Title
Investigation into the Nazarov Cyclization of Aryl Dienyl Ketones and Synthetic Studies Toward Tetrapetalone A

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Investigation into the Nazarov Cyclization of Aryl Dienyl Ketones
and
Synthetic Studies Toward Tetrapetalone A

by

Andrew Peter Marcus

A dissertation submitted in partial satisfaction of the
requirements for the degree of

Doctor of Philosophy

in

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in the

GRADUATE DIVISION

of the

UNIVERSITY OF CALIFORNIA, BERKELEY

Committee in charge:

Professor Richmond Sarpong, Chair

Professor K. Peter C. Vollhardt

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Fall 2009
Abstract

Investigation into the Nazarov Cyclization of Aryl Dienyl Ketones and Synthetic Studies Toward Tetrapetalone A

by

Andrew Peter Marcus

Professor Richmond Sarpong, Chair

En route to a total synthesis of tetrapetalone A, we have discovered an unexpected steric facilitation of the Nazarov cyclization of aryl dienyl ketones. Chapter 1 describes the success of the Nazarov cyclization of substrates possessing substituents at both the α- and γ-positions of the acyclic dienone. Substrates possessing only one substituent at either the α- or γ-position proceed much more slowly, or not at all. Density functional theory calculations on the Lewis acid-bound substrates and their respective transition states were performed by Rebecca Davis in the research group of Prof. Dean Tantillo at the University of California, Davis. The computations correlate closely with the observed reactivity. The effect is observed across a series of aryl dienyl ketones with an electron-rich arene portion. Further evidence for this effect was shown by the difficulty of effecting the Nazarov cyclization of a cyclic aryl dienone at room temperature.

Chapter 2 describes the application of the findings of the Nazarov study to the synthesis of the indanone portion of tetrapetalone A. Difficulties in differentiation of the C-12 and C-14 positions (tetrapetalone numbering) of the indanone led to the investigation of a meta-bromo-containing aryl dienone, which successfully underwent the Nazarov cyclization with 13:1 regioselectivity. Formation of the C-N bond was achieved by performing a lithium-halogen exchange on the aryl bromide and quenching with tosyl azide, the product of which was then reduced to the free amine using lithium aluminum hydride.

Chapter 3 describes the elaboration of the aniline intermediate to a late-stage tetracycle en route to tetrapetalone A. Closure of the tetracycle was achieved by Friedel-Crafts acylation onto a pyrrole in a double oxidation cascade. This sequence is promoted by Dess-Martin periodinane as both the oxidant and the activating agent for the carbonyl moiety. Installation of the angular ethyl group at C-4 was achieved by Birch reduction of the resulting 2-ketopyrrole followed by quenching with iodomethane. The correct substitution pattern on the tetramic acid was achieved following oxidation to the α,β-unsaturated lactam and subsequent copper-mediated conjugate addition of bis(pinacolato)diboron, followed by further oxidation.
To Dr. Gustav Raspitha, for inspiration,

Dr. Bryce A. Harrison, for taking a chance,

and Dr. Michael G. Johnson, for guidance.
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Acknowledgments

First and foremost, I would like to thank my advisor, Professor Richmond Sarpong. His boundless enthusiasm for synthetic chemistry is infectious, and even with his vast array of knowledge, he always strives to be a better chemist and constantly encouraged me to do so as well. He taught me to be passionate about my project, and he acted as a pillar of stability when my frustrations got the better of me. I only hope that now that Richmond has tenure and a baby on the way, he lives up to his mantra: “Don’t think things are going to change around here.”

I also owe a debt of gratitude to all the current and former members of the Sarpong Group. In particular, I must thank the other three founding graduate students of the Sarpong Group. Kimberly Larson has been at my side for all of the ups and downs of graduate school and has acted as a sounding board for all of my ideas. I never cease to be amazed by her persistence, and I’m happy to say that being in our group has broadened her horizons quite a bit. Eric Bunnelle was a fantastic labmate for my first three years of graduate school and was always the first person I turned to for a question about physical organic chemistry. His deadpan sense of humor led to quite a few jokes at Richmond’s expense, and I’m grateful that we’re now living near each other on the other side of the country. Eric Simmons forced everyone around him to become better synthetic chemists and was my editor-in-chief for all of my papers and reports. His institution of 80s Saturday in the lab inspired me to set up the not-quite-as-awesome 70s Friday, and I always appreciated his multitude of impersonations, particularly of Zoolander.

Our first year was truly a trial by fire, with group meetings lasting until 11 PM and research presentations on a three-week rotation. Luckily, we also had our two postdocs, Maina Ndungu (the self-proclaimed slowest Kenyan alive) and B. A. Bhanu Prasad (who first experienced snow in Richmond’s car during the ill-fated 2006 Tahoe ski trip). The two of them were enormously helpful as we all tried to learn together, and I appreciated their good advices and good humor all along the way.

Fortunately, we survived that first year and acquired a number of great people along the way. Brian Pujanauski was always full of ideas, many of them good, and would keep everyone on their toes by throwing an argument our way. I should also thank him for introducing me to some random obscure bands. Laura Miller not only provided a lot of helpful chemistry advice, but also exposed me to the wonderful world of Bruce Campbell. She also made the best red velvet cake this side of Mount Rushmore. Scott West took the thankless job of solvent still maintenance off my hands, for which I will be eternally grateful. Sarah House deserves a medal for dealing with the revolving door of the black hole that was her lab. I only hope that her next position provides her with a window.

As the years went on, we picked up another great postdoc, Alakesh Bisai, who was thrown into a lab with me for my last two years of grad school. Others fondly called this lab “The Nursing Home” due to our advanced ages. Alakesh was always in good spirits and managed to tolerate my loud American music. Later, his wife Vishnumaya joined us, and she taught me quite a bit about Indian culture (including several amusing Hindi phrases). It was a pleasure to work with both of them, and I wish them great success in starting up their new institute in India.

I am also confident in the bright future of the Sarpong Group. Alison Hardin, Jesse Cortez, Jessica Wood and Jenna Jeffrey have all acquired a vast amount of expertise over the time that I’ve known them, and I’m thrilled to see their names in the literature when I open up my
journal ASAPs. I hope they continue to maintain their positive attitudes and mentor the army of new students Richmond has recruited.

I am also extremely grateful for the help of my undergrad, Amy Lee. She came into the group as eager to help and to learn as anyone I’ve ever seen and left for graduate school in much the same way, all the while maintaining her youthful innocence in the presence of such “immoral” characters. Without a doubt, much of the work on the Nazarov cyclization would not have been completed without her help. I’m confident that she will go on to do great things in her career.

It would be an understatement to say that the Sarpong Group received quite a bit of outside help when we first started. I always laughed in my later years when people came to search our inventory. The entire Trauner, Toste and Ellman Groups were each an invaluable resource in my first two years whenever I had a question about technique, NMR, or theory. Chris Beaudry, Aubry Miller, Andy Patterson, Ben Sherry, Alex Radosevich, Paul Roethle, Jenn Barbarow and J. P. Lumb were just a few of the people who went out of their way to help me or others in the Sarpong Group.

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Finally, I would like to thank all the friends and family I neglected over the past five years. To my friends in San Francisco, I thank you for patiently waiting those extra two hours for me when I promised I’d be on an earlier BART train. To my friends around the country, I thank you for understanding when I couldn’t visit as often as I’d like. And especially, I thank my family, particularly my mother (Rosemarie), my father (Peter) and my sister (Annemarie), who patiently dealt with my eight-year sojourn to the west coast and have provided me with encouragement and support every step of the way. I couldn’t have done it without you guys!
1.1. Introduction

1.1.1. Lipoxygenases in Nature

The cyclooxygenase and human lipoxygenase enzymes catalyze the addition of two molecules of $O_2$ to arachidonic acid (1.1) to create prostaglandin G$_2$ (1.2, Scheme 1.1). Prostaglandin G$_2$ can subsequently be converted to several other prostaglandins (e.g., 1.3), or to the thromboxanes (e.g., 1.4), leukotrienes (e.g., 1.5), or lipoxins (e.g., 1.6), which are important signaling molecules that have been implicated in a wide variety of human diseases.$^{1-3}$

Scheme 1.1. The arachidonic acid pathway.

Soybean lipoxygenase (SBL) is an enzyme that has been shown to have 15-lipoxygenase activity; that is, it catalyzes the addition of oxygen to the 15-position of arachidonic acid. As a
result, an SBL inhibitor could also inhibit human lipoxygenase or cyclooxygenase. For example, nordihydroguaiareic acid (NDGA, 1.7, Figure 1.1) has been shown to inhibit the activity of SBL ($IC_{50} = 290 \mu M$), as well as human lipoxygenase and cyclooxygenase.\(^4\)

\[\text{Figure 1.1. Nordihydroguaiareic acid (NDGA, 1.7).}\]

1.1.2. Isolation of the Tetrapetalones

Tetrapetalone A (1.8, Figure 1.2) was isolated in 2003 by Komoda and coworkers from a soil sample of *Streptomyces* sp. USF-4727 strain.\(^5\-7\) This compound was shown to have an $IC_{50}$ of 190 $\mu M$ in a soybean lipoxygenase (SBL) inhibition assay, comparable to NDGA and kojic acid ($IC_{50} = 110 \mu M$), another known SBL inhibitor.\(^5\) Upon methylation of the oxygen at C-3, however, activity disappeared completely, suggesting that the free hydroxyl group is necessary for activity.\(^6\) Upon further investigation of the original soil sample, tetrapetalones B-D (1.9-1.11) were isolated from the same strain of *Streptomyces* and exhibited similar activity toward SBL.\(^8\) Another compound isolated from the same strain, anseratherone (1.12), was shown to be a radical scavenger with an $ED_{50}$ of 300 $\mu M$ in the 1,1-diphenyl-2-picrylhydrazyl (DPPH) assay; tetrapetalone A did not exhibit any radical scavenging activity in the DPPH assay.\(^9\)
1.1.3. NMR Studies

Komada and coworkers had originally proposed structure 1.13 for tetrapetalone A (Figure 1.3).\(^5\) The C-5 to C-9 and C-17 to C-18 fragments were derived from an analysis of the \(^1\)H NMR, \(^{13}\)C NMR, DEPT and COSY data. HMBC data indicated an \(\alpha,\beta\)-unsaturated carbonyl from C-1 to C-3, and 2D-INADEQUATE data revealed the presence of the tetrahydropyran and dienone portions of the molecule. These partial structures were brought together into the proposed skeleton of tetrapetalone A.

Structure 1.13 was later proven to be incorrect by using the \(^1\)H-\(^{15}\)N HMBC technique, which measures the long-range correlation between a nitrogen atom and a proton.\(^6,7\) In this case, the nitrogen was shown to have a correlation with protons at C-13 and C-17, inconsistent with structure 1.13. The revised structure for tetrapetalone A, 1.8, was then proposed. The relative stereochemistry of 1.8 was elucidated by NOESY correlations, and the absolute stereochemistry was determined by derivatization at C-9 using Mosher’s method.\(^10\)

1.1.4. Feeding Studies and Proposed Biosynthesis

The isolation chemists added \(^{13}\)C-labeled compounds to the culture of *Streptomyces* sp. USF-4727 and examined the incorporation ratio of each compound.\(^11\) It was discovered that three molecules of \([1^{-13}\)C\] propanoate, one \([1^{-13}\)C\] butanoate, one \([1^{-13}\)C\] glucose and one \([\text{carbonyl}^{-13}\)C\] 3-amino-5-hydroxybenzoic acid (AHBA) were efficiently incorporated into tetrapetalone A, while \([1^{-13}\)C\] and \([2^{-13}\)C\] acetate were only incorporated in low levels. Because AHBA is known to be a biological starter unit in several ansamycin antibiotics,\(^12,13\) Komoda et al. have proposed that ansaetherone precedes tetrapetalone A along the biosynthetic pathway (Scheme 1.2). Additionally, Komada et al. have demonstrated that exposure of tetrapetalone A to hydrogen peroxide produces tetrapetalone C, indicating that an oxidative enzyme is likely responsible
for this conversion *in vivo*. Analogously, tetrapetalone B is assumed to be converted to tetrapetalone D by a similar process.

**Scheme 1.2.** Biosynthesis of the tetrapetalones.
1.2. Synthetic Approaches

1.2.1. Porco’s Biomimetic Approach

In 2005, Wang and Porco reported a synthesis of the tetracyclic framework of the aglycon of tetrapetalone A. Porco recognized that the tetrapetalones could be biosynthetically derived from the oxidation of a macrocyclic ansa mycin precursor, a hypothesis which was later supported by the discovery of ansaetherone (see Scheme 1.2, vide supra). The authors initially attempted to close the macrocycle through a ring-closing metathesis of triene 1.15 (Scheme 1.3), which was created through an amide bond coupling of fragments 1.16 and 1.17. This strategy ultimately proved to be unsuccessful, however, presumably because the meta substituents of the aromatic ring were likely positioned away from each other and could therefore not achieve the geometry required for the ring-closing metathesis.

Scheme 1.3. Porco’s initial retrosynthesis.
Porco then redesigned the synthesis such that the key macrolactam 1.14 could be derived from an intramolecular acyl transfer from macrolactone 1.23 which, retrosynthetically, could be taken back to triene 1.22 (Scheme 1.5). In this case, the substituents participating in the ring-closing metathesis are now in an ortho relationship and should be in much closer proximity than the meta substituents of the prior attempt. Indeed, exposure of triene 1.22 to Grubbs’ second-generation catalyst (1.18) produced macrolactone 1.23 in an excellent 85% yield, following cleavage of the TBS ether. After some experimentation, the authors found that the use of Pd/CaCO3 with 1 atm of H2 in 10% Et3N/THF chemoselectively reduced the nitro group of 1.23 without effecting hydrolysis of the lactone moiety, thereby directly affording macrolactam 1.14.

Scheme 1.4. Unsuccessful ring-closing metathesis.

Scheme 1.5. Porco’s revised synthesis.
With 1.14 in hand, the authors hoped to be able to perform a transannular oxidative [4+3] cyclization. This reaction would be promoted by oxidation of the hydroquinone, presumably followed by intramolecular proton transfer from aminoquinone 1.24 to create a dipole that could undergo the cyclization. While the authors initially believed that tetracycle 1.25 had been formed, later investigations showed that what had been isolated was in fact aminoquinone 1.24.15

1.2.2. Hong’s N-Acyliminium Cyclization Approach

In 2009, Hong and coworkers described the use of an N-acyliminium ion to form the seven-membered ring of the tetrapetalones.16 On the basis of work developed by Speckamp and Hiemstra,17-20 it was anticipated that treatment of a 5-hydroxypyrrolidinone (e.g., 1.27, Scheme 1.6) with either a protic or Lewis acid would create an N-acyliminium species, which could then be intercepted with an appropriate nucleophile. Hong demonstrated that 1,1-disubstituted double bonds can react in an intramolecular fashion with such N-acyliminium ions and create a seven-membered ring, with FeCl3 in conjunction with TMSCl proving to be the optimal conditions for this system. As a part of Hong’s strategy, the resultant carbocation was trapped with a nearby oxygen atom to yield ether 1.28. After oxidation to lactone 1.29, an intramolecular Friedel-Crafts acylation was performed with polyphosphoric acid (PPA) to produce tetracycle 1.30 in 30% yield (with 55% recovery of starting material). This represents the first published report of a fused [6-5-7-5] tetracycle where the carbon atoms of the core have the same constitution as that
of tetrapetalone A, although several key structural features are absent, such as the C-4 ethyl group or any substitution on the aromatic ring.

Scheme 1.6. Hong’s approach to the tetracyclic framework.

1.3. Our Initial Retrosynthesis

Our initial retrosynthesis (Scheme 1.7) focused on the formation of aglycon 1.31. Reasoning that the \( p \)-quinol moiety on the B-ring would likely be unstable, a late-stage oxidation of phenol 1.32 was planned to unveil the \( p \)-quinol. Diastereoselective installation of the angular ethyl group at C-4 could occur through the addition of an ethyl nucleophile to \( N \)-acyliminium intermediate 1.33. This intermediate could be further disconnected by opening the seven-membered C-ring, possibly through a Heck reaction. The C-N bond could arise from a Buchwald-Hartwig-type heteroatom coupling, taking intermediate 1.33 back to indanone 1.34. It was our presumption that this indanone could be formed from the Nazarov cyclization of aryl dienone 1.35, which itself could be derived from Weinreb amide 1.36 and aryl bromide 1.37.

Scheme 1.7. Initial retrosynthesis of tetrapetalone A.
1.4. Forward Synthesis

1.4.1. Forming the Aryl Dienone

Weinreb amide 1.36 was readily prepared in three steps from commercially available starting materials (Scheme 1.8). In the first step of this sequence, methacrolein (1.39) and (carbethoxymethylene)triphenylphosphorane (1.38) were heated together in dichloromethane at reflux for 2 h to produce dienone ester 1.40 in 59% yield. Only the trans dienone is produced in this Wittig reaction; computational studies performed by Aggarwal and coworkers have shown that the strong E selectivity observed in the Wittig reaction of stabilized ylides is primarily due to a strong dipole-dipole interaction in the transition state.21 Dienone ester 1.40 was then saponified by treatment with lithium hydroxide in 3:1 THF:H₂O at 80 ºC to produce acid 1.41, which was subsequently converted to Weinreb amide 1.36 following formation of the corresponding acid chloride, for a two-step yield of 67%. Commercially available 1-bromo-3,5-dimethoxybenzene 1.37 was then treated with n-butyllithium at -78 ºC, followed by addition of Weinreb amide 1.36 to create aryl dienone 1.35.

Scheme 1.8. Formation of aryl dienone 1.35.
1.4.2. Background to the Nazarov Cyclization

The Nazarov cyclization is the 4π-electrocyclic ring closure of a divinyl carbinol species to form a five-membered ring. In recent years, its synthetic utility has been exploited by a number of investigators for the formation of a variety of complex molecules. Despite the wide usage of the Nazarov cyclization, the application of vinyl or aryl dienyl ketones as Nazarov substrates is sparse. Moreover, the handful of vinyl or aryl dienone systems that to date have been reported to undergo Nazarov cyclization appear to be special cases (vide infra).

In their exploration of enantioselective Nazarov conditions, the Trauner group employed an activated system containing a dihydropyran moiety (1.42, eq. 1.1). In this example, the Lewis acid (aluminum chloride) can presumably coordinate in a bidentate manner to both the carbonyl and dihydropyran (DHP) oxygen atoms, which improves the likelihood of the geometry required for cyclization being adopted. Furthermore, the strong electron-donating ability of the DHP fragment likely facilitates the reaction.

Similarly, the Frontier group has reported that aryl dienyl ketones with an electron-withdrawing ethyl ester moiety at the α-position (1.44, eq. 1.2) will readily undergo the Nazarov cyclization. Again, two-point binding of the Lewis acid (in this case, copper (II) perchlorate) likely accelerates the reaction.
In an older example, Braude and Forbes reported that treatment of cycloheptenyl pentadienyl ketone (1.46, eq. 1.3) with a mixture of formic acid and phosphoric acid at 90 °C produces a hexahydroazulene product, which was assigned as 1.47. The authors’ characterization was based primarily on the recovery of acetaldehyde in the ozonolytic degradation of the product; their ultraviolet spectrum of the Nazarov product suggested the presence of a dienone rather than an enone, however. To confirm the structure of 1.47, we independently synthesized ketone 1.46 and exposed it to the conditions reported by Braude and Forbes. Instead of the formation of product 1.47, we instead observed the formation of isomer 1.48, a product which was more consistent with the reported UV spectral data. Notably, this Nazarov product is only formed under the reported harsh acidic conditions; exposure of ketone 1.46 to aluminum chloride at room temperature returned only the starting material.

1.4.3. Screening Nazarov Cyclization Conditions

In an attempt to achieve indanone formation en route to tetrapetalone A, we exposed our aryl diene 1.35 to an array of Lewis and protic acids in various solvents (Table 1.1). In all cases, the bulk of the starting material (at least 75%) was recovered unchanged, with no detectable formation of the desired indanone. Under some of the harsher conditions (PPA or MeSO₃H at 70 °C), slight decomposition of 1.35 was observed.
Table 1.1. Unsuccessful attempts to convert aryl dienone 1.35 to indanone 1.34.

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Solvent</th>
<th>Temperature (ºC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sc(OTf)_3</td>
<td>CH₂Cl₂</td>
<td>23</td>
</tr>
<tr>
<td>Yb(OTf)_3</td>
<td>CH₂Cl₂</td>
<td>23</td>
</tr>
<tr>
<td>Zn(OTf)_2</td>
<td>CH₂Cl₂</td>
<td>23</td>
</tr>
<tr>
<td>1.0 M HCl in ether</td>
<td>CH₂Cl₂</td>
<td>23</td>
</tr>
<tr>
<td>TFA</td>
<td>CH₂Cl₂</td>
<td>23</td>
</tr>
<tr>
<td>AlCl₃</td>
<td>CH₂Cl₂</td>
<td>23</td>
</tr>
<tr>
<td>AlCl₃</td>
<td>CH₂Cl₂</td>
<td>40</td>
</tr>
<tr>
<td>AlCl₃</td>
<td>benzene</td>
<td>23</td>
</tr>
<tr>
<td>AlCl₃</td>
<td>toluene</td>
<td>23</td>
</tr>
<tr>
<td>Pd(OAc)₂</td>
<td>HOAc</td>
<td>23</td>
</tr>
<tr>
<td>PPA</td>
<td>toluene</td>
<td>23</td>
</tr>
<tr>
<td>MeSO₃H</td>
<td>neat</td>
<td>70</td>
</tr>
<tr>
<td>TFA</td>
<td>neat</td>
<td>70</td>
</tr>
<tr>
<td>Hg(OAc)₂</td>
<td>toluene</td>
<td>23</td>
</tr>
<tr>
<td>hᵥ</td>
<td>benzene</td>
<td>23</td>
</tr>
</tbody>
</table>

Our initial explanation for the failure of 1.35 to undergo the Nazarov cyclization was the inability of the dienone moiety to achieve the requisite s-trans configuration for 4π-electrocyclization (1.49, Scheme 1.9). We believe that the dienone instead adopts an unreactive s-cis configuration (1.50) due to coordination of the second double bond to the Lewis acid. To obviate this obstacle, we reasoned that building a new Nazarov substrate with a substituent at the α-position should favor the desired s-trans configuration on the basis of steric considerations (see 1.52, Scheme 1.9).
1.4.4. Reconfiguring the Nazarov Substrate

For our new substrate, we opted to place a methyl group α to the carbonyl moiety due to its eventual presence in tetrapetalone A at C-8 (see Figure 1.3). Construction of aryl dienone 1.51 followed the same synthetic scheme as the original aryl dienone 1.35, with comparable yields. Exposure of 1.51 to 25 mol % aluminum chloride in toluene for 1 h led to complete consumption of the dienone and produced indanone 1.55 in 71% yield as a 4:1 inseparable mixture of syn and anti diastereomers (Scheme 1.10). The prevalence of the syn diasteromer 1.55a can be explained by considering the protonation of the aluminum-bound enolate, which is the last step of the Nazarov cyclization. Kinetic protonation should occur from the face opposite to the isopropenyl group, thus placing the methyl and isopropenyl substituents on the same face of the molecule. In tetrapetalone A, however, these groups have an anti relationship; it was our hope that the mixture of diastereomers could be epimerized to the thermodynamically favored anti diastereomer 1.55b. Indeed, exposure of the mixture to a catalytic amount of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in methanol for 10 h produced a 9:1 mixture of 1.55b:1.55a.
Scheme 1.10. Successful Nazarov cyclization of α-methyl-containing aryl dienone 1.51.

To probe our hypothesis in which the α-substituent is the sole determinant of reactivity in the Nazarov cyclization, we synthesized aryl dienone 1.56, using the general synthetic sequence described previously. Should our postulate concerning the failure of aryl dienone 1.35 to undergo cyclization hold true, aryl dienone 1.56 should be readily converted to indanone 1.57 upon exposure to a Lewis acid. In the event, only a small amount (14%) of indanone 1.57 was observed upon treatment of 1.56 with AlCl₃, with recovered starting material constituting the remainder of the mass balance (eq. 1.4).

1.4.5. A Proposed “Twisted” Transition State

To account for these observations, a new hypothesis was required. We noted that in the case of 1.51, methyl groups reside at both the α- and γ-positions. This sets up the possibility of a steric clash between the two methyl groups somewhere along the Nazarov reaction pathway for 1.51, which causes the second double bond to rotate out of conjugation to alleviate this building 1,3-allylic strain (Scheme 1.11). Once this rotation begins to occur, the 4π electron-containing pentadienyl molecular orbital system that is distributed among the five carbon atoms undergoing the Nazarov cyclization now electronically resembles a traditional Nazarov system. In the cases of 1.35 and 1.56, however, only one position in the dienone portion of the molecule bears a methyl substituent (at the α- and γ-positions, respectively), while the other position is occupied by a hydrogen atom. As there is far less 1,3-allylic strain in these systems, the second double bond can stay in conjugation, thus drastically changing the electronics of the system from that of a traditional Nazarov substrate to an extended, 6π electron-containing heptadienyl system that does not readily undergo electrocyclization.
1.5. Computational Studies on Aryl Dienones 1.35 and 1.51

To test the premise of a “twisted” intermediate, we first considered the possibility that the relative stabilities of the uncomplexed aryl dienones might be playing a role. If this were indeed the case, we would expect to see large differences in the ultraviolet absorption spectra of the α-hydrogen and α-methyl substrates. Upon examining the UV absorption traces for several sets of substrates, however, no discernable differences between the $\lambda_{\text{max}}$ values were observed.

We next turned our attention to the geometries of the AlCl$_3$-complexed aryl dienones and transition states. To do so, we established a collaboration with Prof. Dean Tantillo and his graduate student, Rebecca Davis, at the University of California, Davis. They performed geometry optimizations and frequency analyses at the B3LYP/6-31+G(d,p) level on the Lewis-acid bound intermediate structures for 1.35 and 1.51, as well as the transition states along the reaction pathway.$^{33-37}$ Energy barriers for electrocyclization of the AlCl$_3$-bound intermediates were computed in the $s$-trans configuration.

It was determined that the activation barrier for electrocyclization of 1.35 ($\Delta G^\ddagger$) was 30.6 kcal/mol, significantly larger than that calculated for 1.51 ($\Delta G^\ddagger = 24.0$ kcal/mol). Moreover, the Lewis-acid bound intermediate structure for 1.35 (int-1.35) does indeed exist in a nearly planar configuration, with the dihedral angle between the α-H-C and γ-C-C bonds determined to be 3.5º. On the other hand, the comparable dihedral angle in int-1.51 was calculated to be 136.9º, representing a severe deviation from planarity. Notably, in both cases, the dihedral angle in the transition state is representative of a substantial twist (47.1º for TS-1.35; 110.2º for TS-1.51). Furthermore, the geometry of the Lewis-acid bound adduct of the more substituted aryl dienone (int-1.51) more closely resembles the geometry of the transition state than that of the correspond-
ing adduct of 1.35. Additionally, when the γ-methyl groups of 1.35 and 1.51 were replaced with hydrogens, the energy difference ($\Delta \Delta G^\ddagger$) between the two systems was reduced from 6.6 kcal/mol to 3.2 kcal/mol, further demonstrating the importance of the 1,3-allylic interaction.\textsuperscript{38}

![Figure 1.4](image)

**Figure 1.4.** Calculated Lewis acid-bound intermediates and transition states for substrates 1.35 and 1.51. Computations were performed by Prof. Dean Tantillo and Rebecca Davis (UC Davis).

### 1.6. Examining the Scope of Arene Cores

We constructed several substrates with different arene cores to examine the generality of the aryl dienone Nazarov cyclization. The substrates were constructed in a manner analogous to that previously described for the synthesis of the original aryl dienones 1.35 and 1.51 (i.e., by performing a lithium-halogen exchange on the aryl or heteroaryl bromide, then quenching the intermediate anion with dienone Weinreb amide 1.36 or 1.54) unless otherwise noted.

#### 1.6.1. Electron-Rich Arenes

Both 1-bromo-3,4,5-trimethoxyphenyl and 4-bromo-1,2-(methylenedioxy)phenyl dienones were exposed to 25 mol % AlCl$_3$ in toluene. α-Methyl-substituted dienones 1.58 and 1.62 were converted to the corresponding indanones, 1.59 and 1.63 respectively. Notably, the reactions were incomplete after 6 h at room temperature; the trimethoxyphenyl system (1.58) had only partially converted (22%) to indanone 1.59, while the (methylenedioxy)phenyl system (1.62) had undergone 11% conversion to 1.63. Upon raising the temperature to 70 °C, the trimethoxyphenyl system had completely converted to indanone 1.59 after 6 h (eq. 1.5), while the (methylenedioxy)phenyl system still had 31% of the starting aryl dienone remaining (eq. 1.6). When contrasting these systems to aryl dienone 1.51, the relative electron density at the ortho position (the bond-forming carbon atom on the arene moiety) decreases from 1.51 to 1.58 to 1.62, correlating with the increased time required for these reactions to reach completion. In both cases, the α-hydrogen-substituted substrates (1.60 and 1.64, respectively) failed to undergo the Nazarov cyclization at both room temperature and at 70 °C.
N-Methylindole dienones 1.66 and 1.67 were constructed via the ortho-lithiation of N-methylindole, followed by quenching the intermediate anion with dienone Weinreb amides 1.36 and 1.54, respectively. Substrate 1.66 was exposed to the standard reaction conditions and was successfully converted to the pentannulated product 1.68 in 84% yield after 1 h (eq. 1.7). Again, α-hydrogen-bearing dienone 1.67 did not undergo the Nazarov cyclization up to 70 °C. Interestingly, when the N-methyl group was changed to a benzenesulfonamide, the reaction failed in both cases. This highlights the need for an electron-rich arene core in order for the aryl dienone Nazarov cyclization to be successful, in concordance with literature precedent.

Upon exposure of benzothiazole substrates 1.70 and 1.72 to the standard conditions, the α-methyl-containing substrate successfully underwent the Nazarov cyclization (eq. 1.8). In this case, the temperature was increased to 70 °C to drive the reaction to completion after 6 h, as only 25% conversion was observed at room temperature over 24 h. Interestingly, exposure of the α-hydrogen-containing substrate 1.72 to AlCl₃ did not return starting material, as expected; instead, dimerized product 1.73 was recovered in 50% yield (eq. 1.9). Presumably, the intermolecular [4+2] cycloaddition pathway competes with the Nazarov cyclization; because dimerization is not observed with substrate 1.70, we can conclude that the Nazarov out-competes the Diels-Alder reaction in this case.
1.6.2. Electron-Neutral Arenes

Both benzyl and \textit{para}-tolyl cores were constructed and subjected to the standard Nazarov conditions. No reaction was observed at room temperature in any of the four cases (substrates 1.74, 1.76, 1.79 and 1.81). Upon increasing the temperature to 70 °C, the \(\alpha\)-hydrogen-containing substrates (1.76 and 1.81) both decomposed. The substrates bearing \(\alpha\)-methyl groups, however, each produced an anomalous Nazarov product (1.75 and 1.80). Instead of the \(4\pi\)-electrocyclization taking place between the aromatic ring and the \(\alpha\)- and \(\beta\)-carbons of the dienone, the five carbon atoms of the dienone undergo electrocyclization. This process initially places the aryl group at the same carbon atom as the oxygen substituent on the newly formed five-membered ring (see intermediate 1.78). Upon collapse of the negative charge, the aryl ring undergoes a 1,2-shift to quench the allylic cation.\(^{41}\)

1.6.3. Unsuccessful Substrates

A variety of other substrates were also synthesized (Figure 1.5) which did not undergo the Nazarov cyclization. Regardless of position, it appears that substituted amino groups around the benzene ring prevent the Nazarov cyclization from taking place. Also, C-2-substituted \(N\)-methylpyrrole, furan and benzofuran cores were not amenable to a successful reaction.
1.7. δ-Substituents on the Dienone

We also explored the effects of substitution at the δ-position of the dienone, constructing substrates 1.89, 1.90 and 1.92. δ,δ-Dimethyl dienyl ketone 1.89, which does not possess an α-methyl group, is unreactive under the standard conditions (eq. 1.12). α-Methyl-containing dienones 1.90 and 1.92, on the other hand, cleanly converted to indanones 1.91 and 1.93 in 77% and 91% yields, respectively, after two hours (eq.1.13 and 1.14). The computed ΔG‡ for 1.89 is 31.9 kcal/mol, a greater barrier than that for 1.35 (another unreactive substrate). The barriers for 1.90 and 1.92 are 27.4 kcal/mol and 27.3 kcal/mol, respectively; these are greater than that for 1.51, but still lower than α-hydrogen-containing 1.35.

The success of 1.90 and 1.92 in the Nazarov cyclization can partially be attributed to the energetic preference for the s-trans conformation for the Lewis acid-bound intermediates, as op-
posed to the s-cis conformation for 1.89. In addition, since all calculations of ΔG‡ are performed in the s-trans configuration, we believe that small geometric distortions (similar to the 1,3-allylic interactions in 1.51) aid in the cyclization of these substrates.

1.8. Examination of a Cyclic Substrate

To determine whether the steric interaction between the α- and γ-substituents was in fact facilitating the Nazarov cyclization of 1.51, we postulated that the introduction of a covalent tether between these two substituents should lock the substrate into a defined configuration, thus preventing the cyclization from taking place. To test this hypothesis, we first needed to synthesize a cyclic substrate such as 1.94 (Figure 1.6).

Figure 1.6. Cyclic substrate 1.94.

1.8.1. Initial Synthetic Efforts toward the Cyclic Substrate

We began by attempting to employ our previously optimized route to the other Nazarov substrates (i.e., coupling an aryl bromide with a Weinreb amide) to access 1.94. Therefore, our initial goal became the synthesis of cyclic Weinreb amide 1.95. Our first attempt (Scheme 1.12) began with the deprotonation of tributyltin hydride, followed by quenching the resulting anion first with formaldehyde, then chloro-tert-butyldimethylsilane (TBSCl), leading to alkyl tributyltin species 1.97. Treatment of 1.97 with n-butyllithium followed by quenching with 3-methoxycyclohex-2-enone (1.96) produced enone 1.98. Unfortunately, all attempts to form exo-methylene compound 1.99 (Scheme 1.13), including treatment of 1.98 with the Petasis reagent, 44,45 Peterson olefination conditions, 46,47 or use of the methyltriphenylphosphonium-derived Wittig reagent, resulted only in decomposition.

Scheme 1.12. Unsuccessful methylation of enone 1.98.

It appeared that the decomposition observed in our attempted methylenations of 1.98 might be due to the instability of exo-methylene compound 1.99. To prevent such an isomerization from taking place, we attempted to block the position α to the exo-methylene by doubly methylating the corresponding ketone with LDA and iodomethane (Scheme 1.13). This modification introduced sufficient steric hindrance to prevent access to the carbonyl moiety, however, and
all attempts to form the *exo*-double bond from enone \textbf{1.92} led only to recovery of starting material.

Scheme 1.13. Unsuccessful methylenation of enone \textbf{1.102}.

Alternatively, we explored the use of non-silyl protecting groups on the primary hydroxyl group. Upon switching to a methoxymethyl (MOM) ether, we were able to form *exo*-methylene compound \textbf{1.106} in 57% yield by treating enone \textbf{1.105} with methyltriphenylphosphonium bromide and *n*-butyllithium. This strategy ultimately failed, however, as all attempts to cleave the MOM group of \textbf{1.106} led to decomposition.


1.8.2. Successful Synthesis of the Cyclic Substrate

We next modified our strategy to reverse the polarity of our initial disconnection. We now sought to form vinyl bromide \textbf{1.110} and couple this species with Weinreb amide \textbf{1.111}, which was obtained in one step from commercially available 3,5-dimethoxybenzoic acid. Treatment of 1,3-cyclohexanedione (\textbf{1.108}) with triphenylphosphine and bromine led to the formation of vinylogous acid bromide \textbf{1.109} in 44% yield (Scheme 1.15). Treatment of \textbf{1.109} with methyltriphenylphosphonium bromide and *n*-butyllithium did produce vinyl bromide \textbf{1.110}; this product proved to be both unstable to silica gel and volatile enough such that it was lost on attempted concentration, however. After careful experimentation, we discovered that we could purify the crude product by Kugelrohr distillation and recover pure \textbf{1.110} in 70% yield. Finally, treatment of vinyl bromide \textbf{1.110} with *n*-butyllithium and quenching the resulting vinyl anion with Weinreb amide \textbf{1.111} delivered cyclic aryl dienone \textbf{1.94} in 60% yield.
1.8.3. Testing the Cyclic Substrate

Exposure of cyclic dienone 1.94 to the standard Nazarov conditions returned only the starting material in 82% yield (eq. 1.15); we note that no isomerization of the exo-double bond to an internal position was observed. Upon performing computational studies on this substrate, we determined that the activation barrier was 29.2 kcal/mol, which was slightly higher than the barriers for 1.51 and 1.90, but slightly lower than those for 1.35 and 1.89. We hypothesized that heating the reaction mixture might lead to the cyclized product; indeed, at 70 ºC, we observed a 37% conversion of dienone 1.94 to tricycle 1.112 in a 1.8:1 ratio of endo to exo double bond isomers (eq. 1.16). Presumably, the isomerization occurs after cyclization, as no isomerized starting material was observed.

1.9. Epimerization of the Nazarov Products

As stated earlier, we had hoped to be able to epimerize the mixture of diastereomers obtained from the Nazarov cyclization to the thermodynamically favored anti diastereomer using a substoichiometric amount of DBU (0.2 equiv) in MeOH. Table 1.2 summarizes these findings; in most cases, the anti diastereomer was obtained in a greater than 9:1 ratio.
Table 1.2. Epimerization of Nazarov products.

<table>
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<tr>
<th>Structure</th>
<th>dr after Nazarov (a:b)</th>
<th>dr after epimerization with DBU</th>
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</thead>
<tbody>
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<td><img src="image" alt="Structure 1.55a" /> <img src="image" alt="Structure 1.55b" /></td>
<td>81:19 11:89</td>
<td></td>
</tr>
<tr>
<td><img src="image" alt="Structure 1.59a" /> <img src="image" alt="Structure 1.59b" /></td>
<td>82:18 8:92</td>
<td></td>
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<tr>
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</tr>
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<td></td>
</tr>
<tr>
<td><img src="image" alt="Structure 1.71a" /> <img src="image" alt="Structure 1.71b" /></td>
<td>61:39 6:94</td>
<td></td>
</tr>
</tbody>
</table>
1.10. Attempts to Vary the α-Substituent on the Aryl Dienone Substrate

1.10.1. Attempts to Place an α-Halogen on the Dienone

In addition to variations of the arene portion, it was desirable to be able to access a variety of groups at the α-position of the dienone. We attempted to accomplish this by placing a halogen at this position, reasoning that cross-couplings could easily be performed with this functionality. Treatment of (carboethoxymethylene)triphenylphosphorane (1.38) with iodobenzene diacetate and tetrafluoroboric acid produced iodonium salt 1.113,48-50 which we attempted to convert to the α-bromodienone ester by treatment with tetrabutylammonium bromide.51 Unfortunately, attempts to effect this transformation were met with decomposition.

Scheme 1.16. Unsuccessful α-halogenation of phosphorane ester 1.38.

1.10.2. An Electron-Withdrawing Group as a “Masked” α-Hydrogen Substituent

While these studies were being performed, the Frontier group reported that aryl dienyl ketones bearing an electron-withdrawing ethyl ester at the α-position (1.44, vide supra) can undergo Nazarov cyclization.31 These systems were different than ours, in that the electrocyclizations reported by the Frontier group were primarily electronically driven, whereas ours were promoted by steric effects. Nevertheless, the use of a cleavable activating group at the α-position presented an elegant strategy for the introduction of a “masked” α-hydrogen for the Nazarov cyclization.

Knoevenagel condensation of cinnamaldehyde with β-keto ester 1.115 produced aryl dienone 1.116 in 60% yield (Scheme 1.17). While this aryl dienone could itself undergo the Nazarov reaction, we sought to create a system that was more structurally similar to our set of substrates. We therefore converted aryl dienone 1.116 to 1.117 by performing a cross-metathesis
with 1-heptene using Grubbs’ Second Generation catalyst (1.18). Exposure of aryl dienone 1.117 to our standard conditions produced indanone 1.118 in 59% yield in a 68:32 dr (syn:anti). Saponification of the α-ethyl ester moiety with lithium hydroxide yielded indanone 1.119, which bears only hydrogens at the α-position.

Scheme 1.17. Creation of a “masked” α-hydrogen substrate.

1.11. Conclusion

A strong steric effect in the Nazarov cyclization of aryl dienyl ketones was discovered and analyzed in detail. Examination of a range of α-, γ- and δ-substituted dienones showed that both a preference for the s-trans over the s-cis conformation and 1,3-allylic strain favored the Nazarov cyclization. Computational studies of several substrates revealed that systems with a ΔG‡ less than 28 kcal/mol for the s-trans Lewis acid-bound intermediate would be likely to undergo the Nazarov cyclization, while those with a barrier greater than 30 kcal/mol would be unlikely to cyclize, even if they possess an α-substituent. For systems with barriers in the 28-29 kcal/mol range, the predictions become less certain, and cyclization may be effected by increasing the reaction temperature.

It was further determined that an electron-rich aromatic moiety was an essential part of the aryl dienone substrate in order for the reaction to proceed, consistent with previous reports. Electron-poor arenes resulted in the recovery of starting material, while relatively electron-neutral arenes led to ‘anomalous’ Nazarov products. The syn indanone was produced as the kinetically favored product in most cases. The mixture of indanones could be readily epimerized to the thermodynamically favored anti diastereomer, in most cases with a dr greater than 9:1.
Additionally, placement of an ethyl ester at the α-position led to the formation of an α-unsubstituted indanone after saponification.

1.12. Experimental Methods

Unless otherwise stated, reactions were performed in flame-dried glassware sealed with rubber septa under a nitrogen atmosphere using dry solvents. Tetrahydrofuran (THF) and ether were distilled over sodium/benzophenone ketyl; dichloromethane, toluene, benzene and acetonitrile were distilled over calcium hydride. Reaction temperatures were controlled by an IKA®Mag® temperature modulator. Determinations of pH were obtained by Color pHast® Indicator Strips pH = 0 – 14. Thin layer chromatography was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV and anisaldehyde stain. Fisher silica gel 240-400 mesh (particle size 0.032 – 0.063 mm) was used for flash chromatography. \(^1\)H NMR spectra were recorded on Bruker spectrometers (at 300, 400 and 500 MHz), as were \(^{13}\)C NMR (at 75, 100 and 125 MHz, respectively). Chemical shifts (δ ppm) are reported relative to Me₄Si (δ = 0.0) or CHCl₃ (δ = 7.26 for \(^1\)H NMR and δ = 77.2 for \(^{13}\)C NMR). Data for \(^1\)H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, dd = doublet of doublets, dt = doublet of triplets, dq = doublet of quartets, m = multiplet, br = broad), integration and coupling constant (Hz). IR spectra were recorded on a Nicolet MAGNA-IR 850 spectrometer and are reported in frequency of absorption (cm⁻¹). Ultraviolet spectra were recorded on a Cary 50 Bio UV-Visible spectrophotometer (Varian). Both low and high resolution mass spectra were obtained from the University of California, Berkeley Mass Spectral Facility.

\[\text{(E)}\text{-ethyl 4-methylpenta-2,4-dienoate (1.40)}\]\(^{53}\)

To a 100-mL round-bottom flask equipped with a stir bar was added 95% (carbethoxymethylene)-triphenylphosphorane (1.51 g, 4.12 mmol), 90% methacrolein (379 μL, 4.12 mmol) and dichloromethane (15 mL). The reaction mixture was stirred at reflux for 2 h, then cooled to 23 °C and concentrated by rotary evaporation. Pentane (50 mL) was added to the concentrate to precipitate triphenylphosphine oxide. The mixture was filtered through Celite, then concentrated by rotary evaporation. The filtration and concentration steps were repeated to yield 336 mg of a light yellow liquid (58% yield). The crude product was carried directly to the next step. \(R_f 0.65\) (4:1 hexanes:ethyl acetate). \(^1\)H NMR (400 MHz): δ 7.35 (d, 1H, J = 16.0 Hz), 5.87 (d, 1H, J = 16.0 Hz), 5.34 (d, 2H, J = 8.0 Hz), 4.21 (q, 2H, J = 7.2 Hz), 1.88 (s, 3H), 1.30 (t, 3H, J = 7.2 Hz). \(^{13}\)C NMR (100 MHz): δ 167.2, 147.0, 140.5, 124.3, 118.8, 60.4, 18.1, 14.3.
(E)-4-methylpenta-2,4-dienoic acid (1.41). To a 100-mL round-bottom flask equipped with a stir bar was added 1.40 (1.20 g, 8.56 mmol), lithium hydroxide monohydrate (1.80 g, 42.8 mmol), THF (36 mL) and water (12 mL). The reaction mixture was stirred at reflux for 14 h, then cooled to 23 °C and concentrated by rotary evaporation. Aqueous 1 N HCl was added to the mixture until pH = 2. The mixture was extracted with ethyl acetate (2 x 75 mL), then the combined organic phase was washed with brine (50 mL). The mixture was dried over MgSO₄, filtered through a frit, and concentrated by rotary evaporation and high vacuum to yield 960 mg of a light yellow liquid (quantitative yield). Rf 0.42-0.70 (streaks, 1:1 hexane:ethyl acetate).

1H NMR (400 MHz): δ 11.61 (br s, 1H), 7.44 (d, 1H, J = 16.0 Hz), 5.87 (t, 1H, J = 16.0 Hz), 5.39 (s, 2H), 1.89 (s, 3H).

13C NMR (100 MHz): δ 172.7, 149.3, 140.4, 125.4, 118.0, 18.0.

(E)-N-methoxy-N,4-dimethylpenta-2,4-dienamide (1.36). To a 100-mL round-bottom flask equipped with a stir bar was added 1.41 (960 mg, 8.56 mmol) and dichloromethane (25 mL). The reaction flask was cooled to 0 °C, then oxalyl chloride (747 µL, 8.56 mmol) was added via syringe. After 5 min, dimethylformamide (66.3 µL, 8.56 µmol) was added via syringe, resulting in the evolution of gas. Stirring was continued for 30 min at 0 °C, then the reaction mixture was allowed to equilibrate to 23 °C. Stirring was continued for an additional 1 h. In a separate 100-mL round-bottom flask equipped with a stir bar was added N,O-dimethylhydroxylamine hydrochloride (835 mg, 8.56 mmol), triethylamine (3.60 mL, 25.7 mmol) and dichloromethane (25 mL). This flask was cooled to -78 °C, and the acid chloride mixture was added via cannula over 10 min. Stirring was continued at -78 °C for 30 min, then the reaction mixture was allowed to equilibrate to 23 °C before the reaction was quenched with saturated aqueous sodium bicarbonate (50 mL). The organic phase was washed with brine (50 mL), dried over MgSO₄, filtered through a frit, and concentrated by rotary evaporation and high vacuum to afford 1.33 g of a clear liquid (quantitative yield). Rf 0.59 (1:1 hexanes:ethyl acetate).

1H NMR (400 MHz): δ 7.39 (d, 1H, J = 15.6 Hz), 6.43 (d, 1H, J = 15.6 Hz), 5.33 (t, 2H, J = 18.0 Hz), 3.69 (s, 3H), 3.23 (s, 3H), 1.91 (s, 3H). 13C NMR (100 MHz): δ 172.7, 149.3, 140.4, 125.4, 118.0, 18.0. MS (EI): m/z 155 (M+); HRMS (EI): found 155.0943, calcd for [C₈H₁₃NO₂]+ 155.0946.

IR: ν 3442 (br), 2939, 2937, 1716, 1652, 1447, 1368 cm⁻¹.

(E)-ethyl 2,4-dimethylpenta-2,4-dienoate. 54% yield. The crude product was carried directly to the next step. Rf 0.65 (4:1 hexanes:ethyl acetate).

1H NMR (400 MHz): δ 7.10 (s, 1H), 5.22 (t, 1H, J = 1.6 Hz), 5.07 (s, 1H), 4.21 (q, 2H, J = 7.2 Hz), 2.02 (d, 3H, J = 1.6 Hz), 1.94 (s, 3H), 1.31 (t, 3H, J = 7.2 Hz). 13C NMR (100 MHz): δ 168.9, 140.8, 140.4, 127.7, 119.6, 60.7, 22.9, 14.3, 13.9. MS (EI): m/z 155 (M+); HRMS (EI): found 154.0995, calcd for [C₉H₁₄O₂]+ 154.0994. IR: ν 3486 (br), 2983, 2937, 1716, 1652, 1447, 1368 cm⁻¹.
**(O)-ethyl 2,4-dimethylpenta-2,4-dienoic acid.** Quantitative yield. Rf 0.29 (4:1 hexanes:ethyl acetate). $^1$H NMR (400 MHz): δ 11.27 (br s, 1H), 7.25 (s, 1H), 5.27 (t, 1H, $J = 1.6$ Hz), 5.13 (s, 1H), 2.03 (d, 3H, $J = 1.6$ Hz), 1.97 (s, 3H). $^{13}$C NMR (100 MHz): δ 174.6, 142.9, 140.7, 126.7, 120.9, 22.7, 13.5. MS (EI): $m/z$ 126 (M+); HRMS (EI): found 126.0683, calcd for [C$_7$H$_{10}$O$_2$]$^+$ 126.0681. IR: ν 2981, 2935, 1765, 1711, 1439, 1378 cm$^{-1}$.

**(E)-N-methoxy-N,2,4-trimethylpenta-2,4-dienamide (1.54).** 80% yield for two steps. Rf 0.18 (4:1 hexanes:ethyl acetate). $^1$H NMR (300 MHz): δ 6.18 (s, 1H), 5.09 (t, 1H, $J = 1.5$ Hz), 4.95 (s, 1H), 3.63 (s, 3H), 3.21 (s, 3H), 2.01 (d, 3H, $J = 1.5$ Hz), 1.89 (s, 3H). $^{13}$C NMR (75 MHz): δ 173.6, 140.7, 133.6, 131.9, 118.0, 63.3, 33.9, 23.3, 15.9. MS (EI): $m/z$ 169 (M+); HRMS (EI): found 169.1103, calcd for [C$_9$H$_{15}$NO$_2$]$^+$ 169.1103. IR: ν 3493 (br), 3084, 2971, 2937, 2819, 1651, 1443, 1377 cm$^{-1}$.

**N,3,5-trimethoxy-N-methylbenzamide (1.111).** 65% yield. $^1$H NMR (500 MHz): δ 6.79 (d, 2H, $J = 2.0$ Hz), 6.54 (t, 1H, $J = 2.0$ Hz), 3.80 (s, 6H), 3.59 (s, 3H), 3.34 (s, 3H). $^{13}$C NMR (125 MHz): δ 169.8, 160.5, 136.2, 106.1, 103.0, 61.3, 55.6, 34.1.

**(E)-ethyl 2,5-dimethylhexa-2,4-dienoate.** 64% yield. $^1$H NMR (400 MHz): δ 7.44 (d, 1H, $J = 12.0$ Hz), 6.12 (d, 1H, $J = 12.0$ Hz), 4.21 (q, 2H, $J = 7.2$ Hz), 1.97-1.89 (m, 9H), 1.31 (t, 3H, $J = 7.2$ Hz).
**OON**

*O*-**N**,2,5-trimethylhexa-2,4-dienamide. Procedure modified from literature. To a 50-mL round-bottom flask equipped with a stir bar was added N,O-dimethylhydroxylamine hydrochloride (597 mg, 6.12 mmol), *(E)*-ethyl 2,5-dimethylhexa-2,4-dienoate (644 mg, 3.83 mmol), and THF (12 mL). The reaction flask was cooled to -20 °C, then isopropylmagnesium chloride (2.0 M in THF, 5.74 mL) was added via syringe over 15 minutes, maintaining a bath temperature of -20 °C. Stirring was continued at -20 °C for 45 min, then the reaction was quenched with saturated aqueous ammonium chloride (40 mL). The organic layer was diluted with ether (100 mL) and washed with brine (25 mL). It was dried over MgSO4, filtered through a frit, and concentrated by rotary evaporation. The residue was purified by silica gel chromatography (9:1 hexanes:ethyl acetate, then 4:1, then 1:1) to afford 422 mg of a yellow oil (60% yield).

**1H NMR (500 MHz):** δ 6.71 (d, 1H, J = 11.5 Hz), 6.05 (d, 1H, J = 11.5 Hz), 3.64 (s, 3H), 3.23 (s, 3H), 1.95 (s, 3H), 1.86 (s, 3H), 1.80 (s, 3H). **13C NMR (125 MHz):** δ 173.4, 140.9, 129.4, 128.1, 120.4, 61.1, 33.9, 26.8, 18.7, 14.3. MS (EI): m/z 183 (M+); HRMS (EI): found 183.1255, calcd for [C<sub>10</sub>H<sub>17</sub>N=O<sub>2</sub>]<sup>+</sup> 183.1259. IR: v 2936, 1658, 1613, 1421, 1383 cm<sup>-1</sup>.

**OET**

*(2E,4E)*-ethyl 2-methylhexa-2,4-dienoate. 66% yield. **1H NMR (400 MHz):** δ 7.15 (d, 1H, J = 11.2 Hz), 6.37 (ddd, 1H, J = 1.6 Hz, 11.2 Hz, 14.8 Hz), 6.08 (dt, 1H, J = 6.8 Hz, 14.8 Hz), 4.20 (q, 2H, J = 7.2 Hz), 1.86 (s, 3H), 1.83 (d, 3H, J = 6.8 Hz), 1.30 (t, 3H, J = 7.2 Hz).

**OON**

*(E)*-N-methoxy-N,5-dimethylhexa-2,4-dienamide. 59% yield. **1H NMR (400 MHz):** δ 7.60 (dd, 1H, J = 11.6, 15.2 Hz), 6.35 (d, 1H, J = 15.2 Hz), 6.04 (d, 1H, J = 11.6 Hz), 3.69 (d, 1H, J = 1.6 Hz), 3.24 (d, 1H, J = 1.6 Hz), 1.89 (s, 3H), 1.86 (s, 3H). **13C NMR (100 MHz):** δ 168.0, 145.6, 140.0, 124.3, 116.4, 61.8, 32.6, 26.7, 19.1. MS (EI): m/z 169 (M+); HRMS (EI): found 169.1107, calcd for [C<sub>9</sub>H<sub>15</sub>N=O<sub>2</sub>]<sup>+</sup> 169.1103. IR: v 2933, 1660, 1609, 1421, 1384, 1344 cm<sup>-1</sup>.
(E)-ethyl 5-methylhexa-2,4-dienoate. 87% yield. $^1$H NMR (300 MHz): $\delta$ 7.55 (dd, $J = 11.7$ Hz, 15.0 Hz), 5.98 (d, 1H, $J = 11.7$ Hz), 5.75 (d, 1H, $J = 15.0$ Hz), 4.19 (q, 2H, $J = 7.2$ Hz), 1.89 (s, 3H), 1.87 (s, 3H), 1.29 (t, 3H, $J = 7.2$ Hz).

(2E,4E)-N-methoxy-N,2-dimethylhexa-2,4-dienamide. 48% yield. $^1$H NMR (400 MHz): $\delta$ 6.44 (d, 1H, $J = 10.8$ Hz), 6.30 (ddd, 1H, $J = 1.6$ Hz, 10.8 Hz, 14.8 Hz), 5.90 (dt, 1H, $J = 6.8$ Hz, 14.8 Hz), 3.64 (s, 3H), 3.23 (s, 3H), 1.96 (s, 3H), 1.84 (d, 3H, $J = 6.8$ Hz). $^{13}$C NMR (100 MHz): $\delta$ 172.9, 134.5, 133.0, 128.5, 126.8, 61.1, 33.9, 18.8, 14.4. MS (EI): $m/z$ 169 (M+); HRMS (EI): found 169.1103, calcd for [C$_9$H$_{15}$NO$_2$]$^+$ 169.1103. IR: $\nu$ 2930, 1650, 1611, 1428, 1379, 1332 cm$^{-1}$.

(1H)-1-(3,5-dimethoxyphenyl)-4-methylpenta-2,4-dien-1-one (1.35). To a 100-mL round-bottom flask equipped with a stir bar was added 1-bromo-3,5-dimethoxybenzene (1.61 g, 7.43 mmol) and THF (15 mL). The reaction flask was cooled to -78 °C, then butyllithium (2.5 M in hexanes, 2.97 mL) was added over 5 min. The reaction mixture was stirred at -78 °C for 20 min, at which point a solution of 1.36 (887 mg, 5.72 mmol) in THF (5 mL) was added over 5 min. Stirring was continued at -78 °C for 20 min, then the reaction mixture was allowed to equilibrate to 23 °C. Stirring was continued for an additional 1 h before the reaction was quenched with saturated aqueous ammonium chloride (25 mL). The organic layer was diluted with ether (100 mL) and washed with brine (25 mL). It was dried over MgSO$_4$, filtered through a frit, and concentrated by rotary evaporation. The residue was purified by silica gel chromatography (9:1 hexanes:ethyl acetate, then 7:1, then 6:1) to afford 900 mg of a yellow oil (67% yield). $R_f$ 0.40 (4:1 hexanes:ethyl acetate). $^1$H NMR (500 MHz): $\delta$ 7.47 (d, 1H, $J = 15.5$ Hz), 7.08 (d, 2H, $J = 2.5$ Hz), 6.86 (d, 1H, $J = 15.5$ Hz), 6.65 (t, 1H, $J = 2.5$ Hz), 5.46 (t, 2H, $J = 16.5$ Hz), 3.85 (s, 6H), 1.98 (s, 3H). $^{13}$C NMR (125 MHz): $\delta$ 190.6, 160.8, 147.2, 141.0, 140.1, 125.8, 122.6, 106.3, 104.8, 55.6, 18.2. MS (EI): $m/z$ 232 (M+); HRMS (EI): found 232.1101, calcd for [C$_{14}$H$_{16}$O$_3$]$^+$ 232.1099. IR: $\nu$ 3442 (br), 2938, 2839, 1673, 1593, 1456, 1426, 1353, 1301 cm$^{-1}$. UV: $\lambda_{max}$ = 220, 265 nm.
(E)-1-(3,5-dimethoxyphenyl)-2,4-methylpenta-2,4-dien-1-one (1.51). 72% yield. Rf 0.54 (4:1 hexanes:ethyl acetate). 1H NMR (400 MHz): δ 6.79 (d, 2H, J = 2.4 Hz), 6.64 (s, 1H), 6.60 (t, 1H, J = 2.4 Hz), 5.25 (t, 1H, J = 1.6 Hz), 5.10 (s, 1H), 3.82 (s, 6H), 2.14 (d, 3H, J = 1.6 Hz), 1.96 (s, 3H). 13C NMR (100 MHz): δ 199.4, 160.5, 144.0, 140.8, 140.4, 135.7, 120.4, 107.2, 103.8, 55.6, 22.9, 14.2. MS (EI): m/z 246 (M+); HRMS (EI): found 246.1257, calcd for [C15H18O3]+ 246.1256. IR: ν 3435 (br), 2937, 2838, 1648, 1593, 1456, 1423, 1349 cm⁻¹. UV: λmax = 210 nm.

syn-4,6-dimethoxy-3-isopropenyl-2-methylindan-1-one (1.55a). To a 25-mL round-bottom flask equipped with a stir bar was added aluminum chloride (23.1 mg, 173 µmol) and toluene (2 mL). 1.51 (415 mg, 1.68 mmol) in toluene was added via syringe. The reaction mixture immediately turned red. It was stirred at 23 °C for 1 h before being quenched with saturated aqueous sodium bicarbonate (15 mL). The organic phase was diluted with ether (20 mL), separated, and washed with brine (15 mL). It was dried over MgSO₄, filtered through a frit, and concentrated by rotary evaporation. The residue was purified by silica gel chromatography (6:1 hexanes:ethyl acetate) to afford 298 mg of a yellow solid (71% yield, an inseparable 81:19 mixture of diastereomers). Rf 0.50 (4:1 hexanes:ethyl acetate). 1H NMR (400 MHz): δ 6.80 (d, 1H, J = 2.0 Hz), 6.63 (d, 1H, J = 2.0 Hz), 4.92 (t, 1H, J = 1.6 Hz), 4.67 (s, 1H), 4.11 (d, 1H, J = 8.0 Hz), 3.84 (s, 3H), 3.82 (s, 3H), 2.82 (quint, 1H, J = 7.6 Hz), 1.73 (s, 3H), 1.16 (d, 3H, J = 7.6 Hz). 13C NMR (100 MHz): δ 208.3, 161.5, 157.9, 144.0, 138.8, 137.5, 114.0, 105.5, 96.1, 55.9, 55.8, 47.8, 47.4, 21.7, 10.6. MS (EI): m/z 246 (M+); HRMS (EI): found 246.1260, calcd for [C15H18O3]+ 246.1256. IR: ν 3427 (br), 2937, 2841, 1713, 1615, 1494, 1449, 1455, 1435, 1359, 1327, 1310 cm⁻¹.

anti-4,6-dimethoxy-3-isopropenyl-2-methylindan-1-one (1.55b). To a vial equipped with a stir bar was added an 81:19 mixture of 1.55a:1.55b (22.7 mg, 92.2 µmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (2.76 µL, 18.4 µmol), and methanol (1 mL). The reaction was stirred at 23 °C for 10 h, at which point the solvent was removed by rotary evaporation. The residue was placed directly on a silica gel column (6:1 hexanes:ethyl acetate) to afford 298 mg of a yellow solid (71% yield, an inseparable 81:19 mixture of diastereomers). Rf 0.50 (4:1 hexanes:ethyl acetate). 1H NMR (400 MHz): δ 6.80 (d, 1H, J = 2.0 Hz), 6.65 (d, 1H, J = 2.0 Hz), 4.79 (s, 1H), 4.76 (s, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.51 (d, 1H, J = 3.0 Hz), 2.39 (dq, 1H, J = 3.0 Hz, 7.5 Hz), 1.64 (s, 3H), 1.29 (d, 3H, J = 7.5 Hz). 13C NMR (100 MHz): δ 208.3, 161.7, 158.3, 145.6, 138.7, 136.9, 111.3, 105.9, 96.3, 55.9, 55.8, 52.7, 49.7, 19.5, 16.1.
(E)-1-(3,4,5-trimethoxyphenyl)-4-methylpenta-2,4-dien-1-one (1.60). 60% yield. $^1$H NMR (500 MHz): $\delta$ 7.47 (d, 1H, $J = 15.0$ Hz), 7.21 (s, 1H), 6.86 (d, 1H, $J = 15.0$ Hz), 5.48 (s, 1H), 5.45 (s, 1H), 3.93 (s, 3H), 3.91 (s, 6H), 2.01 (s, 3H). $^{13}$C NMR (125 MHz): $\delta$ 190.0, 153.3, 147.3, 142.6, 141.1, 133.7, 125.9, 122.4, 106.3, 61.1, 56.5, 18.4. MS (EI): $m/z$ 262 (M$^+$); HRMS (EI): found 262.1209, calcd for [C$_{15}$H$_{18}$O$_4$]$^+$ 262.1205. UV: $\lambda_{max} = 220, 280$ nm. IR: v 3479 (br), 2939, 2839, 1668, 1584, 1505, 1463, 1338 cm$^{-1}$.

(E)-1-(3,4,5-trimethoxyphenyl)-2,4-dimethylpenta-2,4-dien-1-one (1.58). 63% yield. $^1$H NMR (500 MHz): $\delta$ 6.95 (s, 2H), 6.61 (s, 1H), 5.26 (s, 1H), 5.12 (s, 1H), 3.93 (s, 3H), 3.90 (s, 6H), 2.16 (s, 3H), 1.99 (s, 3H). $^{13}$C NMR (125 MHz): $\delta$ 198.9, 152.9, 143.1, 141.4, 140.9, 135.7, 133.5, 120.4, 107.2, 61.1, 56.4, 23.1, 14.6. MS (EI): $m/z$ 276 (M$^+$); HRMS (EI): found 276.1369, calcd for [C$_{16}$H$_{20}$O$_4$]$^+$ 276.1362. UV: $\lambda_{max} = 220, 285$ nm. IR: v 3456 (br), 2932, 2855, 1670, 1609, 1575, 1521, 1444, 1409, 1338, 1303 cm$^{-1}$.

syn-3-isopropenyl-4,5,6-trimethoxy-2-methylindan-1-one (1.59a). $^1$H NMR (500 MHz): $\delta$ 7.03 (d, 1H, $J = 4.5$ Hz), 4.86 (s, 1H), 4.84 (s, 1H), 3.93 (s, 3H), 3.90 (s, 3H), 3.87 (s, 3H), 3.56 (d, 1H, $J = 3.5$ Hz), 2.39 (quint, 1H, $J = 3.5$ Hz), 1.56 (s, 3H), 1.30 (d, 3H, $J = 7.5$ Hz). $^{13}$C NMR (125 MHz): $\delta$ 207.6, 154.9, 150.8, 148.4, 145.6, 141.2, 131.9, 112.0, 100.8, 61.2, 60.7, 53.1, 49.2, 21.6, 16.1. MS (EI): $m/z$ 276 (M$^+$); HRMS (EI): found 276.1361, calcd for [C$_{16}$H$_{20}$O$_4$]$^+$ 276.1362. IR: v 3400 (br), 3076, 2973, 2940, 2839, 1713, 1646, 1599, 1472, 1419, 1344 cm$^{-1}$.

anti-3-isopropenyl-4,5,6-trimethoxy-2-methylindan-1-one (1.59b). $^1$H NMR (500 MHz): $\delta$ 7.03 (d, 1H, $J = 4.5$ Hz), 4.96 (s, 1H), 4.73 (s, 1H), 4.17 (d, 1H, $J = 7.5$ Hz), 3.93 (s, 3H), 3.90 (s, 3H), 3.87 (s, 3H), 3.56 (d, 1H, $J = 3.5$ Hz), 2.80 (quint, 1H, $J = 7.5$ Hz), 1.38 (s, 3H), 1.16 (d,
3H, J = 7.5 Hz). $^{13}$C NMR (125 MHz): δ 207.3, 154.7, 150.4, 148.0, 144.5, 141.9, 132.1, 114.5, 100.6, 61.1, 60.6, 56.3, 48.1, 46.9, 19.4, 10.6.

(E)-1-(benzo[d][1,3]dioxol-6-yl)-4-methylpenta-2,4-dien-1-one (1.64). 39% yield. $^1$H NMR (500 MHz): δ 7.58 (dd, 1H, J = 2.0 Hz, 8.0 Hz), 7.48 (d, 1H, J = 2.0 Hz), 7.44 (s, 1H), 6.89 (t, 2H, 8.0 Hz), 6.06 (s, 2H), 5.46 (s, 1H), 5.43 (s, 1H), 1.99 (s, 3H). $^{13}$C NMR (125 MHz): δ 188.9, 153.8, 148.4, 146.8, 141.1, 133.1, 125.6, 124.8, 122.4, 108.6, 108.0, 102.0, 18.4. MS (EI): m/z 216 (M+); HRMS (EI): found 216.0783, calcd for [C$_{13}$H$_{12}$O$_3$]$^+$ 216.0786. IR: ν 3446 (br), 2916, 1670, 1603, 1504, 1488, 1440, 1356 cm$^{-1}$. UV: $\lambda_{max}$ = 230, 275, 310 nm.

(E)-1-(benzo[d][1,3]dioxol-6-yl)-2,4-dimethylpenta-2,4-dien-1-one (1.62). 49% yield. $^1$H NMR (500 MHz): δ 7.30 (dd, 1H, J = 1.5 Hz, 8.0 Hz), 7.24 (d, 1H, J = 1.5 Hz), 6.83 (d, 1H, J = 8.0 Hz), 6.52 (s, 1H), 6.04 (s, 2H), 5.24 (s, 1H), 5.09 (s, 1H), 2.13 (s, 3H), 1.97 (s, 3H). $^{13}$C NMR (125 MHz): δ 198.3, 151.1, 147.9, 142.0, 140.9, 136.0, 132.5, 125.8, 120.0, 109.8, 107.8, 101.8, 23.1, 14.9. MS (EI): m/z 230 (M+); HRMS (EI): found 230.0943, calcd for [C$_{14}$H$_{14}$O$_3$]$^+$ 230.0943. IR: ν 2965, 2918, 1645, 1603, 1504, 1486, 1438, 1356 cm$^{-1}$. UV: $\lambda_{max}$ = 205, 225, 275, 310 nm.

syn-7-isopropenyl-6-methylindano[5,6-d][1,3]dioxol-5-one (1.63a). $^1$H NMR (500 MHz): δ 7.11 (s, 1H), 6.79 (s, 1H), 6.07 (s, 2H), 4.97 (s, 1H), 4.81 (s, 1H), 4.01 (d, 1H, J = 7.5 Hz), 2.86 (quint, 1H, J = 7.5 Hz), 1.39 (s, 3H), 1.14 (d, 3H, J = 7.5 Hz). $^{13}$C NMR (125 MHz): δ 206.5, 154.2, 152.8, 148.6, 144.3, 131.3, 115.1, 106.0, 102.4, 51.2, 46.7, 21.3, 11.4. MS (EI): m/z 230 (M+); HRMS (EI): found 230.0943, calcd for [C$_{14}$H$_{14}$O$_3$]$^+$ 230.0943. IR: ν 3380 (br), 3075, 2972, 2917, 1704, 1646, 1609, 1503, 1472, 1376, 1299 cm$^{-1}$.
anti-7-isopropenyl-6-methylindano[5,6-d][1,3]dioxol-5-one (1.63b). $^1$H NMR (500 MHz): $\delta$ 7.10 (s, 1H), 6.74 (s, 1H), 6.06 (s, 1H), 4.97 (s, 1H), 4.94 (s, 1H), 3.44 (d, 1H, $J = 4.0$ Hz), 2.48 (dq, 1H, $J = 4.0$ Hz, 7.5 Hz), 1.56 (s, 3H), 1.29 (d, 3H, $J = 7.5$ Hz). $^{13}$C NMR (125 MHz): $\delta$ 206.2, 154.6, 152.5, 148.8, 144.5, 131.0, 114.3, 105.3, 102.4, 102.3, 55.9, 48.3, 18.3, 15.3.

(E)-4-methyl-1-(1-methyl-1H-indol-2-yl)penta-2,4-dien-1-one (1.68). Procedure modified from literature. To a 50-mL Schlenk flask equipped with a stir bar was added 1-methylindole (1.00 g, 7.39 mmol) and ether (14 mL). Butyllithium (3.10 mL, 2.5 M in hexanes) was added dropwise over 10 min, then the flask was washed with ether (3 mL). The solution was heated at reflux (40 °C) for 5 h, then equilibrated to 23 °C. To a separate 25-mL round-bottom flask equipped with a stir bar was added 1.41 (75.0 mg, 483 µmol) and ether (1 mL). The solution was cooled to 0 °C, then the contents of the Schlenk flask (1.19 mL, 0.368 M in ether) were added over 5 min. It was stirred at 0 °C for 1 h before being quenched with saturated aqueous ammonium chloride (15 mL) and diluted with ether (15 mL). The organic layer was separated and washed with brine (10 mL). It was dried over MgSO$_4$, filtered through a frit, and concentrated by rotary evaporation. The residue was purified by silica gel chromatography (19:1 hexanes:ethyl acetate, then 9:1) to afford 44.5 mg of a yellow oil (45% yield). $^1$H NMR (500 MHz in $d_6$-acetone): $\delta$ 7.72 (d, 1H, $J = 8.0$ Hz), 7.59 (d, 1H, $J = 4.0$ Hz), 7.52 (dd, 1H, $J = 4.5$ Hz, 8.5 Hz), 7.47 (d, 1H, $J = 15.5$ Hz), 7.38 (dq, 1H, $J = 4.0$ Hz, 8.5 Hz), 7.20 (dd, 1H, $J = 4.0$ Hz, 15.5 Hz), 7.15 (dd, 1H, $J = 4.5$ Hz, 8.0 Hz), 5.52 (s, 1H), 5.46 (s, 1H), 4.11 (d, 3H, $J = 4.0$ Hz), 2.05 (s, 3H). $^{13}$C NMR (125 MHz in $d_6$-acetone): $\delta$ 183.8, 145.7, 143.0, 141.9, 137.7, 127.6, 127.3, 126.0, 125.8, 124.3, 122.1, 112.9, 112.0, 33.0, 19.0. MS (EI): $m/z$ 225 (M+); HRMS (EI): found 225.1148, calcd for [C$_{15}$H$_{15}$NO]$^+$ 225.1154. IR: $\nu$ 3623 (br), 2924, 2854, 1658, 1650, 1612, 1512, 1463, 1390, 1320 cm$^{-1}$. UV: $\lambda_{max} = 220, 310$ nm.

(E)-2,4-dimethyl-1-(1-methyl-1H-indol-2-yl)penta-2,4-dien-1-one (1.66). 50% yield. $^1$H NMR (500 MHz): $\delta$ 7.68 (d, 1H, $J = 7.5$ Hz), 7.39 (m, 2H), 7.16 (t, 1H, $J = 7.5$ Hz), 6.98 (s, 1H), 6.91 (s, 1H), 5.28 (s, 1H), 5.15 (s, 1H), 4.00 (s, 3H), 2.18 (s, 3H), 2.00 (s, 3H). $^{13}$C NMR (125 MHz): $\delta$ 191.8, 142.6, 141.1, 140.2, 137.4, 135.5, 125.9, 125.5, 122.9, 120.7, 120.1, 112.8, 110.4, 31.9, 23.2, 14.5. MS (EI): $m/z$ 239 (M+); HRMS (EI): found 239.1311, calcd for [C$_{16}$H$_{17}$NO]$^+$ 239.1310. IR: $\nu$ 2918, 1741, 1717, 1628, 1613, 1541, 1509, 1465, 1392 cm$^{-1}$. UV: $\lambda_{max} = 215, 255$ nm.
**syn-1,2-dihydro-1-isopropenyl-2,4-dimethylcyclopenta[b]indol-3(4H)-one (1.67a).**  
$^1$H NMR (400 MHz): $\delta$ 7.64 (d, 1H, $J = 8.0$ Hz), 7.40 (m, 2H), 7.16 (dt, 1H, $J = 1.6$ Hz, 8.0 Hz), 5.04 (s, 1H), 4.84 (s, 1H), 4.14 (d, 1H, $J = 6.4$ Hz), 3.94 (d, 3H, $J = 2.0$ Hz), 3.22 (quint, 1H, $J = 7.2$ Hz), 1.61 (s, 3H), 1.21 (d, 3H, $J = 7.6$ Hz).  
$^{13}$C NMR (100 MHz): $\delta$ 197.4, 145.1, 144.4, 143.4, 138.3, 126.8, 123.3, 122.5, 120.4, 114.6, 111.1, 51.1, 45.3, 30.3, 22.5, 12.5.  
MS (EI): $m/z$ 239 (M$^+$); HRMS (EI): found 239.1310, calcd for $[C_{16}H_{17}NO]^+$ 239.1310.  
IR: $\nu$ 2971, 2932, 1691, 1679, 1614, 1547, 1493, 1453, 1432, 1377, 1349 cm$^{-1}$.  

**anti-1,2-dihydro-1-isopropenyl-2,4-dimethylcyclopenta[b]indol-3(4H)-one (1.67b).**  
$^1$H NMR (500 MHz): $\delta$ 7.63 (d, 1H, $J = 8.0$ Hz), 7.40 (m, 2H), 7.16 (t, 1H, $J = 8.0$ Hz), 4.98 (s, 1H), 4.91 (s, 1H), 3.94 (s, 1H), 3.61 (d, 1H, $J = 2.0$ Hz), 2.72 (dt, 1H, $J = 5.0$ Hz, 7.5 Hz), 1.61 (s, 3H), 1.40 (d, 3H, $J = 7.5$ Hz).  
$^{13}$C NMR (125 MHz): $\delta$ 196.8, 145.1, 145.0, 143.8, 138.1, 126.8, 123.3, 122.3, 120.5, 112.5, 111.1, 54.1, 50.5, 30.3, 19.7, 16.1.  

**(E)-1-(benzo[b]thiophen-2-yl)-4-methylpenta-2,4-dien-1-one (1.72).**  
$^1$H NMR (500 MHz): $\delta$ 8.04 (s, 1H), 7.91 (d, 1H, $J = 8.0$ Hz), 7.89 (d, 1H, $J = 8.0$ Hz), 7.57 (d, 1H, $J = 15.5$ Hz), 7.47 (dt, 1H, $J = 1.0$ Hz, 8.0 Hz), 7.41 (dt, 1H, $J = 1.0$ Hz, 8.0 Hz), 6.95 (d, 1H, $J = 15.5$ Hz), 5.53 (s, 1H), 5.49 (s, 1H), 2.03 (s, 3H).  
$^{13}$C NMR (125 MHz): $\delta$ 184.0, 146.9, 145.3, 142.8, 140.9, 139.4, 128.9, 127.5, 126.6, 126.1, 125.2, 123.1, 121.8, 18.4.  
MS (EI+): $m/z$ 228 (M$^+$); HRMS (EI+): found 228.0609, calcd for $[C_{14}H_{12}SO]^+$ 228.0609.  
IR: $\nu$ 3058, 2921, 2850, 1685, 1657, 1650, 1644, 1609, 1593, 1513, 1456, 1428, 1375, 1276 cm$^{-1}$.  
UV$\max$: $\lambda = 220, 315$ nm.  

**Diels-Alder dimer of 1.72 (1.73).**  
50% yield.  
$^1$H NMR (500 MHz): $\delta$ 8.04 (s, 1H), 7.99-7.85 (m, 3H), 7.81 (d, 1H, $J = 7.5$ Hz), 7.47 (t, 1H, $J = 7.5$ Hz), 7.42-7.34 (m, 4H), 7.21 (d, 1H, $J = 16.0$ Hz), 6.90 (d, 1H, $J = 16.0$ Hz), 5.46 (s, 1H), 4.16 (s, 1H), 2.26-2.13 (m, 2H), 1.76 (s, 3H), 1.71 (s, 3H), 1.63 (s, 3H), 1.56 (s, 3H), 1.38 (s, 3H), 1.34 (s, 3H), 1.29 (s, 3H), 1.23 (s, 3H), 1.18 (s, 3H), 1.12 (s, 3H), 1.06 (s, 3H), 0.99 (s, 3H), 0.95 (s, 3H), 0.90 (s, 3H), 0.85 (s, 3H), 0.81 (s, 3H), 0.77 (s, 3H), 0.73 (s, 3H), 0.69 (s, 3H), 0.65 (s, 3H), 0.61 (s, 3H), 0.57 (s, 3H), 0.53 (s, 3H), 0.49 (s, 3H), 0.45 (s, 3H), 0.41 (s, 3H), 0.37 (s, 3H), 0.33 (s, 3H), 0.29 (s, 3H), 0.25 (s, 3H), 0.21 (s, 3H), 0.17 (s, 3H), 0.13 (s, 3H), 0.09 (s, 3H), 0.05 (s, 3H).  
IR: $\nu$ 3070, 2960, 2850, 1700, 1670, 1640, 1580, 1500, 1450, 1380, 1360, 1270, 1240, 1170, 1130, 1090, 1050, 970 cm$^{-1}$.  
UV$\max$: $\lambda = 220, 280, 315$ nm.
1.75 (m, 1H), 1.39 (m, 1H), 1.23 (s, 3H). $^{13}$C NMR (125 MHz): δ 195.4, 184.0, 156.1, 145.2, 144.8, 142.9, 142.8, 139.3, 129.8, 129.1, 127.7, 127.5, 126.3, 126.1, 125.2, 125.1, 123.1, 123.0, 122.3, 117.5, 52.0, 38.7, 32.0, 27.6, 23.8, 22.7. MS (EI): m/z 456 (M+); HRMS (EI): found 456.1217, calcd for $[C_{28}H_{24}S_2O_2]^+$ 456.1218. IR: ν 3534 (br), 2923, 2851, 1710, 1691, 1657, 1535, 1482, 1430 cm$^{-1}$.

(E)-1-(benzo[b]thiophen-2-yl)-2,4-dimethylpenta-2,4-dien-1-one (1.70). $^1$H NMR (500 MHz): δ 7.88 (d, 2H, $J = 8.5$ Hz), 7.81 (s, 1H), 7.46 (dt, 1H, $J = 1.0$ Hz, 7.5 Hz), 7.41 (dt, 1H, $J = 1.0$ Hz, 7.5 Hz), 6.90 (s, 1H), 6.31 (t, 1H, $J = 1.5$ Hz), 5.18 (s, 1H), 2.19 (d, 3H, $J = 1.5$ Hz), 2.02 (s, 3H). $^{13}$C NMR (125 MHz): δ 192.4, 143.2, 142.6, 141.8, 140.9, 139.1, 136.1, 130.6, 127.2, 126.0, 125.0, 123.0, 120.5, 23.1, 14.9. MS (EI+): m/z 242 (M+); HRMS (EI+): found 242.0768, calcd for $[C_{15}H_{14}SO]^+$ 242.0765. IR: ν 2962, 2921, 1625, 1558, 1512, 1456, 1429, 1355 cm$^{-1}$. UV$_{\text{max}}$: λ = 225, 300 nm.

(1S, 2S)-1,2-dihydro-1-isopropenyl-2-methylcyclopentabenzo[b]thiophen-3-one (1.71a). $^1$H NMR (400 MHz): δ 7.91 (d, 1H, $J = 8.0$ Hz), 7.84 (d, 1H, $J = 8.0$ Hz), 7.49 (dt, 1H, $J = 1.2$ Hz, 7.2 Hz), 7.42 (dt, 1H, $J = 1.2$ Hz, 7.2 Hz), 5.09 (s, 1H), 4.88 (s, 1H), 4.30 (d, 1H, $J = 6.8$ Hz), 3.28 (quint, 1H, $J = 7.2$ Hz), 1.51 (s, 3H), 1.26 (d, 3H, $J = 7.2$ Hz). $^{13}$C NMR (100 MHz): δ 200.7, 164.4, 148.3, 142.6, 140.8, 134.3, 128.2, 125.2, 124.6, 124.4, 116.0, 50.3, 48.8, 21.9, 11.5.

(1R, 2S)-1,2-dihydro-1-isopropenyl-2-methylcyclopentabenzo[b]thiophen-3-one (1.71b). $^1$H NMR (500 MHz): δ 7.91 (d, 1H, $J = 8.0$ Hz), 7.87 (d, 1H, $J = 8.0$ Hz), 7.49 (t, 1H, $J = 7.5$ Hz), 7.42 (t, 1H, $J = 7.5$ Hz), 5.06 (s, 1H), 5.01 (s, 1H), 3.75 (d, 1H, $J = 3.0$ Hz), 2.84 (dq, 1H, $J = 3.0$ Hz, 7.5 Hz), 1.63 (s, 3H), 1.42 (d, 3H, $J = 7.5$ Hz). $^{13}$C NMR (125 MHz): δ 200.3, 163.6, 148.6, 143.7, 140.7, 134.4, 128.2, 125.2, 124.6, 124.4, 114.2, 54.0, 52.9, 19.0, 15.8. MS (EI+): m/z 242 (M+); HRMS (EI+): found 242.0764, calcd for $[C_{15}H_{14}SO]^+$ 242.0765. IR: ν 3445 (br), 2967, 2928, 1701, 1647, 1593, 1558, 1519, 1456, 1426, 1371, 1320 cm$^{-1}$. 

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(E)-4-methyl-1-p-tolylpenta-2,4-dien-1-one (1.81). $^1$H NMR (400 MHz): $\delta$ 7.87 (d, 2H, $J = 8.0$ Hz), 7.47 (d, 1H, $J = 15.6$ Hz), 7.28 (d, 2H, $J = 8.0$ Hz), 6.93 (d, 1H, $J = 15.6$ Hz), 5.46 (s, 1H), 5.43 (s, 1H), 2.43 (s, 3H), 2.00 (s, 3H). $^{13}$C NMR (100 MHz): $\delta$ 190.7, 146.9, 143.7, 141.2, 129.4, 128.9, 128.7, 125.6, 122.8, 21.8, 18.4. IR: $\nu$ 3412 (br), 2923, 1722, 1692, 1659, 1605, 1572, 1451, 1409, 1379 cm$^{-1}$. UV$\text{max}$: $\lambda = 210, 250$ nm.

(E)-2,4-dimethyl-1-p-tolylpenta-2,4-dien-1-one (1.79). $^1$H NMR (500 MHz): $\delta$ 7.60 (d, 1H, $J = 8.0$ Hz), 7.23 (d, 1H, $J = 8.0$ Hz), 6.57 (s, 1H), 5.24 (s, 1H), 5.09 (s, 1H), 2.41 (s, 3H), 2.15 (s, 3H), 1.96 (s, 3H). $^{13}$C NMR (125 MHz): $\delta$ 199.6, 143.0, 142.2, 140.9, 135.9, 135.5, 129.6, 128.8, 120.0, 22.9, 21.5, 14.4. IR: $\nu$ 3435 (br), 2925, 1720, 1694, 1654, 1607, 1571, 1509, 1446, 1409, 1376, 1311 cm$^{-1}$. UV$\text{max}$: $\lambda = 205, 250$ nm.

2,4-dimethyl-2-p-tolycyclopent-3-one (1.80). $^1$H NMR (500 MHz): $\delta$ 7.25 (d, 2H, $J = 8.0$ Hz), 7.13 (d, 2H, $J = 8.0$ Hz), 5.85 (d, 1H, $J = 2.0$ Hz), 2.95 (d, 1H, $J = 22.5$ Hz), 2.83 (d, 1H, $J = 22.5$ Hz), 2.31 (s, 3H), 1.94 (s, 3H), 1.48 (s, 3H). $^{13}$C NMR (125 MHz): $\delta$ 217.9, 139.1, 136.6, 136.1, 132.1, 129.3, 126.2, 58.0, 45.5, 30.7, 23.9, 21.1, 17.8. MS (EI): $m/z$ 200 (M$^+$); HRMS (EI): found 200.1204, calcd for [C$_{14}$H$_{16}$O]$^+$ 200.1201. IR: $\nu$ 3404 (br), 2965, 2922, 2852, 1747, 1702, 1632, 1607, 1513, 1450, 1409, 1377, 1312, 1292, 1274 cm$^{-1}$.

(E)-4-methyl-1-phenylpenta-2,4-dien-1-one (1.76). $^1$H NMR (500 MHz): $\delta$ 7.96 (d, 2H, $J = 7.5$ Hz, 7.57 (t, 1H, $J = 7.5$ Hz), 7.48 (t, 2H, $J = 7.5$ Hz), 7.47 (d, 1H, $J = 15.0$ Hz), 6.93 (d, 1H, $J = 15.0$ Hz), 5.47 (s, 1H), 5.44 (s, 1H), 2.00 (s, 3H). $^{13}$C NMR (125 MHz): $\delta$ 191.2, 147.4, 141.1, 138.3, 132.8, 128.7, 128.6, 125.9, 122.8, 18.4. MS (EI$+$): $m/z$ 172; HRMS (EI$+$): found 172.0880, calcd for [C$_{12}$H$_{12}$O]$^+$ 172.0888. IR: $\nu$ 3085, 3060, 2921, 1664, 1614, 1599, 1577, 1447, 1321 cm$^{-1}$. UV$\text{max}$: $\lambda = 205, 250$ nm.
(E)-2,4-dimethyl-1-phenylpenta-2,4-dien-1-one (1.74). $^1$H NMR (500 MHz): $\delta$ 7.67 (d, 2H, $J = 7.0$ Hz), 7.51 (t, 1H, $J = 7.0$ Hz), 7.43 (t, 1H, $J = 7.0$ Hz), 6.60 (s, 1H), 5.26 (s, 1H), 5.10 (s, 1H), 2.16 (s, 3H), 1.97 (s, 3H). $^{13}$C NMR (125 MHz): $\delta$ 199.9, 144.1, 141.0, 138.6, 136.1, 131.7, 129.5, 128.3, 120.4, 23.0, 14.3. MS (EI+): $m/z$ 186; HRMS (EI+): found 186.1040, calcd for [C$_{13}$H$_{14}$O]+ 186.1045. IR: $\nu$ 3418 (br), 3083, 3061, 2968, 2924, 1648, 1597, 1577, 1446, 1384, 1356, 1316 cm$^{-1}$. UV$_{\text{max}}$: $\lambda = 205, 255$ nm.

(2E,4E)-1-(3,5-dimethoxyphenyl)-5-methylhexa-2,4-dien-1-one (1.74). $^1$H NMR (500 MHz): $\delta$ 6.77 (d, 1H, $J = 11.0$ Hz), 6.72 (d, 2H, $J = 2.0$ Hz), 6.58 (d, 1H, $J = 2.0$ Hz), 6.48 (ddd, 1H, $J = 2.0$ Hz, 11.0 Hz, 15.0 Hz), 6.04 (dt, 1H, $J = 7.0$ Hz, 15.0 Hz), 3.81 (s, 6H), 2.04 (s, 3H), 1.88 (d, 3H, $J = 7.0$ Hz). $^{13}$C NMR (125 MHz): $\delta$ 198.9, 160.5, 143.4, 141.1, 139.1, 133.5, 127.9, 107.0, 103.5, 55.7, 19.2, 12.6. MS (EI): $m/z$ 246 (M+); HRMS (EI): found 246.1256, calcd for [C$_{15}$H$_{18}$O$_3$]$^+$ 246.1256. IR: $\nu$ 2945, 2928, 1632, 1591, 1485, 1464, 1421, 1371, 1337, 1303 cm$^{-1}$. UV: $\lambda_{\text{max}} = 220, 270$ nm.

(E)-1-(3,5-dimethoxyphenyl)-5-methylhexa-2,4-dien-1-one (1.89). 66% yield. $^1$H NMR (400 MHz): $\delta$ 7.74 (dd, 1H, 11.6 Hz, 14.8 Hz), 7.08 (d, 2H, $J = 2.4$ Hz), 6.82 (d, 1H, $J = 14.8$ Hz), 6.64 (t, 1H, $J = 2.4$ Hz), 6.14 (d, 1H, $J = 11.6$ Hz), 3.84 (s, 6H), 1.95 (s, 3H), 1.93 (s, 3H). $^{13}$C NMR (100 MHz): $\delta$ 190.7, 160.9, 148.9, 141.6, 140.7, 124.8, 123.0, 106.2, 105.0, 55.7, 27.0, 19.4. MS (EI): $m/z$ 246 (M+); HRMS (EI): found 246.1260, calcd for [C$_{15}$H$_{18}$O$_3$]+ 246.1256. IR: $\nu$ 2945, 2928, 1632, 1591, 1485, 1464, 1421, 1371, 1337, 1303 cm$^{-1}$. UV: $\lambda_{\text{max}} = 220, 270$ nm.
syn-2,3-dihydro-4,6-dimethoxy-2-methyl-3-((E)-prop-1-enyl)inden-1-one (1.91a). $^1$H NMR (500 MHz): $\delta$ 6.79 (d, 1H, $J = 2.0$ Hz), 6.64 (d, 1H, $J = 2.0$ Hz), 5.39 (dq, 1H, $J = 7.0$ Hz, 15.0 Hz), 5.13 (dd, 1H, $J = 8.0$ Hz, 15.0 Hz), 4.03 (t, 1H, $J = 8.0$ Hz), 3.84 (s, 3H), 3.82 (s, 3H), 2.81 (quint, 1H, $J = 7.5$ Hz), 1.65 (dd, 3H, $J = 1.5$ Hz, 6.5 Hz), 1.16 (d, 3H, $J = 7.5$ Hz). $^{13}$C NMR (125 MHz): $\delta$ 208.7, 161.4, 158.0, 138.1, 137.6, 129.6, 127.4, 105.7, 96.2, 55.9, 55.7, 48.0, 43.4, 18.1, 11.4. MS (EI): m/z 246 (M+); HRMS (EI): found 246.1259, calcd for [C$_{15}$H$_{18}$O$_3$]$^+$ 246.1256. IR: $\nu$ 2924, 1712, 1612, 1513, 1494, 1462, 1453, 1355, 1327 cm$^{-1}$. UV: $\lambda_{\text{max}}$ = 220, 260, 325 nm.

anti-2,3-dihydro-4,6-dimethoxy-2-methyl-3-((E)-prop-1-enyl)inden-1-one (1.91b). $^1$H NMR (500 MHz): $\delta$ 6.78 (d, 1H, $J = 2.0$ Hz), 6.65 (d, 1H, $J = 2.0$ Hz), 5.53 (m, 2H), 3.83 (s, 3H), 3.82 (s, 3H), 3.44 (dd, 1H, $J = 3.0$ Hz, 7.5 Hz), 2.42 (dq, 1H, $J = 3.0$ Hz, 7.5 Hz), 1.69 (d, 3H, $J = 5.5$ Hz), 1.28 (d, 3H, $J = 7.5$ Hz). $^{13}$C NMR (125 MHz): $\delta$ 208.9, 161.5, 158.4, 138.0, 137.6, 131.6, 125.4, 106.1, 96.3, 55.9, 55.7, 50.5, 48.0, 18.1, 15.5.

(E)-1-(3,5-dimethoxyphenyl)-2,5-dimethylhexa-2,4-dien-1-one (1.92). 74% yield. $^1$H NMR (400 MHz): $\delta$ 7.09 (d, 1H, $J = 11.6$ Hz), 6.75 (d, 2H, $J = 2.0$ Hz), 6.58 (t, 1H, $J = 2.0$ Hz), 6.25 (d, 1H, $J = 11.6$ Hz), 3.81 (s, 6H), 2.03 (s, 3H), 1.92 (s, 3H), 1.75 (s, 3H). $^{13}$C NMR (100 MHz): $\delta$ 198.9, 160.5, 146.1, 141.4, 139.5, 133.0, 121.8, 107.1, 103.7, 55.7, 27.2, 19.2, 12.5. MS (EI): m/z 260 (M+); HRMS (EI): found 260.1416, calcd for [C$_{16}$H$_{20}$O$_3$]$^+$ 260.1412. IR: $\nu$ 2931, 1622, 1591, 1455, 1424, 1385, 1347, 1330, 1313, 1297 cm$^{-1}$. UV: $\lambda_{\text{max}}$ = 205, 305 nm.

4,6-dimethoxy-2-methyl-3-(2-methylprop-1-enyl)indan-1-one (1.93a). $^1$H NMR (400 MHz): $\delta$ 6.76 (s, 1H), 6.62 (s, 1H), 4.93 (d, 1H, $J = 10.0$ Hz), 3.82 (s, 3H), 3.78 (s, 3H), 3.70 (d, 1H, $J = 10.0$ Hz), 2.34 (quint, 1H, $J = 7.6$ Hz), 1.81 (s, 3H), 1.71 (d, 3H, $J = 8.4$ Hz), 1.28 (d, 3H, $J = 7.6$ Hz). $^{13}$C NMR (100 MHz): $\delta$ 209.1, 161.2, 157.8, 139.4, 137.8, 133.4, 123.3, 105.6, 96.2, 55.9, 55.7, 47.7, 39.6, 26.0, 18.2, 11.2. MS (EI): m/z 260 (M+); HRMS (EI): found 260.1416, calcd
for $[C_{16}H_{20}O_3]^+$ 260.1412. IR: $\nu$ 2965, 2931, 2871, 2839, 1713, 1614, 1592, 1494, 1454, 1435, 1358, 1306 cm$^{-1}$.

4,6-dimethoxy-2-methyl-3-(2-methylprop-1-enyl)inden-1-one (1.93b). $^1$H NMR (400 MHz): $\delta$ 6.78 (s, 1H), 6.62 (s, 1H), 4.60 (d, 1H, $J = 10.0$ Hz), 4.28 (t, 1H, $J = 8.8$ Hz), 3.82 (s, 3H), 3.80 (s, 3H), 2.81 (quint, 1H, $J = 7.6$ Hz), 1.81 (s, 3H), 1.71 (d, 3H, $J = 8.4$ Hz), 1.12 (d, 3H, $J = 7.6$ Hz). $^{13}$C NMR (100 MHz): $\delta$ 209.5, 161.4, 158.3, 138.7, 138.0, 132.4, 125.8, 106.1, 96.2, 55.9, 55.7, 51.1, 44.2, 26.0, 18.4, 15.9.

3-bromocyclohex-2-enone (1.109). To a 1-L three-necked round-bottom flask equipped with a stir bar and an addition funnel was added triphenylphosphine (18.4 g, 70.1 mmol) in benzene (200 mL). The solution was cooled to 0 °C, then bromine (3.59 mL, 70.1 mmol) in benzene (20 mL) was added using the addition funnel over 1 h. Triethylamine (9.77 mL, 70.1 mmol) was added over 10 min at 0 °C via syringe. 1,3-cyclohexanedione (5.06 g, 43.8 mmol) in chloroform (65 mL) was added using the addition funnel over 45 min. The reaction mixture was allowed to equilibrate to 23 °C, and stirring continued for another 6 h. The mixture was then filtered through Celite that had been prepacked with 2:1 hexane:ethyl acetate. The filtrate was washed with water (200 mL) and brine (100 mL). It was dried over MgSO$_4$, filtered through a frit, and concentrated by rotary evaporation. The material was passed through a silica gel plug (2:1 hexane:ethyl acetate) to afford 3.33 g of a yellow oil (43%). $^1$H NMR (500 MHz): $\delta$ 6.47 (t, 1H, $J = 1.5$ Hz), 2.81 (dt, 2H, $J = 1.5$ Hz, 6.0 Hz), 2.40 (m, 2H), 2.07 (m, 2H). $^{13}$C NMR (125 MHz): $\delta$ 196.4, 150.3, 132.8, 36.5, 36.4, 23.1.

1-bromo-3-methylene cyclohex-1-ene (1.110). To a 50-mL round-bottom flask equipped with a stir bar was added methyltriphenylphosphonium bromide (1.16 g, 3.18 mmol) and THF (8.0 mL). The suspension was cooled to 0 °C, then $n$-butyllithium (2.5 M in hexanes, 1.27 mL) was added dropwise over 5 min. The reaction mixture was stirred at 0 °C for 2 h, then 1.109 (464 mg, 2.65 mmol) in THF (1.0 mL) was added via cannula. The reaction mixture was allowed to equilibrate to 23 °C, then stirring continued for 18 h. The THF was distilled from the crude mixture at 80 °C under nitrogen. The crude material was then distilled using a Kugelrohr at 50 °C at 0.5 Torr to afford 320 mg (70% yield). The product decomposes readily upon standing and exposure to air. R$_f$ 0.90 (9:1 hexanes:ethyl acetate). $^1$H NMR (500 MHz): $\delta$ 6.51 (s, 1H), 4.78 (s,
(3,5-dimethoxyphenyl)(3-methylene cyclohex-1-enyl)methanone (1.94). To a 25-mL round-bottom flask equipped with a stir bar was added 1.110 (152 mg, 878 µmol) and THF (2.5 mL). The reaction mixture was cooled to -78 °C, then n-butyllithium (2.5 M in hexanes, 369 µL) was added dropwise over 5 min. The resulting solution was stirred for 5 min, then 1.111 (218 mg, 968 µmol) in THF (0.5 mL) was added via cannula. Stirring was continued at -78 °C for 45 min before the reaction was quenched with saturated aqueous ammonium chloride (15 mL). Ether (15 mL) was added, then extracted. The organic layer was washed with brine (10 mL), then dried over MgSO₄, filtered through a frit, and concentrated by rotary evaporation. The residue was purified by silica gel chromatography (9:1 hexanes:ethyl acetate, then 7:1) to afford 136 mg product (60% yield). Rf 0.39 (4:1 hexanes:ethyl acetate).

2,3,4,4a-tetrahydro-5,7-dimethoxy-4-methylene-1H-fluoren-9(9aH)-one (1.112a) and 1,2-dihydro-5,7-dimethoxy-4-methyl-4aH-fluoren-9(9aH)-one (1.112b). Recovered a 37:63 mixture of 20a:20b. ¹H NMR (500 MHz): δ 6.83 (20a, d, 1H, J = 2.0 Hz), 6.81 (20b, d, 1H, J = 2.0 Hz), 6.69 (20a, d, 1H, J = 2.0 Hz), 6.67 (20b, d, 1H, J = 2.0 Hz), 5.39 (20b, s, 1H), 4.80 (20a, s, 1H), 4.48 (20a, s, 1H), 4.09 (20a, d, 1H, J = 7.5 Hz), 3.96 (20b, d, 1H, J = 6.5 Hz), 3.86 (20b, s, 3H), 3.85 (20a, s, 3H), 3.84 (20a, s, 3H), 3.82 (20b, s, 3H), 2.97 (20b, m, 1H), 2.89 (20a, m, 1H), 2.42 (20a, m, 1H), 2.39 (20a, m, 1H), 2.14 (20b, t, 1H, J = 7.0 Hz), 2.09 (20a, m, 1H), 1.82 (20a, m, 1H), 1.79 (20b, s, 3H), 1.67 (20b, m, 3H), 1.43 (20a, m, 1H), 1.26 (20a, m, 1H). ¹³C NMR (125 MHz): δ 207.7 (20b), 207.4 (20a), 161.4 (20a), 161.1 (20b), 158.4 (20a), 157.9 (20b), 147.1 (20a), 139.0 (20b), 138.9 (20a), 138.7 (20b), 137.2 (20a), 136.1 (20b), 123.6 (20b), 111.8 (20a), 105.4 (20a), 105.3 (20b), 96.9 (20b), 96.7 (20a), 55.9 (20b), 55.7 (20a), 55.4 (20b), 55.4 (20a), 51.4 (20a), 50.5 (20b), 43.3 (20a), 41.1 (20b), 31.8 (20a), 23.8 (20b), 23.1 (20a), 23.0 (20a), 21.7 (20b), 21.5 (20b). MS (EI+): m/z 258 (M+); HRMS (EI+): found 258.1259, calcd for [C₁₆H₁₈O₃]⁺ 258.1256. IR: ν 2924, 2851, 1713, 1611, 1492, 1453, 1434, 1380, 1323 cm⁻¹. UV: λ max = 220, 260, 325 nm.
Ethyl 3-(3,5-dimethoxyphenyl)-3-oxopropanoate (1.115). To a 100-mL flask equipped with a stir bar was added diisopropylamine (500 μL, 3.54 mmol) and THF (10 mL). The reaction flask was cooled to 0 °C, then butyllithium (2.5 M in hexanes, 1.42 mL) was added dropwise over 5 min. The reaction mixture was stirred at 0 °C for 20 min, then cooled to -78 °C. Ethyl acetate (329 μL, 3.37 mmol) was added dropwise at -78 °C. The reaction mixture was stirred at -78 °C for 60 min, then 3,5-dimethoxybenzaldehyde (534 mg, 3.22 mmol) in THF (2 mL) was added via cannula. Stirring continued at -78 °C for 90 min, at which point the reaction was quenched with saturated aqueous ammonium chloride. The organic layer was diluted with ether (50 mL), then separated and washed with brine (20 mL). It was then dried over MgSO₄, filtered through a frit, and concentrated by rotary evaporation. The residue was purified by silica gel chromatography (4:1 hexanes:ethyl acetate, then 3:1, then 2:1) to yield 714 mg (87%) of the intermediate alcohol.

1H NMR (500 MHz): keto form: δ 7.07 (s, 2H), 6.67 (s, 1H), 4.21 (q, 2H, J = 7.0 Hz), 3.95 (s, 2H), 3.83 (s, 6H), 1.26 (t, 3H, J = 7.0 Hz); enol form: δ 12.56 (s, 1H), 6.92 (s, 1H), 6.56 (s, 1H), 5.63 (s, 1H), 4.25 (q, 2H, J = 7.0 Hz), 3.82 (s, 6H), 1.33 (t, 3H, J = 7.0 Hz). 13C NMR (125 MHz): keto form: δ 192.4, 167.6, 161.1, 138.0, 106.4, 104.1, 61.6, 55.8, 46.3, 14.2; enol form: δ 173.3, 171.4, 160.9, 135.6, 106.1, 103.8, 87.9, 60.5, 55.6, 14.4. MS (EI+): m/z 252 (M+); HRMS (EI+): found 252.0994, calcd for [C₁₃H₁₆O₅]₊ 252.0998.

IR: ν 2918, 2849, 1740, 1686, 1593, 1463, 1428, 1356, 1323 cm⁻¹.

2-(3’,5’-dimethoxybenzoyl)-5-phenyl-penta-2,4-dienoic acid ethyl ester (1.116). To a 100-mL flask equipped with a stir bar and a Dean-Stark apparatus was added ester 1.115 (172 mg, 682 μmol) and benzene (10 mL). Cinnamaldehyde (78.0 μL, 619 μmol), piperidine (6.12 μL, 61.9 μmol) and glacial acetic acid (17.7 μL, 310 μmol) were added, then the reaction mixture was heated at reflux for 2 h. It was then cooled to 23 °C, at which point the reaction was quenched with saturated aqueous sodium bicarbonate (20 mL). The organic phase was diluted with ether (50 mL) and washed with brine (20 mL). It was then dried over MgSO₄, filtered through a frit, and concentrated by rotary evaporation. The residue was purified by silica gel chromatography (4:1 hexanes:ethyl acetate) to yield 411 mg of a viscous light yellow oil, approx. 2.5:1 E:Z ratio. 1H NMR (500 MHz): δ 7.67 (d, 1H, J = 14.5 Hz), 7.38 (m, 2H), 7.31 (m, 3H), 7.06 (s, 2H), 7.03 (d, 1H, 19.0 Hz), 6.78 (dd, 1H, J = 14.5 Hz, 19.0 Hz), 6.68 (t, 1H, J =
2.5 Hz), 4.20 (q, 2H, J = 9.0 Hz), 3.83 (s, 6H), 1.18 (t, 3H, J = 9.0 Hz). $^{13}$C NMR (125 MHz): $\delta$ 194.3, 165.2, 161.1, 144.0, 139.2, 135.7, 131.4, 129.8, 128.9, 127.8, 123.1, 107.0, 106.3, 61.4, 55.8, 14.2. MS (EI+): m/z 366 (M+); HRMS (EI+): found 366.1468, calcd for [C$_{22}$H$_{22}$O$_5$]$^+$ 366.1467. IR: $\nu$ 3427 (br), 2957, 2929, 2855, 1717, 1673, 1634, 1593, 1460, 1427, 1367, 1351, 1316, 1298 cm$^{-1}$.

2-(3',5'-dimethoxybenzoyl)deca-2,4-dienoic acid ethyl ester (1.117). To a 10-mL flask equipped with a stir bar was added ester 1.116 (100 mg, 273 $\mu$mol), Grubbs' second generation catalyst (23.2 mg, 27.3 $\mu$mol), 1-heptene (769 $\mu$L, 5.46 mmol) and dichloromethane (3 mL). The reaction mixture was heated at reflux for 12 h. It was then cooled to 23 $^\circ$C, then the solvent was removed by rotary evaporation. The residue was purified by silica gel chromatography (5:1 hexanes:ethyl acetate) to yield 60.1 mg of a yellow oil (61%). $^1$H NMR (500 MHz): $\delta$ 7.48 (d, 1H, J = 11.5 Hz), 7.02 (d, 2H, J = 2.5 Hz), 6.67 (t, 1H, J = 7.0 Hz), 4.17 (q, 2H, J = 7.0 Hz), 3.82 (s, 6H), 2.11 (q, 2H, J = 7.0 Hz), 1.37 (quint, 2H, J = 7.0 Hz), 1.30-1.14 (m, 4H), 1.15 (t, 3H, J = 7.0 Hz), 0.85 (t, 3H, J = 7.0 Hz). $^{13}$C NMR (125 MHz): $\delta$ 194.4, 165.3, 161.0, 149.2, 144.3, 139.2, 129.6, 125.5, 107.0, 106.3, 61.2, 55.8, 33.4, 31.5, 28.3, 22.6, 14.2, 14.1. MS (EI+): m/z 360 (M+); HRMS (EI+): found 360.1942, calcd for [C$_{21}$H$_{28}$O$_5$]$^+$ 360.1937. IR: $\nu$ 2962, 2840, 1712, 1669, 1592, 1460, 1427, 1367, 1351, 1296, 1281 cm$^{-1}$. UV: $\lambda_{max}$ = 210, 325 nm.

**syn-ethyl 3-((E)-hept-1-enyl)-2,3-dihydro-4,6-dimethoxy-1-oxo-1H-indene-2-carboxylate (1.118).** $^1$H NMR (500 MHz): $\delta$ 6.77 (d, 1H, J = 2.0 Hz), 6.67 (d, 1H, J = 2.0 Hz), 5.51 (m, 2H), 4.28 (dd, 1H, J = 3.0 Hz, 7.0 Hz), 4.22 (q, 2H, J = 7.0 Hz), 3.84 (d, 1H, J = 3.0 Hz), 3.83 (s, 3H), 3.82 (s, 3H), 1.99 (quint, 2H, J = 7.0 Hz), 1.35-1.24 (m, 4H), 1.29 (t, 3H, J = 7.0 Hz), 0.87 (t, 3H, J = 7.0 Hz). $^{13}$C NMR (125 MHz): $\delta$ 199.3, 168.8, 161.8, 158.1, 138.4, 137.3, 132.5, 129.1, 106.7, 96.7, 61.8, 61.6, 55.9, 55.6, 43.5, 32.5, 31.3, 29.0, 22.6, 14.3, 14.2. MS (EI+): m/z 360 (M+); HRMS (EI+): found 360.1938, calcd for [C$_{21}$H$_{28}$O$_5$]$^+$ 360.1937. IR: $\nu$ 3525 (br), 2958, 2852, 1710, 1691, 1656, 1641, 1550, 1535, 1501, 1467, 1435, 1364, 1318 cm$^{-1}$. UV: $\lambda_{max}$ = 205, 310 nm.
3-((E)-hept-1-enyl)-2,3-dihydro-4,6-dimethoxyinden-1-one (1.119). To a 4-mL vial equipped with a stir bar was added 1.118 (12.5 mg, 34.7 μmol), lithium hydroxide monohydrate (7.27 mg, 173 μmol), THF (300 μL) and water (100 μL). The reaction mixture was stirred at 100 °C for 36 h. It was then cooled to 23 °C and quenched with 1 N HCl until the aqueous layer was acidic. The organic phase was diluted with ether (3 mL) and washed with brine (1 mL). It was then dried over MgSO₄, filtered through a plug, and concentrated by rotary evaporation. The residue was purified by silica gel chromatography (6:1 hexanes:ethyl acetate) to yield 6.6 mg (66%). ¹H NMR (500 MHz): δ 6.77 (d, 1H, J = 2.0 Hz), 6.65 (d, 1H, J = 2.0 Hz), 5.46 (m, 2H), 3.96 (t, 1H, J = 6.0 Hz), 3.83 (s, 3H), 3.82 (s, 3H), 2.94 (dd, 1H, J = 2.0 Hz, 19.0 Hz), 2.48 (dd, 1H, J = 19.0 Hz), 1.97 (sept, 2H, J = 6.5 Hz), 1.35-1.22 (m, 6H), 0.87 (t, 3H, J = 7.0 Hz). ¹³C NMR (125 MHz): δ 206.5, 161.5, 158.2, 139.5, 138.8, 131.2, 130.7, 105.9, 96.0, 55.9, 55.6, 44.7, 38.6, 32.4, 31.3, 29.2, 22.7, 14.2. MS (EI+): m/z 288 (M+); HRMS (EI+): found 288.1728, calcd for [C₁₈H₂₄O₃]⁺ 288.1725. IR: ν 3426 (br), 2957, 2924, 2853, 1716, 1683, 1652, 1635, 1616, 1558, 1506, 1456, 1435, 1361, 1320 cm⁻¹. UV: λmax = 215, 260, 325 nm.

1.13. References

(69) N. Müller, A. Falk, Ball & Stick 4.0a12, Molecular Graphics Software for MacOS, Johannes Kepler University: Linz, 2004.

Appendix I: Selected Spectra
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1.36 (CDCl₃, 100 MHz)
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1D NOESY with selected excitation at Ha
1D NOESY with selected excitation at Hb
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7:93
1.63b (CDCl₃, 1:25 MHz)

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1.63b (CDCl₃, 1:25 MHz)

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6.94

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6:9:4

+ [Structural formula]
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1.93b (CDCl3, 400 MHz)
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Appendix II: Calculations

All calculations described below were performed by Rebecca L. Davis in the labs of Dean Tantillo (University of California, Davis) with GAUSSIAN03. Structures were optimized without symmetry constraints at the B3LYP/6-31+G(d,p) level of theory. Frequency analyses were used to characterize each stationary point, and energies reported in the manuscript include zero-point corrections left unscaled. Solvent calculations were run using the CPCM method (solvent = toluene) with UAKS radii. Structural drawings were produced using Ball&Stick.

1.35 (B3LYP/6-31+G(d,p))

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1.35
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HF = -2392.0908486 hartrees (-1501060.92840499 kcal/mol)

Imaginary Frequencies: none found

Zero-point correction = 0.276665 (Hartree/Particle)

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Imaginary Frequencies: 1 (-402.9892 1/cm)

Zero-point correction = 0.275550 (Hartree/Particle)

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Sum of electronic and thermal Free Energies = -2391.82315

**1.51 (B3LYP/6-31+G(d,p))**

*NOTE: Reported energy difference is base on comparison between 13 and 13TS2.

HF = -2431.4012919 hartrees (-1525728.62468017 kcal/mol)

Imaginary Frequencies: none found

Zero-point correction = 0.304644 (Hartree/Particle)

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Sum of electronic and thermal Free Energies = -2431.156407

1.51 (alpha s-cis) (B3LYP/6-31+G(d,p))

![Chemical Structure](image)

HF = -2431.3995894 hartrees (-1525727.55634439 kcal/mol)
Imaginary Frequencies: none found

Zero-point correction = 0.304720 (Hartree/Particle)

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Sum of electronic and thermal Free Energies = -2431.154299 hartrees

1.51-TS (B3LYP/6-31+G(d,p))
*NOTE: 13TS is a conformational isomer of 13-TS2 in which the Lewis Acid is rotated

HF = -2431.3650104 hartrees (-1525705.8576761 kcal/mol)

Imaginary Frequencies: 1 (-354.0800 1/cm)

Zero-point correction = 0.303390 (Hartree/Particle)

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1.51 TS2

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Imaginary Frequencies: 1 (-347.6502 1/cm)

Zero-point correction = 0.303011 (Hartree/Particle)

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Sum of electronic and thermal Free Energies = -2431.118098
1.89 (B3LYP/6-31+G(d,p))

HF = -2431.4164746 hartrees (-1525738.15197625 kcal/mol)

Imaginary Frequencies: none found

Zero-point correction = 0.304316 (Hartree/Particle)

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1.89-TS (B3LYP/6-31+G(d,p))

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Imaginary Frequencies: 1 (-398.5878 1/cm)

Zero-point correction = 0.303549 (Hartree/Particle)

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Sum of electronic and thermal Free Energies= -2431.121889

1.90 (B3LYP/6-31+G(d,p))
HF = -2431.4110988 hartrees (-1525734.77860799 kcal/mol)

Imaginary Frequencies: none found

Zero-point correction = 0.304179 (Hartree/Particle)

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HF = -2431.4241012 hartrees (-1525742.93774401 kcal/mol)

Imaginary Frequencies: none found

Zero-point correction = 0.303268 (Hartree/Particle)

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1.90 (alpha s-cis) (B3LYP/6-31+G(d,p))
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Imaginary Frequencies: none found

Zero-point correction = 0.304430 (Hartree/Particle)

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Sum of electronic and thermal Free Energies = -2431.165568 hartrees

1.90-TS (B3LYP/6-31+G(d,p))

HF = -2431.3691904 hartrees (-1525708.4806679 kcal/mol)

Imaginary Frequencies: 1 (-363.3807 1/cm)

Zero-point correction = 0.303260 (Hartree/Particle)

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Sum of electronic and thermal Free Energies= -2431.124164

1.90-TS (B3LYP/6-31+G(d,p)) solv

HF = -2431.3869806 hartrees (-1525719.64419631 kcal/mol)

Imaginary Frequencies: 1 (-344.3473 1/cm)

Zero-point correction = 0.302453 (Hartree/Particle)

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1.92 (B3LYP/6-31+G(d,p))

HF = -2470.7330408 hartrees (-1550409.69043241 kcal/mol)

Imaginary Frequencies: none found

Zero-point correction = 0.332123 (Hartree/Particle)

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Sum of electronic and thermal Free Energies = -2470.463144
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HF = -2470.7315332 hartrees (-1550408.74439833 kcal/mol)

Imaginary Frequencies: 1 (-12.7078 1/cm)

Zero-point correction = 0.332104 (Hartree/Particle)

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Sum of electronic and thermal Free Energies = -2470.459610 hartrees
1.92-TS (B3LYP/6-31+G(d,p))

![Chemical structure diagram]

HF = -2470.6904531 hartrees (-1550382.96622478 kcal/mol)

Imaginary Frequencies: 1 (-362.4797 1/cm)

Zero-point correction = 0.331177 (Hartree/Particle)

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Sum of electronic and thermal Free Energies= -2470.419559

1.94 (B3LYP/6-31+G(d,p))

*NOTE: Energy difference between 19 and 19TS is a comparison of two different conformational isomers

![Chemical Structure]

HF = -2469.5201206 hartrees (-1549648.57087771 kcal/mol)

Imaginary Frequencies: none found

Zero-point correction = 0.313420 (Hartree/Particle)

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Sum of electronic and thermal Free Energies= -2469.265255

**1.94 (alpha s-cis) (B3LYP/6-31+G(d,p))**
HF = -2469.5165828 hartrees (-1549646.35087283 kcal/mol)

Imaginary Frequencies: none found

Zero-point correction = 0.313466 (Hartree/Particle)

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Sum of electronic and thermal Free Energies = -2469.261529 hartrees

HF = -2469.4749307 hartrees (-1549620.21376356 kcal/mol)

Imaginary Frequencies: 1 (-390.8435 1/cm)

Zero-point correction = 0.312522 (Hartree/Particle)

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Sum of electronic and thermal Free Energies = -2469.218706

Solvent:
Cyclization energy barriers of 15 and 16 were calculated with the continuous dielectric solvent model CPCM (solvent = toluene) with UAKS radii.

1.92 \((\text{B3LYP/6-31+G(d,p) toluene})\)
HF = -2470.7451818 hartrees (-1550417.30903132 kcal/mol)

Imaginary Frequencies: none found

Zero-point correction = 0.331524 (Hartree/Particle)

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Chapter 2: Initial Synthetic Studies into Tetrapetalone A: Formation of the C-N Bond

2.1. Elaborating the Nazarov Product

2.1.1. Cleavage of the Methyl Ethers

Our initial synthetic plan called for a Buchwald-Hartwig-type heteroatom coupling on an indanone such as 2.1 (Scheme 2.1). To do so, we needed to convert the methyl ether at C-14 to a halide or a halide equivalent. Therefore, it became necessary to differentiate the oxygens at the C-12 and C-14 positions.

Scheme 2.1. Hypothetical differentiation of the C-12 and C-14 oxygens.

It was our hope to be able to either selectively deprotect one of the hydroxyl groups at C-12 or C-14, or to be able to convert bis-ether 1.55b to bis-phenol 2.2 and selectively re-protect the hydroxyl group at C-12. The realization of either of these transformations would thus allow us to convert the hydroxyl group at C-14 to a triflate. In the event, exposure of indanone 1.55b to 6 equivalents of BBr$_3$ at -78 °C resulted in the formation of bis-phenol 2.2 (eq. 2.1). It was noted that upon quenching the reaction at room temperature, isomerization to tetrasubstituted olefin 2.3 was observed (Figure 2.1). When the reaction was quenched at 0 °C, this isomerization was not observed and bis-phenol 2.2 could be isolated in 60% yield. Using less than 6 equivalents of BBr$_3$ merely resulted in a mixture of starting material 1.55b, bis-phenol 2.3, and both of the intermediate phenols 2.4 and 2.5. Despite extensive effort, we were unable to optimize the deprotection conditions to selectively provide either 2.4 or 2.5.

Figure 2.1. Isomerization product and intermediates recovered from BBr$_3$ deprotection.

2.1.2. Forming a Bis-TBS-Protected Indanone
As we were unable to produce either 2.4 or 2.5 in reasonable yield, we constructed a new indanone (2.10, Scheme 2.2). To do so, we cleaved the two methyl ether groups of 1-bromo-3,5-dimethoxybenzene (1.37) by heating with hydroiodic acid. These conditions also led to exchange of the bromide for an iodide to produce bis-phenol 2.7; presumably, halide exchange occurs by a conjugate addition/elimination sequence via tautomer 2.6. Bis-phenol 2.7 was then doubly protected with TBSCI and imidazole; a subsequent lithium-halogen exchange on the bis-TBS ether and quenching of the intermediate anion with Weinreb amide 1.54 yielded aryl dienone 2.9. Following the protocol of our previous studies (see Chapter 1), aryl dienone 2.9 was exposed to 10 mol % AlCl$_3$ in toluene at 80 ºC to provide indanone 2.10 in 90% yield. While the combination of tetrabutylammonium fluoride (TBAF) and potassium carbonate led to the cleavage of both silyl groups, the use of potassium trimethylsilanolate produced mono-TBS-protected indanones 2.11 and 2.12 in 35% and 24% yield, respectively. Importantly, 2.11 and 2.12 were separable by silica gel chromatography. As an added bonus, these deprotection conditions also led to epimerization of the α-position to produce solely the anti diastereomer of each indanone.

**Scheme 2.2.** Formation of mono-TBS-protected phenols.
Phenol 2.11 was exposed to N-phenyltriflamide and Hünig’s base to produce triflate 2.13 in 92% yield (Scheme 2.3). We attempted to couple this compound directly with pyrrole using conditions reported by Buchwald; only decomposition was observed, however.

**Scheme 2.3.** Attempted C-N bond formations on triflate 2.13.

2.2. Functionalizing the δ-Position of the Dienone

2.2.1. Hydroboration/Oxidation of the Nazarov Product

As a result of our struggles in both differentiating between the C-12 and C-14 hydroxyl groups and effecting the C-N bond formation, we sought other means to install the atoms of the C and D rings of tetrapetalone A. To that end, we first looked at installing a hydroxyl group at the δ-position of the diene.

Exposure of indanone 1.55 to borane-dimethyl sulfide complex followed by quenching with hydrogen peroxide and 10% aqueous sodium hydroxide did convert 1.55 to a primary alcohol (eq. 2.2); the reaction conditions had the unintended side effect, however, of also reducing the carbonyl group to produce diol 2.15. This reduction proceeded with poor diastereoselectivity (approx. 1:1 dr) and, because the starting indanone 1.55 existed as a mixture of syn:anti diastereomers, produced an unacceptable mixture of four diastereomers which were inseparable by silica gel chromatography.

To circumvent this issue, indanone 1.55 was epimerized to primarily the anti diasteromer 1.55b (9:1 dr). This compound, in turn, was exposed to sodium borohydride, which led to selective reduction of the carbonyl group from the β-face of the molecule and placed the resulting hydroxyl and methyl groups in a syn relationship to provide alcohol 2.16 (Scheme 2.4). Alcohol 2.16 was then exposed to the same hydroboration-oxidation sequence as before, resulting in the formation of diol 2.15b as primarily one diastereomer.

Diol 2.15b was then subjected to sequential oxidation by Dess-Martin periodinane, yielding aldehyde 2.17, followed by Pinnick oxidation conditions, resulting in clean conver-
sion to carboxylic acid 2.18. At this stage, we hoped to be able to cleave the two methyl ethers at C-12 and C-14 and then use the carboxylic acid moiety to effect a lactonization of the hydroxyl group at C-14, which would allow us to differentiate the two hydroxyl groups. Unfortunately, exposure of 2.18 to BBr$_3$ at -78 °C resulted only in decomposition.

**Scheme 2.4.** Formation of δ-carboxylic acid 2.18 and unsuccessful methyl ether cleavage.

2.2.2. Building an Aryl Enone With a δ-Hydroxyl Group

We also examined the possibility of installing the δ-hydroxyl group prior to the Nazarov cyclization. To do so, we would need to build an aryl enone, rather than a dienone. Notably, such a system would be akin to a traditional Nazarov reaction, rather than the aryl dienone Nazarov described in Chapter 1.

To that end, we began with the mono-protection of 1,3-propanediol (2.19, Scheme 2.5). Treatment of 2.19 with $p$-methoxybenzyl chloride (PMBCl) and 1.0 equivalent of sodium hydride resulted in the formation of singly-protected alcohol 2.20. Swern oxidation conditions readily converted this compound to the aldehyde (2.21), which was then stirred at reflux with 1-carbethoxyethylidene triphenylphosphorane (2.22) to create α,β-unsaturated ester 2.23. We initially attempted to convert ester 2.23 to Weinreb amide 2.24 through the same protocol for the formation of Weinreb amides 1.36 and 1.54 for our Nazarov investigations. Upon attempted saponification of 2.24 to the corresponding acid, however (eq. 2.3), we instead observed decomposition of our substrate. Presumably, the strongly basic conditions of this reaction facilitate the elimination of $p$-methoxybenzyl alcohol (PMBOH).

**Scheme 2.5.** Formation of the δ-OPMB ester 2.23.
To circumvent the observed decomposition of 2.23 under saponification conditions, we employed a method to convert the ethyl ester to the Weinreb amide directly, using Me(OMe)NH·HCl and isopropylmagnesium chloride at -20 °C (eq. 2.4). This reaction proceeds by initial formation of the free base of the Weinreb amine, followed by deprotonation of the amine by a second equivalent of the Grignard reagent to create a chloromagnesiumamide species. This species then adds into ethyl ester 2.23, resulting in the formation of Weinreb amide 2.24 upon workup.

At this stage, lithium-halogen exchange of 1-bromo-3,5-dimethoxybenzene (1.37) followed by addition into our Weinreb amide was expected to produce our aryl enone Nazarov substrate (eq. 2.5). Curiously, this reaction failed to achieve any coupling, possibly due to the steric bulk of the Weinreb amide.
We were ultimately able to build aryl enone 2.27 by a sequence that employed aldehyde 2.25. This compound could be obtained in 57% yield by treatment of Weinreb amide 2.24 with diisopropylaluminum hydride (DIBAL-H). Alternatively, lithium aluminum hydride (LAH) reduction of ethyl ester 2.23, followed by Swern oxidation of the intermediate allylic alcohol provided 2.25 in 54% overall yield (Scheme 2.6). Aldehyde 2.25 proved to be a sufficient electrophile for the addition of the 1-lithio-3,5-dimethoxybenzene; oxidation of the resulting secondary alcohol (2.26) under Swern conditions produced aryl enone 2.27 in 73% yield.

Scheme 2.6. Formation of aryl enone 2.27.

Exposure of aryl enone 2.27 to 25 mol % AlCl₃ in toluene at 80 ºC failed to achieve conversion to the desired indanone (Figure 2.2). Concerned that the PMB group might be interfering with the Nazarov cyclization, we removed this protective moiety by treating 2.27 with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to produce primary alcohol 2.28. This compound, as well, failed to undergo Nazarov cyclization under the same reaction conditions. Oxidation of 2.28 to carboxylic acid 2.29 was attained through Jones oxidation conditions,⁸,⁹ this substrate was similarly unsuccessful in the Nazarov reaction, however.

Figure 2.2. Unsuccessful Nazarov substrates.

2.2.3. Using a TBS-Protecting Group on the δ-Hydroxyl
As difficulties emerged with conversion of aryl enones 2.27, 2.28 and 2.29 to their respective indanones, we adjusted their composition slightly. First, the PMB-protecting group was replaced with a TBS group (performed in the initial step of the synthetic sequence). Second, to make the sequence more amenable to the synthesis of tetrapetalone A, we revised our procedure to now begin with 2-methyl-1,3-propanediol (2.30, Scheme 2.7). The incorporation of the addi-
tional methyl group was important to test the viability of bringing in the C-19 methyl group at an earlier stage of the synthesis. γ-Methyl Weinreb amide 2.34 was synthesized in the same manner as 2.24 (eq. 2.4, vide supra). We were pleased to discover, however, that aryl enone 2.35 could be successfully created by quenching 1-lithio-3,5-dimethoxybenzene with 2.34 directly.

Scheme 2.7. Formation of aryl enone 2.35.

Nazarov cyclization was readily achieved upon exposure of 2.35 to 1.0 equivalent of AlCl₃ in toluene at room temperature, resulting in the formation of indanone 2.36 in 88% yield (eq. 2.6). It should be noted that there is now one additional stereocenter, as compared to indanone 1.55, thus creating four possible diastereomers (instead of two, not considering enantiomers). We had observed earlier that epimerization at the α-position could be effected by treatment with DBU in methanol; additionally, we had hoped that there would be some steric preference for either a syn or anti relationship between the β- and γ-hydrogens, due to the large bulk of the TBS group. If such a steric preference could be achieved, it might be possible to use the δ-oxygen atom to help coordinate a chiral catalyst en route to an enantioselective synthesis of tetrapetalone A. Unfortunately, under our standard Nazarov conditions, no such preference was observed and 2.36 was formed with approximately 1:1 dr at the γ-position. As the γ-stereocenter would eventually be converted to an sp² carbon, this became important only for clarity of the intermediate NMR spectra.
The silyl group of 2.36 was then cleaved with tetrabutylammonium fluoride (TBAF) and potassium carbonate to produce primary alcohol 2.37 (Scheme 2.8). This species was then oxidized to aldehyde 2.38 and exposed to BBr₃ at -78 ºC to cleave the two methyl ethers at C-12 and C-14. This sequence was successful in creating a mixture of diol 2.39 and lactol 2.40. Using the same strategy as with 2.2 (see Section 2.1.1), we attempted to selectively protect the oxygen at C-12. Unfortunately, all efforts to effect such a transformation resulted only in recovery of starting material.


Aldehyde 2.38 was oxidized to carboxylic acid 2.41, which was then exposed to BBr₃ at -78 ºC (Scheme 2.9). In this case, none of the lactone was observed, making differentiation of the aromatic hydroxyl groups non-trivial.

Scheme 2.9. Pinnick oxidation of aldehyde 2.38 and subsequent methyl ether cleavage.

Alternatively, we considered the possibility of appending the D-ring to the carboxylic acid at this stage, followed by attempting to close the C-ring concurrently with the C-N bond formation. A Friedel-Crafts acylation onto the 2-position of pyrrole would provide the requisite connectivity for the formation of our seven-membered ring. To that end, we formed the corresponding acid chloride of 2.41, which was followed by its addition to a solution of AlCl₃ and N-Boc-pyrrole (2.43, eq. 2.7). Unfortunately, no acylation was achieved, nor was any desired product observed when unsubstituted pyrrole (2.44) was used instead.
Acylation did occur, however, when pyrrole Grignard (generated in situ by the addition of isopropylmagnesium chloride to pyrrole)\textsuperscript{11} was used as the nucleophile, albeit in only 33% yield (Scheme 2.10). Alternatively, we attempted to effect this transformation by adding the acid chloride to a solution of pyrrole with zinc;\textsuperscript{12} this proceeded in a slightly depressed 20% yield. While we were able to cleave the two methyl ether groups of 2.45 using BBr\textsubscript{3}, we failed once again to effect the selective protection of the C-12 hydroxyl group.

**Scheme 2.10.** Acylation of carboxylic acid 2.41 with pyrrole.

2.2.4. Using an exo-Methylene at the γ-Position

In a similar vein to the strategy described above, we envisioned a sequence commencing with 2-methylene-1,3-propanediol (2.47, Scheme 2.11). In the case of 2.47, we hoped to eventually isomerize the exo-methylene to the Δ\textsuperscript{5,6} double bond of tetrapetalone A. Moreover, replacing the methyl group with a methylene would provide the added bonus of incorporating one fewer stereocenter in the Nazarov product 2.53 (Scheme 2.12). Toward this end, we constructed aryl dienone 2.52 by a procedure analogous to that employed for the synthesis of aryl enone 2.35 (Scheme 2.7, \textit{vide supra}).

**Scheme 2.11.** Construction of aryl dienone 2.52.
Exposure of dienone 2.52 to AlCl₃ produced indanone 2.53, which was deprotected with TBAF and oxidized under Swern conditions to achieve aldehyde 2.55 in 60% yield over three steps. Pinnick oxidation provided carboxylic acid 2.56 in 90% yield, which was then exposed to BBr₃ to produce diol 2.57. Rather than attempt to differentiate the hydroxyl groups as previously described, we opted to try to oxidize the aromatic ring system, which is described in the following section.

Scheme 2.12. Production of exo-methylene-bearing diol 2.57.

2.3. Oxidation of the Aromatic Ring System
Our original synthetic plan had called for a late-stage oxidation of the aromatic ring to unveil the p-quinol moiety of tetraketalone A. We had anticipated that this functionality would be somewhat unstable; indeed, Pettus\textsuperscript{13,14} and others\textsuperscript{15-19} have employed a series of oxidative dearomatization reactions to generate compounds of this type that can subsequently serve as excellent dienophiles in Diels-Alder cycloadditions, for example. Despite the potential lability of these species, we considered the possibility of performing the phenol oxidation at an earlier stage and exploiting the propensity of the resulting dienone to serve as a Michael acceptor as a means to install the nitrogen at C-14 via a conjugate addition/elimination sequence (see Scheme 2.13). With appropriate Lewis acid promotion, the newly-formed conjugate addition product (2.59) could be envisioned to undergo an intramolecular acyl transfer event to form the seven-membered ring, generating ketone 2.60 and leaving the p-quinol moiety intact.

Scheme 2.13. A potential conjugate addition into an oxidized aromatic system.

2.3.1. CAN Oxidation

Ceric ammonium nitrate is a single electron oxidant that is commonly used in oxidative dearomatizations.\textsuperscript{20} Cerium, as an f-block metal, is most stable as cerium (III), whereas the cerium in CAN is cerium (IV) and thus has a strong propensity to accept an electron, particularly from electron-rich aromatic systems. Exposure of indanone 1.55b to CAN in CH$_3$CN/H$_2$O led to a mixture of products which included p-quinol 2.61 (eq. 2.8), thereby providing us with a proof of concept for this transformation.

We next attempted this oxidation on bis-phenol 2.39, with the expectation that the aldehyde could trap the created partial positive charge at the para-position, allowing for a potentially stable intermediate that could be tested as a conjugate addition substrate. Unfortunately, upon exposure of 2.39 to CAN, only decomposition was observed (eq. 2.9). Similar oxidations were also attempted on aldehyde 2.38 and carboxylic acid 2.41 (eqs. 2.10 and 2.11), but in these cases only starting material was recovered.
2.3.2. Hypervalent Iodine Oxidation

Due to its position in the fifth row of the periodic table, iodine can more readily attain high oxidation states than the other halides. As a result, a number of hypervalent iodine oxidants have been developed for various purposes.\textsuperscript{21-27} For example, iodoxybenzoic acid (IBX, \textsuperscript{2.62}, Figure 2.3) and the Dess-Martin periodinane (\textsuperscript{2.63}) can be used to oxidize alcohols to ketones; these reagents have been utilized heavily in organic synthesis, particularly in the later stages of a total synthesis, when functionalities elsewhere on the molecule may be sensitive to harsher metal- or DMSO-based oxidation conditions. More in line with our particular synthetic requirements, several hypervalent iodine compounds have been developed for the purpose of oxidative dearomatization. In particular, diacetoxyiodobenzene (PIDA, \textsuperscript{2.64}) and [bis(trifluoroacetoxy)iodo]benzene (PIFA, \textsuperscript{2.65}) have been used extensively to effect such transformations.
Aldehyde 2.39, carboxylic acid 2.57 and alcohol 2.66 were all separately exposed to PIFA; in none of the cases was oxidative dearomatization observed (eqs. 2.12-2.14). Curiously, while heating alcohol 2.66 in the presence of PIFA failed to oxidize the aromatic ring, oxidation of the α-position of the indanone was instead observed. It appears that mechanistically, the iodine must coordinate to the carbonyl oxygen rather than the methyl-protected aromatic oxygens, thus promoting oxidation of the enolate.

2.3.3. Silver (II) Oxide

Rapoport reported that silver (II) oxide in the presence of 6 N HNO₃ can be used for the oxidative dearomatization of methyl ethers. These conditions presented an opportunity for us, as this would allow us to avoid a separate cleavage of the methyl ethers prior to oxidation, thus
shaving a step off the synthesis. Yet even under these harsh conditions, only starting material was observed when aldehyde 2.38 was used as the substrate (eq. 2.16). Exposure of alcohol 2.37 or carboxylic acid 2.41 to silver (II) oxide, however, produced ether 2.68 and lactone 2.58 respectively (eqs. 2.17-2.18). Interestingly, carboxylic acid 2.42 failed to undergo conversion to the corresponding lactone (eq. 2.19); it appears that the methyl ethers are actually necessary to effect the oxidation.

\[
\begin{align*}
\text{AgO, 6 N HCl} & \quad \text{dioxane, rt} \\
\text{2.38} & \quad \text{N. R.} \\
\end{align*}
\]

\[
\begin{align*}
\text{AgO, 6 N HCl} & \quad \text{dioxane, rt} \\
\text{2.37} & \quad \text{2.68} (19\%) \\
\end{align*}
\]

\[
\begin{align*}
\text{AgO, 6 N HCl} & \quad \text{dioxane, rt} \\
\text{2.41} & \quad \text{2.58} (42\%) \\
\end{align*}
\]

\[
\begin{align*}
\text{AgO, 6 N HCl} & \quad \text{dioxane, rt} \\
\text{2.42} & \quad \text{N. R.} \\
\end{align*}
\]

2.4. A Mukaiyama-Michael Approach

Another approach to installing the carbons of the C- and D-rings of tetrapetalone A was to disconnect the molecule between C-6 and C-7, taking it back to indenone 2.69 and pyrrole 2.70 (Scheme 2.14). Conceivably, these two pieces could be linked together through a Mukaiyama-Michael addition of the corresponding silyl enol ether of 2.70 into the indenone.\(^{30-35}\) As there would inherently be no stereochemical information contained in the achiral indanone or pyrrole fragments, we hoped to be able to employ a chiral catalyst to achieve an enantioselective addition into the \(\beta\)-position of 2.69.\(^{31-33,35}\) While kinetic protonation of the intermediate enolate would likely result in a \textit{syn} relationship between the \(\alpha\)- and \(\beta\)-hydrogens, our previous work (see Section 1.9) suggested that we should be able to epimerize the \(\alpha\)-position to provide the desired, thermodynamically-favored \textit{anti} relationship.
2.4.1. Building the Indenone Fragment

Treatment of 1-bromo-3,5-dimethoxybenzene (1.37) with n-butyllithium followed by quenching the resulting anion with methacrolein (1.39) led to secondary alcohol 2.71 (Scheme 2.15). We attempted to oxidize 2.71 using the Swern conditions but found only 37% recovery of the enone, with sulfide 2.74 constituting the remainder of the mass balance. The formation of 2.74 presumably occurs after the initial oxidation of 2.71, and can be rationalized by the addition of dimethylsulfide (DMS) into the enone to give intermediate species 2.73, which is then demethylated in a Krapcho-like fashion.

We discovered that immediate chromatography (after workup) of the Swern reaction prevented formation of 2.74 (Scheme 2.16). Our initial attempts to effect the Nazarov cyclization of enone 2.72 were only moderately successful; exposure of 2.72 to AlCl₃ produced indanone 2.75 in only 35% yield. Along with the desired Nazarov product, we also observed the formation of product 2.76 in 12% yield, which likely occurs through a Michael addition of the intermediate enolate generated from the Nazarov cyclization into the starting enone 2.72. We hypothesized that we could disfavor the Michael addition product by slow addition of the enone to the reaction mixture. In the event, it was found that syringe pump-addition of enone 2.72 to a suspension of AlCl₃ in toluene over a 10 h period provided indanone 2.75 in 63% yield.
To form the desired indenone, we initially examined Saegusa-Ito oxidation conditions.\(^{36,37}\) Conversion of indanone 2.75 to the corresponding silyl enol ether was effected by treatment with lithium diisopropylamide (LDA) and quenching the resulting enolate with chlorotrimethylsilane (TMSCl). The crude product was then exposed to palladium (II) acetate in DMSO under an O\(_2\) balloon; only indanone 2.75 was recovered, however.

We next attempted to form the \(\alpha\)-bromoindanone (2.77) by treating 2.75 with bromine in methanol (eq. 2.20). These conditions led to clean bromination of the starting indanone; unfortunately, the bromine atom was installed on the electron-rich aromatic ring to produce aryl bromide 2.78.

We could achieve the desired result by first treating 2.75 with LDA and subsequently quenching with N-bromosuccinimide (NBS); we observed only 14% conversion to 2.69, however, with 83% recovery of the starting indanone (Scheme 2.17). We reasoned that a stronger base might accomplish this transformation to a greater degree. Indeed, the use of lithium 2,2,6,6-tetramethylpiperidine (LiTMP) in place of LDA resulted in complete conversion of indanone 2.75 to \(\alpha\)-bromoindanone 2.77. Treatment of 2.77 with DBU then generated indenone 2.69 in 53% yield over the two steps.
Scheme 2.17. Formation of indanone 2.69 through α-bromination.

\[
\begin{align*}
\text{MeO} & \quad \text{LiTMP, NBS} \\
\text{OMe} & \quad \text{THF, -78 °C} \\
\text{OMe} & \quad \text{DBU} \\
\text{CH}_2\text{Cl}_2, \text{rt} & \quad (53\% \text{ over two steps})
\end{align*}
\]

2.4.2. Building the Pyrrole Fragment

With the key indanone in hand, we turned our attention to the construction of an appropriate pyrrole coupling partner that could be employed in a Mukaiyama-Michael addition. Beginning with pyrrole (2.44), treatment with trichloroacetyl chloride formed 2-acylpyrrole 2.79 in 70% yield (Scheme 2.18). We hoped to be able to install the C-2 methyl group on the D-ring of tetrapetalone A prior to the Mukaiyama-Michael addition, which would mean methylating at the 4-position of pyrrole 2.79. This was not possible to do directly (treatment of 2.79 with iodomethane returned only the starting material); we were able to form 4-bromopyrrole 2.80 in 93% yield, however, by treating 2.79 with bromine in chloroform.

Scheme 2.18. Formation of 4-bromopyrrole 2.80.

\[
\begin{align*}
\text{H} & \quad \text{Cl} \quad \text{CCl}_3 \\
\text{N} & \quad \text{Et}_2\text{O, rt} (70\%) \\
\text{CCl}_3 & \quad \text{Br}_2 \quad \text{CHCl}_3, 0 \text{ °C} (93\%)
\end{align*}
\]

We then treated 2.80 with a solution of sodium methoxide to produce ester 2.81 (Scheme 2.19). After benzyl protection of the pyrrole nitrogen, we attempted to exchange the 4-bromo group for a methyl group. Treatment of 2.82 with either t-BuLi or n-BuLi, followed by quenching with iodomethane, led either to recovery of starting material or addition of the alkyl lithium species into the ester moiety, with only trace amounts of the desired methylated product observed. The use of Suzuki conditions with trimethylboroxine produced approximately a 30% conversion to the desired product; pyrrole 2.84 was inseparable from the starting material 2.82, however.

Scheme 2.19. Attempted methylations of pyrrole 2.82.
In an alternative sequence, pyrrole (2.44) was treated with \(N, N\)-dimethylpropionamide in the presence of phosphorous oxychloride to produce 2-acylpyrrole 2.85 in 54% yield (Scheme 2.20).\(^4\) This compound was then regioselectively brominated at 4-position by subjecting it to bromine in acetic acid. Following Boc-protection of pyrrole 2.86 to generate carbamate 2.87, we attempted to convert this species to the 4-methylpyrrole by treatment with trimethylindium,\(^4\) but were met only with decomposition.

Scheme 2.20. Formation of 2-propionylpyrrole 2.85 and attempted 4-methylation.

With our struggles in producing a viable 4-methyl-2-acylpyrrole derivative for the Mukaiyama-Michael reaction, we decided to attempt the key reaction without the 4-methyl group in place. To that end, treatment of 2.85 with Boc-anhydride produced \(N\)-Boc-pyrrole 2.88, which was then converted to silyl enol ether 2.89 (Scheme 2.21). Careful addition to indanone 2.69 at -78 °C in the presence of boron trifluoride diethyl etherate resulted in the recovery of starting material. Similarly, no Michael product was observed when the reaction was run with \(\text{AlCl}_3\) as the Lewis acid.
Scheme 2.21. Attempted Mukaiyama-Michael addition.

2.4.3. Alternate Uses For Indenone 2.69

Our struggles with the reactivity of the pyrrole fragment led us to explore other strategies involving indenone 2.69. We first attempted cleavage of the aromatic methyl ethers of 2.69 using BCl$_3$. To our surprise, no cleavage was observed; rather, the dimeric species 2.90 was the sole recovered product (eq. 2.21). It is noted that this result is consistent with similar reactivity observed previously in the literature for related indenones.$^{42}$

We also attempted to perform a Nagata cyanation on indenone 2.69.$^{43}$ Addition of diethylaluminum cyanide to 2.69 at -78 ºC, followed by quenching with triethylamine and triethylsilyl chloride produced silyl enol ether 2.91, albeit only in 15% yield (eq. 2.22). We were unable to optimize this route, however, and this sequence was set aside.

2.5. Differentiation of the C-12 and C-14 Positions Prior to the Nazarov Cyclization

Most of our efforts had focused on the differentiation of the C-12 and C-14 positions after the Nazarov cyclization. As the ortho positions in aryl dienone 1.51 are chemically equivalent, a single regioisomer is necessarily obtained following Nazarov cyclization. We had hoped that the chemical environments of the two methoxy groups in 1.55 would be different enough
such that they could be differentiated, but this task proved to be quite challenging (see Section 2.1).

Alternatively, we considered the possibility of differentiating the two positions before performing the Nazarov cyclization (see Figure 2.4). While this could potentially lead to a mixture of two regioisomers, it would solve the problem of chemical differentiation of the C-12 and C-14 positions if one regioisomer could be favored over the other.

Figure 2.4. Two regioisomers are possible with differentiation at C-12 and C-14.

2.5.1. Silyl Protection of One Hydroxyl Group

To build a series of non-symmetric substrates for the Nazarov cyclization, we began with 1,3-dibromo-5-methoxybenzene (2.95). Subjecting this species to n-BuLi and trimethylborate followed by in situ treatment with hydrogen peroxide and aqueous sodium hydroxide solution produced phenol 2.96 in 82% yield (Scheme 2.22). Standard silyl protection conditions produced compounds 2.97, 2.98 and 2.99, which were each coupled with Weinreb amide 2.34 to create aryl enones 2.100, 2.101 and 2.102.

Scheme 2.22. Construction of meta-differentiated aryl enones 2.100-2.102.

Each aryl enone was subjected to 1.0 equivalent of AlCl₃ in toluene at room temperature. It was our supposition that the ortho positions of these aryl enones should be virtually equivalent electronically, and that any observed regioselectivity would be due to steric effects as a result of the bulk of the silyl group. We noted, however, that at best, a regioisomeric ratio of 2:1 was observed (Scheme 2.23), which we deemed unacceptable for the purposes of the total synthesis. Curiously, the ratio appeared to deteriorate with increasing size of the silyl group. Although
these results contrasted with our initial hypothesis, they served to demonstrate that a differentiation of the two meta positions on the basis of steric effects would likely be prohibitively difficult.


![Diagram showing the reaction scheme for Nazarov cyclization of silyl-protected aryl enones](image)

\textbf{2.5.2. Exchange of One Hydroxyl Group for a Bromide}

In addition to exploring a steric differentiation of the two meta positions of the Nazarov substrate, we also examined the possibility of an electronic differentiation. As we ultimately needed to convert the C-14 group to a halide or halide equivalent, we chose to examine the feasibility of starting with a bromide already in place at one of the meta positions.

To form the requisite Nazarov substrate, we again started with 1,3-dibromo-5-methoxybenzene (2.95). A direct coupling of the corresponding lithio species to Weinreb amide 2.34 readily provided aryl enone 2.109 in 91% yield (Scheme 2.24). Exposure of 2.109 to AlCl$_3$ in toluene at room temperature did lead to partial conversion to an indanone species. Analysis of the resulting crude product was complicated, however, by partial cleavage of the silyl protecting group, and it was difficult to discern whether we were achieving any preference for one regiomer over the other. Moreover, prolonged exposure of 2.109 to AlCl$_3$ did not appear to drive the reaction further toward completion; rather, we merely observed silyl cleavage to a greater extent.

\textbf{Scheme 2.24.} Unsuccessful Nazarov cyclization of meta-bromo-containing aryl enone 2.109.
To obviate the issue of undesired silyl ether deprotection, we examined a substrate derived from our original Weinreb amide 1.54 (Scheme 2.25). Exposure of aryl dienone 2.110 to AlCl3 in toluene at room temperature produced a 13:1 mixture of indanones 2.111 and 2.112 in 79% yield. The connectivity of the major indanone 2.111 was confirmed by exposure to t-BuLi followed by quenching with H2O; the 1H NMR spectra for the resulting desbromo-indanone matched that expected for 2.113.

Scheme 2.25. Successful Nazarov cyclization on regio-differentiated aryl dienone 2.110.

We rationalize the regioselective Nazarov cyclization of 2.110 by considering the electronics of both the methoxy and bromo substituents on the aromatic ring. Resonance donation by an oxygen lone pair should not be a factor, as both ortho positions should experience this influence approximately equally. Rather, the key difference lies in the greater inductive withdrawing ability of the methoxy group relative to the bromo group.44 Due to its greater distance from this
substituent, the position \textit{para} to the methoxy group should be more electron-rich than the \textit{ortho} position (Figure 2.5). If the cyclization is considered in a stepwise manner, attack onto the \(\beta\)-position of the Lewis acid-activated dienone will occur preferentially from the \textit{para} carbon.

![Figure 2.5. 2.110a is preferred to 2.110b due to greater electron density at the position \textit{para} to the methoxy group over the \textit{ortho} position.](image)

\textbf{2.6. Epimerization of Indanone 2.111}

With indanone 2.111 in hand, we could now begin to explore the formation of the aromatic C-N bond with our bromide as a viable handle. Before we could do this, however, it was first necessary to epimerize the \(\alpha\)-position to produce an \textit{anti} relationship between the methyl and isopropenyl groups, as described in section 1.9, since indanone 2.111 had been recovered from the Nazarov reaction as a 9:1 mixture of \textit{syn:anti} diastereomers. Exposure of indanone 2.111 to 0.2 equivalents DBU in methanol (the same conditions applied in section 1.9) resulted in a 43% recovery of a 4:1 mixture of \textit{anti:syn} diastereomers; unfortunately, the remainder of the mass balance was lost to non-specific decomposition. It appeared that the choices of both DBU and methanol were problematic (Table 2.1), as any attempts to perform the epimerization with these substances present resulted in low recovery of the \textit{anti} product. After a small screen of conditions, we found that the use of potassium carbonate in dioxane at 80 °C resulted in nearly quantitative recovery of a 4:1 mixture of \textit{anti:syn} diastereomers. This value appeared to be the thermodynamic ratio of epimers, as prolonged reaction times or increased temperature did not result in any improvement in the dr. Similarly to the compounds described in Chapter 1, 2.111a and 2.111b were not separable by column chromatography and were thus carried through further synthetic manipulations as a mixture.

\textbf{Table 2.1. Epimerization of indanone 2.111.}

![Table 2.1](image)
2.7. Attempts to Form the C-N Bond

2.7.1. Screening Conditions on Indanone 2.111b

Metal-mediated cross-coupling reactions have become powerful tools in the arsenal of synthetic chemists for the purpose of forming carbon-carbon bonds. Nevertheless, the formidable challenge of forming carbon-heteroatom bonds via cross-couplings has only started to be addressed within the last 15 years. Buchwald and Hartwig have been at the forefront of this research, primarily by developing new palladium- and copper-based catalyst systems for C-O and C-N bond formation.

We first examined the possibility of using succinimide (2.114) or 2-pyrrolidinone (2.115) as nitrogen sources for the cross-coupling, reasoning that if we could incorporate the D-ring with an appropriately placed amide, it would provide an avenue to generate an N-acyliminium intermediate (a strategy we considered for closure of the C-ring, see section 3.1, vide infra).

Attempted coupling of 2.111b with either succinimide or 2-pyrrolidinone in the presence of tris(dibenzylideneacetone)dipalladium (0) (Pd$_2$(dba)$_3$) and Xantphos (2.116) did not produce any reaction (eq. 2.23). To test these conditions with an amide substrate that has been reported in the literature, we attempted to couple 2.111b with the tert-butyl ester of alanine (2.117). Under the previously employed conditions, however, no C-N bond formation occurred, and some isomerization of the terminal double bond was observed. This coupling was also attempted under copper iodide-mediated conditions without any added ligand (eq. 2.24), but only starting material was observed.

\[
\text{MeO} \quad \text{HNR}_2 \quad \text{Cs}_2\text{CO}_3, \text{Pd}_2(\text{dba})_3, \text{Xantphos} \quad \text{N. R.} \quad \text{dioxane, 100 ºC} \\
\text{N} \quad \text{O} \quad \text{Me} \quad \text{O} \quad \text{Me} \quad \text{HNR}_2 = \text{O} \quad \text{O} \quad \text{H}_2\text{N} \quad \text{Me} \quad \text{O} \quad \text{Xantphos (2.116)}
\]

<table>
<thead>
<tr>
<th>conditions</th>
<th>ratio (2.111a:2.111b)</th>
<th>recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.2 equiv DBU, MeOH, rt</td>
<td>1:4</td>
<td>43% (remainder decomposition)</td>
</tr>
<tr>
<td>1.0 equiv K$_2$CO$_3$, benzene, rt</td>
<td>4.5:1</td>
<td>approx. 95%</td>
</tr>
<tr>
<td>benzene, 70 ºC</td>
<td>9:1</td>
<td>approx. 95%</td>
</tr>
<tr>
<td>1.0 equiv DBU, benzene, rt</td>
<td>1:4</td>
<td>approx. 15% (remainder decomposition)</td>
</tr>
<tr>
<td>1.0 equiv K$_2$CO$_3$, benzene, 70 ºC</td>
<td>1:3.5</td>
<td>approx. 95%</td>
</tr>
<tr>
<td>1.0 equiv DBU, benzene, 70 ºC</td>
<td>1:4</td>
<td>approx. 15% (remainder decomposition)</td>
</tr>
<tr>
<td>1.0 equiv NaOMe, MeOH/CH$_2$Cl$_2$, rt</td>
<td>1:3</td>
<td>approx. 40% (remainder decomposition)</td>
</tr>
<tr>
<td>1.0 equiv NaOMe, MeOH/benzene, rt</td>
<td>1:3</td>
<td>approx. 40% (remainder decomposition)</td>
</tr>
<tr>
<td>0.5 N HCl, THF/H$_2$O, 80 ºC</td>
<td>1:4</td>
<td>approx. 80% (remainder decomposition)</td>
</tr>
<tr>
<td>1.0 equiv K$_2$CO$_3$, toluene, 100 ºC</td>
<td>1:2</td>
<td>81%</td>
</tr>
<tr>
<td>1.0 equiv K$_2$CO$_3$, dioxane, 80 ºC</td>
<td>1:4</td>
<td>95%</td>
</tr>
</tbody>
</table>
2.7.2 Boronic Acid-Mediated C-N Formations

In addition to the numerous examples presented by Buchwald and Hartwig involving aryl halides, Chan and Lam have reported the copper-mediated coupling of aryl boronic acids with a variety of nitrogen-containing substrates, such as pyrimidines, purines, triazoles, pyrazoles (Scheme 2.26).


To examine the applicability of these conditions to our system, we constructed a boronic acid from 1,3-dibromo-5-methoxybenzene (2.95). Treatment of 2.95 with n-BuLi, followed by quenching with trimethylborate and subsequent hydrolysis, led to a mixture of boronic acid 2.126 and boroxine 2.127 (Scheme 2.27). Although it was difficult to purify the boronic acid on small scale, both boronic acids and boroxines have been shown to be viable substrates in the Chan-Lam reaction. As such, the crude mixture was exposed to copper (II) acetate along with Hüning’s base and pyrrole (2.44), but no C-N bond formation was observed. Switching the nucleophile, however, from pyrrole to the previously described 2-acylpyrrole 2.85 under otherwise identical conditions produced N-arylpyrrole 2.128 in 35% yield. Similarly, pyrrolidine (2.129) was successfully coupled to boronic acid 2.126 with the use of copper (II) acetate, palmitic acid and 2,6-lutidine.

Scheme 2.27. Successful C-N bond formations with boronic acid 2.126.
We sought to achieve the installation of a boronic acid at the C-14 position on \( \text{2.95} \) at the C-14 position, to attempt the C-N bond formations reported by Chan and Lam on a more complex system. Upon sequential exposure of indanone \( \text{2.111b} \) to \( t \)-BuLi and trimethyl borate, some des-bromo product was observed, but no boronic acid was recovered (Scheme 2.28). Although we were able to cross-couple \( \text{2.111b} \) with pinacolborane into this position to create boronic ester \( \text{2.131} \), treatment of this species with sodium periodate in an attempt to effect cleavage to the boronic acid\(^{56} \) led only to decomposition.

**Scheme 2.28.** Unsuccessful attempt to form the boronic acid at C-14 of \( \text{2.111b} \).
2.7.3. Reduction of the Ketone and Subsequent Protection

An attempt to form the C-N bond using Pd(P(t-Bu)_3)2 with zinc hexamethyldisilazide\(^57\) led to the identification of what appeared to be an imine-containing species, with none of the desired C-N bond formation observed. This led us to consider the possibility that the carbonyl group might be interacting unfavorably with the various nitrogen sources employed in our other cross-coupling attempts. We had initially chosen to keep this moiety in place due to the desire to avoid any unnecessary protecting group manipulations, in addition to the hope that we could further epimerize a future compound to provide an improved diastereomeric ratio. At this stage, however, it became obvious that subsequent chemistry would be adversely affected by the presence of the carbonyl group.

To that end, we reduced indanone \(2.111b\) with sodium borohydride in methanol to provide indanol \(2.132a\) (eq. 2.25). The major indanone diastereomer was reduced solely from the \(\beta\)-face of the molecule, producing a \textit{syn} relationship between the resultant hydroxyl group and the adjacent methyl group. Reduction of the minor diastereomer \(2.111a\) resulted in approximately a 1:1 mixture of the all \textit{syn} indanol \(2.132b\) and \textit{anti-syn} indanol \(2.132c\) (eq. 2.26).

The diastereoselectivity of this reduction can be rationalized by the avoidance of a steric clash with the \(\alpha\)-methyl group during the delivery of the hydride (Figure 2.6). Additionally, a torsional steering argument can be made in which hydride delivery from the \(\alpha\)-face would result in an eclipsing interaction in the transition state between the C-O bond and the adjacent C-H bond. Such an interaction is avoided when hydride delivery occurs from the \(\beta\)-face. It should be noted that the relative stereochemistry of the hydroxyl group is incorrect with respect to the stereochemistry of tetrapetalone A. Several methods exist, however, for the inversion of hydroxyl group stereochemistry (such as the Mitsunobu reaction), so this issue could be addressed at a later stage of the synthesis.
Figure 2.6. Hydride delivery into indanone 2.111b occurs diastereoselectively from the β-face.

Silyl protection of alcohol 2.132 was first attempted with TBSCl and imidazole at room temperature; no reaction was observed, however. We could effect silylation of 2.132 with chlorotriethylsilane (TESCl) at room temperature (eq. 2.27), or by heating at 80 ºC with TBSCl (eq. 2.28). Interestingly, it appeared that a slight improvement in the diastereomeric ratio occurred during TBS-protection, from 4:1 to 5.5:1. This could possibly be the result of a faster rate of reaction in the protection step for the desired diastereomer relative to the undesired minor diastereomers. Both the TES-protected and TBS-protected indanols 2.133 and 2.134 were used in further C-N bond formation studies.

2.7.4. Attempts to Form the Boronic Acid From the Protected Indanol

We attempted to form the boronic acid by exposing TES-indanol 2.133 to either n-BuLi or t-BuLi, followed by quenching with trimethyl borate; only trace amounts of the desired boronic acid were formed, however. Quenching the intermediate aryl anion with borolane 2.135 led to the formation of pinacolboronic ester 2.136, but we were again unable to hydrolyze the ester to the corresponding boronic acid using sodium periodate (Scheme 2.29). Attempts to form the boronic acid by transferring the pinacol moiety to a different boronic acid similarly failed.

Scheme 2.29. Unsuccessful attempt to form the boronic acid at C-14 of 2.133.
2.7.5. Palladium-Mediated C-N Bond Formation Attempts on the Protected Indanol

A variety of palladium-mediated C-N bond formations were attempted with 2-pyrrolidinone as the nitrogen source (Scheme 2.30). Xantphos (2.116), JohnPhos (2.138) and (±)-BINAP (2.139) were all employed as ligands, with only starting material observed. Additionally, Hartwig’s zinc hexamethyldisilazide method was attempted, leading to decomposition (eq. 2.29).

Scheme 2.30. Failed Pd-mediated C-N bond formations with aryl bromide 2.133 and 2-pyrrolidinone 2.115.
2.7.6. Attempted Ullmann Couplings on the Protected Indanol

We attempted to form the C-N bond with succinimide as the nitrogen source with both copper (0) powder and copper (I) thiophene carboxylate (CuTC, 2.140, Scheme 2.31) but in both cases, only desilylation of the starting material was observed. We also examined the use of copper (I) iodide with dimethylcyclohexanediamine (2.141) as a ligand, as well as copper (II) oxide with iron (III) acetylacetonate, \(^{59}\) and again observed exclusively desilylation.

**Scheme 2.31.** Attempted Ullmann couplings with aryl bromide 2.133.

We also considered the possibility of using the azide anion as our nitrogen source. If azide could be incorporated into the molecule, we could potentially reduce this species to the corresponding free amine and elaborate the nitrogen from there. With sodium azide as the nucleophile, we attempted cross-coupling of 2.133 using copper (I) iodide and sodium ascorbate, with dimethylcyclohexanediamine (2.141) as a ligand (eq. 2.30), \(^{60}\) but these conditions did not produce any reaction. Switching the ligand to L-proline, \(^{61}\) however, led to the recovery of aryl azide 2.142 in 13% yield, with starting material constituting the remainder of the mass balance.
2.7.7. Incorporating Nitrogen Using an Electrophilic Azide Source

Although we were able to achieve small amounts of 2.142 using CuI with L-proline, we also considered the possibility of forming the C-N bond by using an electrophilic nitrogen source. We performed a lithium-halogen exchange on aryl bromide 2.134 and attempted to quench the resulting anion with N-nitropyrazole in an attempt to incorporate a nitro group; only an unidentified compound was recovered, however. Gratifyingly, performing the analogous reaction with tosyl azide led to an 84% recovery of aryl azide 2.143, which was inseparable from the des-bromo product 2.144 (Scheme 2.32). We were able to reduce this azide to aniline 2.145 by treatment with either triphenylphosphine and water or lithium aluminum hydride (LAH). At this stage, we were able to separate the diastereomers that had been carried through by silica gel chromatography. The LAH reduction has been performed on multi-gram scale with no deterioration in yield, providing a robust method for the production of aniline 2.145a.

Scheme 2.32. Formation of aniline 2.145 via aryl azide formation.

2.8. Conclusion

The development of a Nazarov cyclization of aryl dienones has been applied to the synthesis by creating an unsymmetrical aryl substrate in a regioselective Nazarov reaction. The aryl bromide has been converted to the free amine through a lithium-halogen exchange followed by quenching with tosyl azide and reduction with lithium aluminum hydride. In Chapter 3, the application of the aniline toward the total synthesis of tetrapetalone A is described.
2.9. Experimental Methods

Unless otherwise stated, reactions were performed in flame-dried glassware sealed with rubber septa under a nitrogen atmosphere using dry solvents. Tetrahydrofuran (THF) and ether were distilled over sodium/benzophenone ketyl; dichloromethane, toluene, benzene and acetonitrile were distilled over calcium hydride; 1,4-dioxane was obtained from a Seca Solvent System by GlassContour (solvent dried over alumina under a \( \text{N}_2 \) atmosphere). Reaction temperatures were controlled by an IKAmag® temperature modulator. Determinations of pH were obtained by Color pHas® Indicator Strips pH = 0 – 14. Thin layer chromatography was performed using SiliCycle silica gel 60 Å F-254 precoated plates (0.25 mm) and visualized by UV and either anisaldehyde or ceric ammonium molybdate (CAM) stain. Sorbent silica gel 230-400 mesh (particle size 0.040 – 0.063 mm) was used for flash chromatography. \(^1\)H NMR spectra were recorded on Bruker spectrometers (at 300, 400, 500 and 600 MHz), as were \(^{13}\)C NMR (at 75, 100, 125 and 150 MHz, respectively). Chemical shifts (\( \delta \) ppm) are reported relative to Me\(_4\)Si (\( \delta = 0.0 \)) or CHCl\(_3\) (\( \delta = 7.26 \) for \(^1\)H NMR and \( \delta = 77.2 \) for \(^{13}\)C NMR). Data for \(^1\)H NMR are reported as follows: chemical shift (\( \delta \) ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, dd = doublet of doublets, dt = doublet of triplets, dq = doublet of quartets, m = multiplet, br = broad), integration and coupling constant (Hz). IR spectra were recorded on a Nicolet MAGNA-IR 850 spectrometer and are reported in frequency of absorption (cm\(^{-1}\)). Both low and high resolution mass spectra were obtained from the University of California, Berkeley Mass Spectral Facility.

![1,3-dibromo-5-methoxybenzene](image)

1,3-dibromo-5-methoxybenzene (2.95).\(^{62}\) To a 500-mL Schlenk flask equipped with a stir bar was added 98% 1,3,5-trimethoxybenzene (17.2 g, 53.4 mmol) and DMF (100 mL). In a separate 250-mL round-bottom flask, freshly cut sodium (1.29 g, 56.1 mmol) was added to methanol (100 mL, pre-dried over potassium carbonate). Once the sodium was dissolved, DMF (45 mL) was added, and the methanol was removed by rotary evaporation. The sodium methoxide solution was then added via cannula to the Schlenk flask, which was then sealed. The reaction mixture was stirred at 100 °C for 12 h, then cooled to room temperature and quenched with aqueous 1 N HCl (200 mL). The mixture was extracted with ether (3 x 150 mL), then the combined organic phase was washed with water (2 x 150 mL) and brine (100 mL). The organic phase was dried over MgSO\(_4\), filtered through a frit, and concentrated by rotary evaporation. The residue was purified by silica gel chromatography (100% hexanes) to afford 11.8 g of colorless solid (83% yield). \( R_f 0.50 \) (100% hexanes). \(^1\)H NMR (500 MHz): \( \delta \) 7.25 (t, 1H, \( J = 1.6 \) Hz), 6.99 (d, 1H, \( J = 1.6 \) Hz), 3.78 (s, 3H). \(^{13}\)C NMR (125 MHz): \( \delta \) 160.9, 126.5, 123.3, 116.6, 55.9. The data match literature values.
(E)-1-(3-bromo-5-methoxyphenyl)-2,4-dimethylpenta-2,4-dien-1-one (2.110). To a 100-mL round-bottom flask equipped with a stir bar was added 2.95 (3.00 g, 11.3 mmol) and ether (25 mL). The reaction flask was cooled to -78 °C, then butyllithium (2.5 M in hexanes, 4.64 mL) was added over 20 min. The reaction mixture was stirred at -78 °C for 5 min, at which point a solution of 1.54 (1.82 g, 10.8 mmol) in THF (5 mL) was added over 5 min. Stirring was continued at -78 °C for 45 min, then the reaction mixture was quenched with saturated aqueous ammonium chloride (30 mL). The organic layer was diluted with ether (100 mL), extracted and washed with brine (25 mL). The organic phase was dried over MgSO₄, filtered through a frit, and concentrated by rotary evaporation. The residue was purified by silica gel chromatography (30:1 hexanes:ethyl acetate, then 25:1, then 20:1) to afford 2.78 g of a yellow oil (88% yield). Rf 0.25 (19:1 hexanes:ethyl acetate). ¹H NMR (500 MHz): δ 7.33 (t, 1H, J = 1.5 Hz), 7.19 (t, 1H, J = 2.0 Hz), 6.86 (dd, 1H, J = 1.5 Hz, 2.5 Hz), 6.61 (s, 1H), 5.28 (s, 1H), 5.13 (s, 1H), 3.83 (s, 3H), 2.13 (s, 3H), 1.97 (s, 3H). ¹³C NMR (125 MHz): δ 198.1, 160.2, 144.9, 141.3, 140.8, 135.7, 124.6, 122.7, 121.1, 120.4, 113.6, 55.9, 23.0, 14.1. MS (ESI+): m/z 295 (MH⁺); HRMS (ESI+): found 295.0325, calcd for [C₁₄H₁₆BrO₂]⁺ 295.0328. IR: ν 3081, 2965, 2933, 1657, 1643, 1591, 1565, 1452, 1277, 1219 cm⁻¹.

cis-4-bromo-6-methoxy-2-methyl-3-(prop-1-en-2-yl)-2,3-dihydro-1H-inden-1-one (2.111a). To a 250-mL round-bottom flask equipped with a stir bar was added aluminum chloride (4.59 g, 34.4 mmol) and toluene (60 mL). Aryl dienone 2.110 (10.2 g, 34.4 mmol) in toluene (40 mL) was added via syringe. The reaction mixture immediately turned red. It was stirred at room temperature for 2 h before being quenched with saturated aqueous ammonium chloride (100 mL). The aqueous phase was extracted with ether (3 x 100 mL), then the combined organic phase was washed with brine (75 mL), dried over MgSO₄, filtered through a frit, and concentrated by rotary evaporation. The residue was purified by silica gel chromatography (30:1 hexanes:ethyl acetate, then 25:1, then 23:1) to afford 7.94 g of a yellow solid (78% yield, an inseparable 9:1 mixture of 2.111a:2.111b). Rf 0.23 (19:1 hexanes:ethyl acetate). ¹H NMR (500 MHz):
\[ \delta \ 7.36 \ (d, \ 1H, \ J = 2.0 \ Hz), \ 7.18 \ (d, \ 1H, \ J = 2.5 \ Hz), \ 5.01 \ (s, \ 1H), \ 4.68 \ (broad \ s, \ 1H), \ 4.08 \ (d, \ 1H, \ J = 8.0 \ Hz), \ 3.83 \ (s, \ 3H), \ 2.90 \ (quint, \ 1H, \ J = 7.5 \ Hz), \ 1.32 \ (broad \ s, \ 3H), \ 1.20 \ (d, \ 3H, \ J = 7.5 \ Hz). \ ]

$^{13}$C NMR (125 MHz): $\delta$ 207.4, 160.5, 146.6, 142.5, 139.4, 126.3, 122.6, 115.9, 113.2, 104.9, 56.1, 51.3, 48.1, 10.5. MS (ESI+): $m/z$ 295 (MH$^+$); HRMS (ESI+): found 295.0330, calcd for [C$_{14}$H$_{16}$BrO$_2$]$^+$ 295.0328. IR: $\nu$ 3078, 2968, 2933, 1721, 1713, 1653, 1606, 1506, 1475, 1433, 1377, 1321, 1293, 1266 cm$^{-1}$.

*trans*-4-bromo-6-methoxy-2-methyl-3-(prop-1-en-2-yl)-2,3-dihydro-1H-inden-1-one (2.111b). To a 250-mL round-bottom flask equipped with a stir bar was added an 9:1 mixture of 2.111a:2.111b (7.94 mg, 26.9 mmol), potassium carbonate (744 mg, 5.38 mmol), and dioxane (90 mL). The reaction was stirred at 80 ºC for 10 h, at which point the solvent was removed by rotary evaporation. The residue was dissolved in ether and filtered through Celite to afford a 1:4 mixture of 2.111a:2.111b, which were carried forward without further purification. $R_f$ 0.23 (19:1 hexanes:ethyl acetate). $^1$H NMR (500 MHz): $\delta$ 7.39 (d, 1H, $J = 2.5$ Hz), 7.18 (d, 1H, $J = 2.5$ Hz), 4.88 (t, 1H, $J = 1.5$ Hz), 4.76 (s, 1H), 3.84 (s, 3H), 3.51 (d, 1H, $J = 3.0$ Hz), 2.50 (dq, 1H, $J = 3.0$ Hz, 7.5 Hz), 1.60 (s, 3H), 1.32 (d, 3H, $J = 7.5$ Hz). $^{13}$C NMR (125 MHz): $\delta$ 207.8, 160.7, 146.0, 144.4, 139.2, 127.2, 123.0, 113.2, 105.2, 56.1, 55.5, 50.4, 20.0, 16.7. IR: $\nu$ 3078, 2968, 2933, 1721, 1713, 1653, 1606, 1506, 1476, 1432, 1377, 1321, 1293, 1266 cm$^{-1}$.

*(1R,2R,3S)*-4-bromo-6-methoxy-2-methyl-3-(prop-1-en-2-yl)-2,3-dihydro-1H-inden-1-ol (2.132a). To a 100-mL round-bottom flask equipped with a stir bar was added 2.111b (1.96 g, 6.64 mmol) in methanol (20 mL). The reaction flask was cooled to 0 ºC, then sodium borohydride (251 mg, 6.64 mmol) was added as a solid in one portion. The reaction mixture was stirred at 0 ºC for 30 min, then it was quenched with saturated aqueous ammonium chloride (50 mL). The aqueous layer was extracted with ether (2 x 50 mL), then the combined organic phase was washed with brine (30 mL), dried over MgSO$_4$, filtered through a frit, and concentrated by rotary evaporation. The residue was carried forward without further purification. $R_f$ 0.26 (4:1
hexanes:ethyl acetate. $^1$H NMR (500 MHz): \( \delta \) 7.05 (d, 1H, \( J = 2.0 \) Hz), 6.93 (d, 1H, \( J = 2.0 \) Hz), 4.87 (s, 1H), 4.63 (s, 1H), 4.59 (dd, 1H, \( J = 4.5 \) Hz, 8.5 Hz), 3.81 (s, 3H), 3.78 (d, 1H, \( J = 8.5 \) Hz), 3.21 (d, 1H, \( J = 5.0 \) Hz), 2.12 (dq, 1H, \( J = 4.5 \) Hz, 7.5 Hz), 1.72 (s, 3H), 1.17 (d, 3H, \( J = 7.5 \) Hz). $^{13}$C NMR (125 MHz): \( \delta \) 160.3, 147.7, 147.2, 134.7, 121.5, 118.9, 112.6, 109.2, 82.6, 58.8, 55.9, 49.3, 20.7, 18.0. MS (ESI+): \textit{m/z} 319 (MNa+); HRMS (ESI+): found 319.0313, calcd for \([\text{C}_{14}\text{H}_{17}\text{BrO}_2\text{Na}]^+\) 319.0304. IR: \( \nu \) 3384 (br), 3074, 2958, 2930, 2872, 2835, 1607, 1566, 1470, 1436, 1375, 1314, 1266, 1181, 1140, 1110 cm$^{-1}$.

\[(1R,2R,3S)-4-bromo-6-methoxy-2-methyl-3-(prop-1-en-2-yl)-2,3-dihydro-1H-inden-1-yloxy)(\text{tert-butyl})dimethylsilane (2.134).\] To a 250-mL round-bottom flask equipped with a stir bar was added 2.132a (7.46 g, 25.1 mmol), 98\% tert-butyldimethylsilyl chloride (4.25 g, 27.6 mmol), imidazole (2.56 g, 37.7 mmol) and DMF (75 mL). The reaction flask was heated at 80 \(^\circ\)C for 12 h, then the reaction mixture was cooled to room temperature. Water (150 mL) and ether (150 mL) were added, then the aqueous layer was separated and extracted with ether (2 x 100 mL). The combined organic phase was washed with water (3 x 100 mL) and brine (50 mL), then dried over MgSO$_4$, filtered through a frit, and concentrated by rotary evaporation. The residue was purified by silica gel chromatography (100\% hexanes, then 35:1 hexanes:ethyl acetate) to yield 8.61 g of a colorless oil (83\% over three steps). \( R_f \) 0.45 (19:1 hexanes:ethyl acetate). $^1$H NMR (500 MHz): \( \delta \) 6.95 (d, 1H, \( J = 2.5 \) Hz), 6.77 (d, 1H, \( J = 2.0 \) Hz), 4.90 (s, 1H), 4.87 (s, 1H), 4.60 (d, 1H, \( J = 6.5 \) Hz), 3.79 (s, 3H), 3.21 (d, 1H, \( J = 7.5 \) Hz), 2.12 (sext, 1H, \( J = 7.0 \) Hz), 1.63 (s, 3H), 1.16 (d, 3H, \( J = 6.5 \) Hz), 0.94 (s, 9H), 0.19 (s, 3H), 0.15 (s, 3H). $^{13}$C NMR (125 MHz): \( \delta \) 160.0, 149.0, 145.6, 133.9, 121.0, 117.9, 113.5, 109.1, 82.2, 58.8, 55.7, 49.5, 26.0, 19.5, 18.2, 17.2, -3.91, -3.96. MS (EI): \textit{m/z} 410 (M+); HRMS (EI): found 410.1275, calcd for \([\text{C}_{20}\text{H}_{31}\text{BrO}_2\text{Si}]^+\) 410.1277. IR: \( \nu \) 3582, 3400 (br), 2956, 2929, 2856, 1723, 1605, 1566, 1469, 1432, 1315, 1259, 1148, 1115 cm$^{-1}$.

\[(1R,2R,3S)-4-bromo-6-methoxy-2-methyl-3-(prop-1-en-2-yl)-2,3-dihydro-1H-inden-1-yloxy)(\text{tert-butyl})dimethylsilane (2.134).\] To a 250-mL round-bottom flask equipped with a stir bar was added 2.132a (7.46 g, 25.1 mmol), 98\% tert-butyldimethylsilyl chloride (4.25 g, 27.6 mmol), imidazole (2.56 g, 37.7 mmol) and DMF (75 mL). The reaction flask was heated at 80 \(^\circ\)C for 12 h, then the reaction mixture was cooled to room temperature. Water (150 mL) and ether (150 mL) were added, then the aqueous layer was separated and extracted with ether (2 x 100 mL). The combined organic phase was washed with water (3 x 100 mL) and brine (50 mL), then dried over MgSO$_4$, filtered through a frit, and concentrated by rotary evaporation. The residue was purified by silica gel chromatography (100\% hexanes, then 35:1 hexanes:ethyl acetate) to yield 8.61 g of a colorless oil (83\% over three steps). \( R_f \) 0.45 (19:1 hexanes:ethyl acetate). $^1$H NMR (500 MHz): \( \delta \) 6.95 (d, 1H, \( J = 2.5 \) Hz), 6.77 (d, 1H, \( J = 2.0 \) Hz), 4.90 (s, 1H), 4.87 (s, 1H), 4.60 (d, 1H, \( J = 6.5 \) Hz), 3.79 (s, 3H), 3.21 (d, 1H, \( J = 7.5 \) Hz), 2.12 (sext, 1H, \( J = 7.0 \) Hz), 1.63 (s, 3H), 1.16 (d, 3H, \( J = 6.5 \) Hz), 0.94 (s, 9H), 0.19 (s, 3H), 0.15 (s, 3H). $^{13}$C NMR (125 MHz): \( \delta \) 160.0, 149.0, 145.6, 133.9, 121.0, 117.9, 113.5, 109.1, 82.2, 58.8, 55.7, 49.5, 26.0, 19.5, 18.2, 17.2, -3.91, -3.96. MS (EI): \textit{m/z} 410 (M+); HRMS (EI): found 410.1275, calcd for \([\text{C}_{20}\text{H}_{31}\text{BrO}_2\text{Si}]^+\) 410.1277. IR: \( \nu \) 3582, 3400 (br), 2956, 2929, 2856, 1723, 1605, 1566, 1469, 1432, 1315, 1259, 1148, 1115 cm$^{-1}$.
((1R,2R,3S)-4-azido-6-methoxy-2-methyl-3-(prop-1-en-2-yl)-2,3-dihydro-1H-inden-1-yl oxy)(tert-butyl)dimethylsilane (2.143). To a 250-mL round-bottom flask equipped with a stir bar was added 2.134 (8.61 g, 20.9 mmol) and THF (50 mL). The reaction flask was cooled to -78 °C, then t-butyllithium (1.6 M in pentane, 26.8 mL, 42.9 mmol) was added via syringe pump over 40 min. The reaction mixture turned pink, then reddish-orange, over the course of the addition. Tosyl azide (4.95 g, 25.1 mmol) in THF (10 mL) was then added via cannula over 15 min, leading to a deep red colored reaction mixture. Stirring at -78 °C was continued for 20 min, then the reaction mixture was allowed to equilibrate to room temperature over 2 h, slowly turning the color to brown. It was then quenched with saturated aqueous ammonium chloride (100 mL) and extracted with ether (150 mL). The organic phase was washed with brine (50 mL), dried over MgSO₄, filtered through a frit, and concentrated by rotary evaporation. The residue was purified by silica gel chromatography (35:1 hexanes:ethyl acetate) to yield 7.40 g of a red oil, as a 12:1 mixture of 2.143 to the desbromo product 2.144 (87%). Rf 0.48 (19:1 hexanes:ethyl acetate).

1H NMR (500 MHz): δ 6.63 (d, 1H, J = 2.0 Hz), 6.55 (d, 1H, J = 2.0 Hz), 4.88 (s, 1H), 4.87 (s, 1H), 4.59 (d, 1H, J = 7.5 Hz), 3.81 (s, 3H), 3.14 (d, 1H, J = 8.5 Hz), 2.02 (sext, 1H, J = 7.5 Hz), 1.61 (s, 3H), 1.15 (d, 3H, J = 6.5 Hz), 0.98 (s, 9H), 0.21 (s, 3H). 13C NMR (125 MHz): δ 160.6, 149.6, 145.7, 137.2, 125.5, 112.6, 105.7, 104.2, 81.8, 55.9, 55.7, 49.7, 26.0, 25.8, 18.8, 18.3, 16.3, -3.86, -3.93. MS (EI): m/z 373 (M+); HRMS (EI): found 373.2183, calcd for [C₂₀H₃₁N₃O₂Si]+ 373.2186. IR: ν 3583, 3390 (br), 2956, 2929, 2857, 2107, 1722, 1643, 1611, 1591, 1483, 1463, 1440, 1360, 1337, 1255, 1220, 1148, 1103 cm⁻¹.

OMe NH₂
TBSO
Me
Me
(1R,2R,3S)-1-(tert-butyldimethylsilyloxy)-6-methoxy-2-methyl-3-(prop-1-en-2-yl)-2,3-dihydro-1H-inden-4-amine (2.145a). To a 250-mL round-bottom flask equipped with a stir bar was added 2.143 (92% pure, 7.34 g, 18.3 mmol) and THF (50 mL). The reaction flask was cooled to 0 °C, then lithium aluminum hydride (463 mg, 12.2 mmol) was added as a solid; gas evolved upon addition. After having been stirred for 30 min, the reaction mixture was quenched with water (463 μL), followed by 15% aqueous sodium hydroxide (463 μL), then water (1.39 mL). Once the gray color faded to a light yellow, the mixture was filtered through a funnel, and the solvent was removed by rotary evaporation. The residue was purified by silica gel chromatography (35:1 hexanes:ethyl acetate, then 11:1) to afford 4.63 g of a yellow oil (73%), plus 891 mg of the all-cis diastereomer (13%), carried though from the epimerization step. Rf 0.21 (9:1 hexanes:ethyl acetate). 1H NMR (500 MHz): δ 6.29 (d, 1H, J = 1.5 Hz), 6.06 (d, 1H, J = 1.5 Hz), 5.07 (d, 1H, J = 2.0 Hz), 4.96 (t, 1H, J = 1.5 Hz), 4.59 (d, 1H, J = 7.5 Hz), 3.84 (broad s, 2H), 3.75 (s, 3H), 3.17 (d, 1H, J = 8.0 Hz), 3.02 (sext, 1H, J = 8.0 Hz), 1.66 (s, 3H), 1.15 (d, 3H, J = 7.0 Hz), 0.97 (s, 9H), 0.21 (s, 3H), 0.15 (s, 3H). 13C NMR (125 MHz): δ 160.7, 148.3, 147.1, 144.5, 118.3, 114.0, 100.4, 98.9, 82.2, 56.2, 55.3, 49.1, 26.1, 18.3, 16.2, -3.78, -3.92. MS
(EI): m/z 347 (M+); HRMS (EI): found 347.2285, calcd for [C_{20}H_{33}NO_{2}Si]^+ 347.2281. IR: ν 3583, 3476 (br), 3380 (br), 3071, 2954, 2929, 2856, 1641, 1620, 1612, 1492, 1468, 1360, 1255, 1207, 1151 cm\(^{-1}\).

2.10. References

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Appendix III: Selected Spectra
2.111a (CDCl₃, 500 MHz)
2.11 ppm (CDCl₃, 500 MHz)

Compound structure:

- OMe
- Br
- Me
- O
- Me
2.132 (CDCl₃, 500 MHz)
2.132 ppm (CDCl₃, 125 MHz)
2.134 (CDCl₃, 500 MHz)
2.134 (CDCl₃, 125 MHz)
2.143 (CDCl₃, 125 MHz)
2.145a (CDCl₃, 500 MHz)
2.145a (CDCl₃, 125 MHz)
Chapter 3: Toward the Total Synthesis of Tetrapetalone A: Creation of a Late-Stage Tetra cyclic Intermediate

3.1. Attempts to Close the Tetracycle through an $N$-Acyl Iminium Intermediate

3.1.1. Using a Bischler-Napieralski Sequence

In Chapter 2, we described the formation of aniline 2.145a; with this aniline in hand, we turned our attention to forming the tetracyclic core of tetrapetalone A. Revisiting our $N$-acyliminium strategy, we considered the possibility of using a Bischler-Napieralski reaction to close the C-ring. The Bischler-Napieralski reaction is a modification of the Friedel-Crafts acylation where the electrophile used is derived from an activated amide.\(^1\,^2\) The amide is treated with a dehydrating agent (e.g., POCl\(_3\), Tf\(_2\)O, or PPA) to create an $N$-acyliminium species, which is then attacked by the aromatic system. In our case, the nucleophile would be the 1,1-disubstituted double bond of the isopropenyl group.\(^3\)

In order to test the Bischler-Napieralski reaction, we first needed to build an appropriate amide to act as the electrophile. To that end, aniline 2.145a was treated with propionyl chloride to provide amide 3.1 in quantitative yield (eq. 3.1).

\[
\begin{align*}
\text{MeO} & \quad \text{NH}_2 \\
\text{Me} & \quad \text{Me} \\
\text{MeO} & \quad \text{OTBS} \\
\text{NH}_2 & \quad \text{Me} \\
\text{Me} & \quad \text{Me}
\end{align*}
\]

Amide 3.1 was subjected to a variety of conditions in attempt to effect the closure of the seven-membered ring (Table 3.1). Exposure to POCl\(_3\) with 2,4,6-collidine led to decomposition, as did Tf\(_2\)O with 2-chloropyridine,\(^4\) as well as triphosgene with triethylamine. We also attempted to form the iminium chloride species through a reaction with oxalyl chloride and silver carbonate. After aqueous workup, the enamine chloride was observed by \(^1\)HNMR, although this compound was unstable to silica gel.

Table 3.1. Attempts to close the seven-membered ring through iminium chloride formation.
3.1.2. Building the Succinimide

We next attempted to build a succinimide onto the amine. Exposure of aniline 2.145a to succinic anhydride (3.3) in toluene at 120 ºC led to nearly quantitative formation of amide 3.4 (Scheme 3.1). This amide was then converted to the corresponding succinimide by heating with sodium acetate in acetic anhydride; no silyl ether cleavage was observed under these conditions.

Scheme 3.1. Formation of succinimide 3.5.

Succinimide 3.5 was exposed to oxalyl chloride in an attempt to effect the Bischler-Napieralski cyclization; only starting material was observed, however (eq. 3.2). We also sought to form the N-acyliminium species from an α-hydroxy amide precursor. In an attempt to form such a compound, we treated succinimide 3.5 with ethyllithium or ethylmagnesium bromide (note that an ethyl group needs to be incorporated at C-4 of tetrapetalone A). Rather than form the desired α-hydroxy amide, the addition led to opening of the succinimide ring to yield amide 3.6 (eq. 3.3).
Reports of an “assisted” N-acyliminium formation\(^5\) led us to synthesize succinimide \(3.7\), bearing an acetoxy group. Theoretically, the N-acyliminium ion can be stabilized by the carbonyl oxygen of the adjacent acetoxy group, and in this particular reference the authors report that attack upon the N-acyliminium ion failed unless the acetoxy group was present. In our hands, however, succinimide \(3.7\) exhibited similar behavior to \(3.5\) when subjected to ethyllithium or ethylmagnesium bromide (eq. 3.4).

3.2. Attempts to Close the Tetracycle with a Heck Reaction

The Heck reaction is unique in the class of palladium-mediated reactions in that the “coupling partner” for the Heck reaction is a double- or triple-bond rather than organometallic reagent.\(^6\)\(^-\)\(^8\) In our system, we sought to employ a 2-halopyrrole substrate (e.g., \(3.9\)) and use the Heck reaction to form the seven-membered ring of tetrapetalone A (Scheme 3.2). It should be noted that such a Heck reaction would be classified as 7-endo-trig by Baldwin’s rules.\(^9\) In cases where there is the potential to form a bond in either a 6-exo or a 7-endo fashion under these conditions, most Heck reactions lead to formation of a six-membered ring,\(^10\) although there a few notable examples of 7-endo-trig Heck cyclizations in organic synthesis.\(^11\)\(^-\)\(^14\) We speculated that formation of the seven-membered ring would be preferred in our system due to the severe strain involved in forming a six-membered ring. Additionally, six-membered ring formation would lead to intermediate \(3.11\), which does not possess a β-hydride and therefore could not undergo β-hydride elimination. The seven-membered ring could potentially form through such an intermediate, via a bond migration.
Scheme 3.2. Proposed Heck reaction for the formation of the seven-membered ring.

3.2.1. Building a Pyrrole from Aniline 2.145a

The Paal-Knorr pyrrole synthesis involves the acid-catalyzed condensation of a 1,4-diketone onto an amine. While 1,4-dialdehydes may be used in this transformation, they are frequently unstable species; hence, 2,5-dimethoxymethylenetetrahydrofurans are often used as dialdehyde or diketone equivalents. We were able to form pyrrole 3.13 in excellent yield by treating aniline 2.145a with 2,5-dimethoxymethylenetetrahydrofuran (3.12) in the presence of a catalytic amount of acetic acid (eq. 3.5).

3.2.2. Attempts to Effect the Heck Cyclization

To prepare for the Heck cyclization, we first needed to brominate the pyrrole ring at the 2-position. Treatment of pyrrole 3.13 with bromine in DMF at 0 ºC yielded bromopyrrole 3.14, where bromination occurred exclusively at the undesired 3-position of the pyrrole (eq. 3.6).

Switching to 1,3-dibromo-5,5-dimethylhydantoin as the brominating agent provided an inseparable mixture of mono- and di-brominated products. Using N-bromosuccinimide instead resulted in bromination at both the 2- and 5-positions to yield dibromide 3.15 (Scheme 3.3). Although this species contains an additional unneeded bromine atom, it was nevertheless a viable substrate to attempt the Heck reaction. Unfortunately, exposure of 3.15 to di-
chlorobis(triphenylphosphine)palladium (II) and triethylamine resulted in no seven-membered ring formation, but provided only cleavage of the TBS group.

Scheme 3.3. Attempted Heck cyclization on 2,5-dibromopyrrole 3.15.

3.3. Attempts to Close the Tetracycle through Epoxide Formation

We next sought to increase the electrophilicity of the pyrrole through epoxidation, thus making it prone to attack by the nearby double bond in a strategy that would use the inherent nucleophilicity of the 1,1-disubstituted double bond to our advantage. We anticipated that such an attack would occur first by opening of the epoxide through conjugation to the lone pair on nitrogen; the resulting iminium ion would then be attacked by the neighboring double bond. We found, however, that we were unable to form the mono-epoxide as desired; instead, exposure of pyrrole 3.13 to \textit{m}-chloroperbenzoic acid (\textit{m}-CPBA) led to the formation of epoxide 3.18 (Scheme 3.4). Presumably, epoxidation of one of the pyrrole double bonds happens first, followed by attack at the 5-position by residual \textit{m}-chlorobenzoic acid (\textit{m}-CBA) to open up the intermediate epoxide (3.16); finally, the newly formed $\Delta^{3,4}$-double bond reacts with a second equivalent of \textit{m}-CPBA to yield the observed product. Other attempts to effect the desired mono-epoxidation with DMDO were unsuccessful.

Scheme 3.4. Formation of epoxide 3.18.
3.4. Attempts to Close the Tetracycle through a Friedel-Crafts Acylation

As we were unable to harness the nucleophilicity of the 1,1-disubstituted double bond to attack an activated pyrrole, we considered the possibility of switching the polarity of the bond formation; that is, using the nucleophilicity of the pyrrole at the 2-position to attack the activated terminal position of the double bond. To do so, we would need to convert the terminal position into a carboxylic acid equivalent.

3.4.1. Oxidation of the Terminal Position of the Double Bond

Hydroboration of the double bond of 3.13 with borane-THF complex followed by oxidation with 30% hydrogen peroxide and aqueous sodium hydroxide produced primary alcohol 3.19 in 79% yield as a single diastereomer (eq. 3.7). It would appear that the diastereoselectivity of the hydroboration is driven by the position of isopropenyl group above the 6-5 ring system, making the β-face of the double bond more prone to delivery of BH₃.

We attempted to oxidize the alcohol 3.19 to aldehyde 3.20 under a variety of conditions. The Swern¹⁶ or Parikh-Doering¹⁷ oxidations merely returned the starting material, as did exposure to pyridinium chlorochromate (PCC) or pyridinium dichromate (PDC). Upon subjection to the Dess-Martin periodinane (2.63),¹⁸,¹⁹ however, we observed the formation of small amounts of tetracycle 3.22 (Scheme 3.5). Presumably, this occurs through initial formation of aldehyde 3.20. Activation of the aldehyde to attack by the pyrrole either occurs due residual acetic acid in the Dess-Martin periodinane or from the Lewis acidity of the periodinane itself. The newly formed secondary alcohol 3.21 is then further oxidized by another equivalent of Dess-Martin periodinane to form tetracyclic ketone 3.22.

Scheme 3.5. A double oxidiation cascade to produce tetracyclic ketone 3.22.
3.4.2. Optimization of the Dess-Martin Periodinane Tetracycle Formation

We noted that our proposed mechanism of the formation of tetracyclic ketone 3.22 required two equivalents of Dess-Martin periodinane; indeed, using fewer than two equivalents provided a mixture of aldehyde 3.20, secondary alcohol 3.21 and ketone 3.22 (we were not able to isolate aldehyde 3.20, as it decomposed on silica gel). To test whether the residual acetic acid might be playing a role in the closure of the seven-membered ring, we performed the reaction in the presence of sodium bicarbonate. We discovered the formation of a new tetracyclic ketone, 3.24, where the ketone has transposed to the 5-position of the pyrrole (Scheme 3.6). Mechanistically, secondary alcohol 3.21 must be slow to oxidize, allowing for elimination assisted by the lone pair of the nitrogen. Water can then add back into the intermediate iminium ion at the 5-position, followed by further oxidation to yield 3.24.

We had hoped to be able to optimize for this new transposed tetracycle, as it more closely resembled the atomic structure of tetrapetalone A and provided possible access to the insertion of the necessary functionality around the D-ring. We noted, however, that the production of transposed tetracycle 3.24 varied between batches of Dess-Martin periodinane, and we were never able to achieve greater than 30% recovery of 3.24. Moreover, running the reaction in the presence of water (which has been reported to accelerate the Dess-Martin oxidation) favored the production of the original tetracycle 3.22. We also noted that running the reaction at reflux accelerated the formation of 3.22, while the addition of sodium bicarbonate seemed to inhibit the reaction (lending credence to the postulate that residual acetic acid was helping to promote ring closure).

With the optimized conditions (2.5 equivalents of Dess-Martin periodinane and water, stirring at reflux in CH₂Cl₂ for 18 h), we were able to achieve a 92% yield for tetracycle 3.22. The yield deteriorated slightly (82%) when running the reaction on a scale greater than one gram of substrate. The low solubility of the Dess-Martin periodinane required a large volume of CH₂Cl₂ to be used, and large quantities of solids needed to be extracted on larger scale, leading to the possibility that the depressed yield was due to the inability to separate some of the product from the Dess-Martin periodinane byproducts.

3.4.3. Attempting the Dess-Martin Oxidation With a 3-Methylpyrrole

To create a more convergent synthesis, we examined the possibility of incorporating the methyl group at C-2 (tetrapetalone numbering) prior to the closure of the C-ring. To do so, we would need to create a 3-methylpyrrole in the Paal-Knorr step. Starting from methylsuccinic acid, we formed the diester 3.25 by methylating with HCl in methanol. Treatment with DIBAL-H at -78 ºC formed the dialdehyde; due to its potential instability, we added aniline 2.145a in situ at -78 ºC, then allowed the mixture to warm to room temperature and added water (eq. 3.8).

\[
\begin{align*}
\text{MeO} & \quad \text{MeO} \\
\text{O} & \quad \text{O} \\
\text{Me} & \quad \text{Me} \\
\text{3.25} & \quad \text{DIBAL-H, THF, -78 ºC, then} \\
\text{MeO} & \quad \text{MeO} \\
\text{NH}_2 & \quad \text{OTBS} \\
\text{2.145a, H}_2\text{O, rt} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\text{25%} & \quad \text{3.26} \\
\end{align*}
\]

This protocol provided small amounts (25%) of 3-methylpyrrole 3.26 for exploratory studies, which was then carried forward by subjecting it to hydroboration and oxidation. The resulting primary alcohol (3.27) was then exposed to Dess-Martin periodinane and sodium bicarbonate, providing a mixture of tetracyclic ketones 3.28 and 3.29 (eq. 3.9). In both cases, the methyl group was located at the undesired 3-position, rather than the required 4-position; the regioselectivity of this transformation can be rationalized by considering the methyl group as an inductively electron-donating substituent. This should place greater electron density at the 2-position of the pyrrole, rather than the 5-position, rendering the former position more nucleophilic in the key cyclization step and providing the observed products.
3.4.4. Attempts to Build More Substituted Pyrroles

On the basis of the results of the Dess-Martin periodinane oxidation of 3.27, we reasoned that placing a methoxy group at the 3-position of the pyrrole should provide access to tetracyclic ketone 3.31. Having a methoxy group at this position would be advantageous, as we need to eventually install an oxygen atom at C-3 (tetrapetalone numbering). Moreover, we could attempt to form a pyrrole with either a methyl or a bromo group at the 4-position, which would lead to installation of the methyl group at C-2. The methoxy group should be more electron-donating than either a methyl or a bromo group, so closure of the C-ring should occur at the position α to the methoxy group (Scheme 3.7).

Scheme 3.7. Proposed seven-membered ring closure from a 3-methoxypyrrole.

To build pyrrole 3.31, we planned to use the same Paal-Knorr chemistry as before; therefore, our first target was tetrahydrofuran 3.33. Exposure of 2,5-dimethoxy-2,5-dihydrofuran (3.32) to either bromine or NBS in water did not produce bromohydrin 3.33 as expected (eq. 3.10). Using bromine with silver nitrate in methanol appeared to form tetrahydrofuran 3.34 as a mixture of diastereomers (eq. 3.11), but attempts to perform the Paal-Knorr pyrrole synthesis with aniline 2.145a led only to the recovery of starting material.
We were able to build tetrahydrofuran 3.35 by treating 3.32 with BF₃·OEt₂ and sodium methoxide, leading to a successful Paal-Knorr reaction with 2.145a to form 3-methoxypyrrole 3.36 in 29% yield (Scheme 3.8). Hydroboration-oxidation led to primary alcohol 3.30a, which was then exposed to Dess-Martin periodinane; no products related to ketone 3.22 could be detected, however, and only decomposition was observed.

**Scheme 3.8.** Unsuccessful tetracycle formation with 3-methoxypyrrole 3.30a.

3.5. Attempts to Install the C-4 Ethyl Group Through a [1,2]-Pinacol Shift

As a result of the inability to effect the C-ring closure with any substitution on the pyrrole, we decided to synthesize large quantities of tetracycle 3.22 (as described in section 3.4.2) and turned our attention to the next major challenge: installation of the angular ethyl group at C-4. As we had created a carbonyl group in the formation of the tetracycle, we hoped to take advantage of this functionality for the installation of the adjacent ethyl group. Three-dimensional modeling of 3.22 showed a substantial degree of concavity, with the α-face of the molecule appearing to be more sterically accessible (Figure 2.7). Indeed, the addition of ethyllithium into 3.22 gave exclusively tertiary alcohol 3.37, where the ethyl group is on the back face of the molecule (eq. 3.12). If the pyrrole could be properly activated, we could potentially perform a [1,2]-shift on the ethyl group to the desired position.
3.5.1. Attempts to Epoxidize the Pyrrole Ring

We expected that epoxidation of the pyrrole ring would create a system where a pinacol shift would be possible through Brønsted or Lewis acid activation of the epoxide. Epoxidation of either double bond would be advantageous, as oxygen atoms are present at both the 3- and 5-positions of the pyrrole in tetrapetalone A. We first attempted epoxidation of 3.37 with \( m \)-CPBA (eq. 3.13); as we had observed with pyrrole 3.13, however (section 3.3), the recovered product was the result of a double epoxidation with \( m \)-CBA addition into the 5-position. Attempts to effect the pinacol shift on this compound by treating with boron trifluoride etherate led only to the recovery of starting material. Other epoxidation attempts with vanadyl acetoacetonate, tert-butylhydroperoxide (TBHP) with Triton B, methyltrioxorhenium (MTO) with urea-H\(_2\)O\(_2\), or DMDO led only to decomposition.

3.5.2. Attempts to Brominate the Pyrrole Ring

Treatment of 3.37 with an electrophilic bromine source could potentially lead to a similar pinacol-type shift as the intended epoxidation sequence. NBS in the presence of a base (such as DABCO) appeared to brominate 3.37 at the 5-position (eq. 3.14). Only trace amounts of product
3.39 were recovered, however, and 3.39 was unstable to silica gel. NBS by itself overbrominated the pyrrole, leading to the cleavage of the carbon-carbon bond between the pyrrole and the tertiary hydroxyl position (eq. 3.15). On the basis of this result, it appeared that this carbon-carbon bond fragmentation was more facile than a shift of the ethyl group, and we would need to revise our strategy.

![Chemical structures](image)

3.6. Attempts to Add Singlet Oxygen across the Pyrrole

Singlet oxygen is a versatile reagent that has been used extensively in [4+2] cycloadditions with pyrroles.\textsuperscript{23-26} The conditions used to generate singlet oxygen, however, are often critical to the success of the reaction. Due to the fact that oxygen naturally exists in the triplet state, a sensitizer is required to produce singlet oxygen. Similar to epoxidization, if we could effect the [4+2] cycloaddition, we could promote the desired pinacol shift and create a peroxide species, which could subsequently be reduced to a hydroxyl group at the 5-position of the pyrrole.

Exposure of pyrrole 3.37 to oxygen with tetraphenylporphyrine under exposure to a broadband wavelength lamp resulted in partial conversion to the cycloaddition product, with desilylation (Table 3.2). Similar attempts with Rosebengal or methylene blue as the sensitizer led to decomposition. Attempts to effect this transformation with DDQ led to decomposition,\textsuperscript{27} and cobalt carbonyl with an O\textsubscript{2} balloon led to recovery of starting material.\textsuperscript{28}

**Table 3.2.** Attempts to add singlet oxygen across pyrrole 3.37.
3.7. A Tandem Birch Reduction-Alkylation Sequence

Donohoe and coworkers have reported extensively on the Birch reduction of substituted pyrroles. In a system bearing an amide or an ester at the 2-position of the pyrrole and an electron-withdrawing group on the nitrogen (such as Boc), Donohoe has shown that an excess of either lithium or sodium metal will reduce the pyrrole, leading to the generation of a dianion (3.43, Scheme 3.9). The first negative charge will be quenched by a proton source, which can be ammonia, napthelene, or 4,4’-di-tert-butylbiphenyl (all of which can be used to solvate the electrons), leaving enolate 3.44. This enolate can then be alkylated or acylated, depending upon the specific conditions used, to create dihydropyrrole 3.45.

Scheme 3.9. Reduction of an electron-deficient pyrrole under Birch reduction conditions.

3.7.1. Birch Reduction-Alkylation of Pyrrole 3.22

There were several differences between Donohoe’s systems and substrate 3.22. First, all of Donohoe’s substrates have electron-withdrawing groups on the nitrogen of the pyrrole; our system bore an electron-rich aromatic ring. Furthermore, the possibility existed for a reduction of methoxyphenyl ring instead of the pyrrole. Finally, Donohoe’s substrates all have either an ester or an amide at the 2-position of the pyrrole, but never a ketone, as is present in our system.

Undaunted by these potential pitfalls, we subjected pyrrole 3.22 to sodium with a vast excess of bis(methoxyethyl)amine (3.46) in 3:1 ammonia/THF at -78 °C, followed by quenching with iodoethane, and were gratified to find that these conditions resulted in a 59% yield of dihydropyrrole 3.47 (eq. 3.16). Importantly, no reduction of the methoxyphenyl ring was observed. Additionally, the ethyl group is installed exclusively on the back face of the molecule.
The addition of bis(methoxyethyl)amine 3.46 was critical to the success of the reaction, as Donohoe has shown this compound to sequester the metal cation produced from the single electron reduction (3.48, Figure 3.2). Without this additive, sodium amide is produced, which not only depresses the yield, but also leads to extensive silyl cleavage.

**Figure 3.2.** Bis(methoxyethyl)amine (3.46) can sequester the metal cation produced in the Birch reduction.

### 3.8. Oxidation of the Dihydropyrrole

Critical to the success of the Birch reduction strategy was the ability to subsequently perform an allylic oxidation to convert dihydropyrrole 3.47 to α,β-unsaturated lactam 3.49. Donohoe reported the use of chromium trioxide with 3,5-dimethylpyrazole to perform such oxidations. In our hands, we were able to convert dihydropyrrole 3.47 to lactam 3.49 using these conditions; the yield never exceeded 46%, however, and was frequently much lower (eq. 3.17). Donohoe reported the use of 20 equivalents of CrO$_3$ to effect this transformation; we were able to reduce this to 10 equivalents, but no less than that. Moreover, it was difficult to separate the product from the chromium byproducts generated in this reaction, in accord with related literature reports that have described this general phenomenon with basic amine functionalities and chromium species.

As an alternative to the above conditions, we looked to a procedure by Shing and co-workers using catalytic manganese (III) acetate with TBHP as the stoichiometric oxidant. After discovering that the reaction needed to be performed in the dark, we were able to convert dihydropyrrole 3.47 to lactam 3.49 in 56% yield (eq. 3.18).
3.9. Attempts to Form the Double Bond in the Seven-Membered Ring

The carbonyl group at C-5 had served us well in closing the C-ring and installing the ethyl group at C-4. At the present stage, we needed to convert this functionality to the \( \Delta^{5,6} \) double bond of tetrapetalone A.

3.9.1. Attempts at the Alcohol Oxidation State

We were able to diastereoselectively reduce the carbonyl with sodium borohydride to produce secondary alcohol 3.50 (eq. 3.19). Examination of a 3D model of 3.50 led us to note that the dihedral angle between the hydroxyl group and the adjacent hydrogen was nearly 0º; therefore, we focused on methods that employ a syn elimination (Figure 3.3).

We first attempted to perform this elimination with methanesulfonic anhydride and triethylamine. Prolonged exposure of 3.50 to this combination of reagents resulted in partial formation of the corresponding mesylate (3.51), but no production of the desired double bond; rather, we observed partial desilylation, followed by elimination of the benzylic hydroxyl group (eq. 3.20).
We also explored the use of the Burgess reagent (3.53) and the Martin sulfurane (3.54, Figure 3.4), both of which are dehydrating agents that are frequently employed at the later stages of a total synthesis. On alcohol 3.50, however, neither reagent had any effect. Additionally, we attempted to use Mitsunobu conditions (triphenylphosphine with diethyl azodicarboxylate) to effect this elimination, under the pretense that olefins are frequently observed side products in the Mitsunobu reaction. Again, only starting material was recovered. Another potential alternative was the use of potassium bisulfate, which commonly used to assist in the elimination of pseudo-benzylic hydroxyl groups. This reagent also failed to effect the desired dehydration, although it should be noted that a poor orbital overlap between the pyrrole $\pi$ system and the $\sigma^{*}_{C-O}$ antibonding orbital (see Figure 3.3) suggested that these conditions were unlikely to be successful.

The Chugaev elimination is a two step elimination process involving a xanthate intermediate (Scheme 3.10). Heating the xanthate to 200 °C promotes the syn elimination, presumably through a six-membered transition state. The sequential addition of sodium hydride, carbon disulfide and iodomethane to alcohol 3.50 produced two products, both of which were consistent with the expected xanthate by $^1$H NMR. Heating each product separately at 200 °C in 1,2-dichlorobenzene resulted only in decomposition.

**Scheme 3.10.** Attempted Chugaev elimination.

3.9.2. Attempts at the Ketone Oxidation State
We also examined several methods for forming the double bond without prior reduction of the carbonyl group. The Shapiro reaction is a method for forming a vinylolithium species from arylsulfonylhydrazones.\(^{41}\) After treating the hydrazone with two equivalents of butyllithium, the hydrazone is deprotonated at both the \(\alpha\)-position and at the sulfonamide, leading to the elimination of both \(\text{N}_2\) and \(\text{ArSO}_2^-\) and creation of a vinyl anion. We intended to create this vinyl anion and quench it with a proton source; unfortunately, attempts to form the hydrazone led only to recovery of starting material.

The Stille reaction involves the palladium catalyzed cross-coupling of an aryl or vinyl halide with a tributyltin species;\(^{42,43}\) if tributyltin hydride is used, then the halide is replaced with a hydrogen atom. To attempt the Stille coupling, we needed to form a vinyl triflate species. Treatment of \(3.49\) with LDA and \(N\)-phenyl-bis(trifluoromethanesulfonamide) did not produce any reaction (eq. 3.21). The replacement of LDA with a less sterically-hindered base (sodium hydride) or a stronger base (LiTMP) was equally unproductive.

\[
\text{MeO} \quad \text{OTBS} \quad \text{base, PhNTf}_2 \quad \text{THF, temp} \quad \rightarrow \quad \text{N. R.} \quad (3.21)
\]

conditions: \(\text{NaH, 70 }^\circ\text{C}\), \(\text{LDA, -78 }^\circ\text{C}\), \(\text{LiTMP, -78 }^\circ\text{C}\)

It appeared that steric hindrance was significantly affecting our attempts to access both the carbonyl and the \(\alpha\)-position. Because of this, we opted to try to form the vinyl triflate by first forming the silyl enol ether, then treating that compound successively with methyllithium and a triflating agent. To our surprise, however, treatment of ketone \(3.49\) with LDA and TMSCl produced only C-silyl compound \(3.56\) (eq. 3.22). It appeared that the mild acidity of the proton at C-2 combined with the extraordinary difficulty in accessing the proton at C-6 led to installation of the trimethylsilyl group on the D-ring. On the basis of this result, we hoped to be able to exploit the acidity of the C-2 proton at a later stage of the synthesis (see Section 3.10.3, \textit{vide infra}).

![Diagram](image-url)

3.10. Attempts to Oxidize the Methoxyphenyl Ring

Given the difficulties in forming the \(\Delta^{5,6}\) double bond, we turned our attention to another necessary transformation in the synthesis of tetrapetalone A – the formation of the \(p\)-quinol moiety on the A-ring. We began by attempting to perform this oxidation using the same methods described in Section 2.4. Using BBr\(_3\), we cleaved both the methyl and TBS ethers from \(3.49\) to produce a mixture of diol \(3.57\) and bromide \(3.58\) (Scheme 3.11). The production of bromide
3.58 suggested that ionization of the benzylic hydroxyl group had occurred, followed by addition of Br⁻. We noted that the observation of such a mechanism suggested a potential method for the addition of the β-rhodinosyl fragment present in tetrapetalone A. This would be important since we would not be able to add the benzylic alcohol directly to a rhodinosyl fragment due to the fact that the C-9 position of 3.49 bears the opposite stereochemistry to that found in tetrapetalone A. Returning to diol 3.57, treatment of this species with diacetoxyiodobenzene in methanol resulted in possible oxidation to the p-quinol as judged by ¹H NMR; the resulting compound achieved was acid-sensitive and decomposed readily, however, making characterization difficult.

Scheme 3.11. Cleavage of the methyl and silyl ethers of 3.49 with BBr₃ and attempted aromatic oxidation.

Exposure of methoxyphenyl compound 3.49 to CAN in an acetonitrile/water mixture did not lead to oxidation of the aromatic system, but rather, oxidation occurred at the benzylic ring juncture to produce tertiary alcohol 3.62. Mechanistically, this could transpire by initial removal of an electron from the aromatic system (Scheme 3.12). To achieve the observed product, the resulting radical cation (3.59) could subsequently be deprotonated at the benzylic position to yield neutral radical 3.60. Removal of a second electron would lead to benzylic cation 3.61, which would then be quenched by nucleophilic addition of water. In contrast to this mechanism, in the desired route, we hoped that stabilization of 3.59 by the lone pair on the methoxy group would lead to hydrolysis, and removal of a second electron followed by quenching of the positive charge by water would provide the p-quinol. It was unclear to us whether oxidation of the benzylic position would be preferred in all attempts on similar systems, or if the degree of concavity of the C-ring might have a substantial effect on the outcome of such reactions.

3.11. Attempts to Form the Tetramic Acid

We next turned our attention to the construction of the tetramic acid moiety present in the D-ring of tetrapetalone A. From $\alpha,\beta$-unsaturated lactam 3.49, we would need to methylate the $\alpha$-position and oxidize the $\beta$-position in order to achieve the tetramic acid.

3.11.1. Dihydroxylation and Epoxidation Attempts

Several methods exist for the epoxidation of enones; should we be able to achieve this transformation, we planned to treat the resulting epoxide with methylcuprate to add a methyl group to the $\alpha$-position. While cuprates are commonly used for the purpose of 1,4-addition into enones, such species have been shown to attack preferentially at the $\alpha$-position of $\alpha,\beta$-epoxyketones. Two explanations have been proposed to rationalize this selectivity: in the first scenario, the methyl group initially adds to the ipso carbon of the carbonyl and then undergoes a $[1,2]$-shift to open the epoxide, which is activated by the copper species. Alternatively, the $\alpha$-position can be considered more electrophilic than the $\beta$ position, as the $\delta^+$ charge created at the $\alpha$-position can be stabilized by overlap with the $\pi$ system of the carbonyl.

In an attempt to epoxidize $\alpha,\beta$-unsaturated lactam moiety of alcohol 3.50, we separately treated this species with $m$-CPBA or Triton B with TBHP, both of which unfortunately led to a mixture of several undesired products (eq. 3.23).
Similar epoxidation attempts on ketone 3.49 with TBHP and DBU led only to the recovery of starting material at room temperature (Table 3.3), although a complex mixture of products was created at elevated temperature. Pre-mixing TBHP with n-BuLi prior to addition also only resulted in starting material recovery; in contrast, trace amounts (11%) of the desired epoxide were produced with TBHP and potassium tert-butoxide. Attempted addition of methyllithium into the epoxide resulted only in recovery of the starting material, while the use of the Davis oxaziridine also produced no reaction.

We also attempted to dihydroxylate the double bond of 3.49; if we could create diol 3.65, then further oxidation would produce a trione. The central carbonyl should be the most electrophilic, and thus exposure of this compound to methyllithium should produce the correct oxidation pattern for tetrapetalones B and D. Disappointingly, prolonged exposure of 3.49 to either potassium permanganate or osmium tetroxide and N-methylmorpholine oxide did not result in any conversion to diol 3.65.

Table 3.3. Summary of epoxidation and dihydroxylation attempts on ketone 3.49.

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBHP, DBU, CH2Cl2, 0 °C</td>
<td>starting material</td>
</tr>
<tr>
<td>TBHP, DBU, DCE, 70 ºC</td>
<td>complex mixture, no epoxide</td>
</tr>
<tr>
<td>TBHP, n-BuLi, THF, -78 ºC to rt</td>
<td>starting material</td>
</tr>
<tr>
<td>TBHP, KO2-Bu, THF, 0 ºC</td>
<td>3.64 (11%)</td>
</tr>
<tr>
<td>Davis oxaziridine, CH2Cl2, -78 ºC</td>
<td>starting material</td>
</tr>
<tr>
<td>KMnO4, Cy2-18-C-6, CH2Cl2, rt</td>
<td>starting material</td>
</tr>
<tr>
<td>OsO4, NMO, acetone/H2O, rt</td>
<td>starting material</td>
</tr>
</tbody>
</table>

3.11.2. Silyl Addition and Tamao-Fleming Oxidation

As an alternative to epoxidation or dihydroxylation, we considered the addition of an oxygen equivalent into the β-position of the lactam. For example, the Tamao-Fleming oxidation is a method that converts a silyl group to a hydroxyl group, with retention of stereochemistry, by treatment with an oxidizing agent such as H2O2. Importantly, the silyl group must be activated with a fluoride source prior to oxidation.

Our first attempt at silyl addition involved the use of dimethylphenylsilyllithium 3.66, which is readily generated by treating commercially available chlorodimethylphenylsilane with lithium metal. Treatment of α,β-unsaturated lactam 3.49 with 3.66 and diethylzinc did not result in any conversion; replacing diethylzinc with copper (I) cyanide, however, yielded 33% of the desired silyl product 3.67 (eq. 3.24).
We also were able to effect a two-stage transformation by quenching the intermediate enolate with iodomethane, which installed the requisite methyl group at α-position and produced 3.68 (Scheme 3.13). Unfortunately, we were unable to convert 3.68 to the corresponding alcohol using either mercury (II) trifluoroacetate with peroxyacetic acid in THF\(^{55}\) or hydrogen peroxide (\(\text{H}_2\text{O}_2\)) with potassium fluoride (KF).\(^{56}\) Conversion to the alcohol could not be effected without using harshly acidic fluoride conditions (HBF\(_4\)) with H\(_2\text{O}_2\)/KF;\(^{52}\) these conditions also cleaved the TBS group, however, eliminated the benzylic hydroxyl group and isomerized the double bond to form 3.69.

**Scheme 3.13.** Attempted Tamao-Fleming oxidation of silane 3.68.

Due to the harsh conditions required to effect the Tamao-Fleming oxidation upon the dimethylphenylsilyl moiety, we examined alternative silyl groups for this transformation. Treatment of hexamethyldisilane with methyllithium has been shown to create silyllithium species 3.71 (eq. 3.25), which, after addition into an enone, can be oxidized under much more mild conditions than products deriving from 3.66.\(^{57}\) We were, however, unable to add 3.71 into our substrate.
Another alternative is the diphenyl-diethylamino-silyllithium species 3.73\textsuperscript{57,58} upon addition into an enone, the compound is treated with ammonium chloride in ethanol to displace the unstable diethylamino group with ethoxide. This compound can be oxidized by treatment with potassium hydrogen fluoride (KHF\textsubscript{2}) and either \textit{m}-CPBA or H\textsubscript{2}O\textsubscript{2}. In our system, 3.73 was successfully added into \(\alpha,\beta\)-unsaturated lactam 3.49; upon quenching with iodomethane, then ethanol, we recovered ethoxysilane 3.74 in 28\% yield (Scheme 3.14). We successfully performed the Tamao-Fleming oxidation with KHF\textsubscript{2} and H\textsubscript{2}O\textsubscript{2} to produce alcohol 3.75 in 79\% yield. While this method provided a means to access the desired tetramic acid (which could be achieved with further oxidation, see Scheme 3.18, \textit{vide infra}), results were irreproducible due to the air sensitivity and instability of 3.73, and large quantities of alcohol 3.74 could not be produced by this process.

**Scheme 3.14.** A successful Tamao-Fleming oxidation.

\[
\begin{align*}
\text{Ph}_2(\text{Et}_2\text{N})\text{SiLi (3.73), CuCN} & \rightarrow \text{MeI, then EtOH} \rightarrow \text{THF, } -78 \, ^\circ \text{C} \rightarrow \text{(28\%)} \\
\text{H}_2\text{O}_2, \text{KHF}_2 & \rightarrow \text{DMF, rt} \rightarrow \text{(79\%)}
\end{align*}
\]

\[3.74 \rightarrow 3.75\]

### 3.11.3. Pinacolborane Addition and Oxidation

Another potential surrogate for an oxygen atom is a boron species. Boranes can be readily oxidized to alcohols through the use of mild oxidizing agents such as \(\text{H}_2\text{O}_2\) or NaBO\textsubscript{3}. Several conditions exist for the addition of pinacolborane into enones, with bis(pinacolato) diboron 3.76 as the boron source.\textsuperscript{59-62} A screen of these conditions (Scheme 2.48) revealed that treatment of 3.49 with 3.76, copper (I) chloride, sodium tert-butoxide and \(N\)-heterocyclic carbene 3.77\textsuperscript{63} in the glovebox produced pinacolborane 3.78 in 59\% yield.\textsuperscript{62} Subsequent treatment with NaBO\textsubscript{3} cleanly converted 3.78 to alcohol 3.79.

**Scheme 3.15.** Successful addition of pinacolborane into \(\alpha,\beta\)-unsaturated lactam 3.49.
At this stage, we needed to install the methyl group at the α-position and oxidize the hydroxyl group to achieve the desired tetramic acid. Attempts at oxidation of the hydroxyl group, however, resulted in decomposition. We also tried to alkylate pinacolborane 3.78 by treating it with LDA and iodomethane, but were unsuccessful. Attempts to quench the pinacolborane reaction with iodomethane before workup – a strategy which had proven successful in the case of our silyl group conjugate additions – resulted in no alkylation. Though we were able to perform an aldol reaction by quenching 3,5-dimethoxybenzaldehyde (3.80) to produce 3.81 (Scheme 3.16), simpler aldehydes (formaldehyde, Eschenmoser’s salt) were unsuccessful in this reaction. Oxidation of diol 3.82 to 3.83 was effected by subjection to IBX in ethyl acetate. Attempts to alkylate 3.83 with LDA and iodomethane were unsuccessful.

Scheme 3.16. Attempted installation of the α-methyl group on the tetramic acid.
It appeared that oxidation of the β-hydroxyl group would not be successful without the presence of an α-substituent. To attempt to install the α-methyl group, we protected the hydroxyl group by treating 3.79 with hexamethyldisilazide and a sub-stoichiometric amount of tert-butyldimethylsilyl triflate (TBSOTf). We attempted to methylate 3.84 by treating with LDA and iodomethane (Scheme 3.17); to our surprise, we recovered eliminated product 3.85, where the methyl group had been incorporated into the α-position.


As a more direct means to produce 3.85, we considered exploiting the side reaction observed in Section 3.9.2 (see eq. 3.21, vide supra). Subjecting 3.49 to 5.0 equivalents of LDA and
iodomethane produced $3.85$ in 70% yield (eq. 3.26). The remainder of the mass balance appeared to derive from methylation at the $\beta$-position; this could possibly occur through coordination to the carbonyl group at C-5 followed by lithiation at the $\beta$-position.

With a means to produce $3.85$, we were now able to convert this species to $\beta$-hydroxy lactam $3.75$ by pinacolborane addition followed by NaBO$_3$ oxidation. Pinacolborane addition produced $3.86$ in a 2:1 ratio of anti diastereomers, with the major product arising from addition to the $\alpha$-face of $3.85$ (Scheme 3.18). We attempted to form the corresponding tetramic acid by treatment of $3.75$ with Dess-Martin periodinane; rather than achieving the tetramic acid, however, we observed further oxidation to $\alpha$-hydroxytetramic acid $3.87$, representing the D-ring substitution pattern for tetrapetalones C and D. To achieve the tetramic acid for tetrapetalones A and B, we exposed $3.75$ to Swern oxidation conditions, recovering $3.88$ in 65% yield.

**Scheme 3.18.** Formation of the tetramic acid.
3.12. Proposed Conversion to Tetrapetalone A

Several transformations need to be performed to complete the total synthesis of tetrapetalone A (Scheme 3.19). First, the $\Delta_{5,6}^5$ double bond needs to be installed, possibly through a sequence similar to those described in Section 3.9. The order of steps will be critical at this phase; formation of this double bond would likely need to occur prior to tetramic acid formation. Second, oxidation of the methoxyphenyl ring to the $p$-quinol could occur through methyl ether cleavage followed by treatment with a hypervalent iodine reagent (see Section 3.10). Finally, we needed to remove the TBS-protection and invert the stereocenter at C-9. This could occur through a Mitsunobu reaction, or perhaps through ionization of the hydroxyl group to generate a benzylic cation, followed by readdition of water to C-9 from the $\beta$-face.

Scheme 3.19. Potential endgame for the synthesis of tetrapetalone A.

To append the $\beta$-rhodinosyl moiety to the aglycon, we might use the protocol developed by Shair for forming a $\beta$-linkage of a carbohydrate. Because the $\alpha$-linkage is thermodynamically preferred due to the anomeric effect, forming $\beta$-carbohydrate linkages is an ongoing challenge with few general solutions, particularly when the 2'-hydroxyl group is missing, as it is in rhodinose. Recently, Shair demonstrated that formation of the anion at the 1'-hydroxyl posi-
tion of a carbohydrate will exploit the greater reactivity of the β-anomer (Figure 3.5). Though the β-linkage is thermodynamically disfavored, the electronic repulsion between the lone pairs of adjacent oxygens will increase the nucleophilicity of the β-anomer, causing the β-anomeric anion to react significantly faster than the α-anomeric anion.

![Figure 3.5](image-url). The electronic repulsions present in the β-anomeric anion increase its nucleophilicity.

### 3.13. Conclusion

We have successfully developed a robust synthetic strategy to a late-stage intermediate en route to tetrapetalone A. Closure of the C-ring occurs through a Friedel-Crafts acylation in a double oxidation cascade with Dess-Martin periodinane as the oxidant. We successfully installed the ethyl group at C-4 using a Birch reduction-alkylation sequence through application of chemistry originally developed by Donohoe. Installation of the oxygen at C-3 occurred following conjugate addition of bis(pinacolato)diboron.

### 3.14. Experimental Methods

Unless otherwise stated, reactions were performed in flame-dried glassware sealed with rubber septa under a nitrogen atmosphere using dry solvents. Tetrahydrofuran (THF) and ether were distilled over sodium/benzophenone ketyl; dichloromethane, toluene, benzene and acetonitrile were distilled over calcium hydride; 1,4-dioxane was obtained from a Seca Solvent System by GlassContour (solvent dried over alumina under a N₂ atmosphere). Reaction temperatures were controlled by an IKAmag® temperature modulator. Determinations of pH were obtained by Color pHast® Indicator Strips pH = 0 – 14. Thin layer chromatography was performed using SiliCycle silica gel 60 Å F-254 precoated plates (0.25 mm) and visualized by UV and either anisaldehyde or ceric ammonium molybdate (CAM) stain. Sorbent silica gel 230-400 mesh (particle size 0.040 – 0.063 mm) was used for flash chromatography. ¹H NMR spectra were recorded on Bruker spectrometers (at 300, 400, 500 and 600 MHz), as were ¹³C NMR (at 75, 100, 125 and 150 MHz, respectively). Chemical shifts (δ ppm) are reported relative to Me₄Si (δ = 0.0) or CHCl₃ (δ = 7.26 for ¹H NMR and δ = 77.2 for ¹³C NMR). Data for ¹H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, dd = doublet of doublets, dt = doublet of triplets, dq = doublet of quartets, m = multiplet, br = broad), integration and coupling constant (Hz). IR spectra were recorded on a Nicolet MAGNA-IR 850 spectrometer and are reported in frequency of absorption (cm⁻¹). Both low and high resolution mass spectra were obtained from the University of California, Berkeley Mass Spectral Facility.
1-((1R,2R,3S)-1-(tert-butyldimethylsilyloxy)-6-methoxy-2-methyl-3-(prop-1-en-2-yl)-2,3-dihydro-1H-inden-4-yl)-1H-pyrrole (3.13). To a 250-mL round-bottom flask equipped with a stir bar was added 2.145a (4.05 g, 11.7 mmol), 2,5-dimethoxytetrahydrofuran (1.81 mL, 14.0 mmol), acetic acid (180 μL), 1,2-dichloroethane (40 mL) and water (10 mL). The reaction mixture was stirred at 90 ºC for 4 h, then it was cooled to room temperature and partitioned between ether (150 mL) and water (80 mL). The organic phase was extracted and washed with brine (50 mL), then dried over MgSO₄, filtered through a frit, and concentrated by rotary evaporation. The residue was purified by silica gel chromatography (40:1 hexanes:ethyl acetate) to afford 4.54 g of a yellow oil (97%). Rₓ 0.55 (19:1 hexanes:ethyl acetate). ¹H NMR (500 MHz): δ 6.82 (d, 1H, J = 1.5 Hz), 6.76 (t, 2H, J = 2.0 Hz), 6.73 (d, 1H, J = 2.0 Hz), 6.20 (d, 2H, J = 2.0 Hz), 4.71 (d, 1H, J = 7.5 Hz), 4.60 (d, 1H, J = 1.5 Hz), 4.59 (s, 1H), 3.82 (s, 3H), 3.37 (d, 1H, J = 8.5 Hz), 2.02 (sext, 1H, J = 7.5 Hz), 1.32 (s, 3H), 1.18 (d, 3H, J = 7.0 Hz), 0.98 (s, 9H), 0.24 (s, 3H), 0.18 (s, 3H). ¹³C NMR (125 MHz): δ 160.0, 149.8, 144.4, 138.9, 127.8, 122.1, 113.2, 110.4, 108.8, 107.7, 81.7, 56.5, 55.7, 50.4, 26.1, 18.7, 18.3, 16.4, -3.86, -3.90. MS (EI): m/z 397 (M⁺); HRMS (EI): found 397.2435, calcld for [C₂₄H₃₅NO₂Si]⁺ 397.2437. IR: ν 3583, 3367 (br), 2956, 2929, 2856, 1721, 1711, 1692, 1590, 1493, 1470, 1450, 1365, 1256, 1215, 1148, 1103 cm⁻¹.

(S)-2-((1R,2R,3R)-3-(tert-butyldimethylsilyloxy)-5-methoxy-2-methyl-7-(1H-pyrrol-1-yl)-2,3-dihydro-1H-inden-1-yl)propan-1-ol (3.19). To a 500-mL round-bottom flask equipped with a stir bar was added 3.13 (2.31 g, 5.81 mmol), and borane-THF complex (1.0 M, 58.1 mL). The reaction mixture was stirred at room temperature for 12 h, then it was cooled to 0 ºC before the successive addition of ethanol (20 mL), 10% aqueous sodium hydroxide (50 mL) and 30% aqueous hydrogen peroxide (150 mL). The reaction mixture was warmed to room temperature and stirred for 24 h. It was then extracted with ether (3 x 150 mL), then the combined organic phase was washed with brine (50 mL), dried over MgSO₄, filtered through a frit, and concentrated by rotary evaporation. The residue was purified by silica gel chromatography (11:1 hex-
anes:ethyl acetate) to afford 2.09 g of a yellow oil (87%). \( R_f \) 0.22 (9:1 hexanes:ethyl acetate).

\( ^1H \) NMR (500 MHz): δ 6.85 (t, 2H, \( J = 2.5 \) Hz), 6.82 (d, 1H, \( J = 3.0 \) Hz), 6.80 (d, 1H, \( J = 3.0 \) Hz), 6.30 (t, 2H, \( J = 2.5 \) Hz), 4.72 (s, 1H), 3.82 (s, 3H), 3.16 (m, 2H), 2.96 (t, 1H, \( J = 2.5 \) Hz), 2.81 (t, 1H, \( J = 9.0 \) Hz), 2.42 (q, 1H, \( J = 9.0 \) Hz), 1.15 (d, 3H, \( J = 9.0 \) Hz), 0.92 (s, 9H), 0.88 (d, 3H, \( J = 8.5 \) Hz), 0.98 (s, 9H), 0.22 (s, 6H).

\( ^{13}C \) NMR (125 MHz): δ 160.2, 146.5, 139.1, 132.3, 121.1, 112.4, 109.8, 109.7, 83.9, 64.4, 55.7, 55.3, 42.3, 36.6, 26.0, 22.4, 18.3, 16.0, -3.43, -4.21.

MS (FAB): \( m/z \) 415 (M+); HRMS (FAB): found 415.2540, calcd for [C\(_{24}\)H\(_{37}\)NO\(_3\)Si]\(^+\) 415.2543.

IR: ν 3583, 3400 (br), 2955, 2928, 2856, 1721, 1711, 1613, 1590, 1494, 1469, 1364, 1256, 1151, 1121 cm\(^{-1}\).

\( ^1H \) NMR (500 MHz): δ 7.37 (t, 2H, \( J = 2.0 \) Hz), 6.91 (d, 1H, \( J = 2.0 \) Hz), 6.75 (d, 1H, \( J = 1.5 \) Hz), 6.39 (t, 1H, \( J = 3.5 \) Hz), 4.74 (d, 1H, \( J = 4.0 \) Hz), 3.86 (s, 3H), 3.09 (dd, 1H, \( J = 2.5 \) Hz, 6.5 Hz), 2.84 (dd, 1H, \( J = 2.5 \) Hz, 7.0 Hz), 2.07 (q, 1H, \( J = 6.5 \) Hz), 1.25 (d, 3H, \( J = 8.0 \) Hz), 0.97 (s, 9H), 0.93 (d, 3H, \( J = 7.5 \) Hz), 0.23 (s, 3H), 0.18 (s, 3H).

\( ^{13}C \) NMR (125 MHz): δ 193.0, 160.6, 149.1, 136.8, 133.0, 126.4, 123.2, 122.5, 111.3, 106.5, 105.8, 82.6, 55.7, 48.6, 47.2, 47.0, 26.0, 18.2, 17.9, 11.9, -3.89, -3.94. MS (EI): \( m/z \) 411 (M+); HRMS (EI): found 411.2235, calcd for [C\(_{24}\)H\(_{33}\)NO\(_3\)Si]\(^+\) 411.2230.

IR: ν 3583, 3400 (br), 2955, 2930, 2856, 1642, 1596, 1530, 1493, 1473, 1449, 1435, 1411, 1366, 1284, 1231, 1205, 1148, 1112 cm\(^{-1}\).

(4R,5R,5aS,6S)-4-(tert-butyldimethylsilyloxy)-2-methoxy-5,6-dimethyl-5a,6-dihydro-4H-indeno[1,7-e]pyrrolo[1,2-a]azepin-7(5S)-one (3.22). To a 250-mL round-bottom flask equipped with a stir bar was added 3.19 (1.70 g, 4.09 mmol), Dess-Martin periodinane (4.34 g, 10.2 mmol), water (184 μL, 10.2 mmol) and dichloromethane (110 mL). The reaction flask was heated at 50 ºC for 16 h, then the reaction mixture was cooled to room temperature and quenched with saturated aqueous sodium bicarbonate (100 mL). The organic layer was separated and washed sequentially with saturated aqueous sodium metabisulfate (100 mL), saturated aqueous sodium bicarbonate (100 mL), saturated aqueous sodium metabisulfate (100 mL) and brine (50 mL). The organic phase was dried over MgSO\(_4\), filtered through a frit, and concentrated by rotary evaporation. The residue was purified by silica gel chromatography (11:1 hexanes:ethyl acetate) to afford 1.53 g of a light yellow solid (91%). \( R_f \) 0.22 (9:1 hexanes:ethyl acetate).
(4R,5R,5aS,6S,7aR)-4-(tert-butyldimethylsilyloxy)-7a-ethyl-2-methoxy-5,6-dimethyl-5a,6,7a,10-tetrahydro-4H-indeno[1,7-ef]pyrrolo[1,2-a]azepin-7(5H)-one (3.47). To a 100-mL round-bottom flask equipped with a stir bar was added 3.22 (312 mg, 758 μmol), bis(methoxyethyl)amine (2.22 mL, 15.2 mmol) and THF (6 mL). The reaction mixture was cooled to -78 ºC, then ammonia (25 mL) was added by cannula from a separate flask. Sodium (87.1 mg, 3.79 mmol) was added as several solid flakes, then the reaction flask was briefly removed from the -78 ºC bath until the reaction maintained a greenish-blue color. The flask was returned to the -78 ºC bath and stirred for 45 minutes. Isoprene (15 drops) was added until the blue color faded to yellow, then iodoethane (303 μL, 3.79 mmol) was added. The reaction mixture was stirred at -78 ºC for an additional 1 h, then it was quenched with saturated aqueous ammonium chloride (40 mL). The mixture was allowed to equilibrate to room temperature, then it was extracted with ethyl acetate (3 x 50 mL). The combined organic phase was washed with brine (30 mL), dried over MgSO₄, filtered through a frit, and concentrated by rotary evaporation. The residue was purified by silica gel chromatography (15:1 hexanes:ethyl acetate, then 9:1) to afford 198 mg of a yellow oil (59% yield), plus 50.2 mg of 3.22 (16%). Rf 0.40 (9:1 hexanes:ethyl acetate). ¹H NMR (500 MHz): δ 6.39 (d, 1H, J = 1.5 Hz), 6.13 (d, 1H, J = 1.5 Hz), 6.01 (d, 1H, J = 6.5 Hz), 5.94 (d, 1H, J = 6.5 Hz), 4.71 (d, 1H, J = 8.5 Hz), 4.40 (d, 1H, J = 14.0 Hz), 3.97 (d, 1H, J = 14.0 Hz), 3.81 (s, 3H), 2.85 (dd, 1H, J = 2.5 Hz, 7.5 Hz), 2.01 (ddd, 1H, J = 2.5 Hz, 6.5 Hz, 9.0 Hz), 1.82 (m, 2H, J = 7.0 Hz), 1.18 (d, 3H, J = 6.5 Hz), 1.04 (d, 3H, J = 7.0 Hz), 0.99 (s, 3H), 0.66 (t, 3H, J = 7.0 Hz), 0.24 (s, 3H), 0.18 (s, 3H). ¹³C NMR (125 MHz): δ 213.8, 160.7, 149.1, 142.6, 132.2, 125.7, 118.0, 100.4, 97.7, 83.7, 81.6, 57.2, 55.3, 49.6, 49.0, 47.2, 32.6, 26.1, 18.3, 15.1, 10.8, 7.72, -3.83, -3.93. MS (ESI+): m/z 440 (M-H⁺); HRMS (ESI+): found 440.2609, calcd for [C₂₆H₃₈NO₃Si]⁺ 440.2615. IR: ν 3583, 2956, 2925, 2854, 1703, 1611, 1462, 1377, 1258, 1173, 1113 cm⁻¹.

(4R,5R,5aS,6S,7aR)-4-(tert-butyldimethylsilyloxy)-7a-ethyl-2-methoxy-5,6-dimethyl-5a,6-dihydro-4H-indeno[1,7-ef]pyrrolo[1,2-a]azepine-7,10(5H,7aH)-dione (3.49). To a 50-mL
round-bottom flask equipped with a stir bar was added 3.47 (228 mg, 516 μmol), crushed 3Å molecular sieves (60 mg) and dry ethyl acetate (10 mL). Tert-butyl hydroperoxide (5.0-6.0 M in decane, 516 μL, 2.58 mmol) was added, then the reaction mixture was stirred at room temperature for 30 min. Manganese (III) acetate dehydrate (13.8 mg, 51.6 μmol) was added as a solid, then the reaction mixture was stirred in the dark for 48 h. The mixture was filtered through Celite and concentrated by rotary evaporation. The residue was purified by silica gel chromatography (6:1 hexanes:ethyl acetate, then 7:2) to afford 132 mg of a yellow foamy solid (56% yield). Rf 0.15 (4:1 hexanes:ethyl acetate). 

$^1$H NMR (500 MHz): δ 7.31 (d, 1H, $J = 2.0$ Hz), 7.11 (d, 1H, $J = 5.5$ Hz), 6.77 (s, 1H), 6.32 (d, 1H, $J = 6.0$ Hz), 4.67 (d, 1H, $J = 8.5$ Hz), 3.85 (s, 3H), 2.86 (dq, 1H, $J = 2.5$ Hz, 7.0 Hz), 2.64 (dd, 1H, $J = 2.0$ Hz, 12.5 Hz), 2.18 (sext, 1H, $J = 7.0$ Hz), 2.08 (m, 1H), 1.79 (sext, 1H, $J = 7.0$ Hz), 1.18 (d, 3H, $J = 6.5$ Hz), 0.98 (s, 9H), 0.96 (d, 3H, $J = 7.5$ Hz), 0.63 (t, 3H, $J = 7.5$ Hz), 0.24 (s, 3H), 0.18 (s, 3H). 

$^{13}$C NMR (125 MHz): δ 208.8, 169.8, 160.0, 148.8, 148.7, 132.2, 127.8, 123.2, 108.6, 107.6, 82.3, 81.1, 55.7, 49.3, 49.0, 46.6, 29.1, 26.0, 18.3, 14.8, 9.19, 6.73, -3.82, -3.94. MS (ESI+): $m/z$ 456 (MH$^+$); HRMS (ESI+): found 456.2556, calcd for [C$_{26}$H$_{38}$NO$_4$Si]$^+$ 455.2492. IR: ν 3625, 3583, 2956, 2928, 2855, 2283, 1703, 1652, 1594, 1462, 1442, 1377, 1259, 1196, 1175, 1113 cm$^{-1}$.

(4R,5R,5aS,6S,7aR,8R,9R)-4-(tert-butyl(dimethyl)silyloxy)-7a-ethyl-8-hydroxy-2-methoxy-5,6,9-trimethyl-5a,6,8,9-tetrahydro-4H-indeno[1,7-ef]pyrrolo[1,2-al]azepine-7,10(5H,7aH)-dione (3.75). To a 10-mL round-bottom flask equipped with a stir bar was added diethylamino-diphenylchlorosilane (200 μL, 793 μmol) and THF (3 mL). Lithium metal (21.9 mg, 3.17 mmol) was added as a solid in one portion. The reaction mixture was stirred at room temperature for 5 min, then the flask was cooled to 0 ºC. Stirring was continued for 3 h at 0 ºC during which time the color changed from light green to reddish-purple to brown. In a separate 4-mL vial equipped with a stir bar was added copper cyanide (3.6 mg, 40.2 μmol) and THF (200 μL). The reaction flask was cooled to 0 ºC, at which point the silyllithium in THF (414 μL, 96.5 μmol) was added dropwise via syringe. The reaction mixture was stirred at 0 ºC for 10 min, then the flask was cooled to -78 ºC. 3.49 (7.3 mg, 16.0 μmol) in THF (200 μL) was added via cannula. The reaction mixture was stirred at -78 ºC for 30 min, then iodomethane (5.0 μL, 80.3 μmol) was added. The reaction mixture was stirred for an additonal 30 min, then it was quenched cold with saturated aqueous ammonium chloride (2 mL) and extracted with ethyl acetate (2 mL). The organic phase was washed with brine (1 mL), dried over MgSO$_4$, filtered through a cotton plug, and concentrated by rotary evaporation. The residue was purified by silica gel chromatography (6:1 hexanes:ethyl acetate, then 4:1) to yield 10.2 mg of an oil, as a mixture of 3.74 with phenylsilyl byproducts. Rf 0.38 (4:1 hexanes:ethyl acetate). 

$^1$H NMR (500 MHz): δ 7.74-7.60 (m, 4H), 7.48-7.36 (m, 6H), 6.92 (d, 1H, $J = 2.0$ Hz), 6.72 (d, 1H, $J = 1.5$ Hz), 5.23 (d, 1H, $J = 1.5$ Hz), 2.56
4.60 (d, 1H, J = 8.5 Hz), 3.90 (q, 2H, J = 7.0 Hz), 3.75 (s, 3H), 2.92 (dq, 1H, J = 2.5 Hz, 7.5 Hz), 2.72 (quint, 1H, J = 7.5 Hz), 2.56 (dd, 1H, J = 2.5 Hz, 12.5 Hz), 2.31 (dd, 1H, J = 1.5 Hz, 8.5 Hz), 2.12 (sext, 1H, J = 7.5 Hz), 1.12 (d, 3H, J = 7.5 Hz), 0.97 (s, 9H), 0.96 (d, 3H, J = 7.5 Hz), 0.88 (t, 3H, J = 7.5 Hz), 0.73 (t, 3H, J = 7.5 Hz), 0.22 (s, 3H), 0.16 (s, 3H).

Silane containing phenylsilyl byproducts) was then transferred to a 4-mL vial equipped with a stir bar and dissolved in DMF (200 μL), to which m-chloroperbenzoic acid (70%, 10.8 mg, 43.8 μmol), and potassium hydrogen fluoride (3.4 mg, 43.5 μmol) were added. The reaction mixture was stirred at room temperature for 16 h, at which point the mixture was quenched with saturated aqueous sodium bicarbonate (2 mL). Ethyl acetate (2 mL) was added, then the organic phase was separated and washed with water (1 mL) and brine (1 mL). The organic phase was dried over MgSO

, filtered through a cotton plug, and concentrated by rotary evaporation. The residue was purified by silica gel chromatography (9:1 hexanes:ethyl acetate, then 2:1) to afford 1.7 mg of 3.75 as a colorless oil (22% over two steps). Rf 0.18 (2:1 hexanes:ethyl acetate).

1H NMR (600 MHz): δ 7.02 (d, 1H, J = 2.5 Hz), 6.76 (d, 1H, J = 1.0 Hz), 4.76 (t, 1H, J = 5.0 Hz), 4.68 (d, 1H, J = 8.5 Hz), 3.82 (s, 3H), 2.84 (dq, 1H, J = 3.0 Hz, 7.5 Hz), 2.79 (dd, 1H, J = 3.0 Hz, 10.5 Hz), 2.43 (m, 1H), 2.07 (m, 1H), 1.95 (quint, 1H, J = 7.5 Hz), 1.83 (sext, 1H, J = 7.5 Hz), 1.67 (d, 1H, J = 6.0 Hz), 1.28 (d, 3H, J = 7.5 Hz), 1.18 (d, 3H, J = 6.5 Hz), 0.98 (s, 9H), 0.96 (d, 3H, J = 7.5 Hz), 0.92 (t, 3H, J = 7.5 Hz), 0.23 (s, 3H), 0.17 (s, 3H).

13C NMR (150 MHz): δ 211.6, 174.1, 159.9, 148.4, 132.8, 123.9, 110.3, 108.4, 81.1, 79.6, 72.0, 55.8, 49.1, 49.0, 46.2, 41.9, 26.0, 25.0, 24.8, 18.3, 14.8, 11.8, 8.73, 8.23, -3.80, -3.95. MS (ESI+): m/z 488 (MH+); HRMS (ESI+): found 488.2819, calcd for [C27H42NO5Si]+ 488.2827. IR: ν 3380 (br), 2956, 2928, 2856, 1703, 1692, 1680, 1653, 1594, 1462, 1378, 1258, 1223, 1197 cm⁻¹.

OMe

N

Me

Me

H

TBSO

Et

Me

(4R,5R,5aS,6S,7aR)-4-(tert-butyldimethylsilyloxy)-7a-ethyl-2-methoxy-5,6,9-trimethyl-5a,6-dihydro-4H-indeno[1,7-ef]pyrrolo[1,2-a]azepine-7,10(5H,7aH)-dione (3.85). To a 5-mL round-bottom flask equipped with a stir bar was added diisopropylethylamine (15.9 μL, 113 μmol) and THF (300 μL). The reaction mixture was cooled to 0 ºC, then butyllithium (2.5 M in hexanes, 40.8 μL, 102 μmol) was added dropwise. The reaction mixture was stirred at 0 ºC for 30 min, then it was cooled to -78 ºC, at which point 3.49 (15.5 mg, 34.0 μmol) in THF (300 μL) was added via cannula. The reaction mixture was stirred at -78 ºC for 30 min, then iodomethane (12.7 μL, 204 μmol) was added. Stirring was continued for 1 h, then the reaction mixture was quenched with saturated aqueous ammonium chloride (2 mL). Ethyl acetate (2 mL) was added, then the organic phase was separated, washed with brine (1 mL), dried over MgSO4, filtered through a cotton plug, and concentrated by rotary evaporation. The residue was purified by silica gel chromatography (8:1 hexanes:ethyl acetate, then 7:1, then 7:2) to afford 9.3 mg of a white
solid (58% yield), along with 1.9 mg of starting material (12%). Rf 0.41 (4:1 hexanes:ethyl acetate). $^1\text{H}$ NMR (600 MHz): $\delta$ 7.33 (d, 1H, $J$ = 1.8 Hz), 6.76 (d, 1H, $J$ = 1.2 Hz), 6.74 (d, 1H, $J$ = 1.8 Hz), 4.67 (d, 1H, $J$ = 9.0 Hz), 3.84 (s, 3H), 2.84 (dq, 1H, $J$ = 2.4 Hz, 7.2 Hz), 2.64 (dd, 1H, $J$ = 2.4 Hz, 10.8 Hz), 2.13 (sext, 1H, $J$ = 7.2 Hz), 2.06 (m, 1H), 1.98 (d, 3H, $J$ = 1.8 Hz), 1.74 (sext, 1H, $J$ = 7.2 Hz), 1.18 (d, 3H, $J$ = 6.6 Hz), 0.98 (s, 9H), 0.93 (d, 3H, $J$ = 7.8 Hz), 0.59 (t, 3H, $J$ = 7.2 Hz), 0.24 (s, 3H), 0.17 (s, 3H). $^{13}\text{C}$ NMR (150 MHz): $\delta$ 209.5, 170.5, 160.0, 148.7, 141.6, 135.6, 132.6, 123.6, 108.2, 107.8, 81.1, 55.7, 49.4, 40.8, 29.1, 26.0, 18.3, 14.8, 11.2, 9.20, 6.73, -3.80, -3.94. MS (ESI+): m/z 470 (MH$^+$); HRMS (ESI+): found 470.2722, calcd for [C$_{27}$H$_{40}$NO$_4$Si]$^+$ 470.2721. IR: $\nu$ 2956, 2928, 2856, 1703, 1697, 1653, 1613, 1594, 1484, 1463, 1442, 1377, 1247, 1210 cm$^{-1}$.

$\text{(4R,5R,5aS,6S,7aR,8R,9R)-4-(\text{tert}-\text{butyldimethylsilyloxy})-7a-ethyl-2-methoxy-5,6,9-\text{trimethyl}-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5a,6,8,9-tetrahydro-4\text{H}-\text{indenol}[1,7-ef]\text{pyrrolo}[1,2-a]azepine-7,10(5\text{H},7\text{aH})$-dione (3.86). To an oven-dried 4-mL vial equipped with a stir bar in a glove box was added copper (I) chloride (132 $\mu$g, 1.33 $\mu$mol), sodium tert-butoxide (261 $\mu$g, 2.66 $\mu$mol), 1,3-dicyclohexylimidazolium chloride (357 $\mu$g, 1.33 $\mu$mol) and THF (150 $\mu$L). The reaction mixture was stirred at room temperature for 2 h, at which point a solution of 3.85 (7.8 mg, 16.6 $\mu$mol), bis(pinacolato)diboron (4.6 mg, 18.3 $\mu$mol) and THF (150 $\mu$L) was added. Stirring was continued for an additional 18 h, at which point the reaction mixture was quenched with saturated aqueous ammonium chloride (2 mL). Ethyl acetate (2 mL) was added, then the organic phase was separated, washed with brine (1 mL), dried over MgSO$_4$, filtered through a cotton plug, and concentrated by rotary evaporation. The residue was purified by silica gel chromatography (8:1 hexanes:ethyl acetate, then 7:1, then 4:1) to afford 5.2 mg of 3.86 as a colorless oil (52% yield, a 2:1 mixture of anti diastereomers, major diastereomer shown), along with 3.7 mg of 3.85 (47%). Rf 0.23 (4:1 hexanes:ethyl acetate). $^1\text{H}$ NMR (500 MHz): $\delta$ 7.01 (d, 1H, $J$ = 2.0 Hz), 6.76 (d, 1H, $J$ = 1.0 Hz), 4.66 (d, 1H, $J$ = 8.5 Hz), 3.84 (s, 3H), 2.86 (dq, 1H, $J$ = 2.5 Hz, 7.5 Hz), 2.81 (d, 1H, $J$ = 8.5 Hz), 2.75 (dd, 1H, $J$ = 3.0 Hz, 10.5 Hz), 2.40 (quint, 1H, $J$ = 7.5 Hz), 2.07 (m, 1H), 1.89 (sext, 1H, $J$ = 7.5 Hz), 1.75 (sext, 1H, $J$ = 7.5 Hz), 1.24 (s, 12H), 1.23 (d, 3H, $J$ = 10.5 Hz), 1.16 (d, 3H, $J$ = 6.5 Hz), 0.98 (s, 9H), 0.96 (d, 3H, $J$ = 7.5 Hz), 0.87 (t, 3H, $J$ = 7.5 Hz), 0.23 (s, 3H), 0.16 (s, 3H). $^{13}\text{C}$ NMR (150 MHz): $\delta$ 212.0, 176.0, 159.8, 148.3, 133.3, 124.4, 110.8, 107.8, 84.0, 81.1, 77.5, 55.8, 49.3, 48.6, 46.5, 38.6, 29.9, 28.1, 26.0, 25.3, 18.3, 14.8, 13.2, 11.7, 8.07, -3.83, -3.95. MS (ESI+): m/z 598 (MH$^+$); HRMS (ESI+): found 598.3721, calcd for [C$_{33}$H$_{53}$BNO$_6$Si]$^+$ 598.3730. IR: $\nu$
(4R,5R,5aS,6S,7aR,8R,9R)-4-(tert-butyldimethylsilyloxy)-7a-ethyl-8-hydroxy-2-methoxy-5,6,9-trimethyl-5a,6,8,9-tetrahydro-4H-indeno[1,7-e]pyrrolo[1,2-a]azepine-7,10(5H,7aH)-dione (3.75). To a 4-mL vial equipped with a stir bar was added 3.86 (7.9 mg, 13.2 μmol), THF (200 μL) and water (200 μL). The reaction mixture was stirred at room temperature for 2 h, then it was partitioned between ethyl acetate (2 mL) and water (2 mL). The organic phase was separated, washed with brine (1 mL), dried over MgSO₄, filtered through a cotton plug, and concentrated by rotary evaporation to afford 6.4 mg of a colorless oil (quantitative yield).

(4R,5R,5aS,6S,7aR)-4-(tert-butyldimethylsilyloxy)-7a-ethyl-8-hydroxy-2-methoxy-5,6,9-trimethyl-5a,6,8,9-dihydro-4H-indeno[1,7-e]pyrrolo[1,2-a]azepine-7,10(5H,7aH)-dione (3.88). To a 4-mL vial equipped with a stir bar was added oxalyl chloride (1.1 μL, 12.6 μmol) in dichloromethane (200 μL). The reaction flask was cooled to -78 ºC, then dimethylsulfoxide (1.7 μL, 23.9 μmol) in dichloromethane (100 μL) was added. Stirring at -78 ºC was continued for 30 min, then 3.75 (2.0 mg, 4.1 μmol) in dichloromethane (150 μL) was added via cannula. Stirring at -78 ºC was continued for an additional 30 min, then triethylamine (6.9 μL, 49.5 μmol) was added. After additional stirring at -78 ºC for 1 h, the reaction mixture was quenched with saturated aqueous sodium bicarbonate (2 mL). It was extracted with ethyl acetate (2 mL), then the organic phase was washed with brine (1 mL), dried over MgSO₄, filtered through a cotton plug, and concentrated by rotary evaporation. The residue was purified by silica gel chromatography (5:1 hexanes:ethyl acetate) to yield 1.3 mg of a colorless oil (65%, appears to be 3:1 mixture of enol:keto tautomers). Rₜ 0.63 (2:1 hexanes:ethyl acetate). ¹H NMR (500 MHz): δ 7.21 (d, 1H, J = 2.0 Hz), 6.85 (d, 1H, J = 1.5 Hz), 4.67 (d, 1H, J = 8.5 Hz), 3.84 (s, 3H), 3.02 (dq, 1H, J = 3.0 Hz, 7.5 Hz), 2.67 (dd, 1H, J = 2.5 Hz, 10.5 Hz), 2.44 (sext, 1H, J = 7.0 Hz), 2.13 (m, 1H), 1.83 (sext, 1H, J = 7.0 Hz), 1.79 (s, 3H), 1.25 (d, 3H, J = 7.5 Hz), 1.19 (d, 3H, J = 6.5 Hz), 0.99 (s,
9H), 0.68 (t, 3H, J = 7.0 Hz), 0.25 (s, 3H), 0.18 (s, 3H). $^{13}$C NMR (150 MHz): $\delta$ 203.8, 195.1, 167.7, 159.9, 149.3, 130.6, 124.1, 110.1, 109.3, 83.9, 80.9, 77.4, 55.9, 49.6, 49.3, 46.7, 29.9, 26.0, 19.6, 18.2, 14.7, 11.4, 8.55, -3.82, -3.93. MS (EI+): m/z 485 (MH$^+$); HRMS (EI+): found 485.2585, calcd for [C$_{27}$H$_{39}$NO$_5$Si]$^+$ 485.2597. IR: $\nu$ 3390 (br), 2950, 2928, 2855, 1788, 1725, 1708, 1618, 1591, 1462, 1377, 1287, 1250, 1202, 1147 cm$^{-1}$.

(4R,5R,5aS,6S,7aS,9S)-4-(tert-butyldimethylsilyloxy)-7a-ethyl-9-hydroxy-2-methoxy-5,6,9-trimethyl-5a,6-dihydro-4H-indeno[1,7-ef]pyrrolo[1,2-a]azepine-7,8,10(5H,7aH,9H)-trione (3.87). To a solution of 3.75 (3.4 mg, 7.0 $\mu$mol) in dichloromethane (400 $\mu$L) was added Dess-Martin periodinane (4.4 mg, 10.4 $\mu$mol). The reaction mixture was stirred at room temperature for 16 h, then it was quenched with saturated aqueous sodium metabisulfate (3 mL). Ethyl acetate (3 mL) was added, then the organic layer was separated and washed with saturated aqueous sodium bicarbonate (3 mL) and brine (1 mL). The organic phase was dried over MgSO$_4$, filtered through a cotton plug, then concentrated by rotary evaporation. The residue was purified by silica gel chromatography (4:1 hexanes:ethyl acetate, then 2:1) to afford 1.3 mg of a colorless oil (37%). R$_f$ 0.25 (2:1 hexanes:ethyl acetate). $^1$H NMR (600 MHz): $\delta$ 7.05 (d, 1H, J = 2.4 Hz), 6.85 (t, 1H, J = 1.2 Hz), 4.67 (d, 1H, J = 8.4 Hz), 3.84 (s, 3H), 2.98 (dq, 1H, J = 2.4 Hz, 7.2 Hz), 2.67 (dd, 1H, J = 2.4 Hz, 10.8 Hz), 2.55 (s, 1H), 2.47 (sext, 1H, J = 7.2 Hz), 2.11 (m, 1H), 1.79 (sext, 1H, J = 7.2 Hz), 1.55 (s, 3H), 1.19 (d, 3H, J = 6.6 Hz), 1.17 (d, 3H, J = 7.2 Hz), 0.99 (s, 9H), 0.72 (t, 3H, J = 7.2 Hz), 0.25 (s, 3H), 0.18 (s, 3H). $^{13}$C NMR (150 MHz): $\delta$ 204.0, 199.2, 171.2, 156.0, 149.4, 130.6, 124.7, 110.6, 109.2, 84.4, 81.0, 69.9, 55.9, 49.6, 49.3, 46.8, 29.2, 26.0, 19.2, 18.3, 14.7, 10.2, 8.65, -3.83, -3.94. MS (EI+): m/z 501 (M$^+$); HRMS (EI+): found 501.2533, calcd for [C$_{27}$H$_{39}$NO$_6$Si]$^+$ 501.2547. IR: $\nu$ 3365 (br), 2955, 2927, 2854, 1788, 1722, 1710, 1693, 1653, 1636, 1620, 1593, 1421, 1380, 1291, 1251, 1202, 1147 cm$^{-1}$.

3.15. References

(59) Lawson, Y. G.; Lesley, M. J. G.; Marder, T. B.; Norman, N. C.; Rice, C. R. Chem. Commun. 1997, 2051.
(63) 3.77 was synthesized and graciously supplied by Melissa Herbage of the Ellman Group.

Appendix IV: Selected Spectra
3.13 (CDCl$_3$, 125 MHz)
3.19 (CDCl₃, 500 MHz)
3.22 (CDCl₃, 500 MHz)
3.22 (CDCl₃, 125 MHz)
3.47 (CDCl3, 50.0 MHz)
3.47 (CDCl₃, 125 MHz)

270
ppm (f1)

3.49 (CDCl₃, 500 MHz)

TBSO

Me

Me

H

Et

O

Me

O

N

OMe

3.49 (CDCl₃, 500 MHz)
3.85 (CDCl₃, 600 MHz)
3.85 (CDCl₃, 150 MHz)
3.86 (CDCl$_3$, 500 MHz)
3.75 (CDCl₃, 600 MHz)
3.87 (CDCl₃, 500 MHz)
3.87 (CDCl₃, 150 MHz)
3.88 (CDCl₃, 600 MHz)
OMe

3.88 (CDCl3, 150 MHz)