Approaches to terpenoid natural products using reactive intermediates

Steven Barse Laramay
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Approaches to terpenoid natural products using reactive intermediates

Laramay, Steven Barse, Ph.D.
Iowa State University, 1990
Approaches to terpenoid natural products
using reactive intermediates

by

Steven Barse Laramay

A Dissertation Submitted to the
Graduate Faculty in Partial Fulfillment of the
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DOCTOR OF PHILOSOPHY
Department: Chemistry
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For the Major Department

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For the Graduate Office

Iowa State University
Ames, Iowa
1990
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DEDICATION

This manuscript is dedicated to the memory of my late grandmother Helen Smith Barse who had the greatest influence in my education.
The goal of a synthetic organic chemist is not only the synthesis of complex natural products, but also to synthesize these products using novel methodology and to develop a concise, efficient route. A problem that one learns while developing an approach is that the first route rarely works, so one must be ready to adapt to the inevitable stumbling blocks that lie in the original approach. The purpose of this research was to develop convergent routes to natural products that contain [3.2.1] bicyclic ring systems. What will be shown is the evolution of these approaches toward that goal. Part I describes an approach to kaurenoid natural products using bridgehead enone Diels-Alder methodology to synthesize the tetracyclic carbon framework. Part II describes a conceptually different approach to kaurenoid natural products. Finally, Part III describes an approach to trixikingolides natural products using bridgehead carbocation methodology.
EXPLANATION OF THESIS FORMAT

This thesis is written so that each section can be regarded as a separate article in publishable form. Therefore, the numbering of the figures, schemes, tables, and references is independent in each section.
PART I: AN ATTEMPTED APPROACH TO KAURENOID NATURAL PRODUCTS USING A BRIDGEHEAD ENONE DIELS-ALDER REACTION
INTRODUCTION

This manuscript will outline the synthetic program directed toward the synthesis of kaurenoic natural products. The proposed route would allow a convergent synthesis that starts with the bicyclic unit intact. Previous syntheses of this class of natural products used linear approaches that usually synthesized the bicyclic unit late in the synthesis. Our attempts used a bridgehead enone Diels-Alder reaction to construct advanced intermediates in our synthesis.
Unsaturation at a bridgehead position was long considered an unrealizable intermediate because of the strain that would be inherent in a compound such as 1. Compound 1 cannot conform to a 120° bond angle needed for the classic carbon–carbon double bond. Recently two comprehensive reviews by Warner,¹ and Kraus and coworkers² have appeared that discuss reactive bridgehead intermediates. Bridgehead enones (2) could play an important role in organic synthesis because of their high reactivity. Bridgehead enones would allow for the construction of quaternary carbons. Because of the constraints of the ring system, reactions could be highly stereospecific.

The classical study of [n.3.1] bridgehead enones is attributed to reports by House and coworkers in the late 1970s and early 1980s.³⁻⁸ House and coworkers have synthesized a
A variety of bridgehead enones including the bicyclo[5.3.1]undecenone 3, bicyclo[4.3.1]decenone 4, bicyclo[3.3.1]nonenone 5, and bicyclo[3.2.1]octenone 6 were studied by House to determine their stability and reactivity. House found that as the ring size decreased, the reactivity of the enone increased due to the increasing strain of the double bond, forcing it to twist from planarity. Using Allinger's MMPI molecular mechanics program, House calculated the average twist of the double bond and the inherent strain of each of the bicyclic systems (Table I).

Table I. Selected Theoretical Data for Bridgehead Enones

<table>
<thead>
<tr>
<th>Enone</th>
<th>average twist of C=C bond (°)</th>
<th>inherent strain (Kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>4</td>
<td>16.9</td>
</tr>
<tr>
<td>4</td>
<td>14</td>
<td>17.7</td>
</tr>
<tr>
<td>5</td>
<td>21</td>
<td>21.3</td>
</tr>
<tr>
<td>6</td>
<td>36</td>
<td>32.3</td>
</tr>
</tbody>
</table>
theoretical results correlate well with the experimental results. Whereas enones 3 and 4 can be isolated in the absence of nucleophiles and show no propensity to dimerize upon heating, enones 5 and 6 cannot be isolated. If there is no nucleophile present, enone 5 undergoes a facile [2 + 2] dimerization. The \textit{in situ} generation of enone 5 produced three adducts 7, 8, and 9.\textsuperscript{5} Enone 6, like 5, undergoes facile 1,4-additions in the presence of a variety of nucleophiles, such as methanol, water and sodium phenylselenide.\textsuperscript{7} House and coworkers have also shown that enones 5 and 6 undergo facile [4 + 2] cycloaddition with furan at ambient temperature. Enone 5 produced both the exo adduct 13 (as the major product) and the endo adduct 14 (as the minor product) in the Diels-Alder reaction.\textsuperscript{5} Recently Campbell and coworkers proved the existence of enone 5 by preparing enone 5 by flash vacuum pyrolysis, and enone 5 was stable in solution at -78°C.\textsuperscript{9}
Bestmann and Schade have also been successful in preparing bicyclo [4.3.1] decenone 15, bicyclo [3.3.1] nonenone 16, and bicyclo[3.2.1] octenone 17 via
intramolecular Wittig reactions. These bridgehead enones were trapped with ethanol to give bridgehead ethers.

The use of bridgehead enones as electrophiles has increased in recent years. Magnus and coworkers were the first to report the synthetic utility of bridgehead enones. In their elegant synthesis of (+)-kopsanone (18), they used the high reactivity of bridgehead enones to effect a facile 1,2-shift of phenylsulfenic acid. Starting with aldehyde 19 they were able to convert 19 to the sulfoxide 20, which upon heating eliminated the phenylsulfenic acid to provide the bridgehead enone 21. The resulting phenylsulfenic acid added across the enone to form the sulfoxide 22. Sulfoxide 22 was then converted in three steps to (+)-kopsanone.
Kraus and Hon also successfully employed a bridgehead enone in one of their two short approaches to (+)-lycopodine 23. The bridgehead enone was generated *in situ* by a dehydrohalogenation reaction of the bridgehead bromide 24. Compound 24 was formed in seven steps from 25. The enone 26 was generated by the addition of 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU) and was then trapped with 3-amino-1-propanol to give 27. Ketone 27 has been previously converted to lycopodine in two steps by Heathcock et al.13

\[
\begin{align*}
25 & \quad \text{\textbf{K}} \quad \text{\textbf{O}} \\
24 & \quad \text{\textbf{Br}} \quad \text{\textbf{O}} \\
26 & \quad \text{\textbf{DBU}} \quad \text{\textbf{O}} \\
27 & \quad \text{\textbf{OH}} \\
23 & \quad \text{\textbf{OH}}
\end{align*}
\]

Kraus and Yi have also been successful in adding cuprates to *in situ* generated bridgehead enones. A variety of cuprates such as methyl, vinyl, and phenyl have added 1,4 in greater than 50% yield to bridgehead enones derived from bromides 28 or 29. Either potassium tert-butoxide or lithium 2,6-di-tert-butyl-4-methylphenoxide was used as the base. This methodology allows for the alkylation at a bridgehead position.
Kraus and coworkers have also reported the synthetic utility of the [2 + 2] addition of electron rich alkenes to bridgehead enones. In the reaction of bridgehead bromide 28 and 1,1-dimethoxyethene 30 in the presence of triethylamine, adduct 31 was formed in 100% yield. After reduction followed by deacetylation, diketone 32 was formed. This diketone was proposed to be a key intermediate in the synthesis of the taxane class of natural products.
A systematic study of the potential of bicyclo[3.3.1] nonenones as dienophiles has been completed by Kraus and coworkers. In this study it was determined that a variety of dienes formed exclusively exo Diels-Alder adducts when excess triethylamine was added to a solution of the bridgehead bromide and 2 to 4 equivalents of the diene (Table II). It is important to note that 1,1-3-trisubstituted dienes (entries 5, 6, and 7) which are usually unreactive in the Diels-Alder reaction gave satisfactory yields of Diels-Alder adducts. The identity of the adducts were proven by using 2D NMR COSY and NOESY techniques on the adduct in entry 5 Table II.

Kraus has proposed transition state 33 as the rationale for the exclusive formation of the exo adduct. In normal Diels-Alder reactions, the endo products are favored due to favorable secondary orbital overlap interactions, but in this case the endo transition state 34 is sterically congested. The secondary orbital overlap interaction can not be attained; therefore, the less sterically demanding transition state 33 determines the stereochemical course of the reaction. Kraus has also suggested that the mechanism may not be concerted.
### Table II. Reported Deils-Alder Reactions with Bridgehead Enones

![Chemical Structure]

<table>
<thead>
<tr>
<th>Entry</th>
<th>$R_1$</th>
<th>$R_2$</th>
<th>$R_3$</th>
<th>$R_4$</th>
<th>$R_5$</th>
<th>$R_6$</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$(\text{CH}_2)_4$</td>
<td>OTMS</td>
<td>H</td>
<td>SPh</td>
<td>H</td>
<td>97</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>$(\text{CH}_2)_4$</td>
<td>OTMS</td>
<td>H</td>
<td>H</td>
<td>CH$_3$</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>$(\text{CH}_2)_4$</td>
<td>OTMS</td>
<td>CH$_3$</td>
<td>H</td>
<td>CH$_3$</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>OTMS</td>
<td>H</td>
<td>OCH$_3$</td>
<td>H</td>
<td>SPh</td>
<td>H</td>
<td>98</td>
</tr>
<tr>
<td>5</td>
<td>OTMS</td>
<td>H</td>
<td>CH$_3$</td>
<td>SPh</td>
<td>H</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>OTMS</td>
<td>H</td>
<td>CH$_3$</td>
<td>SPh</td>
<td>H</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>OTMS</td>
<td>CH$_3$</td>
<td>H</td>
<td>CH$_3$</td>
<td>SPh</td>
<td>H</td>
<td>46</td>
</tr>
</tbody>
</table>
and that an ionic or polarized transition state may be more appropriate. The possibility of
an ionic mechanism was supported since the α–β unsaturated ester 35 is the sole product
formed in the reaction of diene 36 with the bridgehead enone derived from 28. Kraus

\[
\begin{align*}
28 + & \\
+ & TMSO & \text{OCH}_3 \\
\text{OCH}_3 & \text{Et}_3N & \text{CO}_2\text{CH}_3 \\
\text{SPh} & \text{OCH}_3 & \text{OTMS} \\
\text{SPh} & & \\
\end{align*}
\]

has proposed that this type of mechanism would also produce exclusively exo adducts by
minimizing steric interactions in the intermediate 37. Kraus and Liras have also reported
further evidence of an ionic mechanism in the report of the inverse selectivity of diene 38
in the bridgehead enone Diels-Alder reaction. The adduct 39 is the only adduct that was
detected, and was the expected product from an ionic mechanism. Liras has since reported
the bridgehead Diels-Alder reaction using diene 40. This diene was reported as the
definitive test for the ionic mechanism, since products of a cyclopropyl-carbonyl cation
rearrangements were expected if an ionic mechanism was involved. The only product
detected was adduct 41, which has led Kraus to propose a polarized rather than an ionic or a concerted mechanism for the bridgehead enone Diels-Alder reaction.

\[
\begin{align*}
28 + \text{TMSO} & \xrightarrow{\text{Et}_3\text{N}} \begin{cases}
\text{OTMS} & \text{Et}_3\text{N} \\
\text{SPh} & \text{OTMS}
\end{cases} \\
\text{37} & \xrightarrow{\text{H}} \text{R} \\
\text{39}
\end{align*}
\]
28 + TMSO

40

ET3N

\[
\begin{align*}
&\text{28} + \text{TMSO} \\
&\text{40} \rightarrow \text{Et}_{3}\text{N} \\
&\text{41}
\end{align*}
\]
RESULTS AND DISCUSSION

The key to our approach centered around the use of a bridgehead enone Diels-Alder reaction to construct the tetracyclic ring system. This approach would allow for a convergent synthesis if an appropriate diene was used and would allow for a synthesis that contains a latent bicyclo[3.2.1]octane ring system early in the synthesis. The retro-synthetic analysis of the approach to corymbol 42\textsuperscript{21} is depicted in Scheme I. Corymbol will be synthesized from intermediate 43 by known functional group manipulations.

Scheme I
Ketone 44 will be formed from 43 by a previously reported ring contraction. This ring contraction involves oxidation of the sulfide to the sulfoxide followed by elimination. The alkene is oxidation to the dialdehyde, then intramolecular aldol condensation to form a ring contracted unsaturated aldehyde. This aldehyde is reduced to the 43. An iterative methyl cuprate addition was envisioned to transform 45 to 44. Enone 45 will be synthesized by chlorotrimethylsilane assisted methyl cuprate addition to 46 followed by oxidation to the enone. Enone 46 is then synthesized by a bridgehead enone Diels-Alder reaction between the bridgehead bromide 28 and diene 47, followed by oxidation to the enone.

Our first goal was the synthesis of the tetracyclic enone 46 from the bridgehead bromide and the previously reported diene 47. The bridgehead enone Diels-Alder reaction with the bridgehead bromide 28 and diene 47 yielded the Diels-Alder adduct 48 in 70% yield as the only diastereomer. The next task was the oxidation of the enol silyl ether to an enone. A Saegusa reaction [Pd(OAc)$_2$, 1,4-benzoquinone] was used to regioselectively oxidize 48 to the needed enone 46. Two possible enones 46 and 49 could be formed. Enone 46 is the only isomer formed because of nonbonded interactions with the β-phenylthio group (PhS) only allowing intermediate 50 to form. The cis addition across the C - H bond occurs regioselectively to the weaker tertiary C - H bond.
Pd(0Ac)$_2$, 1,4-benzoquinone, CH$_3$CN, 25 °C

\[ \xrightarrow{\text{Pd(OAc)$_2$, 1,4-benzoquinone, CH$_3$CN, 25 °C}} \]

\[ 48 \quad 46 \]

\[ 49 \]

giving the intermediate 51 which eliminates to enone 46 as the sole product.

With the enone in hand, the next objective was the addition of the C-10 angular methyl group (kaurene numbering) to form 52. Several methyl cuprate reagents, such as

\[ \xrightarrow{(\text{CH}_3)_x\text{CuM}_y} \]

\[ 46 \quad 52 \]
heterocuprates, boron trifluoride etherate assisted cuprates, and chlorotrimethylsilane assisted cuprates were employed to add to the enone, but all attempts failed. One group that did add to the enone was a cyano group. Using the conditions of Utimoto and coworkers (diethyl aluminum chloride and trimethylsilyl cyanide) the nitrile 53 was produced efficiently. Nitrile 53 was not able to be reduced to aldehyde 54 with diisobutyl aluminum hydride (DIBAL) nor could it be oxidized to the peroxyimidic acid using hydrogen peroxide. The later reaction could have led to the amide 55. The failure of
these reactions was attributed to a steric effect due to nonbonded interactions between the cyano group and the axial hydrogen at C-4 (kaurene numbering). If the enol silyl ether could be oxidized to enone 56, the non-bonded interaction would be minimized. First the Saegusa reactions conditions were attempted, but these conditions failed to provide enone 56. There had been a report by Minami and coworkers of the success of oxidizing enol silyl ethers to enones using Pd(OAc)$_2$, diallyl carbonate, and 1,2-bis(diphenylphosphino)ethane. These conditions were also unsuccessful in oxidizing 53 to 56.

\[
\begin{align*}
\text{Pd(OAc)$_2$} & \quad \text{benzoquinone} \\
53 & \quad \text{CH}_3\text{CN} \quad 25 ^\circ\text{C} \\
\text{or} & \\
\text{Pd(OAc)$_2$, DPPE, diallyl carbonate} & \\
\text{CH}_3\text{CN} \quad 25 ^\circ\text{C}
\end{align*}
\]

Because of the difficulty in transforming the cyano group to the angular methyl group, a strategy to 43 was devised which would allow the addition of the angular methyl group as part of the diene. A tricyclic precursor would be formed in the bridgehead Diels-Alder reaction instead of a tertracyclic precursor. The fourth ring would be annulated later in the synthesis. This strategy is outlined in Scheme II. Enone 57 would allow for the synthesis of the geminal dimethyl group by a methyl cuprate addition. Enone 57 would be prepared by a Diels-Alder reaction between enone 58 and piperylene followed by isomerization of the double bond. Enone 58 would be synthesized from the bridgehead Diels-Alder adduct 59 by oxidation to the enone, deprotection of the ethoxy ethyl ether,
then oxidation of the allylic alcohol to the aldehyde. Adduct 59 would be prepared by a bridgehead enone Diels-Alder reaction between bridgehead bromide 28 and diene 60.

Scheme II

The diene 60 is prepared in four steps from 2-butene-1,4-diol (61). Protection of the diol as the diethoxyethyl ether was followed by ozonolysis which produced the protected hydroxy acetaldehyde 62. Aldehyde 62 was transformed to diene 60 by a Wittig reaction with the keto phosphonate 63 to form enone 64, followed by reaction of the resulting enone with trimethylsilyl triflate (TMSOTf) and triethylamine, formed diene 60. The bridgehead enone Diels-Alder reaction with the bridgehead bromide 28 and 1.2 equivalents of diene 60 produced the Diels-Alder adduct 59 as a single diastereomer. This adduct was
converted to the enone 63 using the Saegusa reaction and then was deprotected with dilute acid in tetrahydrofuran to form the allylic alcohol 66.

\[ \text{HO-}\text{CHOH} \text{CH}_2\text{OH} \rightarrow \text{EEO-CHO} \rightarrow \text{C}_8\text{H}_6, \text{reflux} \]

\[ \text{OEt, PPTS} \quad \text{CH}_2\text{Cl}_2, 25 \, ^\circ\text{C} \]

\[ \text{O}_3, \text{CH}_2\text{Cl}_2, -78 \, ^\circ\text{C} \quad \text{then, (Ph)}_3\text{P} \quad -78 \, ^\circ\text{C} - 25 \, ^\circ\text{C} \quad 80 \% \]

\[ \text{TMSOTf, Et}_3\text{N} \quad \text{CH}_2\text{Cl}_2, 0 \, ^\circ\text{C} - 25 \, ^\circ\text{C} \quad 82 \% \]

\[ \text{Et}_3\text{N, CH}_2\text{Cl}_2 \quad 0 \, ^\circ\text{C} - 25 \, ^\circ\text{C} \quad 72 \% \]

\[ \text{Pd(OAc)}_2, \text{benzoquinone} \quad \text{CH}_3\text{CN} 25 \, ^\circ\text{C} \]

\[ \text{OEE} \]

\[ \text{OTMS} \]

\[ \text{OEE} \]

\[ \text{OTMS} \]

\[ \text{OEE} \]

\[ \text{OTMS} \]

\[ \text{OEE} \]

\[ \text{OTMS} \]
The conversion of the allylic alcohol to the aldehyde proved not to be a simple task. The conditions attempted are reported in Table III. None of the conditions attempted gave satisfactory yields of the aldehyde. The best, PDC, produced the aldehyde in 53% yield with significant decomposition of the starting material. Also of note are the attempts with conditions described by Rousch and Franck, where in the only detectable product was the starting material.

Table III. Oxidation of Allylic Alcohol 66 to Aldehyde 58

<table>
<thead>
<tr>
<th>Oxidant</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDC</td>
<td>53 %</td>
</tr>
<tr>
<td>PCC</td>
<td>40 %</td>
</tr>
<tr>
<td>Jones</td>
<td>decomposition</td>
</tr>
<tr>
<td>(COCl)$_2$, DMSO, Et$_3$N</td>
<td>no reaction</td>
</tr>
<tr>
<td>TFAA, DMSO, Et$_3$N</td>
<td>no reaction</td>
</tr>
</tbody>
</table>
In view of these results, a diene which had the allylic carbon at the proper oxidation state was envisioned. Diene 67 was prepared in a similar manner as diene 60 from the previously reported aldehyde 68. Diene 67 was used in the bridgehead Diels-Alder reaction to form adduct 69 which was oxidized to the enone using the Saegusa reaction. The acetal was deprotected using PTSA in wet acetone to give the required aldehyde 58. Two different Diels-Alder reaction conditions were attempted to annulate the fourth
ring of kaurenoid ring system to aldehyde 58. Using piperylene with Lewis acid catalysis (SnCl\(_4\)) resulted in the isolation of the starting material. The other attempt with Danishefsky's diene\(^{37}\) at 190 °C resulted in the decomposition of the aldehyde 58.

\[
\begin{align*}
\text{No Reaction} & \quad \text{SnCl}_4, \text{CH}_2\text{Cl}_2 \quad 25 \, ^\circ\text{C} \\
\text{Decomposition of 58} & \quad \text{SnCl}_4, \text{CH}_2\text{Cl}_2 \quad 190 \, ^\circ\text{C}
\end{align*}
\]

The last avenue in this area that was investigated was a Michael addition to enone 65. Maruoka and coworkers have reported the 1,4 addition of organolithiums and Grignard reagents to enones using a excess of methylaluminium bis-(2,6-di-t-butyl)-4- methyl phenoxide (MAD).\(^{38}\) There has been a report by Stem and Swenton that ketals direct the addition of organolithiums to quinone monoketals using MAD.\(^{39}\) The ethoxyethyl protecting group in 65 could be used to direct the addition to the enone. This reaction was attempted using \(n\)-butyl lithium as a model study, but none of the addition product was detected in our system.
The attention was then turned to the previously reported bridgehead enone Diels-Alder adduct 70. If this adduct could be cyclized to 71, all of the carbons of the kaurenoid ring system would be in place. The problem would be reduced to modifying the functionality to produce corymbol. In the key cyclization the trisubstituted double bond has to be activated in the presence of the more electron-rich enol silyl ether. The hope was that the enol silyl ether was sufficiently hindered that a large and soft coordinating group (Y) would preferentially attack the trisubstituted double bond to form 72. With the knowledge that normal Lewis acids decompose adduct 70, various reagents were attempted to cyclize adduct 70.
The first reagent was N-phenylselenophthalimide (NPSP), previously reported by Nicolaou and coworkers. The reagent has been shown to activate a variety of alkenes to intramolecular nucleophilic attack. In our hands, this reagent did not form the cyclized product 73. Another reagent that was attempted was the sterically demanding, weak Lewis acid mercury (II) iodide, but the reaction produced an uncharacterizable product. Next dimethyl-(thiomethyl)sulfonium tetrafluoroborate was tried. This reagent, developed by Trost and Murayama, has been shown to activate double bonds to nucleophilic attack, but the same uncharacterizable product was formed as in the mercury (II) iodide case. The reaction was also attempted with a iron complex that has been previously used to activate...
double bonds to nucleophilic attack by enol silyl ethers. This reaction condition also did not afford any of the cyclized product 75.

Our current strategy is centered around the formation of a five membered ring, then ring expansion to the needed six membered ring. Ito and coworkers have reported the intramolecular cyclization of enol silyl ethers to alkenes. In our system the expected product was 76. Compound 76 could be oxidized to the epoxide 77 which could be
rearranged to the ring expanded alcohol 78. Alcohol 78 will allow the synthesis of kaurenoic acids which have important biological activity.
EXPERIMENTAL

General

Unless otherwise stated, reagents used were purchased from commercial suppliers and were not purified unless stated. Dry diethyl ether and tetrahydrofuran were distilled from benzophenoneketyl, benzene was distilled from lithium aluminum hydride, methylene chloride and acetonitrile were distilled from calcium hydride, and toluene was distilled from sodium. Unless otherwise noted, all reactions were conducted in an argon atmosphere. For reactions requiring anhydrous conditions, the apparatus was flamed dried under a stream of argon. Melting points were determined using a Fisher-Johns melting point apparatus and are uncorrected. Silica gel used for flash chromatography was EM Science Kieselgel 60 (230-400 mesh) or Merck 60 grade (230-400 mesh). Thin layer chromatography was performed using EM Science Kieselgel F254 prepared plates with thickness of 0.25 cm. The solvent systems were suitable mixtures of hexanes (H) and ethyl acetate (EA). High field proton nuclear magnetic resonance spectra were obtained at 300 MHz using Nicolet Magnetics Corporation 1280 spectrometer. All chemical shifts are reported in δ relative to tetramethylsilane as an internal standard. Coupling constants (J) are reported in Hz. Splitting patterns are designated: s (singlet), d (doublet), t (triplet), q (quartet), bs (broad singlet), m (multiplet) ABq (AB quartet). Carbon-13 nuclear magnetic resonance spectra were recorded at 75.46 MHz using a Nicolet Magnetics Corporation 1280 spectrometer and are reported in δ relative to the central peak of CDCl3 (77.06 ppm). Infarred spectra were recorded using a Perkin-Elmer 1320 infrared spectrophotometer and are reported in cm⁻¹. EI and CI (using the gas reported) low resolution mass spectra were
recorded on a Finnegan 4023 mass spectrometer. High resolution mass spectra were recorded using a Kratos model MS-50 spectrometer.

2,3,4,6,8,9,10,11,12α-Nonahydro-7α-(phenylthio)-
6α,10-methanocyclo[a]napthalene-12,5-dione 46

To a solution of 48 (632 mg, 1.44 mmol) in 15 mL of CH₂CN at ambient temperature was added Pd(OAc)₂ (190 mg, 0.86 mmol) and 1,4-benzoquinone (90 mg, 0.86 mmol). The solution was stirred at ambient temperature for 16 h (a black suspension formed). The suspension was filtered through celite, then concentrated in vacuo. The crude product was purified by flash chromatography using 3 : 1 H₂O : EA as eluent to yield 484 mg (92%) of 46. TLC (3 : 1, H₂O : EA) Rf = 0.29. ¹H NMR (CDCl₃) δ 1.2-1.5 (m, 3 H), 1.6-1.85 (m, 6 H), 1.9-2.15 (m, 3 H), 2.55-2.15 (m, 6 H), 2.95 (dd, J = 17.2 Hz, 4.9 Hz, 1 H), 3.28 (d, J = 15.9 Hz, 1 H), 3.66 (bs, 1 H), 7.20-7.40 (m, 5 H). ¹³C NMR (CDCl₃) δ 21.59, 22.05, 22.49, 27.93, 28.52, 31.80, 35.25, 43.73, 45.54, 48.69, 57.54, 58.94, 127.40, 129.12, 132.47, 132.86, 134.96, 148.16, 197.83, 211.28. IR (CDCl₃ solution) 2935, 2860, 1710, 1662, 1620, 1375, 1295, 900, 690 cm⁻¹. Low resolution mass spectrum m/e 55, 67, 84, 109, 215, 257, 366. High resolution mass spectrum for C₂₃H₂₄BO₂S requires 366.16536, measured 366.16599 (+ 1.7 ppm).

7β-Cyano-2,3,4,6,8,9,10,11,12αβ,12βα-decahydro-7α-(phenylthio)-5-[(trimethylsilyl)oxy]-6αα,10α-methanocycloocta[a]napthalene-12-one 53

To a solution of enone 46 (133 mg, 0.36 mmol) in 3.5 mL of dry toluene at 0 °C, was added freshly distilled cyanotrimethylsilane (0.12 mL, 0.92 mmol). Diethylaluminum chloride (1.8 M in toluene) (0.62 mL, 1.12 mmol) was added dropwise. The solution was
warmed to ambient temperature over 3h, then saturated NH₄Cl (10 mL) was added followed by 5% NaHCO₃ (25 mL). The resulting aqueous layer was extracted 3 x 10 mL of benzene, then dried over MgSO₄. The crude material was purified by flash chromatography to yield 150 mg (89%) of 53. TLC (3 : 1 H : EA) Rₜ = 0.27. §NMR (CDCl₃) δ 0.18 (s, 9 H), 1.38 - 2.00 (m, 12 H), 2.10 - 2.65 (m, 8 H), 3.05 (dd, J = 17.2, 4.9 Hz, 1 H), 3.33 (bs, 1 H), 7.15 - 7.28 (m, 3 H), 7.35 - 7.42 (m, 2 H). IR (CHCl₃) 3018, 2942, 2860, 2300, 1705, 1660, 1435, 1248, 1110, 850 cm⁻¹. Low resolution mass spectrum m/e 73, 110, 224, 247, 265, 287, 357, 375, 438, 465.

To 2-(r-Ethoxyethyl)oxy-acetaldehyde 61
To 2-butene-1,4-diol 60 (2.0 g, 22.6 mmol) suspended in 40mL of dry methylene chloride at ambient temperature was added ethyl vinyl ether (5.40 mL, 56.5 mmol) and PPTS (0.14 g, 0.57 mmol). The suspension was vigorously stirred (a homogeneous solution resulted after 30 min) for 2 h. The resulting solution was diluted with 50 mL of methylene chloride, and washed 1 x 20 mL water, 2 x 20 mL 5% NaHCO₃, and 1 x 20 mL brine. The organic layer was dried over Na₂SO₄. The product was concentrated in vacuo to yield 5.05 g (96%) of the diprotected alcohol which was directly used in the ozonolysis.

$^1$H NMR (CDCl₃) δ 1.21 (t, J = 7.1 Hz, 6 H), 1.32 (d, J = 5.35 Hz, 6 H), 3.40 - 3.70 (m, 4 H), 4.20 - 4.04 (bq, 4 H), 4.73 (q, J = 5.35 Hz, 2 H), 5.70 (t, J = 3.96 Hz, 2 H).

$^{13}$C NMR (CDCl₃) δ 15.31, 19.80, 60.47, 99.02, 129.04. IR (CDCl₃) 2990, 2970, 2950, 1450, 1385, 1130, 1085 cm⁻¹. Low resolution mass spectrum CI (NH₃) m/e 90, 116, 158, 178, 204, 250 (M+ NH₄), 276 (M+ OCH₂CH₂). To the crude product (5.05 g, 1.92 mmol) dissolved in dry methylene chloride (200 mL) at -78 °C was bubbled ozone until a blue color resulted (30 min). The excess ozone was removed by bubbling N₂ into
the solution. Triphenylphosphine (5.53 g, 21.1 mmol) was added in five equal portions at 
-78 °C over 30 min. The solution was then warmed to ambient temperature, and the 
solution was concentrated in vacuo. The residue was diluted with 75 mL of hexanes and 
filtered through glass wool to remove the triphenylphosphine oxide. The crude product 
was distilled at 2 mm Hg in a Kugelrohr oven at 55 °C to yield 4.6 g (72%) of 61. TLC (3 
: 1 H : EA) Rf = 0.25. 1 H NMR (CDCl3) δ 1.20 (t, J = 7.1 Hz, 3 H), 1.36 (d, J = 5.35 
Hz, 3 H), 3.46 - 3.70 (m, 2 H), 4.12 (s, 2 H), 4.81 (q, J = 5.35 Hz, 1 H), 9.73 (s, 1 H). 
13C NMR (CDCl3) δ 14.94, 19.24, 61.18, 69.82, 99.69, 200.59. IR (thin film) 2990, 
2980, 2720, 1735, 1440, 1380, 1340, 721, 695 cm⁻¹. Low resolution mass spectrum CI 
(NH₃) m/e 90, 132, 150 (M⁺ NH₄), 176 (M⁺ OCH₂CH₂), 282 (2M⁺ NH₄).

5-(1-Ethoxyethyl)oxy-3-penten-2-one 64

To a solution of 62 (4.0 g, 30.27 mmol) in 75 mL of benzene, was added 
phosphoylde 63 (14.5 g, 45.41 mmol). The resulting suspension was heated at 80 °C for 
3.5 h. The solution was cooled to ambient temperature, then concentrated in vacuo. The 
residue was diluted with a 3 : 1 mixture of hexanes : diethyl ether (100 ml), then filtered 
through glass wool. The crude material was purified flash chromatography eluting with 3 : 
1 H : EA to yield 3.0 g (57%) of 64. TLC (3 : 1 H : EA) Rf = 0.36; 1 H NMR (CDCl3) δ 
1.20 (t, J = 7.1 Hz, 3 H), 1.35 (d, J = 5.35 Hz, 3 H), 2.29 (s, 3 H) 3.40 - 3.75 (m, 2 H), 
4.10-4.35 (m, 2 H), 4.78 (q, J = 5.35 Hz, 1 H), 6.33 (d, J = 15.9 Hz, 1 H), 6.82 (dt, J = 
15.9 Hz, 4.5 Hz, 1 H). 13C NMR (CDCl3) δ 15.17, 19.61, 27.67, 60.77, 63.23, 
99.29, 129.84, 143.25, 197.99. IR (thin film) 3005, 2990, 2900, 1675, 1635, 1445, 
1360, 1257 cm⁻¹. Low resolution mass spectrum CI (NH₃) m/e 90, 118, 127, 144, 173 
(M⁺ NH₄), 216 (M⁺ OCH₂CH₂).
5-[(1'-ethoxyethyl)oxy]-1,3-pentadiene-2-oxy]-trimethylsilane 60

To a solution of enone 64 (0.86 g, 5.0 mmol) in dry methylene chloride (25 mL) cooled in an ice bath, was added triethylamine (1.39 mL, 10.0 mmol). TMSOTf (1.16 mL, 6.0 mmol) was added dropwise to the stirred solution. The solution was slowly warmed to ambient temperature and stirred for a total of 8 h. The methylene chloride was removed *invacuo*, diluted with 50 mL of hexanes, then decanted. The solution was concentrated *invacuo* to yield 1.0 g (82%) of 60. The crude material was of high purity and was not purified before use. \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 0.23 (s, 9 H), 1.21 (t, \(J = 7.1\) Hz, 3 H), 1.33 (d, \(J = 5.35\) Hz, 3 H), 3.45 - 3.60 (m, 2 H), 4.05 - 4.25 (m, 2 H), 4.31 (s, 2 H), 4.75 (q, \(J = 5.35\) Hz, 1 H), 5.95 - 6.15 (m,\(J = 15.9\) Hz, 2 H), 6.82 (dt, \(J = 15.9\) Hz, 4.5 Hz, 1 H); \(^1\)C NMR (CDCl\(_3\)) \(\delta\) 15.17, 19.61, 27.67, 60.77, 63.23, 99.29, 129.84, 143.25, 197.99; IR (thin film) cm\(^{-1}\). Low resolution mass spectrum CI (NH\(_3\)) m/e 90, 116, 155, 172, 199, 245 (M+H); High resolution mass spectrum for C\(_{12}\)H\(_{24}\)O\(_3\)Si requires 244.14947, measured 244.1487.

1α-[(1'-Ethoxyethyl)methyloxy]-1,6,7,8,9,10αα-hexahydro-5α-(phenylthio)-
3-[(trimethylsilyloxy]-4αβ, 8β-methanobenzocycloocten-10-one 59

To a solution of diene 60 (0.82 g, 3.35 mmol) and bridgehead bromide 28 (0.90 g, 2.79 mmol) in 2.8 mL of dry methylene chloride at 0 \(^\circ\)C was added dropwise triethylamine (0.51 g, 3.69 mmol). The resulting solution was slowly warmed to ambient temperature and stirred for 10 h. The resulting suspension was diluted with hexanes, then filtered. The crude product could not be separated from 64 by flash chromatography and crude material was taken directly to the next step. An analytical sample was obtained by preparative thin
layer chromatography to yield the following data. TLC (3 : 1, H : EA) Rf = 0.26.  

1H NMR (CDCl₃) δ 0.19 (s, 9 H), 1.16 (bt, J = 7.0 Hz, 3 H), 1.24 (dd, J = 7.2 Hz, 5.35 Hz, 3 H), 1.30 - 1.68 (m, 3 H), 1.80 - 1.95 (m, 2 H), 2.0 (bs, 1 H), 2.60 - 3.05 (m, 3 H), 3.26 - 3.63 (m, 3 H), 4.58 - 4.63 (m, 1 H), 4.95 (d, J = 5.2 Hz, 2 H), 4.75 (q, J = 5.35 Hz, 1 H), 7.18 - 7.32 (m, 3 H), 7.38 - 7.43 (m, 2 H).  

13C NMR δ 14.14, 29.55, 34.81, 38.74, 40.23, 41.80, 46.17, 50.49, 60.60, 66.46, 68.95, 89.07, 98.26, 99.79, 103.25, 126.96, 128.91, 132.42, 133.33, 135.52, 149.86, 150.38, 214.02. IR (thin film) 2980, 2940, 1690, 1690, 1480, 1250, 1180, 1090, 900, 850 cm⁻¹. Low resolution mass spectrum m/e 73, 110, 153, 247, 291, 385, 398, 488.

1-[(1'-Ethoxyethyl)methyloxy]-6,7,8,9,10α,5α-pentahydro-4αβ,8β-methanobenzocycloocten-3,10-dione 65

To a solution of crude 59 (0.90 g) in 25 mL of dry acetonitrile at ambient temperature was added Pd(OAc)₂ (310 mg, 1.40 mmol) and 1,4-benzoquinone (150 mg, 1.40 mmol). The mixture was stirred for 10 h at ambient temperature. The resulting black suspension was purified by flash chromatography and yielded 0.72 g (62%) of 65. TLC (3 : 1 H : EA) Rf = 0.31; 1H NMR δ 1.10 - 1.40 (m, 2 H), 1.45 - 1.60 (m, 2 H), 1.95 - 2.10 (m, 2 H), 2.25 - 2.60 (m, 3 H), 2.98 (dd, J = 14 Hz, 6 Hz, 1 H), 3.30 (d, J = 16.5 Hz, 1 H), 3.42 - 3.65 (m, 1 H), 3.70 - 4.20 (m, 2 H), 4.62 - 4.75 (m, 1 H), 6.32 (d, J = 8.3 Hz, 1 H), 7.21 - 7.32 (m, 3 H), 7.36 - 7.45 (m, 2 H).  

13C NMR δ 28.22, 30.28, 31.80, 38.63, 39.34, 44.94, 53.91, 54.94, 58.89, 60.98, 61.19, 64.13, 99.46, 125.50, 127.61, 129.22, 152.62, 134.66, 137.09, 140.90, 197.98, 214.02. IR (CDCl₃) 2980, 2925, 1705, 1675, 1630, 1480, 1380, 1230, 1135, 1085, 900, 685.
1-(hydroxymethyl)-6,7,8,9,10α-pentahydro-5α-(phenylthio)-
4αβ, 8β-methanobenzocycloocten-3,10-dione 66

To a solution of enone 65 (0.72 g, 1.74 mmol) in 200 mL of THF at ambient
temperature, was added 0.04 N HCl (60 mL). The solution was stirred for 12 h at ambient
temperature. The crude material was purified by flash chromatography eluting with 3 : 1 H
: EA to yield 0.40 g (67%) of 66. TLC (3 : 1 H : EA) Rf = 0.24. ¹H NMR δ 1.38 - 1.40
(m, 4 H), 1.80 - 2.14 (m, 2 H), 2.22 - 2.42 (m, 4 H), 2.46 (bs, 1 H), 3.00 (dd, J = 14
Hz, 6 Hz, 1 H), 3.31 (d, J = 15.5 Hz, 1 H), 3.91 (bs, 1 H), 4.02 (dd, J = 16.5 Hz, 6 Hz,
1 H), 6.32 (bs, 1 H), 7.24 - 7.35 (m, 3 H), 7.38 - 7.48 (m, 2 H). IR (CDCl₃ solution)
3420, 2950, 2900, 1680, 1645, 1445, 1360,1257, 1050 cm⁻¹.
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PART II: AN ATTEMPTED CONVERGENT APPROACH TO KAURENE NATURAL PRODUCTS
This manuscript will describe an attempted convergent approach to kaurene natural products. The first approach was planned to use a Michael addition followed by an oxy-ene reaction to construct an advanced intermediate. The precursor to the oxy-ene reaction could not be prepared, so other types of cyclization were attempted. These approaches were also unsuccessful. A planned approach is also presented, but this approach has not been tested at this time.
Kaurenes are a subclass of the family tetracyclic diterpene natural products.\(^1\) Examples of this class of natural products are kaurene 1,\(^2\) the furandiol cafestol 2,\(^3\) the diterpene alkoloid garryfoline 3,\(^4\) 7-hydroxykaurenolide 4,\(^5\) and our synthetic target corymbol 5.\(^6\) Of interest is that the higher functionalized members of this class are derived from (-) kaurene not (+) kaurene. The biological activity of this class is varied. Both kaurene 1 and corymbol 5 have been proposed as intermediates in the biosynthesis of natural products. (+) Kaurene has been proposed as a key intermediate in a variety of
gibberlen plant growth regulators, such as 6. Perezamador and Jiminez have proposed corymbol as the precursor of turbicoryn 7 which was isolated in 1964.

All diterpene natural products have geranyl geraniol pyrophosphate 8 or geranyl linalool pyrophosphate 9 as a common ancestor in their biosynthetic pathway. The
accepted biosynthetic pathway of tetracyclic, diterpene natural products was proposed by Wenkert in 1955 (Scheme I). The first step was the formation of copalyl pyrophosphate
10,10 which was later proved by Sheeter and West\textsuperscript{11a} and Fall and West.\textsuperscript{11b} The second step was the formation of carbocation 11 by a carbocation cyclization, it is trapped by the vinyl group to provide the nonclassical carbocation 12. The mode of carbocation collapse determined whether kaurene 1, atisirene 13, or stachene 14 natural products are produced. Kaurene is a product of a Wagner-Meerwein shift of intermediate 12a. In 1980 Coates and Cavender reported their investigation into the stereochemistry of the conversion of copalyl pyrophosphate 10 to kaurene 1.\textsuperscript{12} They synthesized geranyl geraniol pyrophosphate-1-tritium 15 as a racemic mixture (15a) and the pure S form (15b). These products were separately converted to (-) kaurene-14-t (16) using enzyme preparations from \textit{Marah macrocarpus}. These products were transformed to ketone 17 in five steps. The ring

\[
\begin{align*}
15a & \quad C_1 \quad R,S \\
15b & \quad C_1 \quad S \\
16a & \quad X = T, \quad Y = H \\
16b & \quad X = T, \quad Y = H \\
17a & \quad X = H, \quad Y = T \\
17b & \quad X = T, \quad Y = H \\
18a & \quad X = H, \quad Y = T \\
18b & \quad X = T, \quad Y = H
\end{align*}
\]
opened product 18 was then provided by a photolysis of ketone 17. In the case of 15a 59% of the tritium had been retained, whereas 99% of the tritium had been lost in 15b. From this result Coates and Cavender infers that the product from 15b is 16b which was the product of a net inversion at C-1 of 15b. They also synthesized copalyl pyrophosphate-17(E)-tritium (19a) or S 17(E)-deuterium (19b). In this study 19 was converted to (-) kaurene-15-tritium (20a) and 15-deuterium (20b) using the same enzyme.

They determined using equilibrium deuterium exchange reactions that the tritium and deuterium was contained at the exo position. This was further verified by the conversion of 20a to 21, since essentially all of the tritium had been lost. From the data, Coates proposed two possible mechanisms (Scheme II). Coates and Cavender contend that the anti $S_N'$ pathway (path a) is favored over the syn $S_N'$ pathway (path b) by the principle of least motion.

The bicyclic ring system of diterpene natural products have been synthesized by a variety of methods. One of the first reports was the synthesis of the kaurene diterpene phyllocladine 22 by Turner and Ganshirt in 1961. They converted the keto ester 23
Scheme II

Path a
syn $S_n'$

Path b
syn $S_n'$
to the diacid 24. The barium salt of 24 was heated to provide ketone 25. Ketone 25 was then converted to phyllocladene.

Bell and Ireland developed a versatile method that allowed for the synthesis of kaurene 1,15 atisirene 13,16 and hibaene 26.16 Their strategy was based on a Claisen rearrangement to construct a unit for the bicyclic ring system. Enone 2717 was reduced and the resulting alcohol was converted to enol ether 28. The aldehyde was protected as an ethylene acetal, and the alcohol was oxidized to a mixture of ketones 30 and 31. Ketone 30 was converted to aldol product 32 which was used as a precursor to atisirene 13. After deprotection of ketone 31, aldol product 33 was provided upon treatment with sodium methoxide. This intermediate was converted to kaurene 1. Ketone 31 was also used in the synthesis of a stachene diterpene, hibaene 26.

Masamune has developed a synthesis of keto acid 3418 which was used as a common intermediate in the synthesis of kaurene 1,19 garryime 35,20 and atisine 36.21
Keto acid 34 was synthesized from phenol 37. The key in Masamune's synthesis is the intramolecular alkylation to form the tricyclic dienone 38. This was accomplished by treating 37 with potassium t-butoxide. Dienone 38 was converted to acid 34 using standard functional group manipulations.
Carbenes have been useful intermediates in the construction of the bicyclic unit of tetracyclic diterpenes. In a synthesis of isohibaene 39 by Kitadani and coworkers the bicyclic ring system was constructed by a carbene insertion into a carbon-hydrogen bond. Enol 40 was transformed to the β-diazoketone 41. Upon heating 41 in cyclohexane in the presence of copper (II) oxide and light, the tetracyclic ketone 44 was provided. Ketone 42 was then used to prepare isohibaene 39. Tahara and coworkers used a similar strategy in their synthesis of phyllocladene 22 and kaurene 1. Starting with abietic acid 43 (available from pine resin), diazoketone 44 was synthesized. Heating ketone 45 in the presence of copper (II) sulfate formed the carbene which added across the double bond to provide a 1:1 mixture of cyclopropanes 46 and 47. These cyclopropanes
were reduced with lithium in liquid ammonia to form tetracyclic ketones 48 and 49. Ketone 48 was used in the synthesis of phyllocladene 22. Ketone 49 was used in the synthesis of kaurene 1.

In a report of the total synthesis of cafestol 2, Corey and coworkers used a carbene insertion into a double bond to prepare a precursor of corymbol. Diazoketone 50 was decomposed to the carbene by heating 50 with copper (II) bis-(salicylaldehyde-t-butylamine) to provide keto ester 51. The keto ester was converted to alcohol 52 in three steps. Alcohol 52 was then employed in an acid catalyzed cyclization to synthesized pentacycle 53. Pentacycle 53 was then converted to corymbol 2.
$\text{CO}_2\text{-Bu}$

1) NaBH₄
2) NaH, PhCH₂Br
3) DIBAL,

TFFA, 2,6-lutidine 
-78 °C
RESULTS AND DISCUSSION

The bicyclo [3.2.1] octene 54 previously reported by Marinovic and Ramanathan appeared to be an attractive starting point for a convergent route to kaurene natural products. This route would entail a Michael addition followed by an oxy-ene reaction to construct the tetracyclic ring system (Scheme I). The elegance of this approach

Scheme I

\[
\text{TBSO} \quad + \quad \text{CO}_2\text{CH}_3
\]

\[
\text{CO}_2\text{CH}_3
\]
would be the few steps required to construct a tetracyclic ring system which contains varied functionality that would allow the synthesis of many members of this class. This route would require the transformation of 54 to the Michael donor 55. Ketone 55 will be used in a Michael addition with the readily available dienone 56 to give the tricyclic oxy-ene precursor 57, which would be employed in the oxy-ene reaction to afford the key tetracyclic intermediate 58.

The bicyclic keto-ester 54 was synthesized in a three step sequence starting with m-anisic acid 59. m-Anisic acid was reductively alkylated with 2,3-dibromopropene followed by acidic workup to yield the enone 60 in 67% yield. The acid-enone 60 was esterified with diazomethane, then the [3.2.1] bicyclic ring system was formed via a vinylic radical cyclization (n-Bu3SnH, AIBN) to yield the bicyclic keto ester 54 in 59% yield.

The ester 1 was then transformed to the required enol ether 55 in three steps. The mixture of enol silyl ethers 62 and 63 were formed by reacting the keto-ester 54 with
N,N-diisopropylethlyamine and t-butyldimethylsilyl triflate (TBSOTf).\textsuperscript{26} The mixture of 61 and 62 was condensed with the lithium enolate of ethyl acetate to give the mixture of β-keto-esters 63 and 64 which were decarboalkoxylated with diazabicyclo [2.2.2] octane (DABCO)\textsuperscript{27} to form a mixture of 55 and 65.

The feasibility of the Michael addition and the oxy-ene reaction sequence was tested with model studies. The results of the Michael additions to the known dienone 56\textsuperscript{28} are contained in Table 1. The Michael adducts were formed in fair to good yields as
Table 1. Michael Additions to Ester Dienone 56

\[
\begin{align*}
\text{R} & \quad \overset{\text{LDA, THF}}{\xrightarrow{-78 \, ^\circ\text{C}}} \quad \text{R}^- \quad \overset{\text{O}^+ \text{Li}^+}{\xrightarrow{\text{O}^- \text{Li}^+}} \quad \text{CO}_2\text{R} \quad \overset{\text{CO}_2\text{CH}_3}{\xrightarrow{\text{CO}_2\text{CH}_3}} \quad \text{CO}_2\text{CH}_3 \end{align*}
\]

<table>
<thead>
<tr>
<th>Methyl Ketone</th>
<th>Adduct</th>
<th>R</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>66</td>
<td>83</td>
<td></td>
<td></td>
</tr>
<tr>
<td>67</td>
<td>45</td>
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<td></td>
</tr>
<tr>
<td>68</td>
<td>50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>69</td>
<td>33</td>
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mixtures of cis and trans isomers. Usually 30% of the mixture was the enol form of the β-keto ester. The Michael adducts 67 and 68 were also used in a model study of the feasibility of the oxy-ene reaction. Neither the thermal (heating ≥ 200 °C) nor the Lewis acid catalyzed oxy-ene reaction promoted the formation of 70 or 71. Considering the failure to effect an oxy-ene reaction plus the uncertainty of the composition of the keto-enolsilyl ether 54, the strategy for the synthesis of kaurenoid natural products was changed.

If a bromopropenyl group was substituted for the methyl group on the Michael adduct
68, the synthesis is reduced to cyclizing 72 to the tricyclic intermediate 73. Michael adduct 68 was employed as a model system for the cyclization. First a reversible carbocation cyclization was attempted. The carbocation 74 was expected to react with the acidic β-keto ester to form the tricyclic ring system. None of the reaction conditions employing iodine and a Lewis acid afforded the expected cyclized product. Nicolaou and
coworkers have reported the use of N-phenylseleno-phthalimide (NPSP) / SnCl$_4$ as a promoter of cyclizations in certain systems.$^{30}$ NPSP is not as reactive as other selenium reagents and is also sterically demanding because of the phthalimide moiety. In our case NPSP did not afford the expected product, but new and unidentifiable products were formed.

Next a radical cyclization was studied. There have been reports of the formation of radicals of the type 76 using manganese (III)$^{31,32}$ or silver (I)$^{33}$ salts. The radical formed could
then add to the double bond forming 77 which could be oxidized by a second equivalent of the salt to give a carbocation 78. Carbocation 78 could then lose a proton to form diene 79. The standard reaction conditions [Mn(OAc)_3 / HOAc] failed in this system. The enone 80 was believed to have been formed in low yield, since phenol 82 was produced when β-keto ester 81 was submitted to the standard reaction conditions. The failure of the reaction may have been due to an equilibrium between 77 and 78 that favors 77. Therefore copper (II) acetate was added as a co-oxidant. Copper (II) acetate is known to oxidize carbon radicals to carbocations more readily than other metal salts. This addition did not promote the cyclization to the tricyclic ring system. Next, silver salts were tried. Either using standard conditions (Ag_2O / DMSO, Δ) or conditions involving enolate formation (NaH, AgNO_3, Cu(OAc)_2) did not result in the formation of the desired tricyclic ring system 80.

Snider and coworkers have reported the intramolecular cyclization of β-keto ester
radicals to electron-rich benzene rings. The cyclization was attempted with Michael adduct 69 using Manganese (III) and silver (I) salts, but the tricyclic product 83 did not form, probably because the acetophenone moiety deactivated the benzene ring.

\[ \text{68} \xrightarrow{\text{Ag}_2\text{O, DMSO, 70°C}} \text{79} \]

\[ \text{68} \xrightarrow{\text{1) NaH, CH}_3\text{CN, 2) AgNO}_3, \text{Cu(OAc)}_2, \text{CH}_3\text{CN, 70°C}} \text{79} \]

\[ \text{70} \xrightarrow{\text{Ag}_2\text{O, DMSO, 70°C}} \text{83} \]

\[ \text{70} \xrightarrow{\text{1) NaH, CH}_3\text{CN, 2) AgNO}_3, \text{Cu(OAc)}_2, \text{CH}_3\text{CN, 70°C}} \text{83} \]
With the failures of the carbocation and radical cyclizations, an anionic route has been devised, but has yet to be tested. This route is centered around an intramolecular Michael addition of 84 to form the tricyclic product 85. This intermediate was envisioned to be available from a Diels-Alder reaction between enone 86 and 2-trimethylsilyloxy-1,3-butadiene (87). Enone 86 will be synthesized following a method developed by Baraldi and coworkers. The Diels-Alder adduct will then be oxidized to the dienone 88 by an Ito and coworkers reaction. Dienone 88 will be used as a Michael donor to form the precursor 84 to the Michael addition. After cyclization to the tricyclic intermediate 85 the
bicyclo [3.2.1] octene ring system will be prepared by a vinyl radical cyclization which should provide our key tetracyclic intermediate 58. This intermediate will be used to synthesize a variety of kaurenoid natural products using known functional group manipulations.
EXPERIMENTAL

General

Unless otherwise stated, reagents used were purchased from commercial suppliers and were not purified unless stated. Dry diethyl ether and tetrahydrofuran were distilled from benzophenoneketyl, benzene was distilled from lithium aluminum hydride, methylene chloride and acetonitrile were distilled from calcium hydride, and toluene was distilled from sodium. Unless otherwise noted, all reactions were conducted in an argon atmosphere. For reactions requiring anhydrous conditions, the apparatus was flamed dried under a stream of argon. Melting points were determined using a Fisher-Johns melting point apparatus and are uncorrected. Silica gel used for flash chromatography was EM Science Kieselgel 60 (230-400 mesh) or Merck 60 grade (230-400 mesh). Thin layer chromatography was performed using EM Science Kieselgel F_{254} prepared plates with thickness of 0.25 cm. The solvent systems were suitable mixtures of hexanes (H) and ethyl acetate (EA). High field proton nuclear magnetic resonance spectra were obtained at 300 MHz using Nicolet Magnetics Corporation 1280 spectrometer. All chemical shifts are reported in \( \delta \) relative to tetramethylsilane as an internal standard. Coupling constants (J) are reported in Hz. Splitting patterns are designated: s (singlet), d (doublet), t (triplet), q (quartet), bs (broad singlet), m (multiplet) ABq (AB quartet). Carbon-13 nuclear magnetic resonance spectra were recorded at 75.46 MHz using a Nicolet Magnetics Corporation 1280 spectrometer and are reported in \( \delta \) relative to the central peak of CDCl\textsubscript{3} (77.06 ppm). Infrared spectra were recorded using a Perkin-Elmer 1320 infrared spectrophotometer and are reported in cm\textsuperscript{-1}. EI and CI (using the gas reported) low resolution mass spectra were recorded on a Finnegan 4023 mass spectrometer. High resolution mass spectra were
recorded using a Kratos model MS-50 spectrometer

1- (2-Bromo-2-propenyl)-4-cyclohexen-3-one-1-carboxylic acid 60

To the m-anisic acid 59 (7.61g, 50 mmol) suspended in THF (40 mL) / NH₃ (160 mL) at -78 °C, was added in small pieces Li (0.83g, 120 mmol) until a blue color persisted. The mixture was then stirred an additional 25 min to which 2,3-dibromo-1-propene (6.20 mL, 60 mmol) was added dropwise over 10 min (solution changed from blue to yellow to orange to white). The mixture was stirred for 15 min at -78 °C, then solid NH₄Cl was cautiously added in three portions. Ammonia was removed under a stream of N₂ while warming to ambient temperature. The residue was dissolved in H₂O and washed twice with 100 mL Et₂O. The aqueous layer was cooled to 0 °C, then carefully acidified to pH 4 with cold concentrated HCl. The aqueous layer was extracted thrice with 200 mL of CHCl₃ and dried over Na₂SO₄. The chloroform solution was concentrated in vacuo to yield 14.1 g (103 %) of crude product which was dissolved in 40 mL of THF. To this solution was added 10% HCl (16.13 mL, 50 mmol), and the mixture was stirred for 2 h at ambient temperature. The solution was concentrated and 200 mL of Et₂O was added. A precipitate formed immediately which was filtered to yield 8.74 g (67 %). The melting point was 176 - 178 °C. NMR (D₆ acetone) δ 2.82 - 3.05 (m, 4 H), 5.59 (d, J = 1.8 Hz 1 H), 5.76 (m, 1 H), 5.92 (dd J = 10.2 Hz, 2.7 Hz, 1 H), 6.98 (ddd, J = 10.2 Hz, 3.0 Hz, 5.4 Hz, 1 H). ¹³C NMR (D₆ Acetone) 34.70, 45.15, 48.70, 40.06, 122.03, 127.81, 129.31, 147.34, 175.09, 195.96 ppm. Low resolution mass spectrum m/e: 55, 77, 95, 109, 179, 213, 215, 240, 242, 258, 259, 260, 261; High resolution mass spectrum for C₁₀H₁₁BrO₃ requires 257.98915, measured 257.98915.
Methyl 1-(2-bromo-2-propenyl)-4-cyclohexen-3-one-1-carboxylate 60a

To a solution of the acid 60 (8.41 g, 32.46 mmol) in a 2 : 1 solution of CH₂Cl₂ : Et₂O (165 mL) separated in 5 lots was added diazomethane until the evolution of N₂ gas had ceased. The solution was concentrated under a stream of N₂, and the residue was purified by flash chromatography eluting with 2 : 1 Hex : EA to yield 60a 8.87 g (83%) as a light yellow solid. TLC (3 : 1 H : EA) Rₓ = 0.21. ¹H NMR (CDCl₃) δ 2.45 - 2.60 (m, 2 H), 2.80 - 3.00 (m, 4 H), 3.69 (s, 3 H), 5.58 (s, 2 H), 6.00 - 6.07 (dt, J = 1.8 Hz, 10.2 Hz, 1 H), 6.85 - 6.92 (m, 1 H). ¹³C NMR (CDCl₃) δ 33.98, 44.85, 48.35, 48.35, 48.60, 52.62, 121.93, 129.80, 146.71, 174.21, 196.24. IR (CDCl₃) 3150, 2990, 2950, 2900, 1810, 1792, 1730, 1680, 1621, 1437, 1385, 1212 cm⁻¹. Low resolution mass spectrum: m/e 59, 68, 79, 105, 121, 133, 193, 213, 215, 242, 243, 272, 274. High resolution mass spectrum for C₁₁H₁₃BrO₃ requires 272.00480, measured 272.00466.

Methyl 6-methylene-3-oxo-bicyclo[3.2.1]octane-1-carboxylate 54

To a solution of the ester 60a (5.0 g, 18.31 mmol) in dry benzene (180 mL) at 80 °C was added a solution of n-Bu₃SnH (5.91 mL, 21.97 mmol) and AIBN (0.30 g, 1.83 mmol) in benzene (40 mL) over 2 h. The solution was stirred an additional 1 h, then the benzene was removed in vacuo. The residue was dissolved in 85 mL of Et₂O to which 35 mL of H₂O and KF·2H₂O (8.24 g, 87.55 mmol) was added. The mixture was vigorously stirred overnight. The mixture was separated and washed twice with 50 mL of H₂O, 50 mL of brine and dried over Na₂SO₄. The ethereal solution was concentrated in vacuo, and the residue was purified by flash chromatography using Florisil and eluting with hexanes to afford 2.52 g (71%) of 54. TLC (3 : 1 H : EA) Rₓ = 0.27. ¹H NMR (CDCl₃) δ. ¹³C
Methyl 3-(t-butyldimethylsilyloxy)-6-methylene-bicyclo [3.2.1] oct-2-ene-1-carboxylate 55 and 65

To a solution of the ketone 54 (2.05 g, 10.55 mmol) in CH$_2$Cl$_2$ at 0 °C was added N,N-diisopropylethylamine (3.59 mL, 20.60 mmol) followed by dropwise addition of TBSOTf (2.72 mL, 11.85 mmol). The solution was slowly warmed to ambient temperature 16 h. The CH$_2$Cl$_2$ was removed in vacuo and hexanes were added. The precipitate was removed by filtering through Celite, then concentrated. The mixture was purified by flash chromatography using 6:1 H : EA to yield 0.59 g (93%) of a mixture of 55 and 65. TLC (6:1 H : EA) R$_f$ = 0.47. $^1$H NMR (CDCl$_3$) $\delta$ 0.12 (s, 4.8 H), 0.14 (s, 1.2 H), .90 (s, 7.2 H), .93 (s, 1.8 H), 1.70 - 2.22 (m, 4 H), 2.40 - 2.55 (m, 2 H), 2.60 - 2.80 (m, 2 H), 2.91 (dd, J = 6.9 Hz, 4.5 Hz, 1 H), 4.54 (s, 0.8 H), 4.74 (s, 0.8 H), 4.94 (s, 0.2 H) 5.03 (s, 0.8 H), 5.05 (s, 0.2 H), 5.32 (s, 0.2 H). $^{13}$C NMR (CDCl$_3$) $\delta$ 18.02, 25.69, 41.20, 41.97, 41.85, 48.67, 52.01, 101.60, 107.92, 109.40, 110.0, 148.26, 155.38, 176.60. IR (CHCl$_3$) 3030, 2930, 2860, 1720, 1718, 1655, 1360, 1200, 1150, 835, 780, 680 cm$^{-1}$. Low resolution mass spectrum: m/e 45, 59, 73, 89, 105, 117, 191, 251, 267, 308.
Ethyl 3-(t-butyldimethylsilyloxy)-1-(2-carboxylate-1-ethanone)-6-methylene-2-bicyclo[3.2.1]octene 63 and 64

To a solution of LDA [prepared by the addition of n-BuLi (0.96 mL, 2.35 mmol) to a solution of diisopropylamine (0.36 mL, 2.57 mmol) in 5 mL of dry THF at 0 °C] at -94 °C, was added a solution of ethyl acetate (0.21 mL, 2.14 mmol) in 1 mL of dry THF over 10 min. The solution was stirred at -94 °C for 15 min, then warmed to -78 °C. A solution of the mixture of 63 and 64 (300 mg, 0.97 mmol) in 2.5 mL of dry THF was added over 15 min. The solution was warmed slowly to ambient temperature and was quenched with 1 mL of saturated NH₄Cl. The THF was removed in vacuo, and the residue was diluted with 20 mL of Et₂O. The ethereal solution was washed twice with 10 mL of H₂O, 10 mL of brine and dried over Na₂SO₄. The crude product was purified by flash chromatography eluting with 3:1 H₂O:EA to yield 244 mg (69%) of a mixture of 63 and 64. TLC (6:1 H₂O:EA) Rf = 0.47. ¹H NMR (CDCl₃) δ 0.12 (s, 6 H), 0.90 (s, 9 H), 1.28 (t, J = 7.2 Hz, 3 H), 1.60 - 2.25 (m, 3 H), 2.40 - 3.00 (m, 4 H), 3.52 (s, 0.8 H), 3.72 (s, 1.2 H), 4.20 (q, J = 7.2 Hz, 2 H), 4.53 (bs, 0.4 H), 4.68 (bs, 0.6 H), 4.74 (bs, 0.4 H), 4.89 (bs, 0.6 H), 4.90 - 5.10 (m, 1 H). IR (CHCl₃) 3060, 2940, 2860, 1735, 1710, 1655, 1470, 1460, 1360, 1200, 870, 780 cm⁻¹. Low resolution mass spectrum: m/e 59, 73, 89, 117, 191, 237, 251, 265, 308, 322, 364.

General Procedure for Michael Additions

To a solution of LDA (1.2 equivalents) in dry THF at -78 °C, was added dropwise over 15 min a solution of the methyl ketone (1.1 equivalents) in dry THF. The solution was stirred for 20 min at -78 °C. A solution of 56 (1 equivalent) in dry THF was added dropwise to the solution and stirred for 45 min at -78 °C. The solution was warmed to
ambient temperature and quenched by the addition of excess saturated NH₄Cl. The mixture was extracted thrice with 10 mL of Et₂O, then washed with 20 mL of brine and dried over Na₂SO₄. The crude product was purified by flash chromatography.

Adduct 66

TLC (2 : 1 H : EA) Rₚ = 0.43. ¹H NMR (CDCl₃) δ 1.0 - 1.40 (m, 6 H), 2.60 - 3.50 (m, 4 H), 3.70, (s, 1.5 H), 3.72 (s, 0.9 H), 3.78 (s, 0.6 H), 5.80 - 6.00 (m, 1 H), 6.60 - 6.80 (m, 1 H), 7.30 - 7.70 (m, 3 H), 7.85 - 8.00 (m, 2 H), 11.94 (s, 0.2 H). IR (CHCl₃) 3000, 2950, 1735, 1710, 1670, 1605, 1450, 1460, 1260, 845 cm⁻¹. Low resolution mass spectrum: m/e 51, 77, 105, 121, 149, 181, 199, 225, 253, 268, 300.

Adduct 67

TLC (3 : 1 H : EA) Rₚ = 0.25. ¹H NMR (CDCl₃) δ 1.0 - 1.29 (m, 6 H), 1.88 (s, 1 H), 1.90 (s, 2 H), 2.13 (s, 1 H), 2.14 (s, 2 H), 2.25 - 3.50 (m, 4 H), 3.33, (s, 0.6 H), 3.68 (s, 0.6 H), 3.71 (s, 1 H), 5.80 - 6.10 (m, 2 H), 6.39 (d, J = 10.1 Hz, 0.34 H), 6.72 (d, J = 10.1 Hz, 0.76 Hz), 7.30 - 7.70 (m, 3 H), 11.97 (s, 0.34 H). IR (CHCl₃) 2950, 2920, 1730, 1675, 1612, 1440, 1380, 1355, 1232, 900, 730 cm⁻¹. Low resolution mass spectrum: m/e 51, 77, 105, 121, 149, 181, 199, 225, 253, 268, 300.

Adduct 68

TLC (2 : 1 H : EA) Rₚ = 0.29. ¹H NMR (CDCl₃) δ 0.8 - 1.80 (m, 9 H), 2.20 - 3.60 (m, 6 H), 3.69 (s, 2 H), 3.72 (s, 1 H), 5.50 - 5.60 (m, 2 H), 5.75 - 5.95 (m, 3 H), 6.70 (d, J = 10.1 Hz, 0.67 H), 7.10 (d, J = 10.1 Hz, 0.33 Hz), 11.94 (s, 0.33 H). IR
(CHCl₃) 3010, 2970, 2930, 1720, 1670, 1615, 1510, 1460, 1380, 1355, 1225, 1160, 1120, 1090 cm⁻¹.

Adduct 69

TLC (2 : 1 H : EA) Rf = 0.27. ¹H NMR (CDCl₃) δ 1.00 - 1.20 (m, 6 H), 2.64 (dd, J = 14.8 Hz, 5.7 Hz, 0.3 Hz, 0.3 H), 2.96 (dd, J = 17.8 Hz, 5.5 Hz, 0.7 H), 3.06 - 3.72 (m, 3 H), 3.58 (s, 2 H), 3.62 (s, 1 H), 3.85 (s, 4 H), 3.89 (s, 2 H), 5.85 - 6.02 (m, 2 H), 6.42 - 6.56 (m, 2 H), 6.62 (d, J = 10.1 Hz, 0.3 H), 6.74 (d, J = 10.1 Hz, 0.7 Hz), 7.38 (d, J = 8.8 Hz, 0.7 H), 7.83 (d, J = 8.8 Hz, 0.3 H) 11.97 (s, 0.3 H). IR (CHCl₃) 3000, 2960, 2840, 1740, 1650, 1600, 1498, 1460, 1420, 1260, 1240, 1060, 1030, 840, 830 cm⁻¹. Low resolution mass spectrum m/e 41, 53, 77, 91, 107, 122, 149, 165, 180, 207, 313, 345, 360. High resolution mass spectrum for C₂₀H₂₄O₆ requires 360.15729, measured 360.15719.
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PART III: AN APPROACH TO ISOCEDRANE NATURAL PRODUCTS
USING A BRIDGEHEAD CARBOCATION
INTRODUCTION

This manuscript will describe the synthetic program directed toward the synthesis of trixikingolide, an isocedrane natural product. The route uses a bridgehead carbocation to construct an advanced intermediate. The key step in the synthesis is a regioselective aldol condensation reaction to construct the cis fused five membered ring common in this class of natural products. The testing of this route is still in the infant stages, so this is only a preliminary communication.
The trixikingolides 1 are a family of natural products that are earmarked by an unusual bicyclic ring system related to isocederene 2. The pentacyclic ring system of the trixikingolides contains a central bicyclo [3.2.1] octane unit with a cis fused five membered ring at carbons 6 and 10, and a six membered ring containing an enol acetal. The fifth ring is a lactone that bridges carbons 4 and 12. Many examples of trixikingolide natural products have been isolated and characterized. The discovery of this class was due entirely to Bohlman and coworkers in their chemotaxological investigation of *Nassauvinea*, a subtribe of the tribe *Mutisieae*. In their study of many genera of this tribe, Bohlmann discovered that the aerial parts contained unusual highly oxygenated isocederene type natural products. This class of natural products was called trixikingolides. There are many examples in this class; such as, trixikingolide 1 isolated from *Trixis compostia*, ester diene 3 isolated from *Trixis vantheric*, ester lactone 4 isolated from *Gungia stuebii*, diacetate 5 isolated from *Moscharia pinnatitida*, triacetate 6 isolated from *Pronstia cuneifolic* Don formamendocina, and the trixikingolide 7 isolated from *Perezia multiflora*. 
The biosynthetic pathway of isocederene natural products has to this date not been elucidated, but many groups have proposed the pathway outlined in Scheme I.\textsuperscript{1,8,9} The
only uncertainty of this pathway is the unusual 1,2 carbon shifts that are needed to prepare isocederane.

The synthesis of angular fused sesquiterpenes has been an active area of research, but there have not been any reports of the total synthesis of trixikingolide. Paquette\textsuperscript{10} and Cheney\textsuperscript{11} have reported an attempted synthesis of trixikingolide. Their approach was centered around an intramolecular alkylation to form the central bicyclo [3.2.1] octane unit from the tricyclic precursor 8. They were never successful in the cyclization of 8 to form tetracycle 9. Paquette and Cheney prepared a variety of precursors for the cyclization starting with diketone 10. Their first attempt was using a Prins reaction on aldehyde 11.

\[ \text{X} \quad \text{X} \quad \text{CO}_2\text{CH}_3 \]
\[
\begin{array}{c}
\text{8} \\
\end{array}
\quad \xrightarrow{\text{arrow}} \quad 
\begin{array}{c}
\text{HO} \\
\text{HO} \\
\text{CO}_2\text{CH}_3 \\
\end{array}
\]
\[
\begin{array}{c}
\text{9} \\
\end{array}
\]

Heating 11 with a variety of Lewis acids did not provide the cyclized product 12. They also tried an aldol condensation to effect the cyclization. Using ketone 13 in both basic and acidic reaction conditions, aldol product 14 was not obtained. An initial alkylation to form
the bicyclo[3.2.1]octane moiety followed by an aldol condensation strategy was also attempted. An intermediate in the synthesis of 13 was converted to the ketone 15, but
none of the alkylation conditions employed resulted in the formation of 16. Ester 17 was also prepared, and like 15 none of the cyclized product was detected. Both Paquette and Cheney concluded that the cyclization of 13, 15, and 17 failed due to unattainable reaction trajectories and proximity effects even though there was precedent for such a cyclization. Danishefsky and coworkers were successful in the intramolecular alkylation of 19 to afford 20.¹²

Bridgehead Carbocations in Organic Synthesis

Bridgehead carbocations have the potential to be powerful intermediates in organic synthesis. These carbocations have been extensively studied in the physical organic community, and these results have been tabulated.¹³ The potential of these intermediates is due to the lack of rearrangements generally found in smaller bicyclic ring systems, and stereoselective additions to these intermediates. The use of bridgehead carbocations in organic synthesis has not been extensively explored. The thrust of the work has been reported in a review by Kraus and coworkers.¹⁴

One of the first examples was a report by Gray and Kelly,¹⁵ who employed bridgehead bromides in a Friedel-Crafts reaction. They found that treatment of bridgehead bromide 21 (R = alkyl) with aluminum trichloride and bromobenzene afforded 22. Kraus
and Hon were also successful in generating bridgehead carbocations of bicyclo [2.2.2] octanes and reacting them with a variety of nucleophiles. The carbocation from bridgehead bromide 23 was formed by the addition of silver (I) tetrafluoroborate in the presence of nucleophiles. When benzene was used as the nucleophile, 24 was obtained in 90% yield. Other nucleophiles reported were enol silyl ether 25 which afforded ketone 26 in 65% yield and allyltrimethylsilane which afforded 27 in 72% yield. They also reported the intramolecular version of this reaction. They employed bridgehead bromide 28.
and used allyltrimehylsilane as the trapping agent to form alkene 29 in 71% yield. Benzene and enol silyl ethers have been shown also to be suitable nucleophiles in this sequence.

\[
\begin{align*}
\text{23} & \xrightarrow{\text{AgBF}_4, \text{TMS}} \text{29}
\end{align*}
\]

Kraus and Hon have been successful in forming bridgehead carbocations of bicyclo[3.3.1]nonanes. Bridgehead bromides 30 and 31 reacted in a similar manner as bridgehead bromide 23. Allyltrimehylsilane, amines, and enol silyl ethers were all suitable nucleophiles. They also discovered that diene 32 could be used as a nucleophile to afford 33. One observation was the formation of appreciable amounts of bridgehead fluoride when silver (I) tetrafluoroborate was used, but this type of side product could be avoided with the use of silver (I) triflate. They have shown the utility of bridgehead carbocation chemistry in their direct synthesis of \((\pm\))-lycopodine 34. Kraus and
Hon regioselectively oxidized the alcohol 35 to a diol, then formed the benzene sulfonate 36. The bridgehead bromide 37 was obtained by treatment of 36 with phosphorus tribromide. Bridgehead bromide 37 was converted to 38 using silver (I) triflate and 1-amino-3-benzylxyloxypropane. Kraus and Hon intersected with the synthesis of (+)-lypodine reported by Heathcock and coworkers by the deprotection of the benzylxyloxy group to provide 39.
RESULTS AND DISCUSSION

In envisioning the synthesis of trixikingolide 1, bridgehead bromide 40 was predicted to be a key intermediate in the synthesis. The intermediate would allow for appendage of the C ring using bridgehead carbocation chemistry. Our approach is outlined retrosynthetically in Scheme II. The advanced intermediate 41 was envisioned to be available from 42 by hydrogenation, elimination of the trimethylsilyloxy group, and deesterification. Lactone 42 would be available from 43 by a Pummerer rearrangement, followed by cyanoxydrin formation and lactonation. The transformation of 44 to 43 is the key to our approach. After ozonolysis to form the dialdehyde, a regioselective aldol condensation must occur. Using molecular models, the aldehyde linkage at the bridgehead appears to be the most accessible to deprotonation which would afford 43 after reduction. Ester 44 will be synthesized from 43 by a Buchi ring contraction followed by Michael addition of an allyl group and alkylation. Compound 45 is obtained from a bridgehead carbocation reaction with allyltrimethylsilane 46 serving as the nucleophile.

Starting the synthesis with bridgehead bromide 40, the bridgehead position was alkylated with allyltrimethylsilane in the presence of silver (I) triflate to afford 45 in 78% yield. Ketone 45 was carbomethoxylated by the addition of potassium hydride and
Scheme II.

\[
1 \xrightarrow{TMS} 41 \xrightarrow{HCO_2} 42
\]

\[
\begin{align*}
45 &\xleftarrow{ (+, SPh)} 44 \\
40 + TMS &\xrightarrow{46} 45
\end{align*}
\]

\[
40 \xrightarrow{\text{AgOTf, 46}} 45 \xrightarrow{\text{CH}_2\text{Cl}_2, 0^\circ\text{C}-25^\circ\text{C}} 78\%
\]

\[
45 \xrightarrow{\text{KH, (CH}_3\text{O})_2\text{CO}} 47 \xrightarrow{0^\circ\text{C}-25^\circ\text{C}} 81\%
\]
dimethylcarbonate to provide β-keto ester 47 in 81% yield. Now the stage was set for the Buchi ring contraction. The first step was the chlorination of the β-keto ester with tert-butyl hypochlorite. In the case of 47, this intermediate could not be chlorinated. The β-keto ester moiety was activated by the formation of the enolate with sodium hydride, but none of the chlorinated product 48 was produced. The failure of the reaction is rationalized by the presence of the phenylthio group. There has been a report of the oxidation of a sulfide to a sulfoxide using tert-butyl hypochlorite.

At this point there were three different avenues to circumvent this problem. First the dianion of β-keto ester 47 could be formed and alkylated with allyl iodide. Second a photochemical ring contraction could be employed which had been previously reported for bicyclic ring systems. Third the sulfoxide could be formed followed by the completion of the scheme. Formation of the dianion was accomplished by using 2.3 equivalents of lithium tetramethylpiperidinamide at -78 °C. Upon the addition of allyl iodide, a disappointing 1:1.5 mixture of 49:50 resulted which could be separable by chromatography. With the material in hand, the ozonolysis-aldol condensation sequence
was attempted.\textsuperscript{25} None of the desired product was detected in the reaction mixture. The photochemical avenue did not show any promise either. The β-keto ester was methylated with potassium t-butoxide and methyl iodide\textsuperscript{24} to provide 51 in 61\% yield. Irradiating 51 with a Hanovia 450W medium pressure mercury lamp did not afford the expected product, but desulfurization products might have been formed by NMR spectroscopy.

Compound 45 was oxidized with sodium periodate to yield 52 as a mixture of diastereomers that were not separable by flash chromatography in 87\% yield. Sulfoxide
52 was then carbomethoxylated by deprotonation with potassium hydride and dimethylcarbonate to prepare 53 in 78% yield. This is our current point of progress in this area. β-Keto ester 53 has been chlorinated, but the conditions for the ring contraction have not been worked out at this point.

\[ 45 \xrightarrow{\text{NaIO}_4, \text{NaHCO}_3, \text{MeOH, H}_2\text{O, 25°C, 2 days}} 52 \]

\[ 52 \xrightarrow{\text{KH, (H}_3\text{CO)}_2\text{CO, THF, 0°C - 25°C}} 51 \]
EXPERIMENTAL

General

Unless otherwise stated, reagents used were purchased from commercial suppliers and were not purified unless stated. Dry diethyl ether and tetrahydrofuran were distilled from benzophenoneketyl, benzene was distilled from lithium aluminum hydride, methylene chloride and acetonitrile were distilled from calcium hydride, and toluene was distilled from sodium. Unless otherwise noted, all reactions were conducted in a argon atmosphere. For reactions requiring anhydrous conditions, the apparatus was flamed dried under a stream of argon. Melting points were determined using a Fisher-Johns melting point apparatus and are uncorrected. Silica gel used for flash chromatography was EM Science Kieselgel 60 (230-400 mesh) or Mereck 60 grade (230-400 mesh). Thin layer chromatography was performed using EM Science Kieselgel F_{254} prepared plates with thickness of 0.25 cm. The solvent systems were suitable mixtures of hexanes (H) and ethyl acetate (EA). High field proton nuclear magnetic resonance spectra were obtained at 300 MHz using Nicolet Magnetics Corporation 1280 spectrometer. All chemical shifts are reported in \( \delta \) relative to tetramethylsilane as an internal standard. Coupling constants (J) are reported in Hz. Splitting patterns are designated: s (singlet), d (doublet), t (triplet), q (quartet), bs (broad singlet), m (multiplet) ABq (AB quartet). Carbon-13 nuclear magnetic resonance spectra were recorded at 75.46 MHz using a Nicolet Magnetics Corporation 1280 spectrometer and are reported in \( \delta \) relative to the central peak of CDCl\(_3\) (77.06 ppm). Infrared spectra were recorded using a Perkin-Elmer 1320 infrared spectrophotometer and are reported in cm\(^{-1}\). EI and CI (using the gas reported) low resolution mass spectra were
recorded on a Finnegan 4023 mass spectrometer. High resolution mass spectra were recorded using a Kratos model MS-50 spectrometer.

1-(2-Propenyl)-8-(phenylthio) bicyclo [3.3.1] nonan-3-one 45

To a solution of bridgehead bromide 40 (0.75 g, 2.33 mmol) and allyltrimethylsilane (1.11 mL, 6.99 mmol) in 4.70 mL of dry methylene chloride at 0 °C, was added silver (I) triflate (0.66 g, 2.56 mmol). The suspension was slowly warmed to ambient temperature while stirring for 10 h. The suspension was diluted with 10 mL of brine, extract twice with 15 mL of methylene chloride and dried over Na₂SO₄. The solution was concentrated in vacuo and purified by flash chromatography eluting with 4 : 1 H : EA to afford 0.62 g (91%) of 45. TLC (4 : 1 H : EA) Rf = 0.27. ¹H NMR δ 1.40 - 1.95 (m, 7 H), 2.08 (d, J = 17.6 Hz, 1 H), 2.21 (dd, J = 13.7 Hz, 7.8 Hz, 1 H), 2.33 - 2.55 (m, 3 H), 2.65 (bd, J = 17 Hz, 1 H), 3.03 (dd, J = 11.4 Hz, 4.7 Hz, 1 H), 5.10 - 5.20 (m, 2 H), 5.75 - 5.93 (m, 1 H), 7.20 - 7.30 (m, 3 H), 7.35 - 7.48 (m, 2 H). ¹³C NMR δ 28.21, 30.04, 32.17, 38.07, 41.31, 45.21, 46.13, 47.88, 55.90, 119.28, 126.92, 128.81, 132.47, 132.93, 134.88, 211.50. IR (CHCl₃) 3080, 3010, 2930, 2860, 1705, 1640, 1585, 1440, 1230, 925, 690 cm⁻¹. Low resolution mass spectrum m/e 55, 67, 79, 91, 109, 119, 135, 150, 177, 245, 286.

Methyl 4-carboxylate-1-(2-propenyl)-8-(phenylthio)-bicyclo [3.3.1] nonan-3-one 47

To pentane washed KH (0.20 g, 5.0 mmol) at 0 °C, was added dropwise a solution of 45 (0.60 g, 2.09 mmol) in 7.5 mL of dry dimethylcarbonate. The suspension was warmed to ambient temperature and stirred for 16 h. Excess saturated NH₄Cl was added
cautiously to quench the reaction. The mixture was extracted thrice with 25 mL of Et₂O, washed with 25 mL of brine and dried over Na₂SO₄. The crude product was purified by flash chromatography eluting with 3 : 1 H : EA to yield 0.58 g (81%) of 47. TLC (4 : 1 H ; EA) R_f = 0.63. ^1H NMR δ 1.36 - 1.46 (m, 1 H), 1.50 - 1.82 (m, 3 H), 2.10 - 2.23 (m, 2 H), 2.45 (dd, J = 13.7 Hz, 7.8 Hz, 1 H), 2.59 (d, J = 19.8 Hz, 1 H), 2.90 (apparent q, J = 3 Hz, 1 H), 2.97 (dd, J = 14.7 Hz, 4.8 Hz, 1 H), 5.05 - 5.15 (m, 2 H), 5.70 - 5.90 (m, 1 H), 7.20 - 7.30 (m, 3 H), 7.35 - 7.48 (m, 2 H). ^13C NMR δ 28.19, 30.06, 32.30, 38.00, 41.38, 46.73, 47.92, 55.90, 57.90, 102.65, 119.30, 127.04, 128.90, 132.60, 132.23, 133.23, 148.06, 172.35, 199.36. IR (CHCl₃) 3080, 3010, 2930, 2860, 1705, 1640, 1585, 1440, 1230, 925, 690 cm⁻¹. Low resolution mass spectrum m/e 55, 67, 91, 107, 119, 133, 159, 177, 302.

1-(2-Propenyl)-8-(benzenesulfenyl) bicyclo [3.3.1] nonan-3-one 52

To a solution of 45 (150 mg, 0.52 mmol) in a 6 : 1 mixture of methanol and water (23 mL) at 0 °C, was added sodium periodate (235 mg, 1.10 mmol) and sodium bicarbonate (49 mg, 0.58 mmol). The suspension was warmed to ambient temperature and stirred for two days. The suspension was diluted with 24 mL of water, extracted thrice with 20 mL of Et₂O, and dried over Na₂SO₄. The crude material was purified by flash chromatography eluting with 1 : 6 H : EA to yield 137 mg (87%) of 52 which was a mixture of diastereomers. TLC (1 : 6 H : EA) R_f = 0.43. ^1H NMR δ 0.80 - 1.20 (m, 2 H), 1.42 - 1.56 (m, 1 H), 1.60 - 1.95 (m, 3 H), 2.16 (d, J = 16.5 Hz, 1 H), 2.25 - 2.55 (m, 3 H), 2.79 (dd, J = 14.0 Hz, 8.8 Hz, 1 H), 2.99 (dt, J = 16.5 Hz, 2.1 Hz, 1 H), 3.19 (bd, J = 16.5 Hz, 1 H), 5.18 - 5.44 (m, 2 H), 5.83 - 6.10 (m, 1 H), 7.40 - 7.80 (m, 5 H). IR (CDCl₃) 3010, 2860, 2400, 1705, 1440, 1220, 1185, 1040, 930, 770 cm⁻¹. Low
High resolution mass spectrum requires 302.13405, found 302.13333.

Methyl 4-carboxylate-1-(2-propenyl)-8-(benzenesulfenyl)-bicyclo[3.3.1]nonan3-one 53

To pentane washed KH (87 mg, 0.76 mmol) at 0 °C, was added dropwise a solution of 52 (100 mg, 0.33 mmol) in 1.2 mL of dry dimethylcarbonate and 1.2 mL of dry THF. The suspension was warmed to ambient temperature and stirred for 16 h. Excess saturated NH4Cl was added cautiously to quench the reaction. The mixture was extracted thrice with 210 mL of Et2O, washed with 10 mL of brine and dried over Na2SO4. The crude product was purified by flash chromatography eluting with 3:2 H : EA to yield 110 mg (92%) of 53. TLC (3:2 H : EA) Rf = 0.31. 1H NMR δ 0.80 - 1.10 (m, 2H) 1.20 - 1.38 (m, 2H), 1.64 - 1.75 (m, 2H), 1.85 - 2.02 (m, 1H), 2.02 - 2.49 (m, 3H), 2.73 - 2.98 (m, 3H), 3.18 - 3.41 (m, 1H), 5.18 - 5.42 (m, 2H), 5.82 - 6.08 (m, 1H), 7.42 - 7.60 (m, 5H). IR (CHCl3) 3090, 3980, 2790, 1730, 1692, 1640, 1452, 1392, 1280, 910, 700 cm⁻¹. Low resolution mass spectrum m/e 69, 83, 98, 111, 123, 151, 195, 223, 271, 313, 326, 343.
REFERENCES


OVERALL SUMMARY

Part I of this manuscript described a variety of approaches to kaurene natural products. Even though the final goal was not achieved, much information was gained in this study. A tetracyclic intermediate was constructed, but the angular methyl group could not be attached. Two tricyclic intermediates were prepared. In one example an appropriate appendage could not be added that would have allowed the construct of the fourth ring. The other example contained the necessary carbons to achieve the synthesis of kaurene, but the fourth ring could not be realized from this intermediate.

Part II contained an approach to kaurene natural products that was also not successful. This approach was based on a Michael addition followed by an oxy-ene reaction. The precursor to the oxy-ene reaction could not be prepared. The strategy was then changed and based on the cyclization of a bicyclic intermediate to a tricyclic intermediate. This intermediate would contain the necessary functionality to construct the bicyclo [3.2.1] octane moiety found in this class of natural products. A variety of cyclizations were attempted, but the tricyclic precursor was not prepared.

Part III describes an approach to trixiingolide. This project is only in the infant stages, but the route to an advanced intermediate is described. One question yet to be answered is the regioselective aldol condensation.
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