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Ham, Won Hun

TOTAL SYNTHESIS OF THE MARINE SESQUITERPENES (+/-)-DACTYLOL AND (+/-)-AFRICANOL. A SYNTHETIC APPROACH TOWARD (+/-)-NEOLEMNANYL ACETATE

The Ohio State University

Ph.D. 1986

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TOTAL SYNTHESIS OF THE MARINE SESQUITERPENES
(±)-DACTYLOL AND (±)-AFRICANOL. A SYNTHETIC APPROACH
TOWARD (±)-NEOLEMNANYL ACETATE

DISSERTATION

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

By

Won-Hun Ham, B.S., M.S.

* * * * * * * * *

The Ohio State University

1986

Reading Committee:
Dr. Leo A. Paquette
Dr. David J. Hart
Dr. Anthony W. Czarnik

Approved By

Leo A. Paquette
Adviser
Department of Chemistry
To my parents, my wife

Yoon-Jeong, and Chung-Hyun
Acknowledgement

I wish to express my gratitude to Professor Leo A. Paquette for his invaluable advice, support, and contagious enthusiasm for chemistry throughout this endeavor. I wish to thank my parents for financial support of my education. The author is also deeply grateful to his family, especially his wife, Myoung Won, for their love, patience and strength. Also, I thank the many graduate students and postdocs of the Paquette group who enriched my learning experience. In particular, I am grateful to Richard, Jean-Claude, Robert and Ho-Shen for their friendship. I acknowledge Kay's help in the typing of this document.
VITA

December 12, 1952 . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . Born, Incheon, Korea

1975 . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . B.S. (Pharmacy)
Seoul National University
Seoul, Korea

1977-1979 . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . M.S. (Pharmacy)
Seoul National University
Seoul, Korea

1979-1981 . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . M.S. (Organic Chemistry)
Illinois State University
Normal, Illinois

1981-present . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . Department of Chemistry
The Ohio State University
Columbus, Ohio

Publications


Major Field: Organic Chemistry

Studies in Natural Product Synthesis.
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Chapter I

Total synthesis of the Marine Sesquiterpenes
Dactylol and Africanol. de novo Construction of a
Cyclooctanoid Natural Product from Cycloheptane Precursors.
Introduction

Nature is seemingly unlimited in its ability to produce molecules of widely varying and structurally complex architecture. The organic chemist who seeks to construct natural products with unusual molecular structure and functionality confronts formidable challenges. As a direct result of these challenges, new synthetic methods must be developed and well-established chemical reactions with newer methods must be utilized in new settings. The synthetic plan also presupposes several novel chemical transformations of an exploratory nature, which if successful would demonstrate new concepts in organic synthesis. The goal of the present work was to synthesize, from readily available materials, the sesquiterpene alcohols africanol (1) and dactylol (10).

The sesquiterpene africanol (1) was isolated in 1974 by Tursch and coworkers\(^1\) from the soft coral \textit{Lemnalia africana}. The structure of this interesting tricyclic alcohol, established by means of x-ray analysis\(^2\), serves as the prototype of the africane group of natural products that presently also includes\(^\Delta(15)\)-africane (2, source: soft corals \textit{Sinularia erecta}\(^3\) and \textit{S. polydactyla}\(^4\)), africanone (3, source: leafy plant \textit{Lippia integrifolia}\(^5\)), and \(8\beta\)-angeloxy-senoxyri-4-en-3-ol (4a, source: roots of \textit{Senecio oxyriifolius}\(^6\)).
Shirahama has proposed that 1 is biosynthetically derived from humulene, which in its CT conformer (5) undergoes initial acid-catalyzed closure to the 9-africyl cation (6). Proton loss and subsequent hydration presumably occur to provide 1.

More recently, the possibility has been entertained that 6 may find it possible to experience 1,2-prototropic shift and formation of the 6-africyl cation (8).
Should the neighboring cyclopropane ring in 8 subsequently enter into 1,2-migration in the manner illustrated, arrival at dactylol (10) becomes possible. This irregular isoprenoid alcohol was characterized by Schmitz in 1978 as a substance produced by the Caribbean sea hare Aplysia dactylomela\textsuperscript{10,11}. Dactylol also has been isolated along with poitediol\textsuperscript{12} (25) from the red seaweed Laurencia poitei\textsuperscript{13}.

Scheme I
Synthetic Studies on Africanol

Africanol presents an interesting synthetic target. To date, a preliminary approach and one total synthesis achieved by Lewis acid-catalyzed rearrangement of humulene-9,10-epoxide have been reported. Widener\(^{14}\) employed rearrangement of the cyclopropylcarbinyl alcohol 12 to the seven-membered ring compound 13, which was suitably functionalized for the preparation of ketone 14. Subsequently, several elaborate approaches to cyclopentane annulation by using enone (15) and ketone (16) turned out to be unsuccessful. No additional work has been reported on this approach (Scheme II).
Shirahama and coworkers synthesized racemic africanol through a newly developed conformationally selective transannular cyclization of humulene-9,10-epoxide. Subsequent transformations led to africanol as shown below (Scheme III).
Synthetic Studies on Dactylool

Dactylool is a relatively simple member of a growing family of cyclo-octanoid natural products which continue to attract interest as challenging synthetic targets.

Gadwood employed an anionic oxy-Cope rearrangement of a dialkenyl cyclobutoxide to synthesize substituted cyclooctenones, one of which was successfully functionalized to arrive at poitediol (25). Subsequently, poitediol was treated with sodium and ethanol in liquid ammonia to provide dactylool (Scheme IV).

Scheme IV
Hayasaka and coworkers\textsuperscript{9} have recently demonstrated that the outlined biosynthesis from humulene through an apparent 1,2-shift of a methyl group could be utilized to synthesize dactylool. For the first time, cyclooctanoid natural products were produced by isomerization of suitable cycloheptane precursors (Scheme V).

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

Scheme V
A possible reaction course is described in Scheme VI.

Scheme VI

Retrosynthetic Analysis

Africanol is a new type of tricyclic monohydroxylated sesquiterpene. Africanol possesses a cyclopropane ring and a tertiary hydroxyl group attached to a perhydroazulene ring system.

Five chiral centers are present in the molecule, two in the cyclopropane ring, two at the ring fusion and one where the secondary methyl group is attached to the five-membered ring. The methyl group in the five-membered ring is anti to the hydroxyl substituent which is positioned at the ring fusion.
Stereochemical control is required to develop both the cis-ring fusion and the proper relationship of the methyl and tertiary hydroxyl groups. Particularly noteworthy is recognition that the five stereo-centers are contiguous to each other. In planning construction of the tricyclic hydroazulenoid framework present in the africanes, one should take account of previous studies involving the synthesis of hydroazulene compounds.

Much of the work in the synthesis of perhydroazulenes has been directed at more elaborate natural products\textsuperscript{17}, which have been known for over a decade. The fundamental strategies that have been utilized can be organized into four general categories (Scheme VII).
1) The first approach begins with a cyclopentane derivative and proceeds to fuse the cycloheptane ring system. This protocol has been employed in most of the successful syntheses reported to this time.

2) The second approach involves formation of the hydroazulene skeleton by transannular cyclization of an appropriately constructed cyclodecane.

3) Another possible approach is to utilize a hydronaphthalene precursor, which is caused to undergo skeletal rearrangement to provide the desired hydroazulene skeleton.

4) A complementary strategy would be to add the cyclopentane ring onto a preformed cycloheptane nucleus.

Analysis of the africanol structural features in a retrosynthetic sense suggested several worthy strategies for its successful preparation. One of these involved a scheme that would involve fusion of a functionalized cyclopentane ring onto a preformed bicyclo[5.1.0]-octane nucleus. Although a related tactic has been described on two earlier occasions\textsuperscript{18a,b}, no cyclopropane ring was involved in either study\textsuperscript{18c}. In this strategy, the well established stereoelectronic features of electrocyclic cyclopropane cleavage\textsuperscript{19-23} processes have to be avoided in order to succeed with our goal. Quite naturally,
particular concern had to be focused on the five contiguous chiral centers in 1. For synthetic purposes, there exists the option of generating the first C-C bond at site a or at site b (see A). In either case, it was imperative that all complications stemming from potential cyclopropylcarbinyl cation intervention be avoided. Both of these routes will be explored in turn, shown to be devoid of this potential source of structural rearrangements, and demonstrated to be adaptable to the stringent stereochemical requirements of the target molecule.

Africanol may be viewed as a functionalized africanene nucleus. In addition, epoxide 28 that has previously been converted in two steps to dactylol is a functionalized africanene derivative. Accordingly, an efficient synthesis of the africanene nucleus became our first goal.
In the later stages of our approach to africanol, we envisioned the possibility of epoxide (33 or 35) ring opening via the Wharton rearrangement or related reactions.

As concerns dactylol, we envisioned use of the Friedel-Crafts cyclization of acid 37 as a preferred means of cyclopentanoid annulation.

Although 1 and 4a (as 4b) have been prepared by Lewis acid-catalyzed rearrangement of humulene-9,10- and 4,5-epoxides, no de novo synthesis of a representative africane had been reported. Herein, we describe stereocontrolled total syntheses of africanol and epiafricanol. In addition, a route to epoxide 28 that has previously been converted in two steps to dactylol is presented.
Results and Discussion

To begin the synthesis, an expedient preparation of cis-1,5,5-trimethylbicyclo[5.1.0]octan-2-one (43) was sought. Given the ready availability of 4,4-dimethyl-2-cyclohexenone via acid-catalyzed annulation of isobutyraldehyde and methyl vinyl ketone, and its reported quantitative hydrogenation to 38, our efforts were concentrated on suitable ring expansion of this intermediate.

The silylenol ether of 38 prepared by the method of House and coworkers, was treated with dibromocarbene resulting from reaction of bromoform and potassium tert-butoxide. Thermolysis of the crude reaction mixture in benzene solution led to bromocycloheptenone 39, which was directly ketalized (Scheme VIII). Replacement of the halogen by reaction with lithium dimethylcuprate gave 40 in good yield (61%).
The silylenol ether of 38 was similarly treated with chloromethylcarbene, in turn generated from 1,1-dichloroethane and n-butyl-lithium\(^{30}\). Thermolysis of the pair of stereoisomeric cyclopropane derivatives (41) in toluene smoothly led directly to 42 (Scheme IX).

This adaptation of Conia's methodology proved particularly efficient (82\%)\(^{31,32}\).

The reaction of enone 42 with dimethylsulfoxonium methylide, prepared from trimethylsulfoxonium iodide and sodium hydride\(^{33}\) in DMSO, gave cyclopropyl ketone 43. However, under a number of reaction
conditions in which the reaction temperature and time were varied, the yields were at best poor (25-45%). At a temperature of approximately 0°C (achieved by the addition of THF as cosolvent), the reaction did not proceed at an appreciable rate, whereas at room temperature a large amount of an unidentified impurity was isolated along with the desired compound.

Since large amounts of intermediate were required in a short period of time, a more efficient route was made mandatory. To this end, enone 42 was ketalized with ethylene glycol in refluxing benzene to afford ketal 40 in excellent yield. Importantly, double bond migration did not occur during conversion to the ethylenedioxy derivative.

At this point, the stage was set for lateral fusion of the cyclopropane ring. The use of ethylzinc iodide\(^\text{34}\) (modified Simmons-Smith reaction) proved particularly suitable. Following hydrolytic removal of the blocking group under mild acidic conditions, 43 was isolated in quantitative yield.

\[
\begin{array}{c}
\text{CH}_3 \\
\text{CH}_3 \\
\text{CH}_3 \\
\text{CH}_3 \\
\end{array}
\]

\[
\begin{array}{c}
\text{CH}_3 \\
\text{CH}_3 \\
\text{CH}_3 \\
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\end{array}
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\text{CH}_3 \\
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\text{CH}_3 \\
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\]

\[
\begin{array}{c}
\text{CH}_3 \\
\text{CH}_3 \\
\text{CH}_3 \\
\text{CH}_3 \\
\end{array}
\]

1. HO$\sim$OH, H$^+$
2. C$_2$H$_5$ZnI,
3. H$_3$O$^+$
With the synthesis of an appropriately functionalized seven-membered ring completed, the first goal had been attained. In the following sections, the investigation of cyclopentane ring annulation will be discussed in detail.

The enolate anion of 43 entered readily into aldol condensation with acetaldehyde. The assignment of stereochemistry to 44 is based on a combination of aldol-type reaction mechanism\textsuperscript{35} (chain-type pericyclic intermediate) and conformational analysis of the bicycloheptanone.

Some time ago, Zimmerman and Traxler proposed for the Ivanov reaction a chair-type pericyclic intermediate\textsuperscript{36} that proved useful in explaining the stereochemical course of several aldol-type reactions. According to this proposal, the transition state of the aldol reaction is that shown in Scheme X.
According to Pearson, the enolate derived from 2-cycloheptenone is essentially a cyclohepta-1,3-diene derivative, and its reactivity can be analyzed on the basis of related diene conformations. At relatively low temperatures, he favors the twisted diene conformation E relative to the planar diene conformation D.
Thus, assuming that the bicyclo[5.1.0]octanes are conformationally similar to cycloheptenes\textsuperscript{38}, the stereochemistry of aldol adduct 44 can be deduced as follows.

As can be seen by inspection of molecular models (F), the $\alpha$-face of the twisted diene is concave. Approach of the electrophile (CH\textsubscript{3}CHO) is clearly preferred on the convex $\beta$-face for steric reasons. With the enolate of 37, acetaldehyde approach to the $\beta$-face will lead to 44, which indeed is the observed major product (>20:1; no isomer can be detected by $^1$H NMR at 300 MHz).

Although acid-catalyzed dehydration\textsuperscript{39} of the resulting $\beta$-hydroxy ketone proceeded well when small amounts (100 mg) were involved, the process did not scale up satisfactorily.

A simple solution to this obstacle consisted of acetylation and subsequent $\beta$-elimination of acetic acid with DBU in hot benzene\textsuperscript{40}. Only 45 resulted (71% overall), the anti stereochemistry of which was evident from the appearance of its olefinic proton at $\delta$ 6.91 in CDCl\textsubscript{3} solution. The downfield displacement of this signal owes its origin to
positioning within the deshielding region of the neighboring carbonyl group\textsuperscript{39,41}. No evidence was found for formation of syn isomer (olefinic proton absorption anticipated at ca $\delta$ 5.5).

With 45 in hand, our attention was next focused on the stereochemistry of reduction at the carbonyl site. This stereochemistry was of importance because of our impending plan to transfer the chirality induced at the resulting carbinol center to the olefinic side chain by Claisen rearrangement. Following treatment with the Luche\textsuperscript{42} reagent, alcohol 46a was produced almost exclusively. As expected, it was difficult to define its stereochemistry. A tentative assignment has been made on the basis of the previous work of Cope and of Smith.
Evidence concerning the stereochemistry of the bicyclo[5.1.0]octanols was thoroughly summarized by Cope and coworkers in 1962. This stereochemical analysis is based on the chair conformation shown below in Figure 1.

![Figure 1. Conformational analysis of bicyclo[5.1.0]octane](image)

The proton α to the hydroxyl group in 47 (Fig 1, $R_1 = \text{OH}, R_2 = R_3 = R_4 = R_5 = R_6 = H$) is axially oriented forming bond angles of 180° with two adjacent axial hydrogen atoms ($R_3$ and the $C_1$-hydrogen atom); whereas in 48 ($R_2 = \text{OH}, R_1 = R_4 = R_5 = R_5 = R_6 = H$), the proton α to the hydroxyl group is equatorially located, forming bond angles of 30-90° with adjacent hydrogen atoms. From results of NMR studies in the cyclohexane series, it was concluded that the axial α proton of 47 should appear at higher field and have a greater halfwidth than that of 48. Thus, in 47 the axial proton was observed at $\delta = 3.3$ with half-width of 15 Hz, while in 48 the equatorial proton was observed at $\delta = 4.2$ with a half-width of 10 Hz.

Similar circumstantial evidence has also been provided for the bicyclo[5.1.0]octan-4-ols 49 and 50. The NMR spectra due to the equatorial $C_4$ hydrogen of 50 appears at lower field ($\delta = 4.1$) with a small half-width (8 Hz) than the axial $C_4$ hydrogen of 49 ($\delta = 3.5$, half-width 22 Hz).
This difference in coupling pattern at the C-4 methine proton in various bicyclo[5.1.0]octanes was observed as well by Smith and coworkers. The relative stereochemistry of 51t was also defined via x-ray crystallographic analysis. The spectroscopic observations are consistent with the existence of both isomers in chair-like conformations.

\( (51c) \; R^1 = H, \; R^2 = OC\text{OMe} \)  \( (52c) \; R^1 = H, \; R^2 = OH \)  \( (53c) \; R^1 = H, \; R^2 = OH \)  

\( (51t) \; R^1 = OC\text{OMe}, \; R^2 = H \)  \( (52t) \; R^1 = OH, \; R^2 = H \)  \( (53t) \; R^1 = OH, \; R^2 = H \)
Table I. $^1$H NMR Data for Diastereomers 51, 52 and 53

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<tr>
<th>compd</th>
<th>cis</th>
<th>trans</th>
<th>(cis-trans)</th>
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<tr>
<td>51</td>
<td>5.20 (br s)</td>
<td>4.60 (tt, J = 10.8, 3.7 Hz)</td>
<td>0.60</td>
</tr>
<tr>
<td>52</td>
<td>4.26 (br s)</td>
<td>3.48 (tt, J = 10.8, 3.7 Hz)</td>
<td>0.78</td>
</tr>
<tr>
<td>53</td>
<td>4.22 (br s)</td>
<td>3.44 (tt, J = 10.8, 3.7 Hz)</td>
<td>0.78</td>
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In 51c, the C-4 methine proton occupies a pseudoequatorial position (see Figure 1) and enjoys a dihedral angle relationship of approximately 90° relative to one of the adjacent methylene protons. Thus, one would expect a relatively simple coupling pattern. In 51t, the corresponding proton is pseudoaxial, the neighboring proton is pseudoaxial, and the dihedral angles to the adjacent methylene protons are approximately 40° and 155°, again consistent with the observed coupling pattern.

The Cope proposal, based solely on NMR spectra, correlates very well with Smith's observations. The 300 MHz NMR spectrum of 46a shows the proton α to the hydroxy group to reside at δ 4.18, which compares very favorably with Cope's findings (e.g. δ 4.2 in 48). The structure of alcohol 46a was firmly established by x-ray crystal structure of its p-nitrobenzoate (46b). This compound also resides in a chair-like conformation (Figure 2). The conformation adopted by this alcohol suggests that the delivery of hydride is as illustrated in G for steric reasons.
Figure 2. ORTEP diagram of 46b with hydrogens omitted for clarity (courtesy of Prof. I. Bernal and Dr. J. D. Korp, Univ. of Houston).
Associated with the triethyl orthoacetate variant of the Claisen rearrangement within 46a are two limiting transition states. Of these, the chair-like conformation H gave a priori indication of being clearly favored. At the experimental level, the usual conditions for this transformation as applied to allyl alcohol 46a delivered a stereochemically homogeneous ester (72%) whose saponification furnished 54 (Scheme XI). The totality of the chirality transfer is noteworthy. The configuration of the sidechain methyl group, inferred from the preceding stereoelectronic considerations, is seen to be proper in relation to dactylol (10), but opposite to that present in africanol (1).
The next goal, cyclization with generation of a functionalized five-membered ring, was pursued from several directions:

(a) carboxylic acid 54 was treated with trifluoroacetic anhydride in CH$_2$Cl$_2$ under various conditions (RT, 0°C, -78°C). These reactions gave only decomposition product and starting material.

(b) carboxylic acid 54 was treated with stannic chloride in acetic anhydride at 0°C. This reaction produced a myriad of decomposition products.

(c) carboxylic acid 54 was transformed into its acid chloride. Exposure of this intermediate to aluminum chloride in carbon disulfide solution gave rise to a dark reaction mixture from which only 56 could be isolated (34%). The stereostructure assigned to 56 is based on consideration of its $^1$H NMR spectrum and examination of molecular models. Furthermore, catalytic reduction of 56, anticipated to proceed with delivery of hydrogen and formation of 57, does indeed lead to a saturated tricyclic ketone possessing methyl absorptions closely comparable to those exhibited by africanol. The preceding results were disappointing, but not totally unexpected. Büchi and coworkers used this method in the preparation of patchouli alcohol with only fair results.

(d) alternate recourse to stannic chloride in anhydrous 1,2-dichloroethane at 0°C led in 96% yield to a mixture of 34 (12%), 55

\[ \text{HOOC} \quad \xrightarrow{1. \text{oxalyl chloride}} \quad \xrightarrow{2. \text{AlCl}_3} \]

\[ \text{Ko} \]
Our findings indicate that the strain energy residing in fused perhydroazulene systems resists placement of a double bond at the ring junction. The excellent efficiency of the cyclization process coupled with subsequent treatment with rhodium trichloride proved to be an especially attractive route to the preparation of 34. That is, exposure to the transition metal in hot ethanol induced double bond isomerization to an extent that eventually led to dominance by 34 of the three isomers (68%).

\[ \text{Scheme XI} \]
Significantly, the proportion of 56 is drastically reduced to only 3%. Proper stereochemical distinction between 34 and 55 was made by conversion of 34 to epoxy alcohol 62 and x-ray analysis this highly crystalline compound (Figure 3).

The alternative possible construction of a stereochemically defined annulated cyclopentanone ring by rhodium (I)-catalyzed intramolecular hydroacylation also appeared attractive. To assess this option, aldehyde 59 was prepared conveniently from 54 in two steps. Unfortunately, all attempts to effect the cyclization of 59 in presence of various rhodium (I) complexes led exclusively to recovery of unreacted aldehyde.

![Scheme XII](image_url)
Figure 3. Perspective drawing of 62 derived from the x-ray coordinates with hydrogens omitted for clarity (courtesy of Dr. J. P. Springer, Merck, Sharp, and Dohme).
As expected on the basis of Baldwin's rules, aldehyde 59 reacted with SnCl₄ to give only decomposition products.

![Chemical structure of 59 and 61](image)

Ring formation in this manner is disfavored because of the requirement that severe distortion in bond angles and distances take place in such a trajectory.

The chromatographic separation of enones 34, 55, 56 proved not to be necessary, since dithioketalization of the mixture gave only 63 and 64 in an 83:17 ratio (Scheme XIII). Initially, the relative stereochemical assignments to 63 and 64 were made tentatively on the basis of the apparent thermodynamic bias of the secondary methyl group for the α environment, as encountered earlier. Unequivocal definition of stereochemistry was readily achieved by sequential Raney nickel desulfurization and epoxidation. Chromatographic purification gave 28 as the overwhelmingly major product.

The successful elaboration of 28 from 54 requires no chromatography until completion of the epoxidation step. As an important point of stereochemical reference, the peracid can be seen to prefer approach to the π bond in 27 predominantly from the α face to deliver
28. Its $^1$H NMR spectra was identical to that provided by Professor Matsumoto$^9$. The facility with which 28 undergoes Lewis acid-catalyzed isomerization with cleavage of both three-membered rings and conversion to dactylol (10) has been earlier detailed by the Matsumoto group$^9$. Thus, it is now possible to view 5/8-fused sesquiterpenes such as 10 as being usefully accessible from hydroazulenoid precursors.

Scheme XIII

[Diagram of chemical structures and reactions involving compounds 62, 63, 64, 65, 10, and 28, with reactions and reagents labeled.]
A series of epoxidations with the mixture of enones 34 and 55 [1]

30% H_2O_2, OH^-, acetone; 2) 30% H_2O_2, OH^-, methanol and 3) 30% H_2O_2, tetra-t-butylammonium hydroxide] gave only starting material due to steric hindrance.

At this point, the possibility of synthesizing a β-epoxy alcohol stereoselectively was investigated from two different directions.

The alcohol mixture was initially reacted with trimethylsilyl chloride in triethylamine and the silyl ether was directly reacted with MCPBA and deblocked with aqueous ammonium chloride in methanol. Surprisingly, the major isolated product was identical to α-epoxy alcohol 62 originally separated from the sequential reaction involving Dibal and MCPBA. From this result can be inferred the fact that the double bond is sterically hindered by the cyclopropyl group (Scheme XIV). The next approach was designed to invert the stereochemistry of the α-alcohol with DEAD, benzoic acid, and triphenylphosphine. The resulting benzoate was reduced with lithium aluminum hydride and the alcohol was treated with MCPBA to give epoxy alcohols, which were separated by MPLC. The major isolated product (62) was identical to the α-epoxy alcohol separated earlier (Scheme XV).
Scheme XIV

1. DIBAL
2. (Me)$_3$SiCl, Et$_3$N
3. MCPBA
4. deblocking

+ stereoisomers
Scheme XV
Usually, the Mitsunobu reaction proceeds with inversion of configuration. However, our allylic alcohol is so sterically hindered on the β face that benzoate ion cannot attack from this side.

Attention next turned to an investigation of the displacement by thiophenol\(^{57}\) of an allylic hydroxyl as shown below.

\[
\begin{align*}
\text{CH}_2\text{N-(phenylthio)succinimide} & \quad \text{1. Dibal} \\
\text{34,55} & \quad 2. \text{N-(phenylthio)succinimide, (n-Bu)}_3\text{P} \\
\end{align*}
\]

The crude alcohol was reacted with tri-n-butylphosphine and N-(phenylthio)succinimide at room temperature to give inseparable thio-compounds (35%) and starting material (25%). These experiments revealed the lack of reactivity of this allylic alcohol, presumably due again to the sterically hindered environment. A more detailed investigation of these procedures was postponed because of ambiguous stereochemistry in the intermediates and a lack of reactivity.

Quite unexpectedly, epoxy ketone 71 proved to be resistant to conversion to allylic alcohol 72 after heating in hydrazine hydrate at temperatures as high as 118°C\(^{58-59}\).
An alternate possible route to africanol that was investigated involved cuprate\textsuperscript{60} additions to 34/55.

Under a variety of conditions, only starting material or presently uncharacterized products were obtained. It became clear that difficulties with the organocopper reactions were going to plague this approach to africanol. No successful conjugate addition has yet been accomplished, which is not too surprising in light of the incipient quaternary center that would develop.

A doubly unsaturated cyclopentadiene ring is recognized to be present in artabsin\textsuperscript{61} (74), the major sesquiterpene lactone constituent\textsuperscript{62} of \textit{Artemisia absinthium}. 
Since, the preparation of conjugated dienes in synthetic organic chemistry is well known to be possible from tosylhydrazones of \( \alpha,\beta \)-unsaturated ketones and alkyl lithium reagents, the ketone mixture was therefore treated with tosylhydrazine and methanol at room temperature to give compounds 75/76 in a ratio of 4:1.

Interestingly, a similar double bond migration was earlier encountered in the predescribed Rh(I) isomerization and dithioketalization experiments.

The relative thermodynamics in this tricyclic compound are thereby made quite clear. The tosylhydrazones (75, 76), when treated with several reagent combinations [1) n-BuLi (1 eq.) in diglyme; CH\(_3\)ONa in diglyme; 3) n-BuLi (4 eq), TMEDA; 4) n-BuLi (1.1 eq) in diethylcarbitol; 5) CH\(_3\)ONa in diethylcarbitol\(^{64}\) led to myriads of products.
On the other hand, treatment of the enone triad (34/55/56) with Dibal followed by SOCl₂/Et₃N gave two diene compounds (77/78; ratio of 2:3), the structures of which were deduced by NMR spectroscopy.

Armed with this information, ready conversion of (34/55) to the cyclopentadiene could be achieved when the α,β unsaturated enone mixture rich in 34/55 was treated with Dibal and subsequently with thionyl chloride and triethylamine (45-60%).
The proposed route to 77 and 78 outlined below was to proceed via chlorination, elimination, and [1,5]sigmatropic hydrogen migration to 77.
However, 78 was formed instead, presumably because the hydrogen at C\textsubscript{10} is sterically hindered and not readily available to the base.

\[
\begin{align*}
\text{CH}_3 & \quad \text{OH} \\
\text{H} & \quad \text{CH}_3 \\
\text{CH}_3 & \quad \text{CH}_3 \\
\end{align*}
\]

\[
\begin{align*}
\text{SOCl}_2, \text{Et}_3\text{N} & \quad \rightarrow \quad \text{CH}_3 \\
\text{CH}_3 & \quad \text{Cl} \\
\text{CH}_3 & \quad \text{CH}_3 \\
\end{align*}
\]

\[
\begin{align*}
\text{E}_2 & \quad \rightarrow \quad \text{H} \\
\text{CH}_3 & \quad \text{CH}_3 \\
\text{CH}_3 & \quad \text{CH}_3 \\
\end{align*}
\]

Reactions of the allylic alcohols as shown below also gave rise to 77 but in inferior yields (30-45%).

\[
\begin{align*}
\text{CH}_3 & \quad \text{OH} \\
\text{H} & \quad \text{CH}_3 \\
\text{CH}_3 & \quad \text{CH}_3 \\
\end{align*}
\]

\[
\begin{align*}
\text{n-BuLi or} & \quad \text{TsCl} \\
(\text{Ac})_2\text{O}, \text{Et}_3\text{N} & \quad \rightarrow \quad \text{CH}_3 \\
\text{DMAP} & \quad \rightarrow \quad \text{CH}_3 \\
\text{CH}_3 & \quad \text{CH}_3 \\
\end{align*}
\]

As anticipated, controlled hydrogenation of 77 proceeds at its less substituted double bond to give 80 and 7 (ratio 73:19), in addition to a small amount of an unknown by-product. Of the two hydroazulenes formed, the known natural product 7 was easily recognized from the characteristic upfield portion of its \textsuperscript{1}H NMR spectrum\textsuperscript{11}. No synthesis of 7 has previously been documented.
All attempts to realize regiospecific epoxidation of the more highly substituted double bond in 77 was met with exceedingly rapid capture of the oxidizing agent. m-Chlorobenzoate 81 and acetate 82 are exemplary of the observed chemical behavior. The ease of conversion to these end products is believed to be the combined result of exhaustive alkyl substitution of the intermediate oxirane and the presence of an immediately adjoining olefinic center.
Saturation of m-chlorobenzoate 81a was attempted by means of catalytic hydrogenation (PtO₂) and diimide reduction⁶⁶ (generated from hydrazine and H₂O₂). These two attempts returned only starting material.

The elimination of water from 81a failed due to the instability of the resulting diene, which polymerized when formed.

Treatment of cyclopentadiene 77 with 70% HClO₄ gave two unidentified compounds, both of which lacked a cyclopropyl ring.
In 1963, Nickon and Mendelson reported on two very interesting observations. These workers noted that photooxygenation of 4-cholesten-3β-ol (84β) in the presence of hematoporphyrin as sensitizer produced the 4α,5-epoxy ketone (I, 75%) along with a lesser amount of enone J (10%). Under analogous conditions, the 3α-ol (84α) gave rise to the 4β,5-epoxy ketone (K, 50%) and L (10%). Given this insight, our hope was that 68 would behave analogously and thereby make available a particularly expeditious route to 85. Neglected by us in this comparison was the fact that the double bond in 68 is appreciably more congested on both of its surfaces than the conditions prevailing in either isomer of 84. The reaction of 68 with singlet oxygen was examined under conditions similar to those used by Nickon and Mendelson. However, a myriad of products was formed (Scheme XVI). The desired epoxy ketone 85 was isolated chromatographically, but only in 7.7% yield. Two somewhat more polar compounds tentatively identified as 86 (12%) and 87 (16%) also resulted. Not unexpectedly, 22% of the enone pair 34/55 was recovered. The complexity of this process obviously did not lend itself to our synthetic objectives and was not
obviously did not lend itself to our synthetic objectives and was not further pursued.

![Chemical Structure](image)

**Scheme XVI**

Although tricyclic compounds were successfully produced, the lack of stereocontrol and the increasing length of the synthesis made it evident that a totally fresh approach to the synthesis of africanol was required.
Structural information culled from the x-ray analyses of 1, 46b, and 62, coupled with independent examination of Dreiding models for related molecules, indicated the bicyclo[5.1.0]octane ring common to this group to be essentially locked into a single preferred conformation$^{43-45,68}$. Our expectations were that this topological feature could be translated into stereoselective chemical transformations under the proper circumstances.

To this end, carbomethoxylation of 43 with dimethyl carbonate and a mixture of sodium and potassium hydride$^{69}$ produced 88 in 85% yield. The conversion of 88 to α,β-unsaturated ester 89, realized by reduction to the alcohol, acetylation, and $E_2$ elimination$^{40}$, afforded 81 as a colorless liquid in 77% yield. α,β-Unsaturated ketone 90 was subsequently obtained via reaction of the carboxylic acid with methyllithium$^{70}$ (66.7% yield).
A potential route to africanol involves the use of (trimethyl-silyl)allene 93, which serves as the three carbon component in the (trimethylsilyl)cyclopentene annulation. The reaction involves initial complexation of an α,β-unsaturated ketone with titanium tetrachloride to generate an alkoxy allylic carbocation. Regiospecific electrophilic substitution of this cation by the (trimethylsilyl)allene 93 provides a vinyl cation stabilized by interaction with the adjacent
carbon-silicon bond. A 1,2 shift of the trimethylsilyl group affords an isomeric vinyl cation which is intercepted by the titanium enolate to produce a new five membered ring.

The requisite 1-substituted dimethylallene 93 is easily obtained by the method of Westmijze and Vermeer.²²

\[
\begin{align*}
\text{Me}_3\text{Si} &\xrightarrow{1.\text{n-BuLi, (Me)}_3\text{SiCl}} \text{Me}_3\text{Si}=\xrightarrow{2.\text{H}_3\text{O}^+} \text{Me}_3\text{Si}-\text{OH} \\
\text{Me}_3\text{Si} &\xrightarrow{1.\text{MsCl, TiCl}_4} \text{SiMe}_3
\end{align*}
\]

The condensation of ketone 90 with 93 afforded two compounds (ratio 1:1) in 45% yield. Although both appeared cyclic, their exact structures could not be determined and efforts to obtain good crystals for x-ray analysis turned out to be fruitless.

\[
\begin{align*}
\text{90} &\xrightarrow{\text{CuBr, LiBr}} \text{91} + \text{92} \\
\text{93} &\xrightarrow{\text{TiCl}_4} \text{94}
\end{align*}
\]

Concomitantly, ketone 90 was treated with a variety of hydride reducing agents to obtain 95 and 96. The results of a series of reductions are summarized in Table 2.
Table 2. Reduction of ketone 90.

<table>
<thead>
<tr>
<th>Reducing Agent</th>
<th>Solvent</th>
<th>Product 95</th>
<th>Product 96</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>((i-C_4H_9)_2AlH^a)</td>
<td>dichloromethane</td>
<td>88</td>
<td>12</td>
<td>83</td>
</tr>
<tr>
<td>((i-C_4H_9)_2AlH^a)</td>
<td>ether</td>
<td>88</td>
<td>12</td>
<td>76</td>
</tr>
<tr>
<td>(NaBH_4-CeCl_3^b)</td>
<td>methanol</td>
<td>1</td>
<td>2</td>
<td>92</td>
</tr>
</tbody>
</table>

^a Reductions were carried out at -78°C; the reducing agent employed was 1.0 M in hexane.  ^b Reaction was carried out at 25°C.
The selection of 90 was predicated on the results of molecular mechanics calculations\textsuperscript{73} that demonstrated conformer 90b to be 0.7 kcal/mol more stable than 90a. The indicated methyl-methyl interaction evidently destabilizes the structural arrangement present in 90a.

Central to our synthetic plan for arrival at africanol was the availability of an efficient method for reducing the carbonyl group in 90 stereoselectively to allylic alcohol 95. In view of the mechanism by which aluminum hydride reagents add to carbonyl compounds\textsuperscript{74} we considered it most plausible that the attack of Dibal on 90b would be relegated to "below-plane" (see M) because of steric shielding on the alternate surface by one of the geminal methyl groups. In point of fact, the end product of this reaction conducted at -78°C was an 88:12 mixture of two easily separable carbinols, the major constituent of which was formulated as the desired 95 for the above reasons.

Exposure of 90 to cerium trichloride-doped sodium borohydride\textsuperscript{42}, a reagent system noted for prior coordination of the lanthanide to the electronegative carbonyl oxygen\textsuperscript{75}, was expected to favor conformer N in order to minimize CH\textsubscript{3}-CeCl\textsubscript{3} interactions (see illustration). Attack by BH\textsubscript{4}\textsuperscript{-} from below in order to avoid related steric complications should consequently lead to predominant formation of 96. When 90 was treated in this manner, the resulting 95/96 ratio was substantially in favor of 96 (ratio 1:2). Thus, respectable stereoselectivity can indeed be realized without difficulty in the 1,2 reduction of 90.
The correctness of our configurational assignments to 95 and 96 surfaced quickly. The projected ortho ester Claisen rearrangement of 95 is seen to be governed by two chair-like transition state options (Scheme XVIII). The first (99a), which involves C-C bond formation trans to the cyclopropane ring, does not experience the 1,3-diaxial
interaction so clearly evident in 100a. Accordingly, thermal activation of 97 was predicted with reasonable confidence to proceed predominantly via "bottom side" bonding. Since 101a was actually formed exclusively (Scheme XIV), the level of chirality transfer in this instance is seen to be excellent.

The comparable handling of 98 proved informative. In this instance, esters 103a and 104a were formed in a 1:1 ratio. Evidently, the nonbonded steric interactions that develop in transition state 100b induce a level of destabilization entirely comparable to that arising from 1,3-diaxial interactions in 99b.

Ester 101a was hydrolyzed with potassium hydroxide in ethanol to give the corresponding acid (101b). Following proper introduction of the third chiral center as in 101, the derived acid chloride (via oxalyl chloride) was cyclized by means of alicyclic Friedel-Crafts chemistry. The success of this step rested on the expectation that the intermediate tricyclic carbocation would undergo β-elimination to form the conjugated ketone at a rate faster than hydride migration leading to the cyclopropylcarbinyl cation. The latter event would likely lead to unwanted expansion of the seven-membered ring via cyclopropane rupture. As anticipated, the stereochemically homogeneous cyclopropane substituted ketone 36 was produced in good yield when use was made of stannic chloride in dichloromethane solution at -78°C. Of course, 104b led comparably to 36 while 103b furnished
Scheme XVIII

97, 98

99a, R1=H, R2=CH3
b, R1=CH3, R2=H

100a, R1=H, R2=CH3
b, R1=CH3, R2=H
the epimeric enone 105. To increase the throughput of 36, we ultimately took advantage of the ease of its chromatographic separation from 105 and effected no intermediate purification during the several steps that intervene between 90 and these enones.

**Scheme XIX**
To improve the yield of the cyclization step, the corresponding acids (101b, 103b, 104b) were treated with a variety of Lewis acids and temperatures to produce 36 and 105. The results of a series of cyclizations are summarized in Table 3.

Table 3. Cyclization of 101b, 103b and 104b in Dichloromethane Solutiona.

<table>
<thead>
<tr>
<th>acid distribution</th>
<th>Lewis acid</th>
<th>temp, °C</th>
<th>time, min</th>
<th>product distribution</th>
<th>yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>101b:103b:104b</td>
<td>36:105</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1:1:1b</td>
<td>SnCl₄</td>
<td>0°C</td>
<td>100</td>
<td>2:1</td>
<td>28</td>
</tr>
<tr>
<td>1:1:1</td>
<td>SnCl₄</td>
<td>-78°C</td>
<td>60</td>
<td>2:1</td>
<td>46</td>
</tr>
<tr>
<td>88:6:6c</td>
<td>SnCl₄</td>
<td>-78°C</td>
<td>40</td>
<td>96:4</td>
<td>53</td>
</tr>
<tr>
<td>88:6:6</td>
<td>TiCl₄</td>
<td>-78°C</td>
<td>40</td>
<td>e</td>
<td>32</td>
</tr>
</tbody>
</table>

a corresponding acid chloride was used without purification
b compounds from 90 with 1) NaBH₄·CeCl₃, 2) CH₃C(OEt)₃, CH₃CH₂CO₂H, 3) KOH
c compounds from 90 with 1) Dibal, 2) CH₃C(OEt)₃, CH₃CH₂CO₂H, 3) KOH
d 1.5 eq of Lewis acid was employed
e Ratio was not determined

With a viable route to the structural framework of africanol secure, completion of the synthesis required proper installation of the angular hydroxyl and setting of methyl stereochemistry. A series of epoxidations involving enone 36 (30%, H₂O₂, OH⁻, methanol; t-BuOOH, OH⁻, methanol) returned only starting material.
The alternate means uncovered for effecting these transformations began with low temperature (-78°C) diisobutylaluminum hydride reduction of 36. A 95:5 mixture of allylic alcohols was obtained, the major constituent of which was assigned as 106 for reasons of steric approach control (Scheme XX). This conclusion was confirmed by eventual elaboration of the natural product (1).

Pure α-alcohol 106, after conversion to its trimethylsilyl ether, was submitted to peracid oxidation and desilylation with aqueous ammonium chloride in methanol to give the two diastereoisomers 108 and 109 in a ratio of 1:1.
Reaction of the \(\alpha\)-allylic alcohol with VO(acac)\(_2\), and \(t\)-BuOOH gave \(\alpha\)-epoxy alcohol 109 in 59% yield. Ultimately, the pure \(\alpha\) alcohol, after conversion to its tert-butyldimethylsilyl ether, was submitted to peracid oxidation and desilylation with tetra-\(n\)-butylammonium fluoride. Epoxide formation happened to be quite slow and its stereochemical outcome sensitive to solvent. For example, the customarily small change from chloroform to dichloromethane resulted here in a product distribution crossover at \(-20^\circ\text{C}\) from 60:40 in favor of 108 to 40:60. The \(\alpha\) surface of double bond is clearly not as encumbered as one might initially expect.

The results of a series of expoxidations are summarized in Table 4.

**Table 4. Expoxidation Results**

<table>
<thead>
<tr>
<th>solvent</th>
<th>reaction time</th>
<th>temp</th>
<th>(\beta)-epoxy(108) : (\alpha)-epoxy(109)</th>
<th>yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHCl(_3)</td>
<td>1 hour</td>
<td>25(^\circ\text{C})</td>
<td>5 : 5(^b)</td>
<td>c</td>
</tr>
<tr>
<td>CHCl(_3)</td>
<td>7 hours</td>
<td>0(^\circ\text{C})</td>
<td>6 : 4(^b)</td>
<td>c</td>
</tr>
<tr>
<td>CHCl(_3)</td>
<td>20 hours</td>
<td>-20(^\circ\text{C})</td>
<td>6 : 4(^b)</td>
<td>87</td>
</tr>
<tr>
<td>CH(_2)Cl(_2)</td>
<td>20 hours</td>
<td>-20(^\circ\text{C})</td>
<td>4 : 6(^b)</td>
<td>87</td>
</tr>
</tbody>
</table>

\(^a\) all reactions were carried out 1:1 eq MCPBA  
\(^b\) ratio were determined by high field \(^1\text{H}\) NMR  
\(^c\) yields were not determined
Scheme XX (continued)
Nevertheless, the availability of both 108 and 109 allowed us to proceed separately to both africanol and its stereoisomer 113. To achieve simultaneous removal of the hydroxyl group and cleavage of the oxirane ring, 108 was exposed to sulfene and the resulting mesylate was reduced with lithium in liquid ammonia. With access to 111 in this manner, subsequent hydrogenation proceeded with 100% stereoselectivity from the β face to give africanol (1). 300 MHz 1H NMR spectra of the synthetic sample and the natural product were superimposable.

When 109 was treated analogously, the isomeric saturated tricyclic alcohol 113 was obtained. The α orientation of a secondary methyl group was examined by NOE experiments at 500 MHz. With irradiation of the
hydroxy proton singlet, there was realized a 4% enhancement of the integral associated with the methyl doublet at δ 0.76 (figure 4).

An alternative, more abbreviated route from 106 to 111 deserves brief comment despite its inapplicability. As shown in Scheme XX, reaction of 106 with o-nitrophenyl selenocyanate in the presence of tri-n-butylphosphine\textsuperscript{79} occurred smoothly with inversion of configuration to yield the β-selenide 110. Although allylic selenoxides are known\textsuperscript{80} to undergo [2,3]sigmatropic shift, the oxidized form of 110 failed to undergo this reaction, presumably because of a kinetic preference for cyclopentadiene ring formation. In this conversion, we have subsequently come to realize that this contrathermodynamic isomerization of allylic alcohols has been applied successfully only to acyclic and six-membered cyclic systems\textsuperscript{81}. Perhaps our present experience with a cyclopentenyl derivative (i.e., eventual polymer formation) will prove equally problematic in other structurally related contexts.
EXPERIMENTAL

All melting points were taken with a Thomas-Hoover capillary melting point apparatus and are uncorrected. $^1H$ nuclear magnetic resonance spectra were recorded on Varian T-60, Varian Associates EM-390 (90 MHz), Bruker WP-200 (200 MHz), or Bruker WM-300 (300 MHz) spectrometers and are reported in parts per million on the $\delta$ scale. Data are reported as follows: chemical shift [multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, qu=quintet, m=multiplet), coupling constants (in hertz), integration]. For interpretations, if a multiplet has several different protons, the upfield proton is reported first. $^{13}C$ nuclear magnetic resonance spectra were recorded on a Bruker WM-300 (75 MHz) spectrometer and are reported in parts per million from internal tetramethylsilane. Most $^{13}C$ NMR spectra were recorded as broad-band or DEPT (Distortionless Enhancement by Polarization Transfer) spectra. Infrared spectra were recorded on a Perkin-Elmer Model 467 spectrophotometer.

Elemental analyses were performed by the Scandinavian Microanalytical Laboratory, Herlev, Denmark. All reactions were performed under nitrogen. Mass spectra were determined on a Kratos MS-30 spectrometer at an ionization potential of 70 eV.
Solvents and reagents were dried and purified prior to use when deemed necessary: acetic anhydride (distilled from P₂O₅); tetrahydrofuran and diethyl ether (distilled from sodium metal); dichloromethane and chloroform (passed through activity I alumina or distilled from CaH₂); benzene, dimethylformamide, toluene, and triethylamine (distilled from CaH₂); methanol (distilled from magnesium methoxide). All reaction temperatures refer to those of the reaction mixture unless indicated otherwise. Reactions requiring an inert atmosphere were run under a blanket of argon or nitrogen. Medium pressure liquid chromatography (MPLC) was performed over EM Laboratories Lobar columns using an FMI RPSY lab pump.

4,4-Dimethyl-2-cyclohexene-1-one.

A mixture of 136 mL (1.5 mol) of isobutyraldehyde and 81 mL (1 mol) of methyl vinyl ketone was treated at room temperature with 1.0 mL of concentrated H₂SO₄. The solution was warmed cautiously to 45-50°C and maintained at that temperature by means of occasional cooling with a cold water bath. The exothermic reaction subsided within 1 h. The solution was then refluxed under a Dean-Stark trap until water removal ceased (ca. 3h). Distillation of the mixture at 6 torr of pressure gave a forerun of isobutyraldehyde followed by the product. Distillation at higher temperature gave enone as a colorless liquid [86-89 g (70%), bp 53-57° (4 torr)]; IR (neat, cm⁻¹) 1683;
$^1$H NMR (60 MHz, CDCl$_3$) δ 6.7 (d, $J = 10$ Hz, 1 H), 5.8 (d, $J = 10$ Hz, 1 H), 3.6-1.7 (m, 4H), 1.14 (s, 6H).

4,4-Dimethylcyclohexanone (38).

4,4-Dimethylcyclohex-2-enone (31 g) was dissolved in 250 mL of glacial acetic acid and 1.24 g of 5% palladium on carbon was added. The mixture was shaken under 2-3 atm of hydrogen for 30 min, after which time the uptake of hydrogen ceased. The mixture was filtered twice through Celite and poured into a mixture of water (1 L) and ether (800 mL). The acetic acid was neutralized by slow addition of solid sodium bicarbonate. The aqueous layer was separated and washed twice with ether. The ether layers were combined and dried over sodium sulfate. Concentration gave 26.8 g of prism-like needles, mp. 36-38°C; IR (KBr, cm$^{-1}$) 1718; $^1$H NMR (60 MHz, CDCl$_3$) δ 2.57-1.45 (m, 8H), 1.03 (s, 6H).

1-[4,4-Dimethyl-1-cyclohexenyl]-oxytrimethylsilane.

To a stirred solution of triethylamine (48.48 g, 0.48 mol) in dry dimethylformamide (80 mL; both components were freshly distilled from calcium hydride) was added 26.08 g (0.24 mol) of chlorotrimethylsilane (distilled before use) and 25.2 g (0.20 mol) of
4,4-dimethylcyclohexanone (38). This mixture was heated at the reflux temperature for 6 h, cooled to room temperature, and diluted with 300 ml of pentane. The precipitated triethylamine hydrochloride was separated by filtration and washed well with pentane (3 x 100 mL). The combined filtrates were washed with ice-cold saturated sodium bicarbonate solution (3 x 300 mL) and brine (50 mL) prior to drying. Solvent evaporation left 34.12 g (86%) of the silyl enol ether that was used directly without further purification; $^1$H NMR (60 MHz, CDCl$_3$) $\delta$ 4.60 (m, 1 H), 2.12-1.18 (m, 6H), 0.89 (s, 6H), 0.13 (s, 9H).

2-Bromo-5,5-dimethyl-2-cyclohepten-1-one (39).

To 34.24 g (0.165 mol) of silyl enol ether was added 200 mL of pentane. The solution was cooled to -10°C in an ice-salt bath. Then, 21.03 g of potassium $t$-butoxide was added, and 44 g of bromoform was introduced dropwise over 1 hr. The mixture was allowed to warm to room temperature and stirred for a further 4 hr at room temperature. The reaction mixture was poured into water (1 L), shaken, and separated (emulsion could be dispersed by the addition of a small amount of CH$_2$Cl$_2$). The combined organic layers were dried over MgSO$_4$ and concentrated to give a dark brown oil (53.79 g), which was used directly without purification. The preceding product (53.99 g) was dissolved in 50 mL of benzene. The reaction mixture was heated at reflux under argon for 14 hr. The solution was allowed to cool and worked up in usual manner. Solvent was removed and the residue (40.38
9) was distilled (2 torr, bp 81-86°C) to give 21.83 g (61.3%) of product; IR (neat, cm⁻¹) 2960, 1770, 1600, 1142, 903, 859, 803; ¹H NMR (60 MHz, CDCl₃) δ 7.14 (t, J = 7.8 Hz, 1H), δ 2.68-2.46 (m, 2H), 2.18 (d, J = 7 Hz, 2H), 1.56-1.43 (m, 2H), 1.06 (s, 6H); MS m/z (M⁺) calcd 216.0150. obsd 216.0155.

Anal. Calcd for C₈H₁₅BrO: C, 49.79; H, 6.03. Found: C, 50.10; H, 6.10.

1-(2,5,5-Trimethyl-2-cycloheptenyl)-1,3-dioxolane (40).

In a 100 mL flask was placed 2.17 g (0.01 mol) of 39. To this was added 0.08 g of ethylene glycol and 50 mL of benzene. Then a small amount of p-TsOH·H₂O was added and heated at reflux overnight. The mixture was poured into aqueous NaHCO₃ solution and the organic layer was washed with aqueous NaHCO₃ solution. The reaction mixture was dried over magnesium sulfate and concentrated to give a yellow liquid (2.39 g). The product was directly used in the next reaction; IR (neat, cm⁻¹) 2960, 1690, 1640, 1470, 1368, 1252, 1216, 1069, 998, ¹H NMR (60 MHz, CDCl₃) δ 6.28 (t, J = 7.4 Hz, 1H), 4.20-3.87 (m, 4H), 2.10-1.40 (m, 6H), 0.97 (s, 6H) MS m/z (M⁺) calcd for 260.0412, obsd. 260.0415.

A 250 mL three-necked flask containing 9.15 g of CuI was flame-dried. Then 30 mL of dry THF was added via syringe and 44 mL of 1.8 M CH₃Li in ether was added dropwise to the reaction mixture at 0°C. The
reaction flask was cooled to -78°C and 2.39 g (9.15 mmol) of bromoketal was added in 5 mL of THF.

Then an extra 20 mL of THF was added to dissolve a precipitate that had formed. The mixture was stirred at -78°C for 12 hr and allowed to warm to room temperature overnight. The usual workup with ether extraction afforded a pale yellow liquid (1.1 g, 61%). The spectra were identical to those of 40 obtained from the other route.

2,5,5-Trimethyl-2-cyclohepten-1-one (42).

\[
\begin{align*}
\text{CH}_3 & \quad \text{CH}_3 \\
\text{CH}_3 & \quad \text{CH}_3
\end{align*}
\]

\(n\)-Butyllithium in hexane (201.3 mL of 1.55 M, 0.372 mol) was slowly added under nitrogen during 6 h to a cold (-40°C) magnetically stirred solution of the preceding product (27.2 g, 0.130 mol) and 1,1-dichloroethane (41.2 g, 0.416 mol) in anhydrous ether (50 mL). The mixture was allowed to warm to 0°C over 1 h, at which point it was diluted with ether (100 mL), washed with water (4 x 50 mL), dried, and concentrated. The residual oil (25.5 g) was dissolved in a mixture of toluene (500 mL) and ethylene glycol (45 mL) and heated at the reflux temperature under nitrogen for 24 h. The toluene was removed to leave 42 dissolved in ethylene glycol. Characterization of the enone was achieved by subjecting a small aliquot to chromatography on silica gel followed by preparative VPC (6 ft x 0.25 in 5% SE-30, 92°C); IR (neat, cm\(^{-1}\)) 1669; \(^1H\) NMR (300 MHz, CDCl\(_3\)) \(\delta\) 6.44-6.38 (m, 1H), 2.44-2.40 (m, 2H), 2.07 (dd, \(J = 7.5, 0.87\) Hz, 2H), 1.79 (dd, \(J = 1\), 2.44-2.40 (m, 2H), 2.07 (dd, \(J = 7.5, 0.87\) Hz, 2H), 1.79 (dd, \(J = 1\))
2.1, 0.87 Hz, 3H), 1.49-1.45 (m, 2H), 0.95 (s, 6H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) ppm 205.61, 139.15, 138.95, 39.66, 39.57, 34.48, 33.23, 29.61 (2C), 18.69; MS m/z (M\(^{+}\)) calcd 152.1201, obsd 152.1205.

Anal. Calcd for C\(_{10}\)H\(_{16}\): C, 78.89; H, 10.60. Found: C, 78.51; H, 10.96.

Ketalization of 42. 1-(2,5,5-Trimethyl-2-cycloheptenyl]-1,3-dioxolane. (40).

The bulk of material (crude product in ethylene glycol) was taken up in benzene (500 mL), treated with p-toluenesulfonic acid (550 mg), and heated at reflux for 48 h with azeotropic removal of water (Dean-Stark trap). The cooled mixture was washed with saturated sodium bicarbonate solution (50 mL) and water (2 x 50 mL) before drying. Solvent evaporation was followed by vacuum distillation to afford 21.0 g (82.5%, overall from silylenol ether to the ketal), bp 63-66°C/1.3 torr; IR (neat, cm\(^{-1}\)) 3080, 1260, 1070, 1050; \(^{1}\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 5.55 (dt, \(J = 7, 1.3\) Hz, 1H), 3.95 (s, 4H), 1.98 (d, \(J = 7.1\) Hz, 2H), 1.80-1.76 (m, 2H), 1.71 (s, 3H), 1.51-1.47 (m, 2H), 0.89 (s, 6H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) ppm 139.62, 126.26, 111.11, 64.69 (2C), 38.99, 36.52, 32.56, 32.01, 29.40 (2C), 20.05; MS m/z (M\(^{+}\)) calcd 196.1463, obsd 196.1467.
Ethyl Zinc Iodide Complex.

Into a 500 mL flask equipped with a magnetic stirrer, a N₂ line, and reflux condenser was placed 34 g (0.5 mol) of acid-washed zinc and 5.0 g (0.05 mol) of CuCl. The flask was flame-dried under nitrogen. After cooling, 400 mL of dry ether was added through a septum. The mixture was heated at reflux under nitrogen for 3 h, 78 g (0.5 mol) of ethyl iodide was added and the mixture was stirred in the dark overnight at room temperature. The salts were allowed to settle (usually 1 day) and the supernatant liquid was transferred by syringe to a brown glass bottle for storage.

2-(cis-1,5,5-Trimethylbicyclo[5.1.0]octanyl)-1.3-dioxolane.

A solution of ethylzinc iodide in ether (12 mL of 1 M, 0.012 mol) was introduced via syringe into a flame-dried 250 mL three-necked flask. Following the addition of diiodomethane (0.76 g, 2.8 mmol), the reaction mixture was magnetically stirred under nitrogen at room temperature for 1.5 h. The above ketal (50 mg, 2.25 mmol) was next introduced and heating at the reflux temperature was maintained for 25 h. The solution was carefully poured into 1 M hydrochloric acid (20 mL) and the layers were separated. The aqueous phase was extracted with ether (2 x 25 mL) and the combined organic layers were washed with sodium thiosulfate solution (1 M; 2 x 25 mL) and water (25 mL). Drying the solvent evaporation left 493 mg (92%) of the cyclo-
propanated ketal as a colorless oil which was directly hydrolyzed; IR (neat, cm\(^{-1}\)) 2950, 1455, 1360; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta 3.93-3.82\) (m, 4H), 2.25 (dt, \(J = 4.7, 2.7\) Hz, 1H), 1.71 (ddd, \(J = 14, 6.1, 1.5\) Hz, 1H), 1.57-1.46 (m, 2H), 1.28-1.18 (m, 2H), 1.11 (s, 3H), 0.97 (s, 3H), 0.87 (s, 3H), 0.62-0.45 (m, 2H), 0.41 (dd, \(J = 8.4, 3.4\) Hz, 1H); MS m/z (M\(^+\)) calcd 210.1620, obsd 210.1624.

**cis-1,5,5-Trimethylbicyclo[5.1.0]octan-2-one (43).**

The ketal (215 mg, 1.0 mmol) was dissolved in acetone (10 mL) containing 2 drops of 1 N sulfuric acid and stirred at room temperature for 8 h. The reaction mixture was poured into saturated sodium bicarbonate solution (50 mL) and extracted with dichloromethane (3 x 25 mL). The combined organic layers were washed with water (50 mL), dried, and concentrated to give 170 mg (100%) of 43 as a colorless oil; IR (neat, cm\(^{-1}\)) 1705; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta 2.74-2.65\) (m, 1H), 2.23 (ddd, \(J = 15, 10, 3.5\) Hz, 1H), 1.89 (dd, \(J = 15, 4.9\) Hz, 1H), 1.83 (ddd, \(J = 13.9, 10.2, 3.8\) Hz, 1H), 1.33-1.29 (m, 1H), 1.29 (s, 3H), 1.00 (s, 3H), 0.89-0.83 (m, 1H), 0.86 (s, 3H), 0.74-0.55 (m, 3H); \(^13\)C NMR (75 MHz, CDCl\(_3\)) ppm 212.44, 42.97, 37.66, 37.21, 33.13, 31.76, 30.59, 26.60, 20.65, 19.76, 19.03; MS m/z (M\(^+\)) calcd 16.1358, obsd 166.1361.

(αR*, 1R*, 7S*)-3-(Hydroxymethyl)-α,1,5,5-tetramethylbicyclo[5.1.0]octan-2-one (44).

Cold (0°C), dry tetrahydrofuran (1 L) was treated sequentially with n-butyllithium (112.7 mL of 1.55 M, 0.17 mol) and isopropyl cyclohexylamine (28.6 mL, 0.17 mol) under a nitrogen atmosphere. After 15 min, the solution was cooled to -78°C and 23.32 g (0.14 mol) of 43 dissolved in anhydrous ether (50 mL) was introduced by syringe. The enolate was allowed to form during 1.5 h, whereupon acetaldehyde (13.4 mL, ca 2 equiv, dried over K$_2$CO$_3$ at -78°C for 15 min) was added dropwise from a syringe. The reaction mixture was stirred for 30 min and immediately neutralized with 1 equiv of acetic acid in ether (50 mL). The mixture was poured into saturated ammonium chloride solution and the organic phase was separated. The aqueous layer was extracted with ether (500 mL) and the combined organic solutions were washed with saturated sodium bicarbonate solution and brine, dried, and evaporated. There was obtained 22.50 g (76.5%) of aldol product as a colorless oil that was immediately acetylated; IR (CCl$_4$, cm$^{-1}$) 3500, 3080, 1674; $^1$H NMR (300 MHz, CDCl$_3$) δ 3.84 (dt, $\delta = 6.1, 6.0$ Hz, 1H), 3.34 (br, 1H), 2.16 (ddd, $\delta = 12, 9.8, 6.0$ Hz, 1H), 1.97 (dd, $\delta = 14, 7.5$ Hz, 1H), 1.46 (dd, $\delta = 13.4, 12.4$ Hz, 1H), 1.30-1.02 (m, 5H), 1.19 (s, 3H), 1.15 (d, $\delta = 6.3$ Hz, 3H), 0.92 (s, 3H), 0.87 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) ppm 215.40, 69.25, 50.92, 40.34, 39.60, 33.50, 33.40, 32.0, 28.1, 24.1, 23.51, 21.0, 18.9; MS m/z (M$^+$) calcd 210.1620, obsd 210.1615.
(\textit{aR^*,1R^*, 7S^*})-3-(Acetoxymethyl)-\textit{a}-1,5,5-tetramethylbicyclo[5.1.0]-octan-2-one.

A solution of the aldol (21.50 g, 0.102 mol), acetic anhydride (19.8 mL, 2 equiv), triethylamine (30.34 mL, 1.3 equiv), and 4-dimethylaminopyridine (113 mg) in dichloromethane (500 mL) was heated at the reflux temperature for 6 h. The cooled reaction mixture was washed with saturated sodium bicarbonate solution and brine, dried, and evaporated to furnish the acetoxy ketone as a colorless liquid (24.8 g, 96.1%); IR (neat, \text{cm}^{-1}) 1740, 1695; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.24 (dt, $J$ = 6.1, 6.0 Hz, 1H), 2.43 (ddd, $J$ = 9.6, 6.1, 3.1 Hz, 1H), 1.99 (s, 3H), 1.92 (dd, $J$ = 15, 5.7 Hz, 1H), 1.64 (dd, $J$ = 12.9, 13.1 Hz, 1H), 1.33 (dd, $J$ = 13.8, 3.3 Hz, 1H), 1.24 (s, 3H), 1.20 (d, $J$ = 6.3 Hz, 3H), 1.06-0.79 (m, 3H), 0.98 (s, 3H), 0.89 (s, 3H); MS m/z (M$^+$-HOAc) calcd 192.1514, obsd 192.1533.

(\textit{1R^*,7S^*})-3-[\textit{(E)}-Ethylidene]-1,5,5-trimethylbicyclo[5.1.0]octan-2-one (45).

A solution of the acetoxy ketone (24.8 g, 98.4 mmol) and DBU (29.4 mL, 2 equiv) in 450 mL of benzene was heated to reflux for 6 h, cooled, washed with water, and dried. Evaporation gave 17.64 g (93.2%) of 45 as a colorless liquid; IR (neat, \text{cm}^{-1}) 1690, 1620, $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 6.91 (q, $J$ = 7.4 Hz, 3H), 2.41, 2.32 (ABq,
\( J = 13.8 \text{ Hz}, 2\text{H}), 1.82-1.75 (\text{m}, 1\text{H}), 1.79 (d, J = 7.4 \text{ Hz}, 3\text{H}), 1.27 (s, 3\text{H}), 1.13 (s, 3\text{H}), 0.97-0.87 (\text{m}, 1\text{H}), 0.81 (s, 3\text{H}), 0.67 (dd, J = 4.9, 6.8 \text{ Hz}, 1\text{H}), 0.43-0.34 (\text{m}, 2\text{H}); \) \(^{13}\text{C NMR (75 MHz, CDCl}_{3})\text{ ppm 202.66, 137.14, 136.59, 42.50, 37.92, 35.86, 28.69, 28.59, 27.22, 21.24, 19.40, 17.76, 14.47; MS m/z (M^+) calcd 192.1518, obsd 192.1514.}

Anal. Calcd for C\(^{13}\)H\(_{20}\)O: C, 81.20; H, 10.48. Found: C, 81.13; H, 10.50.

\((1R^*,2S^*,7S^*)-3-[(E)-Ethylidene]-1,5,5-trimethylbicyclo[5.1.0]octan-2-ol (46a).\)

A solution of 45 (585 mg, 3.04 mmol) and cerium trichloride (824 mg, 10% excess) in methanol (3 mL) was stirred for 15 min and sodium borohydride (0.23 g, 6.05 mmol) was added carefully in small portions. With protection from atmospheric moisture, the reaction mixture was stirred at room temperature for 2 h before being poured into 1 N sodium hydroxide solution (50 mL). After 15 min of stirring, the mixture was filtered through Celite and the filter cake washed with ether (50 mL). The layers in the filtrate were separated and the aqueous phase was extracted with ether (3 x 30 mL). The combined organic solutions were washed with water (50 mL), dried, and concentrated to give 581 mg (97%) of 46a as a clear oil. An analytical sample was obtained by preparative VPC (2 ft x 0.25 in 5% SE-30, 110°C); IR (neat, cm\(^{-1}\)) 3410; \(^{1}H\text{ NMR (300 MHz, CDCl}_{3})\text{ \(\delta 5.44 (q, J = 6.8 \text{ Hz}, 1\text{H}), 4.18 (s, 1\text{H}), 2.15 (dd, J = 13.2, 2.3 \text{ Hz}, 1\text{H}), 1.96 (d, J = 6.8 \text{ Hz}, 1\text{H}), 1.85 (d, J = 7.4 \text{ Hz}, 3\text{H}), 1.27 (s, 3\text{H}), 1.13 (s, 3\text{H}), 0.97-0.87 (\text{m}, 1\text{H}), 0.81 (s, 3\text{H}), 0.67 (dd, J = 4.9, 6.8 \text{ Hz}, 1\text{H}), 0.43-0.34 (\text{m}, 2\text{H}); \) \(^{13}\text{C NMR (75 MHz, CDCl}_{3})\text{ ppm 202.66, 137.14, 136.59, 42.50, 37.92, 35.86, 28.69, 28.59, 27.22, 21.24, 19.40, 17.76, 14.47; MS m/z (M^+) calcd 192.1518, obsd 192.1514.}

Anal. Calcd for C\(^{13}\)H\(_{20}\)O: C, 81.20; H, 10.48. Found: C, 81.13; H, 10.50.
= 13.2 Hz, 1H), 1.78-1.70 (m, 1H), 1.64 (dd, J = 6.1, 1.1 Hz, 3H), 1.38 (s, 1H), 1.31 (dd, J = 15, 10.4 Hz, 1H), 1.01 (s, 3H), 0.95 (s, 3H), 0.90 (s, 3H), 0.69 (t, J = 4.5 Hz, 1H), 0.60-0.50 (m, 1H), 0.46 (dd, J = 8.4, 3.8 Hz, 1H).


The p-nitrobenzoate 46b, prepared in the usual way, was obtained as pale yellow crystals, mp 125-126°C (from hexane). An X-ray analysis was carried out on this material.

Ethyl (BR*, IR*, 7S*)-B,1,5,5-tetramethylbicyclo[5.1.0]oct-2-ene-3-propionate.

A solution of 46a (37 mg, 0.19 mmol) and triethyl orthoacetate (310 mg, 1.91 mmol) in xylene (0.5 mL) containing a trace of propionic acid was heated at the reflux temperature under nitrogen for 3 h. The cooled reaction mixture was diluted with ether (10 mL) and washed successively with 10% hydrochloric acid (10 mL), saturated sodium bicarbonate solution (2 x 10 mL), and saturated brine (10 mL). Following drying and solvent evaporation, there was isolated 39 mg of pale yellow oil. Purification by MPLC on silica gel (elution with 5% ethyl acetate in petroleum ether) gave the ethyl ester as a colorless oil (35.5 mg, 72%); IR (neat, cm\(^{-1}\)) 3060, 1735; \(^1\)H NMR (200 MHz, CDCl\(_3\)) \(\delta\) 5.33 (s, 1H), 4.09 (q, J = 7 Hz, 2H), 2.50-2.35 (m, 3H), 2.08 (dd, J = 15.7, 8.6 Hz, 1H), 1.8-1.5 (m, 3H), 1.23 (t, J = 7 Hz,
3H), 1.02 (d, J = 7 Hz, 3H), 0.99 (s, 3H), 0.98 (s, 3H), 0.80 (s, 3H), 0.67-0.61 (m, 1H), 0.38 (dd, J = 7.3, 3.9 Hz, 1H), 0.05 (t, J = 4 Hz, 1H); MS m/z (M⁺) 264.2089, obsd 264.2128.

Anal. Calcd for C₁₇H₂₈O₂: C, 77.22; H, 10.69. Found: C, 77.21; H, 10.60.

(βR*,1R*,7S*)-β,1,5,5-Tetramethylbicyclo[5.1.0]oct-2-ene-3-proionic Acid (54).

The ester (117 mg, 0.442 mmol) was added to 10 equiv of potassium hydroxide in methanol (30 mL) and this mixture was heated at the reflux temperature for 5 h. Following reaction with dichloromethane (30 mL), the separated aqueous layer was acidified with concentrated hydrochloric acid and extracted with dichloromethane (2 x 30 mL). The combined extracts were washed with brine, dried, and concentrated to furnish 89 mg (85%) of pure 54. Crystallization from ether gave colorless crystals, mp 44-45.5 C; IR (CCl₄, cm⁻¹) 3600-3000, 1710; ¹H NMR (300 MHz, CDCl₃) δ 5.39 (s, 1H), 2.54-2.45 (m, 3H), 2.15 (dd, J = 6.0, 5.7 Hz, 1H), 1.72 (dd, J = 12.6, 3.2 Hz, 1H), 1.56 (d, J = 13.3 Hz, 1H), 1.09 (d, J = 6.7 Hz, 3H), 1.03 (s, 3H), 1.02 (s, 3H), 0.84 (s, 3H), 0.78-0.62 (m, 2H), 0.42 (dd, J = 7.4, 3.8 Hz, 1H), 0.05 (t, J = 4.1 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) ppm 179.44, 142.01, 126.23, 43.71, 42.31, 41.56, 37.59, 30.93, 30.72, 29.83, 24.32, 20.10, 19.14, 18.53, 18.53; MS m/z (M⁺) calcd 236.1776, obsd 236.1858.
Friedel-Crafts Cyclization of 54. A. Aluminum Chloride Method.

Acid 54 (157 mg, 0.665 mmol) was dissolved in dry benzene (60 mL). The solution was cooled in ice and oxalyl chloride (0.68 mL) was added with swirling. The mixture was stirred at 0°C for 30 min and allowed to stand at room temperature for 1.5 h. Volatiles were removed at 40-45°C and 30 torr. Benzene (10 mL) was added and the solution was evaporated. Following repetition of this treatment, the acid chloride was taken up in carbon disulfide (3 mL) and 0.35 g of anhydrous aluminum chloride was introduced with rapid swirling. The flask was flushed with dry nitrogen, sealed, and shaken for 20 h. Hydrolysis was accomplished by slow addition of 1 mL of acetic acid and subsequent careful dilution with 10 mL of water. The product was taken up into pentane (3 x 25 mL) and the combined organic layers were washed with water and dried. The dark-colored solution was evaporated, diluted with ether, filtered through Celite, and again concentrated. Purification of the major component by preparative TLC on silica gel (elution with 10% ethyl acetate in petroleum ether) afforded 50 mg (34%) of 56 as a colorless liquid; IR (CCl₄, cm⁻¹) 1710, 1620; ¹H NMR (300 MHz, CDCl₃) δ 5.87 (dd, ̸J = 1.7, 1.2 Hz, 1H), 2.89 (d, ̸J = 12 Hz, 1H), 2.05 (s, 3H), 1.96-1.85 (m, 2H), 1.86, 1.06 (ABq, ̸J = 13.6 Hz, 2H), 1.10 (s, 3H), 1.12-0.99 (m, 1H), 0.95 (s, 6H), 0.83-0.77 (m, 1H), 0.52-0.45 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) ppm 208.2, 178.4, 131.0, 60.9, 46.4, 45.1,
44.1, 34.1, 33.6, 24.2, 23.7, 16.9; MS m/z (M⁺) calcd 218.1670, obsd 218.1664.

B. Stannic Chloride Method.

A 405 mg (1.716 mmol) sample of 54 was transformed into the acid chloride in the predescribed manner and dissolved in 120 mL of 1,2-dichloroethane. This solution was cooled to 0°C under nitrogen and stirred rapidly while 0.312 mL of stannic chloride was introduced. After 25 min, the reaction mixture was washed with saturated sodium bicarbonate solution, diluted with 50 mL of dichloromethane, and rapidly filtered through a short silica gel column before concentration. The resulting oil (360 mg, 96%) was found by VPC analysis (6 ft x 0.25 in. OV-11, 160°C) to consist of a mixture of 34, 55, and 56 in a ratio of 12:24:64. The three components were subsequently isolated preparatively.

For 34: colorless oil: IR (neat, cm⁻¹) 1705, 1640; ¹H NMR (300 MHz, CDCl₃) δ 2.69-2.54 (m, 3H), 2.09 (d, J = 13.6 Hz, 1H), 1.98 (dd, J = 16.8, 1.0 Hz, 1H), 1.83 (dd, J = 12, 3.8 Hz, 1H), 1.16 (d, J = 8.2 Hz, 3H), 1.14 (s, 3H), 1.13 (s, 3H), 0.86 (s, 3H), 0.83-0.73 (m, 2H), 0.54-0.49 (m, 1H), 0.27 (s, 1H); MS m/z (M⁺) calcd 218.1670, obsd 218.1664.
For 55: colorless oil: IR (neat, cm\(^{-1}\)) 1705, 1635; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 2.71-2.62 (m, 1H), 2.64 (dd, \(\text{J} = 18.1, 16\) Hz, 1H), 2.62-2.13 (ABq, \(\text{J} = 14.7\) Hz, 2H), 1.95 (dd, \(\text{J} = 18, 16\) Hz, 1H), 1.84 (dd, \(\text{J} = 13.5, 3.6\)Hz, 1H), 1.17 (s, 3H), 1.15 (d, \(\text{J} = 7.0\) Hz, 3H), 1.13 (s, 3H), 0.94 (s, 3H), 0.87-0.28 (m, 3H); MS m/z (M\(^+\)) calcd 218.1670, obsd 218.1676.

Ketone 56 exhibited spectral data identical to the material isolated in Part A.

Anal. (for 34, 55, 56): Calcd for C\(_{15}\)H\(_{22}\)O: C, 82.51; H, 10.16. Found: C, 82.15; H, 10.51.

**Rhodium Trichloride-Promoted Isomerization of 34, 55, 56.** A 360 mg sample of the enone mixture and 16.7 mg of rhodium trichloride trihydrate in absolute ethanol (3 mL) was placed in a sealed tube and heated at 100°C for 24 h. The solvent was evaporated and the residue was partitioned between dichloromethane (300 mL) and the water (20 mL). The organic layer was dried and concentrated and the residual oil was purified by MPLC on silica gel (elution with 15% ethyl acetate in petroleum ether). The colorless oil (210 mg, 58%) was determined by VPC analysis to consist of 34 (68%), 55 (29%), and 56 (3%).
(1R*,4R*,5R*,7αS*,7βS*)-Decahydro-3,3,5,7b-tetramethyl-7H-cycloprop[e]azulen-7-one (57).

A solution of 56 (16.6 mg) in ethyl acetate (2 mL) containing 3.8 mg of platinum oxide was hydrogenated at 40 psi in a Parr apparatus for 24 h. The catalyst was separated by filtration and the filtrate was concentrated to give 15 mg of 57; IR (neat, cm⁻¹) 3090, 1750; ¹H NMR (300 MHz, CDCl₃) δ 2.47-1.60 (series of m, 9H), 1.12 (d, J = 6.3 Hz, 3H), 1.04 (s, 3H), 0.93 (s, 3H), 0.91 (s, 3H), 0.85-0.41 (m, 3H); ¹³C NMR (75 MHz, CDCl₃) ppm 190.45, 62.17, 49.36, 48.32, 44.42, 43.90, 35.97, 33.69, 29.66, 24.20, 23.55, 20.10, 19.91, 19.00, 18.09; MS m/z (M⁺) calcd 220.1827, obsd 220.1823.

(γR*,1R*,7S*)-γ-1,5,5-Tetramethylbicyclo[5.1.0]oct-2-ene-3-propanol (58).

A mixture of 54 (25 mg) and lithium aluminum hydride (12 mg) in dry ether (5 mL) was stirred for 10 h. The mixture was cooled in ice and excess hydride was carefully decomposed with ethanol (1 mL) and water (2 mL). The product was extracted into ether (3 x 25 mL) and the combined solutions were dried and evaporated to give 20.7 mg (88%) of 58 as a colorless oil; IR (neat, cm⁻¹) 3500-3300, 3040, 3000-2880; ¹H NMR (300 MHz, CDCl₃) δ 5.31 (s, 1H), 3.61 (octet, J = 6.9 Hz, 2H), 2.46 (d, J = 13 Hz, 1H), 2.12 (sextet, J = 6.8 Hz, 1H),
1.71-1.51 (m, 4H), 1.47 (br s, 1H), 1.01 (s, 3H), 1.00 (d, \( J = 7 \) Hz, 3H), 0.99 (s, 3H), 0.79 (s, 3H), 0.72-0.41 (m, 2H), 0.39 (dd, \( J = 5.6 \), 3.8 Hz, 1H), 0.02 (t, \( J =3.7 \) Hz, 1H); MS m/z (M+) calcd 222.1984, obsd 222.1988.

\((\beta R^*, 1R^*, 7S^*)-\beta, 1, 5, 5\text{-Tetramethylbicyclo[5.1.0]oct-2-ene-3-propionaldehyde (59)}\).

Chromium trioxide (150 mg) was slowly added to 1.5 mL of pyridine at such a rate that the temperature was kept below 30°C. The resulting yellow solid was washed with hexane (3.2 mL) and quickly dissolved in dichloromethane (3 mL). Alcohol 58 (50 mg) was slowly introduced with stirring and after 10 min the supernatant was decanted from the gummy black deposit. The solution was washed with water and 1 N hydrochloric acid prior to drying. The solvent was evaporated and the residual oil was purified by preparative TLC on silica gel. There was isolated 30.2 mg (61%) of 59 as a colorless oil: IR (neat, cm\(^{-1}\)) 3055, 2700, 1725, 1453; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 9.67 (m, 1H), 5.34 (s, 1H), 2.52-2.42 (m, 2H), 2.45, 1.49 (ABq, \( J = 13 \) Hz, 2H), 2.27-2.18 (m, 1H), 1.68 (dd, \( J = 13, 3.7 \) Hz, 1H), 1.49 (d, \( J =.13 \) Hz, 1H), 1.01 (d, \( J = 7 \) Hz, 3H), 0.98 (s, 3H), 0.97 (s, 3H), 0.79 (s, 3H), 0.71-0.55 (m, 2H), 0.38 (dd, \( J = 7.6, 3.9 \) Hz, 1H), 0.00 (t, \( J = 3.9 \) Hz, 1H); MS m/z (M+) calcd 220.1857, obsd 220.1814.
(1aR*,4aR*,5R*,7S*,7aS*,7bS*)-4a,7a-Epoxydecahydro-3,3,5,7b-tetramethyl-1H-cycloprop[e]azulen-7-ol (62) and Isomers.

A cold (0°C), magnetically stirred solution of enones 34,55,56 (from RhCl₃, 85 mg, 0.390 mmol) in anhydrous ether (10 mL) was treated with diisobutylaluminum hydride (0.8 mL of 1 M in hexane) and stirred at 0°C for 5 h. The reaction mixture was allowed to warm to room temperature, washed with saturated ammonium chloride solution, dried, and concentrated. The resulting alcohols (85 mg, 100%) were dissolved in dry benzene (10mL), cooled to 5°C, and treated with m-chloroperbenzoic acid (75.2 mg, 10% excess). After 4 h of stirring at 0°C, the mixture was set aside overnight at room temperature. Solid calcium hydroxide was added and the mixture was stirred for 10 min. Filtration and evaporation of the solvent gave a mixture which was separated by MPLC on silica gel (elution with 5% ethyl acetate in petroleum ether). Three stereoisomers (72%) were separated in ratio of 72:25:3. The major constituent was isolated as a colorless crystalline solid, mp 88-91°C, and identified as 62 by X-ray crystallography; IR (KBr, cm⁻¹) 3500-3300, 3062, 2950, 1455, 1390, 1200, 1050, 910; ¹H NMR (300 MHz, CDCl₃) δ 4.06 (t, J = 5.7 Hz, 1H), 2.03-1.21 (series of m, 4H), 1.89, 1.47 (ABq, J = 14.3 Hz, 2H), 1.18 (s, 3H), 1.00 (d, J = 6.5 Hz, 3H), 0.98 (s, 3H), 0.92 (s, 3H), 0.95-0.53 (series of m, 4H), 0.41 (t, J = 3.4 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) ppm 75.08, 71.36, 70.76, 43.59,
40.20, 37.41, 35.28, 31.89, 30.96, 29.37, 22.92, 20.46, 18.99, 17.18, 13.46; MS m/z (M⁺) calcd 236.1759, obsd 236.1761.

For 62a (25%): m.p. 84-86.5°C; IR (CCl₄, cm⁻¹) 3400, 3070, 2960, 1463, 1375, 1055, 858; ¹H NMR (300 MHz, CDCl₃) δ 4.30 (t, J = 5.7 Hz, 1H), 2.05-1.52 (series of m, 8H), 1.21 (s, 3H), 0.98 (s, 3H), 0.94 (d, J = 6.7 Hz, 3H), 0.87 (s, 3H), 0.88-0.59 (m, 3H); ¹³C NMR (75 MHz, CDCl₃) 77.30, 74.45, 72.88, 40.26, 38.82, 37.27, 36.46, 38.81, 32.71, 29.06, 23.11, 20.66, 19.22, 14.26, 13.40; MS m/z (M⁺) calcd 236.1759, obsd 236.1761.

For 62b (3%): IR (neat, cm⁻¹) 3480, 3070, 2960, 1470, 1395, 1055, 925; ¹H NMR (300 MHz, CDCl₃) δ 4.32 (t, J = 5.8 Hz, 1H), 2.05-0.34 (series of m, 11H), 1.34 (s, 3H), 1.10 (s, 3H), 0.87 (d, J = 7.1 Hz, 3H), 0.86 (s, 3H); MS m/z (M⁺) calcd 236.1759, obsd 236.1790.

Dithioketalization of 34,55,56.

A mixture of the three enones (105 mg, 0.482 mmol, ratio 12:24:64), 1,2-ethane-dithiol (0.5 mL), p-toluenesulfonic acid monohydrate (10 mg), and benzene (10 mL) was heated at reflux under a Dean-Stark trap for 13 h. The cooled reaction mixture was diluted with ether, washed several times with 1 N sodium hydroxide solution, dried, and freed of solvent. The desired products were separated from unreacted starting material (31 mg) by MPLC on silica gel (elution with
petroleum ether). There was isolated 74 mg (75%) of an 83:17 mixture of 63 and 64 (capillary VPC analysis); IR (neat cm\(^{-1}\)) 3070, 2750, 1745, 1457, 1370, 1360, 1275; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 3.47-3.17 (m, 4H), 2.77-2.56 (m, 1H), 2.68, 1.75 (ABq, \(J = 12.7\) Hz, 2H), 2.25 (d, \(J = 13.1\) Hz, 1H), 2.08-1.97 (m, 1H), 1.69-1.62 (m, 1H), 1.26 (s, 3H), 1.02 (d, \(J = 6.8\) Hz, 3H), 1.01 (s, 3H), 0.77 (s, 3H), 0.68-0.46 (m, 4H); MS m/z (M\(^+\)) calcd 294.1476, obsd 294.1476.

Raney Nickel Desulfurization of 63 and 64.

An 83:17 mixture of 63 and 64 (87 mg, 0.296 mmol), W-2 Raney nickel (3 g), and absolute ethanol (0.5 mL) was stirred at 25°C for 10 min. The nickel was removed by filtration and rinsed with ethanol.

The combined filtrates were evaporated and the hydrocarbon mixture was separated by chromatography on silica gel impregnated with 2.2% silver nitrate. These conditions gave 40 mg (66%) of 27 and 65 (ratio, 83:17).

For 27: IR (neat, cm\(^{-1}\)) 3060, 2800, 2680, 1460, 1380-1370, 1200; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 2.48-1.99 (m, 5H), 1.76-1.56 (m, 2H), 1.37-1.22 (m, 2H), 1.06 (s, 3H), 1.03 (s, 3H), 0.96 (d, \(J = 6.8\) Hz, 3H), 0.78 (s, 3H), 0.76-0.59 (m, 1H), 0.42 (dd, \(J = 3.9, 2.8\) Hz, 1H), 0.019 (t, \(J = 4.1\) Hz, 1H), MS m/z (M\(^+\)-1) calcd 203.1800, obsd 203.1807.
(1aR*,4aR*,5S*,7aR*,7bR*)-4a,7a-Epoxydecahydro-3,3,5,7b-tetramethyl1H-cycloprop[e]azulene (28).

An unpurified mixture of hydrocarbons 27 and 65 (17 mg) dissolved in 0.5 mL of dry dichloromethane was treated with m-chloroperbenzoic acid (43.7 mg, 3 equiv) at room temperature. The reaction mixture was stirred for 10 min and washed with saturated sodium bicarbonate solution. The organic layer was dried and concentrated. The residual oil was separated into its two components by MPLC on silica gel (elution with 3% ethyl acetate in petroleum ether). There was isolated 8 mg (44%) of 28 and 1.7 mg (11%) of its epimer.

For 28: IR (neat, cm\(^{-1}\)) 2790, 1450, 1375, 1362, 1190, 918; \(^1\)H NMR (300 MHa, CDCl\(_3\)) \(\delta\) 2.06-1.92 (m, 1H), 1.89-1.79 (m, 1H), 1.83 (d, \(J = 15\) Hz, 1H), 1.58 (d, \(J = 15\) Hz, 1H), 1.57-1.40 (m, 1H), 1.25-1.19 (m, 1H), 1.12 (s, 3H), 1.00 (s, 3H), 0.97 (d, \(J = 6.7\) Hz, 3H), 0.98-0.85 (m, 3H), 0.92 (s, 3H), 0.70-0.56 (m, 2H), 0.26 (t, \(J = 4.2\) Hz, 1H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) ppm 71.69 (2C), 45.75, 41.06, 37.89, 31.85, 31.56, 29.39, 28.56, 28.15, 22.37, 21.09, 19.57, 18.90, 13.78; MS m/z (M\(^+\)) calcd 220.1827, obsd 220.1835.
Formation of Thiophenyl Compound (70).

To a stirred solution of tri-n-butylphosphine (0.45 mL, 1.82 mmol) in benzene (5 mL) at room temperature was added solid n-(phenylthio)succinimide (376.4 mg, 1.82 mmol) in one portion. After 5 min of stirring at room temperature, allylic alcohol mixture 68 (200 mg, 0.91 mmol) which was isolated from reaction with Dibal in 2 mL of benzene was added all at once. Stirring was continued at room temperature for 40 hr, the solvent was evaporated and the residue was treated with water (20 mL). The pentane was added and precolumned on silica gel (10% ethyl acetate in petroleum ether). The reaction mixture was subjected to MPLC on silica gel (3%, ethyl acetate in petroleum ether) to give 70 [57 mg (20%) as two stereoisomers] and starting material (76 mg, 38%).

For 70: IR (neat, cm⁻¹) 3020, 1580; ¹H NMR (300 MHz, CDCl₃) δ 7.39-7.14 (m, 5H), 4.49 (d, J = 1.5 Hz, 0.66H), 4.47 (d, J = 1.5 Hz, 0.3H), 2.27-0.53 (series of m, 13H), 1.29 (s, 1H), 1.12 (s, 2H), 1.05 (s, 2H), 0.84 (s, 1H), 0.83 (s, 3H); MS m/z (M⁺) calcd 312.1872, obsd 312.1867.
(1aR*,4aR*,5R*,7aR*,7bR*)-4a,7a-Epoxycylohepta-3,5,5,7b-tetramethyl-7H-"cycloprop[e]azulen-7-one (71).

A solution of 62 (190 mg, 0.804 mmol) in dichloromethane (5 mL) was added via syringe to a magnetically stirred suspension of pyridinium chlorochromate (0.35 g, 2 equiv) in the same solvent (10 mL). After 6 h, 20 mL of dry ether was added and the supernatant was decanted from the black gum. The insoluble residue was rinsed thoroughly with ether (3 x 10 mL) and the combined organic solutions were concentrated. The residue was purified by MPLC on silica gel (elution with 8% ethyl acetate in petroleum ether) to give 122.4 mg (65%) of 71 as a colorless oil; IR (neat, cm⁻¹) 3078, 2778, 1740, 1360, 1210, 1000, 865; ¹H NMR (300 MHz, CDCl₃) δ 2.21-1.80 (m, 4H), 2.12 (d, J = 14.7 Hz, 1H), 1.69 (d, J = 15 Hz, 1H), 1.12 (d, J = 6.4 Hz, 3H), 1.10 (s, 3H), 0.99 (s, 3H), 0.93 (s, 3H), 0.88-0.82 (m, 1H), 0.64-0.57 (m, 2H), 0.50-0.47 (m, 1H), ¹³C NMR (75 MHz, CDCl₃) ppm 209.85, 69.57, 65.33, 43.77, 40.89, 40.38, 32.97, 31.63, 29.71, 28.63, 21.85, 19.81, 19.24, 13.93, 13.68; MS m/z (M⁺) calcd 234.1620, obsd 234.1607.

Wharton rearrangement of 71. A mixture of 70 (65 mg, 0.278 mmol) and 0.26 ml of 99% hydrazine hydrate was heated for 5 min at 90°C while nitrogen was evolved. The two-phase mixture was then heated for an additional 15-min period at 120°C. Cooling, dilution with water, and extraction with ether provided a pale yellow oil, which was separated by MPLC to give only 77 (21 mg, 38%).
Tosylhydrazone Formation from 34,55,56.

Into a stirred solution of 34,55,56 (60 mg, 0.28 mmol) in 0.5 mL of dry methanol was added tosylhydrazine (51 mg). The resulting mixture was stirred at room temperature under an anhydrous atmosphere for 36 h and concentrated in vacuum at room temperature. The residue was purified by MPLC on silica gel (elution with 13% ethyl acetate in petroleum ether) to give 75 and 76 (88 mg, combined yield 83%, ratio 4:1).

For 75: \(^1\text{H NMR} (300\text{ MHz, CDCl}_3)\) \(\delta\) 8.71 (s, 1H), 7.89 (d, \(\text{J} = 8.2\) Hz, 2H), 7.28 (d, \(\text{J} = 8.0\) Hz, 2H), 2.62 (m, 2H), 2.28-1.69 (series of m, 4H), 2.41 (s, 3H), 1.08-1.02 (m, 9H), 0.83 (s, 3H), 0.68 (dd, \(\text{J} = 7.7, 4.2\) Hz, 1H), 0.57-0.14 (m, 3H).

For 76: \(^1\text{H NMR} (300\text{ MHz, CDCl}_3)\) \(\delta\) 8.54 (s, 1H), 7.83 (m, 2H), 7.27 (m, 2H), 5.86 (m, 1H), 2.78 (m, 1H), 2.40 (s, 3H), 2.07-0.52 (series of m, 8H), 1.81 (m, 3H), 1.02 (s, 3H), 0.93 (s, 3H), 0.66 (s, 3H).
cis-1a,2,3,4,6,7b-Hexahydro-3,3,5,7b-tetramethyl-1H-cycloprop[e]azulene (77).

A magnetically stirred solution of allylic alcohol 68 (250 mg, 1.14 mmol) in cold (-50°C) tetrahydrofuran (8 mL) was treated with triethylamine (0.4 mL, 2.5 equiv) and thionyl chloride (90 µL, 1.1 equiv). After 30 min, the reaction mixture was allowed to warm to -20°C and stirred for an additional 2 h at -20 to -10°C. Ether (20 mL) was added and the mixture was shaken with sodium bicarbonate solution and brine. Following drying and evaporation of the organic phase, the resulting oil was quickly subjected to flash chromatography on silica gel (elution with petroleum ether). There was obtained 140 mg (60%) of 77 as a sensitive colorless oil; IR (neat, cm⁻¹) 3078, 2960, 2935, 2920, 2875, 1650, 1590, 1480-1450, 1380, 1360; ¹H NMR (300 MHz, CDCl₃) δ 5.94 (s, 1H), 2.84 (t, J = 1.7 Hz, 2H), 2.25-0.07 (series of m, 7H), 1.92 (s, 3H), 1.18 (s, 3H), 1.10 (s, 3H), 0.74 (s, 3H); MS m/z (M+) calcd 202.1721, obsd 202.1725.

Hydrogenation of 77.

A solution of 77 (8 mg, 0.04 mmol) in ethyl acetate (1 mL) was shaken under 1.5 atmospheres of hydrogen at 0°C with platinum oxide (2 mg) for 3 days. The mixture was
filtered and the filtrate evaporated to give a mixture of 80 and 7 in a ratio of 73:19 in addition to a small amount of an unknown substance (VPC analysis). Hydrocarbon 7, also a natural product, exhibits characteristic methyl shifts at 1.86, 0.91, 0.86, and 0.86 and these signals were clearly observed for the minor hydroazulenoid component of this hydrogenation mixture.

\((1aR^*,7bS^*)\)-Decahydro-3,3,5,7b-tetramethyl-4aH-cycloprop[e]azulene-4a,5-diol 4a-m-Chlorobenzoate (81a) and Isomer 81b.

Buffer-washed m-chlorobenzoic acid (75.2 mg, 1.1 equiv) in dichloromethane (3 mL) was added dropwise to a cold (-40°C), magnetically stirred solution of 77 (80 mg, 0.40 mmol) in dichloromethane (7 mL) containing sodium bicarbonate (109.3 mg, 1.5 equiv). The reaction mixture was stirred at -40°C for 3 h, at -5 to -10°C for 2 days, and at 10°C for 12 h. Solid calcium hydroxide was added and the mixture was stirred for 10 min. Filtration and solvent evaporation gave a residue that was subjected to MPLC on silica gel (elution with 15% ethyl acetate in petroleum ether). One stereoisomer of 81a (sometimes, separated double bond isomer 81b in 10-20%) was isolated in pure condition (128 mg, 90%); IR (neat, cm\(^{-1}\)) 3450, 3065, 2930, 2880, 1720, 1575, 1460, 1426, 1365, 1350, 1285, 1250, 1120, 1085, 1070; \(^1H\) NMR (300 MHz, CDCl\(_3\)) \& 8.01-7.35 (m, 4H), 5.69 (m, 1H), 2.58 (dd, J = 14.7, 7.2 Hz, 1H), 2.45 (dd, J = 14.4, 1.8 Hz, 1H), 2.08-2.00 (m, 2H), 1.81-1.72 (m, 2H), 1.33 (s, 3H), 1.19 (s, 3H), 0.87 (s, 3H), 0.85-0.66
(m, 1H), 0.59-0.48 (m, 2H), 0.18 (t, J = 4.8 Hz, 1H); MS m/z (M+-H2O), calcd 356.1543, obsd 356.1568.

For 81b: IR (neat, cm⁻¹) 3500, 3080, 2960, 1730, 1583, 1290, 1260, 1030, 984; ¹H NMR (300 MHz, CDCl₃) δ 8.05-7.37 (m, 4H), 5.75 (m, 1H), 5.41 (m, 1H), 2.89 (dd, J = 13.0, 4.2 Hz, 1H), 2.38 (br, 1H), 1.90-1.82 (m, 1H), 1.62-1.56 (m, 2H), 1.32 (s, 3H), 1.24 (s, 3H), 1.05 (s, 3H), 0.90 (s, 3H), 0.88-0.53 (m, 4H); MS m/z (M+-H2O) calcd 356.1543, obsd 356.1541.

(1aR*,7bS*)-Decahydro-3,3,5,7b-tetramethyl-4aH-cycloprop[e]azulene-4a,5-diol 4a-Acetate (82a) and Isomer 82b.

To a cold (-40°C), magnetically stirred mixture of 77 (38 mg, 0.188 mmol), sodium bicarbonate (70 mg, 0.812 mmol), and dichloromethane (3 mL) was added 40% peracetic acid (43.2 μL, 0.18 mmol) dropwise. The reaction mixture was stirred at this temperature for 2 h and at 0°C for 24 h. Water and dichloromethane were added, and the separated organic layer was dried and concentrated. By means of MPLC on silica gel, it proved possible to separate three products in 85% combined yield. In order of elution, these products were the double bond isomer of 82b (11 mg), an unknown substance (11 mg), and 82a (21 mg).

For 82a: IR (neat, cm⁻¹) 3450-3300, 1730, 1240, 1040; ¹H NMR (300 MHz, CDCl₃) δ 5.43 (m, 1H), 2.47-2.36 (m, 2H), 2.06 (s, 3H), 1.99-1.64 (m, 4H), 1.27 (s, 3H), 1.14 (s, 3H), 1.10 (s, 3H), 0.84 (s, 3H), 0.86-
0.76 (m, 1H), 0.57-0.49 (m, 2H), 0.14-0.11 (m, 1H); MS m/z (M+−CH₃CO₂) calcd 219.1749, obsd 219.1758.

For 82b: IR (neat, cm⁻¹) 3450-3300, 3080, 2960, 1740, 1240, 1037; ¹H NMR (300 MHz, CDCl₃) δ 5.48 (m, 1H), 5.32 (m, 1H), 2.29-2.14 (m, 1H), 2.13 (s, 3H), 1.56-1.08 (m, 5H), 1.26 (s, 3H), 1.21 (s, 3H), 1.03 (s, 3H), 0.87 (s, 3H), 0.89-0.72 (m, 3H); MS m/z (M+−CH₃CO₂) calcd 219.1749, obsd 219.1708.

Singlet Oxygenation of 68.

A solution of 68 (220 mg, 1.0 mmol) in 5 mL of dry pyridine containing 2 mg of meso-tetraphenylporphine was irradiated with 450W Hanovia lamp through pyrex for 4 days as oxygen was continuously bubbled through. The reaction mixture was filtered through charcoal and evaporated under reduced pressure. The crude product was separated into its four components by MPLC on silica gel (elution with 9% ethyl acetate in petroleum ether).

For 85: 15 mg (7.7%); IR (neat, cm⁻¹) 3090, 3050, 2940, 2900, 1705, 1425, 1385, 1370, 1230-1175, 1050; ¹H NMR (300 MHz, CDCl₃) δ 2.72-1.57 (series of m, 6H), 1.24 (s, 3H), 1.14 (s, 3H), 0.95 (d, J =
7.1 Hz, 3H), 0.91 (s, 3H), 0.86 (m, 1H), 0.68 (m, 2H), 0.34 (t, \( J = 5.2 \) Hz, 1H); MS m/z (M⁺) calcd 236.1611, obsd 236.1610.

For 86: 24 mg (12%); IR (neat, cm⁻¹) 3400, 3090, 2850, 1780, 1690, 1635, 1385; \(^1\)H NMR (300 MHz, CDCl₃) δ 2.85-0.70 (series of m, 9H), 1.21 (s, 3H), 1.14 (s, 3H), 0.99 (d, \( J = 6.4 \) Hz, 3H), 0.89 (s, 3H), 0.86 (m, 1H), 0.51 (dd, \( J = 4.4, 2.4 \) Hz, 1H), 0.13 (t, \( J = 4.4 \) Hz, 1H); MS m/z (M⁺) calcd 236.1773, obsd 236.1803.

For 87: 32 mg (16%); IR (neat, cm⁻¹) 3500, 3090, 3050, 2850, 1755, 1653, 1480, 1390, 1372, 1310, 1220; \(^1\)H NMR (300 MHz, CDCl₃) δ 5.66 (d, \( J = 1.3 \) Hz, 1H), 2.2-0.8 (series of m, 6H), 1.96 (d, \( J = 1.3 \) Hz, 3H), 1.27 (s, 3H), 1.20 (s, 3H), 0.89 (s, 3H), 0.89-0.84 (m, 1H), 0.58 (dd, \( J = 4.4, 2.4 \) Hz, 1H), 0.20 (t, \( J = 4.5 \) Hz, 1H); \(^{13}\)C NMR (75 MHz, CDCl₃) ppm 174.50, 114.59, 114.30, 92.35, 51.91, 44.51, 42.65, 35.32, 34.50, 27.25, 26.18, 24.97, 21.72, 17.10, 13.32; MS m/z (M⁺) calcd 234.1620, obsd 234.1637.

For 34/55: 40 mg (22%); spectra as described earlier.

Also isolated was 35 mg of unreacted 68.

**Methyl (1R*,3S*,7S*)-1,5,5-Trimethyl-2-oxobicyclo[5.1.0]octane-3-carboxylate (88).**

Into a dry 250 mL three-necked flask was placed 3.88 g of 50% sodium hydride oil dispersion. While under nitrogen, the solid was washed three times with dry toluene and three times with anhydrous tetrahydrofuran (solvent removed by syringe). A solution
of dimethyl carbonate (6.46 mL) in dry tetrahydrofuran (10 mL) was added dropwise and the stirred mixture was heated to the reflux temperature. At this point, approximately 10% of a solution containing 4.50 g (27.1 mmol) of 43 in 10 mL of tetrahydrofuran was slowly added. Following introduction of a previously washed slurry of potassium hydride (0.23 g) in 4 mL of the same solvent, the reaction mixture was again heated to reflux and the remaining ketone solution was dripped in during 45 min. Heating was continued for 15 h. The flask was then cooled in ice while acetic acid (50 mL) and saturated brine (60 mL) were added, followed by ether (200 mL) and solid sodium bicarbonate (to completion of gas evolution). The layers were separated and the aqueous phase was extracted with ether (2 x 100 mL). The combined organic layers were washed with brine, dried and evaporated. Distillation of the residue afforded 5.16 g (85%) of 88 as a colorless oil; IR (neat, cm⁻¹) 3070, 1760, 1718, 1640, 1610, 1440; ¹H NMR (300 MHz, CDCl₃) δ 8.88 (s, 1H), 3.70 (s, 3H), 2.17 (ABq, J = 27, 8 Hz, 2H), 1.72 (dd, J = 14, 4.4 Hz, 1H), 1.22 (s, 3H), 0.97 (s, 3H), 0.79-0.75 (m, 1H), 0.72 (s, 3H), 0.65-0.49 (m, 2H), 0.44 (t, J = 4.8 Hz, 1H); MS m/z (M⁺) calcd 224.1413, obsd 224.1453.
Methyl(1R*,3S*,7S*)-1,5,5-Trimethyl-2-hydroxybicyclo[5.1.0]octane-3-carboxylate.

A solution of sodium borohydride (2.20 g) in ethanol (200 mL) was added dropwise during 1 h to a cold (0°C), magnetically stirred solution of 88 (4.5 g, 20.1 mmol) in the same solvent (100 mL). After 15 min, dilute acetic acid was introduced and solvent was removed under reduced pressure. The residue was dissolved in dichloromethane and this solution was washed with water, dried, and concentrated. There was obtained 4.27 g (94%) of the hydroxy ester which was directly acetylated; IR (neat, cm⁻¹) 3650, 3070, 1720; ¹H NMR (300 MHz, CDCl₃) δ 4.13 (s, 1H), 3.68 (s, 3H), 2.94 (d, J = 2.9 Hz, 1H), 2.90 (m, 1H), 1.86-1.62 (m, 2H), 1.39-1.27 (m, 2H), 1.06 (s, 3H), 1.02 (s, 3H), 0.89 (s, 3H), 0.89-0.84 (m, 1H), 0.65-0.54 (m, 1H), 0.38 (dd, J = 8.6, 3.9 Hz, 1H); MS m/z (M⁺) calcd 226.1569, obsd 226.1560.

Methyl (1R*,3S*,7S*)-1,5,5-Trimethyl-2-acetoxybicyclo[5.1.0]octane-3-carboxylate.

A solution consisting of β-hydroxy ester (1.27 g, 5.62 mmol), acetic anhydride (1.085 mL, 2 equiv), triethylamine (1.665 mL, 1.3 equiv), 4-dimethylaminopyridine (62 mg), and dichloromethane (100 mL) was heated to the reflux temperature for 2 days. After cooling,
5% sodium acetate solution was added and the separated organic phase was washed with saturated sodium bicarbonate solution and brine. Following drying and solvent evaporation, there was isolated 1.39 g (92%) of the acetoxy ester as a colorless liquid; IR (neat, cm$^{-1}$) 3075, 1755-1735; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.36 (s, 1H), 3.62 (s, 3H), 2.94 (dd, $\tilde{J}$ = 12.7, 2.8 Hz, 1H), 2.03 (s, 3H), 1.80-1.71 (m, 3H), 1.51-1.46 (m, 1H), 1.14 (s, 3H), 1.21-1.10 (m, 1H), 1.01 (s, 3H), 0.91 (s, 3H), 0.66-0.56 (m, 1H), 0.44 (dd, $\tilde{J}$ = 8.5, 4.5 Hz, 1H), 0.31 (t, $\tilde{J}$ = 4.8 Hz, 1H); MS m/z (M$^+$) calcd 268.1674, obsd 268.1677.

Methyl cis-1,5,5-Trimethylbicyclo[5.1.0]oct-2-ene-3-carboxylate (89).

A solution of the $\beta$-acetoxy ester (1.52 g, 5.67 mmol) and DBU (1.69 g) in dry benzene (10 mL) was heated at the reflux temperature for 3 days. The cooled mixture was washed with water, dried, and evaporated to give 1.05 g (89%) of 89 as a colorless liquid; IR (neat, cm$^{-1}$) 3070, 1715, 1625; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 6.83 (s, 1H), 3.69 (s, 3H), 2.34 (m, 2H), 1.74 (dd, $\tilde{J}$ = 14, 4.6 Hz, 2H), 1.10 (s, 3H), 1.02 (s, 3H), 0.80-0.75 (m, 1H), 0.75 (s, 3H), 0.56-0.52 (m, 2H), 0.15 (t, $\tilde{J}$ = 4.4 Hz, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) ppm 168.65, 144.31, 131.21, 51.62, 43.38, 37.12, 30.41, 29.97, 29.46, 23.00, 20.19, 19.75, 19.23; MS m/z (M$^+$) calcd 208.1464; obsd 208.1465.

Anal. Calcd for C$_{13}$H$_{20}$O$_2$: C, 74.96; H, 9.68. Found: C, 74.90; H, 9.75.
**cis-1,5,5-Trimethylbicyclo[5.1.0]oct-2-ene-3-carboxylic acid.**

A solution of 89 (1.04 g, 5 mmol) and potassium hydroxide (930 mg) in 95% ethanol (50 mL) was heated at the reflux temperature for 6 h, cooled, and evaporated. The solid was dissolved in water and extracted twice with ether. The aqueous phase was acidified with 10% hydrochloric acid and the precipitated acid was extracted with ether, dried, and evaporated. There was obtained 910 mg (94%) of colorless solid, mp 107-109°C; IR (CCl₄, cm⁻¹) 3200-2600, 1680, 1620; ¹H NMR (300 MHz, CDCl₃) δ 12.24 (s, 1H), 7.01 (s, 1H), 2.41-2.36 (m, 2H), 1.78 (dd,  J = 14, 4.5 Hz, 1H), 1.14 (s, 3H), 1.05 (s, 3H), 0.94-0.82 (m, 1H), 0.80 (s, 3H), 0.61-0.53 (m, 2H), 0.21 (t,  J = 4.4 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) ppm 173.70, 147.06, 130.83, 43.38, 36.74, 30.35, 30.03, 29.40, 22.88, 20.26, 19.94, 19.24; MS m/z (M⁺) calcd 194.1307, obsd 194.1316.

**Methyl cis-1,5,5-Trimethylbicyclo[5.1.0]oct-2-en-3-yl Ketone (90).**

A cold (-78°C), nitrogen-blanketed solution of the carboxylic acid (208 mg, 1.07 mmol) in anhydrous ether (10 mL) was treated slowly with methyllithium (1.49 mL of 1.55 M in ether, 2.34 mmol). After 15 min, the reaction mixture was warmed to 0°C, stirred for 3 h, and carefully treated with water. The ether phase was separated, washed with water, dried, and evaporated. The residue was purified by
MPLC on silica gel (elution with 6% ethyl acetate in petroleum ether) to give 146 mg (71%) of 90 as a colorless oil; IR (neat, cm\(^{-1}\)) 3075, 1665, 1620; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 6.74 (s, 1H), 2.54 (d, \(J = 12.9\) Hz, 1H), 2.28 (s, 3H), 2.11 (d, \(J = 12.4\) Hz, 1H), 1.74 (dd, \(J = 14.4, 4.6\) Hz, 1H), 1.14 (s, 3H), 1.03 (s, 3H), 0.90-0.83 (m, 1H), 0.68 (s, 3H), 0.62-0.57 (m, 1H), 0.53-0.48 (m, 1H), 0.20-0.19 (t, \(J = 4.4\) Hz, 1H); \(^1^3\)C NMR (75 MHz, CDCl\(_3\)) ppm 199.38, 144.95, 140.74, 43.51, 35.08 30.29, 29.97, 29.46, 25.37, 23.00, 20.45, 20.19, 19.36; MS m/z (M\(^+\)) calcd 192.1514, obsd 192.1514.


3-Trimethylsilyl-2-propyn-1-ol (92).

To a solution of propargyl alcohol (11.2 g, 200 mmol) in 400 ml of tetrahydrofuran at 0°C was added \(n\)-butyllithium (1.55 M in hexane, 258 mL, 400 mmol) dropwise over 1.5 h. The reaction mixture was treated dropwise over 1 h with chlorotrimethylsilane (43.4 g, 400 mmol), allowed to warm to 25°C over 0.5 h, and stirred 0.5 h further. The mixture was poured into 300 mL of 3M HCl and stirred at 25 °C for 0.5 h. The organic phase was separated and washed with water, satd NaHCO\(_3\) solution, and satd NaCl solution, dried over MgSO\(_4\), filtered, and distilled to give 21.8 g (85%) of 92 as a colorless oil (bp 92-95°C/24 torr) (lit\(^\text{71}\): bp 52-53°C (90 torr)); IR
(neat, cm$^{-1}$) 3350, 2170, 1410, 1245, 1030, 970; $^1$H NMR (300 MHz, CDCl$_3$) δ 4.34 (s, 2H), 3.08 (br, 1H), 0.24 (s, 9H).

1-Methyl-1-(trimethylsilyl)allene (93).

To a solution of 3-trimethylsilyl-2-propyn-1-ol (5 g) and Et$_3$N (5.92 g) in 20 mL of CH$_2$Cl$_2$ at -50°C was added dropwise over 0.5 h methanesulfonyl chloride (6 g). The resulting mixture was allowed to warm to 25°C over 1.5 h and stirred 0.5 h further at that temperature. The mixture was poured into 600 mL of water, the aqueous phase was separated and extracted with CH$_2$Cl$_2$, and finally the combined organic layers were washed with water and satd NaCl solution, dried over MgSO$_4$, filtered, and concentrated to afford 8 g of the mesylate as a pale yellow oil; IR (neat, cm$^{-1}$) 2180, 1410, 1250, 1130, 1020; $^1$H NMR (300 MHz, CDCl$_3$) δ 4.80 (s, 2H), 3.12 (s, 3H), 0.26 (s, 9H).

To a solution of LiBr (3.72 g, 43.3 mmol) and cuprous bromide (6.15 g, 43.3 mmol) in 50 mL of THF at -10°C was added dropwise over 1 h MeMgBr (43.3 mmol in 50 mL ether). The resulting suspension was stirred at -10°C for 1 h, cooled to -60°C, and treated dropwise over 20 min with a solution of the mesylate prepared before in 10 mL of THF. The mixture was stirred at -60°C for 0.5 h, allowed to warm to 25°C over 1 h, maintained at 25°C for 2 h, and then poured into 100 mL of satd NH$_4$Cl solution (adjusted to pH 8 by addition of NH$_4$OH). The resulting mixture was stirred at 25°C for 1 h, and the organic phase
satd NH₄Cl solution (adjusted to pH 8 by addition of NH₄OH). The resulting mixture was stirred at 25°C for 1 h, and the organic phase was separated and washed with satd pH 8 NH₄Cl solution until the extracts were no longer blue. The combined aqueous layers were back-extracted with CH₂Cl₂, and the combined organic layers were finally washed with water and satd NaCl solution, dried over MgSO₄, filtered, and concentrated by distillation of the solvent at 760 torr. Distillation then gave 2.1 g of 93 as a colorless oil, bp 51-52°C (88 torr). IR (neat, cm⁻¹) 2955, 2920, 2900, 1925, 1440, 1400, 1250; ¹H NMR (300 MHz, CDCl₃) δ 4.27 (q, J = 3 Hz, 2H), 1.71 (t, J = 3 Hz, 3H), 0.13 (s, 9H).

**Attempted (Trimethylsilyl)cyclopentene Annulation.**

To a solution of methylvinyl ketone 90 (180 mg, 0.93 mmol) and 1-methyl-1-(trimethylsilyl)allene 93 (234 mg, 2 equiv) in 2 mL of CH₂Cl₂ at -78°C was added dropwise TiCl₄ (20 µL) over 5 min. The resulting red solution was stirred at -78°C for 15 h and TiCl₄ (20 µL) was added again. The resulting mixture was allowed to increase to -50°C, and TiCl₄ (20 µL) was added. After 30 min, the reaction mixture was transferred over 1 min by cannula into a flask containing 50 mL of a rapidly stirred 1:1 mixture of ether and water. The ether layer was separated and reextracted with diethyl ether and water. The aqueous layer was separated and extracted with ether, and the combined organic layer was then washed with saturated NaCl aq, dried over magnesium sulfate, filtered, concentrated to afford a yellow oil. MPLC on silica
For less polar compound: m.p. 27-30°C; IR (neat, cm⁻¹) 3970, 1450, 1378, 1250, 985; ¹H NMR (300 MHz, CDCl₃) δ 2.29-1.58 (series of m, 8H), 1.74 (t, J = 2.5 Hz, 3H), 1.54 (s, 3H), 1.43-1.37 (m, 1H), 1.22 (s, 3H), 1.05 (s, 3H), 1.00 (s, 3H), 0.83-0.76 (m, 1H), 0.07 (s, 9H); MS m/z (M⁺-1) calcd 317.2301, obsd 317.2270.

For more polar compound: IR (neat, cm⁻¹) 2960, 1710, 1622, 1450, 1381, 1250, 833; ¹H NMR (300 MHz, CDCl₃) δ 2.45-1.41 (series of m, 6H), 1.70 (t, J = 2.2 Hz, 3H), 1.59 (m, 3H), 1.22 (s, 3H), 1.13 (s, 3H), 1.11 (s, 3H), 1.00 (d, J =7.3 Hz, 3H), 0.92 (s, 1H), 0.80 (s, 1H). 0.08 (s, 9H); MS m/z (M⁺) calcd 318.2379, obsd 318.2384.

Sodium Borohydride-Cerium Trichloride Reduction of 90.

A solution containing 90 (700 mg, 3.65 mmol) and cerium trichloride (0.99 g, 10% excess) in methanol (25 mL) was stirred for 15 min before 280 mg of sodium borohydride was carefully introduced in small portions. The reaction mixture was stirred for 2 h, poured into 1 N sodium hydroxide solution (50 mL), and again stirred (15 min). Solids were removed by suction filtration through Celite. The filter cake was washed with ether (60 mL), the filtrate was shaken in a separatory funnel, the layers were separated, and the aqueous phase was further extracted with ether (3 x 40 mL). The combined organic layers were washed with water (50 mL), dried, and concentrated. The residue (650 mg, 92%) was separated by MPLC on
silica gel (elution with 3% ethyl acetate in petroleum ether) into pure 95 and 96 (ratio 1:2).

For 95: colorless oil; IR (neat, cm\(^{-1}\)) 3350, 3060, 2958, 1455, 1360, 1094, 1060; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 5.60 (s, 1H), 4.14 (q, \(\text{J} = 6.4\) Hz, 1H), 1.53 (br, 1H), 1.74-1.69 (m, 1H), 2.40 and 1.58 (ABq, \(\text{J} = 3.5\) Hz, 2H), 1.23 (d, \(\text{J} = 6.4\) Hz, 3H), 1.05 (s, 3H), 1.02 (s, 3H), 0.82 (s, 3H), 0.78-0.61 (m, 2H), 0.44 (dd, \(\text{J} = 6.0, 3.8\) Hz, 1H), 0.06 (t, \(\text{J} = 3.9\) Hz, 1H); MS m/z (M\(^+\)) calcd 194.1670, obsd 194.1621.

For 96: colorless oil; IR (neat, cm\(^{-1}\)) 3350, 3080, 2990, 2952, 2862, 1465, 1455, 1363, 1090, 1080; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 5.53 (s, 1H), 4.14 (q, \(\text{J} = 6.2\) Hz, 1H), 1.73-1.69 (m, 1H), 2.37 and 1.82 (ABq, \(\text{J} = 3.5\) Hz, 2H), 1.25 (d, \(\text{J} = 6.5\) Hz, 3H), 1.03 (s, 6H), 0.83 (s, 3H), 0.94-0.61 (m, 2H), 0.43 (dd \(\text{J} = 6.0, 3.8\) Hz, 1H), 0.06 (t, \(\text{J} = 4\) Hz, 1H); \(^1\)H NMR (300 MHz, CDCl\(_3\)) ppm 141.82, 127.67, 71.81, 43.68, 38.22, 30.97, 30.69, 29.94, 24.14, 21.99, 19.98, 19.11, 18.80; MS m/z (M\(^+\)) calcd 194.1671, obsd 194.1653.

Diisobutylalumium Hydride Reduction of 90. A Dichloromethane Solution. A cold (-78°C), magnetically stirred solution of 90 (2.45 g, 12.8 mmol) in dry dichloromethane (125 mL) was treated dropwise with 33.5 mL of Dibal (1 M in hexane) during 1.5 h. The reaction mixture was stirred for 30 min, then quenched with water. The product was extracted into dichloromethane (3x) and the combined organic layers were dried and concentrated. MPLC separation of the allylic alcohols (ratio 88:12) as described above furnished the pure isomers 95 and 96 in a combined yield of 83% (2.05 g).
B. Ether Solution. Reduction of a cold (-78°C), magnetically stirred solution of 90 (47 mg, 0.245 mmol) in dry ether (3 mL) with 0.64 mL of Dibal (1 M in hexane) as described above furnished 36 mg (76%) of an identical 88:12 mixture of 95 and 96.

Ethyl (1R*,2R*,7S*)-3-[(Z)-Ethylidene]-1,5,5-trimethylbicyclo[5.1.0]-octane-2-acetate (101a).

A solution of 95 (35.8 mg, 0.185 mmol) and triethyl orthoacetate (0.36 mL) in xylene (1 mL) containing 1.8 μL of propionic acid was heated at the reflux temperature under nitrogen for 2h. During this time, the progress of reaction was carefully monitored by VPC and TLC. The cooled reaction mixture was diluted with ether (10 mL) and this solution was washed successively with 10% hydrochloric acid (5 mL), saturated sodium bicarbonate solution (2 x 5 mL), and brine (5 mL). Drying and solvent evaporation gave pure 101a (41 mg, 84%) as a colorless oil: IR (neat, cm⁻¹) 3062, 2960, 1764, 1460, 1380, 1374, 1287, 1160; ¹H NMR (300 MHz, CDCl₃) δ 5.21 (q, J = 6.5 Hz, 1H), 4.09 (q, J = 6.0 Hz, 2H), 2.48-2.43 (m, 3H), 2.13 (t, J = 8.1 Hz, 1H), 1.84-1.78 (m, 1H), 1.61 (d, J = 6.5 Hz, 3H), 1.52 and 1.26 (ABq, J_AB = 2.9 Hz, 2H), 1.22 (t, J = 7.1 Hz, 3H), 0.94 (s, 3H), 0.88 (s, 3H), 0.87 (s, 3H), 0.54 (dd, J = 8.2, 4.0 Hz, 1H), 0.45-0.41 (m, 1H), 0.23 (t, J = 4.3 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) ppm 173.13, 138.32, 117.36, 60.03, 47.46, 46.43, 43.46, 35.58, 35.46, 32.86, 32.86, 23.96, 22.81, 22.09, 20.79, 18.95, 14.26, 13.20; MS m/z (M⁺) calcd 264.2089, obsd 264.2057.
(1R*,2R*,7S*)-3-[(Z)-1,5,5-Trimethylbicyclo[5.1.0]octane-2-acetic Acid
(101b).

A solution of 101a (24 mg) and potassium hydroxide (16.4 mg) in 95% ethanol (0.9 mL) was heated at reflux for 2 h, cooled, and evaporated. Workup in the manner described above afforded 20 mg (94%) of 101b as a colorless solid, mp 114-115.5°C; IR (CCl4, cm⁻¹) 3200-2550, 1690, 1385; ¹H NMR (300 MHz, CDCl₃) δ 5.24 (q, J = 6.6 Hz, 1H), 2.69-2.44 (m, 3H), 2.16-2.11 (m, 1H), 1.83 (dq, J = 4.2, 2.1 Hz, 1H), 1.63 (d, J = 6.9 Hz, 3H), 1.53 (d, J = 13.3 Hz, 1H), 1.28-1.20 (m, 1H), 0.95 (s, 3H), 0.89 (s, 3H), 0.88 (s, 3H), 0.57 (dd, J = 6.1, 4.0 Hz, 1H), 0.49-0.41 (m, 1H), 0.26 (t, J = 4.5 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) ppm 179.02, 138.14, 117.50, 47.46, 46.20, 43.45, 35.49, 35.22, 32.84, 23.96, 22.83, 22.15, 20.89, 18.91, 13.24; MS m/z (M⁺) calcd 236.1776, obsd 236.1783.
Ortho-Ester Claisen Rearrangement of 96.

Ethyl (1R*, 2S*, 7S*)-3-[(Z)-Ethylidene]-1,5,5-trimethylbicyclo[5.1.0]- octane-2-acetate (103a) and Ethyl (1R*, 2R*, 7S*)-3-[(E)-Ethylidene]- 1,5,5-Trimethylbicyclo[5.1.0]octane-2-acetate (104a).

A solution of 96 (41 mg, 0.21 mmol) and triethyl orthoacetate (0.41 mL) in xylene (1.1 mL) containing propionic acid (2.1 µL) was heated at reflux under nitrogen for 3.2 h. Following the predescribed workup, there was isolated 40 mg (72.5%) of an inseparable 1:1 mixture of 103a and 104a; IR (neat, cm⁻¹) 3060, 2950, 1735, 1460, 1378, 1263, 1158, 1030; ¹H NMR (300 MHz, CDCl₃) δ 5.40 (103a, q, J = 6.7 Hz, 0.5 H), 5.19 (104a, q, J = 7.4 Hz, 0.5H), 4.16-4.07 (m, 2H), 2.91-2.70 (m, 2H), 2.37-2.21 (m, 2H), 1.87-1.77 (m, 2H), 1.71 (104a, d, J = 7.2Hz, 3/2H), 1.59 (103a, d, J = 6.8 Hz, 3/2H), 1.24 (t, J = 7 Hz, 3/2H), 1.22 (t, J = 7 Hz, 3/2H), 1.04 (s, 3/2H), 1.01 (s, 3/2H), 0.94 (s, 3/2H), 0.91 (s, 3/2H), 0.88 (s, 3/2H), 0.86 (s, 3/2H), 0.51-0.43 (m, 2H), 0.26 (s, 1/2H), 0.22 (s, 1/2H); MS m/z (M⁺) calcd 264.2089, obsd 264.2061.
(1R*,2S*,7S*)-3-[(Z)-Ethylidene]-1,5,5-trimethylbicyclo[5.1.0]octane-2-acetic Acid (103b) and (1R*,2R*,7S*)-3-[(Z)-Ethylidene]-1,5,5-trimethylbicyclo[5.1.0]octane-2-acetic Acid (104b).

Saponification of 29 mg of this mixture as before gave in 93% yield a 1:1 mixture of 103b and 104b; IR (CCl₄, cm⁻¹) 3500-3100, 3090, 1710; ¹H NMR (300 MHz, CDCl₃) δ (only distinctive signals listed) 5.42 (q, $\delta$ = 6.7 Hz, 1H), 5.22 (q, $\delta$ = 7.3 Hz, 1H), 1.73 (d, $\delta$ = 7.3 Hz, 3H), 1.59 (d, $\delta$ = 6.6 Hz, 3H), 1.06 (s, 3H), 1.03 (s, 3H), 0.95 (s, 3H), 0.92 (s, 3H), 0.89 (s, 3H), 0.87 (s, 3H), 0.45-0.56 (m, 4H), 0.29 (s, 1H), 0.27 (s, 1H); MS m/z (M⁺) calcd 236.1777, obsd 236.1800.

(1aR*,7aR*,7bS*)-1,1a,2,3,4,7,7a,7b-Octahydro-3,3,5,7b-tetramethyl-6H-cycloprop[e]azulen-6-one (36) and Stereoisomer 105.

A mixture of acids 101b, 103b, and 104b (ratio 88:6:6, 160 mg, 0.68 mmol) was dissolved in benzene (96 mL), cooled in ice, and treated dropwise with oxalyl chloride (0.68 mL). The reaction mixture was stirred for 1 h intervals at 5° and 20°C before solvent evaporation. The residue was redissolved in benzene (10 mL) and the concentration
process was repeated to give the acid chloride as a brownish oil that was used without further purification.

A cold (−78°C), magnetically stirred solution of the above material in dichloromethane (60 mL) was blanketed with nitrogen and treated dropwise with 0.04 mL (0.5 equiv) of stannic chloride. After 20 min, an additional 0.08 mL of SnCl₄ was introduced and stirring was continued for 20 min longer. Water was added and the organic phase was washed with saturated sodium bicarbonate solution and dried. This solution was treated with 10 mL of a 2:1 mixture of dichloromethane and triethylamine and stirred at room temperature for 8 h. Filtration, concentration of the filtrate and MPLC purification on silica gel (elution with 8% ethyl acetate in petroleum ether) afforded in a combined yield of 53% (78 mg) the tricyclic enones 36 and 105 (ratio 94:6).

For 36: IR (neat, cm⁻¹) 3060, 2960, 1760, 1698, 1640, 1370; H NMR (300 MHz, CDCl₃) δ 2.61 and 2.13 (ABq, J_AB = 3.4 Hz, 2H), 2.50-2.30 (m, 2H), 1.96 (dd, J = 14.7, 4.7 Hz, 1H), 1.7 (s, 3H), 1.35-1.03 (m, 2H), 1.01 (s, 3H), 0.98 (s, 3H), 0.78 (s, 3H), 0.69-0.61 (m, 2H), 0.32 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) ppm 209.43, 173.45, 136.19, 48.86, 46.61, 45.20, 42.32, 38.44, 34.97, 32.16, 27.52, 22.41, 21.91, 19.00, 18.66; MS m/z (M⁺) calcd 218.1671, obsd 218.1669.

Anal. Calcd for C₁₅H₂₂O: C, 82.51; H, 10.16. Found: C, 82.29; H, 10.07.

For 105: IR (neat, cm⁻¹) 3060, 2960, 1775, 1700, 1640, 1370; H NMR (300 MHz, CDCl₃) δ (only distinctive signals listed) 1.64 (d, J = 2.0 Hz, 3H), 1.18 (s, 3H), 1.17 (s, 3H), 0.94 (s, 3H), 0.38-0.34
(m, 1H), -0.01 (t, J = 4.6 Hz, 1H); MS m/z (M+) calcd 218.1671, obsd 218.1688.

Cyclization of 1:1:1 Mixture of the Carboxylic Acids 101b, 103b and 104b.

The acid (three compounds, 165 mg, 0.699 mmol) was dissolved in 5 mL of benzene. The solution was cooled in ice and oxalyl chloride (0.7 mL) was added during 5 min with stirring. The reaction mixture was stirred for 1 h at 5°C and allowed to stand at room temperature. After 1 h at room temperature, the solution was evaporated under reduced pressure. Benzene (10 mL) was added and the solution was evaporated under the reduced pressure to give oily brown acid chloride which was used directly. The crude acid chloride in 6 mL of dichloromethane under N₂ was cooled to -78°C and 0.02 mL of stannic chloride was added dropwise with stirring. After 20 min, 0.02 mL of stannic chloride was added dropwise with stirring. The reaction mixture was stirred at -78°C for 1 h. The reaction mixture was washed with NaHCO₃ solution and 20 mL of CH₂Cl₂ was poured into the separatory funnel. The organic layer was dried over MgSO₄, concentrated, and treated with CH₂Cl₂ containing triethylamine (10 mL). The mixture was stirred for 2 h at room temperature and separated by MPLC (elution with 8% ethyl acetate in petroleum ether) to give 36 and 105 (70 mg, 46%, ratio 2:1).
(1aR*,6R*,7aR,7bS*)-1a,2,3,4,6,7,7a,7b-Octahydro-3,3,5,7b-tetramethyl-1H-cycloprop[e]azulen-6-ol (106).

A cold (-78°C), magnetically stirred solution of 105 (235 mg, 1.08 mmol) in dry dichloromethane (17 mL) was treated dropwise with 2.82 mL of Dibal (1 M in hexane), stirred for 30 min, and treated with water. The product was extracted into dichloromethane (3x) and the combined organic layers were dried and evaporated. The residue was purified by MPLC on silica gel (elution with 10% ethyl acetate in petroleum ether) to give 202 mg (85%) of 106 containing 5% of 107 (NMR analysis); mp 83-85°C (from hexane); IR (CCl₄, cm⁻¹) 3700, 3058, 2750, 1462, 1380, 1035; ¹H NMR (300 MHz, CDCl₃) δ 4.55 (t, J = 5.9 Hz, 1H), 2.28 (dt, J = 12, 4.0 Hz, 1H), 2.20 -2.05 (m, 2H), 1.97 (d, J = 4.8 Hz, 1H), 1.79 (dd, J = 9, 4 Hz, 1H), 1.68 (d, J = 1 Hz, 3H), 1.52-1.43 (m, 2H), 1.25 (s, 1H), 1.00 (s, 3H), 0.88 (s, 3H), 0.80 (s, 3H), 0.67-0.57 (m, 1H), 0.51 (dd, J = 4, 6 Hz, 1H), 0.11 (t, J = 4 Hz, 1H); MS m/z (M⁺) calcd 220.1827, obsd 220.1823.
(1aR*,6S*,7aR*,7bS*)-1a,2,3,4,6,7,7a,7b-Octahydro-3,3,5,7b-tetramethyl-6-(phenylselenyl)-1H-cycloprop[e]azulene (110).

Tri-n-butylphosphine (43.8 μL, 1.6 equiv) was added via syringe to a solution of 106 (24 mg, 0.109 mmol) and o-nitrophenyl selenocyanate (37 mg, 1.5 equiv) in 0.6 mL of dry tetrahydrofuran over a 5 min period at 0°C. The reaction mixture was stirred at this temperature for 5.3 h, allowed to warm to room temperature, and diluted with ethyl acetate (5 mL). This solution was washed with 5% sodium bicarbonate solution and brine, dried, and concentrated. The residual oil was purified by MPLC on silica gel (elution with 2% ethyl acetate in petroleum ether) to give 24.3 mg (55%) of 110 as a yellow solid mp 106-107°C (hexane) IR (CCl₄, cm⁻¹) 3067, 2960, 1740, 1590, 1522, 1463, 1337, 1305, 730; ¹H NMR (300 MHz, CDCl₃) δ 8.28 (d, J = 8.2 Hz, 1H), 7.67 (d, J = 7.2 Hz, 1H), 7.51 (dt, J = 7.0, 6.8 Hz, 1H), 7.31 (d, J = 8.3 Hz, 1H), 4.42 (d, J = 4.6 Hz, 1H), 2.45-2.34 (m, 2H), 2.14-2.03 (m, 3H), 1.80 (s, 3H), 1.76-1.75 (m, 1H), 1.25 (br, 1H), 1.03 (s, 3H), 0.89 (s, 3H), 0.85 (s, 3H), 0.89-0.66 (m, 1H), 0.49 (dd, J = 4.7, 8.1 Hz, 1H), 0.12 (t, J = 3.2 Hz, 1H); MS m/z (M⁺-2-NO₂C₆H₄Se) calcd 203.1800, obsd 203.1634.
To a cold (0°C) mixture of 106 (122 mg, 0.55 mmol), tert-butyldimethylsilyl chloride (102 mg, 0.68 mmol), and imidazole (95 mg, 1.4 mmol) was added dry dimethylformamide (1.6 mL) dropwise. After being allowed to warm to room temperature, the mixture was stirred for 5 h and diluted with water and petroleum ether. The aqueous phase was extracted with petroleum ether (3x) and the combined organic layers were dried and concentrated. Purification of the residue by MPLC on silica gel (elution with 2% ethyl acetate in petroleum ether) afforded 163.5 mg (89%) of silylated ether; IR (neat, cm⁻¹) 3060, 2960, 2868, 1463, 1253, 1265, 1090, 890, 847, 777; ¹H NMR (300 MHz, CDCl₃) δ 4.59 (t, J = 6.3 Hz, 1H), 2.19-2.13 (m, 2H), 2.08-1.95 (m, 2H), 1.76 (dd, J = 4.9, 9.7 Hz, 1H), 1.62 (br, 3H), 1.55-1.46 (m, 2H), 1.01 (s, 3H), 0.93 (s, 9H), 0.89 (s, 3H), 0.78 (s, 3H), 0.69-0.57 (m, 1H), 0.49 (dd, J = 4.2, 8.1 Hz, 1H), 0.11 (s, 3H), 0.10 (s, 3H), 0.07-0.04 (m, 1H); MS m/z (M⁺) calcd 334.2692, obsd 334.2736.

The silyl product (176 mg, 0.527 mmol) dissolved in dry chloroform (2 mL) was treated with m-chloroperbenzoic acid (128 mg, 0.83 mmol) at -20°C. After the reaction mixture had been stirred for 20 h, solid calcium hydroxide was added and stirring was continued for 10 min. Filtration and solvent evaporation left a residue (159 mg), the ratio of stereoisomers in which was established by 300 MHz ¹H NMR spectroscopy.
For the more polar β-epoxy isomer: IR (neat, cm⁻¹) 3067, 2950, 1470, 1370, 1260, 1080, 845, 780; ¹H NMR (300 MHz, CDCl₃) δ 4.07 (d, J = 6.7 Hz, 1H), 2.25 and 1.10 (ABq, J = 4.8 Hz, 2H), 1.86 (dd, J = 14.9, 4.9 Hz, 1H), 2.07-1.14 (series of m, 4H), 1.31 (s, 3H), 1.02 (s, 3H), 1.01 (s, 3H), 0.98 (s, 3H), 0.90 (s, 3H), 0.82-0.60 (m, 1H), 0.47 (dd, J = 8.0, 4.4 Hz, 1H), 0.13 (t, J = 4.4 Hz, 1H), 0.09 (s, 3H), 0.08 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) ppm 75.79, 74.15, 69.40, 46.56, 42.34, 40.20, 34.87, 33.47, 31.71, 30.14, 25.82, 22.00, 21.52, 20.27, 18.32, 18.01, 12.75, -4.47, -5.04; MS m/z (M⁺) calcd 350.2641, obsd 350.2620.

For the less polar α-epoxy isomer: colorless solid, mp 106-108.5°C (from hexane): IR (CCl₄, cm⁻¹) 3070, 2958, 1474, 1370, 1255, 1113, 892, 843; ¹H NMR (300 MHz, CDCl₃) δ 3.93 (m, 1H), 1.99-0.86 (series of m, 7H), 1.24 (s, 3H), 1.15 (s, 3H), 1.13 (s, 3H), 0.92 (s, 12H), 0.84-0.66 (m, 1H), 0.55 (dd, J = 8.4, 4.3 Hz, 1H), 0.13 (t, J = 4.7 Hz, 1H), 0.08 (s, 3H), 0.07 (s, 3H); MS m/z (M⁺-C₄H₉) calcd 293.1936, obsd 293.1942.

The unpurified epoxy silyl ether mixture (159 mg) was dissolved in dry tetrahydrofuran (2 mL) and treated with tetra-n-butylammonium fluoride (1.36 mL of 1 M in THF, 3 equiv) at 0°C. The reaction mixture was allowed to warm to room temperature and stirred for 7 h. Water and ether were added, and the organic phase was dried and concentrated. The residue was purified by MPLC on silica gel (elution with 21% ethyl
acetate in petroleum ether) to give pure samples of 108 and 109 (ratio 60:40; combined yield 66.8%).

For 108 (50 mg); oil; IR (neat, cm⁻¹) 3464, 3063, 2980, 1470, 1390, 1230, 1055; ¹H NMR (300 MHz, CDCl₃) δ 4.13 (d, J = 7.1 Hz, 1H), 2.24 and 1.10 (Abq, J = 4.7 Hz, 2H), 2.16-1.84 (m, 3H), 1.69-1.54 (m, 2H), 1.38 (s, 3H), 1.24-1.14 (m, 1H), 1.02 (s, 6H), 1.00 (s, 3H), 0.72-0.62 (m, 1H), 0.50 (dd, J = 8.0, 4.5 Hz, 1H), 0.15 (t, J = 4.5 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) ppm 75.63, 73.95, 68.94, 46.46, 42.30, 40.12, 34.54, 33.54, 31.66, 30.14, 21.74, 21.56, 20.18, 17.99, 12.27; MS m/z (M⁺) calcd 236.1776, obsd 236.1783.

For 109 (33 mg); colorless solid, mp 127-129°C (from hexane); IR (CCl₄, cm⁻¹) 3460, 3060, 2960, 1470, 1452, 1385, 1265, 1053, 730, 710; ¹H NMR (300 MHz, CDCl₃) δ 3.92 (t, J = 6.2 Hz, 1H), 2.06-1.92 (m, 2H), 1.68-1.59 (m, 3H), 1.49-1.37 (m, 2H), 1.31 (s, 3H), 1.28-1.23 (m, 1H), 1.15 (s, 3H), 1.11 (s, 3H), 0.92 (s, 3H), 0.76-0.69 (m, 1H), 0.55 (dd, J = 4.1, 8.4 Hz, 1H), 0.14 (t, J = 4.8 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) ppm 75.65, 70.41, 65.98, 46.51, 45.32, 42.65, 33.34, 31.49, 25.05, 24.38, 23.18, 22.86, 17.46, 12.73; MS m/z (M⁺) calcd 236.1776, obsd 236.1762.
(1aR*,4aR*,5R*,6R*,7aR*,7bS*)-4a,5-Epoxydecahydro-3,3,5,7b-tetramethyl-1H-cycloprop[e]azulen-6-ol (109).

A mixture of 106 (11 mg, 0.05 mmol), tert-butylhydroperoxide (6.9 μL of 72% aqueous solution, 1.1 equiv), and VO(acac)₂ (1 mg) in benzene (0.25 mL) was stirred at room temperature under nitrogen for 17 h and heated at the reflux temperature for 2 h. The reaction mixture was diluted with benzene and successively washed with saturated sodium bicarbonate solution and brine. After drying and solvent removal, the crude product was purified by MPLC on silica gel (elution with 23% ethyl acetate in petroleum ether) to give 7 mg (59%) of pure 109. The spectra were identical to those of 109 obtained from the other route.

(1aR*,4R*,7aR*,7bR*)-1,1a,2,3,4,7,7a,7b-Octahydro-3,3,5,7b-tetramethyl-4aH-cycloprop[e]azulen-4a-ol (111).

Methanesulfonyl chloride (42 μL, 2 equiv) was added dropwise to a magnetically stirred solution of 108 (62 mg, 0.263 mmol) and triethylamine (73 μL, 2 equiv) in 3 mL of dichloromethane at -20°C. After 2 h, water and dichloromethane were added, and the separated organic phase was washed successively with saturated sodium bicarbonate solution, water, and brine. Drying and solvent evaporation
gave the epoxy mesylate as a white solid (93 mg) that was used directly in the next step.

A solution of this solid in dry tetrahydrofuran (1.5 mL) was added to liquid ammonia (30 mL) and 9.1 mg (5 equiv) of lithium wire was added in three pieces. When the reaction mixture turned colorless (ca 2 h), another 9.1 mg of lithium wire was introduced. After 3 h, solid ammonium chloride was carefully added followed by 20 mL of hexane. Stirring was continued for 2 h, water was added, and the layers were separated. The aqueous phase was extracted with ether and the combined ethereal solutions were washed with water and brine, dried, filtered, and concentrated. Purification by column chromatography (alumina activity III, elution with 3.8% ethyl acetate in petroleum ether) returned 41 mg of 108 and gave 12 mg of 111 (61% based on recovered starting material); IR (neat, cm⁻¹) 3600-3465, 3062, 2964, 1464, 1387, 1367, 1025, 990, 900, 820; ¹H NMR (300 MHz, C₆D₆) δ 5.21 (m, 1H), 2.38-2.29 (m, 1H), 2.16-2.11 (m, 1H), 1.87 (d, J = 7.4 Hz, 1H), 1.79-0.57 (series of m, 6H), 1.57 (m, 3H), 1.37 (s, 3H), 1.03 (s, 3H), 0.76 (s, 3H), 0.40 (dd, J = 3.9 Hz, 1H), 0.16 (t, J = 4.5 Hz, 1H); MS m/z (M⁺) calcd for 220.1827, obsd 220.1833.
Africanol (1).

Allylic alcohol (8 mg, 0.036 mmol) in ethyl acetate (1.5 mL) containing 6 mg of platinum oxide was shaken under 50 psi of hydrogen for 3 days. The mixture was filtered and filtrate evaporated. MPLC purification on silica gel (elution with 3.8% ethyl acetate in petroleum ether) gave 7 mg (88%) of 1 as a colorless solid, mp 46-47°C (lit\textsuperscript{15} m.p. 47-48°C); IR (CCl\textsubscript{4}, cm\textsuperscript{-1}) 3480, 3078, 2965, 1460, 1388, 1266, 1109, 1088, 1024, 993; \textsuperscript{1}H NMR (300 MHz, C\textsubscript{6}D\textsubscript{6}) δ 1.99-1.25 (series of m, 11H), 1.22 (s, 3H), 1.02 (s, 3H), 0.85 (s, 3H), 0.76 (d, J = 7.4 Hz, 3H), 0.73-0.60 (m, 1H), 0.45 (dd, J = 8.5, 3.9 Hz, 1H), 0.16 (t, J = 4.4 Hz, 1H); MS m/z (M\textsuperscript{+}-H\textsubscript{2}O) calcd 204.1878, obsd 204.1862.

\((1aR^*,4aS^*,7aR,7bS^*)-1,1a,2,3,4,7,7a,7b-Octahydro-3,3,5,7b-tetramethyl-4aH-cycloprop[e]azulen-4-ol\) (112).

Methanesulfonyl chloride (27 μL, 0.34 mmol) was added dropwise to a cold (-20°C), magnetically stirred solution of 109 (40 mg, 0.169 mmol) and triethylamine (47 μL, 0.34 mmol) in dichloromethane (2 mL). After 1.5 h, water and dichloromethane were added and the organic phase was washed successively with saturated sodium bicarbonate solution, water, and brine. After drying and concentration, the oily epoxy mesylate (58.8 mg) was used directly in the next step.
To 20 mL of liquid ammonia was added a solution of the above material in 1 mL of dry tetrahydrofuran, followed by 5.9 mg (5 equiv) of lithium wire in 3 pieces. When the reaction mixture turned colorless (ca 1 h), an additional 5.9 mg of lithium wire was introduced. After an additional hour, solid ammonium chloride was carefully added followed by 20 mL of hexane. This mixture was stirred for 2 h and treated with water. The aqueous phase was extracted with ether and the combined organic phases were washed with water and brine, dried, filtered, and concentrated. Purification of the residue by column chromatography (alumina activity III, elution with 2.5% ethyl acetate in petroleum ether) furnished 24 mg (64.5%) of 112; IR (neat, cm\(^{-1}\)) 3600-3465, 3070, 2936, 1455, 1380, 1067, 892, 824; \(^1\)H NMR (300 MHz, C\(_6\)D\(_6\)) \(\delta\) 5.30 (br, 1H), 2.23-2.31 (m, 1H), 2.01-0.76 (series of m, 7H), 1.53 (d, \(\text{J} = 1.2\) Hz, 3H), 1.41 (s, 3H), 1.20 (s, 3H), 0.87 (s, 3H), 0.51-0.42 (m, 2H), 0.13 (t, \(\text{J} = 4.2\) Hz, 1H); \(^{13}\)C NMR (75 MHz, C\(_6\)D\(_6\)) ppm 146.29, 127.00, 86.41, 52.45, 52.30, 44.53, 35.41, 34.55, 30.72, 26.22, 25.45, 23.17, 22.27, 18.24, 11.99; MS m/z (M\(^+\)-H\(_2\)O) calcd 202.1721, obsd 202.1700.
(1aR*,4aR*,5S*,7aR,7bS*)-Decahydro-3,3,5,7b-tetramethyl-4aH-cycloprop[e]azulen-4a-ol (113).

Allylic alcohol 112 (21 mg, 0.095 mmol) in ethyl acetate (3 mL) containing 10 mg of platinum oxide was shaken under 50 psi of hydrogen for 24 h. The mixture was filtered and the filtrate evaporated. MPLC purification on silica gel (elution with 4.5% ethyl acetate in petroleum ether) gave 19 mg (90%) of 113; IR (neat, cm⁻¹) 3620, 3080, 2970, 1460, 1170, 1035; ¹H NMR (300 MHz, C₆D₆) 2.05-0.71 (series of m, 11H), 1.27 (s, 3H), 1.25 (s, 3H), 0.83 (s, 3H), 0.76 (d, J = 6.6 Hz, 3H), 0.54 (s, 1H), 0.50 (dd, J = 8.3, 3.6 Hz, 1H), 0.11 (t, J = 4.2 Hz, 1H); ¹³C NMR (75 MHz, C₆D₆) ppm 84.22, 54.81, 52.43, 46.53, 44.16, 35.29, 34.13, 30.57, 25.50, 25.45, 23.83, 23.67, 22.97, 18.33, 12.81; MS m/z (M⁺) calcd 222.1984, obsd. 222,1973.
References and Notes


(59) For a useful modification of the Wharton rearrangement, see Burke, S.D.; Murtiashaw, C.W.; Saunders, J.O.; Oplinger, J.A.; Dike, M.S. J. Am. Chem. Soc. 1984, 106, 4558. This modification was not utilized because of its acetic acid requirement and the acid sensitivity of our substrate. At the highly elevated temperatures employed, substrate polymerization and conversion to diene 77 was observed.


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(73) We thank Dr. M.-A. Poupart for performing these calculation in the Department Computer Graphics Facility.


(78) We thank Dr. J.C. Braekman of the Universite Libre de Bruxelles for providing us with a generous sample of africanol.


Appendix 1.  $^1$H NMR (300 MHz, CDCl$_3$) at 28°.
Appendix 2.1 $^1$H NMR (300 MHz, CDCl$_3$) of 36.
Appendix 3. $^1$H NMR (300 MHz, CDCl$_3$) of 109.
Appendix 4. $^1H$ NMR (300 MHz, CDCl$_3$) of 108.
Appendix 5. NOE spectrum of \textbf{113} (500 MHz, C$_6$D$_6$).
Appendix 6. NOE spectrum of $113$ (500 MHz, C$_6$D$_6$).
Appendix 7. $^1$H NMR (300 MHz, $C_6D_6$) of Authentic *Africanol* (1).
Appendix 8. $^1$H NMR (300 MHz, $C_6D_6$) of Synthetic Africanol (1).
Appendix 9. $^1$H NMR (300 MHz, $D_2O + C_6D_6$) of Synthetic *Africanol* (1).
Chapter II

A Synthetic Approach Toward Neolemnanyl Acetate
Introduction

The unusual sesquiterpenes neolemnane (1) and neolemnanyl acetate (2) were isolated in 1981 by Fenical and Izac\(^1\) from the Pacific soft coral *Lemnalia africana*\(^2\). X-ray crystallography was utilized to elucidate the structure of 2.

![Structure of neolemnane and neolemnanyl acetate]

These new and unusual sesquiterpenoid structures represent an extension of the biosynthetic capability of soft corals from this genus. It is currently believed that the biosynthesis of 2 begins with \(\text{1(10)-aristolene (3)}\)\(^3\) and follows the pathway outlined in Scheme 1\(^4\). In the proposed biosynthetic pathway, enol acetate 6 is an important intermediate. Indeed, this compound has been isolated from the soft coral *Paralemnalia Thyrsoide*\(^4\). Although the proposed precursor of the nardosinanes, namely 3, has not yet been isolated from this soft coral genus, it has been reported to have been found in Gorgonian soft corals\(^5\).

Related interesting structural characteristics have been uncovered in dactylol (8)\(^6\), poitediol (9)\(^7\), and precapnelladiene (10)\(^8\), as well as the ophiobolins\(^9,10,11\) typified by ophiobolin F (11), the fusicocccins\(^12\) such as cotylenol (12), the ceroplastols\(^13\) typified by ceroplastol I (13), and pleuromutilin (14)\(^14\).
Scheme I
Figure 4. Natural products containing an eight-membered ring.
Much of the work in the syntheses of eight-membered rings has been limited to the last five years. A few total syntheses (e.g. precapnelladiene, poitediol, dactylol and pleuromutilin) have appeared in the literature during this time.

From the synthetic standpoint, the notable features of neolemnanyl acetate (2) are its fused 6/8 ring system, pair of double bonds, cis disposition of the two methyl groups, and the presence of two acetoxy groups.

Majetich has reported that the cyclization of extended dienone 15 using ethylaluminum dichloride produced solely the 6/6 fused bicyclic enone 16 in 77% yield via an intramolecular Sakurai reaction. In dramatic contrast to this result, treatment of substrate 15 with fluoride ion led to a 6/8 bicyclic enone (17), possessing the neolemnane ring system in 42% yield (Scheme II). No other published work has been targeted at the synthesis of the neolemnanes.

Scheme II
In this laboratory, the total synthesis of precapnelladiene was earlier accomplished via aliphatic Claisen rearrangement. Central to the overall strategy was the Claisen rearrangement of a 6-alkenyl-2-methylenetetrahydropyran. This general procedure constitutes a new approach to annulated 4-cyclooctenones.

Adaptation of this aliphatic Claisen rearrangement strategy to the total synthesis of neolemnanyl acetate could produce the requisite 6/8 bicyclic ring system. Therefore, our retrosynthetic analysis of 2 centers upon key intermediate 22 as the entry point.
Results and Discussion

To begin the synthesis, a preparation of 22 was sought. To this end, 5-methyl-1,3-cyclohexanedione was synthesized via Robinson annulation of ethyl acetoacetate and methyl crotonate, followed by hydrolysis and decarboxylation\textsuperscript{17}.

\[
\begin{array}{c}
\text{Me}\text{C}==\text{O} & + & \text{CH}_3\text{C}==\text{CO}\text{OC}_2\text{H}_5 \\
\text{1.NaOC}_2\text{H}_5 & \rightarrow & \text{Na}+\text{C}_2\text{H}_3\text{OC}_2\text{H}_5 \\
\text{2.KOH} & \rightarrow & \text{O} & \text{O} \\
\text{3.} & \Delta & \rightarrow & \text{Me}\text{C}==\text{O} & \text{Me}\text{C}==\text{O}
\end{array}
\]

Isobutoxy-5-methylcyclo-hex-2-en-1-one was prepared by the method of House and co-workers in excellent yield\textsuperscript{18}.

An earlier investigation by Stork and Danheiser\textsuperscript{19} suggested that the correct stereochemistry could be established by successive alkylation of 24, the relative configuration being determined as usual by the order of alkylation.

The regiospecific alkylation of 24 with methyl iodide and LDA in tetrahydrofuran at -78°C gave two stereoisomers 25 (ratio 1:1), which were easily separated by medium pressure liquid chromatography.
Attention was next turned toward introducing an alkyl substituent at C-6 suitably functionalized for the elaboration of 22. Various considerations led to the expectation that Michael addition of 25 to methyl acrylate would give rise to 26 which could then be selectively cyclized via vinyl lithium to compound 27.

However, the Michael reaction of 25 with methyl acrylate in the presence of sodium ethoxide or potassium t-butoxide returned only unreacted starting material.
In retrospect, this result was not surprising. The site of desired carbon-carbon bond formation in 25 happens to be a quaternary center that is also adjacent to a tertiary center. Closer inspection of the literature on this topic disclosed that the construction of quaternary carbon center is among the most restricted in organic synthesis.

Reaction of the kinetic enolate of 25 with methyl acrylate proceeded in good yields at -78°C to give bicyclo[2.2.2]octane 26.

\[
\begin{align*}
25 + \text{MeCO} & \xrightarrow{\text{LDA}} 26
\end{align*}
\]

This product can be seen to result from a sequential pair of Michael additions. The stereochemical questions relevant to the conversion to 26 could not be unequivocally ascertained by detailed ¹H NMR analysis. However, the assumed stereochemistry is based on examination of Dreiding models and steric factors operating in the transition state. This untoward development required that suitable conditions be found for efficiently preparing 27 and for converting it to 22. In this regard, experiments aimed at elucidation of the alkylation of sterically hindered ketones had to be considered.

When the readily available 3-[(trimethylsilyl)oxy]-1-bromopropane was reacted with 25 under kinetically controlled conditions (LDA, HMPA) at -78°C, only starting material was returned again.
A second attempt to effect alkylation was investigated by making use of allyl bromide. Treatment of 25 with allyl bromide under comparable kinetic alkylation conditions at -78°C afforded a 79% yield of 29 as a 95:5 mixture (based on 1H NMR analysis) of diastereomers, of which compound 29 is the major isomer.

A third alternative was investigated by using homoallyl bromide. Under the same conditions, kinetic alkylation with 25 and 3-butenyl bromide gave only starting material.

These results demonstrated that the limitation of steric hindrance toward alkylation was going to prove troublesome in this system and may not be applicable to suitable functionalization as required for preparation of 27.
Attempts to produce 31 via oxidation of olefin 30 with diborane or 9-BBN were thwarted because of the formation of a myriad of products resulting from reduction of the other functional groups.

A significant and useful alternative to the alkylation methods just described was realized with methyl cis-3-chloroacrylate. Addition of this reagent following generation of the cross-conjugated enolate of 25 (LICA, -78°C) afforded, by addition-elimination, a mixture of trans-acrylate 32 and cis-acrylate 33 in ratio of 2:1.

Previous work in this laboratory has shown that the nucleophilic addition of vinylmagnesium bromide or vinyl lithium to 34 and 35 proceeds trans to the α substituent to deliver lactones 36 and 37 in isomerically pure form.
Unfortunately, treatment of 32 with vinyl lithium at -78°C gave only 38 and unreacted starting material.

If the nucleophilic addition of vinyl lithium to carbonyl group had occurred, the desired product 39 would have resulted.
This result demonstrated that nucleophilic addition of vinyllithium proceeds preferentially at the carboxylate carbonyl group due to the sterically hindered nature of the ketone carbonyl group in this system. Treatment of 32 with Dibal proved fruitless in preliminary attempts to reduce the ester functionality selectively because only 40 was formed.

It became clear that preparation of key intermediate 22 was not as easy as originally expected. As a result, new approaches are mandated to successfully gain access to the Claisen rearrangement precursor.
Experimental

5-Methyl-1,3-cyclohexanedione (23).

Sodium metal (23.677 g) was added to 0.5 L of absolute ethanol in a three-necked 1 L reaction flask equipped with a mechanical stirrer, dropping funnel, and high capacity reflux condenser. The sodium was added at a rate sufficient to maintain a gentle reflux. After all the sodium had reacted, ethyl acetoacetate (136.36 g) was added over a 3-h period via the dropping funnel. Methyl crotonate (106.82 g, 96% pure) was then added rapidly over a 1-h period. The yellow solution was very carefully heated to gentle reflux. When precipitation of the product began, the reaction became extremely exothermic, and external heating was removed. Once the reaction returned to a gentle reflux, external heat was reapplied in order to maintain gentle reflux overnight. The white precipitate was filtered. Potassium hydroxide (22.4 g) was added to a stirred solution of the above dione salt (44.07 g) in 0.21 L of water. The dark orange solution was heated to reflux and allowed to remain at that temperature for 4 h. The methanol and most of the water was removed by distillation under reduced pressure. The residue was diluted with 200 ml of water and concentrated HCl was added dropwise until a pH of 6 was reached. Concentrated HCl was then added at a rate equal to the reflux rate. The HCl was added until the color of the solution turned to yellow and the pH change reached 1-2. The yellow solution was then quickly cooled to 0°C in order to precipitate the
product from the acidic solution. The precipitate was filtered and the mother liquor was extracted with dichloromethane. The organic layer was dried over MgSO₄ and the solvent was removed under reduced pressure. This procedure was repeated twice until all of the dione salt was converted to the dione. The crude dione was recrystallized from ethyl acetate to afford 65 g (50%) of colorless prisms, mp 128-129°C. (lit17 129.5-130°C): ¹H NMR (60 MHz, CDCl₃) δ 5.49 (s, 1H), 3.40 (s, 1H), 2.90-1.80 (m, 5H), 1.08 (d, J = 4 Hz, 3H), MS m/z (M⁺) calcd 126.0680, obsd 126.0661.

3-Isobutoxy-5-methylcyclohex-2-en-1-one (24).

In a 1 L flask equipped with a Dean-Stark trap was placed 23 (43 g, 0.341 mol), 200 mg of p-toluenesulfonic acid, 33 ml (1.2 equiv) of isobutyl alcohol, and 500 ml of benzene. The mixture was heated at the reflux temperature for 7 h until water ceased to be liberated. The resulting mixture was washed with water, dried over magnesium sulfate, and concentrated under reduced pressure. The residual liquid was distilled under reduced pressure (bp 125-127°C/2.5 mmg). The yield of enol ether was 48.4 g (78%); IR (neat, cm⁻¹) 2960-2865, 1655, 1603; ¹H NMR (300 MHz, CDCl₃) δ 5.27 (s, 1H), 3.54 (dd, J = 7, 1 Hz, 2H), 2.40-1.22 (m, 6H), 1.03 (d, J = 6.2 Hz, 3H), 0.93 (d, J = 6.6 Hz, 6H); ¹³C NMR (75 MHz, CDCl₃) ppm 199.60, 177.43, 102.20, 74.62, 44.99, 37.06, 28.70, 27.56, 20.76, 18.93 (2C); MS m/z (M⁺) calcd 182.1289, obsd 182.1287.
3-Isobutoxy-5,6-dimethylcyclohex-2-en-1-one (25).

A 1000 ml three-necked flask equipped with a nitrogen line, magnetic stirring bar, and septum inlet was flame dried. Then 400 ml of dry THF was added by syringe. The flask was cooled to 0°C and 27.12 ml of n-BuLi (1.45 M in hexane) was added, followed by 55.1 ml of diisopropylamine (1.1 eq). After 15 min, the solution was cooled to -78°C and 65.07 g (0.358 mmol) of 24 was added via syringe in ether (10 ml). The anion was allowed to form for 2 h, then 26.7 ml of CH₃I (1.2 eq) was added dropwise via syringe. After 3 h, the etheral solution (after workup with NH₄Cl solution and more ether) was dried over MgSO₄ and concentrated under reduced pressure. The residual oil was purified by distillation (5 mmHg, 118-120.5°C) to give 59.29 g (84%) of 25 as a colorless liquid. A small amount of dimethyl compound was more highly purified by MPLC (elution with 4% ethyl acetate in petroleum ether) to give samples of each isomer (ratio 1:1).

For the less polar isomer: IR (neat, cm⁻¹) 2960-2870, 1600, 1615; ¹H NMR (300 MHz, CDCl₃) δ 5.29 (s, 1H), 3.55 (d, J = 6.67 Hz, 2H), 2.45-1.90 (m, 5H), 1.13 (d, J = 6.5 Hz, 3H), 1.07 (d, J = 6.3 Hz, 3H), 0.94 (d, J = 6.8 Hz, 6H); ¹³C NMR (75 MHz, CDCl₃) ppm 201.54, 175.80, 101.70, 74.62, 47.28, 36.87, 34.95, 27.73, 20.26, 19.81, 18.98, 12.85; MS m/z (M⁺) calcd 196.1464, obsd 196.1466.

For the more polar isomer: IR (neat, cm⁻¹) 2960-2870, 1655, 1600; ¹H NMR (300 MHz, CDCl₃) δ 5.23 (s, 1H), 3.55 (d, J = 6.5 Hz, 2H), 2.46-1.94 (m, 5H), 1.03 (d, J = 7 Hz, 3H), 0.95 (d, J = 6.5 Hz, 3H), 0.94
(d, J = 6.7 Hz, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) ppm 202.90, 175.84, 101.21, 74.70, 45.12, 34.68, 32.00, 27.79, 19.09 (2C), 15.87, 11.06; MS m/z (M$^+$) calcd 196.1464, obsd 196.1462.

3-[(Trimethylsilyl)oxy]-1-bromopropane.

To 3-bromopropanol (2.46 g, 17.7 mmol) and 2,6-lutidine (2.1 g, 19.4 mmol) in CCl$_4$ (18 ml) was added trimethylchlorosilane (2.1 g, 19.5 mmol) dropwise at 0°C. The mixture was stirred at room temperature for 4h. After filtration, carbon tetrachloride was distilled off under reduced pressure. Distillation gave an oil: 3.27 g (88%) (lit$^{22}$; bp 57°C (10 mm)); $^{1}$H NMR (60 MHz, CCl$_4$) δ 3.66 (t, 2H), 3.42 (t, 2H), 2.20-1.77 (m, 2H), 0.10 (s, 9H).

Kinetic Enolate of 25 with Methyl Acrylate (26).

A solution of 25 (300 mg, 1.53 mmol) in dry THF (2 ml) was treated dropwise while being stirred with LDA (3.2 mmol) and THF (10 ml) under nitrogen at -78°C. Methyl acrylate (0.2 ml, 1.5 eq) in THF (2 ml) was added dropwise to the stirred enolate solution. The mixture was maintained at -78°C for 4h, and was allowed to warm to room temperature over 3h. The reaction mixture was treated with saturated aqueous NH$_4$Cl solution. The ethereal extract was successively washed with saturated aqueous NaHCO$_3$ solution and brine, dried over magnesium sulfate, and evaporated to yield a crude
oil which was purified by MPLC (elution with 18% ethyl acetate in petroleum ether) to give 180 mg of 26 (82% based on recovered starting material) and 139 mg of starting material; IR (neat, cm\(^{-1}\)) 2800, 1750-1725, 1375, 1205, 1162, 1110; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 3.66 (s, 3H), 3.24-2.89 (m, 4H), 2.41-1.66 (m, 5H), 1.42-1.03 (m, 2H), 0.94 (s, 3H), 0.84 (d, \(J = 6.7\) Hz, 6H), 0.83 (d, \(J = 7\) Hz, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) ppm 211.3, 174.5, 68.5, 51.6, 46.6, 45.2, 44.0, 43.3, 39.9, 35.5, 34.8, 31.9, 28.9, 19.2, 19.0, 16.4; MS m/z (M\(^+\)) calcd 282.1829, obsd 282.1869.

\((5S^*,6S^*)\)-3-Isobutoxy-5,6-dimethyl-6-allylcyclohex-2-en-1-one (29).

A 25 ml three-necked flask equipped with nitrogen line, magnetic stirrer, and septum inlet was flame dried. Then, 2 ml of THF was added by syringe. The flask was cooled to 0°C and 0.85 ml of n-BuLi (1.5 M in hexane) was added, followed by 0.25 ml of diisopropylamine. After 15 min, the solution was cooled to -78°C and 200 mg (1.02 mmol) of 25 was added via syringe in 0.5 ml of ether. The anion was allowed to form for 30 min, then 0.8 ml of HMPA was added via syringe. After 1 h, 0.186 ml of allyl bromide was added dropwise by syringe. The reaction mixture was allowed to warm to room temperature during 3h, then stirred overnight. The mixture was poured into saturated NH\(_4\)Cl solution and extracted with ether. Brine was added and the organic phase was dried over MgSO\(_4\). The mixture was purified by MPLC (elution with 32% ethyl acetate in petroleum ether) to give 192 mg (79%) of 29 containing 5% of its isomer.
(NMR analysis); IR (neat, cm\(^{-1}\)) 3080, 2965, 1655, 1605, 1470, 1220, 1003; \(^1H\) NMR (300 MHz, CDCl\(_3\)) \(\delta\) 5.70-4.98 (ABC system, 3H), 5.28 (s, 1H), 3.57 (d, \(J = 6.6\) Hz, 2H), 3.57-1.01 (m, 6H), 0.97-0.95 (12 H, m); \(^13C\) NMR (75 MHz, CDCl\(_3\)) ppm 203.66, 175.17, 134.92, 117.10, 101.39, 74.62, 47.47, 39.94, 34.18, 32.84, 27.73, 19.04 (2C), 18.15, 14.76; MS m/z (M\(^+\)) calcd 236.1776, obsd 236.1779.

**Methyl cis-3-Chloroarylate.**

Esterification of cis-3-chloroacrylic acid (100 mg, cr) with diazomethane (2 eq) in ether (5 ml) gave a quantitative yield of the ester; IR (neat, cm\(^{-1}\)) 1739, 1626, 1353, 1002, 809, 705; \(^1H\) NMR (60 MHz, CC\(_4\)) \(\delta\) 6.84 (d, \(J = 8.1\) Hz, 1H), 6.27 (d, \(J = 8.0\) Hz, 1H), 3.92 (s, 3H).

**Methyl (5S*,6S*)-6-(5,6-Dimethyl-1-oxycyclohex-2-enyl)-3-trans-acrylate (32) and Methyl (5S*,6S*)-6-(5,6-Dimethyl-1-oxycyclohex-2-enyl)-3-cis-acrylate (33).**

To the flame-dried flask cooled to 0°C was added 2.1 ml of THF and 1.38 ml of n-BuLi (1.52 M in hexane, 2.1 mmol) followed by 373 \(\mu\)l (2.3 mmol) of isopropylcyclohexylamine. After 15 min, the solution was
cooled to -78°C and 274 mg (1.62 mmol) of 25 in 1 ml of THF was added via cannula. The anion was allowed to form for 30 min, then 1 ml of HMPA was added dropwise via syringe. After 1 h, 233 mg (1.94 mmol) of methyl cis-3-chloroacrylate in 1 ml of ether was introduced via cannula. The reaction mixture was maintained at -78°C for 22 h and then quenched with saturated ammonium chloride solution. Usual workup and MPLC on silica gel (elution with 27% ethyl acetate in petroleum ether) afforded 141 mg (31%) of 32 and 75 mg (17%) of 33.

For 32: IR (neat, cm⁻¹) 3083, 2978, 1730, 1660, 1612, 1200, 1012; ¹H NMR (300 MHz, CDCl₃) δ 6.90 and 5.85 (d, J = 16.1 Hz, 2H), 5.29 (s, 1H), 3.71 (s, 3H), 3.57 (d, J = 6.5 Hz, 2H), 2.53-1.81 (m, 4H), 1.16 (s, 3H), 0.95 (d, J = 6.7 Hz, 6H), 0.93 (d, J = 6.3 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) ppm 200.46, 175.29, 166.74, 151.72, 121.57, 100.87, 74.05, 51.43, 51.24, 35.91, 34.12, 27.73, 18.98 (2C), 15.91, 15.40; MS m/z (M⁺) calcd 280.1675, obsd 280.1676.

For 33: IR (neat, cm⁻¹) 3070, 2962, 1720, 1652, 1610, 1380, 1200, 1008, 820; ¹H NMR (300 MHz, CDCl₃) δ 6.00 and 5.92 (d, J = 10.2 Hz, 2H), 5.30 (s, 1H), 3.61 (s, 3H), 3.62-3.55 (m, 2H), 2.94 (m, 1H), 2.34-1.91 (m, 3H), 1.21 (s, 3H), 0.93 (d, J = 6.8 Hz, 9H); ¹³C NMR (75 MHz, CDCl₃) ppm 201.16, 174.03, 165.91, 152.63, 120.82, 101.37, 74.60, 51.33, 50.79, 34.75, 34.47, 27.90, 19.31, 19.24, 19.20, 16.21; MS m/z (M⁺) calcd 280.1675, obsd 280.1650.
Condensation of 32 with Vinylithium (39).

A solution of vinylvithium in ether was prepared by adding excess vinyl bromide (0.2 ml, 1.85 mmol) via a cold syringe to cold (-78°C) ether (3 ml) under argon and then by adding 1.45 M tert-butyllithium (0.2 ml, 0.29 mmol) in pentane. After 30 min, a cooled (-78°C) solution of 32 (57.5 mg, 0.205 mmol) in ether (2 ml) was injected via cannula. The reaction mixture was maintained at -78°C for 1 h and allowed to warm to room temperature over 25 min. The reaction mixture was quenched with saturated ammonium chloride solution. Usual workup and MPLC on silica gel (elution with 27% ethyl acetate in petroleum ether) afforded 19.3 mg (31%) of 39 and 12 mg of starting material; IR (neat, cm⁻¹) 3400, 3087, 2967, 1612, 1216; ^1H NMR (300 MHz, CDCl₃) 6 6.00-5.12 (ABX system, J = 17.4, 10.7, 1.1 Hz, 6H), 5.68 and 5.59 (d, J = 16.2 Hz, 2H), 5.27 (s, 1H), 3.58 (d, J = 6.5 Hz, 2H), 2.53-1.85 (m, 5H), 1.12 (s, 3H), 0.96 (d, J = 6.5 Hz, 6H), 0.94 (d, J = 5.7 Hz, 3H), MS m/z (M⁺-C₅H₇O) calcd 221.1541, obsd 221.1512.

(4S*,5S*)-4-[(E)-Hydroxymethylethyli dene-3-yl]-4,5-dimethylcyclohex-2-en-1-one (40).

A cold (-78°C) magnetically stirred solution of 32 (36 mg, 0.13 mmol) in dry methanol (2 ml) was treated dropwise with 0.28 ml of Dibal (1 M hexane), stirred for 30 min and treated with water. The product was
extracted with dichloromethane (3x) and the combined organic layers were dried and evaporated. The residue was purified by MPLC on silica gel (elution with 35% ethyl acetate in petroleum ether) to give 17 mg (78%) of 40; IR (neat, cm⁻¹) 3500-3400, 2980, 1720-1650, 1285, 1170, 985; ¹H NMR (300 MHz, CDCl₃) δ 6.59 (d, J = 10.2 Hz, 1H), 5.92 (d, J = 10.2 Hz, 1H), 5.67 (m, 2H), 4.16 (m, 2H), 2.48-1.86 (m, 4H), 1.12 (s, 3H), 0.94 (d, J = 6.5 Hz, 3H).
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