AN ABSTRACT OF THE THESIS OF


Title: Structural and Synthetic Studies of Higher Terpenoids:
Part I. The Absolute Configuration of (-)-Botryococcene.
Part II. Total Synthesis of (±)-2-Desoxystemodinone.

Abstract approved:  

U James D. White

Part I. Complete structural and stereochemical elucidation of the unusual triterpenoid metabolite botryococcene (1), produced by the alga Botryococcus braunii (Kützing) was carried out. Botryococcene was degraded to 4-methyl-7-butyrolactone, 2,5-dimethyl-8-valerolactone, and 2-ethyl-2,5-dimethyl-8-valerolactone, and the absolute configuration of these lactones was determined by $^1$H NMR correlation with the optically pure substances synthesized from (R)- and (S)-propylene oxide, using the chiral shift reagent Eu(hfc)$_3$. This led to the specification of the six stereogenic centers in 1 as 3S,7S,10S,13R,16S,20S.

Application of a similar degradation protocol to braunicene (10), a congener of 1, produced dimethyl 2-ethyl-2-methylglutarate (42) and ketoester 41. The absolute configuration of 42 was determined to be R by $^1$H NMR correlation with optically pure material obtained from synthetic 2-ethyl-2,5-dimethyl-8-valerolactone by haloform oxidation.
The stereochemical assignments to 1 and 10 are consistent with a biogenesis via presqualene pyrophosphate but which deviates from the squalene pathway in the fragmentation of the cyclopropane ring.

Preliminary to the NMR studies on which stereochemical correlation of the degradation products from 1 and 10 are based, a complete NMR analysis of the ionophore antibiotic boromycin was carried out (Appendix). This exercise, which exploited COSY, HETCOR, and long-range HETCOR 2-D NMR techniques, led to a complete proton and carbon assignment to this structurally complex metabolite of *Streptomyces Antibioticus*.

Part II. The total synthesis of (±)-2-desoxystemodinone (3) from the tricyclic ketone 64 in nine steps is described. Reductive alkylation of 64 with benzyl chloromethyl ether in the presence of samarium diiodide gave 76 which was converted to hydroxy aldehyde 78. An internally hydrogen-bonded conformation of 78 facilitated a unique intramolecular ene reaction to afford 79 in 94% yield upon heating to 110 °C. In contrast, oxetane 81 was obtained as the major product when 79 was exposed to dimethyl-aluminum chloride. The failure of 85, prepared by the reduction of 78 with samarium diiodide, to undergo the ene reaction demonstrated the importance of the hydroxyl substituent in this process. Swern oxidation of 79 gave 87, which was reductively deoxygenated to 88 using samarium diiodide in the presence of tert-butanol. Wolff-Kishner reduction of 88, followed by epoxidation and reduction with lithium triethylborohydride, gave (±)-3.
Structural and Synthetic Studies of Higher Terpenoids:
Part I. The Absolute Configuration of (-)-Botryococcene.
Part II. Total Synthesis of (±)-2-Deoxystemodinone.

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Todd Charles Somers

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APPROVED:

Redacted for Privacy

Professor of Chemistry in charge of major

Redacted for Privacy

Head of Department of Chemistry

Redacted for Privacy

Dean of Graduate School

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STRUCTURAL AND SYNTHETIC STUDIES OF HIGHER TERPENOIDS:

PART I. THE ABSOLUTE CONFIGURATION OF (-)-BOTRYOCOCCENE.

PART II. TOTAL SYNTHESIS OF (±)-2-DESOXYSTEMODINONE.

GENERAL INTRODUCTION

The terpenoids (or isoprenoids) are the largest and most structurally diverse group of secondary metabolites. Many of the more volatile compounds have been used as medicines and cosmetics by man for at least two thousand years. The rapid expansion, within the last three decades, of our structural and biosynthetic understanding of the terpenoids has paralleled the great advances in physical and spectroscopic techniques. Of particular significance are the development and exploitation of nuclear magnetic resonance and X-ray crystallography.

In Part I of the discussion herein, we describe a structural and stereochemical investigation of two irregular triterpene metabolites of the green alga Botryococcus braunii (Kützing). The use of a rapid and technically simple high-field NMR technique for the stereochemical identification of the degradation products derived from these hydrocarbons is detailed. The results obtained from this study allow speculation on the synthesis of irregular terpenes in this alga and further an understanding of general terpenoid biogenesis.

A description of our efforts, culminating in the total synthesis of (±)-2-desoxystemodinone, is contained in Part II. Our approach to this unusual tetracyclic diterpene exploits a number of emerging synthetic technologies such as samarium(II) reduction and manganese(III) oxidation. The key step in this synthesis makes use of a unique intramolecular ene reaction which assembles the bicyclo[3.2.1]octane framework of the stemodanes in a stereospecific fashion.
PART I: THE ABSOLUTE CONFIGURATION OF (-)-BOTRYOCOCENE

I-A. Introduction

The unicellular green alga *Botryococcus braunii* (Kützing) is found throughout the world under a wide range of climatic conditions.\(^1\) The unusually high level of hydrocarbon production (17-90% by dry weight)\(^2\) found in this organism has generated interest in its exploitation as a renewable energy source and role in the formation of oil-rich geochemical deposits.

It has been established that *B. braunii* is responsible for a variety of oil-bearing sediments dating from the Ordovician period to the present.\(^3\) Microscopic examination of the high grade oil-shale known as torbanite (carboniferous, 3x10\(^8\) years) and the rubbery deposit coorongite, reveals fossilized colonies of the alga. It has also been suggested that Paleozoic oil-bearing rocks and Tertiary sediments, such as lignite, also derive their oil content from this organism. More recently, a chemical marker characteristic of *B. braunii* has been detected in two Sumatran crude oils.\(^4\)

Progress has been made in utilization of the alga as a renewable source of liquid hydrocarbons.\(^5\) Despite the difficulties associated with commercial scale cultivation, the occurrence of large unialgal blooms and the possibility of reduced harvesting costs due to the alga's natural buoyancy and extracellular localization of hydrocarbons has provided economic incentive.

The unusual morphology of active cultures of *B. braunii* has been extensively studied. Each cell (roughly spherical) is embedded
in a small cup of oil and when a cell divides into two daughter cells, the latter secrete oil and remain within the cup of the mother cell. In this manner, a matrix of the colony is built up and large free-floating blooms of the alga, ranging in color from green to red-brown, often result.\textsuperscript{6}

Metzger and Casadevall have shown that the bulk of hydrocarbon biosynthesis occurs in the outer cell walls and, to a lesser extent, within the cell interior.\textsuperscript{7} The latter pool is actively excreted to the cell’s exterior, maintaining the internal hydrocarbon concentration at a value of \(<1\%\).\textsuperscript{8} This result, coupled with the inability of \emph{B. braunii} to catabolize its own hydrocarbons,\textsuperscript{7b} partially accounts for its unusually high oil production.

The chemical composition of the organism was the subject of several early investigations. When placed in iodine solution, cells of \emph{B. braunii} absorb so much iodine that they sink,\textsuperscript{6} implying a high concentration of unsaturated hydrocarbons. Belcher found the living organism to contain 7-12\% of a saponifiable lipid and 16-23\% of an unsaponifiable lipid which was a liquid at room temperature.\textsuperscript{9} From a sample collected in Cheshire, England, Maxwell and Eglinton isolated, by hexane extraction, a 9:1 mixture of two hydrocarbons which accounted for 76\% of the algal biomass. The structure of the major component, named botryococcene, and its degradation products were investigated in detail through NMR, IR, and mass spectral methods.\textsuperscript{10}

The infrared spectrum of botryococcene exhibited bands at 891(2), 916 and 1002, and 979 cm\(^{-1}\), which were assigned to exomethylene, vinyl, and \textsuperscript{trans}-disubstituted carbon-carbon double bonds
respectively. Intensity measurements on these absorptions were consistent with the presence of one *trans*-disubstituted double bond, one vinyl group, and four exomethylene double bonds in the hydrocarbon.

The $^1$H NMR spectrum showed a fairly sharp singlet at $\delta 4.6$ which was assigned to the eight exomethylene protons. A distinct ABX pattern for a vinyl group attached to a fully substituted carbon and an AB quartet for a *trans*-disubstituted double bond ($J_{\text{trans}} = 16$ Hz) with one allylic proton, were identified by comparison with assigned spectra of similar spin systems. Integration of the six-proton singlet at $\delta 1.62$ and the saturated methyl region, indicated the presence of two vinyl methyl groups and five or six methyl groups on saturated carbon.

Spectral analysis of the minor component of the isolate, named *isobotryococcene*, demonstrated an overall structural similarity to botryococcene with one of the exomethylene groups of the latter isomerized to a trisubstituted double bond.

Hydrogenation of both botryococcene and *isobotryococcene* gave one hydrocarbon, named botryococcane. From mass spectral data it was concluded that both olefin isomers have the molecular formula $C_{34}H_{58}$ and botryococcane the formula $C_{34}H_{70}$. The intense ions at mass 449 and 448 of the latter were presumed to arise via loss of the ethyl group formed upon hydrogenation of botryococcene, and support the attachment of the vinyl substituent to a tetrasubstituted carbon atom.

Oxidative cleavage of botryococcene with permanganate-periodate gave in low yield, a single diketo acid (Scheme 1) that
Scheme 1

was assigned structure 3.\textsuperscript{11} It was assumed that 3 arises from both halves of botryococcene through decarboxylation of the intermediate diacid 2. These data, with additional support from \textsuperscript{13}C chemical shift assignments and general biosynthetic principles, allowed Eglinton et al. to propose the gross structure 1 for botryococcene.

Further investigation\textsuperscript{12} has shown that \textit{B. braunii} is capable of producing a variety of hydrocarbons which can be divided into two major classes. These are: a) n-alkadienes and trienes, odd numbered from C\textsubscript{23} to C\textsubscript{31}, and b) polymethylated triterpenes of the general formula C\textsubscript{n}H\textsubscript{2n-10} (n=30-37), which have been given the generic name botryococcenes. On the basis of observations made
on wild strains of *B. braunii*, it has been suggested that these two classes of hydrocarbons could be produced at different stages of growth. According to this postulate, the unbranched linear hydrocarbons would be produced by green cells during active growth and the botryococcenes from orange senescent colonies.

It was shown recently that most wild strains of *B. braunii* are actually composed of two closely related races. These races, A and B, have no detectable morphological differences but produce quite different hydrocarbon metabolites. The A- and B-races have been successfully separated and independently cultivated by a group at CNRS in Paris. The straight-chain hydrocarbons which have been characterized from the A-race of *B. braunii* are shown in Figure I.1. In laboratory cultures, the A-race alga contains 19-61% by dry weight of these odd-numbered hydrocarbons. Through 14C-radiolabeling studies, it has been shown that these hydrocarbons are derived biosynthetically from oleic acid, and that the whole carbon chain of the latter is incorporated into the final hydrocarbons.

![Figure I.1 Hydrocarbons of the A-race of *B. braunii*.](image)

In contrast, the B-race produces no detectable amount of these straight-chain hydrocarbons, but rather a large number of cyclized
and unycylized irregular triterpenes. At least 30 of these "botryococcenes" have been detected by GC-MS, but only eleven have been characterized to date (Figure I.2). The structural assignments to these hydrocarbons have been made using only spectral data and partial degradation. No attempt has been made to assign absolute stereochemistry to any of the botryococcenes, a prerequisite to rational structure proof by total synthesis.

The B-race metabolites are conveniently subclassified into two main groups: the normal chain \( \text{n-botryococcenes} \) (botryococcene (1) and 4-7) and the more highly modified \( \text{m-botryococcenes} \) (isobotryococcene (8), \( 9,17a \) braunicene (10), \( 11,17a \) darwinene (12), 18 and 13). The latter are presumably derived from anomalous methylation or cyclization of the \( \text{n-botryococcenes} \). The relative amounts of each of these hydrocarbons in a given sample shows a wide variation as does the total hydrocarbon production of the organism (25-86%).

The biogenesis of the botryococcenes has been addressed by a number of researchers. Eglinton, who characterized the C34 compound botryococcene (1), reasonably conjectured its biogenesis as isoprenoid. Subsequent studies by Wolf and Metzger have confirmed this hypothesis. Wolf, in pulse chase experiments utilizing sodium \([14C]\)bicarbonate, noted an initial incorporation of label (91%) into the C30 compound 4 which, during the chase, lost radioactivity to the higher homologues (C31 - C34). From these data it was concluded that the C30 compound is the precursor to all higher homologues in the B-race of the alga. Metzger, et al. through feeding studies with sodium \([1,2-14C]\)acetate have firmly
Figure 1.2 The Botryococcenes.
established this pathway. In addition, they found that L-methionine acts as a methyl donor in the methylation process (presumably through S-adenosyl methionine) and that each hydrocarbon is produced from its lower homologue by successive methylation. $^{13}$C NMR spectra of the botryococcenes, produced when the alga was fed L-[Me-$^{13}$C]methionine, indicate that methylation takes place on the C$_{30}$ backbone in positions 3, 7, 16, and 20 (Figure I.2).

The biogenesis of the C$_{30}$ precursor 4 has been postulated to proceed through a tail to tail coupling of two C$_{15}$ units, involving a 1'-3 condensation (Figure I.3). An analogous biogenesis from C$_{5}$ and C$_{10}$ precursors has been proposed for the formation of the irregular terpenoids artemisia ketone (14) and isodigeranyl (15) respectively.

![Figure I.3 Irregular Terpenoid Numbering.](image)
I-B. Discussion and Results

The elucidation of the stereochemistry of botryococcene is important for a number of reasons. First, a rational asymmetric synthesis of 1 requires prior knowledge of the stereochemistry of the six resident chiral centers. This determination should also allow a rigorous proof of the gross structure proposed for 1 by Eglinton et al. through application of spectral methods (vide supra). Second, comparison of the stereochemistry at the methyl-bearing centers will provide some insight into the specificity and mode of action of the unusual methylation system operating in B. braunii. Third, the stereochemical relationship between C-10 and C-13 will afford evidence bearing on the mechanism by which the two farnesyl units are joined and provide information relating to general irregular terpenoid biogenesis. Fourth, the absolute stereochemistry of 1 will facilitate biosynthetic studies on the production of hydrocarbons in B. braunii, possibly leading to higher producing strains and bringing closer its exploitation as a source of combustible fuels.

For designation of chirality at the six stereogenic centers of botryococcene, a degradation plan that allows direct correlation to materials of rigorously defined absolute stereochemistry is preferred over indirect methods. The application of high-field NMR techniques to this task was suggested by cognate $^1$H and $^{13}$C NMR studies of the macrolide antibiotic boromycin (see Appendix). The obvious advantages offered by NMR for this correlation are the small sample sizes which can be routinely handled (~0.5 mg), and the
ability to obtain meaningful results from impure substances. The overall plan for the stereochemical assignment to botryococcene was thus reduced to finding a suitable set of degradation targets which could be prepared in chiral form by unambiguous synthesis and direct comparison of these by $^1$H NMR in the presence of chiral lanthanide shift reagents.

The finding by Eglinton$^{11}$ that botryococcene could be oxidatively cleaved to the C$_{14}$ keto acid 3 (Scheme 1) suggested...
a possible pathway for degradation. Conversion of botryococcene to the known\textsuperscript{10,11} 28,29-dihydro derivative (Scheme 2), followed by oxidative cleavage, would provide the two diketo esters 17 and 18. Baeyer-Villiger oxidation, saponification, and lactonization should give a set of \(\gamma\) - and \(\delta\) - lactones (19-22) containing all of the stereochemical information present in botryococcene. Correlation of these lactones with specimens of known absolute configuration would then establish the complete stereochemistry of botryococcene.

Treatment of botryococcene (1) with diimide selectively reduced the vinyl substituent to afford the dihydro derivative 16\textsuperscript{24} (Scheme 3). Exhaustive ozonolysis of 16 followed by an oxidative workup with Jones’ reagent and treatment with diazomethane, gave the diketo esters 17 and 18 in 38 and 40\% yields respectively, after chromatographic purification. For preparative purposes, higher overall yields of 17 and 18 could be obtained by direct conversion of crude 16.

The migratory preference of methine carbon over methylene carbon in the Baeyer-Villiger reaction is well documented.\textsuperscript{25} Moreover, since the process occurs with retention of configuration at the migrating atom,\textsuperscript{26} we were confident that the stereochemical integrity of 17 and 18 would remain intact during the oxidation. Upon subjection of 17 and 18 independently to Baeyer-Villiger oxidation with \textit{m}-chloroperbenzoic acid, the regio- and stereochemically homogeneous triesters 24 and 25 were obtained in excellent yield (Scheme 4). That the bis-oxidation process had proceeded as expected was evidenced by the observation of only two downfield
signals (~$\delta$4.9) in the $^1$H NMR spectra of 24 and 25 and the absence of detectable diastereomeric impurities by $^{13}$C NMR.

Saponification of 24 followed by acidification, afforded a pair of hydroxy acids which were lactonized by azeotropic removal of water to a 1:1 mixture of $\tau$- and $\delta$-lactones 19 and 20. Similar treatment of 25 yielded 21 and the $\tau$-lactone 22. Although pure samples of $\delta$-lactones 20 and 21 were easily obtained by chromatography, isolation of pure 19 and 22 proved difficult due to their high volatility. The small sample size and impurity of
lactones 19 and 22, however, was not expected to pose difficulties in their stereochemical identification.

The absolute configurations of 19 - 22 were determined by correlation with the optically pure substances synthesized from (S)-(−)-propylene oxide (23).^{27} (S)-4-methylbutyrolactone (27) was prepared by slight modification of a published procedure.^{28} Thus, 23 was reacted with the dilithio dianion of
2-thiophenoxyacetic acid (Scheme 5) and the resultant hydroxy acid lactonized to 26 in refluxing benzene. Reductive cleavage of the \( \alpha \)-thiophenyl group with Raney nickel gave the desired \((S)\)-27.

\[
\begin{align*}
1) & \quad \text{PhSCH}_2\text{CO}_2\text{H, 2 eq.} \\
& \quad \text{LDA, THF, -78°} \\
2) & \quad \text{TsOH, benzene, } \Delta \\
\text{23} & \quad \begin{array}{c}
\text{SPh} \\
\text{O} \\
\text{H}
\end{array} \\
\rightarrow & \quad \begin{array}{c}
\text{O} \\
\text{H} \\
\text{26 (80%)}
\end{array} \\
\text{Raney nickel (W6),} & \quad \text{MeOH, } \Delta \\
\rightarrow & \quad \begin{array}{c}
\text{O} \\
\text{H} \\
\text{27 (78%)}
\end{array}
\end{align*}
\]

Scheme 5

For synthesis of the \( \delta \)-lactones, 23 was reacted with lithium trimethylsilylacetylide (Scheme 6) to afford 28 which was converted to its tetrahydropyranyl ether 29. Removal of the silyl group and carbomethoxylation of the resulting pentyne 30 gave 31. This ester was hydrogenated to the saturated derivative 32, from which the tetrahydropyranyl ether was removed by methanolysis and the crude hydroxy ester 33 lactonized to \((5S)\)-34. The optical rotation of 34, \([\alpha]_D^{25} = -35.5° \) (EtOH), was in agreement with a value of \([\alpha]_D^{20} = -34.3° \) (EtOH) reported by Mori for 34 of an estimated 87.7% ee.

Alkylation of the lithium enolate of 34 with methyl iodide gave a 3:2 mixture of the known \textit{cis}-(35) and \textit{trans}-(36) 2,5-dimethylvalerolactones respectively (Scheme 7). These were separated by preparative gas-liquid chromatography and the major diastereomer 35, which was identical with the lactone 20 obtained by degradation, was assigned \textit{cis} relative stereochemistry by comparison of its \( ^1H \) and \( ^{13}C \) spectra with those reported in the literature. It is noteworthy that 35 has been identified
in nature as the major sex pheromone of the male carpenter bee Xylocopa hirsutissima. The preparation of 35 described herein compares favorably with the numerous published syntheses in both efficiency and optical purity. Alkylation of the mixture of 35 and 36 with ethyl iodide gave the (2R,5S) and (2S,5S) lactones 37 and 38 (3:1) which were separated by HPLC (μPorisil). The major diastereomer 37, was found to correspond with the lactone obtained from botryococcene and was shown to be the Z isomer by an X-ray crystal structure (Figure I.4) of the dicyclohexylamine salt 39, from the derived hydroxy acid (Scheme 8). The X-ray structure determination of 39 was carried out on material...
Scheme 7

derived from racemic 37, due to difficulty in obtaining suitable crystals of 39. Racemic 37 was prepared from racemic 34 by an identical methylation/ethylation sequence to that in Scheme 7.

Scheme 8

A parallel series of transformations to that described above starting from $R$-$(+)$-propylene oxide$^{32}$ provided the enantiomers of 27, 35 and 37.$^{33}$
The absolute configuration of the lactones derived from botryococcene were determined from the $^1$H NMR spectra at 400 MHz of 1:1 mixtures of natural and synthetic lactones in the presence of tris[3-(heptafluoropropylhydroxymethylene)-(+)camphorato]europium(III) (Eu(hfc)$_3$).\textsuperscript{34} Progressive induced shifts of the methyl signals were observed (Figures I.5-8) with increasing Eu(hfc)$_3$ concentration for unmatched lactones. Thus, racemic 35 displayed marked non-equivalence of the $^1$H NMR spectra of the diastereomeric complexes in the presence of Eu(hfc)$_3$ (Figure I.5b). Treatment of 1:1 mixtures of 20 and (2S,5R)-35 (Figure I.5d) or (2R,5S)-35 (Figure I.5c) with Eu(hfc)$_3$ established homochirality of 20 with the latter. The stereochemistry of 21 was determined as (2R,5S) by an analogous procedure.
Figure I.5 Eu(hfc)$_3$ Induced Shift Comparison of 20 with Synthetic Lactones
Figure 1.6 Eu(hfc)$_3$ Induced Shift Comparison of 21 with Synthetic Lactones
Figure 1.7  Eu(hfc)$_3$ Induced Shift Comparison of 19 with Synthetic Lactones
Figure 1.8 Eu(hfc)$_3$ Induced Shift Comparison of 22 with Synthetic Lactones
The isolation of pure samples of butyrolactones 19 and 22 from the degradation was, as mentioned earlier, difficult. Nevertheless, assignment of their absolute stereochemistry was possible directly on the crude mixture of lactones obtained from degradation as shown in Figure I.7 for 19 and Figure I.8 for 22. The non-equivalence of 19 and 22 with (R)-4-methylbutyrolactone (Figures I.7d and I.8d, respectively) allowed the confident designation of S chirality to these remaining centers.

The stereochemistry of lactones 19-22, as secured by correlation with synthetic materials, is depicted in Figure I.9. These results establish the absolute stereochemistry of botryococcene as 3S,7S,10S,13R,16S,20S. It should be noted that the designation of configuration at the C-10 quaternary center of 1 is necessarily reversed from that in 21 due to a priority change when the vinyl substituent replaces ethyl.

An interesting feature of the botryococcene topography is the stereochemistry of the four non-mevalonoid methyl substituents attached to carbons 3, 7, 16, and 20. Each successive methylation from the C30 precursor 4 to botryococcene occurs stereospecifically from the si face of the trisubstituted double bond. This finding reveals an unexpected specificity during the methylation sequence which may provide insight into the biosynthetic process and stereochemistry of other Botryococcus metabolites. The discovery by Casadevall of methylated squalene in B. braunii extracts, a process previously unobserved prior to cyclization to lanosterol, attests to the generality of the methylation mechanism in this organism.
Figure 1.9 The Absolute Configuration of (-)-Botryococcene.

Assuming that the stereochemistry of the two internal chiral centers of botryococcene (C-10 and C-13) remains unchanged during these methylation steps, the C\textsubscript{30} precursor 4 would exhibit the stereochemistry shown in Figure 1.9. This assignment is consistent with a biogenesis proceeding through (1R,2R,3R)-prequalene pyrophosphate (vide infra) and provides the first stereochemical evidence for this pathway in irregular terpene biosynthesis.

In order to ascertain whether there is stereochemical consistency among \textit{B. braunii} B-race metabolites, the C\textsubscript{32} congener 10
of botryococcene, for which we propose the name braunicene, was examined. This monocyclic variant of the botryococcenes was isolated from a laboratory strain of \textit{B. braunii} by C. D. Poulter at the University of Utah and its gross structure was assigned as 10 by application of $^1\text{H}$, $^{13}\text{C}$, and multiquantum 2-D NMR techniques.

![10]

A sample of braunicene, provided by Professor Poulter, was subjected to a degradation protocol (Scheme 9) similar to that used previously for botryococcene. Thus, selective diimide reduction afforded the dihydro derivative 40 which, without purification, was oxidatively cleaved to afford 41 and 42. The expected 1,5-diketone 43 produced by cleavage of the right hand portion of braunicene could not be isolated under the conditions employed.

The most direct route for determination of the three stereogenic centers in keto ester 41 is single-crystal X-ray analysis and, as 41 itself was not crystalline, attempts were made to prepare a suitable derivative. Disappointingly, the reaction of keto acid 44, prepared by saponification of 41 with lithium hydroxide, failed to give a crystalline salt with either (S)-(−)-1-phenylethylamine or brucine. Although an amide could be prepared from 44 and (S)-(−)-1-(1-naphthyl)ethyamine, this likewise failed to crystallize. The small quantity of 44 available from degradation of 10 prevented us from pursuing this approach further and elucidation of the stereochemistry of this segment remains for future research.
The 1,5-diester 42 is a known degradation product of (+)-bakuchiol (Psoralea corylifolia Linn.). Although the reported rotation of (R)-42 ([α]_D^{25} = +9.8°) is consistent with that measured on the sample from degradation of 10 ([α]_D^{25} = +8.5°), a combination of factors make this correlation tenuous. The small amount of 42 obtained in pure form and the low rotation that it exhibits led to a large experimental error in measurement of its optical rotation. Additionally, Dev et al. failed to report the solvent used for their rotation measurement on 42 and, since the solvent dependence of optical rotation values can often be substantial, the apparent concurrence of these measurements could be meaningless.
For comparison of 42 with independently synthesized material, an expedient preparation of both optical antipodes of 42 of rigorously defined absolute configuration was required. The single reported synthesis of (R)-(+)-42 by Dev36 involves eleven steps and an arduous optical resolution, clearly unacceptable for our purposes. After cursory examination of several routes, a remarkably simple access to (R)- and (S)-42 came to light in which the previously prepared diastereomeric lactones 37 and 38 were degraded by means of the haloform reaction. Thus, the reaction of (2R,5S)-37 with basic sodium hypobromite, followed by treatment of the resulting dicarboxylic acid with ethereal diazomethane (Scheme 10), afforded (R)-(+)-42, while (2S,5S)-38 afforded (S)-(-)-42.

\[
\begin{align*}
\text{37} & \xrightarrow{1) Br_2, NaOH, 0^\circ C} \text{MeO}_2\text{C} \quad \text{R} \quad \text{CO}_2\text{Me} \\
& \quad \xrightarrow{2) \text{Na}_2\text{SO}_3; \Delta} \\
& \quad \xrightarrow{3) \text{CH}_2\text{N}_2, \text{Et}_2\text{O}} \\
\text{R-}(+)-42 & \quad \text{(64\%)} \\
\end{align*}
\]

\[
\begin{align*}
\text{38} & \xrightarrow{\text{"}} \text{MeO}_2\text{C} \quad \text{S} \quad \text{CO}_2\text{Me} \\
& \quad \xrightarrow{\text{"}} \\
\text{S-}(+)-42 & \quad \text{(64\%)} \\
\end{align*}
\]

Scheme 10

A probable mechanism for this conversion is presented in Scheme 11. The secondary alcohol 45, produced upon hydrolysis of lactone
Scheme 11

37, is oxidized to 46 by hypobromite\(^{37}\) and this methyl ketone then undergoes a haloform reaction\(^ {38}\) in the presence of excess oxidant. The intermediate tribromoketone 47, after cleavage to 48 and esterification, affords 42.

Examination of the Eu(hfc)\(_3\) shifted \(^{1}\)H NMR spectrum of racemic 42, prepared from racemic 37, showed clear separation of all four major signals (Figure I.10b). Eu(hfc)\(_3\) treatment of 1:1 mixtures of synthetic (R)-\(^{-}\) (Figure I.10c) and (S)-42 (Figure I.10d) with the natural sample, unambiguously defined the absolute configuration of the latter as R.

The designation of R stereochemistry for 42 identifies the configuration of braunicene as S, in agreement with C-10 of
Figure I.10  Eu(hfc)$_3$ Induced Shift Comparison of 42 with Synthetic Diesters.
botryococcene (1). Thus, at least two B. braunii congeners display identical stereogenicity at the quaternary center that arises from the irregular linkage of two farnesyl units. Whether this implies a stereochemical consistency among the B-race metabolites must await the stereochemical identification of other members of the series, including the C₃₀ compound 4.

The stereochemistry of the two internal centers (C-10 and C-13) of the botryococcenes is consistent with a biogenetic pathway proceeding through (1R,2R,3R)-presqualene pyrophosphate, as for normal triterpene biosynthesis, but which deviates from this pathway in the subsequent cyclopropane fragmentation. One proposal for formation of presqualene pyrophosphate⁵¹ᵇ commences with a 1'-2 coupling of two farnesyl pyrophosphate units (Scheme 12) to give an intermediate tertiary carbocation ⁴⁹. Abstraction of the 1' pro-S hydrogen then gives ⁵⁰ which displays R stereochemistry at all three centers of the cyclopropane. A cyclopropylcarbinyl cation rearrangement (path b) gives ⁵² which collapses to allylic carbocation ⁵₃. Hydride delivery from NADPH to the si face of this cation at carbon 3 then affords squalene. In the biosynthesis of botryococcene, an alternative fragmentation of ⁵⁰ (path a) to allylic carbocation ⁵₁ presumably occurs. This pathway has been shown to predominate in in vitro model systems³⁹ and, in the case of ⁵₁, would be terminated by reduction from the si face of the tertiary center to give the C₃₀ compound 4.

Why pathway a should predominate in the B-race of B. braunii is at present unknown. Coates and Robinson⁴⁰ have suggested that, in order for path b to obtain, squalene synthetase must twist the
double bond in 50 so that the interaction between its \( \pi \)-cloud and the neighboring cyclopropane ring is minimized, thereby introducing a substantial barrier for the cyclopropylcarbinyl to allyl rearrangement. The active site of the enzyme responsible for conversion of presqualene pyrophosphate in \( B. \) braunii possibly exerts less steric constraint on the substrate and thus allows this rearrangement to occur.
Speculation on the evolutionary advantages afforded the alga by the production of such quantities of energetically costly metabolites is intriguing. As their density is less than that of water, the hydrocarbons give the algal colonies a buoyancy and allow greater access to sunlight, important to photosynthetic organisms growing in brackish waters. Additionally, the oil content may impart a bad taste to the alga inhibiting predation by other organisms.

Clearly much work remains to be done to elucidate the individual biosynthetic steps leading to the botryococcenes. Stereochemical information of the type gathered in this research should lead to a better understanding of triterpene biosynthesis and may contribute to clarification of the unusual morphology of Botryococcus braunii.
I-C. Experimental

General

Solvents were dried by distillation shortly before use from an appropriate drying agent. Tetrahydrofuran, ether, benzene, and toluene were distilled from sodium benzophenone ketyl under argon. Methylene chloride, dimethyl sulfoxide, pyridine, diisopropylamine, and other amines were distilled from calcium hydride under argon. All solvents for routine chromatography and reaction workup were reagent grade and distilled through glass prior to use. Unless otherwise noted, starting materials were obtained from commercial suppliers and used without further purification. Brine refers to a saturated aqueous solution of sodium chloride.

For isolation of reaction products, solvents were removed at water aspirator pressure by rotary evaporation and the residual solvent removed by vacuum pump at less than 0.5 Torr. Flasks and syringes were oven dried at 165 °C overnight and cooled in a desiccator over anhydrous calcium sulfate prior to use. Alternatively, flasks were flame-dried under a stream of argon.

Analytical thin layer chromatography (TLC) was done on 2.5 x 7.0 cm precoated TLC plates (silica gel 60 F-254, layer thickness 0.2 mm) manufactured by E. Merck. Flash chromatography was carried out with E. Merck silica gel 60 (230-400 mesh ASTM). High pressure liquid chromatography (HPLC) was performed with a Waters M-45 solvent delivery system equipped with two Waters semi-preparative silica columns and a refractive index detector. Gas-liquid
chromatography (GC) was conducted with a Varian Aerograph 2700 with constant oven temperature and helium as carrier gas.

Melting points were measured on a Büchi melting point apparatus and are uncorrected. Infrared spectra (IR) were recorded on either a Perkin-Elmer 727B or a Nicolet 5DXB FT-IR spectrometer. Optical rotations were measured in 1 decimeter cells (1 mL capacity) on a Perkin-Elmer model 243 polarimeter at ambient temperature. Coffee was prepared via aqueous extraction on either a Mr. Coffee MCS-1212 or Braun 4062 and consumed without further dilution. Nuclear magnetic resonance spectra (NMR) were recorded on either an IBM NR-80F or a Bruker AM-400 spectrometer. Carbon NMR spectra were measured on a Bruker AM-400 spectrometer. Chemical shifts are reported downfield from internal tetramethylsilane on the $\delta$ scale. $^1$H NMR data are tabulated in order: number of protons, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad), and coupling constant in Hertz. Mass spectra (MS) were obtained with either a Varian MAT CH-7 or a Finnigan 4500 spectrometer at an ionization potential of 70 eV. High resolution mass spectra were determined on a Kratos MS-50. Elemental analyses were performed by MicAnal, Tucson, Arizona.

Molecular mechanics calculations were performed using MODEL version KS 2.9 and MMX version 87 available from Serena Software, c/o Kosta Steliou, University of Montreal, and were run on a VAX 11-750.

28,29-Dihydrobotryococcene (16)

Botryococcene (1) (332 mg, 0.712 mmol) was dissolved in 25 mL of isopropanol, 75 mL of ethanol, and 0.5 mL of a 1.0 $\times$ 10$^{-3}$ M
aqueous copper(II) acetate solution. The mixture was cooled in an ice bath and flushed with nitrogen. A 3 mL aliquot of a solution of 9.16 mL of 30% hydrogen peroxide (89.7 mmol total) in 21 mL of ethanol was added, followed by 200 μL (42.7 mmol total) of 85% hydrazine hydrate. Addition was repeated every 10 min until the total hydrogen peroxide solution had been transferred. After 20 min, the mixture was concentrated in vacuo and water and pentane were added. The organic phase was separated and the aqueous layer was washed twice with pentane. The combined organics were washed with brine and dried over magnesium sulfate. Concentration afforded 354 mg of a light yellow oil that was chromatographed on 35 g of silica gel 60 (230-400 mesh) containing 17% by weight of silver nitrate. Pure 16 (136 mg, 41%) was eluted with ethyl acetate-hexanes (1:3): $^1\text{H} \text{NMR}$ (400 MHz, CDCl$_3$) $\delta$ 5.13 (1H, d, J=15.8), 5.03 (1H, dd, J=15.8, 7.7), 4.69 (8H, bs), 2.2-1.8 (9H, m), 1.66 (6H, s), 1.6-1.1 (14H, m), 1.02 (6H, d, J=6.8), 0.98 (6H, d, J=6.8), 0.94 (3H, d, J=6.7), 0.86 (3H, s), 0.74 (3H, t, J=7.4); $^{13}\text{C} \text{NMR}$ (100 MHz, CDCl$_3$) $\delta$ 155.04, 154.98, 150.02, 150.02, 137.08, 133.43, 109.49, 109.48, 107.14, 107.13, 41.02, 41.00, 40.65, 40.12, 38.73, 38.33, 37.51, 35.16, 33.62, 33.47, 33.40, 33.34, 31.64, 31.64, 29.92, 22.74, 21.51, 20.48, 20.26, 19.79, 19.76, 18.92, 18.89, 8.45.

Methyl (2R,5S,9S)-2,5,9-trimethyl-6,10-dioxoundecanoate (17) and Methyl (2R,5S,9S)-2-ethyl-2,5,9-trimethyl-6,10-dioxoundecanoate (18)

Dihydrobotryococcene (16) (136 mg, 0.290 mmol) was dissolved in 10 mL of methylene chloride, 2 mL of methanol, and 2 mL of ethyl acetate and the solution was cooled to -78 °C. Ozone was passed
through the solution for 15 min and an additional 3 mL of methanol was added. The ozone flow was interrupted, the blue solution was stirred for 30 min and then flushed with nitrogen and warmed to room temperature. The solvent was removed in vacuo and the resultant colorless oil was dissolved in acetone and treated with an excess of Jones' reagent at 0 °C. After 30 min, isopropanol was added and the mixture was filtered through a pad of Celite. Concentration of the solution gave a light yellow oil that was redissolved in ether and treated with excess ethereal diazomethane at room temperature. Evaporation of the solvent and chromatography (25 g of silica gel 60, ethyl acetate-hexanes 1:3) afforded 30.6 mg (35%) of 18 and 48.5 mg of slightly impure 17. The sample of 17 was subjected to preparative HPLC (υPorisil, ethyl acetate-hexanes 1:4) giving 27.5 mg (35%) of pure 17: [α]$_D^{25}$ = -1.09° (c=1.37, CHCl$_3$); IR (neat) 2950, 1735, 1715, 1710, 1460 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.67 (3H, s), 2.35-2.60 (5H, m), 2.16 (3H, s), 1.92 (1H, m), 1.65 (2H, m), 1.30 (2H, m), 1.15 (3H, d, J=7.0), 1.11 (3H, d, J=7.2), 1.06 (3H, d, J=7.1); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 213.66, 212.14, 176.87, 51.57, 46.19, 46.19, 39.49, 38.31, 31.34, 30.46, 28.03, 26.19, 17.22, 16.43, 16.34; MS m/z 270(M$^+$), 239, 171, 156, 143, 139, 127, 111, 99; Calcd for C$_{15}$H$_{26}$O$_4$: 270.1831. Found: 270.1829.

18: [α]$_D^{25}$ = +10.6° (c=0.38, CHCl$_3$); IR (neat) 2975, 1735, 1720, 1715, 1470 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.66 (3H, s), 2.38-2.60 (4H, m), 2.15 (3H, s), 1.92 (1H, m), 1.70-1.22 (7H, m), 1.11 (3H, d, J=7.2), 1.10 (3H, s), 1.05 (3H, d, J=7.1), 0.80 (3H, t, J=7.5); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 213.75, 212.17, 177.61, 51.57, 46.61, 46.23, 46.22, 38.27, 36.18, 32.04, 28.04, 27.82, 26.19, 20.60,
16.58, 16.36, 8.89; MS m/z 298 (M⁺), 171, 156, 139, 127, 111, 99;

Methyl [2R,5S(S)]-5-[[4-(acetoxy)-1-oxopentyl]oxy]-2-methylhexanoate (24)

To a suspension of 82.0 mg (0.380 mmol, 80-85% tech.) of m-chloroperbenzoic acid and 53.6 mg (0.638 mmol) of sodium bicarbonate in 3 mL of dry methylene chloride was added 27.9 mg (0.103 mmol) of 17. The mixture was magnetically stirred at ambient temperature for 5 days, then warmed in a 40 °C oil bath for 3 days. The reaction mixture was diluted with methylene chloride and washed with 10% aqueous sodium sulfite, water, and brine. Concentration gave a colorless oil that was chromatographed (3 g silica gel 60, ethyl acetate-hexanes 1:5) affording 20.1 mg (64%) of pure triester 24: [α]D²⁵ = -4.30° (c=0.54, CHCl₃); IR (neat) 2975, 2940, 1730 (broad), 1375, 1240 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.92 (2H, m), 3.68 (3H, s), 2.20-2.40 (3H, m), 2.03 (3H, s), 1.93-1.44 (6H, m), 1.24 (3H, d, J=6.1), 1.21 (3H, d, J=6.4), 1.16 (3H, d, J=7.2); ¹³C NMR (100 MHz, CDCl₃) δ 176.85, 172.58, 170.60, 70.85, 70.03, 51.59, 39.27, 33.50, 30.93, 30.67, 30.64, 29.46, 21.27, 19.91, 17.14; MS (CI, CH₄) 303 (M+1), 243, 227, 195, 161, 143, 129, 117, 101.

Methyl [2R,5S(S)]-5-[[4-(acetoxy)-1-oxopentyl]oxy]-2-ethyl-2-methylhexanoate (25)

To a suspension of m-chloroperbenzoic acid (60.0 mg, 0.279 mmol, 80-85% tech.) and sodium bicarbonate (40.0 mg, 0.477 mmol) in 3 mL of dry methylene chloride was added 23.7 mg (79.5 µmol) of
diketoester 18. This was stirred at room temperature for 5 days and an excess of m-chloroperbenzoic acid (34 mg, 0.159 mmol) and sodium bicarbonate (26.7 mg, 0.318 mmol) were added. The mixture was heated at reflux for 24 h, then diluted with methylene chloride and washed successively with 10% aqueous sodium sulfite, water, and brine. The solution was dried over magnesium sulfate, concentrated and chromatographed (6 g silica gel 60, ethyl acetate-hexanes 1:5) to afford 21.9 mg (83%) of pure triester 25: $[\alpha]_D^{25} = +5.4^\circ$ (c=1.08, CHCl$_3$); IR (neat) 2975, 2925, 1730 (broad), 1460, 1370, 1240 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.92 (1H, m), 4.84 (1H, m), 3.66 (3H, s), 2.32 (2H, m), 2.03 (3H, s), 1.90-1.25 (8H, m), 1.24 (3H, d, J=6.2), 1.20 (3H, d, J=6.3), 1.11 (3H, s), 0.81 (3H, t, J=7.5); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 177.59, 172.59, 170.61, 71.29, 70.07, 51.59, 46.00, 34.29, 32.00, 31.00, 30.95, 30.71, 21.28, 20.69, 19.92, 19.90, 8.90; MS m/z 205, 187, 171, 143, 116, 111, 101, 87.

4-Methyl-β-butyrolactone (19) and 2,5-Dimethyl-6-valerolactone (20) from 17

A solution of 11.0 mg of 24 (36.4 µmol), 1 mL of tetrahydrofuran, and 1 mL of 2.5 N potassium hydroxide, was stirred at room temperature for 18 h and then acidified with 1 M hydrochloric acid. Solid sodium chloride was added and the saturated solution continuously extracted with ether for 24 h, dried over magnesium sulfate, and concentrated. Dry benzene was added and the flask was fitted with a reflux condenser and dropping funnel containing 4 Å molecular sieves. The mixture was heated at reflux for 4 h and concentrated to afford 7.4 mg of a mixture of 24 and lactones 20 and 19.
(0.5:0.7:1). Chromatography (3 g silica gel 60, ether-pentane 1:1) afforded 1.1 mg of pure 20.

In another experiment, a more vigorous saponification of 24 (8 h at 70 °C) gave 80% of a 1:1 mixture of lactones 20 and 19.

2-Ethyl-2,5-dimethyl-δ-valerolactone (21) and 4-Methyl-γ-butyrolactone (22) from 18

A solution of 25 (8.3 mg, 25.1 μmol) in 1 mL of tetrahydrofuran and 1 mL of 2.5 N potassium hydroxide was heated in a 70 °C oil bath for 12 h then acidified with 3.0 M hydrochloric acid. Solid sodium chloride was added and the saturated solution continuously extracted with ether for 20 h, dried over magnesium sulfate, and concentrated. 20 mL of dry benzene was added and the flask fitted with a dropping funnel containing 4 Å molecular sieves topped with a reflux condenser. The apparatus was purged with argon and heated to reflux for 2.5 h. Concentration afforded 5.5 mg (86%) of a 1:1 mixture of lactones 21 and 22.

Determination of the Stereochemistry of Lactones 19-22

The comparison of the degradation lactones 19-22 with synthetic lactones 27, 35, and 37 was carried out as follows. A solution of the degradation and synthetic lactones (1-2 mg) in 0.5 mL of CDCl₃ was treated portionwise with increasing amounts of Eu(hfc)₃ and the 400 MHz ¹H NMR spectra recorded. This procedure was then repeated using the enantiomeric synthetic lactone. Increasing induced shifts of the methyl signals were observed for optically unmatched lactones in each case. The stereochemical
identity of 19 and 22 was thus determined as S. Lactones 20 and 21 were likewise shown to be homochiral with (2R,5S)-35 and (2R,5S)-37 respectively.

(S)-5-(Trimethylsilyl)-4-pentyne-2-ol (28)

To a solution of 4.17 g (43.0 mmol) of trimethylsilylacetylene in 50 mL of dry tetrahydrofuran at -78 °C was added dropwise 29.0 mL (44.0 mmol) of a 1.5 M solution of n-butyllithium in hexanes. After 5 min, 4 mL of freshly distilled hexamethylphosphoramide was added, followed by 3.2 mL (46.0 mmol) of (S)-propylene oxide (23). The mixture was allowed to warm to 0 °C over 6 h, then stirred at ambient temperature for 10 h. After addition of 10 mL of water, the product was extracted with ether and dried over magnesium sulfate. Concentration of the solution and chromatography (ethyl acetate-hexanes 1:3) gave 5.52 g of pure (S)-28 as a colorless oil: [α]_D^{23} = +13.5° (c=3.0, CHCl₃); IR (neat) 3400, 2950, 3170, 1250, 1120 cm⁻¹; ^1H NMR (400 MHz, CDCl₃) δ 3.93 (1H, m), 2.65 (1H, m), 2.65 (1H, bs), 2.39 (2H, d, J=6.6), 1.25 (3H, d, J=6.0), 0.16 (9H, s); ^13C NMR (100 MHz, CDCl₃) δ 103.41, 87.25, 66.25, 30.40, 22.22, 0.08; Calcd for C₈H₁₆O₄Si: C, 61.48; H, 10.32. Found: C, 61.21; H, 10.41.

(S)-5-(Trimethylsilyl)-2-[(tetrahydro-2H-pyran-2-yl)oxy]-4-pentyne (29)

To a solution of 2.99 g (19.1 mmol) of (S)-28 in 50 mL of dry methylene chloride was added 4.0 mL (3.70 g, 44.0 mmol) of dihydropyran and 73 mg (2 mol%) of p-toluenesulfonic acid. The mixture was stirred at room temperature for 3 h and then transferred to a
separatory funnel, diluted with ether, and washed with saturated sodium bicarbonate, water, brine, and dried over sodium sulfate. Concentration of the solution gave 4.70 g of a pale yellow oil that, after chromatography (75 g of silica gel 60, ethyl acetate-hexanes 1:7), afforded 4.12 g (90%) of (S)-29 as a 1:1 mixture of diastereomers: IR (neat) 2950, 2175, 1250, 1025, 840 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 4.78 (2H, m), 3.93 (4H, m), 3.49 (2H, m), 2.66-2.25 (4H, m), 1.93-1.45 (12H, m), 1.30 (3H, d, J=6.2), 1.22 (3H, d, J=6.2), 0.14 (18H, s); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 104.32, 103.97, 98.04, 95.90, 85.80, 85.68, 71.39, 70.31, 62.45, 61.75, 30.76, 30.71, 28.43, 27.40, 25.38, 25.32, 21.18, 19.64, 19.08, 18.76, -0.12, -0.14; MS m/z 240 (M\(^+\)), 224, 210, 180, 172, 168, 166, 158, 138, 128; Calcd for C\(_{13}\)H\(_{24}\)O\(_2\)Si: 240.1546. Found: 240.1557.

(S)-2-[(Tetrahydro-2H-pyran-2-yl)oxy]-4-pentyne (30)

Tetra-n-butylammonium fluoride (25.0 mL of a 1.0 M solution in tetrahydrofuran, 25.0 mmol) was added via syringe to a solution of (S)-29 (4.01 g, 16.7 mmol) in 30 mL of dry tetrahydrofuran. After 1 h at ambient temperature, 100 mL of water was added, followed by 200 mL of ether. The organic phase was separated and washed with 100 mL of water and 100 mL of brine. The combined aqueous phase was extracted with ether and the combined organic solution was dried over magnesium sulfate. Concentration of the solution and chromatography (75 g of silica gel 60, ethyl acetate-hexanes 1:7) afforded 2.20 g (78%) of pure (S)-30: IR (neat) 2942, 2121, 1201, 1033, 998, 869, 670 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 4.75 (2H, m),
Methyl (S)-5-[(Tetrahydro-2H-pyran-2-yl)oxy]hexynoate (31)

To a flame-dried three-neck flask fitted with an argon inlet and thermometer adapter was added 2.17 g (12.9 mmol) of (S)-30 and 20 mL of dry tetrahydrofuran. The stirred solution was cooled to -78 °C and 10.1 mL (1.6 M in hexanes, 16.1 mmol) of n-butyllithium was added dropwise while maintaining the temperature below -60 °C. After 10 min, 6.0 mL of freshly distilled methyl chloroformate (7.31 g, 77.4 mmol) was added rapidly (the temperature initially rose to -20 °C and then fell to -70 °C). The solution was stirred for 1 h at -70 °C, allowed to slowly warm to room temperature over 2 h, and then stirred for an additional 1.5 h. Water (50 mL) was added and the mixture was transferred to a separatory funnel and diluted with 100 mL of ether. The organic phase was separated and washed successively with water, brine, and dried over magnesium sulfate. Concentration of the solution and chromatography (70 g of silica gel 60, ethyl acetate-hexanes 1:6) afforded 2.70 g (92%) of pure (S)-31 as a light yellow oil: IR (neat) 2950, 2230, 1715, 1430, 1250, 1060, 980, 740 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.73 (2H, m), 4.03-3.84 (4H, m), 3.76 (6H, s), 2.77-2.42 (4H, m), 1.91-1.45 (12H, m), 1.34 (3H, d, J=6.2), 1.26 (3H, d, J=6.2); ¹³C NMR (100 MHz,
Methyl (S)-5-[(tetrahydro-2H-pyran-2-yl)oxyl]hexanoate (32)

To a solution of 2.63 g (11.6 mmol) of (S)-31 in 100 mL of ethyl acetate was added 260 mg of 10% palladium on carbon and the flask was attached to a hydrogenation apparatus. After 3 h under 1 atmosphere of hydrogen, uptake had ceased and the solution was filtered through a pad of Celite. Concentration of the filtrate afforded 2.59 g (97%) of pure (S)-32: IR (neat) 2950, 1740, 1440, 1245, 1165, 1020, 860 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.70 (1H, m), 4.63 (1H, m), 3.97-3.68 (4H, m), 3.67 (6H, s), 3.48 (2H, m), 2.32 (4H, m), 1.93-1.40 (20H, m), 1.23 (3H, d, J=6.2), 1.12 (3H, d, J=6.2); ¹³C NMR (100 MHz, CDCl₃) δ 174.14, 174.02, 98.85, 95.65, 73.69, 70.56, 62.83, 62.54, 51.48, 51.44, 36.83, 35.94, 34.09, 34.03, 31.22, 31.20, 25.57, 25.52, 21.58, 21.31, 20.94, 20.06, 19.79, 19.09; MS m/z 231 (M+1), 186, 168, 157, 154, 147, 145, 130, 101, 85; Exact mass calcd for C₇H₁₃O₃ (M-THP): 145.0865. Found: 145.0865.

(S)-5-Methyl-8-valerolactone (34)

p-Toluenesulfonic acid (87 mg, 0.458 mmol) was added to a solution of 530 mg (2.29 mmol) of (S)-32 in 40 mL of dry methanol in a flame dried flask under argon and stirred in a 40 °C oil bath for 1.5 h. Anhydrous potassium carbonate (95 mg, 0.687 mmol) was added
followed, after 10 min, by dry benzene and the methanol was removed azeotropically by repeated addition of benzene and partial concentration of the solution in vacuo. The benzene solution was then concentrated to 15 mL and the flask was fitted with a dropping funnel containing 4 Å molecular sieves and a reflux condenser. The apparatus was flushed with argon and 45 mL of benzene was added followed by 131 mg (0.687 mmol) of p-toluenesulfonic acid. The mixture was heated at reflux for 2 h, cooled to room temperature and diluted with 40 mL of water and 40 mL of ether. The organic layer was separated and the aqueous layer was washed with two 20 mL portions of ether. The combined organics were washed with brine, dried over magnesium sulfate, and concentrated to give 226 mg of a pale yellow oil. Chromatography of this oil (20 g of silica gel 60, ethyl acetate-hexanes 1:1) afforded 203 mg (78%) of pure (S)-34: $\left[\alpha\right]_{D}^{22} = -35.5^\circ$ (c=1.5, ethanol); Lit.29 $\left[\alpha\right]_{D}^{20} = -34.30$ (c=2.1, ethanol); IR (neat) 2950, 1730, 1240, 1060 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.45 (1H, m), 2.62-2.40 (2H, m), 1.97-1.80 (3H, m), 1.53 (1H, m), 1.38 (3H, d, J=6.1); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 171.88, 76.94, 29.56, 29.21, 21.69, 18.52; MS m/z 114 (M$^+$), 99, 88, 70, 60, 55.

(2R,5S)-2,5-Dimethyl-$\delta$-valerolactone (35) and (2S,5S)-2,5-Dimethyl-$\delta$-valerolactone (36)

To a flame-dried flask, equipped with an argon inlet and thermometer adapter, was added 9 mL of dry tetrahydrofuran and 685 µL (495 mg, 4.89 mmol) of freshly distilled diisopropylamine. The solution was cooled to 0 °C and 3.05 mL (1.6 M in hexanes, 4.89 mmol) of n-butyllithium was added dropwise via syringe. After 1 h the solution
was cooled to -78 °C, (S)-34 (507 mg, 4.44 mmol) in 2 mL of tetrahydrofuran was added dropwise and the mixture was stirred at -78 °C for 30 min. Hexamethylphosphoramide (928 μL, 956 mg, 5.33 mmol) was added, followed by 304 μL (694 mg, 4.89 mmol) of methyl iodide in 2 mL of tetrahydrofuran. The reaction was warmed to -40 °C for 3 h then allowed to warm to room temperature overnight. Saturated aqueous ammonium chloride was added dropwise until the mixture was neutral to litmus, then ether was added and the organic phase was separated. Following saturation of the aqueous layer with sodium chloride and extraction with ethyl acetate, the combined organic solutions were dried over magnesium sulfate and concentrated. The resultant 1.10 g of dark oil was chromatographed (60 g of silica gel 60, ether-pentane 1:1) to afford 424 mg (74%) of lactones 35 and 36 as a 3:2 mixture of diastereomers. Preparative gas-liquid chromatography (3/8"x16' Carbowax 20M on Chromosorb P, 155 °C, 50 mg injections) was used to separate these lactones:

35: Mp (hexanes) 51.0-51.5 °C; [α]_D^{25} = -95.2° (c=1.5, CHCl₃), IR (KBr) 2975, 2940, 2875, 1730, 1460, 1380, 1220, 1200, 1085, 960 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.48 (1H, m), 2.60 (1H, m), 2.08 (1H, m), 1.94 (1H, m), 1.80-1.47 (2H, m), 1.36 (3H, d, J=6.0), 1.22 (3H, d, J=6.7); ¹³C NMR (100 MHz, CDCl₃) δ 176.32, 74.44, 32.97, 28.42, 25.61, 21.11, 16.22; MS m/z 128 (M⁺), 113, 85, 84, 69, 57, 56, 55, 53; Exact mass calcd for C₇H₁₂O₂: 128.0837. Found: 128.0841.

36: Mp (hexanes) 75.0-75.5 °C; [α]_D^{28} = -13.2° (c=1.2, CHCl₃), IR (KBr) 2975, 2940, 2875, 1715, 1250, 1190, 1090 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.45 (1H, m), 2.43 (1H, m), 2.07-1.92 (2H, m), 1.59 (2H, m), 1.37 (3H, d, J=6.1), 1.31 (3H, d, J=6.9); ¹³C NMR
(100 MHz, CDCl₃) δ 174.45, 78.24, 35.79, 31.02, 28.55, 22.18, 17.36; MS m/z 128 (M⁺) 113, 85, 84, 69, 67, 57, 56, 55, 53; Exact mass calcd for C₇H₁₂O₂: 128.0837. Found: 128.0841.

(2R,55)-2-Ethyl-2,5-dimethyl-5-valerolactone (37) and (2S,5S)-2-Ethyl-2,5-dimethyl-5-valerolactone (38)

Lithium diisopropylamide in tetrahydrofuran was prepared by addition of 1.25 mL (1.94 mmol, 1.44 M in hexanes) of n-butyllithium to a solution of 0.272 mL (196 mg, 1.94 mmol) of freshly distilled diisopropylamine in 1.5 mL of dry tetrahydrofuran at 0 °C. Upon cooling to -78 °C, 207 mg (1.62 mmol) of a mixture of (S)-35 and 36 in 1.5 mL of tetrahydrofuran was added dropwise. After 30 min, a solution of 0.188 mL (328 mg, 2.10 mmol) of ethyl iodide and 0.394 mL (405 mg, 2.26 mmol) of hexamethylphosphoramide in 1 mL of tetrahydrofuran was added, the reaction was warmed to -40 °C for 3 h, and then kept at room temperature overnight. The mixture was neutralized with saturated ammonium chloride and diluted with ether. The organic phase was separated and the aqueous layer extracted with three portions of ethyl acetate. The combined organics were dried over magnesium sulfate, concentrated, and chromatographed (10 g of silica gel 60, ethyl acetate-hexanes 1:5) to afford 139 mg (54%) of 37 and 38 as a 3:1 mixture of diastereomers that were separated by HPLC (µPorisil, ethyl acetate-hexanes 1:5):

37: [α]D²⁵ = -30.7° (c=1.7, CHCl₃); IR (neat) 2970, 2930, 1720, 1460, 1390, 1120 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.48 (1H, m), 1.92-1.55 (6H, m), 1.37 (3H, d, J=6.5), 1.24 (3H, s), 0.91 (3H, t, J=7.4); ¹³C NMR (100 MHz, CDCl₃) δ 177.20, 77.52, 41.25, 32.35,

38: [α]<sup>25</sup><sub>D</sub> = +9.1° (c=0.73, CHCl<sub>3</sub>); IR (neat) 2970, 2930, 1720, 1460, 1380, 1125 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 4.39 (1H, m), 1.93-1.44 (6H, m), 1.37 (3H, d, J=6.1), 1.26 (3H, s), 0.90 (3H, t, J=7.4); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 177.08, 77.74, 41.99, 33.21, 30.83, 28.02, 26.64, 22.14, 8.74; MS m/z 156 (M<sup>+</sup>), 143, 129, 128, 95, 84, 83, 71, 70, 55. Anal. calcd for C<sub>9</sub>H<sub>16</sub>O<sub>2</sub>: C, 69.19; H, 10.32. Found: C, 69.36; H, 10.50.

(2RS,2SR)-2-Ethyl-5-hydroxy-2-methylhexanoate (39)

A solution of 8.6 mg (55.0 μmol) of (±)-37 in 1 mL of tetrahydrofuran and 2 mL of 2.5 M potassium hydroxide was stirred at room temperature overnight and then acidified with 3.0 M hydrochloric acid. The aqueous mixture was extracted with three portions of ether-ethyl acetate (1:1) and the combined organics were washed with brine and dried over magnesium sulfate. Concentration of the solution gave a colorless oil that was redissolved in ethyl acetate and treated with 16 μL (15 mg, 82.5 μmol) of dicyclohexylamine. The solution was allowed to stand at room temperature with slow evaporation of the solvent. The colorless crystals (prisms) obtained were washed with ether and dried in vacuo: Mp (hexanes-methylene chloride) 108-109 °C; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 3.73 (1H, m), 2.97 (2H, m), 2.07-1.15 (26H, m), 1.15 (3H, d, J=6.1), 1.08 (3H, s), 0.86 (3H, t, J=7.4); MS (FAB) m/z (+ion): 356 (DCA M+1), 182, 157, 93, 56, 55, (-ion): 173 (M<sup>-</sup>), 91, 89, 71, 60.
Compound \(39, (\pm)-C_{21}H_{41}O_3N\), crystallized in space group P1 with 
\(a = 9.698(2)\ \text{Å},\ b = 11.001(2)\ \text{Å},\ c = 11.074(4)\ \text{Å},\ \alpha = 71.61(2)^\circ,\ \beta = 104.21(2)^\circ,\ \gamma = 95.43(2)^\circ,\ V = 1086\ \text{Å}^3,\ Z = 2,\ \rho_{\text{calc}} = 1.09\ \text{g/cm}^3,\) and \(\rho_{\text{obsd}} = 1.08\ \text{g/cm}^3.\) All nonequivalent reflections in the range \(3^\circ < \theta < 42^\circ\) were measured by the 0-2\(\theta\) technique on a Syntex P1 diffractometer with graphite-monochromated MoK\(\alpha\) radiation. At the present stage of refinement, a total of 1680 independent reflections having \(F^2 > 3\sigma(F^2)\) has afforded \(R = 10.2\%\) and \(R_w = 12.8\%\).

**Braunicene (10)**

This hydrocarbon, provided by Professor C.D. Poulter, showed the following spectral properties: \(^1\text{H NMR (400 MHz, CDCl}_3\) & 5.79 (1H, dd, \(J=17.2,19.9\)), 5.32 (1H, d, \(J=15.7\)), 5.16 (1H, dd, \(J=15.7,7.9\)), 5.09 (1H, bt, \(J=7.1\)), 4.95 (1H, dd, \(J=10.9,1.5\)), 4.93 (1H, dd, \(J=17.2,1.5\)), 4.67 (2H, bs), 4.67 (1H, bs), 4.51 (1H, bs), 1.65 (3H, t, \(J=1\)), 1.56 (3H, bs), 1.07 (3H, s), 1.00 (3H, d, \(J=6.9\)), 0.94 (3H, d, \(J=6.7\)), 0.86 (3H, s), 0.77 (3H, d, \(J=6.8\)), 0.73 (3H, s); \(^{13}\text{C NMR (100 MHz, CDCl}_3\) & 150.07, 149.64, 146.83, 135.46, 134.92, 134.27, 124.65, 111.08, 109.41, 109.16, 56.66, 42.01, 41.40, 40.76, 37.41, 37.39, 36.81, 35.83, 34.77, 33.37, 32.11, 30.97, 26.88, 24.04, 23.59, 23.14, 21.67, 21.01, 19.71, 18.95, 15.93, 15.82.

**27,28-Dihydrobraunicene (40)**

To a solution of 46.7 mg (0.106 mmol) of braunicene (10) in 3 mL of isopropanol and 6 mL of ethanol at 0 °C was added 3 drops of
a 1.0 \times 10^{-3} \text{ M aqueous solution of copper(II) acetate. To this mixture was added in several batches at 10 min intervals 0.50 mL of a solution of 1.36 mL (13.4 mmol total) of 30\% hydrogen peroxide in 3.6 mL of ethanol, followed by 30 \mu L (6.36 mmol total) of hydrazine hydrate. After the addition was complete, the mixture was warmed to ambient temperature and concentrated. The product was partitioned between water and pentane, the organic phase was washed with brine and was dried over magnesium sulfate. Concentration of the solution gave 41.1 mg of a colorless viscous oil that was used without further purification. The 400 MHz $^1$H NMR spectrum of 40 indicated that complete reduction of the vinyl group had taken place.

Methyl 2-Methyl-4-(1-oxo-3,3,4-trimethylcyclohexan-2-yl)butanoate (41) and Dimethyl (R)-2-Ethyl-2-methylglutarate (42).

Crude dihydrobraunicene (40) was dissolved in 7 mL of methylene chloride-ethyl acetate-methanol (5:1:1) and cooled to -78 °C. Ozone was passed through the solution until a blue color persisted. An additional 2 mL of methanol was added and, after 10 min, the excess ozone was removed with a stream of argon and the mixture warmed to ambient temperature and concentrated. The resultant oil was dissolved in acetone and treated with excess Jones’ reagent at 0 °C for 30 min, then quenched with isopropanol, filtered through Celite, and the filtrate concentrated. Treatment of the residue with excess ethereal diazomethane for 4 h, followed by concentration of the solution, gave 42.7 mg of a light yellow oil. Chromatography of this oil (5 g of silica 60, ethyl acetate-hexanes 1:10 → 1:1) gave 22.3 mg of a 1:1 mixture of 41 and 42. HPLC separation (uPorisil, ethyl
acetate-hexanes 1:5) of this mixture gave 10.4 mg (39%) of 41 and 6.04 mg (34%) of 42. The diester 42 ([α]D^25 = +8.5, c=0.3, CHCl₃) was shown to be identical with synthetic (R)-42 by 400 MHz ¹H and 100 MHz ¹³C NMR, IR, MS, and Eu(hfc)₃ shifted 400 MHz ¹H NMR spectra.

41: [α]D^23 = -21.3° (c=0.48, CHCl₃); IR (neat) 2968, 2878, 1735, 1708, 1198, 1163 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.67 (3H, s), 2.5-2.2 (3H, m), 2.02 (1H, m), 1.93-1.80 (2H, m), 1.14 (3H, d, J=7.4), 0.97 (3H, d, J=6.8), 0.89 (3H, s), 0.83 (3H, s); ¹³C NMR (100 MHz, CDCl₃) δ 214.73, 176.90, 60.81, 51.53, 40.20, 39.48, 37.85, 35.82, 32.15, 30.69, 25.72, 23.50, 22.99, 16.92, 14.94.

(S)- and (R)-Dimethyl 2-Ethyl-2-methylglutarate (42)

To a stirred solution of 385 mg (9.60 mmol) of sodium hydroxide in 2.5 mL of water and 3.5 mL of dioxane at 0 °C was added 165 µL (511 mg, 3.20 mmol) of bromine, dropwise. After 10 min, a solution of 50.0 mg (0.320 mmol) of 37 in 1.5 mL of dioxane was added and the solution maintained at 0 °C for 15 h. The mixture was warmed to room temperature, quenched with 10% aqueous sodium sulfite, and heated to 100 °C for 25 min. The cooled solution was acidified to pH 2 with 3 M hydrochloric acid and extracted with 4 portions of ethyl acetate. Concentration of the dried solution (sodium sulfate) gave a diacid which was dissolved in ether and treated with excess diazomethane for 10 h. Chromatography of the concentrate (13 g of silica 60, ethyl acetate-hexanes 1:5) gave 41.4 mg (64%) of pure (R)-(-)-42 as a colorless oil: [α]D^23 = +7.5° (c=2.07, CHCl₃) Lit. ³⁶ [α]D^25 = +9.8°. Similar treatment of 33.0 mg of 38 gave 27.5 mg (64%) of pure S-(-)-42: [α]D^23 = -7.3° (c=1.38, CHCl₃); IR (neat) 2972, 1730,
1242, 1175 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \& 3.67 (6H, s), 2.28 (2H, m), 2.00 (1H, m), 1.73 (2H, m), 1.48 (1H, m), 1.12 (3H, s), 0.83 (3H, t, J=7.5); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \& 177.12, 173.91, 51.69, 51.64, 45.72, 33.40, 31.89, 29.75, 20.66, 8.87; MS m/z 202 (M\(^+\)), 171, 143, 129, 116, 111, 83, 69, 55.
I-D. References


8. Metzger, P.; David, M.; Casadevall, E. Phytochemistry 1987, 26, 129.


33. The syntheses of (S)- and (R)-4-methylbutyrolactone (27) as well as (2S,5R)-35 and (2S,5R)-37 were performed by G. Nagabhushana Reddy.


35. Presented in part before the 41st Northwest Regional Meeting of the American Chemical Society; Paper #131; June 17, 1986; Portland, OR and the 193rd National Meeting of the American Chemical Society; Paper #180; April 7, 1987; Denver, CO. For a preliminary account of this work see: White, J.D.; Somers, T.C.; Reddy, G.N. J. Am. Chem. Soc. 1986, 108, 5352.


PART II: TOTAL SYNTHESIS OF (±)-2-DESOXYSTEMODINONE

II-A. Introduction

Extracts of leaves of the rare littoral plant, *Stemodia maritima* L. (Scrophulariaceae),\(^1\) are reported in Caribbean lore to be a treatment for venereal disease. Attracted by the reported medicinal properties of this shrubbery, known locally as Jamaican sea mint, White and Manchand in 1973 isolated and characterized two new diterpenoid natural products, stemodin (1) and stemodinone (2).\(^2\) These were shown by interconversion and X-ray crystallography to possess the new tetracyclic structure depicted in Figure II.1. Subsequently,

![Chemical structure](image)

**Figure II.1 The Naturally Occurring Stemodane Diterpenes**

2-desoxystemodinone (3),\(^3\) maritimol (4),\(^4\) and stemarin (5, Figure II.2)\(^5\) were isolated from the same source, the latter exhibiting yet another new diterpene skeleton.

A third variant possessing the C/D bicyclo[3.2.1]octane ring system is represented by the fungal metabolite aphidicolin (6),
isolated from *Cephalosporium aphidica* Petch by Hesp at I.C.I. in England, and later found to occur in *Nigrosporum sphaerica* as well. Aphidicolin, in spite of its relatively simple functionality, displays a wide range of interesting biological activity, including potent antibiotic and antitumor properties. This biological activity has been attributed to its ability to disrupt DNA synthesis by specifically inhibiting DNA polymerase-α.

More recently, 3-deoxyaphidicolin (7) and the 17-monoacetate (8) of aphidicolin were found in the culture broth of *Phoma betae* Frank PS-13, and were shown to markedly inhibit in vivo DNA synthesis of sea urchin embryos and HeLa cells.

The structural relationship between stemodanes 1-3 was demonstrated by White and Manchand through chemical interconversion (Scheme 1). Thus, Jones oxidation of stemodin (1) gave stemodinone (2), which could be reduced under Huang-Minlon conditions to afford 2-deoxystemodinone (3). Dehydration of the latter with
phosphorus oxychloride gave, in addition to a small amount of the exo olefin 9, the crystalline hydrocarbon 10.

Scheme 1

Structurally, the stemodane and aphidicolane diterpenes are related through inversion at carbons 9, 13, and 14. The configurations at carbons 5, 8, and 10, however, are identical and, moreover, are the same as those found at the corresponding centers in the stemarane skeleton. This consistency led White to propose a biogenesis for these three tetracyclic diterpenes which centers around a common bicyclo[2.2.2]octyl cation 12\textsuperscript{11} (Scheme 2), derived from the pimarane cation 11 as suggested for the biosynthesis of aphidicolin.\textsuperscript{12a,b} In this view, the three interconvertible cyclopropane structures 13, 14, and 15, derived from 12 by a series of 1,3-eliminations and protonations, give rise to the aphidicolane, stemarane, and stemodane skeletons respectively, via Markovnikov hydration. The reasoning which underlies this scheme is similar to that proposed by Wenkert\textsuperscript{13a} and Coates\textsuperscript{13b} for the formation of the atiserane (16), kaurane (17), and beyerane (18) diterpene skeletons (Scheme 3). Although the occurrence of the trachylobane skeleton 19\textsuperscript{13c} and studies of its in vitro chemistry lend strong support to this unified biogenesis, the intermediacy of an unprotonated cyclopropane is not fully established.
Scheme 2
Labeling studies performed by Bu'Lock and others have probed the biogenesis of the aphidicolane diterpenes and are in accord with the pathway in Scheme 2, although the proposed cyclopropane intermediates 13, 14, and 15 await experimental verification.

The unique carbon skeleta and alleged medicinal properties of 1-8 have drawn considerable attention to their total synthesis. To date, five successful total syntheses of stemodane diterpenes have appeared in the literature. The most popular approach has paralleled the rearrangement of a bicyclo[2.2.2]octyl system to a bicyclo[3.2.1]octyl framework that was suggested for their biogenesis. van Tamelen reported the first approach along these
lines in 1981.\textsuperscript{14c} Lewis acid promoted cyclization of 20 (Scheme 4) provided the tricyclic ABC ring system 21 that was converted to diene 22, thereby establishing four of the five AB ring chiral centers. The Diels-Alder adduct 23 with maleic anhydride was decarboxylated with lead tetraacetate and the latent ketone was reduced to give the

Scheme 4
key alcohol 24 as the major diastereomer. It was known from earlier work of Wiesner\textsuperscript{18} that bicyclo[2.2.2]octyl systems like 24 undergo a facile, stereospecific migration of the bond anti and periplanar to the leaving group, to afford the thermodynamically more stable bicyclo[3.2.1]octyl skeleton. Under the conditions employed for tosylation of 24, this rearrangement occurred in high yield (path a) to afford 25 which was converted to (±)-maritimol (4) in five steps.

Subsequently, van Tamelen demonstrated the applicability of this strategy to the synthesis of (±)-aphidicolin (6).\textsuperscript{16g} The Diels-Alder
adduct 27 (Scheme 5), of diene 26 and maleic anhydride, was hydrogenated and oxidatively decarboxylated to olefin 28. Epoxidation and reduction gave, stereospecifically, the secondary alcohol 29. Solvolysis of the derived mesylate 30 induced a migration of the antiperiplanar bond (path b) to give the tetracycle 31, possessing the correct relative stereochemistry for the aphidicolane system. Completion of the synthesis of (±)-aphidicolin from 31 elegantly demonstrated the feasibility of this biomimetic approach for two of the three classes of diterpene skeletons in this family.

Independently, Kelly developed a variation of this approach in his synthesis of (+)-2-desoxystemodinone (3, Scheme 6). The tricyclic enone 32, readily derived from podocarpic acid, was subjected to
a de Mayo-type annulation to give 33. Reductive removal of the keto function, followed by tosylation, gave 34 which smoothly rearranged to endo dehydro-2-desoxystemodinone (10). Epoxidation of 10 occurred predominantly from the less hindered α-face, and reduction of the epoxide afforded (+)-2-desoxystemodinone (3). This synthesis established unambiguously the absolute stereochemistry of the natural material. Cognate studies with racemic intermediate 36 have also yielded (±)-3 and (±)-stemarin (5). During the preparation of 38 from 37, a minor amount of the C-14 epimer 39 (Scheme 7) was obtained that was transformed to tosylate 40. Base-catalyzed rearrangement
produced dehydrostemin (41) and ultimately (±)-stemarin itself. Bettolo, utilizing an approach very similar to that of Kelly, has also reported a total synthesis of stemodanes 1-414f and aphidicolin (6).16h

In contrast to the AB[2.2.2]CD to ABCD strategy employed by van Tamelen, Kelly, and Bettolo, two other groups have developed quite different ring construction sequences. Piers, adopting an AB to ABD to ABCD route, completed the total synthesis of (±)-stemodin (1) and (±)-2-desoxystemodinone (3) via a Thorpe-Ziegler cyclization of dinitrile 46.14g Thus, photoaddition of allene to 43 (Scheme 8), followed by ozonolysis and cleavage with methoxide, gave ketoester 45. It was presumed that the α-cyclobutane isomer of 44 could be converted to 9-epi-45 and that this intermediate would provide an entry to the aphidicolanes. However, an unexpected rearrangement intervened that produced only 45 from both isomers of 44. The bis nitrile 46 was prepared from 45 and the D-ring was established by base-catalyzed cyclization to 47. The basic hydrolysis of enaminonitrile 47 failed and at this point the approach became pedestrian. Acidic hydrolysis and decarboxylation, though proceeding in high yield, concomitantly removed the A-ring ketal to give 48, in which the similar keto functions had to be chemically distinguished. Five synthetic operations were required to produce 49, which was taken forward to (±)-stemodin (1) and (±)-maritimol (4). Although this approach demonstrates a distinctly different strategy for construction of the stemodane system, the more than 27 synthetic steps required detract from its overall utility.
Corey, in an extension of the AB to ABD to ABCD strategy elegantly demonstrated in his synthesis of (±)-aphidicolin, has also reported an approach to the stemodane diterpenes (Scheme 9).\textsuperscript{14b} Mercuric trifluoroacetate induced cyclization of enol phosphate 50 gave, after four steps, the bicyclic β-ketoester 51, to which the D-ring was annulated via 52. The one-carbon homologation of spiroketone 53 required for construction of the stemodane C-ring proved
difficult but was overcome by the unusual sequence shown in Scheme 10. Reduction of aldehyde 54, tosylation and dethioketalization gave the key enone 55 which, on treatment with base, cyclized to 53.

$$\text{Scheme 9}$$

$$\text{Scheme 10}$$
Completion of the synthesis required reduction of the D-ring unsaturation and introduction of the C-13 methyl group. Most of the standard methods examined for these transformations gave poor stereoselectivity, but this obstacle was eventually overcome by epoxide formation from 56 with dimethylsulfoxonium methylide and reduction with lithium triethylborohydride. Adjustment of the A-ring oxidation finally afforded stemodanes 1-3.

For elaboration of the aphidicolane skeleton, keto tosylate 57 (Scheme 11) was prepared by a procedure analogous to that described above but with the requisite A-ring functionality incorporated from the outset. Reduction of the D-ring double bond prior to cyclization gave the spiroketone 57 which, under conditions of kinetic deprotonation, underwent internal alkylation at C-12. Conditions that favored thermodynamic alkylation (sodium methoxide in methanol) led almost entirely to C-ring closure at C-14. The tetracyclic ketone 58, after reaction with 1-ethoxyethoxymethyl lithium and hydrolysis, gave (±)-aphidicolin (6).
II-B. Discussion and Results

The sequence of carbon-carbon bond forming steps that were envisioned for synthesis of (±)-2-desoxystemodinone (3) is outlined in retrosynthetic form in Scheme 12. Disconnection of the C-14,15 bond would give the seco-stemodane system shown, and this could, in principle, be obtained by a one-carbon homologation of the spiroketone 64, previously prepared in our laboratories. It was initially anticipated that closure of the C-14,15 bond could be accomplished through direct solvolysis of 59 (R=H, X=OTs) to 3 or via nucleophilic opening of a C-13,14 α-epoxide with C-15 as a carbanionic center. A retro Diels-Alder reaction of 64 leads to the carbon framework of the AB ring synthon 62, itself available from geraniol and methyl acetoacetate.

Scheme 12
The synthesis of spiroketone 64, as originally developed by White, Trammell, and Skeean, was used with only minor modifications (Scheme 13). Thus, geranyl chloride (60), prepared by the method of Corey and Kim, was added to a solution of methyl acetoacetate dianion in tetrahydrofuran to give 61 in 64% yield. Stannic chloride-promoted cyclization of 61 afforded the trans-fused ketoester 62 in 53% yield. Optimum yields of 62 were obtained using methylene chloride saturated with water as the solvent, in contrast to an earlier reported procedure. Under completely anhydrous reaction conditions, the yield of 62 is greatly diminished and polymerization of 61 becomes the major reaction pathway.

Scheme 13
The conversion of 62 to methylene ketone 63 was accomplished by the simple, four-step sequence shown and was subjected immediately to a stannic chloride-catalyzed Diels-Alder reaction with isoprene to give 64. This eight-step sequence, proceeding in 20% overall yield, easily provided multigram quantities of 64 for subsequent synthetic studies.

With the objective of preparing an AB ring synthon which would have greater versatility, we briefly examined an alternative cyclization tactic to that described in Scheme 13. A serious limitation to 62 is its lack of A-ring functionality. The placement of a double bond in the C-1,2 position during cyclization of a monocyclic precursor (Figure II.3) could provide access to stemodanes 1-4 as well as other, highly oxidized diterpenes such as forskolin (65).

In order to test the feasibility of this approach, β-ketoester 67 was prepared from commercially available α-ionone as shown in
Scheme 14. Saturation of the conjugated double bond of α-ionone could be accomplished smoothly by either dissolving metal or silane reduction. Acylation of the kinetic enolate of 66 with methyl cyanoformate gave a 65% yield of the key β-ketoester 67. The use of dimethyl carbonate and sodium hydride or methyl chloroformate and lithium diisopropylamide for this acylation always produced lower yields of the desired β-ketoester. Methyl cyanoformate has recently become the reagent of choice for this synthetically valuable transformation; the high yields of β-ketoester generally obtained are attributed to the stability of the tetrahedral intermediate formed on alkylation of the cyanoformate, which does not revert to starting material or collapse to the ketoester until the reaction is quenched.

Initial attempts to effect the cyclization of 67 employed mercuric ion or selenium reagents, but neither of these reagent
systems afforded a tractable product. However, manganese(III) acetate, a reagent exploited by Fristad and Snider for cyclization of β-ketoesters, caused a rapid and relatively clean reaction of 67. The single isolable product of this reaction (43%, unoptimized), clearly did not possess the expected decalin ring system but displayed $^1\text{H}$ NMR (δ 4.93, 4.76) and IR (906 cm$^{-1}$) signals characteristic of an exo-methylene function. $^{13}\text{C}$ NMR (δ 206.50, 170.30) and IR (1744, 1713 cm$^{-1}$) demonstrated that the β-ketoester was intact and established the presence of only one olefin function (δ 147.26, 114.37). The elemental composition of the product showed that a two electron oxidation had occurred, and the one proton doublet at δ 4.08 (J=8.7 Hz) in the $^1\text{H}$ NMR spectrum of 68 indicated that this oxidation was manifested as a new carbo-cyclic ring, formed between the ketoester α-carbon and a carbon bearing a single proton. Collectively, these data allow the confident assignment of structure 68 to this product.

Mechanistically, the formation of 68 can be rationalized by comparison of the relative stabilities of the radical intermediates A and B (Scheme 15) that could be produced by closure of the initially generated β-ketoester radical at the cyclohexene double bond.

\[ 67 \xrightarrow{\text{Mn(III)}} \]
Although the seven membered ring in B is slightly disfavored entropically, the increased stability of the tertiary over the secondary radical is apparently sufficient to steer cyclization toward this species. The alkene 68 is then derived via β-hydride elimination through an organocopper species.\textsuperscript{31}

This rare bicyclo[4.3.1]decane ring system occurs in nature within the pallescensin class of marine metabolites. Pallescencin D (69, Figure II.4) was isolated in 1975 by Cimono et al. from the sponge \textit{Disidea pallescens} and was assigned the structure shown by NMR and other spectral methods.\textsuperscript{32} Although a few of its much more simple congeners have been prepared,\textsuperscript{33} the structure of 69 has yet to be confirmed by synthesis. Ketoester 68, or a functional analog from a similar cyclization, may prove to be a valuable intermediate in the synthesis of pallescensin D.

\begin{center}
\begin{tabular}{c}
\includegraphics[width=0.5\textwidth]{69_68.png}
\end{tabular}
\end{center}

\textbf{Figure II.4} Retrosynthetic Analysis of Pallescensin D.

Although cyclization of 67 to 68 precluded access to the A-ring functionalized skeleton of stemodin, the strategy implied in Scheme 12 could still be tested in the context of a synthesis of 2-desoxystemodinone (3). It was known from early work in our
laboratories and others\textsuperscript{34} that the ketone function of 64 was resistant to nearly all types of nucleophiles. Excess methyllithium or forcing Wittig reaction conditions, for example, yielded only recovered starting material, probably as a result of enolization. During attempts to find a suitable reagent for introduction of the C-ring carbon (C-15) into 64, three noteworthy results were obtained. First, condensation of 64 with dimethylsulfonium methyldide in hexamethylphosphoramide was found to give a nearly quantitative yield of the exo epoxide 70 (Scheme 16). However, all attempts to effect the rearrangement of 70 to an aldehyde afforded products that clearly had undergone the deep seated skeletal change first noted by Trammell.\textsuperscript{35} Thus, treatment of 70 with catalytic perchloric acid in aqueous

\begin{center}
\begin{tikzpicture}
\node (64) at (0,0) {\includegraphics[width=0.3\textwidth]{64.png}};
\node (Me2SCH2) at (0.5,0) {Me\textsubscript{2}SCH\textsubscript{2}, HMPA};
\node (70) at (1.5,0) {$\text{H}$; O};
\node (70_1) at (2,0) {70 ($\sim$100\%)};
\node (HClO4) at (0,1) {HClO\textsubscript{4}, aq. THF};
\node (71) at (1,1) {71 (39\%)};
\node (72) at (2,1) {72 (17\%)};
\end{tikzpicture}
\end{center}

Scheme 16
tetrahydrofuran produced alcohols 71 and 72 in a 2:1 ratio, respectively.\textsuperscript{19a}

Subsequently, it was found that application of a rather unusual Wittig condensation to 64,\textsuperscript{36} previously employed by Smith in a total synthesis of (±)-modhephene,\textsuperscript{37} produced a quantitative yield of diene 73 (Scheme 17). Unfortunately, hydroboration of 73 with 9-BBN or thexylborane failed to afford any of the desired alcohol and oxymercuration likewise, did not yield a tractable product.

\begin{center}
\begin{tikzpicture}
\node (64) {64 \begin{array}{c}
\text{Ph}_3\text{PCH}_3\text{Br}, \\
\text{KCl-Am}, \text{C}_6\text{H}_6, \\
\text{C}_6\text{H}_5\text{CH}_3, 80^\circ\text{C}
\end{array}};
\node (73) at (2,0) {73 (\text{-100\%})};
\node (74) at (2,-2) {74 (62\%)};
\node (75) at (2,-4) {75 (40\%)};
\node (1) at (-2,-1) {1) \text{R}_2\text{BH}};
\node (2) at (-2,-2) {2) \text{H}_2\text{O}_2};
\node (3) at (-2,-3) {m-\text{CPBA}, \text{CH}_2\text{Cl}_2};
\node (4) at (-2,-4) {\text{TMSI, NaI, CH}_2\text{Cl}_2};
\end{tikzpicture}
\end{center}

Scheme 17

On the other hand, epoxidation of 73 occurred selectively at the trisubstituted olefin, producing 74. The stereochemistry of 74 was
assumed to be that depicted in Scheme 17 based on approach by the peracid to the more accessible face of the olefin. Although attempts to hydroborate the exo olefin of 74 led only to products of epoxide reduction, it was hoped that treatment of 74 with trimethylsilyl iodide\textsuperscript{38} would give 8-iodo-2-desoxystemodinone. Instead a product was obtained that clearly possessed a quite different ring system. Spectral analysis allowed a tentative assignment of 75 to this product, which results from a Wagner-Meerwein rearrangement cascade similar to that seen in the conversion of 70 to 71. It was obvious at this point that a successful synthesis of 3 would require circumvention of the C-8 carbocation in the elaboration of an intermediate possessing the crucial C-15 appendage. This prompted us to develop a quite different strategy based upon organosamarium chemistry.

In 1984, Imamoto and coworkers reported a procedure,\textsuperscript{39} in extension of Kagans' earlier work,\textsuperscript{40} for hydroxymethylation of ketones. They found that treatment of even highly enolizable ketones with benzyl chloromethyl ether in the presence of samarium diiodide produced high yields of alkylated products. The reaction is believed to proceed via electron transfer from an organosamarium halide and thus takes advantage of the powerful reducing properties of samarium(II). Subsequent cleavage of the resulting benzyl ether affords 1,2-diols. Although hindered substrates had not previously been examined, it was expected that spiroketone 64 would undergo alkylation with this reagent system to provide the requisite C-ring carbon. In the event, a 92% yield of tertiary alcohol 76 (Scheme 18) was obtained which was tentatively assigned the configuration.
shown. It was assumed that the bulky organosamarium complex should attack at the less hindered \( \alpha \)-face of the ketone in 64, as observed previously with other reagents.\(^{19a}\) This stereochemical assignment was subsequently confirmed by X-ray analysis on a latter synthetic intermediate (vide infra). Attempts were made at this stage to replace the C-8 hydroxyl substituent of 76 by a hydrogen to attain a comparable oxidation level with 3. However, the highly hindered environment of this axial alcohol negated even forcing conditions for mesylate or xanthate formation and we were thus obligated to retain this tertiary alcohol until a latter stage of the synthesis.

Examination of a molecular model of hydroxy aldehyde 78 indicated that, should the aldehyde carbonyl adopt an internally hydrogen-bonded conformation, a suitable alignment for an intra-molecular ene reaction\(^{41}\) would obtain. This formal [4+2] process, depicted in Figure II.5, would establish the bicyclo[3.2.1]octane system of the stemodanes and implant a D-ring double bond for further elaboration. It was unclear from models which of hydrogens A or B were better situated for transfer to the aldehyde oxygen at the
transition state and thus the possibility existed for a mixture of endo and exo olefin isomers. Molecular mechanics calculations on 78, based on Allinger's force field and using the MMX-MODEL program, confirmed that the lowest energy conformer was indeed hydrogen bonded with the spiro-ring in a half-chair orientation. An ORTEP drawing derived from these calculations is shown in Figure II.6.

Encouraged by these predictions, we converted 76 to 78 as shown in Scheme 18. Cleavage of the benzyl ether with sodium in liquid ammonia gave the diol 77 in 95% yield after chromatography and this was oxidized to 78 under Swern conditions. Examination of the 400 MHz $^1$H NMR spectrum of 78 indicated a 1.5 Hz coupling between the aldehyde ($\delta9.33$) and the hydroxyl ($\delta3.73$) protons, clearly suggesting a stable, internal hydrogen bond. Infrared absorptions at 3437 (sharp) and 1704 cm$^{-1}$ supported this conclusion. Final confirmation of the stereochemistry of 78 came via
The ORTEP drawing provided from this structural analysis (Figure II.7) unambiguously establishes the relative stereochemistry and conformation of 78 as that shown.
Although 78 was analytically pure, its TLC analysis always displayed the presence of two more polar components. Suspecting an acid-catalyzed reaction on the silica, we subjected 78 to a two-fold excess of dimethylaluminum chloride in methylene chloride solution at -78 °C. A near instantaneous reaction ensued and three products, only partially separable by column chromatography, were isolated in 93% combined yield. These corresponded with the

\[ \text{Scheme 19} \]

\[ 78 \xrightarrow{\text{Me}_2\text{AlCl, CH}_2\text{Cl}_2,} \text{-78}^\circ \text{C, 1 min} \]

\[ 79/80/81 \ 1:1.2:2.4 \ (93\%) \]
materials previously observed by TLC. The two minor components were recognized as the exo and endo olefin isomers, 79 and 80, respectively (Scheme 19), derived through a formal ene process. The major product, 81, could not be obtained free of 80 at this stage. The assignment of its structure was facilitated by the recovery of pure 81 after subjection of the 79-81 mixture to thiophosgene in chloroform. The cis diols 79 and 80 were smoothly converted to thiocarbonates 82 and 83, from which 81 was now easily separable. It was clear from the $^1$H and $^{13}$C NMR spectra of 81 that there were no olefinic carbons present. The broad vinyl methyl group of 78 appeared as a singlet at 81.36, assignable to a methyl substituent on a tertiary carbon bearing an oxygen. The mass spectral data were consistent with the assignment of this product to a pentacyclic, oxo-bridged structure but it was not possible to distinguish between the two formulations 81 and 84. The appearance of the hydroxyl proton as a $^3$3.20 doublet (J=1.8 Hz) weighted our assignment in favor of the tetrahydrofuran structure 84 but, since a more profound rearrangement of the carbon skeleton of 78 could not be unambiguously ruled out, the substance was subjected to single crystal X-ray analysis. The ORTEP drawing shown in Figure 11.8 establishes the structure as 81 and reveals a surprisingly stable oxetane bridge between C-15 and
The origin of the hydroxyl proton doublet in the $^1H$ NMR spectrum remains somewhat of an enigma. One possibility is long-range coupling to the proton at C-15, facilitated by internal hydrogen bonding of the hydroxyl to the oxetane oxygen atom.

The formation of the unusual ring system of 81, along with the mixture of olefin isomers, can be rationalized through a cationic process (Figure II.9)\textsuperscript{47} that terminates by loss of protons A or B leading to 79 and 80 respectively, or oxetane
closure to \(81\). Alternatively, \(81\) could be formed by a different pathway involving direct Lewis acid catalyzed \([2+2]\) cycloaddition of the aldehyde carbonyl to the olefin.

![Figure II.9 Mechanistic Rationale for the Lewis Acid Catalyzed Ene Reaction.](image)

In contrast to the product mixture obtained from \(78\) with a Lewis acid catalyst, the thermal reaction proceeded in high yield to give a single compound. Upon heating in toluene solution at reflux, \(78\) gave a 94\% yield of \(79\) (Scheme 20). The extreme facility of this ene reaction is, to the best of our knowledge, unprecedented and is presumably due to the simultaneous directing and activating effect of the hydroxyl substituent.

In order to probe the role of the hydroxyl function in this process it was removed from \(78\) with samarium diiodide in the presence of tert-butanol. This remarkable reduction proceeds at room temperature to give aldehyde \(85\) in 63\% yield after chromatography. The aldehyde carbonyl was assigned to the thermodynamically favored equatorial position shown by comparison of measured \(^1\)H chemical shift values with those reported by Corey for \(54\). The ring-expanded by-product \(86\), isolated from this reaction in
32% yield, is formally derived from a samarium induced α-ketol rearrangement\(^4\) of 78.

Although Molander has reported a related general procedure for the reductive removal of heteroatom substituents α to a ketone,\(^4\) poor yields are suffered with α-hydroxy ketones under the conditions employed. Our results with 78 and an additional substrate (vide infra) indicate that optimum conditions are met with tert-butanol as the proton source in a 0.1 M solution of samarium diiodide in tetrahydrofuran.\(^4\) The use of concentrated samarium diiodide, generated in situ in methanol, causes a rapid reduction of the starting carbonyl function and only the diol is produced.
The necessity of the 8β-hydroxyl group for the successful intramolecular ene reaction of 78 was evidenced by the complete failure of 85 to yield any trace of an ene product, either thermally (toluene, 250 °C, 8 h) or in the presence of a Lewis acid (excess dimethylaluminum chloride, methylene chloride, 25 °C). Whether this is due to an insurmountable activation barrier for the reaction or to the adoption by the aldehyde carbonyl of a stable conformation that does not permit the reaction is unclear.

With an efficient route to a substance, 79, possessing the complete carbon framework of the stemodanes in hand, attention was focused on the adjustment of the C and D ring oxidation levels. Completion of the synthesis of 3 requires the reductive removal of the cis hydroxyl groups at carbons 8 and 15 and stereospecific introduction of the tertiary alcohol at C-13.

Although methodology exists for the synthesis of alkenes from 1,2-diols, the direct reduction to alkanes has received less attention.50 Our initial attempts to effect the conversion of 79 to exo dehydro-2-desoxystemodinone (9) were via thiocarbonate 82. However, tri-n-butyltin hydride reduction51 of 82 under a variety of conditions gave complex mixtures containing little, if any, 9.

The failure to convert 79 directly to 9 necessitated a more circuitous route. To this end, 79 was oxidized in nearly quantitative yield under Swern conditions (Scheme 21) to afford the α-hydroxy ketone 87. The tertiary hydroxyl group was cleanly removed from 87 by reduction with samarium diiodide in the presence of tert-butanol to give 88 in 87% isolated yield. The
stereochemical assignment at C-8 of 88, though not unequivocal, was supported by a number of observations. First, the gross similarities seen in the $^1$H and $^{13}$C NMR spectra of 87 and 88 are
explainable only by a close structural correspondence between these compounds. Had protonation of the intermediate enolate, formed during the samarium diiodide reduction, occurred at the \(\alpha\)-face, the resulting configuration at C-8 would have forced major conformational changes upon the A and B rings. In particular, the B-ring would be confined to a highly strained boat conformation to which the five-membered ring would necessarily be trans-fused. Second, the failure to detect any stereoisomer of 88 from the reaction of 87 with samarium(II), or during the subsequent Huang-Minlon reduction to 9 and 10, supports the assumption that the C-8 \(\beta\)-hydrogen stereoisomer is thermodynamically more stable and is the configuration produced during the samarium(II) reduction. Moreover, the chemical shift correspondence between major signals in the \(^1\)H NMR spectra of 88 and 9 discredits the possibility that the C-8 epimer of 88 was produced and that it simply isomerized during the Huang-Minlon reduction to give the correct stemodane stereochemistry.

Huang-Minlon reduction\(^52\) of 88 gave an inseparable 2.5:1 mixture of exo and endo dehydro-2-desoxystemodinone exhibiting \(^1\)H NMR, IR, and mass spectral properties identical with those recorded on an authentic sample, prepared as shown in Scheme 1. The double bond isomerization that occurred during reduction of 88, although giving a mixture of isomers, proved to be a fortunate outcome. It was known from the work of Kelley\(^3\) that endo olefin 10 would undergo peracid epoxidation predominantly from the \(\alpha\)-face leading to the correct relative configuration at C-13. In contrast, examination of models of 9 did not indicate a steric bias for epoxidation.
of the exo olefin. The stereoselectivity problems that Corey, et al.\textsuperscript{14b} encountered in the alkylation of ketone 56 supported this view.

Upon oxidation with \textit{m}-chloroperbenzoic acid and direct reduction with lithium triethylborohydride\textsuperscript{53} the mixture of 9 and 10 afforded an easily separable mixture (1.4:1) of (±)-2-desoxy-stemodinone (3) and its C-13 epimer 89. The latter, presumably arising from the $\beta$-epoxide of 9, could be recycled to a favorable mixture of 9 and 10 (1:1.7, respectively) by dehydration with phosphorous oxychloride in pyridine\textsuperscript{2} (66\%, unoptimized), thereby providing a route that converts 88 to 3 in 55\% overall yield.

The synthesized (±)-2-desoxystemodinone (3) displayed TLC properties and $^1$H NMR, $^{13}$C NMR, IR, and mass spectra that were identical to those of an authentic sample. However, the measured melting point of (±)-3, 108-109.5 °C was in serious disagreement with two values, 144 °C\textsuperscript{14a,17} and 146-147 °C\textsuperscript{14f} reported in the literature for this compound. The coincidence of the latter melting points, recorded for racemic synthetic material, with that of naturally occurring (+)-3 (144 °C)\textsuperscript{2} is surprising and, in at least one case, suspect. Fortunately, a single crystal X-ray structure determination\textsuperscript{46} was able to fully confirm the identity of our synthetic material as (±)-2-desoxystemodinone (3, Figure II.10).

Several approaches designed to improve the stereoselectivity of the epoxidation reaction and/or avoid the olefin mixture obtained during Huang-Minlon reduction of 88 were surveyed but these were not successful. Epoxidation of the 9/10 mixture with monoperphthalic acid\textsuperscript{54} or peroxybenzimidic acid,\textsuperscript{55} followed by reduction, gave either
equal or diminished selectivity compared to $m$-chloroperbenzoic acid. However, it was surmised from examination of a model of 88 that the $\beta$-face of the exo olefin could be effectively blocked by reduction of the ketone to the $\beta$-alcohol and attachment of a substituent to this hydroxyl group. Therefore, 88 was reduced with lithium aluminum hydride and was found to afford 90 (Scheme 22) as the only detectable diastereomer. The mesylate 91 was epoxidized to give, in excellent yield, a 10:1 mixture of epimeric epoxides, in which the major product was assumed to possess the desired configuration shown in 92. Having thus solved the stereochemical problem en route to 3, the reduction\textsuperscript{53,56} of the epoxide and mesylate of
92 appeared straightforward. To our surprise, treatment of 92 with excess lithium triethylborohydride, in a more sluggish reaction than the corresponding reduction of the epoxide from 9, gave not the expected 2-desoxystemodinone (3) but a 1:1 mixture of two stereoisomeric secondary alcohols for which structure 93 was deduced by spectral methods. This interesting, albeit disheartening, fragmentation of the stemodane nucleus probably arises via the mechanism shown.
in Scheme 23. Initial reduction of the epoxide would give a tertiary alkoxide 94 that can undergo a rate-limiting Grob fragmentation to ketone 95. This ketone is then rapidly reduced by a second equivalent of the hydride reagent to a 1:1 mixture of alcohols 93.

In conclusion, several aspects of the chemistry presented above deserve comment. First, a stereoselective route was devised that converts geraniol in seventeen synthetic steps to (±)-2-desoxystemodinone (3) in approximately 7% overall chemical yield. This compares favorably with the published syntheses of 3. Second, the use of a unique, hydroxyl-assisted, intramolecular ene reaction for construction of the C-ring of 3 demonstrates a new concept in carbon-carbon bond formation that may find application in other areas of organic synthesis. In particular, entry to the aphidicolane and stemarane ring systems might be gained through this strategy. Finally, the novel applications of samarium diiodide reduction and manganese triacetate oxidation in this research illustrate the remarkable properties of these relatively new reagents and affirm their place in the organic chemist's general arsenal of synthetic methods.
II-C. Experimental

For a general description of methods and apparatus, see Part I experimental.

\( \alpha, \beta \)-Dihydro-\( \alpha \)-ionone (66)

Method A: To an oven dried 1L three-neck flask, equipped with a dry ice condenser and 250 mL dropping funnel, was added 400 mL of freshly distilled ammonia and 0.72 g (0.104 mol) of lithium wire. The dropping funnel was charged with 125 mL of dry ether, 5.0 g (26.0 mmol, 90% tech.) of \( \alpha \)-ionone, and 2.45 mL (1.92 g, 26.0 mmol) of tert-butanol. This solution was added dropwise over 30 min and maintained the ammonia at reflux. After an additional 15 min, 11.0 g (0.208 mol) of solid ammonium chloride was added carefully, and the solvent was allowed to evaporate overnight. Upon addition of 200 mL of water and 200 mL of ether, the organic phase was separated and the aqueous phase was saturated with sodium chloride and extracted with 100 mL of ether. The combined organic solutions were washed with 0.5 M aqueous hydrochloric acid and brine, and were dried over magnesium sulfate. Concentration of the solution and chromatography (150 g of silica gel 60, ethyl acetate-hexanes 1:10) afforded 3.49 g (70%) of pure 66 as a colorless oil (77% from 90% ionone).

Method B: To a stirred solution of 5.00 g of \( \alpha \)-ionone (90% tech., 23.4 mmol) and 6.23 g (33.8 mmol) of diphenylsilane in 75 mL of chloroform was added 2.05 g of zinc chloride (15.1 mmol) and 300 mg of tetrakis(triphenylphosphine)palladium(0). The orange solution
was stirred at ambient temperature for 5 h and then concentrated in vacuo to a volume of about 30 mL. The viscous residue was eluted from a column of 30 g of silica gel 60 with methylene chloride, and the eluate was concentrated and chromatographed (200 g of silica gel 60, ethyl acetate-hexanes 1:10) to afford 3.28 g (73%) of 66: IR 2956, 2933, 2916, 2869, 2843, 1717, 1363 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) 2.48 (2H, m), 2.13 (3H, s), 1.96 (2H, m), 1.67 (3H, bs), 0.92 (3H, s), 0.87 (3H, s); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) 208.90, 135.52, 120.99, 48.45, 43.72, 32.55, 31.51, 29.90, 27.65, 27.60, 24.35, 23.51, 22.95.

**Methyl (±)-3-Oxo-5-(2,6,8-trimethylcyclohexen-2-yl)pentanoate (67)**

To a solution of lithium diisopropylamide (prepared from 0.91 mL (6.45 mmol) of diisopropylamine and 4.3 mL (6.45 mmol, 1.5 M in hexanes) of n-butyllithium at 0 °C) in 5 mL of dry tetrahydrofuran at -78 °C under argon was added dropwise 1.14 g (5.87 mmol) of 66 in 5 mL of tetrahydrofuran. The solution was stirred for 40 min and hexamethylphosphoramide (1.12 mL, 6.45 mmol) was slowly added, followed by 0.55 mL (7.04 mmol) of methyl cyanoformate, dropwise. After 15 min, the mixture was poured into 50 mL of water and extracted with ether. The combined organic extracts were washed with water and brine, and were dried over magnesium sulfate. Concentration gave an orange oil that was chromatographed (55 g of silica gel 60, ethyl acetate-hexanes 1:5) to afford 957 mg (65%) of 67 as a colorless oil: IR (neat) 2956, 2916, 2869, 1754, 1719, 1437, 1275 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) 3.74 (3H, s), 3.45 (2H, s), 2.59 (2H, m), 1.67 (3H, bs), 0.91 (3H, s), 0.87 (3H, s); \(^{13}\)C NMR (100 MHz,
Methyl (±)-(1α,6α)-7,7-Dimethyl-10-methylene-3-oxabicyclo[4.3.1]-decane-2-carboxylate (68)

A suspension of 412 mg of manganese(III) acetate (1.54 mmol) and 153 mg of copper(II) acetate (0.769 mmol) in 7 mL of glacial acetic acid was warmed to 70 °C under argon for 15 min, cooled to room temperature, and 194 mg (0.769 mmol) of 67 in 1.5 mL of acetic acid was added. The homogeneous mixture was stirred at ambient temperature for 1.5 h and concentrated in vacuo. The resulting paste was dissolved in ether-dichloromethane-water 1:1:1 and the organic phase was separated and washed with water and brine, and was dried over magnesium sulfate. Chromatography of the concentrate (20 g of silica gel 60, ethyl acetate-hexanes 1:5) gave 83 mg (43%) of 68 as a colourless solid: Mp (hexanes) 92-93 °C; IR (Nujol) 2925, 1744, 1713, 1273, 1168, 906 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.93 (1H, d, J=1.9), 4.76 (1H, d, J=1.9), 4.08 (1H, d, J=8.7), 3.75 (3H, s), 3.16 (1H, m), 2.48-2.22 (2H, m), 2.10 (1H, bt, J=9.4), 1.95-1.78 (4H, m), 1.45 (1H, m), 1.20 (1H, m), 0.96 (3H, s), 0.95 (3H, s); ¹³C NMR (100 MHz, CDCl₃) δ 206.50, 170.30, 147.26, 114.37, 58.98, 52.32, 51.16, 40.21, 40.04, 34.71, 28.87, 27.59, 27.23, 27.03, 22.16; MS m/z 250 (M⁺, 100%), 218, 190, 162, 149, 135, 107, 79; Exact mass calcd for C₁₅H₂₂O₃: 250.1569. Found: 250.1569; Anal calcd for C₁₅H₂₂O₃: C, 71.97; H, 8.86. Found: C, 71.99; H, 8.89.
(±)-(1′α,4′α,8′αβ)-3′,4′,4′a,5′,6′,7′,8′,8′a-Octahydro-4,5′,5′,8′a-tetramethyl-2′-methylene[3-cyclohexene-1,1′(2′H)-naphalene] (73)

Methyl triphenylphosphonium bromide (1.25 g, 3.50 mmol) was placed in a 10 mL two-neck flask equipped with a reflux condenser and argon inlet. The apparatus was purged with argon and preheated in an oil bath to 85 °C. Potassium tert-amylate in benzene (2.69 mL, 1.30 M, 3.50 mmol) was added in one portion, followed by 0.5 mL of dry toluene. After heating at 85 °C for 30 min, the orange solution became homogeneous. A solution of 64 (121 mg, 0.442 mmol) in 0.2 mL of toluene was added via syringe and the solution was maintained at reflux for 4 h. After cooling, 2 mL of water was added and the mixture was diluted with ether. The organic layer was separated and washed with two 25 mL portions of water and brine, and was dried over magnesium sulfate. After concentration, the crude mixture was redissolved in pentane and filtered through 5 g of silica gel 60. Evaporation afforded 120 mg (99%) of 73 as a colorless oil: IR (neat) 2950, 1635, 890, 730 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 5.30 (1H, bs), 4.88 (1H, s), 4.73 (1H, s), 2.4-2.1 (5H, m), 1.9-1.8 (2H, m), 1.59 (3H, bs), 0.87 (6H, s), 0.83 (3H, s); ¹³C NMR (100 MHz, CDCl₃) δ 150.86, 133.00, 119.44, 108.21, 46.02, 45.36, 42.08, 41.70, 34.09, 33.61, 33.52, 32.69, 28.72, 28.28, 24.57, 23.27, 23.12, 22.01, 19.46, 16.04; MS m/z 272 (M⁺), 257, 154, 134 (100%); Exact mass calcd for C₂₀H₃₂: 272.2506. Found: 272.2496.
$^{(+)}\text{[1'\alpha,3'\beta(4aS*,8aS*),6'\alpha]-Octahydro-5,5,6',8a\text{-tetramethyl-2-}
\text{methyleneSpiro[naphthalene-1(2H),3'-7]oxabicyclo[4.1.0]heptane]}$ (74)

To a stirred solution of 73 (114 mg, 0.418 mmol) in 2 mL of dry methylene chloride at 0 °C was added portionwise 89 mg (0.516 mmol, 85% tech.) of m-chloroperbenzoic acid. After 3 h the suspension was warmed to room temperature and 10% aqueous sodium sulfite was added. The mixture was transferred to a separatory funnel and washed with water and brine, and was dried over magnesium sulfate. Concentration of the solution gave an oil that was chromatographed (20 g of silica gel 60, ethyl acetate-hexanes 1:30) to afford 74.8 mg (62%) of 74 as a glass: IR (CHCl₃) 3050, 2900, 1615, 1380, 1210, 900, 820 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.97 (1H, s); 4.63 (1H, s), 2.93 (1H, bs), 2.35 (1H, m), 2.15 (3H, m), 2.00 (1H, m), 1.8 (1H, m), 1.26 (3H, s), 0.87 (3H, s), 0.81 (3H, s), 0.80 (3H, s); ¹³C NMR (100 MHz, CDCl₃) δ 151.39, 110.03, 59.54, 56.89, 45.41, 44.45, 42.25, 41.89, 34.09, 33.82, 33.45, 32.56, 28.78, 27.26, 24.28, 23.01, 21.97, 20.24, 19.28, 15.97; MS m/z 288 (M⁺), 270, 177, 151, 137 (100%); Exact mass calcd for C₂₀H₃₂O: 288.2453. Found: 288.2453.

$^{(+)}\text{-[6a\alpha,8\beta,9\alpha,11a\alpha]-1,2,3,4,5,6,7,8,9,10,11,11a-Dodecahydro-4,4,9,}
\text{11a-tetramethyl-6a,9-methano-6aH-cyclohepta[a]naphthalen-8-ol}$ (75)

To a stirred solution of 74 (74.8 mg, 0.259 mmol) in 5 mL of dry methylene chloride was added 390 mg (2.60 mmol) of sodium iodide and 184 μL (1.30 mmol) of trimethylsilyl iodide. After 10 min, water and ether were added and the organic phase was separated and washed with water, 5% aqueous sodium thiosulfate, and brine, and was dried over magnesium sulfate. Concentration gave a dark oil that was chromatograph-
graphed (20 g of silica gel 60, ethyl acetate-hexanes 1:10) to afford 30.3 mg (40%) of 75 as an oil: IR (neat) 3335, 2921, 2858, 1457, 1047 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 3.82 (1H, dd, J=10.7, 4.3), 1.01 (3H, s), 0.96 (3H, s), 0.93 (3H, s), 0.91 (3H, s); \(^1\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 133.48, 133.11, 79.17, 45.69, 44.05, 43.22, 42.70, 40.59, 39.96, 33.95, 31.19, 30.48, 30.28, 29.09, 27.78, 25.57, 24.79, 22.64, 21.23, 19.99; MS m/z 288 (M\(^+\)), 274, 273 (100%), 255, 232, 213, 199; Exact mass calcd for C\(_{20}\)H\(_{32}\)O: 288.2453. Found: 288.2452.

\((\pm)-\(1'\alpha,2'\beta,4'a\alpha,8'a\beta\)-3',4',4'a,5',6',7',8',8'a\text{-octahydro-}4,5',5',
8'a\text{-tetramethyl-}2'\text{-}[(\text{phenylmethoxy})\text{methyl}]\text{spiro}[3\text{-cyclohexene-}1,1'
(2'\text{H})\text{-naphthalen}]-2'\text{-ol} (76)

Freshly prepared samarium diiodide in dry tetrahydrofuran (0.1 M, 33 mL, 3 eq) was added via cannula to a stirred solution of 64 (300 mg, 1.09 mmol) and benzyl chloromethyl ether (205 mg, 1.31 mmol, 1.2 eq) in 5 mL of tetrahydrofuran under an argon atmosphere. The dark blue solution was stirred at ambient temperature for 22 h and then 10 mL of 0.1 M aqueous hydrochloric acid was added. The inorganic precipitate dissolved and the mixture was diluted with ether. The organic phase was separated and washed successively with hydrochloric acid, water, 10\% aqueous sodium sulfite, water, and brine, and was dried over magnesium sulfate. Concentration of the solution gave 455 mg of a viscous yellow oil that was chromatographed (60 g of silica gel 60, ethyl acetate-hexanes 1:20) to afford 396 mg (92\%) of pure 76 as a colorless solid: Mp 81.5-82.0 °C (hexanes); IR (KBr) 3553, 2949, 2868, 1454, 1095, 611 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.30 (5H, m), 5.30 (1H, m), 4.49 (2H, s), 3.48 (1H, d, J=8.8
(±)-(1'α,2′β,4′α,8′αβ)-3',4',4'a,5',6',7',8',8'a-Octahydro-2′-hydroxy-4,5',5',8'a-tetramethylspiro[3-cyclohexene-1,1′(2'H)-naphthalene]-2′-methanol (77)

To 20 mL of distilled ammonia at -78 °C under an argon atmosphere was added 462 mg (1.16 mmol) of 76 in 10 mL of dry tetrahydrofuran. Sodium metal (54.0 mg, 2.33 mmol) was added in one portion and after 5 min the stirred solution turned deep blue. The cooling bath was removed and the mixture was allowed to reflux for 0.5 h, at which time the blue color dissipated. Solid ammonium chloride was added and the ammonia was removed under a stream of argon. The mixture was dissolved in a combination of ether, ethyl acetate, and water (2:1:3), and the aqueous phase was separated and extracted with ether. The combined organic phase was washed with water and brine, and dried over anhydrous sodium sulfate. Concentration of the solution gave a colorless glass that was chromatographed (30 g of silica gel 60, ethyl acetate-hexanes 1:4) to afford 337 mg (94%) of 77 as a colorless solid. An analytical sample was prepared by recrystallization from methylene chloride-hexanes: Mp 99.5-100.5 °C (needles);
IR (Nujol) 3430, 2923 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 5.36 (1H, bm), 3.62 (1H, dd, J=10.7, 4.9), 3.32 (1H, dd, J=10.7, 7.1), 2.30 (1H, bd, J~10), 1.64 (3H, bs), 1.21 (3H, s), 0.88 (3H, s), 0.87 (3H, s); ¹³C NMR (100 MHz, CDCl₃) δ 133.91, 121.59, 78.32, 68.21, 46.81, 44.54, 43.49, 41.65, 34.18, 34.05, 33.29, 33.01, 29.63, 27.52, 23.25, 22.10, 21.90, 18.61, 18.25, 17.43; MS m/z 306 (M⁺), 288, 275 (100%), 270, 257, 163, 150, 137, 95, 69; Anal. calcd for C₂₀H₃₄O₂: C, 78.39; H, 11.18. Found: C, 78.63; H, 11.18.

(±)-(1′α,2′β,4′αα,8′αβ)-3′,4′,4′a,5′,6′,7′,8′,8′α-Octahydro-2′-hydroxy-4,5′,5′,8′α-tetramethylspiro[3-cyclohexene-1,1′(2′H)-naphthalene]-2′-carboxaldehyde (78)

To a flame dried flask, purged with argon, was added 154 µL (1.76 mmol) of oxalyl chloride and 2.5 mL of dry methylene chloride. The solution was cooled to -60 °C and 261 µL (3.68 mmol) of dimethyl sulfoxide was added dropwise. After 5 min, a solution of 246 mg (0.801 mmol) of 77 in 5 mL of methylene chloride was added, followed, after 3 min, by 1.06 mL (7.61 mmol) of triethylamine. The mixture was warmed to ambient temperature and quenched by the addition of 15 mL of water. The aqueous phase was separated and extracted with methylene chloride and the combined organics were washed with water and concentrated in vacuo. The resultant light yellow solid (257 mg) was chromatographed (25 g of silica gel 60, ethyl acetate-hexanes 1:10) to afford 226 mg (93%) of 78 as a colorless crystalline solid: Mp 100.5-101.5 °C (prisms, hexanes); IR (Nujol) 3437 (sharp), 2953, 1704, 810 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 9.33 (1H, d, J=1.5), 5.47 (1H, m), 3.73 (1H, d, J=1.5, -OH), 2.56 (1H, bd, J=19.0), 2.24 (1H,
Compound 78 crystallized in space group P2₁2₁2₁ with a=6.392(1) Å, b=10.974(2) Å, c=24.922(2) Å, V=1748.2(6) Å³, z=4, d$_\text{calc} = 1.16$ g/cm$^3$, d$_\text{obsd} = 1.14$ g/cm$^3$. All non-equivalent reflections in the range 3.5° < 2θ < 45.0° were measured by the 0-2θ technique on a Nicolet R3m/V diffractometer with graphite monochromated Mo Kα radiation. The structure was solved with SHELXTL PLUS using 1109 unique reflections with F > 3σ(F). Full-matrix least-squares refinement with anisotropic temperature factors and calculated hydrogen atom positions led to final discrepancy indices of R = 0.0591 and R$_w$ = 0.0655.

Thermal Ene Reaction of 78: \((\pm)-(4\alpha,6\alphaβ,7\alpha,8\alpha,11\alphaα,11ββ)-\) Dodecahydro-4,4,11b-trimethyl-9-methylene-8,11a-methano-11aH-cyclohepta[α]naphthalene-6a(7H),7-diol (79)

A solution of 106 mg (0.348 mmol) of 78 in 20 mL of dry toluene was heated at reflux under an argon atmosphere for 16 h. The solvent was removed in vacuo and the resultant solid chromatographed (19 g of silica gel 60, cyclohexane-acetone 5:1) to afford 100 mg (94%) of 79 as a colorless crystalline solid: Mp 162-163 °C (plates, methylene chloride-hexanes); IR (KBr) 3500 (broad), 2935, 2867, 1446, 1102,
909, 895 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.81 (1H, bs), 4.69 (1H, bs), 3.66 (1H, dd, J=5.6, 7.3), 2.93 (1H, dd, J=7.3, 5.6), 2.81 (1H, s, -OH), 2.33 (1H, d, J=5.6, -OH), 2.25 (2H, m), 1.90 (3H, m), 1.09 (3H, s), 0.90 (6H, s); ¹³C NMR (100 MHz, CDCl₃) δ 148.91, 109.51, 78.82, 76.48, 51.96, 48.06, 47.20, 42.82, 41.78, 38.91, 35.78, 34.55, 33.31, 33.10, 28.85, 25.48, 22.76, 19.49, 18.43, 16.75; MS m/z 304 (M⁺), 286, 271, 268, 253, 205, 189, 150, 123, 69 (100%); Anal. calcd for C₂₀H₃₂O₂: C, 78.90; H, 10.59. Found: C, 78.97; H, 10.78.

Lewis Acid Mediated Ene Reaction of 78: (79), (±)-(4α, 6α, 7β, 8α, 11α, 11β)-1, 2, 3, 4, 4a, 5, 6, 8, 11, 11b-Decahydro-4, 4, 9, 11b-tetramethyl-8, 11a-methano-11aH-cyclohepta[a]naphthalene-6a(7H), 7-diol (80), and (±)-(4α, 6α, 6β, 8α, 8β, 9α, 9β, 9bβ)-Decahydro-4, 4, 8, 9b-tetrahydro-8H-8, 9a-ethanobenz[4, 5]inden[1, 2-b]oxet-6a(6bH)-ol (81)

To a stirred solution of 102.3 mg (0.336 mmol) of 78 in 2 mL of dry methylene chloride under argon at -78 °C, was added 0.70 mL (0.70 mmol, 1.0 M in hexanes) of dimethylaluminum chloride, dropwise. After 1 min, 2 mL of water was added, the frozen mixture was warmed to room temperature, and 1.0 M hydrochloric acid was added until the solution was acidic to litmus. The product was isolated by extraction with methylene chloride, and the combined organic extracts were dried over anhydrous sodium sulfate and concentrated to give 113 mg of a light yellow oil. Chromatography of this oil (25 g of silica gel 60, ethyl acetate-hexanes 1:4) gave 95.4 mg (93%) of 79/80/81 (1:1.2:2.4) as an inseparable mixture. Pure samples of 79 and 81 were obtained during the course of further transformations.
80: (by spectral subtraction) $^1$H NMR (400 MHz, CDCl$_3$) δ 5.50 (1H, b), 3.55 (1H, dd, J=7.3, 11.2), 2.73 (1H, s, -OH), 2.53 (1H, dd, J=7.3, 5.2), 2.40 (1H, bd, J=16.7), 2.33 (1H, d, J=11.2, -OH), 1.97 (1H, bd, J=16.7), 1.87 (1H, dd, J=5.2, 12.2), 1.69 (3H, b), 1.03 (3H, s), 0.89 (6H, s); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 136.47, 124.65, 80.50, 76.79, 51.16, 48.30, 43.10, 41.99, 41.51, 38.84, 35.12, 34.54, 33.41, 31.26, 28.92, 23.90, 22.72, 19.23, 18.46, 15.45.

81: Mp 149.5-150.5 °C (hexanes); IR (Nujol) 3300, 2854, 2923, 1490 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 3.94 (1H, d, J=5.9), 3.20 (1H, d, J=1.8, -OH), 2.76 (1H, dd, J=5.9, 5.4), 1.36 (3H, s), 1.08 (3H, s), 0.89 (6H, s); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 86.73, 83.99, 78.07, 49.91, 48.07, 42.08, 40.15, 38.77, 35.20, 34.46, 33.43, 33.09, 31.07, 28.18, 27.43, 22.37, 20.19, 18.58, 18.42, 14.08; MS m/z 304 (M$^+$), 289, 286, 271, 228, 179, 163, 109, 94, 81, 69. Compound 81 crystallized in space group P2$_1$/c with a=12.804(1) Å, b=63.13(2) Å, c=21.64(1) Å, β=102.15(1)°, Z=4, $d_{calcld}$ = 1.183 g/cm$^3$. The intensity data were measured on an Enraf-Nonius CAD4 diffractometer (graphite-monochromated Cu Kα radiation, ω-2θ scans). Of the 3512 independent reflections for θ < 75°, 2964 were considered to be observed [I > 3.0 σ (I)]. The structure was solved by a multiple-solution procedure and was refined by full-matrix least-squares. Two reflections which were strongly affected by extinction were excluded from the final refinement and difference map. In the final refinement, anisotropic thermal parameters were used for the non-hydrogen atoms and isotropic temperature factors were used for the hydrogen atoms. The final discrepancy indices are R=0.052 and $R_w$=0.076 for the remaining 2962
observed reflections. The final difference map has no peaks greater than 0.3 e/Å³.

\((±)-(4α,4bβ,8β,8αβ,11αR*,13αβ)\)-Dodecahydro-1,1,4a-trimethyl-7-
methylen-5H-4b,8-methanophtho[2′,1′:1,7]cyclohepta[1,2-d]-
[1,3]dioxole-10-thione \((82)\) and \((±)-(4αα,4b,8β,8αβ,11αR*,13αβ)\)-
1,2,3,4,4a,8,8a,12,13,13α-Decahydro-1,1,4a,7-tetramethyl-5H-4b,8-
methanophtho[2′,1′:1,7]cyclohepta[1,2-d][1,3]dioxole-10-thione \((83)\)

To an ice-cooled solution of 61.6 mg (0.202 mmol) of a mixture of 79-81 and 130 mg (1.06 mmol) of 4-dimethylaminopyridine in 2 mL of chloroform was added 28.5 μL (0.506 mmol) of thiophosgene. The orange solution was warmed to room temperature for 5 h then 1 g of silica gel 60 was added and the solvent was removed in vacuo. The resultant solid was placed atop 10 g of silica gel 60 and eluted with methylene chloride-hexanes (1:1) to afford 23.1 mg (56% based on recovered 81) of a 1:2 mixture of 82 and 83 respectively, that was used without further purification: IR (KBr) 3017, 2924, 1443, 1300,
909, 800, 658 cm⁻¹; \(^1\)H NMR (400 MHz, CDC\(_3\)) 8 5.41 (1H, bs), 4.72
(2.5H, m), 3.10 (0.5H, bt, J=6.5), 2.64 (1H, bt, J=6.0), 1.68 (3H,
bs), 1.06 (1.5H, s), 1.01 (3H, s), 0.92 (9H, s); \(^13\)C NMR (100 MHz,
CDC\(_3\) ) 8 192.91, 192.26, 144.89, 135.61, 121.92, 110.16, 96.49,
95.58, 95.56, 93.65, 55.81, 53.26, 47.29, 47.16, 45.52, 42.14, 41.53,
41.40, 38.33, 38.31, 37.93, 37.11, 35.70, 35.30, 34.39, 34.31, 33.64,
33.37, 33.33, 29.83, 26.70, 25.27, 23.36, 22.75, 22.69, 18.99, 18.76,

Further elution with ethyl acetate gave 25.3 mg of pure 81.
(±)-(1'α,2'α,4'aβ,8'aβ)-3',4',4'a,5',6',7',8',8'a-Octahydro-4,5',5',8'a-tetramethylspiro[3-cyclohexene-1,1'(2'H)-naphthalene]-2'-carboxaldehyde (85) and (±)-(4aα,5β,9aβ)-2,3,4,4a,7,8,9,9a-Octahydro-7-hydroxy-1,1',4',4a-tetramethylspiro[5H-benzocycloheptene-5,1'-[3]cyclohexen]-6(1H)-one (86)

To a solution of 22.3 mg (73.2 μmol) of 78 in 2 mL of dry tetrahydrofuran containing 28.0 μL (0.293 mmol) of tert-butanol under argon was added 2.9 mL (0.293 mmol, 0.1 M in tetrahydrofuran) of freshly prepared samarium diiodide. The resultant deep blue solution was stirred at room temperature for 14 h and then 0.1 M hydrochloric acid was added to dissolve the inorganic precipitate. The mixture was diluted with ether and the organic phase was washed with 0.1 M hydrochloric acid, 10% aqueous sodium sulfite, water, and brine, and dried over anhydrous magnesium sulfate. Concentration of the solution gave a colorless oil that was chromatographed (9 g of silica gel 60, methylene chloride-hexanes 2:1) to afford 13.3 mg (63%) of pure 85:  IR (neat) 2945, 1697 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 10.04 (1H, s), 5.36 (1H, b), 1.66 (3H, b), 0.87 (3H, s), 0.86 (3H, s), 0.80 (3H, s); ¹³C NMR (100 MHz, CDCl₃) δ 205.41, 132.57, 120.60, 47.74, 45.35, 43.21, 41.86, 40.83, 33.98, 33.21, 32.30, 30.24, 27.77, 23.69, 22.85, 21.92, 19.86, 18.93, 18.68, 16.38; MS m/z 288 (M⁺), 270, 231, 205, 177, 163, 137, 105, 95 (100%), 79, 67, 55; Exact mass calcd for C₂₀H₃₂O: 288.2453. Found: 288.2453.

Further elution gave 7.1 mg (32%) of 86: Mp 106-108 °C (hexanes); IR (KBr) 3469 (sharp), 2932, 1681, 1392, 1099, 801 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 5.38 (1H, m), 4.37 (1H, bd, J=7.1), 4.12 (1H, d, J=2.5), 2.62 (1H, bd, J=18), 2.43 (1H, bd, J=18), 1.55 (3H,
bs), 0.93 (3H, s), 0.85 (3H, s), 0.79 (3H, s); $^{13}$C NMR (100 MHz, CDC$_3$) δ 215.78, 135.48, 119.87, 73.87, 56.11, 51.25, 41.98, 41.64, 35.15, 34.68, 34.18, 33.74, 28.41, 27.37, 25.62, 23.00, 22.05, 21.71, 18.89, 15.61; MS m/z 304 (M$^+$, 100%), 286, 162, 149, 136, 123, 107, 93, 69; Exact mass calcd for C$_{20}$H$_{32}$O$_2$: 304.2402. Found: 304.2402.

(±)-(4αα,6αβ,8αα,11αα,11ββ)-Dodecahydro-6a-hydroxy-4,4,11b-trimethyl-9-methylene-8,11a-methano-11aH-cyclohepta[a]naphthalen-7-one (87)

To a solution of 79 μL (0.898 mmol) of oxalyl chloride in 2 mL of dry methylene chloride at -60 °C under argon was added 133 μL of dry dimethylsulfoxide (1.88 mmol). The diol 79 (124 mg, 0.408 mmol) in 4 mL of dry methylene chloride was added after 5 min, followed by triethylamine (0.54 mL, 3.88 mmol). The suspension was warmed to room temperature and quenched by the addition of 20 mL of water. The aqueous phase was separated and extracted twice with methylene chloride, and the combined organic extracts were concentrated in vacuo to leave a yellow solid. Chromatography of this material (20 g of silica gel 60, ethyl acetate-hexanes 1:5 after packing with methylene chloride-hexanes 1:1) afforded 121 mg (98%) of pure 87: Mp 197-198 °C (needles, hexanes); IR (KBr) 3449 (sharp), 2938, 1738, 885 cm$^{-1}$; $^1$H NMR (400 MHz, CDC$_3$) δ 4.71 (1H, s), 4.67 (1H, d, J=1.0), 3.12 (1H, d, J=5.8), 2.40 (1H, s, -OH), 2.37 (1H, m), 2.22 (2H, m), 2.12 (1H, m), 1.16 (3H, s), 0.93 (3H, s), 0.91 (3H, s); $^{13}$C NMR (100 MHz, CDC$_3$) δ 221.02, 147.77, 107.25, 79.98, 53.11, 50.99, 47.39, 41.74, 37.94, 34.56, 34.55, 34.10, 33.47, 33.31, 29.98, 26.94, 22.46, 18.24, 17.78, 16.25; MS m/z 302 (M$^+$), 274 (100%), 259, 256, 207,
136, 93, 55; Anal. calcd for C_{20}H_{30}O_{2}: C, 79.42; H, 10.00. Found: C, 79.55; H, 10.15.

(±)-(4α,6αβ,8α,11αβ,11ββ)-Dodecahydro-4,4,11b-trimethyl-9-methylene-8,11α-methano-11αH-cyclohepta[a]naphthalen-7(6αH)-one (88)

To a stirred solution of 87 (87.7 mg, 0.289 mmol) in 2 mL of dry tetrahydrofuran under an argon atmosphere at room temperature was added via syringe 82 μL (0.869 mmol) of dry tert-butanol and 8.70 mL (0.1 M in tetrahydrofuran, 0.869 mmol) of freshly prepared samarium diiodide. The deep blue solution was stirred for 12 h and then opened to the atmosphere to destroy excess samarium(II). The resultant yellow suspension was transferred to a separatory funnel, diluted with 30 mL of ether and washed with 0.1 M hydrochloric acid, 10% aqueous sodium sulfite, water and brine. After drying over anhydrous magnesium sulfate, the solution was concentrated to give a colorless solid that was chromatographed (16 g of silica gel 60, ethyl acetate-hexanes 1:10) to afford 71.8 mg (87%) of 88 as a colorless crystalline solid: Mp 110.5-111.0 °C (prisms, hexanes); IR (KBr) 2960, 2929, 2866, 1735, 1652, 895 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.67 (1H, bs), 4.65 (1H, bs), 3.04 (1H, d, J=5.8), 2.47 (1H, dd, J=5.8, 11.7), 2.25 (3H, m), 1.97 (1H, m), 1.73 (2H, m), 1.00 (3H, s), 0.90 (3H, s), 0.90 (3H, s); ¹³C NMR (100 MHz, CDCl₃) δ 220.24, 147.37, 107.10, 56.37, 49.72; 48.59, 46.85, 41.72, 37.78, 35.15, 34.45, 33.90, 33.23, 31.25, 38.54, 25.96, 22.56, 20.97, 19.41, 18.13; MS m/z 286 (M⁺, 100%), 268, 163, 135, 119, 105, 93; Exact mass calcd for C_{20}H_{30}O: 286.2297. Found: 286.2296; Anal. calcd for C_{20}H_{30}O: C, 83.85; H, 10.56. Found: C, 84.16; H, 10.65.
(±)-Exo-dehydro-2-desoxystemodinone (9) and (±)-Endo-dehydro-2-desoxystemodinone (10)

Method A: A stirred solution of 137.4 mg (0.479 mmol) of 88, 1.0 g (17.8 mmol) of powdered potassium hydroxide, and 1.5 mL (30.9 mmol) of hydrazine monohydrate in 10 mL of diethylene glycol was warmed to 140 °C under argon during 30 min. The mixture was maintained at 140 °C for 30 min and then warmed to 205 °C as the excess hydrazine and water were collected in a Dean-Stark trap. After 2 h at 205 °C, the solution was cooled to room temperature, diluted with 10 mL of water, and poured into 20 mL of brine. The aqueous solution was extracted with three portions of ether and the combined organic extracts were washed twice with brine and dried over magnesium sulfate. Concentration of the solution gave a light yellow oil that was chromatographed on 5 g of silica gel 60 with pentane to afford 98.9 mg (76%) of a colorless oil as a 1:2.5 mixture of 10/9 by NMR, identical with natural dehydro-2-desoxystemodinone (exo and endo) by 1H NMR, IR, and MS. This material was used in subsequent transformations without further purification.

Method B: A solution of 35.9 mg (0.124 mmol) of 89 in 5 mL of dry pyridine under argon was treated with excess phosphorous oxychloride (0.23 mL, 2.48 mmol) and warmed to 70 °C for 15 min. The solution was cooled to room temperature, poured into 30 mL of water and extracted with three portions of pentane. The combined organic extracts were washed with saturated aqueous copper(II) sulfate, water and brine, and dried over magnesium sulfate. Concentration of the solution gave 23.7 mg of an oil that was eluted from 1 g of silica
gel 60 with pentane to afford 22.2 mg (66%) of a 1.7:1 mixture of 10 and 9 respectively.

9: $^1$H NMR (400 MHz, CDCl$_3$) δ 4.44 (1H, m), 4.36 (1H, m), 2.69 (1H, bt, J=6.6), 2.28 (1H, m), 2.10 (2H, m), 0.96 (3H, s), 0.88 (3H, s), 0.87 (3H, s).

10: $^1$H NMR (400 MHz, CDCl$_3$) δ 4.99 (1H, b), 1.64 (3H, d, J=1.4), 0.95 (3H, s), 0.88 (3H, s), 0.87 (3H, s).

$\pm$)-2-Desoxystemodinone (3) and $\pm$)-13-Epi-2-desoxystemodinone (89)

A stirred solution of 98.9 mg (0.363 mmol) of a 1:2.5 mixture of 10 and 9 in 5 mL of dry benzene was treated with 102 mg of m-chloroperbenzoic acid (80-85% tech., 0.472 mmol) for 12 h under an argon atmosphere in the dark. The mixture was diluted with methylene chloride and washed with 10% aqueous sodium sulfite and water, and was concentrated to give 109.4 mg of a colorless semi-solid that was dissolved in 5 mL of dry tetrahydrofuran. Lithium triethylborohydride (1.14 mL, 1.14 mmol, 1.0 M in tetrahydrofuran) was added via syringe and the solution was stirred at ambient temperature under argon for 4 h. A few drops each of 1.0 M potassium hydroxide and 30% hydrogen peroxide were added and, after 5 min, the mixture was transferred to a separatory funnel, diluted with ether and washed with water and brine, and dried (magnesium sulfate). Concentration of the solution gave 122 mg of an oil that was chromatographed (25 g of silica gel 60, ethyl acetate-hexanes 1:5) to afford 50.5 mg (48%) of pure $\pm$)-2-desoxystemodinone (3), identical with authentic material by IR, MS, $^1$H and $^{13}$C NMR, and thin layer chromatographic behavior in three solvent systems: Mp 108.0-109.5 °C (prisms, hexanes); IR (KBr)
Compound 3 crystallized in space group P2\(_1\) with \(a=12.874(2)\ \text{Å}\), \(b=21.345(4)\ \text{Å}\), \(c=12.887(2)\ \text{Å}\), \(\beta=93.38(1)^\circ\), \(Z=8\), and \(d_{\text{calc}} = 1.091\ \text{g/cm}^3\). The intensity data were measured on a Hilger-Watts diffractometer (Ni-filtered Cu K\(\alpha\) radiation, \(\theta\)-2\(\theta\) scans, pulse-height discrimination). Of the 6758 accessible reflections for \(\theta < 70^\circ\), 4934 were considered to be observed \([I < 2.5\sigma(I)]\).

The structure was solved by a multiple-solution procedure and was refined by block-diagonal least squares in which the matrix was partitioned into four blocks. Seven reflections which were strongly affected by extinction were excluded from the final refinement and difference map. In the final refinement, anisotropic thermal parameters were used for the hydrogen atoms. The final discrepancy indices are \(R = 0.064\) and \(wR = 0.067\) for the remaining 4927 observed reflections. The final difference map has no peaks greater than \(\pm 0.2\ \text{e Å}^{-3}\).

Further elution gave 35.0 mg (33%) of pure (+)-13-epi-2-desoxy-stemodinone (89): \(\text{Mp} 182.5-183.5^\circ\ \text{C (needles, hexanes)}\); IR (KBr) 3300, 2936, 2865, 1469, 1451, 1129, 1116, 949, 930 cm\(^{-1}\); \(^1\text{H NMR (400 MHz, CDCl}\textsubscript{3}) \delta 2.09 (1\text{H, bdd, } J=8.3, 14.0), 1.90 (3\text{H, m}), 1.23 (3\text{H, s}), 0.95 (3\text{H, s}), 0.88 (3\text{H, s}), 0.87 (3\text{H, s}); \(^{13}\text{C NMR (100 MHz, CDCl}\textsubscript{3}) \delta 72.80, 50.52, 47.41, 47.11, 41.90, 38.25, 27.63, 36.67,
36.22, 35.78, 34.58, 33.92, 33.21, 32.77, 29.11, 26.18, 22.80, 22.31, 19.10, 18.80; MS m/z 290 (M⁺), 257, 219, 149, 133, 123, 94 (100%), 69; Anal. calcd for C₉0H₃₄O: C, 82.70; H, 11.80. Found: C, 83.10; H, 12.16.

(±)-(4α,6α,7β,8α,11α,11β)-Tetradecahydro-4,4,11β-trimethyl-9-methylene-8,11α-methano-11αH-cyclohepta[a]naphthalen-7-ol (90)

To a solution of 35.0 mg (0.122 mmol) of 88 in 3 mL of dry tetrahydrofuran under argon at 0 °C, was added 2.3 mg (61 μmol) of lithium aluminum hydride. After 5 min, 4 drops of saturated aqueous Rochelle’s salt was added and the mixture was diluted with ether and washed with water and brine, and dried over magnesium sulfate. Concentration of the solution gave 34.7 mg (99%) of pure 90 as a colorless crystalline solid: Mp (prisms, hexanes) 120-121 °C; IR (KBr) 3277, 2917, 878 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.77 (1H, bs), 4.64 (1H, bs), 3.88 (1H, dd, J=1.8, 6.9), 2.85 (1H, dd, J=6.1, 6.4), 2.46 (1H, m), 2.22 (2H, m), 2.04 (1H, ddd, J=2.4, 5.5, 11.8), 0.95 (3H, s), 0.88 (3H, s), 0.87 (3H, s); ¹³C NMR (100 MHz, CDCl₃) δ 149.74, 108.57, 83.13, 49.62, 49.45, 48.10, 47.32, 41.87, 38.63, 35.46, 35.16, 34.40, 33.81, 33.26, 31.79, 28.63, 22.75, 21.66, 18.63, (19 signals, 2 carbons coincidental); MS m/z 288 (M⁺, 100%), 270, 257, 255, 201, 190, 175, 161, 147, 132, 119, 105, 95, 69; Anal. calcd for C₂₀H₃₂O: C, 83.27; H, 11.18. Found: C, 83.40; H, 11.48.
Methyl (±)-(4α,6αβ,7β,8α,11αα,11ββ)-Tetradecahydro-4,4,11b-trimethyl-9-methylene-8,11α-methano-11αH-cyclohepta[a]naphthalen-7-yl sulfate (91)

A solution of 10.6 mg (36.7 µmol) of 90, 10.2 µL (73.4 µmol) of triethylamine, and 1 mL of dry methylene chloride at 0 °C under argon was treated with 4.3 µL (55.0 µmol) of methanesulfonyl chloride. After 20 min, water was added and the aqueous layer was separated and extracted with methylene chloride. The combined organic extracts were concentrated to afford 13.2 mg (97%) of 91 that was used without further purification: ¹H NMR (80 MHz, CDCl₃) δ 4.80-4.50 (3H, m), 2.94 (3H, s), 0.97 (3H, s), 0.87 (6H, s).

(±)-(4α,6αβ,7β,8α,9α,11αα,11ββ)-Dodecahydro-4,4,11b-trimethylspiro-[8,11α-methano-11αH-cyclohepta[a]naphthalene-9(2H),2’-oxiran]-7-yl methyl sulfate (92)

To a solution of 13.2 mg of 91 (35.9 µmol) in 1 mL of dry methylene chloride under argon was added 11.6 mg (54.0 µmol, 80-85% tech.) of m-chloroperbenzoic acid in one portion. After 45 min the mixture was warmed to ambient temperature for 3 h and then diluted with water and ether. The organic phase was washed with water and brine, and dried over magnesium sulfate. The solution was evaporated and the resultant colorless solid was dissolved in ethyl acetate-hexanes (1:1) and filtered through a plug of silica gel 60. Concentration of the filtrate afforded 11.9 mg (86%) of a 10:1 mixture of the diastereomeric epoxides 92, which were used in the subsequent transformation without further purification: ¹H NMR (80 MHz, CDCl₃)
$ \delta 4.70 (1H, m), 3.08 (0.3H, -OSO_2CH_3 of minor diastereomer), 2.99 (3H, s), 2.71 (2H, s), 0.99 (3H, s), 0.89 (6H, s).

$^{(+)}(3a\alpha, 6a\beta, 9a\alpha, 9b\beta)$-Dodecahydro-$\alpha, 6, 6, 9a$-tetramethyl-$9b$H-benz[e]-indene-$9b$-propanol (93)

A solution of crude 92 (11.9 mg, 31.0 \text{ \textmu mol}) in 1 mL of dry tetrahydrofuran under argon was treated with 310 \text{ \textmu L} (310 \text{ \textmu mol}, 1.0 M in tetrahydrofuran) of lithium triethylborohydride in tetrahydrofuran. After 1 h at room temperature, the solution was heated at reflux for 5 h, then cooled and the excess hydride quenched by addition of water. Five drops of 1 M potassium hydroxide were added, followed by 3 drops of 50% hydrogen peroxide and, after the initially exothermic reaction subsided, water and ether were added. The organic layer was separated, washed with water and brine, and dried over magnesium sulfate. Concentration of the solution gave 11.3 mg of a semisolid that was chromatographed (5 g of silica 60, ethyl acetate-hexanes 1:3) to afford 7.3 mg of 93 (1:1 mixture of diastereomers) as a colorless oil: IR (neat) 3354 (broad), 2934, 2866, 1457, 1377, 706 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.74 (1H, m), 5.49 (1H, m), 3.59 (1H, m), 2.47 (1H, bd, J=16.4), 2.14 (1H, m), 1.98 (1H, m), 1.88 (1H, dd, J=2.3, 16.2), 1.14 (3H, d, J=5.8), 1.01 (1.5H, s), 1.00 (1.5H, s), 0.90 (3H, s), 0.88 (3H, s); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 137.82, 137.73, 126.86, 126.81, 69.63, 69.50, 52.48, 48.20, 46.58, 46.52, 41.85, 39.31, 37.95, 37.88, 37.75, 35.71, 34.38, 33.22, 33.00, 32.93, 23.57, 23.51, 22.78, 19.55, 18.61; MS m/z 290 (M$^+$), 257, 219, 217, 152, 147, 137, 123, 119, 105, 94 (100%), 81, 69, 55; Exact mass calcd for C$_{20}$H$_{34}$O: 290.2610. Found: 290.2610.
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For bibliographic citations relating to Part I see pp. 51-55.


17. The synthesis of (±)-2-desoxystemodinone (3) reported by Chatterjee (ref. 14a) is called into question by a quite implausible hydrogenation at the final stage. The data for 3 presented by this author has been challenged by Corey (ref. 14b, footnote 21) and also conflicts with our NMR and melting point data. For comment on another publication by this author, see Cornforth, J. Tetrahedron Lett. 1980, 21, 709.


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43. We are grateful to Dr. C. Campana, Nicolet Analytical Instruments, X-Ray Division, for the crystal structure determination of 78.


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A. Introduction

Boromycin (1), first reported in 1967 by Prelog et al., was isolated from the culture broth of *Streptomyces antibioticus* (Waksmann et Woodruff) obtained from an African soil sample. The unusual constitution and structure of this boron-containing isolate was revealed through subsequent chemical and crystallographic studies performed by Prelog, Dunitz, et al.\textsuperscript{2} Single-crystal x-ray analysis of the rubidium complex 2, obtained by selective removal of the valine residue from 1 with rubidium hydroxide, unveiled the tertiary structure of boromycin and several unique chemical features.
The most notable feature of the boromycin topography is the presence, at the core of the 28-membered macro-dilactone, of a borate Bøseken complex linking the oxygen atoms at carbons 2,2' and 3,3'. If dissected through this and the lactone linkages, the macrocycle is seen to be composed of two halves that differ only in minor respects. The "southern" portion contains a cis double bond between carbons 12 and 13 and a secondary hydroxyl at C-16, esterified with the unusual amino acid D-valine. This segment has been modified in the "northern" half and appears as a tetrahydrofuran ring. Additionally, the absolute stereochemistry at each stereocenter in both halves is identical except for the C-9 and C-9' hydroxyls, which are R and S respectively. These secondary alcohols, as well as other hydrophilic portions of the boromycin structure, are directed toward the interior of the molecule, forming a coordination sphere that can complex alkali metal cations (Figure A.1). Conversely, the exterior structure of 1 is comprised of mostly hydrophobic functionality, endowing the molecule with the ability to function as a transport
system that conveys cations across cell membranes. A similar x-ray conformation is observed for 3 in which the borate is absent, attesting to the structural integrity of the macrocycle.
The transport properties of boromycin, though demonstrated, have not been unequivocally linked to its antibiotic activity. Boromycin has been shown to be active against gram-positive bacteria such as *Staphylococcus aureus* SG511 and *Streptococcus mitas* but is inactive against gram negative bacteria. Its ability to inhibit certain fungi and protozoae has also been evaluated.\(^5\)

Subsequent to the discovery of boromycin, three related ionophores, aplasmomycins A (4), B (5), and C (6) were isolated from *Streptomyces griseus*, occurring in shallow sea sediment.\(^6\) X-ray analysis of the silver salt of 4 established several structural similarities with boromycin, including configurational identity with the "northern" half of 1 and the presence of a central borate complex.\(^7\) Two other closely related derivatives of 1, the N-formyl and N-acetyl derivatives have also been isolated.\(^8\)

\[\begin{align*}
4, & \quad R = R' = H \\
5, & \quad R = H, \quad R' = Ac \\
6, & \quad R = R' = Ac
\end{align*}\]
Boromycin and aplasmomycin represent the first well-characterized organic natural products that contain boron. The unique constitution and complex functionality displayed in these macrocycles, have stimulated interest in their total synthesis and biogenesis. To date, two syntheses of the C$_2$-symmetrical aplasmomycin have been reported. A complete synthesis of boromycin has not yet been accomplished, although the synthesis of advanced intermediates has been announced and at least one approach is in its final stages.

Biosynthetic studies by Floss et al. have indicated that the carbon skeleta of these metabolites are derived from acetate/malonate units by the polyketide pathway with the methyl branches coming from either methionine or propionate.

During the course of synthetic and biosynthetic studies of boromycin, partial attribution of its $^1$H NMR spectrum had been achieved. However, in order to facilitate accurate analysis of precursor incorporation experiments and identify certain advanced synthetic intermediates, it was clear that a more complete assignment of the NMR spectrum was necessary. The purpose of the study described in the following section was to assign, as far as possible, all $^1$H and $^{13}$C signals of 1 and also to rigorously test the capability of a newly acquired Bruker AM 400 NMR spectrometer.
B. Discussion and Results

Complete assignment of the $^{13}$C and $^1$H NMR spectra of a molecule as complex as boromycin is a formidable task. Complicating the identification of its 45 carbon and 73 proton resonances is the loss of proton connectivity across 7 quaternary centers and the near identity of the two tetrahydropyran subunits. Nevertheless, we have undertaken and completed\textsuperscript{14} this assignment through the use of homonuclear and long-range $^1$H-$^{13}$C heteronuclear shift correlation.\textsuperscript{15}

$^1$H Assignments

Examination of the two-dimensional $^1$H-shift correlated spectrum (COSY-45) of sodium boromycinate (7),\textsuperscript{16} measured at 400 MHz, permitted a nearly complete assignment of the 7-18, 9-17, 7'-18', 9'-17', and 2"-5" spin systems (Table A.1). These assignments were derived by drawing rectangles between off-diagonal peaks on the contour plots shown in Figure A.2 for the "northern" segment (C9'-C17') and Figure A.3 for the "southern" segment (C9-C17, 2"-5") of 7. Although connectivity between protons in the 4-6, 4'-6', and 10'-12' regions of 7 was difficult to determine because of the high signal density in the aliphatic region of the spectrum, it was possible to identify these protons by examination of the individual columns and rows of the two dimensional matrix. For example, columns corresponding to $\delta$1.18 and 1.38 (H10' R,S) showed cross peaks in each case at $\delta$1.24 and 1.65 (H11' R,S). The connectivity between H11' R,S and H12' R,S was established in a similar fashion.
Figure A.2 Two-Dimensional $^1$H Chemical Shift Correlated NMR Spectrum of the C9'-C17' Segment of 7.
Figure A.3 Two-Dimensional $^1$H Chemical Shift Correlated NMR Spectrum of the C9 - C17 and C2''-C5'' Segments of 7.
Application of the same protocol to the H4-H6 and H4'-H6' spin systems completed the proton assignments to the segments of 7 that are separated by quaternary carbons.

It was not possible through this analysis to distinguish between the proton signals arising from the tetrahydropyran rings, the geminal methyl groups, or the H2, H2' methines in the "northern" and "southern" segments of 7. The observation of long-range coupling between H15' and H2' in the COSY-45 spectrum of 7, however, allowed a tentative assignment to the latter proton. The remaining 1H assignments of 7 were completed during the course of its 13C spectral analysis.

13C Assignments

A standard DEPT pulse sequence at 100 MHz was employed to delineate the 13C signals due to the 10 methyl, 11 methylene, 17 methine, and 7 quaternary carbons of 7. With the previously deduced 1H assignments, a heteronuclear 1H-13C shift correlation (HETCOR, Figure A.4) permitted a detailed analysis of the 13C spectrum. This led to the identification of all carbons shown in Table A.2 except the C2,2' - C8,8' pairs, the 4 geminal methyl substituents (C19, 19', C20, 20') and the three carbonyl carbons (C1, C1', C1'').

Several published methods exist for the determination of carbon-carbon connectivity across quaternary centers, of which the best known is the 13C-13C INADEQUATE pulse sequence. This experiment is limited, however, by a requirement for long acquisition times and high sample concentration. In addition, carbonyl carbons are often difficult to observe due to their long relaxation
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<td>d</td>
<td>4' (6.6)</td>
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<tr>
<td>19' (3H)</td>
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<td>s</td>
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<tr>
<td>20 (3H)</td>
<td>0.94</td>
<td>s</td>
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<td>dqq</td>
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<tr>
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<td>5.15</td>
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<td>25'</td>
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Table A.2 $^{13}$C NMR Assignments to Sodium Boromycinolate (7) (100.614 MHz)

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<td>2'</td>
<td>77.25</td>
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Figure A.4: Heteronuclear $^1$H-$^{13}$C Chemical Shift Correlated NMR Spectrum of 7.
times. The use of long-range $^1\text{H}$$^{13}\text{C}$ shift correlation\textsuperscript{18} appeared to be an attractive alternative and application of a pulse program,\textsuperscript{19} modified from an earlier sequence,\textsuperscript{20} solved the assignment difficulties with the remaining thirteen centers of 7. The results of this experiment are shown in Figure A.5 and an expanded version of the carbonyl region is shown in Figure A.6. Examination of the latter allows identification of the three carbonyl carbons of 7. A cross-peak that correlates the carbon at $\delta$172.22 and the proton at $\delta$3.40 unambiguously identifies the former as the valine ester carbonyl (C1$''$). The carbon resonance at $\delta$170.51 shows coupling to H15$'$ at $\delta$4.99 and to a proton at $\delta$4.41. This allows simultaneous assignment of not only the C1 carbonyl and H2 proton but the C2 methine carbon as well. The third carbonyl (C1$'$) at $\delta$170.20 shows a complementary correlation to H2$'$ and H15.

In order to assign the $^1\text{H}$ and $^{13}\text{C}$ resonances to the tetrahydropyran rings of 7 it was necessary to establish connectivity between C9 and C7 and between C9$'$ and C7$'$. The long-range HETCOR experiment nicely solved this problem (Figure A.5) by revealing a coupling between the C9 carbon and two signals at $\delta$0.74 and 0.94, which are clearly the C19 and C20 geminal methyl substituents. These same resonances were found to be coupled to C7 and C8 at $\delta$73.05 and 39.28 respectively, thus providing the logic necessary for assignment of this segment. The C9$'$-C7$'$ spin system was identified in an analogous fashion.

The distinction between the pro-R (C19, C19$''$) and pro-S (C20, C21$'$) geminal methyl groups could not be made through our analysis but was addressed independently by Floss et al. in NOE experiments.
Figure A.5 Long-Range Heteronuclear 1H-13C Chemical Shift Correlation NMR Spectrum of 7.
Figure A.6 Carbonyl Region of the Long-Range Heteronuclear $^1$H-$^{13}$C Chemical Shift Correlated NMR Spectrum of 7.
performed on 7. For example, irradiation at $\delta 0.72$ resulted in a major NOE at H25' and at H16, thereby identifying the irradiated signal as H20'. The folding of 7 evidently brings this methyl group into close proximity with H25' and H16. Similar procedures established the identity of the remaining geminal methyls and indicated that the solution conformation of 7 closely approximates the tertiary structure observed in the crystalline state.

The last crucial piece of information to be gleaned from the long-range HETCOR of 7 was the assignment of the C3 and C3' quaternary carbons. A strong correlation between the down-field signal ($\delta 105.73$) and the C-18' methyl protons at $\delta 0.95$ (Figure A.5) established the C3' resonance while a parallel correlation between the C18 methyl group ($\delta 0.98$) and the C3 resonance ($\delta 105.13$) afforded the final data needed to complete a full carbon and proton spectral analysis of 7.

The NMR analysis of 7 is among the most comprehensive exercises in spectral interpretation that has been applied to a non-polymeric system and illustrates the power of the NMR method as a structural tool. The experience gained from this study laid much of the groundwork for subsequent applications of the new Bruker AM400 spectrometer and its related software to the solution of complex structural problems. In addition, the $^1$H and $^{13}$C assignments made to 7 have proven invaluable for identification of synthesized segments of 1 as the total synthesis of this macrolide has advanced towards completion.
C. Experimental

The boromycin sodium complex (7) used in this study was obtained from Merck and Co. Approximately 80 mg of the complex was dissolved in 0.5 mL of CDCl₃, containing 0.1% TMS as an internal standard, resulting in a concentration of 0.18M. The solution was transferred to a 5 mm NMR tube and used for all subsequent 2-D NMR studies.

All two-dimensional spectra of 7 were recorded at 297K with a Bruker AM400 spectrometer equipped with an Aspect 3000 computer operating in the Fourier transform mode with quadrature detection. Standard Bruker pulse programs (version 840301.1) were used unless otherwise noted.

The two-dimensional ¹H-¹H shift correlated (COSY-45) data for 7 were acquired at a sweep width of 2500 Hz (4096 data points) in the F₂ domain; 1024 spectra (16 scans each) were accumulated with 0.400 msec increments across the interval 3 μsec to 409.603 msec. A 1 sec recycle delay was inserted between scans to allow spin relaxation. The digital resolution was 1.221 Hz/pt in both dimensions after zero-filling in F₁. Resolution enhancement was accomplished by application of a x/2 shifted sinebell window function to F₁ and F₂ prior to Fourier transformation.

The heteronuclear ¹H-¹³C shift correlated (HETCOR) experiment for 7 was performed with a 14,285 Hz (4096 data point) spectral width in the F₂ (¹³C) dimension and a ±1231 Hz (512 data point) window in the F₁ (¹H) domain; 512 individual spectra (32 transients each) were acquired at an incremental delay of 0.203 msec.
across the interval 3 µsec to 103.939 msec. Two dummy scans were used between files with a 1 sec recycle delay between scans. Zero-filling afforded digital resolution in the F1 and F2 dimensions of 2.405 and 6.975 Hz/pt, respectively. A Gauss-Lorentz resolution enhancement of 0.300 with a -1.000 line broadening was applied to both domains before Fourier transformation.

The long-range heteronuclear shift correlated (LR HETCOR) spectral data for 7 were acquired with sweep widths of 17,241 Hz (4096 data points) in the F2 (13C) domain and ±1400 Hz (256 data points) in the F1 (1H) dimension. Zero-filling afforded digital resolution in F1 and F2 of 5.469 and 8.419 Hz/pt, respectively; 256 spectra were accumulated of 128 transients each, with an incremental delay of 0.3571 msec over the interval 3 µsec to 91.4206 msec. Two dummy scans were used between files with a 1 sec recycle delay between scans. Resolution enhancement was achieved by application of a Gauss-Lorentz multiplication of 0.500 and a line broadening of -1.000 in F2 and a π/4 shifted sinebell in the F1 domain prior to transformation.
D. References


16. We are indebted to Drs. Ralph Hirshmann and John Hannah, Merck and Co., for a sample of boromycin sodium salt.


