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AN APPROACH TO THE ENANTIOSELECTIVE SYNTHESIS OF POLYCAVERNOSIDE A.
INVESTIGATION OF SULFUR-STABILIZED CARBANION CHEMISTRY
FOR UNION OF THE SOUTHERN AND NORTHERN FRAGMENTS OF THE AGLYCONE

DISSERTATION

Presented in partial fulfillment of the Requirements for
The Degree Doctor of Philosophy in the Graduate
School of The Ohio State University

By

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*****

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ABSTRACT

Polycavernoside A is a highly toxic marine glycosidic macrolide isolated in 1991 from the red alga *Polycavernosa tsudai*. The unusual structural features of polycavernoside A include a masked α-dicarbonyl moiety incorporated into a macrocycle and an appended triene side chain.

A convergent synthetic program directed toward a total synthesis of polycavernoside A is described. The northern tetrahydrofuran fragment of the aglycone was enantioselectively synthesized from D-pantolactone via previously reported (3S)-2,2-dimethyl-3,4-oxo-1-butanol. The southern tetrahydropyran fragment was obtained from L-malic acid via known (3R,4S,6S)-6-[(tert-butylidiphenylsiloxy)methyl]tetrahydro-4-hydroxy-3-methyl-2H-pyran-2-one.

The union of the northern and southern sectors with concomitant formation of an α-dicarbonyl bridge was envisioned to be possible via condensation of a sulfur-stabilized acyl anion equivalent with a carbonyl electrophile. Attempted coupling of the lithiated dithiane derived from the southern fragment with the lactone of the northern fragment was thwarted by steric hindrance at the lactone. Conversion of the northern fragment to a dithiane and attempted coupling with the aldehyde present in the southern fragment was
also prevented due to decomposition of the aldehyde via α-elimination. Finally, transformation of the southern fragment into a sulfone and subsequent condensation with an aldehyde located in the northern fragment took place in 71% yield and proved the most attractive strategy for completion of the synthesis.
Dedicated to my mother
I would like to express my gratitude to Professor Leo A. Paquette for sharing his expertise, creating an atmosphere in which there is a continual interest and stimulus to learn, and for setting high standards for quality and productivity of research by his own example. His insights, enthusiasm, and inspiration will never be forgotten.

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Finally, I wish to express my gratitude to my parents for their love, support and encouragement over the years.
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1. “(Dialkylamino)methylation of Hydride Spirophosphoranes”; Prishchenko, A. A.; Livantsov, M. V.; Zhutskii, P. V.; Pisarnitskii, D. A.; Shagi-Mukhametova N. M.; Petrosyan, V. S. *Journal of General Chemistry of the USSR* 1990, 60, 398.


4. Reaction of Tris(trimethylsilyl)phosphine with Chloromethylamines (Chloromethylamides); Prishchenko, A. A.; Livantsov, M. V.; Pisarnitskii, D. A.; Petrosyan, V. S. *Journal of General Chemistry of the USSR* 1991, 61, 922.


FIELDS OF STUDY

Major Field: Organic Chemistry
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CHAPTER 1

POLYCAVERNOSIDES: SURVEY OF LITERATURE

1.1 Discovery and Preliminary Structure of the Polycavernosides

Unlike many compounds isolated from marine sources as a result of the systematic pursuit of biologically active compounds, the polycavernoside family of macrocyclic toxins was discovered due to a food poisoning accident which occurred in the Guam province of Japan in late April 1991. Thirteen people became ill as a result of the ingestion of the red alga Polycavernosa tsudai (formerly Gracilaria edulis), which was widely used in Japanese cuisine without any previous indication of health risk. The symptoms included vomiting, diarrhea, stomach cramps, respiratory distress, muscle spasms and numbness of the extremities. Three of the victims died about 31, 72, and 120 hours after ingesting amounts of seaweed described by family members as equivalent to half to one cereal bowl. The toxicity of the alga decreased rapidly after the incident, but rose again, albeit at lower levels, in the same season of the following year, which called attention to the seasonal character of the toxicity.
The major causative toxin, named polycavernoside A, was isolated by Yasumoto shortly after the outbreak of algal poisoning by extraction with acetone, partitioning between water and dichloromethane, and extensive purification by column chromatography on normal and reverse phases, guided by mouse bioassays. Polycavernoside A was obtained as a colorless solid with LD$_{99}$ in mice of 200-400 µg/kg. The structure elucidation was hampered by sample size: only 400 µg was available. The originally proposed structure of polycavernoside A is shown in Figure 1.

Architecturally, polycavernoside A belongs to a wide class of naturally occurring glycosidic macrolactones. Partial structures H2-H8, H11-H13, H15-H23 of the macrolide and H1'-H5', H1''-H6'' of the glycoside were deduced from detailed analysis.
of $^1\text{H}-^1\text{H}$ COSY and 2D HOHAHA spectra. The presence of the conjugated triene unit H16-H21 was also supported by the UV maxima. The $E,E,E$-geometry was assigned in light of the large (15 Hz) values of $^3J_{\text{HH}}$ observed in the 2D $J$ spectrum. The majority of the remaining assignments was accomplished by HMQC and HMBC techniques, with

Figure 2. Congeners of polycavernoside A.
stereochemical aspects clarified by NOESY. The stereochemistry of the cyclic hemiketal was corroborated by MM2 energy calculations with calculated coupling constants of H11-H13 in good agreement with experiment.

The highly methylated fucopyranosyl-xylopyranosyl disaccharide unit is consistent with the algal origin of polycavernoside A. The carbon backbone of the aglycone, a 3,5,7,13,15-pentahydroxy-9,10-dioxotricosanoic acid, is so far unprecedented.

Additionally, four structurally related toxins, polycavernosides A2, A3, B and B2, were isolated from alga collected in Guam in June 1992, a year after the first reported incident of algal toxicity (Figure 2). Available NMR and MS data point to a close structural similarity of these compounds to polycavernoside A. All signals corresponding to the aglycone of polycavernoside A were also observed in 1H NMR spectra of polycavernosides A2 and A3. The signals corresponding to H1-H15, Me24, Me25, Me26 and Me27 of polycavernoside A were also found in polycavernosides B and B2 at the same chemical shifts. 1H-1H COSY of B and B2 indicated that a conjugated diene H16-H19 replaced the conjugated triene of polycavernoside A, with the result that the side chain is two atoms shorter.

As was evident from the 3JHH values of H1'-H5' and H1"'-H6" of each analog in their respective 1H-1H COSY spectra, the fucopyranosyl-xylopyranosyl disaccharide remained a common structural feature of each analog, with differences only in the substitution pattern. Detailed HMBC and NOE studies were prevented by extremely
small sample sizes, and for this reason only planar structures of polycavernosides A2, A3, B and B1 were reported.

1.2 Revised Structure of Polycavernoside A

The architectural similarity between polycavernosides and known macrolide antibiotics is noteworthy. Erythromycin A,\textsuperscript{5} perhaps the most well studied representative of the macrolide antibiotic class, is shown on Figure 3 to illustrate this point.

![Erythromycin A](image)

\textbf{Figure 3.} Erythromycin A.

Johnston\textsuperscript{6} performed an analysis of the absolute configuration of polycavernoside A based on the Celmer model.\textsuperscript{7} This model provides an empirical tool for the prediction
of the absolute and relative stereochemistries of macrolide antibiotics. Although the method is not claimed to be universally applicable, structural homology between an "unraveled" view of polycavernoside A and the Celmer model allowed Johnston to propose the absolute configuration of the aglycone.

Figure 4. The revised stereochemical structure of polycavernoside A proposed on the basis of the Celmer model.
Combined with the fact that D-xylose and L-fucose are Nature's predominant enantiomers and the observation that α-L and β-D linkages appear regularly in macrolide antibiotics, the revised structure 1 of polycavernoside A is shown on Figure 4.

The variations between the structure of polycavernoside A and the Celmer model presented in this case are not atypical and therefore do not provide sufficient cause to abandon the method of comparison.

The relative configuration of polycavernoside A proposed by Johnston was supported by studies undertaken by Murai. Murai's approach to the elucidation of the stereochemical structure of polycavernoside A included the synthesis of diastereomeric substructures of the natural product followed by $^1$H NMR chemical shift analysis. First, two disaccharides prepared from derivatives of natural L-fucose, unnatural D-fucose and natural D-xylose were synthesized. Subsequent $^1$H NMR investigation revealed that the chemical shifts and splitting patterns of protons in the disaccharide prepared from both natural sugars were almost identical with those of the respective protons of polycavernoside A, whereas in the case of one unnatural sugar the shifts had significant deviations (Figure 5). Accordingly, it was concluded that the disaccharide moiety of polycavernoside A consists of a combination of D-xylose and L-fucose.

Next, the most probable disaccharide unit was linked to the two diastereomeric models of the tetrahydropyran fragment of polycavernoside A (Figure 6). Analysis of $^1$H NMR data revealed that the chemical shifts of both 2 and 3 gave rise to apparent deviations from those recorded for polycavernoside A because of acetoxyl and
methoxycarbonyl groups not resident in the natural product. Notwithstanding, when the chemical shifts of the protons at C5 and C4-CH3 are compared, both differences from 2 are less in magnitude.

**Figure 5.** Comparison of 1H NMR data of synthetic disaccharides and glycoside of polycavernoside A. The numbers indicate deviations of chemical shifts.

Furthermore, in 2 the chemical shifts of the proton at C1' and the protons on methoxy groups at C2', C4', C2'', C3'' are much more coincident with the natural product.
Based on these data, Murai concluded that substructure 2 is the most likely constituent of polycavernoside A. This assignment of absolute configuration of the natural product is therefore identical to that proposed by Johnston (1, Figure 4).

Details of the synthesis of substructures 2 and 3 as well as other efforts toward the total synthesis of polycavernoside A will be discussed in the next chapter.

1.3 Progress toward the Total Synthesis of Polycavernoside A

The retrosynthetic analysis of polycavernoside A proposed by Murai is shown in Figure 7. Compound 4 is a precursor of the northern (C10-C17) portion of the aglycone.
The southern tetrahydropyran portion is assembled in compound 5. An additional carbon atom, C9, has to be incorporated into one of the fragments prior to the union of two. The disaccharide unit, in the form of a reactive thioglycoside, will be ready for attachment after deprotection of the benzyl group at C5 of the aglycone.

Figure 7. Murai's retrosynthetic analysis.
The construction of fragment 4\textsuperscript{11} started from Sharpless epoxidation of diol 7 (91% yield, 98% ee) (Scheme 1). The resulting bisepoxy diol 8 was treated with iodine, triphenylphosphine and imidazole to afford, after reaction with saturated sodium thiosulfate, bisallylic diol 9 in 83% yield. The C\textsubscript{2}-symmetric diol 9 was converted to \(p\)-methoxybenzylidene acetal 10 in 93% yield. Compound 10 was reduced quantitatively to furnish mono-PMB protected diol 11 and oxidized with osmium tetraoxide and NMO to obtain triol 12 as a single product in 75% yield.

The primary hydroxyl of 12 was protected as a TBDPS ether, the less hindered of the two secondary hydroxyls was mesylated and reductively removed with lithium aluminum hydride to provide 13 in a 54% yield. One-carbon chain elongation of 13 was accomplished in a four-step process by virtue of \(S\textsubscript{N}1\) displacement of the primary tosylate with cyanide ion followed by reduction of the cyano group with DIBAL to deliver the aldehyde 14. Aldehyde 14 was oxidized to the carboxylic acid and converted to oxazolidone 15 according to Evans' protocol\textsuperscript{12} in quantitative yield.

Compound 15 was diastereoselectively methylated to furnish 16 in 69% yield. Reductive removal of the chiral auxiliary with lithium aluminum hydride quantitatively provided the desired northern fragment 4.
Reagents: a) (+)-DET, Ti(O-i-Pr)₄, TBHP, MS4A, CH₂Cl₂, -20 °C, 2 days, 91%; b) I₂, Imid., PPh₃, THF, 20 °C, 1.5 h, then satd Na₂S₂O₃ aq., 20 °C, 2 h, 83%; c) p-anisaldehyde, PPTS, PhH, reflux, 3 h, 93%; d) DIBAL, CH₂Cl₂, -20 °C, 3 h, 100%; e) OsO₄, NMO, dioxane-H₂O (3:1), 20 °C, 2 h, 75%; f) TBDPSCI, Imid., DMF, 20 °C, 17 h, 98%; MsCl, Et₃N, CH₂Cl₂, 0 °C, 3 h; LiAlH₄, THF, 20 °C, 30 min (54%); g) TsCl, Et₃N, DMAP, CH₂Cl₂, 0 °C, 17 h, 98%; TBSOTf, 2,6-lutidine, CH₂Cl₂, 0 °C, 40 min; KCN, DMSO, 20 °C, 16 h, 92%; DIBAL, CH₂Cl₂, -78 °C, 3 h; satd. Roschelle salt, 20 °C, 2 h, 96%; h) NaClO₂, NaH₂PO₄, 2-methyl-2-butene, i-BuOH-H₂O (3.75:1), 0 °C, 1 h; PivCl, Et₃N, ether, 0 °C, 1 h, then N-lithio-(4R)-4-isopropyl-2-oxazolidone, THF, -78 °C, 15 min to 0 °C, 30 min, 100%; i) LDA, Mel, THF, -25 °C, 20 h, 69%; j) LiAlH₄, THF, 0 °C, 55 min, 100%.

Scheme 1. Murai’s synthesis of the northern fragment.
Scheme 2. Murai's synthesis of southern fragment.
Synthesis of the southern fragment $S^{13}$ started from $(R)$-$(+)$-glycidol. After TBS protection, the epoxide ring of 17 was opened with the anion of THP-protected propargyl alcohol in the presence of boron trifluoride etherate to provide the coupling product, which was desilylated and then subjected to acetonide protection to furnish propargyl alcohol 18 in 71% yield. Partial hydrogenation of 18 over a Lindlar catalyst and subsequent Sharpless epoxidation using $(−)$-diethyl tartrate yielded $(2R,3S)$-2,3-epoxy alcohol 19 (75%). Treatment of 19 with excess of methyllithium and copper iodide provided the 1,3-diol as a major product (69%) together with the 1,2-diol, which was removed by oxidation with sodium periodate. The 1,3-diol was converted to monobenzyl ether 20 in a three-step procedure which included silylation of the primary alcohol, benzylation of the secondary alcohol followed by desilylation. Swern oxidation of 20 followed by Wittig-Horner-Emmons olefination in the presence of 18-crown-6 afforded $(Z)$-olefin ester as the major stereoisomer in 78% yield. Deprotection of the acetonide group provided diol 21 in 92% yield. After considerable experimentation, intramolecular Michael addition was effectuated with one equivalent of potassium tert-butoxide to furnish the desired 5 together with dimeric by-product 22. Fortunately, dimer 22 could be converted to 5 with potassium tert-butoxide in methanol. The overall yield from 21 amounted to 91%. Noteworthily, the $(Z)$-olefin ester is required for successful installation of the requisite C3 stereocenter (polycavernoside numbering) during Michael cyclization.

The enantiomer of 5 was available via the same chemistry starting from $(S)$-$(−)$-glycidol.
Murai's synthesis of the disaccharide moiety utilized the functionalized thioglycosides of L-fucose and D-xylose 27 and 30, respectively. The synthesis commenced with acquisition of glycoside 23 of L-fucose, which was further converted into a 1:1 diastereomeric mixture of 3,4-benzylidene acetals 24 in a high overall yield (Scheme 3).

Reagents: a) CH$_3$OH, PTSA, reflux, 95%; b) PhCH(OMe)$_2$, PTSA, CH$_2$CN, 95%; c) MeI, t-BuOK, THF, 91%; DIBAL, CH$_2$Cl$_2$, 0°C, 96%; d) MeI, t-BuOK, THF, 93%; e) PhSTMS, TMSOTf, CH$_2$Cl$_2$, 96%; f) TBSOTf, 2,6-lutidine, CH$_2$Cl$_2$, 98%; g)PhSTMS, ZnI$_2$, TBAI, (CH$_2$Cl)$_2$, 60 °C; TBAF, THF, 68%.

Scheme 3. Murai's synthesis of thioglycosides.
The mixture was methylated with methyl iodide and potassium tert-butoxide to furnish, after DIBAL reduction, the 4-benzyl ether 25 in an overall yield of 87%. The hydroxyl at C4 in 25 was further methylated under established conditions to afford 26 in 93% yield. The conversion of methyl acetal 26 to a separable (1.8:1) mixture of phenylthioglycosides 27 was effected with phenylthiotrimethylsilane and trimethylsilyl triflate in 96% yield.

Synthesis of phenylthioglycoside 30 started from the known derivative of D-xylose 28, whose free hydroxyl was protected as a TBS ether in 98% yield using tert-butyldimethylsilyl triflate and 2,6-lutidine. Conversion of the resulting methyl acetal 29 to phenylacetal 30 took place using trimethylsilyl triflate and zinc iodide in refluxing dichloroethane, followed by desilylation with TBAF in a combined yield of 68%. Phenylthioglycoside 30 was obtained as an inseparable 1:1 diastereomeric mixture.

Prior to the union of the two monosaccharides, phenylthioglycoside 27 was converted to glycosyl fluoride 31 (1:1 diastereomeric mixture) by reaction with dimethylaminosulfur trifluoride and NBS in 82% yield (Scheme 4). The coupling between fluoride 31 and thioglycoside 30 was accomplished according to the Nicolaou and Kunz protocol by treatment with boron trifluoride etherate and 4Å molecular sieves in a respectable 86% yield. Product 32 was formed as a separable mixture of α and β-anomers at C1 of xylose in a ratio of 1.7:1, respectively. In both cases, the configuration of the anomeric C1’ of fucose was deduced to be exclusively α.
Scheme 4. Murai’s synthesis and attachment of the disaccharide moiety.

Next, attachment of the disaccharide to the southern fragment of the aglycone moiety was investigated. The primary hydroxyl of tetrahydropyran 5 was quantitatively protected as an acetate by means of acetyl chloride and pyridine in dichloromethane followed by the cleavage of benzyl ether under hydrogenolysis to afford monoprotected diol 33 in 87% yield. Glycosidation of 33 was performed according to Nicolaou’s
procedure by addition of NBS to a cold (-40-45 °C) suspension of 32, 33, and 4 Å molecular sieves in acetonitrile. Desired β-anomer 2 was isolated in 74% yield after chromatography, together with 26% of the α-anomer.

Comparable studies involving the enantiomer of 5 afforded compound 3 (Figure 6). As was described above, compounds 3 and 2 were used as references for the assignment of relative and absolute configuration to polycavernoside A.\textsuperscript{9}

![Scheme 5: Johnston's synthesis of a glycoside acceptor.](image)

\textsuperscript{a) TrCl, Et\textsubscript{3}N, (DMAP), DMF; BnBr, NaH, TBAI, DMF; (TsOH), MeOH, Et\textsubscript{2}O, H\textsubscript{2}O, 81%; \textsuperscript{b) 50% aq AcOH, 100 °C; Ac\textsubscript{2}O, Pyr, 85%; H\textsubscript{2}, Pd-C, EtOAc, 97%; \textsuperscript{c) PhSSiMe\textsubscript{3}, SnCl\textsubscript{4}, C\textsubscript{6}H\textsubscript{6}, 60%.}
An alternative synthesis of the disaccharide in the activated thioglycoside form was accomplished by Johnston.\textsuperscript{6,17} The acceptor glycoside 37 was approached from two directions (Scheme 5). Commercially available 1,2-isopropylidene-\(\alpha\)-D-xylofuranose (34) was transformed into 35 in an effective sequence involving tritylation of the primary alcohol, \(O\)-benzylation, and detritylation in an 81% overall yield. Hydrolysis of acetonide 35 occurred upon warming in 50% aqueous acetic acid, making possible equilibration to the pyranose form followed by exhaustive acetylation of the free hydroxyls (acetic anhydride in pyridine, 85% yield for two steps). Hydrogenolysis uneventfully resulted in cleavage of the benzyl ether to furnish 36 in 97% yield.

An alternative route to 36 took advantage of the selectivity of controlled acetylation of \(D\)-xylose,\textsuperscript{18} but the transformation suffered from a low yield (22%).

Treatment of 36 with phenylthiotrimethylsilane and tin tetrachloride in dry benzene afforded phenylthioglycoside 37 in 60% yield.

Synthesis of the donor glycoside started from peracetylation of \(L\)-fucose followed by treatment of the product with thiophenol and tin tetrachloride (Scheme 6). Subsequent saponification of the acetate protecting groups resulted in the formation of thioglycoside 38 in 91% overall yield. Generation of the 3,4-acetonide, \(O\)-methylation of the C2 carbinol, and hydrolytic removal of the protecting group furnished diol 39 in an 83% combined yield. Selective protection of the C3 hydroxyl was accomplished by taking advantage of the high propensity exhibited by \(O\)-stannylene acetals to undergo equatorial
methylation. Thus, sequential treatment of 39 with di-n-butylin oxide and a combination of methyl iodide with cesium fluoride afforded 40 in nearly quantitative yield. Protection of the axial alcohol as a TBDPS ether gave the fully protected thioglycoside (77%), which was transformed into fluoride 41 with diethylamino-sulfur trifluoride and NBS in 88% yield.

The coupling of 41 and 37 proceeded under Mukaiyama’s conditions (tin dichloride, silver perchlorate) to provide the desired disaccharide 42 (Scheme 6) as the only detectable anomer in 57% yield. The conversion of 42 into 43 was carried out by saponification of the acetate groups followed by O-methylation in 84% combined yield.

With the two highly efficient routes to the sugar part of polycavernoside A published in the literature, we concentrated our efforts on the development of an original synthetic approach to the macrocyclic aglycone of this challenging molecule, as described in the subsequent section.
CHAPTER 2

STUDIES TOWARD THE SYNTHESIS OF POLYCAVERNOSIDE A

2.1 ATTEMPTED DITHIANE TO LACTONE COUPLING

2.1.1 Retrosynthetic Analysis

Although the structural similarity between polycavernoside A and macrolide antibiotics has been pointed out in the previous section, the presence of an α-dicarbonyl functional group (C9-C10) and appended polyene chain make this algal metabolite unique and challenging for synthesis. Our intention was to start with the synthesis of the aglycone of polycavernoside A (44) and to introduce the sugar component at a late stage of the synthesis.

The first retrosynthetic disconnection of the ester bond would provide seco acid 45 as the first acyclic precursor. In light of the number of macrolactonization techniques that became available in the course of studies involving macrolide antibiotics, this approach is likely to be rewarding. Seco acid 45 should be available from the advanced intermediate 46 as follows: the masked alcohol at C15 will be transformed into the derived aldehyde followed by the addition of polyene unit 47 in Grignard fashion; the
acetic acid side chain (C1-C2) will be introduced onto the six-membered lactol by means of the Wittig reaction. \(^{23}\)

![Chemical structures and retrosynthetic analysis](image)

**Figure 8.** Retrosynthetic analysis with dithiane to lactone coupling as the key step.
A wise choice of protecting groups is crucial for the success of any but the most trivial synthesis. In consideration of chemical compatibility of the triene side chain to protic and Lewis acids, as well as catalytic hydrogenation conditions (i.e., competing double bond reduction), a protecting group removable under mild oxidative conditions was chosen. It is well precedented that a substituted methoxybenzyl group can be selectively removed by oxidative cleavage with dichlorodicyanobenzoquinone (DDQ) or cerium (IV) ammonium nitrate (CAN).24

![Diagram of chemical reactions]

**Figure 9.** Literature examples of dithiane condensations resulting in α-keto thioacetals.
The reactivities of various substituted benzyl ethers and alcohols toward DDQ and CAN have also been reported. With this information in mind, we chose the p-methoxybenzyl (PMB) group to protect both C5 and C13 hydroxyls, with the intent of cleaving both groups in a single step after the macrolactonization.

Intermediate 46 was envisioned as a coupling product between lithiated dithiane 48 and lactone 49. The anticipated feasibility of this reaction was based on several literature reports describing direct production of α-keto thioacetals such as 50 and 51 by condensation of lithio dithiane with lactones and esters.

2.1.2 Synthesis of Dithiane Fragment 48

Construction of fragment 48 was envisioned via lactone 57, which contained three out of four of the requisite stereocenters. Acquisition of lactone 57 started from bisesterification of commercial L-malic acid in methanol with catalysis by hydrogen chloride as generated by the addition of acetyl chloride. In our hands, partial hydrolysis of the bis-ester proved inevitable during evaporation of solvent in vacuo, and repeated treatment of the product with a premixture of methanol and acetyl chloride was required for better yields. The bis-ester of L-malic acid was sequentially treated with the borane-methyl sulfide complex and catalytic sodium borohydride to afford diol 52 in 76% yield. The free hydroxyl group served as a handle to direct the reduction to the neighboring ester group selectively.
Scheme 7. Synthesis of lactone 57.

Conditions: a) 25 °C, 8 h, repeat; b) BH$_3$Me$_2$S, THF, 25 °C, 1 h; then (NaBH$_4$), 25 °C to 40 °C, 1.5 h; MeOH; c) Imid., DMF, 0 °C, 1 h; 25 °C, 8 h; d) CH$_3$COO-t-Bu, 4 eq; LDA, 4 eq; THF, -70 °C to -5 °C, 1 h; e) AcOH, CH$_3$CN, 0 °C, 24 h; sat NaK-tartrate aq; f) CH$_2$Cl$_2$, 25 °C, add TFA in 3 portions over 24 h; g) THF:HMPA=5.4:1, -78 °C to -40 °C, 3 h.
A short initiation period was typical after the addition of sodium borohydride, after which an exothermic reaction took place. Careful control of the reaction temperature (not to exceed 40 °C) was required to avoid a dangerous build-up of pressure. The primary hydroxyl of labile 52 was selectively protected as a TBDPS ether to furnish ester 53 (85%) which was subjected to Claisen condensation with the lithium enolate of i-butyl acetate to produce β-keto ester 54 in 77% yield. The reaction was successful as long as an excess (4 eq) of the reagent was used to account for deprotonation of the free hydroxyl in 53. Stereoselective reduction of ketone 54 occurred on treatment with the premixed tetrabutylammonium borohydride\(^\text{30}\) and acetic acid in acetonitrile at 0 °C over 24 hours to afford diol 55 in 88% yield. Lactonization of 55 was effected using trifluoroacetic acid in dichloromethane. The best yields (85%) were realized when the acid was added to a solution of 55 in three portions over a period of 24 hours. In our hands, this procedure was advantageous over the saponification/lactonization originally proposed in the literature.\(^\text{26}\) The resulting lactone 56 was stereoselectively methylated using an excess of LDA and methyl iodide in a mixture of THF and HMPA (5.4:1) as the solvent to furnish the desired 57 in 78% yield. It is noteworthy that O-methylation of the free secondary hydroxyl was not a problem due to the sterically hindered environment around it.

Apparently, this steric hindrance precluded the free hydroxyl of 57 from undergoing base-promoted O-alkylation with p-methoxybenzyl chloride under the usual conditions (sodium hydride, DMF\(^\text{31}\)), even in the presence of tetrabutylammonium
iodide. Application of \( p \)-methoxybenzyltrichloroacetimidate\(^{32} \) with triflic acid as a catalyst was more rewarding, providing the desired \( p \)-methoxybenzyl ether \( 58 \) in 77\% yield (Scheme 8). A mixture of ether and dichloromethane (6:1) was the solvent of choice, with the latter component added to enhance the solubility of lactone \( 57 \).

Arrival at cyclic acetal \( 59 \) became possible via a two-step procedure that included chemoselective reduction of lactone \( 58 \) with diisobutylaluminum hydride to the lactol\(^{33} \) and subsequent methylation. Conveniently, when the latter procedure was performed with silver oxide and methyl iodide at the reflux temperature,\(^{34} \) only \( \beta \)-anomer \( 59 \) was isolated. This outcome, opposite to the expectations based on the anomeric effect, is explainable in terms of kinetic control of the reaction. Attempts to convert the intermediate lactol into acetal \( 59 \) in acidic methanol resulted in no detectable reaction at room temperature. Warming of such solutions led to decomposition.

At this point, construction of the target \( 48 \) was envisioned via cleavage of the TBDPS ether and transformation of the liberated hydroxyl into a suitable leaving group, followed by displacement with lithio 1,3-dithiane. The first reaction of the sequence occurred without event on treatment of \( 59 \) with tetrabutylammonium fluoride in THF. Direct conversion of the resulting alcohol \( 60 \) into a bromide or iodide using triphenylphosphine-carbon tetrabromide or iodine, respectively, resulted in the significant formation of by-products. Improved yields and selectivity were realized by the two-step route involving intermediate mesylate \( 61 \), which was obtained in nearly quantitative yield from the alcohol \( 60 \). Displacement of the mesylate by iodide ion in \( S_N2 \) fashion cleanly delivered the desired \( 62 \).
Conditions: a) Et₂O:CH₂Cl₂ = 6:1, 0.3 mol% TfOH, then PMBO-C(NH)CCl₃, 24 h; b) Dibal, CH₂Cl₂, -78 °C, 5 min; Ag₂O, CH₃I, reflux, 6 h; c) THF, 25 °C, 8 h; d) CH₂Cl₂, -10 °C to 25 °C, 1 h; e) C₆H₆, reflux, 40 h; f) THF:Hexanes = 2:1, -78 °C, 10 min.

Scheme 8. Completion of the synthesis of dithiane 48.
The displacement of iodide 62 with lithio 1,3-dithiane was not a trivial task. The reaction was sluggish in cold (-78 °C) THF solution and resulted in the decomposition of reagents on warming. Addition of 10-20% HMPA to the reaction medium led only to a marginal improvement of the yield. Fortunately, application of Schlosser's base boosted the yield of 48 to an acceptable 72%. Apparently, the presence of potassium ions in the system results in potassium-lithium exchange, dramatically increasing the nucleophilicity of the 1,3-dithianyl anion. Alternative explanations may include alteration in the lithium coordination phenomena or in the aggregation state of the reagent in solution.

As was expected in the light of literature data, comparable studies on mesylate 61 were not productive.

2.1.3 Synthesis of Lactone Fragment 49

Epoxy alcohol 66, in turn available in several steps from D-pantolactone, was chosen as the precursor for fragment 49. The synthesis of 66 started from the tosylation of the secondary carbinol of D-pantolactone, which proceeded nearly quantitatively using tosyl chloride in pyridine (Scheme 9). Reduction of the resulting 63 with diisobutylaluminum hydride in THF at 0 °C provided monotosylated triol 64, which was treated with potassium carbonate in methanol to furnish epoxy alcohol 65, in 70% overall yield after short-path distillation.
Conditions: a) Pyr, 25°C, 8 h; b) 3 eq DIBAL, THF, 0°C, 0.5 h; sat NaK-tartrate aq; c) MeOH, 25°C, 1.5 h; d) Imid., CH₂Cl₂, 25°C, 2.5 h.


The primary carbinol of 65 was protected as a TBDPS ether using TBDPSCI in dichloromethane with imidazole as a base to afford epoxide 66 in 95% yield.

The structural features of intermediate 66 are set in particular to enhance the regioselectivity of nucleophilic ring opening of the epoxide. Copper (I) iodide-catalyzed reaction with allylmagnesium bromide in ether furnished alcohol 67 in 61% yield.
(Scheme 10). This somewhat disappointing yield can be attributed to the steric blockade of the \( \alpha \)-face of the epoxide by the bulky protecting group.

![Scheme 10](image)

**Conditions:**

- a) 3 eq allylmagnesium bromide, 0.5 eq Cul, \( \text{Et}_2\text{O}, -78^\circ \text{C} \) to \( 25^\circ \text{C} \);
- b) DMF, Imid., \( 25^\circ \text{C}, 1 \text{ h} \)

**Scheme 10.** Studies on the epoxide ring opening.

An alternative route to alcohol 67 included ring-opening reaction of the less hindered epoxy alcohol 65. An excess of allylmagnesium bromide was required to account for deprotonation of the unprotected hydroxyl in 65. The resulting diol 68 was
selectively monoproected as a TBDPS ether (TBDPSCI, imidazole, DMF) to furnish 67 in a combined yield of 72%.

Scheme 11. Synthesis of lactone 70.

The double bond of intermediate 67 was oxidatively cleaved using N-methylmorpholine-N-oxide and catalytic osmium tetroxide in a mixture of THF and water (3:1) followed by the addition of sodium periodate to furnish lactol 69 in 83%
yield (Scheme 11). Despite an indication in the literature that catalytic osmylation-cleavage can be effected by sodium periodate alone,\textsuperscript{39} the reaction was sluggish in the absence of $N$-methylmorpholine-$N$-oxide. Lactol 69 was converted into lactone 70 by oxidation with pyridinium chlorochromate in 77% unoptimized yield.

\begin{center}
\begin{tikzpicture}
    \node at (0,0) [draw] {66};
    \node at (4,0) [draw] {70};
    \draw [->] (0.5,0) -- node [above] {CH$_2$OTBDPS} (4.5,0);
    \draw [->] (0.5,0) -- node [right] {72\%} (4.5,0);
    \node at (0.5,0.5) [draw] {a) $\mathcal{O}$Li $\mathcal{O}$Li, DME, reflux, 8 h; 4N HCl aq, 8 h.};
\end{tikzpicture}
\end{center}

**Scheme 12.** Alternative synthesis of lactone 70.

A more straightforward synthesis of lactone 70 from epoxide 66 was effected by reaction with dilithioacetate\textsuperscript{40} in refluxing dimethoxyethane as solvent. An acidic work-up of the reaction mixture triggered lactonization, and the desired lactone 70 was isolated in 72% yield. This somewhat harsh reaction conditions were compatible with the TBDPS
group, but not with a less robust TBS equivalent. Dimethoxyethane is the solvent of choice for this transformation. Considerable decomposition was encountered when THF was utilized and only 40% of 70 was isolated, while no reaction was observed in ether and the starting epoxide 66 was recovered unchanged.

Scheme 13. Completion of lactone 49.

Attempts to force α-methylation of lactone 70 to completion were accompanied by the formation of unwanted dimethylated product 73. For this reason, monoalkylation
was allowed to proceed to approximately the 80% level of production of 71, followed by recycling of the unconsumed 70 (Scheme 13). Also, application of a more bulky LiHMDS as the base gave preferable results over LDA in this process. The steric bulk of the side chain at C5 ensures a high degree of anti-stereoselectivity for methylation of the lithium enolate of 70. Likewise, protonation of the lithium enolate of 71 with ammonium chloride occurred stereoselectively, resulting in the inversion of $\alpha$-methyl configuration to produce the desired cis-lactone 49.

The relative trans-stereochemistry of lactone 49 was proven by the existence of a 5% NOE between $H_a$ and $H_d$ (Figure 10). In lactone 71, $H_b$ showed the NOE enhancements when either $H_a$ or the methyl group was irradiated. This demonstrated that $H_a$, $H_b$ and the methyl group are all situated on the same face of lactone 71.

Figure 10. NOE experiments on lactones 71 and 49.
2.1.4 Approach to the Enantiomer of Polycavernoside A

At the time when our experimental work started, the absolute stereochemistry of polycavernoside A was not yet known. It was important, therefore, to develop a flexible strategy allowing for the synthesis of both enantiomeric forms of the target structure.

![Diagram of the synthesis process](image)

**Figure 11.** A route to the enantiomeric dithiane fragment.

The enantiomer of the southern dithiane fragment, **ent-48**, should be available by the developed route from the commercially available *D*-malic acid. All synthetic intermediates up to ent-59 were obtained in the predescribed manner from *D*-malic acid.
and exhibited expected values and signs of optical rotation. Final conversion of ent-59 to the dithiane fragment was not attempted.

Instead of repeating the steps described in Scheme 9 merely starting from unnatural L-pantolactone, a more engaging approach to the enantiomer of the northern fragment was undertaken. As one might notice, epoxide ent-66 could be obtained in a single step from monoprotected triol 76, in turn available by reduction of the natural D-pantolactone followed by protecting group manipulation (Figure 12).

\[ \text{Figure 12. Approach to the enantiomer of northern fragment.} \]

In the course of this work it became clear that the inadequate hydrolytic stability of the TBDPS group dwarfed the yields of the sequence. Recourse was therefore made to the more robust PMB group.
The synthesis began with lithium aluminum hydride reduction of D-pantolactone to a 1,2,4-triol, which was subsequently treated with 3-pentanone in the presence of camphorsulfonic acid as catalyst, with azeotropic removal of water. The process favored formation of the dioxolane over the dioxane, as was expected from the literature, providing 77 in 90% yield over two steps (Scheme 14).

D-pantolactone \[ \xrightarrow{\text{a) LAH, b) EtC(O)Et}} \] \[ \xrightarrow{90\%} \]

\[ \xrightarrow{\text{c) PMBCI}} \] \[ \xrightarrow{89\%} \]

77

78

a) THF, reflux, 1 h; Na\(_2\)SO\(_4\)-H\(_2\)O; b) (CSA), C\(_6\)H\(_5\), Dean-Stark, 48 h; c) NaH, DMF, 0 °C to 25°C, 8 h.


The primary hydroxyl was protected as a p-methoxybenzyl ether by PMB chloride in DMF with sodium hydride as a base. An 89% yield was achieved by
conducting the reaction overnight at room temperature, and was not improved by more prolonged reaction times.

![Scheme 15. Deprotection of triol and synthesis of epoxide 74.](image)

Hydrolytic cleavage of the cyclic ketal moiety in 78 was cleanly achieved in a 1:1 mixture of 1 M hydrochloric acid and THF, providing diol 75 in 82% yield (Scheme 15). The reaction was troublesome for the TBDPS analog of 78. Desilylation competed under numerous tested conditions, and diol 75 could not be obtained in a synthetically useful yield. For this reason, the studies involving the TBDPS group were abandoned in favor of PMB.
The conversion of 75 into epoxide 74 was best achieved (74% yield) by the combination of sodium hydride and $N$-p-tosylimidazole in DMF. Other successful conditions included the combination of trimethyl orthoacetate/TMSCl/$K_2$CO$_3$ developed by Sharpless and Kolb.

\[
\begin{align*}
    &\text{74} \\
    \text{a) THF, reflux, 8 h; 1 N HCl; 8 h; b) 3 eq LDA, THF:HMPA=17:1, -78 \, ^\circ\text{C} \text{to} -40 \, ^\circ\text{C}, 1 \, h; 1.1 \text{eq Mel, -78 } ^\circ\text{C} \text{to} -40 \, ^\circ\text{C}, 1 \, h; NH_4\text{Cl, -78 } ^\circ\text{C}.}
\end{align*}
\]

Scheme 16. Elaboration of lactone 80.

Conversion of epoxide 74 into lactone 79 occurred in the same manner as was described earlier for the preparation of lactone 70 by reaction with dilithioacetate (Scheme 16). The presence of a more stable PMB in 79 (as compared to TBDPS in 70)
allowed the attainment of an acceptable 60% yield in refluxing THF without recourse to more expensive dimethoxyethane.

Methylation of lactone 79 and inversion of the newly introduced stereocenter were accomplished by a two-step one-pot procedure (Scheme 16). Lactone 79 was treated with LDA, followed by the addition of iodomethane. The expected anti-methylation product could be enolized by the excess LDA and the enolate so formed quenched with saturated ammonium chloride solution to give the syn-methylated lactone 80. Although the yield for this procedure was lower as compared to that previously described for 49 (48% versus 78%), the operational simplicity favored the method. The relative stereochemistry of 80 was proven by NOE experiments (Figure 13). Positive NOE effects of 3-4% were observed between protons Hₐ, Hₜ, and Hₜ, confirming that all three protons are situated on the same α-face of the five-membered ring. The proton Hc, located on the opposite face on the ring did not exhibit significant NOE effects with protons Hₐ and Hₜ.

![Image](https://example.com/image.png)

**Figure 13.** NOE studies on lactone 80.
In conclusion, the present study clearly indicates that the flexibility of the proposed routes to the southern (48) and northern (49) fragments of the aglycone can allow acquisition of the dithiane and lactone building blocks in both enantiomeric forms.

2.1.5 Studies on the Coupling of Fragments 48 and 49

Attempted coupling of fragments 48 and 49 involved deprotonation of the dithiane with a strong base followed by the addition of the lactone at low temperature. With \( n- \) and \( t- \) butyl lithium in THF, both lactone and dithiane were recovered unchanged after 1.5 h of reaction time at \(-78 \, ^\circ\text{C}\) followed by gradual warm-up to \(-10 \, ^\circ\text{C}\) over 2 h. In an attempt to increase the reactivity of 48, Schlosser’s base was employed in the process.

\[
\begin{align*}
\text{S} & \quad \text{S} \\
\text{O} & \quad \text{OMe}
\end{align*}
\]

\[
\begin{align*}
\text{O} & \quad \text{OPMB}
\end{align*}
\]

Figure 14. Attempted coupling of fragments 48 and 49.
Unfortunately, this only resulted in decomposition with complete consumption of lactone 49. Dithiane 48 was again recovered from the reaction unchanged. Equally without success, HMPA was tested as a solvent additive.

**Scheme 17.** Deprotonation experiment.

In order to confirm that the chosen reaction conditions were adequate for the deprotonation of the dithiane, a deuteration experiment was conducted. It took only a couple of minutes to achieve 85% level of deuterium incorporation (\(^1\)H NMR) with \(n\)-butyllithium as a base in the 5:1 mixture of THF and HMPA.
Since the deprotonation step was feasible, we opted to test if it was the steric hindrance in 48 that precluded the coupling.

Scheme 18. Attempted condensation of 49 with 1,3-dithiane.

Underivatized 1,3-dithiane was tested as a coupling partner with lactone 49 under a variety of conditions. Again, no reaction took place at low temperature, with decomposition of 49 materializing under more forcing conditions. In light of the feasibility of similar reactions described in the literature, this outcome was unexpected and very disappointing.

Finally, we decided to elucidate if the steric hindrance introduced into lactone 49 by the α-methyl branching is responsible for the failure of this reaction. When lactone 70
lacking substituents α- to the carbonyl was added to the solution of lithio 1,3-dithiane in THF at -78 °C followed by a gradual warmup rt, the desired condensation finally occurred. Presumably, dehydration of the originally formed adduct 81 took place during chromatography on silica gel, providing compound 82 in 40% unoptimized yield.

Scheme 19. Condensation of 70 with 1,3-dithiane.

This experiment clearly demonstrates that the α-methyl group present in 49 creates sufficient steric hindrance to preclude the lactone from condensing with the dithiane species.
2.2 ATTEMPTED DITHIANE TO ALDEHYDE COUPLING

2.2.1 Evaluation of the Wittig Reaction for Introduction of the Acetic Acid Side Chain

The failure of the reaction between dithiane and lactone urged us to reconsider the coupling strategy between the southern and northern fragments. Prior to addressing this major problem of the earlier proposed route, we desired to investigate another potential pitfall lurking therein. The synthetic scheme (Figure 8, Figure 15) calls for the transformation of a lactol into a tetrahydropyran with concomitant introduction of an acetic acid side chain.

![Desired transformation of lactol](image)

*Figure 15. Desired transformation of lactol.*
The literature precedence suggested that the desired transformation could be accomplished in one pot using stabilized ylides of phosphorus.\textsuperscript{23} We decided to proceed cautiously and to test the feasibility of this transformation on a simple model. Thus, lactone 58 was reduced (DIBAL, dichloromethane, -78 °C) to lactol 83 and treated with (carbomethoxymethylene)triphenylphosphorane in refluxing acetonitrile.

\begin{center}
\textbf{Scheme 20. Evaluation of Wittig reaction.}
\end{center}
Since the intrinsic basicity of the Wittig reagent was evidently not sufficient to effect the intramolecular oxy-Michael addition to the resulting α,β-unsaturated ester 84, a catalytic amount of potassium tert-butoxide was used. This resulted in the formation of mixtures of the two diastereomers, 85 and 86, in variable yield and proportion depending on the reaction conditions (Scheme 20). The best yield for the reaction (80%) was achieved when the cyclization was conducted in cold (-60 °C) THF solution. Unfortunately, the undesired diastereomer 85 was heavily favored under these conditions.

![Diagram of favored and disfavored structures](image)

**Figure 16.** Analogy between the anomeric effect and ring closure transition states.
This result is in accord with the literature, which describes formation of axially substituted tetrahydropyran rings under kinetic control from compounds structurally similar to 84.\(^{44,45}\) Figure 16 demonstrates the analogy between the anomeric effect\(^{46}\) and the principle of transition state energy stabilization leading to 85. In both cases, the axial positioning of the electronegative substituent proved to be energetically favorable, and preferable formation of 85 is therefore a manifestation of the kinetic stereoelectronic effect. Application of oxymercuration – sodium borohydride reduction\(^{47}\) did not change the stereochemical outcome of the reaction.

Scheme 21. Equilibration of 85 to 86.
Thermodynamic conditions (THF, 25 °C) favored formation of the desired compound 86, but the yield unfortunately dropped to a meager 42% (Scheme 20). Likewise, thermodynamic equilibration of 85 to 86 mediated by a strong base via β-elimination – Michael addition (Scheme 21) resulted in poor yields due to extensive decomposition.

The relative stereochemistry of both 85 and 86 was proven by NOE experiments (Figure 17). Positive NOE values of 4-5% were observed in 85 between H_a and H_d, and between H_a and H_c. No measurable NOE was exhibited between H_a and H_d. These observations are consistent with the axial configuration of the acetic acid side chain. On the other hand, NOE effects of 6 and 7% were observed in 86 between H_a, H_b and H_d, thus unequivocally proving the equatorial configuration of its acetic acid side chain.

![Figure 17. NOE experiments on 85 and 86.](image)
In conclusion, the Wittig methodology for the introduction of the acetic acid side chain produces the undesired axial diastereomer 85 under kinetic control. Attempts to carry out the reaction under thermodynamic conditions or to effect the equilibration of 85 into desired 86 resulted in a dramatic decrease of the yield due to decomposition. It is therefore desirable to introduce the acetic acid side chain stereoselectively at an early stage of the synthesis prior to coupling of the northern and southern fragments.

2.2.2 Retrosynthetic Analysis

The second generation retrosynthetic analysis is meant to take into account the lessons learned above. The major problem of the earlier discussed route (Figure 8) was the lack of reactivity between the coupling partners 48 and 49. Evidently, sterically encumbered lactones are sluggish in the reactions with lithio dithianes. In the newly proposed plan (Figure 18), the connection between the southern and northern parts of the aglycone is to be accomplished via addition of lithio dithiane B to aldehyde A. Application of this more reactive carbonyl component hopefully will circumvent the reactivity problem.

The shortcomings associated with introduction of the acetic acid side chain (C1-C2 unit of polycavernoside A) included poor yields and undesired stereoselectivity (Chapter 2.2.1). For the development of an efficient synthetic route, it is crucial to accomplish problematic steps early in the synthesis.
Figure 18. Second generation retrosynthetic analysis.

For this reason, stereoselective installation of the acetic acid side chain was now planned within fragment A before coupling with the northern portion.

Attachment of the triene side chain is foreseen as before, by making connection between organometallic species C and the C15 aldehyde of fragment B.
2.2.3 Synthesis of Fragment A

Tetrahydropyran 87 was planned to be the first synthetic intermediate for the preparation of the southern fragment A. Acquisition of 87 could be accomplished via the stereoselective installation of a two-carbon unit, the acetic acid side chain, onto compounds 83 or 58 (Figure 19). The exact chemistry for the transformations of this type had been extensively studied in the course of C-glycoside syntheses.48,49

![Diagram showing the installation of the acetic acid side chain](image)

Figure 19. Installation of the acetic acid side chain.

While the requisite group is positioned equatorialy in 87, most of the known C-glycosidation procedures provide axial substitution under kinetic control. This means
that in order to achieve the desired equatorial stereochemistry, one must avoid thermodynamic equilibration under basic conditions, which in this particular case causes decomposition (see section 2.2.1). Fortunately, a protocol developed in the laboratories of Kishi\textsuperscript{50} leads to axial C-glycosidation under kinetic kontrol.

According to the latter procedure, lactone 58 was treated with the lithium enolate of ethyl acetate\textsuperscript{51} in THF at \(-78^\circ\text{C}\) to provide the aldol product 88 in the form of a cyclic hemiketal as a single major anomer. Ionic reduction of 88 with triethylsilane in the presence of a Lewis acid furnished tetrahydropyran 90.

Scheme 22. Application of Kishi's C-glycosidation procedure.
Among several protic and Lewis acids screened (TFA, BF₃·Et₂O, TiCl₄, Ti(Oi-Pr)₄, SnCl₄), the best result was achieved with the tetrachlorides of titanium or tin. Nevertheless, the accompanying loss of the PMB protecting group was unavoidable under all conditions examined. Cleavage of the PMB ether by the combined action of reducing agent and Lewis acid (e.g., NaCNBH₃ and BF₃·Et₂O) is preceded in the literature and can be used for preparative removal of this protecting group.⁵²

We considered it reasonable to investigate whether an analogous transformation of the unprotected hydroxy lactone 57 would be met with success. Accordingly, an excess (5 eq) of lithio ethyl acetate was employed to account for the deprotonation of the free hydroxyl (Scheme 23).

Scheme 23. Reaction of unprotected hydroxy lactone 57.
The expected product 91 (42%) was accompanied by the \(\textit{O}\)-acetylated by-product 92 (26%). Formation of the latter could be explained by partial decomposition of the enolate with generation of ketene, which acetylates the unprotected secondary hydroxyl group.

If this explanation is correct, then application of a more stable \textit{tert}-butyl acetate in place of ethyl acetate could shut off the undesired acetylation. Indeed, under similar conditions the aldol adduct 93 was isolated in 77% yield! Subsequent reduction of 93 by the combination of triethylsilane and tin tetrachloride in acetonitrile as solvent furnished 94 in 57% unoptimized yield (Scheme 24).

![Scheme 24. Application of tert-butyl acetate enolate.](image)

Conditions: a) 5 eq \(\text{CH}_2\text{C(O\text{Li})}t-\text{Bu}\), THF, -78 °C; b) \(\text{CH}_3\text{CN}\), 0 °C, 3 h.
While this experiment clearly demonstrated the applicability of bulky ester enolates to reaction with the unprotected hydroxy lactone 57, tert-butyl ester 94 was of little direct value to the projected synthesis. Because the tert-butyl group resists cleavage with base, it has to be removed under acidic conditions prior to the macro lactonization, which conditions are not compatible with the labile triene side chain of polycavernoside A. A methyl or at least an ethyl group would suit our synthetic plan a lot better.

The lithium enolate of the trimethylsilyl ester of acetic acid is reported to be rather stable at low temperature.\textsuperscript{53,54} We expected that cleavage of the trimethylsilyl group would occur under the reaction conditions to provide carboxylic acid 95, which could be converted in a subsequent step into methyl ester 86 (Scheme 25). Unfortunately, the method failed to provide any desired 95 under a variety of conditions.

\textbf{Scheme 25.} Attempted application of trimethylsilyl ester.
In light of the above studies, it proved somewhat more expeditious to employ preliminary trimethylsilation of the 4-hydroxyl group in 57. The resulting 96 was smoothly converted to 90 in the predescribed manner in an overall yield of 59%. The trimethylsilyl group was spontaneously cleaved during acidic work-up.

Scheme 26. An efficient synthesis of 90.

With compound 90 in hand, the remaining advance to fragment A was straightforward. The secondary hydroxyl of 90 was protected as a PMB ether by means of PMB trichloroacetimidate and catalytic triflic acid, providing 97 in a modest 59%
yield. Desilylation of the primary hydroxyl occurred uneventfully with TBAF in THF. The primary carbinol 98 was oxidized with Dess-Martin periodinane\textsuperscript{55} in dichloromethane to afford aldehyde 99 in 71\% yield. One carbon homologation of 99 was performed in a two-stage process involving Wittig olefination with (methoxymethyl)triphenylphosphorane\textsuperscript{56} followed by hydrolysis of the resulting enol ether in a 1:4 mixture of 1 M HCl and THF.

\begin{center}
\textbf{Scheme 27. Completion of the southern fragment A.}
\end{center}
The resulting aldehyde 100, obtained in 45% overall yield, constitutes the southern fragment A of polycavernoside A.

Scheme 28. Synthesis of methyl ester analog of fragment A.
Methyl ester analog of 100 was synthesized using the very same chemistry, as shown in Scheme 28.

As an alternative,* synthesis of aldehyde 104 was accomplished via alkene 105, available from 103 by Wittig olefination in 66% yield (Scheme 29). Direct conversion of the terminal olefin 105 into the aldehyde was achieved in 61% yield via hydroboration-PCC oxidation according to a known method.57

\[
\begin{align*}
\text{COOMe} & \quad \text{COOMe} & \quad \text{COOMe} \\
\text{H} & \quad \text{b) BH}_3\text{THF} & \quad \text{c) PCC} \\
\text{OPMB} & \quad \text{THF} & \quad 25^\circ\text{C}, 10\text{ min} & \quad \text{CH}_2\text{Cl}_2, \text{reflux} 2\text{ h.}
\end{align*}
\]

**Scheme 29.** Alternative conversion of 103 to 104.

*The method was developed by Dr. L. Barriault. The author is thankful to Dr. Barriault for sharing his experimental data.*
The overall yield for the transformation and the reproducibility of the procedure are comparable to those realized in the previously developed route (Scheme 28).

2.2.4 Synthesis of Fragment B

Fragment B, containing both dithiane and aldehyde functionalities, was expected to be derived from aldehyde 106 in three steps including dithioacetalization, desilylation, and oxidation (Figure 20). Aldehyde 106 was in turn expected to be available from compound 107 or 108 via protection of the secondary carbinol and chemoselective DIBAL reduction of the ester or Weinreb amide.

The ring opening of the previously synthesized lactone 49 would be a logical entry to the linear chain compounds 107 and 108.

Figure 20. A plan for the synthesis of fragment B.
Unfortunately, all attempts to isolate the desired ester 107 from lactone 49 were unsuccessful. Even if traces of the ester were formed, the compound was prone to cyclization back to the starting lactone during workup.

Scheme 30. Ring opening of lactone 49.

The experiment on the synthesis of Weinreb amide 109 was more promising (Scheme 30). Ring opening of lactone 49 was accomplished by a premixture of $N,O$-dimethylhydroxylamine and trimethylaluminum in benzene as solvent in 44%
yield.\textsuperscript{58} Further application of 109 for the synthesis was limited by its instability in both basic and acidic medium. Thus, the protection of the secondary hydroxyl of 109 could not be accomplished in a synthetically useful yield due to decomposition.

Next, our attention was turned to the reduction of lactone 49. Application of lithium aluminum hydride as the reducing agent was studied in a broad temperature range. The desired acyclic diol 110 was obtained at best in 58\% yield. Gradual formation of triol 111 was a manifestation of the insufficient stability of the TBDPS protecting group.

\begin{center}
\begin{align*}
\text{Conditions: } & \quad \text{a) LAH, THF, } 25\, ^\circ\text{C to reflux;} \text{b) LAH, THF, } -78\, ^\circ\text{C to } 25\, ^\circ\text{C} \\
\end{align*}
\end{center}

\textbf{Scheme 31.} LAH reduction of lactone 49.
An attempt to arrest the cleavage of the TBDPS ether by decreasing the reaction temperature resulted in incomplete reduction, with lactol 112 being the major product.

Lactol 112 was obtained in a much better yield (99%) by DIBAL reduction of 49 (Scheme 32). Ring opening of 112 was achieved by Wittig reaction in toluene to furnish the linear chain alkene 113 in 94% yield. Alternatively, dithioacetalization with 1,3-propanedithiol in the presence of titanium tetrachloride provided dithiane 114 in 93% yield.

Scheme 32. Transformation of 49 into linear the chain compounds.

As was shown by Dr. L. Barriault, application of LiBH₄ results in clean formation of 110.
Application of other Lewis acids, such as boron trifluoride etherate or zinc triflate, led to diminished dithioacetalization yields.

Not surprisingly, PMB protection of the hindered secondary hydroxyl groups of 113 and 114 was not a trivial task. Under the basic conditions (NaH and PMBCl in DMF or THF), both starting molecules gave rise to a complex mixture of products, from which the desired 115 and 107 could not be isolated (Scheme 33).

Scheme 33. PMB protection of hindered alcohols 113 and 114.
Evidently, positioning of the oxy-anion in the close proximity to the silyl protecting group (1,3-disposition) induces migration and cleavage of the latter. On the other hand, the behaviour of 113 and 114 toward electrophilic p-methoxytrichloroacetimidate under acidic catalysis was markedly different. The expected protection occurred smoothly in the case of alkene 113, but not with dithiane 114. Evidently, sulfur as the most reactive nucleophilic center in the molecule undergoes alkylation prior to oxygen, precluding the desired course of the reaction.

One could see that PMB protection of the alcohol in 114 presents a logistical problem. The sulfur of the dithiane moiety is more nucleophilic than oxygen under neutral or acidic conditions, diverging the alkylation onto itself. Formation of an oxy-anion by deprotonation of the hydroxyl with a strong base might sufficiently increase the reactivity of the oxygen to compete for the electrophile with sulfur, but those conditions are not compatible with the neighboring TBDPS protecting group.

In light of the above analysis, further functional group manipulations leading to fragment B are outlined in Scheme 34. The TBDPS ether 114 was cleaved with TBAF in THF in high yield (94%). The resulting diol 117 was converted into p-methoxybenzylidene acetal 118 by acid-catalyzed reaction with p-anisaldehyde (azeotropic reflux in benzene) in 89% yield. Reduction of 118 with DIBAL caused the transformation of the p-methoxybenzylidene acetal into p-methoxybenzyl ether with concomitant liberation of the less hindered primary alcohol, as in 119.

---

* The procedure was developed by Dr. L. Barrault.
Finally, the acquisition of fragment B was accomplished by oxidation of the primary hydroxyl of 119 to the aldehyde level. Dess-Martin\textsuperscript{55} and Swern\textsuperscript{63} protocols gave comparable results for this transformation, with the latter preferred due to commercial availability of the reagent.
2.2.5 Synthesis of Fragment C

Our early attempts to synthesize fragment C (Figure 18) took advantage of the readily available aldehyde 120,\(^{64}\) bearing a strong structural resemblance to the desired molecule (Scheme 35). While modifications of the Wittig reaction for the synthesis of vinylic halides from aldehydes predominantly provide undesired cis-stereoisomers,\(^{65}\) the stereochemistry of the Takai reaction\(^{66}\) is preceded to favor the formation of trans-substituted iodoalkenes from nonconjugated aldehydes.

\[
\begin{align*}
\text{OCH}_2\text{CH} &= 120 \\
\text{a) Takai} &\quad \text{40\%} \\
\text{b) Corey-Fuchs} \\
\text{or c) } &\text{Br}^+\text{PPh}_3\text{CH}_2\text{Br/KO}^\text{t-Bu} \\
\text{E:Z} &= 1:1 \\
\text{121} \\
\text{122} \\
\text{Fragment C, M = Sn, Zr, Al}
\end{align*}
\]

Conditions: a) CHI\(_3\), CrCl\(_2\) (8 eq), THF; b) PPh\(_3\), CBr\(_4\), CH\(_2\)Cl\(_2\), 25 °C; LDA, BuLi, THF, -78 °C; c) 2 eq KOt-Bu, THF, -78 °C to 25 °C.

**Scheme 35.** Aldehyde 120 as a precursor for fragment C.
In accordance with the Takai reaction conditions, 120 was treated with a premixture of iodoform and chromium (II) chloride in THF or dioxane (Scheme 35) with strict protection from daylight, with monitoring of the reaction course by GCMS. The analysis revealed that the reaction eventually produced a 1:1 mixture of the two isomers, except for the initial period of reaction time when one of the two isomers dominated. Application of the in situ generated chromium (II) chloride\(^7\) in place of the commercial reagent resulted in a higher overall reaction rate but did not affect the selectivity.

The deterioration of Takai reaction stereoselectivity in the case of monoconjugated aldehydes has been noted before.\(^6\) Evidently, the effect of the twofold conjugation as in 120 on the reaction selectivity is even more deleterious.

Next, we attempted to obtain alkyne 122 as a potential precursor of fragment C. Hydrometallation of 122 (viz., hydrostannylation,\(^6\) hydroalumination,\(^6\) or hydrozirconation\(^7\)) would provide a straightforward entry to the desired triene C.

Conditions for the conversion of aldehydes into terminal alkynes were developed by Corey and Fuchs\(^7\) and since then have been widely used in synthesis.\(^7\)

Unfortunately, compound 122 could not be isolated from the reaction mixture after numerous attempts including addition of LDA into the reaction mixture in order to suppress undesired carbene formation.\(^7\)

The alternative method involving the synthesis of a terminal vinylic bromide by Wittig chemistry and subsequent dehydrohalogenation to form the triple bond\(^7\) also proved disappointing.
The phosphorane derived from propargylic phosphonium salt 123 is known to favor trans-selective Wittig reaction with conjugated aldehydes.\textsuperscript{74} Accordingly, a silicon-substituted dienyne 125 was smoothly obtained in 93\% yield and 5:1 stereoselectivity from aldehyde 124 (Scheme 36). Attempted desilylation failed to provide 122 under the standard conditions\textsuperscript{74a} resulting in complete decomposition of the starting material.
When dienyne 122 proved to be elusive, our attention turned to the synthesis of the equivalent of fragment C having a preinstalled terminal tributystannyl group. Previously described aldehyde 127\textsuperscript{75} was chosen as the starting material and was obtained as follows (Scheme 37). Propargyl alcohol was treated with tributyltin hydride in benzene at the reflux temperature with AIBN as the radical initiator. Alcohol 126\textsuperscript{76} obtained in 65% yield was the major regio- and stereoisomer and could be readily separated from the by-products by flash chromatography. Application of Pd(0)-catalyzed hydrostannylation\textsuperscript{77} instead of the radical process failed to improve the regioselectivity or yield of the reaction.

\[
\begin{align*}
\text{propargyl alcohol} & \overset{	ext{a) HSnBu3, (AIBN)}}{\longrightarrow} \text{Bu3Sn-propargyl alcohol} \quad \text{65\%} \\
& \overset{\text{b) Swern}}{\longrightarrow} \text{Bu3Sn-aldehyde} \quad \text{93\%}
\end{align*}
\]

Conditions: a) C\textsubscript{6}H\textsubscript{6}, reflux; chromatography; b) (COCl)\textsubscript{2}, DMSO, CH\textsubscript{2}Cl\textsubscript{2}, -78 °C, 15 min; Et\textsubscript{3}N, -78 °C to -30 °C, 1 h.

**Scheme 37.** Synthesis of aldehyde 127.
Oxidation of the allylic alcohol 126 into aldehyde 127 was studied under a variety of conditions, including treatment with active MnO₂, sulfur trioxide-pyridine with triethylamine complex in DMSO, and the classical Swern conditions. The latter method proved to be the most suitable, providing 127 in 93% yield.

Chain extension with the phosphorane derived from 128 under modified Wittig conditions known to favor formation of E-alkenes (potassium tert-butoxide, 18-crown-6) failed to proceed stereoselectively (Scheme 38). Attempts to photoisomerize the undesired Z-stereoisomer of 130 using a sunlamp led to decomposition.

Scheme 38. The chain extension of 127.
Application of phosphonate 129 in place of Wittig phosphorane did not yield any of the desired product. Lack of the reactivity of 129 was linked to insufficient stabilization of the reagent by the isolated double bond. We reasoned that application of a more stabilized dienyl phosphonate such as 133 (Scheme 39) would improve the chances for success of the reaction.

Scheme 39. Completion of fragment C.
The synthesis commenced with the transformation of 127 into the dienyl ester 131 under Wadsworth-Emmons conditions.\textsuperscript{84} As has been established by other workers in a closely related context,\textsuperscript{85} chemoselective reduction of the ester functionality and transformation of the resulting allylic alcohol into the rather labile bromide with carbon tetrabromide and triphenylphosphine\textsuperscript{86} was immediately followed by a Michaelis-Becker reaction.\textsuperscript{87} Formation of the halide and its ensuing treatment with the sodium salt of dimethyl phosphite in THF proceeded in 43% overall yield. Deprotonation of 133 (\textit{n}-BuLi, THF, \textdegree C) and condensation with isobutyraldehyde uneventfully provided the desired fragment C in the form of stannane 134 in 62% yield. The all-trans geometry of the product was assigned on the strength of extensive precedent.

Thus, the tributylstannyl equivalent of fragment C was obtained in 7 steps from commercially available starting materials.

2.2.6 Attempts to Achieve the Union of Fragments

With fragment C (134) in hand, its practical coupling to aldehyde B was scrutinized. Transmetallation of 134 with \textit{n}-butyllithium\textsuperscript{88} in THF at \textdegree C to \textdegree C proved to be uncomplicated. Subsequent introduction of aldehyde B into the reaction mixture resulted in clean formation of adduct 135 (83% yield, Scheme 40). Although the efficiency of this C-C carbon bond formation was considered acceptable, the 2:1 diastereoselectivity was not. Apparently, the \textit{p}-methoxybenzyl group located at \textit{\textbeta}-position to the carbonyl did not provide sufficient chelation control.
Addition of magnesium dibromide to the reaction mixture had little or no effect on the distribution of the diastereomers. These experiments were conducted on the model aldehyde 136, (Figure 21).

While a number of chiral ligands have been shown to induce stereoselectivity in Grignard-type additions to aldehydes, little success has been reported for vinylic organometallics.
A short model study conducted with titanium-TADDOLate\(^9\) (Figure 21) did not show much promise either.

![Chemical structure](image)

**Figure 21.** Attempts to induce diastereoselectivity.

An alternative strategy for the acquisition of the desired \((R)\)-135 might involve chromatographic separation of the diastereomers followed by inversion at the chiral center in question. The inversion would be achieved either by a one-step Mitsunobu
protocol,\textsuperscript{91} or by the conversion of alcohol (S)-135 into the intermediate ketone 137 followed by chiral reduction.\textsuperscript{92}

\textbf{Figure 22.} Proposed inversion of the alcohol stereocenter.
This plan, however, was thwarted by the unfavorable chromatographic behavior of 135. After significant experimentation with solvent systems, a partial separation of the diastereomers was attained by MPLC using 10:1:14 dichloromethane-acetone-hexanes as the eluent. Unfortunately, significant decomposition of the material on the column was unavoidable. A possible mechanism for the decomposition could involve dehydration of the alcohol on the intrinsically acidic silica gel (Figure 22). Attempts to buffer the column with 1-2% of triethylamine resulted in the loss of separation power.

Even more disappointing were experiments on the coupling of fragment A to the nucleophiles (Figure 23).

**Figure 23.** Attempted coupling of fragment A to nucleophiles.
The ester aldehyde fragment A proved to be extremely sensitive to basic reagents such as dithianes. Protected cyanohydrins are known to be much milder acyl anion equivalents than dithianes. Unfortunately, the reaction with model cyanohydrin 139 also resulted in complete decomposition of fragment A.

The instability of fragment A may be explained by the fact that it is set to undergo β-elimination from both the ester and aldehyde carbonyl groups (Figure 24):

![Figure 24. A possible reason for the instability of fragment A.](image)

* Experiments were conducted in close collaboration with Dr. L. Barrault.
These unsatisfactory coupling experiments prompted us to reconsider the dithiane approach to polycavernoside A. The newly proposed route is discussed in the next chapter.
2.3 SULFONE STRATEGY FOR SUBUNIT ASSEMBLY

2.3.1 Retrosynthetic Analysis

As was discussed above, the primary reasons for the failure of the previous route included the following:

a) Excessive basicity of the lithiated dithiane coupling partner;

b) Instability of the aldehyde fragment due to β-elimination;

c) Lack of the diastereoselectivity associated with introduction of the triene side chain;

d) Lability of the triene on silica gel.

After a survey of available equivalents of acyl anions, our choice fell on phenyl sulfones. Methyl phenyl sulfone was intended to serve as a bridge for the union of the southern fragment 143 with the northern fragment 142 (Figure 25). The stereochemistry of the oxygen atom bonded to C15 was to be preset as in 142 by Sharpless asymmetric dihydroxylation of its appropriate olefinic precursor. An allyl side chain was chosen as a surrogate for the acetic acid side chain C1-C2 in order to avoid potential β-elimination under basic conditions. Liberation of the carboxylic acid functionality was to be attained by a two-step procedure involving osmylation-cleavage of the double bond to an aldehyde followed by oxidation of the aldehyde.

Notably, introduction of the triene side chain is to be postponed to a late stage of the synthesis and shall be accomplished by means of Wittig or Julia olefination of
aldehyde 140. Application of the one-pot Julia olefination protocol developed by Kocienski is especially enticing in this context.

As far as the particular order for the union of fragments 143 and 142 with methyl phenyl sulfone is concerned, two routes can be envisioned. In Route 1 (Figure 26),

Figure 25. Sulfone-based synthetic plan.
methyl phenyl sulfone is first combined with fragment 142 to yield β-keto sulfone 144, whose anion could be alkylated with 143. Alternatively, 143 could be first converted into sulfone 145, which could be deprotonated and subsequently added to aldehyde 142 (Route 2, Figure 26).

![Figure 26. Two strategies for the union of fragments.](image)

An evaluation of these two possible routes is presented in the next chapter.
2.3.2 Synthesis of the Southern Fragment and Evaluation of the Coupling Strategies

Both synthetic avenues depicted on Figure 26 require iodide 143 as the starting material. Acquisition of 143 commenced with the transformation of lactone 57 to allyl-substituted tetrahydropyran 148. Preparation of 148 was studied using both unprotected hydroxy lactone 57 and TMS-protected 96. Reaction of both compounds with allylmagnesium bromide in THF at low temperature (-78 °C) provided cyclic hemiketals 146 and 147, respectively, both of which proved difficult to characterize due to a lack of chemical stability.

Conditions: a) THF, -78 °C; b) CH₂Cl₂, -78 °C -> -20°C.

Scheme 41. Synthesis of 148.
Ionic reduction of hemiketals 146 and 147 was accomplished with an excess of triethylsilane in combination with 1 eq of tin tetrachloride in dichloromethane. The reactions were initiated at \(-78^\circ C\) with subsequent gradual warming to \(-20^\circ C\), and were accompanied by the formation of a white precipitate. Higher temperatures or longer reaction times resulted in a decrease in the yield of 148. Cleavage of the TMS ether in the case of 147 occurred spontaneously during the aqueous work-up.

Overall, when unprotected 57 was used as the starting material for the sequence, the process offered operational simplicity and slightly higher yields (71% vs. 65%). The downside was the necessity of an excess of Grignard reagent to allow for deprotonation of the free hydroxyl.

Scheme 42. Synthesis of alcohol 150.
The secondary hydroxyl of 148 was protected as a benzyl ether using benzyl bromide\(^7\) in the presence of an iodide ion source, with sodium hydride as a base (Scheme 42). The reaction was completed by TLC during 20 min in refluxing THF to furnish 149 in 87% yield after chromatography. The use of DMF as solvent resulted in diminished yields of 149 due to partial decomposition. Cleavage of the TBDPS ether in 149 was performed uneventfully with TBAF in THF to reveal the primary hydroxyl of 150 in 98% yield.

Conversion of alcohol 150 into iodide 143 was achieved in 94% yield by a combination of triphenylphosphine, imidazole, and iodine\(^8\) in benzene. Albeit that the literature recommends acetonitrile as solvent, its application resulted in lower yields.

\[
\begin{align*}
\text{OH} & \quad \text{a)} \quad \text{PPh}_3, \text{Imidazole}, \text{I}_2, \\
\text{150} & \quad \text{94\%} \\
\text{143} & \\
\text{Conditions: a)} \quad \text{benzene, 10 °C, 10 min, 25 °C, 1.5 h.}
\end{align*}
\]

Scheme 43. Synthesis of iodide 143.
Next, the prospects for Route 1 in Figure 26 were investigated. The literature suggests that β-keto sulfones of type 144 or 151 are best alkylated with iodides in polar aprotic solvents. Accordingly, 151* was deprotonated with sodium hydride in DMF or DMSO and treated with iodide 143 in the same solvent. In a more rigorous approach, a solution of dimethyl sodium was prepared in DMSO, titrated, and then used for the deprotonation of 151. Unfortunately, none of the experiments resulted in formation of the desired coupling product. Keto sulfone 151 typically could be recovered from the reaction mixture unchanged, while iodide 143 slowly decomposed in the basic medium.

![Chemical Structures](image)

**Figure 27.** Attempted coupling of 143 and 151.

* The compound was generously provided by Dr. L. Barriault.
In the light of these experiments, we turned our attention to Route 2, Figure 26. The requisite sulfone 145 first was obtained from alcohol 150 via the triflate\textsuperscript{101} 152. Displacement of the triflate with lithiated methyl phenyl sulfone took place at $-78^\circ\text{C}$ in THF in the presence of 25% HMPA to furnish 145 in 31% yield over two steps. Apparently, the limited stability of triflate 152 impacted negatively on the yield of the process.

![Scheme 44](image)

Conditions: a) 2,6-di-tert-butyl-4-methylpyridine, $\text{CH}_2\text{Cl}_2$, $-40^\circ\text{C}$ to $-15^\circ\text{C}$, 20 min; b) THF:HMPA = 3:1, $-78^\circ\text{C}$, 15 min.

Scheme 44. The early route to sulfone 145.

When iodide 143 was employed under similar conditions (high concentration of HMPA), it rapidly decomposed into a complex mixture, even at $-78^\circ\text{C}$, from which no
desired 145 could be isolated. Application of HMPT ([Me₂N]₃P) instead of HMPA ([Me₂N]₃P=O) as precedented by other researchers¹⁰² required extended reaction times at rt and resulted in generally higher, but less reproducible yields (Scheme 45).

We associated the irreproducibility observed with variable amounts of HMPA present in the HMPT to be the result of air oxidation. With this idea in mind, the HMPA-mediated reaction was repeated, this time with only 1% of the additive introduced into

Scheme 45. Improved synthesis of 145.
the reaction mixture. The achieved reproducibility and yield (69% on 4 g scale) were considered acceptable (Scheme 45).

\[
\begin{align*}
\text{Ph-S} & \quad \text{PMB} \\
\text{OTES} & \quad \text{a) H OTBDPS} \\
\text{OBn} & \quad \text{145} \\
\end{align*}
\]

\[
\begin{align*}
\text{PMB} & \quad \text{OTES} \\
\text{153} & \quad \text{recovered 153, 10%} \\
\text{OBn} & \quad \text{154, 71%} \\
\end{align*}
\]

Conditions: a) n-BuLi, THF, -78 °C, 1 h; 153, 20 min.

Scheme 46. Coupling of 145 and 153.
Coupling of fragment 145 with the northern portion was studied using aldehyde 153* structurally matching the desired 142 except for the stereochemistry of the hydroxyl group.

* Compound 153 and the experimental procedure for the coupling were provided by Dr. L. Barriault.
at C15 (polycavernoside A numbering system). α-Deprotonation of the sulfone was achieved with n-butyllithium in THF, and the addition of aldehyde 153 resulted in the formation of condensation product 154 as a mixture of four diastereomers in 71% yield (Scheme 46). Additionally, 16% of unreacted 145 and 10% of 153 were recovered from the reaction mixture.

Oxidation of the diastereomeric alcohol mixture to the ketone level was smoothly achieved with the Dess-Marin periodinane, thereby lowering the total number of diastereomers to two (Scheme 47). The last experiment conducted in the course of these studies included chemoselective removal of the TES group in the presence of TBDPS functionality. Treatment of 155 with a 0.005 M solution of p-toluenesulfonic acid monohydrate in methanol resulted in liberation of the C15 carbinol, providing 156 in 91% yield.

As was mentioned above, the stereocenter at C15 in 156 is opposite to the one present in polycavernoside A. We expect, however, that by starting from aldehyde 142 and repeating the chemistry outlined in Scheme 46 and Scheme 47, diastereomeric epi-156 would be available. Conversion of the olefin epi-156 to secoacid 157 will be accomplished by osmylation-cleavage of the double bond and oxidation of the intermediate aldehyde with sodium chlorite. Oxidative removal of the sulfone is widely preceded in the literature and will be undertaken after the macrolactonization.
Figure 28. Plan for completion of the polycavernoside A synthesis.

Deprotection of both benzylic groups in 158, attachment of the PMB-protected disaccharide, and conversion of the TBDPS-protected primary hydroxyl into the aldehyde will provide intermediate 159. From this point, introduction of the triene side chain by
olefination and final deprotection of the PMB group can be expected to deliver the desired natural product.
CHAPTER 3

EXPERIMENTAL SECTION

**General Methods.** Melting points are uncorrected. The column chromatographic separations were performed with Woelm silica gel (230-400 mesh). Solvents were reagent grade and in most cases dried prior to use. The purity of all compounds was shown to be >95% by TLC and high field $^1H$ and $^{13}C$ NMR. The high-resolution and fast-atom-bombardment spectra were recorded at The Ohio State University Campus Chemical Instrumentation Center. Elemental analyses were performed at the Scandinavian Microanalytical Laboratory, Herlev, Denmark or at Atlantic Microlab, Inc., Norcross, Georgia, USA.

**Dimethyl (S)-(-)-malate.** A mixture of 13.34 g (85.57 mmol) of (S)-(-)-malic acid, 5.0 mL of acetyl chloride and 200 mL of methanol was magnetically stirred for 8 h. After concentration, the residue was redissolved in a premixture of 200 mL of methanol and 5.0 mL of acetyl chloride and stirred for additional 8 h. Evaporation of solvent and distillation of the residue afforded 11.65 g (85%) of dimethyl (S)-(-)-malate, bp 75 °C/0.3 mm.
Methyl (S)-3,4-dihydroxybutanoate (52). To a solution of 19.93 g (122.9 mmol) of dimethyl (S)-(-)-malate in 250 mL of THF was added 64.5 mL (123 mmol) of a 2 M solution of borane-methylsulfide complex in THF. The mixture was stirred for 1 h before the addition of 244 mg (6.45 mmol) of sodium borohydride. An exothermic reaction started after approx. a 5 min lag time, and the flask was cooled in ice-water to maintain the internal temperature at or below 40 °C. After a period of 1.5 h the reaction mixture was quenched with 100 mL of methanol, followed by evaporation of solvent. The residue was passed through a short column of silica gel (elution with a 5:1 mixture of ethyl acetate and hexanes) to furnish 12.53 g (76%) of 52.

Methyl (S)-4-(tert-butyldiphenylsiloxy)-3-hydroxybutanoate (53). To a solution of 11.52 g (87.90 mmol) of 52 and 11.97 g (175.8 mmol) of imidazole in 70 mL of DMF at 0 °C was added dropwise a solution of 26.58 g (96.7 mmol) of tert-butyldiphenylchlorosilane in 30 mL of DMF. The mixture was stirred for 1 h at 0 °C and overnight at room temperature, then poured into 300 mL of 1:1 ice-water mixture and extracted with ether (3 x 200 mL). The organic phase was washed with brine, dried over MgSO₄, concentrated, and purified by chromatography (silica gel, gradient elution with 5-20% ether in petroleum ether) to afford 27.99 g (85%) of 53.

tert-Butyl (S)-6-(tert-butyldiphenylsiloxy)-5-hydroxy-3-oxobutanoate (54). A solution of LDA prepared by the addition of 133.0 mL (212.8 mmol) of 1.6 M solution of n-butyllithium in hexanes to a mixture of 21.53 g (212.8 mmol) of diisopropylamine in 260 mL of THF was cooled to -70 °C prior to the addition of 21.53 g (212.8 mmol) of diisopropylamine in 260 mL of THF. The mixture was stirred in the cold for 25 min followed
by the addition of 19.81 g (53.20 mmol) of 53 in 50 mL of THF. The mixture was let to warm up gradually to −5 °C over a period of 1 h prior to being quenched with saturated NH₄Cl solution. Extraction with ether, drying over MgSO₄, concentration and purification of the residue by chromatography (silica gel, gradient elution with 20-50% ether in hexanes) provided 18.67 g (77%) of 54 as a colorless oil.

**tert-Butyl (3S,5S)-6-(tert-butyldiphenylsiloxy)-3,5-dihydroxybutanoate (55).** To 5.29 g (59.5 mmol) of tetramethylammonium borohydride was added dropwise 60 mL of acetic acid under ice/water cooling. The mixture was stirred for 15 min at room temperature prior to the addition of 60 mL of acetonitrile and recooling to 0 °C. A mixture of 18.11 g (39.66 mmol) of 54 in 60 mL of acetonitrile was added dropwise. The mixture was stirred for 24 h at 0 °C quenched with saturated sodium potassium tartrate solution, and extracted with ether. The organic phase was washed with 10% NaOH and saturated NaHCO₃ solutions, dried over MgSO₄, and concentrated. Purification of the residue by column chromatography (silica gel, gradient elution with 25-60% ether in hexanes) afforded 16.01 g (88%) of 55 as a colorless oil.

**(4S,6S)-6-[(tert-Butyldiphenylsiloxy)methyl]tetrahydro-4-hydroxy-2H-pyran-2-one (56).** A solution of 1.36 g (2.97 mmol) of 55 in 30 mL of dichloromethane was treated with three 0.3 mL portions of trifluoroacetic acid added in equal intervals over 24 h. The mixture was washed with 1 M NaOH and water, dried over MgSO₄, and concentrated. Purification of the residue by chromatography on silica gel (gradient elution with 60-90% ether in petroleum ether) furnished 970 mg (85%) of lactone 56 as a colorless oil.
(3R,4S,6S)-6-[(tert-Butyldiphenylsiloxy)methyl]tetrahydro-4-hydroxy-3-methyl-2H-pyran-2-one (57). A solution of LDA was prepared by the addition of 3.3 mL (5.28 mmol) of 1.6 M n-butyllithium in hexanes to a mixture of 578 mg (5.71 mmol) of diisopropylamine in THF at -15 °C. The solution of LDA was cooled to -78 °C, followed by the addition of a mixture of 508 mg (1.32 mmol) of lactone 56 in 3.0 mL THF and 1.5 mL of HMPA. The mixture was allowed to warm up to -40 °C over 1.5 h prior to recooling to -78 °C and addition of 2.60 g (18.3 mmol) of iodomethane. After being stirred for 3 h, the reaction mixture was quenched with 20 mL of saturated NH₄Cl solution and 20 mL of water, then extracted with ether. The organic phase was washed with brine, dried over MgSO₄, and concentrated. Purification of the residue by chromatography on silica gel (gradient elution with 50-70% ether in petroleum ether) provided 411 mg (78%) of 57 as an off-white solid, mp 109 °C (lit mp 108-110 °C).

(3R,4S,6S)-6-[(tert-Butyldiphenylsiloxy)methyl]tetrahydro-4-[(p-methoxy benzyl)oxy]-3-methyl-2H-pyran-2-one (58). A solution of 57 (317 mg, 0.80 mmol) in ether (6 mL) and CH₂Cl₂ (1 mL) was treated sequentially with ethereal triflic acid (0.023 mL of 0.1 M in ether, 0.3 mol %) and a solution of p-methoxybenzyl trichloroacetimidate (337 mg, 0.80 mmol) in ether (1 mL) in dropwise fashion via syringe. The reaction mixture was allowed to stir overnight, taken up in ether (50 mL), washed in turn with 1 M NaOH solution, 1 M HCl, water, and brine, dried, and concentrated. Purification of the residue by chromatography on silica gel (elution with 30% ether in hexanes) furnished 58 as a colorless oil (316 mg, 77%); IR (film, cm⁻¹) 1732; ¹H NMR (300 MHz, CDCl₃) δ 7.67-7.60 (m, 4 H), 7.46-7.32 (m, 6 H), 7.28-7.22
(m, 2 H), 6.91-6.85 (m, 2 H), 4.61 (d, J = 11.3 Hz, 1 H), 4.44 (d, J = 11.3 Hz, 1 H), 4.22 (dq, J = 11.4, 4.0 Hz, 1 H), 3.80-3.72 (m, 5 H), 3.46 (td, J = 3.6, 10.1 Hz, 1 H), 2.49 (dq, J = 9.7, 7.0 Hz, 1 H), 2.36 (dt, J = 13.3, 3.6 Hz, 1 H), 1.79 (dt, J = 13.2, 11.4 Hz, 1 H), 1.37 (d, J = 7.0 Hz, 3 H), 1.06 (s, 9 H); 13C NMR (75 MHz, CDCl3) ppm 173.1, 159.4, 135.6 (2 C), 135.5 (2 C), 133.1 (2 C), 132.8, 129.8, 129.7, 129.3 (2 C), 127.8 (4 C), 113.9 (2 C), 76.4, 76.3, 70.8, 65.6, 55.3, 43.4, 31.0, 26.8 (3 C), 19.2, 13.9; MS m/z (M^+-t-Bu) calcd 461.1787, obsd 461.1767; [α]D^20 -38.2 (c 0.39, CHCl3).


tert-Butyldiphenyl[(2S,4S,5R,6R)-tetrahydro-6-methoxy-4-[(p-methoxy benzyl)oxy]-5-methyl-2H-pyran-2-yl]methoxy]silane (59). To a solution of 58 (570 mg, 1.10 mmol) in CH2Cl2 (20 mL) at -78 °C was added diisobutylaluminum hydride in hexanes (1.2 mL of 1 M, 1.2 mmol). The reaction mixture was stirred for 5 min. quenched with saturated sodium potassium tartrate solution (15 mL), and extracted with ether (3 × 5 mL). After drying and evaporation of the organic phase, the residue was eluted through a column of silica gel with 40% ether in hexanes, concentrated, dissolved in methyl iodide (10 mL), treated with silver oxide (509 mg, 2. 20 mmol), and refluxed for 6 h. After dilution with ether (20 mL), the insoluble solids were separated by filtration and the filtrate was evaporated. Purification of the product by chromatography (silica gel, elution with 15% ether in hexanes) provided 365 mg (62%) of 59 as a colorless oil:

IR (film, cm\(^{-1}\)) 1613; 1H NMR (300 MHz, C6D6) δ 7.86-7.82 (m, 4 H), 7.26-7.21 (m, 8 H), 6.83-6.80 (m, 2 H), 4.46 (d, J = 11.6 Hz, 1 H), 4.21 (d, J = 11.6 Hz, 1 H), 3.87 (dd, J
= 5.9, 10.5 Hz, 1 H), 3.80 (d, J = 8.5 Hz, 1 H), 3.70 (dd, J = 4.5, 10.5 Hz, 1 H), 3.39 (s, 3 H), 3.39-3.31 (m, 1 H), 3.31 (s, 3 H), 2.95 (td, J = 11.6, 5.1 Hz, 1 H), 1.82-1.75 (m, 2 H), 1.27 (q, J = 11.6 Hz, 1 H), 1.21 (d, J = 7.0 Hz, 3 H), 1.20 (s, 9 H); 13C NMR (75 MHz, CDCl3) ppm 159.7, 136.09 (2 C), 136.06 (2 C), 134.11, 134.06, 131.4, 130.0 (2 C), 129.3 (2 C) 128.1 (4 C), 114.0 (2 C), 106.3, 79.0, 72.8, 70.1, 67.4, 56.1, 54.8, 43.2, 33.4, 27.1 (3 C), 19.5, 12.9; MS m/z (M+) calcd 534.2801, obsd 534.2751; [α]D20 +13.0 (c 0.95, CHCl3).


(2S,4S,5R,6R)-Tetrahydro-6-methoxy-4-[(p-methoxybenzyl)oxy]-5-methyl-2H-pyran-2-methanol (60). A solution of 59 (309 mg, 0.58 mmol) in THF (20 mL) was treated with a 1.0 M solution of tetra-n-butylammonium fluoride in THF (0.75 mL, 0.75 mmol) and stirred for 8 h. Following solvent evaporation, the product was purified by chromatography on silica gel (elution with 75% ether in hexanes) to provide 166 mg (97%) of 60 as a colorless oil; IR (film, cm⁻¹) 3460 (br), 1613; 1H NMR (300 MHz, C6D6) δ 7.24-7.20 (m, 2 H), 6.84-6.80 (m, 2 H), 4.43 (d, J = 11.5 Hz, 1 H), 4.15 (d, J = 11.5 Hz, 1 H), 3.73 (d, J = 8.5 Hz, 1 H), 3.50 (m, 2 H), 3.32 (s, 3 H), 3.30 (s, 3 H), 3.16-3.08 (m, 1 H), 2.91 (dt, J = 4.7, 10.5 Hz, 1 H), 2.03 (br s, 1 H), 1.83-1.75 (m, 1 H), 1.59 (ddd, J = 1.8, 4.6, 12.4 Hz, 1 H), 1.28 (q, J = 11.6 Hz, 1 H), 1.17 (d, J = 6.5 Hz, 3 H); 13C NMR (75 MHz, C6D6) ppm 159.7, 131.3, 129.3 (2 C), 114.1 (2 C), 106.3, 78.8, 72.6, 70.1, 65.7, 56.2, 54.8, 43.1, 32.8, 12.8; MS m/z (M+) calcd 296.1623, obsd 296.1617; [α]D23 +31.1 (c 0.84, CH2Cl2).
Anal. Calcd for C\textsubscript{16}H\textsubscript{24}O\textsubscript{5}: C, 64.84; H, 8.16. Found: C, 64.62; H, 8.64.

(2S,4S,5R,6R)-Tetrahydro-6-methoxy-4-[(p-methoxybenzyl)oxy]-5-methyl-2H-pyran-2-methanol Methanesulfonate (61). A cold (-10 °C) solution of 60 (22 mg, 0.073 mmol) and triethylamine (0.20 mL) in CH\textsubscript{2}Cl\textsubscript{2} (2.5 mL) was treated with methanesulfonyl chloride (8.5 μL, 0.11 mmol). The reaction mixture was allowed to warm to rt, stirred for 1 h, and concentrated under reduced pressure. The product, purified by chromatography on silica gel (elution with 60% ether in hexanes), was a white solid of mp 98-99 °C (27 mg, 95%); IR (film, cm\textsuperscript{-1}) 1512, 1367, 1339; ¹H NMR (300 MHz, C\textsubscript{6}D\textsubscript{6}) δ 7.31-7.24 (m, 2 H), 6.94-6.85 (m, 2 H), 4.46 (d, J = 11.4 Hz, 1 H), 4.19 (d, J = 6.4 Hz, 1 H), 4.02-3.94 (m, 2 H), 3.67 (d, J = 8.6 Hz, 1 H), 3.38 (s, 3 H), 3.31 (s, 3 H), 3.26-3.12 (m, 1 H), 2.87 (dt, J = 4.6, 10.6 Hz, 1 H), 2.38 (s, 3 H), 1.82-1.68 (m, 2 H), 1.18 (d, J = 6.5 Hz, 3 H), 1.15 (q, J = 11.9 Hz, 1 H); ¹³C NMR (75 MHz, C\textsubscript{6}D\textsubscript{6}) ppm 159.8, 131.1, 129.3 (2 C), 114.1 (2 C), 106.1, 78.2, 71.6, 70.3, 69.7, 56.3, 54.8, 42.9, 37.0, 32.5, 12.6; MS m/z (M⁺) calcd 374.1399, obsd 374.1387; [α\textsubscript{D}]	extsuperscript{22} +24.8 (c 0.93, CH\textsubscript{2}Cl\textsubscript{2}).

Anal. Calcd for C\textsubscript{17}H\textsubscript{26}O\textsubscript{7}S: C, 54.53; H, 7.00. Found: C, 54.37; H, 7.04.

(2R,3R,4S,6S)-Tetrahydro-6-(iodomethyl-2-methoxy-4-[(p-methoxybenzyl)oxy]-3-methyl-2H-pyran (62). A mixture of 61 (90 mg, 0.24 mmol) and tetra-n-butylammonium iodide (622 mg, 1.68 mmol) in benzene (10 mL) was refluxed for 40 h, cooled, diluted with ether (20 mL), washed with water and brine, then dried. After solvent evaporation, the residue was purified by chromatography on silica gel (elution
with 30% ether in hexanes) to provide 93 mg (95%) of 62 as a white solid, mp 58 °C; IR (film, cm⁻¹) 1614; ¹H NMR (300 MHz, C₆D₆) δ 7.22-7.17 (m, 2 H), 6.84-6.78 (m, 2 H), 4.40 (d, J = 11.5 Hz, 1 H), 4.13 (d, J = 11.5 Hz, 1 H), 3.63 (d, J = 8.5 Hz, 1 H), 3.38 (s, 3 H), 3.33 (s, 3 H), 2.97-2.86 (m, 2 H), 2.86-2.73 (m, 2 H), 1.83-1.75 (m, 1 H), 1.75-1.66 (m, 1 H), 1.13 (d, J = 6.5 Hz, 3 H), 1.04-0.93 (m, 1 H); ¹³C NMR (75 MHz, C₆D₆) ppm 159.7, 131.2, 129.3 (2 C), 114.1 (2 C), 106.0, 78.5, 71.5, 70.3, 56.3, 54.8, 42.7, 36.5, 12.6, 8.5; MS m/z (M⁺) calcd 406.0641, obsd 406.0657; [α]D²¹ +37.8 (c 2.52, CH₂Cl₂).

Anal. Calcd for C₁₆H₂₃IO₄: C, 47.30; H, 5.71. Found: C, 47.17; H, 5.67.

(2R,3R,4S,6S)-6-(m-Dithian-2-ylmethyl)tetrahydro-2-methoxy-4-[(p-methoxy benzyl)oxy]-3-methyl-2H-pyran (48). To a slurry of potassium tert-butoxide (38 mg, 0.34 mmol) in hexanes (0.5 mL) cooled to 0 °C was added n-butyllithium in hexanes (0.19 mL of 1.6 M, 0.31 mmol). The mixture was stirred at rt for 1 h, cooled to -78 °C, and treated with a solution of 1,3-dithiane (37 mg, 0.31 mmol) in THF (0.5 mL). After 20 min of stirring at this temperature, a THF solution (0.5 mL) of 62 (25 mg, 0.06 mmol) was introduced and reaction was allowed to proceed for 10 min prior to an aqueous quench (1 mL) and extraction with ether (2 x 3 mL). The organic layers were washed with brine, dried, and evaporated. Chromatography of the residue (silica gel, elution with 30% ether in hexanes) furnished 48 as a colorless oil (18 mg, 72%); IR (film, cm⁻¹) 1614; ¹H NMR (300 MHz, C₆D₆) δ 7.22 (d of m, J = 8.7 Hz, 2 H), 6.82 (dm, J = 8.7 Hz, 2 H), 4.41 (d, J = 11.4 Hz, 1 H), 4.41-4.36 (m, 1 H), 4.13 (d, J = 11.4 Hz, 1 H), 3.80 (d, J = 8.6 Hz, 1 H), 3.62 (tm, J = 8.5 Hz, 1 H), 3.40 (s, 3 H), 3.31 (s, 3 H), 2.89 (dt, J = 4.7,
10.5 Hz, 1 H), 2.48-2.30 (m, 4 H), 2.17 (ddd, J = 4.6, 11.8, 14.1 Hz, 1 H), 1.90 (ddd, J = 3.4, 10.1, 14.1 Hz, 1 H), 1.84-1.80 (m, 1 H), 1.73 (ddd, J = 2.0, 4.7, 12.3 Hz, 1 H), 1.65-1.57 (m, 1 H), 1.50-1.42 (m, 1 H), 1.18 (d, J = 6.5 Hz, 3 H), 1.22-1.09 (m, 1 H); $^{13}$C NMR (75 MHz, C$_6$D$_6$) ppm 159.7, 131.5, 129.4 (2 C), 114.0 (2 C), 106.2, 79.1, 70.2, 67.8, 56.0, 54.8, 44.3, 43.0, 41.9, 37.0, 30.3, 30.0, 26.2, 12.8; MS m/z (M$^+$) calcd 398.1585, obsd 398.1617; $\mu$D$^{20}$ +19.5 (c 1.93, CH$_2$Cl$_2$).

**D-Pantolactone tosylate (63).** To a mixture of 10.00 g (76.84 mmol) of $D$-pantolactone in 50 mL of pyridine was added 15.38 g (80.69 mmol) of tosyl chloride. The mixture was stirred overnight, diluted with 200 mL of ether and washed with 1 M hydrochloric acid until acidic. The organic phase was dried over MgSO$_4$ and concentrated to furnish 21.63 g (99%) of the title compound as a white solid which was used without further purification.

**3S)-2,2-Dimethyl-3,4-oxo-1-butanol (65).** To a mixture of 8.20 g of 63 in 200 mL of THF at 0°C was added 89.4 mL (89.41 mmol) of 1 M solution of DIBAL in hexanes. The mixture was stirred for 0.5 h prior to transfer via cannula to a stirred saturated sodium potassium tartrate solution (200 mL). The mixture was exhaustively extracted with ethyl acetate, dried over MgSO$_4$, and concentrated. The residue was dissolved in 50 mL of methanol and treated 3.98 g (28.84 mmol) of K$_2$CO$_3$ over a period of 1.5 h. After filtration, the residue was diluted with 100 mL of ether, washed with 50 mL of water and brine, dried over MgSO$_4$, concentrated, and passed through a silica gel column using a 1:1 mixture of ether and petroleum ether for elution. Solvent was
evaporated and the residue distilled in a Kugelrohr apparatus to afford 2.33 g (70%) of 65 as a clear liquid.

**tert-Butyl[(S)-3,4-epoxy-2,2-dimethylbutoxy]diphenylsilane (66).** A solution of 65 (229 mg, 1.92 mmol) and imidazole (262 mg, 3.84 mmol) in CH$_2$Cl$_2$ (10 mL) was admixed with a solution of tert-butyldiphenylsilyl chloride (581 mg, 2.11 mmol) in CH$_2$Cl$_2$ (3 mL). After 2.5 h of stirring, the reaction mixture was diluted with ether (50 mL), washed with water (10 mL) and brine (10 mL), dried, and concentrated. Purification of the residue by chromatography on silica gel (elution with 3% ether in hexanes) gave 66 as a colorless oil (647 mg, 95%); IR (film, cm$^{-1}$) 1361, 1111; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.71-7.67 (m, 4 H), 7.48-7.37 (m, 6 H), 3.54 (d, $J$ = 9.7 Hz, 1 H), 3.44 (d, $J$ = 9.7 Hz, 1 H), 2.99 (t, $J$ = 3.5 Hz, 1 H), 2.68 (d, $J$ = 3.5 Hz, 2 H), 1.09 (s, 9 H), 0.92 (s, 3 H), 0.89 (s, 3 H); $^{13}$C NMR (75 MHz, CDCl$_3$) ppm 135.6 (4 C), 133.6, 133.5, 129.6 (2 C), 127.6 (4 C), 70.6, 57.2, 44.0, 36.1, 26.8 (3 C), 20.2, 19.8, 19.4; MS $m/z$ (M$^+$) calcd 354.2015, obsd 354.2030; $[^{22}]$$\alpha$D +9.0 (c 1.30, CHCl$_3$).

**Anal. Calcd for C$_{22}$H$_{30}$O$_2$Si: C, 74.53; H, 8.53. Found: C, 74.27; H, 8.53.**

**(R)-1-(tert-Butyldiphenylsiloxy)-2,2-dimethyl-6-hepten-3-ol (67).**

**A. By Ring Opening of Epoxide 66.** To a suspension of 95 mg (0.50 mmol) of copper (I) iodide in 10 mL of ether at −78 °C was added 2.0 mL (2.0 mmol) of 1 M solution of allylmagnesium bromide in ether. The mixture was stirred for 20 min followed by the addition of 254 mg (1.0 mmol) of 66 in 2 mL of ether. The reaction mixture was allowed to warm to 0 °C over a period of 1 h. After aqueous work-up and
extraction with ether, the combined organic phases were sequentially washed with aqueous ammonium hydroxide solution, water, and brine. Drying, evaporation, and purification of the residue by chromatography (silica gel, elution with 5% ether in petroleum ether) afforded 243 mg (61%) of 67 as a colorless oil; IR (film, cm⁻¹) 3502;¹H NMR (300 MHz, CDCl₃) δ 7.72-7.49 (m, 4H), 7.46-7.38 (m, 6H), 5.96-5.82 (m, 1H), 5.08 (dm, J = 17.0 Hz, 1 H), 4.99 (dm J = 10.2 Hz, 1 H), 3.57 (dd, J = 2.4, 10.2 Hz, 1 H), 3.55 (d, J = 9.9 Hz, 1 H), 3.49 (d, J = 9.9 Hz, 1 H), 2.46-2.36 (m, 1 H), 2.18-2.11 (m, 1 H), 1.61-1.22 (m, 2 H), 1.10 (s, 9 H), 0.91 (s, 3 H), 0.86 (s, 3 H) (one OH not seen); ¹³C NMR (75 MHz, CDCl₃) ppm 139.0, 135.7 (2 C), 135.6 (2 C), 132.8, 132.7, 129.9 (2 C), 129.8 (2 C), 127.8 (2 C), 114.5, 77.8, 73.3, 38.9, 31.0, 30.9, 26.9 (3 C), 22.2, 19.2, 19.11; FAB MS m/z (M+H) calcd 397.26, obsd 397.23; [α]D²⁰ +18.0 (c 1.63, CHCl₃).

Anal. Calcd for C₂₅H₃₆O₂Si: C, 75.70; H, 9.15. Found: C, 75.60; H, 9.10.

B. Alternative Route from 65. To a suspension of 1.64 g (8.6 mmol) of copper (I) iodide in 25 mL of dry ether at -78 °C was added 28.4 mL (25.8 mmol) of 0.9 M solution of allylmagnesium bromide in ether. The reaction mixture was allowed to warm to -20°C and recooled to -78°C prior to the addition of 1.00 g (8.61 mmol) of epoxide 65 in 5 mL of ether. The reaction mixture was allowed to warm to 0°C, quenched with ice water, extracted with ether, dried over MgSO₄, and passed through a silica gel column (elution with 50% ether in petroleum ether) to provide 1.362 g of crude diol 68. A 200 mg (1.26 mmol) portion of the resulting material and 173 mg (2.5 mmol) of imidazole was dissolved in 3 mL of DMF, cooled to 0°C and treated with a solution of 382 mg (1.39 mmol) of TBDPSCl in 1 mL of DMF. The reaction mixture was allowed to warm to
room temperature over a period of 2 h and stirred for an additional 4 h. Aqueous work-
up and column chromatography (silica gel, elution with 5% ether in petroleum ether) 
furnished 270 mg (72%) of 67.

\((5R)-S-[2-(tert-Butyldiphenylsiloxy)-1,1-dimethylethyl]-tetrahydro-3-methyl-
2-furanol\) (69). A mixture of 188 mg (473 mmol) of 67 in 3 mL of THF and 0.5 mL of 
water was treated with 78 mg (0.574 mmol) of NMOH2O and 0.3 mL (0.024 mmol) of a 
0.079 M solution of OsO4 in THF. The stirring was continued for 1.5 h followed by the 
addition of 303 mg (1.42 mmol) of NaI04 and 2 mL of water. After being vigorously 
stirred for 2 h, the reaction mixture was diluted with 20 mL of ether and washed 
sequentially with saturated sodium hydrosulfite solution and brine. The organic phase 
was dried over MgSO4 and concentrated. Purification of the residue by chromatography 
on silica gel (elution with 30% ether in petroleum ether) provided 156 mg (83%) of 69 as 
a colorless oil; IR (film, cm⁻¹) 3409; \(^1\)H NMR (300 MHz, CD2D2) (major anomer) δ 7.88-
7.79 (m, 4 H), 7.30-7.25 (m, 6 H), 4.93 (m, 1 H), 4.26 (dd, \(J = 5.9, 10.3\) Hz, 1 H), 3.69 (d, 
\(J = 9.5\) Hz, 1 H), 3.61 (d, \(J = 9.5\) Hz, 1 H), 3.11 (br s, 1 H), 1.78-1.52 (m, 1 H), 1.28 (m, 
1 H), 1.23 (s, 9 H), 1.15-1.00 (m, 1 H), 1.00-0.87 (2 singlets and a doublet - overlapping 
with minor anomer); \(^13\)C NMR (75 MHz, CD2D6) ppm (136.2, 136.1, 4 C), (134.23, 
134.10, 134.17, 2 C), 129.9 (4 C), 128.2 (2 C), (104.9, 98.8), (84.3, 82.2), (71.0, 70.9), 
(41.4, 39.5), (38.73, 38.66), (34.2, 31.8), 27.2 (3 C), 19.7, (21.3, 20.9), (19.9, 19.8), 
(17.5, 12.9); MS \(m/z\) (M⁺-OH) calcd 395.2406, obsd 395.2438; \([\alpha]_D^{20}\) +1.3 (c 1.38, 
CHCl3).

*Anal.* Calcd for C25H36O3Si: C, 72.77; H, 8.79. Found: C, 72.84; H, 8.83.

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(R)-5-[2-(tert-Butyldiphenylsiloxy)-1,1-dimethylethyl]dihydro-2(3H)-furanone (70). A. By Oxidation of Lactol 69. A mixture of 156 mg (0.391 mmol) of 69 and 3 mL of dichloromethane was treated with 255 mg (1.18 mmol) of PCC over a period of 1 h. The reaction mixture was diluted with 20 mL of ether, the liquid phase was decanted, and the remaining solid was washed with 3 x 10 mL of ether and 10 mL of acetone. The combined organic phases were concentrated to a volume of approx. 5 mL and passed through a pad of silica gel (elution with ether) to furnish after concentration 120 mg (77%) of 69. The analytical sample was prepared by subsequent chromatography on silica gel (elution with 30% ether in petroleum ether) to provide 70 as a colorless oil; IR (film, cm\(^{-1}\)) 1778; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(~7.70-7.63\) (m, 4 H), \(~7.47-7.37\) (m, 6 H), \(~4.61\) (dd, \(\text{J} = 7.1, 8.9\) Hz, 1 H), \(~3.57\) (d, \(\text{J} = 9.9\) Hz, 1 H), \(~3.41\) (d, \(\text{J} = 9.9\) Hz, 1 H), \(~2.59-2.49\) (m, 2 H), \(~2.15-2.00\) (m, 2 H), \(~1.08\) (s, 9 H), \(~0.95\) (s, 3 H), \(~0.91\) (s, 3 H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) ppm 177.2, 135.6 (4 C), 133.3, 133.2, 129.7 (2 C), 127.6 (4 C), 84.1, 69.6, 38.9, 29.3, 26.9 (3 C), 22.7, 19.6, 19.3, 19.2; MS \(\text{m/}Z\) (M\(^+\)-t-Bu) calcd 339.1416, obsd 339.1427; \([\alpha]_{D}^{20}\) -17.8 (c 2.35, CHCl\(_3\)).

B. One Step From Epoxide 66. To a solution of LDA, prepared by the addition of \(n\)-butyllithium (81.2 mL of 1.6 M in hexanes, 130 mmol) to diisopropylamine (14.6 g, 144 mmol) in DME (120 mL) cooled to -20 °C with a subsequent warmup to 0 °C was added acetic acid (3.89 g, 64.9 mmol). The reaction mixture was stirred at rt for 40 min and at 40 °C for 20 min to complete the metalation. This white suspension was treated with 66 (2.60 g, 7.22 mmol) 10 mL of DME, heated to reflux overnight, cooled, and diluted with water. The separated aqueous phase was acidified to pH 3 and extracted
with ether, and the combined organic solutions were washed with 1 M HCl until the washes were acidic. The organic phase was refluxed for 4 h in order to complete the lactonization process, or alternatively left overnight at rt, then evaporated. The residue was chromatographed on silica gel (elution with 30% ether in petroleum ether) to provide 2.05 g (72%) of 70.

*(3S,5R)-5-[2-(tert-Butyldiphenylsiloxy)-1,1-dimethylethyl]dihydro-3-methyl-2(3H)-furanone* (71). A solution of 70 (1.05 g, 2.65 mmol) in cold (-78 °C) THF (10 mL) was treated with lithium hexamethyldisilazide (3.17 mL of 1.0 M in THF, 3.17 mmol), stirred for 1 h at this temperature, quenched with methyl iodide (0.3 mL), and diluted with ether prior to washing with saturated NH₄Cl solution and brine, drying, and solvent evaporation. Chromatographic purification of the residue on silica gel (elution with 15% ether in petroleum ether) afforded 71 as a colorless oil (2.15 g, 81%) together with recovered starting 70 (95 mg, 9%). For 71: IR (film, cm⁻¹) 1777; ¹H NMR (300 MHz, CDCl₃) δ 7.68-7.60 (m, 4 H), 7.47-7.34 (m, 6 H), 4.61 (t, J = 7.4 Hz, 1 H), 3.53 (d, J = 9.9 Hz, 1 H), 3.39 (d, J = 9.9 Hz, 1 H), 2.65 (ddq, J = 9.5, 7.4, 5.4 Hz, 1 H), 2.28 (ddd, J = 13.1, 7.0, 9.5 Hz, 1 H), 1.79 (ddd, J = 13.1, 7.7, 5.4 Hz, 1 H), 1.29 (d, J = 7.4 Hz, 3 H), 1.07 (s, 9 H), 0.93 (s, 3 H), 0.88 (s, 3 H); ¹³C NMR (75 MHz, C₆D₆) ppm 178.6, 136.02 (2 C), 135.99 (2 C), 133.8, 133.6, 130.13, 130.10, 128.14 (2 C), 128.11 (2 C), 80.6, 69.9, 39.3, 34.7, 30.1, 27.1 (3 C), 19.8, 19.6, 19.0, 16.5; MS m/z (M⁺-CH₃) calcld 395.2042, obsd 395.2038; [α]₂°D -25.7 (c 3.39, CHCl₃).

Anal. Calcd for C₂₅H₃₄O₃Si: C, 73.13; H, 8.35. Found: C, 73.13; H, 8.43.
35,5J?)-5-[2-(tert-Butyldiphenylsiloxy)-1,1-dimethylethyl]dihydro-3,3-di-

methyl-2(3H)-furanone (73). Colorless oil; IR (film, cm⁻¹) 1776; ¹H NMR (300 MHz, 

CDCl₃) δ 7.68-7.65 (m, 4 H), 7.47-7.37 (m, 6 H), 4.55 (dd, J = 7.1, 9.9 Hz, 1 H), 3.56 (d, 

J = 9.9 Hz, 1 H), 3.43 (d, J = 9.9 Hz, 1 H), 1.92-1.88 (series of m, 2 H), 1.27 (s, 3 H), 

1.266 (s, 3 H), 1.09 (s, 9 H), 0.96 (s, 3 H), 0.89 (s, 3 H); ¹³C NMR (75 MHz, CDCl₃) ppm 

181.90, 135.58 (2 C), 135.56 (2 C), 133.39, 133.22, 129.67 (2 C), 127.64 (4 C), 80.00, 

69.67, 40.44, 38.37, 37.88, 26.86 (3 C), 24.80, 24.34, 19.41, 19.38, 19.21; MS m/z (M⁻-

CH₃) calcd 409.2199, obsd 409.2236.

(3R,5R)-5-[2-(tert-Butyldiphenylsiloxy)-1,1-dimethylethyl]dihydro-3-methyl-

2(3H)-furanone (49). A solution of LDA (9.39 mmol) in THF (10 mL), prepared in the 

predescribed manner, was cooled to -78 °C, treated with a solution of 71 (772 mg, 1.88 

mmol) in THF (1 mL), stirred for 2 h at -78 °C, and quenched with saturated NH₄Cl 

solution. The product was extracted into ether, washed with brine, dried, evaporated, and 

purified chromatographically (silica gel, elution with 35% ether in hexanes). There was 

obtained 741 mg (96%) of 49 as a colorless oil; IR (film, cm⁻¹) 1770; ¹H NMR (300 

MHz, CDCl₃) δ 7.66-7.60 (m, 4 H), 7.46-7.35 (m, 6 H), 4.45 (dd, J = 5.6, 11.1 Hz, 1 H), 

3.55 (d, J = 9.9 Hz, 1 H), 3.40 (d, J = 9.9 Hz, 1 H), 2.67 (ddq, J = 7.0, 8.6, 12.5 Hz, 1 H), 

2.23 (ddd, J = 5.6, 8.6, 12.5 Hz, 1 H), 1.68 (q, J = 12.2 Hz, 1 H), 1.26 (d, J = 7.0 Hz, 3 

H), 1.07 (s, 9 H), 0.93 (s, 3 H), 0.89 (s, 3 H); ¹³C NMR (75 MHz, CDCl₃) ppm 179.5, 

135.6 (4 C), 133.4, 133.3, 129.7 (2 C), 127.7 (4 C), 81.6, 69.7, 38.5, 36.0, 31.9, 26.9 (3
C), 19.6, 19.4, 19.2, 14.9; MS m/z (M+) calcd 410.2277, obsd 410.2316; [α]_D^19 -8.3 (c 3.95, CHCl₃).

*Anal.* Calcd for C_{25}H_{34}O_{3}Si: C, 73.13; H, 8.35. Found: C, 72.70; H, 8.44.

(R)-2,2-Diethyl-β,β-dimethyl-1,3-dioxolane-4-ethanol (77). A mixture of 781 mg (6.0 mmol) of D-pantolactone in 25 mL of THF was treated with 228 mg (6.0 mmol) of lithium aluminum hydride. The reaction mixture was refluxed over a period of 1 h, cooled to room temperature, and quenched by the addition of 1.0 g of Na₂SO₄·10 H₂O in several portions. The heterogeneous mixture was stirred for 2 h, the solid was removed by filtration and the filtrate evaporated. To the residue was added 60 mL of benzene. 1.031 g (12.0 mmol) of diethyl ketone, and 5 mg of CSA. The mixture was refluxed under a Dean-Stark trap filled with 4Å molecular sieves over a period of 48 h, cooled, and passed through a silica gel pad (elution with 60% of ether in hexanes) to furnish 1.094 g (90%) of 77 as a colorless liquid; \(^1\)H NMR (300 MHz, CDCl₃) δ 3.98-3.61 (series of m, 2 H), 3.58-3.54 (m, 1 H), 3.46 (m, 2 H), 2.54 (s, 1 H), 1.72-1.56 (series of m, 4 H), 0.94 (s, 3 H), 0.87 (s, 3 H), 0.96-0.77 (series of m, 6 H); [α]_D^{20} -1.5 (c 4.81, CHCl₃) (lit\(^{38}\) [α]_D -1.5, (c 5.6, CHCl₃)).

(R)-2,2-Diethyl-4-[2-[(p-methoxybenzyl)oxy]-1,1-dimethylethyl]-1,3-dioxolane (78). A solution of 1.02 g (5.04 mmol) of 77 was dissolved in 10 mL of DMF and treated with 145 mg (6.05 mmol) of sodium hydride at 0 °C over a period of 30 min. To the reaction mixture was added 947 mg (6.05 mmol) of p-methoxybenzylchloride and stirring was continued overnight. The reaction mixture was diluted with 50 mL of ether and
washed with 20 mL of water, then brine. The organic phase was dried over MgSO₄ and concentrated, and the product was purified by chromatography on silica gel (gradient elution with 30% ether in hexanes) to provide 1.45 g (89%) of 78 as a colorless oil; IR (film, cm⁻¹) 1613, 1514, 1463, 1247; ¹H NMR (300 MHz, CDCl₃) δ 7.23 (dm, J = 8.7 Hz, 2 H), 6.86 (dm, J = 8.7 Hz, 2 H), 4.41 (s, 2 H), 3.99 (dd, J = 6.3, 8.9 Hz, 1 H). 3.86 (dd, J = 6.3, 7.9 Hz, 1 H), 3.78 (s, 3 H), 3.68 (dd, J = 7.9, 8.9 Hz, 1 H), 3.26 (d, J = 8.9 Hz, 1 H), 3.18 (d, J = 8.9 Hz, 1 H), 1.64-1.56 (series of m, 4 H), 0.95 (s, 3 H), 0.91 (s, 3 H), 0.90 (t, J = 7.5 Hz, 3 H), 0.88 (t, J = 7.5 Hz, 3 H); ¹³C NMR (75 MHz, CDCl₃) ppm 159.0, 130.9, 128.9 (2 C), 113.7 (2 C), 111.8, 80.4, 77.1, 73.0, 65.7, 55.2, 36.8, 29.6, 29.2, 20.8, 20.5, 8.3, 8.0; MS m/z (M⁺) calcd 322.2144, obsd 322.2141; [α]D²⁰ -2.7 (c 1.91, CHCl₃).


(R)-4-[(p-Methoxybenzyl)oxy]-3,3-dimethyl-1,2-butanediol (75). To a mixture of 278 mg (0.865 mmol) of 78 and 10 mL of THF was added 10 mL of 1 N hydrochloric acid. The resulting emulsion was stirred for 5 h, diluted with 70 mL of ether, and washed with 1 N NaOH solution, water and brine. The organic phase was dried over MgSO₄ and concentrated. The residue was purified by chromatography (silica gel, elution with ether) to furnish 180 mg (82%) of 75 as a colorless oil; IR (film, cm⁻¹) 3416, 1089; ¹H NMR (300 MHz, CDCl₃) δ 7.21 (dm, J = 8.5 Hz, 2 H), 6.86 (dm, J = 8.5 Hz, 2 H), 4.42 (s, 2 H), 3.78 (s, 3 H), 3.64-3.47 (m, 3 H), 3.30-3.25 (m, 2 H), 3.25-3.20 (br, 2 H), 0.93 (s, 3 H), 0.90 (s, 3 H); ¹³C NMR (75 MHz, CDCl₃) ppm 159.2, 129.7, 129.1 (2 C), 113.8 (2 H), 113
C), 78.1, 77.9, 73.1, 62.8, 55.1, 37.4, 22.8, 20.6; MS m/z (M⁺) calcd 254.1518, obsd 254.1515; [α]D 20 -6.2 (c 1.21, CHCl₃).


α-[(R)-3,4-Epoxy-2,2-dimethylbutoxy]-p-methoxytoluene (74). To a solution of 1.540 g (6.05 mmol) of diol 75 in 120 mL of DMF at 0 °C was added 320 mg (13.3 mmol) of sodium hydride. The mixture was stirred at rt for 30 min, recooled to 0 °C, and treated slowly with a mixture of 1.41 g (6.35 mmol) of N-tosylimidazole in 10 mL of DMF. The mixture was allowed to warm slowly and stirred at rt for 48 h, then diluted with 200 mL of ether, washed with sequentially with water and brine, dried over MgSO₄, and concentrated. The residue was purified by chromatography on silica gel (elution with 20% ether in hexanes) to provide 74 as a colorless oil (1.059g, 74%); IR (film, cm⁻¹) 1513, 1247, 1095; ¹H NMR (300 MHz, CDCl₃) δ 7.16 (dm, J = 8.6 Hz, 2 H), 6.78 (dm, J = 8.6 Hz, 2 H), 4.27 (s, 2 H), 3.31 (s, 3 H), 3.14 (d, J = 8.7 Hz, 1 H), 3.07 (d, J = 8.7 Hz, 1 H), 2.81-2.79 (m, 1 H), 2.40-2.38 (m, 1 H), 2.33-2.30 (m, 1 H), 0.85 (s, 3 H), 0.84 (s, 3 H); ¹³C NMR (75 MHz, CDCl₃) ppm 159.7, 131.2, 129.2 (2 C), 114.1 (2 C), 77.0, 73.1, 57.0, 54.8, 43.5, 35.3, 20.7, 20.6; MS m/z (M⁺) calcd 236.1412, obsd 236.1408; [α]D 20 -12.7 (c 1.00, CHCl₃).

Anal. Calcd for C₁₄H₂₀O₃: C, 71.16; H, 8.53. Found: C, 71.20; H, 8.56.

(S)-Dihydro-5-[2-[(p-methoxybenzyl)oxy]-1,1-dimethylethyl]-2(3H)-furanone (79). To a solution of LDA, prepared by the addition of n-butyllithium (52.9 mL of 1.6 M in hexanes, 84.6 mmol) to diisopropylamine (8.56 g, 84.6 mmol) in THF (100 mL) cooled to −50 °C with a subsequent warmup to 0 °C was added acetic acid (2.540 g, 42.3
mmol). The reaction mixture was stirred at 40 °C for 30 min to complete the metalation. The resulting white suspension was treated with 1.046 g (4.42 mmol) of epoxide 74 in 5 mL of THF, heated to reflux overnight, cooled, and quenched with water. The aqueous phase was acidified with 1 N HCl to pH 2 and extracted with ether. The combined organic phases were dried with MgSO₄ overnight, concentrated, and the residue was purified by chromatography (silica gel, gradient elution with 30-50% of ether in petroleum ether) to furnish 746 mg (60%) of 79; IR (film, cm⁻¹) 1613; ¹H NMR (300 MHz, CDCl₃) δ 7.22 (dm, J = 8.5 Hz, 2 H), 6.86 (dm, J = 8.5 Hz, 2 H), 4.50 (t, J = 8.0 Hz, 1 H), 4.43 (d, J = 11.7 Hz, 1 H), 4.39 (d, J = 11.7 Hz, 1 H), 3.79 (s, 3 H), 3.26 (d, J = 9.0 Hz, 1 H), 3.23 (d, J = 9.0 Hz, 1 H), 2.52-2.40 (m, 2 H), 2.09-1.95 (m, 2 H), 0.94 (s, 3 H), 0.90 (s, 3 H); ¹³C NMR (75 MHz, CDCl₃) ppm 177.4, 159.0, 130.4, 128.9 (2 C), 113.7 (2 C), 84.4, 75.9, 72.9, 55.2, 37.8, 29.2, 22.6, 20.0, 19.6; MS m/z (M⁺) calcd 278.1518, obsd 278.1518; [α]D⁺ 22.2 (c 4.20, CHCl₃).


(3S,5S)-Dihydro-5-[2-[(p-methoxybenzyl)oxy]-1,1-dimethyl-2(3H)]-furanone (80). A solution of LDA, prepared in 15 mL of THF from 163 mg (1.61 mmol) of diisopropylamine and 1.00 mL (1.6 mmol) of 1.6 M butyllithium in hexanes, was cooled to -78 °C and treated with 149 mg (0.54 mmol) of lactone 79 dissolved in 2 mL of THF and 1 mL of HMPA. The reaction mixture was stirred at -40 °C for 1 h, then recooled to -78 °C, followed by the addition of 84 mg (58.3 mmol) of iodomethane. After being warmed up to -40 °C for a period of 30 min, the reaction mixture was recooled to -78 °C, and quenched with 10 mL of saturated ammonium chloride solution.
The mixture was extracted with ether, the combined organic phases were dried over Na$_2$SO$_4$ and concentrated, and the residue was purified chromatographically (silica gel, elution with 40% ether in hexanes) to provide 73 mg (47%) of 80 as a colorless oil;

IR (film, cm$^{-1}$) 1790; $^1$H NMR (300 MHz, C$_6$D$_6$) $\delta$ 7.22 (dm, $J = 8.6$ Hz, 2 H), 6.87 (dm, $J = 8.6$ Hz, 2 H), 4.34 (d, $J = 11.6$ Hz, 1 H), 4.27 (d, $J = 11.6$ Hz, 1 H), 4.04 (dd, $J = 5.6$, 11.0 Hz, 1 H), 3.36 (s, 3 H), 3.21 (d, $J = 8.8$ Hz, 1 H), 3.07 (d, $J = 8.8$ Hz, 1 H), 2.09-1.99 (m, 1 H), 1.57-1.48 (m, 1 H), 1.26 (q, $J = 12.6$ Hz, 1 H), 1.05 (d, $J = 7.0$ Hz, 3 H), 0.86 (s, 3 H), 0.78 (s, 3 H); $^{13}$C NMR (75 MHz, C$_6$D$_6$) ppm 178.2, 159.8, 131.0, 129.3 (2 C), 114.1 (2 C), 81.2, 76.3, 73.2, 54.8, 37.4, 35.8, 31.8, 20.2, 19.7, 15.0; MS $m/z$ (M$^+$) calcd 292.1675, obsd 292.1674; $[\alpha]_D^{20} +7.5$ (c 0.75, CHCl$_3$).

Anal. Calcd for C$_{17}$H$_{24}$O$_4$: C, 69.84; H, 8.27. Found: C, 69.74; H, 8.30.

*tert-Butyl[2-[(R)-5-m-dithian-2-ylidene]tetrahydro-2-furyl]-2-methylpropoxy]-diphenylsilane* (82). To a solution of 30 mg (0.2521 mmol) of 1,3-dithiane in 1 mL of THF at −78 °C was added 0.168 mL (0.2521 mmol) of 1 M n-butyllithium in hexanes. The reaction mixture was allowed to warm to −40 °C over 40 min, stirred for additional 20 min at this temperature, and recooled to −78 °C. Lactone 70 dissolved in 0.5 mL of THF was introduced, and the reaction mixture was gradually allowed to warm to rt (1 h) prior to being quenched with saturated ammonium chloride solution and extracted with ether. The organic layers were washed with brine, dried, and evaporated. Chromatography of the residue (silica gel, elution with 7-10% ether in petroleum ether) furnished 82 (25 mg, 40%) as a colorless oil; IR (film, cm$^{-1}$) 1625, 1472, 1425, 1108; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.70-7.65 (m, 4 H), 7.41-7.37 (m, 6 H), 4.52 (dd, $J = 6.6$ Hz, 116
8.7, 1 H), 3.62 (d, J = 9.8 Hz, 1 H), 3.37 (d, J = 9.8 Hz, 1 H), 2.80-2.60 (series of m, 6 H), 2.40-2.13 (series of m, 2 H), 1.97-1.88 (series of m, 2 H), 1.06 (s, 9 H), 0.94 (s, 3 H), 0.92 (s, 3 H); 13C NMR (75 MHz, CDCl3) ppm 161.0, 135.7 (2 C), 135.6 (2 C), 133.6, 133.5, 129.55, 129.51, 127.8 (2 C), 127.6 (2 C), 88.7, 87.5, 70.0, 39.2, 31.4, 30.9, 30.2, 26.9 (3 C), 26.6, 24.6, 20.2, 19.5, 19.4; MS m/z (M+) calcd 498.2082, obsd 498.2123; [α]D 20 -7.0 (c 2.92, CHCl3).

**Methyl (2R,3R,4S,6S)-6-[(tert-Butyldiphenylsiloxy)methyl]tetrahydro-4-[(p-methoxybenzyl)oxy]-3-methyl-2H-pyran-2-acetate (85).** To a mixture of 147 mg (0.283 mmol) of lactone 58 in 5 mL of dichloromethane at −78 °C was added 0.311 mL (0.311 mmol) of 1 M DIBAL in hexanes. The reaction mixture was stirred for 8 min, quenched with saturated sodium potassium tartrate solution, and extracted with dichloromethane. The combined organic layers were dried over MgSO4, concentrated, and passed through a short silica gel column (elution with 30% ether in petroleum ether). The residue was dissolved in 10 mL of acetonitrile and treated with 104 mg (0.311 mmol) of (carbomethoxymethylene)triphenylphosphorane at the reflux temperature for 48 h. The reaction mixture was cooled, diluted with ether, washed with water and brine, dried, concentrated and passed through a pad of silica gel (elution with 30% ether in petroleum ether). The resulting α,β-unsaturated ester was dissolved in 5 mL of THF, cooled to −60 °C, and treated with 0.083 mL of a 1 M solution of potassium tert-butoxide in THF. The reaction mixture was stirred for 15 min, quenched with saturated ammonium chloride solution, and extracted with ether. The combined organic phases were dried over MgSO4 and purified by chromatography on silica gel (elution with 20 % ether in petroleum ether)
to furnish 130 mg (80%) of 85 as a colorless oil; IR (film, cm⁻¹) 1734; ¹H NMR (300 MHz, CD₂Cl₂) δ 7.86-7.78 (m, 4 H), 7.27-7.17 (series of m, 8 H), 6.82 (dm, J = 8.7 Hz, 2 H), 4.56-4.51 (m, 1 H), 4.41 (d, J = 11.5 Hz, 1 H), 4.17 (d, J = 11.5 Hz, 1 H), 3.90 (dd, J = 5.1, 9.6 Hz, 1 H), 3.88-3.78 (m, 1 H), 3.74 (dd, J = 4.6, 9.6 Hz, 1 H), 3.37 (s, 3 H), 3.31 (s, 3 H), 3.07 (bt, J = 4.3, 9.5 Hz, 1 H). 2.47 (dd, J = 10.6, 14.3 Hz, 1 H), 2.15 (dd, J = 4.7, 14.3 Hz, 1 H), 2.01-1.88 (m, 2 H), 1.41-1.27 (m, 1 H), 1.2 (s, 9 H), 0.75 (d, J = 6.9 Hz, 3 H); ¹³C NMR (75 MHz, CD₂Cl₂) ppm 171.4, 159.6, 136.13 (2 C), 136.11 (2 C), 134.2 (2 C), 131.5, 129.9 (2 C), 129.2 (2 C), 128.1 (4 C), 114.0 (2 C), 76.3, 73.6, 70.7, 69.9, 67.3, 54.8, 51.3, 39.2, 33.9, 32.8, 27.1 (3 C), 19.6, 13.3; MS m/z (M⁺-C₄H₉) calcd 519.2203, obsd 519.2192; [α]D²⁰ +23.2 (c 0.31, CHCl₃).

Anal. Caled for C₃₄H₄₄O₆Si: C, 70.80; H, 7.69. Found: C, 71.01; H, 7.76.

Methyl (2S,3R,4S,6S)-6-[(tert-Butyldiphenylsiloxy)methyl]tetrahydro-4-[(p-methoxybenzyl)oxy]-3-methyl-2H-pyran-2-acetate (86). A. From 85. A mixture of 107 mg (0.186 mmol) of 85 was dissolved in 5 mL of THF and treated with 0.055 mL of 1 M solution of potassium tert-butoxide in THF for a period of 4 h. The reaction mixture was diluted with ether (20 mL) and washed with 5 mL of saturated ammonium chloride solution, water, and brine. The organic phase was dried over MgSO₄, concentrated, and purified by chromatography over silica gel (elution with 25% ether in petroleum ether) to afford 45 mg (42%) of 86 as a colorless oil; IR (film, cm⁻¹) 1742; ¹H NMR (300 MHz, CDCl₃) δ 7.70-7.67 (m, 4 H), 7.43-7.37 (m, 6 H), 7.27 (dm, J = 8.5 Hz, 2 H), 6.89 (dm, J = 8.5 Hz, 2 H), 4.59 (d, J = 11.2 Hz, 1 H), 4.38 (d, J = 11.2 Hz, 1 H), 3.80-3.49 (series of m, 4 H), 3.81 (s, 3 H), 3.64 (s, 3 H), 3.16 (td, J = 4.5, 10.5 Hz, 1 H), 2.64 (dd, J = 3.2,
15.1 Hz, 1 H), 2.43 (dd, J = 9.1, 15.1 Hz, 1 H), 2.16 (dd, J = 1.7, 4.5, 12.3 Hz, 1 H),
1.48-1.40 (m, 1 H), 1.34-1.21 (m, 1 H), 1.06 (s, 9 H), 0.97 (d, J = 6.5 Hz, 3 H); \(^{13}\)C NMR
(75 MHz, CDCl\(_3\)) ppm 172.1, 159.2 (2 C), 135.7 (2 C), 135.6 (2 C), 133.6 (2 C), 130.6,
129.5 (2 C), 129.3 (2 C), 127.6 (4 C), 113.8 (2 C), 79.6, 78.1, 76.1, 70.1, 66.8, 55.2, 51.6,
41.8, 39.1, 33.5, 26.8 (3 C), 19.2, 13.1; FAB MS \(m/z\) (M\(^{+}\)+H) calcd 577.30, obsd 577.43;
[\(\alpha\)]\(_D\) \(^{20}\) +20.4 \((c \ 1.35, \text{CHCl}_3)\).

\textit{Anal.} Calcd for C\(_{34}\)H\(_{44}\)O\(_6\)Si: C, 70.80; H, 7.69. Found: C, 71.01; H, 7.76.

B. From 101. To a solution of 101 (1.62 g,3.54 mmol) in 100 mL of ether was
added 0.11 mL (0.011 mmol, 0.3 mol%) of 0.1 M triflic acid immediately followed by a
rapid dropwise addition of 2.00 g (7.08 mmol) of \(p\)-methoxybenzyl trichloroacetimidate.
The reaction mixture was stirred for an additional 30 min, diluted with 50 mL of ether,
washed with saturated sodium bicarbonate solution and brine. The organic phase was
dried over MgSO\(_4\) and concentrated, and residue was purified by chromatography (silica
gel, elution with 15\% of ether in petroleum ether) to furnish 1.80 g (88\%) of 86.

\textit{Ethyl \((3R,4S,6S)-6-[(\text{tert-Butyldiphenylsiloxy})\text{methyl]}\text{tetrahydro-2-hydroxy-}
4-\[(\text{\(p\)-methoxybenzyl)}\text{oxy}]\text{3-methyl-2H-pyran-2-acetate \(88\).} A solution containing
0.77 mmol of LDA in THF (2 mL) was cooled to -78 °C, treated during 10 min with dry
ethyl acetate (0.073 mL, 0.75 mmol), and stirred for 10 min prior to the introduction of
58 (100 mg, 0.19 mmol) dissolved in THF (1 mL). The reaction mixture was agitated for
an additional 10 min, quenched with saturated NH\(_4\)Cl solution (1 mL), and extracted
with ether. The combined organic layers were dried and concentrated to leave a residue
that was purified chromatographically (silica gel, elution with 10\% ether in petroleum
ether). There was isolated 82 mg (70%) of 88 as a colorless oil; IR (film, cm⁻¹) 3443, 1713; ¹H NMR (300 MHz, C₆D₆) 8 7.82-7.76 (m, 4 H), 7.29-7.19 (m, 8 H), 6.81 (dm, J = 8.7 Hz, 2 H), 5.56 (d, J = 1.8 Hz, 1 H), 4.44 (d, J = 11.3 Hz, 1 H), 4.40-4.18 (m, 1 H), 4.21 (d, J = 11.3 Hz, 1 H), 3.97-3.82 (m, 2 H), 3.78 (dd, J = 5.7, 10.5 Hz, 1 H), 3.72-3.63 (m, 2 H), 3.30 (s, 3 H), 2.51 (d, J = 15.3 Hz, 1 H), 2.37 (d, J = 15.3 Hz, 1 H), 2.02 (ddd, J = 2.3, 4.5, 12.2 Hz, 1 H), 1.58-1.40 (m, 1 H), 1.38-1.27 (m, 1 H), 1.21 (d, J = 6.5 Hz, 3 H), 1.19 (s, 9 H), 0.87 (t, J = 7.1 Hz, 3 H); ¹³C NMR (75 MHz, CDCl₃) ppm 172.8, 159.2, 135.7 (2 C), 135.6 (2 C), 133.8 (2 C), 130.9, 129.58, 129.56, 129.3 (2 C), 127.6 (4 C), 113.8 (2 C), 98.8, 76.2, 70.7, 69.1, 66.9, 60.9, 55.3, 45.2, 42.3, 33.8, 26.8 (3 C), 19.3, 14.1, 12.4; MS m/z (M⁺-C₄H₉-H₂O) calcd 531.2203, obsd 531.2216; [α]D²⁰ +36.3 (c 1.84, CHCl₃).

Anal. Calcd for C₃₅H₄₆O₇Si: C, 69.28; H, 7.64. Found: C, 69.28; H, 7.66.

Ethyl (2S,3R,4S,6S)-6-[(tert-Butyldiphenylsiloxy)methyl]tetrahydro-4-hydroxy-3-methyl-2H-pyran-2-acetate (90). A. By Ionic Reduction of 88. A solution of 88 (15 mg, 0.025 mmol) in CH₂Cl₂ (1 mL) at 0 °C was treated sequentially with titanium tetrachloride (0.025 mL of 1 M in CH₂Cl₂, 0.025 mmol) and triethylsilane (6 mg, 0.050 mmol), allowed to warm to rt, washed with water and brine, dried, and evaporated. Purification of the residue by chromatography on silica gel (elution with 30% ether in petroleum ether) furnished 9 mg (74%) of 90 as a colorless oil; IR (film, cm⁻¹) 3471, 1738; ¹H NMR (300 MHz, CDCl₃) 8 7.67-7.65 (m, 4 H), 7.44-7.27 (m, 6 H), 4.15-4.05 (m, 2 H), 3.71-3.60 (m, 1 H), 3.57-3.41 (m, 4 H), 2.62 (dd, J = 3.3, 15.1
Hz, 1 H), 2.41 (dd, J = 8.9, 15.1 Hz, 1 H), 2.07 (dd, J = 4.3, 11.6 Hz, 1 H), 1.57 (br s, 1 H), 1.39-1.23 (m, 2 H), 1.20 (t, J = 7.1 Hz, 3 H), 1.04 (s, 9 H), 1.00 (d, J = 6.5 Hz, 3 H);

13C NMR (75 MHz, CDCl3) ppm 171.6, 135.63 (2 C), 135.60 (2 C), 133.6 (2 C), 129.6 (4 C), 127.6 (2 C), 77.8, 76.0, 73.3, 66.6, 60.4, 43.8, 39.2, 37.6, 26.8 (3 C), 19.2, 14.2, 12.8; FAB MS m/z (M++H) calcd 471.26, obsd 471.32; [α]D20 -17.8 (c 0.54, CHCl3).


B. Alternate Route from 57. A solution of 57 (100 mg, 0.25 mmol), hexamethyldisilazane (2 mL), and chlorotrimethylsilane (1 drop) was refluxed for 2 h, cooled, and freed of solvent under reduced pressure. In a separate flask, a THF solution containing 1.76 mmol of LDA was cooled to -78 °C, treated with ethyl acetate (155 mg, 1.76 mmol), and stirred for 1 h at -78 °C prior to introduction of the silylated lactone. The reaction mixture was stirred for 5 min, quenched with saturated NH4Cl solution (1 mL), diluted with ether (50 mL), washed with 1 M HCl, dried, and concentrated. The resulting material was dissolved in CH2Cl2 (2 mL), cooled to -78 °C, treated with triethylsilane (292 mg, 2.51 mmol) and then tin tetrachloride (0.25 mL of 1 M in CH2Cl2, 0.25 mmol), allowed to warm during 1 h to -20 °C, and stirred at this temperature for an additional 30 min before being quenched with water (2 mL). The product was extracted into ether and purified in the predescribed manner to deliver 69 mg (59% for 3 steps) of 90.

Ethyl (3R,4S,6S)-6-[(tert-Butyldiphenylsiloxy)methyl]tetrahydro-2,4-dihydroxy-3-methyl-2H-pyran-2-acetate (91) and Ethyl (3R,4S,6S)-6-[(tert-Butyldiphenylsiloxy)methyl]tetrahydro-2,4-dihydroxy-3-methyl-2H-pyran-2-
acetate, 4-acetate (92). To a solution of LDA prepared by the addition of 0.7 mL (1.1 mmol) of 1.6 M butyllithium in hexanes to 0.16 mL (1.1 mmol) of diisopropylamine in 1 mL THF was added at -78 °C 88.4 mg (1.1 mmol) of dry ethyl acetate. The reaction mixture was stirred for 20 min prior to the addition of 100 mg (0.25 mmol) of lactone 57 in 0.5 mL of THF. The reaction mixture was quenched with saturated ammonium chloride solution, extracted with ether, dried over MgSO₄, and concentrated. The residue was separated by chromatography (silica gel, elution with 20% of ethyl acetate in hexanes) to furnish 52 mg (42%) of 91 and 34 mg (26%) of 92.

For 91: colorless oil; IR (film, cm⁻¹) 3444, 1714; ¹H NMR (300 MHz, CDCl₃) δ 7.69-7.67 (m, 4 H), 7.44-7.36 (m, 6 H), 5.06 (d, J = 1.2 Hz, 1 H), 4.23-4.05 (m, 3 H), 3.82 (dt, J = 4.6, 10.6 Hz, 1 H), 3.69 (dd, J = 5.3, 10.6 Hz, 1 H), 3.58 (dd, J = 5.1, 10.3 Hz, 1 H), 2.78 (d, J = 15.1 Hz, 1 H), 2.51 (d, J = 15.1 Hz, 1 H), 2.08-2.01 (m, 1 H). 1.80 (br, 1 H), 1.4-1.26 (series of m, 2 H), 1.21 (t, J = 7.1 Hz, 3 H), 1.13 (d, J = 6.6 Hz, 3 H), 1.05 (s, 9 H); ¹³C NMR (75 MHz, CDCl₃) ppm 172.6, 135.58 (2 C), 135.56 (2 C), 133.6 (2 C), 129.51 (2 C), 129.49 (2 C), 127.6 (2 C), 98.7, 69.3, 69.0, 66.7, 60.9, 46.7, 42.2, 37.3, 26.7 (3 C), 19.2, 14, 12; FAB MS m/z (M⁻H₂O+H) calcd 469.24, obsd 469.31; [α]D⁺⁺⁺ 7.7 (c 0.93, CHCl₃).


For 92: colorless oil; IR (film, cm⁻¹) 3401, 1745, 1716; ¹H NMR (300 MHz, CDCl₃) δ 7.67-7.64 (m, 4 H), 7.44-7.34 (m, 6 H), 5.08-5.01 (series of m, 2 H), 4.21-4.07 (series of m, 3 H), 3.65 (dd, J = 5.2, 10.5 Hz, 1 H), 3.58 (dd, J = 4.6, 10.5 Hz, 1 H), 2.78 (d, J = 15.1 Hz, 1 H), 2.52 (d, J = 15.1 Hz, 1 H), 2.11-2.03 (m, 1 H), 2.06 (s, 3 H), 1.61-
1.56 (m, 1 H), 1.40 (q, $J = 11.6$ Hz, 1 H), 1.22 (t, $J = 7.1$ Hz, 3 H), 1.04 (s, 9 H), 1.00 (d, $J = 6.7$ Hz, 3 H); $^1$H NMR (75 MHz, CDCl$_3$) ppm 172.4, 170.50, 135.63 (2 C), 135.6 (2 C), 133.65 (2 C), 129.50 (2 C), 127.6 (4 C), 98.6, 72.2, 68.7, 66.6, 60.9, 43.7, 42.2, 33.7, 26.7 (3 C), 21.2, 19.2, 14.0, 12.1; FAB MS $m/z$ (M$^+\cdot$H$_2$O+H) calcd 511.25, obsd 511.26; $[\alpha]_{D}^{21}$ +39.3 (c 0.85, CHCl$_3$).

*Anal.* Calcd for C$_{29}$H$_{40}$O$_7$Si: C, 65.88; H, 7.63. Found: C, 65.86; H, 7.72.

**tert-Butyl (3R,4S,6S)-6-[(tert-Butyldiphenylsiloxy)methyl]tetrahydro-2,4-dihydroxy-3-methyl-2H-pyran-2-acetate (93).** To a solution of LDA, prepared by the addition of 0.90 mL (1.26 mmol) of 1 M butyllithium in hexanes to 127 mg (1.26 mmol) of diisopropylamine in 3 mL of THF at $-20^\circ$C, was added via syringe 146 mg (1.26 mmol) of dry tert-butylacetate. The reaction mixture was stirred for 20 min before the addition of 100 mg (0.25 mmol) of lactone 57 in 1 mL of THF. After a period of 5 min, the reaction mixture was quenched with 3 mL of saturated ammonium chloride solution, and extracted with ether (3 x 10 mL). The combined organic phases were dried over MgSO$_4$ and concentrated. The residue was purified by chromatography on silica gel (elution with 35% of ether in petroleum ether) to furnish 99 mg (77%) of 93 as a colorless oil; IR (film, cm$^{-1}$) 3428, 1704; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.71-7.66 (m, 4 H), 7.45-7.35 (m, 6 H), 5.17 (br, 1 H), 4.10-4.03 (m, 1 H), 3.82 (td, $J = 4.6$, 10.5 Hz, 1 H), 3.70 (dd, $J = 4.8$, 10.3 Hz, 1 H), 3.58 (dd, $J = 5.6$, 10.3 Hz, 1 H), 2.71 (d, $J = 15.0$ Hz, 1 H), 2.40 (d, $J = 15.0$ Hz, 1 H), 2.09 (ddd, $J = 2.2$, 4.6, 12.2 Hz, 1 H), 1.90 (br, 1 H), 1.41 (s, 9 H), 1.49-1.27 (series of m, 2 H), 1.11 (d, $J = 6.7$ Hz, 3 H), 1.06 (s, 9 H); $^1$C NMR (75 MHz, CDCl$_3$) ppm 172.0, 135.63 (2 C), 135.60 (2 C), 133.7 (2 C), 129.60 (2
tern-Butyl \((2S,3R,4S,6S)\)-6-[\((\text{tert-Butyldiphenylsiloxy})\text{methyl}\]tetrahydro-4-hydroxy-3-methyl-2\(H\)-pyran-2-acetate \((94)\). A mixture of 39.4 mg (0.077 mmol) of 93 in 2 mL of acetonitrile was treated with 89 mg (0.77 mmol) of triethylsilane and 0.077 mL (0.077 mmol) of 1 M solution of tin tetrachloride in dichloromethane. The reaction mixture was stirred for 3 h, diluted with 15 mL of ether, and washed with 5 mL of water and 5 mL of brine. The organic phase was dried over MgSO\(_4\) and concentrated, and the residue was chromatographed on silica gel (elution with 30% ether in petroleum ether) to afford 22 mg (57%) of 94 as a colorless oil; IR (film, cm\(^{-1}\)) 3430, 1731; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.65-7.71 (m, 4 H), 7.44-7.25 (m, 6 H), 3.75-3.67 (m, 1 H), 3.60-3.54 (m, 2 H), 3.53-3.36 (series of m, 2 H), 2.54 (dd, \(J = 3.6, 15.1\) Hz, 1 H), 2.31 (dd, \(J = 8.7, 15.1\) Hz, 1 H), 2.21 (ddd, \(J = 1.4, 4.6, 12.3\) Hz, 1 H), 1.90 (br, 1 H), 1.40 (s, 9 H), 1.43-1.18 (series of m, 2 H), 1.05 (s, 9 H), 0.98 (d, \(J = 6.5\) Hz, 3 H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) ppm 170.8, 135.6 (2 C), 135.5 (2 C), 133.6, 133.5 (2 C), 129.5 (2 C), 127.6 (4 C), 80.4, 78.0, 75.9, 73.2, 66.6, 43.8, 40.3, 37.8, 28.0 (3 C), 26.8 (3 C), 19.2, 12.7; MS m/z \((M^+ - C_4H_9O)\) calcd 425.2148, obsd 425.2103; [\(\alpha\)]\(^{19}\)\(_D\) +13.9 (c 1.40, CHCl\(_3\)).


Ethyl \((2S,3R,4S,6S)\)-6-[\((\text{tert-Butyldiphenylsiloxy})\text{methyl}\]tetrahydro-4-[\((\text{p-methoxybenzyl})\text{oxy}\]]-3-methyl-2\(H\)-pyran-2-acetate \((97)\). A solution of 90 (594 mg, 124
1.26 mmol) in dry ether (20 mL) was treated with triflic acid (0.037 mL of 0.1 M in ether, 0.3 mol %) followed immediately by p-methoxybenzyl trichloroacetimidate (535 mg, 1.89 mmol) dissolved in ether (1 mL). The reaction mixture was stirred for 20 min, washed with water and saturated NaHCO₃ solution, dried, and concentrated. Chromatography of the residue on silica gel (elution with 15% ether in petroleum ether) gave 437 mg (59%) of 97 as a colorless oil; IR (film, cm⁻¹) 1738; ¹H NMR (300 MHz, CDCl₃) δ 7.71-7.68 (m, 4 H), 7.46-7.36 (m, 6 H), 7.28 (dm, J = 8.6 Hz, 2 H), 6.90 (dm, J = 8.6 Hz, 2 H), 4.60 (d, J = 11.2 Hz, 1 H), 4.39 (d, J = 11.2 Hz, 1 H), 4.17-4.06 (m, 2 H), 3.81 (s, 3 H), 3.74 (dd, J = 5.2, 10.0 Hz, 1 H), 3.62-3.50 (series of m, 3 H), 3.18 (td, J = 4.5, 10.6 Hz, 1 H), 2.63 (dd, J = 3.2, 15.1 Hz, 1 H), 2.42 (dd, J = 9.1, 15.1 Hz, 1 H), 2.23-2.18 (m, 1 H), 1.50-1.41 (m, 1 H), 1.35-1.25 (m, 1 H), 1.21 (t, J = 7.1 Hz, 3 H), 1.07 (s, 9 H), 0.98 (d, J = 6.5 Hz, 3 H); ¹³C NMR (75 MHz, CDCl₃) ppm 171.6, 159.2, 135.68 (2 C), 135.65 (2 C), 133.7 (2 C), 130.7, 129.6 (2 C), 129.4 (2 C), 127.6 (4 C), 113.8 (2 C), 80.0, 78.2, 76.1, 70.2, 66.9, 60.4, 55.3, 41.9, 39.4, 33.6, 26.8 (3 C), 19.3, 14.2, 13.1; FAB MS m/z (M⁺+H) calcd 591.31, obsd 591.42; [α]$_{D}^{20}$ +23.3 (c 1.22, CHCl₃).

Anal. Calcd for C₃₅H₄₆O₆Si: C, 71.15; H, 7.85. Found: C, 71.04; H, 7.82.

Ethyl (2S,3R,4S,6S)-Tetrahydro-6-(hydroxymethyl)-4-[(p-methoxybenzyl)oxy]-3-methyl-2H-pyran-2-acetate (98). To a solution of 97 (486 mg, 0.82 mmol) in THF (5 mL) was added tetra-n-butylammonium fluoride (1.07 mL of 1 M in THF, 1.07 mmol). The reaction mixture was stirred for 1.5 h, diluted with ether (50 mL), washed with water and brine, dried, and concentrated. Purification of the residue by chromatography (silica gel, gradient elution with 30-70% ethyl acetate in petroleum ether 125
ether) provided 275 mg (95%) of 98 as a colorless oil; IR (film, cm⁻¹) 3454, 1732; ¹H NMR (300 MHz, CDCl₃) δ 7.25 (dm, J = 8.5 Hz, 2 H), 6.87 (dm, J = 8.5 Hz, 2 H), 4.58 (d, J = 11.1 Hz, 1 H), 4.36 (d, J = 11.1 Hz, 1 H), 4.41 (q, J = 7.1 Hz, 2 H), 3.80 (s, 3 H), 3.61-3.42 (m, 4 H), 3.17 (td, J = 4.6, 10.6 Hz, 1 H), 2.64 (dd, J = 3.4, 15.1 Hz, 1 H), 2.40 (dd, J = 9.1, 15.1 Hz, 1 H), 2.11-1.46 (m, 2 H), 1.51-1.44 (m, 1 H), 1.43-1.29 (m, 1 H), 1.25 (t, J = 7.1 Hz, 3 H), 0.96 (d, J = 6.5 Hz, 3 H); ¹³C NMR (75 MHz, CDCl₃) ppm 171.4, 159.1, 130.4, 129.2 (2 C), 113.7 (2 C), 79.2, 78.0, 75.8, 70.1, 65.7, 60.4, 55.2, 41.8, 39.2, 32.7, 14.1, 12.9; FAB MS m/z (M⁺+H) calcd 353.20, obsd 353.21; [α]D +48.9 (c 2.22, CHCl₃).

Anal. Calcd for C₁₉H₂₈O₆: C, 64.75; H, 8.01. Found: C, 64.47; H, 8.08.

Ethyl (2S,3R,4S,6S)-6-Formyltetrahydro-4-[(p-methoxybenzyl)oxy]-3-methyl-2H-pyran-2-acetate (99). A solution of 98 (264 mg, 0.75 mmol) in CH₂Cl₂ (10 mL) was treated with the Dess-Martin periodinane (508 mg, 1.20 mmol), stirred for 1 h, and subjected directly to chromatography on silica gel. Elution with 50% ether in petroleum ether provided 187 mg (71%) of 99 as a colorless oil; IR (film, cm⁻¹) 1732; ¹H NMR (300 MHz, CDCl₃) δ 9.61 (s, 1 H), 7.24 (dm, J = 8.5 Hz, 2 H), 6.87 (dm, J = 8.5 Hz, 2 H), 4.61 (d, J = 11.1 Hz, 1 H), 4.36 (d, J = 11.1 Hz, 1 H), 4.16 (q, J = 7.1 Hz, 2 H), 3.84-3.79 (m, 1 H), 3.80 (s, 3 H), 3.61 (td, J = 3.3, 9.7 Hz, 1 H), 3.18 (td, J = 4.4, 10.3 Hz, 1 H), 2.67 (dd, J = 3.3, 15.3 Hz, 1 H), 2.49 (dd, J = 9.0, 15.3 Hz, 1 H), 2.36 (ddd, J = 2.5, 4.4, 12.6 Hz, 1 H), 1.54-1.49 (m, 1 H), 1.47-1.32 (m, 1 H), 1.26 (t, J = 7.1 Hz, 3 H), 0.97 (d, J = 6.5 Hz, 3 H); ¹³C NMR (75 MHz, CDCl₃) ppm 201.2, 171.3, 126.
159.3, 130.1, 129.4 (2 C), 113.9 (2 C), 79.6, 78.7, 78.4, 70.3, 60.6, 55.3, 41.6, 39.1, 31.6, 14.2, 12.9; FAB MS m/z (M$^+$+H) calcd 351.18, obsd 351.17; [$\alpha$]$^D_D +17.5$ (c 1.50, CHCl$_3$).

**Ethyl (2S,3R,4S,6S)-6-(Formylmethyl)tetrahydro-4-[(p-methoxybenzyl)oxy]-3-methyl-2H-pyran-2-acetate (100).** A magnetically stirred suspension of (methoxymethyl)triphenylphosphonium chloride (94 mg, 0.27 mmol) in THF (2 mL) was cooled to 0 °C, treated with potassium hexamethyldisilazide (0.55 mL of 0.5 M in toluene, 0.27 mmol), and stirred for 15 min in advance of the addition of 99 (32 mg, 0.091 mmol) dissolved in THF (0.5 mL). The reaction mixture was stirred at 0 °C for 30 min, quenched with saturated NH$_4$Cl solution, and extracted with ether. The combined organic phases were dried, concentrated, and passed through a pad of silica gel (elution with 30% ether in petroleum ether). The resulting enol ether was dissolved in THF (1 mL), treated with 1 M HCl (0.25 mL), stirred for 5 h, diluted with ether, and washed with water and saturated NaHCO$_3$ solution prior to drying, concentration, and chromatography on silica gel (elution with 50-60% ether in petroleum ether) to furnish 15 mg (45%) of 100 as a colorless oil; IR (film, cm$^{-1}$) 1731; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.70 (m, 1 H), 7.24 (dm, $J = 8.6$ Hz, 2 H), 6.87 (dm, $J = 8.6$ Hz, 2 H), 4.57 (d, $J = 11.1$ Hz, 1 H), 4.36 (d, $J = 11.1$ Hz, 1 H), 4.11 (q, $J = 7.1$ Hz, 2 H), 3.92-3.83 (m, 1 H), 3.79 (s, 3 H), 3.52 (td, $J = 3.2$, 9.7 Hz, 1 H), 3.17 (td, $J = 4.5$, 10.3 Hz, 1 H), 2.65-2.57 (m, 2 H), 2.45 (ddd, $J = 1.7$, 4.7, 16.4 Hz, 1 H), 2.35 (dd, $J = 9.5$, 14.9 Hz, 1 H), 2.15 (ddd, $J = 1.8$, 4.5, 12.4 Hz, 1 H), 1.48-1.39 (m, 1 H), 1.36-1.24 (m, 1 H), 1.23 (t, $J = 7.1$ Hz, 3 H),
0.95 (d, J = 6.5 Hz, 3 H); $^{13}$C NMR (75 MHz, CDCl$_3$) ppm 200.8, 171.4, 159.2, 133.8 (2 C), 130.3, 129.3 (2 C), 79.1, 78.3, 70.7, 70.3, 60.5, 55.2, 49.2, 41.5, 39.2, 36.8, 14.1, 12.9; FAB MS $m/z$ (M$^{++}$H) calcd 365.20, obsd 365.27; $[^{19}$D$]_{D} +41.3$ (c 1.21, CHCl$_3$).

**Methyl (2S,3R,4S,6S)-6-[(tert-Butyldiphenylylsiloxy)methyl]tetrahydro-4-hydroxy-3-methyl-2H-pyran-2-acetate (101).** A mixture of 57 (2.25 g, 5.64 mmol), hexamethyldisilazane (10 mL), and chlorotrimethylsilane (3 drops) was refluxed for 6 h, cooled, and freed of solvent under reduced pressure. In a separate flask, a THF solution containing 56.4 mmol of LDA in 60 mL of THF was cooled to -78 °C, treated with methyl acetate (4.18 g, 56.4 mmol), and stirred for 45 min at -78 °C prior to introduction of the silylated lactone in 10 mL of THF. The reaction mixture was stirred for 5 min, quenched with saturated NH$_4$Cl solution, diluted with ether, washed with 1 M HCl, dried, and concentrated. The resulting material was dissolved in CH$_2$Cl$_2$ (120 mL), cooled to -60 °C, treated with triethylsilane (6.56 g, 56.4 mmol) and tin tetrachloride (6.21 mL of 1 M in CH$_2$Cl$_2$, 6.21 mmol). The reaction mixture was allowed to warm to -10 °C over 1 h, at which time a white precipitate had formed, and stirred at -10 °C for an additional 10 min before being quenched with saturated sodium bicarbonate solution. The product was extracted into dichloromethane and ether, the combined organic layers were washed with 1 M HCl and brine, dried over MgSO$_4$, and concentrated. The residue was purified chromatographically (silica gel, elution with 40% ether in petroleum ether) to afford 1.62 g (63%) of 101 as a colorless oil; IR (film, cm$^{-1}$) 3440, 1738; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.70-7.67 (m, 4 H), 7.42-7.35 (m, 6 H), 3.64 (s, 3 H), 3.72-3.42 (128
(series of m, 4 H), 3.40 (td, J = 4.7, 10.5 Hz, 1 H), 2.65 (dd, J = 3.2, 15.1 Hz, 1 H), 2.44 (dd, J = 9.0, 15.1 Hz, 1 H), 2.04 (ddd, J = 1.4, 4.6, 11.1 Hz, 1 H), 1.88 (br, 1 H), 1.35-1.19 (series of m, 2 H), 1.05 (s, 9 H), 1.00 (d, J = 6.5 Hz, 3 H); 13C NMR (75 MHz, CDCl3) ppm 172.0, 135.58 (2 C), 135.56 (2 C), 133.5 (2 C), 129.5 (2 C), 127.6 (4 C), 77.8, 76.0, 73.1, 66.6, 51.6, 43.6, 38.9, 37.4, 26.7 (3 C), 19.2, 12.8; FAB MS m/z (M+H) calcd 457.24, obsd 457.33; [α]D^19 +21.2 (c 1.18, CHCl3).

**Anal.** Calcd for C26H36O5Si: C, 68.39; H, 7.95. Found: C, 68.24; H, 8.01.

Methyl (2S,3R,4S,6S)-Tetrahydro-6-(hydroxymethyl)-4-[(p-methoxybenzyl)oxy]-3-methyl-2H-pyran-2-acetate (102). A solution of 1.80 g (3.11 mmol) of 86 in 50 mL of THF was treated with 3.42 mL (3.42 mmol) of a 1 M solution of TBAF in THF. The reaction mixture was stirred for 4 h, diluted with 200 mL of ethyl acetate, washed with water and brine, dried over MgSO4, and concentrated. The residue was purified by chromatography on silica gel (elution with ether in petroleum ether) to provide 1.01 g (95%) of 102 as a colorless oil; IR (film, cm⁻¹) 3460, 1738; 1H NMR (300 MHz, CDCl3) δ 7.50 (dm, J = 8.5 Hz, 2 H), 6.87 (dm, J = 8.5 Hz, 2 H), 4.59 (d, J = 11.1 Hz, 1 H), 4.36 (d, J = 11.1 Hz, 1 H), 3.80 (s, 3 H), 3.68 (s, 3 H), 3.60-3.45 (series of m, 4 H), 3.17 (td, J = 4.6, 10.6 Hz, 1 H), 2.65 (dd, J = 3.3, 15.1 Hz, 1 H), 2.42 (dd, J = 9.1, 15.1 Hz, 1 H), 2.03 (ddd, J = 1.6, 4.6, 12.3 Hz, 1 H), 1.63 (br, 1 H), 1.49-1.25 (series of m, 2 H), 0.96 (d, J = 6.5 Hz, 3 H); 13C NMR (75 MHz, CDCl3) ppm 171.9, 159.2, 130.4, 129.3 (2 C), 113.8 (2 C), 79.3, 78.0, 75.9, 70.2, 65.8, 55.3, 51.7, 41.8, 38.9, 32.7, 13.0; [α]D^20 46.5 (c 0.34, CHCl3).
Methyl (2S,3R,4S,6S)-6-Formyltetrahydro-4-[(p-methoxybenzyl)oxy]-3-methyl-2H-pyran-2-acetate (103). A mixture of 110 mg (0.33 mmol) of 102 and 5 mL of dichloromethane was treated with 166 mg (0.39 mmol) of the Dess-Martin periodinane. The reaction mixture was stirred for one hour prior to the addition of 2 mL of saturated sodium bicarbonate solution and 500 mg of solid sodium thiosulfate. After 30 min of stirring, the mixture was extracted with dichloromethane, and the combined organic layers were dried over MgSO₄ and concentrated. The residue was purified by chromatography (silica gel, elution with 50% of ethyl acetate in petroleum ether) to furnish 97 mg (89%) of 103 as a colorless oil; IR (film, cm⁻¹) 1738; ¹H NMR (300 MHz, CDCl₃) δ 9.60 (s, 1 H), 7.40 (dm, J = 8.6 Hz, 2 H), 6.87 (dm, J = 8.6 Hz, 2 H), 4.60 (d, J = 11.1 Hz, 1 H), 4.36 (d, J = 11.1 Hz, 1 H), 3.79 (s, 3 H), 3.70 (s, 3 H), 3.67-3.57 (m, 2 H), 3.18 (td, J = 4.3, 10.3 Hz, 1 H), 2.68 (dd, J = 15.4, 3.2 Hz, 1 H), 2.50 (dd, J = 8.9, 15.4 Hz, 1 H), 2.35 (ddd, J = 2.5, 4.3, 12.6 Hz, 1 H), 1.56-1.20 (series of m, 2 H), 0.97 (d, J = 6.6 Hz, 3 H); ¹³C NMR (75 MHz, CDCl₃) ppm 201.1, 171.7, 159.3, 130.0, 129.4 (2 C), 113.8 (2 C), 79.5, 78.6, 78.3, 70.3, 55.2, 51.8, 41.5, 38.8, 31.6, 12.9; FAB MS m/z (M⁺+H) calcd 337.16, obsd 337.15; [α]D²⁰ +19.7 (c 1.13, CHCl₃).

Methyl (2S,3R,4S,6S)-6-(Formylmethyl)tetrahydro-4-[(p-methoxybenzyl)oxy]-3-methyl-2H-pyran-2-acetate (104). A. From 103. A magnetically stirred suspension of (methoxymethyl)triphenylphosphonium chloride (101 mg, 0.29 mmol) in THF (2 mL) was cooled to 0 °C, treated with potassium hexamethyldisilazide (0.26 mL of 1 M in THF, 0.26 mmol), and stirred for 15 min in advance of the addition of 103 (31 mg, 0.091 mmol) dissolved in THF (0.5 mL). The reaction mixture was stirred at 0 °C
for 10 min, quenched with saturated NH₄Cl solution, and extracted with ether. The combined organic phases were dried, concentrated, and passed through a pad of silica gel (elution with 30% ethyl acetate in petroleum ether). The resulting enol ether was dissolved in a 1:4 mixture of 1 M HCl and THF (1 mL), stirred for 4 h, diluted with ethyl acetate, and washed with saturated NaHCO₃ solution prior to drying over MgSO₄, concentration, and chromatography on silica gel (gradient elution with 50-60% ether in petroleum ether) to furnish 14 mg (42%) of 104 as a colorless oil; IR (film, cm⁻¹) 1731; ¹H NMR (300 MHz, CDCl₃) δ 9.71 (t, J = 2.1 Hz, 1 H), 7.25 (dm, J = 8.7 Hz, 2 H), 6.87 (dm, J = 8.7 Hz, 2 H), 4.58 (d, J = 11.1 Hz, 1 H), 4.36 (d, J = 11.1 Hz, 1 H), 3.92-3.84 (m, 1 H), 3.80 (s, 3 H), 3.66 (s, 3 H), 3.52 (td, J = 4.6, 10.3 Hz, 1 H), 3.17 (td, J = 4.6, 10.3 Hz, 1 H), 2.67-2.58 (series of m, 2 H), 2.46 (ddd, J = 1.8, 4.7, 16.0 Hz, 1 H), 2.38 (dd, J = 9.5, 14.9 Hz, 1 H), 2.16 (dd, J = 2, 4.6, 12.4 Hz, 1 H), 1.81-1.48 (series of m, 2 H), 9.53 (d, J = 6.5 Hz, 3 H); ¹³C NMR (75 MHz, CDCl₃) ppm 200.8, 171.90, 159.20, 130.3, 129.33 (2 C), 113.80 (2 C), 79.2, 78.3, 70.7, 70.4, 55.3, 51.7, 49.3, 41.6, 39.9, 36.8, 12.9; FAB MS m/z (M+H) calcd 351.18, obsd 351.14; [α]D²⁰ +42.1 (c 1.42, CHCl₃).

B. Alternate Route from 105. A solution of 105 (59 mg, 0.18 mmol) in 3 mL of THF was treated with 0.186 mL (0.19 mmol) of 1 M borane in THF. The reaction mixture was stirred for 15 min and volatiles were evaporated in vacuo. The residue was dissolved in 6 mL of dichloromethane and treated with 114 mg (0.53 mmol) of PCC. The reaction mixture was stirred for 1 h at the reflux temperature, cooled, diluted with 20 mL of ether and filtered through a pad of silica gel. The filtrate was concentrated and the
residue was purified by chromatography (silica gel, gradient elution with 50-60% of ether in petroleum ether) to furnish 38 mg (61%) of 104.

**Methyl (2S,3R,4S,6S)-tetrahydro-4-[(p-methoxybenzyl)oxy]-methyl-6-vinyl-2H-pyran-2-acetate (105).** A suspension of 180 mg (0.45 mmol) of methyltriphenylphosphonium iodide in 2 mL of toluene was treated at 0 °C with 0.89 mL (0.45 mmol) of 0.5 M solution of KHMDS in toluene. The reaction mixture was stirred for 20 min, cooled to −78 °C, and treated with a solution of 103 in 1 mL of toluene. The reaction mixture was allowed to warm to 0 °C over a 50 min period, and stirred for an additional 25 min at this temperature prior to being quenched with saturated ammonium chloride solution. The product was extracted with ether, the combined organic phases were washed with brine and dried over MgSO₄ followed by solvent evaporation. The residue was purified by chromatography (silica gel, elution with 20% of ethyl acetate in hexanes) to furnish 68 mg (66%) of 105 as a colorless oil; IR (film, cm⁻¹) 1740; ¹H NMR (300 MHz, CDCl₃) δ 7.25 (dm, J = 8.6 Hz, 2 H), 6.87 (dm, J = 8.6 Hz, 2 H), 5.85 (ddd, J = 17.3, 10.6, 5.1 Hz, 1 H), 5.25 (ddd, J = 17.3, 3.0, 1.5 Hz, 1 H), 5.11 (ddd, J = 10.6, 2.8, 1.4 Hz, 1 H), 4.58 (d, J = 11.1 Hz, 1 H), 4.36 (d, J = 11.1 Hz, 1 H), 3.84 (m, 1 H), 3.78 (s, 3 H), 3.66 (s, 3 H), 3.53 (ddd, J = 9.9, 8.8, 3.5 Hz, 1 H), 3.17 (ddd, J = 14.6, 10.6, 4.4 Hz, 1 H), 2.65 (dd, J = 15.1, 3.6 Hz, 1 H), 2.48 (dd, J = 15.1, 8.8 Hz, 1 H), 2.17 (ddd, J = 12.5, 4.4, 2.1 Hz, 1 H), 1.46 (m, 1 H), 1.33 (q, J = 14.8 Hz, 1 H), 0.98 (d, J = 6.3 Hz, 3 H); ¹³C NMR (75 MHz, CDCl₃) ppm 171.9, 159.1, 138.1, 130.4, 129.2 (2 C), 114.7, 113.7 (2 C), 79.5, 77.9, 75.6, 70.1, 55.1, 51.9, 41.6, 39.0, 36.6, 12.9; MS m/z (M⁺) calcd 334.1780, obsd 334.1805; [α]D²⁰ +43.4 (c 1.00, CHCl₃).
Anal. Calcd for C_{19}H_{26}O_{5}: C, 68.24; H, 7.84. Found: C, 68.14; H, 7.89.

(2R,4R)-6-(tert-Butyldiphenylsiloxy)-4-[(p-methoxybenzyl)oxy]-2,2,5-trimethylhexanal (106). To a solution of 100 mg (0.19 mmol) of 115 in 3 mL of 4:1 THF-water mixture was added 0.06 mL (0.01 mmol) of 0.16 M solution of osmium tetroxide in THF followed by 31 mg (0.23 mmol) of N-methylmorpholine-N-oxide monohydrate. The reaction mixture was stirred for 4 h prior to the addition of 121 mg (0.57 mmol) of sodium periodate. After a 2 h period of stirring, the reaction mixture was diluted with 50 mL of ether and washed with water and brine. The organic phase was dried over MgSO_{4}, concentrated, and the residue was chromatographed (silica gel, gradient elution with 15-20% ether in petroleum ether) to afford 72 mg (72%) of 106 as a colorless oil; IR (film, cm\(^{-1}\)) 1723; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \& 9.32 (d, \(J = 2.6 \) Hz, 1 H), 7.76-7.72 (m, 4 H), 7.23-7.17 (series of m, 8 H), 6.78 (dm, \(J = 8.6 \) Hz, 2 H), 4.46 (s, 2 H), 3.65 (d, \(J = 9.7 \) Hz, 1 H), 3.48 (d, \(J = 9.7 \) Hz, 1 H), 3.52-3.49 (m, 1 H), 3.32 (s, 3 H), 2.30 (ddd, \(J = 2.5, 6.9, 13.8 \) Hz, 1 H), 1.89 (ddd, \(J = 6.5, 10.5, 14.2 \) Hz, 1 H), 1.23-1.15 (m, 1 H), 1.18 (s, 9 H), 0.94 (s, 3 H), 0.88 (d, \(J = 6.7 \) Hz, 3 H), 0.85 (s, 3 H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) ppm 203.0, 159.6, 136.1 (2 C), 133.9, 131.3 (2 C), 130.0 (2 C), 129.4 (4 C), 128.1 (4 C), 114.0 (2 C), 81.6, 74.5, 70.8, 54.8, 44.5, 41.4, 32.8, 27.3 (3 C), 21.8, 20.6, 19.6, 14.0; MS m/z (M\(^+\)) calcd 533.3087, obsd 533.3078; \([\alpha]^{20}_D\) +1.1 (c 1.00, CHCl\(_3\)).

(2R,4R)-6-(tert-Butyldiphenylsiloxy)-4-hydroxy-N-methoxy-N,2,5,5-tetramethylhexanamide (108). To a suspension of N,O-dimethylhydroxylamine hydrochloride (98 mg, 1.00 mmol) in 1 mL of benzene at 5 °C was added 1.05 mL (2.1
mmol) of 2 M trimethylaluminum in toluene. The reaction mixture was stirred for 2 h at rt, treated with a mixture of 49 (100 mg, 0.24 mmol) in 1 mL of benzene and stirred overnight. After being quenched with saturated sodium potassium tartrate solution, the reaction mixture was extracted with ether. The organic phase was washed with 1 M hydrochloric acid and saturated sodium bicarbonate solution, dried over MgSO₄, and concentrated. The residue was purified by chromatography (silica gel, elution with 80% ether in petroleum ether) to furnish 51 mg (44%) of 108 as a colorless oil; IR (film, cm⁻¹) 3490, 1645; ¹H NMR (300 MHz, CDCl₃) δ 7.60-7.57 (m, 4 H), 7.40-7.29 (m, 6 H), 3.46 (d, J = 9.9 Hz, 1 H), 3.40 (d, J = 9.9 Hz, 1 H), 3.29 (d, J = 4.6 Hz, 1 H), 3.01 (s, 3 H), 2.98-2.92 (m, 1 H), 2.88 (s, 3 H), 1.63 (ddd, J = 4.2, 10.4, 14.2 Hz, 1 H), 1.55-1.44 (series of m, 2 H), 1.06 (d, J = 6.7 Hz, 3 H), 1.00 (s, 9 H), 0.80 (s, 3 H), 0.77 (s, 3 H); ¹³C NMR (75 MHz, CDCl₃) ppm 177.4, 135.59 (2 C), 135.55 (2 C), 132.8, 132.7, 129.79, 129.75, 127.68 (4 C), 75.9, 72.8, 38.9, 37.1, 35.6, 35.50, 32.6, 26.8 (3 C), 21.9, 19.2, 19.1, 16.4.

Studies on Reduction of 49.

A. (2R,4R)-6-(tert-Butyldiphenyilsiloxy)-2,5,5-trimethyl-1,4-hexanediol (110) and (3R,5R)-2,2,5-Trimethyl-1,3,6-hexanetriol (111).

A solution of 68 mg (0.166 mmol) of lactone 49 in 5 mL of THF was treated with 6 mg (0.166 mmol) of lithium aluminum hydride at 0 °C. The reaction mixture was allowed to warm to rt over 1 h. Since TLC analysis revealed incomplete reduction, an additional 6 mg (0.166 mmol) of lithium aluminum hydride was added to the reaction mixture followed by brief (20 min) heating to reflux. The reaction mixture was quenched
with methanol, diluted with ether, and washed with 2 M hydrochloric acid. The combined organic phases were washed with saturated sodium bicarbonate solution, dried over MgSO₄, and concentrated. The products were separated by column chromatography (silica gel, gradient elution with 30-60% ether in petroleum ether) to provide 40 mg (58%) of 110 and 15 mg (21%) of 111.

For 110: colorless oil; IR (film, cm⁻¹) 3348; ¹H NMR (300 MHz, C₆D₆) δ 7.79-7.72 (m, 4 H), 7.24-7.20 (m, 6 H), 3.69 (dd, J = 1.3, 10.2 Hz, 1 H), 3.58 (d, J = 9.8 Hz, 1 H), 3.51 (d, J = 9.8 Hz, 1 H), 3.60-3.43 (m, 1 H), 3.36 (dd, J = 7.3, 10.6 Hz, 1 H), 1.89-1.84 (m, 1 H), 1.52-1.32 (m, 1 H), 1.29-1.27 (m, 1 H), 1.14 (s, 9 H), 0.89 (s, 3 H), 0.86 (d, J = 6.5 Hz, 3 H), 0.74 (s, 3 H) (OH protons not detected); ¹³C NMR (75 MHz, C₆D₆) ppm 136.1 (2 C), 136.0 (2 C), 133.5, 133.4, 130.2, 130.1, 128.1 (4 C), 76.7, 72.9, 68.9, 39.4, 37.3, 35.0, 27.0 (3 C), 21.9, 19.5, 19.4, 18.1; FAB MS m/z (M⁺+H) calcd 415.27, obsd 415.27; [α]D⁰ +16.6 (c 1.50, CHCl₃).


For 111: colorless oil; IR (film, cm⁻¹) 3331; ¹H NMR (300 MHz, CDCl₃) δ 5.00-4.00 (br, 3 H), 3.60-3.40 (series of m, 3 H), 3.41 (d, J = 10.6 Hz, 1 H), 3.33-3.26 (t, J = 9.0 Hz, 1 H), 1.82-1.71 (m, 1 H), 1.40 (t, J = 5.8 Hz, 2 H), 0.89 (d, J = 6.8 Hz, 3 H), 0.84 (s, 6 H); ¹³C NMR (75 MHz, CDCl₃) ppm 78.3, 72.2, 68.6, 38.1, 37.5, 34.6, 22.7, 18.6, 18.0; FAB MS m/z (M⁺+H) calcd 177.15, obsd 177.17; [α]D⁰ +45.5 (c 0.640, CHCl₃).


B. (2R,4R)-6-(tert-Butyldiphenylsiloxy)-2,5,5-trimethyl-1,4-hexanediol (110) and (3R,5R)-5-[2-(tert-Butyldiphenylsiloxy)-1,1-dimethylethyl]-tetrahydro-3-methyl-
2-furanol (112). A solution of lactone 49 (85 mg, 0.21 mmol) in 10 mL of THF was cooled to -78 °C and treated with 12 mg (0.83 mmol) of lithium aluminum hydride (added under nitrogen flow). The reaction mixture was allowed to warm to rt over 1 h, stirred for an additional 1.5 h, and quenched with methanol. With the predescribed workup followed by chromatography (silica gel, elution with 60% ether in hexanes), there was isolated 31 mg (36%) of 110 (see analytical data above) and 45 mg (52%) of 112.

For 112: colorless oil; IR (film, cm\(^{-1}\)) 3409; \(^1\)H NMR (300 MHz, C\(_6\)D\(_6\)) (major anomer) \(\delta\) 7.88-7.79 (m, 4 H), 7.30-7.25 (m, 6 H), 4.93 (m, 1 H), 4.26 (dd, \(J = 5.9, 10.3\) Hz, 1 H), 3.69 (d, \(J = 9.5\) Hz, 1 H), 3.61 (d, \(J = 9.5\) Hz, 1 H), 3.11 (br s, 1 H), 1.78-1.52 (m, 1 H), 1.28 (m, 1 H), 1.23 (s, 9 H), 1.15-1.00 (m, 1 H), 1.00-0.87 (2 singlets and a doublet - overlapping with minor anomer); \(^13\)C NMR (75 MHz, C\(_6\)D\(_6\)) ppm (136.2, 136.1, 4 C), (134.23, 134.10, 134.17, 2 C), 129.9 (4 C), 128.2 (2 C), (104.9, 98.8), (84.3, 82.2), (71.0, 70.9), (41.4, 39.5), (38.73, 38.66), (34.2, 31.8), 27.2 (3 C), 19.7, (21.3, 20.9), (19.9, 19.8), (17.5, 12.9); MS \(m/z\) (M\(^+\)-OH) calcd 395.2406, obsd 395.2438; [\(\alpha\)]\textsubscript{D}\(^{20}\) +1.3 (c 1.38, CHCl\(_3\)).

*Anal.* Calcd for C\(_{25}\)H\(_{36}\)O\(_3\)Si: C, 72.77; H, 8.79. Found: C, 72.84; H, 8.83.

C. Improved Synthesis of (3R,5R)-5-[2-(tert-Butyldiphenylsiloxy)-1,1-dimethylethyl]-tetrahydro-3-methyl-2-furanol (112). Lactone 49 (247 mg, 0.60 mmol) was dissolved in CH\(_2\)Cl\(_2\) (5 mL), cooled to -78 °C, treated with diisobutylaluminum hydride (0.72 mL of 1 M in CH\(_2\)Cl\(_2\), 0.72 mmol), stirred for 10 min,
quenched with saturated sodium potassium tartrate solution (2 mL), and partitioned between ether (10 mL) and water (10 mL). The aqueous phase was extracted with ether (3 x 10 mL) and the combined organic solutions were processed as described earlier. Passage through a short silica gel column (elution with 30% ether in hexanes) afforded 245 mg (99%) of 112 as a colorless oil (see analytical data above).

(3R,5R)-3-[(p-Methoxybenzyl)oxy]-2,2,5-trimethyl-6-heptenol (113).

A suspension of 465 mg (1.15 mmol) of methyltriphenylphosphonium iodide in 7 mL of toluene was treated at 0 °C with 2.3 mL (1.15 mmol) of KHMDS in toluene. The reaction mixture was stirred for 20 min, cooled to -78 °C, and treated with 316 mg (0.77 mmol) of lactol 112 in 3 mL of toluene. The reaction mixture was allowed to warm to rt over a period of 1 h and stirred for an additional 2 h before being poured into saturated ammonium chloride solution (20 mL) and extracted with ether (3 x 20 mL). The combined organic phases were washed with brine, dried over MgSO₄, and concentrated. The residue was purified by chromatography (silica gel, elution with 7% ether in petroleum ether) to furnish 294 mg (94%) of 113 as a colorless oil; IR (film, cm⁻¹) 3501; ¹H NMR (300 MHz, CDCl₃) δ 7.71-7.65 (m, 4 H), 7.48-7.37 (m, 6 H), 5.87 (ddd, J = 7.0, 10.3, 17.3 Hz, 1 H), 5.04 (dt, J = 1.6, 17.0 Hz, 1 H), 4.94 (ddd, J = 1.1, 1.8, 10.3 Hz, 1 H), 3.67 (d, J = 10.5 Hz, 1 H), 3.54 (d, J = 9.9 Hz, 1 H), 3.48 (d, J = 9.9 Hz, 1 H), 3.08 (br, 1 H), 2.51-2.47 (m, 1 H), 1.52 (ddd, J = 3.8, 9.9, 14.3 Hz, 1 H), 1.34-1.25 (m, 1 H), 1.09 (s, 9 H), 1.05 (d, J = 6.7 Hz, 3 H), 0.88 (s, 3 H), 0.85 (s, 3 H); ¹³C NMR (75 MHz, CDCl₃) ppm 145.7, 135.7 (2 C), 135.6 (2 C), 132.9, 132.8, 129.82, 129.78, 127.7 (4 C).
111.8, 75.7, 73.0, 38.9, 38.5, 34.1, 26.9 (3 C), 22.2, 19.2 (2 C), 18.6; MS m/z (M^-C_4H_9) calcd 353.1937, obsd 1353.1959; [α]^20_D +19.8 (c 2.65, CHCl_3)

Anal. Calcd for C_{26}H_{38}O_2Si: C, 76.04; H, 9.33. Found: C, 75.91; H, 9.33.

(αR,γR)-α-[2-(tert-Butyldiphenylsiloxy)-1,1-dimethylethyl]-γ-methyl-m-dithiane-2-propanol (114). A solution of 112 (78 mg, 0.19 mmol) and 1,3-propanedithiol (41 mg, 0.38 mmol) in benzene (2 mL) was treated with titanium tetrachloride (0.19 mL of 1.0 M in CH_2Cl_2, 0.19 mmol), stirred for 30 min, and diluted with ether (7 mL) and water (5 mL). The organic phase was washed with brine, dried, and evaporated to leave a residue which was purified by chromatography on silica gel (elution with 15% ether in petroleum ether) to give 89 mg (93%) of 114 as a colorless oil:

IR (film, cm^-1) 3500; ^1H NMR (300 MHz, CDCl_3) δ 7.71-7.63 (m, 4 H), 7.48-7.40 (m, 6 H), 4.20 (d, J = 3.9 Hz, 1 H), 3.59-3.49 (m, 1 H), 3.56 (d, J = 9.9 Hz, 1 H), 3.44 (d, J = 9.9 Hz, 1 H), 3.17 (br s, 1 H), 2.97-2.81 (m, 4 H), 2.37-2.28 (m, 1 H), 2.16-2.06 (m, 1 H), 1.93-1.78 (m, 1 H), 1.70 (ddd, J = 3.2, 11.1, 13.9 Hz, 1 H), 1.50-1.42 (m, 1 H), 1.13 (d, J = 6.8 Hz, 3 H), 1.07 (s, 9 H), 0.88 (s, 3 H), 0.86 (s, 3 H); ^13C NMR (75 MHz, CDCl_3) ppm 135.7 (2 C), 135.6 (2 C), 132.7, 132.6, 129.84, 129.80, 127.8 (4 C), 75.9, 73.0, 56.8, 38.9, 36.3, 35.0, 31.0, 30.8, 26.9 (3 C), 26.4, 22.4, 19.5, 19.1, 16.3; MS m/z (M^+) calcd 502.2395, obsd 502.2391; [α]^20_D +29.5 (c 1.47, CHCl_3).

Anal. Calcd for C_{28}H_{42}O_2S_2Si: C, 66.88; H, 8.42. Found: C, 66.79; H, 8.44.

tert-Butyl[(3R,S'R)-3-[(p-methoxybenzyl)oxy]-2,2,5-trimethyl-6-heptenyl]oxy]-diphenylsilane (115). A mixture of 196 mg (0.720 mmol) of 113 and 5 mL of ether
was sequentially treated with 0.090 mL (0.004 mmol) of 0.05 M triflic acid in ether and 407 mg (1.44 mmol) of \( p \)-methoxybenzyl trichloroacetimidate. The reaction mixture was stirred for 1 h, quenched with saturated sodium bicarbonate solution, and extracted with ether. The combined organic phases were washed with brine, dried over MgSO\(_4\), and concentrated. The residue was purified by chromatography (silica gel, gradient elution with 7-10\% ether in petroleum ether) to furnish 295 mg (77\%) of 115 as a colorless oil; IR (film, cm\(^{-1}\)) 1513, 1112, 1087; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.78-7.76 (m, 4 H), 7.24-7.20 (series of m, 8 H), 6.80 (d, \( J = 8.6 \) Hz, 2 H), 5.80 (ddd, \( J = 7.2, 10.1, 17.3 \) Hz, 1 H), 5.07-4.94 (series of m, 2 H), 4.62 (d, \( J = 11.0 \) Hz, 1 H), 4.53 (d, \( J = 11.0 \) Hz, 1 H), 3.77 (d, \( J = 9.5 \) Hz, 1 H), 3.67 (dd, \( J = 8.2, 3.0 \) Hz, 1 H), 3.50 (d, \( J = 9.5 \) Hz, 1 H), 3.34 (s, 3 H), 2.45-2.41 (m, 1 H), 1.76-1.68 (m, 1 H), 1.53-1.44 (m, 1 H), 1.21 (s, 9 H), 1.07 (d, \( J = 6.6 \) Hz, 3 H), 0.98 (s, 3 H), 0.95 (s, 3 H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) ppm 159.8, 145.9 (2 C), 136.5 (2 C), 134.4, 132.4 (2 C), 130.3 (4 C), 129.3 (4 C), 128.7 (2 C), 114.3, 112.8, 81.2, 74.3, 71.2, 55.1, 41.8, 38.8, 36.0, 27.7 (3 C), 22.5, 20.5, 20.2, 20.0; MS \( m/z \) (M\(^+\)) calcd 530.3345, obsd 530.3215; \([\alpha]\)\(^D\) +9.5 (c 1.00, CHCl\(_3\)).

*Anal.* Calcd for C\(_{34}\)H\(_{46}\)O\(_5\)Si: C, 76.93; H, 8.74. Found: C, 76.88; H, 8.52.

\((3R,5R)-5\text{-m-Dithian}-2\text{-yl}-2,2\text{-dimethyl}-1,3\text{-hexanediol} \) (117). A solution of 114 (188 mg, 0.37 mmol) in THF (5 mL) was reacted with tetra-\( n \)-butylammonium fluoride (0.45 mL of 1.0 M in THF, 0.45 mmol) as described earlier to give after chromatography (silica gel, gradient elution with 50-80\% ether in petroleum ether) 93 mg (94\%) of 117 as a colorless oil; IR (film, cm\(^{-1}\)) 3408; \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 4.19 (d, \( J = 3.9 \) Hz, 1 H), 3.58-3.42 (series of m, 3 H), 2.95-2.77 (series of m, 6 H), 2.23-
2.05 (m, 2 H), 1.90-1.75 (m, 1 H), 1.65 (ddd, = 3.8, 10.5, 14.0 Hz, 1 H), 1.49 (ddd, =
1.8, 9.8, 14.0 Hz, 1 H), 1.09 (d, = 6.8 Hz, 3 H), 0.87 (s, 3 H), 0.86 (s, 3 H); ^13^C NMR
(75 MHz, CDCl3) ppm 76.5, 71.8, 56.3, 38.2, 36.3, 35.1, 30.9, 30.6, 26.1, 22.4, 18.7.
16.3; FAB MS m/z (M^+H) calcd 265.13, obsd 265.11; [a]^D +27.8 (c 1.44, CHCl3).


(4R)-4-[2R)-2-m-Dithian-2-ylpropyl]-2-(p-methoxyphenyl)-5,5-dimethyl-m-
dioxane (118). A mixture of 117 (773 mg, 2.92 mmol), p-methoxybenzaldehyde (418
mg, 3.07 mmol), and camphorsulfonic acid (10 mg) was refluxed under a modified Dean-
Stark trap filled with 4Å molecular sieves for 6 h. The cooled reaction mixture was
concentrated and the residue was purified by chromatography on silica gel (elution with
15% ether in petroleum ether) to furnish 993 mg (89%) of 118 as a white solid, mp 144-
145 °C (from ether-hexanes); IR (CHCl3, cm⁻¹) 1615, 1249, 1106; ^1H NMR (300 MHz.
CDCl3) δ 7.42 (dm, = 8.7 Hz, 2 H), 6.88 (dm, = 8.7 Hz, 2 H), 5.41 (s, 1 H), 4.17 (d, =
3.8 Hz, 1 H), 3.80 (s, 3 H), 3.71 (d, = 11.0 Hz, 1 H), 3.58 (d, = 11.5 Hz, 1 H), 3.51
(dd, = 1.6, 10.7 Hz, 1 H), 2.94-2.80 (m, 4 H), 2.26-2.20 (m, 1 H), 2.08 (dm, = 13.6
Hz, 1 H), 1.87-1.73 (m, 2 H) 1.48 (ddd, = 1.7, 10.2, 13.9 Hz, 1 H), 1.13 (s, 3 H), 1.11
(d, = 6.9 Hz, 3 H), 0.76 (s, 3 H); ^13^C NMR (75 MHz, CDCl3) ppm 159.7, 131.3, 127.2
(2 C), 113.4 (2 C), 101.5, 82.5, 78.9, 56.4, 55.2, 34.5, 33.8, 32.6, 31.1, 30.7, 26.2, 21.3.
18.6, 16.1; MS m/z (M^+) calcd 382.1636, obsd 382.1647; [a]^D +29.6 (c 1.08, CHCl3).

(γR,εR)-γ-[(p-Methoxybenzyl)oxy]-β,β,ε-trimethyl-m-dithiane-2-pentanol (119). A cold (0 °C), magnetically stirred solution of 118 (106 mg, 0.277 mmol) in CH₂Cl₂ (2 mL) was treated with Dibal-H (0.42 mL of 1.0 M in hexanes, 0.42 mmol), stirred for 1 h at 0 °C and 30 min at rt, quenched with saturated sodium potassium tartrate solution (5 mL), and extracted with ether (3 x 20 mL). The combined organic layers were dried and concentrated, and the residue was purified chromatographically (silica gel, elution with 30% ether in petroleum ether) to give 119 (79 mg, 73%) as a white solid. mp 46 °C; IR (film, cm⁻¹) 3477, 1613; ¹H NMR (300 MHz, CDCl₃) δ 7.27 (dm, J = 8.5 Hz, 2 H), 6.86 (dm, J = 8.5 Hz, 2 H), 4.56 (s, 2 H), 4.14 (d, J = 3.8 Hz, 1 H), 3.78 (s, 3 H), 3.62 (d, J = 10.8 Hz, 1 H), 3.37 (dd, J = 1.8, 9.5 Hz, 1 H), 3.31 (d, J = 10.8 Hz, 1 H), 2.93-2.78 (m, 4 H), 2.70 (br s, 1 H), 2.17-2.04 (m, 2 H), 1.92-1.75 (m, 2 H), 1.52 (dd, J = 2.0, 10.5 Hz, 1 H), 1.11 (d, J = 6.8 Hz, 3 H), 1.02 (d, J = 3.8 Hz, 1 H), 0.85 (s, 3 H) ; ¹³C NMR (75 MHz, CDCl₃) ppm 159.2, 130.4, 129.3 (2 C), 113.8 (2 C), 84.5, 74.6, 70.4, 56.5, 55.2, 39.8, 36.3, 35.8, 31.0, 30.7, 26.2, 23.2, 20.8, 16.7 ; MS m/z (M⁺) calcd 384.1793, obsd 384.1762; [α]D²³ +7.0 (c 1.51, CHCl₃).


(βR,δR)-β-[(p-Methoxybenzyl)oxy]-α,α,δ-trimethyl-m-dithiane-2-valeraldehyde (fragment B). A solution of oxalyl chloride (0.136 mL, 1.56 mmol) in CH₂Cl₂ (3 mL) was cooled to -78 °C, treated dropwise with a solution of DMSO (244 mg, 3.12 mmol) in CH₂Cl₂ (1 mL), and stirred for 15 min in the cold prior to the dropwise addition of 119 (500 mg, 1.30 mmol) dissolved in CH₂Cl₂ (1 mL). After 15
min at this temperature, triethylamine (1.08 mL, 7.8 mmol) was introduced followed by warming to -40 °C during 40 min. The reaction mixture was poured into water, extracted with CH₂Cl₂, washed with brine, dried, and concentrated. The residue was chromatographed on silica gel (elution with 25% ether in petroleum ether) to furnish fragment B (428 mg, 86%) as a white solid, mp 63 °C; IR (film, cm⁻¹) 1724, 1612; ¹H NMR (300 MHz, CDCl₃) δ 9.62 (s, 1 H), 7.23 (dm, J = 8.7 Hz, 2 H), 6.86 (dm, J = 8.7 Hz, 2 H), 4.49 (s 2 H), 4.11 (d, J = 3.9 Hz, 1 H), 3.79 (s, 3 H), 3.61 (dd, J = 2.1. 9.7 Hz, 1 H), 2.92-2.87 (m, 4 H), 2.17-2.04 (m, 2 H), 1.91-1.77 (m, 2 H), 1.61-1.39 (m, 1 H), 1.13 (s, 3 H), 1.11 (d, J = 6.8 Hz, 3 H), 1.05 (s, 3 H); ¹³C NMR (75 MHz, CDCl₃) ppm 206.0, 159.2, 130.3, 129.2 (2 C), 113.8 (2 C), 80.8, 74.1, 56.2, 55.2, 51.2, 36.2, 35.5, 31.0, 30.7, 26.2, 19.4, 17.6, 16.6; FAB MS m/z (M⁺+H) calcd 383.17, obsd 383.25; [α]D⁻¹ -1.5 (c 0.88, CHCl₃).


(E)-3-(Tributylstannyl)-2-propenal (127). A mixture of 1.75 g (30.97 mmol) of propargyl alcohol, 11.72 g (40.27 mmol) of tributyltin hydride, 260 mg (1.6 mmol) of AIBN, and 40 mL of benzene was refluxed for 1 h, treated with an additional 260 mg (1.57 mmol) of AIBN, and refluxing was continued for an additional 1 h. The reaction mixture was cooled to rt, concentrated, and applied to the chromatographic column (silica gel, elution with 10% ether in petroleum ether) to furnish 6.98 g (65%) of (E)-3-(tributylstannyl)-2-propenol (126) together with 2.69 g (25%) of isomeric stannanes.

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Alcohol 126 (3.00 g, 8.64 mmol) was added to a premixture of 1.21 g (9.51 mmol) of oxalyl chloride, 1.62 g (20.74 mmol) of DMSO, and 30 mL of dichloromethane at -78 °C. The reaction mixture was stirred at this temperature for 15 min, treated with 6.00 mL (43.20 mmol) of triethylamine, and allowed to warm to -30 °C over 1 h prior to the aqueous quench. The aqueous layer was extracted with ether, the combined organic phases were washed with brine, dried over MgSO₄, and concentrated. The residue was passed through a layer of silica gel (elution with 5% ether in petroleum ether) to afford 2.79 g (93%) of 127 as a colorless oil.

**Ethyl (2E,4E)-5-(TributyIstannyl)-2,4-pentadienoate (131).** A solution of LDA in THF (1.74 mmol) was cooled to -60 °C, treated with triethyl phosphonoacetate (338 mg, 1.51 mmol), and allowed to warm to -40 °C at which point 127 (400 mg, 1.16 mmol) dissolved in THF (3 mL) was introduced. The reaction mixture was brought to rt during 2 h, diluted with an equal volume of ether, washed with water and brine, dried, and concentrated. Chromatographic purification of the residue on silica gel (elution with 1% ether in petroleum ether) furnished 340 mg (71%) of 131 as a colorless oil; IR (film, cm⁻¹) 1716, 1626; ¹H NMR (300 MHz, CDCl₃) δ 7.18 (dd, J = 10.0, 15.4 Hz, 1 H), 6.81 (d, J = 18.7 Hz, 1 H), 6.64 (dd, J = 10.0, 18.7 Hz, 1 H), 5.79 (d, J = 15.4 Hz, 1 H), 4.20 (q, J = 7.1 Hz, 2 H), 1.55-1.41 (m, 6 H), 1.36-1.24 (series of m, 9 H), 1.03-0.85 (series of m, 15 H); ¹³C NMR (75 MHz, CDCl₃) ppm 167.4, 147.2, 146.3, 144.2, 119.9, 60.2, 29.0 (3 C), 27.2 (3 C), 14.3, 13.6 (3 C), 9.6 (3 C); MS m/z (M⁺) calcd 416.1737, obsd 416.1693.
Dimethyl [(2E,4E)-5-(TributylstannyI)-2,4-pentadienyl]phosphonate (133). A solution of 131 (301 mg, 0.725 mmol) in THF (5 mL) was cooled to -78 °C and treated dropwise with Dibal-H (2.17 mL of 1 M in hexanes, 2.17 mmol). After 20 min, saturated sodium potassium tartrate solution was introduced, vigorous stirring was maintained for 2 h, and the separated aqueous layer was extracted with ether. The combined organic layers were dried and concentrated to leave a residue which was purified chromatographically (silica gel, elution with 25% ether in petroleum ether) to furnish 247 mg (91%) of the primary alcohol 132 as a colorless oil; IR (film, cm$^{-1}$) 3330; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 6.54 (dd, $J$ = 9.8, 18.7 Hz, 1 H), 6.28-6.19 (m, 2 H), 5.79 (dt, $J$ = 5.8, 15.4 Hz, 1 H), 4.19 (dt, $J$ = 0.9, 5.7 Hz, 2 H), 1.59-1.24 (series of m, 13 H), 0.98-0.77 (series of m, 15 H); $^{13}$C NMR (75 MHz, CDCl$_3$) ppm 145.9, 135.0, 134.6, 130.7, 63.3, 29.1 (3 C), 27.2 (3 C), 13.7 (3 C), 9.5 (3 C); MS m/z (M$^+$-C$_4$H$_9$) calcd 317.0927, obsd 317.0896.


A solution of alcohol 132 (911 mg, 2.44 mmol) and carbon tetrabromide (1.62 g, 4.88 mmol) in acetonitrile (10 mL) was treated with triphenylphosphine (1.28 g, 4.88 mmol) in portions during 30 min. The reaction mixture was poured into saturated NaHCO$_3$ solution (50 mL), extracted with a 1:10 mixture of ether and petroleum ether (2 x 50 mL), dried, and concentrated. The solid was rinsed with petroleum ether and the filtrate was concentrated prior to rapid elution through silica gel with 5% ether in petroleum ether. After solvent evaporation, there remained 957 mg (91%) of the bromide.
A solution of sodium dimethyl phosphite was prepared by the addition of dimethyl phosphite (660 mg, 6.00 mmol) to a suspension of sodium hydride (144 mg, 6.00 mmol) in dry THF (22 mL) and the mixture was warmed with a heat gun until a clear solution was obtained. The above bromide was dissolved in THF (5 mL), added to the anion solution, and stirred for 2 h during which time sodium bromide precipitated. The mixture was diluted with ether and water, and the organic phase was dried, concentrated and chromatographed on silica gel (elution with ether) to provide 491 mg (43% for 2 steps) of 133 as a colorless oil; IR (film, cm\(^{-1}\)) 1032; ¹H NMR (300 MHz, CDCl₃) δ 6.49 (dd, \(J = 9.8, 18.9\) Hz, 1 H), 6.22-6.10 (m, 2 H), 5.64-5.51 (m, 1 H), 3.75 (d, \(J = 10.8\) Hz, 6 H), 2.64 (ddd, \(J = 1.1, 7.6, 22.4\) Hz, 2 H), 1.52-1.40 (m, 6 H), 1.36-1.20 (m, 6 H), 1.00-0.15 (series of m, 15 H); ¹³C NMR (75 MHz, CDCl₃) ppm 145.8 (d, \(J = 4.3\) Hz), 138.5 (d, \(J = 14.6\) Hz), 134.4 (d, \(J = 3.9\) Hz), 120.4 (d, \(J = 12.3\) Hz), 52.7 (d, \(J = 7.1\) Hz, 2 C), 29.6 (d, \(J = 139.4\) Hz), 29.1 (3 C), 27.3 (3 C), 13.7 (3 C), 9.5 (3 C); MS \(m/z\) (M⁺-C₄H₉) calcd 409.0954, obsd 409.0989.

*Anal.* Calcd for C₁₉H₃₉O₃Psn: C, 49.06; H, 8.45. Found: C, 48.56; H, 8.36.

**Tributyl [(1E,3E,5E)-7-MethyH₃,5-octatrienyl]stannane (Fragment C).** A cold (-78 °C) solution of 133 (152 mg, 326 mmol) in dry THF (1 mL) was treated with \(n\)butyllithium (0.24 mL of 1.5 M in hexanes, 0.36 mmol), stirred for 5 min, and treated with isobutyraldehyde (24 mg, 0.33 mmol). After 10 min at -78 °C, the reaction mixture was placed in an ice bath for 30 min, diluted with ether, washed with water and brine, dried, and concentrated. The residue was chromatographed on silica gel (elution with petroleum ether) to provide Fragment C (83 mg, 62%) as a colorless oil; ¹H NMR (300 MHz, CDCl₃) δ 6.49 (dd, \(J = 9.8, 18.9\) Hz, 1 H), 6.22-6.10 (m, 2 H), 5.64-5.51 (m, 1 H), 3.75 (d, \(J = 10.8\) Hz, 6 H), 2.64 (ddd, \(J = 1.1, 7.6, 22.4\) Hz, 2 H), 1.52-1.40 (m, 6 H), 1.36-1.20 (m, 6 H), 1.00-0.15 (series of m, 15 H); ¹³C NMR (75 MHz, CDCl₃) ppm 145.8 (d, \(J = 4.3\) Hz), 138.5 (d, \(J = 14.6\) Hz), 134.4 (d, \(J = 3.9\) Hz), 120.4 (d, \(J = 12.3\) Hz), 52.7 (d, \(J = 7.1\) Hz, 2 C), 29.6 (d, \(J = 139.4\) Hz), 29.1 (3 C), 27.3 (3 C), 13.7 (3 C), 9.5 (3 C); MS \(m/z\) (M⁺-C₄H₉) calcd 409.0954, obsd 409.0989.
MHz, C6D6) δ 6.81 (ddd, J = 1.9, 7.2, 18.7 Hz, 1 H), 6.30-6.20 (m, 2 H), 6.05 (ddd, J =
1.0, 9.3, 15.3 Hz, 1 H), 5.61 (d, J = 6.9 Hz, 1 H), 5.59 (dd, J = 6.9, 15.0 Hz, 1 H), 2.24-
2.17 (m, 1 H), 1.63-1.51 (m, 6H), 1.50-1.27 (m, 6 H), 1.08-0.87 (series of m, 21 H); 13C
NMR (75 MHz, CDCl3) ppm 147.0, 142.9, 133.7, 133.4, 132.2, 127.4, 31.3, 29.1 (3 C),
27.3 (3 C), 22.3 (2 C), 13.7 (3 C), 9.6 (3 C); MS m/z (M+-C4H9) calcd 355.1448, obsd
355.1422.

(2R,4R,7E,9E,11E)-2-m-Dithiaii-2-yl-4-[(p-methoxybenzyl)oxy]-5,5,13-
trimethyl-7,9,11-tetradecatrien-6-ol (135). A solution of 134 (90 mg, 0.22 mmol) in
dry THF (0.7 mL) was cooled to -78 °C, treated dropwise with n-butyllithium in hexanes
(0.160 mL of 1.5 M, 0.24 mmol), allowed to warm to -40 °C during 70 min, and cooled
back to -78 °C. A solution of B (59 mg, 0.15 mmol) in THF (0.5 mL) was introduced via
cannula and the reaction mixture was allowed to warm to 0 °C, diluted with ether,
washed with water and brine, dried, and concentrated. The residue was passed down a
column of silica gel (elution with 30% ether in petroleum ether) to furnish 64 mg (83%)
of a 2:1 diastereomeric mixture of 135. Partial separation could be achieved by MPLC
(silica gel, elution with 10:1:14 dichloromethane-acetone-hexanes). For the major
alcohol: 1H NMR (300 MHz, CDCl3) δ 7.26 (dm, J = 8.6 Hz, 2 H), 6.86 (dm, J = 8.6
Hz, 2 H), 6.26-6.18 (m, 1 H), 6.17-6.15 (m, 2 H), 6.13-6.01 (m, 1 H), 5.98-5.62 (m, 2 H),
4.57 (s, 2 H), 4.19-4.16 (m, 1 H), 4.13 (d, J = 3.9 Hz, 1 H), 3.79 (s, 3 H), 3.64 (br s, 1 H),
3.39 (dd, J = 1.6, 9.5 Hz, 1 H), 2.88-2.80 (m, 4 H), 2.47-2.30 (m, 1 H), 2.15-1.75 (series
of m, 4 H), 1.68-1.55 (m, 1 H), 1.10 (d, J = 6.8 Hz, 3 H), 1.00 (s, 3 H), 0.99 (d, J = 6.7
Hz, 6 H), 0.81 (s, 3 H); 13C NMR (75 MHz, CDCl3) ppm 159.3, 142.4, 133.0, 132.2,
(2S,3R,4S,6S)-2-Allyl-6-[(tert-bulyldiphenylsiloxy)methyl]tetrahydro-3-methyl-2H-pyran-4-ol (148). A solution of 15.00 g (37.6 mmol) of lactone 57 in 200 mL of THF was treated at -78 °C with 112.9 mL (112.9 mmol) of 1 M allylmagnesium bromide in ether, stirred for 5 min, quenched with 100 mL of saturated ammonium chloride solution, and allowed to warm to rt. The product was extracted into ether (ca 50 mL of 1 M HCl was added to break the emulsion), the combined organic phases were washed with brine, dried over MgSO₄, and concentrated. The residue (ketal 146, yellow oil) was dried at high vacuum for 2 h.

The above product was admixed with 42.60 g (376.3 mmol) of triethylsilane and 200 mL of dichloromethane, cooled to -78 °C, and treated with 41.4 mL (41.4 mmol) of 1 M tin tetrachloride in dichloromethane. The reaction mixture was allowed to warm gradually to -20 °C over 80 min and quenched with 100 mL of water and 50 mL of 1 M HCl. The product was extracted into dichloromethane and ether. The combined organic phases were dried over MgSO₄ and concentrated, and the residue was purified by chromatography (silica gel, elution with 15% ether in petroleum ether) to furnish 11.43 g (71%) of 148 as a colorless oil; IR (film, cm⁻¹) 3355, 1113; ¹H NMR (300 MHz, CDCl₃) δ 7.72-7.66 (m, 4 H), 7.45-7.34 (m, 6 H), 6.00-5.87 (m, 1 H), 5.11-5.00 (m, 2 H), 3.76 (dd, J = 5.4, 10.3 Hz, 1 H), 3.61 (dd, J = 5.1, 10.3 Hz, 1 H), 3.55-3.47 (m, 1 H), 3.37 (td, J = 4.6, 10.4 Hz, 1 H), 3.06 (ddd, J = 3.0, 7.0, 9.9 Hz, 1 H), 2.44 (dm, J = 14.0 Hz, 1 H),
2.21 (m, 1 H), 2.04 (ddd, J = 1.9, 4.7, 12.3 Hz, 1 H), 1.51 (br, 1 H), 0.56-0.40 (m, 2 H), 1.06 (s, 9 H), 0.98 (d, J = 6.5 Hz, 3 H); $^{13}$C NMR (75 MHz, CDCl$_3$) ppm 135.7 (4 C), 135.7, 133.72 (2 C), 129.54 (2 C), 127.6 (4 C), 116.3, 80.4, 76.0 73.6, 66.9, 43.1, 37.6, 37.1, 26.8 (3 C), 19.3, 12.6; FAB MS m/z (M+H) calcld 425.25, obsd 425.19; $[^{21}\alpha]_D^{25.3}$ (c 0.79, CHCl$_3$).

Anal. Calcd for C$_{26}$H$_{36}$O$_3$Si: C, 73.54; H, 8.54. Found: C, 73.81; H, 8.59.

$[(2S',4S,5R,6S)-6-Allyl-4-(benzylxyloxy)tetrahydro-5-methyl-2H-pyran-2-
\text{yl)]methoxy}\text{-}^{\text{tert}}\text{-butyldiphenylsilane} (149)$. A suspension of 80% sodium hydride in mineral oil (2.40 g, 80.1 mmol) was placed in a 250 mL flask, washed once with 20 mL of THF and treated with a solution of 148 (11.33 g, 26.69 mmol) in 80 mL of THF followed by 12.0 g (80.1 mmol) of flame-dried sodium iodide. The reaction mixture was refluxed for 5 min, treated with 9.1 g (53 mmol) of benzyl bromide, and refluxed for an additional 20 min prior to cooling, dilution with 200 mL of ether, quenching with water, and extraction with ether. The combined organic layers were washed with brine, dried over MgSO$_4$ and concentrated. The residue was chromatographed (silica gel, gradient elution with 2-5% ether in petroleum ether) to furnish 11.93 g (87%) of 149 as a colorless oil; IR (film, cm$^{-1}$) 1454, 1428, 1113; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.78-7.69 (m, 4 H), 7.49-7.27 (m, 11 H), 6.00-5.89 (m, 1 H), 5.52-5.02 (m, 2 H), 4.68 (d, $J$ = 11.6 Hz, 1 H), 4.46 (d, $J$ = 11.6 Hz, 1 H), 3.80 (dd, $J$ = 5.5, 10.4 Hz, 1 H), 3.66 (dd, $J$ = 5.0, 10.4 Hz, 1 H), 3.52-3.43 (m, 1 H), 3.16 (td, $J$ = 6.0, 10.4 Hz, 1 H), 3.09 (ddd, $J$ = 2.9, 7.0, 9.9 Hz, 1 H), 2.46 (dm, $J$ = 12.0 Hz, 1 H), 2.29-2.17 (m, 2 H), 1.55-1.46 (m, 1 H), 1.31 (q, $J$ = 11.6 Hz, 1 H), 1.09 (s, 9 H), 0.99 (d, $J$ = 6.5 Hz, 3 H); $^{13}$C NMR (75 MHz, CDCl$_3$) ppm
138.7, 135.7 (4 C), 135.2, 133.8 (2 C), 129.6 (2 C), 128.3 (2 C), 127.7 (2 C), 127.6 (5 C), 116.2, 80.7, 80.4, 76.0, 70.4, 67.1, 41.1, 37.3, 33.5, 26.8 (3 C), 19.3, 13.0; MS m/z (M−C₄H₉) calcd 457.2199, obsd 457.2201; [α]D +34.0 (c 1.04, CHCl₃).

Anal. Calcd for C₃₃H₄₂O₅Si: C, 77.00; H, 8.22. Found: C, 77.18; H, 8.29.

(2S,4S,5R,6S)-6-Allyl-4-(benzyloxy)tetrahydro-5-methyl-2H-pyran-2-methanol (150). A solution of 10.96 g (21.29 mmol) of 149 in 80 mL of THF was treated with 31.90 mL (31.90 mmol) of 1 M solution of TBAF in THF. The reaction mixture was stirred for 1.5 h prior to dilution with ether and aqueous workup. Combined organic phases were dried over MgSO₄ and concentrated, and the residue was purified by column chromatography on silica gel (gradient elution with 20-40% ether in petroleum ether) to furnish 5.78 g (98%) of 150 as a colorless oil; IR (film, cm⁻¹) 3442, 1454, 1072; ¹H NMR (300 MHz, CDCl₃) δ 7.37-7.27 (m, 5 H), 5.96-5.82 (m, 1 H), 5.11-5.03 (m, 2 H), 4.66 (d, J = 11.5 Hz, 1 H), 4.43 (d, J = 11.5 Hz, 1 H), 3.63-3.53 (m, 2 H), 3.49-3.41 (m, 1 H), 3.22-3.08 (br m, 2 H), 2.47 (dm, J = 14.7 Hz, 1 H), 2.26-2.17 (m, 2 H), 2.03 (ddd, J = 1.9, 4.6, 12.3 Hz, 1 H), 1.76-1.42 (m, 1 H), 1.31 (q, J = 11.4 Hz, 1 H), 0.99 (d, J = 6.5 Hz, 3 H); ¹³C NMR (75 MHz, CDCl₃) ppm 138.5, 134.8, 128.4 (2 C), 127.7 (2 C), 127.6, 116.6, 80.5, 80.0, 75.6, 70.5, 66.0, 41.2, 37.2, 32.8, 12.9; MS m/z (M⁺) calcd 276.1725, obsd 276.1715; [α]D +75.41 (c 1.11, CHCl₃).

Anal. Calcd for C₁₇H₂₄O₃: C, 73.88; H, 8.75. Found: C, 73.62; H, 8.71.

(2S,3R,4S,6R)-2-Allyl-4-(benzyloxy)-6-iodomethyltetrahydro-3-methyl-2H-pyran (143). A solution of 1.00 g (3.62 mmol) of alcohol 150, 1.42 g (5.42 mmol) of triphenylphosphine, and 0.37 g (5.4 mmol) in imidazole in 50 mL of benzene was cooled
to 10 °C and treated with 1.38 g (5.42 mmol) of iodine (added in portions over 10 min) with vigorous magnetic stirring. The cooling bath was removed and stirring was continued for an additional 1.5 h, during which time an amorphous precipitate that originally deposited on the walls of the flask was being converted into a suspension. The reaction mixture was quenched with 10 mL of 25% aqueous solution of sodium thiosulfate, and the product was extracted into ether. The combined organic phases were washed with brine, dried over MgSO₄, and concentrated. Chromatographic purification of the residue on silica gel (elution with 3% ether in petroleum ether) afforded 1.31 g (94%) of 143 as a colorless oil; IR (film, cm⁻¹) 1354, 1074; ¹H NMR (300 MHz, CDCl₃) δ 7.36-7.27 (m, 5 H), 6.05-5.91 (m, 1 H), 5.12-5.04 (m, 2 H), 4.67 (d, J = 11.5 Hz, 1 H), 4.44 (d, J = 11.5 Hz, 1 H), 3.41-3.32 (m, 1 H), 3.24-3.06 (m, 4 H), 2.49-2.33 (m, 2 H), 2.27-2.18 (m, 1 H), 1.57-1.41 (m, 1 H), 1.26 (q, J = 11.4 Hz, 1 H), 0.98 (d, J = 6.5 Hz, 3 H); ¹³C NMR (75 MHz, CDCl₃) ppm 138.4, 135.0, 128.4 (2 C), 127.7 (2 C), 127.6, 116.4, 81.0, 79.9, 74.8, 70.6, 40.9, 37.2, 36.7, 12.8, 9.0; MS m/z (M⁺-C₃H₅) calcd 345.0351, obsd 345.0309; [α]D²⁰ +57.52 (c 1.33, CHCl₃).

Anal. Calcd for C₁₇H₂₃IO₂: C, 52.86; H, 6.00. Found: C, 52.65; H, 6.06.

(2S,3R,4S,6S)-2-Allyl-4-(benzyloxy)tetrahydro-3-methyl-6-[2-(phenylsulphonyl)ethyl]-2H-pyran (145). A solution of 5.074 g (32.5 mmol) of methyl phenyl sulfone in 70 mL of THF was cooled to -78 °C and treated with 21.0 mL (32.5 mmol) of a 1.5 M solution of n-butyllithium in hexanes. The reaction mixture was stirred for 25 min prior to the addition of 1.88 mL of HMPA and a solution of 4.183 g (10.83 mmol) of 143 in 70 mL of THF. The reaction mixture was allowed to warm to rt gradually and
stirred for an additional 8 h prior to aqueous workup and extraction with ether. The combined organic phases were dried and concentrated, and the residue was purified by chromatography (silica gel, elution with 30% ether in petroleum ether) to furnish 3.09 g (69%) of 145 as a white solid, mp 57 °C (from ether-petroleum ether); IR (film, cm⁻¹) 1450, 1357, 1305, 1137, 1075; ¹H NMR (300 MHz, CDCl₃) δ 7.97-7.89 (m, 2 H), 7.69-7.54 (m, 3 H), 7.38-7.27 (m, 5 H), 5.87-5.73 (m, 1 H), 5.06-4.99 (m, 2 H), 4.62 (d, J = 11.5 Hz, 1 H), 4.40 (d, J = 11.5 Hz, 1 H), 3.37-3.27 (m, 2 H), 3.21 (dd, J = 5.8, 9.9 Hz, 1 H), 3.17-3.04 (m, 1 H), 2.95 (ddd, J = 2.8, 7.6, 10.1 Hz, 1 H), 2.42-2.33 (m, 1 H), 2.16-1.99 (m, 2 H), 1.99-1.77 (m, 2 H), 1.46-1.32 (m, 1 H), 1.20 (q, J = 11.3 Hz, 1 H), 0.93 (d, J = 6.5 Hz, 3 H); ¹³C NMR (75 MHz, CDCl₃) ppm 139.2, 138.4, 135.0, 133.6, 129.3 (2 C), 128.4 (2 C), 128.0 (2 C), 127.7 (2 C), 127.6, 116.4, 80.6, 80.0, 72.9, 70.6, 52.8, 41.2. 37.2, 37.0, 29.2, 12.9; MS m/z (M⁺-C₃H₅) calcd 341.1575, obsd 341.1517; [α]D⁺51.2 (c 0.215, CHCl₃). 


Studies Involving Coupling of sulfone 145.

A. (4R,6R,8S)-1-[(2S,4S,5R,6S)-6-Allyl-4-(benzyloxy)tetrahydro-5-methyl-2H-pyran-2-yl]-9-(tert-butylidiphenylsiloxy)-6-[(p-methoxybenzyl)oxy]-4,7,7-trimethyl-2-(phenylsulfonyl)-8-(triethylsyloxy)-3-nonanol (154). A solution of 149 mg (0.36 mmol) of 145 in 2 mL of THF was cooled to −78 °C and treated with 0.32 mL (0.38 mmol) of a 1.2 M solution of n-butyllithium in hexanes. The yellow solution was stirred for 1 h prior to its addition via cannula to a precooled (-78 °C) solution of 198 mg (0.29 mmol) of aldehyde 153 in 2 mL of THF. The reaction mixture was stirred for an
additional 20 min and quenched with saturated ammonium chloride solution. The product was extracted into ether. The combined organic phases were washed with brine, dried, and concentrated. The residue was purified chromatographically (silica gel, elution with 25% ethyl acetate in hexanes) to provide 227 mg (71%) of 154 as an inseparable mixture of four diastereomers, together with 19 mg (10%) of unreacted 153 and 24 mg (16%) of unreacted 145.

B. (4R,6R,8S)-1-[(2S,4S,5R,6S)-6-Allyl-4-(benzyloxy)tetrahydro-5-methyl-2H-pyran-2-yl]-9-(tert-butyldiphenylsiloxy)-6-[(p-methoxybenzyl)oxy]-4,7,7-trimethyl-2-(phenylsulfonyl)-8-(triethylsiloxy)-3-nonanone (155). A solution of 70 mg (0.064 mmol) of 154 in 1.5 mL of dichloromethane was treated with 41 mg (0.096 mmol) of the Dess-Martin periodinane. The reaction mixture was stirred for 1 h (a white precipitate formed), diluted with 4 mL of dichloromethane, quenched with 2 mL of saturated sodium bicarbonate solution and 100 mg of solid sodium thiosulfate, and stirred for additional 20 min. The separated aqueous layer was extracted with ether. The combined organic phases were dried over MgSO₄ and concentrated. The residue was purified by chromatography on silica gel (elution with 20% ether in petroleum ether) to provide 64 mg (91%) of ketone 155 as a mixture of two diastereomers.

C. (4R,6R,8S)-1-[(2S,4S,5R,6S)-6-Allyl-4-(benzyloxy)tetrahydro-5-methyl-2H-pyran-2-yl]-9-(tert-butyldiphenylsiloxy)-8-hydroxy-6-[(p-methoxybenzyl)oxy]-4,7,7-trimethyl-2-(phenylsulfonyl)-3-nonanone. A solution of 113 mg (0.1033 mmol) of 155 in 2 mL of methanol was treated with 2 mL of 0.01 M solution of p-toluenesulfonic acid in methanol. The reaction mixture was stirred for 1 h, diluted with
10 mL of 1:1 ether-hexanes mixture, washed with 1 mL of saturated sodium bicarbonate solution, dried over MgSO₄ and concentrated. The residue was chromatographed (silica gel, elution with 20% ethyl acetate in hexanes) to afford 92 mg (91%) of 156 as a colorless oily mixture of two diastereomers; IR (film, cm⁻¹) 3530, 1111, 1072; ¹H NMR (300 MHz, CDCl₃) δ 7.75-7.60 (m, 6 H), 7.55-7.25 (m, 16 H), 6.91 and 6.81 (two d, J = 8.7 Hz, total 2 H), 5.75-5.62 (m, 1 H), 5.00-4.68 (m, 2 H), 4.67-4.53 (m, 3 H), 4.42 and 4.37 (two d, J = 11.6 Hz, total 1 H), 3.81 and 3.79 (two s, total 3 H), 3.78-3.53 (m, 3 H), 3.53-3.44 (m, 1 H), 3.20-3.07 (m, 1 H), 3.05-2.74 (m, 4 H), 2.35-2.26 (m, 1 H), 2.10-1.60 (m, 4 H), 1.35-1.07 (m, 6 H), 1.05 (s, 9 H), 1.02-0.64 (series of m, 11 H); ¹³C NMR (75 MHz, CDCl₃) ppm 205.6, 205.4, 159.0, 158.9, 138.4, 137.0, 136.9, 135.4, 136.9, 135.4, 134.5, 134.05, 134.0, 133.9, 133.0, 132.9, 132.8, 131.1, 130.9, 129.8, 129.7, 129.4, 129.1, 129.0, 128.9, 128.7, 128.6, 128.3, 127.7, 127.6, 127.58, 127.5, 116.9, 116.6, 113.8, 113.6, 81.9, 81.4, 80.2, 79.9, 79.8, 79.6, 75.7, 75.2, 74.4, 72.7, 70.9, 70.5, 70.3, 69.9, 69.6, 65.7, 64.9, 64.7, 55.15, 45.6, 44.7, 41.6, 41.5, 40.5, 40.3, 40.2, 37.1, 37.0, 36.9, 34.4, 33.6, 33.3, 32.6, 26.8, 19.8, 19.5, 19.3, 19.2, 19.1, 15.3, 15.2, 12.7, 122.6; FAB MS m/z (M⁺+H) calcd 975.49, obsd 975.78.
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10 The completion of the first total synthesis of polycavernoside A was announced recently: Murai, A. The Ohio State University Organic Chemistry Colloquium, 1998.


20 For additional synthetic work in this area, see Robarge, L. A.; Wardrop, D. J.; White, J. D. *Abstracts of Papers*, 213th National Meeting of the American Chemical Society, San Francisco, CA; American Chemical Society: Washington, DC, 1997: Abstract 557.


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APPENDIX

$^1$H NMR Spectra
100 = fragment A
fragment B
$\text{Bu}_3\text{Sn}$

$134 = \text{fragment C}$