured by NMR spectroscopy and calculated wt/wt percentage), which were then used immediately. Alkylations of these allyl alcohols with benzyl bromide **78** under typical conditions afforded the allyl benzyl ethers in excellent yields. A drawback of this method is that the residual methanol produced in the reduction (or ethanol of the ethyl tiglate/angelate was used) will go on to alkylate **78** in the following reaction. Usually this byproduct is inseparable from **79**, but in the next step **80** can be isolated without these byproducts. While lithium halogen exchange with *n*-butyllithium for these substrates was much more easily achieved, addition to Weinreb acetamide **74** was not without issue, as mentioned above. Due to the basicity of the aryllithium species generated *in situ*, the acidic *alpha*-proton of the acetamide is deprotonated in a competitive side reaction to the desired addition to the amide carbonyl. For this reason, the yields of acetophenones **80** are restricted to <50%, but due to the ease of operation and separation of the two products, no better yielding synthesis was pursued for these substrates. Condensation with hydrazine was effective at room temperature to achieve the acetophenone hydrazones in high yield. This is in marked difference to the synthesis of benzophenone hydrazones discussed in section 1.5 of this dissertation, where elevated temperatures are required. With a reliable and facile synthesis of the hydrazone intermediate **81** established, optimization of the key bond-forming C–H insertion reaction attempted.

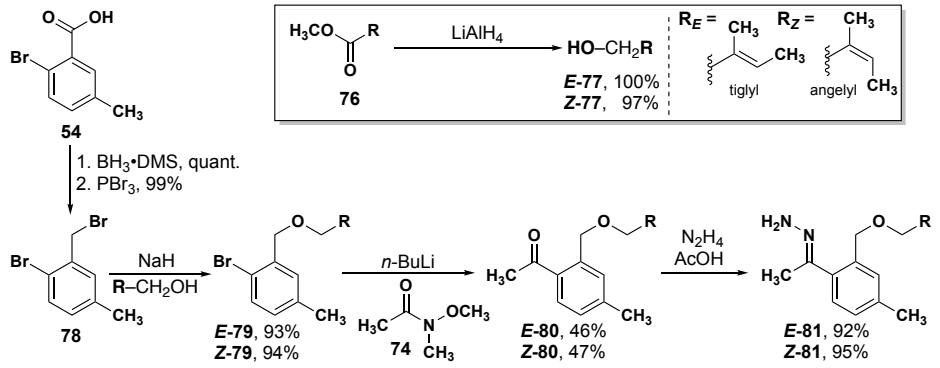


Figure 9. Synthesis of tiglyl and angelyl acetophenone hydrazone intermediates

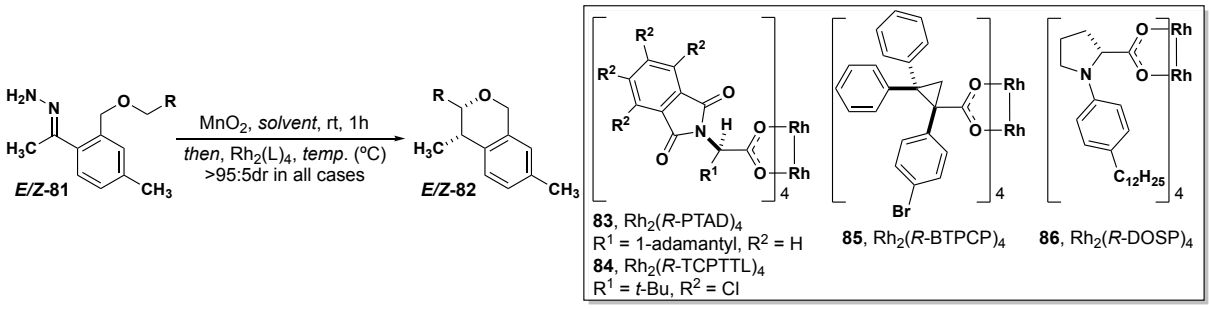
2.3.1 C–H insertion reaction optimization

As described in section 1.3.1 of this dissertation, the only example of an acetophenone-derived donor/donor carbene using a chiral dirhodium carboxylate catalyst was reported to have 60:40 er. Prior to this work, there were no acetophenone-derived carbene insertion reactions that were reported to be enantioselective. As such, we were satisfied to see that the pairing between a methyl/aryl carbene and an allylic insertion site resulting in an insertion reaction with a much higher degree of enantioselectivity (Table 4). For the tiglyl-derived substrate, optimal conditions were achieved at –20 °C in acetonitrile; with commercially available chiral dirhodium catalysts (i.e. Rh_2(*R*-PTAD)$_4$, Rh_2(*S*-TCPTTL)$_4$, and Rh_2(*R*-BTPCP)$_4$), enantioselectivity greater than 80:20 er was observed, with Rh_2(*S*-TCPTTL)$_4$ giving the best result at 93:7 er in 65% (entry 4). As was observed with our prior work synthesizing isochromans (see chapter 1 of this dissertation), >95:5 dr *cis* selectivity was observed in all cases for the tiglyl-derived isochroman product *E*-**82**.

For the angelyl-derived hydrazone *Z*-**81**, similar selectivity was observed (Table 4). Adopting the conditions from the tiglyl-derived substrate optimization, a desirable increase in yield was observed, but enantioselectivity was decreased (entry 7, 86:14 er). A reduction in temperature to –45 °C necessitated switching the solvent to DCM and improved yield and selectivity in this reaction (entry 8). Rh_2(*S*-

DOSP)$_4$ and Rh$_2$(*R*-BTPCP)$_4$ catalysts were also screened at this temperature, but were conducted in acetonitrile with partial freezing of the solvent, perhaps contributing to their lowered selectivity and low yield (entries 5 and 6). Given all of these observations, Rh$_2$(*R*-PTAD)$_4$ was screened in DCM at –78 °C, affording *E*-**82** in 80% yield and 93:7 er. While entry 8 gave a better yield of isochroman product with comparable enantioselectivity, –45 °C temperatures were inconvenient to maintain and entry 9 was operationally more convenient, even more so during scale-up.

Table 4. Screening conditions for stereoselective C–H insertion with a methyl/aryl carbene and an tiglyl and angelyl-derived insertion sites



entry	**81**	temp	solvent	catalyst[a]	er	yield (%)
1	*E*	-20	ACN	Rh$_2$(*R*-PTAD)$_4$	17:83	94
2	*E*	-20	ACN	Rh$_2$(*R*-PTAD)$_4$[b]	10:90	69
3	*E*	-20	ACN	Rh$_2$(*R*-BTPCP)$_4$	81:19	56
4	*E*	-20	ACN	Rh$_2$(*S*-TCPTTL)$_4$	93:7	65
5	*Z*	-45	ACN	Rh$_2$(*S*-DOSP)$_4$	16:84	59
6	*Z*	-45	ACN	Rh$_2$(*S*-BTPCP)$_4$	86:14	25
7	*Z*	-20	DCM	Rh$_2$(*S*-TCPTTL)$_4$	86:14	83
8	*Z*	-45	DCM	Rh$_2$(*S*-TCPTTL)$_4$	92:8	85
9	*Z*	-78	DCM	Rh$_2$(*R*-PTAD)$_4$[b]	7:93	79

[a] 0.1 mmol scale and 1 mol % catalyst loading, [b] 8 mmol scale and 0.07 mol % catalyst loading

Having discovered that C–H insertion reactions with methyl/aryl carbenes can be made to be enantioselective, the feasibility of the synthesis was established. In all cases with the above substrates,

>95:5 dr was observed, without competing Stevens rearrangement, and without any Bamford-Stevens elimination products.[59]

2.3.2 Synthesis of 12-*epi* panowamycin B, 13-*epi*-panowamcyin B, and TM-135

First, the tiglyl-derived substrate was oxidized with pyridinium chlorochromate to afford lactone **87**; a crystal structure of this intermediate was obtained and the relative and absolute stereochemistry of the molecule was in accordance with previously observed selectivity (Figure 10). In earlier efforts with this synthesis, attempts were made to add vinyl magnesium bromide to the lactone. This would enable a *double* hydroboration/oxidation to furnish both secondary and primary alcohols featured on **2** (not shown). However, addition to the lactone with a vinyl nucleophile was unsuccessful, showing only starting material in the unpurified NMR spectrum. Instead, the addition of the lithium enolate of *tert*-butyl acetate to the carbonyl was then achieved in a stereoselective fashion to give hemi acetal **88**. Facial selectivity was dictated by the lesser degree of steric hindrance on the *re*-face of the prochiral carbonyl. Reduction of **88** was also achieved in a stereoselective manner and under the same auspices: the Lewis acid coordinates to the hemi acetal hydroxyl and forms an oxocarbenium ion. A hydride can then be added to this electrophilic species, affording **89** as a single diastereomer. The literature precedent for this reaction used triethylsilane as the reducing agent, but stereoselectivity was not adequate (~70:30 dr). The increased steric bulk of the triisopropylsilane increased diastereoselectivity and the reaction was run at –40 °C overnight in a temperature-controlled refrigeration apparatus (Cryo-Cool™).

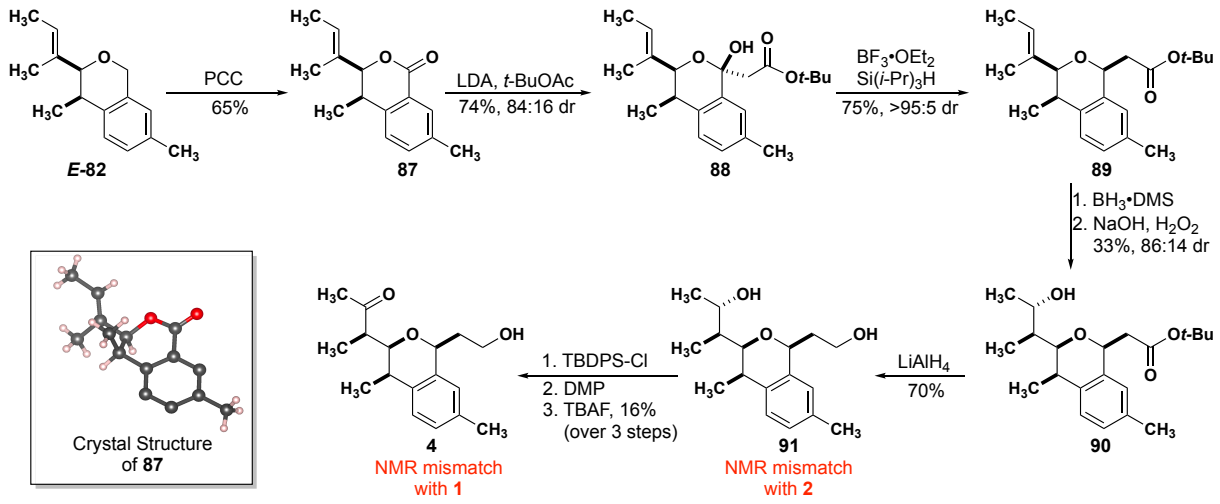
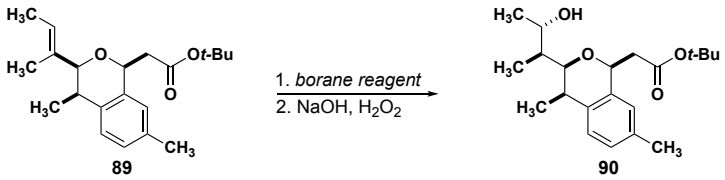


Figure 10. Tiglyl-derived synthesis of TM-135

With the desired stereogenic centers about the isochroman ring set in place, only changes in oxidation state of the substrate were required. Hydroboration/oxidation of the vinyl isochroman not only provides the desired change in oxidation, but generates the key vicinal stereogenic sites on the leftward sidechain. With a good diversity of available borane reagents, it was imagined that alteration of the steric bulk about the borane would allow us to achieve good stereoselectivity for the desired diastereomer (Table 5). Screening of commonly used borane reagents demonstrated that the tri-substituted alkene was relatively unreactive. With this substrate, only the smaller, more reactive boranes gave any consumption of **89** (entries 1 and 2), whereas the bulkier, potentially more selective reagents only showed starting material (entries 3-5). As such, we were limited to using borane dimethyl sulfide complex or borane tetrahydrofuran complex, where entry 1 shows the highest diastereoselectivity observed for the tiglyl-derived substrate at a modest 73:27 dr with poor yield (40%, Figure 5). However, it was not yet known which isomer of **90** was produced in this reaction.

Table 5. Screening reagents for hydroboration/oxidation of tiglyl-derived vinyl isochroman



entry	reagent	consumption (%)	dr
1	BH_3•DMS	100	73:27
2	BH_3•THF	100	65:35
3	9-BBN	0	NA
4	BH_2(*t*-hexyl)	0	NA
5	$BH(Cy)_2$	0	NA

With a synthetically useful method to achieve **90**, the pendent ester was reduced in a straightforward manner with lithium aluminum hydride to afford a molecule that could correspond to panowamcyin B (**2**) (Figure 10). When compared to the NMR spectra provided by Ōmura and coworkers, **91** did not match. At the time, it was deemed probable that we had produced the undesired C12 or C13 epimer of **2**, and that a three step protection/oxidation/deprotection scheme could produce the proposed structure of panowamycin A (**1**). This sequence was relatively low yielding and was conducted on small scale (Figure 10). However, the NMR spectrum of **4** was again not consistent with the published data. This suggested that either we had produced the undesired C12 epimer in the hydroboration oxidation, or that the proposed structure was misassigned. It is worthwhile to note that through this sequence, TM-135 (**4**) was produced, but at that time Mahmud and coworkers had not yet published its isolation.

To investigate the former hypothesis, the angelyl-derived substrate was pursued on larger scale; this would allow us to explore potentially better selectivity outcomes in the hydroboration/oxidation reaction (Figure 11). If a crystal structure was obtained as a result of a the scale-up of the sequence, this would reveal the absolute and relative configuration of the angelyl-derived route and prove or disprove the notion of a structural misassignment. ***Z*-82** was subjected to the same sequence in figure 10, where a

noticeable increase in yield and diastereoselectivity in the hydroboration/oxidation reaction was observed (**94**, 81%, 91:9 dr). Reduction of the pendent ester gave **95** and was again inconsistent with the NMR spectra for the isolated natural substance **2**. Protection/oxidation/deprotection was performed to generate **96**: this compound was also not spectroscopically consistent with the natural substance **1**. Bis-acylation of **95** with *para*-nitrobenzoyl chloride afforded **97** as a crystalline solid and an X-ray structure was obtained, showing that the angelyl substrate underwent hydroboration/oxidation to afford the C12 epimer. At the time of obtaining this crystallography data, we had not produced **4** (Figure 10) and were under the assumption that both alkene isomers were giving us the same C12 epimer. As such, we did not proceed with any further hydroboration/oxidation-based synthetic strategies.

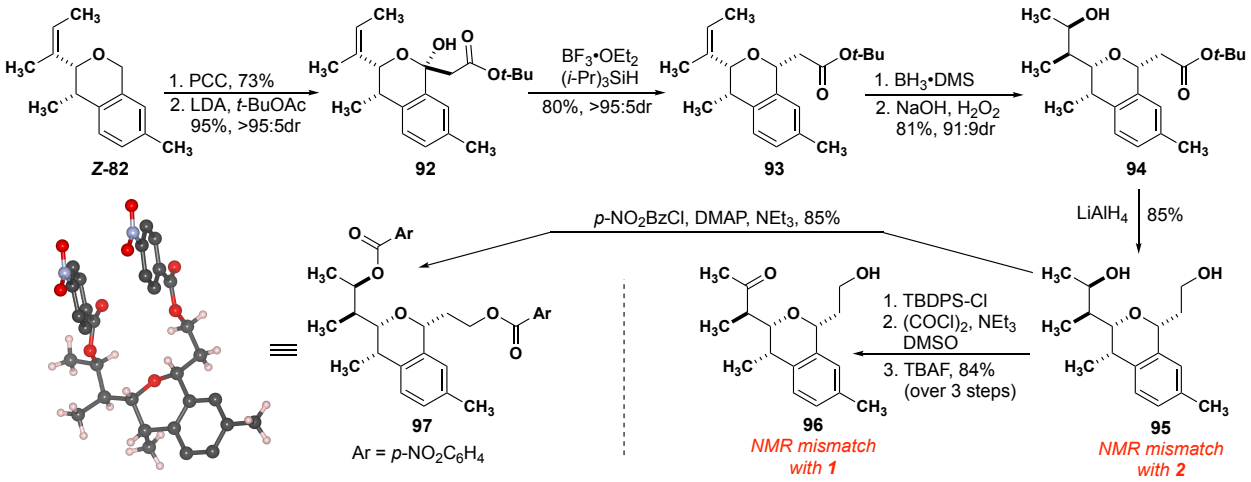


Figure 11. Angelyl-derived synthesis of 12-*epi*-TM-135

To obtain full characterization for the publication of this natural product synthesis, the tiglyl and angelyl-derived substrates were synthesized again at a much later date. When **4** and **96** were generated, it became clear that the two isomers of alkene were in fact giving different facial selectivities in the hydroboration/oxidation reaction. Furthermore, after the publication of Mahmud's TM-135 isolation paper, it became clear that TM-135 (**4**) was accessed through the tiglyl-derived route from **88**, albeit in poor yield and with modest diastereoselectivity (Figure 10). The difference in stereoselectivity here was

rationalized on the basis of minimized allylic-1,3 strain for **93** as the *H-in-plane* conformer, which favored facial selectivity to produce **95** (Figure 12). On the other hand, allylic-1,2 strain was minimized in the *O-in-plane* conformer, favoring facial selectivity to produce **88**, and later TM-135.

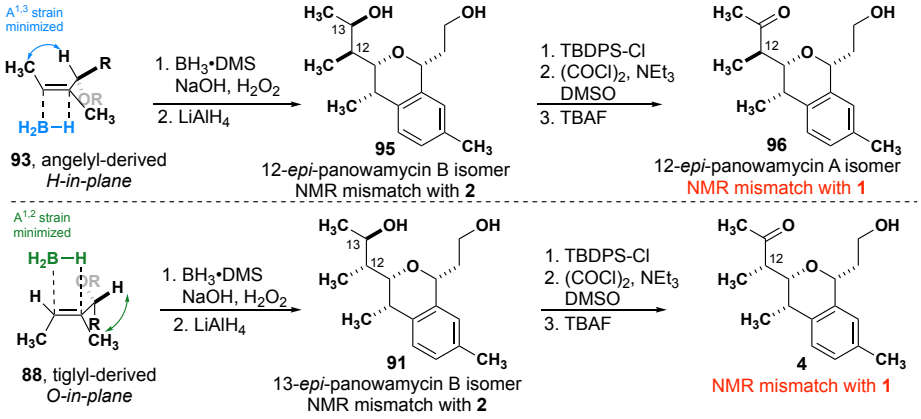


Figure 12. Stereoselectivity model for tiglyl and angelyl-derived hydroboration/oxidation substrates

2.3.3 Attempts at accessing the desired C12 epimer from the vinyl-isochroman scaffold

Due to the effort spent on optimizing and route-scouting for allylic insertion sites and the high enantioselectivity observed in the insertion reaction, it was not immediately attractive to re-route to the homoallylic insertion site strategy. Therefore, several methods were used to attempt to retain the vinyl-isochroman scaffold, without relying on hydroboration/oxidation to produce the acyclic vicinal stereodiad (Figure 13). The first of these attempts was to simply epoxidize ***Z*-82**. Several epoxidations were carried out and *meta*-chloroberoxybenzoic acid (*m*CPBA) ultimately gave a 60:40 dr of epoxide isomers (**98**:**100** assuming the same facial selectivity as the previous hydroboration/oxidation) in modest yield. Dimethyldioxyrane (DMDO) gave more favorable selectivity with 83:17 dr, but with much poorer conversion (not shown). Because we were not *certain* which isomer of epoxide was being produced in this reaction, the *m*CPBA reaction was used for the benefit of higher yield and the ability to isolate a synthetically useful amount of each diastereomer for the purposes of structural identification. Both isomers were sent into a Lewis acid mediated reduction, where the major isomer gave the undesired

regioisomer **99** and the minor isomer gave the desired regioisomer **101**. Crystal growth was attempted for **101** after derivatization with *para*-nitrobenzoyl chloride, but was unsuccessful. A Lewis acid-mediated isomerization of **98** was also attempted, but no reaction was observed (Figure 13). Due to the lack of knowledge of the configuration of these diastereomers and the low yielding and unselective epoxidation, this strategy was abandoned as other efforts gained steam.

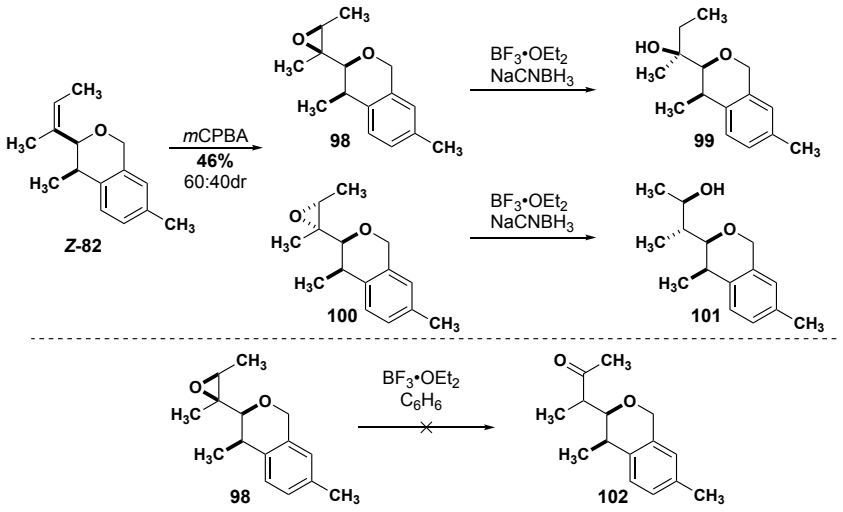


Figure 13. Epoxide-based strategies for derivatizing vinyl isochromans to synthesize panowamycins

Intending to take advantage of the high enantioselectivity of the allylic insertion site, we sought to generate a substrate that would be amenable to an intramolecular ring closing methathesis (RCM) strategy, based on similar literature reports (Figure 14).[60,61] By reaching intermediate **112**, we envisioned a Grubbs-type RCM reaction to produce nine-membered ring **113**, which could then undergo a Tamao-Fleming oxidation to afford aldehyde **114** after tautomerization of the resultant enol. **114** could then be attacked by a methyllithium nucleophile in a stereoselective manner to produce panowamycin B. As such, a methallyl substituted acetophenone hydrazone **105** was constructed with similar efficiency to the sequences described above. The C–H insertion reaction was optimized with $Rh_2(R\text{-PTAD})_4$ at cryogenic temperatures (Table 6, entry 7) in dichloromethane, giving 94:6 er and 81% yield. Carrying this substrate

through the same synthesis as the tiglyl and angelyl-derived substrates to the nucleophilic addition of the lithium enolate of *tert*-butyl acetate gave hemi acetal **108**. This substrate was reduced with complete diastereoselectivity to afford **109**. However, we were unable to reduce the ester functionality in subsequent reactions. Lithium aluminum hydride was not effective in this reduction, even with a gross excess of reagent; later it was suspected that the reagent was no longer potent. Thionyl chloride was used in an attempt to convert the *tert*-butyl ester into the acid chloride per Sammakia and coworkers, likely due to the HCl present in most thionyl chloride reagent samples.[62] This reaction appeared to be successful, but generated several unidentified byproducts. As such, when the acid chloride was subjected to lithium aluminum hydride or sodium borohydride reductions, the results were inconclusive. Without sufficient starting material to continue with further route-scouting, this RCM-based strategy was discontinued in favor of other efforts.

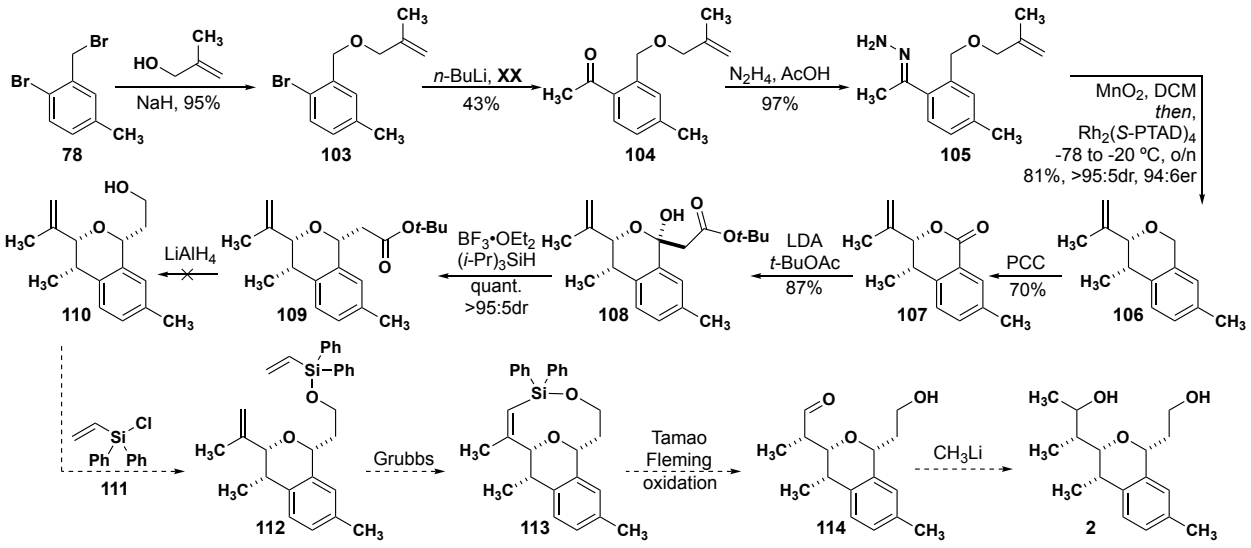
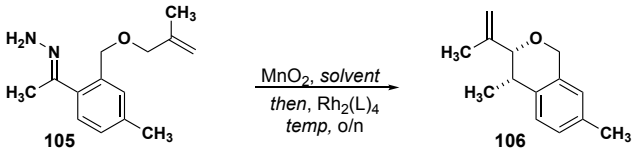


Figure 14. Ring-Closing Metathesis based strategy

Table 6. Methallyl substrate insertion optimization



entry	catalyst	temperature (°C)	solvent	yield (%)	dr	er
1	Rh_2(*S*-TCPTTL)$_4$	–45 to –20	ACN	65		89:11
2	Rh_2(PTCC)$_4$[a]	–45 to –20	ACN	77		50:50
3	Rh_2(*R*-BTPCP)$_4$	–45 to –20	ACN	25		86:14
4	Rh_2(*S*-DOSP)$_4$	–45 to –20	ACN	59	>95:5	84:16
5	Rh_2(*R*-PTAD)$_4$	–45 to –20	ACN	75	*in all cases*	9:91
6	Rh_2(*R*-PTAD)$_4$	–50	ACN	54		10:90
7	Rh_2(*R*-PTAD)$_4$	–78 to –20	DCM	81		6:94

[a] PTCC catalyst as reported by Fokin and coworkers[63]

2.4 Wacker Oxidation Strategy: Synthesis of the Desired C12 Epimers

Having had sufficient difficulty producing the desired C12 isomer of panowamycin A or B in high yield or with certainty of relative configuration, a synthesis was devised based on having the C12 stereogenic center pre-determined prior to insertion (Figure 15). Due to the fact that the presence of a ketone at C13 would interfere with nucleophilic additions and hydrazine condensations, having a methyl ketone (later providing panowamycin A) was not desirable. An acetal could be utilized to protect the ketone during the aforementioned steps, but this group would likely not survive any Lewis acidic conditions (e.g. boron trifluoride) nor was the use of any protecting group desirable. This left us with the idea of masking the desired methyl ketone in panowamycin A as a terminal olefin, which would serve as the functional group handle for a Wacker oxidation (or Wacker-Tsuji oxidation).[64–67]

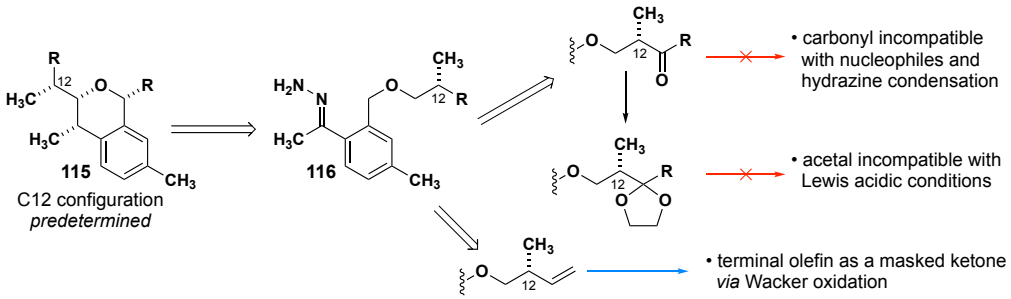


Figure 15. Retrosynthetic strategy for predetermined C12 stereogenic center

2.4.1 Homoallylic fragment synthesis: Stereoselective alkylations and isomerizations with chiral auxiliaries

There are several reported methods to synthesize the homoallylic alcohol required for the Wacker oxidation strategy shown above (Figure 16). A frequently reported method is to derive the C12 stereogenic center from either isomer of Roche ester (Figure 16A).[68] This strategy has the marked advantage of using a chiral reagent where both isomers are commercially available and with known enantiopurity. Unfortunately, this route was not synthetically feasible: tosylation of the Roche ester, followed by a facile reduction/oxidation sequence afforded aldehyde **119** in synthetically useful quantities. All attempts to generate the terminal olefin with a methyl phosphonium Wittig reagent were not fruitful. In most cases, a significant quantity of the *alpha*-elimination product was observed. Figure 16B shows a unique approach using the isopropyl Evans auxiliary to perform a stereoselective protonation of an enolate generation from *gamma*-deprotonation.[69] With this method, only starting material was observed after exposure to reaction conditions, likely due to the fact that the literature precedent uses a *beta*-ethyl group, where our requisite substrate **122** is *beta*-methyl would have a higher pKa. Similarly, there is a report of asymmetric alkylation *via* a *gamma*-deprotonation enolate using the Oppolzer auxiliary (i.e. derived from camphor sultam) and crotonic acid (Figure 16C).[70] Despite the assistance of the lead author (thank you to Chad Normandin and Prof. Pierre-Luc Boudreault and in memory of Prof. Éric Marsault), this reaction was not functional in our hands, showing only the isomerized product (á la **128**) when **126** was exposed to lithium hexamethyldisilazane and methyl iodide. Using vinylacetic acid as the starting material was more fruitful; figure 16D shows the use of the Myers auxiliary (i.e. derived from pseudoephedrine) to perform asymmetric alkylations with methyl iodide.[71] Per the literature report, this asymmetric alkylation worked quite well, giving a modest yield of **130** in >95:5 dr. However, attempts to cleave the auxiliary were not successful. Typical conditions for the cleavage of amides is with the use of

lithium amino borohydride reagents, developed by Prof. Bakthan Singaram; despite Prof. Singaram's advice (thank you), this sequence was not functional in our hands. This strategy was also repeated using the Oppolzer auxiliary, but no alkylation product was observed (not shown). Using the same starting material **128**, the benzyl Evans auxiliary finally gave the desired product (Figure 16E).[72] Using these conditions, a maximum diastereoselectivity of 82:18 was achieved (at 20g, 80mmol scale). While this would typically not be of much concern, the separations of these diastereomers by flash column chromatography was particularly laborious, requiring up to 6 sequential columns to receive **132** in suitable diastereomeric purity (>95:5 dr). Cleavage of the auxiliary with lithium borohydride was high yielding and facile, allowing for the synthesis of a modest quantity of homoallylic alcohol **124**.

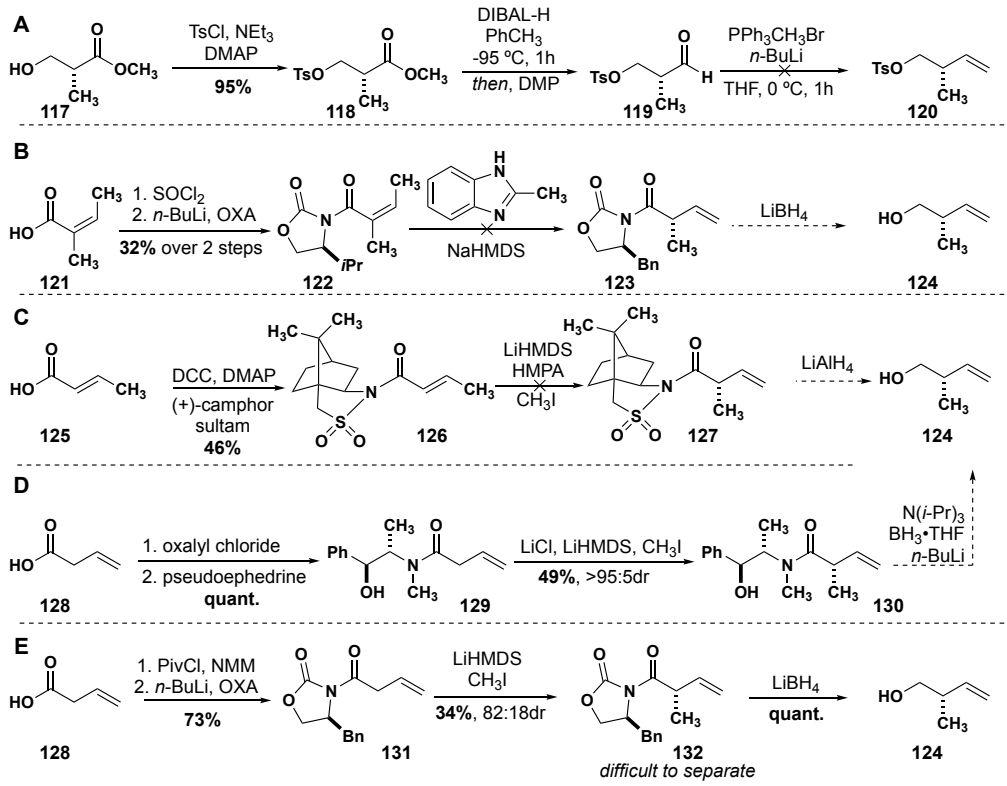


Figure 16. Homoallylic fragment synthesis

2.5 Wacker Oxidation Strategy: Reaching the limits of reactivity/chemoselectivity with donor/donor carbenes

With a synthetically useful quantity of the requisite homoallylic alcohol in hand, the Wacker oxidation strategy was further explored. Acetophenone hydrazone **135** was accessed in a straightforward manner (Figure 17). **135** was then sent into the conditions optimized for the tiglyl and angelyl-derived substrates; that is, the one-pot sequential conditions where the hydrazone is oxidized to the diazo, then the rhodium catalyst is added to the heterogenous mixture. Where the previously fuchsia solution usually turns clear within minutes, this experimental protocol swiftly produced a yellow mixture with an unexpected product, observed by TLC. When the unpurified NMR spectrum was analyzed, it was apparent that nearly no insertion product was synthesized. By the broadened peaks and occasional doubling of peaks observed in the proton NMR spectrum, it was concluded that the substrate almost entirely formed the azine byproduct. This is a byproduct of C–H insertion reactions that occurs when the insertion step is particularly slow. That is, once the electrophilic metal-carbene is formed, instead of intramolecular C–H insertion, the substrate is attacked by another equivalent of the diazo species, generating azine-dimer **136**. This byproduct has not been observed in the lab in significant quantities, and is a testimony to the low reactivity of the substrate. The methyl/aryl carbene, due to the hyperconjugation of the CH_3 group, should be less electrophilic than the aryl/aryl carbenes described in chapter 1 of this dissertation. Furthermore, the insertion site of **135** is far less activated than the previous allylic insertion sites and features adjacent alkyl branching; these two factors decrease the nucleophilic character of the C–H bond to insertion and introduce steric repulsion towards the crowded metal-carbene-ligand complex, respectively.

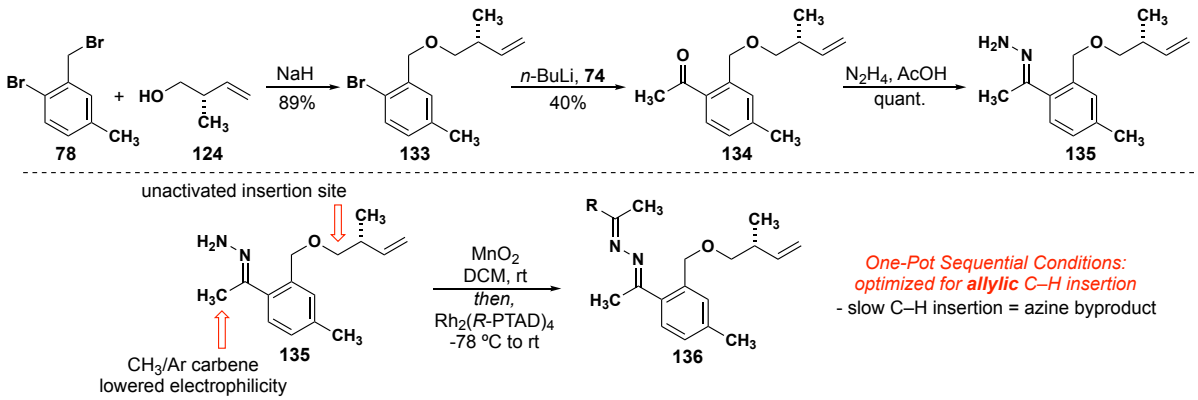


Figure 17. Wacker oxidation route substrate synthesis and azine byproduct formation

2.5.1 Modification of C–H insertion reaction methodology: a model substrate

Due to the difficulties associated with obtaining a large amount of the requisite homoallylic alcohol **124** for further optimizations of this C–H insertion reaction, it was decided that a more easily constructed model substrate would be assessed for feasibility. A substrate derived from isobutyl alcohol was determined to be a suitable model system (Figure 18): **139** features an unactivated insertion site and adjacent alkyl branching. This acetophenone hydrazone was constructed in a straightforward manner and was sent into C–H insertion optimization procedures.

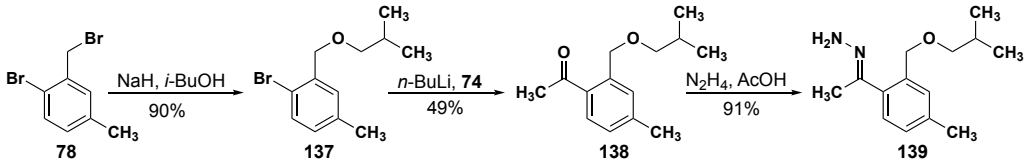


Figure 18. Synthesis of the model substrate to test inverse addition C–H insertion protocols

The reason for the appearance of the azine byproduct is two-fold: the C–H insertion reaction is slow and, even in dilute reaction conditions (i.e. 0.015M), the diazo species is available to attack the metal carbene prior to insertion. As such, it is desirable to limit the relative concentration of diazo and rhodium carbene in the reaction mixture at any given time. That is, if a concentrated solution of the diazo was slowly added to a very dilute solution of the catalyst, the rhodium carbene would have time to react

intramolecularly without diazo molecules intervening intermolecularly. We call this type of protocol *inverse addition* and it is accomplished with the use of slow addition of diazo *via* syringe pump (Figure 19) This procedure involves the oxidation of the diazo as a concentrated solution with manganese dioxide until complete, then the heterogenous oxidant is filtered off with a glass frit filter, leaving only the fuchsia diazo solution. This solution is then attached to the syringe pump, which is added to a dilute, green-colored solution of the dirhodium catalyst dropwise over the course of 1-4 hours depending on scale. Smaller scale insertion reactions (10-50 mg) can forgo the filtration by glass frit and simply use a syringe filter with 0.2μm pore size.

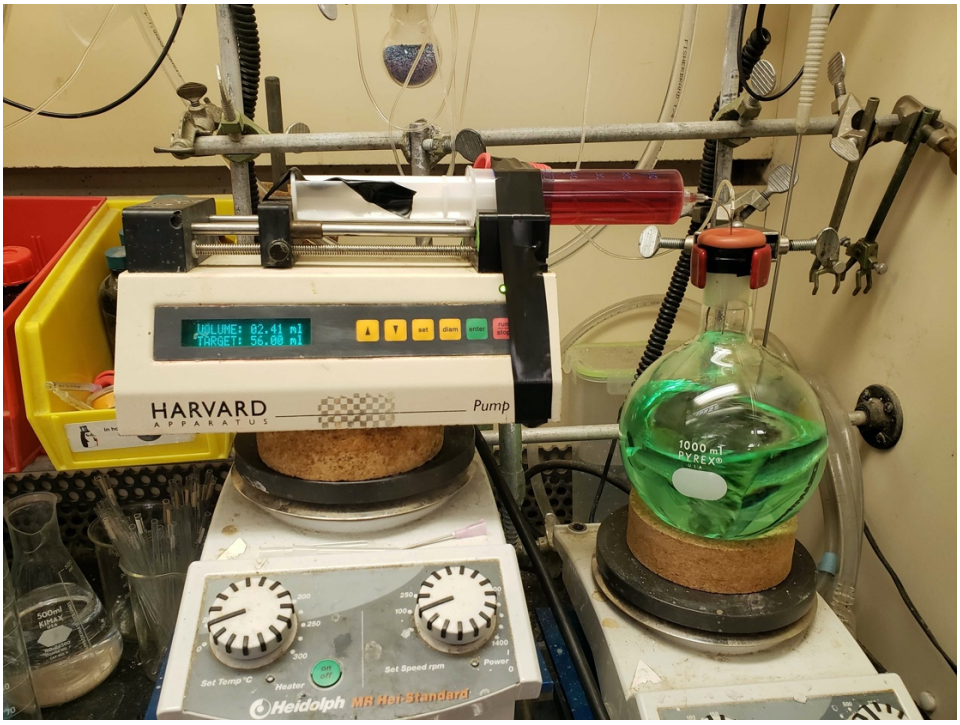
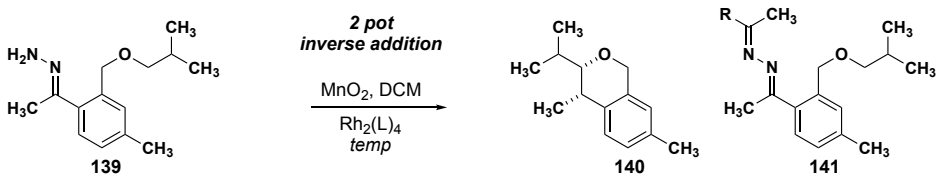


Figure 19. Experimental setup for the *inverse addition* C–H insertion reaction

This modified protocol was used in combination with the model substrate to assess the feasibility of the Wacker oxidation-based route (Table 7). In all cases except entry 5, the catalyst solution was cooled to 0 °C before the diazo solution was added. In this catalyst and temperature screen, it was observed that the inverse addition protocol reduced the amount of azine formation! Entries 1-4 demonstrate that yields

for this substrate are fairly low, due still to the formation of azine, but enantioselectivities were still observed to be >80:20 and diastereoselectivity is still >95:5. Enantioselective ratios here are expressed as ">80:20" because of the difficulty purifying the isochroman away from the azine and other trace byproducts, so chiral HPLC data was not completely conclusive. Cooling the catalyst solution down to –78 °C (as was successful with tiglyl, angelyl, and methallyl substrates) primarily produced the azine byproduct, suggesting that the lowered temperature decreases the favorability of the intramolecular insertion to occur. However, these results were encouraging enough for further pursuit of the Wacker oxidation-based strategy.

Table 7. Optimization of C–H insertion reaction for model substrate featuring inverse addition



entry	catalyst	temp. (°C)	**140**:**141**	yield (%)	dr	er
1	Rh_2(*R*-BTPCP)$_4$	0 to rt	43:57	30	>95:5 *in all cases*	>85:15
2	Rh_2(S-TCPTTL)$_4$	0 to rt	40:60	36		>85:15
3	Rh_2(*R*-PTAD)$_4$	0 to rt	77:23	41		~20:80
4	Rh_2(PTCC)$_4$	0 to rt	93:7	65		49:51
5	Rh_2(*R*-PTAD)$_4$	–78 to –20	9:91	NA		NA

2.6 Wacker Oxidation Strategy: racemic synthesis of TM-135 and panowamycin B

Again, due to the difficulty of obtaining a sufficient amount of the enantiopure **124**, it was decided that a racemic synthesis be conducted as a full validation of the sequence before significant efforts were placed into finding a practical synthesis for the enantiopure fragment. Racemic 2-methylbut-3-enoic acid is a commercially available reagent and was used as the starting material of this synthesis by reducing the carboxylic acid down to the homoallylic alcohol (±)-**124** with lithium aluminum hydride in quantitative yield (not shown). This alcohol was then sent into the usual sequence to produce acetophenone

hydrazone (±)-**135** (Figure 20). Using our *inverse addition* insertion protocol, this substrate performed adequately with the achiral $Rh_2(PTCC)_4$ catalyst, affording (±)-**142** in a 65% yield and 50:50 dr. It is worthwhile to discuss the stereoselective outcomes of this reaction, as it will be important later to understand the enantioselective outcomes of the final synthesis (Figure 21). If a racemic starting material is used, that means that both **135a** and **135b** are present *in situ*. In the insertion reaction, the catalyst will induce an enantioselective outcome (if a chiral catalyst is used) which in the case of the achiral PTCC catalyst will be a 50:50 dr of **142a** and **146b** from **135a**, and **146c** and **142d** from **135b**. The observed outcome is a 50:50 dr of (±)-**142** and (±)-**146**. Importantly, if an enantiopure starting material is used, that is to say, if enantiopure substrate (e.g. only **135a**) were reacting with a chiral catalyst, the catalyst induction would be represented in the diastereomer ratio between **142a** and **146b**, where each diastereomer would be a single enantiomer. It is also worthwhile to note that the diastereomers produced from this reaction were inseparable by column chromatography, but were easily separated in the next step as the isochromanone (±)-**52**.

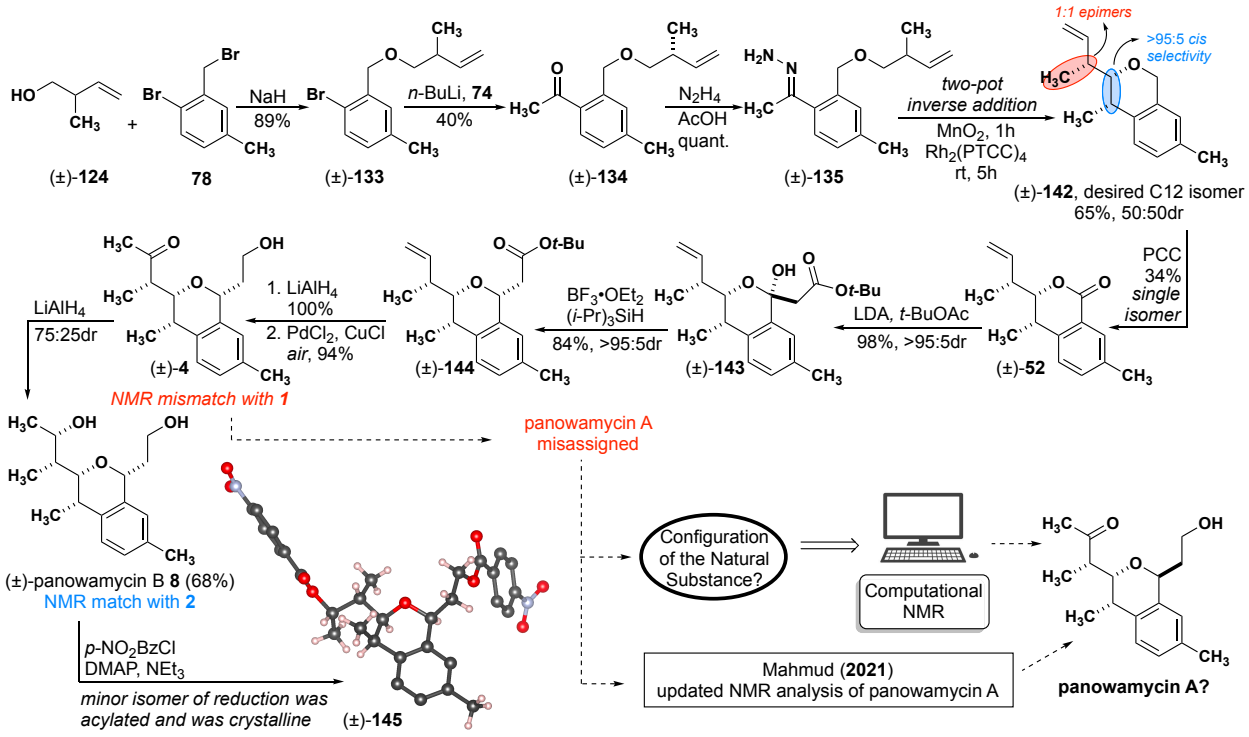


Figure 20. Racemic synthesis of panowamycin B and TM-135

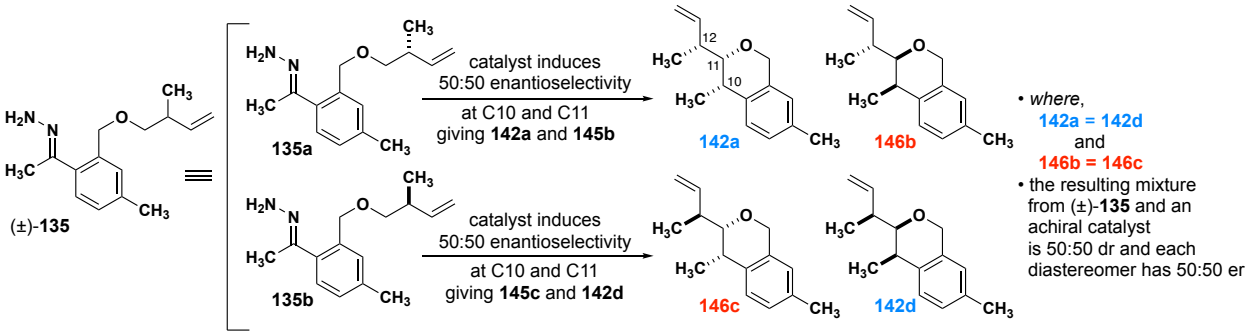


Figure 21. Stereoselectivity outcomes for racemic insertion substrate with an achiral catalyst

With the insertion protocol successfully modified to avoid the formation of azine byproduct **136**, the isochroman products were sent into the remainder of the synthetic sequence. This mixture of diastereomers ((±)-**142**) was oxidized with pyridinium chlorochromate and separated by column chromatography from the other isochromanone isomer to afford (±)-**52**. This intermediate was then sent into the enolate addition/reduction sequence described above to afford (±)-**143** as a single diastereomer. Reduction of the pendent ester was accomplished in quantitative yield. In a test sequence, the primary

alcohol was protected with a TBDPS silyl ether out of concern that a hydroxyl may interfere with the Wacker oxidation reaction. However, when the protected substrate (not shown) was exposed to Wacker Oxidation conditions, the expected methyl ketone with the silyl ether was isolated in 34% yield. To understand the loss of mass, the column flush was concentrated and examined by NMR spectroscopy, showing the desilylated methyl ketone (±)-**4** in 64% yield. Therefore, during scale-up the substrate was subjected to the Wacker oxidation without protection and the reaction proceeded in 94% yield to afford a structure that should correspond to the proposed structure of panowamycin A (**1**). An overlay of the NMR spectra of the synthetic sample and the NMR spectra of the natural substance revealed their incongruence, confirming a structural misassignment. In order to determine the absolute configuration of the synthetic sample, (±)-**4** was reduced with lithium aluminum hydride in 75:25 dr and both isomers were isolated and acylated with *para*-nitrobenzoyl chloride. A crystal structure of the acylated minor isomer of the reduction was obtained ((±)-**145**), confirming that the C12, C11, C10, and C3 configuration of the synthetic substance was properly synthesized, and that the proposed structural of panowamycin A was incorrect. On the other hand, the major isomer of reduction (±)-**8** was compared to the NMR spectrum of the natural substance for panowamycin B and it was confirmed to be a match. In this way, the structural identity of (±)-panowamycin B ((±)-**8**) was elucidated for the first time by total synthesis. As mentioned above, the methyl ketone (±)-**4** corresponds to the structure of TM-135, but our synthesis was performed before the structure of TM-135 was published (September 2021) and its discovery will be discussed in section 2.8.2.

2.7 Computational NMR

Having synthesized the proposed structure of panowamycin A and with the discovery of the structural misassignment, we were deeply interested in the identity of the natural isomer. As there are 4 stereocenters on panowamycin A, there are 8 diastereomers to be explored and it would be ineffective to synthesize

them blindly. As such, we approached our frequent collaborators in the Tantillo lab about performing computational NMR calculations for these eight diastereomers to reveal which isomer best matches the reported NMR chemical shift values.

2.7.1 Computational NMR methods

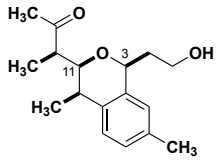
The Tantillo lab is preeminent in the field of computational chemistry and Dr. Amy T. Merrill had previous expertise in natural product structural analysis by computational NMR. It was therefore a natural fit for her to assist with the project. Very generally put, our collaborators searched for the lowest energy conformers of each diastereomer and optimized the geometry of those conformers using more advanced levels of theory. Isotropic shielding was then calculated for each of the protons and carbons in the structure, giving a full set of theoretical NMR spectral data. Based on the deviations between the natural and theoretical NMR chemical shifts, the probability of each isomer being the natural substance was calculated. More technically, conformational searching for the isomers of Panowamycin A was performed with *CREST,* version 2.9 using the gfnff and the generalized born model with solvent accessible surface (SASA) chloroform solvent model.[73,74] Optimizations and NMR calculations were calculated with *Gaussian 16*, Revision A. 03.[75] Conformers within 5 kcal/mol of the lowest energy conformer from the conformational search were optimized with the B3LYP-D3(BJ)/3-21G[76–80] level of theory. Conformers with relative energies within 5 kcal/mol of the lowest energy conformation were re-optimized at the B3LYP-D3(BJ)/6-31G+(d,p)[76,79–81] level of theory. Conformers with energies within 3 kcal/mol of the lowest energy conformer from this level of theory were used to calculate ^{1}H and ^{13}C chemical shifts using a Boltzmann weighted averaging of the chemical shifts for these conformers at the PCM(chloroform)-mPW1PW1/6-311+G(2d,p)//B3LYP-D3(BJ)/6-31+G(d,p)[76,79–84] level of theory with the GIAO method[85–89] of calculating isotropic shielding constants. The ^{1}H and ^{13}C chemical shifts were calculated

using scaling factors (^{13}C: Slope = -1.0420, Intercept = 186.3567; ^{1}H: Slope = -1.0719, Intercept = 31.8733) from CHESHIRE[90].

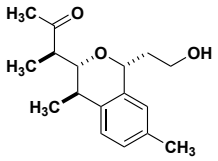
2.7.2 Discussion of results and conclusions about the structure of panowamycin A

As is detailed in section 2.7.1, our collaborators assembled tables for the comparison of these computed NMR shifts to those of the natural substance panowamcyin A. Based on these data, it was clear that the shifts corresponding to H3/C3 and H11/C11 were most indicative of chemical shift change between diastereomers (Table 8). For this computational method, tolerances for outlying values are 0.3 ppm for ^{1}H signals and 5 ppm for ^{13}C signals. The structure proposed by Ōmura and coworkers in 2012 (isomer A) was calculated to have significant outlying values for both C3 and C11, whereas H3 and H11 were within tolerance. Isomer A was calculated to have relatively low mean average deviations (MAD) for both ^{13}C (1.7 ppm) and ^{1}H (0.14 ppm), meaning that Ōmura and coworker's original assignment was fairly close. However upon examination of the results for isomer E, it is clear that the absolute deviation for C11 is much lower that isomer A, and that the MAD for the ^{1}H signals is the lowest of all isomers.

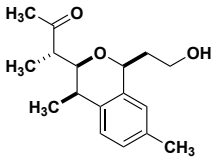
Table 8. Computed NMR chemical shifts of panowamycin isomers compared to the natural substance



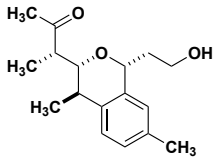
Isomer **A** (**4**)



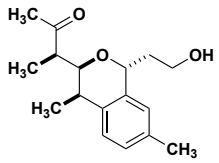
Isomer **B** (**147**)



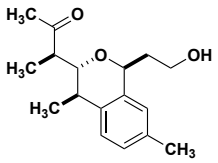
Isomer **C** (**96**)



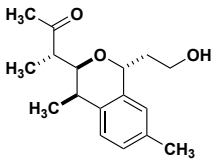
Isomer **D** (**148**)



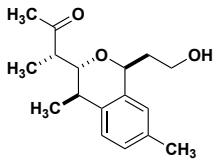
Isomer **E** (**3**)



Isomer **F** (**149**)



Isomer **G** (**150**)



Isomer **H** (**151**)

isomer	Absolute Deviation (ppm)				MAD (ppm)[a]	
	C3	C11	H3	H11	C	H
A	7.3	**5.6**	0.08	0.15	1.7	**0.14**
B	6.1	9.0	0.03	0.31	2.1	0.15
C	6.4	7.4	0.12	0.07	2.2	0.14
D	5.5	8.5	0.00	0.10	2.1	0.14
E	4.9	**0.2**	0.05	0.25	1.2	**0.08**
F	0.6	7.1	0.00	0.06	2.0	0.14
G	1.2	1.7	0.38	0.24	1.9	0.18
H	1.3	6.9	0.08	0.17	2.3	0.15

[a] MAD = Mean Absolute Deviation, for all chemical shift values of each respective isomer. See supporting information for isomer structures.

Our computational collaborators also generated a graphical representation of how each isomer deviates from the published ^{13}C NMR spectral data (Figure 22). In this representation, it is clear that isomer E has the lowest C11 and MAD. Although it appears that isomer G is a better overall fit by ^{13}C NMR calculations, the MAD for ^{1}H signals for isomer E makes it the overall better fit for the natural substance. Additionally, isomer E was the only isomer where all of the absolute chemical shift deviations for both ^{1}H and ^{13}C nuclei were within the tolerated deviations for outlying values for this computational method.[91] DP4 analysis was performed for the four isomers with the lowest MADs to give the probability of each isomer being the natural isomer.[92] Using ^{1}H and ^{13}C chemical shifts with the DP4-database2 (with t-distribution), isomer E was predicted to have a 99.9% probability of being the natural product, whereas

isomer A was predicted to have only a 0.1% probability.[93] Overall, this data highlights not only how difficult the structural assignments for these polyketide natural products can be, but also how valuable computational NMR can be in structural elucidation. With these insights in hand, we set about with a second generation synthesis to pursue the construction of isomer E.

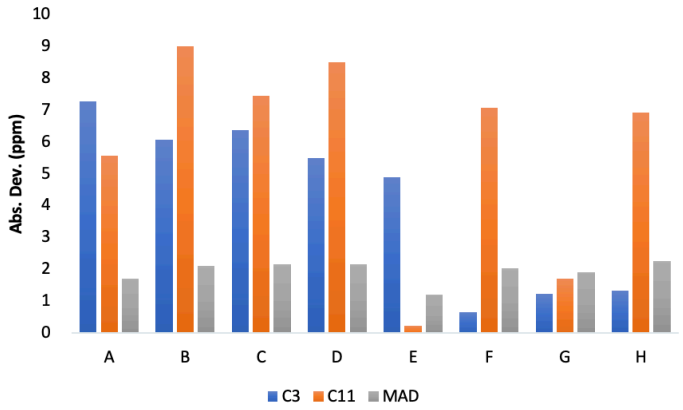


Figure 22. Graphical representation of the absolute deviations for the C3 and C11 ^{13}C chemical shifts and the MAD's for isomers A-H

2.8 Wacker Oxidation Strategy: Roche Ester-Derived Route and Divergent Asymmetric Synthesis of Panowamycin A, Panowamycin B, TM-135, and Veramycin F

The NMR calculations performed by Dr. Amy T. Merrill in the Tantillo group indicated that isomer E (**3**) is the diastereomer most closely corresponding to the reported NMR signals of the natural substance for panowamycin A. Based on our previous efforts, which successfully synthesized the C10, C11, C12 stereotriad using the Wacker oxidation strategy, it was obvious that the main objective in synthesizing isomer E (**3**) would be installing the C3 sidechain with inverse diastereoselectivity from the previous sequence to afford **152** (Figure 23). However, our previous difficulty in obtaining the homoallylic fragment necessitated a second-generation synthesis of key intermediate **52**. From here, the

enantioselective synthesis of panowamycin B (**8**) and isomer E (**3**) would be possible in a divergent sequence.

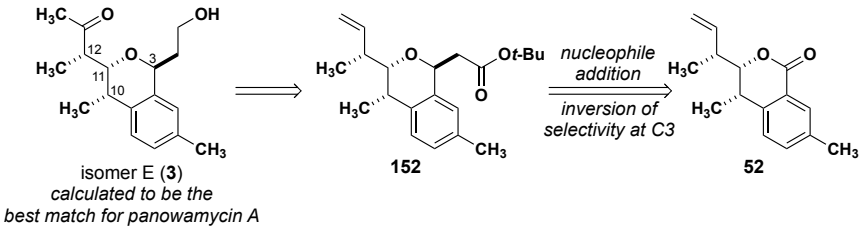


Figure 23. Retrosynthetic analysis of isomer E

2.8.1 Optimization of the second-generation synthesis using the Roche ester

Given the prior efforts with the Roche ester, we knew that synthesizing the fragment would be problematic under basic conditions due to the various degradation and elimination pathways that can occur. Furthermore, working with a fragment with a relatively low boiling point was anticipated to be troublesome. It was therefore decided that the Roche ester portion would be linked with the 2-bromo-5-methyl benzyl fragment to add molecular weight earlier on in the synthesis (Figure 24). Previous attempts at making the ether **155** under basic conditions (e.g. NaH in THF as described above) were unsuccessful due to the anticipated elimination reaction. Several procedures were found that accomplish the desired coupling between a benzyl fragment and the Roche ester *via* acidic conditions with a trichloroacetimidate.[94–98] Common starting material **153** was sent into acetimidate formation conditions; many reports list NaH as the preferred base for this reaction but we found that reactions with diazabicycloundecane (DBU) gave superior yields of **154** and were easily purified. It is worth mentioning that the workup for this reaction is to concentrate the reaction mixture *in vacuo*, which is very desirable for large-scale preparations. However, trichloroacetonitrile is used in large excess (10 equiv.) and is acutely toxic by inhalation: therefore the concentration *MUST* be carried out using a rotary evaporator located inside a fume hood.

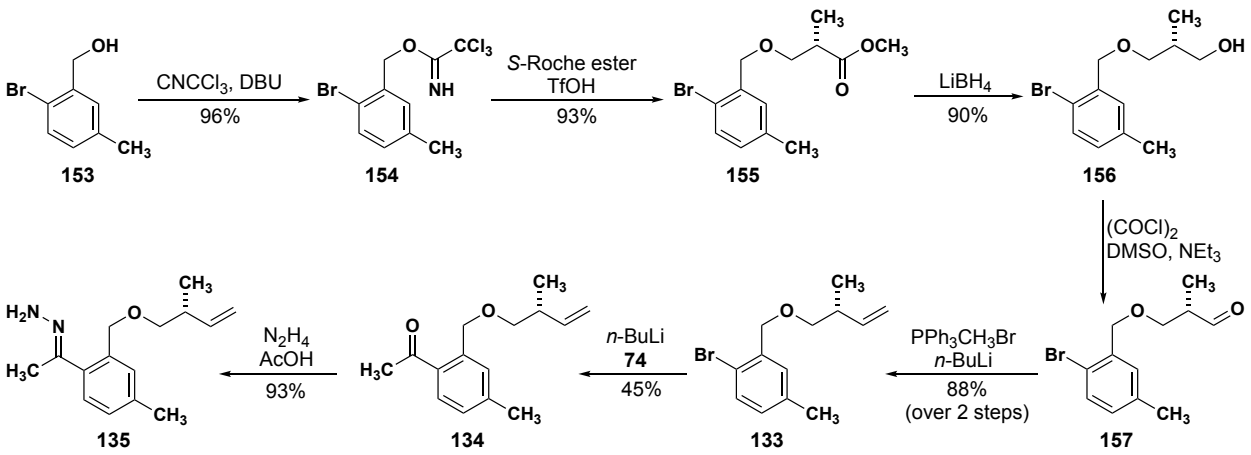


Figure 24. Synthesis of acetophenone hydrazone intermediate using the Roche ester

The alkylation of benzylic electrophiles using acidic conditions with acetimidates occurs by protonation of the imine, generating an excellent leaving group (i.e. trichloroacetamide) for S_N2 substitution. Several acids were screened for this reaction: pyridinium *para*-toluenesulfonic acid (PPTS) in a cyclohexane:DCM mixture, triflic acid in a cyclohexane/DCM, triflic acid in diethyl ether, and camphorsulfonic acid (CSA) in DCM. Of these, CSA gave no conversion to product and PPTS and TfOH gave similar conversion. TfOH gave a much cleaner reaction mixture and the volatility of the quenched byproducts resulted in an operationally more simple protocol at large scale to afford **155** (~15 g, 45 mmol). When solvents were screened, it was similarly clear that the reactivity of this substrate was higher in diethyl ether than the more often used cyclohexane:DCM mixture. In addition, the workup with diethyl ether was more operationally simple, where concentration *in vacuo* would be with a more volatile solvent. It should be noted that triflic acid is a *super acid* and its use must be a tightly controlled procedure with safety being a clear objective. During large scale procedures it was observed that triflic acid quickly melts through the plastic used in hypodermic needles and that it *very quickly* penetrates the standard nitrile glove. Therefore, double-gloving should be employed whenever handling, and dropping funnels should be used whenever scale permits.

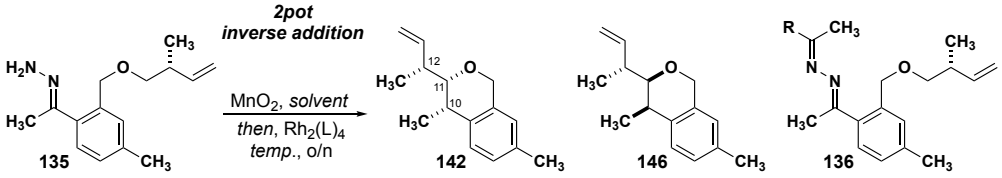
Conditions for the formation of the requisite homoallylic ether were subsequently explored. Lithium aluminum hydride was observed to generate the documented proto-dehalogenation byproducts associated with *ortho*-bromo arenes as noted above (Figure 24). As such, lithium borohydride was chosen as a reductant and excellent yields were achieved without any byproduct formation. **156** was then oxidized: the precedented TEMPO oxidation was attempted first,[95] but the Swern oxidation was chosen due to fewer components, higher yields, and the lack of purification.[99] Satisfyingly, the Wittig reaction with methyltriphenylphosphonium bromide produced the ether **133** in high yield (88% over two steps) without the need for optimization or screening.

Anticipating the low yields in the acylation reaction, one last attempt was made to produce acetophenone **134** without using the Weinreb acetamide. **133** underwent lithium halogen exchange with *n*-butyllithium and the aryl nucleophile attacked 4-morpholinoyl chloride to form the aryl amide in 44% yield (not shown). This Weinreb-type electrophile underwent attack by a methyllithium nucleophile to form methyl ketone in 22%, demonstrating that this 2-step sequence was less efficient (not shown). Magnesium halogen exchange was also attempted but proved to have similar proto-debromination ratios with lithium halogen exchange and was operationally inconvenient. As such, it was determined that the low yields observed in the Weinreb-acetamide acylation were acceptable (45% yield). Hydrazone formation with acetophenone **134** formed hydrazone **135** in high yield at room temperature.

The next challenge presented in this synthesis was the minimization of azine formation and optimization of stereoselectivity in the C–H insertion reaction (Table 9). It was observed in the racemic synthesis that at room temperature, the inverse addition protocol still proceeded with some formation of azine. At –78 °C it was observed that azine was formed in large amounts. Therefore, there was a "sweet spot" temperature where azine formation is kinetically unfavorable (temperatures lower than room temperature) and C–H insertion is kinetically favorable (temperatures higher than –78 °C). Moreover,

the temperature must be low enough to ensure good stereo-induction with the chiral catalyst. Based on the above discussion regarding stereochemical outcomes with a substrate containing a stereogenic center, the stereo-induction of the reaction conditions and catalyst choice would be observed as a *diastereomeric ratio* in this case because the starting material is enantiopure.

Table 9. Roche-based substrate C–H insertion optimization



entry[a]	catalyst	temperature (°C)	solvent	**142**:**146**:**136** (**142**:**146**)	yield **142**+**146** (%)
1[b]	Rh_2(*S*-PTAD)$_4$	–20 to rt	DCM	55:19:26 (68:32)	63
2	Rh_2(*S*-TCPTTL)$_4$	–20 to rt	DCM	52:9:39 (85:15)	NA
3	Rh_2(*R*-BTPCP)$_4$	–20 to rt	DCM	41:13:47 (76:24)	NA
4	Rh_2(*R*-DOSP)$_4$	–20 to rt	DCM	22:10:68 (67:33)	NA
5	Rh_2(*S*-PTAD)$_4$	–20 to rt	ACN	22:11:67 (66:34)	NA
6	Rh_2(*S*-TCPTTL)$_4$	–20 to rt	ACN	61:14:25 (81:19)	NA
7	Rh_2(*R*-BTPCP)$_4$	–20 to rt	ACN	52:15:34 (77:23)	NA
8	Rh_2(*R*-DOSP)$_4$	–20 to rt	ACN	13:7:80 (65:35)	NA
9[b]	Rh_2(*S*-TCPTTL)$_4$	–20 to –15	ACN	58:14:27 (80:20)	66
10[c]	Rh_2(*S*-TCPTTL)$_4$	–20 to –10	ACN	49:13:37 (79:21)	45
11[d]	Rh_2(*S*-TCPTTL)$_4$	–20 to rt	ACN	63:17:20 (78:22)	79

[a] 10 mg, 0.04 mmol scale, 1 mol % catalyst loading; [b] 100 mg, 0.41 mmol scale, 0.7 mol % catalyst loading; [c] 300 mg, 1.3 mmol scale, 0.25 mol % catalyst loading; [d] 2 g, 10 mmol scale, 0.5 mol % catalyst loading

Using the conditions optimized for the model substrate as a starting point, a test-scale reaction with the enantiopure substrate was conducted with Rh_2(*R*-PTAD)$_4$ in DCM at –20 °C (Table 9, entry 1). Despite the favorable enantiomeric ratios observed with the model substrate (**140**, ~>85:15 er), this substrate showed only modest selectivity with 68:32 dr and with some azine. A catalyst screen at smaller test scales (10 mg) showed that in DCM, Rh_2(*S*-TCPTTL)$_4$ gave the most favorable diastereomeric ratio

out of the four catalysts, but also generated an appreciable amount of azine (entries 2-4). Increased byproduct formation is frequently observed when using Rh_2(*S*-TCPTTL)$_4$ for six-membered ring insertions due to the increased electrophilicity and modulated electrostatic properties of the catalyst. The solvent was switched to acetonitrile in order to see if azine formation and/or stereoselectivity was improved (entries 5-11). For all catalysts screened, the general trend for stereoselectivity remained consistent (entries 5-8), albeit with slightly eroded selectivity in entry 6. However, among the entries with acetonitrile, a general reduction in the amount of azine was observed. For example, the **142**:**146**:**136** ratio in entry 6 is much more favorable than in entry 2 and therefore theoretically much higher yielding.

With this information, the use of Rh_2(*S*-TCPTTL)$_4$ in acetonitrile was established and the reaction was screened for temperature variation and catalyst loading (entries 9-11). When the syringe pump is used for these inverse addition protocols at reduced temperatures, the reaction temperature was always maintained for the duration of the slow addition (2-4 hours). After the addition of the diazo to the catalyst solution, the flask is typically allowed to warm over several hours (e.g. –20 °C to rt). For entries 9 and 10, the flask was transferred to freezers with approximate temperatures of –15 and –10 °C, respectively. Stereoselectivity in these entries was not affected by the extended period of reduced temperature and therefore the mixture was allowed to warm to room temperature very slowly (entry 11). More impactful on reaction yield was catalyst loading. Anecdotal evidence from colleagues and previous efforts with donor/donor carbene C–H insertion reactions suggest that changes in catalyst loading can increase both the stereoselectivity and yield of the insertion product. The typical test-scale reaction operates at a default 1 mol % catalyst loading because our balances are not capable of reliably measuring smaller than 1-2 mg. When scale-up reactions are performed however, the catalyst loading can be reduced by at least an order of magnitude without any unfavorable outcomes. In this case, there appeared to be another "sweet spot" for catalyst loading: the reaction yield was 66% with 0.7 mol % loading and decreased to 45% with 0.25

mol % and slightly larger reaction scale (entries 9 and 10). Considering these results, it was decided that in a full-scale reaction (~2 g, 10mmol) 0.5 mol % catalyst loading would be used to maintain good yields, selectivities, and to reduce catalyst loadings (~80 mg of dirhodium catalyst at this scale). With these conditions, a favorable diastereomeric ratio was observed in high yield (entry 11).

2.8.2 Asymmetric synthesis of panowamycin A

The key step of the reaction was now optimized and a reliable and robust synthetic route to a substrate with the homoallylic fragment installed was developed (Figure 25). The major challenge of the synthesis would then be to achieve the opposite selectivity during the nucleophilic addition of the sidechain at C3. It was during this time that the paper from Mahmud and coworkers was discovered, where they report the isolation of TM-135 and the structural revision of panowamycin A to the same isomer E that we had determined computationally. In their work (see Section 2.1.2), they perform an updated NMR spectral analysis of the panowamycin A in deuterated methanol instead of deuterated chloroform. This solvent choice shifted the H3, H10, and H11 signals in a way that more clearly elucidated NOESY cross-peaks. That is, the previously overlapping H1/H3 and H3/H11 cross-peaks were now resolved showing no cross-peaks for H3/H11, making it more clear that H3 and H11 have an *anti* relationship rather than the originally proposed *syn* relationship. Additionally, Mahmud and coworkers performed computational circular dichroism measurements on a related natural product that contains the same C10, C11, C12 stereotriad, proposing the absolute stereochemistry of the compound. By extension, it was highly likely that panowamycin A, panowamycin B, and TM-135 would also have the same absolute stereochemistry at the triad. We had noticed a similar concept in the total synthesis of NFAT-133 by Ogura and coworkers, where they assign absolute stereochemistry by total synthesis and optical rotation comparison. Therefore, these two pieces of evidence heavily suggested to us that the desired isomer of Roche ester would be the *S*-enantiomer and that the enantiomer of catalyst to achieve the triad would be Rh_2(*S*-TCPTTL)$_4$ (based

on previous work with $Rh_2(PTTL)_4$-like catalysts). With the knowledge of TM-135 as another natural product, it became immediately apparent that a divergent synthesis of **3**, **4**, and **8** would be possible using **52** as a key intermediate.

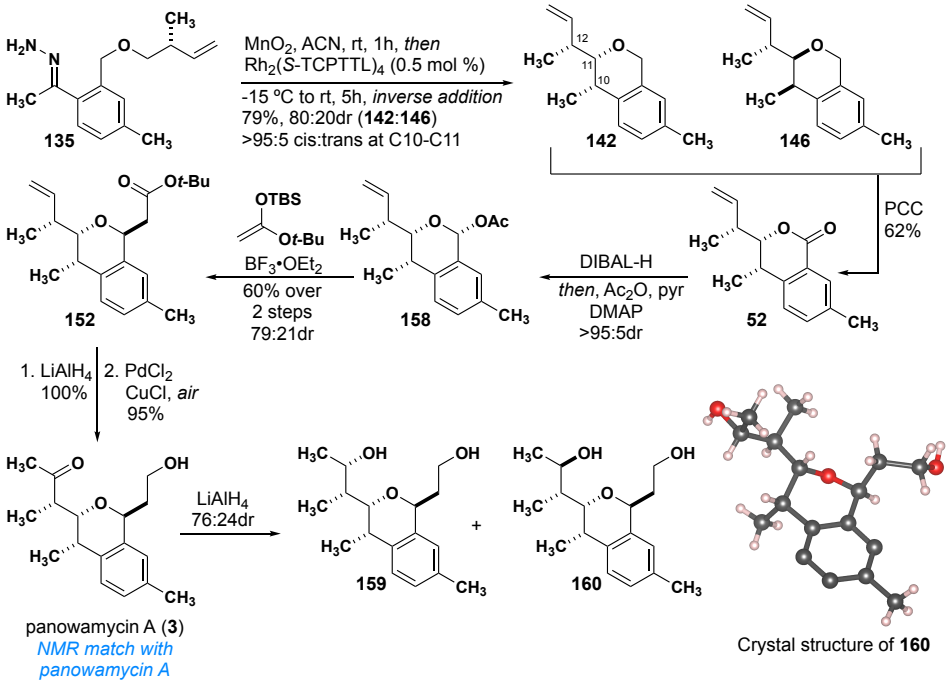


Figure 25. The first asymmetric total synthesis of panowamycin A

The mixture of diastereomers generated in the insertion reaction were both sent into the PCC oxidation, affording **52** in 65% as a single diastereomer after column chromatography. Based on a report by Hosokawa and coworkers,[100] which is derivative of the chemistry developed by Prof. Scott Rychnovsky,[101–103] we imagined that reduction of the lactone to the hemi acetal with DIBAL and *in situ* acylation with acetic anhydride should afford **158**. This intermediate could then be cleaved in the presence of a Lewis acid and the resultant oxocarbenium ion would be subject to *si*-face attack by a Mukaiyama-type silyl ketene acetal nucleophile, creating the C3 selectivity we required for panowamycin A. Satisfyingly, this sequence gave a single diastereomer of the acetoxy C3-substituted isochroman **158** (irrelevant with subsequent ablation), which then produced intermediate **152** in 79:21 dr. Of note, acetal

158 was observed to degrade and epimerize on silica during purification; the reduction/acylation/addition sequence was then performed without purification in between, giving **152** in 60% yield over two steps. Quantitative reduction of the pendant ester and subjection to the Wacker oxidation conditions afforded **3** in 95% yield. Inspection of and comparison to the NMR spectra reported by both Ōmura and Mahmud revealed a *match* and that we had completed the first total synthesis of panowamycin A, assisted by computational NMR to elucidate the natural isomer. Reduction of the ketone with lithium aluminum hydride afforded **159** and **160** in 76:24 dr and a crystal structure of minor isomer **160** was obtained. The optical rotation of panowamycin A matched the values reported by both Ōmura and Mahmud and we were then confident that we had unambiguously determined the relative and absolute stereochemistry of panowamycin A.

2.8.3 Asymmetric synthesis of TM-135 and panowamycin B

With Mahmud and coworkers' report of the isolation and elucidation of TM-135, we recognized the ability to synthesize **3** and **4** in a divergent sequence (Figure 26). By extension, this strategy would also allow us to synthesize panowamycin B (**8**) from the reduction of **4** (see Figure 20). The sequence shown in figure 20 was repeated again, this time using enantiopure **52**. Reduction of the pendant ester of **144** and subsequent Wacker oxidation afforded **4** in accordance with Mahmud's published NMR spectra for TM-135 and in alignment with their optical rotation measurements. Again, the major isomer of the reduction was consistent with the published NMR spectra for panowamycin B. However, optical rotation data for these products were not in agreement.

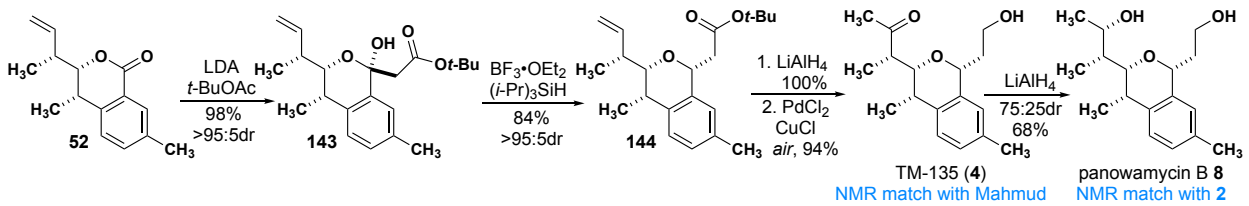


Figure 26. Divergent asymmetric total synthesis of TM-135 and panowamycin B

As mentioned above, optical rotation measurements for panowamycin A and TM-135 are consistent with Ōmura and Mahmud in both sign and magnitude (confirming Mahmud's proposed absolute configuration). However, panowamycin B was measured to be the *opposite* sign with similar magnitude. Although it is possible that we have synthesized *ent*-panowamycin B, we consider it unlikely that this natural product would not conserve the three C10, C11, C12 stereotriad shared by **3**, **4**, and **6**. While the major diastereomer from the reduction of **3** (**159**, Figure 25) has a more similar sign and magnitude when compared to Ōmura's measurements, the NMR spectra of these compounds are noticably incongruent. Futhermore, ketones **3**, **4**, and **96** maintain the same sign as their diol analogues (both diastereomers). As such, we are confident in our stereochemical assignements and propose that there was a transcription error in the recording of the original measurement.

Table 10. Optical Rotation Comparison

	Panowamycin A	Panowamycin B	TM-135
Ōmura[104]	–49.4	–61.6	-
Mahmud[29]	–61.6	-	+39.0
Bergstrom[1]	–55.3	+69.2	+61.6

2.8.4 Asymmetric synthesis and structural reassignment of veramycin F

As we were preparing the supporting information and manuscript for the publication of the asymmetric total synthesis of panowamycin A, B, and TM-135, it came to our attention that a new class of related natural products, the veramycins, had been isolated by Schäberle and Bauer from *Streptomyces* sp. ST157608 in February of 2022.[22] One of the published structures, veramycin F (**44**), was immediately recognized as being accessible in a divergent synthesis, as it features the same isochroman core as the panowamycins and TM-135. Taking advantage of intermediate **52**, the Wacker oxidation produced **44**, which was not spectroscopically consistent with veramycin F (Figure 27). Lactone **161**, derived from C–H insertion minor isomer **146**, was also oxidized to produce **7**. This sample matched the NMR spectrum reported in the isolation publication and thereby completed the asymmetric synthesis and structural reassignment of the relative configuration of veramycin F (**7**). Interestingly, veramycin F contains a different relative configuration compared to the other related natural products isolated in their report (i.e. NFAT-133, panowamycins, benwamcyins, TM-123). Under biological or isolation/purifcation conditions, it is possible that the relatively acidic protons *alpha* to the ketone of **52** could epimerize to form *ent*-**7**.

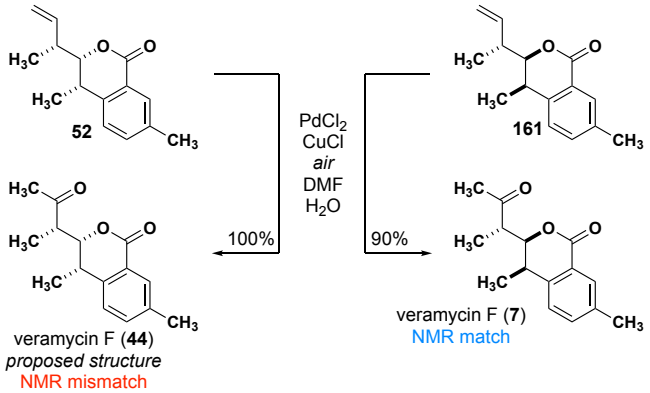


Figure 27. Asymmetric synthesis of veramycin F

2.9 Conclusions

In conclusion, we report the first synthesis of panowamycins A and B, as well as TM-135 and veramycin F through a common intermediate. These syntheses were accomplished asymmetrically by a C–H insertion reaction using a donor/donor carbene in the key bond-forming step. Having synthesized the originally proposed structure of panowamcyin A, we determined that Ōmura and coworkers had misassigned the structure of panowamycin A. Using NMR chemical shift computations, we predicted the structure of the natural substance, which was later confirmed to be correct by synthesis and NMR spectra comparison. Contemporaneous reports by Mahmud and coworkers provide independent support of these computational and synthetic efforts by an updated NMR spectral analysis of their isolated samples of panowamycin A. In this way, we report the unambiguous determination of the relative and absolute configuration of these natural products, thus enabling future studies of their biological activity.

2.10 Experimental Section

2.10.1 Synthetic and Natural Product NMR Spectra Comparison Tables

Note: Spectra for the natural substance panowamycin A (**3**) and TM-135 (**4**) were provided by Prof. Dr. Taifo Mahmud.[29] Spectra for panowamycin B (**5**) were provided by Prof. Dr. Satoshi Ōmura.[104] Spectra for veramycin F (**46**) were provided by Dr. Armin Bauer.[22]

Table 2.10.1 Optical Rotation Comparison

	Panowamycin A	Panowamycin B	TM-135
Ōmura[104]	–49.4	–61.6	-
Mahmud[29]	–61.6	-	+39.0
Bergstrom	–55.3	+69.2	+61.6

Table 2.10.2 Panowamycin A (**3**) and **3** ^{1}H, ^{13}C NMR, MeOD Comparison

	^{1}H NMR (ppm)*		^{13}C NMR (ppm)†	
	Mahmud (**3**)	Bergstrom (**3**)	Mahmud (**3**)	Bergstrom (**3**)
1	3.79 (ddd)	3.77 (ddd)	60.0	59.9
	3.89 (ddd)	3.86 (ddd)	-	-
2	1.90 (m)	1.88 (m)	39.5	39.4
	2.13 (m)	2.12 (m)	-	-
3	5.00 (dd)	4.98 (dd)	73.5	73.4
4	-	-	138.2	138.2
5	6.88 (s)	6.86 (s)	126.8	126.8
6	-	-	136.9	136.9
6-CH_3	2.30 (s)	2.28 (s)	21.3	21.3
7	6.99 (dd)	6.99-6.93 (2H, m)	128.6	128.6
8	6.97 (d)		129.9	129.9
9	-	-	138.5	138.5
10	2.68 (m)	2.66 (qd)	35.5	35.6
10-CH_3	1.10 (d)	1.08 (d)	17.7	17.6
11	3.94 (dd)	3.92 (dd)	72.9	72.9
12	2.92 (m)	2.90 (dq)	50.6	50.6
12-CH_3	1.31 (d)	1.29 (d)	15.9	15.9
13	-	-	213.6	213.6
14	2.27 (s)	2.24 (s)	29.4	29.3

*referencing Mahmud and Bergstrom MeOD residual solvent peak to 3.31 ppm
†referencing Mahmud and Bergstrom MeOD residual solvent peak to 49.00 ppm

Table 2.10.3 Panowamycin B (**2**) and **5** ^{1}H, ^{13}C NMR, $CDCl_3$ Comparison

	^{1}H NMR (ppm)*		^{13}C NMR (ppm)†	
	Ōmura (**2**)	Bergstrom (**5**)	Ōmura (**2**)	Bergstrom (**5**)
1	3.82 (ddd)	3.90-3.78 (m)	61.3	61.4
	3.87		-	-
2	2.02 (d)	2.01 (m)	37.9	38.1
	2.30 (m)	2.30 (m)	-	-
3	4.97 (dd)	4.95 (dd)	78.6	78.7
4	-	-	136.5	136.7
5	6.83 (s)	6.83 (s)	124.5	124.7
6	-	-	135.8	135.9
6-CH_3	2.29 (s)	2.30 (s)	21.2	21.3
7	7.00 (dd)	7.03-6.98 (m)	127.5	127.6
8	7.01 (d)		129.0	129.1
9	-	-	138.3	138.4
10	2.90 (qd)	2.91 (qd)	34.5	34.5
10-CH_3	1.18 (2)	1.18 (d)	17.4	17.5
11	3.60 (dd)	3.59 (dd)	79.2	79.3
12	1.71 (ddd)	1.70 (dddd)	40.3	40.4
12-CH_3	1.06 (d)	1.06 (d)	8.9	9.0
13	4.08 (qd)	4.06 (dd)	67.2	67.2
14	1.23 (d)	1.23 (d)	21.5	21.6

*referenced $CDCl_3$ residual solvent peak to 7.26 ppm

†referenced $CDCl_3$ residual solvent peak to 77.16 ppm

Table 2.10.4 TM-135 and **4** ^{1}H, ^{13}C NMR, MeOD Comparison

	^{1}H NMR (ppm)*		^{13}C NMR (ppm)†	
	Mahmud (**4**)	Bergstrom (**4**)	Mahmud (**4**)	Bergstrom (**4**)
1	3.70 (m)	3.70 (m)	59.8	59.8
	3.82 (dt)	3.82 (dt)	-	-
2	1.88 (m)	1.89 (dddd)	40.3	40.3
	2.26 (m)	2.26 (m)	-	-
3	4.85 (dd)	4.84 (dd)	76.3	76.4
4	-	-	138.1	138.1
5	6.94 (s)	6.93 (s)	125.5	125.5
6	-	-	136.9	136.9
6-CH_3	2.29 (s)	2.28 (s)	128.4	128.4
7	6.98 (d)	6.99-6.94 (m)	129.9	129.9
8	6.96 (d)		139.0	139.0
9	-	-	35.7	35.8
10	2.67 (qd)	2.67 (qd)	79.1	79.1
10-CH_3	1.12 (d)	1.11 (d)	50.6	50.6
11	3.67 (dd)	3.70 (m)	213.6	213.5
12	2.90 (dq)	2.90 (m)	29.1	29.1
12-CH_3	1.29 (d)	1.29 (d)	21.3	21.3
13	-	-	17.8	17.8
14	2.23 (s)	2.22 (s)	15.3	15.2

*referenced Mahmud and Bergstrom MeOD residual solvent peak to 3.31 ppm

†referenced Mahmud and Bergstrom MeOD residual solvent peak to 49.00 ppm

Table 2.10.5 Veramycin F and **46** ^{1}H, ^{13}C NMR, MeOD Comparison$^{\Delta}$

	^{1}H (ppm)		^{13}C (ppm)	
	Schäberle, et al.[22]	Bergstrom (**46**)	Schäberle, et al.	Bergstrom (**46**)
3	-	-	167.3	167.0
4	-	-	124.4	124.4
5	7.79	7.76	131.2	131.1
6	-	-	139.0	139.0
7	7.46	7.44	136.4	136.4
8	7.29	7.27	128.4	128.4
9	-	-	144.8	144.7
10	3.12	3.19-3.07	34.0	33.9
11	4.69	4.68	83.8	83.5
12	3.15	3.19-3.07	48.5	48.5
13	-	-	212.4	212.3
14	2.30	2.30	30.2	30.2
18	2.38	2.37	20.9	21.0
19	1.17	1.16	14.8	14.8
20	1.13	1.12	12.7	12.7

$^{\Delta}$numbering convention preserved from Schäberle et al.
*referenced MeOD residual solvent peak to 3.31 ppm
†referenced MeOD residual solvent peak to 49.00 ppm

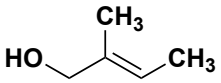
2.10.2 Experimental Procedures

2.10.2.1 General Comments.

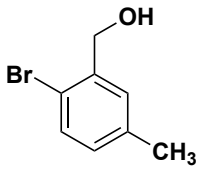
Chemicals were purchased and used without further purification unless otherwise specified. All reactions used anhydrous solvents and were carried out under an atmosphere of industrial argon in flame-dried glassware with magnetic stirring (unless otherwise specified). Anhydrous tetrahydrofuran (THF), diethyl ether, dichloromethane (DCM), and toluene were dispensed from a solvent purification system that passes solvent through two columns of dry neutral alumina. Reactions were monitored by thin layer chromatography (TLC, Merck), and detected by examination under UV light (254 nm and 365 nm) and/or aqueous, basic, $KMnO_4$ stain. Flash column chromatography was performed using silica gel [230–400 mesh (40–63 μm)]. Extracts were concentrated *in vacuo* using both a rotary evaporator (bath temperatures up to 40 °C) at a pressure of ≥10 torr (diaphragm pump). High vacuum procedures were carried out at room temperature at a pressure of 1 mtorr (diaphragm pump) or ≥1000 mtorr (oil pump). ^1H and proton-decoupled ^{13}C spectra were measured in $CDCl_3$ at 300, 400, or 600 MHz, and 75, 100, or 150 MHz, respectively, unless otherwise noted. All spectra in $CDCl_3$ were referenced at TMS = 0 ppm. Multiplicities are given as: s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), m (multiplet), or combinations of these signals. Apparent signals are indicated with *app*. And are used when signals with multiple couplings appear to form a specific peak type. High-resolution mass spectrometry was performed on positive mode and ESI/Orbitrap, and APCI techniques were generally used. For substrate ***E*-15**, high-resolution mass spectrometry using the aforementioned techniques was not achieved; low-resolution mass spectrometry using an Advion ASAP-APCI-MS was achieved and the corresponding data is reported for that compound. Melting points were taken on an EZ-melting apparatus and are uncorrected. A Harvard Apparatus syringe pump (Pump 11, cat.# 55-1199) was used for slow addition for the inverse

addition insertion reaction protocol. Infrared spectra were taken on a Bruker Tensor 27 spectrometer. NOTE: it is *necessary* that the MnO_2 used for the oxidation of hydrazones be ~85% pure with an average particle size of 2 microns, appearing as a *fine black powder* (e.g. Sigma Aldrich CAS #: 1313-13-9, cat. # 217646, lot #: MKCJ7777, or Oakwood Chemical, CAS #: 1313-13-9, cat. #: 094454, lot #: 094454K03K).

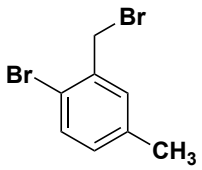
2.10.2.2 Tiglyl route



tiglyl alcohol (***E*-77**) was synthesized, following a modified literature procedure,[105] by preparing a suspension of lithium aluminum hydride (0.592 g, 15.6 mmol, 1 equiv.) in diethyl ether (1.5 M). The suspension was cooled to 0 °C and ethyl tiglate (2.008 g, 15.60 mmol, 1 equiv.) was added dropwise; the reaction mixture was allowed to stir to room temperature overnight. The heterogenous solution was then cooled to 0 °C, H_2O (0.60 mL) was added dropwise, allowing to stir for 15 minutes, then 10% aqueous NaOH (0.6 mL) was added dropwise. The ice bath was then removed and H_2O (1.8 mL) was added dropwise, allowing to stir to room temperature for 30 minutes. A large quantity of magnesium sulfate was added to the mixture, allowing to stir for 30 minutes, and the mixture was filtered through a glass frit funnel under gentle vacuum, washing generously with diethyl ether (30 mL). The solution was then concentrated *in vacuo* (≥200 torr, 0 °C bath temperature) and ***E*-77** (7.606 g, 100%) was used without further purification as a colorless 44% w/w solution in diethyl ether. ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.49 (q, J = 6.8 Hz, 1H), 4.00 (s, 2H), 1.67 (s, 3H), 1.63 (d, J = 6.8 Hz, 3H), 1.57 – 1.46 (m, 1H). ^{1}H NMR spectrum is consistent with literature.[105]

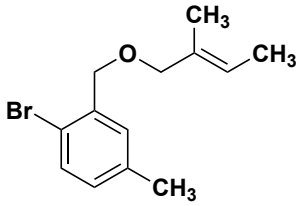


2-bromo-5-methyl-benzyl alcohol (**153**) was synthesized, following a modified literature procedure,[106] by preparing a solution of 2-bromo-5-methyl benzoic acid (5.069 g, 23.57 mmol, 1.0 equiv.) in THF (0.33 M). This solution was cooled to 0 °C and a solution of borane dimethyl sulfide complex (35 mL, 70.00 mmol, 3 equiv.) was slowly added to the mixture. The reaction mixture was stirred at 0 °C for 3 hours, then allowed to warm to room temperature overnight. The reaction was then *carefully* quenched at room temperature with 1M HCl until bubbling no longer persisted. This mixture was then extracted with diethyl ether (50mL x3); the combined organic layers were washed with brine (50mL x1), dried over sodium sulfate, and concentrated *in vacuo* to afford **153** (4.741 g) as a white solid in quantitative yield without purification. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41 (d, J = 8.0 Hz, 1H), 7.29 (s, 1H), 6.98 (d, J = 7.9 Hz, 1H), 4.71 (s, 2H), 2.32 (s, 3H), 2.00 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 139.4, 137.8, 132.5, 130.1, 129.9, 119.9, 64.4, 23.7; ^{1}H and ^{13}C NMR spectra are consistent with literature.[107]

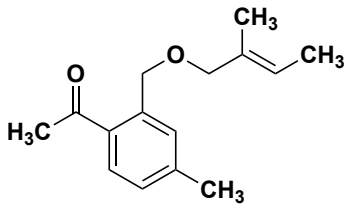


2-bromo-5-methyl-benzyl bromide (**78**) was synthesized, following a modified literature procedure,[108] by preparing a solution of **153** (4.785 g, 23.80 mmol, 1 equiv.) in THF (0.85 M). This solution was cooled to 0 °C and phosphorous tribromide (1.34 mL, 14.28 mmol, 0.6 equiv.) was added dropwise. The reaction mixture was stirred for 1 hour at 0 °C and concentrated *in vacuo* (NOTE: concentration *in vacuo* should be performed in a fume hood). The crude product was purified using flash column chromatography (90hexanes:10EtOAc) affording **78** (6.220 g, 99%) as a white solid. ^{1}H NMR (600 MHz, CD_2Cl_2) δ 5.91

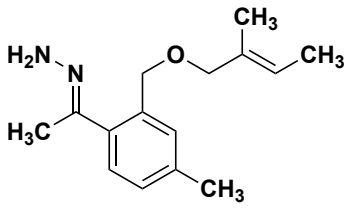
(d, *J* = 8.2 Hz, 1H), 5.75 (s, 1H), 5.47 (t, *J* = 8.0 Hz, 1H), 3.04 (s, 2H), 0.76 (s, 3H); ^{13}C NMR (150 MHz, CD_2Cl_2) δ 138.3, 136.7, 133.0, 132.0, 131.1, 117.3, 33.7, 20.5; ^{1}H and ^{13}C NMR spectra are consistent with literature.[107]



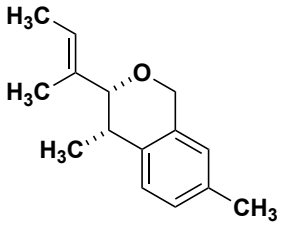
1-bromo-4-methyl-2-((tiglyloxy)methyl)benzene (***E*-79**) was synthesized, following a modified literature procedure,[109] by preparing a suspension of sodium hydride (1.602 g, 40.05 mmol, 3 equiv.) in THF (0.89 M), allowing to stir for 10 minutes. **78** (2.502 g, 20.02 mmol, 1.5 equiv.) was then added dropwise to the suspension, allowing to stir for 1 hour; ***E*-77** (3.524 g, 13.35 mmol, 1 equiv., as a 0.89 M solution in THF) was then added dropwise, allowing to stir overnight. The reaction mixture was carefully quenched with saturated aqueous ammonium chloride until the opaque mixture became clear. The crude mixture was extracted with ethyl acetate (10 mL x3), washed with saturated aqueous sodium chloride (30 mL x 1), dried over sodium sulfate, concentrated *in vacuo*, and purified using flash column chromatography (95hexanes:5ethyl acetate), affording ***E*-79** (0.9521 g, 93%) as a clear oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.1 Hz, 1H), 7.30 (s, 1H), 6.94 (d, *J* = 8.1 Hz, 1H), 5.55 (q, *J* = 6.9 Hz, 1H), 4.47 (s, 2H), 3.97 (s, 2H), 2.31 (s, 3H), 1.70 (s, 3H), 1.65 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.1, 137.4, 132.9, 132.3, 130.0, 129.7, 123.1, 119.5, 77.1, 71.0, 21.1, 15.7, 13.4; IR (neat) 2924, 2867, 1468, 905, 728 cm^{-1}; LRMS (see Section 3.1) *m/z* calcd $C_{13}H_{18}BrO^+$ $[M+H]^+$ 269.0536, found 269.9401.



2-((tiglyloxy)methyl)-4-methyl acetophenone (***E*-80**) was synthesized, following a modified literature procedure,[110] by preparing a solution of ***E*-79** (2.793 g, 10.37 mmol, 1 equiv.) in THF (0.27 M). This solution was cooled to -78 °C and *n*-butyl lithium (5.86 mL, 13.5 mmol, 1.3 equiv., as a solution in *n*-hexanes) was added dropwise, allowing to stir for 2 hours. The reaction mixture was then cooled to -78 °C and *N*-methoxy-*N*-methylacetamide **74** (1.299 g, 12.45 mmol, 1.2 equiv., as a 0.8 M solution in THF) was added dropwise, allowing to stir and warm to room temperature overnight. The mixture was cooled to -78 °C and the reaction was quenched dropwise with saturated aqueous ammonium chloride, allowing the solution to warm to room temperature. The crude mixture was then extracted with ethyl acetate (10 mL x3); organic layers were combined, washed with saturated aqueous sodium chloride (30 mL x1), dried over sodium sulfate, concentrated *in vacuo*, and purified by flash column chromatography (90hexanes:10ethyl acetate) to afford ***E*-80** (1.107 g, 46%) as a clear oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.9 Hz, 1H), 7.55 (s, 1H), 7.14 (d, *J* = 7.9 Hz, 1H), 5.55 (q, *J* = 6.7 Hz, 1H), 4.77 (s, 2H), 3.97 (s, 2H), 2.56 (s, 3H), 2.41 (s, 3H), 1.69 (s, 3H), 1.64 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 200.3, 142.4, 139.9, 133.3, 133.1, 130.7, 128.5, 127.4, 123.9, 77.1, 70.0, 27.4, 21.1, 13.8, 13.3; IR (neat) 2918, 2858, 1678, 1356, 1252, 1082 cm^{-1}; AMM (ESI) *m/z* calcd $C_{15}H_{21}O_2^+$ $[M+H]^+$ 233.1536, found 233.1531.

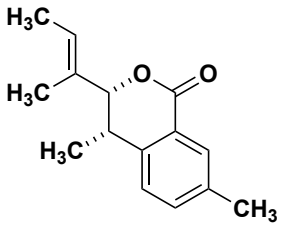


2-((tiglyloxy)methyl)-4-methyl acetophenone hydrazone (***E*-81**) was synthesized, following our literature procedure,[111] by preparing a solution of ***E*-80** (0.100 g, 0.429 mmol, 1 equiv.) in anhydrous ethanol (0.1 M), which was then sparged vigorously with argon for 15 minutes. Hydrazine (80 µL, 2.58 mmol, 6 equiv.) and glacial acetic acid (30 µL, 0.500 mmol, 1.2 equiv.) were then added to the solution and the mixture was sparged vigorously with argon for 1 minute. A reflux condenser was attached to the flask and the solution was heated to 80 °C, allowing to stir overnight. The reaction mixture was allowed to cool to room temperature, diluted with diethyl ether (10 mL), and washed with H_2O (10 mL), washed with saturated aqueous sodium chloride (10 mL), dried over sodium sulfate, and concentrated *in vacuo*. ***E*-81** (0.106g 100%) was isolated as a ~50:50 mixture of stereoisomers and used without purification in the next step; this complex ^{1}H NMR spectrum is included for informational purposes. IR (neat) 3384, 3210, 2918, 2859, 1613, 1445, 1365 cm^{-1}; AMM (ESI) *m/z* calcd $C_{15}H_{23}N_2O^+$ $[M+H]^+$ 247.1805, found 247.1803.



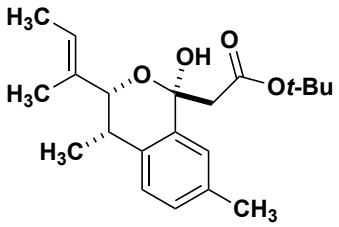
(3*S*,4*R*)-3-((*E*)but-2-en-2-yl)-4,7-dimethylisochroman (***E*-82**) was synthesized, following our two-pot literature procedure,[112] by preparing a solution of the crude mixture of ***E*-81** (1.243 g, 5.044 mmol, 1 equiv.) in acetonitrile (0.05 M). MnO_2 (3.506 g, 40.328 mmol, 8 equiv., see section 1.1 for reagent details) was added, allowing to stir for 30 minutes, producing a bright fuchsia colored solution when stirring is halted. This heterogenous mixture was then filtered through celite, washing with acetonitrile to a final concentration of 0.015M (335mL total). The headspace of the receiving flask was then purged with argon and the solution was cooled to -20 °C. Rh_2(*R*-PTAD)$_4$ (0.006 g, 0.004 mmol, 0.07 mol %) was added and

the mixture was allowed to stir overnight. The clear solution was then concentrated *in vacuo* and purified by flash column chromatography (90hexanes:10ethyl acetate) to afford ***E*-82** (0.857g, 69%, >95:5dr, 10:90er) as a clear oil. At 0.2 mmol scale, the above procedure yielded 79% (>95:5dr, 93:7er) with Rh_2(*S*-TCPTTL)$_4$ as catalyst. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.05 (d, *J* = 7.8 Hz, 1H), 7.00 (d, *J* = 7.9 Hz, 1H), 6.82 (s, 1H), 5.64 (q, *J* = 7.0 Hz, 1H), 4.90 (d, *J* = 15.0 Hz, 1H), 4.82 (d, *J* = 15.0 Hz, 1H), 4.06 (s, 1H), 2.84 (q, *J* = 7.3 Hz, 1H), 2.30 (s, 3H), 1.68 (d, *J* = 6.9 Hz, 3H), 1.63 (s, 3H), 1.02 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.6, 135.6, 133.9, 133.4, 128.9, 127.3, 124.4, 118.5, 80.2, 68.8, 34.4, 21.5, 17.1, 13.7, 12.9; IR (neat) 2967, 2926, 1446, 1119, 816 cm^{-1}; AMM (APCI) *m/z* calcd $C_{15}H_{21}O^+$ $[M+H]^+$ 217.1587, found 217.1588; $[\alpha]^{19}_D$ +138.1 (c = 0.12, CH_3OH).



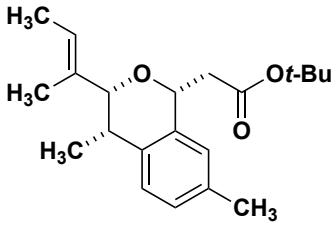
(3*R*,4*S*)-3-((*E*)but-2-en-2-yl)-4,7-dimethylisochroman-1-one (**87**) was synthesized, following a modified literature procedure,[113] by preparing a solution of ***E*-82** (0.0.275 g, 1.294 mmol, 1 equiv.) in DCM (0.2 M). Pyridinium chlorochromate (2.529 g, 11.743 mmol, 9 equiv.) was then added to the flask, a reflux condenser attached, and the mixture was lowered into a 60 °C oil-bath, allowing to reflux overnight. The mixture was then diluted with diethyl ether (20mL), silica gel (~2 g) was then added, allowing the heterogenous mixture to stir for 30 minutes. The mixture was filtered through a celite/silica plug, eluting with diethyl ether (50 mL), concentrated *in vacuo*, then purified by flash column chromatography (90hexanes:10ethyl acetate) to afford **87** (0.220 g, 75%) as a white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.36 (d, *J* = 7.8 Hz, 1H), 7.17 (d, *J* = 7.7 Hz, 1H), 5.86 (q, *J* = 6.8 Hz, 1H), 4.88 (s, 1H), 3.05 (q, *J* = 6.9 Hz, 1H), 2.39 (s, 3H), 1.71 (d, *J* = 6.9 Hz, 3H), 1.67 (s, 3H), 1.06 (d, *J* = 7.1

Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.1, 143.3, 137.4, 134.9, 130.7, 130.1, 126.9, 123.9, 121.4, 84.8, 35.1, 21.0, 15.2, 13.4, 13.1; IR (neat): 2919, 2862, 1713, 1276, 1187 cm^{-1}; m.p. 107-108 °C; AMM (ESI) *m/z* calcd for $C_{15}H_{19}O_2^+$ $[M+H]^+$ 231.1380, found 231.1382; $[\alpha]^{17}_D$ –184.8 (c = 0.09, CH_3OH); the provided crystal structure was obtained from an analogous reaction using Rh_2(*R*-PTAD)$_4$ and therefore has (3*S*,4*R*) configuration.



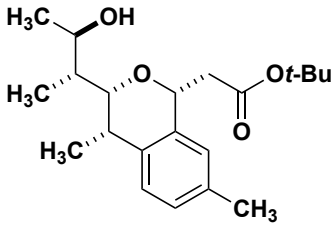
tert-butyl 2-(1*R*,3*S*,4*R*)-3-((*E*)but-2-en-2-yl)-1-hydroxy-1-4,7-dimethylisochroman-1-yl) acetate (**88**) was synthesized, following a modified literature procedure,[114] by preparing a solution of diisopropylamine (0.16 mL, 1.1 mmol, 1.6 equiv.) in THF (0.56 M). The solution was cooled to -78 °C and *n*-butyllithium (0.46 mL, 1.1 mmol, 1.6 equiv.) was added dropwise, allowing to stir for 15 minutes. The solution was warmed to 0 °C, stirred for 15 minutes, cooled down to -78 °C, and *tert*-butyl acetate (0.15 mL, 1.1 mmol, 1.6 equiv.) was added dropwise, allowing to stir for 10 minutes. The *tert*-butyl acetate enolate was then quickly transferred dropwise via syringe into a -78 °C solution of **87** (0.161 g, 0.699 mmol, 1 equiv.) in THF (0.14 M), allowing to stir at -78 °C for 15 minutes. The reaction was quenched with saturated aqueous ammonium chloride (4 mL), warmed to room temperature, extracted with dichloromethane (5 mL x 3), dried over sodium sulfate, concentrated *in vacuo*, and purified by flash column chromatography (90hexanes:10ethyl acetate) to afford **88** (0.230 g, 95%, 84:16 dr) as a yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.13 (s, 1H), 7.07 (d, *J* = 7.7 Hz, 1H), 7.03 (d, *J* = 7.8 Hz, 1H), 5.64 (q, *J* = 8.5, 7.7 Hz, 1H), 5.57 (s, 1H), 3.01 (d, *J* = 14.7 Hz, 1H), 2.80 (q, *J* = 7.1 Hz, 1H), 2.63 (d, *J* = 14.7 Hz, 1H), 2.32 (s, 3H), 1.65 (d, *J* = 6.9 Hz, 3H), 1.62 (s, 3H), 1.53 (s, 9H), 0.97 (d, *J* = 8.5 Hz, 3H); ^{13}C

NMR (150 MHz, $CDCl_3$) δ 171.6, 138.3, 136.2, 135.8, 133.1, 129.9, 128.2, 127.0, 118.4, 96.6, 82.1, 73.3, 46.9, 35.0, 28.2, 21.3, 16.1, 13.6, 12.9; IR (neat) 3439, 2973, 2928, 1703, 1369, 1146 cm^{-1}; AMM (ESI) *m/z* calcd $C_{21}H_{30}O_4Na^+$ $[M+Na]^+$ 369.2036, found 369.2017; $[\alpha]^{21}_D$ +11.6 (c = 0.22, CH_3OH).



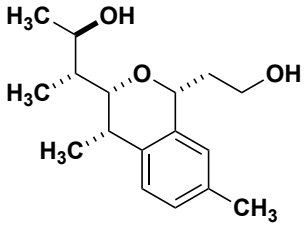
tert-butyl 2-(1*S*,3*S*,4*R*)-3-((*E*)but-2-en-2-yl)-1-4,7-dimethylisochroman-1-yl) acetate (**89**) was synthesized, following a modified literature procedure,[114] by preparing a solution of **88** (0.158 g, 0.455 mmol, 1 equiv.) and triisopropylsilane (1.86 mL, 9.092 mmol, 20 equiv.) in dichloromethane (0.15 M). This solution was cooled to -78 °C and boron trifluoride diethyl etherate complex (0.56 mL, 4.546 mmol, 10 equiv.) was added dropwise, allowing the mixture to stir for 4 hours at -78 °C. The reaction was then placed in an acetonitrile/dry ice bath and stirred for 20 hours at -40 °C. The reaction mixture was then cooled to -78 °C and syringed dropwise into a 0 °C solution of dichloromethane (5mL, 0.1 M) and saturated aqueous sodium bicarbonate (9mL) (2:3 ratio of dichloromethane:saturated aqueous sodium bicarbonate by volume), allowing to stir at 0 °C for 15 minutes. The mixture was allowed to warm to room temperature, stirred for 15 minutes, extracted with dichloromethane (10 mL x2); combined extracts were dried over sodium sulfate, concentrated *in vacuo*, and purified by column chromatography (100% hexanes flush, then 95hexanes:5ethyl acetate) to afford **89** (0.151g, 100%, >95:5 dr) as a clear oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.03 (d, *J* = 7.9 Hz, 1H), 7.01 (d, *J* = 8.0 Hz, 1H), 6.88 (s, 1H), 5.66 (q, *J* = 6.8 Hz, 1H), 5.18 (dd, *J* = 9.2, 3.8 Hz, 1H), 4.06 (s, 1H), 2.86 (dd, *J* = 14.7, 3.3 Hz, 1H), 2.81 (q, *J* = 13.7, 7.2 Hz, 1H), 2.62 (dd, *J* = 14.6, 9.0 Hz, 1H), 2.30 (s, 3H), 1.65 (d, *J* = 6.9 Hz, 3H), 1.59 (s, 3H), 1.48 (s, 9H), 1.02 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.9, 138.4, 136.4, 135.8, 132.5, 129.1, 127.6, 124.7,

118.5, 80.6, 79.1, 74.7, 43.7, 35.1, 28.2, 21.3, 17.3, 13.5, 12.9; IR (neat) 2975, 2928, 1731, 1366, 1151 cm^{-1}, AMM (ESI) *m/z* calcd $C_{21}H_{30}O_3Na^+$ $[M+Na]^+$ 353.2087, found 353.2089; $[\alpha]^{21}_D$ +11.7 (c = 0.06, CH_3OH).



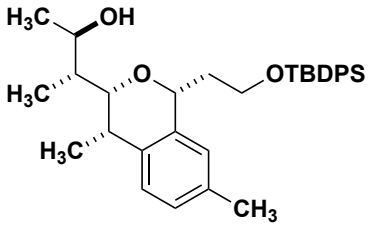
tert-butyl 2-((1*R*,3*R*,4*S*)-3-((2*R*,3*R*)-3-hydroxybutan-2-yl)-4,7-dimethylisochroman-1-yl) acetate (**90**) was synthesized, following a modified literature procedure,[115] by preparing solution of BH_3•DMS (0.32mL, 3.115mmol, 2.7equiv.) in THF (1.3M) which was cooled to -78 °C. A solution of **89** (0.382g, 1.155mmol, 1equiv.) in THF (0.75M) was then added dropwise to the borane solution and the mixture was allowed to stir to room temperature overnight (13h). The mixture was then cooled to 0 °C and a solution of NaOH (8.4equiv., 0.5M) and NaCl (1equiv., 0.05M) was added. After 30 minutes of stirring, 30% aqueous H_2O_2 (1.25mL, 11.023mmol, 9.5equiv.) was added whereupon the clear solution turned opaque white, stirring at 0 °C for 2 hours, then stirring at room temperature for 2 hours. The organic layer was then separated, the aqueous layer was acidified with 1M HCl (~8mL), and extracted with diethyl ether (20mL x3). The combined organic extracts were washed with brine (30mL), dried over Na_2SO_4, concentrated *in vacuo*, and purified by flash column chromatography (80hexanes:20ethyl acetate to 70hexanes:30ethyl acetate gradient) to afford **90** (0.1315g, 33%) as a clear oil. The NMR spectrum of the unpurified reaction showed 79:21dr and the purified product was obtained as a 86:14 mixture of diastereomers and used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.03 – 7.00 (m, 2H), 6.86 (s, 1H), 5.13 (dd, J = 9.6, 3.3 Hz, 1H), 4.04 – 3.92 (m, 1H), 3.43 (dd, J = 8.3, 2.4 Hz, 1H), 2.85 (dd, J = 15.0, 3.3 Hz, 1H), 2.74 – 2.64 (m, 1H), 2.55 (dd, J = 15.0, 9.6 Hz, 1H), 2.30 (s, 3H), 2.04 – 1.91 (m,

1H), 1.49 (s, 9H), 1.25 (d, J = 7.0 Hz, 3H), 1.10 (d, J = 6.3 Hz, 3H), 1.03 (d, J = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.0, 138.6, 136.4, 136.0, 129.0, 127.8, 124.7, 80.8, 78.7, 75.0, 68.2, 43.4, 41.3, 35.1, 28.3, 21.3, 18.5, 17.8, 10.1; IR (neat) 3423, 2972, 2932, 1729, 1368, 1152, 1092 cm^{-1}; AMM (ESI) *m/z* calcd for $C_{21}H_{32}O_4Na^+$ $[M+Na]^+$ 371.2193, found 371.2194; $[\alpha]^{20}_D$ +11.9 (c = 0.13, CH_3OH).



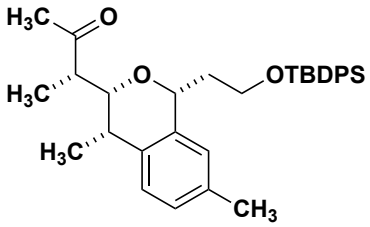
13-*epi*-panowamycin B (**91**) was synthesized, following a modified literature procedure,[105] by preparing a suspension of lithium aluminum hydride (0.026 g, 0.689 mmol, 2 equiv.) in diethyl ether (1.0 M). The suspension was cooled to 0 °C and **90** (0.107 g, 0.344 mmol, 1 equiv.) was added dropwise as a solution in diethyl ether (0.3 M); the reaction mixture was allowed to stir to room temperature overnight. The heterogenous solution was then cooled to 0 °C, H_2O (26 μL) was added dropwise, allowing to stir for 15 minutes, then 10% aqueous NaOH (26 μL) was added dropwise. The ice bath was then removed and H_2O (78 μL) was added dropwise, allowing to stir to room temperature for 30 minutes. A generous quantity of magnesium sulfate was added to the mixture, allowing to stir for 30 minutes, and the mixture was filtered through a glass frit funnel under gentle vacuum, washing generously with diethyl ether (30 mL). The solution was then concentrated *in vacuo*, purified by flash column chromatography (30hexanes:70ethyl acetate), affording **91** (0.060 g, 70%) as a white amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 – 6.99 (m, 2H), 6.85 (s, 1H), 4.97 (dd, J = 8.4, 3.3 Hz, 1H), 4.04 – 3.96 (m, 1H), 3.91 – 3.79 (m, 2H), 3.41 (dd, J = 8.7, 2.4 Hz, 1H), 2.96 (s, 1H), 2.70 (qd, J = 7.0, 2.2 Hz, 1H), 2.34 – 2.26 (m, 4H), 2.08 – 1.94 (m, 2H), 1.72 (s, 1H), 1.25 (d, J = 6.9 Hz, 3H), 1.09 (d, J = 6.4 Hz, 3H), 1.06 (d, J = 6.8 Hz, 3H); ^{1}H NMR (400 MHz, MeOD) δ 7.02 – 6.97 (m, 2H), 6.95 (s, 1H), 4.82 (dd, J = 9.0, 2.7 Hz, 1H), 3.99 (qd, J = 6.4,

4.1 Hz, 1H), 3.84 (dt, J = 10.5, 7.3 Hz, 1H), 3.77 – 3.69 (m, 1H), 3.29 (dd, J = 9.4, 2.4 Hz, 1H), 2.71 (qd, J = 6.9, 2.2 Hz, 1H), 2.33 – 2.23 (m, 4H), 2.02 – 1.95 (m, 1H), 1.90 (dddd, J = 13.8, 8.9, 7.0, 4.7 Hz, 1H), 1.21 (d, J = 6.9 Hz, 3H), 1.08 – 1.04 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.2, 136.6, 136.1, 129.0, 127.7, 124.8, 79.3, 78.6, 67.6, 61.3, 41.2, 38.1, 35.1, 21.3, 18.1, 17.5, 10.1; ^{13}C NMR (100 MHz, MeOD) δ 139.5, 138.4, 136.8, 129.9, 128.3, 125.5, 80.2, 76.4, 67.6, 60.1, 42.2, 40.2, 36.0, 21.3, 17.7, 17.2, 10.0; IR (neat) 3333, 2967, 2926, 1374, 1057, 905, 731 cm^{-1}; AMM (ESI) *m/z* calcd $C_{17}H_{26}NaO_3^+$ $[M+Na]^+$ 301.1779, found 301.1786; $[\alpha]^{21}_D$ +80.1 (c = 0.30, CH_3OH).



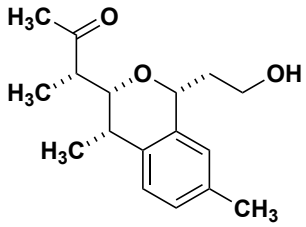
(2*R*,3*R*)-3-((1*R*,3*R*,4*S*)-1-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)-4,7-dimethylisochroman-3-yl)butan-2-ol (**162**) was synthesized, following a modified literature procedure,[116] by preparing a solution of **91** (0.060 g, 0.216 mmol, 1 equiv.) in DCM (0.2 M). Net_3 (60 μL, 0.431 mmol, 2 equiv) and DMAP (0.003g, 0.022 mmol, 0.1 equiv) were added and the mixture was cooled to 0 °C. TBDPS-Cl (57 μL, 0.220 mmol, 1.02 equiv) was then added and the solution was allowed to stir to room temperature overnight. H_2O (1 mL) was then added; the organic layer separated, washed with sat. aq. NaCl (4 mL), dried over Na_2SO_4, concentrated *in vacuo*, and purified by flash column chromatography (80hexanes:20ethyl acetate) to afford **162** (0.100 g, ~90%) as a clear oil. The silyl ether was unable to be separated from residual TBDPS-OH and the impure mixture was carried through to the next step. NMR spectra are included for informational purposes. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.66 (m, 4H), 7.40 – 7.34 (m, 4H), 7.01 – 6.93 (m, 2H), 6.84 (s, 1H), 4.89 (d, *J* = 7.0 Hz, 1H), 4.08 – 4.00 (m, 1H), 4.00 – 3.93 (m, 1H), 3.90 – 3.82 (m, 1H), 3.33 (dd, *J* = 8.8, 2.3 Hz, 1H), 2.67 (q, *J* = 5.8 Hz, 1H), 2.33 – 2.21 (m, 4H), 1.96 – 1.84 (m,

2H), 1.18 (d, *J* = 6.9 Hz, 3H), 1.07 (s, 9H), 0.98 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 137.8, 135.8, 135.7, 135.7, 134.3, 134.2, 129.7, 128.8, 127.7, 127.3, 124.8, 78.7, 74.4, 67.8, 60.8, 60.5, 41.3, 39.7, 35.0, 27.0, 21.3, 19.4, 18.2, 17.6, 14.3, 9.9; IR(neat) 3388, 2963, 2930, 1109, 907, 731, 701 cm^{-1}; AMM (ESI) *m/z* calcd $C_{33}H_{45}O_3SiNa^+$ $[M+Na]^+$ 539.2952, found 539.2956; $[\alpha]^{21}_D$ +2.4 (c = 0.08, CH_3OH).



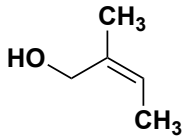
(*S*)-3-((1*R*,3*R*,4*S*)-1-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)-4,7-dimethylisochroman-3-yl)butan-2-one (**163**) was synthesized, following a modified literature procedure,[99] by preparing a solution of oxalyl chloride (35 μL, 0.387 mmol, 2 equiv.) in DCM (0.27 M). The solution was cooled to -78 °C and DMSO (57 μL, 0.774 mmol, 4 equiv.) was added, stirring for 30 minutes. A solution of **162** (0.100 g, 0.194 mmol, 1 equiv.) in DCM (0.27 M) was added dropwise and the solution was stirred at – 78 °C for 1 hour. Net_3 (0.13 mL, 0.968 mmol, 5 equiv.) was then added and the mixture was allowed to stir to room temperature overnight. The reaction was quenched with 1M $NaHSO_4$ (1 mL), extracted with DCM (2 mL x 3), washed with sat. aq. $NaHSO_4$ (3 mL), H_2O (3 mL), sat. aq NaCl (3 mL), dried over Na_2SO_4, concentrated *in vacuo*, and purified by flash column chromatography (92hexanes:8ethyl acetate) to afford **163** (0.069 g, 69%) as a clear oil. ^{1}H NMR has overlapping signals with solvent in MeOD and $CDCl_3$; both spectra are reported for clarity and completeness. ^{1}H NMR (400 MHz, MeOD) δ 7.66 (td, *J* = 8.0, 1.7 Hz, 4H), 7.44 – 7.34 (m, 6H), 6.93 (d, *J* = 7.9 Hz, 1H), 6.90 (d, *J* = 7.8 Hz, 1H), 6.82 (s, 1H), 4.87 – 4.83 (m, 2H), 3.97 (ddd, *J* = 10.0, 8.1, 6.5 Hz, 1H), 3.79 (ddd, *J* = 10.1, 7.6, 4.1 Hz, 1H), 3.62 (dd, *J* = 9.8, 2.4 Hz, 1H), 2.80 (dq, *J* = 9.9, 6.9 Hz, 1H), 2.63 (qd, *J* = 7.5, 7.0, 2.2 Hz, 1H), 2.34 – 2.22 (m, 4H), 2.18 (s, 3H), 1.86 (dddd,

J = 13.9, 8.8, 6.6, 4.1 Hz, 1H), 1.18 (d, *J* = 6.9 Hz, 3H), 1.05 – 1.00 (m, 12H).; 1H NMR (300 MHz, $CDCl_3$) δ 7.72 – 7.65 (m, 4H), 7.46 – 7.33 (m, 6H), 6.97 (d, J = 9.4 Hz, 1H), 6.93 (d, J = 7.8 Hz, 1H), 6.83 (s, 1H), 4.90 (dd, J = 9.1, 0.9 Hz, 1H), 4.07 – 3.96 (m, 1H), 3.85 (ddd, J = 10.4, 7.1, 3.9 Hz, 1H), 3.70 (dd, J = 9.9, 2.4 Hz, 1H), 2.85 – 2.74 (m, 1H), 2.74 – 2.65 (m, 1H), 2.34 – 2.22 (m, 4H), 2.18 (s, 3H), 1.87 (dddd, J = 13.6, 9.6, 5.9, 3.9 Hz, 1H), 1.21 (d, J = 6.9 Hz, 3H), 1.10 – 1.04 (m, 12H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 211.1, 138.4, 137.7, 136.1, 136.0, 136.0, 134.6, 134.6, 130.0 (2 carbons overlapping), 129.2, 128.1 (2 carbons overlapping), 127.6, 125.0, 78.0, 74.8, 61.1, 49.9, 40.0, 34.9, 29.1, 27.1, 21.4, 19.5, 17.7, 15.4.; IR (neat) 2962, 2958, 2857, 1712, 1112, 702 cm^{-1}; AMM (ESI) *m/z* calcd $C_{33}H_{43}O_3SiNa^+$ $[M+Na]^+$ 537.2795, found 537.2805; $[\alpha]^{21}_D$ +2.0 (c = 0.10, CH_3OH).

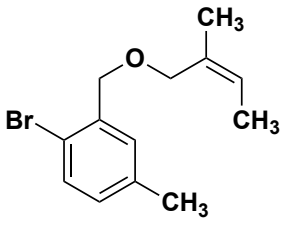


TM-135 (**4**) was synthesized, following a modified literature procedure,[117] by preparing a solution of **163** (0.056 g, 0.097 mmol, 1 equiv.) in tetrahydrofuran (0.1 M). Tetrabutylammonium fluoride (0.19 mL of a 1M solution in tetrahydrofuran, 0.19 mmol, 2 equiv.) was then added dropwise and the mixture was stirred 3 hours at room temperature. The mixture was then quenched with sat. aq. $NaHCO_3$ (2 mL), organic layer separated, aqueous layer extracted with dichloromethane (3 mL x 2), the combined extracts were dried over Na_2SO_4, concentrated *in vacuo*, and purified by flash column chromatography (70hexanes:30ethyl acetate) to afford **4** (0.007 g, 25%) as a clear residue. Characterization data matches with TM-135 (**4**).[29]

2.10.2.3 Angelate Route

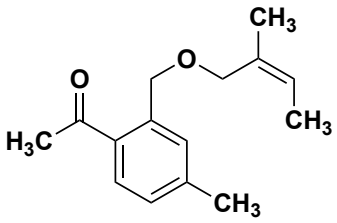


Angelyl alcohol (*Z*-77) was synthesized, following a modified literature procedure,[118] by preparing a suspension of lithium aluminum hydride (2.007 g, 52.885 mmol, 1.2 equiv.) in diethyl ether (1.5 M). The suspension was cooled to 0 °C and methyl angelate (5.002 g, 43.822 mmol, 1 equiv.) was added dropwise; the reaction mixture was allowed to stir to room temperature overnight. The heterogenous solution was then cooled to 0 °C, H_2O (2 mL) was added dropwise, allowing to stir for 15 minutes, then 10% aqueous NaOH (2 mL) was added dropwise. The ice bath was then removed and H_2O (6 mL) was added dropwise, allowing to stir to room temperature for 30 minutes. A large quantity of magnesium sulfate was added to the mixture, allowing to stir for 30 minutes, and the mixture was filtered through a glass frit funnel under gentle vacuum, washing generously with diethyl ether (100 mL). The solution was then concentrated *in vacuo* (≥200 torr, 0 °C bath temperature) and *Z*-77 (8.888 g, 97%, as a 41% w/w solution in diethyl ether) was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.40 (q, J = 7.1 Hz, 1H), 4.17 (d, J = 5.4 Hz, 2H), 1.80 (s, 3H), 1.66 (d, J = 7.0 Hz, 3H), 1.30 (t, J = 5.7 Hz, 1H); ^{1}H NMR spectrum is consistent with literature.[118]



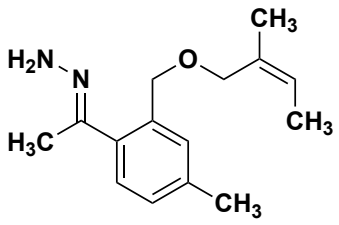
1-bromo-4-methyl-2-((angeloxy)methyl)benzene (*Z*-79) was synthesized, following a modified literature procedure,[109] by preparing a suspension of sodium hydride (1.903 g, 47.563 mmol, 3 equiv.) in THF (0.89 M), allowing to stir for 10 minutes. Alcohol *Z*-77 (3.1646 g of a 56% w/w solution in diethyl

ether, 20.575 mmol, 1.3 equiv.) was then added dropwise to the suspension, allowing to stir for 1 hour; **78** (1.884 g, mmol, 1 equiv., as a 0.89 M solution in THF) was then added dropwise, allowing to stir overnight. The reaction mixture was carefully quenched with saturated aqueous ammonium chloride until the opaque mixture became clear. The crude mixture was extracted with ethyl acetate (30 mL x3), washed with saturated aqueous sodium chloride (100 mL x 1), dried over sodium sulfate, concentrated *in vacuo*, and purified using flash column chromatography (gradient: 100%hexanes to 95hexanes:5ethyl acetate), affording ***Z*-79** (4.021 g, 94%) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J = 8.0 Hz, 1H), 7.30 (s, 1H), 6.95 (d, J = 8.1 Hz, 1H), 5.49 (q, J = 7.1 Hz, 1H), 4.49 (s, 2H), 4.10 (s, 2H), 2.31 (s, 3H), 1.81 (s, 3H), 1.65 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5, 137.3, 132.5, 132.2, 129.9, 129.6, 124.0, 119.4, 71.0, 68.7, 22.2, 21.0, 13.3; IR (neat) 2938, 2864, 1472, 907, 731 cm^{-1}; AMM (ESI) *m/z* calcd $C_{13}H_{18}BrO^+$ $[M+H]^+$ 269.0536, found 269.0533.



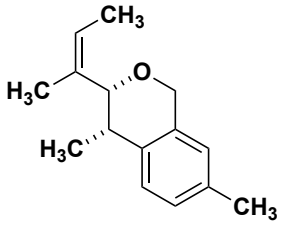
2-((tiglyloxy)methyl)-4-methyl acetophenone (***Z*-80**) was synthesized, following a modified literature procedure,[110] by preparing a solution of ***Z*-79** (4.009 g, 14.886 mmol, 1 equiv.) in THF (0.27 M). This solution was cooled to -78 °C and *n*-butyl lithium (7.74 mL, 19.351 mmol, 1.3 equiv., as a solution in *n*-hexanes) was added dropwise, allowing to stir for 2 hours. The reaction mixture was then cooled to -78 °C and *N*-methoxy-*N*-methylacetamide **74** (1.842 g, 17.863 mmol, 1.2 equiv., as a 0.8 M solution in THF) was added dropwise, allowing to stir and warm to room temperature overnight. The mixture was cooled to -78 °C and the reaction was quenched dropwise with saturated aqueous ammonium chloride, allowing the solution to warm to room temperature. The crude mixture was then extracted with ethyl acetate (30

mL x3); organic layers were combined, washed with saturated aqueous sodium chloride (100 mL x1), dried over sodium sulfate, concentrated *in vacuo*, and purified by flash column chromatography (95hexanes:5ethyl acetate) to afford ***Z*-80** (1.555 g, 45%) as a clear oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68 (d, J = 7.9 Hz, 1H), 7.55 (s, 1H), 7.14 (d, J = 9.6 Hz, 1H), 5.47 (q, J = 7.0 Hz, 1H), 4.79 (s, 2H), 4.10 (s, 2H), 2.57 (s, 3H), 2.40 (s, 3H), 1.81 (s, 3H), 1.66 (d, J = 6.9 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 200.9, 142.9, 140.6, 133.3, 132.9, 130.1, 128.5, 127.4, 123.7, 70.1, 69.0, 29.1, 21.9, 21.8, 13.4; IR (neat): 2921, 2859, 1676, 1253, 1082 cm^{-1}; AMM (ESI) *m/z* calcd $C_{15}H_{21}O_2^+$ $[M+H]^+$ 233.1536, found 233.1532.

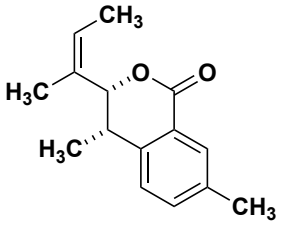


2-((tiglyloxy)methyl)-4-methyl acetophenone hydrazone (***Z*-81**) was synthesized, following our literature procedure,[111] by preparing a solution of ***Z*-80** (1.555 g, 6.692 mmol, 1 equiv.) in anhydrous ethanol (0.1 M), which was then sparged vigorously with argon for 15 minutes. Hydrazine (1.26 mL, 40.152 mmol, 6 equiv.) and glacial acetic acid (0.46 mL, 8.030 mmol, 1.2 equiv.) were then added to the solution and the mixture was sparged vigorously with argon for 1 minute. A reflux condenser was attached to the flask and the solution was heated to 80 °C, allowing to stir overnight. The reaction mixture was allowed to cool to room temperature, diluted with diethyl ether (40 mL), and washed with H_2O (100 mL), washed with saturated aqueous sodium chloride (100 mL), dried over sodium sulfate, and concentrated *in vacuo*. ***Z*-81** (1.565g, 95%) was isolated as a ~50:50 mixture of stereoisomers and used without purification in the next step; this complex ^{1}H NMR spectrum is included for informational

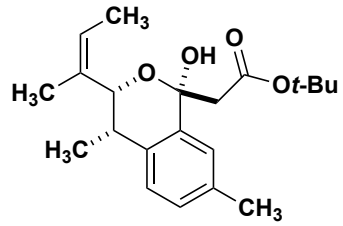
purposes. IR (neat) 3388, 3214, 2918, 2860, 1612, 1454, 1365 cm^{-1}; AMM (ESI) *m/z* calcd $C_{15}H_{23}N_2O^+$ $[M+H]^+$ 247.1805, found 247.1803.



(3*S*,4*R*)-3-((*Z*)but-2-en-2-yl)-4,7-dimethylisochroman (***Z*-82**) was synthesized, following our two-pot literature procedure,[112] by preparing a solution of the crude mixture of ***Z*-81** (1.025 g, 4.161 mmol, 1 equiv.) in dichloromethane (0.04 M). MnO_2 (2.823 g, 32.473 mmol, 8 equiv., see section 1.1 for reagent details) was added, allowing to stir for 30 minutes, producing a bright fuchsia colored solution when stirring is halted. This heterogenous mixture was then filtered through celite, washing with acetonitrile to a final concentration of 0.015M (300mL total). The headspace of the receiving flask was then purged with argon and the solution was cooled to -78 °C. Rh_2(*R*-PTAD)$_4$ (0.006 g, 0.004 mmol, 0.1 mol %) was added and the mixture was allowed to stir overnight. After ~14 hours, the solution was warmed to room temperature and concentrated *in vacuo*. This procedure was performed in duplicate and the unpurified mixtures were combined and purified by flash chromatography (90hexanes:10ethyl acetate) to afford ***Z*-82** (1.426g, 79%, >95:5dr, 93:7er) as a clear oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.04 (d, J = 7.7 Hz, 1H), 7.01 (d, J = 8.1 Hz, 1H), 6.82 (s, 1H), 5.37 (qt, *J* = 7.0, 1.5 Hz, 1H), 4.87 (d, J = 15.0 Hz, 1H), 4.81 (d, J = 15.0 Hz, 1H), 4.57 (d, J = 3.7 Hz, 1H), 2.79 (qd, J = 7.0, 2.4 Hz, 1H), 2.31 (s, 3H), 1.80 (s, 3H), 1.60 (d, *J* = 7.1 Hz, 3H), 1.20 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.5, 136.3, 135.7, 134.1, 128.8, 127.4, 124.6, 120.3, 77.4, 68.7, 36.1, 21.2, 20.7, 18.0, 13.5; IR (neat) 2968, 1930, 1449, 1115, 816 cm^{-1}; AMM (APCI) *m/z* calcd $C_{15}H_{21}O^+$ $[M+H]^+$ 217.1587, found 217.1588; $[\alpha]^{18}_D$ +86.9 (c = 0.10, CH_3OH).

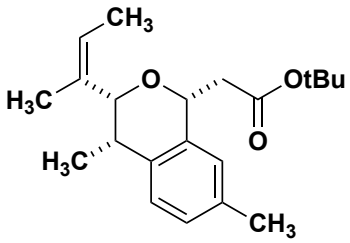


(3*S*,4*R*)-3-((*Z*)but-2-en-2-yl)-4,7-dimethylisochroman-1-one (**164**) was synthesized, following a modified literature procedure,[113] by preparing a solution of ***Z*-82** (1.049 g, 4.848 mmol, 1 equiv.) in DCM (0.2 M). Pyridinium chlorochromate (3.449 g, 15.998 mmol, 3.3 equiv.) was then added to the flask, a reflux condenser attached, and the mixture was lowered into a 60 °C oil-bath, allowing to reflux overnight. The mixture was then diluted with diethyl ether (25 mL), silica gel (~2 g) was then added, allowing the heterogenous mixture to stir for 30 minutes. The mixture was filtered through a celite/silica plug, eluting with diethyl ether (100 mL), concentrated *in vacuo*, then purified by flash column chromatography (90hexanes:10ethyl acetate) to afford **164** (0.813 g, 73%) as a clear oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.38 (d, J = 9.7 Hz, 1H), 7.16 (d, J = 7.6 Hz, 1H), 5.49 (q, J = 7.1 Hz, 1H), 5.43 (d, J = 3.2 Hz, 1H), 3.01 (qd, J = 7.2, 3.3 Hz, 1H), 2.40 (s, 3H), 1.88 (s, 3H), 1.63 (d, J = 7.0 Hz, 3H), 1.22 (d, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.9, 143.0, 137.6, 135.0, 133.3, 130.6, 126.7, 123.9, 122.8, 79.8, 36.6, 21.1, 20.8, 16.2, 13.5; 2972, 2924, 1719, 1281, 1188, 1117 cm^{-1}; AMM (ESI) *m/z* calcd $C_{15}H_{19}O_2^+$ $[M+H]^+$ 231.1380, found 231.1376; $[\alpha]^{17}_D$ +105.7 (c = 0.11, CH_3OH).



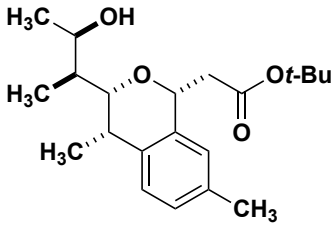
tert-butyl 2-(1*R*,3*S*,4*R*)-3-((*Z*)but-2-en-2-yl)-1-hydroxy-1-4,7-dimethylisochroman-1-yl) acetate (**92**) was synthesized, following a modified literature procedure,[114] by preparing a solution of diisopropylamine (0.82 mL, 5.82 mmol, 1.6 equiv.) in THF (0.56 M). The solution was cooled to -78 °C

and *n*-butyllithium (2.20 mL, 5.5 mmol, 1.5 equiv.) was added dropwise, allowing to stir for 15 minutes. The solution was warmed to 0 °C, stirred for 15 minutes, cooled down to -78 °C, and *tert*-butyl acetate (0.78 mL, 5.82 mmol, 1.6 equiv.) was added dropwise, allowing to stir for 10 minutes. The *tert*-butyl acetate enolate was then quickly transferred dropwise via syringe into a -78 °C solution of **164** (0.838 g, 3.640 mmol, 1 equiv.) in THF (0.14 M), allowing to stir at -78 °C for 15 minutes. The reaction was quenched with saturated aqueous ammonium chloride (10 mL), warmed to room temperature, extracted with dichloromethane (20 mL x 3), dried over sodium sulfate, concentrated *in vacuo*, and purified by flash column chromatography (90hexanes:10ethyl acetate) to afford (X) (1.019 g, 81%, >95:5 dr) as a clear oil. Note: ~52:48dr was observed in the unpurified mixture; hemi-acetal **92** appears to epimerize on silica to the major isomer. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.13 (s, 1H), 7.08 (d, J = 7.8 Hz, 1H), 7.01 (d, J = 7.8 Hz, 1H), 5.61 (s, 1H), 5.39 – 5.33 (m, 1H), 5.05 (d, J = 2.8 Hz, 1H), 3.01 (d, J = 14.8 Hz, 1H), 2.74 (tt, J = 7.3, 3.7 Hz, 1H), 2.63 (d, J = 14.8 Hz, 1H), 2.33 (s, 3H), 1.77 (s, 3H), 1.59 (d, J = 6.4 Hz, 3H), 1.51 (s, 9H), 1.15 (d, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.7, 138.2, 136.3, 136.0, 135.8, 129.2, 128.5, 127.0, 120.5, 96.5, 82.1, 70.7, 46.8, 36.7, 28.3, 21.3, 20.9, 17.0, 13.6; IR (neat) 3434, 2972, 2928, 1705, 1369, 1148 cm^{-1}; AMM (ESI) *m/z* calcd $C_{21}H_{30}O_4Na^+$ $[M+Na]^+$ 369.2036, found 369.2017; $[\alpha]^{18}_D$ +34.9 (c = 0.18, CH_3OH).



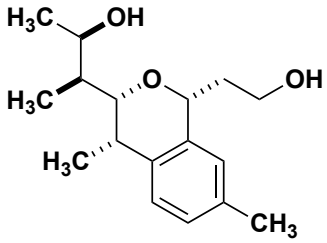
tert-butyl 2-((1*S*,3*R*,4*S*)-3-((1*R*)-1-methylprop-2-en-1-yl)-1-4,7-dimethylisochroman-1-yl) acetate (**93**) was synthesized, following a modified literature procedure,[114] by preparing a solution of **92** (1.019g, 2.942 mmol, 1 equiv.) and triisopropylsilane (12 mL, 58.575 mmol, 20 equiv.) in dichloromethane (0.15

M). This solution was cooled to -78 °C and boron trifluoride diethyl etherate complex (3.63 mL, 29.417 mmol, 10 equiv.) was added dropwise, allowing the mixture to stir for 4 hours at -78 °C. The reaction was then placed in an acetonitrile/dry ice bath and stirred for 20 hours at -40 °C. The reaction mixture was then cooled to -78 °C and syringed dropwise into a 0 °C solution of dichloromethane (0.1 M) and saturated aqueous sodium bicarbonate (2:3 ratio of dichloromethane:saturated aqueous sodium bicarbonate by volume), allowing to stir at 0 °C for 15 minutes. The mixture was allowed to warm to room temperature, stirred for 15 minutes, extracted with dichloromethane (10 mL x2); combined extracts were dried over sodium sulfate, concentrated *in vacuo*, and purified by column chromatography (gradient: 100%hexanes to 95hexanes:5ethyl acetate) to afford **93** (0.757 g, 78%, >95:5 dr) as a clear oil. ^{1}H NMR (600 MHz, CD_2Cl_2) δ 7.02 (s, 2H), 6.88 (s, 1H), 5.36 (q, J = 7.0 Hz, 1H), 5.16 (dd, J = 9.4, 3.4 Hz, 1H), 4.58 (d, J = 3.0 Hz, 1H), 2.86 (dd, J = 14.7, 3.3 Hz, 1H), 2.78 (q, J = 6.6 Hz, 1H), 2.56 (dd, J = 14.7, 9.3 Hz, 1H), 2.30 (s, 3H), 1.76 (s, 3H), 1.60 (d, J = 6.9 Hz, 3H), 1.46 (s, 9H), 1.18 (d, J = 7.1 Hz, 3H).^{13}C NMR (150 MHz, CD_2Cl_2) δ 171.1, 138.7, 136.8, 136.7, 136.3, 129.3, 128.0, 125.0, 120.5, 80.8, 77.1, 75.0, 43.9, 37.1, 28.4, 21.5, 21.0, 18.3, 13.8; IR (neat) 2971, 2931, 1732, 1367, 1151 cm^{-1}, AMM (ESI) *m/z* calcd $C_{21}H_{30}O_3Na^+$ $[M+Na]^+$ 353.2087, found 353.2101; $[\alpha]^{19}_D$ +86.3 (c = 0.05, CH_3OH).



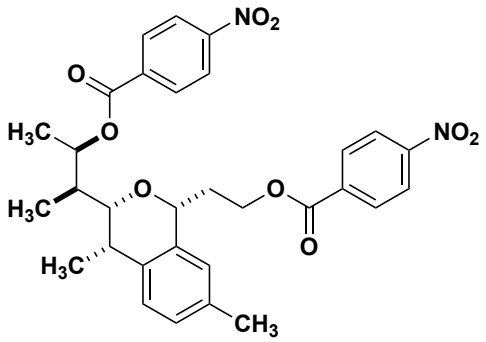
tert-butyl 2-((1*R*,3*R*,4*S*)-3-((2*S*,3*R*)-3-hydroxybutan-2-yl)-4,7-dimethylisochroman-1-yl)acetate (**94**) was synthesized, following a modified literature procedure,[115] by preparing a solution of BH_3•DMS (1.42 mL, 2.845 mmol, 2 equiv.) in THF (1.3 M) and cooling it to -78 °C. A solution of **93** (0.470 g, 1.422 mmol, 1 equiv.) in THF (0.75 M) was then added to the borane solution dropwise. This mixture was then

warmed to -20 °C with stirring for 4 hours, then allowed to warm to room temperature overnight. The solution was then cooled to 0 °C and solution of NaOH and NaCl (0.95 M, 8.4equiv with respect to NaOH, 0.11 M, 1 equiv. with NaCl) was added, stirring for 10 minutes. H_2O_2 (1.45 mL, 30% aq., 12.80 mmol, 9 equiv.) was then added at 0 °C, stirring for 2 hours, allowed to warm to room temperature, stirring for another 2 hours. The mixture was then extracted with diethyl ether (10 mL x 2), the aqueous layer was acidified then extracted with diethyl ether (5 mL x 2). Organic extracts were then combined and dried with Na_2SO_4 , concentrated *in vacuo*, and purified by flash column chromatography (70hexanes:30ethyl acetate) to afford **94** (0.347, 70%, 93:7dr) as a clear oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.03 (s, 2H), 6.85 (s, 1H), 5.18 (d, J = 10.1 Hz, 1H), 3.86 (s, 1H), 3.72 (d, J = 10.6 Hz, 1H), 3.43 (d, J = 9.8 Hz, 1H), 2.89 (d, J = 17.1 Hz, 1H), 2.70 (q, J = 7.3 Hz, 1H), 2.57 (dd, J = 16.0, 10.2 Hz, 1H), 2.30 (s, 3H), 2.13 – 2.06 (m, 1H), 1.50 (s, 9H), 1.21 (t, J = 7.7 Hz, 6H), 0.83 (d, J = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.9, 138.3, 136.0, 135.5, 129.2, 127.8, 124.6, 81.4, 78.8, 74.0, 71.5, 43.1, 39.3, 34.2, 28.2, 21.3, 18.2, 16.8, 12.9; IR (neat) 3501, 2971, 2932, 1728, 1368, 1150, 1103 cm^{-1}; AMM (ESI) *m/z* calcd for $C_{21}H_{32}O_4Na^+$ $[M+Na]^+$ 371.2193, found 371.2194; $[\alpha]^{17}_D$ +87.3 (c = 0.11, CH_3OH).



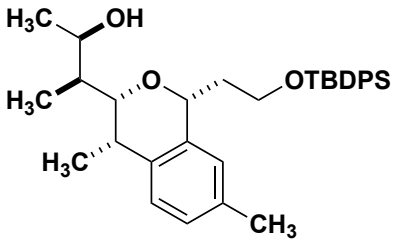
12,13-*epi*-TM-135 (**95**) was synthesized, following a modified literature procedure,[118] by preparing a suspension of $LiAlH_4$ (0.077 g, 2.024 mmol, 2 equiv.) in diethyl ether (1 M). The heterogenous solution was cooled to 0 °C and a solution of **94** (0.347 g, 0.995 mmol, 1 equiv.) in diethyl ether (1 M) was added to it dropwise. This mixture was allowed to stir to room temperature over 4 hours, then was quenched at 0 °C with 75μL of H_2O, stirred for 15 minutes; 75μL of 10% aq. NaOH was then added and the ice bath

was removed, allowing to stir for 5minutes. 225μL of H_2O was then added at room temperature, allowing to stir for 15 minutes; a generous amount of $MgSO_4$ was added and the heterogenous mixture was stirred for 30 minutes. This mixture was then filtered through a glass frit, eluting with diethyl ether (50 mL), concentrated *in vacuo*. **95** (0.257g, 93%) was afforded without further purification as a white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.01 (d, J = 2.7 Hz, 2H), 6.88 (s, 1H), 4.99 (d, J = 6.0 Hz, 1H), 4.06 (q, J = 7.4, 6.7 Hz, 1H), 3.87 (td, J = 9.8, 8.4, 4.1 Hz, 1H), 3.79 (dt, J = 10.7, 5.2 Hz, 1H), 3.70 (d, J = 10.5 Hz, 1H), 3.35 (s, 1H), 2.71 (q, J = 8.1, 7.6 Hz, 1H), 2.30 (s, 4H), 1.95 (td, J = 12.7, 10.5, 6.9 Hz, 2H), 1.20 (dd, J = 13.6, 6.8 Hz, 6H), 0.85 (d, J = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.1, 136.7, 136.0, 129.0, 127.6, 124.8, 78.4, 76.0, 69.7, 59.8, 39.6, 38.5, 34.1, 21.3, 19.2, 16.8, 11.3; m.p. 75-76 °C; IR (neat): 3353, 3264, 2970, 1276, 1187 cm^{-1}; AMM (ESI) *m/z* calcd for $C_{17}H_{26}O_3Na^+$ $[M+Na]^+$ 301.1774, found 301.1775; $[\alpha]^{18}_D$ +52.4 (c = 0.12, CH_3OH).



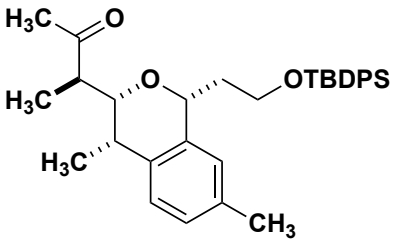
(2*R*,3*S*)-3-((1*R*,3*R*,4*S*)-4,7-dimethyl-1-(2-((4-nitrobenzoyl)oxy)ethyl)isochroman-3-yl)butan-2-yl 4-nitrobenzoate (**97**) was synthesized, following a modified literature procedure,[119] by preparing a solution of **95** (0.048 g, 0.174 mmol, 1 equiv.), 4-NO_2-benzoyl chloride (0.109 g, 0.587 mmol, 3 equiv.), and dimethylaminopyridine (0.006 g, 0.050 mmol, 0.22 equiv) in dichloromethane (0.09 M). Triethylamine (80 μL, 0.574 mmol 3 equiv.) was then added to the mixture and it was allowed to stir at room temperature for 20 hours. H_2O (2 mL) was added to the reaction, the organic layer was separated, and the aqueous

layer was extracted with ethyl acetate (2mL x 2). Combined organic extracts were dried with Na_2SO_4, concentrated *in vacuo* and purified by column chromatography (80hexanes:20ethyl acetate). White needles formed spontaneously in the column fractions and were sent for X-Ray diffraction. The ^{1}H NMR spectrum of the unpurified product is included for informational purposes. See Section 6.2 for crystallography data.



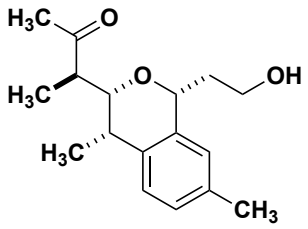
(2*S*,3*S*)-3-((1*R*,3*R*,4*S*)-1-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)-4,7-dimethylisochroman-3-yl)butan-2-ol (**165**) was prepared, following a modified literature procedure,[116] by preparing a solution of **95** (0.1684 g, 0.605 mmol, 1 equiv.) in dichloromethane (0.2 M). Triethylamine (170 μL, 1.210 mmol, 2 equiv.) and DMAP (0.008 g, 0.061 mmol, 0.1 equiv.) were then added and the mixture was cooled to 0 °C. TBDPS-Cl (160 μL, 0.617 mmol, 1.02 equiv.) was added and the mixture was stirred to room temperature over 1 hour. H_2O (2 mL) was added, the aqueous layer was extracted with DCM (3 mL x 2), combined extracts washed with sat. aq. NaCl (5 mL), dried over Na_2SO_4, concentrated *in vacuo*, and purified by flash column chromatography (85hexanes:15ethyl acetate) to afford **165** (0.310g ~99%) as a clear oil. The silyl ether was unable to be separated from TBDPS-OH, and the impure mixture was carried through to the next step. NMR spectra are included for informational purposes. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.73 – 7.67 (m, 7H), 7.43 – 7.37 (m, 10H), 7.00 – 6.97 (m, 2H), 6.78 (s, 1H), 5.02 (d, *J* = 9.5 Hz, 1H), 4.01 – 3.94 (m, 1H), 3.92 – 3.86 (m, 1H), 3.82 – 3.77 (m, 1H), 3.69 (d, *J* = 12.9 Hz, 1H), 3.24 (d, *J* = 9.1 Hz, 1H), 2.67 (q, *J* = 7.2, 6.8 Hz, 1H), 2.29 (s, 3H), 2.25 – 2.15 (m, 2H), 2.04 – 2.00 (m, 1H), 1.90 – 1.83 (m, 1H), 1.19 (d, *J* = 6.6 Hz, 3H), 1.13 (d, *J* = 7.0 Hz, 3H), 1.07 (s, 9H), 0.83 (d, *J* = 7.1 Hz,

3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 137.0, 135.9, 135.8, 135.7, 135.0, 134.3, 134.0, 129.8, 128.9, 127.8, 127.8, 127.4, 124.9, 78.7, 74.1, 71.2, 60.6, 39.5, 39.3, 34.3, 27.0, 26.7, 21.4, 19.4, 18.7, 16.7, 12.5; IR (neat) 3466, 2963, 2930, 1106, 733, 701 cm^{-1}; AMM (ESI) *m/z* calcd $C_{33}H_{45}O_3SiNa^+$ $[M+Na]^+$ 539.2952, found 539.2960; $[\alpha]^{21}_D$ +35.0 (c = 0.08, CH_3OH).



(*R*)-3-((1*R*,3*R*,4*S*)-1-(2-((*tert*-butyldiphenylsilyl)oxy)ethyl)-4,7-dimethylisochroman-3-yl)butan-2-one (**166**) was synthesized by following a modified literature procedure,[99] by preparing a solution of oxalyl chloride (70 μL, 0.77 mmol, 2 equiv.) in DCM (0.27 M). The solution was cooled to -78 °C and DMSO (112 μL, 1.548 mmol, 4 equiv.) was added, stirring for 30 minutes. A solution of **165** (0.192 g, 0.370 mmol, 1 equiv.) in DCM (0.27 M) was added dropwise and the solution was stirred at – 78 °C for 1 hour. Net_3 (0.28 mL, 1.94 mmol, 5 equiv.) was then added and the mixture was allowed to stir to room temperature overnight. The reaction was quenched with 1M $NaHSO_4$ (1 mL), extracted with DCM (2 mL x 3), washed with sat. aq. $NaHSO_4$ (3 mL), H_2O (3 mL), sat. aq NaCl (3 mL), dried over Na_2SO_4, concentrated *in vacuo*, and purified by flash column chromatography (92hexanes:8ethyl acetate) to afford **166** (0.203 g, 85%) as a clear oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68 – 7.65 (m, 4H), 7.44 – 7.36 (m, 6H), 6.98 (s, 2H), 6.79 (s, 1H), 4.79 (d, J = 6.9 Hz, 1H), 3.94 – 3.88 (m, 1H), 3.81 – 3.75 (m, 1H), 3.72 (dd, J = 10.4, 2.3 Hz, 1H), 2.79 – 2.72 (m, 1H), 2.70 (q, J = 7.4, 6.7 Hz, 1H), 2.30 (s, 3H), 2.22 – 2.14 (m, 1H), 2.09 (s, 3H), 1.90 – 1.82 (m, 1H), 1.12 (d, J = 7.0 Hz, 3H), 1.05 (s, 9H), 1.00 (d, J = 7.0 Hz, 3H); ^{1}H NMR (400 MHz, MeOD) δ 7.68 – 7.62 (m, 4H), 7.43 – 7.36 (m, 6H), 7.00 – 6.94 (m, 2H), 6.81 (s, 1H), 4.76 (dd, *J* = 8.8, 2.7 Hz, 1H), 3.89 (dt, *J* = 10.1, 7.5 Hz, 1H), 3.73 (ddd, *J* = 10.1, 8.1, 4.2 Hz, 1H), 3.68

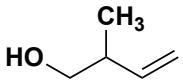
(dd, *J* = 10.5, 2.4 Hz, 1H), 2.83 – 2.75 (m, 1H), 2.72 (qd, *J* = 7.0, 2.2 Hz, 1H), 2.26 (s, 3H), 2.21 (dtd, *J* = 13.8, 8.0, 2.8 Hz, 1H), 2.10 (s, 3H), 1.89 – 1.78 (m, 1H), 1.09 (d, *J* = 6.9 Hz, 3H), 1.03 (s, 9H), 1.00 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, MeOD) δ 215.2, 138.6, 137.9, 137.0, 136.7, 136.0, 135.1, 135.0, 130.8, 130.4, 129.9, 128.8, 128.6, 128.4, 125.6, 80.3, 75.6, 63.5, 49.3, 40.5, 34.6, 30.2, 27.4, 21.3, 20.0, 16.9, 12.7; IR (neat): 2965, 2931, 2857, 1717, 1112, 702cm^{-1}; AMM (ESI) *m/z* calcd $C_{33}H_{43}O_3SiNa^+$ $[M+Na]^+$ 537.2795, found 537.2807; $[\alpha]^{21}_D$ +43.3 (c = 0.12, CH_3OH).



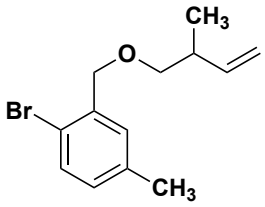
12-*epi*-TM-135 (**96**) was synthesized, following a modified literature procedure,[117] by preparing a solution of **166** (0.028 g, 0.054 mmol, 1 equiv.) in tetrahydrofuran (0.1 M). Tetrabutylammonium fluoride (0.11 mL of a 1M solution in tetrahydrofuran, 0.11 mmol, 2 equiv.) was then added dropwise and the mixture was stirred 3 hours at room temperature. The mixture was then quenched with sat. aq. $NaHCO_3$ (2 mL), organic layer separated, aqueous layer extracted with dichloromethane (3 mL x 2), the combined extracts were dried over Na_2SO_4, concentrated *in vacuo*, and purified by flash column chromatography (50hexanes:50ethyl acetate) to afford **96** (0.015 g, 100%) as a clear oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.04 – 7.00 (m, 2H), 6.84 (s, 1H), 4.91 (dd, J = 8.6, 3.1 Hz, 1H), 3.85 (dd, J = 10.5, 2.3 Hz, 1H), 3.77 (t, J = 5.6 Hz, 2H), 2.87 – 2.80 (m, 1H), 2.75 (q, J = 6.5, 5.8 Hz, 1H), 2.50 – 2.36 (m, 1H), 2.30 (s, 3H), 2.25 (s, 4H), 1.99 – 1.92 (m, 1H), 1.20 (d, J = 7.0 Hz, 3H), 1.06 (d, J = 7.2 Hz, 3H); ^{1}H NMR (400 MHz, MeOD) δ 7.02 (d, J = 7.8 Hz, 1H), 6.99 (dd, J = 8.0, 1.6 Hz, 1H), 6.92 (s, 1H), 4.75 (dd, J = 8.9, 2.7 Hz, 1H), 3.76 – 3.70 (m, 2H), 3.62 (ddd, J = 10.5, 7.9, 4.6 Hz, 1H), 2.84 (dq, J = 10.5, 7.1 Hz, 1H), 2.76 (qd, J = 7.0, 2.3 Hz, 1H), 2.28 (s, 3H), 2.24 (s, 3H), 2.19 (ddd, J = 15.6, 7.0, 2.9 Hz, 1H),

1.84 (dddd, J = 13.7, 9.0, 7.2, 4.6 Hz, 1H), 1.16 (d, J = 7.0 Hz, 3H), 1.04 (d, J = 7.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 212.04, 137.37, 136.37, 136.22, 129.06, 127.74, 124.80, 79.04, 77.43, 60.64, 48.38, 38.11, 33.41, 30.14, 21.34, 16.75, 12.62; ^{13}C NMR (100 MHz, MeOD) δ 215.14, 138.61, 137.84, 137.05, 129.95, 128.44, 125.59, 80.21, 76.09, 59.73, 49.54, 40.21, 34.52, 29.80, 21.27, 16.97, 12.73; IR (neat) 3424, 2967, 2933, 1709, 1356, 1119, 1055, 730 cm^{-1}; AMM (ESI) *m/z* calcd $C_{17}H_{25}O_3Na^+$ $[M+Na]^+$ 299.1617, found 299.1620; $[\alpha]^{21}_D$ +66.7.0 (c = 0.08, CH_3OH).

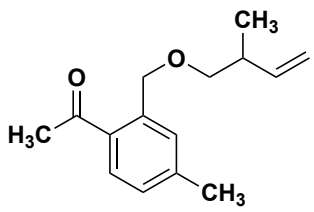
2.10.2.4 (2*rac*)-2-methyl-but-3-en-yl Route



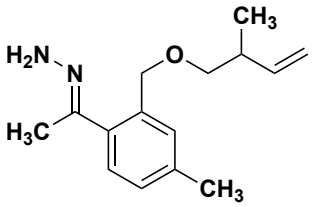
rac-2-methyl-but-3-en-1-ol ((±)-**124**) was synthesized, following a modified literature procedure,[105] by preparing a suspension of lithium aluminum hydride (1.661 g, 43.759 mmol, 1 equiv.) in diethyl ether (1.5 M). The suspension was cooled to 0 °C and (±)-2-methyl-but-3-enoic acid (4.381 g, 43.759 mmol, 1 equiv.) was added dropwise; the reaction mixture was allowed to stir to room temperature overnight. The heterogenous solution was then cooled to 0 °C, and H_2O (1.66 mL) was added dropwise, allowing to stir for 15 minutes, then 10% aqueous NaOH (1.66 mL) was added dropwise. The ice bath was then removed and H_2O (5 mL) was added dropwise, allowing to stir to room temperature for 30 minutes. A generous quantity of magnesium sulfate was added to the mixture, allowing to stir for 30 minutes, and the mixture was filtered through a glass frit funnel under gentle vacuum, washing generously with diethyl ether (100 mL). The solution was then concentrated *in vacuo* (≥120 torr, 0 °C bath temperature) and (±)-**124** (11.513 g, 97%, as a 32% w/w solution in diethyl ether) was isolated as a clear solution without further purification. ^{1}H NMR spectrum is consistent with the literature.[120] ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.72 (ddd, J = 17.7, 10.4, 7.6 Hz, 1H), 5.15 – 5.08 (m, 2H), 3.54 – 3.50 (m, 1H), 3.46 – 3.41 (m, 1H), 2.37 (dq, J = 14.3, 7.9, 7.3 Hz, 1H), 1.02 (dd, J = 6.8, 1.1 Hz, 3H).



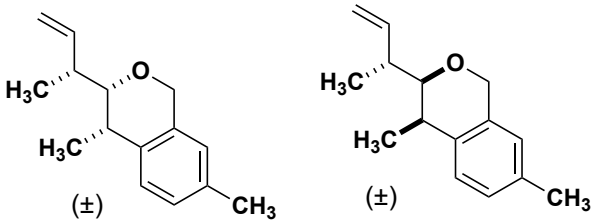
rac-1-bromo-4-methyl-2-(((2-methylbut-3-en-1-yl)oxy)methyl)benzene ((±)-**133**) was synthesized, following a modified literature procedure,[109] by preparing a suspension of sodium hydride (4.598 g, 114.940 mmol, 4 equiv.) in tetrahydrofuran (0.8 M with respect to sodium hydride), allowing to stir for 10 minutes. (±)-**124** (11.513 g (as a 32% w/w solution in diethyl ether), 42.772 mmol, 1.5 equiv.) was then added dropwise to the suspension, allowing to stir for 1 hour; **78** (7.551 g, 28.515 mmol, 1 equiv., as a 0.7 M solution in tetrahydrofuran) was then added dropwise, allowing to stir overnight. The reaction mixture was carefully quenched with saturated aqueous ammonium chloride until the opaque mixture became clear. The crude mixture was extracted with ethyl acetate (25 mL x3), washed with saturated aqueous sodium chloride (150 mL x 1), dried over sodium sulfate, concentrated *in vacuo*, and purified using flash column chromatography (gradient: 100%, to 95hexanes:5ethyl acetate), affording (±)-**133** (7.693 g, 100%) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, J = 8.1 Hz, 1H), 7.29 (d, J = 2.3 Hz, 1H), 6.94 (dd, J = 8.1, 2.3 Hz, 1H), 5.84 (ddd, J = 17.3, 10.4, 6.8 Hz, 1H), 5.10 (d, J = 17.4 Hz, 1H), 5.04 (d, J = 10.4 Hz, 1H), 4.53 (s, 2H), 3.47 (dd, *J* = 9.2, 6.5 Hz, 1H), 3.39 (dd, *J* = 9.1, 6.9 Hz, 1H), 2.56 (hept, J = 6.8 Hz, 1H), 2.31 (s, 3H), 1.08 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4, 137.6, 137.4, 132.3, 129.8, 129.7, 119.3, 114.3, 75.8, 72.3, 38.0, 21.2, 16.8 ppm ; IR (neat): 2861, 1468, 1160, 1100, 806 cm^{-1}; AMM (ESI) *m/z* calcd for $C_{13}H_{18}BrO^+$ $[M+H]^+$ 269.0536, found 269.0538.



rac-2-((2-methyl-but-3-en-1-yl)methyl)-4-methyl acetophenone ((±)-**134**) was synthesized, following a modified literature procedure,[110] by preparing a solution of (±)-**133** (7.627 g, 28.333 mmol, 1 equiv.) in THF (0.27 M). This solution was cooled to -78 °C and *n*-butyl lithium (16.25 mL, 34.613 mmol, 1.2 equiv., as a solution in *n*-hexanes) was added dropwise, allowing to stir for 2 hours. The reaction mixture was then cooled to -78 °C and *N*-methoxy-*N*-methylacetamide **74** (3.835 g, 37.192 mmol, 1.3 equiv., as a 0.8 M solution in THF) was added dropwise, allowing to stir and warm to room temperature overnight. The mixture was cooled to -78 °C and the reaction was quenched dropwise with saturated aqueous ammonium chloride, allowing the solution to warm to room temperature. The crude mixture was then extracted with ethyl acetate (50 mL x3); organic layers were combined, washed with saturated aqueous sodium chloride (150 mL x1), dried over sodium sulfate, concentrated *in vacuo*, and purified by flash column chromatography (90hexanes:10ethyl acetate) to afford (±)-**134** (2.456 g, 37%) as a clear oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.65 (d, J = 7.9 Hz, 1H), 7.52 (s, 1H), 7.13 (d, J = 8.0 Hz, 1H), 5.83 (ddd, J = 17.4, 10.3, 7.0 Hz, 1H), 5.08 (d, J = 17.3 Hz, 1H), 5.02 (d, J = 10.4 Hz, 1H), 4.80 (s, 3H), 3.46 (dd, J = 9.2, 6.7 Hz, 1H), 3.38 (dd, J = 9.2, 6.8 Hz, 1H), 2.55 (s, 3H), 2.39 (s, 3H), 1.06 (d, J = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 200.9, 142.9, 141.5, 140.5, 133.3, 130.1, 128.4, 127.4, 114.2, 75.9, 71.2, 38.0, 29.1, 21.9, 16.8; IR (neat): 2960, 2868, 1675, 1354, 1251, 1096 cm^{-1}; AMM (ESI) *m/z* calcd $[M+Na]^+$ 255.1356, found 255.1358.

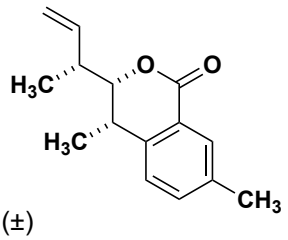


rac-2-((2-methyl-but-3-en-1-yl)methyl)-4-methyl acetophenone hydrazone ((±)-**135**) was synthesized, following our literature procedure,[111] by preparing a solution of (±)-**134** (2.446 g, 10.528 mmol, 1 equiv.) in anhydrous ethanol (0.1 M), which was then sparged vigorously with argon for 20 minutes. Hydrazine (2.0 mL, 63.72 mmol, 6 equiv.) and glacial acetic acid (0.73 mL, 12.68 mmol, 1.2 equiv.) were then added to the solution and the mixture was sparged vigorously with argon for 1 minute. After the solution was stirred at room temperature overnight, it was diluted with diethyl ether (50 mL), and washed with H_2O (50 mL), washed with saturated aqueous sodium chloride (100 mL), dried over sodium sulfate, and concentrated *in vacuo* and purified by flash column chromatography (50hexanes:50ethyl acetate) to afford (±)-**135** (2.443 g, 94%) as a yellow oil. The product is isolated as a ~50:50 mixture of isomers, and the complex ^{1}H NMR spectrum is included for informational purposes; IR (neat): 3386, 3214, 2959, 2869, 1612, 1359, 1090 cm^{-1}; AMM (ESI) *m/z* calcd for $C_{15}H_{23}N_2O^+$ $[M+H]^+$ 247.1805, found 247.1807.



rac-(3*R*,4*R*)-3-(but-3-en-2-yl)-4,7-dimethylisochroman ((±)-**142**) and *rac*-(3*R*,4*R*)-3-((*R*)-but-3-en-2-yl)-4,7-dimethylisochromane ((±)-**146**) were synthesized, following a modified two-pot procedure developed in the lab,[112] by preparing a solution of (±)-**135** (1.007 g, 4.059 mmol, 1 equiv.) in acetonitrile (0.16 M). MnO_2 (2.824 g, 32.474 mmol, 8 equiv., see section 1.1 for reagent details) was added (producing a bright fuchsia colored solution when stirring is halted) and allowed to stir for 1 hour. This

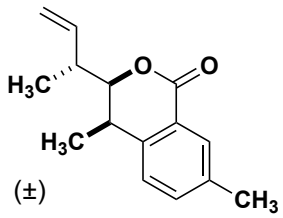
heterogenous mixture was then filtered through a glass frit (MnO_2 will likely stain the frit permanently), washing with acetonitrile (5 mL), into a dry, clean flask. In a separate flask, Rh_2(*R/S*-TCPTTL)$_4$ (0.040 g, 0.020 mmol, 0.5 mol %) was dissolved in acetonitrile (0.015 M with respect to hydrazone) and cooled to 0 °C. The filtered fuchsia diazo solution was then added to the catalyst solution by syringe pump (Harvard Apparatus, Pump 11, 0.15 mL/min) over ~3 hours. After addition was completed, the syringe previously containing the diazo species was washed with 10 mL of DCM and the rinsate added dropwise over 30minutes; this mixture was allowed to stir to room temperature for overnight (shorter reaction times, about 5 hours, are suitable as well). The stirbar was then removed and rinsed with DCM (2mL), the solution was concentrated *in vacuo*, and the product was purified by flash column chromatography (95Hexanes:5EtOAc) to afford (±)-**142**/(±)-**146** as a clear oil (0.577 g, 65%). The product was isolated as the 50:50 mixture of diastereomers epimers and carried into the next reaction; the ^{1}H NMR of the mixture is complex and is provided for informational purposes. See Section 3.5 for less complex NMR data of the desired isomer in diastereomeric excess. IR (neat) 2964, 2930, 1642, 1455, 1097, 815 cm^{-1}; AMM (ESI) *m/z* calcd $[M+H]^+$ 217.1587, found 217.1584. Azine Byproduct (±)-**31** NMR spectrum is shown for informational purposes only. Note: while care was taken to keep the reaction as free from moisture as possible, the solutions and intermediates were exposed to air during each transfer step without appreciable byproduct formation.



(±)

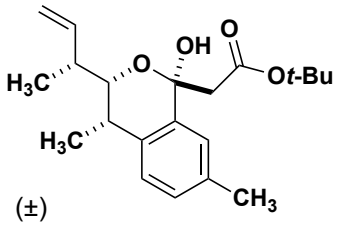
rac-(3*S*,4*R*)-3-((1*R*)-1-methylprop-2-en-1-yl)-4,7-dimethylisochroman-1-one ((±)-**52**) was synthesized, following a modified literature procedure,[113] by preparing a solution of (±)-**142**/(±)-**146**

(1.107 g, 5.115 mmol, 1 equiv.) in DCM (0.2 M). Pyridinium chlorochromate (5.916 g, 27.444 mmol, 5.4 equiv.) was then added (in two equal portions over 3 hours) to the flask, a reflux condenser attached, and the mixture was lowered into a 70 °C oil-bath, allowing to reflux overnight. The mixture was then diluted with diethyl ether (50 mL), silica gel (~2 g) was then added, allowing the heterogenous mixture to stir for 30 minutes. The mixture was filtered through a celite/silica plug, eluting with diethyl ether (100 mL), concentrated *in vacuo*, then purified by flash column chromatography (90hexanes:10ethyl acetate) to afford (±)-**52** (0.396 g, 34%) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.34 (dd, J = 7.8, 1.9 Hz, 1H), 7.11 (d, J = 7.7 Hz, 1H), 5.68 (ddd, J = 17.1, 10.2, 8.9 Hz, 1H), 5.24 (d, J = 17.2 Hz, 1H), 5.15 (dd, J = 10.2, 1.7 Hz, 1H), 4.14 (dd, J = 10.4, 2.5 Hz, 1H), 2.95 (qd, J = 7.1, 2.6 Hz, 1H), 2.74 – 2.60 (m, 1H), 2.38 (s, 3H), 1.26 (d, J = 6.5 Hz, 3H), 1.16 (d, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 143.8, 138.4, 137.4, 134.8, 130.5, 126.6, 123.9, 116.6, 83.9, 40.0, 34.4, 21.0, 17.6, 14.4; IR (neat): 2972, 2932, 2251, 1712, 1279, 906, 729 cm^{-1}; AMM (ESI) *m/z* calcd for $C_{15}H_{19}O_2^+$ $[M+H]^+$ 231.1380, found 231.1375.



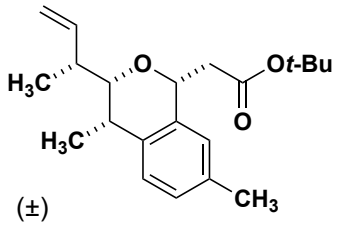
rac-(3*S*,4*R*)-3-((1*S*)-1-methylprop-2-en-1-yl)-4,7-dimethylisochroman-1-one (±)-**161** was isolated from the above procedure/purification as a clear oil (0.422g, 36%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.36 (dd, J = 7.8, 2.0 Hz, 1H), 7.15 (d, J = 7.8 Hz, 1H), 5.99 (ddd, J = 17.4, 10.4, 7.1 Hz, 1H), 5.19 (d, J = 17.3 Hz, 1H), 5.14 (d, J = 10.4 Hz, 1H), 4.19 (dd, J = 10.0, 2.6 Hz, 1H), 3.02 (qd, J = 7.1, 2.7 Hz, 1H), 2.71 – 2.60 (m, 1H), 2.38 (s, 3H), 1.20 (d, J = 7.1 Hz, 3H), 1.10 (d, J = 6.9 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.9, 143.4, 140.0, 137.6, 134.9, 130.6, 126.8, 124.0, 115.6, 84.2, 38.6, 34.0, 21.1,

15.5, 14.6; IR (neat) 2972, 2932, 1717, 1194, 980 cm^{-1}; AMM (ESI) *m/z* calcd $C_{15}H_{19}O_2^+$ $[M+H]^+$ 231.1380, found 231.1387.



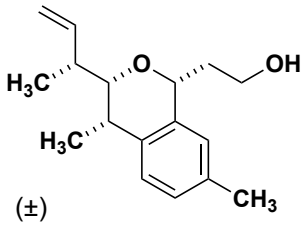
rac-tert-butyl 2-(1*R*,3*S*,4*R*)-3-((1*R*)-1-methylprop-2-en-1-yl)-1-hydroxy-4,7-dimethylisochroman-1-yl) acetate (±)-**143** was synthesized, following a modified literature procedure,[114] by preparing a solution of diisopropylamine (0.39 mL, 2.76 mmol, 1.6 equiv.) in THF (0.56 M with respect to the amine). The solution was cooled to -78 °C and *n*-butyllithium (1.82 mL, 2.58 mmol, 1.5 equiv.) was added dropwise, allowing to stir for 15 minutes. The solution was warmed to 0 °C, stirred for 15 minutes, cooled down to -78 °C, and *tert*-butyl acetate (0.37 mL, 2.75 mmol, 1.6 equiv.) was added dropwise, allowing to stir for 10 minutes. The *tert*-butyl acetate enolate was then quickly transferred dropwise via syringe into a -78 °C solution of (±)-**12** (0.396 g, 1.719 mmol, 1 equiv.) in THF (0.14 M with respect to (±)-**52**), allowing to stir at -78 °C for 15 minutes. The reaction was quenched with saturated aqueous ammonium chloride (10 mL), warmed to room temperature, extracted with dichloromethane (10 mL x 3), dried over sodium sulfate, and concentrated *in vacuo*. The unpurified product ^{1}H NMR spectrum shows a 96:4 dr and upon purification by flash column chromatography (90hexanes:10ethyl acetate) (±)-**143** (0.476 g, 80%, 70:30dr) is afforded as a yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.15 (s, 1H), 7.05 (d, J = 7.3 Hz, 1H), 6.95 (d, J = 7.8 Hz, 1H), 6.57 (s, 1H), 5.73 – 5.65 (m, 1H), 5.19 (d, J = 15.6 Hz, 1H), 5.09 (d, J = 10.3 Hz, 1H), 3.49 (d, J = 10.1 Hz, 1H), 2.97 (d, J = 16.0 Hz, 1H), 2.79 (d, J = 16.1 Hz, 1H), 2.71 (q, J = 6.8 Hz, 1H), 2.57 – 2.47 (m, 1H), 2.31 (s, 3H), 1.50 (s, 9H), 1.20 (d, J = 7.0 Hz, 3H), 1.15 (d, J = 6.7 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.5, 139.7, 138.6, 136.4, 136.1, 129.4, 128.3, 127.2, 115.7, 98.3, 82.6,

78.6, 43.1, 40.2, 34.5, 28.2, 21.3, 18.1, 16.7; IR (neat) 3432, 2976, 2932, 1705, 1370, 1156 cm^{-1}; AMM (ESI) *m/z* calcd for $C_{15}H_{19}O_2^+$ $[M+H]^+$ 347.2217, found 347.2203.

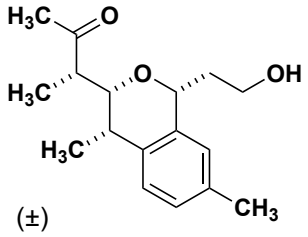


rac-tert-butyl 2-((1*S*,3*R*,4*S*)-3-((1*R*)-1-methylprop-2-en-1-yl)-1-4,7-dimethylisochroman-1-yl) acetate (±)-**144** was synthesized, following a modified literature procedure,[114] by preparing a solution of (±)-**143** (0.476 g, 1.373 mmol, 1 equiv.) and triisopropylsilane (5.6 mL, 27.3 mmol, 20 equiv.) in dichloromethane (0.15 M). This solution was cooled to -78 °C and boron trifluoride diethyl etherate complex (1.68 mL, 13.61 mmol, 10 equiv.) was added dropwise, allowing the mixture to stir for 4 hours at -78 °C. The reaction was then placed in an acetonitrile/dry ice bath and stirred for 20 hours at -40 °C. The reaction mixture was then cooled to -78 °C and syringed dropwise into a 0 °C solution of dichloromethane (0.1 M) and saturated aqueous sodium bicarbonate (2:3 ratio of dichloromethane:saturated aqueous sodium bicarbonate by volume), allowing to stir at 0 °C for 15 minutes. The mixture was allowed to warm to room temperature, stirred for 15 minutes, extracted with dichloromethane (10 mL x2); combined extracts were dried over sodium sulfate, concentrated *in vacuo*, and purified by column chromatography (95pentanes:5diethyl ether) to afford (±)-**144** (0.138 g, 30%, >95:5 dr) as a clear oil. ^{1}H NMR (600 MHz, $CDCl_2$) δ 7.02 – 6.96 (m, 2H), 6.86 (s, 1H), 5.71 – 5.64 (m, 1H), 5.16 – 5.10 (m, 2H), 5.05 (d, J = 10.3 Hz, 1H), 3.28 (d, J = 10.2 Hz, 1H), 2.85 (dd, J = 14.9, 3.3 Hz, 1H), 2.70 (q, J = 7.8 Hz, 1H), 2.56 (dd, J = 14.9, 9.7 Hz, 1H), 2.42 (h, J = 6.9 Hz, 1H), 2.29 (s, 3H), 1.49 (s, 9H), 1.17 (d, J = 7.0 Hz, 3H), 1.13 (d, J = 6.5 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.9, 140.3,

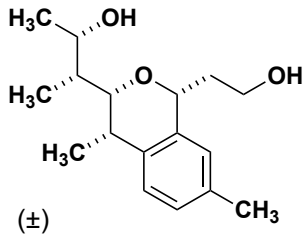
138.9, 136.5, 135.7, 129.0, 127.7, 124.6, 115.2, 80.6, 75.2, 43.6, 40.3, 34.8, 28.3, 21.3, 17.8, 17.0; IR (neat) 2975, 2932, 1732, 1368, 1151 cm^{-1}; AMM (ESI) *m/z* calcd $[M+H]^+$ 331.2268, found 331.2264.



rac-2-((1*R*,3*S*,4*S*)-3-((*R*)-but-3-en-2-yl)-4,7-dimethylisochroman-1-yl)ethan-1-ol ((±)-**167**) was synthesized following a modified literature procedure,[105] by preparing a suspension of lithium aluminum hydride (0.037 g, 0.970 mmol, 2.3 equiv.) in diethyl ether (0.1 M) which was cooled to 0 °C. A solution of ester (±)-**144** (0.138 g, 0.417 mmol, 1 equiv) in diethyl ether (0.4 M) was then added to the suspension dropwise and allowed to warm to room temperature over 16h. The reaction mixture was then cooled to 0 °C and the Fieser workup was performed: 32 μL H_2O was carefully added and allowed to stir for 15minutes, 32 μL 10% aqueous NaOH was added and allowed to stir for 15 minutes, the ice bath was removed and 95 μL H_2O was added and allowed to stir for 10min, and finally a generous quantity of $MgSO_4$ was added and allowed to stir for 10 minutes. The white suspension was filtered through a glass frit filter and the filtrate was concentrated *in vacuo*. (±)-**167** (0.109g, 100%) was afforded as a clear oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.03 – 6.97 (m, 2H), 6.84 (s, 1H), 5.67 (ddd, J = 17.2, 10.3, 8.7 Hz, 1H), 5.16 (d, J = 17.2 Hz, 1H), 5.07 (dd, J = 10.3, 1.8 Hz, 1H), 4.97 (dd, J = 8.4, 3.2 Hz, 1H), 3.93 – 3.79 (m, 2H), 3.33 (dd, J = 10.1, 2.3 Hz, 1H), 2.97 (dd, J = 6.6, 4.6 Hz, 1H), 2.73 (qd, J = 7.0, 2.2 Hz, 1H), 2.48 – 2.37 (m, 1H), 2.35 – 2.26 (m, 4H), 2.08 – 1.99 (m, 1H), 1.18 (d, J = 6.9 Hz, 3H), 1.16 (d, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.82, 138.53, 136.58, 135.90, 129.00, 127.68, 124.73, 115.54, 81.12, 78.88, 61.50, 40.36, 38.24, 34.76, 21.34, 18.05, 16.85; IR (neat) 3345, 2963, 2928. 1370, 1056 cm^{-1}; AMM (ESI) *m/z* calcd $[M+H]^+$ 261.1849, found 261.1851.

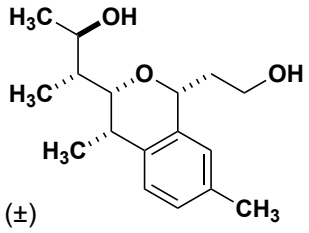


(±)-TM-135 ((±)-**4**) was synthesized following a modified literature procedure,[121] by dissolving (±)-**167** (0.090 g, 0.345 mmol, 1 equiv.) in a 3DMF:1H_2O mixture (0.01 M), and $PdCl_2$ (0.031 g, 0.173 mmol, 0.5 equiv.), and CuCl (0.046 g, 0.449 mmol, 1.3 equiv.) were added. The reaction flask was left open to air and the mixture was allowed to vigorously stir for 2 days. Upon completion, the mixture was filtered through a silica gel-ethyl acetate slurry, the silica mixture was rinsed with ethyl acetate (15 mL) and concentrated *in vacuo*. The remaining DMF/H_2O was then co-evaporated with toluene (100 mL x 3) and the residue was purified by flash column chromatography (50hexanes:50ethyl acetate) to afford TM-135 (±)-**4**, (0.0898g 94%) as a clear oil. Characterization data is consistent with that which is previously reported (see section 2.0 for NMR comparison). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (d, J = 9.4 Hz, 1H), 6.97 (d, J = 7.8 Hz, 1H), 6.84 (s, 1H), 4.99 (dd, J = 8.3, 3.1 Hz, 1H), 3.91 – 3.81 (m, 2H), 3.78 (dd, J = 9.9, 2.4 Hz, 1H), 2.87 (dq, J = 9.9, 7.0 Hz, 1H), 2.77 (qd, J = 7.2, 2.2 Hz, 1H), 2.67 (t, J = 5.5 Hz, 1H), 2.36 – 2.27 (m, 4H), 2.22 (s, 3H), 2.08 – 1.98 (m, 1H), 1.31 (d, J = 7.0 Hz, 3H), 1.15 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.7, 137.8, 136.2, 136.1, 129.2, 127.8, 124.7, 78.5, 78.4, 61.2, 38.2, 34.4, 29.2, 21.3, 17.6, 15.2; IR (neat) 3394, 2965, 2930, 2875, 1708, 1356, 1051 cm^{-1}; AMM (ESI) *m/z* calcd $[M+H]^+$ 277.1798, found 277.1791

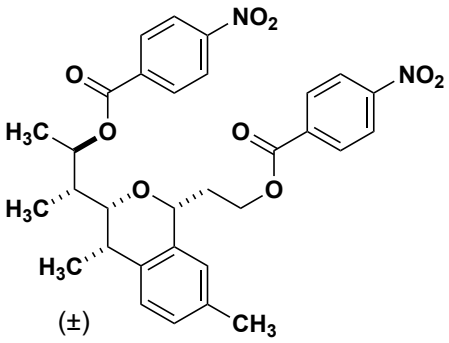


(±)-**Panowamycin B** ((±)-**8**) was synthesized, following a modified literature procedure,[105] by preparing a suspension of $LiAlH_4$ (0.014g, 0.369 mmol, 1.8 equiv.) in diethyl ether (0.1 M with respect to **4**) and cooling it to 0 °C. A solution of (±)-**4** (0.056 g, 0.201 mmol, 1 equiv.) in diethyl ether (0.2 M with respect to **4**) was added to this mixture dropwise and the mixture was allowed to stir to room temperature overnight. The reaction mixture was then cooled to 0 °C and the Fieser workup was performed: 15 μL H_2O was carefully added and allowed to stir for 15minutes, 15 μL 10% aqueous NaOH was added and allowed to stir for 15minutes, the ice bath was removed and 45 μL H_2O was added and allowed to stir for 10min, and finally a generous quantity of $MgSO_4$ was added and allowed to stir for 10 minutes. The white suspension was filtered through a glass frit filter and the filtrate was concentrated *in vacuo*. The ^{1}H NMR spectrum of the unpurified mixture showed a 72:28dr, and the diastereomers were separable by flash column chromatography (50hexanes:50ethyl acetate). (±)-**8** (0.038 g, 68%) was afforded as a clear oil. Characterization data is consistent with that which is previously reported (see section 2.0 for NMR comparison).[104] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 – 6.98 (m, 2H), 6.83 (s, 1H), 4.95 (dd, J = 8.5, 3.2 Hz, 1H), 4.06 (dd, J = 6.3, 3.0 Hz, 1H), 3.90 – 3.78 (m, 2H), 3.59 (dd, J = 9.2, 2.3 Hz, 1H), 3.09 (s, 1H), 2.91 (qd, J = 6.9, 2.2 Hz, 1H), 2.30 (s, 4H), 2.06 – 1.96 (m, 1H), 1.75 – 1.65 (m, 1H), 1.52 (s, 1H), 1.23 (d, J = 6.5 Hz, 3H), 1.18 (d, J = 6.9 Hz, 3H), 1.06 (d, J = 6.8 Hz, 3H); ^{1}H NMR (400 MHz, MeOD) δ 7.02 (d, J = 7.8 Hz, 1H), 6.98 (d, J = 7.8 Hz, 1H), 6.94 (s, 1H), 4.82 (dd, J = 9.0, 2.7 Hz, 1H), 4.05 (qd, J = 6.4, 2.0 Hz, 1H), 3.84 (dt, J = 10.5, 7.2 Hz, 1H), 3.73 (ddd, J = 10.5, 7.7, 4.8 Hz, 1H), 3.52 (dd, J = 9.6, 2.3 Hz, 1H), 2.93 (qd, J = 7.4, 2.2 Hz, 1H), 2.33 – 2.23 (m, 4H), 1.91 (dddd, J = 13.8, 8.9, 7.0, 4.8 Hz, 1H), 1.73 – 1.63 (m, 1H), 1.22 (d, J = 6.5 Hz, 3H), 1.15 (d, J = 6.9 Hz, 3H), 1.07 (d, J = 6.7 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.4, 136.7, 135.9, 129.1, 127.6, 124.7, 79.3, 78.7, 67.2, 61.4, 40.4, 38.1, 34.5, 21.6, 21.3, 17.5, 9.0; ^{13}C NMR (100 MHz, MeOD) δ 139.8, 138.5, 136.7, 129.9, 128.2, 125.5, 79.9, 76.6,

67.2, 60.1, 41.8, 40.2, 35.4, 21.3, 21.3, 17.7, 9.4; IR (neat) 3350, 2967, 2928, 1372, 1053, 905, 731 cm^{-1}; AMM (ESI) *m/z* calcd $C_{17}H_{26}NaO_3^+$ $[M+Na]^+$ 301.1779, found 301.1786.



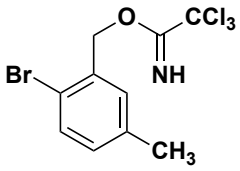
(±)-13*epi*-panowamycin B ((±)-**91**) was isolated from the above procedure/purification as a clear oil (0.014 g, 25%). Characterization data is consistent with section 2.10.2.5.



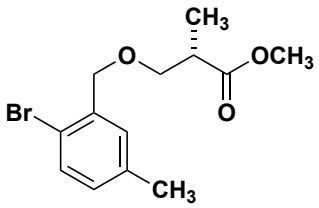
rac-(2*R*,3*R*)-3-((1*R*,3*R*,4*S*)-4,7-dimethyl-1-(2-((4-nitrobenzoyl)oxy)ethyl)isochroman-3-yl)butan-2-yl 4-nitrobenzoate (±)-**145** was synthesized, following a modified literature procedure,[119] by preparing a solution of (±)-**91** (0.022 g, 0.079 mmol, 1 equiv.), 4-NO_2-benzoyl chloride (0.035 g, 0.189 mmol, 2.4 equiv.), and dimethylaminopyridine (0.002 g, 0.016 mmol, 0.2 equiv) in dichloromethane (0.03 M). Triethylamine (50 μL, 0.35 mmol 4.5 equiv.) was then added to the mixture and it was allowed to stir at room temperature for 20 hours. H_2O (3 mL) was added to the reaction, the organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3mL x 2). Combined organic extracts were dried with Na_2SO_4, concentrated *in vacuo* and purified by column chromatography (85hexanes:15ethyl acetate) to afford (±)-**145** (0.044 g, 96%) as clear colorless crystals. The ^1H NMR spectrum of the

unpurified product is included for informational purposes. Crystals were grown by slow diffusion from MTBE, pentane, and diethyl ether.

2.10.2.5 (2*S*)-2-Methyl-but-3-en-yl Route

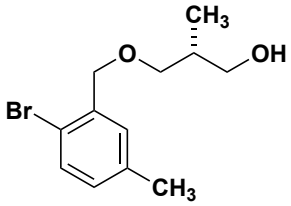


2-bromo-5-methylbenzyl 2,2,2-trichloroacetimidate (**154**) was prepared, following a modified literature procedure,[95] by preparing a solution of **153** (9.130 g, 45.409 mmol, 1 equiv.), trichloroacetonitrile (45 mL, 452 mmol, 10 equiv.), and 1,8-diazabicyclo[5.4.0]undec-7-ene (1.50 mL, 0.453 mmol, 0.3 equiv) in dichloromethane (0.5 M). The mixture was allowed to stir at room temperature overnight, observing a dark brown color change. Upon completion, the mixture was concentrated *in vacuo* (NOTE: the rotary evaporator apparatus was placed *inside* of a fume hood for inhalation safety.) and purified by flash column chromatography (90hexanes:10ethyl acetate) to afford **154** (15.460g, 99%) as a clear oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.46 (d, J = 8.1 Hz, 1H), 7.33 (s, 1H), 7.02 (dd, J = 8.2, 2.2 Hz, 1H), 5.37 (s, 2H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 162.7, 138.3, 135.0, 133.0, 131.3, 131.1, 120.3, 91.8, 70.9, 21.3; IR (neat) 3341, 2922, 1633, 1303, 1075, 794 cm^{-1}; AMM (ESI) *m/z* calcd $C_{10}H_{10}BrCl_3NO^+$ $[M+H]^+$ 343.9006, found 343.9009.



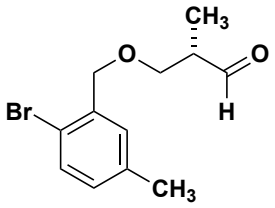
methyl (*S*)-3-((2-bromo-5-methylbenzyl)oxy)-2-methylpropanoate (**155**) was prepared , following a modified literature procedure,[97] by preparing a solution of **154** (15.458 g, 44.754 mmol, 1.2 equiv.) and *S*-Roche ester (4.408 g, 37.313 mmol, 1 equiv) in diethyl ether (0.34 M). This mixture was cooled to 0 °C

and triflic acid (495 μL, 5.594 mmol, 0.15 equiv) was carefully added as three 165 μL portions over 5 hours and allowed to stir to room temperature overnight (*Note*: triflic acid can melt plastic syringes if not handled quickly and safely, use caution). The mixture was diluted with diethyl ether (50 mL) and the mixture was carefully washed with sat. aq. $NaHCO_3$ (150 mL), washed with sat. aq. NaCl (150 mL), dried over Na_2SO_4, concentrated *in vacuo*, and purified by flash column chromatography (90hexanes:10ethyl acetate) to afford **155** (6.437 g, 57%) as a clear oil. At 3 mmol scale, this procedure yielded **155** in 93% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 (d, J = 8.1 Hz, 1H), 7.24 (d, J = 2.3 Hz, 1H), 6.95 (dd, J = 7.6, 1.9 Hz, 1H), 3.75 (dd, J = 9.1, 7.2 Hz, 1H), 3.71 (s, 3H), 3.58 (dd, J = 9.2, 5.9 Hz, 1H), 2.88 – 2.80 (m, 1H), 2.31 (s, 3H), 1.22 (d, J = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.9, 137.4, 137.1, 132.3, 129.9, 129.8, 119.4, 72.7, 72.5, 51.9, 40.3, 21.1, 14.2; IR (neat) 2949, 2864, 1736, 1093, 808 cm^{-1}; AMM (ESI) *m/z* calcd $C_{13}H_{17}BrNaO_3^+$ $[M+Na]^+$ 323.0258, found 323.0273; $[\alpha]^{21}_D$ +11.8 (c = 0.20, $CHCl_3$).



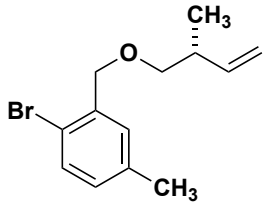
(*R*)-3-((2-bromo-5-methylbenzyl)oxy)-2-methylpropan-1-ol (**156**) was synthesized, following a modified literature procedure,[122] by preparing a solution of **155** (6.804 g, 22.591 mmol, 1 equiv.) in tetrahydrofuran (0.15M). After cooling the solution to 0 °C, lithium borohydride (34.8 mL, 69.6 mmol, 3.1 equiv., 2 M solution in THF) was added dropwise and allowed to stir for 10 minutes. Anhydrous methanol (3.1 mL, 76.6 mmol, 3.4 equiv.) was then added dropwise and the mixture was allowed to stir for 30 minutes at 0 °C. The solution was then allowed to warm to room temperature and stirring continued for 2 hours. This mixture was then carefully quenched with 10% aq. NaOH (50mL), extracted with ethyl acetate (50 mL x 3), washed with brine (150 mL x 1), and dried over Na_2SO_4., concentrated *in*

vacuo and purified by flash column chromatography (60hexanes:40ethyl acetate) to afford **156** (5.581 g, 90%) as clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 8.1 Hz, 1H), 7.23 (d, J = 1.6 Hz, 1H), 6.97 (dd, J = 8.2, 2.2 Hz, 1H), 4.54 (s, 2H), 3.71 – 3.57 (m, 3H), 3.50 (dd, J = 9.1, 8.0 Hz, 1H), 2.31 (s, 3H), 2.17 – 2.06 (m, 1H), 0.92 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.4, 136.8, 132.4, 130.0, 129.9, 119.6, 75.8, 72.8, 67.7, 35.7, 21.0, 13.5; IR (neat) 3357, 2921, 2869, 1467, 1094, 1026 cm^{-1}; AMM (ESI) *m/z* calcd $C_{12}H_{17}BrNaO_2^+$ $[M+Na]^+$ 295.0309, found 295.0321; $[\alpha]^{22}_D$ +10.3 (c = 0.23, $CHCl_3$).



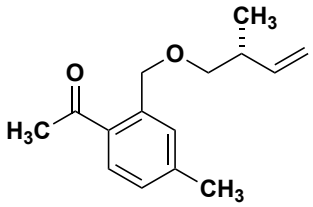
(*S*)-3-((2-bromo-5-methylbenzyl)oxy)-2-methylpropanal (**157**) was synthesized, following a modified literature procedure,[99] by preparing a solution of oxalyl chloride (2.44 mL, 28.42 mmol, 2 equiv.) in dichloromethane (0.6 M) and cooling the mixture to -78 °C. Dimethyl sulfoxide (4 mL, 56 mmol, 4 equiv.) was then added dropwise over 15 minutes, allowing to stir for an additional 30 minutes. A solution of **156** (3.854 g, 14.110 mmol, 1 equiv.) in dichloromethane (0.9 M) was then added dropwise and allowed to stir at -78 °C for 1 hour before triethylamine (9.8 mL, 70.5 mmol, 5 equiv.) was added dropwise. This mixture was allowed to stir to room temperature for 5 hours before carefully quenching with Na_2HSO_4 (50 mL of a 1 M aq. Solution). The organic layer separated and the aqueous layer was extracted with dichloromethane (25 mL x 3), the combined organic extracts were washed with sat. aq. Na_2HSO_4, washed with $NaHCO_3$, then H_2O, then sat. aq. NaCl, dried over Na_2SO_4, concentrated *in vacuo*, and **157** was used in the next reaction without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (s, 1H), 7.40 (d, J = 8.1 Hz, 1H), 7.22 (d, J = 1.6 Hz, 1H), 6.96 (dd, J = 8.1, 2.3 Hz, 1H), 4.55 (s, 2H), 3.82 – 3.69 (m, 2H), 2.78 – 2.65 (m, 1H), 2.31 (s, 3H), 1.17 (d, J = 7.1 Hz, 3H). ^{13}C NMR (150 MHz,

$CDCl_3$) δ 204.7, 137.5, 136.8, 132.4, 130.0, 129.9, 119.5, 72.7, 70.8, 46.9, 21.1, 10.9; IR (neat) 2858, 2722, 1722, 1469, 1097, 1026, 808 cm^{-1}; AMM (ESI) *m/z* calcd $C_{12}H_{15}BrNaO_2^+$ $[M+Na]^+$ 293.0153, found 293.0161; $[\alpha]^{21}_D$ +2.8 (c = 0.94, $CHCl_3$).

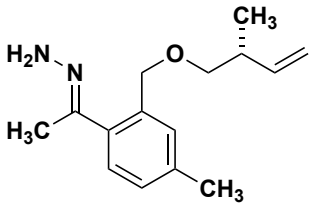


(*R*)-1-bromo-4-methyl-2-(((2-methylbut-3-en-1-yl)oxy)methyl)benzene (**133**) was synthesized, following a modified literature procedure,[123] by azeotropic drying of methyltriphenylphosphonium bromide (10.092 g, 28.227 mmol, 2 equiv.) in toluene (150 mL) three times. The dry solids were suspended in tetrahydrofuran (0.18 M) and cooled to -78 °C. *n*-Butyllithium (12.55 mL of a 2.13 M solution in hexanes, 26.73 mmol, 1.9 equiv.) was added dropwise and the mixture was stirred for 1 hour at -78 °C. A solution of **156** (assumed quantitative from previous reaction, 14.110 mmol, 1 equiv.) in tetrahydrofuran (0.9 M) was prepared, cooled to -78 °C, and transferred dropwise to the solution of ylide. This mixture was stirred at -78 °C for 1 hour, then allowed to warm to room temperature, stirring overnight. The mixture was quenched with sat. aq. NH_4Cl (100 mL), diluted with diethyl ether (75 mL), and the organic layer was collected. This solution was then washed with H_2O (100 mL x 2), washed with sat. aq. NaCl (150 mL x 1), dried over Na_2SO_4, concentrated *in vacuo*, and purified by flash column chromatography (95hexanes:5ethyl acetate) to afford **133** (3.437 g, 90% over 2 steps) as a clear oil. Properties match with (±)-**37** (section 3.4). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 (d, J = 8.1 Hz, 1H), 7.29 (d, J = 2.2 Hz, 1H), 6.94 (d, J = 8.1 Hz, 1H), 5.84 (ddd, J = 17.3, 10.4, 6.9 Hz, 1H), 5.10 (d, J = 18.7 Hz, 1H), 5.04 (d, J = 10.4 Hz, 1H), 4.53 (s, 2H), 3.47 (dd, J = 9.2, 6.5 Hz, 1H), 3.39 (dd, J = 9.1, 6.9 Hz, 1H), 2.56 (hept, J = 6.8 Hz, 1H), 2.31 (s, 3H), 1.08 (d, J = 6.7 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 141.34,

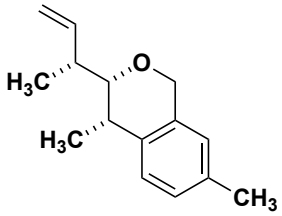
137.55, 137.40, 132.28, 129.83, 129.69, 119.30, 114.33, 75.77, 72.32, 37.95, 21.16, 16.77; IR (neat) 2861, 1468, 1150, 1100, 806 cm^{-1}; AMM (ESI) *m/z* calcd $C_{13}H_{18}BrO^+$ $[M+H]^+$ 269.0536, found 269.0538; $[\alpha]^{20}_D$ +4.2 (c = 1.1, $CHCl_3$).



(*R*)-1-(4-methyl-2-(((2-methylbut-3-en-1-yl)oxy)methyl)phenyl)ethan-1-one (**134**) was synthesized per section 2.10.2.4 with matching characterization data. $[\alpha]^{21}_D$ +4.0 (c = 0.75, $CHCl_3$).

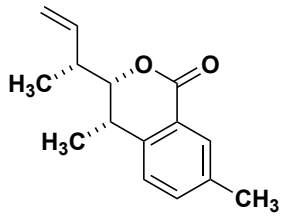


(*R,E*)-(1-(4-methyl-2-(((2-methylbut-3-en-1-yl)oxy)methyl)phenyl)ethylidene)hydrazine (**135**) was synthesized per Section 2.10.2.4 with matching characterization data. $[\alpha]^{22}_D$ +3.4 (c = 0.85, $CHCl_3$).

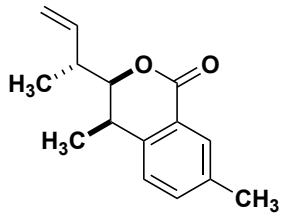


(3*S*,4*S*)-3-((*R*)-but-3-en-2-yl)-4,7-dimethylisochroman (**142**) was synthesized, following a modified two-pot procedure developed in the lab,[112] by preparing a solution of **135** (1.994 g, 8.094 mmol, 1 equiv.) in acetonitrile (0.16 M). MnO_2 (5.646 g, 83.132 mmol, 8 equiv., see section 1.1 for reagent details) was added (producing a bright fuchsia colored solution when stirring is halted) and allowed to stir for 1 hour. This heterogenous mixture was then filtered through a glass frit, washing with DCM (50 mL), into a dry, clean flask. In a separate flask, Rh_2(*S*-TCPTTL)$_4$ (0.083 g, 0.042 mmol, 0.5 mol %) was dissolved in DCM

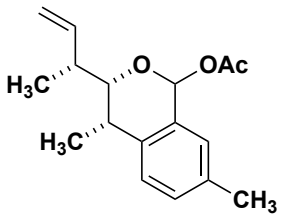
(0.015 M with respect to hydrazone) and the solution was cooled to -15 °C. The filtered fuchsia diazo solution was then added to the catalyst solution by syringe pump (Harvard Apparatus, Pump 11, 0.35 mL/min) over ~6 hours keeping the temperature at approximately -15 °C. After addition was completed, the syringe previously containing the diazo species was washed with 15 mL of DCM and the rinsate added dropwise over 30minutes; this mixture was stirred overnight. The stirbar was then removed and rinsed with DCM (2mL), the solution was concentrated *in vacuo*, and the product was purified by flash column chromatography (95hexanes:5ethyl acetate) to afford **142** as a clear oil (1.3791 g, 79%, 81:19dr). The product was isolated as the 80:20 mixture of diastereomers and carried into the next reaction; the ^{1}H NMR of the mixture is complex and is provided for informational purposes. Characterization data is consistent with (Section 2.10.2.4).



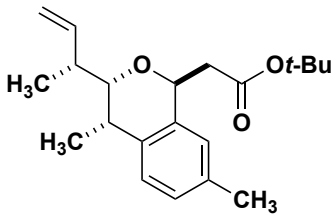
(3*S*,4*S*)-3-((*R*)-but-3-en-2-yl)-4,7-dimethylisochroman-1-one (**52**) was synthesized per Section 3.4 using **32** (1.379 g, 6.472 mmol, 1 equiv.) and PCC (6.818 g, 31.629 mmol, 5 equiv.) in DCM (0.2 M) to afford **12** (0.915 g, 62%) with matching characterization data. $[\alpha]^{19}_{D}$ +39.5 (c = 0.09, CH_3OH).



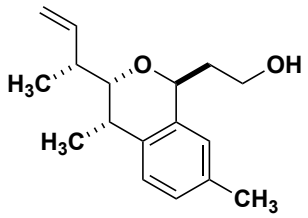
(3*R*,4*R*)-3-((*R*)-but-3-en-2-yl)-4,7-dimethylisochroman-1-one (**161**) was separated from **52** in the above procedure to afford **161** (0.237 g, 16%). Characterization data is consistent with Section 2.10.2.4. $[\alpha]^{17}_{D}$ +59.1 (c = 0.09, CH_3OH).



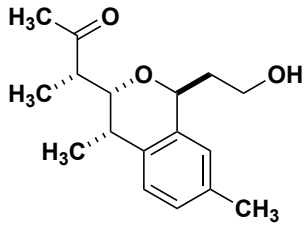
(3*S*,4*S*)-3-((*R*)-but-3-en-2-yl)-4,7-dimethylisochroman-1-yl acetate (**158**) was synthesized, following a modified literature procedure,[100] by preparing a solution of **52** (0.209 g, 0.909 mmol, 1 equiv.) in dichloromethane (0.056 M). This solution was cooled to -78 °C and diisobutylammonium hydride (2 mL, 2 mmol, 2.2 equiv.) was added dropwise and allowed to stir for 20 minutes at -78 °C (or until complete, monitored by TLC). Acetic anhydride (0.45 mL, 4.34 mmol, 5 equiv.), pyridine (0.29 mL, 3.47 mmol, 4 equiv.), and dimethylaminopyridine (0.162 g, 1.327 mmol, 1.5 equiv.) were then added and the mixture was allowed to warm to 0 °C, stirring for 1 hour, then warming to room temperature and stirred for more 3 hours. The reaction was then quenched with a 1:1 mixture of sat. aq. Rochelle salt and sat. aq. NH_4Cl (5 mL) and stirred for 30 minutes. The organic layer was separated, the aqueous layer was extracted with dichloromethane (10 mL x 3), the combined extracts were dried over Na_2SO_4, and concentrated *in vacuo*. Acetal **158** was observed to decompose under flash column chromatography and was therefore used in the next reaction without further purification. ^1H NMR spectrum is included for informational purposes and shows >95:5 dr. ^1H NMR (400 MHz, $CDCl_3$) δ 7.12 (dd, J = 7.9, 1.8 Hz, 1H), 7.04 (d, J = 7.8 Hz, 1H), 6.99 (d, J = 1.8 Hz, 1H), 6.94 (s, 1H), 5.68 (ddd, J = 17.2, 10.3, 8.8 Hz, 1H), 5.18 (d, J = 18.1 Hz, 1H), 5.09 (dd, J = 10.2, 1.8 Hz, 1H), 3.76 (dd, J = 10.3, 2.5 Hz, 1H), 2.75 (qd, J = 7.0, 2.4 Hz, 1H), 2.46 (ddt, J = 12.7, 9.2, 6.4 Hz, 1H), 2.33 (s, 3H), 2.12 (s, 3H), 1.12 (m, 6H); IR (neat) 2966, 2929, 1736, 1225, 999, 915cm^{-1}; AMM (ESI) *m/z* calcd $C_{17}H_{23}O_3^+$ $[M+H]^+$ 275.1642, found 275.1635.



tert-butyl 2-((1*S*,3*S*,4*S*)-3-((*R*)-but-3-en-2-yl)-4,7-dimethylisochroman-1-yl)acetate (**152**) was synthesized, following a modified literature procedure,[100] by preparing a solution of **158** (assumed quantitative from previous step, 0.868 mmol, 1 equiv.) and ((1-(*tert*-butoxy)vinyl)oxy)(*tert*-butyl)dimethylsilane (1.031 g, 4.342 mmol, 5 equiv.) in dichloromethane (0.05 M). This mixture was cooled to -78 °C and $BF_3 \bullet Oet_2$ (0.13 mL, 1.04 mmol, 1.2 equiv.) was added dropwise. This mixture was stirred at -78 °C for 30 minutes and then quenched with pyridine (0.35 mL, 4.34 mmol, 5 equiv.) and allowed to stir to room temperature. Sat. Aq. NH_4Cl (20 mL) was then added, the organic layer was collected, the aqueous layer was extracted with dichloromethane (10 mL x 3), the combined extracts were dried over Na_2SO_4, concentrated *in vacuo*, and purified by flash column chromatography (95pentane:5diethyl ether) to afford **152** (0.162 g, 54% over 2 steps) as a white crystalline solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.99 (d, J = 1.1 Hz, 2H), 6.84 (s, 1H), 5.71 (ddd, J = 17.2, 10.3, 8.7 Hz, 1H), 5.41 (dd, J = 10.6, 3.2 Hz, 1H), 5.16 (ddd, J = 17.2, 1.9, 0.9 Hz, 1H), 5.06 (dd, J = 10.3, 1.9 Hz, 1H), 3.45 (dd, J = 10.0, 2.4 Hz, 1H), 2.82 (dd, J = 15.5, 10.6 Hz, 1H), 2.70 (qd, J = 7.0, 2.3 Hz, 1H), 2.58 (dd, J = 15.5, 3.2 Hz, 1H), 2.51 – 2.32 (m, 1H), 2.29 (s, 3H), 1.50 (s, 9H), 1.14 (d, J = 6.9 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.5, 140.2, 138.3, 135.6, 135.6, 128.8, 127.2, 125.6, 115.2, 80.7, 74.5, 72.9, 42.2, 40.0, 34.4, 28.1, 21.1, 18.0, 16.3; IR (neat) 2975, 2930, 2250, 1723, 1156, 906, 729 cm^{-1}; MP 70.7-71.2°C; AMM (ESI) *m/z* calcd $C_{21}H_{31}O_3^+$ $[M+H]^+$ 331.2268, found 331.2264; $[\alpha]^{17}_D$ –50.3 (c = 0.42, CH_3OH).

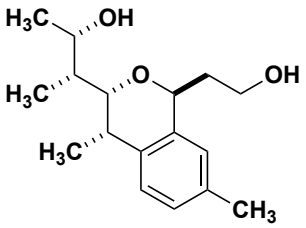


2-((1*S*,3*S*,4*S*)-3-((*R*)-but-3-en-2-yl)-4,7-dimethylisochroman-1-yl)ethan-1-ol (**168**) was synthesized, following a modified literature procedure,[105] by preparing a suspension of $LiAlH_4$ (0.038 g, 1.004 mmol, 2.1 equiv.) in diethyl ether (0.1 M). This mixture was cooled to 0 °C and a solution of **152** (0.156 g, 0.472 mmol, 1 equiv.) in diethyl ether (0.5 M) was added dropwise. This solution was allowed to stir to room temperature for 1 hour and then the Fieser workup was performed: 37 μL H_2O was carefully added and allowed to stir for 15 minutes, 37 μL 10% aqueous NaOH was added and allowed to stir for 15 minutes, the ice bath was removed and 111 μL H_2O was added and allowed to stir for 10 minutes, and finally a generous quantity of $MgSO_4$ was added and allowed to stir for 10 minutes. The white suspension was filtered through a glass frit filter and the filtrate was concentrated *in vacuo*, to afford **168** (0.124 g, 100%) as a clear oil without purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06 – 7.00 (m, 2H), 6.90 (s, 1H), 5.75 (ddd, J = 17.2, 10.3, 8.7 Hz, 1H), 5.21 (dd, J = 17.1, 1.7 Hz, 1H), 5.13 (ddd, J = 10.3, 4.2, 2.1 Hz, 2H), 4.11 – 3.98 (m, 1H), 3.98 – 3.88 (m, 1H), 3.53 (dd, J = 10.0, 2.4 Hz, 1H), 2.76 (qd, J = 6.9, 2.4 Hz, 1H), 2.63 (s, 1H), 2.56 – 2.41 (m, 1H), 2.34 (s, 3H), 2.25 – 2.11 (m, 1H), 2.04 – 1.92 (m, 1H), 1.22 (d, J = 6.5 Hz, 3H), 1.19 (d, J = 6.9 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 140.1, 138.0, 136.8, 135.6, 128.7, 127.5, 125.9, 115.3, 74.4, 73.0, 60.2, 40.2, 38.1, 34.5, 21.2, 18.4, 16.4; IR (neat) 2426, 2966, 2928, 1456, 1060, 1000, 816 cm^{-1}; AMM (ESI) *m/z* calcd $C_{17}H_{25}O_2^+$ $[M+H]^+$ 261.1845, found 261.1849; $[\alpha]^{17}_D$ –68.6 (c = 0.26, CH_3OH).



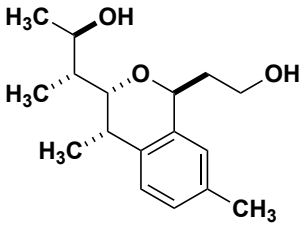
Panowamycin A (**3**) was prepared, following a modified literature procedure,[121] by dissolving **168** (0.124 g, 0.474 mmol, 1 equiv.) in a 3DMF:1H_2O mixture (0.01 M), and $PdCl_2$ (0.045 g, 0.255 mmol, 0.5 equiv.), and CuCl (0.065 g, 0.657 mmol, 1.3 equiv.) were added. The reaction flask was left open to air and the mixture was allowed to vigorously stir for 2 days. Upon completion, the mixture was filtered through a silica gel-ethyl acetate slurry, the silica mixture was rinsed with ethyl acetate (20 mL) and concentrated *in vacuo*. The remaining DMF/H_2O was then co-evaporated with toluene (100 mL x 3) and the residue was purified by flash column chromatography (50hexanes:50ethyl acetate) to afford panowamycin A (**3**), (0.125 g. 95%) as a clear oil. Characterization data is consistent with that which is previously reported.[29,104] ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (dd, J = 7.8, 1.6 Hz, 1H), 6.96 (d, J = 7.8 Hz, 1H), 6.84 (s, 1H), 5.07 (dd, J = 11.1, 2.5 Hz, 1H), 4.02 – 3.93 (m, 2H), 3.90 (dt, J = 10.7, 5.2 Hz, 1H), 2.89 (dq, J = 9.8, 6.9 Hz, 1H), 2.74 (qd, J = 7.0, 2.5 Hz, 1H), 2.30 (s, 3H), 2.24 (s, 3H), 2.22 – 2.13 (m, 1H), 1.95 (dddd, J = 14.6, 8.5, 6.1, 2.5 Hz, 1H), 1.81 (s, 1H), 1.30 (d, J = 7.0 Hz, 3H), 1.11 (d, J = 7.1 Hz, 3H); ^{1}H NMR (400 MHz, MeOD) δ 6.99 – 6.93 (m, 2H), 6.86 (s, 1H), 4.98 (dd, *J* = 11.1, 2.5 Hz, 1H), 3.92 (dd, *J* = 9.9, 2.5 Hz, 1H), 3.86 (ddd, *J* = 5.8, 4.9, 3.4 Hz, 1H), 3.77 (ddd, *J* = 10.7, 6.9, 4.0 Hz, 1H), 2.90 (dq, *J* = 9.9, 7.0 Hz, 1H), 2.66 (qd, *J* = 7.1, 2.4 Hz, 1H), 2.28 (s, 3H), 2.24 (s, 3H), 2.17 – 2.06 (m, 1H), 1.93 – 1.82 (m, 1H), 1.29 (d, *J* = 7.0 Hz, 3H), 1.08 (d, *J* = 7.2 Hz, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.04, 137.24, 136.51, 135.84, 128.88, 127.71, 125.83, 73.10, 71.83, 60.49, 49.32, 38.11, 34.18, 29.34, 21.27, 17.24, 15.49; ^{13}C NMR (100 MHz, MeOD) δ 213.4, 138.4, 138.0, 136.7, 129.7, 128.5, 126.7, 73.4, 72.8,

59.9, 50.4, 39.4, 35.4, 29.2, 21.2, 17.5, 15.7; IR (neat) 3398, 2963, 2930, 2875, 1706, 1353, 1051 cm^{-1}; AMM (ESI) *m/z* calcd $C_{17}H_{25}O_3^+$ $[M+H]^+$ 277.1798, found 277.1790; $[\alpha]^{21}_D$ –55.3 (c = 0.11, CH_3OH).



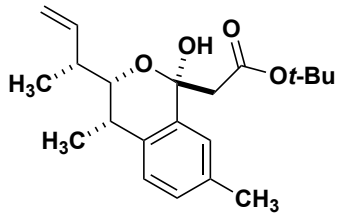
(3*epi*)-panowamycin B (**159**) was prepared, following a modified literature procedure,[105] by preparing a suspension of $LiAlH_4$ (0.026 g, 0.672 mmol, 1.5 equiv.) in diethyl ether (0.1 M). This mixture was cooled to 0 °C and a solution of **3** (0.107 g, 0.386 mmol, 1 equiv.) in diethyl ether (0.5 M) was added dropwise. This solution was allowed to stir to room temperature for 1 hour and then the Fieser workup was performed: 25 μL H_2O was carefully added and allowed to stir for 15 minutes, 25 μL 10% aqueous NaOH was added and allowed to stir for 15 minutes, the ice bath was removed and 75 μL H_2O was added and allowed to stir for 10 minutes, and finally a generous quantity of $MgSO_4$ was added and allowed to stir for 10 minutes. The white suspension was filtered through a glass frit filter and the filtrate was concentrated *in vacuo*, to afford a 76:24 mixture of diastereomers. This mixture was purified by flash column chromatography (30hexanes:70ethyl acetate) and the major isomer **159** (0.078 g, 73%) was isolated as an amorphous white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.02 – 6.98 (m, 2H), 6.85 (s, 1H), 5.07 (dd, J = 11.1, 2.3 Hz, 1H), 4.12 (qd, J = 6.4, 2.1 Hz, 1H), 4.00 (ddd, J = 10.6, 8.3, 5.1 Hz, 1H), 3.94 – 3.88 (m, 1H), 3.77 (dd, J = 9.5, 2.3 Hz, 1H), 2.92 (qd, J = 7.1, 2.3 Hz, 1H), 2.31 (s, 3H), 2.18 (ddt, J = 15.9, 10.5, 5.1 Hz, 1H), 1.93 (dddd, J = 14.6, 8.4, 6.0, 2.4 Hz, 1H), 1.71 (tt, J = 8.9, 6.8 Hz, 1H), 1.26 (d, J = 6.4 Hz, 3H), 1.14 (d, J = 7.0 Hz, 3H), 1.07 (d, J = 6.8 Hz, 3H); ^{1}H NMR (400 MHz, MeOD) δ 7.00 (d, *J* = 7.8 Hz, 1H), 6.96 (d, *J* = 7.9 Hz, 1H), 6.86 (s, 1H), 4.97 (dd, *J* = 11.0, 2.4 Hz, 1H), 4.09 – 4.04 (m, 1H), 3.93 – 3.85 (m, 1H), 3.83 – 3.77 (m, 1H), 3.74 (dd, *J* = 10.0, 2.3 Hz, 1H), 2.92 (qd, *J* = 6.9, 2.3 Hz, 1H), 2.28

(s, 3H), 2.12 (dddd, *J* = 14.7, 10.9, 5.7, 4.0 Hz, 1H), 1.90 – 1.81 (m, 1H), 1.69 – 1.60 (m, 1H), 1.22 (d, *J* = 6.5 Hz, 3H), 1.09 (d, *J* = 7.0 Hz, 3H), 1.06 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.9, 137.0, 135.7, 128.8, 127.6, 125.9, 73.2, 72.8, 67.3, 60.7, 40.3, 38.2, 34.2, 22.0, 21.3, 17.0, 9.3; ^{13}C NMR (150 MHz, MeOD) δ 139.1, 138.4, 136.6, 129.8, 128.3, 126.7, 73.7, 67.0, 60.1, 41.5, 39.5, 34.9, 21.6, 21.2, 17.2, 15.0, 10.1; IR (neat) 3393, 2969, 2930, 1375, 1055, 904, 669 cm^{-1}; AMM (ESI) *m/z* calcd $C_{17}H_{27}O_3^+$ $[M+H]^+$ 279.1955, found 279.1945; $[\alpha]^{20}_D$ –37.0 (c = 0.05, CH_3OH).

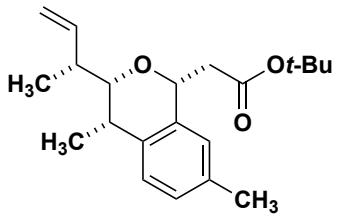


(3,13-*epi*)-panowamycin B (**160**) (0.020 g, 18%) was isolated as the minor diastereomer prepared from the reduction of **3** in the above procedure. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.02 – 6.98 (m, 2H), 6.85 (s, 1H), 5.07 (dd, J = 11.2, 2.4 Hz, 1H), 4.06 – 4.01 (m, 1H), 4.01 – 3.97 (m, 1H), 3.95 – 3.90 (m, 1H), 3.61 (dd, J = 8.6, 2.3 Hz, 1H), 2.69 (qd, J = 7.0, 2.3 Hz, 1H), 2.31 (s, 3H), 2.16 (ddt, J = 16.1, 10.8, 5.1 Hz, 1H), 2.01 – 1.91 (m, 2H), 1.21 (d, J = 6.9 Hz, 3H), 1.11 (d, J = 6.3 Hz, 3H), 1.06 (d, J = 6.8 Hz, 3H); ^{1}H NMR (400 MHz, MeOD) δ 6.99 (d, *J* = 7.8 Hz, 1H), 6.96 (d, *J* = 9.4 Hz, 1H), 6.86 (s, 1H), 4.95 (dd, *J* = 11.2, 2.4 Hz, 1H), 4.03 – 3.95 (m, 1H), 3.88 (ddd, *J* = 10.6, 8.9, 5.8 Hz, 1H), 3.79 (ddd, *J* = 10.7, 7.0, 4.0 Hz, 1H), 3.50 (dd, *J* = 9.6, 2.3 Hz, 1H), 2.68 (qd, *J* = 6.9, 2.3 Hz, 1H), 2.28 (s, 3H), 2.14 – 2.04 (m, 1H), 1.96 (dqd, *J* = 13.4, 6.7, 4.1 Hz, 1H), 1.86 (dddd, *J* = 14.6, 9.1, 7.0, 2.4 Hz, 1H), 1.15 (d, *J* = 6.9 Hz, 3H), 1.06 (d, *J* = 3.1 Hz, 3H), 1.05 (d, *J* = 3.4 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.8, 136.8, 135.9, 129.4, 127.7, 124.0, 73.5, 72.6, 67.8, 60.8, 41.3, 37.9, 34.8, 21.3, 18.4, 17.1, 10.8; ^{13}C NMR (100 MHz, MeOD) δ 138.8, 138.3, 136.7, 129.7, 128.3, 126.7, 73.8, 73.4, 67.5, 60.0, 42.0, 39.4, 35.6, 21.2, 17.2, 17.2, 10.6; IR (neat) 3358, 2968, 2924, 1455, 1377, 1090, 1055, 906, 733 cm^{-1}; AMM (ESI) *m/z* calcd

$C_{17}H_{27}O_3^+$ $[M+H]^+$ 279.1955, found 279.1945; $[\alpha]^{20}_D$ –31.8 (c = 0.04, CH_3OH). See section 6.4 for x-ray crystallography data for this compound.

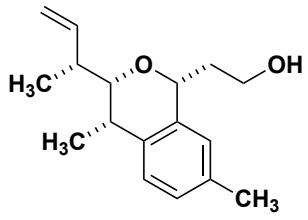


tert-butyl 2-(1*R*,3*S*,4*R*)-3-((1*R*)-1-methylprop-2-en-1-yl)-1-hydroxy-4,7-dimethylisochroman-1-yl) acetate (**143**) was synthesized, following a modified literature procedure,[114] by preparing a solution of diisopropylamine (0.35 mL, 2.43 mmol, 1.6 equiv.) in THF (0.56 M). The solution was cooled to -78 °C and *n*-butyllithium (1.10 mL, 2.28 mmol, 1.5 equiv.) was added dropwise, allowing to stir for 15 minutes. The solution was warmed to 0 °C, stirred for 15 minutes, cooled down to -78 °C, and *tert*-butyl acetate (0.33 mL, 2.43 mmol, 1.6 equiv.) was added dropwise, allowing to stir for 10 minutes. The *tert*-butyl acetate enolate was then quickly transferred dropwise via syringe into a -78 °C solution of **52** (0.345 g, 1.520 mmol, 1 equiv.) in THF (0.14 M), allowing to stir at -78 °C for 15 minutes. The reaction was quenched with saturated aqueous ammonium chloride (5 mL), warmed to room temperature, extracted with dichloromethane (10 mL x 3), dried over sodium sulfate, concentrated *in vacuo*, affording **143** was afforded without further purification as a clear oil (0.506 g, 98%) with 91:9dr. Characterization data is consistent with Section 2.10.2.4. $[\alpha]^{20}_D$ –1.2 (c = 0.14, CH_3OH).



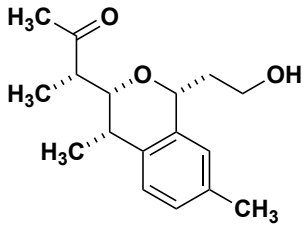
tert-butyl 2-((1*S*,3*R*,4*S*)-3-((1*R*)-1-methylprop-2-en-1-yl)-1-4,7-dimethylisochroman-1-yl) acetate (**144**) was synthesized, following a modified literature procedure,[114] by preparing a solution of **143**

(0.506 g, 1.461 mmol, 1 equiv.) and triisopropylsilane (6.0 mL, 29 mmol, 20 equiv.) in dichloromethane (0.15 M). This solution was cooled to -78 °C and boron trifluoride diethyl etherate complex (1.8 mL, 15 mmol, 10 equiv.) was added dropwise, allowing the mixture to stir for 4 hours at -78 °C. The reaction was then placed in an acetonitrile/dry ice bath and stirred for 20 hours at -40 °C. The reaction mixture was then cooled to -78 °C and syringed dropwise into a 0 °C solution of dichloromethane (0.1 M) and saturated aqueous sodium bicarbonate (2:3 ratio of dichloromethane:saturated aqueous sodium bicarbonate by volume), allowing to stir at 0 °C for 15 minutes. The mixture was allowed to warm to room temperature, stirred for 15 minutes, extracted with dichloromethane (10 mL x2); combined extracts were dried over sodium sulfate, concentrated *in vacuo*, and purified by column chromatography (100% hexanes flush, then 95hexanes:5ethyl acetate) to afford **144** (0.406 g, 84%, >95:5 dr) as a clear oil. Characterization data is consistent with Section 2.10.2.4. $[\alpha]^{19}_{D}$ +67.3 (c = 0.05, CH_3OH).

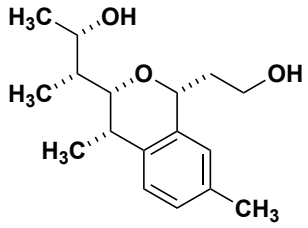


2-((1*R*,3*S*,4*S*)-3-((*R*)-but-3-en-2-yl)-4,7-dimethylisochroman-1-yl)ethan-1-ol (**167**) was synthesized following a modified literature procedure,[105] by preparing a suspension of lithium aluminum hydride (0.093 g, 2.421 mmol, 2 equiv.) in diethyl ether (0.1 M) which was cooled to 0 °C. A solution of ester **144** (0.388 g, 1.173 mmol, 1 equiv.) in diethyl ether (0.6 M with respect to **144**) was then added to the suspension dropwise and allowed to warm to room temperature over 16h. The reaction mixture was then cooled to 0 °C and the Fieser workup was performed: 93 μL H_2O was carefully added and allowed to stir for 15minutes, 93 μL 10% aqueous NaOH was added and allowed to stir for 15minutes, the ice bath was removed and 275 μL H_2O was added and allowed to stir for 10min, and finally a generous quantity of

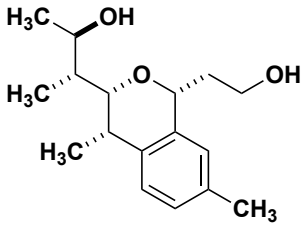
$MgSO_4$ was added and allowed to stir for 10 minutes. The white suspension was filtered through a glass frit filter, rinsing with diethyl ether and the filtrate was concentrated *in vacuo*. **167** was afforded as a clear oil (0.307 g, 100%). Characterization data is consistent with Section 2.10.2.4. $[\alpha]^{18}_D$ +65.6 (c = 0.09, CH_3OH).



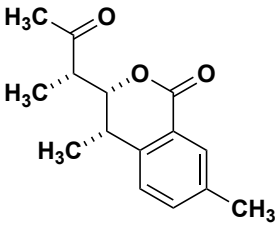
TM-135 (**4**) was synthesized following a modified literature procedure,[121] by dissolving **167** (0.295 g, 1.134 mmol, 1 equiv.) in DMF/ H_2O (0.01 M, 3DMF:1H_2O ratio), and $PdCl_2$ (0.116 g, 0.655 mmol, 0.5 equiv.), and CuCl (0.165 g, 1.668 mmol, 1.3 equiv.) were added. The reaction flask was left open to air and the mixture was allowed to vigorously stir for 2 days. Upon completion, the mixture was filtered through a silica gel-ethyl acetate slurry, the silica mixture was rinsed with ethyl acetate (15 mL) and concentrated *in vacuo*. The remaining DMF/H_2O was then co-evaporated with toluene (100 mL x 3) and the residue was purified by flash column chromatography (50hexanes:50ethyl acetate) to afford TM-135 (**4**), (0.272 g 87%) as a clear oil. Characterization data is consistent with section 2.10.2.4. $[\alpha]^{20}_D$ +61.6 (c = 0.11, CH_3OH).



Panowamycin B (**5**) was synthesized per section 2.10.2.4 and the characterization data is consistent. $[\alpha]^{19}_D$ +69.2 (c = 0.10, CH_3OH).

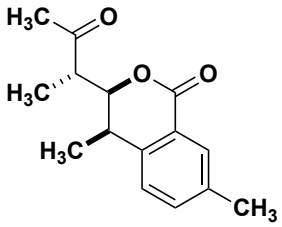


13*epi*-panowamycin B (**91**) was synthesized with **5** and separated by flash column chromatography per Section 2.10.2.4; characterization data is consistent with section 2.10.2.4. $[\alpha]^{14}_{D}$ +84.6 (c = 0.33, CH_3OH).



(3*R*,4*S*)-4,7-dimethyl-3-((*S*)-3-oxobutan-2-yl)isochroman-1-one (**52**) was synthesized following a modified literature procedure,[121] by dissolving **142** (0.295 g, 1.134 mmol, 1 equiv.) in DMF/ H_2O (0.01 M, 3DMF:1H_2O ratio), and $PdCl_2$ (0.026 g, 0.013 mmol, 0.5 equiv.), and CuCl (0.033 g, 0.331 mmol, 1.3 equiv.) were added. The reaction flask was left open to air and the mixture was allowed to vigorously stir for 2 days. Upon completion, the mixture was filtered through a silica gel-ethyl acetate slurry, the silica mixture was rinsed with ethyl acetate (15 mL) and concentrated *in vacuo*. The remaining DMF/H_2O was then co-evaporated with toluene (100 mL x 3) and the residue was purified by flash column chromatography (75hexanes:25ethyl acetate) to afford (**52**), (0.062 g 100%) as a clear oil. ^{1}H NMR (400 MHz, MeOD) δ 7.80 (s, 1H), 7.44 (dd, J = 7.7, 1.9 Hz, 1H), 7.22 (d, J = 7.8 Hz, 1H), 4.60 (dd, J = 10.1, 2.7 Hz, 1H), 3.17 (dq, J = 10.1, 7.0 Hz, 1H), 3.07 (qd, J = 7.2, 2.6 Hz, 1H), 2.38 (s, 3H), 2.29 (s, 3H), 1.37 (d, J = 7.0 Hz, 3H), 1.12 (d, J = 7.2 Hz, 3H); 1H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.35 (dd, J = 7.8, 1.9 Hz, 1H), 7.11 (d, J = 7.8 Hz, 1H), 4.60 (dd, J = 10.2, 2.7 Hz, 1H), 3.14 – 3.02 (m, 2H), 2.37 (s,

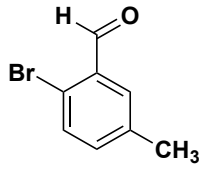
3H), 2.27 (s, 3H), 1.41 (d, J = 7.0 Hz, 3H), 1.12 (d, J = 7.2 Hz, 3H);^{13}C NMR (100 MHz, $CDCl_3$) δ 209.8, 165.7, 143.2, 137.6, 135.1, 130.5, 127.0, 123.6, 81.4, 48.5, 33.7, 29.4, 21.0, 15.3, 14.9; ^{13}C NMR (100 MHz, MeOD) δ 211.6, 167.6, 145.0, 138.9, 136.4, 131.0, 128.3, 124.5, 83.0, 49.4, 35.1, 29.2, 21.0, 15.4, 14.9; IR (neat): 2972, 2936, 1708 (broad, lumpy), 1280, 1191 cm^{-1}; AMM (ESI) m/z calcd for $C_{15}H_{19}O_3Na^+$ $[M+Na]^+$ 269.1148, found 269.1151; $[\alpha]^{20}_D$ +42.0 (c = 0.09, CH_3OH).



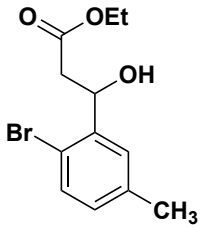
Veramycin F (**7**) was synthesized following a modified literature procedure,[121] by dissolving **161** (0.066 g, 0.287 mmol, 1 equiv.) in DMF/ H_2O (0.01 M, 3DMF:1H_2O ratio), and $PdCl_2$ (0.023 g, 0.130 mmol, 0.5 equiv.), and CuCl (0.034 g, 0.339 mmol, 1.3 equiv.) were added. The reaction flask was left open to air and the mixture was allowed to vigorously stir for 2 days. Upon completion, the mixture was filtered through a silica gel-ethyl acetate slurry, the silica mixture was rinsed with ethyl acetate (15 mL) and concentrated *in vacuo*. The remaining DMF/H_2O was then co-evaporated with toluene (100 mL x 3) and the residue was purified by flash column chromatography (75hexanes:25ethyl acetate) to afford (**7**), (0.064 g, 90%) as a clear oil. Characterization data is consistent with that which is previously reported.[22] ^{1}H NMR (400 MHz, MeOD) δ 7.76 (s, 1H), 7.44 (dd, J = 7.8, 2.0 Hz, 1H), 7.27 (d, J = 7.8 Hz, 1H), 4.68 (dd, J = 10.6, 2.6 Hz, 1H), 3.19 – 3.07 (m, 2H), 2.37 (s, 3H), 2.30 (s, 3H), 1.16 (d, J = 7.1 Hz, 3H), 1.12 (d, J = 7.1 Hz, 3H);^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.37 (dd, J = 7.8, 1.9 Hz, 1H), 7.16 (d, J = 7.7 Hz, 1H), 4.72 (dd, J = 10.4, 2.6 Hz, 1H), 3.16 – 3.04 (m, 1H), 2.97 (qd, J = 7.1, 2.6 Hz, 1H), 2.38 (s, 3H), 2.34 (s, 3H), 1.20 (d, J = 7.1 Hz, 3H), 1.12 (d, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.8, 165.1, 142.6, 137.8, 135.0, 130.6, 126.8, 123.7, 81.7, 47.1, 33.0, 30.7, 21.0, 14.5, 12.5; ^{13}C NMR

(100 MHz, MeOD) δ 212.3, 167.0, 144.7, 139.0, 136.4, 131.1, 128.4, 124.4, 83.5, 48.5, 33.9, 30.2, 21.0, 14.8, 12.7; IR (neat) 2973, 2935, 1712(broad, lumpy), 1279, 1194, 979 cm^{-1}; AMM (ESI) m/z calcd for $C_{15}H_{19}O_3Na^+$ $[M+Na]^+$ 269.1148, found 269.1151 ; $[\alpha]^{22}_D$ +58.8 (c = 0.08, CH_3OH).

2.10.2.6 Miscellaneous characterization data for other routes

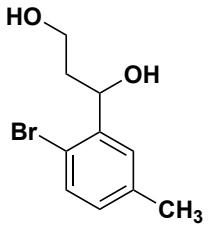


2-bromo-5-methylbenzaldehyde (**55**) was synthesized by dissolving **153** (6.545 g, 32 mmol 1 equiv) in DCM (0.33 M). Dess-Martin Periodinane (15.19 g, 36 mmol, 1.1 equiv) was then added portionwise and the mixture was stirred at room temperature for 1 hour. The reaction was then quenched with sat. aq. sodium thiosulfate (50 mL), filtered, extracted with DCM (50 mL x3), washed with water (250 mL), and dried over sodium sulfate to afford **55** (5.987 g, 92%) as a yellow solid. BDB-II-170

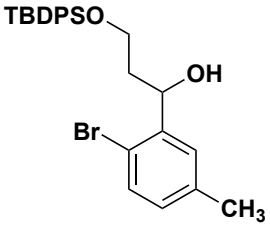


ethyl 3-(2-bromo-5-methylphenyl)-3-hydroxypropanoate (**56**) was synthesized by preparing a solution of diisopropylamine (8.5 mL, 60 mmol, 2 equiv) in THF (1.4 M). This solution was then cooled to –78 °C and *n*-butyllithium (26.2 mL, 60 mmol, 2 equiv) was added dropwise, allowing the LDA to form with stirring at –78 °C for 15minutes. A solution of ethyl acetate (5.9 mL, 60 mmol, 2 equiv) in THF (3 M) was then added dropwise and the mixture was allowed to stir for 30 minutes at –78 °C. A solution of **55** (5.987 g, 30 mmol, 1 equiv) in THF (3 M) was then added dropwise to this mixture at –78 °C, stirred for 30 minutes at –78°C, then allowed to warm to rt over 2 hours. The brown mixture was then quenched

with 1 M HCl (30 mL), extracted with EtOAc (50 mL x 3), washed with water (200 mL), washed with brine (200 mL), dried over sodium sulfate, and purified by flash column chromatography (90H:10EtOAc to 80H:20EtOAc) to afford **56** (5.868 g, 68%) as a yellow oil. BDB-II-171

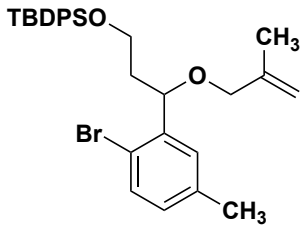


1-(2-bromo-5-methylphenyl)propane-1,3-diol (**57**) was synthesized by preparing a suspension of lithium aluminum hydride (2.326 g, 61 mmol, 3 equiv) in diethyl ether (1 M) and cooling the suspension to 0 °C. A solution of **56** (5.868 g, 20 mmol, 1 equiv) in diethyl ether (0.5 M) was then added dropwise and the mixture was allowed to stir to room temperature over 1 hour. The Fieser workup was then performed: 2.33 mL water (stir 15 minutes), 2.33 mL 10% aq. NaOH (stir 15 minutes), remove ice bath, 6.99 mL water (stir 10 minutes), and magnesium sulfate (stir 30 minutes) were added sequentially. The clear solution was then concentrated *in vacuo* to afford **57** (4.755 g, 95%) as a white crystalline solid and used without further purification. BDB-II-173

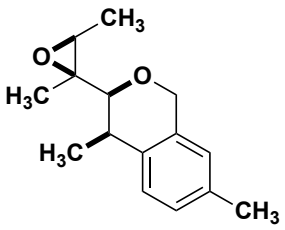


1-(2-bromo-5-methylphenyl)-3-((*tert*-butyldiphenylsilyl)oxy)propan-1-ol (**58**) was synthesized by preparing a solution of **57** (4.755 g, 20 mmol, 1 equiv) in DCM; triethylamine (5.4 mL, 39 mmol, 2 equiv) and DMAP (0.237 g, 2 mmol, 0.1 equiv) were then added and the mixture was cooled to 0 °C. TBDPS–Cl (5.2 mL, 20 mmol, 1 equiv) was added and the solution was allowed to stir to rt over 2 hours before

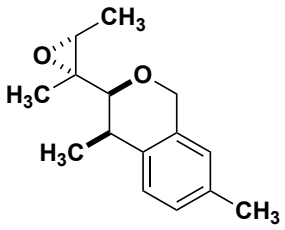
quenching with water (50 mL), washing with brine (100 mL), drying over sodium sulfate, and purifying by flash column chromatography (95H:5EtOAc) to afford **58** (6.258 g, 67%) as a clear oil. BDB-II-174



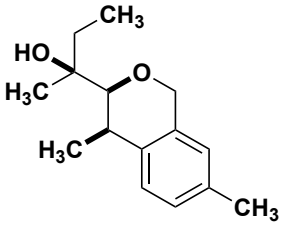
(3-(2-bromo-5-methylphenyl)-3-((2-methylallyl)oxy)propoxy)(*tert*-butyl)diphenylsilane (**59**) was synthesized by preparing a solution of **58** (2.010 g, 4 mmol, 1 equiv), methallyl bromide (0.82 mL, 8.3 mmol, 2 equiv), and potassium *tert*-butoxide (1.115 g, 9 mmol, 2.2 equiv) in THF (0.14 M) and stirring the mixture at room temperature overnight. This heterogeneous solution was then quenched with sat. aq. ammonium chloride (20 mL), extracted with DCM (10 mL x 3), washed with brine (50 mL), dried over sodium sulfate, and purified by flash column chromatography (95H:5EtOAc) to afford **59** (1.538 g, 69%) as a yellow oil. BDB-II-184



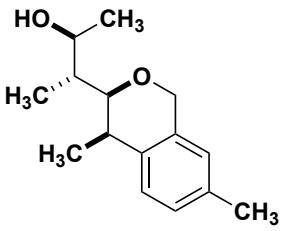
(3*S*,4*R*)-3-((2*S*,3*S*)-2,3-dimethyloxiran-2-yl)-4,7-dimethylisochromane (**98**) was synthesized following a modified literature procedure,[124] by preparing a solution of ***Z*-82** (0.155 g, 0.7 mmol, 1 equiv) in DCM (0.1 M). *meta*-Chloroperoxybenzoic acid (0.686 g, 2.8 mmol, 4 equiv) was then added and stirred overnight at room temperature. The reaction was then concentrated *in vacuo*, dissolved in ethyl acetate, washed with sodium bicarbonate (5 mL x 2), dried over sodium sulfate, concentrated *in vacuo*, and purified by flash column chromatography to afford **98** (0.040 g, 24%) as a clear oil. BDB-IV-037f24-30



(3*S*,4*R*)-3-((2*R*,3*R*)-2,3-dimethyloxiran-2-yl)-4,7-dimethylisochromane (**100**) was isolated (0.022 g, 13%) as a clear oil as the minor product from the above reaction. BDB-IV-037f18-22

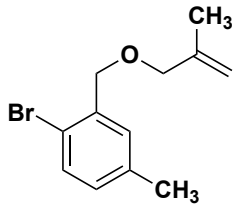


(*S*)-2-((3*S*,4*R*)-4,7-dimethylisochroman-3-yl)butan-2-ol (**99**) was synthesized following a modified literature procedure,[125] by preparing a suspension of sodium cyanoborohydride (0.045 g, 0.7 mmol, 4 equiv) in diethyl ether (0.07 M). **98** (0.044 g, 0.17 mmol, 1 equiv) was added as a solution in diethyl ether (1 M) followed by the dropwise addition of boron trifluoride diethyl etherate (90 μL, 0.7 mmol, 4 equiv). The reaction was quenched after 2 hours with a 50:50 mixture of water and sat. aq. sodium bicarbonate, extracted with ethyl acetate (5 mL x 2), washed with brine (10 mL), dried over sodium sulfate, concentrated *in vacuo*, and purified by flash column chromatography (80H:20EtOAc) to afford **99** (0.006 g, 12%) as a clear oil. BDB-IV-046

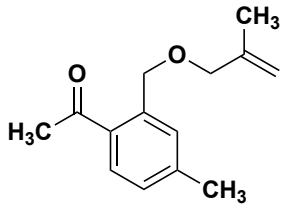


(2*S*,3*R*)-3-((3*S*,4*R*)-4,7-dimethylisochroman-3-yl)butan-2-ol (**101**) was synthesized following a modified literature procedure,[125] by preparing a suspension of sodium cyanoborohydride (0.025 g, 0.4

mmol, 4 equiv) in diethyl ether (0.07 M). **100** (0.022 g, 0.09 mmol, 1 equiv) was added as a solution in diethyl ether (1 M) followed by the dropwise addition of benzyloxyboron difluoride diethyl etherate (0.42 mL, 0.4 mmol, 4 equiv). The reaction was quenched after 2 hours with a 50:50 mixture of water and sat. aq. sodium bicarbonate, extracted with ethyl acetate (5 mL x 2), washed with brine (10 mL), dried over sodium sulfate, concentrated *in vacuo*, and purified by flash column chromatography (80H:20EtOAc) to afford **101** with residual boron reagent as a clear oil. BDB-IV-043

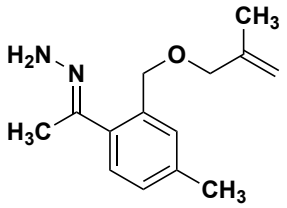


1-bromo-4-methyl-2-(((2-methylallyl)oxy)methyl)benzene (**103**) was synthesized by preparing a suspension of NaH (1.795 g, 45 mmol, 3 equiv) in THF (0.8 M). Methallyl alcohol (1.63 mL, 19 mmol, 1.3 equiv) was added dropwise and the mixture was allowed to stir at room temperature for 1 hour. A solution of **78** (3.944 g, 15 mmol, 1 equiv) in THF (1.2 M) was then added and the mixture was allowed to stir at room temperature overnight. The reaction was then quenched with sat. aq. ammonium chloride (50 mL), extracted with ethyl acetate (25 mL x 3), washed with brine (100 mL), dried over sodium sulfate, and purified by flash column chromatography (100H to 90H:10EtOAc) to afford **103** (3.628 g, 95%) as a clear oil. BDB-III-072

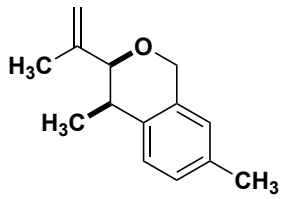


1-(4-methyl-2-(((2-methylallyl)oxy)methyl)phenyl)ethan-1-one (**104**) was synthesized by preparing a solution of **103** (3.628 g, 14 mmol, 1 equiv) in THF (0.27 M) and cooling the solution to –78 °C. *n*-

Butyllithium (7.39 mL, 18 mmol, 1.3 equiv) was then added dropwise and the solution was allowed to stir for 2 hours. The mixture was cooled to –78 °C and a solution of **74** (1.759 g, 17 mmol, 1.2 equiv) was added, allowing to stir to room temperature overnight. The reaction was quenched with sat. aq. ammonium chloride (30 mL), extracted with ethyl acetate (15 mL x3), washed with brine (50 mL), dried over sodium sulfate, and purified by flash column chromatography to afford **104** (1.336 g, 43%) as a yellow oil. BDB-III-075

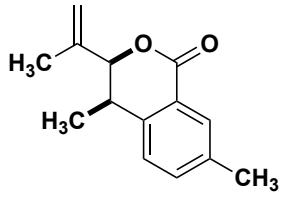


(*E*)-(1-(4-methyl-2-(((2-methylallyl)oxy)methyl)phenyl)ethylidene)hydrazine (**105**) was synthesized by preparing a solution of **104** (1.336 g, 6 mmol, 1 equiv) in ethanol (0.1 M), sparging this solution with argon for 15 minutes. Hydrazine (1.15 mL, 37 mmol, 6 equiv) and glacial acetic acid (0.42 mL, 7 mmol, 1.2 equiv) were then added and the solution was sparged with argon for 1 minute. This mixture was allowed to stir at room temperature overnight, then diluted with diethyl ether (30 mL), washed with water (25 mL), washed with brine (20 mL), dried over sodium sulfate, and purified by flash column chromatography (70H:30EtOAc to 50H:50EtOAc) to afford **105** (1.373 g, 97%) as a yellow oil. BDB-III-076

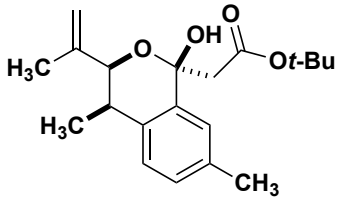


(3*S*,4*R*)-4,7-dimethyl-3-(prop-1-en-2-yl)isochromane (**106**) was synthesized using the 1 pot sequential C–H insertion reaction conditions developed in the lab. A solution of **105** (0.051 g, 0.22 mmol, 1 equiv)

in DCM (0.015 M) was prepared and manganese dioxide (0.150 g, 1.722 mmol, 8 equiv) was added. The heterogenous mixture was allowed to stir for 1 hour, then cooled to –78 °C before adding Rh_2(*R*-PTAD)$_4$ (0.003 g, 0.002 mmol, 0.01 equiv). The solution was allowed to stir at –78 °C for 1 hour before transferring the flash to a –20 °C freezer for stirring overnight. It was visually noted that the reaction was complete after 5 minutes. The oxidant was filtered off through a celite plug and concentrated *in vacuo*, purified by flash column chromatography (90H:10EtOAc) to afford **106** (0.036 g, 81%, >95:5 dr, 6:94 er) as a clear oil. BDB-III-085

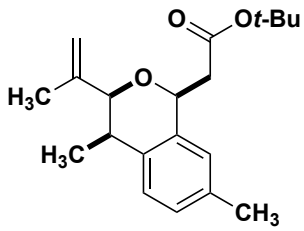


(3*S*,4*R*)-4,7-dimethyl-3-(prop-1-en-2-yl)isochroman-1-one (**107**) was synthesized by preparing a solution of **106** (0.643 g, 3 mmol, 1 equiv) in DCM (0.2 M). PCC (2.268 g, 10 mmol, 3.3 equiv) was then added portionwise and the reaction was fitted with a reflux condenser and was heated to 60 °C overnight. The reaction was diluted with diethyl ether (20 mL) and stirred over silica gel for 1 hour. This mixture was then filtered through a celite/silica gel plug, concentrated *in vacuo*, and purified by flash column chromatography (90H:10EtOAc) to afford **107** (0.480 g, 70%) as a clear oil. BDB-III-084



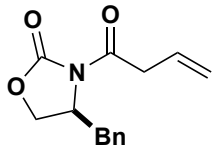
tert-butyl 2-((1*R*,3*S*,4*R*)-1-hydroxy-4,7-dimethyl-3-(prop-1-en-2-yl)isochroman-1-yl)acetate (**108**) was synthesized by preparing a solution of diisopropylamine (0.50 mL, 3.6 mmol, 1.6 equiv) in THF (0.56 M). This solution was then cooled to –78 °C and *n*-butyllithium (1.4 mL, 3.3 mmol, 1.5 equiv) was added

dropwise, allowing the LDA to form with stirring at –78 °C for 15minutes. *tert*-Butyl acetate (0.48 mL, 3.6 mmol, 1.6 equiv) was then added dropwise and the mixture was allowed to stir for 30 minutes at –78 °C. A solution of **107** (0.480 g, 2.2 mmol, 1 equiv) in THF (0.14 M) was then added dropwise to this mixture at –78 °C, stirred for 30 minutes at –78°C, then allowed to warm to rt over 2 hours. The brown mixture was then quenched with 1 M HCl (5 mL), extracted with EtOAc (10 mL x 3), washed with water (50 mL), washed with brine (50 mL), dried over sodium sulfate, and purified by flash column chromatography (90H:10EtOAc to 80H:20EtOAc) to afford **108** (0.644 g, 87%) as a clear oil. BDB-III-087

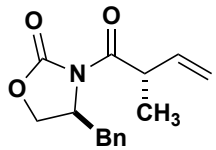


tert-butyl 2-((1*S*,3*S*,4*R*)-4,7-dimethyl-3-(prop-1-en-2-yl)isochroman-1-yl)acetate (**109**) was synthesized by preparing a solution of **108** (0.644 g, 2 mmol, 1 equiv) and triisopropylsilane (8 mL, 39 mmol, 20 equiv) in DCM (0.15 M). This solution was cooled to -78 °C and boron trifluoride diethyl etherate complex (2.4 mL, 19 mmol, 10 equiv.) was added dropwise, allowing the mixture to stir for 4 hours at -78 °C. The reaction was then placed in an acetonitrile/dry ice bath and stirred for 20 hours at -40 °C. The reaction mixture was then cooled to -78 °C and syringed dropwise into a 0 °C solution of dichloromethane (0.1 M) and saturated aqueous sodium bicarbonate (2:3 ratio of dichloromethane:saturated aqueous sodium bicarbonate by volume), allowing to stir at 0 °C for 15 minutes. The mixture was allowed to warm to room temperature, stirred for 15 minutes, extracted with dichloromethane (10 mL x2); combined extracts were dried over sodium sulfate, concentrated *in vacuo*,

and purified by column chromatography (100% hexanes flush, then 95hexanes:5ethyl acetate) to afford **109** (0.631 g, 100%, 70:30 dr) as a clear oil. BDB-III-088

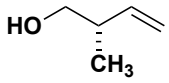


(*S*)-4-benzyl-3-(but-3-enoyl)oxazolidin-2-one (**131**) was synthesized by preparing a solution of vinylacetic acid (7 mL, 82 mmol, 1 equiv) in THF (0.15 M). The solution was cooled to 0 °C, pivaloyl chloride (10.2 mL, 82 mmol, 1 equiv) was added, followed by dropwise addition of *N*-methylmorpholine (9 mL, 82mmol, 1 equiv) and stirring at 0 °C for 30 minutes, then the mixture was then cooled to – 78 °C. In a separate flask, *S*-benzyloxazolidinone (14.542 g, 82 mmol, 1 equiv) was dissolved in THF (0.23 M), cooled to –78 °C, and *n*-butyllithium (40 mL, 90 mmol, 1.1 equiv) was added dropwise and allowed to stir for 15 minutes. The lithiated oxazolidinone was then cannulated into the –78 °C solution of the mixed anhydride over 1 hour, stirred at –78 °C for 30 minutes, then warmed to room temperature with stirring for 4 hours. The reaction was quenched with sat. aq. ammonium chloride (300 mL), extracted with EtOAc (100 mL x3), dried over sodium sulfate, and purified by flash column chromatography (5 sequential columns: 60H:40EtOAc x3, then 100% DCM x2) to afford **131** (12.317 g, 58%) as a yellow oil. BDB-IV-082

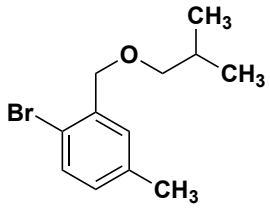


(*S*)-4-benzyl-3-((*S*)-2-methylbut-3-enoyl)oxazolidin-2-one (**132**) was synthesized by preparing a solution of hexamethyldisilazane (12.8 mL, 57 mmol, 1.3 equiv) in THF (0.56 M) and cooled to –78 °C. *n*-Butyllithium (23 mL, 53 mmol, 1.2 equiv) was then added dropwise and stirred for 15 minutes, then

warmed to 0 °C and stirred for 15 minutes, then cooled back down to –78 °C and stirred for 10 minutes. A solution of **131** (10.678 g, 43 mmol, 1 equiv) in THF (0.17 M) was then cannulated to the cryogenic solution of LiHMDS over 1 hour, and the solution was warmed to 0 °C and stirred for 15 minutes. Methyl iodide (11 mL, 175 mmol, 4 equiv) was then added at 0 °C and the solution was allowed to warm to room temperature over 2 hours and stirred overnight. The reaction was then quenched with sat. aq. ammonium chloride (200 mL), extracted with EtOAc (100 mL x3), dried over sodium sulfate, and purified by flash column chromatography (5 sequential columns: 56DCM:40H:4EtOAc x5) to afford **132** (2.605 g, 23% >95:5dr) as a yellow oil. BDB-IV-085

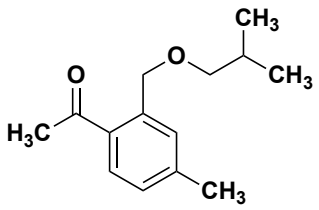


(*S*)-2-methylbut-3-en-1-ol (**124**) was synthesized by preparing a solution of **132** (2.602 g, 11 mmol, 1 equiv) in diethyl ether (0.1 M) and ethanol (62 µL, 1 mmol, 0.1 equiv). The solution was cooled to 0 °C and lithium borohydride (16 mL, 32 mmol, 3 equiv) was added dropwise and stirred for 1 hour. The reaction was quenched with sat. aq. ammonium chloride (50 mL), extracted with diethyl ether (50 mL x3), dried over magnesium sulfate, concentrated gently *in vacuo* (vacuum not below 150 torr with a 0 °C bath temperature), and purified by flash column chromatography (55pentane:45diethyl ether) to afford **132** (7.513 g, 77%) as a clear 9.4% w/w solution in diethyl ether. BDB-IV-87

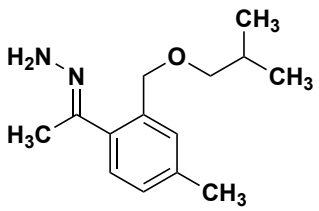


1-bromo-2-(isobutoxymethyl)-4-methylbenzene (**137**) was synthesized by preparing a suspension of NaH (0.530 g, 13 mmol, 3.5 equiv) in THF (0.8 M). Isobutyl alcohol (0.53 mL, 6 mmol, 1.5 equiv) was added dropwise and the mixture was allowed to stir at room temperature for 1 hour. A solution of **78**

(1.011 g, 4 mmol, 1 equiv) in THF (1.2 M) was then added and the mixture was allowed to stir at room temperature overnight. The reaction was then quenched with sat. aq. ammonium chloride (10 mL), extracted with ethyl acetate (10 mL x 3), washed with brine (20 mL), dried over sodium sulfate, and purified by flash column chromatography (100H to 95H:5EtOAc) to afford **137** (0.889 g, 90%) as a clear oil. BDB-IV-023

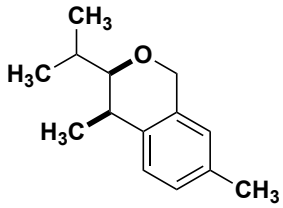


1-(2-(isobutoxymethyl)-4-methylphenyl)ethan-1-one (**138**) was synthesized by preparing a solution of **137** (0.886 g, 3.5 mmol, 1 equiv) in THF (0.27 M) and cooling the solution to –78 °C. *n*-Butyllithium (2.08 mL, 4.5 mmol, 1.3 equiv) was then added dropwise and the solution was allowed to stir for 2 hours. The mixture was cooled to –78 °C and a solution of **74** (0.428 g, 4 mmol, 1.2 equiv) was added, allowing to stir to room temperature overnight. The reaction was quenched with sat. aq. ammonium chloride (10 mL), extracted with ethyl acetate (10 mL x3), washed with brine (25 mL), dried over sodium sulfate, and purified by flash column chromatography to afford **104** (0.369 g, 49%) as a yellow oil. BDB-IV-025



(*E*)-(1-(2-(isobutoxymethyl)-4-methylphenyl)ethylidene)hydrazine (**139**) was synthesized by preparing a solution of **138** (0.369 g, 1.7 mmol, 1 equiv) in ethanol (0.1 M), sparging this solution with argon for 15 minutes. Hydrazine (0.33 mL, 10 mmol, 6 equiv) and glacial acetic acid (0.12 mL, 2 mmol, 1.2 equiv) were then added and the solution was sparged with argon for 1 minute. This mixture was

allowed to stir at room temperature overnight, then diluted with diethyl ether (20 mL), washed with water (25 mL), washed with brine (20 mL), dried over sodium sulfate, and concentrated *in vacuo* to afford **139** (0.357 g, 91%) as a yellow oil. BDB-IV-028



(3*R*,4*R*)-3-isopropyl-4,7-dimethylisochromane (**140**) was synthesized, following a modified two-pot procedure developed in the lab,[112] by preparing a solution of **139** (0.025 g, 0.107 mmol, 1 equiv.) in acetonitrile (0.15 M). MnO_2 (0.074 g, 0.85 mmol, 8 equiv) was added (producing a bright fuchsia colored solution when stirring is halted) and allowed to stir for 1 hour. This heterogenous mixture was then filtered through a glass frit, washing with DCM (50 mL), into a dry, clean flask. In a separate flask, Rh_2(*R*-PTAD)$_4$ (0.002 g, 0.001 mmol, 1 mol %) was dissolved in DCM (0.015 M with respect to hydrazone) and the solution was cooled to 0 °C. The filtered fuchsia diazo solution was then added to the catalyst solution by syringe pump (Harvard Apparatus, Pump 11, 0.35 mL/min) over ~2 hours keeping the temperature at approximately 0 °C. After addition was completed, the syringe previously containing the diazo species was washed with 15 mL of DCM and the rinsate added dropwise over 30minutes; this mixture was stirred overnight. The stirbar was then removed and rinsed with DCM (2mL), the solution was concentrated *in vacuo*, and the product was purified by flash column chromatography (90hexanes:10ethyl acetate) to afford **140** as a clear oil (0.009 g, 41%, >80:20 er). BDB-IV-029

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Chapter 3.0

One-Pot Assembly and Applications of Novel Tetrasubstituted Geminal Acyl/Alkoxy Allenes[1]

3.1 Introduction

Serendipitous discovery is not uncommon in organic chemistry.[2–4] Though the most elegant and complex synthetic strategies and synthetic transformations appear to be meticulously planned out, the final iteration is often the result of many failed experiments and accidental/incidental findings. Moreover, the most interesting and novel scientific phenomena often occur *counter* to the expected or predicted result. It is within this framework that an emphasis must be placed on the individual researcher to maintain diligence and not to disregard errant or undesired results. Such is the case for the original research featured in this dissertation chapter describing the synthesis of novel tetrasubstituted geminal acyl/alkoxy allenes.

In the first reported synthesis of an allene in 1887, von Pechman and coworkers isolated glutinic acid (**4**) through an elimination of an *in situ* generated unsaturated *beta*-chloro ketone (Figure 1).[5,6] This discovery of a new form of a carbon-containing molecule was, in fact, an attempt to verify the *non-existence* of this type of structure; instead of refuting van't Hoff's prediction of a linear three-carbon-based molecule, von Pechman confirmed it.[7,8] Van't Hoff also theorized that an appropriately substituted allene could have axial asymmetry. It would not be until decades later that this was empirically proven by Maitland and Mills with their enantioselective dehydration of an allylic alcohol to form optically-active, tetrasubstituted, naphthyl-phenyl allene **6** (Figure 1).[9]

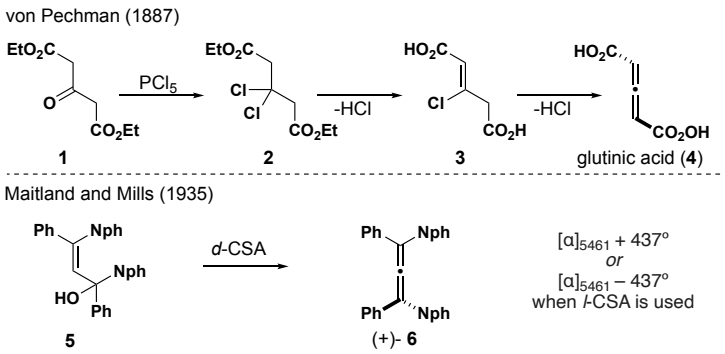


Figure 1. First reported synthesis of an allene (glutinic acid), and the validation of van't Hoff's prediction of axial asymmetry by the asymmetric synthesis of a tetrasubstituted allene

Since the structural validation by Maitland and Mills, the study of allenes has been driven largely by a curiosity in their structural and stereochemical features. Allenes are the simplest form of cumulated diene, where a three-carbon diene features two orthogonal π-bonds (Figure 2). It is these orthogonal π-bonds that define the axial symmetry element by creating an extended tetrahedron-type structure, where two opposing pairs of tetragonal vertices are not connected directly at a central carbon atom, but distally through a central axis. This geometry is unique in organic chemistry and creates opportunities for axial asymmetry, a feature precluded in single carbon tetrahedrons (i.e. point chirality). Distal disubstitution (e.g. where $R^1 = R^4 = CH_3$, *or* $R^1 \neq R^4 \neq H$) results in a chiral molecule, while geminal disubstitution (e.g. where $R^1 = R^2 = CH_3$, *or* $R^1 \neq R^2 \neq H$, *and* $R^3 = R^4$) creates a plane of symmetry (i.e. σ_d) and eliminates the potential for stereogenicity. It is worth mentioning that cumulenes with even numbers of π-bonds (e.g. allenes) have the potential for this axial chirality, while cumulenes with odd numbers of π-bonds do not due their planarity.

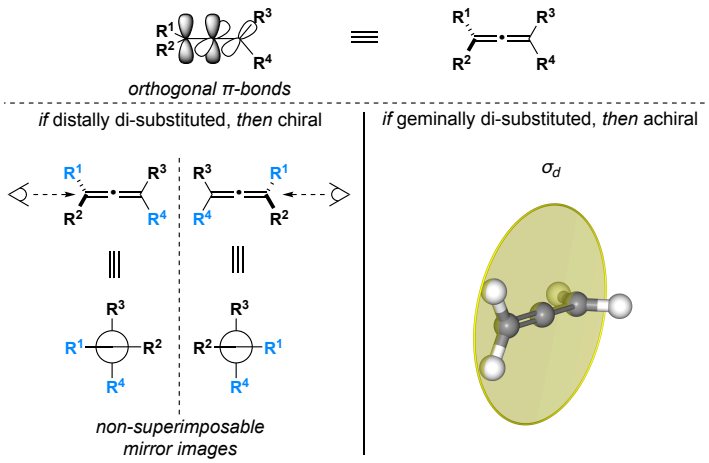


Figure 2. Allene geometry and axial chirality; mirror plane image created via Symmetry@Otterbein[10]

The type of substitution on an allene has a drastic impact on the kinetic and thermodynamic stability of the molecule (Figure 3). Electron-withdrawing groups (EWG) appended to an allene create an electron-deficient central carbon that is primarily electrophilic. Electron-donating groups (EDG) appended to an allene create an electron-rich central carbon that is primarily nucleophilic. An ambiphilic allene can be produced by appending both EWD and EDG to the allene; these types of allenes are uncommon in the literature and can be more difficult to synthesize.[11,12] As such, the type of substitution on an allene will also affect the utility of the compound in further chemical transformations. As will be discussed in this dissertation chapter, allenes are useful intermediates in the synthesis of heterocycles and functionally dense structures and their applications are be largely dependent on both steric and electronic properties.

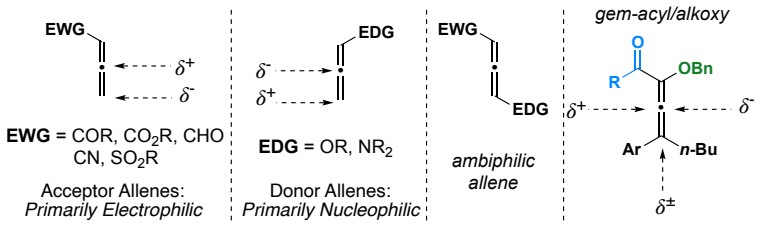


Figure 3. Allene substitution and reactivity patterns

Allenes are typically considered to be chemically unstable and furthermore are not commonly found in nature.[13,14] There are 146 allene-containing natural products reported as of 2004, where 38 feature a linear allene, 46 are allenyl carotinoids and terpenoids, 33 are bromo-allenes, 29 are miscellaneous naturally-occurring allenes, and 4 natural products contain a cumulene structure (Figure 4A). These natural products are typically isolated as a single enantiomer and exhibit interesting biological activity.[13] With modern characterization methods, allenes can be identified in a straightforward manner: the *sp*-hybridized allene carbon has a chemical shift similar to that of a ketone carbonyl and the indicative IR C–C vibration of an allene is at ~1950 cm^{-1}. In several instances before the advent of nuclear magnetic spectroscopy and infrared spectroscopy, allenes were proposed as structural features of several natural products in error, where dienes or alkynes were the correct natural moiety.[15–22] Difficulties in elucidating allenes in natural products are also prevalent. In many cases, it is not until decades later that a natural product's structure is correctly identified as having an allene incorporated (e.g. 80 years between the isolation of peridinin **8** and its elucidation, Figure 4A).

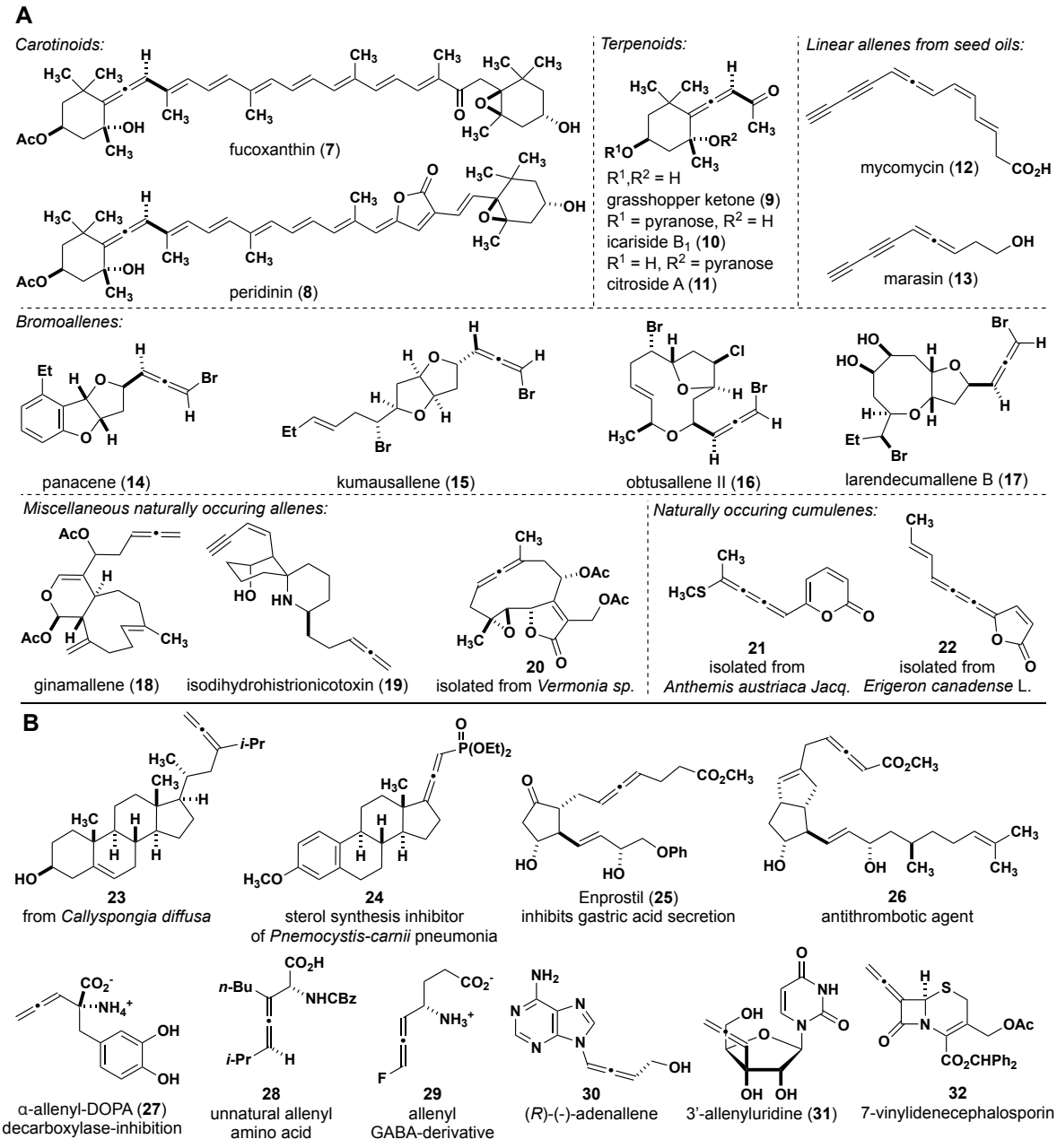


Figure 4. Abbreviated list of A) allenyl natural products and B) biologically relevant molecules containing allenes

Allene substructures are featured in natural products in a variety of ways. Carotinoids **7** and **8** are prevalent in nature and contain the same exocyclic allene present in several terpenoids (i.e. **9** - **11**). Due to the instability of polyenynes **12** and **13**, their structural elucidation is often challenging. Bromoallenes

make up a significant portion of naturally occurring allenes and have been the source of several excellent natural product syntheses.[23–31] They typically feature di-oxygenated 5,5-ring systems (e.g. **14** and **15**), but may also feature larger, more complex ring structures (e.g. **16** and **17**). As the incorporation of bromine suggests, these bromoallene natural products are found in marine algae and other organisms. One interesting total synthesis of a laurendecumallene B (**17**) by Snyder and coworkers involves a novel ring-expansion induced by reactive bromenium reagent BDSB to generate the eight-membered ring of with its pendant bromoallene.[32–34] Other natural products containing allenes have been identified that do not easily fall into the above categories; the unique structure of marine natural product ginamallene **18** has not yet been synthesized and shows activity in the cytotoxicity of leukemia cell lines.[35–39] Alkaloid **19** was isolated from the skin of wild poison-dart frogs and is thought to be a diet-based metabolite, as it is not detected in captive specimens;[40] these fascinating spirocycles have not yet been synthesized. Isolated from the *Vernonia* plants endemic to South America, **20** is the only known example of an endocyclic allene natural product. Its ten-membered allene-containing structure makes it an attractive and challenging target for a total synthesis and has not yet been synthesized.[41–45] While not directly pertaining to the research described in this dissertation, cumulenes have also been isolated from natural sources and present unique synthetic challenges (e.g. **21** and **22**). Though the structures of these natural products themselves are fascinating, they have also been shown to have myriad applications in biological and medicinal contexts. Allene-containing natural products have been shown to have antibiotic, anti-fungal, antileukemia, anti-angiogenetic, anti-inflammatory, and anti-rheumatic biological activity. They also inhibit urchin egg growth, modulate nicotin acetylcholine ion channel, and are signaling agents in the dinoflagellate photosystem.[13]

Allenes have also been incorporated into pharmaceutically relevant molecules (Figure 4B). Steroid-like compounds continue to be studied extensively in medicine and allenyl steroids are reported

to inhibit various enzyme activities:[16] ironically, the only known allenyl steroid natural product **23** was synthesized prior to its isolation.[46] Most allenyl steroid-like compounds bear their allenyl-substitution at the 17-position. **24** features a phosphonic ester substituted allene and inhibits the biosynthesis of sterol in the pathogen responsible for *Pneumocystis-carinii* pneumonia (PCP), the most commonly occurring AIDS-related disease. Prostaglandin-analogue **25**, known as Enprostil and marketed under the trade-name Gardrin, Camleed, or Syngard, is 600 times more potent than PGE_2; the allene and phenoxy functionalities were introduced to make the molecule better for oral administration but unexpectedly increased potency in a synergistic manner (i.e. either modification is only modestly effective by itself).[47,48] The prostaglandin-analogue carbacyclin (**26**) features an allene substructure and shows strong activity as an antithrombotic agent.[47] Allenyl amino acid analogues **27**, **28**, and **29**, adenosine-analogue **30** and nucleoside-analogue **31** have been synthesized and screened for potential biological activity.[49,50,59–61,51–58] Interestingly, **30** showed inhibitory activity against HIV-1 and hepatitis-B viruses, but only as the *R*-enantiomer; phosphorylated derivatives of cytallene were also found to be even more active in HIV-1 inhibition (not shown). Finally, **32** was prepared with the expectation of increased inhibition of human leukocyte elastase which was not observed; instead the compound was found to weakly inhibit porcine pancreas elastase.[62] Therefore, while the list of natural substances and pharmaceutically relevant molecules containing allenes is relatively limited, the usefulness of allenes in drug discovery is far from insignificant. Allenes can provide orthogonal sources of chirality and steric volume, allowing medicinal chemists to subtly modulate a target compound in hit-to-lead protocols. In this way, the future of allenes in medicine is only limited by the diversity and quantity of methods to synthesize the allene scaffold.

In this chapter, the synthesis of tetrasubstituted, acyl-substituted, and alkoxy-substituted allenes, as well as synthetic applications of alkoxy allenes will be discussed as introductory information. The

methodology developed to synthesize novel, geminally substituted acyl/alkoxy tetrasubstituted allenes will then be discussed as a contribution to this field of research.

3.1.1 Synthesis of tetrasubstituted allenes

As suggested above, the long history of interest in the allene structure has produced a sizable quantity of research on their synthesis and reaction involving them as starting materials or intermediates; a keyword search of the term "allene" affords 13,000 results (Table 1). However, the frequency of reports drops off significantly when the search term is refined to chiral allenes, monosubstituted allenes or terminal allenes, disubstituted, and trisubstituted allenes. Finally, only 32 SciFinder hits are registered for the keyword "tetrasubstituted allene". While this analysis is not complete without a much more extensive meta-analysis, it is suitable as a simple way to acknowledge the relative rarity of tetrasubstituted allenes in the literature. As such, the current methods for the synthesis of these functionally-dense tetrasubstituted allenes will be discussed, giving a frame of reference for the relevance of the original research reported in this dissertation chapter.

Table 1. Frequency of reports of allenes in the literature accessed in 2022

keyword	SciFinder Hits
"allene"	16,000
"chiral allene"	361
"terminal allene"	284
"disubstituted allene"	95
"trisubstituted allene"	58
"tetrasubstituted allene"	32

The synthesis of tetrasubstituted allenes can be accomplished with a variety of methods, but their construction can be generalized into three categories: elimination/addition, Claisen-rearrangement, and transition-metal catalyzed (Figure 5). Some elimination/addition or Claisen-rearrangement type reactions may be mediated or catalyzed by transition-metals and will be discussed in those respective

categories, leaving metal-catalyzed reactions that are not readily understood as elimination/addition or Claisen-rearrangements to be described in the third category.

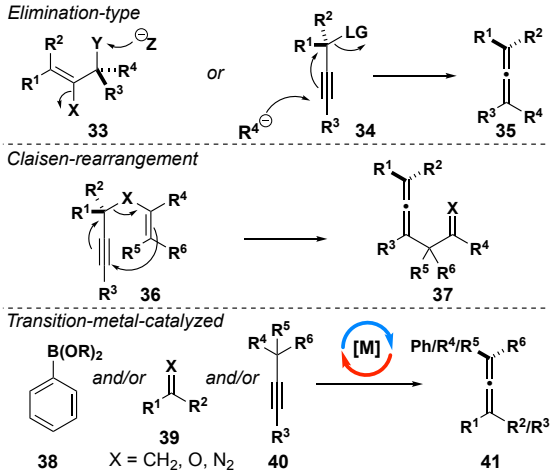


Figure 5. General categories for the synthesis of tetrasubstituted allenes

Elimination/addition reactions to synthesize tetrasubstituted allenes are the most frequently reported due to the simplicity of the method: nucleophiles can be added to propargyl alcohols that can then undergo base or acid mediated/catalyzed elimination/dehydration. As mentioned above, the first example of allene formation from von Pechman involved the sequential elimination of hydrochloric acid from the substrate to form an allene diacid (Figure 1). Later work involved the dehydration of **5** with camphor sulfonic acid to product optically active **6**, confirming van't Hoff's theory about axial chirality (Figure 6A).[9] Indolyl allene **44** was formed using the indole C3 as a nucleophile with catalytic acid to form the electrophile from propargyl alcohol **42** (Figure 6B).[63] As an interesting adaptation of this general strategy, a cuprate nucleophile was added to a propargyl cyclopropane to form alkyl tetrasubstituted allene **46** (Figure 6C).[64] Wittig-type or Horner-Wadsworth-Emmons procedures are also amenable to the construction of allenes, where the extrusion of the phosphorous-oxide species may be considered an elimination sequence: ester-substituted allenes are readily accessible by this method (Figure 6, D and E).[65,66] In an interesting protocol featuring a Wolff rearrangement from diazo **53**, the

cyclopropanation product of ketene **54** can rearrange to form tetrasubstituted silyl ether allene **55** (Figure 6F)[67] Strained allene **57** is accessible *via* desilylation/elimination of vinyl triflate **56**; this reactive intermediate was subsequently trapped in a Diels-Alder reaction with various five-membered ring dienes to form polycyclic alkaloid-like compounds (**59**) (Figure 6G). Finally, the deprotonation of the acidic propargylic *alpha* proton of **61** affords a nucleophile which can add *via* transposition to aldehyde electrophiles, forming allenyl alcohols **62** (Figure 6H). These intermediates were then useful in subsequent transformations.

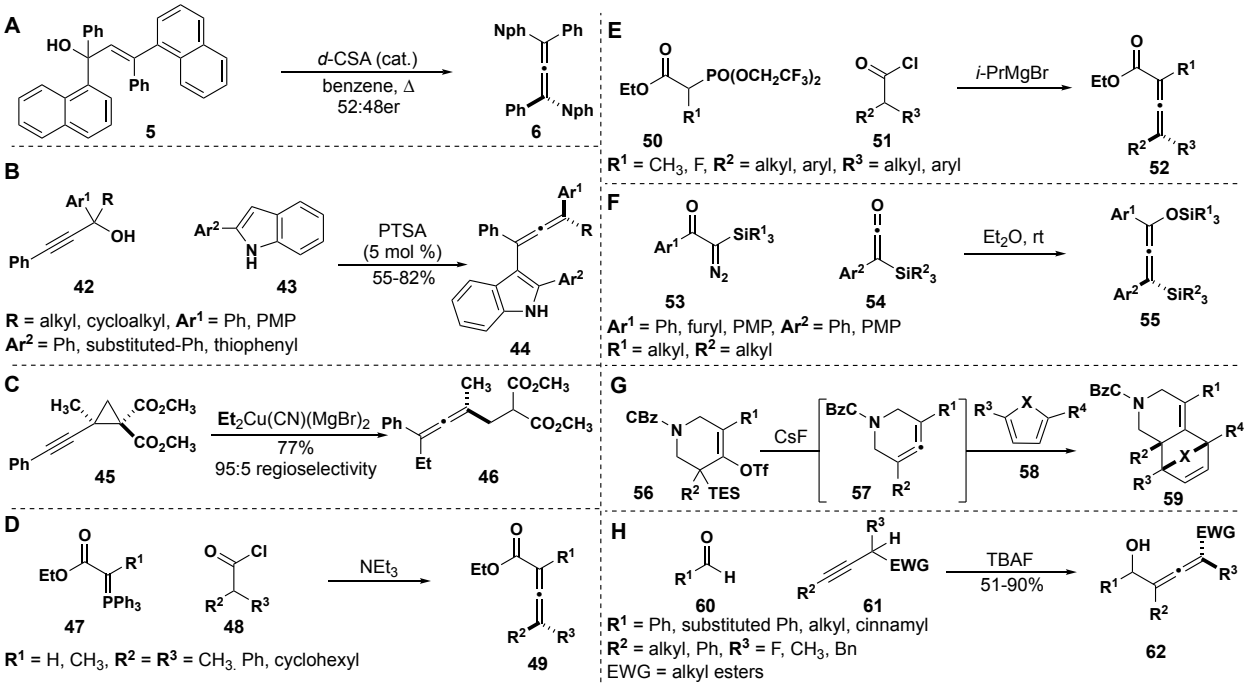


Figure 6. Elimination/addition-based strategies for tetrasubstituted allene synthesis

While qualifying as transition metal mediated reactions, Tebbe-olefinations operate similarly to their Wittig/HWE analogues and are therefore included in Figure 7 as examples of allene formation by elimination/addition. In two similar synthetic strategies for the construction of allenes *via* Tebbe olefination reactions, titanocene **64** is used to form Tebbe intermediates **64** and **73**.[68–70] Once the titanium intermediate is formed, it reacts with carbonyls to form titanooxetane **67**. This reactive four-

membered ring then undergoes elimination or sigma-bond metathesis to generate allene **68**. In another interesting example, **64** facilitates a Pauson-Khand-type reaction to form titanocycle **71**, which then undergoes elimination and a subsequent reductive desulfurization to form titanium vinylvinylidene **73**. Though requiring stoichiometric titanium, these unique methods allow for the synthesis of diverse allene structures featuring various arenes and several examples of vinyl allenes.

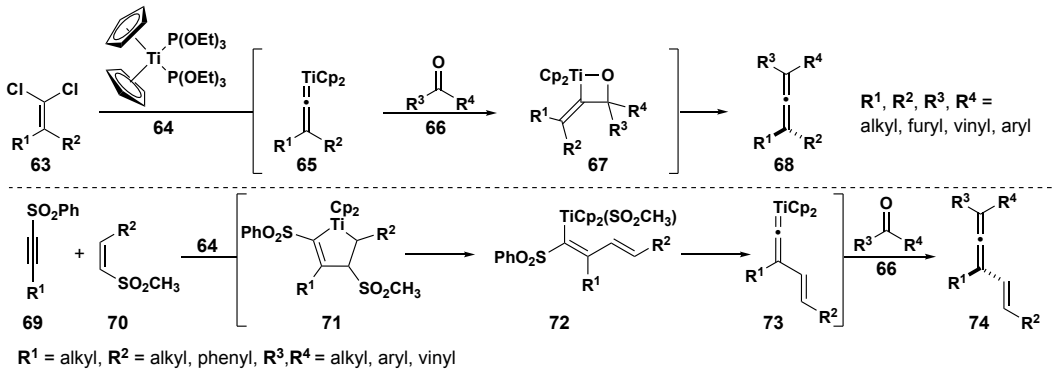


Figure 7. Tebbe olefination-based strategies for tetrasubstituted allene synthesis

The elimination/addition strategy for the synthesis of tetrasubstituted allenes can also be enantioselective (Figure 8). Intramolecular cyclization facilitated by cinchona alkaloid **77** followed by intermolecular reaction with *N*-bromosuccinimide allowed for the construction of bromoallene **76** in good yield and enantioselectivity.[71] Aggarwal and coworkers demonstrated a fascinating example of divergent reactivity/selectivity with geminal boryl/selenyl alkene **78** and chiral lithiate **79** (Figure 8).[72] After homologation and 1,2-metallate rearrangement (extruding carbamate group 'CbO'), allylic boronate **80** is formed. This intermediate can then undergo stereoselective oxidation of the C–B bond with *m*CPBA at room temperature to form allene **84** as a single enantiomer *via* point-to-point chirality transfer (i.e. *syn* elimination of selenoether). From the same intermediate **80**, the methyl triflate salt of the selenoether was generated and upon exposure to aqueous sodium bicarbonate, the other enantiomer **82** was accessed through *anti*-elimination. This protocol generates alkyl and aryl tetrasubstituted allenes in

good yields and with a high degree of selectivity for each enantiomer of allene, diverging from the same starting material.

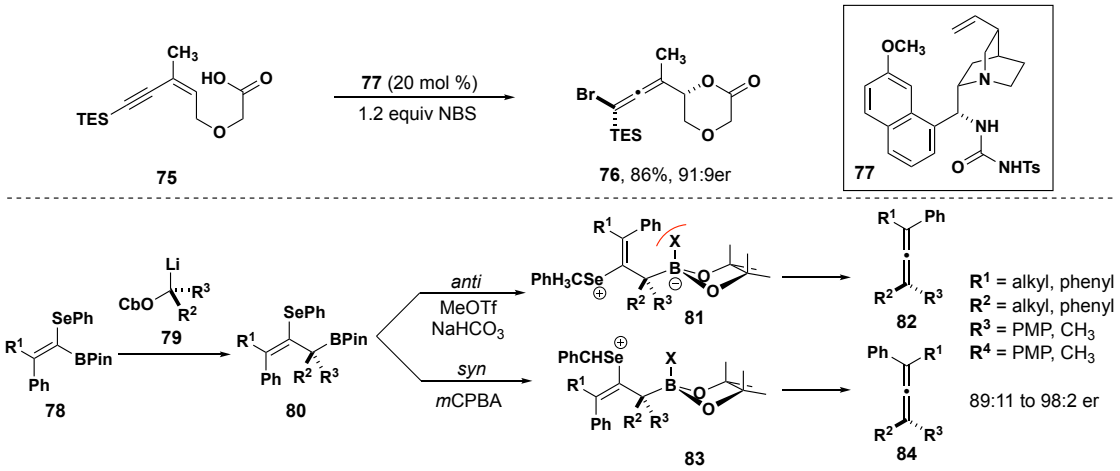


Figure 8. Enantioselective elimination/addition-based strategies for tetrasubstituted allene synthesis

Claisen-rearrangement based strategies for synthesizing tetrasubstituted allenes take advantage of the accessibility of propargyl alcohols prepared from acetylenic nucleophiles and ketones, or propargyl ketones and alkyl nucleophiles (e.g. **87** and **90**, Figure 9A). The resulting propargyl alcohols can then be treated with orthoesters to generate substrates for the Johnson-Claisen rearrangement variant, giving tetrasubstituted allenes **94** and **98** (Figure 9, B and C).[65] Bromoallene **98** can then undergo elimination under basic conditions to afford cumulene **99**.[73] An interesting variation of this strategy comes from Davies and coworkers, where a donor/acceptor dirhodium carbene (**101**) undergoes O–H insertion; the resultant propargyl ylide can then rearrange to form the highly functionalized allenylic alcohol **103** in good yields and excellent enantio- and diastereoselectivity.[74]

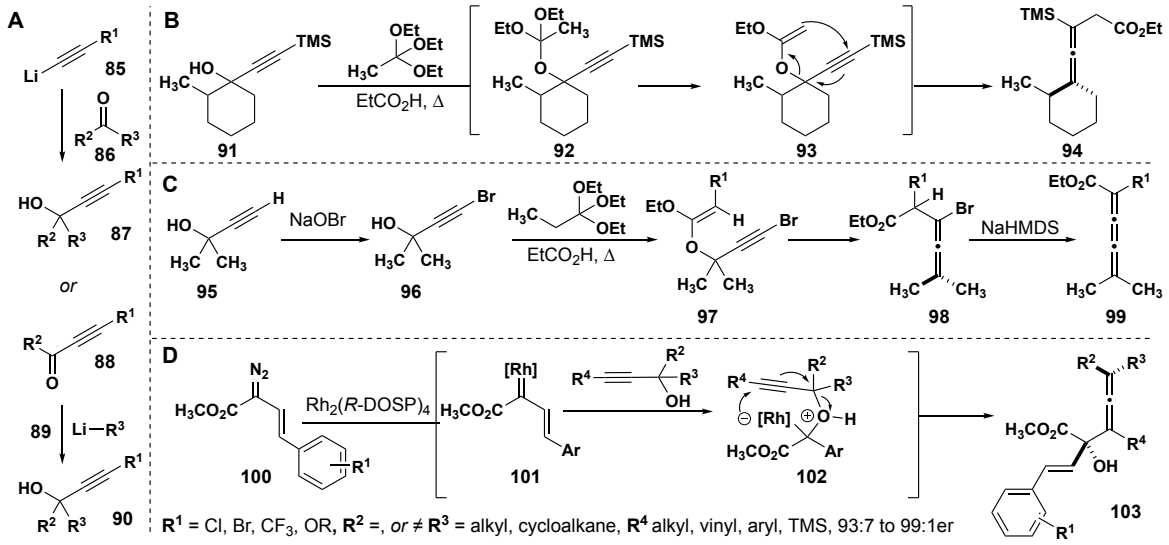


Figure 9. Claisen-rearrangement-based strategies for tetrasubstituted allene synthesis

Transition-metal catalyzed strategies constitute a large proportion of examples for the construction of tetrasubstituted allenes (Figure 10). Allene syntheses derived from propargyl moieties are quite common, yet others are derived from multi-component reactions or Tsuji-Trost-type π-allyl palladium derived Wittig reactions. For the sake of brevity, a selection of interesting examples will be discussed. Diazo compounds may be used in the synthesis of aryl-substituted allenes: a palladium catalyst oxidatively adds to the styryl bromide, followed by nitrogen extrusion to form the palladium carbene (Figure 10A). Isomerization and reductive elimination then occur, giving **106**.[75,76] Lewis acids that are π-philic (e.g. Ag and Au) are commonly used, where coordination to an alkyne can result in nucleophilic addition and cyclization to afford interesting allenyl scaffolds **108** and **121** (Figure 10, B and F).[77,78] In an example of a modified Wittig reaction, decarboxylation of **110** gives a π-allyl complex which can be attacked by a phosphorous nucleophile (**109**) (Figure 10C).[79] Deprotonation of the resultant phosphonium affords the desired ylide which is then exposed to ketene **111**. *Via* this Wittig-type reaction, tetrasubstituted allenes **112** are formed in moderate yields. Propargyl carbonates and carboxylic acids can decarboxylate when aryl iodide or diboron pinacolate nucleophiles are added in the presence of palladium or copper

catalysts, affording allenes **115** and **117**, respectively (Figure 10, D and E).[80,81] In a multicomponent reaction, alkyne **123** can form a copper acetylide, *á la* Sonogashira, which reacts with diazo **122** to produce a copper carbene; this intermediate then goes on to add to allyl electrophile **124** *via* propargylic transposition to form highly substituted allene **125** (Figure 10G).[82,83] In the lone report of tetrasubstituted allene formation by a radical process, enynes (**126**) are cross-coupled with bromide electrophiles by radical addition to the alkene; the resultant carbon-centered-radical then isomerizes to form an allenyl radical which then reductively cross-couples with an aryl nickel (II) species derived from boronic acid **128** to form allene **129** (Figure 10H).[84] In a particularly effective method, palladium catalysts with chiral SEGPHOS ligands enable the enantioselective carboxylative formation of allenes (**131**) by kinetic resolution of racemic propargyl alcohols **130**. (Figure 10I).[85] Finally, Hayashi and coworkers were also successful in utilizing chiral SEGPHOS ligands to enantioselectively synthesize Mukaiyama-like silyl ether eneallenes **134** from 4-alkynylcyclohexenones (**132**) and aryl titanates *via* 1,6-addition at room temperature (Figure 10J).[86]

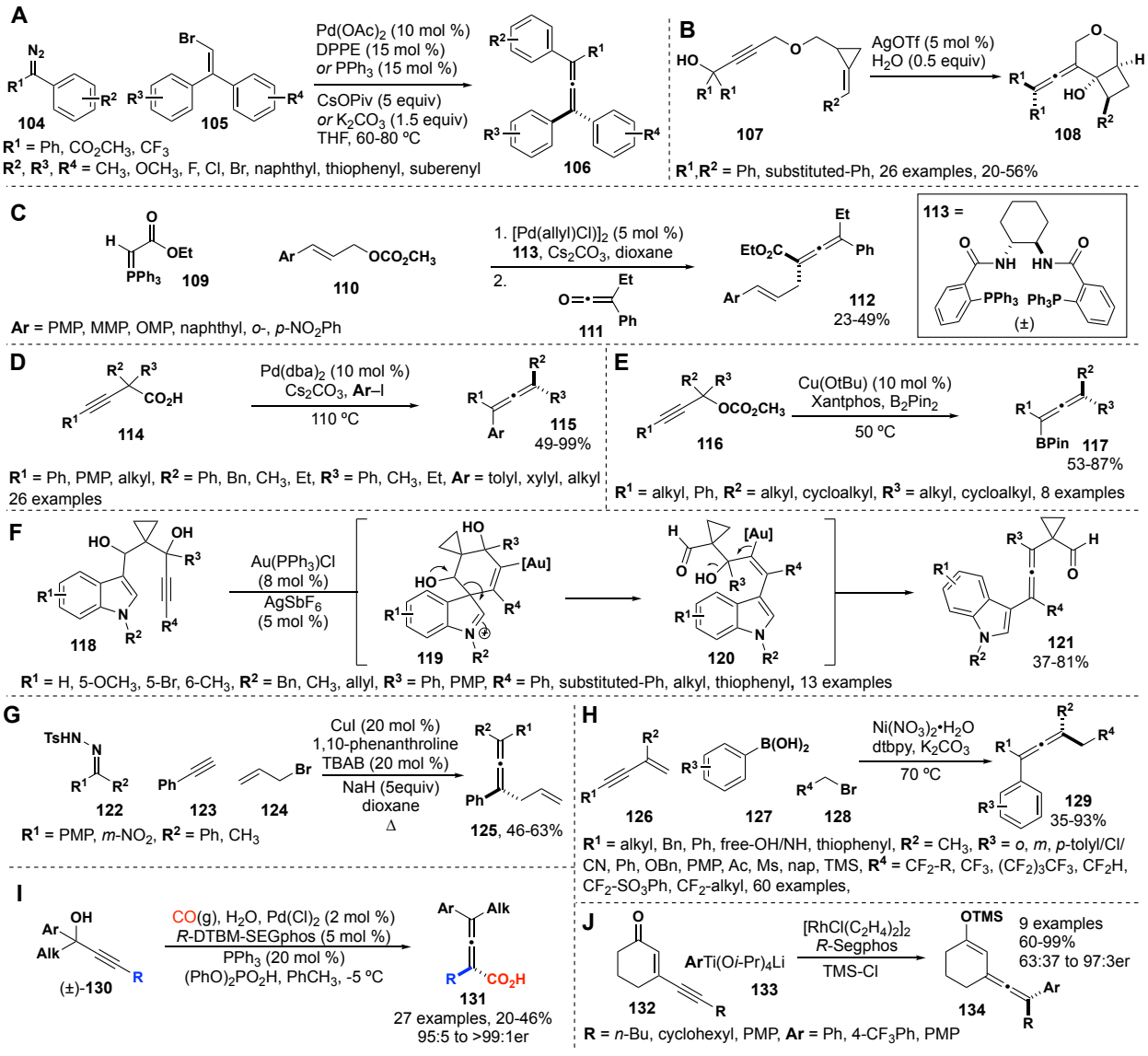


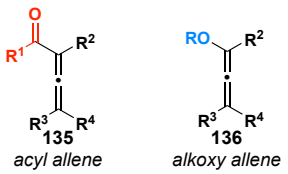
Figure 10. Transition-metal catalyzed strategies for tetrasubstituted allene synthesis

With the discussion of these methods for the synthesis of tetrasubstituted allenes, it is apparent that there are many interesting ways to synthesize a variety of allenes. Whether through elimination/addition, Claisen-rearrangement, or transition-metal catalysis, aryl, alkyl, boryl, vinyl, silyl, bromo, and EWG substituted allenes are accessible. With the exception of a single report of siloxy-substituted allenes (Figure 6F, **55**), tetrasubstituted allenes with EDGs are rare and geminal EDG/EWG-substituted allenes are unreported, leaving the window of opportunity open for their synthesis.

3.1.2 Synthesis of alkoxy-substituted allenes

Many of the common methods for the synthesis of allenes as described above require the presence of an electron-withdrawing group to induce nucleophilic addition or to facilitate Wittig-type reactions. As a result, acyl/amide/ester-substituted allenes are quite common in the literature and their synthesis will not be given special description in this dissertation (Table 2). On the other hand, the synthesis of alkoxy-substituted allenes represents a much smaller, more specialized proportion of the literature, due to their generally high reactivity. Therefore, in this section, the synthesis of alkoxy-substituted allenes will be discussed to highlight the need for more diversity in the synthesis of these uniquely activated compounds.

Table 2. Frequency of reports of acyl- and alkoxy-substituted allenes (accessed 2022)



Keyword	SciFinder Hits
"allene"	16,000
"allenoate"	1013
"allenamide"	476
"acyl allene"	48
"alkoxy allene"	16

The first synthesis of an alkoxy allene was reported by Arens and coworkers in 1967, where the allenes are synthesized from propargyl ethers and catalytic potassium *tert*-butoxide (Figure 11).[87] In this reaction, it is likely that a propargyl proton is deprotonated with base which results in an allenyl carbanion that can deprotonate the *tert*-butanol generated in the previous step. Reissig saw this report as an opportunity to use these alkoxy allenes in cyclization reactions and has subsequently been one of the most prominent researchers in this field.[88–93] Using the Arens precedent, Reissig established that alkoxy allenes **142** or **143** can be synthesized from methyl propargyl ethers **137** or **139** *via* deprotonation at the

propargylic position and metallotropic shift to allenyl lithiate **141** which is trapped with a proton or methyl group (Figure 11). The alkoxy allenes generated in this sequence are unstable at temperatures above 0 °C and are prone to degradation over time.[94] As such, these compounds are typically generated *in situ* and used immediately in subsequent reactions.

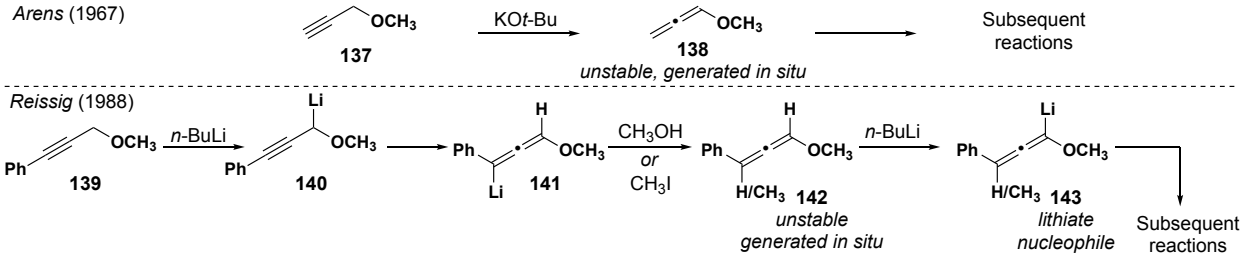


Figure 11. The synthesis of alkoxy-substituted allenes by Arens and Reissig

Tius and coworkers synthesized alkoxy allenes in a different manner only a year later than Reissig and has been similarly prolific in the field (Figure 12).[12,94] Propargylic deprotonation of **144** with two equivalents of *n*-butyllithium results in a nucleophile that can be trapped with a chlorosilane to give **145** after quench with sodium bicarbonate. Protection of the propargylic alcohol with a methoxy methyl ether affords allene precursor **146**, which upon subjection to *sec*-butyllithium and an electrophile, a variety of silyl/alkoxy allenes **147** were accessible in good yields. Interestingly, *sec*-butyllithium was required for this protocol; with *n*-butyllithium or *tert*-butyllithium the reaction did not go to completion. It is notable that in all cases these alkoxy allenes were sensitive to acid and temperature, requiring storage at 0 °C. These allenes could then be desilylatated with TBAF under basic conditions to form **148**. These highly functionalized alkoxy-substituted allenes were then used in subsequent transformations to achieve the synthesis of Δ7-prostaglandin A1 derivatives which are known to have high antineoplastic activity.[95]

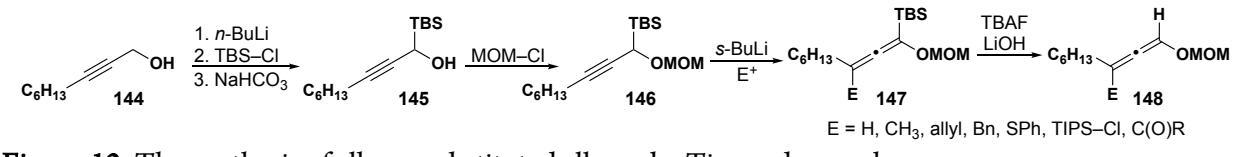


Figure 12. The synthesis of alkoxy-substituted allenes by Tius and coworkers

3.1.3 Reactions with alkoxy-substituted allenes

Due to the relative instability of alkoxy-substituted allenes, they are often generated *in situ* and used in subsequent transformations. Overall, they are the least-explored substrate for further reactivity, when compared to EWG-substituted allenes or alkyl/aryl allenes. There are, however, several prominent reaction pathways that these electronically unique allenes have been reported to follow. Lithiation geminal to the alkoxy group of an alkoxy allene forms allenyl lithiates nucleophiles, which go on to react with a variety of electrophiles. When a pendant alkene is present, Nazarov cyclizations predominate. Lastly, there are several transition metal-catalyzed pathways which further functionalize the alkoxy allene platform. This section will describe several reports of alkoxy allene reactivity so as to understand the context of the reactivity of the geminal acyl/alkoxy allenes reported later in this work.

As a result of the electron-donating capacity of the alkoxy group, the allenyl proton geminal to the alkoxy group is acidic and is selectively deprotonated to form alkoxy allenyllithiate **149** (Figure 13). This reagent exhibits similar reactivity to many other vinyl Grignard or lithium reagents (i.e. nucleophilic attack of a suitable electrophile). Significant success has been had using lithiated alkoxy allenes to attack imines, nitriles, ketones, aldehydes, and isothiocyanates. Figure 13A shows the reaction between alkoxy allene **149** and an imine: in one report by Reissig and coworkers, they are able to isolate **150** and subject it to catalytic potassium *tert*-butoxide in DMSO to afford alkoxy-substituted dihydropyrrole **151**.[96] This method was applied towards the synthesis of codonopsinine (**152**) with alkoxy allene reagent **149**;[91] other natural product syntheses have been achieved in a similar fashion.[97–99] Utilizing a similar intermediate, Reissig and coworkers accomplish a four-component reaction where imidazoles (**154**) can be formed after **150** is subjected to a nitrile species (Figure 13B).[100,101] In a further adaptation of this general method, pyridines are accessible when an alkoxy allene **149** attacks a nitrile species to form alkoxy/imino allene **155** which can be functionalized to **156** when a carboxylic acid is introduced (Figure

13C).[102,103] Similar methods continue to be popular for the synthesis of substituted pyridines.[104] Lithiated alkoxy allenes have been used extensively as precursors for dihydrofuran synthesis (Figure 13D).[87,105–110] This protocol has been adapted to include stereoselective and multicomponent reaction variants. Finally, alkoxy allene nucleophiles have been used to attack isothiocyanates, forming intermediate **164**; in the presence of methyl iodide, the resultant thiolithiate is capped and can rearrange to form dihydropyridine **167**. Alternatively, if the thioether intermediate is heated, it cyclizes to form alkoxy/thioxy-substituted pyrrole **165** (Figure 13E).[111,112]

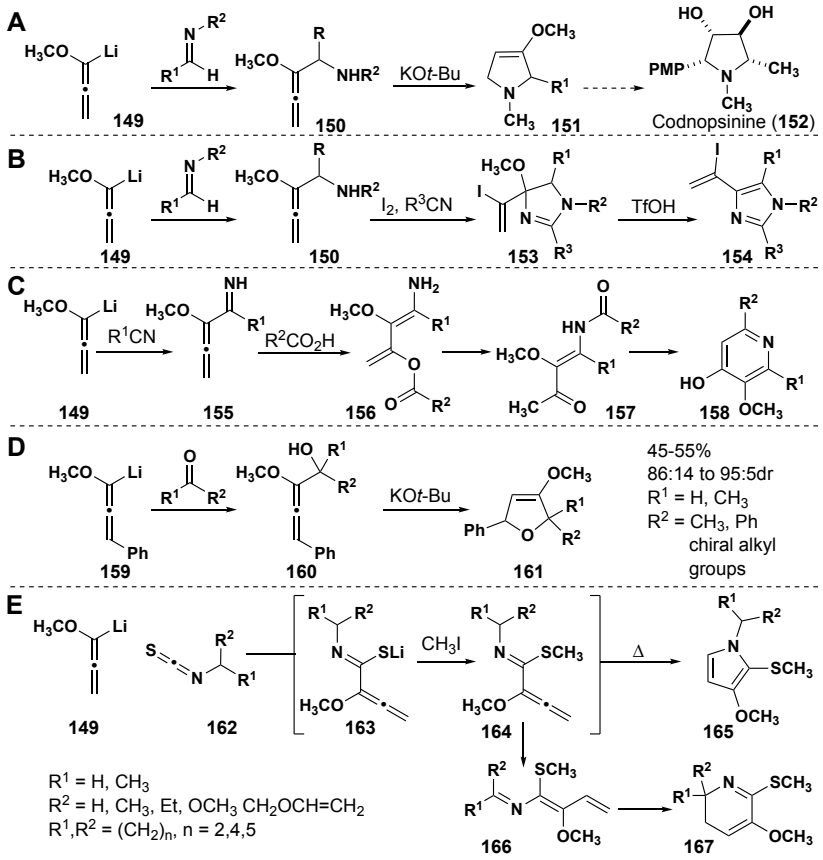


Figure 13. Reactions involving alkoxy allenes as nucleophiles

Nazarov cyclizations are useful for the synthesis of five-membered rings and many variants of this reaction have been developed.[113–115] Alkoxy substituted allenes have been found to undergo the Nazarov cyclization with particular efficiency when an alkene is appended to the allene substructure. Tius and

coworkers have been active in this field and have written a review dedicated to the topic (Figure 14).[116] As discussed above, lithiated alkoxy allenes are suitable nucleophiles for attacking carbonyl species. If the carbonyl is *alpha-beta* unsaturated, then the resulting intermediate is geometrically arranged for a Nazarov cyclization. Figure 14A shows the most basic example of this reaction, where alkoxy allene **168** is lithiated and exposure of this nucleophile to unsaturated morpholine amide **170** and a Lewis acid produces **171**.[12] The loss of morpholine generates a more recognizable Nazarov precursor and the Lewis acid can induce the 4π cyclization to afford **173**. This method has been modified for use nitrile and ketone electrophiles to access *alpha*-amino and *alpha*-alkyl cyclopentenones, respectively, enabling the construction of a diverse set of densely functionalized scaffolds (not shown).[12] The cyclopentenone substructure is a prominent moiety in natural product synthesis; as such, alkoxy allene Nazarov cyclizations have been used effectively in the synthesis of several natural products.[117,118] Allenyl benzofuran **174** can undergo epoxidation to form **175**; a proton source (likely from *meta*-chlorobenzoic acid impurity in *m*CPBA) opens up this epoxide to generate Nazarov precursor **176** (Figure 14B).[119,120] After the loss of tributylstannane, the subsequent electrocyclization affords tricycle **178**, which is later converted to natural product (±)-rocaglamide (**179**). Tius and coworkers accomplished the synthesis of (±)-xanthocidin (**186**) through a methodology similar to figure 14A, where an alkoxy allene lithiate attacks a ketone electrophile to produce intermediate **183** (Figure 14C).[121] Differing from more typical Nazarov cyclizations derived from ketones, the pentadienyl cation **184** is generated when the allylic alcohol is removed with trifluoroacetic anhydride and lutidine. The electrocyclization produces cyclopentenone **185** and the racemic synthesis of xanthocidine is achieved after Upjohn dihydroxylation of the unsaturated ketone. Finally, this reaction has been rendered stereoselective by the use of chiral alkoxy allenes (Figure 14D). Sugar-substituted alkoxy allenes and camphor-derived lithiated alkoxy allenes are reacted with unsaturated morpholine amides to undergo the same Nazarov cyclization shown in figure 14A; as a result

of the chiral alkoxy group, the analogous intermediate of **172** is a stereoselective process.[122] When the sugar auxiliary is not attached with anomeric effect stabilization ($R^1 = X_c1$), enantioselectivity for pentanone **189a** is somewhat poor (78:22 er), but when the anomeric effect ($R^1 = X_c2$) is invoked enantioselectivity is significantly increased for the opposite enantiomer (**189b**, 91:9 er). Camphor-derived auxiliary X_c3 was used to explore the effect of distal steric bulk on the allene.[123] When **187c** is a terminal allene (i.e. R^2, R^3 = H), moderate stereoselectivity (88:12 er) is observed. Similarly, when R^2 = H and $R^3 = CH_3$, a nearly insignificant increase in selectivity occurs (89:11 er). However, when R^2, R^3 = *t*-butyl, the steric hindrance is dramatically increased, resulting in excellent enantioselectivity to form **189c** in 98:2 er. While the entire scope of this reaction has not been reported here for the sake of brevity, it is clear from these efforts that this field of alkoxy allene chemistry is dominated by Tius and the methodological space has been thoroughly investigated.

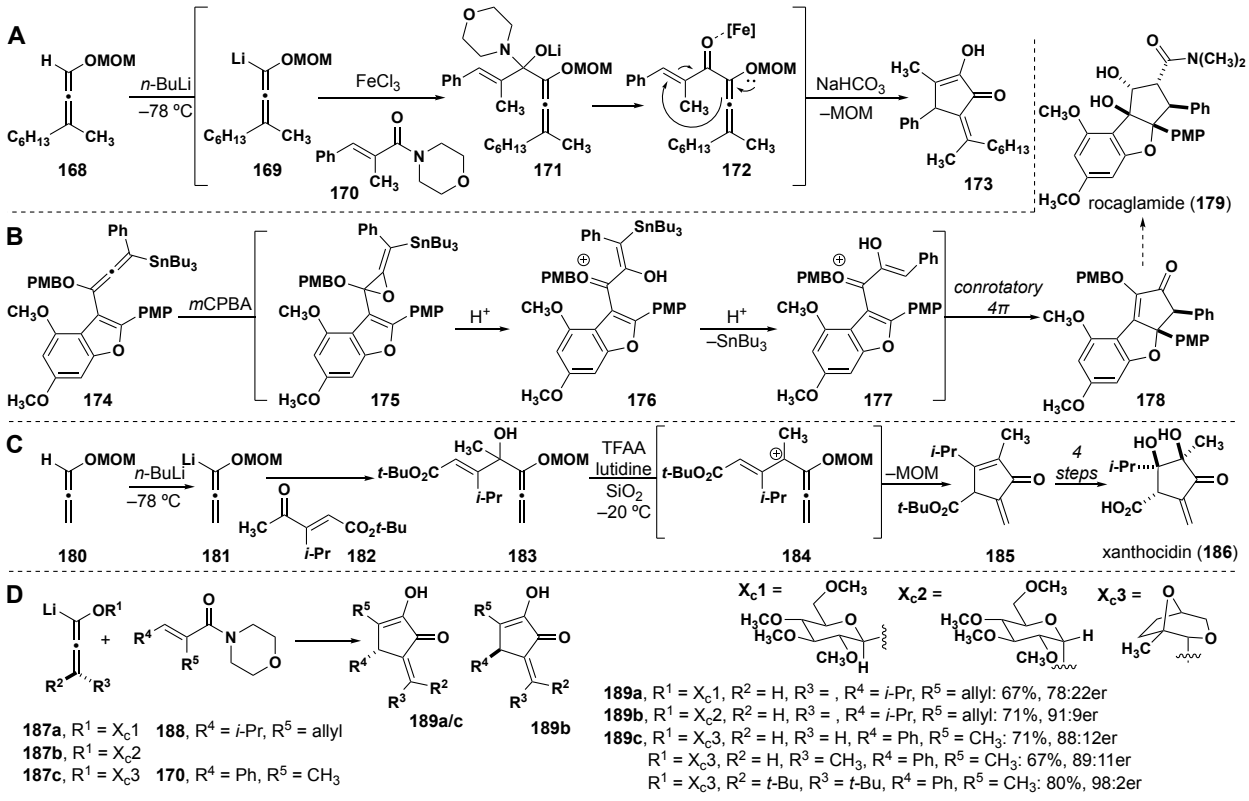


Figure 14: Nazarov cyclizations with alkoxy allenes

Finally, alkoxy-substituted allenes may be used in transition metal-catalyzed reactions; as a result of the limited research of alkoxy allenes, these reports are comparatively less common than the analogous acyl-substituted allene reactions (Figure 15). While many transition metals have been used in reactions with allenes, gold is certainly the most prominent.[124–129] Gold is particularly π-philic as a Lewis acid and has been shown to effectively catalyze a variety of transformations with activated allene substrates.[11] In an example of divergent reactivity with alkoxy allenes, **190** is subjected to a gold (III) picolinate catalyst (Figure 15A).[130] Though this substrate appears to be predisposed to a Nazarov cyclization as detailed above, the catalyst induces 1,6-cyclization to form cationic intermediate **191**. A transannular rearrangement forms gold carbene **192**, which then releases the ring strain of the cyclopropane to form cyclopentene **193**. Proto-deauration and loss of trimethylsilane (likely in the form of TMSOH) furnishes cyclopentenyl ketones. This methodology was extended to the synthesis of benzyl protected phenols from a similarly substituted allene **195** (Figure 15B).[131] As above, instead of undergoing a Nazarov cyclization, the acyl-protected alcohol of **195** serves as a leaving group in the gold-catalyzed cyclization, which leads to phenolic ether **197**. Hydroaminations of alkoxy allenes are also achieved with triazoles and a gold(I) phosphine catalyst (Figure 15C).[132] In one example of a palladium-catalyzed alkoxy allene functionalization, *ortho*-iodoarenes are used to generate benzofuranyl π-allyl palladium intermediate **201** (Figure 15D).[133,134] This intermediate can then be attacked by an azide nucleophile, which is subsequently intercepted by an alkyne in a Huisgen dipolar cycloaddition to afford triazole **204**.

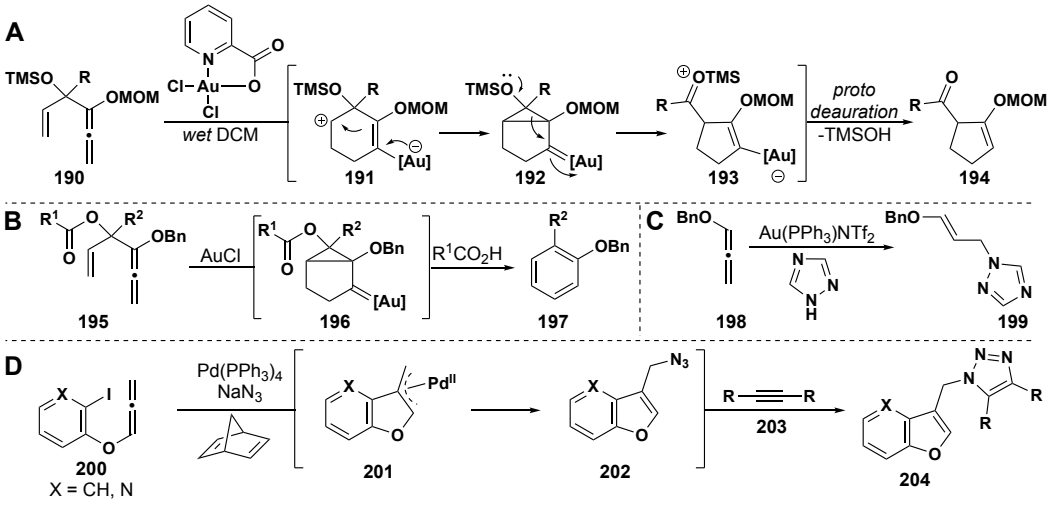


Figure 15. Transition metal-catalyzed reactions with alkoxy allenes

The selected examples of reactions involving alkoxy-substituted allenes have summarized the general modes of reactivity for these uniquely activated substrates. These EDG-substituted allenes have been shown to undergo nucleophilic attack with carbonyl electrophiles and nitriles, Nazarov cyclizations when there is a pendant alkene, and various transition metal-catalyzed cyclization and hydroamination reactions. While this list has not been exhaustive, it details a literature basis for the novel and divergent transformations described later in section 3.4.

3.2 Reaction Discovery, Proposed Mechanism, and Reaction Development

The synthesis of geminally substituted acyl/alkoxy allenes was discovered serendipitously; guided by the structural elucidation of byproducts, the reaction mechanism was subsequently investigated, leading to the development of a general method. Within the context of the method development described in chapter 1 of this dissertation, propargylic insertion sites were desirable substrates for C–H insertion reactions (Figure 16). This interest was in analogy to the previous method to synthesize benzodihydrofurans, where the corresponding C–H insertion product (**206**) was synthesized enantioselectively when Rh_2(*R*-PTAD)$_4$ was used (Figure 16A).[135] However, when no catalyst was

added, the dipolar cycloaddition product **208** was observed. Upon heating, this substrate undergoes a [1s, 5s]-sigmatropic shift (i.e. Van Alphen-Hüttel rearrangement) to form **209**; this discovery was further developed into an excellent methodology for generating spirobicyclic pyrazoles.[136] In our synthesis of isochromans, we were successful in generating methyl-substituted alkynyl isochroman **211** in 53% yield, >95:5 dr, and 92:8 er (Figure 16B). Interestingly, we did not observe any instance of dipolar cycloaddition with this substrate without any catalyst added and with heating. We hypothesized that the geometry of the substrate (generating a 7-membered intermediate) was not suitable for the 1,3-dipolar cycloaddition. While it was favorable for the insertion methodology that we were not generating this byproduct in the reaction, we were curious to see if we could encourage this reaction to occur by using phenyl alkynyl substrate **212**, which was shown in the previous report to be more reactive. In order to test this hypothesis, we set about the construction of the substrate according to the general sequence described in chapter 1 of this dissertation.

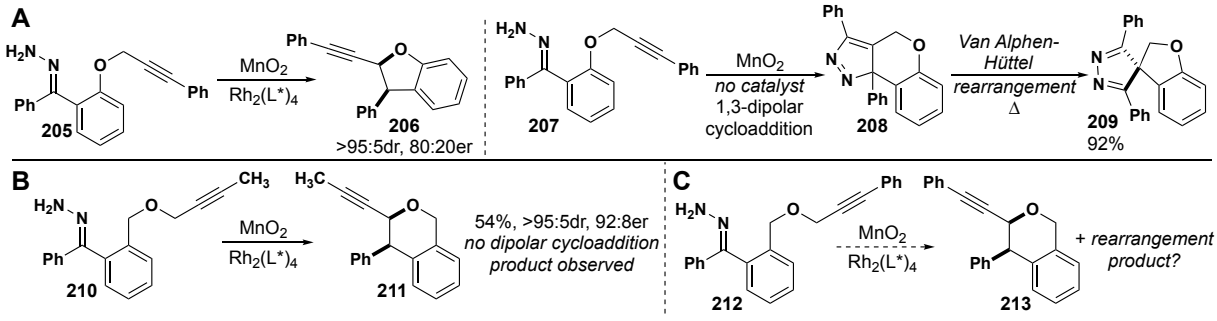


Figure 16. Motivation for synthesizing benzyl propargyl ethers for the purposes of isochroman synthesis

3.2.1 Initial discovery and structural elucidation

The requisite benzyl propargyl ether was constructed in a straightforward manner by nucleophilic substitution with **214** and propargyl alcohol **215** (Figure 17A). Upon exposure of the *ortho*-bromo benzyl ether to lithium halogen exchange with *n*-butyllithium and Weinreb benzamide **217**, it was not apparent that the desired ketone was formed by review of the ^{1}H and ^{13}C NMR spectra (Figure 17, B and C). After

purification by column chromatography, a single product was isolated that accounted for the majority of the mass recovery from the reaction. Both of the etheric methylene proton signals of the starting material **216** (i.e. singlets at ~4.50 and 4.75ppm) were not present in the ^{1}H NMR spectrum of the purified product. In the ^{1}H spectrum of the product there was only a single diastereotopic signal at ~5ppm accounting for 2 nuclides. Additionally, it was unexpected to see the incorporation of an *n*-butyl fragment on the molecule, evidenced by diastereotopic aliphatic signals (i.e. multiplets between ~0.75 and 2.25 ppm).

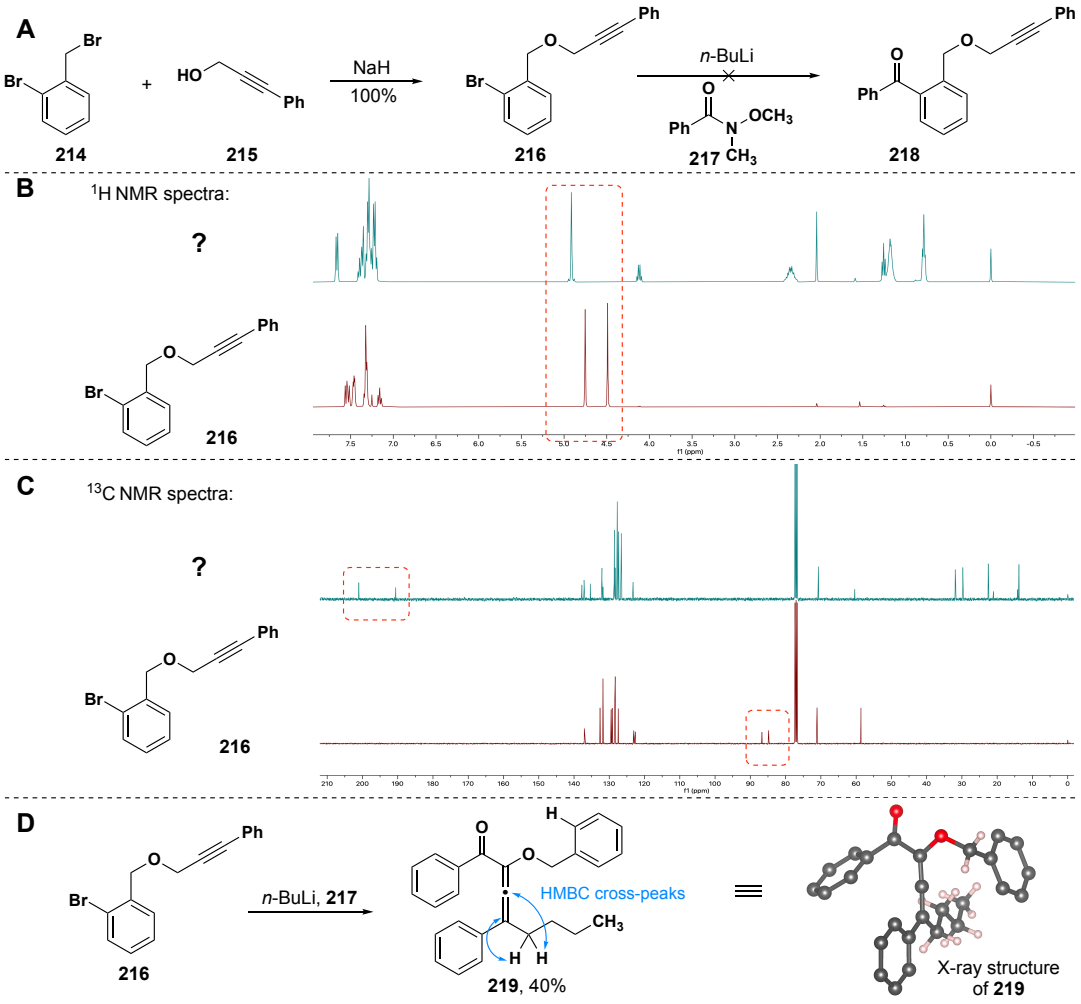


Figure 17. A) Substrate synthesis for a potential C–H insertion/dipolar cycloaddition reaction, B) ^{1}H NMR spectra and C) ^{13}C NMR spectra for **216** and **219**, and D) the first example of an acyl/alkoxy allene

Analysis of the ^{13}C NMR spectra was more helpful in identifying the product. Indicative alkyne carbon signals (i.e. between 80 and 90 ppm) were no longer present and two signals appeared in the typical range for carbonyls (i.e. between 190 and 210 ppm). With this data, we proposed that the alkyne group was transformed into something acyl-substituted. Additionally, literature values for allene C_{sp} ^{13}C NMR chemical shifts suggested that an allene could also have been formed from **216**. The formation of an allene would also explain the diastereotopicity of the methylene at ~5 ppm. Putting these pieces together, **219** was suggested as a possible structure (Figure 17D). Two-dimensional NMR data further reinforced this hypothesis, showing HMBC cross-peaks between the most downfield n-butyl methylene and the allene C_{sp} carbon and the adjacent arene. Later, a crystal structure of **219** was obtained and the proposed structure was unambiguously confirmed.

3.2.2 Proposed mechanism and the isolation/elucidation of reaction byproducts

Having confirmed the structure of **219** by X-ray crystallography, we researched the potential routes of formation. Because there are no reports of geminal acyl/alkoxy allenes, we were especially interested in the mechanism of formation for this unexpected structure (Figure 18). There are also very few reports of using benzyl propargyl ethers as alkoxy allene precursors and nearly all of the reported methods pertain to monosubstituted alkoxy allenes.[137–143] Based on the reported reaction kinetics for lithium halogen exchange *versus* deprotonation,[144] we were certain that upon exposure to *n*-butyllithium, lithium-bromine exchange would occur first, forming **220** and one equivalent of *n*-butyl bromide. From here, we envisioned an intramolecular deprotonation of the propargylic position; the resulting propargyl lithiate **221** would then be in equilibrium with allenyl lithiate **222** through a metallotropic shift. This species, most likely more thermodynamically stable than **221**, can then go on to be alkylated with the previously generated *n*-butyl bromide. The following reactivity is similar to that shown by Tius, Reissig, and others:

alkoxy allene **223** is lithiated to form **224** and the resulting nucleophile attacks the Weinreb amide. Upon quenching the reaction, geminal acyl/alkoxy allene **219** was afforded in 40% yield.

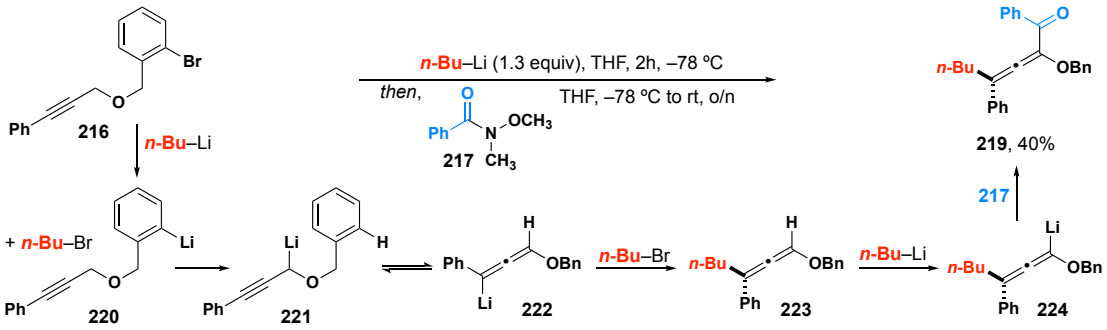


Figure 18. Proposed mechanism for the formation of acyl/alkoxy allene **219**

While the general mechanism above sufficiently explains the chemical transformations that take place to produce the novel structure **219**, several byproducts were identified which informed subsequent experiments. The formation of these byproducts and the results of the mechanistic experiments helped to explain the mechanism in more accurate and fine detail. Two byproducts were initially isolated from the complex unpurified reaction mixture (Figure 19). Propargyl alcohols **226** and **227** were isolated in low yields and are the apparent product of an *ortho*-[2,3]-Wittig rearrangement. This reaction is precedented with similarly functionalized propargyl benzyl ethers but was not used for the synthesis of allenes.[145] After the Wittig rearrangement forms the triene **225**, it can either re-aromatize with a proton source to generate **226**, or it can re-aromatize incorporating the available *n*-butyl bromide generated from lithium halogen exchange to form **227**. The identification of these byproducts affords two valuable pieces of information: the propargyl lithiate **221** is a known intermediate in the reaction mechanism and the Wittig rearrangement pathway is kinetically feasible based on the lifetime of **221** in its equilibrium with **222**.

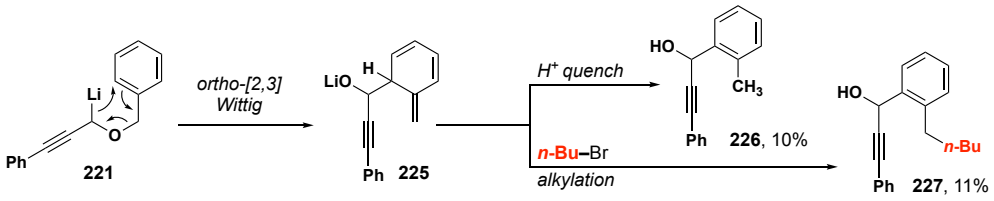


Figure 19. Mechanism of formation for observed *ortho*-[2,3]-Wittig rearrangement byproducts

In addition to the byproducts described above, a more prominent byproduct was observed as reaction conditions were being explored (see section 3.2.3). The NMR spectra of this new byproduct showed two carbonyl signals in the ^{13}C NMR spectrum. The ^{1}H NMR spectrum was nearly identical to that of **216**, although now the characteristic diastereotopic methylene corresponding to the benzyloxy group had a much larger *J*-coupling and was visually very different (i.e. a much more widely spaced roof-topping doublet of doublets). While initially confusing to us, upon further study of the reaction mechanism, it became apparent that this spectral data showed the existence of double-acylation product **228** (Figure 20A). The identification of this byproduct suggested two important mechanistic details: the occurrence of intermolecular deprotonations in the reaction mechanism and existence of a dilithiate as an intermediate therein.

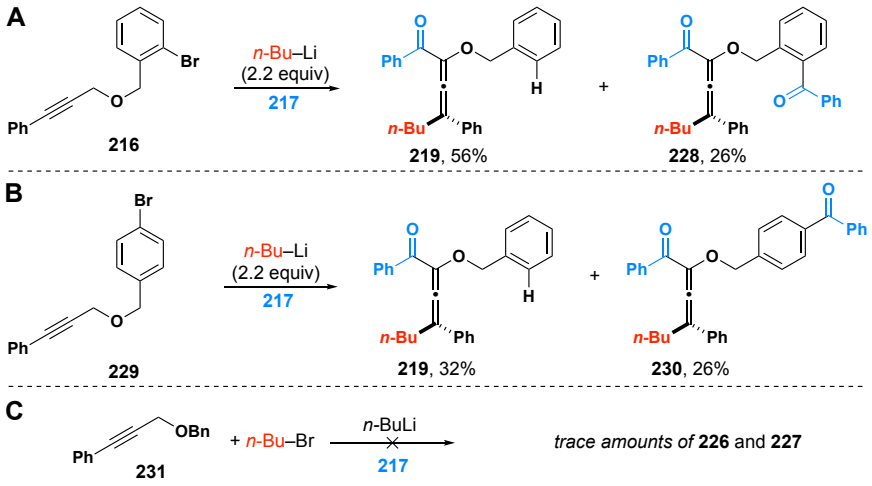


Figure 20. Mechanistic evidence and experiments: A) double-acylation byproduct isolation, B) intermolecular deprotonation experiment, and C) dehalogenated substrate experiment

To test the former hypothesis, the *para*-bromo substrate **229** was constructed (Figure 20B). If the reaction were explicitly enabled by intramolecular deprotonations, then **229** should fail to produce any product (**219**). As was expected, however, intermolecular deprotonation/lithiation events are involved in this reaction mechanism, showing that both **219** and double-acylation product **230** were isolated from this reaction. What this also told us was that there is the potential for a dilithiated intermediate that is persistent in sufficient quantities by the time the Weinreb amide is added. The next experiment was originally designed as a control experiment to see if the halogen was necessary for the reaction mechanism, but ended up giving us more information about the necessity of the dilithiate (Figure 20C). Non-halogenated substrate **231** was constructed and exposed to allene formation conditions; after quenching the reaction, no allene products were observed in the unpurified reaction mixture. Immediately, this suggested to us that the halogen is necessary for the formation of geminal acyl/alkoxy allenes. Additionally, upon further inspection of the NMR spectra, the only identifiable products were the Wittig rearrangement products **226** and **227**, indicating the susceptibility of the propargyl lithiate intermediate to that side-reaction.

Based on the mechanistic data and hypotheses discussed above, we then posit a revised reaction mechanism for the formation of tetrasubstituted geminal acyl/alkoxy allenes (Figure 21). The new mechanism involves two pathways that can potentially go on to form mono-acylation product **219** and/or double-acylation product **228** and involves a persistent dilithiate. After lithium halogen exchange, **220** can go on to be deprotonated at the propargylic position intermolecularly to form **232**, or intramolecularly to form **221**. In accordance with the previously proposed mechanism and new mechanistic evidence, **221** can either undergo the *ortho*-[2,3]-Wittig rearrangement, or equilibrate *via* metallotropic shift to form **222**. Allenyl lithiate **222** can then go on to be alkylated with *n*-butyl bromide, forming trisubstituted alkoxy allene **223**, followed by another deprotonation/lithiation, eventually leading to mono-acylation product

219. While this mechanism is only slightly modified from the original, we propose that the equilibrium between **221** and **222** is not entirely productive for the eventual formation of **219**, but favors the Wittig rearrangement pathway to form **226** and **227**.

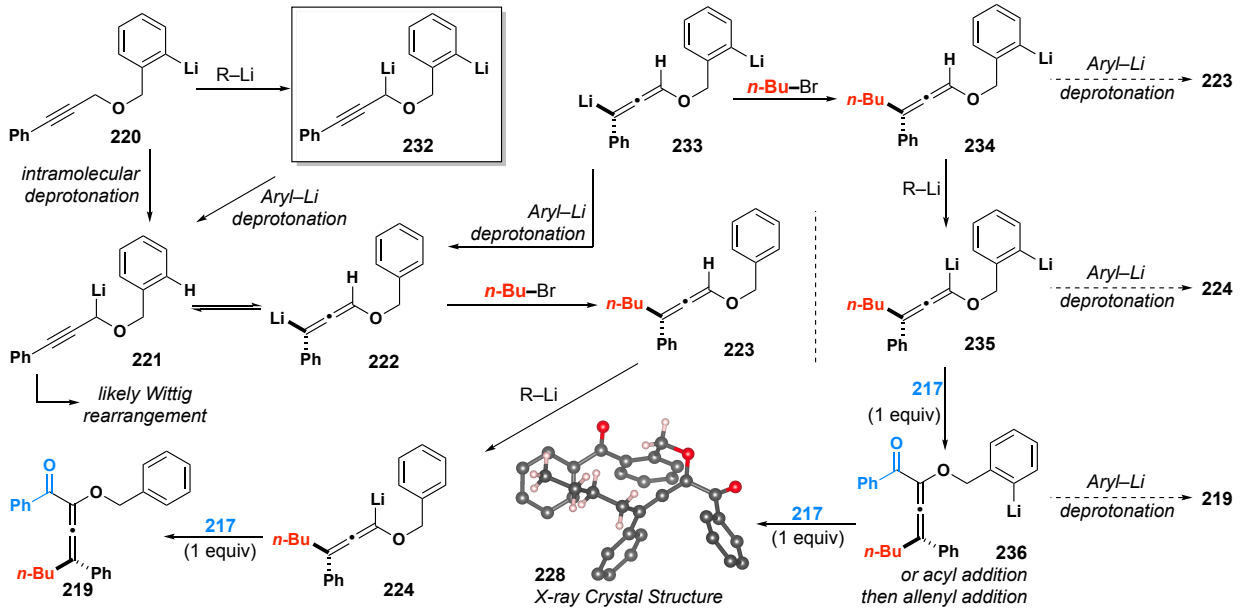


Figure 21. A revised proposed mechanism for geminal acyl/alkoxy allene formation

Alternatively, what we believe to be the more productive pathway in the formation of **219** is through the dilithiated intermediate **232**. Again, there is a likely equilibrium between propargyl lithiate **232** and allenyl lithiate **233** *via* metallotropic shift; the extent to which the equilibrium lays more towards **232** or **233** could depend on several factors. Taking into account the tendency of organolithium species to aggregate, this could either favor or disfavor **232** depending on the stability of the potential oligomeric complexes.[146–148] Based on the principle of dipole moment and charge separation, it could also be proposed that the equilibrium lays more towards **233**. Furthermore, a C_{sp}^2 lithiate is usually more thermodynamically stable than a C_{sp}^3 lithiate, which may influence the equilibria in this sequence. Regardless of the favored isomer in this equilibrium, we suggest that the most productive pathway is that **233** is alkylated with *n*-butyl bromide leading to mono-lithiated trisubstituted allene **234**. If the

aryllithium site of either **232** or **233** deprotonates another species in the reaction mixture, **221** and **222** are formed, respectively. Again, based on the previous discussion, we imagine that these intermediates are in equilibrium with each other and may unproductively form Wittig rearrangement products. Similar to the originally proposed mechanism, **234** can be deprotonated to form **235**, which can then be acylated when the Weinreb amide is added to form **236**. While we propose that the aryllithium site is maintained throughout this sequence, any deprotonation event involving these species will convert them to their delithiated analogues, which are likely still productive in the formation of mono-acylation product **219**. It is worthwhile to note that after the addition of the Weinreb amide, **235** can be acylated at the aryllithiate or allenyllithiate sites. If **236** is formed, this intermediate can be acylated a second time, leading to double-acylation product **228**, for which a crystal structure was obtained, confirming its identity.

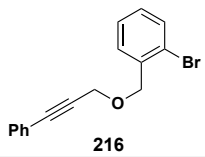
In conclusion, the originally proposed mechanism shown in figure 18 was revised following the isolation and identification of a series of informative byproducts. *ortho*-[2,3]-Wittig rearrangement products were observed, confirming the presence of the propargyl lithiate intermediate and suggesting a competing reaction pathway. The identification of the double-acylation product suggested the presence of persistent dilithiated intermediates; these species are likely important to avoiding the competing Wittig rearrangement pathway and help to form the desired allene product. Due to the large number of lithiated intermediates generated *in situ*, there are many proto-delithiation pathways that can convert dilithiated intermediates to their delithiated analogues, which may or may not be productive in generating allene **219**. As a result, the reaction mechanism is quite complex, which is in agreement with the observed mixture of products afforded in the reaction and lower reaction yields.

3.2.3 Optimization of reaction conditions

Following the initial discovery of a one-pot synthesis of acyl/alkoxy allenes, reaction conditions were optimized to produce a general method (Table 3). While the optimizations discussed below are not

exhaustively representative of all of the conditions attempted, these entries give the most cohesive account. In the original reaction, the intent was to synthesize ketone (Figure 17A, **218**), so a small excess of *n*-butyllithium was used so as to ensure complete lithium halogen exchange (entry 1). Per the first proposed mechanism, two equivalents of *n*-butyllithium were employed and an increase in the yield of allene was observed (entry 2). Next, several solvents were screened to assess the effect of solvation/aggregation of lithiated intermediates.[146–150] Interestingly, in diethyl ether, hexanes, and toluene no allene was observed (entries 3-5). Several temperatures were then explored to determine any kinetic control over the sequence of deprotonations and the stability of the lithiates. At –100 °C, the yield of product was suppressed and at –40 °C only trace product was observed, while at –20 °C, no product was detected by NMR (entries 6-8). Therefore, the careful control of temperature (–78 °C) was necessary for achieving optimal yields of allene **219**. Common additives for organolithium-mediated reactions lithium chloride and tetramethylethylenediamine (TMEDA), were then investigated;[148,150] LiCl was observed to give a significantly cleaner and more easily purified reaction mixture, albeit in reduced yield (entry 9). TMEDA was observed to produce allene **219** with no pronounced effect other than to suppress yield (entry 10). Reaction times were also explored: stirring **216** with *n*-BuLi at –78 °C for 6 hours then adding **217** produced no pronounced increase in allene formation (not shown). Stirring **216** with *n*-BuLi from –78 °C to –20 °C or room temperature, then cooling again to –78 °C to add **217** also had no perceptible benefit (not shown). Attempts were also made to intentionally increase the yield of double-acylation product **228** by adding 2 equivalents of **217**, but there was no significant change in the relative amounts of the two allenes (not shown). Therefore, with the above optimization attempts, entry 2 was established as the most effective protocol for synthesizing allene **219**.

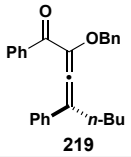
Table 3. Optimization of allene formation reaction conditions



216

conditions

217



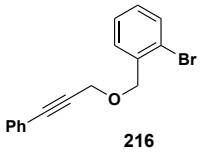
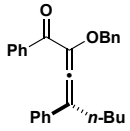
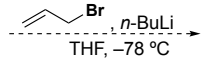
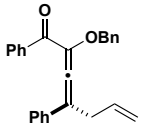
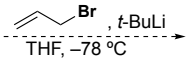
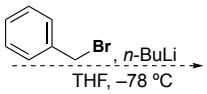
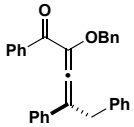
219

entry	*n*-BuLi equiv	solvent	temp (°C)	additive (equiv)	yield (%)
1	1.3	THF	–78	-	40
2	2.0	THF	–78	-	68
3	2.0	Et_2O	–78	-	ND
4	2.0	hexane	–78	-	ND
5	2.0	$PhCH_3$	–78	-	ND
6	2.0	THF	–100	-	22
7	2.0	THF	–40	-	*trace*
8	2.0	THF	–20	-	ND
9	2.0	THF	–78	LiCl (6)	54
10	2.0	THF	–78	TMEDA (2)	39

As an obvious alteration of the method that would provide a marked increase in the versatility of the reaction and the diversity of the products formed, a multi-component reaction (MCR) variation of the method was attempted (Table 4). If successful, this reaction would allow for varied substitution at the *n*-butyl alkylation site. As a means of simple structural identification, *n*-butyl bromide electrophiles were used first (entries 1-4). In this protocol, propargyl benzyl ether **216**, Weinreb amide **217**, and alkyl bromide electrophile were dissolved in THF, cooled, and the lithium base was added. Interestingly, with *n*-butyllithium, *tert*-butyllithium, phenyllithium, and magnesium, no allene products were identified. Having no success with unactivated alkyl electrophiles, allyl bromide and benzyl bromide were attempted in hopes of better reactivity due to increased electrophilicity (entries 5-7). However, none of these reactions generated any identifiable allene products. These attempts at MCR-type allene formation were most likely unsuccessful due to the complex mixture of lithiated intermediates proposed in the revised mechanism. The potential for byproduct formation with this reaction is significant and having a better electrophile in the reaction mixture likely leads to intermediates that are unstable and/or not productive

in subsequent mechanistic steps. These intermediates are most likely degraded upon acidic quench, as it is known that alkoxy-substituted allenes are not particularly stable to acidic conditions.

Table 4. Multi-component reaction feasibility screen

entry	reaction	result
1	 + **217** ; ***n*-BuBr**, *n*-BuLi, THF, –78 °C	 **219**, *ND*
2	**216** + **217** ; ***n*-BuBr**, *t*-BuLi, THF, –78 °C	**219**, *ND*
3	**216** + **217** ; ***n*-BuBr**, PhLi, THF, –78 °C	**219**, *ND*
4	**216** + **217** ; ***n*-Bu–Br**, Mg°, THF, –78 °C	**219**, *ND*
5	**216** + **217** ; 	 **237**, *ND*
6	**216** + **217** ; 	**237**, *ND*
7	**216** + **217** ; 	 **238**, *ND*

3.3 Substrate Scope

With suitable reaction conditions in place, the substrate scope was explored with the assistance of Garrett Toth-Williams and undergraduate student Jeffrey Toman. Without any successful MCR reaction conditions, variations in the Weinreb amide component and at the terminus of the allene were the most easily accessible modifications. EWG and EDG-substituted arenes, heterocycles, and sterically encumbered alkyl Weinreb amides were tolerated. In addition, it is of note that the majority of these allene structures were bench-stable compounds and did not degrade appreciably over time, in favorable contrast to previously reported alkoxy allenes decomposing above 0 °C.[94] In general, we found yields of the allene products to be low; varying amounts of double-acylation products and *ortho*-[2,3]-Wittig rearrangement products were observed but with no discernible trend per substrate. Despite this, with a method for the construction of these uniquely-substituted structures, we expect further development in the synthesis and application of these bench-stable acyl/alkoxy allenes.

3.3.1 Variation of Weinreb amides

Modifications of the Weinreb amide component were accessed in a straightforward manner by synthesizing Weinreb amides from their corresponding carboxylic acids or acid chlorides. Both electron withdrawing and electron donating substituents on the aryl Weinreb amides were tolerated, affording **241**, **242**, and **243** in comparatively low yields (Figure 22). Fluoro-arene **244** was also generated in high yield. Heterocycles were successfully synthesized with this protocol, affording nicotinyl, furyl, and thiophenyl substituted acyl allenes (**245**-**247**). Alkyl Weinreb amides were also synthesized; *iso*-propyl and cyclopropyl allenes were afforded despite having an acidic *alpha*-proton that could quench the various lithiated reaction intermediates (**249** and **251**). However, the reaction with Weinreb acetamide did not produce any identifiable allene product (**248**), likely due to the more acidic and less sterically hindered *alpha*-protons. Sterically demanding *tert*-butyl and adamantyl Weinreb amides were tolerated in the reaction, giving unique allene products **250** and **252**. A dimethyl-Weinreb urea was employed to furnish allene **253**; interestingly, the allenyl lithiate intermediate **224** or **235** attacked the dimethylamine portion of the urea rather than the Weinreb portion.

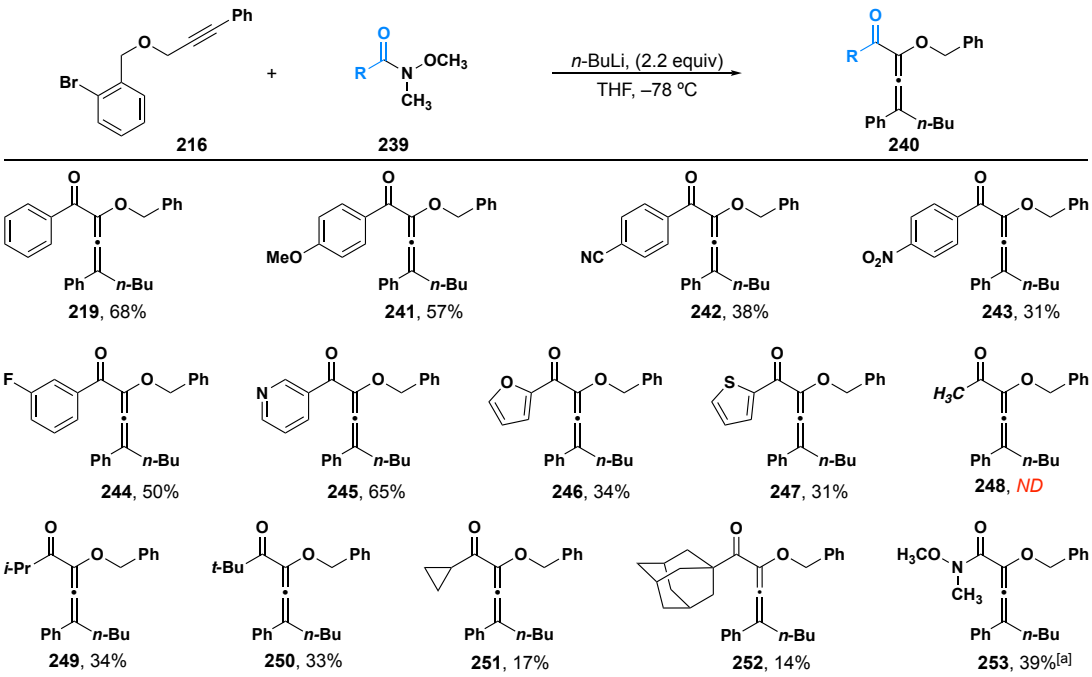


Figure 22. Substrate scope with variation of the Weinreb amide, [a]dimethylamino urea electrophile used

3.3.2 Variation of alkyne substitution

Modifications to the alkyne terminus of the allene precursor were investigated as well. The synthesis of these substrates was usually accomplished by Sonogashira coupling with the respective aryl-iodides and propargyl alcohol, followed by a facile alkylation with 2-bromobenzyl bromide (Figure 23A). As a way to potentially invoke a stereoselective synthesis of the acyl/alkoxy allenes, chiral auxiliary substituted substrates **260** and **261** were generated (Figure 23B). Alkylation of propargyl alcohol with 2-bromobenzyl bromide afforded **258**, which was then brominated.[151] In a variation of the Sonogashira coupling, Evans auxiliary (i.e. 2*R*-benzyloxazolidinone) and Oppolzer auxiliary (camphorsultam) were cross-coupled to alkynyl bromide **259** using copper sulfate and a phenanthroline ligand.[152]

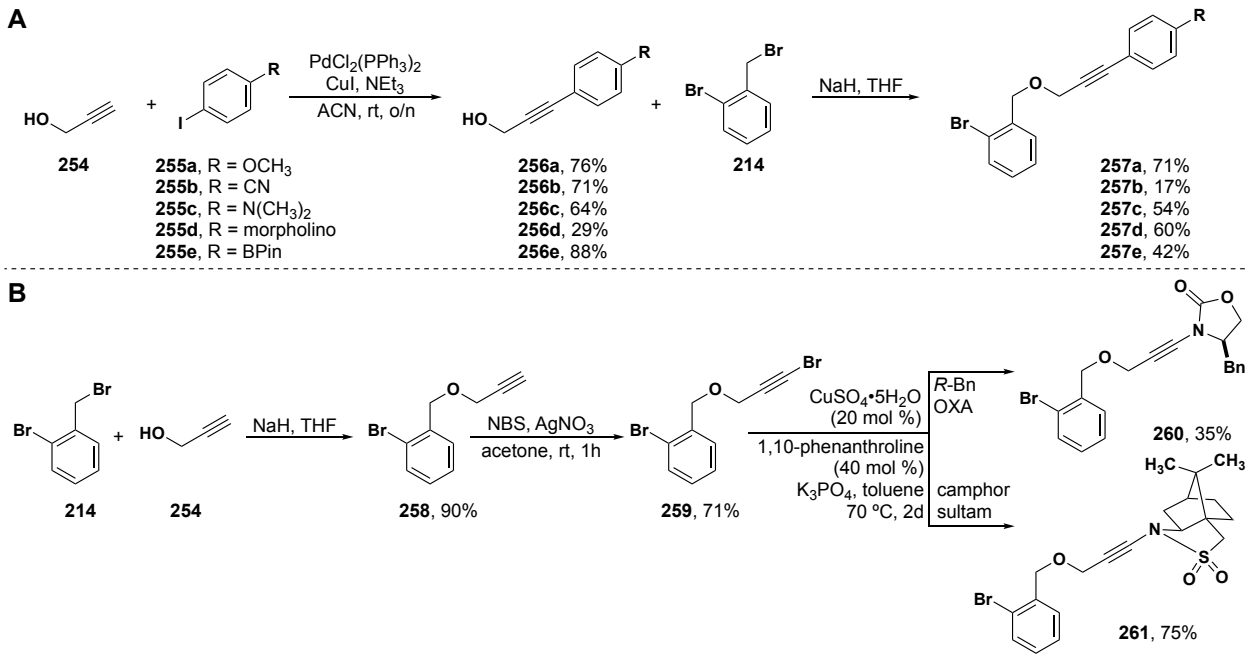


Figure 23. Synthesis of substrates with varying alkyne substitution

After the synthesis of the varied alkynyl substrates, we exposed the compounds to the optimized allene formation conditions (Figure 24). Interestingly, a methoxy electron donating group led to allene **264** in 57% yield, while a EDG cyano-substituent led to only trace allene formation (**265**). This suggested that intermediate **222** or **233** may be destabilized by increased *para* electron donation, leading to increased nucleophilicty to form **264**. On the other hand, **222** or **233** would be stabilized by *para*-EWG groups, leading to reduced nucleophilicity. In an effort to expand the scope of EDG-substituted alkynyl arenes, *para*-dimethylamino, and *para*- morpholino phenyl alkynes **266** and **267**, respectively, were attempted. No formation of allene was observed in the unpurified reaction NMR and it was hypothesized that the EDG-capacity of nitrogen resulted in *too much* destabilization of intermediate **222** or **223**, increasing the reactivity of the substrate and leading to degradation products. Motivated by the utility of aryl boron-pinacolate moieties in Suzuki couplings and other transition metal-catalyzed reactions, substrate **268** was attempted, but did not result in any observed formation of product. Finally, chiral auxiliary-substituted

substrates **260** and **261** were tested for the potential diastereoselective construction of tetrasubstituted geminal acyl/alkoxy allenes; these substrates were not isolated and only proto-dehalogenated starting material was recovered. These results suggested that the *N*-alkynyl substitution is not tolerated in this this synthesis. Overall, modifications to the alkyne terminus in the propargyl benzyl ether starting material were minimally tolerated, although the variations attempted were not exhaustive.

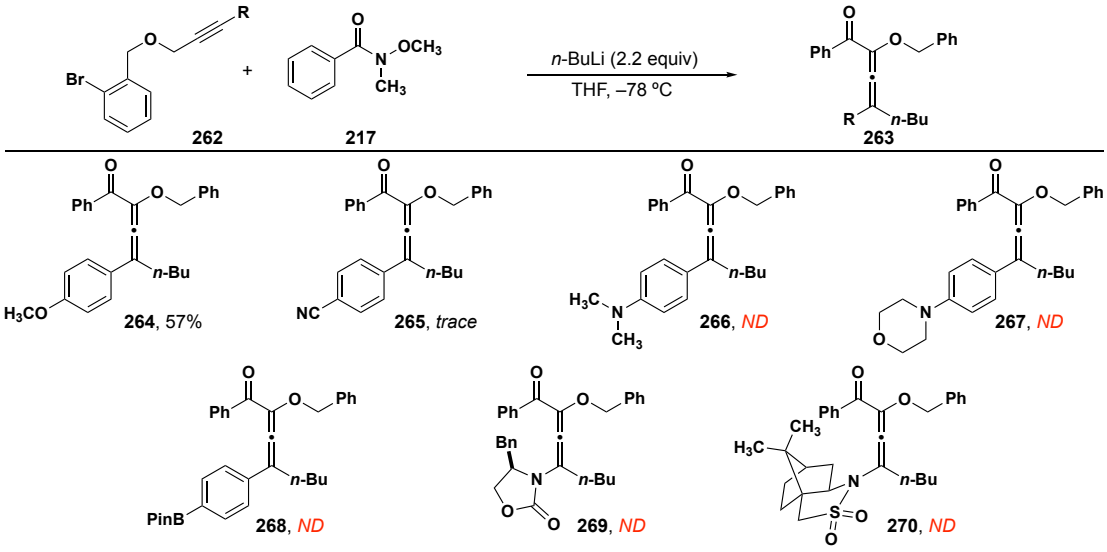


Figure 24. Substrate Scope with variation of the distal alkyne substitution

3.3.3 Miscellaneous attempted variations

Seeking to further diversify the reaction scope and allene products afforded in this reaction, several other modifications were attempted (Table 5). The use of other lithium sources was explored (i.e. methyllithium and *sec*-butyllithium), where after intermediate **222** or **233** is formed, allenyl lithiate alkylation would occur with their respective electrophiles (entries 1 and 2). These reactions did not yield any observable allene products; in any future exploration of this reaction, iodo-arenes could be used so that the resultant alkyl halide would be a better electrophile. Non-amide carbonyl electrophiles were also attempted: no allene formation was observed when using benzaldehyde and phenylisocyanate (entries 3 and 4). Finally, switching the haloarene from 2-bromo to 2-iodo propargyl benzyl ether **275** showed

successful formation of allene **219** but without any improvement of reaction yield (entry 5). Any future development of this reaction would include analogous 2-chloro and the 3-bromo ethers for completeness.

Table 5. Attempted variations

entry	reaction	result
1	**216** + **217** → **CH$_3$Li**, THF, –78 °C	**271**, *ND*
2	**216** + **217** → ***sec*BuLi**, THF, –78 °C	**272**, *ND*
3	**216** + → *n*-BuLi, THF, –78 °C	**273**, *ND*
4	**216** + → *n*-BuLi, THF, –78 °C	**274**, *ND*
5	**275** + **217** → *n*-BuLi, THF, –78 °C	**219**, 20%

3.4 Reactions with Novel Tetrasubstituted Geminal Acyl-Alkoxy Allenes

While there are many modes of reactivity accessible with allenes, acyl allenes, and alkoxy allenes, we were interested in broadly exploring the unique electronic structure of the geminal acyl/alkoxy allenes in further reactions. As such, we exposed the parent allene **219** to a variety of reaction conditions; although many reactions were attempted, an assortment of selected reactions will be listed below. As for the strategy for choosing which reactions to attempt, we considered the density of the functional groups on **219**, initially screening reactions that were noted in the literature for similar tetrasubstituted acyl allenes. These reactions generally fell into two categories: cyclization reactions and functionalizations. The investigation of further reactivity of these acyl/alkoxy allenes demonstrated their unique electronic structure though

divergent reactivity, affording useful chemical scaffolds. This research, therefore, expands the field of knowledge and sets a basis for the use of these allenes in other applied contexts outside of the research aims of this laboratory.

3.4.1 Cyclization reactions with acyl/alkoxy allenes

Simple condensations of allenyl ketones with hydrazines afforded hydrazones that subsequently formed heterocycles after intramolecular attack with the pendant nitrogen lone pair (Figure 25). Interestingly, the reactions with hydrazine and *N*-tosylhydrazine afforded cyclization products with differing regioselectivity. Hydrazine, after condensation to the hydrazone, proceeded to form the pyrazole 1,5-cyclization product, isolated as a mixture of **276** (*sans* benzyloxy fragment) and **277** (*with* the benzyloxy intact) in a 85:15 ratio (Figure 25A). We currently do not have a reasonable mechanism to describe the debenzylation process, other than to point out that hydrazine was used in gross excess (10 equiv) and hydrazine has been shown to be a reductant with organic compounds.[153] The analogous reaction with *N*-tosyl hydrazine underwent 1,6-cyclization to form the corresponding 1,5-dihydropyridazine **278** with the benzyloxy group intact; this type of 5-substituted heterocycle is uncommon in the literature (Figure 25B).[154–157] As for the preference for hydrazine to undergo 1,5-cyclization and *N*-tosylhydrazine to undergo 1,6-cyclization, we speculate that the selectivity is controlled by a balance of steric hindrance at the point of cyclization and the relative nucleophilicity of the nitrogen lone pair. For the tosylhydrazone substrate, the toluene-sulfonamide fragment decreases the nucleophilicity of the nitrogen atom and introduces steric bulk proximal to the nucleophile, potentially interfering with the more kinetically favorable 1,5-cyclization. A condensation/cyclization reaction was attempted using *N*-phenylhydrazine, but the NMR spectrum of the unpurified reaction mixture did not suggest any cyclization product was formed (not shown).

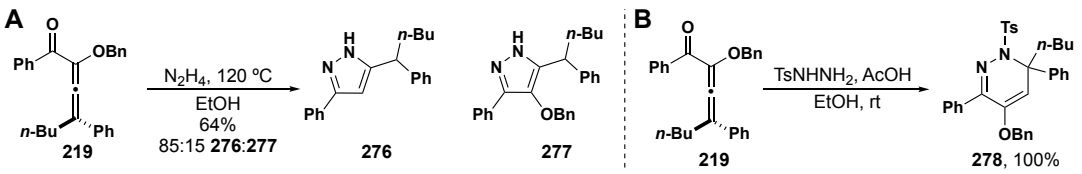


Figure 25. Hydrazine condensation/cyclization reactions

Gevorgyan and coworkers report the metal catalyzed cyclization and 1,2-phenyl migration of tetrasubstituted acyl allenes to form polysubstituted furans.[158] In this report, they demonstrate a wide variety of phenyl ketone-substituted allenes undergoing this transformation, with a single tetrasubstituted example (**280**) afforded in 79% yield using silver triflate (Figure 26A). Compared to the other substrates in that publication, this example was achieved at elevated temperatures, possibly due to the lowered reactivity of a tetrasubstituted allene. To explore the potential for these acyl/alkoxy allenes to undergo metal-catalyzed cyclizations, we exposed **219** to several of the catalysts used in their work, (i.e. $[Au(PPh_3)]OTf$, AgOTf, and $Sn(OTf)_2$) and found $Sn(OTf)_2$ to give the best conversion to a cyclization product (Figure 26B). Upon purification of the reaction product and analysis of its spectra, we discovered that the expected furan product **281** was not formed and instead a new debenzylated product **282** was generated as a single diastereomer. In the report by Gevorgyan and coworkers, the metal catalyst coordinates to the more electron rich π-bond that is distal to the acyl substituent and subsequently generates the furan **280**. Our observed formation of the *alpha*-hydroxy unsaturated ketone **282** diverges from reported reactivity. We hypothesize the coordination of the metal to the more electron rich π-bond proximal to the benzyloxy substituent (**283**), subsequently affording **282** (Figure 26C). The high diastereoselectivity of this reaction was also of interest to us. Graduate student colleague Anna Lo employed computational methods to determine which diastereomer was the lowest in energy and which corresponding computed NMR spectrum would have the closest match with that of the observed product. The relative configuration of the major diastereomer was calculated using B3LYP computational methods

to find the lowest energy conformer of each diastereomer.[159,160] Using Gaussian16, geometry optimizations in the gas phase and NMR GIAO calculations under implicit solvent were conducted on the functional using the 6-31+G(d,p) basis set.[161] DFT calculations ultimately demonstrated that diastereomer **282** was most likely the major diastereomer. In further support of these results, the cyclization product is also similar to those reported by Liu and coworkers, where they observe a single diastereomer when their *geminal* vinyloxy unsaturated ketone substrates are subjected to catalytic base and acetone.[162]

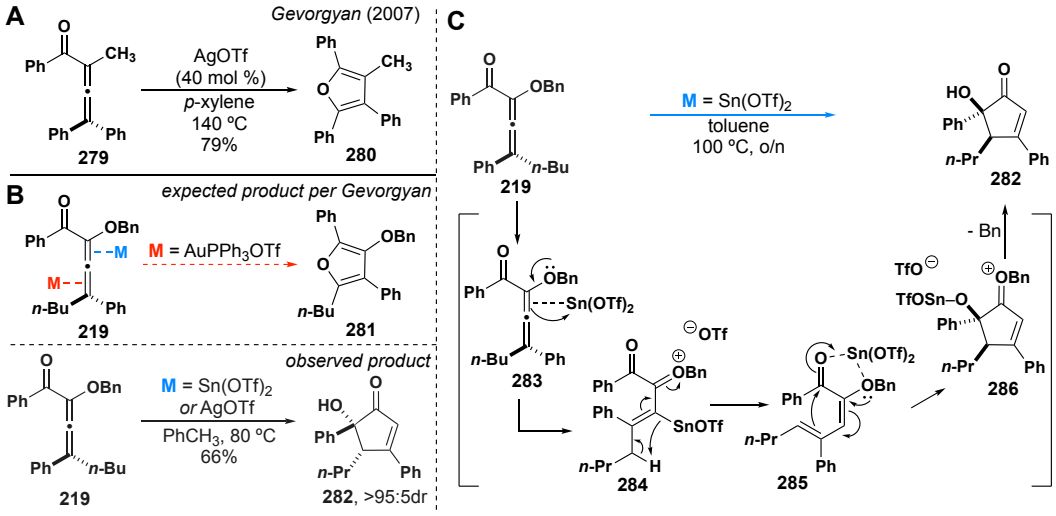


Figure 26. Metal-catalyzed cyclization reaction of tetrasubstituted acyl allenes

With the above-described reactions, we have demonstrated that the uniquely substituted geminal acyl/alkoxy allenes are reactive in cyclizations. Condensation/cyclization reactions afforded five or six membered heterocycle products based on the steric and electronic nature of the hydrazine reagent used. We also achieved a metal-catalyzed cyclization reaction that showed divergent reactivity when compared to the literature precedent for a similar allene substrate.

3.4.2 Functionalization of the allene scaffold

The second mode of reactivity that was explored for the application of geminal acyl/alkoxy allenes was that of functionalization. Generally, we desired to modify the allene scaffold in ways that could enable further reactivity or give insight into the types of reactivity tolerated. Again, all of the attempted reactions were using the parent allene **219** (Figure 27). Allenyl alcohols are known to participate in a variety of further reactions, including cyclizations and eliminations.[163,164] We were therefore quite interested in reducing the carbonyl of **219** to produce allenol **287**; however, none of the attempted reduction conditions afforded any identifiable product or subsequent cyclization products (Figure 27A). In one example, we showed that the Luche reduction conditions afforded the debenzylated reduction product **288** in 35% yield (Figure 27B).[165,166] Demonstrating the selective functionalization of the parent allene, **219** was epoxidized in the Johnson-Corey-Chaykovsky reaction to form **289** in 60:40 dr and without any observed cyclopropanation products (Figure 27C).[167,168] Figure 27D shows the use of the Bestman-Ohira reagent to undergo the Seyferth-Gilbert homologation, converting the ketone to an alkynyl-substituent.[169] Finally, a Horner-Wadsworth-Emmons reaction was successful in producing ene-allene **291** when the reaction mixture was purified using basic alumina (Figure 27E).[170] Debenzylation product **292** was also formed when silica gel was used for purification. With these functionalization reactions, we demonstrated a small variety of applications of the parent allene in further chemical transformations. Overall, simple carbonyl reductions were not successful, although other functional group interconversions that target the ketone moiety were productive. While the list reactions attempted here is not exhaustive, it demonstrates the potential for geminal acyl/alkoxy allenes to be used in the synthesis of densely functionalized compounds.

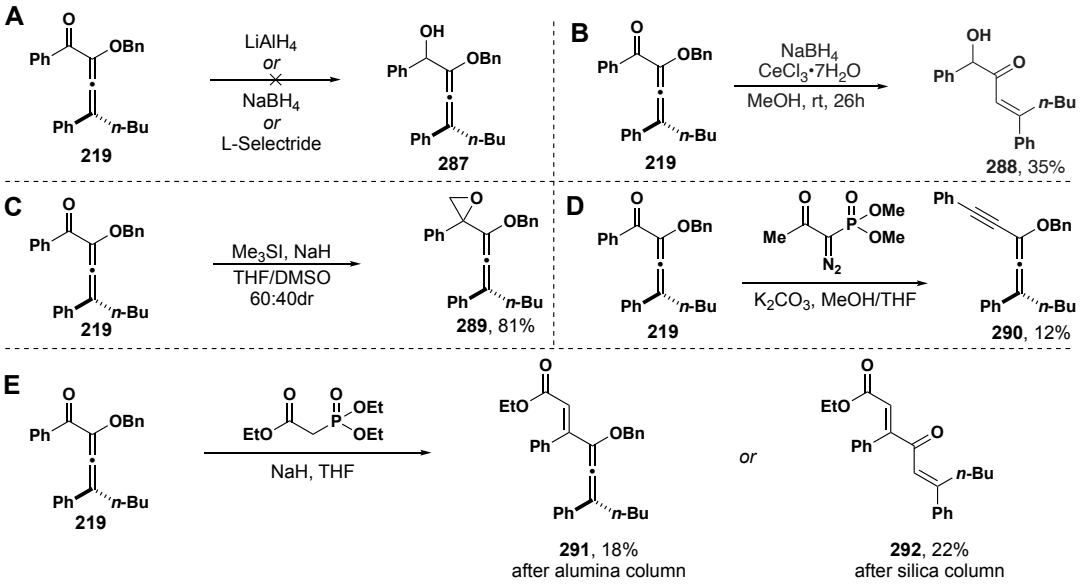


Figure 27. Attempted functionalization reactions

3.5 Conclusions

In conclusion, we have shown the first example of an isolated geminal acyl/alkoxy-substituted allene. Though these uniquely activated compounds have been implicated as intermediates in other reports by Tius and coworkers, they were never isolated or characterized. In our efforts to isolate and identify reaction byproducts, we propose a reaction mechanism that involves dilithiated intermediates which reduce or eliminate the occurrence of the *ortho*-[2,3]-Wittig rearrangement byproducts. As such, we also identified double-acylation byproducts, supporting this hypothesis. The substrate scope for this reaction was developed, demonstrating that electron-deficient, electron-rich, and various alkyl-substituted Weinreb amide electrophiles can be employed. Variation of substitution at the alkyne terminus was also explored, showing limited tolerance at this position. Finally, the parent allene substrate was used to explore this new chemical space by applying this scaffold in further chemical transformations. Cyclization reactions were largely successful and allowed for the synthesis of interesting heterocycles. Functionalization of the parent allene was also successful, showing that the ketone moiety can be

selectively targeted. In this way, we have assessed the synthesis of tetrasubstituted geminal acyl/alkoxy allenes and their application in subsequent reactions. With this work as a basis, we expect further development in the field using these bench-stable allenes.

3.6 Experimental Section

3.6.1 General Comments

Chemicals were purchased and used without further purification unless otherwise specified. All reactions using anhydrous solvents were carried out under an atmosphere of industrial argon in flame-dried glassware with magnetic stirring. Anhydrous solvent was dispensed from a solvent purification system that passes solvent through two columns of dry neutral alumina. Reactions were monitored by thin layer chromatography (TLC, Merck), and detected by examination under UV light (254 nm and 365 nm). Flash column chromatography was performed using silica gel [230–400 mesh (40–63 μm)]. Extracts were concentrated in vacuo using both a rotary evaporator (bath temperatures up to 40 °C) at a pressure of ≥10 torr (diaphragm pump). High vacuum procedures were carried out at room temperature at a pressure of 1 mtorr (diaphragm pump) or ≥1000 mtorr (oil pump). ^{1}H and ^{13}C spectra were measured in $CDCl_3$ at 300, 400, or 600 MHz, and 75, 100, or 150 MHz, respectively, unless otherwise noted. All spectra in $CDCl_3$ were referenced at TMS = 0 ppm. Multiplicities are given as: s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), m (multiplet), or combinations of these signals. Apparent signals are indicated with app. and are used when signals with multiple couplings appear to form a certain peak type. High-resolution mass spectrometry was performed on positive mode and ESI/Orbitrap™, ESI/TOF, and CI/TOF techniques were generally used. Melting points were taken on an EZ-melting apparatus and were uncorrected. Infrared spectra were taken on a Bruker Tensor 27 spectrometer.

3.6.2 General Procedures

General Procedure A: Weinreb Amide Synthesis[171]

N,O-dimethylhydroxylamine hydrochloride (1.0 equiv) and DCM (0.4 M). Triethylamine (3.0 equiv) was added slowly at 0 °C. Benzoyl chloride (1.0 equiv) was then added dropwise into the mixture the solution was stirred at rt overnight. Upon completion, the reaction was quenched with sat. aq. $NaHCO_3$

(10 mL) and the mixture was extracted with DCM (3 X 30 mL) and the combined organic layers were washed with H_2O (20 mL) and brine (20 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude reaction mixture was purified by flash column chromatography to yield the desired Weinreb amide.

General Procedure B: Weinreb Amide Synthesis[171]

The requisite carboxylic acid (1 equiv) was dissolved in DCM (0.3 M), the solution was cooled to 0 °C, and oxalyl chloride (2 equiv) was added dropwise. Dimethylformamide (1.3 equiv) was carefully added dropwise and the solution was allowed to stir to room temperature over 1 hour. The solution was then concentrated *in vacuo* (Caution, concentration should be performed in a fume hood), and redissolved in DCM (0.6 M). N,O-dimethylhydroxylamine hydrochloride (1.2 equiv) and triethylamine (2 equiv) were added and the mixture was allowed to stir overnight. Upon completion, the reaction was quenched with 1 M HCl (10 mL) and the mixture was extracted with DCM (3 X 30 mL) and the combined organic layers were washed with H_2O (20 mL) and brine (20 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude reaction mixture was purified by flash column chromatography to yield the desired Weinreb amide.

General Procedure C: Sonogashira coupling to form phenyl propargyl alcohols[172]

$Pd_2(PPh_3)_2Cl_2$ (0.01 equiv) and CuI (0.02 equiv) were added to a flask, put under vacuum, and backfilled with argon. Acetonitrile (1.0 M), iodobenzene (or iodoarene) (1.1 equiv), and triethylamine (4.5 equiv) were added, followed by slow addition of propargyl alcohol (1 equiv) and the mixture was stirred at room temperature for 8 hours. The reaction was then diluted with DCM, washed with 1 M HCl (10 mL), the aqueous layer extracted with DCM, then the combined organic layers were dried over Na_2SO_4, concentrated *in vacuo*, and purified by flash column chromatography to afford the desired phenyl propargyl alcohol.

General Procedure D: Ether Synthesis[171]

NaH (60% suspension in mineral oil, 1.5-3.0 equiv) and anhydrous THF (0.56 M with NaH) were added to a flame-dried round bottom flask. The suspension of NaH in THF was stirred and a solution of the desired alcohol (1.0 equiv) in anhydrous THF (0.78 M) dropwise and stirred for 1 h. The respective bromide (1.1-1.7 equiv) was added dropwise and the reaction was warmed to rt and stirred for 2-16 hours. Upon completion by TLC, the reaction was quenched with sat. aq. NH_4Cl or H_2O (20 mL) dropwise. The crude mixture was extracted with EtOAc (3 X 40 mL) and the combined organic layers were washed with brine (1 X 30 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude reaction mixture was purified by flash column chromatography to yield the desired ether.

General Procedure E: allene formation conditions[171]

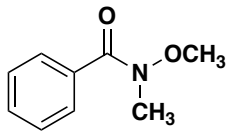
A 7 mL flame dried vial was charged with allene precursor (1.0 equiv) in dry THF (0.27 M) and cooled to -78 °C. *n*-BuLi (2.0 equiv, ~2.0 M in hexanes) was added dropwise to the reaction, which subsequently stirred at -78 °C for 2 hours. A solution of the electrophile (1.2 equiv) in dry THF (0.8 M) was slowly added to the reaction. The mixture was slowly allowed to warm to room temperature, then stirred overnight (20-24 h). At the completion of the reaction as determined by TLC, the reaction mixture was quenched with saturated aq. NH_4Cl. The aqueous layer was extracted three times with EtOAc. The combined organic extracts were washed with H_2O, brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*.

General Procedure F: allene formation conditions[172]

LiCl (6.0 equiv) was added to a 7 mL vial and flame dried. The vial was then charged with allene precursor (1.0 equiv) in dry THF (0.27 M) and cooled to -78 °C. *n*-BuLi (2.0 equiv, ~2.0 M in hexanes) was added dropwise to the reaction, which subsequently stirred at -78 °C for 2 hours. A solution of the electrophile (1.2 equiv) in dry THF (0.8 M) was slowly added to the reaction. The mixture was slowly allowed to warm

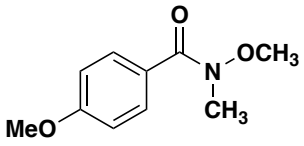
to room temperature, then stirred overnight (20-24 h). At the completion of the reaction as determined by TLC, the reaction mixture was quenched with saturated aq. NH_4Cl. The aqueous layer was extracted three times with EtOAc. The combined organic extracts were washed with H_2O, brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*.

3.6.3 Weinreb Amides



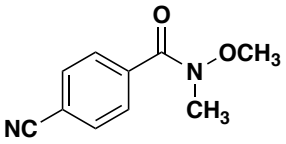
N-methoxy-*N*-methylbenzamide **(217)**

According to general procedure A, NEt_3 (19.8 mL, 142.029 mmol, 2.0 equiv) was added to a suspension of N,O-dimethylhydroxylamine hydrochloride (8.312 g, 85.217 mmol, 1.2 equiv) in DCM (142.0 mL, 0.5 M) at 0 °C. Benzoyl chloride (8.25 mL, 71.014 mmol, 1.0 equiv) was then added dropwise into the mixture and the solution was stirred at rt overnight. At the completion of the reaction as determined by TLC, the reaction mixture was quenched with 3.0 M aq. HCl. The aqueous layer was extracted three times with DCM. The combined organic extracts were washed with H_2O, brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified using flash column chromatography (SiO_2, 5:95 to 35:65, EtOAc:hexanes) affording **217** as a colorless oil (11.027 g, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71-7.64 (m, 2H), 7.50 – 7.36 (m, 3H), 3.56 (s, 3H), 3.36 (s, 3H). ^{1}H NMR data was consistent with literature values.[173]



N,4-dimethoxy-*N*-methylbenzamide **(293)**

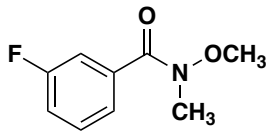
According to general procedure A, NEt_3 (8 mL, 58.198 mmol, 2.0 equiv) was added to a suspension of N,O-dimethylhydroxylamine hydrochloride (3.438 g, 35.172 mmol, 1.2 equiv) in DCM (120 mL, 0.25 M) at 0 °C. 4-methoxybenzoyl chloride (5.003 g, 29.310 mmol, 1.0 equiv) was then added dropwise into the mixture and the solution was stirred at rt overnight. At the completion of the reaction as determined by TLC, the reaction mixture was quenched with 1 M aq. HCl. The aqueous layer was extracted three times with DCM. The combined organic extracts were washed with H_2O, brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified using flash column chromatography (SiO_2, 10:90 to 30:70, EtOAc:hexanes) affording **293** as a colorless oil (5.078 g, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 – 7.69 (m, 2H), 6.94 – 6.86 (m, 2H), 3.85 (s, 3H), 3.56 (s, 3H), 3.36 (s, 3H). ^{1}H NMR data was consistent with literature values.[173]



4-cyano-*N*-methoxy-*N*-methylbenzamide **(294)**

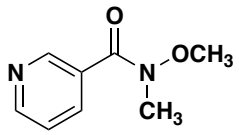
According to general procedure B, 4-cyano-benzoic acid (2.501 g, 16.992 mmol, 1 equiv), oxalyl chloride (2.9 mL, 34.0 mmol, 2 equiv), and DMF (1.7 mL, 21.0 mmol, 1.3 equiv) were dissolved in DCM (85 mL, 0.3 M). After concentration, the mixture was taken up in DCM (55 mL, 0.6 M) and NEt_3 (4.7 mL, 34 mmol, 2 equiv) and N,O-dimethylhydroxylamine hydrochloride (1.987 g, 20.340 mmol, 1.2 equiv) were added. The crude product was purified using flash column chromatography (SiO_2, 30:70, EtOAc:hexanes) affording **294** as a white solid (1.140 g, 35%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 – 7.74

(m, 2H), 7.74 – 7.67 (m, 2H), 3.53 (s, 3H), 3.38 (s, 3H). ^{1}H NMR data was consistent with literature values.[174]



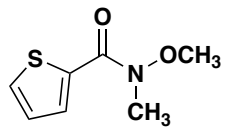
3-fluoro-*N*-methoxy-*N*-methylbenzamide **(295)**

According to general procedure A, NEt_3 (0.88 mL, 6.307 mmol, 2.0 equiv) was added to a suspension of N,O-dimethylhydroxylamine hydrochloride (0.369 g, 3.784 mmol, 1.2 equiv) in DCM (13.0 mL, 0.25 M) at 0 °C. 3-fluorobenzoyl chloride (0.38 mL, 71.014 mmol, 1.0 equiv) was then added dropwise into the mixture and the solution was stirred at rt overnight. At the completion of the reaction as determined by TLC, the reaction mixture was quenched with 1.0 M aq. HCl. The aqueous layer was extracted three times with DCM. The combined organic extracts were washed with H_2O, brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified using flash column chromatography (SiO_2, 40:60, EtOAc:hexanes) affording **295** as a colorless oil (0.502 g, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.44 (m, 1H), 7.44 – 7.33 (m, 2H), 7.23 – 7.11 (m, 1H), 3.56 (s, 3H), 3.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4 (d, J = 2.4 Hz), 162.2 (d, J = 246.5 Hz), 136.0 (d, J = 7.3 Hz), 129.7 (d, J = 8.1 Hz), 124.0 (d, J = 3.3 Hz), 117.6 (d, J = 20.9 Hz), 115.5 (d, J = 23.5 Hz), 61.2, 33.6; AMM (ESI) *m/z* calcd for $C_9H_{11}FNO_2^+$ $[M+H]^+$ 184.0768, found 184.0772; IR (neat): 3077, 2937, 1648, 1585, 1246 cm^{-1}. ^{1}H NMR data was consistent with literature values.[175]



N-methoxy-*N*-methylnicotinamide **(296)**

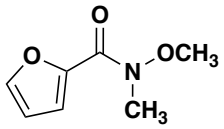
According to general procedure A, nicotinoyl chloride•HCl (2.00 g, 11.23 mmol, 1 equiv), NEt_3 (6.30 mL, 44.94 mmol, 4 equiv) and N,O-dimethylhydroxylamine hydrochloride (1.318 g, 13.482 mmol, 1.2 equiv) were dissolved in DCM (45 mL, 0.25 M). After workup, the crude product was purified using flash column chromatography (SiO_2, 95:5 DCM:MeOH) affording **296** as a light yellow oil (1.237 g, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 – 8.93 (m, 1H), 8.72 – 8.65 (m, 1H), 8.07 – 7.99 (m, 1H), 7.40 – 7.32 (m, 1H), 3.56 (s, 3H), 3.40 (s, 3H); AMM (ESI) *m/z* calcd for $C_8H_{10}N_2O_2Na^+$ $[M+Na]^+$ 189.0639, found 189.0638; IR (neat): 3035, 2938, 1639, 1589, 1223 cm^{-1}. ^{1}H NMR data was consistent with literature values.[176]



N-methoxy-*N*-methylthiophene-2-carboxamide **(297)**

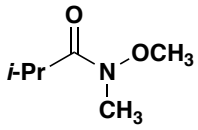
According to general procedure A, NEt_3 (1.3 mL, 9.353 mmol, 2.0 equiv) was added to a suspension of N,O-dimethylhydroxylamine hydrochloride (0.547 g, 5.612 mmol, 1.2 equiv) in DCM (18.7 mL, 0.25 M) at 0 °C. 2-thiophenecarbonyl chloride (0.5 mL, 4.676 mmol, 1.0 equiv) was then added dropwise into the mixture and the solution was stirred at rt overnight. At the completion of the reaction as determined by TLC, the reaction mixture was quenched with 3.0 M aq. HCl. The aqueous layer was extracted three times with DCM. The combined organic extracts were washed with H_2O, brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*, affording **297** as a colorless oil (0.622 g, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97

(dd, J = 3.9, 1.3 Hz, 1H), 7.56 (dd, J = 5.0, 1.3 Hz, 1H), 7.11 (dd, J = 5.1, 3.8 Hz, 1H), 3.79 (s, 3H), 3.38 (s, 3H). ^{1}H NMR data was consistent with literature values.[177]



N-methoxy-*N*-methylfuran-2-carboxamide **(298)**

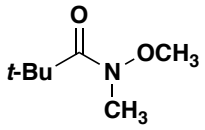
According to general procedure A, NEt_3 (2.8 mL, 20.287 mmol, 2.0 equiv) was added to a suspension of N,O-dimethylhydroxylamine hydrochloride (1.187 g, 12.172 mmol, 1.2 equiv) in DCM (20.3 mL, 0.5 M) at 0 °C. 2-furoyl chloride (1.0 mL, 10.143 mmol, 1.0 equiv) was then added dropwise into the mixture and the solution was stirred at rt overnight. At the completion of the reaction as determined by TLC, the reaction mixture was quenched with 3.0 M aq. HCl. The aqueous layer was extracted three times with DCM. The combined organic extracts were washed with H_2O, brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified using flash column chromatography (SiO_2, 5:95 to 50:50, EtOAc:hexanes) affording **298** as a white solid (0.597 g, 38%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (dd, J = 1.8, 0.8 Hz, 1H), 7.15 (dd, J = 3.5, 0.8 Hz, 1H), 6.51 (dd, J = 3.5, 1.7 Hz, 1H), 3.77 (s, 3H), 3.36 (s, 3H). ^{1}H NMR data was consistent with literature values.[173]



N-methoxy-*N*-methylisobutyramide **(299)**

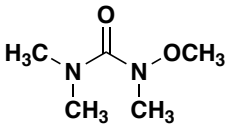
According to general procedure A, NEt_3 (2.66 mL, 19.090 mmol, 2.0 equiv) was added to a suspension of N,O-dimethylhydroxylamine hydrochloride (0.931 g, 9.545 mmol, 1.0 equiv) in DCM (23.9 mL, 0.4 M) at 0 °C. Isobutyryl chloride (1.0 mL, 9.545 mmol, 1.0 equiv) was then added dropwise into the mixture and the solution was stirred at rt overnight. At the completion of the reaction as determined by TLC, the

reaction mixture was quenched with sat. aq. $NaHCO_3$. The aqueous layer was extracted three times with DCM. The combined organic extracts were washed with 1.0 M aq. HCl, H_2O, brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified using flash column chromatography (SiO_2, 5:95 to 30:70, EtOAc:hexanes) affording **299** as a colorless oil (0.205 g, 16%). ^1H NMR (400 MHz, $CDCl_3$) δ 3.70 (s, 3H), 3.19 (s, 3H), 3.06 – 2.90 (m, 1H), 1.13 (m, 6H). ^1H NMR data was consistent with literature values.[174]



N-methoxy-*N*-methylpivalamide **(300)**

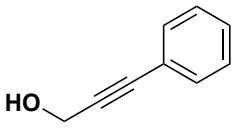
According to general procedure A, NEt_3 (2.28 mL, 9.353 mmol, 2.0 equiv) was added to a suspension of N,O-dimethylhydroxylamine hydrochloride (0.797 g, 8.169 mmol, 1.0 equiv) in DCM (20.4 mL, 0.4 M) at 0 °C. Trimethylacetyl chloride (1.0 mL, 8.169 mmol, 1.0 equiv) was then added dropwise into the mixture and the solution was stirred at rt overnight. At the completion of the reaction as determined by TLC, the reaction mixture was quenched with sat. aq. $NaHCO_3$. The aqueous layer was extracted three times with DCM. The combined organic extracts were washed with 1.0 M HCl, H_2O, brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*, affording **300** as a colorless oil (0.861 g, 73%). ^1H NMR (400 MHz, $CDCl_3$) δ 3.68 (s, 3H), 3.18 (s, 3H), 1.25 (s, 9H). ^1H NMR data was consistent with literature values.[173]



1-methoxy-1,3,3-trimethylurea **(301)**

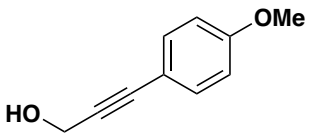
According to general procedure A, DMAP (0.066 g, 0.543 mmol, 0.1 equiv) and pyridine (0.87 mL, 10.861 mmol, 2.0 equiv) were added to a suspension of N,O-dimethylhydroxylamine hydrochloride (0.636 g, 6.517 mmol, 1.2 equiv) in DCM (21.7 mL, 0.25 M) at 0 °C. Dimethylcarbamoyl chloride (0.5 mL, 5.431 mmol, 1.0 equiv) was then added dropwise into the mixture and the solution was stirred at rt overnight. At the completion of the reaction as determined by TLC, the reaction mixture was quenched with 3.0 M aq. HCl. The aqueous layer was extracted three times with EtOAc. The combined organic extracts were washed with H_2O, brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*, affording **301** as a colorless oil (0.355 g, 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.51 (s, 3H), 2.87 (s, 6H), 2.86 (s, 3H). ^{1}H NMR data was consistent with literature values.[178]

1.4 Propargyl Alcohols



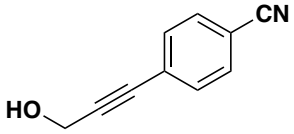
3-phenylprop-2-yn-1-ol **(215)**

According to general procedure C, propargyl alcohol (2.33 mL, 40 mmol, 1 equiv), iodobenzene (4.93 mL, 44.0 mmol, 1.1 equiv), $Pd(PPh_3)_2Cl_2$ (0.289 g, 0.4 mmol, 0.01 equiv), CuI (0.156 g, 0.8 mmol, 0.02 equiv), and triethylamine (25.07 mL, 180 mmol, 4.5 equiv) were dissolved in acetonitrile (1 M). After workup, the crude product was purified using flash column chromatography (SiO_2, 30:70, EtOAc:hexanes) affording **215** as a red solid (4.640 g, 88%). ^{1}H NMR (599 MHz, cdcl$_3$) δ 7.44 (d, J = 7.8 Hz, 2H), 7.31 (m, 3H), 4.50 (s, 2H); ^{1}H NMR data was consistent with literature values.[179]



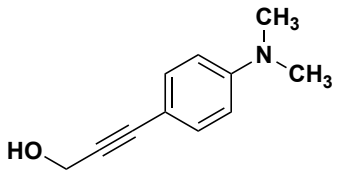
3-(4-methoxyphenyl)prop-2-yn-1-ol **(256a)**

According to general procedure C, propargyl alcohol (0.59 mL, 10 mmol, 1 equiv), 4-iodoanisole (2.574 g, 11 mmol, 1.1 equiv), $Pd(PPh_3)_2Cl_2$ (0.072 g, 0.1 mmol, 0.01 equiv), CuI (0.040 g, 0.2 mmol, 0.02 equiv), and triethylamine (6.5 mL, 45 mmol, 4.5 equiv) were dissolved in acetonitrile (1 M). After workup, the crude product was purified using flash column chromatography (SiO_2, 40:60, EtOAc:hexanes) affording **256a** as a red solid (1.241 g, 76%). ^{1}H NMR (600 MHz, $CDCl_3$) δ7.38 (d, J= 8.1 Hz, 2H), 6.84 (d, J= 8.1 Hz, 2H), 4.49 (d, J= 6.0 Hz, 2H), 3.81 (s, 3H), 1.66 (d, J= 6.0 Hz, 1H). ^{1}H NMR data was consistent with literature values.[179,180]



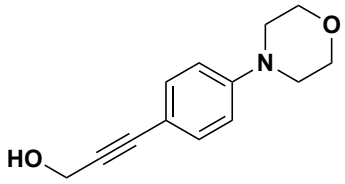
4-(3-hydroxyprop-1-yn-1-yl)benzonitrile **(256b)**

According to general procedure C, propargyl alcohol (0.29mL, 5 mmol, 1 equiv), 4-cyano-iodobenzene (1.260 g, 5.5 mmol, 1.1 equiv), $Pd(PPh_3)_2Cl_2$ (0.036 g, 0.05 mmol, 0.01 equiv), CuI (0.020 g, 0.10 mmol, 0.02 equiv), and triethylamine (3.25 mL, 22.5 mmol, 4.5 equiv) were dissolved in acetonitrile (1 M) and allowed to stir overnight. After workup, the crude product was purified using flash column chromatography (SiO_2, 40:60, EtOAc:hexanes) affording **256b** as a yellow solid (0.555 g, 71%). ^{1}H NMR (600 MHz, $CDCl_3$) δ7.61 (d, J= 7.9 Hz, 2H), 7.51 (d, J= 7.9 Hz, 2H), 4.53 (d, J= 5.9 Hz, 2H), 1.87 – 1.76 (m, 1H). ^{1}H NMR data was consistent with literature values.[179,181]



3-(4-(dimethylamino)phenyl)prop-2-yn-1-ol (**256c**)

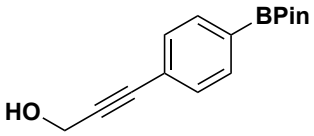
According to general procedure C, propargyl alcohol (0.18 mL, 3 mmol, 1.1 equiv), 4-dimethylamino-iodobenzene (0.668 g, 2.7 mmol, 1 equiv), $Pd(PPh_3)_2Cl_2$ (0.020 g, 0.03 mmol, 0.01 equiv), CuI (0.012 g, 0.05 mmol, 0.02 equiv), and triethylamine (1.7 mL, 12 mmol, 4.5 equiv) were dissolved in acetonitrile (1 M) and allowed to stir overnight. After workup, the crude product was purified using flash column chromatography (SiO_2, 90DCM:10MeOH) affording **256c** as a yellow solid (0.302 g, 64%). JWT-I-011



3-(4-morpholinophenyl)prop-2-yn-1-ol (**256d**)

According to general procedure C, propargyl alcohol (0.12 mL, 2.07 mmol, 1 equiv), 4-morpholino-iodobenzene (0.544 g, 1.88 mmol, 1.1 equiv), $Pd(PPh_3)_2Cl_2$ (0.014 g, 0.0188 mmol, 0.01 equiv), CuI (0.008 g, 0.038 mmol, 0.02 equiv), and triethylamine (1.15 mL, 8.5 mmol, 4.5 equiv) were dissolved in acetonitrile (1 M) and allowed to stir overnight. After workup, the crude product was purified using flash column chromatography (SiO_2, 95DCM:5MeOH) affording **256d** as a yellow solid (0.118 g, 29%).

JWT-I-022

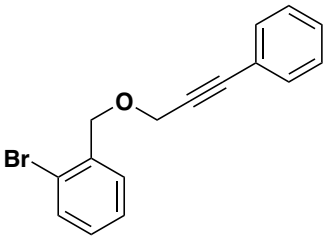


3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)prop-2-yn-1-ol (**256e**)

According to general procedure C, propargyl alcohol (0.802 mL, 1.4 mmol, 1 equiv), 4-boropinacolato-iodobenzene (0.503 g, 1.5 mmol, 1.1 equiv), $Pd(PPh_3)_2Cl_2$ (0.010 g, 0.014 mmol, 0.01 equiv), CuI (0.006 g, 0.028 mmol, 0.02 equiv), and triethylamine (0.86 mL, 6.2 mmol, 4.5 equiv) were dissolved in acetonitrile (1 M) and allowed to stir overnight. After workup, the crude product was purified using flash column chromatography (SiO_2, 60H:40EtOAc) affording **256e** as a yellow solid (0.315 g, 88%).

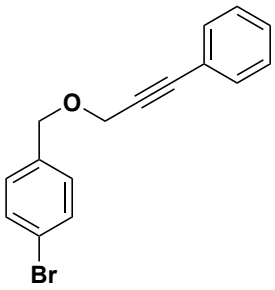
JWT-I-006

3.6.4 Benzyl Propargyl Ethers



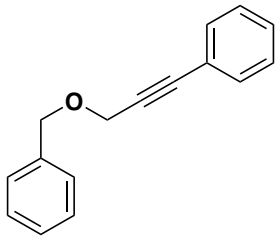
1-bromo-2-(((3-phenylprop-2-yn-1-yl)oxy)methyl)benzene **(216)**

According to general procedure D, 2-bromo-benzyl bromide (1.902 g, 7.413 mmol, 1 equiv), **215** (1.411 g, 11.120 mmol, 1.5 equiv), and NaH (0.910 g, 22.240 mmol, 3 equiv) were dissolved in THF (0.2 M) and allowed to stir overnight. After workup, the crude product was purified using flash column chromatography (SiO_2, 10:90, EtOAc:hexanes) affording **216** as a colorless oil (2.248 g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ7.59 – 7.42 (m, 4H), 7.37 – 7.27 (m, 4H), 7.21 – 7.12 (m, 1H), 4.75 (s, 2H), 4.49 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.0, 132.6, 131.8, 129.5, 129.1, 128.5, 128.3, 127.4, 123.0, 122.6, 86.7, 84.8, 71.1, 58.6; AMM (ESI) *m/z* calcd for $C_{16}H_{14}BrO^+$ $[M+H]^+$ 301.0223, found 301.0228; IR (neat): 3064, 2850, 2235, 1490, 1094 cm^{-1}.



1-bromo-4-(((3-phenylprop-2-yn-1-yl)oxy)methyl)benzene **(229)**

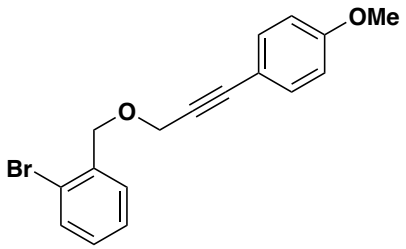
According to general procedure D, 4-bromo-benzyl bromide (1.140 g, 4.540 mmol, 1.2 equiv), **215** (0.509 g, 3.7483 mmol, 1 equiv), and NaH (0.469 g, 11.350 mmol, 3 equiv) were dissolved in THF (0.3 M) and allowed to stir overnight. After workup, the crude product was purified using flash column chromatography (SiO_2, 100% hexanes to 95:5 hexanes:EtOAc) affording **229** as a colorless oil (1.402 g, quant.). ^{1}H NMR (400 MHz, $CDCl_3$) δ7.51 – 7.43 (m, 4H), 7.36 – 7.29 (m, 3H), 7.28 – 7.25 (m, 2H), 4.62 (s, 2H), 4.40 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ136.6, 131.8, 131.6, 129.7, 128.5, 128.3, 122.5, 121.8, 86.7, 84.7, 70.9, 58.1; AMM (ESI) *m/z* calcd for $C_{16}H_{14}BrO^+$ $[M+H]^+$ 301.0223, found 301.0224; IR (neat): 3065, 2923, 2225, 1489, 1071 cm^{-1}.



(3-(benzyloxy)prop-1-yn-1-yl)benzene **(231)**

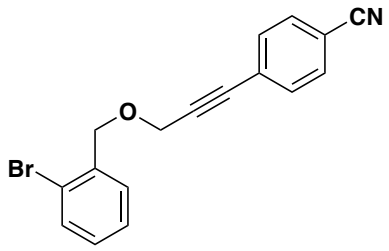
According to general procedure D, benzyl bromide (1.194 g, 5.847 mmol, 1 equiv), **215** (1.162 g, 8.770 mmol, 1.5 equiv), and NaH (0.702 g, 17.540 mmol, 3 equiv) were dissolved in THF (0.2 M) and allowed to stir overnight. After workup, the crude product was purified using flash column chromatography (SiO_2, 100% hexanes to 95:5 hexanes:EtOAc) affording **231** as a pale yellow oil (1.555 g, 100%). ^{1}H NMR (600

MHz, $CDCl_3$) δ7.47 – 7.45 (m, 2H), 7.41 – 7.34 (m, 4H), 7.33 – 7.29 (m, 4H), 4.68 (s, 2H), 4.40 (s, 2H). ^{1}H NMR data was consistent with literature values.[182]



1-bromo-2-(((3-(4-methoxyphenyl)prop-2-yn-1-yl)oxy)methyl)benzene **(257a)**

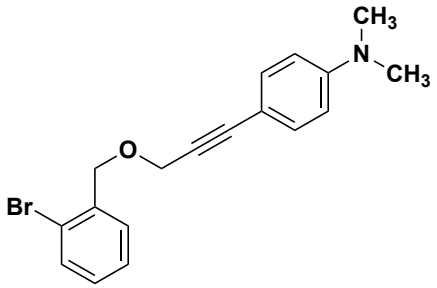
According to general procedure D, 2-bromo-benzyl bromide (0.916 g, 6 mmol, 1.5 equiv), **256a** (1.009 g, 4 mmol, 1 equiv), and NaH (0.486 g, 12 mmol, 3 equiv) were dissolved in THF (0.2 M) and allowed to stir overnight. After workup, the crude product was purified using flash column chromatography (SiO_2, 100% hexanes to 90:10 hexanes:EtOAc) affording **257a** as a pale yellow oil (1.320 g, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ7.59 – 7.49 (m, 2H), 7.46 – 7.36 (m, 2H), 7.32 (td, J = 7.5, 1.2 Hz, 1H), 7.16 (td, J = 7.7, 1.8 Hz, 1H), 6.89 – 6.80 (m, 2H), 4.74 (s, 2H), 4.47 (s, 2H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 137.1, 133.3, 132.6, 129.5, 129.1, 127.4, 123.0, 114.7, 113.9, 86.6, 83.4, 71.0, 58.7, 55.3; AMM (ESI) *m/z* calcd for $C_{17}H_{15}BrO_2Na^+$ $[M+Na]^+$ 353.0153, found 353.0152; IR (neat): 3051, 2837, 2234, 1508, 1092 cm^{-1}.



4-(3-((2-bromobenzyl)oxy)prop-1-yn-1-yl)benzonitrile **(257b)**

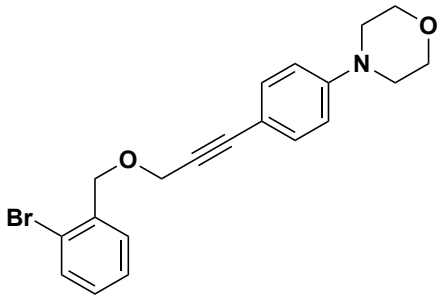
According to general procedure D, 2-bromo-benzyl bromide (0.736 g, 2.941 mmol, 1 equiv), **256b** (0.555 g, 3.529 mmol, 1.2 equiv), and NaH (0.356 g, 8.823mmol, 3 equiv) were dissolved in THF (0.2 M) and

allowed to stir overnight. After workup, the crude product was purified using flash column chromatography (SiO_2, 100% hexanes to 90:10 hexanes:EtOAc) affording **257b** as a pale yellow oil (0.199 g, 17%). ^{1}H NMR (600 MHz, $CDCl_3$) δ7.61 (d, J = 8.2 Hz, 2H), 7.59 – 7.49 (m, 5H), 7.37 – 7.30 (m, 1H), 7.21 – 7.15 (m, 1H), 4.74 (s, 2H), 4.51 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ136.7, 132.7, 132.3, 132.0, 129.4, 129.3, 127.5, 127.4, 123.1, 118.4, 111.9, 89.4, 85.0, 71.4, 58.4.



4-(3-((2-bromobenzyl)oxy)prop-1-yn-1-yl)-*N,N*-dimethylaniline (**257c**)

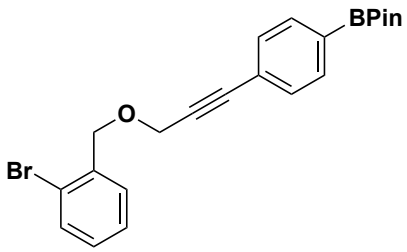
According to general procedure D, 2-bromo-benzyl bromide (0.475 g, 1.9 mmol, 1 equiv), **256c** (0.302 g, 1.7 mmol, 1.2 equiv), and NaH (0.212 g, 5.2 mmol, 3 equiv) were dissolved in THF (0.2 M) and allowed to stir overnight. After workup, the crude product was purified using flash column chromatography (SiO_2, 100% hexanes to 90:10 hexanes:EtOAc) affording **257c** as a pale yellow oil (0.322 g, 54%). JWT-I-012



4-(4-(3-((2-bromobenzyl)oxy)prop-1-yn-1-yl)phenyl)morpholine (**257d**)

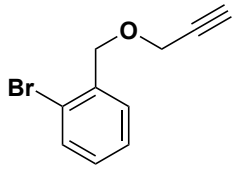
According to general procedure D, 2-bromo-benzyl bromide (0.150 g, 0.6 mmol, 1 equiv), **256d** (0.117 g, 0.5 mmol, 1.2 equiv), and NaH (0.067 g, 1.6 mmol, 3 equiv) were dissolved in THF (0.2 M) and allowed

to stir overnight. After workup, the crude product was purified using flash column chromatography (SiO_2, 100% hexanes to 90:10 hexanes:EtOAc) affording **257d** as a yellow oil (0.125 g, 60%). JWT-I-023



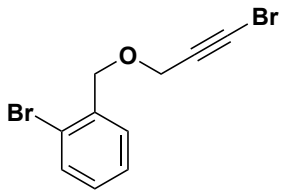
2-(4-(3-((2-bromobenzyl)oxy)prop-1-yn-1-yl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**257e**)

According to general procedure D, 2-bromo-benzyl bromide (0.202 g, 0.810 mmol, 1 equiv), **256e** (0.315 g, 0.74 mmol, 1.2 equiv), and NaH (0.884 g, 2.21 mmol, 3 equiv) were dissolved in THF (0.2 M) and allowed to stir overnight. After workup, the crude product was purified using flash column chromatography (SiO_2, 100% hexanes to 90:10 hexanes:EtOAc) affording **257e** as a yellow oil (0.221 g, 42%). JWT-I-006



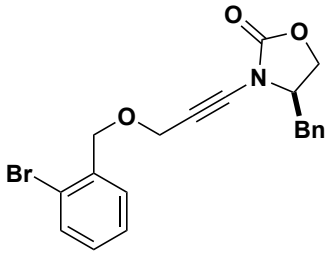
1-bromo-2-((prop-2-yn-1-yloxy)methyl)benzene (**258**)

According to general procedure D, 2-bromo-benzyl bromide (0.554 g, 2 mmol, 1 equiv), propargyl alcohol (0.15 mL, 2.2 mmol, 1.2 equiv), and NaH (0.260 g, 6 mmol, 3 equiv) were dissolved in THF (0.2 M) and allowed to stir overnight. After workup, the crude product was purified using flash column chromatography (SiO_2, 100% hexanes to 90:10 hexanes:EtOAc) affording **258** as a clear oil (0.450 g, 90%). BDB-IV-185



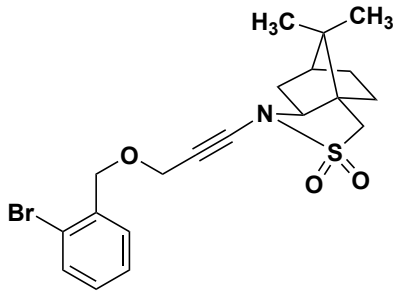
1-bromo-2-(((3-bromoprop-2-yn-1-yl)oxy)methyl)benzene (**259**)

Using a modified literature procedure,[151] **258** (0.450 g, 1.998 mmol, 1 equiv) was dissolved in acetone (0.7 M) and *N*-bromosuccinimide (0.398 g, 2.197 mmol, 1.1 equiv) and silver nitrate (0.040 g, 0.200 mmol, 0.1 equiv) were added. After stirring for 1 hour, the reaction mixture was cooled to 0 °C, quenched with water (3 mL), extracted with diethyl ether (5 mL x2), dried with sodium sulfate, concentrated *in vacuo*, and purified by flash colum chromatography (95H:5EtOAc) to afford **259** (0.431 g, 71%) as a yellow oil. BDB-IV-187



(*R*)-4-benzyl-3-(3-((2-bromobenzyl)oxy)prop-1-yn-1-yl)oxazolidin-2-one (**260**)

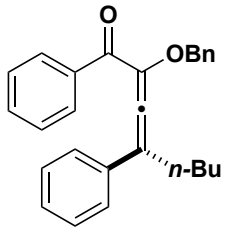
Using a modified literature procedure,[152] **259** (0.205 g, 0.658 mmol, 1 equiv) was dissolved in toluene (0.6 M) and potassium phosphate tribasic (0.279 g, 1.316 mmol, 2 equiv), *R*-benzyloxazolidinone (0.118 g, 0.658 mmol, 1 equiv), copper sulfate pentahydrate (0.034 g, 0.132 mmol, 0.2 equiv) and 1,10-phenanthroline (0.048 g, 0.263 mmol, 0.4 equiv) were added to the microwave/pressure tube and crimp-sealed. This mixture was then heated to 70 °C for 2 days before diluting with DCM (5 mL), filtering through celite and silica, concentrated *in vacuo*, and purified by flash column chromatography (80H:20EtOAc) to afford **260** (0.096 g, 35%) as a clear oil. BDB-IV-191



(6*S*,7a*S*)-1-(3-((2-bromobenzyl)oxy)prop-1-yn-1-yl)-8,8-dimethylhexahydro-3*H*-3a,6-methanobenzo[*c*]isothiazole 2,2-dioxide (**261**)

Using a modified literature procedure,[152] **259** (0.186 g, 0.658 mmol, 1 equiv) was dissolved in toluene (0.6 M) and potassium phosphate tribasic (0.283 g, 1.316 mmol, 2 equiv), (+)-camphorsultam (0.144 g, 0.658 mmol, 1 equiv), copper sulfate pentahydrate (0.036 g, 0.132 mmol, 0.2 equiv) and 1,10-phenanthroline (0.048 g, 0.263 mmol, 0.4 equiv) were added to the microwave/pressure tube and crimp-sealed. This mixture was then heated to 70 °C for 2 days before diluting with DCM (5 mL), filtering through celite and silica, concentrated *in vacuo*, and purified by flash column chromatography (80H:20EtOAc) to afford **261** (0.202 g, 75%) as a clear oil. BDB-IV-192

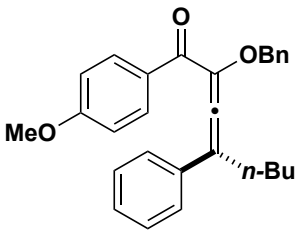
3.6.5 Allenes



2-(benzyloxy)-1,4-diphenylocta-2,3-dien-1-one (**219**)

According to general procedure E, *n*-BuLi (4.16 mL, 8.330 mmol, 2.0 equiv, ~2.0 M in hexanes) was added dropwise to a 25 mL RBF containing a solution of allene precursor **216** (1.254 g, 4.165 mmol, 1.0 equiv) in dry THF (16.0 mL, 0.27 M) at -78 °C. After 2 hours, a solution of Weinreb amide **2** (0.826 g, 4.998 mmol, 1.2 equiv) in dry THF (6.0 mL, 0.8 M) was slowly added to the reaction, which was allowed

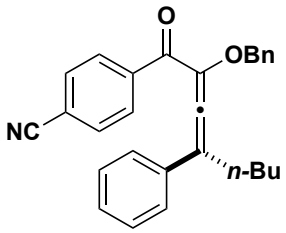
to warm to room temperature overnight. At the completion of the reaction as determined by TLC, the reaction mixture was quenched with saturated aq. NH_4Cl. The aqueous layer was extracted three times with EtOAc. The combined organic extracts were washed with H_2O, brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified using flash column chromatography (SiO_2, 1:99 to 10:90, EtOAc:hexanes) to afford **219** as a yellow crystalline solid (1.082 g, 68%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.63 (m, 2H), 7.44 – 7.18 (m, 13H), 4.97 – 4.86 (m, 2H), 2.43 – 2.26 (m, 2H), 1.27 – 1.10 (m, 4H), 0.78 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 200.7, 190.1, 138.0, 137.2, 135.4, 132.0, 131.9, 128.6, 128.5, 128.4, 128.3, 127.8, 127.7, 127.6, 126.6, 123.3, 70.7, 31.9, 29.9, 22.5, 13.6; AMM (ESI-TOF) m/z calculated for $C_{27}H_{27}O_2^+$ $[M + H]^+$ 383.2006, found 383.2009; IR (neat): 3031, 2959, 1918, 1701, 1157 cm^{-1}, M.P. 55.2-55.7 °C.



2-(benzyloxy)-1-(4-methoxyphenyl)-4-phenylocta-2,3-dien-1-one **(241)**

According to general procedure F, *n*-BuLi (0.33 mL, 0.664 mmol, 2.0 equiv, ~2.0 M in hexanes) was added dropwise to a 7 mL vial containing a solution of allene precursor **216** (0.100 g, 0.332 mmol, 1.0 equiv) and LiCl (0.084 g, 1.992 mmol, 6.0 equiv) in dry THF (1.23 mL, 0.27 M) at -78 °C. After 2 hours, a solution of Weinreb amide **293** (0.078 g, 0.398 mmol, 1.2 equiv) in dry THF (0.50 mL, 0.8 M) was slowly added to the reaction, which was allowed to warm to room temperature overnight. At the completion of the reaction as determined by TLC, the reaction mixture was quenched with saturated aq. NH_4Cl. The aqueous layer was extracted three times with EtOAc. The combined organic extracts were washed with H_2O, brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified using

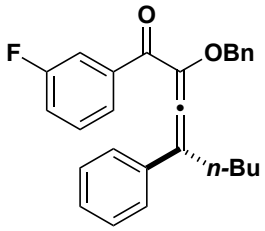
flash column chromatography (SiO_2, 3:97 to 15:85, EtOAc:hexanes) to afford **241** as a yellow oil (0.039 g, 29%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 – 7.69 (m, 2H), 7.40 – 7.21 (m, 10H), 6.76 – 6.67 (m, 2H), 4.93 – 4.85 (m, 2H), 3.77 (s, 3H), 2.48 – 2.29 (m, 2H), 1.32 – 1.14 (m, 4H), 0.80 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.0, 188.7, 163.0, 137.3, 135.5, 131.7, 131.1, 130.2, 128.6, 128.4, 128.2, 127.7, 127.3, 126.6, 122.9, 113.1, 70.6, 55.3, 31.9, 29.8, 22.6, 13.8; AMM (ESI-TOF) m/z calculated for $C_{28}H_{28}O_3Na^+$ $[M + Na]^+$ 435.1936, found 435.1961; IR (neat): 3029, 2954, 1913, 1651, 1146 cm^{-1}.



4-(2-(benzyloxy)-4-phenylocta-2,3-dienoyl)benzonitrile **(242)**

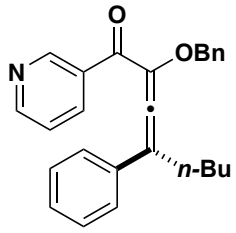
According to general procedure E, *n*-BuLi (0.33 mL, 0.664 mmol, 2.0 equiv, ~2.0 M in hexanes) was added dropwise to a 7 mL vial containing a solution of allene precursor **216** (0.100 g, 0.332 mmol, 1.0 equiv) in dry THF (1.23 mL, 0.27 M) at -78 °C. After 2 hours, a solution of Weinreb amide **294** (0.076 g, 0.398 mmol, 1.2 equiv) in dry THF (0.50 mL, 0.8 M) was slowly added to the reaction, which was allowed to warm to room temperature overnight. At the completion of the reaction as determined by TLC, the reaction mixture was quenched with saturated aq. NH_4Cl. The aqueous layer was extracted three times with EtOAc. The combined organic extracts were washed with H_2O, brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified using flash column chromatography (SiO_2, 10:90, EtOAc:hexanes) to afford **242** as a yellow oil (0.051 g, 38%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68 (d, J = 7.9 Hz, 2H), 7.50 (d, J = 7.9 Hz, 2H), 7.37 – 7.25 (m, 8H), 7.21 – 7.17 (m, 2H), 4.96 – 4.89 (m, 2H), 2.39 – 2.28 (m, 2H), 1.24 –1.07 (m, 4H), 0.79 (t, J = 6.5 Hz, 3H);^{13}C NMR (100 MHz, C_6D_6) δ 200.9, 188.1, 141.4, 137.4, 135.5, 132.4, 132.0, 131.5, 129.1, 128.9, 128.8, 128.8, 127.6, 126.9, 124.0,

118.0, 115.6, 70.5, 31.9, 30.0, 22.9, 13.9; AMM (ESI-TOF) *m/z* calculated for $C_{28}H_{26}NO_2^+$ $[M + H]^+$ 408.1958, found 408.1966; IR (neat): 3068, 2958, 2228, 1930, 1705, 1096 cm^{-1}.



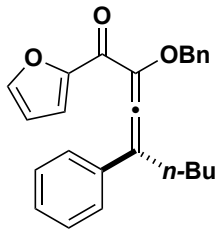
2-(benzyloxy)-1-(3-fluorophenyl)-4-phenylocta-2,3-dien-1-one **(244)**

According to general procedure E, *n*-BuLi (1.66 mL, 3.320 mmol, 2.0 equiv, ~2.0 M in hexanes) was added dropwise to a 25 mL RBF containing a solution of allene precursor **216** (0.500 g, 1.660 mmol, 1.0 equiv) in dry THF (6.15 mL, 0.27 M) at -78 °C. After 2 hours, a solution of Weinreb amide **295** (0.364 g, 1.992 mmol, 1.2 equiv) in dry THF (2.49 mL, 0.8 M) was slowly added to the reaction, which was allowed to warm to room temperature overnight. At the completion of the reaction as determined by TLC, the reaction mixture was quenched with saturated aq. NH_4Cl. The aqueous layer was extracted three times with EtOAc. The combined organic extracts were washed with H_2O, brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified using flash column chromatography (SiO_2, 10:90, EtOAc:hexanes) to afford **244** as a yellow oil (0.330 g, 50%). ^1H NMR (600 MHz, $CDCl_3$) δ7.43 (d, J = 7.7 Hz, 1H), 7.38 – 7.33 (m, 3H), 7.32 – 7.25 (m, 6H), 7.23 – 7.15 (m, 3H), 7.13 – 7.07 (m, 1H), 4.95 – 4.87 (m, 2H), 2.44 – 2.29 (m, 2H), 1.29 – 1.13 (m, 4H), 0.80 (t, J = 6.9 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 201.0, 162.8, 161.2, 139.6, 136.9, 135.0, 131.5, 129.4 (d, J = 7.8 Hz), 128.7, 128.5, 127.8, 127.4, 126.5, 124.2 (d, J = 3.0 Hz), 123.8, 119.0 (d, J = 21.3 Hz), 115.5 (d, J = 22.8 Hz), 70.7, 31.9, 29.7, 22.5, 13.8; AMM (ESI-TOF) *m/z* calculated for $C_{27}H_{26}FO_2^+$ $[M + H]^+$ 401.1911, found 401.1921; IR (neat): 3028, 2961, 1955, 1704, 1152 cm^{-1}.



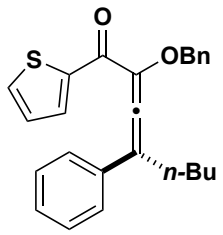
2-(benzyloxy)-4-phenyl-1-(pyridin-3-yl)octa-2,3-dien-1-one **(245)**

According to general procedure F, *n*-BuLi (0.83 mL, 1.660 mmol, 2.0 equiv, ~2.0 M in hexanes) was added dropwise to a 10 mL RBF containing a solution of allene precursor **216** (0.250 g, 0.830 mmol, 1.0 equiv) and LiCl (0.211 g, 4.980 mmol, 6.0 equiv) in dry THF (3.07 mL, 0.27 M) at -78 °C. After 2 hours, a solution of Weinreb amide **296** (0.166 g, 0.996 mmol, 1.2 equiv) in dry THF (1.25 mL, 0.8 M) was slowly added to the reaction, which was allowed to warm to room temperature overnight. At the completion of the reaction as determined by TLC, the reaction mixture was quenched with saturated aq. NH_4Cl. The aqueous layer was extracted three times with EtOAc. The combined organic extracts were washed with H_2O, brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified using flash column chromatography (SiO_2, 20:80, EtOAc:hexanes) to afford **245** as a brown oil (0.204 g, 64%). ^{1}H NMR (600 MHz, $CDCl_3$) δ8.87 (dd, J= 2.2, 0.9 Hz, 1H), 8.62 (dd, J= 4.8, 1.7 Hz, 1H), 7.93 (dt, J= 7.9, 2.0 Hz, 1H), 7.38 – 7.27 (m, 8H), 7.25 – 7.16 (m, 4H), 4.98 – 4.87 (m, 2H), 2.48 – 2.31 (m, 1H), 1.28 – 1.12 (m, 4H), 0.81 (d, J= 7.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ201.4, 188.7, 152.5, 149.3, 136.8, 135.9, 134.7, 133.4, 131.9, 128.8, 128.7, 128.5, 127.9, 127.4, 126.6, 124.2, 122.8, 70.8, 31.9, 29.8, 22.5, 13.8; AMM (ESI-TOF) m/z calculated for $C_{26}H_{26}NO_2^+$ $[M + H]^+$ 384.1958, found 384.1963; IR (neat): 3032, 2957, 1915, 1665, 1163 cm^{-1}.



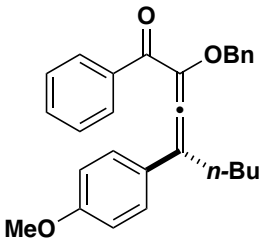
2-(benzyloxy)-1-(furan-2-yl)-4-phenylocta-2,3-dien-1-one **(246)**

According to general procedure F, *n*-BuLi (0.33 mL, 0.664 mmol, 2.0 equiv, ~2.0 M in hexanes) was added dropwise to a 7 mL vial containing a solution of allene precursor **216** (0.100 g, 0.332 mmol, 1.0 equiv) and LiCl (0.084 g, 1.992 mmol, 6.0 equiv) in dry THF (1.23 mL, 0.27 M) at -78 °C. After 2 hours, a solution of Weinreb amide **297** (0.062 g, 0.398 mmol, 1.2 equiv) in dry THF (0.50 mL, 0.8 M) was slowly added to the reaction, which was allowed to warm to room temperature overnight. At the completion of the reaction as determined by TLC, the reaction mixture was quenched with saturated aq. NH_4Cl. The aqueous layer was extracted three times with EtOAc. The combined organic extracts were washed with H_2O, brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified using flash column chromatography (SiO_2, 3:97 to 20:80, EtOAc:hexanes) to afford **246** as a yellow oil (0.042 g, 34%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.50 (m, 1H), 7.39 – 7.19 (m, 10H), 7.11 (d, J = 3.6 Hz, 1H), 6.37 (dd, J = 3.6, 1.7 Hz, 1H), 4.93 – 4.82 (m, 2H), 2.60 – 2.40 (m, 2H), 1.43 – 1.18 (m, 4H), 0.84 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.1, 175.7, 151.1, 146.7, 137.1, 135.1, 131.3, 128.7, 128.5, 128.4, 127.7, 127.4, 126.6, 124.1, 118.8, 111.9, 70.6, 31.8, 29.7, 22.6, 13.8; AMM (ESI-TOF) m/z calculated for $C_{25}H_{25}O_3^+$ $[M + H]^+$ 373.1798, found 373.1794; IR (neat): 3061, 2957, 1917, 1650, 1150 cm^{-1}.



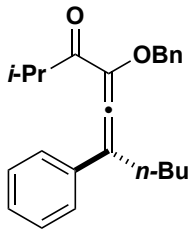
2-(benzyloxy)-4-phenyl-1-(thiophen-2-yl)octa-2,3-dien-1-one **(247)**

According to general procedure F, *n*-BuLi (0.33 mL, 0.664 mmol, 2.0 equiv, ~2.0 M in hexanes) was added dropwise to a 7 mL vial containing a solution of allene precursor **216** (0.100 g, 0.332 mmol, 1.0 equiv) and LiCl (0.084 g, 1.992 mmol, 6.0 equiv) in dry THF (1.23 mL, 0.27 M) at -78 °C. After 2 hours, a solution of Weinreb amide **298** (0.092 g, 0.398 mmol, 1.2 equiv) in dry THF (0.50 mL, 0.8 M) was slowly added to the reaction, which was allowed to warm to room temperature overnight. At the completion of the reaction as determined by TLC, the reaction mixture was quenched with saturated aq. NH_4Cl. The aqueous layer was extracted three times with EtOAc. The combined organic extracts were washed with H_2O, brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified using flash column chromatography (SiO_2, 3:97 to 20:80, EtOAc:hexanes) to afford **247** as a yellow oil (0.040 g, 31%). ^{1}H NMR (400 MHz, $CDCl_3$) δ7.85 (dd, J= 3.8, 1.2 Hz, 1H), 7.50 (dd, J= 5.0, 1.2 Hz, 1H), 7.41 – 7.19 (m, 10H), 6.98 (dd, J= 5.0, 3.9 Hz, 1H), 4.93 – 4.82 (m, 2H), 2.63 – 2.41 (m, 2H), 1.47 – 1.17 (m, 4H), 0.85 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.0, 179.8, 141.2, 137.1, 135.1, 133.6, 133.6, 132.2, 128.6, 128.5, 128.4, 127.7, 127.5, 127.4, 126.7, 125.0, 70.6, 31.9, 29.7, 22.7, 13.9; AMM (ESI-TOF) m/z calculated for $C_{25}H_{25}O_2S^+$ $[M + H]^+$ 389.1570, found 389.1601; IR (neat): 3061, 2954, 1915, 1635, 1141 cm^{-1}.



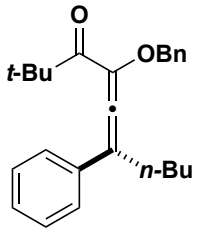
2-(benzyloxy)-4-(4-methoxyphenyl)-1-phenylocta-2,3-dien-1-one **(264)**

According to general procedure E, *n*-BuLi (0.51 mL, 1.02 mmol, 2.0 equiv, ~2.0 M in hexanes) was added dropwise to a 25 mL RBF containing a solution of allene precursor **257a** (0.500 g, 1.510 mmol, 1.0 equiv) in dry THF (5.59 mL, 0.27 M) at -78 °C. After 2 hours, a solution of Weinreb amide **217** (0.299 g, 1.812 mmol, 1.2 equiv) in dry THF (2.27 mL, 0.8 M) was slowly added to the reaction, which was allowed to warm to room temperature overnight. At the completion of the reaction as determined by TLC, the reaction mixture was quenched with saturated aq. NH_4Cl. The aqueous layer was extracted three times with EtOAc. The combined organic extracts were washed with H_2O, brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified using flash column chromatography (SiO_2, 10:90, EtOAc:hexanes) to afford **264** as a yellow oil (0.123 g, 57%). ^{1}H NMR (600 MHz, $CDCl_3$) δ7.66 (d, J= 8.9 Hz, 2H), 7.40 – 7.34 (m, 3H), 7.32 – 7.27 (m, 2H), 7.27 – 7.23 (m, 1H), 7.23 – 7.19 (m, 2H), 7.18 – 7.12 (m, 2H), 6.82 (d, J= 8.9 Hz, 2H), 4.90 (s, 2H), 3.81 (s, 3H), 2.38 – 2.24 (m, 2H), 1.24 – 1.10 (m, 4H), 0.78 (d, J= 7.4 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ200.2, 190.6, 159.7, 137.8, 137.3, 132.0, 131.5, 128.5, 128.4, 127.9, 127.7, 127.7, 127.5, 127.3, 122.8, 114.0, 70.5, 55.2, 31.8, 29.8, 22.5, 13.8; AMM (ESI-TOF) m/z calculated for $C_{28}H_{29}O_3^+$ $[M + H]^+$ 413.2111, found 413.2114; IR (neat): 3056, 2933, 1956, 1663, 1251, 1154 cm^{-1}.



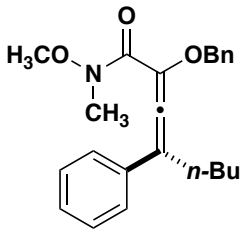
4-(benzyloxy)-2-methyl-6-phenyldeca-4,5-dien-3-one **(249)**

According to general procedure F, *n*-BuLi (0.33 mL, 0.664 mmol, 2.0 equiv, ~2.0 M in hexanes) was added dropwise to a 7 mL vial containing a solution of allene precursor **216** (0.100 g, 0.332 mmol, 1.0 equiv) and LiCl (0.084 g, 1.992 mmol, 6.0 equiv) in dry THF (1.23 mL, 0.27 M) at -78 °C. After 2 hours, a solution of Weinreb amide **299** (0.071 g, 0.398 mmol, 1.2 equiv) in dry THF (0.50 mL, 0.8 M) was slowly added to the reaction, which was allowed to warm to room temperature overnight. At the completion of the reaction as determined by TLC, the reaction mixture was quenched with saturated aq. NH_4Cl. The aqueous layer was extracted three times with EtOAc. The combined organic extracts were washed with H_2O, brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified using flash column chromatography (SiO_2, 1:99 to 10:90, EtOAc:hexanes) to afford **249** as a yellow crystalline solid (0.039 g, 34%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.20 (m, 10H), 4.88 – 4.75 (m, 2H), 3.08 (hept, J = 6.9 Hz, 1H), 2.64 – 2.43 (m, 2H), 1.50 – 1.23 (m, 4H), 1.13 (d, J = 6.8 Hz, 3H), 1.07 (d, J = 6.8 Hz, 3H), 0.92 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.1, 198.9, 137.1, 135.0, 132.1, 128.6, 128.4, 128.3, 127.7, 127.3, 126.4, 123.4, 70.6, 36.2, 31.7, 30.0, 22.7, 19.4, 19.2, 13.9; AMM (ESI-TOF) m/z calculated for $C_{24}H_{29}O_2^+$ $[M + H]^+$ 349.2162, found 349.2187; IR (neat): 3030, 2958, 1914, 1689, 1199 cm^{-1}; M.P. 37.4-38.2 °C.



4-(benzyloxy)-2,2-dimethyl-6-phenyldeca-4,5-dien-3-one **(250)**

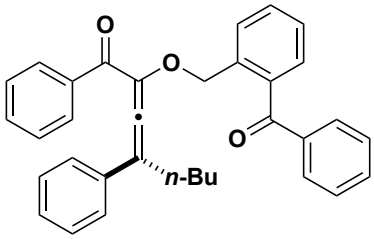
According to general procedure F, *n*-BuLi (0.33 mL, 0.664 mmol, 2.0 equiv, ~2.0 M in hexanes) was added dropwise to a 7 mL vial containing a solution of allene precursor **216** (0.100 g, 0.332 mmol, 1.0 equiv) and LiCl (0.084 g, 1.992 mmol, 6.0 equiv) in dry THF (1.23 mL, 0.27 M) at -78 °C. After 2 hours, a solution of Weinreb amide **300** (0.078 g, 0.398 mmol, 1.2 equiv) in dry THF (0.50 mL, 0.8 M) was slowly added to the reaction, which was allowed to warm to room temperature overnight. At the completion of the reaction as determined by TLC, the reaction mixture was quenched with saturated aq. NH_4Cl. The aqueous layer was extracted three times with EtOAc. The combined organic extracts were washed with H_2O, brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified using flash column chromatography (SiO_2, 1:99 to 10:90, EtOAc:hexanes) to afford **250** as a yellow crystalline solid (0.039 g, 33%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.19 (m, 10H), 4.79 – 4.70 (m, 2H), 2.61 – 2.48 (m, 2H), 1.51 – 1.31 (m, 4H), 1.20 (s, 9H), 0.90 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.8, 197.3, 137.3, 135.2, 130.6, 128.5, 128.4, 128.2, 127.6, 127.3, 126.6, 122.5, 70.1, 44.0, 31.9, 29.9, 27.4, 22.8, 13.9; AMM (ESI-TOF) m/z calculated for $C_{25}H_{30}O_2Na^+$ $[M + Na]^+$ 385.2143, found 385.2166; IR (neat): 3030, 2955, 1917, 1679, 1171 cm^{-1}; M.P. 70.5-71.1 °C.



2-(benzyloxy)-*N*-methoxy-*N*-methyl-4-phenylocta-2,3-dienamide **(253)**

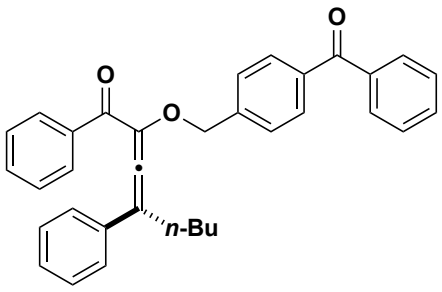
According to general procedure F, *n*-BuLi (0.66 mL, 1.328 mmol, 2.0 equiv, ~2.0 M in hexanes) was added dropwise to a 7 mL vial containing a solution of allene precursor **216** (0.200 g, 0.664 mmol, 1.0 equiv) and LiCl (0.169 g, 3.984 mmol, 6.0 equiv) in dry THF (2.46 mL, 0.27 M) at -78 °C. After 2 hours, a solution of Weinreb amide **301** (0.105 g, 0.797 mmol, 1.2 equiv) in dry THF (1.0 mL, 0.8 M) was slowly added to the reaction, which was allowed to warm to room temperature overnight. At the completion of the reaction as determined by TLC, the reaction mixture was quenched with saturated aq. NH_4Cl. The aqueous layer was extracted three times with EtOAc. The combined organic extracts were washed with H_2O, brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified using flash column chromatography (SiO_2, 3:97 to 30:70, EtOAc:hexanes) to afford **253** as a yellow oil (0.094 g, 39%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.18 (m, 10H), 4.78 (s, 2H), 3.49 (s, 3H), 3.23 (s, 3H), 2.53 – 2.44 (m, 2H), 1.50 – 1.27 (m, 4H), 0.89 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.2, 164.5, 137.3, 136.0, 128.4, 128.3, 128.0, 127.6, 127.5, 126.7, 126.6, 122.3, 70.4, 61.2, 34.0, 31.8, 29.9, 22.7, 13.9; AMM (ESI-TOF) m/z calculated for $C_{23}H_{27}NO_3Na^+$ $[M + Na]^+$ 388.1883, found 388.1893; IR (neat): 3032, 2956, 1933, 1653, 1159 cm^{-1}.

1.7 Byproducts



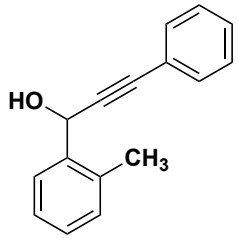
2-((2-benzoylbenzyl)oxy)-1,4-diphenylocta-2,3-dien-1-one **(228)**

According to general procedure E, *n*-BuLi (16.6 mL, 33.203 mmol, 2.0 equiv, ~2.0 M in hexanes) was added dropwise to a 500 mL RBF containing a solution of allene precursor **216** (5.000 g, 16.601 mmol, 1.0 equiv) in dry THF (61.5 mL, 0.27 M) at -78 °C. After 2 hours, a solution of Weinreb amide **217** (3.291 g, 19.922 mmol, 1.2 equiv) in dry THF (24.9 mL, 0.8 M) was slowly added to the reaction, which was allowed to warm to room temperature overnight. At the completion of the reaction as determined by TLC, the reaction mixture was quenched with saturated aq. NH_4Cl. The aqueous layer was extracted three times with EtOAc. The combined organic extracts were washed with H_2O, brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. **228** was generated as a byproduct during the formation of **219**. The crude product was purified using flash column chromatography (SiO_2, 1:99 to 30:70, EtOAc:hexanes) to afford **228** as a white crystalline solid (1.243 g, 26%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 7.9 Hz, 1H), 7.64 – 7.45 (m, 6H), 7.40 – 7.28 (m, 5H), 7.26 – 7.15 (m, 5H), 7.09 – 7.01 (m, 2H), 5.12 (d, J = 14.2 Hz, 1H), 4.98 (d, J = 14.2 Hz, 1H), 2.36 – 2.18 (m, 2H), 1.21 – 1.06 (m, 4H), 0.71 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.6, 197.3, 190.2, 137.8, 137.6, 137.5, 137.0, 134.9, 132.9, 132.1, 131.6, 131.1, 130.1, 129.7, 128.5, 128.5, 128.3, 128.2, 127.8, 127.7, 126.8, 126.6, 123.4, 68.4, 31.7, 29.9, 22.5, 13.7; AMM (ESI-TOF) m/z calculated for $C_{34}H_{31}O_3^+$ $[M + H]^+$ 487.2268, found 487.2258; IR (neat): 3060, 2959, 1915, 1659, 1645, 1153 cm^{-1}; M.P. 81.1-81.6 °C.



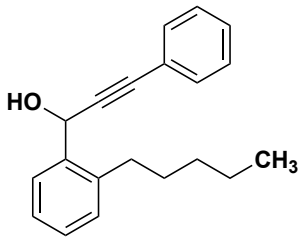
2-((4-benzoylbenzyl)oxy)-1,4-diphenylocta-2,3-dien-1-one **(230)**

According to general procedure E, *n*-BuLi (1.66 mL, 3.320 mmol, 2.0 equiv, ~2.0 M in hexanes) was added dropwise to a 25 mL RBF containing a solution of allene precursor **229** (0.500 g, 1.660 mmol, 1.0 equiv) in dry THF (6.15 mL, 0.27 M) at -78 °C. After 2 hours, a solution of Weinreb amide **217** (0.329 g, 1.992 mmol, 1.2 equiv) in dry THF (2.49 mL, 0.8 M) was slowly added to the reaction, which was allowed to warm to room temperature overnight. At the completion of the reaction as determined by TLC, the reaction mixture was quenched with saturated aq. NH_4Cl. The aqueous layer was extracted three times with EtOAc. The combined organic extracts were washed with H_2O, brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. **230** was generated as a byproduct during the formation of **219**. The crude product was purified using flash column chromatography (SiO_2, 10:90, EtOAc:hexanes) to afford **15** as an orange oil (0.214 g, 26%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 – 7.64 (m, 6H), 7.63 – 7.54 (m, 1H), 7.52 – 7.37 (m, 5H), 7.36 – 7.17 (m, 7H), 5.05 – 4.92 (m, 2H), 2.49 – 2.28 (m, 2H), 1.32 – 1.13 (m, 4H), 0.80 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.7, 196.2, 190.3, 142.0, 137.6, 137.6, 136.9, 135.0, 132.4, 132.2, 131.6, 130.4, 130.0, 128.7, 128.5, 128.5, 128.3, 127.8, 126.9, 126.5, 123.6, 70.1, 31.9, 29.9, 22.5, 13.8; AMM (ESI-TOF) m/z calculated for $C_{34}H_{31}O_3^+$ $[M + H]^+$ 487.2268, found 487.2283; IR (neat): 3058, 2956, 1915, 1659, 1277, 1153 cm^{-1}.



3-phenyl-1-(*o*-tolyl)prop-2-yn-1-ol **(226)**

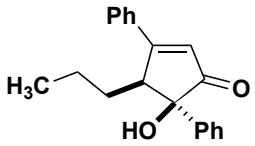
According to general procedure E, *n*-BuLi (16.6 mL, 33.203 mmol, 2.0 equiv, ~2.0 M in hexanes) was added dropwise to a 500 mL RBF containing a solution of allene precursor **216** (5.000 g, 16.601 mmol, 1.0 equiv) in dry THF (61.5 mL, 0.27 M) at -78 °C. After 2 hours, a solution of Weinreb amide **217** (3.291 g, 19.922 mmol, 1.2 equiv) in dry THF (24.9 mL, 0.8 M) was slowly added to the reaction, which was allowed to warm to room temperature overnight. At the completion of the reaction as determined by TLC, the reaction mixture was quenched with saturated aq. NH_4Cl. The aqueous layer was extracted three times with EtOAc. The combined organic extracts were washed with H_2O, brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. **226** was generated as a byproduct during the formation of **219**. The crude product was purified using flash column chromatography (SiO_2, 1:99 to 30:70, EtOAc:hexanes) to afford **226** as a yellow oil (0.373 g, 10%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (dd, J = 5.4, 3.7 Hz, 1H), 7.50 – 7.42 (m, 2H), 7.34 – 7.29 (m, 3H), 7.28 – 7.24 (m, 2H), 7.23 – 7.19 (m, 1H), 5.85 (d, J = 4.8 Hz, 1H), 2.51 (s, 3H), 2.16 (d, J = 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 136.1, 131.7, 130.8, 128.6, 128.5, 128.3, 126.6, 126.3, 122.5, 88.5, 86.5, 63.0, 19.0; AMM (ESI-TOF) m/z calculated for $C_{16}H_{15}O^+$ $[M + H]^+$ 223.1117, found 223.1118; IR (neat): 3587-3186 (bs), 3061, 2929, 2195, 1600, 1037 cm^{-1}.



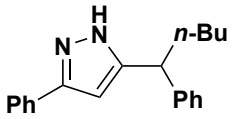
1-(2-pentylphenyl)-3-phenylprop-2-yn-1-ol **(227)**

According to general procedure E, *n*-BuLi (16.6 mL, 33.203 mmol, 2.0 equiv, ~2.0 M in hexanes) was added dropwise to a 500 mL RBF containing a solution of allene precursor **216** (5.000 g, 16.601 mmol, 1.0 equiv) in dry THF (61.5 mL, 0.27 M) at -78 °C. After 2 hours, a solution of Weinreb amide **217** (3.291 g, 19.922 mmol, 1.2 equiv) in dry THF (24.9 mL, 0.8 M) was slowly added to the reaction, which was allowed to warm to room temperature overnight. At the completion of the reaction as determined by TLC, the reaction mixture was quenched with saturated aq. NH_4Cl. The aqueous layer was extracted three times with EtOAc. The combined organic extracts were washed with H_2O, brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. **227** was generated as a byproduct during the formation of **219**. The crude product was purified using flash column chromatography (SiO_2, 1:99 to 30:70, EtOAc:hexanes) to afford **227** as a yellow oil (0.506 g, 11%). ^{1}H NMR (400 MHz, $CDCl_3$) δ7.77 (dd, J = 7.0, 2.1 Hz, 1H), 7.49 – 7.41 (m, 2H), 7.34 – 7.29 (m, 5H), 7.29 – 7.19 (m,1H), 5.90 (d, J = 4.5 Hz, 1H), 2.96 – 2.71 (m, 2H), 2.19 – 2.13 (m, 1H), 1.67 (p, J = 7.6 Hz, 2H), 1.46 – 1.29 (m, 4H), 0.98 – 0.82 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ140.7, 138.1, 131.7, 129.8, 128.6, 128.5, 128.3, 127.0, 126.3, 122.6, 89.1, 86.4, 62.4, 32.4, 32.0, 31.3, 22.6, 14.0; AMM (ESI-TOF) m/z calculated for $C_{20}H_{23}O^+$ $[M + H]^+$ 279.1743, found 279.1746; IR (neat): 3560-3201 (bs), 3061, 2927, 2195, 1601, 1030 cm^{-1}.

3.6.6 Applications

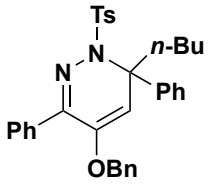


5-hydroxy-3,5-diphenyl-4-propylcyclopent-2-en-1-one **(282)** was synthesized following a modified literature procedure,[158] by preparing a solution of **219** (0.050 g, 0.131 mmol, 1.0 equiv) in anhydrous toluene (1.31 mL, 0.1 M). $Sn(OTf)_2$ (0.006 g, 0.014 mmol, 0.10 equiv) was then added and the mixture was heated to 80 °C for 11 hours. After the reaction was cooled to room temperature, the reaction was quenched with NEt_3 (0.05 mL, 0.393 mmol, 3.0 equiv). After letting the reaction stir for 5 minutes, the crude reaction mixture was filtered over silica with EtOAc and concentrated *in vacuo*. The crude product was purified using flash column chromatography (SiO_2, 5:95 to 15:85, EtOAc:hexanes) to afford **282** as an orange-yellow oil (0.025 g, >95:5 dr, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.63 (m, 2H), 7.56 – 7.45 (m, 3H), 7.45 – 7.36 (m, 2H), 7.34 – 7.20 (m, 3H), 6.65 (s, 1H), 3.68 (dd, J = 6.6, 4.5 Hz, 1H), 3.22 (s, 1H), 1.81 – 1.67 (m, 2H), 1.54 – 1.42 (m, 1H), 1.42 – 1.30 (m, 1H), 0.86 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.2, 177.7, 143.8, 133.2, 131.7, 129.2, 128.5, 127.5, 127.2, 124.6, 123.9, 82.3, 54.0, 33.1, 21.4, 14.3; AMM (ESI-TOF) m/z calculated for $C_{20}H_{21}O_2^+$ $[M + H]^+$ 293.1536, found 293.1539; IR (neat): 3530-3320 (bs), 3061, 2959, 1697, 1591, 1568, 1135, 1094, 1074 cm^{-1}.



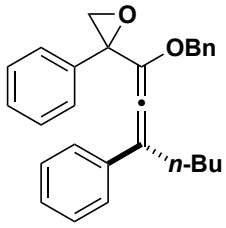
3-phenyl-5-(1-phenylpentyl)-1*H*-pyrazole **(276)** was synthesized following a modified literature procedure,[171] by preparing a solution of **219** (0.056 g, 0.131 mmol, 1 equiv.) in anhydrous ethanol (0.1 M). Hydrazine (50 µL, 1.307 mmol, 10 equiv.) was then added and the mixture was heated to 120 °C for 24 hours. The reaction was cooled to room temperature, diluted with diethyl ether (5 mL), washed with

H_2O (10 mL), washed with brine (10 mL), dried over sodium sulfate, concentrated *in vacuo*, and purified by flash column chromatography (SiO_2, EtOAc:hexanes) to afford **276** (0.027 g, 64%, as a 85:15 mixture of **276** and **277**) as a clear oil. NMR signals are reported for the major debenzoxylated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.34 (m, 3H), 7.31 – 7.26 (m, 4H), 7.26 – 7.22 (m, 3H), 6.43 (s, 1H), 4.58 (d, J = 11.0 Hz, 0H), 4.49 (d, J = 11.1 Hz, 0H), 3.99 – 3.91 (m, 1H), 2.17 – 2.05 (m, 1H), 2.05 – 1.93 (m, 1H), 1.37 – 1.20 (m, 5H), 0.86 (t, J = 7.1 Hz, 4H);^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3, 132.3, 128.7, 128.7, 127.9, 127.0, 126.8, 126.1, 125.6, 100.8, 65.2, 44.0, 35.4, 29.9, 22.6, 14.0; AMM (ESI-TOF) m/z calculated for $C_{20}H_{23}N_2^+$ $[M + H]^+$ 291.1856, found 291.1858; IR (neat): 3205, 2954, 2930, 1494, 1027 cm^{-1}.



4-(benzyloxy)-6-butyl-3,6-diphenyl-1-tosyl-1,6-dihydropyridazine **(278)** was synthesized following a modified literature procedure,[171] by preparing a solution of **219** (0.051 g, 0.131 mmol, 1 equiv.) in anhydrous ethanol (0.1 M). *N*-tosylhydrazine (0.243 g, 1.307 mmol, 10 equiv.) and glacial acetic acid (10μL, 0.157 mmol, 1.2 equiv.) were then added and the mixture was stirred at room temperature for 3 days. The reaction was then diluted with diethyl ether (5 mL), washed with H_2O (10 mL), washed with brine (10 mL), dried over sodium sulfate, concentrated *in vacuo*, and purified by flash column chromatography (SiO_2, 90:10, hexanes:EtOAc) to afford **278** (0.0734 g, 100%) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.65 (m, 2H), 7.44 – 7.39 (m, 2H), 7.36 – 7.25 (m, 11H), 7.23 – 7.19 (m, 2H), 7.07 (d, J = 8.1 Hz, 2H), 4.84 – 4.72 (m, 2H), 4.57 (s, 1H), 3.18 – 3.06 (m, 1H), 2.35 (s, 3H), 1.88 – 1.76 (m, 1H), 1.61 – 1.38 (m, 4H), 0.93 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.4, 143.2, 142.4, 139.9, 136.4, 135.9, 133.8, 128.9, 128.6, 128.6, 128.5, 128.4, 128.0, 127.9, 127.7, 127.6,

126.8, 107.3, 69.1, 69.1, 60.4, 39.7, 27.1, 22.9, 21.5, 14.2; AMM (ESI-TOF) *m/z* calculated for $C_{34}H_{35}N_2O_3S^+$ $[M + H]^+$ 551.2363, found 551.2373 IR (neat): 3061, 2958, 1701, 1597, 1359, 1171 cm^{-1}.

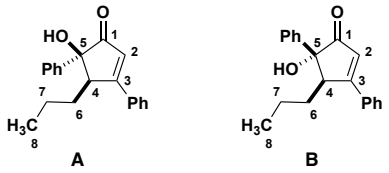


2-(1-(benzyloxy)-3-phenylhepta-1,2-dien-1-yl)-2-phenyloxirane **(289)** was synthesized following a modified literature procedure.[168] In a 7 mL flame-dried vial, NaH (0.008 g, 0.197 mmol, 1.5 equiv, 60% by weight) and Me_3SI (0.032 g, 0.157 mmol, 1.2 equiv) were suspended in dry THF (0.26 mL, 0.5 M) and dry DMSO (0.26 mL, 0.5 M). The reaction was then cooled to 0 °C and **219** (0.050 g, 0.131 mmol, 1.0 equiv) was added. The resulting mixture was stirred at 0 °C for 30 minutes, then allowed to warm to room temperature and stirred overnight. At the completion of the reaction as determined by TLC, the reaction mixture was quenched with H_2O. The aqueous layer was extracted three times with EtOAc. The combined organic extracts were washed with H_2O, brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified using flash column chromatography (Basic Al_2O_3, 1:99 to 30:70, EtOAc:hexanes) to afford **289** as a yellow oil (0.042 g, 60:40 dr, 81%). ^1H NMR signals are a complex, overlapping mixture of diastereomers and are reported for informational purposes normalized to the major isomer. ^1H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.42 (m, 3H), 7.33 – 7.19 (m, 22H), 4.77 – 4.68 (m, 3H), 3.47 (d, *J* = 5.9 Hz, 1H), 3.40 (d, *J* = 5.9 Hz, 1H), 2.96 (d, *J* = 5.9 Hz, 1H), 2.90 (d, *J* = 5.9 Hz, 1H), 2.42 – 2.27 (m, 3H), 1.39 – 1.15 (m, 10H), 0.86 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.7, 137.8, 137.6, 136.7, 132.6, 128.3, 128.0, 127.6, 127.6, 127.4, 126.8, 126.2, 121.4, 70.6, 60.6, 54.8, 31.7, 30.1, 22.6, 14.0; AMM (ESI-TOF) *m/z* calculated for $C_{28}H_{29}O_2^+$ $[M + H]^+$ 397.2162, found 397.2163; IR (neat): 3060, 2927, 1939, 1495, 1165, 1119 cm^{-1}.

3.6.7 Computational Methods and Data

Computed ^{1}H and ^{13}C chemical shifts were produced for the diastereomers that may arise from the methodology described in the manuscript to provide stereochemical information for product **282**. All significantly contributing conformers were located by scanning rotatable bonds using 30 degree intervals. All conformers found to be > 3.0 kcal/mol than the lowest energy conformer were deemed statistically insignificant in their contributions to the computed chemical shifts of the molecule. Computed chemical shifts were determined using *Gaussian16* on all energetically relevant conformers. Geometry optimizations for computed chemical shifts were conducted at the B3LYP/6-31+G(d,p) level of theory in gas phase unless otherwise indicated. Computed chemical shifts were then determined from the optimized structure using the GIAO method at the B3LYP/6-311+G(2d,p) level of theory in chloroform (SCRF). Computed chemical shifts were empirically scaled using the appropriate scaling factors, compiled by Rablen *et al.*, and made available on the cheshirenmr.info website. Empirical scaling using such methods were shown to reduce systematic error resulting from a variety of sources and is all delineated in this review.[160]

Compound 282:



^{1}H and ^{13}C chemical shifts were computed for the lowest energy conformers of compound **A** and **B**. The computed chemical shifts of each diastereomer was then scaled using the procedure described in the computational NMR methods section using $CHCl_3$ as implicit solvent whenever indicated. Computed ^{1}H and ^{13}C chemical shifts for **A** and **B** were compared with all the assignable observed chemical shifts for **282** (obtained in $CDCl_3$) (Tables 1–4). Computed chemical shifts of chemically equivalent atoms were

averaged prior to comparison with experimental shifts. Computed ^{1}H and ^{13}C chemical shifts for diastereomer **A** more consistently matched with the experimental data than computed chemical shifts for diastereomer **B**. Deviations of greater than 0.3 ppm are highlighted for Tables 1 and 2. Furthermore, through optimization calculations, **A** was determined to be the lower energy diastereomer. Based on these determinations, we concluded that **A** most likely depicted the correct relative stereochemistry of **282**.

Table A–^{1}H. Computed ^{1}H chemical shifts for **A**

H #	Scaled Computed Chemical Shifts	Experimental Chemical Shifts
2	6.42	6.65
4	3.45	3.68
6'	1.40	1.37
6"	1.48	1.48
7	1.55	1.73
8	0.85	0.86

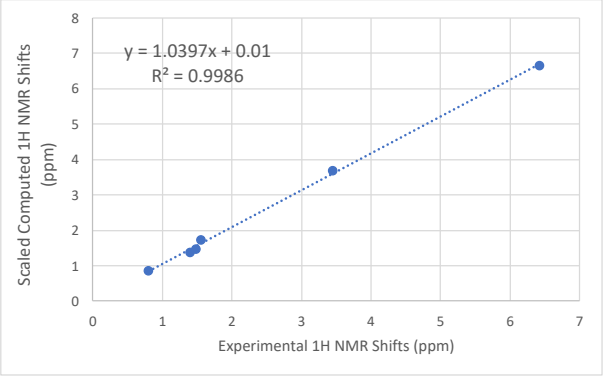


Figure A–^{1}H. Correlation graph for computed ^{1}H chemical shift of **A** and experimental ^{1}H shifts.

Table A–^{13}C. Computed ^{1}H chemical shifts for **B**

C #	Scaled Computed Chemical Shifts	Experimental Chemical Shifts
1	203.1	208.2
3	182.6	177.7
4	59.1	54.0
5	81.5	82.3
6	36.0	33.1
7	25.3	21.4
8	13.3	14.3

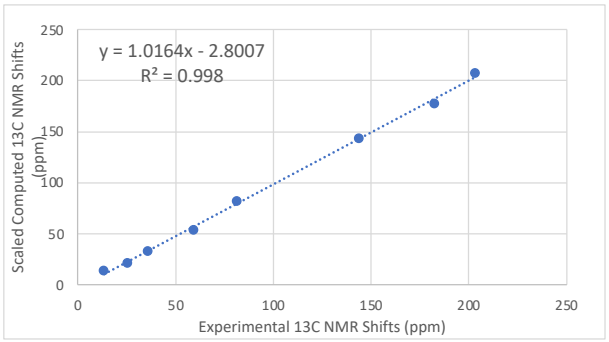


Figure A–^{13}C. Correlation graph for computed ^{13}C chemical shift of **A** and experimental ^{13}C shifts.

Table B–^{1}H. Computed ^{13}C chemical shifts for **A**

H #	Scaled Computed Chemical Shifts	Experimental Chemical Shifts
2	6.22	6.65
4	3.49	3.68
6'	0.87	1.37
6"	1.58	1.48
7	1.20	1.73
8	0.46	0.86

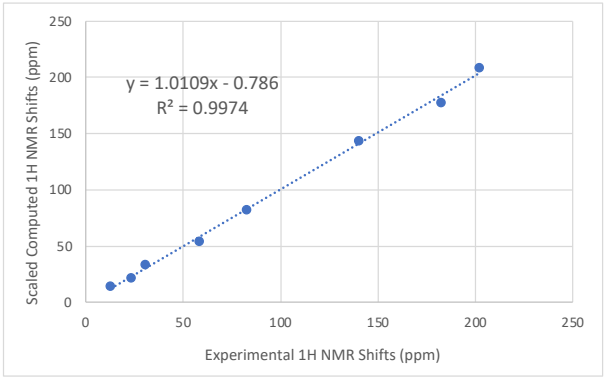


Figure B–^{1}H. Correlation graph for computed ^{1}H chemical shift of **B** and experimental ^{1}H shifts.

Table B–^{13}C. Computed ^{13}C chemical shifts for **B**

C #	Scaled Computed Chemical Shifts	Experimental Chemical Shifts
1	201.9	208.2
3	182.7	177.7
4	58.2	54.0
5	82.9	82.3
6	30.6	33.1
7	23.4	21.4
8	12.9	14.3

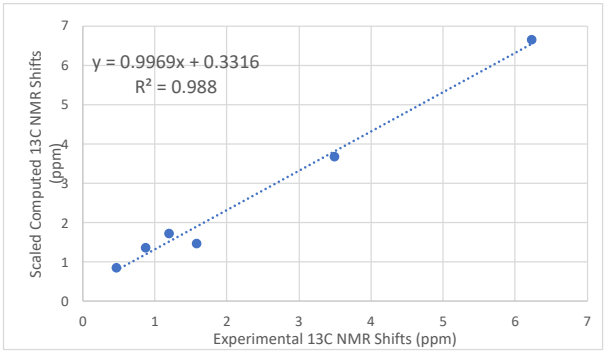


Figure B–^{13}C. Correlation graph for computed ^{13}C chemical shift of **B** and experimental ^{13}C shifts.

Computed Coordinates and Energies:

282 (A)

G16 optfreq B3LYP/6-31G(d,p) gas-phase

Sum of electronic and thermal Free Energies = –924.344933 hartrees

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Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-1.256606	0.408753	0.712023
2	6	0	0.100549	0.638686	-0.031824
3	6	0	1.053009	-0.340354	0.653068
4	6	0	0.513509	-0.886727	1.769410
5	1	0	-0.006034	0.367415	-1.085543
6	1	0	0.990877	-1.582430	2.446781
7	6	0	-0.835192	-0.391451	1.974666
8	8	0	-1.554315	-0.490829	2.953294
9	6	0	2.402952	-0.617655	0.137918
10	6	0	3.414217	-1.098234	0.989920
11	6	0	2.711966	-0.427838	-1.220007
12	6	0	4.681939	-1.385340	0.499472
13	1	0	3.209426	-1.227838	2.045902
14	6	0	3.979346	-0.726787	-1.711054
15	1	0	1.954997	-0.060416	-1.901557

16	6	0	4.968781	-1.204682	-0.854211
17	1	0	5.449659	-1.746855	1.174348
18	1	0	4.194181	-0.583242	-2.764015
19	1	0	5.958198	-1.430090	-1.236072
20	8	0	-1.848143	1.621146	1.151587
21	1	0	-2.295639	1.413881	1.986436
22	6	0	-2.248981	-0.427035	-0.111062
23	6	0	-3.581066	-0.020531	-0.225062
24	6	0	-1.857975	-1.618058	-0.739405
25	6	0	-4.498615	-0.778198	-0.952962
26	1	0	-3.895307	0.901373	0.245981
27	6	0	-2.774572	-2.375096	-1.464456
28	1	0	-0.834342	-1.966416	-0.663197
29	6	0	-4.100833	-1.958352	-1.574971
30	1	0	-5.526289	-0.440239	-1.032868
31	1	0	-2.450983	-3.293234	-1.942861
32	1	0	-4.814322	-2.548200	-2.139734
33	6	0	0.627360	2.090793	0.032097
34	1	0	0.514855	2.465894	1.053004
35	1	0	1.700448	2.079791	-0.184421
36	6	0	-0.064272	3.042579	-0.951810
37	1	0	0.071769	2.662890	-1.972143
38	1	0	-1.139561	3.046547	-0.757503

39	6	0	0.478274	4.470973	-0.863660
40	1	0	1.553095	4.504178	-1.072164
41	1	0	-0.019362	5.129000	-1.582443
42	1	0	0.321264	4.892780	0.134491

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282 (B)

G16 optfreq B3LYP/6-31G(d) gas-phase

Sum of electronic and thermal Free = –924.341438 hartrees

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	1.093987	-0.604796	-1.017609
2	6	0	-0.208691	0.251589	-0.867731
3	6	0	-1.233549	-0.748610	-0.319182
4	6	0	-0.767589	-2.022476	-0.327269
5	1	0	-1.336612	-2.913464	-0.089357
6	6	0	0.575169	-2.062133	-0.896703
7	8	0	1.206331	-3.017426	-1.319623
8	6	0	-2.602477	-0.372598	0.072836
9	6	0	-3.257660	-1.054895	1.114107
10	6	0	-3.299731	0.645314	-0.602881

11	6	0	-4.565247	-0.731609	1.466387
12	1	0	-2.725138	-1.827606	1.659945
13	6	0	-4.612414	0.958959	-0.257248
14	1	0	-2.820278	1.175003	-1.419840
15	6	0	-5.248301	0.274886	0.780204
16	1	0	-5.050789	-1.262915	2.279472
17	1	0	-5.139099	1.738889	-0.798877
18	1	0	-6.268497	0.526136	1.054266
19	8	0	1.625505	-0.440633	-2.324121
20	1	0	2.056244	-1.288977	-2.529431
21	6	0	2.165637	-0.368929	0.057702
22	6	0	3.425175	0.116910	-0.309793
23	6	0	1.929679	-0.664089	1.409721
24	6	0	4.420981	0.315019	0.648614
25	1	0	3.614157	0.338264	-1.353813
26	6	0	2.924653	-0.467080	2.366542
27	1	0	0.965669	-1.055013	1.720717
28	6	0	4.175769	0.024543	1.990020
29	1	0	5.391365	0.695391	0.342110
30	1	0	2.722335	-0.703723	3.407278
31	1	0	4.951525	0.175046	2.735022
32	1	0	-0.505372	0.487510	-1.900160
33	6	0	-0.098511	1.581065	-0.098703

34	1	0	-1.106372	1.961911	0.100166
35	1	0	0.357937	1.407709	0.881811
36	6	0	0.695287	2.653240	-0.857802
37	1	0	0.216078	2.832820	-1.830057
38	1	0	1.700673	2.280400	-1.080949
39	6	0	0.796554	3.969799	-0.082554
40	1	0	1.351994	4.723676	-0.649620
41	1	0	-0.195439	4.382156	0.136037
42	1	0	1.312614	3.826615	0.873285

Gaussian Reference:

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Appendix A1

Progress Towards the Asymmetric Total Synthesis of Phayomphenol A1

A1.1 Introduction

Phayomphenol A1(**1**) was isolated in 2012 from the bark of *Shorea roxburghii*, an abundant species of tree found in Thailand and surrounding countries (Figure 1).[1,2] The bark of this plant has historically been used as an astringent, a beverage preservative, and as a treatment for dysentery, diarrhea, and cholera. The methanol extract of this bark was analyzed and several common resveratrol oligomer natural products were isolated: hopeaphenol, isohopeaphenol, hemsleyanol D, ampelopsin H, vaticanols, and *alpha*-viniferin, among others. This class of natural products has been studied extensively and several of these compounds have been synthesized.[3–6] Typically, this class of natural products contains benzodihydrofuran-based scaffolds, which is why the discovery of an isochroman-containing resveratrol oligomer is of interest. Furthermore, the crude isolate of *Shorea roxburghii* has been studied for its anti-hyperlipidemic effects, demonstrating modest activity.[1] Phayomphenol A1 has also been tested for anti-cancer activity but showed negligible potency.[7] Having a robust synthetic route to this natural product scaffold would enable further studies and structure activity relationship elucidation. Given the success of the methods and protocols used in the total synthesis of panowamycin A and B, TM-135, and veramycin F (see Chapter 2 of this dissertation), it was clear that other isochroman-based natural products would also be attractive synthetic targets. As such, we conceived that polyphenolic natural product (**1**) could be synthesized by C–H insertion using a donor/donor carbene to stereoselectively construct the isochroman core.

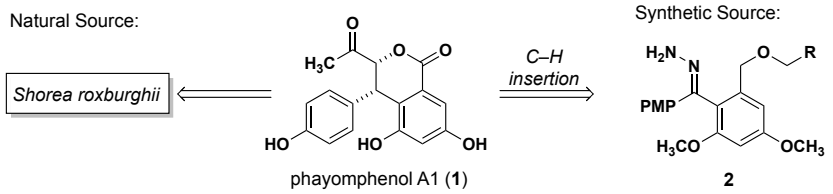


Figure 1. Natural origin of phayomphenol A1 and its potential total synthesis

A1.2 Progress Towards the Total Synthesis of phayomphenol A1

Based on the efforts detailed in Chapter 2 of this dissertation, we imagined that using a similar strategy based on the Wacker oxidation of a terminal olefin would be a robust method to furnish methyl ketone required for phayomphenol A1 (Figure 2). Global methyl deprotection (e.g. with boron tribromide) of isochromanone **3** would access the natural substance. Wacker oxidation of terminal olefin of vinyl-isochroman **4** would furnish the requisite acetyl-substituted isochroman and PCC oxidation of the benzylic position would generate the lactone moiety. As mentioned above, a C–H insertion reaction using an aryl/aryl (donor/donor) carbene would be a useful method to stereoselectively construct the isochroman core of **4** from hydrazone precursor **5**. Furthermore, we have demonstrated that insertion into an activated allylic C–H bond is typically a highly enantioselective, diastereoselective, and high-yielding process, making this an attractive strategy (see Chapter 1 of this dissertation). However, this route suffers from one main difficulty: previous work in the lab has shown that di-*ortho*-substituted ketones and hydrazones are difficult to synthesize. Given other contemporaneous advances in the lab by graduate students Jack Shiue and Matt Dyer pertaining to the synthesis of hindered hydrazones, it was decided that this total synthesis was plausible.

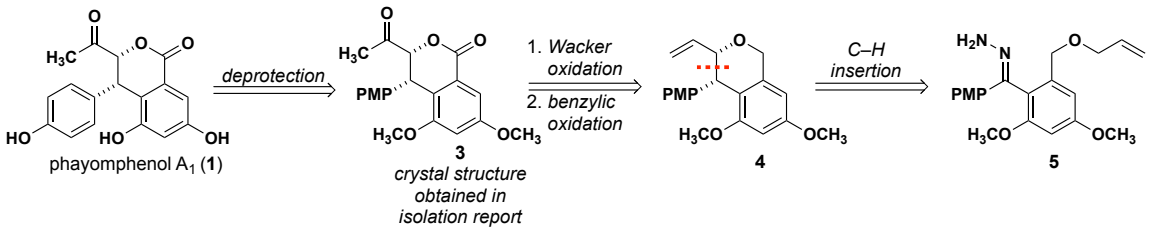


Figure 2. Retrosynthetic strategy for the total synthesis of phayomphenol A1

The synthesis of the benzyl, allyl ether **9** was achieved in a straightforward manner. Commercially available benzoic acid **6** was reduced in high yield to afford benzyl alcohol **7** (Figure 3). With one equivalent of *N*-bromosuccinimide, brominated arene **8** was afforded in 99% yield. Iodination of this substrate with *N*-iodosuccinimide was also achieved in high yield (95%) (not shown). Alkylation of this synthetic intermediate was achieved under typical conditions with allyl bromide to generate **9** in high yield.

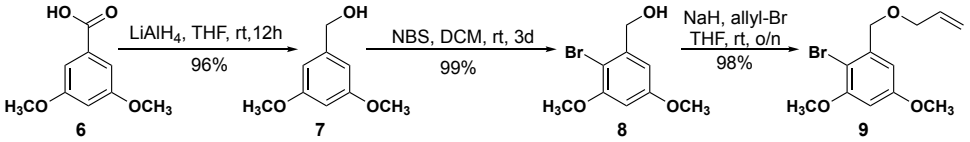


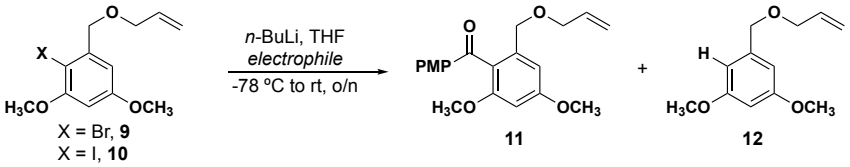
Figure 3. Synthesis of the allyl benzyl ether intermediate

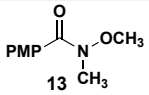
A1.2.1 Ketone formation optimization

Based on precedent within the group, it was expected that the synthesis of the requisite ketone **10** would require some optimization (Table 1). Due to the ease of preparation of both bromo- and iodo-arenes, both were screened in the optimization of the ketone synthesis. The usual ketone formation conditions were not suitable for this substrate (entries 1 and 2). Lithium halogen exchange followed by addition of Weinreb benzamide electrophile (**13**) afforded only the proto-debromination product **12** after quenching the reaction mixture. This indicated that lithium halogen exchange was quantitative, but no addition to the Weinreb amide occurred. More reactive electrophiles **14** and **15** were attempted next. We hypothesized that the steric hindrance about the nucleophile would disfavor double addition to acid chloride **14**. We also thought that addition to aldehyde followed by an oxidation of the resultant benzylic alcohol would furnish **11** in a straightforward manner. Entry 3 contained the best ratio of **11** to **12** when compared to its iodo-analogue (entry 4), and after purification, the reaction afforded ketone **11** in 82%

yield. A scale-up of the procedure increased this yield to 96%. Nucleophilic addition to **15** did not produce any products identifiable as the desired benzylic alcohol (entries 5-6).

Table 1. Ketone formation optimization



entry	X	electrophile	11:12	yield
1	Br	 **13**	<5:95	ND
2	I	**13**	<5:95	ND
3	Br	 **14**	76:24	74 (96)[a]
4	I	**14**	45:55	ND
5	Br	 **15**	ND	ND
6	I	**15**	ND	ND

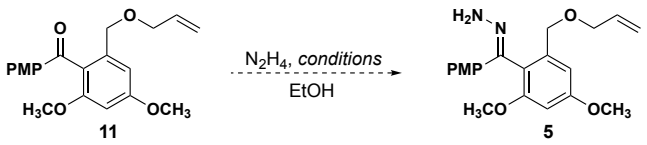
[a] reaction conducted on 2 g (~8 mmol) scale

A1.2.2 Attempts at Hydrazone Formation

With a reliable and high-yielding four-step sequence to produce **11**, the feasibility of the hydrazone synthesis was then tested. Exposure of the substrate to the usual condensation conditions with hydrazine and acetic acid at room temperature showed no conversion to hydrazone. Heating of this mixture for five hours at 100 °C was also ineffective (entry 2). Heating to 140 and 170 °C overnight in a microwave reactor only resulted in the reduction of the pendant alkene to the corresponding *n*-propyloxy benzyl ether (entries 3 and 4). Exploring other ways to activate the hindered ketone, several Lewis and Brønsted acids were employed. Two different sources of scandium triflate were used; one was an older bottle and one was unopened (entries 5 and 6). In both circumstances, hydrazone **5** was not formed at room temperature. With the newer source of scandium triflate at elevated temperature, only alkene reduction was observed.

When boron trifluoride diethyl etherate was employed, no conversion was observed at room temperature and alkene reduction was observed at elevated temperatures (50 °C). Brønsted acids were screened as well. Triflic acid, camphorsulfonic acid, *para*-toluenesulfonic acid and trifluoroacetic acid were all individually added to ketone **11** at room temperature and allowed to stir for 5 hours (entries 8-11). By TLC, no conversion was observed; magnesium sulfate was added as a drying agent and the mixture was stirred for an addition 2 hours. Still, no conversion was observed and the mixture was heated to 90 °C overnight. TLC showed significant amounts of the alkene reduction product in all circumstances except entry 8. This reaction was subsequently heated to 120 °C for another 5 hours, at which point reduction of the alkene was observed. Finally, the condition using acetic acid was repeated, but with hexafluoroisopropanol (HFIP) as the solvent (entry 12). A purple color change was observed, but no conversion to hydrazone **5** was observed after 24 hours at 50 °C.

Table 2. Attempted optimization of hydrazone formation



entry	temperature (°C)	time (h)	acid	result
1	rt	5	AcOH	no conversion
2	100	5	AcOH	no conversion
3	140	18	AcOH	alkene reduction
4	170	12	AcOH	alkene reduction
5	rt to 90	24	$Sc(OTf)_3$[a]	no conversion
6	rt to 90	24	$Sc(OTf)_3$[b]	alkene reduction
7	rt to 50	24	$BF_3 \bullet OEt_2$	alkene reduction
8	60 to 120	48	TfOH[c]	alkene reduction
9	rt to 90	24	CSA[c]	alkene reduction
10	rt to 90	24	*p*TSA[c]	alkene reduction
11	rt to 90	24	TFA[c]	alkene reduction
12	rt to 50	24	AcOH and HFIP	no conversion

[a]older bottle of Lewis acid used, [b] fresh bottle of Lewis Acid used [c] $MgSO_4$ added before heating

While these screening efforts have laid the basis of reactivity and susceptibility for ketone **11**, these conditions may need only slight optimizations to be productive. Graduate student coworkers Jack Shiue and Matt Dyer have had success with more specialized conditions involving drying agents. In any future exploration of this synthesis, one should consider using drying agents, in addition to exploring more oxophilic Lewis acids such has titanium tetrachloride, aluminum trichloride, cerium trichloride, or even zirconium tetrachloride.[8]

Alternatively, this total synthesis would be aided by a new method for the construction of hindered benzophenone hydrazones that is orthogonal to condensation reactions. As new methodology is reported in the literature, it could be straightforward to apply it in the synthesis of phayomphenol A1. For example, Livingstone and coworkers report a transition-metal-free method utilizing aryl boronic acids and hydrazonoyl chlorides to construct diaryl hydrazones; however this strategy requires the use of phenylhydrazine, which is not suitable for our purposes (Figure 4A).[9] This method could potentially be modified to afford the construction of our desired hydrazone from different starting materials, perhaps circumventing the steric and electronic challenges with the current approach. Similarly, Studer and coworkers report a method utilizing Togni's reagent to construct aryl/trifluoromethyl hydrazones; however this method requires the use of dimethylhydrazones, which are again not suitable for our purposes (Figure 4B).[10] By modifying the hypervalent iodide reagent and the hydrazone precursor, it is possible that we could modify the protocol for the synthesis of our desired diaryl hydrazone. A report by Horner and coworkers shows the preparation of acyl/aryl hydrazone **26** when hydrazone derivative **25** is treated with peroxyacetic acid, and this procedure could reasonably be applied towards the synthesis of **5** (Figure 4C).[11] Finally, Micouin and coworkers report the use of alkynyl aluminum reagents and trimethylsilyldiazomethane to afford hydrazones (**31**); this method could potentially be modified to produce **5** from aryl aluminum reagent **32** and diazo **33** (Figure 4D).[12]

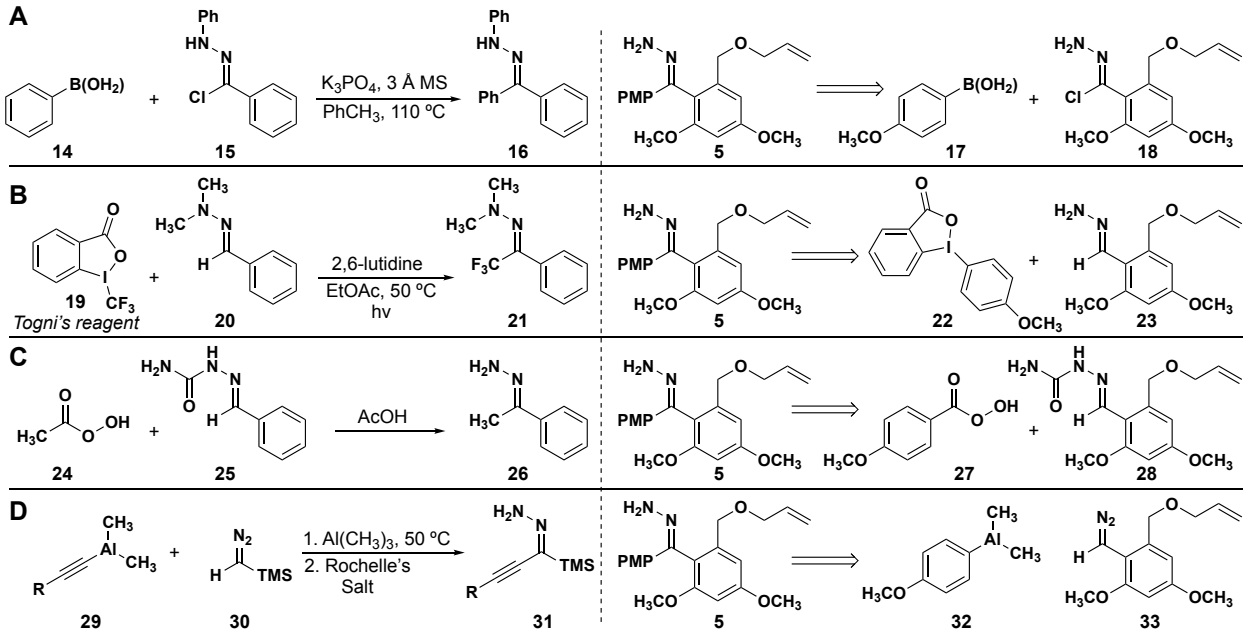


Figure 4. Alternative methods for the synthesis of hydrazone intermediates

A1.3 Conclusions

In conclusion, we have developed a high yielding and robust synthesis of ketone **11** but have been unable to form the hydrazone **5** (Figure 5). This is likely due to the steric hindrance of the substrate and the high degree of electron donation into the ketone from the adjacent aryl rings, making it a poor electrophile in a condensation reaction. The C–H insertion reaction to form **4** may also be problematic due to the steric hindrance of the substrate, but preliminary results in the group from Jack Shiue suggest the that the protocol may work if the oxidation of the hydrazone is successful. Subsequent PCC and Wacker oxidation steps are likely to be successful based on their similarity to the analogous reactions used in the total synthesis of panowamycins, TM-135, and veramycin F (see chapter 2 of this dissertation). This would furnish the methylated phayomphenol A1 (**3**) that was reported in the original isolation paper and for which a crystal structure was obtained. A global phenolic ether deprotection would then afford phayomphenol A1 (**1**) in 9 steps from commercially available 3,5-dimethoxybenzoic acid **6**. If the synthesis is successful, the anti-hyperlipidemic properties of this substance may be tested by a

collaborator. This information will be of interest to the broader scientific community because the properties of phayomphenol A1 have only been assessed as a component of the *Shorea roxburghii* extract and not as an individual compound.

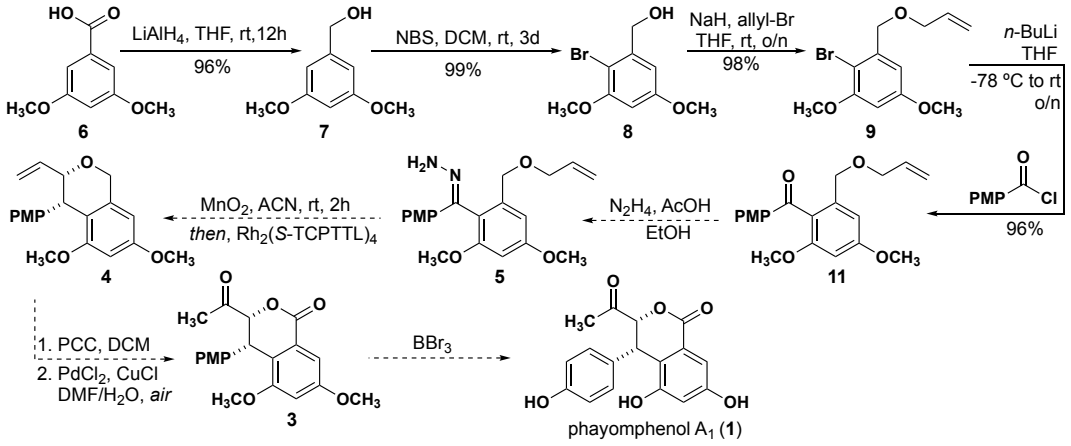
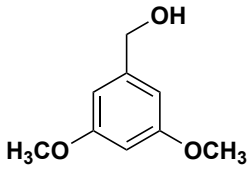
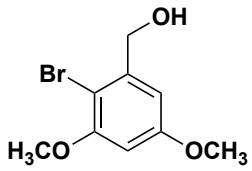


Figure 5. Summary of progress towards the total synthesis of phayomphenol A1

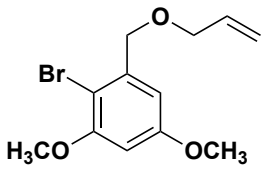
A1.4 Experimental Section



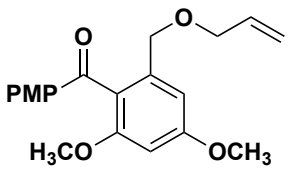
(3,5-dimethoxyphenyl)methanol (**7**) was synthesized following a modified literature procedure,[13] by preparing a suspension of lithium aluminum hydride (1.567 g, 41 mmol, 1.5 equiv) in THF (0.5 M) and cooling the mixture to 0 °C. 3,5-dimethoxybenzoic acid (5.021 g, 27 mmol, 1 equiv) was then added dropwise to the suspension as a solution in diethyl ether (1 M). The mixture was allowed to stir to room temperature overnight and the Fieser workup was conducted: water (1.5 mL) was added dropwise at 0 °C with stirring for 15 minutes, 10% aqueous NaOH (1.5 mL) was added with stirring for 15 minutes, the ice bath was removed, water (4.5 mL) was added with stirring for 10 minutes, magnesium sulfate was generously added with stirring for 30 minutes, the mixture was filtered, and concentrated *in vacuo* to afford **7** (4.464 g, 96%) as a white solid without further purification. BDB-IV-183



(2-bromo-3,5-dimethoxyphenyl)methanol (**8**) was synthesized following a modified literature procedure,[14] by preparing a solution of **7** (1.012 g, 6 mmol, 1 equiv) in DCM (0.4 M) and cooling to 0 °C. *N*-Bromosuccinimide (1.058 g, 6 mmol, 1 equiv) was then added portionwise over 30 minutes, allowing to stir to room temperature overnight. The reaction mixture was quenched with sat. aq. sodium bicarbonate (10 mL), diluted with water (10 mL), extracted with DCM (15 mL x 3), washed with sat. aq. sodium bicarbonate (25 mL), dried over magnesium sulfate, and concentrated *in vacuo* to afford **8** (1.484 g, 99%) as a white solid without further purification. BDB-IV-184



1-((allyloxy)methyl)-2-bromo-3,5-dimethoxybenzene (**9**) was synthesized following a modified literature procedure,[15] by preparing a suspension of sodium hydride (0.735 g, 18 mmol, 3 equiv) in THF (0.8 M) and **8** (1.484 g, 6 mmol, 1 equiv) was added dropwise as a solution in THF (0.3 M). Afterin stirring at room temperature for 1 hour, allyl bromide (0.8 mL, 9 mmol, 1.5 equiv) was added and the mixture was stirred overnight. The reaction was then quenched with sat. aq. ammonium chloride (20 mL), extracted with ethyl acetate (25 mL x 3), washed with brine (20 mL), dried over sodium sulfate, concentrated *in vacuo*, and purified by flash column chromatography (100% H to 90H:10EtOAc) to afford **9** (1.682 g, 98%) as a clear oil. BDB-IV-189



(2-((allyloxy)methyl)-4,6-dimethoxyphenyl)(4-methoxyphenyl)methanone (**11**) was prepared by following a modified literature procedure,[15] by preparing a solution of **9** (1.248 g, 4 mmol, 1 equiv) in THF (0.27 M) and cooling the mixture to –78 °C. *n*-BuLi (2.55 mL, 5.4 mmol, 1.3 equiv) was then added and the mixture was stirred for 2 hours at –78 °C before adding 4-methoxybenzoyl chloride (0.68 mL, 5 mmol, 1.2 equiv) to the mixture dropwise. The reaction was allowed to stir to room temperature overnight, quenched with sat. aq. ammonium chloride (15 mL), extracted with ethyl acetate (10 mL x 3), washed with brine (20 mL), dried over sodium sulfate, concentrated *in vacuo*, and purified by flash column chromatography (70H:30EtOAc) to afford **11** (1.365 g, 95%) as a yellow oil. BDB-V-146

A1.5 References

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Appendix A2

Exploration and Feasibility of New C–H Insertion Substrates

A2.1 Stereoselective C–H Insertion Reactions into Chiral Centers to form Isochromans

In our efforts to study donor/donor carbene insertion reactions into C–H bonds located on stereogenic centers,[1] we were interested in expanding these experiments from five-membered rings into six-membered rings. As detailed in Chapter 1 of this dissertation, the six-membered ring substrates demonstrate perfect diastereoselectivity in C–H insertion reactions when using achiral starting materials (i.e. >95:5 dr). As such, we were curious as to whether the diastereoselective outcomes for these substrates would differ from the corresponding five-membered ring substrates. In analogy to the substrates studied in the our recent publication,[1] a small group of benzophenone hydrazone substrates were synthesized in a straightforward sequence (Figure 1).

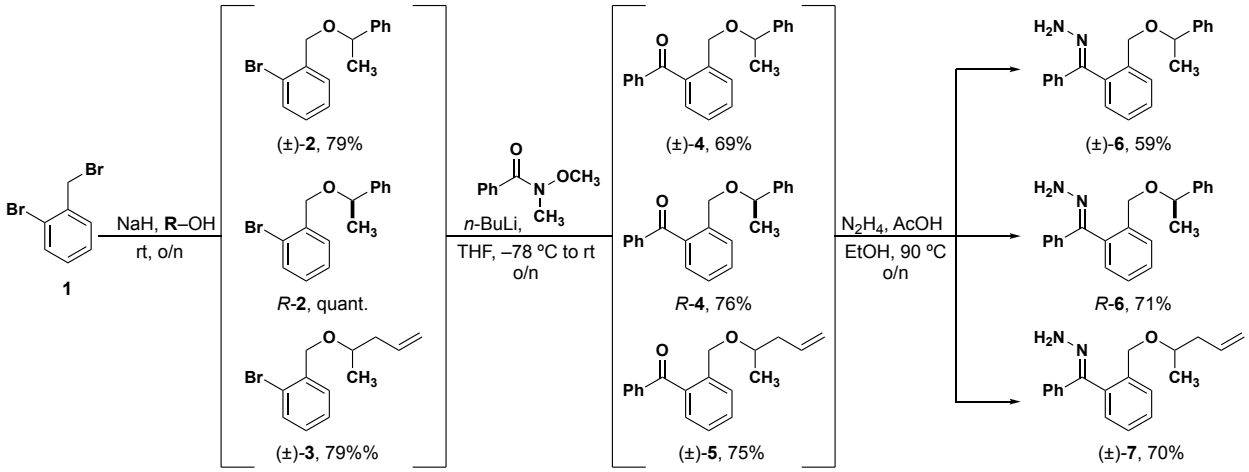
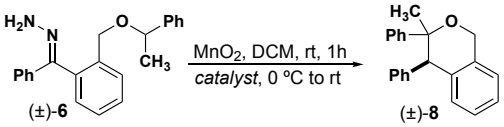


Figure 1. Synthesis of hydrazone substrates featuring stereogenic insertion sites

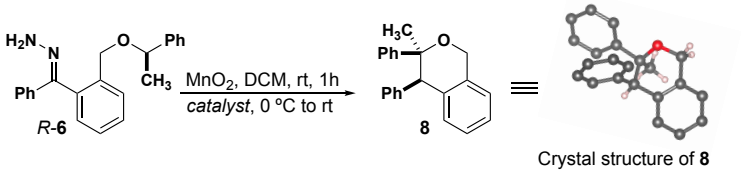
In concert with the work published by Dishman et al.,[1] chiral and achiral catalysts were used to synthesize the six-membered ring heterocycles **8** and **9**. Entries 1 and 2 show that bulky, racemic substrates are subject to high diastereoselectivity *via* catalyst control, but the products remain racemic. Entries 3-5 again confirm that enantiopure starting materials retain their enantiomer configuration and are highly

diastereoselective. Entries 7 and 9 demonstrate that substrates with less steric bulk are less influenced by the catalyst, giving no diastereoselectivity and affording racemic products. As noted in previous efforts (see chapter 1 of this dissertation), $Rh_2(mes)_4$ is largely ineffectual as an achiral catalyst, giving poor yields of the isochroman products and complex reaction mixtures. $Rh_2(PTCC)_4$ has been identified as a far superior catalyst in terms of production of byproducts and reaction yield. These results were tabulated as preliminary information for the submission of an NIH research proposal and are not published.

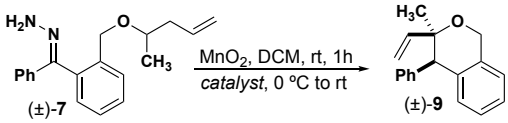
Table 1. C–H insertion reactions using six-membered ring substrates with stereogenic insertion sites



entry	catalyst	dr	er	yield (%)
1	$Rh_2(R\text{-PTAD})_4$	95:5	50:50	93
2	$Rh_2(PTCC)_4$	95:5	50:50	86



entry	catalyst	dr	er	yield (%)
3	$Rh_2(R\text{-PTAD})_4$	97:3	1:99	99
4	$Rh_2(S\text{-PTAD})_4$	96:4	0:100	98
5	$Rh_2(PTCC)_4$	97:3	0:100	81
6	$Rh_2(mes)_4$	NA	NA	NA



entry	catalyst	dr	er	yield (%)
7	$Rh_2(R\text{-PTAD})_4$	50:50	48:52	51[a]
8	$Rh_2(S\text{-PTAD})_4$	50:50	ND	ND
9	$Rh_2(PTCC)_4$	50:50	50:50	30[a]
10	$Rh_2(mes)_4$	NA	NA	NA

[a] yield of the less polar isomer (i.e. first compound off of the column)

A2.2 Homobenzylic Insertion Sites and the Reversal of Diastereoselectivity

In our continued efforts to seek out applications for our C–H insertion methodology, we came across the drug candidate TRXE-002-01 (**1**), or Cantrixil™ (Figure 2).[2,3] This drug is currently under development with Swedish pharmaceutical company Vivesto (recently acquired from Kazia therapeutics in 2021) and is in phase II clinical trials for the treatment of ovarian, fallopian, and primary peritoneal cancers. This molecule features a benzopyran core; although never attempted in the group, we were curious to see if this scaffold could be stereoselectively synthesized by C–H insertion using a donor/donor carbene. This strategy would require the reaction to proceed with selectivity for 1,6-insertion, rather than 1,5-insertion. It was imagined that due to the increased donation of the tri-alkoxy aryl group, benzylic C–H insertion would be competitive.

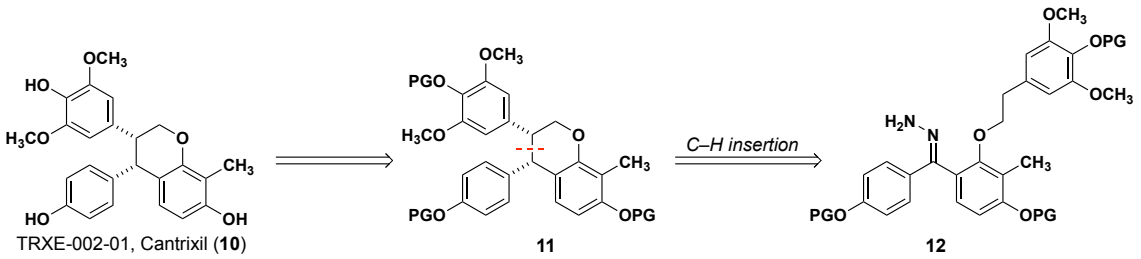


Figure 2. Retrosynthetic analysis of TRXE-002-01; donor/donor carbene C–H insertion strategy

In order to explore the feasibility of the 1,6-insertion, two test substrates were constructed based on ease and speed of preparation: a phenethyl substrate **15** and a dimethoxyphenethyl substrate **18**. These intermediates were synthesized in a straightforward manner, affording hydrazones in high yields (Figure 3). When subjected to the typical one-pot sequential C–H insertion conditions, it was quickly identified that the substrates had undergone the more favorable 1,5-insertion pathway to form **16** without any observed 1,6-insertion products (**19**).

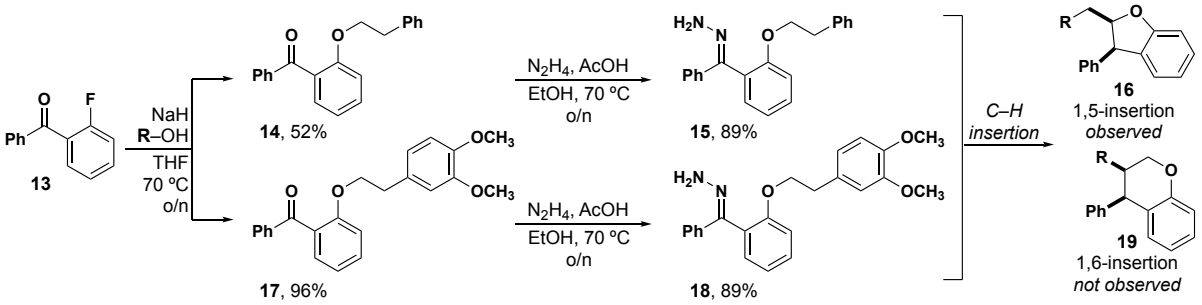
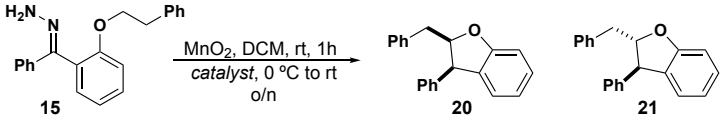


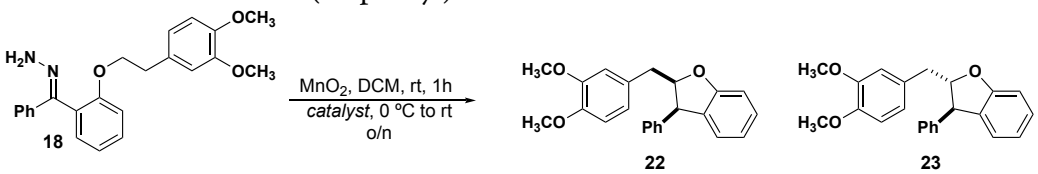
Figure 3. Synthesis of homobenzylic insertion site substrates

Several catalysts were screened for the potential to alter the regioselectivity of the reaction and some unexpected effects were observed (Table 2). While we were not able to increase any selectivity for 1,6-insertion, we did see a pronounced change in diastereoselectivity for the five-membered ring insertion products **20** and **22**. When comparing between reactions using phthalimidated catalyst Rh_2(*S*-TCPTTL)$_4$ (entry 2) and cyclopropane-based catalyst Rh_2(*S*-BTPCP)$_4$ (entry 4), we observed a flip in the selectivity for *cis* and *trans* isomers. These results were considered to be an interesting test of the Quantitative Structure-Selectivity Relationship (QSSR) model that Lucas Souza and the lab of Matt Sigman (Universtity of Utah) had developed. Therefore, more catalysts were tested in order to get a more complete picture of the capabilities and potential predictive accuracy of the QSSR model. This publication is forthcoming and the results here will only be reported and not discussed. Therefore, while it was discovered that donor/donor carbene C–H insertion reactions may not be suitable for the synthesis of Cantrixil™, we will use these interesting stereochemical results to test our QSSR model so that predictions can be made for optimal catalyst use in C–H insertion reactions.

Table 2. C–H insertion reaction results for homobenzylic insertion sites



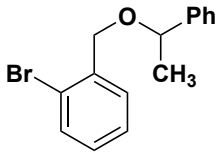
entry	catalyst	**20**:**21**[a]	yield (%)[a]
1	Rh_2(*R*-PTAD)$_4$	66:33	ND
2	Rh_2(*S*-TCPTTL)$_4$	17:83 (16:84)	94
3	Rh_2(*S*-PTTL)$_4$	57:43	ND
4	Rh_2(*S*-BTPCP)$_4$	92:8 (93:7)	86
5	Rh_2(PTCC)$_4$	55:45	ND
6	Rh_2(*R*-DOSP)$_4$	49:51	ND
7	Rh_2(ACyp)$_4$	46:54	ND
8	Rh_2(ACB)$_4$	49:51	ND
9	Rh_2(ACP)$_4$	43:57	ND
10	Rh_2(OAc)$_4$	58:42	ND
11	Rh_2(Triphenyl)$_4$	86:14	ND



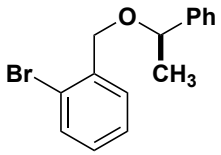
entry	catalyst	**22**:**23**[b]	yield (%)
12	Rh_2(*R*-PTAD)$_4$	71:29	ND
13	Rh_2(*S*-TCPTTL)$_4$	13:87	83
14	Rh_2(*S*-BTPCP)$_4$	91:9	86
15	Rh_2(*R*-DOSP)$_4$	50:50	ND
16	Rh_2(PTCC)$_4$	59:41	ND
17	Rh_2(ACyp)$_4$	56:44	ND
18	Rh_2(ACB)$_4$	54:46	ND
19	Rh_2(ACP)$_4$	49:51	ND
20	Rh_2(OAc)$_4$	63:37	ND
21	Rh_2(Triphenyl)$_4$	83:17	ND

[a] reactions conducted at 10mg scale; **20**:**21** ratio in parentheses and yields obtained at 50mg scale, [b]All reactions conducted at 50mg scale

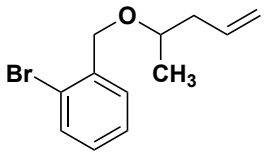
A2.3 Experimental Section



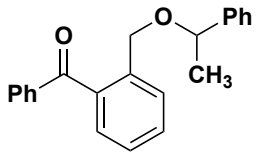
1-bromo-2-((1-phenylethoxy)methyl)benzene ((±)-**2**) was synthesized following a modified literature procedure,[4] by preparing a suspension of sodium hydride (0.493 g, 12 mmol, 3 equiv) in THF (0.3 M) and adding 1-phenylethanol (0.5 mL, 4 mmol, 1 equiv) dropwise, allowing to stir at room temperature for 1 hour. 2-bromobenzyl bromide (1.239 g, 5 mmol, 1.2 equiv) was then added as a solution in THF (0.8 M) and stirred overnight. The reaction was quenched with sat. aq. ammonium chloride (15 mL), extracted with ethyl acetate (15 mL x 3), washed with brine (25 mL), dried over sodium sulfate, concentrated *in vacuo*, and purified by flash column chromatography (100% H to 95H:5EtOAc) to afford (±)-**2** (1.139 g, 79%) as a clear oil. BDB-IV-151



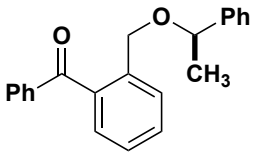
(*R*)-1-bromo-2-((1-phenylethoxy)methyl)benzene (*R*-**2**) was synthesized following a modified literature procedure,[4] by preparing a suspension of sodium hydride (0.508 g, 12 mmol, 3 equiv) in THF (0.3 M) and adding 1-phenylethanol (0.5 mL, 4 mmol, 1 equiv) dropwise, allowing to stir at room temperature for 1 hour. 2-bromobenzyl bromide (1.228 g, 5 mmol, 1.2 equiv) was then added as a solution in THF (0.8 M) and stirred overnight. The reaction was quenched with sat. aq. ammonium chloride (15 mL), extracted with ethyl acetate (15 mL x 3), washed with brine (25 mL), dried over sodium sulfate, concentrated *in vacuo*, and purified by flash column chromatography (100% H to 95H:5EtOAc) to afford *R*-**2** (1.237 g, quant.) as a clear oil. BDB-IV-144



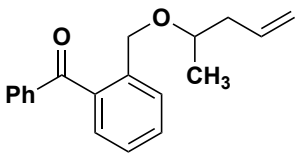
1-bromo-2-((pent-4-en-2-yloxy)methyl)benzene ((±)-**3**) was synthesized following a modified literature procedure,[4] by preparing a suspension of sodium hydride (0.610 g, 15 mmol, 3 equiv) in THF (0.3 M) and adding 1-methylbuten-1-ol (0.44 mL, 4.2 mmol, 1 equiv) dropwise, allowing to stir at room temperature for 1 hour. 2-bromobenzyl bromide (1.250 g, 5 mmol, 1.2 equiv) was then added as a solution in THF (0.8 M) and stirred overnight. The reaction was quenched with sat. aq. ammonium chloride (15 mL), extracted with ethyl acetate (15 mL x 3), washed with brine (25 mL), dried over sodium sulfate, concentrated *in vacuo*, and purified by flash column chromatography (100% H to 95H:5EtOAc) to afford ((±)-**3** (0.851 g, 79%) as a clear oil. BDB-IV-145



phenyl(2-((1-phenylethoxy)methyl)phenyl)methanone ((±)-**4**) was synthesized following a modified literature procedure,[4] by preparing a solution of (±)-**2** (1.139 g, 4 mmol, 1 equiv) in THF (0.3 M) and cooling the mixture to –78 °C. *n*-Butyllithium (2.14 mL, 5.4 mmol, 1.3 equiv) was then added dropwise and the mixture was allowed to stir for 2 hours. Weinreb benzamide (0.756 g, 5 mmol, 1.2 equiv) was then added at –78 °C as a solution in THF (0.8 M) and the solution was stirred to room temperature overnight. The reaction was then quenched with sat. aq. ammonium chloride (15 mL), extracted with ethyl acetate (15 mL x 3), washed with brine (25 mL), dried over sodium sulfate, concentrated *in vacuo*, and purified by flash column chromatography (90H:10EtOAc) to afford (±)-**4** (0.855 g, 69%) as a yellow oil. BDB-IV-160

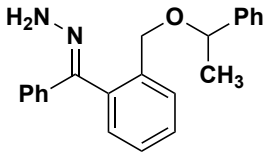


(*R*)-phenyl(2-((1-phenylethoxy)methyl)phenyl)methanone (*R*-**4**) was synthesized following a modified literature procedure,[4] by preparing a solution of *R*-**2** (1.237 g, 4 mmol, 1 equiv) in THF (0.3 M) and cooling the mixture to –78 °C. *n*-Butyllithium (2.31 mL, 5.4 mmol, 1.3 equiv) was then added dropwise and the mixture was allowed to stir for 2 hours. Weinreb benzamide (0.818 g, 5 mmol, 1.2 equiv) was then added at –78 °C as a solution in THF (0.8 M) and the solution was stirred to room temperature overnight. The reaction was then quenched with sat. aq. ammonium chloride (15 mL), extracted with ethyl acetate (15 mL x 3), washed with brine (25 mL), dried over sodium sulfate, concentrated *in vacuo*, and purified by flash column chromatography (90H:10EtOAc) to afford *R*-**4** (1.020 g, 76%) as a yellow oil. BDB-IV-146

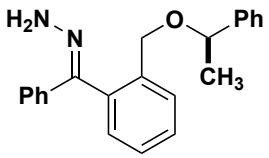


(2-((pent-4-en-2-yloxy)methyl)phenyl)(phenyl)methanone ((±)-**5**) was synthesized following a modified literature procedure,[4] by preparing a solution of (±)-**3** (0.851 g, 3 mmol, 1 equiv) in THF (0.3 M) and cooling the mixture to –78 °C. *n*-Butyllithium (1.88 mL, 4.3 mmol, 1.3 equiv) was then added dropwise and the mixture was allowed to stir for 2 hours. Weinreb benzamide (0.818 g, 4 mmol, 1.2 equiv) was then added at –78 °C as a solution in THF (0.8 M) and the solution was stirred to room temperature overnight. The reaction was then quenched with sat. aq. ammonium chloride (15 mL), extracted with ethyl acetate (15 mL x 3), washed with brine (25 mL), dried over sodium sulfate, concentrated *in vacuo*,

and purified by flash column chromatography (90H:10EtOAc) to afford *R*-**4** (0.700 g, 75%) as a yellow oil. BDB-IV-147

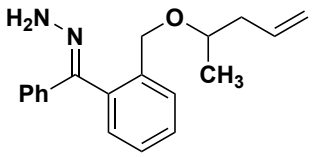


(phenyl(2-((1-phenylethoxy)methyl)phenyl)methylene)hydrazine ((±)-**6**) was synthesized by following a modified literature procedure,[4] by preparing a solution of (±)-**4** (0.855 g, 2.7 mmol, 1 equiv) in ethanol (0.1 M), adding hydrazine (0.51 mL, 16 mmol, 6 equiv), glacial acetic acid (0.18 mL, 3.2 mmol, 1.2 equiv), and heating the mixture to 90 °C overnight with a reflux condenser attached. Cooling the mixture to room temperature, the reaction was diluted with diethyl ether (50 mL), washed with water (15 mL), washed with brine (15 mL), dried over sodium sulfate, concentrated *in vacuo*, and purified by automated flash column chromatography (80H:20EtOAc gradient) to afford (±)-**6** (0.524 g, 59%) as a yellow oil. BDB-IV-164

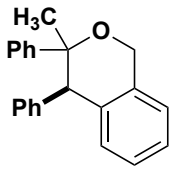


(*R*)-(phenyl(2-((1-phenylethoxy)methyl)phenyl)methylene)hydrazine (*R*-**6**) was synthesized by following a modified literature procedure,[4] by preparing a solution of *R*-**4** (0.102 g, 3 mmol, 1 equiv) in ethanol (0.1 M), adding hydrazine (0.61 mL, 19 mmol, 6 equiv), glacial acetic acid (0.22 mL, 4 mmol, 1.2 equiv), and heating the mixture to 90 °C overnight with a reflux condenser attached. Cooling the mixture to room temperature, the reaction was diluted with diethyl ether (50 mL), washed with water (15 mL), washed with brine (15 mL), dried over sodium sulfate, concentrated *in vacuo*, and purified by automated

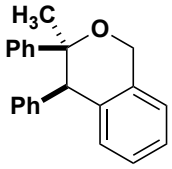
flash column chromatography (80H:20EtOAc gradient) to afford (*R*-**6**) (0.755 g, 71%) as a yellow oil. BDB-IV-148



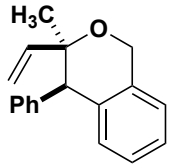
((2-((pent-4-en-2-yloxy)methyl)phenyl)(phenyl)methylene)hydrazine ((±)-**7**) was synthesized by following a modified literature procedure,[4] by preparing a solution of (±)-**5** (0.700 g, 2.5 mmol, 1 equiv) in ethanol (0.1 M), adding hydrazine (0.49 mL, 15 mmol, 6 equiv), glacial acetic acid (0.17 mL, 3 mmol, 1.2 equiv), and heating the mixture to 90 °C overnight with a reflux condenser attached. Cooling the mixture to room temperature, the reaction was diluted with diethyl ether (50 mL), washed with water (15 mL), washed with brine (15 mL), dried over sodium sulfate, concentrated *in vacuo*, and purified by automated flash column chromatography (80H:20EtOAc gradient) to afford (±)-**7** (0.515 g, 70%) as a yellow oil. BDB-IV-149



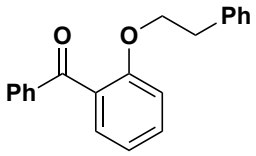
(4*R*)-3-methyl-3,4-diphenylisochromane ((±)-**8**) was synthesized by following a modified literature procedure,[4] by preparing a solution of (±)-**6** (0.026 g, 0.076 mmol, 1 equiv) in DCM (0.015 M) and adding manganese dioxide (0.053 g, 0.605 mmol, 8 equiv). This heterogenous mixture was allowed to stir at room temperature for 4 hours before cooling to 0 °C. Rh_2(*R*-PTAD)$_4$ (0.001 g, 0.7 μmol, 1 mol %) was then added and the mixture was allowed to stir to room temperature overnight. The reaction was then filtered through celite, concentrated *in vacuo*, and purified by flash column chromatography (90H:10EtOAc) to afford (±)-**8** (0.022 g, 93%) as a crystalline white solid. BDB-IV-165



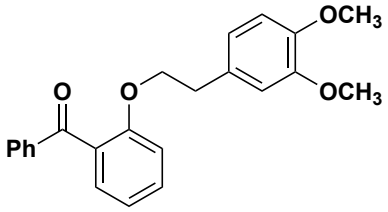
(3*S*,4*R*)-3-methyl-3,4-diphenylisochromane (**8**) was synthesized by following a modified literature procedure,[4] by preparing a solution of *R*-**6** (0.026 g, 0.076 mmol, 1 equiv) in DCM (0.015 M) and adding manganese dioxide (0.054 g, 0.605 mmol, 8 equiv). This heterogenous mixture was allowed to stir at room temperature for 4 hours before cooling to 0 °C. Rh_2(*R*-PTAD)$_4$ (0.001 g, 0.7 μmol, 1 mol %) was then added and the mixture was allowed to stir to room temperature overnight. The reaction was then filtered through celite, concentrated *in vacuo*, and purified by flash column chromatography (90H:10EtOAc) to afford **8** (0.024 g, 99%) as a crystalline white solid. BDB-IV-152



(3*R*,4*R*)-3-methyl-4-phenyl-3-vinylisochromane ((±)-**9**) was synthesized by following a modified literature procedure,[4] by preparing a solution of (±)-**7** (0.024 g, 0.085 mmol, 1 equiv) in DCM (0.015 M) and adding manganese dioxide (0.062 g, 0.679 mmol, 8 equiv). This heterogenous mixture was allowed to stir at room temperature for 4 hours before cooling to 0 °C. Rh_2(*R*-PTAD)$_4$ (0.001 g, 0.8 μmol, 1 mol %) was then added and the mixture was allowed to stir to room temperature overnight. The reaction was then filtered through celite, concentrated *in vacuo*, and purified by flash column chromatography (90H:10EtOAc) to afford (±)-**8** (0.011 g, 51%) as a crystalline white solid. BDB-IV-156

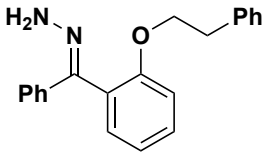


(2-phenethoxyphenyl)(phenyl)methanone (**14**) was synthesized by following a modified literature procedure,[5] by preparing a suspension of NaH (0.229 g, 5 mmol, 4 equiv) in THF (0.25 M). 2-phenylethanol (0.3 mL, 2.5 mmol, 2 equiv) and 2-fluorobenzophenone (0.274 g, 1.25 mmol, 1 equiv) were then added and the mixture was heated to 60 °C with stirring overnight. The reaction was then cooled to room temperature, quenched with sat. aq. ammonium chloride (5 mL), washed with brine (10 mL), dried over sodium sulfate, concentrated *in vacuo*, and purified by flash column chromatography (90H:10EtOAc to 70H:30EtOAc) to afford **14** (0.217 g, 52%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 6.8 Hz, 2H), 7.56 (t, J = 7.4 Hz, 1H), 7.46 – 7.37 (m, 4H), 7.18 – 7.12 (m, 3H), 7.03 (t, J = 7.4 Hz, 1H), 6.99 – 6.90 (m, 3H), 4.08 (t, J = 6.9 Hz, 2H), 2.71 (t, J = 6.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.9, 156.8, 138.4, 138.1, 132.9, 132.1, 129.8, 129.8, 129.3, 129.0, 128.5, 128.3, 126.5, 120.9, 112.5, 69.5, 35.6; IR (neat) 3061, 3028, 2928 ,2873, 1663, 1598, 1450, 1315, 1295, 1240 cm^{-1}; AMM (ESI) *m/z* calcd $C_{21}H_{19}O_2^+$ $[M+H]^+$ 303.1380, found 303.1382.

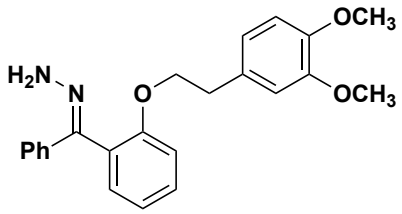


(2-(3,4-dimethoxyphenethoxy)phenyl)(phenyl)methanone (**17**) was synthesized by following a modified literature procedure,[5] by preparing a suspension of NaH (0.275 g, 5 mmol, 4 equiv) in THF (0.25 M). 2-(3,4-dimethoxy)phenylethanol (0.472 g mL, 2.5 mmol, 2 equiv) and 2-fluorobenzophenone (0.277 g, 1.25 mmol, 1 equiv) were then added and the mixture was heated to 60 °C with stirring overnight. The reaction was then cooled to room temperature, quenched with sat. aq. ammonium chloride

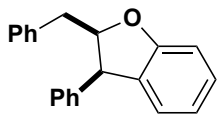
(5 mL), washed with brine (10 mL), dried over sodium sulfate, concentrated *in vacuo*, and purified by flash column chromatography (90H:10EtOAc to 70H:30EtOAc) to afford **14** (0.217 g, 52%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 6.9 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.45 – 7.36 (m, 4H), 7.03 (t, *J* = 7.5 Hz, 1H), 6.94 (d, *J* = 8.4 Hz, 1H), 6.67 (d, *J* = 8.0 Hz, 1H), 6.58 (d, *J* = 1.9 Hz, 1H), 6.53 (dd, *J* = 8.0, 2.1 Hz, 1H), 4.08 (t, *J* = 6.8 Hz, 2H), 3.82 (s, 3H), 3.78 (s, 3H), 2.68 (t, *J* = 6.8 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.7, 156.8, 148.8, 147.7, 138.3, 132.9, 132.1, 130.8, 129.8, 129.2, 128.3, 120.9, 120.8, 112.6, 112.4, 111.2, 69.7, 56.0, 55.9, 35.2; IR (neat) 2935, 2834, 1663, 1597, 1259, 1234 cm^{-1}; AMM (ESI) *m/z* calcd $C_{23}H_{23}O_4^+$ $[M+H]^+$ 363.1591, found 363.1595.



((2-phenethoxyphenyl)(phenyl)methylene)hydrazine (**15**) was synthesized by following a modified literature procedure,[5] by preparing a solution of **14** (0.195 g, 0.661 mmol, 1 equiv) in ethanol (0.1 M), adding hydrazine (0.19 mL, 4 mmol, 6 equiv), glacial acetic acid (80 μL, 0.8 mmol, 1.2 equiv), and heating the mixture to 90 °C overnight with a reflux condenser attached. Cooling the mixture to room temperature, the reaction was diluted with diethyl ether (50 mL), washed with water (15 mL), washed with brine (15 mL), dried over sodium sulfate, concentrated *in vacuo*, and purified by automated flash column chromatography (80H:20EtOAc gradient) to afford **15** (0.222 g, quant.) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.44 (m, 2H), 7.42 – 7.36 (m, 1H), 7.32 – 7.25 (m, 3H), 7.19 – 7.13 (m, 3H), 7.13 – 7.07 (m, 3H), 7.05 (d, *J* = 7.4 Hz, 1H), 7.01 (d, *J* = 8.3 Hz, 1H), 5.26 (s, 2H), 4.14 (t, *J* = 6.6 Hz, 2H), 2.89 (t, *J* = 6.6 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.9, 147.6, 138.6, 138.2, 130.5, 130.4, 129.1, 128.3, 128.1, 127.9, 126.4, 126.2, 122.0, 121.6, 112.6, 69.3, 35.7; IR (neat) 3406, 3027, 2926, 2873, 1597, 1488, 1444, 1240 cm^{-1}.

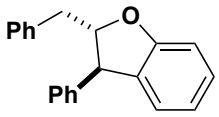


((2-(3,4-dimethoxyphenethoxy)phenyl)(phenyl)methylene)hydrazine (**18**) was synthesized by following a modified literature procedure,[5] by preparing a solution of **17** (0.456 g, 1.25 mmol, 1 equiv) in ethanol (0.1 M), adding hydrazine (0.25 mL, 7.5 mmol, 6 equiv), glacial acetic acid (100 μL, 1.5 mmol, 1.2 equiv), and heating the mixture to 90 °C overnight with a reflux condenser attached. Cooling the mixture to room temperature, the reaction was diluted with diethyl ether (50 mL), washed with water (15 mL), washed with brine (15 mL), dried over sodium sulfate, concentrated *in vacuo*, to afford **18** (0.422 g, 89%) as a yellow oil without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (dd, J = 7.5, 2.4 Hz, 1H), 7.42 – 7.37 (m, 1H), 7.27 (dd, J = 5.2, 2.2 Hz, 2H), 7.13 (dd, J = 7.5, 1.9 Hz, 1H), 7.01 (d, J = 8.4 Hz, 1H), 6.67 – 6.64 (m, 1H), 5.32 (s, 1H), 4.12 (s, 1H), 3.82 (s, 2H), 3.77 (s, 2H), 2.83 (t, J = 6.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.1, 148.8, 147.7, 147.4, 138.7, 131.0, 130.6, 130.5, 128.2, 128.0, 126.3, 122.1, 121.7, 121.1, 112.8, 112.6, 111.2, 69.7, 56.0, 55.9, 35.5; IR (neat) 3402, 2932, 1596, 1516, 1488, 1261 cm^{-1}.

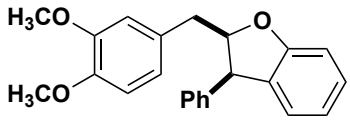


(2*R*,3*R*)-2-benzyl-3-phenyl-2,3-dihydrobenzofuran (**20**) was synthesized by following a modified literature procedure,[5] by preparing a solution of **19** (0.050 g, 0.156 mmol, 1 equiv) in DCM (0.015 M) and adding manganese dioxide (0.112 g, 1.264 mmol, 8 equiv). This heterogenous mixture was allowed to stir at room temperature for 4 hours before cooling to 0 °C. Rh_2(*S*-BTPCP)$_4$ (0.002 g, 1.6 μmol, 1 mol %) was then added and the mixture was allowed to stir to room temperature overnight. The reaction was

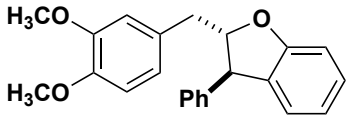
then filtered through celite, concentrated *in vacuo*, and purified by flash column chromatography (95H:5EtOAc to 90H:10EtOAc) to afford **20** (0.039 g, 86%) as a crystalline white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.22 (m, 5H), 7.21 – 7.15 (m, 2H), 7.11 – 7.04 (m, 3H), 7.04 – 6.99 (m, 2H), 6.91 – 6.84 (m, 2H), 5.15 (td, *J* = 9.1, 4.9 Hz, 1H), 4.57 (d, *J* = 8.3 Hz, 1H), 2.71 (dd, *J* = 14.6, 9.1 Hz, 1H), 2.52 (dd, *J* = 14.6, 4.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 139.6, 138.4, 131.5, 129.4, 129.2, 128.8, 128.5, 128.4, 127.3, 126.5, 125.8, 121.1, 110.1, 87.6, 51.8, 38.0; IR (neat) 3029, 2922, 1478, 1453, 1231, 728 cm^{-1}.



(2*S*,3*R*)-2-benzyl-3-phenyl-2,3-dihydrobenzofuran (**21**) was synthesized by following a modified literature procedure,[5] by preparing a solution of **19** (0.050 g, 0.16 mmol, 1 equiv) in DCM (0.015 M) and adding manganese dioxide (0.113 g, 1.264 mmol, 8 equiv). This heterogenous mixture was allowed to stir at room temperature for 4 hours before cooling to 0 °C. Rh_2(*S*-TCPTTL)$_4$ (0.002 g, 1.6μmol, 1 mol %) was then added and the mixture was allowed to stir to room temperature overnight. The reaction was then filtered through celite, concentrated *in vacuo*, and purified by flash column chromatography (95H:5EtOAc to 90H:10EtOAc) to afford **21** (0.042 g, 94%) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.21 (m, 8H), 7.16 (t, *J* = 7.7 Hz, 1H), 7.03 (d, *J* = 6.6 Hz, 2H), 6.93 (d, *J* = 7.4 Hz, 1H), 6.85 (dd, *J* = 10.2, 7.6 Hz, 2H), 4.84 (td, *J* = 7.4, 5.4 Hz, 1H), 4.32 (d, *J* = 7.3 Hz, 1H), 3.18 (dd, *J* = 14.2, 7.5 Hz, 1H), 3.07 (dd, *J* = 14.2, 5.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7, 142.7, 137.3, 130.6, 129.7, 128.8, 128.7, 128.6, 128.2, 127.1, 126.8, 125.5, 120.9, 109.9, 92.1, 53.8, 41.0; IR (neat) 3029, 2922, 1478, 1453, 1231, 728 cm^{-1}.



(2*R*,3*R*)-2-(3,4-dimethoxybenzyl)-3-phenyl-2,3-dihydrobenzofuran (**22**) was synthesized by following a modified literature procedure,[5] by preparing a solution of **18** (0.050 g, 0.133 mmol, 1 equiv) in DCM (0.015 M) and adding manganese dioxide (0.095 g, 1.063 mmol, 8 equiv). This heterogenous mixture was allowed to stir at room temperature for 4 hours before cooling to 0 °C. Rh_2(*S*-BTPCP)$_4$ (0.002 g, 1.33 μmol, 1 mol %) was then added and the mixture was allowed to stir to room temperature overnight. The reaction was then filtered through celite, concentrated *in vacuo*, and purified by flash column chromatography (95H:5EtOAc to 90H:10EtOAc) to afford **22** (0.039 g, 86%) as a crystalline white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 – 7.23 (m, 3H), 7.18 (t, *J* = 7.7 Hz, 1H), 7.08 – 6.98 (m, 3H), 6.93 – 6.84 (m, 2H), 6.77 (d, *J* = 8.3 Hz, 1H), 6.66 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.55 (d, *J* = 2.1 Hz, 1H), 5.13 (td, *J* = 8.7, 5.2 Hz, 1H), 4.55 (d, *J* = 8.3 Hz, 1H), 3.85 (s, 3H), 3.81 (s, 3H), 2.69 (dd, *J* = 14.5, 8.8 Hz, 1H), 2.49 (dd, *J* = 14.5, 5.2 Hz, 1H).; ^{13}C NMR (76 MHz, $CDCl_3$) δ 159.7, 148.7, 147.6, 139.6, 131.6, 130.8, 129.4, 128.7, 128.4, 127.2, 125.8, 121.1, 121.0, 112.6, 111.2, 110.0, 87.7, 56.0, 55.8, 51.6, 37.4; IR (neat) 2932, 2834, 1666, 1515, 1479, 1461, 1261, 1231, 1141, 1028 cm^{-1}; AMM (ESI) *m/z* calcd $C_{23}H_{23}O_3^+$ $[M+H]^+$ 347.1642, found 347.1643.



(2*S*,3*R*)-2-(3,4-dimethoxybenzyl)-3-phenyl-2,3-dihydrobenzofuran (**23**) was synthesized by following a modified literature procedure,[5] by preparing a solution of **18** (0.050 g, 0.133 mmol, 1 equiv) in DCM (0.015 M) and adding manganese dioxide (0.098 g, 1.063 mmol, 8 equiv). This heterogenous mixture was allowed to stir at room temperature for 4 hours before cooling to 0 °C. Rh_2(*S*-TCPTTL)$_4$ (0.002 g,

1.33 μmol, 1 mol %) was then added and the mixture was allowed to stir to room temperature overnight. The reaction was then filtered through celite, concentrated *in vacuo*, and purified by flash column chromatography (95H:5EtOAc to 90H:10EtOAc) to afford **23** (0.038 g, 83%) as a crystalline white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 – 7.24 (m, 3H), 7.19 – 7.13 (m, 1H), 7.08 – 7.03 (m, 2H), 6.93 (dt, *J* = 7.4, 1.5 Hz, 1H), 6.88 – 6.84 (m, 1H), 6.84 – 6.75 (m, 4H), 4.84 (td, *J* = 7.3, 5.5 Hz, 1H), 4.31 (d, *J* = 7.4 Hz, 1H), 3.86 (s, 3H), 3.81 (s, 3H), 3.12 (dd, *J* = 14.3, 7.2 Hz, 1H), 3.03 (dd, *J* = 14.3, 5.5 Hz, 1H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 159.7, 148.9, 147.9, 142.7, 130.6, 129.8, 128.8, 128.7, 128.3, 127.1, 125.5, 121.8, 120.9, 112.9, 111.3, 109.8, 92.1, 56.0, 55.9, 53.7, 40.4.

A2.4 References

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