Rhodium-Catalyzed Epoxide-Opening Cascades Toward Brevisin and Hemibrevetoxin B

by

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Sc.B. with Honors, Chemistry
Brown University, 2007

Submitted to the Department of Chemistry in Partial Fulfillment of the Requirements for the Degree of

DOCTOR OF PHILOSOPHY IN ORGANIC CHEMISTRY

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Massachusetts Institute of Technology

September 2014

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Department of Chemistry
August 20, 2014

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Professor of Chemistry
Thesis Supervisor

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Chairman, Department Committee on Graduate Students
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Professor Rick L. Danheiser ______

Signature redacted

Professor Timothy F. Jamison ______

Signature redacted

Professor Stephen L. Buchwald ______
to my wife, Holly, and my parents
Synthetic Studies Toward Strychnine; Rhodium-Catalyzed Epoxide-Opening Cascades

by

Kurt W. Armbrust

Submitted to the Department of Chemistry on August 20, 2014
in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy in Organic Chemistry

ABSTRACT

CHAPTER I. Rhodium-Catalyzed Epoxide-Opening Cascades: Formal Synthesis of (−)-Brevisin

[\text{Rh(CO)}_2\text{Cl}]_2 was found to be an effective catalyst for endo-selective cyclizations and cascades of epoxy-(E)-enoate alcohols, thus enabling the synthesis of oxepanes and oxepane-containing polyethers from di- and trisubstituted epoxides. Syntheses of the ABC and EF ring systems of (−)-brevisin via all endo-diepoxide-opening cascades using this method constitute a formal total synthesis and demonstrate the utility of this methodology in the context of the synthesis of marine ladder polyether natural products.

CHAPTER II. Synthetic Studies Toward Hemibrevetoxin B

[4]
We report progress toward a biomimetic epoxide-opening cascade of the marine ladder polyether hemibrevetoxin B. Model studies demonstrate the ability of both [Rh(CO)$_2$Cl]$_2$ and cationic Rh(I) species to override the typical exo-directing of proximal methyl groups on in epoxy alcohol cyclizations for the synthesis of oxepanes. The synthesis of tri-epoxide cascade precursor and initial investigations toward an epoxide-opening cascade are described as well.

Thesis Supervisor: Timothy F. Jamison  
Title: Professor of Chemistry
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I must first thank my research advisor, Professor Tim Jamison, for his continual guidance and support throughout my studies at MIT. From our initial interactions in tutorial and 5.511, to the years of challenging research projects, Tim’s enthusiasm and vast knowledge of chemistry have provided guidance and inspiration. He encourages us to take full ownership of our projects, a hallmark of Tim’s mentoring style, and this has enabled me to grow significantly as a scientist. Furthermore, Tim’s ability to attract talented graduate students and post-docs has provided a rich environment where I’ve been able to develop as a chemist, mentor, and leader.

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August 2014
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**Curriculum Vitae**

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<th>Abbreviation</th>
<th>Meaning</th>
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Chapter I
Rhodium-Catalyzed Epoxide-Opening Cascades: Formal Synthesis of (−)-Brevisin
A. Introduction to Ladder Polyether Natural Products

The marine ladder polyether family of natural products, isolated from marine dinoflagellates found in harmful algal blooms, is a fascinating class of potent toxins. Isolated from cultures of *Karenia brevis*, brevetoxin B (1) was the first structure fully elucidated for this class of molecules in 1981 (Figure 1). The potent ichthyotoxicity ($LC_{50} = 15$ nM) and low natural abundance (5 mg/50 L cell culture) of brevetoxin B typify this class of natural products. The potent toxicity of the class results from their complex binding and interaction with voltage-gated ion channels. Upon binding, these molecules lower the activation voltage necessary for channel opening and inhibit inactivation of opened channels, resulting in persistent ion-channel activation. The net result is an array of neurotoxic effects, including temperature sensitivity, muscle pain, and breathing difficulties. Conversely, a few molecules in the class have demonstrated desirable biological effects, such as antifungal (gambieric acid A) and antitumor activity (gymnocin A). Additionally, brevenal (4) has demonstrated antagonist activity to brevetoxins A (2) and B (1) for voltage gated sodium ion channels, sparking potential interest for treatment of brevetoxin poisoning in manatees. Further, brevenal’s ability to bind and modify the conformation of voltage-gated sodium ion-channels without additional toxic side effects has shown potential in sheep models for the treatment of cystic fibrosis.

Figure 1. Structure of brevetoxin B (producing organism in italics)

![Brevetoxin B (1)](image)

Karenia brevis

---

As a class, the ladder polyether natural products share a number of defining features (Figure 2). First, the molecules consist of fused oxygen heterocycles ranging from 5–9 membered sized rings, most commonly 6-membered tetrahydropyrans and 7-membered oxepanes. Second, the trans-syn-trans stereochemistry observed at ring junctions, in combination with the repeating C–C–O backbone give these molecules their “ladder-like” geometry. Third, the substitution at ring junctions is limited to hydrogen and methyl groups. Finally, as demonstrated with structurally modified variants of brevetoxin B, the positioning of 7-, 8-, and 9-membered rings at the ring junctions heavily influences the overall geometry and biological activity of these molecules.2

Figure 2. Selected examples of marine ladder polyether natural products with structural features common to the family highlighted

brevetoxin A (2)
Karenia brevis
Fused 5– to 9-Membered Cyclic Ethers

gamblerol (3)
Gambierdiscus toxicus
Repeating O–C–C–C Backbone Highlighted

brevenal (4)
Karenia brevis
Stereochemistry at Ring Fusions Highlighted

hemibrevetoxin B (5)
Karenia brevis
Methyl Substitution at Ring Junctions Highlighted
The limited natural abundance and potent biological activity of this class has inspired many innovative achievements in their total synthesis. Additionally, their unique structural features have provided the impetus for development of new methods to efficiently access these molecules. Most method development for the synthesis of this class utilizes ingenious strategies to append rings one by one, with subsequent fragment coupling to complete the molecules. However, an alternative strategy to synthesize this class via epoxide-opening cascades, emulating the biosynthetic hypothesis, has long intrigued synthetic chemists. The biosynthetic hypothesis proposed by Nakanishi\textsuperscript{8,9} invokes a three-step sequence shown in Scheme 1. After biosynthesis of polyene precursor (6), an enzymatic stereoselective epoxidation yields poly-epoxide 7. Finally, an all-\textit{endo} epoxide-opening cascade generates the desired ladder polyether framework (1). One limitation of this proposal is that formation of the larger ring, \textit{endo}-product\textsuperscript{10} via epoxide-opening is kinetically disfavored (vide infra), suggesting enzymatic assistance during the cascade to enforce high \textit{endo}-selectivity. While only limited evidence for this pathway exists from feeding studies with labeled precursors,\textsuperscript{11} support for the proposal can be found in \textit{endo}-selective epoxide-opening enzymes that have been characterized from other organisms,\textsuperscript{12} as well as the generation and theoretical studies of catalytic antibodies for \textit{endo}-selective epoxy alcohol cyclizations by Janda, Lerner and Houk.\textsuperscript{13}


\textsuperscript{8} Nakanishi, K. \textit{Toxicon} \textbf{1985}, \textit{23}, 473.


\textsuperscript{10} Cyclizations of epoxy alcohols are not "\textit{exo}" and "\textit{endo}" in the traditional sense, as the C-O bond broken during the cyclization is outside the forming ring in both instances. Historically, Baldwin applied the nomenclature referenced in his work to intramolecular opening of epoxides, with terminology "\textit{exo}" and "\textit{endo}" referencing the smaller and larger ring products, respectively. See: Baldwin, J. E. \textit{J. Chem. Soc., Chem. Comm.} \textbf{1976}, \textit{734}.


Scheme 1. Proposed biosynthetic hypothesis for brevetoxin B (1)

Guided by the proposed biogenesis of these compounds, several groups, including ours, have investigated the feasibility of all-endo epoxide-opening cascades as a rapid and general approach to these and other polyethers.\textsuperscript{14} Cascades proceeding in an entirely endo\textsuperscript{10} selective fashion have been of particular interest to us, as they would allow direct access to the ladder polyether class. We are further motivated by the success of total syntheses utilizing biomimetic all-exo epoxide-opening cascades patterned after the related Cane–Celmer–Westley biosynthetic hypothesis for marine polyether ionophore natural products.\textsuperscript{15,16} However, unlike the all-exo cascades, the proposed all-endo cascades present an ongoing challenge, as formation of the larger endo ring product is generally kinetically disfavored relative to the exo ring product.

\textsuperscript{14} Vilotijevic, I.; Jamison, T. F. \textit{Angew. Chem., Int. Ed.} \textbf{2009}, \textit{48}, 5250.
\textsuperscript{15} In addition to the discussion of biomimetic all-exo epoxide opening cascades in ref. 14, please see the following illustrative examples: (a) Xiong, Z.; Corey, E. J. \textit{J. Am. Chem. Soc.} \textbf{2000}, \textit{122}, 9328. (b) Yang, P.; Li, P.-F.; Qu, J.; Tang, L.-F. \textit{Org. Lett.} \textbf{2012}, \textit{14}, 3932.
Scheme 2. Two possible transition states and products from epoxy alcohol cyclization

Cyclization of an epoxy-alcohol can proceed via two transition states shown in Scheme 2: the spiro transition state, leading to the exo product, and the fused transition state, leading to the endo product. Experimentally, the exo product is favored in systems without electronic-bias present, as seen in Scheme 3. The reaction of epoxy alcohol 8a produces two products: the smaller ring, 5-membered tetrahydrofuran 9a (THF) via an exo-type closing, or the larger ring, 6-membered tetrahydropyran 10a (THP) via an endo-type closing. Subjecting 8a to BF₃·OEt₂ yields a 16:84 ratio of the endo product (10a) to the exo product (9a), demonstrating the strong kinetic preference for the exo pathway. Increasing the tether length by one methylene to epoxy alcohol 8b yields two possible products: the exo product THP 9b, and the endo product, oxepane 10b. As seen with 8a, cyclization of 8b provides exo THP 9b as the major product, with none of the endo oxepane 10b observed.

Scheme 3. Product distribution from BF₃·OEt₂-promoted cyclization of epoxy alcohols 8a and 8b

---

17 The THP product 9a is actually lower in energy due to the lower ring strain in the THP relative to THF product 9a. However, this reaction is irreversible under the reaction conditions, yielding the THF as the primary product.

B. Endo-Selective Epoxide-Opening Cyclizations and Cascades

Methodology developed in the Jamison group has addressed the challenge of poor endo-selectivity through the use of template-guided, water-promoted cascades to enable rapid synthesis of poly-tetrahydropyran fragments.\(^1\)\(^9\) This methodology is capable of promoting cyclizations of THP-templated epoxy alcohols (11) and poly-epoxy alcohols (14) with high endo-selectivity (Scheme 4, eq 1 and 2). Further work has demonstrated tolerance of methyl substitution on the epoxides without significant loss to yields and selectivity.\(^2\)\(^0\) Most recently, modification of the THP-template to a 1,3-dioxane type template (16) has yielded cascade products amenable for use in synthesis of ladder polyethers, for example 17, which can be further elaborated towards the FGH rings of gambierol (3) (Scheme 4, eq 3).\(^2\)\(^1\)

Importantly, however, this methodology is not amenable to the synthesis of oxepanes, which represent an important structural motif present in nearly every ladder polyether natural product isolated to date.\(^2\)\(^2\)\(^3\) Attempts to promote formation of an oxepane via an endo-selective epoxy alcohol cyclization utilizing this methodology have proven unsuccessful, providing only the exo THP product 20 (Scheme 4, eq 4).\(^2\)\(^4\) Detailed mechanistic studies have revealed that the THP template and water disproportionately reduce the rate of exo cyclization relative to endo cyclization, leaving the 6-endo product 12 as both the thermodynamic and kinetic product.\(^2\)\(^4\) With regard to the cyclization of 18, the 6-exo THP product (20) is predicted to be the kinetic and thermodynamic product under most conditions, likely minimizing the impact of the THP template and water activation towards formation of the 7-endo oxepane 19. To expand our synthetic efforts in this field, we have undertaken the goal of developing alternative methods for the synthesis of oxepanes utilizing epoxide-opening cascades.

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\(^2\) A variety of alternative methods for the synthesis of oxepanes have been reported. Please see the following review for recent developments of alternative methods for the synthesis of oxepanes and medium-ring cyclic ethers: Kleinke, A. S.; Webb, D.; Jamison, T. F. *Tetrahedron* 2012, *68*, 6999.

\(^2\) OXepanes, oxocanes, and oxonanes in ladder polyethers are often used as sites of fragment coupling for the convergent synthesis of these natural products.

Historically, alternative approaches to synthesizing oxepanes via epoxy alcohol cyclizations and cascades have utilized various directing groups. Nicolaou and coworkers investigated the ability of alkenyl epoxides to bias the cyclization toward the endo product, utilizing π-stabilization of the epoxonium intermediate to impart the desired selectivity. Cyclization of 21 under acid catalysis provided high endo-selectivity with vinyl substituents, providing oxepane 22 in good yield (Scheme 5, eq 1).\textsuperscript{25} Unfortunately, this methodology appears to be limited to cyclization of substrates with primary alcohol trapping nucleophiles, as attempts to use secondary alcohol 24 with a preformed THP template led to trapping of the conjugate base during epoxide opening, yielding only 25 (Scheme 5, eq 2). While epoxide activation with CSA appears suitable for poly-THP formation,\textsuperscript{25a} the higher activation barrier with respect to formation of oxepanes appears to limit use of weaker nucleophiles such as the secondary alcohols necessary for our goals.

Scheme 5. Brønsted acid catalyzed epoxy alcohol cyclizations towards oxepanes with vinyl directing groups

![Scheme 5](image)

To circumvent the poor reactivity observed above, McDonald and coworkers have utilized a second epoxide as a trapping nucleophile, generating a highly reactive bicyclo[\text{n.1.0}] epoxonium. Subsequent trapping by a terminating nucleophile generates (poly-fused) oxygen heterocycles. McDonald and coworkers have reported all-\textit{endo} epoxide-opening cascades utilizing this strategy in concert with suitable methyl-directing groups to successfully form oxepane (27) and poly-oxepane (29a) products under BF\textsubscript{3}•OEt\textsubscript{2} promotion (Scheme 6, eq 1 and 2).\textsuperscript{26} While the use of methyl-directing groups is necessary for successful \textit{endo}-trapping of the pendant carbonate nucleophile (eq 4), substrate 28b with a \textit{trans}-disubstituted epoxide yields all-\textit{endo} product 29b (eq 3), demonstrating an alternative influence on regioselectivity for epoxonium trapping by a subsequent epoxide.\textsuperscript{27}

The proposed mechanism for these reactions requires activation of the epoxide furthest from the carbonate trapping nucleophile (26 to 32, Scheme 7), followed by \textit{endo}-trapping of the next epoxide directed by the methyl group (32 to 33a). In addition to the electronic bias of the methyl substituent, the high \textit{endo}-selectivity is thought to result from the difference in ring strain between \textit{exo}-trapping, providing highly-strained bicyclo[3.1.0] epoxonium 33b, versus the \textit{endo}-trapping leading to a slightly less strained bicyclo[4.1.0] epoxonium 33a. This difference in ring strain is thought to account for the successful cyclization of 28b, which lacks a directing methyl on the central epoxide. Potential limitations of this methodology center on the non-selective activation method, as BF\textsubscript{3}•OEt\textsubscript{2} is capable of activating any of the epoxides. This non-selective activation


could promote out-of-order cyclization, interrupting the desired cascade. The observed decrease in yield with additional epoxides is suggestive of such processes. Additionally, only weak nucleophiles such as esters and carbonates can be used as trapping nucleophiles, as the authors suggest primary alcohols are too nucleophilic, leading to undesired spontaneous epoxy alcohol cyclization outcompeting the desired pathway.

**Scheme 6.** Methyl-directed, Lewis acid promoted epoxide-opening cascades for the synthesis of oxepanes and poly-oxepanes

1. BF$_3$·OEt$_2$, CH$_2$Cl$_2$, -40 °C
2. Ac$_2$O, Et$_3$N, CH$_2$Cl$_2$, rt 60% over 2 steps

(1)  

(2) Methyl-directed bicyclo[4.1.0] epoxoniumendo-trapping

(3) alternative bicyclo[3.1.0] epoxonium not formed

(4) Methyl-directed endo-trapping

**Scheme 7.** Mechanistic hypothesis for endo-selective epoxide-opening cascades toward oxepanes
C. First Generation Approach Toward a Formal Synthesis of (-)-Brevisin

In line with the Jamison group’s ongoing interest in synthesis of the ladder polyether natural products via epoxide-opening cascades, we undertook a formal synthesis of (-)-brevisin (34) (Scheme 8). Isolated from cell cultures (2.8 mg from 200 L), structural elucidation of 34 was reported in 2009 by Baden, Wright, and coworkers.28 (-)-Brevisin was found to inhibit the binding of brevetoxin B (1) to voltage-gated sodium-ion channels at nearly 10 μM (ED₅₀), a level similar to that of brevenal (2). Structurally, 34 consists of two tricyclic fragments connected by a methylene bridge, representing a possible “interrupted” cascade product.

Tachibana and coworkers reported the first and only total synthesis of (-)-brevisin (34) in 2011, utilizing an aldol addition to couple the ABC and EF fragments 35 and 36, while simultaneously forming the D-ring hydroxyl.29 The ABC fragment was prepared via Suzuki coupling of the A and C rings (37 and 38), with a cyclization/methylation sequence resulting in synthesis of the B ring. The EF fragment was synthesized via an allyl-tin cyclization onto an aldehyde, providing the E-ring oxepane from 39. The overall synthesis was achieved in 29 steps via the longest linear sequence (LLS), 57 total steps, and yielded over 70 mg of (-)-brevisin for further biological testing.

Scheme 8. Structure of (-)-brevisin and summary of first and only total synthesis by Tachibana and coworkers

Toward our aim of developing a formal synthesis, we were inspired by two intermediates in the previously described synthesis, tricycles 40 and 41 (Scheme 9). Dr. Matthew Beaver, a postdoctoral fellow in the Jamison lab, initiated this project. We envisioned intercepting two tricyclic fragments via Lewis acid promoted diepoxide cascades: ABC tricycle 40 from diepoxide 42 and EF-dioxane tricycle 41 from diepoxide 43. While the use of alcohol trapping nucleophiles has limited precedence in Lewis acid promoted epoxide-opening cascades, we hoped the electronic deactivation from the neighboring oxygen atoms and decreased nucleophilicity of the secondary alcohol would slow the rate of epoxy alcohol cyclization relative to the desired epoxide trapping. Additionally, we were interested in exploring the electronic requirements for promoting selective activation of the epoxide furthest from the template, as McDonald had previously explored trisubstituted epoxides with either di-methyl or methyl-vinyl groups biasing openings in an endo-fashion. The cascades proposed in Scheme 9 rely on either a vinyl activating group (43), or a trisubstituted epoxide with an electronically deactivating OTBS group (42), which were untested prior to this work.

\[\text{Dr. Matthew Beaver completed the EF-dioxane fragment and the first generation route toward the ABC fragment.}\]

\[\text{Previous work in the epoxide-opening cascades toward poly-THP fragments had found oxygen substitution to be detrimental to endo-selectivity. See ref. 18c.}\]
Scheme 9. First generation retrosynthetic analysis of ABC and EF-dioxane formal synthesis targets

For the ABC fragment, synthesis of the A ring proceed via the previously reported route to lactone $\text{44}^{29c}$ in five steps from 1,3-propanediol (Scheme 10). This lactone was elaborated by diastereoselective dihydroxylation, and the incipient side chain was installed through allyl Grignard addition. Triethylsilane reduction of intermediate lactol $\text{45}$, and acetylation provided the fully elaborated A ring ($\text{46}$). Elaboration of the allyl group of $\text{46}$ was accomplished via cross metathesis with $\text{48}^{32}$ providing trisubstituted alkene $\text{50}$, albeit in low yield and stereoselectivity.$^{33}$ Subsequent asymmetric Shi epoxidation$^{34}$ and acetate removal by basic methanolysis provided the desired diepoxide $\text{52}$.

Subjecting $\text{52}$ to Lewis acids (BF$_3$-OEt$_2$, La(OTf)$_3$) or aqueous conditions (pH 2 or pH 7) produced none of the desired all-endo ABC tricycle $\text{53}$. The lack of product formation was attributed to epoxide closest to the A ring cyclizing first to provide bis-THP $\text{55}$ (Scheme 11). Our rationale is the electron-withdrawing CH$_2$OTBS deactivated the second epoxide toward activation and subsequent attack by the neighboring epoxide, allowing the template alcohol to react with the first epoxide ($\text{54}$). Formation of the desired ABC tricycle would necessitate a 7-endo cyclization of a secondary alcohol onto an electronically deactivated epoxide, generally disfavored under the conditions explored (vide supra). Ideally, an alternative biasing group and/or activation method could be applied to accelerate the desired bicyclo[4.1.0] epoxonium formation. However, given the difficulty of the cross metathesis and subsequent low material throughput, we decided to turn our attention toward the EF cascade.

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$^{33}$ Please see the second-generation synthesis for a discussion and optimization of the cross metathesis.
Scheme 10. First generation synthetic sequence toward ABC tricycle

Scheme 11. Mechanistic hypothesis for unsuccessful cascade of diepoxide 52
The route illustrated in Scheme 12 was pursued for synthesis of the EF diepoxy alcohol cascade precursor 43. Ozonolysis of known enoate 56, subsequent nucleophilic addition of isopropenyl magnesium bromide, and a tandem vinylation–Claisen process36 afforded aldehyde 58. Stabilized-Wittig olefination, followed by reduction with DIBAL-H and Sharpless asymmetric epoxidation37 provided epoxy alcohol 59. Oxidation and Wittig methylenation installed the desired vinyl epoxide (60). Finally, asymmetric Shi epoxidation and TBAF desilylation provided the desired cascade precursor 43 in ten steps from 56.

Scheme 12. Synthesis of EF diepoxy cascade precursor

Scheme 12: Synthesis of EF diepoxy cascade precursor

Initial attempts to promote the desired all-endo diepoxy cascade with BF$_3$*OEt$_2$ led to 23% isolated yield of the desired tricycle 41 (Table 1, entry 1). Attempts to improve the yield with alternative solvents, such as THF or MeCN, or alternative Lewis acids, such as Eu(OTf)$_3$ or Yb(OTf)$_3$, yielded similar results. The low yield of this process is ascribed to the sensitivity of the benzylidene acetal under the reaction conditions and the use of the alcohol trapping nucleophile, which could cyclize prior to bicyclo[4.1.0] epoxonium formation, similar to the ABC fragment (Scheme 11). CSA was found to provide similar yields, suggesting the choice of acid catalyst is inconsequential to the outcome of the reaction (entry 2). Attempts to limit benzylidene acetal

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hydrolysis via silica gel promotion utilizing methodology developed by Dr. Aaron van Dyke for 6-endo selective cyclization of a similar epoxy alcohol provided only trace product (entry 3). Inspired by results from Inoue and coworkers (Scheme 15, eq 4),\textsuperscript{38} [Rh(CO)\textsubscript{2}Cl]\textsubscript{2} was found to also promote the desired transformation (entry 4). Although the yield was similar to previous conditions, the observation of a cleaner crude reaction mixture with less acetal hydrolysis, as well as 28% recovered diepoxide (43), suggested ample opportunity for reaction optimization.

**Table 1. Investigation of epoxide-opening cascade of vinyl epoxide 43**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>Temp</th>
<th>Yield (%)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BF\textsubscript{3}OEt\textsubscript{2} (10 mol %)</td>
<td>CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>−78 °C</td>
<td>23</td>
</tr>
<tr>
<td>2</td>
<td>CSA (10 mol %)</td>
<td>CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>rt</td>
<td>22</td>
</tr>
<tr>
<td>3</td>
<td>SiO\textsubscript{2} (50 mg/mg)</td>
<td>CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>rt</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>[Rh(CO)\textsubscript{2}Cl]\textsubscript{2} (5 mol %)</td>
<td>THF</td>
<td>rt</td>
<td>21$^b$</td>
</tr>
</tbody>
</table>

$^a$isolated yield. $^b$28% of 43 was also recovered.

**D. A New Approach to Endo-Selective Epoxide-Opening Cascades via [Rh(CO)\textsubscript{2}Cl]\textsubscript{2} Catalysis**

The initial results catalyzing an epoxide-opening cascade with [Rh(CO)\textsubscript{2}Cl]\textsubscript{2} prompted us to rethink our approach to the diepoxide cascades. Rather than utilizing traditional Lewis acid catalysis, which does not readily discriminate between epoxides beyond minor differences in Lewis basicity, we sought to explore the potential of transition metal catalysis to selectively activate an alkenyl epoxide,\textsuperscript{39} initiating the cascade in a site-selective fashion. Our design is depicted in Scheme 13 and can be summarized as follows: incorporation of an electronically tailored alkene at the distal epoxide would provide a specific site for complexation and activation by a transition metal (61 to 62). Activation would be selective for the C–O bond closest to the alkene, providing high endo-selectivity in the subsequent bicyclo[4.1.0] epoxonium formation (63). The remainder


\textsuperscript{39} For a recent review on alkenyl epoxides in organic synthesis, see: He, J.; Ling, J.; Chiu, P. *Chem. Rev.* 2014, 114, DOI: 10.1021/cr400709j
of the cascade would be subject to previously observed endo versus exo selectivities in epoxide-opening cascades (63 to 64), as proposed by McDonald and further elaborated by Floreancig and Houk.  

Scheme 13. Substrate and promoter combination designed for selective initiation of all-endo epoxide-opening cascades.

The concept of site-selective initiation of cascades has rich precedence, such as in the synthesis of sterols in which epoxides and allylic alcohols are used as orthogonal initiators of polyene cyclizations. Methods for site-selective epoxide-opening cascade initiation have been reported, resulting in cascades yielding oxepane-containing products. Floreancig and Houk reported oxidative generation of an oxocarbenium intermediate, which upon trapping of the nearest epoxide initiates the cascade (Scheme 14, eq 1). The oxocarbenium ion is generated under neutral conditions via photochemical initiated electron transfer, limiting indiscriminate epoxide activation. By varying the number, spacing, substitution, and stereochemistry of the epoxides, Floreancig and Houk were able to compare selectivity and efficiency of epoxide-opening cascades. Computational modeling provided further insight into the regioselectivity observed in openings of bicyclo[4.1.0]epoxoniums, providing additional support for the desired endo-selectivity in trapping of our proposed epoxonium (63 to 64) for our proposed epoxide-opening cascades.

Selective activation of a distal alkene and subsequent intramolecular trapping of an epoxide has also seen success as a method for selective cascade initiation. For example, in Holton’s synthesis of hemibrevetoxin B, a distal alkene was activated via an electrophilic selenium

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reagent, initiating an epoxide-opening cascade in high yield (Scheme 14, eq 2).\textsuperscript{42} An additional example of this strategy is the total synthesis of the bromotriterpene ent-dioxepandehydrothyrsiferol via a bromonium-initiated epoxide-opening cascade from our lab (Scheme 14, eq 3).\textsuperscript{43} Utilizing N-bromosuccinimide to initiate the cascade, the tricyclic fragment 70 was rapidly formed from triepoxy-alkene precursor 69, utilizing the inherent methyl directing groups to control epoxide-opening regioselectivity.

**Scheme 14.** Previous work demonstrating examples of site-selective initiation of epoxide-opening cascades

With the previous examples of site-selective activation as inspiration, we hoped to develop the combination of an alkenyl epoxide and a transition metal catalyst to develop further this area of research. Specifically, we planned to use a transition metal to selectively activate alkenyl epoxides for nucleophilic attack, as this concept has excellent and diverse precedents. Although Pd catalysis is the most well known,\textsuperscript{44} we eschewed this path because of the limited examples of oxygen


nucleophiles in this context and, more importantly, the likelihood that an undesired stereochemical outcome would be observed, i.e., net retention (double inversion) at the site of epoxide opening, rather than the necessary inversion of configuration.

In contrast, [Rh(CO)₂Cl]₂ has been shown to catalyze openings of alkenyl epoxides with inversion. Berchtold observed that highly activated arene oxides (71) with [Rh(CO)₂Cl]₂ in MeOH gave a moderate yield of 74, corresponding to opening and net inversion by MeOH at the more electronically stabilized position (Scheme 15, eq 1).⁴⁵ Further work by Fangou and Lautens led to the development of [Rh(CO)₂Cl]₂ as a catalyst for regio- and stereo-selective intermolecular opening of trans-epoxides with alcohols and anilines, utilizing a variety of alkene stabilizing groups, such as styrenes, alkyl-substituted alkenes, and enoates, (eq 2).⁴⁶ [Rh(CO)₂Cl]₂ was shown to also be a competent catalyst for cyclizations of trans-disubstituted enolate epoxy-alcohols and carbamates (78a-e) to provide five- and six-membered saturated heterocycles (79a-e, eq 3) by Ha and coworkers.⁴⁷ Lastly, Inoue observed that [Rh(CO)₂Cl]₂ catalyzed the cyclization of epoxy alcohol 80 with limited acetal hydrolysis, whereas PPTS activation caused significant acetal cleavage (eq 4).³⁸ Prior to our investigations, however, no examples of oxepane formation via [Rh(CO)₂Cl]₂, activation of trisubstituted epoxides, or use in initiation of epoxide-opening cascades had been reported.

Scheme 15. Previous work utilizing [Rh(CO)\(_2\)Cl\(_2\)] as a site-selective activator for epoxide-opening with alcohols.

Berchtold, 1977

(1) \[
\begin{align*}
\text{Scheme 15. Previous work utilizing [Rh(CO)\(_2\)Cl\(_2\)] as a site-selective activator for epoxide-opening with alcohols.}
\end{align*}
\]

Fagnou and Lautens, 2000

(2) \[
\begin{align*}
\text{Scheme 15. Previous work utilizing [Rh(CO)\(_2\)Cl\(_2\)] as a site-selective activator for epoxide-opening with alcohols.}
\end{align*}
\]

Ha, 2004

(3) \[
\begin{align*}
\text{Scheme 15. Previous work utilizing [Rh(CO)\(_2\)Cl\(_2\)] as a site-selective activator for epoxide-opening with alcohols.}
\end{align*}
\]

Inoue, 2007

(4) \[
\begin{align*}
\text{Scheme 15. Previous work utilizing [Rh(CO)\(_2\)Cl\(_2\)] as a site-selective activator for epoxide-opening with alcohols.}
\end{align*}
\]

With these precedents in mind, we returned to the EF fragment of (−)-brevisin, investigating the use of an enoate as the activating group of the distal epoxide, used in both reports of epoxy alcohol cyclizations catalyzed by [Rh(CO)\(_2\)Cl\(_2\)] (Scheme 16). From epoxy alcohol 59 in our previous synthetic route (Scheme 12), alcohol oxidation and stabilized-Wittig olefination installed the desired epoxy enoate functionality (82). Asymmetric Shi epoxidation and TBAF desilylation provided the desired cascade precursor 83.
Scheme 16. Synthesis of EF diepoxy enoate cascade precursor

Investigation of cascade promoters for diepoxy alcohol 83 containing an (E)-enoate revealed [Rh(CO)₂Cl]₂ to be a highly chemo-, stereo-, and regioselective promoter. For example, [Rh(CO)₂Cl]₂ catalyzed the regioselective epoxide-opening cascade of (E)-enoate-diepoxy alcohol 83 to provide the desired product 84 in 38% isolated yield (Table 2, entry 1). Exploration of a variety of solvents found that CH₂Cl₂, toluene, and Et₂O provided similar yields as THF. TFE and HFIP provided complex mixtures, while acetonitrile and hexanes led to significant recovery of starting material. We were pleased to find use of 1,4-dioxane as the solvent and performing the reaction at elevated temperatures (65 °C) provided a slight increase to 45% yield (entry 3). A further improvement was observed by adding polymer-bound Ph₃P⁴⁸ at the end of the reaction to release the product from the residual Rh, boosting the isolated yield to 61% (entry 4), a three-fold increase relative to acid catalysis of vinyl diepoxide 43. Subjection of 83 to Lewis or Brønsted acid activation, provided none of the desired 84, again highlighting the selectivity of [Rh(CO)₂Cl]₂ catalysis with epoxy enoates (entries 5 and 6). The ester functional group appears to be critical to the success of the method. These results support the mechanistic hypothesis that Rh(I) activates alkenyl epoxides via π-coordination and oxidative addition of into the allylic C-O bond of the epoxide, which contrasts the generally non site-selective epoxide activation with Lewis acids. Importantly, these results represent the first examples of both a cascade process and a seven-membered ring formation using this method.

⁴⁸ See Section E, Table 3 for discussion of polymer-bound Ph₃P for improvement of product isolation.
Following identification of the enoate as the ideal activating group, a streamlined synthesis to 83 was developed (Scheme 17). Olefination of 58 with phosphonate 85\(^{49}\) provides triene 86,\(^{50}\) and subsequent asymmetric Shi epoxidation and TBAF desilylation provides cascade precursor 83. The low yield of the epoxidation is due to the reduced reactivity of the dienoate, and is improved with resubjection of the crude reaction mixture to the standard conditions. Post-cyclization, the enoate was readily converted to a vinyl substituent via a two step sequence of ozonolysis and Wittig methylation to provide 41, intercepting the previously synthesized EF ring fragment of (−)-brevisin in 12 steps LLS, compared to 13 LLS in the Tachibana synthesis and 16 LLS for our previous route.

\(^{49}\) The phosphonate ester was prepared in two steps by the literature method: Mitton-Fry, M. J.; Cullen, A. J.; Sammakia, T. Angew. Chem., Int. Ed. 2007, 46, 1066.

Scheme 17. Streamlined synthesis to EF-diepoxyl alcohol 83 and completion of EF fragment synthesis

\[
\text{O} \quad \text{Me} \quad \text{H} \quad \text{H} \\
\text{TBSO} \quad \text{58} \quad \text{EtO} \quad \text{85} \quad \text{LDA, THF, -78 °C to rt} \\
\text{2:1 E/Z 84%} \\
\text{Me} \quad \text{O} \quad \text{Me} \quad \text{H} \quad \text{H} \\
\text{TBSO} \quad \text{86} \quad \text{Me} \quad \text{EtO} \quad \text{H} \\
\text{83} \\
\text{EtO} \quad \text{O} \quad \text{Ph} \quad \text{[Rh(CO)\textsubscript{2}C]} \quad \text{(5 mol %).} \\
1. (-)-51, Oxone, Bu\textsubscript{4}NHSO\textsubscript{4}, K\textsubscript{2}CO\textsubscript{3}, pH 10.5, DMM/CH\textsubscript{3}CN, 22% \\
2. TBAF, THF, 69%
\]

E. Model Studies of Epoxy Alcohol Cyclizations Catalyzed by [Rh(CO)\textsubscript{2}Cl\textsubscript{2}]

With the success of the epoxide-opening cascade toward the EF fragment, we sought to explore the limits of [Rh(CO)\textsubscript{2}Cl\textsubscript{2}] catalysis for epoxy alcohol cyclization with respect to ring size and investigate the epoxide substitution patterns found in the proposed (-)-brevisin cascades. We were especially interested in distal-methyl trisubstituted epoxides, as we hoped to use the [Rh(CO)\textsubscript{2}Cl\textsubscript{2}] methodology in the synthesis of the ABC tricycle. The difficulty of oxepane synthesis via acid-catalyzed epoxy alcohol cyclization and the lack of any epoxy alcohol methodology towards oxocanes (8-membered oxygen heterocycles) also piqued our interest.

With these goals in mind, we undertook the synthesis of epoxy alcohol model systems 92a,b (Scheme 18). Starting from mono-TBDPS protected diols 87a,b, tandem alcohol oxidation and stabilized-Wittig olefination provided the desired trans-enoates 88a,b. DIBAL-H reduction of the ester and mCPBA epoxidation provided epoxy alcohol 90a,b. Finally, a second alcohol oxidation and in situ stabilized-Wittig olefination followed by TBAF desilylation affords the desired enoate-epoxy alcohols (92a,b) for our model studies. While this route requires two sequential homologation steps relative to the streamlined route utilized to afford the same substructure in Scheme 17, the products obtained in Scheme 18 are readily purified to >20:1 dr, free of cis-epoxide or cis-enoate by 'H NMR spectroscopy, simplifying analysis during cyclization studies.
Scheme 18. Synthesis of trans-disubstituted epoxy-alcohol for cyclization model studies

Our first attempts to cyclize epoxy-alcohol 92b to form oxepane 93b proved successful; however, we were puzzled by a low mass recovery, as the reaction appeared to produce no side products (Table 1, entry 1). We thought the Rh might be interfering with analysis, so we attempted to remove the Rh post-reaction by filtering through a silica gel plug, eluting with EtOAc to obtain the product (entry 2). While this improved the resolution of the 1H NMR, likely by removing Rh aggregates, the yield didn’t significantly improve. Next we screened additives to coordinate to the Rh, attempting to displace any bound product. While Ph₃P did increase the recovery of the product, it also hampered analysis by overlapping with the key enoate signals in the 1H NMR spectrum (entry 3). Switching to polymer-bound Ph₃P was the ideal solution, as seen in both the significant increase in product recovery and lack of other impurities in the 1H NMR spectrum (entry 4). Other readily available additives, such as pyridine, polymer-bound pyridine, Na₄EDTA, or florisil were inferior (entries 5-8). The identification of Ph₃P resin to isolate clean product significantly streamlined reaction optimization, and greatly assisted in our studies.
Table 3. Exploration of additives to remove rhodium impurities and improve product recovery from the cyclization of 92b

![Chemical structure of 92b, 93b, and 94b]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Rh removal additivea</th>
<th>NMR yield 93b (%)b</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None, no SiO₂ plug</td>
<td>69</td>
<td>poor resolution in ¹H NMR</td>
</tr>
<tr>
<td>2</td>
<td>SiO₂ plug only</td>
<td>76</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Ph₃P</td>
<td>83</td>
<td>significant Ph₃P overlap in ¹H NMR</td>
</tr>
<tr>
<td>4</td>
<td>Ph₃P polymer bound</td>
<td>91</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>pyridine</td>
<td>79</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>pyridine polymer bound</td>
<td>76</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>Na₄EDTA</td>
<td>62</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>florisil</td>
<td>66</td>
<td>-</td>
</tr>
</tbody>
</table>

a Added after complete consumption of SM, prior to filtering through SiO₂ plug with EtOAc.

b Yields determined by ¹H NMR spectroscopy.

Investigation of epoxy alcohol 92a is shown in Table 4. We found similar results as Ha reported with this substrate, observing near complete endo selectivity but with a slight increase in yield upon application of the Ph₃P resin (entries 1 and 2). Investigation of lower catalyst loading found that 1 mol % [Rh(CO)₂Cl]₂ produced full conversion, while 0.5 mol % only gave 60% conversion of 92a after 18 h. Finally, to explore the selectivity of the enoate activating group under traditional acid catalysis, we subjected 92a to CSA catalysis and observed a 1:1 endo to exo ratio, similar to the observations of Nicolaou with the methyl ester enoate. It should be noted alternative stabilizing groups, such as vinyl, provide complete endo selectivity under CSA catalysis; rather the comparison of [Rh(CO)₂Cl]₂ to CSA catalysis is primarily to assess if [Rh(CO)₂Cl]₂ is acting as a traditional Lewis acid via direct activation of the epoxide at oxygen or interacting with the substrate in a more elaborate manor.
Table 4. Cyclization of epoxy alcohol 92a

![Chemical structures and conditions]

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>solvent, temp</th>
<th>93a/94a endo/exo</th>
<th>yield 93a (%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b</td>
<td>[Rh(CO)₂Cl₂ (2 mol %)]</td>
<td>THF, rt</td>
<td>&gt;20 : 1</td>
<td>90</td>
</tr>
<tr>
<td>2c</td>
<td>[Rh(CO)₂Cl₂ (2.5 mol %)]</td>
<td>THF, rt</td>
<td>&gt;20 : 1</td>
<td>94</td>
</tr>
<tr>
<td>3</td>
<td>(±)-CSA (10 mol %)</td>
<td>CH₂Cl₂, rt</td>
<td>1 : 1</td>
<td>50</td>
</tr>
</tbody>
</table>

a Isolated yield. b Ref. 47. c Polymer-bound Ph₃P resin added at completion of reaction.

Returning to epoxy alcohol 92b for the synthesis of oxepane 93b, we found 5 mol % [Rh(CO)₂Cl₂] loading to provide the desired product in high yield and selectivity (Table 5, entry 1). Attempts to lower the catalyst loading in THF or a variety of other solvents provided only partial conversion, attesting to the longer tether and ring strain for formation of oxepane 93b versus THP 93a. This is also seen in the results of CSA catalysis, which demonstrated lower regioselectivity and yields as compared to 92a (entry 2). Of note, however, is constant high regioselectivity and yield afforded by [Rh(CO)₂Cl₂] as compared to the further erosion in selectivity provided by traditional acid catalysis.

Table 5. Comparison of activation methods for cyclization of epoxy alcohol 92b

![Chemical structures and conditions]

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>solvent, temp</th>
<th>93b/94b endo/exo</th>
<th>yield 93b (%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[Rh(CO)₂Cl₂ (5 mol %)]</td>
<td>THF, rt</td>
<td>&gt;20 : 1</td>
<td>81</td>
</tr>
<tr>
<td>2</td>
<td>(±)-CSA (100 mol %)</td>
<td>CH₂Cl₂, rt</td>
<td>1 : 3</td>
<td>21</td>
</tr>
</tbody>
</table>

a Isolated yield.
With successful synthesis of oxepanes with this methodology, we next attempted to form oxocanes, or 8-membered oxygen heterocycles, via epoxy-alcohol cyclizations. Unfortunately, all attempts to promote endo-selective cyclization of epoxy alcohol 92c led to complex mixtures of more polar products (Scheme 19). Our attempts to improve the reaction by increasing the catalyst loading, cooling or heating the reaction mixture, use of alternative solvents, high dilution, or even slow reverse addition of substrate to catalyst failed to provide oxocane 93c. Our hypothesis for the stark difference between the cyclization of 92b and 92c is the increase in the tether and ring strain of the oxocane product are reflected in a preference toward many alternative pathways, overwhelming the desired pathway. Oligomerization and epoxide rearrangements are likely the major products, although none could be isolated in pure form for structural elucidation.

Scheme 19. Attempted cyclization of epoxy alcohol 92c for oxocane synthesis

Following the successful formation of oxepanes from endo-selective epoxide opening cyclizations and cascades of trans-disubstituted epoxides, we next looked to the proposed ABC diepoxide opening cascade. We hoped the combination of the enoate directing group and [Rh(CO)2Cl]2 catalysis would provide site-selective initiation of the desired cascade (Scheme 20). However, given the lack of precedence for methyl substitution on the epoxide neighboring the enoate coupled with the complexity of the synthesis of 95, we decided to pursue model studies to explore the ability and efficiency of [Rh(CO)2Cl]2 to promote endo-selective cyclization. Synthesis of the necessary substrates is shown in Scheme 21. Beyond utilizing an alternative phosphorane in the first homologation, substrate synthesis followed as described for the disubstituted-epoxide substrates.
Scheme 20. Proposed second-generation cascade toward ABC tricycle

![Scheme 20](image)

Can [Rh(CO)_2Cl]_2 tolerate methyl substitution?

Scheme 21. Synthesis of distal-methyl (E)-trisubstituted epoxy-alcohol for model studies

![Scheme 21](image)

Critical to the success of this method for the synthesis of the ABC tricycle of (-)-brevisin, distal methyl substitution was well tolerated under [Rh(CO)_2Cl]_2 promotion, providing complete endo selectivity for the synthesis of both tetrahydropyran (101a) and oxepane (101b) from epoxy alcohols 100a and 100b respectively (Table 6, entries 1 and 3). Of particular note, these substrates tolerated lower catalyst loadings than the disubstituted epoxide substrates, suggesting the addition of the distal methyl group might be beneficial. In comparison, promotion with (+)-CSA yielded a mixture of endo- and exo-products, albeit with a slight improvement in regioselectivity compared to disubstituted epoxides 92a and 92b (entries 2 and 4).
Comparison of activation methods for cyclization of trisubstituted epoxy alcohols 100a and 100b

![Diagram of epoxy alcohols and cyclization products]

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>catalyst</th>
<th>solvent, temp</th>
<th>101 / 102</th>
<th>yield 101 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100a</td>
<td>[Rh(CO)₂Cl₂] (1 mol %)</td>
<td>THF, rt</td>
<td>&gt;20 : 1</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>100a</td>
<td>(±)-CSA (10 mol %)</td>
<td>CH₂Cl₂, rt</td>
<td>3.4 : 1</td>
<td>69</td>
</tr>
<tr>
<td>3</td>
<td>100b</td>
<td>[Rh(CO)₂Cl₂] (2.5 mol %)</td>
<td>THF, rt</td>
<td>&gt;20 : 1</td>
<td>88</td>
</tr>
<tr>
<td>4</td>
<td>100b</td>
<td>(±)-CSA (100 mol %)</td>
<td>CH₂Cl₂, rt</td>
<td>1 : 1.8</td>
<td>43</td>
</tr>
</tbody>
</table>

a Isolated yield.

Following the successful endo-selective cyclizations of the distal-methyl epoxides 100a and 100b, we investigated the synthesis of oxocanes utilizing the trisubstituted-epoxides, subjecting epoxy alcohol 100c to [Rh(CO)₂Cl₂] catalysis (Table 7). The crude reaction mixtures obtained were not as pristine as for the smaller ring products, but we were able to isolate small quantities of oxocane 101c, along with diene 103, ketone 104, and diene-diol 105. Preforming the reaction at elevated or reduced temperatures did not improve the yield significantly, but did impact side product formation. Attempts to use either CH₂Cl₂ or 1,4-dioxane as the reaction solvent did not yield any of the desired oxocane (101c). Running the reaction at a lower concentration or utilizing a reverse addition procedure resulted in decreased conversion and lower yields. In comparison, activation with CSA provided diene-diol 105 as the exclusive product. Although limited examples of benzo-oxocane synthesis by endo-selective epoxy alcohol cyclization are known, to the best of our knowledge this work represents the first isolated oxocane synthesized via an endo-selective epoxy alcohol cyclization. Additionally, these results are

51 Formation of side products by net deoxygenation (103) or 1,2 hydride shifts (104) have been reported previously by Berchtold (see ref 41.)

especially intriguing for possible application towards the synthesis of oxocanes found in marine ladder polyethers, such as brevetoxin A (2).

**Table 7.** Oxocane formation and product distribution from cyclization attempts of epoxy alcohol **100c**.

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>solvent, temp</th>
<th>yield (%)</th>
<th>101c</th>
<th>103</th>
<th>104</th>
<th>105</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[Rh(CO)₂Cl]₂ (10 mol %)</td>
<td>THF, rt</td>
<td>17</td>
<td>17</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>[Rh(CO)₂Cl]₂ (20 mol %)</td>
<td>THF, 4 °C</td>
<td>19</td>
<td>21</td>
<td>-</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>(+)-CSA (100 mol %)</td>
<td>CH₂Cl₂, rt</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>62</td>
<td></td>
</tr>
</tbody>
</table>

* Isolated yield.

**F. Synthesis of the (−)-Brevisin ABC tricycle**

Following the success of the model studies, we resumed efforts towards a formal synthesis of the ABC tricycle of (−)-brevisin (40). Our revised retrosynthetic analysis is shown in Scheme 22. We planned to use the combination of [Rh(CO)₂Cl]₂ catalysis and an enoate directing group as described previously in Scheme 20 to effect the desired all-endo epoxide-opening cascade of diepoxide 95, key to our formal synthesis. Revisiting our previous efforts (Scheme 10), we wanted to improve the low yield and stereoselectivity of the cross metathesis to synthesize alkene 50 to ensure sufficient material throughput to explore the cascade.
Scheme 22. Revised retrosynthetic analysis of ABC tricycle 40

![Chemical structure](image)

Synthesis of trisubstituted alkenes via cross metathesis of α-olefins and geminal disubstituted alkenes has seen limited success in comparison to cross metathesis to generate 1,2 disubstituted alkenes. Grubbs demonstrated the ability of Ru alkylidene 49 to promote cross metathesis of simple α-olefins with geminal disubstituted alkenes. From our attempts to couple 46 and 48, we observed full conversion of 46, leading us to suspect our low yields were from significant non-productive cross metathesis events such as homo-dimerization of 46 (Table 8, entries 1–3). Further work by Grubbs suggested modification to the NHC ligand could reduce non-productive metathesis events by utilizing catalyst 108. However, application of 108 did not lead to improvement in yield (entry 4).

Motivated by reports of higher yields in cross metathesis of allyl groups with increased steric hindrance, alkene 107 was prepared from 46 via cross metathesis with 2-methyl-2-butene (Scheme 23). Metathesis of 48 and trisubstituted alkene 107 provided a significantly higher yield, particularly when performed in the absence of additional solvent (Table 8, entries 5-8). The significant improvement in yield is thought to result from a decrease of non-productive cross metathesis events, such as homo-dimerization and methylene exchange, by increasing the steric match of the alkylidene and incoming metathesis partner. Despite the modest stereoselectivity, the 2:1 E/Z mixture of alkene isomers could be enriched to 10:1 E/Z by repeated careful column chromatography.

56 Concurrent with our studies, a similar report was published with mechanistic experiments to support these hypotheses: Z. J.; Jackson, W. R.; Robinson, A. J. Org. Lett. 2013, 15, 3006.
Table 8. Optimization of cross metathesis to synthesize trisubstituted alkene 50

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Eq. 48</th>
<th>Solvent</th>
<th>Yield 50 (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>E/Z</th>
<th>rsm (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>46</td>
<td>1</td>
<td>toluene</td>
<td>22</td>
<td>nd</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>46</td>
<td>3</td>
<td>&quot;</td>
<td>29</td>
<td>nd</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>46</td>
<td>1.2</td>
<td>&quot;</td>
<td>34</td>
<td>nd</td>
<td>-</td>
</tr>
<tr>
<td>4&lt;sup&gt;b&lt;/sup&gt;</td>
<td>46</td>
<td>1.5</td>
<td>DCE</td>
<td>31</td>
<td>nd</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>107</td>
<td>2</td>
<td>toluene</td>
<td>54</td>
<td>2:1</td>
<td>39</td>
</tr>
<tr>
<td>6</td>
<td>107</td>
<td>2</td>
<td>neat</td>
<td>90&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2:1</td>
<td>9&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>7&lt;sup&gt;d&lt;/sup&gt;</td>
<td>107</td>
<td>2</td>
<td>neat</td>
<td>89&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2:1</td>
<td>8&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>8</td>
<td>107</td>
<td>2</td>
<td>neat</td>
<td>78</td>
<td>2:1</td>
<td>7</td>
</tr>
</tbody>
</table>

<sup>a</sup>Isolated yield. <sup>b</sup>Reaction run with catalyst 108. <sup>c</sup>Yields determined by <sup>1</sup>H NMR spectroscopy. <sup>d</sup>Reaction run under static vacuum of 30 torr.

Scheme 23. Synthesis of trisubstituted alkene 107

The enoate directing group was installed by desilylation of 50, alcohol oxidation, and in situ stabilized-Wittig olefination (109, Scheme 24). Asymmetric Shi epoxidation, followed by acetate ethanolysis provided the diepoxide cascade precursor 95. We utilized a guanidine-based buffer made in-situ from NaOEt and the guanidine·HCl, as attempts with K<sub>2</sub>CO<sub>3</sub> in ethanol yielded significant amounts of product representing spontaneous cyclization of the first epoxide.
Scheme 24. Completion of the ABC tricycle synthesis

Exposure of diepoxide 95 to catalytic \([\text{Rh}(\text{CO})_2\text{Cl}]_2\) at ambient temperature in THF led to full conversion and 78% yield of the desired ABC tricycle (106). Efforts directed toward lowering the catalyst loading (5 or 2 mol %) led to inferior yields. Unlike the monocyclic products from the model studies, the product of the cascade is a fused tricycle, locking the enoate and pendant alcohol into pseudo-equatorial conformations. We presume this conformation to have a higher affinity for the active rhodium species, slowing turnover. Additionally, we observed Brønsted acid promotion with (±)-CSA did not provide any desired product, further differentiating \([\text{Rh}(\text{CO})_2\text{Cl}]_2\) from acid promoted conditions.

Following the success of the cascade, completion of formal synthesis of (−)-brevisin required protection of the A- and C-ring hydroxyls as benzyl ethers and cleavage of the enoate to provide the desired methylene alcohol functional group. Bis-benzylation of 106 under gentle heating proceeded smoothly to provide 110. Our first attempts to oxidatively cleave enoate 110 via ozonolysis with subsequent reductive quenching with NaNBH₄ yielded only small amounts of the desired formal synthesis intermediate (40), with what appeared to be significant amounts of oxidation of benzyloxy to benzoate groups. With limited quantities of 110, we synthesized 111 for model studies to allow rapid screening of oxidation conditions (Scheme 25).
Attempts to limit undesired benzyl oxidation by reverse addition of a saturated O₃ solution in CH₂Cl₂, or use of Ph₃P to first provide an aldehyde saw no improvement in product yield. The combination of low yields and difficulty obtaining high purity product prompted us to explore an alternative sequence of dihydroxylation, oxidative diol cleavage, and reduction. Dihydroxylation of 111, followed by periodate cleavage and subsequent reduction with NaBH₄ provided the desired alcohol (112). In addition to the moderate yield of 112, a significant side product was observed: diol 113. We reasoned the acidic nature of NaIO₄ was resulting in opening the oxepane, with subsequent oxidative cleavage yielding a ketone and ultimately producing diol 113. Use of a neutral diol oxidative cleavage reagent, Ph₃BiCO₃, provided the desired 112 in 75% yield.⁵⁷ Application of this three-step sequence to tricycle 110 provided 40 in high purity and 60% yield over three steps.

Scheme 25. Model studies of enoate oxidative cleavage and application of improved sequence to the synthesis of ABC tricycle

In summary, the synthesis of the ABC tricycle intercept 40 was completed in 18 steps LLS compared to the previously reported 17 steps LLS by Tachibana and coworkers. Our synthesis features a highly selective epoxide opening cascade to synthesize the fully elaborated B and C rings in a single step. Additionally, the improvement of the fragment coupling via cross metathesis of a trisubstituted alkene streamlined the synthesis, allowing rapid access to the cascade precursor.

G. Conclusion

In conclusion, we have completed a formal synthesis of (-)-brevisin (34) utilizing \([\text{Rh(CO)}_2\text{Cl}]_2\) catalysis to selectively initiate diepoxide cascades as the key step in each fragment. During the course of this study, we have shown the combination of an enoate group and \([\text{Rh(CO)}_2\text{Cl}]_2\) catalysis is effective not only for the synthesis of 6-, 7, and 8-membered oxygen heterocycles from epoxy alcohols bearing a variety of substitution patterns (Tables 4–7), but also cascades of diepoxides where control of the sequence of epoxide opening events is tantamount to success (Table 3; Scheme 24). In comparison to the first generation approach utilizing Lewis acid catalysis, the high yield, stereospecificity, functional group compatibility, and endo-selectivity make this approach particularly well suited for target-directed synthesis, as highlighted by the synthesis of the ABC and EF fragments of (-)-brevisin.
H. General Experimental

All reactions were performed under an atmosphere of argon under anhydrous conditions, unless otherwise noted. Dichloromethane, tetrahydrofuran (THF), Et₂O, benzene, dioxane and triethylamine were purified via an SG Water USA solvent column system. Unless otherwise noted, all reagents were commercially obtained and used without further purification. Analytical thin layer chromatography (TLC) was performed using EM Science silica gel 60 F₂₅₄ plates, visualizing with a UV lamp (254 nm), KMnO₄, p-anisaldehyde, or CAM. Liquid chromatography was performed using forced flow (flash chromatography) of the indicated solvent system on Silicycle silica gel (230-400 mesh) or Biotage® Isolera flash purification system on SNAP HP-SIL columns.

¹H NMR and ¹³C Nuclear Magnetic Resonance (NMR) spectra were recorded at ambient temperature at 600 MHz and 150 MHz, respectively, using a Bruker AVANCE-600 spectrometer or 500 MHz and 125 MHz, respectively, using a Varian Inova-500 spectrometer. The ¹H NMR data are reported as follows: chemical shift in parts per million (ppm) from an internal standard of residual CHCl₃ in CDCl₃ (7.27 ppm) on the d scale, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants in hertz (Hz), and integration (H). Chemical shifts of ¹³C NMR spectra are reported in ppm from the central peak of CDCl₃ (77.2 ppm).

Infrared (IR) spectra were recorded on a Perkin-Elmer Model 2000 FT-IR or an Agilent Cary 630 FTIR Spectrometer. High-resolution mass spectra (HR-MS) were acquired on a Bruker Daltronics APEXIV 4.7 Tesla Fourier Transform Ion Cyclotron Resonance Mass Spectrometer at the Massachusetts Institute of Technology Department of Chemistry Instrumentation Facility.

Optical rotations were measured using a Jasco Model 1010 digital polarimeter at 589 nm and calculated using the formula: [α]D = αdeg/(l(c/1000)), where c = (g of substrate/100 mL of solvent) and l = 1 dm.

Enoate 88a: To a solution of TBDPS-protected alcohol 87a (2.0 g, 6.09 mmol) in CH₂Cl₂ (61 mL) was added DMSO (6.1 mL, 85.9 mmol) and Et₃N (4.3 mL, 30.5 mmol), cooled to 0 °C, and PyrSO₃ (1.94 g, 12.2 mmol) added as a solid. The reaction was allowed to warm to room temperature and stirred for 3 h. At this point, (carbethoxymethylene)triphenylphosphorane (4.25 g, 12.2 mmol) was added as a solid at room temperature and stirred for 30 min. The reaction was quenched by addition of H₂O (35 mL) and diluted with CH₂Cl₂ (35 mL). The aqueous layer was separated and extracted twice with CH₂Cl₂ (20 mL each). The combined organics were washed with H₂O (20 mL), sat. NaCl (20 mL), dried over Na₂SO₄, filtered and concentrated in vacuo to afford crude enoate 88a as a yellow oil. The crude product was purified by flash chromatography (5% EtOAc in hexanes to 10% EtOAc in hexanes) to afford 88a as a colorless oil (2.24 g, 5.67 mmol, 93%, 95:5 E/Z). The product could be purified further by MPLC (Biotage Ultra Column) with a gradient of solvents (100% hexanes to 6% EtOAc in hexanes) to afford 88a as only the E alkene (1.98 g, 82%).

Data were consistent with those reported by Beauchemin and coworkers.⁵⁹

\[\text{'H NMR (500 MHz, CDCl}_3\): } \delta 7.69-7.67 (m, 4H), 7.45-7.39 (m, 6H), 7.00 (dt, \textit{J} = 15.6, 6.9 Hz, 1H), 5.84 (dt, \textit{J} = 15.6, 1.6 Hz, 1H), 4.21 (q, \textit{J} = 7.1 Hz, 2H), 3.70 (t, \textit{J} = 6.1 Hz, 2H), 2.39-2.31 (m, 2H), 1.78-1.69 (m, 2H), 1.31 (t, \textit{J} = 7.1 Hz, 3H), 1.07 (s, 9H).\]

\[\text{'C NMR (100 MHz, CDCl}_3\): } \delta 166.8, 149.1, 135.7, 134.0, 129.8, 127.8, 121.7, 63.1, 60.3, 31.1, 28.8, 27.0, 19.4, 14.5.\]

IR (thin film): 3069, 2933, 2858, 1718, 1654, 1472, 1427, 1265, 1203, 1105, 1041 cm\(^{-1}\).

HR-MS (DART) \textit{m/z} calcd for C\(_{24}\)H\(_{32}\)O\(_3\)Si (M+NH\(_4\))\(^+\): 414.2459, found 414.2460.

![Enoate 88b](image)

\textbf{Enoate 88b:} To a solution of TBDPS-protected alcohol 87b\(^8\) (2.50 g, 7.30 mmol) in CH\(_2\)Cl\(_2\) (73 mL) was added DMSO (7.3 mL, 0.10 mol) and Et\(_3\)N (5.1 mL, 36.5 mmol), cooled to 0 °C, and Pyr•SO\(_3\) (2.32 g, 14.6 mmol) added as a solid. The reaction was allowed to warm to room temperature and stirred for 3h. At this point, (carbethoxymethylene)triphenylphosphorane (5.1 g, 14.6 mmol) was added as a solid at room temperature and stirred for 30 min. The reaction was quenched by addition of H\(_2\)O (50 mL) and diluted with CH\(_2\)Cl\(_2\) (50 mL). The aqueous layer was separated and extracted twice with CH\(_2\)Cl\(_2\) (30 mL each). The combined organics were washed with H\(_2\)O (50 mL), sat. NaCl\(_{aq}\) (50 mL), dried over Na\(_2\)SO\(_4\), filtered and concentrated \textit{in vacuo} to afford crude enoate 88b as a yellow oil. The crude product was purified by flash chromatography (5% EtOAc in hexanes to 10% EtOAc in hexanes) to afford 88b as a colorless oil (2.68 g, 6.53 mmol, 89%, 95:5 E/Z). The product was purified further by flash chromatography with a gradient of solvents (100% hexanes to 3% EtOAc in hexanes) to afford 88b enriched to 98:2 E/Z (1.20 g, 40%).

\[\text{'H NMR (500 MHz, CDCl}_3\): } \delta 7.69-7.67 (m, 4H), 7.45-7.38 (m, 6H), 6.97 (dt, \textit{J} = 15.6, 6.9 Hz, 1H), 5.81 (dt, \textit{J} = 15.6, 1.5 Hz, 1H), 4.20 (q, \textit{J} = 7.1 Hz, 2H), 3.68 (t, \textit{J} = 5.9 Hz, 2H), 2.20 (qd, \textit{J} = 7.1, 1.3 Hz, 2H), 1.63-1.55 (m, 4H), 1.31 (t, \textit{J} = 7.1 Hz, 3H), 1.06 (s, 9H).\]

\[\text{'C NMR (125 MHz, CDCl}_3\): } \delta 166.9, 149.4, 135.7, 134.1, 129.7, 127.8, 121.5, 63.6, 60.3, 32.11, 32.05, 27.0, 24.5, 19.4, 14.5.\]

IR (thin film): 3069, 2932, 2858, 1719, 1653, 1473, 1428, 1265, 1195, 1159, 1108, 1043 cm\(^{-1}\).

HR-MS (DART) \textit{m/z} calcd for C\(_{25}\)H\(_{34}\)O\(_3\)Si (M+NH\(_4\))\(^+\): 428.2615, found 428.2617.
Alcohol 89a: To a solution of enoate 88a (1.97 g, 4.97 mmol) in CH₂Cl₂ (20 mL) at -78 °C was added DIBAL-H (1.0 M in CH₂Cl₂, 17.4 mL, 17.4 mmol) dropwise over three min. The reaction was stirred for 20 min, and then quenched by slow addition of MeOH (5 mL) at -78 °C. The reaction mixture was then poured into an Erlenmeyer flask containing sat. aq. Rochelle’s salt (150 mL) and stirred vigorously for 2 h at room temperature. The aqueous layer was separated and extracted with CH₂Cl₂ (2x20 mL). The combined organics were dried over MgSO₄, filtered and concentrated in vacuo to afford crude alcohol 89a as a colorless oil. The crude product was purified by flash chromatography (10% EtOAc in hexanes to 35% EtOAc in hexanes) to afford 89a as a colorless oil (1.59 g, 4.48 mmol, 90%).

1H NMR (500 MHz, CDCl₃): δ 7.71-7.70 (m, 4H), 7.47-7.39 (m, 6H), 5.72-5.62 (m, 2H), 4.09-4.07 (br, 2H), 3.71 (t, J = 6.3 Hz, 2H), 2.18 (q, J = 6.9 Hz, 2H), 1.69 (quint, J = 7.1 Hz, 2H), 1.48-1.44 (br, 1H), 1.09 (s, 9H).

13C NMR (125 MHz, CDCl₃): δ 135.7, 134.1, 132.9, 129.7, 129.4, 127.8, 63.9, 63.3, 32.1, 28.6, 27.0, 19.4.

IR (thin film): 3325, 3068, 2932, 2857, 1670, 1589, 1472, 1389, 1361, 1105, 998, 967 cm⁻¹.

HR-MS (DART) m/z calcd for C₂₂H₃₄O₂Si (M+NH₄)⁺: 372.2353, found 372.2346.

Alcohol 89b: To a solution of enoate 88b (1.20 g, 2.92 mmol) in CH₂Cl₂ (12 mL) at -78 °C was added DIBAL-H (1.0 M in CH₂Cl₂, 10.5 mL, 10.5 mmol) dropwise over three min. The reaction was stirred for 25 min, and then quenched by slow addition of MeOH (3 mL) at -78 °C. The reaction mixture was then poured into an Erlenmeyer flask containing sat. aq. Rochelle’s salt (100 mL) and stirred vigorously for 2 h at room temperature. The aqueous layer was separated and extracted with CH₂Cl₂ (2x20 mL). The combined organics were dried over MgSO₄, filtered and concentrated in vacuo to afford crude alcohol 89b as a colorless oil. The crude product was purified by flash chromatography (10% EtOAc in hexanes to 35% EtOAc in hexanes) to afford 89b as a colorless oil (1.02 g, 2.77 mmol, 94%).

1H NMR (500 MHz, CDCl₃): δ 7.70-7.68 (m, 4H), 7.46-7.38 (m, 6H), 5.72-5.60 (m, 2H), 4.10 (br, 2H), 3.68 (t, J = 6.4 Hz, 2H), 2.06 (q, J = 6.9 Hz, 2H), 1.59 (dq, J = 8.7, 6.1 Hz, 2H), 1.51-1.45 (m, 2H), 1.35 (br, 1H), 1.07 (s, 9H).

13C NMR (125 MHz, CDCl₃): δ 135.7, 134.2, 133.4, 129.7, 129.2, 127.8, 63.98, 63.89, 32.20, 32.08, 27.0, 25.5, 19.4.

IR (thin film): 3324, 3057, 2931, 2859, 1669, 1590, 1472, 1428, 1389, 1105 cm⁻¹.

HR-MS (DART) m/z calcd for C₂₃H₃₂O₂Si (M+NH₄)⁺: 386.2510, found 386.2520.
Epoxide 90a: To a solution of alcohol 89a (1.57 g, 4.43 mmol) in CH₂Cl₂ (44 mL) at 0 °C was added mCPBA (≤ 77 wt %, 1.49 g, 6.64 mmol) as a solid in one portion. The reaction was allowed to warm to room temperature and stirred for 2 h, and then quenched by addition of 10% Na₂CO₃(aq) (60 mL). The aqueous layer was separated and extracted twice with CH₂Cl₂ (30 mL each). The combined organic layer was washed with sat. NaHSO₃(aq) (30 mL), and 10% Na₂CO₃(aq) (30 mL). The combined organics were dried over Na₂SO₄, filtered and concentrated in vacuo to afford crude alcohol 90a as a colorless oil. The crude product was purified by flash chromatography (15% EtOAc in hexanes to 45% EtOAc in hexanes) to afford 90a as a colorless oil (1.47 g, 3.94 mmol, 89%).

1H NMR (500 MHz, CDCl₃): δ 7.69-7.66 (m, 4H), 7.44-7.38 (m, 6H), 3.88 (dd, J = 12.6, 2.5 Hz, 1H), 3.73-3.71 (m, 2H), 3.59 (dd, J = 12.6, 4.4 Hz, 1H), 2.98-2.96 (m, 1H), 2.91 (ddd, J = 4.5, 2.3, 2.3 Hz, 1H), 1.90-1.80 (br, 1H), 1.75-1.66 (m, 4H), 1.07 (s, 9H).

13C NMR (125 MHz, CDCl₃): δ 135.7, 133.98, 133.97, 129.8, 127.8, 63.4, 61.8, 58.6, 55.9, 29.0, 28.2, 27.0, 19.4.

IR (thin film): 3407, 2932, 2858, 1472, 1428, 1389, 1361, 1105 cm⁻¹.

HR-MS (DART) m/z calcd for C₂₂H₃₀O₃Si (M+NH₄)⁺: 388.2302, found 388.2292.

Epoxide 90b: To a solution of alcohol 89b (0.97 g, 2.63 mmol) in CH₂Cl₂ (26 mL) at 0 °C was added mCPBA (≤ 77 wt %, 0.88 g, 3.95 mmol) as a solid in one portion. The reaction was allowed to warm to room temperature and stirred for 2 h, and then quenched by addition of 10% Na₂CO₃(aq) (30 mL). The aqueous layer was separated and extracted twice with CH₂Cl₂ (20 mL each). The combined organic layer was washed with sat. NaHSO₃(aq) (20 mL), and 10% Na₂CO₃(aq) (20 mL). The combined organics were dried over Na₂SO₄, filtered and concentrated in vacuo to afford crude alcohol 90b as a colorless oil. The crude product was purified by flash chromatography (10% EtOAc in hexanes to 40% EtOAc in hexanes) to afford 90b as a colorless oil (0.89 g, 2.31 mmol, 88%).

1H NMR (500 MHz, CDCl₃): δ 7.68-7.67 (m, 4H), 7.45-7.38 (m, 6H), 3.93-3.90 (m, 1H), 3.68 (t, J = 6.1 Hz, 2H), 3.65-3.61 (m, 1H), 2.96-2.94 (m, 1H), 2.91 (dt, J = 4.4, 2.3 Hz, 1H), 1.74 (t, J = 5.8 Hz, 1H), 1.65-1.50 (m, 6H), 1.06 (s, 9H).

13C NMR (125 MHz, CDCl₃): δ 135.7, 134.1, 129.7, 127.8, 63.7, 61.8, 58.5, 56.0, 32.4, 31.4, 27.0, 22.5, 19.4.

IR (thin film): 3420, 3069, 2931, 2858, 1589, 1472, 1428, 1389, 1361, 1188, 1105 cm⁻¹.

HR-MS (DART) m/z calcd for C₂₃H₃₂O₃Si (M+NH₄)⁺: 402.2459, found 402.2443.
Epoxy Enoate 91a: To a solution of epoxy alcohol 90a (1.40 g, 3.78 mmol) in CH$_2$Cl$_2$ (38 mL) was added DMSO (3.8 mL, 53.5 mmol) and Et$_3$N (2.6 mL, 19 mmol), cooled to 0°C, and Pyr*S0$_3$ (1.20 g, 7.56 mmol) added as a solid. The reaction was allowed to warm to room temperature and stirred for 3 h. At this point, (carbethoxymethylene)triphenylphosphorane (2.63 g, 7.56 mmol) was added as a solid at room temperature and stirred for 30 min. The reaction was quenched by addition of H$_2$O (25 mL) and diluted with CH$_2$Cl$_2$ (25 mL). The aqueous layer was separated and extracted twice with CH$_2$Cl$_2$ (20 mL each). The combined organics were washed with H$_2$O (20 mL), sat. NaCl(aq) (20 mL), dried over Na$_2$SO$_4$, filtered and concentrated in vacuo to afford crude enoate 91a as a yellow oil. The crude product was purified by flash chromatography (10% EtOAc in hexanes) to afford 91a as a colorless oil (1.39 g, 3.17 mmol, 84%, 92:8 E/Z). The product was purified further by MPLC (Biotage Ultra Column) with a gradient of solvents (100% hexanes to 8% EtOAc in hexanes) to afford 91a as only the (E)-alkene (1.07 g, 65%).

$^1$H NMR (500 MHz, CDCl$_3$): δ 7.68-7.66 (m, 4H), 7.46-7.38 (m, 6H), 6.65 (dd, $J = 15.7, 7.2$ Hz, 1H), 6.11 (dd, $J = 15.7, 0.7$ Hz, 1H), 4.22 (q, $J = 7.1$ Hz, 2H), 3.71 (t, $J = 5.4$ Hz, 2H), 3.20 (ddd, $J = 7.2, 1.9, 0.5$ Hz, 1H), 2.89 (td, $J = 5.1, 2.0$ Hz, 1H), 1.76-1.69 (m, 4H), 1.31 (t, $J = 7.1$ Hz, 3H), 1.06 (s, 9H).

$^{13}$C NMR (125 MHz, CDCl$_3$): δ 165.8, 144.9, 135.7, 133.92, 133.89, 129.8, 127.84, 127.83, 123.8, 63.2, 61.3, 60.7, 56.5, 28.8, 28.6, 27.0, 19.4, 14.4.

IR (thin film): 3067, 2933, 2858, 1719, 1655, 1589, 1472, 1428, 1390, 1368, 1258, 1182, 1106 cm$^{-1}$.

HR-MS (DART) m/z calcd for C$_{26}$H$_{34}$O$_4$Si (M+NH$_4$)$^+$: 456.2565, found 456.2557.

Epoxy Enoate 91b: To a solution of epoxy alcohol 90b (0.83 g, 2.16 mmol) in CH$_2$Cl$_2$ (21 mL) was added DMSO (2.2 mL, 31 mmol) and Et$_3$N (1.5 mL, 10.8 mmol), cooled to 0°C, and Pyr*S0$_3$ (0.69 g, 4.3 mmol) added as a solid. The reaction was allowed to warm to room temperature and stirred for 3 h. At this point, (carbethoxymethylene)triphenylphosphorane (1.5 g, 4.3 mmol) was added as a solid at room temperature and stirred for 30 min. The reaction was quenched by addition of H$_2$O (25 mL) and diluted with CH$_2$Cl$_2$ (25 mL). The aqueous layer was separated and extracted twice with CH$_2$Cl$_2$ (20 mL each). The combined organics were washed with H$_2$O (20 mL), sat. NaCl(aq) (20 mL), dried over Na$_2$SO$_4$, filtered and concentrated in vacuo to afford crude enoate 91b as a yellow oil. The crude product was purified by flash chromatography (5% EtOAc in hexanes to 10% EtOAc in hexanes) to afford 91b as a colorless oil (0.69 g, 1.52 mmol, 70%, 95:5 E/Z). The product was purified further by MPLC (Biotage Ultra Column) with a gradient of solvents (100% hexanes to 6% EtOAc in hexanes) to afford 91b as only the (E)-alkene (0.38 g, 38%).
'H NMR (500 MHz, CDCl₃): δ 7.68-7.66 (m, 4H), 7.45-7.37 (m, 6H), 6.68 (dd, J = 15.7, 7.1 Hz, 1H), 6.12 (dd, J = 15.7, 0.6 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 3.68 (t, J = 5.9 Hz, 2H), 3.19 (ddd, J = 7.1, 2.0, 0.6 Hz, 1H), 2.89-2.86 (m, 1H), 1.62-1.52 (m, 6H), 1.30 (t, J = 7.1 Hz, 3H), 1.06 (s, 9H).

13C NMR (100 MHz, CDCl₃): δ 165.9, 144.9, 135.7, 134.1, 129.7, 127.8, 123.7, 63.7, 61.5, 60.7, 56.4, 32.3, 31.8, 27.0, 22.4, 19.4, 14.4.

IR (thin film): 3067, 2933, 2858, 1719, 1655, 1589, 1473, 1428, 1390, 1368, 1302, 1256, 1180, 1093, 1041 cm⁻¹.

HR-MS (DART) m/z calcld for C₂₇H₃₆O₄Si (M+NH₄)⁺: 470.2721, found 470.2703.

Epoxy Alcohol 92a: To a solution of enoate 91a (0.60 g, 1.37 mmol) in THF (2.7 mL) at 0 °C was added TBAF (1.0 M in THF, 2.7 mL, 2.7 mmol) dropwise over 1 min. The reaction was stirred and allowed to warm to room temperature over 2 h. The crude reaction mixture was purified without concentration by flash chromatography (pretreated with 1% Et₃N in 50% EtOAc in hexanes, then 50% EtOAc in hexanes to 60% EtOAc in hexanes) to afford 92a as a colorless oil (0.25 g, 1.25 mmol, 91%).

'H NMR (500 MHz, CDCl₃): δ 6.67 (dd, J = 15.7, 7.1 Hz, 1H), 6.12 (d, J = 15.7 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.69 (t, J = 5.9 Hz, 2H), 3.25 (ddd, J = 7.1, 1.5 Hz, 1H), 2.94 (td, J = 5.4, 1.8 Hz, 1H), 1.84-1.61 (m, 5H), 1.28 (t, J = 7.1 Hz, 3H).

13C NMR (100 MHz, CDCl₃): δ 165.8, 144.6, 123.9, 62.3, 61.3, 60.8, 56.6, 29.0, 28.6, 14.4.

IR (thin film): 3414, 2983, 2934, 2875, 1715, 1654, 1446, 1369, 1303, 1259, 1182, 1142, 1033 cm⁻¹.

HR-MS (DART) m/z calcld for C₁₀H₁₈O₄ (M+NH₄)⁺: 218.1387, found 218.1391.

Epoxy Alcohol 92b: To a solution of enoate 91b (0.38 g, 0.84 mmol) in THF (1.7 mL) at 0 °C was added TBAF (1.0 M in THF, 1.7 mL, 1.7 mmol) dropwise over 1 min. The reaction was stirred and allowed to warm to room temperature over 2 h. The crude reaction mixture was purified without concentration by flash chromatography (pretreated with 1% Et₃N in 50% EtOAc in hexanes, then 50% EtOAc in hexanes to 60% EtOAc in hexanes) to afford 92b as a colorless oil (0.17 g, 0.79 mmol, 94%).

'H NMR (500 MHz, CDCl₃): δ 6.64 (dd, J = 15.7, 7.1 Hz, 1H), 6.10 (d, J = 15.7 Hz, 1H), 4.17 (q, J = 7.1 Hz, 2H), 3.62 (t, J = 6.2 Hz, 2H), 3.21 (ddd, J = 7.1, 1.7 Hz, 1H), 2.90-2.87 (m, 1H), 1.91 (br, 1H), 1.65-1.50 (m, 6H), 1.26 (t, J = 7.1 Hz, 3H).
13C NMR (125 MHz, CDCl3): δ 165.8, 144.8, 123.8, 61.4, 60.7, 56.4, 32.3, 31.7, 22.3, 14.3.

IR (thin film): 3423, 2978, 2936, 2865, 1716, 1655, 1446, 1369, 1258, 1180, 1141, 1033 cm⁻¹.

HR-MS (DART) m/z calcd for C₁₁H₁₈O₄(M+NH₄)⁺: 232.1543, found 232.1541.

[Rh(CO)₂Cl₂] promoted cyclization of epoxy alcohol 92a: To a 20 ml vial equipped with a magnetic stir bar was added epoxide 92a (57 mg, 0.28 mmol), THF (1.4 mL), and a solution of [Rh(CO)₂Cl₂] in THF (2.8 mg, 7 μmol, in 1.4 mL THF) and stirred at room temperature. After consumption of the starting material (1 h, as determined by TLC analysis), 40 mg of polymer-bound triphenylphosphine resin was added and stirred for 30 min. The cloudy brown solution was filtered through a plug of silica gel (preshawned with 2% Et₃N in EtOAc then 2xEtOAc), eluted with EtOAc, and concentrated in vacuo. 'H NMR spectroscopic analysis of the unpurified mixture indicated a 97.5:1.5 [endo(93a)/exo(94a)] ratio of products. The resultant pale yellow film was purified by flash chromatography (20–40% EtOAc/hexanes) to afford 93a as a colorless oil (53.2 mg, 0.27 mmol, 94%).

Characterization Data for 93a:
'1H NMR (500 MHz, CDCl₃): δ 7.08 (dd, J = 15.8, 4.9 Hz, 1H), 6.09 (dd, J = 15.8, 1.5 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 3.95 (d, J = 12.1 Hz, 1H), 3.67 (ddd, J = 9.0, 4.9, 1.4 Hz, 1H), 3.41-3.34 (m, 2H), 2.54-2.50 (br, 1H), 2.16-2.13 (m, 1H), 1.72-1.67 (m, 2H), 1.52-1.44 (m, 1H), 1.27 (t, J = 7.1 Hz, 3H).

13C NMR (100 MHz, CDCl₃): δ 166.7, 145.4, 122.2, 81.3, 70.0, 67.5, 60.7, 32.7, 25.4, 14.4.

IR (thin film): 3422, 2940, 2857, 1700, 1658, 1445, 1368, 1303, 1265, 1174, 1077, 1041, 982 cm⁻¹.

HR-MS (DART) m/z calcd for C₁₀H₁₆O₄(M+NH₄)⁺: 218.1387, found 218.1385.

(±)-CSA Promoted cyclization of epoxy alcohol 92a: To a 20 ml vial equipped with a magnetic stir bar was added epoxide 92a (60 mg, 0.30 mmol) in CH₂Cl₂ (15 mL) and (±)-CSA (7.0 mg, 0.03 mmol) and stirred at room temperature. After consumption of the starting material (15 h, as determined by TLC analysis), the clear solution was filtered through a plug of silica gel (preshawned with 2% Et₃N in EtOAc then 2xEtOAc), eluted with EtOAc, and concentrated in vacuo. 'H NMR spectroscopic analysis of the unpurified mixture indicated a 1:1 [endo(93a)/exo(94a)] ratio of products. The resultant clear film was purified by flash chromatography (20–40% EtOAc/hexanes) to afford 93a as a colorless oil (25.9 mg, 0.13 mmol, 43%) and 94a as a colorless oil (30.3 mg, 0.15 mmol, 50%).
Characterization Data for 94a:

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 6.90 (dd, $J = 15.7, 4.3$ Hz, 1H), 6.15 (dd, $J = 15.7, 2.0$ Hz, 1H), 4.53 (td, $J = 3.9, 1.9$ Hz, 1H), 4.21 (q, $J = 7.1$ Hz, 2H), 3.98 (td, $J = 7.3, 3.7$ Hz, 1H), 3.92 (dt, $J = 8.2, 6.6$ Hz, 1H), 3.80 (dt, $J = 8.2, 6.8$ Hz, 1H), 2.45-2.38 (br, 1H), 1.92-1.87 (m, 2H), 1.81-1.77 (m, 2H), 1.30 (t, $J = 7.1$ Hz, 4H).

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 166.5, 145.4, 121.8, 81.0, 71.9, 69.3, 60.6, 26.3, 25.2, 14.4.

IR (thin film): 3426, 2977, 2932, 2872, 1717, 1659, 1464, 1447, 1368, 1302, 1267, 1175, 1067, 1039 cm$^{-1}$.

HR-MS (DART) $m/z$ calcd for C$_{10}$H$_{16}$O$_4$ (M+NH$_4$)$^+$: 218.1387, found 218.1380.

[Rh(CO)$_2$Cl]$_2$ promoted cyclization of epoxy alcohol 92b: To a 20 ml vial equipped with a magnetic stir bar was added epoxide 92b (54 mg, 0.25 mmol), THF (1.25 mL), and a solution of [Rh(CO)$_2$Cl]$_2$ in THF (4.9 mg, 13 $\mu$L, in 1.25 mL THF) and stirred at room temperature. After consumption of the starting material (9 h, as determined by TLC analysis), 45 mg of polymer-bound triphenylphosphine resin was added and stirred for 30 min. The cloudy brown solution was filtered through a plug of silica gel (prewashed with 2% Et$_3$N in EtOAc then 2xEtOAc), eluted with EtOAc, and concentrated in vacuo. $^1$H NMR spectroscopic analysis of the unpurified mixture indicated a 99:1 [endo(93b)/exo(94b)] ratio of products. The resultant pale yellow film was purified by flash chromatography (20–40% EtOAc/hexanes) to afford 93b as a colorless oil (43.6 mg, 0.20 mmol, 81%).

Characterization Data for 93b:

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.09 (dd, $J = 15.7, 4.4$ Hz, 1H), 6.10 (dd, $J = 15.7, 1.8$ Hz, 1H), 4.19 (q, $J = 7.1$ Hz, 2H), 3.94 (dt, $J = 12.2, 5.3$ Hz, 1H), 3.88 (ddd, $J = 8.5, 4.4, 1.8$ Hz, 1H), 3.70-3.60 (m, 2H), 2.13 (br, 1H), 2.01-1.97 (m, 1H), 1.80-1.67 (m, 4H), 1.61-1.55 (m, 1H), 1.28 (t, $J = 7.1$ Hz, 3H).

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 166.9, 147.2, 121.1, 83.4, 74.7, 70.8, 60.6, 36.1, 30.7, 21.0, 14.4.

IR (thin film): 3425, 2932, 2864, 1700, 1656, 1446, 1368, 1300, 1270, 1172, 1135, 1102, 1038 cm$^{-1}$.

HR-MS (DART) $m/z$ calcd for C$_{11}$H$_{18}$O$_4$ (M+NH$_4$)$^+$: 232.1543, found 232.1543.
HO OR OEt

(±)-CSA Promoted cyclization of epoxy alcohol 92b: To a 20 ml vial equipped with a magnetic stir bar was added epoxide 92b (54 mg, 0.25 mmol) in CH2Cl2 (12 mL) and (±)-CSA (58 mg, 0.25 mmol) and stirred at room temperature. After consumption of the starting material (7 h, as determined by TLC analysis), the clear solution was filtered through a plug of silica gel (prewashed with 2% Et3N in EtOAc then 2xEtOAc), eluted with EtOAc, and concentrated in vacuo. 1H NMR spectroscopic analysis of the unpurified mixture indicated a 1:3 [endo(93b)/exo(94b)] ratio of products. The resultant clear film was purified by flash chromatography (20–40% EtOAc/hexanes) to afford 94b as a colorless oil (35.8 mg, 0.167 mmol, 67%) and 93b as a colorless oil (11.4 mg, 0.053 mmol, 21%).

Characterization Data for 94b:

1H NMR (500 MHz, CDCl3): δ 6.93 (dd, J = 15.7, 4.7 Hz, 1H), 6.12 (dd, J = 15.7, 1.9 Hz, 1H), 4.33 (br, 1H), 4.20 (q, J = 7.1 Hz, 2H), 4.02 (ddt, J = 11.4, 4.1, 2.0 Hz, 1H), 3.50-3.43 (m, 2H), 2.56 (br, 1H), 1.89-1.86 (m, 1H), 1.58-1.42 (m, 5H), 1.29 (t, J = 7.1 Hz, 3H).

13C NMR (125 MHz, CDCl3): δ 166.5, 145.8, 122.1, 79.7, 73.4, 69.0, 60.6, 26.0, 25.7, 23.1, 14.4.

IR (thin film): 3429, 2936, 2851, 1717, 1659, 1443, 1368, 1306, 1270, 1092, 1043 cm⁻¹.

HR-MS (DART) m/z calcd for C11H18O4 (M+NH4)⁺: 232.1543, found 232.1539.

Me

Enoate 96a: To a solution of TBDPS-protected alcohol 87a® (3.33 g, 10.1 mmol) in CH2Cl2 (100 mL) was added DMSO (10 mL, 0.14 mol) and Et3N (7.0 mL, 50 mmol), cooled to 0 °C, and Pyr*SO3 (3.22 g, 20.2 mmol) added as a solid. The reaction was allowed to warm to room temperature and stirred for 3 h. At this point, (Carbethoxyethylidene)triphenylphosphorane (7.32 g, 20.2 mmol) was added as a solid at room temperature and stirred for 12 h. The reaction was quenched by addition of H2O (75 mL) and diluted with CH2Cl2 (25 mL). The aqueous layer was separated and extracted twice with CH2Cl2 (30 mL each). The combined organics were washed with H2O (50 mL), sat. NaCl(aq) (50 mL), dried over Na2SO4, filtered and concentrated in vacuo to afford crude enoate 96a as a yellow oil. The crude product was purified by flash chromatography (5% EtOAc in hexanes to 10% EtOAc in hexanes) to afford 96a as a colorless oil (2.92 g, 6.88 mmol, 89%, 96:4 E/Z). The product was purified further by flash chromatography with a gradient of solvents (2% EtOAc in hexanes to 4% EtOAc in hexanes) to afford 96a enriched to >99:1 E/Z (1.27 g, 39%).

1H NMR (500 MHz, CDCl3): δ 7.69-7.66 (m, 4H), 7.46-7.38 (m, 6H), 6.77 (tq, J = 7.5, 1.4 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 3.69 (t, J = 6.1 Hz, 2H), 2.30 (q, J = 7.4 Hz, 2H), 1.85 (d, J = 1.3 Hz, 3H), 1.73-1.67 (m, 2H), 1.31 (t, J = 7.1 Hz, 3H), 1.07 (s, 9H).
$^{13}$C NMR (125 MHz, CDCl$_3$): δ 168.4, 142.0, 135.7, 134.0, 129.8, 128.2, 127.8, 63.4, 60.6, 31.6, 27.0, 25.3, 19.4, 14.5, 12.5.

IR (thin film): 3073, 2933, 2858, 1708, 1651, 1590, 1473, 1428, 1389, 1366, 1261, 1234, 1190, 1106, 1030 cm$^{-1}$.

HR-MS (DART) m/z calcd for C$_{25}$H$_{34}$O$_3$Si (M+NH$_4^+$): 428.2615, found 428.2635.

Enoate 96b: To a solution of TBDPS-protected alcohol 87b (2.64 g, 7.7 mmol) in CH$_2$Cl$_2$ (77 mL) was added DMSO (7.7 mL, 0.11 mol) and Et$_3$N (5.4 mL, 39 mmol), cooled to 0 °C, and Pyr$^*$SO$_3$ (2.45 g, 15.4 mmol) added as a solid. The reaction was allowed to warm to room temperature and stirred for 3 h. At this point, (Carbethoxyethylidene)triphenylphosphorane (5.60 g, 15.4 mmol) was added as a solid at room temperature and stirred for 12 h. The reaction was quenched by addition of H$_2$O (75 mL) and diluted with CH$_2$Cl$_2$ (25 mL). The aqueous layer was separated and extracted twice with CH$_2$Cl$_2$ (30 mL each). The combined organics were washed with H$_2$O (50 mL), sat. NaCl$_{aq}$ (50 mL), dried over Na$_2$SO$_4$, filtered and concentrated in vacuo to afford crude enoate 96b as a yellow oil. The crude product was purified by flash chromatography (5% EtOAc in hexanes to 10% EtOAc in hexanes) to afford 96b as a colorless oil (2.92 g, 6.88 mmol, 89%, 96:4 E/Z). The product was purified further by flash chromatography with a gradient of solvents (2% EtOAc in hexanes to 4% EtOAc in hexanes) to afford 96b enriched to >99:1 E/Z (1.27 g, 39%).

$^1$H NMR (500 MHz, CDCl$_3$): δ 7.69-7.68 (m, 4H), 7.46-7.38 (m, 6H), 6.77 (d, J = 7.4 Hz, 1H), 4.21 (q, J = 7.1 Hz, 2H), 3.69 (t, J = 5.9 Hz, 2H), 2.18 (q, J = 7.2 Hz, 2H), 1.83 (s, 3H), 1.63-1.53 (m, 4H), 1.32 (t, J = 7.1 Hz, 3H), 1.07 (s, 9H).

$^{13}$C NMR (125 MHz, CDCl$_3$): δ 168.4, 142.3, 135.7, 134.1, 129.7, 128.0, 127.8, 63.7, 60.6, 32.4, 28.5, 27.0, 25.1, 19.4, 14.5, 12.5.

IR (thin film): 3055, 2932, 2858, 1708, 1651, 1590, 1472, 1428, 1389, 1365, 1254, 1223, 1185, 1104 cm$^{-1}$.

HR-MS (DART) m/z calcd for C$_{26}$H$_{36}$O$_3$Si (M+NH$_4^+$): 442.2772, found 442.2772.

Enoate 96c: To a solution of TBDPS-protected alcohol 87c (2.23 g, 6.26 mmol) in CH$_2$Cl$_2$ (62 mL) was added DMSO (6.3 mL, 88 mmol) and Et$_3$N (4.4 mL, 31 mmol), cooled to 0 °C, and Pyr$^*$SO$_3$ (2.00 g, 12.5 mmol) added as a solid. The reaction was allowed to warm to room temperature and stirred for 3 h. At this point, (Carbethoxyethylidene)triphenylphosphorane (5.60 g, 15.4 mmol) was added as a solid at room temperature and stirred for 12 h. The reaction was quenched by addition of H$_2$O (75 mL) and diluted with CH$_2$Cl$_2$ (25 mL). The aqueous layer was separated and extracted twice with CH$_2$Cl$_2$ (30 mL each). The combined organics were washed with H$_2$O (50 mL), sat. NaCl$_{aq}$ (50 mL), dried over Na$_2$SO$_4$, filtered and concentrated in vacuo to afford crude enoate 96c as a yellow oil. The crude product was purified by flash chromatography (5% EtOAc in hexanes to 10% EtOAc in hexanes) to afford 96c as a colorless oil (2.14 g, 5.13 mmol, 82%, 96:4 E/Z). The product was purified further by flash chromatography with a gradient of solvents (2% EtOAc in hexanes to 4% EtOAc in hexanes) to afford 96c enriched to >99:1 E/Z (1.06 g, 27%).

$^1$H NMR (500 MHz, CDCl$_3$): δ 7.69-7.68 (m, 4H), 7.46-7.38 (m, 6H), 6.77 (d, J = 7.4 Hz, 1H), 4.21 (q, J = 7.1 Hz, 2H), 3.69 (t, J = 5.9 Hz, 2H), 2.18 (q, J = 7.2 Hz, 2H), 1.83 (s, 3H), 1.63-1.53 (m, 4H), 1.32 (t, J = 7.1 Hz, 3H), 1.07 (s, 9H).

$^{13}$C NMR (125 MHz, CDCl$_3$): δ 168.4, 142.3, 135.7, 134.1, 129.7, 128.0, 127.8, 63.7, 60.6, 32.4, 28.5, 27.0, 25.1, 19.4, 14.5, 12.5.

IR (thin film): 3055, 2932, 2858, 1708, 1651, 1590, 1472, 1428, 1389, 1365, 1254, 1223, 1185, 1104 cm$^{-1}$.

HR-MS (DART) m/z calcd for C$_{26}$H$_{36}$O$_3$Si (M+NH$_4^+$): 442.2772, found 442.2772.

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temperature and stirred for 3h. At this point, (Carbethoxyethylidene)triphenylphosphorane (4.5 g, 12.5 mmol) was added as a solid at room temperature and stirred for 12 h. The reaction was quenched by addition of H₂O (75 mL) and diluted with CH₂Cl₂ (25 mL). The aqueous layer was separated and extracted twice with CH₂Cl₂ (30 mL each). The combined organics were washed with H₂O (50 mL), sat. NaCl (50 mL), dried over Na₂SO₄, filtered and concentrated in vacuo to afford crude enoate 96c as a yellow oil. The crude product was purified by flash chromatography (5% EtOAc in hexanes to 10% EtOAc in hexanes) to afford 96c as a colorless oil (2.22 g, 5.06 mmol, 81%, 96:4 E/Z).

The product was purified further by flash chromatography with a gradient of solvents (2% EtOAc in hexanes to 4% EtOAc in hexanes) to afford 96c enriched to >99:1 E/Z (1.44 g, 52%).

'H NMR (600 MHz, CDCl₃): δ 7.71-7.69 (m, 4H), 7.46-7.39 (m, 6H), 6.78 (tq, J = 7.5, 1.4 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 3.69 (t, J = 6.4 Hz, 2H), 2.18 (q, J = 6.8 Hz, 2H), 1.86 (d, J = 1.1 Hz, 3H), 1.60 (quint, J = 6.9 Hz, 2H), 1.47-1.41 (m, 4H), 1.32 (t, J = 7.1 Hz, 3H), 1.08 (s, 9H).

'13 C NMR (150 MHz, CDCl₃): δ 168.4, 142.4, 135.7, 134.2, 129.7, 127.86, 127.74, 63.9, 60.5, 32.5, 28.8, 28.5, 27.0, 25.7, 19.4, 14.5, 12.5.

IR (thin film): 2932, 2858, 1708, 1651, 1589, 1473, 1428, 1389, 1365, 1259, 1175, 1129, 1092, 1036 cm⁻¹.

HR-MS (DART) m/z calcd for C₂₇H₃₈O₃Si (M+NH₄)+: 456.2928, found 456.2939.

Alcohol 97a: To a solution of enoate 96a (2.37 g, 5.77 mmol) in CH₂Cl₂ (25 mL) at -78 °C was added DIBAL-H (1.0 M in CH₂Cl₂, 20 mL, 20 mmol) dropwise over three min. The reaction was stirred for 2.5 h, and then quenched by slow addition of MeOH (6 mL) at -78 °C. The reaction mixture was then poured into an Erlenmeyer flask containing sat. aq. Rochelle's salt (150 mL) and stirred vigorously for 2 h at room temperature. The aqueous layer was separated and extracted with CH₂Cl₂ (2x30 mL). The combined organics were dried over MgSO₄, filtered and concentrated in vacuo to afford crude alcohol 97a as a colorless oil. The crude product was purified by flash chromatography (15% EtOAc in hexanes to 20% EtOAc in hexanes) to afford 97a as a colorless oil (1.98 g, 5.43 mmol, 94%).

'H NMR (500 MHz, CDCl₃): δ 7.69-7.68 (m, 4H), 7.45-7.38 (m, 6H), 5.39 (tq, J = 7.2, 1.3 Hz, 1H), 3.99 (d, J = 5.0 Hz, 2H), 3.68 (t, J = 6.3 Hz, 2H), 2.14 (q, J = 7.3 Hz, 2H), 1.67 (d, J = 0.4 Hz, 3H), 1.65-1.61 (m, 2H), 1.26 (t, J = 5.9 Hz, 1H), 1.07 (s, 9H).

'13 C NMR (150 MHz, CDCl₃): δ 135.7, 135.2, 134.2, 129.7, 127.8, 126.1, 69.2, 63.5, 32.5, 27.0, 24.0, 19.4, 13.8.

IR (thin film): 3300, 2931, 2858, 1472, 1428, 1388, 1109, 1007 cm⁻¹.

HR-MS (DART) m/z calcd for C₂₃H₃₂O₂Si (M+NH₄)+: 386.2510, found 386.2492.
Alcohol 97b: To a solution of enoate 96b (1.21 g, 2.85 mmol) in CH$_2$Cl$_2$ (12 mL) at -78 °C was added DIBAL–H (1.0 M in CH$_2$Cl$_2$, 10 mL, 10 mmol) dropwise over three min. The reaction was stirred for 2.5 h, and then quenched by slow addition of MeOH (3 mL) at -78 °C. The reaction mixture was then poured into an Erlenmeyer flask containing sat. aq. Rochelle’s salt (100 mL) and stirred vigorously for 5 h at room temperature. The aqueous layer was separated and extracted with CH$_2$Cl$_2$ (2x20 mL). The combined organics were dried over MgSO$_4$, filtered and concentrated in vacuo to afford crude alcohol 97b as a colorless oil. The crude product was purified by flash chromatography (10% EtOAc in hexanes to 30% EtOAc in hexanes) to afford 97b as a colorless oil (1.06 g, 2.77 mmol, 97%).

$^1$H NMR (500 MHz, CDCl$_3$): δ 7.68 (m, 4H), 7.45-7.37 (m, 6H), 5.40 (tq, $J = 7.1, 1.2$ Hz, 1H), 4.01 (s, 2H), 3.67 (t, $J = 6.4$ Hz, 2H), 2.04 (q, $J = 7.3$ Hz, 2H), 1.65 (s, 3H), 1.61-1.56 (m, 2H), 1.48-1.42 (m, 2H), 1.39 (br, 1H), 1.06 (s, 9H).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 135.8, 135.0, 134.3, 129.7, 127.8, 126.6, 69.2, 64.0, 32.4, 27.5, 27.1, 25.9, 19.4, 13.9.

IR (thin film): 3321, 3069, 2931, 2857, 1472, 1428, 1389, 1361, 1189, 1109, 1007 cm$^{-1}$.

HR-MS (DART) m/z calc'd for C$_{24}$H$_{34}$O$_2$Si (M+NH$_4$)$^+$: 400.2666, found 400.2669.

Alcohol 97c: To a solution of enoate 96c (1.42 g, 3.24 mmol) in CH$_2$Cl$_2$ (13 mL) at -78 °C was added DIBAL–H (1.0 M in CH$_2$Cl$_2$, 11.3 mL, 11.3 mmol) dropwise over three min. The reaction was stirred for 1 h, and then quenched by slow addition of MeOH (3 mL) at -78 °C. The reaction mixture was then poured into an Erlenmeyer flask containing sat. aq. Rochelle’s salt (100 mL) and stirred vigorously for 4 h at room temperature. The aqueous layer was separated and extracted with CH$_2$Cl$_2$ (2x20 mL). The combined organics were dried over MgSO$_4$, filtered and concentrated in vacuo to afford crude alcohol 97c as a colorless oil. The crude product was purified by flash chromatography (10% EtOAc in hexanes to 20% EtOAc in hexanes) to afford 97c as a colorless oil (1.21 g, 2.76 mmol, 95%).

$^1$H NMR (600 MHz, CDCl$_3$): δ 7.69-7.68 (m, 4H), 7.45-7.38 (m, 6H), 5.41 (tq, $J = 7.2, 1.2$ Hz, 1H), 4.01 (s, 2H), 3.67 (t, $J = 6.5$ Hz, 2H), 2.03 (q, $J = 6.8$ Hz, 2H), 1.67 (s, 3H), 1.58 (quint, $J = 7.0$ Hz, 2H), 1.42 (br, 1H), 1.39-1.36 (m, 4H), 1.06 (s, 9H).

$^{13}$C NMR (150 MHz, CDCl$_3$): δ 135.7, 134.8, 134.2, 129.7, 127.7, 126.7, 69.2, 64.1, 32.6, 29.4, 27.7, 27.0, 25.6, 19.4, 13.9.
IR (thin film): 3320, 3076, 2930, 2857, 1590, 1472, 1426, 1388, 1361, 1262, 1189, 1109, 1007 cm⁻¹.

HR-MS (DART) m/z calcd for C₂₅H₃₆O₂Si (M+NH₄)⁺: 414.2823, found 414.2808.

Epoxide 98a: To a solution of alcohol 97a (1.94 g, 5.32 mmol) in CH₂Cl₂ (53 mL) at 0 °C was added mCPBA (≤ 77 wt %, 1.78 g, 8.00 mmol) as a solid in one portion. The reaction was allowed to warm to room temperature and stirred for 2 h, and then quenched by addition of 10% Na₂CO₃(aq) (60 mL). The aqueous layer was separated and extracted twice with CH₂Cl₂ (30 mL each). The combined organic layer was washed with sat. NaHSO₃(aq) (30 mL), and 10% Na₂CO₃(aq) (30 mL). The combined organics were dried over Na₂SO₄, filtered and concentrated in vacuo to afford crude alcohol 98a as a colorless oil. The crude product was purified by flash chromatography (10% EtOAc in hexanes to 40% EtOAc in hexanes) to afford 98a as a colorless oil (1.87 g, 4.91 mmol, 92%).

¹H NMR (500 MHz, CDCl₃): δ 7.68-7.66 (m, 4H), 7.44-7.37 (m, 6H), 3.75-3.70 (m, 2H), 3.67 (dd, J = 12.1, 4.4 Hz, 1H), 3.56 (dd, J = 12.2, 8.7 Hz, 1H), 3.04 (t, J = 6.0 Hz, 1H), 1.78-1.67 (m, 4H), 1.60 (dd, J = 8.7, 4.4 Hz, 1H), 1.27 (s, 3H), 1.06 (s, 9H).

¹³C NMR (150 MHz, CDCl₃): δ 135.73, 135.72, 134.0, 129.8, 127.8, 65.4, 63.5, 61.0, 60.0, 29.5, 27.0, 24.9, 19.4, 14.3.

IR (thin film): 3400, 2931, 2858, 1472, 1428, 1387, 1258, 1191, 1106, 1039 cm⁻¹.

HR-MS (DART) m/z calcd for C₂₃H₃₂O₃Si (M+NH₄)⁺: 402.2459, found 402.2450.

Epoxide 98b: To a solution of alcohol 97b (1.02 g, 2.67 mmol) in CH₂Cl₂ (27 mL) at 0 °C was added mCPBA (≤ 77 wt %, 0.90 g, 4.0 mmol) as a solid in one portion. The reaction was allowed to warm to room temperature and stirred for 2 h, and then quenched by addition of 10% Na₂CO₃(aq) (30 mL). The aqueous layer was separated and extracted twice with CH₂Cl₂ (20 mL each). The combined organic layer was washed with sat. NaHSO₃(aq) (20 mL), and 10% Na₂CO₃(aq) (20 mL). The combined organics were dried over Na₂SO₄, filtered and concentrated in vacuo to afford crude alcohol 98b as a colorless oil. The crude product was purified by flash chromatography (20% EtOAc in hexanes to 40% EtOAc in hexanes) to afford 98b as a colorless oil (0.98 g, 2.46 mmol, 92%).

¹H NMR (500 MHz, CDCl₃): δ 7.70-7.67 (m, 4H), 7.45-7.38 (m, 6H), 3.71-3.68 (m, 3H), 3.58 (dd, J = 12.1, 8.1 Hz, 1H), 3.04 (t, J = 5.8 Hz, 1H), 1.87 (dd, J = 8.0, 4.3 Hz, 1H), 1.66-1.52 (m, 6H), 1.28 (s, 3H), 1.07 (s, 9H).
Epoxide 98c: To a solution of alcohol 97c (1.20 g, 3.03 mmol) in CH2Cl2 (30 mL) at 0 °C was added mCPBA (77 wt %, 1.02 g, 4.54 mmol) as a solid in one portion. The reaction was allowed to warm to room temperature and stirred for 1 h, and then quenched by addition of 10% Na2CO3 (aq) (30 mL). The aqueous layer was separated and extracted twice with CH2Cl2 (20 mL each). The combined organic layer was washed with sat. NaHSO3 (aq) (20 mL), and 10% Na2CO3 (aq) (20 mL). The combined organics were dried over Na2SO4, filtered and concentrated in vacuo to afford crude alcohol 98c as a colorless oil. The crude product was purified by flash chromatography (20% EtOAc in hexanes to 30% EtOAc in hexanes) to afford 98c as a colorless oil (1.08 g, 2.62 mmol, 87%).

1H NMR (600 MHz, CDCl3): δ 7.69-7.67 (m, 4H), 7.45-7.38 (m, 6H), 3.70-3.66 (m, 3H), 3.58 (dd, J = 12.2, 8.6 Hz, 1H), 3.03 (t, J = 6.2 Hz, 1H), 1.75 (dd, J = 8.6, 4.4 Hz, 1H), 1.62-1.39 (m, 8H), 1.28 (s, 3H), 1.06 (s, 9H).

13C NMR (150 MHz, CDCl3): δ 135.7, 134.1, 129.7, 127.8, 65.4, 63.9, 61.0, 60.2, 32.6, 28.3, 27.0, 26.4, 25.9, 19.4, 14.4.

IR (thin film): 3424, 3069, 2931, 2859, 1589, 1472, 1428, 1388, 1260, 1188, 1105, 1039 cm⁻¹.

HR-MS (DART) m/z calcld for C24H34O3Si (M+NH4)⁺: 416.2615, found 416.2593.

Epoxy Enoate 99a: To a solution of epoxy alcohol 98a (1.82 g, 4.78 mmol) in CH2Cl2 (48 mL) was added DMSO (4.8 mL, 67.6 mmol) and Et3N (3.4 mL, 24 mmol), cooled to 0 °C, and PyrSO3 (1.53 g, 9.6 mmol) added as a solid. The reaction was allowed to warm to room temperature and stirred for 3 h. At this point, (carbethoxymethylene)triphenylphosphorane (3.34 g, 9.6 mmol) was added as a solid at room temperature and stirred for 30 min. The reaction was quenched by addition of H2O (50 mL) and diluted with CH2Cl2 (25 mL). The aqueous layer was separated and extracted twice with CH2Cl2 (25 mL each). The combined organics were washed with H2O (30 mL), sat. NaCl (aq) (30 mL), dried over Na2SO4, filtered and concentrated in vacuo to afford crude enoate 99a as a yellow oil. The crude product was purified by flash chromatography (7% EtOAc in hexanes to 10% EtOAc in hexanes) to afford 99a as a colorless oil (2.06 g, 4.55 mmol, 95%, 95:5 E/Z).
**Epoxy Enoate 99b**: To a solution of epoxy alcohol 98b (0.94 g, 2.36 mmol) in CH2Cl2 (24 mL) was added DMSO (2.4 mL, 34 mmol) and Et3N (1.6 mL, 12 mmol), cooled to 0 °C, and Pyr-SO3 (0.94 g, 5.9 mmol) added as a solid. The reaction was allowed to warm to room temperature and stirred for 3 h. At this point, (carbethoxymethylene)triphenylphosphorane (1.64 g, 4.7 mmol) was added as a solid at room temperature and stirred for 30 min. The reaction was quenched by addition of H2O (30 mL) and diluted with CH2Cl2 (15 mL). The aqueous layer was separated and extracted twice with CH2Cl2 (15 mL each). The combined organics were washed with H2O (20 mL), sat. NaCl (20 mL), dried over Na2SO4, filtered, and concentrated in vacuo to afford crude enoate 99b as a yellow oil. The crude product was purified by flash chromatography (5% EtOAc in hexanes to 10% EtOAc in hexanes) to afford 99b as a colorless oil (1.04 g, 2.23 mmol, 94%, 95:5 E/Z). The product was purified further by MPLC (Biotage Ultra Column) with a gradient of solvents (2% EtOAc in hexanes to 10% EtOAc in hexanes) to afford 99b as only the (E)-alkene (0.50 g, 45%).

1H NMR (500 MHz, CDCl3): δ 7.69-7.67 (m, 4H), 7.45-7.38 (m, 6H), 6.77 (d, J = 15.8 Hz, 1H), 6.03 (d, J = 15.8 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 3.69 (t, J = 6.0 Hz, 2H), 2.84 (t, J = 5.7 Hz, 1H), 1.66-1.53 (m, 6H), 1.42 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H), 1.07 (s, 9H).

13C NMR (100 MHz, CDCl3): δ 166.3, 150.1, 135.7, 134.1, 129.7, 127.8, 121.6, 66.0, 63.6, 60.7, 58.5, 32.4, 28.4, 27.0, 22.9, 19.4, 15.3, 14.4.

IR (thin film): 2933, 2858, 1718, 1654, 1472, 1428, 1388, 1366, 1303, 1262, 1210, 1166, 1105, 1033 cm⁻¹.

HR-MS (DART) m/z calcd for C28H38O4Si (M+NH4)⁺: 484.2878, found 484.2858.
Epoxy Enoate 99c: To a solution of epoxy alcohol 98c (1.08 g, 2.62 mmol) in CH₂Cl₂ (26 mL) was added DMSO (2.6 mL, 36.6 mmol) and Et₃N (1.8 mL, 13 mmol), cooled to 0 °C, and Pyr·SO₃ (1.24 g, 6.55 mmol) added as a solid. The reaction was allowed to warm to room temperature and stirred for 3 h. At this point, (carbethoxymethylene)triphenylphosphorane (1.83 g, 5.24 mmol) was added as a solid at room temperature and stirred for 12 h. The reaction was quenched by addition of H₂O (30 mL) and diluted with CH₂Cl₂ (15 mL). The aqueous layer was separated and extracted twice with CH₂Cl₂ (15 mL each). The combined organics were washed with H₂O (20 mL), sat. NaCl(aq) (20 mL), dried over Na₂SO₄, filtered and concentrated in vacuo to afford crude enoate 99c as a yellow oil. The crude product was purified by flash chromatography (5% EtOAc in hexanes to 10% EtOAc in hexanes) to afford 99c as a colorless oil (1.19 g, 2.48 mmol, 94%, 95:5 E/Z).

1H NMR (600 MHz, CDCl₃): δ 7.68-7.67 (m, 4H), 7.45-7.38 (m, 6H), 6.76 (d, J = 15.8 Hz, 1H), 6.02 (d, J = 15.8 Hz, 1H), 4.21 (q, J = 7.1 Hz, 2H), 3.67 (t, J = 6.4 Hz, 2H), 2.84 (t, J = 6.2 Hz, 1H), 1.65-1.42 (m, 8H), 1.43 (s, 3H), 1.30 (t, J = 7.1 Hz, 3H), 1.06 (s, 9H).

13C NMR (150 MHz, CDCl₃): δ 166.3, 150.2, 135.7, 134.1, 129.7, 127.8, 121.6, 66.0, 63.8, 60.7, 58.6, 32.5, 28.7, 27.0, 26.2, 25.8, 19.4, 15.3, 14.4.

IR (thin film): 3069, 2933, 2858, 1718, 1654, 1463, 1428, 1388, 1366, 1304, 1262, 1165, 1105, 1034 cm⁻¹.

HR-MS (DART) m/z calcd for C₂₉H₄₀O₄Si (M+NH₄)⁺: 498.3034, found 498.3027.

Epoxy Alcohol 100a: To a solution of enoate 99a (0.42 g, 0.93 mmol) in THF (1.9 mL) at 0 °C was added TBAF (1.0 M in THF, 1.9 mL, 1.9 mmol) dropwise over 1 min. The reaction was stirred and allowed to warm to room temperature over 1.5 h. The crude reaction mixture was purified without concentration by flash chromatography (pretreated with 1% Et₃N in 50% EtOAc in hexanes, then 50% EtOAc in hexanes to 60% EtOAc in hexanes) to afford 100a as a colorless oil (0.18 g, 0.84 mmol, 90%).

1H NMR (600 MHz, CDCl₃): δ 6.73 (d, J = 15.7 Hz, 1H), 6.00 (d, J = 15.7 Hz, 1H), 4.19-4.16 (m, 2H), 3.69 (br, 2H), 2.89-2.87 (m, 1H), 2.01 (br, 1H), 1.77-1.63 (m, 4H), 1.43 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H).

13C NMR (150 MHz, CDCl₃): δ 166.3, 149.8, 121.7, 65.8, 62.2, 60.7, 58.9, 29.4, 25.2, 15.3, 14.3.

IR (thin film): 3453, 2938, 2885, 1716, 1654, 1456, 1368, 1304, 1264, 1174, 1032 cm⁻¹.

HR-MS (DART) m/z calcd for C₁₁H₁₈O₄ (M+H)⁺: 215.1278, found 215.1290.
Epoxy Alcohol 100b: To a solution of enoate 99b (0.53 g, 1.14 mmol) in THF (2.3 mL) at 0 °C was added TBAF (1.0 M in THF, 2.3 mL, 2.3 mmol) dropwise over 1 min. The reaction was stirred and allowed to warm to room temperature over 1.5 h. The crude reaction mixture was purified without concentration by flash chromatography (pretreated with 1% Et3N in 50% EtOAc in hexanes, then 50% EtOAc in hexanes to 60% EtOAc in hexanes) to afford 100b as a colorless oil (0.21 g, 0.92 mmol, 88%).

\[
\begin{align*}
\text{TBDPSO} & \quad \text{OEt} \\
99b & \quad \text{HO} \\
\text{Me} & \quad \text{Me} \\
\rightarrow & \\
\text{TBDPSO} & \quad \text{OEt} \\
100b & \quad \text{HO} \\
\text{Me} & \quad \text{Me}
\end{align*}
\]

\[\begin{align*}
{^1}H \text{ NMR (400 MHz, CDCl}_3): & \ 6.72 (d, J = 15.8 \ Hz, 1H), 5.98 (d, J = 15.8 \ Hz, 1H), 4.17 (q, J = 7.1 \ Hz, 2H), 3.63 (t, J = 6.1 \ Hz, 2H), 2.83 (t, J = 5.9 \ Hz, 1H), 1.92 (br, 1H), 1.65-1.49 (m, 6H), 1.41 (s, 3H), 1.26 (s, 1H). \\
{^{13}}C \text{ NMR (100 MHz, CDCl}_3): & \ 166.3, 150.1, 121.6, 65.9, 62.6, 60.7, 58.6, 32.4, 28.4, 22.8, 15.3, 14.3. \\
\text{IR (thin film):} & \ 3400, 2933, 2870, 1716, 1654, 1457, 1388, 1368, 1305, 1264, 1175, 1031 \text{ cm}^{-1}. \\
\text{HR-MS (DART)} m/z & \text{ calcd for C}_{12}H_{20}O_4 (M+NH}_4^+: 246.1700, \text{ found 246.1699.}
\end{align*}\]

Epoxy Alcohol 100c: To a solution of enoate 99c (0.48 g, 1.00 mmol) in THF (2.0 mL) at 0 °C was added TBAF (1.0 M in THF, 2.0 mL, 2.0 mmol) dropwise over 1 min. The reaction was stirred and allowed to warm to room temperature over 1.5 h. The crude reaction mixture was purified without concentration by flash chromatography (pretreated with 1% Et3N in 50% EtOAc in hexanes, then 50% EtOAc in hexanes to 60% EtOAc in hexanes) to afford 100c as a colorless oil (0.23 g, 0.95 mmol, 95%).

\[
\begin{align*}
\text{TBDPSO} & \quad \text{OEt} \\
99c & \quad \text{HO} \\
\text{Me} & \quad \text{Me} \\
\rightarrow & \\
\text{TBDPSO} & \quad \text{OEt} \\
100c & \quad \text{HO} \\
\text{Me} & \quad \text{Me}
\end{align*}
\]

\[\begin{align*}
{^1}H \text{ NMR (500 MHz, CDCl}_3): & \ 6.72 (d, J = 15.8 \ Hz, 1H), 5.98 (d, J = 15.8 \ Hz, 1H), 4.16 (q, J = 7.0 \ Hz, 2H), 3.61 (t, J = 6.5 \ Hz, 2H), 2.82 (t, J = 6.1 \ Hz, 1H), 1.94 (br, 1H), 1.60-1.42 (m, 8H), 1.40 (s, 3H), 1.26 (s, 1H). \\
{^{13}}C \text{ NMR (125 MHz, CDCl}_3): & \ 166.3, 150.1, 121.6, 66.0, 62.8, 60.7, 58.6, 32.7, 28.6, 26.3, 25.7, 15.3, 14.4. \\
\text{IR (thin film):} & \ 3451, 2934, 2870, 1716, 1654, 1457, 1388, 1368, 1305, 1264, 1175, 1032 \text{ cm}^{-1}. \\
\text{HR-MS (DART)} m/z & \text{ calcd for C}_{13}H_{22}O_4 (M+NH}_4^+: 260.1856, \text{ found 260.1852.}
\end{align*}\]

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[Rh(CO)$_2$Cl]$_2$ promoted cyclization of epoxy alcohol 100a: To a 20 ml vial equipped with a magnetic stir bar was added epoxide 100a (60 mg, 0.28 mmol), THF (2.3 mL), and a solution of [Rh(CO)$_2$Cl]$_2$ in THF (1.1 mg, 3 µmol, in 0.5 mL THF) and stirred at room temperature. After consumption of the starting material (3 h, as determined by TLC analysis), 11 mg of polymer-bound triphenylphosphine resin was added and stirred for 30 min. The cloudy brown solution was filtered through a plug of silica gel (prewashed with 2% Et$_3$N in EtOAc then 2xEtOAc), eluted with EtOAc, and concentrated in vacuo. $^1$H NMR spectroscopic analysis of the unpurified mixture indicated only endo-101a present and no exo-102a was observed. The resultant pale yellow film was purified by flash chromatography (15–35% EtOAc/hexanes) to afford 101a as a colorless oil (56 mg, 0.26 mmol, 93%).

Characterization Data for 101a:
$^1$H NMR (600 MHz, CDCl$_3$): δ 7.05 (d, $J = 16.0$ Hz, 1H), 6.04 (d, $J = 16.0$ Hz, 1H), 4.21 (q, $J = 7.1$ Hz, 2H), 3.72 (ddd, $J = 11.5$, 6.7, 4.5 Hz, 1H), 3.67 (ddd, $J = 11.6$, 7.4, 3.8 Hz, 1H), 3.62-3.59 (m, 1H), 1.92 (d, $J = 6.7$ Hz, 1H), 1.86-1.71 (m, 3H), 1.56-1.50 (m, 1H), 1.31 (s, 3H) 1.30 (t, $J = 7.1$ Hz, 6H).

$^{13}$C NMR (150 MHz, CDCl$_3$): δ 166.8, 151.4, 120.8, 77.07, 70.9, 61.8, 60.7, 27.7, 22.6, 19.8, 14.4.

IR (thin film): 3452, 2979, 2940, 2870, 1700, 1654, 1445, 1368, 1302, 1268, 1230, 1178, 1117, 1083, 1056 cm$^{-1}$.

HR-MS (DART) m/z calcld for C$_{11}$H$_{16}$O$_4$ (M+H)$^+$: 215.1278, found 215.1278.

($\pm$)-CSA Promoted cyclization of epoxy alcohol 100a: To a 20 ml vial equipped with a magnetic stir bar was added epoxide 100a (54 mg, 0.25 mmol) in CH$_2$Cl$_2$ (12 mL) and ($\pm$)-CSA (6 mg, 0.025 mmol) and stirred at room temperature. After consumption of the starting material (2 h, as determined by TLC analysis), the clear solution was filtered through a plug of silica gel (prewashed with 2% Et$_3$N in EtOAc then 2xEtOAc), eluted with EtOAc, and concentrated in vacuo. $^1$H NMR spectroscopic analysis of the unpurified mixture indicated a 3.4:1 [endo(101a)/exo(102a)] ratio of products. The resultant clear film was purified by flash chromatography (10–30% EtOAc/hexanes) to afford 102a as a colorless oil (10.5 mg, 0.049 mmol, 20%) and 101a as a colorless oil (37 mg, 0.17 mmol, 69%).

$^1$H NMR (500 MHz, CDCl$_3$): δ 6.90 (d, $J = 15.6$ Hz, 1H), 6.12 (d, $J = 15.6$ Hz, 1H), 4.20 (q, $J = 7.1$ Hz, 2H), 3.88-3.79 (m, 3H), 2.39 (br, 1H), 1.91-1.79 (m, 3H), 1.72 (dq, $J = 12.2$, 8.2 Hz, 1H), 1.36 (s, 3H), 1.30 (t, $J = 7.1$ Hz, 3H).
**13C NMR (125 MHz, CDCl₃):** δ 166.9, 149.8, 120.5, 84.4, 74.2, 69.3, 60.6, 26.60, 26.51, 25.6, 14.4.

**IR (thin film):** 3481, 2979, 2933, 2874, 1716, 1657, 1456, 1368, 1304, 1256, 1178, 1072, 1034 cm⁻¹.

**HR-MS (DART) m/z calcd for C₁₁H₁₈O₄ (M+NH₄)⁺: 232.1543, found 232.1533.**

[**[Rh(CO)₂Cl]₂** promoted cyclization of epoxy alcohol 100b: To a 20 ml vial equipped with a magnetic stir bar was added epoxide 100b (60 mg, 0.26 mmol), THF (2.0 mL), and a solution of [**[Rh(CO)₂Cl]₂** in THF (2.5 mg, 7 μmol, in 0.6 mL THF) and stirred at room temperature. After consumption of the starting material (5 h, as determined by TLC analysis), 25 mg of polymer-bound triphenylphosphine resin was added and stirred for 30 min. The cloudy brown solution was filtered through a plug of silica gel (prewashed with 2% Et₃N in EtOAc then 2xEtOAc), eluted with EtOAc, and concentrated in vacuo. ¹H NMR spectroscopic analysis of the unpurified mixture indicated only endo-101b present and no exo-102b was observed. The resultant pale yellow film was purified by flash chromatography (10–35% EtOAc/hexanes) to afford 101b as a colorless oil (53 mg, 0.23 mmol, 88%).

**Characterization Data for 101b:**
¹H NMR (500 MHz, CDCl₃): δ 7.12 (d, J = 15.8 Hz, 1H), 6.05 (d, J = 15.8 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 3.85 (dd, J = 9.7, 1.0 Hz, 1H), 3.77 (dd, J = 12.5, 3.9, 0.9 Hz, 1H), 3.44 (t, J = 12.7, 7.0, 5.5 Hz, 1H), 2.02 (ddddd, J = 13.6, 11.1, 9.7, 2.5 Hz, 1H), 1.95 (br, 1H), 1.83-1.80 (m, 1H), 1.69-1.59 (m, 3H), 1.45-1.37 (m, 1H), 1.30 (t, J = 7.1 Hz, 3H), 1.25 (s, 3H).

**13C NMR (125 MHz, CDCl₃):** δ 167.2, 152.2, 119.4, 80.2, 76.0, 64.7, 60.7, 32.5, 30.8, 24.6, 21.2, 14.4.

**IR (thin film):** 3452, 2981, 2934, 1699, 1653, 1446, 1368, 1299, 1271, 1175, 1118, 1096, 1072, 1045 cm⁻¹.

**HR-MS (DART) m/z calcd for C₁₂H₂₀O₄ (M+NH₄)⁺: 246.1700, found 246.1694.**

(±)-**CSA** Promoted cyclization of epoxy alcohol 100b: To a 20 ml vial equipped with a magnetic stir bar was added epoxide 100b (54 mg, 0.24 mmol) in CH₂Cl₂ (12 mL) and (±)-CSA (55 mg, 0.24 mmol) and stirred at room temperature. After consumption of the starting material (4 h, as
determined by TLC analysis), the clear solution was filtered through a plug of silica gel (prewashed with 2% Et₃N in EtOAc then 2xEtOAc), eluted with EtOAc, and concentrated in vacuo. ¹H NMR spectroscopic analysis of the unpurified mixture indicated a 1:1.8 [endo(101b)/exo(102b)] ratio of products. The resultant clear film was purified by flash chromatography (15–35% EtOAc/hexanes) to afford 102b as a colorless oil (23.1 mg, 0.10 mmol, 43%) and 101b as a colorless oil (13.3 mg, 0.058 mmol, 25%).

**Characterization Data for 102b:**
¹H NMR (500 MHz, CDCl₃): δ 6.97 (d, J = 15.6 Hz, 1H), 6.10 (d, J = 15.6 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 4.03 (dt, J = 11.1, 2.1 Hz, 1H), 3.44 (td, J = 11.5, 2.7 Hz, 1H), 3.22 (dd, J = 11.3, 1.9 Hz, 1H), 2.87 (br, 1H), 1.89-1.86 (in, 1H), 1.59-1.33 (m, 5H), 1.29 (t, J = 7.1 Hz, 3H), 1.28 (s, 3H).

**13C NMR (125 MHz, CDCl₃):** δ 166.9, 150.6, 120.4, 83.6, 74.5, 69.2, 60.5, 26.2, 25.9, 24.2, 23.4, 14.4

IR (thin film): 3487, 2936, 2854, 1715, 1655, 1443, 1367, 1302, 1283, 1265, 1174, 1089, 1034 cm⁻¹.

HR-MS (DART) m/z calcd for C₁₂H₂₀O₄ (M+NH₄)⁺: 246.1700, found 246.1694.

[100c] → [101c]

[Rh(CO)₂Cl₂]₂ promoted cyclization of epoxy alcohol 100c: To a 20 ml vial equipped with a magnetic stir bar was added epoxide 100c (70 mg, 0.29 mmol), THF (4.8 mL), and a solution of [Rh(CO)₂Cl₂]₂ in THF (11.3 mg, 0.03 mmol, in 1.0 mL THF) and stirred at 4 °C. After 30 h, an additional portion of [Rh(CO)₂Cl₂]₂ in THF (11.3 mg, 0.03 mmol, in 1.0 mL THF) and stirred at 4 °C until consumption of the starting material (43 h, as determined by TLC analysis). 180 mg of polymer-bound triphenylphosphine resin was added and stirred for 2 h. The cloudy brown solution was filtered through a plug of silica gel (prewashed with 2% Et₃N in EtOAc then 2xEtOAc), eluted with EtOAc, and concentrated in vacuo. The resultant yellow film was purified by flash chromatography (20–100% EtOAc/hexanes) to afford 101c as a colorless oil (13.1 mg, 0.054 mmol, 19%), 103 as colorless film (13.4 mg, 0.06 mmol, 21%), and 105 as a colorless film (4.5 mg, 0.019 mmol, 6%).

**Characterization Data for 101c:**
¹H NMR (500 MHz, CDCl₃): δ 7.22 (d, J = 16.0 Hz, 1H), 6.07 (d, J = 16.0 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 4.13-4.10 (m, 1H), 3.82 (dt, J = 12.3, 3.7 Hz, 1H), 3.53 (td, J = 12.0, 2.7 Hz, 1H), 1.89-1.65 (m, 6H), 1.50 (ddq, J = 14.5, 5.7, 2.9 Hz, 1H), 1.46-1.40 (m, 1H), 1.38 (d, J = 5.9 Hz, 1H), 1.31 (t, J = 7.1 Hz, 3H), 1.28 (s, 3H).

**13C NMR (125 MHz, CDCl₃):** δ 167.0, 151.5, 120.8, 80.0, 70.1, 64.8, 60.7, 34.4, 30.7, 25.3, 24.4, 20.3, 14.5

IR (thin film): 3447, 2983, 2929, 2863, 1717, 1700, 1650, 1452, 1368, 1301, 1276, 1183, 1117, 1090, 1063, 1037 cm⁻¹.

HR-MS (DART) m/z calcd for C₁₃H₂₂O₄ (M+NH₄)⁺: 260.1856, found 260.1840.
Characterization Data for 103:
IR (thin film): 3418, 2977, 2931, 2859, 1708, 1447, 1394, 1367, 1303, 1266, 1166, 1035 cm\(^{-1}\).

\(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta\) 7.32 (d, \(J = 15.7\) Hz, 1H), 5.90 (t, \(J = 7.4\) Hz, 1H), 5.79 (d, \(J = 15.7\) Hz, 1H), 4.21 (q, \(J = 7.1\) Hz, 2H), 3.66 (t, \(J = 6.4\) Hz, 2H), 2.22 (q, \(J = 7.3\) Hz, 2H), 1.77 (s, 3H), 1.61-1.56 (m, 2H), 1.49-1.44 (m, 2H), 1.42-1.36 (m, 2H), 1.31 (t, \(J = 7.1\) Hz, 3H), 1.26 (br, 1H).

\(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 167.8, 149.8, 142.1, 133.1, 115.7, 63.0, 60.3, 32.8, 29.03, 28.91, 25.6, 14.5, 12.3.

HR-MS (DART) \(m/z\) calcd for C\(_{13}\)H\(_{22}\)O\(_3\) (M+\(\text{NH}_4\)\(^+\)): 244.1907, found 244.1906.

Characterization Data for 104:
IR (thin film): 3441, 2927, 2863, 1734, 1668, 1391, 1369, 1305, 1261, 1180, 1050, 1026 cm\(^{-1}\).

\(^1\)H NMR (600 MHz, CDCl\(_3\)): \(\delta\) 6.82 (tq, \(J = 6.8, 1.4\) Hz, 1H), 4.20 (q, \(J = 7.1\) Hz, 2H), 3.67 (t, \(J = 6.4\) Hz, 2H), 3.29 (dd, \(J = 6.8, 0.9\) Hz, 2H), 2.73 (t, \(J = 7.4\) Hz, 2H), 1.80 (d, \(J = 1.0\) Hz, 3H), 1.66 (quint, \(J = 7.6\) Hz, 2H), 1.62-1.59 (m, 2H), 1.42-1.37 (m, 2H), 1.32-1.29 (br, 1H), 1.30 (t, \(J = 7.1\) Hz, 3H).

\(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 201.7, 170.8, 139.6, 133.0, 62.9, 61.4, 37.3, 34.6, 32.7, 25.6, 24.5, 14.4, 12.0.

HR-MS (DART) \(m/z\) calcd for C\(_{12}\)H\(_{22}\)O\(_4\) (M+\(\text{NH}_4\)\(^+\)): 260.1856, found 260.1865.

(\(\pm\))-CSA Promoted cyclization of epoxy alcohol 100c: To a 20 ml vial equipped with a magnetic stir bar was added epoxide 100c (65 mg, 0.27 mmol) in CH\(_2\)Cl\(_2\) (13 mL) and (\(\pm\))-CSA (124 mg, 0.54 mmol) and stirred at room temperature. After consumption of the starting material (4 h, as determined by TLC analysis), the clear solution was filtered through a plug of silica gel (prewashed with 2\% Et\(_3\)N in EtOAc then 2xEtOAc), eluted with EtOAc, and concentrated in vacuo. The resultant clear film was purified by flash chromatography (40–100\% EtOAc/hexanes) to afford 105 as a colorless oil (40 mg, 0.17 mmol, 62\%).
Characterization Data for 105:

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.30 (dd, $J$ = 16.2, 0.6 Hz, 1H), 6.03 (d, $J$ = 16.2 Hz, 1H), 5.59 (s, 1H), 5.49 (s, 1H), 4.43 (dd, $J$ = 7.8, 4.4 Hz, 1H), 4.22 (q, $J$ = 7.1 Hz, 2H), 3.64 (t, $J$ = 6.5 Hz, 2H), 1.98 (br, 1H), 1.71-1.65 (m, 1H), 1.60-1.55 (m, 4H), 1.49-1.47 (m, 1H), 1.44-1.37 (m, 3H), 1.31 (t, $J$ = 7.1 Hz, 3H).

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 167.2, 147.6, 143.9, 121.5, 119.0, 71.6, 63.0, 60.7, 36.4, 32.8, 25.72, 25.60, 14.4.

IR (thin film): 3372, 2935, 2860, 1700, 1632, 1464, 1393, 1368, 1310, 1278, 1181, 1038 cm$^{-1}$.

HR-MS (DART) $m/z$ calcd for C$_{13}$H$_{22}$O$_4$ (M+H)$^+$: 243.1591, found 243.1591.

Epoxide 48: To a cooled (−40 °C) solution of 3Å molecular sieves (180 mg) in CH$_2$Cl$_2$ (42 mL) was added (+)-diethyl tartrate (0.10 mL, 0.55 mmol), Ti(iOPr)$_4$ (0.13 mL, 0.42 mmol), then a solution of 47 (0.60 g, 4.24 mmol) in CH$_2$Cl$_2$ (5 mL). The solution was stirred for 20 min and then a solution of tBuOOH in decane (1.16 mL, 5.5 M, 6.36 mmol) was added dropwise over 5 min. The reaction mixture was stirred at −20 °C for 18 h and then diluted with EtOAc (75 mL) and allowed to warm to room temperature. The organic layer was washed with sat. Na$_2$SO$_4$ and then dried over MgSO$_4$, filtered and concentrated in vacuo. The resultant yellow oil was purified by flash chromatography (20–50% EtOAc/hexanes) to an epoxy alcohol, which was used directly in the next step.

To a solution of the epoxy alcohol in CH$_2$Cl$_2$ (22 mL) cooled to 0 °C was added Et$_3$N (0.93 mL, 6.7 mmol) and TBSCl (0.40 g, 2.68 mmol), and then warmed to room temperature. After 24 h, the reaction was quenched by the addition of sat. NH$_4$Cl(aq) (25 mL) and extracted with CH$_2$Cl$_2$ (2 x 20 mL). The combined organic layers were dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo. The resultant yellow oil was purified by flash chromatography (5–20% EtOAc/hexanes) to yield 48 as a colorless oil (0.53g, 1.96 mmol, 46% over two steps). The ee of 48 was determined to be 93%.

Determination of the ee of 48 was accomplished by formation of the benzoate ester of the intermediate epoxy alcohol, and comparison to the racemic epoxy benzoate on chiral analytical HPLC analysis (Chiracel OJ-H; 0.5% iPrOH in hexanes, 1.00 mL/min; $t_R$(major) = 13.0 min, $t_R$(minor) = 14.2 min.

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ 4.75 (s, 1H), 4.72 (s, 1H), 3.58 (s, 2H), 2.88 (t, $J$ = 6.3 Hz, 1H), 2.20 (dt, $J$ = 14.9, 7.5 Hz, 1H), 2.13 (dt, $J$ = 14.9, 7.6 Hz, 1H), 1.75 (s, 3H), 1.70 (m, 2H), 1.29 (s, 3H), 0.90 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H).

$^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 145.0, 110.6, 68.0, 61.2, 60.8, 34.7, 26.7, 26.0, 22.7, 18.5, 14.3, −5.2.

IR (thin film): 3076, 2957, 2858, 1651, 1473, 1463, 1376, 1253, 1135, 1098, 1007 cm$^{-1}$.

HR-MS (ESI) $m/z$ calcd for C$_{13}$H$_{36}$O$_2$Si (M+Na)$^+$: 293.1907, found 293.1907.

$[^{13}]$D$_{24}$ = −2.5 (c = 0.51, CHCl$_3$).

Alkene 46: To a solution of 46 (3.42 g, 13.9 mmol) and NMO (50 wt% in H₂O, 4.3 mL, 20.8 mmol) in acetone/H₂O (4:1, 139 mL) cooled to 0 °C was added OsO₄ (2.5 wt% in i-BuOH, 8.7 mL, 0.70 mmol). After 10 min at 0 °C, the reaction was allowed to warm to room temperature. After 5 h, the reaction was diluted with EtOAc (250 mL), mixed with H₂O (50 mL), and the two layers separated. The aqueous layer was extracted with EtOAc (3 x 100 mL), and the combined organic layers were dried over MgSO₄, filtered, and concentrated in vacuo. The resultant brown oil was purified via flash chromatography (70% EtOAc in hexanes to 100% EtOAc) to yield a colorless oil that was used directly in the next reaction.

The previously obtained oil was diluted in THF (700 mL), cooled -78 °C, and allylmagnesium bromide in Et₂O (97 mL, 1.0 M, 97 mmol) was added dropwise over 1 h. After an additional 2.5 h at -78 °C, the reaction was warmed to 0 °C and quenched by dropwise addition of sat. NH₄Cl(aq) (50 mL). The reaction mixture was extracted with EtOAc (3 x 100 mL), and the combined organic layers were dried over MgSO₄, filtered, and concentrated in vacuo to provide a yellow-brown oil that was carried forward into the next reaction.

To the previously obtained oil diluted in CH₂Cl₂ (60 mL) was added DMAP (12 mg, 0.1 mmol), pyridine (4.4 mL, 55 mmol), and Ac₂O (3.4 mL, 36.4 mmol). The reaction was heated to 30 °C for 18 h, then concentrated in vacuo. The resultant yellow oil was purified by flash chromatography (15–30% EtOAc in hexanes) to yield 46 as a colorless oil (2.02 g, 6.1 mmol, 37% over 4 steps).

1H NMR (600 MHz, CDCl₃): δ 7.36-7.29 (m, 5H), 5.83 (ddt, J = 17.1, 10.3, 6.8 Hz, 1H), 5.20 (t, J = 3.0 Hz, 1H), 5.07-5.03 (m, 2H), 4.80 (dd, J = 10.2, 3.1 Hz, 1H), 4.55-4.49 (m, 1H), 4.01 (dt, J = 9.5, 2.9 Hz, 1H), 3.74 (ddd, J = 10.5, 7.9, 2.9 Hz, 1H), 3.62-3.54 (m, 2H), 2.31-2.27 (m, 1H), 2.12 (s, 3H), 1.89-1.83 (m, 1H), 1.80 (ddd, J = 14.4, 9.6, 4.9 Hz, 1H), 1.64-1.58 (m, 1H), 1.06 (d, J = 7.3 Hz, 3H).

13C NMR (150 MHz, CDCl₃): δ 170.4, 170.1, 138.6, 134.3, 128.6, 127.83, 127.77, 117.0, 73.9, 73.2, 72.6, 71.3, 68.8, 67.1, 38.1, 36.4, 32.4, 21.3, 21.1, 10.6.

IR (thin film): 2965, 2919, 2860, 1743, 1454, 1370, 1242, 1102, 1054 cm⁻¹.

HR-MS (DART) m/z calcld for C₂₂H₃₀O₆ (M+H)⁺: 391.2115, found 391.2114.

[α]D²⁴ = +0.86 (c = 0.40, CHCl₃).

Trisubstituted Alkene 107: To a solution of 46 (417 mg, 1.07 mmol) in 2-methyl-2-butene (3.4 mL, 31.6 mmol) was added benzoquinone (17 mg, 0.16 mmol) and Hoveyda-Grubbs 2nd Generation Catalyst (49, 15 mg, 0.024 mmol) and stirred at room temperature. After consumption of 46 (1 h, determined by 1H NMR of aliquot of reaction mixture), the reaction mixture was concentrated in vacuo. The resultant green oil was purified by flash chromatography (10–25% EtOAc/hexanes) to afford 107 as a pale green oil (387 mg, 0.93 mmol, 87%).

1H NMR (500 MHz, CDCl3): δ 7.37-7.28 (m, 5H), 5.21-5.17 (m, 2H), 4.80 (dd, J = 10.2, 3.1 Hz, 1H), 4.55-4.50 (m, 2H), 4.00 (ddd, J = 9.5, 3.6, 2.5 Hz, 1H), 3.68 (ddd, J = 10.5, 7.4, 3.3 Hz, 1H), 3.62-3.54 (m, 2H), 2.25-2.20 (m, 1H), 2.13-2.08 (m, 1H), 2.11 (s, 3H), 2.00 (s, 3H), 1.87-1.77 (m, 1H), 1.69 (s, 3H), 1.63-1.60 (m, 1H), 1.57 (s, 3H), 1.06 (d, J = 7.3 Hz, 3H).

13C NMR (125 MHz, CDCl3): δ 170.4, 170.1, 138.7, 133.8, 128.6, 127.80, 127.77, 119.6, 74.5, 73.3, 72.8, 71.3, 69.0, 67.2, 38.2, 32.5, 30.8, 26.0, 21.3, 21.1, 18.1, 10.6.

IR (thin film): 2965, 2919, 2860, 1743, 1454, 1370, 1242, 1219, 1102, 1054 cm⁻¹.

HR-MS (ESI) m/z calcd for C24H34O6 (M+Na)+: 441.2248, found 441.2260.

[α]24 D = −21 (c = 1.51, CH2Cl2).

Trisubstituted Alkene 50: To a 10 mL Schlenk tube containing 107 (350 mg, 0.86 mmol), 48 (465 mg, 1.72 mmol), and benzoquinone (10 mg, 0.09 mmol) was added Hoveyda-Grubbs 2nd Generation Catalyst (49, 27 mg, 0.043 mmol) and flushed Ar. This mixture was heated with stirring on an oil bath at 80 °C. After 18 h, the reaction mixture was transferred out of the Schlenk tube with CH2Cl2 (3x5 mL) and the reaction mixture was concentrated in vacuo. The resultant green oil was purified by flash chromatography (5–20% EtOAc/hexanes) to afford 50 as a pale green oil (423 mg, 0.67 mmol, 78%, 2:1 E/Z). Enrichment to >9:1 E/Z of 50 could be achieved through three rounds of flash chromatography (10–20% EtOAc/hexanes), utilizing 1H NMR to assay individual fractions for enrichment.

1H NMR (500 MHz, CDCl3): δ 7.37-7.29 (m, 5H), 5.27-5.17 (m, 1H), 5.20 (t, J = 3.1 Hz, 1H), 4.79 (dd, J = 10.2, 3.1 Hz, 1H), 4.54-4.48 (m, 2H), 4.00 (ddd, J = 9.4, 3.6, 2.5 Hz, 1H), 3.70 (ddd, J = 10.4, 7.5, 3.1 Hz, 1H), 3.60-3.55 (m, 4H), 2.85 (t, J = 6.3 Hz, 1H), 2.24-2.21 (m, 1H), 2.18-2.05 (m, 3H), 2.11 (s, 3H), 2.00 (s, 3H), 1.87-1.78 (m, 2H), 1.67-1.62 (m, 3H), 1.58 (s, 3H), 1.27 (s, 3H), 1.05 (d, J = 7.3 Hz, 3H), 0.90 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H).
\[^{13}\text{C} \text{NMR (125 MHz, CDCl}_3\): } \delta 170.4, 170.1, 138.7, 136.6, 128.6, 127.8, 120.0, 74.4, 73.2, 72.7, 71.4, 68.9, 68.0, 67.3, 61.2, 38.1, 36.5, 32.5, 30.6, 27.3, 21.3, 21.1, 18.5, 16.5, 14.3, 10.6, -5.2.

IR (thin film): 2958, 2930, 2850, 1748, 1455, 1371, 1245, 1223, 1101, 1057 cm\(^{-1}\).

HR-MS (ESI) \(m/z\) calcld for C\(_{35}\)H\(_{36}\)O\(_8\)Si (M+Na\(^+\)): 655.3637, found 655.3644.

\([\alpha]^{24}_D = -8.0 \ (c = 0.92, \text{CH}_2\text{Cl}_2)\).
**Diol 95**: To a solution of 109 (36 mg, 0.06 mmol) and chiral ketone (+)-51\(^{63}\) (16 mg, 0.061 mmol) in DMM/MeCN (2:1, 2.8 mL) was added a solution of 0.05 M Na\(_2\)B\(_4\)O\(_7\)-10H\(_2\)O in 4 x 10\(^{-4}\) Na\(_2\)EDTA (1.85 mL) and nBu\(_4\)HSO\(_4\) (4 mg, 0.01 mmol), and the mixture was cooled to -10 °C. To this vigorously stirred reaction mixture was added, simultaneously over 1 h via syringe pump, a 0.212 M solution of Oxone® in 4 x 10\(^{-4}\) Na\(_2\)EDTA (0.86 mL) and a 0.89 M solution of K\(_2\)CO\(_3\) in H\(_2\)O (0.86 mL). Upon completion of syringe pump addition, the reaction mixture was diluted with Et\(_2\)O/H\(_2\)O (1:1, 10 mL) and warmed to room temperature. The aqueous layer was extracted with EtOAc (2 x 5 mL) and the combined organic layers were washed with sat. NaCl(aq) (5 mL), dried over Na\(_2\)SO\(_4\), filtered and concentrated in vacuo. The crude diepoxide was purified by flash chromatography (20% EtOAc in hexanes to 40% EtOAc in hexanes) to provide a diepoxide intermediate as a colorless oil (31 mg).

To the previous diepoxide in EtOH (0.9 mL) at 0 °C was added a premixed solution of EtOH (0.25 mL) containing guanidinium-HCl (0.7 mg, 7 μmol) and NaOEt (0.4 mg, 6 μmol). After 2 h, the reaction was allowed to warm to room temperature. After 6 h, the reaction was concentrated in vacuo, and directly purified by flash chromatography (50% EtOAc in hexanes to 100% EtOAc) to provide 95 as a colorless film (19.1 mg, 0.037 mmol, 72%).

**1H NMR** (500 MHz, CDCl\(_3\)): \(\delta\) 7.36-7.28 (m, 5H), 6.74 (d, \(J = 15.7\) Hz, 1H), 6.01 (d, \(J = 15.7\) Hz, 1H), 4.53-4.48 (m, 2H), 4.20 (q, \(J = 7.1\) Hz, 2H), 4.03 (ddd, \(J = 9.3, 3.7, 2.4\) Hz, 1H), 3.89 (br, 1H), 3.69-3.65 (m, 2H), 3.57 (dd, \(J = 7.3, 5.8\) Hz, 2H), 3.01 (dd, \(J = 7.3, 4.5\) Hz, 1H), 2.84 (t, \(J = 5.8\) Hz, 1H), 2.57 (d, \(J = 6.0\) Hz, 1H), 2.45 (br, 1H), 2.01-1.96 (m, 1H), 1.93-1.87 (m, 1H), 1.84-1.77 (m, 2H), 1.75-1.68 (m, 3H), 1.68-1.60 (m, 2H), 1.43 (s, 3H), 1.29 (t, \(J = 7.1\) Hz, 3H), 1.28 (s, 3H), 0.96 (d, \(J = 7.3\) Hz, 3H).

**13C NMR** (125 MHz, CDCl\(_3\)): \(\delta\) 166.3, 149.8, 138.7, 128.5, 127.75, 127.70, 121.8, 74.5, 73.6, 73.1, 71.0, 68.1, 67.6, 65.5, 60.8, 60.4, 59.8, 58.9, 39.7, 35.2, 32.5, 31.6, 24.4, 16.9, 15.3, 14.4, 10.8.

**IR** (thin film): 3434, 2965, 2927, 2866, 2362, 1717, 1659, 1456, 1387, 1368, 1307, 1266, 1210, 1177, 1104, 1071, 1038 cm\(^{-1}\).

**HR-MS (DART)** \(m/z\) calcd for C\(_{29}\)H\(_{42}\)O\(_8\) (M+H\(^+\)): 519.2925, found 519.2937.

\([\alpha]^{24}_D = -16.0\) (c = 0.40, CH\(_2\)Cl\(_2\)).

[Rh(CO)₂Cl]₂ promoted cyclization of 95: To a 2 dram vial equipped with a magnetic stir bar was added 95 (7.8 mg, 0.015 mmol), THF (0.5 mL), and a solution of [Rh(CO)₂Cl]₂ in THF (0.6 mg, 1.5 µmol, in 0.25 mL THF) and stirred at room temperature. After consumption of the starting material (3 h, as determined by TLC analysis), 10 mg of polymer-bound triphenylphosphine resin was added and stirred for 30 min. The cloudy brown solution was filtered through a plug of silica gel (prewashed with 2% Et₃N in EtOAc then 2xEtOAc), eluted with EtOAc, and concentrated in vacuo. The resultant pale yellow film was purified by flash chromatography (40–70% EtOAc/hexanes) to afford 106 as a colorless oil (6.1 mg, 0.011 mmol, 78%).

¹H NMR (500 MHz, CDCl₃): δ 7.36-7.28 (m, 5H), 6.72 (d, J = 15.4 Hz, 1H), 6.08 (d, J = 15.4 Hz, 1H), 4.55-4.47 (m, 2H), 4.25-4.16 (m, 2H), 4.02 (td, J = 6.1, 3.3 Hz, 1H), 3.98 (d, J = 6.8 Hz, 1H), 3.89 (dd, J = 11.9, 4.8 Hz, 1H), 3.80 (t, J = 2.6 Hz, 1H), 3.57 (dd, J = 7.4, 5.8 Hz, 2H), 3.48 (ddd, J = 11.9, 9.9, 4.2 Hz, 1H), 3.36 (ddd, J = 9.8, 2.8 Hz, 1H), 3.19-1.88 (m, 4H), 1.86-1.74 (m, 3H), 1.68-1.61 (m, 2H), 1.57 (q, J = 11.9 Hz, 1H), 1.50 (ddd, J = 13.3, 5.0, 2.3 Hz, 1H), 1.36 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H), 1.26 (s, 3H), 1.26 (s, 3H), 0.98 (d, J = 7.4 Hz, 3H).

¹³C NMR (125 MHz, CDCl₃): δ 167.0, 151.9, 138.8, 128.5, 127.82, 127.64, 120.3, 80.5, 78.5, 74.0, 73.0, 72.10, 71.99, 71.6, 71.0, 69.3, 67.6, 60.7, 39.0, 34.22, 34.63, 32.6, 24.9, 20.7, 16.4, 14.4, 11.2.

IR (thin film): 3427, 2929, 2871, 1715, 1655, 1455, 1367, 1292, 1224, 1179, 1088, 1075, 1029 cm⁻¹.

HR-MS (DART) m/z calcd for C₂₉H₄₂O₈ (M+H)+: 519.2925, found 519.2953.

[α]²⁰_D = -50.5 (c = 0.30, CH₂Cl₂).

Enoate 110: To a solution of 106 (5.0 mg, 9.6 µmol) in THF (0.96 mL) was added NaH (95%, 9 mg, 0.38 mmol), TBAI (7 mg, 0.02 mmol), and BnBr (45 µL, 0.38 mmol). The reaction was heated in an oil bath at 40 °C for 3 h, then at 60 °C for an additional 2 h. After cooling to room temperature, the reaction was quenched by the careful addition of sat. NH₄Cl(aq) (2 mL) and extracted with EtOAc (3 x 3mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated in vacuo. The resultant colorless film was purified by flash chromatography (5–40% EtOAc/hexanes) to afford 110 as a colorless oil (5.0 mg, 7 µmol, 75%).
\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta 7.37-7.29 (m, 10H), 7.27-7.23 (m, 5H), 6.68 (d, \(J = 15.4\) Hz, 1H), 6.08 (d, \(J = 15.4\) Hz, 1H), 4.86 (d, \(J = 12.0\) Hz, 1H), 4.65 (d, \(J = 11.9\) Hz, 1H), 4.60 (d, \(J = 12.0\) Hz, 1H), 4.51 (d, \(J = 12.0\) Hz, 1H), 4.47 (d, \(J = 11.9\) Hz, 1H), 4.32 (d, \(J = 11.9\) Hz, 1H), 4.25-4.15 (m, 2H), 4.02 (dt, \(J = 9.4, 3.1\) Hz, 1H), 3.96 (dd, \(J = 12.0, 4.8\) Hz, 1H), 3.64 (ddd, \(J = 11.8, 10.0, 4.5\) Hz, 1H), 3.60-3.52 (m, 4H), 3.45 (dd, \(J = 9.9, 2.5\) Hz, 1H), 1.96-1.77 (m, 5H), 1.60-1.55 (m, 4H), 1.34 (s, 3H), 1.31 (t, \(J = 7.1\) Hz, 3H), 1.25 (s, 3H), 0.96 (d, \(J = 7.3\) Hz, 3H).

\(^1\)C NMR (125 MHz, CDCl\(_3\)): \(\delta 167.1, 152.4, 139.9, 138.8, 138.2, 128.63, 128.48, 128.32, 127.88, 127.74, 127.62, 127.53, 127.3, 120.1, 81.1, 80.7, 79.6, 76.9, 73.10, 73.07, 71.92, 71.79, 71.69, 71.4, 70.4, 67.7, 60.7, 39.3, 34.9, 34.1, 32.7, 21.32, 21.22, 16.0, 14.5, 11.8.

IR (thin film): 3065, 3032, 2926, 2863, 1717, 1660, 1497, 1454, 1365, 1291, 1241, 1179, 1096, 1064, 1028 cm\(^{-1}\).

HR-MS (ESI) \(m/z\) calcd for C\(_{43}\)H\(_{58}\)O\(_8\) (M+Na\(^+\)): 721.3711, found 721.3725.

[\(\alpha\)]\(^{24}\)D = -17.5 (c = 0.18, CH\(_2\)Cl\(_2\)).

**Alcohol 40:** To a solution of 110 (4.0 mg, 5.7 \(\mu\)mol) in t-BuOH/H\(_2\)O (2:1, 0.42 mL) was added citric acid monohydrate (2.4 mg, 0.012 mmol), NMO (as solid, 2.0 mg, 0.017 mmol), and K\(_2\)OsO\(_3\)(OH)\(_2\)\(_2\)H\(_2\)O (0.4 mg, 12 \(\mu\)mol), and the green reaction mixture was stirred at room temperature. After 16 h, the colorless reaction was quenched by addition of 1M HCl\(_{aq}\) (0.2 mL), then extracted EtOAc (3 x 2 mL). The combined organic layers were washed sat. Na\(_2\)CO\(_3\) (<) (1 x 2.5 mL), sat. NaCl\(_{aq}\) (1 x 2.5 mL), dried over Na\(_2\)SO\(_4\), filtered and concentrated in vacuo to provide the crude diol as a pale green oil, which was used without further purification.

To a solution of the crude diol in CH\(_2\)Cl\(_2\) (0.3 mL) was added Ph\(_3\)BiCO\(_3\) (17 mg, 0.034 mmol) and heated to 60 °C in an oil bath. After 2 h, the reaction was removed from the oil bath, filtered through Celite (washed CH\(_2\)Cl\(_2\) x 1 mL), and concentrated in vacuo. The crude beige gel was purified by flash chromatography (10%-30% EtOAc/hexanes) to afford an aldehyde that was used immediately in the next step.

To a solution of aldehyde in MeOH (0.3 mL) at 0 °C was added NaBH\(_4\) (1.6 mg, 0.04 mmol). The reaction was quenched after 5 min by the addition of 1M HCl\(_{aq}\) (0.1 mL), EtOAc (1 mL), and H\(_2\)O (0.2 mL). The reaction mixture was extracted with EtOAc (3 x 2 mL), and the combined organic layers were washed with sat. NaCl\(_{aq}\) (2 mL), dried over Na\(_2\)SO\(_4\), filtered and concentrated in vacuo. The colorless film was purified by flash chromatography (20%-50% EtOAc/hexanes) to yield 40 as a colorless film (2.1 mg, 3.3 \(\mu\)mol, 60% over 3 steps).

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta 7.36-7.28 (m, 10H), 7.27-7.22 (m, 5H), 4.84 (d, \(J = 12.0\) Hz, 1H), 4.64-4.56 (m, 2H), 4.51 (d, \(J = 12.0\) Hz, 1H), 4.47 (d, \(J = 12.0\) Hz, 1H), 4.30 (d, \(J = 11.8\) Hz, 1H), 4.04-4.00 (m, 1H), 3.80 (dd, \(J = 12.1, 4.7\) Hz, 1H), 3.66-3.61 (m, 1H), 3.59 (t, \(J = 2.6\) Hz, 1H), 3.56-3.52 (m, 2H), 3.45-3.42 (m, 2H), 3.38 (d, \(J = 10.7\) Hz, 1H), 3.24 (d, \(J = 10.7\) Hz, 1H), 2.02-
1.93 (m, 3H), 1.89 (dt, J = 11.7, 4.7 Hz, 1H), 1.80-1.77 (m, 1H), 1.72-1.67 (m, 1H), 1.60-1.58 (m, 1H), 1.57-1.53 (m, 1H), 1.52-1.49 (m, 1H), 1.29 (s, 3H), 1.21 (s, 3H), 0.95 (d, J = 7.3 Hz, 3H).

\(^{13}\text{C NMR (125 MHz, CDCl}_3\):} \delta 139.8, 138.74, 138.57, 128.56, 128.49, 128.32, 127.88, 127.70, 127.64, 127.58, 127.54, 127.3, 81.1, 80.4, 79.6, 77.4, 73.11, 73.08, 72.08, 71.95, 71.51, 71.34, 70.4, 69.3, 67.6, 39.3, 35.1, 34.0, 32.7, 22.8, 17.5, 15.7, 11.8.

IR (thin film): 3427, 3030, 2925, 2858, 1718, 1670, 1605, 1496, 1453, 1361, 1260, 1215, 1156, 1089, 1062, 1027 cm\(^{-1}\).

HR-MS (DART) \textit{m/z} calcd for C\(_{39}\)H\(_{50}\)O\(_7\) (M+H): 631.3629, found 631.3629.

\([\alpha]_D^24 = -17.5 (c = 0.105, \text{CHCl}_3)\).\(^{64}\)

\begin{align*}
\text{Enoate 111: To a solution of 101b (190 mg, 0.83 mmol) in THF (8.3 mL) was added NaH (95\%, 40 mg, 1.66 mmol), TBAI (30 mg, 0.08 mmol), and BnBr (217 \mu L, 1.83 mmol). The reaction was stirred at room temperature for 17 h then quenched by the careful addition of sat. NH}_4\text{Cl (aq) (5 mL) and extracted with EtOAc (3 x 10mL). The combined organic layers were dried over Na}_2\text{SO}_4, filtered, and concentrated in vacuo. The resultant colorless film was purified by flash chromatography (5–20% EtOAc/hexanes) to afford 110 as a colorless oil (160 mg, 0.5 mmol, 60%).}
\end{align*}

\(^1\text{H NMR (400 MHz, CDCl}_3\):} \delta 7.39-7.29 (m, 5H), 7.02 (d, J = 15.7 Hz, 1H), 6.04 (d, J = 15.7 Hz, 1H), 4.65 (d, J = 11.7 Hz, 1H), 4.41 (d, J = 11.7 Hz, 1H), 4.21 (q, J = 7.1 Hz, 2H), 3.83-3.78 (m, 1H), 3.51 (d, J = 9.1 Hz, 1H), 3.44 (ddd, J = 12.4, 8.2, 3.8 Hz, 1H), 1.95-1.89 (m, 1H), 1.86-1.79 (m, 2H), 1.67-1.60 (m, 2H), 1.40-1.35 (m, 1H), 1.31 (t, J = 7.1 Hz, 3H), 1.29 (s, 3H).

\(^{13}\text{C NMR (100 MHz, CDCl}_3\):} \delta 167.1, 152.4, 138.4, 128.5, 127.78, 127.72, 119.3, 83.4, 80.3, 71.8, 64.7, 60.5, 31.1, 26.8, 24.6, 21.8, 14.4.

IR (thin film): 2980, 2934, 2875, 1715, 1654, 1497, 1453, 1366, 1298, 1272, 1214, 1173, 1115, 1096, 10671 1029 cm\(^{-1}\).

HR-MS (DART) \textit{m/z} calcd for C\(_{19}\)H\(_{26}\)O\(_4\) (M+H): 319.1904, found 319.1912.

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\(^{64}\)Characterization data for 40 matches except the optical rotation data differs by a factor of 10 (reported: \([\alpha]_D^27= -168 (c = 0.111, \text{CHCl}_3)) as reported in Kuranaga, T.; Ohtani, N.; Tsutsumi, R.; Baden, D. G.; Wright, J. L. C.; Satake, M.; Tachibana, K. \textit{Org. Lett.} 2011, 13, 696. Attempts to contact the corresponding author were unsuccessful.
Alcohol 112: To a solution of 111 (8.9 mg, 0.028 mmol) in t-BuOH/H2O (1:1, 0.56 mL) was added citric acid monohydrate (6 mg, 0.028 mmol), NMO (as solid, 7 mg, 0.056 mmol), and K2OsO3(OH)2*2H2O (0.5 mg, 1.4 μmol), and the green reaction mixture was stirred at room temperature. After 8 h, the colorless reaction was quenched by addition of 1M HCl(aq) (0.2 mL), then extracted EtOAc (3 x 2 mL). The combined organic layers were washed sat. Na2CO3(aq) (1 x 2.5 mL), sat. NaCl(aq) (1 x 2.5 mL), dried over Na2SO4, filtered and concentrated in vacuo to provide the crude diol as a pale green oil, which was used without further purification.

To a solution of the crude diol in CH2Cl2 (0.55 mL) was added NaIO4/SiO2 (1.2 g/mmol, 100 mg, 0.084 mmol) and stirred at room temperature. After 30 min, the reaction was filtered through a cotton plug and washed CH2C2 (1 x 1 mL), then Et2O (2 x 1 mL), and concentrated in vacuo. The crude aldehyde was used directly without purification.

To a solution of crude aldehyde in MeOH (0.3 mL) at 0 °C was added NaBH4 (6 mg, 0.15 mmol). The reaction was quenched after 10 min by the addition of 1M HCl(aq) (0.3 mL), EtOAc (2 mL), and H2O (0.4 mL). The reaction mixture was extracted with EtOAc (3 x 5 mL), and the combined organic layers were washed with sat. NaCl(aq) (5 mL), dried over Na2SO4, filtered and concentrated in vacuo. The resultant colorless film was purified by flash chromatography (20-60% EtOAc/hexanes) to afford 112 as a colorless oil (4.2 mg, 0.017 mmol, 60%) and 113 as a colorless film (1.5:1 d.r., 3 mg, 0.012 mmol, 43%).

Characterization Data For 112:
'H NMR (500 MHz, CDCl3): δ 7.37-7.27 (m, 5H), 4.63 (d, J = 11.7 Hz, 1H), 4.35 (d, J = 11.7 Hz, 1H), 3.73 (ddd, J = 12.6, 6.2, 3.6 Hz, 1H), 3.60 (ddd, J = 12.6, 7.3, 3.6 Hz, 1H), 3.52 (d, J = 10.9 Hz, 1H), 3.47-3.43 (m, 2H), 1.94-1.87 (m, 2H), 1.83-1.79 (m, 1H), 1.67-1.61 (m, 2H), 1.44-1.39 (m, 1H), 1.24 (s, 3H).

13C NMR (125 MHz, CDCl3): δ 138.6, 128.5, 127.77, 127.74, 82.3, 79.9, 71.5, 68.6, 63.8, 31.2, 27.6, 23.3, 17.3.

IR (thin film): 3415, 2930, 2873, 1718, 1497, 1453, 1400, 1367, 1267, 1206, 1062, 1027 cm⁻1.

HR-MS (DART) m/z calcd for C15H22O3 (M+H)⁺: 251.1642, found 251.1653.

Characterization Data For 113 (major diastereomer):
'H NMR (500 MHz, CDCl3): δ 7.37-7.30 (m, 5H), 4.67 (d, J = 11.3 Hz, 1H), 4.53 (d, J = 11.3 Hz, 1H), 3.77 (quintet, J = 6.4 Hz, 1H), 3.66 (t, J = 6.4 Hz, 2H), 3.25 (q, J = 5.4 Hz, 1H), 1.67-1.48 (m, 6H), 1.20 (d, J = 6.4 Hz, 3H).

13C NMR (125 MHz, CDCl3): δ 138.5, 128.7, 128.03, 127.95, 84.1, 72.8, 69.1, 63.0, 33.2, 30.2, 21.3, 19.3.

IR (thin film): 3359, 2925, 2859, 1717, 1497, 1454, 1371, 1276, 1208, 1068 cm⁻1.

HR-MS (ESI) m/z calcd for C14H22O3 (M+Na)⁺: 261.1461, found 261.1467.
Alcohol 112: To a solution of 111 (27 mg, 0.085 mmol) in t-BuOH/H₂O (1:1, 0.86 mL) was added citric acid monohydrate (18 mg, 0.085 mmol), NMO (as solid, 20 mg, 0.17 mmol), and K₂OsO₂(OH)₄•2H₂O (1.5 mg, 4 μmol), and the green reaction mixture was stirred at room temperature. After 14 h, the colorless reaction was quenched by addition of 1M HCl(aq) (0.4 mL), then extracted EtOAc (3 x 3 mL). The combined organic layers were washed sat. Na₂CO₃(aq) (1 x 5 mL), sat. NaCl(aq) (1 x 5 mL), dried over Na₂SO₄, filtered and concentrated in vacuo to provide the crude diol as a pale green oil, which was used without further purification.

To a solution of the crude diol in CH₂Cl₂ (1 mL) was added Ph₃BiCO₃ (85 mg, 0.17 mmol) and heated to 50 ºC in an oil bath. After 3 h, the reaction was removed from the oil bath, filtered through Celite (washed CH₂Cl₂ 3 x 1 mL), and concentrated in vacuo. The crude gel was purified by flash chromatography (100% hexanes–6% EtOAc/hexanes) to afford an aldehyde that was used immediately in the next step.

To a solution of aldehyde in MeOH (2 mL) at 0 ºC was added NaBH₄ (12 mg, 0.31 mmol). The reaction was quenched after 5 min by the addition of 1M HCl(aq) (0.4 mL), EtOAc (2 mL), and H₂O (0.4 mL). The reaction mixture was extracted with EtOAc (3 x 5 mL), and the combined organic layers were washed with sat. NaCl(aq) (5 mL), dried over Na₂SO₄, filtered and concentrated in vacuo to yield 112 as a colorless film (16 mg, 0.064 mmol, 75% over 3 steps).
I. $^1$H and $^{13}$C NMR Spectra
TBDPSO

96b
TBDPSO

98b
Me

TBDPSO

OEt

99a
100c
Chapter II
Rhodium-Catalyzed Epoxide-Opening Cascades:
Synthetic Studies Toward Hemibrevetoxin B
A. Introduction to Hemibrevetoxin B

Having demonstrated the ability of \([\text{Rh} (\text{CO})_2 \text{Cl}]_2\) to promote site-selective initiation of cascades for the synthesis of the ABC and EF fragments of brevisin, we next wanted to explore the utility of Rh catalysis in a more challenging setting. We selected hemibrevetoxin B (1) as a suitable target, hoping to exploit the similarity of the ABC rings of 1 and brevisin. Isolated from cultures of *Karenia brevis*, hemibrevetoxin B shows cytotoxicity against mouse neuroblastoma cells (IC$_{50}$ = 5 μM). This natural product has attracted significant synthetic interest since the reported structural elucidation in 1989. While hemibrevetoxin B is smaller in comparison to closely related brevetoxins A (2) and B (3), it contains the key structural features found throughout the class, making it an ideal target to test new synthetic methodology (Figure 1). Additionally, the structural similarity of the AB rings of hemibrevetoxin B to fragments of 2 and 3 provide additional motivation for synthetic studies. Specifically, with four fused rings, 10 stereogenic centers, an axial methyl groups at the AB ring junction, and two fused oxepanes, hemibrevetoxin B provides an intricate challenge to synthetic chemists.

Figure 1. Structure of hemibrevetoxin B (1) and closely related brevetoxins A (2) and B (3)

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Nicolaou and coworkers reported in 1992 the first total synthesis of hemibrevetoxin B, which was also the first total synthesis of any ladder polyether. This landmark synthesis, achieved in 51 steps longest linear sequence (LLS) in 0.08% overall yield, utilized methodology developed towards a total synthesis of brevetoxin B. The synthesis proceeded in a linear fashion, with stepwise formation of the A–D rings (Figure 2). The A ring was synthesized from D-mannose, followed by an epoxy alcohol cyclization to form the B ring. The C and D rings were formed sequentially by lactone formation, transformation to the thionolactone and cuprate addition. The D-ring methyl was installed via Grignard addition into a ketone, now typically used for this part of the molecule. Finally, the (Z)-diene was installed by a Wittig olefination, and the enal portion was synthesized via a in situ Swern oxidation and methylene transfer from Eschenmoser’s salt. Attempts at shortening the LLS via a more convergent approach utilizing fragment coupling to form the CD rings provided the wrong stereochemistry at the CD ring junction.

Figure 2. Summary of hemibrevetoxin B total synthesis by Nicolaou and coworkers

A number of additional formal and total syntheses have been published, many utilizing transformations from Nicolaou’s groundbreaking effort. Instead of reviewing the large number of syntheses comprehensively, we will only highlight the key transformations used in the various syntheses toward the CD ring system. Yamamoto and coworkers reported the second synthesis, with the C and D rings generated via the cyclization of γ-alkoxyallylstannanes onto aldehydes. Nakata and coworkers first synthesized fused THPs and utilized a double ring expansion. Mori

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3 See the following for an account of efforts towards the total synthesis of brevetoxin B and hemibrevetoxin B: Nicolaou, K. C. Angew. Chem., Int. Ed. Eng. 1996, 35, 588.
and coworkers synthesized the C and D rings sequentially through a two-step epoxy alcohol cyclization directed by a deactivating sulfone group to form a THP, followed by ring expansion.\textsuperscript{8} Holton and coworkers synthesized the C ring as part of an epoxy alcohol cascade onto an in situ generated selenium ion, while the D ring was assembled via ring-closing metathesis.\textsuperscript{9} Rainer and coworkers utilized a sequential cyclic enol ether formation via ring-closing metathesis, DMDO epoxidation, and in situ epoxide opening with an allyl Grignard reagent for the formation of each ring.\textsuperscript{10} Rainer's synthesis also represents the shortest synthesis to date, in 29 steps LLS.

In line with our group's long-standing interest in the biosynthetic hypothesis for ladder polyethers, we looked to the epoxide-opening cascades proposed for hemibrevetoxin B for inspiration (Scheme 1). The first cascade, put forth by Shimizu in the isolation report, is very similar to the original brevetoxin B proposal.\textsuperscript{1} Protonation of polyepoxide 4 would initiate the cascade by a 1,2-hydride shift, followed by trapping of the next epoxide by the newly generated carbocation. Subsequent all-\textit{endo} epoxide trapping with a final methyl-directed quench by water would lead to 1. Alternatively, switching the direction of the cascade leads to polyepoxide precursor 5 proposed by McDonald.\textsuperscript{11} The initiation phase of this epoxide-opening cascade appears more straightforward, as it avoids hydride shifts; however, the need to override the \textit{exo} directing effect of the proximal methyl group in the first ring closure also adds to the complexity of this cascade.

\textbf{Scheme 1.} Two proposals for the biosynthesis of hemibrevetoxin B

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B. Introduction and Previous Work on Triepoxide Cascade Toward Hemibrevetoxin B

Inspired by the proposed epoxide-opening cascades for hemibrevetoxin B, we were hoping to build upon our results from the synthesis of the ABC tricycle of brevisin. We were further encouraged to pursue the synthesis of hemibrevetoxin B as the same tricyclic fragment and side chain of hemibrevetoxin B (BCD rings) is also observed in brevenal (7, CDE rings), a potential lead for treating brevetoxin poisoning and cystic fibrosis (Scheme 2). We anticipated that developing an epoxide-opening cascade for hemibrevetoxin B would allow us to leverage the similarities between 1 and 7 and readily translate the cascade to brevenal by modification of the template. We chose to pursue hemibrevetoxin B first, given the known synthesis of templates similar to the A ring.

Scheme 2. Similarities between hemibrevetoxin B and brevenal, with proposed epoxide-opening cascades

Our previous success in utilizing THP templates for biasing epoxy alcohol cyclizations to favor 6-endo closings, both in the water promoted reactions and in the site-selective, [Rh(CO)₂Cl]²-catalyzed initiation of cascades for the synthesis of the ABC and EF ring systems of brevisin, led

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13 While isolated oxepanes have been shown to be poor templates for water-promoted epoxy alcohol cyclizations toward THPs, the proposed template for the synthesis of brevenal would be a fused 6,7 system, likely reducing the conformational flexibility and restoring the proposed template effect. For a discussion of template rigidity and endo selectivity in water-promoted epoxy alcohol cyclizations, see: Byers, J. A.; Jamison, T. F. Proc. Natl. Acad. Sci. U. S. A. 2013, 110, 16724.
us to envision preforming the A ring for its potential use as a template in 6. Mechanistically, we envisioned activation of the distal epoxide followed by endo-selective opening by the neighboring epoxide to generate a bicyclo[4.1.0] epoxonium (7 to 8, Scheme 3). We anticipated that this intermediate 8, although lacking a methyl directing group, would react at least partially through the desired endo pathway based on the precedent from McDonald and Floreancig groups (8 to 9). Finally, trapping of the second bicyclo[4.1.0] epoxonium intermediate 9 by the template alcohol would conclude the cascade (9 to 10), forming three rings including the challenging fused trans-bis-oxepane CD rings.

Scheme 3. Proposed cascade for the all-endo cascade toward the synthesis of hemibrevetoxin B

Preliminary investigations toward this end were initiated Dr. Kazuyoshi Obitsu, a former visiting scientist in our lab. The first question that needed to be addressed was how to promote the desired endo regioselectivity in the first epoxide cyclization (7 to 8). The distal epoxide in the sequence contains a methyl group that could direct the next epoxide toward an exo-opening, forming an undesired bicyclo[3.1.0] epoxonium (11 to 12, Scheme 4). While limited examples of

15 Dr. Kazuyoshi Obitsu developed the first generation synthesis of the cascade precursor, and investigated the cascade under various Lewis acid activators.
biasing cyclizations of similarly substituted epoxy alcohol toward the endo pathway are known,\textsuperscript{16} no such reports exist for acid-promoted polyepoxide-opening cascades toward fused oxepanes. We hoped that a suitable directing group such as a vinyl substituent at the endo site of the distal epoxide (shown as $R^2$ in Schemes 2–4) would be able to successfully direct the first cyclization toward the desired endo product.

**Scheme 4.** Alternative exo epoxide closing for the first ring formation directed by methyl group

![Scheme 4](image)

An outline of our first generation synthesis of vinyl-substituted triepoxide 13 is shown in Scheme 5. The central two epoxides closest to the template ring were installed via asymmetric Shi epoxidation after fragment coupling of sulfone 14 and aldehyde 15 via Julia–Kocienski olefination. Aldehyde 15 was synthesized from alkene 16 through a sequence of oxidative alkene cleavage, Grignard addition and a one-pot Pd-catalyzed vinylation–Claisen rearrangement. Alkene 16 was formed from an asymmetric Ti/BINOL catalyzed hetero-Diels–Alder [4+2] cycloaddition of aldehyde 17 and Danishefsky’s diene 18, followed by elaboration of the ring system and acid-catalyzed allylation with 19. The overall sequence to 13 was accomplished in 13 steps LLS and 21 steps overall.

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Scheme 5. First generation synthesis of cascade precursor 13

Subjecting epoxide 13 to a variety of conditions, e.g., BF₃·OEt₂ in THF or CH₂Cl₂, La(OTf)₃, or various aqueous conditions, failed to yield any desired product. All but BF₃·OEt₂ in THF gave complex mixtures likely resulting from epoxide hydrolysis (aqueous conditions), epoxide rearrangements, and undesired exo-pathways. The major product from BF₃·OEt₂ in THF could not be conclusively identified, but we proposed a likely structure 20 (Scheme 6) based on analysis of the vinyl cross peaks in the ¹H-¹H COSY spectrum of the acylated cascade product, which confirmed the exo opening of the vinyl epoxide.

Scheme 6. Proposed product from cascade of polyepoxide 13

We currently have two mechanistic proposals for the formation of 20. The first involves an epoxonium-based, vinyl-to-template cascade, where the vinyl epoxide is opened by the next epoxide in an exo fashion (Scheme 4). The second pathway, shown in Scheme 7, invokes a template-to-vinyl cascade, where the nucleophilicity of the hydroxy group promotes rapid cyclization, outcompeting the desired bicyclo[4.1.0] epoxonium formation. The final cyclization from 22 to 23, a 5-exo, methyl-directed cyclization, would be expected to predominate over the vinyl-directed, 6-endo cyclization. Most importantly, a template-to-vinyl cascade would be unable
to form the desired oxepane C-ring, as in 21 to 22, a 6-exo cyclization would be significantly favored.

Scheme 7. Alternative mechanistic hypothesis for the formation of 20

At this juncture, rather than investigating alternative π-stabilizing groups beyond vinyl, which could also suffer from similar side product formation, we wanted to explore the ability of Rh catalysis to both override the exo-methyl directing effect for this epoxide substitution class, and to investigate Rh catalysis in a more challenging epoxide-opening cascade. Additionally, we hoped to eliminate alternative mechanisms, such as the template to vinyl pathway (Scheme 7), and further explore the potential for site-selective initiation to control the direction of epoxide-opening cascades (see Chapter 1 for further discussion).

C. Model Studies of Proximal-Methyl Substituted Epoxy Alcohol Cyclizations Catalyzed by [Rh(CO)₂Cl]₂

Our previous success using model studies to explore the directing ability of [Rh(CO)₂Cl]₂ toward brevisin led us to pursue a similar approach for hemibrevetoxin B. We commenced by synthesizing a pair of epoxy alcohols (28a,b) to test the ability of the enoate/Rh combination to favor 6-endo and 7-endo cyclizations (Scheme 8). We synthesized the substrates for the model

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17 Model studies toward alternative π-stabilizing groups for 7-endo cyclizations of similar proximal-methyl substituted epoxy alcohols were studied in the Jamison lab by a former post-doctoral researcher Dr. Oleg Vechorkin (unpublished results). He found that (Z)-ethyl and p-NO₂-phenyl substituted alkenes had improved regioselectivity compared to vinyl, but some cis-oxepane formation was also observed.
studies in a similar manner as previously described, with the exception of the synthesis of the allylic alcohol 25. We utilized a Zr-catalyzed carboalumination procedure with in situ aluminate formation and formaldehyde trapping to generate the desired (E)-trisubstituted allylic alcohols in >20:1 E/Z selectivity from alkyne 24.\textsuperscript{18} From allylic alcohol 25, mCPBA epoxidation, alcohol oxidation, and in situ stabilized Wittig olefination, followed by desilylation provided the desired epoxy alcohols 28a and 28b.

Scheme 8. Synthesis of epoxy alcohols 28 for model studies

We first used (\textpm)-CSA in CH\textsubscript{2}Cl\textsubscript{2} to explore the relative directing ability of the exo-methyl and endo-enoate epoxide substituents with the tethered nucleophile. With epoxy alcohol 28a, we found a 1:20 ratio for 6-endo/5-exo, demonstrating a significant barrier to overcome (Table 1, entry 1). This substrate proved to be very acid sensitive, readily cyclizing to the 5-exo product on unbuffered silica gel. Investigation of epoxy alcohol 28a under [Rh(CO)\textsubscript{2}Cl\textsubscript{2}] catalysis at room temperature provided a slight improvement in the regioselectivity, although the 5-exo product was still favored (entry 2). Inspired by the improvement in yields by heating the cascade toward the EF fragment of brevisin, we explored the effect of temperature on this reaction. To our delight, we found an increase in endo selectivity with increasing temperature, with 100 °C providing the best selectivity and yields at 9.8:1 endo/exo and 92% yield (entry 6).

Table 1. Initial regioselectivity results for the cyclization of epoxy alcohol 28a

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>solvent</th>
<th>temp(^a)</th>
<th>29a/30a endolexo</th>
<th>yield 29a (%)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(±)-CSA (10 mol %)</td>
<td>CH(_2)Cl(_2)</td>
<td>rt</td>
<td>1 : &gt;20</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>[Rh(CO)(_2)Cl(_2)] (10 mol %)</td>
<td>THF</td>
<td>rt</td>
<td>1 : 3.4</td>
<td>21</td>
</tr>
<tr>
<td>3</td>
<td>[Rh(CO)(_2)Cl(_2)] (10 mol %)</td>
<td>THF</td>
<td>40 °C</td>
<td>1 : 1.6</td>
<td>36</td>
</tr>
<tr>
<td>4</td>
<td>[Rh(CO)(_2)Cl(_2)] (10 mol %)</td>
<td>THF</td>
<td>60 °C</td>
<td>1.9 : 1</td>
<td>65</td>
</tr>
<tr>
<td>5</td>
<td>[Rh(CO)(_2)Cl(_2)] (10 mol %)</td>
<td>THF</td>
<td>80 °C</td>
<td>3.3 : 1</td>
<td>78</td>
</tr>
<tr>
<td>6</td>
<td>[Rh(CO)(_2)Cl(_2)] (10 mol %)</td>
<td>THF</td>
<td>100 °C</td>
<td>9.8 : 1</td>
<td>92</td>
</tr>
</tbody>
</table>

\(^a\) Reactions run in sealed vials in oil bath. \(^b\) Yields determined by \(^1\)H NMR spectroscopy.

A screen of alternative solvents found 1,4-dioxane to also yield promising results (Table 2). Interestingly, we observed a similar increase in endo selectivity with increasing temperature for reactions in dioxane. While higher endo selectivity was observed at room temperature compared to THF (entry 1), we found a nearly identical maximum of 9.9:1 endo/exo selective at 80 °C (entry 4). A slight drop in selectivity and yield was observed at 100 °C, which we attributed to decomposition of the catalyst in 1,4-dioxane.

Table 2. Effect of temperature on regioselectivity in 1,4-dioxane

<table>
<thead>
<tr>
<th>entry</th>
<th>temp(^a)</th>
<th>time</th>
<th>29a/30a endolexo</th>
<th>yield 29a (%)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>rt</td>
<td>18 h</td>
<td>1.6 : 1</td>
<td>42</td>
</tr>
<tr>
<td>2</td>
<td>40 °C</td>
<td>18 h</td>
<td>3.2 : 1</td>
<td>69</td>
</tr>
<tr>
<td>3</td>
<td>60 °C</td>
<td>18 h</td>
<td>6.5 : 1</td>
<td>91</td>
</tr>
<tr>
<td>4</td>
<td>80 °C</td>
<td>3 h</td>
<td>9.9 : 1</td>
<td>89</td>
</tr>
<tr>
<td>5</td>
<td>100 °C</td>
<td>1 h</td>
<td>7.1 : 1</td>
<td>85</td>
</tr>
</tbody>
</table>

\(^a\) Reactions run in sealed vials in oil bath. \(^b\) Yields determined by \(^1\)H NMR spectroscopy.
Attempting to run this reaction on larger scale (0.23 mmol instead of 0.02 mmol) in 1,4-dioxane at 80 °C, we observed a significant drop in regioselectivity (from 9.9:1 to 5:1 endo/exo) and yield of the desired 6-endo product 29a. We investigated a few explanations for the change of reaction outcome. Previously the reaction was run for 3 h, but TLC monitoring during the scale-up found 30 min to be sufficient for full conversion of starting material. Given the time difference between the two reactions, we investigated whether the 5-exo product 30a could be converted to the 6-endo product 29a under the reaction conditions. Subjection of 30a to [Rh(CO)\(\text{Cl}_2\)] catalysis in either THF or 1,4-dioxane at elevated temperatures resulted in full recovery of starting THF 30a, demonstrating that the reaction is irreversible (Scheme 9).

**Scheme 9.** Subjection of 5-exo product 30a to reaction conditions to test for reversibility

![Scheme 9](image)

We also considered the difference in the headspace between the screening and scale-up reactions, as these reactions are run in sealed vials. The ratio of headspace volume to solvent volume in the screening reaction was 25:1, while the scale up reaction only had a 3:1 headspace to reaction volume ratio, suggesting a key variable to investigate. We screened the reaction by varying the size of the vials to explore different headspace ratios from 1:1 up to 50:1, which allowed us to study the relationship between reactor headspace and regioselectivity. As shown in Table 3, we found that increasing the headspace correlated well with improved endo selectivity for this reaction, even to the extreme of 50:1. From these results we hypothesized the increase in headspace was allowing CO (after dissociating from Rh) to transfer out of solution, changing the active catalytic species to Rh(CO)\(_n\)Cl.
We next attempted to investigate directly the relationship between the carbonyl/Rh ratio and regioselectivity, hoping to gain more insight by more directly modifying the catalyst structure. We conducted these experiments at 40 °C in dioxane (Table 4, entry 1), as these conditions yielded a moderate 3:1 endo/exo ratio and any change in regioselectivity would be easily observed. We first tested our hypothesis that excess CO in solution negatively impacts regioselectivity. Purging the headspace of the vial with CO(g) to form Rh(CO)₃Cl resulted in the complete reversal of the regioselectivity toward the exo product, strongly supporting our hypothesis (entry 2).

We postulated that the endo-selective catalyst resembled the structure of Rh(CO)(solv)Cl, with one CO undergoing exchange with a solvent molecule, likely a disfavored process given the strong affinity of CO for Rh(I). We attempted to assist this process by preheating the catalyst under a static vacuum followed by an Ar refill. Under this protocol, only a small increase in endo selectivity was observed, suggesting that 1,4-dioxane alone was not able to displace CO (entry 3). Alternatively, using a singly-carbonylated Rh(I) species, [Rh(CO)(coe)Cl]₂, led to an improvement in regioselectivity to the highest observed in our headspace optimization studies at 10.5:1 endo/exo (entry 4). The conversion was lower, likely due to competitive binding between

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IR spectrum of the THF solution saturated with CO(g) was consistent with literature reports. See: Morris, D. E.; Burnham Tinker, H. J. Organomet. Chem. 1973, 49, C53.

Premixing [Rh(CO)₂Cl]₂ with [Rh(coe)₂Cl]₂ in a 1:1 ratio has been shown to equilibrate to [Rh(CO)(coe)Cl]₂. Key signals from the IR spectrum matched the reported signals of interest. See the following report for more details: Varshavsky, Y. S.; Cherkasova, T. G.; Buzina, N. A.; Kormer, V. A. J. Organomet. Chem. 1974, 77, 107.
the coe and the substrate enoate. Importantly, [Rh(coe)_2Cl]_2 alone yielded poor regioselectivity and yield, lending additional evidence that a 1:1 carbonyl/Rh ratio is ideal (entry 5).

Table 4. Investigation of carbonylation state of catalyst on regioselectivity and yield

<table>
<thead>
<tr>
<th>entry</th>
<th>change from standard conditions</th>
<th>conversion 28a (%)</th>
<th>29a/30a endo/exo</th>
<th>yield 29a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>&gt;95</td>
<td>2.8 : 1</td>
<td>65</td>
</tr>
<tr>
<td>2</td>
<td>Flush rxn headspace with CO(g)</td>
<td>87</td>
<td>1 : &gt;20</td>
<td>&gt;5</td>
</tr>
<tr>
<td>3</td>
<td>Preheat catalyst to 80 °C for 1 h, then flush with Ar</td>
<td>&gt;95</td>
<td>3.2 : 1</td>
<td>63</td>
</tr>
<tr>
<td>4</td>
<td>1:1 [Rh(CO)_2Cl]_2[Rh(coe)_2Cl]_2</td>
<td>54</td>
<td>10.5 : 1</td>
<td>21</td>
</tr>
<tr>
<td>5</td>
<td>[Rh(coe)_2Cl]_2</td>
<td>55</td>
<td>1 : 2.3</td>
<td>6</td>
</tr>
<tr>
<td>6</td>
<td>80 °C, open to air, 3 h</td>
<td>&gt;95</td>
<td>13.5 : 1</td>
<td>81</td>
</tr>
<tr>
<td>7</td>
<td>0.25 mmol (10x scale), 80 °C, open to air, 3 h</td>
<td>&gt;95</td>
<td>12.5 : 1</td>
<td>76^b</td>
</tr>
</tbody>
</table>

^a Yields determined by 1H NMR spectroscopy. ^b Isolated yield.

With the above results supporting to support our theory of the ideal CO/Rh ratio of 1:1 and the recognition that additional alkenes present in the reaction mixture result in lower reactivity and side-product formation, we sought to find optimal reaction conditions that didn’t rely on a large reactor headspace. We found that running the reaction open to air at 80 °C provided the highest regioselectivity and yield (Table 4, entry 6). We hypothesized that quickly heating the solution of catalyst and 28a more rapidly forms a species similar to Rh(CO)(enoate)Cl, which can catalyze the endo cyclization selectively.\(^{21}\) We think that the small amount of exo product 30a likely forms during an equilibration period, prior to loss of a CO to the atmosphere. Unlike the reaction run in sealed vials, the variant run open to the air was successfully performed at 0.25 mmol without significant erosion of yield or selectivity (entry 7).

We next explored the formation of oxepane 29b from epoxy alcohol 28b, hoping to capitalize on our previous discoveries concerning the carbonylation state of the catalyst. We

\(^{21}\) Wender and Houk in their studies of [Rh(CO)_2Cl]_2 catalyzed [5+2] annulations with vinylcyclopropanes and alkynes suggest that coordination of the alkene and then loss of a CO is necessary prior to entering the catalytic cycle. See: Yu, Z.; Wender, P. A.; Houk, K. N. J. Am. Chem. Soc. 2004, 126, 9154.
screened both THF and 1,4-dioxane, and were surprised to observe considerably lower conversion, selectivity, and yield (Table 5). Additionally, we isolated significant amounts of diene 31b, a similar deoxygenated side product observed in small quantities in attempt to from oxocanes (see Chapter 1).22 We reasoned the increased tether length and ring strain in the formation of oxepanes relative to THPs slowed the desired reaction enough to allow for side processes to prevail, especially at higher temperatures.

Table 5. Investigation of temperature and solvent effects on the cyclization of 28b

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>temp</th>
<th>conversion 28b (%)a</th>
<th>28b/30b endo/exo</th>
<th>yield 29b (%)a</th>
<th>yield 31b (%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>THF</td>
<td>rt</td>
<td>40</td>
<td>ndb</td>
<td>15</td>
<td>&lt;5</td>
</tr>
<tr>
<td>2</td>
<td>THF</td>
<td>50 °C</td>
<td>55</td>
<td>3 : 1</td>
<td>24</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>THF</td>
<td>80 °C</td>
<td>&gt;95</td>
<td>5 : 1</td>
<td>28</td>
<td>32</td>
</tr>
<tr>
<td>4</td>
<td>1,4-dioxane</td>
<td>rt</td>
<td>32</td>
<td>nd</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>5</td>
<td>1,4-dioxane</td>
<td>50 °C</td>
<td>58</td>
<td>nd</td>
<td>11</td>
<td>18</td>
</tr>
<tr>
<td>6</td>
<td>1,4-dioxane</td>
<td>80 °C</td>
<td>&gt;95</td>
<td>nd</td>
<td>11</td>
<td>27</td>
</tr>
</tbody>
</table>

a Yields determined by ¹H NMR spectroscopy. b nd = not determined, as yield of 30b was <5%.

Also of note was the lower yields of oxepane 29b in 1,4-dioxane compared to THF (entries 4–6 versus 1–3), as these results contrasted with the higher selectivity and yield for formation of THP 29a in 1,4-dioxane versus THF (Table 1 versus Table 2). Given the lower polarity of 1,4-dioxane (ε = 2) versus THF (ε = 8), we think that the higher 6-endo selectivity in 1,4-dioxane with 28a results from slowing of the 5-exo pathway relative to formation of the endo selective catalytic species via loss of CO, suggesting this pathway proceeds through a more polar intermediate.

22 Also see the following report for examples of deoxygenation of arene oxides with [Rh(CO)₂Cl]₂: Ashworth, R. W.; Berchtold, G. A. Tetrahedron Lett. 1977, 18, 343.
However, it is possible the substantial decrease in rate for cyclization of 28b could increase the lifetimes of the relevant catalytic intermediates, creating a greater importance for stabilizing such intermediates. We think THF is a superior solvent compared to 1,4-dioxane as it is best able to stabilize the various intermediates due to its greater polarity and coordinating ability, limiting catalyst decomposition and side processes.

Attempting to optimize the headspace/solvent ratio provided little improvement in yield and selectivity (Table 6). Performing the reaction in THF at 80 °C open to air provided a decrease in yield and conversion, in stark contrast to the previous work with epoxy alcohol 28a (entry 3 versus Table 3). We observed the optimum headspace/solvent ratio to be 35:1 on small scale; producing a respectable 5.6:1 endo/exo ratio and 33% yield of oxepane 29b. However, we were disappointed to observe incomplete conversion with lower yield and selectivity when attempting to increase the scale 10-fold. Rather than attempting to optimize further this system with [Rh(CO)₂Cl]₂, we set out to identify a new catalyst to overcome the low yield, selectivity and side product formation.

Table 6. Optimization of solvent/headspace ratio for selective formation of 29b

<table>
<thead>
<tr>
<th>entry</th>
<th>headspace/solvent</th>
<th>conversion 28b (%)</th>
<th>29b/30b endo/exo</th>
<th>yield 29b (%)</th>
<th>yield 31b (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8 : 1</td>
<td>&gt;95</td>
<td>5.0 : 1</td>
<td>28</td>
<td>32</td>
</tr>
<tr>
<td>2</td>
<td>35 : 1</td>
<td>&gt;95</td>
<td>5.6 : 1</td>
<td>33</td>
<td>29</td>
</tr>
<tr>
<td>3</td>
<td>open to air</td>
<td>82</td>
<td>nd</td>
<td>18</td>
<td>25</td>
</tr>
<tr>
<td>4²</td>
<td>35 : 1</td>
<td>85</td>
<td>4 : 1</td>
<td>22²</td>
<td>12 ²</td>
</tr>
</tbody>
</table>

² Yields determined by ¹H NMR spectroscopy. ³ nd = not determined, as yield of 30b was <5%. ⁴ 10x scale (0.24 mmol), run in 200 mL Schlenk tube. ⁵ Isolated yield.
D. Cationic Rh(I) as Endo-Selective Catalysts for Epoxy Alcohol Cyclizations

To overcome the issues observed with [Rh(CO)₂Cl]₂ catalysis toward the formation of oxepane 29b, we explored alternative Rh(I) species. We focused on CO-free species in hopes of limiting formation of diene 31b, as well as potentially increasing the lifetime of the catalyst. We screened a variety of related Rh(I) Cl-containing catalysts, however no conversion was observed (Table 7, entries 1–3). Switching to more electron-deficient cationic Rh(I)(diene)₂, we observed the first Rh-based catalysts beyond [Rh(CO)₂Cl]₂ to produce measurable amounts of 29b (entries 4–5). While both the bis-cod and bis-nbd species were exo-selective, we were intrigued by the improved yield and selectivity with nbd. We rationalized that the improvement in selectivity was correlated to increased backbonding from Rh to nbd relative to cod, with the more electron deficient Rh less able to directly activate the exo C–O bond of the epoxide. Further improvement in endo selectivity was achieved by reducing the diene/Rh ratio from 2:1 to 1:1, likely by opening additional sites at Rh for coordination of the enoate (entry 6).

Table 7. Exploration of alternative Rh(I) catalysts

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>conversion 28b (%)a</th>
<th>29b/30b endolexo</th>
<th>yield 29b (%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rh(PPh₃)₃Cl</td>
<td>&lt;5</td>
<td>nd b</td>
<td>nd b</td>
</tr>
<tr>
<td>2</td>
<td>Rh(CO)(PPh₃)₂Cl</td>
<td>&lt;5</td>
<td>nd b</td>
<td>nd b</td>
</tr>
<tr>
<td>3</td>
<td>[Rh(cod)Cl]₂</td>
<td>&lt;5</td>
<td>nd b</td>
<td>nd b</td>
</tr>
<tr>
<td>4</td>
<td>Rh(cod)₂BF₄</td>
<td>81</td>
<td>1 : 7.5</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>Rh(nbd)₂BF₄</td>
<td>88</td>
<td>1 : 1.7</td>
<td>31</td>
</tr>
<tr>
<td>6</td>
<td>[Rh(nbd)Cl]₂/AgBF₄ (1:1)</td>
<td>89</td>
<td>2 : 1</td>
<td>53</td>
</tr>
</tbody>
</table>

a Yields determined by ¹H NMR spectroscopy. b nd = not determined, as yield of 30b was <5%. "--" represents product not observed by ¹H NMR spectroscopy.

Encouraged by the improvement in yield and lack of side product formation, we pursued a preformed variant of the active species formed in the anion exchange reaction, likely
Rh(nbd)(THF)$_n$BF$_4$. Investigation of alternative solvents and anions showed variability in selectivity and conversion with the in situ catalyst formation process, which we attributed to incomplete Cl abstraction and/or excess Ag$^+$ salts. To overcome these issues, we explored a series of bis-CH$_3$CN cationic Rh(I) catalysts, which are readily isolated from ligand exchange of a single diene from the Rh(diene)$_2$X species in CH$_3$CN. Surprisingly, we observed primarily exo opening with the preformed Rh(nbd)(CH$_3$CN)$_2$SbF$_6$ catalyst (Table 8, entry 1). Addition of the non-nucleophilic base DTBMP significantly limited the formation of the exo product, pointing to Brønsted acid catalysis as the source of the exo product 30b (entry 2). Increasing the temperature improved conversion and yield, but failed to exceed 55% conversion (entry 3). Modifying either the counterion or diene component yielded improved conversion, however this was concurrent with a decline in endo selectivity (entries 4–5). We explored a variety of alternative solvents (CH$_2$Cl$_2$, toluene, 1,4-dioxane, 2-MeTHF, DMF, acetone, HFIP, and TFE), however, only THF provided conversions >10%.

Table 8. Exploration of preformed cationic Rh(I) catalysts

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>temp</th>
<th>base (100 mol %)</th>
<th>conversion 28b (%)$^a$</th>
<th>29b/30b endo/exo</th>
<th>yield 29b (%)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rh(nbd)(CH$_3$CN)$_2$SbF$_6$</td>
<td>rt</td>
<td>–</td>
<td>&gt;95</td>
<td>1 : 11</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>Rh(nbd)(CH$_3$CN)$_2$SbF$_6$</td>
<td>rt</td>
<td>DTBMP</td>
<td>15</td>
<td>nd$^b$</td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td>Rh(nbd)(CH$_3$CN)$_2$SbF$_6$</td>
<td>50 °C</td>
<td>DTBMP</td>
<td>55</td>
<td>4 : 1</td>
<td>40</td>
</tr>
<tr>
<td>4</td>
<td>Rh(nbd)(CH$_3$CN)$_2$BF$_4$</td>
<td>50 °C</td>
<td>DTBMP</td>
<td>100</td>
<td>1.3 : 1</td>
<td>45</td>
</tr>
<tr>
<td>5</td>
<td>Rh(cod)(CH$_3$CN)$_2$BF$_4$</td>
<td>50 °C</td>
<td>DTBMP</td>
<td>94</td>
<td>1 : 10</td>
<td>5</td>
</tr>
</tbody>
</table>

$^a$ Yields determined by $^1$H NMR spectroscopy. $^b$ nd = not determined, as yield of 30b was <5%.

24 AgBF$_4$ in THF at room temperature provided 20% of 30b as the only product observed, suggesting excess Ag salts can promote the undesired exo pathway via Lewis acid catalysis.
To improve further the endo/exo selectivity, we explored a more electron-rich vinyl substituent as an alternative π-stabilizing group, hoping to improve the binding with the electron-deficient catalyst. Vinyl epoxide 32 was readily synthesized from epoxide 26b in three steps via alcohol oxidation, Wittig methylenation, and desilylation (Scheme 10).

Scheme 10. Synthesis of vinyl epoxy alcohol for model studies

Subjection of vinyl epoxy alcohol 32 to Brønsted acid demonstrated a modest improvement in electronic biasing for the endo product by the vinyl substituent compared to the enoate, although the reaction was still exo selective (Table 9, entry 1). Use of [Rh(CO)\(_2\)Cl\(_2\)] only returned unreacted epoxide 32, even at elevated temperatures (entry 2). Gratifyingly, the preformed Rh(diene)(CH\(_3\)CN)\(_2\)X (X = SbF\(_6\) or BF\(_4\)) catalysts provided higher yields and selectivities with the vinyl epoxide compared to the enoate epoxide, reaching 8:1 endo/exo selectivity and 60% yield of oxepane 33 (entries 3–5). While the cod-based catalyst was inferior for the enoate substrate, it provided a slight improvement over the nbd catalyst with the vinyl substituent. Attempting to lower the temperature proved unsuccessful, providing only partial conversion (entries 6–7). With our optimized conditions for the vinyl epoxide and cationic Rh(I) catalysts (entry 5), we returned our attention to the synthesis of the triepoxide cascade precursor for hemibrevetoxin B.

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26 Epoxy alcohol 32 was explored by Nakata and coworkers under PPTS catalysis, yielding similar results. See ref 16a.
Table 9. Cyclization studies of vinyl epoxy alcohol 32

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>temp</th>
<th>base (100 mol %)</th>
<th>conversion 32 (%)</th>
<th>33/34</th>
<th>33 (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>(±)-CSA (50 mol %)</td>
<td>rt</td>
<td>–</td>
<td>&gt;95</td>
<td>1 : 2.8</td>
<td>19</td>
</tr>
<tr>
<td>2</td>
<td>[Rh(CO)&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;2&lt;/sub&gt;]</td>
<td>rt or 50 °C</td>
<td>–</td>
<td>&lt;5</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>Rh(nbdt)(CH&lt;sub&gt;3&lt;/sub&gt;CN)&lt;sub&gt;2&lt;/sub&gt;SbF&lt;sub&gt;6&lt;/sub&gt;</td>
<td>50 °C</td>
<td>DTBMP</td>
<td>&gt;95</td>
<td>6 : 1</td>
<td>53</td>
</tr>
<tr>
<td>4</td>
<td>Rh(cod)(CH&lt;sub&gt;3&lt;/sub&gt;CN)&lt;sub&gt;2&lt;/sub&gt;BF&lt;sub&gt;4&lt;/sub&gt;</td>
<td>50 °C</td>
<td>DTBMP</td>
<td>&gt;95</td>
<td>1 : 1.5</td>
<td>28</td>
</tr>
<tr>
<td>5</td>
<td>Rh(cod)(CH&lt;sub&gt;3&lt;/sub&gt;CN)&lt;sub&gt;2&lt;/sub&gt;SbF&lt;sub&gt;6&lt;/sub&gt;</td>
<td>50 °C</td>
<td>DTBMP</td>
<td>88</td>
<td>8 : 1</td>
<td>60</td>
</tr>
<tr>
<td>6</td>
<td>Rh(cod)(CH&lt;sub&gt;3&lt;/sub&gt;CN)&lt;sub&gt;2&lt;/sub&gt;SbF&lt;sub&gt;6&lt;/sub&gt;</td>
<td>35 °C</td>
<td>DTBMP</td>
<td>54</td>
<td>7 : 1</td>
<td>33</td>
</tr>
<tr>
<td>7</td>
<td>Rh(cod)(CH&lt;sub&gt;3&lt;/sub&gt;CN)&lt;sub&gt;2&lt;/sub&gt;SbF&lt;sub&gt;6&lt;/sub&gt;</td>
<td>rt</td>
<td>DTBMP</td>
<td>27</td>
<td>nd&lt;sup&gt;d&lt;/sup&gt;</td>
<td>14</td>
</tr>
</tbody>
</table>

<sup>a</sup> Yields determined by <sup>1</sup>H NMR spectroscopy. <sup>b</sup> Reaction performed with CH<sub>2</sub>Cl<sub>2</sub> as solvent. <sup>c</sup> "-" represents product not observed by <sup>1</sup>H NMR. <sup>d</sup> nd = not determined, as yield of 34 was <5%.

E. Synthesis of Cascade Precursor for Hemibrevetoxin B

Returning to the synthesis of cascade precursor 13, we sought to modify the previous synthetic route to enable late-stage diversification of the π-stabilizing group, as well as improve the convergence by moving the site of fragment coupling closer to the more elaborate preformed A ring template (35, Scheme 11). We planned to implement an sp<sup>2</sup>-sp<sup>3</sup> Suzuki cross-coupling of alkenyl iodide 36 and alkyl borane 37, based on precedent from Corey and coworkers. We planned on accessing alkenyl iodide 36 from THP 38, which ultimately could be derived from a related sequence as used in the previous synthetic efforts (Scheme 5). We planned to utilize 2,3-epoxy geraniol to access alkyl borane 37, via oxidative alkene cleavage and subsequent homologation.
Scheme 11. Retrosynthetic analysis for the second-generation synthesis of 13

Synthesis of the A-ring THP was initiated with a [4+2] asymmetric hetero-Diels–Alder cycloaddition of aldehyde 40 and diene 41, catalyzed in good yield and enantioselectivity by Cr catalyst 42 (Scheme 12). Elaboration of pyrone 43 proceeded by stereoselective Luche reduction, epoxidation, methanolysis, and silyl protection. Lewis acid mediated allylation of 44 installed the allyl functionality with high stereoselectivity and yield. Cross metathesis with isoprenyl boronic ester 45 provided 47, which could readily be separated from the undesired E isomer. Finally, stereoretentive iodo-deboronation yielded the desired (E)-alkenyl iodide in moderate yield.

Scheme 12. Synthesis of alkenyl iodide 36

Synthesis of the cross coupling partner was accomplished starting from 2,3-epoxy-geraniol 39, via TBDPS protection of the alcohol, ozonolysis of the alkene, and in situ stabilized Wittig olefination to provide enoate 48 (Scheme 13). Subsequent DIBAL-H reduction to the allylic alcohol, oxidation to the enal, and finally Wittig methylenation provided diene 49.

Scheme 13. Synthesis of diene 49
Fragment coupling via Suzuki cross coupling provided diene 35 in excellent yield and stereochemical purity, with good functional group tolerance for the preinstalled epoxide (Scheme 14). Selective desilylation of the 1° TBDPS ether in the presence of two 2° TBS ethers, followed by alcohol oxidation and methylenation provided triene 50. Finally, exhaustive desilylation and asymmetric Shi epoxidation afforded the desired cascade precursor 13. We attributed the low yield of the final two steps to incomplete epoxidation of the disubstituted alkene as well as modest amounts of epoxidation of the vinyl group.

**Scheme 14.** Fragment coupling and synthesis of triepoxide 13

<table>
<thead>
<tr>
<th>Reaction Steps</th>
<th>Product Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>i. 9-BBN-H, THF, rt, 3 h</td>
<td>OTBS</td>
</tr>
<tr>
<td>ii. 1M NaOH(aq)</td>
<td>OTBS</td>
</tr>
<tr>
<td>iii. PdCl₂(dppf) (5 mol %), Me₃ (1.0 equiv), rt, 3 h</td>
<td>36 (75%)</td>
</tr>
</tbody>
</table>

1. TBAF (1 equiv), THF, 0 °C to 2. pyr-SO₂Et₃N, DMSO/CH₂Cl₂
3. Ph₃PCH₂Br, t-BuOK
65% (over 3 steps)

1. TBAF (3 equiv), THF, rt
2. (+)-51, Oxone®, Bu₄NOH, K₂CO₃, DMM/CH₃CN (2:1)
36% (over 2 steps), 3.5:1 dr

F. Exploration of Epoxide-Opening Cascade and Future Directions

With triepoxide 13 in hand, we explored the proposed epoxide-opening cascade for the synthesis of hemibrevetoxin B. Application of the optimized conditions utilizing the cationic Rh(I) catalyst proved too reactive for the sensitive substrate, producing >10 products from analysis of the 1H NMR spectrum of the crude reaction mixture (Table 10, entry 1). While we lacked an authentic sample of the desired tetracycle 52, Yamamoto’s route for the synthesis of hemibrevetoxin B proceeded through a nearly identical structure, differing only by the protecting group on the A-ring side chain (TIPS instead of Bn).³⁰ Comparison of the data provided for Yamamoto’s intermediate to the 1H NMR spectrum of the crude reaction mixture highly suggested that the complex mixture

did not contain any of the desired product 52. Attempts to lower the temperature or utilize the nbd catalyst did not significantly impact the reaction outcome (entries 2–3).

We hypothesized that the lower nucleophilicity of the disubstituted epoxide trapping nucleophile relative to the 1° alcohol used in the model studies could result in significant side reactivity. Additionally, THF could potentially outcompete intramolecular trapping by the neighboring epoxide, as these electrophilic epoxide-opening cascades are often performed in weakly or non-nucleophilic solvents like HFIP, CH₂Cl₂, or toluene. Since we observed significant signals corresponding to polymerized THF by ¹H NMR spectroscopy, we attempted to run this reaction in cosolvent mixtures of either HFIP or TFE, however, no improvement was observed (entries 4–5).

Table 10. Investigation of epoxide-opening cascade of triepoxide 13

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>temp</th>
<th>base (100 mol %)</th>
<th>solvent</th>
<th>result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rh(cod)(CH₃CN)₂SbF₆</td>
<td>50 °C</td>
<td>DTBMP</td>
<td>THF</td>
<td>complex mixture</td>
</tr>
<tr>
<td>2</td>
<td>Rh(cod)(CH₃CN)₂SbF₆</td>
<td>rt</td>
<td>DTBMP</td>
<td>THF</td>
<td>complex mixture</td>
</tr>
<tr>
<td>3</td>
<td>Rh(nbd)(CH₃CN)₂SbF₆</td>
<td>rt</td>
<td>DTBMP</td>
<td>THF</td>
<td>complex mixture</td>
</tr>
<tr>
<td>4</td>
<td>Rh(cod)(CH₃CN)₂SbF₆</td>
<td>rt</td>
<td>DTBMP</td>
<td>3:1 HFIP/THF</td>
<td>complex mixture</td>
</tr>
<tr>
<td>5</td>
<td>Rh(cod)(CH₃CN)₂SbF₆</td>
<td>rt</td>
<td>DTBMP</td>
<td>3:1 TFE/THF</td>
<td>complex mixture</td>
</tr>
</tbody>
</table>

In addition to the solvent compatibility issues with the substrate, we also think that the cationic Rh(I) catalysts are too Lewis acidic for the sensitive triepoxide substrate. The proposed cascade shown in Scheme 3 requires site-selective initiation of the epoxide-opening cascade at the alkenyl epoxide in order to achieve the desired all-endo selectivity. Given the slow rate of cyclization observed in the model studies, an additional possibility is the early attack of the A-ring hydroxyl on the closest epoxide. While we lack direct evidence to support this theory, acid-catalyzed 6-endo cyclizations of this type are rapid, and could easily outcompete the desired

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pathway. At this juncture, further work is needed to explore alternative \( \pi \)-stabilization groups and Rh catalysts that would allow for the desired reactivity under milder conditions.

Alternatively, we have proposed a modified synthesis of hemibrevetoxin B outlined in Scheme 15. Instead of utilizing a triepoxide cascade to form the BCD rings, we propose a \([\text{Rh(CO)}_2\text{Cl}]_2\)-catalyzed diepoxide cascade to form the BC rings (55 to 56), similar to the ABC tricycle, and a subsequent cyclization of the D ring, utilizing \(\text{Rh(cod)}(\text{CH}_3\text{CN})_2\text{SbF}_6\) to catalyze the endo-selective closure of the vinyl epoxy alcohol (60 to 52). While modifying the alcohol nucleophile from 1° to 2° could potential slow down the rate of D-ring cyclization, this would likely be balanced by the increase in rate by removal of degrees of rotational freedom imposed by the ABC tricycle as compared to the model study substrates.

Starting from 47, we envision a Pd-catalyzed \(sp^3\)-\(sp^2\) Suzuki cross-coupling utilizing conditions developed by the Fu lab to synthesize epoxide 54.\(^{32,33}\) Subsequent Shi asymmetric epoxidation and desilylation should generate cascade precursor 55. Given the similarities to the cascades for the synthesis of the EF and ABC fragments of brevisin, we think the cascade from 55 to 56 has a high likelihood of success. Synthesis of D-ring cyclization precursor 60 is proposed as a five-step sequence from ABC tricycle 56. Following protection of the diol to a bis-silyl ether, cross metathesis with ethylene should provide alkene 57. Hydroboration of alkene 57 and a subsequent in situ Pd-catalyzed Suzuki cross-coupling with alkenyl iodide 58 should rapidly generate the desired (E)-trisubstituted alkene 59. Shi asymmetric epoxidation and desilylation should provide the D-ring cyclization precursor 60. Cyclization of vinyl epoxy alcohol 60 under cationic Rh(I) catalysis would provide ABCD tetracycle 52, representing the full core of hemibrevetoxin B. This modified sequence would only add two steps to the LLS toward 52 as compared to the previous triepoxide cascade approach.

To complete our proposal for a total synthesis of hemibrevetoxin B, we propose utilizing a second hydroboration/Suzuki cross-coupling to rapidly form the (Z)-diene side chain (52 to 62). To install the enal functional group, we could utilize alcohol oxidation and in situ methylation utilizing Eschenmoser’s reagent, similarly to the synthesis of hemibrevetoxin B reported by Nicolaou and coworkers.\(^2\) A final desilylation should complete the total synthesis of hemibrevetoxin B (1) in 22 steps LLS. Synthesis of the D ring via an epoxy alcohol cyclization would represent the first example of oxepane formation from an endo-selective proximal-methyl-

substituted epoxide in the context of a ladder polyether synthesis, while also avoiding the late-stage methyl group installation utilized in other syntheses of 1.

Scheme 15. Proposed synthesis of hemibrevetoxin B utilizing D ring cyclization
G. Conclusions

In summary, we have developed several combinations of Rh catalysts and π-stabilizing groups to override the typically high \textit{exo} selectivity observed in cyclizations of proximal-methyl-substituted epoxy alcohols, allowing for the rapid synthesis of THPs and oxepanes. During the course of this study, we found that the optimum carbonyl/Rh ratio is 1:1 when using $[\text{Rh(CO)}_2\text{Cl}]_2$ as a catalyst to achieve high \textit{endo} selectivity. Furthermore, we have found cationic Rh diene species to be highly efficient catalysts for these epoxy alcohol cyclizations as well. Towards the goal of a rapid synthesis of hemibrevetoxin B, we have developed a streamlined synthesis of triepoxide 13 that also allows for late-stage diversification of the π-stabilizing group for future studies.
H. General Experimental

All reactions were performed under an atmosphere of argon under anhydrous conditions, unless otherwise noted. Dichloromethane, tetrahydrofuran (THF), Et₂O, benzene, dioxane and triethylamine were purified via an SG Water USA solvent column system. Unless otherwise noted, all reagents were commercially obtained and used without further purification. Analytical thin layer chromatography (TLC) was performed using EM Science silica gel 60 F₂₅₄ plates, visualizing with a UV lamp (254 nm), KMnO₄, p-anisaldehyde, or CAM. Liquid chromatography was performed using forced flow (flash chromatography) of the indicated solvent system on Silicycle silica gel (230–400 mesh) or Biotage® Isolera flash purification system on SNAP HP-SIL columns.

¹H NMR and ¹³C Nuclear Magnetic Resonance (NMR) spectra were recorded at ambient temperature at 600 MHz and 150 MHz, respectively, using a Bruker AVANCE-600 spectrometer or 500 MHz and 125 MHz, respectively, using a Varian Inova-500 spectrometer. The ¹H NMR data are reported as follows: chemical shift in parts per million (ppm) from an internal standard of residual CHCl₃ in CDCl₃ (7.27 ppm) on the d scale, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants in hertz (Hz), and integration (H). Chemical shifts of ¹³C NMR spectra are reported in ppm from the central peak of CDCl₃ (77.2 ppm).

Infrared (IR) spectra were recorded on a Perkin-Elmer Model 2000 FT-IR or an Agilent Cary 630 FTIR Spectrometer. High-resolution mass spectra (HR-MS) were acquired on a Bruker Daltronics APEXIV 4.7 Tesla Fourier Transform Ion Cyclotron Resonance Mass Spectrometer at the Massachusetts Institute of Technology Department of Chemistry Instrumentation Facility. Optical rotations were measured using a Jasco Model 1010 digital polarimeter at 589 nm and calculated using the formula: [α]D = aobs/(l(c/1000)), where c = (g of substrate/100 mL of solvent) and l = 1 dm.

Alkyne 24a: To a solution of 4-pentyn-1-ol (4.21 g, 50.0 mmol) and imidazole (4.77 g, 70.0 mmol) in DMF (50 mL) cooled to 0 °C was added TBDPSCI (15.6 mL, 60.0 mmol). After 5 h, the reaction was quenched with the addition of H₂O (50 mL) and diluted with Et₂O (50 mL). The aqueous layer was separated and extracted twice with Et₂O (20 mL each). The combined organics were washed with H₂O (2 x 25 mL), sat. NaCl(aq) (25 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo to afford crude alkyne 24a as a pale yellow oil. The crude product was purified by flash chromatography (100% hexanes to 5% EtOAc in hexanes) to afford 24a as a colorless oil (16.3 g, 48.5 mmol, 97%).

¹H NMR (500 MHz, CDCl₃): δ 7.71-7.69 (m, 4H), 7.47-7.39 (m, 6H), 3.78 (t, J = 6.0 Hz, 2H), 2.38 (td, J = 7.2, 2.6 Hz, 2H), 1.94 (t, J = 2.7 Hz, 1H), 1.83-1.78 (m, 2H), 1.08 (s, 9H).

¹³C NMR (125 MHz, CDCl₃): δ 135.7, 134.0, 129.8, 127.8, 84.4, 68.5, 62.4, 31.6, 27.0, 19.4, 15.2.

IR (thin film): 3303, 3069, 2932, 2857, 1889, 1824, 1589, 1472, 1426, 189, 1361, 1259, 1189, 1104, 1007 cm⁻¹.

HR-MS (DART) m/z calcd for C₂₁H₂₆OSi (M+H)⁺: 323.1826, found 323.1816.
Alkyne 24b: To a solution of 5-pentyn-1-ol (3.93 g, 40.0 mmol) and imidazole (3.81 g, 56.0 mmol) in DMF (40 mL) cooled to 0 °C was added TBDPSCI (12.5 mL, 48.0 mmol). After 5 h, the reaction was quenched with the addition of H2O (40 mL) and diluted with Et2O (40 mL). The aqueous layer was separated and extracted twice with Et2O (20 mL each). The combined organics were washed with H2O (2 x 40 mL), sat. NaCl(aq) (40 mL), dried over Na2SO4, filtered, and concentrated in vacuo to afford crude alkyne 24b as a pale yellow oil. The crude product was purified by flash chromatography (100% hexanes to 5% EtOAc in hexanes) to afford 24b as a colorless oil (12.8 g, 38 mmol, 95%).

1H NMR (500 MHz, CDCl3): δ 7.69-7.67 (m, 4H), 7.45-7.38 (in, 6H), 3.69 (t, J = 5.9 Hz, 2H), 2.21 (td, J = 6.8, 2.6 Hz, 2H), 1.95 (t, J = 2.6 Hz, 1H), 1.72-1.62 (m, 4H), 1.06 (s, 9H).

13C NMR (125 MHz, CDCl3): δ 135.7, 134.1, 129.7, 127.8, 84.7, 68.4, 63.5, 31.7, 27.0, 25.1, 19.4, 18.4.

IR (thin film): 3306, 3069, 2932, 2858, 1888, 1824, 1589, 1472, 1427, 1389, 1361, 1261, 1188, 1106, 1008 cm⁻¹.

HR-MS (DART) m/z calcd for C22H28OSi (M+H)⁺: 337.1982, found 337.1969.

Alcohol 25a:34 To (±)-(ebi)ZrCl235 (0.20 g, 0.48 mmol) was added AlMe3 in toluene (7.2 mL, 2.0 M, 14.4 mmol), MAO in toluene (0.32 mL, 10 wt%, 0.48 mmol), and finally alkyne 24b (3.10 g, 9.6 mmol). The reaction, which became very viscous, was stirred at room temperature. After 20 h, the reaction mixture was concentrated in vacuo (25 °C, 1 torr) and refilled with Ar. The viscous oil was diluted with THF (10 mL), and n-BuLi in hexanes (5.2 mL, 1.94 M, 10.1 mmol) was added dropwise over 2 min. After stirring at room temperature for 30 min, a suspension of paraformaldehyde (0.86 g, 28.8 mmol) in THF (20 mL) was added. After an additional 4 h, the reaction was diluted with hexanes (10 mL) and quenched with the dropwise addition of 1 M HCl(aq) (5 mL), and the combined mixture was poured into sat. Rochelle’s salt in water (100 mL). After stirring vigorously for 10 min, the mixture was allowed to stand for 10 min, and the organic layer was separated from the gelatinous aqueous layer. To the aqueous layer was added hexanes (10 mL) and EtOAc (10 mL), and the combined mixture was vigorously stirred for 1 h, followed by separation of the organic layer. The combined organic layers were dried Na2SO4, filtered, and concentrated in vacuo to afford a yellow oil. The crude product was purified by flash chromatography (5–45% EtOAc in hexanes) to afford 25a as a colorless oil (1.60 g, 4.3 mmol, 45%).

35 Purchased from Strem Chemicals Inc.
\[ ^1\text{H NMR (500 MHz, CDCl}_3\]: } \delta 7.70-7.68 \text{ (m, 4H), 7.46-7.38 \text{ (m, 6H), 5.40 (t, } J = 6.9 \text{ Hz, 1H), 4.14 (d, } J = 6.9 \text{ Hz, 2H), } 3.67 \text{ (t, } J = 6.4 \text{ Hz, 2H), 2.12 (t, } J = 7.7 \text{ Hz, 2H), 1.73-1.67 \text{ (m, 2H), 1.66 (s, 3H), 1.23 (br, 1H), 1.07 (s, 9H).} \\
\[ ^{13}\text{C NMR (125 MHz, CDCl}_3\]: } \delta 139.7, 135.7, 134.2, 129.7, 127.8, 123.6, 63.6, 59.5, 35.9, 30.8, 27.0, 19.4, 16.4. \\
\text{IR (thin film): } 3326, 2068, 2931, 2856, 1888, 1825, 1668, 1589, 1472, 1427, 1388, 1304, 1253, 1188, 1106 \text{ cm}^{-1}. \\
\text{HR-MS (DART) } m/z \text{ calcld for C}_{23}H_{32}O_2Si (M+NH}_4\): 386.2510, found 386.2501. \\

\[ \text{Alcohol 25b:}^\text{36} \text{ To } (\pm)-(ebi)ZrCl}_2 \text{ (0.40 g, 0.96 mmol) was added } \text{AlMe}_3 \text{ in toluene (14.4 mL, 2.0 M, 28.8 mmol), MAO in toluene (0.64 mL, 10 wt%, 0.96 mmol), and finally alkyne 24b (6.46 g, 19.2 mmol). The reaction, which became very viscous, was stirred at room temperature. After 20 h, the reaction mixture was concentrated } \text{in vacuo} \text{ (25 °C, 1 torr) and refilled with Ar. The viscous oil was diluted with THF (19 mL), and n-BuLi in hexanes (9.4 mL, 2.25 M, 21.1 mmol) was added dropwise over 2 min. After stirring at room temperature for 30 min, a suspension of paraformaldehyde (1.73 g, 57.6 mmol) in THF (40 mL) was added. After an additional 4 h, the reaction was diluted with hexanes (20 mL) and quenched with the dropwise addition of 1 M HCl(aq) (5 mL), and the combined mixture was poured into sat. Rochelle’s salt in water (200 mL). After stirring vigorously for 10 min, the mixture was allowed to stand for 10 min, and the organic layer was separated from the gelatinous aqueous layer. To the aqueous layer was added hexanes (20 mL) and EtOAc (20 mL), and the combined mixture was vigorously stirred for 2.5 h, followed by separation of the organic layer. The combined organic layers were dried Na$_2$SO$_4$, filtered, and concentrated } \text{in vacuo } \text{to afford a yellow oil. The crude product was purified by flash chromatography (10–30% EtOAc in hexanes) to afford 25b as a colorless oil (4.1 g, 10.7 mmol, 56%).} \\
\[ ^1\text{H NMR (500 MHz, CDCl}_3\]: } \delta 7.69-7.67 \text{ (m, 4H), 7.45-7.37 \text{ (m, 6H), 5.39 (tq, } J = 7.0, 1.3 \text{ Hz, 1H), 4.15 (d, } J = 6.9 \text{ Hz, 2H), 3.67 (t, } J = 6.1 \text{ Hz, 2H), 2.01 (t, } J = 7.1 \text{ Hz, 2H), 1.66 (d, } J = 0.4 \text{ Hz, 3H), 1.57-1.49 \text{ (m, 5H), 1.06 (s, 9H).} \\
\[ ^{13}\text{C NMR (150 MHz, CDCl}_3\]: } \delta 139.7, 135.7, 134.1, 129.6, 127.7, 123.5, 63.8, 59.4, 39.3, 32.2, 27.0, 23.9, 19.3, 16.2. \\
\text{IR (thin film): } 3336, 3067, 2931, 2858, 1665, 1589, 1472, 1428, 1388, 1361, 1305, 1187, 1106 \text{ cm}^{-1}. \\
\text{HR-MS (DART) } m/z \text{ calcld for C}_{24}H_{34}O_2Si (M+NH}_4\): 400.2666, found 400.2654. \\

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\text{36} \text{ Procedure modified from the following report: Lipshutz, B. H.; Butler, T.; Lower, A. J. Am. Chem. Soc. 2006, 128, 15396.} \\
\text{37} \text{ Purchased from Strem Chemicals Inc.}
Epoxide 26a: To a solution of alcohol 25a (1.28 g, 3.47 mmol) in CH₂Cl₂ (34 mL) at 0 °C was added mCPBA (≤ 77 wt %, 1.13 g, 5.0 mmol) as a solid in one portion. The reaction was allowed to warm to room temperature and stirred for 2 h, and then quenched by addition of 10% Na₂CO₃ (aq) (50 mL). The aqueous layer was separated and extracted twice with CH₂Cl₂ (25 mL each). The combined organic layer was washed with sat. NaHSO₃ (aq) (25 mL), and 10% Na₂CO₃ (aq) (25 mL). The combined organics were dried over Na₂SO₄, filtered and concentrated in vacuo to afford crude alcohol 26a as a colorless oil. The crude product was purified by flash chromatography (10% EtOAc in hexanes to 40% EtOAc in hexanes) to afford 26a as a colorless oil (1.28 g, 3.33 mmol, 96%).

¹H NMR (500 MHz, CDCl₃): δ 7.68-7.65 (m, 4H), 7.45-7.38 (m, 6H), 3.80 (dd, J = 11.9, 3.9 Hz, 1H), 3.70-3.66 (m, 3H), 2.95 (dd, J = 6.6, 4.4 Hz, 1H), 1.73-1.58 (m, 5H), 1.28 (s, 3H), 1.06 (s, 9H).

¹³C NMR (125 MHz, CDCl₃): δ 135.7, 134.01, 134.00, 129.79, 129.79, 127.8, 63.6, 62.9, 61.6, 61.3, 35.0, 28.3, 27.0, 19.4, 17.0.

IR (thin film): 3410, 3054, 2931, 2857, 2857, 1590, 1472, 1427, 1386, 1361, 1255, 1188, 1105, 1087, 1026 cm⁻¹.

HR-MS (ESI) m/z calcd for C₂₃H₃₂O₃Si (M+Na⁺): 407.2013, found 407.2029.

Epoxide 26b: To a solution of alcohol 25b (3.50 g, 9.2 mmol) in CH₂Cl₂ (92 mL) at 0 °C was added mCPBA (≤ 77 wt %, 3.08 g, 13.7 mmol) as a solid in one portion. The reaction was allowed to warm to room temperature and stirred for 2 h, and then quenched by addition of 10% Na₂CO₃ (aq) (90 mL). The aqueous layer was separated and extracted twice with CH₂Cl₂ (50 mL each). The combined organic layer was washed with sat. NaHSO₃ (aq) (50 mL), and 10% Na₂CO₃ (aq) (50 mL). The combined organics were dried over Na₂SO₄, filtered and concentrated in vacuo to afford crude alcohol 26b as a colorless oil. The crude product was purified by flash chromatography (10% EtOAc in hexanes to 40% EtOAc in hexanes) to afford 26b as a colorless oil (3.36 g, 8.43 mmol, 92%).

¹H NMR (MHz, CDCl₃): δ 7.69-7.67 (m, 4H), 7.45-7.38 (m, 6H), 3.84 (d, J = 11.4 Hz, 1H), 3.71-3.66 (m, 3H), 2.95 (dd, J = 6.7, 4.2 Hz, 1H), 1.90 (br, 1H), 1.66-1.43 (m, 6H), 1.29 (s, 3H), 1.07 (s, 9H).

¹³C NMR (125 MHz, CDCl₃): δ 135.7, 134.1, 129.7, 127.8, 63.7, 63.0, 61.6, 61.5, 38.3, 32.5, 27.0, 21.6, 19.4, 16.8.

IR (thin film): 3405, 3069, 2931, 2858, 1472, 1428, 1386, 1187, 1105, 1027 cm⁻¹.
HR-MS (ESI) m/z calcd for C$_{24}$H$_{34}$O$_3$Si (M+Na)$^+$: 421.2169, found 421.2186.

**Epoxy Enolate 27a**: To a solution of epoxy alcohol 26a (1.24 g, 3.21 mmol) in CH$_2$Cl$_2$ (31 mL) was added DMSO (3.1 mL, 44 mmol) and Et$_3$N (2.2 mL, 16 mmol), cooled to 0 ºC, and Pyr*SO$_3$ (0.99 g, 6.2 mmol) added as a solid. The reaction was allowed to warm to room temperature and stirred for 3 h. At this point, (carbethoxymethylene)triphenylphosphorane (2.63 g, 7.56 mmol) was added as a solid at room temperature and stirred for 4 h. The reaction was quenched by addition of H$_2$O (20 mL) and diluted with CH$_2$Cl$_2$ (20 mL). The aqueous layer was separated and extracted twice with CH$_2$Cl$_2$ (20 mL each). The combined organics were washed with H$_2$O (20 mL), sat. NaCl$_{aq}$ (20 mL), dried over Na$_2$SO$_4$, filtered and concentrated in vacuo to afford crude enoate 27a as a yellow oil. The crude product was purified by flash chromatography (5–10% EtOAc in hexanes) to afford 27a as a colorless oil (1.36 g, 3.00 mmol, 94%, 4:1 E/Z).

The product was purified further by MPLC (Biotage Ultra Column) with a gradient of solvents (6–12% EtOAc in hexanes) to afford 27a as only the (E)-alkene (0.77 g, 1.70 mmol, 53%).

$^1$H NMR (500 MHz, CDCl$_3$): δ 7.68-7.66 (m, 4H), 7.46-7.38 (m, 6H), 6.08 (dd, J = 15.7, 6.5 Hz, 1H), 6.08 (dd, J = 15.7, 1.0 Hz, 1H), 4.23 (qd, J = 7.1, 2.3 Hz, 2H), 3.68 (t, J = 5.7 Hz, 2H), 3.30 (dd, J = 6.5, 0.7 Hz, 1H), 1.79-1.62 (m, 4H), 1.32 (t, J = 7.1 Hz, 3H), 1.26 (s, 3H), 1.06 (s, 9H).

$^{13}$C NMR (125 MHz, CDCl$_3$): δ 165.9, 143.0, 135.7, 133.95, 133.92, 129.82, 129.81, 127.84, 127.82, 125.0, 64.3, 63.5, 61.4, 60.7, 34.9, 28.3, 27.0, 19.4, 16.8, 14.4.

IR (thin film): 3069, 2932, 2858, 1718, 1653, 1589, 1472, 1428, 1387, 1366, 1301, 1259, 1175, 1105, 1038 cm$^{-1}$.

HR-MS (DART) m/z calcd for C$_{27}$H$_{36}$O$_4$Si (M+NH$_4$)$^+$: 470.2721, found 470.2737.

**Epoxy Enolate 27b**: To a solution of epoxy alcohol 26b (1.38 g, 3.46 mmol) in CH$_2$Cl$_2$ (34 mL) was added DMSO (3.5 mL, 49 mmol) and Et$_3$N (2.4 mL, 17 mmol), cooled to 0 ºC, and Pyr*SO$_3$ (1.10 g, 6.9 mmol) added as a solid. The reaction was allowed to warm to room temperature and stirred for 3 h. At this point, (carbethoxymethylene)triphenylphosphorane (2.41 g, 6.9 mmol) was added as a solid at room temperature and stirred for 5 h. The reaction was quenched by addition of H$_2$O (20 mL) and diluted with CH$_2$Cl$_2$ (20 mL). The aqueous layer was separated and extracted twice with CH$_2$Cl$_2$ (20 mL each). The combined organics were washed with H$_2$O (20 mL), sat. NaCl$_{aq}$ (20 mL), dried over Na$_2$SO$_4$, filtered and concentrated in vacuo to afford crude enoate 27b as a yellow oil. The crude product was purified by flash chromatography (5–10% EtOAc in hexanes) to afford 27b as a colorless oil (1.37 g, 2.93 mmol, 85%, 5:1 E/Z).
purified further by MPLC (Biotage Ultra Column) with a gradient of solvents (5–10% EtOAc in hexanes) to afford 27b as only the (E)-alkene (1.13 g, 2.42 mmol, 70%).

\[ \text{H NMR (600 MHz, CDCl}_3\text{): } \delta 7.68-7.67 (m, 4H), 7.45-7.38 (m, 6H), 6.85 (dd, \text{J} = 15.7, 6.4 \text{ Hz, 1H}), 6.11 (d, \text{J} = 15.7 \text{ Hz, 1H}), 4.26-4.20 (m, 2H), 3.68 (t, \text{J} = 6.0 \text{ Hz, 2H}), 3.29 (d, \text{J} = 6.5 \text{ Hz, 1H}), 1.70-1.65 (m, 1H), 1.60-1.48 (m, 5H), 1.32 (t, \text{J} = 7.1 \text{ Hz, 3H}), 1.27 (s, 3H), 1.06 (s, 9H). \]

\[ \text{C NMR (150 MHz, CDCl}_3\text{): } \delta 165.9, 143.1, 135.7, 134.1, 129.7, 127.8, 124.9, 64.5, 63.6, 61.5, 60.8, 38.2, 32.5, 27.0, 21.6, 19.4, 16.6, 14.4. \]

IR (thin film): 2934, 2858, 1716, 1654, 1472, 1428, 1387, 1366, 1301, 1175, 1105, 1041 cm\(^{-1}\).

HR-MS (ESI) \( m/z \) calcd for C\(_{28}\)H\(_{38}\)O\(_4\)Si (M+Na): 489.2432, found 489.2423.

Epoxy Alcohol 28a: To a solution of enolate 27a (0.77 g, 1.70 mmol) in THF (3.4 mL) at 0 °C was added TBAF (1.0 M in THF, 3.4 mL, 3.4 mmol) dropwise over 1 min. The reaction was stirred and allowed to warm to room temperature over 2 h. The crude reaction mixture was purified without concentration by flash chromatography (pretreated with 1% Et\(_3\)N in 50% EtOAc in hexanes, then 50% EtOAc in hexanes to 60% EtOAc in hexanes) to afford 28a as a colorless oil (0.35 g, 1.63 mmol, 96%).

\[ \text{H NMR (MHz, CDCl}_3\text{): } \delta 6.81 (dd, \text{J} = 15.7, 6.4 \text{ Hz, 1H}), 6.08 (dd, \text{J} = 15.7, 0.8 \text{ Hz, 1H}), 4.18 (qd, \text{J} = 7.1, 1.4 \text{ Hz, 2H}), 3.63 (t, \text{J} = 4.4 \text{ Hz, 2H}), 3.34 (dd, \text{J} = 6.4, 0.6 \text{ Hz, 1H}), 2.18 (br, 1H), 1.73-1.63 (m, 4H), 1.27 (t, \text{J} = 7.1 \text{ Hz, 3H}), 1.26 (s, 3H). \]

\[ \text{C NMR (125 MHz, CDCl}_3\text{): } \delta 165.8, 142.6, 125.1, 64.2, 62.3, 61.6, 60.8, 34.7, 28.0, 16.6, 14.3. \]

IR (thin film): 3421, 2941, 2877, 1716, 1654, 1449, 1387, 1368, 1302, 1259, 1177, 1134, 1095, 1032 cm\(^{-1}\).

HR-MS (DART) \( m/z \) calcd for C\(_{11}\)H\(_{18}\)O\(_4\) (M+NH\(_4\))+: 232.1543, found 232.1550.

Epoxy Alcohol 28b: To a solution of enolate 27b (0.76 g, 1.63 mmol) in THF (3.3 mL) at 0 °C was added TBAF (1.0 M in THF, 3.3 mL, 3.3 mmol) dropwise over 1 min. The reaction was stirred and allowed to warm to room temperature over 2 h. The crude reaction mixture was purified without concentration by flash chromatography (pretreated with 1% Et\(_3\)N in 50% EtOAc in
hexanes, then 50% EtOAc in hexanes to 70% EtOAc in hexanes) to afford 28b as a colorless oil (0.32 g, 1.40 mmol, 87%).

1H NMR (MHz, CDCl₃): δ 6.82 (dd, J = 15.7, 6.5 Hz, 1H), 6.09 (d, J = 15.7 Hz, 1H), 4.24-4.17 (m, 2H), 3.66 (t, J = 6.1 Hz, 2H), 3.32 (d, J = 6.5 Hz, 1H), 1.73-1.67 (m, 1H), 1.61-1.47 (m, 6H), 1.31-1.27 (m, 6H).

13C NMR (125 MHz, CDCl₃): δ 165.9, 142.9, 125.1, 64.4, 62.7, 61.4, 60.8, 38.2, 32.6, 21.6, 16.7, 14.4.

IR (thin film): 3425, 2939, 2867, 1718, 1653, 1459, 1368, 1304, 1260, 1176, 1096, 1038 cm⁻¹.

HR-MS (ESI) m/z calcd for C₁₂H₂₀O₄ (M+Na)⁺: 251.1254, found 251.1240.

HO
OEt

28a

[±]-CSA promoted cyclization of epoxy alcohol 28a: To a 20 ml vial equipped with a magnetic stir bar was added epoxide 28a (50 mg, 0.23 mmol) in CH₂Cl₂ (12 mL) and (±)-CSA (5 mg, 0.02 mmol) and stirred at room temperature. After consumption of the starting material (30 min, as determined by TLC analysis), the clear solution was filtered through a plug of silica gel (prewashed with 2% Et₃N in EtOAc then 2xEtOAc), eluted with EtOAc, and concentrated in vacuo. 1H NMR spectroscopic analysis of the unpurified mixture indicated a 1:20 [endo(29a) / exo(30a)] ratio of products. The resultant clear film was purified by flash chromatography (20-40% EtOAc/hexanes) to afford 30a as a colorless oil (48 mg, 0.22 mmol, 96%).

1H NMR (400 MHz, CDCl₃): δ 6.93 (dd, J = 15.6, 4.6 Hz, 1H), 6.18 (dd, J = 15.6, 1.9 Hz, 1H), 4.25 (dd, J = 4.6, 1.9 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 3.95-3.85 (m, 2H), 2.57 (br, 1H), 2.02-1.87 (m, 3H), 1.50-1.44 (m, 1H), 1.29 (t, J = 7.1 Hz, 3H), 1.21 (s, 3H).

13C NMR (100 MHz, CDCl₃): δ 166.6, 145.4, 122.5, 85.1, 76.2, 68.7, 60.6, 31.4, 26.5, 23.8, 14.4.

IR (thin film): 3435, 2976, 2873, 1717, 1656, 1448, 1369, 1305, 1272, 1175, 1094, 1036 cm⁻¹.

HR-MS (DART) m/z calcd for C₁₁H₁₆O₄ (M+H)⁺: 215.1278, found 215.1291.

HO
OEt

28a

[Rh(CO)₂Cl]₂ promoted cyclization of epoxy alcohol 28a: To a 100 ml round bottom flask equipped with a magnetic stir bar open to air was added epoxide 28a (47.4 mg, 0.22 mmol) and a solution of [Rh(CO)₂Cl]₂ in 1,4-dioxane (8.5 mg, 22 μmol, in 4.4 mL 1,4-dioxane) and quickly heated to 80 °C in an oil bath. After consumption of the starting material (30 min, as determined
by TLC analysis), the reaction was removed from the oil bath and 150 mg of polymer-bound triphenylphosphine resin was added and stirred for 2 h. The cloudy brown solution was filtered through a plug of silica gel (prewashed with 2% Et$_3$N in EtOAc then 2xEtOAc), eluted with EtOAc, and concentrated in vacuo. $^1$H NMR spectroscopic analysis of the unpurified mixture indicated a 12.5:1 [endo(29a)/exo(30a)] ratio of products. The resultant pale yellow film was purified by flash chromatography (20–40% EtOAc/hexanes) to afford 29a as a colorless oil (35.5 mg, 0.20 mmol, 76%).

Characterization Data for 29a:

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.07 (dd, $J = 15.8, 4.2$ Hz, 1H), 6.08 (dd, $J = 15.8, 1.9$ Hz, 1H), 4.19 (q, $J = 7.1$ Hz, 2H), 4.01 (ddt, $J = 11.4, 3.1, 1.6$ Hz, 1H), 3.80 (dd, $J = 4.2, 1.9$ Hz, 1H), 3.43 (td, $J = 11.7, 2.5$ Hz, 1H), 1.90-1.87 (m, 2H), 1.77-1.70 (m, 1H), 1.67-1.61 (m, 2H), 1.28 (t, $J = 7.1$ Hz, 3H), 1.16 (s, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 166.6, 144.2, 122.4, 83.3, 70.3, 68.0, 60.5, 39.2, 24.7, 21.4, 14.4.

IR (thin film): 3448, 2976, 2939, 2856, 1700, 1658, 1449, 1368, 1304, 1262, 1174, 1116, 1069, 1050, 1033 cm$^{-1}$.

HR-MS (DART) $m/z$ calcd for C$_{18}$H$_{18}$O$_4$, found 215.1292.

(±)-CSA promoted cyclization of epoxy alcohol 28b: To a 20 ml vial equipped with a magnetic stir bar was added epoxide 28b (44.6 mg, 0.20 mmol) in CH$_2$Cl$_2$ (10 mL) and (±)-CSA (10 mg, 0.04 mmol) and stirred at room temperature. After consumption of the starting material (5 h, as determined by TLC analysis), the clear solution was filtered through a plug of silica gel (prewashed with 2% Et$_3$N in EtOAc then 2xEtOAc), eluted with EtOAc, and concentrated in vacuo. $^1$H NMR spectroscopic analysis of the unpurified mixture indicated a 1:20 [endo(29b)/exo(30b)] ratio of products. The resultant clear film was purified by flash chromatography (20–40% EtOAc/hexanes) to afford 30b as a colorless oil (40.4 mg, 0.18 mmol, 90%).

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 6.92 (dd, $J = 15.6, 4.8$ Hz, 1H), 6.16 (dd, $J = 15.6, 1.9$ Hz, 1H), 4.19 (q, $J = 7.1$ Hz, 2H), 4.11 (dd, $J = 4.8, 1.8$ Hz, 1H), 3.77-3.67 (m, 2H), 3.00 (br, 1H), 1.73-1.57 (m, 3H), 1.52-1.48 (m, 2H), 1.28 (t, $J = 7.1$ Hz, 3H), 1.22 (s, 3H), 1.19 (dt, $J = 12.9, 3.4$ Hz, 1H).

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 166.6, 145.0, 122.7, 77.51, 75.6, 62.1, 60.5, 28.4, 26.0, 19.0, 18.1, 14.4.

IR (thin film): 3449, 2980, 2937, 2867, 1717, 1656, 1466, 1449, 1369, 1305, 1273, 1212, 1176, 1114, 1081, 1046 cm$^{-1}$.

HR-MS (ESI) $m/z$ calcd for C$_{26}$H$_{20}$O$_4$, found 251.1273.
[Rh(CO)$_2$Cl]$_2$ promoted cyclization of epoxy alcohol 28b: To a 200 ml Schlenk tube equipped with a magnetic stir bar was added epoxide 28b (53 mg, 0.23 mmol) and a solution of [Rh(CO)$_2$Cl]$_2$ in THF (8.9 mg, 23 µmol, in 4.6 mL THF), then the tube was sealed and quickly heated to 80 °C in an oil bath. After 18 h, the reaction was removed from the oil bath and 150 mg of polymer-bound triphenylphosphine resin was added and stirred for 1 h. The cloudy brown solution was filtered through a plug of silica gel (prewashed with 2% Et$_3$N in EtOAc then 2xEtOAc), eluted with EtOAc, and concentrated in vacuo. $^1$H NMR spectroscopic analysis of the unpurified mixture indicated a 4:1 [endo(29b)/exo(30b)] ratio of products. The resultant pale yellow film was purified by flash chromatography (20–40% EtOAc/hexanes) to afford 29b as a colorless oil (11 mg, 0.05 mmol, 21%) and 31b as a colorless oil (1 mg, 5 µmol, 2%).

Characterization Data for 29b:

$^1$H NMR (500 MHz, CDCl$_3$): δ 7.10 (dd, $J$ = 15.7, 3.9 Hz, 1H), 6.14 (d, $J$ = 15.7 Hz, 1H), 4.20 (q, $J$ = 7.1 Hz, 2H), 4.04 (dt, $J$ = 11.8, 5.7 Hz, 1H), 3.95 (d, $J$ = 1.7 Hz, 1H), 3.61-3.56 (m, 1H), 1.86-1.73 (m, 4H), 1.64-1.59 (m, 2H), 1.30 (t, $J$ = 7.1 Hz, 3H), 1.26 (br, 1H), 1.13 (s, 3H).

$^{13}$C NMR (125 MHz, CDCl$_3$): δ 166.8, 146.3, 121.8, 84.8, 75.5, 71.8, 60.5, 44.4, 31.1, 24.3, 20.8, 14.4.

IR (thin film): 3443, 2929, 2859, 1700, 1654, 1457, 1369, 1300, 1260, 1166, 1105, 1043 cm$^{-1}$.

HR-MS (DART) m/z calcd for C$_{12}$H$_{20}$O$_4$ (M+H)$^+$: 229.1434, found 229.1441.

Characterization Data for 31b:

$^1$H NMR (500 MHz, CDCl$_3$): δ 7.58 (dd, $J$ = 15.2, 11.6 Hz, 1H), 6.00 (d, $J$ = 11.6 Hz, 1H), 5.79 (d, $J$ = 15.2 Hz, 1H), 4.21 (q, $J$ = 7.1 Hz, 2H), 3.69-3.66 (m, 2H), 2.19-2.16 (m, 2H), 1.90 (d, $J$ = 0.9 Hz, 3H), 1.58-1.56 (m, 5H), 1.30 (t, $J$ = 7.1 Hz, 3H).

$^{13}$C NMR (125 MHz, CDCl$_3$): δ 167.9, 149.7, 141.0, 123.6, 119.2, 62.9, 60.3, 40.1, 32.5, 24.0, 17.5, 14.5.

IR (thin film): 3404, 2926, 2855, 1706, 1634, 1368, 1306, 1272, 1214, 1157, 1137, 1033 cm$^{-1}$.

HR-MS (DART) m/z calcd for C$_{12}$H$_{20}$O$_3$ (M+H)$^+$: 213.1485, found 213.1496.
**Vinyl Epoxide 32** : To a solution of epoxy alcohol 26b (1.15 g, 2.89 mmol) in CH₂Cl₂ (29 mL) was added DMSO (2.9 mL, 40.8 mmol) and Et₃N (2.0 mL, 14.4 mmol), cooled to 0 °C, and Pyr·SO₃ (0.92 g, 5.8 mmol) added as a solid. The reaction was allowed to warm to room temperature and stirred for 3 h. The reaction was quenched by addition of H₂O (20 mL) and diluted with CH₂Cl₂ (20 mL). The aqueous layer was separated and extracted twice with CH₂Cl₂ (20 mL each). The combined organics were washed with sat. NH₄Cl (20 mL), H₂O (20 mL), sat. NaCl (20 mL), dried over Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by flash chromatography (5–20% EtOAc in hexanes) to afford a colorless oil that was used immediately in the next reaction.

To a solution of tBuOK (323 mg, 2.88 mmol) and Ph₃PCH₃Br (1.07 g, 3.00 mmol) in THF (12 mL) aged for 30 min at 50 °C then cooled to room temperature was added the previously obtained oil in THF (5 mL). After 1 h, the reaction was quenched by the addition of SiO₂ gel (8.0 g) and diluted with Et₂O (20 mL). The reaction mixture was concentrated in vacuo to afford a free flowing powder. This powder was purified by flash chromatography (5–15% EtOAc in hexanes) to yield a colorless oil.

To a solution of the previously obtained oil in THF (3.0 mL) at 0 °C was added TBAF (1.0 M in THF, 3.0 mL, 3.0 mmol) dropwise over 1 min. The reaction was stirred and allowed to warm to room temperature over 1.5 h. The crude reaction mixture was purified without concentration by flash chromatography (pretreated with 1% Et₃N in 30% EtOAc in hexanes, then 30% EtOAc in hexanes to 60% EtOAc in hexanes) to afford 32 as a colorless oil (0.21 g, 1.36 mmol, 47%).

**NMR and spectra**

**'H NMR (500 MHz, CDCl₃):** δ 5.74 (ddd, J = 17.3, 10.4, 7.1 Hz, 1H), 5.44 (ddd, J = 17.2, 1.5, 0.9 Hz, 1H), 5.34 (ddd, J = 10.5, 1.5, 0.7 Hz, 1H), 3.65 (t, J = 6.4 Hz, 2H), 3.21 (d, J = 7.2 Hz, 1H), 1.69-1.63 (m, 1H), 1.59-1.47 (m, 5H), 1.26 (s, 3H).

**13C NMR (125 MHz, CDCl₃):** δ 133.6, 120.2, 63.6, 62.86, 62.83, 38.2, 32.7, 21.6, 16.7.

**IR (Thin film):** 3419, 3088, 2936, 2865, 1640, 1458, 1385, 1242, 1162, 1066, 1046 cm⁻¹.

**HR-MS (DART) m/z calcd for C₉H₁₆O₂ (M+H⁺):** 157.1223, found 157.1224.

(±)-CSA promoted cyclization of epoxy alcohol 32: To a 20 ml vial equipped with a magnetic stir bar was added epoxide 32 (19 mg, 0.12 mmol) in CH₂Cl₂ (6 mL) and (±)-CSA (13 mg, 0.06 mmol) and stirred at room temperature. After consumption of the starting material (30 min, as determined by TLC analysis), the reaction was quenched with Et₃N (50 μL) and concentrated in vacuo. **'H NMR spectroscopic analysis of the unpurified mixture indicated a 1:2.8 [endo(33)/exo(34)] ratio of products. The resultant clear film was purified by flash chromatography (10–50% EtO/pentanes) to afford 34 as a colorless oil (10.2 mg, 0.065 mmol, 54%) and 33 as a colorless oil (3.7 mg, 0.024 mmol, 19%).
Characterization Data for 34:

\(^1H\) NMR (500 MHz, CDCl\(_3\)): \(\delta\) 5.83 (dd, \(J = 17.2, 10.6, 6.6\) Hz, 1H), 5.37 (dd, \(J = 17.2, 1.7, 1.5\) Hz, 1H), 5.23 (dd, \(J = 10.5, 1.8, 1.2\) Hz, 1H), 3.92 (d, \(J = 6.4\) Hz, 1H), 3.78-3.67 (m, 2H), 2.86 (s, 1H), 1.76 (td, \(J = 13.1, 4.4\) Hz, 1H), 1.72-1.68 (m, 1H), 1.66-1.59 (m, 1H), 1.53-1.47 (m, 2H), 1.24 (dt, \(J = 13.1, 3.3\) Hz, 1H), 1.18 (s, 3H).

\(^13C\) NMR (125 MHz, CDCl\(_3\)): \(\delta\) 135.6, 117.9, 79.6, 75.6, 62.2, 28.0, 26.2, 19.1, 18.0.

IR (thin film): 3471, 2936, 2864, 1473, 1374, 1349, 1259, 1211, 1084, 1049 cm\(^{-1}\).

HR-MS (DART) \(m/z\) calcd for C\(_9\)H\(_{16}\)O\(_2\) (M+H): 157.1223, found 157.1241.

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Rh(nbd)(CH\(_3\)CN)\(_2\)SbF\(_6\) promoted cyclization of 32: To alcohol 32 (20 mg, 0.13 mmol) was added DTBMP (13 mg, 0.065) in THF (1.3 mL) and Rh(nbd)(CH\(_3\)CN)\(_2\)SbF\(_6\) (6.6 mg, 0.013 mmol) in THF (1.3 mL). The reaction was heated to 50 °C in an oil bath. After 18 h, the reaction mixture was allowed to cool to room temperature and then concentrated in vacuo. \(^1H\) NMR spectroscopic analysis of the unpurified mixture indicated a 5:1 [endo(33)/exo(34)] ratio of products. The resultant clear film was purified by flash chromatography (10–50% Et\(_2\)O/pentanes) to afford 33 as a colorless oil (10.7 mg, 0.069 mmol, 54%).

Characterization Data for 33:

\(^1H\) NMR (500 MHz, CDCl\(_3\)): \(\delta\) 5.92 (dd, \(J = 17.2, 10.7, 6.5\) Hz, 1H), 5.33 (dd, \(J = 17.3, 2.0, 1.4\) Hz, 1H), 5.27 (dd, \(J = 10.6, 2.0, 1.3\) Hz, 1H), 3.99 (dt, \(J = 12.0, 5.9\) Hz, 1H), 3.76 (d, \(J = 6.4\) Hz, 1H), 3.64 (dd, \(J = 12.1, 7.9, 5.7\) Hz, 1H), 1.84-1.69 (m, 5H), 1.63-1.58 (m, 2H), 1.15 (s, 3H).

\(^13C\) NMR (125 MHz, CDCl\(_3\)): \(\delta\) 135.8, 117.5, 86.8, 74.9, 70.6, 43.4, 31.1, 24.0, 20.7

IR (thin film): 3417, 2933, 2864, 1456, 1374, 1274, 1104, 1054 cm\(^{-1}\).

HR-MS (DART) \(m/z\) calcd for C\(_9\)H\(_{16}\)O\(_2\) (M+H): 157.1223, found 157.1231.

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Pyrone 43: To a suspension of aldehyde 40 (5.0 g, 28.1 mmol), 4 Å MS (5.0 g) and Cr cat. 42\(^{38}\) (0.41 g, 0.84 mmol) in acetone (6.2 mL, 84 mmol) aged for 30 min at room temperature then cooled to 0 °C was added diene 41 (7.3 mL, 33.7 mmol). The reaction was allowed to warm to

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\(^{38}\) From (1S,2R)-1-Amino-2-indanol following the reported procedure: Chavez, D. E.; Jacobsen, E. N. Org. Synth. 2005, 82, 34.
room temperature and stirred vigorously. After 3 d, the reaction mixture was cooled to 0 °C, diluted with CH₂Cl₂ (10 mL), and TFA (2.8 mL) was added. After stirring for 1 h, the reaction mixture was filtered through Celite and the Celite was flushed with CH₂Cl₂ (3 x 20 mL). The combined filtrate was quenched with sat. NaHCO₃(aq) (20 mL), and the layers separated. The aqueous layer was reextracted with CH₂Cl₂ (2 x 10 mL). The combined organic layers were washed with sat. NaCl(aq) (20 mL), dried over Na₂SO₄, filtered and concentrated in vacuo. The resultant red oil was purified by flash chromatography (20-50% EtOAc in hexanes) to afford 43 as a yellow oil (6.5 g, 26.4 mmol, 94%). Determination of the ee of 43 was accomplished by chiral analytical HPLC analysis (Chiracel OD-H; 10% iPrOH in hexanes, 1.00 mL/min; t_R(major) = 17.3 min, t_R(minor) = 24.2 min.

¹H NMR (500 MHz, CDCl₃): δ 7.38-7.28 (m, 6H), 5.41 (d, J = 6.0, 1H), 4.52 (s, 2H), 4.42 (ddt, J = 13.1, 8.3, 4.3 Hz, 1H), 3.57-3.50 (m, 2H), 2.53 (dd, J = 16.7, 13.5 Hz, 1H), 2.44 (ddd, J = 16.7, 3.7, 1.0 Hz, 1H), 1.94-1.86 (m, 1H), 1.86-1.71 (m, 3H).

¹³C NMR (125 MHz, CDCl₃): δ 192.8, 163.4, 138.4, 128.5, 127.8, 107.1, 79.4, 73.1, 69.6, 42.0, 31.4, 25.3.

IR (thin film): 3059, 3032, 2934, 2857, 2798, 1672, 1592, 1496, 1454, 1405, 1362, 1270, 1229, 1203, 1095, 1033 cm⁻¹.

HR-MS (ESI) m/z calcd for C₁₃H₁₈O₃ (M+Na)⁺: 269.1148, found 269.1156.

[α]D² = +103.6 (c = 1.00, CHCl₃).³⁹

**THP 44:** To a solution of pyrone 43 (4.48 g, 18.2 mmol) in MeOH (91 mL) open to air was added CeCl₃·7H₂O (3.4 g, 9.1 mmol) at room temperature. After 30 min, the reaction mixture was cooled to -20 °C, and NaBH₄ (0.69 g, 18.2 mmol) was added as a solid in three portions over 10 min. After 30 min, the reaction was quenched by the addition of acetone (18 mL). The reaction was carefully concentrated in vacuo. The solid obtained was dissolved in Et₂O (100 mL) and H₂O (100 mL). After separating the layers, the aqueous layer was reextracted with Et₂O (2 x 50 mL), and the combined organic layers were washed H₂O (50 mL) and sat. NaCl(aq) (50 mL), dried Na₂SO₄, filtered, and concentrated in vacuo to afford a yellow oil.

To a solution of the previously obtained oil and NaHCO₃ (1.5 g, 18 mmol) in MeOH (91 mL) at 0 °C was added mCPBA (6.3 g, 36.4 mmol) as a solid, and then the reaction was allowed to warm to room temperature. After 1 h, the reaction was concentrated in vacuo, suspended between EtOAc (50 mL), H₂O (20 mL), and sat. Na₂SO₃(aq) (30 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with sat. K₂CO₃(aq) (20 mL), H₂O (20 mL), sat. NaCl(aq) (20 mL), dried over Na₂SO₄, filtered, and

³⁹ Lit. Reported [α]D² = +94.7 (c = 0.530, CHCl₃) for 90% ee material; Gleason, M. M.; McDonald, F. E. J. Org. Chem. 1997, 62, 6432.
concentrated in vacuo. The yellow oil was purified by flash chromatography (70% EtOAc in hexanes to 100% EtOAc) to afford a pale yellow oil that was used immediately in the next reaction.

To a solution of the previously obtained pale yellow oil, imidazole (11.4 g, 168 mmol), and DMAP (0.37 g, 3.1 mmol) in DMF (76 mL) cooled to 0 °C was added TBSCI (11.5 g, 76 mmol), then allowed to warm to room temperature. After 20 h, the reaction was cooled to 0 °C, quenched with the addition of H2O (80 mL), and vigorously mixed for 15 min. The reaction mixture was extracted with Et2O (3 x 50 mL). The combined organic layers were washed with H2O (2 x 50 mL) and sat. NaCl(aq) (50 mL), dried over Na2SO4, filtered, and concentrated in vacuo. The resultant yellow oil was purified by flash chromatography (100% hexanes to 10% EtOAc in hexanes) to afford 44 as a pale yellow oil (6.30 g, 12.0 mmol, 66%).

1H NMR (500 MHz, CDCl3): δ 7.37-7.28 (m, 5H), 4.54-4.49 (m, 3H), 3.94 (ddd, J = 11.6, 4.3, 2.8 Hz, 1H), 3.65-3.59 (m, 2H), 3.54-3.46 (s, 3H), 3.30 (s, 3H), 1.86-1.78 (m, 2H), 1.71-1.53 (m, 3H), 1.40-1.37 (m, 1H), 0.90 (s, 9H), 0.90 (s, 9H), 0.08-0.06 (m, 12H).

13C NMR (125 MHz, CDCl3): δ 138.8, 128.5, 127.84, 127.69, 102.9, 73.1, 71.0, 70.6, 68.7, 68.0, 54.7, 35.0, 32.4, 26.28, 26.14, 26.04, 18.46, 18.39, -4.13, -4.26, -4.40, -4.57.

IR (thin film): 2953, 2929, 2900, 2857, 1472, 1388, 1361, 1313, 1253, 1160, 1128, 1102, 1067, 1007 cm⁻¹.

HR-MS (ESI) m/z calcd for C28H52O5Si2 (M+Na)⁺: 547.3245, found 547.3227.

[α]D = +18.3 (c = 1.00, CH2Cl2).

OTBS OTBS

BnO

H OMe

44

1H NMR (500 MHz, CDCl3): δ 7.37-7.28 (m, 5H), 4.54-4.49 (m, 3H), 3.94 (ddd, J = 11.6, 4.3, 2.8 Hz, 1H), 3.65-3.59 (m, 2H), 3.54-3.46 (s, 3H), 3.30 (s, 3H), 1.86-1.78 (m, 2H), 1.71-1.53 (m, 3H), 1.40-1.37 (m, 1H), 0.90 (s, 9H), 0.90 (s, 9H), 0.08-0.06 (m, 12H).

13C NMR (125 MHz, CDCl3): δ 138.8, 128.5, 127.84, 127.69, 102.9, 73.1, 71.0, 70.6, 68.7, 68.0, 54.7, 35.0, 32.4, 26.28, 26.14, 26.04, 18.46, 18.39, -4.13, -4.26, -4.40, -4.57.

IR (thin film): 2953, 2929, 2889, 2857, 1464, 1369, 1252, 1100, 1059, 1004 cm⁻¹.

**Allyl THP 38:** To a solution of 44 (7.50 g, 14.3 mmol), DTBMP (5.87 g, 28.6 mmol), and allyltrimethylsilane (4.5 mL, 28.6 mmol) in CH3CN (143 mL) at 0 °C was added TMSOTf (2.6 mL, 14.3 mmol) dropwise over 2 min. The reaction was then allowed to warm to room temperature. After 2.5 h, the reaction was cooled to 0 °C and quenched by the addition of sat. NaHCO3 (aq) (70 mL) and H2O (30 mL). The mixture was extracted with EtOAc (3 x 100 mL) and the combined organic layers were washed with sat. NaCl(aq) (100 mL), dried over Na2SO4, filtered, and concentrated in vacuo. The oil obtained was purified by flash chromatography (3–6% EtOAc in hexanes) to afford 38 as a pale yellow oil (6.70 g, 12.5 mmol, 88%).

1H NMR (500 MHz, CDCl3): δ 7.37-7.27 (m, 5H), 5.80 (ddt, J = 17.0, 10.1, 6.9 Hz, 1H), 5.10-5.06 (m, 2H), 4.53-4.48 (m, 2H), 3.90 (ddd, J = 10.3, 4.0, 2.7 Hz, 1H), 3.84 (ddd, J = 9.0, 6.2, 2.8 Hz, 1H), 3.60-3.56 (m, 2H), 3.52-3.48 (m, 2H), 3.27-3.21 (m, 1H), 2.29-2.21 (m, 1H), 1.83 (dt, J = 12.4, 10.2 Hz, 1H), 1.79-1.61 (m, 3H), 1.56-1.52 (m, 1H), 1.49 (dt, J = 12.7, 3.6 Hz, 1H), 0.91 (m, 18H), 0.07-0.05 (m, 12H).

13C NMR (125 MHz, CDCl3): δ 138.8, 135.2, 128.5, 127.84, 127.65, 116.9, 77.9, 73.0, 72.0, 70.5, 69.9, 68.6, 35.6, 34.9, 32.5, 26.30, 26.20, 26.11, 18.53, 18.37, -4.02, -4.20, -4.24, -4.44.

IR (thin film): 2951, 2929, 2889, 2857, 1464, 1369, 1252, 1100, 1059, 1004 cm⁻¹.
HR-MS (ESI) \( m/z \) calcd for \( C_{30}H_{50}O_{4}Si_{2} (M+H)^+ \): 535.3633, found 535.3619.

\( [\alpha]_D^{24} = +12.3 \) (c = 1.01, CHCl₃).

Vinyl Boronic Ester 47: A mixture of 38 (0.54 g, 1.00 mmol), benzoquinone (11 mg, 0.10 mmol), Hoveyda-Grubbs 2nd generation catalyst (64 mg, 0.10 mmol) and isopropenylboronic acid pinacol ester \(^{40}\) (0.94 mL, 5.00 mmol) was heated to 60 °C. After 36 h, the reaction was cooled to room temperature, diluted with CH₂Cl₂ (10 mL), and concentrated in vacuo. \(^1\)H NMR spectroscopic analysis of the unpurified mixture indicated a 3:1 \( Z/E \) ratio of products. The resultant green oil was purified by flash chromatography (100% hexanes to 10% EtOAc in hexanes) to afford (Z)-47 as a pale green oil (414 mg, 0.61 mmol, 61%) and (E)-47 as a pale green oil (174 mg, 0.26 mmol, 26%).

Characterization Data for (Z)-47:

\(^1\)H NMR (500 MHz, CDCl₃): \( \delta \) 7.35-7.33 (m, 4H), 7.29-7.26 (m, 1H), 6.36 (td, \( J = 6.9, 1.6 \) Hz, 1H), 4.53-4.47 (m, 2H), 3.92-3.88 (m, 2H), 3.60-3.56 (m, 1H), 1.82 (dt, \( J = 12.3, 10.1 \) Hz, 1H), 1.70 (s, 3H), 1.58-1.53 (m, 1H), 1.49 (dt, \( J = 12.5, 3.2 \) Hz, 1H), 1.25 (s, 12H), 0.90 (s, 18H), 0.06-0.04 (m, 12H).

\(^{13}\)C NMR (125 MHz, CDCl₃): \( \delta \) 142.3, 138.9, 128.5, 127.8, 127.6, 83.3, 77.8, 73.0, 72.2, 70.5, 70.1, 68.7, 35.6, 32.4, 29.5, 26.27, 26.12, 26.10, 24.9, 18.48, 18.35, 14.3, -4.08, -4.15, -4.24, -4.5.

IR (thin film): 2952, 2929, 2857, 1635, 1412, 1370, 1341, 1306, 1251, 1214, 1131, 1098, 1068, 1005 cm⁻¹.

HR-MS (ESI) \( m/z \) calcd for \( C_{37}H_{67}BO_{6}Si_{2} (M+H)^+ \): 674.4678, found 674.4671.

\( [\alpha]_D^{24} = +9.8 \) (c = 0.99, CHCl₃).

Vinyl Iodide 36: To a solution of 47 (0.41 g, 0.61 mmol) in THF (4.1 mL) at room temperature was added 6 M NaOH(aq) (0.92 mL, 5.5 mmol). After stirring vigorously for 10 minutes, I₂ in THF (9.15 mL, 0.2 M, 1.83 mmol) was added dropwise by syringe pump over 1 h. After an additional 1 h of stirring, the reaction was diluted with Et₂O (25 mL) and quenched with sat. Na₂S₂O₃(aq) (25

\(^{40}\)Purchased from Sigma-Aldrich.
mL). After partitioning of the layers, the aqueous layer was extract with Et₂O (2 x 20 mL), and the combined organic layers were washed with H₂O (25 mL), sat. NaCl (25 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo. The resultant yellow oil was purified by flash chromatography (100% hexanes to 8% EtOAc in hexanes) to afford 36 as a colorless oil (233 mg, 0.35 mmol, 56%).

³¹H NMR (500 MHz, CDCl₃): δ 7.36-7.34 (m, 4H), 7.31-7.26 (m, 1H), 6.21 (td, J = 7.3, 1.4 Hz, 1H), 4.52 (s, 2H), 3.87 (ddd, J = 9.2, 3.7, 2.8 Hz, 1H), 3.81 (ddd, J = 9.2, 5.5, 3.8 Hz, 1H), 3.59-3.54 (m, 1H), 3.53-3.45 (m, 3H), 2.37 (d, J = 1.4 Hz, 3H), 2.29-2.17 (m, 2H), 1.84-1.73 (m, 3H), 1.66-1.60 (m, 1H), 1.58-1.52 (m, 2H), 0.91 (m, 18H), 0.07-0.06 (m, 12H).

IR (thin film): 2929, 2885, 2857, 1472, 1361, 1252, 1152, 1102, 1054, 1006 cm⁻¹.

HR-MS (ESI) m/z calcld for C₃₁H₅₅IO₄Si₂ (M+H)⁺: 675.2756, found 675.2778.

[α]₂⁵D = +22.8 (c = 1.00, CHCl₃).

Enolate 48: To a solution of epoxide 39 (0.32 g, 1.9 mmol) and imidazole (0.19 g, 2.8 mmol) in DMF (10 mL) cooled to 0 °C was added TBDPSCl (0.62 mL, 2.4 mmol). The reaction was allowed to warm up to room temperature. After 18 h, the reaction was quenched with H₂O (10 mL) and diluted with Et₂O (20 mL). After partitioning of the layers, the aqueous layer was extracted with Et₂O (2 x 10 mL). The combined organic layers were washed with H₂O (2 x 20 mL), sat. NaCl (20 mL), dried over Na₂SO₄, filtered, and concentrated in vacuo. The resultant pale yellow oil was used in the next reaction without purification.

The previously obtained oil was diluted in CH₂Cl₂ (34 mL), cooled to -78 °C, and sparged with O₂ for 10 min. When the reaction changed to blue from colorless, the O₂ flow was stopped and replace with N₂ sparging for 5 minutes, followed by the addition of Ph₃P (0.6 g, 2.6 mmol) dissolved in CH₂Cl₂ (5 mL). The reaction was allowed to warm to room temperature over 1 h, then (carbethoxymethylene)triphenylphosphorane (1.19 g, 3.4 mmol) was added. After 30 min, the reaction was concentrated in vacuo, and the resultant yellow oil was purified by flash chromatography (5-15% EtOAc in hexanes) to afford 48 as a colorless oil (0.65 g, 1.44 mmol, 76%).

³¹H NMR (500 MHz, CDCl₃): δ 7.72-7.68 (m, 4H), 7.47-7.39 (m, 6H), 6.96 (dt, J = 15.6, 6.8 Hz, 1H), 5.85 (dt, J = 15.6, 1.6 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 3.82 (dd, J = 11.5, 5.5 Hz, 1H), 3.75 (dd, J = 11.5, 5.3 Hz, 1H), 3.00 (t, J = 5.4 Hz, 1H), 2.31-2.26 (m, 2H), 1.75-1.62 (m, 2H), 1.29 (t, J = 7.1 Hz, 3H), 1.14 (s, 3H), 1.08 (s, 9H).

³¹C NMR (125 MHz, CDCl₃): δ 166.6, 148.1, 135.74, 135.70, 133.6, 133.3, 130.0, 127.91, 127.90, 121.9, 62.85, 62.82, 60.4, 60.1, 36.7, 27.8, 26.9, 19.4, 16.9, 14.4.

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IR (thin film): 3069, 2933, 2856, 1719, 1428, 1388, 1367, 1315, 1266, 1193, 1156, 1112, 1082, 1045 cm⁻¹.

HR-MS (ESI) m/z calcd for C₇₇H₃₆O₄Si (M+Na)⁺: 475.2274, found 475.2275.

[α]²₃D = -11.2 (c = 1.01, CHCl₃).

Diene 49: To a solution of enoate 48 (0.80 g, 1.77 mmol) in Et₂O (18 mL) at -78 °C was added DIBAL-H (1.0 M in hexanes, 5.3 mL, 5.3 mmol) dropwise over three min. The reaction was stirred for 20 min, and then poured into an Erlenmeyer flask containing sat. aq. Rochelle’s salt (30 mL), Et₂O (30 mL), and H₂O (30 mL) and stirred vigorously for 13 h at room temperature. The aqueous layer was separated and extracted with Et₂O (2×20 mL). The combined organics were washed with sat. NaCl(aq) (30 mL), dried over Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by flash chromatography (10% EtOAc in hexanes to 40% EtOAc in hexanes) to afford a colorless oil that was used directly in the next reaction.

To a solution of previously obtained oil in CH₂Cl₂ (16 mL) was added DMSO (1.6 mL, 22.5 mmol) and Et₃N (1.1 mL, 7.8 mmol), cooled to 0 °C, and PyrOSO₃ (0.50 g, 3.12 mmol) added as a solid. The reaction was allowed to warm to room temperature and stirred for 3 h. The reaction was quenched by addition of H₂O (20 mL) and diluted with CH₂Cl₂ (20 mL). The aqueous layer was separated and extracted twice with CH₂Cl₂ (20 mL each). The combined organics were washed with sat. NH₄Cl(aq) (20 mL), H₂O (20 mL), sat. NaCl(aq) (20 mL), dried over Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by flash chromatography (5–25% EtOAc in hexanes) to afford a colorless oil that was used immediately in the next reaction.

To a solution of tBuOK (185 mg, 1.65 mmol) and Ph₃PCH₃Br (0.71 g, 2.0 mmol) in THF (13 mL) aged for 30 min at room temperature was added the previously obtained oil in THF (5 mL). After 1 h, the reaction was quenched by the addition of SiO₂ gel (5.0 g) and diluted with Et₂O (20 mL). The reaction mixture was concentrated in vacuo to afford a free flowing powder. This powder was purified by flash chromatography (5–15% EtOAc in hexanes) to afford 49 as a colorless oil (394 mg, 0.97 mmol, 55%).

¹H NMR (500 MHz, CDCl₃): δ 7.71–7.67 (m, 4H), 7.47–7.39 (m, 6H), 6.30 (dt, J = 17.0, 10.3 Hz, 1H), 6.08 (dd, J = 15.2, 10.4 Hz, 1H), 5.70 (dt, J = 14.8, 7.3 Hz, 1H), 5.11 (d, J = 17.0 Hz, 1H), 4.99 (d, J = 10.1 Hz, 1H), 3.81 (dd, J = 11.5, 5.5 Hz, 1H), 3.74 (dd, J = 11.5, 5.3 Hz, 1H), 3.00 (t, J = 5.4 Hz, 1H), 2.24–2.15 (m, 2H), 1.72 (dd, J = 13.7, 9.1, 6.4 Hz, 1H), 1.55 (dd, J = 13.7, 9.6, 6.8 Hz, 1H), 1.14 (s, 3H), 1.08 (s, 9H).

¹³C NMR (125 MHz, CDCl₃): δ 137.2, 135.77, 135.73, 134.1, 133.6, 133.4, 131.6, 129.9, 127.91, 127.90, 115.5, 63.07, 62.96, 60.5, 38.1, 28.4, 27.0, 19.4, 16.9.

IR (thin film): 3073, 2998, 2931, 2858, 1652, 1590, 1472, 1428, 1385, 1361, 1308, 1246, 1189, 1112, 1075, 1003 cm⁻¹.

HR-MS (ESI) m/z calcd for C₂₆H₃₄O₂Si (M+Na)⁺: 429.2220, found 429.2210.

[α]³₃D = -11.5 (c = 1.00, CHCl₃).
Diene 35: To a cooled (0 °C) solution of diene 49 (122 mg, 0.30 mmol) in THF (0.3 mL) was added 9-BBN-H in THF (0.90 mL, 0.5 M, 0.45 mmol). The reaction was allowed to warm to room temperature. After 2 h, degassed 1 M NaOH (aq) (0.83 mL, 0.83 mmol) was added and the mixture was stirred for an additional 30 min.

In a separate vessel, alkene 36 (100 mg, 0.15 mmol) and PdCl$_2$(dppf) (6.0 mg, 7.4 µmol) were premixed in THF (0.37 mL) then cooled to 0 °C. The mixture containing 49 was then transferred by cannula, and the reaction was stirred at 0 °C. After 3 h, the reaction mixture was diluted with Et$_2$O (5 mL) and H$_2$O (5 mL). The aqueous layer was separated and extracted with Et$_2$O (2 x 5 mL). The combined organic layers were washed with H$_2$O (5 mL) and sat. NaCl (aq) (5 mL), dried over MgSO$_4$, filtered, and concentrated in vacuo. The resultant orange oil was purified by flash chromatography (1-10% EtOAc in hexanes) to afford 35 as a colorless oil (105 mg, 0.11 mmol, 75%).

$^1$H NMR (500 MHz, CDCl$_3$): δ 7.71-7.69 (m, 4H), 7.46-7.39 (m, 7H), 7.36-7.33 (m, 4H), 7.29-7.26 (m, 1H), 5.47-5.38 (m, 2H), 5.17 (t, J = 6.7 Hz, 1H), 4.54-4.48 (m, 2H), 3.92 (dt, J = 10.0, 3.1 Hz, 1H), 3.82-3.73 (m, 3H), 3.60-3.57 (m, 2H), 3.53-3.45 (m, 2H), 3.00 (t, J = 5.4 Hz, 1H), 2.29-2.20 (m, 2H), 2.10-2.06 (m, 6H), 1.84 (q, J = 11.3 Hz, 1H), 1.78-1.74 (m, 1H), 1.71-1.64 (m, 3H), 1.62 (s, 3H), 1.58-1.46 (m, 3H), 1.13 (s, 9H), 1.08 (s, 9H), 0.92 (s, 19H), 0.08-0.06 (m, 12H).

$^{13}$C NMR (125 MHz, CDCl$_3$): δ 138.8, 136.8, 135.74, 135.69, 133.6, 133.4, 130.6, 129.9, 129.4, 128.5, 127.88, 127.78, 127.61, 120.6, 78.8, 73.0, 71.8, 70.5, 69.9, 68.7, 63.05, 63.01, 60.6, 39.9, 38.6, 35.6, 32.5, 31.4, 28.9, 28.4, 26.9, 26.26, 26.12, 26.10, 19.4, 18.47, 18.35, 16.9, 16.6, -4.09, -4.16, -4.26, -4.43.

IR (thin film): 2929, 2885, 2856, 1482, 1386, 1361, 1252, 1104, 1074, 1006 cm$^{-1}$.

HR-MS (ESI) m/z calcd for C$_{57}$H$_{90}$O$_6$Si$_3$ (M+NH$_4$)$^+$: 972.6383, found 972.6371.

[α]$^{24}_{D} = -0.3$ (c = 2.07, CHCl$_3$).

Triene 50: To a solution of triene 35 (57 mg, 0.060 mmol) in THF (0.60 mL) at 0 °C was added TBAF in THF (60 µL, 1.0 M, 0.05 mmol). After 1.5 h, the reaction was diluted with H$_2$O (3 mL) and Et$_2$O (3 mL). The aqueous layer was separated and extracted with Et$_2$O (2 x 3 mL). The combined organic layers were washed with sat. NaCl (aq), dried over Na$_2$SO$_4$, filtered, and
concentrated in vacuo. The afforded colorless oil was purified by flash chromatography (10–40% EtOAc in hexanes) to afford a colorless oil that was used directly in the next reaction.

To a solution of previously obtained oil in CH₂Cl₂ (0.6 mL) was added DMSO (0.12 mL, 1.7 mmol) and Et₃N (0.10 mL, 0.71 mmol), cooled to 0 °C, and Pyr•SO₃ (38 mg, 0.24 mmol) added as a solid. The reaction was allowed to warm to room temperature and stirred for 2 h. The reaction was quenched by addition of H₂O (3 mL) and diluted with CH₂Cl₂ (3 mL). The aqueous layer was separated and extracted twice with CH₂Cl₂ (3 mL each). The combined organics were washed with sat. NH₄Cl (2 mL), H₂O (2 mL), sat. NaCl (2 mL), dried over Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by flash chromatography (5–30% EtOAc in hexanes) to afford a colorless oil that was used immediately in the next reaction.

To a solution of tBuOK (8 mg, 0.07 mmol) and Ph₃PCH₃Br (29 mg, 0.08 mmol) in THF (0.6 mL) aged for 30 min at room temperature was added the previously obtained oil in THF (1 mL). After 10 min, the reaction was quenched by the addition of SiO₂ gel (50 mg) and diluted with Et₂O (5 mL). The reaction mixture was concentrated in vacuo to afford a free flowing powder. This powder was purified by flash chromatography (5-25% EtOAc in hexanes) to afford 50 as a colorless oil (28 mg, 0.039 mmol, 65%).

'H NMR (500 MHz, CDCl₃): δ 7.35-7.27 (m, 5H), 5.74 (ddd, J = 17.3, 10.4, 7.1 Hz, 1H), 5.46-5.37 (m, 3H), 5.34 (ddd, J = 10.5, 1.5, 0.7 Hz, 1H), 5.16 (t, J = 6.6 Hz, 1H), 4.53-4.48 (m, 2H), 3.90 (ddd, J = 10.4, 3.9, 2.8 Hz, 1H), 3.77 (td, J = 7.6, 2.5 Hz, 1H), 3.59-3.55 (m, 2H), 3.52-3.44 (m, 2H), 3.20 (d, J = 7.2 Hz, 1H), 2.29-2.17 (m, 2H), 2.11-2.03 (m, 6H), 1.86-1.79 (m, 1H), 1.75-1.63 (m, 4H), 1.61 (s, 3H), 1.55-1.52 (m, 2H), 1.47 (d, J = 12.5 Hz, 1H), 1.26 (s, 3H), 0.90 (m, 18H), 0.07-0.04 (m, 12H).

'13C NMR (125 MHz, CDCl₃): δ 138.8, 136.8, 133.7, 130.8, 129.4, 128.5, 127.81, 127.63, 120.6, 120.1, 78.8, 73.0, 71.9, 70.6, 70.0, 68.7, 63.8, 62.7, 39.9, 38.6, 35.6, 32.5, 31.5, 28.9, 28.4, 26.28, 26.15, 26.11, 18.49, 18.37, 16.8, 16.6, -4.08, -4.15, -4.24, -4.42.

IR (thin film): 2929, 2855, 1462, 1385, 1251, 1098, 1051, 1005 cm⁻¹.

HR-MS (ESI) m/z calcd for C₄₂H₇₂O₅Si₂ (M+Na)⁺: 735.4810, found 735.4824.

[α]D = +9.5 (c = 1.31, CHCl₃).

Tryepoxide 13: To a solution of triene 50 (20 mg, 0.028 mmol) in THF (2.0 mL) at 0 °C was added TBAF in THF (200 μL, 1.0 M, 0.20 mmol). After 3 h, the reaction was diluted with H₂O (5 mL) and Et₂O (5 mL). The aqueous layer was separated and extracted with Et₂O (2 x 5 mL). The combined organic layers were washed with sat. NaCl, dried over Na₂SO₄, filtered, and concentrated in vacuo. The afforded yellow oil was purified by flash chromatography (30–80% EtOAc in hexanes) to afford a colorless oil that was used directly in the next reaction.

To a solution of the previously obtained oil and chiral ketone (+)-5142 (37 mg, 0.14 mmol) in DMM/MeCN (2:1, 3.3 mL) was added a solution of 0.05 M Na₂B₄O₇•10H₂O in 4 x 10⁻⁴
Na₂EDTA (2.2 mL) and nBu₄HSO₄ (10 mg, 0.03 mmol), and the mixture was cooled to 0 °C. To this vigorously stirred reaction mixture was added, simultaneously over 1 h via syringe pump, a 0.212 M solution of Oxone® in 4 x 10⁻⁴ Na₂EDTA (1.6 mL) and a 0.89 M solution of K₂CO₃ in H₂O (1.6 mL). Upon completion of syringe pump addition, the reaction mixture was diluted with Et₂O/H₂O (1:1, 5 mL) and warmed to room temperature. The aqueous layer was extracted with EtOAc (2 x 5 mL) and the combined organic layers were washed with sat. NaCl(ω) (5 mL), dried over Na₂SO₄, filtered and concentrated in vacuo. The afforded colorless oil was purified by flash chromatography (70% EtOAc in hexanes to 100% EtOAc) to provide a 13 as a colorless oil (5.1 mg, 9.9 μmol, 3.5:1 dr, 36% over two steps).

¹H NMR (500 MHz, CDCl₃): δ 7.37-7.32 (m, 4H), 7.30-7.26 (m, 1H), 5.73 (ddd, J = 17.3, 10.4, 7.0 Hz, 1H), 5.45 (d, J = 17.1 Hz, 1H), 5.35 (d, J = 10.5 Hz, 1H), 4.53-4.47 (m, 2H), 4.06 (dt, J = 8.8, 4.4 Hz, 1H), 3.93 (dt, J = 8.6, 4.3 Hz, 1H), 3.66 (dt, J = 8.3, 4.3 Hz, 1H), 3.63 (t, J = 3.3 Hz, 1H), 3.53-3.45 (m, 2H), 3.22 (d, J = 7.2 Hz, 1H), 2.88 (t, J = 5.9 Hz, 1H), 2.71-2.68 (m, 2H), 1.93 (ddd, J = 14.9, 8.9, 6.2 Hz, 1H), 1.83 (dt, J = 13.3, 4.0 Hz, 1H), 1.78-1.56 (m, 14H), 1.27-1.26 (m, 6H).

¹³C NMR (125 MHz, CDCl₃): δ 138.7, 133.3, 128.5, 127.78, 127.65, 120.5, 74.0, 73.0, 70.34, 70.25, 69.5, 66.5, 63.4, 62.2, 60.2, 59.9, 58.39, 58.31, 35.2, 34.6, 34.4, 32.0, 29.1, 27.71, 27.56, 26.2, 16.94, 16.80.

IR (thin film): 3423, 2924, 2857, 1454, 1386, 1246, 1208, 1094, 1074 cm⁻¹.

HR-MS (ESI) m/z calcd for C₃₀H₄₄O₇ (M+Na)*: 539.2979, found 539.2975.

[α]²⁵ = +1.5 (c = 0.99, CHCl₃).
I. $^1H$ and $^{13}C$ NMR Spectra
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EDUCATION AND RESEARCH EXPERIENCE

2008-Present
Massachusetts Institute of Technology, Cambridge, MA
National Science Foundation Graduate Research Fellow
Robert T. Haslam Presidential Graduate Fellow
  • Synthesis of oxepanes and formal synthesis of marine ladder polyether brevisin via rhodium-catalyzed epoxy-alcohol cyclizations and cascades

2003-2007
Brown University, Providence, RI
B.Sc. in Chemistry with Honors, magna cum laude, Advisor: Matthew B. Zimmt
  • Synthesis and investigation of enantioenriched diols towards patterned monolayer formation

PUBLICATIONS


PRESENTATIONS


AWARDS AND HONORS

2009 Award for Outstanding Teaching by a Graduate Student
2007 ACS Outstanding Senior Prize, Brown University
2006 Pfizer Summer Undergraduate Research Fellowship

TEACHING AND MENTORSHIP EXPERIENCE

2013 Organic Chemistry Teaching Assistant, MIT
2011-2013 MIT Chemistry Outreach: Chemistry Demonstrations in Massachusetts High Schools
2012 MIT Graduate Student Teaching Certificate Program
2010-2012 Graduate Synthetic Organic Chemistry Teaching Assistant, MIT
2008-2009 Introductory Organic Chemistry Teaching Assistant, MIT
2007 Summer Organic Chemistry Lab Teaching Assistant, Brown University