Efforts towards the Asymmetric de novo Synthesis of Lanostanes and Euphanes

Htoo Tint Wai

Dartmouth College, htoo.tint.wai.gr@dartmouth.edu

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Efforts towards the Asymmetric de novo Synthesis of Lanostanes and Euphanes

A thesis
Submitted to the Faculty
in partial fulfillment of the requirements for the
degree of

Doctor of Philosophy

in

Chemistry

By Htoo Tint Wai

Guarini School of Graduate and Advanced Studies
Dartmouth College
Hanover, New Hampshire

December 2022

Examining Committee:

________________________
Glenn Micalizio

________________________
Jimmy Wu

________________________
Dale Mierke

________________________
Jon Njarðarson

F. Jon Kull, Ph. D.
Dean of the Guarini School of Graduate and Advanced Studies
Abstract

Tetracyclic triterpenoids are ubiquitous in nature and biology, with members displaying a wide range of medically relevant properties and occupying rather distinct regions of chemical space. Members of this large class include well-known steroid hormones and sterols as well as structurally interesting subclasses such as lanostanes and euphanes, among others. Comprised of the tetracyclic skeleton with three stereodefined quaternary centers at ring-junction positions, lanostanes and euphanes present synthetic challenges that are different from those encountered in efforts targeting the structurally less complex steroid hormones. Lanostanes, in particular, stand as a historically important class of compounds as significant attention has been directed at understanding the biosynthesis of lanosterol, the primary precursor to cholesterol, for the past 50 years. Though studies in this area have led to the development of new reaction methods and synthesis strategies, lanostanes and the structurally related euphanes continue to stand as challenges for asymmetric de novo synthesis. This thesis work describes progress towards the asymmetric total syntheses of lucidadone H, a hexanorlanostane natural product, and euphol, a euphane natural product. While the chemical technology that is central to both syntheses features metallacycle-mediated annulative cross-coupling, diastereoselective Friedel–Crafts cyclization and oxidative dearomatization/Wagner–Meerwein rearrangement to establish a functionalized tetracyclic intermediate, my efforts resulted in a concise synthesis of hexanorlanostanes, and an asymmetric approach to a C14-desmethyl euphane system, which was identified to be a novel modulator of the Liver X Receptor.
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<tbody>
<tr>
<td>Å</td>
<td>angstrom(s)</td>
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<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>acac</td>
<td>acetylacetonate</td>
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<td>app</td>
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<td>aq.</td>
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<td>9-BBN</td>
<td>9-Borabicyclo[3.3.1]nonane</td>
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<td>Binap</td>
<td>2,2'-bis(diphenylphosphino)-1,1'-binaphthyl</td>
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<td>DHP</td>
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<td>DIBAI-H</td>
<td>diisobutylaluminum hydride</td>
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DIPEA  diisopropylethylamine
DMAP  4-dimethylaminopyridine
DMP  Dess-Martin Periodinane
dpm  dipivaloylmethanato
dr  diastereomeric ratio
$E$  $E$-olefin geometry
ESI  electrospray ionization
Et  ethyl
et al.  and others
g  gram(s)
h  hour(s)
HFIP  hexafluoroisopropanol
HMPA  hexamethylphosphoramide
HPLC  high performance liquid chromatography
HRMS  high resolution mass spectrometry
Hz  hertz
IR  infrared spectroscopy
$J$  coupling constant
L  liter
LHMDS  lithium hexamethyldisilazide
liq.  liquid
M  molar or molecular ion
Me  methyl
mg  milligram(s)
min  minute(s)
mL  milliliter(s)
mmol  millimole(s)
mol   mole(s)
Ms    methanesulfonyl (mesyl)
MS    molecular sieves
m/z   mass-to-charge ratio
NMR   nuclear magnetic resonance
PDD   pyridinium chlorochromate
Ph    phenyl
PIDA  phenyliodine(III)diacetate
PMP   pentamethylpiperidine
ppm   parts per million
PPTS  pyridinium para-toluenesulfonate
Pr    propyl
i-pr  isopropyl
q     quartet
R     alkyl group
R     rectus
Rf    retention factor
s     singlet
S     sinister
sat.  saturated
t     triplet
TBAF  tetra-n-butylammonium fluoride
TBS   tert-butyldimethylsilyl
TES   triethylsilyl
Tf    triflate
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<tr>
<td>TOF</td>
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<tr>
<td>Ts</td>
<td>para-toluenesulfonyl (tosyl)</td>
</tr>
<tr>
<td>Z</td>
<td>Z-olefin geometry</td>
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Chapter 1: History of the Lanostane and Euphane Families of Tetracyclic Triterpenoids

1.1 Triterpenoids: Origin and Structural Diversity

Triterpenoids are a large class of natural products possessing a diverse array of structures and a wide range of important biological properties.\textsuperscript{1–3} To date, there are at least 20,000 known structures, existing as acyclic and polycyclic triterpenoids.\textsuperscript{4} Cyclic triterpenoids are skeletally diverse with well over 100 distinct scaffolds and include the biologically important sterols and steroids.\textsuperscript{5} Examples include acyclic structures such as squalene-1,10,24,25,30-pentol (1),\textsuperscript{6} as well as cyclic structures (2 – 5) (Figure 1).

**Figure 1.** Examples of triterpenes and triterpenoids.

Despite possessing unique structures, these terpenoids all originate from isoprene – a C\textsubscript{5} unit that was identified to be the basic building block for terpenoid biosynthesis.\textsuperscript{7} Beginning his studies on terpenes in 1884, Otto Wallach hypothesized that individual terpenes could be comprised of multiples of a 5-carbon unit and can be classified into different groups based on the number of 5-carbon units that are present in them although the exact structure of isoprene was not known at the time of his proposal.\textsuperscript{8–10} This notion became known as the “isoprene rule” which states that C\textsubscript{10} monoterpenes contain two isoprene units, C\textsubscript{15} sesquiterpenes contain three isoprene units and was later extended to include C\textsubscript{20} diterpenes and C\textsubscript{30} triterpenes, containing four and six isoprene units.
respectively (Figure 2). The “isoprene rule” served as the foundation for Leopold Ruzicka’s research that led to the classification of cholesterol and steroid hormones as triterpenoids for which he won the 1939 Nobel Prize in Chemistry. Later in the early 1950s, Ruzicka developed the “isoprene rule” into the “biogenetic isoprene rule” that provides a mechanistic hypothesis for prediction and explanation of biosynthesis of terpenoid structures from acyclic alkene chains such as geraniol, farnesol and geranylgeraniol that are made up of multiples of C₅ isoprene units.

**Figure 2.** Structures of terpenes.

Increasing interest in the synthesis and biosynthesis of terpenes and sterols saw additional landmark discoveries in the history of terpenoids – in 1945, Bloch and Rittenberg outlined the pathway from acetic acid to cholesterol (3) by using isotopic labeling experiments and hypothesized C₃₀ squalene (6; Figure 3) to be an intermediate; in 1953, Bloch and Langdon demonstrated the conversion of labeled squalene (6) to cholesterol (3), confirming Robinson’s initial proposal in 1934 that squalene (6) could cyclize to form cholesterol (3); radioisotope tracer experiments by Woodward and Bloch regarding squalene cyclization suggested that cholesterol (3) is derived from squalene (6) through the key intermediate, lanosterol (7; Figure 3); in 1958, Feodor Lynen identified isopentenyl pyrophosphate (the biologically active form of isoprene) to be the initiating C₅ unit for terpenoid biosynthesis. Proposed biosynthetic pathway from isopentenyl pyrophosphate (IPP) to cholesterol (3) is shown in Figure 3.
In addition to these discoveries, numerous research efforts emerged that focused on studying the mechanistic details regarding the biosynthesis of cholesterol (3) and lanosterol (7) as well as squalene cyclizations that lead to the generation of diverse polycyclic terpenoid structures.\textsuperscript{17,23–32} In bacteria (prokaryotes) cyclization of squalene (6) into various polycyclic terpene structures such as hopene (8; Figure 4) and hopanol (9) is catalyzed by triterpene synthase enzymes known as squalene cyclases (SC; triterpene synthase), and in plants, animals and fungi (eukaryotes), cyclization of (3S)-2,3-oxidosqualane (10; Figure 4), produced from 2,3-epoxidation of squalene, to various polycyclic terpenoid structures such as lanosterol (7) and β-amyrin (11) is catalyzed by oxidosqualene cyclases (OSC; triterpene synthase).\textsuperscript{4,20,21} The enzymatic cyclization of squalene (6) or (3S)-2,3-oxidosqualene (10) is considered to be first diversifying step in the biosynthesis of triterpenoids.\textsuperscript{4,5,20} The cyclic terpenoids produced from such reactions then serve as precursors to various metabolites (which include sterols, steroids and saponins), contributing to the diverse polycyclic terpenoid structures.\textsuperscript{4,26,33}
1.2 Tetracyclic Triterpenoids: Lanosterol and Euphol

Among the classes of polycyclic terpenoids that are produced from enzymatic cyclizations of (3S)-2,3-oxidosqualene (10), the tetracyclic terpenoids present a major class of natural products that include lanostane and euphane subclasses.\(^{26}\)

Lanosterol (7; Figure 5) is the prototypical lanostane structure and was first found in the “isocholesterol” mixture of wool wax.\(^{34,35}\) In 1944, Ruzicka and co-workers separated the components of the “isocholesterol” mixture to obtain lanosterol (7), dihydrolanosterol (known today as lanostenol; 12), agnosterol (13) and dihydroagnosterol (14) (Figure 5).\(^{34,35}\) The structural elucidation of lanosterol (7) was largely credited to the work by Ruzicka and co-workers,\(^{17,18}\) and many related structural studies such as rearrangement and dehydration experiments to investigate the structure of A-ring and the location of the C3 hydroxyl group, oxidation reactions to examine details regarding B- and C-rings including the tetrasubstituted olefin, methods established in the steroid chemistry field used towards side-chain degradation to establish the structure of the D-ring as well as

**Figure 4.** Cyclizations of squalene (6) and (3S)-2,3-oxidosqualene (10).
spectroscopic studies and X-ray analysis by multiple scientists during 1949–1954 assisted in the final structural determination.\textsuperscript{34}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{structures.png}
\caption{Structures of tetracyclic terpenoids.}
\end{figure}

Euphol (15; Figure 5), the prototypical euphane terpenoid, was first isolated in 1944 by Newbold and Spring from euphorbium, a resinified latex of \textit{Euphorbia} \textit{spp.}\textsuperscript{36} While Newbold and Spring proposed euphol (15) to be a tetracyclic alcohol with the formula \( \text{C}_{30}\text{H}_{50}\text{O} \), experimental studies regarding the structural determination of euphol (15) by various scientists continued for another decade.\textsuperscript{34–36} Reactions that were used in structural elucidation of lanosterol (7) were also employed for that of euphol (15). Although these studies provided evidence that the ABC-ring system, the location of tetrasubstituted alkene and the number of methyl groups in euphol (15) were the same as in lanosterol (7), euphol (15) was not identical to any known compound related to lanosterol (7). Gradually, as additional experiments proceeded, the difference in reactivity of the tetrasubstituted alkene (compared to that of the tetrasubstituted alkene in lanosterol) in acidic conditions, selenium dioxide oxidations and epoxidation reactions was observed, leading to the conclusion that the C- and D-rings in euphol (15) are fused in a different way than in lanosterol (7).\textsuperscript{34,35} Eventually, the final structure of euphol (15) was proposed in the mid 1950s by Barton \textit{et al.} and Jeger \textit{et al.},\textsuperscript{34,37–39} and the crystal structure of euphol (15) was elucidated in 1984 by Nes \textit{et al.}\textsuperscript{40}
While lanosterol (7) and euphol (15) are identical in terms of constitutional arrangement, the difference in stereochemistry at the C13, C14 and C17 positions of the two compounds is evident (Figure 5). Notably, the stereochemistry observed in lanosterol (7) is similar to that observed in steroids.\textsuperscript{34,35} By the time steroids and terpenoids were found to be related, the chemistry of steroids had been more established than that of triterpenoids. As a result, steroid conventions in terms of numbering and stereochemistry were often employed when lanostanes were discussed. Lanosterol (7) is typically referred to as a “trimethyl steroid” and has been named 4,4’,14\(\alpha\)-trimethyl-cholesta-8,24-dien-3\(\beta\)-ol [based on the structure of cholesterol (3)].\textsuperscript{17,34,35}

The disparity in stereochemistry observed in lanosterol (7) and euphol (15) has been hypothesized to originate from different substrate conformations that (3\(S\))-2,3-oxidosqualene (10) is preorganized into by OSC enzymes.\textsuperscript{26} The two different conformations of (3\(S\))-2,3-oxidosqualene (10; Figure 6) that lead to the formation of lanosterol (7) and euphol (15) are proposed to be the chair-boat-chair conformation (sterol folding) and the chair-chair-chair conformation (non-sterol folding) respectively.\textsuperscript{26,33,41–43}

![Figure 6](image)

**Figure 6.** Different conformations of (3\(S\))-2,3-oxidosqualene (10) leading to lanosterol (7) and euphol (15).
1.3 Biosynthesis of Lanosterol

Though lanosterol (7) was established as a precursor to cholesterol (3) since 1953, and cholesterol (3) was believed to be derived from squalene (6), it was not until 1966 when Corey and van Tamelen independently proposed and demonstrated the intermediacy of (3S)-2,3-oxidosqualene (10) in the biosynthesis of lanosterol (7) and cholesterol (3; Figure 7). It is now widely accepted that in nature, lanosterol (7) is produced from (3S)-2,3-oxidosqualene (10), the cyclization of which is catalyzed by an OSC enzyme, lanosterol synthase. Additionally, it has been found that eukaryotic OSC enzymes are selective for (3S)-2,3-oxidosqualene (10), but not its enantiomer (3R)-2,3-oxidosqualene. Regarded as a remarkable process due to its efficient stereocontrol in the generation of the tetracyclic system with six new stereocenters, the biotransformation of (3S)-2,3-oxidosqualene (10) to lanosterol (7) has captivated the interest of chemists and biologists for over 50 years and has remained as one of the most studied reactions by the community among the numerous OSC-catalyzed reactions.

![Figure 7](image-url)

**Figure 7.** Proposed biosynthetic pathway from (3S)-2,3-oxidosqualene (10) to cholesterol (3).

1.3.1 Overview of General Mechanism

While mechanistic details regarding the conversion of (3S)-2,3-oxidosqualene (10) to lanosterol (7) continue to be a topic of further investigations, it is believed that the chair-boat-chair conformation (sterol folding) of (3S)-2,3-oxidosqualene (10) is involved in its cyclization to lanosterol (7; Figure 8). Protonation of the epoxide initiates a cascade
of cationic cyclization, resulting in the formation of protosterol cation A. Subsequent carbocation rearrangements and termination of the carbocation then deliver lanosterol (7).\textsuperscript{20,25,26}

Figure 8. Proposed overall mechanism for conversion of (3S)-2,3-oxidosqualene (10) to lanosterol (7).

1.3.2 Epoxide Opening and AB-Ring Formation

It was first proposed in 1955 that all transformations of trans squalene to C\textsubscript{30} cyclic triterpenoids take place as “nonstop-reactions” that proceed through antiperiplanar cationic 1,2-addition, 1,2-rearrangement, and 1,2-elimination.\textsuperscript{25,27} However, based on multiple experimental and theoretical studies, it is now accepted that the overall cyclization is a non-concerted process that occurs through a series of discrete conformationally rigid and partially cyclized carbocationic intermediates.\textsuperscript{47-49}

The initial aspect of the overall transformation is the activation of the epoxide and formation of the A-ring (Figure 9). The cyclization is proposed to be initiated by an acid-catalyzed epoxide opening with anchimeric assistance from the neighboring π-bond to form intermediate B.\textsuperscript{25} Investigations regarding reaction rates of Lewis acid-initiated cyclizations of oxidosqualene analogs by van Tamelen,\textsuperscript{47} and more recent studies with
various oxidosqualene analogs in the presence of lanosterol synthase by Corey\textsuperscript{50,51} suggest that epoxide cleavage and cyclization of A-ring by C–C bond formation occurs in a concerted manner. These findings have also been supported by computational results providing further information for a concerted mechanism for epoxide opening and A-ring formation.\textsuperscript{52} Following the A-ring closure, cyclization of the B-ring through a boat conformation should occur as the positive charge builds up at C5.\textsuperscript{33} While there are no known experimental studies regarding the concertedness of A- and B-ring formations, a computational study by Jenson and Jorgensen suggested that the B-ring is likely formed in concert with A-ring.\textsuperscript{53}

\begin{center}
\includegraphics[width=\textwidth]{figure9.png}
\end{center}

\textbf{Figure 9.} Epoxide opening and AB-ring formation.

\subsection*{1.3.3 Protosterol Cation Formation and Rearrangement to Lanosterol}

The next stage in the biosynthesis of lanosterol (7), which continues to be a topic of interest, is the formation of the protosterol cation A (Figure 10). While the initially proposed concerted reaction to protosterol cation A suggests direct cyclization from the 6-6 bicyclic cationic intermediate B to the six-membered C-ring (6-6-6 tricycle C), followed by D-ring formation, direct formation of the 6-6-6 tricycle C would represent an anti-Markovnikov ring closure.\textsuperscript{33} As such, a number of experimental and theoretical studies has emerged offering an alternate pathway to the protosterol cation A.\textsuperscript{50,53–58} Protosterol cation A is proposed to be generated through initial formation of the five-membered C-ring intermediate (6-6-5 tricycle D) containing the more stable tertiary carbocation, which is the product of Markovnikov-favored ring closure.\textsuperscript{50,55,56}
Corey et al. reported that cyclization of 20-oxa-2,3-oxidosqualene (16) with yeast lanosterol synthase resulted in the formation of two products, where the major product is the expected 6-6-6-5 fused tetracycle 17 and the minor product, 6-6-5 fused product 18 (Figure 11). The minor 6-6-5 fused product 18 is likely produced from internal trapping of 6-6-5 tertiary carbocation E (analogous to 6-6-5 intermediate D in the proposed pathway to protosterol cation A; Figure 10) by the electron rich C18–C19 olefin. Selected experimental studies (Figure 11) that further support the presence of a five-membered C-ring intermediate D include 1) cyclization of 15-ethyl oxidosqualene (19) with pig liver oxidosqualene cyclase, producing a 71:29 mixture of ethyl lanosterol (20) and 6-6-5 tricyclic product 21, 2) cyclization of 18,19-dihydro oxidosqualene (22) with rat liver oxidosqualene cyclase, affording 6-6-5 tricyclic product 23, and 3) cyclization of 10,15-didemethyl oxidosqualene (24) with pig liver oxidosqualene cyclase, delivering 6-6-5 fused product 25 as the major product. In addition to these laboratory studies, there are computational studies that provide support for the intermediacy of 6-6-5 tertiary cation D (Figure 10) en route to protosterol cation A.
Following the formation of cationic intermediate D (Figure 1), earlier reports in the literature suggested ring expansion to the six-membered C-ring intermediate C and subsequent D-ring cyclization to produce protosterol cation A.\textsuperscript{20,33,50} This proposed pathway, however, has been the subject of debate as it raises the question of how the six-membered C-ring formation overcomes the energy barrier required to expand the tertiary cyclopentyl carbocation D to the less stable secondary cyclohexyl carbocation C.\textsuperscript{57,58}

Recently, Hess published a computational study, proposing a concomitant C-ring expansion and D-ring formation. It was suggested that protosterol cation A would be generated directly from the tertiary cationic intermediate D through a transition structure such as F (Figure 12), with anchimeric assistance from the neighboring C18–C19 double

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**Figure 11.** Experimental studies that support the presence of five-membered C-ring intermediate.

A. Cyclization of 20-oxa-2,3-oxidosqualene (16) with yeast lanoster synthase.

B. Cyclization of 15-ethyl oxidosqualene (19) with pig liver oxidosqualene cyclase.

C. Cyclization of 18,19-dihydro oxidosqualene (22) with rat liver oxidosqualene cyclase.

D. Cyclization of 10,15-didemethyl oxidosqualene (24) with pig liver oxidosqualene cyclase.
bond in the cyclopentylcarbinyl–cyclohexyl ring expansion. As such, this proposed concerted mechanism excludes the formation of the less stable secondary cyclohexyl carbocation C.\textsuperscript{57,58}

Figure 12. Protosterol cation formation.

Finally, after generation of the 17β protosterol cation A, formation of lanosterol (7) is proposed to take place through cationic rearrangements, including hydride and methyl shifts, and a final termination step (Figure 13).\textsuperscript{20,25,33} It is postulated that a 60° rotation about C17–C20 bond of the C17 side chain is required so that the empty p-orbital at C20 is held parallel to the C–H bond at C17, allowing for 1,2-migration of the hydride from C17 to C20 and establishing the natural C20-(R) configuration.\textsuperscript{61} Subsequent hydride and methyl shifts, and termination of the C8 carbocation by deprotonation at C9 then lead to lanosterol (7).\textsuperscript{5,25,33,62}

Figure 13. From protosterol cation A to lanosterol (7).

1.4 Previous Laboratory Synthetic Studies of Lanostane and Euphane Triterpenoids

Enzymatic and non-enzymatic investigations directed at studying the efficient biosynthesis of lanosterol (7) and cholesterol (3) have inspired synthetic chemists to
develop biomimetic strategies for synthesis of polycyclic terpenoid structures. These efforts have led to the extensive use of biomimetic polyene cyclization chemistry for synthesis of lanostane and euphane terpenoids. To date, there are only four syntheses of lanostane natural products, and three of them rely on the use of polyene cyclization chemistry. Alternatively, preparation of lanostanes and euphanes is enabled by semisynthesis, a method in which target terpenoids are produced from sequential functionalizations of triterpenoid natural product starting materials that already possess the core skeleton and some complex structural features. There is only one synthesis of a euphane and no known asymmetric total synthesis of any euphanes. The following sections include a brief discussion of previous synthetic efforts along with the inefficiencies and limitations associated with the existing preparation methods.

1.4.1 Woodward’s Synthesis of Lanosterol (1957)

The synthesis of lanosterol (7) accomplished by Woodward and his colleagues in 1957 represents the first ever synthesis of a lanostane. This synthesis can be described as a semisynthesis since cholesterol (3) was used as the starting material. Cholesterol (3; Figure 14) was first converted through a 10-step sequence to enone 26 – a structure that contains the gem dimethyl group at C4 and an enone functionality in the CD-ring that would allow for installation of the requisite C14 quaternary center. Exposure of enone 26 to potassium tert-butoxide and methyl iodide resulted in the successful installation of the C14 quaternary center, producing ketone 27. Notably, ketone 27 possesses all the quaternary centers seen in both lanostenol (12) and lanosterol (7). While lanostenol (12) was accessed in 4 steps from ketone 27, it took 14 additional steps to prepare lanosterol (7) from lanostenol (12). Overall, this work serves as a landmark achievement in organic synthesis, and cholesterol (3) was converted to lanosterol (7) in 29 steps.
While this work suggests that semisynthesis can be used to prepare lanostanes, the inefficiencies associated with this method of preparation are evident. Semisynthesis methods are limited in absolute stereochemistry as it allows access to only one enantiomer based on the stereochemistry of the natural product starting material.\textsuperscript{68,69} Although beginning the synthesis with an intact tetracyclic core of cholesterol (3) that already contains part of the required structural features of lanosterol (7) might seem advantageous, this is not the case. In fact, having to alter the existing structural features and insert functionality around the sparsely functionalized hydrocarbon core of cholesterol proved demanding, requiring 29 total steps to introduce three C–C bonds and establish two alkenes in order to produce lanosterol (7).

1.4.2 van Tamelen’s Biogenetic-type Total Synthesis of Parkeol and 24,25-Dihydroparkeol (1972)

An example of the early efforts directed at laboratory simulation of the biogenetic production of terpenoids is the studies by van Tamelen \textit{et al.} that resulted in the synthesis of parkeol (34) and 24,25-dihydroparkeol (36) in 1972 (Figure 16).\textsuperscript{64} A general requirement...
in synthetic campaigns involving cation polyene cyclizations is the suitably functionalized polyene substrates. With (S)-limonene (30) and farnesyl acetate (28) serving as the starting materials, the cyclization substrate epoxide 33 was prepared, as a mixture of diastereomers at C3, in a total of 24 steps (Figure 15).

Epoxide 33 was then treated with SnCl₄ in MeNO₂ at 0 °C to produce parkeol (34) in 2% yield (Figure 16). A similar synthetic sequence was used for the preparation of dihydroepoxide 35 which was subjected to the same cyclization conditions to deliver 24,25-dihydroparkeol (36) in 3.5% yield.

**Figure 15.** Synthesis of cyclization substrate 33.

**Figure 16.** Polyene cyclizations to produce parkeol (34) and dihydroparkeol (36).
1.4.3 Reusch’s Approach to Lanostane and Euphane Tetracyclic Systems (1984)

In the mid 1980s, Reusch’s group reported a synthetic strategy directed towards both lanostane and euphane tetracyclic systems. While the application of the strategy was not demonstrated in the context of the total synthesis of a natural product, Reusch’s approach to access the tetracyclic ring system involved a conceptually different strategy from the two syntheses presented above.

Starting with a racemic mixture of the readily available Wieland–Miescher ketone (37; Figure 17), trans-hydrindane 38 was prepared through a two-step procedure involving reductive cyclopropanation and opening of the cyclopropane. Realizing that hydrindane 38 could serve as the CD-ring system of lanostane and euphane tetracyclic systems due to its two angular methyl groups that are in anti-orientation to each other, the Reusch group directed their attention towards selective functionalization of the carbonyl on the six-membered ring of trans-hydrindane 38 to produce diene 39 and to subsequently introduce the AB-ring system. Lewis acid-catalyzed Diels–Alder cycloaddition of diene 39 with substituted benzoquinone 40 then delivered the α-endo adduct 41 – a lanostane-like structure consisting of three quaternary centers at C10, C13 and C14 in the correct positions and relative stereochemistry typically seen in lanostane terpenoid natural products.

From this lanostane-like structure, euphane system 42 was accessed through photoisomerization of the quaternary center at C10 in ent-41 (Figure 17). Although the group initially assumed that solvolysis of enol acetate 42 produced the desired AB-trans ring fusion, it was later discovered that AB-ring fusion was in fact cis. Therefore, their efforts resulted in the synthesis of 5-epi-euphane system 45, the configuration of which was confirmed by X-ray analysis.
With no known asymmetric total synthesis of euphanes, Johnson’s relay synthesis of euphol (15) in 1990 serves as the only known synthesis of a euphane. The synthesis is among the numerous syntheses of polycyclic terpenoid targets that employ biomimetic cation-olefin cyclization as the key step. Johnson et al. demonstrated the use of a polyene substrate containing two alkynes (40) in the cation-olefin cyclization (Figure 18). Starting with 2,3-dimethyl-1,3-butadiene (46) and 2-methyl-furan (48), the cyclization substrate (40) was prepared in 10 total steps. While the cyclization of dienediylnol (40) was initially explored with a variety of acids, optimum results were obtained when the cyclization was conducted in a vigorously stirred biphasic mixture of formic acid and pentane (5:1) at 0 °C. Methanolysis of the resulting enol formates then resulted in 28% yield of a mixture of...
tetracyclic ketones (56:44), from which ketone 51 was isolated as the major product after recrystallization.

Ketone 51 was then advanced to dione 52 that possesses the euphane tetracyclic system in 7 steps resulting in 9% overall yield (Figure 19A). Reduction of methyl ketone 51 produced a diastereomeric mixture of alcohols which was acetylated to deliver the corresponding mixture of acetates. This mixture was then used in a two-step sequence for formation of the six-membered A-ring. Selective ozonolysis of the tetrasubstituted olefin in the five-membered A-ring and cyclodehydration of the resulting dione afforded 52, which upon installation of the gem dimethyl group at C4 and reoxidation of the secondary alcohol produced tetracycle 53. The structure and stereochemistry of racemic dione 53 was confirmed by comparing an enantiomerically pure dione 53 which was obtained through degradation of euphol (15) that was isolated from nature. The enantiomerically pure sample of dione 53 was then used as the starting material to construct the side chain at C17 (Figure 19B) and synthesize euphol (15), making the synthesis a relay synthesis of euphol (15).

Figure 18. Johnson’s polyolefin cyclization.
1.4.5 Corey’s Synthesis of Lanostenol (1994)

Following the first two syntheses of lanostane natural products by Woodward in 1957\(^6\) and by van Tamelen in 1972\(^6\), Corey and co-workers reported the synthesis of lanostenol (12; Figure 20) in 1994, serving as the third synthesis of a lanostane target.\(^6\)

Similar to many other syntheses of polycyclic terpenoid targets, biomimetic polyene cyclization chemistry played an important role in Corey’s approach towards lanostenol (15). The AB-ring system of the target natural product, lanostenol (15), was constructed from a densely functionalized hydrindane substrate 57 through cation olefin cyclization (Figure 20). The key cyclization substrate, hydrindane 57, was derived from a convergent synthesis of vinyl iodide 58 and aldehyde 59, which in turn were prepared from vitamin D\(_3\) and geranyl acetate respectively.

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**Figure 19.** Johnson’s relay synthesis of euphol (15).

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A. Seven-step sequence to the euphane tetracyclic system:

1. LiAlH\(_4\), quant.
2. Ac\(_2\)O, pyridine, quant.
3. O\(_3\), CH\(_2\)Cl\(_2\), MeOH then Zn, AcOH, 94%
4. NaOH, MeOH, 63%

B. Relayed synthesis of euphol (15) through enantiopure dione 53 derived from degradation of euphol (15):
As illustrated in Figure 21, starting with vitamin D₃ (60), the desired vinyl iodide 58 was prepared in six steps. Grundmann’s ketone (61), produced from ozonolysis of vitamin D₃ (60), was used in the subsequent three-step sequence to install the requisite quaternary center at C14 in 62. Formation of silyl enol ether from ketone 61, Simmons-Smith cyclopropanation and base-catalyzed cleavage of the resulting cyclopropanol delivered 62. Ketone 62 was then converted to vinyl iodide 58 through initial formation of the corresponding hydrazone followed by Barton vinyl iodide synthesis.

Figure 20. Retrosynthesis of lanostenol (12).

Figure 21. Synthesis of lanostenol (12).
Next, addition of a vinyl lithium species derived from 58 to aldehyde 59 resulted in a 1:1 mixture of 63 (C7α) and its diastereomer (C7β) (Figure 21). It was mentioned that the two diastereomers were separable by silica gel chromatography, and the undesired diastereomer (C7β) was converted to the desired one (C7α) by sequential oxidation of the secondary alcohol and reduction of the resulting ketone to give a 6:1 (C7α:C7β) mixture of diastereomers. The desired diastereomer 63 was then advanced to allyl silane 57, setting up for the key cation olefin cyclization. Treatment of allyl silane 57 with MeAlCl2 and subsequent acetylation delivered tetracycle 64 as the major product. The cyclization of allyl silane 57 was proposed to proceed through a chair-boat-like transition state depicted as H for the formation of the AB-ring system, resulting in C9β-H and C10β-Me stereochemistry in tetracycle 64. Finally, a three-step sequence of redox manipulations to install the tetrasubstituted olefin afforded lanostenol (12).

Overall, lanostenol (12) was synthesized in 16 steps, longest linear sequence from geranyl acetate, and in 22 steps in total. Notably, the approach featured is based on cation olefin cyclization chemistry, allowing for rapid assembly of the tetracyclic system. However, it is important to recognize that one of the starting materials, vitamin D3 (60), already contains the CD-ring system with requisite structural features – C13 quaternary center and the side chain at C17 (Figure 21). While it may have been favorable in the case of lanostenol (12) to have vitamin D3 (60) as a starting material, the side chain at C17 is limited to being the simple saturated hydrocarbon, and the absolute stereochemistry is dictated by that of the natural product starting material.

1.4.6 Kobayashi’s Synthesis of Fomitelllic Acid B (2009)

The most recent synthesis and the only known asymmetric total synthesis of a lanostane is the synthesis of fomitelllic acid B (65; Figure 22) by Kobayashi’s group in
Inspired by Corey’s approach to lanostenol (12; Figure 21), Kobayashi’s total synthesis of fomitellic acid B (65; Figure 22) features a biomimetic polyene cyclization approach to generate the AB-ring system from a similar hydrindane substrate, although formation of AB-ring system is accomplished through a radical-based polyene cyclization.

The cyclization substrate, hydrindane 66a, was prepared through a convergent synthesis that employed vinyl iodide 67 and aldehyde 68 (Figure 22).

**Figure 22. Retrosynthesis of fomitellic acid B (65).**

Although vinyl iodide 67 (Figure 22) is structurally similar to the vinyl iodide 58 (Figure 21) that was used in Corey’s synthesis of lanostenol (12; Figure 21), 67 could not be prepared through the same sequence of chemical transformations from vitamin D₃ (60; Figure 21) as in Corey’s synthesis. Because the side chain at C17 in fomitellic acid B (65; Figure 22) is different from that in lanostenol (12; Figure 21) and in vitamin D₃ (60; Figure 21), Kobayashi’s approach to prepare vinyl iodide 67 began with the readily available Wieland–Miescher ketone (37; Figure 23) where a 14-step sequence was involved (38 → 69; Figure 23) to install an appropriate precursor at C17 that could later be converted to the desired side chain. As such, vinyl iodide 67 was assembled in 19 steps starting from the readily available Wieland–Miescher ketone (37; Figure 23). With the desired vinyl iodide 67 in hand, attention was directed towards synthesis of the cyclization substrate. Addition of the vinyl lithium species derived from vinyl iodide 67 to aldehyde 68 produced a 1:1 mixture of diastereomers, which upon subsequent acetylation of the corresponding secondary alcohol was separated to give epoxypolyenes 66a and 66b.
Moving forward, both epoxypolyenes 66a and 66b were used to explore the radical-based polyyne cyclization (Figure 24). While cyclization of epoxypolyene 66b by the action of Cp₂TiCl produced the monocyclization product 71, cyclization of its diastereomer 66a resulted in the formation of the desired tetracycle 73. As a result, 66b was converted to its diastereomer 66a through a four-step sequence which includes deacetylation, oxidation, Luche reduction and reacetylation. Formation of the desired tetracycle 73, containing C9β-H and C10β-Me, was considered to occur through chair-boat-like intermediate 72 whereas cyclization of the diastereomer 66b leading to the monocyclization product 71 was proposed to proceed through intermediate 70 in which non-bonded steric interactions between the C7 acetoxy group and the C14 quaternary center would destabilize the conformation required for B-ring formation. With the tetracyclic system established, isomerization of the C7–C8 olefin to the desired tetrasubstituted C8–C14 olefin was performed. This isomerization resulted in a mixture of regioisomers 74 and 75, and occurred along with deprotection of the TBS groups. The desired tetracycle 75 was separated from its regioisomer 74 and then advanced to the target natural product, fomitellic acid B (65), in nine additional steps.
Figure 24. Synthesis of fomitelic acid B (65).

In conclusion, representing the first and only known asymmetric total synthesis of a lanostane, the synthesis of fomitelic acid B (65) was accomplished in 33 steps longest linear sequence and a total of 45 steps, starting from the Wieland–Miescher ketone (37). The significant amount of effort evident in completion of this synthesis serves to highlight that lanostanes continue to stand as synthetically challenging targets and that a concise and efficient means to prepare them remains elusive.
1.5 References


Chapter 2: Progress towards the Asymmetric Total Synthesis of Lucidadone H

2.1 Development of an Approach towards Lucidadone H

Lucidadone H (2-1; Figure 2-1) is a hexanorlanostane natural product that has been isolated from several species of the genus *Ganoderma* which consists of about 80 species of the wood-decaying fungi.1–7 Representing a type of lanostanes that contains six fewer carbons on the side chain at C17 (2-1 and 2-2; Figure 2-1) than the prototypical lanosterol (2-4) and various lanostanes alike (2-5 and 2-6), the hexanorlanostane, lucidadone H (2-1), possesses synthetically challenging structural features inherent to lanostane natural products. The prominent features of lucidadone H (2-1) include 1) four quaternary centers at C4, C10, C13 and C14 (the latter two of which are vicinal), 2) oxygenation present in all four rings at the C3, C7, C11 and C15 positions, 3) the stereodefined substitution at C17, 4) trans-AB ring fusion, and 5) the tetrasubstituted olefin at C8–C9 embedded within the tetracyclic system. Bearing common structural features of lanostanes as well as a unique highly oxygenated system, lucidadone H (2-1) was chosen as a target for a synthesis program aimed at solving synthetic challenges associated with lanostanes.

![Figure 2-1. Structures of lanostane natural products.](image-url)
With the knowledge that there are substantial limitations and challenges present in semisynthesis and polyene cyclization chemistry which continue to be the primary means of preparing lanostanes,8–11 our approach towards the synthesis of lucidadone H (2-1) features a conceptually unique and non-biomimetic de novo synthesis that is based on the alkoxide-directed metallacyle-mediated annulation technology that was established in the Micalizio lab in 2012.12,13 The metallacyle-mediated annulation delivers highly substituted stereodefined hydrindanes such as 2-7 from readily available acyclic starting materials, TMS-alkyne 2-8 and enyne 2-9 (Figure 2-2). Notably, since the annulation substrate, enyne 2-9, can be easily prepared in three steps from epichlorohydrin (2-10) that is accessible in either enantiopure form, this annulation reaction provides access to either enantiomer of the highly functionalized hydrindane.12,13 It has been established that the titanium-mediated annulation between TMS-propyne (2-11) and enyne 2-12 is effective in producing the stereodefined hydrindane 2-13 that possesses a quaternary center at C13.14 While this annulation product resembles the CD-ring system of lanostane triterpenoids and could potentially serve as an intermediate of relevance in accessing lucidadone H (2-1), there are still major synthetic challenges that need to be addressed in converting the functionalized hydrindane 2-13 to a tetracyclic system that would contain structural features of lanostanes. The remaining challenges to be addressed in developing a synthetic plan for lucidadone H (2-1) include 1) establishing the tetracyclic skeleton through C9–C10 bond formation, 2) installation of the two quaternary centers at C10 and C14, 3) introduction of the stereodefined side chain at C17, and 4) formation of the tetrasubstituted olefin between the B and C rings.
2.1.1 Identifying the Key Tetracyclic Intermediates

Previous studies in the Micalizio lab regarding construction of the tetracyclic system through C9–C10 bond formation of hydrindane 2-13 (Figure 2-3) and relocation of the quaternary center from C9 to C10 were taken into consideration when exploring potentially useful tetracyclic intermediates to be employed in the synthesis of lucidadone H (2-1; Figure 2-1).\textsuperscript{14–16}

As illustrated in Figure 2-3A, tandem protodesilylation followed by a matched double asymmetric Friedel–Crafts type cyclization in the presence of (R)-Binol and SnCl\textsubscript{4} affords C9,C13-\textit{anti} product 2-14 with $\geq$20:1 diastereoselection at C9.\textsuperscript{14} Next, a two-step sequence of demethylation of methyl ether at C3 followed by a unique oxidative dearomatization and group-selective Wagner–Meerwein rearrangement converts 2-14 to the corresponding tetracycle 2-15 – a product with C10,C13-\textit{anti} stereochemistry.\textsuperscript{14} While
this sequence of reactions is efficient in delivering the tetracyclic product 2-15 with two quaternary centers at C10 and C13, the relative stereochemistry of these quaternary centers is not what is observed in lanostane natural products. Attempts to favor the C9,C13-syn product 2-16 by using (S)-Binol and SnCl₄ in the cyclization of 2-13 unfortunately led to 1.3:1 mixture of diastereomers.¹⁴,¹⁶ The syn-isomer 2-16 could be separated from its diastereomer and advanced to C10,C13-syn tetracycle 2-17 that could potentially serve as an intermediate in accessing lanostanes.¹⁴ However, both 2-16 and 2-17 were considered as unsuitable intermediates to be employed in the de novo synthesis of lucidadone H (2-1; Figure 2-1) since the cyclization reaction leading to 2-16 proceeds without stereoselection, and designing a total synthesis that relies on such a strategy in the early stage of the synthesis seemed inefficient. Additionally, the tetracyclic products prepared from this strategy lack functionality at C17 that could be of assistance in installation of the requisite C17 side chain. Alternatively, a distinct mode of C9–C10 bond formation through intramolecular Heck cyclization of a related hydrindane substrate 2-18 has been discovered to be effective in selectively producing the syn-isomer 2-19.¹⁵ However, the product of this cyclization lacks the C17 functionality as well.
Given such concerns, it was decided that tetracycle 2-20 (Figure 2-4), which was employed in the recent total synthesis of marine pregnene (+)-03219A, was more appropriate to serve as a key intermediate in our synthesis campaign towards lucidadone H (2-1; Figure 2-4). Tetracycle 2-20 was viewed as a valuable intermediate due to the presence of 1) the carbonyl group at C17, 2) a D-ring enone moiety and 3) the two quaternary centers at C9 and C13 that are in syn-orientation to each other. While the carbonyl group at C17 provides a useful handle for introducing the C17 side chain, the D-ring enone moiety could facilitate installing the C14 quaternary center. Additionally, the C9,C13-syn stereochemistry in 2-20 could assist in realizing the C10,C13-syn stereochemistry observed in lucidadone H (2-1) as the methyl group at C9 could be migrated to C10 through the two-step sequence involving oxidative dearomatization and Wagner–Meerwein rearrangement that was previously described in Figure 2-3 (2-16 → 2-17). Furthermore, because the C9,C13-syn stereochemistry in 2-20 is established through
formal inversion of the C13 quaternary center of 2-21 – a compound with C9,C13-anti stereochemistry, this approach would take advantage of the high stereoselectivity observed in the matched double asymmetric cyclization to produce 2-21 from 2-22 (analogous to 2-13 → 2-14 in Figure 2-3).14,17 As such, 2-21, which possesses the incorrect absolute stereochemistry at C13, was regarded as another key tetracyclic intermediate in the retrosynthetic strategy for lucidadone H (2-1). Finally, hydrindane 2-22 could be derived from (R)-epichlorohydrin (ent-2-10) in four steps.14

![Figure 2-4. Retrosynthetic strategy of lucidadone H (2-1).](image)

### 2.2 Preparation of the Key Tetracyclic Intermediates

Having identified the key tetracyclic intermediates for the approach towards lucidadone H (2-1), the starting material enyne 2-23 was prepared in large quantities. As anticipated, the titanium-mediated annulative cross-coupling between TMS-propyne (2-11) and enyne 2-2314 proceeded with outstanding levels of regio- and stereoselectivity and delivered hydrindane 2-22 as the major product. Subsequent tandem protodesilylation and matched double asymmetric Friedel–Crafts cyclization in the presence of (S)-Binol and SnCl₄14 set the quaternary center at C9, affording the C9,C13-anti product 2-21 which was isolated as a single diastereomer in 51% yield over the two steps. With ample quantities of 2-21 prepared, an established three-step sequence was performed to produce the key tetracyclic intermediate 2-20.17 This sequence of reactions would achieve formal inversion of the quaternary center at C13 and transform the D-ring into an enone with a carbonyl at
the C17 position. From 2-21, ozonolytic cleavage of the C8–C14 alkene followed by dehydrative elimination of the resulting β-hydroxy ketone 2-24 produced dione 2-25 in 67% over the two steps. Suitably functionalized for an intramolecular vinylogous Aldol condensation, dione 2-25 was converted to 2-20 in 48% isolated yield.¹⁷

![Chemical diagram](image)

**Figure 2-5.** Synthesis of key intermediate 2-20.

2.3 Installation of the C14 Quaternary Center

With key intermediate 2-20 accessed in just five steps from the readily available enyne 2-23, attention was directed towards devising a plan for the stereoselective installation of the C14 quaternary center. Being vicinal to the C13 quaternary center, the C14 quaternary center poses a major synthetic challenge.

![Chemical diagram](image)

**Figure 2-6.** Proposed vinyl epoxide rearrangement.
From **2-20**, it was thought possible to prepare vinyl epoxide **2-26** – a substrate that could be used in establishing the C14 quaternary center to potentially provide the lanostane-like product **2-27** (Figure 2-6). It was anticipated that upon exposure to a Lewis acid, vinyl epoxide **2-26** would undergo a semi-pinacol rearrangement. Opening of the epoxide could generate a stable tertiary allylic carbocation along the C9, C8 and C14 carbons. Concomitant formation of the ketone at C15 and 1,2-methyl shift from C15 to C14 would then set the quaternary center at C14, delivering diketone **2-27**.

![Chemical structures](image)

**Figure 2-7.** Installation of the C14 quaternary center.

In order to investigate this rearrangement, dienone **2-20** was smoothly converted to vinyl epoxide **2-26** in five efficient steps (Figure 2-7). Site- and stereoselective conjugate addition at C15 with an organocopper reagent derived from methyl Grignard and copper iodide delivered a C15-substituted tetracycle **2-28** in 72% yield. Reduction of the C17 ketone and demethylation of the C3 methyl ether\(^{21}\) in a one-pot reaction with DIBAI-H afforded the corresponding diol in 91% yield. Subsequent oxidative dearomatization and group selective Wagner–Meerwein rearrangement by the action of PIDA in HFIP\(^{14,22,23}\) resulted in the formation of **2-29** possessing an A-ring dienone and the desired C10 quaternary center and diene spanning the CD-ring system. Following these transformations, chemoselective hydrogenation in the presence of Wilkinson’s catalyst reduced the C1–C2 alkene and delivered **2-30** in 83% yield. Hydroxyl-directed
epoxidation\textsuperscript{24–26} of the C14–C15 alkene generated the desired tetrasubstituted vinyl epoxide 2-26 in 72% yield. Exposure of 2-26 to BF\textsubscript{3}•OEt\textsubscript{2} then resulted in an efficient semi-pinacol rearrangement\textsuperscript{18–20} affording a product 2-27 that contains both the desired vicinal quaternary centers at C13 and C14 as well as a ketone at C15.

2.4 Initial C–C Bond Formation at the C17 Position

Having completed our goal of establishing the C14 quaternary center through a Lewis acid-mediated semi-pinacol rearrangement, we next turned our attention towards the installation of the C17 side chain. It was recognized that enone 2-31 (Figure 2-8), easily derived from β-hydroxy ketone 2-27, could be a valuable intermediate for functionalizing the C17 position. Two approaches for the initial C–C bond formation at C17 were envisioned: a direct nucleophilic addition to C17, or manipulation of the C15 ketone to set the stage for a [3,3]-sigmatropic rearrangement. In order to quickly obtain some data that would allow us to evaluate the most promising method to pursue, a few qualitative experiments were conducted on enone 2-31 that would enable us to better understand the facial selectivity of nucleophilic additions at the C17 and C15 positions.

\textbf{Figure 2-8.} Initial C–C bond formation at C17.

Conjugate addition at C17 with a simple nucleophile derived from methyl Grignard and Cu(OAc)\textsubscript{2} revealed that the addition takes place on the \(\alpha\)-face of the D-ring, affording 2-32 with the undesired stereochemistry at C17 (Figure 2-8). However, this result was considered to be inconsequential since it was reasoned that the correct stereochemistry at C17 could be established either through epimerization at a later stage once the requisite
acetyl group is in place or through conjugate addition with an appropriate nucleophile followed by regeneration of the C16–C17 alkene and subsequent hydrogenation. With this plan in mind, addition of an isopropenyl nucleophile, which could serve as a surrogate for the requisite acetyl group, was attempted, and unfortunately, this resulted in no reaction. Rather than screening multiple conjugate addition conditions on a late-stage intermediate, we decided to explore the second approach that was described above: manipulation of the C15 ketone to set the stage for a [3,3]-sigmatropic rearrangement.

![Chemical structure](image)

**Figure 2-9.** Attempted C–C bond formation at C17.

When a simple hydride reduction was carried out on enone 2-31 (Figure 2-9), it was observed that the hydride was delivered to the C15 ketone from the β-face, delivering 2-33 as the major product. This suggests that if an allyl group were to be added to the C15 ketone and followed by a successful oxy-Cope rearrangement, the allyl group could be installed with the correct stereochemistry at C17. As such, oxy-Cope rearrangement conditions were briefly explored. The rearrangement precursor 2-35 was prepared in three steps from enone 2-31. Unfortunately, when a number of standard conditions was screened for invoking the anionic oxy-Cope rearrangement, it resulted in either no reaction or a complex mixture of products with no trace of desired product. The difficulties encountered in functionalizing enone 2-31 led us to reconsider our synthetic plan from 2-
and focus on introducing the C17 side chain first before setting the C14 quaternary center.

2.5 Successful Synthesis of the Lanostane Tetracycle and Efforts Towards Lucidadone H

Putting this plan to practice, from C15-methylated tetracycle 2-28, a two-step sequence of Wittig olefination of the C17 ketone with an unstabilized ylide and hydroboration–oxidation of the resulting Z-olefin was used to install a two-carbon chain at C17, delivering 2-37 in 76% yield over the two steps (Figure 2-10).\(^2\) This material was then advanced to 2-38 through demethylation\(^2\) followed by oxidative dearomatization and group selective Wagner–Meerwein rearrangement.\(^1\),\(^2\),\(^2\) Next, hydroxyl-directed epoxidation\(^2\),\(^2\) of the C14–C15 olefin was performed to introduce the desired vinyl epoxide functionality in the CD-ring system. Notably, the directing hydroxyl group in 2-38 is one additional carbon away than the directing hydroxyl group in the substrate (2-30; Figure 2-7) that was previously employed. Regardless, hydroxyl-directed epoxidation of 2-38 proved to be effective and afforded the desired product 2-39 in 77% yield. Protection of the secondary alcohol in 2-39 with a TES group followed by installation of the gem dimethyl group at C4 produced dimethyl ketone 2-40, which upon exposure to BF\(_3\)•OEt\(_2\) resulted in an efficient and stereospecific rearrangement as well as desilylation, leading to the hexanorlanostane 2-41. Chemoselective reduction of C1–C2 alkene in the presence of Wilkinson’s catalyst and subsequent oxidation of the remaining secondary alcohol\(^2\) then delivered 2-43 – a late-stage intermediate that is only a couple of redox manipulations away from the target natural product, lucidadone H (2-1).
Moving forward towards lucidadone H, hydrogenation of the C5–C6 alkene to set the correct stereochemistry at C5 presented a challenge. There are examples in the literature that demonstrate stereoselective reductions of structurally related C5–C6 alkenes.\textsuperscript{30–34} As shown in the selected examples in Figure 2-11A, reduction of \textit{2-44} with Pd/C and H\textsubscript{2}\textsuperscript{30} reduction of \textit{2-46} under PtO\textsubscript{2} and H\textsubscript{2} conditions\textsuperscript{31} and reduction of \textit{2-48} with the use of metal-catalyzed hydrogen atom transfer conditions\textsuperscript{32,35,36} selectively delivered \textit{2-45}, \textit{2-47} and \textit{2-49} respectively, all of which contain \textit{trans}-fused AB-ring systems. Unlike these examples, stereoselective reductions of the C5–C6 alkene on lanostanes prepared in this synthesis all led to \textit{cis}-fused products selectively (Figure 2-11B). Reduction of norlanostane \textit{2-41} with Pd/C and H\textsubscript{2} resulted in \textit{2-50} with a \textit{cis}-fused AB-ring system. The same stereoselectivity was observed when hydrogenation of \textit{2-43} was performed under a higher pressure of hydrogen (88 psi), resulting in the \textit{cis}-fused product \textit{2-54}. Similarly, reactions with PtO\textsubscript{2} and H\textsubscript{2} or metal-catalyzed hydrogen atom transfer conditions...
transfer conditions\textsuperscript{35,36} delivered cis-fused products 2-50 and 2-55, isolated from a complex mixture of products.

A. Stereoselective reductions of C5–C6 alkenes on related systems.

1. Mao et al., 2016:

\[
\text{Pd/C, H}_2, \text{EtOAc} \rightarrow \text{MeCO}_2\text{Me} \quad 98\%
\]

\[
\text{Pd/C, H}_2, \text{MeOH} \rightarrow \text{MeCO}_2\text{Me} \quad 83\%
\]

\[
\text{Pd/C, H}_2, (88 \text{ psi}) \rightarrow \text{MeCO}_2\text{Me} \quad 62\%
\]

B. Stereoselective reduction of the C5–C6 alkene, delivering cis-fused products, 2-53, 2-55 and 2-57.

\[
\text{PtO}_2\text{H}_2, \text{HCl, C}_6\text{H}_12 \rightarrow \text{MeCO}_2\text{Me} \quad 50\%
\]

\[
\text{PtO}_2\text{H}_2, \text{HCl, C}_6\text{H}_12 \rightarrow \text{MeCO}_2\text{Me} \quad 50\%
\]

\[
\text{PtO}_2\text{H}_2, \text{HCl, C}_6\text{H}_12 \rightarrow \text{MeCO}_2\text{Me} \quad 50\%
\]

\[
\text{PtO}_2\text{H}_2, \text{HCl, C}_6\text{H}_12 \rightarrow \text{MeCO}_2\text{Me} \quad 50\%
\]

**Figure 2-11.** Reduction of C5–C6 alkene.

Though the three-dimensional structures of synthetic lanostanes (e.g., 2-41 on bottom right corner in Figure 2-11) and the selectivity observed in the literature examples on related structures suggest that hydrogenation on these synthetic lanostanes should occur on the more accessible \( \alpha \)-face of the molecule to generate products that contain trans-fused AB-ring system, this was not the case. While the reason for the observed stereoselectivity is unclear, it is important to note that examples reported in the literature regarding hydrogenation of the C5–C6 alkene are not demonstrated on lanostane structures with the additional quaternary center at C14.
2.6 Future Directions and Conclusion

While there are several known lanostane natural products that possess the C5–C6 alkene or the cis-fused AB-ring system, the majority of the lanostanes found in nature, including lucidadone H (2-1), contain a trans-fused AB-ring system. As such, future studies should be directed at establishing the trans-fused AB-ring system by a different strategy at an earlier stage of the synthesis pathway. For example, dissolving metal reduction and alkylation of 2-59 could be investigated. This would result in 2-60—a product that contains the desired stereochemistry at C5 and a gem dimethyl group at C4. Enone 2-59 could be produced from dienone 2-38 through a sequence of three steps involving chemoselective reduction of C1–C2 alkene in the presence of Wilkinson’s catalyst, protection of the secondary alcohol as a tetrahydropyranyl (THP) ether, and treatment of the resulting product with aqueous formaldehyde, thiophenol and triethylamine.

Upon successful generation of 2-60 from reductive methylation of 2-59, installation of the C14 quaternary center through removal of the THP protecting group, hydroxyl-directed epoxidation and semi-pinacol rearrangement of vinyl epoxide 2-61, and global oxidation

Figure 2-12. Future directions.
oxidation to introduce the enedione moiety in the B- and C-rings and the acetyl group at C17 would deliver the target natural product, lucidadone H (2-1).

In conclusion, efforts towards lucidadone H (2-1) have led to an efficient and asymmetric de novo synthesis to prepare hexanorlanostanes. Based on early chemical technology developed in the Micalizio lab, the non-biomimetic approach described here is capable of accessing a hexanorlanostane (e.g., 2-41) in as few as 14 steps from a simple chiral enyne and will serve as an inspiration for synthesis of various lanostane natural products in the future.
2.7 References


2.8 Supplementary Information

2.8.1 Materials and Methods

A. Reagents and Solvents

All reagents and starting materials were purchased from commercial sources and used as received, unless otherwise indicated. Anhydrous dichloromethane (CH$_2$Cl$_2$), diethyl ether (Et$_2$O), tetrahydrofuran (THF) and toluene (PhMe) were obtained by passing HPLC grade solvents through a column of activated alumina using a Glass Contour Solvent Purification System by Pure Process Technology, LLC. Hexafluoroisopropanol (HFIP) was purchased from Oakwood Chemical and used as received. Anhydrous methanol (MeOH), anhydrous isopropanol (i-PrOH), anhydrous triethylamine (NEt$_3$) and SnCl$_4$ (1.0 M in CH$_2$Cl$_2$) were purchased in a Sure-Seal™ bottle from Sigma-Aldrich. PTFE syringe tubing, Pd/C (10 wt. %), Wilkinson’s catalyst, t-butyl hydrogenperoxide (t-BuOOH) (5.5 M in decane), Mn(dpm)$_3$ and PhSiH$_3$ were purchased from Sigma-Aldrich. For flash column chromatography, HPLC grade solvents were used without further purification.

Solutions of n-BuLi and t-BuLi were purchased from Sigma-Aldrich and titrated against N-benzylbenzamide in accordance with the procedure reported by Chong.$^1$

B. Reaction Set-Up and Purification

All reactions were conducted in flame-dried glassware under an atmosphere of dry nitrogen unless otherwise indicated. Reaction mixtures were magnetically stirred and their progress was monitored by thin layer chromatography (TLC) on EMD TLC silica gel 60 F$_{254}$ glass-backed plates. Compounds were visualized by initial exposure of TLC plates to UV-light (254 nm), followed by staining with p-anisaldehyde.

Purification of crude isolates was achieved by flash column chromatography on a Biotage® Isolera One™ Automated Liquid Chromatography System using Biotage® SNAP Ultra HP-Sphere 10–25 g or Biotage® KP-Sil 10–100 g silica gel cartridges, or performed using a forced flow of the indicated solvent system on Sorbent Technologies™ silica gel
60 Å (40–63 µm particle size). Purification of co-eluting compounds was performed using the indicated solvent system on Agilent Technologies semi-preparative High Performance Liquid Chromatography (HPLC) system with Varian Dynamax HPLC Microsorb silica column (normal phase, pore size: 100 Å, particle size: 5.0 µm, inner diameter: 21.4 mm, length: 250 mm). Concentration of reaction product solutions and chromatography fractions was accomplished by rotary evaporation at 30–35 °C under the appropriate pressure, followed by concentration at room temperature on a vacuum pump (approx. 0–1 mbar). Yields refer to chromatographically purified and spectroscopically pure compounds, unless otherwise indicated.

C. Characterization Data for New Compounds

i. Nuclear Magnetic Resonance Spectroscopy

$^1$H-NMR data were recorded on a Bruker Avance III 500 MHz NMR spectrometer (TBI probe) and a Bruker Avance III 600 MHz spectrometer (BBFO probe). $^1$H chemical shifts are reported in parts per million (ppm, δ scale) downfield from tetramethylsilane and are referenced to the residual CHCl₃ or C₆D₅H in the deuterated solvents: CDCl₃ (7.26 ppm), C₆D₆ (7.16 ppm). NMR coupling constants are measured in Hertz (Hz), and splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; app d, apparent doublet; app dd, apparent doublet of doublets; app t, apparent triplet; app dt, apparent doublet of triplets; app td, apparent triplet of doublets; app q, apparent quartet; app p, apparent pentet. $^{13}$C {1H decoupled} NMR data were recorded at 150 MHz on a Bruker Avance III 600 MHz spectrometer (BBFO probe). $^{13}$C chemical shifts are reported in parts per million (ppm, δ scale) and are referenced to the central line of the carbon resonances of the solvents: CDCl₃ (77.16 ppm), C₆D₆ (128.06 ppm).

Structural assignments for new compounds were supported by two-dimensional NMR experiments (COSY, HSQC, HMBC and NOESY) recorded on a Bruker Avance III
600 MHz spectrometer (BBFO probe), while the relative stereochemical assignments were
determined by analysis of the data obtained from 1D- or 2D-NOESY experiments,
recorded on a Bruker Avance III 500 MHz NMR spectrometer (TBI probe) or a Bruker
Avance III 600 MHz spectrometer (BBFO probe), respectively.

ii. Infrared Spectroscopy

Infrared spectra were collected on a JASCO FT/IR-4100 Fourier Transform
Infrared Spectrometer.

iii. Accurate Mass Determination

HRMS (EI-TOF) analyses were performed at the Mass Spectrometry Laboratory
of the University of Illinois at Urbana-Champaign.

iv. Optical Rotation

Optical rotations ($\alpha$) were obtained on a JASCO-P-2000 polarimeter equipped with
tungsten-halogen lamp (WI) and interface filter set to 589 nm, using a sample cell with a
pathlength of 100 nm. Specific rotations are reported as: $[\alpha]_\lambda^{(c)}$ (c, solvent) and are
based on the equation $[\alpha]_\lambda^{(c)} = (100\cdot\alpha)/(l\cdot c)$, where the concentration (c) is reported as
g/100 mL and the pathlength (l) in decimeters.

Note: Copies of NMR spectra for compounds that appear in the successful asymmetric
route to synthetic lanostane 2-43 have been published$^2$ and are available online.
2.8.2 Experimental Procedures

**Synthesis of enyne 2-23:**

To a stirred solution of alkyne S2-1 \(^3\) (13 g, 82 mmol, 2.0 equiv.) in THF (271 mL) at –78 °C was added \(n\)-BuLi (2.5 M in hexanes, 25 mL, 61 mmol, 1.5 equiv.) dropwise by syringe. The resulting mixture was stirred at –78 °C for approximately 30 mins, and BF\(_3\)•OEt\(_2\) (9.1 mL, 73 mmol, 1.8 equiv.) was added dropwise by syringe. The mixture was then stirred for another 30 mins at the same temperature, and a solution of epoxide S2-2 \(^4\) (4.0 g, 41 mmol, 1.0 equiv.) in THF (31 mL) was added dropwise via addition funnel. After the complete addition of epoxide S2-2, the addition funnel was rinsed with THF (10 mL). The reaction mixture was stirred for approximately 1 h, and the reaction was quenched by the addition of a saturated aqueous solution of NaHCO\(_3\) and further diluted with ethyl acetate. The resulting mixture was then warmed to room temperature, and the aqueous and organic phases were separated. The aqueous layer was extracted with ethyl acetate (× 3). The combined organic layers were dried over anhydrous Na\(_2\)SO\(_4\), filtered and concentrated *in vacuo* to afford the crude product, which was purified by flash column chromatography on a Biotage® KP-Sil 100 g cartridge with 100:0 to 85:15 hexanes–ethyl acetate gradient elution to afford enyne 2-23 (9.0 g, 86%) as a yellow oil. Spectroscopic data are in accordance with the reported values.\(^5\)

**Analytical data for enyne 2-23:**

**TLC** (SiO\(_2\)) \(R_f = 0.26\) (hexanes–ethyl acetate, 80:20); \(^1\)H NMR (600 NMR, CDCl\(_3\)) \(\delta 7.21\) (t, \(J = 7.8\) Hz, 1H), 6.81 (d, \(J = 7.5\) Hz, 1H), 6.80 – 6.74 (m, 2H), 4.89 – 4.84 (m, 1H), 4.81
\(-4.75\ (m,\ 1H),\ 3.85\ -\ 3.80\ (m,\ 1H),\ 3.80\ (s,\ 3H),\ 2.79\ (t,\ J = 7.5\ Hz,\ 2H),\ 2.49\ (tt,\ J = 7.5,\ 2.4\ Hz,\ 2H),\ 2.38\ (ddt,\ J = 16.5,\ 5.0,\ 2.4\ Hz,\ 1H),\ 2.32\ (ddt,\ J = 16.5,\ 6.2,\ 2.4\ Hz,\ 1H),\ 2.24\ (dd,\ J = 13.8,\ 4.8\ Hz,\ 1H),\ 2.17\ (dd,\ J = 13.9,\ 8.3\ Hz,\ 1H),\ 1.93\ (d,\ J = 4.1\ Hz,\ 1H),\ 1.75\ (s,\ 3H);^{13}{C}\ NMR\ (150\ MHz,\ CDCl_3)\ \delta\ 159.7,\ 142.5,\ 129.4,\ 120.9,\ 114.4,\ 113.5,\ 111.6,\ 82.4,\ 77.1,\ 67.9,\ 55.2,\ 44.8,\ 35.4,\ 27.3,\ 22.6,\ 20.9.\)

**Synthesis of estrane 2-21:**

To a solution of TMS-propyne \((2-11)\) \((17\ mL,\ 114\ mmol,\ 3.3\ equiv.)\) in toluene \((380\ mL)\) was added Ti(O-i-Pr)_4 \((34\ mL,\ 114\ mmol,\ 3.3\ equiv.)\) at room temperature. The flask was cooled to \(-78\ °C\) and \(n-BuLi\) \((2.5\ M\ in\ hexanes,\ 90\ mL,\ 226\ mmol,\ 6.5\ equiv.)\) was added dropwise via addition funnel. Upon complete addition of \(n-BuLi,\) the flask was warmed to room temperature, and then heated in a water bath at 50 °C for 1 h. After the indicated time, the flask was cooled to room temperature.

Meanwhile, to a separate flask containing a solution of enyne \(2-23\) \((9.0\ g,\ 35\ mmol,\ 1.0\ equiv.)\) in toluene \((10\ mL)\ at\ -78\ °C\) was added \(n-BuLi\) \((2.5\ M\ in\ hexanes,\ 14\ mL,\ 35\ mmol,\ 1.0\ equiv.)\) dropwise by syringe. The cooling bath was removed, and the resulting mixture was warmed to room temperature. This lithium-alkoxide solution was then transferred dropwise via a cannula to the black Ti-alkyne complex solution at room temperature, and the reaction mixture was stirred overnight (approximately 14 h). The following morning, the reaction mixture was quenched by the addition of 130 mL saturated aqueous solution of NaHCO_3 and further diluted with ethyl acetate. The organic layer was separated, and the aqueous layer was extracted with 300 mL of ethyl acetate \((\times 6).\) The
combined organic layers were dried over anhydrous Na$_2$SO$_4$, filtered and concentrated \textit{in vacuo} to afford the crude product, which was purified by flash column chromatography on a Biotage® KP-Sil 100 g cartridge with 100:0 to 75:25 hexanes–ethyl acetate gradient elution to afford the impure hydindane \textbf{2-22} (8.5 g), which was carried on to the next step.

To a stirred suspension of (S)-Binol (8.0 g, 28 mmol, 1.2 equiv.) in CH$_2$Cl$_2$ (172 mL) at –78 °C was added SnCl$_4$ (1.0 M in CH$_2$Cl$_2$, 23 mL, 23 mmol, 1.0 equiv.) dropwise by syringe. The resulting mixture was then stirred for 30 mins at –78 °C, and a solution of hydindane \textbf{2-22} (8.5 g, 23 mmol, 1.0 equiv.) in CH$_2$Cl$_2$ (143 mL) was added dropwise via addition funnel. The reaction mixture was stirred at the same temperature for 45 mins, and then warmed to room temperature over 1 h. The reaction was then quenched by the addition of a saturated aqueous solution of NH$_4$Cl, and the biphasic mixture was vigorously stirred for 1 h. The aqueous and organic layers were separated, and the aqueous layer was extracted with CH$_2$Cl$_2$ (× 3). The combined organic extracts were washed with 5% aqueous solution of NaOH, dried over anhydrous Na$_2$SO$_4$, filtered and concentrated \textit{in vacuo} to afford the crude product, which was purified by flash column chromatography on a Biotage® KP-Sil 100 g cartridge with 100:0 to 70:30 hexanes–ethyl acetate gradient elution to afford estrane \textbf{2-21} (5.3 g, 51% over 2 steps) as a yellow foam. Spectroscopic data are in accordance with the reported values.$^5$

**Analytical data for estrane 2-21:**

<table>
<thead>
<tr>
<th>Method</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TLC (SiO$_2$) R$_f$</strong></td>
<td>0.16 (hexanes–ethyl acetate, 80:20)</td>
</tr>
<tr>
<td><strong>$^1$H NMR (600 NMR, CDCl$_3$)</strong></td>
<td>δ 7.21 (d, $J = 8.7$ Hz, 1H), 6.76 (dd, $J = 8.7, 2.8$ Hz, 1H), 6.59 (d, $J = 3.1$ Hz, 1H), 4.65 – 4.56 (m, 1H), 3.78 (s, 3H), 2.92 – 2.81 (m, 2H), 2.77 – 2.68 (m, 1H), 2.46 – 2.40 (m, 1H), 2.37 (app td, $J = 12.7, 5.5$ Hz, 1H), 2.27 (dd, $J = 16.8, 4.3$ Hz, 1H), 2.17 (dd, $J = 11.9, 6.7$ Hz, 1H), 2.09 (app dt, $J = 13.1, 3.4$ Hz, 1H), 1.85 (app td, $J = 12.3, 5.8$ Hz, 1H), 1.77 – 1.69 (m, 2H), 1.19 (s, 3H), 0.87 (t, $J = 7.2$ Hz, 3H).</td>
</tr>
</tbody>
</table>
2H), 1.61 (br s, 1H), 1.41 – 1.30 (m, 4H), 0.90 (s, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) δ 157.1, 140.1, 137.3, 136.4, 132.0, 127.3, 113.1, 112.5, 71.6, 55.3, 52.0, 41.6, 38.1, 37.7, 34.4, 33.4, 32.3, 31.4, 25.9, 25.0.

**Synthesis of dienone 2-20:**

A solution of estrane 2-21 (510 mg, 1.71 mmol, 1.0 equiv.) in CH$_2$Cl$_2$ (125 mL) and MeOH (25 mL) was cooled to −78 °C, and ozone was bubbled through the solution (Welsbach ozone generator, 1.0 SCFM, 90 V, 8.0 psi) for approximately 5 mins (1 min per 100 mg of 10) before being quenched with dimethyl sulfide (3.0 mL). The resulting mixture was then warmed to room temperature. This reaction was repeated in 500 mg batches until starting material estrane 2-21 (5.3 g) was exhausted. The quenched reaction mixture from each batch was combined and concentrated in vacuo. The residue was then diluted with ethyl acetate and washed with DI water. The organic phase was collected, dried over anhydrous Na$_2$SO$_4$, filtered and concentrated in vacuo to afford the crude product, which was purified by flash column chromatography on a Biotage® KP-Sil 100 g cartridge with 90:10 to 30:70 hexanes–ethyl acetate gradient elution to afford the tentatively assigned 2-24 (1.3 g) as a yellow oil, and the tentatively assigned 2-25 (2.6 g) as a yellow oil.

To a solution of 2-24 (1.3 g, 4.1 mmol, 1.0 equiv.) in PhMe (135 mL) was added p-TsOH•H$_2$O (1.0 g, 5.3 mmol, 1.3 equiv.) in one portion. The resulting mixture was then
heated in an oil bath at 60 °C for approximately 30 mins, and then cooled to room temperature. DI water (70 mL) was added to the flask, and the aqueous and organic phases were separated. The aqueous layer was extracted with CH$_2$Cl$_2$ ($\times$ 3). The combined organic extracts were dried over anhydrous Na$_2$SO$_4$, filtered and concentrated in vacuo to afford the crude product (pure by $^1$H NMR analysis) 2-25 (1.1 g, total 3.7 g [2.6 g from previous step], 67% over 2 steps), which was used in the next step without further purification.

To a stirred solution of dione 2-25 (1.8 g, 5.7 mmol, 1.0 equiv.) in MeOH (280 mL) was added KOT-Bu (1.9 g, 17 mmol, 3.0 equiv.) in one portion. The resulting mixture was heated at reflux using an oil bath for approximately 42 h. After the indicated time, the reaction mixture was cooled to room temperature and quenched by the addition of a saturated aqueous solution of NH$_4$Cl. This mixture was concentrated in vacuo, and the resulting residue was diluted with ethyl acetate and DI water. The aqueous and organic layers were separated, and the aqueous layer was extracted with ethyl acetate ($\times$ 3). The combined organic extracts were dried over anhydrous Na$_2$SO$_4$, filtered and concentrated in vacuo to afford the crude product, which was purified by flash column chromatography on a Biotage® KP-Sil 100 g cartridge with 95:5 to 65:35 hexanes–ethyl acetate gradient elution to afford dienone 2-20 (800 mg, 48%) as a yellow oil, and recovered dione 2-25 (140 mg). Spectroscopic data are in accordance with the reported values.$^6$

**Analytical data for dienone 2-20:**

TLC (SiO$_2$) $R_f = 0.29$ (hexanes–ethyl acetate, 75:25); $^1$H NMR (600 NMR, CDCl$_3$) $\delta$ 8.04 (d, $J = 5.8$ Hz, 1H), 7.27 (d, $J = 8.8$ Hz, 1H), 6.76 (dd, $J = 8.8, 3.0$ Hz, 1H), 6.52 (d, $J = 3.1$ Hz, 1H), 6.07 (d, $J = 5.8$ Hz, 1H), 3.75 (s, 3H), 2.93 (ddd, $J = 15.9, 5.9, 2.2$ Hz, 1H), 2.88 (dd, $J = 12.7, 5.6, 2.2$ Hz, 1H), 2.81 – 2.73 (m, 1H), 2.56 (app td, $J = 12.6, 5.8$ Hz, 1H),
2.50 (app dt, $J = 14.6$, 3.8 Hz, 1H), 2.18 (app td, $J = 14.3$, 4.0 Hz, 1H), 1.71 (app dt, $J = 12.9$, 3.7 Hz, 1H), 1.51 (s, 3H), 1.27 (s, 3H), 1.17 (app td, $J = 13.4$, 4.0 Hz, 1H); $^{13}$C NMR (150 MHz, CDCl$_3$) δ 212.0, 157.5, 153.1, 141.4, 138.9, 138.3, 137.5, 129.3, 127.4, 113.1, 112.9, 55.3, 46.6, 40.9, 35.3, 33.9, 33.0, 26.4, 24.6, 22.8.

**Synthesis of ketone 2-28:**

To a stirred suspension of Cul (58 mg, 0.31 mmol, 1.8 equiv.) in THF (1.0 mL) at –78 °C was added MeMgCl (3.0 M in THF, 0.17 mL, 0.51 mmol, 3.0 equiv.) dropwise by syringe. The resulting mixture was stirred at –78 °C, and then warmed to –30 °C and stirred at this temperature for 10 mins. Next, a solution of dienone 2-20 (50 mg, 0.17 mmol, 1.0 equiv.) in THF (1.0 mL) was added dropwise and stirring was maintained at –30 °C for approximately 30 mins. The reaction mixture was quenched at –30 °C by the addition of a saturated aqueous solution of NH$_4$Cl. After warming to room temperature, the mixture was transferred to a separatory funnel, and the aqueous layer was extracted with ethyl acetate ($\times 3$). The combined organic extracts were dried over anhydrous Na$_2$SO$_4$, filtered and concentrated in vacuo to afford the crude product, which was purified by flash column chromatography on a Biotage® KP-Sil 10 g cartridge with 90:10 to 70:30 hexanes–ethyl acetate gradient elution to afford ketone 2-28 (41 mg, 72%) as a yellow oil.

**Analytical data for ketone 2-28:**

TLC (SiO$_2$) $R_f = 0.45$ (hexanes–ethyl acetate, 80:20); $[\alpha]_{D}^{11.0} = -22.0$ (c 2.0, CHCl$_3$); $^1$H NMR (600 NMR, CDCl$_3$) δ 7.24 (d, $J = 8.7$ Hz, 1H), 6.73 (dd, $J = 8.7$, 2.8 Hz, 1H), 6.55 (d,
$J = 2.7 \text{ Hz, 1H}$, 3.76 (s, 3H), 3.18 – 3.09 (m, 1H), 2.87 (ddd, $J = 16.0, 6.4, 2.7 \text{ Hz, 1H}$), 2.76 (ddd, $J = 16.4, 11.5, 6.2 \text{ Hz, 1H}$), 2.69 (ddd, $J = 13.6, 6.1, 2.7 \text{ Hz, 1H}$), 2.52 – 2.41 (m, 2H), 2.35 (dd, $J = 19.5, 3.8 \text{ Hz, 1H}$), 2.20 (app dt, $J = 14.3, 4.6 \text{ Hz, 1H}$), 1.93 (ddd, $J = 14.9, 12.1, 3.7 \text{ Hz, 1H}$), 1.58 (ddd, $J = 13.2, 5.3, 3.8 \text{ Hz, 1H}$), 1.40 (s, 3H), 1.37 – 1.31 (m, 4H), 1.27 (s, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 220.9, 157.4, 138.2, 138.1, 137.9, 137.4, 126.6, 113.6, 112.3, 55.3, 48.5, 44.0, 39.5, 33.9, 33.1, 31.8, 30.6, 28.0, 25.6, 23.5, 23.3; IR (thin film, cm$^{-1}$) 2958, 2868, 2836, 1739, 1607, 1575, 1498, 1465, 1271, 1235, 1039, 814, 736; HRMS (ESI-TOF) m/z: Calculated for C$_{21}$H$_{27}$O$_2$ [M+H]$^+$ 311.2011; found 311.2024.

Synthesis of phenol S2-3: To a stirred solution of ketone 2-28 (260 mg, 0.84 mmol, 1.0 equiv.) in toluene (8.4 mL) at $–78 \text{ °C}$ was added a solution of DIBA-H (1.0 M in toluene, 1.7 mL, 1.7 mmol, 2.0 equiv.) dropwise by syringe. The resulting mixture was stirred at $–78 \text{ °C}$ for approximately 45 mins before being warmed to room temperature. Additional DIBA-H (1.0 M in toluene, 8.4 mL, 8.4 mmol, 10 equiv.) was added to the reaction flask, and the reaction mixture was heated at reflux with stirring overnight (approximately 14 h). The following morning, the flask was cooled to room temperature, and small ice chunks were slowly added to quench the reaction. The mixture was diluted with ethyl acetate, followed by addition of an aqueous solution of HCl (1.0 M) and stirred vigorously for 15 mins. The two phases were separated, and the aqueous layer was extracted with ethyl acetate ($\times$ 3). The combined organic layers were dried over anhydrous Na$_2$SO$_4$, filtered and concentrated in vacuo to afford the crude product, which was purified by flash column
chromatography on a Biotage® KP-Sil 25 g cartridge with 70:30 to 40:60 hexanes–ethyl acetate gradient elution to afford phenol S2-3 (227 mg, 91%) as a white solid.

**Analytical data for phenol S2-3:**

**TLC (SiO₂)** \( R_f = 0.26 \) (hexanes–ethyl acetate, 60:40); \( [\alpha]^{22.7}_{D} = -133.3 \) (c 0.630, CHCl₃);

**¹H NMR** (500 NMR, CD₃OD) \( \delta 7.14 \) (d, \( J = 8.6 \) Hz, 1H), 6.56 (dd, \( J = 8.5, 2.7 \) Hz, 1H), 6.42 (d, \( J = 2.4 \) Hz, 1H), 3.35 (dd, \( J = 11.0, 7.4 \) Hz, 1H), 2.77 (ddd, \( J = 16.1, 6.5, 2.7 \) Hz, 1H), 2.72 – 2.61 (m, 2H), 2.58 (ddd, \( J = 13.3, 6.3, 2.7 \) Hz, 1H), 2.37 (ddd, \( J = 13.2, 11.3, 6.3 \) Hz, 1H), 2.26 (ddd, \( J = 14.1, 5.3, 3.2 \) Hz, 1H), 2.19 – 2.12 (m, 1H), 1.86 (ddd, \( J = 14.1, 12.8, 3.2 \) Hz, 1H), 1.57 (ddd, \( J = 12.7, 5.2, 3.2 \) Hz, 1H), 1.42 (ddd, \( J = 12.5, 11.0, 8.5 \) Hz, 1H), 1.30 (s, 3H), 1.19 (d, \( J = 7.1 \) Hz, 3H), 1.05 – 0.96 (m, 4H); **¹³C NMR** (150 MHz, CD₃OD) \( \delta 156.6, 143.1, 140.3, 139.4, 138.1, 127.9, 116.7, 115.0, 82.4, 46.0, 41.2, 40.4, 35.9, 35.0, 34.6, 33.6, 33.2, 25.1, 24.2, 19.9; **IR** (thin film, cm⁻¹) 3337, 2953, 2868, 1609, 1584, 1497, 1454, 1284, 1146, 1048, 1027, 864, 814; **HRMS** (ESI-TOF) \( m/z \): Calculated for C₂₀H₂₇O₂ [M+H]+ 299.2011; found 299.2021.

**Synthesis of dienone 2-29:** To a stirred solution of phenol S2-3 (36 mg, 0.12 mmol, 1.0 equiv.) in HFIP (4 mL) at 0 °C was added PIDA (39 mg, 0.12 mmol, 1.0 equiv.) in one portion. After 1 min of stirring at 0 °C, the reaction mixture was quenched by the addition of a saturated aqueous solution of NaHCO₃. The mixture was warmed to room temperature, and the phases were separated. The aqueous layer was extracted with ethyl acetate (× 3), and the combined organic phases were dried over anhydrous Na₂SO₄. The
supernatant was separated from the drying agent by vacuum filtration through a pad of silica gel over a coarse glass fritted funnel. The filtrate was then concentrated in vacuo to afford the crude residue, which was again vacuum filtered through a pad of silica gel over a coarse glass fritted funnel. The filtrate was then concentrated in vacuo, and this process of filtration over a pad of silica gel and concentration of the filtrate was repeated five times. The crude product was purified by flash column chromatography on a Biotage® SNAP Ultra HP-Sphere 10 g cartridge with 60:40 to 35:65 hexanes–ethyl acetate gradient elution to afford dienone 2-29 (18 mg, 51%) as a white film.

**Analytical data for dienone 2-29:**

**TLC (SiO₂)** Rf = 0.27 (hexanes–ethyl acetate, 40:60); [α]_D^{21.0} = −43.0 (c 0.600, CHCl₃);

**¹H NMR** (600 MHz, CDCl₃) δ 7.22 (d, J = 10.2 Hz, 1H), 6.23 (dd, J = 10.2, 2.0 Hz, 1H), 6.11 (s, 1H), 3.91 (dd, J = 9.3, 7.9 Hz, 1H), 2.75 – 2.61 (m, 3H), 2.56 – 2.43 (m, 3H), 2.41 – 2.31 (m, 2H), 1.93 – 1.85 (m, 2H), 1.80 (s, 3H), 1.46 (s, 3H), 1.39 (app td, J = 12.2, 6.1 Hz, 1H), 0.91 (s, 3H);

**¹³C NMR** (150 MHz, CDCl₃) δ 185.9, 167.3, 153.8, 137.6, 134.3, 128.5, 128.1, 128.0, 123.1, 80.0, 47.3, 46.2, 45.1, 34.7, 33.9, 30.7, 29.1, 23.6, 17.5, 15.3;

**IR** (thin film, cm⁻¹) 3386, 2960, 2925, 2874, 2849, 2116, 1661, 1613, 1603, 1442, 1298, 1235, 1079, 1020, 885, 816; **HRMS** (ESI-TOF) m/z: Calculated for C₂₀H₂₅O₂ [M+H]⁺ 297.1855; found 297.1846.

![Chemical structure of 2-29](image)

**Synthesis of triene 2-30:** Wilkinson’s catalyst (11 mg, 0.012 mmol, 10 mol%) was added, in one portion, to a stirred solution of dienone 2-29 (36 mg, 0.12 mmol, 1.0 equiv.) in
benzene (1.2 mL) under an atmosphere of nitrogen at room temperature. A balloon was used to introduce an atmosphere of hydrogen gas into the flask. The atmosphere of nitrogen was exchanged for hydrogen gas by bubbling through the reaction mixture with hydrogen. The needle was then lifted above the solvent head, and the reaction mixture was stirred under a positive pressure of hydrogen for approximately 6 h. The mixture was then concentrated to dryness to afford the crude product, which was purified by flash column chromatography on a Biotage® SNAP Ultra HP-Sphere 10 g cartridge with 80:20 to 45:55 hexanes–ethyl acetate gradient elution to afford triene 2-30 (30 mg, 83%) as a yellow solid.

Analytical data for triene 2-30:

TLC (SiO₂) Rᵢ = 0.35 (hexanes–ethyl acetate, 35:65); [α]₂₅⁺₀ = +67.5 (c 0.240, CHCl₃); ¹H NMR (600 NMR, CDCl₃) δ 5.79 (s, 1H), 3.94 (app t, J = 7.0 Hz, 1H), 2.67 – 2.58 (m, 1H), 2.60 – 2.47 (m, 3H), 2.50 – 2.41 (m, 2H), 2.42 – 2.34 (m, 2H), 2.30 – 2.14 (m, 3H), 1.91 – 1.79 (m, 5H), 1.45 – 1.34 (m, 4H), 0.92 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 199.1, 171.1, 138.1, 137.6, 127.4, 126.6, 123.1, 80.4, 47.2, 46.2, 40.3, 35.1, 34.8, 34.6, 31.7, 31.4, 23.5, 21.9, 17.4, 15.2; IR (thin film, cm⁻¹) 3408, 2960, 2924, 2852, 1660, 1631, 1444, 1359, 1327, 1274, 1235, 1078, 753; HRMS (ESI-TOF) m/z: Calculated for C₂₀H₂₇O₂ [M+H]⁺ 299.2011; found 299.2005.
Synthesis of vinyl epoxide 2-26: To a stirred solution of triene 2-30 (72 mg, 0.24 mmol, 1.0 equiv.) in toluene (2.4 mL) at –15 °C was added VO(acac)₂ (9.6 mg, 0.036 mmol, 0.15 equiv.) followed by the dropwise addition of TBHP (5.5 M in nonane, 0.22 mL, 1.2 mmol, 5.0 equiv.). The resulting mixture was gradually warmed to room temperature and stirred overnight (approximately 14 h). The following morning, a few drops of dimethyl sulfide was added to the flask, and the mixture was concentrated in vacuo to afford the crude product, which was purified by flash column chromatography on a Biotage® SNAP Ultra HP-Sphere 10 g cartridge with 60:40 to 40:60 hexanes–ethyl acetate gradient elution to afford vinyl epoxide 2-26 (55 mg, 72%) as a white solid.

Analytical data for vinyl epoxide 2-26:

**TLC (SiO₂)** \(R_t = 0.23\) (hexanes–ethyl acetate, 40:60); \([\alpha]_{D}^{22.1} = +198.7\) (c 0.260, CHCl₃);

**¹H NMR** (600 NMR, CDCl₃) \(\delta 5.78\) (s, 1H), 3.44 (dd, \(J = 12.2, 6.0\) Hz, 1H), 2.60 – 2.51 (m, 1H), 2.51 – 2.41 (m, 3H), 2.35 (dd, \(J = 11.9, 5.2\) Hz, 1H), 2.33 – 2.27 (m, 1H), 2.21 – 2.11 (m, 4H), 1.99 (app d, \(J = 15.4\) Hz, 1H), 1.95 – 1.86 (m, 1H), 1.82 (app td, \(J = 13.9, 4.9\) Hz, 1H), 1.61 (app dd, \(J = 13.2, 6.5\) Hz, 1H), 1.46 – 1.38 (m, 4H), 1.35 (s, 3H), 1.04 (s, 3H);

**¹³C NMR** (150 MHz, CDCl₃) \(\delta 198.7, 170.3, 140.0, 124.5, 123.6, 77.0, 76.5, 69.7, 45.0, 41.5, 39.8, 34.9, 34.5, 31.1, 30.7, 27.0, 23.6, 21.0, 16.4, 12.5; IR (thin film, cm⁻¹) 3504, 2966, 2925, 2856, 1659, 1619, 1447, 1376, 1241, 1089, 747; **HRMS** (ESI-TOF) \(m/z: \) Calculated for \(C_{20}H_{27}O_3\) [M+H]⁺ 315.1960; found 315.1956.
**Synthesis of β-hydroxy ketone 2-27:** To a stirred solution of epoxide 2-26 (55 mg, 0.18 mmol, 1.0 equiv.) in toluene (1.7 mL) at 0 °C was added BF₃•OEt₂ (22 μL, 0.18 mmol, 1.0 equiv.) dropwise by syringe. The reaction mixture was stirred at 0 °C for approximately 40 mins, after which point the reaction was quenched by the addition of a saturated aqueous solution of NaHCO₃ and further diluted with ethyl acetate. The aqueous and organic phases were separated, and the aqueous layer was extracted with ethyl acetate (∙3). The combined organic extracts were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to afford the crude product, which was purified by flash column chromatography on a Biotage® SNAP Ultra HP Sphere 10 g cartridge with 60:40 to 40:60 hexanes–ethyl acetate gradient elution to afford β-hydroxy ketone 2-27 (47 mg, 85%) as a white solid.

**Analytical data for β-hydroxy ketone 2-27:**

**TLC (SiO₂)** R₁ = 0.36 (hexanes–ethyl acetate, 20:80); [α]²⁰.²⁰⁰ ≈ +209.3 (c 1.23, CHCl₃); \(^1\)H **NMR** (600 NMR, CDCl₃) δ 5.77 (s, 1H), 4.33 (app t, J = 8.0 Hz, 1H), 3.21 – 3.14 (m, 1H), 2.82 (dd, J = 18.2, 8.5 Hz, 1H), 2.57 – 2.45 (m, 2H), 2.42 – 2.30 (m, 3H), 2.28 (dd, J = 19.2, 7.7 Hz, 1H), 2.22 – 2.16 (m, 2H), 2.07 (ddd, J = 13.1, 5.1, 2.7 Hz, 1H), 1.90 – 1.83 (m, 2H), 1.79 (app td, J = 14.1, 4.6 Hz, 1H), 1.35 (s, 3H), 1.05 (s, 3H), 0.92 (s, 3H); \(^13\)C **NMR** (150 MHz, CDCl₃) δ 213.0, 199.1, 170.6, 133.8, 133.0, 123.3, 72.1, 57.4, 44.9, 43.9, 39.4, 34.6, 34.3, 30.1, 26.2, 26.0, 23.1, 21.7, 20.5, 15.4; **IR** (thin film, cm⁻¹) 3429, 2965, 2937, 1739, 1711, 1661, 1631, 1588, 1236, 1051, 955, 748; **HRMS** (ESI-TOF) m/z: Calculated for C₂₀H₂₇O₃ [M+H]⁺ 315.1960; found 315.1956.
Synthesis of enone 2-31: To a stirred solution of β-hydroxy ketone 2-27 (44 mg, 0.14 mmol, 1.0 equiv.) in anhydrous pyridine (1.5 mL) at 0 °C was added MsCl (22 μL, 0.28 mmol, 2.0 equiv.) dropwise by a syringe. The cooling bath was removed, and the resulting solution was stirred at room temperature for 2 h. The reaction mixture was then concentrated in vacuo, and the crude isolate was taken up in toluene (1.5 mL). DBU (0.21 mL, 1.4 mmol, 10 equiv.) was added to the reaction flask, and the resulting mixture was stirred at room temperature overnight (approximately 12 h). The following morning, a solution of aqueous HCl (1.0 M) was added to the flask, and the resulting mixture was further diluted with DI water. The aqueous and organic layers were separated, and the aqueous phase was extracted with ethyl acetate (× 3). The combined organic extracts were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to afford the crude product, which was purified by flash column chromatography on a Biotage® SNAP Ultra HP-Sphere 10 g cartridge with 85:15 to 60:40 hexanes–ethyl acetate gradient elution to afford enone 2-31 (33 mg, 80%) as a white solid.

Analytical data for enone 2-31:
TLC (SiO₂) Rₜ = 0.32 (hexanes–ethyl acetate, 60:40); [α]^{21.6}_{D} = +308.4 (c 0.795, CHCl₃);

¹H NMR (600 NMR, CDCl₃) δ 7.44 (d, J = 5.9 Hz, 1H), 5.86 (dd, J = 5.9, 1H), 5.79 (s, 1H), 3.01 – 2.92 (m, 1H), 2.59 – 2.46 (m, 3H), 2.43 – 2.35 (m, 2H), 2.29 – 2.18 (m, 2H), 2.17 – 2.10 (m, 1H), 2.03 (ddd, J = 13.1, 5.1, 2.6 Hz, 1H), 1.82 (app td, J = 14.0, 4.6 Hz, 1H), 1.71 (ddd, J = 12.7, 8.0, 3.1 Hz, 1H), 1.37 (s, 3H), 1.23 (s, 3H), 0.98 (s, 3H); ¹³C NMR
(150 MHz, CDCl$_3$) δ 209.8, 198.9, 170.1, 165.1, 134.3, 132.9, 130.6, 123.6, 56.9, 48.6, 39.3, 34.3 (× 2), 30.1, 29.9, 28.8, 27.0, 24.5, 22.7, 20.2; **IR** (thin film, cm$^{-1}$) 3196, 2921, 2850, 1710, 1666, 1631, 1463, 818, 757; **HRMS** (ESI-TOF) m/z: Calculated for C$_{20}$H$_{25}$O$_2$ [M+H]$^+$ 297.1855; found 297.1858.

**Synthesis of ketone 2-32:** To a stirring solution of enone 2-31 (17 mg, 0.057 mmol, 1.0 equiv.) in THF (0.6 mL) was added Cu(OAc)$_2$ (6.3 mg, 0.34 mmol, 0.60 equiv.). The resulting mixture was cooled to –78 ºC and stirred for 30 mins, and MeMgCl (3.0 M in THF, 38 μL, 0.11 mmol, 2.0 equiv.) was added dropwise. After the reaction mixture was stirred for 10 mins at –78 ºC, it was warmed up to –20 ºC and stirred for approximately 40 mins. The reaction mixture was quenched at –20 ºC by the addition of a saturated aqueous solution of NH$_4$Cl. The two phases were separated, and the aqueous layer was extracted with ethyl acetate (× 3). The combined organic layers were dried over anhydrous Na$_2$SO$_4$, filtered and concentrated *in vacuo* to afford the crude product, which was purified by flash column chromatography on silica gel with 80:20 to 60:40 hexanes:ethyl acetate gradient elution to afford ketone 2-32 (5.4 mg, 30%) as a yellow solid.

**Analytical data for ketone 2-32:**

**TLC** (**SiO$_2$**) $R_f$ = 0.18 (hexanes:ethyl acetate-80:20); [α]$^2_{D}^{20}$ = +131.5 (c 0.340, CHCl$_3$); $^1$H NMR (600 NMR, C$_6$D$_6$) δ 5.81 (s, 1H), 3.44 – 3.35 (m, 1H), 2.42 (dd, $J = 19.1$, 9.9 Hz, 1H), 2.30 (dddd, $J = 17.1$, 5.0, 2.7, 1.0 Hz, 1H), 2.27 – 2.17 (m, 2H), 2.11 (dddd, $J = 13.7$, 12.1, 6.7, 1.7 Hz, 1H), 2.00 – 1.96 (m, 1H), 1.94 (ddd, $J = 13.1$, 6.1, 2.2 Hz, 1H), 1.70 – 1.69
(m, 2H), 1.65 – 1.58 (m, 1H), 1.49 (ddd, J = 13.0, 5.1, 2.7 Hz, 1H), 1.37 (td, J = 13.8, 4.9 Hz, 2H), 1.06 – 1.02 (m, 1H), 0.88 (s, 3H), 0.87 (s, 3H), 0.82 (d, J = 7.8 Hz, 3H), 0.70 (s, 3H); ^13C NMR (150 MHz, C6D6) δ 214.82, 196.63, 168.22, 134.96, 132.69, 123.71, 54.64, 43.66, 42.56, 39.12, 35.33, 34.70, 34.60, 29.86, 26.63, 25.50, 24.67, 24.01, 22.56, 21.00, 18.23; IR (thin film, cm⁻¹) 3451, 2928, 2850, 1736, 1669, 1449, 1378, 1236, 1045, 755; HRMS (ESI-TOF) m/z: Calculated for C21H29O2 [M+H]^+ 313.2168; found 313.2162.

Synthesis of diol 2-33: To a stirring solution of enone 2-31 (17 mg, 0.057 mmol, 1.0 equiv.) in MeOH (0.3 mL) was added CeCl₃·7H₂O (106 mg, 0.29 mmol, 5.0 equiv.). The resulting mixture was stirred at room temperature until all CeCl₃·7H₂O was dissolved. The flask was then cooled to 0 ºC and NaBH₄ (5.4 mg, 0.14 mmol, 2.5 equiv.) was added. The reaction mixture was stirred at 0 ºC for approximately 5 mins and quenched by the addition of a saturated aqueous solution of NH₄Cl. The two phases were separated, and the aqueous layer was extracted with ethyl acetate (× 3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to afford the crude product, which was purified by flash column chromatography on silica gel with 75:25 to 50:50 hexanes:ethyl acetate gradient elution to afford diol 2-33 (6.8 mg, 40%) as a yellow solid.

Analytical data for diol 2-33:

TLC (SiO₂) Rᵣ = 0.25 (hexanes:ethyl acetate-60:30); [α]_D20,9 = +102.5 (c 0.325, CHCl₃); ^1H NMR (600 NMR, CDCl₃) δ 5.83 (dd, J = 5.8, 2.0 Hz, 1H), 5.51 (dd, J = 5.8, 1.3 Hz, 1H),
5.32 (s, 1H), 4.94 (s, 1H), 4.22 – 4.15 (m, 1H), 2.50 – 2.39 (m, 1H), 2.39 – 2.28 (m, 2H),
2.15 (ddd, J = 12.4, 4.9, 2.5 Hz, 1H), 2.13 – 2.07 (m, 2H), 2.04 – 1.96 (m, 2H), 1.71 (ddd,
J = 13.1, 4.6, 2.7 Hz, 1H), 1.57 – 1.51 (m, 2H), 1.45 – 1.40 (m, 2H), 1.24 (s, 3H), 0.97 (s,
3H), 0.84 (s, 3H); \(^{13}\)C NMR (150 MHz, CDCl\(_3\)) \(\delta\) 146.15, 140.53, 134.09, 133.15, 132.50,
122.96, 67.84, 54.62, 49.07, 37.89, 33.57, 29.70, 29.23, 29.13, 27.65, 24.59, 22.56, 20.66,
18.65; IR (thin film, cm\(^{-1}\)) 3331, 2932, 2871, 1658, 1598, 1369, 1095, 1060, 1015, 756;
HRMS (ESI-TOF) \(m/z\): Calculated for C\(_{20}\)H\(_{28}\)O\(_2\)Na [M+Na]\(^+\) 323.1987; found 323.1996.

\[ \text{Synthesis of allylic alcohol 2-34:} \]

To a stirring solution of enone 2-31 (10 mg, 0.033 mmol, 1.0 equiv.) in THF (0.5 mL) at –78 °C was added DIBAl-H (40 \(\mu\)L, 0.040 mmol, 1.2 equiv.) dropwise. The resulting mixture was stirred at –78 °C for approximately 20 mins, at which point the reaction was quenched by the addition of Rochelle’s salt. The biphasic system was stirred vigorously for about 10 mins. The phases were separated, and the aqueous layer was extracted with ethyl acetate (\(\times\) 3). The combined organic layers were dried over anhydrous Na\(_2\)SO\(_4\), filtered and concentrated in vacuo to afford the crude product, which was purified by flash column chromatography on silica gel with 95:5 to 80:20 hexanes:ethyl acetate gradient elution to afford alcohol 2-34 (4.2 mg, 40%) as a white solid.

\[ \text{Analytical data for allylic alcohol 2-34:} \]

\(\text{TLC (SiO}_2\) \(R_t = 0.25\) (hexanes:ethyl acetate-85:15); [\(\alpha\)]\(_{D}^{20}\) = +206.2 (c 0.210, CHCl\(_3\)); \(^1\)H NMR (600 NMR, CDCl\(_3\)) \(\delta\) 7.42 (d, \(J = 5.9\) Hz, 1H), 5.84 (d, \(J = 5.9\) Hz, 1H), 5.34 (s, 1H),
4.20 (t, J = 7.7 Hz, 1H), 2.82 – 2.71 (m, 1H), 2.53 – 2.40 (m, 1H), 2.35 (tdt, J = 11.7, 6.7, 1.7 Hz, 1H), 2.21 – 2.13 (m, 3H), 2.09 (dt, J = 12.5, 8.2 Hz, 1H), 2.05 – 1.95 (m, 1H), 1.72 (ddd, J = 13.0, 4.6, 2.7 Hz, 1H), 1.65 (ddd, J = 12.6, 7.1, 4.0 Hz, 1H), 1.55 (dddd, J = 14.9, 12.5, 9.8, 2.7 Hz, 2H), 1.42 (ddd, J = 16.8, 11.2, 2.7 Hz, 2H), 1.25 (s, 3H), 1.22 (s, 3H), 0.95 (s, 3H); \(^{13}\)C NMR (150 MHz, CDCl\(_3\)) δ 210.41, 165.33, 145.76, 134.17, 133.59, 130.56, 123.03, 67.82, 57.04, 48.88, 38.08, 33.53, 30.14, 29.58, 28.95, 28.07, 24.61, 24.55, 20.36; IR (thin film, cm\(^{-1}\)) 2937, 1932, 1349, 1724, 1630, 1547, 1447, 1383, 1065, 821; HRMS (ESI-TOF) m/z: Calculated for C\(_{20}\)H\(_{27}\)O\(_2\) [M+H]\(^{+}\) 299.2011; found 299.2009.

**Synthesis of alcohol 2-35:** To a stirring solution of allylic alcohol 2-34 (13 mg, 0.044 mmol, 1.0 equiv.) in CH\(_2\)Cl\(_2\) (1.0 mL) at 0 °C was added 2,6-lutidine (25 μL, 0.22 mmol, 5.0 equiv.) and TBSOTf (20 μL, 0.087 mmol, 2.0 equiv.). The resulting mixture was stirred until complete consumption of starting material was observed on TLC. The reaction mixture was quenched by the addition of a saturated aqueous solution of NH\(_4\)Cl. The two phases were separated, and the aqueous layer was extracted with ethyl acetate (\(\times 3\)). The combined organic layers were dried over anhydrous Na\(_2\)SO\(_4\), filtered and concentrated \textit{in vacuo} to afford the crude product, which was filtered through a pad of silica gel to afford the corresponding silyl ether (19 mg), which was used in the next step.

The silyl ether product (19 mg, 0.050 mmol, 1.0 equiv.) was dissolved in THF (1.0 mL), and allyl Grignard (1.0 M in Et\(_2\)O, 0.099 mmol, 98 μL, 2.0 equiv.) was added at 0 °C dropwise. The resulting mixture was stirred until complete consumption of starting material was observed on TLC. The reaction mixture was quenched by the addition of a saturated
aqueous solution of NH₄Cl. The two phases were separated, and the aqueous layer was extracted with ethyl acetate (× 3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo* to afford the crude product, which was purified by flash column chromatography on silica gel with 100:0 to 85:15 hexanes:ethyl acetate gradient elution to afford alcohol 2-35 (13 mg, 62%) as a white solid.

**Analytical data for alcohol 2-35:**

**TLC (SiO₂)** Rₚ = 0.20 (hexanes:ethyl acetate-93:7); [α]₂⁰⁰¹⁺ = −21.0 (c 0.230, CHCl₃); **¹H NMR** (600 NMR, CDCl₃) δ; **¹³C NMR** (150 MHz, MeOD) δ 146.05, 140.36, 136.17, 136.10, 135.44, 124.44, 116.66, 87.34, 69.98, 58.51, 50.06, 46.73, 39.27, 34.86, 30.85, 30.69, 30.31, 29.15, 26.52, 26.42, 26.01, 25.84, 21.84, 19.10; **IR** (thin film, cm⁻¹) 3477, 3040, 2929, 2854, 1665, 1639, 1462, 1361, 1077, 836, 774; **HRMS** (ESI-TOF) m/z: Calculated for C₂₉H₄₅OSi [M+H]+ 437.3240; found 437.3233.

**Synthesis of alcohol 2-37:**

To a stirred solution of PPh₃EtBr (1.3 g, 2.9 mmol, 5.0 equiv.) in THF (5.0 mL) was added KOt-Bu (325 mg, 2.9 mmol, 5.0 equiv.) in one portion. The resulting mixture was stirred for 30 mins at room temperature and cooled to −78 °C. A solution of ketone 2-28 (180 mg, 0.58 mmol, 1.0 equiv.) in THF (3.0 mL) was then added dropwise to the reaction mixture. After the addition, the resulting solution was gradually warmed up to room temperature and stirred overnight (approximately 14 h). The following morning, the reaction mixture was concentrated *in vacuo*, and the resulting residue was filtered through a pad of silica
gel, rinsing with hexanes, followed by a mixture of hexanes–diethyl ether (70:30). The filtrate was then concentrated \textit{in vacuo} to afford the crude product, which was carried on to the next step.

A solution of 9-BBN (0.5 M in THF, 11.6 mL, 5.8 mmol, 10 equiv.) was added to a flask containing the crude olefin product from the previous step. The resulting mixture was stirred at room temperature for 2 days. After the indicated time, the flask was cooled to 0 °C, and a mixture of 10% aqueous NaOH (5 mL) and 30% aqueous H₂O₂ (10 mL) was added dropwise. The resulting mixture was warmed to room temperature and stirred overnight (approximately 16 h). The following morning, the reaction mixture was diluted with DI water. The aqueous and organic layers were separated, and the aqueous layer was extracted with ethyl acetate (× 3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated \textit{in vacuo} to afford the crude product, which was purified by flash column chromatography on a Biotage® SNAP Ultra HP-Sphere 25 g cartridge with 95:5 to 75:25 hexanes–ethyl acetate gradient elution to afford alcohol 2-37 (150 mg, 76%) as a colorless oil.

\textbf{Analytical data for alcohol 2-37:}

\textbf{TLC (SiO₂)} Rᵣ = 0.21 (hexanes–ethyl acetate, 75:25); [α]^{21.4}_{589} = −127.1 (c 0.34, CHCl₃);

\textbf{¹H NMR} (600 NMR, CDCl₃) δ 7.24 (d, J = 8.7 Hz, 1H), 6.71 (d, J = 7.7 Hz, 1H), 6.56 (s, 1H), 3.82 – 3.77 (m, 1H), 3.76 (s, 3H), 2.85 (ddd, J = 16.1, 7.3, 2.6 Hz, 1H), 2.82 – 2.74 (m, 1H), 2.74 – 2.65 (m, 1H), 2.57 (ddd, J = 13.7, 6.7, 2.7 Hz, 1H), 2.42 (app td, J = 12.2, 6.6 Hz, 1H), 2.34 (app dt, J = 14.4, 3.7 Hz, 1H), 2.21 – 2.12 (m, 1H), 1.90 (app td, J = 14.2, 3.0 Hz, 1H), 1.61 (app dt, J = 12.7, 3.7 Hz, 1H), 1.43 – 1.35 (m, 1H), 1.32 (s, 3H), 1.25 – 1.20 (m, 1H), 1.20 – 1.15 (m, 6H), 1.03 (s, 3H), 1.01 – 0.95 (m, 1H);

\textbf{¹³C\{¹H} NMR (150 MHz, CDCl₃) δ 157.3, 145.5, 138.83, 138.80, 132.9, 125.9, 113.7, 111.9, 69.2, 58.3, 55.2,
43.2, 39.1, 35.1, 34.1, 34.0, 33.6, 33.0, 32.0, 23.9, 23.4, 23.3, 19.8; IR (thin film, cm⁻¹) 3376, 2957, 2863, 1607, 1496, 1231, 1039; HRMS (ESI-TOF) m/z: Calculated for C₂₃H₃₃O₂ [M+H]+ 341.2481; found 341.2466.

Synthesis of diol S2-4: To a stirred solution of 2-37 (30 mg, 0.088 mmol, 1.0 equiv.) in PhMe (0.88 mL) was added DIBAI-H (1.0 M in toluene, 0.88 mL, 0.88 mmol, 10 equiv.). The reaction mixture was then heated in an oil bath at reflux with stirring overnight (approximately 14 h). The following morning, the flask was cooled to room temperature, and the reaction mixture was quenched by the addition of a saturated aqueous solution of Rochelle's salt and stirred vigorously for approximately 40 mins. The two phases were separated, and the aqueous layer was extracted with ethyl acetate (× 3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to afford the crude product, which was purified by flash column chromatography on a Biotage® KP-Sil 10 g cartridge with 90:10 to 55:45 hexanes–ethyl acetate gradient elution to afford diol S2-4 (22 mg, 76%) as a white solid.

Analytical data for diol S2-4:

**TLC (SiO₂)** Rₖ = 0.16 (hexanes–ethyl acetate, 70:30); [α]⁺₂⁵⁺⁺ = −96.3 (c 1.1, CHCl₃); **¹H NMR** (600 NMR, CDCl₃) δ 7.19 (d, J = 8.5 Hz, 1H), 6.62 (dd, J = 8.5, 2.7 Hz, 1H), 6.49 (d, J = 2.8 Hz, 1H), 4.82 (s, 1H), 3.80 (app p, J = 6.4 Hz, 1H), 2.81 (dd, J = 16.4, 6.0 Hz, 1H), 2.78 – 2.64 (m, 2H), 2.56 (ddd, J = 13.7, 6.5, 2.6 Hz, 1H), 2.41 (app td, J = 12.2, 6.7 Hz, 1H), 2.32 (app dt, J = 14.5, 3.7 Hz, 1H), 2.18 (app dt, J = 12.4, 8.0 Hz, 1H), 1.89 (app td,
$J = 14.2, 3.0 \text{ Hz, 1H}$, 1.61 (app dt, $J = 12.7, 3.7 \text{ Hz, 1H}$), 1.44 – 1.34 (m, 1H), 1.31 (s, 3H), 1.26 – 1.22 (m, 1H), 1.21 – 1.14 (m, 6H), 1.02 (s, 3H), 0.99 (app t, $J = 13.2 \text{ Hz, 1H}$);

$^{13}$C($^1$H) NMR (150 MHz, CDCl$_3$) δ 153.3, 145.4, 139.1, 138.9, 132.9, 126.1, 115.3, 113.1, 69.4, 58.3, 43.2, 39.1, 35.1, 34.2, 33.9, 33.6, 33.0, 31.8, 23.8, 23.4, 23.2, 19.8; IR (thin film, cm$^{-1}$) 3335, 2960, 2866, 1496, 1454, 1232; HRMS (ESI-TOF) m/z: Calculated for C$_{22}$H$_{29}$O [M–H]$^-$ 309.2218; found 309.2209.

**Synthesis of dienone 2-38:**

To a stirred solution of phenol S2-4 (18 mg, 0.056 mmol, 1.0 equiv.) in HFIP (2.0 mL) at 0 °C was added phenyliodine(III) diacetate (PIDA) (18 mg, 0.056 mmol, 1.0 equiv.) in one portion. After 1 min of stirring at 0 °C, the reaction mixture was quenched by the addition of a saturated aqueous solution of NaHCO$_3$. The mixture was warmed to room temperature, and the phases were separated. The aqueous layer was extracted with ethyl acetate ($\times$ 3), and the combined organic phases were dried over anhydrous Na$_2$SO$_4$, filtered and concentrated in vacuo to afford the crude product, which was purified by flash column chromatography on a triethylamine-treated Biotage® SNAP Ultra HP-Sphere 10 g cartridge with 88:12 to 50:50 hexanes–ethyl acetate gradient elution to afford dienone 2-38 (11 mg, 62%) as a white solid.

**Analytical data for dienone 2-38:**

TLC (SiO$_2$) $R_f = 0.18$ (hexanes–ethyl acetate, 80:20); $[\alpha]^{21.1}_{589} = -33.3$ (c 0.55, CHCl$_3$); $^1$H NMR (600 NMR, CDCl$_3$) δ 7.23 (d, $J = 10.0 \text{ Hz, 1H}$), 6.24 (d, $J = 10.2 \text{ Hz, 1H}$), 6.12 (s,
1H), 3.94 – 3.83 (m, 1H), 2.78 – 2.60 (m, 3H), 2.59 – 2.41 (m, 3H), 2.38 – 2.26 (m, 2H),
1.92 (dd, J = 12.9, 6.0 Hz, 1H), 1.85 (s, 3H), 1.75 – 1.64 (m, 1H), 1.53 – 1.40 (m, 4H),
1.29 (app d, J = 4.8 Hz, 1H), 1.26 (d, J = 6.0 Hz, 3H), 0.87 (s, 3H); $^{13}$C{^1}H NMR (150
MHz, CDCl$_3$) δ 185.9, 167.2, 153.8, 139.2, 133.7, 130.9, 128.0, 127.8, 123.1, 69.2, 56.9,
46.7, 45.0, 42.2, 36.4, 34.1, 30.8, 29.1, 24.0, 23.7, 17.5, 16.4; IR (thin film, cm$^{-1}$) 2954,
2933, 2875, 1668, 1632, 1447, 1239, 1066; HRMS (ESI-TOF) m/z: Calculated for
C$_{22}$H$_{29}$O$_2$ [M+H]$^+$ 325.2168; found 325.2158.

Synthesis of vinyl epoxide 2-39:
To a stirred solution of tetraene 2-38 (32 mg, 0.099 mmol, 1.0 equiv.) in toluene (2.0 mL)
at −15 °C was added VO(acac)$_2$ (4.0 mg, 0.015 mmol, 0.15 equiv.) followed by the
dropwise addition of TBHP (5.5 M in nonane, 49 μL, 0.012 mmol, 5.0 equiv.). The resulting
mixture was gradually warmed to room temperature, and progress of the reaction was
monitored by TLC. Once full consumption of starting material was observed
(approximately 4 h), a few drops of dimethyl sulfide was added to the flask, and the mixture
was concentrated in vacuo to afford the crude product, which was purified by flash column
chromatography on a Biotage® SNAP Ultra HP-Sphere 10 g cartridge with 90:10 to 45:55
hexanes–ethyl acetate gradient elution to afford vinyl epoxide 2-39 (26 mg, 77%) as a
yellow solid.
Analytical data for vinyl epoxide 2-39:

**TLC (SiO$_2$)** $R_f = 0.36$ (hexanes–ethyl acetate, 35:65); $[\alpha]_{589}^{23} = +98.3$ (c 0.23, CHCl$_3$); $^1$H NMR (600 NMR, CDCl$_3$) $\delta$ 7.16 (d, $J = 10.1$ Hz, 1H), 6.25 (d, $J = 10.2$ Hz, 1H), 6.11 (s, 1H), 4.43 (s, 1H), 3.91 (app q, $J = 6.5$ Hz, 1H), 2.72 – 2.57 (m, 2H), 2.57 – 2.44 (m, 2H), 2.31 (app dt, $J = 18.0$, 4.9 Hz, 1H), 2.23 (d, $J = 15.2$ Hz, 1H), 2.09 – 1.98 (m, 1H), 1.91 (dd, $J = 15.3$, 10.3 Hz, 1H), 1.71 – 1.63 (m, 2H), 1.55 (app d, $J = 10.3$ Hz, 1H), 1.49 (s, 3H), 1.37 (s, 3H), 1.10 (s, 3H), 1.05 (d, $J = 6.3$ Hz, 3H); $^{13}$C($^1$H) NMR (150 MHz, CDCl$_3$) $\delta$ 185.7, 166.6, 152.9, 137.1, 128.3, 126.2, 123.6, 77.4, 71.1, 64.4, 50.9, 44.7, 44.3, 34.9, 31.1, 30.0, 29.5, 28.9, 23.4, 23.2, 16.2, 14.1; IR (thin film, cm$^{-1}$) 3399, 2969, 2929, 2855, 1666, 1629, 1604, 1449, 1048, 888, 754; HRMS (ESI-TOF) m/z: Calculated for C$_{22}$H$_{29}$O$_3$ [M+H]$^+$ 341.2117; found 341.2112.

Synthesis of silyl ether S2-5:

Imidazole (100 mg, 0.15 mmol, 5.0 equiv.) was added to a stirred solution of alcohol 2-39 (100 mg, 0.30 mmol, 1.0 equiv.) in CH$_2$Cl$_2$ (2.0 mL). Once all the imidazole was dissolved, the resulting mixture was cooled to 0 °C, and TESCl (0.15 mL, 0.90 mmol, 3.0 equiv.) was added dropwise. After the reaction mixture was stirred at 0 °C for 1.5 h, it was quenched by the addition of a saturated aqueous solution of NaHCO$_3$ and was warmed to room temperature. The two phases were separated, and the aqueous layer was extracted with CH$_2$Cl$_2$ ($\times$ 3). The combined organic layers were dried over anhydrous Na$_2$SO$_4$, filtered and concentrated in vacuo to afford the crude product, which was purified by flash column chromatography on a Biotage$^\circledR$ SNAP Ultra HP-Sphere 10 g cartridge with 100:0 to 85:15
hexanes–ethyl acetate gradient elution to afford silyl ether S2-5 (113 mg, 85%) as a white solid.

**Analytical data for silyl ether S2-5:**

**TLC (SiO$_2$)** $R_f = 0.24$ (hexanes–ethyl acetate, 80:20); $[\alpha]^{21}_D = +107.8$ (c 1.05, CHCl$_3$); $^1$H NMR (600 NMR, CDCl$_3$) $\delta$ 7.15 (d, $J = 10.1$ Hz, 1H), 6.24 (d, $J = 10.1$ Hz, 1H), 6.10 (s, 1H), 3.75 (dq, $J = 11.7$, 6.1 Hz, 1H), 2.67 – 2.52 (m, 2H), 2.50 – 2.37 (m, 2H), 2.23 (dd, $J = 14.9$, 3.9 Hz, 1H), 2.16 (d, $J = 17.0$ Hz, 1H), 2.05 – 1.94 (m, 1H), 1.82 – 1.71 (m, 2H), 1.62 (td, $J = 9.1$, 3.8 Hz, 1H), 1.56 – 1.49 (m, 1H), 1.46 (s, 3H), 1.27 (s, 3H), 1.16 (d, $J = 5.8$ Hz, 3H), 0.99 (s, 3H), 0.96 (t, $J = 7.9$ Hz, 9H), 0.61 (q, $J = 7.9$ Hz, 6H); $^{13}$C($^1$H) NMR (150 MHz, CDCl$_3$) $\delta$ 185.9, 167.2, 153.1, 136.7, 128.1, 127.8, 123.5, 70.0, 69.3, 54.3, 44.8, 42.6, 36.4, 34.7, 30.2, 29.8, 28.7, 25.7, 22.7, 16.9, 16.2, 7.1, 5.2; IR (thin film, cm$^{-1}$) 2954, 2932, 2875, 1667, 1631, 1457, 1076, 742; HRMS (ESI-TOF) $m/z$: Calculated for C$_{28}$H$_{43}$O$_3$Si [M+H]$^+$ 455.2981; found 455.2976.

**Synthesis of dimethyl ketone 2-40:**

$t$-BuOH (20 mL) was degassed for approximately 20 min by bubbling dry nitrogen through the solvent in a flask that was placed in a water bath at 30 °C. The degassed t-BuOH was then used to prepare a stock solution of KOt-Bu (370 mg) in t-BuOH (4.0 mL) at 30 °C. Half of this stock solution of KOt-Bu (185 mg, 1.7 mmol, 3.0 equiv.) in t-BuOH (2.0 mL) was then transferred to a stirred solution of dienone S2-5 (250 mg, 0.55 mmol, 1.0 equiv.) in degassed t-BuOH (1.0 mL) at 30 °C. The resulting solution was stirred for 15 min and
Mel (0.17 mL, 2.8 mmol, 5.0 equiv.) was added dropwise by syringe. The water bath was removed, and the reaction mixture was stirred at room temperature for 1.5 h. After the indicated time, the reaction mixture was quenched by the addition of a saturated aqueous solution of NH₄Cl and diluted with Et₂O and DI water. The two phases were separated, and the aqueous layer was extracted with Et₂O (× 3). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to afford the crude product. The crude isolate was purified by flash column chromatography on a Biotage® SNAP Ultra HP-Sphere 25 g cartridge with 100:0 to 85:15 hexanes–ethyl acetate gradient elution to afford dimethyl ketone 2-40 (160 mg, 61%) as a yellow solid and recovered starting material dienone S2-5 (16 mg).

**Analytical data for dimethyl ketone 2-40:**

**TLC (SiO₂)** Rf = 0.41 (hexanes–ethyl acetate, 85:15); [α]ᵢₓ⁺ = +44.5 (c 0.50, CHCl₃); $^1$H

**NMR** (600 NMR, CDCl₃) δ 6.95 (d, J = 10.5 Hz, 1H), 5.97 (d, J = 10.5 Hz, 1H), 5.87 (dd, J = 6.2, 2.0 Hz, 1H), 3.77 (app dq, J = 8.8, 5.8 Hz, 1H), 2.72 (dd, J = 21.8, 6.0 Hz, 1H), 2.49 (d, J = 21.5 Hz, 1H), 2.45 – 2.37 (m, 1H), 2.35 (dd, J = 15.1, 2.6 Hz, 1H), 2.20 – 2.08 (m, 1H), 1.76 (dd, J = 15.1, 9.7 Hz, 1H), 1.74 – 1.65 (m, 1H), 1.63 – 1.57 (m, 1H), 1.54 (app td, J = 9.3, 2.5 Hz, 1H), 1.41 – 1.35 (m, 6H), 1.33 (s, 3H), 1.30 (s, 3H), 1.18 (d, J = 5.8 Hz, 3H), 1.02 – 0.90 (m, 12H), 0.63 (q, J = 7.9 Hz, 6H); $^{13}$C($^1$H) NMR (150 MHz, CDCl₃) δ 203.1, 151.4, 145.1, 139.3, 126.1, 125.3, 121.4, 76.4, 69.4, 69.1, 53.3, 48.6, 42.3, 41.9, 36.1, 34.5, 31.4, 27.0, 25.9, 25.5, 23.3, 23.1, 16.1, 15.5, 7.1, 5.2; IR (thin film, cm⁻¹) 2958, 2919, 2876, 1686, 1460, 1379, 1078, 743; HRMS (ESI-TOF) m/z: Calculated for C₃₀H₄₇O₃Si [M+H]$^+$ 483.3294; found 483.3289.
Synthesis of C15-keto lanostane 2-41:

Dimethyl ketone 2-40 (20 mg, 0.041 mmol, 1.0 equiv.) was dissolved in PhMe (3.0 mL), and the resulting solution was cooled to 0 °C. BF$_3$•OEt$_2$ (15 μL, 0.12 mmol, 3.0 equiv.) was added dropwise by syringe, and the reaction mixture was stirred for 1 h at 0 °C. After complete consumption of the starting material, the reaction mixture was quenched by the addition of a saturated aqueous solution of NaHCO$_3$ and diluted with ethyl acetate. The ice bath was removed and the quenched mixture was allowed to warm to room temperature. The mixture was then transferred to a separatory funnel, and the two phases were separated. The aqueous layer was extracted with ethyl acetate ($\times$ 3), and combined organic layers were washed with brine. The combined organic phases were then dried over anhydrous Na$_2$SO$_4$, filtered and concentrated \textit{in vacuo} to afford the crude product. The crude material was purified by flash column chromatography on a Biotage® SNAP Ultra HP-Sphere 10 g cartridge with 100:0 to 50:50 hexanes–ethyl acetate gradient elution to afford C15-keto lanostane 2-41 (13 mg, 86%) as a white solid.

Analytical data for C15-keto lanostane 2-41:

TLC (SiO$_2$) $R_f$ = 0.18 (hexanes–ethyl acetate, 50:50); $[\alpha]_{589}^{20.9} = -29.1$ (c 0.49, CHCl$_3$); $^1$H NMR (600 NMR, CDCl$_3$) $\delta$ 6.90 (d, $J = 10.5$ Hz, 1H), 5.94 (d, $J = 10.6$ Hz, 1H), 5.92 (app d, $J = 6.4$ Hz, 1H), 3.85 (app p, $J = 6.4$ Hz, 1H), 3.30 (dd, $J = 22.4$, 6.2 Hz, 1H), 2.86 (app d, $J = 23.1$ Hz, 1H), 2.70 (dd, $J = 19.3$, 8.6 Hz, 1H), 2.38 – 2.29 (m, 1H), 2.25 (dd, $J = 19.6$, 8.5 Hz, 1H), 2.18 (app dd, $J = 18.6$, 7.9 Hz, 1H), 2.05 (app q, $J = 8.6$ Hz, 1H), 1.96
– 1.82 (m, 2H), 1.35 (s, 3H), 1.34 – 1.28 (m, 9H), 1.10 (s, 3H), 0.84 (s, 3H); $^{13}$C\{$^1$H\} NMR (150 MHz, CDCl$_3$) δ 215.1, 203.3, 151.6, 143.7, 133.1, 132.7, 125.3, 122.5, 69.6, 56.9, 48.5, 47.9, 42.3, 41.2, 39.6, 31.5, 28.2, 27.4, 26.0, 24.5, 23.3, 23.0, 21.1, 16.0; IR (thin film, cm$^{-1}$) 3455, 2968, 2926, 1737, 1683, 1669, 1453, 1380, 1056, 755; HRMS (ESI-TOF) $m/z$: Calculated for C$_{24}$H$_{32}$O$_3$ [M$^+$] 368.2352; found 368.2352.

Synthesis of diketone 2-42:

Wilkinson’s catalyst (9.0 mg, 0.010 mmol, 20 mol%) was added, in one portion, to a stirred solution of enone 2-41 (19 mg, 0.052 mmol, 1.0 equiv.) in anhydrous benzene (0.5 mL) under an atmosphere of nitrogen at room temperature. A balloon was used to introduce an atmosphere of hydrogen into the flask. The atmosphere of nitrogen was exchanged for hydrogen gas by bubbling through the reaction mixture with hydrogen for approximately 3 min. The needle attached to the hydrogen balloon was then lifted above the solvent level, and the vent needle was removed. After the reaction mixture was stirred under a positive pressure of hydrogen for approximately 6 h, the hydrogen balloon was removed. The reaction mixture was concentrated to dryness to afford the crude product. The crude isolate was purified by column chromatography with 90:10 to 75:25 hexanes–ethyl acetate gradient elution followed by 75:25 hexanes–ethyl acetate isocratic elution to afford diketone 2-42 (18 mg, 93%) as a yellow solid.
Analytical data for diketone 2-42:

**TLC** (SiO₂) R₁ = 0.16 (hexanes–ethyl acetate, 60:40); [α]ᵢ²¹¹ᵇ = +55.5 (c 0.60, CHCl₃); **¹H NMR** (600 NMR, CDCl₃) δ 5.75 (dd, J = 5.3, 2.5 Hz, 1H), 3.87 – 3.80 (m, 1H), 3.29 – 3.16 (m, 1H), 2.97 (ddd, J = 22.8, 5.5, 2.6 Hz, 1H), 2.68 (dd, J = 19.5, 8.9 Hz, 1H), 2.59 – 2.44 (m, 2H), 2.24 (app dd, J = 19.2, 9.0 Hz, 1H), 2.21 – 2.10 (m, 2H), 2.08 – 1.99 (m, 2H), 2.00 – 1.90 (m, 2H), 1.83 (app dt, J = 13.3, 5.3 Hz, 1H), 1.42 (s, 1H), 1.31 (d, J = 6.2 Hz, 3H), 1.30 (s, 3H), 1.26 (s, 3H), 1.15 (s, 3H), 1.03 (s, 3H), 0.80 (s, 3H); **¹³C{¹H} NMR** (150 MHz, CDCl₃) δ 216.3, 215.4, 146.9, 132.3, 131.3, 119.8, 69.8, 56.9, 49.1, 48.1, 42.5, 39.8, 38.4, 34.1, 31.1, 29.5, 28.6, 27.7, 27.5, 24.4, 23.6, 21.6, 21.1, 16.3; **IR** (thin film, cm⁻¹) 3494, 2965, 2929, 2884, 1736, 1708, 1462, 1380, 1056, 756; **HRMS** (ESI-TOF) m/z: Calculated for C₂₄H₃₅O₃ [M+H]⁺ 371.2586; found 371.2575.

**Synthesis of triketone 2-43:**

Alcohol 2-42 (5.0 mg, 0.013 mmol, 1.0 equiv.) was dissolved in CH₂Cl₂ (1.0 mL), and NaHCO₃ (11 mg, 0.14 mmol, 10 equiv.) was added in one portion. The resulting mixture was cooled to 0 °C, and Dess-Martin Periodinane (DMP) (9.0 mg, 0.020 mmol, 1.5 equiv.) was added in one portion. The ice bath was removed, and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was then quenched by the addition of a 1:1 mixture of saturated aqueous NaHCO₃ and saturated aqueous Na₂S₂O₃. The organic and aqueous layers were separated, and the aqueous layer was extracted with CH₂Cl₂ (× 5). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to afford the crude product. The crude material was purified by
column chromatography with 90:10 to 75:25 hexanes–ethyl acetate gradient elution followed by 75:25 hexanes–ethyl acetate isocratic elution to afford triketone 2-43 (3.9 mg, 83%) as a white solid.

Analytical data for triketone 2-43:

**TLC (SiO$_2$)** $R_f = 0.24$ (hexanes–ethyl acetate, 40:60); $[\alpha]^2_{589} = +132.2$ (c 0.20, CHCl$_3$); $^1$H NMR (600 NMR, CDCl$_3$) $\delta$ 5.76 (dd, $J = 5.3, 2.5$ Hz, 1H), 3.22 (ddd, $J = 22.9, 5.3, 2.7$ Hz, 1H), 3.15 (app t, $J = 8.8$ Hz, 1H), 2.99 – 2.93 (m, 1H), 2.90 (dd, $J = 19.0, 9.0$ Hz, 1H), 2.58 – 2.45 (m, 2H), 2.40 (dd, $J = 19.4, 8.9$ Hz, 1H), 2.28 – 2.18 (m, 6H), 2.07 – 1.94 (m, 3H), 1.30 (s, 3H), 1.26 (s, 3H), 1.20 (s, 3H), 1.03 (s, 3H), 0.73 (s, 3H); $^{13}$C($^1$H) NMR (150 MHz, CDCl$_3$) $\delta$ 216.1, 213.6, 207.3, 146.9, 132.4, 131.2, 119.7, 56.9, 54.2, 49.1, 44.3, 38.4, 36.7, 34.1, 31.7, 31.1, 29.5, 28.8, 27.6, 27.5, 23.6, 21.8, 21.4, 17.5; IR (thin film, cm$^{-1}$) 2966, 2931, 2871, 1736, 1699, 1449, 1384; HRMS (ESI-TOF) $m/z$: Calculated for C$_{24}$H$_{33}$O$_3$ [M+H]$^+$ 369.2430; found 369.2429.

Synthesis of cis-decalin 2-50:

From enone 2-41: Pd/C (10 wt. %, 8.0 mg, 0.0078 mmol, 30 mol%) was added, in one portion, to a stirred solution of enone 2-41 (9.5 mg, 0.026 mmol, 1.0 equiv.) in anhydrous
MeOH (1.6 mL) under an atmosphere of nitrogen at room temperature. A balloon was used to introduce an atmosphere of hydrogen into the flask. The atmosphere of nitrogen was exchanged for hydrogen gas by bubbling through the reaction mixture with hydrogen for approximately 3 min. The needle attached to the hydrogen balloon was then lifted above the solvent level, and the vent needle was removed. After the reaction mixture was stirred under a positive pressure of hydrogen for approximately 13 h, the hydrogen balloon was removed. The reaction mixture was filtered through a pad to silica gel, and the pad of silica gel was flushed with EtOAc. The filtrate was then concentrated to dryness to afford the crude product. The crude isolate was purified by column chromatography with 100:0 to 85:15 dichloromethane–ethyl acetate gradient elution followed by 85:15 dichloromethane–ethyl acetate isocratic elution to afford cis-decalin 2-50 (8 mg, 83%) as a white solid.

**From ketone 2-42:** Anhydrous i-PrOH (10 mL) was degassed for approximately 20 min by bubbling argon through the solvent. A stock solution of Mn(dpm)₃ (20 mg) in degassed anhydrous i-PrOH (1.0 mL) was prepared. The degassed anhydrous iPrOH (0.5 mL) was added by syringe to a flask containing ketone 2-42 (12 mg, 0.032 mmol, 1.0 equiv.) under argon atmosphere. Next, CH₂Cl₂ (0.1 mL), PhSiH₃ (24 μL, 0.19 mmol, 6.0 equiv.) and t-BuOOH (5.5 M in decane, 24 μL, 0.13 mmol, 4.0 equiv.) were sequentially added by syringe; a PTFE syringe tubing was used for the addition of t-BuOOH. The resulting mixture was then degassed by bubbling argon through a PTFE syringe tubing into the reaction mixture for 10 min. After the indicated time, half of the prepared stock solution of Mn(dpm)₃ (10 mg, 0.016 mmol, 50 mol%) in i-PrOH (0.5 mL) was transferred to the reaction mixture. The resulting mixture was degassed again by by bubbling argon through a PTFE syringe tubing into the mixture for no more than 30 sec. The reaction mixture was then stirred under argon atmosphere overnight (approximately 16 h). The next morning,
the reaction mixture was concentrated in vacuo to afford the crude product, which was purified by column chromatography with 100:0 to 90:10 dichloromethane–ethyl acetate gradient elution followed by 90:10 dichloromethane–ethyl acetate isocratic elution to afford cis-decalin 2-50 (2.6 mg, 22 %) as a white solid, and recovered starting material ketone 2-42 (1.4 mg).

Analytical data for cis-decalin 2-50:

TLC (SiO₂) Rf = 0.21 (dichloromethane–ethyl acetate, 80:20); [α]²¹¹ʰ = +51.3 (c 0.15, CHCl₃); ¹H NMR (600 NMR, CDCl₃) δ 3.88 – 3.80 (m, 1H), 2.67 (dd, J = 19.3, 8.8 Hz, 1H), 2.62 – 2.51 (m, 1H), 2.52 – 2.44 (m, 1H), 2.41 (ddd, J = 15.6, 9.0, 5.5 Hz, 1H), 2.30 – 2.21 (m, 2H), 2.21 – 2.13 (m, 2H), 2.10 (ddd, J = 13.6, 7.8, 5.5 Hz, 1H), 2.02 (app q, J = 8.7 Hz, 1H), 1.98 – 1.88 (m, 2H), 1.82 (dt, J = 13.4, 5.3 Hz, 1H), 1.79 – 1.70 (m, 1H), 1.62 (ddd, J = 14.1, 9.0, 5.1 Hz, 1H), 1.52 (app t, J = 5.4 Hz, 1H), 1.31 (d, J = 6.1 Hz, 4H), 1.14 (s, 3H), 1.13 – 1.09 (m, 6H), 1.07 (s, 3H), 0.83 – 0.76 (m, 3H); ¹³C{¹H} NMR (150 MHz, CDCl₃) δ 217.5, 215.5, 134.5, 131.4, 69.7, 57.4, 50.4, 48.1, 48.0, 42.6, 39.7, 37.3, 35.5, 33.3, 28.8, 28.6, 25.8, 24.7, 24.4, 22.9, 21.9, 21.2, 20.5, 16.4; IR (thin film, cm⁻¹) 3484, 2964, 2925, 2877, 1735, 1707, 1456, 1382, 1057, 754; HRMS (ESI-TOF) m/z: Calculated for C₂₄H₃₆O₃Na [M+Na]⁺ 395.2562; found 395.2561.

Synthesis of cis-decalin 2-54:

Pd/C (10 wt%, 4 mg, 0.0033 mmol, 30 mol%) was added, in one portion, to a stirred solution of diene 2-43 (4 mg, 0.011 mmol, 1.0 equiv.) in MeOH (0.6 mL) and EtOAc (0.4
mL) under an atmosphere of nitrogen at room temperature. A balloon was used to introduce an atmosphere of hydrogen into the reaction vessel. The atmosphere of nitrogen was exchanged for hydrogen gas by bubbling through the reaction mixture with hydrogen for approximately 3 min. The hydrogen balloon was removed, and the reaction vessel was placed in a Parr reactor. The Parr reactor was sealed, and the reaction chamber was evacuated and purged with hydrogen to a psi of 88 (repeat x 5) before the reaction chamber was pressurized to 88 psi. The reaction mixture was then stirred under an atmosphere of hydrogen at 88 psi at room temperature overnight (approximately 19 h). The following morning, hydrogen was released from the reaction chamber, and the reaction mixture was filtered through a pad of silica gel, and the pad of silica gel was flushed with EtOAc. The filtrate was then concentrated to dryness to afford the crude product. The crude isolate was purified by column chromatography with 100:0 to 97:3 dichloromethane–ethyl acetate gradient elution followed by 97:3 dichloromethane–ethyl acetate isocratic elution to afford cis-decalin 2-54 (2.5 mg, 62%, 82% brsm) as a white solid, and recovered starting material diene 2-43 (1 mg).

**Analytical data for cis-decalin 2-54:**

- **TLC (SiO₂)** \( R_f = 0.16 \) (dichloromethane–ethyl acetate, 95:5); \([\alpha]_{D}^{21.2} = +69.3 \) (c 0.13, CHCl₃);
- **¹H NMR** (600 NMR, CDCl₃) \( \delta \) 3.13 (app t, J = 8.9 Hz, 1H), 2.90 (dd, \( J = 19.5, 9.2 \) Hz, 1H), 2.62 – 2.52 (m, 1H), 2.51 – 2.34 (m, 3H), 2.34 – 2.16 (m, 7H), 2.11 (ddd, \( J = 13.5, 7.7, 5.5 \) Hz, 1H), 2.03 – 1.97 (m, 1H), 1.97 – 1.88 (m, 1H), 1.75 (ddt, \( J = 14.4, 7.1, 4.9 \) Hz, 1H), 1.64 (ddd, \( J = 14.2, 9.0, 5.1 \) Hz, 1H), 1.53 (app t, \( J = 5.3 \) Hz, 1H), 1.18 (s, 3H), 1.15 – 1.10 (m, 6H), 1.07 (s, 3H), 0.72 (s, 3H); **¹³C{¹H} NMR** (150 MHz, CDCl₃) \( \delta \) 217.3, 213.7, 207.4, 134.3, 131.5, 57.4, 54.1, 50.3, 48.1, 44.4, 37.3, 36.7, 35.5, 33.2, 31.8, 29.0, 28.6,
25.8, 24.6, 22.9, 22.0, 21.5, 20.4, 17.5; IR (thin film, cm\(^{-1}\)) 2954, 2929, 2877, 1739, 1704, 1383; HRMS (ESI-TOF) m/z: Calculated for C\(_{24}H_{35}O_3\) [M+H]\(^+\) 371.2586; found 371.2584.

Synthesis of cis-decalin 2-55:

PtO\(_2\) (6 mg, 0.027 mmol, 2.0 equiv.) was added, in one portion, to a stirred solution of diketone 2-42 (5 mg, 0.014 mmol, 1.0 equiv) in acetic acid (1.5 mL) under an atmosphere of nitrogen at room temperature. A balloon was used to introduce an atmosphere of hydrogen into the flask. The atmosphere of nitrogen was exchanged for hydrogen gas by bubbling through the reaction mixture with hydrogen. After the reaction mixture was stirred under a positive pressure of hydrogen for approximately 2.5 h, the hydrogen balloon was removed. The reaction mixture was filtered through a pad of silica gel, and the pad of silica gel was flushed with EtOAc. The filtrate was then concentrated to dryness to afford the crude product. The crude isolate was purified by column chromatography with 100:0 to 70:30 hexanes–ethyl acetate gradient elution followed by 70:30 hexanes–ethyl acetate isocratic elution to afford cis-decalin 2-55 (1 mg, 20%) as a white solid.

Analytical data for cis-decalin 2-55:

**TLC** (SiO\(_2\)) \(R_f = 0.27\) (hexanes–ethyl acetate, 60:40); \([\alpha]^\text{21.5}_{589}\) = +86.0 (c 0.050, CHCl\(_3\)); \(^1\)H NMR (600 NMR, CDCl\(_3\)) \(\delta 3.88 - 3.79\ (m, 1H), 3.34\ (app t, J = 3.1\ Hz, 1H), 2.64\ (dd, J = 19.4, 8.8\ Hz, 1H), 2.57 - 2.44\ (m, 2H), 2.23\ (dd, J = 19.5, 9.1\ Hz, 1H), 2.19 - 2.11\ (m, 2H), 2.11 - 2.01\ (m, 1H), 1.99\ (app q, J = 8.7\ Hz, 1H), 1.94 - 1.85\ (m, 1H), 1.84 - 1.76\ (m, 2H), 1.72 - 1.65\ (m, 1H), 1.65 - 1.57\ (m, 1H), 1.56 - 1.50\ (m, 3H), 1.30\ (d, J = 6.1\ Hz,
3H), 1.11 (s, 3H), 1.06 (s, 3H), 1.02 (s, 3H), 0.94 (s, 3H), 0.78 (s, 3H); $^{13}$C($^1$H) NMR (150 MHz, CDCl$_3$) $\delta$ 215.8, 132.8, 132.1, 77.1, 69.8, 57.5, 48.0, 43.5, 42.7, 39.8, 38.7, 36.9, 31.3, 30.0, 28.9, 27.8, 27.1, 24.4, 24.0, 23.9, 22.4, 20.9, 17.8, 16.2; IR (thin film, cm$^{-1}$) 3384, 2929, 2895, 2849, 1443, 1062; HRMS (ESI-TOF) m/z: Calculated for C$_{24}$H$_{39}$O$_3$ [M+H]$^+$ 375.2899; found 375.2886.

2.8.3 References


Chapter 3: Progress towards the De Novo Asymmetric Synthesis of Euphol

3.1 Development of an Approach towards Euphol

Euphol (3-1) is the prototypical euphane terpenoid and is well-known for its biological activities. For instance, euphol (3-1) has been reported to exhibit anti-inflammatory, anti-tumor, anti-cancer and antinociceptive properties.1–9 Comprised of the fused tetracyclic skeleton, euphanes bear structural resemblance to the well-studied class of steroid hormones (3-2 and 3-3; Figure 3-1). However, euphanes stand out as structurally interesting targets as they contain an additional quaternary center at C14, and the absolute stereochemistry of the substituents at C13 and C17 positions is opposite to that in steroid hormones. As a result, the challenges associated with synthesizing euphanes are distinct from those encountered in approaches used to prepare the structurally less complex steroid hormones. A search for previous syntheses of euphanes revealed that an efficient and flexible de novo asymmetric synthesis of euphanes remains elusive. To our knowledge, there has only been one synthesis of a euphane (see Johnson's relay synthesis of euphol in Chapter 1),10 and no known asymmetric total synthesis of any euphanes. In an effort to establish the first asymmetric de novo synthesis of a euphane and enable exploration of the medicinal potential of euphane-based compounds, efforts were directed towards achieving a synthesis of euphol (3-1).

Figure 3-1. Structures of euphol and steroid hormones.

The key structural features of euphol (3-1; Figure 3-1) were identified as 1) three stereodefined quaternary centers (C10, C13 and C14), where C10 and C13 are in anti-orientation to one another, and the vicinal quaternary centers C13 and C14 exist at ring-
junction positions of the trans-CD ring system, 2) trans-AB ring fusion, and 3) the stereodefined and unsaturated alkyl chain at C17. It was reasoned that the chemical technology previously established in the Micalizio lab to access a structure such as F (Figure 3-2) could be strategically utilized in designing the synthesis of euphol (3-1). As illustrated, the titanium-mediated annulative cross-coupling reaction\textsuperscript{11–13} is capable of constructing an enantiodefined CD-ring system C with a quaternary center at C13. Subsequent protodesilylation and diastereoselective Friedel–Crafts cyclization is effective in establishing a second quaternary center at C9, affording a tetracyclic product D that has the C9,C13-anti stereochemistry.\textsuperscript{12} Tetracycle D can then be advanced to dienone F through a two-step sequence involving demethylation followed by oxidative dearomatization and group selective Wagner–Meerwein rearrangement.\textsuperscript{12} Notably, tetracyclic dienone F possesses the C10,C13-anti stereochemistry, which is part of the substitution pattern observed in euphol (3-1). Thus, the key challenges to be addressed in order to access euphol (3-1) through these key reactions were installation of the C17 side chain and the C14 quaternary center, and functionalization of the A-ring.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure3-2.png}
\caption{Approach to the ABCD-ring system.}
\end{figure}
With the goal of demonstrating the value of this sequence of bond-forming reactions in a total synthesis campaign targeted at euphol (3-1), a synthetic strategy based on the use of a highly functionalized hydrindane 3-6 was imagined (Figure 3-3). Hydrindane 3-6 was anticipated to be generated from the metallacycle-mediated annulation reaction between TMS-propyne (3-5) and novel enyne 3-4. While the titanium-mediated annulation between readily available enynes and alkynes has been effectively employed in other synthetic programs in the Micalizio lab, the use of a polyunsaturated enyne such as 3-4 for the annulation is unprecedented. Having two alkenes present in enyne 3-4 is of concern since the annulation reaction is thought to occur through a process in which the 1,1-disubstituted alkene participates in a stereoselective intramolecular [4+2] cycloaddition with metallacyclopentadiene intermediate (I; Figure 3-3). Furthermore, C17 bears a stereodefined α-branched moiety and is vicinal to C13 which would become a quaternary center. Upon successful execution of this annulation, hydrindane 3-6 would be converted to tetracycle 3-9 through the stereoselective three-step sequence that was previously discussed. Stereoselective installation of the C14 quaternary center, removal of the C16 alcohol and functionalization of the A-ring would then deliver euphol (3-1).

Figure 3-3. Synthetic strategy.
3.2 Towards the Euphane Tetracyclic System

3.2.1 Synthesis of a Novel Enyne

Initial efforts to explore the strategy outlined in Figure 3-3 focused on synthesizing enyne 3-4 in order to investigate whether the highly substituted and unsaturated enyne 3-4 would be compatible with the conditions typically employed for the titanium-mediated annulation with TMS-propyne (3-5) to deliver hydrindane 3-6. Chiral 1,6-enynes such as G (Figure 3-4) that are typically employed in the annulation reaction are prepared by the sequential addition of two organometallic reagents to the commercially available (R)- or (S)-epichlorohydrin.\(^\text{12}\) If the desired enyne 3-4 were to be prepared from (R)-epichlorohydrin (3-10) in the same way that enyne G is prepared, selective functionalization of the carbon that would later become C17 would be required to attach the desired alkyl chain at that position. Rather than selectively functionalizing that position of enyne G, which was considered difficult to achieve, it was thought that the desired enyne 3-4 would be prepared from epoxide 3-11 through addition of a lithium acetylide derived from treatment of alkyne 3-12\(^\text{12}\) with \(n\)-BuLi. Epoxide 3-11 would then be accessed from geraniol through what was thought to be a series of straightforward functional group manipulations.

![Figure 3-4. Preparation of enynes.](image)

Moving forward with this plan, as illustrated in Figure 3-5, geraniol (3-13) was first converted to the known allylic alcohol 3-14\(^\text{14,15}\) through a sequence of five steps that include Sharpless asymmetric epoxidation,\(^\text{16}\) regioselective epoxide opening,\(^\text{17}\) cleavage
of the corresponding diol, Wittig olefination and reduction of the resulting ester to a primary alcohol. Next, a second Sharpless asymmetric epoxidation of the allylic alcohol 3-14 delivered epoxide 3-15 with moderate levels of diastereoselectivity. After silylation of the primary alcohol, the resulting epoxide was converted to the monosubstituted epoxide 3-11 in four steps. Addition of a nucleophile derived from 2-lithiopropene and CuCN unfortunately resulted in a 1:1 mixture of inseparable regioisomers 3-16 and 3-17. Treatment of this mixture with TBAF, selective tosylation of the primary alcohol of the resulting diol and exposure to K₂CO₃ in MeOH resulted in the formation of epoxide 3-11. Finally, nucleophilic addition of the lithium acetylide of 3-12 to epoxide 3-11 in the presence of BF₃•OEt₂ proceeded smoothly, delivering the desired polyunsaturated enyne 3-4 in 51% isolated yield.¹²

Figure 3-5. Synthesis of enyne 3-4.
3.2.2 Establishing the ABCD-Ring System with a Stereodefined Side Chain at C17

While it was evident that there were significant issues associated with the route used to prepare enyne 3-4, resulting in a 2.4% yield over 12 steps, sufficient quantities of 3-4 were acquired to be used in the subsequent key ring-forming reactions. Consistent with the previous studies reported by the Micalizio group regarding the regio- and stereoselective coupling of 4-hydroxy-1,6-enynes with TMS-alkynes,\textsuperscript{11,13} the titanium-mediated annulation between TMS-propyne 3-5 and enyne 3-4 proceeded efficiently and delivered a highly functionalized hydridane 3-6 that retains the unsaturation on the C17 side chain (Figure 3-6A). Notably, this represents the first demonstration that the annulative cross-coupling reaction is effective with an enyne substrate 3-4 containing an unsaturated alkyl chain at C17 – a feature that is observed in numerous euphanes and related tetracyclic triterpenoids.\textsuperscript{18} Next, tandem protodesilylation and C9–C10 bond formation of hydridane 3-6 in the presence of (S)-Binol and SnCl\textsubscript{4} afforded tetracyclic product 3-7 with a quaternary center at C9. Here, tetracycle 3-7 is thought to be generated through removal of the TMS group at C11 followed by regioselective protonation of the alkene to generate a fully substituted allylic cation H that is thought to undergo regio- and stereoselective Friedel–Crafts cyclization. While the major product of this reaction was identified as tetracycle 3-7 in which the electron rich trisubstituted alkene on the side chain was not perturbed, a small amount of side-product 3-18 (Figure 3-6B; 3-7:3-18 = 3:1) was isolated as well.
Next, demethylation of the C3 methyl ether was accomplished by exposure of tetracycle 3-7 to DIBAl-H in PhMe at reflux (Figure 3-6A). Though these reaction conditions for demethylation have been proven to be efficient in other tetracyclic terpenoid-based synthesis programs in the Micalizio lab, in the case of demethylation of tetracycle 3-7, these conditions resulted in the formation of a 1:1.5 mixture of two products, 3-8 and 3-19 (Figure 3-6B), where the major product contained a saturated C17 side chain. It is understood that there are alternative methods for demethylation that could avoid the undesired reduction of the olefin on the C17 side chain. However, for the batch of material that was in hand, the mixture of 3-8 and 3-19 was moved forward to the next step after a small amount of the desired product 3-8 was isolated from the product mixture for characterization purposes. Oxidative dearomatization and 1,2-alkyl shift in the presence of PIDA in HFIP then afforded a mixture of dienone products 3-9 and 3-20, a small amount
of which was separated to enable structural elucidation of each compound. In this way, a highly functionalized tetracycle 3-9 that contains multiple structural features of euphol (3-1) was accessed in just four steps from enyne 3-4.

### 3.2.3 Attempted Installation of the C14 Quaternary Center

Having established a tetracyclic system that possesses the desired stereodefined side chain at C17, attention was then focused on stereoselective installation of the C14 quaternary center. Recognized as a major synthetic problem to solve, this task would require a large amount of the late-stage dienone 3-9. While the route outlined in Figure 3-6A was capable of delivering dienone 3-9, the inefficient preparation of enyne 3-4 prohibited our ability to access ample quantities of the late-state intermediate 3-9 to enable screening of conditions for introduction of the quaternary center at C14. We imagined that it might be possible to achieve a more efficient route to enyne 3-4, however, pursuing a novel synthesis of enyne 3-4 was not of interest and was considered to be beyond the scope of our original objective. As a result, an alternate strategy that does not require the use of enyne 3-4 was explored.

![Figure 3-7. Carbocation rearrangements.](image)

In considering ways to install the C14 quaternary center to potentially establish the euphane tetracyclic system, it was reasoned that a literature example of a carbocation rearrangement could provide insight. Figure 3-7 illustrates two examples: an observed rearrangement (A) and a proposed rearrangement (B) to achieve the desired quaternary center.

![A. Literature example featuring a carbocation rearrangement.](image)

![B. Proposed rearrangement.](image)
rearrangement\textsuperscript{21} shown in Figure 3-7A could be relevant. Here, protonation of the C14–C15 alkene in 3-21 is thought to generate a stable tertiary allylic carbocation. Then, 1,2-methyl shift from C13 to C14 followed by a semi-pinacol rearrangement would yield dione 3-22. With the knowledge that a substrate such as tetracycle 3-23 (Figure 3-7B) can be accessed through the chemical technology established in the Micalizio lab, we contemplated the possibility of invoking a similar transformation for dienone 3-23. It was recognized that competitive ionization of the C17 tertiary alcohol could occur in the presence of a protic acid. However, selective protonation of the C14–C15 alkene in 3-23 was thought to be possible as this would lead to a stable tertiary allylic carbocation which could promote 1,2-methyl shift from C13 to C14. A semi-pinacol rearrangement would then lead to ketone 3-24. If successful, this strategy would convert an intermediate 3-23 that possesses the C10,C13-syn stereochemistry to 3-24 that possesses the C10,C13-anti stereochemistry while also establishing the C14 quaternary center, with the core structure of 3-24 being that of a euphane.

In pursuit of this strategy, key substrate 3-23 was prepared from dienone 3-25\textsuperscript{22,23} in four steps (Figure 3-8A). Synthesis of dienone 3-25 has been previously discussed in Chapter 2. When 3-23 was treated with TFA at low temperatures (Figure 3-8B), phenol 3-26 was isolated in 50% yield instead of the anticipated product 3-24. While this result was unexpected, there are a number of studies reported in the literature to support this type of dienone–phenol rearrangement.\textsuperscript{24–26} The mechanism for the transformation, as proposed by Woodward \textit{et al.},\textsuperscript{24} is depicted in Figure 3-8C. Protonation of the dienone is thought to generate cation intermediate I, which then undergoes a 1,2-shift to afford the proposed spiro intermediate II. Next, a 1,2-shift of the more substituted carbon in intermediate III and loss of proton would lead to phenol 3-26. With this mechanism in mind, we aimed to mitigate this undesired rearrangement by converting 3-23 to 3-27. By removing the C1–C2 olefin, we expect to prevent the formation of the stable tertiary allylic cation II from
intermediate I, and thus, avoiding the undesired pathway to 3-26. Unfortunately, when 3-27 was treated with TFA at low temperatures, it resulted in no reaction, and starting material was recovered. When the reaction was carried out at ambient temperature, no desired product was observed while proton NMR spectrum of the isolated product suggested a structure that is consistent with elimination of tertiary alcohol at C17.

Figure 3-8. Experimental results.

3.3 Summary

Overall, the work described here has resulted in the synthesis of C14-desmethyl euphane system 3-9 (Figure 3-6A) that possesses the correct stereochemistry at C10, C13, C17 and C20 as well as five differentially substituted and electronically distinct alkenes. Showcasing the first demonstration that the metallacycle-mediated annulation is effective with the polyunsaturated enyne 3-4 to deliver a hydrindane containing an appropriate stereodefined and unsaturated side chain at C17, the chemical technology that enabled this synthesis also features conversion of the highly functionalized
hydrindane 3-6 into a complex tetracyclic dienone 3-9. In addition to the chemical synthesis described here, these studies have led to the discovery of a novel modulator of Liver X Receptor (LXR). Although the euphane-inspired tetracyclic compounds prepared during this synthesis lack the C14 quaternary center, it was realized that these compounds bear structural features similar to cholestane-based LXR agonists,\textsuperscript{27} despite having fundamentally distinct stereochemistry at C13 and C17, and possessing a C3 ketone rather than the typical $\beta$-OH. Investigations of these tetracyclic compounds (3-7, 3-8, 3-9, 3-18 and 3-20) as potential functional ligands of LXR were performed by our collaborators at Professor Thomas Burris lab at University of Florida, and dienone 3-9 was found to be first example of a selective modulator of LXR target genes that has structural features of a euphane, albeit with modest potency [$K_i = 2.1 \mu M$ (LXR$\alpha$) and $K_i = 2.4 \mu M$ (LXR$\beta$)].\textsuperscript{18}

3.4 Future Directions

Acknowledging that installation of the C14 quaternary center to realize a euphane tetracyclic system continues to pose a synthetic challenge, addressing this issue will undoubtedly be the focus of future studies. Inspired by the transformation (Figure 3-9B; 3-31 $\rightarrow$ 3-32) that was successfully employed in accessing the lanostane tetracyclic system (See Chapter 2 for details), Lewis-acid mediated rearrangement of vinyl epoxide 3-29 (Figure 3-9A) is expected to deliver 3-30 – a tetracyclic product that contains all the quaternary centers observed in euphanes.

**Figure 3-9.** Proposed strategy for installation of the C14 quaternary center.
Currently, efforts in the Micalizio lab are directed at accessing vinyl epoxide 3-29 through the approach described in Figure 3-10. Based on a related stereoselective Friedel–Crafts cyclization recently reported by the Micalizio lab to deliver C9,C13-anti product 3-35\(^\text{28}\) possessing C17 oxygenation (Figure 3-10A), vinyl epoxide 3-29 is proposed to be accessed in 11 steps from hydrindane 3-37 (Figure 3-10B). It is reasoned that tetracycle 3-38 could be prepared in three steps from TBS-protected Hajos–Parrish ketone 3-33. Conversion of the aromatic A-ring to a dienone moiety and introduction of C15 methyl group is expected to deliver 3-39. Further functionalization of the A-ring and hydroxyl-directed epoxidation of the C14–C15 olefin could then afford the desired vinyl epoxide 3-29.

**Figure 3-10. Proposed route to access vinyl epoxide 3-29.**
3.5 References


3.6 Supplementary Information

3.6.1 Materials and Methods

D. Reagents and Solvents

All reagents and starting materials were purchased from commercial sources and used as received, unless otherwise indicated. Anhydrous dichloromethane (CH$_2$Cl$_2$), diethyl ether (Et$_2$O), tetrahydrofuran (THF) and toluene (PhMe) were obtained by passing HPLC grade solvents through a column of activated alumina using a Glass Contour Solvent Purification System by Pure Process Technology, LLC. Hexafluoroisopropanol (HFIP) was purchased from Oakwood Chemical and used as received. Anhydrous methanol (MeOH), anhydrous isopropanol (i-PrOH), anhydrous triethylamine (NEt$_3$), t-butyl hydrogenperoxide (t-BuOOH) (5.5 M in decane) and SnCl$_4$ (1.0 M in CH$_2$Cl$_2$) were purchased in a Sure-Seal™ bottle from Sigma-Aldrich. For flash column chromatography, HPLC grade solvents were used without further purification. Solutions of n-BuLi and t-BuLi were purchased from Sigma-Aldrich and titrated against N-benzylbenzamide in accordance with the procedure reported by Chong.¹

E. Reaction Set-Up and Purification

All reactions were conducted in flame-dried glassware under an atmosphere of dry nitrogen unless otherwise indicated. Reaction mixtures were magnetically stirred and their progress was monitored by thin layer chromatography (TLC) on EMD TLC silica gel 60 F$_{254}$ glass-backed plates. Compounds were visualized by initial exposure of TLC plates to UV-light (254 nm), followed by staining with p-anisaldehyde.

Purification of crude isolates was achieved by flash column chromatography on a Biotage® Isolera One™ Automated Liquid Chromatography System using Biotage® SNAP Ultra HP-Sphere 10–25 g or Biotage® KP-Sil 10–100 g silica gel cartridges, or performed using a forced flow of the indicated solvent system on Sorbent Technologies™ silica gel 60 Å (40–63 µm particle size). Purification of co-eluting compounds was performed using
the indicated solvent system on Agilent Technologies semi-preparative High Performance Liquid Chromatography (HPLC) system with Varian Dynamax HPLC Microsorb silica column (normal phase, pore size: 100 Å, particle size: 5.0 µm, inner diameter: 21.4 mm, length: 250 mm). Concentration of reaction product solutions and chromatography fractions was accomplished by rotary evaporation at 30–35 °C under the appropriate pressure, followed by concentration at room temperature on a vacuum pump (approx. 0–1 mbar). Yields refer to chromatographically purified and spectroscopically pure compounds, unless otherwise indicated.

F. Characterization Data for New Compounds

v. Nuclear Magnetic Resonance Spectroscopy

$^1$H-NMR data were recorded on a Bruker Avance III 500 MHz NMR spectrometer (TBI probe) and a Bruker Avance III 600 MHz spectrometer (BBFO probe). $^1$H chemical shifts are reported in parts per million (ppm, δ scale) downfield from tetramethylsilane and are referenced to the residual CHCl$_3$ or C$_6$D$_6$H in the deuterated solvents: CDCl$_3$ (7.26 ppm), C$_6$D$_6$ (7.16 ppm). NMR coupling constants are measured in Hertz (Hz), and splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; app d, apparent doublet; app dd, apparent doublet of doublets; app t, apparent triplet; app dt, apparent doublet of triplets; app td, apparent triplet of doublets; app q, apparent quartet; app p, apparent pentet. $^{13}$C {1H decoupled} NMR data were recorded at 150 MHz on a Bruker Avance III 600 MHz spectrometer (BBFO probe). $^{13}$C chemical shifts are reported in parts per million (ppm, δ scale) and are referenced to the central line of the carbon resonances of the solvents: CDCl$_3$ (77.16 ppm), C$_6$D$_6$ (128.06 ppm).

Structural assignments for new compounds were supported by two-dimensional NMR experiments (COSY, HSQC, HMBC and NOESY) recorded on a Bruker Avance III 600 MHz spectrometer (BBFO probe), while the relative stereochemical assignments were
determined by analysis of the data obtained from 1D- or 2D-NOESY experiments, recorded on a Bruker Avance III 500 MHz NMR spectrometer (TBI probe) or a Bruker Avance III 600 MHz spectrometer (BBFO probe), respectively.

vi. Infrared Spectroscopy

Infrared spectra were collected on a JASCO FT/IR-4100 Fourier Transform Infrared Spectrometer.

vii. Accurate Mass Determination

HRMS (EI-TOF) analyses were performed at the Mass Spectrometry Laboratory of the University of Illinois at Urbana-Champaign.

viii. Optical Rotation

Optical rotations (α) were obtained on a JASCO-P-2000 polarimeter equipped with tungsten-halogen lamp (WI) and interface filter set to 589 nm, using a sample cell with a pathlength of 100 nm. Specific rotations are reported as: \([\alpha]^T_{589} (\circlearrowright, \text{solvent})\) and are based on the equation \([\alpha]^T_{589} (\circlearrowright) = (100\times\alpha)/(l\times c)\), where the concentration (c) is reported as g/100 mL and the pathlength (l) in decimeters.

Note: Copies of NMR spectra for compounds 3-4, 3-7, 3-8, 3-9, 3-11, 3-15, 3-18 and 3-20 have been published\(^2\) and are available online.

3.6.2 Experimental Procedures

\[
\begin{align*}
\text{CH}_2\text{Cl}_2 & \quad 10 \degree C \text{ to } -20 \degree C \text{ to rt} \quad 79\% (7:1 \text{ dr}) \\
3-14 & \quad \text{Ti(Oi-Pr)}_4 \quad \text{t-BuOOH} \quad (+)-\text{diethyl tartrate} \\
OH & \quad \text{Me} \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\end{align*}
\]

Synthesis of epoxide 3-15: To a stirred suspension of 4Å molecular sieves (0.50 g) in CH\(_2\)Cl\(_2\) (11 mL) at 10 \degree C were added L-(+)-diethyl tartrate (0.15 mL, 0.89 mmol, 0.15
equiv.), Ti(O-i-Pr)_4 (0.18 mL, 0.59 mmol, 0.10 equiv.) and t-BuOOH (5.5 M in decane, 2.2 mL, 12 mmol, 2.0 equiv.) sequentially. After the reaction mixture was stirred at 10 °C for approximately 20 mins, it was cooled to −20 °C, and allylic alcohol 3-14^3 (1.0 g, 5.9 mmol, 1.0 equiv.) in CH_2Cl_2 (2.0 mL) was added dropwise by syringe. The reaction mixture was stirred for 1 h, maintaining a bath temperature between −20 °C and −15 °C, and then warmed to 0 °C before being quenched by addition of deionized water (10 mL). The resulting mixture was warmed to room temperature, and NaOH (5.0 mL, 30% aqueous solution) was added. The mixture was stirred for approximately 30 mins and then filtered through a pad of Celite®. The aqueous and organic layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (× 3). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and then concentrated in vacuo. The crude isolate was purified by flash column chromatography on silica gel using 85:15 to 70:30 hexanes–ethyl acetate gradient elution to afford epoxide 3-15 (7:1 dr; 869 mg, 79%) as a colorless oil.

**Analytical data for epoxide 3-15:**

**TLC (SiO_2)** R_f = 0.26 (hexanes–ethyl acetate, 70:30); [α]_D^21.2 = −35.4 (c 0.36, CHCl_3); ^1H NMR (600 NMR, CDCl_3) δ 5.06 (app t, J = 7.0 Hz, 1H), 3.91 (d, J = 12.6 Hz, 1H), 3.61 (app dt, J = 12.7, 4.3 Hz, 1H), 2.96 (app dt, J = 4.7, 2.5 Hz, 1H), 2.72 (dd, J = 7.3, 2.4 Hz, 1H), 2.10 – 1.95 (m, 2H), 1.88 (s, 1H), 1.67 (d, J = 1.8 Hz, 3H), 1.59 (s, 3H), 1.49 – 1.35 (m, 2H), 1.35 – 1.26 (m, 1H), 1.02 (d, J = 6.4 Hz, 3H); ^13C NMR (150 MHz, CDCl_3) δ 132.0, 124.2, 61.9, 60.7, 58.5, 35.2, 33.8, 25.8, 25.7, 17.8, 17.2; IR (thin film, cm⁻¹) 3419, 2966, 2918, 2871, 1455, 1377, 1100, 1062; HRMS (ESI-TOF) m/z: Calculated for C_{11}H_{20}O_2 [M]⁺ 184.1463; found 184.1468.
Synthesis of epoxide 3-11: TBSCI (6.7 g, 45 mmol, 2.0 equiv.), imidazole (3.0 g, 45 mmol, 2.0 equiv.) and DMAP (135 mg, 1.1 mmol, 5 mol%) were added sequentially to a stirred solution of epoxide 3-15 (4.1 g, 22 mmol, 1.0 equiv.) in THF (200 mL). The reaction mixture was stirred at room temperature overnight. The following morning, the reaction was quenched by the addition of deionized water (50 mL) and diluted with diethyl ether. The aqueous and organic layers were separated, and the aqueous phase was extracted with diethyl ether (×3). The combined organic extracts were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to afford the crude silylated product, which was used in the subsequent step without further purification.

To a solution of isopropenyl bromide (8.0 mL, 90 mmol, 4.0 equiv.) in diethyl ether (60 mL) at −78 °C was added t-BuLi (1.54 M in pentane, 116 mL, 180 mmol, 8.0 equiv.) dropwise through an additional funnel. The resulting mixture was stirred at −78 °C for approximately 20 mins, and the contents of this flask were transferred to a second flask containing a suspension of CuCN (4.0 g, 45 mmol, 2.0 equiv.) in diethyl ether (13 mL) at −78 °C. The cold bath was removed, and the reaction mixture was stirred vigorously at 0 °C for approximately 10 mins. Next, the crude silylated alcohol (22 mmol, 1.0 equiv.) from the previous step was added dropwise by syringe, and the resulting mixture was stirred at 0 °C for 3 h, before gradually warming to room temperature overnight. The next day, the
reaction was quenched by the slow addition of a saturated aqueous solution of NaHCO₃ and diluted with diethyl ether. The two phases were separated, and the aqueous layer was extracted with diethyl ether (× 3). The combined organic extracts were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to afford the crude product as a mixture of regioisomers, which was used in the subsequent step without further purification.

TBAF (1.0 M in THF, 30 mL, 29 mmol, 1.3 equiv.) was added to a stirred solution of the crude regiosomers in THF (20 mL) at 0 °C. The resulting mixture was warmed to room temperature, stirred for 2 h and then quenched by the addition of a saturated aqueous solution of NH₄Cl and diluted with diethyl ether. The two phases were separated, and the aqueous layer was extracted with diethyl ether (× 3). The combined organic extracts were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel with 85:15 to 40:60 hexanes–ethyl acetate gradient elution to afford an inseparable mixture of regioisomers S₁ and S₂ (3.7 g).

Anhydrous triethylamine (3.5 mL, 25 mmol, 1.5 equiv.) and DMAP (405 mg, 3.3 mmol, 20 mol%) were added sequentially to a solution of regioisomers S₁ and S₂ (3.7 g, 17 mmol, 1.0 equiv.) in CH₂Cl₂ (20 mL). The flask was cooled to 0 °C, and TsCl (3.8 g, 19.94 mmol, 1.2 equiv.) was added portion wise. The ice bath was removed, and the reaction mixture was stirred at room temperature for 4 h. The reaction was quenched by the addition of a saturated aqueous solution of NaHCO₃. The two phases were separated, and the aqueous layer was extracted with CH₂Cl₂ (× 3). The combined organic phases were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to afford the crude inseparable mixture of 3-16 and 3-17, which was used in the next step without further purification.
Potassium carbonate (4.4 g, 32 mmol, 4.0 equiv.) was added, in one portion, to a stirred solution of 3-16 and 3-17 (3.0 g, 7.9 mmol, 1.0 equiv.) in methanol (20 mL). The resulting mixture was stirred at room temperature overnight. The following morning, the solids were removed by vacuum filtration over a pad of Celite®, and the filtrate was concentrated in vacuo. The crude isolate was purified by flash column chromatography on silica gel with 99:1 to 92:8 hexanes–ethyl acetate gradient elution to afford epoxide 3-11 (900 mg, 20% over five steps) as a clear, colorless oil.

**Analytical data for epoxide 3-11:**

TLC (SiO₂) Rₜ = 0.27 (hexanes–ethyl acetate, 95:5); [α]²¹.³⁵⁺ = +13.2 (c 0.46, CHCl₃); ¹H NMR (600 NMR, CDCl₃) δ 5.09 (app t, 1H), 4.81 (app t, 1H), 4.68 (app m, 1H), 2.92 (ddd, J = 8.2, 4.1, 2.8 Hz, 1H), 2.70 (app t, 1H), 2.37 (dd, J = 5.1, 2.8 Hz, 1H), 2.09 – 2.01 (m, 1H), 1.97 – 1.89 (m, 1H), 1.83 – 1.73 (m, 1H), 1.70 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H), 1.51 – 1.42 (m, 2H), 1.16 – 1.08 (m, 1H), 1.06 (d, J = 6.7 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 145.3, 131.5, 124.8, 112.7, 56.4, 54.4, 45.4, 34.9, 34.6, 25.9, 25.4, 21.3, 17.8, 16.8; IR (thin film, cm⁻¹) 2966, 2921, 2857, 1644, 1452, 1097; HRMS (ESI-TOF) m/z: Calculated for C₁₄H₂₄O [M⁺] 208.1827; found 208.1834.
Synthesis of enyne 3-4: n-BuLi (2.5 M in hexanes, 1.5 mL, 3.8 mmol, 1.9 equiv.) was added, dropwise, to a stirred solution of alkyne 3-12\(^4\) (761 mg, 4.4 mmol, 2.2 equiv.) in THF (8.0 mL) at \(-78\) °C. After the resulting mixture was stirred at \(-78\) °C for 30 mins, BF\(_3\)•OEt\(_2\) (0.49 mL, 4.0 mmol, 2.0 equiv) was added dropwise by syringe. The resulting mixture was stirred for 30 mins at \(-78\) °C before adding epoxide 3-11 (413 mg, 2.0 mmol, 1.0 equiv.) as a solution in THF (2.0 mL) dropwise by syringe. The reaction mixture was then stirred at \(-78\) °C for 2 h, and the reaction was quenched by the addition of a saturated aqueous solution of NaHCO\(_3\). The quenched mixture was transferred into a separatory funnel, rinsing the flask with ethyl acetate. The two phases were separated, and the aqueous layer was extracted with ethyl acetate (× 3). The combined organic layers were dried over anhydrous Na\(_2\)SO\(_4\), filtered and concentrated \(\textit{in vacuo}\). The crude product was purified by flash column chromatography on silica gel with 100:0 to 93:7 hexanes–ethyl acetate gradient elution to afford enyne 3-4 (388 mg, 51\%) as a yellow oil.

Analytical data for enyne 3-4:

\textbf{TLC (SiO\(_2\)) R\(_f\) = 0.28 (hexanes–ethyl acetate, 90:10); [\(\alpha\)]\(_{2\text{deg}}^\text{21.6}\) = +1.4 (c 0.73, CHCl\(_3\)); \(^1\text{H} \text{NMR}\) (600 NMR, CDCl\(_3\)) \(\delta\ 7.11 (t, J = 7.9 \text{ Hz}, 1\text{H}), 6.81 (d, J = 7.6 \text{ Hz}, 1\text{H}), 6.74 (d, J = 8.2 \text{ Hz}, 1\text{H}), 5.12 (\text{app t}, 1\text{H}), 4.87 (s, 1\text{H}), 4.65 (s, 1\text{H}), 3.85 – 3.77 (m, 4\text{H}), 2.84 (\text{app t, 2H}), 2.47 – 2.40 (m, 3\text{H}), 2.23 – 2.17 (m, 4\text{H}), 2.11 – 2.04 (m, 1\text{H}), 2.02 (dd, \(J = 9.2, 5.8 \text{ Hz}, 1\text{H}), 1.96 – 1.86 (m, 2\text{H}), 1.86 – 1.79 (m, 1\text{H}), 1.69 (\text{app d}, 6\text{H}), 1.61 (s, 3\text{H}), 1.57 – 1.49 (m, 1\text{H}), 1.15 – 1.06 (m, 1\text{H}), 0.96 (d, \(J = 6.9 \text{ Hz}, 3\text{H}); \(^{13}\text{C} \text{NMR}\) (150 MHz, CDCl\(_3\)) \(\delta\)
157.9, 144.6, 140.3, 126.2, 125.1, 124.8, 121.6, 114.2, 108.5, 82.6, 70.1, 57.0, 55.6, 33.6, 33.1, 32.9, 26.4, 26.3, 25.9, 23.7, 19.9, 17.9, 17.8, 11.4; IR (thin film, cm⁻¹) 3549, 2957, 2928, 1586, 1258, 1101; HRMS (ESI-TOF) m/z: Calculated for C₂₆H₃₉O₂ [M+H]+ 383.2950; found 383.2949.

Synthesis of tetracycles 3-7 and 3-18: Ti(Oi-Pr)₄ (3.2 mL, 11 mmol, 3.3 equiv.) was added to a flask containing a stirred solution of TMS-propyne 3-5 (1.6 mL, 11 mmol, 3.3 equiv.) in anhydrous toluene (35 mL) at room temperature. The flask was then cooled to −78 °C, and n-BuLi (2.5 M in hexanes, 8.2 mL, 21 mmol, 6.5 equiv.) was added dropwise by syringe. After the addition of n-BuLi was complete, the resulting mixture was warmed to room temperature, and then heated at 50 °C using an oil bath for 1 h. After the indicated time, the mixture (Ti-alkyne complex) was cooled to room temperature.

Meanwhile, in a separate flask, n-BuLi (2.5 M in hexanes, 1.3 mL, 3.3 mmol, 1.0 equiv.) was added to a solution of enyne 3-4 (1.3 g, 3.3 mmol, 1.0 equiv.) in anhydrous toluene (11 mL) at −78 °C. The resulting lithium-alkoxide solution was warmed up to room temperature and transferred, via a cannula, to the flask containing Ti-alkyne complex. The
resulting mixture was stirred at room temperature overnight (approximately 15 h). The following morning, the reaction mixture was quenched by the addition of a saturated aqueous solution of NaHCO$_3$ (one third of total volume of toluene). The aqueous and organic layers were separated, and the aqueous layer was extracted with ethyl acetate ($\times$ 6). The combined organic phases were dried over anhydrous Na$_2$SO$_4$, filtered and concentrated $\textit{in vacuo}$. The crude isolate was purified by flash column chromatography on silica gel with 90:10 to 50:50 hexanes–ethyl acetate gradient elution to afford hydridane 3-6 (880 mg) along with some impurities.

To a stirred solution of (S)-BINOL (553 mg, 1.9 mmol, 1.1 equiv.) in CH$_2$Cl$_2$ (19 mL) at $-78 ^\circ$C was added a solution of SnCl$_4$ (1.0 M in CH$_2$Cl$_2$, 1.8 mL, 1.8 mmol, 1.0 equiv.) dropwise by syringe. The resulting mixture was stirred for approximately 30 mins at $-78 ^\circ$C, and then a solution of hydridane S3 (870 mg, 1.8 mmol, 1.0 equiv.) in CH$_2$Cl$_2$ (22 mL) was added dropwise by syringe. The resulting mixture was stirred for approximately 1 h at $-78 ^\circ$C, and then warmed up to room temperature over 1 h. The reaction was quenched by the addition of a saturated aqueous solution of NH$_4$Cl, and the resulting mixture was stirred vigorously at room temperature for 30 mins. The aqueous and organic phases were separated, and the aqueous layer was extracted with CH$_2$Cl$_2$ ($\times$ 3). The combined organic layers were washed with an aqueous solution of NaOH (5% w/v), dried over anhydrous Na$_2$SO$_4$, filtered and concentrated $\textit{in vacuo}$. The crude isolate was purified by flash column chromatography on silica gel with 95:5 to 80:20 hexanes–ethyl acetate gradient elution to afford 3-7 (560 mg, 44% over two steps) and 3-18 (70 mg, 9%) as white solids.
Analytical data for tetracycle 3-7:

**TLC (SiO$_2$)** $R_f$ = 0.28 (hexanes–ethyl acetate, 85:15); $[\alpha]_{D}^{23.3} = -110$ (c 0.17, CHCl$_3$); $^1$H NMR (600 NMR, CDCl$_3$) $\delta$ 7.13 (d, $J$ = 8.6 Hz, 1H), 6.76 (d, $J$ = 8.6 Hz, 1H), 5.13 (app t, 1H), 4.33 (app td, 1H), 3.80 (s, 3H), 2.97 – 2.79 (m, 2H), 2.57 – 2.42 (m, 2H), 2.42 – 2.20 (m, 2H), 2.10 (s, 3H), 2.09 – 2.02 (m, 2H), 2.03 – 1.94 (m, 1H), 1.84 – 1.74 (m, 2H), 1.75 – 1.66 (m, 5H), 1.63 (s, 3H), 1.61 – 1.53 (m, 1H), 1.35 (app s, 4H), 1.34 – 1.28 (m, 2H), 1.09 (d, $J$ = 6.8 Hz, 3H), 0.81 (s, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 155.0, 140.5, 136.6, 136.0, 131.4, 131.1, 124.9, 124.2, 123.7, 108.7, 75.0, 64.4, 55.7, 44.6, 38.2, 37.9, 37.3, 34.9, 34.1, 31.8, 31.4, 29.6, 25.9, 25.7, 24.6, 20.5, 18.3, 17.9, 11.5; IR (thin film, cm$^{-1}$) 3304, 2961, 2937, 1588, 1261, 1100; HRMS (ESI-TOF) m/z: Calculated for C$_{29}$H$_{43}$O$_2$ [M+H]$^+$ 423.3263; found 423.3252.

Analytical data for tetracycle 3-18:

**TLC (SiO$_2$)** $R_f$ = 0.26 (hexanes–ethyl acetate, 85:15); $[\alpha]_{D}^{23.0} = -46.0$ (c 0.08, CHCl$_3$); $^1$H NMR (600 NMR, CDCl$_3$) $\delta$ 7.13 (d, $J$ = 8.7 Hz, 1H), 6.76 (d, $J$ = 8.7 Hz, 1H), 4.35 (app td, $J$ = 9.2, 4.1 Hz, 1H), 3.80 (s, 3H), 2.97 – 2.80 (m, 2H), 2.54 – 2.43 (m, 2H), 2.38 – 2.22 (m, 2H), 2.14 – 2.02 (m, 4H), 1.82 – 1.74 (m, 3H), 1.74 – 1.65 (m, 3H), 1.59 (app s, 7H), 1.56 – 1.53 (m, 1H), 1.52 – 1.45 (m, 1H), 1.35 (s, 3H), 1.34 – 1.28 (m, 2H), 1.09 (d, $J$ = 6.8 Hz, 3H), 0.81 (s, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 155.0, 140.4, 136.4, 136.0, 131.2, 124.2, 123.7, 108.7, 74.8, 71.5, 64.3, 55.7, 46.3, 44.6, 38.2, 37.9, 37.3, 34.9, 34.0, 32.7, 32.6, 31.9, 31.4, 29.6, 24.5, 22.7, 20.4, 18.2, 11.5; IR (thin film, cm$^{-1}$) 3306, 2961, 2933, 1588, 1261, 1100; HRMS (ESI-TOF) m/z: Calculated for C$_{29}$H$_{44}$O$_3$Na [M+Na]$^+$ 463.3188; found 463.3187.
Synthesis of enones 3-9 and 3-20: DIBAI-H (1.0 M in toluene, 13 mL, 13 mmol, 10 equiv.) was added to a stirred solution of tetracycle 3-7 (550 mg, 1.3 mmol, 1.0 equiv.) in toluene (10 mL) at room temperature. The reaction mixture was then heated to reflux using an oil bath and stirred overnight (approximately 15 h). The next morning, the reaction mixture was cooled to room temperature, and quenched by the careful addition of Rochelle's salt. The biphasic system was stirred vigorously for about 30 mins. The phases were separated, and the aqueous layer was extracted with ethyl acetate (× 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to afford the crude product as a mixture* of 3-8 and 3-19 (1:1.5), which was used in the next step without further purification.

To a flask containing a solution of crude 3-8 and 3-19 (299 mg, 0.73 mmol, 1.0 equiv.) in HFIP (7.3 mL) at 0 °C was added PIDA (235 mg, 0.73 mmol, 1.0 equiv.) in one portion. The resulting mixture was stirred for 1 min at 0 °C, and then quenched by the addition of a saturated aqueous solution of NaHCO_3 and diluted with ethyl acetate. The aqueous and organic layers were separated, and the aqueous layer was extracted with ethyl acetate (× 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo to afford crude product, which was purified by flash column chromatography on silica gel with 90:10 to 60:40 hexanes–ethyl acetate gradient.
elution to afford a mixture* of 3-9 and 3-20 (1:1.5) (201 mg, 54% over 2 steps) as a white solid.

*Small amounts of the mixture of 3-8 and 3-19, and the mixture of 3-9 and 3-20 were purified on Agilent Technologies semi-preparative HPLC system with Varian Dynamax HPLC Microsorb silica column using 90:10 to 80:20 hexanes–ethyl acetate gradient elution to afford 3-8, as a clear, colorless oil, and using 85:15 to 75:25 hexanes–ethyl acetate gradient elution to afford 3-9 and 3-20, as white solids, to be evaluated as ligands to LXRα and LXRβ.

**Analytical data for phenol 3-8:**

**TLC (SiO₂)** Rᵣ = 0.13 (hexanes–ethyl acetate, 85:15); [α]²¹³₀⁶⁹ = +74.6 (c 0.024, CHCl₃); 

**¹H NMR (500 NMR, CDCl₃)** δ 7.04 (d, J = 8.5 Hz, 1H), 6.66 (d, J = 8.4 Hz, 1H), 5.12 (app t, 1H), 4.49 (s, 1H), 4.33 (app s, 1H), 2.96 – 2.79 (m, 2H), 2.55 – 2.42 (m, 2H), 2.37 – 2.22 (m, 2H), 2.11 (s, 3H), 2.10 – 1.93 (m, 3H), 1.80 – 1.71 (m, 2H), 1.72 – 1.66 (m, 5H), 1.67 – 1.55 (m, 4H), 1.39 – 1.32 (m, 4H), 1.33 – 1.23 (m, 3H), 1.08 (dd, J = 6.9, 1.4 Hz, 3H), 0.81 (s, 3H); 

**¹³C NMR (150 MHz, CDCl₃)** δ 151.0, 140.6, 136.6, 136.2, 131.5, 131.0, 124.9, 124.5, 121.1, 113.3, 75.0, 64.4, 44.6, 38.2, 37.9, 37.3, 34.9, 34.1, 31.8, 31.3, 29.7, 25.9, 25.7, 24.5, 20.5, 18.3, 17.9, 11.5; 

**IR (thin film, cm⁻¹)** 3338, 2961, 2928, 1451, 1278, 1068; 

**HRMS (ESI-TOF) m/z:** Calculated for C₂₈H₄₁O₂ [M+H]+ 409.3107; found 409.3107.

**Analytical data for enone 3-9:**

**TLC (SiO₂)** Rᵣ = 0.29 (hexanes–ethyl acetate, 65:35); [α]²²⁶₁⁰⁹ = +227.1 (c 0.025 CH₂Cl₂); 

**¹H NMR (600 NMR, CDCl₃)** δ 6.59 (d, J = 10.1 Hz, 1H), 6.37 (d, J = 10.1 Hz, 1H), 5.34 (s, 1H), 5.30 (app t, 1H), 4.58 (app d, 1H), 2.49 (dd, J = 12.8, 4.2 Hz, 1H), 2.30 (dd, J = 16.4,
4.7 Hz, 1H), 2.22 – 2.13 (m, 1H), 2.13 – 2.04 (m, 1H), 2.00 (s, 4H), 1.95 – 1.75 (m, 5H),
1.73 (s, 3H), 1.72 – 1.65 (m, 1H), 1.63 (s, 3H), 1.41 (app t, 1H), 1.38 – 1.27 (m, 2H), 1.19
(d, J = 6.7 Hz, 3H), 1.06 (s, 3H), 1.00 – 0.93 (m, 1H), 0.73 (s, 3H); $^{13}$C NMR (150 MHz,
C$_6$D$_6$) δ 184.3, 157.7, 150.6, 148.9, 137.2, 131.3, 128.4, 128.1, 128.0, 125.4, 124.9, 80.1,
65.6, 45.7, 44.2, 37.1, 36.7, 32.8, 28.4, 28.1, 25.9, 25.4, 25.1, 24.4, 19.1, 18.8, 17.8, 10.6;
IR (thin film, cm$^{-1}$) 3407, 2962, 2924, 1660, 1631, 1045; HRMS (ESI-TOF) m/z: Calculated
for C$_{28}$H$_{39}$O$_2$ [M+H]$^+$ 407.2950; found 407.2938.

Analytical data for enone 3-20:

TLC (SiO$_2$) R$_f$ = 0.31 (hexanes–ethyl acetate, 65:35); [$\alpha$]$^{23}$$_{589}^0$ = +202.4 (c 0.033, CH$_2$Cl$_2$);
$^1$H NMR (600 NMR, C$_6$D$_6$) δ 6.60 (d, J = 10.1 Hz, 1H), 6.37 (d, J = 10.1 Hz, 1H), 5.35 (s,
1H), 4.61 (d, J = 7.3 Hz, 1H), 2.50 (dd, J = 13.0, 5.7 Hz, 1H), 2.32 (dd, J = 16.5, 6.5 Hz,
1H), 2.07 – 1.98 (m, 4H), 1.97 – 1.90 (m, 2H), 1.90 – 1.85 (m, 1H), 1.85 – 1.79 (m, 1H),
1.79 – 1.71 (m, 1H), 1.62 – 1.55 (m, 2H), 1.48 – 1.40 (m, 2H), 1.41 – 1.35 (m, 1H), 1.34 –
1.21 (m, 4H), 1.18 (dd, J = 6.7, 1.7 Hz, 3H), 1.07 (s, 3H), 0.95 (d, J = 6.6 Hz, 6H), 0.75 (s,
3H); $^{13}$C NMR (150 MHz, C$_6$D$_6$) δ 184.3, 157.7, 150.6, 148.9, 137.2, 128.7, 128.4, 125.4,
125.0, 80.0, 65.5, 45.7, 44.2, 39.8, 37.2, 36.7, 33.0, 28.5, 28.4, 28.1, 25.1, 24.5, 24.4,
22.9, 22.9, 19.3, 18.8, 10.6; IR (thin film, cm$^{-1}$) 3406, 2955, 2925, 1661, 1631; HRMS
(ESI-TOF) m/z: Calculated for C$_{28}$H$_{41}$O$_2$ [M+H]$^+$ 409.3107; found 409.3107.

Synthesis of ketone S3: To a stirring solution of enone 3-25$^{5,6}$ (620 mg, 2.1 mmol, 1.0
equiv.) in anhydrous toluene (1.0 mL) under nitrogen atmosphere was added Wilkinson’s
catalyst at room temperature. A balloon was used to introduce an atmosphere of hydrogen gas into the flask (allowing first for exchange of the nitrogen atmosphere), and the reaction was stirred under a positive pressure of hydrogen for approximately 16 hr. The mixture was concentrated \textit{in vacuo} to afford the crude product, which was purified by flash column chromatography on silica gel with 90:10 to 80:20 hexanes:ethyl acetate gradient elution to afford ketone \textbf{S3} (598 mg, 98\%) as a white solid.

\textbf{Analytical data for ketone S3:}

\textbf{TLC (SiO$_2$)} \textit{R$_f$} = 0.39 (hexanes:ethyl acetate-80:20); [\(\alpha\)]$_{589}^{19.8}$ = +71.1 (c 0.30, CHCl$_3$); \(\text{^1}H\) \textbf{NMR} (600 NMR, CDCl$_3$) \(\delta\) 7.22 (d, \(J = 8.7\) Hz, 1H), 6.73 (dd, \(J = 8.6, 2.8\) Hz, 1H), 6.59 – 6.56 (m, 1H), 3.76 (s, 3H), 2.90 – 2.83 (m, 1H), 2.82 – 2.65 (m, 3H), 2.65 – 2.54 (m, 2H), 2.44 – 2.34 (m, 1H), 2.20 – 2.06 (m, 1H), 1.95 – 1.84 (m, 1H), 1.83 – 1.78 (m, 1H), 1.78 – 1.72 (m, 1H), 1.71 – 1.63 (m, 1H), 1.37 (s, 3H), 1.17 (s, 3H); \(\text{^13}C\) \textbf{NMR} (126 MHz, CDCl$_3$) \(\delta\) 219.53, 157.35, 138.03, 137.95, 137.54, 126.87, 113.53, 112.34, 55.31, 48.52, 38.98, 36.34, 35.03, 31.70, 30.55, 26.74, 24.62, 24.09, 22.90; \textbf{IR} (thin film, cm$^{-1}$) 2958, 2926, 2863, 1740, 1608, 1498, 1450, 1272, 1234, 1039, 814; \textbf{HRMS (ESI-TOF)} m/z: Calculated for C$_{20}$H$_{25}$O$_2$ [M+H]$^+$ 297.1855; found 297.1854.

\textbf{Synthesis of alcohol S4:} To a stirring solution of ketone \textbf{S3} (590 mg, 1.9 mmol, 1.0 equiv.) in THF (20 mL) at –78 °C was added MeLi (1.4 M in THF, 2.8 mL, 3.9 mmol, 2.0 equiv.) dropwise. After the addition, the reaction mixture was gradually warmed up to room temperature and was stirred at room temperature for approximately 1 hr. The reaction
mixture was quenched by the addition of a saturated aqueous solution of \( \text{NH}_4\text{Cl} \). The two phases were separated, and the aqueous layer was extracted with ethyl acetate (× 3). The combined organic layers were dried over anhydrous \( \text{Na}_2\text{SO}_4 \), filtered and concentrated \textit{in vacuo} to afford the crude product, which was purified by flash column chromatography on silica gel with 85:15 to 70:30 hexanes:ethyl acetate gradient elution to afford alcohol \( \text{S4} \) (270 mg, 43%) as a yellow solid.

**Analytical data for alcohol S4:**

\textbf{TLC (SiO\(_2\))} \( R_f = 0.19 \) (hexanes:ethyl acetate-80:20); \( [\alpha]^{19.8}_{369} = -149.5 \) (c 0.93, CHCl\(_3\)); \( ^{1}\text{H NMR} \) (600 MHz, CDCl\(_3\)) δ 7.25 (d, \( J = 8.7 \) Hz, 1H), 6.74 (dd, \( J = 8.7, 2.8 \) Hz, 1H), 6.58 (d, \( J = 2.7 \) Hz, 1H), 3.77 (s, 3H), 2.79 (ddd, \( J = 15.7, 5.4, 3.2 \) Hz, 1H), 2.69 (ddd, \( J = 16.1, 12.0, 5.3 \) Hz, 1H), 2.48 (ddd, \( J = 13.5, 5.3, 3.2 \) Hz, 1H), 2.39 (ddt, \( J = 16.5, 11.7, 2.3 \) Hz, 1H), 2.32 – 2.20 (m, 2H), 2.04 – 1.88 (m, 2H), 1.78 (ddd, \( J = 13.8, 9.8, 4.6 \) Hz, 1H), 1.72 – 1.61 (m, 2H), 1.48 (ddd, \( J = 14.2, 9.9, 4.5 \) Hz, 1H), 1.35 (s, 3H), 1.13 (s, 3H), 0.99 (d, \( J = 1.1 \) Hz, 3H); \( ^{13}\text{C NMR} \) (150 MHz, CDCl\(_3\)) δ 157.14, 138.91, 138.34, 136.69, 134.80, 127.18, 111.32, 112.23, 80.75, 55.72, 45.40, 38.59, 36.74, 36.42, 31.44, 30.43, 27.28, 25.04, 24.98, 24.74, 23.67, 23.17; \( \text{IR} \) (thin film, cm\(^{-1}\)) 3434, 2953, 2923, 2832, 1653, 1608, 1497, 1457, 1271, 1233, 1121, 1034, 814, 750; \( \text{HRMS (ESI-TOF)} \) \( m/z \): Calculated for \( \text{C}_{21}\text{H}_{28}\text{O}_2 \) [M+Na]\(^+\) 335.1987; found 335.1982.

**Synthesis of dieone 3-23:** To a stirring solution of \( \text{S4} \) (270 mg, 0.86 mmol, 1.0 equiv.) in toluene (8.6 mL) at room temperature was added DIBAI-H (1.0 M in toluene, 8.6 mL, 8.6
mmol, 10 equiv.). The resulting mixture was then heated to reflux and stirred overnight (approximately 15 hr). The next morning, the reaction mixture was cooled to room temperature, and quenched by the careful addition of Rochelle’s salt. The biphasic system was stirred vigorously for about 30 mins. The phases were separated, and the aqueous layer was extracted with ethyl acetate (× 3). The combined organic layers were dried over anhydrous Na$_2$SO$_4$, filtered and concentrated in vacuo to afford the crude product, which was purified by flash column chromatography on silica gel with 80:20 to 60:40 hexanes:ethyl acetate gradient elution to afford tentatively assigned phenol S5 (160 mg) as a white solid.

To a stirring solution of phenol S5 (87 mg, 0.29 mmol, 1.0 equiv.) in HFIP (3.0 mL) at 0 ºC was added PIDA (94 mg, 0.29 mmol, 1.0 equiv.). The resulting mixture was stirred for 1 min (or until PIDA is fully dissolved) at 0 ºC, and then quenched by the addition of a saturated aqueous solution of NH$_4$Cl. The mixture was warmed to room temperature. The aqueous and organic layers were separated, and the aqueous layer was extracted with ethyl acetate (× 3). The combined organic layers were dried over anhydrous Na$_2$SO$_4$, filtered and concentrated in vacuo to afford the crude product, which was purified by flash column chromatography on silica gel with 60:40 to 20:80 hexanes:ethyl acetate gradient elution to afford dienone 3-23 (52 mg, 60%) as a white solid.

**Analytical data for dienone 3-23:**

**TLC (SiO$_2$)** $R_f = 0.15$ (hexanes:ethyl acetate-60:40); $[\alpha]^{21}_D = -29.31$ (c 0.35, CHCl$_3$); $^1$H NMR (600 NMR, MeOD) $\delta$ 7.51 (d, $J = 10.2$ Hz, 1H), 6.24 (dd, $J = 10.2$, 2.0 Hz, 1H), 6.13 (t, $J = 1.7$ Hz, 1H), 5.43 (s, 1H), 2.87 – 2.77 (m, 1H), 2.68 (dt, $J = 16.4$, 2.2 Hz, 1H), 2.66 – 2.60 (m, 1H), 2.60 – 2.52 (m, 2H), 2.49 – 2.38 (m, 2H), 2.19 (dd, $J = 16.4$, 3.5 Hz, 1H), 1.58 (tt, $J = 8.4$, 4.6 Hz, 2H), 1.50 (s, 3H), 1.14 (s, 3H), 0.99 (s, 3H); $^{13}$C NMR (150 MHz,
MeOD) $\delta$ 187.99, 171.03, 157.09, 148.14, 136.33, 128.00, 123.57, 119.40, 82.63, 46.51, 46.41, 30.86, 30.49, 29.18, 28.44, 25.14, 24.55, 18.31; IR (thin film, cm$^{-1}$) 3410, 2968, 2933, 2871, 2843, 1728, 1661, 1622, 1450, 1368, 1238, 1160, 949, 888, 754, 665; HRMS (ESI-TOF) m/z: Calculated for C$_{20}$H$_{25}$O$_2$ [M+H]$^+$ 297.1855; found 297.1854.

**Synthesis of phenol 3-26**: To a stirring solution of dienone 3-23 (13 mg, 0.044 mmol, 1.0 equiv.) in CH$_2$Cl$_2$ at $-20$ °C was added TFA (50 µL, 0.088 mmol, 2.0 equiv.). The resulting mixture was stirred at $-20$ °C for approximately 1 hr and quenched by the addition of DI water followed by a saturated aqueous solution of NaHCO$_3$. The aqueous and organic layers were separated, and the aqueous layer was extracted with CH$_2$Cl$_2$ ($\times$ 3). The combined organic layers were dried over anhydrous Na$_2$SO$_4$, filtered and concentrated in vacuo to afford the crude product, which was purified by flash column chromatography on silica gel with 90:10 to 60:40 hexanes:ethyl acetate gradient elution to afford phenol 3-26 (7.0 mg, 50%).

**Analytical data for phenol 3-26:**

TLC (SiO$_2$) $R_f = 0.31$ (hexanes:ethyl acetate-60:40); $^1$H NMR (600 NMR, CDCl$_3$) $\delta$ 6.86 (d, $J = 8.1$ Hz, 1H), 6.53 (d, $J = 8.1$ Hz, 1H), 5.56 (s, 1H), 3.15 – 3.02 (m, 1H), 2.82 (d, $J = 15.5$ Hz, 1H), 2.69 (dd, $J = 32.6$, 17.1 Hz, 2H), 2.50 (d, $J = 14.0$ Hz, 1H), 2.41 – 2.29 (m, 2H), 2.21 (s, 3H), 2.02 (t, $J = 15.5$ Hz, 1H), 1.64 – 1.57 (m, 2H), 1.27 (s, 4H), 1.08 (s, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 151.22, 146.84, 138.05, 130.58, 129.19, 128.99, 126.78,
3.6.3 References


