The stereocontrolled synthesis of the southern lactone 17 of boromycin and of the northern segments of both boromycin and aplasmomycin are described. The syntheses begin with enantioselective epoxidation of 3-buten-2-ol (42) to provide the optically active 2(S),3(R) epoxy alcohol 43. The absolute configuration was confirmed by preparing 43 from (-)-2,3-dihydroxybutyric acid (45). 2,5-Dideoxyribofuranose (54) and 2,5-dideoxyribo-γ-lactone (55) were synthesized from 43.

Segments 61 and 39, corresponding to the southeast quadrant of boromycin, and 100 and 107, representing northwest quadrants of aplasmomycin and boromycin, were also prepared from 43. The northeast and southwest quadrants of boromycin and aplasmomycin, 74, were synthesized in optically active form from isobutyraldehyde. Coupling of 74 with 61, followed by modification of functionalities, provided the southern lactone 17 of boromycin. In an intramolecular oxyselenation study for the formation of the tetrahydrofuran ring in the northern segments of boromycin and aplasmomycin, treatment of cis olefinic sulfone 96 with phenylselenyl chloride provided predominantly
the 2,5-cis isomer, whereas the trans olefinic sulfone 106 gave the desired 2,5-trans isomer as a major product.

The acyl dithiane 129 was prepared from 83, but coupling of this compound with carboimide 131 failed, presumably due to the weak nucleophilicity of the anion of the dithiane. The more reactive 1,3-dithiane 137 was prepared from 124 for the purpose of adding C(1) and C(2) to aplasomycin.
Studies on the Synthesis of the "Northern" and "Southern" Segments of Boromycin and Aplasmomycin.

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Typed by Judy Davies for Myung Chol Kang
To my father and fellow chemist,

Seong Ho Kang.
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STUDIES ON THE SYNTHESIS OF THE "NORTHERN" AND "SOUTHERN" SEGMENTS OF BOROMYCIN AND APLASOMOMYCIN.

I. INTRODUCTION

The chemistry of macrolide antibiotics has attracted intense interest in recent years. Generally, a macrolide is defined as a molecule containing a medium- to large-ring lactone within its structure. Since the first isolation of pikromycin by Brockmann and Henkel in 1950, a large number of macrolide antibiotics have been isolated from natural sources, and many have proved to be of considerable pharmacological importance. In addition to the macrocyclic lactone, their structures incorporate numerous substituents, varying from simple methyl or hydroxyl groups to glycoside units, positioned asymmetrically on the perimeter. Examples of polyoxo macrolides, which usually contain 12, 14, or 16 membered rings, include methymycin (1), pikromycin (2), erythromycin A (3) and B (4), oleandomycin (5), leucomycin A3 (6), carbomycin A (7) and B (8), and tylosin (9). Several of these compounds are used in clinical medicine today.

A second subclass of macrolides, the polyene antibiotics, which includes amphotericin B (10) and chainin (11), are characterized by larger rings and distinct hydrophilic (polyhydroxy) and hydrophobic (polyene) portions. Most of these compounds are antifungal but not antibacterial agents. Macrolide structures containing two or more ester linkages within the macrocyclic ring and possessing antibiotic
Polycrystalline Macrolide Antibiotics

Methymycin (1)
R: Desosaminyl

Pikromycin (2)
R: Desosaminyl

Erythromycin A (3)
R1: Desosaminyl
R2: Cladinosyl

Erythromycin B (4)
R1: Desosaminyl
R2: Cladinosyl

Oleandomycin (5)
R1: Desosaminyl
R2: Oleandrosyl

Leucomycin A3 (6)
R: (Isovaleryl)-
mycarosyl-mycaminosyl

OH

COCH3
Glycosidic Components of Polyoxo Macrolides

- **D-Desosamine**
- **L-Cladinose**
- **D-Mycinose**
- **L-Mycarose**
- **L-Oleandrose**
- **D-Mycaminose**
and ionophoric properties are also known to occur in nature. Aplasmomycin (12) and boromycin (13) are unusual boron-containing natural products with 28-membered rings, which are included in this group. A family of 32-membered tetrolides, which includes nonactin (14), has also become known recently. This group of antibiotics has a hydrophilic cavity capable of complexing an alkali metal cation, and thus plays a key role in the transport of ions across membranes in biological systems.

Although many of these biologically important macrolides have been known for some time, they have only recently received the attention of synthetic organic chemists. As revealed by the structures
Aplasmomycin (12)

Boromycin (13)

Nonactin (14)
shown above, the synthesis of these compounds presents a substantial challenge which is due to two fundamental problems; first, the construction of a large, highly functionalized lactone ring and, second, the stereochemical control of numerous chiral centers. A successful approach to the synthesis of these macrolides thus hinges upon the development of new methods for both large ring formation and for stereo-specific construction of the seco-chain.

Aplasmomycin is a novel antibiotic which was obtained from strain SS-20 of *Streptomyces griseus* isolated from a sample of shallow sea sediment.\(^{12}\) The complete structure of aplasmomycin was determined by a single-crystal X-ray analysis of its silver salt, which revealed the formula \(^{15}\) This structural analysis showed several interesting features. The molecule possesses a two-fold rotation axis of symmetry passing through the boron and silver atom. Thus, the compound is composed of two identical subunits, each containing a tetrahydrofuran ring along with a trans olefinic linkage. It has been shown that the tetrahydropyran ring adopts a regular chair conformation and the tetrahydrofuran ring a puckered orientation. The five-membered ring, formed by complexation of the diolide with boric acid, has an envelope conformation. This Böeseken complex of boric acid is also a structural feature of boromycin.

Boromycin (13) is also a metabolite of a *Streptomyces* strain, in this case obtained from an African soil sample.\(^{11}\) The structure of boromycin was determined by an X-ray crystallographic study of the rubidium salt of desvalylboromycin, a substance obtained by saponification of the D-valine ester of 13 with rubidium hydroxide.\(^{16}\) The structure of boromycin is seen to be similar in many respects to that
of aplasmomycin (12). In the case of 13, the molecule consists of
two halves which differ in only minor respects. First, a cis double
bond at C(12)-C(13) and an esterified hydroxyl at C(16) in the south-
ern half have been modified to a tetrahydrofuran ring in the north-
ern half. Second, the configuration at C(9) and C(9') are epimeric
in the two half structures. All other pairs of corresponding chiral
centers have the same configuration.

The biological activity of aplasmomycin is essentially the same
as that of boromycin. Aplasmomycin is active against gram-positive
bacteria in vitro and plasmodia in vivo when administered orally to
mice infected with Plasmodium berghei.17 Boromycin is also active
against gram-positive bacteria such as Staphylococcus aureus SG511
and Streptococcus mitis, as well as certain fungi and protozoae, but
is inactive against gram-negative bacteria.18 Although these two com-
pounds have the same spectrum of activity, a higher concentration of
aplasmomycin appears to be required to inhibit bacterial growth. The
acute toxic dose in mice (LD 50) for aplasmomycin is 125 mg/kg when
administered by intraperitoneal injection, while that for boromycin
is 180 mg/kg orally.

As ionophoric antibiotics, these compounds are exquisitely de-
signed for their biological roles in ion transport. Their tertiary
structures possess an inward directed orientation of the oxygen lig-
ands, providing an ideal geometry to accommodate a potassium ion, while
the backbone of the molecule surrounds this hydrophilic core to pro-
vide a lipophilic surface which presumably facilitates penetration of
the cell membrane. However, although such transportation of metal
cations across the cellular membrane has been demonstrated, it is not
at all clear that this property is related to the antibiotic activity of these molecules.

The study of the biosynthesis of aplasmomycin and boromycin by Foss and his co-workers\textsuperscript{19} showed that the major portion of the carbon skeleton of these molecules is derived from acetate/malonate units, which provide carbons (1)-(14) and (1')-(14'). The six methyl groups at carbons (4), (4'), (8) and (8') are derived from methionine. The three-carbon starter units probably come from either propionate or glycerol, but there is no firm evidence for this as yet.

Limited degradation studies\textsuperscript{16} and a partial synthesis\textsuperscript{20} of boromycin have been reported. Alkaline hydrolysis of boromycin, gave desvalylboromycin (15) and acidic hydrolysis of the latter provided desvalyldesboroboromycin (16). More vigorous saponification of boromycin yielded two lactones 17 and 18, resulting from a retro-Claisen scission of the glycolate moiety in the northern and southern halves respectively.

Hanessian and his co-workers\textsuperscript{23} also carried out a degradation of boromycin to 17 and 18 by acetylation of desvalylboromycin (15) with acetic anhydride, followed by acidic hydrolysis to give the monoacetylated hexaol 19. Periodate cleavage of the C(2)-C(3) unit, followed by saponification and relactonization, gave southern and northern lactones 17 and 18, respectively in a 1:1 ratio. The partial synthesis of boromycin from desvalyldesboroboromycin (16) was accomplished by introducing a boron unit with trimethylborate, followed by esterification with a protected D-valine.\textsuperscript{20}

The total synthesis of aplasmomycin has been reported recently by Corey and his co-workers.\textsuperscript{21} In this synthesis, two chiral starting
materials, (+)-pulegone and D-mannose, were employed for construction of the key segments 20 and 21. Coupling of these two units was followed by the addition of the C(1)-C(2) moiety with dimethyl oxalate to give half of the aplasmomycin skeleton in the form of carboxylic acid 23 and its ester 24. Esterification of 23 with 24 provided 25, and lactonization of the latter gave the macrocyclic α-keto dilactone 26. The protected macrocycle was transformed into desboroaplasmomycin (27), obtained as a mixture of diastereomers differing in configuration at C(2), by reduction of the α-keto groups followed by desilylation and hydrolysis of the protected dithiane. Treatment of 27 with trimethylborate afforded synthetic aplasmomycin.

Synthesis of the northern and southern lactones of boromycin has also been reported by Hanessian and co-workers. Their approach begins with the optically active sugars, D-arabinose and D-glucose, and builds up the four quadrants 28, 29 and 30. Alkylation of sulfoxide
28 with aldehyde 29 provided sulfoxide 31 as an epimeric mixture at C-9. Further functionalization of this compound gave the northern lactone 18. Likewise, the southeast quadrant 29 was synthesized in optically active form from D-arabinose. Alkylation of sulfone 30 with aldehyde 29 provided intermediate 32 in good yield. Oxidation of the C(9) alcohol, followed by desulfurization of the sulfone and reduction of the resultant ketone, yielded the southern lactone 17. It is noteworthy that the hydroxyl groups at C(15) and C(16) were distinguished with different protecting groups at an earlier stage of this synthesis. This should facilitate lactonization at the C(15) hydroxyl function to form the macrocyclic lactone at a latter point.
These studies on the synthesis of boromycin and aplasmomycin illustrate in vivid fashion how the stereochemistry at multiple chiral centers in complex molecules can be controlled with high precision. In both Corey's synthesis of aplasmomycin and Hanessian's construction of the boromycin lactones this is achieved primarily through the clever manipulation of chiral starting materials. The discussion which follows describes an alternative approach, based on chiral subunits obtained by resolution techniques, which leads to synthesis of the southern lactone 17 of boromycin and the northern segments of boromycin and aplasmomycin.
II. THE SYNTHESIS OF THE "SOUTHERN" LACTONE OF BOROMYCIN

The synthesis of such highly complex molecules as aplasmomycin and boromycin, containing a 28-membered macrolide ring, 16 and 17 chiral centers respectively, and a broad array of functionality, should embrace at least two major features. The first of these is the introduction of the chiral centers in their correct absolute configurations at an early stage in the synthesis. The second is the efficient synthesis of major segments of these structures for their combination in a convergent approach to the completed macrolide. The discussion which follows discloses results which pertain to the development of useful and general strategies for synthesis of these macrolides.

The synthetic approach to aplasmomycin and boromycin is based in part upon degradation studies of boromycin. As was pointed out earlier, cleavage of the macrocyclic lactone linkage of boromycin would produce two similar halves, 33 and 34, of desvalyldesboroboromycin (16), differing only in the configuration at C(9) and C(9'), and in respect to the tetrahydrofuran moiety in the northern half. This tetrahydrofuran ring can be envisaged as the product of cyclization of the C(16) hydroxyl onto C(13) of the olefin in the southern half.

A further disconnection in this retrosynthetic analysis can be visualized with cleavage of the bond between C(2') and C(3') in 33. This affords the northern lactone 18 of boromycin, together with the identical northern and southern lactones 35 of aplasmomycin containing a trans olefinic unit at C(11)-C(12). Thus, the intermediates 18 and 35 can be viewed as cyclization products of 36, which is also a
precursor to the southern half 34 of boromycin.

For the synthesis of boromycin, the primary target 37 can be conveniently dissected into two components, 38 and 39, or 40 and 41 depending upon the particular mode of coupling chosen. Cleavage of C(9) and C(10) would provide two subunits - lactone aldehyde or lactone ester 38, and the sulfone 39 as the source of a stabilized anion. Another possible disconnection which can be made in this retrosynthetic analysis is the cleavage of 37 between C(10) and C(11). This would afford a means for assembling the southern lactone via union of
keto sulfone 40 and the allylic halide 41. On this basis, these four segments, in optically active form, became primary targets in the approach to the southern lactone 17 of boromycin.

The synthesis of the southeast quadrant of boromycin in the form of 39 or 41 began from the optically active epoxy alcohol 43. This was prepared by enantioselective epoxidation of the corresponding allylic alcohol, following the method developed by Sharpless. Thus,
epoxidation of racemic 3-buten-2-ol (42) with anhydrous t-butyldihydroperoxide\textsuperscript{25} and titanium tetraisopropoxide in the presence of (-)-diethyl-D-tartrate accomplished asymmetric epoxidation via kinetic resolution of the allylic alcohol, giving the desired 2(S),3(R) anti-pode of 43 in high enantiomeric excess.

The rationale for the stereochemical outcome of this reaction is derived from the fact that, with the allylic alcohol oriented as shown in Figure 1, use of (-)-D-tartrate causes delivery of the epoxide oxygen from the "top" face of the \( \pi \) system.\textsuperscript{24} In the case of 42,
the 2(R) enantiomer should be the faster-reacting antipode, yielding predominantly the erythro epoxide in which attack has occurred selectively from the $\text{si}$ face. However, although this rationale appeared secure, an unambiguous proof of the stereochemistry of 43 was desired.

Crotonic acid has been converted to (-)-erythro-2(R),3(R)-dihydroxybutyric acid (45) by tungstic acid-catalyzed oxidation with aqueous hydrogen peroxide, followed by resolution of the resulting acid via its quinine salt. The absolute configuration of the levorotatory isomer of 45 has been shown to be 2(R),3(R) by correlation of its optical rotatory dispersion curve with that of tartaric acid. The acid was converted to its cyclopentylidene ketal 46 with cyclopentanone and a trace amount of p-toluenesulfonic acid in refluxing benzene. Acid 46 was reduced to the alcohol 47 with lithium aluminum hydride in tetrahydrofuran. Conversion of 47 to its tosylate 48 with p-toluenesulfonyl chloride in pyridine and removal of the cyclopentylidene moiety with a catalytic quantity of p-toluenesulfonic acid in methanol then gave the diol 49 as a white crystalline solid. Treatment of 49 with sodium hydride in tetrahydrofuran containing a
trace amount of dimethyl sulfoxide afforded the 2(S),3(R) epoxy alcohol 43, which was identical by both spectroscopic and gas chromatographic comparison with the material obtained from 42. From this result it was determined that asymmetric epoxidation of 42 had afforded a 91% enantiomeric excess of 43.

This readily available optically active epoxy alcohol was shown
to be a useful synthon for the preparation of chiral 1,2-diols. Thus, 2,5-dideoxyribofuranose was prepared via an approach based upon the alkylation of 43 with an aldehyde synthon, followed by a Pummerer-type rearrangement. Kocienski has reported the use of phenylthiomethyltrimethylsilane (50) as a formyl synthon.\(^{28}\) The anion of 50 is derived in quantitative yield by metalation with n-butyllithium, and is rapidly alkylated with certain halides and epoxides. The resulting \(\alpha\)-phenylthioalkyltrimethylsilanes are stable towards acid, base, and chromatography, and are distinguished by the extremely mild oxidative conditions required for their transformation to aldehydes.

Phenylthiomethyltrimethylsilane (50) was prepared from chlorotrimethylsilane and thioanisol.\(^{28a}\) Treatment of epoxide 43 with the lithium anion of 50 resulted in exclusive attack of the epoxide at the terminal position to give diol 51 as a mixture of diastereomers.
However, an attempt to carry out a sila-Pummerer rearrangement by treating diol 51 with m-chloroperbenzoic acid in dichloromethane failed.

Since it is known that Pummerer rearrangements involving selenium usually require less vigorous conditions than for sulfur, a selenium analogue 52 of the aldehyde synthon was investigated. Phenylselenomethyltrimethylsilane (52) was prepared by a known procedure from diphenyldiselenide, sodium borohydride and chloromethyltrimethylsilane in methanol, and its lithium anion was allowed to react with 43 in tetrahydrofuran to provide 53 as an epimeric mixture at C(1). This mixture was subjected to Pummerer rearrangement with 30% hydrogen peroxide in tetrahydrofuran-ether mixture to yield 2,5-dideoxyribofuranose (54), accompanied by the 2,5-dideoxyribo-\(\gamma\)-lactone (55). It was suggested by Sachdev that two equivalents of hydrogen peroxide
are necessary for this rearrangement but, in our case, the excess hydrogen peroxide apparently oxidized the resulting lactol 54 to the lactone 55.

The elaboration of optically active epoxy alcohol 43 to the southeast quadrant of boromycin required a three-carbon chain extension by a synthon which would permit incorporation of the cisoid olefinic unit. The tetrahydropyranyl ether 56, obtained by treatment of propargyl alcohol with dihydropyran and p-toluenesulfonic acid, was converted to the lithio acetylide 57 with n-butyllithium in tetrahydrofuran. Alkylation of epoxide 43 with two equivalents of 57 proceeded in good yield to give 58, with epoxide opening again occurring selectively at the terminal position. Separation of 58 from excess 56 was easily accomplished using flash column chromatography on silica gel. Reduction of acetylene 58 to the cis olefin 59 was carried out quantitatively by catalytic hydrogenation over 10% palladium on barium sulfate poisoned with quinoline. Removal of the tetrahydropyranyl protecting group from 59, and conversion of the diol to its acetonide 60, was carried out in methanol with p-toluensulfonic acid, followed by azeotropic removal of the volatiles with acetone-benzene. The allylic alcohol function was then cleanly converted to the chloride 61 using N-chlorosuccinimide and dimethyl sulfide in dichloromethane. As was pointed out earlier in our retrosynthetic plan, alkylation of the southeast quadrant of boromycin 40 with the allylic chloride 61 would provide one possible avenue to the southern lactone 36 possessing a keto group at C(9). For investigation of the second prospective route involving coupling with the southwest quadrant 38 of boromycin, 61 was converted to the corresponding sulfone 39.
\[ \text{THP} \]

\[ \text{OTHP} \]

\[ \text{THPO} \]

\[ \text{H}_2, \text{BaSO}_4 \]

\[ \text{NCS, DMS} \]

\[ \text{PHO}_2\text{S} \]

\[ \text{CH}_3\text{SO}_2\text{Ph} \]

\[ \text{n-BuLi} \]

\[ \text{Cul} \]
Julia reported that the lithium anion of a sulfone reacts readily with an allylic halide, but that a large amount of dialkylated compound is observed as a byproduct.\textsuperscript{34a} Reaction of allylic chloride 61 with lithium dimethycuprate was examined as a model system but, in this case, a substantial amount of 1,4-addition product 63 was observed along with the 1,2-addition product 62. Alkylation of allylic chlor-

\[ \text{61} \xrightarrow{\text{LiCuMe}_2} \text{62} + \text{63} \]

de 61 with the copper anion of methyl phenyl sulfone\textsuperscript{34} was then tried, as it is less basic than the lithium anion, and this reaction gave the desired 1,2-addition product 39, in good yield.

Our route to the southwest and northeast quadrants of boromycin and aplasmomycin was centered on synthesis of the lactone acetal 68 which had previously been prepared from isobutyraldehyde.\textsuperscript{35} Thus, aldol condensation of isobutyraldehyde with formaldehyde, followed by acetylation with acetic acid, provided acetoxy aldehyde 64. Protection of the aldehyde function of 64 as its dimethyl acetal with trimethyl orthoformate in the presence of p-toluenesulfonic acid furnished 65. Basic hydrolysis of the acetate with sodium hydroxide, followed by oxidation of the resulting alcohol with pyridinium chlorochromate, gave the monoprotected malondialdehyde 66. This aldehyde
was treated with the lithium dianion of tiglic acid and the product was subjected to catalytic hydrogenation and treatment with N,N-dicyclohexylcarbodiimide to yield the lactone acetal 68 as a ca 1:1 mixture of epimers. In preparation for coupling with sulfone 39, the acetal protecting group was removed by treatment with titanium tetrachloride in the presence of acetyl chloride to give the lactone aldehyde 69.
Our first attack on the southern lactone 17 of boromycin centered on the condensation of lactone aldehyde 69 with sulfone 39. The lithium anion of 39, prepared with 1 equivalent of n-butyllithium, was added to 69 at -78°C to 0°C, but only the starting sulfone could be recovered from these reactions. Failure of the sulfone to condense with the lactone aldehyde was believed to be due to the acidic proton α to the lactone carbonyl which should be easily deprotonated by the sulfone anion.

In view of these difficulties, another synthetic route to the southern lactone of boromycin was examined, in which the joining of quadrants takes place by construction of the C(10)-C(11) bond. It was hoped that steric impediments to formation of the C(9)-C(10) bond in coupling of the quadrants would be overcome by this tactic. The lactone aldehyde 69 was first converted to its acid 70 with ruthenium trichloride, sodium periodate in carbon tetrachloride and water in the presence of acetonitrile, according to the method of Sharpless, and the acid was esterified with diazomethane in ether to provide the methyl ester 71.

For the convergent chiral synthesis of the southern lactone of boromycin, optical resolution of lactone ester 71 was carried out by introducing a chiral protecting group. Treatment of 71 with (2R,3R)-(-)-butanediol in the presence of a catalytic amount of d-camphorsulfonic acid in refluxing benzene afforded the orthoester 73 as a mixture of four diastereomers, in which the trans/cis ratio was 3.7:1. An attempt to carry out a kinetic resolution in this reaction gave disappointingly poor results. The reaction was stopped
at intervals from 20% to 84% conversion to the orthoester 73, and each fraction was converted to its keto sulfone 74 by treatment with methyl phenyl sulfone. High performance liquid chromatographic analysis of 74 showed all four diastereomers to be present, with an almost negligible increment of the desired 4(R),7(S) enantiomer. Conversion of the 1:1 epimeric ratio of trans to cis isomers of lactone aldehyde 69 to a 3.7:1 mixture favoring trans 73 indicated that configurational equilibrium at the center α to the lactone carbonyl is attained in this process. This is presumed to proceed via a ketene acetal intermediate 72.

It has been shown by Kondo that sulfonil dianions readily react
with esters to generate β-keto sulfones. Two equivalents of base are necessary, as half of the base is consumed by the resulting β-keto sulfone. Condensation of 73 with the dianion of methyl phenyl sulfone gave a diastereomeric mixture of keto sulfones 74, from which the diastereomers 75 and 76 were separated by high performance liquid chromatography. However, although the proton NMR spectra of the two isomers 75 and 76 are different, it was not possible to conclusively assign their absolute configurations at C(4) and C(7). Hence, it was necessary to carry both isomers 75 and 76 forward to 17 for correlation with boromycin.

Alkylation of the enolates of isomers 75 and 76 with allylic chloride 61, using n-butyllithium in dimethyl sulfoxide in the presence of potassium iodide, afforded the pair of stereoisomers 79 and 80. The sulfonyl group was easily removed from each compound with aluminum-amalgam in aqueous tetrahydrofuran to provide ketones 81 and 82. Reduction of each of these ketones with sodium borohydride in methanol afforded alcohols 83 and 84, and 85 and 86 re-
$73 \xrightarrow{\text{CH}_3\text{SO}_2\text{Ph}, \text{n-BuLi}} 74$

$\downarrow \text{HPLC}$

$75 + 76$

$77 + 78$
n-BuLi, KI, DMSO.
61

75

Al-Hg

79

76

n-BuLi, KI, DMSO.
61

80

81

82
respectively. Application of Cram's rule$^41$ leads to the prediction that the 9(R) isomers 83 and 85 should predominate over the 9(S) isomers 84 and 86. In fact, the ratio of 83 to 84 was found to be 2:1 at room temperature and 3.3:1 at 0°C. Although 83 and 84 were distinguishable on analytical thin-layer chromatography, they were not easily separated by preparative column chromatography. In contrast, 85 and 86 were quite readily separable by column chromatography. Therefore, for separation purposes, the mixture of 83 and 84 was treated with acetic anhydride in the presence of pyridine and 4-di-

\[ \text{NaOMe} \]

methylyaminopyridine in dichloromethane to yield a mixture of acetates 87 and 88. These two isomers were easily separated by column chromatography on silica gel, and each isomer was converted back to its respective alcohol with sodium methoxide in methanol. As seen from Table I, the proton NMR spectra of the four isomers 83, 84, 85, and 86 show chemical shifts for the geminal methyl groups at C(8), depending upon the configuration at C(9). The chemical shifts of the geminal methyl substituents of the 9(R) isomers 83 and 85 are δ 0.75 and δ 0.93, whereas those of the 9(S) isomer 84 and 86 showed
Table I. Proton NMR Chemical Shifts for the Geminal Methyl Groups at C(8) of 17, 18, 83, 84, 85 and 86.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Absolute Configuration at C(9)</th>
<th>Chemical Shifts (δ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td>S</td>
<td>0.82, 0.88</td>
</tr>
<tr>
<td>18</td>
<td>R</td>
<td>0.84, 1.00</td>
</tr>
<tr>
<td>83</td>
<td>R</td>
<td>0.75, 0.93</td>
</tr>
<tr>
<td>84</td>
<td>S</td>
<td>0.85, 0.87</td>
</tr>
<tr>
<td>85</td>
<td>R</td>
<td>0.75, 0.93</td>
</tr>
<tr>
<td>86</td>
<td>S</td>
<td>0.85, 0.89</td>
</tr>
</tbody>
</table>

at δ 0.85 and δ 0.87, and δ 0.85 and δ 0.89. This pattern of chemical shifts is also observed in the naturally derived southern and northern lactones 17 and 18.

The 9(S) acetate 88 underwent hydrolysis to 89 with a catalytic amount of p-toluenesulfonic acid in aqueous tetrahydrofuran. Sap-

\[ \text{88} \xrightarrow{\text{H}^+} \text{89} \]

\[ \text{88} \xrightarrow{1. \text{NaOH}} \xrightarrow{2. \text{HCl}} \text{17} \]

onification of the esters with sodium hydroxide, followed by lactonization with aqueous hydrochloric acid, provided 17, identical in all
respects to the degradation product obtained from natural boromycin. For a rigorous comparison with the naturally derived material, synthetic 17 was converted to the triacetate 90 with acetic anhydride and pyridine in the presence of 4-dimethylaminopyridine in dichloromethane. This compound was also spectroscopically identical to the substance obtained from boromycin. The specific rotation of naturally derived 17 showed \([\alpha]_D +17.6^\circ\), whereas synthetic 17 possessed \([\alpha]_D +14.2^\circ\).

\[
\begin{align*}
17 & \xrightarrow{\text{Ac}_2\text{O}, \text{Py.}} \quad 90 \\
86 & \xrightarrow{\text{AcOH}} \quad 91
\end{align*}
\]

In parallel with this sequence, the 4(S),7(R) isomer, 86, was converted to lactone triol 91 with acetic acid. This substance, when compared to the naturally derived 17, showed not only a different \(R_f\) value on analytical thin-layer chromatography, but also possessed a different proton NMR spectrum. In particular, the geminal methyl
groups at C(8) of the natural material showed chemical shifts at δ 0.88 and δ 0.82, whereas synthetic 91 showed shifts of δ 0.89 and δ 0.85. From these results, the configuration at the five chiral centers in the C(3)-C(17) segments of our synthetic lactone 17 was authenticated.
III. STUDIES ON THE SYNTHESIS OF THE "NORTHERN" SEGMENTS OF BOROMYCIN AND APLASMOMYCIN

The plan for construction of the tetrahydrofuran moiety of the northern half of boromycin and aplasmomycin hinged on the intramolecular closure of the C(16) hydroxyl onto the C(13) terminus of the olefinic bond in compound 93 to provide 35. From the latter structure, which serves as both the northern and southern lactone of aplasmomycin, the northern lactone 18 of boromycin would be easily obtained by hydrogenation. Attachment of the two carbon unit,
comprising C(1) and C(2), to the C(3) carbonyl of both 18 and 35 would give the northern half 33 of boromycin, and the northern and southern halves 92 of aplasmomycin.

An alternative approach, which is more highly convergent, makes use of the coupling of 38 with precyclized entities 94 and 95. The
The former had already been prepared in the course of the synthesis of the southern lactone of boromycin, while the quadrants 94 and 95 can be viewed as the cyclization products of 39, which had also been synthesized in optically active form. This latter plan seemed the more attractive and was pursued at the outset.

The acetonide 39 was converted to diol 96 with a trace amount of p-toluenesulfonic acid in methanol, and ring closure was attempted via an intramolecular oxyselenation. The desired mode of cyclization, involving the C(16) hydroxyl and C(13) terminus of the olefin, would be designated a "5-exo-trig" process according to the Baldwin nomenclature, and his analysis of vectorial approach control in similar systems predicts this cyclization mode to be favored over the alternative attack of the C(15) hydroxyl onto C(12). Further-
more, it is known that a five-membered ring closure is favored over six-membered ring formation in oxyselenation reactions.\textsuperscript{44,45} When 96 was treated with phenylselenyl chloride in dichloromethane,\textsuperscript{44} the tetrahydrofuran 97 was obtained exclusively, although a mixture of diastereomers was present. Oxidative elimination of the phenylselenyl group with hydrogen peroxide in tetrahydrofuran afforded 99 as an inseparable mixture of cis/trans isomers at the tetrahydrofuran.

\[
\begin{align*}
\begin{array}{c}
\text{97} \\
\text{H}_2\text{O}_2 \\
\text{99}
\end{array}
\end{align*}
\]

\[
\begin{align*}
\begin{array}{c}
\text{TBDMSCl,} \\
\text{Imidazole}
\end{array}
\end{align*}
\]

\[
\begin{align*}
\begin{array}{c}
\text{100} \\
\text{101}
\end{array}
\end{align*}
\]

In order to accomplish separation of this mixture, 99 was converted to the silyl ethers 100 and 101 with t-butyldimethylsilyl chloride and imidazole in dimethylformamide.\textsuperscript{46} Separation was effected at this stage by high performance liquid chromatography on silica gel, resulting in a disappointing 1:3.9 ratio of 100 to 101. The proton NMR spectra of these substances showed very different chemical shifts for the C(14) methylene protons. The major isomer 101 displayed one
of the C(14) methylene protons at δ 1.82, with the other at δ 1.61, whereas minor isomer 100 exhibited the same protons at δ 2.25 and δ 1.46. The downfield chemical shift of one proton in 100 is thought to be due to the C(15) oxygen, although it is not clear why the same proton in isomer 101 shows little effect. Such a downfield chemical shift of one of the C(14) protons of 100 is consonant with the NMR spectrum of naturally derived 18 and with the spectrum of boromycin itself.

The relative stereochemistry of 100 and 101 was confirmed by a nuclear Overhauser enhancement study of the two isomers. Initially, it was expected that the methyl group at C(16) would show a nuclear Overhauser enhancement when the C(13) methyne proton in the 2,5-trans isomer 100 was irradiated. Instead, no nuclear Overhauser enhancement was observed on the methyl protons of either isomer upon irradiation of the methyne proton. This is probably due to the conformation of the tetrahydrofuran ring, which places the methyl group in an orientation which minimizes the steric interaction between the silyl ether and the olefinic side chain. In contrast, it was found that irradiation of the methyne proton of 101 showed a pronounced nuclear Overhauser enhancement on the t-butyl group of the silyl ether. On this basis, the major isomer is assigned the undesired 2,5-cis configuration of 101.

The stereochemical outcome of the cyclization can probably be ascribed to a steric interaction between the protons at C(14) and C(16) and the cis olefinic side-chain. The transition state A, leading to 2,5-trans isomer 100, suffers from severe steric compression between the two pseudo axial hydrogens at C(14) and C(16) and the
R group, whereas transition state B, leading to the 2,5-cis isomer, experiences only minor steric interaction with the pseudo axial proton at C(15).

The unsatisfactory stereochemical outcome of the oxyselenation of cis olefin 96 led us to consider the cyclization of the alternative trans olefinic sulfone. In the intramolecular oxyselenation of this trans olefin, neither transition state C, leading to the desired 2,5-trans isomer, nor D, leading to the 2,5-cis isomer, exhibit steric hindrance between the side-chain (R) and pseudo axial hydrogens at C(14) and C(16). Transition state C has the alkylselenyl substituent in a developing, pseudo equatorial conformation whereas, in transition state D, the alkylselenyl group occupies a
developing pseudo axial conformation. The latter is thermodynamically less favorable, but such an effect is presumed to be smaller than the steric effects apparent in the cyclization of the cis olefin.

On this premise, diol 58 was converted to the acetonide 102 with 2,2-dimethoxypropane and methanol in the presence of a catalytic amount of p-toluenesulfonic acid in benzene. The latter was reduced with lithium aluminum hydride in the presence of a trace of aluminum chloride.
chloride to furnish the trans allylic alcohol 103, which was then transformed to the allylic chloride 104 with N-chlorosuccinimide and dimethyl sulfide in dichloromethane. Elaboration of 104 to 105 with the copper anion of methyl phenyl sulfone, followed by acidic hydrolysis of the acetonide, provided the trans sulfone diol 106. Treatment of 106 with phenylselenyl chloride in dichloromethane, followed by oxidative elimination with hydrogen peroxide, gave an inseparable mixture of diastereomers 99. For comparison with the cyclization

\[
\begin{align*}
\text{106} & \xrightarrow{1. \text{PhSeCl}} \text{107} & \xrightarrow{2. \text{H}_2\text{O}_2} & \text{99} & \xrightarrow{\text{TBDMSI, Imidazole}} & \text{100} + \text{101}
\end{align*}
\]

product mixture from the cis olefin 96, 99 was converted to t-butyl-dimethylsilyl ethers 100 and 101. High performance liquid chromatography separated the two isomers and showed a 1:1.4 ratio, with the desired 2,5-trans isomer 100 being the major product in this case. These results offer another possible synthetic entry to the synthesis of the northern half of boromycin and to the northern and southern halves of aplasmomycin. Finally, the northeast quadrant 107 of boromycin was prepared by hydrogenation of 100 with 10% palladium on carbon. Since the pure cis isomer 101 was more readily accessible than 100 this sulfone was employed for the purpose of developing the alkylation chemistry necessary for construction of the northern half of boromycin. Thus, 101 was first converted to 108, using the same procedure as in the preparation of 107. In initial attempts to link the two quadrants of boromycin and aplasmomycin,
sulfones 101 and 108 were reacted with lactone aldehyde 69; however, none of the desired condensation product was observed. In the case of 108, only unreacted starting sulfone was recovered, whereas with 101 a large amount of the conjugated sulfone 109 was obtained.

As was the case in our approach to the southern lactone of boromycin, the proton α to the lactone carbonyl was probably removed by the basic sulfonyl anion. To avoid this complication, the lactone function of 69 was converted to a methyl acetal, and the aldehyde was changed to a methyl ester. Thus, the previously prepared lactone ester 71 was reduced with diisobutylaluminum hydride and then converted by methylation with trimethyl orthoformate and p-toluenesulfonic acid to acetal 110. This substance was exposed to the dianion of
108, prepared using two equivalents of n-butyllithium but, disappointingly no condensation product was observed. On the other hand, ester 110 reacted readily with the dianion of methyl phenyl sulfone to yield keto sulfone 111. Furthermore, condensation of the
dianion of sulfone 108 with dimethylacetal ester 112 was also well behaved, affording keto sulfone 113 in good yield. From these results, it is apparent that the failure of the condensation of 108 with 110 is due primarily to steric factors. The heavily α substituted carbonyl group of 110 is sterically encumbered and, hence, it is not surprising that only a relatively small sulfone dianion (which is almost linear) reacts successfully. The smaller ester 112, which has more flexibility than 110, is more easily accessible and hence reacts normally with 108.

The intermediate 113 provided a convenient opportunity to synthesize a C(13) epimeric version of the northern lactone of boromycin, and this material was therefore carried forward in order to establish methodology for construction of the carbon skeleton of this segment.

Reductive removal of the sulfonyl group of 113 with aluminum-amalgam in aqueous tetrahydrofuran provided ketone 114. Subsequent reduction of ketone 114 with sodium borohydride at 0°C afforded an alcohol 115 as a pair of diastereomers. This mixture of alcohols was converted to the benzyl ether 116 with benzyl bromide in the presence of potassium hydride, and deprotection of the dimethyl acetal was carried out in acetone with p-toluenesulfonic acid to give aldehyde 117. Condensation of 117 with the lithium dianion of tiglate, followed by catalytic hydrogenation of the double bond and hydrogenolysis of the benzyl protecting group with 10% palladium on carbon, provided the dihydroxy acid 118. This material was lactonized with dicyclohexylcarbodiimide and 4-dimethylaminopyridine in
dichloromethane to give two major, isomeric lactones 119 after column chromatography on silica gel. Finally, an epimeric mixture of lactones 120 was obtained by treatment of 119 with tetra-n-butylammonium fluoride in tetrahydrofuran. The two major products from this sequence are believed to be the 9(R) and 9(S) isomers. The fast-moving isomer on thin-layer chromatography showed two widely separated methyl singlets at $\delta$ 0.82 and $\delta$ 0.98, whereas the slow-moving isomer displayed a much narrower pattern of methyl singlets at $\delta$ 0.92 and $\delta$ 0.94. This same distinguishing feature, involving the chemical shifts of geminal dimethyl groups, is also apparent in the spectra of the 9(R) and 9(S) epimers of the southern lactone of boromycin. However, it was not possible to obtain unambiguous proof of the stereochemistry of 120.

The unsatisfactory stereochemical outcome of the selenation reaction led us to consider an alternative synthetic route for the synthesis of aplasmomycin. If macrocyclic lactonization of the segment corresponding to C(1)-C(17) in open chain form gave 122, closure of the tetrahydropyran hemiacetal followed by introduction of borate should provide 121 with the correct absolute configuration at C(3)-
C(17). Careful examination of a model of 121 suggested that the borate might serve as a template for the formation of the tetrahydrofuran ring and steer the attack of the C(16) hydroxyl to the \textit{si} face of C(13) to provide correct stereochemistry at C(13) and C(13').

The first obstacle to be overcome in this approach toward the macroclide 122 was the addition of the required two carbon moiety C(1) and C(2).

Selective hydrolysis of the orthoester 83 with a catalytic amount of p-toluenesulfonic acid in aqueous tetrahydrofuran provided triol 123. Subsequent silylation of 123 with t-butyldimethylsilyl trifluoromethanesulfonate and 2,6-lutidine in dichloromethane gave trisilyl ether 124. Hydrolysis of the acetonide protecting group of 124 with p-toluenesulfonic acid in methanol yielded diol 125. At this point, it appeared likely that the hydroxyl groups at C(15) and C(16) might be differentiated chemically by virtue of their different steric environments, leading to selective esterification at
C(15). Selective protection of the C(16) hydroxyl group in 125 was easily achieved upon its exposure to t-butyldimethylsilyl chloride and 4-dimethylaminopyridine in dichloromethane. That the C(16) hydroxyl had reacted in preference to the C(15) function was confirmed by oxidation of 126 with Collins' reagent.\textsuperscript{54} This gave ketone 127, in which the two allylic C(14) protons had shifted downfield to give a $\delta$ 3.40-3.25 multiplet in the NMR spectrum. Esterification of 126 with 1,3-dithiane-2-carboxylic acid (128)\textsuperscript{55} in the presence of N,N-bis[2-o xo-3-oxazolidinyl]phosphorodiamidic chloride (BOPCl)\textsuperscript{56} and triethylamine in dichloromethane afforded 129. This substance now has the complete skeleton of semi-aplasmomycin. Unfortunately, a head-to-tail coupling of 129 via the dithiane anion failed to provide the macrocyclic lactone 122. Apparently, the entropically more favored polymerization prevailed in this reaction.

In an attempt to bring about macrolactonization in a controlled, stepwise fashion, an alternative plan involving activation of the carbonyl group of 124 was devised. Saponification of 124 with sodium hydroxide in methanol provided acid 130, which was converted to its acyl imidazole 131 with carbonyldiimidazole\textsuperscript{57} in tetrahydrofuran. The lithium anion obtained from the reaction of 129 with lithium di-isopropylamide in tetrahydrofuran, was added to a tetrahydrofuran solution of 131; however, none of the desired coupled product was observed. A possible explanation, which was reinforced by model reactions which were carried in parallel with this study, is that the acyldithiane anion is not sufficiently nucleophilic to attack an acyl imidazole. Instead, removal of the $\alpha$-proton of the acyl imidazole competes successfully and yields a ketene intermediate which
is hydrolyzed to the acid 130 upon work-up.

Our failure to effect coupling by means of an acyl 1,3-dithiane prompted us to consider the use of the more reactive alkyl dithiane. It is known that certain esters and acyl halides react with 1,3-dithiane\textsuperscript{58,59} to give, after hydrolysis, \(\alpha\)-keto aldehydes or \(\alpha\)-diketones.\textsuperscript{60} As a model for our projected elaboration of the C(1)-C(2) moiety of aplasmomycin, isopropylidithiane 132 was prepared from isobutyraldehyde and 1,3-propanedithiol in the presence of boron trifluoride-etherate,\textsuperscript{55} and the lithium anion was reacted with either dimethyl oxalate or methyloxalyl chloride. \(\alpha\)-Keto ester 133 was obtained from these reactions in 74\% to 84\% yield.

\[
\begin{align*}
\text{CHO} & \xrightarrow{\text{HS-SH}} \xrightarrow{\text{BF}_3\cdot\text{Et}_2\text{O}} \xrightarrow{\text{MeO-CO}} \xrightarrow{\text{Cl}} \xrightarrow{\text{OMe}} \xrightarrow{\text{OMe}} \xrightarrow{\text{S-S}} \text{132} \\
\text{133} \\
\end{align*}
\]

In order to extrapolate this study to aplasmomycin, it was first necessary to prepare a suitably protected aldehyde, eg 135. Hence, 124 was reduced to the alcohol 134 with diisobutylaluminum hydride, which was then oxidized to the aldehyde 135 with Collins' reagent in dichloromethane. Condensation of 135 with 1,3-propanedithiol in the presence of boron trifluoride-etherate in dichloromethane provided tetraol 136, in which dithiane formation was accompanied by cleavage of both the acetonide and silyl protecting groups. Conversion of 136 to the tetra-t-butyldimethylsilyl ether 137 was accomplished
124 \[\text{DIBAL}\] \rightarrow 134

\[\text{CrO}_3 \cdot 2\text{Py}^\cdot\]

136

\[\text{HS} + \text{SH} \rightarrow \text{BF}_3 \cdot \text{Et}_2\text{O}\]

135

\[\text{TBDMS}^\cdot\]

137
with t-butyldimethylsilyl trifluoromethanesulfonate and 2,6-lutidine in dichloromethane. Thus far, attempts to acylate the anion of 137 with dimethyl oxalate along lines employed in the model system 132 have met with failure. However, a similar process was exploited successfully in the Corey synthesis of aplasmomycin, suggesting that conditions may perhaps be found for the elaboration of 137 to a half structure of aplasmomycin.

This sequence, although as yet incomplete, demonstrates a convergent approach to synthesis of the C(3)-C(17) segments of boromycin and aplasmomycin. The extension of this route by addition of the two-carbon unit, C(1)-C(2), together with the final macrocyclic lactonization will be the objective of future investigations.
IV. EXPERIMENTAL

General

Melting points were obtained on a Büchi melting-point apparatus and are uncorrected. Infrared spectra (IR) were obtained with a Perkin-Elmer 727B infrared spectrometer. Nuclear magnetic resonance spectra (NMR) were obtained with a Varian EM-360A, HA-100, or FT-80A and are reported in δ units with tetramethylsilane (TMS) as the internal standard; the abbreviations s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br s=broad singlet, etc. are used throughout. Data are reported as follows: chemical shift (integrated intensity, multiplicity, coupling constants). NOE experiments were done on the Varian XL-200 NMR spectrometer at Palo Alto, California. Mass spectra (MS) were obtained with a Varian MAT CH-7 or a Finnagan 4500 spectrometer at an ionization potential of 70 ev. Exact mass determinations were performed on a CEC-110 C spectrometer at an ionization potential of 70 ev. Optical rotations were measured in 1-dm cells of 1-mL capacity by using a Perkin-Elmer 243 polarimeter. Gas chromatography was performed using 10% silicon OV-17 on 80/100 chromosorb W-HP, supplied by Alltech associates, Inc. Analytical thin-layer chromatography (TLC) was conducted on precoated TLC plates: silica gel 60F-254, layer thickness 0.20 mm, manufactured by E. Merck and Co. Column chromatography was performed using neutral silica gel 60 230-400 mesh ASTM. Medium pressure liquid chromatography (MPLC) was performed using an FMI solvent pump. High performance liquid chromatography (HPLC) was carried out using a Water M45 solvent pump with a Waters UA5 injector and Waters μ-Porasil 7.8 mm x 50 cm column. An ISCO UV detector
or a Waters R-40 differential refractometer was used for both high pressure and medium pressure liquid chromatography. Dry solvents were distilled shortly before use from an appropriate drying agent. Benzene, pyridine, n-hexane, and dichloromethane were distilled from powdered calcium hydride. Diisopropylamine was distilled under argon from powdered calcium hydride. Dimethyl sulfoxide ($\text{Me}_2\text{SO}$), dimethylformamide (DMF), and hexamethylphosphoramide (HMPA) were distilled under reduced pressure from powdered calcium hydride. Tetrahydrofuran (THF) and diethyl ether (ether) were distilled under nitrogen from sodium metal with sodium benzophenone ketyl as an indicator. All organic solutions were dried and filtered through a sintered glass funnel prior to rotary evaporation at water aspirator pressure. All reactions were routinely carried out under an inert atmosphere of argon or nitrogen. All glassware was dried in an oven at 150°C.

(2S,3R)-(-)-1,2-Epoxy-3-butanol (43).

A. From 3-Buten-2-ol (42).

A 500 mL, three-necked round-bottomed flask equipped with a magnetic stirrer was dried and then flushed with argon. The flask was charged with 200 mL of dichloromethane and cooled to -20°C (Dry Ice/carbon tetrachloride bath). The following were added sequentially via syringe: 5.94 mL (20 mmol) of titanium tetraisopropoxide, 3.43 mL (20 mmol) of (-)-diethyl D-tartrate (stirred for 5 min before the next addition), 1.79 mL (20 mmol) of 3-butene-2-ol (42), and finally 11 mL of a dichloromethane solution of 40 mmol of anhydrous t-butylhydroperoxide. The resulting solution was stirred at -20°C.
for 1 h and allowed to stand in the freezer at -20°C. After 48 h, 5.9 mL (80 mmol) of dimethyl sulfide was added to the reaction mixture at -20°C under argon. After the mixture was stirred for 10 h at -20°C, the reaction mixture was diluted with an equal volume of diethyl ether at room temperature. Saturated aqueous sodium sulfate solution (1 mL per mL of titanium tetraisopropoxide used) was added and the mixture was stirred vigorously at room temperature for 2 h. The heavy precipitate which had formed was removed by filtration through a Celite pad, and the filtrate was concentrated by distillation. The crude residue was purified by flash column chromatography (1:1 diethyl ether/pentane to 2:1 diethyl ether/pentane) to provide 457 mg (52%) of 43 after distillative removal of diethyl ether and pentane: IR (film) 3400, 1740, 1240 cm⁻¹; ¹H NMR (CDCl₃) δ 3.96 (1H, dq, J=7, 3 Hz), 3.00 (1H, q, J=3 Hz), 2.78 (2H, bd, J=3 Hz), 2.30 (1H, bs, exchanges with D₂O), 1.23 (3H, d, J=7 Hz); MS m/e 88.051 (M⁺, calc for C₄H₈O₂ 88.052); [α]D²₀ -16.3° (C, 0.97, CH₃OH).

B. From (2R,3R)-(-)-1-p-Toluenesulfonyl-1,2,3-butanetriol (49).

To a solution of 49 (1.0 g, 3.8 mmol) and 2 drops of dimethyl sulfoxide in freshly distilled 20 mL of tetrahydrofuran under nitrogen was added 184 mg (3.83 mmol) of a 50% suspension of sodium hydride in mineral oil. After stirring at room temperature for 8 h, the reaction mixture was filtered and solvent was evaporated. The resulting brown oil was distilled (50°C, 12 mm Hg) to yield 0.24 g (71%) of 43: [α]D²₀ -17.9° (C, 1.16, CH₃OH).
(2R,3R)-2,3-O-Cyclopentylidene-2,3-dihydroxybutyric Acid (46).

To a solution of (2R,3R)-(−)-dihydroxybutyric acid (45) (12.0 g, 0.1 mole, $[\alpha]_D^{20} = -10.78^\circ$ (C, 1.17, H$_2$O)) in 150 mL of benzene was added 100 mg of p-toluenesulfonic acid and 10.0 g (0.12 mol) of cyclopentanone and the resultant solution was heated to 80°C. After 10 h the reaction mixture was cooled, decanted from a small amount of brown residue, and concentrated in vacuo to yield 17.7 g (95%) of 46 as thick brown oil: IR (film) 3430 (br), 2980, 1800, 1740 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 4.60-4.10 (2H, m), 1.70 (8H, br s), 1.20 (3H, d, J=6 Hz); MS m/e 186.089 (M$^+$, calc for C$_9$H$_{14}$O$_4$ 186.089).

(2S,3R)-2,3-O-Cyclopentylidene-1,2,3-butanetriol (47).

To a suspension of lithium aluminum hydride (3.8 g, 0.1 mol) in 200 mL of freshly distilled tetrahydrofuran at 0°C under nitrogen was added 17.7 g (0.095 mol) of 46 dissolved in 100 mL of tetrahydrofuran. The mixture was refluxed for 1 h, cooled, and quenched with 5 mL of ethyl acetate. Workup was accomplished by adding sequentially 4 mL of water, 4 mL of 15% aqueous sodium hydroxide, and 12 mL of water. The precipitate was filtered and washed three times with 200 mL of diethyl ether, and the combined organic layer was dried over anhydrous magnesium sulfate. Filtration and concentration of the filtrate afforded 11.7 g (72%) of 47 as a colorless oil: IR (film) 3400, 2960, 1340 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 3.50 (2H, d, J=6 Hz), 3.25 (1H, br s, exchanges with D$_2$O), 1.60 (8H, br s), 1.15 (3H, d,
(2S,3R)-(-)-2,3-O-Cyclopentylidene-1-p-toluenesulfonyl-1,2,3-butanetriol (48).

A solution of 47 (11.7 g, 0.068 mol) in 150 mL of dry pyridine was cooled in an ice-bath and freshly crystallized p-toluenesulfonyl chloride (25 g, 0.14 mol) was added in several portions with stirring. The reaction mixture was allowed to stand in the freezer at -20°C for 24 h, and was worked up by pouring the mixture onto 400 g of ice and extracting the resultant aqueous solution three times with 150 mL of ether. The combined organic extracts were washed with aqueous saturated copper sulfate, water, and brine, and were dried over anhydrous magnesium sulfate. Filtration and evaporation of the filtrate in vacuo gave 18.0 g (81%) of 48 as a colorless oil.

An analytical sample was prepared by crystallization of a small portion at 0°C (dichloromethane/carbon tetrachloride) to yield 48 as colorless needles: m.p. 41-43°C; racemic mixture m.p. 45-47°C; IR (Nujol) 1360, 1180, 660 cm⁻¹; ¹H NMR (CDCl₃) δ 7.80 (2H, d, J=7 Hz), 7.30 (2H, d, J=7 Hz), 4.00 (4H, m), 2.40 (3H, s), 1.70 (8H, br s), 1.20 (3H, d, J=7 Hz); MS m/e 326.118 (M⁺, calc for C₁₆H₂₂O₅S 326.119); [α]D²⁰ -20.9° (C, 0.35, MeOH).

(2S,3R)-(−)-1-p-Toluenesulfonyl-1,2,3-butanetriol (49).

A solution of 48 (13.3 g, 41 mmol) and p-toluenesulfonic acid (200 mg, 1.0 mmol) in 150 mL of methanol was stirred for 10 h at room temperature. Solid potassium carbonate was added and the mixture was filtered and concentrated in vacuo to provide 7.5 g (70%)
of 49 as a pink oil. An analytical sample was prepared by recrystallization of a small portion (dichloromethane/carbon tetrachloride) to yield 49 as prismatic crystals: m.p. 69-71°C; IR (Nujol) 3550, 1600, 1350 cm⁻¹; ¹H NMR (CDCl₃) δ 7.80 (2H, d, J=8 Hz), 7.40 (2H, d, J=8 Hz), 4.20 (1H, s), 4.15 (1H, d, J=2 Hz), 4.00-3.70 (2H, m), 2.80 (2H, br s, exchanges with D₂O), 2.45 (3H, s), 1.16 (3H, d, J=6 Hz); MS m/e 215 (M⁺-C₅H₅₂O); [α]²⁰D -14.24° (C, 1.05, H₂O).

(2S,3R)-5-Phenylthio-5-trimethylsilylpentane-2,3-diol (51).

To a solution of phenylthiomethyltrimethylsilane (50) (784 mg, 4.0 mmol) in 20 mL tetrahydrofuran, stirred under nitrogen at 0°C, was added 2.5 mL (4.0 mmol) of n-butyllithium (1.6 M/hexane). After stirring for 30 min at 0°C a solution of 43 (176 mg, 2.0 mmol) in 10 mL of tetrahydrofuran was added slowly. The mixture was stirred for 1 h at 0°C and an additional 1 h at room temperature, and was diluted with ether, washed with saturated ammonium chloride, and dried over magnesium sulfate. Filtration and evaporation of solvent gave 931 mg of a pale yellow oil. Purification by column chromatography (silica gel, 20% acetone/benzene) afforded 442 mg (77.8%) of 51 as an epimeric mixture: IR (film) 3400, 1580, 1480, 1250 cm⁻¹; ¹H NMR (CDCl₃) δ 7.50-7.10 (5H, m), 4.00-3.60 (2H, m), 2.80-2.60 (2H, m), 2.40 (2H, br s, exchanges with D₂O), 1.80-1.60 (2H, m), 1.10 and 1.05 (3H, d, J=7 Hz), 0.15 (9H, s).

(2S,3R)-(-)-5-Phenylseleno-5-trimethylsilylpentane-2,3-diol (53).

To a stirred solution of lithium diisopropylamide in 3 mL of te-
trahydrofuran at -78°C, prepared from 0.28 mL (2.0 mmol) of freshly distilled diisopropylamine and 1.25 mL (2.0 mmol) of n-butyllithium (1.6 M/hexane) was added a solution of phenylselenomethyltrimethylsilane (52) (486 mg, 2.0 mmol) in 5 mL of tetrahydrofuran under argon. After 45 min at -78°C, a solution of 43 (88 mg, 1 mmol) in 5 mL of tetrahydrofuran was added dropwise. The mixture was stirred for 3 h at -78°C and then was kept at room temperature for 5 h before pouring into a 2:1 ether-water solution. The organic layer was separated, and the aqueous portion was extracted twice with 10 mL of ether, washed with brine, and dried over anhydrous magnesium sulfate. Filtration and evaporation afforded 420 mg of a yellow oil. Purification by column chromatography on silica gel (dichloromethane) gave 203 mg (61%) of an epimeric mixture of 53: IR (film) 3400, 1580, 1480, 1250 cm\(^{-1}\); \(^{1}\)H NMR (CDCl\(_3\)) \(\delta\) 7.50-7.30 (2H, m), 7.25-7.10 (3H, m), 4.00-3.60 (2H, m), 2.80-2.60 (2H, m), 2.40 (2H, s, exchanges with D\(_2\)O), 1.80-1.60 (2H, m), 1.10 and 1.05 (3H, d, J=6 Hz), 0.15 (9H, s); MS m/e 332.069 (M\(^{+}\), calc for C\(_{14}\)H\(_{24}\)O\(_2\)SiSe 332.071); \([\alpha]\)\(_D\)\(^{24}\) -38.2° (C, 0.10, CHCl\(_3\)).

2,5-Dideoxyribofuranose (54) and 2,5-Dideoxyribono-\(\gamma\)-lactone (55).

To a stirred solution of 53 (162 mg, 0.49 mmol) in 3 mL of a 4:6 tetrahydrofuran-ether mixture at 0°C was added 100 \(\mu\)L (113 mg, 0.98 mmol) of 30% hydrogen peroxide. After 10 min at 0°C, the reaction mixture was allowed to warm to room temperature for 2 h. The solvent was evaporated and the residue was diluted with ether. Fil-
tration and concentration yielded 57 mg of a yellowish oil. Preparative thin layer chromatography on silica gel (5:4 acetone/benzene) afforded 13.4 mg (23%) of 55 (R_f 0.42) and 23 mg (40%) of 54 (R_f 0.27).

Compound 54: IR (CHCl_3) 3400, 1460, 1380 cm^{-1}; ^1H NMR (CDCl_3) 5.70-5.50 (1H, m), 4.45 (1H, dq, J=6, 7 Hz), 4.10 (1H, br s), 3.80 (1H, m), 3.20 (1H, br s), 2.35-1.90 (2H, m), 1.30 (3H, d, J=6 Hz); MS m/e 119 (M^+1). Compound 55: IR (film) 3400, 1760, 1315, 1190 cm^{-1}; ^1H NMR (CDCl_3) 4.70-4.50 (1H, m), 4.40-4.20 (1H, m), 2.75 (2H, dd, J=17, 6 Hz), 1.45 (3H, d, J=6 Hz); MS m/e 117 (M^+1): [α]_D^18 21.0 (C, 0.67, CHCl_3).

(5S,6R)-1-Tetrahydropyran-4-yl-2-heptyn-5,6-diol (58).

To a solution of 56 (4.31 g, 30.8 mmol) in 25 mL of tetrahydrofuran at -78°C under argon was added 19.25 mL (30.8 mmol) of n-butyl-lithium (1.6 M/hexane). The reaction mixture was warmed to -20°C for 20 min and then cooled to -78°C. This cold mixture was added to a stirred solution of 1.36 g (15.4 mmol) of 43 in 25 mL of tetrahydrofuran at -78°C. After 24 h at room temperature, the reaction mixture was diluted with ether and washed with brine. The aqueous layer was extracted twice with diethyl ether and the combined organic layer was dried over anhydrous sodium sulfate. Filtration and evaporation in vacuo afforded 4.13 g of a pale yellow oil. The mixture was purified by column chromatography (silica gel, gradient elution from 1:1 ethyl acetate/hexane to 3:1 ethyl acetate/hexane) afforded 2.56 g (73%) of 58 as a yellow oil: IR (film) 3400, 2950, 2870 cm^{-1}; ^1H NMR (CDCl_3) 4.90 (1H, br s), 4.30 (2H, d, J=2 Hz), 4.00-3.60 (2H, m), 3.60 (2H, br s), 2.45 (2H, dt, J=2, 6 Hz), 1.80-1.40 (6H, m),
A suspension of 99 mg of 10% palladium on barium sulfate was stirred in 100 mL of methanol under a hydrogen atmosphere for 20 min. A solution of 58 (2.45 g, 10.7 mmol) in 25 mL of methanol containing 25 mg of quinoline was added. The mixture took up one equivalent of hydrogen in 3 h, after which the catalyst was removed by filtration through Celite and the methanol was evaporated. The residue was taken up into ether, filtered, and evaporated to yield 2.30 g (93%) of 59: IR (film) 3400, 2950 cm⁻¹; ¹H NMR (CDCl₃) δ 5.75 (2H, m), 4.70 (1H, br s), 4.30-4.10 (2H, m), 3.90-3.60 (2H, m), 3.50 (2H, br s, exchanges with D₂O), 2.30 (2H, m), 1.80-1.40 (6H, m), 1.20 (3H, d, J=6 Hz); MS m/e 231 (M⁺+1).

(2Z,5S,6R)-(−)-5,6-O-Isopropylidene-2-hepten-1,5,6-triol (60).

A solution of 59 (2.30 g, 10 mmol) in 25 mL of methanol containing p-toluenesulfonic acid (190 mg, 1 mmol) was stirred for 1 h at room temperature. The methanol and methoxytetrahydropyran were removed by evaporation in vacuo. The residue was taken up into a mixture of 50 mL of benzene and 50 mL of acetone and the solution was heated to reflux. A total of 75 mL of distillate was collected in 1 h. Solid sodium bicarbonate was added to the reaction mixture and, after filtration, the reaction mixture was concentrated in vacuo. Purification of the residue by chromatography (silica gel, gradient
elution from 30% ethyl acetate/hexane to 75% ethyl acetate/hexane) afforded 1.37 g (74%) of 60: IR (film) 3430, 1380, 1220, 1080 cm\(^{-1}\);
\(^{1}\)H NMR (CDCl\(_3\)) \(\delta\) 5.70 (2H, m), 5.00 (1H, br s, exchanges with D\(_2\)O), 4.20 (5H, m), 2.30 (2H, dd, J=6, 14 Hz), 1.45 (3H, s), 1.30 (3H, s), 1.17 (3H, d, J=6 Hz); MS m/e 186.124 (M\(^{+}\), calc for C\(_{10}\)H\(_{18}\)O\(_3\) 186.126);
\([\alpha]_{D}^{20}\) -22.5° (C, 4.92, CHCl\(_3\)).

\((2Z,5S,6R)-(-)-1\)-Chloro-5,6-\(\text{O}\)-isopropylidene-2-hepten-5,6-diol (61).

To a solution of N-chlorosuccinimide (970 mg, 7.2 mmol) dissolved in 35 mL of dichloromethane at -20°C under an argon atmosphere was added dimethyl sulfide (0.62 mL, 9.0 mmol). After a few minutes a white precipitate formed and a solution of 60 (1.23 g, 6.6 mmol) in 10 mL of dichloromethane was added. The mixture was warmed to 0°C and, after 1 h, saturated aqueous sodium chloride was added and the mixture was extracted with 200 mL of ether. The organic layer was washed with brine and dried over anhydrous sodium sulfate. Filtra-
tion and concentration of the mixture afforded 1.29 g of an oil which was purified by flash column chromatography on silica gel (50% ethyl acetate/hexane) to give 970 mg (72%) of 61: IR (film) 1660, 1450, 1375 cm\(^{-1}\); \(^{1}\)H NMR (CDCl\(_3\)) \(\delta\) 5.90-5.70 (2H, m), 4.50-4.05 (4H, m), 2.50-2.30 (2H, m), 1.55 (3H, s), 1.45 (3H, s), 1.30 (3H, d, J=7 Hz); MS m/e 189.069 (M\(^{+}\)-CH\(_3\), calc for C\(_9\)H\(_{14}\)O\(_2\)Cl 189.068);
\([\alpha]_{D}^{22}\) -1.6 (C, 2.12, CHCl\(_3\)).
(3Z,6S,7R)-6,7-0-Isopropylidene-3-octene-6,7-diol (62) and
(5S,7R)-5,6-0-Isopropylidene-1-hepten-5,6-diol (63).

To a suspension of copper(I) iodide (102 mg, 0.40 mmol) in 5 mL
of ether was added methyllithium (566 μL, 0.79 mmol, 1.4 M/ether)
slowly at -78°C under an argon atmosphere. The reaction mixture was
warmed to -20°C for 30 min and then cooled to -78°C. To this mix-
ture, a solution of the allylic chloride 61 (75 mg, 0.36 mmol) in
0.75 mL of tetrahydrofuran was added. After 30 min. at 0°C, the
solution was diluted with ether and quenched with aqueous ammonium
chloride. The aqueous layer was extracted twice with ether, and the
combined organic layer was washed with aqueous 2% sodium thiosulfate,
brine, and dried over anhydrous sodium sulfate. Filtration and con-
centration, followed by flash column chromatography on silica gel (9%
ethyl acetate/hexane), provided 58 mg (86%) of an inseparable mixture
of 62 and 63. Compound 62: IR (film) 1460, 1375, 1240 cm⁻¹; ¹H NMR
(CDC摧3) δ 5.75-5.25 (2H, m), 4.47-3.90 (2H, m), 2.45-1.80 (4H, m),
1.45 (3H, s), 1.33 (3H, s), 1.17 (3H, d, J=6 Hz), 0.95 (3H, t,
J=8 Hz); MS m/e 184 (M⁺). Compound 63: ¹H NMR (CDC摧3) δ 5.45-4.80
(3H, m), 4.47-3.90 (2H, m), 2.10-1.65 (3H, m), 1.45 (3H, s), 1.34
(3H, s), 1.15 (3H, d, J=6 Hz), 1.02 (3H, d, J=7 Hz).

(3Z,5S,6R)-1-Phenylsulfonyl-6,7-0-isopropylidene-
3-octen-6,7-diol (39).

To a solution of methyl phenyl sulfone (967 mg, 6.2 mmol) dis-
solved in 20 mL of tetrahydrofuran at -78°C under an argon atmosphere
was added n-butyllithium (1.6 M in hexane, 3.87 mL, 6.2 mmol).
The mixture was allowed to warm to 0°C for 30 min, then cooled to -78°C. Anhydrous copper(I) iodide (1.18 g, 6.2 mmol) was added and the mixture was stirred at -20°C for 1 h. To this solution was added a solution of 61 (553 mg, 2.71 mmol) in 10 mL of tetrahydrofuran, and the mixture was warmed to 25°C and stirred for 24 h. This mixture was poured into saturated aqueous ammonium chloride and extracted twice with 200 mL of ethyl acetate. The combined organic layer was washed with 2% aqueous sodium thiosulfate and with saturated aqueous ammonium chloride. The organic phase was dried over anhydrous magnesium sulfate, filtered and solvent was removed. Flash column chromatography of the residual oil on silica gel (50% ethyl acetate/hexane) afforded 508 mg (58%) of 39 as a colorless oil: IR (film) 1580, 1440, 1300 cm⁻¹; ¹H NMR (CDCl₃) δ 7.95 (2H, m), 7.65 (3H, m), 5.70-5.25 (2H, m), 4.40-3.90 (2H, m), 3.25-3.05 (2H, m), 2.60-2.05 (4H, m), 1.43 (3H, s), 1.32 (3H, s), 1.14 (3H, d, J=7 Hz); MS m/e 324.138 (M⁺ calc for C₁₇H₂₄O₄S 324.140).

cis and trans-2,6,6-Trimethyl-6-formyl-5-hydroxyhexanoic Acid, 6-Lactone (69).

To a solution of titanium tetrachloride (118 mg, 0.625 mmol) and acetyl chloride (196 mg, 2.5 mmol) in 5 mL of dichloromethane at 0°C under argon was added a solution of lactone acetal 68 (116 mg, 0.5 mmol) in 5 mL of dichloromethane. After 20 min, the reaction mixture was quenched with a few drops of water, and 2.5 g of solid sodium bicarbonate followed by 10 mL of dichloromethane were added. The mixture was stirred for 2 h at 0°C and dried over anhydrous potassium carbonate. Filtration and concentration, followed by
column chromatography on silica gel (50% ethyl acetate/hexane), afforded 47 mg (51%) of 69 as a mixture of cis/trans isomers: IR (CHCl$_3$) 1715, 1460, 1380 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 9.57 (1H, s), 4.50-4.20 (1H, m), 2.85-2.30 (1H, m), 2.25-1.40 (4H, m), 1.13 (3H, d, J=6 Hz), 1.10 (3H, s), 1.05 (3H, s); MS m/e 184 (M$^+$).

cis and trans-2,6,6-Trimethyl-5-hydroxyheptanedioic Acid, $\delta$-Lactone (70).

To a solution of sodium periodate (12.2 g, 57 mmol) in 48 mL of carbon tetrachloride were added 69 mL of water, ruthenium(III) chloride trihydrate (284 mg, 1.1 mmol) and a solution of 69 (2.5 g, 13.5 mmol) in 24 mL of acetonitrile at room temperature. After 4 h, the reaction mixture was diluted with ether and the aqueous layer was extracted twice with ether. The combined organic layer was dried over anhydrous sodium sulfate. Filtration and concentration, followed by column chromatography on silica gel (4% acetic acid in 32% ethyl acetate/hexane), gave 2.13 g (78%) of 70: IR (KBr) 2900, 1710, 1460, 1360 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 10.45 (1H, br s), 4.68 (1H, dd, J=10, 4 Hz), 2.90-2.50 (1H, m), 2.40-1.55 (4H, m), 1.40 (3H, s), 1.32 (3H, s), 1.30 (3H, d, J=6 Hz); MS m/e 201 (M$^+$+1).

cis and trans-Methyl 2,6,6-Trimethyl-5-hydroxyheptanedioate, $\delta$-Lactone (71).

To a solution of 70 (2.13 g, 10.6 mmol) in ether was added an ethereal solution of diazomethane dropwise until a yellow color persisted. Evaporation of the solvent in vacuo yielded 2.0 g (88%)
of lactone ester 71 as a mixture of diastereomers: IR (film) 1725, 1460, 1360, 1270 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 4.50 (1H, dd, J=9, 5 Hz), 3.67 (3H, s), 2.75-2.30 (1H, m), 2.30-1.40 (4H, m), 1.21 (3H, d, J=6 Hz), 1.24 (3H, s), 1.17 (3H, s); MS m/e 214.121 (M\(^+\) calc for C\(_{11}\)H\(_{18}\)O\(_4\) 214.121).

Methyl (2'R,3'R)-2-Methyl-2,7'-[2',3',10'-trimethyl-1',4',6'-trioxaspiro[4'.5']decyl]propionate (73).

To a solution of 71 (267 mg, 1.25 mmol) and 20 mg of d-camphor-sulfonic acid in 20 mL of benzene was added (2R,3R)-(−)-butanediol (162 mg, 1.8 mmol) under argon. This mixture was heated to 80° C in the presence of 4A molecular sieves. After 18 h, the mixture was diluted with ether, washed with aqueous saturated sodium bicarbonate and dried over anhydrous sodium sulfate. Filtration and concentration afforded 375 mg of a crude mixture which was purified by flash column chromatography (silica gel, 25% ethyl acetate/hexane to 50% ethyl acetate/hexane) to yield 284 mg (80%) of 73 as a mixture of four diastereomers: IR (film) 2950, 1735, 1460 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 4.15-3.85 (1H, m), 3.85-3.40 (2H, m), 2.65 (3H, s), 2.10-1.30 (5H, m), 1.52 (two 3H, d, J=6 Hz), 1.20 (3H, s), 1.13 (3H, s), 0.90 (3H, d, J=6 Hz); MS m/e 286.179 (M\(^+\) calc for C\(_{15}\)H\(_{26}\)O\(_5\) 286.178).

(2'R,3'R)-3-Methyl-1-phenylsulfonyl-3,7'-[2',3',10'-trimethyl-1',4',6'-trioxaspiro[4'.5']decyl]butan-2-one (74).

To a solution of methyl phenyl sulfone (233 mg, 1.5 mmol) in 7 mL of tetrahydrofuran at 0°C under argon was added n-butyllithium
(1.55 M in hexane, 1.88 mL, 2.8 mmol) slowly. The mixture was warmed to room temperature for 30 min and cooled to 0°C. To this mixture was added a solution of 73 (284 mg, 1.0 mmol) in 3 mL of tetrahydrofuran. After 1 h at room temperature, the mixture was diluted with ether and quenched with aqueous ammonium chloride. The aqueous layer was extracted twice with ether and the combined organic layer was washed with brine and dried over anhydrous sodium sulfate. Filtration and concentration afforded 450 mg of crude material which was purified by flash column chromatography on silica gel (33% ethyl acetate/hexane) to yield 336 mg (83%) of 74 as a mixture of four diastereomers. High performance liquid chromatography (µ-Porasil, 7.8 mm x 30 cm, 10 µ; 17% ethyl acetate/hexane) of this mixture afforded 27 mg (8%) of 77 or 78: Rt 28 min; 1H NMR (CDCl₃) δ 8.10-7.75 (2H, m), 7.70-7.35 (3H, m), 4.42 (2H, s), 3.95-3.45 (3H, m), 2.15-1.35 (5H, m), 1.20 (3H, d, J=6 Hz), 1.18 (3H, d, J=6 Hz), 1.12 (6H, s), 0.92 (3H, d, J=7 Hz), followed by 108 mg (32%) of 76: Rt 29 min; 1H NMR (CDCl₃) δ 8.10-7.75 (2H, m), 7.70-7.35 (3H, m), 4.55 (1H, d, J=16 Hz), 4.35 (1H, d, J=16 Hz), 4.07-3.35 (3H, m), 1.90-1.30 (5H, m), 1.24 (3H, d, J=6 Hz), 1.22 (3H, d, J=6 Hz), 1.12 (3H, s), 1.08 (3H, s), 0.87 (3H, d, J=6 Hz); [α]D²⁰ -2.48° (C, 2.1, CHCl₃).

Further elution gave 32 mg (9%) of 77 or 78: Rt 30 min; 1H NMR (CDCl₃) δ 8.10-7.75 (2H, m), 7.70-7.35 (3H, m), 4.52 (1H, d, J=16 Hz), 4.28 (1H, d, J=16 Hz), 3.95-3.40 (3H, m), 2.15-1.35 (5H, m), 1.22 (3H, d, J=6 Hz), 1.21 (3H, d, J=6 Hz), 1.15 (6H, s), 0.95 (3H, d, J=7 Hz), followed by 118 mg (35%) of 75 (m.p. 96-98°C): Rt 34 min; IR (KBr) 1715, 1440, 1360, 1300 cm⁻¹; 1H NMR (CDCl₃) δ 8.10-7.75
To a solution of keto sulfone 75 (280 mg, 0.68 mmol) and potassium iodide (216 mg, 1.3 mmol) in 6 mL of dimethyl sulfoxide at 0°C under an argon atmosphere was added 472 μL (0.73 mmol) of n-butyl-lithium (1.55 M/hexane). After 1 h at room temperature, a solution of 61 (179 mg, 0.87 mmol) in 1.8 mL of tetrahydrofuran was added via cannula and the mixture was warmed to 40°C. After 24 h, the mixture was diluted with ether and quenched with a 0.5% solution of aqueous potassium hydroxide. The aqueous layer was extracted twice with ether and the combined organic layer was washed with brine and dried over anhydrous sodium sulfate. Filtration and concentration afforded 517 mg of crude β-keto sulfone 79 as a mixture of diastereomer. An analytical sample was prepared by flash column chromatography on silica gel (25% ethyl acetate/hexane to 33% ethyl acetate/hexane) to yield oily 79 as a mixture of two diastereomers: ¹H NMR (CDCl₃) δ 8.10-7.52 (5H, m), 5.67-5.35 (2H, m), 4.70 (1H, m), 4.50-3.40 (5H, m), 2.75-2.40 (2H, m), 2.35-1.95 (2H, m), 1.95-1.50 (5H, m), 1.42 (3H, s), 1.32 (3H, s), 1.25 (3H, d, J=6 Hz), 1.18 (3H, d, J=6 Hz), 1.15 (3H, d, J=6 Hz), 1.15 (3H, s), 1.09 (3H, s), 0.85 (3H, d, J=7 Hz); MS m/z 578 (M⁺).

To a solution of crude 79 in 50 mL of 10% aqueous tetrahydro-
furan was added aluminum-amalgam, prepared from 350 mg of aluminum and 50 mL of 2% aqueous mercuric chloride. The mixture was refluxed for 1 h under a nitrogen atmosphere, then diluted with ether and filtered through a Celite pad. The organic layer was washed with water and brine, and dried over anhydrous sodium sulfate. Filtration and concentration afforded 350 mg of crude material which was purified by flash column chromatography on silica gel (25% ethyl acetate/hexane) to yield 221 mg (74%) of 81 as a colorless oil:

IR (film) 1705, 1460, 1370 cm⁻¹; ¹H NMR (CDCl₃) δ 5.65-5.15 (2H, m), 4.45-3.40 (5H, m), 2.75-2.45 (4H, m), 2.40-2.05 (2H, m), 1.90-1.35 (5H, m), 1.44 (3H, s), 1.33 (3H, s), 1.25 (two 3H, d, J=6 Hz), 1.17 (3H, d, J=6 Hz), 1.16 (3H, s), 1.05 (3H, s), 0.87 (3H, d, J=6 Hz); MS m/e 438.296 (M⁺ calc for C25H₄2O₆ 438.298); [α]D²⁰ +3.46° (C, 15.5, CHCl₃).

(5Z,2R,3S,2'R,3'R,7'R,10'S)-(−)-82.

In analogy to the preparation of 79, the reaction of 76 (29 mg, 0.071 mmol) with n-butyllithium (1.55 M in hexane, 46 μL, 0.071 mmol) and then with a solution of 61 (20 mg, 0.1 mmol) and potassium iodide (166 mg, 0.1 mmol) in 3 mL of dimethyl sulfoxide afforded, after flash column chromatography, 38 mg (90%) of 80: ¹H NMR (CDCl₃) δ 8.00-7.30 (5H, m), 5.50-5.25 (2H, m), 4.83 (2H, t, J=7 Hz), 4.45-3.35 (5H, m), 2.65-2.35 (2H, m), 2.15-1.85 (2H, m), 1.85-1.50 (5H, m), 1.40 (3H, s), 1.35 (3H, d, J=6 Hz), 1.28 (3H, s), 1.25 (3H, s), 1.20 (3H, d, J=6 Hz), 1.13 (3H, s), 1.08 (3H, d, J=6 Hz), 0.83 (3H, d, J=6 Hz).
As for the preparation of 81, 80 (38 mg, 0.065 mmol) was treated with aluminum-amalgam, prepared from 114 mg of aluminum and 10 mL of 2% aqueous mercuric chloride in 8 mL of 10% aqueous tetrahydrofuran, to give, after flash column chromatography on silica gel (25% ethyl acetate/hexane), 21 mg (75%) of 82: IR (film) 1705, 1460, 1370 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 5.65-5.15 (2H, m), 4.45-3.40 (5H, m), 2.75-2.45 (4H, m), 2.40-2.05 (2H, m), 1.90-1.35 (5H, m), 1.45 (3H, s), 1.33 (3H, s), 1.25 (two 3H, d, J=6 Hz), 1.22 (3H, d, J=6 Hz), 1.18 (3H, s), 1.06 (3H, s), 0.87 (3H, d, J=6 Hz); \([\alpha]_D^{21} = -35.6\) (C, 1.60, CHCl\(_3\)).

(5Z,2R,3S,9R,2'R,3'R,7'R,10'S)-(83).

To a solution of 87 (96 mg, 0.20 mmol) in 4 mL of methanol at room temperature under nitrogen was added sodium methoxide (40 mg, 0.74 mmol). After 2 h, the mixture was diluted with ether and washed with water. The aqueous layer was extracted twice with ether and the combined organic layer was dried over anhydrous sodium sulfate. Filtration and concentration yielded 83 mg (95%) of 83 as a colorless oil: IR (film) 3500, 1450, 1360, 1240, 1200 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 5.65-5.15 (2H, m), 4.40-3.25 (6H, m), 2.45-2.00 (4H, m), 1.90-1.40 (7H, m), 1.45 (3H, s), 1.33 (3H, s), 1.28 (3H, d, J=6 Hz), 1.27 (3H, d, J=6 Hz), 1.16 (3H, d, J=6 Hz), 0.93 (3H, s), 0.91 (3H, d, J=6 Hz), 0.75 (3H, s); MS m/e 440.316 (M\(^+\) calc for C\(_{25}\)H\(_{44}\)O\(_6\) 440.314).

(5Z,2R,3S,9S,2'R,3'R,7'R,10'S)-(84).

Following the procedure for the preparation of 83, the reaction of 88 (14 mg, 0.029 mmol) and sodium methoxide (10 mg, 0.185 mmol) in 2 mL of methanol afforded 11 mg (90%) of alcohol 84: \(^1\)H NMR
(CDCl₃) δ 5.65-5.15 (2H, m), 4.40-3.25 (6H, m), 2.45-2.00 (4H, m), 1.90-1.40 (7H, m), 1.45 (3H, s), 1.33 (3H, s), 1.28 (3H, d, J=6 Hz), 1.27 (3H, d, J=6 Hz), 1.15 (3H, d, J=6 Hz), 0.87 (3H, s), 0.85 (two 3H, s).

(5Z,2R,3S,9R,2'R,3'R,7'S,10'R)-(85) and (5Z,2R,3S,9S,2'R,3'R,7'S,10'R)-(86).

To a suspension of sodium borohydride (15 mg, 0.390 mmol) in 1 mL of dry methanol at 0°C under a nitrogen atmosphere was added a solution of ketone 82 (16 mg, 0.036 mmol) in 1 mL of methanol. After stirring for 1 h at 0°C, the mixture was diluted with ether and quenched with water. The aqueous layer was extracted twice with ether and the combined organic layer was dried over anhydrous sodium sulfate. Filtration and concentration afforded 13.5 mg (84%) of 85 and 86 as a mixture of diastereomers. Separation of the mixture by high performance column chromatography on silica gel (20% ethyl acetate/hexane) provided first 2.4 mg of 86, and then 5.7 mg of 85 as colorless oils. Compound 85; ¹H NMR (CDCl₃) δ 5.65-5.15 (2H, m), 4.40-3.25 (6H, m), 2.45-2.00 (4H, m), 1.90-1.40 (7H, m), 1.45 (3H, s), 1.33 (3H, s), 1.29 (3H, d, J=6 Hz), 1.25 (3H, d, J=6 Hz), 1.15 (3H, d, J=6 Hz), 0.93 (3H, s), 0.92 (3H, d, J=6 Hz), 0.75 (3H, s). Compound 86; IR (CHCl₃) 3500, 1450, 1360, 1240, 1200 cm⁻¹; ¹H NMR (CDCl₃) δ 5.65-5.15 (2H, m), 4.40-3.25 (6H, m), 2.45-2.00 (4H, m), 1.90-1.40 (7H, m), 1.43 (3H, s), 1.32 (3H, s), 1.27 (3H, d, J=6 Hz), 1.23 (3H, d, J=6 Hz), 1.15 (3H, d, J=6 Hz), 0.87 (3H, d, J=6 Hz), 0.89 (3H, s), 0.85 (3H, s).
(5Z,2R,3S,9R,2'R,3'R,7'R,10'S)-(+)-(87) and
(5Z,2R,3S,9S,2'R,3'R,7'R,10'S)-(−)-(88).

To a solution of 81 (74 mg, 0.169 mmol) in 5 mL of dry methanol at 0°C under argon was added 68 mg (1.8 mmol) of sodium borohydride. After 1 h at 0°C, the mixture was diluted with ether and quenched with water. The aqueous layer was extracted twice with ether and the combined organic layer was washed with brine and dried over anhydrous sodium sulfate. Filtration and concentration provided 72 mg (97%) of an inseparable epimeric mixture of 83 and 84. To a solution of this mixture in 5 mL of dichloromethane were added acetic anhydride (300 mg, 2.8 mmol), pyridine (300 μL), and a catalytic amount (10 mg) of 4-dimethylaminopyridine. After 14 h, the mixture was diluted with ether and washed with aqueous saturated sodium bicarbonate. The aqueous layer was extracted twice with ether and the combined organic layer was dried over anhydrous sodium sulfate. Filtration and concentration furnished 72 mg (91%) of an epimeric mixture of acetates, 87 and 88. Flash column chromatography on silica gel (9% ethyl acetate/hexane to 11% ethyl acetate/hexane) afforded first 14 mg of 88: IR (CHCl₃) 2950, 1715, 1460, 1370 cm⁻¹; ᵃ⁄H NMR (CDCl₃) δ 5.50-5.27 (2H, m), 4.96 (1H, t, J=7 Hz), 4.35-3.35 (5H, m), 2.30-1.80 (4H, m), 2.03 (3H, s), 1.80-1.45 (5H, m), 1.43 (3H, s), 1.32 (3H, s), 1.28 (3H, d, J=7 Hz), 1.27 (3H, d, J=6 Hz), 1.25 (3H, d, J=6 Hz), 1.13 (3H, d, J=6 Hz), 0.87 (3H, d, J=6 Hz), 0.86 (3H, s), 0.85 (3H, s); MS m/e 482 (M⁺); [α]₂₀° -0.47° (C, 5.3, CHCl₃). Further elution gave 46 mg of 87: ᵃ⁄H NMR (CDCl₃) δ 5.50-5.27 (2H, m), 5.02 (1H, dd, J=8, 4 Hz), 4.35-3.40 (5H, m), 2.30-1.75 (4H, m), 2.05 (3H,
s), 1.75-1.45 (5H, m), 1.43 (3H, s), 1.33 (3H, s, J=6 Hz), 1.32 (3H, s), 1.23 (3H, d, J=6 Hz), 1.15 (3H, d, J=7 Hz), 0.89 (3H, d, J=6 Hz), 0.88 (3H, s), 0.82 (3H, s); [a]$_D$$^\text{20}$ +3.38° (C, 12.0, CHCl$_3$).

(10Z,2R,5S,7S,13S,14R)-(−)-5-Hydroxy-7,13,14-triacetoxy-2,6,6-trimethylpentadecenoic Acid, δ-Lactone (90).

To a solution of 88 (53 mg, 0.11 mmol) in 20% aqueous tetrahydrofuran was added 12 mg of p-toluenesulfonic acid at room temperature. The reaction mixture was warmed up to 55°C. After 12 h, the mixture was treated with 0.5 mL of 20% aqueous sodium hydroxide. After 3 h at room temperature, the mixture was poured into a mixture of 40 mL of chloroform, 20 mL of water and 10 mL of 5% aqueous hydrochloric acid. After 6 h at room temperature, the organic layer was separated and the aqueous layer was extracted two times with chloroform. The combined organic layer was washed with saturated aqueous sodium bicarbonate and dried over anhydrous sodium sulfate. Filtration and concentration afforded 32.8 mg of 17 as a colorless oil: IR (CHCl$_3$) 3450, 1720, 1460, 1380 cm$^{-1}$; $^1$H NMR (CDCl$_3$) δ 5.70-5.30 (2H, m), 4.60-4.40 (1H, m), 4.10-3.95 (3H, m), 2.74-1.40 (14H, m), 1.30 (3H, d, J=6 Hz), 1.21 (3H, d, J=7 Hz), 0.88 (3H, s), 0.82 (3H, s); MS m/e 329 (M$^+$+1). To the solution of lactone triol 17 (32.8 mg, 0.10 mmol) in 6 mL of dichloromethane were added 32 mg of 4-dimethylaminopyridine, 1.0 mL of acetic anhydride and 0.5 mL of pyridine at room temperature under argon. After 23 h, the reaction mixture was diluted with ether and washed with saturated aqueous sodium bicarbonate. The organic layer was dried over anhydrous sodium sulfate. Filtration and concentration followed by column chromatography on
silica gel (33% ethyl acetate/hexane to 50% ethyl acetate/hexane) provided 31.0 mg (62% from 88) of 90 as a colorless oil; IR (CHCl₃) 1710, 1360, 1240 cm⁻¹; ¹H NMR (CDCl₃) δ 5.60-5.15 (2H, m), 5.15-4.80 (3H, m), 4.15-3.97 (1H, m), 2.55-1.35 (11H, m), 2.06 (3H, s), 2.04 (3H, s), 2.03 (3H, s), 1.27 (3H, d, J=7 Hz), 1.20 (3H, d, J=7 Hz), 0.95 (two 3H, s); MS m/e 394.234 (M+ -C₂H₄O₂, calc for C₂₂H₃₄O₆ 394.236; [α]D²⁰ +14.2° (C, 4.07, CHCl₃) (naturally derived 90: [α]D²⁰ +17.6° (C, 5.24, CHCl₃)).

(10Z,2S,5R,7S,13S,14R)-5,7,13,14-Tetrahydroxy-2,6,6-trimethylpentacontadienoic Acid, δ-Lactone (91).

To a solution of 86 (1.5 mg, 0.0034 mmol) in tetrahydrofuran was added 1.5 mL of acetic acid and 0.4 mL of water. The mixture was refluxed for 13 h and solvent was removed in vacuo to yield 0.5 mg (42%) of 91: Rf (100% ethyl acetate) 0.348 (Rf of 17 0.502); IR (CHCl₃) 3400, 1710 cm⁻¹; ¹H NMR (CDCl₃) δ 5.60-5.20 (2H, m), 4.65-4.25 (1H, m), 3.85-3.40 (3H, m), 2.20-1.30 (11H, m), 1.20 (3H, d, J=6 Hz), 1.17 (3H, d, J=6 Hz), 0.82 (3H, s), 0.80 (3H, s).

(3Z,6S,7R)-(-)-1-Phenylsulfonyl-3-octen-6,7-diol (96).

To a solution of 39 (85 mg, 0.26 mmol) in 2 mL of methanol was added a catalytic amount (5 mg, 0.026 mmol) of p-toluenesulfonic acid. The reaction mixture was stirred for 8 h at room temperature and solid, anhydrous sodium carbonate was added. This mixture was filtered, the solvent was removed in vacuo to yield 65 mg (87%) of 96: IR (film) 3450, 1600, 1330, 750 cm⁻¹; ¹H NMR (CDCl₃) δ 7.95-7.75 (2H, m), 7.75-7.35 (3H, m), 5.65-5.35 (2H, m), 3.90-3.35 (2H,
m), 3.20 (2H, t, J=8 Hz), 2.65-2.00 (6H, m), 1.17 (3H, d, J=6 Hz); MS m/e 239.075 (M^+ - CH_2O, calc for C_{12}H_{15}O_3S 239.074); [α]_D^{22} -7.28° (C, 6.0, CHCl_3).

(2R,3S)-3-Hydroxy-2-methyl-5-(1-phenylselenyl-3-phenylsulfonylpropyl)tetrahydrofuran (97).

To a solution of 96 (500 mg, 1.76 mmol) in 50 mL of dichloromethane at -78°C under an argon atmosphere was added solid phenylselenyl chloride (404 mg, 2.11 mmol) in one portion. The mixture was stirred until all the solid had dissolved (3 h). The reaction was diluted with 150 mL of dichloromethane and washed with 10% aqueous potassium bicarbonate. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. Filtration and concentration afforded 870 mg of crude material which was subjected to column chromatography on silica gel (50% ethyl acetate/hexane) to give 715 mg (93%) of 97 as a mixture of diastereomers: IR (film) 3400, 1470, 1440, 1310 cm^{-1}; ^1H NMR (CDCl_3) δ 7.95-7.65 (2H, m), 7.65-7.30 (5H, m), 7.30-7.05 (3H, m), 4.25-3.60 (3H, m), 3.60-3.25 (2H, m), 3.25-2.80 (1H, m), 2.50-1.90 (5H, m), 1.19 and 1.13 (3H, d, J=7 Hz); MS m/e 440.053 (M^+ calc for C_{20}H_{24}O_4S 440.056).

(2R,3S)-3-Hydroxy-2-methyl-5-(1E-3-phenylsulfonyl-1-propenyl)tetrahydrofuran (99).

A. From 96

To an ice-cold solution of 97 (797 mg, 1.81 mmol) in 50 mL of tetrahydrofuran was added 2.73 mL (2.73 mmol) of 1N hydrogen peroxide in tetrahydrofuran. The reaction mixture was slowly warmed to
room temperature. After 5 h, the mixture was diluted with ether and washed with 10% aqueous potassium bicarbonate. The organic layer was washed with 10% aqueous sodium thiosulfate, brine, and was dried over anhydrous magnesium sulfate. Filtration and concentration, followed by flash column chromatography on silica gel (66% ethyl acetate/hexane), afforded 470 mg (92%) of 99 as an inseparable mixture of diastereomers: IR (film) 3400, 1620, 1420, 1330 cm⁻¹; ¹H NMR (CDCl₃) δ 7.95-7.70 (2H, m), 7.70-7.40 (3H, m), 5.80-5.55 (2H, m), 4.71-4.45 (1H, m), 4.15-3.98 (2H, m), 3.90 (2H, m), 2.60-2.25 (1H, br s), 2.20-1.65 (2H, m), 1.25 (3H, d, J=6 Hz); MS m/e 281 (M⁺+1).

B. From 106

Following the procedure used for 97, the reaction of 106 (30 mg, 0.105 mmol) with phenylselenyl chloride (25 mg, 0.13 mmol) in dichloromethane and then with 150 μL (0.15 mmol) of 1N hydrogen peroxide in tetrahydrofuran afforded, after column chromatography on silica gel (75% ethyl acetate/hexane), 26.5 mg (89%) of 99 as a mixture of diastereomers.

(2R,3S,5S)-3-t-Butyldimethylsiloxy-2-methyl-5-(1E-3-phenylsulfonyl-1-propenyl)tetrahydrofuran (100) and

(2R,3S,5R)-3-t-Butyldimethylsiloxy-2-methyl-5-(1E-3-phenylsulfonyl-1-propenyl)tetrahydrofuran (101).

To a solution of t-butyldimethylsilyl chloride (377 mg, 2.50 mmol) in 15 mL of N,N-dimethylformamide at room temperature under nitrogen atmosphere was added imidazole (358 mg, 6.17 mmol). The mixture was stirred for 10 min and a solution of 99 (470 mg, 1.67
mmol) in 5 mL of N,N-dimethylformamide was added. After 18 h at room temperature, the reaction mixture was diluted with ether and washed with water. The organic layer was washed with 10% aqueous copper sulfate solution and water. The aqueous layer was extracted twice with ether and the combined organic layer was washed with brine and dried over anhydrous sodium sulfate. Filtration and concentration under high vacuum followed by column chromatography on silica gel (30% ethyl acetate/hexane), afforded 581 mg (88%) of a mixture of 100 and 101 as a colorless oil. High performance liquid chromatography (μ-Porasil, 25% ethyl acetate/hexane) of the mixture showed a 1:3.9 ratio of 100:101 derived from 96 and a 1.4:1 ratio of 100:101 derived from 106. Compound 100: Rt 7.2 min; $^1$H NMR (CDCl$_3$) $\delta$ 7.95-7.65 (2H, m), 7.65-7.35 (3H, m), 5.70-5.50 (2H, m), 4.55-4.25 (2H, m), 3.95-3.50 (4H, m), 2.25 (1H, ddd, J=13, 7, 7 Hz), 1.46 (1H, ddd, J=13, 7, 7 Hz), 1.13 (3H, d, J=6 Hz), 0.90 (9H, s), 0.05 (6H, s). Compound 101: Rt 6.4 min; IR (film) 1450, 1430, 1300, 1235 cm$^{-1}$; $^1$H NMR (CDCl$_3$) $\delta$ 7.95-7.65 (2H, m), 7.65-7.35 (3H, m), 5.85-5.30 (2H, m), 4.60-4.30 (2H, m), 3.97-3.55 (4H, m), 1.82 (1H, ddd, J=13, 7, 3 Hz), 1.61 (1H, ddd, J=13, 9, 7 Hz), 1.13 (3H, d, J=6 Hz), 0.90 (9H, s), 0.05 (6H, s); MS m/e 339.107 (M$^+$-C$_4$H$_9$, calc for C$_{16}$H$_{23}$O$_4$Si 339.109).

\[(5S,6R)-(-)-5,6-O-isopropylidene-2-heptyn-1,5,6-triol\] (102).

To a solution of 58 (200 mg, 0.87 mmol) in 3 mL of benzene were added 1 mL of methanol, 1 mL of 2,2-dimethoxypropane, and 7 mg of p-toluenesulfonic acid. The reaction mixture was stirred for 18 h.
and solid sodium carbonate was added. Filtration and concentration, followed by flash column chromatography on silica gel (67% ethyl acetate/hexane), afforded 107 mg (68%) of 102 as a colorless oil; IR (CHCl₃) 3450, 2200, 1460, 1370 cm⁻¹; ¹H NMR (CDCl₃) δ 4.47-4.05 (4H, m), 2.50-2.20 (3H, m), 1.46 (3H, s), 1.35 (3H, s), 1.25 (3H, d, J=7 Hz); MS m/e 169.086 (M⁺-CH₃, calc for C₉H₁₃O₃ 169.086); [α]D²⁶ -38.1° (C, 3.15, CHCl₃).

(2E,5S,6R)-(-)-0-Isopropylidene-2-hepten-1,5,6-triol (103).

To a suspension of lithium aluminum hydride (12 mg, 0.31 mmol) and 1 mg of aluminum chloride in 5 mL of tetrahydrofuran was added a solution of 102 (48 mg, 0.26 mmol) in 1 mL tetrahydrofuran. The reaction mixture was refluxed for 3 h and quenched with 15 µL of ethyl acetate. Work up was accomplished by adding sequentially 12 µL of water, 12 µL of 15% aqueous sodium hydroxide solution, and 36 µL of water. The precipitate was filtered and the organic layer was dried over anhydrous sodium sulfate. Filtration and concentration in vacuo yielded 42 mg (88%) of 103 as a colorless oil: IR (CHCl₃) 3500, 1440, 1380, 1080 cm⁻¹; ¹H NMR (CDCl₃) δ 5.92-5.45 (2H, m), 4.40-3.95 (4H, m), 2.45-2.00 (2H, m), 1.70 (1H, br s), 1.46 (3H, s), 1.35 (3H, s), 1.18 (3H, d, J=7 Hz); MS m/e 171.102 (M⁺-CH₃, calc for C₉H₁₅O₃ 171.102); [α]D²³ -58.8° (C, 1.17, CHCl₃).

(2E,5S,6R)-(-)-1-Chloro-5,6-0-isopropylidene-2-hepten-5,6-diol (104).

Following the procedure used for the preparation of 61, the re-
action of 103 (42 mg, 0.23 mmol) with N-chlorosuccinimide (33 mg, 0.25 mmol) and dimethyl sulfide (22 μL, 0.30 mmol) in 5 mL of dichloromethane afforded, after column chromatography on silica gel (33% ethyl acetate/hexane), 42 mg (91%) of 104 as a colorless oil: IR (CHCl₃) 1660, 1450, 1375 cm⁻¹; ¹H NMR (CDCl₃) δ 6.00-5.45 (2H, m), 4.28 (1H, dd, J=14, 7 Hz), 4.05 (1H, dd, J=14, 7 Hz), 4.20-3.80 (2H, m), 2.45-1.95 (2H, m), 1.45 (3H, s), 1.33-1.60 (3H, s), 1.16 (3H, d, J=6 Hz); MS m/e 204.091 (M⁺, calc for C₁₀H₁₇O₂C₁₂ 204.092); [α]_D^20 -28.2° (C, 0.50, CHCl₃).

(3E,6S,7R)-6,7-O-Isopropylidene-1-phenylsulfonyl-3-octen-6,7-diol (105).

Following the procedure used for the preparation of 39, the reaction of 104 (38 mg, 0.186 mmol) with methyl phenyl sulfone (45 mg, 0.288 mmol), copper(I) iodide (55 mg, 0.288 mmol), and n-butyllithium (186 μL, 0.288 mmol, 1.55 M in hexane) in 3 mL of tetrahydrofuran afforded 62 mg (103%) of crude 105. An analytical sample was obtained as a colorless oil by column chromatography on silica gel (50% ethyl acetate/hexane): IR (CHCl₃) 1580, 1440, 1300 cm⁻¹; ¹H NMR (CDCl₃) δ 7.95-7.75 (2H, m), 7.65-7.45 (3H, m), 5.75-5.15 (2H, m), 4.35-3.82 (2H, m), 3.30-3.00 (2H, m), 2.60-2.23 (2H, m), 2.23-1.95 (2H, m), 1.42 (3H, m), 1.31 (3H, s), 1.12 (3H, d, J=6 Hz).

(3E,6S,7R)-(-)-1-Phenylsulfonyl-3-octen-6,7-diol (106).

Following the procedure used for the preparation of 96, the reaction of crude 105 (62 mg, 0.19 mmol) with 10 mg of p-toluensul-
fonic acid in 5 mL of methanol afforded, after column chromatography on silica gel (75% ethyl acetate/hexane), 40.5 mg (77% from 104) of 106 as a colorless oil; IR (CHC\(_3\)) 3500, 1600, 1440, 1300 cm\(^{-1}\); \(^1\)H NMR (CDC\(_3\)) \(\delta\) 8.00-7.75 (2H, m), 7.75-7.35 (3H, m), 5.76-5.25 (2H, m), 3.95-3.40 (2H, m), 3.16 (2H, t, J=8 Hz), 2.70-2.00 (5H, m), 1.93 (1H, br s), 1.26 (3H, d, J=6 Hz); MS m/e 239.073 (M\(^+\)-C\(_2\)H\(_5\)O, calc for C\(_{12}\)H\(_{15}\)O\(_3\)S 239.074).

\((2R,3S,5S)-3\text{-t-Butyldimethylsiloxy-2-methyl-5-(3-phenylsulfonylpropyl)tetrahydrofuran (107)}\) and \((2R,3S,5R)-3\text{-t-Butyldimethylsiloxy-2-methyl-5-(3-phenylsulfonylpropyl)-tetrahydrofuran (108)}\).

To a suspension of 50 mg of 10% palladium on carbon in 50 mL of ethyl acetate under a hydrogen atmosphere was added a mixture of 100 and 101 (581 mg, 1.47 mmol) dissolved in 5 mL of ethyl acetate. The mixture took up one equivalent of hydrogen in 1 h, after which the catalyst was removed by filtration through Celite and the solvent was evaporated to yield 524 mg (92%) of 107 and 108 as a mixture of diastereomers. Medium pressure column chromatography on silica gel (33% ethyl acetate/hexane) eluted first 376 mg (65%) of 108, followed by 110 mg (19%) of 107 as colorless oils. Compound 107: \(^1\)H NMR (CDC\(_3\)) \(\delta\) 7.95-7.70 (2H, m), 7.65-7.30 (3H, m), 4.15-3.40 (3H, m), 3.25-2.93 (2H, m), 2.40-2.05 (1H, m), 2.05-1.35 (5H, m), 1.13 (3H, d, J=6 Hz), 0.90 (9H, s), 0.05 (6H, s). Compound 108: IR (film) 1440, 1300, 1240, 1140 cm\(^{-1}\); \(^1\)H NMR (CDC\(_3\)) \(\delta\) 7.95-7.70 (2H, m), 7.65-7.30 (3H, m), 4.15-3.40 (3H, m), 3.25-2.93 (2H, m),
cis and trans-Methyl 2,6,6-Trimethyl-5-hydroxy-heptanedioate, δ-Lactone Methylacetal (110).

To a solution of lactone ester 71 (797 mg, 3.72 mmol) in 40 mL of dichloromethane at -78°C under argon atmosphere was added diisobutylaluminum hydride (3.5 mL, 3.53 mmol, 1 M/hexane). After 1 h, the reaction mixture was quenched by adding 4 mL of ethyl acetate and 0.5 mL of acetic acid. This mixture was poured into 50 mL of aqueous 2% hydrochloric acid and extracted three times with ether. The combined organic layer was washed with aqueous saturated sodium bicarbonate and dried over anhydrous sodium sulfate. Filtration and concentration, followed by flash column chromatography on silica gel (25% ethyl acetate/dichloromethane), provided 453 mg (56.3%) of lactol ester. To this compound in 20 mL of benzene were added 3 mL of methanol, 3 mL of trimethyl orthoformate and 40 mg of p-toluene-sulfonic acid at room temperature. After 17 h, the reaction mixture was diluted with ether and washed with aqueous saturated sodium bicarbonate. The aqueous layer was extracted twice with ether and the combined organic layer was dried over anhydrous sodium sulfate. Filtration and concentration afforded 432 mg (89.5%) of 110 as a mixture of diastereomers: IR (CHCl₃) 1730, 1460, 1375, 1260 cm⁻¹; \(^1\)H NMR (CDCl₃) δ 4.30 (1H, br s), 3.95-3.80 (1H, m), 3.65 (3H, s), 3.30 (3H, s), 2.00-1.35 (5H, m), 1.20 (3H, s), 1.13 (3H, s), 0.91 (3H, d, J=7 Hz); MS m/e 230 (M⁺).
cis and trans-5-Hydroxy-7-oxo-8-phenylsulfonyl-2,6,6-trimethyloctanoic Acid, δ-Lactone Methylacetal (111).

To a solution of methyl phenyl sulphone (808 mg, 5.2 mmol) in 10 mL of tetrahydrofuran at 0°C under argon was added n-butyllithium (6.25 mL, 9.7 mmol, 1.55 M/hexane). After 20 min at room temperature, a solution of 110 (337 mg, 1.47 mmol) in 5 mL of tetrahydrofuran was added via cannula. After stirring for 1 h at room temperature, the reaction mixture was poured into aqueous, saturated ammonium chloride and extracted three times with ether. The combined organic layer was dried over anhydrous sodium sulfate. Filtration and concentration yielded 842 mg of crude material, which was purified by column chromatography on silica gel (20% ethyl acetate/hexane to 33% ethyl acetate/hexane) to give 349 mg (67.2%) of 111 as a mixture of diastereomers: IR (CHCl₃) 1715, 1445, 1320, 1145 cm⁻¹; ¹H NMR (CDCl₃) δ 8.05-7.85 (2H, m), 7.65-7.35 (3H, m), 4.58 (1H, d, J=16 Hz), 4.37 (1H, d, J=16 Hz), 4.25 (1H, br s), 3.72-3.60 (1H, m), 3.15 (3H, s), 2.10-1.25 (5H, m), 1.14 (6H, s), 0.93 (3H, d, J=7 Hz); MS m/e 354 (M⁺).

2,3-trans-3,5-trans-3-t-Butyldimethylsiloxy-5-(6,6-dimethoxy-5,5-dimethyl-4-oxo-3-phenylsulfonylhexyl)tetrahydrofuran (113).

To a solution of 108 (87 mg, 0.22 mmol) in 1 mL of tetrahydrofuran at -78°C under argon was added n-butyllithium (282 μL, 0.04 mmol, 1.55 M/hexane). The mixture was warmed to room temperature for 30 min, cooled to -78°C, and transferred to a solution of 112
(38 mg, 0.22 mmol in 1 mL of 1:4 hexamethylphosphoramide:tetrahydrofuran) via cannula. This reaction mixture was stirred for 1 h at -78°C and then warmed to room temperature. After 7 h, the mixture was diluted with ether and quenched with aqueous saturated ammonium chloride. The aqueous layer was extracted twice with ether and the combined organic layer was washed with brine and dried over anhydrous magnesium sulfate. Filtration and concentration afforded 106 mg (89%) of crude 113 as a mixture of diastereomers. An analytical sample was purified by flash column chromatography on silica gel (25% ethyl acetate/hexane): IR (film) 1710, 1460, 1320, 1140 cm⁻¹; 

\[ \text{H NMR (CDCl}_3\text{)} \delta 7.90-7.70 (2H, m), 7.70-7.45 (3H, m), 4.75 (1H, br t, J=6 Hz), 4.23 (1H, s), 3.50-4.00 (3H, m), 3.53 (3H, s), 3.40 (3H, s), 2.00-1.45 (6H, m), 1.34 and 1.32 (3H, s), 1.18 and 1.16 (3H, s), 1.15 and 1.13 (3H, d, J=6 Hz), 0.87 (9H, s), 0.03 (6H, s).

2,3-trans-3,5-trans-3-t-Butyldimethylsiloxy-5-(6,6-dimethoxy-5,5-dimethyl-4-oxohexyl)tetrahydrofuran (114).

To a solution of crude 113 (106 mg, 0.19 mmol) in 10 mL of 10% aqueous tetrahydrofuran was added aluminum-amalgam, prepared from 570 mg of aluminum and 50 mL of a 2% aqueous mercuric chloride solution. The reaction mixture was heated at reflux for 2 h and, after cooling, was filtered through Celite and washed with ether. The organic layer was washed with water and brine, and was dried over anhydrous magnesium sulfate. Filtration and concentration, followed by flash column chromatography on silica gel (25% ethyl acetate/hexane), yielded 56 mg (63%) of 114 as a colorless oil: IR (film) 1710,
To a suspension of sodium borohydride (45 mg, 1.2 mmol) in 3 mL of dry methanol at 0°C was added 114 (70 mg, 0.174 mmol). The reaction mixture was stirred for 30 min at 0°C, and quenched with water. The aqueous layer was extracted twice with ether and the combined organic layer was dried over anhydrous magnesium sulfate. Filtration and concentration gave 65 mg (93%) of 115 as a mixture of diastereomers: IR (film) 3500, 1460, 1240 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 4.10-3.35 (4H, m), 3.95 (1H, s), 3.49 and 3.48 (6H, s), 3.10 (1H, br s), 1.80-1.20 (8H, m), 1.13 and 1.12 (3H, d, J=6 Hz), 0.88 (9H, s), 0.85 (6H, s), 0.05 (6H, s).

2,3-trans-3,5-trans-3-t-Butyldimethyldisiloxy-5-(4-benzyloxy-6,6-dimethoxy-5,5-dimethyl-4-hydroxyhexyl)-tetrahydrofuran (115).

To a suspension of potassium hydride (130 mg, 24.6% in oil) in 1 mL of tetrahydrofuran at room temperature was added a solution of 115 (65 mg, 0.16 mmol) in 1 mL tetrahydrofuran. After 30 min, benzyl bromide (95 \(\mu\)L, 0.8 mmol) was added and the reaction mixture was stirred for 1 h at room temperature. The mixture was diluted with ether and quenched with water. The aqueous layer was extracted
twice with ether and the combined organic layer was dried over anhydrous magnesium sulfate. Filtration and concentration, followed by flash column chromatography on silica gel (25% ethyl acetate/hexane), afforded 65 mg (82%) of 116 as a colorless oil: IR (film) 1460, 1370 cm\(^{-1}\); \(\text{\textsuperscript{1}H NMR (CDCl}_3\text{)}\) \(\delta\) 7.46-7.25 (5H, m), 4.47 (1H, d, J=16 Hz), 4.60 (1H, d, J=16 Hz), 4.22 (1H, s), 4.20-3.70 (4H, m), 3.62 (3H, s), 3.54 (3H, s), 1.95-1.46 (8H, m), 1.30 (3H, d, J=6 Hz), 1.06 (3H, s), 1.00 (9H, s), 0.98 (3H, s), 0.05 (6H, s).

2,3-trans-3,5-trans-3-t-Butyldimethylsiloxy-5-(3-benzyloxy-4,4-dimethyl-5-formylpentyl)tetrahydrofuran (117).

To a solution of 116 (64 mg, 0.130 mmol) in 7 mL of acetone was added 10 mg of p-toluenesulfonic acid. The mixture was stirred for 30 min and diluted with ether. The organic layer was washed with aqueous saturated sodium bicarbonate, and dried over anhydrous magnesium sulfate. Filtration and concentration afforded 55 mg (94%) of 117 as a colorless oil: IR (film) 1710, 1460, 1365, 1240 cm\(^{-1}\); \(\text{\textsuperscript{1}H NMR (CDCl}_3\text{)}\) \(\delta\) 9.61 (1H, s), 7.34 (5H, s), 4.74 (1H, d, J=14 Hz), 4.62 (1H, d, J=14 Hz), 4.26-3.58 (4H, m), 1.96-1.54 (8H, m), 1.34 (3H, d, J=6 Hz), 1.24 (3H, s), 1.20 (3H, s), 1.04 (9H, s), 0.05 (6H, s).

10-(2,3-trans-3,5-trans-3-t-Butyldimethylsiloxy-2-methyl-5-tetrahydrofuryl)-5,7-dihydroxy-2-methyldecanoic Acid (118).

To a solution of diisopropylamine (38 \(\mu\)L, 0.26 mmol) in 0.5 mL of tetrahydrofuran at -78°C was added n-butyllithium (148 \(\mu\)L, 0.26
mmol, 1.50 M/hexane). The mixture was warmed to 0°C for 30 min and cooled to -78°C. To this mixture was added tiglic acid (11.2 mg, 0.11 mmol) in 1 mL of tetrahydrofuran. The reaction mixture was warmed to 0°C for 45 min and then cooled to -78°C. To this mixture was added aldehyde 117 (50 mg, 0.11 mmol) in 1 mL of tetrahydrofuran and, after warming to 0°C for 20 min, the mixture was stirred for 18 h at room temperature. The mixture was then diluted with ether, and ice cold 2% aqueous hydrochloric acid was added. The aqueous layer was extracted twice with ether and the combined organic layer was washed with aqueous sodium bicarbonate and brine, and was dried over anhydrous magnesium sulfate. Filtration and concentration yielded 70 mg of crude material which was used without purification: $^1$H NMR (CDCl$_3$) $\delta$ 7.34 (5H, s), 6.55 (1H, m), 5.84 (1H, br s), 4.62 (2H, br s), 4.30-3.15 (5H, m), 2.70-2.10 (2H, m), 2.00-1.30 (8H, m), 1.20 (3H, d, J=6 Hz), 0.92 (9H, 6H, s, overlapped), 0.05 (6H, s).

To a suspension of 41 mg of 10% palladium on carbon in 4 mL of ethyl acetate under a hydrogen atmosphere was added the crude acid (70 mg, 0.127 mmol). The mixture was stirred for 18 h, filtered through Celite, and concentrated to give 41 mg (70%) of crude 118, which was used without further purification: $^1$H NMR (CDCl$_3$) $\delta$ 4.90-4.30 (2H, m), 4.30-3.30 (3H, m), 2.60-1.30 (15H, m), 1.20 (3H, d, J=6 Hz), 1.18 (3H, d, J=6 Hz), 0.90 (6H, 3H, s, overlapped), 0.05 (6H, s).

10-(2,3-trans-3,5-trans-3-t-Butyldimethylsiloxy-2-methyl-5-tetrahydrofuryl)-5,7-dihydroxy-2-methyldecanoic Acid, $\delta$-Lactone (119).

To a solution of 118 (15 mg, 0.03 mmol) in 1 mL dichloromethane
at 0°C was added 3 mg of dimethylaminopyridine. The mixture was stirred for 10 min and a solution of dicyclohexylcarbodiimide (11 mg, 0.05 mmol) in 1 mL of dichloromethane was added. The mixture was stirred for 30 min at 0°C and quenched with water. The aqueous layer was extracted twice with dichloromethane and the combined organic layer was washed with brine and dried over anhydrous magnesium sulfate. Filtration and concentration afforded 11 mg (76%) of 119 as a mixture of diastereomers. Analytical samples of the two major isomers were separated by column chromatography on silica gel (50% ethyl acetate/hexane). "Fast-moving isomer" of 119: IR (CHCl₃) 3400, 1710, 1460, 1380, 1100 cm⁻¹, ¹H NMR (CDCl₃) δ 4.60-4.15 (1H, m), 4.15-3.35 (4H, m), 2.70-2.25 (1H, m), 2.25-1.85 (12H, m), 1.30 (3H, d, J=6 Hz), 1.20 (3H, d, J=6 Hz), 0.98 (3H, s), 0.90 (9H, s), 0.87 (3H, s), 0.05 (6H, s); MS m/e 385.243 (M⁺-C₄H₉, calc for C₂₀H₃₇O₄Si 385.241). "Slow-moving isomer" of 119: ¹H NMR (CDCl₃) δ 4.30-3.25 (5H, m), 2.75-2.25 (1H, m), 2.25-1.85 (12H, m), 1.25 (3H, d, J=6 Hz), 1.20 (3H, d, J=6 Hz), 0.91 (9H, 6H, s, overlapped), 0.05 (6H, s).

10-(2,3-trans-3,5-trans-3-hydroxy-2-methyl-5-tetrahydrofuryl)-5,7-dihydroxy-2-methyldecanoic Acid, δ-Lactone (120).

To a solution of the "fast-moving isomer" of 119 (4 mg, 0.009 mmol) in 1 mL of tetrahydrofuran at room temperature was added 50 μL of tetra-n-butylammonium fluoride (1 M in tetrahydrofuran). The mixture was stirred for 30 min and was quenched with saturated aqueous ammonium chloride. The aqueous layer was extracted twice
with ether, and the combined organic layer was washed with brine and
dried over anhydrous magnesium sulfate. Filtration and concentration,
followed by column chromatography (100% ethyl acetate), afforded
1.5 mg (50%) of "fast-moving isomer" of 120: IR (CHCl₃) 3500, 1720,
1400 cm⁻¹; ¹H NMR (CDCl₃) δ 4.30-4.15 (1H, m), 4.15-3.50 (4H, m),
2.40-2.00 (1H, m), 1.90-1.35 (12H, m), 1.25 (3H, d, J=6 Hz), 1.15
(3H, d, J=6 Hz), 0.98 (3H, s), 0.82 (3H, s); MS m/e 328 (M⁺). A
"slow-moving isomer" of 120 was prepared by the same procedure as
above from 3 mg of "slow-moving isomer" of 119 and 50 μL of tetra-
butylammonium fluoride, giving 0.7 mg (31%) of "slow-moving isomer"
of 120: ¹H NMR (CDCl₃) δ 4.40-3.35 (5H, m), 2.40-2.20 (1H, m), 2.15-
1.40 (12H, m), 1.27 (3H, d, J=6 Hz), 1.20 (3H, d, J=6 Hz), 0.94 (3H,
s), 0.92 (3H, s).

(1R,2R)-2-Hydroxy-1-methylpropyl (10Z,2R,5S,7R,-
13S,14R)-(-)-5,7-Dihydroxy-13,14-0-isopropylidene-
2,6,6-trimethyl-10-pentadecenoate (123).

To a solution of 83 (13 mg, 0.03 mmol) in 2 mL of 20% aqueous
tetrahydrofuran at room temperature was added 4 mg of p-toluenesul-
fonic acid. After 20 h the reaction mixture was diluted with ether
and washed with aqueous sodium bicarbonate. The aqueous layer was
extracted three times with ether and the combined organic layer was
washed with brine and dried over anhydrous sodium sulfate. Filtra-
tion and concentration afforded 12.4 mg of crude material which was
chromatographed on silica gel (75% ethyl acetate/hexane) to yield
2.3 mg of 80 and 9.4 mg (84% based on recovered starting material) of
123 as a colorless oil: IR (film) 3450, 1730, 1450, 1370 cm⁻¹; ¹H NMR (CDCl₃) δ 5.65-5.15 (2H, m), 4.73 (1H, dq, J=6, 6 Hz), 4.40-3.85 (2H, m), 2.60-1.40 (11H, m), 1.45 (3H, s), 1.33 (3H, s), 1.18 (two 3H, d, J=6 Hz), 1.16 (two 3H, d, J=6 Hz), 0.86 (3H, s), 0.72 (3H, s); MS m/e 459 (M⁺+1); [α]D²⁰ -31.2° (C, 0.9, CHCl₃).

(1R,2R)-2-t-Butyldimethylsiloxy-1-methylpropyl (10Z,2R,5S,7R,13S,-14R)-(-)-5,7-Di-t-butyldimethylsiloxy-13,14-O-isopropylidene-2,6,6-trimethyl-10-pentadecenoate (124).

To a solution of triol 123 (43 mg, 0.094 mmol) in 2 mL of dichloromethane at -20°C under an argon atmosphere were added 2,6-lutidine (82 µL, 0.705 mmol) and t-butyldimethylsilyl trifluoromethanesulfonate (97 µL, 0.423 mmol). After 2 h at -20°C, the reaction mixture was diluted with ether and was washed with saturated aqueous sodium bicarbonate and water. The organic layer was dried over anhydrous sodium sulfate. Filtration and concentration, followed by flash column chromatography on silica gel (10% ethyl acetate/hexane) afforded 74 mg (98%) of 124 as a colorless oil: IR (CHCl₃) 1720, 1460, 1375 cm⁻¹; ¹H NMR (CDCl₃) δ 5.65-5.20 (2H, m), 4.80 (1H, dq, J=6, 7 Hz), 4.40-3.70 (3H, m), 3.70-3.35 (2H, m), 2.55-1.40 (11H, m), 1.45 (3H, s), 1.34 (3H, s), 1.23 (3H, d, J=6 Hz), 1.17 (3H, d, J=6 Hz), 1.16 (3H, d, J=6 Hz), 1.08 (3H, d, J=6 Hz), 0.92 (27H, 3H, s, overlapped), 0.76 (3H, s), 0.07 (18H, s); MS m/e 743 (M⁺-C₄H₉); [α]D²⁰ -4.97° (C, 7.80, CHCl₃).
(1R,2R)-2-t-Butyldimethylsiloxy-1-methylpropyl (10Z,2R,5S,7R, 13S,14R)-5,7-Di-t-butyldimethylsiloxy-13,14-dihydroxy- 2,6,6-trimethyl-10-pentadecenoate (125).

To a solution of 124 (73 mg, 0.091 mmol) in 5 mL of methanol was added 5 mg of p-toluenesulfonic acid. The reaction mixture was stirred for 2 h at room temperature and diluted with ether. The organic layer was washed with saturated aqueous sodium bicarbonate and the aqueous layer was extracted twice with ether. The combined organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated. Column chromatography of the residue on silica gel (40% ethyl acetate/hexane) afforded 16 mg of starting material 124 and 41 mg (76% based on recovered starting material) of 125: IR (CHCl₃) 3450, 1730, 1460, 1380, 1245 cm⁻¹; ¹H NMR (CDCl₃) δ 5.70-5.12 (2H, m), 4.77 (1H, dq, J=7, 6 Hz), 3.90-3.35 (5H, m), 2.55-1.30 (11H, m), 1.17 (3H, d, J=6 Hz), 1.15 (two 3H, d, J=6 Hz), 1.08 (3H, d, J=6 Hz), 0.92 (27H, s), 0.87 (3H, s), 0.75 (3H, s), 0.07 (18H, s); MS m/e 745 (M⁺-CH₃).

(1R,2R)-2-t-Butyldimethylsiloxy-1-methylpropyl (10Z,2R,5S,- 7R,13S,14R)-13-Hydroxy-5,7-14-tri-t-butyldimethyl- siloxy-2,6,6-trimethyl-10-pentadecenoate (126).

To a solution of 125 (22 mg, 0.029 mmol) in 1 mL of dichloromethane at room temperature was added a solution of t-butyldimethylsilyl chloride (9.3 mg, 0.062 mmol) and 4-dimethylaminopyridine (15 mg, 0.123 mmol) in 1 mL of dichloromethane. After 5 h, the mixture was washed with 5% aqueous sodium bicarbonate. The aqueous
layer was extracted twice with ether and the combined organic layer was dried over anhydrous sodium sulfate. Filtration and concentration, followed by column chromatography on silica gel (20% ethyl acetate/hexane), afforded 22 mg (88%) of 126 as a colorless oil:

IR (film) 3500, 1730, 1460, 1370, 1245 cm⁻¹; ¹H NMR (CDCl₃) δ 5.70-5.12 (2H, m), 4.81 (1H, dq, J=6, 7 Hz), 3.90-3.35 (5H, m), 2.55-1.30 (11H, m), 1.22 (two 3H, d, J=6 Hz), 1.09 (3H, d, J=6 Hz), 1.08 (3H, d, J=6 Hz), 0.92 (36H, s), 0.87 (3H, s), 0.75 (3H, s), 0.07 (24H, s); MS m/e 743 (M⁺-C₄H₉OSi).

(1R,2R)-2-t-Butyldimethylsiloxy-1-methylpropyl (10Z,2R,5S,-7R,14R)-13-Oxo-5,7,14-tri-t-butyldimethylsiloxy-2,6,6-trimethyl-10-pentadecenoate (127).

To a solution of 126 (4.0 mg, 0.0045 mmol) in 0.5 mL of dichloromethane at room temperature was added 100 μL of Collins' reagent, freshly prepared from 36.4 mg of chromium(VI) oxide and 29.4 μL of pyridine, in 0.8 mL of dichloromethane. After 30 min, 2 drops of isopropyl alcohol was added, and the reaction mixture was passed through a column of silica gel (11% ethyl acetate/hexane) to provide 3.4 mg (85%) of 127: IR (film) 1725, 1460, 1250 cm⁻¹; ¹H NMR (CDCl₃) δ 5.70-5.25 (2H, m), 4.76 (1H, dq, J=6, 6 Hz), 4.25-4.00 (1H, m), 3.95-3.40 (3H, m), 3.40-3.25 (2H, m), 2.50-1.30 (9H, m), 1.22 (two 3H, d, J=6 Hz), 1.09 (3H, d, J=6 Hz), 1.08 (3H, d, J=6 Hz), 0.91 (36H, s), 0.88 (3H, s), 0.75 (3H, s), 0.07 (24H, s); MS m/e 741 (M⁺-C₆H₁₅OSi).

To a solution of 126 (4 mg, 0.0045 mmol) in 0.3 mL of dichloromethane at room temperature were added a solution of 16 μL of triethylamine, 1,3-dithiane-2-carboxylic acid (128, 4.7 mg, 0.029 mmol) and N,N-bis[2-oxo-3-oxazolidinyl]phosphorodiamidic chloride (13.3 mg, 0.058 mmol) in 0.3 mL of dichloromethane. After 3 h, the reaction mixture was diluted with ether and washed with aqueous sodium bicarbonate. The aqueous layer was extracted three times with ether and the combined organic layer was washed with brine, and dried over anhydrous sodium sulfate. Filtration and concentration, followed by column chromatography on silica gel (11% ethyl acetate/hexane), afforded 4.2 mg (89%) of 129: IR (film) 1725, 1460, 1380 cm⁻¹; ¹H NMR (CDCl₃) δ 5.60-5.15 (2H, m), 4.92-4.63 (2H, m), 4.10 (1H, s), 3.95-3.70 (2H, m), 3.65-3.20 (2H, m), 2.70-2.53 (1H, m), 2.53-1.30 (14H, m), 1.18 (3H, d, J=6 Hz), 1.15 (two 3H, d, J=6 Hz), 1.08 (3H, d, J=6 Hz), 0.85 (3H, s), 0.75 (3H, s).

(10Z,2R,5S,7R,13S,14R)-5,7-Di-t-butyldimethylsiloxy-13,14-0-isopropylidene-2,6,6-trimethyl-10-pentadecenoic Acid (130).

To a solution of 124 (16 mg, 0.02 mmol) in 3 mL of a 1:1 methanol-tetrahydrofuran mixture was added 0.4 mL of 20% aqueous sodium hydroxide and the reaction mixture was warmed up to 40-50°C for 10 h. The mixture was diluted with ether, and cooled to 0°C while 2% aqueous hydrochloric acid was added until the solution was slightly acidic. The aqueous layer was extracted twice with ether and the combined
organic layer was washed with brine and dried over anhydrous sodium sulfate. Filtration and concentration, followed by column chromatography on silica gel (25% ethyl acetate/hexane), afforded 8.5 mg (71%) of 130: IR (film) 3100, 1705, 1460, 1370 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) δ 5.65-5.20 (2H, m), 4.42-3.95 (2H, m), 3.65-3.35 (2H, m), 2.60-1.40 (11H, m), 1.46 (3H, s), 1.35 (3H, s), 1.20 (two 3H, d, J=6 Hz), 0.93 (18H, s), 0.87 (5H, s), 0.77 (3H, s), 0.06 (12H, s).

2-Isopropyl-2-methyloxalyl-1,3-dithiane (133).

To a solution of 132 (53 mg, 0.327 mmol) in 5 mL of tetrahydrofuran at -20°C under an argon atmosphere was added n-butyllithium (253 μL, 0.392 mmol, 1.6 M/hexane). After 2 h, the reaction mixture was cooled to -78°C and methyloxalyl chloride (398 mg, 3.27 mmol) was added. The reaction mixture was maintained at -20°C for 2 h and then diluted with ether and quenched with aqueous saturated sodium bicarbonate. The organic layer was washed with water and dried over anhydrous sodium sulfate. Filtration and concentration, followed by column chromatography on silica gel (11% ethyl acetate/hexane), gave 60.5 mg of 133 (74%) as a colorless oil: IR (CHCl\(_3\)) 1735, 1710, 1270, 1050 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) δ 3.85 (3H, s), 3.07-2.48 (4H, m), 2.15-1.70 (2H, m), 1.35-1.02 (1H, m), 1.15 (two 3H, d, J=8 Hz).

(10Z,2R,5S,7R,13S,14R)-5,7-Di-t-butyldimethylsiloxy-13,14-o-isopropylidene-2,6,6-trimethyl-10-pentadecenal (135).

To a solution of 124 (12 mg, 0.015 mmol) in dichloromethane at -78°C under an argon atmosphere was added diisobutylaluminum hydride
(34 μL, 0.034 mmol, 1 M in hexane). Thin layer chromatography of the mixture after 20 min showed that both alcohol 134 and aldehyde 135 was present. The reaction mixture was diluted with ether and quenched with water. The aqueous layer was extracted twice with ether and the combined organic layer was dried over anhydrous magnesium sulfate. Filtration and concentration afforded 8.5 mg of a mixture of 134 and 135. This mixture was dissolved in 1 mL of dichloromethane and 300 μL of Collins' reagent, prepared from 320 mg of chromium(VI) oxide and 680 μL of pyridine in 8 mL of dichloromethane, was added.

After 20 min at room temperature, the mixture was filtered through a short column of silica gel (25% ethyl acetate/hexane) to yield 8.3 mg (91%) of 135: IR (film) 1715, 1460, 1375, 1245 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 9.69 (1H, d, J=2 Hz), 5.70-5.25 (2H, m), 4.42-3.90 (2H, m), 3.65-3.40 (2H, m), 2.65-1.30 (11H, m), 1.47 (3H, s), 1.35 (3H, s), 1.19 (3H, d, J=6 Hz), 1.12 (3H, d, J=6 Hz), 0.95 (18H, s), 0.87 (3H, s), 0.78 (3H, s), 0.07 (12H, s); MS m/e 541.379 (M\(^+\) -C\(_4\)H\(_9\), calc for C\(_{29}\)H\(_{57}\)O\(_5\)Si\(_2\) 541.374).

(10Z,2R,5S,7R,13S,14R)-5,7,13,14-Tetra-t-butyldimethylsiloxy-2,6,6-trimethyl-10-pentadecenal, Propyl-1,3-dithiane (137).

To a solution of 135 (25 mg, 0.042 mmol) in 4 mL of dichloromethane was added 1,3-propanedithiol (50 μL, 0.5 mmol). After 2 h at room temperature, the reaction mixture was cooled to 0°C and 25 μL of 5% boron trifluoride-etherate in dichloromethane was added. The reaction mixture was stirred for 1 h at 0°C, and diluted with dichloromethane. The organic layer was washed with water, and 2% aqueous potassium hydroxide, and the aqueous layer was extracted
three times with chloroform. The combined organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated to give 26.4 mg of crude 136: IR (film) 3400, 1400 cm⁻¹; ¹H NMR (CDCl₃) δ 5.65-5.20 (2H, m); 4.10 (1H, d, J=4 Hz), 3.95-3.30 (4H, m), 2.95-2.63 (8H, m), 2.45-1.35 (11H, m), 1.15 (3H, d, J=6 Hz), 1.07 (3H, d, J=6 Hz), 0.87 (3H, s), 0.74 (3H, s).

This material was dissolved in 2 mL of dichloromethane at -20°C and t-butyldimethylsilyl trifluoromethanesulfonate (100 µL, 0.42 mmol) and 2,6-lutidine (73 µL, 0.63 mmol) were added. After 1 h at -20°C, the reaction mixture was warmed to 0°C and, after an additional 1 h, the reaction mixture was diluted with ether and washed with saturated, aqueous sodium bicarbonate. The organic layer was washed with water and dried over anhydrous sodium sulfate. Filtration and concentration, followed by flash column chromatography on silica gel (5% ethyl acetate/hexane), provided 36 mg (98% from 135) of 137 as a colorless oil: IR (film) 1460, 1380 cm⁻¹; ¹H NMR (CDCl₃) δ 5.50-5.25 (2H, m), 4.12 (1H, d, J=4 Hz), 3.80-3.40 (4H, m), 3.00-2.75 (4H, m), 2.30-1.35 (11H, m), 1.11 (two 3H, d, J=6 Hz), 0.92 (36H and 3H, s, overlapped), 0.78 (3H, s), 0.07 (24H, s). MS m/e 745 (M⁺⁻C₆H₁₅OSi).
V. BIBLIOGRAPHY


