PART I: A SYNTHESIS OF JIADIFENOLIDE
PART II: EFFORTS TOWARD A SYNTHESIS OF PLEUROTIN

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A DISSERTATION
PRESENTED TO THE FACULTY
OF PRINCETON UNIVERSITY
IN CANDIDACY FOR THE DEGREE
OF DOCTOR OF PHILOSOPHY

RECOMMENDED FOR ACCEPTANCE
BY THE DEPARTMENT OF CHEMISTRY

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June 2014
Abstract

Jiadifenolide, isolated in 2009, is a pentacyclic sesquiterpenoid natural product with a densely oxidized architecture. Because of both the challenge of constructing this unique structure as well as its ability to promote neurite outgrowth in primary cultured rat cortical neurons, we were drawn to jiadifenolide as a synthetic target. The hallmarks of our strategy for synthesis include the reliance on the time-honored Robinson annulation to build the cyclohexane ring, the use of a catalytic, palladium-mediated C–H oxidation to generate local asymmetry at a carbon atom bearing a geminal methyl motif, and the incorporation of an iodoso Pummerer-like rearrangement of an α-iodo lactone to produce the corresponding α-keto lactone. The successful implementation of this strategy resulted in a successful, eighteen step synthesis of the natural product.

The intriguing chemical structure of pleurotin posed an additional opportunity for creativity in chemical synthesis. We have demonstrated through a series of model studies that the venerable Diels–Alder reaction can be used to construct two adjacent cyclohexane ring systems while establishing the configuration of four stereogenic carbon atoms. Our efforts to address the two cycloaddition reactions in the full structural context required for the total synthesis are also discussed.
To Heather and Gavin –
Thank you for the joy you bring.
Acknowledgements

The work described in this thesis would not have been possible without the advice and support of my research advisor, Erik Sorensen. I have been extraordinarily fortunate to be a member of his lab, and I am thankful for being able to grow into an independent scientist under his guidance. Erik’s creativity and passion for chemistry and teaching are a source of inspiration that I will carry with me beyond graduate school. In addition to their scientific well-being, Erik truly cares about each of his students, in and out of lab, and I am happy to call him my friend. There have been a lot of ups and downs throughout this experience, and I cannot sufficiently express how grateful I am for his support during the difficult times.

I have also been fortunate to have a great thesis committee, and I thank Professors Abigail Doyle, David MacMillan, and Martin Semmelhack for all of the helpful suggestions and advice during my time here. In particular, I would like to thank Abby for writing recommendation letters on many occasions and Marty for agreeing to be the second reader of this thesis. In addition, I have greatly benefitted from conversations with Professors Paul Reider and Edward Taylor. I learned a lot from taking Paul’s courses as well as mentoring several of his students; he also wrote several effective recommendation letters for me, for which I am grateful. Ted is a wonderful person who loves chemistry, and I’m happy that I had the opportunity to know him.

I was lucky to be paired with two fantastic coworkers during my time in graduate school. Dr. David Ebner introduced the Sorensen lab to the problem posed by the structural complexity of pleurotin, and he graciously accepted me onto the project during my first year. Dave’s work ethic was inspiring for a young, impressionable graduate student, and I can only hope to have adopted a portion of this.
I could write many pages trying to describe the debt of gratitude that I owe Erik, and I could write equally as much about Jeffrey Mighion. Jeff’s creativity, insight, and recall of the literature make him a fantastic chemist, but he is an equally fantastic person and friend. We spent many hours together everyday in the lab, and yet our families spent a great deal of time together outside of the lab as well, and for that I am grateful. Just as with Erik, Jeff’s support through the tough times was unending, and I thank him for that.

There have been many people that have come and gone from the Sorensen lab during my time at Princeton, and they have all helped to make my time here more fun and interesting. I learned a lot from all of these past and present members of the lab, and I thank them for their friendship. In particular, I want to thank Keith Reber, Matthew Naylor, Christopher Jeffrey, and Jessica Frie. Keith is a great scientist, teacher, and friend, and my scientific knowledge has grown immensely from my interactions with him. I thank Matt for introducing me to Killer Bunnies, as this was a welcome diversion from chemistry. Chris and Jess welcomed me onto their project during my first six months in the lab, and I thank them for their patience and for improving my laboratory technique. Jeff, Matt, Keith, and Aaron Bedell are also thanked for proofreading this document and for providing helpful suggestions.

I spent many semesters in Princeton as a teaching assistant, and I thank Professors Michael Hecht, Robert L’esperance, and Henry Gingrich, as well as Marty and Erik, for serving as mentors in this role. In particular, I thank Rob for his guidance and support. I often complained to Rob about being assigned to general chemistry courses, but as I look back I realize that I learned a lot while teaching with him. He allowed me to grow with increasing responsibilities, and I thank him for that; I’m happy to now call him my friend.
Much of my time in Princeton was spent in the lab, and there were several people within the chemistry department that made this easier. Phil Fairall is gratefully acknowledged not only for keeping me stocked with chemicals and supplies, but also for his friendship. Kevin Wilkes and Vicky Lloyd (stockroom and ordering), Jean Bausmith and Katie Comstock (front office coordinators), and Meghan Krause and Sallie Dunner (graduate administrators) were all immensely helpful. The facilities at Princeton are amazing, and I have to thank Dr. István Pelczer, Ken Conover, and Dr. Carlos Pacheco for NMR support and Dr. John Eng for IR and HRMS support.

Prior to coming to Princeton, there were several people who were instrumental to my education. I thank Professor Suri Iyer for taking a chance and allowing me to join his lab for summer research while I was an undergraduate student; I’m happy that this experience turned into two and a half years in his lab. Suri was extraordinarily generous with his time, serving as my initial mentor in the lab. After working with Suri for several months, I had the good fortune to work with his postdoc, Dr. Ramesh Kale, and then his graduate student, Daniel Lewallen. I learned a lot from both of them, and I thank them for their time and patience. Professors Allen Pinhas and Deborah Lieberman are thanked for their invitation to the honors laboratory sections for CHM 202 and 203, as it was this experience that developed my interest for research as a sophomore. I also would like to thank Professor Joel Shulman. Joel is a great teacher and advisor, and the time that he spent with me discussing options for graduate school was invaluable. Finally, I would like to thank my high school chemistry teacher, Mr. Gray. If it weren’t for this class, I never would have become a chemistry major.

I have been fortunate to be able to rely on a large network of family and friends for support. I thank my parents for teaching me the value of a good education and for providing the support that I needed for success. My sister, Chrissy, and brother, Matt, are also thanked for their friendship and helpful distractions from graduate school. My
extended family is wonderful, and in particular, I thank my grandparents Vernon and Phyllis Siler, my uncle Vernon Siler, and my aunt Annette Owens for their love and support. I also would like to thank my friends Brad and Nikita Hopkins for their support. Brad has been a close friend for more than fifteen years, and I thank him for helping to keep me sane during this entire process. I hope that we will be able to see more of each other going forward, and we will certainly need to take in many hockey games to make up for the lost time.

Finally, and most importantly, I must thank my beautiful wife, Heather, and adorable son, Gavin. Heather, you have been my rock through all of the ups and downs over the last six years, and none of this would have been possible without your unending love and support. Unfortunately, you have suffered the most from the long hours and weekends that I have spent in lab, and while I can never replace this time with you, I will certainly try. Gavin, I am looking forward to making up for all of the time we have spent apart over this last year. Thank you being a constant source of smiles and laughs. You have been the greatest source of inspiration for wrapping things up here. Your mom and I are blessed to have such a perfect little boy, and I’m happy that we will have more time together going forward.
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<tr>
<td>9-BBN</td>
<td>9-borabicyclo[3.3.1]nonane</td>
</tr>
<tr>
<td>Å</td>
<td>angstroms</td>
</tr>
<tr>
<td>$[\alpha]_d^{20}$</td>
<td>specific rotation at 20 °C and 589 nm</td>
</tr>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>ACS</td>
<td>American Chemical Society</td>
</tr>
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<td>AIBN</td>
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<tr>
<td>DMDO</td>
<td>dimethylidioxirane</td>
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<td>N,N-dimethylformamide</td>
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<td>Dess–Martin periodinane</td>
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<tr>
<td>DMSO</td>
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<tr>
<td>dppe</td>
<td>1,2-bis(diphenylphosphino)ethane</td>
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<tr>
<td>dr</td>
<td>diastereomeric ratio</td>
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<td>enantiomeric excess</td>
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<td>ESI</td>
<td>electrospray ionization</td>
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<tr>
<td>i-Pr</td>
<td>isopropyl</td>
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<tr>
<td>IR</td>
<td>infrared</td>
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<tr>
<td>J</td>
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<tr>
<td>Jones's reagent</td>
<td>chromium(VI) trioxide in dilute sulfuric acid</td>
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<tr>
<td>KHMDS</td>
<td>potassium bis(trimethylsilyl)amide</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
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<td>R&lt;sub&gt;f&lt;/sub&gt;</td>
<td>retention factor</td>
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<td>trifluoromethanesulfonyle</td>
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<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
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<td>TosMIC</td>
<td>para-tosylmethyl isonitrile</td>
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Chapter 1

Overview of jiadifenolide and related neurotrophic natural products
1.1. Overview of neurodegenerative diseases

Neurodegenerative disease is a catchall term used to describe the various conditions resulting from the degradation and/or death of neurons, the primary components of both the brain and the central nervous system.¹ The most common neurodegenerative diseases include Alzheimer’s disease, Parkinson’s disease, Huntington’s disease, and amyotrophic lateral sclerosis (also known as Lou Gehrig’s disease). In many cases, these diseases affect the elderly and are thus more prevalent in industrialized societies where higher life expectancies are common. Although it has been debated whether or not neurons are permanently postmitotic,² the ability to grow new neuron cells would be extremely valuable. To date, this has not been possible, and with no current cures for any of the neurodegenerative diseases, symptomatic relief is generally the only recourse for patients with these afflictions; therefore, new technologies are required to combat this issue.

One potential source of new therapeutics is neurotrophins.³ This family of proteins helps to regulate the growth and survival of neurons and could be viewed as a therapeutic option to help grow new neurons in patients suffering from neurodegenerative diseases. Unfortunately, the use of neurotrophins as a therapy suffers from their poor stability in the blood, poor bioavailability, and inability to penetrate the blood-brain barrier.⁴ As a result, small molecules, including natural products, may be the only answer to address these debilitating conditions.⁵ In fact, several classes of natural products have already been identified that possess neurotrophic activity,¹ and thus the ability to synthesize these molecules, which contain challenging frameworks for the synthetic chemist, could prove to be vital (Figure 1.1). In response to this challenge and as a way of introducing his synthesis of merrilactone A (1.1), Professor Samuel Danishefsky (of Columbia University and Memorial Sloan Kettering Cancer Center) commented, “We felt that gaining a mastery of the total synthesis of such small-molecule
natural products could be most helpful, not only in improving access to these difficultly available agents, but also in providing the basis for probing their SAR profiles.\textsuperscript{6}

Figure 1.1. Representative neurotrophic natural products.
1.2. Isolation, structural determination, and bioactivity of jiadifenolide

As a continuation of their efforts to identify small molecules possessing neurotrophic activity, the Fukuyama group at Tokushima Bunri University disclosed the structures of three new seco-prezizaane-type sesquiterpenoids in 2009 (Figure 1.2). Named jiadifenolide (1.2), jiadifenoxolane A (1.8), and jiadifenoxolane B (1.9), these natural products were isolated from the pericarps of *Illicium jiadifengpi*, a flowering plant found in southwestern China, along with six additional natural products of the majucin family that had been previously isolated.⁸

![Chemical structures](image_url)

Figure 1.2. Various isolates from *Illicium jiadifengpi*.

The structures of all three new isolates were determined by a combination of ¹H-, ¹³C-, and 2D-NMR (COSY, HMQC, HMBC, and NOESY) studies and supported by
infrared spectroscopy and high-resolution mass spectrometry; in addition, an X-ray crystal structure was obtained for jiadifenolide (1.2), rigorously proving its structure.

In addition to their isolation and structural determination work, the Fukuyama group evaluated these new isolates for neurotrophic activity. In their experiments, they treated primary cultured rat cortical neurons with varying concentrations of each new natural product, and then the length of the longest neurite extending from each cell body was measured. While jiadifenoxolane B (1.9) showed no significant activity, both jiadifenolide (1.2) and jiadifenoxolane A (1.8) exhibited the ability to significantly potentiate outgrowth at concentrations ranging from 0.01 – 10 µM, with increased potency observed for jiadifenolide (1.2).
1.3. Related *Illicium* sesquiterpenoids possessing neurotrophic activity

The exciting biological activity described above is not unique to these new isolates from *Illicium jiadifengpi*. In fact, the *Illicium* genus of plants has provided a wealth of interesting natural products that display a wide variety of biological function. Many of these isolates bear close structural similarity with one another, and the members of the sesquiterpenoid class of *Illicium* natural products, in particular, are believed to arise from a common tricyclic cationic intermediate (1.17, Scheme 1.1).

![Scheme 1.1. Proposed origins of the *Illicium* sesquiterpenoids.](image)

Arising from a series of cationic cyclizations from farnesol pyrophosphate (1.16), this intermediate was initially only hypothetical; however, the isolation of tashironin (1.18)
from *Illicium tashiroi* by Fukuyama and coworkers in 1995\textsuperscript{10} provided evidence for the intermediacy of this structure. Cleavage of the C6–C11 bond would provide the seco-prezizaane skeleton \textbf{1.20} found in the aforementioned jiadifenolide (\textbf{1.2}) as well as the closely related jiadifenin (\textbf{1.21}), also isolated by Fukuyama and coworkers from *Illicium jiadifengpi* in 2002.\textsuperscript{11} In addition, a different set of rearrangements of tricyclic structure \textbf{1.17} would provide the [3.3.0]-bicyclic structure \textbf{1.19} found in merrilactone A (\textbf{1.1}), isolated from *Illicium merrillianum* by Fukuyama in 2000.\textsuperscript{12} All of these natural products have been shown to exhibit neurotrophic activity and have attracted much attention from the synthetic community.\textsuperscript{1,13}
1.4. Theodorakis's synthesis of jiadifenolide

In 2011, Emmanuel Theodorakis and his group at the University of California, San Diego disclosed the first total synthesis of jiadifenolide (1.2).\textsuperscript{14} The key aspect of their strategy was the insight that the bridging lactone ring might arise from a structural rearrangement enabled by the oxidation of tetracycle 1.33 (Scheme 1.2). With this plan in mind, they founded their synthesis on the well-known Hajos–Parrish type of cyclization of triketone 1.25, the synthesis of which had been previously described by Yannick Landais and coworkers.

Thus, an enantioselective aldol condensation reaction in the presence of 30 mol\% of D-prolinamide (1.26) provided access to their foundational enone (1.27) in 74\% yield with greater than 90\% ee, although 14 days were required for good levels of enantioselectivity. With this in hand, ketone reduction, silyl ether formation, and sequential alkylations provided \( \beta \)-ketoester 1.29. Further oxidation state adjustments advanced this material to ketone 1.30, which was poised to undergo a carbonylation reaction following conversion of the oxo group to a vinyl triflate; subsequent acidic deprotection of the silyl ether cleanly provided lactone 1.31. Nucleophilic epoxidation of the \( \alpha,\beta \)-unsaturated ester function of 1.31 proceeded nearly quantitatively to provide epoxide 1.32 as a single diastereomer. While the initial hope of utilizing a one-step, Ru(VIII)-mediated oxidative cleavage of the terminal alkene to the carboxylic acid to trigger an epoxide opening was unsuccessful, a more traditional two-step procedure involving a Johnson–Lemieux oxidation (OsO\(_4\)/NaIO\(_4\)) followed by Jones oxidation yielded desired tetracycle 1.33.
Scheme 1.2. Synthesis of the rearrangement precursor 1.33 by Theodorakis.

In order to affect their key rearrangement, this intermediate was advanced to epoxide 1.34 (Scheme 1.3) through fluoride-mediated desilylation and epoxidation with meta-chloroperoxybenzoic acid (m-CPBA). In the presence of Dess–Martin periodinane (DMP), epoxide 1.34 gratifyingly underwent oxidation and rearrangement to yield tetracycle 1.35, albeit in 36% yield from alcohol 1.33. The authors proposed that an initial oxidation of the alcohol to the corresponding ketone (1.36) was followed by an \( \text{E}_{1cb} \)-like opening of the epoxide to generate an enone and a tertiary hydroxyl group. The
tertiary hydroxyl group, being formed in close proximity to the lactone carbonyl, could then participate in a translactonization to yield the observed product.

Scheme 1.3. Rearrangement leading to the bridging lactone of jiadifenolide (1.2).

With the accomplishment of their desired rearrangement, the Theodorakis group was quite close to realizing a complete synthesis of jiadifenolide (1.2, Scheme 1.4). To complete this goal, they needed to replace the oxo group at C1 with a methyl-bearing stereocenter as well as introduce additional oxidation at C10. Thus, hydrogenation allowed for the saturation of the cyclopentene ring, and the secondary hydroxyl group was protected as a silyl ether to afford ketone 1.37. The oxo group was then converted to a vinyl triflate, which served as a handle for the introduction of the methyl group through cross-coupling with trimethylaluminum. The requisite stereocenter was then established with simple hydrogenation, providing tetracycle 1.39. Drawing inspiration from the Danishefsky group’s total synthesis of the related Illicium natural product jiadifenin (1.21, Scheme 1.1), the Theodorakis group closed their synthesis with a two-stage oxidation: 1) oxidation at C10 with Davis’s oxaziridine (1.40) provided intermediate alcohol 1.41; and 2) treatment with Jones’s reagent affected an oxidation of the newly formed hydroxyl group to give an α-ketolactone, which underwent spontaneous
hemiacetal formation with the secondary hydroxyl group (liberated under the acidic reaction conditions). In total, the Theodorakis group's enantioselective synthesis of jiadifenolide (1.2) is comprised of 26 steps from known triketone 1.25 with an overall yield of 0.7%.

\[
\text{Scheme 1.4. Completion of the synthesis of jiadifenolide (1.2) by Theodorakis.}
\]

As a continuation of their interest in small molecules exhibiting neurotrophic activity, the Theodorakis group adapted an intermediate from their successful synthesis of jiadifenolide (1.2) to access the structurally related natural products (1R,10S)-2-oxo-3,4-dehydroxyneomajucin (ODNM, 1.46) and jiadifenin (1.21, Scheme 1.5).\textsuperscript{15} Tetracycle 1.42 (accessible via deprotection of 1.33) was chosen as the best common intermediate, although this immediately imposed a problem for their synthesis, namely that it required transposition of the oxidation found in the cyclopentene ring (from C1 to C2). To install the enone found in the target compounds, dehydration using Martin's sulfurane and hydrogenation allowed for the removal of the superfluous hydroxyl group (1.43) while
oxidation with Mn$_3$O(OAc)$_9$ and tert-butylhydroperoxide (TBHP) provided the oxo group.
With enone 1.44 in hand, hydroxylation at C10 with Davis’s oxaziridine followed by
methylation adjacent to the enone afforded ODNM (1.46). Following the precedent
established by the Danishefsky lab, oxidation of ODNM (1.46) with Jones’s reagent then
provided access to jiadifenin (1.21).

Scheme 1.5. Application to the synthesis of ODNM (1.46) and jiadifenin (1.21).

With access to jiadifenolide (1.2), ODNM (1.46), and jiadifenin (1.21) as well as
many other intermediates and analogues, the Theodorakis lab undertook a series of
pharmacophore mapping studies.$^{16}$ Their results demonstrated several interesting
findings: 1) while all three natural products displayed the ability to promote neurite
outgrowth in the presence of nerve growth factor (NGF), they were inactive in the
absence of NGF, supporting the notion that these interesting natural products serve to
enhance the activity of NGF; 2) the natural enantiomer of jiadifenin (1.21) exhibited
activity similar to that of the racemic natural product; 3) an $\alpha$-substituent at C-10 appears
to be essential for activity, as compounds either possessing a β-substituent at C-10 or no substituent were inactive; and 4) the hemiketal function of jiadifenolide (1.2) and jiadifenin (1.21) may not be essential for biological activity, as analogues without this function also possessed the desired activity.
1.5. References


Chapter 2

The synthesis of jiadifenolide
2.1. Initial synthetic design

The structure of jiadifenolide (2.1, Scheme 2.1) poses a significant challenge even to those skilled in the art of organic synthesis. Embedded within the fifteen-carbon framework are five fused ring systems consisting of seven stereogenic centers, all of which are contiguous and five of which are fully substituted. Five of these stereocenters are found within the central cyclohexane ring, and an effective method for dealing with this dense functionality is vital.

![Scheme 2.1. C–H oxidation strategy for jiadifenolide (2.1).](image)

The C5 all-carbon quaternary stereocenter was identified as a particularly challenging motif, and our strategy for dealing with the complex architecture of jiadifenolide was developed around this specific problem (see Scheme 2.1). It was our thought that perhaps a C–H oxidation reaction would allow for the conversion of a simple methyl group into the oxidized methylene found at C14 in the lactone. While this was a simple idea, the power of this strategy would be the direct incorporation of the all-carbon quaternary stereocenter through a prochiral geminal methyl motif (for example, compound 2.2). While the identity of the requisite directing group was initially unclear, propellane ketone 2.7 quickly became a target for synthesis (see Scheme 2.2).
Our hope was to generate a rapid synthesis of this key intermediate (2.7), which was expected to be a flexible intermediate through simple modification of the keto group. When looking at the problem at hand, we envisioned a cascade of reactions that could advance a simple, known keto ester\(^1\) (2.3) to the desired tricycle in one chemical step. If successful, this cascade would initiate with a Michael addition\(^2\) of the thermodynamic enolate of 2.3 into isopropyl vinyl ketone\(^3\) (2.4) to give intermediate enolate 2.5. After isomerization to the more substituted enolate (2.6), an aldol addition into the pendent ketone with concomitant lactonization would provide tricycle 2.7 in rapid fashion. While aldol addition reactions are generally disfavored with bulky ketone enolates, we hoped that the final lactonization process would serve as a thermodynamic sink.

In the lab, however, this process was unattainable. Although a variety of reaction conditions were explored, the results were typically the same (\textit{i.e.} recovered starting material). In fact, the only identifiable product was \(\beta\)-diketone 2.8 (Scheme 2.3), obtained by first treating ketone 2.3 with lithium diisopropylamide (LDA) followed by addition of the
Michael acceptor 2.4. This product, obtained in low yield (10%), is the result of a Dieckmann condensation between the enolate of the Michael adduct (see 2.5, Scheme 2.2) and the pendent ester group. In this reaction, the remaining mass balance was recovered starting material.

Scheme 2.3. Attempts to implement the initial concept.

In light of the lack of reactivity observed with isopropyl vinyl ketone (2.4), we wondered whether the isopropyl ketone was too sterically hindered to undergo the desired aldol/lactonization reaction. In an effort to avoid this potential issue, various experiments were undertaken with methyl vinyl ketone (2.10, Scheme 2.4) or an equivalent (see 2.11, 2.12, and 2.13). Unfortunately, a variety of substrates (2.9 where R = Me, Et, i-Pr, and t-Bu) failed to react under either acidic or basic conditions in a variety of solvents at temperatures ranging from −78 °C to 110 °C. In almost all cases, starting material was recovered along with varying quantities of decomposition. Without any tangible results, it was decided to investigate strategies that did not rely on a Michael addition to forge the all-carbon quaternary center.
Although the desired Michael/aldol/lactonization cascade was unsuccessful in our hands, we were still drawn to the idea of using an intramolecular aldol addition with concomitant lactonization as an entry into the tricyclic architecture. Because the initial Michael addition was problematic, our focus shifted toward intermediates with the quaternary center already in place. Through a search of the literature, spirocycle 2.15 (Scheme 2.5) became an attractive starting material.

Accessible through Diels–Alder chemistry\(^8\) as well as through a hydroacylation strategy\(^9\), spirocycle 2.15 contains all of the carbon atoms needed to generate tricyclic ketone 2.14. Although all known methods produce 2.15 as a mixture of diastereomers, often with the desired diastereomer being the minor component of the mixture, simple chromatographic separation affords the desired diastereomer cleanly. My coworker demonstrated that the action of \textit{in situ} generated ruthenium tetroxide\(^{10}\) affected an
oxidative cleavage of the trisubstituted alkene, with subsequent treatment with trimethylsilyldiazomethane providing diketone 2.16. Heating with piperidine and acetic acid or para-toluenesulfonic acid cleanly converts the diketone into the tricyclic architecture found in 2.14.

Scheme 2.6. Addressing the diastereoselectivity problem of spirocycle 2.15.

While this three-step procedure reliably provided access to the desired propellane architecture required for a synthesis of jiadifenolide, the availability of the desired diastereomer of 2.15 was a major concern. The β-methyl of cyclopentenone 2.17 directs Diels–Alder reactions away from the desired face of reactivity (see 2.17 to 2.15 Scheme 2.6), while the Claisen rearrangement utilized in the hydroacylation route provides a one to one mixture of diastereomers (see 2.18 to 2.15). In an effort to overturn this lack of selectivity, a plan was devised to make use of the facial differentiation possible from a β-methyl group. It was thought that the lithium enolate
derived from 2.19 could engage known dibromide 2.20\textsuperscript{11,12} in a diastereoselective (although inconsequential) alkylation reaction; treatment of the resulting intermediate with a second equivalent of base could then allow a second diastereoselective alkylation to give rise to spirocycle 2.15.\textsuperscript{12} In practice, this plan was effective. Silyl enol ether 2.19\textsuperscript{13} was first treated with methyllithium to afford an intermediate lithium enolate, which underwent a subsequent alkylation at the more activated site of dibromide 2.20. The crude product (2.21) was then immediately treated with potassium hydride at room temperature to induce the ring-forming alkylation. While the diastereoselectivity was good (none of the undesired diastereomer was observed by \textsuperscript{1}H-NMR), the reaction efficiency was, unfortunately, quite poor (25\%). Facing this low reaction efficiency, we decided to adopt a new strategy.
2.2. Chain elongation strategy for synthesizing the key tricyclic ketone

Given the troubles encountered while trying to realize the previously described synthetic plans, the use of a Robinson annulation\textsuperscript{14} to build the foundation for a synthesis of jiadifenolide (2.1) became attractive. In light of the issues with the Michael addition as well as the observation of a subsequent Dieckmann condensation, we decided to investigate β-ketoester 2.22 (Scheme 2.7) as an alternative starting material. The advantages of 2.22 include simple, regioselective enolate formation as well as reduced proclivity to undergo an undesired Dieckmann condensation (such a reaction would form a cyclobutane product). In addition, β-ketoester 2.22 is readily synthesized in racemic form\textsuperscript{15} in two steps from commercially available methyl 3-oxoheptanoate or as a single enantiomer\textsuperscript{8,16} in three steps from the monoterpenic (R)-(−)-pulegone. Both routes have provided ample material in our hands.

Scheme 2.7. Synthesis of bicyclic ketone 2.25.
Starting with the ethyl ester derivative of \textbf{2.22}, Robert Coates and coworker at the University of Illinois demonstrated a two-step Robinson annulation with methyl vinyl ketone (\textbf{2.10}) consisting of a triethylamine-mediated conjugate addition followed by an aldol condensation with pyrrolidinium acetate;\textsuperscript{17} however, the Michael reaction suffered from poor kinetics and took seven to ten days for full conversion. Modifying this procedure, we utilized 1,8-diazabicycloundec-7-ene (DBU) to promote a rapid Michael addition between \textbf{2.22} and \textbf{2.10} to give diketone \textbf{2.23} in excellent yield within five minutes. After a quick purification, \textbf{2.23} was heated in the presence of \textit{para}-toluenesulfonic acid under Dean–Stark\textsuperscript{18} conditions to provide ready access to bicycle \textbf{2.24}. Gratifyingly, deconjugative dimethylation\textsuperscript{19} with potassium \textit{tert}-butoxide and iodomethane afforded dimethyl ketone \textbf{2.25} in 91\% yield with excellent regioselectivity. This three-step procedure proved to be quite scalable and was reproducible on over 100 mmol scale, providing more than 18 g of \textbf{2.25} in a single batch.

With a reliable synthesis of \textbf{2.25}, we next needed to address the major problem with using \textbf{2.22} as a starting material: the need to affect a one-carbon chain elongation of the ester group. Historically, the Arndt–Eistert ester homologation method\textsuperscript{20} has been a popular way to affect a one-carbon chain elongation of esters. This multi-step process involves conversion of a carboxylic acid into the corresponding $\alpha$-diazoketone, generally by way of an acid chloride intermediate. The newly formed $\alpha$-diazoketone is then induced to undergo a Wolff rearrangement\textsuperscript{21} in the presence of silver (I) oxide and a nucleophilic solvent (typically water or an alcohol). While hydrolysis of ester \textbf{2.25} was difficult, the action of sodium propanethiolate in hot DMF afforded carboxylic acid \textbf{2.26} nearly quantitatively (Scheme 2.8); however, the conversion of this acid to the corresponding diazoketone (\textbf{2.27}) proved too challenging. In fact, treatment of the acid chloride derived from acid \textbf{2.26} with either freshly distilled diazomethane or commercially
available trimethylsilyldiazomethane in THF resulted in no reaction. It is likely that the acid chloride is too sterically crowded for addition of diazomethane to occur, and as a testament to this fact, the acid chloride was reisolated even after column chromatography. The corresponding acid mesylate\textsuperscript{22} also failed to react under these conditions.

Scheme 2.8. Initial chain elongation attempts.

A suitable alternative to this chain elongation method would be the conversion of the ester to a methylene bearing a leaving group followed by $S\textsubscript{N}2$ displacement by cyanide anion; the resulting nitrile (see 2.30) would provide the elongated product after simply hydrolysis. While mesylate 2.29 could be generated through a three-step procedure, involving protection of the ketone as a cyclic acetal, ester reduction, and mesylation of the primary hydroxy group, it, too, suffered from a lack of reactivity, and all attempts to synthesize nitrile 2.30 via this method were unfruitful.
Scheme 2.9. Use of the Peterson olefination to perform a chain homologation.

We then turned our attention toward chain elongation methods from the aldehyde oxidation state, which was accessible by a simple Swern oxidation\(^2^3\) of alcohol \(2.28\) to afford aldehyde \(2.31\) in good yield (Scheme 2.9). While we initially planned to employ a Wittig olefination reaction\(^2^4\) to generate an enol ether, making use of the commercially available (methoxymethyl)triphenylphosphonium chloride, this reaction proved unsuccessful in our hands. Formation of the corresponding ylide in the presence of potassium bis(trimethylsilyl)amide (KHMDS) proceeded uneventfully; however, no addition was observed at low temperatures while decomposition of the ylide occurred at higher temperatures. In the face of this disappointment, we next investigated the alternative Peterson olefination.\(^2^5\) It is conceivable that reversible addition of the phosphonium ylide is the culprit for the diminished reactivity with aldehyde \(2.31\), and we hoped that an \(\alpha\)-silyl anion might lead to an irreversible reaction. After preparation of the anion derived from (methoxymethyl)trimethylsilane \((2.32)\) with sec-butylthium, aldehyde \(2.31\) was added at low temperature for one hour; subsequent addition of potassium tert-butoxide and warming to room temperature then afforded the desired enol ether \(2.33\) in 85% yield as a twenty to one mixture of \(Z/E\) isomers.

While the Peterson olefination performed admirably to provide ready access to \(2.33\), manipulation of this intermediate proved arduous (Scheme 2.10). We were disappointed to observe that the treatment of \(2.33\) with aqueous HCl in THF produced none of the desired aldehyde \(2.34\); instead, \(2.33\) underwent full conversion to \(\beta\)-
hydroxyketone 2.36. While this product is the result of an intramolecular aldol addition of the *in situ* derived 2.34, β-hydroxy ketone 2.36 was resistant to attempts to reverse this process. Fortunately, modulation of the pH of the reaction allowed for a reduction in the rate of this process, and the use of para-toluenesulfonic acid afforded aldehyde 2.34 in 66% yield along with 25% of 2.35 (resulting from only acetal hydrolysis) and 9% of the aforementioned aldol product 2.36. While usable quantities of 2.34 could likely be obtained *via* this method, we came to favor the use of formic acid in a mixture of THF and water. Under these conditions, a mixture of 2.34 (47%) and 2.35 (52%) could be obtained without any formation of 2.36. Simple separation with silica gel chromatography provided the desired aldehyde, while the recovered enol ether 2.35 could be resubjected to the reaction conditions. In this manner, enol ether 2.33 could be converted to aldehyde 2.34 in nearly quantitative yield through only a few cycles.

Scheme 2.10. Conditions for the hydrolysis of enol ether 2.33.

With ready access to aldehyde 2.34, the desired tricyclic architecture was tantalizingly close. A Lindgren–Kraus–Pinnick oxidation26 yielded carboxylic acid 2.37, setting the stage for a pivotal cyclization (Scheme 2.11). While the classic method for
addressing this type of problem is the iodolactonization reaction\textsuperscript{27}, followed by reduction of the newly formed C–I bond, we hoped to make use of a one-step, acid-mediated reaction to help ease the pain of the cumbersome chain elongation. Pleasingly, simply stirring a solution of \textbf{2.37} and \textit{tin(IV)} chloride\textsuperscript{28} in dichloromethane provided an 85\% yield of tricyclic ketone \textbf{2.7}. In total, ten steps were required to advance the known, pulegone-derived \(\beta\)-ketoester \textbf{2.22} to the key tricyclic ketone \textbf{2.7} in 17\% overall yield (37\% after recycling through the hydrolysis of enol ether \textbf{2.35}).

\begin{scheme}
\begin{align*}
\text{Me} & \quad \text{CHO} & \quad \text{NaClO}_2 & \quad \text{2-methyl-2-butene} & \quad \text{NaH}_2\text{PO}_4\cdot\text{H}_2\text{O} & \quad \text{t-BuOH, H}_2\text{O} \\
\text{CH}_2\text{Cl}_2 & \quad \text{Me} & \quad \text{CO}_2\text{H} & \quad \text{SnCl}_4 & \quad \text{CH}_2\text{Cl}_2 & \quad \text{Me} \\
\text{2.34} & \quad \text{2.37} & \quad \text{2.7} \\
\end{align*}
\end{scheme}

\textbf{Scheme 2.11.} Lewis acid-mediated lactonization to access tricyclic ketone \textbf{2.7}.

While the previously described sequence of reactions proved to be quite scalable, providing gram quantities of tricyclic ketone \textbf{2.7}, we still longed for a shorter sequence. While searching for related chain elongation methods, we were reminded of the van Leusen reaction\textsuperscript{29}. While typically involving ketones as substrates, this reaction involves the addition of the anion of \textit{para}-tosylmethyl isonitrile (TosMIC, \textbf{2.38}, Scheme 2.12) into a ketone or aldehyde; treatment of the putative \textit{N}-formyliminoketene with an alcohol solvent then unveils the homologated nitrile product. While we were concerned about the sterically congested nature of our aldehyde, the results obtained by Brückner and coworker on a similar angular aldehyde\textsuperscript{30} bolstered our confidence. Gratifyingly, aldehyde \textbf{2.31} underwent clean conversion to the homologated nitrile when added to a mixture of potassium tert-butoxide and \textbf{2.38} in cold THF followed by refluxing in methanol. Perhaps more importantly, simply treating the newly formed nitrile \textbf{2.30} with
concentrated sulfuric acid in wet methanol at 100 °C\textsuperscript{31} brought about three needed changes, ultimately affording tricyclic ketone 2.7: the hydrolysis of the nitrile function, the heterocyclization of the resulting \(\gamma,\delta\)-unsaturated acid, and the hydrolysis of the dioxolane acetal. This powerful transformation provided 2.7 in a reduced eight steps from 2.22, with an improved 34% overall yield without the need to recycle intermediates.

Scheme 2.12. Use of the van Leusen reaction as an alternate homologation.
2.3. C–H oxidation strategy for jiadifenolide

As previously discussed (*vide supra*, Scheme 2.1), we were drawn to the idea that a C–H oxidation reaction may allow for a desymmetrization of the pro-chiral carbon atom bearing the geminal methyl groups. With a reliable and scalable route to tricyclic ketone 2.7, we were poised to convert our abstract idea into something tangible. In order for this idea to be successful, three aspects needed to be successfully implemented: simple conversion of the keto group of 2.7 into a directing group, selective oxidation of only the β-methyl group, and facile removal of the directing group to provide a useful handle for further functionalization.

Based on the requirements described above, the oxime-directed palladation/oxidation reaction was chosen as a suitable method to accomplish the desired transformation. The use of an oxime as a directing group for the palladium-mediated activation of “inert” methyl groups can be traced to a communication from McDonald, Shaw, and coworkers from the University of Leeds in 1978. In their pioneering studies, they demonstrated that the treatment of oximes derived from ketones bearing a tert-butyl group with sodium tetrachloropalladate and sodium acetate promoted cyclopalladation of one of the methyl groups of the tert-butyl group (providing products such as 2.38, Scheme 2.13). This reaction was selective for palladation of the tert-butyl group over methyl (2.38), ethyl, and even phenyl groups, substrates which had previously been shown to be effective for palladation by Onoue, Minami, and Nakagawa; this result is dictated by the strong preference for the hydroxyl group to be located distal to the sterically bulky tert-butyl group. Following up on these results, Carr and Sutherland demonstrated the ability to functionalize these cyclic palladium complexes through reactions with NaBD₄, replacing the palladium atom with a deuterium, or CCl₃I, affording the β-iodide.
Scheme 2.13. Baldwin’s pioneering work toward oxime-directed C–H oxidations.

As an expansion of this powerful and growing methodology, the Baldwin group at the University of Oxford accomplished the first oxygenation of these oxime-derived dimeric organopalladium complexes in 1985. As shown in Scheme 2.13, successive treatment of 2.38 with pyridine, lead(IV) acetate, and sodium borohydride procured the acetoxylated oxime 2.39 in quantitative yield; if desired, the use of two equivalents of lead(IV) acetate leads to further oxidation to return the keto group (2.40), although this comes about in a diminished 64% yield. In fact, this reaction was effective in several molecular constructs, including oximes derived from 2,2-dimethylcyclohexanone (to give 2.41), 2,2,6,6-tetramethylcyclohexanone (to give 2.42), as well as steroidal frameworks (such as luponone where the equatorial methyl group is oxidized in preference to give
2.43, based on coplanarity with the oxime). These findings have prompted the syntheses of several terpenoids via this method.\(^{36}\)

Perhaps the most glaring problem with the chemistry described above is the use of both stoichiometric palladium to generate the organopalladacycle as well as stoichiometric lead to oxidize this organometallic intermediate. In 2004, Melanie Sanford and her lab at the University of Michigan reported that similar transformations could be accomplished with a substoichiometric quantity of palladium without the need for a lead-based oxidant.\(^ {37}\) In this event, heating O-methyl oximes (such as 2.44, Scheme 2.14) with only 5 mol% of palladium(II) acetate and at least one equivalent of (diacetoxy)iodobenzene in a mixture of acetic acid and acetic anhydride (1:1) at 100 °C afforded \(\beta\)-acetoxy oximes (such as 2.45) in good yields (39 – 86%).

**Scheme 2.14.** Sanford’s catalytic oxime-directed C–H oxidation reactions.

While providing a simple method to accomplish the oxidation of unactivated C–H bonds, the O-methyl oxime proved quite resistant to the functional group conversion needed to reintroduce a keto group.\(^ {38}\) Under acidic conditions, the group generally
observed a mixture of elimination products; while the use of titanium(III) chloride was effective in some cases, this method, too, suffered due to the air sensitivity and the high cost of the reagent. Fortunately, Sanford and coworker offered a creative and simple solution to this problem. In 2010, they demonstrated that the parent oximes (such as \textbf{2.46}) could also undergo this transformation using the previously described reaction conditions. In this particular case, the oxime is pre-stirred in the acetic acid and acetic anhydride solvent system before addition of the catalyst and oxidant. It is presumed that during this time, the oxime is acetylated, providing the more stable O-acetyl oxime; in the absence of acetic anhydride, the parent ketone is the only observable product. In order to demonstrate the utility of this alteration to their method, the authors then described a simple, high-yielding two-step procedure for the conversion of the oxime to the ketone (see \textbf{2.47} to \textbf{2.48}). In fact, this procedure could be carried out in a single reaction flask. Although this powerful method was applied to a variety of substrates in their disclosure, the fate of this reaction in a complex setting had yet to be determined at the outset of our work.

In order to apply the Sanford group’s oxidation protocol to the complex, tricyclic architecture of tricycle \textbf{2.7}, it was first converted to its corresponding oxime (\textbf{2.49}, Scheme 2.15) through heating with hydroxylamine hydrochloride in pyridine. Pleasingly, application of the Sanford protocol resulted in the formation of the desired acetoxyalted compound \textbf{2.50}; however, the yield was unfortunately less than desirable at only 22%. Examination of the crude reaction mixture showed that \textbf{2.50} was formed along with diastereomer \textbf{2.51}, epimeric at the newly formed stereocenter, as well as the product resulting from acetoxylation of both methyl groups in an overall 1 : 1.3 : 0.7 mixture, respectively. Attempts to vary the reaction temperature as well as time were unsuccessful in improving the yield of \textbf{2.50}. This result was disappointing. It is well known that selectivity for this type of reaction arises from a conformational bias where
one methyl group is more coplanar with the oxime and the palladium catalyst. The inspection of handheld models as well as low-level calculations indicated a possible preference for the β-methyl to reside in a more coplanar relationship with the oxime group; however, the experimental results clearly did not match these expectations.

Scheme 2.15. Application of Sanford’s oxidation to the jiadifenolide (2.1) problem.

While looking at the reaction conditions, we hypothesized that perhaps the high temperature requirement was the culprit for this lack of diastereoselectivity. At this high temperature, oxime 2.49 would be more flexible, allowing for more rapid changes in conformation and, ultimately, for the palladium catalyst to sample both methyl groups and palladate indiscriminately. In order to test this hypothesis, we turned to the original conditions developed by the Baldwin research group; under their protocol, palladation proceeds at room temperature, thus allowing us to directly investigate the role of temperature in the selectivity of our substrate. Treatment of oxime 2.49 with Na₂PdCl₄ and NaOAc in methanol followed by subsequent treatment with pyridine and then Pb(OAc)₄ afforded a 2.2 : 1 mixture of oxidation products in a combined yield of 63%. While our hypothesis proved correct, the diastereoselectivity in this reaction favored the undesired epimer (possessing the same stereochemistry as 2.51).

In the face of these disappointing results, a number of other substrates were investigated for C–H oxidation in hopes of altering the reaction sequence to place the
oxidation reaction at a more favorable stage of our synthesis. For example, oxime 2.52 (Scheme 2.16) was prepared utilizing the same protocol from ketone 2.25. It was our hope that the bicyclic structure would adopt a conformation differing from that of the propellane system, and that perhaps the angular carbomethoxy group might help to force the β-methyl group into a pseudoequatorial position. Unfortunately, subjection of 2.52 to Sanford’s oxidation conditions resulted in the formation of oxidation product 2.53 as a five to one mixture favoring the undesired diastereomer (shown). Carboxylic acid 2.37 was also investigated as a possible substrate. Alkylative ester formation followed by oxime formation provided oxime 2.54; however, this substrate failed to undergo the desired oxidation reaction and only decomposition was observed. The loss of the alkene H signal in the 1H-NMR spectrum was noted, and it is possible that the homologated ester directed the palladium catalyst to the alkene in the course of the reaction.

Scheme 2.16. C–H oxidation attempts on earlier substrates (2.25 and 2.37).

As a continuation of our efforts to evaluate related substrates in hopes of finding a more favorably selective C–H oxidation, the tricyclic oxime 2.56 (Scheme 2.17) was briefly investigated. Because we will ultimately need a β-hydroxy group at C7, we
wondered whether a direct, oxidative lactone formation would be possible from the vantage of acid 2.37 and, if so, whether this newly formed ring system would have a positive influence on the conformation of the central cyclohexane ring.

![Scheme 2.17](image)

**Scheme 2.17.** An additional substrate for oxidation.

While underutilized, it is known that carboxylic acids can be induced to cyclize with pendent ketones under the influence of a hypervalent iodine species.\(^{39}\) Although typically successful with aryl ketones, we were pleased to find that simple treatment of 2.37 with Koser’s reagent\(^{40}\) ([hydroxy(tosyloxy)iodo]benzene) in hot dichloromethane afforded the desired lactone 2.55, albeit in modest yield. The keto group of 2.55 was then successfully converted to the oxime under the standard conditions; however, oxime 2.56 proved to be unstable under Sanford’s conditions. The use of Baldwin’s more mild conditions did produce oxidized product, but it was formed in low yield; NOE analysis of the crude product indicated that selectivity was, again, in favor of the undesired diastereomer.
2.4. Completion of the synthesis of jiadifenolide

With the disappointment of being unable to find a substrate capable of undergoing an oxime-directed C–H oxidation to favor the production of the desired oxidation diastereomer, it was easy to overlook that we were able to get our hands on oxidation compound 2.50 (vide supra, Scheme 2.15). In fact, the reaction was reproducible on larger scale and 2.50 was easily separated from the other components of the reaction mixture via column chromatography. In one batch, nearly 1.5 g of 2.50 is obtainable.

Scheme 2.18. Endgame strategy for the synthesis of jiadifenolide (2.1).

From the vantage of 2.50, several moves still needed to be accomplished (see Scheme 2.18). Looking at C6, the oxime group needed to be replaced by an oxidized carbon atom to form the lactone carbonyl. It was hoped that hydrolysis of the oxime to the keto group would pave the way for a carbomethoxylation of an intermediate vinyl triflate. Not only would this install the requisite carbon atom, but it also would facilitate the introduction of the oxygen atoms needed at C6 and C7 as it was anticipated that epoxidation of the resulting enoate would be possible. Finally, oxidation would also need to be introduced at C10 of the bridging lactone ring, which would presumably follow the design employed by the Theodorakis lab (enolate oxidation with Davis’s oxaziridine followed by oxidation to the keto group, see Chapter 1.4).
In order to accomplish the first goal, a method for the clean removal of the oxime was needed; however, a variety of common protocols were ineffective in the case of oxime \textbf{2.50}. For example, reduction with titanium(III) chloride, reduction with zinc metal, and ozonolysis all returned only starting material. Fortunately, the use of iron metal in the presence of catalytic chlorotrimethylsilane and acetic acid, conditions developed by Steven Weinreb and coworkers\textsuperscript{44} at the Pennsylvania State University, proved to be effective at cleanly reducing the N–O bond of \textbf{2.50} (Scheme 2.19); addition of water afforded desired ketone \textbf{2.57} in good yield. While this reaction worked well on scales less than 30 mg, aggregation of the iron metal on the magnetic stirring bar led to decreased efficiency on larger scales; fortunately, the reaction could be performed in multiple 30 mg batches before being combined for workup and purification. For example, 660 mg of \textbf{2.50} could be evenly spread among twenty two-dram vials to ultimately yield 490 mg of \textbf{2.57}.

\begin{center}
\textbf{Scheme 2.19.} Three-step sequence to synthesize enoate \textbf{2.60}.
\end{center}
With 2.57 in hand, a quick, two-step sequence allowed for the introduction of the remaining carbon atom required for jiadifenolide (2.1). Thus, conversion of 2.57 to vinyl triflate 2.59 was accomplished by reaction of the corresponding potassium enolate with Comins’s reagent\textsuperscript{15} (2.58). After a quick purification, triflate 2.59 was then treated with a palladium catalyst under an atmosphere of carbon monoxide; in situ methanolysis of the putative acylpalladium species provided enoate 2.60 in 49% yield over the two-step protocol.

With an expedient route to enoate 2.60, it was now possible to build the remaining lactone. While we were pleased to find that the treatment of 2.60 with potassium carbonate in methanol afforded the desired lactone 2.61 (Scheme 2.20), we were surprised to find that the lactonization reaction was not clean. Along with a 43% yield of the desired lactone 2.61, lactones 2.62 (formed from the conjugate addition of methanol to 2.61) and 2.63 (formed from isomerization of the alkene) were produced in 26% and 20% yield, respectively.

\[ \text{Scheme 2.20. Lactonization/epoxidation sequence to yield key epoxide 2.64.} \]
Fortunately, this mixture proved to be inconsequential. Given that we needed to epoxidize an olefin containing an electron-withdrawing group, nucleophilic epoxidation seemed to be the most logical choice. This led us to wonder whether 2.61, 2.62, and 2.63 might exist in equilibrium in a reaction medium of 3 M sodium hydroxide and methanol. If so, only 2.61 would be capable of undergoing the epoxidation reaction. Gratifyingly, all three lactones can be taken forward without the need for separation and converted to epoxide 2.64 by simple treatment with aqueous hydrogen peroxide and sodium hydroxide in methanol in 69% yield.

At this stage of the synthesis, the only remaining objectives were the introduction of oxidation at C10 on the bridging lactone in the form of an oxo group and then the addition of a molecule of water. Given that the most acidic protons of epoxide 2.64 are the α hydrogens at C10, the most straightforward method for installing oxygenation is the oxidation of an enolate at this position. With this in mind, the corresponding enolate was formed via treatment of 2.64 with sodium bis(trimethylsilyl)amide (NaHMDS) at −78 °C, and then Davis’s oxaziridine (2.65) was added (Scheme 2.21).

Scheme 2.21. Oxidation attempt with Davis’s oxaziridine (2.65).
While the starting material was fully consumed, none of the desired alcohol 2.66 was observed; however, both $^1$H-NMR and mass spectrometric analysis indicated that oxidation had occurred. While much of the NMR spectrum was consistent with 2.66, a large downfield shift of the proton at C7 indicated ring opening of the epoxide. In fact, the spectral data was fully consistent with the structure of bridged ether 2.67. This product, the result of attack on the epoxide by the intermediate alkoxide formed in the reaction, shares many of the structural features of jiadifenolide (2.1), with the exception of the hydroxy group at C10. Investigation of handheld models made the prospects of introducing this last group look rather dim. In addition, variations in the reaction time, temperature, and quenching method, as well as direct introduction of an oxidant (Dess–Martin periodinane$^{46}$) were all unsuccessful at allowing for the isolation of alcohol 2.66 or its oxidized form.

The findings from the enolate oxidation reaction led us to believe that the hydroxyl group of 2.66 lies too close to the epoxide, and thus other methods that would generate the same product would likely be similarly unsuccessful. This led us to adapt our strategy and investigate methods that would allow for the introduction of an oxo group at C10 without the intermediacy of a hydroxyl group. We were quickly drawn to chemistry developed by Prof. Harry Wassermann and coworker at Yale University in the 1970s.$^{47}$ In that work, they were able to demonstrate that simply heating (trisdimethylamino)methane (2.69, see Scheme 2.22) with lactones (such as 2.68) allowed for facile formation of $\alpha$-enamino lactones (2.70); these products could then undergo oxidative cleavage in the presence of singlet oxygen to unveil $\alpha$-keto lactones (2.71, although typically existing as the enol tautomer 2.72). We first investigated this methodology on a model substrate (2.73), accessible by a route for an alternative strategy that we developed (see Chapter 2.5). Indeed, we were able to accomplish this
two-step procedure with 2.73, although we chose to use ozone for the oxidative cleavage for simplicity. While yields were not calculated, the overall conversion looked quite good.

Studies from the Wasserman lab (ref. 47):

Our studies with a model system:

Scheme 2.22. Application of the Wasserman method to a model system.

Thus, on the basis of this precedent, we sought to apply the Wasserman method to our advanced intermediate 2.64 (see Scheme 2.23). In the event, a solution of 2.64 in a one to one mixture of toluene and Bredereck’s reagent (2.76, used due to improved solubility of 2.64) was heated to 100 °C and followed by mass spectrometry. Over the course of several time points, all of the starting material had been consumed, but none of the desired product was observed; the only observed mass was the result of the addition of C5H11N2 to 2.64. It was hypothesized that perhaps the identity of this compound was an intermediate aminal (2.77), which would be formed prior to elimination of dimethylamine to give enamine 2.78. With this in mind, heating was continued, but at no point did this intermediate undergo the requisite elimination. In order to sort out what
was going on in the reaction, the reaction was concentrated under reduced pressure, and the crude product was analyzed by $^1$H- and $^{13}$C-NMR. It was immediately apparent that an enamine was formed, given the new signal observed at 6.09 ppm; however, there were two signals for the $N$-methyl groups, each integrating to six hydrogens relative to the enamine signal. After working through additional data, it became clear that the spectra were consistent with the structure of 2.80.

Scheme 2.23. Application of the Wasserman method to epoxy lactone 2.64.

A simple explanation for this result could be that excess dimethylamine participates in a ring-opening reaction with our epoxide following the formation of the enamine; however, it is interesting to note that this is in contrast to the results obtained with the model substrate (2.73), where none of the ring-opened product was observed. This observation has led us to propose an alternate mechanism. The formation of the intermediate aminal 2.77 should proceed as expected; however, prior to elimination, one
of the nitrogen atoms could participate in an intramolecular alkylation with the pendent epoxide (see 2.77 to 2.79). This bridged ammonium ion could then lead to the observed product either through iminium formation and deprotonation or through a more concerted E2 elimination (handheld models indicate an antiperiplanar relationship between the nitrogen and hydrogen atoms).

Scheme 2.24. Attempts to alkylate 2.64 with Eschenmoser’s salt (2.81).

It is instructive to note that this "atom transfer" reactivity is not unique to the use of Bredereck’s reagent. Although poorly soluble in (trisdimethylamino)methane (2.69), epoxy lactone 2.64 proceeded to the same product in its presence as well. In addition, we briefly investigated an alkylation with Eschenmoser’s salt\(^49\) (2.81, Scheme 2.24), and although some of the desired exocyclic methylene compound 2.82 was formed, it was the minor component of a two to one mixture favoring the ring-opened product 2.83 (along with some recovered starting material).

Clearly, the issues with intramolecular epoxide ring-opening reactions were placing a strain on the methods available for the installation of the \(\alpha\)-keto group on the bridging lactone. As we contemplated a way forward from the vantage of epoxy lactone 2.64, we took notice of a unique finding disclosed by Danishefsky and coworker in their synthesis of the CDEF ring system of the antibiotic lactonamycin.\(^50\) Faced with the difficult task of installing \(\alpha,\beta\)-unsaturation into a strained, structurally complex \(\gamma\)-lactone (2.84, Scheme 2.25), they had hoped to employ a syn elimination of a putative iodoso
intermediate; however, upon treatment of their $\alpha$-iodo lactone with dimethyldioxirane (DMDO, 2.85), they observed the formation of $\alpha$-keto lactone 2.86 instead. They proposed an iodoso Pummerer-like mechanism to explain this transformation, although a few other mechanisms were proposed in a footnote of their report.

**Scheme 2.25.** Danishefsky’s iodoso Pummerer-like transformation.

We were drawn to this idea, as it would offer a solution to our present oxidation problem that would potentially bypass our previous troubles. In the case at hand, iodination of epoxy lactone 2.64 (Scheme 2.26) proceeded uneventfully by treatment of an intermediate cyclic silyl ketene acetal with $N$-iodosuccinimide (NIS). Iodide 2.87, produced as an inconsequential mixture of diastereomers, was immediately treated with freshly distilled DMDO$^{51}$ (2.85) in the dark; gratifyingly, this reaction generated the desired $\alpha$-keto lactone 2.88 for the first time. If desired, the crude product could be purified via tedious column chromatography to provide 2.88 in a 66% yield from 2.64; however, it was operationally simpler to carry this forward crude. While numerous acidic and basic conditions enable a synthesis of jiadifenolide (2.1) from 2.88, we found that the use of lithium hydroxide in a mixture of THF and water gave the most reproducible results.
In total, the sequence described in detail above afforded synthetic jiadifenolide in a total of eighteen chemical steps from the known β-ketoester 2.22. As this starting material is available in two (racemic) or three (enantiopure) steps from commercially available starting materials, the overall sequence consists of twenty steps racemically, or twenty one if a single enantiomer is desired. The spectroscopic data for synthetic jiadifenolide (2.1) produced from this sequence from (R)-(+) -pulegone matched the data reported previously by Fukuyama and coworkers\(^2\) as well as Theodorakis and coworkers\(^4\). As shown in the full reaction scheme (Scheme 2.27), our synthesis made use of the stereochemistry contained within 2.22 to build jiadifenolide (2.1) in a diastereoselective manner. Of particular note, we were able to rapidly generate the propellane core (2.7) of the target using rather simple yet powerful transformations, we employed Sanford’s catalytic C–H oxidation to introduce local asymmetry at C5, and we made use of an iodoso Pummerer-like transformation to solve a difficult, late-stage lactone oxidation.
Scheme 2.27. Successful route to jiadifenolide (2.1).
2.5. Alternative route toward jiadifenolide

As is often the case when engaging in target-directed synthesis, we explored several alternative routes while we tackled some of the roadblocks described above. While many of these were abandoned at an early stage of exploration, one alternate pathway toward jiadifenolide (2.1) was explored in-depth.

Scheme 2.28. Alternative route toward jiadifenolide (2.1).

Still drawn to the idea of utilizing a C–H oxidation to address the fully substituted stereocenter at C5, we wondered whether a late stage oxidation would allow for the direct formation of the lactone as the final step of the synthesis. More specifically, it was hoped that the carboxylic acid group of 2.89 (Scheme 2.28) would be able to direct a transition metal catalyst to the β-methyl group, which would then undergo an insertion of a C–H bond. We then hoped that the resulting palladacycle would be able to be oxidized and then undergo a subsequent reductive elimination to generate jiadifenolide (2.1). The advantage of this route is that the carboxylic acid group is attached to an sp³ center with defined stereochemistry, and it was thought that this would prohibit undesired oxidation of the α-methyl group. Ultimately, a synthesis of 2.89 was realized utilizing tricyclic ketone 2.7 as a common intermediate; however, the desired oxidation to advance 2.89 to jiadifenolide (2.1) has been unsuccessful under a wide variety of reactions conditions. The details of this work will be described elsewhere.
2.6. Summary

In total, we were able to accomplish a synthesis of jiadifenolide (2.1) in eighteen overall steps from a known, (R)-(+-)‐pulegone‐derived building block (itself available from this terpene in three steps). A mixture of classic ideas (such as the time‐honored Robinson annulation to build a cyclohexane ring and the deconjugative dimethylation to install the geminal methyl motif), and modern methods (such as Sanford’s catalytic oxime‐directed C–H oxidation reaction to generate local chirality and an iodoso Pummerer‐like rearrangement to solve a challenging lactone oxidation problem) were employed in concert to effectively address the challenges posed by the target’s unique architecture. Although the directed oxidation lacked diastereoselectivity in our molecular context, this may still be used to access jiadifenolide‐like structures that differ in the stereochemistry about the central cyclohexane ring system. This would allow further biological evaluation of the interesting activity displayed by the parent natural product and other members of the *Illicium* family of natural products.
2.7. References


51) Lotesta, S. D. Spirodiepoxides: Mechanism studies and applications in synthesis. Ph.D. Thesis, Rutgers the State University of New Jersey, New Brunswick, NJ, **2008**.

Chapter 3

Overview of pleurotin
3.1. Isolation, structural determination, and bioactivity of pleurotin

Pleurotin (3.1, Figure 3.1) was isolated from a liquid culture of the fungus *Pleurotus griseus* by Robbins, Kavanagh, and Hervey in 1947, and the isolate was found to exhibit antibacterial activity against gram-positive bacteria, such as *Staphylococcus aureus*. Although its structure was unknown at isolation, its chemical and physical properties differentiated it from the known antibiotics at the time. The unique hexacyclic structure possessed by pleurotin (3.1) was later determined through spectroscopic analysis and subsequently verified through X-ray crystallography of the natural product and derivatives.

![Pleurotin Structure](image)

**Figure 3.1.** Planar and three-dimensional representations of pleurotin (3.1).

More recently, pleurotin (3.1) has been shown to be a potent inhibitor of the thioredoxin-thioredoxin reductase (Trx/TrxR) cellular redox system, having an IC$_{50}$ value of 170 nM. An increase in Trx-1 leads to the expression of hypoxia-inducible factor-1α (HIF-1α), which is found in human primary tumors but not in normal cells. HIF-1α dimerizes with HIF-1β to give HIF-1, a transcription factor that is activated by hypoxia and is linked to angiogenesis, vascular remodeling, glucose and energy metabolism, cell proliferation and survival, and erythropoiesis and iron homeostasis. Pleurotin (3.1) has been shown to prevent an increase in HIF-1α in MCF-7 human breast cancer and HT-29 human colon carcinoma cells. Its impact as a therapeutic agent could be significant, as
hypoxia has been shown to be a driving force in more than 70% of human cancers, including cancers of the lung, prostate, head and neck, ovary, and brain.\(^7\)

Scheme 3.1. Proposed bioreductive alkylation of pleurotin (3.1).

It is believed that the biological activity brought about by pleurotin (3.1) is due to an ability to undergo bioreductive alkylation.\(^8\) After being reduced in the cell to leucopleurotin (3.2, Scheme 3.1), elimination of the carboxylate unveils ortho-quinone methide 3.3. This quinone methide could be trapped by a biological nucleophile to give acid 3.4. Acid 3.4 also possesses a benzylic heteroatom; elimination of this group could then be followed by a second alkylation (see 3.4 to 3.5 to 3.6). If this second nucleophile were covalently attached to the first, cross-linking would occur.
3.2. Hart's synthesis of pleurotin

In 1983, David Hart and Che-Ping Chuang from the Ohio State University disclosed their studies directed at the synthesis of perhydroindans via a radical cyclization reaction. In this report, they demonstrated that iodide 3.10 (Scheme 3.2), prepared in two steps from meta-toluic acid (3.8) through a Birch reduction and subsequent alkylation with 4-bromo-1-butene (3.9) followed by iodolactonization, could undergo a cyclization reaction upon heating with tributyltin hydride and azobisisobutyronitrile (AIBN) in benzene. Although a mixture of four products was produced, the major product 3.11 possessed the desired perhydroindan skeleton.

![Scheme 3.2: Synthesis of the perhydroindan skeleton via radical cyclization.](image)

While the two to one selectivity for the exo cyclization (3.11 and 3.12) over the endo cyclization (3.13) was less than desirable, they were able to show that the simple addition of an electron-withdrawing group at the distal end of the alkene allowed for control over the formation of the desired exo cyclization product. For example, an analog of 3.10 containing a distal tert-butyl ester was prepared using an analogous procedure.
Subjection of this derivative to the cyclization conditions resulted in the formation of diastereomeric perhydridans in 96% yield.

**Scheme 3.3.** Synthesis of radical cyclization precursor 3.22 for pleurotin (3.1).

Hoping to demonstrate the utility of their radical cyclization, the Hart group were drawn to the intriguing biological activity and the molecular structure of pleurotin (3.1), which contains a perhydroindan within its skeleton. Starting from benzoic acid (3.15, Scheme 3.3), a Birch reduction and *in situ* alkylation with bromide 3.16 afforded acid 3.17. Although a straightforward iodolactonization failed in this context, a simple two-step procedure, involving conversion of the carboxylic acid to amide 3.18 followed by iodolactonization in the presence of iodine in aqueous THF, provided access to key iodide 3.19. With this in hand, hydrolysis of the acetal function afforded aldehyde 3.20, which then underwent a Wittig olefination with phosphonium ylide 3.21; in the event, ester 3.22 was formed in 90% yield as a single olefin isomer.
Scheme 3.4. Radical cyclization in the context of a synthesis of pleurotin (3.1).

With ready access to 3.22, the group next sought to apply their radical cyclization to build the perhydroindan framework (Scheme 3.4). They were pleased to find that heating 3.22 with tributyltin hydride and AIBN in benzene afforded perhydroindan 3.24 in 81% yield. This reaction was remarkably diastereoselective, with diastereomers 3.25, 3.26, and 3.27 being formed in only 4% yield each. Hart proposed two hypotheses for the origin of this selectivity. In both cases, the carbon-carbon bond-forming reaction (3.28 to 3.30 and 3.32) was expected to favor the formation of intermediate 3.30 based upon results obtained from related radical cyclizations. In the case of the selectivity between 3.24 and 3.25, one hypothesis was that the bridging lactone ring restricted C–C bond rotation, and thus the initial olefin geometry was responsible for the observed selectivity; the other hypothesis was that 3.30 was simply the most thermodynamically stable conformation (compared to 3.31). In order to test these hypotheses, 3.23 was synthesized, possessing the opposite geometry at the alkene. Subjection of 3.23 to the
same reaction conditions resulted in 37%, 2%, 15% and 12% yield of 3.24, 3.25, 3.26, and 3.27, respectively. While the selectivity of the carbon-carbon bond-forming step was diminished, the selectivity of 3.24 over 3.25 was preserved, implying that the initial alkene geometry is not responsible for the selectivity.

Scheme 3.5. Elaboration of the perhydroindan framework.

Bolstered by the fortuitous diastereoselectivity in their key radical cyclization, the Hart group then advanced their synthesis through further functionalization of the newly built perhydroindan framework (Scheme 3.5).\(^\text{11}\) In order to differentiate between the similar reactivities of the ester and lactone functionalities, the ester was hydrolyzed, converted to an acid chloride, and reduced with sodium borohydride; the newly formed hydroxyl group was then protected as a silyl ether to give tricycle 3.34. At this stage, they no longer had use for the bridging lactone, so they began to dismantle it. Epoxidation of the alkene gave 3.35, which was rearranged with base to afford allylic alcohol 3.36. Finally, a lithium metal reduction in ethylamine produced a crude carboxylic
acid, which was esterified with diazomethane to give 3.37. An oxidation of the secondary hydroxyl group via the method of Swern advanced them to ketone 3.38.

Scheme 3.6. Introduction of the quinone precursor.

The synthesis of ketone 3.38 now allowed them to bring in a surrogate for the para-quinone moiety expressed in the target (Scheme 3.6). Addition of Grignard reagent 3.39 proceeded uneventfully to produce alcohol 3.40 as a single diastereomer, although this selectivity was inconsequential. Unfortunately, dehydration of this alcohol was unselective, affording an equal mixture of two olefin isomers. While separation was not possible at this stage, reduction with lithium aluminum hydride gave the corresponding alcohols, of which alcohol 3.41 was readily separated from its isomer containing an
exocyclic, conjugated alkene. Oxidation of 3.41 yielded aldehyde 3.42, which underwent spontaneous mixed acetal formation (see 3.43) following removal of the silyl protecting group under acidic conditions.

This set the stage for a ring-forming reaction through the creation of the needed C6–C7 bond. In the event, treatment of 3.43 with BF₃•OEt₂ in cold toluene gave rise to pentacycle 3.44 in 52% yield as a single diastereomer. While the yield for this step is modest, the transformation is remarkable. Not only did this reaction build the seven-membered ring found in pleurotin (3.1) and provide an intermediate containing five of the six rings, but it also overcame previous reports that similar structures undergo rearrangement when treated with the same acid. For example, Lewis acid coordination of the ether oxygen can induce ionization at C7; a ring expansion then generates a six-membered ring as well as a tertiary carbocation. The Hart group did in fact observe this type of rearrangement in the transformation of 3.43 to 3.44 when their reaction was in dichloromethane, chlorobenzene, or toluene at room temperature.

With five rings in place, the remaining task for the Hart group was to build the final γ-lactone ring to complete their synthesis (Scheme 3.7). Hydroboration-oxidation of 3.44 provided a secondary alcohol, which was subsequently oxidized to give ketone 3.45 containing a functional handle for further elaboration. With this in mind, 3.45 was reacted with the anion of para-tosylmethyl isonitrile (TosMIC, 3.46), giving the homologated nitrile 3.47 in 75% yield. While direct hydrolysis of the cyano group proved difficult, a two-step procedure proceeding through an intermediate aldehyde accomplished the goal of generating acid 3.48. The action of ceric ammonium nitrate allowed for facile oxidation of the arene ring to the corresponding para-quinone 3.49, which set the stage for a final, biomimetic oxidation. While they had hoped to accomplish this transformation with base and air, bases such as triethylamine, 1,8-diazabicycloundec-7-ene (DBU), and potassium carbonate were all ineffective with or without the presence of air. Fortunately,
they found that the use of a large excess of manganese dioxide (around 75 equivalents) afforded pleurotin (3.1) in 32% yield along with 33% of recovered 3.49, thus completing their synthesis.

Scheme 3.7. Completion of the Hart synthesis.
3.3. Kraus’s approach toward pleurotin

Shortly following the disclosures made by the Hart group, Professor George Kraus and coworker reported an alternative strategy for addressing the framework of pleurotin (3.1). Their approach began with the para-quinone precursor 3.50 (Scheme 3.8). Treatment of the dianion of 3.50 with DMF gave hemiacetal 3.51 following hydrolysis. While it is known that lactols are able to equilibrate with their open form, attempts to directly acylate the primary hydroxyl group failed. Thus, conversion to a thioacetal was required, using ethanedithiol and catalytic BF$_3$•OEt$_2$; the resulting intermediate underwent facile acylation with dihydrobenzoic acid (3.52) in the presence of $N,N'$-dicyclohexylcarbodiimide (DCC) to give ester 3.53. The thioacetal was then restored to the formyl group via the action of iodomethane in aqueous acetonitrile. They were pleased to find that photoenolization in a Rayonet reactor provided a 31% yield of the desired lactone along with 33% of a benzocyclobutene (arising from
electrocyclization of transient intermediate 3.55). They found that simply heating the resulting mixture afforded the desired tetracycle 3.56 in a 50% yield from 3.54. Although they obtained the incorrect stereochemistry at C7 and C14, it is likely that C14 could undergo epimerization in the full structural context of pleurotin (3.1).

While no attempts to advance 3.56 or similar intermediates have been reported, Kraus and coworker have pursued biological testing of their synthetic intermediate. Tetracycle 3.56 was oxidized with silver(II) oxide and nitric acid in THF to unveil the para-quinone moiety in the left-hand ring; this compound was then sent to the National Cancer Institute and was found to possess comparable activity with pleurotin (3.1) against SR leukemia and most colon cancer cell lines. The activity of 3.56 and other intermediates has not been reported.
3.4. References


Chapter 4

Progress toward a synthesis of pleurotin
4.1. Synthetic design

The unique structure of pleurotin (4.1, Scheme 4.1) presents several challenges to the synthetic community, including a redox sensitive para-quinone moiety, a fused hexacyclic core, eight contiguous stereocenters (one of which, C18, is an all-carbon quaternary center joining four ring systems), and few functional handles.

Scheme 4.1. Intramolecular Diels–Alder-based approach toward pleurotin (4.1).

The Diels–Alder cycloaddition reaction is a powerful method for the synthesis of cyclohexane ring systems. Given the utility of this reaction, we wondered whether it could be used to install the central cyclohexane ring embedded within the target’s framework. More specifically, we hoped that an intramolecular variant of the Diels–Alder reaction would allow the simultaneous formation of this cyclohexane and the seven-membered heterocyclic ring. In order to accomplish this goal, we would need to build a system resembling 4.3; although the diene represented in this structure is not isolable,
the simple heating of functionalized benzocyclobutene structures is known to induce an
electrocyclic ring-opening of the cyclobutene ring to unveil a highly reactive diene.\textsuperscript{2} Thus, we hoped that exposure of a cyclobutene resembling \textit{4.2} to heat might allow access to pentacycle \textit{4.4}. This reaction would be notable due to its ability to rapidly generate five of the six rings of pleurotin (\textit{4.1}) while generating three new stereocenters. Depending on the identity of the R group, successful implementation of this strategy would require several subsequent oxidation reactions to complete a synthesis of the natural product.

\textbf{Scheme 4.2.} Proposal for the synthesis of cyclobutene \textit{4.2}.

While we were excited by the prospects of this design, cyclobutene \textit{4.2} would still contain a significant amount of structural complexity, and we were mindful of the fact that the setup cost to test this idea must be low. Because benzocyclobutene \textit{4.8} is known\textsuperscript{3} and accessible in relatively few steps from commercially available starting materials, it seemed convenient to install this piece through a coupling reaction with alcohol \textit{4.7}
through activation of either 4.7 or 4.8 (Scheme 4.2). Thus, a robust synthesis of 4.7 was thought to be crucial. Recognizing the cyclohexene embedded within 4.7, we wondered if a Diels–Alder reaction could be invoked again; however, this mental disconnection leaves ethylene as the requisite dienophile, which is known to be a poor player in this role. To address this problem, we thought that tethering an ethylene equivalent might increase the reactivity in an intramolecular Diels–Alder reaction. In the forward direction, an enyne metathesis or related rearrangement of enyne 4.5, which bears the expected structural pattern of an Ireland–Claisen rearrangement, would provide access to alcohol 4.6 after an oxidation state adjustment. It was hoped that the hydroxyl group of 4.6 would allow flexibility in the evaluation of tethering elements for the intramolecular Diels–Alder cycloaddition.
4.2. Model studies of the proposed tethered Diels–Alder cycloaddition

While we worked to minimize the setup costs associated with our proposed synthesis, the unknown challenges presented by both of the proposed intramolecular Diels–Alder cycloadditions were still a cause for concern. To alleviate these concerns, we decided to build a model system that would closely resemble the needed structure of diene 4.6 while being easier to access synthetically. We identified the relative stereochemistry of the contiguous stereocenters as a source of the increased costs associated with synthesis, and felt that excision of the methyl group would ease our early efforts. In addition, we assumed that R may not be necessary in the two cycloaddition reactions, and so a structure where R = H seemed like a logical simplification.

Combining the needs of our synthesis, diene 4.14 (Scheme 4.3) became a clear target. Gratifyingly, the synthesis of diene 4.14 was realized through a simple three-step procedure, starting with known silyl enol ether 4.9, available in a single step through the unification of 2-cyclopenten-1-one and vinylmagnesium bromide.9 The silyl enol ether was converted to vinyl triflate 4.11 with retention of the enolate configuration by treating the lithium enolate (from reaction of 4.9 and methyllithium) with Comins’s reagent.10 The triflate was taken forward crude after aqueous workup, and a hydroboration-oxidation sequence produced triflate 4.12 in 55% yield from 4.9. While the yield is modest, multiple gram quantities of 4.12 were obtainable via this method. It is important to note that 4.12 was expected to be a flexible intermediate through diverse modifications of the vinyl triflate motif. Palladium-catalyzed cross-coupling could potentially provide a wealth of substrates, allowing for direct evaluation of the role and compatibility of the R group needed in the synthesis of pleurotin (4.1, see structures within Schemes 4.1 and 4.2). To satisfy our immediate interest toward testing our key cyclization, however, cross-coupling with tributyl(vinyl)stannane (4.13) gave rise to model diene 4.14 in good yield.

In 1992, the research groups of Gilbert Stork\textsuperscript{11} and Scott Sieburth\textsuperscript{12} independently reported that diene alcohol 4.15 (Scheme 4.4) can undergo productive Diels–Alder cycloaddition reactions when first tethered with a chloro(vinyl)silane (4.16 or 4.17). While this required heating trienes 4.18 and 4.19 at temperatures in excess of 160 °C, the corresponding cycloadducts 4.20 and 4.21 were obtainable in good yields (as mixtures of diastereomers at the silicon-bearing carbon atoms). As a demonstration of the utility of these cycloadducts, both research groups chose to showcase the formation of diols through Tamao–Fleming oxidations\textsuperscript{13} of the carbon-silicon bonds.

Perhaps the more relevant precedent for our synthesis was the protodesilylation disclosed by Stork, whereby cycloadduct 4.20 could be converted to alcohol 4.23 by simple heating with an excess of tetrabutylammonium fluoride (TBAF, four equivalents) in DMF. If successful with our substrate, this series of transformations would generate the needed ethylene equivalent in our first Diels–Alder cycloaddition.
Scheme 4.4. Stork and Sieburth’s silicon-tethered Diels–Alder reactions.

The reaction of the model diene 4.14 with chloro(vinyl)silanes 4.16 and 4.17 was trivial, producing trienes 4.24 and 4.25, respectively (Scheme 4.5). Following aqueous workup, both trienes were sufficiently pure for the subsequent Diels–Alder cycloaddition. Moving forward, we were pleased to find that both 4.24 and 4.25 were competent substrates, affording their respective cycloadducts in reasonable yields. Both substrates were selective for the exo Diels–Alder products depicted in Scheme 4.2, with the larger phenyl groups exerting a stronger preference (ten to one selectivity for 4.27 versus four to one selectivity for 4.26). Unfortunately, all attempts to carry out the desired protodesilylation have been ineffective (4.26 or 4.27 to 4.28). Employing the reaction conditions described by Stork and coworkers (TBAF in hot DMF) resulted only in the
cleavage of the silicon-oxygen bond; the addition of water or acetic acid also had no effect. Roush and coworkers\textsuperscript{14} reported that they were able to cleave an unactivated carbon-silicon bond using a combination of potassium tert-butoxide, 18-crown-6, and TBAF in a mixture of dimethylsulfoxide (DMSO) and water; however, these conditions also failed in our hands.


With the disappointment of being unable to functionalize the adducts of the silicon-tethered Diels–Alder reactions, we began a search to find a tethering element that would allow for facile formation of 4.28. In 1995, Stork and Chan reported a follow-up to their previous silicon-tethered Diels–Alder chemistry in which they showed that both magnesium and aluminum could function as “temporary tethers” for the same cycloaddition reactions.\textsuperscript{15} In fact, these reactions proceeded at lower temperatures and for shorter amounts of time than their silicon counterparts. As an added bonus, simple
quenching with a proton source at the end of the reaction delivers the necessary C–H bond. Unfortunately, treatment of lithium salt 4.29 (Scheme 4.6) with vinylimagnesium bromide (4.30) failed to yield the desired cycloadduct; at 80 °C, only starting material was recovered, while complete decomposition was observed at 160 °C. Decomposition was also observed when 4.29 was added to a pre-formed mixture of 4.30 and diethylaluminum chloride and heated to 130 °C. We briefly investigated the use of a vinyl sulfonate ester; however, this failed to undergo the desired cycloaddition as well.

Scheme 4.6. Attempts to use magnesium and aluminum tethers.

Scheme 4.7. Boron-tethered Diels–Alder cycloaddition.

We next turned our attention to the use of boron as a tethering element, which has been used previously in a variety of Diels–Alder reactions (Scheme 4.7). Vinylboronic acid dibutyl ester (4.31) was chosen as our cycloaddition partner due to its commercial availability and previous use in similar contexts. Assuming the success of this reaction, we hoped that the resulting carbon-boron bond could be reduced under
radical conditions as demonstrated by Renaud and coworkers at the University of Bern.\textsuperscript{18} In our system, simple heating of a mixture of alcohol 4.14 and vinylborane 4.31 in toluene at high temperature in a sealed tube produced the desired cycloadduct 4.32. Although the $^1$H-NMR spectrum was complex, this material was usable after removal of the solvent under reduced pressure. While it was pleasing to see that the deborylated product 4.28 was formed in the wake of the radical deborylation reaction (using catechol and air), these reactions produced erratic results, with many attempts resulting in only recovered starting material.
4.3. Model studies of the cyclobutene Diels–Alder cycloaddition

Although it was unfortunate that the efforts toward the tethered Diels–Alder reaction were largely unsuccessful, they did provide access to compounds that closely resembled the perhydrindan system needed to investigate our electrocyclic ring-opening/Diels–Alder sequence (*vide supra*, Scheme 4.1). At this juncture, we felt that the silicon-tethered Diels–Alder adducts could still model the key cyclobutene Diels–Alder step despite the superfluous silicon moieties.

Scheme 4.8. Attempts at joining alcohols 4.35 and 4.8.

Cycloadduct 4.27 was chosen as a substrate for initial studies as it was available in good yield and with better diastereoselectivity (Scheme 4.8). We found that opening of the siloxane ring was most facile and reproducible via the action of methylthionium. The distal positioning of the superfluous methyldiphenylsilyl group on the cyclohexene should
render it inconsequential for testing the key chemistry. With alcohol 4.35 in hand, we were prepared to join the left- and right-hand portions of our model. Activation of 4.35 was easily accomplished with methanesulfonyl chloride and triethylamine; however, this common coupling method proved unsuccessful. Alcohol 4.8 proved to be too reactive under these basic conditions, unraveling to produce 4.38 under a variety of reaction conditions. With this in mind, we were able to prepare a variety of activated cyclobutenes (4.37 where X = OM₃, Br, I). Unfortunately, 4.35 failed to react using various reaction conditions, possibly due to steric crowding around the alcohol, and it was recovered along with varying levels of decomposition of its reaction partner.

After we screened a number of conditions to affect the formation of the desired ethereal carbon-oxygen bond, my coworker, Dr. David Ebner, was able to make a breakthrough (Scheme 4.9). Working with alcohol 4.40 (made in analogous fashion to 4.35, starting from cycloadduct 4.26), he showed that the action of pyridinium para-toluenesulfonate (PPTS) allows for the coupling with the trichloroacetimidate derived from 4.8 (4.41). Although the yield for this reaction was low (25%), it produced a sufficient quantity of coupled product 4.42 for the subsequent reaction. 4.42 was thus heated in ortho-dichlorobenzene at 230 °C; solid potassium carbonate and activated molecular sieves were added in order to keep the reaction acid- and moisture-free, as decomposition was observed in the absence of these additives (decomposition occurred through cleavage of the ether carbon-oxygen bond in presumed intermediate 4.43, producing 4.38). After five days of heating, Dr. Ebner was able to isolate pentacycle 4.44. Unfortunately, only a 5% yield of 4.44 was obtained along with significant decomposition. We assume that the ether tether directs the cycloaddition to occur from the top face of the perhydrindan framework, although the relative stereochemistry (and thus the endo/exo selectivity) is unknown.
Scheme 4.9. Initial results for the electrocyclic ring-opening/Diels–Alder sequence.
4.4. Progress toward addressing the shortcomings of the model system

Although the previously described model system allowed for a thorough evaluation of the key transformations that are vital to our proposal, the methods used for its synthesis did not leave an apparent opportunity for introducing the requisite methyl group at C9 (see Scheme 4.9). Furthermore, we were wary of investing additional energy into optimizing reactions with the model system, as no model system is a perfect substitute.\textsuperscript{19} It was at this juncture that we returned to our initial synthetic proposal (\textit{vide supra}, Scheme 4.2).

Scheme 4.10. Use of the Ireland–Claisen rearrangement.

As mentioned above, we felt that the vicinal stereocenters at C9 and C10 might be best controlled through the classic Ireland–Claisen rearrangement (Scheme 4.10). Retrosynthetically, this maneuver leads to great simplification, and we quickly identified known aldehyde 4.45\textsuperscript{20} as an excellent foundational element for our synthesis. A Wittig olefination\textsuperscript{21} between aldehyde 4.45 and the commercially available stabilized ylide
(carbethoxymethylene)triphenylphosphorane (4.46) afforded alkene 4.47, greatly favoring the E alkene isomer. Reduction of the carbethoxy group with diisobutylaluminum hydride (DIBAL-H) provided alcohol 4.48, which underwent a subsequent acylation at the hydroxyl group with propionyl chloride (4.49) to give rise to linear ester 4.50. Pleasingly, ester 4.50 underwent a smooth transformation to carboxylic acid 4.51 upon warming of the in situ derived silyl ketene acetal via an Ireland–Claisen rearrangement. A five to one mixture of diastereomers was obtained from this reaction; the relative stereochemistry was assumed based on analogy with related systems and is drawn in Scheme 4.7. In order to facilitate easy handling, acid 4.51 was advanced to methyl ester 4.52 after treatment with iodomethane and potassium carbonate; the yield of 4.52 was 40% across the three-step procedure beginning with alcohol 4.48 (although greater than 50% of 4.50 is recovered following the Ireland–Claisen rearrangement).

Scheme 4.11. Structural rearrangement provides access to diene alcohol 4.54.

While it is known that Grubbs's second generation ruthenium catalyst is capable of promoting the ring-closing metathesis reaction of enyne systems, we became interested in the body of literature surrounding the related skeletal rearrangements of 1,5-enynes using a variety of transition metals. We were pleased to find that the first metal catalyst explored, platinum(II) chloride, promoted the desired structural rearrangement cleanly after two hours of stirring in toluene at room temperature (4.52 to 4.53, Scheme 4.11). In fact, we came to favor these conditions due to their operational
simplicity as well as mild nature, although my coworker was able to demonstrate that Grubbs’s catalyst worked as well. It is instructive to note that the advantage of the Grubbs system is the ability to perform a subsequent cross-metathesis reaction; if needed, this would allow introduction of a variety of R groups at C14 of the diene moiety. With ester 4.53 in hand, rapid reduction with lithium aluminum hydride generated diene alcohol 4.54.


Although our success with boron-tethered Diels–Alder reactions was good, our ability to reductively cleave the carbon-boron bond was modest at best; however, given that this method was the only one to produce the perhydrindan framework without the tethering element remaining intact, we decided to re-examine this reaction with our real system (Scheme 4.12). Indeed, the Diels–Alder reaction between alcohol 4.54 and vinylboronic acid dibutyl ester (4.31) was successful within this closely related context, as evident by our ability to oxidize the carbon-boron bond to produce diol 4.57 in good yield (79% from 4.54 as a two to one mixture of diastereomers). Unfortunately, all conditions
to affect the desired reductive removal of the boron group were unsuccessful, including the aforementioned catechol and air\textsuperscript{17} as well as acid-mediated protodeborylation\textsuperscript{24} and tetrabutylammonium fluoride trihydrate.\textsuperscript{25} Attempts to remove the secondary hydroxyl group of 4.57 were similarly ineffective, as neither hydride displacement of the corresponding mesylate nor radical deoxygenation of the corresponding xanthate ester provided any of the desired perhydrindan 4.56.

Scheme 4.13. Utilizing an ester linkage for a tethered Diels–Alder cycloaddition.

Given the troubles encountered with removal of the extraneous silicon atom in the course of our model studies (\textit{vide supra}, Scheme 4.5), we only briefly investigated its viability in the case at hand; however, it is instructive to note that the presence of the methyl group appears to have a negative effect on the course of the cycloaddition, as products were obtained in lower yields even with elongated reaction times. As we contemplated on our options, we thought that the simplest way of covalently attaching
our dienophile would be through an ester bond formation. This was briefly explored in
the context of the model system, but it was unsuccessful, likely due to the known
preference for the groups attached to the ester to exist in the \textit{s-trans} conformation.\textsuperscript{26}
Fortunately, perusal of the chemical literature revealed methods that allow alteration of
this conformational preference.\textsuperscript{27} Thus, triene \textbf{4.59} (Scheme 4.13) was prepared from
simple acylation of alcohol \textbf{4.54} with acryloyl chloride (\textbf{4.58}). This was then heated with
bis[chloro(methyl)aluminum]trifluoromethanesulfonamide, a bidentate Lewis acid catalyst
developed by Taguchi and coworkers and formed \textit{in situ}, affording the corresponding
cycloadduct \textbf{4.60} in 42\% yield over the two steps from \textbf{4.54}. From the vantage of \textbf{4.60},
reduction to lactol \textbf{4.61} was followed by \textit{in situ} equilibration with the hydroxy aldehyde
form with subsequent silylation of the primary alcohol to afford aldehyde \textbf{4.62}. It is
important to point out the need for the bulky \textit{tert}-butyldiphenylsilyl (TBDPS) group in this
reaction; with \textit{tert}-butyl(chloro)dimethylsilane, the desired aldehyde is formed as a
mixture with the silylated lactol (55\% and 35\%, respectively). Although some of the
TBDPS lactol is formed, the ratio of five to one greatly favors \textbf{4.62}. It is known that
organic molecules can undergo deformylation reactions in the presence of transition
metal catalysts.\textsuperscript{28} We have obtained preliminary results indicating that the use of
chlorotris(triphenylphosphine)rhodium(I) (Wilkinson’s catalyst)\textsuperscript{29} may provide a path
forward, but the reaction currently suffers from poor efficiency as well as poor selectivity
for the desired perhydrindan \textbf{4.63}.
4.5. Future directions

With a clear route to aldehyde 4.62, only a few key transformations remain on the pathway toward a synthesis of pleurotin (4.1). As described above, it is hoped that a transition metal-mediated deformylation will provide access to perhydrindan 4.63 after some reaction optimization. If successful, coupling to imidate 4.41 (vide supra, Scheme 4.9) would set the stage for the key Diels–Alder cycloaddition (Scheme 4.14). It is important to note, however, that if successful, it would likely be difficult to further functionalize the pentacyclic framework of 4.65 toward the target natural product.


Fortunately, we feel that our strategy is adaptable to earlier incorporation of functionality at C14 at two key places (Scheme 4.15). The more direct strategy would make use of an allylic oxidation\textsuperscript{30} of perhydrindan 4.63. In fact, successful incorporation of the oxo group (4.66) would both withdraw electron density to activate the subsequent
Diels–Alder chemistry and provide an intermediate found in the synthesis of pluerotin (4.1) by the Hart group. An equally attractive alternative to this strategy would be the incorporation of the C15 carbon atom at the stage of the rearrangement of enyne 4.52. As discussed earlier, it is possible to perform tandem enyne metathesis and cross-metathesis reactions when Grubbs’s second generation catalyst is employed; addition of known allyl silyl ether 4.67 into this process would lead to diene 4.68, which would likely be elaborated to bicycle 4.69 via the chemistry already described for the synthesis of 4.63.

Scheme 4.15. Plans for the functionalization of C14.
4.6. Summary

Through studies of a closely analogous model system, we have been able to demonstrate the feasibility of a strategy for the synthesis of the natural product pleurotin (4.1) that uses consecutive Diels–Alder cycloadditions to build up three of the target’s six ring systems while establishing the configuration of four stereocenters. We have also been able to advance material that could be used directly in the proposed synthesis through a series of eleven steps from a known compound (itself available in two steps from commercially available materials). From that vantage point, a formal synthesis of pleurotin could be achieved in as few as four additional steps, although extensive optimization of the final Diels–Alder reaction may be necessary.
4.7. References


General experimental details
Methods

All reactions were carried out in oven- or flame-dried glassware (unless water was present in the reaction mixture) with rubber septa under a positive pressure of argon unless otherwise indicated. Air- and moisture-sensitive liquids were transferred via a plastic syringe or stainless steel canula. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm Merck silica gel plates (60 F254) impregnated with a fluorescent indicator (254 nm). TLC plates were first visualized using UV light and subsequently stained with either ethanolic para-anisaldehyde solution, aqueous basic potassium permanganate, or aqueous acidic ceric ammonium molybdate. In all cases, brief heating on a hot plate was used to develop the TLC plates after staining. Flash column chromatography was performed using Silicycle SiliaFlash P60 silica gel (60 Å pore size, 40–63 µm particle size, 230–400 mesh) and ACS reagent grade solvents. Yields refer to isolated material that was found to be chromatographically and spectrscopically homogenous unless otherwise noted.

Materials

Commercial reagents of high purity were purchased from Sigma Aldrich, Acros, or Strem and used without further purification. Methyllithium, butyllithium, sec-butyllithium methylmagnesium bromide, and vinylmagnesium bromide were purchased from Sigma Aldrich and titrated with salicylaldehyde phenylhydrazone before use. Methanol (99.8%), acetone (99.8%), and 1,2-dichloroethylene (DCE, 99.8%) were purchased from Acros in anhydrous bottles and used without further purification. Anhydrous tetrahydrofuran (THF), dichloromethane (CH₂Cl₂), toluene, diethyl ether, benzene, acetonitrile, dimethyl sulfoxide (DMSO), N,N-dimethylformamide (DMF), triethylamine, and pyridine were dried by passing previously degassed solvents through activated alumina columns. Organic solvents used for transfers and/or workups,
including ethyl acetate (EtOAc), diethyl ether, methanol, dichloromethane, and hexanes, were at ACS reagent grade specifications or similar levels of purity.

**Instrumentation**

Optical rotations were recorded on a Perkin-Elmer model 241 polarimeter using a 1 mL, 1 dm cell. Infrared (IR) spectra were recorded on a Thermo Electron Corporation Nicolet 6700 FT-IR spectrometer equipped with a Smart Orbit diamond anvil accessory; samples were prepared by evaporation of a solution of the substrate in dichloromethane, leaving a residual thin film of material to be analyzed. Proton nuclear magnetic resonance (\(^1\)H-NMR) spectra were obtained on 500 MHz Bruker AVANCE spectrometers equipped with Cryo-TCI, Cryo-DCH, or Cryo-QNP probes. The \(^1\)H-NMR spectra were calibrated to the residual solvent peak (\(\delta = 7.26\) for CDCl\(_3\) or \(\delta = 3.31\) for CD\(_3\)OD) and coupling constant values were extracted assuming first-order coupling. The corresponding peak multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, and br = broad. Carbon nuclear magnetic resonance (\(^{13}\)C-NMR) spectra were obtained on the same instruments at 125 MHz as attached proton test (APT) experiments and calibrated to the residual solvent peaks (\(\delta = 77.16\) for CDCl\(_3\) and \(\delta = 49.00\) for CD\(_3\)OD). The resulting \(^{13}\)C-NMR spectra were phased so that methyl and methine signals are negative and methylene and fully substituted carbon signals are positive. High resolution mass spectrometry (HRMS) was performed on an Agilent Technologies 6210 series time-of-flight mass spectrometer with electrospray ionization (ESI).
Experimental for chapter 2
Diketone 2.23

To a solution of 2.22 (16.1 g, 103 mmol) in 1 L of ethanol was added methyl vinyl ketone (10.3 mL, 124 mmol, 1.2 eq.) followed by DBU (3.9 mL, 25.8 mmol, 0.25 eq.). The solution slowly became yellow in color. After 5 min, TLC analysis (20% EtOAc in hexanes, anisaldehyde) indicated complete consumption of the starting material and formation of the product, R_f = 0.15. The solvent was removed under reduced pressure, and the residual dark orange oil was purified by flash column chromatography (20% EtOAc in hexanes) to afford 2.23 as a colorless oil (22.7 g, 97%).

^1H-NMR (500 MHz, CDCl_3): δ 3.68 (s, 3H), 2.84 (ddd, J = 17.9, 10.4, 5.0 Hz, 1H), 2.55 – 2.44 (m, 2H), 2.28 – 2.02 (m, 7H), 1.85 (ddd, J = 15.0, 10.5, 5.0 Hz, 1H), 1.78 – 1.68 (m, 1H), 1.02 (d, J = 6.8 Hz, 3H); ^13C-NMR (125 MHz, CDCl_3): δ 216.6, 208.2, 170.9, 61.8, 52.0, 42.2, 38.7 (2 overlapping carbons), 30.1, 28.3, 26.6, 16.0; IR (neat) ν 2956, 2878, 2850, 1746, 1726, 1711, 1456, 1435, 1375, 1355, 1234, 1159, 1124 cm\(^{-1}\); [α]_D\(^{20}\) = + 52.6 (c 1.19, CH_2Cl_2); HRMS (ESI+) calcd. for C_{12}H_{19}O_4\(^+\) ([M + H]^+): 227.12779, found: 227.12740.
Enone 2.24

To a solution of 2.23 (22.7 g, 100 mmol) in 1.25 L of benzene was added para-toluenesulfonic acid monohydrate (15.3 g, 80.3 mmol, 0.8 eq.). A Dean–Stark apparatus and condenser were attached, and the reaction was refluxed for 12 h, after which TLC analysis (20% EtOAc in hexanes, anisaldehyde) indicated complete consumption of the starting material and formation of the product, \( R_f = 0.41 \). The reaction was quenched with saturated sodium bicarbonate and diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with two portions of EtOAc. The combined organics were washed with brine before drying over anhydrous Na\(_2\)SO\(_4\). The solvent was removed under reduced pressure, and the residual oil was purified by flash column chromatography (20% EtOAc in hexanes) to afford 2.24 as a yellow solid (17.7 g, 85%).

\[^1\text{H-NMR} \ (500 \text{ MHz, CDCl}_3): \delta 5.88 - 5.86 \ (m, 1\text{H}), 3.71 \ (s, 3\text{H}), 2.93 - 2.84 \ (m, 1\text{H}), 2.77 - 2.71 \ (m, 1\text{H}), 2.60 - 2.50 \ (m, 1\text{H}), 2.43 - 2.32 \ (m, 2\text{H}), 2.02 - 1.88 \ (m, 2\text{H}), 1.69 - 1.59 \ (m, 2\text{H}), 1.02 \ (d, J = 6.6 \text{ Hz, 3H}); \[^{13}\text{C-NMR} \ (125 \text{ MHz, CDCl}_3): \delta 199.1, 171.8, 171.7, 123.7, 57.3, 52.1, 46.1, 34.9, 32.1, 31.1, 30.7, 15.0; \text{IR} \ (\text{neat}) \ \nu 2955, 2937, 2873, 1724, 1667, 1641, 1454, 1334, 1238, 1172 \text{ cm}^{-1}; [\alpha]_D^{20} = -132.5 \ (c 1.06, \text{CH}_2\text{Cl}_2); \text{HRMS (ESI+)} \text{ calcd. for } C_{12}H_{17}O_3^+/([M + H]^+) : 209.11722, \text{found: 209.11663.} \]
To a solution of 2.24 (17.6 g, 84.6 mmol) in 560 mL tert-butanol (reagent grade) was added potassium tert-butoxide (29.4 g, 262 mmol, 3.1 eq.). The resulting solution became orange then black in color. After 15 min, iodomethane (31.6 mL, 508 mmol, 6 eq.) was added, after which a precipitate formed and the solution became a light red color. After 1.5 h, TLC analysis (30% EtOAc in hexanes, CAM) indicated complete consumption of the starting material and formation of the product, R_f = 0.71. The reaction was cooled to 0 °C and then quenched with saturated ammonium chloride and diluted with diethyl ether. The layers were separated, and the aqueous layer was extracted with two additional portions of diethyl ether. The combined organics were washed with brine before drying over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residual oil was purified by flash column chromatography (15% EtOAc in hexanes) to afford 2.25 as a white solid (18.2 g, 91%).

^1H-NMR (500 MHz, CDCl_3): δ 5.75 – 5.73 (m, 1H), 3.72 (s, 3H), 2.80 – 2.69 (m, 2H), 2.49 – 2.39 (m, 1H), 2.31 – 2.19 (m, 3H), 1.53 – 1.44 (m, 1H), 1.25 (s, 3H), 1.08 (s, 3H), 0.99 (d, J = 6.7 Hz, 3H); ^13C-NMR (125 MHz, CDCl_3): δ 214.2, 175.0, 150.2, 127.9, 58.7, 51.7, 49.4, 47.8, 39.9, 35.9, 33.0, 27.3, 22.0, 14.4; IR (neat) ν 2959, 2931, 2874, 2849, 1714, 1636, 1457, 1433, 1229, 1200 cm⁻¹; [α]_D^{20} = + 93.8 (c 0.61, CH_2Cl_2); HRMS (ESI+) calcd. for C_{14}H_{21}O_3⁺ ([M + H]^⁺): 237.14852, found: 237.14888.
Carboxylic acid 2.26

To a solution of 2.25 (150 mg, 0.635 mmol) in 9.1 mL of DMF was added sodium propanethiolate (311 mg, 3.17 mmol, 5 eq.). The resulting solution was heated to 80 °C for 12 h, after which TLC analysis (40% EtOAc in hexanes, CAM) indicated complete consumption of the starting material and formation of the product, $R_f = 0.33$. The reaction was cooled to room temperature and quenched with 2 M HCl and diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with two additional portions of EtOAc. The combined organics were washed with brine before drying over anhydrous Na$_2$SO$_4$. The solvent was removed under reduced pressure, and the residual oil was purified by flash column chromatography (30% EtOAc in hexanes) to afford 2.26 as a yellow solid (136 mg, 96%).

$^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 11.40 – 10.90 (brm, 1H), 5.82 – 5.79 (m, 1H), 2.78 (ddd, $J = 15.0, 12.1, 5.3$ Hz, 1H), 2.69 (dt, $J = 13.5, 5.2$ Hz, 1H), 2.50 – 2.42 (m, 1H), 2.37 – 2.27 (m, 3H), 1.58 – 1.49 (m, 1H), 1.27 (s, 3H), 1.18 (s, 3H), 1.10 (d, $J = 6.6$ Hz, 3H);

$^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 214.0 (214.0), 180.3 (180.0), 150.0 (149.9), 128.6, 58.6 (58.6), 49.6, 48.0, 39.7, 35.8, 32.1 (32.1), 27.4, 22.1, 14.2; IR (neat) $\nu$ 3058, 2963, 2930, 2874, 2852, 1692, 1460, 1445, 1381, 1245, 1170, 1132, 1103 cm$^{-1}$; HRMS (ESI+) calcd. for C$_{13}$H$_{19}$O$_3^+$ ([M + H]+): 223.13287, found: 223.13278.
Alcohol 2.28

To a solution of 2.25 (12.2 g, 51.6 mmol) in 260 mL of benzene was added ethylene glycol (17.3 mL, 310 mmol, 6 eq.) followed by para-toluenesulfonic acid (0.98 g, 5.16 mmol, 0.1 eq.). A Dean–Stark apparatus and condenser were attached, and the reaction was refluxed for 12 h. The reaction was cooled to room temperature and quenched with aqueous sodium bicarbonate and diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with two additional portions of EtOAc. The combined organics were washed with brine before drying over anhydrous Na₂SO₄. The solvent was removed under reduced pressure to give 13.6 g of the crude acetal as a pale yellow solid.

A solution of this crude product in 240 mL of CH₂Cl₂ was cooled to −78 °C. DIBAL-H (1.0 M in toluene, 150 mL, 150 mmol, 3.1 eq.) was slowly added, and the reaction was stirred at −78 °C for 1.5 h followed by 15 min at 0 °C. TLC analysis (20% EtOAc in hexanes, CAM) indicated complete consumption of the starting material and formation of the product, \( R_f = 0.32 \). The reaction was quenched at 0 °C with saturated Rochelle’s salt (potassium sodium tartrate) and the mixture was stirred for 12 h at room temperature before being diluted with CH₂Cl₂. The layers were separated, and the aqueous layer was extracted with two additional portions of CH₂Cl₂. The combined organics were washed with brine before drying over anhydrous Na₂SO₄. The solvent was removed under reduced pressure, and the residual oil was purified by flash column chromatography (20% EtOAc in hexanes) to afford 2.28 as a colorless oil (11.1 g, 77%).
$^1$H-NMR (500 MHz, CDCl$_3$): δ 5.83 (d, $J = 2.8$ Hz, 1H), 3.98 – 3.92 (m, 4H), 3.79 (d, $J = 11.3$ Hz, 1H), 3.55 (t, $J = 10.9$ Hz, 1H), 2.37 – 2.30 (m, 1H), 2.06 – 1.99 (m, 2H), 1.90 (td, $J = 13.9$, 4.3 Hz, 1H), 1.64 – 1.45 (m, 3H), 1.25 – 1.21 (m, 4H), 1.14 (s, 3H), 1.08 (d, $J = 6.4$ Hz, 3H); $^{13}$C-NMR (125 MHz, CDCl$_3$): δ 151.5, 127.4, 113.2, 65.6, 65.3, 64.7, 51.9, 47.8, 43.2, 40.3, 32.4, 28.2, 26.1, 21.6, 14.1; IR (neat) ν 3488, 2952, 2927, 2873, 1630, 1454, 1132, 1111 cm$^{-1}$; [α]$^D_{20} = – 2.4$ (c 1.97, CH$_2$Cl$_2$); HRMS (ESI+) calcd. for C$_{15}$H$_{25}$O$_3$ $^+$ ([M + H]$^+$): 253.17982, found: 253.17917.
To a solution of 2.28 (54 mg, 0.214 mmol) in 2.2 mL of \( \text{CH}_2\text{Cl}_2 \) at 0 °C was added triethylamine (120 µL, 0.856 mmol, 4 eq.) followed by methanesulfonyl chloride (50 µL, 0.647 mmol, 3 eq.). The reaction was slowly warmed over 1 h. TLC analysis (20% EtOAc in hexanes, CAM) indicated a small amount of the starting material along with the formation of the product, \( R_f = 0.15 \). The reaction was diluted with water and \( \text{CH}_2\text{Cl}_2 \). The layers were separated, and the aqueous layer was extracted with two additional portions of \( \text{CH}_2\text{Cl}_2 \). The combined organics were washed with brine before drying over anhydrous \( \text{Na}_2\text{SO}_4 \). The solvent was removed under reduced pressure, and the residual oil was purified by flash column chromatography (25% EtOAc in hexanes) to afford 2.29 (63 mg, 89%).

\(^1\text{H-NMR} (500 MHz, \text{CDCl}_3): \delta 5.73 – 5.67 (m, 1H), 4.31 (d, \( J = 9.9 \text{ Hz} \), 1H), 4.24 (d, \( J = 9.9 \text{ Hz} \), 1H), 4.02 – 3.88 (m, 4H), 2.98 (s, 3H), 2.31 (ddd, \( J = 15.9, 15.0, 4.1 \text{ Hz} \), 1H), 2.13 – 1.98 (m, 2H), 1.96 – 1.87 (m, 1H), 1.81 (dt, \( J = 13.6, 3.4 \text{ Hz} \), 1H), 1.61 – 1.49 (m, 2H), 1.21 (s, 3H), 1.12 (s, 3H), 1.09 (d, \( J = 6.8 \text{ Hz} \), 3H); \(^{13}\text{C-NMR} (125 MHz, \text{CDCl}_3): \delta 150.2, 127.1, 112.9, 69.9, 65.6, 65.3, 49.7, 47.8, 43.0, 39.5, 37.5, 31.6, 27.7, 26.4, 21.6, 14.0; IR (neat) \nu 2934, 2876, 1455, 1378, 1352, 1332, 1172, 1133, 1112, 1078, 1065, 1046, 1021 \text{ cm}^{-1}; \text{HRMS (ESI+)} \text{ calcd. for C}_{18}\text{H}_{27}\text{O}_5\text{S}^+ ([M + H]^+): 331.15737, \text{found: 331.15727.}
To a solution of oxalyl chloride (6.7 mL, 79.3 mmol, 1.5 eq.) in 210 mL of CH$_2$Cl$_2$ at –78 °C was added DMSO (11.3 mL, 159 mmol, 3 eq.) dropwise. After 5 min, a solution of 2.28 (13.3 g, 53.0 mmol) in 410 mL of CH$_2$Cl$_2$ was added, and stirring was continued at –78 °C for 15 min. Triethylamine (37 mL, 264 mmol, 5 eq.) was then added, the cooling bath was removed, and stirring was continued. After 1 h, TLC analysis (30% EtOAc, CAM) indicated complete consumption of the starting material and formation of the product, $R_f = 0.66$. The reaction was quenched with saturated sodium bicarbonate and diluted with CH$_2$Cl$_2$. The layers were separated, and the aqueous layer was extracted with two additional portions of CH$_2$Cl$_2$. The combined organics were washed with brine before drying over anhydrous Na$_2$SO$_4$. The solvent was removed under reduced pressure, and the residual oil was purified by flash column chromatography (10% EtOAc in hexanes) to afford 2.31 as a white solid (11.9 g, 90%).

$^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 9.57 – 9.54 (m, 1H), 5.94 – 5.91 (m, 1H), 3.97 – 3.89 (m, 4H), 2.58 (ddd, $J = 15.1$, 7.6, 3.0 Hz, 1H), 2.47 (dt, $J = 13.0$, 3.4 Hz, 1H), 2.37 – 2.19 (m, 2H), 1.78 (td, $J = 14.0$, 4.4 Hz, 1H), 1.53 (ddd, $J = 14.1$, 4.3, 2.7 Hz, 1H), 1.31 – 1.22 (m, 1H), 1.13 (s, 3H), 0.99 (d, $J = 7.1$ Hz, 3H), 0.94 (s, 3H); $^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 205.4, 151.3, 127.4, 112.7, 65.5, 65.3, 63.4, 48.7, 43.5, 39.8, 28.0, 27.9, 25.4, 20.2, 14.5; IR (neat) $\nu$ 2961, 2936, 2874, 2797, 2704, 1714, 1131, 1101, 1045 cm$^{-1}$; $[\alpha]_D^{20} = + 260.3$ (c 2.25, CH$_2$Cl$_2$); HRMS (ESI+) calcd. for C$_{15}$H$_{23}$O$_3$$^+$ ([M + H$^+$]): 251.16417, found: 251.16401.
Enol ether 2.33

To a solution of (methoxymethyl)trimethylsilane (11.2 mL, 71.3 mmol, 1.5 eq.) in 95 mL of THF at −60 °C was slowly added a solution of sec-BuLi (1.20 M in cyclohexane, 60 mL, 71.3 mmol, 1.5 eq.) dropwise. The resulting solution became bright yellow in color, and was allowed to slowly warm to −20 °C over a period of 1.5 h. The solution was cooled to −78 °C, and a solution of 2.31 (11.9 g, 47.5 mmol) in 48 mL of THF was slowly added. The reaction was allowed to warm to −50 °C over a period of 1 h, after which TLC analysis (20% EtOAc in hexanes, anisaldehyde) showed complete consumption of the starting material and formation of an intermediate, R_f = 0.89. Potassium tert-butoxide (10.7 g, 95.1 mmol, 2 eq.) was then added, the cooling bath was removed, and the reaction was stirred 2 h, at which time TLC analysis (5% Et_2O in hexanes, anisaldehyde) indicated formation of the product, R_f = 0.40. The reaction was quenched with water and diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with two additional portions of EtOAc. The combined organics were washed with brine before drying over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residual oil was purified by flash column chromatography (5% EtOAc in hexanes) to afford 2.33 as a pale yellow oil (11.1 g, 78%, 20:1 E:Z isomers).

**Z-Isomer:** ¹H-NMR (500 MHz, CDCl₃): δ 5.83 (d, J = 7.3 Hz, 1H), 5.46 – 5.43 (m, 1H), 4.00 – 3.86 (m, 5H), 3.51 (s, 3H), 2.59 (d, J = 12.9 Hz, 1H), 2.27 (ddd, J = 14.2, 6.6, 3.0 Hz, 1H), 2.07 (td, J = 13.8, 3.6 Hz, 1H), 2.03 – 1.90 (m, 2H), 1.53 (dt, J = 14.4, 3.5 Hz,
1H), 1.35 (td, \( J = 13.4, 3.5 \) Hz, 1H), 1.22 (s, 3H), 1.06 (s, 3H), 0.95 (d, \( J = 6.6 \) Hz, 3H);

\(^{13}\)C-NMR (125 MHz, CDCl\(_3\)): \( \delta \) 146.2, 122.1, 113.7, 109.5, 65.4, 65.2, 59.7, 52.6, 48.8, 43.7, 39.1, 34.4, 28.8, 26.9, 20.9, 14.8; IR (neat) \( \nu \) 2951, 2927, 2871, 2832, 165, 1451, 1391, 1376, 1286, 1214, 1187, 1130, 1097, 1080, 1058, 1043 cm\(^{-1}\); HRMS (ESI+) calcd. for C\(_{17}\)H\(_{27}\)O\(_3\)\(^+\) ([M + H]\(^+\)): 279.19547, found: 279.19508.
Aldehyde 2.34 and enol ether 2.35

To a solution of 2.33 (11.1 g, 40.0 mmol) in 200 mL of THF was added 100 mL of water followed by 100 mL of formic acid (88%). After 36 h, TLC analysis (20% EtOAc in hexanes, anisaldehyde) indicated a mixture of two products, R\textsubscript{f} = 0.65 and R\textsubscript{f} = 0.42. The reaction was quenched by pouring into a mixture of ice and saturated sodium bicarbonate. Solid sodium bicarbonate was added to the mixture until the pH was basic, and then diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with two additional portions of EtOAc. The combined organics were washed with brine before drying over anhydrous Na\textsubscript{2}SO\textsubscript{4}. The solvent was removed under reduced pressure, and the residual oil was purified by flash column chromatography (10% EtOAc in hexanes to 20% EtOAc in hexanes) to afford 2.35 (4.85 g, 52%, 2:1 E:Z) and 2.34 (4.13 g, 47%), both as pale yellow oils.

2.35 (E isomer): \textsuperscript{1}H-NMR (500 MHz, CDCl\textsubscript{3}): δ 6.14 (d, J = 13.1 Hz, 1H), 5.62 (dd, J = 3.2, 1.1 Hz, 1H), 4.48 (d, J = 13.1 Hz, 1H), 3.53 (s, 3H), 2.63 (ddd, J = 15.9, 12.0, 5.6 Hz, 1H), 2.32 (dt, J = 15.9, 4.8 Hz, 1H), 2.26 (ddd, J = 14.6, 6.2, 3.3 Hz, 1H), 2.09 (dt, J = 13.5, 5.1 Hz, 1H), 2.03 – 1.91 (m, 2H), 1.69 (ddd, J = 13.3, 12.2, 5.0 Hz, 1H), 1.26 (s, 3H), 1.23 (s, 3H), 0.92 (d, J = 6.6 Hz, 3H); \textsuperscript{13}C-NMR (125 MHz, CDCl\textsubscript{3}): δ 215.4, 154.3, 148.7, 124.5, 103.8, 56.3, 50.6, 48.7, 47.7, 38.2, 35.2, 33.7, 28.3, 25.2, 14.2; IR (neat) ν 2958, 2927, 2869, 2835, 1711, 1643, 1454, 1377, 1207, 1128 cm\textsuperscript{-1}; HRMS (ESI+) calcd. for C\textsubscript{15}H\textsubscript{23}O\textsubscript{2}\textsuperscript{+} ([M + H]\textsuperscript{+}): 235.16926, found: 235.16931.
**2.34:** $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 9.73 (dd, $J = 3.8, 2.5$ Hz, 1H), 5.69 (dd, $J = 3.2, 1.3$ Hz, 1H), 2.65 (dd, $J = 15.5, 2.3$ Hz, 1H), 2.58 (ddd, $J = 16.0, 10.4, 5.4$ Hz, 1H), 2.49 – 2.37 (m, 3H), 2.19 – 2.09 (m, 1H), 2.02 (dt, $J = 13.7, 5.9$ Hz, 1H), 1.93 (ddd, $J = 16.3, 10.6, 1.4$ Hz, 1H), 1.78 (ddd, $J = 13.9, 10.4, 5.5$ Hz, 1H), 1.32 (s, 3H), 1.29 (s, 3H), 1.09 (d, $J = 7.1$ Hz, 3H); $^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 214.6, 203.0, 153.0, 126.0, 49.7, 48.5, 46.9, 46.9, 39.0, 35.0, 34.4, 27.8, 25.1, 13.9; IR (neat) $\nu$ 2967, 2930, 2872, 2839, 1710, 1629, 1461, 1417, 1379, 1101 cm$^{-1}$; HRMS (ESI+) calcd. for C$_{14}$H$_{21}$O$_2$ $^+$ ([M + H]$^+$): 221.15361, found: 221.15334.
Tricyclic ketone 2.7 (from 2.34)

![Chemical Structure](image)

To a solution of 2.34 (4.14 g, 18.8 mmol) in 375 mL of tert-butanol was added 2-methyl-2-butene (50 mL, 470 mmol, 25 eq.) followed by a solution of NaH₂PO₄•H₂O (104 g, 752 mmol, 40 eq.) in 450 mL of water. NaClO₂ (80% technical grade, 6.59 g, 58.3 mmol, 3.1 eq.) was then added, and the resulting yellow mixture was stirred for 2 h, after which TLC analysis (30% EtOAc in hexanes, CAM) indicated complete consumption of the starting material and formation of the product, R₁ = 0.13. The reaction was diluted with water and EtOAc. The layers were separated, and the aqueous layer was extracted with two additional portions of EtOAc. The combined organics were washed with brine before drying over anhydrous Na₂SO₄. The solvent was removed under reduced pressure to give crude 2.37 as a white solid.

To a solution of this crude product in 375 mL of CH₂Cl₂ was added a solution of SnCl₄ (1.0 M in CH₂Cl₂, 21 mL, 20.7 mmol, 1.1 eq.). The resulting mixture was stirred for 36 h, during which it became first orange then purple in color. TLC analysis (40% EtOAc in hexanes, anisaldehyde) indicated complete consumption of the starting material and formation of the product, R₁ = 0.26. The reaction was quenched with saturated sodium bicarbonate and stirred for 30 min before being diluted with CH₂Cl₂. The layers were separated, and the aqueous layer was extracted with two additional volumes of CH₂Cl₂. The combined organics were washed with brine before drying over anhydrous Na₂SO₄. The solvent was removed under reduced pressure, and the resulting oil was purified by flash column chromatography (30% EtOAc in hexanes) to afford 2.7 as a yellow solid (3.25 g, 73%).
$^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 2.90 (d, $J = 19.1$ Hz, 1H), 2.48 – 2.35 (m, 2H), 2.32 (d, $J = 19.1$ Hz, 1H), 2.06 – 1.88 (m, 4H), 1.79 (dt, $J = 12.5$, 6.1 Hz, 1H), 1.49 (td, $J = 14.0$, 6.5 Hz, 1H), 1.30 (qd, $J = 12.8$, 6.4 Hz, 1H), 1.19 (s, 3H), 1.17 (s, 3H), 1.03 (d, $J = 6.8$ Hz, 3H); $^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 212.5, 176.1, 99.7, 51.8, 49.6, 43.4, 38.3, 36.4, 33.9, 31.4, 30.4, 21.0, 21.0, 14.4; IR (neat) ν 2963, 2936, 2878, 1765, 1709, 1470, 1383, 1280, 1207, 1111 cm$^{-1}$; HRMS (ESI+) calcd. for C$_{14}$H$_{21}$O$_3$ $^+$ ([M + H]$^+$): 237.14852, found: 237.14872.
Nitrile 2.30

To a suspension of potassium tert-butoxide (9.39 g, 83.7 mmol, 2.6 eq.) in 60 mL of THF at –50 °C was added a solution of TosMIC (10.69 g, 54.7 mmol, 1.7 eq.) in 60 mL of THF to give an orange solution. After 15 min, a solution of 2.31 (8.06 g, 32.2 mmol) in 250 mL of THF was added slowly. After 1 hr, 46 mL of methanol was added, and the reaction was then placed in a room temperature oil bath and heated to 65 °C over 10 min. After 1 hr, the reaction became very viscous and was then cooled to room temperature. The reaction was diluted with water and diethyl ether. A small portion of brine was added for full separation of the layers. The aqueous layer was extracted with two additional portions of diethyl ether. The combined organics were washed with brine before drying over MgSO₄. The solvent was removed under reduced pressure, and the solid residue was purified by flash column chromatography (20% EtOAc in hexanes) to afford 2.30 as a white solid (7.60 g, 90%).

¹H-NMR (500 MHz, CDCl₃): δ 5.78 – 5.74 (m, 1H), 4.02 – 3.88 (m, 4H), 2.65 (d, J = 17.3 Hz, 1H), 2.40 – 2.31 (m, 2H), 2.28 – 2.21 (m, 1H), 2.16 – 2.07 (m, 1H), 1.88 (td, J = 14.5, 4.0 Hz, 1H), 1.76 (dt, J = 14.0, 3.5 Hz, 1H), 1.63 – 1.52 (m, 2H), 1.25 (s, 3H), 1.15 – 1.11 (m, 6H); ¹³C-NMR (125 MHz, CDCl₃): δ 151.6, 126.8, 119.1, 112.7, 65.6, 65.4, 49.0, 47.7, 43.0, 39.0, 35.3, 27.4, 26.2, 21.9, 21.5, 14.1; IR (neat) ν 2982, 2952, 2935, 2878, 2851, 2243, 1461, 1451, 1377, 1225, 1184 cm⁻¹; [α]D²⁰ = +67.8 (c 1.11, CH₂Cl₂); HRMS (ESI+) calcd. for C₁₆H₂₄NO₂⁺ ([M + H]⁺): 262.18016, found: 262.18054.
Tricyclic ketone 2.7 (from 2.30)

To a suspension of 2.30 (3.60 g, 13.8 mmol) in 16.5 mL of methanol was added 2.8 mL of concentrated H$_2$SO$_4$ to give an orange solution. The mixture was heated at 100 °C with a reflux condenser for 36 h. The reaction was cooled to room temperature and then diluted with EtOAc and water. The layers were separated, and the aqueous layer was extracted with two additional portions of EtOAc. The combined organics were washed with brine before drying over Na$_2$SO$_4$. The solvent was removed under reduced pressure, and the residual oil was purified by flash column chromatography (30% EtOAc in hexanes) to afford 2.7 as a pale orange solid (2.38 g, 73%).

$^1$H-NMR (500 MHz, CDCl$_3$): δ 2.90 (d, $J = 19.1$ Hz, 1H), 2.48 – 2.35 (m, 2H), 2.32 (d, $J = 19.1$ Hz, 1H), 2.06 – 1.88 (m, 4H), 1.79 (dt, $J = 12.5$, 6.1 Hz, 1H), 1.49 (td, $J = 14.0$, 6.5 Hz, 1H), 1.30 (qd, $J = 12.8$, 6.4 Hz, 1H), 1.19 (s, 3H), 1.17 (s, 3H), 1.03 (d, $J = 6.8$ Hz, 3H); $^{13}$C-NMR (125 MHz, CDCl$_3$): δ 212.5, 176.1, 99.7, 51.8, 49.6, 43.4, 38.3, 36.4, 33.9, 31.4, 30.4, 21.0, 21.0, 14.4; IR (neat) ν 2963, 2936, 2878, 1765, 1709, 1470, 1383, 1280, 1207, 1111 cm$^{-1}$; [α]$_D^{20} = -30.7$ (c 1.12, CH$_2$Cl$_2$); HRMS (ESI+) calcd. for C$_{14}$H$_{21}$O$_3$ $^+$ ([M + H]$^+$): 237.14852, found: 237.14872.
Oxime 2.49

To a solution of 2.7 (4.62 g, 19.6 mmol) in 130 mL of pyridine was added hydroxylamine hydrochloride (2.04 g, 29.3 mmol, 1.5 eq.). The reaction was heated at 80 °C for 12 h, after which TLC analysis (50% EtOAc in hexanes, CAM) indicated complete consumption of the starting material and formation of the product, Rf = 0.65. The reaction was quenched with 20% acetic acid and diluted with EtOAc. The layers were separated, and the organic layer was washed with four additional portions of 20% acetic acid, followed by saturated sodium bicarbonate and then brine, and finally dried over anhydrous Na2SO4. The solvent was removed under reduced pressure, and the residual oil was purified by flash column chromatography (40% EtOAc in hexanes) to afford 2.49 as a white solid (4.46 g, 91%).

1H-NMR (500 MHz, CDCl3): δ 8.92 (s, 1H), 2.82 (d, J = 19.1 Hz, 1H), 2.67 (ddd, J = 20.1, 5.9, 4.5 Hz, 1H), 2.54 (ddd, J = 20.1, 10.9, 6.8 Hz, 1H), 2.25 (d, J = 19.1 Hz, 1H), 1.97 – 1.77 (m, 4H), 1.71 (dt, J = 12.2, 5.9 Hz, 1H), 1.53 (td, J = 13.5, 6.3 Hz, 1H), 1.28 – 1.16 (m, 7H), 0.99 (d, J = 6.7 Hz, 3H); 13C-NMR (125 MHz, CDCl3): δ 176.5, 162.3, 99.6, 49.6, 44.0, 42.6, 38.2, 35.6, 30.2, 30.1, 23.1, 22.7, 20.0, 14.2; IR (neat) ν 3287, 2957, 2938, 2879, 1766, 1653, 1458, 1420, 1384, 1290, 1252, 1207, 1186 cm⁻¹; [α]D²⁰ = -24.0 (c 0.84, CH2Cl2); HRMS (ESI+) calcd. for C14H22NO3⁺ ([M + H]⁺): 252.15942, found: 252.15955.
**β-Acetoxylated oximes 2.50 and 2.51**

70 mL of acetic acid and 70 mL of acetic anhydride were added to 2.49 (4.46 g, 17.7 mmol), which slowly dissolved over 2 h. Pd(OAc)$_2$ (199 mg, 0.887 mmol, 0.05 eq.) was then added followed by PhI(OAc)$_2$ (8.57 g, 26.6 mmol, 1.5 eq.). The reaction mixture was sparged with an argon balloon for 5 min, then heated to 100 °C for 12 h. TLC analysis (40% EtOAc in hexanes, UV/KMnO$_4$) indicated complete consumption of the starting material and formation of both the undesired oxidation diastereomer ($R_f = 0.27$) and the desired diastereomer ($R_f = 0.32$). After cooling to room temperature, the reaction mixture was filtered through Celite, washing with EtOAc. The organics were washed with four portions of sodium bicarbonate (or until washings were basic) and then with brine before drying over anhydrous Na$_2$SO$_4$. The solvent was removed under reduced pressure, and the residual oil was purified by flash column chromatography (40% EtOAc in hexanes to 50% EtOAc in hexanes) to afford 2.50 as a pale yellow oil (1.39 g, 22%).

**2.50**: $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 4.78 (d $J = 11.2$ Hz, 1H), 3.94 (d, $J = 11.2$ Hz, 1H), 2.84 (d, $J = 19.3$ Hz, 1H), 2.73 (dt, $J = 20.1$, 4.8 Hz, 1H), 2.57 – 2.47 (m, 1H), 2.30 (d, $J = 19.3$ Hz, 1H), 2.20 – 2.02 (m, 8H), 1.97 – 1.90 (m, 1H), 1.82 (dt, $J = 12.6$, 6.2 Hz, 1H), 1.75 (dt, $J = 12.0$, 5.8 Hz, 1H), 1.54 (td, $J = 13.6$, 6.2 Hz, 1H), 1.44 (s, 3H), 1.27 – 1.17 (m, 1H), 1.01 (d, $J = 6.6$ Hz, 3H); $^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 175.4, 171.3, 168.7, 166.6, 98.3, 65.3, 49.6, 48.8, 42.7, 37.5, 36.5, 29.9, 29.5, 22.1, 21.1, 19.9, 18.2, 14.2; IR (neat) $\nu$ 2958, 2940, 2881, 1768, 1743, 1388, 1368, 1240, 1208, 1189 cm$^{-1}$;
[α]_D^{20} = + 20.6 (c 1.25, CH₂Cl₂); HRMS (ESI+) calcd. for C₁₈H₂₆NO₆⁺ ([M + H]⁺): 352.17546, found: 352.17576.

2.51: ¹H-NMR (500 MHz, CDCl₃): δ 4.55 (d, J = 11.4 Hz, 1H), 4.19 (d, J = 11.4 Hz, 1H), 2.81 (d, J = 19.1 Hz, 1H), 2.71 – 2.65 (m, 1H), 2.23 (d, J = 19.1 Hz, 1H), 2.18 (s, 3H), 2.08 (s, 3H), 2.06 – 1.86 (m, 3H), 1.82 – 1.74 (m, 2H), 1.71 – 1.63 (m, 1H), 1.42 (s, 3H), 1.34 – 1.22 (m, 1H), 1.00 (d, J = 6.3 Hz, 3H); ¹³C-NMR (125 MHz, CDCl₃): δ 175.6, 171.1, 169.1, 166.4, 97.8, 65.8, 50.5, 48.3, 42.9, 37.5, 35.2, 30.3, 29.5, 21.6, 21.2, 20.0, 18.4, 14.1; IR (neat) ν 2957, 2881, 1764, 1740, 1366, 1238, 1190 cm⁻¹; [α]_D^{20} = − 17.9 (c 1.49, CH₂Cl₂); HRMS (ESI+) calcd. for C₁₈H₂₆NO₆⁺ ([M + H]⁺): 352.17546, found: 352.17547.
Oxime 2.52

To a solution of 2.25 (100 mg, 0.423 mmol) in 2.8 mL of pyridine was added hydroxylamine hydrochloride (59 mg, 0.846 mmol, 2 eq.). The reaction was heated at 80 °C for 2 h, after which TLC analysis (20% EtOAc in hexanes, CAM) indicated complete consumption of the starting material and formation of the product, R<sub>f</sub> = 0.45. The reaction was quenched with 20% acetic acid and diluted with EtOAc. The layers were separated, and the organic layer was washed with four additional portions of 20% acetic acid, followed by saturated sodium bicarbonate and then brine, and finally dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed under reduced pressure, and the residual oil was purified by flash column chromatography (15% EtOAc in hexanes) to afford 2.52 as a white solid (99 mg, 93%).

<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>): δ 8.58 (s, 1H), 5.74 – 5.71 (m, 1H), 3.69 (s, 3H), 3.21 (dt, J = 15.2, 4.0 Hz, 1H), 2.67 (dt, J = 13.1, 4.2 Hz, 1H), 2.44 – 2.35 (m, 1H), 2.27 – 2.08 (m, 3H), 1.35 (s, 3H), 1.21 (td, J = 13.3, 4.6 Hz, 1H), 1.10 (s, 3H), 0.96 (d, J = 6.7 Hz, 3H); <sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>): δ 175.1, 165.0, 150.6, 126.4, 59.1, 51.5, 47.9, 41.8, 39.5, 33.9, 28.4, 24.1, 18.9, 14.6; IR (neat) ν 3267, 2957, 2930, 2848, 1724, 1455, 1435, 1379, 1231, 1198, 1175 cm<sup>-1</sup>; HRMS (ESI+) calcd. for C<sub>14</sub>H<sub>22</sub>N<sub>3</sub>O<sub>3</sub>: 252.15942, found 252.15936.
2.8 mL of acetic acid and 2.8 mL of acetic anhydride were added to 2.52 (176 mg, 0.700 mmol), which slowly dissolved over 2 h. Pd(OAc)$_2$ (8 mg, 0.035 mmol, 0.05 eq.) was then added followed by PhI(OAc)$_2$ (339 g, 1.05 mmol, 1.5 eq.). The reaction mixture was sparged with an argon balloon for 5 min, then heated to 100 °C for 12 h. TLC analysis (20% EtOAc in hexanes, KMnO$_4$) indicated complete consumption of the starting material and formation of the product, $R_f = 0.14$. After cooling to room temperature, the reaction mixture was filtered through Celite, washing with EtOAc. The organics were washed with four portions of sodium bicarbonate (or until washings were basic) and then with brine before drying over anhydrous Na$_2$SO$_4$. The solvent was removed under reduced pressure, and the residual oil was purified by flash column chromatography (15% EtOAc in hexanes to 20% EtOAc in hexanes) to afford 2.53 as a pale yellow oil (62 mg, 25%).

$^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 5.84 – 5.77 (m, 1H), 4.47 (d, $J$ = 11.1 Hz, 1H), 4.22 (d, $J$ = 11.1 Hz, 1H), 3.68 (s, 3H), 2.94 – 2.81 (m, 1H), 2.64 – 2.53 (m, 2H), 2.48 – 2.42 (m, 1H), 2.25 – 2.21 (m, 1H), 2.16 (s, 3H), 2.06 – 1.99 (m, 4H), 1.39 – 1.33 (m, 1H), 1.29 (s, 3H), 0.97 (d, $J$ = 6.6 Hz, 3H); $^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 174.1, 171.0, 168.6, 162.0, 145.5, 128.6, 68.6, 59.5, 51.8, 47.1, 45.3, 41.6, 39.7, 31.3, 24.0, 22.3, 21.1, 20.1, 14.6; IR (neat) $\nu$ 2953, 2933, 2875, 2847, 1767, 1722, 1434, 1367, 1226, 1190, 1037 cm$^{-1}$; HRMS (ESI+) calcd. for C$_{18}$H$_{26}$NO$_6^+$ ([M + H]$^+$): 352.17546, found: 352.17628.
Oxime 2.54

To a solution of 2.37 (50 mg, 0.212 mmol) in acetone was added potassium carbonate (117 mg, 0.846 mmol, 4 eq.) followed by iodomethane (30 µL, 0.423 mmol, 2 eq.). After 3.5 h, TLC analysis (40% EtOAc in hexanes, CAM) indicated complete consumption of the starting material and formation of the product, $R_f = 0.69$. The solvent was removed under reduced pressure, and the solid residue was taken up in diethyl ether and filtered through Celite. The solvent was removed under reduced pressure, and the residual oil was quickly passed through a plug of silica gel (20% EtOAc in hexanes) to afford the methyl ester.

To a solution of the crude product in 1.4 mL of pyridine was added hydroxylamine hydrochloride (30 mg, 0.423 mmol, 2 eq.). The reaction was heated at 80 °C for 3 h, after which TLC analysis (20% EtOAc in hexanes, CAM) indicated complete consumption of the starting material and formation of the product, $R_f = 0.34$. The reaction was quenched with 20% acetic acid and diluted with EtOAc. The layers were separated, and the organic layer was washed with four additional portions of 20% acetic acid, followed by saturated sodium bicarbonate and then brine, and finally dried over anhydrous Na$_2$SO$_4$. The solvent was removed under reduced pressure, and the residual oil was purified by flash column chromatography (15% EtOAc in hexanes) to afford 2.54 as a white solid (49 mg, 88%).

$^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 8.42 (s, 1H), 5.59 (d, $J = 2.8$ Hz, 1H), 3.60 (s, 3H), 2.79 (ddd, $J = 18.2$, 11.7, 6.6 Hz, 1H), 2.64 (ddd, $J = 17.9$, 6.4, 3.2 Hz, 1H), 2.36 – 2.19 (m, 2.54
4H), 2.07 – 1.95 (m, 2H), 1.46 (td, J = 13.0, 12.5, 6.4 Hz, 1H), 1.35 (s, 3H), 1.30 (s, 3H), 1.06 (d, J = 6.7 Hz, 3H); $^{13}$C-NMR (125 MHz, CDCl$_3$): δ 172.6, 165.1, 155.0, 123.4, 51.4, 50.3, 47.1, 40.3, 38.3, 35.2, 32.1, 31.0, 28.1, 19.5, 13.7; IR (neat) ν 3264, 2969, 2949, 2928, 2876, 2839, 1736, 1457, 1434, 1379, 1359, 1196, 1160, 1141 cm$^{-1}$; HRMS (ESI+) calcd. for C$_{15}$H$_{23}$NO$_3$ $^+$ ([M + H]$^+$): 266.17507, found: 266.17527.
Lactone 2.55

To a solution of 2.37 (50 mg, 0.212 mmol) in 4.3 mL of CH₂Cl₂ was added hydroxy(tosyloxy)iodobenzene (88 mg, 0.222 mmol, 1.05 eq.). A reflux condenser was attached and the reaction was refluxed for 12 h. TLC analysis (40% EtOAc, CAM) indicated complete consumption of the starting material and formation of the product, Rf = 0.55. The reaction was cooled to room temperature, quenched with saturated sodium thiosulfate, and diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with two additional portions of EtOAc. The combined organics were washed consecutively with saturated ammonium chloride, saturated sodium bicarbonate, and brine before drying over anhydrous Na₂SO₄. The solvent was removed under reduced pressure, and the crude product was purified by flash column chromatography (15% EtOAc in hexanes) to afford 2.55 (22 mg, 44%).

¹H-NMR (500 MHz, CDCl₃): δ 5.75 – 5.70 (m, 1H), 4.73 (dd, J = 4.3 1.4 Hz, 1H), 2.69 (d, J = 18.3 Hz, 1H), 2.56 (dd, J = 18.3, 2.5 Hz, 1H), 2.50 – 2.41 (m, 1H), 2.36 (dd, J = 14.3, 4.4 Hz, 1H), 2.14 – 2.03 (m, 2H), 1.72 (dt, J = 14.3, 1.9 Hz, 1H), 1.34 (s, 3H), 1.33 (s, 3H), 1.05 (d, J = 6.6 Hz, 3H); ¹³C-NMR (125 MHz, CDCl₃): δ 207.7, 170.1, 153.5, 126.1, 80.7, 46.2, 45.7, 45.0, 38.5, 37.8, 34.4, 31.5, 26.6, 13.8; IR (neat) ν 2958, 2931, 2873, 2838, 1743, 1720, 1631, 1461, 1446, 1362, 1268, 1238, 1212, 1193, 1159, 1085, 1048 cm⁻¹; HRMS (ESI+) calcd. for C₁₄H₁₉O₃⁺ ([M + H]⁺): 235.13287, found: 235.13292.
Oxime 2.56

To a solution of 2.55 (54 mg, 0.231 mmol) in 2.3 mL of pyridine was added hydroxylamine hydrochloride (20 mg, 0.277 mmol, 1.2 eq.). The reaction was heated at 80 °C for 3 h, after which TLC analysis (40% EtOAc in hexanes, CAM) indicated complete consumption of the starting material and formation of the product, R<sub>f</sub> = 0.46. The reaction was cooled to room temperature and diluted with EtOAc. The organics were washed with consecutively with saturated ammonium chloride, saturated sodium bicarbonate, and brine before drying over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed under reduced pressure, and the residual oil was purified by flash column chromatography (15% EtOAc in hexanes to 20% EtOAc in hexanes) to afford 2.56 as a white solid (42 mg, 74%).

<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>): δ 9.13 – 8.55 (br, 1H), 6.24 (dd, J = 4.2, 1.5 Hz, 1H), 5.73 – 5.70 (m, 1H), 2.63 (d, J = 18.3 Hz, 1H), 2.47 – 2.36 (m, 2H), 2.24 (dd, J = 13.9, 4.3 Hz, 1H), 2.08 – 1.94 (m, 2H), 1.47 (d, J = 14.0 Hz, 1H), 1.40 (s, 3H), 1.34 (s, 3H), 1.02 (d, J = 6.6 Hz, 3H); <sup>13</sup>C-NMR (125 MHz, CDCl<sub>3</sub>): δ 171.2, 160.4, 153.6, 124.5, 67.0, 45.6, 44.8, 38.8, 37.9, 37.8, 34.6, 34.2, 28.6, 13.9; IR (neat) ν 3316, 2959, 2930, 2873, 2838, 1707, 1457, 1374, 1347, 1338, 1271, 1217, 1202, 1161, 1119, 1091, 1048 cm<sup>-1</sup>; HRMS (ESI+) calcd. for C<sub>14</sub>H<sub>20</sub>NO<sub>3</sub><sup>+</sup> ([M + H]<sup>+</sup>): 250.14377, found: 250.14365.
To a solution of 2.50 (33 mg, 0.0939 mmol) in 940 µL of THF was added iron filings (53 mg, 0.939 mmol, 10 eq.) followed by one drop of acetic acid and one drop of chlorotrimethylsilane. The solution became yellow in color, and then black. After 30 min, 940 µL of water was added and the resulting mixture was stirred rapidly for 30 min, after which TLC analysis (30% EtOAc in hexanes, CAM) indicated complete consumption of the starting material and formation of the product, \( R_f = 0.24 \). The reaction was diluted with EtOAc and water. The layers were separated, and the aqueous layer was extracted with two additional portions of EtOAc. The combined organics were washed with brine before drying over anhydrous \( \text{Na}_2\text{SO}_4 \). The solvent was removed under reduced pressure, and the residual oil was purified by flash column chromatography (25% EtOAc in hexanes to 30% EtOAc in hexanes) to afford 2.57 as a colorless oil (24 mg, 89%).

Note: Due to inefficiencies in stirring encountered with magnetic stirrers, this reaction was difficult to run on larger scales. Two strategies were utilized to counter this problem: 1) Stirring worked well on 30 mg scale in a 2 dram vial, so multiple batches were run on this scale and combined [for example, 660 mg of 2.50 could be run across 20 vials before being combined for workup and purification to yield 490 mg of 2.57 (89%)]; or 2) Overhead stirring could also be used but with diminished efficiency [for example, 1.0 g of 2.50 gave 250 mg of 2.57 (30%) and 660 mg of recovered starting material (66%)].
$^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 4.65 (d, $J = 11.4$ Hz, 1H), 4.01 (d, $J = 11.4$ Hz, 1H), 2.89 (d, $J = 19.2$ Hz, 1H), 2.50 – 2.33 (m, 3H), 2.23 (ddd, $J = 15.6$, 9.4, 6.3 Hz, 1H), 2.09 – 1.99 (m, 5H), 1.96 – 1.86 (m, 1H), 1.79 (dt, $J = 12.4$, 6.0 Hz, 1H), 1.60 – 1.52 (m, 1H), 1.34 – 1.24 (m, 4H), 1.04 (d, $J = 6.7$ Hz, 3H); $^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 209.6, 175.4, 170.8, 98.7, 65.7, 55.1, 50.0, 43.5, 37.5, 36.8, 34.3, 30.5, 30.1, 21.0, 17.0, 14.3; IR (neat) $\nu$ 2959, 2937, 2879, 1768, 1739, 1710, 1231, 1190, 1033, 989 cm$^{-1}$; $[\alpha]_D^{20} = +3.0$ (c 1.59, CH$_2$Cl$_2$); HRMS (ESI+) calcd. for C$_{16}$H$_{23}$O$_5$ $^+$ ([M + H]$^+$): 295.15400, found: 295.15474.
To a solution of 2.57 (480 mg, 1.63 mmol) in 17 mL of THF at −78 °C was slowly added a solution of KHMDS (0.5 M in toluene, 3.6 mL, 1.79 mmol, 1.1 eq.) after which the reaction became yellow in color. Stirring was continued for 1 h at −78 °C, and then Comins's reagent (769 mg, 1.96 mmol, 1.2 eq.) was added. After 1 h at −78 °C, TLC analysis (20% in EtOAc in hexanes, CAM) indicated complete consumption of the starting material and formation of the product, R<sub>f</sub> = 0.15. The reaction was quenched with saturated ammonium chloride and diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with two additional portions of EtOAc. The combined organics were washed with brine before drying over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed under reduced pressure, and the residual oil was passed through a plug of silica (20% EtOAc in hexanes) to afford the crude triflate as a white solid.

To a solution of this crude product in 8.2 mL of DMF was added Pd(OAc)<sub>2</sub> (37 mg, 0.163 mmol, 0.1 eq.) and Ph<sub>3</sub>P (86 mg, 0.326 mmol, 0.2 eq.) to give a yellow solution. Triethylamine (460 µL, 3.26 mmol, 2 eq.) was then added followed by 2.8 mL of methanol. The reaction mixture was sparged for 5 min with an argon balloon followed by 10 min with a CO balloon, during which time the reaction mixture became orange in color. The reaction was then heated at 40 °C under a CO balloon for 12 h. After cooling to room temperature, the reaction was diluted with diethyl ether and water. The layers were separated, and the aqueous layer was extracted with two additional portions of diethyl ether. The combined organics were washed with brine before drying over anhydrous Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed under reduced pressure, and the residual
oil was purified by flash column chromatography (20% EtOAc in hexanes to 30% EtOAc in hexanes) to afford **2.60** as a pale yellow oil (271 mg, 49%).

**^1H-NMR (500 MHz, CDCl\textsubscript{3}):** \(\delta 6.76 \text{ (dd, } J = 6.0, 4.0 \text{ Hz, 1H), 4.38 (d, } J = 11.1 \text{ Hz, 1H), 4.18 (d, } J = 11.1 \text{ Hz, 1H), 3.72 (s, 3H), 2.79 (d, } J = 19.1 \text{ Hz, 1 H), 2.52 – 2.41 (m, 2H), 2.39 (d, } J = 19.1 \text{ Hz, 1H), 2.04 (dd, } J = 13.5, 5.6 \text{ Hz, 1 H), 2.01 (s, 3H), 1.72 – 1.57 (m, 3H), 1.38 (s, 3H), 1.20 – 1.10 (m, 1H), 1.01 (d, } J = 6.6 \text{ Hz, 3H); ^13C-NMR (125 MHz, CDCl\textsubscript{3}):** \(\delta 176.0, 170.5, 167.4, 138.5, 136.1, 100.8, 67.1, 51.9, 50.4, 47.2, 43.8, 37.6, 37.1, 36.4, 29.7, 21.1, 18.8, 14.0; \text{ IR (neat) } \nu 2953, 2874, 1771, 1743, 1717, 1633, 1435, 1375, 1235, 1192, 1041, 990 \text{ cm}^{-1}; [\alpha]_{D}^{20} = -118.5 \text{ (c 1.06, CH}_2\text{Cl}_2); \text{ HRMS (ESI+)} \text{ calcd. for C}_{18}\text{H}_{25}\text{O}_6^+ ([M + H]^+): 337.16456, \text{ found: 337.16430.}
Lactones 2.61, 2.62 and 2.63.

To a solution of 2.60 (196 mg, 0.583 mmol) in 23 mL of methanol was added potassium carbonate (162 mg, 1.17 mmol, 2 eq.). After 12 h, TLC analysis (50% EtOAc in hexanes, KMnO₄) indicated complete consumption of the starting material and the formation of new products, Rᵢ = 0.55 and 0.25. The reaction was concentrated to 1/3 volume under reduced pressure, then 3 M HCl and THF were added. The resulting mixture was stirred for 1 h, then diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with two additional portions of EtOAc. The combined organics were washed with brine before drying over anhydrous Na₂SO₄. The solvent was removed under reduced pressure, and the combined mixture is generally taken forward as is. If desired, 2.63 can be separated from 2.61 and 2.62 (these co-elute) by flash column chromatography (50% EtOAc in hexanes) to afford a 2.2 : 1.3 : 1 mixture of 2.61 : 2.62 : 2.63 (89% combined).
Epoxide 2.64

To a solution of 2.61, 2.62, and 2.63 (0.519 mmol combined) in 5.2 mL of methanol at 0 °C was added a pre-mixed solution of aqueous H₂O₂ (30%, 530 µL, 5.19 mmol, 10 eq.) and aqueous NaOH (3 M, 520 µL, 1.56 mmol, 3 eq.). The cooling bath was removed and the mixture was rapidly stirred for 5 h, after which TLC analysis (40% EtOAc in hexanes, KMnO₄) indicated complete consumption of the starting material and formation of the product, Rₚ = 0.31. The reaction was quenched with 3 M HCl until acidic, then diluted with water and EtOAc. The layers were separated, and the aqueous layer was extracted with two additional portions of EtOAc. The combined organics were washed with brine before drying over anhydrous Na₂SO₄. The solvent was removed under reduced pressure, and the residual oil was purified by flash column chromatography (50% EtOAc in hexanes) to afford 2.64 as a white foam (99 mg, 69%).

¹H-NMR (500 MHz, CDCl₃): δ 4.82 (d, J = 9.5 Hz, 1H), 4.12 (d, J = 9.5 Hz, 1H), 3.80 (t, J = 5.6 Hz, 1H), 2.85 (d, J = 19.1 Hz, 1H), 2.53 (dd, J = 15.0, 6.1 Hz, 1H), 2.24 (d, J = 19.1 Hz, 1H), 2.00 – 1.95 (m, 2H), 1.92 – 1.85 (m, 1H), 1.73 – 1.63 (m, 1H), 1.58 – 1.47 (m, 1H), 1.30 (dd, J = 15.0, 5.1 Hz, 1H), 1.08 (s, 3H), 0.97 (d, J = 6.6 Hz, 3H);

¹³C-NMR (125 MHz, CDCl₃): δ 173.5, 172.2, 99.3, 75.5, 60.1, 55.4, 53.1, 45.0, 41.3, 37.9, 35.8, 31.8, 31.0, 19.7, 14.1; IR (neat) ν 2959, 2877, 1783, 1465, 1428, 1379, 1271, 1206 cm⁻¹; [α]D²⁰ = −44.2 (c 0.83, CH₂Cl₂); HRMS (ESI⁺) calcd. for C₁₅H₁₉O₅⁺ ([M + H]⁺): 279.12270, found: 279.12249.
Amine 2.74

To a solution of 2.64 (23 mg, 0.0826 mmol) in 4.1 mL of toluene was added Bredereck’s reagent (1.4 mL, 6.78 mmol, 82 eq.). The resulting solution was heated at 100 °C for 12 h. The reaction was then cooled to room temperature and the solvent was removed under reduced pressure, and the residual oil was purified by flash column chromatography (2% methanol in CH$_2$Cl$_2$ to 5% methanol in CH$_2$Cl$_2$) to afford 2.74 (13 mg, 42%).

$^1$H-NMR (500 MHz, CDCl$_3$): δ 6.09 (s, 1H), 4.42 (d, $J = 9.9$ Hz, 1H), 3.94 (d, $J = 9.9$ Hz, 1H), 3.24 (s, 6H), 2.91 (dd, $J = 14.0$, 2.8 Hz, 1H), 2.26 (s, 6H), 2.04 – 1.93 (m, 2H), 1.82 (dd, $J = 13.4$, 2.9 Hz, 1H), 1.78 – 1.69 (m, 2H), 1.68 – 1.63 (m, 2H), 1.29 (s, 3H), 0.88 (d, $J = 6.6$ Hz, 3H); $^{13}$C-NMR (125 MHz, CDCl$_3$): δ 177.9, 168.8, 149.3, 148.2, 92.9, 76.7, 74.4, 67.5, 53.7, 49.0, 44.7, 35.9, 30.5, 29.6, 17.8, 15.1; HRMS (ESI+) calcd. for C$_{20}$H$_{31}$N$_2$O$_5$$^+$ ([M + H]$^+$): 379.22275, found: 379.22309.
α-Methylene lactones 2.76 and 2.77

To a solution of 2.64 (10 mg, 0.036 mmol) in 720 µL of THF at −78 °C was added a solution of LiHMDS (1.0 M in THF, 43 µL, 0.043 mmol, 1.2 eq.). After 1 h, Eschenmoser’s salt (15 mg, 0.079 mmol, 2.2 eq.) was added. The reaction was warmed to room temperature and stirred an additional 12 h. The reaction was quenched with saturated ammonium chloride and diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with two additional portions of EtOAc. The combined organics were washed with brine before drying over anhydrous Na$_2$SO$_4$. The solvent was removed under reduced pressure to afford the crude product mixture (see spectra).
To a solution of 2.64 (30 mg, 0.108 mmol) in 4.9 mL of THF at −78 °C was added chlorotrimethylsilane (35 µL, 0.269 mmol, 2.5 eq.) followed by a solution of LiHMDS (1.0 M in THF, 230 µL, 0.226 mmol, 2.1 eq.). The resulting yellow solution was stirred for 30 min at −78 °C, then a solution of NIS (27 mg, 0.119 mmol, 1.1 eq.) in 0.5 mL of THF was added. Stirring was continued at −78 °C for 30 min, after which TLC analysis (50% EtOAc in hexanes, CAM) indicated complete consumption of the starting material and formation of the two diastereomeric products, Rf = 0.31 and 0.68. The reaction was quenched with saturated ammonium chloride, warmed to room temperature, and diluted with CH₂Cl₂. The layers were separated, and the aqueous layer was extracted with two additional portions of CH₂Cl₂. The combined organics were washed with brine before drying over anhydrous Na₂SO₄. The solvent was removed under reduced pressure to give the crude intermediate iodide.

The crude product was immediately dissolved in 5.4 mL of CH₂Cl₂ in the dark. A solution of DMDO (~0.05 M in acetone, 6.5 mL, 0.323 mmol, 3 eq.) was added, and the mixture was stirred 24 h in the dark. A second charge of DMDO (6.5 mL) was added and stirring was continued an additional 24 h, after which TLC analysis (50% EtOAc in hexanes, CAM) indicated complete consumption of the starting material and formation of the product, Rf = 0.26. The solvent was removed under reduced pressure, and then EtOAc and saturated sodium thiosulfate were added. The layers were separated, and the aqueous layer was extracted with two additional portions of EtOAc. The combined organics were washed with brine before drying over anhydrous Na₂SO₄. The solvent
was removed under reduced pressure, and the residual oil was purified by flash column chromatography (30% EtOAc in hexanes) to afford 2.80 as a white solid (21 mg, 66%).

Note: the separation is tedious so the crude product is generally moved forward without separation.

$^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 5.02 (d, $J = 9.7$ Hz, 1H), 4.21 (d, $J = 9.7$ Hz, 1H), 3.57 (t, $J = 5.6$ Hz, 1H), 2.98 (dd, $J = 14.8$, 6.1 Hz, 1H), 2.24 – 2.13 (m, 2H), 2.05 – 1.99 (m, 1H), 1.90 (dq, $J = 12.6$, 6.7 Hz, 1H), 1.41 (dd, $J = 14.8$, 5.2 Hz, 1H), 1.31 – 1.28 (m, 1H), 1.19 (s, 3H), 1.07 (d, $J = 6.9$ Hz, 3H); $^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 198.4, 171.2, 157.8, 97.8, 73.9, 59.6, 59.0, 55.0, 48.0, 41.1, 32.6, 32.5, 32.3, 20.3, 13.5; IR (neat) $\nu$ 2960, 2920, 2850, 1788, 1717, 1462, 1379, 1263, 1029, 1010 cm$^{-1}$; $[\alpha]_D^{20} = -12.0$ (c 0.37, CH$_2$Cl$_2$); HRMS (ESI+) calcd. for C$_{15}$H$_{17}$O$_6^+$ ([M + H]$^+$): 293.10196, found: 293.10240.
Jiadifenolide (2.1)

To a solution of crude 2.80 (from 0.0736 mmol 2.64) in 1.5 mL of THF was added 1.5 mL of water followed by LiOH (3.5 mg, 0.147 mmol, 2 eq.). After 12 h, the reaction was quenched with 3 M HCl and stirred for 15 min before being diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with two additional portions of EtOAc. The combined organics were washed with brine before drying over anhydrous Na₂SO₄. The solvent was removed under reduced pressure, and the resulting oil was purified by flash column chromatography (2% methanol in CH₂Cl₂ to 4% methanol in CH₂Cl₂) to afford 2.1 as a white solid (9.1 mg, 40% from 2.64).

¹H-NMR (500 MHz, CDCl₃): δ 4.61 (d, J = 9.4 Hz, 1H), 4.42 (d, J = 6.0 Hz, 1H), 3.80 (d, J = 9.4 Hz, 1H), 2.47 (dd, J = 13.0, 6.0 Hz, 1H), 2.27 – 2.17 (m, 1H), 2.14 – 2.16 (m, 2H), 2.01 (dd, J = 13.7, 4.7 Hz, 1H), 1.92 – 1.86 (m, 1H), 1.33 – 1.26 (m, 1H), 1.23 (s, 3H), 1.21 (d, J = 7.3 Hz, 3H); ¹³C-NMR (125 MHz, CDCl₃): δ 178.3, 173.6, 101.9, 97.4, 79.1, 77.6, 74.6, 58.8, 48.1, 41.6, 35.2, 33.0, 32.1, 19.9, 14.7; IR (neat) ν 3419, 2925, 2855, 1772, 1458, 1379, 1205, 1085 cm⁻¹; [α]D²⁰ = −60.6 (c 0.17, MeOH); HRMS (ESI⁺) calcd. for C₁₅H₁₉O₇⁺ ([M + H]⁺) 311.11253, found: 311.11166.
Experimental for chapter 4
To a solution of 4.9 (4.22 g, 23.1 mmol) in 46 mL of THF at 0 °C was added a solution of methyllithium (1.6 M in diethyl ether, 16.3 mL, 25.9 mmol, 1.12 eq.). After 30 min, N,N,N',N'-tetramethylethylenediamine (17.3 mL, 116 mmol, 5 eq.) and Comins’s reagent (10.91 g, 27.8 mmol, 1.2 eq.) were added. After 1 h, the reaction was warmed to room temperature, and then the solvent was removed under reduced pressure. The residue was taken up in hexanes (+ 1% EtOAc), and washed consecutively with ice cold water, ice cold saturated copper(II) sulfate and water (1:4), and then two additional portions of ice cold water. The organics were dried over anhydrous Na₂SO₄, and the solvent was removed under reduced pressure to afford the crude triflate.

To a solution of the crude triflate in 116 mL of THF was added a solution of 9-borabicyclo[3.3.1]nonane (0.5 M in THF, 47 mL, 23.1 mmol, 1 eq.). After 2.5 h, ethanol (13.9 mL, 238 mmol, 10.3 eq.) was slowly added, followed by aqueous sodium hydroxide (6 M, 28.2 mmol, 1.2 eq.) and aqueous hydrogen peroxide (30%, 9.3 mL, 91 mmol, 3.9 eq.). The resulting mixture was heated at 50 °C for 1 h. TLC analysis (50% diethyl ether in pentane, KMnO₄) indicated complete consumption of the starting material and formation of the product, Rf = 0.26. The reaction was cooled to room temperature and diluted with saturated potassium carbonate and diethyl ether. The layers were separated, and the aqueous layer was extracted with two additional portions of diethyl ether. The combined organics were dried over anhydrous MgSO₄ before being filtered through Celite. The solvent was removed under reduced pressure, and the residual oil
was purified by flash column chromatography (50% diethyl ether in pentane) to afford **4.12** as a yellow oil (3.28 g, 55%).

$^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 5.64 (q, $J = 1.9$ Hz, 1H), 3.74 – 3.66 (m, 2H), 2.96 – 2.87 (m, 1H), 2.62 – 2.54 (m, 2H), 2.28 – 2.19 (m, 1H), 1.76 – 1.56 (m, 4H); $^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 149.5, 121.5, 118.6 (q, $J = 319$ Hz), 61.1, 38.5, 38.2, 30.7, 28.0.
Diene 4.14

To a solution of 4.12 (2.07 g, 7.95 mmol) in 160 mL of THF was added Pd(PPh$_3$)$_4$ (184 mg, 0.159 mmol, 2 mol%) and lithium chloride (2.36 g, 55.7 mmol, 7 eq.). After 15 min, tributyl(vinyl)stannane (2.6 mL, 8.75 mmol, 1.1 eq.) was added, a reflux condenser was attached, and the resulting mixture was heated at reflux. After 6 h, TLC analysis (40% EtOAc in hexanes, KMnO$_4$) indicated complete consumption of the starting material and formation of the product, R$_f$ = 0.49. The reaction was cooled, and potassium fluoride was added. After 30 min, the reaction mixture was diluted with diethyl ether and water. The layers were separated. The organics were washed with two portions of 1 M HCl before drying over anhydrous Na$_2$SO$_4$. The solvent was removed under reduced pressure, and the residual oil was purified by flash column chromatography (30% diethyl ether in pentane) to afford 4.14 as a yellow oil (850 mg, 77%).

$^1$H-NMR (500 MHz, CDCl$_3$): δ 6.55 (dd, $J$ = 17.3, 10.7 Hz, 1H), 5.68 (s, 1H), 5.13 – 5.01 (m, 2H), 3.78 – 3.63 (m, 2H), 2.91 – 2.81 (m, 1H), 2.51 – 2.45 (m, 1H), 2.43 – 2.33 (m, 1H), 2.20 – 2.21 (m, 1H), 1.76 – 1.46 (m, 4H); $^{13}$C-NMR (125 MHz, CDCl$_3$): δ 142.9, 134.8, 133.7, 114.5, 61.9, 42.5, 38.9, 30.2, 30.1.
Cycloadduct 4.26

To a solution of **4.14** (25 mg, 0.181 mmol) in 460 µL of CH₂Cl₂ was added triethylamine (130 µL, 0.904 mmol, 5 eq.) followed by chloro(dimethyl)vinylsilane (30 µL, 0.217 mmol, 1.2 eq.). After 12 h, TLC analysis (5% EtOAc in hexanes, CAM) indicated complete consumption of the starting material and formation of the product, Rᵢ = 0.55. The reaction was quenched with saturated sodium bicarbonate and diluted with CH₂Cl₂. The layers were separated, and the aqueous layer was extracted with two additional portions of CH₂Cl₂. The combined organics were washed with 1 M HCl followed by brine before being dried over anhydrous MgSO₄ and filtered through Celite. The solvent was removed under reduced pressure to afford the crude silyl ether.

In a sealed tube, the crude silyl ether was dissolved in 3.6 mL of toluene. The reaction vessel was sealed and heated at 180 °C behind a blast shield. After 72 h, TLC analysis (5% EtOAc in hexanes, CAM) indicated complete consumption of the starting material and formation of the product, Rᵢ = 0.40. The solvent was removed under reduced pressure, and the residual oil was purified by flash column chromatography (2% EtOAc in hexanes) to afford **4.26** (19 mg, 48%).

**¹H-NMR** (500 MHz, CDCl₃): δ 5.38 (s, 1H), 3.97 (dt, J = 11.5, 3.3 Hz, 1H), 3.75 (td, J = 11.7, 2.7 Hz, 1H), 2.53 – 2.44 (m, 1H), 2.40 – 2.29 (m, 1H), 2.17 – 2.11 (m, 2H), 2.07 – 1.69 (m, 6H), 1.41 – 1.31 (m, 1H), 1.05 (p, J = 10.5 Hz, 1H), 0.75 (t, J = 12.8 Hz, 1H),
0.14 (s, 3H), 0.06 (s, 3H); $^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 147.3, 116.1, 65.3, 41.4, 41.0, 35.4, 34.2, 34.1, 25.5, 25.3, 24.3, –2.2, –4.7.
Cycloadduct 4.27

To a solution of 4.14 (200 mg, 1.45 mmol) in 3.6 mL of CH$_2$Cl$_2$ was added triethylamine (1 mL, 7.24 mmol, 5 eq.) followed by chloro(diphenyl)vinylsilane (335 µL, 1.52 mmol, 1.05 eq.). After 12 h, TLC analysis (5% EtOAc in hexanes, CAM) indicated complete consumption of the starting material and formation of the product, $R_f = 0.19$. The reaction was quenched with saturated sodium bicarbonate and diluted with CH$_2$Cl$_2$. The layers were separated, and the aqueous layer was extracted with two additional portions of CH$_2$Cl$_2$. The combined organics were washed with 1 M HCl followed by brine before being dried over anhydrous MgSO$_4$ and filtered through Celite. The solvent was removed under reduced pressure to afford the crude silyl ether.

In a sealed tube, the crude silyl ether was dissolved in 29 mL of toluene. The reaction vessel was sealed and heated at 180 °C behind a blast shield. After 72 h, TLC analysis (5% EtOAc in hexanes, CAM) indicated complete consumption of the starting material and formation of the product, $R_f = 0.13$. The solvent was removed under reduced pressure, and the residual oil was purified by flash column chromatography (2% EtOAc in hexanes) to afford 4.26 (398 mg, 79%).

$^1$H-NMR (500 MHz, CDCl$_3$): δ 7.58 (d, $J = 5.0$ Hz, 2H), 7.47 (d, $J = 6.6$ Hz, 2H), 7.36 – 7.29 (m, 4H), 7.27 (d, $J = 7.4$ Hz, 2H), 5.32 (s, 1H), 4.06 – 4.00 (m, 1H), 3.93 (td, $J = 12.2, 3.2$ Hz, 1H), 2.63 (t, $J = 11.9$ Hz, 1H), 2.47 – 2.35 (m, 1H), 2.12 – 2.05 (m, 2H), 1.95 – 1.73 (m, 5H), 1.52 – 1.46 (m, 1H), 1.40 – 1.30 (m, 1H), 1.26 – 1.19 (m, 1H), 1.03
(p, J = 10.8 Hz, 1H); $^{13}$C-NMR (125 MHz, CDCl₃): δ 147.3, 135.3, 135.0, 134.7, 134.5, 130.1, 129.8, 128.2, 127.7, 116.3, 66.2, 41.1, 40.8, 35.0, 34.1, 34.0, 25.9, 25.4, 23.4.
Alcohol 4.28

In a sealed tube, 4.14 (100 mg, 0.724 mmol) was dissolved in 2.9 mL of toluene. Vinylboronic acid dibutyl ester (160 µL, 0.724 mmol, 1 eq.) and BHT (8 mg, 0.0362 mmol, 5 mol%) were added, the reaction vessel was sealed, and the reaction mixture was heated at 190 °C for 24 h behind a blast shield. The solvent was removed under reduced pressure to afford the crude cycloadduct.

To a solution of half of the crude cycloadduct from above (0.362 mmol) in 730 µL of CH₂Cl₂ was added catechol (40 mg, 0.362 mmol, 1 eq.). The solution was sparged with a balloon of air, and the reaction was then stirred under air for 30 min. The reaction was quenched with saturated sodium thiosulfate and diluted with diethyl ether. The layers were separated, and the aqueous layer was extracted with two additional portions of diethyl ether. The combined organics were washed with consecutively with three portions of saturated potassium carbonate and one portion of brine before drying over anhydrous Na₂SO₄. The solvent was removed under reduced pressure, and the residual oil was purified by flash column chromatography (25% EtOAc in hexanes) to afford 4.28 (25 mg, 42% combined)

^1H-NMR (500 MHz, CDCl₃): δ 4.53 (s, 1H), 3.76 – 3.57 (m, 2H), 2.36 (s, 1H), 2.31 – 2.22 (m, 1H), 2.21 – 2.08 (m, 2H), 1.99 (s, 2H), 1.85 – 1.71 (m, 2H), 1.67 – 1.55 (m, 2H), 1.52 – 1.42 (m, 2H), 1.23 – 1.13 (m, 2H); ^13C-NMR (125 MHz, CDCl₃): δ 143.7, 118.1, 62.1, 44.4, 37.6, 31.9, 28.9, 28.8, 25.4, 24.7, 22.9.
Alcohol 4.35

4.14 (180 mg, 1.30 mmol) was advanced to 4.27 as described previously without purification. To a solution of crude 4.27 in 2.6 mL of diethyl ether at 0 °C was added a solution of methyllithium (1.6 M in diethyl ether, 1.3 mL, 2.0 mmol, 1.5 eq.). After 30 min, the reaction was warmed to room temperature and stirred an additional 12 h. TLC analysis (30% EtOAc in hexanes, CAM) indicated complete consumption of the starting material and formation of the product, R_f = 0.66. The reaction was quenched with saturated ammonium chloride and diluted with diethyl ether. The layers were separated, and the aqueous layer was extracted with an additional two portions of diethyl ether. The combined organics were washed with brine before being dried over anhydrous MgSO_4 and filtered through Celite. The solvent was removed under reduced pressure, and the residual oil was purified by flash column chromatography (20% EtOAc in hexanes) to afford 4.35 as a colorless oil (352 mg, 75%).

^1H-NMR (500 MHz, CDCl_3): δ 7.60 (d, J = 7.2 Hz, 4H), 7.40 – 7.35 (m, 6H), 5.48 (s, 1H), 3.40 – 3.32 (m, 1H), 3.07 – 2.96 (m, 1H), 2.47 – 2.39 (m, 1H), 2.27 – 2.16 (m, 1H), 2.15 – 2.06 (m, 1H), 1.97 (s, 2H), 1.86 (d, J = 12.1 Hz, 1H), 1.75 – 1.67 (m, 1H), 1.53 – 1.28 (m, 5H), 1.24 – 1.13 (m, 1H), 0.95 – 0.85 (m, 1H), 0.63 (s, 3H); ^13C-NMR (125 MHz, CDCl_3): δ 143.4, 137.6, 136.6, 135.1, 134.9, 129.3, 129.3, 128.0, 128.0, 127.9, 118.7, 61.3, 46.5, 37.0, 29.8, 27.0, 26.7, 26.3, 24.9, 21.2, –6.0.
Enoate 4.47

To a solution of 4.45 (3.16 g, 20.5 mmol) in 80 mL of CH₂Cl₂ was added (carbethoxymethylene)triphenylphosphorane (9.28 g, 26.6 mmol, 1.3 eq.). After 48 h, TLC analysis (20% EtOAc in hexanes, anisaldehyde) indicated complete consumption of the starting material and formation of two products, \( R_f = 0.76 \) (Z isomer) and \( R_f = 0.68 \) (E isomer). The solvent was removed under reduced pressure to afford a crude solid. This was taken up in a 1:1 mixture of diethyl ether and pentane, and the resulting suspension was passed through a sintered glass funnel containing ~ 60 mL of silica gel. The silica was washed with a second portion of diethyl ether and pentane. The solvent was removed under reduced pressure, and the residual oil was purified by flash column chromatography (hexanes to 4% EtOAc in hexanes) to afford 4.47 as an oil (3.05 g, 66%, E isomer).

\(^1\)H-NMR (500 MHz, CDCl₃): \( \delta \) 6.96 (dt, \( J = 15.7, 6.5 \) Hz, 1H), 5.87 (d, \( J = 15.7 \) Hz, 1H), 4.19 (q, \( J = 7.1 \) Hz, 2H), 2.46 – 2.32 (m, 4H), 1.28 (t, \( J = 7.1 \) Hz, 3H), 0.14 (s, 9H); \(^{13}\)C-NMR (125 MHz, CDCl₃): \( \delta \) 166.5, 146.6, 122.6, 105.5, 86.0, 60.4, 31.4, 19.0, 14.4, 0.18.
To a solution of 4.47 (325 mg, 1.45 mmol) in 5 mL of CH₂Cl₂ at −78 °C was added a solution of DIBAL-H (1.0 M in toluene, 3.2 mL, 3.19 mmol, 2.2 eq.) over 5 min. After 45 min, TLC analysis (20% EtOAc in hexanes, anisaldehyde) indicated complete consumption of the starting material and formation of the product, Rₚ = 0.26. The reaction was quenched by the addition of saturated Rochelle’s salt (potassium sodium tartrate) at −78 °C and warming to room temperature over 1 h before dilution with CH₂Cl₂. The layers were separated, and the aqueous layer was extracted with two additional portions of CH₂Cl₂. The combined organics were washed consecutively with 1 M HCl and brine before drying over anhydrous Na₂SO₄. The solvent was removed under reduced pressure, and the residual oil was purified by flash column chromatography (20% EtOAc in hexanes) to afford 4.48 as a colorless oil (252 mg, 95%).

¹H-NMR (500 MHz, CDCl₃): δ 5.77 – 5.67 (m, 2H), 4.13 – 4.08 (m, 2H), 2.33 – 2.23 (m, 4H), 1.34 – 1.23 (b, 1H), 0.14 (s, 9H); ¹³C-NMR (125 MHz, CDCl₃): δ 131.0, 130.5, 106.7, 85.2, 63.8, 31.5, 20.1, 0.3.
To a solution of 4.48 (2.48 g, 13.6 mmol) in 70 mL of CH$_2$Cl$_2$ was added pyridine (3.3 mL, 40.8 mmol, 3 eq.) followed by propionyl chloride (2.4 mL, 27.2 mmol, 2 eq.), dropwise. After 15 min, TLC analysis (20% EtOAc in hexanes, anisaldehyde) indicated complete consumption of the starting material and formation of the product, $R_f = 0.70$. The reaction was quenched with 1 M HCl and diluted with diethyl ether. The layers were separated, and the organic layer was washed consecutively with saturated sodium bicarbonate and brine before drying over anhydrous Na$_2$SO$_4$. The solvent was removed under reduced pressure to afford the crude ester.

To a solution of diisopropylamine (2.5 mL, 17.7 mmol, 1.3 eq.) in 60 mL of THF at 0 °C was added a solution of butyllithium (1.49 M in hexanes, 11 mL, 16.3 mmol, 1.2 eq.). After 20 min, the solution was further cooled to –78 °C. A solution of the crude ester in 45 mL of THF was then added by canula over 15 min. Chlorotrimethylsilane (2.6 mL, 20.4 mmol, 1.5 eq.) was then added and the resulting solution was slowly warmed to room temperature. After 12 h, TLC analysis (50% EtOAc in hexanes, anisaldehyde) indicated formation of a new product, $R_f = 0.26$, along with remaining starting material. The reaction was diluted with diethyl ether and extracted with 1% aqueous sodium hydroxide (the organic layer could be concentrated to give 1.95 g of crude material containing the recovered starting material). The aqueous layer was then acidified with concentrated HCl (pH = 1), and then extracted with three portions of diethyl ether. The combined organics were then dried over anhydrous Na$_2$SO$_4$, and the solvent was removed under reduced pressure to afford the crude carboxylic acid.
The crude acid (1.35 g) was dissolved in 35 mL of acetone. Potassium carbonate (4.50 g, 32.5 mmol, 4 eq.) was added, followed by iodomethane (1.1 mL, 16.2 mmol, 2 eq.). After 2 h, TLC analysis (30% EtOAc in hexanes, anisaldehyde) indicated complete consumption of the starting material and formation of the product, $R_f = 0.75$. The solvent was removed under reduced pressure to give a crude solid, which was taken up in diethyl ether and filtered through Celite. After removal of the solvent under reduced pressure, the crude oil was purified by flash column chromatography (5% EtOAc in hexanes) to afford 4.52 as a colorless oil (984 mg, 40%).

$^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 5.44 (dt, $J = 17.1$, 9.6 Hz, 1H), 5.13 (dd, $J = 10.2$, 1.6 Hz, 1H), 5.09 (dd, 17.0, 1.6 Hz, 1H), 3.68 (s, 3H), 2.46 – 2.35 (m, 2H), 2.22 (dddd, $J = 16.2$, 7.9, 4.9, 2.6 Hz, 1H), 2.07 (dtd, $J = 16.6$, 8.2, 2.6 Hz, 1H), 1.94 (t, $J = 2.6$ Hz, 1H), 1.66 – 1.57 (m, 1H), 1.50 – 1.41 (m, 1H), 1.10 (d, $J = 6.5$ Hz, 3H); $^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 176.2, 138.0, 118.2, 84.1, 68.6, 51.7, 46.4, 43.9, 31.4, 16.6, 14.6.
Diene 4.54

To a solution of 4.52 (980 mg, 5.44 mmol) in 27 mL of toluene was added platinum(II) chloride (73 mg, 0.272 mmol, 0.05 eq.). The resulting suspension was stirred with vigorous stirring for 2 h, after which TLC analysis (10% EtOAc in hexanes, anisaldehyde) indicated complete consumption of the starting material and formation of the product, \( R_f = 0.47 \). The reaction mixture was filtered through Celite, and the solvent was removed under reduced pressure to give the crude diene.

The crude diene was dissolved in 22 mL of diethyl ether and cooled to 0 °C. A solution of lithium aluminum hydride (1.0 M in THF, 11 mL, 10.9 mmol, 2 eq.) was added. After 5 min, TLC analysis (20% EtOAc in hexanes, anisaldehyde) indicated complete consumption of the starting material and formation of the product, \( R_f = 0.22 \). The reaction was quenched carefully with saturated sodium sulfate at 0 °C. The mixture was warmed to room temperature and stirred for 30 min before being diluted with diethyl ether and water. The layers were separated, and the aqueous layer was extracted with two additional portions of diethyl ether. The combined organics were washed with brine before drying over anhydrous \( \text{Na}_2\text{SO}_4 \). The solvent was removed under reduced pressure, and the residual oil was purified by flash column chromatography (10% EtOAc in hexanes to 20% EtOAc in hexanes) to afford 4.54 as a colorless oil (678 mg, 82%).

\(^1\text{H-NMR (500 MHz, CDCl}_3\): \( \delta \) 6.56 (dd, \( J = 17.2, 10.8 \text{ Hz, 1H} \)), 5.70 (s, 1H), 5.12 – 5.00 (m, 2H), 3.64 (dt, \( J = 10.4, 5.1 \text{ Hz, 1H} \)), 3.48 – 3.42 (m, 1H), 2.84 – 2.72 (m, 1H), 2.52 – 2.43 (m, 1H), 2.42 – 2.33 (m, 1H), 2.09 (ddt, \( J = 13.1, 8.8, 4.3 \text{ Hz, 1H} \)), 1.68 – 1.58 (m,
2H), 1.34 (t, \( J = 5.6 \) Hz, 1H), 0.94 (d, \( J = 6.8 \) Hz, 3H); \(^{13}\)C-NMR (125 MHz, CDCl\(_3\)): \( \delta \) 143.6, 133.7, 132.9, 114.4, 67.1, 48.3, 40.7, 30.5, 27.8, 14.7.
Diol 4.57

In a sealed tube, 4.54 (300 mg, 1.97 mmol) was dissolved in 20 mL of toluene. Vinylboronic acid dibutyl ester (480 µL, 2.17 mmol, 1.1 eq.) and BHT (22 mg, 0.0985 mmol, 5 mol%) were added, the reaction vessel was sealed, and the reaction mixture was heated at 190 °C for 24 h behind a blast shield. After cooling to room temperature, the mixture was filtered through Celite, washing with additional toluene, and the solvent was removed under reduced pressure to give the crude cycloadduct.

The crude cycloadduct was dissolved in 10 mL of THF. Ethanol (1.2 mL, 20.6 mmol, 10.4 eq.), aqueous sodium hydroxide (6 M, 400 µL, 2.37 mmol, 1.2 eq.), and aqueous hydrogen peroxide (30%, 790 µL, 7.74 mmol, 3.9 eq.) were added, and the reaction was heated at 50 °C. After 1 h, the reaction was cooled to room temperature and diluted with saturated potassium carbonate and diethyl ether. The layers were separated, and the aqueous layer was extracted with two additional portions of diethyl ether. The combined organics were washed with brine before drying over anhydrous Na₂SO₄. The solvent was removed under reduced pressure, and the residual oil was purified by flash column chromatography (75% diethyl ether in hexanes to 100% diethyl ether to 100% EtOAc) to afford 4.57 as a white solid (274 mg, 71%, 2:1 dr).

**Major diastereomer:** $^1$H-NMR (500 MHz, CDCl₃): δ 5.36 (s, 1H), 3.92 – 3.82 (m, 1H), 3.57 (dd, $J = 10.9, 5.9$ Hz, 1H), 3.36 – 3.27 (m, 1H), 2.49 – 2.33 (m, 3H), 2.24 – 2.13 (m, 3H), 2.02 – 1.87 (m, 2H), 1.75 – 1.65 (m, 4H), 1.58 – 1.45 (m, 1H), 1.00 (d, $J = 6.9$ Hz, 3H), 0.94 (d, $J = 6.9$ Hz, 3H).
$^1$H; $^{13}$C-NMR (125 MHz, CDCl$_3$): δ 143.0, 116.8, 69.4, 65.9, 53.0, 42.5, 36.2, 32.6, 29.6, 25.8, 25.8, 17.0.
Lactone 4.60

To a solution of 4.54 (500 mg, 3.28 mmol) in 16.5 mL of CH$_2$Cl$_2$ was added triethylamine (2.3 mL, 6.57 mmol, 5 eq.) followed by acryloyl chloride (540 µL, 6.57 mmol, 2 eq.). After 10 min, TLC analysis (20% EtOAc in hexanes, CAM) indicated complete consumption of the starting material and formation of the product, R$_f$ = 0.75. The reaction was diluted with CH$_2$Cl$_2$ and washed consecutively with saturated ammonium chloride, saturated sodium bicarbonate, and brine before drying over anhydrous Na$_2$SO$_4$. The solution was filtered through Celite, and the solvent was removed under reduced pressure to afford the crude trienoate.

To a solution of trifluoromethanesulfonamide (539 mg, 3.61 mmol, 1.1 eq.) in 33 mL of CH$_2$Cl$_2$ at 0 °C was added a solution of dimethylaluminum chloride (1.0 M in hexanes, 7.3 mL, 7.23 mmol, 2.2 eq.), dropwise. The solution was warmed to room temperature. After 30 min, a solution of the crude trienoate in 16 mL of CH$_2$Cl$_2$ was added, and the reaction was heated at 80 °C. After 12 h, TLC analysis (10% EtOAc in hexanes, CAM) indicated complete consumption of the starting material and formation of the product, R$_f$ = 0.14. The reaction was cooled to room temperature, quenched with 1 M HCl, and diluted with diethyl ether. The layers were separated, and the aqueous layer was extracted with two additional portions of diethyl ether. The combined organics were washed with brine before drying over Na$_2$SO$_4$. The solvent was removed under reduced pressure, and the residual oil was purified by flash column chromatography (10% EtOAc in hexanes to 15% EtOAc in hexanes) to afford 4.60 as a mixture of diastereomers (264 mg, 39%).
Major diastereomer: $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 5.45 (s, 1H), 4.31 (d, $J = 12.3$ Hz, 1H), 4.08 (dd, $J = 12.2$, 6.1 Hz, 1H), 3.19 (s, 1H), 2.78 (s, 1H), 2.72 – 2.63 (m, 1H), 2.51 (q, $J = 7.1$ Hz, 1H), 2.32 (s, 2H), 2.26 (dd, $J = 13.1$, 7.0 Hz, 1H), 2.15 (q, $J = 6.6$ Hz, 1H), 2.02 (d, $J = 20.5$ Hz, 1H), 1.81 (dt, $J = 18.0$, 9.2 Hz, 1H), 1.70 – 1.59 (m, 2H), 0.88 (d, $J = 7.3$ Hz, 3H); $^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 174.9, 141.0, 117.7, 71.5, 45.6, 42.7, 38.9, 35.3, 30.1, 28.0, 26.1, 22.8, 12.9.
To a solution of 4.60 (180 mg, 0.873 mmol) in 9.7 mL of toluene at −78 °C was added a solution of diisobutylaluminum hydride (1.5 M in toluene, 580 μL, 0.873 mmol, 1 eq.). After 1.5 h, TLC analysis (30% EtOAc in hexanes, CAM) indicated complete consumption of the starting material and formation of the product, Rf = 0.42. The reaction was quenched with saturated Rochelle’s salt (potassium sodium tartrate) at −78 °C before warming to room temperature over 30 min. The mixture was diluted with EtOAc and water. The layers were separated, and the aqueous layer was extracted with two additional portions of EtOAc. The combined organics were washed with brine before drying over Na₂SO₄. The solvent was removed under reduced pressure to afford 4.61 as a white solid (172 mg, 95%).

1H-NMR (500 MHz, CDCl₃): δ 5.45 (s, 1H), 4.72 (dd, J = 7.4, 4.1 Hz, 1H), 3.69 (dd, J = 12.6, 3.7 Hz, 1H), 3.39 (dd, J = 12.6, 10.2 Hz, 1H), 2.78 – 2.66 (m, 2H), 2.41 – 2.34 (m, 1H), 2.32 – 2.09 (m, 5H), 2.05 – 1.92 (m, 2H), 1.69 – 1.64 (m, 1H), 1.62 – 1.54 (m, 1H), 1.37 (qd, J = 12.2, 6.8 Hz, 1H), 0.85 (d, J = 7.2 Hz, 3H); 13C-NMR (125 MHz, CDCl₃): δ 143.9, 116.6, 97.9, 67.0, 45.3, 42.9, 41.7, 35.1, 33.3, 25.6, 25.6, 21.9, 17.9.
To a solution of 4.61 (81 mg, 0.389 mmol) in 3.9 mL of DMF at 0 °C was added imidazole (40 mg, 0.583 mmol, 1.5 eq.) followed by tert-butyl(chloro)diphenylsilane (150 µL, 0.583 mmol, 1.5 eq.). The reaction was slowly warmed to room temperature and then stirred an additional 12 h. TLC analysis (20% EtOAc in hexanes, CAM) indicated remaining 4.61 along with the formation of the product, R_f = 0.76. The reaction was diluted with diethyl ether and washed consecutively with two portions of water and one portion of brine before drying over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residual oil was purified by flash column chromatography (2% EtOAc in hexanes to 3% EtOAc in hexanes) to afford 4.62 as a colorless, viscous oil (115 mg, 66%).

^1H-NMR (500 MHz, CDCl₃): δ 9.67 (s, 1H), 7.65 (t, J = 6.4 Hz, 4H), 7.47 – 7.33 (m, 6H), 5.48 (s, 1H), 3.64 (dd, J = 9.9, 3.6 Hz, 1H), 3.50 (dd, J = 9.8, 6.2 Hz, 1H), 2.81 – 2.71 (m, 2H), 2.30 (dd, J = 13.8, 6.0 Hz, 1H), 2.21 – 1.97 (m, 5H), 1.82 – 1.71 (m, 2H), 1.27 – 1.23 (m, 2H), 1.09 (d, J = 6.4 Hz, 3H), 1.05 (s, 9H); ^13C-NMR (125 MHz, CDCl₃): δ 206.2, 144.7, 135.8, 134.0, 133.9, 129.7, 129.7, 127.7, 118.4, 67.7, 47.3, 46.2, 41.1, 36.6, 34.3, 31.3, 27.0, 25.9, 21.9, 19.5, 17.7.
Selected spectra
$^1$H-NMR spectrum of 2.23 (CDCl$_3$, 500 MHz)
$^{13}$C-NMR spectrum of 2.23 (CDCl$_3$, 125 MHz)
$^1$H-NMR spectrum of 2.24 (CDCl$_3$, 500 MHz)
$^{13}$C-NMR spectrum of 2.24 (CDCl$_3$, 125 MHz)
$^1$H-NMR spectrum of 2.25 (CDCl$_3$, 500 MHz)
$^{13}\text{C-NMR}$ spectrum of 2.25 (CDCl$_3$, 125 MHz)
$^1$H-NMR spectrum of 2.26 (CDCl$_3$, 500 MHz)
$^{13}$C-NMR spectrum of 2.26 (CDCl$_3$, 125 MHz)
$^1$H-NMR spectrum of 2.28 (CDCl$_3$, 500 MHz)
$^{13}$C-NMR spectrum of 2.28 (CDCl$_3$, 125 MHz)
$^1$H-NMR spectrum of 2.29 (CDCl$_3$, 500 MHz)
$^{13}$C-NMR spectrum of 2.29 (CDCl$_3$, 125 MHz)
$^{1}$H-NMR spectrum of 2.31 (CDCl$_3$, 500 MHz)
$^1$H-NMR spectrum of 2.33 (CDCl$_3$, 500 MHz)
$^{13}$C-NMR spectrum of 2.33 (CDCl$_3$, 125 MHz)
$^1$H-NMR spectrum of 2.34 (CDCl$_3$, 500 MHz)
$^{13}$C-NMR spectrum of 2.34 (CDCl$_3$, 125 MHz)
$^1$H-NMR spectrum of 2.35 (CDCl$_3$, 500 MHz)
$^{13}$C-NMR spectrum of 2.35 (CDCl$_3$, 125 MHz)
$^1$H-NMR spectrum of 2.7 (CDCl$_3$, 500 MHz)
$^{13}$C-NMR spectrum of 2.7 (CDCl$_3$, 125 MHz)
$^1$H-NMR spectrum of 2.30 (CDCl$_3$, 500 MHz)
$^{13}$C-NMR spectrum of 2.30 (CDCl$_3$, 125 MHz)
$^1$H-NMR spectrum of 2.49 (CDCl$_3$, 500 MHz)
$^{13}$C-NMR spectrum of 2.49 (CDCl$_3$, 125 MHz)
$^1$H-NMR spectrum of 2.50 (CDCl$_3$, 500 MHz)
$^{13}$C-NMR spectrum of 2.50 (CDCl$_3$, 125 MHz)
$^1$H-NMR spectrum of 2.51 (CDCl$_3$, 500 MHz)
$^{13}$C-NMR spectrum of 2.51 (CDCl$_3$, 125 MHz)
$^1$H-NMR spectrum of 2.52 (CDCl$_3$, 500 MHz)
$^{13}$C-NMR spectrum of 2.52 (CDCl$_3$, 125 MHz)
$^1$H-NMR spectrum of 2.53 (CDCl$_3$, 500 MHz)
$^{13}$C-NMR spectrum of 2.53 (CDCl$_3$, 125 MHz)
$^1\text{H-NMR}$ spectrum of 2.54 (CDCl$_3$, 500 MHz)
$^{13}$C-NMR spectrum of 2.54 (CDCl$_3$, 125 MHz)
$\text{H-NMR spectrum of 2.55 (CDCl}_3, 500 \text{ MHz)$}
$^{13}$C-NMR spectrum of 2.55 (CDCl$_3$, 125 MHz)
$^1$H-NMR spectrum of 2.56 (CDCl$_3$, 500 MHz)
$^{13}\text{C-NMR}$ spectrum of 2.56 (CDCl$_3$, 125 MHz)
$^1$H-NMR spectrum of 2.57 (CDCl$_3$, 500 MHz)
$^{13}$C-NMR spectrum of 2.57 (CDCl$_3$, 125 MHz)
$^1$H-NMR spectrum of 2.60 (CDCl$_3$, 500 MHz)
\(^{13}\)C-NMR spectrum of 2.60 (CDCl\(_3\), 125 MHz)
$^1$H-NMR spectrum of 2.61 and 2.62 (CDCl$_3$, 500 MHz)
$^{13}$C-NMR spectrum of 2.61 and 2.62 (CDCl$_3$, 125 MHz)
¹H-NMR spectrum of 2.63 (CDCl₃, 500 MHz)
$^{13}$C-NMR spectrum of 2.63 (CDCl$_3$, 125 MHz)
$^1$H-NMR spectrum of 2.64 (CDCl$_3$, 500 MHz)
$^{13}$C-NMR spectrum of 2.64 (CDCl$_3$, 125 MHz)
$^1$H-NMR spectrum of 2.74 (CDCl$_3$, 500 MHz)
$^{13}$C-NMR spectrum of 2.74 (CDCl$_3$, 125 MHz)
$^1$H-NMR spectrum of 2.64, 2.76, and 2.77 (CDCl$_3$, 500 MHz)
$^{13}$C-NMR spectrum of 2.64, 2.76, and 2.77 (CDCl$_3$, 125 MHz)
$^1$H-NMR spectrum of 2.80 (CDCl$_3$, 500 MHz)
$^{13}$C-NMR spectrum of 2.80 (CDCl$_3$, 125 MHz)
$^1$H-NMR spectrum of jiadifenolide (2.1) (CD$_3$OD, 500 MHz)
\[^{13}\text{C-}\text{NMR spectrum of jiadifenolide (2.1) (CD}_3\text{OD}, 125 \text{ MHz)}\]
$^1$H-NMR spectrum of 4.12 (CDCl$_3$, 500 MHz)
$^{13}$C-NMR spectrum of 4.12 (CDCl$_3$, 125 MHz)
$^1$H-NMR spectrum of 4.14 (CDCl$_3$, 500 MHz)
$^{13}$C-NMR spectrum of 4.14 (CDCl$_3$, 125 MHz)
$^1$H-NMR spectrum of 4.26 (CDCl$_3$, 500 MHz)
$^{13}$C-NMR spectrum of 4.26 (CDCl₃, 125 MHz)
$^1$H-NMR spectrum of 4.27 (CDCl$_3$, 500 MHz)
$^{13}$C-NMR spectrum of 4.27 (CDCl$_3$, 125 MHz)
$^1$H-NMR spectrum of 4.28 (CDCl$_3$, 500 MHz)
$^{13}$C-NMR spectrum of 4.28 (CDCl$_3$, 125 MHz)
$^1$H-NMR spectrum of 4.35 (CDCl$_3$, 500 MHz)
$^{13}$C-NMR spectrum of 4.35 (CDCl$_3$, 125 MHz)
$^1$H-NMR spectrum of 4.47 (CDCl$_3$, 500 MHz)
$^{13}$C-NMR spectrum of 4.47 (CDCl$_3$, 125 MHz)
$^1$H-NMR spectrum of 4.48 (CDCl$_3$, 500 MHz)
$^{13}$C-NMR spectrum of 4.48 (CDCl$_3$, 125 MHz)
$^1$H-NMR spectrum of 4.52 (CDCl$_3$, 500 MHz)
$^{13}$C-NMR spectrum of 4.52 ($\text{CDCl}_3$, 125 MHz)
$^1$H-NMR spectrum of 4.54 (CDCl$_3$, 500 MHz)
$^{13}$C-NMR spectrum of 4.54 (CDCl$_3$, 125 MHz)
$^1$H-NMR spectrum of 4.57 (CDCl$_3$, 500 MHz)
$^{13}$C-NMR spectrum of 4.57 (CDCl$_3$, 125 MHz)
$^1$H-NMR spectrum of 4.60 (CDCl$_3$, 500 MHz)
$^{13}$C-NMR spectrum of 4.60 (CDCl$_3$, 125 MHz)
$^1\text{H-NMR}$ spectrum of 4.61 (CDCl$_3$, 500 MHz)
\( ^{13}\)C-NMR spectrum of 4.61 (CDCl\(_3\), 125 MHz)
$^1$H-NMR spectrum of 4.62 (CDCl$_3$, 500 MHz)
$^{13}$C-NMR spectrum of 4.62 (CDCl$_3$, 125 MHz)
Appendix: Publications and presentations


Siler, D. A.; Mighion, J. D.; Sorensen, E. J. Progress towards a total synthesis of jiadifenolide. 15th Biennial Eli Lilly Grantee Symposium, Indianapolis, IN, United States, March 4–6, 2012.


Appendix: Vita

Education

Princeton University, 2008–2014

Ph.D. Organic Chemistry, expected June 2014; advisor: Erik J. Sorensen
M.A. Organic Chemistry, 2010; advisor: Erik J. Sorensen
Research: An enantiospecific synthesis of jiadifenolide, and progress toward a synthesis of pleurotin.

University of Cincinnati, 2004–2008

B.S. Chemistry, 2008; advisor: Suri S. Iyer
Research: Synthesis and evaluation of multivalent glycoconjugates for pathogen detection.

Honors

Margaret and Herman Sokol Fellowship in Chemistry, Princeton University, 2013
Pickering Teaching Award, Princeton University, 2011
Eli Lilly – Edward C. Taylor Fellowship, Princeton University, 2010
Walker McKinney ’50 Life Sciences Fellowship, Princeton University, 2009
Summa Cum Laude, University of Cincinnati, 2008
Chemistry Department High Honors, University of Cincinnati, 2008
Phi Beta Kappa, University of Cincinnati, 2008
Phi Beta Kappa Endowment Fund Scholarship, University of Cincinnati, 2008
Dunn Century Scholarship, University of Cincinnati, 2004–2008
Hypercube Scholar Award, University of Cincinnati, 2008
Stella Potter & Hoke S. Greene Scholarship, University of Cincinnati, 2007
Analytical Chemistry Division of the American Chemical Society Award, University of Cincinnati, 2007.