I. HOMOLOGATION OF ALPHA-DIKETONES. II. SYNTHESIS OF EPIAFRICANOL AND ADVANCES TOWARD LONGITHORONE A AND PACLITAXEL

Dissertation

Presented in Partial Fulfillment of the Requirements for the Degree Doctor of Philosophy in the Graduate School of The Ohio State University

by

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2003

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ABSTRACT

The reaction of open-chain \( \alpha \)-diketones with \( \omega \)-alkenyl organometallics, under the proper conditions, led to 1,2-diols bonded to terminal olefinic chains. Exemplified with biacetyl, allylindation in aqueous THF and application of Grignard reagents proceeded readily to give double addition at both adjacent carbonyls respectively. The subsequent ring closing metatheses have been examined. In case of larger ring formations, the diols reacted only if structurally preorganization, capable of facilitating mutual approach of the two double bonds, was present. For this purpose, the prior conversion of diol to a cyclic carbonate was applied. In the latter setting, saponification must precede the diol cleavage step. This chemistry conveniently lends itself to the controlled intercalation of multiple methylene groups between the carbonyl carbons of readily available \( \alpha \)-diketones to deliver linear or cyclic products.

Longithorones A-H, polycyclic natural products structurally expressed as prenylated quinones, were targeted for total synthesis. In the proposed scheme, the preparation of cyclohexene-based core structure via type II enantioselective intramolecular Diels-Alder reaction was anticipated to provide access to each individual target. In diene formation, Stille reaction was extensively studied, in which the organometallic partner was prepared via hydroalumination-transmetallation of alkyne. The oxazolidinone-based chiral auxiliary was
attached to the dienophile for the proper stereochemical induction. This attractive approach, however, proved to be unsuccessful.

A total synthesis of (+)-epiafricanol has been readily achieved from D-glucose. The tricyclic alcohol target was arrived at by first forming methyl 2-C-methyl-2,3,4-trideoxy-α-D-threo-hexopyranoside, followed by extension of the olefinic unit to give the isopropenyl pyranoside, which was subjected to zirconocene-promoted ring contraction to furnish enantiomerically pure substituted cyclopentanol. Upon extension of the side chain, tertiary carbinol was transformed into the target molecule by sequential ring-closing metathesis and stereocontrolled Simmons-Smith cyclopropanation.

The attempt to expand the utility of the α-ketol rearrangement in the established synthetic route toward taxol and its analogues was studied. In particular, the approach employing the conformational restrictions of the northern part of the molecule with the ketal formation of C9, C10 hydroxyl groups was considered. These studies revealed several limitations of this approach.
Наташе

Hamawue
ACKNOWLEDGMENTS

I would like to begin by expressing my appreciation to the person to whom I am most indebted for the successful completion of my graduate studies at The Ohio State University, Professor Leo Paquette. Professor Paquette’s enormous support, guidance and incredible patience were the key constituents in making my graduate years both challenging and enjoyable. I am most grateful that I was given the opportunity to work under the patronage of such a true scientist.

I wish to thank the members of my dissertation committee Prof. John Swenton (Chemistry), Prof. Sean Taylor (Chemistry), and Prof. Raymond W. Lang (Molecular Virology, Immunology and Medical Genetics). I am thankful to Prof. David J. Hart (Chemistry) and my former adviser and good friend Prof. Viktor V. Zhdankin (University of Minnesota, Duluth) for their advisement and for writing the recommendation letters on my behalf.

I would like to thank my friend and co-worker Dr. Dmitry Sergeevich Zuev with whom I had the privilege of engaging in many thought-provoking and idea-generating discussions, who has shared his knowledge and experience in chemistry and contributed his friendship to me throughout the time of my
graduate studies and well beyond that. I thank my colleague Dr. John Hofferberth for his warmth and friendship and wish to him the best of luck.

I would like to thank my co-workers who have provided friendship, advice, and insightful discussions to me throughout the course of my graduate studies. This list includes: Dr. Dmitri Pissarnitski, Dr. Paul Lobben, Dr. Oliver Long, Prof. Louis Barriault, Dr. Serge Boulet, Dr. Stephan Ciblat, Dmirty Bondar, Kallol Basu, Chris Seekamp, Dr. Steve O’Neil, Dr. Jose Luis Mendez-Andino and Alex Kahane.

I would like to express my sincere thanks to all staff members of Chemistry Department for great service. In particular, the very special thanks go to Donna Rothe and Rebecca Martin for their tremendous support.

Although it is impossible to thank everyone, I would like to especially thank my relatives, who always believed in me even in the hardest time of mine. This list includes my parents, my brother Георгий and a very special person, my mother-in-law Татьяна Васильевна Измайлова, who tragically lost her battle with leukemia on March 30, 2002.

Finally, I want to thank my wife Natalya. Her continuous encouragement kept me to the mission and only with her love I was able to reach my goal. Sometimes I ask myself, what would have happened if I had not been with her? But I know there is no answer to this question.
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LIST OF ABBREVIATIONS AND SYMBOLS

\( \alpha \) ................. alpha

\( [\alpha] \) ................ specific rotation

Ac .................. acetyl

br .................. broad (NMR)

\( \beta \) ................. beta

\(^n\)Bu ............. normal-butyl

\(^t\)Bu .......... tert-butyl

Bz .................. benzoyl

\(^\circ\)C .............. degrees Celsius

calcd ........... calculated

CSA ............... \((1\,S)-(+)\)-10-camphorsulfonic acid

Cy ................ cyclohexyl

\( \delta \) ............. chemical shift in parts per million downfield from tetramethysilane

d .................. doublet (spectra); day(s)

DBU ........... 1,8-diazabicyclo[5.4.0]undec-7-ene

DDQ ............ 2,3-dichloro-5,6-dicyano-1,4-benzoquinone

DCC ............. dicyclohexylcarbodiimide

DMAP .......... 4-(\(N,N\)-dimethylamino)pyridine

DMDO ........ dimethyldioxirane
DMF ........... $N,N$-dimethylformamide
DMP .......... Dess-Martin periodinane
DMSO ........ dimethylsulfoxide
DPS .......... tert-butyldiphenylsilyl
equiv. ......... equivalent
Et ............. ethyl
γ ............... gamma
g ............... gram(s)
h ............... hour(s)
IR ............. infrared
$J$ ............ coupling constant in Hz (NMR)
k ............. kilo
KHMDS ...... potassium hexamethyldisilazide
L ............. liter(s)
LDA .......... lithium diisopropylamide
m ............. milli; multiplet (NMR)
µ ............. micro
M ............. moles per liter
Me ............. methyl
MHz .......... megahertz
min .......... minute(s)
mol .......... mol(s)
Ms .......... methanesulfonyl
MS ........ mass spectrometry; molecular sieves
m/z .......... mass to charge ratio (MS)
NaHMDS .... sodium hexamethyldisilazide
NMO .......... 4-methylmorpholine N-oxide
NMR .......... nuclear magnetic reasonance
p .............. para
Ph .............. phenyl
PMB .......... p-methoxybenzyl
PMP .......... p-methoxyphenyl
ppm .......... parts per million
^{i}Pr .......... iso-propyl
py .............. pyridine
q .............. quartet (NMR)
rt .............. room temperature
s .............. singlet (NMR); second(s)
t .............. tertiary (tert)
t .......... triplet (NMR)
TBAF .......... tetrabutylammonium fluoride
TBAI .......... tetrabutylammonium iodide
TBS .......... tert-butyldimethylsilyl
TBT .......... tributyltin
TES .......... triethylsilyl
Tf .......... trifluoromethanesulfonyl
THF .......... tetrahydrofuran
TLC .......... thin layer chromatography
TMS .......... trimethylsilyl
CHAPTER 1.
HOMOLOGATION OF DICARBONYL COMPOUNDS.

1.1. Introduction.

The significance of dicarbonyl compounds in modern organic synthesis cannot be overlooked. They constitute synthetic building blocks and key intermediates, and sometimes exist as individual synthetic targets of interest for one reason or the other. Therefore, the ongoing search for improved efficiency of synthetic routes leading to these targets constantly produces innovative methods. In an effort to contribute to this exploration, we have developed a scheme where multiple methylene groups would be inserted in a controlled fashion between the carbonyl carbons of readily available α-dicarbonyl compounds of generic structure 1.1 to deliver linear or cyclic

\[ 
\text{Scheme 1.1. Illustration of general concept of intercalation.} 
\]
products such as 1.2. In the development process, we also set a clear goal of designing the synthetic methodology with flexibility and versatility, the elements rather difficult to uncover.

In recent years, the coupling of aldehydes and ketones to allylic indium reagents generated in water as the reaction medium,\(^1\) and ring-closing metathesis promoted by ruthenium-based catalysts such as 1.3\(^2\)\(^{-11}\) have emerged as useful new preparative tools. These remarkably versatile reactions have been successfully applied to the acquisition of various targets of interest. We have presently examined the merging of these two processes in both cyclic and acyclic contexts, with \(\alpha\)-dicarbonyl compounds serving as the starting materials.\(^12\) In addition to the convergency associated with this protocol and the range of possibilities, the reaction sequences are short, flexible and practical. Limitations have surfaced only when entropic, ring strain, and steric effects kinetically deter the ease of large-ring formation.\(^13\)
1.2. *Early Studies Involving Four-Carbon Intercalations.*

In discussion of the preliminary work, which was completed by Dr. José Luis Mendez-Andino,¹⁴ two sets of results are outlined. The first includes experimentation with α-keto aldehyde 1.4 (phenylglyoxal), and the second represents the transformations of two ketones, butane-2,3-dione 1.5 and 1-phenylpropane-1,2-dione 1.6. All three compounds exhibited high reactivity in the addition steps, and cyclization of the subsequent products was also uneventful.¹²

When phenylglyoxal was stirred vigorously with an excess of powdered indium metal and allyl bromide in a THF/H₂O mixture, the bisallylated diols¹⁵,¹⁶ 1.7.1 and 1.7.2 were produced very efficiently and with high diastereoselectivity. We attributed this kinetic bias to the likely intervention of a chelated transition state, as the intermediate α-ketol is brought into the second carbon-carbon bond-forming step.¹⁷ Such a phenomenon is a common

![Scheme 1.2. Intercalation of four carbon atoms: phenyl glyoxal.](image-url)

³
occurrence in allylindation reactions of carbonyl functionalities with α-coordinating substituents. Heating the diol product with the Grubbs’ catalyst\(^2\) gave rise to the cyclized product \(1.8\) almost as efficiently. Following the catalytic hydrogenation of \(1.8\) to generate \(1.9\),\(^{18,19}\) the stage was set for diol cleavage with lead tetraacetate. The return of carbonyl functionalities to furnish keto aldehyde \(1.10\)^{20,21} proceeded smoothly. This homologated product was isolated as a deliquescent solid with all the spectral data matching those

Previously published.

Both diketones \(1.5\) and \(1.6\) allowed the intercalation to proceed as efficiently as that in the preceding example. The allylindation proceeded
smoothly and gave 1.11\textsuperscript{15} and 1.12\textsuperscript{15,22-24} as mixtures of diastereomers. Subsequent to the ring closure of both diols under the influence of Grubbs catalyst, lead tetraacetate was added directly to the reaction mixture to return vicinal diols 1.13 and 1.14 to the dicarbonyl oxidation state. Finally, the catalytic hydrogenation of 1.13 to 1.15\textsuperscript{25} (and of 1.14 to 1.16\textsuperscript{26-29}) made possible the analogous oxidative conversion to 1.17\textsuperscript{30} and 1.18\textsuperscript{31}.

All of the above examples demonstrated a very high efficiency and simplicity of this novel methodology. In order to investigate the versatility of this method, the attempt to extrapolate to the larger insertions was a pressing necessity. Realizing the possibility of some reactivity issues being raised during this investigation, we proceeded with a clear synthetic plan and possible solutions to the obstacles we might encounter.
1.3. **Intercalation of Greater than Four Methylene Units: Results and Discussion.**

The successful four-carbon atom homologation of 1,2-dicarbonyl compounds prompted further attempts towards the introduction of larger numbers of methylene units. This would allow the necessary extension of the intercalation methodology to advertise it as an ultimate tool for 1,\textit{n}-dicarbonyl compound assembly. Additionally, further development of this sequence would allow us to explore the ring-closing metathesis reaction of large-ring systems with unprotected diol functionality, especially since such systems are largely absent in the literature.

The work associated with this part of the intercalation methodology was initiated by Dr. José Luis Mendez-Andino, who is acknowledged for his contributions. Some results related to the formation of cyclic carbonate 1.21 and 1.22 that he obtained are included in this discussion.

1.3.1. **Choosing Biacetyl as Model Compound.**

The successful application of this methodology to 4-carbon intercalation prompted attempts to introduce larger numbers of methylene units in systematic fashion. The most direct approach consisted of the controlled
stepwise addition of ω-unsaturated Grignard reagents of differing chain lengths to the α-diketone. According to the logic of this methodology, the variation of the chain length can be achieved by keeping the number of methylene units in the first alkylation constant and changing it in the other. As an alternative, the variation of both chain lengths should give the same result, since the connection point is not an interest of this scheme and is removed at a later stage (see Scheme 1.6).

Our choice for a model diketone fell on butane-2,3-dione 1.6 due to its extraordinary electrophilic properties. The commercial availability of 11-bromo-1-undecene was a sufficient source for its use in alkylations. This compound was conveniently converted to the Grignard reagent, and under slow addition conditions and lowered temperature the clean monoalkylation was achieved in high yield. This attached chain would be kept constant throughout further experimentation. This α-ketol 1.19 was subjected to the second alkylation with a varying chain. The practicality of monoallylating 1.19 with allyl bromide and indium powder in aqueous THF soon became apparent as a utilitarian route to 1.20.1, the representative with minimum methylene units on the varying chain.

Scheme 1.6. Chain length variation concept.
This process took only 5 hours and yielded a very acceptable 83% yield of product. For others, since the halogen atom in 6-bromo-1-hexene and 8-bromo-1-octene was not comparably activated, their incorporation into 1.19 rested on their reactivity again as Grignard reagents. Competitive enolization proved not to be a problem and diols 1.20.2 and 1.20.3 were obtained in 38% and 40% yield, respectively, with most of the unreacted 1.19 recovered. The formation of the diols was confirmed by observing the disappearance of the methyl ketone singlet at 2.19 ppm in the proton NMR spectrum.

Scheme 1.7. Alkylation of butane-2,3-dione.
1.3.2. **Ring-Closing Metathesis Reaction of Large Rings.**

All attempts to engage \textit{1.20} to undergo productive ring-closing metathesis reaction in the presence of Grubbs’ catalyst\textsuperscript{2} at the reflux temperature of dichloromethane or benzene were not successful. In a number of runs, unreacted diol was recovered with some noticeable degradation. Occasionally, partial conversion to polymerization products was also noted. After several unproductive runs, our observations appeared to contradict the formulated hypotheses in the context of previous findings involving unfunctionalized dienes.\textsuperscript{32-35} Coordination to some type of functionality is generally believed to be required in order to realize efficient ring closure.\textsuperscript{36} In our case the vicinal diol functionality is an ideal coordinating ligand for the ruthenium center, and the failure to obtain cyclized products from \textit{1.20} could be suggestive that entropic factors of the non-rigid nature of these substrates might play a vital role. It is an established fact that metathesis reactions are driven by an increase in entropy, such as, for example, the evolution of

\begin{center}
\textbf{Scheme 1.8.} Failure of ring-closing metathesis reaction on free diol.
\end{center}
ethylene. Molecules such as our problematic diols, which enjoy high levels of entropy prior to cyclization, would consequently incur a smaller gain in entropy during ring formation, the level of which may be too small to drive the reaction to completion. At this point, it was clear that an adjustment should be made in the molecule in order to circumvent this obstacle.

Formation of the heterocyclic ring greatly limits the degrees of freedom available to diols and the availability of cyclic carbonates $1.21$ and $1.22$ could shed added light on this relevant issue. When the diols were reacted with phosgene in the presence of pyridine in dichloromethane, the resulting diastereomeric products could be separated chromatographically. No effort was made to distinguish the stereochemical features of the carbonates. Both of them, however, were investigated further in the synthetic sequence. We decided to label the less polar isomers cis ($1.21$) and the more polar diastereomers –
trans (1.22). With a very high anticipation of successful results, the ring closing metathesis of these cyclic carbonates were carried out at high dilution (≤ 5 mM) with a catalyst loading of 20% for a total reaction time of 40 hours in dichloromethane at 40-50 °C. Every run returned starting material (total accounting of materials approximately 80-85%), with the series when \( n=1 \) providing the lowest yield of cyclized product. The formation of small amounts of more polar, unidentified materials was also noted. Clearly, forcing the diol into the cyclic arrangement dramatically changed the conformational flexibility, which ultimately allowed both olefinic moieties to attain proper positioning at the catalytic site for the ring-closing process to occur.

This finding represents another piece of the global picture of the ring-closing metathesis of large rings and illustrates the importance of the entropy

Scheme 1.10. Ring closure of cyclic carbonates 1.21 and 1.22.
factor for this process. Overall, this discovery demonstrated the remarkable superiority of entropy factor over coordination factors when both of them are present under the same reaction settings.

We also observed that the cis and trans isomers were reacting equally well, which indicated that the process was very little, if any, stereochemically dependent. However, our observations of limited reactivity in the series when \( n=1 \) suggested that it is probably best to have both double bonds as distal as possible from the quaternary centers. This is particularly true if the ring double bond is destined to be saturated as in the present instance.

1.3.3. Concluding Steps.

In an attempt to design the concluding steps of the sequence as short as possible, we combined the double bond saturation and carbonate cleavage into one synthetic operation. In the hydrogenations of 1.23 and 1.24 to ultimately

![Scheme 1.11. Final operations of intercalation sequence.](image-url)
generate 1.25, the reaction mixtures were not freed of catalysts, but treated directly with aqueous NaOH to liberate the diols. The crude products were pure enough to proceed to the next step, which finally would return the diketone and conclude the intercalation process. As planned, exposure of the intermediates to lead tetraacetate furnished the extended diketones. All the compounds were isolated as colorless crystalline solids with the spectroscopic data matching that previously published.37-43,44
1.4. Conclusion.

In conclusion, we successfully developed a highly efficient and simple methodology for the conversion of 1,2-dicarbonyl compounds into their elongated homologues, where the length of the inserted chain can be as high as 20 methylene units. The method merges two powerful synthetic transformations, such as nucleophilic addition onto the carbonyl group and ring-closing metathesis.

The complications associated with the ring-closing metathesis of large-ring systems encountered during the development were solved by the mean of the conformational freedom reduction of the substrates. This discovery serves as a very useful finding to complete the reactivity picture of large ring formation.
1.5. Experimental Section.

**General Considerations.** Melting points were measured on a Thomas Hoover (Uni-melt) capillary melting point apparatus and are uncorrected. A Perkin-Elmer Model 241 Polarimeter was used to measure all optical rotations. Optical rotations were measured at 589 nm with a sodium lamp and concentrations are reported in g/100 mL. A Perkin-Elmer 1600 Series FTIR spectrometer was used to record infrared spectra, which are reported in reciprocal centimeters (cm⁻¹). A Bruker AC 300 FT-NMR spectrometer was used to record proton (¹H) and carbon (¹³C) nuclear magnetic resonance (NMR) spectra at 300 MHz and 75 MHz, respectively, and Bruker AT 500 was used for ¹H NMR spectra at 500 MHz and ¹³C NMR spectra at 125 MHz. Chemical shifts are reported in parts per million (ppm) with the signal of residual protons of deuterated solvent as an internal standard, which is 7.26 ppm for chloroform and 7.16 ppm for benzene. Splitting patterns are designated as follows: s, singlet; t, triplet; q, quartet; m, multiplet; br, broad. The high-resolution mass spectra were recorded at The Ohio State University Campus Chemical Instrumentation Center or at Chemistry Department Mass Spectrometry Facility. Elemental analyses were performed at Atlantic Microlab, Inc., Norcross, Georgia, USA.

All moisture sensitive reactions were performed under a nitrogen (N₂) or argon (Ar) atmosphere in flame-dried glassware. All solvents were pre-dried over 4 Å molecular sieves prior to distillation, and, if necessary, stored over 4 Å
molecular sieves under nitrogen. Acetonitrile (CH\textsubscript{3}CN), chlorotrimethylsilane (TMSCl), dichloromethane (CH\textsubscript{2}Cl\textsubscript{2}), diisopropylamine (\textit{i}Pr\textsubscript{2}NH), \textit{N}, \textit{N}-dimethylformamide (DMF), dimethylsulfoxide (DMSO) and triethylamine (Et\textsubscript{3}N) were individually distilled over calcium hydride. Benzene and toluene were distilled from sodium. Tetrahydrofuran (THF) and diethyl ether (Et\textsubscript{2}O) were distilled from sodium/benzophenone ketyl. Pyridine and 2,6-lutidine were distilled over potassium hydroxide prior to use. All reagents were purchased as “reagent grade” and, unless otherwise noted, used without further purification. The combined organic layer extracts were dried over anhydrous magnesium sulfate (MgSO\textsubscript{4}) or sodium sulfate (Na\textsubscript{2}SO\textsubscript{4}), as noted. The thin layer chromatography plates by Sorbent Technologies (0.2 mm silica gel, UV-254, aluminum backed) were used. The column chromatographic separations were performed with Woelm silica gel (230-400 mesh). The purity of all compounds was shown to be >95% by TLC and high field \textsuperscript{1}H and \textsuperscript{13}C NMR.
**3-Hydroxy-3-methyltetradec-13-en-2-one (1.19).** Magnesium metal (4.63 g, 191 mmol) was ground and added to 10 mL of anhydrous ether. To this mixture was added dropwise a solution of 8.00 g (34.3 mmol) of 11-bromo-1-undecene with vigorous stirring at 0 °C under argon. After the addition was complete, the mixture was warmed to ambient temperature and stirred for an additional 3 h. The resulting Grignard reagent was added to a solution of 3.30 g (38.1 mmol) of 2,3-butanedione during 12 h at ambient temperature under argon. The reaction mixture was stirred for 10 h, quenched with 10% HCl solution, and extracted with 3x200 mL of ether. The combined organic phases were washed with brine, dried, and evaporated. Chromatography of the residue on silica gel (elution with hexanes/ethyl acetate 6:1) gave 6.58 g (72%) of 1.19 as a colorless oil; IR (neat, cm⁻¹) 3474, 1711, 1641; ¹H NMR (300 MHz, CDCl₃): δ = 5.86-5.72 (m, 1 H), 5.01-4.89 (m, 2 H), 2.19 (s, 3 H), 2.06-1.97 (m, 2 H), 1.72-1.62 (m, 2 H), 1.49-1.17 (series of m, 15 H), 1.34 (s, 3 H); ¹³C NMR (75 MHz, CDCl₃): δ = 212.3, 139.1, 114.1, 78.7, 39.4, 33.7, 29.7 (2C), 29.4 (2C), 29.0, 28.8, 25.4, 23.6, 23.3; HRMS (ES): m/z calcd for (M + Na)⁺ 263.1987, obsd 263.1985.

**4,5-Dimethylhexadeca-1,15-diene-4,5-diol (1.20.1).** To a solution of ketol 1.19 (0.725 g, 3.02 mmol) in 65 mL of 4:1 THF/H₂O was added indium powder
(1.73 g, 15.1 mmol, 5.0 equivalents). While vigorously stirred, allyl bromide
(1.3 mL, 5.0 equivalents) was introduced in one portion. The reaction mixture
was stirred for 3 h during which time a milky appearance developed and the
metal separated as pellets. At this point, 25 mL of 2N potassium hydrogen
sulfate solution and 75 mL of CHCl₃ were introduced. The separated aqueous
phase was extracted with CHCl₃ (2x75 mL) and the combined organic layers
were dried and concentrated to leave a residue that was chromatographed on
silica gel (elution with 25% ether in petroleum ether) to give 0.706 g (83%) of
titled diol as a colorless oil; IR (neat, cm⁻¹): 3451; ¹H NMR (300 MHz, CDCl₃): δ
= 6.03-5.89 (m, 1 H), 5.88-5.74 (m, 1 H), 5.20-5.08 (m, 2 H), 5.02-4.89 (m, 2 H),
2.45 (dd, J = 13.7, 7.3 Hz, 1 H), 2.25-2.15 (m, 1 H), 2.10-2.00 (m, 2 H), 1.96 (br
s, 2 H), 1.67-1.20 (series of m, 16 H), 1.15 (s, 6 H); ¹³C NMR (75 MHz, CDCl₃): δ
= 139.2, 134.65, 134.58, 118.9, 118.8, 114.1, 76.7, 76.4, 41.1, 40.8, 36.2,
36.0, 33.8, 30.4, 29.7, 29.6, 29.5, 29.1, 28.9, 23.7, 23.6, 22.0, 21.6, 21.0, 20.7;
HRMS (ES): m/z calcd for (M + Na)⁺ 305.2457, obsd 305.2451.

Anal. Calcd for C₁₈H₃₄O₂: C, 76.54; H, 12.13. Found: C, 76.18; H, 11.86.

**General Procedure for Long Chain Addition via Grignard Reagent.**

Magnesium metal (0.608 g, 25.0 mmol) was ground and added to 3 mL of
anhydrous ether. To this mixture was added dropwise a solution of 6-bromo-1-
hexene (2.04 g, 12.5 mmol) with vigorous stirring at 0 °C under argon. After the addition was complete, the mixture was warmed to ambient temperature and stirred for the additional 3 h. The resulting Grignard reagent was added to the solution of 0.600 g (2.50 mmol) of 3-hydroxy-3-methyltetradec-13-en-2-one 1.19 during a period of 1 h at 0 °C under argon. The mixture was warmed to ambient temperature, stirred for an additional 24 h, quenched with 10% HCl solution, and extracted with 3x50 mL of ether. The combined organic phases were washed with brine, dried with Na₂SO₄, and evaporated. The residue was chromatographed on silica gel (elution with hexanes/ethyl acetate 4:1) to give 0.312 g (38%) of diol 1.20.2 as well as unreacted starting material; colorless oil; IR (neat, cm⁻¹) 3446; ¹H NMR (300 MHz, CDCl₃): δ = 5.88-5.73 (m, 2 H), 5.03-4.91 (m, 4 H), 2.12-1.97 (m, 4 H), 1.80 (br s, 2 H), 1.60-1.20 (series of m, 22 H), 1.14 (s, 6 H); ¹³C NMR (75 MHz, CDCl₃): δ = 139.2, 138.9, 114.3, 114.1, 77.1, 36.3, 36.1, 36.0, 35.7, 33.8, 31.4, 29.7, 29.64, 29.59, 29.53, 29.48, 29.4, 29.1, 28.9, 23.8, 23.5, 23.3, 21.2, 20.9 (2C); HRMS (ES): m/z calcd for (M + Na)+ 347.2926, obsd 347.2919.

For diol 1.20.3: Colorless oil (40% yield); IR (neat, cm⁻¹) 3418; ¹H NMR (300 MHz, CDCl₃): δ = 5.90-5.73 (m, 2 H), 5.04-4.90 (m, 4 H), 2.10-2.00 (m, 4 H), 1.79 (br s, 2 H), 1.63-1.19 (series of m, 26 H), 1.15 (s, 3 H), 1.14 (s, 3 H); ¹³C NMR (75 MHz, CDCl₃): δ = 139.2, 139.1, 114.15, 114.07, 77.1, 36.3, 35.9, 33.8, 33.7, 30.4, 30.3, 29.7, 29.6, 29.5, 29.2, 29.1, 28.9, 23.74, 23.71, 21.1, 20.7 (3C not observed); HRMS (ES): m/z calcd for (M + Na)+ 375.3239, obsd 375.3255.
General Procedure for Cyclic Carbonate Formation. A solution of the diol (0.60 mmol) in dry CH₂Cl₂ (20 mL) was cooled to 0 °C, treated with pyridine (290 µL) and then a 1.9 M solution of phosgene in toluene (0.60 mmol), and allowed to warm to 20 °C over 1 h. The volatiles were evaporated and the residue was chromatographed on silica gel (elution with 5% ether in petroleum ether) to achieve separation of the less polar from the more polar isomer.

For 1.21.1 and 1.22.1: (combined 87% yield; 4:1 ratio); less polar isomer: colorless oil; IR (neat, cm⁻¹) 1801, 1641; \(^1\)H NMR (300 MHz, CDCl₃): \(\delta = 5.84-5.69\) (m, 2 H), 5.22-5.09 (m, 2 H), 4.99-4.85 (m, 2 H), 2.58 (dd, \(J = 14.2, 5.9\) Hz, 1 H), 2.27 (dd, \(J = 14.2, 8.8\) Hz, 1 H), 2.06-1.93 (m, 2 H), 1.85-1.15 (series of m, 16 H), 1.36 (s, 3 H), 1.32 (s, 3 H); \(^1^3\)C NMR (75 MHz, CDCl₃): \(\delta = 153.7, 139.0, 131.2, 120.0, 114.0, 88.2, 87.4, 39.7, 35.0, 33.6, 29.8, 29.3\) (2C), 29.2, 28.9, 28.8, 23.7, 19.1, 18.6; HRMS (ES): \(m/z\) calcd for (M + Na)⁺ 331.2249, obsd 331.2231.

Anal. Calcd for C₁₉H₃₂O₃: C, 73.98; H, 10.46. Found: C, 74.16; H, 10.28.

More polar isomer: colorless oil; IR (neat, cm⁻¹) 1800, 1641; \(^1\)H NMR (300 MHz, CDCl₃): \(\delta = 5.87-5.74\) (m, 2 H), 5.24-5.14 (m, 2 H), 5.04-4.90 (m, 2 H), 2.62 (dd, \(J = 14.6, 5.9\) Hz, 1 H), 2.29 (dd, \(J = 14.6, 8.9\) Hz, 1 H), 2.09-2.00 (m, 2
H), 1.87-1.22 (series of m, 16 H), 1.35 (s, 6 H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 153.8, 139.1, 131.3, 120.2, 114.1, 88.3, 87.5, 39.3, 34.3, 33.7, 29.9, 29.40, 29.36, 29.3, 29.0, 28.9, 23.7, 19.7, 19.5; HRMS (ES): $m/z$ calcd for (M + Na)$^+$ 331.2249, obsd 331.2234.

For 1.21.2 and 1.22.2: (combined 93% yield; 3:1 ratio); less polar isomer: colorless oil; IR (neat, cm$^{-1}$) 1799, 1640; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 5.87-5.72 (m, 2 H), 5.05-4.91 (m, 4 H), 2.15-2.00 (m, 4 H), 1.85-1.28 (series of m, 22 H), 1.35 (s, 6 H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 154.1, 139.2, 138.3, 114.8, 114.1, 88.5, 88.4, 35.0, 34.8, 33.8, 33.4, 29.9, 29.43 (2C), 29.39 (2C), 29.1, 28.9, 23.9, 23.3, 18.9 (2C); HRMS (ES): $m/z$ calcd for (M + Na)$^+$ 373.2719, obsd 373.2723.

More polar isomer: colorless oil; IR (neat, cm$^{-1}$) 1799, 1640; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 5.86-5.72 (m, 2 H), 5.05-4.90 (m, 4 H), 2.13-2.01 (m, 4 H), 1.85-1.29 (series of m, 22 H), 1.36 (s, 6 H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 154.1, 139.2, 138.3, 114.8, 114.1, 88.4, 88.3, 34.4, 34.2, 33.8, 33.4, 30.0, 29.44 (2C), 29.40 (2C), 29.1, 28.9, 23.7, 23.1, 19.42, 19.39; HRMS (ES): $m/z$ calcd for (M + H)$^+$ 351.2899, obsd 351.2904.

For 1.21.3 and 1.22.3: (combined 75% yield; 3:1 ratio); less polar isomer: colorless oil; IR (neat, cm$^{-1}$) 1802, 1640; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 5.88-5.73 (m, 2 H), 5.03-4.91 (m, 4 H), 2.07-2.00 (m, 4 H), 1.81-1.73 (m, 2 H), 1.63-1.20 (series of m, 24 H), 1.35 (s, 6 H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 154.1, 139.2, 138.9, 114.3, 114.1, 88.4 (2C), 35.0, 33.8, 33.6, 29.9, 29.8, 29.43 (2C),
29.39 (2C), 29.1, 28.9, 28.8, 28.7, 23.90, 23.87, 18.9 (2C); HRMS (ES): $m/z$ calcd for (M + Na)$^+$ 401.3032, obsd 401.3034.


More polar isomer: colorless oil; IR (neat, cm$^{-1}$) 1799, 1641; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 5.88-5.73 (m, 2 H), 5.02-4.91 (m, 4 H), 2.07-2.01 (m, 4 H), 1.80-1.70 (m, 2 H), 1.59-1.28 (series of m, 24 H), 1.35 (s, 6 H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 154.2, 139.2, 138.9, 114.3, 114.1, 88.5, 88.4, 34.4, 33.8, 33.7, 29.9, 29.8, 29.42 (2C), 29.40 (2C), 29.1, 28.9 (2C), 28.7, 23.72, 23.68, 19.4 (2C); HRMS (ES): $m/z$ calcd for (M + Na)$^+$ 401.3032, obsd 401.3036.

**General Procedure for Ring Closing Metathesis of Cyclic Carbonates.** To a solution of **1.21** or **1.22** (0.10 mmol) in CH$_2$Cl$_2$ (25 mL) was added 17 mg (0.02 mmol) of Grubbs’ catalyst at 20 °C under argon. The reaction mixture was stirred at 40 °C for 36 h, cooled, treated with 15 mg of lead tetraacetate to destroy the catalyst, and stirred overnight. Following solvent evaporation under reduced pressure, the residue was taken up in hexanes and filtered through a short pad of silica gel. The filtrate was evaporated and final purification was achieved by flash chromatography on silica gel (elution with hexanes to 3% ethyl acetate in hexanes). Unreacted starting material was invariably recovered (25-40%).
Compounds **1.23.1** and **1.24.1**: Ring closing metathesis of **1.21.1** (less polar) gave rise to **1.23.1** in 37% yield; colorless oil; IR (neat, cm⁻¹) 1800; ¹H NMR (300 MHz, CDCl₃): δ = 5.41-5.19 (m, 2 H), 2.42-2.32 (m, 2 H), 2.27-1.08 (m, 18 H), 1.39 (s, 3 H), 1.36 (s, 3 H); ¹³C NMR (75 MHz, CDCl₃): δ = 153.9, 130.8, 129.9, 126.4, 125.6, 88.7, 87.9, 40.3, 39.3, 34.4, 33.5, 33.2, 29.9, 29.7, 29.43, 29.37, 29.2, 29.0, 27.3, 23.2, 23.0, 20.5, 20.4, 19.7, 19.5; HRMS (ES): m/z calcd for (M + Na)⁺ 303.1931, obsd 303.1941.

**Anal.** Calcd for C₁₇H₂₈O₃: C, 72.82; H, 10.06. Found: C, 72.60; H, 10.14.

Ring closure of **1.22.1** (more polar) afforded **1.24.1** (30%) as a colorless oil; IR (neat, cm⁻¹): 1801; ¹H NMR (300 MHz, CDCl₃): δ = 5.30-5.18 (m, 2 H), 2.43-2.30 (m, 2 H), 2.25-1.07 (m, 18 H), 1.38 (s, 3 H), 1.36 (s, 3 H); ¹³C NMR (75 MHz, CDCl₃): δ = 154.0, 130.7, 129.7, 126.2, 125.7, 88.6, 87.7, 41.2, 39.2, 34.2, 34.1, 33.4, 33.2, 29.8, 29.6, 29.2, 29.1, 29.0, 28.9, 23.2, 22.9, 20.6, 20.4, 19.8, 19.7; HRMS (ES): m/z calcd for (M + Na)⁺ 303.1904.

Compounds **1.23.2** and **1.24.2**: Ring closing metathesis of **1.21.2** (less polar) furnished **1.23.2** in 47% yield as a colorless oil; IR (neat, cm⁻¹) 1799; ¹H NMR (300 MHz, CDCl₃): δ = 5.46-5.17 (m, 2 H), 2.26-1.07 (series of m, 26 H), 1.39 (s, 3 H), 1.38 (s, 3 H); ¹³C NMR (75 MHz, CDCl₃): δ = 154.0, 131.8, 131.1, 129.8, 129.6, 88.7, 88.3, 35.4, 34.0, 33.9, 32.6, 32.0, 29.4, 29.01, 28.96, 28.9, 28.04, 27.97, 27.62, 27.57, 27.42, 27.36, 26.6, 26.3, 25.6, 25.3, 23.1, 23.0, 21.9, 21.5, 20.5, 20.4, 19.4; HRMS (ES): m/z calcd for (M + Na)⁺ 345.2400, obsd 345.2398.
Comparable treatment of 1.22.2 (more polar) gave rise to 1.24.2 (45%) as a colorless oil; IR (neat, cm\(^{-1}\)): 1798; \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 5.39-5.29\) (m, 2 H), 2.12-1.95 (m, 4 H), 1.87-1.66 (m, 4 H), 1.61-1.22 (series of m, 18 H), 1.40 (s, 3 H), 1.36 (s, 3 H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta = 154.1, 131.2, 130.3, 130.1, 129.4, 88.6, 88.2, 36.3, 34.54, 34.49, 33.1, 31.8, 31.6, 30.4, 29.9, 28.4, 28.0, 27.9, 27.72, 27.69, 27.5, 27.4, 26.8, 26.6, 26.5, 26.2, 25.9, 22.9, 22.8, 22.1, 21.8, 21.1, 20.6, 20.3, 19.7; HRMS (ES): \(m/z\) calcd for (M + Na\(^+\)) 345.2400, obsd 345.2411.

Compounds 1.23.3 and 1.24.3. Ring closing metathesis of 1.21.3 (less polar) afforded 1.23.3 in 50% yield as a colorless oil; IR (neat, cm\(^{-1}\)) 1800; \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 5.35-5.29\) (m, 2 H), 2.05-1.95 (m, 4 H), 1.76-1.59 (m, 4 H), 1.53-1.17 (series of m, 22 H), 1.39 (s, 6 H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta = 154.0, 130.9, 130.5, 130.3, 129.7, 88.63, 88.57, 34.9, 34.3, 32.6, 32.1, 29.5, 29.0, 28.8, 28.72, 28.67, 28.4, 28.3, 28.0, 27.8, 27.7, 27.6, 27.1, 24.2, 22.9, 22.8, 20.1, 19.9; HRMS (ES): \(m/z\) calcd for (M+Na\(^+\)) 373.2719, obsd 373.2723.

Anal. Calcd for C\(_{22}\)H\(_{38}\)O\(_3\): C, 75.38; H, 10.93. Found: C, 75.26; H, 11.04.

Comparable treatment of 1.22.3 (more polar) furnished 1.24.3 in 46% yield as a colorless oil; IR (neat, cm\(^{-1}\)) 1799, 1641; \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 5.39-5.27\) (m, 2 H), 2.09-2.00 (m, 4 H), 1.80-1.63 (m, 4 H), 1.58-1.24 (series of m, 22 H), 1.36 (s, 6 H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta = 154.2, 130.7, 130.6, 130.3, 130.0, 88.5, 88.3, 35.0, 34.8, 34.3, 33.5, 32.1, 32.0, 29.7, 29.3, 28.9, 28.83, 28.76, 28.7, 28.5, 27.7, 27.4, 26.8, 26.6, 26.3, 23.6, 23.4, 22.9, 22.5, 20.3,
20.2, 20.1, 20.0; HRMS (ES): m/z calcd for (M + Na)$^+$ 373.2719, obsd 373.2714.

**General Procedure for the Generation of Ketones.** A solution of 1.23.2 (22 mg, 0.068 mmol) in absolute ethanol (3 mL) containing 4 mg of 10% palladium on charcoal was vigorously stirred overnight under 1 atm of H$_2$, treated with 2 mL of 2M sodium hydroxide solution, and stirred for an additional 2 h. The mixture was filtered through a small pad of Celite, and the filtrate was partitioned between water (100 mL) and CH$_2$Cl$_2$ (100 mL). The separated aqueous layer was extracted with CH$_2$Cl$_2$ (3x50 mL), and the combined organic layers were dried and evaporated. The residue was taken up in CH$_2$Cl$_2$ (5 mL), treated with lead tetraacetate (60 mg, 0.14 mmol), stirred for 30 min, and freed of solvent. The diketone was purified by flash chromatography on silica gel.

**2,15-Hexadecanedione (1.25.1).** Obtained from 1.23.1 or 1.24.1 in 79% overall yield; white solid, mp 82-83 °C; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 2.40 (t, $J$ = 7.0 Hz, 4 H), 2.12 (s, 6 H), 1.59-1.53 (m, 4 H), 1.27-1.24 (m, 16 H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 208.1 (2C), 43.6 (2C), 29.8 (2C), 29.6 (2C), 29.5 (2C), 29.4 (2C), 29.2 (2C), 23.8 (2C).

**2,18-Nonadecanedione (1.25.2).** Obtained from 1.23.2 or 1.24.2 in 84% overall yield; white solid, mp 89.5-90.5 °C; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 2.40
(t, J = 7.4 Hz, 4 H), 2.12 (s, 6 H), 1.58-1.53 (m, 4 H), 1.26-1.24 (m, 22 H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta = 209.3\) (2C), 43.8 (2C), 29.8 (2C), 29.59 (3C), 29.56 (2C), 29.43 (2C), 29.36 (2C), 29.2 (2C), 23.9 (2C).

\textbf{2,20-Heneicosanedione (1.25.3).}\(^{44}\) Obtained from \textbf{1.23.3} or \textbf{1.24.3} in 80% overall yield; colorless solid, mp 91-92 °C; \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 2.41\) (t, J = 7.4 Hz, 4 H), 2.13 (s, 6 H), 1.61-1.52 (m, 4 H), 1.27-1.25 (m, 26 H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta = 205.7\) (2C), 43.8 (2C), 29.8 (2C), 29.7 (3C), 29.65 (2C), 29.61 (2C), 29.5 (2C), 29.4 (2C), 29.2 (2C), 23.9 (2C).
CHAPTER 2.

LONGITHORONES.

2.1. Introduction.

The ocean has always been a rich source of live organisms generating a steady stream of new molecules. Among a large number of marine species, only a small fraction has been explored. Those which have been investigated have revealed a broad spectrum of natural products. Some of them exhibit extraordinary biological activity, others are less active but possess a structure of high complexity. However, no matter what properties are found for each individual compound, a vast majority of them immediately become highly prioritized synthetic targets for researchers around the globe. The natural product family described in this chapter is one such example.

As one of the marine habitants, tunicates have become noted as a source of a wide variety of natural products among which cyclic peptides and alkaloids are the most common. Tunicates of the genus Aplidium have yielded prenylated hydroquinones and quinones, terpenoids, alkaloids, nucleosides, and bryostatin 4 and 5. Undoubtedly, the most exciting
finding among those was made in 1994, when Schmitz and coworkers isolated the metabolite of structure 2.1 from a specimen of the tunicate *Aplidium longithorax*.\(^{58}\) The heptacyclic structure of this natural product, designated as longithorone A, represents a unique type of prenylated quinone in which a farnesyl unit forms a macrocycle by bridging the 2,5-positions of benzoquinone, and two such units are combined together to form a new carbocyclic skeleton containing 6-, 10-, and 16-membered rings.

The structural complexity of this natural product immediately attracted the attention of synthetic chemists. Whether this compound is possible to prepare by way of well-established synthetic methods or specially developed methodologies, the completion of this synthesis would be accepted by the synthetic community as an outstanding achievement. In this chapter, the first successful synthesis as well as our approach to the family overall and this natural product in particular will be discussed.

*Figure 2.1. Structure of longithorone A.*
2.2. **Isolation, Structural Features and Biosynthetic Hypothesis.**

Tunicates have become noted as sources of a broad spectrum of natural products among which cyclic peptides and alkaloids are the most common\(^\text{45-47}\). As an ongoing exploration of these types of marine life forms, a group of nine farnesylated quinones (2.1-9) have been isolated from the tunicate *Aplidium longithorax*.\(^\text{58,59}\) Their unique structural peculiarities includes an unprecedented macrocyclic skeleton formed by farnesyl units bridging the quinones in the *meta* or *para* positions. Although compounds of mixed biogenesis featuring the farnesyl (or cyclized farnesyl) hydroquinone skeleton are well-known,\(^\text{47,60}\) cyclization of the farnesyl chain with the hydroquinone unit to give a macrocycle is rare, one example being the smenochromenes\(^\text{60}\) which feature *ortho*-bridging of a hydroquinone by the termini of a farnesyl unit. Further investigations toward the structural elucidation revealed that three of the natural products, longithorone B, C and D are monomeric C\(_{21}\) compounds, while longithorone A and E-I are dimeric C\(_{42}\) products (Figure 2.2). The structures of all longithorones were determined by spectroscopic analysis and confirmed by X-ray crystallography.

In addition to the numerous stereogenic centers, all nine of the longithorones exhibit another form of chirality, which is atropisomerism, arising from hindered rotation of quinone ring G through macrocycle F.
Figure 2.2. Longithorone family natural products.

2.1 longithorone A; 2.2 longithorone B; 2.3 longithorone C; 2.4 longithorone D; 2.5 longithorone E; 2.6 longithorone F; 2.7 longithorone G; 2.8 longithorone H; 2.9 longithorone I
Among all of the prenylated quinones or hydroquinones isolated from Aplidium or other tunicates, the most complex is longithorone A (2.1). The biological activity of this marine compound includes weakly cytotoxicity toward P388 murine leukemia cells at ED$_{50} \sim 10 \mu$g/mL. However, what attracted the attention of the synthetic community is the fascinating structure of this compound. This natural product contains an unprecedented carbocyclic skeleton featuring a farnesyl unit cyclized onto benzoquinone to form a [12]-paracyclocphane subunit.

As proposed by Schmitz,$^{58,59}$ the biogenesis of the dimeric longithorones appears to involve the Diels-Alder reaction of suitably unsaturated precursors such as depicted in Figure 2.3 (cycloaddition $a$). The discovery of monomers 2.2-4$^{59}$ closely related to the proposed dimerization partners provided solid support to this hypothesis. Upon closer examination of the structure of the dimeric longithorones, the stereochemistry of the central carbocyclic ring exposes its consistency with a Diels-Alder addition. To complete the

![Figure 2.3. Proposed longithorones biogenesis.](image-url)
construction of the polycyclic structure, a subsequent transannular Diels-Alder reaction (cycloaddition b) occurs to simultaneously assemble rings A, C, and D. Although an intermolecular Diels-Alder reaction has been proposed as a step in the biogenesis of the tetraterpenoid methyl isotortuate,\textsuperscript{61} and intramolecular [4+2] cycloadditions have been invoked to explain the formation of various complex alkaloids (e.g. the manzamines,\textsuperscript{62} xestocyclamine,\textsuperscript{63,64} the ingenamines,\textsuperscript{65,66} and mandangamine\textsuperscript{67}), this process has not been studied and none of the enzymatic equivalents to a dielsalderase was suggested.

All these facts place our knowledge of naturally occurring cycloaddition reactions on the line of doubts and prompt further investigation in this area. As a representative of the synthetic community, we can certainly add some light by attempting to modulate the same process \textit{in vitro}. Such effort is illustrated by the first successful synthesis of longithorone A described in the following section.
2.3. First Successful Synthetic Approach.

The first total synthesis targeted the most elaborate representative of the longithorone family, longithorone A, and emerged as an elegant realization of the provocative biosynthetic hypothesis. It was released by Matthew Shair of Harvard University. To this date, this is the only total synthesis published.

In this synthesis, the problem of the possible diastereomers arising from atropisomerism was addressed very early on the route. For this purpose, the assembly of the protected versions of monomers 2.12 and 2.13 as single atropisomers was undertaken as the initial goal. As planned in accordance with Schmitz’ proposed biogenesis, the unification of enantiopure monomers was achieved by the intermolecular Diels-Alder reaction, followed by its transannular variant to complete construction of the polycyclic framework.

The synthetic strategy for protected versions of paracyclophanes 2.12 and 2.13 involved ene-yne metathesis macrocyclization reactions to generate the 1,3-disubstituted dienes of both paracyclophanes (Scheme 2.1). Such an important strategic decision was made knowing that this type of macrocyclization had not been reported. Moreover, it was unknown whether 1,2-disubstituted dienes or 1,3-disubstituted dienes would be generated since both pathways were possible.

In view of the established rule of the ene-yne metathesis reaction, such a process yields a 1,2-disubstituted diene in intramolecular variant and a 1,3-
Scheme 2.1. First successful synthesis of longithorone A.
disubstituted diene if applied bimolecularly. The critical assumption was made that the macrocyclization of compounds 2.14 and 2.15 would resemble *intermolecular* ene-yne metathesis and generate 1,3-disubstituted dienes since the resulting [12]-paracyclophanes would be less strained than the [11]-paracyclophanes obtained from 1,2-disubstituted diene formation. The experimental results successfully confirmed this hypothesis.

Advancing further into the synthetic approach, strategically positioned benzylic hydroxyl groups would be used to stall the aromatic rings of 2.14 and 2.15 during the ene-yne metathesis macrocyclizations in order to control the atropisomerism of 2.12 and 2.13 (Scheme 2.2). This should disfavor rotamers 2.16 and 2.17 due to the allylic strain and enforce diastereoselective

![Diagram of molecular structures](image)

*Scheme 2.2. Solution to atropisomers formation problem.*
cyclization. Having served their purpose as control elements in the cyclizations, the benzylic hydroxyl groups would be removed reductively, yielding the cyclophanes as single atropisomers.

To summarize, an enantioselective biomimetic synthesis of longithorone A has been accomplished. The syntheses of two [12]-paracyclophanes were realized by using the first examples of ene-yne metathesis macrocyclization to generate dienes having a 1,3-disubstitution pattern. In addition, this synthesis presents a unique example of chirality transfer in complex molecule synthesis involving the use of stereogenic centers to control atropisomerism, removal of the stereogenic centers, and transfer of the atropisomerism back to stereogenic centers in the natural product. Overall, this synthesis is probably the most elegant of all possibilities for this particular structural arrangement.
2.4. **Our Retrosynthetic Scheme.**

We recognized the synthetic challenge of longithorone A from the very first encounter. The assembly of its elaborate polycyclic structure would require a number of consecutive cyclization reactions, or the scrupulous development of an annulative cascade. In both cases, the ability of these methods to create stereogenic centers might not satisfy the requirement of molecular architecture of the target, making the stereochemical outcome highly questionable.

To overcome the obstacle of such an arrangement of structural features, we also considered the proposed biogenesis of this natural product. The projected transannular cycloaddition disclosed a very attractive alternative to the polycyclic structure assembly. In our retrosynthetic scheme, we decided to take advantage of this possible reaction as one of the final steps in the synthesis. Should this reaction proceed as planned, we would be able to construct a pentacyclic fragment of longithorone A with rings A through E set in place with the required absolute configuration (Scheme 2.3).

The major difference that distinguishes our approach from others is the attempt to develop the synthetic scheme with the possibility of adjustment for preparation of all the members of the longithorone family. As a result of further possible disconnections, we envisioned that structure **2.18** might serve as a common advanced intermediate for the synthesis of the natural products of the
Scheme 2.3. Global overview of retrosynthetic analysis.
longithorone family. Indeed, the presence of the substituted unsaturated cyclohexane prompted us to accommodate a Diels-Alder reaction in the synthesis and the stereochemical requirements compelled us to utilize its enantioselective version.\textsuperscript{69-71} In our planning, we separated the core of the natural product as structure \textbf{2.18}, which would serve as an immediate synthetic target. If we succeed in the preparation of structure \textbf{2.18}, we anticipated the fast assembly of the rest of the molecule of any stereochemical configuration leading to easy access of the entire family of this natural product.

To facilitate the initial Diels-Alder reaction, we also proposed to lock the diene and the dienophile fragments of the molecules into one structure.

\textit{Scheme 2.4. Retrosynthetic analysis of key intermediate \textbf{2.18}.}
Although prepared individually, the cycloaddition partners were planned to link together via either an ester group or a silyl tether. The utilization of aforementioned linking fragments in cycloaddition reactions have been widely described in the literature and we anticipated a very fast and uneventful conversion of the diene-dienophile combination to the corresponding cyclohexene.

We also realized that dienophile 2.19 can be easily prepared from butenediol in a short linear sequence where the disconnection of diene 2.20 (see Scheme 2.9) would release two structural fragments. We settled on the Stille coupling to play the role of the convergence point of the diene preparation. Further disconnections exposed the organometallic partner 2.21, which can be ultimately accessed from the 1,2-addition of propargylmagnesium bromide to methyl vinyl ketone followed by acid-catalyzed allylic rearrangement and hydrostannylation. As far as the electrophilic partner 2.22 is concerned, the choice of 4-bromo-4-pentenoic acid derivative prepared by alkylation of tert-butyl acetate with 2,3-dibromopropene fulfilled all structural requirements.

Despite being very attractive, this synthetic plan presented a number of uncertainties and, unfortunately, after numerous attempts the unfeasibility of the enantioselective cycloaddition became more and more evident. Whether it
was due to improper experimental execution or otherwise, we strongly believe in the general strategy of our approach. In the following section, the data acquired while pursuing this route is reported.
2.5. Attempted Construction of Cyclohexene Core of Longithorones.

In accordance with our retrosynthetic scheme, the immediate goal of the synthesis was the preparation of the properly functionalized diene and dienophile. As outlined above, the diene was prepared via Stille coupling\textsuperscript{77,78} which implied the reaction between a vinyl stannane \textit{2.21} and a vinyl halide \textit{2.22}. The preparation of the dienophile includes the attachment of the oxazolidinone-based chiral auxiliary,\textsuperscript{83} which would be utilized further for asymmetric induction in the Diels-Alder reaction. The synthetic advances toward both building blocks and their attempted unification are described in this section.

2.5.1. Preparation of Diene.

In the preparation of compound \textit{2.20}, we adopted the assembly of the 1,3-diene moiety \textit{via} a very well developed and accepted protocol of the coupling of vinyl stannane \textit{2.21} and vinyl halide \textit{2.22}. The quest for the vinyl stannane began with the preparation of 3-methylhex-1-en-5-yn-3-ol \textit{2.23} by an established protocol.\textsuperscript{79} In this reaction, propargylmagnesium bromide, prepared by treatment of 3-bromoprop-1-yn with magnesium and catalytic mercuric chloride, was added in 1,2-fashion to vinyl methyl ketone. The
resulting tertiary alcohol was subjected to acid-catalyzed allylic rearrangement. As a result of this reaction, a mixture of diastereomers \( \text{2.24} \) was obtained in a 4:1 ratio favoring the desired \( E \) configuration. Both isomers were clearly distinguishable in proton NMR spectra. The nOe was used to confirm the configuration of both isomers, first in mixture and then, individually, upon their availability after fractional distillation (\textit{vide infra}).

Noteworthy, the application of the described method\textsuperscript{84} under neutral conditions in boiling acetic anhydride as a solvent did not result in any conversion to product, prompting us to favor a stepwise mechanism rather than the concerted process proposed in the original publication.\textsuperscript{84}

In spite of the low stereoselectivity realized during trisubstituted olefin preparation, we were able to prepare compound \( \text{2.24.1} \) in multigram quantities and after careful optimization we were able to separate stereoisomers by vacuum distillation on the spinning band column. The olefin of interest was isolated as a clear oil and demonstrated reasonable stability under prolonged storage.
The availability of intermediate 2.24.1 in significant quantity made possible a shift of attention to the conversion of the alkyne functionality to vinyl stannane. This part of the molecule should complete the set of functional groups in the substrate needed for Stille coupling and would ultimately end up as a part of the cyclohexene ring of the target.

As a part of early studies, we realized that the conventional protocols\textsuperscript{81,85} of the installation of tributyltin group were absolutely ineffective towards our substrate probably due to the double bond already present in the molecule. All the attempted experiments produced a mixture of E/Z isomers with rather poor selectivity of the newly formed double bond together with a large fraction of unidentifiable side products. For instance, among those undertaken were the conditions of the addition of tributyltin hydride initiated thermally or radically by AIBN\textsuperscript{81,86} the addition of tin hydride mediated by a palladium\textsuperscript{85,86} or molybdenum\textsuperscript{85} catalysis, and others. The ultimate solution was found when an underutilized reaction was applied.\textsuperscript{87} Similar to the process described by Groh,\textsuperscript{88} we treated alkyne 2.24.1 with three equivalents of diisobutylaluminum hydride. As two hydrides were consumed for the acetate reduction, the third

\[ \text{Scheme 2.6. Hydroalumination reaction.} \]
was bound for the addition to the triple bond, resulting in preparation of vinyl allane. The nucleophilicity of the organoaluminum compound was sufficient for the transmetallation with tributylstannyl triflate or even chloride in THF, with three equivalents of HMPA as cosolvent. Although this reaction added more technical complexity to stannylation, the product was isolated in moderate yield and as a single stereoisomer.

An explanation of this remarkable stereoselectivity lies in the mechanistic representation of the aluminum hydride addition to the unsaturation in the molecule. In non-polar solvents, such as hexane or toluene, the addition occurs via a concerted process, much like the action of borane. This assumption, which was made based on the fact that both of these atoms (B and Al) are representatives of third main group of elements in the periodic table, successfully corroborated with numerous experimental facts. Whenever the coordinating solvent is introduced, the addition pattern can be changed, giving rise to the other isomers, which was not relevant in our case.

The resulting vinyl stannane 2.25 exhibited all the expected properties. For instance, in Sn NMR the signal at -40.9 ppm served to corroborate the presence of tributyltin group, and the fast reduction of elemental iodine in an NMR experiment revealed the formation of the E-configured vinyl iodide with a proton coupling constant of 15 Hz and a strong nOe.

In the next step, the hydroxyl group of allylic alcohol 2.25 was protected as the silyl ether via a standard protocol. The silyl ether 2.21 was isolated in
excellent yield. Thus, the organometallic partner for the Stille coupling was prepared in 5 steps with overall 17% yield (54% per step average).

In search of the proper electrophilic partner, we first scanned the literature for a potential precursor. As one of the possibilities, we thought about utilizing 5-hydroxy-2-pentanone with projected formation of the vinyl triflate. Around the time of the optimization of the triflate formation, my colleague, John Hofferberth, uncovered a very convenient procedure\textsuperscript{82} for the preparation of 4-bromopent-4-en-1-ol. Noticing the exact match of the required functionalities, we decided to join John in the pursuit of the preparation of the aforementioned compound. This known vinyl bromide \textbf{2.22} was available from inexpensive commercial starting materials in a single step by alkylation of the lithium enolate of \textit{tert}-butyl acetate with 2,3-dibromopropene. This very reliable procedure allowed the preparation of vinyl bromide \textbf{2.22} on large scale, enough to explore and optimize the forthcoming Stille coupling.

\textit{Scheme 2.7. Protection of allylic alcohol in \textbf{2.25}.}

\textit{Scheme 2.8. Synthesis of electrophile for Stille reaction.}
With the availability of 2.21 and 2.22, attention quickly turned to their palladium-catalyzed unification. Following consultation of numerous articles\textsuperscript{86} and reviews,\textsuperscript{78,90} we selected a list of palladium catalysts. In this list we had the more common catalysts, such as tetrakistriphenylphosphine palladium\textsuperscript{91} and triphenylphosphinepalladium dichloride,\textsuperscript{91} and some less common complexes.\textsuperscript{92} We also planned to test the solvent dependency, as well as the effect of ligands. In our list we included such solvents as THF, DMF, mixtures thereof and dioxane. The results of this optimization are presented in Table 2.1.

<table>
<thead>
<tr>
<th>catalyst (mol %) catalyst / additive or ligand</th>
<th>solvent / cosolvent</th>
<th>conditions °C time</th>
<th>isolated yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pd(Ph$_3$P)$_2$Cl$_2$ (5%)</td>
<td>DMF</td>
<td>60 18</td>
<td>15%</td>
</tr>
<tr>
<td>Pd(Ph$_3$P)$_2$Cl$_2$ (20%) / DIBAL-H</td>
<td>DMF</td>
<td>RT 10</td>
<td>trace</td>
</tr>
<tr>
<td>Pd(CH$_3$CN)$_2$Cl$_2$ (5%)</td>
<td>DMF</td>
<td>80 10</td>
<td>11%</td>
</tr>
<tr>
<td>Pd(CH$_3$CN)$_2$Cl$_2$ (5%) / CuI (10%)</td>
<td>DMF</td>
<td>80 10</td>
<td>10%/29%</td>
</tr>
<tr>
<td>Pd(CH$_3$CN)$_2$Cl$_2$ (5%) / (2-Fu)$_3$P (10%)</td>
<td>DMF</td>
<td>60 10</td>
<td>18%</td>
</tr>
<tr>
<td>Pd(CH$_3$CN)$_2$Cl$_2$ (5%) / Ph$_3$As (20%)</td>
<td>DMF/THF</td>
<td>RT 10</td>
<td>~30%</td>
</tr>
<tr>
<td>Pd(CH$_3$CN)$_2$Cl$_2$ (5%)</td>
<td>DMF/THF</td>
<td>65 10</td>
<td>40%</td>
</tr>
<tr>
<td>Pd(CH$_3$CN)$_2$Cl$_2$ (5%)</td>
<td>DMF/THF</td>
<td>RT 9</td>
<td>39% (75%)</td>
</tr>
</tbody>
</table>

*Table 2.1 Optimization of Stille Reaction.*
Ironically, the best coupling combination of catalyst, ligand and solvent was found unintentionally, when we stumbled across the publication by Williams,\textsuperscript{93} in which the application of “ligandless” conditions was reported. On our first thought, this suggestion was fruitless, since the conventional theory of the Stille coupling postulates that the presence of the strong ligand promotes faster conversion. When we tested these newly found conditions on our pair of the substrates, the difference was recognized immediately. Unlike the reaction with phosphine ligand, the coupling proceeded much faster, the reaction did not produce any byproducts and the workup was less involved. The diene molecule was obtained in 78\% yield. Short optimization resulted in a slightly higher outcome.

In summary, only the application of the “ligandless” conditions for the Stille reaction \textit{en route} to the diene molecule resulted in high conversion. During the preparation of the organometallic coupling partner, we discovered the expediency of the hydroalumination reaction of alkynes. As a consequence,
the vinyl stannane underwent exclusive conversion to the desired geometric isomer. In addition, the developed route was adopted for the preparation of the substrate in large quantity.

2.5.2. Preparation of Dienophile.

The positions of functional groups on our immediate target placed the consequent structural limitations on both participants of the cycloaddition. In particular for the dienophile, the functionalization of C4 was a must but limited to a non-electron withdrawing group due to the possible epimerization of the newly-formed stereocenter. On the other hand, this point of substitution was very important to us strategically, as the hydroxyl group placed in this position would provide us with a convenient functional handle to allow installation of the linkage between diene and dienophile.

In search of a convenient sequence to prepare the dienophile, we came across the publication of Deslongchamps and coworkers,\textsuperscript{94} where he described convenient oxidations of monoprotected Z-butenediols to aldehydes. Depending on the oxidant, it went either with retention of configuration (Swern) or otherwise. In our case, after

\[ \text{Scheme 2.10. PMB protection of 2-butene-1,4-diol.} \]
monoprotection of 2-butene-1,4-diol as a para-methoxybenzyl (PMB) ether under standard conditions of PMB chloride and sodium hydride, the resulting allylic alcohol 2.26 was oxidized with pyridinium chlorochromate in the presence of sodium acetate, which quantitatively converted the double bond configuration of the product from Z to E. The aldehyde was isolated in good yield as a clear oil with the characteristic signals of an α,β-unsaturated carbonyl compound. In fact, the proton NMR spectra matched that of similar compounds reported in the original source. Further oxidation proceeded uneventfully, and carboxylic acid 2.27 was isolated as a crystalline solid in 70% yield for two oxidative steps after treatment with buffered sodium chlorite solution in aqueous tert-butanol.

Advancement towards the enantioselective Diels-Alder reaction began with the process of selection of the chiral auxiliary. After an extensive literature search and long deliberation, we decided to apply the methodology developed by Evans, where the oxazolidinone-based chiral auxiliary was utilized. The attractive part of this methodology is the mild reaction conditions, generally

\[
\text{Scheme 2.11. Preparation of dienophile precursor 2.27.}
\]

![Scheme 2.11](image)

(70% for two steps)
high conversion, and wide availability of the precursors for the chiral auxiliary since all of them are derived from amino acids.

These considerations led us to the preparation of the two compounds **2.28.1** and **2.28.2**. In the synthesis of both, we utilized a mixed anhydride method\(^\text{96}\) for the oxazolidinone acylation, where substrate **2.27** was treated with pivaloyl chloride in the first step producing a highly active acylating agent. Both products were isolated in high yield and characterized accordingly.

To summarize, we prepared two acylated oxazolidinones **2.28** in high-yielding four-step sequences.

### 2.5.3. Attempted Cycloaddition Reactions.

As we were approaching the key transformation, the question of linking the diene and the dienophile became more and more critical. The decision was made to approach this step from two different perspectives. The first and the
most obvious was to connect the reactive pair via the ester linkage. The present carboxylic acid functionality on the back chain of the diene could be used for that. We envisioned that four methylene units should provide sufficient flexibility to the molecule to adopt the right conformation for the cycloaddition transition state. Being aware of the fact that the conformational change could be troublesome due to the high energy barrier of the ester group rotation, we also created a secondary plan involving utilization of a silyl tether. Not only would this ease the rotamer interchange, but also elongate the chain length for improved molecular dynamics. Notably, both approaches would ultimately lead us to the Type 2 intramolecular Diels-Alder (IMDA) reaction, yielding a caged structure.

The liberation of the carboxylic acid in 2.29 was not as straightforward as originally projected. Most of the conditions screened led to the complete decomposition of the starting material due to the strong acidity of the reagents. For example, treatment of the substrate with trifluoroacidic acid, the method extensively used in peptide synthesis to cleave tert-buty1 esters, disclosed itself as being too harsh for substrates such as 2.20. The application of Lewis acids (e.g. TiCl₄) led to the formation of uncharacterizable products as well. Finally, we landed very mild conditions,⁹⁷,⁹⁸ where treatment of the ester with trimethylsilyl triflate (TMSOTf) in the presence of base resulted in a switch with a particularly labile TMS group. Such an exchange allowed us to cleave the ester and prepare compound 2.29 in 91% yield.
Access to ester 2.30 was realized in the manner shown in Scheme 2.14. Dehydrative coupling of the allylic alcohol in 2.19 and the carboxylic acid in 2.29 was conducted under the conventional conditions of dicyclohexylcarbodiimide (DCC). The ester was isolated as an individual compound and exhibited all the properties related to its structural features. For instance, in carbon NMR the olefinic region signals indicated the presence of a total of four double bonds of different degrees of substitution.

Having compound 2.30 in hand, we proceeded to the key step of our synthetic plan, the enantioselective Diels-Alder reaction. With the employment

Scheme 2.13. Cleavage of tert-butyl ester in 2.20.

of the described conditions of Et$_2$AlCl, Me$_2$AlCl,$^{99}$ and other customized alkylaluminum-based Lewis acids, we realized that in all cases the cycloaddition product was to no avail. To probe the stoichiometric dependency, we increased the amount of Lewis acid. In most of the cases, the starting material was fully returned. The introduction of a more potent Lewis acid generally resulted in fast degradation of the material with no trace of product. We envisioned a rather highly strained transition state as the major factor contributing to the low activity. In addition to that, the electronic nature of the ester group could also contribute to the increased free energy of the desirable transition state.$^{100,101}$ In the attempt to eliminate this conclusion, we also elevated the temperature of the reaction and heated the substrate in toluene at 160 °C in a sealed tube. Regretfully, none of these alterations produced any cycloaddition.

In light of such developments, we realized that the exclusion of ester linkage as well as the elongation of the connecting fragment could significantly improve our chances for the reaction to occur. This adjustment would provide

![Scheme 2.15. Installation of silyl tether.](image-url)
a great increase in conformational flexibility to the molecule and potentially lead to strain relief in the transition state. For this purpose, we pictured linking the reactive pair \textit{via} a silyl tether as a next step in our investigation.

Following some preliminary experimentation, we prepared 2.32 by a somewhat modified synthetic scheme. The dienophile 2.19 was introduced to substitute one of the chlorines of \textit{i}Pr$_2$SiCl$_2$, followed by the treatment with an excess of 4-bromopent-4-en-1-ol (prepared by reducing ester 2.22 with lithium aluminum hydride) to achieve the desired linkage. As a result, this reaction yielded 67\% of compound 2.31 under optimized conditions. A subsequent Stille coupling gave the substrate 2.32 ready to be tested in the cycloaddition reaction.

Our numerous efforts to obtain a cycloaddition product of 2.32 were not successful either. In the majority of the attempts, only starting material was recovered. In some cases a product was obtained, which was modified by the applied Lewis acid in some other way\textsuperscript{102} than that desired.
2.6. Conclusion.

To recapitulate, our attempts to implement a planned synthesis of longithorone A was terminated at the step of cyclohexene core formation. In the process of our investigation, we successfully completed the synthesis of the proper partners for the Diels-Alder cycloaddition. The diene was prepared by merging of the vinyl stannane with vinyl bromide on the palladium catalyst, and the dienophile was produced in a very effective four-step sequence. Both compounds were linked by two different means to be tested in cycloaddition conditions.

We strongly believe that our strategy did not lose its attractiveness. As other disconnection possibilities exist, we always have the ability to modify the scheme in the way of keeping the same immediate target structure, but changing the tactical approach to the key transformation itself. Such vision would certainly define this project as a challenging and thought-provoking for the synthetic chemist of any level, experienced or not.
2.7. Experimental Section.\textsuperscript{103}

\((2E,5E)-3\text{-methyl-6-(tributylstannyl)-2,5-hexadien-1-ol (2.25)}:\)

\begin{center}
\begin{tikzpicture}
\node at (0,0) {Bu$_3$Sn\,-\,OH};
\end{tikzpicture}
\end{center}

To the solution of DIBAL-H (69.0 mL at 1.0 M in hexane, 69.0 mmol), 3.35 g (22.0 mmol) of \((E)-3\text{-methyl-2-hexen-5-ynyl acetate 2.24.1}\) was added dropwise with stirring at 0 °C under argon. The mixture was stirred for 15 min at 0 °C, warmed up to ambient temperature and heated at reflux for 4 h. After being cooled to ambient temperature, the solvent was carefully evaporated in inert atmosphere and the residue was dried in vacuum to remove any traces of hexane. The resulting colorless oil of the crude vinyl alane was redissolved in 20 mL of THF and 15.0 mL (88.0 mmol, 4 equivalents) of HMPA was added followed by addition of 15.0 mL (17.9 g, 55.0 mmol) of freshly distilled tributyltin chloride with stirring at ambient temperature under argon. The mixture was stirred at 40 °C for 15 h, quenched with semisaturated aqueous solution of Rochelle salt and extracted with 3x150 mL of ethyl acetate. Combined organic portions were washed with CuSO$_4$ solution, brine and dried over Na$_2$SO$_4$. The solvent was evaporated leaving a yellow oil of the crude product which was purified by flash chromatography on silica gel (gradient elution with hexane to 7:1 hexane/ethyl acetate) to give 4.24 g (47\%) of \((2E,5E)-3\text{-methyl-6-(tributylstannyl)-2,5-hexadien-1-ol}\) as a yellow oil; \textit{IR} (neat, cm$^{-1}$): 3340, 2944, 2867, 1594, 1464, 1377, 1072, 994, 874; \textit{\textsuperscript{1}H NMR} (300 MHz, CDCl$_3$): $\delta$ = 6.10-5.75 (m, 2H), 5.44

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(tq, \( J = 3.1; 6.9 \text{ Hz}, 1\text{H} \)), 4.16 (d, \( J = 6.9 \text{ Hz}, 2\text{H} \)), 2.84 (d, \( J = 4.7 \text{ Hz}, 2\text{H} \)), 1.66 (s, 3\text{H}), 1.60-1.45 (m, 6\text{H}), 1.37-1.22 (m, 6\text{H}), 1.00-0.75 (m, 15\text{H}); \(^{13}\text{C NMR (75 MHz, CDCl}_3\)): \( \delta = 145.5, 138.9, 129.2, 124.7, 59.2, 40.6, 29.1 \) (3\text{C}), 27.2 (3\text{C}), 23.6, 13.7 (3\text{C}), 9.4 (3\text{C}); HRMS (ES): \( m/z \) calcd for \( \text{C}_{19}\text{H}_{38}\text{OSn•H} (\text{M+H})^+ 403.2023; \) obsd 403.2016.

**(1E,4E)-1-(Tributylstannyl)-4-methyl-6-[[[dimethyl)ethyl]dimethylsilyl]oxy]-1,4-hexadiene (2.21):**

To the solution of 3.10 g (7.73 mmol) of (2\text{E},5\text{E})-3-methyl-6-(tributylstannyl)-2,5-hexadien-1-ol in 10 mL of DMF, 1.32 g (19.3 mmol) of imidazole was added followed by 1.46 g (9.66 mmol) of tert-butyldimethylsilyl chloride. The mixture was stirred for 1 h at ambient temperature, quenched with water and extracted with 3x100 mL of hexane/ether (1:1). Combined extracts were washed with brine and dried over \( \text{Na}_2\text{SO}_4 \). The solvent was evaporated and the residue was purified by flash chromatography on silica gel (gradient elution with hexane to 2.5% ethyl acetate in hexane) to yield 3.81 g (95%) of (1\text{E},4\text{E})-4-methyl-1-tributylstannyl-6-[[[dimethyl)ethyl]dimethylsilyl]oxy]hexa-1,4-diene as a colorless oil; IR (neat, \( \text{cm}^{-1} \)): 2954, 1717,1608, 1513, 1464, 1249, 1077, 1039, 876; \(^{1}\text{H NMR (300 MHz, CDCl}_3\)): \( \delta = 6.10-5.75 \) (m, 2\text{H}), 5.30 (tq, \( J = 3.1; 6.9 \text{ Hz}, 1\text{H} \)), 4.06 (d, \( J = 6.9 \text{ Hz}, 2\text{H} \)), 2.84 (d, \( J = 4.7 \text{ Hz}, 2\text{H} \)), 1.66 (s, 3\text{H}), 1.60-1.45 (m, 6\text{H}), 1.37-1.22 (m, 6\text{H}), 1.00-0.75 (m, 15\text{H}), 0.95 (s, 9\text{H}), 0.09 (s, 6\text{H}); \(^{13}\text{C NMR (75 MHz, CDCl}_3\)): \( \delta = 144.9, 138.9, 129.2, 125.9, 59.2, 40.6, 29.1 \) (3\text{C}), 27.2 (3\text{C}), 23.6, 13.7 (3\text{C}), 9.4 (3\text{C}); HRMS (ES): \( m/z \) calcd for \( \text{C}_{19}\text{H}_{38}\text{OSn•H} (\text{M+H})^+ 403.2023; \) obsd 403.2016.
CDCl$_3$): $\delta = 145.5, 138.9, 129.2, 124.7, 60.0, 40.6, 29.1$ (3C), 27.2 (3C), 26.0 (3C), 23.6, 18.5, 13.7 (3C), 9.4 (3C), -5.0 (2C); HRMS (EI): $m/z$ calcd for C$_{25}$H$_{52}$OSiSn (M)$^+$ 516.2809; obsd 516.2805.

**tert-Butyl (5E,8E)-8-methyl-4-methylene-10-[[[(dimethyl)ethyl]dimethyl-silyl]-oxy-5,8-decadienoate (2.20):**

This reaction was carried out in light protected glassware. To the solution of 99 mg (0.19 mmol) of vinyl stannane and 68 mg (0.29 mmol) of vinyl bromide in 2 mL CH$_2$Cl$_2$, 10 mg (0.009 mmol, 5 mol%) of Pd$_2$dba$_3$ was added in one portion at ambient temperature under argon. The mixture was stirred at ambient temperature for 17 h under argon atmosphere. The mixture was filtered through the pad of silica gel, the solvent was evaporated and the residue was chromatographed on silica gel (gradient elution with hexane to 3% ethyl acetate in hexane) to give 57 mg (78%) of compound 2.20 as yellow oil; IR (neat, cm$^{-1}$): 2953, 1781, 1668, 1351, 1098, 822; $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 6.08$ (d, $J = 15.8$ Hz, 2H), 5.69 (dt, $J = 7.0, 15.8$ Hz, 1H), 5.35 (tq, $J = 3.1, 6.3$ Hz, 1H), 4.91 (d, $J = 12.7$ Hz, 1H), 4.20 (d, $J = 6.3$ Hz, 2H), 2.77 (d, $J = 7.0$ Hz, 2H), 2.55-2.37 (m, 4H), 1.62 (s, 3H), 1.45 (s, 9H), 0.90 (s, 9H), 0.07 (s, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta = 172.6, 144.7, 135.6, 133.3, 127.6, 125.6, 113.9, 80.2, 60.3, 42.9, 34.3, 28.1, 27.4$ (3C), 26.0 (3C), 18.4, 16.4, -5.0 (2C); HRMS (El): $m/z$ calcd for C$_{22}$H$_{40}$O$_3$Si (M)$^+$ 380.2747; obsd 380.2740.
(5E,8E)-8-Methyl-4-methylene-10-[[[dimethyl]ethyl]dimethylsilyl]-oxy-5,8-decadienoic acid (2.29):

To the solution of 96 mg (0.25 mmol) of ester 2.20 in 2.5 mL of THF, 0.118 mL (1.01 mmol, 4 equivalents) of 2,6-lutidine was added followed by 0.151 mL (0.757 mmol, 3 equivalents) of TMSOTf. The mixture was stirred for 1 h at ambient temperature under argon atmosphere, quenched with aqueous HCl solution (pH=4-5) and extracted with 3x100 mL of ethyl acetate. Combined extracts were washed with brine, dried over Na$_2$SO$_4$ and concentrated. The product was purified by flash chromatography on silica gel (elution with 3:1 hexane/ethyl acetate) to yield 75 mg (91%) of (5E,8E)-8-methyl-4-methylene-10-[[[dimethyl]ethyl]dimethyl-silyl]oxy-5,8-decadienoic acid as a colorless oil; IR (neat, cm$^{-1}$): 2970, 1690, 1650, 1344, 1198, 1099, 830; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 6.08 (d, $J$ = 15.8 Hz, 2H), 5.69 (dt, $J$ = 7.0; 15.8 Hz, 1H), 5.35 (tq, $J$ = 3.1; 6.3 Hz, 1H), 4.91 (d, $J$ = 12.7 Hz, 1H), 4.20 (d, $J$ = 6.3 Hz, 2H), 2.77 (d, $J$ = 7.0 Hz, 2H), 2.55 (s, 4H), 1.62 (s, 3H), 0.90 (s, 9H), 0.07 (s, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 179.3, 144.1, 135.5, 133.0, 127.8, 125.6, 114.3, 60.3, 42.8, 32.9, 27.0, 26.0 (3C), 18.4, 16.4, -5.1 (2C); HRMS (EI): $m/z$ calcd for C$_{18}$H$_{32}$O$_3$Si (M)$^+$ 324.2121; obsd 324.2117.
(E)-4-(4-Methoxybenzyloxy)-2-butenoic acid (2.27):

A 1L three-necked round-bottomed flask was fitted with mechanical stirrer and charged with the solution of 20.00 g (0.096 mol) of monoprotected alcohol 2.26 in 250 mL of CH$_2$Cl$_2$. Anhydrous NaOAc (23.62 g, 0.288 mol) was added followed by 40 g of 4 Å powdered molecular sieves. This mixture was cooled to 0 °C and 31.05 g (0.144 mol) of pyridinium chlorochromate (PCC) was added portionwise via Gouche tubing with vigorous stirring at 0 °C. The mixture was stirred overnight at ambient temperature and filtered through a pad of Celite and silica gel subsequently. The mixture was concentrated to yield 17.92 g (90%) of a crude aldehyde as yellow oil. Without further purification, the aldehyde (0.087 mol) was dissolved in 700 mL of tBuOH and 250 mL of 2-methyl-2-butene was added. To this mixture, a solution of NaClO$_2$ (47.15 g, 75% wt grade, 0.391 mol) and NaH$_2$PO$_4$ (40 g) in 400 mL of water was added dropwise with stirring at ambient temperature. The mixture was stirred overnight, diluted with brine, the additional solid NaCl was added until no longer soluble and extracted with 5x200 mL of ethyl acetate. Combined extracts were washed with brine and dried over MgSO$_4$. The solvent was evaporated leaving off-white solid of crude product, which was purified by recrystallization (hexane) to give 15.02 g (70%) of an acid as white crystals; mp 88-89 °C; IR (neat, cm$^{-1}$): 3422, 2838, 1686, 1657, 1517, 1312, 1253, 1030, 936; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 7.28 (d, $J$ = 8.0 Hz, 2H), 7.11 (dt, $J$ = 15.5, 4.5 Hz, 1H), 6.93 (d, $J$ = 8.0 Hz, 2H), 6.15 (dt, $J$ =
15.5, 2.5 Hz, 1H), 4.53 (s, 2H), 4.17 (m, 2H), 3.80 (s, 3H); 13C NMR (75 MHz, CDCl₃): δ = 171.3, 159.3, 147.2, 129.7, 129.3 (2C), 120.4, 113.9 (1C), 72.6, 68.2, 55.3; HRMS (El): m/z calcd for C₁₂H₁₄O₄ (M)+ 222.0892; obsd 222.0903.

Anal. Calcd for C₁₂H₁₄O₄: C, 64.85; H, 6.35. Found: C, 64.62; H, 6.33.

**General Procedure for Acylation of Oxazolidinone.** To the solution of 0.821 g (3.70 mmol) of acid 2.27 in 5 mL of THF, 0.502 mL (4.07 mmol) of pivaloyl chloride was added slowly via syringe at –20 °C with stirring under nitrogen, followed by addition in the same manner of 1.56 mL (11.1 mmol) of triethylamine. The mixture was stirred for 2 h and oxazolidinone (0.655 g, 3.70 mmol) was added along with 0.235 g (5.55 mmol) of LiCl. The mixture was stirred for 15 h at ambient temperature, diluted with 100 mL of ethyl acetate, washed with 50 mL of water and 50 mL of brine and dried over Na₂SO₄. The solvent was evaporated leaving a dark oil of the crude product, which was purified by flash chromatography on silica gel (gradient elution with 3:1 to 2:1 hexane/ethyl acetate).

For **(E)-4-(4-methoxybenzyloxy)-1-[(4R,5S)-4-methyl-2-oxo-5-phenyl-1,3-oxazolan-3-yl]-2-buten-1-one or (4R,5S)-3-[4-(4-Methoxybenzyloxy)-(E)-but-2-enoyl]-4-methyl-5-phenyl-oxazolidin-2-one (2.28.1):** 980 mg (70%) of the product as a very viscous oil; IR (neat, cm⁻¹): 2980, 2932, 1780, 1684, 1631, 1429, 1350, 1252, 1156, 890, 847; 1H NMR (300 MHz, CDCl₃): δ = 7.52 (dt, J =
15.5, 1.9 Hz, 1H), 7.46-7.29 (m, 7H), 7.16 (dt, J = 15.5, 4.5 Hz, 1H), 6.90 (d, J = 8.7 Hz, 2H), 5.69 (d, J = 6.8 Hz, 1H), 4.82 (p, J = 6.8 Hz, 1H), 4.53 (s, 2H), 4.23 (dd, J = 4.5, 1.9 Hz, 2H), 3.81 (s, 3H), 0.94 (d, J = 6.8 Hz, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta = 164.5, 157.9, 154.3, 152.0, 146.4, 129.4 \,(2C), 128.8, 128.7 \,(2C), 125.7 \,(2C), 120.7, 113.9 \,(2C), 99.8, 79.1, 72.5, 68.7, 55.3, 55.0, 14.6; \) HRMS (El): \(m/z\) calcd for C\(_{22}\)H\(_{23}\)NO\(_5\) (M)\(^+\) 381.1576; obsd 381.1585; \([\alpha]\)\(^{22}\)D +56.8 (c 1.59, CHCl\(_3\)).

*Anal.* Calcd for C\(_{22}\)H\(_{23}\)NO\(_5\): C, 69.28; H, 6.08. Found: C, 69.52; H, 6.07.

For *(E)-1-(4R)-4-benzyl-2-oxo-1,3-oxazolan-3-yl)-4-(4-methoxybenzylkoxy)-2-buten-1-one or (4R)-4-Benzyl-3-[4-(4-methoxybenzylkoxy)-(E)-but-2-enoyl]-oxazolidin-2-one (2.28.2): 645 mg (85%) of the product as a very viscous oil; IR (neat, cm\(^{-1}\)): 3031, 1778, 1683, 1514, 1355, 1249, 1210, 1104, 1031; \(^{1}\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 7.52 \,(dt, J = 15.5, 1.9 Hz, 1H), 7.36-7.15 \,(m, 8H), 6.90 \,(d, J = 8.7 Hz, 2H), 4.74 \,(m, 1H), 4.53 \,(s, 2H), 4.23 \,(m, 2H), 4.19 \,(d, J = 4.5 Hz, 2H), 3.81 \,(s, 3H), 3.35 \,(dd, J = 13.4, 3.3 Hz, 1H), 2.81 \,(dd, J = 13.4, 9.5 Hz, 1H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta = 164.4, 159.3, 155.5, 150.0, 146.5, 135.3, 130.1, 129.4 \,(2C), 129.0 \,(2C), 128.3, 127.3 \,(2C), 120.6, 113.9 \,(2C), 72.5, 68.7, 66.2, 55.3, 37.9; \) HRMS (El): \(m/z\) calcd for C\(_{22}\)H\(_{23}\)NO\(_5\) (M)\(^+\) 381.1576; obsd 381.1544; \([\alpha]\)\(^{19}\)D -43.9 (c 0.76, CHCl\(_3\)).

*Anal.* Calcd for C\(_{22}\)H\(_{23}\)NO\(_5\): C, 69.28; H, 6.08. Found: C, 69.14; H, 6.01.
**General Procedure for para-Methoxybenzyl Ether Cleavage.** To the solution of 2.28.1 (0.836 g, 2.19 mmol) in 5 mL of CH$_2$Cl$_2$ and 0.3 mL of H$_2$O, 0.697 g (3.07 mmol) of DDQ was added in one portion at ambient temperature. The mixture was stirred for 2 h and diluted with 100 mL of CH$_2$Cl$_2$, washed with 10% aq. NaHCO$_3$ (3x50 mL) and brine, and dried over Na$_2$SO$_4$. The mixture was concentrated and the product was purified by flash chromatography on silica gel (gradient elution with 3:1 to 1:1 hexane/ethyl acetate).

For (E)-4-Hydroxy-1-[(4R,5S)-4-methyl-2-oxo-5-phenyl-1,3-oxazolan-3-yl]-2-buten-1-one or (4R,5S)-3-(4-Hydroxy-(E)-but-2-enoyl)-4-methyl-5-phenyl-oxazolidin-2-one (2.22.1): 0.455 g (80%) of deprotected alcohol as a white solid; mp 98 °C; IR (neat, cm$^{-1}$): 3423, 1778, 1682, 1640, 1352, 1198, 1048; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 7.52-7.30 (m, 6H), 7.23 (dt, $J = 15.5$, 4.5 Hz, 1H), 5.71 (d, $J = 6.9$ Hz, 1H), 4.84 (p, $J = 6.9$ Hz, 1H), 4.44 (dd, $J = 4.5$, 1.9 Hz, 2H), 2.39 (br s, 1H), 0.95 (d, $J = 6.6$ Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 164.6, 153.1, 149.0, 133.3, 128.7 (2C), 128.7, 125.7 (2C), 119.3, 79.1, 62.2, 55.0, 14.5; HRMS (EI): $m/z$ calcd for C$_{14}$H$_{15}$NO$_4$ (M)$^+$ 261.1001; obsd 261.0981; $[\alpha]_{D}^{19}$ +43.3 (c 2.61, CHCl$_3$).

*Anal.* Calcd for C$_{14}$H$_{15}$NO$_4$: C, 64.36; H, 5.79. Found: C, 64.20; H, 5.87.

For (E)-1-[(4R)-4-Benzyl-2-oxo-1,3-oxazolan-3-yl]-4-hydroxy-2-buten-1-one or (4R)-4-Benzyl-3-(4-hydroxy-(E)-but-2-enoyl)-oxazolidin-2-one (2.22.2): 0.560 g (92%) of title compound as a white solid; mp 93-94 °C; IR (neat, cm$^{-1}$):
3437, 1772, 1668, 1642, 1355, 1211, 1098; ¹H NMR (300 MHz, CDCl₃): δ = 7.48 (dt, J = 15.5, 1.9 Hz, 1H), 7.37-7.21 (m, 6H), 4.78-4.70 (m, 1H), 4.44 (dd, J = 3.9, 2.0 Hz, 2H), 4.26-4.16 (m, 2H), 3.33 (dd, J = 13.4; 3.2 Hz, 1H), 2.81 (dd, J = 13.4; 9.5 Hz, 1H), 1.95 (br s, 1H); ¹³C NMR (75 MHz, CDCl₃): δ = 164.8, 149.0, 135.2, 131.2, 129.4 (2C), 129.0 (2C), 127.3, 119.2, 66.2, 62.3, 55.3, 38.0; HRMS (EI): m/z calcd for C₁₄H₁₅NO₄ (M)⁺ 261.1001; obsd 261.1003; [α]D²⁰ -48.8 (c 0.48, CHCl₃).

Anal. Calcd for C₁₄H₁₅NO₄: C, 64.36; H, 5.79. Found: C, 64.36; H, 5.85.

General Procedure for Diene-Dienophile Linking via Ester Group. To the solution of 30 mg (0.093 mmol) of decadienoic acid 2.29 in 1 mL of CH₂Cl₂, 24 mg (0.093 mmol) of (E)-1-[(4R)-4-benzyl-2-oxo-1,3-oxazolan-3-yl]-4-hydroxy-2-buten-1-one 2.19.2 was added at 0 °C followed by 23 mg (0.11 mmol) of dicyclohexylcarbodiimide and 1.1 mg (0.009 mmol, 10 mol%) of 4-DMAP. This mixture was stirred at 0 °C for 30 min, at ambient temperature for 2 h, diluted with brine and extracted with 3×50 mL of ethyl acetate. Combined extracts were washed with brine and dried over MgSO₄. The solvent was evaporated and the residue was purified by flash chromatography on silica gel (elution with 2:1 hexane/ethyl acetate).

For (E)-4-[(4R,5S)-4-Methyl-2-oxo-5-phenyl-1,3-oxazolan-3-yl]-4-oxo-2-butenyl (5E,8E)-8-methyl-4-methylene-10-[[dimethyl]ethyl]dimethyl-
**silyl]oxy-5,8-decadienoate (2.30.1):** 39 mg (73%) of an ester as a colorless oil; IR (neat, cm⁻¹): 2957, 2926, 2870, 1782, 1684, 1611, 1514, 1352, 1250, 1198, 1120, 1032; ¹H NMR (300 MHz, CDCl₃): δ = 7.51-7.29 (series of m, 6H), 7.11 (dt, J = 15.6, 4.6 Hz, 1H), 6.07 (d, J = 15.6 Hz, 2H), 5.76-5.66 (m, 3H), 5.40-5.33 (m, 1H), 4.94 (d, J = 12.1 Hz, 2H), 4.86-4.77 (m, 2H), 4.20 (d, J = 6.3 Hz, 2H), 2.78 (d, J = 7.0 Hz, 2H), 2.59 (s, 3H), 1.62 (s, 3H), 0.93 (d, J = 6.6 Hz, 3H), 0.90 (s, 9H), 0.07 (s, 6H); ¹³C NMR (75 MHz, CDCl₃): δ = 172.5, 164.0, 152.8, 144.2, 143.0, 135.5, 133.2, 133.0, 128.8, 128.7 (2C), 127.8, 125.64 (2C), 125.59, 121.2, 114.3, 79.1, 62.9, 60.3, 54.9, 42.9, 32.9, 27.1, 26.0 (3C), 18.4, 16.4, 14.5, -5.1 (2C); HRMS (EI): m/z calcd for C₃₂H₄₅NO₆Si (M)⁺ 567.3016; obsd 567.3019; [α]D² +28.2 (c 0.79, CHCl₃).

For **(E)-4-[[4R]-4-Benzyl-2-oxo-1,3-oxazolan-3-yl]-4-oxo-2-butenyl-(5E,8E)-8-methyl-4-methylene-10-[[[dimethyl]ethyl]dimethyl-silyl]oxy-5,8-decadienoate (2.30.2):** 553 mg (69%) of an ester as colorless oil; IR (neat, cm⁻¹): 2958, 2930, 2867, 2850, 1778, 1686, 1621, 1512, 1367, 1251, 1120, 932; ¹H NMR (300 MHz, CDCl₃): δ = 7.47 (dt, J = 15.6, 1.7 Hz, 1H), 7.38-7.20 (m, 5H), 7.15 (dt, J = 15.6, 4.6 Hz, 1H), 6.35 (ddd, J = 14.9, 11.2, 1.2 Hz, 1H), 6.13-5.95 (m, 2H), 5.77-5.49 (m, 1H), 5.39-5.29 (m, 1H), 4.84 (dd, J = 4.6, 1.8 Hz, 2H), 4.78-4.68 (m, 1H), 4.23-4.15 (m, 5H), 3.34 (dd, J = 13.5, 3.4 Hz, 1H), 2.82-2.72 (m, 2H), 2.55-2.41 (m, 4H), 1.61 (d, J = 4.6 Hz, 3H), 0.90 (s, 9H), 0.07 (s, 6H); ¹³C NMR (75 MHz, CDCl₃): δ = 172.7, 164.4, 148.6, 144.1, 142.6, 135.5, 131.0, 133.0, 128.9, 128.9 (2C), 128.6 (2C), 127.4, 125.5, 120.0, 114.4, 66.1,
General Procedure for Diene-Dienophile Linking via Silyl Tether. To the solution of 0.138 mL (0.765 mmol) of \( \text{I}^3 \text{Pr}_2\text{SiCl}_2 \) in 0.7 mL of dry THF, a solution of 0.182 g (0.695 mmol) of \((E)-1-[(4R)-4-benzyl-2-oxo-1,3-oxazolan-3-yl]-4-hydroxy-2-buten-1-one \ 2.19.2\), 0.107 mL (0.765 mmol) of Et\(_3\)N and 0.010 mL (0.070 mmol) of DBU in 1 mL of dry THF were added at ambient temperature during 30 min under an inert atmosphere. This mixture was stirred at ambient temperature for 3 h and at 40 ºC for 4 h. The mixture was cooled to ambient temperature and a solution of 0.172 mg (1.04 mmol) of 4-bromo-4-penten-1-ol and 0.195 mL (1.39 mmol) of Et\(_3\)N in 1.4 mL of dry THF was added in one portion. This mixture was stirred at ambient temperature for 3 h, quenched with saturated NaHCO\(_3\) solution and diluted with CH\(_2\)Cl\(_2\). The organic portion was washed with brine and dried over Na\(_2\)SO\(_4\). The solvent was evaporated and the residue was purified by flash chromatography on silica gel (elution with 4:1 hexane/ethyl acetate).

For \((E)-[\{(4R)-4-benzyl-2-oxo-1,3-oxazolan-3-yl]-2-buten-4-one\}-1-oxy-(4-bromo-4-pentenyl-1-oxy)-diisopropylsilane \ 2.31.2\): 0.148 g (40%) of compound \(2.31.2\) as a colorless oil; IR (neat, cm\(^{-1}\)): 2955, 2926, 2857, 1782,
1684, 1611, 1514, 1351, 1032, 767; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 7.61 (dt, $J$ = 15.0, 1.9 Hz, 1H), 7.40-7.20 (m, 6H), 5.59 (d, $J$ = 1.2 Hz, 1H), 5.40 (d, $J$ = 1.2 Hz, 1H), 4.74 (m, 1H), 4.52 (m, 2H), 4.20 (m, 2H), 3.60 (t, $J$ = 6.2 Hz, 2H), 3.35 (dd, $J$ = 13.5, 3.5 Hz, 1H), 2.80 (dd, $J$ = 13.5, 9.0 Hz, 1H), 2.55 (t, $J$ = 6.2 Hz, 2H), 1.80 (m, 2H), 1.08 (m, 14H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 164.9, 153.2, 149.2, 135.3, 134.1, 129.4 (2C), 128.9 (2C), 127.3, 118.7, 116.7, 66.0, 62.2, 61.3, 55.3, 37.8, 37.7, 30.9, 17.3 (4C), 12.0 (2C); HRMS (ES): $m/z$ calcld for C$_{25}$H$_{36}$BrNO$_5$Si•Na (M+Na)$^+$ 560.1444; obsd 560.1461; $[\alpha]_{D}^{20}$ -13.5 (c 0.13, CHCl$_3$).

**General Procedure of Stille Coupling of Silyl Tethered Fragment.** This reaction was carried out in light protected glassware. To a solution of 56 mg (0.11 mmol) of vinyl stannane 2.21 and 56 mg (0.10 mmol) of vinyl bromide 2.32.1 in 1.5 mL CH$_2$Cl$_2$, 10 mg (0.01 mmol, 5 mol %) of Pd$_2$dba$_3$ was added in one portion and stirred at ambient temperature for 20 h under argon atmosphere. The mixture was filtered through a pad of silica gel, the solvent was evaporated, and the residue was chromatographed on silica gel (elution with 7:1 hexane/ethyl acetate).

For (E)-[[((4R)-4-benzyl-2-oxo-1,3-oxazolan-3-yl)-2-buten-4-one]-1-oxy-\((5E,8E)-8\text{-methyl-4-methylene-10-}[[\text{dimethyl}\text{ethyl}]\text{dimethylsilyl}]\text{-oxy-5,8-}$$^\text{68}$
**decadien-1-oxydiisopropylsilane (2.32.2):** 17 mg (24%) of compound as colorless oil. Unreacted vinyl bromide 2.31.2 was recovered, giving a yield of 67% based on recovered starting material; IR (neat, cm⁻¹): 2956, 2926, 1780, 1685, 1611, 1514, 1456, 1351, 1031; ¹H NMR (300 MHz, CDCl₃): δ = 7.61 (dt, J = 15.0, 1.9 Hz, 1H), 7.40-7.20 (m, 6H), 6.08 (d, J = 15.8 Hz, 1H), 5.68 (dt, J = 15.8, 7.0 Hz, 1H), 5.34 (tq, J = 6.3, 3.1 Hz, 1H), 4.95 (s, 1H), 4.93 (s, 1H), 4.74 (m, 1H), 4.52 (m, 4H), 4.20 (m, 2H), 3.60 (t, J = 6.2 Hz, 2H), 3.35 (dd, J = 13.5, 3.5 Hz, 1H), 2.80 (dd, J = 13.5, 9.0 Hz, 3H), 2.27 (t, J = 6.2 Hz, 2H), 1.80 (m, 2H), 1.63 (s, 3H), 1.08 (m, 14H), 0.95 (s, 9H), 0.09 (s, 6H); ¹³C NMR (75 MHz, CDCl₃): δ = 165.0, 149.4, 145.7, 135.4, 133.6, 129.4 (2C), 128.9 (2C), 127.5, 127.3, 125.4, 118.7, 113.9, 84.8, 66.0, 62.6, 62.2, 60.3, 55.3, 45.1, 37.9, 31.3, 28.3, 26.0 (3C), 25.7, 18.4, 17.3 (4C), 16.4, 12.1 (2C), -5.1 (2C); HRMS (ES): m/z calcd for C₃₈H₆₁NO₆Si₂•Na (M+Na)⁺ 706.3935; obsd 706.3957; [α]D0 ⁰ -17.0 (c 0.09, CHCl₃).
CHAPTER 3.
AFRICANE FAMILY OF SESQUITERPENES.

3.1. Introduction.

The current view of the field of sesquiterpene syntheses serves as an excellent testing ground for new preparative methods. Among the variety of natural products of this sub-type, africanol \textbf{3.1} has attracted considerable attention as a consequence of its elaborate tricyclic structure that features five contiguous stereocenters and three different ring sizes. This alcohol was first isolated\textsuperscript{104,105} from the soft coral \textit{Lemnalia africana} and later discovered\textsuperscript{106,107} along with isoaficanol \textbf{3.2} in the ascomycete fungus \textit{Leptographium lundbergii}. Structurally, it also serves as the prototype of the africane group of natural products that presently also includes $\Delta^{9(15)}$-aficanene\textsuperscript{108,109} \textbf{3.3}, africano\textsuperscript{110} \textbf{3.4}, and 8$\beta$-angeloyloxysenoxyr-4-en-3-one\textsuperscript{110} \textbf{3.5} (Figure 3.2).

\textit{Figure 3.1. Structure of africanol.}
These metabolites are assumed to be derived biosynthetically from humulene, which in its CT conformation undergoes initial acid-catalyzed closure to the 9-africanyl cation (Scheme 3.1). The subsequent proton loss followed by hydration provides access to the natural product. The outlined mechanistic proposal prompted researchers to approach this natural product from the biomimetic direction. Such a synthesis, where the Lewis acid-

![Chemical structures](image)

**Scheme 3.1.** Proposed biosynthesis of africanol and biomimetic approach.

**Figure 3.2.** Natural products of africane group.
catalyzed transannular cyclization of humulene-9,10-epoxide 3.8 played the central role, was designed and successfully implemented by Matsumoto and coworkers.111 Subsequent to that, the later approaches to this attractive target have been based on suitable applications of the Claisen113 and anionic oxy-Cope114 rearrangements, oxymercuriation chemistry,115 and intramolecular cyclization reactions.116,117 These protocols have also provided access to the africanol isomers 3.9-3.11.

Despite significant accomplishments in the area of africanol synthesis, all of these synthetic entries are quite lengthy and proceed with rather low overall yield. In this chapter, we outline our most recent approach to this natural product, which ultimately resulted in an unprecedentedly short and efficient enantiospecific assembly of an africane group sesquiterpene that is based on the novel and very powerful synthetic tool described as zirconocene-mediated ring contraction reaction118 of vinyl glycosides.
3.2. **Background and Significance of Zirconocene-Mediated Ring Contraction of Vinyl Furanosides and Pyranosides.**

In recent organic chemistry, the development of new synthetic methodologies brought by organozirconium compounds provides a variety of possibilities for the efficient preparation of a multitude of organic molecules. In particular, the discovery by Negishi’s group that the highly reactive complex 3.12 can be readily generated *in situ* by simply warming a solution of Cp₂Zr("Bu)₂ in toluene or THF has greatly facilitated access to this useful zirconium reagent, now known commonly as "Cp₂Zr".¹¹⁹,¹²⁰ One of the properties of zirconocene prototype 3.12 is its ability to actively participate in ligand exchange with unsaturated compounds. If the substrate is an allylic ether, the high oxophilicity of the zirconium atom center subsequently reveals...
itself via β-elimination of the alkoxy group as in intermediate 3.13 with formation of the allylzirconocene 3.14.\textsuperscript{121}

The Taguchi group has demonstrated in a clever extrapolation of this process that carbohydrates containing a terminal double bond represented by structure 3.15 (notice the similarity to allylic ether) are transformed cleanly and efficiently upon treatment with “Cp₂Zr” and boron trifluoride etherate into stereochemically pure vinyl cyclopentanols 3.16.\textsuperscript{122,123} As a consequence of diastereofacial discrimination the vinyl and hydroxyl centers in the products are consistently cis disposed. The more complete stereoselectivity profile is apparently dictated by nonbonded steric interactions.

For the purpose of an unambiguous understanding of the stereochemical bias of this remarkable rearrangement, we turned our attention to the currently accepted mechanism, originally proposed and investigated by Taguchi and coworkers.\textsuperscript{122} Ligand exchange reaction of “Cp₂Zr” with original 5-vinyl pyranoside followed by β-elimination of the alkoxy group gave Z-allylic zirconacyclic intermediate 3.17, which played a vital role in the process of the mechanism discovery. The structural features of this intermediate were comprehensively studied by proton NMR, revealing the Z-oriented double bond
with the appropriate coupling constants for olefinic protons (10.3 Hz) and nOe.

The addition of boron trifluoride etherate promoted the decomposition of this hemiacetal-zirconate \(3.17\) to the oxocarbenium ion \(3.18\), which simultaneously cyclized intramolecularly through a chair-form transition state to give the product. Upon examination of two possible transition states \(3.18.1\) and \(3.18.2\), the prospect of stereochemical preference became apparent due to the occurrence of severe steric repulsion between the cyclopentadienyl ligand
of zirconocene and benzyloxy substituents residing on the C3 and C4 atoms of the carbohydrate skeleton. Thus, the reaction proceeds via the less sterically hindered transition state 3.18.1 to give product 3.16. According to this mechanistic assumption, removal of the C4 substituent can supposedly drastically downgrade the stereochemical outcome of this rearrangement.

The capacity of this process to convert 4-vinyl furanosides to vinyl cyclobutanols as in the example in Scheme 3.5 became a similar concern to us, since this transformation could be as practical in the stereoselective construction of highly substituted cyclobutanols.

**Scheme 3.5.** Example of furanoside ring contraction.
The attractiveness associated with the conversion of readily available carbohydrates into heavily substituted enantiopure carbocycles has been recognized. However, the application of this new chemistry in tandem with other novel transformations in order to arrive expeditiously at complex targets has not yet been explored. In search of a possible contribution to this area, we decided to deploy the synthetic scheme whose realization could fill the gap in this zirconocene-related chemistry.
3.3. Africanols in view of Ring Contraction Reaction.

The structural inclination of the africane sesquiterpenes toward disassembly, where the aforementioned ring-contraction reaction is used, became obvious when we separated the cyclopentane ring from the rest of the structure. With two substituents vicinally positioned to the hydroxyl group, the carbohydrate precursor emerged in an instant. The only question that remained is what type of pyranose would be preferred to conduct the synthesis. Naturally, we decided to adopt a carbohydrate of gluco configuration due to its high natural occurrence. In view of the projected ring contraction reaction, the remaining disconnections in the molecule became quite obvious. We envisioned

**Scheme 3.6. Disassembly of africanol in view of ring-contraction reaction.**
that the rest of the molecule could be built around this newly-formed five-membered carbocycle.

We decided to focus on the preparation of an unknown stereoisomer of africanol defined in absolute configurational terms as 3.21. Therefore, the original and only retrosynthetic scheme became available as follows. The installation of the cyclopropane ring would be left as a concluding step of the synthesis. In our planning, we would utilize a hydroxyl-directed Simmons-Smith cyclopropanation. This disconnection would conveniently position

\[ \text{Scheme 3.7. Retrosynthetic analysis of epiafricanol.} \]

the olefinic functionality in the seven-membered cycle as illustrated in 3.22 for the next disconnection. Recognizing the superiority of the ring-closing metathesis reaction for medium size ring formation, we visualized the
application of this method to close the cycloheptane ring of the africanol framework. In order to prepare the substrate 3.23 for this step we would need to extend the second olefinic unit with a proper substitution pattern. This could be accomplished by stereocontrolled 1,2-addition of an organometallic reagent to the ketone derived from cyclopentanol 3.19 after oxidation. As a consequence, a cyclopentanol of proper configuration would represent the desired product of the ring contraction reaction of modified methyl glycoside 3.20 (vide supra).

Ultimately, this approach holds considerable flexibility due to the plentiful availability of different carbohydrate starting materials. In consequence of such configurational variation, the possibility of covering the entire group of africane natural products is an advantage of the employed synthetic scheme.
3.4. **Synthesis of Epiafricanol.**

One of the great advantages of the current scheme is the large variety of accessible pyranosidic contenders in enantiopure form. Some are widely occurring in nature and therefore inexpensive, others may be higher in price but synthetically obtainable. Recognizing that the rich knowledge base of carbohydrate transformations would allow synthesis of the glycoside in any configurational mean, we decided to start our synthetic route with the most available carbohydrate, namely glucose.

For a better illustration of the logic of this synthesis, it will be described in three distinctive parts: carbohydrate ring modification, carbohydrate ring extension, and final cyclization and synthesis completion. In addition to that, the ring contraction reaction as a part of the synthesis will be described separately.

3.4.1. *Carbohydrate Ring Modification.*

This work was initiated by the undergraduate researcher Jacques-Alexis Funel, whose advances went as far as deoxygenated pyranoside 3.31. Although we eventually found a more efficient route, credit should be attributed for his
contribution and the multigram quantities of some useful intermediates such as compound \textbf{3.25} he produced, enough to successfully conclude this project.

As an ultimate goal of this part of the synthesis, we would need to perform an exchange of the C2 hydroxyl to a methyl group of opposite configuration as well as to deoxygenate the C3 and C4 positions of the pyranosidic framework. The employment of this sequence required protection of C4 and C6 by forming the 4,6-O-benzylidene derivative. This transformation was achieved by treatment of commercially available methyl \(\alpha\)-D-glucopyranoside with benzaldehyde using standard conditions.\textsuperscript{127} Protected pyranoside \textbf{3.24} was isolated as a crystalline solid and treated under ditosylation conditions,\textsuperscript{128} followed by a quite remarkable cyclization to an epoxide \textbf{3.25}, which was initiated by a solution of MeONa in methanol.\textsuperscript{127,129} Although these two transformations are extensively illustrated in the literature,\textsuperscript{130} we encountered several problems with their reliability. For instance, in the ditosylation step the formation of a monoester was dominating in the majority of the methods we tested. Usually, such a mixture was of no use to us due to tremendous difficulty in resolving mono- and ditosylate apart. Finally, we landed a rather uncommon protocol, where glucopyranoside acetal \textbf{3.24} was treated with tosyl chloride and mixture of

\[ \text{HO} \quad \text{HO} \quad \text{OH} \quad \text{OMe} \quad \text{PhCHO} \rightarrow \text{Ph} \quad \text{O} \quad \text{HO} \quad \text{OH} \quad \text{OMe} \]

\textbf{3.24}

\textbf{Scheme 3.8. Formation of 4,6-O-benzylidene acetal.}
bases (NaOH and $\text{K}_2\text{CO}_3$) in dichloromethane as a solvent. The subsequent step of the epoxide formation was also attempted under a variety of conditions. Eventually the method of slow crystallization of the product from cold dichloromethane solution of ditosylate in the presence of MeONa provided the best outcome. Utilizing these two preparations, we were able to obtain multigram quantities of epoxypyranoside 3.25 as a stable crystalline solid with all the spectral data matching that published earlier.

As a next step, we considered trans-diaxial opening of the oxirane ring with a higher-order methyl cuprate reagent with the intention of C2 deoxygenation and installation of methyl in place of the hydroxy group. After a broad literature search, we landed an excellent protocol perfected by Weiler and coworkers.

Upon treatment of compound 3.25 with MeLi in the presence of

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**Scheme 3.9. Preparation of epoxypyranoside 3.25.**

**Scheme 3.10. Epoxide opening with high order cuprate reagent.**
CuCN in ether we were able to recover altropyranoside 3.26 in good yield with all the properties as described. This crystalline solid was easy to handle and purify, which again allowed us to run this step on multigram quantities.

At this stage of the synthesis, we were facing the challenge of subsequent deoxygenation. For this purpose, the no longer needed benzylidene acetal was removed under acidic conditions, and the primary alcohol in 3.27 was selectively protected with the bulky triphenylmethyl group by treating the triol with triphenylmethyl chloride and triethylamine with catalytic 4-(N, N-dimethylamino)pyridine (DMAP) in DMF. This strategy, which was extensively probed by Jacques-Alexis, allowed us to set the stage for the deoxygenation sequence. Here we turned our attention to a very convenient protocol developed by Tipson and Cohen specifically for the removal of hydroxyls in pyranosides. As a result, vicinal diol 3.28.1 was treated with methanesulfonyl chloride in pyridine in the presence of catalytic DMAP, and the crude dimesylate so obtained was treated with activated zinc dust and sodium iodide in hot DMF. The formation of the product was confirmed by proton
NMR, where the olefinic signals were observed roughly at 5.8 and 5.7 ppm. Although this method was far superior to the classical Barton deoxygenation,\textsuperscript{135} its very sterically demanding nature\textsuperscript{136} did not allow the generation of the expected yields of the unsaturated product \textbf{3.29.1}. Nevertheless, with necessary optimization in mind we proceeded to the next step.

![Scheme 3.12. Tipson-Cohen reaction of trityl ether 3.28.1.](image)

The feasibility of trityl deprotection \textit{via} hydrogenolysis\textsuperscript{137} would have made it possible to unite two synthetic operations in one step. We anticipated that the unsaturation present in the molecule and the protecting group could be easily removed under heterogeneous catalytic hydrogenation. The broad screening of catalytic combinations\textsuperscript{138} resulted in successful saturation, but quite unexpectedly, the problem of the deprotection of the triphenylmethyl group was not trivial. According to several literature precedents, such a

![Scheme 3.13. Hydrogenation-deprotection sequence for trityl ether 3.29.1.](image)
transformation could be accomplished with catalytic hydrogenation with palladium on activated carbon,\textsuperscript{139} acidic hydrolysis\textsuperscript{140} or under the treatment of some Lewis acids, such as SnCl\textsubscript{2},\textsuperscript{141} Et\textsubscript{2}AlCl\textsuperscript{142} or ZnBr\textsubscript{2}.\textsuperscript{143} Unfortunately, the application of each of the aforementioned methods to our system 3.29.1 resulted in total recovery of the starting material. For instance, the triphenylmethyl group remained in place after stirring with several equivalents of palladium on charcoal at 1 atm of hydrogen, and even after prolonged treatment with W-4 Raney Ni at 80 psi of hydrogen. Eventually, we found that the only possible way to remove the trityl group was via dissolving metal reduction,\textsuperscript{144} which did not fit into our anticipated pathway. In order to circumvent this problem, we decided to replace this protecting group with a silyl analogue which was easily removable.

This brought us back to the benzylidene acetal deprotection step, which again was rather low yielding most likely due to either the high solubility of the product in water or competitive hydrolysis of the methyl acetal. The protection step was uneventful and the diol was isolated in good yield after reacting triol 3.27 with tert-butyldiphenylsilyl chloride (DPSCI) and triethylamine with

$$\begin{align*}
\text{HO} & \quad \text{O} \\
\text{H}_3\text{C} & \quad \text{O} \\
\text{OH} & \quad \text{OMe} \\
\text{H}_3\text{C} & \quad \text{O} \\
\text{OH} & \quad \text{OMe}
\end{align*}$$

$$\text{HO} \quad \text{O}$$

$$\begin{align*}
\text{H}_3\text{C} & \quad \text{O} \\
\text{OH} & \quad \text{OMe} \\
\text{H}_3\text{C} & \quad \text{O} \\
\text{OH} & \quad \text{OMe}
\end{align*}$$

\text{DPSO}$$

\text{DPSO}$$

$$\text{H}_3\text{C} \quad \text{O}$$

$$\begin{align*}
\text{HO} & \quad \text{O} \\
\text{H}_3\text{C} & \quad \text{O} \\
\text{OH} & \quad \text{OMe} \\
\text{H}_3\text{C} & \quad \text{O} \\
\text{OH} & \quad \text{OMe}
\end{align*}$$

\text{DPSO}$$

\text{DPSO}$$

$$\text{H}_3\text{C} \quad \text{O}$$

\text{DPSCI, EtN, DMAP, DMF, 140 °C}

\text{MsCl, py, DMAP}

\text{Zn (dust), NaI, DMF, 140 °C}

\text{Scheme 3.14. Utilization of tert-butyldiphenylsilyl (DPS) protecting group.}
catalytic DMAP in DMF. The deoxygenation step yet again demonstrated its requirement of the uncongested approach of the reagents in order to obtain the high yield of the deoxygenated product. Thus prepared and isolated, olefin 3.29.2 exhibited similar spectra to the previously obtained compound 3.29.1. The application of similar conditions gave hydrogenated product 3.30.2 again with the similarity of the spectral data to the previously prepared compound 3.30.1. The silyl ether was cleaved under the standard conditions of tetrabutylammonium fluoride in THF. This modified pyranoside was identical to the previously prepared compound and was isolated in slightly improved yield compared to the earlier developed scheme (19% for 6 steps compared to 16%).

With successful preparation of compound 3.31 we have concluded the carbohydrate skeleton modification part of the synthesis. As we were ready to move forward, a number of disadvantages of the current scheme made us seek alternatives. First of all, the benzylidene acetal hydrolysis step was the major flaw in the current scheme. In the short optimization process, we were unable
to come up with an acceptable procedure and reliable yield. The second and quite significant drawback was the utilization of very large (both molecular weights are over 250) and expensive (in case of DPS) protecting groups. In addition, the extra protection-deprotection step for the development of the short synthesis was not an attractive attribute. The only solution centered on capitalizing on the existing protection and keeping it at C6 for further use. That idea sent us back to the drawing board and, as a result, the following scheme materialized.

We decided to perform the reductive opening of the 4,6-acetal in 3.26 to install a benzyl protecting group at the position needed. Not only would this immediately save us one step, but also it would hopefully allow hydrogenation and deprotection as one synthetic operation to be performed later in the synthesis.

![Scheme 3.16. Failure of acetal reductive opening.](image)

We commenced the search for the proper reduction conditions scanning all the classical protocols first. To our great surprise the combination of triethylsilane and trifluoroacetic acid (TFA) was well suited to the objective of selective reductive cleavage. This method was far superior to the classical sodium cyanoborohydride procedure, developed by Garegg and Hultberg, as well as other metal hydride reductions. The benzyl ether 3.28.3 was isolated in good yield (70%) as a colorless oil and clearly indicated the absence of the
acetal proton in the $^1$H NMR spectrum. The availability of intermediate 3.28.3 made possible generation of the dimesylate and reductive removal of the vicinal methanesulfonate ester groups with zinc and sodium iodide in hot DMF similar to the previously applied Tipson-Cohen protocol. \(^{134}\) The resulting olefin 3.29.3 was obtained in much higher yield (95% vs. 69%), which confirmed the original hypothesis of the high sterically demanding transition state for this type of deoxygenation reactions. \(^{136}\) Clearly, the benzyl protecting group is the smallest among all the groups applied and is the most suitable for the purpose of maximizing the overall yield in this step. As an excellent illustration of the efficiency of this new route, we performed hydrogenolysis and saturation of the double bond simultaneously. Unlike the analogous compounds 3.29.1 and 3.29.2, which required an elevated pressure of hydrogen for the hydrogenation step, the pyranoside 3.29.3 reacted at just 1 atm of hydrogen pressure and provided an almost quantitative yield of product. Thus the modified carbohydrate 3.31 demonstrated spectra identical to that previously obtained.

Scheme 3.17. Reductive opening of benzylidene acetal and deoxygenative olefination
To summarize, we successfully prepared modified pyranoside 3.31 from commercially available methyl α-D-glucopyranoside. During optimization, the synthetic scheme was shortened from 10 to 8 steps and the overall yield was improved from 7.8% to 27% (average yield of 81% per step).

3.4.2. Carbohydrate Ring Extension.

As we were rapidly approaching the key transformation of the carbohydrate ring contraction, the question of installing the olefinic moiety became more and more vital. Initial experimentation, which was mostly conducted by projectmate Sergei Bolshakov, demonstrated the unusual sensitivity and high volatility of the intermediates along the way to the olefin. To avoid taking a big risk, we decided to apply a conventional four-step sequence in order to set up the required isopropylene fragment. Oxidation of
primary alcohol 3.31 with Dess-Martin periodinane\textsuperscript{153} gave the extremely sensitive aldehyde with no evidence of epimerization. This step required considerable effort of optimization. The necessity of a neutral condition was observed very early in optimization; however, when conventional buffered Dess-Martin periodinane conditions were applied, the degradation of the product was noted at about midpoint of total conversion. No matter how the reaction variables were changed (temperature, solvents, periodinane equivalents, buffers, etc.) the product would start to degrade with substantial amounts of the starting material still present in the reaction mixture. Although these compounds were easily separable by column chromatography, we were hoping to exercise this as a very last option in fear of lowering the total yield due to the extreme volatility of these compounds.

The solution to this problem was found accidentally when we studied the literature for similar compounds. Potter and coworkers briefly described the observation of this quite strange behavior of C6 pyranosidoaldehydes in his synthesis of carbocyclic analogues of D-\textit{myo}-inositol triphosphate, which he thought contributed to hydration of the carbonyl group.\textsuperscript{123} Keeping this

\[\text{Scheme 3.19. Installation of olefinic moiety.}\]
obstacle in mind, we conducted the same Dess-Martin oxidation buffered with NaHCO₃, but in the presence of freshly baked powdered molecular sieves. The result was completely different! Full conversion to aldehyde occurred in about one hour and the product could be kept under the reaction conditions for a prolonged period of time without a trace of degradation. A specifically designed non-aqueous workup procedure (vide infra) afforded crude aldehyde 3.34 as a volatile oil. With no further purification, it was introduced to the next step, which was accomplished without difficulty by treating the aldehyde with an excess of methylmagnesium bromide in ether to furnish the product in 84% for two synthetic operations (see Scheme 3.18). As expected, the resulting alcohol 3.32 was found to be a single diastereomer. This compound was isolated chromatographically and exhibited typical spectral data for the secondary alcohol. For instance, the carbinol proton positioned at 3.58 ppm demonstrated a quintet with coupling constants of 6.4 Hz, which corresponded to its neighboring environment in expected product. As we moved closer to the olefin, alcohol 3.32 was subjected to Dess-Martin oxidation under unbuffered conditions, which afforded methyl ketone 3.33 in 80% without any

Scheme 3.20. Hypothetic equilibrium of C6 pyranosidoaldehyde 3.34.
configurational complications (see Scheme 3.18). Bearing structural similarities to the troubled aldehyde 3.34, the compound 3.33 did not show signs of stability problems. As a precaution, the same workup was applied, after which the volatile ketone was isolated by bulb-to-bulb distillation. As a final step in the skeleton extension, ketone 3.33 was subjected to Wittig olefination with methylenetriphenylphosphorane. The unsaturated product was isolated in 81% yield with the help of distillation and validated by all the spectroscopic methods. As an illustration, two broad multiplets with minor splitting on allylic neighboring protons could be seen in the olefinic region of proton NMR (approximately 5.0 ppm and 4.8 ppm), which confirmed the presence of an exo-positioned double bond.

In conclusion, we successfully finished the installation of the olefinic moiety onto the modified carbohydrate skeleton in four steps obtaining the desired compound 3.20 in 54% overall yield for this sequence. The preparation of this compound leads us to the key step of the synthesis: zirconocene-mediated ring contraction.

Scheme 3.21. Installation of olefinic moiety (contd).
3.4.3. **Ring Contraction Reaction.**

Our next task was to introduce our completely deoxygenated unsaturated glycoside into the zirconocene-mediated ring contraction reaction. The structural elements of this molecule raised a number of questions about its reactivity. First and foremost, would the effect of the C2 methyl group create enough free energy difference between the transition states to result in good stereoselectivity. Also, would the isopropylene group be a good coordinating ligand to react with zirconocene and how would the disubstituted double bond behave in this interaction. Since none of these structural features were present in previously attempted reactions, all these concerns needed to be addressed.

To our great surprise, the experimental confirmation of the anticipated ring contraction was immediately realized when substrate 3.20 was treated with “Cp₂Zr”, prepared *in situ* from Cp₂ZrCl₂ in toluene at -78 °C. Upon warming the reaction mixture to ambient temperature, the disappearance of the starting material was evident. The introduction of boron trifluoride etherate at 0 °C and acidic workup completed the reaction with quantitative conversion.

**Scheme 3.22. Preparation of cyclopentanol 3.19.**
This critical step afforded cyclopentanol 3.19 in 63% yield together with 14% of a chromatographically separable diastereomer that was not investigated further.\textsuperscript{155}

The stereochemical assignment to the major diastereomer was done based on the vicinal coupling constants between the carbinol proton and the two neighboring CH groups. We evaluated two newly formed stereocenters (C1

\textbf{Figure 3.6.} \textsuperscript{1}H NMR spectra of compound 3.19 and its diastereomeric relative (see text).
and C2, carbocyclic numbering) relative to the stereocenter of the known configuration at C5. In the proton NMR of cyclopentanol 3.19, the signal of the carbinol hydrogen was represented as a triplet. The proton NMR spectrum of the diastereomeric partner of 3.19 exhibited the same proton as a doublet of doublets (see Figure 3.6). The appearance of a triplet corresponds to having both vicinal hydrogens of very similar magnetic properties. In the case of a cyclopentanol the only possible way to have two neighboring CH groups of the same magnetic nature is when the dihedral angles between the coupled pairs are nearly equal. If we study the conformational dynamics of cyclopentanol 3.19, the only possible arrangement of the substituents to fulfill these obligations is syn,syn, where both dihedral angles are equal to a value of approximately 60°. In addition, the corresponding coupling constant according to the vicinal Karplus correlation156 should have a value of 2-4 Hz, which matches our experimentally obtained results.

In search of a clear understanding of the stereochemical outcome of this reaction, appeal to the established mechanistic representation122 for this reaction is a must. As exemplified in Scheme 3.22, the initial ligand exchange should occur uneventfully. The extra substituent on the double bond would most likely slow down the rate of exchange as a consequence of the steric factors. Meanwhile, the electronic factors would favor such exchange due to the increase of electron density on the alkyl-substituted double bond. Finally, if that is not sufficient, the elevated temperature and high electrophilicity of the
zirconium atom in the reactive intermediate should make this retardation unnoticeable if not to compensate it entirely. Upon treatment of the hemiacetal-zirconate 3.35 with boron trifluoride etherate, we would arrive at two possible transition states, where one of them would be less favorable than the other. Closer inspection of structure 3.36.2 reveals the occurrence of 1,3
steric interactions of the pseudo-axial C2 methyl group (carbohydrate numbering). Since in the alternative transition state this methyl is positioned pseudo-equatorial, the free energy of 3.36.1 must be lower leading to the formation of cis,cis product. As compared with the product structure in Scheme 3.21, this hypothesis is completely in agreement with experimentally obtained results.

To summarize the subsection, this remarkably fast success demonstrated that there is absolutely no effect of the substituent positioned at the coordinating double bond of the substrate on the reaction outcome. As we pioneered such structural element in the conditions of ring contraction reaction, cis,cis-2-isopropenyl-5-methylcyclopentanol 3.19 was prepared in 63% yield and high stereoselectivity.

3.4.4. Final Cyclizations of the Synthesis.

With cyclopentanol 3.19 available in significant quantity, we turned our attention to the preparation of the side chain. This part of the molecule should complete the set of olefins for the ring-closing metathesis reaction and would ultimately end up as a part of the cycloheptane ring of the target sesquiterpene. As a part of early studies, we realized that the corresponding alkyl bromide was absolutely inert towards any type of metal-halogen exchange due to its neo-
pentylic nature. All the attempted experiments produced either homocoupling of two alkyl radicals or a complete recovery of the starting material. Among those undertaken were the conditions with highly activate finely-dispersed reduced\textsuperscript{158} or sublimed\textsuperscript{159-161} magnesium metal, the protocol with magnesium entrainment,\textsuperscript{162,163} and other activation methods,\textsuperscript{164} including sonication.\textsuperscript{165} The preparation of the lithio derivative of the aforementioned alkyl bromide via either action of metal\textsuperscript{166} or tert-butyllithium was also unsuccessful. After all the options were exhausted, we recognized that the substitution of the bromide to the more active iodide might solve the problem. Indeed, this compound was at last reactive under conditions of tert-butyllithium in non-polar hydrocarbon solvent at -50 °C. Thus, 4,4-dimethyl-5-iodopent-1-ene was obtained in three described steps in multigram quantities.\textsuperscript{167-169}

Before the conversion of secondary alcohol \textbf{3.19} to the corresponding ketone could be pursued, we made an effort towards the investigation of its thermodynamic stability. For this purpose, we compared three possible isomeric products. The first was the targeted cyclopentanone having a cis-2,5-substitution pattern \textbf{3.37.1}. The second structure was its trans counterpart

\begin{center}
\textbf{Scheme 3.24.} Synthesis of 4,4-dimethyl-5-iodopent-1-ene.
\end{center}

\begin{center}
Reagents and conditions: (a) CH₂=CHCH₂OH, p-TsOH, \(p\)-cymene, reflux; 80\%. (b) NaBH\(_4\), EtOH; 97\%. (c) Ph\(_3\)P, I\(_2\), benzene, reflux; 60\%.
\end{center}
3.37.2, presumably the more stable isomer. The third was the conjugated isomer 3.37.3, the product of migration of the $\beta,\gamma$-double bond into a conveniently conjugated $\alpha,\beta$-position (Figure 3.7). All these compounds were either products or suspected byproducts of the oxidation. Careful correlation of their thermodynamic stability would be helpful in choosing the reaction conditions. Moreover, if the energetic profiles of these isomers are very different, the conditions of this oxidation reaction will become crucial for the ultimate success of the synthesis. The results of the MM3-based calculations\textsuperscript{170} corroborated our initial hypothesis regarding the stability of these isomeric cyclopentanones. Thus, the cis-2,5-disubstituted isomer was the least

![Chemical structures](image)

**Figure 3.7.** Thermodynamic stability of cis,cis-2-isopropenyl-5-methylcyclopentanone and its isomers.
thermodynamically preferred ($E_{\text{steric}} = 24.4$ kcal/mol). Surprisingly, its trans-counterpart was only 0.6 kcal/mol higher in stability ($E_{\text{steric}} = 23.8$ kcal/mol). And as expected, the conjugated isomer represented the energetic minimum among all of them ($E_{\text{steric}} = 21.5$ kcal/mol).

Being positioned in thermodynamically unfavorable circumstances, we did not encounter the potential complications related to these phenomena when the Dess-Martin periodinane oxidant, in the presence of sodium bicarbonate as a neutralizing agent, was applied. Furthermore, the lithio derivative of 4,4-dimethyl-5-iodopent-1-ene could be added directly to the newly formed ketone without the occurrence of extensive enolization. The desired 1,2-addition was sterically controlled as expected, furnishing 3.23, the stereochemical features of which were supported by NOESY studies.

With arrival at the ring-closing metathesis precursor, we realized that our target molecule was only two steps away. Fortunately for us, the rest of the synthesis was completely uneventful.

\textit{Scheme 3.25. Arrival to ring-closing metathesis precursor 3.23.}
Cyclization of structure 3.23 with the Grubbs ruthenium catalyst\textsuperscript{2,9} by ring-closing metathesis (RCM) protocol led to the bicyclic intermediate 3.22 in excellent 93% yield after only 90 min at ambient temperature in CH\textsubscript{2}Cl\textsubscript{2} as solvent. The formation of polymeric byproducts was avoided by using high dilution. The reaction was conducted at less than 5 mM substrate concentration. The identity of the \textsuperscript{1}H and \textsuperscript{13}C NMR spectra of the bicyclic olefin (+)-3.22 prepared in this manner with that of the known racemate\textsuperscript{114} served to confirm our stereochemical assignments. As a final synthetic operation of the synthesis, the hydroxyl-directed Simmons-Smith cyclopropanation\textsuperscript{125,126} of 3.22 produced the target molecule 3.21 almost as efficient (87%), when performed with diethylzinc and diiodomethane in CH\textsubscript{2}Cl\textsubscript{2}. The proton and \textsuperscript{13}C-carbon NMR spectra of compound (+)-3.21, which was named epiafricanol, bear close similarities to those of 3.1\textsuperscript{104} and 3.2,\textsuperscript{106} but have features that are specifically characteristic of this dextrorotatory end product.


Scheme 3.27. Simmons-Smith cyclopropanation.
3.5. Conclusion.

In conclusion, we successfully implemented the synthetic plan to prepare an unknown isomer of africanol, defined in absolute configurational terms as structure 3.21 and named (+)-epiafricanol. The key operations of this synthesis were the zirconocene-promoted ring contraction of isopropenyl pyranoside to cyclopentanol, followed by the attachment of the proper side chain, which made possible efficient cyclization to form the unsaturated seven-membered ring. This approach holds considerable flexibility in that different carbohydrate starting materials are plentifully available and a great variety of unsaturated pendant groups may be introduced.

Figure 3.8. Structure of (+)-epiafricanol.
3.6. Experimental Section.

Methyl 2-Deoxy-2-C-methyl-α-D-altropyranoside (3.27):

A solution of compound 3.26 (10.0 g, 35.7 mmol) in mixture of 100 mL of absolute ethanol, 100 mL of acetic acid and 150 mL of water was stirred at 55 °C for 3 h. The reaction mixture was concentrated and remaining acetic acid and water were azeotropically removed with toluene. The residue was recrystallized from ethyl acetate to yield 3.36 g (50%) of pure triol 3.27 as white crystals; mp 125-127 °C; IR (neat, cm⁻¹): 2926, 1058; ¹H NMR (300 MHz, CDCl₃): δ = 4.54 (s, 1H), 3.96-3.44 (m, 8H), 3.40 (s, 3H), 2.34-2.29 (m, 1H), 1.04 (d, J=7.5 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ = 102.6, 72.0, 68.8, 64.3, 63.0, 55.3, 38.8, 14.3; HRMS (ES): m/z calcd for C₈H₁₆O₅•Na (M+Na)^+ 215.0895, obsd 215.0884; [α]D⁰ +118.5 (c 0.56, CHCl₃).


Methyl 6-O-(Triphenyl)methyl-2-deoxy-2-C-methyl-α-D-altropyranoside (3.28.1):

A solution of triol 3.27 (3.00 g, 15.6 mmol), triethylamine (3.3 mL, 23.4 mmol, 1.5 equivalents), DMAP (191 mg, 2.34 mmol, 10 mol%) and triphenylmethyl chloride (4.80 g, 17.2 mmol, 1.1 equivalents) in DMF (78 mL) was stirred for 25 h at 55 °C under
nitrogen. The resulting solution was poured into a mixture of ice-water and dichloromethane mixture and acidified with hydrochloric acid solution to pH 4-5. The aqueous layer was extracted with 3x300 mL of dichloromethane and the combined extracts were washed with brine, water and dried over MgSO₄. The solvent was evaporated and the residue was purified by flash chromatography on silica gel (elution with 2:1 hexane/ethyl acetate) to afford 5.47 g (81%) of trityl ether **3.28.1** as a white solid; mp 169-170 °C; IR (cm⁻¹): 3484, 2926, 1490, 1448, 1219, 1062, 761, 708, 632; ¹H NMR (300 MHz, CDCl₃): δ = 7.54-7.51 (m, 5H), 7.47-7.22 (m, 10H), 4.59 (s, 1H), 3.76-3.73 (m, 2H), 3.71 (dd, J = 2.6, 8.1 Hz, 1H), 3.64-3.52 (m, 2H), 3.47 (s, 3H); 3.45-3.38 (m, 1H), 2.55 (d, J = 9.8 Hz, 1H), 2.35-2.28 (m, 1H), 1.08 (d, J = 7.5 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ = 144.1 (3C), 128.8 (6C), 127.7 (6C), 126.9 (3C), 102.5, 86.7, 72.2, 68.6, 64.3, 55.1, 38.8, 14.4; HRMS (ES): m/z calcd for C₂₇H₃₀O₅•Na (M+Na)+ 457.1991, obsd 457.1949; [α]²₃° + 53.2 (c 0.52, CHCl₃).


**Methyl 6-O-(tert-Butyldiphenyl)silyl-2-deoxy-2-C-methyl-α-D-altropyranoside (3.28.2):**

To a solution of triol **3.27** (1.00 g, 5.20 mmol) and imidazole (1.00 g, 15.6 mmol, 3 equivalents) in DMF (35 mL) was added DPSC1 (1.5 mL, 5.72 mmol, 1.1 equivalents). The mixture was stirred for 24 h at 55 °C under nitrogen, cooled to ambient
temperature and quenched with sodium bicarbonate. The mixture was extracted with ether (3x50 mL). The combined organic extracts were washed with brine and dried over MgSO$_4$. The mixture was concentrated to leave yellow oil, which was purified by column chromatography on silica gel (elution with ether) to afford 1.94 g (87%) of silyl ether 3.28.2 as a clear oil; IR (cm$^{-1}$): 3446, 2910, 1632, 1496, 1454, 1058, 736, 698; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 7.79-7.76 (m, 5H), 7.47-7.37 (m, 5H), 4.57 (s, 1H), 4.04 (dd, $J$ = 2.6, 11 Hz, 1H), 3.98 (dd, $J$ = 4.7, 11 Hz, 1H), 3.79-3.65 (m, 3H), 3.60 (d, $J$ = 9.3 Hz, 1H), 3.40 (s, 3H), 2.72 (d, $J$ = 9.1 Hz, 1H), 2.34-2.29 (m, 1H), 1.11 (s, 9H), 1.08 (d, $J$ = 7.5 Hz, 3H); $^{13}$C NMR (75 MHz, CDC$_3$): $\delta$ = 135.7 (4C), 133.5 (2C), 129.5 (2C), 127.5 (4C), 102.6, 72.2, 69.7, 64.0, 63.7, 55.0, 38.8, 26.7, 19.2, 14.3; HRMS (ES): $m/z$ calcd for C$_{24}$H$_{34}$O$_5$$^\cdot$Na (M+Na)$^+$ 453.2073, obsd 453.2070; $[\alpha]_{D}^{23}$ + 52.6 (c 0.56, CHCl$_3$).

*Anal.* Calcd for C$_{24}$H$_{34}$O$_5$: C, 66.94; H, 7.96 Found: C, 67.00; H, 8.16.

**Methyl 6-O-Benzyl-2-deoxy-2-C-methyl-$\alpha$-$\beta$-altropyranoside (3.28.3):**

To a solution of methyl 4,6-O-benzylidene-2-deoxy-2-C-methyl-$\alpha$-$\beta$-altropyranoside (3.05g, 10.9 mmol) in 125 mL of CH$_2$Cl$_2$, 8.7 mL (54.4 mmol, 5.0 eq.) of triethylsilane was added dropwise, followed by addition of 4.2 mL (54.4 mmol, 5 eq.) of trifluoroacetic acid in the same manner with vigorous stirring at 0 ºC under argon. After addition was complete, the mixture was kept at 0 ºC for 1 h and
slowly warmed to ambient temperature and stirred for an additional 2 h. The resulting mixture was carefully quenched with saturated NaHCO$_3$ solution, extracted with 3x300 mL of CH$_2$Cl$_2$. The combined organic portions were washed with saturated NaHCO$_3$ solution and brine, dried over Na$_2$SO$_4$ and evaporated. The residue was chromatographed on silica gel (gradient elution with 2:1 to 1:1 hexane/EtOAc) to give 2.17 g (70%) of benzyl ether 3.28.3 as a colorless oil; IR (neat, cm$^{-1}$) 3472, 1453, 1420, 1384; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 7.38-7.24 (m, 5 H), 4.63 (s, 2 H), 4.56 (s, 1 H), 3.87-3.63 (m, 5 H), 3.40 (s, 3 H), 2.65 (br s, 2 H), 2.30 (qd, $J = 7.5$, 1.7 Hz, 1 H), 1.05 (d, $J = 7.5$ Hz, 3 H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 138.3, 128.3 (2C), 127.5 (2C), 127.4, 102.6, 73.4, 72.1, 70.1, 68.5, 63.6, 55.3, 38.8, 14.4; HRMS (ES): m/z calcd for C$_{15}$H$_{22}$O$_5$$^•$Na (M+Na)$^+$ 305.1359; obsd 305.1389; $\left[\alpha\right]_{D}^{18}$ +91.3 (c 2.63, CHCl$_3$).

Methyl 6-O-(Triphenyl)methyl-2-C-methyl-2,3,4-trideoxy-$\alpha$-$\alpha$-$\alpha$-$\alpha$-$\alpha$-D-threo-hex-3-enopyranoside (3.29.1):

To a solution of 4.32 g (9.9 mmol) of glycoside 3.28.1 in 30 mL of dry pyridine, 120 mg (0.99 mmol, 10 mol%) of DMAP was added. The mixture was cooled to -10 $^\circ$C and 6.2 mL (79.6 mmol, 8 equivalents) of freshly distilled methanesulfonyl chloride was added dropwise with stirring under argon. The mixture was stirred for an additional 21 h at -10 $^\circ$C, slowly warmed to room temperature and allowed to react for 6 h, poured onto ice-water mixture, and extracted with 3x100 mL of
CH$_2$Cl$_2$. The combined organic portions were washed with brine and dried over MgSO$_4$. The solvent was evaporated, and the residue was dried in vacuum to remove any possible traces of pyridine. The crude material as off-white foam (5.70 g, 97% yield) was used in the next step without further purification; IR (cm$^{-1}$) 1362, 1179; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 7.49-7.46 (m, 5H), 7.34-7.23 (m, 10H), 5.05-4.95 (m, 2H), 4.60 (br d, $J$ = 2.2 Hz, 1H), 4.28-4.24 (m, 1H), 3.54-3.50 (m, 1H), 3.44 (s, 3H), 3.28-3.23 (dd, $J$ = 4.3, 10.5 Hz, 1H), 3.06 (s, 3H), 2.79 (s, 3H), 2.52-2.47 (m, 1H), 1.24 (d, $J$ = 7.4Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 143.1 (3C), 128.5 (6C), 127.8 (6C), 127.1 (3C), 102.2, 86.9, 79.2, 72.0, 66.9, 62.4, 55.5, 38.3, 38.2, 14.5; HRMS (ES): m/z calcd for C$_{29}$H$_{34}$O$_9$S$_2$$\cdot$Na (M+Na)$^+$ 613.1542; obsd 613.1529; $[\alpha]_{D}^{23}$ +53.3 (c 0.53, CHCl$_3$).

Anal. Calcd for C$_{29}$H$_{34}$O$_9$S$_2$: C, 58.97, H, 5.81. Found C, 58.69, H, 5.71.

A mixture of the above crude dimesylate (5.70 g, 9.66 mmol), sodium iodide (14.5 g, 96.6 mmol, 10 equivalents) and zinc dust (6.30 g, 96.6 mmol, 10 equivalents, activated prior to use) in dry DMF (50 mL) was heated at reflux with stirring for 36 h. After being cooled to ambient temperature, the mixture was filtered through a pad of Celite. The filtrate was then poured into water and extracted with 1:1 hexane/ether (3x80 mL). The combined organic layers were washed with water and dried over magnesium sulfate. Concentration under reduced pressure gave a residue of the product, which was purified by flash chromatography on silica gel (elution with dichloromethane) to yield 2.70 g (68% over two steps) of the expected alkene 3.29.1 as white crystals; mp 74-
77 °C; IR (cm⁻¹): 3464, 3059, 2929, 1959, 1597, 1491, 1448, 1368, 1217, 900, 758, 708, 648; ¹H NMR (300 MHz, CDCl₃): δ = 7.51-7.49 (m, 5H), 7.33-7.22 (m, 10H), 5.74-5.72 (m, 2H), 4.57 (s, 1H), 4.31 (br s, 1H), 3.47 (s, 3H), 3.29 (dd, J = 6.1, 9.4 Hz, 1H), 3.19 (dd, J = 5.1, 9.4 Hz, 1H), 2.18-2.17 (m, 1H), 1.09 (d, J = 7.2 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ = 146.8 (3C), 143.9 (6C), 128.6, 127.7 (6C), 126.8 (3C), 125.2, 102.1, 86.4, 67.9, 66.1, 55.2, 33.9, 18.5; HRMS (ES): m/z calcd for C₂⁷H₂₈O₃•Na (M+Na)⁺ 423.1936; obsd 423.1943; [α]D²² +71.0 (c 0.10, CHCl₃).

Anal. Calcd for C₂⁷H₂₈O₃: C, 80.96; H, 7.05. Found C, 80.80; H, 7.06.

**Methyl 6-O-(tert-Butyldiphenyl)silyl-2-C-methyl-2,3,4-trideoxy-α-D-threo-hex-3-enopyranoside (3.29.2):**

To a solution of 720 mg (1.67 mmol) of glycoside 3.28.2 in 5 mL of dry pyridine, 20.0 mg (0.160 mmol, 10 mol%) of DMAP was added. The mixture was cooled to -10 °C and 1.0 ml (13.4 mmol, 8 equivalents) of freshly distilled methanesulfonyl chloride was added dropwise with stirring under argon. The mixture was stirred for 1h at -10 °C, slowly warmed to room temperature and allowed to react for 24 h. The mixture was poured onto ice-water mixture and extracted with 3x100 mL of CH₂Cl₂. Combined organic portions were washed with brine and dried over MgSO₄. The solvent was evaporated and the residue was dried azeotropically with toluene to remove any possible traces of pyridine. The crude material as
yellow oil (900 mg, 92%) was used in the next step without further purification;
IR (neat, cm\(^{-1}\)): 2934, 2858, 1742, 1428, 1360, 1130, 1112, 1027, 959, 831,
756, 704; \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 7.74-7.68\) (m, 5H), 7.46-7.35 (m, 5H),
5.15 (dd, \(J = 3.3, 8.3\) Hz, 2H), 4.99-4.96 (m, 1H), 4.50 (d, \(J = 2.8\) Hz, 1H), 4.13-
4.08 (m, 1H), 3.89 (d, \(J = 2.8\) Hz, 1H), 3.33 (s, 3H), 3.1 (s, 3H), 3.0 (s, 3H), 2.49-
2.44 (m, 1H), 1.18 (d, \(J = 7.4\) Hz, 3H), 1.09 (s, 9H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta =
135.9\) (2C), 135.6 (2C), 133.0, 132.6, 129.81, 129.77, 127.7 (2C), 127.6 (2C),
102.3, 79.4, 71.5, 68.0, 62.6, 55.6, 38.7, 38.6, 38.4, 26.8 (3C), 19.2, 14.5;
HRMS (ES): \(m/z\) calcd for C\(_{26}\)H\(_{38}\)O\(_9\)S\(_2\)Si\(\cdot\)Na (M+Na\(^+\) 609.1624; obsd 609.1625;
\([\alpha]^{22}_D\) + 406.2 (c 0.47, CHCl\(_3\)).

A mixture of the above crude dimesylate (0.900 g, 1.5 mmol), sodium iodide
(3.45 g, 23 mmol, 15 equivalents) and activated zinc dust (1.46 g, 23 mmol, 15
equivalents, activated prior to use) in dry DMF (8 mL) was heated at reflux with
stirring for 24 hours. The mixture was filtered through a pad of Celite. The
filtrate was poured into water and extracted with 3x25 mL of hexanes/ether
mixture (1:1). The combined organic layers were washed with brine and dried
over magnesium sulfate. Concentration under reduced pressure yielded 0.350
g (53% over two steps) of the expected alkene 3.29.2 as a yellow oil after
purification by flash chromatography on silica gel (elution with 20:1
hexane/ethyl acetate); IR (cm\(^{-1}\)): 2960, 2930, 2857, 1472, 1427, 1113, 998,
702; \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 7.77-7.74\) (m, 5H), 7.46-7.39 (m, 5H), 5.79
(br s, 2H), 4.60 (s, 1H), 4.30-4.26 (m, 1H), 3.84 (dd, \(J = 5.7, 10.2\) Hz, 1H), 3.76
(dd, $J = 5.6, 10.2$ Hz, 1H), 3.48 (s, 3H), 2.22-2.20 (m, 1H), 1.13 (s, 9H), 1.10 (d, $J = 7.2$ Hz, 3H), $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta = 135.6$ (2C), 133.5 (2C), 133.5, 133.4, 129.6 (2C), 128.6, 127.5 (4C), 125.1, 102.2, 69.1, 66.3, 55.2, 34.1, 26.8 (3C), 19.2, 18.6; HRMS (ES): $m/z$ calcd for C$_{24}$H$_{32}$O$_3$Si•Na (M+Na)$^+$ 419.2018; obsd 419.2007; $[\alpha]^{22}_D + 483.2$ (c 0.54, CHCl$_3$).

**Methyl 6-O-Benzyl-2-C-methyl-2,3,4-trideoxy-α-D-threo-hex-3-enopyranoside (3.29.3):**

To a solution of 100 mg (0.354 mmol) of glycoside 3.28.3 in 5 mL of dry pyridine, 5 mg (0.040 mmol, 10 mol%) of DMAP was added. The mixture was cooled to -10 ºC and 0.110 mL of freshly distilled methanesulfonyl chloride was added dropwise with stirring under argon. The mixture was stirred for an additional 1h at -10 ºC, slowly warmed to room temperature and allowed to react for 6 h. The mixture was poured onto ice-water mixture and extracted with 3x100 mL of CH$_2$Cl$_2$. The combined organic portions were washed with brine and dried over Na$_2$SO$_4$. The solvent was evaporated and the residue was dried in vacuum to remove any possible traces of pyridine. Crude material as off-white solid (154 mg, quantitative yield) was used in the next step without further purification; IR (neat, cm$^{-1}$) 1454, 1359, 1279, 1179; $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 7.36$-7.16 (m, 5 H), 5.03 (dd, $J = 3.4, 8.4$ Hz, 1 H), 4.95 (dd, $J = 3.4, 4.6$ Hz, 1 H), 4.61 (dd, $J = 11.7, 20.5$ Hz, 2 H), 4.52 (d, $J = 2.2$ Hz, 1 H), 4.24 (dt, $J = 8.4, 2.9$ Hz, 2 H).
Hz, 1 H), 3.80-3.71 (m, 2 H), 3.38 (s, 3 H), 3.09 (s, 3 H), 3.04 (s, 3 H), 2.47-2.42 (m, 1 H), 1.16 (d, $J = 7.4$ Hz, 3 H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 137.5, 128.4 (2C), 127.9 (2C), 127.7, 102.5, 79.2, 73.9, 71.7, 68.7, 67.0, 55.7, 38.7, 38.6, 38.4, 14.7; HRMS (ES): $m/z$ calcd for C$_{17}$H$_{26}$O$_9$S$_2$$\cdot$Na (M+Na)$^+$ 461.0910; obsd 461.0929.

The above dimesylate (154 mg, 0.354 mmol) dissolved in DMF (10 mL) was treated with sodium iodide (424 mg, 2.83 mmol) followed by zinc dust (185 mg, 2.83 mmol, activated prior to use). The system was flushed with argon and the mixture was stirred at the reflux temperature for 24 h before being cooled to ambient temperature and diluted with 1:1 hexane/ether (50 mL) and water (50 mL). The separated aqueous layer was extracted with 1:1 hexane/ether (3x50 mL) and the combined organic phases were washed with brine, dried over Na$_2$SO$_4$, and evaporated. Flash chromatography of the residue on silica gel (elution with 10% ethyl acetate in hexane) afforded 3.29.3 as a colorless oil (83 mg, 95%); IR (neat, cm$^{-1}$) 1587, 1496, 1454, 1360; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 7.37-7.25 (m, 5 H), 5.80-5.74 (m, 1 H), 5.68-5.64 (m, 1 H), 4.62-4.56 (m, 3 H), 4.40-4.35 (m, 1 H), 3.57 (dd, $J = 10.1, 20.4$ Hz, 1 H), 3.56 (dd, $J = 10.1, 19.7$ Hz, 1 H), 3.47 (s, 3 H), 2.19-2.14 (m, 1 H), 1.08 (d, $J = 7.2$ Hz, 3 H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 138.2, 129.0, 128.2 (2C), 127.5 (2C), 127.4, 124.7, 102.2, 73.3, 72.6, 67.6, 55.3, 34.0, 18.6; HRMS (ES): $m/z$ calcd for C$_{15}$H$_{20}$O$_3$$\cdot$Na (M+Na)$^+$ 271.1305; obsd 271.1302; $[\alpha]^{18}_D$ +97.5 (c 1.13, CHCl$_3$).

Methyl 6-O-(Triphenyl)methyl-2-C-Methyl-2,3,4-trideoxy-α-D-threo-hex-3-enopyranoside (3.30.1):

To a solution of the unsaturated glycoside 3.29.1 (2.70 g, 6.7 mmol) in absolute methanol (50mL) was added Raney nickel (15.0 g, washed with water and methanol prior to use). The reaction mixture was stirred overnight under 42 psi of hydrogen. The catalyst was filtered off and the filtrate was concentrated leaving 2.52 g (95%) of compound 3.30.1 as a white solid; mp 87-89 °C; IR (neat, cm⁻¹): 2929, 1668, 1448, 1098, 1050; ¹H NMR (300 MHz, CDCl₃): δ = 7.50-7.43 (m, 5H), 7.33-7.20 (m, 10H), 4.41 (s, 1H), 3.95-3.87 (m, 2H), 3.43 (s, 3H), 3.19 (dd, J = 6.3, 9.4 Hz, 1H), 3.00 (dd, J = 4.8, 9.4 Hz, 1H), 2.05-1.95 (m, 1H), 1.80-1.76 (m, 1H), 1.57-1.43 (m, 1H), 1.40-1.34 (m, 1H), 1.04 (d, J = 7.2 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ = 144.2 (3C), 128.7 (6C), 128.3 (6C), 127.7 (3C), 126.9, 102.9, 68.1, 67.2, 54.5, 31.3, 23.4, 22.7, 16.3; HRMS (ES): m/z calcd for C₂₇H₃₀O₃•Na (M+Na)⁺ 425.2093; obsd 425.2068; [α]_{D}^{22} +36.8 (c 0.19, CHCl₃).


Methyl 2-C-Methyl-2,3,4-trideoxy-α-D-threo-hexopyranoside (3.31):

Method A. Anhydrous ammonia (approximately 1 L) was condensed into a three-necked, round-bottomed flask containing a solution of 3.30.1 (3.59 g, 8.92 mmol) in THF (91 mL) cooled to −78 °C. The resulting solution was
warmed to -40 to -30 °C and 2.00 g (86.9 mmol) of sodium metal was added portionwise, maintaining the mixture temperature at -40 to -30 °C and color at deep blue. The resulting solution was stirred for 15 min, with more sodium addition to maintain color as needed. Absolute ethanol was added dropwise until the blue color disappeared. The above sequence was repeated for a total of four additions of sodium. After the final ethanol quenching, the colorless solution was stirred for an additional 5 min at -33 °C and carefully quenched with saturated ammonium chloride solution (600 mL). The remaining liquid ammonia was allowed to evaporate overnight. The mixture was extracted with 3x300 mL of ethyl acetate, the combined extracts were washed with brine and dried over MgSO$_4$. After being concentrated, the residue was purified by flash chromatography (elution with 15:1 hexane/ethyl acetate) to afford 1.09 g (76%) of 3.31 as a colorless oil.

Method B. To a solution of silyl ether 3.30.2 (0.32 g, 0.803 mmol) in THF (5 mL), a solution of TBAF (1.15 mL at 1.0 M in THF, 1.12 mmol, 1.4 equivalents) was added at 0 °C. After being stirred for 1 h, the volatiles were evaporated and the residue was purified by column chromatography (elution with hexanes: ethyl acetate 3:1) to give 0.089 mg (69%) of the title compound 3.31 as a clear oil.

Method C. To a solution of 2.60 g of unsaturated glycoside 3.29.3 (10.47 mmol) in 100 mL of absolute MeOH, 5% palladium on charcoal (0.26 g) was added.
The resulting mixture was stirred for 5 h under 1 atm of hydrogen with an additional 0.15 g of catalyst introduced after 3 h. This mixture was filtered through a short pad of Celite and concentrated to yield 1.67 g (99%) of the product as very volatile colorless oil; IR (neat, cm⁻¹) 3423, 1454, 1383; ¹H NMR (300 MHz, CDCl₃): δ = 4.39 (s, 1 H), 3.84-3.76 (m, 1 H), 3.55 (dd, J = 11.4, 21.4 Hz, 1 H), 3.53 (dd, J = 11.4, 24.8 Hz, 1 H), 3.35 (s, 3 H), 2.14 (br s, 1 H), 2.07-1.95 (m, 1 H), 1.81-1.75 (m, 1 H), 1.57 (dq, J = 13.2, 4.3 Hz, 1 H), 1.42-1.30 (m, 1 H), 1.29-1.22 (m, 1 H), 1.03 (d, J = 7.3 Hz, 3 H); ¹³C NMR (75 MHz, CDCl₃): δ = 102.9, 69.1, 66.1, 54.5, 31.1, 23.5, 21.1, 16.1; HRMS (ES): m/z calcd for C₈H₁₆O₃•Na (M+Na)⁺ 183.0997; obsd 183.1002; [α]D₁₇ +111.4 (c 0.19, CHCl₃).


1-(6-Methoxy-5-methyltetrahydropyran-2-yl)ethanol (3.32):

To a solution of 0.810 g of methyl 2-C-methyl-2,3,4-trideoxy-α-D-syn-hexopyranoside (5.06 mmol) in 12 mL of CH₂Cl₂ along with 4.28 g of NaHCO₃ (10 eq.) and 3.5 g of 4 Å powdered molecular sieves, 2.57 g (6.07 mmol; 1.20 equivalents) of Dess-Martin periodinane was added and the mixture was stirred at room temperature for 2 h, diluted with 100 mL of pentane, and stirred for an additional 30 min. The precipitated solids were filtered off with the help of a Celite pad. The filtrate was stirred with pulverized anhydrous K₂CO₃ (4 g) for another 30 min. The mixture was filtered and the solvent was evaporated,
leaving a yellow oil of the crude product, which was immediately subjected to
the next step; $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 9.66$ (s, 1 H), 4.48 (d, $J = 1.7$ Hz, 1 H), 4.20 (dd, $J = 8.2$, 6.4 Hz, 1 H), 3.41 (s, 3 H), 2.09-1.96 (m, 1 H), 1.86-1.74 (m, 1 H), 1.71-1.63 (m, 2 H), 1.48-1.35 (m, 1 H), 1.05 (d, $J = 7.2$ Hz, 3 H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta = 201.8$, 103.4, 74.1, 55.2, 31.5, 23.8, 20.4, 15.9.

The aldehyde was immediately dissolved in dry ether (25 mL), cooled to 0 ºC, and treated with ethereal methylmagnesium bromide (5.35 mL of 2.65 M, 14.2 mmol). The solution was naturally warmed to ambient temperature and stirred for another 30 min. The reaction mixture was quenched with saturated NH$_4$Cl and the aqueous layer was extracted with 3x150 mL of ether. The combined extracts were washed with brine, dried over Na$_2$SO$_4$ and the solvent was removed under reduced pressure. Purification was achieved by flash chromatography on silica gel (gradient elution with 25% to 35% ethyl acetate in hexane) to give 0.743 g (84%) of the title compound as a very volatile colorless oil; IR (neat, cm$^{-1}$) 3448, 1452, 1383, 1370; $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 4.38$ (s, 1 H), 3.58 (quintet, $J = 6.4$ Hz, 1 H), 3.46-3.39 (m, 1 H), 3.34 (s, 3 H), 2.54 (br s, 1 H), 2.01-1.93 (m, 1 H), 1.78-1.73 (m, 1 H), 1.55-1.28 (series of m, 3 H), 1.12 (d, $J = 6.4$ Hz, 3 H), 1.00 (d, $J = 7.3$ Hz, 3 H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta = 102.9$, 73.0, 70.4, 54.5, 31.0, 23.6, 21.5, 18.3, 16.1; HRMS (ES): $m/z$ calcd for C$_9$H$_{18}$O$_3$•Na (M+Na)$^+$ 197.1148, obsd 197.1155; $[\alpha]_{D}^{23} +112.6$ (c 1.57, CHCl$_3$).
**1-(6-Methoxy-5-methyltetrahydropyran-2-yl)ethanone (3.33):**

To a solution of 1.05 g of pyranoside **3.32** (6.01 mmol) in 15 mL of CH₂Cl₂, 3.06 g (7.21 mmol; 1.20 equivalents) of Dess-Martin periodinane was added and the mixture was stirred at ambient temperature for 3 h. The mixture was diluted with 30 mL of pentane and stirred for an additional 30 min. The precipitated solids were filtered through a Celite pad. The solvent was evaporated leaving a yellow oil of the crude product, which was purified by bulb-to-bulb distillation. There was isolated 827 mg (80%) of **3.33** as a very volatile colorless oil; IR (neat, cm⁻¹) 1721, 1454, 1353; ¹H NMR (300 MHz, CDCl₃): δ = 4.45 (s, 1 H), 4.18-4.13 (m, 1 H), 3.38 (s, 3 H), 2.21 (s, 3 H), 2.06-1.96 (m, 1 H), 1.80-1.75 (m, 1 H), 1.68-1.61 (m, 2 H), 1.41 (dq, J = 13.2, 3.6 Hz, 1 H), 1.04 (d, J = 7.3 Hz, 3 H); ¹³C NMR (75 MHz, CDCl₃): δ = 209.0, 103.3, 74.5, 55.0, 31.1, 25.8, 24.0, 21.8, 16.0; HRMS (ES): m/z calcd for C₉H₁₆O₃•Na (M+Na)⁺ 195.0992, obsd 195.0999; [α]D²² +54.9 (c 0.86, CDCl₃).

**6-Isopropenyl-2-methoxy-3-methyltetrahydropyran (3.20):**

To a slurry of 1.348 g (3.77 mmol) of methyltriphenylphosphonium bromide in 5 mL of dry THF, a solution of n-butyllithium (2.7 mL of 1.40 M, 3.77 mmol) was added at −78 ºC under an inert atmosphere. The mixture was stirred at −78 ºC for 30 min and for 2 h at 0 ºC. To the resulting deep
yellow solution, a solution of 500 mg of methyl ketone **3.33** (2.90 mmol) in 7 mL of dry THF was added and the mixture was naturally warmed up to ambient temperature and stirred for another 3 h. The reaction mixture was quenched with saturated NH₄Cl solution and the separated aqueous layer was extracted with 3x100 mL of ether. The combined extracts were washed with brine, dried over Na₂SO₄ and evaporated. Purification was achieved by bulb-to-bulb distillation giving 402 mg (81%) of olefin **3.20** as a very volatile colorless oil; IR (neat, cm⁻¹) 1652, 1454, 1383; ¹H NMR (300 MHz, CDCl₃): δ = 4.98-4.97 (m, 1 H), 4.84-4.83 (m, 1 H), 4.42 (s, 1 H), 4.11 (dd, J = 11.3, 2.2 Hz, 1 H), 3.37 (s, 3 H), 2.04 (tt, J = 8.5, 4.6 Hz, 1 H), 1.78 (s, 3 H), 1.77-1.62 (m, 2 H), 1.47-1.38 (m, 2 H), 1.06 (d, J = 7.2 Hz, 3 H); ¹³C NMR (75 MHz, CDCl₃): δ = 146.0, 110.7, 103.3, 71.7, 54.6, 31.1, 24.4, 24.1, 18.8, 16.2; HRMS (ES): m/z calcd for C₁₀H₁₈O₂•Na (M+Na)^+ 193.1199, obsd 193.1203; [α]₂¹°D +73.4 (c 0.37, CHCl₃).

**cis,cis-2-Isopropenyl-5-methycyclopentanol (3.19):**

![cis,cis-2-Isopropenyl-5-methycyclopentanol (3.19):](image)

A slurry of zirconocene dichloride (703 mg, 2.41 mmol) in dry toluene (5 mL) was cooled to -78 °C under argon, treated with n-butyllithium (3.6 mL of 1.18 M, 4.21 mmol), and stirred at this temperature for 1 h. A solution of **3.20** (205 mg, 1.202 mmol) in dry toluene (4 mL) was introduced and after 15 min at -78 °C, the mixture was gradually warmed to ambient temperature where it was maintained for 3 h. During this period, the color of the mixture gradually turned from bright yellow
to dark brown. At this point, the mixture was cooled to 0 °C, whereupon boron trifluoride etherate (0.300 mL, 2.405 mmol) was added. The mixture was allowed to warm to ambient temperature, stirred for 1 h, and quenched with 10% HCl (10 mL). The separated aqueous phase was extracted with ether (3 x 50 mL) and the combined organic layers were washed with saturated NaHCO₃ solution and brine. After being dried with Na₂SO₄, the solvent was evaporated. Flash chromatography of the residue on silica gel (elution with 15% ethyl acetate in hexane) delivered 104 mg (63%) of 3.19 and 23 mg (14%) of an unknown diastereomer. Both were very volatile colorless oils.

For 3.19: IR (neat, cm⁻¹) 3448, 1645, 1454; ¹H NMR (300 MHz, CDCl₃): δ = 5.01-4.99 (m, 1 H), 4.86 (s, 1 H), 3.92 (t, J = 3.4 Hz, 1 H), 2.58-2.49 (m, 1 H), 2.10-1.98 (m, 1 H), 1.93-1.78 (m, 2 H), 1.84-1.82 (m, 3 H), 1.76-1.64 (m, 1 H), 1.52-1.38 (m, 1 H), 1.30 (br s, 1 H), 1.07 (d, J = 6.8 Hz, 3 H); ¹³C NMR (75 MHz, CDCl₃): δ = 144.5, 111.7, 75.2, 53.1, 39.7, 29.9, 25.2, 23.7, 14.6; HRMS (ES): m/z calcd for C₉H₁₆O (M+H)+ 141.1274, obsd 141.1263; [α]₂¹_D 5.2 (c 0.38, CHCl₃).

For the diastereomer: IR (neat, cm⁻¹) 3440, 1644, 1456; ¹H NMR (300 MHz, CDCl₃): δ = 5.03-5.00 (m, 1 H), 4.88-4.84 (m, 1 H), 3.74 (dd, J = 4.6, 1.3 Hz, 1 H), 2.55-2.45 (m, 1 H), 2.15-2.00 (m, 2 H), 1.83-1.81 (m, 3 H), 1.87-1.63 (series of m, 2 H), 1.51 (br s, 1 H), 1.24-1.08 (m, 1 H), 1.01 (d, J = 7.1 Hz, 3 H); [α]₂²_D +14.0 (c 0.15, CHCl₃).
cis,cis-1-(2,2-Dimethyl-4-pentenyl)-2-isopropenyl-5-methylcyclopentanol

(3.23):

To a solution of 34 mg of cyclopentanol 3.19 (0.24 mmol) in 2.8 mL of CH$_2$Cl$_2$, 203 mg of NaHCO$_3$ (10 eq.) was added, followed by 118 mg (0.28 mmol; 1.15 equivalents) of Dess-Martin periodinane, and the mixture was stirred at room temperature for 2 h. TLC revealed almost immediate conversion. The mixture was diluted with 30 mL of pentane and stirred for an additional 15 min. The precipitated solids were filtered through a Celite pad, and the solvent was evaporated. The filtration procedure was repeated twice. Final evaporation left a yellow oil of the crude ketone 3.37.1, which was used in the next step without purification; $^1$H NMR (300 MHz, C$_6$D$_6$): $\delta$ = 4.84-4.81 (m, 1 H), 4.73-4.70 (m, 1 H), 2.51 (t, $J$ = 7.8 Hz, 1 H), 1.84 (q, $J$ = 7.3 Hz, 1 H), 1.67 (dd, $J$ = 1.3, 0.9 Hz, 3 H), 1.64-1.49 (m, 2 H), 1.39-1.15 (m, 2 H), 0.92 (d, $J$ = 7.3 Hz, 3 H); $^{13}$C NMR (75 MHz, C$_6$D$_6$): $\delta$ = 217.2, 142.9, 112.3, 55.4, 42.8, 29.4, 26.3, 21.5, 15.3.

4,4-Dimethyl-5-iodopent-1-ene (63 mg, 0.28 mmol) was dissolved in dry pentane (2.0 mL), cooled to -60 °C, and treated dropwise under argon with tert-butyllithium (0.36 mL of 1.55 M, 0.56 mmol) while being stirred. The mixture was stirred at -60 to -50 °C for 60 min, at which point the unpurified cyclopentanone from above dissolved in dry THF (2 mL) was introduced. After 2 h of stirring at -60 to -40 °C, saturated NH$_4$Cl solution was added and the aqueous phase was extracted with ether (3 x 50 mL). The combined organic
phases were washed with brine, dried with Na$_2$SO$_4$, and evaporated. Purification of the residue by chromatography on silica gel (elution with 1% ethyl acetate in hexane) afforded 26 mg (45%) of 3.23 as a colorless oil; IR (neat, cm$^{-1}$) 3553, 1636, 1456, 1374; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 5.92-5.77 (m, 1 H), 5.06-4.95 (m, 3 H), 4.88-4.85 (m, 1 H), 2.45 (dd, $J$ = 9.8, 8.3 Hz, 1 H), 2.16-2.01 (series of m, 3 H), 1.85 (dd, $J$ = 1.4, 0.8 Hz, 3 H), 1.81-1.60 (m, 3 H), 1.53 (br s, 1 H), 1.44 (s, 2 H), 1.34-1.18 (m, 1 H), 1.01 (d, $J$ = 5.6 Hz, 6 H), 1.00 (d, $J$ = 6.9 Hz, 3 H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 146.1, 135.9, 117.0, 113.3, 82.4, 57.8, 49.8, 49.6, 41.7, 34.0, 31.5, 28.4, 27.9, 27.6, 24.7, 15.0; HRMS (ES): m/z calcd for C$_{16}$H$_{28}$O•Na (M+Na)$^+$ 259.2032, obsd 259.2021; $[\alpha]_{D}^{21}$ +36.2 (c 0.07, CHCl$_3$).

3,5,5,8-Tetramethyl-2,3,4,5,6,8a-hexahydro-1H-azulen-3a-ol (3.22):

A solution of the Grubbs’ catalyst (16 mg, 19 µmol) in CH$_2$Cl$_2$ (2 mL) was added under argon to a solution of olefin (15 mg, 64 µmol) in CH$_2$Cl$_2$ (18 mL). After 1.5 h of stirring at ambient temperature, the reaction mixture was concentrated and the residue was purified by flash chromatography on silica gel (elution with 2% ethyl acetate in hexane) to furnish 12 mg (93%) of 3.22 as a colorless oil; IR (neat, cm$^{-1}$) 3602, 1452, 1364, 1241; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 5.71-5.63 (m, 1 H), 2.91 (t, $J$ = 9.5 Hz, 1 H), 2.20 (dd, $J$ = 14.3, 4.9 Hz, 1 H), 2.02-1.11 (series of m, 9 H), 1.78 (d, $J$ = 1.3 Hz, 3 H), 1.03 (s, 3 H),
0.94 (s, J = 6.6 Hz, 1 H), 0.91 (s, 3 H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta = 138.8, 125.5, 80.7, 53.7, 50.1, 46.2, 40.3, 34.9, 31.6, 30.2, 27.1, 24.6, 23.8, 12.9\);
HRMS (ES): \(m/z\) calcd for C\(_{14}\)H\(_{24}\)O•Na (M+Na\(^+\)) 231.1719, obsd 231.1727; \([\alpha]_{D}^{20}\) +37.5 (c 0.24, CHCl\(_3\)).

3,3,5,7b-Tetramethyldecahydrocyclopenta[azulen-4a-ol (3.21):

A solution of olefin 3.22 (6.9 mg, 33.1 \(\mu\)mol) in CH\(_2\)Cl\(_2\) (2 mL) was treated with diethylzinc in hexane (100 \(\mu\)L of 1.0 M, 100 \(\mu\)mol) at 0 °C under argon followed by diiodomethane (150 \(\mu\)L). The reaction mixture was stirred at 0 °C for 1.5 h and at ambient temperature for 30 min, quenched with saturated NH\(_4\)Cl solution, and extracted with CH\(_2\)Cl\(_2\) (3 x 25 mL). The combined organic phases were washed with brine, dried with Na\(_2\)SO\(_4\), and the solvent was evaporated. The residue was purified by flash chromatography on silica gel (gradient elution with 0.5 to 2% ethyl acetate in hexane) to give 6.4 mg (87%) of epiafricanol as a colorless oil; IR (neat, cm\(^{-1}\)) 3609, 1457, 1377, 1363; \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 2.14-1.98\) (m, 3 H), 1.80-1.57 (series of m, 4 H), 1.55 (s, 2 H), 1.33 (dd, \(J = 15.1, 0.9\) Hz, 1 H), 1.30-1.21 (m, 1 H), 1.08 (s, 3 H), 0.99 (s, 3 H), 0.90 (s, 3 H), 0.79 (d, \(J = 6.8\) Hz, 3 H), 0.72-0.66 (m, 1 H), 0.56 (br s, 1 H), 0.22 (dd, \(J = 8.7, 3.6\) Hz, 1 H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta = 80.8, 51.7, 49.7, 47.7, 38.8, 35.2, 31.9, 29.3, 29.1, 29.0, 27.4, 23.8, 21.6, 17.7, 12.3\); HRMS (ES):
$m/z$ calcd for $\text{C}_{15}\text{H}_{26}\text{O} \cdot \text{Na} (\text{M+Na})^+$ 245.1878, obsd 245.1889; $[\alpha]_D^{21} +65.5 \ (c \ 0.16, \text{CHCl}_3)$. 

CHAPTER 4.

EN ROUTE TO TAXOL AND ITS ANALOGUES.

4.1. Introduction.

The subject matter of this chapter cannot be written without overlooking something. This is not just another target molecule for the synthetic chemist. This is not just a natural product with a fascinating structure and not just the battlefield for exercising classical synthetic methods or probing newly developed methodologies. This compound is believed to be one of the most exciting biologically active natural products discovered in the last 30 years. Nowadays, this compound saves the lives of thousands of people battling with cancer, one of the most devastating diseases in the world.

Taxol® (paclitaxel)\textsuperscript{172} was first collected in 1962 in the form of the dried bark of the Pacific Yew tree (\textit{Taxus brevifolia}) by Barclay, a botanist of the United States Department of Agriculture, as part of a natural product collection campaign supported by the National Cancer Institute (NCI).\textsuperscript{173} The initial report of the taxol structure (4.1), which was elucidated by a combination of X-ray crystallographic studies of the degradation products and \textsuperscript{1}H NMR spectroscopy,
and preliminary structure activity relationship (SAR) data was published in 1971 by Wall and coworkers.\textsuperscript{174}

The long journey of the taxol molecule from the isolation bench to the clinical applications began in 1964, when the extract containing this natural product exhibited significant cytotoxic activity against KB cell lines. This discovery turned into an initiation point of meticulous pursuit of additional biological data necessary to evaluate taxol as a drug candidate. Along the way of this development, the researchers came upon a number of predicaments.

The primary problem was the extremely limited supply of the compound from the natural source. Between 1969 and 1990, the NCI effort in isolation made available 3.7 kg of taxol necessary for phase I and II clinical trials. However, this process caused irreversible environmental impact due to the extremely low abundance (ca. 0.02\%) of the natural product. In the meantime, very promising results of the clinical trials gave a preview of the anticipated

\textbf{Figure 4.1.} Structure of taxol.
high demand for the phase III screening and potential production of the drug forcing the evaluation of alternative sources for this compound. The long-term solution to the supply problem, which later became the commercial process, was discovered by Potier and coworkers.\textsuperscript{175} The extracts from the needles of the English Yew (\textit{Taxus baccata}) revealed substantial quantities of 10-deacetylbaccatin III (4.2) and baccatin III (4.3), which now serve as intermediates in the preparation of semi-synthetic taxol. Further developments expanded the variety of the renewable plant resources and therefore completely eliminated the environmental issue.

A second serious obstacle developing taxol as a drug candidate was its extremely low water solubility (less than 0.01 mg/kg).\textsuperscript{176} While formulation in a surfactant solution of Cremophor (polyethoxylated castor oil) and ethanol increased solubility and facilitated the drug delivery, it introduced other toxic side effects, the most serious of them being the hypersensitivity reaction. The problems associated with this phenomenon were resolved by introduction of the premedication course of treatment with steroidal histamine antagonists, which lowered the occurrence of such reactions from 18\% to less than 3\%.\textsuperscript{173}

After the aforementioned issues and other difficulties were resolved, taxol progressed through phase III clinical trials and was ultimately approved for the treatment of refractory ovarian cancer (1992) and metastatic breast cancer.
(1994). Since approval, taxol has been used successfully in a number of therapeutic settings and became accepted as a primary treatment of several forms of cancer as a single agent and in combination with other treatments.\textsuperscript{177}

A detailed review of the SAR and biological function of taxol as well as all the successful total syntheses available to this date is beyond the scope of this dissertation. However, an outline of the retrosynthetic scheme of the route currently being pursued in our research group is presented in the next section.
4.2. *Retrosynthetic Scheme of Currently Pursued Synthesis.*

The highly complex nature of the tetracyclic structure and the unique arrangement of functional groups in this natural product are the attributes that categorize any successful synthesis of this target as an outstanding accomplishment. However, the pathways developed to the present time were mostly designed to demonstrate the possibility that taxol could be prepared in the laboratory. As they were targeting the preparation of the molecule, the efficiency factor was seriously overlooked, producing long routes. In particular, the last two approaches appear to require more than 60 steps each. The existence of sufficient space for the implementation of new and efficient protocols which will deliver taxol and its structural analogs more concisely and in higher overall yield is evident.

As the intention of this section is to highlight the recently developed retrosynthetic scheme, many important details and advancements will be omitted for the purpose of brevity.

Our general approach can be divided into a number of key steps represented by a retrosynthetic analysis (Scheme 4.1). The intermediate represents what is believed to be the branching point from where the analogues would be synthesized. From this advanced intermediate, using the A-ring ketone as a synthetic handle for further functionalization of C12, C13 and C14 of the A-ring, the formal completion of taxol synthesis seemed practical based
on previous research from our group associated with the preparation of taxusin.\textsuperscript{193,194} At the opposite side of the structure, the epoxide function set the

\textbf{Scheme 4.1.} Currently pursued retrosynthetic analysis of taxol.
perfect basis for further conversion to the oxetane ring of the natural product as well as the tetrahydrofuranyl subunit of the D-ring analogue. Overall, the intermediate 4.4 should allow the implementation of the ultimate goal of the synthesis.

The taxane structural arrangement would be secured via a thermodynamically driven α-ketol rearrangement of isotaxane 4.5. Stereoselective intramolecular aldol condensation, involving the aldehyde of the extended side chain and the B-ring ketone at C9 of intermediate 4.6, could effectively be applied to the synthesis of the isotaxane 4.5. Selective dihydroxylation of the strained bridgehead double bond in intermediate 4.7 should allow access to the aldol precursor 4.6. Anion accelerated oxy-Cope rearrangement of the hydroxytriene 4.8 would afford diene intermediate 4.7. Anticipated endoselective addition of lithiated vinyl iodide 4.10 with the camphor-derived coupling partner 4.9 would provide hydroxytriene 4.8.

The retrosynthetic analysis makes clear the use of camphor as a single source of chirality for the synthesis of the taxane core. Synthesis of the camphor-derived coupling partner (4.9) was achieved in 5 steps from readily available (+)-camphorsulfonic acid (CSA). The synthesis of the Z-vinyl iodide coupling partner (4.10) from inexpensive tert-butyl acetate and 2,3-dibromopropene also was short and reliable.
Overall, this scheme allows the preparation of an elaborate and fully functionalized taxane intermediate \textbf{4.4} \textit{only 19 synthetic steps} from camphorsulfonic acid.\textsuperscript{195}
4.3. Optimization of Established Route.

When I joined the taxol project, my ultimate task was the implementation of the synthetic advances toward the D-ring analogues. Soon I realized that a number of the synthetic operations en route to 4.4 were underdeveloped for the conducting of large scale loads of the materials. In particular, major convergence steps posed a variety of limitations due to the scale, reproducibility and byproduct formation. Therefore, before being involved in front line development, we decided to focus on the optimization of the existing route.

At the very beginning, the first four steps of the synthesis of the camphor-based intermediates were uneventful. Installation of the olefinic subunit was conducted under accustomed conditions. The oxidation of an α-position of the resulting optically active β,γ-unsaturated bicycloheptanone was conducted according the procedure developed by Dr. Ho Yin Lo. The only introduced modification was a large scale preparation of a silyl enol ether, the improvement which allowed the simultaneous oxidation of multiple loads of the material, thereby increasing the efficiency of the overall throughput. The procedure was performed at the 50 g level and the yields were consistently high.

In preparation of the side chain, the problem-causing step of Stork iodoolefination was initially attempted on the scale described by my team mates, who also noted high degradation of the product upon prolonged storage. In our latest undertaking, we found the numbers for the maximum load of the
reagents in this step when the highest yield was consistently obtained. The instability issues were not encountered even after a week of storage of the neat material in a freezer.

After these problems were solved, the preparation of both intermediates in multigram quantities was achieved, which brought us to the step of unification of the camphor-based material and olefinic side chain via endoselective nucleophilic addition to the carbonyl group.

From our very first encounter, the available protocol for the endoselective nucleophilic addition was clearly underdeveloped. The factor of scale limitation posed for the purpose of satisfactory reproducibility on this step was severely delaying the overall throughput of the synthesis. In addition, the conversion of the starting materials was never higher that 75% due to unidentified side reactions. At the same time, the presence of the strong nucleophile caused the stereochemistry of the $\alpha$-hydroxy center in the unreacted starting material to be scrambled, thereby making its recovery next to impossible.
In an attempt to optimize this step, we performed a detailed analysis of the cause of epimerization. We visualized the successful epimerization as a competitive process which would require a much higher temperature than the nucleophilic addition to the carbonyl group. We also realized that upon scaling up this reaction in order to satisfy the concentration requirement, the volume of addition solution had to be considerably increased. If the effectiveness of the cooling bath is low, a warmer solution of the starting material would increase the overall temperature of the mixture favoring the epimerization process. On the other hand, if the volume of the solvent is decreased to a comfortable quantity, the side process of the vinyl iodide homocoupling becomes dominant. Overall, we strongly believed in the need to overhaul this procedure.

If the above assumption is correct, the ultimate optimization of this synthetic operation lies in our ability to control the temperature of the starting material solution prior to the addition. The experimental validation of the proposed hypothesis was successfully achieved together with my colleague, Dr. Scheme 4.3. Preparation of 4.8.
Xin Guo. After several minor improvements, we were able to release a final version of this protocol very much simplified compared to that previously developed with reproducible yields in 75 to 85% range and no limitations on scale.

The product of unification of compounds 4.9 and 4.10 was undertaken in the next step in which a pretaxane A and B rings were set. This synthetic transformation was mostly the responsibility of Matt Kreilein, another member of the taxol team, and represented a last step of multigram transformation in the current synthetic scheme.

To summarize, we have successfully performed optimization of early steps in the current synthetic scheme to accommodate high throughput requirements. These steps included silyl enol ether preparation prior to the α-hydroxylation of a camphor-based building block, the critical iodoolefination of the side chain and the unification of two building blocks 4.9 and 4.10. These modified procedures can be claimed as simplified, very flexible to any load of the materials, and consistently reproducible.
4.4. *Studies toward Improvement of α-Ketol Rearrangement.*

Having reached a point in the synthesis where high throughput was no longer critical, we decided to focus on a vital aspect of the synthetic scheme, namely the α-ketol rearrangement. This particular step of the synthesis was extensively studied by Dr. John Hofferberth and Dr. Ho Yin Lo.\textsuperscript{196,199} The molecular modeling and experimental results they obtained eventually resulted in the successful execution of the bridge migration. However, further development of the synthesis experienced a major difficulty in converting the pre-D ring installation of the rearranged product 4.4 to the oxetane unit of the target molecule. As it was later demonstrated,\textsuperscript{196} under the rearrangement conditions, the presence of sp\textsuperscript{3}-hybridized atom at C4 is a must. Knowing that the behavior of taxane can be significantly altered with change of the functional groups placement, we decided to probe the possibility of rearranging an isoxazolidine structure in the same manner but keeping the sp\textsuperscript{2}-hybridized atom at position four. The successful implementation of this idea would broaden the number of the possible routes to D-ring analogues.

Another piece of information supporting this investigation was the abnormal behavior of two isomeric benzylidene acetals 4.11 and 4.12. It was demonstrated that under the same conditions of strong base treatment in the attempt to oxygenate C2 via the nucleophilic attack of the enolate on an O-electrophile, the *syn* isomer rapidly rearranges to form the taxane framework,
whereas the *anti* counterpart does not react at all. Unfortunately, previous investigators failed to introduce the oxygenation on C2 position prior to the bridge migration, leading this pathway to a dead end. As a part of our effort, we were counting on the possible oxygenation after the acetal closure utilizing a much different oxidative source, which does not require the act of the strong base.

On the other hand, we envisioned access to the same type of intermediate from compound 4.5. With the removal of the protecting group, the hydroxyl at C10 could easily enter into hydrogen bonding, which could place the northern edge of the molecule in a similar geometry to the *syn*-acetal and, therefore, facilitate the bridge migration process toward the taxane core. In the next two sections we report the results realized in the investigation of this matter.

*Figure 4.3.* Comparison on *syn*- and *anti*-ketales of C9, C10 hydroxyls.
4.4.1. *Investigation of C10 Deprotected Substrates.*

The decision of testing the PMB-deprotected substrates in $\alpha$-ketol rearrangement was made when my colleague, Dr. Xin Guo, obtained some preliminary results of the similar bridge migration reaction conducting studies toward 1-deoxy analogue of taxol (*vide supra*).\textsuperscript{198} Although the mechanistic representation of this process lacked the exact similarities to our rearrangement, we hoped that the molecular architecture resemblance of the aforementioned substrates to ours might facilitate the progression in general.

In search of the most suitable intermediates to test our idea, we turned our attention toward the end of the pre-taxane sequence. Based on the previous findings while conducting an investigation of the functionalization of the southern edge of the molecule, the installation of the C2 oxygen must be done prior to the bridge migration step due to the absence of a conveniently positioned functional handle to perform this operation later in the synthesis. Therefore, the decision to test this new chemistry on the fully functionalized pre-taxane intermediate was obvious.

The PMB ether was oxidatively cleaved by treating it with dichlorodicyanoquinone in wet dichloromethane, producing free secondary alcohol 4.13 in high yield. The spectroscopic confirmation of the successful deprotection was achieved by observing a changed chemical shift of the
corresponding carbinol hydrogen in $^1$H NMR. Following this deprotection, we attempted the bridge migration reaction with this substrate.

The selection of the reagents for the next step was compelled by numerous experiments performed by two researchers, Dr. Lo and Dr. Guo. Among those were aluminum-based Lewis acids, such as Et$_2$AlCl and Me$_2$AlCl, as well as anionic and neutral amine bases, e.g. KHMDS, pyridine and 2,6-lutidine.

Regrettably, all these attempts resulted in no conversion, and sometimes upon prolonged treatment in decomposition of the starting material. In search of a reasonable explanation, we attempted to question the structure of the starting material compound 4.13. Upon closer look at the spectral data, and particularly, at the nOe of some hydrogens, we realized the existence of the equilibrium in which this compound resided. The availability of the free hydroxyl and the close

\[\text{Scheme 4.4. Attempted bridge migration on substrate 4.13.}\]

\[\text{Scheme 4.5. Proposed hemiketalization of 4.13.}\]
proximity of the back side of the C1 carbonyl group set the perfect basis for transannular hemiketalization with the formation of conveniently positioned polycyclic arrangements. Such behavior of the taxane-like structures with the properly positioned functional groups was experienced earlier, and therefore was not unexpected. However, the surfacing of this behavior was a sufficient cause to discontinue any attempts to study this phenomenon further and abandon this route.

4.4.2. Investigation of Substrates with C9, C10 syn-Acetal.

The present undertaking began with preparation of the benzyl enol ether 4.14 by generating the enolate of ketone 4.15 with potassium tert-butoxide in DMF as the deprotonating agent and performing O-alkylation with benzyl bromide. All the functional groups residing in structure 4.14 seemed to be tolerant to the reductive conditions. The addition of an ethereal solution of lithium aluminum hydride in order to reduce a very hindered C9 carbonyl

![Scheme 4.6. Preparation of benzyl enol ether.](image)

140
group was next examined. This step generated the syn-diol exclusively in almost quantitative yield. The spectroscopic validation of the performed reduction was realized when we observed a difference in the splitting pattern of the C10 carbinol hydrogen in the $^1$H NMR spectrum. In addition, we were easily able to locate a new carbinol proton at C9 and the disappearance of the carbonyl signal in $^{13}$C NMR.

The acetal cyclization proceeded uneventfully when the above diol was subjected to the benzylic oxidation under anhydrous conditions. For that purpose, a dichloromethane solution of dichlorodicyanoquinone was pretreated with powdered molecular sieves and only after that the substrate was introduced. As a consequence of the presence of a neighboring free hydroxyl, the benzylic cation thus generated was immediately trapped intramolecularly to provide the cyclic acetal. This product was obtained in high yield, and exhibited the expected spectral data. For instance, the acetal proton appeared as a singlet at approximately 6 ppm, which is a suitable chemical shift for such a structural subunit.

Scheme 4.7. Cyclization of acetal on new substrate.
The time had now arrived to examine the means of installation of the oxygen functionality at C2. To have the ability to distinguish between two available double bonds, we have selected only mild reagents, hoping that the activation present in the enol ether would favor the desired transformation. Regrettably, none of these oxidants triggered the conversion of the benzyl enol ether to the $\alpha$-hydroxy ketone. Additionally, a more pronounced reactivity of the exocyclic double bond was observed, which resulted in the preparation of epoxy compounds or diols depending on the oxidant. Notably, all the successful reactions produced a single diastereomeric product or a mixture predominant in one of them. And even though this finding was not of assistance to the original idea, it provided a helpful piece of information about

Scheme 4.8. Attempted C2 oxygenation (see Table 4.1 for conditions).

The time had now arrived to examine the means of installation of the oxygen functionality at C2. To have the ability to distinguish between two available double bonds, we have selected only mild reagents, hoping that the activation present in the enol ether would favor the desired transformation. Regrettably, none of these oxidants triggered the conversion of the benzyl enol ether to the $\alpha$-hydroxy ketone. Additionally, a more pronounced reactivity of the exocyclic double bond was observed, which resulted in the preparation of epoxy compounds or diols depending on the oxidant. Notably, all the successful reactions produced a single diastereomeric product or a mixture predominant in one of them. And even though this finding was not of assistance to the original idea, it provided a helpful piece of information about
the reactivity under these functional arrangements. The reaction and conditions applied for this transformation are summarized in Table 4.1.

<table>
<thead>
<tr>
<th>oxidant</th>
<th>conditions</th>
<th>product</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMDO</td>
<td>-20 to 25</td>
<td>2 h</td>
<td>4.17</td>
</tr>
<tr>
<td>PhCN, H₂O₂, KHCO₃</td>
<td>-20 to 25</td>
<td>36 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>iodosobenzene</td>
<td>25</td>
<td>48 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>Davis’ oxaziridine</td>
<td>25 to 60</td>
<td>48 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>Davis’ oxaziridine (modified)</td>
<td>25 to 60</td>
<td>48 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>mCPBA, NaHCO₃</td>
<td>-20 to 0</td>
<td>12 h</td>
<td>degradation</td>
</tr>
<tr>
<td>tBuOOH</td>
<td>-20 to 0</td>
<td>48 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>OsO₄</td>
<td>0 to 25</td>
<td>24 h</td>
<td>4.18</td>
</tr>
</tbody>
</table>

*Table 4.1. Conditions for oxidation attempts.*
4.4. Conclusion.

To summarize, as a part of the studies *en route* to taxol and its analogues we attempted to incorporate the novel approach to the $\alpha$-ketol rearrangement of the pretaxane structure. In the first attempt, the structure with deprotected C10 hydroxyl was examined and we found the strong propensity of it toward formation of transannual hemiacetal, similar to those observed earlier. The isolated compound was not of any synthetic interest and therefore further studies were not conducted. As the second option, the investigation of rearrangement facilitated by acetal formed on C9, C10 hydroxyls was conducted and quickly revealed a very unusual reactivity of the olefins present in the molecule under oxidative condition. The activated double bond of the enol ether exhibited complete inertness compared to the exocyclic counterpart. Under a number of conditions, even specifically designed for the former, the products of oxidation of the latter were recovered in high yield. Clearly, this fact demonstrated a direct relationship between conformational state of the molecule and the reactivity of its functional groups. The investigation of this route extended only to the point when the obstacle of oxidation was not possible to overcome.

Regretfully, my brief involvement did not result in significant contribution. On the other hand, each new finding, even that of lacking further advancement, helps to clarify further the overall picture of taxol chemistry. In this sense, I hope that my contribution provided that help for researchers continuing the exploration toward the better synthetic solution for taxol.
4.4. Experimental Section.\textsuperscript{103}

Procedure for 4.13.

To the solution of 4.5 (5 mg, 7.2 µmol) in 2 mL of CH₂Cl₂ and 0.1 mL of H₂O, 2.6 mg (11 µmol) of DDQ was added in one portion at ambient temperature. The mixture was stirred for 2 h and diluted with 20 mL of CH₂Cl₂, washed with 10% aq. NaHCO₃ (3x10 mL), brine and dried over Na₂SO₄. The mixture was concentrated and the product was purified by flash chromatography on silica gel (gradient elution with 10:1 to 7:1 hexane/ethyl acetate) to yield 3.3 mg (80%) of deprotected alcohol 4.13 as a clear oil; IR (neat, cm\textsuperscript{-1}): 3264, 2954, 2856, 1700, 1656, 1514, 1146, 1182, 835; \textsuperscript{1}H NMR (300 MHz, CDCl₃): δ = 8.20-8.13 (m, 2H), 7.72-7.65 (m, 1H), 7.57-7.49 (m, 2H), 5.76 (br s, 1H), 5.65 (d, J = 11.4 Hz, 1H), 4.93 (s, 1H), 4.70 (s, 1H), 4.67 (s, 1H), 4.33 (dd, J = 9.9, 4.5 Hz, 1H), 3.89-3.85 (m, 1H), 2.79 (d, J = 11.0 Hz, 1H), 2.49-2.34 (m, 2H), 2.30-2.23 (m, 2H), 2.05-1.81 (m, 4H), 1.70 (br s, 2H), 1.61-1.43 (m, 2H), 1.41 (s, 3H), 1.28 (s, 3H), 0.83 (s, 9H), 0.13 (s, 3H), 0.10 (s, 3H); HRMS (ES): m/z calcd for C\textsubscript{32}H\textsubscript{46}O\textsubscript{7}Si•Na (M+Na)\textsuperscript{+} 593.2911; obsd 593.2890; [\textgreek{a}]\textsubscript{D}\textsuperscript{30} -89.2 (c 0.29, CHCl₃).
Procedure for 4.19.

To the solution of 0.294 g (0.446 mmol) of ketone 4.15 in 5 mL of ether, a solution of LiAlH₄ (3.12 mL at 1.0 M in ether, 3.12 mmol, 7 equiv.) was added slowly via syringe in three equal portions at 5 min intervals at ambient temperature. The reaction mixture was stirred for 30 min after the final addition and methanol (1 mL) was carefully added. The mixture was diluted with saturated aqueous Rochelle’s salt solution and the layers were separated. The aqueous layer was extracted with ether (3x15 mL) washed with brine and dried over Na₂SO₄. The solvent was evaporated leaving a white solid of crude product, which was purified by flash chromatography on silica gel (gradient elution with 9:1 to 7:1 hexane/ethyl acetate) to give compound 4.19 as white crystals (0.291 mg, 98%); mp 149-151 °C; IR (neat, cm⁻¹): 3446, 2954, 2856, 1650, 1614, 1514, 1249; ¹H NMR (300 MHz, CDCl₃): δ = 7.37-7.32 (m, 5H), 7.31-7.26 (m, 2H), 6.90-6.84 (m, 2H), 4.84 (s, 1H), 4.71-4.56 (m, 2H), 4.62 (s, 1H), 4.54 (s, 1H), 4.47 (s, 1H), 4.33 (d, J = 9.9 Hz, 1H), 4.03 (dd, J = 10.9, 4.4 Hz, 1H), 3.95 (br s, 1H), 3.82-3.79 (m, 5H), 3.70 (d, J = 3.5 Hz, 2H), 2.68 (d, J = 11.4 Hz, 1H), 2.49-2.30 (m, 2H), 2.23-1.77 (series of m, 6H), 1.74-1.53 (m, 4H), 1.49 (s, 3H), 1.28-1.21 (m, 2H), 1.08 (s, 3H), 1.04 (s, 3H), 0.86 (s, 9H); ¹³C NMR (75 MHz, CDCl₃): δ = 158.7, 147.0, 138.6, 131.3, 128.5 (2C), 128.3, 127.8 (2C), 127.4, 113.5, 107.4, 103.0, 87.7, 87.1, 81.8, 75.2, 69.8, 63.4, 55.2, 47.7, 45.9, 42.3, 39.0, 33.8, 33.0, 32.1, 30.3, 29.7, 29.1, 26.8, 26.2 (3C), 22.7, 21.0, 18.4,
14.3, -2.2, -3.3;  HRMS (ES): $m/z$ calcd for $\text{C}_{40}\text{H}_{58}\text{O}_{6}\text{Si}\cdot\text{Na} (\text{M+Na})^+$ 685.3895; obsd 685.3949; $[\alpha]_{D}^{20}$ -31.1 (c 0.27, CHCl$_3$).

**Procedure for 4.16.**

To the solution of 18.5 mg (0.028 mmol) of PMB protected $\alpha$-dil $4.19$ in 2.5 mL of ether, 20 mg of freshly baked 4 Å molecular sieves and 6.8 mg (0.030 mmol, azeotropically dried with benzene prior to use) of DDQ was added in one portion at ambient temperature. The mixture was stirred for 2 h and diluted with 100 mL of CH$_2$Cl$_2$, washed with 10% aqueous NaHCO$_3$ (3x50 mL), brine and dried over Na$_2$SO$_4$. The mixture was concentrated and the product was purified by flash chromatography on silica gel (gradient elution with 9:1 to 7:1 hexane/ethyl acetate) to yield 14.8 mg (80%) of compound 4.16 as a white solid; mp 131-132 °C;  IR (neat, cm$^{-1}$): 3446, 2855, 1620, 1514, 1250;  $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 7.44-7.27 (m, 7H), 6.85-6.79 (m, 2H), 5.98 (s, 1H), 4.95 (d, $J = 11.7$ Hz, 1H), 4.88 (q, $J = 10.5$ Hz, 2H), 4.84 (s, 1H), 4.66 (s, 1H), 4.24 (t, $J = 5.0$ Hz, 1H), 4.14 (d, $J = 5.0$ Hz, 1H), 3.81-3.77 (m, 5H), 3.69 (dd, $J = 10.8$, 4.8 Hz, 1H), 3.23 (d, $J = 11.7$ Hz, 1H), 2.81-2.72 (m, 1H), 2.47-2.16 (series of m, 4H), 2.07-1.94 (m, 1H), 1.78-1.50 (m, 3H), 1.28-1.21 (m, 2H), 1.13 (s, 3H), 0.99 (s, 3H), 0.53 (s, 9H), -0.06 (s, 3H), -0.24 (s, 3H);  $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 147.0, 138.2, 132.0, 128.4 (2C), 127.8 (2C), 127.7 (2C), 127.6 (2C), 114.3, 106.7, 104.1, 80.0, 79.4, 72.6,
63.0, 44.2, 42.6, 39.9, 39.3, 36.7, 33.6, 31.7, 29.5, 27.1, 25.8 (3C), 25.6, 19.8, 19.3, 18.1, 13.0, -3.0, -5.1, (3C not observed); HRMS (ES): m/z calcd for C$_{40}$H$_{56}$O$_6$Si•Na (M+Na)$^+$ 683.3738; obsd 683.3696; $[\alpha]_{D}^{20}$ -15.2 (c 0.19, CHCl$_3$).

**Procedure for 4.17.**

To the solution of **4.16** (5.2 mg, 7.87 µmol) in 5 mL of CH$_2$Cl$_2$, a solution of freshly prepared DMDO (8.0 mL at ca. 0.01 M in acetone, 0.080 mmol) was added in one portion at 0 °C. The mixture was stirred for 30 min, warmed to ambient temperature and stirred for an additional 2 h. The volatiles were evaporated leaving a crude product in the form of solid, which was purified by flash chromatography on silica gel (gradient elution with 9:1 to 7:1 hexane/ethyl acetate) to yield 4.3 mg (80%) of a compound **4.17** as a white crystals; mp 145-147 °C; IR (neat, cm$^{-1}$): 2943, 1569, 1437, 1248, 1121, 1028, 829; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 7.40-7.27 (m, 7H), 6.84-6.79 (m, 2H), 5.97 (s, 1H), 4.76 (q, $J$ = 11.5 Hz, 2H), 4.42 (d, $J$ = 12.2 Hz, 1H), 4.23 (d, $J$ = 5.6 Hz, 1H), 4.04 (d, $J$ = 5.6 Hz, 1H), 3.78 (s, 3H), 3.65 (dd, $J$ = 5.2, 10.4 Hz, 1H), 3.18 (d, $J$ = 12.2 Hz, 1H), 2.79-2.73 (m, 2H), 2.52 (d, $J$ = 4.5 Hz, 1H), 2.50-2.37 (m, 1H), 2.33-2.23 (m, 1H), 1.96-1.69 (m, 4H), 1.64-1.52 (m, 4H), 1.39-1.21 (m, 2H), 1.13 (s, 3H), 1.09 (s, 3H), 0.54 (s, 9H), -0.04 (s, 3H), -0.23 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 148.1, 139.3, 128.6 (2C), 127.75 (2C), 127.67 (2C), 127.56 (2C), 115.3, 105.4, 80.9, 79.1, 72.6, 63.0,
57.5, 56.5, 44.4, 43.1, 42.8, 39.9, 39.2, 33.8, 32.2, 29.3, 27.7, 27.3, 25.9 (3C),
25.5, 20.9, 19.3, 18.4, 13.2, -3.2, -4.8, (2C not observed); HRMS (ES): m/z
calcd for C_{40}H_{56}O_{7}Si•Na (M+Na)^+ 699.3693; obsd 699.3694; [α]_{D}^{19} -31.4 (c 0.89,
CHCl_{3}).

Procedure for 4.18.

To a solution of olefin 4.16 (12 mg, 18.2 µmol) in
acetone/water (0.5 mL/0.05 mL) was added MeSO_{2}NH_{2}
(5.2 mg, 54.5 µmol, 3 equiv) and OsO_{4} (2.3 mg, 9.1
µmol) at 0 °C. The mixture was stirred for 3h at 0 °C
and an additional 24 h at ambient temperature, treated
with a solution of Na_{2}S_{2}O_{4} (4.9 mg, 0.028 mmol) in water (2 mL), stirred for 1 h,
and extracted with CH_{2}Cl_{2} (3x25 mL). The combined organic extracts were
washed with brine, dried over Na_{2}SO_{4}, filtered and concentrated prior to flash
chromatography (gradient elution with 7:1 to 5:1 hexane/ethyl acetate) to afford
compound 4.18 (7.0 mg, 56%) as a white solid; mp 119-121 °C; IR (neat, cm^{-1}):
3374, 2956, 1614, 1102; ^1H NMR (300 MHz, CDCl_{3}): δ = 7.43-7.27 (m, 7H),
6.92-6.81 (m, 2H), 6.07 (s, 1H), 4.34 (t, J = 5.6 Hz, 1H), 4.08 (d, J = 5.6 Hz, 1H),
3.80-3.73 (m, 5H), 3.58 (dd, J = 4.0, 8.4 Hz, 1H), 3.15-2.97 (m, 2H), 2.90-2.81
(m, 1H), 2.68 (d, J = 8.2 Hz, 1H), 2.55-2.49 (m, 1H), 2.10-2.04 (m, 1H), 2.03-
1.90 (m, 2H), 1.76-1.59 (m, 2H), 1.39-1.11 (m, 2H), 1.25 (br s, 1H), 1.15 (s, 3H),
0.95 (s, 3H), 0.58 (s, 9H), -0.05 (s, 3H), -0.20 (s, 3H); HRMS (ES): m/z calcd for C_{33}H_{52}O_8Si•Na(M+Na)^+ 627.3324; obsd 627.3318; [\alpha]_D^\circ +28.9 (c 0.34, CHCl_3).
REFERENCES AND NOTES.


(103) For general considerations, please refer to Section 1.5.


(132) The procedure was adopted from reference 128.


(134) Tipson, R. S.; Cohen, A. *Carbohydrate Res.* **1965**, *1*, 338.


(138) We attempted different Raney nickel activities, as well as palladium on charcoal. Different stoichiometry was also applied.


(151) Aldrich catalog 2003-2004: 17,044-5 methyl α-D-glucopyranoside, [97-30-3], 500g at $46.20.

(152) Initially, we attempted to oxidize C6 position to the ester and perform the Grignard addition. The resulting methyl ketone could be olefinated further. This three step sequence was not applicable due to the complete degradation of the material on the first step. This work was done mostly by Jacques-Alexis Funel and Sergei Bolshakov.


(155) Although we did not try to study the absolute configuration of this compound, but we believe it is 1R,2R,5S-2-isopropenyl-5-methylcyclopentanol.


(157) The initial experimentation was conducted in close collaboration with Prof. Ho-Jung Kang, who was present in our research group at that time.


(170) The author thanks Dr. John E. Hofferberth for these calculations.

(171) This oxidation was performed under very similar conditions as for compound 3.31.
(172) The name 'Taxol' is a trademark of Bristol-Myers Squibb.


APPENDICES
APPENDIX A

$^1$H NMR SPECTRA OF CHAPTER 1
Figure A.1. $^1$H NMR spectrum of 1,19.
Figure A.2. $^1H$ NMR spectrum of 1.20.1.
Figure A.3. $^1$H NMR spectrum of 1,20,2

$\text{H}_2\text{C}_6\text{O}_4\text{H}$ $\text{H}_2\text{O}$ $\text{CH}_3$
Figure A.4. $^1$H NMR spectrum of 1.20.3.
Figure A.5. $^1H$ NMR spectrum of 1.21.1.
Figure A.6. $^1$H NMR spectrum of 1,22,1.
Figure A.7. $^1$H NMR spectrum of 1,21,2.
Figure A.8. $^1$H NMR spectrum of 1,22,2.

\[ \text{Structural formula of the compound} \]
Figure A.9. $^1$H NMR spectrum of 1,21,3.
Figure A.10. $^1H$ NMR spectrum of 1,2,2,3.
Figure A.11. $^1$H NMR spectrum of 1,2,3,2.
Figure A.12. $^1$H NMR spectrum of 1.24.2.
Figure A.15. $^1H$ NMR spectrum of 1.23.3.
Figure A.16. $^1$H NMR spectrum of 1,24,3.
APPENDIX B

$^1$H NMR SPECTRA OF CHAPTER 2
Figure B.1. $^1$H NMR spectrum of OHBu$_3$Sn.
Figure B.2. $^1$H NMR spectrum of 2.21.
Figure B.3. $^1$H NMR spectrum of 2,20.
Figure B.4. $^1H$ NMR spectrum of 2.29.
Figure B.5. $^1H$ NMR spectrum of 2.27.
Figure B.6. $^1$H NMR spectrum of 2.28.1.
Figure B.7. $^1$H NMR spectrum of 2.28.2
Figure B.8. $^1$H NMR spectrum of 2.19.1.
Figure B.9. $^1H$ NMR spectrum of 2.19.2.
Figure B.10. $^1$H NMR spectrum of 2.30.1.
Figure B.11. $^1$H NMR spectrum of 2.30.2.
APPENDIX C

$^1H$ NMR SPECTRA OF CHAPTER 3
Figure C.1. $^1$H NMR spectrum of 3.27.
Figure C.2. $^1$H NMR spectrum of 3.28.3.
Figure C.3. $^1H$ NMR spectrum of 3.28.1.
Figure C.4. $^1$H NMR spectrum of 3.28.2.
Figure C.5. $^1$H NMR spectrum of vic-dimesylate of 3.28.3.
Figure C.6. $^1$H NMR spectrum of vic-dimesylate of 3.28.1.
Figure C.7. $^1$H NMR spectrum of vic-dimesylate of 3.28.2.
Figure C.8. $^1$H NMR spectrum of 3.29.3.
Figure C.10. $^1$H NMR spectrum of 3.29.2.
Figure C.11. $^1$H NMR spectrum of 3.31 prior to hydrogenation.
Figure C.12. $^1H$ NMR spectrum of 3.30.1.
Figure C.13. $^1H$ NMR spectrum of 3.31.
Figure C.14. $^1$H NMR spectrum of 3.32.
Figure C.15. $^1$H NMR spectrum of 3.33.
Figure C.16. $^1$H NMR spectrum of 3.20.
Figure C.17. $^1$H NMR spectrum of 3.19.
Figure C.18. $^1$H NMR spectrum of isomer of 3.19.
Figure C.19. *1H* NMR spectrum of 3,23.
Figure C.20. $^1H$ NMR spectrum of 3.22.
Figure C.21. 1H NMR spectrum of 3.21.
APPENDIX D

$^1H$ NMR SPECTRA OF CHAPTER 4
Figure D.1. $^1H$ NMR spectrum of 4.13.
Figure D.2. $^1$H NMR spectrum of 4.15 after being reduced with LiAlH$_4$. 
Figure D.3. $^1$H NMR spectrum of 4,16.
Figure D.4. $^1$H NMR spectrum of 4.17.
Figure D.5. $^1$H NMR spectrum of 4.18.