AN ABSTRACT OF THE DISSERTATION OF

Nagarathanam Veerasamy for the degree of Doctor of Philosophy in Chemistry
presented on November 10, 2015.

Title: Enantioselective Total Syntheses of Quinolizidine Lycopodium Alkaloid Cermizine D and Cytotoxic Marine Macrolide Mandelalide A.

Abstract approved:

________________________________________________________
Rich G. Carter

The enantioselective total synthesis of quinolizidine-containing natural product cermizine D and formal syntheses of senepodine G and cermizine C has been achieved. These natural products are members of the lycopodium alkaloids, which have attracted significant attention due to their exciting biological activities and the diverse structural scaffolds. Key steps in the synthetic sequence include the use of an organocatalyzed aza-Michael addition to access a common intermediate aldehyde, matched Evans alkylation using the underexplored iodomethyl thioether to establish the C₁₅ stereocenter and a sulfone aldehyde coupling to link the two major subunits. An unexpected outcome during the key coupling experiment led to a serendipitous, intramolecular cyclization of sulfone
and the formal syntheses of senepodine G and cermizine C. Additionally, an unexpected and rare example of a matched/mismatched relationship using 4-benzyl-3-acyloxazolidin-2-one (Evans’ auxiliary) was observed. Finally, the exploration into the stereoselectivity for a conjugate addition reaction on a series of α, β-unsaturated sulfones was explored which led to the discovery of a highly stereoselective process that could be used to access piperidine-containing alkaloids.

A 22-step enantioselective total synthesis of cytotoxic macrolide mandelalide A has been achieved. This macrolide has attracted considerable synthetic attention due to its complex molecular architecture and compelling cytotoxic activity in early cancer cell screening. The first generation approach exploited a silver-catalyzed cyclization (AgCC) reaction to construct the C_{17}-C_{20} cis-substituted THF ring; however, the subsequent deoxygenation at C_{19} could not be accomplished. The successful synthetic route utilized a diastereoselective Sharpless asymmetric dihydroxylation of cis-enyne to construct the C_{20}-C_{21} anti-diol followed by AgCC cyclization of the C_{20}, C_{21} dibenzoate to construct the C_{17}-C_{20} THF ring system. Additional key steps include the Petasis olefination of the C_{18} ketone followed by hydrogenation to access the C_{18} methyl stereocenter, Wittig reaction to couple the northern and southern fragments and a Yamaguchi macrolactonization to access mandelalide A. Macrolactonization of the C_{23}-C_{24} diol seco-acid furnished the 25-membered ring expanded C_{24}-macrolactone as the major product.
Enantioselective Total Syntheses of Quinolizidine *Lycopodium* Alkaloid Cermizine D
and Cytotoxic Marine Macrolide Mandelalide A

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APPROVED:

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Dean of the Graduate School

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Nagarathanam Veerasamy, Author
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LYCOPODIUM ALKALOIDS:
TOTAL SYNTHESIS OF CERMIZINE D AND FORMAL
SYNTHESES OF SENEPODINE G AND CERMIZINE C
CHAPTER I: INTRODUCTION TO *LYCOPODIUM* AND OTHER QUINOLIZIDINE CONTAINING ALKALOIDS
1.1: Introduction to *Lycopodium* Alkaloids.

*Lycopodium* is a genus of club mosses that is classified under the family of *Lycopodiaceae*, a family of diverse group of vascular plants. The species of the genus *lycopodium* are endemic to the tropical and temperate climates and are identified as non-flowering, terrestrial or epiphytic plants with needle/scale like leaves covering stems and branches. The reproduction of these club mosses happen via gametes in an underground sexual phase or via the spores in an alternating life cycle.¹

These plants have been used for millennia for treatments of a wide range of ailments in traditional folk medicines— from controlling fever to schizophrenia to memory loss. These club mosses were also widely used in the ancient cultures in several parts of world as essential herbal remedies. Celts were reported to have harvested and used *Lycopodium Clavatum* for eye diseases.² Native Americans were known to have utilized *Lycopodium Clavatum* in wound care. A specific group of tribes from Canada called as Blackfoot employed *Lycopodium Complanatum* in the treatment of pulmonary diseases.³ In addition to the traditional use of these plants as medicines, many of the isolated natural products from these species showed significant activities in the initial biological studies and some of them are promising candidates for treatment of diseases. For example, huperzine A (1.5), one of the *lycopodium* alkaloids isolated from *Lycopodium Serratum* has been shown to be a potent, reversible inhibitor of acetylcholinesterase (AChE) and is studied to be a promising drug candidate in the treatment of Alzheimer’s disease and myasthenia gravis.⁴
The *lycopodium* club mosses have been producing a diverse collection of alkaloid natural products. These alkaloids have attracted the attention of many natural product and synthetic organic chemists due to their important biological properties and fascinating structural scaffolds they possess. The parent member of this family of alkaloids, lycopodine (1.1), was isolated from *Lycopodium complanatum* by von Karl Bödeker from Germany in 1881.\(^5\) Professor William A. Ayer from the University of Alberta, one of the pioneers of *lycopodium* research, led the first systematic study of the *lycopodium* club mosses.\(^6\) Since then, numerous advancements were made in a wide range of areas from isolation, characterization and structural elucidation to biological evaluation, biosynthetic pathways and natural product synthesis of *lycopodium* alkaloids. More recently, Professor Jun’ichi Kobayashi’s laboratory at the University of Hokkaido has continued to quarry these plants for additional alkaloid constituents – providing numerous new compounds and new chemical scaffolds.\(^7\) Multiple other laboratories have probed these plants for medicinally useful alkaloids.\(^8\)
1.2: Introduction to Quinolizidine Containing Alkaloids.

Quinolizidine rings are ubiquitously present in the alkaloid natural product scaffolds including *lycopodium* and other types of alkaloids (Figure 1.2). Pelletierine (1.7) the parent *lycopodium* alkaloid serves as a common building block in the biosynthesis of many of the more complicated *lycopodium* alkaloids.\(^9\) Pelletierine (1.7) was first isolated from pomegrante by Tanret in 1878. Despite its deceptively simple structure,\(^10\) this compound has been the target of considerable synthetic attention and numerous total syntheses.\(^11,12\) Many of the quinolizidine-natural products identified by Ayer, Kobayashi and others are derived from pelletierine through the pelletierine condensation.\(^13\) Representative members of these quinolizidine natural products include cermizine C\(^14\) (and its biosynthetic precursor senepodine G), myrtine\(^15\) and lasubines I-II.\(^16\) Incorporation of a second formal unit of pelletierine gives rise to more complex versions such as cermizine D\(^14\) and cernuine.\(^17\) Quinolizidine-containing *lycopodium* alkaloids cermizine C (1.9), senepodine G (1.8), cermizine D (1.13) and cernuine (1.14) were isolated from *Lycopodium Cernuum* and *Lycopodium Chinense* by Kobayashi and co-workers in 2004.\(^14\) Myrtine (1.10) was isolated from *Vaccinium myrtillus* by Hootele and co-workers in 1978.\(^15\) Lasubines I (1.11) and II (1.12) were isolated from *lagerstroemia Subscotata* Koehne by Murata and co-workers in 1978.\(^16\) These quinolizidine natural products 1.7 - 1.14 have attracted considerable synthetic attention\(^18,19,20\) including total syntheses of the more complicated members cernuine (1.14)\(^18c,21a,b\) and cermizine D (1.13).\(^18c,21,22\) This quinolizidine scaffold is also present in other complex members of the *lycopodium* alkaloids such as himeradine A (1.6).\(^23\) Our
interest in the quinolizidine scaffolds has also included our synthetic studies toward himeradine A and thus expanded into developing general approaches to access significant cross sections of the *lycopodium* alkaloid family.\textsuperscript{12b,22,23b,24}

![Chemical structures of alkaloids](image)

**Figure 1.2. Pelletierine and the Quinolizidine Containing Alkaloids.**

1.3: Prior Work on Synthesis of Simple Quinolizidine Alkaloids

*(Senepodine G, Cermizine C, Myrtine, Lasubine I&II)*

In 2006, Snider and co-workers have reported the first synthesis of cermizine C and its biogenetic precursor senepodine G (Scheme 1.1).\textsuperscript{18a} Snider’s synthesis started with 2-piperidineethanol **1.1.1**, which was treated with excess of diethoxy phosphoryl acetyl
chloride 1.1.2 to produce an ester amide. Subsequent selective hydrolysis of the resultant ester amide provided the primary alcohol 1.1.3 in 81% yield over two steps. Quinolizidine ring was constructed via oxidation of C-7 primary alcohol followed by an intramolecular Horner-Wadsworth-Emmons reaction. Addition of Gilman’s reagent to enamide 1.1.4 stereoselectively established the C-7 methyl center. Methyl Grignard reaction with the amide followed by treatment with 3M acidic methanol generated senepodine G (1.8). Subsequent diastereoselective reduction of the iminium ion with sodium borohydride completed the total synthesis of cermizine C (1.9).

Scheme 1.1. Snider’s Synthesis of Cermizine C and Senepodine G
In 2009, Zhang and co-workers reported racemic synthesis of cermizine C (Scheme 1.2).\textsuperscript{18d} Zhang’s synthesis started with 4-methyl piperidine, which over a five-step sequence was converted to cis-2, 4-dimethyl piperidine (1.2.2). Subsequent N-alkylation with 3-butynyl tosylate generated tertiary amine 1.2.3. Next, \textit{in-situ} N-oxide synthesis by the treatment of \textit{mCPBA} followed by gold catalyzed rearrangement constructed the quinolizidine ring in great diastereoselectivity (\textit{dr > 50:1}). Finally, two-step deoxygenative hydrogenolysis sequence of dithiane formation followed by Raney Ni reduction completed the racemic synthesis of cermizine C (1.9).

\begin{center}
\textbf{Scheme 1.2.} Zhang’s Racemic Synthesis of Cermizine C.
\end{center}

In the same year, Wang, Hu and co-workers published their enantioselective synthesis of quinolizidine containing natural products.\textsuperscript{18e} Wang and Hu’s method used (\textit{R})-Betti base (1.3.1) as the chiral auxiliary and as a source of the nitrogen atom (Scheme 1.3). Condensation of Betti base (1.3.1) with 1,5-pentanedial and benzotriazole (BtH) in
the presence of (-)-tartaric acid provided a diastereopure oxazine 1.3.4 in 93% yield. Subsequent treatment with allylsilane in presence of BF$_3$•Et$_2$O constructed the required stereocenter at C-5 in a highly diastereoselective manner. Reductive cleavage of oxazine 1.3.5 with LiAlH$_4$ followed by Boc portection generated piperidine 1.3.6.

**Scheme 1.3.** Wang and Hu’s Enantioselective Synthesis of Piperidine Ring.

Wang and Hu’s total synthesis of pelletierine, lasubine II and cermizine C is shown in scheme 1.4. Wacker oxidation of piperidine 1.3.6 using PdCl$_2$ and CuCl in presence of oxygen set up the required C-7 ketone. Boc deprotection of the resultant ketone completed the synthesis of (+)-pelletierine (1.7). Subsequent base catalyzed condensation of pelletierine (1.7) with 3,4-dimethoxy benzaldehyde and further isomerization under the basic conditions provided the thermodynamically more stable diastereomer at C-9. Final diastereoselective reduction of C7 ketone with K-selectride
completed total synthesis of (-)-lasubine II (1.12). Boc deprotection of piperdine 1.3.6 followed by treatment with acryloyl produced the amide 1.4.1. Next, ring closing metathesis (RCM) reaction using Grubbs-II catalyst constructed the known quinolizidine lactam 1.1.4. Known transformations were used to further convert the lactam 1.1.4 to senepodine G (1.8) and cermizine C (1.9).

**Scheme 1.4.** Wang and Hu’s Approach to Quinolizidine Alkaloids.

In 2010, Taber and co-workers reported the formal synthesis of senepodine G and cermizine C (Scheme 1.5). Conjugate addition of lithiated methyl pyridine to pentenone 1.5.1 produced ketone 1.5.3 in moderate yield. Acetonide protection of ketone with
ethylene glycol followed by Pt-catalyzed hydrogenation provided a 1:1 diastereomeric mixture at C-5. Exposure to acidic conditions constructed the quinolizidine ring to provide senepodine G (1.8) and subsequent reduction with NaBH₄ generated cermizine C (1.9).

Scheme 1.5. Taber’s Racemic Synthesis of Cermizine C and Senepodine G

In 2008, Amat and co-workers published formal synthesis of senepodine G and cermizine C (Scheme 1.6). Condensation of keto diester 1.6.1 with (R)-phenylglycinol (1.6.2) in presence of AcOH provided the bicyclic lactam 1.6.3. One pot reduction of C-1 lactam, C-9 ester and C-5 oxazolidine using lithium borohydride generated the piperidine diol 1.6.4. Next, hydrogenolysis using Pd(OH)₂ in presence of (Boc)₂O provided the
alcohol 1.6.5. Subsequent oxidation, Boc deprotection and cyclization constructed the quinolizidine ring 1.6.6. Subsequent, α-phenyl selenylation followed by ozone oxidation converted the bicyclic lactam 1.6.6 to the known\textsuperscript{18a} unsaturated lactam 1.1.4. Snider and co-workers had previously converted the lactam 1.1.4 to the corresponding quinolizidine natural products senepodine G and cermizine C.\textsuperscript{18a}

Scheme 1.6. Amat’s Formal Synthesis of Cermizine C and Senepodine G

In 2012, González-Goñínez, Foubelo and co-workers reported the formal synthesis of senepodine G and cermizine C (Scheme 1.7).\textsuperscript{18g} Indium mediated one pot amino allylation of 5-bromo pentanal (1.7.2) set up the C-5 stereocenter in high diastereoselectivity (94.6, dr). The crude bromide 1.7.3 was further intramolecularly cyclized under KHMDS conditions to construct the piperidine ring in sulfonamide 1.7.4. Subsequent sulfonamide cleavage under acidic conditions generated the enantiopure amine, which was treated with acryloyl chloride to make the known amide \textit{ent}-1.4.1.
Further, known transformations\textsuperscript{13c} of RCM reaction followed by Gilman reagent addition produced the lactam \textit{ent-1.1.5}, completing the formal synthesis of cermizine C and senepodine G.

\begin{center}
\textbf{Scheme 1.7.} González-Gómez and Foubelo’s Formal Synthesis of Cermizine C and Senepodine G
\end{center}

In 1979, Hootele and co-workers published the first synthesis of myrtine (1.10) (Scheme 1.8).\textsuperscript{15c} The synthesis started with racemic pelletierine (1.7), one of the basic building blocks of quinolizidine natural products. Treatment of pelletierine with acetic-formic mixed anhydride generated N-formyl pelletierine (1.8.2). Subsequent cyclization in refluxing toluene with aluminum tert-butyroxide produced vinylogous lactam 1.8.3. Methyl Grignard addition on to bicyclic quinolizidine 1.8.3 constructed the C-9 stereocenter to complete the racemic synthesis of myrtine (1.10).
In 1993, Pilli and co-workers reported a short racemic total synthesis of myrtine and lasubine II (Scheme 1.9)\textsuperscript{20b,c}. The synthesis started with Boc protected 2-ethoxypiperidine 1.9.1. Multistep one pot coupling with pentenone (1.9.2) produced myrtine (1.10) in 66% yield as a 5.5:1 diastereomeric mixture. Initially, silyl enol ether was formed from pentenone (1.9.2) using TMSOTf and Et\textsubscript{3}N followed by exposure to ethoxypiperidine constructed the C5-C6 bond. Finally, Boc group was \textit{insitu} deprotected with excess TMSOTf and subsequent intramolecular aza-Michael addition reaction produced myrtine (1.10). A similar annulation reaction between enone (1.9.3) and ethoxy piperidine (1.9.1) produced quinolizidines 1.9.4 and 1.9.5 rather in poor (2:3) diastereoselectivity at C-9 stereocenter. Nevertheless, the C-9 center was epimerized under basic conditions (2N NaOH/MeOH) to produce the required quinolizidine 1.9.5 as

\begin{center}
\textbf{Scheme 1.8.} Hootele’s Racemic Synthesis of Myrtine.
\end{center}
a major product. Diastereoselective reduction using L-Selectride set up the C-7 alcohol stereocenter and completed the synthesis of lasubine II (1.12).

Scheme 1.9. Pilli’s Synthesis of Myrtine and Lasubine II.

In 2005, Back and co-workers published their synthesis of myrtine (1.10) (Scheme 1.11) and lasubine II (1.12) (Scheme 1.10). Synthesis of lasubine II started with terminal alkyne 1.10.1. The alkyne 1.10.1 was converted to the C-8 tosyl substituted alkyne 1.10.2 via a two-step sequence of free-radical seleno sulfonylation followed by oxidative elimination. Conjugate addition of amine 1.10.3 to the sulfonyl alkyne 1.10.2 was effectively carried out using MeOH as solvent. The resultant adduct 1.10.4 was intramolecularly cyclized with LDA to produce enone 1.10.5. Further, reduction of enone with NaBH₄, re-oxidation of the resultant alcohol and desulfurization under Li, liq. NH₃
conditions provided the ketone *ent-1.54*. Finally, the ketone *ent-1.54* was further reduced using L-Selectride to complete the synthesis of lasubine II (1.12).

Scheme 1.10. Back’s Synthesis of Lasubine II.

Back and co-workers’ synthesis of myrtine is shown in scheme 1.11. A similar strategy to their lasubine II synthesis was also used in the synthesis of myrtine. Conjugate addition of racemic amine 1.10.3 to alkyne 1.11.1 followed by intramolecular cyclization of the resultant product generated enone 1.11.2 in 42% yields over two steps. A two-step redox sequence of NaBH₄ reduction followed by Moffat oxidation effectively reduced the C-8, C-9 double bond to produce ketone 1.11.3. Finally radical desulfurization employing LiDBB was used to complete the racemic synthesis of myrtine (1.10).
In 2008, Minnaard, Feringa and co-workers reported an enantioselective synthesis of myrtilone (1.10) (Scheme 1.12).\textsuperscript{19f} The synthesis started with Boc-protected 2,3-dehydro-4-piperidinone. A catalytic enantioselective conjugate addition reaction was used to set up the C-9 stereocenter of ketone 1.12.3 in high (96\% ee) enantioselectivity. Cu(OTf)\textsubscript{2} along with the chiral phosphoramidate ligand 1.12.2 was used as catalyst and Me\textsubscript{3}Al as a nucleophilic methyl source. Subsequent ketal protection of C-7 ketone provided Boc protected piperidine 1.12.4. A lithiation-transmetallation procedure was used to construct the C-5 stereocenter. Next, the chloride 1.12.5 was further converted to (+)-myrtilone (1.10) in a single pot by deprotecting ketal and carbamate moieties under acidic conditions followed by \textit{insitu} cyclization using NaHCO\textsubscript{3}.

**Scheme 1.11.** Back’s Synthesis of Myrtilone
In 2010, Hong and co-workers published a total synthesis of myrtine (1.10) (Scheme 1.13). Chiral aziridine 1.13.2 was coupled with the dithiane 1.13.1 using \( t\)BuLi/HMPA conditions to yield allyl alcohol 1.13.4. Further MnO\(_2\) oxidation provided the enal cyclization precursor 1.13.5. Next, intramolecular aza-Michael addition using organocatalyst (\( R\))-1.13.3 provided the piperidine ring in moderate diastereoselectivity (4:1 dr). Gennari-Still reaction of the aldehyde 1.13.5 with the phosphonate ester 1.13.6, produced the C2, C3 unsaturated ester 1.13.7. Next, removal of N-tosyl group, reduction of ester, mesylate formation of the resultant alcohol and cyclization generated the required quinolizidine ring. Final dithiane deprotection under PIFA, TFA conditions completed the total synthesis of (+)-myrtine (1.10).
In 2011, Fustero, del Pozo and co-workers published an enantioselective synthesis of myrtine (1.10) (Scheme 1.14).\(^{19}\) Organocatalyzed aza-Michael addition reaction was used to construct the piperidine aldehyde 1.14.3 in high (94% ee) enantioselectivity from the enal precursor 1.14.1. Treatment with allyl Grignard followed by oxidation with Dess Martin’s reagent produced the ketone 1.14.4. Isomerization of the double bond under basic Et\(_3\)N conditions produced enone 1.14.5. Subsequent deprotection of the Boc group under TFA conditions followed by intramolecular 5-\textit{endo}-trig aza-Michael addition reaction under K\(_2\)CO\(_3\) conditions produced the quinolizidine natural product myrtine in 87% yield.
Scheme 1.14. Fustero and del Pozo’s Synthesis of Myrtine

1.4. Prior Work on Synthesis of More Complicated Members of Quinolizidine Type Alkaloids (Cermizine D and Cernuine).

In 2009, Takayama and co-workers reported the first total synthesis of cermizine D and cernuine.\textsuperscript{21a,b} Their synthesis of common intermediate amine \textbf{1.15.9} is shown in scheme 1.15. Their synthesis started with (+)-citronellal (\textbf{1.15.1}). Acetal protection of the aldehyde followed by oxidative cleavage of the tri-substituted alkene provided the aldehyde \textbf{1.15.2}. Organocatalyzed amination of the aldehyde \textbf{1.15.2} using CbzN=NCbz, \textit{insitu} reduction of the resultant aldehyde using NaBH\textsubscript{4} conditions followed by intramolecular cyclization under basic (K\textsubscript{2}CO\textsubscript{3}) conditions provided the oxazolidinone \textbf{1.15.3} in 94% yield and in high diastereoselectivity. Two-step sequential reduction of Cbz removal using Pd/C conditions followed by treatment with Raney Ni conditions affected the N-N bond cleavage. The resultant amine was cyclized under acidic (pTsOH) conditions in presence of MeOH to provide the aminoacetal \textbf{1.15.4}. Treatment with
trimethyl allylsilane and TiCl$_4$ provided the single isomer of alkene 1.15.5 at C-13 stereocenter. Hydrolysis of oxazolidinone, acryloylation of resultant amine, RCM using Grubbs-I catalyst and hydrogenation conditions constructed the quinoilzidine ring 1.15.6. Oxidation of C-6 alcohol followed by a two-step homologation sequence of wittig reaction and hydrolytic cleavage of resultant enol ether generated the aldehyde 1.15.7. Transfer aminoallylation reaction employing (R)-camphor quinone derived amine 1.15.8 utilizing an aza-Cope rearrangement was used to set up C-5 stereocenter of the homoallylamine 1.15.9 in high yield and high diastereoselectivity.

Scheme 1.15. Takayama’s Synthesis of Common Intermediate Amine 1.15.9.
Conversion of the intermediate amine 1.15.9 to natural products cermizine D and cernuine is shown in Scheme 1.16. Acryloylation of the amine 1.15.9, RCM reaction using Grubbs-II catalyst followed by hydrogenation conditions constructed the final piperidine ring required for cermizine D. Double reduction of the diamide 1.16.1 at C-1 and C-9 positions using LiAlH₄ generated the natural product cermizine D (1.13) in decent yields. Treatment with TFA produced the corresponding trifluoro acetate salt of cermizine D. On the other hand, intramolecular reductive amination of amine 1.15.9 using TiCl₄ under refluxing xylene followed by reduction using NaBH₄ conditions produced the required tricycle 1.16.2. Finally, a similar strategy to that used in cermizine D helped constructing the final piperidine ring to complete the total synthesis of cernuine (1.14).

Scheme 1.16. Takayama’s Synthesis of Cermizine D and Cernuine.
In 2009, Takayama and co-workers have also reported the synthesis of cermizine C and senepodine G (Scheme 1.17).\textsuperscript{21b} Amide 1.17.1 was reduced to tertiary amine 1.93 using diborane reagent. The C-10 hydroxyl group was deoxygenated using a two-step sequence of chlorination employing SOCl\textsubscript{2} followed by reductive dehalogenation using LiAlH\textsubscript{4} to produce cermizine C (1.9) in 52% yield over three steps. Subsequent N-oxidation with \textit{m}CPBA followed by Polonovsky-Potier reaction using TFAA resulted in the regioselective formation of the natural product senepodine G (1.8) in 89% over two steps.

![Scheme 1.17. Takayama’s Synthesis of Cermizine D and Cernuine.](image-url)

In 2015, Comins and co-workers reported their total synthesis of cermizine D.\textsuperscript{21c} Synthesis of intermediate amine 1.18.6 is shown in scheme 1.18. Treatment of 4-methoxy-3-TIPS pyridine 1.18.1 with the chiral acid chloride 1.18.2 generated the N-acylpyridinium ion, which was treated with the Grignard reagent 1.18.3 followed by acid
hydrolysis produced highly substituted enantiopure piperidine 1.18.4 in 77% yield over three steps. Further, KOMe, DMSO conditions hydrolyzed the carbamate followed by intramolecularly cyclized to provide the quinolizidine ring. Oxalic acid conditions removed the TIPS group to furnish the vinylogous lactam 1.8.3. Subsequent conjugate addition of 1.8.3 with Gilman reagent 1.18.5 in presence of TMSCl and workup with NH₄F produced the amine 1.18.6, which contains the complete carbon backbone of cermizine D.

**Scheme 1.18.** Comins’ Synthesis of Intermediate Amine 1.18.6.

Late stage conversion of amine 1.18.6 to cermizine D is shown in scheme 1.19. Wittig reaction with triphenylphosphonium methyl bromide produced the alkene 1.19.1, which was hydrogenated in the following step to produce amine 1.19.2 with the required stereocenter at C-15 in 68% yield. Final hydrogenation under PtO₂, AcOH conditions
produced the natural product cermizine D (1.13) and its C-5 epimer (1.19.3) as a 1:1 diastereomeric mixture.

Scheme 1.19. Comins’ Synthesis of Cermizine D.

1.5. Conclusion.

Significant amount of reports were published in the literature focused on the synthesis of simple quinolizidine containing natural products like cermizine C (1.9), senepodine G (1.8) and lasubines I (1.11) & II (1.12). Only a couple of reports were published regarding the synthesis of more complicated quinolizidine natural products like cermizine D (1.13) and cernuine (1.14). Both C-C and C-N bond forming reactions were involved in the steps constructing the quinolizidine ring. Simple N-alkylation reaction, amide formation, imine/iminium formation and intramolecular aza-Michael addition reactions were used to achieve the C-N bond formation whereas ring closing metathesis
reaction and aldol condensations were used for C-C bond formation to build the quinolizidine rings. In the upcoming chapters, our synthetic efforts and outcomes of our studies towards the successful completion of total synthesis of cermizine D (1.14) and formal syntheses of cermizine C (1.9) and senepodine G (1.8) will be discussed in detail.

References:


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CHAPTER II:

FIRST GENERATION APPROACH TO CERMIZINE D
2.1. Introduction to Cermizine D.

Cermizine D (1.13) is a phlegmarine-type quinolizidine *lycopodium* alkaloid. It was isolated from the club moss of *Lycopodium Cernuum* in 2004 by Kobayashi and co-workers. The natural product was shown to exhibit modest cytotoxic activity against murine lymphoma L1210 cells (7.5 µg / mL). The isolation chemists extracted the club moss of *Lycopodium Cernuum* with MeOH and further extractions were carried out using EtOAc, CHCl₃, and BuOH solvents. Finally an amino-silica gel column followed by regular silica gel column chromatographic techniques were used to isolate cermizine D (1.13) (0.0002%) along with other natural products like cermizine C (1.9) (0.00005%), cermizine B (0.00008%), cernuine (1.14) (0.01%) and lycocernuine (0.004%).

Cermizine D is a C₁₆N₂-type alkaloid containing four stereocenters, a quinolizidine and a piperidine ring connected via a methylene bridge. This natural product possesses an interesting structural skeleton making it a challenging target for total synthesis. 1-D, 2-D NMR data, IR and mass spectrometry techniques were used to deduce the structure of cermizine D. The relative stereochemistry of cermizine D was deduced from the cross peaks observed in phase-sensitive NOESY spectrum.

2.2: Recap on Known Synthetic Strategies.

Due to its interesting biological properties and a challenging structural skeleton, cermizine D and the related alkaloids have attracted the attention of several synthetic laboratories. Though multiple formal and total syntheses have been reported for
structurally simpler alkaloids like cermizine C and senepodine G, only a couple of total syntheses have been disclosed to date,\textsuperscript{3,4} towards the more complicated cermizine D (1.13).

Takayama and co-workers reported an elegant eighteen-step total synthesis of cermizine D (1.13) in 2009 (Scheme 2.1).\textsuperscript{4a,b} A seven carbon fragment (1.81) including the methyl stereocenter was bought from commercially available citronellal A. Organocatalyzed amination reaction was used to set up the C-7 amine stereocenter in oxazolidinone 1.82. Ring closing metathesis (RCM) reaction was performed to construct the quinolizidine ring in 1.86. Transfer aminoallylation reaction employing amine 1.87 and utilizing an aza-Cope rearrangement was used to set up the C-5 stereocenter of the amine 1.88. A second RCM reaction constructed the piperidine tether and a few more trivial transformations completed the total synthesis of cermizine D (1.13).
Scheme 2.1. Takayama’s Total Synthesis of Cermizine D

Recently in 2015, Comins and co-workers disclosed their total synthesis of cermizine D (Scheme 2.2).4c N-acylpyridinium chemistry was used to construct the initial piperidine ring with C-13 stereocenter (1.98). Subsequent transformations produced the vinylogous lactam 1.49. A diastereoselective 1,4-addition of Gilman reagent to the 1.49 generated the complete carbon backbone of cermizine D along with the C-7 stereocenter. Next, a two-step sequence established the C-13 methyl center followed by dearomatizing hydrogenation conditions produced cermizine D and epi-C-5-bermizine D as a 1:1 diastereomeric mixture.
2.3: First Generation Approach to Cermizine D.

We have a long-standing interest in the total synthesis of *lycopodium* alkaloids in our research group. Intrigued by the challenging structural features and in an endeavor to develop a general methodology to synthesize quinolizidine rings, we started our synthetic studies toward cermizine D.

Our original retrosynthetic analysis of cermizine D is shown in Scheme 2.3. Cermizine D was envisioned to be synthesized from amine 2.3.1 via a *N*-C9 alkylation reaction. Amine 2.3.1 could be made from alkene 2.3.2 via ring closing metathesis (RCM) reaction followed by reduction. Alkene 2.3.2 should be accessed from the primary amine 2.3.3 and enone 2.3.4 via reductive amination reaction. Enone 2.3.4 could...
be generated from enal 1.14.1 via an organocatalyzed aza-Michael addition reaction.\textsuperscript{6} Amine 2.3.3 could be produced using an Ellman chiral auxiliary strategy.\textsuperscript{7}

**Scheme 2.3.** First Generation Retrosynthetic Analysis for Cermizine D.

### 2.3.1: Synthesis of the Cyclization Precursor 1.14.1.

To construct the first piperidine ring of cermizine D, we wanted to use enantioselective intramolecular aza-Michael addition reaction strategy developed previously in our laboratory (Scheme 2.4).\textsuperscript{6} Our synthesis started with the commercially available alcohol 2.4.1. Treatment with mesyl chloride under basic conditions produced the mesylate 2.4.2 in quantitative yield. Next, nucleophilic displacement with sodium azide at 50 °C generated the azide 2.4.4 in 92% yield. Alternatively, the azide can also be synthesized from the commercially available 1-bromohexene (2.4.3) in one step via a direct \( S_N2 \) reaction with sodium azide. One-pot Schrodinger reduction of the azide using
PPh$_3$ followed by, in-situ Boc protection of the resultant amine provided the carbamate 2.4.5 in 95% yield. Subsequent cross metathesis with crotonaldehyde using Hoveyda-Grubbs catalyst produced the cyclization precursor 1.14.1 in high yield. For the cross metathesis reaction, Grubbs II-Gen. catalyst produced lower yield of the product in addition to requiring longer reaction times. Excess of crotonaldehyde (5 equiv.) was also used to avoid dimerization of the starting material alkene.

**Scheme 2.4.** Synthesis of the Cyclization Precursor.

### 2.3.2. Enantioselective Intramolecular aza-Michael Addition Reaction.

Having successfully synthesized the cyclization precursor enal 1.14.1, we focused our attention on intramolecular aza-Michael addition reaction. To our surprise, only limited reports were known by 2010,$^{8,6}$ about intramolecular aza-Michael addition with amines bearing electron withdrawing protecting groups (Ex. Carbamates, amides etc).$^{9}$ Other work in the area had focused on intermolecular version using highly nucleophilic...
nitrogen sources. Subsequently, a few other methods have been developed in this area.

An overview of the known methods for aza-Michael addition reaction with carbamate-protected amine is shown in Schemes 2.5 and 2.6.

In 2007, Fustero and co-workers published one of the first reports on highly stereocontrolled intramolecular enantioselective aza-Michael addition reaction. They had reported that the cyclization of the carbamate-bearing amines with tethered enal moieties to generate piperidine, pyrrolidine, oxazolidine and thiazolidine rings in moderate to good yields (30-80%) and with good enantioselectivities (85-96%) in the presence of Jørgensen catalyst and benzoic acid. The optimal conditions required slow warming from -50 °C to -10 °C over a prolonged period.

In 2008, we had reported an improved protocol for the construction of enantioenriched piperidine and pyrrolidine rings using an organocatalyzed intramolecular aza-Michael addition reaction. Our strategy used TMS-prolinol catalyst with no acid additives and more modest temperatures that are practically easy to maintain. A general enantioselective approach was developed using the Jørgensen catalyst to provide the resultant cyclized products in good yield (63-69%) and high eneantioselectivity (79-95%).
More recently in 2013, Asano, Matsubara and co-workers published an intramolecular aza-Michael addition protocol for the asymmetric synthesis of 2-substituted indolines using hydrogen bond activated bifunctional amino thio urea catalyst.\(^\text{11}\) This method accommodated a wide range of acceptor moieties from enones, enoates to \(\alpha,\beta\) unsaturated thioesters due to the flexible catalytic mechanism utilizing non-covalent interactions.

In 2014, Yu and co-workers reported enantioselective synthesis of azaflavanones using an organocatalytic aza-Michael addition reaction.\(^\text{12}\) They had employed quinine-derived thiourea catalyst in addition to using benzoic acid as an additive to synthesis a
variety of 2-aryl, 2-vinyl and 2-methyl substituted azaflavanones in good yields and in excellent enantioselectivities (67-83% yield, 97-99% ee). Their conditions required higher temperatures (90 °C) and prolonged periods of reaction time (2-4 d).

Later in 2014, Lu and co-workers disclosed bifunctional thiourea-mediated intramolecular aza-Michael addition reaction. They reported the asymmetric synthesis of 2-aryl substituted-2, 3-dihydro-4-quinolones using N-tosyl groups as the nucleophilic moiety in good yields and enantioselectivites (80-86% yield, 84-98% ee). The conditions required mild temperatures (0 °C) and moderate reaction times (24-48 h) for the cyclization reaction without any additives.
Scheme 2.6. Recent Developments in Enantioselective Intramolecular Aza-Michael Addition Reaction.
For our synthesis of the aldehyde 2.4.5, we had decided to use a slightly modified version of our previously reported conditions for the intramolecular aza-Michael addition reaction. Our synthesis of the aldehyde 2.4.5 is shown in Scheme 2.6. We employed the TMS-prolinol catalyst ent-1.14.2 to get the best results with the Boc-protected amine precursor 1.14.1. A 3:1 mixture of DCE:MeOH was used as solvent and lower temperatures (-20 °C) and longer reaction times were found to be providing optimal results. The likely transition state 2.7.1 shows the likely stereocontrolling model based on steric hindrance to produce the piperidine aldehyde 2.4.5 in 85% yield and 96% enantioselectivity. Enantioselectivity was readily determined by reduction and protection as its 4-chlorobenzoate ester followed by HPLC analysis.

Scheme 2.7. Synthesis of the Aldehyde 2.4.5.

2.3.3: Synthesis of the Amine Fragment 2.3.3.

Synthesis of the amine fragment is shown in Scheme 2.8. Ellman amine synthesis strategy was used to construct the C13 amine stereocenter of the fragment 2.3.3. The
synthesis starts with 1,5-pentanediol (2.8.1), which was converted to aldehyde 2.8.2 in two steps. Subsequent treatment with (R)-2-methyl-2-propane sulfonamide (2.8.3) in presence of anhydrous CuSO₄ produced the sulfinimine 2.8.4 in quantitative yield. Next, allyl Grignard (2.8.5) addition to the sulfinimine 2.8.4 constructed the C13 stereocenter in 6:1 diastereoselectivity. Finally, acid hydrolysis of the sulfonamide 2.8.6 produced the required primary amine fragment 2.3.3.

Scheme 2.8. Synthesis of the Primary Amine 2.3.3.

2.4. Synthesis of Enone and Coupling with the Amine Fragment.

After the successful synthesis of the intermediate aldehyde 2.4.5, it was converted to the enone fragment 2.3.4 (Scheme 2.5). Styrenyl Grignard 2.9.1 addition to the aldehyde 2.4.5 produced mixture of diastereomeric allyl alcohols 2.9.2. The crude
mixture of diastereomers was oxidized using Dess-Martin Periodinane to produce the required enone moiety 2.3.4 in 70% yield over two steps. During this two-step sequence, a small amount of stereoerosion (90% ee for 2.3.4 compared to 96% ee for 2.4.5) was observed. Nevertheless, the problem was solved through a single recrystallization of the enone product to improve the enantioselectivity to 99%.

![Scheme 2.9](image)

**Scheme 2.9.** Synthesis of the Enone Subunit and Coupling of the Fragments.

With the enone 2.3.4 in hand a reductive amination strategy was used to couple the subunits (Scheme 2.9). Though the imine formation was achieved under forcing conditions [Ti(Oi-Pr)_4, rt, neat], the following reduction of the imine using NaBH_4 proved unselective. More importantly, the C5 stereocenter was also found to epimerize under the reaction conditions.

One explanation for the C5 epimerization could be the β-elimination of the intermediate imine followed by reclosure (Scheme 2.10). Initially, the enone must
coordinate to the titanium isopropoxide, followed by the condensation of the amine with the ketone should generate the imine 2.10.2. Isomerization of the imine to the enamine 2.10.3 could then occur under the reaction conditions. A retro-Michael type ring opening of the piperidine ring would produce the open-chain compound 2.10.4. This enimine 2.10.4 upon reclosure would produce the enamine 2.10.5 with epimerized C5 stereocenter. It is worth noting that there are no stereocenters closer to the reaction center (C5) in the molecule to inculcate any stereoselectivity during the reclosure. Subsequent unselective reduction of the imine at C7 further complicated the problem providing more mixtures of diastereomers.

**Scheme 2.10.** Mechanistic Explanation for the Epimerization of C5 Stereocenter.
Based on these results, it became clear that a revised approach towards cermizine D was necessary. In addition, the β-elimination phenomenon observed in the reductive amination process would likely need to be circumvented.

### 2.5. Conclusion.

As opposed to the other total syntheses of cermizine D, a convergent retrosynthetic analysis of the alkaloid was designed. An organocatalyzed intramolecular aza-Michael reaction was used to successfully construct the first piperidine ring in high yield and enantioselectivity. The solvent combination (DCE:MeOH, 1:3) and the reaction temperature (-20 °C) were found to be the key while employing a modified version of our own method. Ellman’s chiral amine synthesis method was employed to produce the amine fragment in high yield and enantioselectivity. Unfortunately, the reductive amination condition used to stitch the fragments together, epimerized the C5 stereocenter in addition to being unselective for reduction at the imine center. Hence, there is need to devise an alternate strategy that should potentially circumvent the problem of β-elimination and so, solve the epimerization issues.
References:


(bb) Kriis, Kadri; Ausmees, Kerti; Pehk, Tonis; Lopp, Margus; Kanger, Tonis Org. Lett. 2010, 12, 2230-2233.  


CHAPTER 3: REVISED RETROSYNTHETIC ANALYSIS
AND COMPLETION OF TOTAL SYNTHESIS OF
CERMIZINE D
3.1. Revised Retrosynthetic Analysis.

Given the roadblock encountered in our previous C-N bond forming approach to couple the two subunits of cermizine D, we sought an alternate approach. Key to our revised strategy was a method to suppress the β-elimination phenomenon observed in the reductive amination.

Careful investigation of cermizine D revealed that two of the three-piperidine rings present in the molecule (rings A and C) contain the same absolute configuration at C5 and C13 stereocenters respectively. Hence, we envisioned that both the A and C rings could be accessed from a common intermediate (Scheme 3.1).

Through a disconnection at the C7-N bond, we obtained the alcohol 3.1.1 intermediate from which cermizine D could be accessed via an intramolecular S_N2-type N-alkylation. Alcohol 3.1.1 could further be synthesized from sulfone 3.1.2 and aldehyde 2.4.5 via a sulfone coupling/desulfurization sequence. The sulfone fragment 3.1.2 could be obtained from the common intermediate aldehyde 2.4.5 via homologation followed by methyl incorporation sequence. This homologation on approach of the common intermediate aldehyde 2.4.5 should suppress the β-elimination problem.
3.2. Evans Diastereoselective Methylation (Matched/Mismatched Alkylations).

As we had already synthesized the common intermediate aldehyde 2.4.5 (Scheme 2.4) using an intramolecular aza-Michael addition reaction, next, we focused our attention on further homologation (Scheme 3.2). Wittig reaction of methoxymethyl triphenyl phosphonium chloride salt with the aldehyde 2.4.5 yielded a 1.3:1 (E:Z) mixture of enol ether 3.2.1. Phenyllithium was found to be the best base for this reaction as BuLi and other bases provided much lower yields. Subsequent acid hydrolysis of the enol ether 3.2.1 provided the homologated aldehyde 3.2.2, which upon Pinnick oxidation conditions produced the carboxylic acid 3.2.3.

We had planned to utilize the diastereoselective Evans alkylation method to construct the C_{15} methyl stereocenter as this method has been shown to provide reliable
reagent control of stereochemistries. Based on the Evans model, (S)-benzyl oxazolidinone 3.2.5 was found to be the required diastereomer needed to access the C15 stereocenter. Mixed anhydride formation of carboxylic acid 3.2.3 with pivaloyl chloride followed by coupling with Evans chiral auxiliary (S)-3.2.4 provided the necessary oxazolidinone 3.2.5.

Scheme 3.2. Homologation and Coupling with Evans Chiral Auxiliary.

Next, we investigated the alkylation of the oxazolidinone 3.2.5 (Table 3.1). The exploration of the diastereoselectivity in the key alkylation yielded unexpected results. An unexpected matched / mismatched effect was observed - contrary to the typical outcomes for Evans alkylations. The standard conditions using LiHMDS and excess MeI provided low yield (entry 1) and essentially no diastereoselectivity. Use of alternate bases (and at slightly higher equivalencies) led to improved levels of reactivity. NaHMDS (entry 2)
gave a slight preference for the desired stereochemistry [92% yield, 1.5:1 dr (3.1.4: 3.1.5)]. The major required diastereomer 3.1.4 was successfully crystallized and X-ray crystallographic analysis (Figure 3.1) of the resultant crystals conclusively elucidated both the absolute configuration of the newly created stereocenter as well as the stereochemical assignment of the heteroatom Michael reaction. In spite of the low selectivity, a 55% isolated yield of the major diastereomer could be obtained – providing reasonable material throughput. KHMDS (entry 3) gave continued high chemical yields, but now with a slight preference for the undesired stereoisomer [87% yield, 1:1.4 dr (3.1.4: 3.1.5)].

![Chemical structure image]

**Table 3.1:** Exploration of Evans Alkylation.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions*</th>
<th>Yield</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LiHMDS (1.1 equiv.)</td>
<td>29%</td>
<td>1:1 (3.1.4: 3.1.5)</td>
</tr>
<tr>
<td>2</td>
<td>NaHMDS (1.6 equiv.)</td>
<td>92%</td>
<td>1.5:1 (3.1.4: 3.1.5)</td>
</tr>
<tr>
<td>3</td>
<td>KHMDS (2.0 equiv.)</td>
<td>87%</td>
<td>1:1.4 (3.1.4: 3.1.5)</td>
</tr>
</tbody>
</table>

*10 equivalents of MeI was used in each case.
After building the C15 methyl stereocenter, next we focused our attention on synthesizing the sulfone fragment 3.1.2 (scheme 3.3). Reductive cleavage of the oxazolidinone using LiBH$_4$ produced the alcohol 3.3.1. Treatment with diphenyldisulfide and PBu$_3$ generated the sulfide 3.3.2 in excellent yield. Subsequent oxidation of the sulfide using Molybdenum catalyst provided the required sulfone fragment 3.1.2 in quantitative yield.
In order to understand and explain this anomalous diastereoselectivity of the Evans alkylation, we postulated that there is a stereochemical mismatch between the C13 and C3’ stereocenters of the oxazolidinone 3.2.5. To prove our hypothesis, we needed to synthesize the epimeric oxazolidinone series and examine the alkylation outcomes of the resultant product (Scheme 3.4). The known transformations (from Scheme 3.3) produced the carboxylic acid 3.2.3 from the enol ether 3.2.1. Subsequent mixed anhydride formation and coupling with the enantiomeric Evans auxiliary (R)-3.2.4 generated the required epimeric oxazolidinone 3.4.1. Next, the Evans alkylation generated the predicted product (3.4.2) in high yield (77%) and excellent diastereoselectivity (20:1 dr). The stereochemistry at the C15 position was confirmed by comparing the resultant alcohols after reduction of the methylated product 3.4.2 and the minor isomer (3.1.5) from the (S)-oxazolidinone series. This observation of high diastereoselectivity from the (R)-
oxazolidinone series supported our hypothesis about the matched/mismatched stereochemical combinations of the oxazolidinones.

Scheme 3.4. Proving the Hypothesis of Matched/Mismatched Stereochemical Combinations.

One of the possible explanations for this unusual selectivity is the chelation of the metal enolate with the carbonyl groups present in the oxazolidinone ring and the Boc protecting group as shown in the intermediate 3.3.3 in Scheme 3.4. While this would create a typically unfavorable 9-membered cyclic structure, the presence of multiple sp$^2$-hybridized atoms reduces the number of disruptive transannular interactions. Please note that the Boc-protected nitrogen likely forces the C$_{13}$ substituent to adopt an axial conformation. Such a chelation would put the cyclic piperidine ring and the benzyl substituent on the same face of the enolate, forcing the incoming electrophile to come
from the opposite face; thereby bringing about high diastereoselectivity for alkylation of compound 3.4.1. On the other hand, for the (S)-oxazolidinone series (3.2.5), those two mentioned groups would block the opposite faces of the enolate resulting in poor selectivity.

Due to the poor diastereoselectivity observed in the C15 methyl incorporation, we decided to pursue alternate pathways to improve the selectivity (scheme 3.5). We planned to integrate a double bonded methylene group at C15 position and intended to reduce the double bond in a stereoselective fashion. To this end, the homologated aldehyde 3.2.2 was methylenated to produce enal 3.5.1 using Eschenmosher’s salt. In one of our routes, the enal was further reduced to allyl alcohol 3.5.2 using NaBH₄. While compelling precedent existed for diastereoselective hydrogenation of 1,1-disubstituted alkenes similar to 3.5.2,⁹ attempted reduction using 10 mol % (S)-Ru(OAc)₃(T-BINAP) (3.5.4) gave low yield (40%) and no diastereoselectivity. In our other route, the enal 3.5.1 was oxidized using Pinnick oxidation followed by coupled with Evans’ auxiliary (R)-3.2.4 to generate the oxazolidinone 3.5.5. We had hypothesized that the appended oxazolidinone might help with the stereoselective reduction of the double bond. But, the hydride reduction with L-Selectride displayed a slight preference for the undesired C₁₅ stereochemistry after protonation. It is worth pointing out that this reduction strategy relies on multiple factors to produce any diastereoselectivity. Initially, the s-cis versus s-trans confirmations of the starting material will have a direct impact on the selectivity. Also, after the hydride addition, the resultant enolate need to be protonated selectively.
from one of the faces (Re- Vs Si-) to further sway the selectivity.

Scheme 3.5. Auxiliary and Catalyst Based Methods to Improve Diastereoselectivity.

3.3: Strategic Use of Inherent Selectivity of Oxazolidinone to Improve Diastereoselectivity.

Though the selectivity for the construction of C15 stereocenter was poor, we were intrigued by the possibility of harnessing the high diastereoselectivity showcased by the
oxazolidinone 3.4.1 for the methylation reaction (scheme 3.4). After careful analysis of the structure of the target sulfone 3.1.2, we hypothesized use of electrophiles such as thiophenylmethyl iodide (PhSCH$_2$I) or phenyl iodomethyl sulfone (PhSO$_2$CH$_2$I) in place of methyl iodide to exploit the inherent selectivity of the oxazolidinone 3.4.1 to our advantage. We soon realized that phenyl iodomethyl sulfone (PhSO$_2$CH$_2$I) as an electrophile could be problematic due to the presence of the acidic hydrogens in the electrophile under the basic alkylation reaction conditions. Hence, it was decided that thiophenylmethyl iodide (PhSCH$_2$I) would be a wise choice for an electrophile.

To our surprise, there had been only one single example of alkylation reported in the literature utilizing thiophenylmethyl iodide (PhSCH$_2$I) as eletrophile with oxazolidinone-type nucleophiles (scheme 3.6). Baker and co-workers outlined in their total synthesis of (+)-milbemycin β$_3$, the alkylation of oxazolidinone 3.6.1 using thiophenylmethyl iodide (PhSCH$_2$I). Further disheartening was the fact that the reaction afforded only low yield of the product (30% yield) and required long reaction times at lower temperatures (-20 °C, 5 d).$^{10}$ Alternatively, we considered the possibility of a diastereoselective thio-Michael addition based on some compelling literature precedent.$^{11}$ Wu and Raghavan and co-workers accomplished a highly diastereoselective thio-Michael addition reaction of 3.6.3 using acidic and basic conditions respectively.$^{11ab}$ Wu used thiophenol and TiCl$_4$ as a Lewis acid to promote the conjugate addition and Raghavan used BuLi as a base to generate the thiolate anion for the Michael addition reaction. In 2011, Singh and co-workers achieved high enantioselectivity for the thio-Michael addition reaction using quinine based thio-urea catalyst.$^{11c}$ Inspite of the literature
examples, our preliminary exploration of conjugate reduction and hydrogenations as described previously in Scheme 3.5 made the thio-Michael approach seem less attractive. Hence, we decided to stick to the alkylation route using thiophenylmethyl iodide (PhSCH₂I).

![Scheme 3.6. Prior Work in Diastereoselective (and Enantioselective) Construction of β-Thio Carbonyl Compounds.](image)
Our second-generation synthesis of sulfone 3.1.2 is shown in Scheme 3.7. We were delighted to find out that the alkylation reaction using PhSCH$_2$I as an electrophile produced 70% yield and resulted in improved diastereoselectivity (10:1 dr). The reaction was completed at lower temperatures and in shorter times (-78 °C, 1 h) compared to Baker’s conditions (-20 °C, 5 d). It should be noted that the electrophile was used immediately after the preparation, as it was found to be highly unstable – even at lower temperatures. In fact, storage for even 3 hours resulted in dramatically reduced yields. We ascribe the surprising efficiency of the alkylation reaction to the matched relationship of the oxazolidinone and piperidine stereochemistries as shown in intermediate 3.7.1. Reductive cleavage of oxazolidinone generated alcohol 3.7.3. Subsequent oxidation with Molybdenum catalyst produced the corresponding sulfone. Finally, a two-step deoxygenation sequence of iodination followed by hydrogenation conditions resulted in the required sulfone subunit 3.1.2 in high yield. The comparison of spectral data of the resultant sulfone with the previously made compound 3.1.2 confirmed the structure along with the proper stereochemistries.
3.4: Exploration of Conjugate Addition to Vinyl Sulfones.

While the second-generation route for the sulfone fragment provided significant improvement in the diastereoselectivity, we wanted to reduce the number of steps involved in converting the common intermediate aldehyde 2.4.5 to the sulfone 3.1.2. Careful examination of the structures of aldehyde 2.4.5 and sulfone 3.1.2, revealed to us that it should effectively be only two transformations for the conversion: olefination of the aldehyde to make $\alpha, \beta$ unsaturated sulfones followed by conjugate nucleophilic addition to produce the target sulfone fragment. Although this approach sounded very appealing, significant obstacles existed for executing the strategy, especially in the stereoselective conjugate addition step. We relied on the inherent substrate control of the existing piperidine stereochemistry to selectively establish the new stereocenter. While only limited examples of such transformations are known,$^{12}$ Isobe’s work using 1-TMS,
1-phenylsulfonyl alkenes was compelling.\textsuperscript{12b} Regarding reagent-controlled conjugate additions, we were unaware of compelling precedent for conjugate addition of methyl nucleophiles to $\alpha, \beta$-unsaturated sulfones. Feringa and co-workers have reported an elegant catalytic process using pyridinyl sulfones and monodentate phosphoramidite ligands; however, they specifically commented in the manuscript that “…with the less reactive dimethyl zinc no conversion was obtained…”\textsuperscript{13}

In order to explore the nucleophilic addition on to the vinyl sulfones, we synthesized a collection of different vinyl sulfone intermediates (Scheme 3.8). The aldehyde 2.4.5 was treated with $\beta$-sulfone phosphonate ylide 3.8.1 in a Horner-Wordsworth-Emmons type reaction to generate the vinyl sulfones in one step. The reaction proceeded in good yield to deliver a $E:Z$ (4:1, 3.8.2:3.8.3) mixture of $\alpha, \beta$ unsaturated sulfones. This helped us to study the effect of $E$ Vs $Z$ alkenes on the conjugate addition reaction as these compounds were easily separable by column chromatography. In order to analyze the influence of the Boc moiety, the $E$-vinyl sulfone 3.8.2 was further deprotected in acidic conditions followed by N-alkylation under basic conditions provided the non-coordinating benzyl protected vinyl sulfone 3.8.5 in good yield over two steps.
In addition to the simple vinyl sulfones, we also wanted to investigate the impact of silyl substitution on the conjugate addition reaction. Hence, we embarked on the synthesis of silyl vinyl sulfones (scheme 3.9). Isobe’s two-step protocol was used to access the target sulfones. Initially, a Peterson–type olefination reaction was used engaging bis-silyl sulfide 3.9.1 to generate the silyl vinyl sulfides in rather low yield and in modest selectivity. No effort was made to optimize the reaction further as we promptly wanted to study the nucleophilic addition. The bis-silyl sulfide 3.9.1 was made from methylphenyl thioether via a two-step silylation using BuLi and TMSCl.\textsuperscript{14,15} Finally, a Molybdate–mediated oxidation of the resultant sulfides provided the target sulfones in good yield. The $E$ and $Z$ mixtures were comfortably separated using column chromatography at this stage and NOE studies were used to assign the stereochemistry of the alkene. Positive NOE correlation between the vinylic hydrogen and the TMS group.

**Scheme 3.8.** Synthesis of Simple Vinyl Sulfone Intermediates.
was observed for the sulfone 3.9.5 establishing the position of those substituents on the alkene; whereas sulfone 3.9.4 showed no correlation between those groups.


After successful synthesis of a variety of vinyl sulfones, we ventured onto exploring the conjugate addition reaction. We first investigated the potential of silyl vinyl sulfones (Table 3.2). Using a two-step protocol of conjugate addition followed by desilylation sequence. Simple methyl lithium addition triggered preferencial desilylation followed by olefin isomerization to produce 3.2.7 (Entry 1). We are unsure of the enantiomeric purity of this product as a viable epimerization mechanism can be envisioned involving a β-elimination process to form a dienyl sulfone intermediate which might reclose to produce a racemic mixture of 3.2.7. The lower order cuprate reagent (i.e Gilman reagent) was found to result in decomposition in lower equivalencies and while
warming to rt (Entry 2). Interestingly, when used in higher equivalency and at lower temperature, the required conjugate addition proceeded but favoring the undesired C15 isomer as the major product (Entry 3). The optimal conditions furnished the unwanted sulfone 3.2.6 in a high yield and selectivity (93%, 8:1 dr) (Entry 4). Though this result is unrewarding towards our synthesis of cermizine D, this route provides an extremely quick access (6 steps from 6-bromo-1-hexene, 2 steps from known aldehyde 2.4.5) to the sulfone 3.2.6 that contains a piperidine ring with two stereocenters and can be valuable for alternate natural product syntheses. Use of the other olefin isomer 3.9.5 (Entry 5) continued to favor the undesired stereochemistry in the conjugate addition – rather in reduced selectivity (1.9:1 dr).

Table 3.2. Investigation of Conjugate Addition to Silyl Vinyl Sulfones.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Electrophile</th>
<th>Conditions</th>
<th>Result (yield, dr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.9.4</td>
<td>MeLi (1.5 equiv.) Et₂O, -78°C to -50°C</td>
<td>3.2.7 (85%)</td>
</tr>
<tr>
<td>2</td>
<td>3.9.4</td>
<td>CuI (3 equiv.), MeLi (5.9 equiv.) Et₂O, -78°C to rt</td>
<td>Decomposition</td>
</tr>
<tr>
<td>3</td>
<td>3.9.4</td>
<td>CuI (10 equiv.), MeLi (19.6 equiv.) Et₂O, -78°C to 0°C</td>
<td>3.2.6 (60%, 10:1 dr)</td>
</tr>
<tr>
<td>4</td>
<td>3.9.4</td>
<td>CuI (6 equiv.), MeLi (11.8 equiv.) Et₂O, 0°C</td>
<td>3.2.6 (93%, 8:1 dr)</td>
</tr>
<tr>
<td>5</td>
<td>3.9.5</td>
<td>CuI (10 equiv.), MeLi (19.7 equiv.) Et₂O, -78°C to rt</td>
<td>3.2.6 (55%, 1.9:1 dr)</td>
</tr>
</tbody>
</table>

We also examined the feasibility of nucleophilic addition to the simple α, β – unsaturated sulfones (Table 3.3). Methyl lithium addition onto the E-vinyl sulfone 3.8.2 caused decomposition (Entry 1). Initially, reaction with MeLi or other high order cuprates using CuCN resulted in extensive decomposition of the starting material (Entries 1 and 2). We attribute this decomposition pathway to a competitive deprotonation process of γ-hydrogens of the vinyl sulfone via a similar pathway to the product 3.2.7 seen in the previous table. Fortunately, use of lower order cuprate nucleophiles under carefully controlled conditions did produce the desired conjugate addition product – albeit in modest yield and no diastereoselectivity (Entry 3). Despite these shortcomings, this conjugate addition process provides an exceedingly short approach to sulfone 56 – just six steps from commercially available reagents. Attempts to improve the stereoselectivity and chemical yield of this process through use of alternate electrophile
3.8.3 resulted in decomposition (Entry 4). In addition, use of the benzyl protected series 3.8.5 proved similarly ineffective. It is clear from these experiments that a delicate balance exists in controlling the reactivity of these α,β-unsaturated sulfones.

Table 3.3. Exploration of Conjugate Addition to Vinyl Sulfones.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Sulfone</th>
<th>Conditions</th>
<th>Result (yield, dr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.8.2</td>
<td>MeLi (1.5 equiv.) Et₂O, -78°C</td>
<td>Decomposition</td>
</tr>
<tr>
<td>2</td>
<td>3.8.2</td>
<td>CuCN (3 equiv.), MeLi (5.9 equiv.) Et₂O, -78°C to rt</td>
<td>Decomposition</td>
</tr>
<tr>
<td>3</td>
<td>3.8.2</td>
<td>CuI (3 equiv.), MeLi (5.9 equiv.) Et₂O, -78°C</td>
<td>3.1.2 : 3.2.6 (55%, 1:1.2 dr)</td>
</tr>
<tr>
<td>4</td>
<td>3.8.3</td>
<td>CuI (3 equiv.), MeLi (5.9 equiv.) Et₂O, -78°C</td>
<td>Decomposition</td>
</tr>
</tbody>
</table>

3.5. Coupling of Major Subunits and Formal Synthesis of Senepodine G and Cermizine C.

Now that we have successfully developed multiple viable routes to access the sulfone fragment 3.1.2 as well as available route to the other coupling partner aldehyde
2.4.5. We next focused our attention on the coupling (Table 3.4).\textsuperscript{16} We explored a Julia-type coupling reaction utilizing LDA as a base. Our initial attempt resulted in poor yield of the coupled hydroxyl sulfone (Entry 1). Interestingly, the major product of the reaction was attained to be intramolecularly cyclized sulfone 3.4.5. Our attempts to curtail the deprotonation time from 15 min to 7 min was promising as the yield for the desired product went up and the undesired byproduct diminished (entry 2). Following the same trend, the reduction of deprotonation time to just 1 min, successfully improved the yield to 93% with only trace amounts of byproduct. The coupled product provided the complete carbon backbone of the natural product with all the stereocenters albeit as a 1:1:1:1 (approx.) mixture of diastereomers at C7 and C8 positions. It should be noted that the epimeric mixtures at the C8 position is inconsequential as the C8 center is to be removed in the subsequent step. The C7 stereochemistry could likely prove stereoconvergent in the synthesis and we were pleased to see the epimers were completely separable via column chromatography.

\begin{center}
\textbf{Table 3.4.} Coupling of the Fragments.
\end{center}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Deprotonation Time</th>
<th>Temp.</th>
<th>Combined Yield for 3.4.3 &amp; 3.4.4</th>
<th>Yield for 3.4.5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>15 min</td>
<td>-78 °C</td>
<td>10%</td>
<td>38%</td>
</tr>
<tr>
<td>2</td>
<td>7 min</td>
<td>-78 °C</td>
<td>19%</td>
<td>25%</td>
</tr>
<tr>
<td>2</td>
<td>1 min</td>
<td>-78 °C</td>
<td>93%</td>
<td>Trace</td>
</tr>
</tbody>
</table>

The serendipitously formed cyclic sulfone 3.4.5 proved to be a useful intermediate as it expanded routes for constructing quinolizidine rings. Consequently, we aimed to intentionally produce the quinolizidine 3.4.5 (Scheme 3.10). Treatment of sulfone 3.1.2 with LDA in the absence of aldehyde 2.4.5 generated the cyclic sulfone 3.4.5 in good yield. There have been reports in the literature showcasing similar intramolecular cyclization of sulfones on to the carbamate moiety under basic conditions.\(^\text{17}\) Mechanistically, the originally formed sulfone anion must attack the carbonyl carbon of the Boc group followed by expulsion of the tert-butyroxy anion to generate the cyclic sulfone 3.4.5 which was isolated in 87% yield as a single diastereomer with an undetermined stereochemistry at C8 position. Subsequent desulfurization of the sulfone afforded the known lactam 1.1.5\(^\text{18}\)- completing the formal synthesis of the senepodine G and cermizine C. Snider and co-workers have converted the lactam 1.1.5 to senepodine G and cermizine D in 2007.\(^\text{18}\)
Scheme 3.10. Formal Synthesis of Senepodine G and Cermizine C.

Earlier, we had explored an alternate attempt to couple the fragments (scheme 3.11). Treatment of alcohol 3.3.1 with PPh$_3$ and I$_2$ produced the iodide in good yield. Subsequent halogen-metal exchange reaction using $^t$BuLi, produced the lactam via a similar intramolecular cyclization as described earlier. This result is supportive of the model that halogen-metal exchange followed by the intramolecular fusion with the Boc group is faster than the intermolecular coupling in systems not containing addition stabilization of the carbanion.
3.6: Completion of total synthesis of cermizine D.

With the coupling of the major subunits achieved, we pursued to complete the total synthesis of cermizine D. Fortunately the α (3.4.3) and β (3.4.4) alcohols at C7 were easily separable from each other using column chromatography. After separation, we needed to convert the undesired α-alcohols 3.4.3 to the desired β-alcohols 3.4.4. To this end, we explored a Mitsunobu protocol\(^8\) for inverting the C7 alcohol stereocenter (scheme 3.12). Unfortunately, the reaction resulted in decomposition. Consequently, we utilized a redox protocol for the stereoinversion. DMP oxidation of the alcohol 3.4.3 afforded the corresponding keto-sulfone in 93% yield. Subsequent reduction using NaBH\(_4\) conditions provided a 1.5:1 diastereomeric separable mixture of alcohols at C7. Inspite of the poor selectivity, this route proved to be highly stereo-convergent as all the

Scheme 3.11. Alternate Attempt to Couple Fragments.
diastereomers obtained after the coupling reaction could essentially be converted to provide a single pivotal compound that can be eventually transformed to the natural product. It is worth pointing out that the α-alcohols 3.4.3 could be stereoinverted to provide 70% of the β-alcohols 3.4.4 over 3 cycles.

**Scheme 3.12.** Attempted Routes for Stereo-inversion of Alcohols.

The total synthesis of cermizine D is shown in Scheme 18. Using hydroxyl sulfone 97, Raney Ni desulfurization yielded the free alcohol, which proved unstable to purification. Consequently, direct Boc deprotection of the crude material revealed the intermediate 99 as its bis HCl salt. While desulfurizations of keto sulfones are well preceded, proportionally less work has focused on the desulfurization of hydroxy sulfones\(^\text{20}\) – likely due to the competitive elimination pathway commonly seen in Julia couplings.\(^\text{21}\) Treatment of the salt 99 with triphenyl phosphine and carbon tetrabromide in
the presence of triethyl amine generated the natural product 7 in 60% yield over three steps. We were pleased to find that upon comparison of our $^1$H/$^{13}$C NMR and optical rotation data for 7•TFA that it was in good agreement with the data reported by Takayama and co-workers.\textsuperscript{22} While not directly stated in the original isolation paper, the spectroscopic data reported by Hirasawa and co-workers was collected on the TFA salt of cermizine D.\textsuperscript{23}

![Scheme 3.13: Completion of total synthesis of cermizine D](image)

**Scheme 3.13:** Completion of total synthesis of cermizine D

### 3.7. Conclusion.

In summary, we had successfully completed the total synthesis of cermizine D and formal synthesis of senepodine G and cermizine C. Out of the three total syntheses known to date,\textsuperscript{22,24} ours\textsuperscript{23} was the second total synthesis of cermizine D and had included
a shorter route (9 steps, LLS) to access the natural product. We had assimilated multiple viable routes to build our sulfone fragment 3.1.2; hence multiple routes to assemble the target alkaloid. We had also explored many interesting reactions for various chemical transformations including aza-Michael addition reaction, Evans diastereoselective alkylation, conjugate addition to vinyl sulfones etc.

Enantioselective construction of the common intermediate aldehyde was carried out employing slightly modified conditions to ours\(^1\), utilizing an organocatalyzed aza-Michael addition reaction. Many feasible routes were designed for the synthesis of the sulfone building block. Initially, Evans alkylation method was used to establish the C15 methyl stereocenter while discovering the unusual, poor diastereoselectivity arising from mismatched stereochemistries. Later, we explored the matched oxazolidinone series with an uncommon electrophile (PhSCH\(_2\)I) to smoothly establish the C15 stereocenter. Finally, probing conjugate nucleophilic addition to the vinyl sulfones furnished the shortest route (6 steps, LLS) to access the sulfone subunit.

Julia-type coupling was used to stitch the sulfone and the aldehyde fragments together. Serendipitous intramolecular cyclization of the sulfone led us to complete the formal synthesis of senepodine G and cermizine C. A redox protocol was employed to recycle the C7 alcohol stereocenter.
References:


CHAPTER IV: CONCLUSION
4.1. General Conclusion.

Total synthesis of cermizine D\(^1\) and formal total syntheses of senepodine G and cermizine C have been achieved.\(^2\) Our original strategy towards the quinolizidine alkaloid was met with roadblocks that were circumvented in our revised approach. We had utilized modified conditions of our organocatalyzed aza-Michael addition method\(^3\) to construct the common intermediate aldehyde. Our second-generation route contains multiple successful pathways for accessing the pivotal sulfone intermediate. We had explored matched/mismatched Evans alkylations and Michael-type nucleophilic addition to \(\alpha, \beta\)-unsaturated sulfones that led us to intriguing discoveries. We employed Julia-type coupling to join the fragments and also encountered a serendipitous intramolecular cyclization of sulfone that allowed us to accomplish the formal syntheses of senepodine G and cermizine C. A late-stage redox strategy provided us a highly stereoconvergent approach for the synthesis of cermizine D. We had earlier employed Ellman’s chiral amine synthesis strategy\(^4\) to build one of the amine fragments in our previous approach.

4.2. Detailed Conclusion.


Our original strategy towards cermizine D had two major important subunits that are aldehyde 2.4.5 and amine 2.3.3. We had utilized organocatalyzed intramolecular aza-Michael reaction to successfully construct the first piperidine ring in high yield and
enantioselectivity (85% yield, 96% ee). The solvent combination (DCE:MeOH, 1:3) and the reaction temperature (-20 °C) were found to be the key while employing a slightly altered version of our own method.\textsuperscript{3} We employed the TMS prolinol catalyst for the reaction.\textsuperscript{5} In spite of the longer reaction time, our method has been highly consistent and more practically convenient as compared to the other method\textsuperscript{6} available during that time to construct the piperidine aldehyde.

\textbf{Scheme 4.1.} Synthesis of Common Intermediate Aldehyde.

\textbf{4.2.2: Synthesis of Primary Amine Using Ellman’s Strategy.}

We had employed Ellman’s chiral amine strategy\textsuperscript{4} to construct the primary amine \textbf{2.5.6} (Scheme 4.2). The required sulfinimine was synthesized by condensing the the corresponding aldehyde and the (R)-tert butyl sulfonamide. The Grignard addition to the sulfinimine at lower temperature generated the C13 stereocenter with 6:1 diastereoselectivity. Hydrolysis of the resultant sulfinamide \textbf{2.5.6} produced the primary amine \textbf{2.3.3} needed for the synthesis. Our attempts to couple the amine \textbf{2.5.6} and
aldehyde 2.4.5 fragments resulted in poor selectivity and epimerization of the C5 stereocenter. Hence, we opted out for an alternate strategy.

![Scheme 4.2. Synthesis of Primary Amine.](image)

### 4.2.3: Matched/Mismatched Evans Alkylation.

In our revised strategy, we have explored Evans diastereoselective alkylation to build the C15 stereocenter (Scheme 4.3). The required oxazolidinone 3.2.5 was prepared from the common intermediate aldehyde in four steps. Initial methylation of the intermediate 3.2.5 provided surprisingly low diastereoselectivity. It is only one of the few known examples in the literature where an unusually lower selectivity for the Evans auxiliary method. Interestingly high selectivity was obtained for the methylation of epimeric oxazolidinone 3.4.1, which supported our hypothesis of a matched/mismatched stereochemical combination of the piperidine and oxazolidine stereocenters. This inherent selectivity was exploited by use of intermediate 3.4.1 for the alkylation using the uncommon thiophenyl methyl iodide (PhSCH$_2$I) electrophile to furnish the C15 stereocenter in high diastereoselectivity. The oxazolidinone 3.7.2 was eventually converted to the previously prepared sulfone 3.1.2.
4.2.4: Exploration of Conjugate Addition to Vinyl Sulfones.

In spite of the improved selectivity, we wanted to address the higher step count involved in the conversion of the common intermediate aldehyde 2.4.5 to the sulfone subunit. Hence, we decided to pursue the nucelophilic Michael addition to vinyl sulfones that can be accessed from the aldehyde in one step (Scheme 4.4). Various vinyl sulfone electrophiles were synthesized from the aldehyde 2.4.5 using HWE and Peterson type olefination reactions. The vinyl sulfone 3.8.2 generated the target sulfone, which provided the shortest approach to the sulfone building block though in poor selectivity. Interestingly, the silyl substituted vinyl sulfone 3.9.4 generated epimeric sulfone 3.2.6 in great yield and good selectivity (93% yield, 8:1 dr). Though the sulfone 3.2.6 was not useful for the cermizine D synthesis, it could be an important intermediate in alternate natural product synthesis.
4.2.6: Miscellaneous Attempts to Improve Selectivity.

Earlier, we had attempted a few other methods to improve the selectivity for the C15 stereocenter construction (Scheme 4.5). Treatment of specially designed oxazolidinone 3.5.5 with L-Selectride gave only a 2:1 mixture of diastereomers favouring the undesired isomer. Also, the catalytic hydrogenation of 1,1-disubstituted alcohol 3.5.2 failed to induce any selectivity in spite of the strong literature precedents for this type of reactions.10
Scheme 4.5. Miscellaneous Attempts to Improve Selectivity.

4.2.7: Total Synthesis of Cermizine D and Formal Synthesis of Senepodine G and Cermizine C.

Having successfully synthesized the sulfone 3.1.2 and aldehyde 2.4.5, next we employed Julia-type reaction for further coupling the fragments (Scheme 4.5). Serendipitous intramolecular cyclization of the sulfone led us to complete the formal synthesis of senepodine G and cermizine C by making the quinolizidine intermediate 1.1.5. On the other hand, successful coupling of the subunits provided the complete carbon backbone (3.4.3) of the natural product with all the four stereocenters in 93% yield.
Scheme 4.6. Total Synthesis of Cermizine D and Formal Synthesis of Senepodine G and Cermizine C.

A redox sequence was used to convert the undesired alcohol stereocenter at C7 to the desired one. Subsequent, desulfurization of the sulfone at C8 removed the diastereomeric mixtures at that position to provide a single isomer; hence, making it a highly convergent synthesis. The last and final piperidine ring was successfully constructed by the C7-N bond formation to complete the total synthesis of cermizine D. ²

4.3: Brief Summary.

We had successfully completed and published² the highly convergent, second total synthesis of cermizine D and had disclosed a shorter route (9 steps, LLS) to access the alkaloid.¹¹,¹² We had devised multiple viable routes to build the pivotal sulfone fragment 3.1.2; hence, multiple routes to access the target alkaloid. An organocatalyzed
intramolecular aza-Michael reaction was used to successfully construct the first piperidine ring in high yield and enantioselectivity. One of the primary amines was constructed applying Ellman’s strategy. Intriguing results were discovered during our investigation of diastereoselective Evans alkylation to setup the C15 methyl stereocenter, which led us to understand that stereochemical match/mismatch was a significant factor in controlling selectivity. We also probed conjugate nucleophilic addition to the vinyl sulfones that furnished the shortest route (6 steps, LLS) to access the sulfone subunit. Finally, unexpected intramolecular cyclization of the sulfone led us to complete the formal synthesis of senepodine G and cermizine C. Sulfone coupling followed by desulfurization sequence helped us to complete the total synthesis of cermizine D.

References:


PART II:

TOTAL SYNTHESIS OF MANDELALIDE A:

A SILVER-CATALYZED CYCLIZATION (AgCC)

APPROACH TO CONSTRUCT CIS-SUBSTITUTED THF RING.
CHAPTER 5: INTRODUCTION
5.1: Introduction to Marine Natural Products.

The ocean, which comprises about 72% of the surface of Earth, has been habitat to about a quarter million known species for millions of years now. As vast majority of its depth is not fully explored, about two million species are estimated to exist in ocean. Ocean harbors more than a billion of unicellular and a million of multicellular marine organisms that are ranging wide varieties and differing in their physiology and adaptation capacity. Thanks to evolution, these marine organisms have mastered the art of making chemical warfare in order to protect themselves from the attack of numerous predators and survive in the highly competitive and hostile environment they live in. This ironically, has contributed significantly to the welfare of human health on the planet. These chemical compounds produced by various marine organisms like marine-sourced bacteria, marine-sourced fungi, cyanobacteria, dinoflagellates, algae, sponges, cnidarians, bryozoans, mollusks, tunicates (ascidians etc), echinoderms and mangroves are called as marine natural products. Due to the breathtaking diversity of life and the consequent varieties of natural products produced by them, the ocean provides a myriad of resources to discover crucial leads for potential new drugs and medicines for the treatment of diseases.

5.2: Importance of Marine Natural Products in Drug Discovery.

There has been ever growing number of marine natural products isolated every year from the marine organisms. These natural products possess a wide range of
biological activities including antiparasitic, antitumour, antiviral, antimicrobials, antibacterials, ACE inhibiting and antifoulant activities. They have become an important source or starting point in the field of drug discovery and development for diseases. The growing number of the FDA approved drugs that are marine metabolites (or their derivatives) shows the importance of these natural products in human healthcare.\textsuperscript{4} There has been additional drugs approved in market and many more derivatives were approved and moved in the clinical trial pipelines. There have been many drugs that are currently approved in the market that are either the marine natural products themselves or descendants of marine metabolites.\textsuperscript{5,6}

There are currently three marine natural products that are approved themselves as drugs in the market, with out any modifications (Figure 5.1.) Ziconotide (Prialt\textsuperscript{\textregistered}) is the equivalent form of \(\omega\)-conotoxin MVIIA, which is a polypeptide marine natural product that was isolated from the venom of the marine snail \textit{Conus magus}.\textsuperscript{7} Both FDA and EMEA approved it for treatment of severe chronic pain associated with cancer, AIDS and neuropathy. Iota-carrageenans are a family of linear sulfated polysaccharides containing two sulfate groups per disaccharide unit. These are extracted from edible seaweeds of \textit{Rhodophyceae} family. The antiviral nasal spray developed using this natural product is marketed as over the top counter (OTC) medicine for common cold.\textsuperscript{8} Trabectedin (Ecteinascidin 743, Yondelis\textsuperscript{\textregistered}) is a marine alkaloid that is isolated from the Caribbean sea squirt \textit{Ecteinascidia turbinata}. In spite of the poor isolation yields (0.0001 \%), this active substance is approved by EMEA for the treatment of advanced soft tissue sarcoma in Europe, Russia and South Korea. An industrially feasible semi-synthesis of the
alkaloid was developed to address the supply problems. Trabectedin is currently undergoing clinical trials for the treatment of breast, prostate and paediatric sarcomas.

Figure 5.1: Marine Natural Products that are Approved by FDA and/or EMEA.

The derivatives of marine natural products that are approved as drugs are shown in Figure 5.2. Omega-3-acid ethyl esters (Lovaza®) is a FDA approved drug for lowering high triglyceride levels. Though it is composed of ethyl esters of multiple omega-3-fatty acids that are obtained from fish oils, the major constituents are derived from eicosapentenoic acid and docosahexenoic acid. Cytarabine (Cytosar®) and vidarabine (Vira-A®) are pyrimidine and purine nucleosides that are respectively developed from the marine nucleosides spongorthymidine and spongouridine isolated from the Caribbean
sponge Cryptothya Crypta. Cytarabine is an anticancer drug that is used to treat myeloid leukaemia, non-Hodgkin’s lymphoma and meningeal leukaemia whereas vidarabine is an antiviral drug that is used for the treatment of herpes viruses, poxviruses and certain rhabdoviruses hepadnaviruses and RNA tumor viruses. But, vidarabine has been recently discontinued in USA. Eribulin mesylate (Halaven®) is derivatized based on the structure of macrocyclic polyether Halichondrin B, which was isolated from Halichondria okadai. Eribulin mesylate is approved in 2010 by FDA and in 2011 by EMEA for the treatment of metastatic breast cancer. Brentuximab vedotin 63 (Adcetris®), the highly effective and well-tolerated agent is the latest marine drug to successfully venture into the market. This drug contains a synthetic analog of dolastatin 10 and takes advantage of the development made in the field of antibody drug conjugates (ADCs) for selective drug delivery. It was approved by FDA for use in Hodgkin’s lymphoma and anaplastic large cell lymphoma.
Figure 5.2: Derivatives of Marine Natural Products that are Approved Drugs.
In addition to the above-mentioned approved drugs, several more compounds of marine origin such as DMXBA, PM00104, marizomib, plitidepsin and bryostatin I are at different stages of clinical trials (Figure 5.3).\(^5\) DMXBA (GTS-21) is a structural derivative of the natural product anabeseine that is isolated from sea worm *Paranemertes peregrine*. This compound is currently in phase II clinical trial for treatment of Alzheimer’s and Schizophrenia.\(^6\) PM00104, a structural derivative of jorumycine that is isolated from the seaslug *Joruna funebris* is studied in Phase I/II clinical trials for multiple myeloma.\(^7\) Marizomib is the structural equivalent of the natural product Salinosporamide A, which is isolated from the marine bacteria *Salinispora tropica*. Marizomib is currently being studied in phase I clinical trials as a potential anticancer agent for multiple myeloma.\(^8\) Pliditepsin (Aplidin\(^\text{®}\)) is the natural product ascidian isolated from *Aplidium albicans* is studied in phase II/III human clinical trials to assess its anticancer activities.\(^9\) Bryostatin I is investigated in phase II clinical trials for the treatment of Alzheimer’s diseases and metastatic colorectal cancer.\(^10\)
5.3: Introduction to Mandelalides.

Mandelalides are a new class of polyketide macrolides, isolated by McPhail and co-workers in 2012 from a new species of *Lissoclinum* ascidian collected from Algoa Bay, South Africa. The organic extract of the new *Lissoclinum* ascidian species collected from White Sand Reef was subjected to bioassay-guided fractionation using consecutive LH-20 and RP-HPLC chromatographic techniques to yield submilligram quantities of variously glycosylated mandelalides A-D (5.4.1-5.4.4). 1D, 2D NMR data
along with IR and mass spectroscopy were used to deduce the structures of the mandelalides. Relative configuration of the compounds were assigned from analysis of ROESY data in addition to using homonuclear ($^3J_{HH}$) and heteronuclear ($^{2,3}J_{CH}$) coupling constants. The assignment of absolute configuration was carried out by hydrolysis of the glycosylated mandelalides and chiral GC-MA analysis of the released monosaccharides.

**5.3.1: Structural Features and Biological Activities of Mandelalides.**

Macrocyclic core of the mandelalides contain about 9-12 stereocenters including a *cis*-substituted THF ring in the top northern portion and a *cis*-substituted THP ring in the bottom southern portion. Mandelalide A contains a 24-membered macrolactone core whereas mandelalides B-D contain a 23-membered all carbon macrocycle, an uncommon structural motif present in natural products. In addition, mandelalides A and B possess different sugar substituents in their southern fragment. Interestingly, mandelalide A possesses 2-O-methyl-$\alpha$-L-rhamnose while mandelalide B contains the C-4’ epimer 2-O-methyl-6-dehydro-$\alpha$-L-talose. Mandelalides C and D were found to be devoid of sugar appendages.
In addition to the intriguing structural features, these natural products also show exciting biological activities in the early cell line assays. Mandelalides A and B were reported to produce nanomolar IC\textsubscript{50} values against Neuro-2A (44.0 and 83.8 nM resp. at 48 h) and NCI-H460 (12.0 and 29.4 nM resp. at 48 h) cell lines.\textsuperscript{21} These potent cytotoxic activities are thought-provoking especially when compared with the poor cytotoxicity values of the structurally related glycosylated polyketide madeirolide A.\textsuperscript{22} Madeirolide A

**Figure 5.4:** Proposed Structures of Mandelalides A-D and Madeirolide A.

[Figure showing proposed structures of Mandelalides A-D and Madeirolide A.]

mandelalide A (5.4.1) proposed structure

mandelalide B (5.4.2) \( R = \text{C(O)}n-\text{Pr} \)

mandelalide C (5.4.3) \( R_1 = \text{C(O)}n-\text{Pr} \) \( R_2 = \text{H} \)

mandelalide D (5.4.4) \( R_1 = R_2 = \text{C(O)}n-\text{Pr} \)

madeirolide A (5.4.5)
(5.4.5) contains the similar cis-substituted THF ring along with the diene and the methyl stereocenter on the western side of it like that of mandelalide A. It differs from the latter by possessing an additional THP ring, a different appended sugar moiety and a few other changes in the carbon backbone. Interestingly, madeirolide A shows potent fungicidal activity against *Candida albicans*.

### 5.3.2: Revised Structure of Mandelalide A.

The fascinating structural architecture and interesting biological profile of mandelalide A has garnered the attention from the synthetic community within a relatively short span of time since its isolation in 2012. In 2014, Furstner and co-workers reported the first total synthesis of the proposed structure of mandelalide A and proved the reported structure to be misassigned, as the NMR data of the synthetic sample didn’t match with the isolation data.\(^{23}\) Ghosh and co-workers have individually synthesized the aglycone version of the proposed structure of mandelalide A.\(^{24}\) Later in the same year, Ye and co-workers reassigned the structure by making multiple structural variants of the proposed mandelalide A.\(^{25}\) They realized that the stereochemical relationship between the northern and southern portions has been misassigned. Recently in 2015, Furstner and co-workers published their total synthesis of the corrected structure of mandelalide A.\(^{26}\)
Figure 5.5: Proposed and Revised Structures of Mandelalides A.

5.4: Synthetic Studies Toward Mandelalides

5.4.1: Furstner’s Synthesis of Proposed Structure of Mandelalide A

Furstner and co-workers reported the total synthesis of proposed structure of mandelalide A (5.4.1) and its C11-epimer in 2014.23 They had used an iridium-catalyzed Krische allylation and cobalt-catalyzed carbonylation to build the major subunits and employed a molybdenum-catalyzed terminal-acetylene metathesis reaction to construct the macrocycle.

Furstner’s approach towards synthesis of the southern THP ring is shown in Scheme 5.1. Iridium-catalyzed, two-directional Krische allylation of 1,3-propane diol (5.1.4) constructed $C_7$-symmetric diol 5.1.7 in high diastereoselectivity and enantioselectivity.27 Iodoetherification reaction was used to desymmetrize the diol 5.1.7 to furnish the cis-substituted THP ring in moderate selectivity (5:1 dr). Subsequent TBS
protection produced the iodide 5.1.8. Finally, Myer’s alkylation protocol was used employing the amide 5.1.9 to build the C11 stereocenter in excellent selectivity (97:3 dr).\textsuperscript{28} Subsequent reduction of the auxiliary using borane reduction yielded the alcohol 5.1.11.

Scheme 5.1. Synthesis of THP Ring.

Elaboration of the southern THP ring is shown in Scheme 5.2. Cross metathesis of alkene 5.1.11 with methyl acrylate using Hoveyda-Grubbs 2\textsuperscript{nd} Gen. catalyst set up the C2-C3 \textit{E}-alkene isomer in good selectivity (92:8, \textit{E}:\textit{Z}).\textsuperscript{29} Subsequent oxidation of the C12 alcohol produced aldehyde 5.2.6. Next, coupling with the semi-stabilized phosphonate 5.2.9 generated enyne 5.2.8 in one step in moderate yield. Alternatively, Takai olefination followed by Suzuki propynylation\textsuperscript{30} provided the enyne 5.2.8 in better overall yield. Finally, saponification of methyl ester using potassium trimethylsiloxide conditions
yielded the required southern fragment acid \textbf{5.2.10} along with the isomerized alkene \textbf{5.2.11}.

\begin{center}
\textbf{Scheme 5.2.} Elaboration of Southern Fragment.
\end{center}

Furstner’s synthesis of the cyclization precursor is shown in Scheme 5.2. Cobalt-catalyzed carbonylative epoxide opening of TBS ether \textbf{5.3.6} in presence of \textit{N}-TMS morpholine produced the amide \textbf{5.3.8}. Subsequent Grignard reagent generated the enone \textbf{5.3.9}. On the other hand, scandium triflate-catalyzed crotylation of aldehyde \textbf{5.3.10} with the chlorosilane donor \textbf{5.3.11} provided the alkene \textbf{5.3.12} in good yield and excellent selectivities.\textsuperscript{31} Cross-metathesis of alkene \textbf{5.3.12} with enone \textbf{5.3.9} in presence of catalyst \textbf{5.3.18} yielded enone \textbf{5.3.14}. Next, SmI\textsubscript{2}-catalyzed Evans-Tischenko reaction was used to
set up the anti-diol relationship in 5.3.15. TBDPS protection of C21 alcohol followed by selective desilylation furnished the cyclization precursor 5.3.16.

Scheme 5.3. Synthesis of Cyclization Precursor.

Construction of the northern THF ring is shown in Scheme 5.4. Selenoetherification of alcohol 5.3.16 in presence of N-(phenylseleny)phthalimide was
used to construct the THF ring in high selectivity.\textsuperscript{32} Subsequent deselenation under radical conditions yielded the tetrahydrofuran \textit{5.4.7}. Next, debenzylation and oxidation followed by treatment with the Ohira-Bestmann reagent\textsuperscript{33} provided the alkyne \textit{5.4.10}. Finally, DIBAL-H reduction of the ester furnished the alcohol \textit{5.4.11}.

\begin{center}
\includegraphics[width=\textwidth]{scheme5_4.png}
\end{center}

\textbf{Scheme 5.4.} Construction of THF Ring and Further Elaboration.

Synthesis of sugar fragment \textit{5.6.6} is shown in Scheme 5.6. Allylation of the rhamnosyl sugar \textit{5.6.1} produced the allylated sugar \textit{5.6.2}. Next, C3’ and C4’ alcohols
were protected as a 1,2-diacetal under acidic conditions. Subsequent methylation of the C2’ alcohol generated the methyl ether 5.6.4. The removal of diacetal group followed by bis-acetyl protection yielded the diacetate 5.6.5. Finally, deallylation under SeO₂ conditions followed by trichloroacetimidate formation generated the needed sugar fragment 5.6.6.

**Scheme 5.6.** Synthesis of Sugar Fragment.

Coupling of the fragments and total synthesis of mandelalide A is shown in Scheme 5.7. The northern and southern subunits were coupled using DCC reagent; however significant migration of the C2-C3 alkene to C3-C4 position under the reaction conditions (α,β to β,γ isomers = 1.5:1). Nevertheless, heating the mixture of isomers under basic conditions solved the problem. Next, the alkyne metathesis of diyne 5.7.1 using molybdenum catalyst (5.7.2) yielded the macrocycle. Subsequently, activated Zn(Cu/Ag) conditions were used to selectively reduce the C14-C25 alkyne to the E-
alkene followed by TBS deprotection and TESOTf-catalyzed glycosylation of sugar 5.6.6 to provide the macrolactone 5.7.5. Finally, selective saponification of the acetate groups followed by silyl deprotection using HF•Pyr conditions yielded the proposed structure of mandelalide A (5.4.1). Other conditions for desilylation resulted in significant ring expansion to C24 macrolactone. Unfortunately, the NMR data of the synthetic sample did not match with the isolation data—proving that the structure of mandelalide A was originally misassigned. Furstner and co-workers have also synthesized the C11-epimer of the proposed structure, which also failed to match the NMR data of the isolated natural product.
Scheme 5.7. Total Synthesis of Proposed Structure of Mandelalide A (5.4.1).
5.4.2: Ghosh’s synthetic studies toward mandelalide A

Ghosh and co-workers reported their total synthesis of aglycone of mandelalide A in 2014. Their key steps include \( E \)-selective intramolecular Heck coupling to construct the macrocycle, Masamune-Roush olefination to couple the fragments and a modified Prins cyclization to build the southern THP ring.

Ghosh’s synthesis of the cyclization precursor 5.8.6 is shown in Scheme 5.8. The known alkene 5.8.2 was made from aldehyde 5.8.1 via Brown crotylation followed by PMB protection sequence. Subsequent hydroboration followed by oxidation and Julia-coupling with the known sulfone 5.8.4 produced the \( E \)-alkene 5.8.5 in good yield. Finally, PMB ether was oxidatively cleaved to generate the cyclization precursor alcohol 5.8.6.

Scheme 5.8. Ghosh’s Synthesis of Cyclization Precursor Alcohol (5.8.6).
Synthesis of the northern iodide fragment is shown in Scheme 5.9. Mesylation of C17 alcohol followed by dihydroxylation of the alkene resulted in *in situ* intramolecular cyclization of the mesylate to produce the THF ring **5.9.1** in excellent selectivity. Subsequent protecting group modifications provided the alcohol **5.9.2**. Oxidation followed by Stork-Zhao olefination sequence was used to construct the Z-vinyl iodide **5.9.3** in excellent selectivity. Next, acetonide deprotection and selective silyl protection yielded the alcohol **5.9.4**. Finally, coupling of alcohol with the carboxylic acid was facilitated by EDCI and DMAP conditions to furnish the northern iodide fragment.

**Scheme 5.9.** Synthesis of Northern Iodide Fragment (**5.9.4**).
Ghosh’s synthesis of southern THP ring started with the known alkene 5.10.1 (Scheme 5.10). Ozonolysis followed by Brown’s crotylation generated the alcohol 5.10.2. Next, coupling of the alcohol with the carboxylic acid produced the ester 5.10.3. Selective reduction of ester to the lactol followed by acetate protection produced the α-acetoxy ether, which upon Prins cyclization and C7-acetoxy deprotection provided the THP ring 5.10.4 in moderate yield and in excellent selectivity. Finally, functional group modifications provided the aldehyde at C12 position, which was subjected to Julia-Kocienski olefination to construct the C12-C13 alkene 5.10.6. Further functional group modifications furnished the southern aldehyde fragment 5.10.7.

**Scheme 10. Synthesis of Southern THP Fragment.**
Synthesis of aglycone of mandelalide A is shown in Scheme 5.11. Coupling of the northern phosphonate ester 5.9.6 and southern aldehyde 5.10.7 was carried out under Masamune-Rousch conditions to provide the ester 5.11.1 in good yield. Next, intramolecular Heck-coupling was used to construct the E,Z-diene portion of the macrocycle 5.11.2. Finally, global desilylation generated the aglycone version of the proposed structure of mandelalide A (5.11.3). The authors have pointed out the similarity in the NMR spectral data between aglycone 5.11.3 and the structurally similar macrocyclic core synthesized by Furstner and co-workers.

Scheme 11. Synthesis of Aglycone of Mandelalide A.
5.4.3: Ye’s Structural Revision of Mandelalide A

Ye and co-workers published their total synthesis of proposed structure of mandelalide A and revised the structure of the natural product by synthesizing various structural variants of it. Key steps in their synthetic strategy include Prins cyclization to construct the THP ring, Rychnovsky-Bartlett cyclization to prepare the THF ring and a Horner-Wadsworth-Emmons olefination for the macrocyclization.

Ye’s studies of Rychnovsky-Bartlett cyclization are presented in Scheme 5.11. The known alcol 5.11.1 was protected as its dichlorobenzylether followed by hydroboration conditions provided the alcohol 5.11.2. Next, Ye used a similar strategy to that found in Ghosh’s report to construct the C20-C21 E-alkene. Oxidation of the C20 alcohol followed by Julia-Kocienski olefination with the sulfone 5.8.4 provided the E-alkene 5.11.3. Unfortunately Rychnovsky-Bartlett cyclization of the alkene 5.11.3 resulted in the undesired alcohol 5.11.6 due to the interference of acetonide moiety with the cyclization reaction. Consequently, protecting group modifications yielded the carbonate 5.11.4 over two steps. Though the cyclization proceeded well with the precursor 5.11.4 to provide the THF ring 5.11.5 in excellent yields, the authors were unable to convert the C21 iodide to the corresponding alcohol.
Synthesis of northern phosphonate fragment is shown in Scheme 5.12. The alcohol 5.12.1 was converted to allyl alcohol 5.12.2 in a three-step sequence of oxidation, Horner-Wadsworth-Emmons olefination and reduction. Next, intramolecular cyclization of alcohol with I\(_2\) in acetonitrile provided the THF ring in 5.12.3 in excellent yield and selectivity. Subsequent treatment with potassium carbonate built the C21-C22 epoxide that was opened in the following step to provide homoallylic alcohol 5.12.4. Further, protecting group modifications generated the alcohol 5.12.5. Next, oxidation followed by
Stork-Zhao olefination conditions yielded the Z-vinyl iodide 5.12.6 in a strategy that is almost identical to Ghosh’s report. The C23 stereocenter was constructed using Sharpless asymmetric dihydroxylation rather in poor selectivity (1:2 dr). Finally, selective TBS protection followed by coupling of C23 alcohol with the acid 5.12.9 using a Yamaguchi conditions furnished the known phosphonate ester 5.9.6 in excellent yield.24

**Scheme 5.12.** Synthesis of Northern Phosphonate Ester (5.9.6).

Ye and co-workers had used a similar Prins cyclization strategy to that used by Ghosh *et. al.* to construct the southern THP ring is shown in Scheme 5.13. Prins
cyclization of aldehyde $\text{5.13.1}$ and alcohol $\text{5.13.2}$ under TFA conditions followed by methanolysis of the resultant C7 ester provided the alcohol $\text{5.13.3}$ in moderate yield over two steps. Next, protection group modification provided the bis-PMB ether $\text{5.13.4}$. Further, Ohira-Bestmann reagent was used to construct the C12-C13 alkyne $\text{5.13.5}$. Finally, conversion of alkyne $\text{5.13.5}$ to the pinacol boronate by treatment with pinacolborane in presence of dicyclohexyl borane followed by oxidative removal of PMB groups furnished the diol $\text{5.13.6}$.

Scheme 5.13. Synthesis of Southern Pinacol-Boronate Fragment ($\text{5.13.6}$).

Synthesis of rhamnosyl sugar fragment is shown in Scheme 5.14. Selective protection of the known thioether $\text{5.13.1}$ as its bis-acetal provided the alcohol $\text{5.14.2}$, which was methylated in the subsequent step to yield the methylether $\text{5.14.3}$. Finally,
TFA conditions were used to remove the bis-acetal protecting group followed by oxidation of sulfide to the sulfoxide using mCPBA generated the required sugar fragment 5.14.5.


Ye and co-workers utilized an intermolecular Suzuki coupling to couple the fragments together to provide the C12-C15 diene unit (Scheme 5.15). Oxidation of C3 primary alcohol using TEMPO and bis-acetoxy iodobenzene provided the cyclization precursor aldehyde which was cyclized via an intramolecular Horner-Wadsworth-Emmons olefination employing Masamune-Rousch conditions to generate the macrolactone 5.15.2. Finally, glycosylation of the rhamnosyl sugar 5.14.5 at the C7 alcohol followed by global desilylation under TASF conditions provided the proposed structure of mandelalide A (5.4.1). As observed by Furstner, the synthesized material did not match with the isolation data for the natural product. Also, a smaller amount of ring expanded product 5.15.5 was reported to have been isolated as was observed by Furstner.
and co-workers. Finally, Ye and co-workers synthesized the structural variant 5.5.1 of the natural product using a similar strategy to what was described and showed the NMR data of macrolactone 5.5.1 is in complete agreement with that of the isolated natural product.

**Scheme 5.15.** Total Synthesis and Structural Revision of Mandelalide A.
5.4.4: Furstner’s Synthesis of Revised Structure of Mandelalide A.

Recently in 2015, Furstner and co-workers reported their total synthesis of revised structure of mandelalide (5.5.1) (Scheme 5.16). Enantiomeric northern fragment was synthesized using identical strategy to what was used during the synthesis of proposed structure. Coupling of the major subunits was achieved using DCC coupling to provide the ester 5.16.1. Alkyne metathesis was carried out using Molybdenum catalyst 5.7.2 to provide the macrocyclic enyne 5.16.2. Next, selective alkyne reduction followed by glycosylation at C7 position provided the macrolactone 5.16.4. Finally, careful acetate hydrolysis and subsequent global desilylation accomplished the total synthesis of the revised structure (5.5.1) of mandelalide A confirming the revision made by Ye and co-workers. Furstner and co-workers have also reported the C11 epimer (5.16.5) of the revised structure utilizing an identical strategy.
Scheme 5.16. Synthesis of Revised Structure of Mandelalide A (5.5.1)
5.5. Conclusion.

Mandelalides are a new type of polyketide macrolides that have exciting cytotoxic activities against cancer cells in preliminary biological studies in addition to possessing an interesting structural architecture. These marine natural products have drawn the attention of various synthetic groups including ours in a short span of time since their isolation in 2012.

Furstner and co-workers reported the first total synthesis of the proposed structure mandelalide A and proved the structure has been mis-assigned. They had used an iridium-catalyzed Krische allylation and cobalt-catalyzed carbonylation to build the major subunits and employed a molybdenum-catalyzed terminal-acetylene metathesis reaction to construct the macrocycle. Ghosh and co-workers published their synthesis of aglycone of mandelalide A in which a \( E \)-selective intramolecular Heck coupling was used to construct the macrocycle, Masamune-Roush olefination was employed to couple the fragments and a modified Prins cyclization was utilized to build the southern THP ring. Ye and co-workers disclosed their synthesis of mandelalide A utilizing a similar strategy to what was reported by Ghosh and co-workers. Key steps in Ye’s strategy include Prins cyclization to construct the THP ring, Rychnovsky-Bartlett cyclization to prepare the THF ring and a Horner-Wadsworth-Emmons olefination for the macrocyclization. Ye and co-workers have reassigned the structure by synthesizing various structural variants of the proposed mandelalide A. Recently in 2015, Furstner and co-workers have reconfirmed the structural revision by exclusively synthesizing the revised structure of mandelalide A employing an identical strategy to that used in their original synthesis.
References:


(11) Glueck, C. J.; Khan, N.; Riaz, M.; Padda, J.; Khan, Z.; Wang, P. “Titrating Lovaza from 4 to 8 to 12 grams/day in Patients with Primary Hypertriglyceridemia who had Triglyceride levels >500 mg/dL despite Conventional Triglyceride Lowering Therapy” *Lipids Health Dis.* **2012**, *11*, 143.


(22) Winder, P. L. Ph.D. Thesis, Florida Atlantic University, **2009**.


CHAPTER 6:

ORIGINAL APPROACH TOWARDS MANDELALIDE A
6.1. Introduction to Mandelalide A.

Marine natural products have long proven to be a valuable source of potential leads for pharmaceuticals.\textsuperscript{1} The growing number of the FDA approved drugs that are marine metabolites (or their derivatives) shows the importance of these natural products in human healthcare.\textsuperscript{2} McPhail and co-workers recently reported the isolation of a new class of marine natural products from a new species of \textit{Lissoclinum} ascidian collected from Algoa Bay, South Africa called the mandelalides.\textsuperscript{3} The parent member of this family, mandelalide A, is a polyketide macrolide containing 9 stereocenters embedded within the 24-membered macrocyclic scaffold that has shown impressive cytotoxicity in early screening against Neuro-2A (IC\textsubscript{50} value 44.0 nM at 48 h) and NCI-H460 (IC\textsubscript{50} value 12.0 nM at 48 h) cell lines. The structural complexity of this compound includes a \textit{cis}-substituted THF ring, a \textit{cis}-substituted THP ring and an acid-sensitive C12-C15 diene moiety. In addition, mandelalide A contains a rhamnosyl sugar appended on to its southern fragment.

6.2. Reported Syntheses of Mandelalide A.

Given the structural challenges embedded with mandelalide coupled with its potent biological activity, mandelalide A has attracted considerable synthetic attention from numerous labs throughout the world.\textsuperscript{4,5,6} The challenging stereochemical relationship between the northern and southern hemispheres was initially mis-assigned as discovered by Fürstner and co-workers.\textsuperscript{4a} Ghosh and co-workers followed up quickly on
this synthesis with an independent synthesis of the aglycone of the proposed structure.\textsuperscript{5} Ye and co-workers ultimately resolved this ambiguity through total synthesis – unequivocally establishing the correct stereochemical relationship.\textsuperscript{6} Fürstner and co-workers recently reported a total synthesis of the corrected structure.\textsuperscript{4b}

6.2. First Generation Retrosynthetic Analysis.

Our original retrosynthetic analysis to originally proposed structure of mandlealide A is shown in Scheme 6.1. Please note that we initiated our work in this area prior to the discovery of the structural error. Mandelalide A (5.4.1) was envisioned to be accessible from the northern THF ring (6.1.1) and the southern THP moiety (6.1.3) via a Wittig olefination followed by macrolactonization. The northern \textit{cis}-substituted THF ring could be constructed using an Ag-catalyzed cyclization (AgCC) reaction. Given our group’s interest in the AgCC process,\textsuperscript{7} we were intrigued by the possibility to also access the southern \textit{cis}-THP ring from the propargyl benzoate 6.1.4. To our knowledge, we were unaware of any prior examples of its implementation in the synthesis of 6-member heterocycles. This required cyclization precursor 6.1.4 can be made via an alkyne ring opening of the epoxide. This thesis will primarily focus on the synthesis of northern C15-C24 fragment, its coupling the C1-C14 subunit and further advancements towards the natural product. The C1-C12 southern fragment with the appended sugar was synthesized by Mr. Ankan Ghosh in the Carter laboratory.
Scheme: 6.1. Retrosynthetic Disconnection of Mandelalide A (5.4.1)

The retrosynthetic analysis of the cyclization precursor for the northern THF ring is shown in Scheme 6.2. The required diol precursor 6.1.2 should arise from the corresponding enyne fragment 6.2.1 using a Sharpless dihydroxylation. The enyne 6.2.1 should be available from alkyne 6.2.2 and iodide 6.2.3 via Sonogashira cross coupling reaction. Known alkyne 6.2.2 has been previously prepared in our laboratory\(^7\) from the alcohol 6.2.4 via Corey-Fuchs olefination. The required iodide 6.2.3 should be available from ester 6.2.5 via reduction followed by Takai olefination.
Scheme: 6.2. Retrosynthetic Analysis for the Northern Cyclization Precursor (6.1.2)


The synthesis of the northern fragment commenced with the synthesis of the known alkyne subunit 6.2.2 (Scheme 6.3). Exhaustive reduction of (L)-malic acid with borane provided the triol 6.3.1. Next, selective 1,3-diol protection using dimethoxy benzaldehyde yielded the primary alcohol 6.2.4. Though the reaction conditions primarily provided the 1,3-diol protected product there was a small amount 1,2-diol product observed, which was fortunately separated via column chromatography. Subsequent Swern oxidation followed by a two-step Corey-Fuchs protocol was used to install the alkyne side arm. Succeeding methanolysis of the benzylidene acetal and selective
protection of the resultant alcohols constructed the desired alkyne 6.2.2 in 73% yield from alkyne 6.3.3.


The iodide partner ent-6.2.3 was accessible in 5 steps from dimethyl malanoate 6.4.1 (Scheme 4). Our preliminary work in this area inadvertently used the wrong enantiomer of (L)-malic acid diethyl ester to construct the diol 6.4.2 via a known borane, NaBH₄ protocol. Next, selective 1° TBS protection yielded the silyl ether 6.4.3. Subsequent treatment with TESOTf generated the fully protected product ent-6.2.5. Reduction of the ester moiety with DIBAL-H followed by Takai olefination of the resultant aldehyde produced the iodide ent-6.2.3 in low yield and selectivity (42%, 3:1 E:Z). Evans and co-workers reported that the use of a dioxane and THF (6:1) mixture for the Takai olefination can improve the E/Z selectivity; however, we did not observe this outcome in our hands.
With the model iodide and target alkyne in hand, we focused our attention on the construction of the enyne and its subsequent elaboration (Scheme 6.5). Sonogashira coupling of the iodide \( \text{ent-6.2.3} \) and alkyne \( \text{6.2.2} \) subunits provided the enyne \( \text{6.5.1} \) in good yield. It is worth noting that the \( E:Z \) ratio of the C20-C21 alkene has been improved from 3:1 to 7:1 over the course of the reaction. This unexpected outcome is possibly due to the difference in rate between \( E \) and \( Z \) vinyl iodides in the cross-coupling process. In fact, the Sonogashira reaction was observed to be remarkably fast – proceeding within just 2 h at 0 °C. We proceeded onward to the Sharpless dihydroxylation.\(^\text{14,15}\) To our surprise, a mixture (3:1) of isomers were observed from the reaction. Given the high selectivity of these reactions for the dihydroxylation of \( \text{trans-} \) enynes\(^\text{16}\) including from our own laboratory,\(^7\) we hypothesized that the lower isomeric ratio must have been due to the silyl migration instead of the poor diastereoselectivity. Multiple examples of silyl
migrations under the basic reaction conditions have been reported in the literature.\textsuperscript{17} One possible method to circumvent this process would be to buffer the modestly basic Sharpless conditions with NaHCO\textsubscript{3} – a protocol used previously by our laboratory to suppress problematic base-catalyzed silyl migration.\textsuperscript{18} Unfortunately this technique did not help to reduce the migration problems in our current system. Further problematic was the fact that the isomers proved inseparable by column chromatography. Hence, we sought for alternate protecting group strategy for C23 and C24 alcohols.

Our alternative protecting group strategy is shown in Scheme 6.6. Acetonides are widely known to be stable under even strongly basic conditions. Treatment of bis-silyl ether 6.5.1 with TBAF provided the diol 6.6.1, which was converted to the acetonide 6.6.2 with dimethoxy propane under acidic conditions in good yield. Alternatively, \textit{p}TSA
conditions selectively removed the 1° TBS ether to provide the alcohol 6.6.3. Though TES group is usually more labile than the TBS, the steric must have played a role here to selectively remove the 1° TBS over the 2° TES group. Subsequent treatment with dimethoxy propane and acid effected 2° silyl deprotection followed by acetonide ring closure to produce enyne 6.6.2. The second route suggested us that this transformation can be effected in a single step. As we expected direct treatment of enyne 6.5.1 with dimethoxypropane under acidic conditions provided the required compound 6.6.2 in excellent yield.


While we were able to convert the silyl protected enyne 6.5.1 to the acetonide enyne 6.6.2, a more direct protocol for constructing the acetonide motif in this system was needed (Scheme 6.7). Additionally, we needed to utilize the correct C23
stereochemistry in the iodide fragment. Following a known protocol, the diol \((R)-6.4.2\) was protected using dimethoxy propane under acidic conditions to provide the ester \(6.7.1\). This ester was reduced using Dibal-H to obtain the alcohol \(6.7.2\). Alternately, the alcohol can be made from the triol \((R)-6.3.1\) in one step via selective protection of 1,2-diol in a reasonable yield.\(^{19}\)

**Scheme 6.7.** Different Routes to Synthesize alcohol \(6.7.2\).

As shown previously in the enantiomeric series (Scheme 6.4), the synthesis of the iodide moiety\(^{20}\) proved problematic in both chemical yield and E/Z selectivity. We set out to explore alternate methods to access this compound with greater efficiency (Table 6.1). It should be noted that the direct one-step reduction of ester \(6.7.1\) with Dibal-H did afford the aldehyde; however, the results were found to be irreproducible (Entry 1).\(^{10}\) Swern or DMP oxidation of alcohol \(6.7.2\) followed by Takai olefination produced the vinyl iodide \(6.7.3\) in continued low yields and moderate selectivity (Entry 2 and 3). We hypothesized that the low yield was in part caused by the choice of oxidation conditions...
and the volatility of the product. Encouraging success with chromium-based oxidant systems have been reported in the literature.\textsuperscript{21} We were pleased to see that PCC oxidation in presence of 3 Å molecular sieves produced the aldehyde in good yield.\textsuperscript{22} Subsequent Takai olefination yielded the optimum results (65% yield, 5.7:1, $E:Z$) (Entry 4). We again explored the dioxane:THF solvent system to improve the transformation further, but these conditions again did not have the desired outcome (Entry 5).\textsuperscript{12}

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|}
\hline
Entry & Oxidation conditions & Takai conditions & Yield (2 steps) & $E:Z$ \\
\hline
1 & DIBAL-H Et\textsubscript{2}O, -78 °C (from 6.7.1) & CrCl\textsubscript{2}, CH\textsubscript{3}I, THF & 35\% & 4.8:1 \\
\hline
2 & DMSO, (COCl)\textsubscript{2} CH\textsubscript{2}Cl\textsubscript{2}, -78 °C (from 6.7.2) & CrCl\textsubscript{3}, Zn, CH\textsubscript{3}I, THF & 41\% & 4.4:1 \\
\hline
3 & DMP, Pyr. CH\textsubscript{2}Cl\textsubscript{2}, rt (from 6.7.2) & CrCl\textsubscript{3}, Zn, CH\textsubscript{3}I, THF & 23\% & 4.5:1 \\
\hline
4 & PCC, 3 Å M.S. CH\textsubscript{2}Cl\textsubscript{2}, rt (from 6.7.2) & CrCl\textsubscript{3}, Zn, CH\textsubscript{3}I, THF & \textbf{65\%} & \textbf{5.7:1} \\
\hline
\end{tabular}
\caption{Synthesis of Vinyl Iodide (6.7.3).}
\end{table}
The synthesis of the diol **6.8.2** is shown in Scheme 6.8. Sonogashira coupling\textsuperscript{23} of the fragments proceeded in good yield to produce the enyne **6.8.1**. As observed previously, the $E:Z$ ratio of the alkene was significantly improved during the reaction, likely due to the differential reactivities between the $E$ and $Z$ vinyl iodides. Next, Sharpless asymmetric dihydroxylation using AD mix $\beta^*\text{15}$ generated the cyclization precursor **6.8.2** in good yield and diastereoselectivity (83\%, 10:1 dr). The commercially available AD mix $\beta$ proved sluggish in the reaction conditions. Our laboratory has long employed these conditions with higher ligand and osmium levels to increase reaction rate.\textsuperscript{24}

**Scheme 6.8.** Synthesis of Cyclization Precursor.
6.4. Silver Catalyzed Cyclization (AgCC) Reaction.

6.4.1. Background on Cyclization Reaction for Dihydrofuran Synthesis.

Dihydrofuran and tetrahydrofurans are widely found in the natural product scaffolds and other biologically active compounds.\cite{1,25} Not surprisingly, there have been a significant amount of work devoted towards their construction.\cite{26} In fact, reports of the synthesis of DHF/THF rings from the corresponding propargylic alcohols date as far back as to 1911.\cite{27} Since this pioneering work, there has been a great deal of modifications done to improve the reaction conditions, chemical performance and reaction breadth.\cite{28}

Transition metal catalysis (particularly silver- and gold-catalyzed isomerization/cyclization of the propargyl esters) has attracted considerable attention and is summarized in Scheme 6.9. In 1991, Shigemasa and co-workers reported the construction of the enantiopure dihydrofuran ring from the corresponding enatiopure propargyl acetates.\cite{29} The propargyl alcohol/ester 6.9.1 in presence of a AgBF$_4$ catalyst in refluxing benzene produced the dihydrofuran ring in a highly stereoselective manner with no stereoerosion. Initially, the ester is believed to undergo an isomerization to produce the allenyl alcohol 6.9.2, which would cyclize in presence of silver to generate the dihydrofuran ring. In 2001, Krause and co-workers disclosed their highly stereoselective Au-catalyzed cyclization of dihydrofuran synthesis from the allenyl alcohol 6.9.5.\cite{30} The allenyl alcohol 6.9.5 was accessed in one step from the ring opening of epoxide 6.9.4. In 2006, Gagosz and co-workers published their one-step Au-catalyzed process of propargyl
benzoates 6.9.7 to synthesize trans-substituted dihydrofuran rings 6.9.9 in high yields and selectivity.\textsuperscript{31} Recently in 2009, we have developed a one-pot synthesis of trans-substituted dihydrofuran ring 6.9.12 employing a Ag-catalyzed cyclization (AgCC) of propargyl benzoates 6.9.10. The impactful part of this work is the fact that it was done on diol as the cyclization precursors. We proposed to extend this work to cis-DHF ring systems. Interestingly, we unaware of any reports of the construction of the cis-2,3-disubstituted dihydrofuran rings from the corresponding propargyl benzoates outside of one single substrate by Gagosz and co-workers.\textsuperscript{31}
Shigemasa et al.

\[
\begin{align*}
\text{6.9.1} & \quad \text{(84\% ee)} \\
\text{6.9.2} & \quad \text{THPO} \\
\text{6.9.3} & \quad \text{(59\%, 84\% ee)}
\end{align*}
\]

Krause et al.

\[
\begin{align*}
\text{6.9.4} & \quad \text{98\%, >98\% ee} \\
\text{6.9.5} & \quad \text{THF} \\
\text{6.9.6} & \quad \text{(97\%, 96\% de, >98\% ee)}
\end{align*}
\]

Gagosz et al.

\[
\begin{align*}
\text{6.9.7} & \quad \text{(2 mol \%)} \\
\text{6.9.8} & \quad \text{THF} \\
\text{6.9.9} & \quad \text{(99\%, 9:1 dr)}
\end{align*}
\]

Carter et al.

\[
\begin{align*}
\text{6.9.10} & \quad \text{OPiv} \\
\text{6.9.11} & \quad \text{THF} \\
\text{6.9.12} & \quad \text{(65-70\%, >20:1 dr)}
\end{align*}
\]

**Scheme 6.9.** Au- or Ag- Catalyzed Cyclization Methods for Dihydrofuran Synthesis.
6.4.2 Silver Catalyzed Cyclization (AgCC) Reaction.

Our exploration of the Ag-catalyzed cyclization AgCC to access cis-dihydrofurans is shown in Table 6.2. Based on our prior successes in the area,\textsuperscript{7} we initially used AgBF$_4$ as catalyst in deoxygenated benzene in the absence of light. To our delight, we were able to observe the cyclized product in modest yield and high selectivity (35\% yield, 10:1 dr) (Entry 1). Interestingly, we were also able to isolate the furan 6.8.4 in significant amount. This by-product has been previously observed in our trans-DHF work.\textsuperscript{7} We explored the addition of sterically hindered amine bases to neutralize any possible Brønsted acid present in the reaction media, which might have produced the undesired reaction pathways. Unfortunately, addition of 2,6-di-\textit{tert}-butyl-4-methylpyridine reduced the yield for both the desired and undesired product formations (Entry 2). Lowering of the reaction temperature to 60 °C, as expected, reduced the reaction rate, but no meaningful improvement in the selectivity between the desired and the undesired reaction pathways was observed (Entry 3). We explored the use of coordinating solvents such as 1,4-dioxane that completely suppressed the reaction initially and prolonged reaction times led to slow decomposition of the starting material (Entry 4). Blended solvent systems proved equally ineffective (Entry 5). These outcomes showed that attempting to mute the electrophilicity of the silver catalyst through addition of an amine additive (Entry 2) or by use of a coordinating solvent (Entries 4 and 5) did not help to address the deleterious reaction pathway. Consequently, we sought alternate solutions to this challenge.
Table 6.2. Silver Catalyzed Cyclization (AgCC) Reaction.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temp (°C) &amp; Time</th>
<th>Additives</th>
<th>Yield &amp; dr (2 steps) for 6.2.6</th>
<th>Yield for 6.2.7</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Benzene</td>
<td>80 °C, 1.5 h</td>
<td>-</td>
<td>35%, 10:1 dr</td>
<td>40%</td>
</tr>
<tr>
<td>2</td>
<td>Benzene</td>
<td>80 °C, 1.5 h</td>
<td>Me</td>
<td>22%, 10:1 dr</td>
<td>28%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Bu</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Bu</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Bu</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Benzene</td>
<td>60 °C, 2.5 h</td>
<td>-</td>
<td>5% (60%, borsm)</td>
<td>6%</td>
</tr>
<tr>
<td>4</td>
<td>1,4-Dioxane</td>
<td>90 °C, 4 h</td>
<td>-</td>
<td>Decomp.</td>
<td>Decomp.</td>
</tr>
<tr>
<td>5</td>
<td>Benzene: 1,4-Dioxane (3:1)</td>
<td>80 °C, 10 h</td>
<td>-</td>
<td>25%, 10:1 dr</td>
<td>30%</td>
</tr>
</tbody>
</table>

A detailed analysis of the mechanistic pathways for this AgCC process is presented in Scheme 6.9. We hypothesize that the pathway that leads to the desired dihydrofuran likely starts with the propargyl benzoate cyclizing onto the Ag-activated alkyne in a 6-endo-dig fashion to generate the vinyl silver species 6.10.1. It is worth noting that the benzylic cation is well stabilized by the adjacent oxygen atoms in addition
to being conjugated to the phenyl ring. The carbon-silver bond eventually collapses to open up the dioxane ring to produce allenyl alcohol 6.10.2 and regenerate the Ag species. The allene moiety is then further activated by Ag (I) and undergoes a 5-endo-trig cyclization to generate the dihydrofuran ring 6.10.3. Finally, the vinyl silver species is proto demetalated to provide the desired product 6.10.4.

In contrast, the pathway leading to the undesired furan byproduct likely starts with the attack of the homo propargyl alcohol on to the activated alkyne in a 5-endo-trig fashion. The organo silver intermediate 6.10.5 is further proto demetalated to generate the alcohol 6.10.6. Finally, the dehydration of alcohol 6.10.6 is likely rapid and highly favored to the aromatic nature of the furan by-product 6.2.7.
Based on our analysis of the mechanistic pathways leading to the desired and undesired products, we proposed two options. (i) One possibility would be to increase the rate of the benzoate cyclization and rearrangement faster by installing the

**Scheme 6.10.** Mechanistic Analysis of AgCC Reaction.
electron-donating substituents on the benzoates. (ii) Alternatively, we could block the homo propargyl alcohol from the unwanted cyclization with a suitable protecting group.

**6.5. Improvements Made to Circumvent the By-product Formation.**

**6.5.1. Effect of Substituents on the AgCC reaction.**

In order to study the effect of benzoate substituents on the AgCC reaction, we needed to synthesize differently substituted propargyl benzoates. We planned to install electron-donating substituents (e.g., *p*-methyl and *p*-methoxy groups) to increase the nucleophilicity of the benzoate (Scheme 6.11). Selective hydrolysis of the benzoate ester was carried out using potassium carbonate in presence of MeOH at rt to provide the propargyl alcohol. This selectivity is possible due to the faster rate of hydrolysis of benzoate than the pivaloate moiety on steric grounds. Next, treatment of the propargyl alcohol with *p*-methyl and *p*-methoxy benzoyl chlorides produced the corresponding propargyl esters in decent yields. Not surprisingly, the rate of esterification for the *p*-methoxy benzoate was slow requiring reflux dichloromethane conditions to force it to completion. In contrast, the tolouate ester was formed under milder conditions and shorter reaction times (rt, 1 h). Finally, Sharpless asymmetric dihydroxylation of the corresponding enynes generated the diol cyclization precursors 6.11.4 and 6.11.5 in good yields and high selectivities.
Scheme 6.11. Synthesis of Cyclization Precursors for AgCC Reaction.

With the successful synthesis of the substituted benzoate esters, we next investigated the impact of the different substituents on the AgCC reaction (Table 6.3). As discussed earlier the unsubstituted benzoate 6.8.2 produced the dihydrofuran (DHF) in low yield while simultaneously generating a significant amount of furan byproduct (Entry 1). The toluate 6.11.4 under similar conditions produced similar yield for DHF, but resulted in lower levels of furan by-product formation (Entry 2). As forecast, the $p$-methyl substituent reduced the reaction time as compared to the aryl ring. Increasing the temperature to 97 °C reduced the overall yield, but improved the ratio of product to the furan (1.5:1) (Entry 3). Following the same trend, raising the temperature to 110 °C continued to increase the product to furan ratio (2:1), but led to further reductions in the chemical yield of the required DHF. These results supported the premise that higher temperatures led to differential increase in the decomposition rate of the furan as
compared to corresponding dihydrofuran – resulting in increased product to furan ratio. Change of solvent to toluene produced similar results to benzene (Entry 5). Interestingly, the methoxy-substituted benzoate 6.11.5 provided poor overall yield for both DHF and furan suggesting that the methoxy substituent is too active for the rearrangement-cyclization sequence (Entry 6).

![Structural diagram showing the molecules and reaction conditions.]

**Table 6.3.** Effect of Substituents on Silver Catalyzed Cyclization (AgCC) Reaction.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Precursor</th>
<th>Solvent</th>
<th>Temp (°C) &amp; Time</th>
<th>Yield (2 steps) for DHF</th>
<th>Yield for Furan</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6.8.2</td>
<td>Benzene</td>
<td>80 °C, 1.5 h</td>
<td>35%</td>
<td>40%</td>
</tr>
<tr>
<td>2</td>
<td>6.11.4</td>
<td>Benzene</td>
<td>87 °C, 40 min</td>
<td>32%</td>
<td>28%</td>
</tr>
<tr>
<td>3</td>
<td>6.11.4</td>
<td>Benzene</td>
<td>97 °C, 15 min</td>
<td>27%</td>
<td>18%</td>
</tr>
<tr>
<td>4</td>
<td>6.11.4</td>
<td>Benzene</td>
<td>110 °C, 15 min</td>
<td>24%</td>
<td>12%</td>
</tr>
<tr>
<td>5</td>
<td>6.11.4</td>
<td>Toluene</td>
<td>95 °C, 30 min</td>
<td>30%</td>
<td>20%</td>
</tr>
<tr>
<td>6</td>
<td>6.11.5</td>
<td>Benzene</td>
<td>85 °C, 20 min</td>
<td>18%</td>
<td>9%</td>
</tr>
</tbody>
</table>
6.5.2. Synthesis of Selectively Masked Cyclization Precursor.

As the investigation of the substituent effect on the AgCC reaction failed to increase the yield for the required dihydrofuran, we decided to pursue our alternate option of blocking the homopropargyl (C21) alcohol (Scheme 6.12). Selective masking of the C20 propargyl alcohol followed by TBS protection of the C21 alcohol generated the silyl ether 6.12.1 in decent yield. Next, treatment with PPTS in MeOH preferentially exposed the C20 alcohol to produce the required cyclization precursor 6.12.2. Though this two-step sequence provided the needed precursor, the overall yield over the two steps was too low to be practical. Alternatively, double TBS protection of the diol 6.8.2 afforded the bis-silyl ether 6.12.3 in excellent yield. We screened multiple conditions to the selective deprotect the C20 alcohol. Contrary to the published reports,33 selective deprotection using TBAF conditions proved to be unsuccessful. Acidic conditions such as TFA led to acetonide deprotection prior to any desilylation. Finally, use of HF•Pyr furnished the cyclization precursor 6.12.2 in 75% yield over two cycles from the bis-silyl ether 6.12.3. We also studied the bis-thexyl [-SiMe₂C(Me)₂C(Me)₃] protection34 of the diol 6.8.2 and selective deprotection using HF•Pyr conditions, but that process proved to be futile.

6.6. AgCC Reaction and Late Stage Roadblocks.

6.6.1. Successful AgCC Reaction to Construct the cis-Substituted THF ring.

With the successful synthesis of selectively masked cyclization precursor 6.12.2, next, we studied our AgCC reaction (Scheme 6.13). To our delight, the cyclization reaction proceeds in presence of AgBF$_4$ under reflux benzene conditions to produce the required dihydrofuran 6.13.1 in excellent yield and stereoselectivity. Interestingly, careful inspection of the reaction times as compared to the diol 6.8.2 showed that the silyl protected series is notably slower to undergo cyclization. This is probably due to the unavailability of the homopropargyl alcohol pathway, which forces the entire precursor to go through the DHF formation that is presumably slower than the furan generation pathway. It is important to recognize that the simple reordering of chemical steps (protection of the C$_{21}$ prior to the cyclization as opposed to after cyclization) led to
considerable improvement in chemical yield coupled with the complete suppression of
the furan 6.2.7.

Scheme 6.13. Successful AgCC Reaction and Comparison with Prior Results.

6.6.2. Selective Construction of C18 Methyl Stereocenter.

With the cis-substituted dihydrofuran 6.2.6 in hand, we focused on incorporating
the C18 methyl stereocenter (Scheme 6.14). Cleavage of the enol benzoate using
MeLi•LiBr condition provided the tetrahydrofuranone 6.14.1 in good yield.7 As direct
alkylation would generate the wrong diastereomer at C18 due to the di-substituted cis-
THF ring, we initially methylenated the THF ring at C18 using Eschenmosher’s salt.35
Other conditions for the methylenation reaction such as treatment with paraformaldehyde
in presence DIPA•TFA salt resulted in poor yields.\textsuperscript{36} Next, hydrogenation using Wilkinson’s catalyst established the C18 methyl stereocenter in a highly stereoselective manner and in good yields (80%, >20:1 dr). The reduced product 6.14.3 contained all the carbons and the stereocenters present in the northern fragment of mandelalide A.

![Scheme 6.14. Selective C18 Methylation.](image)

In an attempt to construct the stereocenter differently, we aimed to epimerize the C18 center after intentionally making the wrong epimer (Scheme 6.15). Direct alkylation of the ketone 6.14.1 using LDA, MeI conditions provided the wrong epimer (at the C18 center) 6.15.1 rather in low yield. Next treatment with LDA conditions did epimerize the C18 center as expected; nevertheless produced a 1:1.3 mixture of α:β mixture of C18 methyl stereocenter. As this is not a great result, we stuck with our original route for accessing material (Scheme 6.14).
6.6.3. Attempted Deoxygenation of the C19 Position.

After stereoselective construction the C18 methyl center, all that was required to complete the synthesis of the northern fragment was the deoxygenation at C19 and the conversion of the OPiv moiety into a phosphonium salt (Scheme 6.16). Reduction of C19 ketone with NaBH₄ conditions provided 4:1 mixture of the alcohol 6.16.1. The stereochemical assignment of the 4:1 mixture was not rigorously established; however, we hypothesized that the major isomer possesses a 1,2-cis and 1,3-cis relationship to the existing stereochemistry. Unfortunately, various conditions aimed to activate the alcohol for deoxygenation either resulted in ‘no reaction’ or decomposition. In hindsight, we likely should have foreseen that the highly sterically hindered nature of the cis-THF ring would make C19 alcohol extremely inaccessible. In order to explore the feasibility for incorporating the bromide at C15, DIBAL-H reduction of the ketone 6.14.3 provided the
diol 6.16.2 in good yield. Further supporting the sterically hindered nature of C19, functionalization of the diol 6.16.2 with PPh₃/CBr₄ took place only at C15 position – leaving the C19 alcohol unaffected.

Scheme 6.16. Problems Associated with Functionalization of C19 alcohol.

With the persistent problems of unsuccessful functionalization at C₁₉ alcohol, we decided to opt for smaller electrophiles that can be used in excess (Scheme 6.17). Treatment of alcohol 6.16.1 with NaHMDS in presence of carbon disulfide as a solvent followed by addition of MeI, successfully built the xanthate ester at the C₁₉ position in good yield.³⁷ Unfortunately, attempted deoxygenation resulted in decomposition of the xanthate ester 6.17.1. These late stage deoxygenation / functionalization issues required us to revise our strategy significantly.
6.6. Conclusion.

In summary, we have successfully synthesized cis-2,5-disubstituted THF ring using a Ag-catalyzed cyclization (AgCC). To our knowledge, this result is the few examples of the construction of such rings from their corresponding propargyl esters. The problems faced by the furan by-product was thoroughly investigated and ultimately solved by reordering of the reaction sequence to protect C21 prior to cyclization instead of after cyclized. C18 methyl stereocenter was selectively constructed by exploiting the stereochemical bias of the cis-THF ring through mthylolation followed by hydrogenation.

Unfortunately, this synthetic approach was ultimately thwarted by the inability to successfully deoxygenate the C19 position. This is presumably due to the fact that the alcohol 6.16.1 or the functionalized xanthate ester 6.17.1 were highly sterically hindered as all the four substituents of the THF were congested on only one side of the ring. The
development of a revised approach to circumvent the issue while shortening the synthetic sequence will be disclosed in the following chapter.

References:


CHAPTER 7:
REVISED STRATEGY AND COMPLETION OF TOTAL SYNTHESIS OF MANDELALIDE A
7.1: Revised Retrosynthetic Analysis.

Our revised retrosynthetic analysis for the corrected structure of mandelalide A (5.5.1) is shown in Scheme 7.1. A key aspect to our 2nd generation approach is the reinvention of the Silver (Ag) Catalyzed Cyclization protocol (AgCC), to avoid the deoxygenation issues by building the ketone at C18 position instead of C19. Mandelalide A (5.5.1) can be synthesized from the northern fragment 7.1.1 and southern fragment 6.1.3 via Wittig coupling followed by macrolactonization reactions. Northern fragment 7.1.1 could be accessed from the anti-dibenzoate intermediate 7.1.2. The southern fragment 6.1.3 can be made from the alcohol 6.1.4 via the AgCC reaction as mentioned previously.

Scheme 7.1. Revised Retrosynthetic Analysis of Mandelalide A (5.5.1).

We hypothesized that the C20-C21 anti-stereochemistry could arise from the regioselective ring opening of the epoxide 7.2.1 (Scheme 7.1). The epoxide 7.2.1 could
further be synthesized from enyne 7.2.2 using Shi-epoxidation conditions. Enyne 7.2.2 would be made from alkyne 7.2.3 and iodide (S)-6.7.3 via Sonogashira coupling reaction.

![Scheme 7.2. Retrosynthetic Disconnection for Alcohol 7.1.2.]

7.2: Multiple Attempts to Synthesis the Cyclization Precursor.

Initially we focused our attention on the synthesis of vinyl iodide 6.7.3 (Scheme 7.3). While an existing route for the vinyl iodide 6.7.3 is already known, we pursued an alternate route to improve the E:Z selectivity of the C20-C21 alkene (Scheme 7.3). Initially, epoxide opening of (R)-glycidol (7.3.2) with acetylene 7.3.1 followed by acetonide protection of the resultant diol provided the alkyne 7.3.3 in moderate yield. Next, silyl deprotection generated the terminal alkyne 7.3.4 in good yield. Finally, treatment of alkyne 7.3.4 with Schwartz’s reagent followed by addition of iodine in CCl₄ afforded the required vinyl iodide 6.7.3 in high selectivity but in low, unoptimized yield (32%, 20:1 dr). Though the yield was lower, this method could be used to cleanly synthesize a single enantiopure isomer of vinyl iodide 6.7.3.
Scheme 7.3. Alternate Approach to Vinyl Iodide (S)-6.7.3.

Synthesis of the alkyne fragment 7.2.3 is shown in Scheme 7.4. The known benzylidene acetal 6.2.3 can be deprotected under acidic conditions to provide diol 6.3.4. Subsequently, selective protection of the 1° alcohol as a pivalate ester followed by treatment with TESOTf provided the required alkyne fragment 7.2.3 in good yield. Alternately, the known benzoate 6.2.2 can be preferentially hydrolyzed, followed by silyl protection of the resultant propargyl alcohol to generate the alkyne 7.2.3 in good yield.

Scheme 7.4. Synthesis of Alkyne Fragment 7.2.3.
After the successful synthesis of the required alkyne and iodide fragments, we next turned our attention to coupling the fragments and synthesizing the epoxide 7.5.1 (Scheme 7.5). The Sonogashira coupling between the alkyne 7.2.3 and iodide (S)-6.7.3 afforded the (E)-enyne 7.2.2 in quantitative yield. Next, our goal was to stereoselectively epoxidize the enyne. Nevertheless, the literature reports for the epoxidation of conjugated enynes suggested that we needed to use the enantiomeric oxirane ligand that is derived from the (L)-fructose. While preparing the expensive (L)-fructose from a cheaper polysaccharide source [(L)-sorbose], we decided to synthesize the diastereomeric mixture of epoxides to use as a model system for the subsequent epoxide opening reaction. According to our plan, treatment of enyne 7.2.2 with mCPBA produced 1:1.3 diastereomeric mixtures of epoxides 7.5.1.

Scheme 7.5. Synthesis of Epoxide 7.5.1.
Next, we investigated the epoxide opening reaction using various nucleophiles and conditions (Table 7.1). A combination of benzoic acid and sodium benzoate nucleophilic system resulted in no reaction even in presence of CuCl activator in dichloromethane (Entry 1).\textsuperscript{10} Employing more active Lewis acid like BF\textsubscript{3}•Et\textsubscript{2}O or 1N H\textsubscript{2}SO\textsubscript{4} decomposed the starting material (Entry 2). Nucleophilic opening conditions using sodium benzoate in DMSO at rt, resulted in desilylation of the TES group (Entry 3). Similar conditions under higher temperatures (110 °C) initially produced the desilylated alcohol 7.1.3 but resulted in decomposition over longer reaction times (Entry 4).\textsuperscript{11} While using alcohol 7.1.3 as starting material, both 3% perchloric acid and glacial acetic acid in 1,4-dioxane caused decomposition (Entry 5).\textsuperscript{12}

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|}
\hline
Entry & Nucleophile & Conditions & Results \\
\hline
1 & PhCO\textsubscript{2}H/PhCO\textsubscript{2}Na (20 equiv.) & CuCl, CH\textsubscript{2}Cl\textsubscript{2} rt, 2-6 h & No reaction \\
\hline
2 & PhCO\textsubscript{2}H (3 equiv.) & BF\textsubscript{3}•Et\textsubscript{2}O or 1N H\textsubscript{2}SO\textsubscript{4}, CH\textsubscript{2}Cl\textsubscript{2} -78 °C & Decomposition \\
\hline
\end{tabular}
\caption{Epoxide Opening Conditions.}
\end{table}
<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>PhCO$_2$Na (8 equiv.)</td>
<td>DMSO rt, 12 h</td>
<td>7.1.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(77%)</td>
</tr>
<tr>
<td>4</td>
<td>PhCO$_2$Na or PhCO$_2$H (2 equiv.)</td>
<td>DMSO Upto 110 °C, 12 h</td>
<td>Decomposition</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(7.1.3, up to 1 h)</td>
</tr>
<tr>
<td>5$^a$</td>
<td>3% HClO$_4$ or Glacial Acetic Acid</td>
<td>1,4-dioxane, rt</td>
<td>Decomposition</td>
</tr>
</tbody>
</table>

$^a$ The desilylated alcohol 7.1.3 was used as starting material.

As direct epoxide opening did not yield fruitful results, we planned to utilize cyclic sulfates for the *anti*-diol synthesis, as these cyclic compounds are known$^{13}$ as epoxide equivalents. This would also help us to avoid using the enantiomeric Shi ligand, which is tedious to synthesis. Initially, Sharpless asymmetric dihydroxylation$^{14,15}$ using AD mix $\alpha$$^{16}$ reagent provided the required diol 7.6.1 in good yield and in high selectivity. Next, contrary to a literature reported example,$^{17}$ treatment of diol 7.6.1 with sulfuryl chloride followed by oxidation with RuCl$_3$ resulted only in decomposition of the starting material. Fortunately, reaction of diol with sulfuryl chloride under basic conditions directly produced the cyclic sulfate in moderate yield.$^{18}$ Unfortunately, attempted opening of the cyclic sulfate 7.6.2 using sodium benzoate in acetone/water solvent combination caused only decomposition of the starting material.$^{18}$
7.3: Successful Synthesis of Cyclization Precursor.

Despite the large volume of research towards the synthesis and development of stereocontrolled diols, the enantiopure construction of 1,2-anti vicinal diols continues to be an underdeveloped area. Some of the important strategies for 1,2-anti-diol syntheses are (1) nucleophilic ring opening of chiral epoxides or α-hydroxy epoxides (2) enantioselective α-hydroxylation of aldehydes followed by reduction or nucleophilic addition and (3) allylic reagent addition to aldehydes. Among other methods to synthesize 1,2-anti-diols, asymmetric dihydroxylation of cis-alkenes and desymmetrization techniques are underexplored. As both of our epoxide opening and cyclic sulfate opening strategies failed, we decided to pursue Sharpless dihydroxylation of the Z-alkenes as a means to achieve the enantiopure anti-diols. To construct the Z-enyne, we needed to build the Z-vinyl iodide.

Scheme 7.6. Synthesis and Opening of Cyclic Sulfate 7.6.2.
Our synthesis of the Z-vinyl iodide and coupling with the alkyne 7.2.3 is shown in Scheme 7.7. Our research group member Mr. Jinming Li synthesized the known\textsuperscript{28} Z-vinyl iodide 7.7.2 from the alcohol 6.7.2 via two steps of oxidation followed by Stork-Zhao\textsuperscript{29} reaction. The reaction proceeded to generate the product in moderate yield and high selectivity (40\%, \(E:Z, 20:1\)). Next, Sonogashira coupling\textsuperscript{30} of the Z-vinyl iodide 7.7.2 and alkyne 7.2.3 proceeded smoothly to yield the required Z-enzyme 7.7.3.

Scheme 7.7. Synthesis of Z-Vinyl Iodide and Sonogashira Coupling.

With the Z-enzyme in our hand, next, we turned our attention towards the Sharpless asymmetric dihydroxylation reaction (Table 7.2). Interestingly, here have been only limited examples\textsuperscript{25} known in the literature for the successful asymmetric dihydroxylation of \textit{cis}-alkenes in general despite the fact that one of the earliest examples in this area was published more than two decades ago.\textsuperscript{26} Initially, the AD mix \(\alpha^*\) conditions produced 1:3 diastereomeric mixtures of the diols 7.2.7 and 7.2.8 in moderate yield (Entry 1). Though, we could not immediately identify the stereochemistries of the diols, we established them
by converting the diols to their corresponding THF rings (via AgCC reaction) and analyzing the outcomes of the NOE studies. We also screened AD mix $\beta^*$ in the dihydroxylation reaction to better understand the selectivity in this system. AD mix $\beta^*$ generated the diols 7.2.7 and 7.2.8 in 3:1 selectivity, proving complementary to the results obtained from AD mix $\alpha^*$ (Entry 2). We realized that the higher catalyst/ligand loading coupled with longer reaction times led to the improved yields and to slightly improved selectivities for AD mix $\alpha^{**31}$ and Ad mix $\beta^{**32}$ (Entries 3 and 4). Sharpless’ indane-based ligand (7.2.6)$^{26}$ was specially designed for the dihydroxylation of cis-alkenes unfortunately proved to be less effective on this system– resulting in poor selectivity (2.2:1 dr) (Entry 5). Similarly, other ligands like the pyrimidine-based (DHQD)$_2$Pyr also yielded poor selectivity for the diols (2.3:1 dr) (Entry 6). The indane-based ligand 7.2.6 was accessed from indane 7.2.4 and dihydroquinidine 7.2.5 via one pot reaction in moderate yield.$^{33}$

Table 7.2. Asymmetric Dihydroxylation Conditions.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions (Ligand)</th>
<th>Solvent, Temp, Time</th>
<th>Yield dr</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AD mix α&lt;sup&gt;34&lt;/sup&gt; [with (DHQ)&lt;sub&gt;2&lt;/sub&gt;PHAL]</td>
<td>'BuOH:H&lt;sub&gt;2&lt;/sub&gt;O (1:1) rt, 20 h</td>
<td>44% (54% borsm)</td>
<td>7.2.7:7.2.8 (1:3)</td>
</tr>
<tr>
<td>2</td>
<td>AD mix β&lt;sup&gt;35&lt;/sup&gt; [with (DHQD)&lt;sub&gt;2&lt;/sub&gt;PHAL]</td>
<td>'BuOH:H&lt;sub&gt;2&lt;/sub&gt;O (1:1) rt, 20 h</td>
<td>29% (62% borsm)</td>
<td>7.2.7:7.2.8 (3:1)</td>
</tr>
<tr>
<td>3</td>
<td>AD mix α&lt;sup&gt;**31&lt;/sup&gt; [with (DHQ)&lt;sub&gt;2&lt;/sub&gt;PHAL]</td>
<td>'BuOH:H&lt;sub&gt;2&lt;/sub&gt;O (1:1) rt, 30 h</td>
<td>69% (75% borsm)</td>
<td>7.2.7:7.2.8 (1:3.6)</td>
</tr>
<tr>
<td>4</td>
<td>AD mix β&lt;sup&gt;**32&lt;/sup&gt; [with (DHQD)&lt;sub&gt;2&lt;/sub&gt;PHAL]</td>
<td>'BuOH:H&lt;sub&gt;2&lt;/sub&gt;O (1:1) rt, 48 h</td>
<td>76% (79% borsm)</td>
<td>7.2.7:7.2.8 (3.6:1)</td>
</tr>
<tr>
<td>5</td>
<td>7.2.6 (17 mol%) K&lt;sub&gt;2&lt;/sub&gt;OsO&lt;sub&gt;4&lt;/sub&gt;•2H&lt;sub&gt;2&lt;/sub&gt;O (3.7 mol%) K&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;, K&lt;sub&gt;3&lt;/sub&gt;Fe(CN)&lt;sub&gt;6&lt;/sub&gt;</td>
<td>'BuOH:H&lt;sub&gt;2&lt;/sub&gt;O (1:1) rt, 48 h</td>
<td>56% (68% borsm)</td>
<td>7.2.7:7.2.8 (2.2:1)</td>
</tr>
<tr>
<td>5</td>
<td>(DHQD)&lt;sub&gt;2&lt;/sub&gt;Pyr (15 mol%) K&lt;sub&gt;2&lt;/sub&gt;OsO&lt;sub&gt;4&lt;/sub&gt;•2H&lt;sub&gt;2&lt;/sub&gt;O (6.3 mol%) K&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;, K&lt;sub&gt;3&lt;/sub&gt;Fe(CN)&lt;sub&gt;6&lt;/sub&gt;</td>
<td>'BuOH:H&lt;sub&gt;2&lt;/sub&gt;O (1:1) rt, 24 h</td>
<td>52% (74% borsm)</td>
<td>7.2.7:7.2.8 (2.3:1)</td>
</tr>
</tbody>
</table>

### 7.4: Silver Catalyzed Cyclization Reaction (AgCC).

With the successful synthesis of the required anti-diols, next we focused our attention to protecting group modifications and the key AgCC reaction. Initially, we converted the major diol from the AD mix α<sup>**</sup> conditions to the corresponding cyclization precursor (Scheme 7.8). Bis-benzoate protection of the diol 7.2.8, followed by desilylation of the TES ether generated the cyclization precursor 7.8.1 in excellent yield over two steps. We were thrilled to see, the key AgCC reaction successfully proceeded in only 15 minutes under refluxing toluene. This rate is notably faster than the prior results.
One possible explanation for the rate increase is the steric requirements of the dibenzoate provide a favorable conformational pre-organization required for the cyclization. The resultant dibenzoate 7.8.2 was found to be unstable. Consequently, cooling the AgCC reaction to -78 °C, diluting with ether and complete cleavage of both the benzoates followed by protection of the C20 alcohol as TBS ether provided the stable tetrahydrofuranone 7.8.3. Unfortunately, the C17 and C20 methine signals of 7.8.3 were not completely separable in the ¹H NMR spectra, making it difficult to perform the NOE studies on. Fortunately, selective cleavage of the enol benzoate after cyclization provided the tetrahydrofuranone 7.8.4 in moderate yield in one-pot, two steps. The C17 and C20 methine signals were well resolved in the ¹H NMR spectra– allowing us to perform NOE studies.
Using the epimeric series at C20 and C21, conversion of diol 7.2.7 to the cyclization precursor and the subsequent AgCC reaction is summarized in Scheme 7.9. Similar bis-benzoate protection of diol followed by desilylation of TES ether provided the cyclization precursor 7.1.2. As seen before, AgCC reaction followed by cooling the reaction and selective cleavage of the enol benzoate provided the stable ketone 7.9.2 in good yield. Fortunately, significant NOE correlation was observed between the C17 and C20 methines confirming the cis-substituted THF ring; thereby establishing the
corresponding stereochemistries present in the diol 7.2.7. In contrast, no nOe was observed on 7.8.4 between C20 and C21.

![Scheme 7.9. Synthesis of Cyclization Precursor and AgCC reaction.](image)

Though we were able to confirm the C17 and C20 stereochemistries of the diol and the THF rings with the help of ketone 7.9.2, we needed to incorporate the TBS ether at the C21 position (Scheme 7.10). As mentioned above, the silver catalyzed cyclization of the diol 7.2.7 successfully proceeded to completion under refluxing toluene. The resultant dibenzoate was cleaved in situ under lower temperatures to provide the alcohol 7.10.1, which was found to be unstable for purification. Hence, TBS protection of the crude alcohol 7.10.1 eventually furnished the important ketone intermediate 7.10.2 in good yield and selectivity (68% from 7.1.2 and >10:1 dr). This result is a testament to the power of the AgCC reaction as the starting material was specifically constructed to
provide the required stereochemistries in the THF ring and a simple linear starting material 7.1.2 is converted to the complex cis-substituted THF ring in two-pots in 68% yield. To the best of our knowledge, we are the only other group to report the construction of enantiopure cis-substituted THF rings from the corresponding propargyl benzoates apart from a single example reported by Gagosz and co-workers.\textsuperscript{36}

![Scheme 7.10. Synthesis of Required Ketone (7.10.2).]

7.5: Construction of C18 Stereocenter and Completion of Synthesis of Northern Fragment.

With the successful construction of the required tetrahydrofuranone 7.10.2, next we focused on incorporating the C18 methyl stereocenter (Table 3). Initially, treatment of ketone 7.10.2 with the Petasis reagent (\(\text{Cp}_2\text{TiMe}_2\)) at elevated temperatures produced the
1,1-disubstituted alkene 7.3.5 in excellent yield. The Petasis reagent was made from the titanocene dichloride and methyl Grignard reagent using an organic synthesis procedure. Next, hydrogenation of the alkene 7.3.5 using Wilkinson’s catalyst produced the target compound 7.3.6 in high yield but in low selectivity (91%, 3.5:1 dr, Entry 1). Hence, we needed to use a more active catalyst at reduced temperatures to improve the selectivity. Use of Rh/Alumina at lower temperature (-20 °C) introduced the C18 stereocenter in similar selectivity to that mentioned earlier (Entry 2). Further lowering of the temperature to -40 °C, furnished the required product in excellent yield and in improved selectivity (99%, 6.5:1 dr, Entry 3).

![Chemical structure](image)

**Table 7.3. Construction of C18 Methyl Stereocenter.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Hydrogenation Catalyst</th>
<th>Conditions</th>
<th>Yield</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(Ph₃P)₃RhCl (10 mol%), H₂</td>
<td>toluene, rt</td>
<td>91%</td>
<td>3.5:1</td>
</tr>
<tr>
<td>2</td>
<td>Rh/Alumina (5% by wt), H₂</td>
<td>EtOH, -20 °C, 12 h</td>
<td>85%</td>
<td>3.5:1</td>
</tr>
<tr>
<td>3</td>
<td>Rh/Alumina (5% by wt), H₂</td>
<td>EtOH, -40 °C, 24 h</td>
<td><strong>99%</strong></td>
<td><strong>6.5:1</strong></td>
</tr>
</tbody>
</table>
We next required selective protection of the C23 and C24 positions to be able to distinguish between them later in the synthesis (Scheme 7.11). Following the conditions of acetonide deprotection on a highly similar substrate 5.9.3, the acetonide 7.3.6 was treated with CuCl₂•2H₂O in reduced temperatures. Contrary to the published results, only low yield of diol 7.11.2 was observed and a small amount of triol 7.11.1 was also isolated. Longer reaction times led to more of the triol. It was observed that the rate of desilylation of diol 7.11.2 was faster than the rate of acetonide deprotection on 7.3.6. On the other hand, treatment of acetonide 7.3.6 with stronger acids like TFA provided moderate yield for the required diol 7.11.2. Finally, selective 1° alcohol protection of the diol 7.11.2 using TBSCl conditions generated poor yield of the required alcohol 7.11.3. The reaction was noticed to be sluggish. But, the use of more reactive silylating agents like TBSOTf resulted in significant amount of over silylation to trisilyl ether 7.11.4 in addition to producing poor outcome for the required alcohol 7.11.3.
Scheme 7.11. Attempts to Selective Protection of C23 and C24 Alcohols.

As a result of the problems faced with acetonide deprotection and selective protection of the resultant diol, we decided to move forward with the existing acetonide moiety (Scheme 7.12). DIBAL-H reduction of pivaloate ester 7.3.6 produced the known alcohol 5.9.2 in good yield. The NMR data was in complete agreement with the previously reported data – establishing the relative stereochemistries present in the intermediate. Mesylation of the alcohol followed by Finkelstein-type reaction generated the iodide 7.12.2 in high yields. Finally, treatment of iodide 7.12.2 with PPh₃ under
refluxing toluene successfully completed the synthesis of the northern phosphonium salt 7.1.1. It was found that buffering with NaHCO₃ was key to produce better yields as it suppressed the acetonide deprotection likely catalyzed by trace HI.⁴¹

Scheme 7.12. Completion of Synthesis of Northern Fragment.

7.6: Coupling the Fragments and Completion of Total Synthesis.

With successful completion of the synthesis of northern phosphonium salt 7.1.1, next, we turned our attention towards coupling the major subunits (Scheme 7.13). The southern cis-substituted THP ring 7.13.1 was synthesized by Mr. Ankan Ghosh, one of our research group members, using a similar silver-catalyzed cyclization (AgCC) reaction of the corresponding the propargyl benzoates for its contraction. I have taken over from the alcohol 7.13.1 that was provided by Mr. Ankan Ghosh. DMP oxidation of the alcohol provided the enal 7.13.2. Next, selective cross metathesis of the mono substituted alkene 7.13.2 was performed using Grubbs 2nd Gen. catalyst. Selective cross metathesis with
both acrylic acid and methyl acrylate proceeded smoothly to generate the corresponding enals 7.13.3 and 7.13.4 in moderate and good yields respectively. Finally, we planned to use a Wittig reaction to couple the fragments together. The Wittig ylid was made from the corresponding phosphonium salt using NaHMDS and the enoic acid 7.13.3. Please note that two equivalents of the base was required to remove both the C1 carboxylic acid and C15 proton. Unfortunately, the reaction did not produce the expected diene product 7.13.5. This dianion formation may have been problematic on small scale. To avoid this problem, we had synthesized the corresponding methyl ester 7.13.4. To our delight, Wittig coupling of the phosphonium salt 7.1.1 with enal 7.13.4 proceeded smoothly to furnish the E, Z-diene 7.13.6 in 67% yield.
Scheme 7.13. Coupling of the Fragments.

With the complete carbon backbone to mandelalide A in hand, our focus shifts to the exploration of macrolactonization reaction (Scheme 7.14). None of the other syntheses of mandelalide A examine the macrocycle construction with the complete carbon backbone. As shown earlier for the northern fragment, treatment of acetonide 7.13.6 with TFA conditions in biphasic solvent medium (CH₂Cl₂/H₂O, 10:1) provided the diol 7.14.1 in good yield. Saponification of the methyl ester 7.14.1 under heating NaOH/
isopropanol conditions yielded the \textit{seco}-acid \textbf{7.14.3}. Next, Yamaguchi macrolactonization$^{43}$ conditions generated the C24 cyclized macrolactone \textbf{7.14.4} in 37% along with one another macrolactone in less than 10% yield. Subsequent desilylation using TASF conditions$^{44}$ confirmed that the minor compound was the desired mandelalide A (5.5.1). The preferential formation of the C24 cyclized macrolactone is in contrast with Ye and co-workers’ observation that the natural isomer prefers the C23 macrolide whereas the diastereomeric compound \textbf{5.15.3} results in a ring expanded C24 macrolactone (Chapter 5, Scheme 5.15).$^{44}$ Finally, global desilylation of macrolactone \textbf{7.14.4} using TASF deprotection conditions furnished a new 25-membered C24 macrolide \textbf{7.14.5}. 
In order to suppress the preferential macrolactone formation at C24, it was essential to block that position prior to Yamaguchi cyclization reaction. Fortunately, we were able to protect the C24 1° alcohol of 7.14.1 as its silyl ether. It is worth noticing that
selective protection of the C24 1° alcohol on the northern fragment 7.11.2 was highly challenging. Saponification as was performed on diol 7.14.1, caused extensive silyl migration. Consequently, we decided to pursue a redox strategy to access the required seco-acid. DIBAL-H reduction followed by selective oxidation of allyl alcohol using MnO₂ in hexanes and Pinnick oxidation generated the required seco-acid. Finally, Yamaguchi conditions of mixed anhydride formation with trichlorobenzoyl chloride (7.14.3) followed by macrolactonization under dilute conditions produced the known⁴⁴ C23 macro lactone 5.15.3 in 54% over 3 steps. A quick silica gel plug provided a slightly impure macro lactone 5.15.3 at this stage. Finally, global desilylation of the macro lactone 5.15.3 completed the total synthesis of mandelalide A (5.5.1). The final product was found to be very unstable on the silica gel column in our hands; hence, it was subjected through an initial reverse phase C18 column purification followed by HPLC purification. The NMR spectral data obtained after the HPLC purification was in complete agreement with the natural⁴⁵ as well as other synthetic⁴⁰,⁴⁶ materials. The optical rotation value [α_D = -11.5, c = 0.35, MeOH] compared well with the isolation data [α_D = -9, c = 0.25, MeOH].⁴⁵ We are currently in the process of further studying the biological properties of mandelalide A and C24 macrolide before communicating our work for publication.
Scheme 7.15. Completion of Total Synthesis of Mandelalide A (5.5.1).
7.7: Conclusion.

In summary, the total synthesis of mandelalide A has been achieved. The key steps include a Wittig coupling to couple the northern and southern fragments and Yamaguchi protocol was employed to build the macrocycle. Silver-catalyzed cyclization reaction (AgCC) was used to construct the cis-substituted THF rings on the northern subunit.

C19 deoxygenation issues encountered in our earlier approach were effectively solved by devising a revised strategy to form the ketone at the C18 position— a proof to the flexibility and versatility of the AgCC reactions. Different methods were explored for the synthesis of C20-C21 anti-diol that was required by the revised strategy. Ultimately, a diastereoselective dihydroxylation of a cis-eneyne was employed to access the anti-diol functionality. Petasis olefination followed by hydrogenation under reduced temperature conditions were used to incorporate the C18 methyl stereocenter on the more sterically demanding side of the THF ring.

References:


(31) ADmix α** = (DHQ)_2PHAL (300 mg), K₂OsO₄•2H₂O (42.6 mg), K₂CO₃ (478 mg), K₃Fe(CN)₆ (1.22 g).

(32) ADmix β** = (DHQD)_2PHAL (300 mg), K₂OsO₄•2H₂O (42.6 mg), K₂CO₃ (478 mg), K₃Fe(CN)₆ (1.22 g).


(34) ADmix α* = (DHQ)_2PHAL (100 mg), K₂OsO₄•2H₂O (14.2 mg), K₂CO₃ (478 mg), K₃Fe(CN)₆ (1.22 g).

(35) ADmix β* = (DHQD)_2PHAL (100 mg), K₂OsO₄•2H₂O (14.2 mg), K₂CO₃ (478 mg), K₃Fe(CN)₆ (1.22 g).


CHAPTER 8
CONCLUSION
8.1. General Conclusion.

Enantioselective total synthesis of cytotoxic marine natural product mandelalide A has been achieved. Mandelalide A has attracted significant synthetic attention due to its complex molecular architecture and exciting cytotoxic activity in early cancer cell screening. ¹ Our first-generation approach towards mandelalide A utilized a silver-catalyzed cyclization (AgCC) reaction to construct the cis-substituted northern THF ring. The effect of substituents on the AgCC reaction was studied and the furan byproduct formation was avoided by selectively masking the C21 alcohol to improve the yield of the THF ring formation.

Problems associated with C19-deoxygenation from our earlier approach were solved in our second-generation approach by carefully designing the strategy to construct the ketone at the C18 position – a proof to the flexibility and versatility of the AgCC reactions. A diastereoselective Sharpless asymmetric dihydroxylation of cis-ényne was employed to build the C20-C21 anti-diol required for the cyclization. Additional key steps include Petasis olefination of C18 ketone followed by hydrogenation sequence to construct the C18 methyl stereocenter, Wittig reaction to couple the northern and southern fragments and a Yamaguchi macrolactonization to access the macrocycle. Macrolactonization of the C23, C24 diol seco-acid furnished the 25-membered ring expanded C24-macrolactone as the major product.
8.2. Detailed Conclusion.

8.2.1. Silver Catalyzed Cyclization Reaction (AgCC).

The silver-catalyzed cyclization reaction (AgCC) is a powerful tool to construct variously substituted THF rings in synthesis.\textsuperscript{2,3,4} The utility of the versatile AgCC reaction has been demonstrated in our total synthesis of mandelalide A. Cis-substituted THF ring was constructed from its corresponding propargyl benzoate precursor in one step under AgCC conditions as illustrated in Scheme 8.1. The selectively masked alcohol \textit{6.12.2} underwent AgCC in refluxing benzene in presence of Ag-catalyst to construct the cis-substituted THF ring \textit{6.2.6}, which was converted to the C19 ketone \textit{6.14.1} in the subsequent step. To the best of our knowledge it is one of the very few reports of constructing \textit{cis}-substituted THF rings from their corresponding propargyl benzoate precursors. On the other hand, the ketone can also be built at the C18 carbon as required by our revised strategy to avoid the C19 deoxygenation problems encountered in our earlier approach with \textit{6.14.1}. Treatment of the starting material [C20, C21 \textit{anti}-dibenzoate \textit{7.1.2}] under AgCC conditions furnished the ketone at C18 position in addition to constructing the \textit{cis}-THF ring in high selectivity. This demonstrates the power, tolerance and adaptability of the AgCC reaction to synthesize selectively functionalized THF rings from the simple open-chain cyclization precursors.
Scheme 8.1. Silver-Catalyzed Cyclization (AgCC) to Make cis-Substituted THF Rings.

The furan byproduct formation, which was observed in our earlier strategy, was carefully analyzed and successfully avoided by simply changing the order of our reaction—masking the C21 alcohol first and then cyclizing the resultant alcohol (Scheme 8.2). The C21 homopropargyl alcohol that was responsible for the furan formation was protected prior to cyclization.

Scheme 8.2. Solving the Byproduct Formation Problem.
8.2.2. Sharpless Asymmetric Dihydroxylation of cis-Enynes.

Thanks to the Sharpless dihydroxylation method, significant amount of research is devoted to the stereocontrolled synthesis of diols.\(^5\) Nevertheless, the enantiopure construction of 1,2-\textit{anti} vicinal diols continues to be an underdeveloped area.\(^6\) We had explored the under-utilized asymmetric dihydroxylation of cis-enyne to access the C20-C21 \textit{anti}-diol relationship (Scheme 8.3).\(^7\)\(^,\)\(^8\) The most used (DHQD)$_2$PHAL and (DHQ)$_2$PHAL ligands proved complimentary to each other, with each ligand favoring one of the diastereomeric diols over the other. The pyrimidine ligand (DHQD)$_2$Pyr and the ligand 7.2.6,\(^9\) which was specially designed for dihydroxylation of cis-alkene, yielded poor selectivity– proving the need to develop better ligand systems to address this underexplored problem. Currently, studies are underway in our group to improve the ligand design to enhance selectivity of these transformations.

Scheme 8.3. Exploration of Asymmetric Dihydroxylation of cis-Enyne.
8.2.3. Selective Construction of C18 Methyl Stereocenter.

In the earlier route, direct alkylation of ketone 6.14.1 produced the undesired diastereomer at C18 position as expected. Consequently, the inherent stereochemical bias of the THF ring was harnessed to selectively construct the C18 methyl stereocenter by employing a methylenation followed by hydrogenation sequence (Scheme 8.4). Methylenation at C18 position using Eschenmosher’s salt provided the enone in moderate yield.\textsuperscript{10} Subsequent hydrogenation with Wilkinson’s catalyst established the C18 stereocenter in high selectivity. Also, in the revised strategy, the C18 ketone was olefinated using Petasis reagent to provide the 1,1-disubstituted alkene 7.3.5. Further reduction of alkene 7.3.5 under lower temperature with Rh/Alumina introduced the C18 methyl stereocenter selectively.

Scheme 8.4. Construction of C18 Methyl Stereocenter.
8.2.4. Wittig Coupling of Fragments.

Wittig reaction was used to couple the northern and southern fragments of mandelalide A (Scheme 8.5). Northern phosphonium salt 7.1.1 was coupled with the southern aldehyde 7.13.4 using NaHMDS as base. The reaction proceeded smoothly to afford the complete carbon skeleton of the natural product in 67% yield, while simultaneously constructing the challenging C12-C15 E,Z-diene moiety. The coupled diene 7.13.6 also contains all the stereocenters present in mandelalide A.

8.2.5. Yamaguchi Macrolactonizations and Total Synthesis of Mandelalide A.

Yamaguchi macrolactonization protocol was employed to access the macrocyclic core of the target compound (Scheme 8.6). Intriguing observations were made from carrying out the macrolactonization reactions on different precursors. The macrolactonization was explored to understand the natural preference of the C23, C24
seco-acid 7.14.2 for lactonization. Interestingly, preferentially cyclization on the C24 alcohol was observed to produce the 25-membered macrolactone 7.14.4. Finally, TASF conditions to effect global silyl deprotection of 7.14.4 provided the C24 macrolide 7.14.5. This is in contrast with Ye and co-workers’ observation that the natural isomer prefers the C23 macrolide whereas the stereochemical combination of the proposed structure of mandelalide A results in a ring expanded C24 macrolactone.12 On the other hand, selectively silylated alcohol 7.15.1 upon similar macrolactonization conditions was forced to cyclize at C23 alcohol to yield the 24-membered known macrolactone 5.15.3, which was subsequently converted to the natural product mandelalide A (5.5.1) via TASF-mediated global desilylation reaction.
Scheme 8.6. Yamaguchi Macrolactonizations and Completion of Total Synthesis.

8.3. Future Directions.

The synthetic studies that emerged out of total synthesis of mandelalide A has laid a strong foundation for building cis-substituted THF rings in future. There are multiple interesting natural product scaffolds that could be accessed using our AgCC approach including that of other members of the mandelalide family (Figure 8.1). Mandelalides B,
C and D possess an all carbon macrocycle, an uncommon structural motif identified in natural products. Also, the C4-C24 carbon skeleton of mandelalide B, C and D being exactly identical to that of mandelalide A, would greatly help to buy a similar strategy for their synthesis. There has been no report on the total synthesis of any of the other members of mandelalide family except mandelalide A. Furstner and co-workers published their failed synthetic route towards mandelalide B in 2014. And, The recently isolated belizentrin (8.1.2) with the THF ring connected to the tethered side arm of the macrocycle could fall prey to our AgCC strategy. Amphidinolide T (8.1.1) contains a 19 membered macrocycle that possesses substituted THF, can be a potential target as well. Also mucocin (8.1.3) could be easily synthesized utilizing the AgCC reactions.
8.4. Brief Summary.

A 22-step enantioselective total synthesis of mandelalide A has been achieved. In addition, an equally interesting 25 membered C24 macrolide 7.14.5 was also synthesized. The key steps include diastereoselective dihydroxylation of cis-enyne to make C20-C21 anti-diol, AgCC reaction to construct the cis-THF ring, Wittig coupling to couple the major subunits and Yamaguchi protocol to access the macrocycle. Deoxygenation problems faced in our earlier approach was effectively solved by revising the strategy to
form the ketone at the C18 as opposed to C19 position. Petasis olefination followed by hydrogenation conditions were used to incorporate the C18 methyl stereocenter on the more sterically demanding face of the THF ring.

Currently, studies of the biological properties of mandelalide A and the C24-macrolide analog are underway. The results along with the total synthesis will be communicated for publication soon. We also have plans to further study the cytotoxic mechanism of action of mandelalide A in cancer cells.

References:


CHAPTER 9

EXPERIMENTAL SECTION
**General.** Infrared spectra were recorded neat unless otherwise indicated and are reported in cm⁻¹. ¹H NMR spectra were recorded in deuterated solvents and are reported in ppm relative to tetramethylsilane and referenced internally to the residually protonated solvent. ¹³C NMR spectra were recorded in deuterated solvents and are reported in ppm relative to tetramethylsilane and referenced internally to the residually protonated solvent.

Routine monitoring of reactions was performed using EM Science DC-Alufolien silica gel, aluminum-backed TLC plates. Flash chromatography was performed with the indicated eluents on EM Science Gedurian 230-400 mesh silica gel.

HPLC purification was performed on a Shimadzu HPLC system equipped with an SPD-M20A photodiode array detector. HPLC grade solvents were used for solid phase extraction and HPLC.

Air and/or moisture sensitive reactions were performed under usual inert atmosphere conditions. Reactions requiring anhydrous conditions were performed under a blanket of argon, in glassware dried in an oven at 120°C or by flame, then cooled under argon. Dry THF and DCM were obtained via a solvent purification system. All other solvents and commercially available reagents were either purified via literature procedures or used without further purification.
Total Synthesis of Cermizine D and Formal Syntheses of Senepodine G and Cermizine C

Boc protected amine 2.4.5. To a solution 6-bromo-1-hexene (2.4.3) (2.08 g, 12.70 mmol) in DMF / H$_2$O (9:1, 50 mL) was added NaN$_3$ (2.07 g, 31.83 mmol). After 12 h, brine was added and the azide was extracted with ether (3 x 40 mL). The dried (MgSO$_4$) extract was concentrated in vacuo at 0 ºC to give crude azide. The crude azide was then re-dissolved in THF / H$_2$O (5:1, 50 mL) and was added PPh$_3$ (4.00 g, 15.2 mmol). After 15 h, were added Et$_3$N (5.14 g, 7.05 mL, 50.83 mmol) and Boc-anhydride (8.33 g, 8.77 mL, 38.13 mmol). After 12 h, THF was removed in vacuo, brine (100 mL) was added and extracted with ether (3 x 100 mL). The dried (MgSO$_4$) extract was concentrated in vacuo, purified by chromatography over silica gel, eluting with 1-20% EtOAc / hexanes to give 2.4.5 (2.43 g, 12.23 mmol, 96% over 3 steps) as a colorless oil. IR (neat) 3364, 3075, 2931, 1700, 1642, 1365, 1172 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.80 (ddt, $J$ = 13.3, 10.1, 6.6 Hz, 1H), 5.02 (dq, $J$ = 17.2, 1.7 Hz, 2H), 4.52 (br s, 1 H), 3.12-3.15 (m, 2H), 2.07-2.12 (m, 2H), 1.48-1.55 (m, 3H), 1.47 (s, 9H), 1.43-1.45 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 156.0, 138.5, 114.6, 79.0, 40.4, 33.3, 29.5, 28.4, 26.0; HRMS (EI+) calcd. For C$_{11}$H$_{22}$NO$_2$ (M+H) 200.1651, found 200.1648.
**Enal 1.14.1.** To a solution of 2.4.5 (1.5 g, 7.52 mmol) in dry DCM (85 mL) was added crotonaldehyde 2.4.6 (0.266 g, 3.12 mL, 37.5 mmol) and 2nd Gen. Hoveyda-Grubbs catalyst (71 mg, 0.113 mmol) and stirred at room temperature. After 5 h, the solvent was removed *in vacuo* and the crude was purified by chromatography over silica gel, eluting with 25-40% EtOAc / hexanes to give 1.14.1 (1.59 g, 7.01 mmol, 94%) as a dark colored oil. IR (neat) 3357, 2976, 2934, 2865, 1693, 1521, 1366, 1169 cm\(^{-1}\); \(^1\)H NMR (700 MHz, CDCl\(_3\)) \(\delta\) 9.51 (d, \(J = 7.7\) Hz, 1H), 6.85 (dt, \(J = 15.4, 6.3\) Hz, 1H), 6.13 (dd, \(J = 15.4, 7.7\) Hz, 1H), 4.62 (br s, 1H), 3.15-3.16 (m, 2H), 2.36-2.39 (m, 2H), 1.51-1.57 (m, 4H), 1.45 (s, 9H); \(^{13}\)C NMR (175 MHz, CDCl\(_3\)) \(\delta\) 194.1, 158.2, 156.0, 133.2, 79.3, 40.1, 32.3, 29.7, 28.4, 25.0; HRMS (EI+) calcd. for C\(_{12}\)H\(_{22}\)NO\(_3\) (M+H) 228.1600, found 228.1608.

**Aldehyde 2.4.5.** To a solution of 1.14.1 (970 mg, 4.27 mmol), in MeOH (30.6 mL) was added a solution of the catalyst *ent*-1.14.2 (254 mg, 0.43 mmol) in DCE (10.2 mL) via syringe and placed in the freezer unstirred (-25°C). After 10 d, water (50 mL) was added and extracted with DCM (3 x 60 mL). The dried (MgSO\(_4\)) extract was concentrated *in vacuo*, purified by chromatography over silica gel eluting with 0-25%EtOAc/Hexanes to give known\(^1\) 2.4.5 (825 mg, 3.63 mmol, 85%) as a colorless oil. [\(\alpha\)\(_D\)]\(^{20}\) = -36.0 (c = 1.0, CHCl\(_3\)); IR (neat) 2935, 2864, 2727, 1693, 1521, 1416, 1167, 867 cm\(^{-1}\); \(^1\)H NMR (400
MHz, CDCl$_3$) $\delta$ 9.60-9.61 (m, 1H), 4.70-4.71 (m, 1H), 3.86 (d, $J = 12.4$ Hz, 1H), 2.58-2.70 (m, 2H), 2.42 (ddd, $J = 15.2, 6.4, 2.0$ Hz, 1H), 1.36-1.60 (m, 5H), 1.32 (s, 9H), 1.25-1.27 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 200.5, 154.5, 79.7, 45.8, 44.5, 39.1, 28.8, 28.2, 25.1, 18.8. HRMS (EI+) calcd. for C$_{12}$H$_{21}$NO$_3$ (M+) 227.1522, found 227.1513.

**Benzoate SI-2:** To a solution of aldehyde 2.4.5 (89.5 mg, 0.394 mmol) in MeOH (3 mL) at 0 °C was added NaBH$_4$ (44.7 mg, 1.183 mmol). After 30 min, the reaction was quenched with aq. NH$_4$Cl (5 mL) solution, extracted with ether (3 x 10 mL). The dried (MgSO$_4$) extract was concentrated _in vacuo_ to give the crude alcohol SI-1, which was carried to the next step.

To a solution of crude alcohol SI-1 (~0.39 mmol) in DCM (1.97 mL) at 0 °C was added DMAP (144.4 mg, 1.18 mmol) followed by _p_-chlorobenzoyl chloride (103.4 mg, 75.5 mL, 0.591 mmol). After 15 min, the reaction mixture was warmed to rt over a period of 30 min. After 12 h, water (5 mL) was added extracted with ether (3 x 10 mL). The dried (MgSO$_4$) extract was concentrated _in vacuo_ and purified by chromatography over silica gel, eluting with 15-30% EtOAc/Hexanes to obtain known$^1$ SI-2 (121.6 mg, 0.33 mmol, 84% over 2 steps) as a colorless oil. The enantiomeric excess was determined with the aid of HPLC analysis Chiralcel IC (25 cm x 0.46 cm column), hexane:isopropanol 90:10, flow = 1.0 mL/min, $t_{\text{minor}} = 11.5$ min, $t_{\text{major}} = 10.2$ min. $[\alpha]_D^{20} = -11.0$° ($c = 1.0$, CHCl$_3$); IR (neat) 2934, 2861, 1721, 1688, 1595, 1448, 1415, 1365, 1307, 1275, 1169, 1145, 1091, 760 cm$^{-1}$; $^1$H NMR (400 MHz, 40 °C, CDCl$_3$) $\delta$ 7.98 (d, $J = 8.4$ Hz, 2H),
7.41 (d, J = 8.8 Hz, 2H), 4.47 (br s, 1H), 4.29-4.47 (m, 2H), 4.04 (d, J = 13.2 Hz, 1H),
2.82 (t, J = 13.2 Hz, 1H), 2.18-2.25 (m, 1H), 1.81-1.90 (m, 1H), 1.55-1.72 (m, 5H), 1.38-
1.49 (m, 10H); 13C NMR (100 MHz, 40 °C, CDCl3) δ 165.7, 154.9, 139.3, 131.0, 128.9,
128.6, 79.4, 63.0, 48.0, 38.8, 29.0, 28.8, 28.4, 25.5, 19.0; HRMS (ES+) calcd. for
C19H27NO4Cl (M+H) 368.1629, found 368.1618.

**Ketone 2.3.4:** To a solution of aldehyde 2.4.5 (530 mg, 2.09 mmol) in THF (15 mL) at
-78 °C was added a premade solution of 2.9.1 (8 mL, 4.0 mmol, 0.2 M in THF) at rt.
After 30 min, the temperature was raised to -50 °C and stirred at this temperature for the
next 3 h. Then, the reaction was quenched with saturated (aq) NH4Cl (5 mL), extracted
with Et2O (3 x 30 mL) and washed with brine (15 mL). The dried (MgSO4) extract was
concentrated in vacuo to provide crude alcohol 2.9.2. The crude alcohol 2.9.2 was then
re-dissolved in DCM (45 mL) and was added NaHCO3 (877.8 mg, 10.45 mmol) followed
by Dess Martin’s reagent (1.77 g, 4.18 mmol) at rt. After 3 h, the reaction was quenched
with saturated aq. NaHCO3 (15 mL). Then the solution was extracted with Et2O (3 x 30
mL). The dried (MgSO4) extract was concentrated in vacuo and purified by chromatography
over silica gel, eluting with 5-20% EtOAc/Hexanes to give 2.3.4 (trans:cis = 1:0.14), (477 mg, 1.46 mmol, 70% over 2 steps) as pale yellow oil. [α]D20 =
+16.5 (c = 1.05, CHCl3); IR (neat) 2974, 2934, 2862, 1689, 1609, 1164 cm⁻¹; 1H NMR
(400 MHz, CDCl3) δ 7.54-7.63 (m, 3.5 H, mixed isomers), 7.34-7.41 (m, 3.7 H, mixed
isomers), 6.86 (d, $J = 12.8$ Hz, 0.2 H, cis isomer), 6.79 (d, $J = 16$ Hz, 1H, major isomer), 6.24 (d, $J = 12.8$ Hz, 0.2 H, minor isomer), 4.81 (bs, 1.2 H, mixed isomers), 4.05 (bs, 1.20 H, mixed isomers), 2.68-2.92 (m, 3.7 H, mixed isomers), 1.44-1.68 (m, 8.8 H, mixed isomers), 1.44 (s, 10.8 H, mixed isomers); $^{13}$C NMR (400 MHz, CDCl$_3$) $\delta$ 200.9, 198.4, 154.8, 154.7, 143.0, 140.3, 135.2, 134.5, 133.1, 130.5, 129.6, 129.3, 128.9, 128.6, 128.4, 128.3, 126.1, 79.6, 47.9, 44.2, 41.7, 39.4, 28.4, 28.2, 25.3, 18.9. HRMS (Cl+) calcd. For C$_{20}$H$_{28}$NO$_3$ (M+H) 329.1991, found 329.1978.

**Aldehyde 2.8.2.** To a solution of oxalyl chloride (980.7 mg, 7.726 mmol, 0.663 mL) in DCM (15 mL) at -78 ºC was added a solution of DMSO (644 mg, 8.24 mmol, 0.585 mL) in DCM (4 mL). After 10 min, SI-3 (1.0 g, 5.15 mmol) in DCM (5 mL) was added at -78 ºC dropwise. After 1.5 hours, Et$_3$N (2.34 g, 3.23 mL, 23.18 mmol) was added and the mixture was warmed to 0 ºC. Once the mixture reached 0 ºC, the reaction was quenched with water (25 mL) and extracted with DCM (3 x 25 mL). The combined organic layers were washed with brine (25 mL) and the dried (MgSO$_4$) extract was concentrated in vacuo and purified by chromatography over silica gel; eluting with 8-15% EtOAc/Hexanes to obtain 2.8.2 (881 mg, 4.60 mmol, 89%) as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.78 (s, 1H), 7.25-7.40 (m, 5H), 4.52 (s, 2H), 3.51 (t, $J = 6$ Hz, 2H), 2.46-2.50 (m, 2H), 1.73-1.80 (m, 2H), 1.64-1.71 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 202.5, 138.5, 128.4, 127.7, 127.6, 73.0, 69.8, 43.6, 29.2, 19.0.
**Imine 2.8.4.** To a solution of 2.8.2 (881 mg, 4.58 mmol) and 2.8.3 (610 mg, 5.04 mmol) in DCM (8 mL) was added anhydrous CuSO₄ (1.827 g, 11.45 mmol) and the mixture was stirred at rt. After 12 h, the mixture was filtered through a pad of Celite® concentrated in vacuo and purified by chromatography over silica gel eluting with 10-25% EtOAc/Hexanes to obtain 2.8.4 (1339 mg, 4.53 mmol, 99%) as a pale yellow oil. 

$[\alpha]_D^{20} = -188.50^\circ (c = 1.00, \text{CHCl}_3); \text{IR (neat)} 3083, 3061, 3027, 2928, 2864, 1621, 1454, 1362, 1083, 737, 698 \text{ cm}^{-1}; \text{'H NMR (700 MHz, CDCl}_3) \delta 8.08 (t, J = 4.9 Hz, 1H), 7.28-7.31 (m, 1H), 7.33-7.36 (m, 4H), 4.51 (s, 2H), 3.51 (t, J = 6.3 Hz, 2H), 2.54-2.56 (m, 2H), 1.73-1.78 (m, 2H), 1.68-1.72 (m, 2H), 1.20 (s, 9H); \text{'C NMR (175 MHz, CDCl}_3) \delta 169.4, 138.5, 128.4, 127.62, 127.58, 72.9, 69.8, 56.5, 35.9, 29.3, 22.4, 22.3; \text{HRMS (EI+) calcd. for C}_{16}H_{26}NO_2S (M+H) 296.1684, found 296.1690.}

**Sulfonamide 2.8.6.** To a solution of 2.8.4 (1.40 g, 4.74 mmol) in PhMe (24 mL) at -78°C was added a pre-made solution of 2.8.5 (7.10 mmol, 14.22 mL, 0.2 M in THF) slowly. After 2 h the reaction mixture was quenched with aq. sat. NH₄Cl (30 mL) and warmed to rt. The dried (MgSO₄) mixture was filtered through Celite®, concentrated in vacuo, and
purified by chromatography over silica gel eluting with 20-50% EtOAc/Hexanes to obtain sulfonamide **2.8.6** (1.37 g, 3.87 mmol, 82%) as a colorless oil. $[\alpha]_D^{20} = -74.2^\circ$ ($c = 1.00, \text{CHCl}_3$); IR (neat) 3268, 3225, 3069, 3030, 2937, 2861, 1652, 1455, 1363, 1069 cm$^{-1}$; $^1$H NMR (700 MHz, CDCl$_3$) $\delta$ 7.34-7.37 (m, 4H), 7.29-7.32 (m, 1H), 4.81 (m, 1H), 4.90 (t, $J = 2.1$ Hz, 1H), 4.53 (s, 2H), 3.49 (t, $J = 6.3$ Hz, 2H), 3.38-3.43 (m, 1H), 3.26 (d, $J = 4.2$ Hz, 1H), 2.32 (dd, $J = 14.0, 5.6$ Hz, 1H), 2.22 (dd, $J = 14.0, 8.4$ Hz, 1H), 1.76 (s, 3H), 1.62-1.66 (m, 2H), 1.51-1.60 (m, 2H), 1.43-1.50 (m, 2H), 1.20 (s, 9H); $^{13}$C NMR (175 MHz, CDCl$_3$) $\delta$ 142.5, 138.6, 128.4, 127.6, 127.5, 114.2, 72.9, 70.2, 55.6, 51.5, 44.4, 35.1, 29.7, 22.6, 22.0, 21.9. HRMS (EI+) calcd. for C$_{20}$H$_{34}$O$_2$NS (M+H) 352.2310, found 352.2310.

**Amine 2.3.3.** To a solution of sulfonamide **2.8.6** (1.140 g, 3.24 mmol) in MeOH (21 mL) was added conc. HCl (12.8 M, 6.48 mmol, 0.504 mL). The resulting solution was allowed to stir for 1h before being concentrated in vacuo, and purified by chromatography over silica gel eluting with 50% EtOAc/Hexanes to 10% MeOH/DCM to obtain **2.3.3** (930 mg, 3.24 mmol, 99%) as the HCl salt which was then dissolved in aq. sat. Na$_2$CO$_3$ (50 mL), and extracted with DCM (3 x 30 mL) to obtain **2.3.3** as the free amine. $[\alpha]_D^{20} = +5.6^\circ$ ($c = 1.00, \text{CHCl}_3$); IR (neat) 3077, 3026, 2933, 2847, 1656, 1454, 1360, 1095 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.28-7.36 (m, 5H), 4.84 (s, 1H), 4.76 (s,
1H), 4.52 (s, 2H), 3.50 (t, $J = 6.4$ Hz, 2H), 2.91 (br s, 1H), 2.16-2.19 (m, 1H), 1.92 (dd, $J = 13.6, 9.2$ Hz, 1H), 1.73 (s, 3H), 1.62-1.66 (m, 2H), 1.44-1.59 (m, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 143.3, 138.6, 128.4, 127.7, 127.5, 112.8, 72.9, 70.3, 48.4, 47.0, 37.8, 29.9, 23.0, 22.3. HRMS (EI+) calcd. For C$_{16}$H$_{26}$NO (M+H) 248.2014, found 248.2015.

**Enol ether 3.2.1:** To a suspension of methoxymethyl-triphenylphosphonium chloride (15.09 g, 44.01 mmol) in ether (371 mL) was added PhLi (20.7 mL, 41.4 mmol, 2.0 M in Bu$_2$O) at -78 °C dropwise over 10 min period. The resulting solution was then warmed to rt over a period of 15 min. After 20 min, the reaction mixture was cooled back to 0 °C and added a solution of aldehyde 2.4.5 (23.79 mmol) in ether (247 mL). After 2 h, the reaction was quenched with sat. aq. NH$_4$Cl (100 mL), the precipitate was dissolved, extracted with ether (3 x 150 mL), washed with sat. aq. NaHCO$_3$. The dried (MgSO$_4$) extract was concentrated in vacuo and purified by column chromatography over silica gel, eluting with 0-20% EtOAc/Hexanes to obtain the enol ether 3.2.1$^2$ (4.0 g, 15.4 mmol, 65%) as a colorless oil of 1:1.27 (Z:E) diastereomeric mixture. [$\alpha$]$_D^{20}$ = -43.5° (c = 1.0, CHCl$_3$); IR (neat) 2932, 2855, 1693, 1448, 1415, 1270, 1108, 934 cm$^{-1}$; $^1$H NMR (700 MHz, CDCl$_3$) $\delta$ 6.32 (d, $J = 12.6$ Hz, 1H), 5.93 (dt, $J = 6.3, 1.4$ Hz, 1H), 4.67 (dt, $J = 12.6, 7.7$ Hz, 1H), 4.33 (q, $J = 7.0$ Hz, 1H), 4.21 (br s, 2H), 3.97 (br, s, 2H), 3.59 (s, 3H), 3.51 (s, 3H), 2.84 (t, $J = 12.6$ Hz, 1H), 2.76 (td, $J = 13.3, 2.1$ Hz, 1H), 2.42 (m, 1H), 2.27-2.25 (m, 2H), 2.13-2.09 (m, 1H), 1.6-1.51 (m, 9H), 1.47 (s, 18H), 1.43-1.38 (m, 3H); $^{13}$C
NMR (175 MHz, CDCl₃) δ 155.2, 148.1, 147.5, 103.4, 99.6, 79.0, 78.9, 59.5, 55.8, 50.7, 38.9, 28.5, 28.2, 27.8, 27.2, 25.6, 25.5, 24.4, 18.9, 18.8; HRMS (EI+) calcd. for C₁₄H₂₅NO₃ (M+) 255.1835, found 255.1828.

Oxazolidinone 3.2.5: To a stirred solution of enol ether 3.2.1 (8.1 mmol) in acetone (97 mL) was added PTSA•H₂O (771 mg, 4.05 mmol). After 20 min, the reaction was quenched with water (20 mL), extracted with DCM (3 x 50 mL). The dried (MgSO₄) extract was concentrated in vacuo to obtain crude aldehyde 3.2.2. The crude aldehyde 3.2.2 is taken to the next step.

To a solution of crude aldehyde 3.2.2 (~8.1 mmol) in a 1:1 mixture (200 mL) of tBuOH and H₂O was added 2-methyl-2-butene (19.94 mL, 186.3 mmol) followed by NaH₂PO₄•H₂O (11.18 g, 81.0 mmol) and NaOCl₂ (3.68 g, 40.5 mmol). After 2.5 h, the reaction mixture was quenched with aq. sat. NaCl (50 mL) and extracted with ether (3 x 100 mL). The dried (MgSO₄) extract was concentrated in vacuo and to obtain the crude acid 3.2.3. The crude acid 3.2.3 is taken to the next step.
To a solution of crude acid **3.2.3** (~8.1 mmol) in dry THF (66 mL) was added triethylamine (1.64 g, 2.6 mL, 18.3 mmol) followed by pivaloyl chloride (977 mg, 1.0 mL, 8.1 mmol) at -20 °C. After 3 h, LiCl (364 mg, 8.61 mmol) and (4S)-benzyloxazolidin-2-one (S)-**(3.2.4)** (1.21 g, 6.82 mmol) were added sequentially and the mixture was warmed to rt over a period of 3 h. After 30 min, the reaction was quenched with water (50 mL) and extracted with ether (3 x 100 mL). The dried (MgSO₄) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 38-50% Ether/Pentane to obtain **3.2.5** (2.49 g, 5.98 mmol, 73% over 3 steps) as a colorless oil. [α]D²⁰ = +14.87° (c = 1.58, CHCl₃); IR (neat) 2926, 2852, 1783, 1687, 1416, 1389, 1364, 1161, 701 cm⁻¹; ¹H NMR (400 MHz, 40 °C, CDCl₃) δ 7.26-7.34 (m, 3H), 7.20-7.22 (m, 2H), 4.67-4.70 (m, 1H), 4.31-4.32 (m, 1H), 4.13-4.22 (m, 2H), 4.00 (d, J = 12.0 Hz, 1H), 3.30 (dd, J = 13.2, 2.8 Hz, 1H), 2.94-3.00 (m, 1H), 2.74-2.86 (m, 3H), 2.13-2.15 (m, 1H), 1.77-1.80 (m, 1H), 1.59-1.67 (m, 5H), 1.45 (s, 9H), 1.27-1.40 (m, 1H); ¹³C NMR (100 MHz, 40 °C, CDCl₃) δ 173.0, 155.1, 153.4, 135.5, 129.4, 128.9, 127.2, 79.2, 66.2, 55.2, 49.6, 38.7, 38.0, 32.3, 29.0, 28.4, 25.6, 24.3, 19.1; HRMS (EI⁺) calcd. for C₂₃H₃₃N₂O₅ (M+H) 417.2390, found 417.2382.

**Oxazolidinone 3.1.4:** To a solution of oxazolidinone **3.2.5** (708 mg, 1.70 mmol) in dry THF (9.4 mL) at -78 °C was added NaHMDS (1.36 mL, 2.72 mmol, 2.0 M in THF).
After 30 min, MeI (2.4 g, 1.06 mL, 17 mmol) was added. After 2 h, the reaction was quenched with sat. aq. NH₄Cl (20 mL) and extracted with ether (3 x 50 mL). The dried (MgSO₄) extracted was concentrated in vacuo and purified by chromatography over silica gel, eluting with 25-45% Ether/Pentane to obtain 3.1.4 (396 mg, 0.92 mmol, 54%) as a colorless solid. Mp. 135-137 °C; [α]D⁰² = +23.2° (c = 1.00, CHCl₃); IR (neat) 2933, 2863, 1783, 1681, 1475, 1417, 1392, 1163, 741 cm⁻¹; ¹H NMR (700 MHz, CDCl₃) δ 7.32-7.34 (m, 2H), 7.26-7.29 (m, 1H), 7.23-7.24 (m, 2H), 4.77 (br s, 1H), 4.24-4.28 (m, 2H), 4.14 (s, 1H), 3.92 (s, 1H), 3.28 (s, 1H), 3.26 (dd, J = 13.3, 2.8 Hz, 1H), 2.81 (dd, J = 12.6, 9.8 Hz, 1H), 2.75 (t, J = 12.6 Hz, 1H), 1.83-1.89 (m, 2H), 1.59 (m, 5H), 1.41 (s, 9H), 1.39-1.42 (m, 1H), 1.26 (d, J = 6.3Hz, 3H); ¹³C NMR (175 MHz, CDCl₃) δ 176.9, 155.2, 153.2, 135.7, 129.5, 128.8, 127.2, 79.1, 66.3, 55.4, 47.6, 39.2, 38.3, 34.6, 33.4, 29.5, 28.4, 25.7, 19.2, 18.7; HRMS (EI+) calcd. for C₂₄H₃₄N₂O₅ (M+) 430.2468, found 430.2460.

Oxazolidinone 3.4.1: To a solution of crude acid 3.2.3 (~7.17 mmol) in dry THF (58 mL) was added triethylamine (1.45 g, 2.02 mL, 14.34 mmol) followed by pivaloyl chloride (865 mg, 0.883 mL, 7.17 mmol) at -20 °C. After 3 h, LiCl (364 mg, 8.61 mmol) and (4R)-benzyloxazolidin-2-one (R-3.2.4) (1.21 g, 6.82 mmol) were added sequentially and the mixture was warmed to rt over a period of 3 h. After 30 min, the reaction was
quenched with water (50 mL) and extracted with ether (3 x 100 mL). The dried (MgSO₄) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 38-50% Ether/Pentane to obtain oxazolidinone 3.4.1 (2.34 g, 5.62 mmol, 78% over 3 steps) as a colorless oil. [α]D²⁰ = -46.4° (c = 1.12, CHCl₃); IR (neat) 2931, 2857, 1783, 1682, 1477, 1416, 1391, 1271, 1162, 762, 702 cm⁻¹; ¹H NMR (700 MHz, CDCl₃) δ 7.35-7.37 (m, 2H), 7.29-7.31 (m, 1H), 7.24 (d, J = 7.0 Hz, 2H), 4.66-4.69 (m, 1H), 4.36 (br s, 1H), 4.17-4.22 (m, 2H), 4.02 (br s, 1H), 3.38 (d, J = 10.5, 1H), 3.01-3.06 (m, 1H), 2.75-2.86 (m, 3H), 2.17 (br s, 1H), 1.80 (br s, 1H), 1.60-1.70 (m, 5H), 1.49 (s, 9H), 1.39-1.47 (m, 1H); ¹³C NMR (175 MHz, CDCl₃) δ 175.0, 155.1, 153.4, 135.5, 129.4, 128.9, 127.3, 79.4, 66.2, 55.3, 50.0, 38.9, 38.0, 32.7, 28.9, 28.5, 25.6, 24.4, 19.1; HRMS (Cl⁺) calcd. for C₂₃H₃₅N₂O₅ (M⁺H) 417.2390, found 417.2378.

Oxazolidinone 3.4.2: To a solution of oxazolidinone 3.4.1 (66 mg, 0.158 mmol) in dry THF (0.49 mL) at -78 °C was added NaHMDS (0.127 mL, 0.253 mmol, 2.0 M in THF). After 30 min, MeI (224 mg, 0.1 mL, 1.58 mmol) was added. After 2 h, the reaction was quenched with sat. aq. NH₄Cl (5 mL) and extracted with ether (3 x 10 mL). The dried (MgSO₄) extracte was concentrated in vacuo and purified by chromatography over silica gel, eluting with 25-45% Ether/Pentane to obtain oxazolidinone 3.4.2 (53 mg, 0.122 mmol, 77%) as a colorless oil. [α]D²⁰ = -77.2° (c = 1.00, CHCl₃); IR (neat) 2930, 2855, 1782, 1686, 1454, 1415, 1389, 1168, 730 cm⁻¹; ¹H NMR (400 MHz, 40 °C, CDCl₃) δ
7.27-7.36 (m, 4H), 7.22 (d, J = 6.8 Hz, 1H), 4.63 (m, 1H), 4.35 (br s, 1H), 4.23 (d, J = 8.0 Hz, 1H), 4.15 (dd, J = 8.8, 2.0 Hz, 1H) 3.93 (d, J = 12.8, 1H), 3.72-3.81 (m, 1H), 3.27 (dd, J = 13.2, 3.2 Hz, 1H), 2.78-2.85 (m, 2H), 2.48 (br s, 1H), 1.50-1.62 (m, 5H), 1.48 (s, 9H), 1.34-1.43 (m, 2H), 1.31 (d, J = 6.8 Hz, 3H); $^{13}$C NMR (100 MHz, 40 °C, CDCl$_3$) δ 176.9, 155.2, 152.9, 135.4, 129.4, 128.9, 127.3, 79.5, 66.1, 55.4, 49.6, 38.7, 37.9, 35.6, 33.8, 29.7, 28.4, 25.6, 19.4, 18.2; HRMS (EI+) calcd. for C$_{24}$H$_{34}$N$_2$O$_5$ (M+) 430.2468, found 430.2470.

**Alcohol 3.3.1:** To a solution of the oxazolidinone 3.1.4 (151 mg, 0.351 mmol) in dry THF (14.6 mL) at 0 °C was added MeOH (56.1 mg, 0.71 mL, 1.75 mmol) followed by LiBH$_4$ (36.7 mg, 1.68 mmol). After 30 min, the reaction mixture was warmed to rt over a period of 10 min. After 2 h, the reaction mixture was quenched with sat. aq. NH$_4$Cl (25 mL), extracted with ether (3 x 30 mL). The dried (MgSO$_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 20-30% EtOAc/Hexanes to obtain the alcohol 3.1.6 (88.5 mg, 0.344 mmol, 98%) as a colorless oil. $[\alpha]_D^{20} = -44.7^\circ$ (c = 1.00, CHCl$_3$); IR (neat) 3438, 2929, 1682, 1417, 1365, 1317, 1270, 1167, 1026, 991, 877, 768 cm$^{-1}$; $^1$H NMR (400 MHz, 40 °C, CDCl$_3$) δ 4.38 (br s, 1H), 3.97 (d, J = 12.8 Hz, 1H), 3.51 (d, J = 4.8 Hz, 2H), 2.75-2.82 (m, 1H), 1.57-1.60 (m, 8H), 1.47 (s, 9H), 1.32-1.40 (m, 1H), 0.95 (d, J = 6.0 Hz, 3H); $^{13}$C NMR (100 MHz, 40
°C, CDCl$_3$) $\delta$ 155.2, 79.3, 68.4, 48.5, 38.9, 33.7, 32.7, 28.5, 25.6, 18.8, 17.4; HRMS (EI+) calcd. for C$_{14}$H$_{27}$NO$_3$ (M+) 257.1991, found 257.1992.

Sulfide 3.3.2: To a solution of alcohol 3.3.1 (85 mg, 0.33 mmol) in dry THF (0.78 mL) at 0 °C were added PhSSPh (144mg, 0.66 mmol) and Bu$_3$P (153.4 mg, 0.187 mL, 0.76 mmol). After 10 min, the reaction was warmed to rt over a period of 20 min. After 12 h, the solvent was removed in vacuo and purified by chromatography over silica gel, eluting with 15-30% Ether/Pentane to obtain the sulfide 3.3.2 (114 mg, 0.327 mmol, 99%) as a colorless oil. $[\alpha]_{D}^{20} = -33.1^\circ$ ($c = 0.96$, CHCl$_3$); IR (neat) 2920, 2845, 1733, 1683, 1652, 1635, 1540, 1506, 1457 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.34-7.36 (m, 2H), 7.27 (t, $J = 7.6$ Hz, 2H), 7.18 (t, $J = 7.6$ Hz, 1H), 4.29 (br s, 1H), 3.98 (d, $J = 12.8$ Hz, 1H), 2.94 (m, 2H), 2.78 (t, $J = 12.8$ Hz, 1H), 1.69-1.82 (m, 2H), 1.47-1.62 (m, 6H), 1.46 (s, 9H), 1.36-1.45 (m, 1H), 1.08 (d, $J = 6.0$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 154.9, 137.4, 129.1, 128.8, 125.6, 79.2, 48.4, 41.2, 38.9, 35.7, 30.4, 28.5, 27.9, 25.6, 19.6, 18.9; HRMS (EI+) calcd. for C$_{20}$H$_{31}$NO$_2$S (M+) 349.2076, found 349.2076.

Sulfone 3.1.2: To a solution of sulfide 3.3.2 (114 mg, 0.327 mmol) in dry EtOH (3.35 mL) was added (NH$_4$)$_6$Mo$_7$O$_{24}$$\cdot$4H$_2$O (81.6 mg, 0.066 mmol) followed by H$_2$O$_2$ (1.7 mL,
16.5 mmol, 30% aqueous). After 12 h, water (10 mL) was added, extracted with DCM (3 x 20 mL). The dried (MgSO₄) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 20-30% EtOAc/Hexanes to obtain sulfone 3.1.2 (123.4 mg, 0.32 mmol, 99%) as a colorless oil. [α]D^20 = -23.48° (c = 1.15, CHCl₃); IR (neat) 2929, 1733, 1683, 1635, 1418, 1364, 1306, 1148, 1086, 1025 cm⁻¹; ^1H NMR (400 MHz, CDCl₃) δ 7.93 (d, J = 7.6 Hz, 2H), 7.64 (t, J = 7.2 Hz, 1H), 7.56 (t, J = 7.2 Hz, 2H), 4.26 (br s, 1H), 3.94 (d, J = 12.8 Hz, 1H), 3.29 (br s, 1H), 2.93-2.98 (m, 1H), 2.72 (t, J = 12.8 Hz, 1H), 2.13-2.17 (m, 1H), 1.72-1.76 (m, 1H), 1.44-1.60 (m, 6H), 1.45 (s, 9H), 1.25-1.44 (m, 1H), 1.16 (d, J = 6.4 Hz, 3H); ^13C NMR (100 MHz, CDCl₃) δ 154.8, 140.8, 133.3, 129.1, 127.6, 79.3, 62.0, 47.7, 39.1, 36.3, 28.4, 27.8, 26.1, 25.4, 19.9, 18.8; HRMS (EI+) calcd. for C_{20}H_{31}NO_4S (M+) 381.1974, found 381.1962.

Oxazolidinone 3.5.5: To a solution of aldehyde 3.2.2 (26 mg, 0.107 mmol) in DCM (0.8 mL) were sequentially added N, N-dimethylmethyleniminium iodide (49.8 mg, 0.27 mmol) and Et₃N (21.8 mg, 30.3 mL, 0.215 mmol). After 24 h, sat. NaHCO₃ (1 mL) was
added and extracted with DCM (3 x 10 mL). The dried (MgSO₄) extract was concentrated
in vacuo to obtain the crude enal 3.5.1. The crude enal 3.5.1 is taken to the next step.

To a solution of crude enal 3.5.1 (~0.107 mmol) in a 1:1 mixture (2.6 mL) of 'BuOH
and H₂O was added 2-methyl-2-butene (0.26 mL, 2.4 mmol) followed by NaH₂PO₄•H₂O
(146.6 mg, 1.06 mmol) and NaOCl₂ (48.3 mg, 0.53 mmol). After 2.5 h, the reaction
mixture was quenched with aq. sat. NaCl (5 mL) and extracted with ether (3 x 10 mL).
The dried (MgSO₄) extract was concentrated in vacuo and to obtain the crude acid SI-3.
The crude acid SI-3 is taken to the next step.

To a solution of crude acid SI-3 (~0.107 mmol) in dry THF (0.856 mL) was added
triethylamine (21.7 mg, 30.1 mL, 0.214 mmol) followed by pivaloyl chloride (12.9 mg,
13.2 mL, 0.107 mmol) at -20 °C. After 3 h, LiCl (5.4 mg, 0.128 mmol) and (4R)-
benzyloxazolidin-2-one (R-3.2.4) (18 mg, 0.102 mmol) were added sequentially and the
mixture was warmed to rt over a period of 3 h. After 30 min, the reaction was quenched
with water (5 mL) and extracted with ether (3 x 10 mL). The dried (MgSO₄) extract was
concentrated in vacuo and purified by chromatography over silica gel, eluting with 38-
50% Ether/Pentane to obtain oxazolidinone 3.5.5 (19.7 mg, 0.046 mmol, 43% over 3
steps) as a colorless oil. [α]D²⁰ = -38.8° (c = 1.43, CHCl₃); IR (neat) 2934, 1788, 1684,
1413, 1364, 1160, 1042, 918, 735, 703 cm⁻¹; ¹H NMR (700 MHz, CDCl₃) δ 7.36 (t,
J = 7.0 Hz, 2H), 7.29-7.31 (m, 1H), 7.24 (d, J = 7.0 Hz, 2H), 5.60 (s, 1H), 5.57 (s, 1H), 4.72-
4.76 (m, 1H), 4.40-4.41 (m, 1H), 4.26 (t, J = 8.4 Hz, 1H), 4.20 (dd, J = 8.4, 4.2 Hz, 1H),
4.00 (br s, 1H), 3.45-3.47 (m, 1H), 2.81-2.86 (m, 2H), 2.77 (dd, J = 14.0, 7.0 Hz, 1H),
2.65-2.67 (m, 1H), 1.74-1.75 (m, 1H), 1.57-1.64 (m, 5H), 1.48 (s, 9H); ¹³C NMR (175
MHz, CDCl$_3$) $\delta$ 170.2, 154.9, 153.1, 141.0, 135.3, 129.4, 129.0, 127.4, 123.3, 79.4, 66.6, 55.6, 49.0, 39.4, 37.6, 33.5, 28.5, 27.1, 25.5, 18.8; HRMS (ES+) calcd. for C$_{25}$H$_{32}$N$_2$O$_5$Na (M+Na) 451.2209, found 451.2190.

**Alcohol 3.5.2:** To a solution of crude enal 3.5.1 (~0.103 mmol) in MeOH (0.78 mL) and Et$_2$O (0.22 mL) at 0 °C was added NaBH$_4$ (3.9 mg, 0.103 mmol, 3 portions) portionwise over a period of 20 min. After an additional 30 min, the reaction was quenched with H$_2$O (2 mL), extracted with ether (3 x 10 mL). The dried (MgSO$_4$) extract was concentrated in vacuo and purified by column chromatography over silica gel, eluting with 10-30% Et$_2$O/Pentane to obtain a alcohol 3.5.2 (17.5 mg, 0.069 mmol, ~40% over 2 steps). [$\alpha$]$_D^{20}$ = -35.5° ($c$ = 0.96, CHCl$_3$); IR (neat) 3423, 2934, 2860, 1674, 1418, 1366, 1321, 1265, 1162, 1041, 898, 802, 767 cm$^{-1}$; $^1$H NMR (700 MHz, CDCl$_3$) $\delta$ 5.03 (br s, 1H), 4.82 (br s, 1H), 4.52 (br s, 1H), 4.14 (d, $J$ = 6.3 Hz, 2H), 3.90-3.95 (m, 2H), 2.85 (t, $J$ = 12.6 Hz, 1H), 2.61 (br s, 1H), 2.12 (br s, 1H), 1.57-1.66 (m, 6H), 1.45 (s, 9H); $^{13}$C NMR (175 MHz, CDCl$_3$) $\delta$ 156.1, 146.4, 113.8, 79.7, 67.4, 49.1, 39.6, 35.1, 28.4, 25.5, 18.8; HRMS (ES+) calcd. for C$_{14}$H$_{25}$NO$_3$Na (M+Na) 278.1732, found 278.1736.
**Oxazolidinone 3.4.2:** To a solution of 3.5.5 (16.5 mg, 0.039 mmol) in THF (0.53 mL) at -78 °C was added L-Selectride (42.4 mL, 42.4 mmol, 1.0 M solution in THF). After 15 min, the reaction was quenched with aq. sat. NH₄Cl solution (1 mL) and extracted with Et₂O (3 x 5 mL). The dried (MgSO₄) extract was concentrated *in vacuo* to obtain 3.4.2 and its C₁₅-epimer (14.1 mg, 0.033 mmol, 85%) as a (2:1) diastereomeric mixture.

**Alcohol 3.5.3:** To a solution of allylic alcohol 3.5.2 (9.3 mg, 0.036 mmol) in MeOH (0.5 mL) at rt was added (S)-Ru(OAc)₃(T-BINAP) (5.5 mg, 10 mol%), the argon was then removed by flushing with H₂ gas. After 5 min, the reaction was sealed under 1 atm of H₂ (balloon). After 3 d, the hydrogen was removed by flushing with argon and filtered through Celite® washing with EtOH (5 mL). The filtered extract was concentrated *in vacuo* to give alcohol 3.5.3 (3.7 mg, 0.014 mmol, ~40%) as a 1:1 diastereomeric mixture.
**Oxazolidinone 3.7.2:** To a solution of oxazolidione 3.4.1 (40 mg, 0.14 mmol) in THF (0.58 mL) at -78 °C was added NaHMDS (0.115 mL, 0.23 mmol, 2.0 M in THF). After 30 min, neat PhSCH$_2$I$^7$ (350 mg, 1.4 mmol) was added. After 1 h, the reaction was quenched with sat. aq. NH$_4$Cl (5 mL), extracted with ether (3 x 10 mL). The dried (MgSO$_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 20-40% Ether/Pentane to obtain 3.7.2 (48 mg, 0.088 mmol, 63%) as a colorless oil. [$\alpha$]$_D^{20} = -28.2^\circ$ (c = 1.05, CHCl$_3$); IR (neat) 2974, 2929, 1782, 1684, 1482, 1414, 1389, 1364, 1273, 1159, 1107, 739 cm$^{-1}$; $^1$H NMR (400 MHz, 40 °C, CDCl$_3$) $\delta$ 7.42-7.44 (m, 2H), 7.19-7.34 (m, 8H), 4.64 (br s, 1H), 4.34 (br s, 1H), 4.11-4.27 (m, 3H), 3.92 (d, $J = 13.2$ Hz, 1H), 3.27-3.41 (m, 3H), 2.72-2.85 (m, 2H), 2.44 (br s, 1H), 1.70-1.77 (m, 1H), 1.48-1.61 (m, 5H), 1.46 (s, 9H), 1.34-1.42 (m, 1H); $^{13}$C NMR (100 MHz, 40 °C, CDCl$_3$) $\delta$ 174.4, 155.2, 152.9, 136.3, 135.5, 129.8, 129.4, 128.90, 128.86, 127.2, 126.3, 79.7, 66.1, 55.6, 49.2, 40.9, 38.9, 37.8, 36.5, 31.9, 29.4, 28.4, 25.5, 19.3; HRMS (ES+) calcd. for C$_{30}$H$_{39}$N$_2$O$_5$S (M+H) 539.2580, found 539.2593.

**Alcohol 3.7.3:** To a solution of oxazolidinone 3.7.2 (42 mg, 0.078 mmol) in THF (3.3 mL) at 0 °C was added MeOH (12.4 mg, 0.017 mL, 0.39 mmol) followed by LiBH$_4$ (8.2
mg, 0.374 mmol). After 30 min, the reaction mixture was warmed to rt over a period of 10 min. After 2 h, the reaction mixture was quenched with sat. aq. NH₄Cl (5 mL), extracted with ether (3 x 10 mL). The dried (MgSO₄) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 35-45% EtOAc/Hexanes to obtain alcohol 3.7.3 (27.6 mg, 0.076 mmol, 97%) as a colorless oil. [α]D²⁰ = -40.8° (c = 1.30, CHCl₃); IR (neat) 3419, 2927, 2856, 1689, 1665, 1419, 1365, 1272, 1068, 738, 691 cm⁻¹; ¹H NMR (400 MHz, 40 °C, CDCl₃) δ 7.37-7.39 (m, 2H), 7.27-7.31 (m, 2H), 7.18 (t, J = 7.2 Hz, 1H), 4.29 (br s, 1H), 3.95 (d, J = 10.4 Hz, 1H), 3.72-3.77 (m, 2H), 3.16 (dd, J = 12.8, 6.4 Hz, 1H), 3.03 (dd, J = 12.4, 5.2 Hz, 1H), 2.76-2.83 (m, 1H), 1.75 (br s, 2H), 1.59-1.64 (m, 5H), 1.42-1.50 (m, 11H); ¹³C NMR (100 MHz, 40 °C, CDCl₃) δ 155.5, 137.0, 129.2, 128.9, 125.9, 79.6, 64.3, 48.0, 39.4, 37.8, 36.2, 30.8, 28.5, 28.0, 25.4, 18.8; HRMS (EI+) calcd. for C₂₀H₃₂NO₃S (M+H) 366.2103, found 366.2108.

**Sulfone SI-4:** To a solution of sulfide 3.7.3 (12.5 mg, 0.034 mmol) in EtOH (0.36 mL) was added (NH₄)₆Mo₇O₂₄•4H₂O (8.5 mg, 0.007 mmol) followed by H₂O₂ (0.163 mL, 1.7 mmol, 30% aqueous). After 12 h, water (2 mL) was added, extracted with DCM (3 x 5 mL). The dried (MgSO₄) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 50-85% EtOAc/Hexanes to obtain the sulfone SI-4 (12.7 mg, 0.032 mmol, 94%) as a colorless oil. [α]D²⁰ = -21.9° (c = 0.48, CHCl₃); IR (neat) 3434, 2926, 2854, 1681, 1447, 1420, 1366, 1305, 1146, 740 cm⁻¹; ¹H
NMR (400 MHz, 40 °C, CDCl₃) δ 7.95-7.97 (m, 2H), 7.64-7.68 (m, 1H), 7.57-7.60 (m, 2H), 4.25 (br s, 1H), 3.93 (d, J = 12.8 Hz, 1H), 3.84 (br s, 2H), 3.31 (br s, 2H), 2.76 (t, J = 13.2 Hz, 1H), 2.17-2.19 (m, 1H), 1.73-1.87 (m, 2H), 1.53-1.63 (m, 5H), 1.47 (s, 10H); ¹³C NMR (100 MHz, 40 °C, CDCl₃) δ 155.0, 140.5, 133.5, 129.3, 127.7, 79.8, 63.8, 57.5, 47.3, 39.5, 33.7, 31.5, 28.5, 27.9, 25.3, 18.8; HRMS (EI+) calcd. for C₂₀H₃₁NO₅SNa (M+Na) 420.1821, found 420.1816.

**Iodide 3.7.4:** To a solution of sulfone SI-4 (14.0 mg, 0.036 mmol) in THF (1.24 mL) at 0 °C were sequentially added imidazole (7.4 mg, 0.108 mmol), PPh₃ (18.4 mg, 0.07 mmol) and I₂ (17.7 mg, 0.07 mmol). After 20 min, the reaction mixture was warmed to rt over a period of 5 min. After 3 h, the reaction was quenched with aq. sat. sodium thiosulfate (5 mL) and extracted with ether (3 x 5 mL). The dried (MgSO₄) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 20-35% EtOAc/Hexanes to obtain the iodide **3.7.4** (15.3 mg, 0.03 mmol, 84%) as a colorless oil. [α]D²⁰ = -14.6° (c = 1.0, CHCl₃); IR (neat) 2930, 2856, 1681, 1447, 1417, 1365, 1307, 1152, 1086, 738 cm⁻¹; ¹H NMR (400 MHz, 40 °C, CDCl₃) δ 7.97-7.99 (m, 2H), 7.65-7.69 (m, 1H), 7.57-7.61 (m, 2H), 4.31 (br s, 1H), 3.99 (d, J = 14.0 Hz, 1H), 3.53-3.61 (m, 2H), 3.21-3.37 (m, 2H), 2.79 (t, J = 13.2 Hz, 1H), 1.96-2.06 (m, 2H), 1.51-1.71 (m, 6H), 1.49 (s, 9H), 1.32-1.46 (m, 1H); ¹³C NMR (100 MHz, 40 °C, CDCl₃) δ 154.9, 140.4, 133.6,
129.3, 127.8, 79.7, 59.4, 47.5, 39.2, 34.8, 32.7, 28.8, 28.5, 25.5, 19.1, 13.7; HRMS (ES+)
calcd. for C_{20}H_{30}INO_4Sn (M+Na) 530.0838, found 530.0833.

**Sulfone 3.1.2:** To a stirred solution of iodide 3.7.4 (10 mg, 0.0197 mmol) in EtOH (0.48 mL) at under argon was added Pd/C (20 mg, 20 wt %), the argon was then removed by flushing with H\textsubscript{2} gas. After 5 min, the reaction was sealed under 1 atm of H\textsubscript{2} (balloon). After 18 h, the hydrogen was removed by flushing with argon and filtered through Celite\textsuperscript{®} washing with EtOH (5 mL). The filtered extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 20%-30% EtOAc/Hexanes to give sulfone 3.1.2 (7.4 mg, 0.0195 mmol, 99%) as a colorless oil.

**Vinyl sulfones 3.8.2 and 3.8.3:** To a solution of PhSO\textsubscript{2}Me (1.08 g, 6.94 mmol) in THF (61.2 mL) at 0 °C was added "BuLi (6.1 mL, 15.3 mmol, 2.5 M solution in Hexanes). After 20 min, ClP(O)(OEt)\textsubscript{2} (1.19 g, 0.99 mL, 6.88 mmol) was added. After 30 min, the reaction mixture was cooled to -78 °C and was added a solution of aldehyde 2.4.5 (1.16 g, 5.1 mmol) in THF (16.1 mL). After 15 min, the reaction mixture was warmed to 0 °C over a period of 10 min. After 2 h, the reaction was quenched with aq. NH\textsubscript{4}Cl (100 mL)
solution, extracted with ether (3 x 100 mL). The dried (MgSO₄) extract was concentrated
in vacuo and purified by chromatography over silica gel, eluting with 10-30% EtOAc/Hexanes to obtain sequentially 3.8.2 (1.22 g, 3.4 mmol, 66%) followed by 3.8.3 (305 mg, 0.85 mmol, 17%).

(E) vinyl sulfone 3.8.2: [α]D²⁰ = -15.9° (c = 1.10, CHCl₃); IR (neat) 3059, 2975, 2934, 2859, 1693, 1681, 1633, 1476, 1416, 1319, 1147, 1086, 752, 688 cm⁻¹; ¹H NMR (700 MHz, 40 °C, CDCl₃) δ 7.86-7.88 (m, 2H), 7.60-7.62 (m, 1H), 7.53 (t, J = 7.7 Hz, 2H), 6.90-6.95 (m, 1H), 6.39 (d, J = 15.4 Hz, 1H), 4.41 (br s, 1H), 3.98 (br s, 1H), 2.60-2.69 (m, 2H), 2.37-2.41 (m, 1H), 1.49-1.64 (m, 5H), 1.47 (s, 9H), 1.40-1.43 (m, 1H); ¹³C NMR (175 MHz, 40 °C, CDCl₃) δ 154.7, 143.7, 140.6, 133.2, 132.0, 129.2, 127.6, 79.8, 49.3, 39.0, 32.1, 28.4, 28.1, 25.2, 18.8; HRMS (ES+) calcd. for C₁₉H₂₇NO₄NaS (M+Na) 388.1559, found 388.1545.

(Z) vinyl sulfone 3.8.3: [α]D²⁰ = -9.0° (c = 1.0, CHCl₃); IR (neat) 3060, 2974, 2934, 2864, 1688, 1681, 1626, 1476, 1447, 1414, 1365, 1317, 1149, 1086, 750, 688 cm⁻¹; ¹H NMR (400 MHz, 40 °C, CDCl₃) δ 7.92 (d, J = 7.2 Hz, 2H), 7.61-7.65 (m, 1H), 7.54-7.58 (m, 2H), 6.30 (br s, 2H), 4.42 (br s, 1H), 3.97 (d, J = 12.0 Hz, 1H), 3.17-3.22 (m, 1H), 2.83-2.86 (m, 2H), 1.57-1.70 (m, 5H), 1.36-1.47 (m, 10H); ¹³C NMR (100 MHz, 40 °C, CDCl₃) δ 155.0, 143.9, 141.7, 133.3, 131.3, 129.2, 127.2, 79.5, 50.0, 39.1, 28.7, 28.6, 28.4, 25.4, 19.0; HRMS (ES+) calcd. for C₁₉H₂₇NO₄NaS (M+Na) 388.1559, found 388.1555.
Vinyl sulfone 3.8.5: To a solution of sulfone 3.8.2 (105 mg, 0.287 mmol) in DCM (0.66 mL) at 0 °C was added TFA (1.21 g, 0.814 mL, 10.63 mmol). After 30 min, reaction mixture was warmed to rt. After 10 min, the solvent was removed under reduced pressure and the crude TFA salt 3.8.4 was taken to next step.

To a solution of crude TFA salt 3.8.4 (~0.287 mmol) in acetonitrile (0.8 mL) was added K$_2$CO$_3$ (79.4 mg, 0.575 mmol) TBAI (105.3 mg, 0.287 mmol) followed by benzyl bromide (54.1 mg, 37.6 mL, 0.316 mmol). After 1.5 h, the reaction mixture was directly purified by chromatography over silica gel, eluting with 70-100% EtOAc/Hexanes to obtain 3.8.5 (86 mg, 0.242 mmol, 84% over 2 steps). [$\alpha$]$_D^{20}$ = -17.1° (c = 2.20, CHCl$_3$); IR (neat) 3060, 3028, 2932, 2854, 2794, 2756, 1629, 1446, 1318, 1307,1291, 1146, 1086, 1069, 749, 688 cm$^{-1}$; $^1$H NMR (700 MHz, CDCl$_3$) δ 7.9 (d, $J = 7.0$ Hz, 2H), 7.63 (tt, $J = 7.0, 1.4$ Hz, 1H), 7.54 (t, $J = 7.7$ Hz, 2H), 7.24-7.31 (m, 5H), 7.10-7.14 (m, 1H) 6.42 (d, $J = 15.4$ Hz, 1H), 3.93 (d, $J = 14.0$ Hz, 1H), 3.24 (d, $J = 13.3$ Hz, 1H), 2.71-2.74 (m, 1H), 2.52-2.63 (m, 3H), 2.08 (t, $J = 9.1$ Hz, 1H), 1.64-1.67 (m, 2H), 1.52-1.53 (m, 1H), 1.44-1.48 (m, 2H), 1.32-1.38 (m, 1H); $^{13}$C NMR (175 MHz, CDCl$_3$) δ 144.9, 140.7, 139.1, 133.3, 131.6, 129.3, 128.7, 128.3, 127.6, 126.9, 59.4, 58.2, 51.3, 33.5, 30.4, 25.1, 23.1; HRMS (ES+) calcd. for C$_{21}$H$_{26}$NO$_2$S (M+H) 356.1684, found 356.1667.
Sulfides 3.9.2 and 3.9.3: To a solution of 3.9.1 (0.639 g, 2.38 mmol) in THF (12.9 mL) at -78 °C was added nBuLi (1.5 mL, 2.38 mmol, 1.6 M solution in Hexanes). After 5 min, the reaction mixture was warmed to -45 °C over a period of 3 h. After 10 min, it was warmed to -25 °C over a period of 1h. After 5 min, cooled back to -78 °C and added a solution of aldehyde 2.4.5 (250 mg, 1.1 mmol) in THF (1.0 mL). After 5 min, the reaction mixture was warmed to -10 °C over a period of 20 min. After 15 min, the reaction was quenched with aq. NH₄Cl (30 mL) solution, extracted with ether (3 x 30 mL). The dried (MgSO₄) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 5-20% EtOAc/Hexanes to obtain a (3:1) diastereomeric mixture of vinyl sulfides 3.9.3 and 3.9.2 (134 mg, 0.33 mmol, 30%). IR (neat) 2971, 2936, 2860, 1690, 1583, 1476, 1413, 1364, 1248, 1054, 839, 741 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.19-7.28 (m, 5.2 H, mixed isomers), 7.10-7.14 (m, 1.3H, mixed isomers), 6.58 (t, J = 6.8 Hz, 1H, major isomer), 6.46 (t, J = 7.2 Hz, 0.3H, minor isomer), 4.46 (br s, 1H, major isomer), 4.33 (br s, 0.3H, minor isomer), 4.05 (br d, J = 12.4 Hz, 0.3H, minor isomer), 3.96 (br d, J = 10.0 Hz, 1H, major isomer), 2.89 (ddd, J = 15.2, 8.8, 6.8 Hz, 1H, major isomer), 2.74-2.82 (m, 1.3 H, mixed isomers), 2.47-2.64 (m, 1.6 H, mixed isomers), 1.53-1.65 (m, 7H, mixed isomers), 1.49 (s, 9H, major isomer), 1.45 (s, 2.7H, minor isomer), 1.32-1.40 (m, 0.8H, mixed isomers), 0.18 (s, 2.7H, minor isomer), 0.02 (s, 9H, major isomer); ¹³C NMR (100 MHz, 40 °C, CDCl₃) δ 154.9, 149.5,
HRMS (ES+) calcd. for C_{22}H_{36}NO_2SiS (M+H) 406.2236, found 406.2224.

**Sulfones 3.9.4 and 3.9.5**: To a solution of mixture of sulfides 3.9.2 and 3.9.3 (64 mg, 0.158 mmol) in EtOH (1.6 mL) was added (NH_4)_6Mo_7O_24•4H_2O (39 mg, 0.032 mmol) followed by H_2O_2 (0.82 mL, 7.9 mmol, 30% aqueous). After 4 h, water (10 mL) was added, extracted with DCM (3 x 15 mL). The dried (MgSO_4) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 30-50% Ether/Pentane to obtain 92 (48.2 mg, 0.11 mmol, 70%) and 93 (16.1 mg, 0.037 mmol, 23%).

(Z) vinyl sulfone 3.9.4: IR (neat) 2974, 2937, 2863, 1685, 1593, 1476, 1446, 1414, 1299, 1249, 1165, 1141, 1085, 884, 843, 760, 590 cm^{-1}; ^1H NMR (400 MHz, CDCl_3) δ 7.89 (d, J = 7.2 Hz, 2H), 7.52-7.61 (m, 3H), 6.59 (br s, 1H), 4.35 (br s, 1H), 3.86 (br d, J = 12.4 Hz, 1H), 2.91 (br s, 1H), 2.51-2.55 (m, 2H), 1.52-1.66 (m, 3H), 1.45 (s, 9H), 1.27-1.40 (m, 3H), 0.29 (s, 9H); ^13C NMR (100 MHz, CDCl_3) δ 155.3, 154.8, 147.9, 143.4, 132.7, 129.0, 127.0, 79.5, 49.8, 38.9, 31.4, 28.7, 28.5, 25.3, 18.9, -0.4; HRMS (ES+) calcd. for C_{22}H_{36}NO_2SiS (M+H) 438.2134, found 438.2136.

(E) vinyl sulfone 3.9.5: IR (neat) 2974, 2933, 2857, 1686, 1588, 1475, 1446, 1414, 1365, 1295, 1164, 1143, 1086, 847, 761, 721, 691 cm^{-1}; ^1H NMR (400 MHz, CDCl_3) δ
7.81 (d, J = 7.2 Hz, 2H), 7.45-7.57 (m, 4H), 4.48-4.51 (m, 1H), 4.08 (br d, J = 13.6 Hz, 1H), 2.72-2.81 (m, 2H), 2.58 (ddd, J = 14.8, 8.0, 6.8 Hz, 1H), 1.52-1.72 (m, 5H), 1.50 (s, 9H), 1.45-1.47 (m, 1H), 0.18 (s, 9H); \(^1^3\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 155.3, 154.8, 143.9, 141.8, 132.6, 128.8, 127.3, 80.0, 50.1, 39.2, 31.7, 28.5, 28.3, 25.3, 19.1, 0.5; HRMS (ES+) calcd. for C\(_{22}\)H\(_{36}\)NO\(_4\)SiS (M+H) 438.2134, found 438.2137.

**Sulfone 3.2.6:** To a stirred suspension of CuI (24.0 mg, 0.126 mmol) in ether (0.32 mL) at 0 °C was added MeLi (0.155 mL, 0.248 mmol, 1.6 M solution in ether). After 25 min, a solution of vinyl sulfone 3.9.5 (9.2 mg, c) in ether (0.05 mL) was added. After 35 min, the reaction mixture was quenched with aq. NH\(_4\)Cl (5 mL), extracted with ether (3 x 10 mL). The dried (MgSO\(_4\)) extract was concentrated in vacuo to yield the crude sulfone SI-5 and the crude was taken to the next step.

To a solution of crude sulfone SI-5 (~21 mmol) in MeOH (0.26 mL) was added KF (6.3 mg, 0.109 mmol) at rt. Aft 1 h, the reaction mixture was quenched with aq. NaHSO\(_3\) solution (5 mL), extracted with DCM (3 x 10 mL). The dried (MgSO\(_4\)) extract was concentrated in vacuo and purified by column chromatography over silica gel, eluting with 10-30% EtOAc/Hexanes to obtain a 8:1 diastereomeric mixture of sulfones (3.2.6 and epi-C\(_{15}\), 3.2.6 respectively) (7.5 mg, 20 mmol, 93%, 2 steps). \([\alpha]_d^{20} = -21.67^\circ \ (c = 0.48, \text{CHCl}_3);\) IR (neat) 2926, 2852, 1682, 1447, 1416, 1365, 1305, 1271, 1149, 1070 cm\(^{-1}\).
\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.93 (d, \(J = 7.6\) Hz, 2H), 7.67 (t, \(J = 7.2\) Hz, 1H), 7.59 (t, \(J = 7.2\) Hz, 2H), 4.29 (br s, 1H), 3.97 (br s, 1H), 3.16 (dd, \(J = 14.0, 5.6\) Hz, 1H), 3.01 (dd, \(J = 14.4, 6.0\) Hz, 1H), 2.81 (t, \(J = 12.8\) Hz, 1H), 2.15-2.22 (m, 1H), 2.01 (br s, 1H), 1.58 (m, 5H), 1.45 (s, 9H), 1.18-1.30 (m, 2H), 1.13 (d, \(J = 6.8\) Hz, 3H); \(^1^3\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 154.8, 140.2, 133.4, 129.3, 127.9, 79.2, 62.6, 47.7, 38.8, 36.8, 29.2, 28.5, 25.9, 25.6, 20.3, 19.1; HRMS (El+) calcd. for C\(_{20}\)H\(_{31}\)NO\(_4\)S (M+) 381.1974, found 381.1964.

**Sulfone 3.1.2:** To a stirred suspension of CuI (28.8 mg, 0.151 mmol) in ether (0.88 mL) at 0 °C was added MeLi (0.185 mL, 0.296 mmol, 1.6 M solution in ether). After 5 min, the reaction was cooled to -78 °C. After 5 min, a solution of vinyl sulfone 3.8.2 (18 mg, 50 mmol) in ether (0.13 mL) was added. After 5 min, the reaction mixture was slowly warmed to -20 °C over a period of 45 min. After 5 h, the reaction was quenched with aq. NH\(_4\)Cl (5 mL), extracted with ether (3 x 10 mL). The dried (MgSO\(_4\)) extract was concentrated in vacuo and purified by column chromatography over silica gel, eluting with 10-30% EtOAc/Hexanes to obtain a 1.0:1.2 mixture of sulfones (3.1.2 and 3.2.6 respectively) (10.8 mg, 28.3 mmol, 55%).
Hydroxy sulfones 3.4.3 and 3.4.4: To a solution of sulfone 3.1.2 (60 mg, 0.157 mmol) in dry THF (0.253 mL) at -78 °C was added LDA \(^8\) (0.236 mL, 0.236 mmol, 1.0 M in THF/hexanes). After 1 min, a solution of aldehyde 2.4.5 (89.1 mg, 0.392 mmol) in THF (0.147 mL) was added. After 20 min, the reaction was quenched with sat. aq. NH\(_4\)Cl (5 mL) and extracted with ether (3 x 10 mL). The dried (MgSO\(_4\)) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 20-80% ether/pentane to obtain a 1.0:1.5 mixture of 3.4.4 and 3.4.3 respectively (84.9 mg, 0.146 mmol, 93%) as a colorless oil.

3.4.4: \([\alpha]_D^{20} = -45.0^\circ\) (c = 1.00, CHCl\(_3\)); IR (neat) 3391, 2929, 2851, 1683, 1652, 1418, 1366, 1273, 1166, 1145, 868, 723, 613 cm\(^{-1}\); \(^1\)H NMR (400 MHz, 40 °C, CDCl\(_3\)) \(\delta\) 7.88 (d, \(J = 7.6\) Hz, 4H), 7.50-7.56 (m, 6H), 4.30-4.38 (m, 4H), 3.94-3.96 (m, 4H), 3.82 (br s, 2H), 3.38 (br s, 2H), 2.74-2.80 (m, 4H), 2.26 (br s, 4H), 1.67-1.73 (m, 4H), 1.47-1.59 (m, 24H), 1.41-1.42 (m, 40 H), 1.26-1.28 (6H); \(^13\)C NMR (100 MHz, 40 °C, CDCl\(_3\)) \(\delta\) 156.5, 155.0, 142.7, 133.5, 132.8, 129.2, 129.0, 128.7, 128.3, 128.2, 128.1, 128.0, 80.2, 79.4, 79.3, 72.8, 66.1, 49.0, 46.4, 39.2, 34.7, 34.4, 29.6, 29.5, 29.2, 28.6, 28.5, 28.4, 28.3, 28.1,
28.0, 25.6, 25.4, 19.3, 19.0, 18.9, 18.0; HRMS (ES+) calcd. for C$_{32}$H$_{53}$N$_2$O$_7$S (M+H) 609.3573, found 609.3569.

3.4.3: $[\alpha]_D^{20} = -37.7^\circ$ (c = 0.98, CHCl$_3$); IR (neat) 3420, 2929, 2854, 1683, 1652, 1473, 1456, 1418, 1365, 1271, 1165, 1145, 1083 cm$^{-1}$; $^1$H NMR (400 MHz, 40 °C, CDCl$_3$) $\delta$ 7.88-7.96 (m, 4H), 7.50-7.60 (m, 6H), 4.18-4.25 (m, 4H), 4.04 (br s, 2H), 3.80-3.90 (m, 4H), 3.45-3.52 (m, 2H), 3.28 (br s, 2H), 2.69-2.78 (m, 4H), 2.13-2.29 (m, 4H), 1.71-1.80 (m, 8H), 1.32-1.54 (m, 58 H), 1.23-1.25 (6H); $^{13}$C NMR (100 MHz, 40 °C, CDCl$_3$) $\delta$ 155.3, 155.2, 155.1, 154.9, 141.9, 141.6, 140.5, 133.5, 133.3, 129.14, 129.07, 129.0, 128.1, 128.0, 128.0, 79.5, 79.3, 79.2, 71.1, 68.0, 48.4, 39.5, 39.3, 39.1, 37.0, 35.4, 35.1, 34.9, 29.6, 29.1, 28.53, 28.47, 28.46, 28.43, 28.33, 28.30, 28.0, 27.8, 25.5, 25.4, 25.3, 25.2, 19.1, 19.0, 18.9, 18.5, 17.4; HRMS (ES+) calcd. for C$_{32}$H$_{53}$N$_2$O$_7$S (M+H) 609.3573, found 609.3562.

**Keto sulfone 3.12.1:** To a solution of alcohol 3.4.3 (15 mg, 24.6 mmol) in DCM (0.71 mL) at 0 °C was added solid NaHCO$_3$ (10.35 mg, 0.123 mmol) followed by DMP (20.87 mg, 0.049 mmol). After 30 min, the reaction mixture was warmed to rt over a period of 15 min. After 1.5 h, the reaction was quenched with sat. aq. Na$_2$S$_2$O$_3$ (5 mL) solution and extracted with DCM (3 x 10 mL). The dried (MgSO$_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 20-30% EtOAc/Hexanes to obtain the keto sulfone 3.12.1 (13.9 mg, 23.0 mmol, 93%) as a colorless oil. $[\alpha]_D^{20} = -$
13.3° (c = 0.70, CHCl₃); IR (neat) 2929, 2855, 1717, 1684, 1447, 1417, 1365, 1271, 1165, 1083, 872 cm⁻¹; ¹H NMR (400 MHz, 40 °C, CDCl₃) δ 7.79-7.84 (m, 4H), 7.47-7.51 (m, 4H), 4.56 (m, 2H), 4.21-4.37 (m, 4H), 3.84-3.86 (m, 4H), 2.84-2.91 (m, 2H), 2.40-2.65 (m, 6H), 2.24 (br s, 1H), 2.09 (br s, 1H), 1.76-1.80 (m, 2H), 1.49 (m, 10 H), 1.35-1.40 (m, 44H), 1.20-1.31 (m, 8H), 1.16 (d, J = 6.8 Hz, 3H), 1.03-1.04 (m, 3H); ¹³C NMR (100 MHz, 40 °C, CDCl₃) δ 200.8, 200.7, 200.5, 200.4, 154.8, 154.7, 154.5, 139.0, 133.94, 133.90, 129.1, 129.0, 128.9, 128.8, 79.42, 79.38, 79.2, 78.4, 48.0, 47.1, 46.8, 46.0, 45.9, 45.7, 40.0, 39.7, 39.2, 34.5, 33.7, 31.1, 30.5, 28.5, 28.42, 28.35, 27.7, 27.3, 25.3, 25.14, 25.11, 18.9, 18.84, 18.76, 18.67, 17.5, 17.0, 16.8; HRMS (ES+) calcd. for C₃₂H₅₀N₂O₇NaS (M+Na) 629.3236, found 629.3194.

**Hydroxy sulfones 3.4.3 and 3.4.4**: To a solution of keto sulfone SI-16 (4.0 mg, 6.6 mmol) in MeOH (0.12 mL) at rt was added NaBH₄ (2.5 mg, 6.6 mmol). After 1h, the reaction was quenched with aq. NH₄Cl (5 mL) and extracted with DCM (3 x 5 mL). The dried (MgSO₄) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 30-80% ether/pentane to obtain a 1.0:1.5 mixture (4.0 mg, 6.5 mmol, 99%) of 3.4.4 and 3.4.3 respectively as colorless oil.
Cyclic Sulfone 3.4.5: To a solution of sulfone 3.1.2 (20 mg, 52.4 mmol) in THF (0.39 mL) at -78 °C was added LDA\(^9\) (0.131 mL, 0.131 mmol, 1.0 M in THF/hexanes). After 20 min, the reaction mixture was warmed to 0 °C. After 15 min, the reaction was quenched with sat. aq. NH\(_4\)Cl (5 mL) and extracted with ether (3 x 10 mL). The dried (MgSO\(_4\)) extract was concentrated \textit{in vacuo} and purified by chromatography over silica gel, eluting with 70-80% EtOAc/Hexane to obtain 3.4.5 (14 mg, 45.5 mmol, 87%) as a colorless oil. \([\alpha]_D^{20} = +55.0^\circ\ (c = 0.2, \text{CHCl}_3);\) IR (neat) 3064, 2926, 2854, 1645, 1447, 1308, 1148, 1083, 688.6, 525.7, 458.0 cm\(^{-1}\); \(^1\)H NMR (700 MHz, CDCl\(_3\)) \(\delta\) 7.94 (dd, \(J = 8.4, 0.7\) Hz, 2H), 7.67 (tt, \(J = 7.0, 1.4\) Hz, 1H), 7.58 (t, \(J = 7.7\) Hz, 2H), 4.72-4.74 (m, 1H), 3.75 (t, \(J = 1.4\) Hz, 1H), 3.32-3.35 (m, 1H), 3.06-3.07 (m, 1H), 2.44 (td, \(J = 13.3, 2.8\) Hz, 1H), 2.32 (ddd, \(J = 14.7, 11.2, 4.2\) Hz, 1H), 1.86-1.88 (m, 1H), 1.74-1.80 (m, 3H), 1.42-1.50 (m, 3H), 1.13 (d, \(J = 7.7\) Hz, 3H); \(^{13}\)C NMR (175 MHz, CDCl\(_3\)) \(\delta\) 160.3, 139.9, 133.7, 128.93, 128.85, 72.3, 53.3, 42.8, 33.8, 32.2, 25.5, 25.3, 24.2, 18.9; HRMS (ES+) calcd. for C\(_{16}\)H\(_{22}\)NO\(_3\)S (M+H) 308.1320, found 308.1309.

Amide 1.1.5: To a solution of sulfone 3.4.5 (8.5 mg, 28 mmol) in dry MeOH (0.55 mL) at 0 °C was added Na\(_2\)HPO\(_4\) (199 mg, 1.4 mmol) followed by 5% Na/Hg (318 mg, 0.69
mmol). After 20 min, the reaction was quenched with sat. aq. NH₄Cl (2 mL), diluted with EtOAc (5 mL) and filtered through Celite® and extracted with EtOAc (3 x 5 mL). The dried (MgSO₄) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 40-60% EtOAc/Hexanes to obtain the known amide 1.1.5 (4.0 mg, 23.9 mmol, 86%) as a colorless oil. [α]_D²⁰ = -24.4° (c = 0.32, CHCl₃); IR (neat) 2929, 2855, 1636, 1463, 1447, 1279, 1258, 1103 cm⁻¹; ¹H NMR (700 MHz, CDCl₃) δ 4.79 (dq, J = 12.6, 2.1 Hz, 1H), 3.34-3.38 (m, 1H), 2.47 (ddd, J = 16.8, 4.2, 2.1 Hz, 1H), 2.43 (td, J = 12.6, 2.8 Hz, 1H), 2.06-2.10 (m, 1H), 2.02 (dd, J = 16.8, 9.1 Hz, 1H), 1.89-1.92 (m, 1H), 1.61-1.69 (m, 4H), 1.51-1.58 (m, 1H), 1.45-1.49 (m, 1H), 1.37-1.45 (m, 1H), 1.00 (t, J = 6.3 Hz, 3H); ¹³C NMR (175 MHz, CDCl₃) δ 168.5, 55.6, 43.0, 40.6, 36.9, 33.6, 25.4, 25.1, 24.5, 20.5; HRMS (ES+) calcd. for C₁₀H₁₈NO (M+H) 168.1388, found 168.1394.

**Cermizine D (1.13):** To a solution of sulfone 3.4.4 (44.2 mg, 73.0 mmol) in EtOH (1.46 mL) at 80 °C was added skeletal Raney Ni (1.77 g, 3 portions) portionwise over a period of 7 h. After an additional 8 h, the reaction mixture was cooled down to rt and
filtered through Celite®. The solvent was removed *in vacuo* to obtain the crude alcohol *SI-5*, which was unstable to purification and carried on crude.

To a solution of the crude alcohol *SI-5* (~73 mmol) in MeOH (1.53 mL) was added TMSCl (133.3 mg, 0.156 mL, 1.23 mmol). After 4 h, the solvent was removed *in vacuo* to obtain the crude 3.13.1. The crude 3.13.1 is taken to the next step.

To a solution of crude alcohol 3.13.1 (~73 mmol) in DCM (2.1 mL) at 0 °C was added sequentially PPh₃ (28.8 mg, 0.11 mmol), CBr₄ (36.3 mg, 0.11 mmol) and Et₃N (44.3 mg, 0.06 mL, 0.438 mmol). The solution was slowly warmed to rt over a period of 15 min. After 3 h, the solvent was removed *in vacuo* and purified by chromatography over silica gel, by eluting with (2:4:94) to (2:10:88) ratio of NH₄OH:MeOH:CHCl₃ to afford cermizine D (1.13)¹⁰ (11.0 mg, 0.044 mmol, 60% over 3 steps) as a pale yellow oil. [α]₂₀° = +40.8° (*c* = 0.90, MeOH); IR (neat) 3360, 3294, 2926, 2853, 1639, 1455, 1442, 1373, 1121 cm⁻¹; ¹H NMR (700 MHz, MeOH-d₄) δ 3.39 (br d, *J* = 15.4 Hz, 1H), 3.15-3.19 (m, 1H), 3.03-3.07 (m, 2H), 2.59-2.68 (m, 3H), 2.01 (qd, *J* = 12.6, 4.2, 1H), 1.78-1.90 (m, 5H), 1.62-1.74 (m, 3H), 1.53-1.60 (m, 2H), 1.43-1.49 (m, 2H), 1.40 (td, *J* = 12.6, 5.6 Hz, 1H), 1.19-1.24 (m, 3H), 1.12 (ddd, *J* = 14.0, 9.8, 4.2 Hz, 1H), 0.93 (d, *J* = 7.0 Hz, 3H), 0.83 (q, *J* = 11.9 Hz, 1H); ¹³C NMR (175 MHz, MeOH-d₄) δ 57.7, 53.5, 48.6, 46.2, 39.9, 39.8, 39.0, 33.2, 25.3, 25.1, 24.3, 24.0, 21.3, 18.2; HRMS (EI+) calcd. for C₁₆H₃₀N₂ (M+) 250.2409, found 250.2414.
**TFA salt of cermizine-D (1.13•TFA):** To a solution of cermizine D (1.13) (2.0 mg, 8.0 mmol) in dry DCM (0.1 mL) was added TFA (3 drops) at 0 °C. After 10 min, the solvent was removed *in vacuo* to afford the cermizine D bis-TFA salt (7•TFA)\(^{10}\) (3.8 mg, 8.0 µmol, 99%) as pale yellow oil. \([\alpha]_D^{20} = +16.8^\circ\) (c = 0.41, MeOH) \{lit.\(^{11}\) \([\alpha]_D^{20} = +24.2^\circ\) (c = 0.50, MeOH)\}; IR (neat) 3390, 2960, 2925, 2853, 1674, 1455, 1430, 1202, 1139, 799, 721 cm\(^{-1}\); \(^1\)H NMR (700 MHz, MeOH-\(d_4\)) \(\delta\) 3.96 (br t, \(J = 11.2\) Hz, 1H), 3.71-3.74 (m, 2H), 3.45 (br d, \(J = 6.3\) Hz, 1H), 3.35-3.37 (m, 1H), 3.18 (td, \(J = 13.3, 3.5\) Hz, 1H), 3.08 (td, \(J = 14.2, 2.8\) Hz, 1H), 2.33 (ddd, \(J = 11.2, 9.1, 3.5\) Hz, 1H), 2.16-2.25 (m, 2H), 1.93-2.06 (m, 5H), 1.55-1.85 (m, 10H), 1.02 (m, 1H), 1.02 (d, \(J = 6.3\) Hz, 3H); \(^{13}\)C NMR (175 MHz, MeOH-\(d_4\)) \(\delta\) 62.5, 54.2, 51.5, 50.0, 46.0, 39.1, 38.1, 36.4, 31.0, 25.0, 24.7, 23.7, 23.2, 23.1, 21.6, 18.6; HRMS (EI+) calcd. for C\(_{16}\)H\(_{31}\)N\(_2\) (M+H) 251.2487, found 251.2478.

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\[\text{cermizine D} (1.13)\]

\[\text{TFA salt of cermizine D •TFA}\]
Dibromide 6.3.2: To a solution of oxalyl chloride (5.46 g, 3.8 mL, 43.0 mmol) in DCM (94 mL) at -78 °C was cannulated a solution of DMSO (7.03 g, 6.4 mL, 89.9 mmol) in DCM (47 mL). After 15 min, a solution of alcohol 6.2.4\textsuperscript{11} (7.6 g, 39.1 mmol) in DCM (47 mL) was cannulated to it. After 45 min, Et\textsubscript{3}N (19.8 g, 27.2 mL, 195.5 mmol) was added. After 10 min, the cooling bath was removed and the reaction was quenched with H\textsubscript{2}O (100 mL). The aqueous layer was extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 X 60 mL) and the organic phase was washed with sat. aq. NaCl (100 mL). The dried (MgSO\textsubscript{4}) extract was concentrated \textit{in vacuo} to give the crude aldehyde SI-6.

To a solution of PPh\textsubscript{3} (41 g, 156.1 mmol) in DCM (86.4 mL) at 0 °C was added CBr\textsubscript{4} (25.9 g, 78.2 mmol). After 3 min, a solution of crude aldehyde SI-6 (~39.1 mmol) in DCM (27.7 mL) was added. After 30 min, the reaction mixture was warmed to rt. After 13 h, Et\textsubscript{2}O (60 mL) was added causing a lot of precipitation. The precipitate was filtered and (1:1) mixture of Et\textsubscript{2}O:Hexane (50 mL) was added to the filtrate. A precipitate
formed was filtered again, the volume was reduced by 4 times and stored in refrigerator at 0 °C. After 24 h, the precipitate formed was filtered again, the filtrate was concentrated in vacuo and purified by flash chromatography over silica gel, eluting with 3-7% EtOAc / hexanes, to give dibromide 6.3.2 (8.16 g, 23.4 mmol, 60%, 2 steps) as colorless oil: [α]D<sup>23</sup> = +40.6 (c = 0.79, CHCl₃); IR: (neat) 3037, 2921, 2853, 1453, 1373, 1095, 1019, 795, 698 cm<sup>-1</sup>; ¹H NMR (700 MHz, CDCl₃) δ 7.52-7.53 (m, 2H), 7.37-7.42 (m, 3H), 6.63 (d, J = 7.5 Hz, 1H), 5.61 (s, 1H), 4.66 (ddd, J = 10.2, 7.5, 2.7 Hz, 1H), 4.34 (ddd, J = 6.3, 5.0, 1.3 Hz, 1H), 4.06 (td, J = 12.1, 2.5 Hz, 1H), 2.00 (ddd, J = 13.3, 12.4, 11.6, 5.0 Hz, 1H), 1.72 (ddt, J = 13.4, 2.6, 1.5 Hz, 1H); ¹³C NMR (175 MHz, CDCl₃) δ 138.1, 137.9, 129.1, 128.4, 126.1, 101.3, 91.7, 77.9, 66.6, 29.3; HRMS (EI+) calcd. for C₁₂H₁₀Br₂O₂ (M⁺) 345.9204, found 345.9205.

**Alkyne 6.3.3:** To a solution of dibromide 6.3.2 (4.29 g, 12.33 mmol) in THF (39.4 mL) at -78 °C was added °BuLi (10.8 mL, 27.1 mmol, 2.5 M solution in hexanes). The reaction mixture was slowly warmed to rt over 2 h. After an additional 2 h, the reaction was quenched with sat. aq. NH₄Cl (30 mL) and the aqueous layer was extracted with Et₂O (3 X 40 mL). The combined organic phase was washed with sat. aq. NaCl (60 mL). The dried (MgSO₄) extract was concentrated in vacuo and purified by flash chromatography over silica gel, eluting with 5-10% EtOAc / hexanes, to give the known¹²
alkyne 6.3.3 (2.29 g, 12.2 mmol, 99%) as colorless oil: $[\alpha]_D^{23} = -32.6 \text{ (c = 1.25, CHCl}_3$);

IR: (neat) 3287, 2967, 2856, 1455, 1399, 1303, 1119, 1097, 1007, 758, 699 cm$^{-1}$; $^1$H NMR (700 MHz, CDCl$_3$) $\delta$ 7.52-7.54 (m, 2H), 7.35-7.40 (m, 3H), 5.54 (s, 1H), 4.69 (dt, $J = 11.6, 2.4$ Hz, 1H), 4.31 (ddd, $J = 11.7, 4.9, 1.3$ Hz, 1H), 4.00 (td, $J = 12.2, 2.5$ Hz, 1H), 2.57 (d, $J = 2.2$ Hz, 1H), 2.30 (ddddd, $J = 13.6, 12.5, 11.7, 5.0$ Hz, 1H), 1.82 (dddt, $J = 13.6, 2.5, 1.5$ Hz, 1H); $^{13}$C NMR (175 MHz, CDCl$_3$) $\delta$ 137.8, 129.1, 128.3, 126.2, 101.7, 81.6, 73.81, 73.77, 67.3, 66.6, 32.0.

**Ester 6.2.2:**

To a solution of acetal 6.3.3 (3.56 g, 18.9 mmol) in MeOH (72.0 mL) at rt was added p-TSA•H$_2$O (36.0 mg, 0.19 mmol). After 3 h, the reaction was quenched with Et$_3$N (283 mg, 0.4 mL, 2.80 mmol) and the solvent was removed in vacuo to give the crude diol 6.3.4.

To a solution of the crude diol 6.3.4 (~18.9 mmol) in DCM / pyridine (54.0 mL, 2.5:1) at 0 $^\circ$C was added pivaloyl chloride (2.51 g, 2.6 mL, 20.8 mmol). After 1.5 h, DMAP (229 mg, 1.89 mmol) followed by benzoyl chloride (3.32 g, 2.7 mL, 23.6 mmol) were sequentially added and the reaction was warmed to rt. After 2.5 h, the reaction was quenched with sat. aq. NaHCO$_3$ (50 mL) and the aqueous layer was extracted with Et$_2$O (3 X 50 mL). The combined organic phase was washed with sat. aq. NaCl (60 mL). The dried (MgSO$_4$) extract was concentrated in vacuo and purified by flash chromatography.
over silica gel, eluting with 5-10% EtOAc / hexanes, to give the known\textsuperscript{12} ester 6.2.2 (3.98 g, 13.8 mmol, 73% over 2 steps) as colorless oil: \(^1\)H NMR (700 MHz, CDCl\textsubscript{3}) \(\delta\) 8.09-8.10 (m, 2H), 7.61 (tt, \(J = 7.3, 1.3\) Hz, 1H), 7.47-7.50 (m, 2H), 5.76 (td, \(J = 6.7, 2.2\) Hz, 1H), 4.29-4.35 (m, 2H), 2.56 (d, \(J = 2.2\) Hz, 1H), 2.27-2.38 (m, 2H), 1.23 (s, 9H); \(^{13}\)C NMR (175 MHz, CDCl\textsubscript{3}) \(\delta\) 178.4, 165.3, 133.4, 129.8, 129.5, 128.5, 80.3, 74.4, 61.4, 60.1, 38.8, 33.9, 27.2.

Diol (S)-6.4.2. To a solution of dimethylmalate (6.4.1) (10.5 g, 64.8 mmol), in THF (94 mL) was added BH\textsubscript{3}•DMS. After 1 h, NaBH\textsubscript{4} (122.6 mg, 3.24 mmol) was added. After 1 h, the reaction was quenched with MeOH (40 mL). After 20 min, the solvent was concentrated in vacuo and purified by flash chromatography over silica gel, eluting with 2% MeOH / DCM, to give the known\textsuperscript{13} diol (S)-6.4.2 (7.56 g, 56.4 mmol, 87%) as a colorless oil. \(^1\)H NMR (400 MHz, MeOH-d\textsubscript{4}) \(\delta\) 4.00-4.10 (m, 1 H), 3.70 (s, 3 H), 3.45-3.56 (m, 2 H), 3.37 (s, 2 H), 2.60 (dd, \(J = 15.6, 4.6\) Hz, 1 H), 2.42 (dd, \(J = 15.57, 8.55\) Hz, 1 H); \(^{13}\)C NMR (100 MHz, MeOH-d\textsubscript{4}) \(\delta\) 172.5, 68.7, 65.2, 50.7, 38.2.

Alcohol 6.4.3. To a solution of diol (S)-6.4.2 (450 mg, 3.4 mmol), in DCM (7.4 mL) at 0 °C was added Et\textsubscript{3}N (450 mg, 0.65 mL, 4.4 mmol) followed by TBSCI (560 mg,
3.7 mmol). After 5 min, the reaction mixture was warmed to rt. After 10 min, DMAP (45 mg, 0.2 mmol) was added. After 12 h, the reaction was quenched with solution of sat. aq. NH₄Cl (10 mL) and the aqueous layer was extracted with EtOAc (3 X 10 mL). The dried (MgSO₄) extract was concentrated in vacuo and purified by flash chromatography over silica gel, eluting with 30-50% Et₂O / hexanes, to give the alcohol 6.4.3 (793 mg, 3.2 mmol, 94%) as a colorless oil. \([\alpha]_{D}^{20} = -9.7 (c = 1.12, \text{CHCl}_3)\); \(^1\)H NMR (700 MHz, CDCl₃) \(\delta\) 4.05-4.12 (m, 1 H) 3.72 (s, 3 H) 3.64 (dd, \(J = 10.1, 4.8\) Hz, 1 H) 3.57-3.61 (m, 1 H) 2.90 (d, \(J = 4.9\) Hz, 1 H) 2.48-2.57 (m, 2 H) 0.91 (s, 9 H), 0.08 (s, 3 H) 0.08 (s, 3 H); \(^{13}\)C NMR (175 MHz, CDCl₃) \(\delta\) 172.5, 68.6, 66.2, 51.7, 37.8, 25.8, 18.3, -5.44, -5.46.

**Ester ent-6.2.5.** To a solution of alcohol 6.4.3 (560 mg, 23 mmol), in DCM (5.6 mL) at 0 °C was added 2,6-lutidine (480 mg, 0.52 mL, 4.5 mmol) followed by TESOTf (894 mg, 0.73 mL, 33.8 mmol). After 10 min, the reaction mixture was warmed to rt. After 20 min, the reaction was quenched with solution of sat. aq. NH₄Cl (10 mL) and the aqueous layer was extracted with EtOAc (3 X 20 mL). The dried (MgSO₄) extract was concentrated in vacuo and purified by flash chromatography over silica gel, eluting with 15-25% EtOAc / hexanes, to give ester ent-6.2.5 (798 mg, 2.2 mmol, 98%) as a colorless oil. \(^1\)H NMR (700 MHz, CDCl₃) \(\delta\) 4.18 (tt, \(J = 7.5, 4.8\) Hz, 1 H) 3.70 (s, 3 H) 3.63 (dd, \(J = 9.9, 5.2\) Hz, 1 H) 3.44 (dd, \(J = 9.9, 7.2\) Hz, 1 H) 2.68 (dd, \(J = 15.0, 4.5\) Hz, 1 H) 2.41
(dd, J = 15.0, 7.9 Hz, 1 H) 0.97 (t, J = 7.9 Hz, 9 H) 0.91 (s, 9 H) 0.62 (q, J = 8.1 Hz, 6 H) 0.08 (s, 6 H); 13C NMR (175 MHz, CDCl3) δ 172.3, 70.2, 67.1, 51.4, 40.1, 25.9, 18.3, 6.8, 6.7, 6.4, 4.5, -5.40, -5.44.

Aldehyde 6.4.4. To a solution of alcohol ent-6.2.5 (400 mg, 1.1 mmol), in DCM (11 mL) at -78 °C was added DIBAL-H (1.2 mL, 1.2 mmol, 1 M solution in hexanes). After 20 min, the reaction was quenched with MeOH (5 mL). After 5 min, the reaction was warmed to 0 °C and was added aq. sat. solution of Rochelle’s salt (25 mL). After 3 h, the aqueous layer was extracted with DCM (3 X 20 mL). The dried (MgSO4) extract was concentrated in vacuo and purified by flash chromatography over silica gel, eluting with 10-15% Et2O / hexanes, to give unstable aldehyde 6.4.4 (322 mg, 1.0 mmol, 89%) as a colorless oil.

Iodide ent-6.2.3. To suspension of CrCl2 (66.4 mg, 0.54 mmol) in THF (0.38 mL) at 0 °C was added CHI3 (71 mg, 0.18 mmol) followed by a solution of aldehyde 6.4.4 (20 mg, 0.06 mmol) in THF (0.15 mL). After 3 h, the reaction was quenched with H2O (5 mL), the suspension was filtered through celite and the aqueous layer was extracted with EtOAc (3 X 10 mL). The dried (MgSO4) extract was concentrated in vacuo and purified by flash chromatography over silica gel, eluting with 2-10% Et2O / hexanes, to give 3:1, E:Z mixtures of iodide ent-6.2.3 (11.5 mg, 0.03 mmol, 42%) as a pale yellow oil. 1H NMR (700 MHz, CDCl3) δ 6.58 (ddd, J = 14.4, 8.2, 7.1 Hz, 4 H, E-isomer) 6.32 - 6.36
(m, 1 H, Z-isomer) 6.24-6.32 (m, 1 H, Z-isomer) 6.07 (dt, J = 14.4, 1.2 Hz, 4 H, E-isomer) 3.83 (tt, J = 6.4, 5.2 Hz, 1 H, Z-isomer) 3.73 (tt, J = 6.9, 4.8 Hz, 4 H, E-isomer) 3.57 (dd, J = 10.0, 5.3 Hz, 1 H, Z-isomer) 3.55 (dd, J = 9.9, 5.0 Hz, 4 H, E-isomer) 3.46 (dd, J = 14.9, 6.4, 5.1, 1.4 Hz, 1 H, Z-isomer) 2.38 (dddd, J = 14.2, 7.1, 4.4, 1.5 Hz, 4 H, E-isomer) 2.30-2.35 (m, 1 H, Z-isomer) 2.18 (dddd, J = 14.1, 8.2, 6.8, 1.2 Hz, 4 H, E-isomer) 0.98 (t, J = 8.0 Hz, 45 H, E & Z-isomers) 0.93 (m, 9 H, Z-isomer) 0.92 (s, 36 H, E-isomer) 0.59-0.66 (m, 30 H, E & Z-isomers) 0.09 (s, 3 H, Z-isomer) 0.08 (s, 3 H, Z-isomer) 0.07 (s, 12 H, E-isomer) 0.07 (s, 12 H, E-isomer); $^{13}$C NMR (175 MHz, CDCl$_3$) δ 143.1, 138.0, 83.7, 76.6, 71.82, 71.75, 67.06, 66.69, 40.92, 39.84, 25.99, 25.93, 18.3, 6.8, 4.9, 4.8, -5.4.

**Enyne 6.5.1:** To a suspension of Pd(PPh$_3$)$_4$ (26 mg, 22.5 µmol) and CuI (8.6 mg, 45 µmol) in $i$-Pr$_2$NH (15 mL) at 0 °C were added a solution of vinyl iodide ($E$:$Z$ = 3:1) ent-6.2.3 (206 mg, 0.45 mmol) in $i$-Pr$_2$NH (0.3 mL) followed by a solution of alkyne 6.2.2 (130 mg, 0.45 mmol) in $i$-Pr$_2$NH (0.3 mL). After 75 min, the reaction was quenched with aq. NH$_4$Cl (10 mL) solution and extracted with ether (3 x 10 mL). The combined organic phase was washed with sat. aq. NaCl (30 mL). The dried (MgSO$_4$) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 5-
20% Et₂O/hexanes to obtain 7:1 (E:Z) mixture of enyne 6.5.1 (230 mg, 0.38 mmol, 84%) as a pale yellow oil. ¹H NMR (700 MHz, CDCl₃) δ 8.09 (dd, J = 8.4, 1.3 Hz, 2 H) 7.58 - 7.62 (m, 1 H) 7.47 (t, J = 8.0 Hz, 2 H) 6.51 (m, 1 H) 5.89 (td, J = 6.6, 1.8 Hz, 1 H) 5.55 (dq, J = 16.0 1.5 Hz, 1 H) 4.30 (td, J = 6.4, 2.2 Hz, 2 H) 3.70-3.76 (m, 1 H) 3.54 (dd, J = 10.0, 5.1 Hz, 1 H) 3.42 (dd, J = 10.0, 6.9 Hz, 1 H) 2.43 (ddd, J = 14.1, 6.9, 5.0, 1.6 Hz, 1 H) 2.29-2.37 (m, 1 H) 2.20-2.29 (m, 2 H) 1.22 (s, 9 H) 0.97 (t, J = 8.0 Hz, 9 H) 0.91 (s, 9 H) 0.58-0.64 (m, 6 H) 0.06 (s, 3 H) 0.66 (s, 3 H); ¹³C NMR (175 MHz, CDCl₃) δ 178.4, 165.4, 142.8, 133.2, 129.8, 128.4, 110.8, 84.9, 84.2, 72.3, 66.8, 62.8, 60.4, 38.8, 38.3, 34.3, 27.2, 25.9, 18.3, 6.8, 4.9, -5.4.

**Acetonide enyne 6.6.2:** To a solution of enyne 6.5.1 (50 mg, 81 µmol) in THF (0.7 mL) was added TBAF (0.16 mL, 0.16 mmol, 1 M solution in THF). After 12 h, reaction was quenched with aq. NH₄Cl (5 mL) solution and extracted with ether (3 x 5 mL). The combined organic phase was washed with sat. aq. NaCl (20 mL). The dried (MgSO₄) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 20-50% EtOAc/hexanes to obtain diol 6.6.2 (20 mg, 51 µmol, 63%) as colorless oil.

To a solution of diol 6.6.2 (20 mg, 51 µmol) in DCM (0.5 mL) was added dimethoxypropane (41.6 mg, 50 µL, 0.4 mmol) followed by pTSA•H₂O (1.5 mg, 8
µmol). After 6 h, reaction was quenched with Et₃N (0.5 mL) and directly loaded on column to purify by chromatography over silica gel, eluting with 5-20% EtOAc/hexanes to obtain acetonide 6.6.2 (21 mg, 48.5 µmol, 95%) as colorless oil. [α]D²⁰ = -13.8° (c = 1.60, CHCl₃); IR (neat) 2980, 2933, 2872, 1727, 1602, 1452, 1369, 1265, 1154, 1068, 712 cm⁻¹; ¹H NMR (700 MHz, CDCl₃) δ 8.09 (dd, J = 8.4, 1.3 Hz, 2 H) 7.58-7.62 (m, 1 H) 7.45-7.50 (m, 2 H) 6.19 (dt, J = 15.9, 7.3 Hz, 1 H) 5.87 (td, J = 6.7, 1.7 Hz, 1 H) 5.62 (dq, J = 16.0, 1.6 Hz, 1 H) 4.30 (td, J = 6.4, 1.8 Hz, 2 H) 4.16 (quin, J = 6.3 Hz, 1 H) 4.05 (dd, J = 8.2, 6.0 Hz, 1 H) 3.58 (dd, J = 8.2, 6.7 Hz, 1 H) 2.43-2.49 (m, 1 H) 2.30-2.38 (m, 2 H) 2.24-2.30 (m, 1 H) 1.43 (s, 3 H) 1.36 (s, 3 H) 1.22 (s, 9 H); ¹³C NMR (175 MHz, CDCl₃) δ 178.5, 165.4, 140.8, 133.3, 129.8, 129.7, 128.4, 111.5, 109.2, 85.0, 84.3, 74.7, 68.8, 62.1, 60.3, 38.8, 37.4, 34.2, 27.2, 26.9, 25.6; HRMS (ES+) calcd. for C₂₅H₃₂O₆Na (M+Na) 451.2097, found 451.2098.

Alcohol 6.6.3: To a solution of enyne 6.5.1 (51 mg, 83 µmol) in DCM (0.83 mL) was added pTSA•H₂O (1.5 mg, 8 µmol). After 6 h, reaction was quenched with Et₃N (0.5 mL) and directly loaded on column to purify by chromatography over silica gel, eluting with 20-50% EtOAc/hexanes to obtain alcohol 6.6.3 (35.2 mg, 82 µmol, 99%) as colorless oil.
**Acetonide enyne 6.6.2:** To a solution of alcohol 6.6.3 (35.2 mg, 82 µmol) in DCM (0.8 mL) was added dimethoxypropane (67.2 mg, 80 µL, 0.64 mmol) followed by pTSA•H₂O (2.4 mg, 13 µmol). After 12 h, reaction was quenched with Et₃N (0.5 mL) and directly loaded on column to purify by chromatography over silica gel, eluting with 5-20% EtOAc/hexanes to obtain acetonide 6.6.2 (34.5 mg, 80.5 µmol, 97%) as colorless oil.

**Acetonide enyne 6.6.2:** To a solution of enyne 6.5.1 (27 mg, 44 µmol) in DCM (0.44 mL) was added dimethoxypropane (45.6 mg, 54 µL, 0.44 mmol) followed by pTSA•H₂O (1.6 mg, 8.8 µmol). After 12 h, reaction was quenched with Et₃N (0.5 mL) and directly loaded on column to purify by chromatography over silica gel, eluting with 5-20% EtOAc/hexanes to obtain acetonide 6.6.2 (18 mg, 42 µmol, 95%) as colorless oil.

**Acetonide 6.7.1:** To a solution of known¹³ diol (R)-6.4.2 (1.7 g, 12.7 mmol) in DCM (127 mL) was added dimethoxypropane (6.6 g, 7.8 mL, 63.4 mmol) followed by (-)-camphor sulfonic acid (CSA) (294 mg, 1.27 mmol). After 12 h, reaction was quenched with Et₃N (5 mL). Solvent was concentrated in vacuo and directly loaded on column to
purify by chromatography over silica gel, eluting with 5-20% EtOAc/Hexanes to obtain acetonide ester 6.7.1 (1.66 g, 9.5 mmol, 75%) as colorless oil. $^1$H NMR (700 MHz, CDCl$_3$) $\delta$ 4.44-4.50 (m, 1 H) 4.16 (ddt, $J = 8.4$, 6.1, 1.1 Hz, 1 H) 3.70 (s, 3 H) 3.65 (dddd, $J = 8.4$, 6.3, 2.1, 1.0 Hz, 1 H) 2.72 (ddt, $J = 15.9$, 6.4, 1.2 Hz, 1 H) 2.53 (dd, $J = 16.0$, 7.1 Hz, 1 H) 1.41 (s, 3 H) 1.36 (s, 3 H) ppm; $^{13}$C NMR (175 MHz, CDCl$_3$) $\delta$ 171.0, 109.2, 72.0, 69.1, 51.8, 38.8, 26.9, 25.6.

**Alcohol 6.7.2.** To a solution of ester 6.7.1 (295 mg, 1.69 mmol), in DCM (12 mL) at -78 °C was added DIBAL-H (3.7 mL, 3.7 mmol, 1 M solution in hexanes). After 10 min, the reaction was warmed to 0 °C. After 1 h, the reaction was quenched with MeOH (5 mL). After 5 min, the reaction was warmed to rt and was added aq. sat. solution of Rochelle’s salt (25 mL). After 3 h, the aqueous layer was extracted with EtOAc (3 X 20 mL). The dried (MgSO$_4$) extract was concentrated in vacuo and purified by flash chromatography over silica gel, eluting with 30-45% Et$_2$O / hexanes, to give the known$^{14}$ alcohol 6.7.2 (245 mg, 1.67 mmol, 99%) as a colorless oil. $^1$H NMR (700 MHz, CDCl$_3$) $\delta$ 4.30 (quintet, $J = 7.0$ Hz, 1 H) 4.12 t, $J = 7.0$ Hz, 1 H) 3.82-3.85 (m, 2 H), 3.62 (t, $J = 7.7$ Hz, 1 H), 2.23-2.26 (m, 1H), 1.84-1.87 (m, 2H), 1.45 (s, 3H), 1.39 (s, 3H); $^{13}$C NMR (175 MHz, CDCl$_3$) $\delta$ 109.1, 75.2, 69.5, 60.7, 35.6, 26.9, 25.7.
Alcohol 6.7.2. To a solution of triol **(R)**-6.3.1 (110 mg, 1.04 mmol) in DCM (1.6 mL) was added dimethoxypropane (433 mg, 0.51 mL, 4.2 mmol) followed by camphor sulfonic acid (CSA) (24 mg, 0.1 mmol). After 24 h, reaction was quenched with Et$_3$N (3 mL). Solvent was concentrated in vacuo and directly loaded on column to purify by chromatography over silica gel, eluting with 30-45% Et$_2$O / hexanes, to give the alcohol 6.7.2 (245 mg, 1.67 mmol, 53%, 95% brsm) as a colorless oil.

Iodide 6.7.3. To a solution of known$^{16}$ alcohol 6.7.2 (2.14 g, 6.9 mmol), in DCM (28.6 mL) was added 3Å molecular sieves (1.45 g, ground) followed by PCC (2.97 g, 13.8 mmol). After 5 min, the reaction mixture was filtered through silica gel and concentrated in vacuo to yield the known$^{17}$ crude aldehyde SI-7. The crude aldehyde SI-7 was immediately used in the next step.

To a flame dried flask containing CrCl$_3$ (6.6 g, 41.4 mmol), Zn (1.35 g, 20.7 mmol) and NaI (5.2 g, 34.5 mmol) was added THF (20.7 mL).$^{18}$ The slurry was stirred for 16 h. Next, CHI$_3$ (4.2g, 10.35 mmol) was added. After 1 min, a solution of crude aldehyde SI-7 (~6.9 mmol) in THF (121 mL) was added. After 10 min, the reaction was quenched with pyridine (20 mL). After 20 min, a solution of sat. aq. NaCl (100 mL) and the aqueous layer was extracted with EtOAc (3 X 60 mL). The dried (MgSO$_4$) extract
was concentrated *in vacuo* and purified by flash chromatography over silica gel, eluting with 5-20% Et$_2$O / hexanes, to give the known\textsuperscript{19} iodide 6.7.3 as a 5:1 (E:Z) mixture (907 mg, 3.4 mmol, 49% over 2 steps) as a pale yellow oil. [\(\alpha\)]$_D^{20}$ = -4.8° (c = 1.2, CHCl$_3$); IR (neat) 3055, 2984, 1607, 1370, 1213, 1154, 1064, 949 cm$^{-1}$; $^1$H NMR (700 MHz, CDCl$_3$) 6.56 (ddd, $J$ = 14.6, 7.6, 7.1 Hz, 1H, (E-isomer)), 6.41 (dt, $J$ = 7.5, 1.4 Hz, 0.15H, (Z-isomer)), 6.29-6.32 (m, 0.15H, (Z-isomer)), 6.19 (dt, $J$ = 14.5, 1.4 Hz, 1H, (E-isomer)), 4.27 (quint, $J$ = 6.3 Hz, 0.15H, (Z-isomer)), 4.18 (quint, $J$ = 6.2 Hz, 1H, (E-isomer)), 4.08 (dd, $J$ = 8.2, 6.1 Hz, 0.15H, (Z-isomer)), 4.06 (dd, $J$ = 8.2, 6.1 Hz, 1H, (E-isomer)), 3.65 (dd, $J$ = 8.2, 6.9 Hz, 0.15H, (Z-isomer)), 3.60 (dd, $J$ = 8.2, 6.7 Hz, 1H, (E-isomer)), 2.46-2.49 (m, 0.3H, (Z-isomer)), 2.37-2.41 (m, 1H, (E-isomer)), 2.30-2.34 (m, 1H, (E-isomer)), 1.47 (s, 0.45H, (Z-isomer)), 1.44 (s, 3H, (E-isomer)), 1.39 (s, 0.45H, (Z-isomer)), 1.38 (s, 3H, (E-isomer)); $^{13}$C NMR (175 MHz, CDCl$_3$) 141.4, 136.5, 109.3, 109.2, 85.1, 77.6, 74.2, 68.7, 68.6, 40.1, 38.8, 26.9, 26.8, 25.6.

**Enyne 6.8.1:** To a suspension of Pd(PPh$_3$)$_4$ (188 mg, 0.16 mmol) and CuI (62 mg, 0.33 mmol) in i-Pr$_2$NH (10.8 mL) at 0 °C were added a solution of vinyl iodide (E:Z = 5:1) 6.7.3 (872 mg, 3.26 mmol) in i-Pr$_2$NH (2.2 mL) followed by a solution of alkyne 6.2.2 (938 mg, 3.26 mmol) in i-Pr$_2$NH (2.2 mL). After 60 min, the reaction was quenched with aq. NH$_4$Cl (15 mL) solution and extracted with ether (3 x 15 mL). The combined organic phase was washed with sat. aq. NaCl (30 mL). The dried (MgSO$_4$) extract was
concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 5-20% Et₂O / Hexanes to obtain 5:1 ($E$:$Z$) mixture of enyne **6.8.1** (1.38 g, 3.22 mmol, 99%) as a pale yellow oil. [α]$_D^{20}$ = −16.5° ($c$ = 1.85, CHCl$_3$); IR (neat) 2979, 2937, 2222, 1726, 1453, 1369, 1265, 1154, 1068, 712 cm$^{-1}$; $^1$H NMR (700 MHz, CDCl$_3$) δ 8.08-8.10 (m, 2H, ($E$-isomer)), 8.06-8.07 (m, 0.4H, ($Z$-isomer)), 7.59-7.62 (m, 1.2H (mixed isomers)), 7.47-7.49 (m, 2.4H, mixed isomers), 6.19 (dt, $J$ = 15.9, 7.3 Hz, 1H, ($E$-isomer)), 6.05 (dt, $J$ = 10.8, 7.4 Hz, 0.2H, ($Z$-isomer)), 5.87 (td, $J$ = 6.6, 1.7 Hz, 1H, ($E$-isomer)), 5.89-5.91 (m, 0.2H, ($Z$-isomer)), 5.62 (dq, $J$ = 16.0, 1.6 Hz, 1H, ($E$-isomer)), 5.65 (dq, $J$ = 10.9, 1.5 Hz, 0.2H, ($Z$-isomer)), 4.28-4.31 (m, 2.4H, (mixed isomers)), 4.21 (m, 0.2H, ($Z$-isomer)), 4.16 (quint, $J$ = 6.4 Hz, 1H, ($E$-isomer)), 4.06 (dd, $J$ = 8.2, 6.0 Hz, 1H ($E$-isomer)), 4.04 (dd, $J$ = 8.1, 6.0 Hz, 0.2H, ($Z$-isomer)), 3.58 (dd, $J$ = 8.2, 6.8, 1H, ($E$-isomer)), 3.61 (dd, $J$ = 8.2, 6.9 Hz, 0.2H, ($Z$-isomer)), 2.44-2.49 (m, 1H, ($E$-isomer)), 2.61 (ddd, $J$ = 7.6, 6.2, 1.4 Hz, 0.2H, ($Z$-isomer)), 2.25-2.38 (m, 3.6H, mixed isomers), 1.44 (s, 3H, ($E$-isomer)), 1.42 (s, 0.6H, ($Z$-isomer)), 1.369 (s, 3H, ($E$-isomer)), 1.365 (s, 0.6H, ($Z$-isomer)), 1.23 (s, 10.8H, mixed isomers); $^{13}$C NMR (175 MHz, CDCl$_3$) δ 178.4, 165.4, 140.8, 133.3, 129.8, 129.7, 128.4, 111.5, 109.2, 85.0, 84.3, 74.8, 74.7, 68.82, 68.79, 62.1, 60.3, 38.8, 37.4, 34.2, 27.2, 26.9, 25.6; HRMS (ES+) calcd. for C$_{25}$H$_{32}$O$_6$Na (M+Na) 451.2097, found 451.2092.
Diol 6.8.2: To a solution of enyne 6.8.1 (1.15 g, 2.7 mmol), in a 1:1 mixture (54 mL) of tBuOH and H2O was added AD mix β<sup>20</sup> (3.74 g) followed by MeSO<sub>2</sub>NH<sub>2</sub> (255mg, 2.7 mmol) at rt. After 20 h, the reaction was quenched with Na<sub>2</sub>SO<sub>3</sub> (4.25 g) and extracted with EtOAc (3 x 50 mL). The dried (MgSO<sub>4</sub>) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 80-100% Et<sub>2</sub>O/hexanes to obtain diol 6.8.2 (887 mg, 1.92 mmol, 71%) as a colorless oil. [α]<sup>D</sup><sub>20</sub> = -16.1° (c = 1.74, CHCl<sub>3</sub>); IR (neat) 3436, 3066, 2981, 2937, 2869, 1726, 1480, 1370, 1266, 1155, 1096, 1069, 713 cm<sup>-1</sup>; <sup>1</sup>H NMR (700 MHz, CDCl<sub>3</sub>) δ 8.06 (d, J = 7.6 Hz, 2H), 7.61 (t, J = 7.4 Hz, 1H), 7.48 (t, J = 7.4 Hz, 2H), 5.73 (t, J = 6.7 Hz, 1H) 4.34-4.36 (m, 2H), 4.32 (t, J = 5.6 Hz, 1H), 4.25-4.28 (m, 1H), 4.11 (t, J = 7.0 Hz, 1H) 3.91-3.92 (m, 1H), 3.59 (t, J = 7.7 Hz, 1H), 3.00 (d, J = 4.2 Hz, 1H), 2.87 (d, J = 6.4 Hz, 1H), 2.24-2.35 (m, 2H), 1.90-1.93 (m, 1H), 1.79-1.83 (m, 1H), 1.40 (s, 3H), 1.37 (s, 3H), 1.22 (s, 3H); <sup>13</sup>C NMR (175 MHz, CDCl<sub>3</sub>) δ 178.5, 165.4, 133.4, 129.8, 129.4, 128.5, 109.1, 84.6, 83.1, 73.3, 72.1, 69.6, 66.1, 61.6, 60.1, 38.8, 36.1, 33.9, 27.2, 26.9, 25.7; HRMS (ES+) calcd. for C<sub>25</sub>H<sub>34</sub>O<sub>8</sub>Na (M+Na) 485.2151, found 485.2144.
Dihydrofuran 6.2.6: To a solution of diol 6.8.2 (21 mg, 0.043 mmol) in benzene (0.43 mL) was added AgBF$_4$ (0.85 mg, 4.3 µmol). The reaction mixture was refluxed in dark. After 105 min, the reaction mixture was cooled down to 0 °C and diluted with DCM (0.43 mL). To the mixture were sequentially added 2,6-lutidine (18.4 mg, 20 µL, 0.172 mmol) followed by TBSOTf (23 mg, 20 µL, 86 µmol). After 30 min, the reaction was quenched with aq. sat. NH$_4$Cl (5 mL) and extracted with DCM (3 x 5 mL). The dried (MgSO$_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 0-30% EtOAc/Hexanes to obtain the dihydrofuran 6.2.6 (8.7 mg, 15.1 µmol, 35%) as colorless oil along with furan by product 6.2.7 (7.6 mg, 17.2 µmol, 40%) as colorless oil as well.

**Dihydrofuran 6.2.6:** $[\alpha]_D^{20} = +11.8^\circ$ ($c = 1.00$, CHCl$_3$); IR (neat) 2957, 2929, 2856, 1749, 1730, 1473, 1454, 1260, 1157, 1061, 1024, 836, cm$^{-1}$; $^1$H NMR (700 MHz, CDCl$_3$) $\delta$ 8.11-8.13 (m, 2H), 7.65 (tt, $J = 7.4$, 1.2 Hz, 1H), 7.49-7.52 (m, 2H), 6.08 (t, $J = 1.7$ Hz, 1H), 4.99-5.01 (m, 1H), 4.84 (dt, $J = 3.9$, 2.1 Hz, 1H), 4.21-4.32 (m, 3H), 4.07-4.11 (m, 2H), 3.54 (t, $J = 7.7$ Hz, 1H), 2.03-2.07 (m, 1H), 1.96-2.01 (m, 1H), 1.89 (ddd, $J = 12.4$, 8.9, 3.4 Hz, 1H), 1.76 (ddd, $J = 13.3$, 9.0, 3.8 Hz, 1H), 1.43 (s, 3H), 1.37 (s, 3H), 1.23 (s, 9H), 0.87 (s, 9H), 0.12 (s, 3H), 0.05 (s, 3H); $^{13}$C NMR (175 MHz, CDCl$_3$) $\delta$ 178.5, 163.3, 145.4, 133.8, 130.1, 129.0, 128.6, 112.6, 108.8, 84.7, 80.4, 72.6, 70.0, 69.7,
61.2, 38.7, 37.4, 35.8, 27.2, 27.1, 26.0, 25.8, 18.2; HRMS (ES+) calcd. for C$_{31}$H$_{48}$O$_8$SiNa (M+Na) 599.3016 found 599.3032.

**Furan 6.2.7:** [α]$_D^{20}$ = -37.4° (c = 1.43, CHCl$_3$); IR (neat) 2979, 2931, 2872, 1727, 1452, 1369, 1266, 1154, 1067, 711 cm$^{-1}$; $^1$H NMR (700 MHz, CDCl$_3$) δ 8.06-8.07 (m, 2H), 7.58 (t, J = 7.4 Hz, 1H), 7.46 (t, J = 7.8 Hz, 2H), 6.37 (d, J = 3.2 Hz, 1H), 6.20 (dd, J = 7.7, 6.4 Hz, 1H), 6.09 (d, J = 3.1 Hz, 1H), 4.35-4.39 (m, 1H), 4.19-4.23 (m, 1H), 4.13-4.16 (m, 1H), 4.07 (dd, J = 8.2, 6.0 Hz, 1H), 3.73 (dd, J = 8.2, 6.6 Hz, 1H), 3.02 (dd, J = 15.0, 5.5 Hz, 1H), 2.85 (dd, J = 15.1, 7.4 Hz, 1H), 2.47-2.51 (m, 1H), 2.38-2.43 (m, 1H), 1.42 (s, 3H), 1.37 (s, 3H), 1.22 (s, 9H); $^{13}$C NMR (175 MHz, CDCl$_3$) δ 178.4, 165.6, 152.1, 150.7, 133.1, 130.0, 129.7, 128.4, 110.0, 109.3, 107.7, 74.2, 69.0, 66.2, 60.5, 38.8, 32.7, 31.8, 21.1, 26.9, 25.6; HRMS (ES+) calcd. for C$_{25}$H$_{32}$O$_7$Na (M+Na) 467.2046 found 467.2034.

![Furan reaction diagram](image)

**Methyl benzoate 6.11.2:** To a solution of enyne 6.8.1 (115 mg, 0.27 mmol) in MeOH (7.5 mL) was added K$_2$CO$_3$ (75.1 mg, 0.54 mmol). After 1 h, the reaction mixture was filtered through silica gel plug and concentrated *in vacuo* to yield the crude alcohol 6.11.1.

To a solution of crude alcohol 6.11.1 (~0.27 mmol) in DCM (2.7 mL) at 0 °C was added DMAP (8.2 mg, 67 µmol) followed by *p*-methyl benzyol chloride (62 mg, 53 µL,
0.40 mmol). After 5 min, the reaction mixture was warmed to rt. After 1 h, the reaction was quenched with sat. aq. NaHCO$_3$ (10 mL) and extracted with DCM (3 x 10 mL). The combined organic phase was washed with sat. aq. NaCl (20 mL). The dried (MgSO$_4$) extract was concentrated in vacuo and purified by column chromatography over silica gel, eluting with 5-15% EtOAc/Hexanes to obtain the methyl benzoate ester 6.11.2 (97.4 mg, 0.22 mmol, 81%, 2 steps) as a colorless oil. [$\alpha$]$_D^{20} = -4.9^\circ$ (c = 1.18, CHCl$_3$); IR (neat) 2981, 2937, 1726, 1266, 1094, 1068, 753 cm$^{-1}$; $^1$H NMR (700 MHz, CDCl$_3$) $\delta$ 7.97 (d, $J = 8.2$ Hz, 2H), 7.27 (d, $J = 7.9$ Hz, 2H), 6.18 (dt, $J = 15.8$, 7.3 Hz, 1H), 5.85 (td, $J = 6.6$, 1.5 Hz, 1H), 5.61 (dq, $J = 15.9$, 1.5 Hz, 1H), 4.28-4.31 (m, 2H), 4.15 (quint, $J = 6.4$ Hz, 1H), 4.05 (dd, $J = 8.1$, 6.0 Hz, 1H), 3.58 (dd, $J = 8.1$, 6.8 Hz, 1H), 2.43-2.48 (m, 1H), 2.44 (s, 3H), 2.24-2.37 (m, 3H), 1.43 (s, 3H), 1.37 (s, 3H), 1.22 (s, 9H); $^{13}$C NMR (175 MHz, CDCl$_3$) $\delta$ 178.5, 165.4, 144.0, 140.7, 129.9, 129.1, 127.0, 111.5, 109.2, 85.1, 84.2, 74.7, 68.8, 61.9, 60.4, 38.8, 37.4, 34.2, 27.2, 26.9, 25.6, 21.7; HRMS (EI+) calcd. for C$_{26}$H$_{34}$O$_6$Na (M+Na) 465.2253, found 465.2234.

Methoxybenzoate 6.11.3: To a solution of enyne 6.8.1 (37 mg, 0.086 mmol) in MeOH (2.4 mL) was added K$_2$CO$_3$ (24 mg, 0.17 mmol). After 1 h, the reaction mixture
was filtered through silica gel plug and concentrated in vacuo to yield the crude alcohol 11.

To a solution of crude alcohol 6.11.1 (~0.086 mmol) in DCM (0.85 mL) and Et$_3$N (0.25 mL, 0.18 g, 1.8 mmol) at 0 °C was added DMAP (2.6 mg, 21 µmol) followed by p-methoxybenzoyl chloride (22 mg, 0.13 mmol). After 5 min, the reaction mixture was warmed to rt. After 1 h, the reaction was heated to reflux. After 12 h, reaction was cooled down to rt and quenched with sat. aq. NaHCO$_3$ (5 mL) and extracted with DCM (3 x 5 mL). The combined organic phase was washed with sat. aq. NaCl (10 mL). The dried (MgSO$_4$) extract was concentrated in vacuo and purified by column chromatography over silica gel, eluting with 5-15% EtOAc/Hexanes to obtain the methoxybenzoate ester 6.11.3 (25 mg, 0.055 mmol, 65%, 2 steps) as colorless oil. $^1$H NMR (700 MHz, CDCl$_3$) δ 8.04 (d, $J$ = 9.1 Hz, 2 H) 6.94 (d, $J$ = 8.9 Hz, 2 H) 6.18 (dt, $J$ = 15.9, 7.3 Hz, 1 H) 5.84 (td, $J$ = 6.6, 1.6 Hz, 1 H) 5.61 (dq, $J$ = 15.9, 1.6 Hz, 1 H) 4.28 (td, $J$ = 6.4, 2.4 Hz, 2 H) 4.15 (quin, $J$ = 6.3 Hz, 1 H) 4.05 (dd, $J$ = 8.2, 6.0 Hz, 1 H) 3.89 (s, 3 H) 3.57 (dd, $J$ = 8.2, 6.7 Hz, 1 H) 2.43 - 2.49 (m, 1 H) 2.33 - 2.38 (m, 1 H) 2.28 - 2.33 (m, 1 H) 2.22 - 2.28 (m, 1 H) 1.43 (s, 3 H) 1.36 (s, 3 H) 1.22 (s, 9 H); HRMS (EI+) calcd. for C$_{26}$H$_{34}$O$_7$Na (M+Na) 481.2202, found 481.2197.
**Diol 6.11.4** To a solution of enyne 6.11.2 (236 mg, 0.53 mmol), in a 1:1 mixture (5.2 mL) of tBuOH and H₂O was added AD mix β₂0 (720 mg) followed by MeSO₂NH₂ (50 mg, 0.53 mmol) at rt. After 20 h, the reaction was quenched with Na₂SO₃ (750 mg) and extracted with EtOAc (3 x 10 mL). The dried (MgSO₄) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 80-100% Et₂O/hexanes to obtain diol 6.11.4 (202 mg, 0.42 mmol, 80%) as a colorless oil. [α]_D^{20} = -13.4° (c = 1.60, CHCl₃); IR (neat) 3440, 2981, 2933, 1726, 1612, 1268, 1155, 1095, 1069, 753 cm⁻¹; ^1H NMR (700 MHz, CDCl₃) δ 7.94 (d, J = 8.2 Hz, 2H), 7.27 (d, J = 8.2 Hz, 2H), 5.71 (t, J = 6.8 Hz, 1H), 4.33-4.37 (m, 2H), 4.31 (t, J = 6.0 Hz, 1H), 4.24-4.28 (m, 1H), 4.11 (dd, J = 8.2, 6.0 Hz, 1H), 3.89-3.92 (m, 1H), 3.59 (dd, J = 8.2, 7.3 Hz, 1H), 3.01-3.02 (m, 1H), 2.90-2.91 (m, 1H), 2.44 (s, 3H), 2.29-2.35 (m, 1H), 2.23-2.28 (m, 1H), 1.89-1.93 (m, 1H), 1.77-1.82 (m, 1H), 1.40 (s, 3H), 1.37 (s, 3H), 1.22 (s, 9H); ^13C NMR (175 MHz, CDCl₃) δ 178.5, 165.5, 144.3, 129.8, 129.2, 126.7, 109.0, 84.5, 83.3, 73.3, 72.1, 69.6, 66.1, 61.4, 60.1, 38.8, 36.1, 33.9, 27.2, 26.9, 25.7, 21.7; HRMS (ES+) calcd. for C_{26}H_{36}O₈Na (M+Na) 499.2308, found 499.2300.
Diol 6.11.5: To a solution of enyne 6.11.3 (41 mg, 0.089 mmol), in a 1:1 mixture (0.88 mL) of tBuOH and H₂O was added AD mix β²* (120 mg) followed by MeSO₂NH₂ (8.5 mg, 0.089 mmol) at rt. After 20 h, the reaction was quenched with Na₂SO₃ (360 mg) and extracted with EtOAc (3 x 5 mL). The dried (MgSO₄) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 80-100% Et₂O/hexanes to obtain diol 6.11.5 (26.7 mg, 0.054 mmol, 61%) as a colorless oil. 

¹H NMR (700 MHz, CDCl₃) δ 8.02 (d, J = 9.1 Hz, 2 H) 6.95 (d, J = 9.1 Hz, 2 H) 5.71 (td, J = 6.7, 1.5 Hz, 1 H) 4.31 - 4.38 (m, 3 H) 4.26 (dt, J = 11.3, 6.4 Hz, 1 H) 4.11 (dd, J = 8.3, 6.1 Hz, 1 H) 3.90-3.93 (m, 1 H) 3.90 (s, 3 H) 3.60 (dd, J = 8.3, 7.2 Hz, 1 H) 2.93 (d, J = 4.2 Hz, 1 H) 2.71 (d, J = 6.5 Hz, 1 H) 2.28 - 2.35 (m, 1 H) 2.21 - 2.28 (m, 2 H) 1.91 (ddd, J = 14.3, 8.2, 3.0 Hz, 1 H) 1.82 (ddd, J = 14.3, 9.0, 4.2 Hz, 1 H) 1.41 (s, 3 H) 1.38 (s, 3 H) 1.22 (s, 9 H). 

¹³C NMR (175 MHz, CDCl₃) δ 178.6, 165.2, 163.8, 131.9, 121.7, 113.7, 109.0, 84.5, 83.3, 73.3, 72.1, 69.6, 66.1, 61.3, 60.2, 55.5, 43.4, 38.8, 36.2, 33.9, 27.2, 26.9, 25.7.
Dihydrofuran 6.3.5: To a solution of diol 6.11.4 (13 mg, 0.027 mmol) in benzene (0.27 mL) was added AgBF₄ (0.53 mg, 2.7 μmol). The reaction mixture was heated in a sealed tube at 97 °C in dark. After 15 min, the reaction mixture was cooled to rt, passed through a small plug of silica gel to give crude dihydrofuran. To a solution of crude dihydrofuran DCM (0.27 mL) at -78 °C was added 2,6-lutidine (11.6 mg, 12.6 μL, 0.108 mmol) followed by TBSOTf (14 mg, 12.5 μL, 54 μmol). After 3 h, the reaction was quenched with aq. sat. NH₄Cl (5 mL) and extracted with DCM (3 x 5 mL). The dried (MgSO₄) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 0-30% EtOAc/Hexanes to obtain the dihydrofuran 6.3.5 (4.3 mg, 7.3 μmol, 27%) as colorless oil along with furan by product 6.3.4 (2.2 mg, 4.9 μmol, 18%) as colorless oil as well.

Dihydrofuran 6.3.5: ¹H NMR (700 MHz, CDCl₃) δ 8.01 (d, J = 8.4 Hz, 2 H) 7.30 (d, J = 7.8 Hz, 2 H) 6.07 (t, J = 1.7 Hz, 1 H) 5.00 (m, 1 H) 4.80 - 4.84 (m, 1 H) 4.28 - 4.32 (m, 1 H) 4.20 - 4.27 (m, 2 H) 4.06 - 4.11 (m, 2 H) 3.54 (t, J = 7.7 Hz, 1 H) 2.47 (s, 3 H) 2.02 -2.08 (m, 1 H) 1.95 - 2.01 (m, 1 H) 1.88 (ddd, J = 13.9, 8.8, 3.5 Hz, 1 H) 1.76 (ddd, J = 13.6, 9.2, 3.9 Hz, 1 H) 1.43 (s, 3 H) 1.38 (s, 3 H) 1.23 (s, 9 H) 0.88 (s, 9 H) 0.12 (s, 3 H) 0.05 (s, 3 H); HRMS (ES+) calcd. for C₂₆H₃₄O₇Na (M+Na) 481.2202, found 481.2216.
Dihydrofuran 6.3.6: To a solution of diol 6.11.5 (10 mg, 20 µmol) in benzene (0.2 mL) was added AgBF₄ (0.4 mg, 2 µmol). The reaction mixture was heated at 85 °C in dark. After 20 min, the reaction mixture was cooled to rt, passed through a small plug of silica gel to give crude dihydrofuran. To a solution of crude dihydrofuran in DCM (0.2 mL) at -78 °C was added 2,6-lutidine (9.2 mg, 10 µL, 86 µmol) followed by TBSOTf (11.2 mg, 10 µL, 43.2 µmol). After 3 h, the reaction was quenched with aq. sat. NH₄Cl (5 mL) and extracted with DCM (3 x 5 mL). The dried (MgSO₄) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 0-30% EtOAc/Hexanes to obtain the dihydrofuran 6.3.6 (2.2 mg, 3.6 µmol, 18%) as colorless oil along with furan by product 6.3.8 (1 mg, 1.9 µmol, 9%) as colorless oil as well.

Di-TBS ether 6.12.3: To a solution of diol 6.8.2 (260 mg, 0.562 mmol) in DCM (5.6 mL) at 0 °C was added 2,6-lutidine (482 mg, 0.52 mL, 4.5 mmol) followed by TBSOTf (595 mg, 0.52 mL, 2.25 mmol). After 10 min, the reaction mixture was warmed
to rt. After 10 min, the reaction quenched with sat. aq. NaHCO₃ (10 mL) and extracted with ether (3 x 10 mL). The combined organic phase was washed with sat. aq. NaCl (25 mL) solution. The dried (MgSO₄) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 0-5% EtOAc/Hexanes to obtain di-TBS ether 6.12.3 (370 mg, 0.536 mmol, 96%) as a colorless oil. [α]D²₀ = -5.1° (c = 1.60, CHCl₃); IR (neat) 2956, 2931, 2858, 1731, 1473, 1368, 1262, 1154, 1094, 837, 777, 711 cm⁻¹; ¹H NMR (700 MHz, CDCl₃) δ 8.06-8.07 (m, 2H), 7.59 (tt, J = 7.4, 1.3 Hz, 1H), 7.46-7.48 (m, 2H), 5.82 (td, J = 6.7, 1.7 Hz, 1H), 4.44 (dd, J = 4.8, 1.7 Hz, 1H), 4.29 (td, J = 6.4, 1.3 Hz, 2H), 4.2-0.424 (m, 1H), 4.08 (dd, J = 7.9, 5.9 Hz, 1H), 3.85 (ddd, J = 7.0, 4.8, 2.3 Hz, 1H), 2.27-2.32 (m, 1H), 2.19-2.24 (m, 1H) 1.96 (ddd, J = 11.6, 9.3, 2.3 Hz, 1H), 1.71 (ddd, J = 13.8, 10.1, 3.8 Hz, 1H), 1.39 (s, 3H), 1.36 (s, 3H), 1.21 (s, 9H), 0.90 (s, 9H), 0.89 (s, 9H), 0.13 (s, 3H), 0.10 (s, 6H), 0.09 (s, 3H); ¹³C NMR (175 MHz, CDCl₃) δ 178.3, 165.2, 133.2, 129.81, 129.77, 128.4, 108.5, 85.5, 81.6, 72.6, 71.3, 70.0, 66.7, 61.7, 60.3, 38.7, 35.5, 34.2, 27.2, 27.1, 25.9, 25.7, 18.1, 17.9, -4.6, -4.7, -5.0; HRMS (ES+) calcd. for C₃₇H₆₂O₈Si₂Na (M+Na) 713.3881, found 713.3913.

**Alcohol 6.12.2:** To a solution of di-TBS ether 6.12.3 (180 mg, 0.26 mmol) in THF (2.9 mL) at rt was added a stock solution of HF-pyr²¹ (1.6 mL). After 16 h, the reaction was quenched with sat. aq. NaHCO₃ (5 mL) and the aqueous layer was extracted
with EtOAc (3 X 5 mL). The dried (MgSO\(_4\)) extract was concentrated \textit{in vacuo} and purified by flash chromatography over silica gel, eluting with 25-50% EtOAc / hexanes, to give alcohol \textbf{6.12.2} (70 mg, 0.12 mmol, 47%) as a colorless oil. \([\alpha]_D^{20} = -6.0^\circ (c = 1.38, \text{CHCl}_3)\); IR (neat) 3441, 2957, 2930, 1729, 1452, 1369, 1264, 1155, 1108, 1069, 837, 777, 712 cm\(^{-1}\); \(^1\)H NMR (700 MHz, CDCl\(_3\)) \(\delta\) 8.07 (d, \(J = 8.3\) Hz, 2H), 7.60 (tt, \(J = 7.4, 1.1\) Hz, 1H), 7.47 (t, \(J = 7.8\) Hz, 2H), 5.82 (t, \(J = 6.7\) Hz, 1H), 4.37-4.39 (m, 1H), 4.27-4.31 (m, 2H), 4.18-4.21 (m, 1H), 4.09 (dd, \(J = 7.9, 6.0\) Hz, 1H), 3.97-3.99 (m, 1H), 3.52 (t, \(J = 7.8\) Hz, 1H), 2.92 (d, \(J = 8.6\) Hz, 1H), 2.29-2.34 (m, 1H), 2.23-2.28 (m, 1H), 1.92 (ddd, \(J = 14.5, 9.9, 5.3\) Hz, 1H); 1.73 (ddd, \(J = 10.2, 7.4, 2.9\) Hz, 1H), 1.39 (s, 3H), 1.35 (s, 3H), 1.22 (s, 9H), 0.90 (s, 9H), 0.124 (s, 3H), 0.116 (s, 3H); \(^{13}\)C NMR (175 MHz, CDCl\(_3\)) \(\delta\) 178.3, 165.2, 133.3, 129.8, 129.6, 128.4, 109.2, 85.7, 82.1, 72.55, 72.49, 69.8, 66.0, 61.5, 60.2, 38.7, 37.8, 34.2, 27.2, 26.9, 25.9, 18.1, -4.4, -4.6; HRMS (ES+) calcd. for C\(_{31}\)H\(_{49}\)O\(_8\)S (M+H) 577.3197, found 577.3203.

\textbf{Bis silyl ether 17:} To a solution of diol \textbf{14} (10.0 mg, 22 µmol) in DCM (0.22 mL) at -78 °C were sequentially added Et\(_3\)N (4.45 mg, 6 µL, 44 µmol) followed by TMSCl (2.6 mg, 3 µL, 24 µmol). After 15 min the reaction was warmed to rt. After 5 min the reaction was recooled to -78 °C and Et\(_3\)N (2.2 mg, 3 µL, 22 µmol) followed by TMSCl (1.3 mg, 1.5 µL, 12 µmol) were added. After 10 min, 2,6-lutidine (18.9 mg, 20 µL, 0.176
mmol) followed by TBSOTf (23 mg, 20 µL, 88 µmol) were added. After 5 min, the reaction mixture was slowly warmed to rt over a period of 30 min. After 5 min, the reaction was quenched with aq. sat. NH₄Cl (5 mL) and extracted with DCM (3 x 5 mL). The dried (MgSO₄) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 0-5% EtOAc/hexanes to obtain the bis-silyl ether 17 (8.7 mg, 13.4 µmol, 61%) as a colorless oil. [α]D20 = -13.3° (c = 1.20, CHCl₃); IR (neat) 2931, 2857, 1730, 1454, 1368, 1263, 1153, 1094, 776, 712 cm⁻¹; ¹H NMR (700 MHz, CDCl₃) δ 8.07 (dd, J = 8.3 Hz, 1.2 Hz, 2H), 7.60 (tt, J = 7.4, 1.2 Hz, 1H), 7.47 (t, J = 7.8 Hz, 2H), 5.82 (td, J = 6.9, 1.6 Hz, 1H), 4.38 (dd, J = 5.3, 1.7 Hz, 2H), 4.29 (t, J = 6.4 Hz, 2H), 4.21-4.25 (m, 1H), 4.06 (dd, J = 7.8, 5.9 Hz, 1H), 3.87 (ddd, J = 7.6, 5.3, 2.3 Hz, 1H), 3.54 (t, J = 7.7 Hz, 1H), 2.28-2.33 (m, 1H), 2.20-2.25 (m, 1H), 1.97 (ddd, J = 11.6, 9.2, 2.3 Hz, 1H), 1.69 (ddd, J = 13.8, 10.1, 3.7 Hz, 1H), 1.39 (s, 3H), 1.35 (s, 3H), 1.21 (s, 9H), 0.90 (s, 9H), 0.17 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); ¹³C NMR (175 MHz, CDCl₃) δ 178.3, 165.2, 133.2, 129.8, 128.4, 108.6, 85.3, 82.1, 72.5, 71.6, 70.0, 66.6, 61.6, 60.3, 38.7, 35.6, 34.1, 27.2, 27.1, 25.9, 25.8, 18.0, 0.14, -4.4, -4.7; HRMS (ES+) calcd. for C₃₄H₆₆O₈Si₂Na (M+Na) 671.3411, found 671.3421.

**Alcohol 6.12.2** To a stirred solution of bis-silyl ether 6.12.1 (8.7 mg, 13 µmol) in MeOH (0.26 mL) was added PPTS (0.16 mg, 0.65 µmol). After 10 min, the reaction was
quenched with sat. aq. NaHCO₃ solution (1 mL) and extracted with DCM (3 x 4 mL). The dried (MgSO₄) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 25-50% EtOAc/Hexanes to obtain alcohol **6.12.2** (5.3 mg, 9.2 μmol, 71%) as a colorless oil.

**Dihydrofuran 6.2.6:** To a solution of alcohol **6.12.2** (59.0 mg, 0.102 mmol) in benzene (1.0 mL) was added AgBF₄ (2.0 mg, 10.2 μmol). The reaction mixture was refluxed at 95 °C in dark. After 3.5 h, the solvent was removed *in vacuo* and the crude was purified by chromatography over silica gel, eluting with 0-25% EtOAc/Hexanes to obtain the dihydrofuran **6.2.6** (54.3 mg, 0.094 mmol, 92%) as colorless oil.

**Ketone 6.14.1:** To a solution of dihydrofuran **6.2.6** (20 mg, 0.035 mmol) in Et₂O (0.35 mL) at -78 °C was added MeLi•LiBr (31.5 μL, 0.069 mmol, 2.2 M solution in hexanes). After 15 min, the reaction was quenched with sat. aq. NH₄Cl (5 mL) and extracted with ether (3 x 5 mL). The dried (MgSO₄) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 0-25% EtOAc/hexanes to
obtain ketone 6.14.1 (13.2 mg, 0.028 mmol, 80%) as colorless oil. \([\alpha]_D^{20} = -51.9^\circ\) (c = 0.91, CHCl₃); IR (neat) 2957, 2930, 2857, 1760, 1730, 1479, 1369, 1284, 1254, 1155, 1065, 837, 778 cm⁻¹; \(^1\)H NMR (700 MHz, CDCl₃) δ 4.25-4.32 (m, 3H), 4.20-4.24 (m, 1H), 4.13-4.15 (m, 1H), 4.08 (dd, \(J = 7.9, 6.0\) Hz, 1H), 3.82 (d, \(J = 2.7\) Hz, 1H), 3.54 (t, \(J = 7.7\) Hz, 1H), 2.59 (dd, \(J = 17.6, 5.9\) Hz, 1H), 2.22 (dd, \(J = 17.6, 10.3\) Hz, 1H), 2.13-2.18 (m, 1H), 1.98-2.08 (m, 2H), 1.75 (dd, \(J = 11.4, 7.2, 4.2\) Hz, 1H), 1.42 (s, 3H), 1.36 (s, 3H), 1.23 (s, 9H), 0.89 (s, 9H), 0.12 (s, 3H), 0.04 (s, 3H); \(^13\)C NMR (175 MHz, CDCl₃) δ 214.5, 178.4, 109.0, 84.1, 73.0, 72.4, 69.7, 69.5, 60.9, 43.9, 38.7, 38.1, 35.1, 27.2, 27.0, 25.9, 25.8, 18.1, -4.57, -4.59; HRMS (ES+) calcd. for C₂₄H₄₂O₇SiNa (M+Na) 495.2754, found 495.2742.

**Enone 6.14.2:** To a solution of ketone 6.14.1 (40 mg, 0.085 mmol) in THF (0.5 mL) at -78 °C was added LDA₈ (0.17 mL, 0.169 mmol, 1.0 M solution in THF/hexanes). After 5 min, the reaction mixture was slowly warmed to -50 °C over a period of 40 min. After 5 min, Eschenmosher’s salt (314 mg, 1.69 mmol) was added and the reaction mixture was slowly warmed to 0 °C over a period of 45 min. The reaction was quenched with sat. aq. NH₄Cl (5 mL) and extracted with ether (3 x 5 mL). The dried (MgSO₄) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 0-25% EtOAc/hexanes to obtain enone 6.14.2 (17.2 mg, 0.036 mmol, 42%) as
colorless oil. \([\alpha]_D^{20} = -32.0^\circ\) \((c = 1.00, \text{CHCl}_3)\); IR (neat) 2957, 2931, 2857, 1731, 1649, 1463, 1369, 1255, 1158, 1070, 941, 837, 778 \(\text{cm}^{-1}\); \(^1\)H NMR (700 MHz, CDCl\(_3\)) \(\delta\) 6.14 (d, \(J = 2.7 \text{ Hz}, 1\)H), 5.41 (d, \(J = 2.4 \text{ Hz}, 1\)H), 4.90-4.92 (m, 1H), 4.32-4.34 (m, 2H), 4.20-4.23 (m, 2H), 4.08-4.10 (m, 2H), 3.54 (t, \(J = 7.6 \text{ Hz}, 1\)H), 2.14-2.19 (m, 1H), 2.07-2.12 (m, 1H), 2.01 (ddd, \(J = 14.2, 8.8, 6.0 \text{ Hz}, 1\)H), 1.77 (ddd, \(J = 14.0, 6.9, 4.2 \text{ Hz}, 1\)H), 1.43 (s, 3H), 1.36 (s, 3H), 1.23 (s, 9H), 0.83 (s, 9H), 0.10 (s, 3H), -0.02 (s, 3H); \(^13\)C NMR (175 MHz, CDCl\(_3\)) \(\delta\) 203.3, 178.6, 144.5, 117.9, 109.0, 83.9, 75.5, 72.4, 70.4, 69.7, 60.7, 38.8, 38.2, 35.5, 27.2, 27.0, 25.9, 25.8, 18.2, -4.6, -4.7; HRMS (ES+) calcd. for C\(_{24}\)H\(_{44}\)O\(_7\)SiNa (M+Na) 495.2754, found 495.2742.

**Ketone 6.14.3:** To a solution of enone 6.14.2 (11.6 mg, 0.024 mmol) in toluene (0.42 mL) was added Wilkinson’s catalyst (2.2 mg, 2.4 \(\mu\)mol) and the atmosphere was flushed with H\(_2\) gas. After 5 min, the reaction was sealed under 1 atm of H\(_2\) (balloon). After 18 h, the hydrogen was removed by flushing with argon and filtered through celite washing with EtOH (5 mL). The filtered extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 10%-30% EtOAc/Hexanes to give ketone 6.14.3 (9.9 mg, 0.02 mmol, 85%) as a colorless oil. \([\alpha]_D^{20} = -21.8^\circ\) \((c = 0.85, \text{CHCl}_3)\); IR (neat) 2958, 2931, 2858, 1760, 1730, 1462, 1370, 1285, 1254, 1158, 1059, 837, 778 \(\text{cm}^{-1}\); 
\(^1\)H NMR (700 MHz, CDCl\(_3\)) \(\delta\) 4.30-4.34 (m, 1H), 4.25-4.30 (m, 2H), 4.20-4.24 (m, 1H),
4.12 (td, $J = 6.5$, 3.5 Hz, 1H), 4.08 (dd, $J = 7.9$, 5.9 Hz, 1H), 3.89 (d, $J = 3.4$ Hz, 1H), 3.55 (t, $J = 7.6$ Hz, 1H), 2.55 (quint, $J = 7.2$ Hz, 1H), 2.06-2.10 (m, 1H), 1.99-2.04 (m, 1H), 1.85-1.90 (m, 1H), 1.70 (dd, $J = 13.9$, 6.8, 4.3 Hz, 1H), 1.42 (s, 3H), 1.36 (s, 3H), 1.23 (s, 9H), 1.09 (d, $J = 7.6$, 3H), 0.89 (s, 9H), 0.13 (s, 3H), 0.04 (s, 3H); $^{13}$C NMR (175 MHz, CDCl$_3$) $\delta$ 216.3, 178.6, 109.0, 83.7, 75.5, 72.5, 69.7, 69.1, 61.5, 45.0, 38.8, 38.1, 30.0, 27.2, 27.0, 26.0, 25.8, 18.2, 9.3, -4.0, -5.0; HRMS (ES+) calcd. for C$_{25}$H$_{46}$O$_7$SiNa (M+Na) 509.2911, found 509.2892.

**Ketone 6.15.1:** To a solution of ketone 6.14.1 (12 mg, 0.024 mmol) in dry THF (0.12 mL) at -78 °C was added NaHMDS (28 µL, 0.028 mmol, 1.0 M in THF). After 5 min, the reaction mixture was slowly warmed to -50 °C over a period of 40 min. After 20 min, the reaction mixture was cooled back to -78 °C and MeI (17 mg, 7.4 µL, 0.12 mmol) was added. After 30 min, the reaction mixture was slowly warmed to 0 °C over a period of 1h. After 5 min, the reaction was quenched with sat. aq. NH$_4$Cl (3 mL) and extracted with ether (3 x 5 mL). The dried (MgSO$_4$) extracted was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 10-30% EtOAc/Hexane to obtain the methylated ketone 6.15.1 (4.4 mg, 9.1 µmol, 38%) as a colorless oil. $[\alpha]_D^{20}$ = -44.7° ($c$ = 0.95, CHCl$_3$); IR (neat) 2958, 2931, 2858, 1761, 1731, 1473, 1462, 1379, 1255, 1158, 1059, 837, 778 cm$^{-1}$; $^1$H NMR (700 MHz, CDCl$_3$) $\delta$ 4.30-4.37 (m, 2H), 4.20-4.24 (m,
1H), 4.15 (ddd, J = 7.6, 5.5, 2.9 Hz, 1H), 4.08 (dd, J = 7.9, 6.0 Hz, 1H), 3.80 (d, J = 2.9 Hz, 1H), 3.76 (ddd, J = 10.9, 7.9, 3.3 Hz, 1H), 3.54 (t, J = 7.6 Hz, 1H), 2.10-2.17 (m, 2H), 1.98-2.06 (m, 2H), 1.74 (ddd, J = 13.9, 7.4, 4.2 Hz, 1H), 1.42 (s, 3H), 1.36 (s, 3H), 1.23 (s, 9H), 1.10 (d, J = 7.0 Hz, 3H), 0.88 (s, 9H), 0.11 (s, 3H), 0.02 (s, 3H); 13C NMR (175 MHz, CDCl₃) δ 216.3, 178.4, 108.9, 84.0, 79.3, 72.4, 69.7, 69.5, 60.7, 48.3, 38.7, 38.0, 33.6, 31.0, 27.2, 27.0, 25.9, 25.8, 18.1, 10.0, -4.6 HRMS (ES+) calcd. for C₂₅H₄₆O₇SiNa (M+Na) 509.2911, found 509.2900.

Alcohol 6.16.1: To a solution of ketone 6.14.3 (12.0 mg, 0.025 mmol) in MeOH (0.5 mL) at 0 °C was added NaBH₄ (0.9 mg, 0.025 mmol). After 40 min, the reaction was quenched with aq. NH₄Cl (3 mL) and extracted with DCM (3 x 5 mL). The dried (MgSO₄) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 20-50% EtOAc/hexane to obtain alcohol 6.16.1 (11 mg, 0.023 mmol, 90%) as colorless oil. [α]D²⁰ = +27.8° (c = 0.90, CHCl₃); IR (neat) 3472, 2958, 2929, 2856, 1730, 1712, 1462, 1369, 1285, 1250, 1159, 1081, 837, 778 cm⁻¹; ¹H NMR (700 MHz, CDCl₃) δ 4.27-4.33 (m, 2H), 4.15-4.20 (m, 2H), 4.08-4.13 (m, 3H), 3.67 (dd, J = 7.8, 3.1 Hz, 1H), 3.53 (t, J = 7.8 Hz, 1H), 2.51 (d, J = 4.3 Hz, 1H), 2.45-2.50 (m, 1H), 1.86-1.95 (m, 2H), 1.72-1.78 (m, 2H), 1.43 (s, 3H), 1.38 (s, 3H), 1.22 (s, 9H), 1.05 (d, J = 7.3 Hz, 3H), 0.92 (s, 9H), 0.154 (s, 3H), 0.151 (s, 3H); ¹³C NMR (175 MHz, CDCl₃) δ
178.6, 109.0, 85.5, 75.0, 73.2, 70.7, 69.8, 62.3, 40.6, 38.8, 38.6, 31.9, 30.3, 27.3, 27.0, 26.0, 25.8, 18.3, 8.8, -4.1, -4.8; HRMS (ES+) calcd. for C_{25}H_{49}O_{7}Si (M+H) 489.3248, found 489.3261.

Diol 6.16.2: To a solution of ketone 6.14.3 (7.0 mg, 14.3 µmol) in DCM (0.29 mL) at -78 °C was added DIBAL-H (47.3 µL, 47 µmol, 1 M solution in hexanes). After 1 h, the reaction was quenched with MeOH (5 mL). After 5 min, the reaction was warmed to 0 °C and was added aq. sat. solution of Rochelle’s salt (25 mL). After 3 h, the layers were allowed to separate and the aqueous layer was extracted with EtOAc (3 X 5 mL). The combined organic layer was dried (MgSO₄) extract was concentrated in vacuo and purified by flash chromatography over silica gel, eluting with 20-40% EtOAc / hexanes, to give diol 6.16.2 (4.7 mg, 11.6 µmol, 81%) as colorless oil.

Bromide 6.16.3: To a solution of diol 6.16.2 (5 mg, 12 µmol) in THF (0.24 mL) at 0 °C was added imidazole (4.9 mg, 72 µmol), PPh₃ (12.5 mg, 48 µmol) followed by CBr₄ (15.9 mg, 48 µmol). After 5 min, the reaction was warmed to rt. After 1 h, the
reaction was quenched with with aq. NH₄Cl (3 mL) and extracted with DCM (3 x 5 mL). The dried (MgSO₄) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 5-10% EtOAc/hexane to obtain bromide 6.16.3 (2.3 mg, 4.9 µmol, 41%) as colorless oil.

**Xanthate ester 6.17.1:** To a solution of alcohol 6.16.1 (10 mg, 0.020 mmol) in CS₂ (0.52 mL) at -78 °C was added NaHMDS (28.8 µL, 0.029 mmol, 1.0 M in THF). After 30 min, MeI (44 mg, 19.1 µL, 0.31 mmol) was added. After 10 min, the reaction mixture was slowly warmed to rt over a period of 2 h. After 5 min, the reaction was quenched with sat. aq. NH₄Cl (3 mL) and extracted with DCM (3 x 5 mL). The dried (MgSO₄) extracted was concentrated in vacuo and purified by chromatography over silica gel, eluting with 10-40% EtOAc/Hexane to obtain xanthate ester 6.17.1 (9.9 mg, 17.1 µmol, 84%) as a colorless oil. 

**1H NMR (700 MHz, CDCl₃) δ 6.35 (dd, J = 4.9, 3.1 Hz, 1H), 4.33-4.36 (m, 1H), 4.26-4.30 (m, 1H), 4.17-4.23 (m, 2H), 4.10 (ddd, J = 10.2, 8.3, 2.2 Hz, 1H), 4.04 (dd, J = 7.8, 6.0 Hz, 1H), 3.78 (dd, J = 8.1, 3.0 Hz, 1H), 3.44 (t, J = 7.9 Hz, 1H), 2.76-2.79 (m, 1H), 2.59 (s, 3H), 1.74-1.84 (m, 2H), 1.47-1.55 (m, 2H), 1.35 (s, 3H), 1.34 (s, 3H), 1.23 (s, 9H), 0.97 (d, J = 7.3 Hz, 3H), 0.91 (s, 9H), 0.16 (s, 3H), 0.15 (s, 3H); 

**13C NMR (175 MHz, CDCl₃) δ 178.5, 108.8, 85.5, 84.8, 76.6, 71.8, 69.8, 69.5, 61.9, 41.3, 38.8, 37.8, 31.6, 27.3, 26.7, 26.1, 25.9, 18.7, 18.4, 9.3, -4.0, -4.8.**
**Alkyne 7.3.3:** To a solution of (R)-glycidol 7.3.2 (225 mg, 3.0 mmol) in THF (7.5 mL) at -78 °C was added n-BuLi (1.34 mL, 3.34 mmol, 2.5 M in hexanes). To a solution of TMS-acetylene 7.3.1 (418 mg, 4.25 mL) in THF (7.5 mL) in a different flask at -78 °C was added n-BuLi (1.82 mL, 4.55 mmol, 2.5 M in hexanes). After 30 min, the solution of TMS acetylide was transferred to the flask containing solution of glycidol at -78 °C. After 5 min, the reaction was slowly warmed to rt over a period of 3 h. After 16 h, the reaction was quenched with sat. aq. NH₄Cl (20 mL) and extracted with EtOAc (3 x 10 mL). The dried (MgSO₄) extract was concentrated *in vacuo* to obtain the crude diol SI-1.

To a solution of the crude diol SI-1 (~3 mmol) in DCM (7.5 mL) was added dimethoxypropane (344 mg, 0.4 mL, 3.3 mmol) followed by CSA (23 mg, 0.1 mmol). After 12 h, reaction was quenched with Et₃N (3 mL), the solvent was concentrated *in vacuo* and directly loaded on column to purify by chromatography over silica gel, eluting with 1-10% EtOAc/Hexanes to obtain the known alkyne 7.3.3 (255 mg, 1.2 mmol, 40%, 2 steps) as colorless oil. $^1$H NMR (700 MHz, CDCl₃) δ 4.25 (dtd, $J = 7.8, 6.2, 4.5$ Hz, 1 H) 4.13 (dd, $J = 8.4, 6.0$ Hz, 1 H) 3.85 (dd, $J = 8.3, 6.5$ Hz, 1 H) 2.61 (dd, $J = 16.9, 4.4$ Hz, 1 H) 2.51 (dd, $J = 16.9, 7.8$ Hz, 1 H) 1.46 (s, 3 H) 1.39 (s, 3 H) 0.17 (s, 9 H).
**Vinyl iodide (S)-6.7.3:** To a solution of TMS alkyne 7.3.3 (279 mg, 1.3 mmol) in THF (7.5 mL) at 0 °C was added TBAF (1.45 mL, 1.45 mmol, 1.0 M in THF). After 10 min, the reaction was quenched with sat. aq. NH₄Cl (10 mL) and extracted with Et₂O (3 x 10 mL). The dried (MgSO₄) extract was concentrated *in vacuo* and purified by column chromatography over silica gel, eluting with 10-30% Et₂O/hexanes to obtain the acetylene 7.3.4 (173 mg, 1.25 mmol, 95%) as colorless oil.

To a suspension of Cp₂ZrHCl (121 mg, 0.47 mmol) in benzene (1 mL) was added dropwise a solution of acetylene 7.3.4 (55 mg, 0.39 mmol) in benzene (7.5 mL) at rt. After 90 min, a solution of I₂ (100 mg, 0.39 mmol) in CCl₄ (0.35 mL) was added. After 15 min, the reaction was quenched with sat. aq. solution of Na₂S₂O₃ (3 mL) and extracted with DCM (3 x 5 mL). The combined organic phase was washed with sat. aq. NaHCO₃ solution (10 mL) and NaCl solution (10 mL). The dried (MgSO₄) extract was concentrated *in vacuo* and purified by column chromatography over silica gel, eluting with 5-15% EtOAc/hexanes to obtain the iodide 6.7.3 as a single isomer (40.3 mg, 0.15 mmol, 32%, >20:1 E:Z) as pale yellow oil.
**Alkyne 7.2.3:** To a solution of alkyne 6.2.2 (720 mg, 2.5 mmol) in MeOH (45 mL) was added K$_2$CO$_3$ (518 mg, 3.75 mmol). After 1 h, the reaction mixture was filtered through silica gel plug and concentrated *in vacuo* to yield the crude alcohol SI-8.

To a solution of crude alcohol SI-8 (~2.5 mmol) in DCM (12.5 mL) and Et$_3$N (12.5 mL) at 0 °C was added DMAP (30.5 mg, 0.25 mmol) followed by TESCl (565 mg, 0.63 mL, 3.75 mmol). After 5 min, the reaction mixture was warmed to rt. After 1 h, the reaction was quenched with sat. aq. NH$_4$Cl (20 mL) and extracted with DCM (3 x 15 mL). The combined organic phase was washed with sat. aq. NaCl (40 mL). The dried (MgSO$_4$) extract was concentrated *in vacuo* and purified by column chromatography over silica gel, eluting with 5-15% EtOAc/hexanes to obtain the alkyne 7.2.3 (672 mg, 2.25 mmol, 90%, 2 steps) as colorless oil. [α]$_D^{20} = -37.3^\circ$ (c = 1.28, CHCl$_3$); IR (neat) 3311, 2958, 2913, 2878, 1732, 1481, 1460, 1365, 1284, 1157, 1101, 1008, 744 cm$^{-1}$; $^1$H NMR (700 MHz, CDCl$_3$) δ 4.52 (td, $J = 6.3$, 2.1 Hz, 1H), 4.18-4.26 (m, 2H), 2.44 (d, $J = 2.1$ Hz, 1H), 2.03-2.06 (m, 2H), 1.23 (s, 9H), 1.00 (t, $J = 7.7$ Hz, 9H), 0.61-0.73 (m, 6H); $^{13}$C NMR (175 MHz, CDCl$_3$) δ 178.4, 84.7, 72.6, 60.6, 59.3, 38.8, 37.7, 27.2, 6.8, 4.6; HRMS (ES+) calcd. for C$_{16}$H$_{30}$O$_3$SiNa (M+Na) 321.1862, found 321.1874.
Enyne 7.2.2: To a suspension of Pd(PPh3)4 (24 mg, 0.021 mmol) and CuI (8 mg, 0.041 mmol) in i-Pr2NH (1.4 mL) at 0 °C were added a solution of vinyl iodide (E:Z = 5:1) S-(6.7.3) (122 mg, 0.455 mmol) in i-Pr2NH (0.3 mL) followed by a solution of alkyne 7.2.3 (122 mg, 0.41 mmol) in i-Pr2NH (0.3 mL). After 60 min, the reaction was quenched with aq. NH4Cl (10 mL) solution and extracted with ether (3 x 10 mL). The combined organic phase was washed with sat. aq. NaCl (30 mL). The dried (MgSO4) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 5-20% Et2O/hexanes to obtain enyne 7.2.2 (128 mg, 0.291 mmol, 71%) as a pale yellow oil. [α]D20 = -13.6° (c = 0.90, CHCl3); IR (neat) 2958, 2877, 1731, 1480, 1459, 1369, 1284, 1240, 1156, 1066, 745 cm⁻¹; ¹H NMR (700 MHz, CDCl3) δ 6.09 (dt, J = 16.1, 7.7 Hz, 1H), 5.60 (dd, J = 16.1, 1.4 Hz, 1H), 4.62 (t, J = 6.3 Hz, 1H), 4.16-4.23 (m, 3H), 4.06 (dd, J = 8.0, 6.0 Hz, 1H), 3.59 (dd, J = 8.0, 7.0 Hz, 1H), 2.45-2.48 (m, 1H), 2.36-2.39 (m, 1H), 2.01-2.04 (m, 2H), 1.44 (s, 3H), 1.38 (s, 3H), 1.22 (s, 9H), 1.00 (t, J = 7.7 Hz, 9H), 0.63-0.72 (m, 6H); ¹³C NMR (175 MHz, CDCl3) δ 178.5, 139.1, 112.1, 109.2, 89.5, 82.7, 74.8, 68.8, 60.8, 59.8, 38.8, 37.8, 37.2, 27.2, 26.9, 25.6, 6.8, 4.7; HRMS (ES+) calcd. for C24H42O5SiNa (M+Na) 461.2699, found 461.2718.
**Epoxide 7.5.1:** To a solution of enyne 7.2.2 (11.5 mg, 26 µmol) in DCM (0.26 mL) at 0 °C was added mCPBA (25.8 mg, 104 µmol, 70% pure). After 5 min, the reaction mixture was warmed to rt. After 12 h, the reaction was quenched with sat. aq. solution of NaHCO₃ (5 mL) and extracted with DCM (3 x 5 mL). The combined organic phase was washed with sat. aq. NaCl solution (10 mL). The dried (MgSO₄) extract was concentrated *in vacuo* and purified by column chromatography over silica gel, eluting with 20-35% Et₂O/Hexanes to obtain 1:1.3 diastereomeric mixture of epoxides 7.5.1 (5.6 mg, 12.2 µmol, 47%, 1:1.3 dr) as colorless oil. ¹H NMR (700 MHz, CDCl₃) δ 4.53 (t, J = 6.5 Hz, 2 H) 4.27 - 4.33 (m, 1 H) 4.15 - 4.26 (m, 6 H) 4.12 (dd, J = 8.2, 6.0 Hz, 1 H) 4.09 (m, J = 8.1, 6.1 Hz, 1 H) 3.67 (t, J = 7.8 Hz, 1 H) 3.60 (dd, J = 8.2, 6.9 Hz, 1 H) 3.25-3.27 (m, 1 H) 3.20-3.23 (m, 2 H) 3.19 (dd, J = 2.0, 1.1 Hz, 1 H) 2.01 (m, 6 H) 1.91 (t, J = 5.5 Hz, 2 H), 1.46 (s, 3 H) 1.44 (s, 3 H), 1.394 (s, 3 H) 1.389 (s, 3 H) 1.22 (s, 18 H) 0.99 (t, J = 7.90 Hz, 18 H) 0.61 - 0.72 (m, 12 H); ¹³C NMR (175 MHz, CDCl₃) δ 178.4, 109.25, 109.17, 84.9, 80.6, 73.1, 72.5, 69.3, 68.7, 60.5, 59.3, 57.4, 57.0, 53.5, 45.5, 44.8, 38.8, 37.6, 36.4, 34.9, 29.7, 27.2, 27.0, 26.8, 25.7, 14.2, 6.8, 4.6; HRMS (ES+) calcd. for C₂₄H₄₂O₆SiNa (M+Na) 477.2648, found 477.2661.
**Alcohol 7.1.3:** To a solution of epoxide 7.5.1 (2.1 mg, 4.6 µmol) in DMSO (0.1 mL) at rt was added PhCO₂Na (5.2 mg, 36.8 µmol). After 12 h, the reaction was quenched with H₂O (5 mL) and extracted with DCM (3 x 5 mL). The combined organic phase was washed with sat. aq. NaCl solution (10 mL). The dried (MgSO₄) extract was concentrated *in vacuo* and purified by column chromatography over silica gel, eluting with 70-99% Et₂O/Hexanes to obtain a diastereomeric mixture of desilylated alcohol 7.1.3 (1.2 mg, 3.5 µmol, 77%) as colorless oil.

**Diol 7.6.1:** To a solution of enyne 7.2.2 (127 mg, 0.29 mmol), in a 1:1 mixture (5.8 mL) of 'BuOH and H₂O was added AD mix α*₂³ (403 mg) followed by MeSO₂NH₂ (27.5 mg, 0.29 mmol) at rt. After 20 h, the reaction was quenched with Na₂SO₃ (425 mg) and extracted with EtOAc (3 x 5 mL). The dried (MgSO₄) extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 80-100% Et₂O/hexanes to obtain diol 7.6.1 (111 mg, 0.235 mmol, 81%) as a colorless oil. [α]D²⁰ = -30.0° (c = 1.00, CHCl₃); IR (neat) 3434, 2958, 2877, 1731, 1459, 1370, 1285, 1158, 1099, 1069, 1006, 827, 745 cm⁻¹; ¹H NMR (700 MHz, CDCl₃) δ 4.55 (td, J = 7.0, 1.4 Hz, 1H) 4.35-4.40 (m, 1H), 4.27-4.29 (m, 2H), 4.16-4.18 (m, 1H), 4.14 (dd, J = 8.2, 6.0 Hz,
1H), 3.87-3.90 (m, 1H), 3.63 (dd, J = 8.2, 7.4 Hz, 1H), 2.93 (d, J = 4.2 Hz, 1H), 2.62 (d, J = 5.6 Hz, 1H), 2.00-2.05 (m, 2H), 1.92-1.96 (m, 1H), 1.80-1.84 (m, 1H), 1.45 (s, 3H), 1.40 (s, 3H), 1.22 (s, 9H), 1.00 (t, J = 7.7 Hz, 9H), 0.65-0.71 (m, 6H); $^{13}$C NMR (175 MHz, CDCl$_3$) δ 178.5, 109.1, 87.5, 82.3, 73.3, 72.2, 69.6, 66.2, 60.6, 59.4, 38.8, 37.7, 35.9, 30.3, 27.2, 26.9, 25.7, 6.8, 4.7; HRMS (ES+) calcd. for C$_{24}$H$_{44}$O$_7$SiNa (M+Na) 495.2754, found 495.2755.

**Cyclic sulfate 7.6.2**: To a solution of diol 7.6.1 (25 mg, 0.053 mmol), in DCM (1.77 mL) at 0 °C was added N-methylmorpholine (NMM) (16.1 mg, 17.5 µL, 0.159 mmol) followed by SO$_2$Cl$_2$ (8.6 mg, 5.1 µL, 0.063 mmol). After 2 h, the reaction was quenched with with aq. NH$_4$Cl (5 mL) solution and extracted with DCM (3 x 10 mL). The combined organic phase was washed with sat. aq. NaCl (30 mL). The dried (MgSO$_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 5-30% Et$_2$O / hexanes to obtain the cyclic sulfate 7.6.2 (12.2 mg, 0.023 mmol, 43%) as a colorless oil. $[\alpha]_D^{20} = -12.9^\circ$ (c = 0.93, CHCl$_3$); IR (neat) 2965, 2924, 2876, 1726, 1714, 1462, 1397, 1258, 1212, 1165, 1038, 817 cm$^{-1}$; $^1$H NMR (700 MHz, CDCl$_3$) δ 5.25 (dd, J = 8.1, 1.4 Hz, 1H), 5.02-5.05 (m, 1H), 4.60 (t, J = 6.6 Hz, 1H), 4.27-4.31 (m, 1H), 4.21-4.24 (m, 1H), 4.15-4.20 (m, 2H), 3.64 (dd, J = 8.4, 6.2 Hz, 1H), 2.08-2.10 (m, 2H), 2.03-2.06 (m, 2H), 1.45 (s, 3H), 1.39 (s, 3H), 1.23 (s, 9H), 1.00 (t, J = 7.9 Hz, 9H), 0.63-
0.72 (m, 6H); $^{13}$C NMR (175 MHz, CDCl$_3$) $\delta$ 178.3, 109.8, 94.0, 84.3, 84.1, 75.4, 74.1, 71.5, 69.1, 60.1, 59.2, 38.8, 37.2, 36.2, 27.2, 27.0, 25.5, 6.7, 4.6; HRMS (ES+) calcd. for C$_{24}$H$_{42}$O$_9$SiSNa (M+Na) 557.2217, found 557.2223.

Enyne 6.6.2: To a suspension of Pd(PPh$_3$)$_4$ (24 mg, 0.021 mmol) and CuI (8 mg, 0.041 mmol) in $i$-Pr$_2$NH (1.4 mL) at 0 °C were added a solution of vinyl iodide ($E:Z = 5:1$) $S$-(6.7.3) (122 mg, 0.455 mmol) in $i$-Pr$_2$NH (0.3 mL) followed by a solution of alkyne 6.2.2 (118 mg, 0.410 mmol) in $i$-Pr$_2$NH (0.3 mL). After 1 h, the reaction was quenched with aq. NH$_4$Cl (10 mL) solution and extracted with ether (3 x 10 mL). The combined organic phase was washed with sat. aq. NaCl (30 mL). The dried (MgSO$_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 5-20% Et$_2$O / Hexanes to obtain enyne 6.6.2 (140 mg, 0.328 mmol, 80%) as a pale yellow oil. $[\alpha]_D^{20} = -13.8^\circ$ (c = 1.60, CHCl$_3$); IR (neat) 2981, 2934, 2872, 1727, 1480, 1452, 1370, 1266, 1154, 1069, 961, 713 cm$^{-1}$; $^1$H NMR (700 MHz, CDCl$_3$) $\delta$ 8.09 (dd, $J = 8.3, 1.3$ Hz, 2H), 7.60 (tt, $J = 7.5, 1.3$ Hz, 1H), 7.47 (t, $J = 7.8$ Hz, 2H), 6.19 (dt, $J = 15.9, 7.3$ Hz, 1H), 5.87 (td, $J = 6.7$ Hz, 1.5 Hz, 1H), 5.62 (dq, $J = 15.9, 1.6$ Hz, 1H), 4.30 (td, $J = 6.3, 1.6$ Hz, 2H), 4.16 (quint, $J = 6.3$ Hz, 1H), 4.05 (dd, $J = 8.1, 6.0$ Hz, 1H), 3.58 (dd, $J = 8.1, 6.8$ Hz, 1H), 2.44-2.48 (m, 1H), 2.31-2.38 (m, 2H), 2.25-2.31 (m, 1H), 1.43 (s, 3H), 1.36 (s, 3H), 1.22 (s, 9H); $^{13}$C NMR (175 MHz, CDCl$_3$) $\delta$ 178.5, 165.4, 140.8,
133.3, 129.8, 129.7, 128.4, 111.5, 109.2, 85.0, 84.3, 74.7, 68.8, 62.1, 60.3, 38.8, 37.4, 34.2, 27.2, 26.9, 25.6; HRMS (ES+) calcd. for C$_{25}$H$_{32}$O$_6$Na (M+Na) 451.2097, found 451.2098.

**TBS Enyne SI-10:** To a solution of alkyne 7.2.2 (13.5 mg, 0.031 mmol) in MeOH (0.3 mL) was added KF (3.6 mg, 0.062 mmol). After 2 h, the reaction mixture was filtered through silica gel plug and concentrated in vacuo to yield the crude alcohol 32.

To a solution of crude alcohol SI-9 (~0.031 mmol) in DCM (0.3 mL) and Et$_3$N (0.3 mL) at 0 °C was added DMAP (0.4 mg, 3.1 µmol) followed by TBSCl (9.3 mg, 0.062 mmol). After 5 min, the reaction mixture was warmed to rt. After 1 h, the reaction was quenched with sat. aq. NH$_4$Cl (5 mL) and extracted with DCM (3 x 5 mL). The combined organic phase was washed with sat. aq. NaCl (15 mL). The dried (MgSO$_4$) extract was concentrated in vacuo and purified by column chromatography over silica gel, eluting with 5-15% EtOAc/hexanes to obtain the enyne SI-10 (13.5 mg, 0.031 mmol, 99%, 2 steps) as colorless oil. [α]$_D^{20}$ = -17.0° (c = 1.00, CHCl$_3$); IR (neat) 2958, 2931, 2862, 1731, 1472, 1370, 1284, 1257, 1156, 1097, 959, 838, 778 cm$^{-1}$; $^1$H NMR (700 MHz, CDCl$_3$) δ 6.10 (dt, $J = 15.1$, 7.2 Hz, 1H), 5.60 (d, $J = 16.0$ Hz, 1H), 4.62 (t, $J = 6.5$ Hz, 1H), 4.15-4.24 (m, 3H), 4.06 (t, $J = 7.0$ Hz, 1H), 3.59 (t, $J = 7.4$ Hz, 1H), 2.45-2.49
(m, 1H), 2.34-2.38 (m, 1H), 2.02 (q, J = 6.3 Hz, 2H), 1.44 (s, 3H), 1.38 (s, 3H), 1.22 (s, 9H), 0.93 (s, 9H), 0.16 (s, 3H), 0.14 (s, 3H); \(^{13}\)C NMR (175 MHz, CDCl\(_3\)) \(\delta\) 178.4, 139.1, 112.1, 109.2, 89.6, 82.8, 74.8, 68.8, 60.7, 60.1, 38.7, 37.8, 37.2, 27.2, 26.9, 25.8, 25.6, 18.2, -4.5, -5.1; HRMS (ES+) calcd. for C\(_{24}\)H\(_{42}\)O\(_5\)SiNa (M+Na) 461.2699, found 461.2693.

**Iodide 7.7.2.** To a solution of alcohol 6.7.2 (1.2 g, 8.2 mmol) in DCM (20 mL) was added 3 Å molecular sieves (2.0 g) and PCC (5.3 g, 24.6 mmol). After 3 h, the reaction mixture was filtered through silica gel, washed with Et\(_2\)O and concentrated *in vacuo* to yield the known crude aldehyde 7.7.1. The aldehyde 7.7.1 was immediately used in the next step.

To a suspension of iodomethyltriphenylphosphonium iodide (5.5 g, 10.0 mmol) in THF (23 mL) at rt was slowly added NaHMDS (5.0 mL, 10.0 mmol, 2.0 M in THF). After 1 min, the solution was cooled to -78°C. Next, DMPU (5.3 g, 5.0 mL, 41.4 mmol) and aldehyde 7.7.1 (~8 mmol) was added sequentially. After 30 min, the cooling bath was removed. After stirring 3 h, hexane (30 mL) was added and the reaction was quenched with sat. aq. NH\(_4\)Cl (30 mL). The aqueous was extracted with Et\(_2\)O (3 X 100 mL) and the combined organic phase was washed sequentially with NaHCO\(_3\) (100 mL) and brine (100 mL). The dried (MgSO\(_4\)) extract was concentrated *in vacuo* and purified by flash chromatography over silica gel, eluting with 5-20% Et\(_2\)O / pentane, to give the
known as a 20:1 (E:Z) mixture (0.80 g, 3.0 mmol, 36% over 2 steps) as a pale yellow oil. $^1$H NMR (700 MHz, CDCl$_3$) δ 6.40 (d, $J = 7.7$ Hz, 1H), 6.30 (q, $J = 7.7$ Hz, 1H), 4.24-4.28 (m, 1H), 4.07 (dd, $J = 8.0$, 6.0 Hz, 1H), 3.64 (dd, $J = 8.0$, 6.8 Hz, 1H), 2.45-2.49 (m, 2H), 1.46 (s, 3H), 1.38 (s, 3H) ppm; $^{13}$C NMR (175 MHz, CDCl$_3$) δ 136.5, 109.2, 85.1, 74.2, 38.8, 26.8, 25.6 ppm.

**Enyne 7.7.3:** To a suspension of Pd(PPh$_3$)$_4$ (98.2 mg, 0.085 mmol) and CuI (32.4 mg, 0.17 mmol) in $i$-Pr$_2$NH (5.6 mL) at 0 °C were added a solution of vinyl iodide 7.7.2 (457 mg, 1.7 mmol) in $i$-Pr$_2$NH (1.2 mL) followed by a solution of alkyne 7.2.3 (508 mg, 1.7 mmol) in $i$-Pr$_2$NH (1.2 mL). After 10 min, the reaction mixture was warmed to rt. After 4 h, the reaction was quenched with aq. NH$_4$Cl (15 mL) solution and extracted with ether (3 x 15 mL). The combined organic phase was washed with sat. aq. NaCl (50 mL). The dried (MgSO$_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 5-30% Et$_2$O/hexanes to obtain enyne 7.7.2 (686 mg, 1.56 mmol, 92%) as a pale yellow oil. [α]$_D^{20} = -18.3^\circ$ (c = 0.70, CHCl$_3$); IR (neat) 2958, 2938, 2914, 2877, 1732, 1459, 1481, 1369, 1240, 1156, 1097, 1069, 1007, 850, 745 cm$^{-1}$. $^1$H NMR (700 MHz, CDCl$_3$) δ 5.97 (dt, $J = 10.8$, 7.4 Hz, 1H), 5.63 (dq, $J = 10.9$, 1.5 Hz, 1H), 4.67 (t, $J = 6.6$ Hz, 1H), 4.19-4.25 (m, 3H), 4.05 (dd, $J = 8.1$, 6.0 Hz, 1H), 3.61 (dd, $J = 8.0$, 7.0 Hz, 1H), 2.60-2.62 (m, 2H), 2.02-2.08 (m, 2H), 1.44 (s, 3H), 1.37 (s, 3H),
1.22 (s, 9H), 1.00 (t, $J = 7.9$ Hz, 9H), 0.64-0.71 (m, 6H); $^{13}$C NMR (175 MHz, CDCl$_3$) $\delta$ 178.3, 138.2, 111.2, 109.1, 95.1, 80.9, 74.9, 68.8, 60.8, 60.0, 38.7, 37.9, 34.3, 27.2, 26.8, 25.6, 6.7, 4.8; HRMS (ES+) calcd. for C$_{24}$H$_{42}$O$_5$SiNa (M+Na) 461.2699, found 461.2681.

**Diol 7.2.8**: To a solution of enyne 7.7.3 (105 mg, 0.24 mmol), in a 1:1 mixture (1.0 mL) of tBuOH and H$_2$O was added AD mix α**25 (335 mg) followed by MeSO$_2$NH$_2$ (45.5 mg, 0.48 mmol) at rt. After 24 h, the reaction was quenched with Na$_2$SO$_3$ (400 mg) and extracted with EtOAc (3 x 10 mL). The dried (MgSO$_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 80-100% Ether/hexanes to sequentially obtain a 3.6:1 diastereomeric mixture (79.4 mg, 0.168 mmol, 70%) of diol 7.2.8 (61.9 mg, 0.131 mmol, 55%) followed by diol 7.2.7 (17.5 mg, 0.037 mmol, 15%) as colorless oil. Diol 7.2.8 (61.9 mg, 0.131 mmol, 55%) colorless oil. $[\alpha]_D^{20} = -10.1^\circ$ ($c = 1.67$, CHCl$_3$); IR (neat) 3441, 2958, 2877, 2916, 1731, 1459, 1370, 1285, 1240, 1158, 1098, 1064, 827, 746 cm$^{-1}$; $^1$H NMR (700 MHz, CDCl$_3$) $\delta$ 4.56 (td, $J = 6.6, 1.4$ Hz, 1H) 4.48 (dd, $J = 3.8, 1.3$ Hz, 1H), 4.33-4.37 (m, 1H), 4.27 (dt, $J = 11.5, 5.8$ Hz, 1H), 4.14-4.19 (m, 2H), 3.95 (dt, $J = 8.5, 3.7$ Hz, 1H), 3.63 (dd, $J = 8.1, 7.3$ Hz, 1H), 3.39 (br s, 1H), 2.83 (br s, 1H), 2.03 (q, $J = 6.3$ Hz, 2H), 1.87-1.95 (m, 2H), 1.46 (s, 3H), 1.41 (s, 3H), 1.22 (s, 9H), 0.99 (t, $J = 8.0$ Hz, 9H), 0.62-0.71 (m, 6H); $^{13}$C NMR (175 MHz, CDCl$_3$) $\delta$ 178.5, 109.7, 87.6, 81.8, 74.7, 73.0, 69.7, 65.6, 60.6, 59.4, 38.8, 37.7,
34.8, 27.2, 26.9, 25.8, 6.8, 4.7; HRMS (ES+) calcd. for C\textsubscript{24}H\textsubscript{44}O\textsubscript{7}SiNa (M+Na) 495.2754, found 495.2740.

**Dibenzoate SI-11:** To a solution of diol **7.2.8** (30 mg, 0.063 mmol) in DCM (0.15 mL) and Et\textsubscript{3}N (0.15 mL) at 0 °C was added DMAP (1.5 mg, 13 µmol) followed by benzoyl chloride (27 mg, 22 µL, 0.19 mmol). After 5 min, the reaction mixture was warmed to rt. After 45 min, the reaction was quenched with sat. aq. NH\textsubscript{4}Cl (5 mL) and extracted with DCM (3 x 5 mL). The combined organic phase was washed with sat. aq. NaCl (15 mL). The dried (MgSO\textsubscript{4}) extract was concentrated *in vacuo* and purified by column chromatography over silica gel, eluting with 5-15% EtOAc/hexanes to obtain the dibenzoate **SI-11** (36.9 mg, 0.054 mmol, 86%) as colorless oil. \([\alpha]_D^{20} = +4.9^\circ\ (c = 1.47, \text{CHCl}_3)\); IR (neat) 2958, 2915, 2877, 1728, 1452, 1370, 1273, 1155, 1096, 1069, 711 cm\(^{-1}\); \(^1\)H NMR (700 MHz, CDCl\(_3\)) \(\delta\) 8.06 (d, \(J = 7.7\) Hz, 2H), 8.03 (d, \(J = 7.8\) Hz, 2H), 7.60 (t, \(J = 7.4\) Hz, 2H), 7.44-7.47 (m, 4H), 6.01 (dd, \(J = 3.6\), 1.5 Hz, 1H), 5.55 (dt, \(J = 8.9\), 3.9 Hz, 1H), 4.57 (t, \(J = 6.6\) Hz, 1H), 4.30 (quint, \(J = 6.3\) Hz, 1H), 4.17-4.22 (m, 2H), 4.16 (dd, \(J = 8.1\), 5.9 Hz, 1H), 3.70 (dd, \(J = 8.0\), 7.1 Hz, 1H), 2.41 (dd, \(J = 14.7\), 8.9, 6.0 Hz, 1H), 2.20 (ddd, \(J = 14.3\), 6.9, 3.9 Hz, 1H), 2.01-2.04 (m, 2H), 1.40 (s, 3H), 1.33 (s, 3H), 1.21 (s, 9H), 0.93 (t, \(J = 7.9\) Hz, 9H), 0.60-0.67 (m, 6H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 178.3, 165.8, 165.0, 133.4, 133.3, 129.8, 129.7, 129.4, 128.44, 128.42, 125.6,
Alcohol 7.8.1: To a solution of TES ether SI-11 (37 mg, 0.054 mmol) in THF (2.9 mL) at rt was added a stock solution of HF\textsuperscript{p*pyr} (0.23 mL). After 1 h, the reaction was quenched with sat. aq. NaHCO\textsubscript{3} (5 mL) and the aqueous layer was extracted with EtOAc (3 X 5 mL). The dried (MgSO\textsubscript{4}) extract was concentrated \textit{in vacuo} and purified by flash chromatography over silica gel, eluting with 25-40% EtOAc / hexanes, to give alcohol 7.8.1 (30.3 mg, 0.053 mmol, 99%) as a colorless oil. $[\alpha]_D^{20} = +29.2^\circ$ ($c = 1.35$, CHCl\textsubscript{3}); IR (neat) 3442, 2979, 2930, 2875, 1727, 1602, 1452, 1371, 1315, 1274, 1156, 1069, 1095, 1027, 851, 712 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (700 MHz, CDCl\textsubscript{3}) $\delta$ 8.06 (dd, $J = 8.3$, 1.1 Hz, 2H), 8.04 (dd, $J = 8.4$, 1.1 Hz, 2H), 7.61 (t, $J = 7.4$ Hz, 2H), 7.45-7.48 (m, 4H), 5.99 (dd, $J = 3.9$, 1.5 Hz, 1H), 5.58 (dt, $J = 8.3$, 4.0 Hz, 1H), 4.55 (t, $J = 6.1$ Hz, 1H), 4.30-4.35 (m, 2H), 4.18 -4.21 (m, 1H), 4.16 (dd, $J = 8.1$, 5.9 Hz, 1H), 3.71 (dd, $J = 8.1$, 6.7 Hz, 1h), 2.44 (br s, 1H), 2.37-2.41 (m, 1H), 2.21 (ddd, $J = 14.4$, 6.8, 4.2 Hz, 1h), 2.04 (q, $J = 6.2$ Hz, 2H), 1.41 (s, 3H), 1.33 (s, 3H), 1.21 (s, 9H); \textsuperscript{13}C NMR (175 MHz, CDCl\textsubscript{3}) $\delta$ 178.6, 165.8, 165.1, 133.5, 133.4, 129.92, 129.85, 129.6, 129.2, 129.1, 128.5, 128.3, 109.3, 87.8, 79.2, 72.7, 71.5, 69.2, 65.4, 60.6, 59.4, 38.8, 36.6, 34.0, 27.2, 26.9, 25.5; HRMS (ES+) calcd. for C\textsubscript{32}H\textsubscript{39}O\textsubscript{9} (M+H) 567.2594, found 567.2588.
Ketone 7.8.4: To a solution of dibenzoate 7.8.1 (10 mg, 17.6 μmol) in toluene (0.15 mL) was added AgBF₄ (0.3 mg, 1.7 μmol). The reaction mixture was heated to reflux in dark. After 15 min, the reaction was cooled to rt and then further to -78 °C and diluted with Et₂O (0.15 mL). After 5 min, MeLi•LiBr (17.6 μL, 38.7 mmol, 2.2 M in hexanes) was added. After 30 min, the reaction was quenched with aq. sat. NH₄Cl (5 mL) and extracted with EtOAc (3 x 5 mL). The dried (MgSO₄) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 50-70% Et₂O/hexanes to obtain the ketone 7.8.4 (2.5 mg, 7.0 μmol, 40%) as colorless oil. [α]D²⁰ = -10.3° (c = 0.40, CHCl₃); IR (neat) 2964, 2923, 2853, 1760, 1724, 1602, 1453, 1315, 1269, 1157, 1069, 712 cm⁻¹; ¹H NMR (700 MHz, CDCl₃) δ ppm 7.95 (dd, J = 8.4, 1.3 Hz, 2 H) 7.56 - 7.64 (m, 1 H) 7.46 (t, J = 7.8 Hz, 2 H) 5.39 (td, J = 6.6, 3.5 Hz, 1 H) 4.76 (dt, J = 8.8, 3.7 Hz, 1 H) 4.28 - 4.35 (m, 1 H) 4.21 - 4.28 (m, 3 H) 4.14 (dd, J = 8.1, 5.9 Hz, 1 H) 3.65 (dd, J = 8.0, 6.5 Hz, 1 H) 2.75 (dd, J = 18.3, 8.6 Hz, 1 H) 2.45 (dd, J = 18.4, 3.6 Hz, 1 H) 2.17 - 2.23 (m, 1 H) 2.04 - 2.13 (m, 2 H) 1.95 (m, J = 14.4, 7.5 Hz, 1 H) 1.43 (s, 3 H) 1.33 (s, 3 H) 1.21 (s, 9 H); ¹³C NMR (175 MHz, CDCl₃) δ 214.1, 178.1, 165.8, 133.2, 129.4, 129.2, 128.4, 109.1, 74.9, 74.1, 72.3, 69.2, 60.0, 38.1, 34.5, 30.7, 29.5, 26.9, 26.8, 25.4; HRMS (ES+) calcd. for C₂₅H₃₄O₈Na (M+Na) 485.2151 found 485.2162.
Ketone 7.8.3: To a solution of dibenzoate 7.8.1 (10 mg, 17.6 µmol) in toluene (0.15 mL) was added AgBF₄ (0.3 mg, 1.7 µmol). The reaction mixture was refluxed in dark. After 15 min, the reaction was cooled down to -78 °C and diluted withEt₂O (0.15 mL). To the mixture were sequentially added MeLi•LiBr (35.2 µL, 77.4 mmol, 2.2 M in hexanes). After 30 min, the reaction was quenched with aq. sat. NH₄Cl (5 mL) and extracted with DCM (3 x 5 mL). The dried (MgSO₄) extract was concentrated in vacuo to obtain the crude alcohol SI-12 as colorless oil.

To a solution of crude alcohol SI-12 (~17.6 µmol) in THF (0.15 mL) at -78 °C was added 2,6-lutidine (11.3 mg, 12.3 µL, 0.11 mmol) followed by TBSOTf (14 mg, 12 µL, 0.053 mmol). After 1 h, the reaction was quenched with aq. sat. NH₄Cl (5 mL) and extracted with EtOAc (3 x 5 mL). The dried (MgSO₄) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 10-30% Et₂O/hexanes to obtain the ketone 7.8.3 (2.1 mg, 6.1 µmol, 35%) as colorless oil.

Diol 7.2.7: To a solution of enyne 7.7.3 (1.93 g, 4.40 mmol), in a 1:1 mixture (9.0 mL) of t-BuOH and H₂O was added Ad mix β*#26 (6.2 g) followed by MeSO₂NH₂ (0.84 g,
8.82 mmol) at rt. After 24 h, the reaction was quenched with Na$_2$SO$_3$ (10 g) and extracted with EtOAc (3 x 30 mL). The dried (MgSO$_4$) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 80-100% Ether/hexanes to sequentially obtain a 3.6:1 diastereomeric mixture (1.58 g, 3.35 mmol, 76%) of diol 7.2.8 (0.34 g, 0.73 mmol, 17%) followed by diol 7.2.7 (1.24 g, 2.62 mmol, 59%) as colorless oil. **Diol 7.2.7** (1.24 g, 2.62 mmol, 59%) colorless oil. $[\alpha]_D^{20} = -22.6^\circ$ (c = 1.13, CHCl$_3$); IR (neat) 3434, 2957, 2936, 2915, 2877, 1731, 1459, 1398, 1379, 1369, 1158, 1098, 745 cm$^{-1}$; $^1$H NMR (700 MHz, CDCl$_3$) $\delta$ 4.57 (td, $J = 6.6$, 1.5 Hz, 1 H) 4.43 (ddd, $J = 5.6$, 4.2, 1.5 Hz, 1 H) 4.38 - 4.42 (m, 1 H) 4.29 (dt, $J = 11.3$, 6.0 Hz, 1 H) 4.18 (ddd, $J = 11.2$, 7.0, 5.9 Hz, 1 H) 4.14 (dd, $J = 8.1$, 6.1 Hz, 1 H) 3.92 - 3.97 (m, 1 H) 3.63 (dd, $J = 8.2$, 7.5 Hz, 1 H) 2.65 (br. s., 1 H) 2.48 - 2.57 (m, 1 H) 1.99 - 2.07 (m, 2 H) 1.87 (t, $J = 6.1$ Hz, 2 H) 1.45 (s, 3 H) 1.39 (s, 3 H) 1.22 (s, 9 H) 1.00 (t, $J = 8.0$ Hz, 9 H) 0.63 - 0.73 (m, 6 H); $^{13}$C NMR (175 MHz, CDCl$_3$) $\delta$ 178.5, 109.0, 87.8, 81.8, 73.4, 71.5, 69.5, 66.5, 60.6, 59.4, 38.8, 37.8, 35.8, 27.2, 26.9, 25.7, 6.8, 4.7; HRMS (ES+) calcd. for C$_{24}$H$_{44}$O$_7$SiNa (M+Na) 495.2754, found 495.2739.

**Dibenzoate SI-13:** To a solution of diol 7.2.7 (0.75 g, 1.59 mmol) in DCM (4 mL) and Et$_3$N (4 mL) at 0 °C was added DMAP (18.3 mg, 0.16 mmol) followed by benzyol chloride (1.47 g, 1.22 mL, 10.47 mmol). After 5 min, the reaction mixture was
warmed to rt. After 10 h, the reaction was quenched with sat. aq. NH₄Cl (5 mL) and extracted with DCM (3 x 40 mL). The combined organic phase was washed with sat. aq. NaCl (15 mL). The dried (MgSO₄) extract was concentrated in vacuo and purified by column chromatography over silica gel, eluting with 5-15% EtOAc/Hexanes to obtain the dibenzoate **SI-13** (0.974 g, 1.43 mmol, 90%) as a colorless oil. [α]D²⁰ = -54.0° (c = 2.60, CHCl₃); IR (neat) 2958, 2936, 2876, 1729, 1452, 1369, 1273, 1156, 1104, 1095, 1069, 711 cm⁻¹; ¹H NMR (700 MHz, CDCl₃) δ 8.00 - 8.06 (m, 4 H) 7.55 - 7.63 (m, 2 H) 7.41 - 7.49 (m, 4 H) 6.09 (dd, J = 3.3, 1.6 Hz, 1 H) 5.65 (dt, J = 9.7, 3.3 Hz, 1 H) 4.56 - 4.61 (m, 1 H) 4.24 - 4.29 (m, 1 H) 4.19 - 4.23 (m, 2 H) 4.07 (dd, J = 8.1, 5.9 Hz, 1 H) 3.65 (dd, J = 8.0, 6.9 Hz, 1H) 2.32 (ddd, J = 14.4, 8.0, 3.5 Hz, 1 H) 2.21 (ddd, J = 14.4, 9.6, 4.9 Hz, 1 H) 2.01-2.05 (m, 2 H) 1.46 (s, 3 H) 1.34 (s, 3 H) 1.22 (s, 9 H) 0.97 (t, J = 8.0 Hz, 9 H) 0.61-0.72 (m, 6 H); ¹³C NMR (100 MHz, CDCl₃) δ 178.3, 165.7, 165.0, 133.7, 133.33, 133.29, 130.2, 129.9, 129.8, 129.7, 129.5, 128.5, 125.6, 109.1, 88.6, 78.0, 72.7, 71.9, 69.6, 65.6, 60.5, 59.29, 38.7, 37.7, 34.4, 27.2, 27.0, 25.7, 6.7, 4.7; HRMS (ES+) calcd. for C₃₈H₅₂O₅SiNa (M+Na) 703.3278, found 703.3245.

**Alcohol 7.1.2:** To a solution of TES ether **SI-13** (1 g, 1.54 mmol) in THF (18 mL) at rt was added a stock solution of HF•pyr²¹ (1 mL). After 1 h, the reaction was quenched with sat. aq. NaHCO₃ (30 mL) and the aqueous layer was extracted with EtOAc (3 X 30
mL). The dried (MgSO₄) extract was concentrated in vacuo and purified by flash chromatography over silica gel, eluting with 25-40% EtOAc / hexanes, to give alcohol 7.1.2 (0.81 g, 1.43 mmol, 95%) as a colorless oil. [α]D²⁰ = -43.4° (c = 1.80, CHCl₃); IR (neat) 3442, 2979, 2934, 2873, 1726, 1601, 1452, 1370, 1315, 1274, 1156, 1107, 1094, 1068, 1026, 712 cm⁻¹; ¹H NMR (700 MHz, CDCl₃) δ 8.04 (ddd, J = 16.1, 8.5, 1.4 Hz, 4 H) 7.57-7.63 (m, 2 H) 7.46 (ddd, J = 8.2, 7.5, 2.6 Hz, 4 H) 6.06 (dd, J = 3.5, 1.6 Hz, 1 H) 5.66 (dt, J = 9.7, 3.3 Hz, 1 H) 4.53-4.59 (m, 1 H) 4.32-4.36 (m, 1 H) 4.27 (dt, J = 7.9, 6.3, 4.9 Hz, 1 H) 4.21 (dt, J = 11.4, 5.7 Hz, 1 H) 4.08 (dd, J = 8.1, 5.9 Hz, 1 H) 3.67 (dd, J = 8.2, 6.5 Hz, 1 H) 2.30-2.35 (m, 2 H) 2.20 (ddd, J = 14.4, 9.7, 4.8 Hz, 1 H) 2.06 (dt, J = 7.5, 5.7, 1.7 Hz, 2 H) 1.46 (s, 3 H) 1.35 (s, 3 H) 1.21 (s, 9 H) ¹³C NMR (175 MHz, CDCl₃) δ 178.6, 165.7, 165.1, 133.5, 133.4, 129.9, 129.8, 129.7, 129.3, 128.51, 128.49, 109.3, 87.8, 79.1, 72.7, 71.9, 69.6, 65.5, 60.6, 59.4, 38.8, 36.7, 34.5, 27.2, 27.1, 25.7; HRMS (ES+) calcd. for C₃₂H₃₀O₉ (M+H) 567.2594, found 567.2582.

**Ketone 7.9.2:** To a solution of dibenzoate 7.1.2 (14 mg, 25 µmol) in toluene (0.2 mL) was added AgBF₄ (0.48 mg, 2.5 µmol). The reaction mixture was refluxed in dark. After 15 min, the reaction was cooled down to -78 °C and diluted with Et₂O (0.2 mL). After 5 min, MeLi•LiBr (25 µL, 55 µmol, 2.2 M in hexanes) was added. After 30 min, the reaction was quenched with aq. sat. NH₄Cl (5 mL) and extracted with EtOAc (3 x 5
mL). The dried (MgSO₄) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 50-70% Et₂O/hexanes to obtain the ketone 7.9.2 (8.0 mg, 17.5 µmol, 70%) as colorless oil. 1H NMR (700 MHz, CDCl₃) δ 8.05 (dd, J = 8.4, 1.3 Hz, 2 H) 7.60 - 7.65 (m, 1 H) 7.48 (dd, J = 8.2, 7.5 Hz, 2 H) 5.55 (dt, J = 8.8, 3.7 Hz, 1 H) 4.49 (ddd, J = 10.0, 6.3, 3.5 Hz, 1 H) 4.20-4.31 (m, 3 H), 4.03 (dd, J = 8.2, 6.0 Hz, 1 H) 3.94 (dd, J = 6.7, 4.5 Hz, 1 H) 3.60 (dd, J = 8.2, 6.9 Hz, 1 H) 2.57 (dd, J = 18.0, 6.4 Hz, 1 H) 2.41 (dd, J = 18.1, 10.1 Hz, 1 H) 2.09-2.20 (m, 3 H) 1.98-2.05 (m, 1H) 1.43 (s, 3 H) 1.33 (s, 3 H) 1.11 (s, 9 H).

**Ketone 7.10.2:** To a solution of dibenzoate 7.1.2 (570 mg, 1.01 mmol) in toluene (4 mL) was added AgBF₄ (19.6 mg, 0.1 mmol). The reaction mixture was refluxed in dark. After 20 min, the reaction was cooled down to -78 °C and diluted with Et₂O (3.25 mL). After 5 min, MeLi•LiBr (2.75 mL, 6.1 mmol, 2.2 M in hexanes) was added. After 15 min, reaction was quenched with aq. sat. NH₄Cl (20 mL) and extracted with EtOAc (3 x 30 mL). The dried (MgSO₄) extract was concentrated in vacuo to obtain the crude alcohol 7.10.1 as colorless oil.

To a solution of crude alcohol 7.10.1 (1.01 mmol) in THF (6.8 mL) at -78 °C was added 2,6-lutidine (541 mg, 0.59 mL, 5.1 mmol) followed by TBSOTf (667 mg, 0.58
mL, 2.53 mmol). After 1 h, the reaction was quenched with aq. sat. NH₄Cl (10 mL) and extracted with EtOAc (3 x 20 mL). The dried (MgSO₄) extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 10-30% Et₂O/hexanes to obtain the ketone 7.8.3 (324 mg, 0.69 mmol, 68%, 2 steps) as colorless oil. [α]D²₀ = -47.0° (c = 1.35, CHCl₃); IR (neat) 2957, 2927, 2855, 1762, 1731, 1462, 1369, 1282, 1252, 1154, 1105, 837, 778 cm⁻¹; ¹H NMR (700 MHz, CDCl₃) δ 4.09 (dd, J = 7.9, 5.9 Hz, 1 H) 4.07 (td, J = 6.2, 2.9 Hz, 1 H) 3.89 (dd, J = 8.00, 4.2 Hz, 1 H) 3.54 (t, J = 7.6 Hz, 1 H) 2.46 (dd, J = 17.9, 6.1 Hz, 1 H) 2.34 (dd, J = 18.0, 10.2 Hz, 1 H) 2.12 (dddd, J = 14.5, 7.4, 6.1, 4.3 Hz, 1 H) 1.93 (ddt, J = 14.3, 8.1, 6.1, Hz, 1 H) 1.69 - 1.75 (m, 1 H) 1.60 - 1.66 (m, 1 H) 1.43 (s, 3 H) 1.37 (s, 3 H) 1.20 (s, 9 H) 0.92 (s, 9 H) 0.15 (s, 3 H) 0.14 (s, 3 H); ¹³C NMR (175 MHz, CDCl₃) δ 214.5, 178.3, 108.9, 79.0, 78.2, 72.2, 71.2, 69.8, 60.4, 38.9, 38.7, 36.9, 30.3, 29.7, 27.16, 27.11, 25.9, 25.8, 18.2, -4.2, -4.6; HRMS (ES+) calcd. for C₂₄H₄₄O₇NaSi (M+Na) 495.2754, found 495.2774.

Alkene 7.3.5: To a solution of ketone 7.10.2 (240 mg, 0.51 mmol) in toluene (2.4 mL) was added Cp₂TiMe₂ (1.63 mL, 0.81 mmol, 0.5 M solution in THF)²⁷ and the reaction mixture was heated to 90 °C in the dark. After 1 h, the volume of reaction mixture was reduced in vacuo and purified by chromatography over silica gel, eluting
with 10-30% Et₂O/hexanes to obtain the alkene 7.3.5 (220 mg, 0.47 mmol, 92%) as colorless oil. [α]_D<sup>20</sup> = -39.0° (c = 1.00, CHCl₃); IR (neat) 3079, 2956, 2927, 2855, 1732, 1462, 1368, 1283, 1249, 1157, 1100, 837, 777 cm⁻¹; ^1H NMR (700 MHz, CDCl₃) δ 5.00-5.02 (m, 1 H) 4.87 (dt, J = 2.9, 1.9 Hz, 1 H) 4.34-4.39 (m, 1 H) 4.24-4.32 (m, 2 H) 4.19 (ddd, J = 10.9, 7.7, 7.0 Hz, 1 H) 4.08 (dd, J = 7.8, 6.0 Hz, 1 H) 3.98 (ddd, J = 10.0, 6.2, 2.5 Hz, 1 H) 3.82 (dt, J = 10.1, 6.0 Hz, 1 H) 3.53 (t, J = 7.63 Hz, 1 H) 2.47-2.55 (m, 1 H) 2.37 (ddq, J = 15.6, 10.2, 2.5 Hz, 1 H) 2.02 (dtd, J = 14.2, 7.6, 3.6 Hz, 1 H) 1.85 (ddd, J = 13.9, 8.6, 6.9, 5.1 Hz, 1 H) 1.68 (ddd, J = 13.6, 8.9, 2.5 Hz, 1 H) 1.57 (ddd, J = 13.7, 10.0, 3.8 Hz, 1 H) 1.43 (s, 3 H) 1.37 (s, 3 H) 1.22 (s, 9 H) 0.92 (s, 9 H) 0.13 (s, 3 H) 0.13 (s, 3 H); ^13C NMR (175 MHz, CDCl₃) δ 178.5, 150.8, 108.7, 104.8, 81.6, 77.6, 72.5, 71.4, 70.0, 61.4, 38.7, 36.8, 34.7, 34.3, 27.2, 27.1, 26.0, 25.8, 18.3, -4.1, -4.7; HRMS (ES+) calcd. for C₂₅H₄₆O₆NaSi (M+Na) 493.2961, found 493.2974.

**Acetonide 7.3.6:** To a solution of alkene 7.3.5 (217 mg, 0.46 mmol) in EtOH (4.7 mL) under argon atmosphere at -40 °C was added 5% (by wt) Rh/Alumina (434 mg, 10% by wt). The argon was then removed by flushing with H₂ gas. After 5 min, the reaction was sealed under 1 atm of H₂ (balloon). After 24 h, the hydrogen was removed by flushing with argon, and the reaction mixture was filtered through Celite washing with EtOH (20 mL). The filtered extract was concentrated in vacuo and purified by
chromatography over silica gel, eluting with 10-30% Et₂O/hexanes to obtain the acetonide **7.3.6** (216 mg, 0.46 mmol, 99%) as colorless oil. \([\alpha]_{D}^{20} = -42.2^\circ\) (c = 1.00, CHCl₃); IR (neat) 2958, 2930, 2857, 1730, 1480, 1250, 1157, 1093, 777 cm⁻¹; \(^1\)H NMR (700 MHz, CDCl₃) δ 4.27-4.31 (m, 1 H) 4.23-4.27 (m, 1 H) 4.16 (dt, \(J = 10.6, 7.5\) Hz, 1 H) 4.07 (dd, \(J = 7.9, 6.2\) Hz, 1 H) 3.87-3.93 (m, 2 H) 3.73 (dt, \(J = 9.2, 6.4\) Hz, 1 H) 3.52 (t, \(J = 7.7\) Hz, 1 H) 2.35 (spt, \(J = 7.3\) Hz, 1 H) 1.98-2.05 (m, 1 H) 1.68-1.75 (m, 3 H) 1.43 (s, 3 H) 1.37 (s, 3 H) 1.26-1.33 (m, 1 H) 1.22 (s, 9 H) 0.96 (d, \(J = 7.04\) Hz, 3 H) 0.92 (s, 9 H) 0.13 (s, 3 H) 0.13 (s, 3 H); \(^{13}\)C NMR (175 MHz, CDCl₃) δ 178.6, 108.6, 82.0, 77.9, 72.6, 71.7, 70.0, 62.4, 38.7, 37.3, 35.4, 30.3, 27.2, 27.1, 26.0, 25.8, 18.3, 15.3, -4.00, -4.7; HRMS (ES+) calcd. for C₂₅H₄₈O₆NaSi (M+Na) 495.3118, found 495.3106.

**Alcohol 5.9.2.** To a solution of pivaloate ester **7.3.6** (36.6 mg, 77.5 µmol), in DCM (0.78 mL) at -78 °C was added DIBAL-H (0.17 mL, 0.17 mmol, 1 M solution in hexanes). After 10 min, the reaction was quenched with MeOH (3 mL). After 5 min, the reaction was warmed to 0 °C and was added aq. sat. solution of Rochelle’s salt (10 mL). After 3 h, the aqueous layer was extracted with EtOAc (3 X 10 mL). The dried (MgSO₄) extract was concentrated *in vacuo* and purified by flash chromatography over silica gel, eluting with 20-40% Et₂O / hexanes, to give the known** alcohol **5.9.2** (27 mg, 70 µmol,
90%) as a colorless oil. \([\alpha]_D^{20} = -42.4^\circ (c = 1.00, \text{CHCl}_3); \] $^1$H NMR (700 MHz, CDCl$_3$) $\delta$

4.26 (dddd, $J = 9.2, 7.5, 5.7, 3.5$ Hz, 1 H) 4.07 (dd, $J = 7.9, 5.7$ Hz, 1 H) 4.02 (ddd, $J = 10.5, 7.4, 2.9$ Hz, 1 H) 3.96 (ddd, $J = 9.6, 5.4, 2.6$ Hz, 1 H) 3.77-3.86 (m, 3 H) 3.52 (t, $J = 7.9$ Hz, 1 H) 2.50 (br. s., 1 H) 2.36 (spt, $J = 7.26$ Hz, 1 H) 1.96 - 2.02 (m, 1 H) 1.70 - 1.78 (m, 2 H) 1.45-1.63 (m, 2 H) 1.42 (s, 3 H) 1.37 (s, 3 H) 1.33 - 1.38 (m, 1 H) 0.97 (d, $J = 7.0$ Hz, 3 H) 0.93 (s, 9 H) 0.13 (s, 3 H) 0.13 (s, 3 H); $^{13}$C NMR (175 MHz, CDCl$_3$) $\delta$

108.7, 82.1, 81.3, 72.6, 70.8, 70.0, 62.0, 37.3, 35.8, 35.0, 33.1, 27.1, 26.0, 25.8, 18.2, 15.3, -4.1, -4.6.

**Mesylate 7.12.1:** To a solution of alcohol 5.9.2 (40 mg, 0.102 mmol) in DCM (1.0 mL) at 0 °C was added Et$_3$N (20.6 mg, 28.4 mL, 0.2 mmol) followed by MsCl (15.2 mg, 10.3 mL, 0.132 mmol). After 30 min, the reaction was quenched with sat. aq. NH$_4$Cl (5 mL) and extracted with EtOAc (3 x 10 mL). The combined organic phase was washed with sat. aq. NaCl (15 mL). The dried (MgSO$_4$) extract was concentrated in vacuo and passed through a small plug of silica gel, eluting with 40% EtOAc/hexanes to obtain the mesylate 7.12.1 (46.7 mg, 0.1 mmol, 99%) as a colorless oil. \([\alpha]_D^{20} = -46.5^\circ (c = 1.20, \text{CHCl}_3); \] IR (neat) 2956, 2928, 2855, 1471, 1359, 1251, 1176, 1062, 837 cm$^{-1}$; $^1$H NMR (700 MHz, CDCl$_3$) $\delta$

4.37 - 4.42 (m, 1 H) 4.34 (td, $J = 9.1, 6.4$ Hz, 1 H) 4.20 - 4.26 (m, 1 H) 4.04 (dd, $J = 7.7, 5.9$ Hz, 1 H) 3.92 (ddd, $J = 10.5, 7.4, 2.9$ Hz, 1 H) 3.85 (ddd, $J =
9.2, 5.9, 2.9 Hz, 1 H) 3.73 (dt, \( J = 9.2, 6.2 \) Hz, 1 H) 3.48 (t, \( J = 7.7 \) Hz, 1 H) 2.99 (s, 3 H) 2.36 (spt, \( J = 7.3 \) Hz, 1 H) 1.98 (dt, \( J = 12.4, 7.0 \) Hz, 1 H) 1.79 - 1.86 (m, 1 H) 1.72-1.79 (m, 1 H) 1.66 - 1.69 (m, 1 H) 1.54 (ddd, \( J = 13.6, 9.7, 4.0 \) Hz, 1 H) 1.39 (s, 3 H) 1.33 (s, 3 H) 1.26-1.32 (m, 1 H) 0.94 (d, \( J = 7.04 \) Hz, 3 H) 0.88 (s, 9 H) 0.09 (s, 3 H); \( ^{13} \text{C} \) NMR (175 MHz, CDCl\(_3\)) \( \delta \) 108.7, 82.1, 76.8, 72.5, 71.4, 69.9, 68.5, 37.4, 37.2, 35.5, 35.2, 31.0, 29.7, 27.1, 26.0, 25.8, 18.2, 15.1, -4.0, -4.6; HRMS (ES+) calcd. for C\(_{21}\)H\(_{42}\)O\(_7\)SNaSi (M+Na) 489.2318, found 489.2319.

**Iodide 7.12.2:** To a solution of mesylate 7.12.1 (40 mg, 85.7 \( \mu \)mol) in acetone (0.86 mL) was added NaI (89.93 mg, 0.60 mmol) and was heated at 55 °C. After 4 h, the reaction was quenched with H\(_2\)O (5 mL) and the volume of acetone was reduced in vacuo and extracted with EtOAc (3 x 10 mL) and 

The combined organic phase was washed with sat. aq. NaCl (15 mL). The dried (MgSO\(_4\)) extract was concentrated in vacuo and passed through a small plug of silica gel, eluting with 10% EtOAc/Hexanes to obtain the iodide 7.12.2 (42 mg, 84 \( \mu \)mol, 98%) as a pale yellow oil. \([\alpha]_D^{20} = -45.3^\circ \) (c = 1.20, CHCl\(_3\)); IR (neat) 2956, 2927, 2855, 1461, 1378, 1249, 1092, 1062, 836, 776 cm\(^{-1}\); \(^1\)H NMR (700 MHz, CDCl\(_3\)) \( \delta \) 4.28 (dddd, \( J = 9.1, 7.4, 5.7, 3.7 \) Hz, 1 H) 4.07 (dd, \( J = 7.9, 6.2 \) Hz, 1 H) 3.86-3.92 (m, 2 H) 3.76 (dt, \( J = 9.7, 6.2 \) Hz, 1 H) 3.52 (t, \( J = 7.7 \) Hz, 1 H) 3.38 (ddd, \( J = 9.7, 7.9, 4.8 \) Hz, 1 H) 3.25 (dt, \( J = 9.4, 8.1 \) Hz, 1 H) 2.32-2.42 (m, 1 H) 2.00 (ddd, \( J =
12.4, 7.4, 6.2 Hz, 1 H) 1.83-1.93 (m, 2 H) 1.69 (ddd, J = 13.6, 8.8, 2.64 Hz, 1 H) 1.56 (ddd, J = 13.6, 9.7, 4.0 Hz, 1 H) 1.43 (s, 3 H) 1.37 (s, 3 H) 1.26 - 1.32 (m, 1 H) 0.96 (d, J = 7.04 Hz, 3 H) 0.92 (s, 9 H) 0.12 (s, 6 H); \(^{13}\)C NMR (175 MHz, CDCl\(_3\)) \(\delta\) 108.7, 82.0, 80.9, 72.6, 71.6, 70.0, 37.3, 35.6, 35.5, 35.4, 29.7, 27.2, 26.0, 25.8, 18.3, 15.1, 4.0, -4.0, -4.7; HRMS (ES+) calcd. for C\(_{20}\)H\(_{39}\)O\(_4\)INaSi (M+Na) 521.1560, found 521.1576.

**Phosphonium Salt 7.1.1:** To a solution of iodide 7.12.2 (44 mg, 88 \(\mu\)mol) in toluene (0.9 mL) was added NaHCO\(_3\) (11 mg, 0.132 mmol) and PPh\(_3\) (185 mg, 0.71 mmol) and was started to reflux. After 24 h, the reaction mixture was cooled to rt and washed multiple times with hexanes to remove excess PPh\(_3\). Also, dissolved in DCM to get rid off insoluble NaHCO\(_3\). The amorous solid obtained was used in the subsequent step without further purification. \(^1\)H NMR (700 MHz, CDCl\(_3\)) \(\delta\) 7.82-7.88 (m, 9 H), 7.73-7.76 (m, 6 H), 4.39-4.45 (m, 1 H), 4.26-4.28 (m, 1 H), 4.22-4.25 (m, 1 H), 4.08 (dd, J = 13.3, 5.6 Hz, 1 H), 3.91 (ddd, J = 8.4, 6.3, 2.1 Hz, 1 H), 3.73-3.76 (m, 1 H), 3.49 (t, J = 7.7 Hz, 1 H), 3.42-3.44 (m, 1 H), 2.44 (spt, J = 7.0 Hz, 1 H), 2.09 (dt, J = 12.6, 7.7 Hz, 1 H), 1.96-2.02 (m, 1 H), 1.58-1.65 (m, 2 H), 1.50-1.54 (m, 1 H), 1.43 (s, 3 H), 1.37 (s, 3 H), 1.29-1.32 (m, 1 H), 0.88 (s, 9 H), 0.79 (d, J = 7.0 Hz, 3 H), 0.06 (s, 3 H), 0.04 (s, 3 H) ppm; HRMS (ES+) calcd. for C\(_{39}\)H\(_{54}\)O\(_4\)PSi (M+) 633.3529, found 633.3543.
Enal 7.13.4: To a solution of allyl alcohol 7.13.1 (15 mg, 22.1 µmol) in DCM (0.25 mL) at 0 °C was added NaHCO₃ (9.3 mg, 0.11 mmol) followed by Dess-Martin periodinane (23.3 mg, 55.3 µmol). After the 5 min, the reaction mixture was warmed to rt. After 20 min, the reaction was quenched with aq. sat. Na₂S₂O₃ solution (5 mL). After 15 min, the aqueous phase was extracted with DCM (3 x 5 mL). The combined organic phase was washed with sat. aq. NaCl (15 mL). The dried (MgSO₄) extract was concentrated in vacuo to afford the crude enal 7.13.2, which was used in the subsequent step without further purification.

To a solution of crude enal 7.13.2 (~22.1 µmol) in DCM (0.11 mL) at rt was added methyl acrylate (38.2 mg, 40 µL, 0.443 mmol) followed by Grubbs II Gen. cataly (1.88 mg, 2.22 µmol). After 2 h, the reaction mixture was directly loaded on flash column chromatography for purification over silica gel eluting with 10-50% Et₂O/Hexanes to obtain the enal 7.13.4 (13.4 mg, 18.2 µmol, 82%, 2 steps) as colorless oil. [α]D²⁰ = -39.6° (c = 1.00, CHCl₃); IR (neat) 2953, 2928, 2856, 1726, 1692, 1462, 1122, 1096, 1046, 838 cm⁻¹; ¹H NMR (700 MHz, CDCl₃) δ 9.53 (d, J = 7.9 Hz, 1 H) 6.98 (dt, J = 15.6, 7.2 Hz, 1 H) 6.86 (dd, J = 15.6, 7.3 Hz, 1 H) 6.11 (ddd, J = 15.7, 7.8, 1.1 Hz, 1 H)
5.91 (d, \(J = 15.8\) Hz, 1 H) 4.91 (d, \(J = 3.1\) Hz, 1 H) 3.88 (dd, \(J = 7.0, 2.6\) Hz, 1 H) 3.77 (s, 3 H) 3.74-3.80 (m, 1 H) 3.55 - 3.62 (m, 2 H) 3.48 (s, 3 H) 3.37 - 3.44 (m, 2 H) 3.35 (t, \(J = 2.9\) Hz, 1 H) 2.72 (m, \(J = 13.5, 6.7\) Hz, 1 H) 2.43 - 2.50 (m, 1 H) 2.35-2.41 (m, 1 H) 1.96-2.02 (m, 2 H) 1.77 (dd, \(J = 14.0, 9.1, 6.4\) Hz, 1 H) 1.44-1.49 (m, 1 H) 1.28-1.34 (m, 1 H) 1.26 (d, \(J = 5.7\) Hz, 3 H) 1.17 - 1.23 (m, 1 H) 1.13 (d, \(J = 6.6\) Hz, 3 H) 0.95 (s, 9 H) 0.92 (s, 9 H) 0.14 (s, 3 H) 0.13 (s, 3 H) 0.13 (s, 3 H) 0.11 (s, 3 H); \(^{13}\text{C}\) NMR (175 MHz, CDCl\(_3\)) \(\delta\) 194.4, 166.8, 164.1, 145.1, 130.8, 123.1, 96.0, 81.6, 74.2, 73.4, 73.2, 72.9, 70.5, 58.8, 51.5, 41.9, 39.5, 38.7, 37.2, 33.6, 30.3, 29.7, 26.3, 26.1, 18.73, 18.68, 18.4, 18.1, -2.9, -3.8, -4.15, -4.20; HRMS (ES+) calcd. for C\(_{35}\)H\(_{60}\)O\(_9\)NaSi\(_2\) (M+Na) 707.3987, found 707.3956.

**Diene 7.13.6:** To a solution of phosphonium salt 7.1.1 (39 mg, 51.3 \(\mu\)mol) in THF (0.4 mL) at -78 °C was added NaHMDS (28.3 \(\mu\)L, 56.7 \(\mu\)mol, 2.0 M solution in hexanes). After 5 min, the reaction was slowly warmed to rt over a period of 70 min. After 5 min, the reaction mixture was cooled back to -78 °C and was added a solution of
enal \textbf{7.13.4} (32 mg, 43.6 µmol) in THF (0.2 mL). After 5 min, the reaction was slowly warmed to -10 °C over a period of 3.5 h. After 5 min, the reaction was quenched with aq. sat. NH$_4$Cl solution (5 mL). The aqueous phase was extracted with EtOAc (3 x 5 mL). The combined organic phase was washed with sat. aq. NaCl (15 mL). The dried (MgSO$_4$) extract was concentrated \textit{in vacuo} and purified by chromatography over silica gel, eluting with 10-30% Et$_2$O/hexanes to obtain the diene \textbf{7.13.6} (30.3 mg, 29.2 µmol, 67%) as colorless oil. $[\alpha]_D^{20} = -34.7^\circ$ (c = 0.85, CHCl$_3$); IR (neat) 2954, 2927, 2855, 1729, 1471, 1462, 1251, 1122, 1096, 1048, 837, 777 cm$^{-1}$; $^1$H NMR (700 MHz, CDCl$_3$) $\delta$ 7.00 (dt, $J$ = 15.7, 7.1 Hz, 1 H) 6.28 (dd, $J$ = 15.4, 11.0 Hz, 1 H) 6.02 (t, $J$ = 11.0 Hz, 1 H) 5.91 (dt, $J$ = 15.5, 1.5 Hz, 1 H) 5.62 (dd, $J$ = 15.2, 7.7 Hz, 1 H) 5.41 (dt, $J$ = 10.9, 7.1 Hz, 1 H) 4.91 (d, $J$ = 3.08 Hz, 1 H) 4.24-4.34 (m, 1 H) 4.07 (dd, $J$ = 7.70, 5.94 Hz, 1 H) 3.94 (ddd, $J$ = 9.6, 6.7, 2.6 Hz, 1 H) 3.89 (dd, $J$ = 7.5, 2.6 Hz, 1 H) 3.84 (q, $J$ = 6.9 Hz, 1 H) 3.77 (s, 3 H) 3.75-3.79 (m, 2 H), 3.70-3.75 (m, 1 H) 3.56-3.63 (m, 2 H) 3.52 (t, $J$ = 7.70 Hz, 1 H) 3.48 (s, 3 H) 3.39-3.43 (m, 1 H) 3.36-3.39 (m, 1 H) 3.35 (t, $J$ = 2.86 Hz, 1 H) 2.42-2.52 (m, 2 H) 2.38 (dddd, $J$ = 14.9, 7.4, 5.5, 1.3 Hz, 1 H) 2.29-2.35 (m, 2 H) 1.95-2.05 (m, 3 H) 1.66-1.75 (m, 2 H) 1.54 (ddd, $J$ = 13.8, 9.8, 3.7 Hz, 1 H) 1.42 (s, 3 H) 1.36 (s, 3 H) 1.35-1.38 (m, 1H), 1.27-1.34 (m, 2 H) 1.26 (d, $J$ = 6.6 Hz, 3 H) 1.18 (q, $J$ = 11.4 Hz, 1 H) 1.04 (d, $J$ = 6.6 Hz, 3 H) 0.98 (d, $J$ = 7.0 Hz, 3 H) 0.96 (s, 9 H) 0.93 (s, 9 H) 0.91 (s, 9 H) 0.14 (s, 3 H) 0.136 (s, 3 H) 0.132 (s, 3 H) 0.130 (s, 3 H) 0.126 (s, 3 H) 0.11 (s, 3 H); $^{13}$C NMR (175 MHz, CDCl$_3$) $\delta$ 166.9, 145.3, 140.7, 129.8, 126.7, 123.6, 123.0, 108.6, 95.9, 81.6, 81.4, 74.0, 73.5, 73.2, 72.7, 71.7, 70.4, 70.1, 58.8, 51.5, 43.1, 39.4, 38.8, 37.4, 36.9, 35.5, 35.2, 33.1, 30.3, 29.7, 29.5, 27.2, 26.3, 26.12, 26.07, 25.8, 20.0, 18.7, 18.4, 18.3, 18.1,
15.6, -2.90, -3.75, -3.96, -4.14, -4.19, -4.71; HRMS (ES+) calcd. for C_{55}H_{103}O_{12}Si_{3} (M+H) 1039.6757, found 1039.6708.

**Diol 7.14.1:** To a solution of diene 7.13.6 (11 mg, 10.6 µmol) in 10:1 DCM/H_{2}O (0.15 mL) at rt was added trifluoroaceticacid (TFA) (12 mL, 0.159 mmol). After 15 min, the reaction was quenched with aq. sat. NaHCO_{3} solution (5 mL). The aqueous phase was extracted with EtOAc (3 x 5 mL). The dried (MgSO_{4}) organic extract was concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 60-100% Et_{2}O/hexanes to obtain the diol 7.14.1 (9.2 mg, 9.2 µmol, 86%) as colorless oil. [α]_{D}^{20} = -33.7° (c = 0.30, CHCl_{3}); IR (neat) 3375, 2956, 2927, 2855, 1728, 1660, 1554, 1463, 1257, 1096, 1046, 838 cm^{-1}; ^{1}H NMR (700 MHz, MeOH-d_{4}) δ 7.02 (dt, J = 15.6, 7.2 Hz, 1 H) 6.31 (dd, J = 15.0, 11.0 Hz, 1 H) 6.00 (t, J = 11.0 Hz, 1 H) 5.94 (dt, J = 15.7, 1.4 Hz, 1 H) 5.60 (dd, J = 15.2, 8.1 Hz, 1 H) 5.40 (dt, J = 10.8, 7.4 Hz, 1 H) 4.99 (d, J = 2.6 Hz, 1 H) 3.91-3.98 (m, 2 H) 3.87 (td, J = 9.4, 4.6 Hz, 1 H) 3.78-3.85 (m, 2 H) 3.74 (s, 3 H) 3.70-3.74 (m, 1 H) 3.62-3.67 (m, 1 H) 3.57-3.61 (m, 1 H) 3.47-3.50 (m, 2 H) 3.46 (s, 3
H) 3.40-3.45 (m, 1 H) 3.39 (t, J = 2.9 Hz, 1 H) 3.35-3.37 (m, 2 H) 3.26 (q, J = 7.5 Hz, 1 H) 2.41-2.47 (m, 3 H) 2.31-2.38 (m, 3 H) 2.08 (dt, J = 12.4, 7.4 Hz, 1 H) 2.03 (td, J = 12.2, 4.6 Hz, 2 H) 1.62-1.67 (m, 1 H) 1.48-1.53 (m, 2 H) 1.40-1.45 (m, 1 H) 1.28-1.31 (m, 1 H) 1.25 (d, J = 6.3 Hz, 3 H), 1.18-1.24 (m, 1 H) 1.12-1.18 (m, 1 H) 1.05 (d, J = 6.6 Hz, 3 H) 1.00 (d, J = 7.04 Hz, 3 H) 0.97 (s, 9 H) 0.95 (s, 9 H) 0.93 (s, 9 H) 0.161 (s, 3 H) 0.157 (s, 6 H) 0.15 (s, 3 H) 0.14 (s, 3 H) 0.13 (s, 3 H); \[^{13}\text{C}\] NMR (175 MHz, MeOH-d\(_4\)) \(\delta\) 167.2, 145.9, 140.3, 129.5, 126.4, 124.7, 123.7, 122.3, 95.6, 82.1, 81.5, 76.8, 74.0, 73.8, 73.5, 73.1, 72.3, 68.2, 66.8, 58.8, 57.4, 54.9, 50.6, 48.1, 42.7, 39.2, 38.2, 37.4, 36.8, 35.8, 35.4, 34.0, 33.3, 29.5, 29.2, 25.4, 25.33, 25.27, 19.4, 17.89, 17.87, 17.80, 17.5, 14.6, 7.1, -4.9, -5.2, -5.3, -5.7; HRMS (ES+) calcd. for \(\text{C}_{52}\text{H}_{99}\text{O}_{12}\text{Si}_{3}\) (M+H) 999.6444, found 999.6449.

**C-24 Macrolactone 7.14.4:** To a solution of ester 7.14.1 (4.5 mg, 4.51 \(\mu\)mol) in \(^{1}\text{PrOH}\) (0.15 mL) was added NaOH (0.14 mL, 72 \(\mu\)mol, 0.5 M solution in H\(_2\)O). The reaction mixture was heated at 45 °C. After 30 h, the reaction was quenched with solid
NH₄Cl (2-3 mg). After 5 min, the reaction mixture was cooled to rt and the solvent was concentrated *in vacuo* to obtain the crude seco-acid **7.14.2**, which was used in the subsequent step without further purification.

To a solution of crude seco-acid **7.14.2** (~4.3 µmol) in THF (75 µL) was added Et₃N (2.18 mg, 3.0 µL, 21.5 µmol) at 0 °C followed by a solution of 2,4,6-trichlorobenzoyl chloride (1.15 mg, 0.75 µL, 4.73 µmol) in THF (75 µL). After 1 h, the reaction was diluted with toluene (0.3 mL). After 5 min, the reaction mixture was slowly transferred to a flask with DMAP (0.95 mg, 7.74 µmol) and toluene (1.15 mL) at 75 °C. After 3 h, the solvent was removed *in vacuo* and purified by chromatography over silica gel, eluting with 30-60% Et₂O/hexanes to obtain the C-24 macrolactone **7.14.4** (1.5 mg, 1.55 mmol, 37%) as colorless oil. [α]D²⁰ = -26.9° (c = 0.13, CHCl₃); IR (neat) 3376, 2957, 2925, 2853, 1726, 1656, 1463, 1379, 1258, 1096, 1047 cm⁻¹; ¹H NMR (700 MHz, CDCl₃) δ 7.12 (dt, J = 15.7, 6.7 Hz, 1 H) 6.40 (dd, J = 15.0, 11.0 Hz, 1 H) 6.09 (t, J = 11.9 Hz, 1 H) 6.06, (s, 1 H) 5.55 (dd, J = 15.0, 9.2 Hz, 1 H) 5.36 (td, J = 10.1, 6.6 Hz, 1 H) 4.93 (d, J = 2.6 Hz, 1 H) 4.30 (dd, J = 11.0, 3.5 Hz, 1 H) 4.20 (dt, J = 7.0, 4.8 Hz, 1 H) 4.12 (dd, J = 11.4, 4.8 Hz, 1 H) 4.02-4.07 (m, 1 H) 3.93 (ddd, J = 9.0, 7.3, 4.4 Hz, 1 H) 3.84-3.90 (m, 2 H) 3.77-3.84 (m, 1 H) 3.55-3.63 (m, 2 H) 3.48 (s, 3 H) 3.37-3.45 (m, 2 H) 3.35 (t, J = 2.6 Hz, 1 H) 3.12 (d, J = 5.3 Hz, 1 H) 2.51-2.62 (m, 2 H) 2.41-2.47 (m, 1 H) 2.31-2.39 (m, 3 H) 2.09-2.14 (m, 1 H) 2.04-2.09 (m, 1 H) 2.00 (dd, J = 12.1, 4.6 Hz, 1 H) 1.94 (dd, J = 12.5, 4.6 Hz, 1 H) 1.87 (ddd, J = 14.6, 9.8, 5.1 Hz, 1 H) 1.63-1.68 (m, 1 H) 1.54-1.59 (m, 1 H) 1.47-1.51 (m, 1 H) 1.40-1.45 (m, 1 H) 1.30-1.35 (m, 1 H), 1.25 (d, J = 6.2 Hz, 3
H) 1.01 (d, J = 7.0 Hz, 3 H), 0.99 (d, J = 6.6 Hz, 3 H) 0.95 (s, 9 H) 0.92 (s, 9 H) 0.89 (s, 9 H) 0.13 (s, 3 H) 0.13 (s, 3 H) 0.13 (s, 3 H) 0.11 (s, 3 H) 0.09 (s, 3 H) 0.08 (s, 3 H);

$^{13}$C NMR (175 MHz, CDCl$_3$) $\delta$ 166.9, 146.1, 141.2, 130.6, 126.6, 124.0, 122.7, 95.7, 81.8, 80.3, 73.8, 73.2, 72.6, 70.3, 68.6, 67.0, 58.8, 42.9, 38.1, 37.8, 36.3, 35.0, 34.3, 33.8, 33.6, 32.0, 31.6, 30.3, 29.4, 28.9, 26.3, 26.1, 25.8, 23.7, 23.0, 22.74, 22.70, 21.2, 19.6, 18.4, 18.1, 18.0, 15.7, 14.2, 14.1, 11.0, 1.07, -4.13, -4.20, -4.47, -4.81; HRMS (ES+) calcd. for C$_{51}$H$_{95}$O$_{11}$Si$_3$ (M+H) 967.6182, found 967.6157.

**C-24 Macrolide (7.14.5):** To a solution of C-24 macrolactone 7.14.4 (1.2 mg, 1.24 µmol) in a 1:1 mixture of THF/DMF (0.12 mL) at 0°C was added TASF (6.3 mg, 22.9 µmol). After 24 h, the reaction was quenched with aq. sat. NH$_4$Cl solution (5 mL). The aqueous phase was extracted with EtOAc (3 x 5 mL). The combined organic layer was dried (MgSO$_4$), concentrated *in vacuo* and purified by chromatography over silica gel, eluting with 1-2% MeOH/EtOAc to obtain the C-24 macrolide 7.14.5 (0.5 mg, 0.8 mmol, 65%) as colorless oil. $[\alpha]_{D}^{20} = -26.0^\circ$ (c = 0.05, CDCl$_3$); IR (neat) 3409, 2957,
2921, 2851, 1720, 1655, 1463, 1378, 1106, 1077, 1044 cm⁻¹; ¹H NMR (700 MHz, CDCl₃) δ 7.07-7.18 (m, 1 H) 6.36 (dd, J = 14.5, 11.0 Hz, 1 H) 6.07 (t, J = 11.2 Hz, 1 H) 5.98 (d, J = 15.4 Hz, 1 H) 5.60 (dd, J = 15.2, 8.6 Hz, 1 H) 5.35 (m, J = 9.0, 3.3 Hz, 1 H) 5.06 (s, 1 H) 4.20-4.32 (m, 2 H) 4.08-4.15 (m, 1 H) 4.01-4.08 (m, 1 H) 3.82-3.88 (m, 1 H) 3.75-3.82 (m, 2 H) 3.70-3.74 (m, 1 H) 3.67 (dd, J = 9.5, 5.9 Hz, 1 H) 3.50 (s, 3 H) 3.44 (dd, J = 3.7, 1.5 Hz, 2 H) 3.39 (m, J = 5.3 Hz, 1 H), 3.32 (d, J = 7.0 Hz, 1 H) 2.67 (d, J = 4.0 Hz, 1 H) 2.54 (m, J = 11.0 Hz, 1 H) 2.34-2.50 (m, 4 H) 2.26-2.32 (m, 2 H) 2.01-2.09 (m, 3 H) 1.91 (m, J = 7.5 Hz, 1 H) 1.68-1.73 (m, 2 H) 1.64 (ddd, J = 14.2, 10.7, 3.7 Hz, 1 H) 1.35-1.41 (m, 1 H) 1.31 (d, J = 6.2 Hz, 3 H) 1.20-1.35 (m, 4 H) 1.04 (d, J = 7.0 Hz, 3 H) 1.00 (d, J = 6.6 Hz, 3 H); ¹³C NMR (175 MHz, CDCl₃) δ 166.5, 146.4, 141.2, 130.3, 126.6, 123.8, 122.6, 94.0, 82.2, 80.9, 80.6, 74.08, 74.03, 73.2, 72.7, 71.4, 67.9, 66.4, 59.0, 56.0, 53.5, 43.1, 39.5, 38.3, 37.6, 37.3, 35.0, 34.9, 33.6, 33.1, 32.0, 30.8, 29.4, 29.1, 22.7, 19.0, 17.5, 14.3, 14.2; HRMS (ES+) calcd. for C₃₃H₅₅O₁₁ (M+H) 625.3588, found 625.3628.
Alcohol SI-14: To a solution of diol 7.14.1 (9 mg, 9.0 µmol) in DCM (0.45 mL) at -78 °C were added 2,6-lutidine (6 mg, 6.3 µL, 54 µmol) and TBSOTf (7.2 mg, 6.3 µL, 27 µmol) solutions in THF portionwise over a period of 4 h. After 5 min, the reaction was quenched with aq. sat. NH₄Cl solution (5 mL). The aqueous phase was extracted with EtOAc (3 x 5 mL). The combined organic layer was washed with sat. aq. NaCl (5 mL) solution and the dried (MgSO₄) organic extract was concentrated in vacuo and purified by chromatography over silica gel, eluting with 30-60% Et₂O/hexanes to obtain the alcohol SI-14 (8.6 mg, 7.74 µmol, 86%) as colorless oil. [α]D²⁰ = -23.8° (c = 0.34, CHCl₃); IR (neat) 3439, 2953, 2926, 2854, 1727, 1660, 1462, 1361, 1250, 1094, 1045, 835, 775 cm⁻¹; ¹H NMR (700 MHz, CDCl₃) δ 7.00 (dt, J = 15.8, 7.0 Hz, 1 H) 6.27 (dd, J = 15.2, 10.8 Hz, 1 H) 6.01 (t, J = 11.0 Hz, 1 H) 5.91 (d, J = 15.9 Hz, 1 H) 5.61 (dd, J = 15.2, 7.7 Hz, 1 H) 5.41 (dt, J = 10.9, 7.3 Hz, 1 H) 4.90 (d, J = 3.1 Hz, 1 H) 3.96 (td, J = 6.9, 3.7 Hz, 1 H) 3.88 (dd, J = 7.5, 2.6 Hz, 2 H) 3.83-3.86 (m, 1 H) 3.79-3.83 (m, 1 H) 3.76 (s, 3 H) 3.56-3.63 (m, 2 H) 3.49-3.56 (m, 2 H) 3.48 (s, 3 H) 3.40 (dt, J = 11.4, 5.7 Hz, 1 H) 3.35-3.38 (m, 1 H) 3.35 (t, J = 2.9 Hz, 1 H) 3.07 (d, J = 2.6 Hz, 1 H) 2.42-2.52
(m, 2 H) 2.36-2.41 (m, 1 H) 2.32-2.36 (m, 3 H), 2.05 (dt, J = 12.8, 7.5 Hz, 1 H) 1.95-2.01 (m, 2 H) 1.66-1.72 (m, 1 H) 1.53-1.59 (m, 2 H) 1.36 (ddd, J = 13.4, 8.1, 4.8 Hz, 1 H) 1.25 (d, J = 6.2 Hz, 3 H) 1.18 (q, J = 11.4 Hz, 1 H) 1.04 (d, J = 6.6 Hz, 3 H), 0.97 (d, J = 7.0 Hz, 3 H) 0.95 (s, 9 H) 0.92 (s, 9 H) 0.92 (s, 9 H) 0.91 (s, 9 H) 0.14 (s, 6 H) 0.13 (s, 3 H) 0.12-0.13 (m, 6 H) 0.11 (s, 3 H) 0.10 (s, 3 H) 0.08-0.09 (m, 6 H); 13C NMR (175 MHz, CDCl3) δ 166.9, 145.3, 140.7, 129.8, 126.7, 123.7, 123.0, 81.5, 81.3, 74.0, 73.5, 73.3, 73.1, 70.5, 68.8, 67.7, 58.7, 51.5, 43.1, 39.4, 38.8, 37.4, 36.6, 35.9, 35.3, 33.1, 30.3, 29.5, 26.3, 26.1, 25.9, 20.0, 18.7, 18.4, 18.29, 18.27, 18.1, 15.6, 1.0, -4.1, -4.15, -4.19, -4.9, -5.33, -5.34; HRMS (ES+) calcd. for C38H62O12Si4Na (M+Na) 1135.7129, found 1135.7087.

**Allyl alcohol 7.15.1:** To a solution of ester **SI-14** (12 mg, 10.8 µmol), in DCM (0.1 mL) at -78 °C was added DIBAL-H (35.6 µL, 35.6 µmol, 1 M solution in hexanes). After 10 min, the reaction was quenched with MeOH (3 mL). After 5 min, the reaction was warmed to 0 °C and was added sat. aq. solution of Rochelle’s salt (5 mL). After 3 h,
the aqueous layer was extracted with EtOAc (3 X 5 mL). The dried (MgSO₄) extract was concentrated in vacuo and purified by flash chromatography over silica gel, eluting with 40-70% Et₂O / hexanes, to give the allyl alcohol 7.15.1 (11.1 mg, 10.26 µmol, 95%) as colorless oil. [α]D20 = -47.7° (c = 0.90, CHCl₃); IR (neat) 3403, 2958, 2930, 2858, 1473, 1362, 1253, 1121, 1097, 837, 777 cm⁻¹; ¹H NMR (700 MHz, MeOH-d₄) δ 6.27 (dd, J = 15.0, 11.0 Hz, 1 H) 6.00 (t, J = 11.0 Hz, 1 H) 5.69-5.77 (m, 2 H) 5.61 (dd, J = 15.4, 7.9 Hz, 1 H) 5.40 (dt, J = 10.9, 7.3 Hz, 1 H) 4.91 (d, J = 2.6 Hz, 1 H) 4.12 (d, J = 4.0 Hz, 2 H) 3.96 (td, J = 6.9, 3.7 Hz, 1 H) 3.85-3.90 (m, 2 H) 3.79-3.85 (m, 2 H) 3.71-3.76 (m, 1 H) 3.55-3.63 (m, 2 H) 3.49-3.55 (m, 3 H) 3.47 (s, 3 H) 3.34 (t, J = 2.9 Hz, 2 H) 3.26-3.31 (m, 1 H) 3.08 (br. s., 1 H) 2.45 (dt, J = 13.8, 7.0 Hz, 1 H) 2.29-2.38 (m, 3 H) 2.21 (dt, J = 13.6, 5.7 Hz, 1 H) 2.04 (dt, J = 13.1, 8.0 Hz, 1 H) 1.98 (dt, J = 11.7, 6.1 Hz, 2 H) 1.66-1.71 (m, 1 H) 1.52-1.61 (m, 3 H) 1.34-1.39 (m, 1 H) 1.26-1.31 (m, 1 H) 1.25 (d, J = 6.2 Hz, 3 H) 1.11-1.17 (m, 1 H) 1.03 (d, J = 6.6 Hz, 3 H) 0.99-1.02 (m, 1 H) 0.97 (d, J = 7.0 Hz, 3 H) 0.94 (s, 9 H) 0.91-0.92 (m, 18 H) 0.91 (s, 9 H) 0.13 (s, 6 H) 0.12 (m, J = 1.3 Hz, 9 H) 0.10 (s, 3 H) 0.08 (m, J = 1.3 Hz, 6 H); ¹³C NMR (175 MHz, MeOH-d₄) δ 140.9, 131.5, 130.0, 129.0, 126.7, 123.7, 81.65, 81.62, 81.5, 75.3, 73.7, 73.5, 73.4, 73.1, 70.5, 69.0, 67.8, 63.8, 58.9, 43.3, 39.7, 39.1, 37.5, 36.7, 36.0, 33.4, 29.9, 29.6, 26.5, 26.3, 26.2, 26.1, 20.2, 18.8, 18.5, 18.44, 18.42, 18.23, 15.7, -2.8, -3.6, -3.96, -4.0, -4.06, -4.7, -5.2; HRMS (ES+) calcd. for C₅₇H₁₁₃O₁₂Si₄ (M+H) 1085.7360, found 1085.7365.
Macrolactone 5.15.3: To a solution of allyl alcohol 7.15.1 (4 mg, 3.7 µmol), in 10:1 Hexanes/DCM (0.12 mL) at rt was added activated MnO₂ (64 mg, 0.74 mmol). After 12 h, the reaction mixture was filtered through celite and the solvent was concentrated in vacuo to give the crude enal SI-15. The crude enal was taken to the next step without further purification.

To a solution of crude enal SI-15 (~3.7 µmol) in 1:1 mixture of tBuOH:H₂O (0.1 mL) solvents at 0 °C was added 2-methyl-2-buten (13.0 mg, 19.6 µL, 185 µmol) followed by solid NaH₂PO₄•2H₂O (10.2 mg, 74 µmol) and NaClO₂ (1.67 mg, 18.5 µmol). After 5 min, the reaction was warmed to rt. After 2 h, the reaction was quenched with aq. sat. NaCl solution (5 mL). The aqueous phase was extracted with EtOAc (3 x 5 mL). The combined organic layer was dried (MgSO₄) and concentrated in vacuo to obtain the crude seco-acid SI-16, which was used in the next step without further purification.

To a solution of crude seco-acid (SI-16) (~2.5 µmol) in THF (40 µL) was added Et₃N (0.45 mg, 0.6 µL, 4.5 µmol) at 0 °C followed by a solution of 2,4,6-trichloro benzoyl chloride (0.73 mg, 0.5 µL, 3 µmol) in THF (20 µL). After 1 h, the reaction was
diluted with toluene (0.1 mL). After 5 min, the reaction mixture was slowly transferred to a flask with DMAP (0.55 mg, 9 µmol) and THF (0.8 mL) at 70 °C. After 3 h, the solvent was removed in vacuo and passed through a small plug of silica gel to give known\textsuperscript{29} the macrolactone 5.15.3 (2.1 mg, 2.0 µmol, 54% over 3 steps) as colorless oil. The macrolactone isolated from this reaction is still found to be not fully pure.

Mandelalide A (5.5.1): To a solution of macrolactone 5.5.3 (1.2 mg, 1.1 µmol) in a 1:1 mixture of THF/DMF (0.12 mL) at 0°C was added TASF (6.1 mg, 22.2 µmol). After 24 h, the reaction was quenched with aq. sat. NH\textsubscript{4}Cl solution (5 mL). The aqueous phase was extracted with EtOAc (3 x 5 mL). The combined organic layer was dried (MgSO\textsubscript{4}), concentrated in vacuo and purified by HPLC chromatography to obtain the mandelalide A (5.5.1) (0.4 mg, 0.96 µmol, 56%) as amorphous solid. Counter to prior reports in the literature,\textsuperscript{29} we found the natural product to be unstable on silicagel. Nevertheless, the NMR data for the HPLC purified sample was found to be in complete agreement with the literature reported values.\textsuperscript{30}
HPLC purification of mandelalide A (5.5.1) and C-24 macrolide (7.14.5):

Crude reaction mixtures containing mandelalide A (5.5.1) and C-24 macrolide (7.14.5) were each subjected to solid phase extraction on RP18 SPE cartridges (Agilent, 100 and 500 mg C18, respectively) using a stepped solvent system of 70% MeOH-H₂O (5 and 18 mL, respectively) and 100% MeOH (5 and 18 mL, respectively). In each case, HPLC profiling of the resulting two SPE fractions indicated that the 70% MeOH-H₂O fraction contained the desired mandelalide product. The 70% MeOH-H₂O fractions containing 5.5.1 and 7.14.5 were purified further using RP18 HPLC (70% MeOH-H₂O, Phenomenex Synergi Hydro 4 μm, 4.6 x 250 mm, 0.6 mL/min) to yield mandelalide A (5.5.1) (tR 11.5 min) and C-24 macrolide (7.14.5) (tR 16.5 min), respectively. After collection of analytical data (MS, NMR and optical rotation), compounds 5.5.1 and 7.14.5 were transferred, dried and weighed in tapered glass vials for cancer cytotoxicity testing.

Mandelalide A (5.5.1): [α]_D^{20} = -11.40° (c = 0.35, CDCl₃), {Lit.} [α]_D^{20} = -9.0° (c = 0.25, CDCl₃); 'H NMR (700 MHz, CDCl₃) δ 7.01 (ddd, J = 15.4, 10.4, 4.7 Hz, 1 H) 6.32 (dd, J = 14.6, 10.8 Hz, 1 H) 6.10 (t, J = 11.0 Hz, 1 H) 6.05 (d, J = 15.5 Hz, 1 H) 5.49 (dd, J = 15.1, 9.9 Hz, 1 H) 5.3 (td, J = 11.0, 5.6 Hz, 1 H) 5.27 (d, J = 12.1 Hz, 1 H) 5.07 (s, 1 H) 4.02 (m, J = 6.9 Hz, 1 H) 3.86 (m, J = 9.5, 3.0 Hz, 2 H) 3.72 (dd, J = 9.3, 4.1 Hz, 1 H) 3.67 (m, J = 5.6 Hz, 3 H) 3.50 (s, 3 H) 3.43-3.47 (m, 1 H) 3.33-3.42 (m, 3 H) 2.64 (m, J = 5.6 Hz, 1 H) 2.53-2.60 (m, 1 H) 2.38-2.48 (m, 3 H) 2.28-2.37 (m, 2 H) 2.02-2.11 (m, 2 H) 1.92 (m, J = 11.8, 7.1 Hz, 2 H) 1.77-1.83 (m, 1 H) 1.53-1.58 (m, 3 H) 1.47-1.53
(m, 1 H) 1.31 (d, J = 6.5 Hz, 3 H) 1.17-1.26 (m, 4 H) 1.06 (d, J = 6.9 Hz, 3 H) 0.89 (d, J = 6.5 Hz, 3 H); $^{13}$C NMR (175 MHz, CDCl$_3$) δ 167.2, 147.0, 141.3, 131.0, 126.7, 123.6, 122.7, 93.85, 82.9, 80.7, 80.5, 74.0, 73.6, 72.82, 78.80, 72.2, 72.0, 71.3, 67.8, 65.8, 58.9, 42.8, 39.4, 38.5, 37.3, 37.1, 36.5, 33.9, 33.8, 30.8, 18.0, 17.4, 14.3 ppm; HRMS (ES+) calcd. for C$_{33}$H$_{53}$O$_{11}$ (M+H) 625.3588, found 625.3575.

**Comparison of C13 data of mandelalide A (5.5.1):**

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<td>14.3</td>
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References:


(7) **Procedure to make PhSCH$_2$I:** To a solution of PhSCH$_2$Cl (500 mg, 0.42 mL, 3.2 mmol) in acetone (2.7 mL) was added NaI (465 mg, 3.1 mmol) and the reaction was covered with aluminum foil. After 12 h, the reaction mixture was poured into ether (10 mL), washed with sat. aq. sodium thiosulfate solution (15 mL), sat. aq. NaHCO$_3$ solution (15 mL), brine (15 mL). The dried (MgSO$_4$) extract was concentrated *in vacuo* and used immediately as the compound was highly unstable. Trost, B. M.; King, S. A. J. Am. Chem. Soc. 1990, 112, 408-422.
(8) **Procedure to make LDA:** To a solution of diisopropylamine (607 mg, 0.848 mL, 6.0 mmol) in THF (2.75 mL) at -78 °C was added "BuLi (2.4 mL, 6.0 mmol, 2.5 M solution in Hexanes). After 5 min, the white slurry was warmed to -10 °C. After 15 min, the LDA solution (1.0 M in THF/Hexanes) was used for the reaction.


(20) ADmix $\beta^* = (\text{DHQD})_2\text{PHAL}$ (100 mg), $\text{K}_2\text{OsO}_2\cdot\text{H}_2\text{O}$ (14.2 mg), $\text{K}_2\text{CO}_3$ (478 mg), $\text{K}_3\text{Fe(CN)}_6$ (1.22 g).

(21) **HF•pyr stock solution:** The stock solution was prepared by adding pyridine (2.0 mL) to HF•pyr (1.0 mL, 70% HF in pyridine) in THF (5.0 mL).


(23) ADmix $\alpha^* = (\text{DHQ})_2\text{PHAL}$ (100 mg), $\text{K}_2\text{OsO}_2\cdot\text{H}_2\text{O}$ (14.2 mg), $\text{K}_2\text{CO}_3$ (478 mg), $\text{K}_3\text{Fe(CN)}_6$ (1.22 g).

(25) ADmix $\alpha^{**} = (DHQ)_2$PHAL (300 mg), K$_2$OsO$_2$$\cdot$2H$_2$O (42.6 mg), K$_2$CO$_3$ (478 mg), K$_3$Fe(CN)$_6$ (1.22 g).

(26) ADmix $\beta^{**} = (DHQD)_2$PHAL (300 mg), K$_2$OsO$_2$$\cdot$2H$_2$O (42.6 mg), K$_2$CO$_3$ (478 mg), K$_3$Fe(CN)$_6$ (1.22 g).


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APPENDIX 1

NMR DATA
Coupled product with (S) trans-α-ct col-8 & O-C14
metnylation-1H
oxidation to sulfoacetyl chloride
 oxidation to sulfone at C1-C3
Charting of methylated acid w/(R) Evans ch. aux-act col-13
Ke deactivation of arf: Cuprate addition on 3-mesityl sulphone (I spot) after II col.
I spec after Ultra coupling at C=40-C43
**1H NMR Comparison of Lactam 12**

**1.1.5**

(Literature Spectra)

Snider, B. B.; Grabowski, J. F.

*J. Org. Chem. 2007, 72, 1036-1042.*

---

**1.1.5**

(Synthetic)
$^1$H NMR comparison of Cermizine D TFA salt

**Synthetic 1.13-TFA**

![NMR spectrum of Synthetic 1.13-TFA](image)

$^1$H NMR of Cermizine D TFA salt
(700 MHz, in MeOH-d$_4$ at rt)

**Takayama 1.13-TFA**

![NMR spectrum of Takayama 1.13-TFA](image)

$^1$H NMR of (+)-cermizine D TFA salt
(800 MHz, in CD$_3$OD at rt)
Physicochemical analysis of compound: A characterization of the molecular structure and physical properties.
The image contains a diagram of a chemical structure, labeled as 6'74. This appears to be a part of a scientific or technical document, possibly related to organic chemistry or biochemistry. There are no visible textual annotations within the image itself, aside from the label 6'74. The diagram is centered on the page, occupying the majority of the space available.
Akylation of ketone with PhSO₂Cl at col. -1H.
Hydrogenation of enone-afc col-C13

6.143
alcohol-act col-C13
The image contains a chemical structure and spectral data. The spectrum appears to be a 1D NMR spectrum with ppm values on the x-axis and intensity on the y-axis. The spectrum shows multiple peaks at various ppm values.

The chemical structure in the image shows a compound with functionalities that suggest it might be a cyclic or branched molecule. The structure includes oxygen atoms, carbon-carbon double bonds, and other functional groups.

The text at the bottom of the page mentions "cis enyne w/ TES-atr co1-c13." This likely refers to a specific compound or reaction condition, possibly related to the structure shown in the diagram.

Without further context, it's challenging to provide a detailed explanation of the spectral data or the chemical structure. However, the presence of intramolecular hydrogen bonds and other interactions might be inferred from the peaks and the overall shape of the spectrum.
Page from beta-carol 2H
$^1$H NMR comparison of mandelalide A (8.5.1)

Synthetic mandelalide A (8.5.1)

&  

Isolated mandelalide A (8.5.1)

(CP/MAS (100 MHz) 600 MHz (DCO))

$^{13}$C NMR comparison of mandelatide A (8.6.1)

**Synthetic mandelatide A (8.6.1)**

**Related mandelatide A (8.6.1)**

APPENDIX 2

X-RAY CRYSTALLOGRAPHIC DATA
Oxazolidinone 3.1.4:

Table 1. Crystal data and structure refinement for rc65.

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<td>Unit cell dimensions</td>
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</tbody>
</table>
\[ c = 11.480(3) \approx \gamma = 90^\circ. \]

Volume \[ 1194.5(5) \approx^3 \]

\( Z \) 2

Density (calculated) 1.197 Mg/m\(^3\)

Absorption coefficient 0.084 mm\(^{-1}\)

\( F(000) \) 464

Crystal size 0.45 x 0.21 x 0.03 mm\(^3\)

Theta range for data collection 1.84 to 26.99\(^\circ\).

Index ranges -13 \( \leq \) h \( \leq \) 13, -13 \( \leq \) k \( \leq \) 13, -14 \( \leq \) l \( \leq \) 14

Reflections collected 13377

Independent reflections 5209 [R(int) = 0.0341]

Completeness to theta = 26.99\(^\circ\) 100.0 %

Absorption correction Semi-empirical from equivalents

Max. and min. transmission 0.9975 and 0.9634

Refinement method Full-matrix least-squares on \( F^2 \)

Data / restraints / parameters 5209 / 1 / 416

Goodness-of-fit on \( F^2 \) 1.039

Final R indices [I>2sigma(I)] \[ R1 = 0.0416, wR2 = 0.0784 \]

R indices (all data) \[ R1 = 0.0579, wR2 = 0.0865 \]

Absolute structure parameter -0.3(8)

Largest diff. peak and hole 0.143 and -0.157 e.\( \approx^3 \)
Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (≈x 10^3) for rc65. U(eq) is defined as one third of the trace of the orthogonalized U_ij tensor.

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\text{H(3B)-C(3)-H(3A)} & \quad 106.5(15) \\
\text{C(3)-C(4)-C(5)} & \quad 112.78(17) \\
\text{C(3)-C(4)-H(4B)} & \quad 108.6(11) \\
\text{C(5)-C(4)-H(4B)} & \quad 107.6(10) \\
\text{C(3)-C(4)-H(4A)} & \quad 110.8(13) \\
\text{C(5)-C(4)-H(4A)} & \quad 107.0(13) \\
\text{H(4B)-C(4)-H(4A)} & \quad 110.0(18) \\
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\text{C(4)-C(5)-H(5)} & \quad 107.1(10) \\
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\text{C(7)-C(6)-C(5)} & \quad 114.78(15) \\
\text{C(7)-C(6)-H(6A)} & \quad 109.0(11) 
\end{align*}
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C(7)-C(6)-H(6B)  110.9(11)
C(5)-C(6)-H(6B)  107.3(11)
H(6A)-C(6)-H(6B)  104.0(15)
C(8)-C(7)-C(6)  111.27(16)
C(8)-C(7)-C(9)  106.68(17)
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C(9)-C(7)-H(7)  109.7(12)
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O(3)-C(8)-C(7)  122.21(17)
N(2)-C(8)-C(7)  119.91(16)
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H(9C)-C(9)-H(9B)  108.8(19)
C(7)-C(9)-H(9A)  112.8(12)
H(9C)-C(9)-H(9A)  98.1(19)
H(9B)-C(9)-H(9A)  109.3(19)
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Symmetry transformations used to generate equivalent atoms:
Table 4. Anisotropic displacement parameters (≈\(2 \times 10^3\)) for rc65. The anisotropic displacement factor exponent takes the form: 
\[-2\pi^2 [h^2a^*a^{11} + ... + 2hk a^* b^* U^{12}]\]

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Table 5. Hydrogen coordinates (\( x \times 10^4 \)) and isotropic displacement parameters (\( \approx 2 \times 10^3 \)) for rc65.

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Table 6. Torsion angles [°] for rc65.

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O(1)-C(11)-C(12)-C(13)  94.9(2)
N(2)-C(12)-C(13)-C(14)  61.9(2)
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Symmetry transformations used to generate equivalent atoms: