COMPLEX BOTANICAL NATURAL PRODUCTS: SYNTHESIS OF CEPHALOTAXUS ESTERS AND OF THE C19-DITERPENOID SKELETON OF ACONITUM AND DELPHINIUM ALKALOIDS

BY

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DISSERTATION

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ABSTRACT

The *Cephalotaxus* esters are a class of alkaloids extracted from plants of the *Cephalotaxus* genus and have been shown to be potent inhibitors of P-388 murine leukemia cells. While direct acylation of cephalotaxine has been reported to be difficult, the construction and acylation of cephalotaxine using a β-lactone acyl chain surrogate in the synthesis of anhydroharringtonine, deoxyharringtonine, homodeoxyharringtonine, and homoharringtonine is described. The natural esters as well as several non-natural analogues were tested against various human cancer cell lines not previously challenged by these alkaloids. Variations in the structure of the ester chain were found to confer differing activity profiles against vincristine resistant HL-60/RV+.

The *Aconitum* and *Delphinium* alkaloids comprise a family of compounds isolated from the *Aconitum* and *Delphinium* genera. Several compounds within this class show potent Na⁺ ion channel activity ranging from the ion channel activation of aconitine to the ion channel blocking of lappaconitine. The completed synthesis of the skeleton of the C₁₉-diterpenoid alkaloids is described. Key steps include a Diels–Alder cycloaddition of a cyclopropene with a 2,5-dioxycyclopenta-1,3-diene, a second Diels–Alder cycloaddition with a 2,5-dihydroazepine 2π component, an intramolecular N-acyliminium cyclization, and a radical conjugate addition.
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CHAPTER 1. SYNTHESIS OF *CEPHALOTAXUS* ESTERS

1.1 Introduction to the *Cephalotaxus* Esters

A new family of alkaloids was isolated from plants of the *Cephalotaxus* genus in 1963.\(^1\) The structure of cephalotaxine (1), the major constituent of these compounds, was elucidated in 1969 using \(^1\)H NMR, IR, MS, and X-Ray analysis.\(^2,3\) Several minor constituents have also been isolated. These include deoxyharringtonine (2),\(^4\) anhydroharringtonine (3),\(^5\) homoharringtonine (4),\(^6\) and homodeoxyharringtonine (5).\(^7\) Through spectroscopic, degradation, and partial synthesis studies, these compounds were found to differ from 1 only by the presence of an acyl chain attached via a C3-O-ester linkage at the cephalotaxine hydroxyl group.\(^4-7\) These acyl chains vary in the length and oxidation of an alkyl substituent at C2', while a β-hydroxy ester at C2' and C4" is a common feature to the side chains. Anhydroharringtonine (3) is unique in that its C2' hydroxyl has been incorporated into a furan ring. Although cephalotaxine (1) itself has been found to be biologically inactive, the esters are remarkably cytotoxic against P388 and L1210 leukemia cells.\(^8,9\) For instance, deoxyharringtonine (2), homoharringtonine (4), and homodeoxyharringtonine (5) exhibit IC\(_{50}\) values of 7.5, 17, and 56 ng mL\(^{-1}\), respectively, against murine P388 leukemia cells. Likewise, anhydroharringtonine (3) has been reported to induce 98% growth inhibition of murine P388 leukemia cells at 1 µg mL\(^{-1}\),\(^9\) an activity that is comparable to that of deoxyharringtonine (2). In particular, homoharringtonine (4) has reached Phase III clinical trials in the U. S. for the treatment of chronic myelogenous leukemia and has also gained considerable interest in China and Europe.\(^10-13\) The cytotoxicity of the *Cephalotaxus* esters is the result of reversible inhibition of protein synthesis\(^14\) via induction of rapid breakdown of the polyribosome, with concomitant release of the polypeptide chain.\(^15\) Despite production difficulties, hematologic toxicity, and susceptibility to multidrug resistance (MDR),\(^16\)
homoharringtonine (4) has maintained interest as a component of combination therapy in the treatment of chronic myeloid leukemia.

![Figure 1. Selected Constituents of the Cephalotaxus Alkaloids](image)

The development of the *Cephalotaxus* esters as a viable cancer therapy has been hindered by their relative scarcity from natural sources in comparison to that of cephalotaxine (1) itself. Typically, complex *Cephalotaxus* esters are attainable in only <0.1% of the plant dry weight. Therefore, a primary goal of the efforts described herein was the design and execution of a method for the production of both natural and non-natural bioactive *Cephalotaxus* esters that is distinct from previous efforts.

1.2 Previous Approaches for the Acylation of Cephalotaxine

A synthesis of cephalotaxine (1) has recently been completed within our group,\textsuperscript{17} however the biological activity of the esters provide incentive for investigations into their synthesis. The major challenge has been shown to be direct esterification 1 with a fully functionalized acyl chain due to steric encumberance at C2' of the acyl chain combined with the location of the cephalotaxine C3-OH within the concave face of the ring system.\textsuperscript{4} Previously, the few reported esterifications of cephalotaxine (1) have utilized either partially constructed acyl chains with sp\textsuperscript{2} hybridization at C2' to provide steric relief or fully elaborated lactonized acyl chains,\textsuperscript{18} however even these efforts have met with limited success (Scheme 1). For example, acylation of cephalotaxine (1) with α-ketoacyl chloride 6 provided α-ketoester 7, which was treated with the lithium enolate of methyl acetate to yield deoxyharringtonone (2) in just 6% yield.
over two steps (Scheme 1A).\(^1\) This use of an achiral acyl chain equivalent resulted in a C2' epimeric mixture of compounds with a consequent reduction in yield. To our knowledge, no efficient synthesis of 2 has been reported. A similar method was utilized by Hudlicky and co-workers\(^2\) in a synthesis of homoharringtonine (4). Cephalotaxine (1) was treated with \(\alpha\)-ketoacyl chloride 8 to provide an unstable \(\alpha\)-ketoester 9. A subsequent Reformatsky\(^3\) reaction installed the C2' \(\beta\)-hydroxyester 10, and finally methyl Grignard addition to the C6 carbonyl yielded homoharringtonine (4) in 25% yield over three steps (Scheme 1B). In contrast to the lithium enolate addition mentioned in the previous example, Hudlicky reports the Reformatsky reaction to stereoselectively generate a single C2' diastereomer. However, the reported instability of the \(\alpha\)-ketoester intermediate and poor yields of the Grignard addition limit the utility of this method. A notable deviation from these known strategies was introduced by Kelly and co-workers,\(^4\) who demonstrated the ability to attach a fully elaborated acyl chain equivalent with an sp\(^3\) center at C2' using activated macrolactone 11 to produce ester 12. It was postulated that the lactone favors a conformation which reduces the impact of the sterically large substituents and allows for more facile acylation. Subsequent methanolysis of lactone 12 produced methyl ester 13 and deprotection of the benzyl ether yielded harringtonine (14) in 19% yield over three steps (Scheme 1C).
1.3 Synthetic Strategy for the Synthesis of Cephalotaxus Esters

In the development of an efficient synthetic strategy for attaching the acyl chains, evaluation of the existing methods proved useful to the formulation of a new strategy. Kelly’s use of a macrolactone demonstrates the ability to attach the acyl chain by simply incorporating C2’ into a cyclic structure. As anhydroharringtonine (3, Figure 1) naturally constrains C2’ within a ring, direct attachment of an appropriately activated acid should be possible.\(^\text{22}\) However, a more rewarding solution would be the attachment of an acyl chain that would directly lead to any of the esters, even those with no C5’/C6’ hydroxyl, such as deoxyharringtonine (2) and homodeoxyharringtonine (5). A novel and general solution would be to transform the β-hydroxy ester at C2’ and C4”, a structural feature common to many potent Cephalotaxus esters, into a β-lactone such as 16 (Scheme 2). This lactone was hypothesized to sufficiently reduce congestion at C1’ to allow effective acylation to occur. Further retrosynthetic analysis reveals the use of
Seebach’s self reproduction of stereocenters (SRS)\textsuperscript{23} alkylation to set the tetrasubstituted stereocenter at C2'.\textsuperscript{24} The carbon skeleton and chiral information can then be provided by commercially available \(\alpha\)-malic acid. The benefits of this strategy include asymmetry from cheap, commercially available starting materials, no reliance on C5'/C6' oxidation, and consequently, many natural and unnatural cephalotaxus esters would be available by simply varying the electrophile used in the alkylation.

1.4 Cephalotaxine Synthesis Improvement

Prior to embarking on acylation studies of cephalotaxine (1), an improvement upon the recently completed synthesis of 1 itself was desired. Chloroenone 18 was a key intermediate in a synthesis of 1, however, the synthesis of this compound was somewhat lengthy at 10 steps (Scheme 3). Previous efforts to more directly access 18 by chloroselenylation of the previously reported enone 19\textsuperscript{25} had met with failure (Scheme 4), possibly due to the electron poor nature of the olefin. It was thought 1,2-reduction to the allylic alcohol would increase the electron density of the alkene to render it more susceptible to electrophilic attack by selenium. Indeed, Lüche reduction\textsuperscript{26} of the enone in 19 followed by treatment of the resulting allylic alcohol 21 with
phenylselenenyl chloride successfully generated chloroselenide 22. Selenium oxidation with \textit{m}-chloroperbenzoic acid produced a mixture of diastereomeric selenoxides. While one diastereomer underwent spontaneous syn elimination at 20 °C; the other required extensive heating in the presence of triethylamine, likely due to unfavorable 1,3-diaxial interactions of the phenyl group in the conformation required for 1,2-syn elimination, to yield allylic alcohol 23 (Scheme 5). * Oxidation of the hydroxyl group in 23 was effected with Dess–Martin Periodinane (98%) to yield chloroenone 18 in 65% yield over four steps from enone 19; a significant improvement over the previous 10 step route.

1.5 Synthesis of an Acyclic Acyl Chain

With an improved route to cephalotaxine (1) in hand, attention was directed toward the synthesis and attachment of the acyl chains. In order to test the feasibility of the Seebach SRS

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* Inversion of the selenoxide at elevated temperatures to the diastereomer more favorable for elimination cannot be discounted.
approach, a synthesis of the enantiomer of the deoxyharringtonine side chain was conducted (Scheme 6). The enantiomer selected for this proof-of-principle study was chosen due to the lower cost of natural L-malic acid over the unnatural D-malic acid required for the correct C2' stereochemistry. The synthesis began with the preparation of known dioxolanone 24 by treatment of the tris-trimethylsilyl protected derivative of L-malic acid with trimethylacetaldehyde in the presence of catalytic trimethylsilyl trifluoromethanesulfonate (TMSOTf) (82%). In our planned divergent step to the various acyl chains, alkylation of the lithium dianion of 24 with 3,3-dimethylallyl bromide was somewhat problematic following the known procedure, resulting in variable yields. However, mediation of the exotherm caused by the initial deprotonation of the free carboxylic acid by addition of the base in two portions allowed for a reproducible 66% yield of alkene 25. The SRS method has the additional benefit of carboxylic acid differentiation, as the α-hydroxyacid portion is protected as the dioxolanone, leaving the other acid free for manipulation. Thus, methyl esterification of the free acid to provide ester 26 was effected with trimethyl diazomethane in 92% yield. Subsequent olefin hydrogenation over palladium (>99%) generated diester 27 that was one step away from the target. Unfortunately, selective dioxolanone deprotection in the presence of the methyl ester proved to be difficult due to facile overhydrolysis to the diacid. A screen of acidic and basic hydrolysis conditions revealed aqueous acetic acid as the highest yielding hydrolysis reagent, however the yield was an unacceptable 37% of the requisite mono-ester 28. Alternatively, the desired mono-ester has also previously been shown by Mikolajczak and co-workers to be available from diacid 30, available by hydrogenation of 25 to give 29 followed by acidic hydrolysis, via selective Fisher esterification of the less hindered acid (Scheme 7). However,
long reaction times (14 days) combined with moderate yield (57%) made this method unattractive.

Scheme 6

As an alternative to hydrolysis, dioxolanones are known to be susceptible to methanolysis with sodium methoxide.\textsuperscript{28,29} Although chemoselective hydrolysis of the resulting dimethyl ester would be difficult, chemical differentiation could be achieved through the use of benzyl alkoxide, resulting in a benzyl ester that could be selectively cleaved by hydrogenolysis in the presence of a methyl ester. As anticipated, treatment of dioxolanone 25 (Scheme 8) with benzyl alcohol and sodium hydride afforded benzyl ester 31 in 88% yield. Methyl esterification of the carboxylic acid with trimethylsilyldiazomethane (32, 100%) was followed by hydrogenation of the alkene with concomitant hydrogenolysis of the benzyl ester (100%) to yield acyl-chain 28 in five steps and 48% yield from malic acid. This synthesis is also advantageous due to its highly modular nature. The $\beta$-hydroxyacid intermediate 27 would be a viable precursor to the $\beta$-lactone required for deoxyharringtonine (2) and $\beta$-hydroxyalkene 28 could undergo an intramolecular Markovnikov hydration to generate the tetrahydrofuran required for anhydroharringtonine (3).
1.6 Synthesis of (−)-Anhydroharringtonine

As intermediate 32 from the model study (see Scheme 8) contains an unprotected β-hydroxyolefin, it is an ideal candidate for an intramolecular Markovnikov hydration. The resulting furan would be instrumental in the synthesis of anhydroharringtonine (3). Thus, treatment of ent-32 (Scheme 9) with mercury acetate and capture of the transient mercurinium ion by the C2’ hydroxyl followed by reductive demercuration with NaBH4 produced cyclic diester 33 in 85% yield, with no detection of uncylized product. Subsequent benzyl ester hydrogenolysis (100%) provided the key furan acid 34. As anticipated, acylation of cephalotaxine (1) with an activated mixed Yamaguchi anhydride prepared from 34 proceeded well to complete the synthesis of the alkaloid (−)-anhydroharringtonine (3, 88%).
1.7 Synthesis of (−)-Deoxyharringtonine

Although the successful completion of anhydroharringtonine (3) was welcome, the true test of the strain-accelerated acylation strategy was the attachment of a β-lactone acyl chain surrogate to cephalotaxine (1). The strain energy arising from the endocyclic bond compression within the β-lactone ring would necessarily induce exocyclic bond angle expansion, thereby relieving local steric congestion at the electrophilic C1’ carbonyl. In addition, the angle strain resulting from the four-member ring imparts additional hybrid orbital s-character in the exocyclic bonds, an effect that could result in increased C1’ electrophilicity through induction. Despite these potential advantages, the high strain energy inherent in the β-lactone could induce alternate, undesired, ring expansion pathways.

An appropriate β-lactone acylation partner was prepared from ent-31 in the following manner (Scheme 10). Activation of the unprotected carboxylic acid under Yamaguchi conditions31 and subsequent intramolecular nucleophilic attack by the C2’ hydroxyl group provided β-lactone 35 (50%). Hydrogenolysis of the benzyl ester with concomitant alkene reduction furnished key carboxylic acid 36 (99%). This β-lactone was ideal to test our hypothesis of strain-accelerated acylation of cephalotaxine (1). Fortunately, activation of 36 as the Yamaguchi mixed anhydride did not result in β-lactone decomposition and allowed for the efficient acylation of 1 to form the ester 37 (81%). This achievement marks the first acylation of cephalotaxine with a β-lactone as the coupling partner to overcome the steric encumberance at C1’. Methanolysis of the β-lactone then concluded the synthesis of (−)-deoxyharringtonine (2, 76%). To our knowledge, this is the most efficient synthesis of 2 from cephalotaxine (1). To understand better the benefits of the β-lactone moiety in the acylation step, an analogous acyclic acyl chain 38 was prepared from ent-32 (Scheme 11). Acylation of the C2’ hydroxyl was
followed by benzyl ester hydrogenolysis to furnish carboxylic acid 38 (>99%), which lacked the ring strain elements present in β-lactone 36. Attempts at acylating cephalotaxine with 38 under otherwise identical conditions resulted in the detection of only trace quantities of protected deoxyharringtonine. Heating the reaction mixture did not improve conversion, thus confirming the beneficial effects of the β-lactone moiety.

**Scheme 10**

![Scheme 10](image)

1.8 **Synthesis of (−)-Homoharringtonine and (−)-Homodeoxyharringtonine**

As homoharringtonine (4) has gained intense interest within the medical community for treatment of chronic myeloid leukemia,\(^{10-13}\) it was also chosen as a target with which to further demonstrate the utility of β-lactone-accelerated esterification. Initially, synthesis of a suitable coupling partner was envisioned by Seebach alkylation\(^{23}\) of dioxolanone 24 with propargyl
bromide 43, previously prepared by graduate student colleague Joseph Eckelbarger from propargyl alcohol in five steps and 22% overall yield via the route outlined in Scheme 12. The synthesis of 43 began with the protection of propargyl alcohol as the tetrahydropyran acetal by treatment with 2,3-dihydropyran and p-toluenesulfonic acid to provide acetal 39 (81%). Deprotonation of the alkynyl proton with n-butyllithium was followed by nucleophilic attack onto acetone to give propargyl alcohol 40 (89%). Benzyl protection of the tertiary alcohol was accomplished with NaH and BnBr (41, 76%). The THP protecting group was cleaved under acidic conditions to reveal alcohol 42 (76%). The propargyl alcohol was activated as the oxophosphonium and displaced with bromide under Appel conditions\textsuperscript{32} to give the propargyl bromide 43 (98%). The SRS protocol was then applied with 43 as the electrophile (Scheme 13). Although alkylation of the common intermediate dioxolanone 24 proceeded to produce alkyne 44 in moderate yield (42%), transesterification of the dioxolanone with NaH and BnOH (45, 38%) and Yamaguchi lactonization provided β-lactone 46 in only 6% yield over two steps.

**Scheme 12**
Optimization of these steps may have been possible, however the long route to propargyl bromide 43 provided incentive to instead explore another strategy. Alternatively, the required one-carbon homologation and oxygen functionality installation were envisioned to be accomplished by olefin cross-metathesis as outlined in Scheme 14. As the alkylation of dioxolanone 24 with allyl bromide\(^{23}\) and olefin cross metathesis with a TBS protected version of 50\(^{33}\) have been demonstrated by Seebach and Grubbs, respectively, the success of this strategy seemed very likely. Thus, alkylation of the dianion of dioxolanone ent-24 with allyl bromide yielded the previously prepared terminal alkene 47 (59%).\(^{23}\) Transesterification of the dioxolanone to the benzyl ester with sodium hydride and benzyl alcohol (48, 85%) and β-lactone formation from the β-hydroxy acid (67%) under Yamaguchi conditions provided 49 (67%), an appropriate partner for olefin cross-metathesis. Cross-metathesis with previously prepared benzyl protected allylic alcohol 50\(^{34}\) was more difficult than anticipated, requiring 22 equivalents of 50 as a neat mixture with 49 and Hoveyda-Grubbs 2\(^{\text{nd}}\) generation catalyst (56) to disfavor homodimerization of 49. Ultimately, 52 was obtained in 61% yield, but even under these forcing conditions, 23% of homodimer 51 was also isolated. Re-equilibration of 51 in the presence of 56 provided additional quantities of 52. Chemoselective cleavage of the benzyl ester was effected by transfer hydrosilylation with palladium acetate and triethylysilane. The carboxylic acid group
was then revealed by silyl ester hydrolysis during aqueous work-up to afford key carboxylic acid 53 (85%)\(^{35}\) with no detectable reduction of either the alkene or benzyl ether. Acylation of (−)-cephalotaxine (1) under Yamaguchi conditions again proceeded in excellent yield to generate ester 54 (97%). The ease of this acylation further exemplified the generality of the strain-assisted acylation of the cephalotaxine C3 hydroxyl group. Methanolysis of the β-lactone with NaOMe proceeded smoothly to afford the penultimate intermediate 55 (79%).

**Scheme 14**

![Scheme 14 Diagram](image)

Allylic benzyl ether 55 could be advanced to either homoharringtonine (4) or homodeoxyharringtonine (5) depending on the hydrogenation/hydrogenolysis conditions chosen. When intermediate 55 was subjected to hydrogenation conditions with Pd/C in glacial acetic acid, (−)-homodeoxyharringtonine (5, Scheme 15) was isolated as the major product in 69%
yield, presumably by elimination of the benzyl ether followed by hydrogenation of the resulting olefin. Deoxygenation could be inhibited by hydrogenation of the internal olefin in methanol as the solvent, with addition of acetic acid in the latter stages to complete C6'-O-debenzylation and provide (−)-homoharringtonine (4, 79%).

**Scheme 15**

1.9 Synthesis of Non-natural Cephalotaxus Ester Bis(demethyl)deoxyharringtonine

The efficient synthesis and acylation of fully-functionalized acyl chains onto cephalotaxine (1) to produce natural *Cephalotaxus* esters also provided an opportunity to prepare a non-natural analogue for biological evaluation with a minimum of deviation from the synthetic sequence. This analogue took the form of bis(demethyl)deoxyharringtonine (58, Scheme 16). Although much simpler than the natural *Cephalotaxus* esters, this analogue was also anticipated to also show potent antiproliferative activity. The synthesis of 58 began with interception of β-lactone 49, an intermediate in the synthesis of both homoharringtonine (4) and homodeoxyharringtonine (5, refer to Scheme 14). Reduction of the terminal olefin with concomitant benzyl ester hydrogenolysis were accomplished with Pd/C under a hydrogen atmosphere to yield acid 56 (97%). Activation of 56 as the Yamaguchi mixed anhydride allowed acylation of cephalotaxine (1) to provide β-lactone-ester 57 (81%). Methanolysis then completed the synthesis of the non-natural *Cephalotaxus* ester bis(demethyl)deoxyharringtonine 58 in 93% yield.
1.10 Antiproliferative Activity of Natural and Non-natural \textit{Cephalotaxus} Esters

The completed synthesis of several natural and unnatural \textit{Cephalotaxus} esters outlined above combined with our relocation to Memorial Sloan Kettering Cancer Center (MSKCC) allowed us form a collaboration with the MSKCC High Throughput Screening facility to evaluate the antiproliferative activity of these alkaloids against a variety of cell lines. A selected subset of these data is summarized in Table 1. Those cell lines include HL-60 (acute promyelocytic leukemia), HL-60/RV+ (a P-glycoprotein over-expressing multidrug resistant HL-60 variant which was selected by continuous exposure to vinca alkaloid vincristine), JURKAT (T cell leukemia), ALL3 (acute lymphoblastic leukemia recently isolated from a patient treated at MSKCC and characterized as Philadelphia chromosome positive), NCEB1 (Mantle cell lymphoma), SKNLP (neuroblastoma), Y79 (retinoblastoma), PC9 (adenocarcinoma), TC71 (Ewing's sarcoma), HTB-15 (glioblastoma), and WD0082 (well-differentiated liposarcoma). From these data, we were able to deduce that the unprotected C2’ hydroxyl moiety is necessary for potent antitumor activity. In contrast with previous reports that anhydroharringtonine (3) is as
potent as deoxyharringtonine (2) against P388 murine leukemia cells, this alkaloid proved ineffective against the majority of human cancer cell lines. In addition, while β-lactone intermediates 37, 54, and 57 were potent antitumor agents, their activity was around 10-fold less than that of their acyclic counterparts 2, 55, and 58. It could be argued that even the attenuated activity observed for the β-lactone analogues could be mostly due to hydrolysis of the strained lactone under physiological conditions to expose the C2' hydroxyl group. The relative lack of antitumor activity for anhydroharringtonine (3) substantiates this hypothesis, as the C2' oxygen is protected within the hydrolytically stable furan. Thus, the C2' hydroxyl group would not be revealed under physiological conditions.

Table 1. Cytotoxicity of Various Cephalotaxus Esters.

<table>
<thead>
<tr>
<th>Cell Line</th>
<th>3 IC50 (µM)</th>
<th>2 IC50 (µM)</th>
<th>37 IC50 (µM)</th>
<th>55 IC50 (µM)</th>
<th>54 IC50 (µM)</th>
<th>58 IC50 (µM)</th>
<th>57 IC50 (µM)</th>
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</thead>
<tbody>
<tr>
<td>HL-60</td>
<td>22.67</td>
<td>0.01</td>
<td>2.68</td>
<td>0.01</td>
<td>3.68</td>
<td>0.08</td>
<td>5.73</td>
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<tr>
<td>HL-60/RV+</td>
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<td>0.16</td>
<td>21.80</td>
<td>0.10</td>
<td>28.25</td>
<td>0.8</td>
<td>40.3</td>
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<td>JURKAT</td>
<td>42.99</td>
<td>0.04</td>
<td>5.71</td>
<td>0.03</td>
<td>7.32</td>
<td>0.19</td>
<td>12.01</td>
</tr>
<tr>
<td>ALL3</td>
<td>&gt;100</td>
<td>&lt;0.1</td>
<td>1.47</td>
<td>&lt;0.1</td>
<td>1.84</td>
<td>0.16</td>
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<tr>
<td>NCEB1</td>
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<td>8.62</td>
<td>0.06</td>
<td>22.92</td>
<td>0.15</td>
<td>39.24</td>
</tr>
<tr>
<td>SKNLP</td>
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<td>&lt;0.1</td>
<td>6.46</td>
<td>&lt;0.1</td>
<td>8.83</td>
<td>0.11</td>
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</tr>
<tr>
<td>Y79</td>
<td>&gt;100</td>
<td>70.59</td>
<td>&gt;100</td>
<td>&gt;100</td>
<td>42.28</td>
<td>&gt;100</td>
<td>&gt;100</td>
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<td>0.03</td>
<td>4.23</td>
<td>0.04</td>
<td>9.66</td>
<td>0.13</td>
<td>11.29</td>
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<td>0.03</td>
<td>12</td>
<td>0.20</td>
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<tr>
<td>HTB-15</td>
<td>&gt;100</td>
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<td>52</td>
<td>0.10</td>
<td>73</td>
<td>0.50</td>
<td>58</td>
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<tr>
<td>WD0082</td>
<td>&gt;100</td>
<td>0.10</td>
<td>5</td>
<td>0.05</td>
<td>13</td>
<td>0.20</td>
<td>11</td>
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</table>

The completion of the syntheses of natural Cephalotaxus esters 2–5 as well as non-natural analogues bis(demethyl)deoxyharringtonine (58) and benzyldehydrohomoharringtonine (55) allowed the comparison of their antiproliferative activity against multi-drug resistant (MDR) cell line HL-60/RV+ relative to the "sensitive" HL-60 cell line (Figure 2). Although all natural and non-natural Cephalotaxus ester derivatives were highly potent against the sensitive HL-60 cell line (IC50 < 0.08 um), stark differential response levels were observed within this collection. In particular, homoharringtonine (4) displayed a 125-fold decrease in activity against the HL-
60/RV+ cell line relative to that of the HL-60 cell line, resulting in a resistance index of 125. By contrast, much lower resistance indices of 12, 11, 3.3, and 19 were observed for 55, 2, 5, and 58, respectively. That homoharringtonine (4) is much less effective against the MDR cell line is surprising given that 4 is the favored Cephalotaxus ester for advancement in the clinic. In contrast with 4, homodeoxyharringtonine (5) has a resistance index of 3, so the MDR cell line can be considered "sensitive" toward 5. One possible explanation for the medical community's focus on 4 is that of availability. That is, homoharringtonine (4) is both the most naturally abundant Cephalotaxus ester and until now was the only ester produced semi-synthetically based on the work of Kelly (refer to Scheme 1C), wherein only those acyl chains with oxidation at C6' would be amenable to acylation of cephalotaxine (1). Fortunately, the strategies outlined herein, namely the strain-assisted acylation of cephalotaxine (1), do not rely on C6' oxidation and thus allow access to many Cephalotaxus esters such as homodeoxyharringtonine (5).

![Graph](image-url)

**Figure 2.** Resistance index of homoharringtonine (4), bis(demethyl)deoxyharringtonine (55), deoxyharringtonine (2), homodeoxyharringtonine (5), and benzyldehydrohomoharringtonine (58).
1.11 Summary

The development of a novel synthetic strategy has enabled the synthesis of potent anti-tumor C3-O-esters of cephalotaxine (1). Construction of strained C2’–C4” β-lactone acyl chain derivatives was accomplished though a Seebach SRS alkylation of dioxolanone 24, readily available from D-malic acid. The ring strain inherent in the β-lactone moiety reduced the steric encumbrance of the tetrasubstituted C2’ carbon to allow a strain assisted acylation of the sterically congested C3 hydroxyl group of cephalotaxine (1). This technology allowed access to numerous natural and non-natural Cephalotaxus esters that were tested to determine their cytotoxicity against a range of human cancer cell lines. It was concluded that an unprotected C2' hydroxyl group is necessary for potent antitumor activity as evidenced by the lack of antiproliferative activity of anhydroharringtonine (3) as well as the 10-fold lower activity for the β-lactone intermediates relative to the final Cephalotaxus esters. In addition, despite the focus of the medical community on homoharringtonine (4), it was found that homodeoxyharringtonine (5) is much less susceptible to MDR than 4 (resistance index of 3 for 5 vs. 125 for 4). Until now, deoxyharringtonine (2) and homodeoxyharringtonine (5) were not as readily available as homoharringtonine (4) due to the lack of efficient synthetic strategies for those esters lacking a C5’/C6’ oxygen functionality. These advancements should facilitate future endeavors to prepare novel Cephalotaxus esters that are more potent, less toxic, and less susceptible to cellular MDR mechanisms than the current state-of-the-art treatments.
1.12 Experimental

**General Procedures.** All reactions were performed in flame-dried modified Schlenk (Kjeldahl shape) flasks fitted with a glass stopper under a positive pressure of argon, unless otherwise noted. Air- and moisture-sensitive liquids and solutions were transferred via syringe or stainless-steel cannula. Organic solutions were concentrated by rotary evaporation below 30 °C. Flash column chromatography was performed employing 230-400 mesh silica gel under a positive pressure of nitrogen. Thin-layer chromatography (analytical and preparative) was performed using glass plates pre-coated to a depth of 0.25 mm with 230-400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Visualization was achieved using UV light, iodine, para-anisaldehyde, or ceric ammonium molybdenate. Buffered silica gel was prepared by agitating a 10% by weight mixture of commercial pH 7.0 buffer in silica gel for at least 30 m.

**Materials.** Dichloromethane (CH₂Cl₂), tetrahydrofuran (THF), acetonitrile, diethyl ether, hexane, toluene, and benzene were purified by passage through two packed columns of neutral alumina under an argon atmosphere. Methanol was distilled from magnesium turnings under a nitrogen atmosphere at 760 mm Hg. 1,2-Dichloroethane, N,N-dimethylformamide (DMF), dimethylsulfoxide, and 1,4-dioxane were dried over activated 4Å molecular sieves. Triethylamine, 2,6-lutidine, pyridine, Hünig's base, and diisopropylamine were distilled from CaH₂ under a nitrogen atmosphere at 760 mm Hg. Lithium bis(trimethylsilyl)amide (LHMDS) was purchased as a solid from Aldrich and handled under an intert atmosphere. Benzyl alcohol was distilled from CaO under an argon atmosphere at 760 mm Hg. Dess-Martin periodinane was prepared by published methods.³⁶

**Instrumentation.** Infrared (IR) spectra were obtained using a Perkin Elmer Spectrum BX spectrophotometer or a Bruker Tensor 27 referenced to a polystyrene standard. Data are
presented as the frequency of absorption (cm\(^{-1}\)). Proton and carbon-13 nuclear magnetic resonance (\(^1\)H NMR or \(^{13}\)C NMR) spectra were recorded on a Varian 400, a Varian 500, Varian Inova 500 NMR, a Bruker Avance III 500, or a Bruker Avance III 600 spectrometer; chemical shifts are expressed in parts per million (\(\delta\) scale) downfield from tetramethylsilane and are referenced to the residual protium in the NMR solvent (CHCl\(_3\): \(\delta\) 7.26 for \(^1\)H NMR, \(\delta\) 77.16 for \(^{13}\)C NMR; C\(_6\)D\(_6\): \(\delta\) 7.16 for \(^1\)H NMR, \(\delta\) 128.06 for \(^{13}\)C NMR; CD\(_3\)OD: \(\delta\) 3.30 for \(^1\)H NMR, \(\delta\) 49.00 for \(^{13}\)C NMR). Data are presented as follows: chemical shift, multiplicity (s = singlet, bs = broad singlet, d = doublet, bd = broad doublet, t = triplet, dd = doublet of doublets, ddd = doublet of doublet of doublets, td = triplet of doublets, dt = doublet of triplets, m = multiplet and/or multiple resonances).

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\begin{align*}
&\text{Me} \quad \text{O} \quad \text{O} \\
&\text{Me} \quad \text{Me}
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\end{align*}
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6(3aR,4S,5S,6S,6aR)-6-chloro-2,2-dimethyl-5-(phenylselanyl)tetrahydro-3aH-cyclopenta[d][1,3]dioxol-4-ol (22) (II-JTW-010)

To a solution of enone 19 (246 mg, 1.60 mmol, 1.00 equiv) in MeOH (16 mL) was added CeCl\(_3\)\(\cdot\)7H\(_2\)O (715 mg, 1.92 mmol, 1.20 equiv). The solids were allowed to dissolve completely and then NaBH\(_4\) (72.6 mg, 1.92 mmol, 1.20 equiv) was added in several small portions. After the vigorous bubbling had subsided, the reaction was quenched with H\(_2\)O (15 mL) and poured into CH\(_2\)Cl\(_2\) (16 mL). The phases were separated and the aqueous phase was extracted with CH\(_2\)Cl\(_2\) (2x 16 mL). The combined organic phases were dried over MgSO\(_4\) and concentrated under a stream of N\(_2\) to a volume of 16 mL. Allylic alcohol 21 was not isolated to avoid loss due to its volatility. This solution was then cooled to 0 °C and PhSeCl (337 mg, 1.76 mmol, 1.10 equiv) was added and the resulting orange solution was stirred at 0 °C for 1 h. The solvent was
then removed by rotary evaporation and the orange residue was purified by silica gel column chromatography (gradient; 4:1-1:1 Hex:EtOAc) to yield selenide 22 (403 mg, 73% over 2 steps). Rf = 0.5 (2:1 hex:EtOAc); 1H NMR (500 MHz, C6D6) δ 7.55 (m, 2H), 6.94 (m, 3H), 4.68 (s, 1H), 4.42 (pentet, 1H, J=5.5 Hz), 4.34 (d, 1H, J=5.8 Hz), 4.12 (t, 1H, J=5.5), 3.70 (d, 1H, J=6.0 Hz), 3.28 (d, 1H, J=11.2 Hz), 1.48 (s, 3H), 0.95 (s, 3H); 13C NMR (125 MHz, C6D6) δ 185.13, 133.74, 133.69, 133.65, 132.93, 129.403, 111.99, 85.82, 78.88, 71.59, 63.76, 57.71, 25.50, 23.45; IR (neat film) 3509 (m), 3057 (w), 2987 (m), 2940 (m), 1579 (m), 1384 (s), 1208 (s), 972 (m); HRMS (EI) m/z calcd for C14H17O3ClSe (M+) 348.0031 observed 348.0027; [α]D = +14.1º (c 2.19, CHCl3).

\[
\text{O} \quad \text{O} \\
\text{OH} \quad \text{Me} \quad \text{Me} \\
\text{SePh} \quad \longrightarrow \\
\begin{array}{c}
\text{O} \\
\text{OH} \\
\text{Me} \quad \text{Me} \\
\text{Cl} \\
\end{array}
\]

(3aR,4R,6aR)-6-chloro-2,2-dimethyl-4,6a-dihydro-3aH-cyclopenta[d][1,3]dioxol-4-ol (23) (II-JTW-012)

To a solution of selenide 22 (402 mg, 1.16 mmol, 1.00 equiv) in CH2Cl2 (12 mL) was added washed m-CPBA37 (220 mg, 1.28 mm, 1.10 equiv). This solution was stirred for 15 m and then triethylamine (323 μL, 2.32 mmol, 2.00 equiv) was added via syringe and the solution was heated to 40 ºC for 17 h. The solution was then allowed to cool, partitioned between saturated aqueous NaHCO3 solution (15 mL) and CH2Cl2 (15 mL). The phases were separated and the aqueous phase was extracted with CH2Cl2 (2x 15 mL) and the combined organic phases were dried over MgSO4. Solvent removal by rotary evaporation yielded a bright orange oil that was purified by silica gel column chromatography (2:1 hex:EtOAc) to yield allylic alcohol 23 (201 mg, 91%) as a white, crystalline solid.
R_f = 0.25 (2:1 Hex:EtOAc); ^1H NMR (400 MHz, C_6D_6) \( \delta \) 5.51 (m, 1H), 4.24 (d, 1H, \( J = 5.3 \) Hz), 4.06 (m, 2H), 2.68 (d, 1H, \( J = 9.8 \) Hz), 1.22 (s, 3H), 1.15 (s, 3H); ^13C NMR (125 MHz, C_6D_6) \( \delta \) 136.55, 132.08, 113.03, 84.27, 77.76, 71.96, 27.49, 26.85; IR (neat film) 3322 (m), 2989 (m), 2939 (m), 1632 (m), 1380 (m), 1371 (m), 1213 (m), 1125 (s), 1064 (s); HRMS (EI) m/z calcd for C_8H_12O_3Cl (M^+ + H) 191.0475 observed 191.0471; \([\alpha]_D^0 = -37^\circ\) (c 1.98, CHCl_3).

![Graphical representation of the reaction](image)

6(3aS,6aR)-6-chloro-2,2-dimethyl-3aH-cyclopenta[d][1,3]dioxol-4(6aH)-one (18) (II-JTW-014)

To a solution of alcohol 23 (30.0 mg, 0.157 mmol, 1.00 equiv) in CH_2Cl_2 (1.6 mL) was added Dess–Martin Periodane (100 mg, 0.236 mmol, 1.50 equiv). The resulting suspension was stirred at 23 °C for 2 h at which time the suspension was loaded directly onto a plug of silica gel (1 g) and flushed with CH_2Cl_2 (15 mL). Solvent removal by rotary evaporation yielded chloroenone 18 (29 mg, 98%) as a white, crystalline solid.

R_f = 0.35 (25% ethyl acetate in hexane); ^1H NMR (500 MHz, C_6D_6) \( \delta \) 5.54 (s, 1H), 4.21 (d, 1H, \( J = 5.5 \) Hz), 3.94 (d, 1H, \( J = 5.5 \) Hz); 1.19 (s, 3H), 1.10 (d, 3H, \( J = 0.3 \) Hz); ^13C NMR (125 MHz, C_6D_6) \( \delta \) 196.82, 145.39, 131.16, 115.65, 81.01, 79.01, 79.00, 27.30, 26.31; IR (neat film) 2987 (w), 2933 (w), 1722 (s), 1582 (s) cm\(^{-1}\); HRMS (EI) m/z: Calcd for C_8H_9ClO_3 (M^+) 188.0240, observed 188.0242.

![Graphical representation of the reaction](image)
A solution of LHMDS (413 mg, 2.47 mmol, 1.00 equiv) in THF (5 mL) at –78 ºC was transferred via cannula to a stirred solution of acid ent-24 (500 mg, 2.47 mmol, 1.00 equiv) in THF (25 mL) at –78 ºC. The resulting solution was stirred at –78 ºC for 15 minutes. A solution of LHMDS (496 mg, 2.96 mmol, 1.20 equiv) in THF (5 mL) at –78 ºC was then added via cannula and the resulting solution was stirred for 20 min at –78 ºC. 3,3 dimethylallyl bromide (316 μL, 2.72 mmol, 1.10 equiv) was then added via syringe and the resulting solution was stirred at –78 ºC for 19 h, at which time the reaction was quenched with saturate aqueous NH₄Cl solution (25 mL), removed from the cold bath, and allowed to warm to 20 ºC. The solution was then poured into 1 N aqueous HCl (75 mL), extracted with CH₂Cl₂ (3x 75 mL), the combined organic phases were dried over MgSO₄ and concentrated via rotary evaporation to yield an oily solid. Purification by silica gel column chromatography (19:1 MeOH:CH₂Cl₂) yielded ent-25 (438 mg, 66%) as a white powder.

R_f = 0.51 (19:1 CH₂Cl₂:MeOH); ¹H NMR (400 MHz, CDCl₃) δ 5.16 (m, 2H), 2.83 (m, 2H), 2.50 (d, 2H, J=7.7 Hz), 1.74 (d, 3H, J=0.8 Hz), 1.64 (d, 3H, J=0.8 Hz), 0.93 (s, 9H); ¹³C NMR (100mhz, CDCl₃) δ 174.91, 173.84, 137.96, 115.55, 108.42, 80.54, 39.44, 34.28, 32.40, 25.97, 23.60, 18.03; IR (neat film) 2973 (m), 2916 (m), 1800 (s), 1710 (s), 1181 (m), 1156 (m) cm⁻¹; HRMS (ESI) m/z calcd for C₁₄H₂₃O₅ (M⁺) 271.1545, observed 271.1553; [α]D = –266º (c 2.98 CHCl₃).
Methyl 2-((2R,4R)-2-tert-butyl-4-(3-methylbut-2-enyl)-5-oxo-1,3-dioxolan-4-yl)acetate (26) (I-JTW-046).

A solution of acid 25 (150 mg, 0.56 mmol, 1.00 equiv.) in 7:2 benzene:MeOH (5.5 mL) was treated with a 2 M solution of trimethylsilyl diazomethane in Et₂O (416 μL, 0.83 mmol, 1.50 equiv.). The resulting solution was stirred under air for 15 m then concentrated by rotary evaporation. The residue was purified by flash column chromatography (15:1 hexanes:EtOAc) to yield 26 (145 mg, 92%) as a colorless oil that solidified into a white solid upon standing.

1H NMR (400 MHz, CDCl₃) δ 5.17 (m, 1H), 5.16 (s, 1H), 3.66 (s, 3H), 2.81 (s, 2H), 2.50 (d, 2H, J=7.8 Hz), 1.74 (d, 3H, J=0.8 Hz), 1.64 (d, 3H, J=0.8 Hz), 0.94 (s, 9H)

13C NMR (100 MHz, CDCl₃) δ 173.96, 168.83, 137.78, 115.71, 108.32, 80.70, 51.93, 39.70, 34.16, 32.51, 25.97, 23.59, 18.02; HRMS (ESI) m/z calcd for C₁₅H₂₅O₅ (M⁺) 285.1702, observed 285.1713.

methyl 2-((2S,4S)-2-tert-butyl-4-isopentyl-5-oxo-1,3-dioxolan-4-yl)acetate (27) (I-JTW-055).

A solution of alkene 26 (123 mg, 0.43 mmol, 1.00 equiv.) in EtOAc (6 mL) was suspended with 10% Pd/C (12 mg, 10 wt%). The flask was equipped with a rubber septum, evacuated through a needle until the solvent begins to boil. A needle attached to an H₂ filled balloon was then inserted, and the flask evacuated until the pitch of the sound of the pump became high. The suspension was then stirred under balloon pressure H₂ overnight. The suspension was then filtered through a plug of celite and concentrated by rotary evaporation to yield 27 (125 mg, 100%) of a colorless oil.
\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 5.14 (s, 1H), 3.65 (s, 3H), 2.80 (s, 2H) 1.79 (m, 2H), 1.52 (septet, 1H, \(J=6.6\) Hz), 1.28 (m, 2H), 0.93 (s, 9H), 0.88 (d, 6H, \(J=6.6\) Hz); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 174.01, 168.77, 108.12, 80.27, 51.91, 39.61, 34.25, 32.01, 31.73, 28.11, 23.56, 22.37, 22.26; IR (neat film) 2959 (s), 2873 (s), 1799 (s), 1748 (s), 1367 (s), 1163 (br, s) cm\(^{-1}\); HRMS (ESI) m/z calcd for C\(_{15}\)H\(_{27}\)O\(_5\) (M+) 287.1858, observed 287.1866.

(R)-3-(benzyloxycarbonyl)-3-hydroxy-6-methylhept-5-enoic acid (ent-31) (I-JTW-157)

A solution of dioxolanone ent-25 (120 mg, 0.444 mmol, 1.00 equiv) in THF (4.5 mL) was cooled to 0 °C and benzyl alcohol (69 \(\mu\)L, 0.67 mmol, 1.5 equiv) was added via syringe followed by a 60% dispersion of NaH in mineral oil (45 mg, 1.1 mmol, 2.5 equiv) which resulted in vigorous evolution of gas. The solution was allowed to stir at 0 °C for 30 min, at which time the reaction was quenched with saturated aqueous NaHCO\(_3\) solution, removed from the cold bath and allowed to warm to 20 °C. The solution was then poured into H\(_2\)O (4.5 mL), washed with CH\(_2\)Cl\(_2\) (1x 6 mL), acidified to pH <5 with 1 N HCl, and then extracted with Et\(_2\)O (4x 6 mL). The combined ethereal phases were dried over MgSO\(_4\) and concentrated by rotary evaporation to yield a white solid. Purification by silica gel column chromatography (70:28:2 hex:EtOAc:HOAc) to provided ent-31 (114 mg, 88%) as a white solid.

\(R_f = 0.39\) (60:38:2 EtOAc:Hex:HOAc); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.35 (m, 5H), 5.20 (s, 2H), 5.07 (m, 1H), 3.00 (d, 1H, \(J=16.7\) Hz), 2.76 (d, 1H, \(J=16.7\) Hz), 2.41 (m, 2H), 1.67 (d, 3H, \(J=0.7\) Hz), 1.54 (d, 3H, \(J=0.7\) Hz); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 176.43, 174.60, 136.79, 135.21, 128.71, 128.64, 128.61, 116.45, 75.41, 67.95, 42.69, 38.14, 26.06, 18.09; IR (neat film)
3483 (br m), 2968 (m), 1736 (s), 1498 (w), 1195 (s) cm⁻¹; HRMS (ESI) m/z calcd for C₁₆H₂₀O₅Na (M⁺ + Na⁺) 315.1208, observed 315.1214; [α]D = −18° (c 2.98, CHCl₃).

(R)-1-benzyl 4-methyl 2-hydroxy-2-(3-methylbut-2-enyl)succinate (ent-32) (II-JTW-151)

To a solution of acid ent-31 (49.8 mg, 0.171 mmol, 1.00 equiv) in 7:2 PhH:MeOH (170 μL) was added a 2.0 M solution of TMSCHN₂ (128 μL, 0.257 mmol, 1.50 equiv.). After the resulting gas evolution had subsided, the solvent was removed by rotary evaporation to yield methyl ester ent-32 (52.0 mg, 100%) as a clear, colorless oil.

Rᵣ = 0.55 (2:1 hex:EtOAc); ¹H NMR (500 MHz, CDCl₃) δ 7.36 (m, 5H), 5.23 (d, 1H, J=12.1 Hz), 5.19 (d, 1H, J=12.1 Hz), 5.08 (m, 1H), 3.68 (s, 1H), 3.62 (s, 3H), 2.95 (d, 1H, J=16.2 Hz), 2.72 (d, 1H, J=16.3 Hz), 2.41 (m, 2H), 1.67 (s, 3H), 1.54 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 174.84, 171.43, 136.54, 135.46, 128.70, 128.66, 128.60, 116.75, 75.65, 67.79, 51.93, 42.81, 38.11, 26.06, 18.09; IR (neat film) 3514 (m), 3034 (w), 2955 (m), 1742 (s), 1498 (w), 1439 (s), 753 (m), 699 (m) cm⁻¹; LRMS (ESI) calc’d for C₁₇H₂₂O₅Na (M + Na⁺) 329.2, found 329.1.

(S)-2-hydroxy-2-(2-methoxy-2-oxoethyl)-5-methylhexanoic acid (28) (I-JTW-159)

A solution of diester 32 (105 mg, 0.34 mmol, 1.00 equiv) in EtOAc (3.5 mL) was suspended with 10% Pd/C (11 mg, 10 wt%). The flask was equipped with a rubber septum, evacuated through a needle until the solvent begins to boil. A needle attached to an H₂ filled balloon was then inserted, and the flask evacuated until the pitch of the sound of the pump changed. The
suspension was then stirred under balloon pressure H₂ overnight. The suspension was then filtered through a plug of celite and concentration by rotary evaporation yielded 28 (74 mg, 100%) of a clear, colorless oil.

¹H NMR (500 MHz) 3.709 (s, 3H) 2.99 (d, 1H, J=16.6 Hz) 2.74 (d, 1H, J=16.6 Hz) 1.72 (m, 2H) 1.51 (septet, 1H, J=6.6 Hz), 1.38 (m, 1H), 1.12 (m, 1H), 0.89 (d, 3H, J=2.6 Hz), 0.87 (d, 3H, J=2.6 Hz)

(R)-benzyl 2-(2-methoxy-2-oxoethyl)-5,5-dimethyltetrahydrofuran-2-carboxylate (33) (II-JTW-156)

To a solution of alcohol ent-32 (29.8 mg, 0.0979 mmol, 1.00 equiv) in 1:1 THF:H₂O (1.5 mL) was added Hg(OAc)₂ (60.6 mg, 0.196 mmol, 2.00 equiv). The resulting solution was stirred at 20 °C for 30 minutes. A 0.5 M solution of NaBH₄ in 3 M NaOH (196 μL, 0.0979 mmol, 1.00 equiv) was then added by syringe, resulting in an immediate precipitation of Hg⁰. After stirring for 5 m, the suspension was partitioned between saturated aqueous NH₄Cl solution (10 mL) and EtOAc (10 mL). The phases were separated and the aqueous phase was extracted with EtOAc (2x 10 mL). The combined organic phases were dried over MgSO₄ and solvent removal yielded a grey suspension that was redissolved in CH₂Cl₂ and filtered through celite. Concentration by rotary evaporation yielded crude product (27.4 mg, 92%). A portion of this product (18.3 mg) was purified by silica gel column chromatography (6:1 hex:EtOAc) to yield tetrahydrofuran 33 (17.7 mg, 76%) as a clear, colorless oil.

Rᵣ = 0.58 (2:1 hex:EtOAc); ¹H NMR (500 MHz, CDCl₃) δ 7.34 (m, 5H), 5.21 (d, 1H, J=12.3 Hz), 5.17 (d, 1H, J=12.3 Hz), 3.59 (s, 3H), 2.91 (d, 1H, J=15.4 Hz), 2.81 (d, 1H, J=15.4 Hz),
2.41 (m, 1H), 2.16 (m, 1H), 1.85 (m, 1H), 1.78 (m, 1H), 1.30 (s, 3H), 1.24 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 173.70, 170.54, 135.93, 128.59, 128.43, 128.32, 84.26, 83.96, 67.10, 51.80, 43.93, 37.88, 35.58, 29.09, 28.33; IR (neat film) 3036 (w), 2973 (m), 1743 (s), 1500 (w), 1458 (m), 1440 (w), 701 (m) cm$^{-1}$; LRMS (ESI) calc’d for C$_{17}$H$_{22}$O$_5$Na (M+Na$^+$) 329.2, found 329.1.

(R)-2-(2-methoxy-2-oxoethyl)-5,5-dimethyltetrahydrofuran-2-carboxylic acid (34) (II-JTW-157)

To a solution of benzyl ether 33 (17.7 mg, 0.0578 mmol, 1.00 equiv) in EtOAc (550 $\mu$L) was added 10% Pd/C (2.0 mg). The atmosphere in the vessel was replaced with H$_2$ and the reaction was stirred at 20 °C for 2 h, at which time it was filtered through a plug of celite. Solvent removal by rotary evaporation provided acid 34 (12.4 mg, 99%) as a white solid. $R_f$ = 0.07 (2:1 hex:EtOAc); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 3.69 (s, 3H), 3.13 (d, 1H, $J$=15.9 Hz), 2.67 (d, 1H, $J$=15.9 Hz), 2.43 (m, 1H), 2.22 (m, 1H), 1.87 (m, 2H), 1.39 (s, 3H), 1.31 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 175.72, 170.03, 85.91, 84.23, 52.08, 43.66, 37.67, 36.16, 28.69, 28.55; IR (neat film) ~3100-2800 (w), 2983 (s), 1753 (s), 1733 (s), 1459 (w), 1370 (w), 1265 (s), 1192 (m), 1106 (m), 778 (w) cm$^{-1}$; LRMS (ESI) calc’d for C$_{10}$H$_{16}$O$_5$Na (M + Na$^+$) 239.1, found 239.0.
**Anhydroharringtonine (3) (II-JTW-158)**

To a solution of acid 34 (4.2 mg, 0.019 mmol, 2.0 equiv) and triethylamine (8.7 μL, 0.063 mmol, 6.6 equiv) in CH₂Cl₂ (100 μL) was added 2,4,6-trichlorobenzoyl chloride (3.3 μL, 0.021 mmol, 2.2 equiv) *via* syringe. The resulting colorless solution was stirred at 23 °C for 1 h, then transferred *via* syringe to a solution of cephalotaxine (1) (2.95 mg, 0.00935 mmol, 1.00 equiv) and N,N-dimethylaminopyridine (DMAP) (1.46 mg, 0.0120 mmol, 1.28 equiv) in CH₂Cl₂ (100 μL). This solution was then stirred for 2 hours then loaded directly onto a silica gel column. The column was eluted with 2% Et₃N in 9:1 toluene:EtOAc to yield 3 (4.26 mg, 88%) as a light yellow oil.

Rᵣ = 0.31 (2% Et₃N in 9:1 toluene:EtOAc on plates pretreated with 5% Et₃N in pentane); ¹H NMR (500 MHz, CDCl₃) δ 6.58 (s, 1H), 6.56 (s, 1H), 5.87 (m, 3H), 5.02 (s, 1H), 3.80 (d, 1H, J=9.8 Hz), 3.68 (s, 3H), 3.58 (s, 3H), 3.18-3.06 (m, 2H), 2.93 (m, 1H), 2.58 (m, 2H), 2.33 (m, 1H), 2.32 (d, 1H, J=15.1 Hz), 2.26 (d, 1H, J=15.2 Hz), 2.03 (m, 2H), 1.87 (m, 2H), 1.75 (m, 2H), 1.65 (m, 2H), 1.24 (s, 3H), 1.14 (s, 3H); IR (neat film) 2965 (m), 2880 (m), 2796 (w), 1740 (s), 1654 (s), 1503 (s), 1487 (s), 1306 (s) cm⁻¹; LRMS (ESI) calc’d for C₂₈H₃₆NO₈ (M + Na⁺) 514.2, found 514.2.

(R)-benzyl 2-(3-methylbut-2-enyl)-4-oxooxetane-2-carboxylate (35) (I-JTW-262)

A solution of hydroxyester ent-31 (100 mg, 0.342 mmol, 1.00 equiv) and triethylamine (166 μL, 1.20 mmol, 3.50 equiv) in CH₂Cl₂ (14 mL) was added via syringe pump over 4 h to a solution of 2,4,6-trichlorobenzoyl chloride (80 μL, 0.51 mmol, 1.5 equiv) and N,N-dimethylaminopyridine (DMAP) (46 mg, 0.38 mmol, 1.1 equiv) in CH₂Cl₂ (3.4 mL). The solution was then allowed to
stir for 1 h after complete addition after which time it was quenched with H₂O (10 mL). The phases were separated and the aqueous phase was extracted with CH₂Cl₂ (2x 10 mL). The organic phases were combined, dried over Na₂SO₄, and the solvent was removed via rotary evaporation to yield a red solid which was purified by silica gel column chromatography (CH₂Cl₂) to yield 35 (47 mg, 50%) as a pale yellow oil.

\[ R_f = 0.79 \ (60:38:2 \text{ Hex:EtOAc:HOAc}) \]
\[ ^1H \text{ NMR (500 MHz, CDCl}_3\) \delta \ 7.37 \ (m, 5H), 5.25 \ (s, 2H), 5.09 \ (m, 1H), 3.61 \ (d, 1H, } J=16.4 \text{ Hz), 3.36 \ (d, 1H, } J=16.4 \text{ Hz), 2.79 \ (m, 2H), 1.70 \ (d, 3H, } J=0.8 \text{ Hz), 1.60 \ (d, 3H, } J=0.8 \text{ Hz); } ^13\text{C NMR (100 MHz, CDCl}_3\) \delta \ 169.21, 165.84, 138.67, 134.67, 128.68, 128.38, 114.24, 76.28, 67.84, 45.56, 33.43, 25.87, 17.99; IR (neat film) 2966 (m), 2914 (m), 1842 (s), 1737 (s), 1452 (m), 962 (m) cm⁻¹; HRMS (EI) m/z calcd for C₁₆H₁₈O₄ (M⁺) 274.120509, observed 274.120646; \[ [\alpha]_D = +1.2° \ (c 2.92, \text{ CHCl}_3) \].

(R)-2-isopentyl-4-oxooxetane-2-carboxylic acid (36) (1-JTW-229)

To a solution of benzyl ester 35 (220 mg, 0.802 mmol, 1.00 equiv) in EtOAc (8 mL) was added Pd/C (10 wt% on C, 44 mg, 20% by weight). The resulting suspension was stirred under H₂ (1 atm) for 23 h, then filtered through a plug of celite. Solvent removal by rotary evaporation yielded an oil which showed alkene peaks by \(^1H\) NMR, so the residue was resubjected to the reaction conditions to yield carboxylic acid 36 (150 mg, >99%) as a clear, colorless oil.

\[ R_f = 0.11 \ (60:38:2 \text{ Hex:EtOAc:HOAc}) \]
\[ ^1H \text{ NMR (400 MHz, CDCl}_3\) \delta \ 10.30 \ (br s, 1H), 3.71 \ (d, 1H, } J=16.6 \text{ Hz), 3.45 \ (d, 1H, } J=16.6 \text{ Hz), 2.19 \ (ddd, 1H, J=14.2, 12.3, 4.8 Hz), 2.04 \ (ddd, 1H, } J=14.2, 12.3, 4.8 Hz), 1.61 \ (septet, 1H, } J=6.6 \text{ Hz), 1.40 \ (m, 1H), 1.27 \ (m, 1H), 0.92 \ (d, 6H, } J=6.8 \text{ Hz).} \]
$J=6.6$ Hz); $^{13}$C NMR (400 MHz, CDCl$_3$) $\delta$ 174.96, 165.69, 76.43, 46.78, 33.17, 32.109, 27.89, 22.27, 22.20; IR (neat film) 3514 (br m), 3184 (br s), 2958 (s), 1828 (s), 1729 (s), 1408 (m), 1173 (s) cm$^{-1}$; $[\alpha]_D = 22.1^\circ$ (c 1.67, CHCl$_3$).

Deoxyharringtonine, $\beta$-lactone (37) (I-JTW-286)

To a solution of $\beta$-lactone 36 (8.9 mg, 0.048 mmol, 1.5 equiv) and triethylamine (19.9 $\mu$L, 0.143 mmol, 4.50 equiv) in CH$_2$Cl$_2$ (320 $\mu$L) was added 2,4,6-trichlorobenzoyl chloride (8.2 $\mu$L, 0.052 mmol, 1.7 equiv) via syringe. The resulting dark purple solution was stirred at 23 ºC for 1 h. This solution was then transferred via syringe to a solution of cephalotaxine (1) (10 mg, 0.032 mmol, 1.0 equiv) and N,N-dimethylaminopyridine (DMAP) in CH$_2$Cl$_2$ (320 $\mu$L). This solution was then stirred for 15 m, concentrated under a stream of N$_2$, and loaded directly onto a silica gel column that had been packed with 5% triethylamine in hexanes. The column was eluted with 1:1 hex:EtOAc to yield 37 (12.4 mg, 81%) as an oil.

$R_f = 0.39$ (1:1 hex:EtOAc on plates pretreated with 5% Et$_3$N in pentane); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.60 (app d, 2H), 5.91 (dd, 1H, $J=9.6$, 0.7 Hz), 5.86 (dd, 2H, $J=4.1$, 1.4 Hz), 5.08 (s, 1H), 3.81 (d, 1H, $J=9.5$ Hz), 3.69 (s, 3H), 3.10 (m, 2H), 2.98 (d, 1H, $J=16.5$ Hz), 2.93 (m, 1H), 2.73 (d, 1H, $J=16.5$ Hz), 2.58 (m, 2H), 2.35 (dd, 1H, $J=14.3$, 6.9), 2.04 (m, 1H), 1.88 (m, 2H), 1.75 (m, 2H), 1.62 (m, 1H), 1.47 (septet, 1H, $J=6.7$ Hz), 1.15 (m, 1H), 1.02 (m, 1H), 0.85 (dd, 6H, $J=6.7$, 1.2 Hz); $^{13}$C (500 MHz, CDCl$_3$) $\delta$ 171.03, 168.57, 166.25, 113.17, 109.96, 109.91, 101.11, 76.53, 75.62, 65.63, 57.36, 54.05, 48.60, 46.31, 41.74, 33.21, 31.97, 27.91, 22.46, 22.14,
20.39; IR (neat film) 2958 (m), 1842 (s), 1750 (m), 1504 (m), 1488 (s), 1037 (m) cm⁻¹; HRMS (EI) m/z calcd for C₂₇H₃₃NO₇ (M⁺) 483.225703 found 483.224659; [α]D = -95° (c 2.77, CHCl₃).

**Deoxyharringtonine (2) (II-JTW-015)**

To a solution of β-lactone 37 (18 mg, 0.0372 mmol, 1.00 equiv) in MeOH (370 μL) was added a freshly prepared solution of 0.5 M NaOMe in MeOH (82 μL, 0.0409 mmol, 1.10 equiv). After 15 min the solution was quenched with ½ saturated aqueous NH₄Cl solution (300 μL) and partitioned between H₂O (10 mL) and CH₂Cl₂ (10 mL). The phases were separated and the aqueous phase was extracted with CH₂Cl₂ (2x 10 mL), the combined organic phases were dried over MgSO₄, and concentrated by rotary evaporation to yield a yellow oil that was purified by silica gel column chromatography (70:28:2 benzene:hex:Et₃N) to yield 2 (14.6 mg, 76% after correction for residual benzene) as a clear, colorless oil. Residual benzene was very difficult to remove. Several iterations of dissolution in CH₂Cl₂ followed by several hours of high vacuum did not eliminate it.

Rₐ = 0.24 (9:1 benzene:EtOAc on plates pretreated with 5% Et₃N in pentane); ¹H NMR (500 MHz, CDCl₃) δ 6.62 (s, 1H), 6.53 (s, 1H), 5.99 (dd, 1H, J=9.8, 0.7 Hz), 5.86 (dd, 2H, J=11.8, 1.5 Hz), 5.04 (d, 1H, J=0.6 Hz), 3.77 (d, 1H, J=9.8 Hz), 3.67 (s, 3H), 3.57 (s, 3H), 3.48 (s, 1H), 3.12 (m, 2H), 2.94 (td, 1H, J=11.1, 7.1 Hz), 2.58 (m, 2H), 2.37 (dd, 1H, J=14.3, 7 Hz), 2.27 (d, 1H, J=16.6 Hz), 2.04 (m, 1H), 1.91 (m, 1H), 1.88 (d, 1H, J=16.2 Hz), 1.75 (m, 2H), 1.42 (m, 3H),

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1.29 (m, 1H), 0.97 (m, 1H), 0.84 (d, 3H, $J=7.0$ Hz), 0.83 (d, 3H, $J=7.0$ Hz) $^{13}$C NMR (400 MHz, CDCl$_3$) $\delta$ 174.19, 170.57, 157.87, 146.75, 145.92, 133.43, 128.55, 128.46 (residual benzene), 112.75, 109.80, 100.94, 100.16, 74.83, 74.69, 70.70, 57.25, 55.98, 54.12, 51.63, 48.82, 43.54, 42.89, 36.87, 31.70, 31.48, 28.13, 22.83, 22.38, 20.42; IR (neat film) 3527 (w), 2955 (m), 1748 (s), 1653 (m), 1504 (m), 1488 (s), 1225 (s), 1036 (m), 754 (m); HRMS (ESI) calcd for C$_{28}$H$_{38}$NO$_8$ (M$^+$ + H) 516.2597 observed 516.2581; $[\alpha]_D = -110^\circ$ (c 1.46, CHCl$_3$).

(R)-1-benzyl 4-methyl 2-acetoxy-2-(3-methylbut-2-enyl)succinate (S1).

To a solution of tertiary alcohol ent-32 (33.0 mg, 0.109 mmol, 1.00 equiv) in dry pyridine (500 $\mu$L) at 0 ºC was added acetic anhydride (114 $\mu$L, 1.09 mmol, 10.0 equiv) and N,N-dimethylaminopyridine (DMAP) (3.0 mg, 0.0246 mmol, 0.23 equiv). The solution was then stirred at 23 ºC for 17 h at which time further DMAP (13.0 mg, 1.09 mmol, 1.00 equiv) and acetic anhydride (22 $\mu$L, 0.21 mmol, 1.9 equiv) were added. After 1 h the solution was diluted with H$_2$O (10 mL) and extracted with CH$_2$Cl$_2$ (3x 10 mL). The combined organic extracts were washed with 0.1 M aqueous CuSO$_4$ soln, dried over MgSO$_4$, and concentrated by rotary evaporation to yield a dark red oil. Purification by silica gel column chromatography (5:1 hexanes:EtOAc) provided S1 (28.1 mg, 74%) as a colorless oil.

$R_f = 0.32$ (5 : 1 hexanes : ethyl acetate, CAM stain); $^1$H NMR (500MHz, CDCl$_3$) $\delta$ 7.35 (m, 5H), 5.14 (m, 2H), 5.00 (tt, 1H, $J=7.5$, 1.3 Hz), 3.64 (s, 3H), 3.27 (d, 1H, $J=14.7$ Hz), 2.96 (d, 1H, $J=14.7$ Hz), 2.80 (dd, 1H, $J=14.6$, 7.6 Hz), 2.69 (dd, 1H, $J=14.6$, 7.6 Hz), 2.06 (s, 3H), 1.67 (s, 3H), 1.56 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 170.34, 170.10, 169.79, 137.21, 135.45,
(R)-2-acetoxy-2-(2-methoxy-2-oxoethyl)-5-methylhex-4-enoic acid (38). To a solution of benzyl ester S1 (28.0 mg, 0.0804 mmol, 1.00 equiv) in ethyl acetate (1.5 mL) was added 10% Pd/C (3.5 mg, 13 wt %). The resulting suspension was stirred under H\textsubscript{2} (1 atm) for 15 h and filtered through a plug of celite. Solvent removal by rotary evaporation yielded carboxylic acid 38 (20.9 mg, 100%) as a clear, colorless oil.

\( ^{1}H \text{NMR} (500 MHz, \text{CDCl}_3) \delta 10.34 \text{ (br s, 1H)}, 3.68 \text{ (s, 3H)}, 3.29 \text{ (d, 1H, } J=14.8 \text{ Hz)}, 3.00 \text{ (d, 1H, } J=14.8 \text{ Hz)}, 2.09 \text{ (s, 3H)}, 2.02 \text{ (m, 2H), 1.54 \text{ (septet, 1H, } J=6.6 \text{ Hz}), 1.22 \text{ (m, 2H)}, 0.89 \text{ (d, 6H, } J=6.6 \text{ Hz)}; \text{CDCl}_3 \) \( ^{13}C \text{NMR} (125 \text{ MHz, CDCl}_3) \delta 175.83, 170.18, 169.84, 80.49, 52.02, 37.55, 33.54, 31.89, 28.11, 22.55, 22.39, 21.08; \text{IR (neat film) 3182 (v br m), 2958 (m), 2873 (m), 1746 (s), 1440 (m), 1370 (m), 1209 (s), 645 (w); LRMS (ESI) 283.01 (M + Na).}

2-((2R,4R)-4-allyl-2-tert-butyl-5-oxo-1,3-dioxolan-4-yl)acetic acid (47) (II-JTW-072)

A solution of LHMDS (413 mg, 2.47 mmol, 1.00 equiv) in THF (5 mL) at \(-78 \) °C was transferred via cannula to a stirred solution of acid ent-24 (500 mg, 2.47 mmol, 1.00 equiv) in THF (25 mL) at \(-78 \) °C. The resulting solution was stirred at \(-78 \) °C for 10 m. A solution of LHMDS (621 mg, 3.71 mmol, 1.50 equiv) in THF (7 mL) at \(-78 \) °C was then added via cannula and the resulting solution was stirred for 20 m at \(-78 \) °C. Allyl bromide (439 \mu L, 5.19 mmol,
2.10 equiv) was then added via syringe and the resulting solution was stirred at –78 °C for 21 h, at which time the reaction was partitioned between 1 N aqueous HCl (75 mL) and CH₂Cl₂ (75 mL), the phases were separated and the aqueous phase was extracted with CH₂Cl₂ (2x 50 mL). The combined organic phases were dried over MgSO₄ and concentrated via rotary evaporation to yield an oily solid. Purification by silica gel column chromatography (19:1 MeOH:CH₂Cl₂) yielded 47 (344 mg, 59%) as a clear, colorless oil.

R⁻ = 0.69 (60:38:2 EtOAc:Hex:HOAc); ¹H NMR (500 MHz, CDCl₃) δ 5.77 (m, 1H), 5.22 (m, 3H), 2.86 (d, 1H, J=16 Hz), 2.81 (d, 1H, J=16.0 Hz), 2.55 (m, 2H), 0.92 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 174.96, 173.49, 130.11, 121.34, 108.47, 79.90, 39.62, 38.18, 34.45, 23.66; IR (neat film) ~3500-2500 (br s), 2966 (s), 1793 (s), 1718 (s), 1165 (m) cm⁻¹; LRMS (ESI) calcd. for C₁₂H₁₉O₅Na (M + Na⁺) 265.1, observed 264.9.

(R)-3-(benzyloxycarbonyl)-3-hydroxyhex-5-enoic acid (48) (II-JTW-096)

A solution of dioxolanone 47 (1.10 g, 4.54 mmol, 1.00 equiv) in THF (45 mL) was cooled to 0 °C and benzyl alcohol (564 μL, 5.45 mmol, 1.20 equiv) was added via syringe followed by a 60% dispersion of NaH in mineral oil (454 mg, 11.35 mmol, 2.50 equiv) which resulted in vigorous evolution of gas. The solution was allowed to warm to 20 °C over 90 m, at which time the reaction was again cooled to 0 °C, quenched with 1 N aqueous HCl (45 mL), poured into EtOAc (45 mL). The phases were separated and the aqueous phase was extracted with a further EtOAc (3x 45 mL). The combined organic phases were dried over MgSO₄ and solvent removal by rotary evaporation yielded an oil which was purified by silica gel column chromatography (60:40:2 hex:EtOAc:HOAc) to yield 48 (1.02 g, 85%) as a clear, colorless oil.
\[ R_f = 0.60 \ (38:60:2 \ \text{hex:EtOAc:HOAc}) \]

\[ ^1H \ NMR \ (500 \ \text{MHz, CDCl}_3) \ \delta \ 7.37 \ (m, \ 5H), \ 5.74 \ (m, \ 1H), \ 5.22 \ (d, \ 1H, J=10.1 \ \text{Hz}), \ 5.18 \ (d, \ 1H, J=10.1 \ \text{Hz}), \ 5.11 \ (d, \ 1H, J=8.8 \ \text{Hz}), \ 5.06 \ (d, \ 1H, J=17.1 \ \text{Hz}), \ 2.99 \ (d, \ 1H, J=16.6 \ \text{Hz}), \ 2.76 \ (d, \ 1H, J=16.6 \ \text{Hz}), \ 2.45 \ (d, \ 2H, J=7.2) ; \]

\[ ^{13}C \ NMR \ (125 \ \text{MHz, CDCl}_3) \ \delta \ 176.19, \ 174.34, \ 135.14, \ 131.13, \ 128.74, \ 128.68, \ 120.01, \ 74.98, \ 68.08, \ 43.83, \ 42.74; \]

IR (neat film) \ (~3500-2500 \ (br m), 3077, 1737 \ (s), 1641 \ (w), 1219 \ (m) cm\textsuperscript{-1}; \]

LRMS (ESI) calcd. for C\textsubscript{14}H\textsubscript{16}O\textsubscript{5}Na (M + Na\textsuperscript{+}) 287.1, observed 286.9.

\[(R)-\text{benzyl 2-allyl-4-oxooxetane-2-carboxylate (49)} \ (\text{II-JTW-100})\]

A solution of hydroxyester 48 (1.02 g, 3.86 mmol, 1.00 equiv) and triethylamine (519 \ \mu L, 17.37 mmol, 4.50 equiv) in CH\textsubscript{2}Cl\textsubscript{2} (77 mL) was added via syringe pump over 4 h to a solution of 2,4,6-trichlorobenzoyl chloride (904 \ \mu L, 5.79 mmol, 1.50 equiv) and N,N-dimethylaminopyridine (DMAP) (519 mg, 4.25 mmol, 1.10 equiv) in CH\textsubscript{2}Cl\textsubscript{2} (39 mL). The solution was then allowed to stir for 30 min after complete addition after which it was quenched with H\textsubscript{2}O (100 mL). The phases were separated and the aqueous phase was extracted with CH\textsubscript{2}Cl\textsubscript{2} (2x 100 mL). The organic phases were combined, dried over MgSO\textsubscript{4}, and the solvent was removed via rotary evaporation to yield a black oil which was purified by silica gel column chromatography (CH\textsubscript{2}Cl\textsubscript{2}) to yield 49 (639 mg, 67%) as a yellow oil.

\[ R_f = 0.52 \ (CH\textsubscript{2}Cl\textsubscript{2}); \]

\[ ^1H \ NMR \ (500 \ \text{MHz, CDCl}_3) \ \delta \ 7.38 \ (m, \ 5H), \ 5.76 \ (m, \ 1H), \ 5.26 \ (s, \ 2H), \ 5.22 \ (m, \ 2H), \ 3.65 \ (d, \ 1H, J=16.5 \ \text{Hz}), \ 3.42 \ (d, \ 1H, J=16.5 \ \text{Hz}), \ 2.89 \ (dd, \ 1H, J=14.6, 6.8 \ \text{Hz}), \ 2.80 \ (dd, \ 1H, J=14.6, 6.8 \ \text{Hz}); \]

\[ ^{13}C \ NMR \ (125 \ \text{MHz, CDCl}_3) \ \delta \ 169.03, \ 165.61, \ 134.75, \ 129.10, \ 128.95, \ 128.89, \ 128.59, \ 121.82, \ 75.65, \ 68.17, \ 45.86, \ 39.06; \]

IR (neat film) 3034 (w), 1843 (s),
1741 (s), 1644 (w), 1456 (m) cm⁻¹; LRMS (ESI) calcd. for C₁₄H₁₄O₄Na (M + Na⁺) 269.1, observed 269.1.

(R,E)-benzyl 2-(4-(benzyloxy)-4-methylpent-2-enyl)-4-oxooxetane-2-carboxylate (51) (II-JTW-204)

A solution of alkene 49 (58.8 mg, 0.239 mmol, 1.00 equiv) in benzyl ether 50 (842 mg, 4.78 mmol, 20 equiv) was subjected to two freeze-pump-thaw cycles. Grubbs catalyst, 2nd generation (20.1 mg, 0.0237 mmol, 0.10 equiv) was then added and the resulting solution was subjected to one more freeze-pump-thaw cycle then allowed to stir at 20 ºC for 16 h. Another portion of catalyst (10.3 mg, 0.0121 mmol, 0.051 equiv) was then added and the solution was again subjected to one freeze-pump-thaw cycle and allowed to stir at 20 ºC for 8 h. A third portion of catalyst (10.2 mg, 0.0120 mmol, 0.050 equiv) was added and the solution was subjected to one freeze-pump-thaw cycle then allowed to stir at 20 ºC for 25 h. The crude reaction mixture was then loaded directly onto a pH 7.0 buffered silica gel (10 wt% buffer) column which was eluted with a gradient eluant (1:1 hex:CH₂Cl₂ to CH₂Cl₂) to yield 52 (57.6 mg, 61%) as a yellow oil and 51 (11.5 mg 22%) as a yellow oil.

Rᵣ = 0.28 (CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃) δ 7.4-7.2 (m, 10H), 5.76 (d, 1H, J=15.9 Hz), 5.57 (dt, 2H, J=15.8, 7.2 Hz), 5.22 (s, 2H), 4.31 (s, 2H), 3.64 (d, 1H, J=16.4 Hz), 3.37 (d, 1H, J=16.5 Hz), 2.90 (dd, 1H, J=14.6, 7.0 Hz), 2.80 (dd, J=14.5, 7.3 Hz), 1.31 (d, 6H, J=2.8 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 168.98, 165.50, 143.38, 139.56, 134.72, 128.97, 128.93, 128.56, 128.45, 127.41, 127.35, 120.22, 75.82, 75.30, 68.14, 65.11, 46.01, 37.90, 26.49, 26.41; IR (neat
film) 3032 (m), 2976 (m), 1838 (s), 1498 (m), 1455 (m), 1059 cm\(^{-1}\); HRMS (ESI) calcd. for C\(_{24}\)H\(_{26}\)O\(_5\)Na (M + Na\(^+\)) 417.1678, found 417.1673.

Data for dimer 51: \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.37 (m, 10H), 5.54 (m, 2H), 5.24 (s, 4H), 3.60 (d, 2H, \(J=16.5\) Hz), 3.32 (d, 2H, \(J=16.5\) Hz), 2.8 (m, 4H)

Dimer Recycle (II-JTW-272)

A solution of dimer 51 (36.5 mg, 0.0786 mmol, 1.00 equiv) in benzyl ether 50 (576 mg, 3.27 mmol, 41.6 equiv) was subjected to 2x freeze-pump-thaw cycles. Grubbs catalyst, 2\(^{nd}\) generation (6.9 mg, 0.00818 mmol, 0.10 equiv) was added and the resulting solution was subjected to one more freeze-pump-thaw cycle then allowed to stir at 20 \(^\circ\)C for 14 h. Another portion of catalyst (7.1 mg, 0.00836, 0.11 equiv) was added and the solution was subjected to one freeze-pump-thaw cycle then allowed to stir at 20 \(^\circ\)C for 9.5 h. A third portion of catalyst (6.8 mg, 0.0080 mmol, 0.10 equiv) was added and the solution was subjected to one freeze-pump-thaw cycle then allowed to stir at 20 \(^\circ\)C for 18.5 h. The crude reaction mixture was loaded directly onto a pH 7.0 buffered silica gel (10 wt% buffer) column which was eluted with a gradient eluant (1:1 hex:CH\(_2\)Cl\(_2\) to CH\(_2\)Cl\(_2\)) to yield 52 (40.2 mg, 65%) as a colorless oil. Data are identical to that reported above.

\(\text{(R,E)-2-(4-(benzyloxy)-4-methylpent-2-enyl)-4-oxooxetane-2-carboxylic acid (53) (II-JTW-205)}\)

To a solution of benzyl ester 52 (52.8 mg, 0.134 mmol, 1.00 equiv.) in CH\(_2\)Cl\(_2\) (500 \(\mu\)L) were added Et\(_3\)N (3.0 \(\mu\)L, 0.0214 mmol, 0.16 equiv.), triethylsilane (32.1 \(\mu\)L, 0.201 mmol, 1.50
equiv.), and Pd(OAc)$_2$ (1.6 mg, 0.0071 mmol, 0.053 equiv.). The resulting black solution was stirred at 20 ºC for 1 h then partitioned between saturated NH$_4$Cl solution (10 mL) and CH$_2$Cl$_2$ (10 mL). The phases were separated and the aqueous phase was extracted with CH$_2$Cl$_2$ (2x 10 mL). The combined aqueous phases were dried over MgSO$_4$ and solvent removal by rotary evaporation left a brown oil that upon purification by silica gel column chromatography (4% HOAc in 1:1 hex:EtOAc) yielded acid 53 (34.4 mg, 85%) as a clear, colorless oil.

R$^f$ = 0.17 (4% HOAc in 1:1 hex:EtOAc); $^1$H NMR (500 MHz, CDCl$_3$) δ 10.09 (br s, 1H), 7.33-7.23 (m, 5H), 5.81 (d, 1H, $J$=15.9 Hz), 5.62 (m, 1H), 4.35 (s, 2H), 3.57 (d, 1H, $J$=16.6 Hz), 3.36 (d, 1H, $J$=16.6, Hz), 2.87 (dd, 1H, $J$=14.6, 7.1 Hz), 2.74 (dd, 1H, $J$=14.7, 7.3 Hz), 1.35 (s, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 173.48, 165.44, 143.27, 139.13, 128.48, 127.66, 127.53, 120.34, 75.85, 65.24, 46.06, 37.57, 26.51, 26.29; IR (neat film) ~3500-2500 (br m), 3031 (w), 2977 (m), 1843 (s), 1745 (s), 1497 (w), 1453 (w), 1149 (m) cm$^{-1}$; LRMS (ESI) calc’d for C$_{17}$H$_{20}$O$_5$Na 327.1, found 326.9.

(R,E)-2-(4-(benzyloxy)-4-methylpent-2-enyl)-4-oxooxetane-2-cephalotaxyl carboxylate (54)

(II-JTW-145)

To a solution of β-lactone 53 (34.5 mg, 0.114 mmol, 2.00 equiv) and triethylamine (52.4 μL, 0.378 mmol, 6.6 equiv) in CH$_2$Cl$_2$ (570 μL) was added 2,4,6-trichlorobenzoyl chloride (19.6 μL, 0.126 mmol, 2.20 equiv) via syringe. The resulting dark purple solution was stirred at 20 ºC for 1 h, then transferred via syringe to a solution of cephalotaxine (1) (18.0 mg, 0.0571 mmol, 1.00
equiv) and N,N-dimethylaminopyridine (DMAP) (7.8 mg, 0.063 mmol, 1.10 equiv) in CH₂Cl₂ (570 μL). This solution was then stirred for 25 minutes then loaded directly onto a pH 7.0 buffered silica gel column. The column was eluted with 1% Et₃N in 9:1 toluene:EtOAc to yield 54 (33.3 mg, 97%) as a light yellow oil. 

Rᵣ = 0.24 (1% Et₃N in 9:1 toluene:EtOAc on a TLC plate pretreated with 5% Et₃N in pentane); 

¹H NMR (500 MHz, CDCl₃) δ 7.32-7.22 (m, 5H), 6.60 (s, 1H), 6.59 (s, 1H), 5.86 (m, 3H), 5.71 (d, 1H, J=15.9 Hz), 5.47 (dt, 1H, J=15.8, 8.5 Hz), 5.08 (s, 1H), 4.31 (s, 2H), 3.80 (d, 1H, J=9.5 Hz), 3.68 (s, 3H), 3.08 (m, 2H), 2.98 (d, 1H, J=16.4 Hz), 2.94 (m, 1H), 2.64 (d, 1H, J=16.5 Hz), 2.59 (m, 3H), 2.43-2.34 (m, 2H), 2.02 (m, 1H), 1.90 (m, 1H), 1.75 (m, 2H), 1.32 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 168.22, 165.58, 156.71, 147.19, 146.13, 143.19, 139.81, 133.73, 128.49, 128.01, 127.52, 127.37, 120.57, 113.50, 109.98, 101.39, 101.24, 75.95, 75.67, 75.41, 70.87, 65.17, 57.50, 56.66, 54.20, 48.74, 45.39, 43.72, 37.73, 31.70, 26.55, 26.39, 20.60; IR (neat film) 2972 (m), 2801 (w), 1842 (s), 1751 (s), 1654 (s), 1504 (s), 1223 (s) cm⁻¹; LRMS (ESI) calc’d for C₃₅H₄₀NO₈ 602.3, found 602.5.

(R,E)-1-cephalotaxyl 4-methyl 2-(4-(benzyloxy)-4-methylpent-2-enyl)-2-hydroxysuccinate (55) (II-JTW-146)

To a solution of β-lactone 54 (33.0 mg, 0.0548 mmol, 1.00 equiv) in MeOH (550 μL) was added a freshly prepared solution of 0.5M NaOMe in MeOH (121 μL, 0.0603 mmol, 1.10 equiv). After 10 m the solution was quenched with sat’d NH₄Cl solution (300 μL) and partitioned between
saturated NH₄Cl solution (10 mL) and CH₂Cl₂ (10 mL). The phases were separated and the aqueous phase was extracted with CH₂Cl₂ (2x 10 mL), the combined organic phases were dried over MgSO₄, and concentrated by rotary evaporation to yield a yellow oil that was purified by silica gel column chromatography (1% Et₃N in 9:1 toluene:EtOAc) to yield 55 (27.5 mg, 79%) as a clear, colorless oil.

Rₛ = 0.18 (9:1 toluene:EtOAc on plates pretreated with 5% Et₃N in pentane); ¹H NMR (500 MHz, CDCl₃) δ 7.33-7.22 (m, 5H), 6.61 (s, 1H), 6.55 (s, 1H), 5.94 (d, 1H, J=9.7 Hz), 5.85 (app d, 2H), 5.62 (d, 1H), 5.51 (m, 1H), 5.05 (s, 1H), 4.33 (s, 2H), 3.77 (d, 1H, J=9.8 Hz), 3.66 (s, 3H), 3.58 (s, 3H), 3.45 (s, 1H), 3.12 (m, 2H), 2.94 (m, 1H), 2.59 (m, 2H), 2.38 (dd, 1H, J=14.1, 6.9 Hz), 2.29 (d, 1H, J=16.4 Hz), 2.20 (m, 2H), 2.01 (m, 1H), 1.96 (d, 1H, J=16.4 Hz), 1.90 (m, 1H), 1.75 (m, 2H), 1.33 (d, 6H, J=3.1); ¹³C NMR (125 MHz, CDCl₃) δ 173.72, 170.50, 146.98, 146.07, 141.16, 140.02, 128.44, 127.66, 127.29, 123.16, 113.06, 109.86, 101.05, 100.50, 75.47, 75.25, 74.61, 65.15, 57.49, 56.16, 54.15, 51.80, 48.81, 43.56, 41.92, 41.77, 31.63, 26.69, 26.52, 20.50.

**Homoharringtonine (4) (II-JTW-147)**

To a solution of allylic benzyl ether 55 (12.6 mg, 0.0199 mmol, 1.00 equiv.) in MeOH (200 μL) was added 10% Pd/C (2.4 mg, 20% by wt). The atmosphere in the vessel was replaced with H₂ under balloon pressure and the suspension was stirred at 20 ºC until LRMS (ESI) showed complete reduction of the alkene (26 h). Glacial acetic acid (20 μL) was added via syringe and
the solution was stirred under H₂ at 20 ºC for 21 h. Further 10% Pd/C (1.3 mg) and glacial acetic acid (20 μL) were added and the suspension was stirred under H₂ for 24 h then filtered through a plug of celite. The solvent was removed by rotary evaporation and the resulting film was purified by silica gel column chromatography (2% Et₃N in 1:1 toluene:EtOAc) to yield homoharringtonine (4) (8.5 mg, 79%) as a colorless film.

R_f = 0.25 (2% Et₃N in 1:1 toluene:EtOAc on TLC plates pretreated with 5% Et₃N in pentane); ¹H NMR (500 MHz, CDCl₃) δ 6.62 (s, 1H), 6.54 (s, 1H), 6.00 (d, 1H, J=9.8 Hz), 5.87 (app dd, 2H, J=2.9, 1.4), 5.05 (s, 1H), 3.77 (d, 1H, J=9.7 Hz), 3.67 (s, 3H), 3.57 (s, 3H), 3.52 (s, 1H), 3.10 (m, 2H), 3.00 (m, 1H), 2.60 (m, 2H), 2.40 (dd, 1H, J=14.2, 6.9 Hz), 2.26 (d, 1H, J=16.5 Hz), 2.02 (m, 1H), 1.90 (d, 1H, J=16.5 Hz), 1.89 (m, 1H), 1.75 (m, 2H), 1.45-1.36 (m, 5H), 1.27 (br s, 1H), 1.19 (app d, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 173.62, 170.38, 157.63, 146.86, 145.96, 141.06, 139.93, 133.44, 128.43, 128.33, 127.55, 127.18, 123.06, 112.95, 109.75, 100.94, 100.43, 75.37, 75.16, 74.51, 70.66, 65.05, 57.38, 56.11, 54.06, 51.69, 48.73, 43.50, 41.82, 41.67, 31.56, 26.59, 26.43, 20.42; IR (neat film) 3526 (br m), 2960 (s), 1744 (s), 1654 (s), 1503 (s), 1366 (s), 1225 (s), 932 (m), 754 (s) cm⁻¹; LRMS (ESI) calcd for C₂₉H₄₀NO₉ (M⁺ + H) 545.26 found 545.7; [α]D = -112º (c 0.75, CHCl₃).

**Homodeoxyharringtonine (5) (III-JTW-152)**

To a solution of allylic benzyl ether 55 (12.2 mg, 0.0192 mmol, 1.0 equiv) in glacial acetic acid (800 μL) was added degussa grade (E101 NE/W from Aldrich) Pd/C (10 wt % dry basis, 50%
water, 25.3 mg, 62 mol%). The atmosphere in the vessel was replaced with H\(_2\) (1 atm) and the suspension was stirred for 20 h at 20 °C, filtered through a plug of celite, flushed with glacial acetic acid, and the solvent was removed by azeotrope with toluene. The crude product was purified by pH 7.0 buffered (10 wt %) silica gel column chromatography (2% Et\(_3\)N in 1:1 toluene:EtOAc) to yield homodeoxyharringtonine (5) (7.0 mg, 69%) as a colorless film as well as homoharringtonine (4) (2.8 mg 27%) as a colorless film.

R\(_f\) = 0.66 (2% Et\(_3\)N in 1:1 toluene:EtOAc on TLC plates pretreated with 5% Et\(_3\)N in pentane); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 6.62 (s, 1H), 6.53 (s, 1H), 5.99 (d, 1H, \(J=9.8\) Hz), 5.86 (dd, 2H, \(J=9.8, 1.5\) Hz), 5.04 (s, 1H), 3.77 (d, 1H, \(J=9.8\) Hz), 3.66 (s, 3H), 3.57 (s, 3H), 3.48 (s, 1H), 3.11 (m, 2H), 2.95 (m, 1H), 2.59 (m, 2H), 2.38 (dd, \(J=14.8, 6.9\), 1H), 2.31 (d, 1H, \(J=16.5\) Hz), 2.05 (m, 1H), 1.91 (m, 1H), 1.90 (d, 1H, \(J=16.5\) Hz), 1.75 (m, 2H), 1.49 (m, 1H), 1.38 (m, 3H), 1.09 (m, 3H), 0.85 (app t, 6 H, \(J=6.4\) Hz); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 174.24, 170.61, 157.95, 146.82, 145.96, 133.48, 128.55, 112.81, 109.84, 100.96, 100.20, 74.84, 74.80, 70.75, 57.38, 56.00, 54.09, 51.63, 48.75, 43.53, 42.79, 39.16, 39.08, 31.49, 27.93, 22.81, 22.51, 20.71, 20.44; IR (neat film) 3529 (br w), 2953 (s), 1748 (s), 1654 (m), 1504 (m), 1487 (s), 1224 (s), 932 (m) cm\(^{-1}\); LRMS (ESI) calcd for C\(_{29}\)H\(_{40}\)NO\(_8\) (M\(^+\) + H) 530.27 found 530.3; \([\alpha]_D = -112^\circ\) (c 0.7, CHCl\(_3\)).

(R)-4-oxo-2-propyloxetane-2-carboxylic acid (56) (II-JTW-286)

To a solution of benzyl ester 49 (30.3 mg, 0.123 mmol, 1.0 equiv) in EtOAc (1.5 mL) was added 10% Pd/C (3.2 mg, 0.0030 mmol, 2.4 mol%). The atmosphere in the vessel was replaced with
H₂ under balloon pressure and the mixture was stirred at 20 °C for 15 h. The suspension was then filtered through a plug of celite and flushed with EtOAc (25 mL). Solvent removal yielded carboxylic acid 56 (19.0 mg, 97%) as a yellow oil.

1H NMR (500 MHz, CDCl₃) δ 11.3 (br s, 1H), 3.73 (d, 1H, J=16.6 Hz), 3.45 (d, 1H, J=16.5 Hz), 2.20-2.15 (m, 1H), 2.06-2.00 (m, 1H), 1.57-1.50 (m, 1H), 1.48-1.44 (m, 1H), 1.01 (t, 3H, J=7.3 Hz); 13C NMR (125 MHz, CDCl₃) δ 175.04, 165.78, 76.44, 47.07, 37.38, 17.20, 13.93; IR (neat film) 3500-3000 (br m), 2966 (m), 2878 (m), 1834 (s), 1736 (s), 1410 (w), 1143 (m), 960 (w) cm⁻¹.

β-lactone 57 (III-JTW-006)

To a solution of acid 56 (9.9 mg, 0.063 mmol, 2.0 equiv) and cephalotaxine (1) (9.9 mg, 0.031 mmol, 1.0 equiv) in CH₂Cl₂ (630 μL) were added triethylamine (29 μL, 0.21 mmol, 6.6 equiv) and 2,4,6-trichlorobenzoyl chloride (10.9 μL, 0.0697 mmol, 2.20 equiv) via syringe and N,N-dimethylaminopyridine (DMAP) (4.4 mg, 0.0360 mmol, 1.14 equiv) as a solid. The resulting dark purple solution was stirred at 20 °C for 15 min (TLC showed complete consumption of cephalotaxine after 5 min), then loaded directly onto a silica gel column. The column was eluted with 2% Et₃N in 9:1 toluene:EtOAc to yield 57 (11.7 mg, 81%) as a colorless oil.

Rₓ = 0.48 (2% Et₃N in 9:1 toluene:EtOAc on plates pretreated with 5% Et₃N in pentane); ¹H NMR (500 MHz, CDCl₃) δ 6.61 (s, 1H), 6.59 (s, 1H), 5.90 (d, 1H, J=9.5 Hz), 5.86 (dd, 2H, J=7.8, 1.5 Hz), 5.08 (s, 1H), 3.81 (d, 1H, J=9.6 Hz), 3.69 (s, 3H), 3.14-3.07 (m, 2H), 3.02 (d, 1H,
$J=16.5\text{Hz}$, 2.96-2.90 (m, 1H), 2.85 (d, 1H, $J=16.5\text{Hz}$), 2.61-2.56 (m, 2H), 2.36 (dd, 1H, $J=14.3, 6.9\text{Hz}$), 2.05-2.00 (m, 1H), 1.92-1.88 (m, 1H), 1.84-1.72 (m, 3H), 1.64-1.58 (m, 1H), 1.20-1.07 (m, 2H), 0.86 (t, 3H, $J=14.8\text{Hz}$); $^{13}\text{C NMR (125 MHz, CDCl}_3\right)s\delta 168.62, 166.26, 156.79, 147.07, 145.99, 133.86, 127.89, 113.16, 110.02, 101.10, 76.48, 75.75, 70.85, 57.44, 56.43, 54.08, 48.63, 46.35, 43.61, 37.36, 31.55, 20.45, 16.82, 13.94; IR (neat film) 2961 (m), 1838 (s), 1743 (s), 1655 (s), 1516 (m), 1487 (s), 1376 (w), 1037 (s), 731 (s) cm$^{-1}$; LRMS (ESI) (calcd for C$_{25}$H$_{30}$NO$_7$ (M$^+$ + H) 455.19 found 455.96; $[^\alpha]_D = -120^\circ$ (c 1.13, CDCl$_3$).

Bis-demethyldeoxyharringtonine (58) (III-JTW-008)

To a solution of $\beta$-lactone 57 (9.5 mg, 0.021 mmol, 1.0 equiv) in MeOH (210 $\mu$L) was added a freshly prepared solution of 0.5M NaOMe in MeOH (4.2 $\mu$L, 0.0021 mmol, 0.1 equiv). After 15 min the solution was quenched with sat’d NH$_4$Cl solution (10 mL) and extracted with CH$_2$Cl$_2$ (3x 10 mL). The combined organic phases were dried over MgSO$_4$ and concentrated by rotary evaporation to yield 58 (9.5 mg, 93%) as a colorless oil without need for further purification.

$R_f= 0.40$ (2% Et$_3$N in 9:1 toluene:EtOAc on plates pretreated with 5% Et$_3$N in pentane);

$^1\text{H NMR (500 MHz, CDCl}_3\right)s\delta 6.62 (s, 1H), 6.54 (s, 1H), 5.98 (d, 1H, $J=9.8\text{Hz}$), 5.87 (d, 2H, $J=5.7\text{Hz}$), 5.04 (s, 1H), 3.77 (d, 1H, $J=9.8\text{Hz}$), 3.68 (s, 3H), 3.57 (s, 3H), 3.47 (s, 1H), 3.17-3.07 (m, 2H), 2.99-2.90 (m, 1H), 2.63-2.56 (m, 2H), 2.38 (dd, 1H, $J=14.1, 6.8\text{Hz}$), 2.29 (d, 1H, $J=16.5\text{Hz}$), 2.07-2.00 (m, 1H), 2.00 (d, 1H, $J=16.6\text{Hz}$), 1.93-1.87 (m, 1H), 1.80-1.71 (m, 2H), 1.44-1.27 (m, 3H), 1.14-1.05 (m, 1H), 0.83 (t, 3H, $J=7.2\text{Hz}$); $^{13}\text{C NMR (100 MHz, CDCl}_3\right)s\delta 174.15, 170.63, 157.89, 146.83, 145.96, 133.51, 128.44, 112.81, 109.83, 100.95, 100.21, 74.96, 74.85,
IR (neat film) 3525 (w), 2958 (m), 1747 (s), 1654 (m), 1503 (m), 1487 (s), 1225 (s), 1037 (s), 731 (w) cm$^{-1}$; LRMS (ESI) calcd for C$_{26}$H$_{34}$NO$_8$ (M$^+ +$ H) 488.22 found 487.84; $[\alpha]_D = -124^\circ$ (c 0.95, CDCl$_3$).

1.13 References


CHAPTER 2. INTRODUCTION TO THE C\textsubscript{19}-DITERPENOID ALKALOIDS

2.1 History and Characterization

The *Aconitum* and *Delphinium* genera of plants have been used for centuries in traditional Chinese folk medicines. Although the raw leaves and especially the roots are quite toxic, preparations of these plants are known to have medicinal properties.\textsuperscript{1} The long documented history of the medicinal properties of these plants has piqued the interest of many natural product isolation chemists, leading to the identification of the *Aconitum* and *Delphinium* diterpenoid alkaloids (Figure 3).\textsuperscript{2} One diverse class of compounds is the C\textsubscript{20}-diterpenoid alkaloids that include the atisines, denudatines, hetidines, hetisines, vakognavines, and napellines. In addition to the C\textsubscript{20}-alkaloids, another class of compounds isolated from *Aconitum* and *Delphinium* plants includes some of the most potent biologically active members is the C\textsubscript{19}-diterpenoid alkaloids.

\textbf{C\textsubscript{20}-diterpenoid alkaloids}

\textbf{C\textsubscript{19}-diterpenoid alkaloids}

\textit{Figure 3. Aconitum and Delphinium Alkaloid Types.}
This class is further subdivided based on the presence (aconitines) or absence (lappaconitines) of the C18 carbon. Although the structures in Figure 3 are drawn according to the traditional representations meant to highlight their terpene nature, an alternate representation that places emphasis on the C8-C7-C17-C1 backbone of the aconitines is depicted as structure 59 (Figure 4), along with a similar treatment for the atisines (60).†

![Aconitine Core (59) C19-alkaloid](image)

![Atisine Core (60) C20-alkaloid](image)

**Figure 4.** Diterpenoid numbering scheme.

The biosynthesis of the C19-diterpenoid alkaloids was proposed by Wiesner to include a rearrangement from C20-atisine intermediate 61 (Scheme 17) to the aconitine skeleton (63) by a 1,2-shift of C10 from C8 to C9 followed by formation of the C7–C17 bond to complete the F and B rings. Since the original isolation in the early 1900s and the first structural identification of the C19-diterpenoid alkaloids in 1959, hundreds of similar, but distinct, C19-diterpenoid alkaloids have been isolated and more are still being reported on an almost daily basis. The intriguing structure and biological activity of the plant preparations have made these compounds a popular subject of research.

**Scheme 17**

![Atisine Core (61) Aconitine Core (63)](image)

* Although the lappaconitines lack the C18 carbon, historically these have also been denoted as C19-diterpenoid alkaloids.
† The numbering scheme for the C20-alkaloids has been modified from the traditional scheme to more closely overlap with that of the C19-diterpenoid alkaloids for the purpose of clarity and to further highlight the similarities.
2.2 Biological Activity and Structure Activity Relationships

Despite the structural similarity between C_{19}-diterpenoid alkaloids, these compounds display a large variety of potent, yet at times, opposing biological effects. For example, aconitine (64, Figure 5) is a highly toxic sodium channel activator with arrhythmogenic cardiotoxicity. In contrast, lappaconitine (65), while sharing a similar structural skeleton, displays relatively low toxicity and is a sodium ion channel blocker with antiarrhythmic cardiovascular effect. In addition to the cardiovascular effects, these alkaloids are also analgesics. Although aconitine (64) is a much more potent analgesic than lappaconitine (65), its much higher toxicity precludes its use in this capacity.

![Figure 5. Biological activity of Aconitine and Lappaconitine](image)

<table>
<thead>
<tr>
<th>Effect</th>
<th>Aconitine (64)</th>
<th>Lappaconitine (65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LD&lt;sub&gt;50&lt;/sub&gt; (mg/kg)</td>
<td>0.12-0.2 (s.c.)</td>
<td>5.9-11.5 (i.v.)</td>
</tr>
<tr>
<td>Antinociceptive effect ED&lt;sub&gt;50&lt;/sub&gt; (mg/kg)</td>
<td>0.06 (s.c.)</td>
<td>1.2-3.8 (s.c.)</td>
</tr>
<tr>
<td>Cardiovascular effect</td>
<td>Arrhythmogenic</td>
<td>Antiarrhythmic</td>
</tr>
<tr>
<td>Antiinflammatory effect ED&lt;sub&gt;50&lt;/sub&gt; (mg/kg)</td>
<td>0.1 (p.o.)</td>
<td>6-8 (s.c.)</td>
</tr>
</tbody>
</table>

(s.c.) subcutaneous; (i.v.) intravenous; (p.o.) per os.

The therapeutic potential of the C_{19}-diterpenoid alkaloids has prompted the study of structure-activity relationships (SAR) to determine those structural features that contribute to potency and toxicity. Even though these SAR studies have been limited in scope to either naturally isolated C_{19}-diterpenoid alkaloids or to those alkaloids attainable by post-isolation modifications, some relationships have been discovered. The high toxicity of aconitine (64) has
been attributed to the acyl groups at C8 and C14. Alkaloids that lack these acyl groups, such as lappaconitine (65), are much less toxic. In traditional Chinese preparations of these plants for use in traditional folk medicine, they are first boiled or steamed to reduce the toxicity, an effect likely a result of the hydrolysis of these esters.

2.3 Previous Synthetic Approaches to the Aconitum and Delphinium Alkaloids

In addition to being the first group to fully elucidate the structure of the C_{19}-diterpenoid alkaloids, Wiesner and co-workers succeeded in completing the first total synthesis of a C_{19}-diterpenoid alkaloid, talatisamine (66, Figure 6).^{3,10} Their accomplishment was followed by the synthesis of chasmanine (67)^{11} and 13-desoxydelphonine (68).^{12} To date, these are the only published total syntheses for this class of compounds.

Figure 6. Wiesner's Delphinium Alkaloid Targets.

The strategy Wiesner used to construct the C_{19}-diterpenoid alkaloid skeleton centered on his hypothesis concerning the biosynthesis of these molecules (refer to Scheme 17). Based on their recently completed synthesis of atisine^{13}, the foundation of the Wiesner strategy was to access an appropriate rearrangement precursor similar to 62, using the technology they had already developed, to execute a C_{20} to C_{19}-diterpenoid alkaloid skeletal transformation.

2.3.1 Total Synthesis of Talatisamine by Wiesner

The first target to which Wiesner applied his biosynthetic approach was talatisamine (66, Scheme 18).^{3,14} The synthesis closely followed that of atisine^{13} by accessing cyclobutanol 71 from vinylnitrile 69 and bis(vinylacetate) 70. The atisine skeleton was then constructed using a
retroaldol/aldol rearrangement under acidic conditions to give ketone 72. After several functional group installations they were able to access tosylate 73, an appropriate intermediate with which to test the biomimetic approach. A dilute solution of 73 was heated to 180 °C in the presence of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) to give rearranged olefin 74 via 1,2 shift of C10 onto C9 to give transient cation 75. The deprotonation of 75 was unselective, however, and gave a mixture of the desired product as well as its olefin isomer 76. This intermediate was advanced several steps to the penultimate olefin 77 that upon treatment with Hg(OAc)$_2$, afforded talatisamine (66), presumably by nitrogen oxidation to an imminium that underwent nucleophilic attack by the C7 olefin. Water then trapped the resulting C8 cation to provide the necessary C8 hydroxyl group to complete the first synthesis of a C$_{19}$-diterpenoid alkaloid. This oxidation was not selective and resulted in only 40% yield of 66, but did validate this approach to these targets.
2.3.2 Total Synthesis of Chasmanine by Wiesner

The successful synthesis of talatisamine validated Wiesner's approach to these alkaloids, however there were some non-ideal transformations that needed to be addressed. Specifically, the key rearrangement gave a mixture of isomeric olefins, and the final oxidation was also non-selective. Wiesner addressed both of these problems during his synthesis of chasmanine (67)\(^{11,12,15}\) by forming the C7–C17 bond much earlier in the route.

The synthesis of chasmanine (67) began with the advancement of benzyl ketone 78 (Scheme 19) to olefin 79. This olefin was subjected to aziridination with benzenesulfonyl azide, acetic acid, and catalytic p-toluenesulfonic acid to give aziridine 80 that spontaneously rearranged via a strain-release bond migration of C8 onto C7 indicated by the red arrows, resulting in a 48% yield of ketone 81. This rearrangement was not selective and was accompanied by 32% of acetate 82, the product from migration of C10 onto C17, a transformation made favorable by the electron rich nature of C10 due to the presence of the C14 methoxy substituent. This aromatic intermediate was advanced to migration precursor 83 over several steps. When this intermediate was heated to 180 °C in the presence of DBN, C10 migrated to C9 as in the talatisamine synthesis; however, in this case the presence of the C7–C17 bond precluded undesired C7–C8 olefin formation and therefore 84 was isolated as the sole product in 85% yield. Oxymercuration of the olefin with mercury(II)acetate then selectively installed the requisite C8 hydroxyl group to furnish alcohol 85. Several functional group manipulations then completed chasmanine (67). This synthesis addressed the selectivity issue in the key skeletal rearrangement from 83 to 84 as well as the final oxidation, but also introduced a new transformation with poor selectivity, i.e. the strain-release aziridine rearrangement from 80 to 81 that would need to be dealt with in the next generation synthesis.
2.3.3 Total Synthesis of 13-Desoxydelphonine by Wiesner

When Wiesner targeted 13-desoxydelphonine (68), he intended to solve the poor selectivity of the aziridine rearrangement through a clever manipulation of the substitution on the aromatic ring (Scheme 20). Benzyl ketone 86 was advanced to aziridine 87, an intermediate that had a methoxy substituent at C9 rather than C10 (compare with 80, Scheme 19). The presence of the C9 methoxy substituent provided increased electron density at C8, thus favoring the desired C8 shift onto C7 rather than the undesired C10 to C17 shift observed in the chasmanine (67) synthesis to give exclusively the intended product of the strain-release rearrangement (88, 70%). From here, Wiesner deviated further from his previous approach in that rather than the retro-aldo/aldol strain release rearrangement of a cyclobutanol (see 71,
Scheme 18), diene $\textit{89}$ was prepared for a Diels–Alder cycloaddition. Treatment of $\textit{89}$ with an excess of benzylvinyl ether at room temperature effected an inverse-electron demand Diels–Alder to produce dioxolanone $\textit{90}$, thus efficiently completing the atisine skeleton more directly than the cyclobutanol rearrangement. This dioxolanone was transformed over several steps into C9 bromide $\textit{91}$, an intermediate poised to undergo Wiesner's key rearrangement. Similar to the talatisamine and chasmanine syntheses, when $\textit{91}$ was heated to 180 °C in the presence of DBN, the migration of C10 onto C9 took place to afford olefin $\textit{92}$ (89%), thus effecting the transformation of the atisine skeleton into the aconitine skeleton. Further manipulations completed 13-desoxydelphonine (68) as Wiesner's ultimate accomplishment in the synthesis of the C19-diterpenoid alkaloids. This impressive achievement has yet to be matched in the decades since Wiesner's publications.

**Scheme 20**

Bromide $\textit{89b}$ was an inconsequential side product from the oxidative dearomatization in the production of diene $\textit{89}$. This mixture was taken without separation until convergence by dehalogenation in a subsequent reaction.
2.4 Summary

Wiesner's synthesis of talatisamine, chasmanine, and 13-desoxydelphonine are truly watershed moments in the history of total synthesis. That these syntheses have been unmatched in over 30 years is a testament both to Wiesner's skill as well as the challenge these targets pose. Despite this success, there are still issues that could be addressed in a modern approach to these alkaloids. In particular, a large number of functional group manipulations and a linear approach combine to yield a relatively lengthy synthesis. A more convergent approach to these targets that avoids excessive functional group interconversions would significantly shorten the length.

2.5 References

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(4) Schmidt, E.; Schulze, H. Archiv der Pharmazie 1906, 244, 136.


CHAPTER 3. RETROSYNTHETIC ANALYSIS OF THE ACONITINE SKELETON

3.1 General Approach

Our approach to the C_{19}-diterpenoid alkaloids (henceforth referred to as the aconitine alkaloids) centers on a late-stage formation of the C7–C8 and C11–C17 carbon–carbon bonds (Figure 7).

One method for the formation of these bonds begins with an appropriate radical precursor 93 (Scheme 21). Generation of a radical by homolysis of the C–X bond results in a cyclopropylcarbinyl radical (94) that would undergo endocyclic bond cleavage\(^*\) of the highly strained cyclopropane to give a radical at C8. Attack of this radical on an appropriately placed olefin at C7 would occur in a 7-exo manner to form the key C7–C8 bond. The resulting radical at C17 would then attack a second double bond at C11 in a 5-exo manner to complete the cyclization as well as the skeleton of the aconitine alkaloids (95).

While this is an inherently attractive strategy, several issues may emerge as challenges to overcome: (1) cyclopropylcarbinyl radical 94 could instead fragment the exocyclic C16–C15 bond to give a primary radical at C15 rather than the desired C8 radical; (2) the conformation required for overlap between the C8 radical and C7–C17 \(\pi^*\) orbital could be high enough in energy that direct reduction of the C8 radical is more favored than addition into the olefin; and (3) the possibility for attack of the C8 radical onto the C1 olefin in a 5-endo manner rather than the desired 7-exo attack onto C7. Although 7-exo-trig reactions are considered "favored" by

\[\text{Scheme 21}\]

\(^*\) "Endocyclic" refers to the ring-fusion bond (i.e. the C8–C16), whereas "exocyclic" refers to the C15–C16 bond.
Baldwin's rules while 5-endo-trig are considered "disfavored", 1 5-endo-trig radical cyclizations have been well documented. 2,3

A complementary strategy would employ a cation–π cyclization beginning with similar intermediate 96 (Scheme 22). In contrast to homolysis, heterolysis of the C–X bond would give cyclopropylcarbinyl cation 97. This electron deficiency would be shared through the cyclopropyl σ-bond with C8. The olefin at C7 would then attack on C8, again in a 7-exo mode, to form the key C7–C8 bond with the resulting transfer of electron deficiency to C17 in the form of an iminium species. This iminium could then undergo an intramolecular Mannich-type cyclization of C11 onto C17 to complete the skeleton of the aconitine alkaloids.

Scheme 22

An advantage of these approaches would be that both can be accessed from the same or similar intermediates 93 and 96. Should one mode of reactivity prove to be unworkable, minimal effort would need to be expended to explore the other. Also, while a one-pot cascade reaction would be ideal, each step could be performed separately if necessary. Moreover, a stepwise strategy would also not be limited exclusively to a radical or ionic reaction mode, but could employ a radical process for one C–C bond construction and an ionic process for the other.

3.2 Retrosynthetic Analysis

With an overall strategy in hand, we then turned our attention to the challenge of efficient access to key intermediate 101 (Scheme 23). Since 101 incorporates a cis-fused [5.4.0]-bicycloazepine system, it becomes apparent that a Diels–Alder cycloaddition comprising the
building blocks of azepine 103 and diene 104 becomes an attractive strategy. Though to our knowledge there are no examples of the use of a 2,5-dihydroazepine as a dienophile, we were drawn by the convergent nature of this approach. Further retrosynthetic analysis reveals the ring-fused cyclopropane fragment within 104 could also be constructed efficiently though a Diels–Alder cycloaddition; however, in this case the 2π and 4π components would be cyclopropene 105 and 2,5-dioxycyclopenta-1,3-diene† 106, respectively. Again, this plan is not without risk as cyclopropenes have 56 kcal/mol of ring strain and are known to be unstable and reactive. Moreover, substituted cyclopentadienes with at least one hydrogen in the five position tend to undergo 1,5–hydrogen shifts, scrambling the substitution pattern. These difficulties would have to be explored and overcome to acquire the desired cyclization precursor (vide infra).

Scheme 23

† In the interest of clarity, the numbering scheme for unsubstituted cyclopentadiene will be used even in cases where additional substituents of higher priority, such as oxygen, would change the numbering priority.
3.3 References


CHAPTER 4. SYNTHESIS AND EXPLORATORY RADICAL CYCLIZATIONS OF A KEY CYCLOPROPYL CARBINYL RADICAL PRECURSOR

4.1 Synthesis of the [2.1.1.0]-Tricylic Ring System

As proposed in Scheme 23 of chapter 3, a Diels–Alder reaction between a 2,5-dioxcyclopenta-1,3-diene* (106) and a suitable cyclopropene (105) would quickly construct a key portion of the aconitine structure. However, cyclopropenes have seen limited use as dienophiles in synthesis due to their high reactivity and instability. Despite these challenges, there are a number of methods for the generation of cyclopropenes,\(^1\)-\(^4\) including 1,2-elimination from cyclopropanes,\(^2,5\) isomerization of vinyl carbenes,\(^6\)-\(^13\) \([2+1]\) cycloaddition,\(^14\)-\(^19\) ring contraction of 5-membered rings with extrusion of \(\text{N}_2\),\(^3\),\(^20\) \(\text{CO}_2\),\(^3,\(^21\) 1,3/1,2-elimination,\(^22\) ring contraction of 4-membered rings,\(^3\) addition to cyclopropylium salts,\(^5\) 1,1-elimination/1,2-Si shift,\(^5\) retro-Diels–Alder cyclization,\(^2\) and cycloisomerization.\(^4,\(^5\) Of these, the most suitable protocol followed the method explored by Baird and co-workers in which a tribromocyclopropane, easily prepared from an appropriate alkyl acrylate, is subjected to lithium-halogen exchange followed by 1,2-elimination (Scheme 24) to give cyclopropenes in good yields. For example, treatment of (1,2,2-tribromocyclopropyl)methanol (107, available in three steps from methyl acrylate) with two equivalents of methyllithium provided cyclopropenylmethanol (109) in 73% yield, presumably via initial formation and subsequent protonation of dianion 108 upon aqueous workup. As a hydroxyl group could be easily converted to an appropriate radical precursor such as a xanthate, thiocarbonate, selenide, or halogen, this approach proved to be most useful in that: (1) tribromocyclopropanes are easily prepared from methyl acrylate; (2) cyclopropene formation occurs quickly at \(-78\) °C and (3) a latent

\(^*\) In the interest of clarity, the numbering scheme for unsubstituted cyclopentadiene will be used even in cases where additional substituents of higher priority, such as oxygen, would change the numbering priority.
cyclopropylcarbinol group should serve as an appropriate radical precursor. In adapting this protocol, silyl protection of alcohol 107 (Scheme 25) was accomplished using TIPSCI and imidazole\(^{23}\) to give silyl ether 110 in 72% yield. It was confirmed that this protected derivative could in fact give the cyclopropene dienophile 112 after lithium-halogen exchange at –78 °C with two equivalents of methyllithium followed by 1,2-elimination and protonation of vinyl anion 111. Although cyclopropene formation was efficient, its susceptibility to decomposition precluded further purification.\(^5\) Therefore this dienophile was used directly for subsequent Diels–Alder reactions. The synthesis of the 2,5-dioxycyclopenta-1,3-diene component of the Diels–Alder cycloaddition then became a priority.

**Scheme 24**

\[
\begin{align*}
\text{107} & \xrightarrow{\text{Br}^- (2 \text{ equiv})} \text{108} & \xrightarrow{\text{H}^+} \text{109 (73\%)} \\
\end{align*}
\]

**Scheme 25**

Substituted cyclopentadienes with at least one hydrogen at the 5-position are notoriously unstable due to facile 1,5–hydrogen shifts (Scheme 26).\(^{24-27}\) For example, the half-life for the isomerization of 5–methylcyclopenta-1,3-diene (113) to 1–methylcyclopenta-1,3-diene (114) is 1.2 h at 20 °C.\(^{27}\) If the requisite 1,3-dioxycyclopenta-1,4-diene 106 were to undergo this hydrogen shift prior to cycloaddition (Scheme 27), the result would be scrambling of the substituents of 106 to deliver isomeric mixtures of Diels–Alder cycloadducts, including the undesired cycloadduct 116. Therefore, it was important to explore strategies that would limit the extent of this cyclopentadiene isomerization.
Overcoming the challenge of 1,5–hydrogen shift has previously been accomplished with several designs of Diels–Alder cyclopentadiene substrates. One includes 1,2,4-trichloro-3,5,5-trimethoxycyclopenta-1,3-diene (118, Scheme 27), available in one step from commercially available 1,2,3,4-tetrachloro-5,5-dimethoxycyclopenta-1,3-diene. The lack of any allylic hydrogens in the 5-position due to the presence of a ketal precludes the possibility of hydrogen shift isomerization. Moreover, the trihalogen substitution attenuates the reactivity of the diene by reducing the electron density of the $\pi$ system as well as increasing its steric bulk, thereby slowing unwanted dimerization. In fact, this diene is stable for months when stored at –10 °C and can be routinely handled at room temperature without incident. Despite its attenuated reactivity, it has been shown to readily react with cyclopropene (119) at room temperature to give cycloadduct 120 in 65% yield. Reductive removal of the chlorine atoms in 120 affords a ring system (121) that closely resembles the requisite [2.1.1.0]-ring system 104 (Scheme 23).

Scheme 28
The above example provides strong precedent for the key cycloaddition; only the regioselectivity of the Diels–Alder was in question as this diene had only been reported to react with unsubstituted cyclopropene. As a consequence, the chlorinated diene 118 was treated with cyclopropene 112 at 20 °C (Scheme 29), resulting in an efficient Diels–Alder cycloaddition to provide a mixture of cycloadducts in 76% yield over two steps from tribromocyclopropane 110 as a 1 : 3.6 mixture of 122 and 123. Unfortunately, undesired isomer 123 was the major cycloadduct, relegating diene 118 to be non-viable in the synthesis.

Scheme 29

It is likely that the chlorine substituents on 118 significantly reduce the electron density of the diene, leading to an inverse-electron demand cycloaddition pathway\(^{31}\) to afford the unwanted regioselectivity. Accordingly, a similar diene, devoid of the chlorine substituents, was hypothesized to reverse the regiochemical outcome by proceeding through a normal electron demand pathway. At the time, there was no literature precedent for unchlorinated 2,5-dioxycyclopenta-1,3-dienes (106) engaging in a Diels–Alder process; however, it seemed reasonable to be able to access this class of diene through enolization of an appropriate cyclopentenone precursor. Thus, cyclopentenone 124 (Scheme 30), available in one step from cyclopentenone ethylene ketal via a method reported by Corey and Yu,\(^{32}\) was chosen as a model diene precursor as the ethylene ketal group would preclude a 1,5–hydrogen shift. Unfortunately, when a solution of 124 was treated with tert-butyl(dimethyl)silyl trifluoromethanesulfonate (TBSOTf) and Et\(_3\)N in the manner reported by Forsyth and co-workers,\(^{33}\) only a complex
mixture of products was obtained. Mass spectral evidence suggested the presence of dimers that were possibly produced via a Diels–Alder process, presumably a consequence of diene concentration during the isolation process. However, diene dimerization was suppressed when a solution of the freshly prepared diene 125, without prior solvent removal, was treated with para-benzoquinone (126) to provide the cycloadduct 127 in 94% unpurified yield. This promising result suggested the possibility of using a cyclopentenone-derived cyclopentadiene as a key early step in the construction of the structure of the aconitine alkaloid core.

Scheme 30

Emboldened by this success, a similar protocol was applied to 4-hydroxycyclopent-2-enone (128, Scheme 31), previously prepared in one step from furfuryl alcohol,\textsuperscript{34} to generate cyclopentadiene 129. The added risk with 129 lies in the presence of an allylic proton that would be susceptible to hydrogen-shift isomerization. Despite this liability, the potential to directly install the C14 oxygen functionality, common to all aconite alkaloids, during this early Diels–Alder process would certainly enhance efficiency of the synthesis of the aconitine skeleton. Thus, when a solution of 128 was treated with TBSOTf and Et\textsubscript{3}N, followed again by addition of the model dienophile \textit{p}-benzoquinone (126), cycloadduct 130 was obtained in 45% yield. Unfortunately, the facial selectivity of approach of the dienophile 126 on the diene 129 was anti to the bulky silyl ether, confirmed by a strong nOe interaction between the C14 proton and the C8 and C16 protons of cycloadduct 130. Although highly selective, this stereoselectivity produced the undesired C14 configuration relative to the aconitine alkaloids. Nevertheless, this experiment validated the competency of 2,5-dioxydicyclopenta-1,3-dienes such as 129 to proceed
in Diels–Alder reactions without diene isomerization. Notably, the reticence of diene 129 to undergo hydrogen shifts as compared to other cyclopentadienes like 5-methylcyclopenta-1,3-diene (113) likely lies in the presence of the TBS-enol-ether. This effect was quantified by Gleason and co-workers shortly after our above-mentioned experiments. This report (Scheme 32) revealed that 5-methylcyclopenta-1,3-diene (113, Scheme 26) had a $t_{1/2}$ of 1.2 h at 20 °C, whereas the isomerization of diene 131, containing TBS-enol-ether, has a significantly longer half-life ($t_{1/2} = 37$ h at 23 °C).

Having established the viability of cyclopentenone–derived cyclopentadienes as the 4π components in a Diels–Alder reaction with cyclopropene dienophiles, preparations were complete to investigate the key cycloaddition with building blocks directly relevant to the synthesis of the aconitine alkaloids. Toward this end, the γ-hydroxyl group of 4-hydroxycyclopent-2-enone (128, Scheme 33) was methylated (MeI, Ag$_2$O, 75%) to produce allylic methyl ether 133, which was subsequently converted to the cyclopentadienyl enol-ether 134 with TBSOTf and Et$_3$N. Without further manipulation, this solution was directly treated with cyclopropene 112 at 0 °C to give an inseparable mixture of isomeric cycloadducts 135, 136, 137, and 138 in a 9.5 : 5.4 : 1.5 : 1 ratio, respectively, and 99% overall yield, with no evidence of
products arising from hydrogen shift. Out of a host of potential isomeric Diels–Alder cycloadducts, the major product was the constitutional isomer 135, in which the cyclopropene engaged in an endo approach onto the diene in a contra-steric fashion, syn to the methyl ether. While this facial selection was opposite to the prior outcome with the p-quinone dienophile (compare from 130, Scheme 31), the resultant C14 configuration in 135 fortuitously coincides with that in the aconitine natural products. The structure of 135 was confirmed by subsequent hydrolysis of the silyl enol-ether (NaOH, H2O >99%) to provide ketone 139, which exhibited significant nOe correlations of the C14 and C15 protons with those of C12.

![Scheme 33](image)

While the observed contra-steric approach of the cyclopropene dienophile 112 onto diene 134 was initially surprising, this phenomenon is not without precedent. Approach of dienophiles onto cyclopentadienes with heteroatom substituents in the 5-position have been well studied. For example, Jones has shown that when 7,9-dimethyl-8H-cyclopent[a]acenaphthylen-8-ol (143) was allowed to react with dimethylfumarate in a Diels–Alder cycloaddition (Scheme 34), the dienophile approached from the contra-steric face, syn to the hydroxyl substituent, to afford adduct 144 in 73% yield, with no indication of the anti-addition product. Similarly, the Diels–Alder cycloadditions of 5-halogen substituted cyclopentadienes have been shown in the
literature to provide selectivity for the syn-cycloadduct, albeit with increasing amounts of the anti-cycloadduct as the identity of the heteroatom moves down the column of the periodic table. When 5-fluorocyclopenta-1,3-diene (145) was treated with dimethylacetylenedicarboxylate (DMAD), the only isolable product was adduct 146 in which the dienophile had approached from the face syn to the halogen substituent (Scheme 35). While a chlorine substituent at the 5-position also provided the syn adduct as the major product, a small amount (21%) of the anti adduct was also observed in the cycloaddition between 5-chlorocyclopenta-1,3-diene (147) and N-phenylmaleimide (Scheme 6). In contrast to the 5-fluoro and 5-chloro derivatives, 5-bromo (148) and 5-iodocyclopenta-1,3-diene (149) gave the anti-cycloadducts as the major products, possibly due to steric effects resulting from increased size of these halogen atoms. Indeed, in the case of iodine, the Diels–Alder reaction exclusively provided the anti-product with no detectable quantities of the syn-cycloadduct.

Scheme 35

The origin of this heteroatom influence remains a topic of debate. Based on calculations as well as on empirical evidence, several hypotheses have been put forth, including: (1) a
favorable non-bonding interaction between the heteroatom lone pair and the dienophile LUMO;\textsuperscript{49} (2) orbital mixing of the heteroatom n-orbitals with the π-HOMO through the carbon σ framework;\textsuperscript{50} (3) electrostatic interactions that allow the more nucleophilic face of the diene being more reactive toward an electrophilic dienophile;\textsuperscript{37} (4) lower deformation energy required to reach the syn transition state geometry;\textsuperscript{44,47} (5) stabilization of the syn transition state by hyperconjugative participation of the antiperiplanar σ-bonds into the σ*-orbitals of the newly forming bonds according to the Cieplak model.\textsuperscript{39,51} Nevertheless, while the origin for this selectivity remains elusive, the outcome, namely the production of the Diels–Alder cycloadduct \textit{135}, is clearly advantageous to our synthetic approach toward the aconitine skeleton.

### 4.2 Cyclopropylcarbinyl Radical Model Study

With the successful synthesis of the cyclopropane fragment \textit{139} (Scheme 33), efforts were then focused on investigating the cyclopropylcarbinyl radical fragmentation to construct the aconitine core as shown in Scheme 37. A key concept of this process is the homolysis of the endocyclic\textsuperscript{†} C8–C16 bond of the cyclopropane ring upon generation of a cyclopropylcarbinyl radical (\textit{152}), as shown in Path A. This ring expansion results in the formation of a radical at C8 that can then attack the olefin at C7 in a 7-exo cyclization, followed by a 5-exo radical addition from C17 to C11 to complete the radical cascade. An alternative, unproductive, pathway is that

\textsuperscript{†} "Endocyclic" refers to the ring-fusion bond (i.e. the C8-C16), whereas "exocyclic" refers to the C15-C16 bond.
depicted by Path B, in which the exocyclic C15–C16 bond undergoes homolysis, resulting in a primary radical at C15 (154) rather than the productive secondary radical at C8. To our knowledge, the radical fragmentation of a [2.1.1.0]-tricyclic ring system 152 has not previously been reported, so it was unclear whether fragmentation by Path A or by Path B would occur.

![Scheme 37](image)

It has been shown that in the case of cyclopropylcarbinyl radical 156 (Scheme 38) the desired pathway to secondary radical 157 is 120 times faster\(^{52}\) than the competing, undesired pathway to give primary radical 155. While this report was encouraging, a [4.1.0]-system has been reported to give different results. The cyclopropylcarbinyl radical derived from xanthate 158 (Scheme 39) underwent exclusively undesired exocyclic bond cleavage to give 159.\(^{53}\) There was no evidence of the endocyclic bond cleavage product 160. Additionally, the radical derived from simple cyclohexyl xanthate 161 (Scheme 40) exhibited a tributyltin hydride concentration dependent result.\(^{54}\) While at high tributyltin hydride concentration the 7-membered ring product from the desired pathway, 162, was favored. At lower concentrations the reaction was unselective, affording a 1 : 1 mixture of 162 along with the 6-membered ring 163.
The above-mentioned examples provide a somewhat conflicting indication of what could be expected from the radical fragmentation of the [2.1.1.0]-tricyclic ring system in \textbf{152} (Scheme 37). Consequently, the synthesis of a model cyclopropane was embarked upon to determine whether the endocyclic or exocyclic bond would cleave. Toward this end, Diels–Alder cycloadduct \textbf{164} (Scheme 41) was advanced to radical precursor \textbf{165} beginning with fluoride mediated cleavage \textsuperscript{55,56} of the TIPS-ether with concomitant TBS enol-ether removal. This was followed by conversion of the resultant alcohol to thiocarbonate \textsuperscript{57} \textbf{165} (63%, two steps) by nucleophilic attack onto phenylchlorothionoformate. Thiocarbonate \textbf{165} was an ideal intermediate with which to test the selectivity of the fragmentation of a [2.1.1.0]-tricyclic cyclopropylcarbinyl radical. In the event, a benzene solution of \textbf{165}, tributyltin hydride, and AIBN was heated to reflux to give a mixture of two products, neither of which was the result of the undesired exocyclic bond cleavage of \textbf{166} (refer to Path B, Scheme 37) that would have given [2.2.1]-bicyclic product \textbf{167}. The minor product was readily identifiable as the [3.2.1]-bicyclic compound \textbf{168} (30%), derived from the desired fragmentation of the endocyclic bond (refer to...
Path A, Scheme 37) to give transient secondary radical 169 followed by reduction with tributyltin hydride. However, the major product was [2.2.2]-bicyclic compound 170 (47%), the origin of which was immediately less obvious. Fortunately, it too was likely the result of the desired endocyclic bond cleavage to give secondary radical 169, but instead of direct reduction, attack of the radical onto the ketone gave transient cyclopropyl alcoxy radical 171 that then fragmented via a Dowd-Beckwith\textsuperscript{58,59} pathway to provide 170. It is interesting to note that this process is essentially the single electron reverse of Weisner's biosynthetic transformation (See Scheme 20, Chapter 2), and warrants further study following the successful synthesis of the aconitine alkaloids. The above results show the cyclopropylcarbinyl radical of the [2.1.1.0]-skeleton undergoes fragmentation through the ring-expansive endo-cyclic bond cleavage that is necessary for the first step in the proposed radical cascade (Path A, Scheme 37). Therefore, the cyclopropylcarbinyl fragmentation to give a secondary radical at C8 should proceed as planned.

It was then necessary to prepare the fully functionalized precursor for cyclopropylcarbinyl radical 152 in order to conduct the synthesis of the aconitine alkaloids.
4.3 Synthesis of the [5.4.0]-Bicycloazepine System

Confident the cyclopropylcarbinyl radical fragmentation should occur via the desired endocyclic bond scission, an expedient route to prepare the 2π and 4π components for the second Diels–Alder reaction was developed (Scheme 42), continuing from the inseparable isomeric mixture of [2.1.1.0]-tricyclic cyclopropanes 139 and 140. The ketone groups of 139 and 140 were reacted with the potassium salt of methyl diethylphosphonoacetate anion in refluxing THF to effect a Horner–Wadsworth–Emmons olefination, affording a complex mixture of four isomers, the result of unselective olefination of each constitutional isomer (139 and 140). Rather than attempting to separate this mixture, the olefin isomers were converged by stereoselective hydrogenation with palladium on carbon that delivered hydrogen from the sterically less encumbered convex face to afford the constitutionally isomeric methyl esters 172 and 173. Although the reduction of the olefin group simplified the mixture composition, the remaining two isomers were still inseparable by silica gel column chromatography. Therefore, the methyl esters were advanced via trimethylaluminum mediated amidation with N,O-dimethylhydroxylamine hydrochloride to give the separable Weinreb amides 174 and 175 in 20% and 39% yield, respectively, over six steps from tribromocyclopropane 110. Now pure, the single isomer 175 was subjected to nucleophilic addition of vinylmagnesium bromide into the Weinreb amide carbonyl to give the tetrahedral magnesium salt 176. After hydrolysis during acidic work-up, enone 177 emerged as the principal product, which was not purified, but used directly for the next transformation. The enone carbonyl was immediately enolized by treatment with TBSOTf and KHMDS at –78 °C to generate diene 178 as a >25 : 1 mixture of isomers in 77% yield over two steps, favoring the Z-isomer. This final step marked the completion of the 4π
component required for the Diels–Alder cycloaddition to prepare the [5.4.0]-bicycloazepine ring system. Subsequent efforts were focused on constructing the remaining $2\pi$ azepine component.

An efficient synthesis of novel azepine dienophile 186 (Scheme 43) was developed to continue the construction of the [5.4.0]-bicycloazepine system. The synthesis began with commercially available and inexpensive $\varepsilon$-caprolactone (179) as the carbon source. A mixture of

**Scheme 42**

179 and two molar equivalents of benzylamine was heated, without solvent, to 120 °C to affect nucleophilic attack onto the lactone carbonyl. The acyclic hydroxyl-amide 180 was isolated by direct crystallization (ethyl acetate, 78%). Oxidation of the primary alcohol was performed under Parikh–Doering conditions to provide aldehyde 181 (93%). Acid catalyzed condensation of the secondary amide onto the newly-formed aldehyde was accomplished in refluxing toluene with azeotropic removal of water via a Dean–Stark apparatus to afford enamide 182 (77%). The
requisite methyl ester as well as the selenide was installed in a one-pot double addition procedure. α-Deprotonation of the amide carbonyl with two equivalents of LHMDS was followed by the addition of one equivalent of methylchloroformate to give the intermediate enolate 183 that was then trapped with phenylselenyl chloride to deliver selenide 184. This product not purified, but was directly transformed into olefin 185 (60%, two steps) by oxidation of the selenide with aqueous hydrogen peroxide and spontaneous 1,2-syn elimination of the transient selenoxide. Further oxidation of the π-system with chromium (VI) oxide and 3,5-dimethylpyrazole gave an appropriately activated dienophile (186). At this juncture, we had both the 4π and the 2π components in hand to perform the desired Diels–Alder cycloaddition to produce the [5.4.0]-bicycloazepine ring system. However, the use of an azepine-2,7-dione dienophile in a Diels–Alder reaction was unprecedented, so the outcomes of regio-, endo/exo-, and facial stereoselectivities were not clear.

**Scheme 43**

Extensive experimentation by graduate researcher colleague Yuan Shi revealed that the Diels–Alder reaction could indeed be effected by addition of catalytic Yb(OTf)₃ to a solution of the diene 178 with two equivalents of the dienophile 186 at 20 °C to produce an inseparable mixture of two isomers (Scheme 44), one of which incorporated the desired relative...
stereochemistry (i.e. 102, Scheme 23, chapter 3). Subsequent chemoselective hydrogenation of the enimide with palladium on carbon under an atmosphere of hydrogen gave the imides 187 (45%, two steps) and 188 (38%, two steps) that could be separated by silica gel column chromatography. Notably, the above cycloaddition proceeded with complete regio and endo selectivity (relative to the 7-membered ring) as confirmed by the all syn nature of the C11 and C5 protons with the C4 ester. Although the facial approach of azepine 186 onto diene 178 was mildly selective for the undesired isomer 187, this process nonetheless produced a reasonable yield of the desired diastereomer 188. This strategy has provided 188 in quantities sufficient for further investigation (vide infra); however, efforts to improve the diastereoselectivity of this key Diels–Alder cycloaddition are ongoing.

In order to explore our proposed radical cascade to access the aconitine alkaloids (see Scheme 37), it was necessary to transform the imide 188 to incorporate the C7–C17 and C1–C11 olefins. This task was accomplished in five steps beginning with C7 deprotonation (Scheme 44) using KHMDS to provide the potassium enolate that underwent O-sulfonylation with Comins'
reagent\textsuperscript{72} to provide a vinyl triflate that was immediately reduced, without purification, with tributyltin hydride in the presence of catalytic Pd(PPh\textsubscript{3})\textsubscript{4} to afford enamide \textbf{189} in 62\% yield over two steps. Selective cleavage of the TBS enol-ether in the presence of the more bulky TIPS ether was accomplished with one equivalent of TBAF at 0 °C to provide ketone \textbf{190} in 69\% yield. Sodium borohydride reduction stereoselectively delivered hydride from the less hindered convex face to provide an 88\% yield of alcohol \textbf{191} as a single diastereomer. The structure of this crystalline intermediate was unambiguously verified by x-ray structural analysis. A screen of reaction conditions revealed that the alcohol could be selectively transformed into the thermodynamically favored trisubstituted olefin \textbf{192} by activation of the hydroxyl group as an oxophosphonium under Hendrickson's conditions\textsuperscript{73-75} (triphenylphosphine oxide, triflic anhydride, Hünig's base, 42\% yield). Although this intermediate did not contain the complete oxidation pattern of many of the aconitine alkaloids, it did have the required C7–C17 and C1–C11 olefins to explore the key radical cyclization reaction.

4.4 Undesired 5-Endo Cyclization of a C8 Radical onto C1

With the installation of the C7–C17 and C1–C11 olefins as well as the cyclopropylcarbinol of \textbf{192}, preparations were nearly complete to attempt the key radical cyclization cascade (see Scheme 37). However, the primary silyl ether needed to be converted to a more appropriate radical precursor. Therefore, the TIPS ether of \textbf{192} (Scheme 45) was first cleaved with TBAF to reveal the cyclopropylcarbinol \textbf{193} (88\%). Activation of the newly revealed alcohol as an oxophosphonium and displacement with phenylselenylate nucleophile was accomplished with triphenylphosphine and N-(phenylseleno)succinimide (\textbf{194}) to give selenide \textbf{195} in 39\% yield over two steps. The resultant intermediate was ideal to explore the cyclopropylcarbinyl radical cleavage. Although the model cyclopropylcarbinyl radical (\textbf{166}, see
Scheme 41) underwent exclusive endocyclic C8–C16 bond scission, the behavior of the fully elaborated system was unknown. In the event, a benzene solution of selenide 195, tributyltin hydride, and catalytic AIBN were heated at 100 °C to produce a mixture of two compounds, both of which were the result of endocyclic C8–C16 fragmentation. Unfortunately, there was no indication of the productive attack of the secondary C8 radical (197) onto the C7 carbon. The major product was that of direct C8 radical reduction to give 198 in 35% yield. Also isolated was cyclopentane 199 (29%), derived from C8 radical addition in a 5-endo fashion onto C1 rather than 7-exo addition onto C7. The empirical observations detailed by Baldwin76 suggest the observed 5-endo mode would be disfavored relative to the 7-exo pathway, so an alternate explanation was required. One possibility is the conformation in which the C8 radical is in close proximity to the C7 olefin must be higher in energy than that required for attack on the C1 olefin. Thus, the observed direct radical reduction and 5-endo cyclizations are left as the only observed reaction pathways. While this setback was disappointing, we reasoned this 5-endo pathway could be mitigated by the installation of an oxygen bearing a bulky protecting group at C1, which would sterically shield that position from attack by the C8 radical and increase the transition-state energy such that the 7-exo reaction mode would be favorable relative to the 5-endo mode.
4.5 Summary

Two novel Diels–Alder cycloadditions were developed in the synthesis of key radical precursor 195 (Scheme 46). One included a novel cyclopentenone-derived substituted 2,5-dioxycyclopenta-1,3-diene (134) and a cyclopropene dienophile (112) that approached from the sterically more hindered face to rapidly construct the [2.1.1.0]-tricyclic ring system 135 with the appropriate C14 stereochemistry for the aconitine alkaloids. This product was rapidly elaborated to diene 178 that was reacted with azepine-2,7-dione dienophile 186 to install the [5.4.0]-bicycloazepine ring system required for the successful synthesis of the aconitine alkaloids. The synthesis of the key radical cyclization precursor 195 was then completed in 18 steps from tribromocyclopropane 107. Although the initial cyclopropylcarbinyl radical fragmentation occurred by the intended endocyclic pathway, the only isolated products were 198 and 199, neither of which was the result of the desired C8 radical addition onto C7. Rather, 198 was the result of direct reduction of the C8 radical, while an undesired 5-endo cyclization of C8 onto C1 formed cyclopentane 199.
Scheme 46

(107) 108

107 (72%) → Br\_2\_OTIPS

MeI, Ag\_2\_O

(75%)

134

ROH → TBSOTf, Et\_3N

(t)-128 : R = H

(t)-133 : R = Me

135 → NaOH

0 °C

139

1. H_2, Pd/C

2. MeO\_2C, Yb(OTf)_3

186

188 (42%, 2 steps)

> 25 : 1 Z : E

1. KHMDS, Commins

2. Pd(PPh\_3)_4, Bu\_3SnH

189 (62%, 2 steps)

190 (69%)

191 (88%)

1. TBAF

2. PMe_3,

194

192 (42%)

195 (39% 2 steps)

198 (35%) direct reduction

199 (29%) 5-endo reduction

193

Me\_3SnH, AIBN

1. TBAF

2. PMe_3,
4.6 Experimental

**General Procedures.** All reactions were performed in flame-dried modified Schlenk (Kjeldahl shape) flasks fitted with a glass stopper under a positive pressure of argon, unless otherwise noted. Air- and moisture-sensitive liquids and solutions were transferred via syringe or stainless-steel cannula. Organic solutions were concentrated by rotary evaporation below 30 °C. Flash column chromatography was performed employing 230-400 mesh silica gel under a positive pressure of nitrogen. Automated silica gel column chromatography was performed employing an Isco Combiflash Rf with Isco brand columns. Gradient elutions were performed with a linear gradient. Thin-layer chromatography (analytical and preparative) was performed using glass plates pre-coated to a depth of 0.25 mm with 230-400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Visualization was achieved using UV light, iodine, potassium permanganate (KMnO₄), or ceric ammonium molybdenate (CAM).

**Materials.** Dichloromethane (CH₂Cl₂), tetrahydrofuran (THF), acetonitrile, diethyl ether, toluene, and benzene were purified by passage through two packed columns of neutral alumina under an argon atmosphere. Methanol was distilled from magnesium turnings under a nitrogen atmosphere at 760 mm Hg. 1,2-Dichloroethane, N,N-dimethylformamide (DMF), dimethylsulfoxide, and 1,4-dioxane were dried over activated 4Å molecular sieves. Triethylamine, 2,6-lutidine, pyridine, Hünig's base, and diisopropylamine were distilled from CaH₂ under a nitrogen atmosphere at 760 mm Hg. Lithium bis(trimethylsilyl)amide (LHMDS) and potassium bis(trimethylsilyl)amide (KHMDS) were purchased as a solid from Aldrich and handled under an argon atmosphere. Trifluoromethanesulfonic anhydride was distilled from P₂O₅ under a nitrogen atmosphere at 760 mm Hg. All moisture and/or oxygen sensitive solids were handled and stored in a glove box. Organolithium solutions were titrated by known procedures. 77
immediately prior to use. All other reagents were used as purchased without further purification, unless otherwise noted.

**Instrumentation.** Infrared (IR) spectra were obtained using a Bruker Tensor 27 referenced to a polystyrene standard. Data are presented as the frequency of absorption (cm⁻¹). Proton and carbon-13 nuclear magnetic resonance (¹H NMR or ¹³C NMR) spectra were recorded on a Bruker Avance III 500 or a Bruker Avance III 600 spectrometer; chemical shifts are expressed in parts per million (δ scale) downfield from tetramethylsilane and are referenced to the residual protium in the NMR solvent (CHCl₃: δ 7.26 for ¹H NMR, δ 77.16 for ¹³C NMR; C₆D₆: δ 7.16 for ¹H NMR, δ 128.06 for ¹³C NMR). Data are presented as follows: chemical shift, multiplicity (s = singlet, bs = broad singlet, d = doublet, bd = broad doublet, t = triplet, dd = doublet of doublets, ddd = doublet of doublet of doublets, td = triplet of doublets, dt = doublet of triplets, m = multiplet and/or multiple resonances), integration, and coupling constant reported in Hz. X-ray crystallography was performed by Louis Todaro of Hunter College in New York City, NY.

(1,2,2-tribromocyclopropyl)methanol (107) (V-JTW-006)

To a solution of ester S₂ (42.1 g, 125 mmol, 1.00 equiv) in CH₂Cl₂ (250 mL, 0.5 M) at –78 ºC was added a 1.0 M solution of diisobutylaluminum hydride in hexanes (256 mL, 256 mmol, 2.05 equiv) and the solution was removed from the cooling bath for 45 min at which time the reaction was shown to be complete by TLC analysis. The solution was cooled to –78 ºC and quenched with saturated Rochelle's salt solution (250 mL), diluted with Et₂O (500 mL), removed from the cold bath, and stirred vigorously at room temperature until the phases became distinct and clear (1.5 h). The phases were then separated and the aqueous phase was extracted with Et₂O (2x 250 mL) and the combined organic phases were dried over MgSO₄, filtered, and the solvent was
removed to yield alcohol 107 (38.7 g, 100%) as a white solid. NMR analysis indicated the presence of ~10% aldehyde. This was used without purification.

\[ R_f = 0.28 \text{ (CH}_2\text{Cl}_2, \text{KMnO}_4 \text{ stain); all other spectral information was identical with the published values.} \]

**triisopropyl((1,2,2-tribromocyclopropyl)methoxy)silane (110), (V-JTW-007)**

To a solution of alcohol 107 (38.7 g, 125 mmol, 1.00 equiv) in CH$_2$Cl$_2$ (420 mL, 0.3 M) were added imidazole (21.3 g, 313 mmol, 2.50 equiv) and triisopropylsilyl chloride (33.1 mL, 156 mmol, 1.25 equiv). A white precipitate quickly appeared and the mixture was stirred at 20 °C for 16 h, at which time it was cooled in an icewater bath and quenched with ½ saturated NaHCO$_3$ solution (420 mL). The phases were separated and the aqueous phase was extracted with CH$_2$Cl$_2$ (200 mL). The combined organic phases were washed with H$_2$O (400 mL), dried over MgSO$_4$, filtered, and the solvent was removed to yield a yellow oil. This was purified by SiO$_2$ column chromatography (hexanes) yielded triisopropylsilyl ether 110 (41.6g, 72%) as a clear, colorless oil as well as a 41 wt% mixture of aldehyde in triisopropylsilanol (12.8 g, containing 5.3 g aldehyde)

\[ R_f = 0.5 \text{ (hexanes, KMnO}_4 \text{ stain); } ^1\text{H NMR (500 MHz, CDCl}_3 \text{) } \delta \text{ 4.23 (d, 1H, } J=11.5 \text{ Hz), 4.12 (d, 1H, } J=11.5 \text{ Hz), 2.01 (d, 1H, } J=9.3 \text{ Hz), 1.93 (d, 1H, } J=9.3\text{Hz), 1.11 (m, 21H); } ^13\text{C NMR (125 MHz, CDCl}_3 \text{) } \delta \text{ 70.82, 45.16, 35.50, 30.50, 18.12, 18.05, 12.19, 12.08; IR (neat film) 2943 (s), 2866 (s), 1462 (m), 1150 (s), 1119 (s) cm}^{-1}; \]
Cyclopropanes 122 and 123 (II-JTW-251)

To a solution of tribromocyclopropane 110 (113 mg, 0.243 mmol, 1.00 equiv) in diethyl ether (810 μL, 0.3 M) at −78 ºC was added a 1.6 M solution of methyllithium in diethyl ether (311 μL, 0.498 mmol, 2.05 equiv). The resulting cloudy solution was removed from the cold bath for 10 m, then re-cooled to −78 ºC, quenched with H2O (1 mL), then removed from the cold bath and allowed to melt. The aqueous phase was then re-frozen and the organic phase separated, then the aqueous phase allowed to melt and extracted with diethyl ether (2x 1 mL). The combined organic extracts were used added directly to a flask containing diene 118 (315 mg, 1.22 mmol, 5.00 equiv) and stirred at room temperature for 18 h. The solution was then concentrated and purified by silica gel column chromatography (2.5% diethyl ether in petroleum ether) to give a 1 : 3.6 mixture of isomers 122 : 123 (90 mg, 76%)

Major isomer 123:

Rf = 0.27 (2 : 1 hexanes : CH2Cl2, KMnO4 stain); 1H NMR (500 MHz, CDCl3) δ 4.09 (d, 1H, J=9.5 Hz), 4.08 (s, 3H), 4.05 (d, 1H, J=9.5 Hz), 3.60 (s, 3H), 3.54 (s, 3H), 1.76 (dd, 1H, J=7.0, 3.2 Hz), 1.26 (t, 1H, J=6.9 Hz), 1.11-1.04 (m, 21H), 0.61 (dd, 1H, J=6.3, 3.1 Hz)

Dione 127 (II-JTW-259)
To a solution of enone 124 (21.0 mg, 0.150 mmol, 1.00 equiv) in CH$_2$Cl$_2$ (1.4 mL, 0.1 M) at 0 ºC were added triethylamine (30 μL, 0.22 mmol, 1.5 equiv) and tert-butyldimethylsilyl trifluoromethanesulfonate (41 μL, 0.179 mmol, 1.2 equiv). The resulting solution was stirred at 0 ºC for 20 m, then benzoquinone (126) (30 mg, 0.28 mmol, 1.9 equiv) was added. The solution was then stirred at room temperature for 20 m, diluted with H$_2$O (10 mL), and extracted with CH$_2$Cl$_2$ (2x 10 mL). The combined organic extracts were dried over Na$_2$SO$_4$, filtered, and concentrated to give dione 127 (48.6 mg, 94%) as a red oil.

R$_f$ = 0.65 (1 : 1 hexanes : ethyl acetate, KMnO$_4$ stain); $^1$H NMR (500 MHz, CDCl$_3$) δ 6.64 (d, 1H, J=10.3 Hz), 6.61 (d, 1H, J=10.3 Hz), 4.72 (dd, 1H, J=3.5, 1.3 Hz), 3.95 – 3.86 (m, 4H), 3.49 (dd, 1H, J=8.2, 4.1 Hz), 3.43 (dd, 1H, J=8.5, 4.1 Hz), 3.12 (m, 1H), 2.91 (m, 1H), 0.85 (s, 9H), 0.12 (s, 3H), 0.02 (s, 3H).

**Dione 130 (III-JTW-077)**

To a solution of hydroxyl-enone 128 (20 mg, 0.20 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (2.0 mL, 0.1 M) at 0 ºC were added triethylamine (124 μL, 1.22 mmol, 6.0 equiv) and tert-butyldimethylsilyl trifluoromethane sulfonate (140 μL, 0.612 mmol, 3.0 equiv). After 3 m, benzoquinone (126) (44 mg, 0.41 mmol, 2.0 equiv) was added. After 1 h, the solution was diluted with H$_2$O (10 mL) and extracted with CH$_2$Cl$_2$ (3x 10 mL). The combined organic extracts were dried over MgSO$_4$, filtered, and concentrated to give a dark brown oil. Purification by silica gel column chromatography (10 : 1 hexanes : ethyl acetate) gave dione 130 (40 mg, 45%) as a yellow oil.
$R_f = 0.36$ (10 : 1 hexanes : ethyl acetate, CAM stain); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 6.64 (d, 1H, $J=10.3$ Hz), 6.60 (d, 1H, $J=10.3$ Hz), 4.56 (dd, 1H, $J=3.7$, 1.5 Hz), 3.58 (m, 1H), 3.40 (dd, 1H, $J=8.5$, 4.4 Hz), 3.31 (dd, 1H, $J=8.4$, 4.0 Hz), 3.08 (m, 1H), 2.92 (m, 1H), 0.86 (s, 9H), 0.86 (s, 9H), 0.10 (s, 3H), 0.07 (s, 6H), 0.01 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 201.32, 199.60, 157.20, 142.75, 142.51, 100.61, 80.39, 56.93, 52.56, 48.36, 46.01, 25.85, 25.54, 18.02, 18.00, -4.70, -4.72, -4.84.

4-methoxycyclopent-2-enone ((±)133) (IV-JTW-161)

To a solution of 4-hydroxycyclopent-2-enone (128) (13.8 g, 141 mmol, 1.00 equiv) in CH$_2$Cl$_2$ (88 mL, 1.6 M) and iodomethane (88 mL, 1410 mmol, 10.0 equiv) was added Ag$_2$O (44.1 g, 190 mmol, 1.35 equiv). The vessel was wrapped in foil and stirred vigorously for 13 d at room temperature. The reaction was then filtered and the solvent was removed by rotary evaporation at 20 ºC and 150 torr, then purified by silica gel column chromatography (diethyl ether) and the solvent was removed at 20 ºC and 125 torr (CH$_2$Cl$_2$ was used for transfers) to yield 4-methoxycyclopent-2-enone (133) as a yellow oil (16.3 g containing 27 wt% CH$_2$Cl$_2$; corrected yield: 11.9 g, 75%).

$R_f = 0.70$ (ethyl acetate, KMnO$_4$ stain); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.61 (dd, 1H, $J=5.8$, 2.4 Hz), 6.26 (dd, 1H, $J=5.7$, 1.3 Hz), 4.59 (m, 1H), 3.43 (s, 3H), 2.67 (dd, $J=18.2$, 5.9 Hz), 2.30 (dd, 1H, $J=18.2$, 2.2 Hz); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 205.92, 160.80, 135.90, 78.80, 57.16, 41.24; IR (neat film) 2988 (w), 2934 (w), 2826 (w), 1720 (s), 1356 (m), 1112 (m), 794 (w);
Cyclopropene 112 (VI-JTW-070)

To a solution of tribromocyclopropane 108 (37.7 g, 81.0 mmol, 1.00 equiv) in Et₂O (400 mL, 0.20 M) at −78 ºC was added a 1.6 M solution of methyllithium in Et₂O (104 mL, 166 mmol, 2.05 equiv). The resulting solution was removed from the cold bath for 15 m, then re-cooled to −78 ºC, quenched with H₂O (400 mL), removed from the cold bath, and allowed to melt. The still cold phases were separated and the aqueous phase was extracted with Et₂O (2x 200 mL) and the combined organic phases were dried thoroughly over MgSO₄, filtered, and concentrated to give a light yellow oil (112) that was used immediately in the next step.

Rₓ = 0.39 (hexanes, KMnO₄ stain)

Cyclopropane X (VI-JTW-071)

To a solution of cyclopenteneone 133 (27.6 g of a 66 wt% solution in CH₂Cl₂ (18.2 g actual), 162 mmol, 2.00 equiv) in CH₂Cl₂ (400 mL, 0.2 M) at 0 ºC were added cyclopropene 112 (18.4 g, 81.0 mmol, 1.00 equiv) as a solution in CH₂Cl₂ (50 mL) followed by triethylamine (42.8 mL, 308 mmol, 3.80 equiv) and tert-butyldimethylsilyl trifluoromethanesulfonate (35.3 mL, 154 mmol, 1.90 equiv). The resulting red solution was stirred at 0 ºC for 17 h then quenched with H₂O (400 mL). The phases were separated and the aqueous phase was extracted with CH₂Cl₂ (2x 200 mL). The combined organic phases were dried over Na₂SO₄, filtered, and the solvent was removed to give a bloodred oil that was purified by SiO₂ column chromatography (packed
using 5% triethylamine in hexanes and eluted with 9:1 hexanes:CH₂Cl₂) to give cyclopropane **135** (37.2 g, 101%) as a 9.5:5.4:1.5:1 mixture of isomers **135** : **136** : **137** : **138** contaminated by a small amount of tert-butyldimethylsilanol.

Rₐ = 0.63 (9:1 hexanes:CH₂Cl₂ on triethylamine pretreated plates); **¹**H NMR (500 MHz, CDCl₃) (2 major isomers) δ 4.52 (dd, 10H, J=4.1, 1.6 Hz), 4.42 (dd, 6H, J=4.0, 1.7 Hz), 4.20 (d, 6H, J=9.8 Hz), 4.16 (d, 10H, J=9.9 Hz), 3.68 (m, 16H), 3.60 (s, 16H), 3.26 (s, 48H), 3.10 (s, 6H, J=3.6 Hz), 1.30 (p, 10H, J=3.7 Hz), 1.09 (m, 336H), 0.91 (m, 144H), 0.17 (s, 96H); **¹³**C NMR (125 MHz, CDCl₃) δ 155.47, 153.93, 102.65, 102.49, 100.69, 99.50, 66.66, 66.46, 55.70, 50.56, 49.78, 44.25, 43.13, 30.46, 25.85, 25.82, 25.76, 21.97, 21.54, 19.21, 18.24, 18.20, 18.11, 14.67, 12.27, 12.19, -4.21, -4.36; IR (neat film) 2942 (s), 2892 (s), 2865 (s), 1611 (m), 1464 (m), 1254 (s), 1104 (s), 1067 (s) cm⁻¹; HRMS (ESI) calc'd for C₂₅H₄₉O₅Si₂ (M+H) 453.3220 found 453.3214.

**Keto-cyclopropanes 139 and 140 (VI-JTW-073)**

A solution of silyl enol-ethers **135** and **136** (37.2 g, 81.0 mmol, 1.00 equiv) in 2:1 tetrahydrofuran:1 M NaOH (810 mL, 0.1 M) was stirred vigorously at 20 °C for 3 h. The phases were then separated and the aqueous phase extracted with ethyl acetate (3x 250 mL). The combined organic extracts were dried over Na₂SO₄, filtered, and the solvent was removed to yield a yellow oil. Purification by SiO₂ automated column chromatography (25g solid load cartridge, 330g column, 0-40% tert-butyl methyl ether in hexanes) gave keto-cyclopropanes **139** and **140** (28.4 g, 104%) as a yellow oil contaminated with a small amount of tert-butyldimethylsilanol.
Major isomer (139): \( R_f = 0.30 \) (4:1 hexanes : tert-butyl methyl ether, CAM stain); \(^1\)H NMR (500 MHz, CDCl₃) \( \delta \) 4.18 (d, 1H, \( J=9.9 \) Hz), 3.96 (m, 1H), 3.64 (d, 1H, \( J=9.8 \) Hz), 3.35 (s, 3H), 2.79 (m, 1H), 2.62 (m, 1H), 1.95 (dd, 1H, \( J=18.4, 4.4 \) Hz), 1.82 (d, 1H, 18.4 Hz), 1.69 (m, 1H), 1.21 (ddd, 1H, \( J=8.5, 6.8, 2.2 \) Hz), 1.05 (m, 22H); \(^{13}\)C NMR (125 MHz, CDCl₃) \( \delta \) 212.54, 98.76, 66.02, 56.82, 55.01, 42.55, 38.82, 34.12, 22.31, 18.60, 18.16, 18.13, 18.10, 12.17

Minor isomer (140): \( R_f = 0.39 \) (4:1 hexanes : tert-butyl methyl ether, CAM stain); \(^1\)H NMR (500 MHz, CDCl₃) \( \delta \) 4.06 (d, 1H, \( J=9.6 \) Hz), 3.95 (s, 1H), 3.66 (d, 1H, \( J=9.6 \) Hz), 3.35 (s, 3H), 2.69 (m, 1H), 2.65 (s, 1H), 1.90 (dd, 1H, \( J=18.5, 4.1 \) Hz), 1.84 (d, 1H, \( J=18.3 \) Hz), 1.70 (m, 1H), 1.03 (m, 22H); \(^{13}\)C NMR (125 MHz, CDCl₃) \( \delta \) 211.76, 98.87, 65.09, 56.67, 56.00, 41.80. 37.09, 30.01, 22.23, 21.26, 18.12, 18.08, 12.12

Mixture: IR (neat film) 2942 (s), 2865 (s), 1757 (s), 1463 (m), 1382 (m), 1142 (s) cm\(^{-1}\); HRMS (ESI) calc'd for C\(_{19}\)H\(_{34}\)O\(_3\)SiNa (M+Na) 361.2175 found 361.2161.

Cyclopropanes 164 and S4 (III-JTW-073, 074)

To a solution of enone S3 (884 mg, 6.31 mmol, 2.00 equiv) in CH\(_2\)Cl\(_2\) (32 mL, 0.1 M) at 0 ºC were added triethylamine (1.32 mL, 9.47 mmol, 3.00 equiv) and tert-butyldimethylsilyl trifluoromethanesulfonate (1.81 mL, 7.89 mmol, 2.50 equiv). This solution was stirred at this temperature for 20 m, at which time it was transferred to neat cyclopropene 112 (716 mg, 3.16 mmol, 1.00 equiv). The resulting yellow solution was then stirred at room temperature for 4 h, then quenched with H\(_2\)O (30 mL) and the phases were separated. The aqueous phase was
extracted with CH₂Cl₂ (2x 30 mL) and the combined organic phases were dried over MgSO₄, filtered, and concentrated to give a red oil. Purification by silica gel column chromatography (packed with 5% triethylamine in hexanes, eluted with 15-30% CH₂Cl₂ in hexanes, stepwise gradient) yielded desired cyclopropane isomer 164 (640 mg, 42%) as well as a 1:3 mixture of desired isomer 164 : S4 (386 mg, 25%).

Rᵣ = 0.71 (4 : 1 hexanes : CH₂Cl₂, triethylamine pretreated plates, CAM stain, major isomer); ¹H NMR (500 MHz, CDCl₃) δ 4.67 (dd, 1H, J=4.0, 1.7 Hz), 4.24 (d, 1H, J=10.0 Hz), 3.92~3.81 (m, 4H), 3.69 (d, 1H, J=10.0 Hz), 2.54 (m, 1H), 2.47 (m, 1H), 1.23 (m, 1H), 1.06 (m, 21H), 0.92 (s, 9H), 0.77 (dd, 1H, J=7.2, 5.7 Hz), 0.65 (m, 1H), 0.19 (s, 3H), 0.18 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 157.78, 131.10, 100.43, 66.05, 64.64, 64.41, 51.86, 47.46, 26.48, 25.81, 18.22, 18.19, 18.14, 15.14, 12.28, 11.45, -4.11, -4.14; IR (neat film) 2944 (s), 2867 (s), 1618 (s), 1466 (m), 1324 (s), 1099 (s), 842 (s) cm⁻¹; LRMS (ESI) 481.00 (M+H), 503.06 (M+Na).

**Hydroxyketone 164 (III-JTW-042)**

To a solution of silyl ether 164 (81 mg, 0.22 mmol, 1.0 equiv) in tetrahydrofuran (2.2 mL, 0.1 M) was added a 1.0 M solution of tetraethylammonium fluoride in tetrahydrofuran (0.44 mL, 0.44 mmol, 2.0 equiv). After stirring at room temperature for 1.25 h, the solution was diluted with H₂O (10 mL) and extracted with ethyl acetate (3x 10 mL). The combined organic extracts were dried over MgSO₄, filtered, and the solvent was removed to give a yellow oil. Purification by silica gel column chromatography (5 : 2 ethyl acetate : hexanes) yielded hydroxyketone S5 (32 mg, 69%) as a clear, colorless oil.
$R_f = 0.23$ (5 : 2 ethyl acetate in hexanes, CAM stain); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 4.05 ~ 3.91 (m, 5H), 3.51 (d, 1H, $J=11.5$ Hz), 3.01 (s, 1H), 2.64 (m, 1H), 2.54 ~2.48 (m, 2H), 1.79 (d, 1H, $J=17.8$ Hz), 1.60 (m, 1H), 0.94 (dd, 1H, $J=7.4, 3.4$ Hz), 0.81 (dd, 1H, $J=7.7, 7.7$ Hz); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 211.09, 126.43, 67.85, 65.50, 64.74, 55.82, 42.50, 42.41, 29.27, 17.61, 16.71; IR (neat film) 3424 (br m), 2976 (m), 2892 (m), 1753 (s), 1410 (w), 1294 (m) cm$^{-1}$; LRMS (ESI) 232.95 (M+Na)

**Thiocarbonate 165 (III-JTW-043)**

To a solution of hydroxyketone S5 (32 mg, 0.15 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (1.5 mL, 0.1 M) were added N,N-dimethylamino pyridine (9.3 mg, 0.076 mmol, 0.5 equiv), pyridine (25 $\mu$L, 0.30 mmol, 2.0 equiv), and phenylchlorothionoformate (41 $\mu$L, 0.30 mmol, 1.0 equiv). The resulting bright yellow solution was stirred at room temperature for 16 h. The reaction was quenched with H$_2$O (10 mL) and extracted with CH$_2$Cl$_2$ (3x 10 mL). The combined organic extracts were dried over MgSO$_4$, filtered, and the solvent was removed to give a red oil. Purification by silica gel column chromatography (5 : 2 hexanes : ethyl acetate) afforded thiocarbonate 165 (48 mg, 91%) as a brown oil.

$R_f = 0.38$ (2 : 1 hexanes : ethyl acetate, CAM stain); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.42 (m, 2H), 7.28 (m, 1H), 7.12 (m, 2H), 5.20 (dd, 1H, $J=11.5, 1.3$ Hz), 4.22 (d, 1H, $J=11.5$ Hz), 4.07 (m, 1H), 3.99~3.92 (m, 3H), 2.64 (m, 1H), 2.57~2.51 (m, 2H), 1.83 (d, $J=18.1$ Hz), 1.70 (m, 1H), 1.15~1.09 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 210.67, 195.40, 153.49, 129.63, 126.69, 126.45, 122.02, 80.51, 65.53, 64.83, 54.98, 42.39, 42.26, 26.87, 19.10, 16.80; IR (neat film)
2979 (w), 2891 (w), 1756 (s), 1591 (w), 1490 (m), 1295 (s) 1197 (s), 1007 (m) cm⁻¹; LRMS (ESI) 368.92 (M+Na), 715.01 (2M+Na)

Olefins 168 and 170 (III-JTW-044)

To a solution of thiocarbonate 165 (20 mg, 0.058 mmol, 1.0 equiv) in benzene (6 mL, 0.1M) were added tributyltin hydride (77 μL, 0.289 mmol, 5.0 equiv) and 2,2'-azobis(isosobutryonitrile) (1.0 mg, 0.0058 mmol, 0.10 equiv). This solution was then heated to 90 ºC for 30 m, cooled to room temperature, and concentrated at 30 torr and room temperature. The product was purified by silica gel column chromatography (2 : 1 to 1 : 1 petroleum ether : diethyl ether) to yield olefin 168 (3.4 mg, 30%) as an oil and olefin 170 (5.3 mg, 47%) as an oil.

Minor product 168:

Rf = 0.30 (2 : 1 petroleum ether : diethyl ether, CAM stain); ¹H NMR (500 MHz, CDCl₃) δ 4.83 (d, 1H, J=2.0 Hz), 4.82 (d, 1H, J=2.0 Hz), 4.07 – 3.94 (m, 4H), 2.99 (dd, 1H, J=7.0, 2.0 Hz), 2.70 (dd, 1H, J=18.5, 7.1 Hz), 2.34 (br s, 1H), 2.26 (dd, 1H, J=15.5, 6.4 Hz), 2.18 – 2.10 (m, 1H), 2.15 (d, 1H, J=18.4 Hz), 1.98 (tdd, 1H, J=12.7, 6.4, 3.0 Hz), 1.85 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 215.81, 147.50, 113.36, 110.39, 65.42, 64.28, 52.18, 50.28, 44.04, 26.38, 26.24; IR (neat film) 3075 (w), 2954 (m), 2995 (m), 2891 (m), 1747 (s), 1346 (m), 1317 (m), 1146 (m), 1104 (m), 1057 (m), 1012 (m), 947 (m), 894 (m) cm⁻¹; LRMS (ESI) 216.95 (M+Na), 411.04 (2M + Na).

Major product 170:

Rf = 0.20 (2 : 1 petroleum ether : diethyl ether); ¹H NMR (500 MHz, C₆D₆) δ 4.85 (s, 1H), 4.71 (s, 1H), 3.41 – 3.20 (m, 4H), 2.67 (dd, 1H, J=18.6, 2.6 Hz), 2.35 (t, 1H, J=2.9 Hz), 2.28 (m, 1H),
2.20 (m, 2H), 2.05 (m, 1H), 2.01 (m, 1H), 1.83 (dd, 1H, J=14.7, 3.0 Hz); $^{13}$C NMR (125 MHz, C$_6$D$_6$) δ 211.01, 143.15, 110.96, 108.80, 64.18, 63.95, 47.39, 45.09, 40.41, 38.72, 30.98; IR (neat film) 3074 (w), 2955 (m), 2891 (m), 1730 (s), 1347 (m), 1121 (m), 1087 (m), 1085 (m), 1033 (m), 1016 (m), 975 (m), 946 (m), 920 (m), 891 (m) cm$^{-1}$; LRMS (ESI) 216.95 (M+Na), 410.98 (2M+Na).

![Chemical Structures](image)

**Methyl eneates S6 and S7 (VI-JTW-074)**

To a solution of potassium bis(trimethylsilyl)amide (22.6 g, 113 mmol, 1.40 equiv) in tetrahydrofuran (350 mL) at 0 ºC was added methyl diethylphosphonoacetate (22.1 mL, 122 mmol, 1.50 equiv) and the solution was removed from the cold bath and stirred at room temperature for 45 m. A solution of ketones 139 and 140 (27.4 g, 81 mmol, 1.00 equiv) in tetrahydrofuran (30 mL) was added via cannula and the mixture was heated to reflux for 19 h. The solution was then cooled to room temperature, poured into H$_2$O (400 mL) and extracted with ethyl acetate (3x 400 mL). The combined organic extracts were dried over MgSO$_4$, filtered, and the solvent was removed to yield a mixture of E/Z isomers of methyl eneates S6 and S7 (35.4 g, >100%) that was used without purification.
Methyl esters 172 and 173 (VI-JTW-077)

A suspension of 10% Pd/C (4.31 g, 4.05 mmol, 0.05 equiv) and methyl eneotes S6 and S7 (32.0 g, 81 mmol, 1.00 mmol) in ethyl acetate (400 mL, 0.2 M) was stirred at room temperature under an atmosphere of H₂ at balloon pressure for 16 h. The suspension was filtered through a plug of celite (6 x 7 cm) and flushed with ethyl acetate (800 mL). Solvent removal gave methyl esters 172 and 173 (32.1 g, 100%) as a colorless oil.

Data for 172:

R_f = 0.63 (4 : 1 hexanes : ethyl acetate, CAM stain); \(^1^H\) NMR (500 MHz, CDCl₃) \(\delta \) 4.06 (dd, 1H, \(J=9.8, 1.0 \) Hz), 3.89 (s, 1H), 3.65 (s, 3H), 3.33 (s, 3H), 3.26 (d, 1H, \(J=9.8 \) Hz), 2.61 (dd, 1H, \(J=16.3 \) Hz, 7.6 Hz), 2.46 (dd, 1H, \(J=16.2, 6.8 \) Hz), 2.32 (m, 1H), 2.27 (s, 2H), 1.74 (m, 1H), 1.53 (m, 1H), 1.35 (s, 1H), 1.18 (s, 1H), 1.05 (m, 22 H), 0.88 (dd, 1H, \(J=13.3, 6.3 \) Hz); \(^{13}\)C NMR (125 MHz, CDCl₃) \(\delta \) 174.09, 102.12, 68.83, 56.89, 51.55, 45.08, 40.47, 34.79, 33.06, 32.27, 28.73, 25.39, 25.00, 18.17, 18.15, 17.84, 12.15

Data for 173:

R_f = 0.63 (4 : 1 hexanes : ethyl acetate, CAM stain); \(^1^H\) NMR (500 MHz, CDCl₃) \(\delta \) 4.11 (d, 1H, \(J=9.6 \) Hz) 3.88 (s, 1H), 3.65 (s, 3H), 3.52 (d, 1H, \(J=9.6 \) Hz), 3.31 (s, 3H), 2.60 (dd, 1H, \(J=15.7, 9.6 \) Hz)
7.9 Hz), 2.44 (dd, 1H, \( J = 16.1, 6.6 \text{ Hz} \)), 2.27 (m, 2H), 2.24 (m, 1H), 1.79 (td, 1H, \( J = 13.5, 4.7 \text{ Hz} \)), 1.30-1.19 (m, 3H), 1.10 (m, 22 H), 0.91 (dd, 1H, \( J = 13.3, 6.0 \text{ Hz} \))

Mixture:

IR (neat film) 2944 (s), 2865 (s), 1741 (s), 1464 (w), 1169 (w), 1116 (m), 882 (w) 681 (w) cm\(^{-1}\);
LRMS (ESI) 419.32 (M+Na).

**Weinreb amides 174 and 175 (VI-JTW-079)**

To a suspension of N,O-dimethylhydroxylamine hydrochloride (23.7 g, 243 mmol, 3.00 equiv) in toluene (200 mL) at 0 °C was added a 2 M solution of AlMe\(_3\) in heptane (121 mL, 243 mmol, 3.00 equiv) very carefully and dropwise over 10 minutes, resulting in vigorous evolution of gas. The resulting solution was warmed to room temperature and stirred for 1 h. This solution was then transferred via cannula to a solution of methyl esters 172 and 173 (32.1 g, 81.0 mmol, 1.00 equiv) in toluene (200 mL), resulting in a mild exotherm. The resulting yellow solution was stirred at room temperature for 4 h, cooled to 0 °C and very slowly and carefully quenched with 2 M HCl (400 mL), resulting in vigorous evolution of gas and heat. The product was then extracted with ethyl acetate (3x 200 mL) and the combined organic extracts were dried over MgSO\(_4\), filtered, and the solvent was removed to yield a black oil. This was purified by automated silica gel column chromatography (25 g solid load cartridge, 330 g column, 5-10%
acetone in hexanes) to give weinreb amide 175 (13.4 g, 39% from tribromocyclopropane 110) as a yellow oil along with undesired isomer 174 (6.95 g, 20% from tribromocyclopropane 110).

Major isomer (X): R_f = 0.21 (4 : 1 hexanes : ethyl acetate, CAM stain); 'H NMR (500 MHz, CDCl_3) δ 4.11 (d, 1H, J=9.8 Hz), 3.90 (s, 1H), 3.69 (s, 3H), 3.53 (d, 1H, J=9.8 Hz), 3.30 (s, 3H), 3.26 (s, 3H), 2.71 (dd, 1H, J=16.1, 7.7 Hz), 2.54 (dd, 1H, J=16.1, 6.2 Hz), 2.34 (m, 1H), 2.28 (br s, 1H), 2.22 (br d, 1H, J=4.8 Hz), 1.82 (td, 1H, J=13.2, 4.8 Hz), 1.35 (m, 1H), 1.23 (m, 2H), 1.04 (m, 21H), 0.91 (dd, 1H, J=13.3, 6.5 Hz); 'C NMR (125 MHz, CDCl_3) δ 102.50, 67.21, 61.35, 56.89, 43.77, 41.64, 36.41, 33.04, 30.10, 24.24, 21.37, 18.17, 18.16, 12.22;

Minor isomer (X): R_f = 0.30 (4 : 1 hexanes : ethyl acetate, CAM stain); 'H NMR (500 MHz, CDCl_3) δ 4.07 (dd, 1H, J=9.8, 1.0 Hz), 3.91 (m, 1H), 3.68 (s, 3H), 3.33 (s, 1H), 3.28 (d, 1H, J=9.9 Hz), 3.15 (s, 3H), 2.68 (dd, 1H, J=16.5, 7.2 Hz), 2.61 (br dd, 1H, J=16.4, 6.9 Hz), 2.39 (m, 1H), 2.27 (m, 2H), 1.78 (td, 1H, J=13.2, 4.1 Hz), 1.52 (m, 1H), 1.43 (m, 1H), 1.19 (m, 1H), 1.04 (m, 21H), 0.90 (dd, 1H, J=13.3, 6.5 Hz); 'C NMR (125 MHz, CDCl_3) δ 102.20, 68.88, 61.27, 56.87, 45.29, 40.56, 32.52, 32.26, 28.91, 25.46, 24.90, 18.17, 18.15, 12.21, 12.15, 11.91; IR (thin film) 2945 (s), 2867 (s), 1674 (s), 1110 (s), 884 (m), 682 (m) cm⁻¹; LRMS (ESI) 426.38 (M+H), 448.37 (M+Na)

**Vinyl ketone 177 (VI-JTW-120)**

To a solution of weinreb amide 175 (10.0 g, 23.5 mmol, 1.00 equiv) in tetrahydrofuran (235 mL, 0.1 M) at 0 °C was added a 1 M solution of vinylmagnesium bromide in tetrahydrofuran (35.3 mL, 35.3 mmol, 1.50 equiv). The solution was stirred at 0 °C for 25 m when it was quenched
with ½ saturated aqueous NH₄Cl solution (230 mL) and extracted with ethyl acetate (3x 230 mL). The combined organic extracts were dried over MgSO₄, filtered, and the solvent was removed to yield 177 as an oil that was used directly without further purification.

R_f = 0.69 (4 : 1 hexanes : acetone, CAM stain); ^1H NMR (500 MHz, CDCl₃) δ 6.33 (dd, 1H, J=17.7, 10.4 Hz), 6.23 (dd, 1H, J=17.7, 1.2 Hz), 5.81 (dd, 1H, J=10.5, 1.2 Hz), 4.10 (d, 1H, J=9.8 Hz), 3.90 (d, 1H, J=0.8 Hz), 3.54 (d, 1H, J=9.8 Hz), 3.30 (s, 3H), 2.92 (dd, 1H, J=17.0, 7.8 Hz), 2.68 (dd, 1H, J=17.0, 6.3 Hz), 2.35 (m, 1H), 2.23 (m, 2H), 1.82 (td, 1H, J=12.1, 4.7 Hz), 1.25 (m, 2H), 1.04 (m, 21H), 0.87 (dd, 1H, J=13.2, 6.3 Hz); ^13C NMR (125 MHz, CDCl₃) δ 200.64, 136.92, 128.10, 102.48, 67.09, 56.92, 43.72, 41.57, 40.80, 36.43, 32.17, 30.30, 24.37, 21.30, 18.19, 18.16, 12.21; IR (thin film) 3091 (w), 2943 (s), 2865 (s), 1702 (m), 1686 (m), 1616 (w), 1464 (m), 1386 (m) 1114 (s) cm⁻¹; LRMS (ESI) 415.35 (M+Na)

Diene 178 (VI-JTW-121)

To a solution of eneone 177 from above (9.20 g, 23.5 mmol, 1.00 equiv) in tetrahydrofuran (115 mL, 0.2 M) at –78 °C was added tert-butyldimethylsilyl trifluoromethanesulfonate (8.10 mL, 35.3 mmol, 1.50 equiv) and stirred at this temperature of 5 m. This solution was then transferred via cannula to a solution of potassium bis(trimethylsilyl)amide (7.03 g, 35.3 mmol, 1.50 equiv) in tetrahydrofuran (115 mL, 0.2 M) at –78 °C over approximately 8 m and stirred at this temperature for 15 m. The reaction was then quenched with ½ saturated NaHCO₃ solution (230 mL), removed from the cold bath and allowed to melt, then extracted with ethyl acetate (1x 230 mL, 2x 100 mL) and the combined organic extracts were dried over MgSO₄, filtered, and the
solvent was removed to give an oil that was purified by automated SiO₂ column chromatography (25g solid load cartridge, 220 g column, 1-8% ethyl acetate in hexanes) to yield diene 178 (9.18 g, 77% over 2 steps) as a light yellow oil favoring the Z isomer (>25:1 Z:E).

R<sub>f</sub> = 0.35 (4% diethyl ether in hexanes, CAM stain); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 6.16 (dd, 1H, <i>J</i>=17.2, 10.8 Hz), 5.28 (dd, 1H, <i>J</i>=17.1, 1.5 Hz), 5.15 (d, 1H, <i>J</i>=8.4 Hz), 4.96 (dd, 1H, <i>J</i>=10.8, 1.4 Hz), 3.32 (s, 3H), 2.82 (m, 1H), 2.28 (m, 1H), 1.85 (dt, 1H, <i>J</i>=12.5, 4.4 Hz), 1.40 (dd, 1H, <i>J</i>=5.4, 3.3 Hz), 1.30 (m, 1H), 1.20 (m, 1H), 1.05 (m, 21H), 0.90 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 149.09, 135.88, 116.95, 112.49, 102.32, 67.45, 56.89, 44.71, 41.31, 36.18, 33.34, 31.85, 26.15, 24.65, 21.62, 18.59, 18.22, 18.19, 12.26, -3.37, -3.39; IR (thin film) 2943 (s), 2864 (s), 1639 (w), 1602 (w), 1464 (m), 1365 (m), 1255 (m), 1116 (s) 681 (m); HRMS (ESI) calc'd for C<sub>29</sub>H<sub>54</sub>O<sub>3</sub>Si<sub>2</sub>Na (M+Na) 529.3509 found 529.3508.

Hydroxyamide 180 (VI-JTW-166)

A mixture of ε-caprolactone (179) (5.0 mL, 45 mmol, 1.0 equiv) and benzylamine (10 mL, 90 mmol, 2.0 equiv) was heated to 120 °C for 20 h, cooled to room temperature, then dissolved in hot ethyl acetate (100 mL) and hot hexanes (100 mL). The solution was allowed to slowly cool to room temperature. The resulting crystals were collected by filtration to give hydroxyamide 180 (7.8 g, 78%) as a white crystalline solid.

R<sub>f</sub> = 0.29 (ethyl acetate, KMnO₄ stain); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.28 (m, 5H), 5.74 (br s, 1H), 4.44 (d, 2H, <i>J</i>=5.7 Hz), 3.64 (m, 2H), 2.23 (m, 2H), 1.69 (m, 2H), 1.59 (m, 2H), 1.41 (m, 2H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 172.92, 138.49, 128.85, 127.98, 127.66, 62.69, 43.75,
36.69, 32.41, 25.51, 25.40; IR (neat film) 3300 (s), 3084 (m), 3032 (m), 2937 (s), 2860 (s), 1636 (s), 1545 (s), 1427 (s), 1382 (m), 1237 (m), 1060 (m) 728 (s), 629 (s) cm$^{-1}$; LRMS (ESI) 221.9 (M+H), 244.2 (M+Na), 465.2 (2M+Na).

Aldehyde 181 (VI-JTW-190)

To a solution of hydroxyamide 180 (1.37 g, 6.19 mmol, 1.00 equiv) in CH$_2$Cl$_2$ (12.9 mL) and dimethylsulfoxide (2.6 mL) was added triethylamine (3.45 mL, 24.8 mmol, 4.00 equiv) followed by SO$_3$·pyridine (1.97 g, 12.4 mmol, 2.00 equiv) in 4 portions over 20 m, resulting in an exotherm. The solution was stirred at room temperature for 1.5 h, then poured into 10% aqueous citric acid solution (20 mL). The phases were separated. The aqueous phase was extracted with CH$_2$Cl$_2$ (20 mL). The combined organic phases were washed with 10% aqueous citric acid solution (20 mL), sat'd aqueous NaHCO$_3$ solution (20 mL), sat'd aqueous NaCl solution (20 mL), dried over Na$_2$SO$_4$, filtered, and concentrated to give aldehyde 181 (1.26 g, 93%) as an off-white solid. No further purification was performed.

R$_f$ = 0.54 (ethyl acetate, KMnO$_4$ stain); $^1$H NMR (500 MHz, CDCl$_3$) δ 9.70 (s, 1H), 7.26 (m, 5H), 6.42 (br s, 1H), 4.38 (d, 2H, J=5.8 Hz), 2.41 (t, 2H, J=6.7 Hz), 2.20 (m, 2H), 1.63 (m, 4H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 202.47, 202.29, 172.49, 138.44, 128.78, 128.46, 127.85, 127.53, 127.22, 43.68, 43.54, 43.52, 43.45, 43.39, 43.24, 36.27, 36.10, 35.92, 25.05, 21.56; IR (neat film) 3294 (br s), 3065 (m), 3031 (m), 2866 (m), 2725 (w), 1721 (s), 1545 (s), 1497 (m), 1454 (s), 1390 (m), 1242 (m), 1080 (m), 1029 (m), 736 (s), 700 (s) cm$^{-1}$; LRMS (ESI) 220.2 (M+H), 242.0 (M+Na), 461.3 (2M+Na).
Enamide 182 (VI-JTW-192)

A solution of aldehyde 181 (1.26 g, 5.75 mmol, 1.00 equiv) and p-toluenesulfonic acid (78 mg, 0.41 mmol, 0.071 equiv) in toluene (29 mL) was heated to reflux with azeotropic removal of water by a Dean-Stark apparatus for 5 h, cooled to room temperature, and concentrated. The residue was combined with a previous reaction on 2.77 mmol and purified by automated silica gel column chromatography (15-50% ethyl acetate in hexanes) to give enamide 182 (1.33 g, 77%) as a clear, colorless oil.

R\text{f} = 0.40 (2 : 1 hexanes : ethyl acetate, CAM stain); \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \( \delta \) 7.26 (m, 5H), 5.89 (d, 1H, \( J = 9.0 \) Hz), 5.33 (m, 1H), 4.64 (s, 2H), 2.60 (m, 2H), 2.15 (m, 2H), 2.05 (m, 2H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \( \delta \) 174.20, 137.74, 129.77, 128.66, 127.98, 127.44, 117.88, 50.55, 36.05, 26.63, 26.28; IR (neat film) 3031 (w), 2933 (m), 1657 (s), 1495 (m), 1452 (s), 1432 (s), 1391 (s), 1364 (m), 1324 (m), 1285 (m), 1244 (m), 1198 (m), 970 (m), 739 (s), 701 (s) cm\textsuperscript{-1}; LRMS (ESI) 224.0 (M+Na).

Methyl enoate 185 (SY-VI-233 and SY-VI-234) – Yuan Shi

To a solution of enamide 182 (1.19 g, 5.91 mmol, 1.00 equiv) in tetrahydrofuran (50 mL, 0.12 M) at –78 °C was added a solution of lithium bis(trimethylsilyl)amide (2.49 g, 14.9 mmol, 2.50 equiv) in tetrahydrofuran (15 mL). The resulting solution was removed from the cold bath for 10 m, collled back to –78 °C at which time methylchloroformate (470 μL, 6.11 mmol, 1.00 equiv)
was added. The solution was again removed from the cooling bath for 15 m, then cooled to –78 °C and phenylselenyl chloride (1.20 g, 6.27 mmol, 1.10 equiv) was added and the resulting solution removed from the cooling bath for 30 m, then quenched with ½ saturated aqueous NaHCO₃ solution (40 mL), extracted with ethyl acetate (20 mL), and CH₂Cl₂ (2x 20 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated to give 184 as an oil that was used directly in the next reaction.

To a solution of the above oil in CH₂Cl₂ at 0 °C was added a 30 wt% aqueous solution of H₂O₂ (1.2 mL, 12 mmol, 2.0 equiv). The resulting mixture was stirred at 0 °C for 15 m, quenched with ½ saturated aqueous NaHCO₃ solution (20 mL) and extracted with CH₂Cl₂ (3x 10 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated. The crude product was purified by automated silica gel column chromatography (40 g column, 0 – 50% ethyl acetate in hexanes) to give methyl enoate 185 (822 mg, 54% over 2 steps).

Rᵣ = 0.18 (1 : 2 EtOAc : Hexane, KMnO₄ stain);¹ H NMR (600 MHz, CDCl₃) δ 7.34-7.31 (m, 5H), 7.27 (dd, 1H, J=8.5, 4.1 Hz), 6.05 (d, 1H, J=7.5 Hz), 5.51 (dd, 1H, J=14.1, 6.9 Hz), 4.88 (s, 2H), 3.80 (s, 3H), 2.65 (t, 2H, J=7.1 Hz);¹³C NMR (125 MHz, CDCl₃) δ 165.54, 165.44, 148.80, 137.26, 131.20, 130.47, 128.79, 127.76, 117.71, 52.54, 51.14, 24.38; IR (neat film) 2951 (w), 1724 (s), 1687 (s), 1653 (m), 1437 (m), 1412 (m), 1263 (s), 1159 (w), 738 (m) cm⁻¹; HRMS (ESI) calc'd for C₁₅H₁₅NO₃Na (M+Na) 280.0950 found 280.0962.

Dienophile X (SY-VI-041) – Yuan Shi

To a mixture of CrO₃ (12 g, 120 mmol, 9.68 equiv) in CH₂Cl₂ (100 mL) at – 20 °C (cooling bath of EtOH/H₂O=3/7 and dry ice) was added 3,5-dimethylpyrazole (12.5 g, 130 mmol, 10.5 equiv)
in one portion. The dark brown mixture was stirred at –20 °C for 1 h before a solution of 185 (3.20 g, 12.4 mmol, 1.00 equiv) in CH₂Cl₂ (20 mL) was added via cannula transfer, with a CH₂Cl₂ rinse (20 mL). The resulting mixture was stirred at ambient temperature for 3.5 hours then filtered through a short silica gel plug (flushed with CH₂Cl₂). The resulting solution was concentrated, and purified directly by automated SiO₂ column chromatography (25 g solid load cartridge, 40 g column, 0-50% ethyl acetate in hexane) to yield diene 186 (2.45 g, 73%) as a pale yellow oil.

R_f = 0.53 (1 : 20 ethyl acetate : CH₂Cl₂, KMnO₄ stain); ¹H NMR (500 MHz, CDCl₃) δ 7.42 (d, 2H, J=7.2 Hz), 7.31-7.25 (m, 3H), 7.22 (dd, 1H, J=3.5, 0.9 Hz), 6.66 (dd, 1H, J=11.9, 7.0 Hz), 6.60 (dd, 1H, J=12.0, 0.9 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 165.54, 164.94, 164.55, 136.66, 135.23, 134.25, 133.88, 130.68, 129.00, 128.53, 127.81, 53.23, 49.51; IR (neat film) 2902 (m), 2255 (m), 1738 (m), 913 (s), 745 (s) cm⁻¹; HRMS (ESI) calc'd for C₁₅H₁₃NO₄Na (M+Na) 294.0742 found 294.0747.

Enimides S8 and S9 (SY-V-196) – Yuan Shi

To a solution of 178 (2.54 g, 5.01 mmol, 1.00 equiv) and 186 (1.49 g, 5.49 mmol, 1.10 equiv) in toluene (50 mL) was added Yb(OTf)₃ (217 mg, 0.350 mmol, 0.0699 equiv) in tetrahydrofuran (0.35 mL). The resulting golden solution was stirred at ambient temperature for 4 h then quenched with saturated aqueous NaHCO₃ solution (50 mL) and extracted with Et₂O (3x 25 mL). The combined organic extracts were dried over MgSO₄, concentrated, and purified by automated SiO₂ column chromatography (25 g solid load cartridge, 120 g column, 0-10% ethyl
acetate in hexanes) to yield a 1.2 : 1 mixture of S8 and S9 (3.33 g, 85%, 95% brsm) as a white foam. Recovered diene 178 (264 mg, 10%) was also isolated.

**Imides 187 and 188 (SY-V-199)**

To a solution of the mixture of S8 and S9 (3.33 g, 4.28 mmol, 1.00 equiv) in ethyl acetate (80 mL) was added 10% Pd/C (226 mg, 0.212 mmol, 0.0495 equiv). The mixture was sparged three times with H2, and then stirred under balloon pressure H2 for 12 h then filtered through a short silica gel plug, and flushed with ethyl acetate. The solution was concentrated and purified by automated SiO2 column chromatography (25 g solid load cartridge, 220 g column, 0-4% ethyl acetate in toluene) to yield 188 (731 mg, 22%) as a white foam and 187 (900 mg, 27%) as a white foam as well as a mixture of the two diastereomers (1.62 g 49%). The total yield from 178 is 83%, so complete separation would give 38% of 188 and 45% of 187.

Minor isomer (188) Rf = 0.36 (1 : 30 ethyl acetate : toluene, KMnO4 stain); 1H NMR (600 MHz, CDCl3) δ 7.35 (d, 2H, J=7.3 Hz), 7.30 (t, 3H, J=7.5 Hz), 7.25 (t, 1H, J=7.2 Hz), 4.90 (d, 1H, J=14.4 Hz), 4.86 (d, 1H, J=14.3 Hz), 4.74-4.73 (m, 1H), 4.13 (d, 1H, J=9.9 Hz), 3.82 (s, 1H), 3.47 (d, 1H, J=9.9 Hz), 3.33 (s, 3H), 3.28 (s, 3H), 2.98 (dd, 1H, J=17.3, 3.7 Hz), 2.75-2.72 (m, 2H), 2.87-2.82 (m, 2H), 2.41 (d, 1H, J=10.0 Hz), 2.34 (d, 1H, J=17.4 Hz), 1.93-1.86 (m, 2H), 1.84-1.77 (m, 1H), 1.66 (dt, 1H, J=12.4, 4.4 Hz), 1.15-1.13 (m, 1H), 1.09-1.05 (m, 2H), 0.92 (s, 9H), 0.19 (s, 3H), 0.16 (s, 3H); 13C NMR (125 MHz, CDCl3) δ 178.56, 173.46, 170.19, 151.26, 137.07, 129.08, 128.41, 127.54, 102.05, 99.71, 67.51, 60.63, 57.03, 52.83, 48.79, 45.26, 40.90, 38.27, 38.58, 35.85, 35.74, 27.44, 26.39, 26.16, 23.60, 21.15, 20.75, 18.56, 18.21, 18.19, 12.21,
3.58, -4.03; IR (neat film) 2944 (s), 2863 (s), 1757 (m), 1718 (m), 1669 (s), 1207 (m), 1113 (m), 880 (m), 838 (m) cm\(^{-1}\); HRMS (ESI) calc'd for C\(_{44}H_{69}NO_7NaSi_2\) (M+Na) 802.4510 found 802.4517.

Enamide 189 (IV-JTW-208 and IV-JTW-210)

To a solution of imide 188 (177 mg, 0.227 mmol, 1.00 equiv) and Comins' reagent (107 mg, 0.272 mmol, 1.20 equiv) in tetrahydrofuran (2.3 mL, 0.1 M) at –78 ºC was added a 0.5 M solution of potassium hexamethyldisilazide in toluene (681 \(\mu\)L, 0.341 mmol, 1.50 equiv). This solution was stirred at –78 ºC for 25 m, quenched with 1 N aqueous NaOH solution (1.5 mL) and allowed to melt. This mixture was diluted with ½ saturated aqueous NaCl solution (10 mL) and extracted with ethyl acetate (3x 10 mL). The combined organic extracts were dried over MgSO\(_4\), filtered, and concentrated to give an orange oil that was immediately dissolved in tetrahydrofuran (2.3 mL, 0.1 M). To this solution were added tributyltin hydride (90 \(\mu\)L, 0.34 mmol, 1.5 equiv) followed by Pd(PPh\(_3\))\(_4\) (13 mg, 0.011 mmol, 0.050 equiv). This solution was stirred at room temperature for 20 m, diluted with ½ saturated aqueous NaCl solution (10 mL), and extracted with ethyl acetate (3x 10 mL). The combined organic extracts were dried over MgSO\(_4\), filtered, and concentrated to give a brown oil. Purification by silica gel column chromatography (9 : 1 hexanes : ethyl acetate) provided enamide 189 (113 mg, 65%) as a hard white foam.
R_f = 0.18 (9 : 1 hexanes : ethyl acetate, CAM stain); ¹H NMR (500 MHz, CDCl₃) δ 7.26 (m, 5H), 5.73 (dd, 1H, J=8.2, 1.4 Hz), 4.76 (d, 1H, J=14.3 Hz), 4.63 (s, 1H), 4.57 (d, 1H, J=14.6 Hz), 3.94 (br d, 1H, J=8.7 Hz), 3.81 (s, 1H), 3.64 (br s, 3H), 3.30 (s, 3H), 2.23 (s, 1H), 2.10 (td, 1H, J=14.3, 4.2 Hz), 2.03 (br s, 1H), 1.87 (br s, 1H), 1.54 (m, 2H), 1.20 (v br s, 1H), 1.17 (br s, 1H), 1.03 (m, 21H), 0.93 (s, 9H), 0.18 (s, 3H), 0.14 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 137.26, 128.60, 127.59, 56.76, 52.67, 35.63, 31.91, 26.10, 18.32, 18.19, 18.13, 18.06, 12.13; IR (neat film) 2944 (s), 2892 (m), 2863 (s), 1758 (m), 1738 (m), 1648 (s), 1462 (s), 1389 (m), 1254 (s), 1210 (s), 1115 (s), 881 (m), 863 (m), 836 (s), 680 (m) cm⁻¹; LRMS (ESI) 764.66 (M+H), 786.71 (M+Na).

Ketone 190 (VI-JTW-003)

To a solution of enol-ether 189 (214 mg, 0.280 mmol, 1.00 equiv) in tetrahydrofuran (2.8 mL, 0.1 M) at 0 ºC was added a 1 M solution of tetrabutylammonium fluoride in tetrahydrofuran (294 μL, 0.294 mmol, 1.05 equiv). After 30 m at this temperature, the yellow solution was poured into ½ saturated aqueous NaCl solution (10 mL) and extracted with ethyl acetate (3x 10 mL). The combined organic extracts were dried over Na₂SO₄, filtered, and concentrated to give an oil. Purification by automated silica gel column chromatography (5 g solid load cartridge, 12 g

¹ The ¹H NMR and ¹³C NMR have very broad peaks. The ¹³C NMR is missing many of the peaks due to excessive broadening. This effect could be due to hindered rotation about the N-benzyl bond.
column, 10-40% ethyl acetate in hexanes) afforded ketone 190 (126 mg, 69%) as a hard, white foam.

$R_f = 0.47$ (2 : 1 hexanes : ethyl acetate, CAM stain); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.27 (m, 5H), 5.82 (d, 1H, $J$=8.3 Hz), 5.40 (br m, 1H), 4.70 (br d, 1H, $J$=14.5 Hz), 4.60 (br d, 1H, $J$=14.5 Hz), 4.09 (d, 1H, $J$=9.8 Hz), 3.86 (s, 1H), 3.74 (s, 3H), 3.55 (m, 1H), 3.48 (d, 1H, $J$=9.9 Hz), 3.30 (s, 3H), 2.79 (br s, 1H), 2.65 (br s, 1H), 2.62 (m, 1H), 2.53 (m, 1H), 2.21 (m, 3H), 1.90 (m, 2H), 1.51 (m, 1H), 1.19 (m, 3H), 1.04 (m, 21 H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 211.23, 172.79, 171.36, 136.91, 129.05, 128.72, 128.31, 127.79, 101.94, 67.30, 56.94, 53.11, 52.30, 43.31, 41.20, 36.39, 34.02, 29.37, 26.14, 24.50, 21.49, 18.20, 18.17, 12.20; IR (neat film) 2943 (s), 2865 (s), 1736 (s), 1717 (s), 1649 (s), 1462 (m), 1390 (m), 1263 (s), 1100 (s), 1066 (m), 883 (s), 734 (s), 682 (m) cm$^{-1}$; HRMS (ESI) calc'd for C$_{38}$H$_{55}$NO$_6$SiNa (M+Na) 672.3696 found 672.3672

Alcohol 191 (V-JTW-015)

To a solution of ketone 190 (65.0 mg, 0.100 mmol, 1.00 equiv) in methanol§ (1.0 mL, 0.1 M) at 0 ºC was added NaBH$_4$ (18.4 mg, 0.487 mmol, 4.87 equiv). The solution was stirred at 0 ºC for 15 m, diluted with ½ saturated aqueous NH$_4$Cl solution (10 mL), and extracted with CH$_2$Cl$_2$ (3x 10 mL). The combined organic extracts were dried over MgSO$_4$, filtered, and concentrated to give alcohol 191 (62.9 mg, 96%) as a hard white foam. This product required no further purification, though an X-ray quality crystal was grown from hexanes : ethyl acetate.

§ The methanol used for this reaction was undistilled.
Rₖ = 0.40 (4 : 1 CH₂Cl₂ : ethyl acetate, CAM stain); ¹H NMR (500 MHz, CDCl₃) δ 7.27 (m, 5H), 5.89 (d, 1H, J=7.8 Hz), 5.62 (q, 1H, J=7.5 Hz), 4.74 (d, 1H, J=14.6 Hz), 4.51 (d, 1H, J=14.6 Hz), 4.09 (d, 1H, J=9.8 Hz), 3.87 (s, 1H), 3.85 (s, 1H), 3.78 (s, 3H), 3.53 (d, 1H, J=9.8 Hz), 3.46 (q, 1H, J=6.6 Hz), 3.31 (s, 3H), 2.68 (m, 1H), 2.37 (s, 1H), 2.24 (d, 1H, J=4.3 Hz), 2.20~2.00 (m, 4H), 1.92 (m, 1H), 1.77 (dd, 1H, J=11.7, 5.6 Hz), 1.66 (m, 1H), 1.56 (td, 1H, J=13.0, 4.65 Hz), 1.28 (m, 1H), 1.25 (s, 1H), 1.19 (m, 1H), 1.15 (m, 1H), 23.89 (m, 21H); ¹³C NMR (125 MHz, CDCl₃) δ 173.95, 172.69, 137.30, 129.98, 128.67, 128.11, 127.59, 121.14, 102.36, 67.01, 56.91, 52.83, 51.79, 41.89, 41.03, 39.51, 36.57, 36.34, 31.13, 29.84, 24.83, 23.97, 21.25, 18.21, 18.18, 12.21; IR (neat film) 3502 (br m), 2943 (s), 2865 (s), 1737 (s), 1624 (s), 1458 (m), 1389 (m), 1215 (s), 1112 (s), 1017 (s), 883 (m), 735 (m), 687 (m); HRMS (ESI) calc'd for C₃₈H₇₅NO₆SiNa (M+Na) 764.3853 found 764.3848.

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F^2^ > 2sigma(F^2^) is used only for calculating R-factors(gt) etc. and is
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C22 C 0.37910(9) 0.1739(3) -0.1566(2) 0.0599(9) Uani 1 1 d . . .
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H22B H 0.3557 0.1859 -0.1604 0.090 Uiso 1 1 calc R . .
H22C H 0.3816 0.1399 -0.2123 0.090 Uiso 1 1 calc R . .
C23 C 0.34544(8) 0.2264(3) 0.40311(19) 0.0487(7) Uani 1 1 d . . .
H23A H 0.3498 0.1512 0.4290 0.073 Uiso 1 1 calc R . .
H23B H 0.3319 0.2682 0.4351 0.073 Uiso 1 1 calc R . .
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H30D H 0.4782 -0.2521 -0.0659 0.073 Uiso 0.50 1 d PR A 2
C31 C 0.45816(14) -0.3762(5) 0.0325(5) 0.0479(13) Uani 0.50 1 d PD B 1
C32 C 0.47327(18) -0.4411(6) 0.1067(5) 0.074(2) Uani 0.50 1 d PD B 1
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C33 C 0.4573(2) -0.5272(7) 0.1394(6) 0.088(3) Uani 0.50 1 d PD B 1
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C34 C 0.42444(18) -0.5496(7) 0.0962(6) 0.069(2) Uani 0.50 1 d PD B 1
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C41 C 0.33967(6) 0.6401(3) 0.1412(2) 0.0434(6) Uani 1 1 d . . .
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H41B H 0.3435 0.5735 0.1080 0.065 Uiso 1 1 calc R . .
H41C H 0.3510 0.6312 0.2045 0.065 Uiso 1 1 calc R . .
C42 C 0.29563(7) 0.7611(2) 0.17896(19) 0.0408(6) Uani 1 1 d . . .
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C34B 0.052(4) 0.068(5) 0.132(8) -0.034(5) 0.032(5) -0.020(4)
C36B 0.085(8) 0.052(5) 0.073(7) -0.023(5) 0.036(6) -0.028(5)
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; All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

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Olefin 192 (V-JTW-014)

To a solution of triphenylphosphine oxide (24.4 mg, 0.0876 mmol, 2.40 equiv) in CH$_2$Cl$_2$ (1.0 mL) at 0 ºC was added trifluoromethanesulfonic anhydride (6.1 μL, 0.037 mmol, 1.0 equiv). This solution was stirred at 0 ºC for 30 m, then transferred via cannula to a solution of diisopropylethyl amine (14.0 μL, 0.0803 mmol, 2.20 equiv) and alcohol 191 (23.8 mg, 0.0365 mmol, 1.00 equiv) in CH$_2$Cl$_2$ (1.2 mL, 0.03 M) at 0 ºC. The resulting solution was heated to 40 ºC for 35 m, cooled briefly in an icewater bath, diluted with ½ saturated aqueous NaHCO$_3$ solution (10 mL), and extracted with CH$_2$Cl$_2$ (3x 10 mL). The combined organic extracts were dried over MgSO$_4$, filtered, and concentrated to give a white solid. Purification by silica gel prep TLC (4 : 1 hexanes : ethyl acetate) afforded desired olefin 192 (9.8 mg, 42%) as a colorless film along with undesired tetrasubstituted olefin S10 (3.6 mg, 16%) and recovered starting alcohol 191 (4.6 mg, 19%).

Desired isomer 192:

R$_f$ = 0.40 (4 : 1 hexanes : ethyl acetate, CAM stain); $^1$H NMR (500 MHz, CDCl$_3$) δ 7.29 (m, 5H), 5.80 (dd, 1H, $J$=7.2, 1.6 Hz), 5.59 (m, 2H), 4.80 (d, 1H, $J$=14.8 Hz), 4.51 (d, 1H, $J$=15.1 Hz), 4.11 (d, 1H, $J$=9.6 Hz), 3.89 (s, 1H), 3.78 (br d, 1H), 3.59 (s, 3H), 3.45 (d, 1H, $J$=9.8 Hz), 3.33 (s, 3H), 2.92 (br s, 1H), 2.49 (br s, 1H), 2.46 (s, 1H), 2.34 (m, 2H), 2.24 (m, 1H), 2.09 (br d, 1H, $J$=19 Hz), 1.91 (td, 1H, $J$=12.3, 7.2, 1.6 Hz), 1.72 (td, 1H, $J$=12.3, 4.5 Hz), 1.57 (m, 1H), 1.34 (m, 1H), 1.24 (dd, 1H, $J$=12.6, 6.0 Hz), 1.12 – 1.02 (m, 21H), 0.98 (dd, 1H, $J$=5.5, 3.1 Hz)

Undesired tetrasubstituted isomer S10:

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.29 (m, 5H), 5.81 (d, 1H, $J$=7.5 Hz), 5.64 (dd, 1H, $J$=15.1, 7.6 Hz), 4.70 (d, 1H, $J$=14.8 Hz), 4.63 (d, 1H, $J$=14.5 Hz), 4.11 (d, 1H, $J$=9.5 Hz), 4.01 (dd, 1H, $J$=10.5, 5.9 Hz), 3.68 (s, 1H), 3.63 (s, 3H), 3.45 (s, 1H, $J$=9.5 Hz), 3.32 (s, 3H), 2.95 (s, 1H),
2.31 (s, 1H), 2.27 (m, 3H), 2.07 – 1.94 (m, 2H), 1.91 (br s 2H), 1.58 – 1.45 (m, 3H), 1.05 (m, 21H), 0.95 (m, 2H); \(^{13}\text{C}\) NMR (125 MHz, CDCl\(_3\)) \(\delta\) 172.65, 137.29, 132.19, 129.97, 128.63, 128.37, 127.60, 121.82, 100.79, 67.49, 59.41, 56.75, 51.55, 50.99, 44.87, 39.63, 34.14, 32.32, 31.09, 30.11, 29.85, 27.93, 24.86, 23.60, 22.22, 21.78, 18.22, 18.19, 12.22;

Alcohol 193 (V-JTW-061)

To a solution of silyl ether 192 (41.8 mg, 0.0659 mmol, 1.00 equiv) in tetrahydrofuran (660 \(\mu\)L, 0.1 M) was added a 1.0 M solution of tetrabutylammonium fluoride in tetrahydrofuran (165 \(\mu\)L, 0.165 mmol, 2.5 equiv). The resulting yellow solution was stirred at room temperature for 5.5 h, diluted with \(\frac{1}{2}\) saturated aqueous NaCl (10 mL), and extracted with ethyl acetate (3x 10 mL). The combined organic extracts were dried over MgSO\(_4\), filtered, and concentrated to give an oil. Purification by automated silica gel column chromatography (5 g solid load cartridge, 4 g column, 0 – 50\% acetone in hexanes) afforded alcohol 193 (27.8 mg, 88\%) as a hard white foam. \(R_f = 0.27\) (2 : 1 hexanes : acetone, CAM stain); \(^1\text{H}\) NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.29 (m, 5H), 5.82 (dd, 1H, \(J=7.3\), 1.6 Hz), 5.60 (d, 1H, \(J=7.2\) Hz), 5.57 (d, 1H, \(J=7.6\) Hz), 4.79 (d, 1H, \(J=14.9\) Hz), 4.51 (d, 1H, \(J=14.8\) Hz), 4.01 (m, 2H), 3.89 (s, 1H), 2.77 (br d, 1H), 3.59 (s, 3H), 3.41 (s, 3H), 3.11 (d, 1H, \(J=10.5\) Hz), 2.90 (br m, 1H), 2.58 (s, 1H), 2.49 (br s, 1H), 2.43 (m, 1H), 2.34 (ddd, 1H, \(J=12.8\), 5.6, 2.5 Hz), 2.24 (ddd, 1H, \(J=13.4\), 8.0, 6.0 Hz), 2.08 (br d, 1H, \(J=17.7\) Hz), 1.91 (tdd, 1H, \(J=12.8\), 7.2, 1.6 Hz), 1.80 (td, 1H, \(J=12.6\), 4.7 Hz), 1.57 (m, 1H), 1.45 (m, 1H), 1.26 (dd, 1H, \(J=12.8\), 6.4 Hz), 1.07 (dd, 1H, \(J=6.0\), 3.1 Hz), 0.89 (m, 1H); \(^{13}\text{C}\) NMR (125 MHz, CDCl\(_3\)) \(\delta\) 174.68, 171.82, 137.11, 133.55, 130.36, 128.61, 128.44, 127.60, 122.00, 121.93,
100.61, 68.84, 57.07, 56.91, 52.67, 50.42, 48.04, 43.09, 42.77, 39.56, 35.85, 30.73, 28.68, 28.59, 27.09, 24.05, 23.10; IR (neat film) 3429 (br m), 2951 (m), 1734 (s), 1650 (s), 1433 (m), 1389 (m), 1245 (s), 1220 (s), 1110 (m), 914 (m), 733 (s) cm\(^{-1}\); HRMS (ESI) calc'd for C\(_{29}\)H\(_{36}\)NO\(_{5}\) (M+H) 478.2593 found 478.2604

**Selenide 195 (V-JTW-058)**

To a solution of alcohol 193 (3.1 mg, 0.0065 mmol, 1.0 equiv) in tetrahydrofuran (150 \(\mu\)L) were added a 1 M solution of Me\(_3\)P in tetrahydrofuran (19.5 \(\mu\)L, 0.0195 mmol, 3.0 equiv) and N-(phenylseleno)phthalimide (194) (3.9 mg, 0.013 mmol, 2.0 equiv). The yellow solution was stirred for 45 m, then more Me\(_3\)P solution (5.0 \(\mu\)L, 0.0049 mmol, 0.75 equiv) and N(phenylseleno)phthalimide (1.1 mg, 0.0032 mmol, 0.50 equiv) were added. The solution was stirred for 75 m, quenched with ½ saturated aqueous NaCl solution (300 \(\mu\)L), and extracted with ethyl acetate (3x 300 \(\mu\)L). The combined organic extracts were concentrated to give a film that by crude \(^1\)H NMR suggested about 75% conversion. Purification by silica gel column chromatography (4 : 1 hexanes : acetone) provided selenide 195 (1.8 mg, 44%) as a solid film.

\(R_f = 0.52\) (2 : 1 hexanes : acetone, CAM stain); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.50 (d, 2 H, \(J=7.7\) Hz), 7.3 – 7.2 (m, 8H), 5.80 (d, 1H, \(J=7.3\) Hz), 5.58 (q, 1H, \(J=7.4\) Hz), 5.53 (s, 1H), 4.80 (d, 1H, \(J=14.6\) Hz), 4.50 (d, 1H, \(J=14.6\) Hz), 3.87 (s, 1H), 3.75 (br d, 1H, \(J=13.3\) Hz), 3.59 (s, 3H), 3.59 (m, 1H), 3.32 (s, 3H), 2.90 (br s, 1H), 2.81 (d, 1H, \(J=11.8\) Hz), 2.50 (s, 1H), 2.46 (br s, 1H), 2.35 (s, 1H), 2.31 (dd, 1H, \(J=12.8, 3.4\) Hz), 2.22 (m, 1H), 2.04 (m, 1H), 1.90 (td, 1H,
$J=12.9, 7.1 \text{ Hz})$, 1.71 (td, 1H, $J=12.5, 4.7 \text{ Hz})$, 1.54 (m, 1H), 1.39 (s, 1H), 1.19 (dd, 1H, $J=12.7, 6.6 \text{ Hz})$, 1.05 (m, 1H), 0.91 (t, 1H, $J=6.6 \text{ Hz});$

Olefins 198 and 199 (V-JTW-068)

A solution of selenide 195 (4.7 mg, 0.0074 mmol, 1.0 equiv) in benzene (1.5 mL, 0.005 M) was subjected to 3x freeze-pump-thaw cycles. To this solution were then added tributyltin hydride (7.9 $\mu$L, 0.030 mmol, 4.0 equiv) and 2,2’-azobis(isobutyronitrile) (0.4 mg, 0.002 mmol, 0.3 equiv). The solution was heated to 100 °C for 15 m, then cooled to 20 °C. Another portion of 2,2’-azobis(isobutyronitrile) (0.4 mg, 0.002 mmol, 0.3 equiv) was added and the solution again heated to 100 °C for 20 m, then the solvent was removed by vacuum. Purification by silica gel prep TLC (2 : 1 hexanes : ethyl acetate) provided triene 198 (1.2 mg, 35%) and cyclopentane 199 (1.0 mg, 29%).

Triene 198:

$R_f=0.49$ (2 : 1 hexanes : ethyl acetate, CAM stain); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.28 (m, 5H), 5.84 (d, 1H, $J=7.2 \text{ Hz})$, 5.55 (dd, 1H, $J=14.5 \text{ Hz})$, 4.70 (d, 1H, $J=14.5 \text{ Hz})$, 4.64 (s, 1H), 4.62 (d, 1H, $J=14.5 \text{ Hz})$ 4.61 (s, 1H), 3.78 (br d, $J=9.6 \text{ Hz})$, 3.61 (s, 3H), 3.57 (m, 1H), 3.35 (s, 3H), 2.91 (m, 1H), 2.79 (m, 1H), 2.65 (m, 1H), 2.40 – 2.30 (m, 3H), 2.13 – 2.05 (m, 4H), 1.93 (m, 1H), 1.80 (m, 1H), 1.60 (m, 2H); IR (neat film) 3062 (w), 3030 (w), 2932 (m), 1734 (s), 1650 (s), 1389 (m), 1356 (m), 1245 (s), 1219 (s), 1118 (m), 1109 (m), 879 (w), 738 (m), 700 (m); LRMS (ESI) 462.23 (M+H), 484.19 (M+Na).

Cyclopentane 199:
R_f = 0.42 (2 : 1 hexanes : ethyl acetate, CAM stain); ^1H NMR (500 MHz, CDCl_3) δ 7.30 (m, 5H), 5.79 (dd, 1H, J=7.2, 1.9 Hz), 5.60 (dd, 1H, J=14.7, 7.2 Hz), 4.68 (d, 1H, J=14.3 Hz), 4.64 (d, 1H, J=14.3 Hz), 4.64 (s, 1H), 4.59 (s, 1H), 3.75 (t, 1H, J=5.0 Hz), 3.61 (s, 3H), 3.34 (s, 3H), 3.26 (td, 1H, J=12.8, 5.1 Hz), 2.77 (m, 2H), 2.42 (m, 2H), 2.27 (m, 2H), 2.18 (m, 3H), 1.97 (m, 1H), 1.78 (m, 1H), 1.71 (m, 1H), 1.62 (m, 1H), 1.44 (m, 1H); ^13C NMR (125 MHz, CDCl_3) δ 174.91, 171.88, 150.50, 137.22, 129.68, 128.79, 128.59, 128.51, 127.61, 123.41, 106.53, 83.30, 57.54, 56.85, 52.53, 51.07, 49.14, 48.60, 45.81, 44.41, 43.65, 39.58, 38.54, 31.59, 29.38, 29.96, 28.28, 18.99; IR (neat film) 3063 (w), 3031 (w), 2931 (s), 1732 (s), 1648 (s), 1456 (m), 1433 (m), 1401 (m), 1390 (m), 1259 (s), 1213 (s), 1065 (m), 736 (m), 701 (m) cm^{-1};

4.7 References


CHAPTER 5. EXPLORATION OF A CATION-II CYCLIZATION CASCADE TO ACCESS THE ACONITINE ALKALOIDS

5.1 Addition of an Enol-ether onto an N-Acyliminium to Form the C11–C17 Bond

An expedient strategy to install an oxygen at C1 while retaining the C11–C1 double bond and prevent the undesired 5-endo radical cyclization reaction mode would be to form the tetrasubstituted enol ether 201 from ketone 190 (Scheme 47). Unfortunately, a variety of standard methods failed to provide 201 (NaH/MeI, KH/Me2SO4,1 KOt-Bu/Me2SO4,2 (CH3O)3CH/PTSA,3,4 TMSCl/Et3N,5 TMSCl/Nal/Et3N,6 MeOTf/DTBP7). The only isolable product was the kinetic enol-ether 200, formed by deprotonation at the most accessible position α to the ketone of 190 at C2. Isomerization8-10 of the kinetic C1–C2 enol-ether 200 to the more substituted C1–C11 201 also proved fruitless, possibly because the caged carbon structure disfavored the C1–C11 isomer, causing the C1–C2 isomer to be both kinetically and thermodynamically favored. One particular experiment that was intended to produce the C1–C11 methyl enol-ether via an O-methyloxophosphonium gave an unanticipated, but highly beneficial, result (Scheme 48). Treatment of a solution of ketone 190 in CH2Cl2 with triphenylphosphine oxide, triflic anhydride, and methanol resulted not in the formation of a methyl enol-ether as anticipated rather a complex mixture of products, from which the major product was isolated and identified as cyclic enol-ether 202 (26%). Under these conditions, an equivalent of triflic acid was generated that effected protonation of the silyl-ether to form cyclopropylcarbinyl cation 203 that can also be represented by its resonance structure 204. Attack of the cation at C8 by the oxygen of the C1 ketone with subsequent deprotonation at C11 resulted in cyclic enol-ether 205. Further protonation of enamide 205 produced N-acyliminium 206 that underwent intramolecular attack by the newly-formed enol-ether to complete the observed product 202. Although the
original intention was to simply form a C1–C11 methyl enol-ether, it was recognized that this transformation had formed the key C11–C17 bond and so could be employed to complete the synthesis of the aconitine alkaloid skeleton, though there were several challenges to overcome.

**Scheme 47**

![Scheme 47](image)

In order to capitalize on this N-acyliminium addition result to access the aconitine alkaloids, there were several issues that needed to be considered when advancing an intermediate such as 202. First, hydrolysis of the enol-ether would be required, providing hydroxy-ketone 207 (Scheme 49), which when redrawn as the conformational representation 208 maps very well onto the aconitine carbon-nitrogen skeleton in 209. Second, construction of the C7–C8 bond from intermediate 208 would then complete the aconitine skeleton. This task would be challenging,
however, due to the lack of a chemical handle at C7 to facilitate the coupling. Third, the yield of the cyclization in the conversion of 190 to 202 was a paltry 26% and would require significant improvement to be synthetically viable. With these concerns in mind, we envisioned intermediate 210, incorporating a heteroatom functional group handle at C7, as a suitable cyclization substrate. To address the issue of the low yield of the N-acyliminium cyclization, it was hypothesized that deleterious side reactions might arise from the formation of a transient highly reactive cyclopropylcarbinyl cation such as 203 (see Scheme 48). Thus, the introduction of an aldehyde functionality at C16 would likely mitigate potential unproductive side reactions, in which a more stable cyclopropylcarbinyl oxocarbenium, as opposed to a cyclopropylcarbinyl carbocation, would serve as the initial electron-deficient reactive intermediate formed in the cyclization cascade.

Scheme 49

To address the second of these concerns, namely the installation of a C7 functional handle, a bromine atom was installed at C7 early in the synthesis by its incorporation into azepine dienophile 213 (Scheme 50). Treatment of enamide 182 with bromine gave an
intermediate dibromide that was not isolated, but subjected to triethylamine mediated regioselective elimination of the bromine α to the amide nitrogen. This selectivity is likely due to nitrogen stabilization of the positive charge resulting from E1 bromide elimination and deprotonation α to the resulting N-acyliminium to produce bromoenamide 211 in 86% yield. The previously developed strategy for the construction of azepin-2(5H)-one 186 (refer to Scheme 43) was then applied to advance bromoenamide 212 to dienophile 213. Deprotonation of 211 with two equivalents of LHMDS followed by sequential addition of methylchloroformate and phenylselenyl chloride gave selenide 212 that was used without purification. Oxidation of the selenide with H₂O₂ proceeded with spontaneous 1,2-syn elimination of the resultant selenoxide to provide the modified Diels–Alder 2π-component 213 (99%, two steps).

Halogenated dienophile 213 was then used to prepare the cyclization precursor 218 (Scheme 51). Under conditions similar to the cycloaddition with unhalogenated dienophile 179 (see Scheme 44, chapter 4), a solution of diene 178 and dienophile 213 was treated with catalytic Sc(OTf)₃ at 20 °C to effect a Diels–Alder cycloaddition with complete regio and endo selectivity, but gave an inseparable 1 : 1.8 mixture of desired facial isomer cycloadduct 214 to undesired adduct 215 in 69% combined yield (87% based on recovered 178). This Diels–Alder reaction compares favorably with the one described in the previous chapter (See Scheme 44, Chapter 4). Although the facial selectivity will require further optimization, the high combined yield provided sufficient material for exploration of the latter stages of the synthesis. Desilylation of both the TBS enol-ether and the TIPS ether with two equivalents of TBAF provided keto-
alcohols 216 and 217 in 71% yield. Oxidation of the sensitive cyclopropylcarbinol was effected with 2-iodoxybenzoic acid (IBX) activated by ultrasonication. Separation of the resulting aldehydes by silica gel column chromatography produced desired diastereomer 218 (31%) along with the undesired diastereomer 219 (56%). Aldehyde 218 contained all the requisite functionality to test whether activation of cyclopropylcarbinyl aldehyde 218 as an oxocarbenium precursor would in fact increase the yield relative to that of the comparatively unstabilized cyclopropylcarbinyl carbocation 203.

Scheme 51

This hypothesis was tested by protonation of aldehyde 218 (Scheme 52) with one equivalent of triflimide at 0 °C. Subsequent warming of the reaction mixture to 23 °C did in fact provide the desired N-acyliminium adduct 219 as a single diastereomer in 71% yield, a result consistent with the hypothesis of yield augmentation through increasing cation stability via a cyclization with a cyclopropylcarbinyl oxocarbenium intermediate. The likely mechanism of

* A small amount (<5%) of the opposite C(7) diastereomer (226) was also obtained as an inseparable mixture of other unidentifiable products.

† TfOH initially provided the product in a 73% yield, but was found to be dependent on the source and purity of TfOH, while Tf₂NH provided more consistent results.
this transformation begins with initial protonation of the aldehyde to give oxocarbenium 220 that can also be represented as alternate resonance form 221. Intramolecular attack of electron deficient C8 in 221 by the C1 ketone with subsequent C11 deprotonation gave cyclic enol-ether 222. This portion of the reaction occurred very quickly and could be halted at this point to isolate intermediate tetrasubstituted cyclic enol-ether 222. However, if the reaction was warmed to 20 °C for several hours, protonation of the bromoename to then occurred to produce transient N-acyliminium 223. Nucleophilic attack of the electron rich C17 onto the N-acyliminium was followed by deprotonation α to the newly-formed oxocarbenium ion to give the observed product 219 in which the key C11–C17 bond had been successfully formed.

**Scheme 52**

Notably, the observed C7–Br configuration in 219 differed from what was expected from this transformation. Based on the topology of the [5.4.0]-bicycloazepine ring system, it was anticipated that protonation of the ene-lactam π-system would occur from the less hindered convex face (Scheme 53). However, the initially formed N-acyliminium (224) likely exists as
endo bromonium ion 225. In this configuration, the $\sigma^*$ orbital of the C17–Br bond is oriented into the exo face and is therefore inaccessible for attack from C11 of the enol-ether. This process is almost certainly reversible, so protonation from the more hindered concave face would also occur, at least to a minor extent. The electrophilic $\sigma^*$ orbital of the C17–Br bond in the resulting bromonium 227 is much more accessible to the C11 $\pi$-nucleophile. Invertive ring opening of the bromonium intermediate 227 would then close the ring, thus securing the observed C7–Br stereochemistry via a Curtin–Hamnett reactivity profile. The successful installation of a C7 heteroatom as well as the formation of the C11–C17 bond in 219 was a significant step toward the synthesis of the aconitine skeleton.

5.2 Attempts at Enol-ether Hydrolysis

The successful construction of the C11–C17 bond left only the C7–C8 bond to complete the aconitine skeleton. The first step in this effort to bond C7 and C8 was the seemingly routine hydrolysis of enol-ether 219 (Scheme 54), formed from the N-acyliminium cyclization. Unfortunately, the stability of this enol-ether toward acidic hydrolysis was much greater than
anticipated. Standard hydrolysis conditions using a variety of aqueous acids (HCl, HBr, HClO₄) in many cosolvents (THF, DME, DMF, dioxane, CH₂CN) proved ineffective. In all cases, methyl ester hydrolysis to carboxylic acid 228 was the only observed reaction mode. Harsher reaction conditions resulted in co-solvent decomposition; therefore, the use of co-solvents was abandoned. When enol-ether 219 was heated in concentrated 12 N aqueous HCl to 60 °C, the initially formed acid 228 was consumed. The only recovered product, however, was acetal 229, resulting from hydrolysis of the C14 methyl ether. Even under these harsh conditions, the enol-ether remained intact. One possible explanation for this unusual lack of reactivity is steric shielding of the enol-ether by the aldehyde. To address this possible complication, the aldehyde was removed by a two-step process beginning with transformation into the TBS enol-ether using TBSOTf and Et₃N (Scheme 54). At this point, the unreactivity of the cyclic alkyl enol-ether worked to our advantage as chemoselective oxidative cleavage of the silyl enol-ether was accomplished using a Nicolaou modification of the Lemieux-Johnson conditions¹¹ (OsO₄, PhI(OAc)₂, 2,6-lutidine) to provide ketone 230 in 64% yield over two steps, with no evidence of oxidative cleavage of the endocyclic enol-ether. Unfortunately, upon subjecting the enol-ether 230 to progressively harsh conditions, it proved as unreactive toward hydrolysis as aldehyde 219. In one attempt, briefly heating a solution of 230 in concentrated 12 N aqueous HCl to 150 °C did in fact result in C8–O cleavage, but was accompanied by an undesired skeletal fragmentation to give keto-aldehyde 231 that could not easily be advanced to the aconitine alkaloids. We believe this fragmentation is initiated by carbocation formation at C8 instead of initial enol-ether hydrolysis followed by fragmentation. This hypothesis was substantiated by heating a solution of 230 in 33% HBr in HOAc to 75 °C to provide bromide 232. Likely, 232 was obtained by ionization to form a carbocation at C8 that was trapped by bromide.
Although a cursory examination of the structure reveals the enol-ether exists within in a highly sterically congested pocket, the unprecedented stability of the enol-ether was surprising and warranted a closer investigation. We rationalized there are two possible explanations for this difficulty: (1) initial protonation of the olefin is retarded due to stereoelectronic factors or (2) protonation of the olefin does occur, but nucleophilic addition of water into the resultant oxocarbenium is retarded due to steric blockage of the oxocarbenium $\pi^*$ orbitals. The former possibility was tested by a deuterium-exchange experiment in which a solution of 230 (Scheme 55) in $d_8$THF : 3N DCI was heated to 65 °C, at which temperature the $d_8$THF began to hydrolyze, but there was no indication of any deuterium exchange; therefore, the problem seemed to lie with the protonation step of hydrolysis.
Close inspection of models of 230 suggested that as a result of the rigid ring structure, the oxygen lone pair electrons are oriented in such a way that alignment with the \( \pi^* \) orbitals of the olefin is disfavored. The result is decreased electron density and basicity of the olefin that further attenuates the protonation required for oxocarbenium formation and subsequent hydrolysis. This analysis was corroborated spectroscopically by the observation that the enol-ether vinyl proton was electronically de-shielded relative to less-strained enol-ether vinyl protons (Figure 8). For example, the \(^1\)H NMR resonance for vinyl proton of methyl enol-ether 234 occurs at \( \delta 4.12 \). In contrast, the resonance for the vinyl proton of the unreactive cyclic enol-ether 230 is relatively deshielded (\( \delta 5.42 \)), indicating a much lower electron density than the acyclic methyl enol-ether. This observation further substantiates our hypothesis of poor orbital overlap between the oxygen lone-pair electrons and the olefin \( \pi^* \).

![Scheme 55](image)

**Figure 8.** Comparison of \(^1\)H NMR vinyl signals of 234 and 230.

The failure of enol-ether hydrolysis by aqueous acid prompted a screen of alternate electrophiles. The results of these efforts included either no observed reaction (Hg(OAc)$_2$, I$_2$), or an unidentified mixture of products (mercury-(II)-trifluoroacetate, Br$_2$, 1,3-dibromo-5,5-
dimethylhydantoin). One notable exception was observed when 230 (Scheme 56) was treated with ten equivalents of dimethyldioxirane (DMDO). Typically, enol-ethers will react with DMDO at –78 °C; however in this case, appreciable conversion was only observed when the reaction was warmed to 20 °C. Even under these relatively forcing conditions, 4.5 hours were required to completely convert 230 into epoxide 235 (>99%). This result further exemplifies the reticence of 230 to undergo typical electrophilic reactions of the π electrons due to the high steric encumberance combined with the low electron density of the olefin. Clearly, an alternative strategy that does not rely directly upon enol-ether hydrolysis was required in order to advance 230 to the aconitine alkaloids.

Scheme 56

A breakthrough in the project came when graduate student co-worker Yuan Shi hypothesized that the enol-ether could be more easily cleaved via an elimination reaction rather than hydrolysis. To test this theory, an allylic leaving group was installed by allylic oxidation of 230 to alcohol 236 (Scheme 57) with ceric ammonium nitrate followed by activation of the hydroxyl group as a mesylate with methanesulfonyl chloride and Et$_3$N. The product of this reaction was not the mesylate as anticipated, rather only di-enone 238 was isolated in 72% yield over two steps. Likely, in situ ionization of the mesylate provided allyl cation 237 that is an excellent leaving group for cleavage of the C8–O bond β to the ketone to provide the observed di-enone 238. Representation of 238 as its conformational isomer 239 highlights its similarity to
the aconitine alkaloids. Thus, 239 was advanced further toward the completion of the aconitine skeleton by C7–C8 bond formation.

Analysis of models of bis-enone 239 suggested the C7 bromine to be in close proximity to the C8 olefin, suggesting a radical or carbanion addition onto C8 would be facile. Indeed, when the C7 radical was generated under thermal conditions with AIBN as the radical source and tributyltin hydride as the propagator, radical conjugate addition onto C8 completed the aconitine skeleton in the form of 240 (86%). Installation of the C8 oxygen, a necessary component for the majority of aconitine alkaloids, was accomplished by a three-step protocol that consisted of: (1) α-selenylation of the ketone using LHMDS and PhSeCl; (2) selenide oxidation with concomitant 1,2-syn elimination of the resulting selenoxide to give di-enone 241; and (3) selective conjugate addition of water into the highly strained anti-Bredt olefin at C8 to give alcohol 242 in 52% yield over the three steps.

Scheme 57
5.3 Summary

Ultimately, the first synthesis of the aconitine skeleton in over three decades was accomplished through a stepwise ionic and radical manner, beginning with diene 178 (Scheme 58), an intermediate intercepted from the radical pathway synthesis (see Chapter 4). A Diels–Alder cycloaddition with 213 as the $2\pi$ component and 178 as the $4\pi$ component provided bromoenamide 214. This intermediate was advanced to steps to the key cyclopropylcarbinyl oxocarbenium precursor aldehyde 218 in 15% yield over the three steps. Acid catalyzed fragmentation of the cyclopropylcarbinyl aldehyde and addition of the C1 ketone oxygen into the resulting electron deficient C8 was followed by bromoenamide protonation and nucleophilic addition of C11 onto C17, completing one of the remaining carbon-carbon bonds via an ionic pathway. One carbon truncation of aldehyde 219 into ketone 230 was performed by a two-step oxidative cleavage protocol to give keto enol-ether 230. This enol-ether proved quite resistant to hydrolysis and so was instead fragmented to provide bis-enone 237. The final carbon-carbon bond forming reaction proceeded through a secondary radical generated at C7 from homolysis of the C–Br bond. This radical then attacked the C8 enone to provide the completed aconitine skeleton 240. Installation of the C8 oxygen functionality was performed by a three-step process that hinged upon the selective addition of water into the highly strained anti-Bredt enone 241, providing alcohol 242. It is important to note that although intermediate 242 has not yet been advanced to a natural aconitine alkaloid, 242 is ideal for advancement to a number of natural and non-natural aconitine alkaloid analogues that have substituents at C1, C2, C3, C8, C14, C16, and C18. Once completed, these analogues will allow, for the first time, systematic study of the structure activity relationship of the aconitine alkaloids.
5.4 Experimental

General Procedures. All reactions were performed in flame-dried modified Schlenk (Kjeldahl shape) flasks fitted with a glass stopper under a positive pressure of argon, unless otherwise noted. Air- and moisture-sensitive liquids and solutions were transferred via syringe or stainless-steel cannula. Organic solutions were concentrated by rotary evaporation below 30 °C. Flash column chromatography was performed employing 230-400 mesh silica gel under a positive pressure of nitrogen. Automated silica gel column chromatography was performed employing an Isco Combiflash Rf with Isco brand columns. Gradient elutions were performed with a linear
gradient. Thin-layer chromatography (analytical and preparative) was performed using glass plates pre-coated to a depth of 0.25 mm with 230-400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Visualization was achieved using UV light, iodine, potassium permanganate (KMnO₄), or ceric ammonium molybdenate (CAM).

**Materials.** Dichloromethane (CH₂Cl₂), tetrahydrofuran (THF), acetonitrile, diethyl ether, toluene, and benzene were purified by passage through two packed columns of neutral alumina under an argon atmosphere. Methanol was distilled from magnesium turnings under a nitrogen atmosphere at 760 mm Hg. 1,2-Dichloroethane, N,N-dimethylformamide (DMF), dimethylsulfoxide, and 1,4-dioxane were dried over activated 4Å molecular sieves. Triethylamine, 2,6-lutidine, pyridine, Hünig's base, and diisopropylamine were distilled from CaH₂ under a nitrogen atmosphere at 760 mm Hg. Lithium bis(trimethylsilyl)amide (LHMDS) and potassium bis(trimethylsilyl)amide (KHMDS) were purchased as a solid from Aldrich and handled under an argon atmosphere. Trifluromethanesulfonic anhydride was distilled from P₂O₅ under a nitrogen atmosphere at 760 mm Hg. Powdered 4Å molecular sieves were purchased as activated and stored and handled under an Argon atmosphere. Organolithium solutions were titrated by known procedures¹⁵ immediately prior to use. All moisture and/or oxygen sensitive solids were handled and stored in a glove box. All other reagents were used as purchased without further purification, unless otherwise noted.

**Instrumentation.** Infrared (IR) spectra were obtained using a Bruker Tensor 27 referenced to a polystyrene standard. Data are presented as the frequency of absorption (cm⁻¹). Proton and carbon-13 nuclear magnetic resonance (¹H NMR or ¹³C NMR) spectra were recorded on a Bruker Avance III 500 or a Bruker Avance III 600 spectrometer; chemical shifts are expressed in parts per million (δ scale) downfield from tetramethylsilane and are referenced to the residual
protium in the NMR solvent (CHCl₃: δ 7.26 for ¹H NMR, δ 77.16 for ¹³C NMR; C₆D₆: δ 7.16 for ¹H NMR, δ 128.06 for ¹³C NMR). Data are presented as follows: chemical shift, multiplicity (s = singlet, bs = broad singlet, d = doublet, bd = broad doublet, t = triplet, dd = doublet of doublets, ddd = doublet of doublet of doublets, td = triplet of doublets, dt = doublet of triplets, m = multiplet and/or multiple resonances), integration, and coupling constant reported in Hz.

Enol ether 202 (V-JTW-089)

To a solution of triphenylphosphine oxide (8.5 mg, 0.031 mmol, 3.3 equiv) in CH₂Cl₂ (450 μL) was added trifluoromethanesulfonic anhydride (2.3 μL, 0.014 mmol, 1.5 equiv). This solution was stirred at room temperature for 45 m, then transferred via cannula to a solution of ketone 290 (5.9 mg, 0.0091 mmol, 1.0 equiv) in CH₂Cl₂ (450 μL). Methanol (0.6 μL, 0.01 mmol, 1.5 equiv) was immediately added and the solution was stirred at room temperature for 2 h, quenched with saturated aqueous NaHCO₃ solution (300 μL), and extracted with CH₂Cl₂ (3x 400 μL). The combined organic extracts were dried over MgSO₄, filtered, and the solvent was removed to give a film. Purification by silica gel column chromatography (1 : 1 hexanes : ethyl acetate) afforded enol ether 202 (1.1 mg, 26%) as a film.

¹H NMR (500 MHz, CDCl₃) δ 7.28 (m, 5H), 5.42 (d, 1H, J=6.2 Hz), 4.83 (d, 1H, J=14.9 Hz), 4.66 (s, 1H), 4.64 (s, 1H), 4.35 (d, 1H, J=15.0 Hz), 4.33 (m, 1H), 3.79 (s, 3H), 3.53 (m, 2H), 3.27 (s, 3H), 2.84 (m, 1H), 2.80 (s, 1H), 2.71-2.66 (m, 2H), 2.58 (dd, 1H, J=17.0, 9.1 Hz), 2.44 (dd, 1H, J=9.7, 4.6 Hz), 2.34 (d, 1H, J=6.1 Hz), 2.06-1.68 (m, 6H), 1.45 (dd, 1H, J=13.2, 7.5 Hz); ¹³C
NMR (125 MHz, CDCl$_3$) $\delta$ 172.64, 168.81, 147.50, 146.11, 136.83, 128.59, 128.52, 127.47, 113.13, 107.45, 84.01, 72.76, 63.78, 57.54, 56.73, 52.49, 50.00, 49.94, 45.63, 43.97, 38.54, 34.72, 33.71, 31.13, 31.00, 29.86, 27.90, 22.94; IR (neat film) 3056 (w), 2950 (m), 1733 (s), 1648 (s), 1451 (m), 1359 (w), 1264 (m), 1141 (s), 1111 (s), 734 (s), 700 (m) cm$^{-1}$; LRMS (ESI) 476.25 (M+H), 498.14 (M+Na).

Vinyl bromide 211 (SY-VII-092) – Yuan Shi

To a solution of enamide 182 (14.0 g, 69.6 mmol, 1.00 equiv) in CH$_2$Cl$_2$ (500 mL) at 0 °C was added Br$_2$ (3.6 mL, 70.1 mmol, 1.01 equiv) dropwise over 15 m. The resulting pale brown solution was stirred at 0 °C for 20 m before triethylamine (29.0 mL, 208 mmol, 2.99) was added. After 10 m, the reaction was brought to 20 °C and stirred for additional 2 h. The reaction was then quenched with saturated aqueous NaHCO$_3$ (300mL), separated, and the aqueous layer was extracted with CH$_2$Cl$_2$ (100 mL x 2). The combined organic phases were dried over MgSO$_4$, filtered and concentrated. The residue was purified by automated silica gel column chromatography (25 g solid load cartridge, 220 g column, 0-30% EtOAc in hexane) to yield bromoenamide 211 (16.7 g, 86%) as a yellowish oil.

$R_f = 0.41$ (1 : 2 ethyl acetate : hexanes, KMnO$_4$ stain); $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 7.34-7.24 (m, 5H), 6.34 (s, 1H), 4.62 (s, 2H), 2.65-2.61 (m, 3H), 2.15-2.10 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 173.26, 136.92, 129.96, 128.85, 128.12, 127.81, 115.91, 50.58, 36.90, 35.43, 26.54; IR (neat film) 2934 (w), 1663 (s), 1274 (m), 700 (m) cm$^{-1}$; HRMS (ESI) calc'd for C$_{13}$H$_{15}$NO$_4$Br (M+H) 280.0337 found 280.0332.
Methyl enoate 213 (SY-VII-098, SY-VII-099) Yuan Shi

To a solution of bromoenamide 211 (15.7 g, 56.0 mmol, 1.00 equiv) in tetrahydrofuran (500mL) at –78 °C was added lithium bis(trimethylsilyl)amide (19.2 g, 115 mmol, 2.05 equiv) as a solid in one portion. The solution was stirred at –78 °C for 40 m, followed by dropwise addition of methylchloroformate (4.30 mL, 55.9 mmol, 1.00 equiv). The reaction was stirred at –78 °C for additional 40 m before phenylselenyl chloride (11.5 g, 60.0 mmol, 1.07 equiv) was added in one portion. The resulting solution was stirred at –78 °C for 20 m, and then the cooling bath was removed. The reaction was stirred at 20 °C for 1.5 h before being quenched with saturated aqueous NaHCO₃ (300 mL), separated, and the aqueous layer was extracted with CH₂Cl₂ (100 mL x 2), dried over MgSO₄, filtered and concentrated. The yellow residue (212) was used in the next step without further purification.

To a solution of the above phenylselenide 212 in CH₂Cl₂ (500 mL) at 0 °C was added aqueous H₂O₂ (30 wt%, 11.0 mL, 107 mmol, 1.91 equiv). The reaction was stirred vigorously for 25 m before being quenched with saturated aqueous NaHCO₃ (200 mL), and separated. The aqueous layer was extracted with CH₂Cl₂ (100 mL x 2), dried over MgSO₄, filtered and concentrated. The residue was purified by automated silica gel column chromatography (25 g solid load cartridge, 220 g column, 0-30% ethyl acetate in hexane) to yield 213 (18.8 g, 99% over 2 steps) as pale yellow crystals.

Rᶠ = 0.35 (1 : 2 ethyl acetate : hexanes, CAM stain); ᵃ¹H NMR (600 MHz, CDCl₃) δ 7.39-7.30 (m, 6H), 6.35 (s, 1H), 4.83 (s, 2H), 3.81 (s, 3H), 3.16 (d, 2H, J=7.5 Hz); ᵃ¹³C NMR (125 MHz,
CDCl$_3$ $\delta$ 164.88, 164.22, 146.82, 136.50, 131.36, 130.13, 128.95, 128.21, 128.06, 112.00, 52.72, 51.23, 34.78; IR (neat film) 2951 (m), 1733 (s), 1722 (s), 1653 (s), 1620 (s), 1436 (s), 1407 (s), 1264 (s), 1045 (m), 737 (m), 701 (m) cm$^{-1}$; HRMS (ESI) calc’d for $\text{C}_{15}\text{H}_{15}\text{NO}_3\text{Br}$ (M+H) 336.0235 found 336.0235.

Silyl ethers 214 and 215 (SY-VII-097) – Yuan Shi

To a solution of diene 178 (4.02 g, 7.93 mmol, 1.00 equiv) and dienophile 213 (5.52 g, 16.4 mmol, 2.07 equiv) in toluene (160 mL) was added powdered 4 Å molecular sieves (4.00 g) and Sc(OTf)$_3$ (1.92 g, 3.90 mmol, 0.492 equiv). The resulting mixture was stirred at ambient temperature for 4 h before a solution of dienophile 213 (2.60 g, 7.73 mmol, 0.975 equiv) in toluene (20 mL) was added via cannula transfer. The reaction was stirred at 20 °C for additional 4.5 h before being filtered through fritted funnel (Medium). The filtrate was washed with saturated aqueous NaHCO$_3$ (100 mL). The aqueous layer was extracted with CH$_2$Cl$_2$ (3x 50 mL), dried over MgSO$_4$, filtered and concentrated. The crude product was purified by automated silica gel column chromatography (25 g solid load cartridge, 80 g column, 0-50% ethyl acetate in hexane) to yield recovered diene (857 mg, 21%) and mixture of silyl ethers 214 and 215 (4.58 g, 69%, 87% brsm) as white foam.
Alcohols 216 and 217 (SY-VII-100) – Yuan Shi

To a solution of the diastereomeric mixture of cycloadducts 214 and 215 (4.58 g, 5.43 mmol, 1.00 equiv) in tetrahydrofuran (100 mL) was added a 1.0 M solution of TBAF in tetrahydrofuran (17.0 mL, 17.0 mmol, 3.13 equiv). The resulting brownish solution was stirred at 20 °C for 4.5 h before being quenched with saturated aqueous NaHCO₃ (100 mL) and separated. The aqueous layer was extracted with CH₂Cl₂ (3x 50 mL), dried over MgSO₄, filtered and concentrated. The crude mixture was purified by automated silica gel column chromatography (25g solid load cartridge, 40 g column, 0-100% ethyl acetate in hexanes) to yield alcohols 216 and 217 (2.22 g 71%) as a white foam. This mixture was used without further purification or characterization.
Aldehydes 218 and 219 (VII-JTW-017)

To a solution of alcohols 216 and 217 (2.22 g, 3.88 mmol, 1.00 equiv) in acetonitrile (39 mL, 0.1 M) was added 2-iodoxybenzoic acid (IBX) (2.18 g, 7.76 mmol, 1.00 equiv). This mixture was subjected to sonication for 7 h without stirring. At this time the IBX had transformed from a sandy dense solid to a milky suspension. Celite (4.4 g) was added, the mixture stirred for 50 m, filtered through a plug of celite (2.5 x 2.5 cm) that was then flushed with ethyl acetate (200 mL). Solvent removal gave a white crystalline solid that was purified by automated silica gel column chromatography (25 g solid load cartridge, 220 g column, 5 – 75% ethyl acetate in hexanes) to yield undesired aldehyde 219 (1.24 g, 56%) as a white solid and desired aldehyde 218 (677 mg, 31%) as a white solid.

Desired aldehyde 218

Rₚ = 0.26 (1 : 1 hexanes : ethyl acetate, CAM stain); ¹H NMR (500 MHz, CDCl₃) δ 8.82 (s, 1H), 7.30 (m, 5H), 6.15 (s, 1H), 4.66 (d, 1H, J=14.2 Hz), 4.55 (d, 1H, J=14.3 Hz), 3.85 (m, 2H), 3.72 (s, 3H), 3.29 (s, 3H), 2.95 (s, 1H), 2.79 (m, 1H), 2.67 (m, 2H), 2.51 (t, 1H, J=13.8 Hz), 2.39 (m, 1H), 2.24 (s, 1H), 2.2~2.0 (m, 5H), 1.94 (s, 1H), 1.56 (m, 1H), 0.91 (m, 1H); ¹³C NMR (125
MHz, CDCl$_3$) $\delta$ 210.00, 199.80, 172.43, 170.29, 136.08, 128.97, 128.89, 128.73, 128.21, 101.13, 56.99, 53.43, 51.67, 47.96, 46.02, 44.54, 37.59, 37.06, 34.06, 31.54, 30.16, 29.06; IR (neat film) 3057 (w), 2952 (m), 2847 (w), 2725 (w), 1718 (s), 1697 (s), 1655 (s), 1436 (m), 1398 (m), 1265 (s), 1218 (s), 1116 (m), 737 (s), 702 (m) cm$^{-1}$; LRMS (ESI) 593.97 (M+Na).

**Enol ethers 219 (VII-JTW-022)**

To a solution of aldehyde 218 (672 mg, 1.18 mmol, 1.00 equiv) in CH$_2$Cl$_2$ (24 mL, 0.05 M) at 0 $^\circ$C was added bis(trifluoromethanesulfonimide) (332 mg, 1.18 mmol, 1.00 equiv) and the solution was removed from the cooling bath and stirred for 2 h. The resulting brown solution was then poured into ½ saturated aqueous NaHCO$_3$ solution (25 mL), the phases were separated and the aqueous phase was extracted with CH$_2$Cl$_2$ (2x 25 mL). The combined organic phases were dried over MgSO$_4$, filtered, and the solvent was removed to give a yellow oil that was then purified by automated silica gel column chromatography (5 g solid load cartridge, 24 g column, 5-75% acetone in hexanes) to yield a mixture of aldehyde epimers 219 (476 mg, 71%) as a white solid.

Major epimer:

$R_f$ = 0.14 (1 : 1 hexanes : ethyl acetate, CAM stain); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 9.58 (s, 1H), 7.26 (m, 5H), 5.57 (d, 1H, $J$=15.0 Hz), 5.39 (dd, 1H, $J$=6.2, 1.7 Hz), 4.70 (m, 1H), 4.19 (td, 1H, $J$=8.5, 5.9 Hz), 4.02 (d, 1H, $J$=15.0 Hz), 3.81 (s, 3H), 3.71 (dd, 1H, $J$=4.4, 1.4 Hz), 3.55 (dd, 1H, $J$=5.5, 4.0 Hz), 3.32 (s, 3H), 2.93 (ddd, 1H, $J$=12.1, 6.6, 1.5 Hz), 2.84 (dd, 1H, $J$=17.2, 1.8 Hz),
2.70 (dd, 1H, J=17.2, 6.2 Hz), 2.66 (dd, 1H, J=6.6, 6.6 Hz), 2.50 (ddd, 1H, J=15.8, 10.3, 6.3 Hz), 2.43 (dd, 1H, J=15.8, 4.8 Hz), 2.31 (d, 1H, 6.6 Hz), 2.27 (dd, 1H, J=9.9, 4.8 Hz), 2.03 (ddd, 1H, J=15.0, 12.1, 8.5 Hz), 1.89 (ddd, 1H, J=15.4, 7.7, 7.0 Hz), 1.78 (m, 1H), 1.68 (ddd, 1H, J=15.4, 10.6, 7.7 Hz), 1.15 (dd, 1H, J=14.7, 8.5 Hz), IR (neat film) 2917 (w), 1720 (s), 1640 (s), 1460 (m), 1263 (s), 1238 (s), 1144 (s), 1106 (s), 994 (m), 736 (s) cm⁻¹; LRMS (ESI) 593.97 (M+Na).

Silyl ether S11 (VII-JTW-023)

To a solution of aldehyde 219 (476 mg, 0.834 mmol, 1.00 equiv) in CH₂Cl₂ (8.3 mL, 0.1 M) were added triethylamine (349 μL, 2.50 mmol, 3.00 equiv) and tert-butyldimethylsilyl trifluoromethanesulfonate (287 μL, 1.25 mmol, 1.50 equiv). The resulting solution was stirred for 16 h, quenched with ½ saturated aqueous NaHCO₃ solution (10 mL) and the phases were separated. The aqueous phase was extracted with CH₂Cl₂ (2x 10 mL). The combined organic phases were dried over Na₂SO₄ and concentrated to give a yellow oil. Purification by automated silica gel column chromatography (5 g solid load cartridge, 25 g column, 5-90% ethyl acetate in hexanes) afforded silyl ether S11 (493 mg, 86%) as a hard white foam.

Rₛ = 0.70 (minor isomer), 0.58 (major isomer); ¹H NMR (8:1 mixture) (500 MHz, CDCl₃) δ 7.26 (m, 45H), 6.04 (d, 1H, J=2.2 Hz), 5.95 (d, 8H, J=2.0 Hz), 5.58 (d, 9H, J=14.9 Hz), 5.34 (dd, 8H, J=6.1, 1.9 Hz), 5.30 (m, 1H), 4.72 (m, 9H), 4.20 (m, 9H), 3.21 (s, 3H), 3.20 (s, 24H), 2.87 (dd, 8H, J=17.6, 9.8 Hz), 2.77 (dd, 9H, J=17.2, 2.1 Hz), 2.69 (dd, 9H, J=17.1, 6.2 Hz), 2.58 (m, 9H), 2.51 (m, 9H), 2.43 (dd, 9H, J=15.8, 4.7 Hz), 2.30 (m, 18H), 2.23 (m, 9H), 1.90 (m, 9H), 1.82 (m,
9H), 1.37 (dd, 9H, \( J=13.6, 8.0 \) Hz), 0.91 (s, 81H), 0.09 (s, 54H); IR (neat film) 2952 (s), 2930 (s), 2856 (m), 1734 (s), 1654 (s), 1452 (m), 1286 (s), 1140 (s), 1114 (m), 1004 (w), 832 (s) cm\(^{-1}\); LRMS (ESI) 706.41 (M+Na).

Ketone 230 (VII-JTW-024)

To a solution of silyl ether S11 (493 mg, 0.720 mmol, 1.00 equiv) in 10:1 tetrahydrofuran:water (7.2 mL) were added 2,6-lutidine (209 \( \mu \)L, 1.80 mmol, 2.50 equiv), 2.5 wt\% OsO\(_4\) in tert-butanol (181 \( \mu \)L, 0.0144 mmol, 0.02 equiv), and PhI(OAc)\(_2\) (533 mg, 1.66 mmol, 2.30 equiv). The resulting solution was stirred at room temperature for 1 h, at which time a white precipitate appeared. The suspension was then quenched with saturated aqueous Na\(_2\)S\(_2\)O\(_3\) solution (7 mL). This mixture was stirred vigorously for 20 m, diluted with H\(_2\)O (20 mL) and extracted with CH\(_2\)Cl\(_2\) (3x 20 mL). The combined organic extracts were dried over MgSO\(_4\), filtered, and concentrated to give a brown solid. Purification by silica gel column chromatography (2 : 1 CH\(_2\)Cl\(_2\) : hexanes followed by 1 : 1 CH\(_2\)Cl\(_2\) in hexanes) afforded ketone 230 (294 mg, 74\%) as a fluffy white solid.

R\(_f\) = 0.6 (1 : 1 CH\(_2\)Cl\(_2\) in hexanes, KMnO\(_4\) stain); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 7.26 (m, 5H), 5.61 (d, 1H, \( J=14.9 \) Hz), 5.42 (m, 1H), 4.71 (m, 1H), 4.36 (m, 1H), 4.04 (d, 1H, \( J=14.9 \) Hz), 3.83 (m, 1H), 3.81 (s, 3H), 3.79 (m, 1H), 3.25 (s, 3H), 2.90 (dd, 1H, \( J=6.6, 6.6 \) Hz), 2.74 (m, 2H), 2.69 (m, 1H), 2.62-2.46 (m, 4H), 2.30 (d, 1H, \( J=6.4 \) Hz), 2.09 (m, 1H), 1.99 (m, 1H), 1.45 (dd, 1H, \( J=14.4, 8.5 \) Hz); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 208.87, 172.01, 168.77, 144.77, 135.92,
129.40, 128.44, 127.66, 114.00, 84.58, 71.43, 65.34, 57.51, 57.26, 52.75, 52.24, 50.81, 50.42, 50.29, 45.74, 39.69, 38.16, 36.09, 35.22, 33.86, 26.26; IR (neat film) 2930 (w), 1727 (s), 1649 (s), 1452 (m), 1238 (m), 1210 (m), 1143 (m), 1107 (m), 913 (m), 729 (s) cm⁻¹; HRMS (ESI) calc'd for C₂₈H₃₀NO₆BrNa (M+Na) 578.1154 found 578.1154.

Epoxide 235 (VI-JTW-107)

To a solution of enol ether 230 (4.5 mg, 0.0081 mmol, 1.0 equiv) in CH₂Cl₂ (900 μL) at 20 °C was added a 0.09 M solution of dimethyldioxirane in acetone (900 μL, 0.08 mmol, 10 equiv). The vessel was wrapped in aluminum foil and stirred at 20 °C for 4.5 h. The solvent was removed by vacuum to give epoxide 235 as a film (4.6 mg, >99%). No purification was necessary.

Rᶠ = 0.50 (2 : 1 CH₂Cl₂ : ethyl acetate, CAM stain); ¹H NMR (600 MHz, CDCl₃) δ 7.30 (m, 5H), 5.56 (d, 1H, J=14.5 Hz), 4.79 (m, 1H), 4.26 (t, 1H, J=8.8 Hz), 3.99 (d, 1H, J=14.5 Hz), 3.84 (d, 1H, J=3.1 Hz), 3.81 (t, 1H, J=4.6 Hz), 3.78 (s, 3H), 3.28 (s, 3H), 3.11 (d, 1H, J=5.5 Hz), 2.91 (m, 1H), 2.77 (dd, 1H, J=19.2, 10.3 Hz), 2.75 (m, 1H), 2.64 (d, 1H, J=18.7 Hz), 2.60 (dd, 1H, J=15.4, 5.6 Hz), 2.51 (m, 1H), 2.45 (dd, 1H, J=15.9, 4.2 Hz), 2.29 (d, 1H, J=15.4 Hz), 2.23 (m, 2H), 2.17 (d, 1H, J=3.5 Hz), 1.92 (m, 1H); ¹³C NMR (150 MHz, CDCl₃) δ 210.52, 171.18, 169.06, 135.84, 129.84, 128.50, 127.98, 83.57, 82.14, 70.13, 64.72, 57.88, 56.05, 53.63, 53.17, 52.86, 51.41, 50.82, 47.59, 44.25, 43.51, 36.60, 36.30, 35.66, 35.26, 24.39, 1.17; LRMS (ESI) 572.1 (M+H), 594.1 (M+Na), 610.1 (M+K).
Allylic alcohol 236 (SY-VII-117) – Yuan Shi

To a solution of enol-ether 230 (243 mg, 0.436 mmol, 1.00 equiv) in a mixed solvent of CH₃CN and CH₂Cl₂ (v/v 4/1, 18 mL, 0.024 M) was added a 0.5 M aqueous solution of Cerium(IV) Ammonium Nitrate (2.60 mL, 1.30 mmol, 3.00 equiv). The resulting cloudy solution was stirred at 50 °C in a sealed tube for 3 h. A second addition of 0.5 M aqueous solution of Cerium(IV) Ammonium Nitrate (800 μL, 0.400 mmol, 0.920 equiv) was added and the reaction was heated at 50 °C for additional 30 m then cooled to 20 °C. The reaction was diluted with H₂O (20 mL), extracted with CH₂Cl₂ (3x 20 mL), dried over MgSO₄ and concentrated to give 236. The residue was used in the next step without further purification.

A purified sample was obtained by prep TLC for characterization purposes:

Rₛ = 0.23 (1 : 1 ethyl acetate : CH₂Cl₂, KMnO₄ stain); ¹H NMR (500 MHz, CDCl₃) δ 7.28-7.26 (m, 3H), 7.22-7.20 (m, 2H), 5.60 (d, 1H, J=6.3 Hz), 5.52 (d, 1H, J=14.7 Hz), 4.78-4.74 (m, 2H), 4.40-4.36 (m, 1H), 3.98 (d, 1H, J=14.7 Hz), 3.87 (s, 3H), 3.84 (dd, 1H, J=5.5, 4.5 Hz), 3.77 (dd, 1H, J=4.5, 1.4 Hz), 3.25 (s, 3H), 2.91-2.89 (m, 2H), 2.69-2.62 (m, 4H), 2.55-2.52 (m, 1H), 2.13-2.08 (m, 1H), 2.05-1.99 (m, 1H), 1.63 (dd, 1H, J=14.5, 8.4 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 208.29, 173.61, 167.28, 149.61, 135.47, 129.52, 128.52, 127.85, 115.96, 85.54, 72.20, 69.05, 64.35, 60.95, 57.46, 52.98, 52.33, 51.17, 50.99, 50.31, 39.78, 39.27, 38.11, 35.99, 34.59, 29.84, 26.11; IR (neat film) 3436 (m), 2927 (s), 2854 (s), 1724 (s), 1646 (s), 1456 (m), 1242 (s), 1143
(m), 1106 (m), 910 (m), 733 (s) cm$^{-1}$; HRMS (ESI) calc'd for C$_{28}$H$_{30}$NO$_7$BrNa (M+Na$^+$) 594.1103 found 594.1110.

![Chemical structure](image)

**Enone 239 (SY-VII-120) – Yuan Shi**

To a solution of alcohol 236 (crude product from above) in CH$_2$Cl$_2$ (20 mL) was added Et$_3$N (1.8 mL, 12.9 mmol, 29.6 equiv) and methanesulfonyl chloride (170 μL, 2.19 mmol, 5.02 equiv). The resulting solution was stirred at 50 °C in a sealed tube for 1.5 h then cooled 20 °C. Further methanesulfonyl chloride (35 μL, 0.45 mmol, 1.0 equiv) was added and the reaction was heated to 50 °C for additional 15 m then cooled to ambient temperature and quenched with saturated aqueous NaHCO$_3$ (20 mL), extracted with CH$_2$Cl$_2$ (3x 10 mL), dried over MgSO$_4$ and concentrated. The residue was purified by automated silica gel column chromatography (5 g solid load cartridge, 4 g column, 0-50% ethyl acetate in CH$_2$Cl$_2$) to yield enone 239 (139 mg 57% over 2 steps) as a pale purple solid along with recovered starting alcohol 236 (11.0 mg, 4.5 %).

R$_f$ = 0.41 (1 : 1 ethyl acetate : CH$_2$Cl$_2$, KMnO$_4$ stain); $^1$H NMR (500 MHz, CDCl$_3$) δ 7.48 (d, 1H, J=9.5 Hz), 7.33-7.32 (m, 3H), 7.09-7.08 (m, 2H), 6.52-6.48 (m, 1H), 6.17 (d, 1H, J=9.5 Hz), 6.07 (dd, 1H, J=9.8, 1.7 Hz), 5.47 (d, 1H, J=14.6 Hz), 4.43-4.40 (m, 1H), 3.94 (d, 1H, J=14.5 Hz), 3.90 (s, 3H), 3.78 (m, 1H), 3.73 (m, 1H), 3.17 (s, 3H), 2.94 (m, 1H), 2.88 (m, 1H), 2.78-2.74 (m, 1H), 2.71-2.64 (m, 2H), 2.55-2.51 (m, 1H), 2.30-2.27 (dt, 1H, J=14.0, 8.4 Hz), 1.31 (dd, 1H, J=13.9, 9.2 Hz); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 199.89, 195.68, 170.00, 165.83, 150.28,
Ketone 240 (SY-VII-123) – Yuan Shi

A solution of enone 239 (130 mg, 0.234 mmol, 1.00 equivalent) in benzene (9.0 mL) was subjected to 1x freeze-pump-thaw cycle. To this solution was added a solution of AIBN (3.9 mg, 0.024 mmol, 0.10 equiv) and Bu$_3$SnH (70 μL, 0.26 mmol, 1.11 equiv) in benzene (1.20 mL). The resulting solution was heated at 80 °C for 30 m then cooled to 20 °C and concentrated. The residue was purified by automated silica gel column chromatography (5 g solid load cartridge, 4 g column, 0-100% ethyl acetate in hexanes) to yield ketone 240 (96.0 mg, 86%) as an off white solid.

R$_f$ = 0.20 (1 : 5 Acetone : Toluene, KMnO$_4$ stain); $^1$H NMR (500 MHz, CDCl$_3$) δ 7.43 (d, 1H, $J$=9.6 Hz), 7.32-7.30 (m, 3H), 7.14 (m, 2H), 6.17 (d, 1H, $J$=9.5 Hz), 4.61 (d, 1H, $J$=14.5 Hz), 4.38 (d, 1H, $J$=14.6 Hz), 3.89 (s, 3H), 3.84 (t, 1H, $J$=5.0 Hz), 3.62 (s, 1H), 3.28 (s, 3H), 2.87-2.82 (m, 2H), 2.59-2.52 (m, 1H), 2.41-2.35 (m, 2H), 2.28-2.23 (m, 2H), 2.18-2.12 (m, 3H), 1.85 (dd, 1H, $J$=19.6, 3.9 Hz), 1.77 (dd, 1H, $J$=15.1, 7.5 Hz); $^{13}$C NMR (125 MHz, CD$_2$Cl$_2$) δ 211.51, 211.25, 172.44, 168.47, 137.23, 129.29, 129.08, 129.02, 128.10, 83.67, 60.90, 59.69, 58.40, 57.61, 52.98, 51.55, 51.10, 46.81, 46.61, 40.14, 39.09, 36.08, 34.83, 33.19, 30.65, 30.03, 29.74, 28.18, 27.70, 27.19, 17.81, 13.72; IR (neat film) 2947 (s), 2895 (s), 2866 (s), 1757 (s), 1720 (s), 144.55, 135.32, 130.62, 129.48, 128.64, 128.25, 86.81, 68.79, 59.38, 57.89, 57.64, 53.72, 52.63, 51.82, 48.57, 46.48, 44.25, 42.75, 37.05, 26.10; IR (neat film) 2918 (m), 1741 (m), 1661 (s), 1199 (s), 1121 (s), 969 (m) cm$^{-1}$; LRMS (ESI) calc'd for C$_{28}$H$_{35}$NO$_6$BrNa (M+Na) 576.10, 578.10 found 576.27, 578.22.
1672 (s), 1465 (m), 1216 (s), 1143 (s), 883 (m) 687 (m) cm$^{-1}$; LRMS (ESI) calc'd for C$_{28}$H$_{29}$NO$_6$Na (M+Na) 498.19 found 498.14.

**Phenylselenide S12 (SY-VII-132) – Yuan Shi**

To a solution of ketone 240 (85 mg, 0.18 mmol, 1.0 equiv) in tetrahydrofuran (1.8 mL) at –78 °C was added a 0.5 M solution of LHMDS in tetrahydrofuran (360 μL, 0.180 mmol, 1.00 equiv). The resulting enolate solution was stirred at –78 °C for 1 h then transferred via cannula to a solution of phenylselenyl chloride (67.8 mg, 0.354 mmol, 2.00 equivalent) in tetrahydrofuran (1.8 mL) at –78 °C and quantitated with additional tetrahydrofuran (500 μL). The reaction was stirred at –78 °C for another 30 m then warmed to 20 °C over 10 m. The reaction was then quenched with saturated aqueous NaHCO$_3$ solution (10 mL), and extracted with CH$_2$Cl$_2$ (3x 10 mL) The combined organic extracts were dried over MgSO$_4$, filtered, and concentrated. The residue was purified by automated silica gel column chromatography (5 g solid load cartridge, 4 g column, 0-60% acetone in hexane) to yield phenylselenide S12 (85.0 mg, 75%) as a pale yellow solid.

$R_f = 0.28$ (1 : 5 Acetone : Toluene, KMnO$_4$ stain); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.74 (dd, 2H, $J$=7.6, 1.3 Hz), 7.42 (d, 1H, $J$=9.6 Hz), 7.37-7.34 (m, 3H), 7.21-7.14 (m, 3H), 6.88 (d, 2H, $J$=7.2 Hz), 6.15 (d, 1H, $J$=9.5 Hz), 4.78 (d, 1H, $J$=14.6 Hz), 3.88 (s, 3H), 3.83 (d, 1H, $J$=14.5 Hz), 3.80 (t, 1H, $J$=4.9 Hz), 3.53 (s, 1H), 3.33 (d, 1H, $J$=5.7 Hz), 3.21 (s, 3H), 3.03 (m, 1H), 2.83 (d, 1H, $J$=7.5 Hz), 2.59-2.56 (m, 1H), 2.38-2.36 (m, 3H), 2.20-2.17 (m, 2H), 2.07-2.04 (m, 1H), 1.74 (dd, 1H, $J$=13.6, 7.3 Hz); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 208.06, 197.92, 170.47, 165.81,
149.56, 135.96, 135.74, 130.72, 129.34, 129.03, 128.64, 128.25, 83.43, 60.20, 59.66, 57.16, 54.20, 53.58, 53.48, 51.34, 49.73, 48.01, 45.00, 41.84, 37.43, 29.34; IR (neat film) 2953 (m), 2931 (m), 1736 (s), 1724 (s), 1674 (s), 1654 (s), 1451 (m), 1437 (s), 1243 (s), 911 (m), 733 (s) cm⁻¹; LRMS (ESI) calc'd for C₃₄H₃₃NO₆SeNa (M+Na) 654.14 found 654.27.

Alcohol 242 (SY-VII-135, SY-VII-156) – Yuan Shi

To a solution of phenylselenide S12 (25.0 mg, 0.0396 mmol, 1.0 equiv) in CH₂Cl₂ (2.5 mL, 0.016 M) at 0 °C was added a freshly diluted 1.0 M solution of H₂O₂ in H₂O (105 μL, 0.105 mmol, 2.70 equiv) in 4 equal portions slowly, one every 20 m. 20 m after the last addition, the reaction mixture was quenched with saturated aqueous NaHCO₃ (10 mL), and extracted with CH₂Cl₂ (3x 10 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated. The residue was quickly purified by a short pipette silica gel column (40% acetone in hexane) to give enone 241 (17.0 mg, 90%) as an off white solid. This was immediately used in the next step.

Rₐ = 0.21 (1 : 5 Acetone : Toluene, KMnO₄ stain).

To a solution of enone 241 (16.0 mg, 0.0338 mmol, 1.00 equiv) in tetrahydrofuran (1.6 mL) was added a 33% acetic acid in H₂O solution (400 μL diluted to 2.0 mL with H₂O). The resulting mixture was stirred at 20 °C for 23 h then quenched with aqueous 0.5 N aqueous HCl (10 mL) and extracted with CH₂Cl₂ (3x 10 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated. The residue was purified by pipette column (16% acetone in toluene) to give alcohol 242 (12.8 mg, 77%) as an off white solid.
R<sub>f</sub> = 0.22 (3 : 11 Acetone : Toluene, KMnO<sub>4</sub> stain); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.45 (d, 1H, J=9.5 Hz), 7.32 (m, 3H), 7.13 (m, 2H), 6.18 (d, 1H, J=9.5 Hz), 4.69 (d, 1H, J=14.6 Hz), 4.36 (d, 1H, J=14.6 Hz), 3.98 (t, 1H, 5.9 Hz), 3.90 (s, 3H), 3.57 (d, 1H, J=1.1 Hz), 3.32 (s, 3H), 3.30 (s, 1H), 2.94 (m, 1H), 2.82 (m, 1H), 2.57 (d, 1H, J=20.3 Hz), 2.49 (d, 1H, J=20.3 Hz), 2.29-2.27 (m, 4H), 2.17 (m, 1H), 2.13 (m, 1H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 208.86, 197.95, 170.63, 165.80, 149.85, 138.02, 135.96, 130.83, 129.18, 129.14, 128.56, 128.44, 128.37, 125.44, 84.47, 73.44, 62.32, 59.79, 57.81, 54.00, 52.38, 50.33, 50.27, 49.47, 48.72, 44.92, 40.45, 29.84, 28.31, 25.73, 21.61; IR (neat film) 3531 (m), 2956 (s), 2925 (s), 1727 (s), 1656 (s), 1542 (s), 1452 (s), 1242 (s), 913 (m) cm<sup>-1</sup>; LRMS (ESI) calc'd for C<sub>28</sub>H<sub>29</sub>NO<sub>7</sub>Na (M+Na) 514.18 found 514.08.

5.5 References


(2) Rodeschini, V.; Ahmad, N. M.; Simpkins, N. S. Org. Lett. 2006, 8, 5283.


CHAPTER 6. CONCLUSIONS AND PROSPECTUS

6.1 Innovations Resulting from the *Cephalotaxus* Esters Syntheses

The development of a novel approach to the *Cephalotaxus* esters has enabled the synthesis of potent anti-leukemia agents deoxyharringtonine (2), anhydroharringtonine (3), homoharringtonine (4), and homodeoxyharringtonine (5). The construction of non-racemic strained β-lactone acyl chain derivatives allowed the direct C3-O-acylation of cephalotaxine (1), a longstanding challenge within the synthetic community. This technology also allowed the cytotoxicity screening of various natural and non-natural *Cephalotaxus* esters against an array of human hematopoetic and solid cancer cell lines, the results of which led to the discovery of several non-natural cytotoxic compounds. In addition, an unprotected hydroxyl group at the C2' position was found to be necessary for potent anti-tumor activity. Moreover, several members of these alkaloids were found to overcome the multi-drug resistance of the HL/60 RV+ cell line. These discoveries, when applied in concert with ready access to non-natural analogues via our novel strain accelerated acylation of cephalotaxine (1) (Scheme 59), should guide the design and construction of future anti-cancer agents capable of overcoming MDR in leukemia as well as other cancer types.

**Scheme 59**

![Scheme 59](image)

\[ R = H, \text{alkyl, aryl, halogen, etc.} \]
\[ R' = H, \text{alkyl, aryl, etc.} \]
\[ X = N, O \]
6.2 Innovations resulting from the Current Approach to the Aconitine Alkaloids

Several innovations were developed during the synthesis of the carbon-nitrogen skeleton of the aconitine alkaloids. These include: (1) use of a cyclopropene as the $2\pi$ and a $2,5$-dioxycyclopenta-1,3-diene as the $4\pi$ components of a Diels–Alder cycloaddition; (2) Diels–Alder cycloaddition with a azepin-2(5H)-one dienophile; (3) cyclopropylcarbinyl aldehyde fragmentation with subsequent N-acyliminium cyclization (Scheme 60).

C5-hydrogen substituted cyclopentadienes are known to undergo substituent rearrangement via 1,5-hydrogen migrations. In spite of this possible limitation, it was shown that 2,5-dioxycyclopenta-1,3-diene 134 would react with various dienophiles to produce the Diels–Alder cycloadducts without evidence of hydrogen shift. Furthermore, cyclopropene 112 was shown to engage in endo approach to 134 stereoselectively in a contra-steric fashion syn to the methyl ether. The resultant C14, C13, and C9 configuration coincides with that in the aconitine alkaloids. A second Diels–Alder cycloaddition with novel azepin-2(5H)-one 213 as the $4\pi$-component constructed the [5.4.0]-bicycloazepine 214 and set the C4, C5, and C10 stereocenters. Dienophile 213 would have applications beyond that of the aconitine alkaloids in that it is a useful reagent for the introduction of a highly functionalized 7-membered nitrogen containing heterocycle. The successful implementation of the two above-mentioned Diels–Alder reactions installed all the requisite carbons and nitrogen atoms present in the aconitine alkaloid skeleton. However, there were two key carbon-carbon bonds left to be formed, namely the C11–C17 and C7–C8 bonds. The former was installed through the acid-catalyzed strain release fragmentation of a cyclopropylcarbinyl aldehyde followed by addition of electron-rich C11 onto the C17 bromonium (227). The latter was installed via conjugate addition of a C8 radical onto an electron deficient olefin at C7.
The above-mentioned innovations as applied to the synthesis of the aconitine alkaloids have resulted in a convergent synthesis of the carbon and nitrogen aconitine core. The work described herein marks the first successful construction of the complete aconitine skeleton since the seminal accomplishments of the Wiesner group more than 30 years ago. This approach compares favorably with that of Wiesner in that it addresses the key concerns outlined in Chapter 2. Specifically, this strategy is highly convergent in that the two Diels–Alder reactions outlined above collectively install four rings and set five stereocenters that are required for the aconitine alkaloids. A minimum of functional group manipulations should allow access to various natural aconitine alkaloids from alcohol 242.

Moreover, the advanced intermediate bis(eneone) 241 is an ideal precursor for a number of both natural and non-natural aconitine alkaloids. The highly strained anti-Bredt nature of the C8–C15 olefin allows differentiation from the C2–C3 olefin, as demonstrated by the facile addition of water at C8. A variety of nitrogen, sulfur, halogen, and carbon nucleophiles could also undergo nucleophilic addition at C8 or C3. These modifications combined with a number of
potential C16, C1, and C18 carbonyl manipulations provide a pathway for any number of C1, C2, C3, C8, C15, C16, and C18 aconitine analogues. These analogues should not only be ideal to interrogate the neuropharmacology of aconitine alkaloids with Na\(^+\) ion channels, but also provide new tools to study ion channel structure and function in general. These advances hold the promise to develop new therapies for antinociception, arrhythmia, inflammation as well as other cardiovascular and central nervous system diseases.