with abstraction of C-4′ H of deoxyribose by Fe·BLM varied at individual positions within the same region of a DNA duplex, undoubtedly reflecting local variations in the facility of the rate-limiting step in BLM-mediated DNA degradation. While the present results do not suggest any effect of DNA methylation on the facility of formation of the putative C-4′ deoxyribose radical intermediate, they do reflect the same ability of BLM to alter parameters of its chemical behavior in a highly localized fashion in response to variations of substrate structure. Further, in contrast to the alteration in isotope effect at individual DNA nucleotide positions,[19] which would not be predicted to have any effect on product formation, DNA methylation clearly altered the ratio of chemical products formed at the methylated cytidine moiety in the substrate oligonucleotide.

It may be noted that the ability of BLM to mediate its therapeutic effects via DNA degradation is unquestionably affected by normal repair processes that occur in mammalian cells. While it is known that BLM-mediated DNA damage is subject to repair,[20] the facility of repair of strand breaks relative to that of alkali-labile lesions has not been studied. It would be interesting to determine whether, in addition to being somewhat less susceptible to BLM-mediated DNA damage,[6c,d] methylated DNA also affords a larger proportion of products amenable to repair.

Experimental Section

Materials. Blenoxane was obtained from Bristol Laboratories through the courtesy of Dr. William Bradner and was fractionated chromatographically to provide bleomycin A_2.[21] Deglycobleomycin A_2 was obtained by partial hydrolysis of bleomycin A_2.[22] The oligonucleotides used as substrates for BLM were prepared as described previously.[10]

General Methods. (A) Oligonucleotide Degradation Mediated by Fe(II)·BLM A_2. Reaction mixtures (50 μL total volume) were prepared containing 1 mM (nucleotide concentration) of the oligonucleotide to be studied, 50, 100, 200, or 400 μM BLM A_2, and an equimolar amount of $Fe^{II}(NH_4)_2(SO_4)_2$ in 50 mM sodium cacodylate buffer, pH 7.0. Reactions were initiated by the addition of Fe(II), incubated at 0 °C for 15 min, and analyzed by HPLC. Reactions that included both nonmethylated and methylated substrates were carried out as outlined above in the presence of 1.0 mM (nucleotide concentration) of each duplex substrate maintained at 0 °C and 200 μM Fe(II)·BLM. Reactions that employed deglyco-BLM A_2 (200 μM) were carried out as described above.

Dioxygen-purged oligonucleotide degradation reactions were carried out as described above with the addition of a 10-min purge of dioxygen gas before and during the addition of Fe(II), which initiated the reaction.

(B) HPLC Quantification of Oligonucleotide Cleavage Products. Oligonucleotide cleavage products were analyzed and quantitated on a Rainin Microsorb Short-One C-18, 3-μm column equipped with a Brownlee Laboratories HPLC analytical cartridge C-18 precolumn. The column was washed with 0.1 mM NH_4OAc, pH 6.8, at a flow rate of 1.6 mL/min. Products were detected by UV absorbance (A_{254}) with a Varian multiwavelength detector. Quantitation was carried out through the comparison of peak areas of reaction products to those of carefully purified synthetic standards. Product retention times (in minutes) were as follows: cytosine, 1.7; 5-methylcytosine, 3.9; 5′-dGMP, 4.4; $dCpGpCH_2COOH$, 7.8.

Reaction mixtures were analyzed additionally by gradient HPLC to effect the quantitation of base propenals formed. Analysis was carried out on an Alltech C-8 column, 5 μm, which was washed with a 100% H_2O to 25% acetonitrile linear gradient over a 25-min time period at a flow rate of 1.0 mL/min. Products were detected by UV absorbance (A_{300}); peaks were recorded and quantitated as described above. Retention times (in minutes) were as follows: cytosine propenal, 19.0; 5-methylcytosine propenal, 23.0. Also formed, albeit in very low yields, were the base propenals derived from deoxyadenosine and thymidine.[10]

Acknowledgment. We thank Dr. L.-T. Ma for assistance with the preparation of deglyco-BLM A_2 and Mr. David Killian for an authentic sample of 3-(5′-methylcytosin-1′-yl)propenal. This work was supported by PHS Research Grants CA 27603 and CA38544, awarded by the National Cancer Institute, DHHS.

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The Total Synthesis of (+)-Ionomycin

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Abstract: The total synthesis of (+)-ionomycin, a dibasic acid ionophore, is described by using a strategy that capitalizes on the chiron approach and on asymmetric processes. The C_1–C_{22} portion of ionomycin was constructed from smaller segments obtained in optically pure form by systematic functionalization and manipulation of chirons derived originally from L-glutamic acid. A key reaction in the synthesis of the deoxypropionate-containing segments relies on a novel sulfur-assisted organocuprate displacement of a secondary tosylate with complete inversion of configuration. The tetrahydrofuran segment of ionomycin was constructed from an optically pure epoxide obtained via a Sharpless asymmetric epoxidation and a sulfone derived from geraniol.

Since their discovery, the polyether class of antibiotics has commanded much interest on several scientific frontiers.[1,2] Their most fascinating biological function is the ability to chelate various inorganic cations and to transport them across lipid membranes, hence the term ionophore.[3] In view of their challenging structures and the presence of different stereochemical arrays of functional groups, this class of natural products has also been the subject of elegant synthetic[4] and biosynthetic studies.[5]

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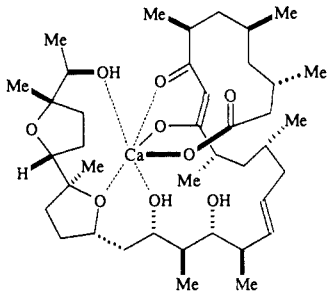


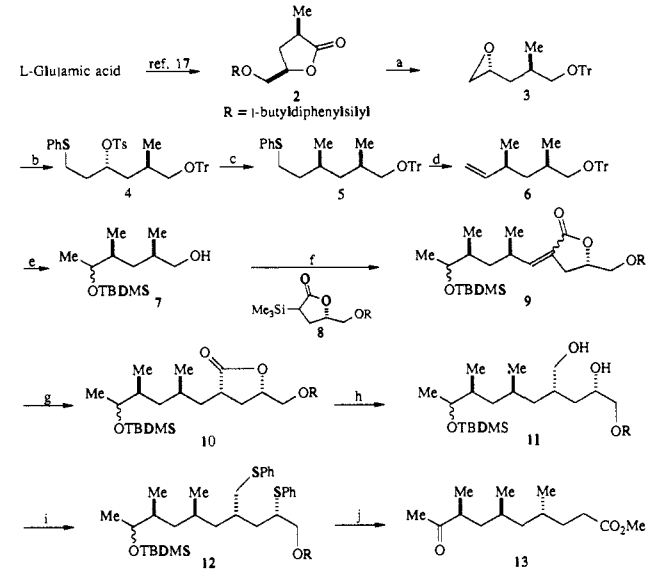
1, Ca Ionomycin

Figure 1. Perspective drawing of calcium ionomycin as reconstructed from its X-ray crystal structure (ref 7).

In 1978, a new polyether antibiotic was isolated from fermentation broths of *Streptomyces congoblatus* and called ionomycin.[6] Its structure, including absolute stereochemistry, was elucidated from elegant X-ray crystallographic and ^1H and ^{13}C NMR spectroscopic studies[7] (Figure 1). Ionomycin is endowed with unique features that distinguishes it from all other ionophores. Especially interesting is its ability to chelate calcium (and other divalent) ions as a *dibasic acid* in an octahedral coordination array, whereas other ionophores exert their chelating effects as monobasic acids.[1] Although ionomycin is not used in humans as a chemotherapeutic agent, it is an important tool in pharmacology because of its preferential binding to divalent cations such as calcium.[8]

The unusual structural features in ionomycin, as exemplified by the presence of a bis-tetrahydrofuran subunit and of stereoregular propionate and deoxypropionate-derived acyclic segments, have fostered imaginative approaches to their synthesis.[9-12] Continuing efforts in the Evans Laboratory have culminated with an impressive total synthesis of ionomycin.[13] In this paper, we report an account of our studies directed at the total synthesis of ionomycin by using a strategy that combines the merits of the chiron approach[14] as well as of asymmetric processes.[15]

Scheme I[a]



[a](a) 1. BH_3·Me_2S, THF, 18 h; 2. TrCl, NEt_3, catalyst DMAP, CH_2Cl_2, 6 h; 3. MsCl, NEt_3, CH_2Cl_2, 0 °C, 1 h; 4. Bu_4NF, THF, 18 h, then NaOMe, 0.5 h, 84% overall; (b) 1. PhSMe, DABCO, BuLi, THF, −78 °C → 0 °C, 18 h, 90%; 2. TsCl, Et_3N, DMAP, CH_2Cl_2, 18 h, 89%; (c) CuI, MeLi, ether, −78 °C → −20 °C, 18 h, ca. 90% (balance consists of ca. 10% elimination product); (d) 1. MCPBA, CH_2Cl_2, −20 °C, 2 h; 2. $CaCO_3$, decalin, reflux 56% overall; (e) 1. O_2, CuCl, $PdCl_2$, DMF–H_2O, 18 h, 85%; 2. L-Selectride, THF, −78 °C, 4 h, 90%; 3. *t*-$BuMe_2SiCl$, Et_3N, catalyst DMAP, CH_2Cl_2, 18 h; 4. excess Na, NH_3, −33 °C. 86% overall; (f) 1. ClCOCOCl, DMSO, CH_2Cl_2, −78 °C, 0.5 h, then excess NEt_3, 85%; 2. **8**, LiHMDS, THF, −78 °C → 0 °C, 18 h, 75%; (g) H_2, Rh–Al_2O_3, EtOAc, 95%; (h) BH_3·Me_2S, THF, 18 h, 88%; (i) Bu_3P, PhSSPh, THF, reflux, 8 h, 67% disulfide (29% of monosulfide); (j) 1. excess Raney-Ni, EtOH, 4 h; 2. excess aqueous HF, CH_3CN, 0 °C, 1 h, 78% overall; 3. Jones reagent, acetone, 0 °C; 0.5 h, then CH_2N_2, Et_2O, 71% overall.

Synthesis Plan. A cursory examination of the structural and stereochemical intricacies present in ionomycin reveals a number of challenges in synthesis design. The molecule consists of 32 backbone carbon atoms that comprise alternating C-methyl groups (C_1–C_{16}), a propionate-derived sequence (C_{17}–C_{22}), a bis-tetrahydrofuran subunit with two tertiary centers (C_{23}–C_{32}), a trans double bond, and a delicately balanced β-diketo system. Fourteen stereogenic centers on a quasi-linear backbone present another opportunity for testing the effectiveness of an overall synthesis strategy, where stereocontrolled C–C bond formation is at a premium, and optical purity is a primordial goal.

Figure 2 depicts ionomycin in a linear perspective, where the orientation of the C-methyl and hydroxyl groups reflect their biosynthetic origins as well as their sense of chirality. Our plan was to construct the backbond of the bis-tetrahydrofuran portion from an optically active epoxide and geraniol. The entire acyclic portion of ionomycin was envisaged to arise from four molecules of L-glutamic acid with one and two carbon atom "spacers" inserted at appropriate sites.

A previous report[16] from our laboratory described a synthesis of two acyclic segments of ionomycin comprising C_2–C_{10} and C_{11}–C_{22} from L-glutamic acid as a single chiral progenitor. However, in spite of its predictive value and its highly stereocontrolled nature, the approach was not ideally suited for the construction of deoxypropionate units since it required a deoxygenation step of propionate-type units that were inherent in the replication strategy[14,16-18] using butenolide templates.[19]

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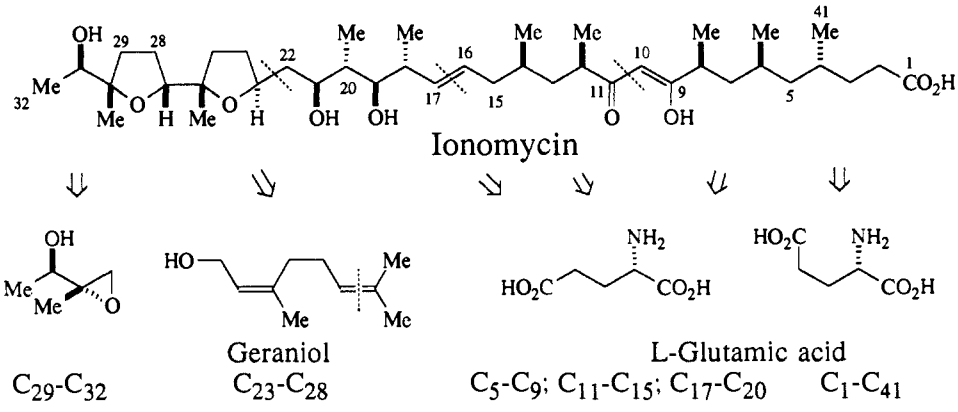

Figure 2. Disconnections of strategic bonds in ionomycin and the discovery of suitable precursors.

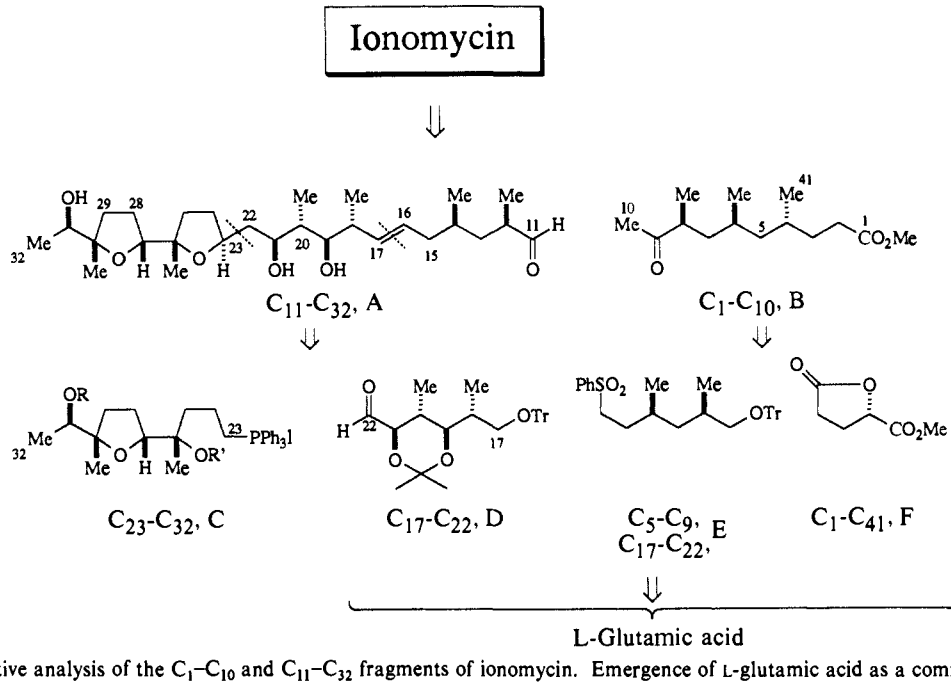

Figure 3. Disconnective analysis of the C_1–C_{10} and C_{11}–C_{32} fragments of ionomycin. Emergence of L-glutamic acid as a common progenitor to the C_1–C_{22} segment.

In contrast to the challenge in achieving the desired stereochemical arrays present in ionomycin, it is easy to recognize logical sites of strategic bond disconnections as depicted in Figures 2 and 3. Thus, disconnective analysis leads to the C_1–C_{10} and C_{11}–C_{32} segments A and B, which can be further simplified to the four subunits C–F, depicted in Figure 3.

With these in hand, it is clear that their assembly would rely on extensive methodology developed in the context of Wittig,[20] Julia,[21] and aldol-type[22] coupling reactions. Indeed, successful union of these and related subunits have already been demonstrated by Evans and Dow in their total synthesis of ionomycin.[13]

Synthesis of the C_1–C_{10} Segment. A previous synthesis of this segment by Evans and co-workers[9] was based on chiral enolate and directed hydrogenation processes proceeding with very high diastereoselection. Schreiber and Wang[12] have reported the synthesis of a C_1–C_9 equivalent to this segment by combining appropriate synthons with use of hydrazone anion methodology followed by stereochemical adjustments. Clearly, a major challenge is to introduce the alternating C-methyl triad on an appropriate carbon backbone with complete stereochemical control.

Our synthesis took advantage of the ready availability of the crystalline lactone **2**[17,23] in which the C-methyl group corresponds to one of the syn-orientated methyl groups in the intended subtarget (Scheme I). Of particular interest was the prospect of introducing a second C-methyl group at the ring oxygen-bearing carbon atom via a direct displacement of a nucleofugal group. In order to test this hypothesis as well as its stereochemical outcome, lactone **2** was transformed into the epoxide **3** by four conventional steps. Treatment with (phenylthiomethyl)lithium in the presence of DABCO[24,25] effected smooth ring opening to

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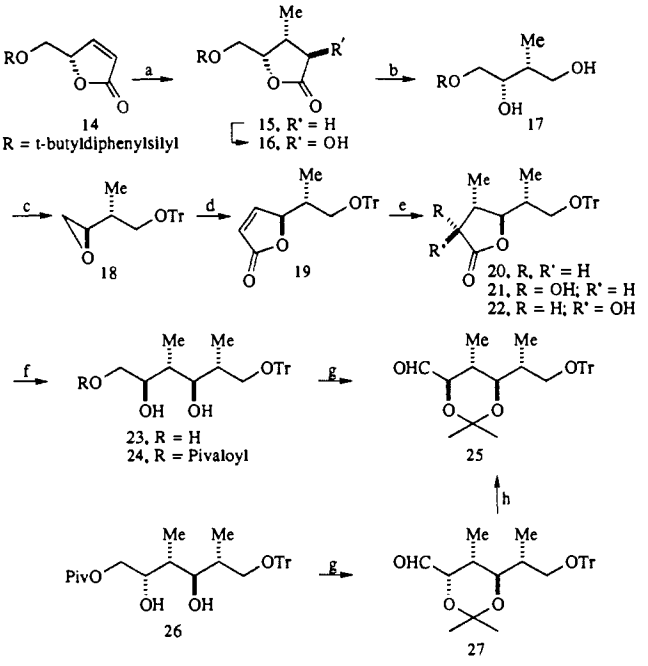
give the corresponding alcohol which was tosylated to afford **4** in excellent overall yield. Reaction with lithium dimethylcuprate[26] resulted in the introduction of the second C-methyl group *with complete inversion of configuration*[27] to give **5** in high yield, accompanied by ca. 10% of an elimination byproduct. The highly beneficial effect of the strategically placed thioether group in this reaction is evident, since elimination was a competitive process when the corresponding sulfoxide group was present, or when the sulfur atom was replaced by an alkyl chain.[28] Direct C–C bond formation with organocuprates and related reagents by displacement of halides and tosylates in synthetically useful substrates has remained largely unexploited,[29] probably due to modest yields and the propensity for elimination and/or reduction rather than substitution.[30] In this regard, the sulfur-assisted[31] direct introduction of C-methyl and other carbon substituents[28] from acyclic secondary tosylates is a most expedient way to construct deoxypropionate and related subunits.

The literature reports other methods for the synthesis of deoxypropionate-derived chirons similar to **5**, since the same motif is also present in many other natural products.[32] In the context of ionomycin, Weiler and co-workers[10b] have cleverly exploited carbohydrate templates in the stereocontrolled elaboration of pyranosidic intermediates containing an alternating 1,3-syn C-methyl substitution pattern.[33] Elaboration of the C_1–C_{10} subunit from **5** involved oxidative elimination of the thioether group to give the olefin **6**. Wacker oxidation,[34] followed by reduction of the resulting ketone, protection as the *tert*-butyldimethylsilyl ether, and detritylation led to **7** in good overall yield. Extension with concomitant introduction of the C-4 methyl equivalent was achieved via a Petersen olefination of the aldehyde derived from **7**, with the 2-trimethylsilyl lactone **8**, readily available from the corresponding lactone enolate. The mixture of *E* and *Z* exocyclic olefins **9** was hydrogenated over rhodium on alumina to produce lactone **10** (as a mixture of C-9 epimers). With the entire C_1–C_{10} carbon skeleton in hand, there now remained to effect adjustments of some functional groups. We had planned to change the oxidation states at C-2 and C-4 simultaneously through the intermediacy of the diol **11**. Treatment with diphenyl disulfide and tributylphosphine[35] led to the bis(phenylthio) ether **12**, (69%) accompanied by the primary thioether (29%) which could be easily separated and converted into **12** by the same procedure. Treatment with Raney-nickel effected smooth desulfurization and the formation of the expected dideoxy compound. There now remained the task of oxidizing this intermediate to the desired subtarget **13**. This was achieved uneventfully by desilylation followed by treatment with the Jones reagent and esterification. The physical and NMR spectroscopic properties of **13** were in excellent agreement with data kindly provided by Professor D. A. Evans.[9]

Thus, the C_1–C_{10} segment was constructed from two molecules of L-glutamic acid via the intermediacy of lactone **2**[17] and (phenylthio)methane as a one carbon synthon. The progeny of the C-methyl triad in **13** can be traced to the ω-carboxyl group of L-glutamic acid, to asymmetric methylation as in **2**, and to the sulfur-assisted lithium dimethylcuprate displacement in **4**. This protocol dramatically reduced the number of reaction steps in a previously published sequence in which L-glutamic acid was also utilized as a chiral template.[16]

The C_{17}–C_{22} Segment. This segment was previously prepared by Evans and Dow[13] through a highly stereocontrolled aldol condensation method utilizing a chiral crotylimide-derived boron enolate[36] and (*S*)-*O*-benzyl-2-methyl-3-hydroxypropionaldehyde. One of the methyl groups arose from the chiral aldehyde, while the other was produced during the asymmetric aldol coupling process. Our approach relies on a previously developed lactone replication protocol[14,17,18] in our laboratory, which permits the sequential introduction of C-methyl and hydroxyl groups on a butenolide template[19] (Scheme II).

Scheme II[a]



[a] (a) Reference 17; (b) 1. KHMDS, THF, MoOPH, −78 °C → −30 °C, 78%; 2. $NaBH_4$, aqueous THF, 98%; 3. $NaIO_4$, aqueous MeOH; then $NaBH_4$, 93%; (c) 1. TrCl, Et_3N, DMAP, CH_2Cl_2, 94%; 2. MsCl, Et_3N, CH_2Cl_2, then *n*-Bu_4NF, THF, 91%; (d) 1. $PhSeCH_2CO_2H$, BuLi; 2. EDAC·HCl, DMAP; 3. 30% H_2O_2, CH_2Cl_2, 75%; (e) 1. CuI, MeLi·LiBr, ether, −20 °C, 97%; 2. KHMDS, THF, −78 °C → −30 °C, MoOPH, 84%; (f) 1. $LiAlH_4$, THF, 93%; 2. pivaloyl chloride, pyridine, 88%; (g) 1. camphorsulfonic acid, acetone, 2,2-dimethoxypropane, 2 min; 2. $LiAlH_4$, THF, 75%; 3. oxalyl chloride, DMSO, CH_2Cl_2, −78 °C → −30 °C, 85%; (h) K_2CO_3, MeOH.

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Thus, the readily available (3*R*,4*S*)-3-methyl 5-hydroxymethylbutyrolactone derivative **15**[18] was treated with KHMDS, and the resulting enolate was oxidized by addition of oxodiperoxymolybdenum pyridine (hexamethylphosphoric triamide), (MoOPH),[37] following a previously established protocol.[17,18,38] In order to secure the correct stereochemical orientation of the desired propionate-type subunit, **16** was transformed into **17** which was selectively protected and converted to the epoxide **18**. Acetate extension and replication of the butenolide template was achieved as previously reported,[17,39] thus affording **19**. We were now poised to introduce the second C-methyl group which was done by conjugate addition[40] as for **15**. While an anti approach was virtually exclusive, thus giving the desired syn orientation of the alternating methyl groups as in **20**, the subsequent introduction of the hydroxyl group via reaction of the enolate with MoOPH led to a 1.7:1 mixture of C-2 epimeric alcohols. Unfortunately it was the minor isomer **21** that was needed for further elaboration into the C_{17}–C_{22} aldehyde subunit **25**. Reduction of the lactone **21**, protection of the primary alcohol as the pivalate ester, followed by acetal formation, deesterification, and Swern oxidation[41] gave the intended subunit **25** in a straightforward manner. The other isomer, **22**, was subjected to the same protocol to afford the thermodynamically less stable aldehyde **27** which could be easily equilibrated to the desired aldehyde **25**. A similar protocol had been previously employed by Evans and Dow[13] in their synthesis of this segment as the benzyl ether as well as by Stork and coworkers[42] in their synthesis of dihydroerythronolide seco ester, where equilibration involved a ketonic intermediate.

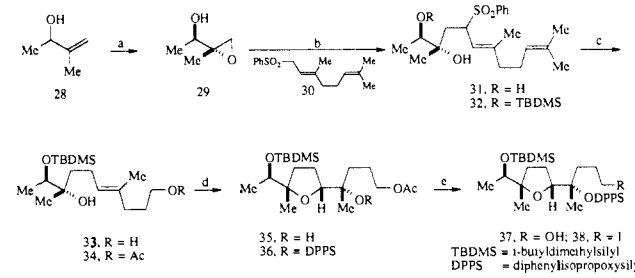
Exclusive formation of **22** could be achieved by conjugate addition of tris(tri(methylthio)methyl)lithium[43] to the butenolide **19**, followed by trapping the resulting enolate with MoOPH and reductive desulfurization in an overall yield of 50% from **19**.[18,44] In view of the higher individual yields in the cuprate MoOPH sequence, we chose to adopt it since the minor isomer could be processed through to **25** directly.

The Tetrahydrofuran Segment, C_{23}–C_{32}. Three independent routes to the tetrahydrofuran segment in ionomycin have been reported. Evans and Shih[45] have utilized an epoxidation–cyclization sequence of a bis-homoallylic alcohol to construct this segment. Although a 1:1 mixture of cyclization products was obtained, the process was useful for further studies because of the high yield and the facile separation of the isomers. Wuts and co-workers[11] utilized geraniol acetate as a source of the carbon skeleton of the tetrahydrofuran segment and exploited the original Sharpless asymmetric epoxidation[46] to introduce chirality, followed by functional group adjustments. Finally, Spino and Weiler[10c] applied a stereocontrolled permanganate induced cyclization[47] of a ten-carbon *Z*,*Z*-dienic ester. Optically pure product was obtained by separation of *O*-acetyl-(*S*)-mandelate esters.

Our approach was based on the coupling of the epoxide **29**, with a nucleophilic specie derived from geraniol (Figure 2), and subsequent stereocontrolled tetrahydrofuran formation via an epoxidation–cyclization sequence. The epoxide **29** was readily prepared by the catalytic version of the Sharpless asymmetric epoxidation[48] of (*R*,*S*)-3-methyl-3-buten-2-ol (**28**), with a kinetic resolution protocol. The optical purity of **29** was estimated to be at least 95% by ^{1}H NMR analysis of the corresponding Mosher ester.[49] Our plan was to effect the opening of the epoxide ring in **29** with a nucleophilic specie derived from geraniol and to ultimately cleave the terminal 2-methylpropenyl appendage, thus giving us the required C_{23}–C_{32} carbon skeleton. Initial attempts to effect such a ring opening with a CuI-catalyzed Grignard reaction using geranyl magnesium bromide led to the expected product in only 48% yield. Curiously, the reaction failed with the Grignard reagent derived from 1-bromo-3-methyl-6-[(triphenylmethyl)oxy]-3-methyl-2*E*-hexene which can be easily prepared by selective ozonolysis of geranyl acetate.[50] Since the corresponding trityl and TBDMS ethers also failed to react, we ascribe this behavior to the presence of the ω-oxygen atom which must adversely coordinate with the organomagnesium component of the reagent.

Attention was then turned to the use of the sulfone anion derived from geraniol[25,51] as the nucleophilic component. Treatment of the epoxide **29** with the lithium anion of the sulfone **30** in the presence of 1 equiv of ethyl magnesium bromide according to Marshall and Andrews[25,52] resulted in a smooth ring opening to give a mixture of diastereomeric sulfones **31**, A and B in 41 and 30% yield, respectively.[53] These were individually protected as the corresponding TBDMS ethers **32**, A and B using *tert*-butyldimethylsilyl trifluoromethanesulfonate[54] (Scheme III). Interestingly, the Grignard-activated opening of epoxide **29** with the lithium anion generated from 3-methyl-1-(phenylsulfonyl)-6-[(triphenylmethyl)oxy]-2*E*-hexene gave very poor yields of the expected product. The terminal double bond in **32** was selectively cleaved with ozone, and the resulting aldehyde was reduced to the corresponding primary alcohol. Our initial plan was to reductively desulfonylate the above mixture of sulfones. Numerous

Scheme III[a]



[a] (a) (D)-Diisopropyl tartrate, $Ti(OiPr)_4$, TBHP, CH_2Cl_2, 4 Å sieves, −20 °C, 30 h, then, Me_2S, −20 °C, 62% based on *R*-alcohol; (b) 1. EtMgBr, THF, then add Li anion of **30**, THF–HMPA, −78 °C → −25 °C, 18 h, 71%; 2. *t*-$BuMe_2SiOTFl$, lutidine, CH_2Cl_2, 0 °C, 1 h, 84%; (c) 1. O_3, then excess $NaBH_4$, MeOH, −78 °C → −25 °C, 3 h, 87%; 2. Ac_2O, Et_3N, catalyst DMAP, CH_2Cl_2, 0 °C, 0.5 h, 62% overall; 3. Na liquid NH_3, −33 °C, 69% of **33**, **34**; (d) 1. *t*-BuOOH, $VO(acac)_2$, 3 Å sieves, hexanes, 24 h, 70% (9:1 mixture); 2. Ph_2-*i*-PrOSiCl, Et_3N, DMAP, CH_2Cl_2, 20 h, 94%; (e) 1. $LiAlH_4$, ether, −25 °C, 20 min, 86%; 2. PPh_3, imidazole, I_2, CH_2Cl_2, 91%.

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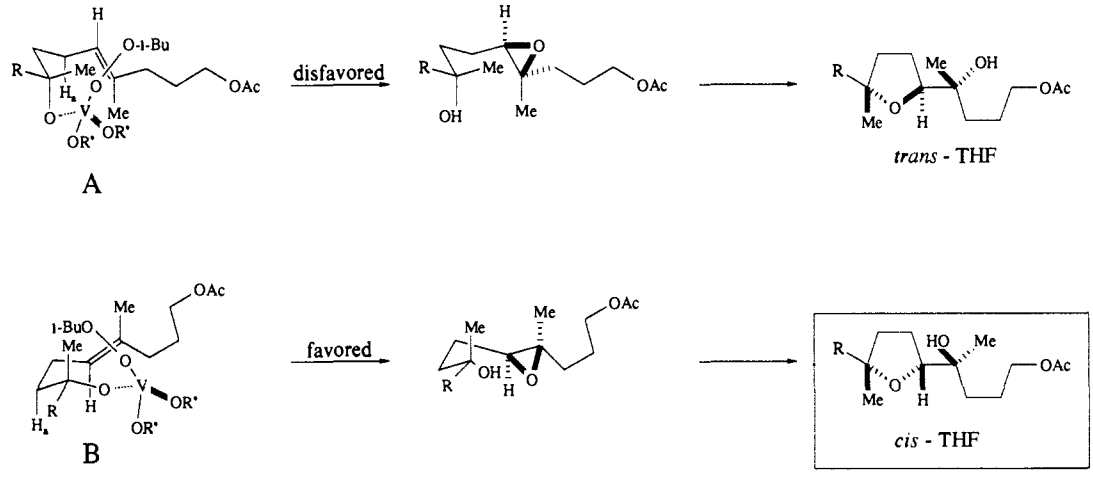

Figure 4. Proposed intermediates for the formation of *cis*- and *trans*-tetrahydrofuran subunits during the $VO(acac)_2$-catalyzed epoxidation of **34**.

attempts with sodium amalgam,[21] in a variety of solvent mixtures, led to mixtures of desulfonylated olefins as a result of concomitant migration of the trisubstituted double bond. Desulfonylation could be cleanly done with sodium in liquid ammonia,[55] where a mixture of **33** and the acetate **34**[56] was obtained in a combined yield of 69%. Trace amounts of isomerized olefinic byproducts were also formed and easily separated by chromatography. Having thus achieved the synthesis of the C_{23}–C_{32} backbone structure, we were now poised to try the epoxidation–cyclization reaction.

Among the several critical issues that had to be addressed in this transformation were the necessity to form a cis-disubstituted tetrahydrofuran, the reactivity of the tertiary hydroxyl group, and the stereoselectivity of the epoxidation reaction. After exploring a number of epoxidation conditions with little or no selectivity, we initiated a systematic study with vanadyl acetylacetonate, $VO(acac)_2$/*tert*-butyl hydroperoxide.[57] In their elegant studies of the total synthesis of lasalocid, Kishi, and co-workers[58] had investigated the $VO(acac)_2$-catalyzed tetrahydrofuran formation from a secondary bis-homoallylic alcohol and a trisubstituted olefin. The preponderant (>20:1) formation of a trans-substituted product was rationalized on the basis of a preferred transition-state model, where $A^{1,3}$ strain was minimized en route to the observed major isomer. Wuts and co-workers[11] had also explored the use of a $VO(acac)_2$-catalyzed epoxidation–cyclization route to the tetrahydrofuran subunit of ionomycin, in an intermediate in which the hydroxyl group was secondary. A 20:1 mixture of the wrong isomer was produced, thus forcing them to adopt the Sharpless asymmetric epoxidation protocol[46] as a means of ensuring the stereochemistry of the epoxide, prior to tetrahydrofuran formation.

Our model studies utilized racemic **33** (R = trityl, pivaloyl, acetyl) with variations in solvent and temperature in the presence of $VO(acac)_2$, *t*-BuOOH, and 4Å molecular sieves, followed by treatment with acetic acid. In each instance the mixture of cyclized products was isolated and carefully analyzed by ^1H NMR and detailed NOE measurements. In dichloromethane, benzene, or toluene the cis/trans ratio was consistently 4–5:1 with yields of ~70–80%. The best stereoselectivity was found with the acetate ester using hexanes as solvent, where a 9:1 cis/trans mixture was obtained. Applying these conditions to the optically pure ester **34**, led to the desired *cis*-tetrahydrofuran isomer **35** in 70% yield (9:1 cis/trans mixture). The cis isomer could be obtained pure after protection of the tertiary alcohol as in **36** and deacetylation.

We can rationalize the formation of the *cis*-tetrahydrofuran in the $VO(acac)_2$-catalyzed epoxidation based on the original Kishi model,[58] as illustrated in Figure 4. Thus, transition state A which ultimately leads to the minor trans isomer can experience steric compression between the vinylic methyl group and the tertiary oxygen bound to the catalyst. In transition state B steric compression is minimized, hence the favored formation of the cis isomer **35**. It is of interest that the observed selectivity is solvent dependent, being at its best in a noncoordinating solvent such as hexanes even when the protective group on the primary carbon atom was changed (trityl, pivaloyl). No improvement in selectivity was observed at 0 °C, and the yield was significantly reduced.

Having successfully constructed the cis-disubstituted tetrahydrofuran segment with the required stereochemistry and the proper complement of functionality, we next addressed the linear appendage of the remaining subunits and the formation of the second tetrahydrofuran ring. In this case a trans ring junction was required, and, following our original plan, we envisaged a hydroxyl-initiated cyclization from an olefin, via electrophilic activation. Inspection of molecular models as well as consideration of previously published studies[4n,13] and the likely involvement of steric and stereoelectronic effects[59] imposed by the acetalic appendage prompted us to attempt an oxymercurycyclization reaction with a *Z* olefin. Although tetrahydrofuran and tetrahydropyran formation by electrophilic activation of hydroxy olefins has ample precedents,[60] those involving mercuric II salts (oxymercurycyclization) are not as numerous, and, with few exceptions,[13,45] they involve secondary hydroxyl groups.[61,62] In order to ensure the *Z* geometry of the olefin we chose to effect a Wittig reaction of the aldehyde **25**, with the phosphonium ylid generated from **39** under so-called salt-free conditions.[20,63] We found it imperative to rigorously dry the iodide **38** as well as the phosphonium iodide **39** before use, the latter being particularly sensitive to moisture. Furthermore, an optimum ratio of 1:1.7 of **25**:**39** was found best for the coupling reaction. Employing these conditions, the olefin **40** could be isolated in 91% yield, and it consisted of >95% of the *Z* isomer as determined by high field ^1H NMR and ^{13}C NMR

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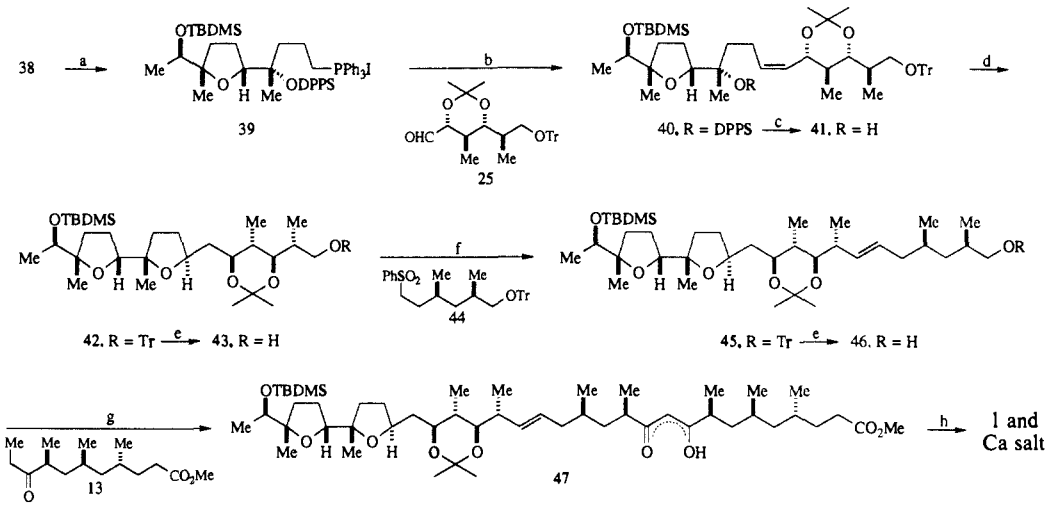
Scheme IV[a]



[a](a) Ph_3P, *i*-Pr_2NEt, CH_3CN, 90 °C, 20 h, 94%; (b) NaHMDS, THF, −78 °C, 15 min then **25**, −78 °C → 25 °C, 18 h, 3 h, 91%; (c) Bu_4NF, THF, 1.5 h, 72% (+14% diol); (d) $Hg(CF_3CO_2)_2$, THF, 0 °C, 2 h then excess $NaBH_4$–aqueous NaOH, 0 °C, 5 min, 81%; (e) excess Na, NH_3–THF, −33 °C, 15 min then EtOH, 87%; (f) 1. ClCOCOCl, DMSO, CH_2Cl_2, −78 °C, 0.5 h, then Et_3N, 90%; 2. **44**, BuLi, THF, −78 °C, 1 h, then Ac_2O, −78 °C → 25 °C, 4 h; 3. excess Na–Hg, EtOAc–MeOH, −50 °C → −30 °C, 17 h, 52% overall (13:1 trans/cis mixture); 4. excess Na, NH_3–THF, −33 °C, 15 min then EtOH, 87%; (g) 1. ClCOCOCl, DMSO, CH_2Cl_2 −78 °C, 0.5 h then excess Et_3N; 91%; 2. ref 13, **13**, Bu_2BOTFl, *i*-Pr_2NEt, CH_2Cl_2, −78 °C, add aldehyde derived from **46** → 0 °C, 3 h, then excess aqueous H_2O_2–MeOH, 0 °C, 1 h; 3. excess CrO_3–Py (1:2) on Celite, CH_2Cl_2, 10 min, 66% overall; (h) 1. excess aqueous HF, CH_3CN, 1 h, 77%; 2. excess aqueous LiOH, DME, 1 h; 3. excess $CaCl_2$ in pH 9.7 buffer solution (*N*,*N*-dimethylglycine·HCl–Me_4NOH), CH_2Cl_2, 2-phase system, 6 h, 77% overall.

analysis (Scheme IV). Employing different protective groups, Evans and Shih[45] had also prepared the same olefin in 98% olefin purity.

It is at this point that one could appreciate the availability of different protective groups and our choice in using the diphenyl isopropoxysilyl ether group (DPPS)[64] for the tertiary hydroxyl group, soon to be needed for the cyclization reaction. The DPPS group could be selectively cleaved to **41** in 72% yield in the presence of tetra-*n*-butylammonium fluoride.[65] The small quantity of diol (14%) formed by concomitant cleavage of the TBDMS ether could be converted to **41** by treatment with *tert*-butyldimethylsilyl trifluoromethanesulfonate.[54]

In order to find the best conditions for cyclization, we initially tried mercuric acetate in aqueous THF on a model *Z* olefin identical with **41** except for the absence of the *syn*-dimethyl groups. Reductive demercuration and detailed NMR analysis including NOE measurements revealed the presence of a 4:1 mixture of *trans*/*cis*-tetrahydrofuran ring products (64% yield). However, difficulties associated with the reduction step compelled us to use mercuric trifluoroacetate[62,66] in the case of the olefin **41**. After reductive demercuration[67] of the intermediate trifluoroacetoxymercurial, we could isolate the desired trans isomer **42** in 81% yield, contaminated with ≤5% of the cis isomer. The much higher selectivity compared to the des-dimethyl model analogue indicates the importance of substituents and their orientation in the cyclization of the trifluoroacetoxymercurinium ion intermediate[68] produced during the reaction, as previously noted by Evans and co-workers[13,45] using mercuric acetate.

The Final Stages—Julia and Aldol Couplings. In spite of the very high level of sophistication in currently recorded synthetic accomplishments,[69] one of the major challenges in natural product synthesis still remains in the final assembly of appropriately functionalized segments. It is at this level, that major problems usually arise to the point of seriously hampering further progress toward the final conquest of the target molecule. In most instances, these difficulties are caused by functional group and protective group incompatibilities, by unexpected reactions, and more importantly by the type of the bond-forming process chosen in the initial synthesis plan. Although there is a plethora of synthetic methods applicable to "small" subunit chemistry, the choices for uniting "larger" pieces in a linear manifold are indeed limited. Sulfone anion (Julia) coupling,[21] phosphonate anion or ylid (Wittig–Horner–Emmons, Wittig) reactions,[20] and aldol condensations[22] are among the most commonly used in *acyclic subunit* assembly.[70] Interestingly all three types of reactions were part of our original assembly plan for ionomycin as well as that reported by Evans and Dow.[13]

We envisaged a Julia-type coupling between the sulfone anion generated from **44** and the aldehyde derived from **43** based on previous experience in our laboratory,[17] numerous literature precedents,[71] and a similar coupling in the Evans and Dow synthesis.[13] This condensation proceeded uneventfully to produce a mixture of β-hydroxysulfones which was acetylated, and the product was subjected to elimination with sodium amalgam.[21] The

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coupled product **45** was obtained in 52% overall yield, and it consisted of a 13:1 mixture of *E* and *Z* isomers as estimated by high field ^{1}H NMR analysis. Upon detritylation, these were easily separated by column chromatography to give the desired major isomer **46** in 81% yield.

The stage was now set for the aldol coupling between the C_1–C_{10} (segment B) and the aldehyde derived from **46** (segment A). Although the stereochemical outcome of the aldol reaction was not an issue here, there was reason to critically evaluate various conditions for effecting this coupling in view of the nature of the expected product. A number of model studies were initiated based on the intermediacy of tin(II) enolates patterned after Mukaiyama.[72] Unfortunately these were either low yielding or unsatisfactory when benzaldehyde and methyl 4-keptopentanoate were used as reacting partners. By using boron enolates[73] derived from the same keto ester and condensation with DL-2-methyl-4,5-di-*O*-[(*tert*-butyldiphenylsilyl)oxy]pentanal, a 73% yield of the corresponding β-keto alcohol was produced. Encouraged by these results, we proceeded with the aldol coupling following a protocol already developed in the Evans and Dow coupling of **13** and the aldehyde derived from **46**.[13] The diastereomeric mixture of alcohols **47** obtained after a Collins oxidation was then converted into ionomycin essentially according to the Dow procedure.[13] Ionomycin was thus isolated as the crystalline calcium salt, and it was found to be identical in all respects with a commercial sample.

Experimental Section

Melting points and boiling points are uncorrected. ^{1}H NMR spectra were recorded on 300 MHz Varian or 400 MHz Bruker spectrometers in $CDCl_3$ with TMS (0δ) or $CHCl_3$ (7.265 δ) as reference. ^{13}C NMR spectra were recorded at 75 MHz in $CDCl_3$ with $CHCl_3$ as reference at δ = 76.90. DEPT and H-correlation measurements were routinely performed. IR spectra were recorded on a Perkin-Elmer 781 spectrophotometer with KBr pellets or as films. Mass spectra were recorded on a Kratos MS-50 spectrometer by using electron impact (EI) at 70 eV, chemical ionization (CI), or by the fast atom bombardment (FAB) techniques. Low-resolution mass spectra were recorded on a VG-1212 mass spectrometer. Optical rotations were measured at the sodium line with a Perkin-Elmer Model 241 spectropolarimeter. Usual processing of reaction mixtures signifies drying the organic solvent after extraction of the product from a water solution, over anhydrous magnesium sulfate, filtration, and evaporation under reduced pressure. Flash column chromatography was done according to Still and co-workers.[74]

(2*R*,4*R*)-1,2-Epoxy-4-methyl-5-(triphenylmethoxy)pentane (3). A solution of 7.7 g (20.89 mmol) of lactone **2** in 30 mL of dry THF was treated with 31.3 mL of (62.6 mmol) 2 M BH_3·Me_2S. The clear solution was stirred overnight and then quenched with methanol. The solution was concentrated to an oil which was purified by flash column chromatography (30% EtOAc–hexanes) affording 7.1 g (91%) of the corresponding diol as a clear oil: $[\alpha]^{25}_D$ 4.1° (*c* 1.1, $CHCl_3$). A solution of the diol (2.25 g, 24.8 mmol) in 30 mL of dichloromethane was treated with trityl chloride (8.98 g, 32.2 mmol) and a catalytic amount of DMAP. After conventional workup and chromatography, the trityl ether was obtained as an oil (14.38 g): $[\alpha]^{25}_D$ 0.64° (*c* 1.41, $CHCl_3$).

Tosylation in the usual way afforded a product which was treated with *n*-Bu_4NF in THF (45 mL, 1 M solution). After stirring overnight, 2 mL of a 30% solution of sodium methoxide in methanol was added, followed by water. Conventional processing, followed by flash column chromatography (4% EtOAc–hexanes) gave 7.71 g (92%) of **3** as a clear oil: $[\alpha]^{25}_D$ 4.1° (*c* 2.8, $CHCl_3$); ^{1}H NMR (300 MHz) δ 1.03 (d, *J* = 7 Hz, Me), 1.3–1.5 (m, CH_2), 1.7–1.8 (m, CH_2), 1.95–2.1 (m, CH), 2.42 (dd, *J* = 5 Hz, *J* = 2.7 Hz, CH_2, epoxide), 2.73 (s, *J* = 5 Hz, CH_2, epoxide), 2.85–2.94 (m, CH epoxide), 3.48 (d, *J* = 7.5 Hz, CH_2OTr), 7.21–7.46 (m, Ar-H); ^{13}C NMR (75 MHz) δ 144.31, 128.70, 127.66, 126.84, 86.26, 68.18, 50.69, 47.44, 36.76, 31.94; M^+ calcd for $C_{25}H_{26}O_2$ 358.1923, found 358.1922.

(2*R*,4*R*)-2-Methyl-4[[(4-methylphenyl)sulfonyl]oxy]-6-(phenylthio)-1-[(triphenylmethyl)oxy]hexane (4). To a solution of 6.56 g (5.85 mmol) of DABCO and 6.9 mL (58.5 mmol) of thioanisole in 90 mL of THF at 0 °C was added 31 mL of 1.9 M *n*-BuLi in hexanes. The resulting solution was stirred for 45 min at room temperature. The mixture was cooled to −78 °C, and 8.39 g (23.4 mmol) of epoxide **3** was added in 40 mL of THF. The reaction was stirred overnight at 0 °C and then quenched with saturated NH_4Cl. The reaction was diluted with water and extracted with ether. The combined ether extracts were processed in the usual way, and the resulting oil was purified by flash column chromatography (15% EtOAc–hexanes) providing 10.2 g (90%) of the phenylthio ether: $[\alpha]^{25}_D$ −5.94° (*c* 1.33, $CHCl_3$).

A solution containing 9.3 g (19.26 mmol) of the preceding thioether in 25 mL of dichloromethane was treated with 4.04 g (21.18 mmol) of *p*-toluenesulfonyl chloride, 3.06 mL (22.0 mmol) of Et_3N, and 2.59 g (21.18 mmol) of DMAP. After being stirred overnight at room temperature, water was added, and the mixture was extracted with ether. The combined ether layers were dried and concentrated to an oil. Purification by flash column chromatography (15% EtOAc–hexanes) yielded 10.9 g (89%) of the title compound **4**: $[\alpha]^{25}_D$ 5.52° (*c* 1.162, $CHCl_3$); ^{1}H NMR (300 MHz) δ 0.87 (d, *J* = 7 Hz, Me), 1.35–1.50, 1.7–1.9 (m, CH_2), 1.95 (q, *J* = 5 Hz, CH_2), 2.43 (s, Ar-H, Me), 2.7–3.0 (m, CH_2OTr, CH_2SPh), 4.90 (t, *J* = 4 Hz, CHOR), 7.18–7.80 (m, Ar-H); ^{13}C NMR (75 MHz) δ 144.43, 144.10, 135.77, 134.27, 129.68, 129.11, 128.87, 128.62, 128.20, 127.69, 127.61, 126.86, 126.00, 86.40, 81.07, 68.45, 39.21, 34.25, 30.16, 28.89, 21.56, 17.30. Anal. Calcd for $C_{39}H_{40}O_4S_2$: C, 73.55; H, 6.33; S, 10.06. Found: C, 73.40; H, 6.21; S, 9.87.

(2*R*,4*R*)-2,4-Dimethyl-6-(phenylthio)-1-[(triphenylmethyl)oxy]hexane (5). To a slurry of 16.1 g (84.8 mmol) of CuI in 80 mL of THF was added 106 mL of 1.6 M MeLi–LiBr complex in ether dropwise at 0 °C. The resulting pale yellow colored solution was cooled to −78 °C, and then 9.0 g (14.1 mmol) of tosylate **4** was added in 10 mL of THF. The mixture was maintained at −20 °C overnight, and then the reaction was quenched carefully with saturated NH_4Cl and 3% NH_4OH. Ether was added, and the organic layer was washed with 3% NH_4OH until the washings were colorless. The blue aqueous layer was back extracted with ether. The combined ether layers were dried and concentrated to an oil which was purified by flash column chromatography (3% EtOAc–hexanes) yielding 6.78 g (90%) of the title compound **5** and ~10% of elimination byproducts: $[\alpha]^{25}_D$ 7.52° (*c* 3.16, $CHCl_3$); ^{1}H NMR (400 MHz) δ 0.85 (d, *J* = 7 Hz, Me), 0.9–1.0 (m, CH), 0.91 (d, *J* = 7 Hz, Me), 1.31–1.4 (m, CH_2), 1.46–1.65 (m, CH), 1.70–1.80 (m, CH), 2.78–2.98 (m, CH_2OTr, CH_2SPh), 5.42 (m, olefinic byproduct), 7.04–7.4 (m, Ar-H); ^{13}C NMR (75 MHz) δ 144.53, 137.07, 128.79, 127.67, 126.8, 125.63, 86.19, 68.27, 41.34, 36.06, 3.40, 31.29.

(3*R*,5*S*)-3,5-Dimethyl-6-[(triphenylmethyl)oxy]-1-hexene (6). To a solution of 2.64 g (5.5 mmol) of **5** in 20 mL of dichloromethane at 0 °C was added 2.37 g (10.1 mmol) of MCPBA. The mixture was stirred for 3 h, and then saturated sodium thiosulfate was added. The mixture was extracted with ether, and the extracts were processed as usual to give an oil. Purification by flash column chromatography (15% EtOAc–hexanes) gave 2.31 g of the sulfone: $[\alpha]^{25}_D$ 6.09° (*c* 1.29, $CHCl_3$); ^{1}H NMR (300 MHz) δ 0.80 (d, *J* = 7 Hz, Me), 0.94 (d, *J* = 7 Hz, Me), 0.88–0.99 (m, CH), 1.3–1.55, 1.65–1.8 (m, CH_2, CH), 2.8–3.1 (m, CH_2OSi, CH_2OTr), 7.2–7.9 (m, Ar-H); ^{13}C NMR (75 MHz) δ 144.26, 139.17, 133.48, 129.15, 128.60, 127.89, 127.60, 126.77, 86.06, 67.74, 54.14, 40.75, 31.12, 29.17, 28.81, 19.62. Anal. Calcd for $C_{33}H_{36}O_3S$: C, 77.31; H, 7.08. Found: C, 76.93; H, 7.47.

A solution of the preceding compound (2.3 g) in 30 mL of decalin was heated under reflux in the presence of calcium carbonate (5 equiv). Water was added, the mixture was extracted with ether, and then the organic layer was processed as usual. The resulting oil was purified by flash column chromatography (1% EtOAc–hexanes) to give 1.25 g (56%) of the olefin **6**: $[\alpha]^{25}_D$ −0.68° (*c* 1.76, $CHCl_3$); ^{1}H NMR (300 MHz) δ 1.01 (d, *J* = 7 Hz, 6 H, Me), 1.06–1.15 (m, 1 H, CH_2), 1.42–1.52 (m, 1 H, CH_2), 1.80–1.88 (m, 1 H, CH), 2.18–2.31 (m, 1 H, CH), 2.9–3.05 (m, 2 H, CH_2OTr), 4.91–5.04 (m, 2 H, vinyl H), 5.6–5.73 (m, 1 H, vinyl H), 7.22–7.54 (m, 15 H, Ar-H); ^{13}C NMR (75 MHz) δ 144.55, 144.48, 128.71, 127.56, 126.09, 112.53 (CH_2), 86.01, 68.66 (CH_2), 40.85 (CH_2), 86.01, 68.66 (CH_2), 40.85 (CH_2), 35.36 (CH), 31.51 (CH), 21.18 (Me), 17.30 (Me). Anal. Calcd for $C_{27}H_{30}O$: C, 87.52; H, 8.16. Found: C, 87.34; H, 7.88.

(2*R*,4*S*,5*R*,*S*)-2,4-Dimethyl-5-[(*tert*-butyldimethylsilyl)oxy]-1-hexanol (7). A slurry of cuprous chloride (386 mg, 3.9 mmol) and 138 mg (0.78 mmol) of palladium dichloride in 3.5 mL of DMF and 0.5 mL of water was stirred, while a slow stream of oxygen was passed through the flask. After 1 h, 1.37 g (3.7 mmol) of **6** was added in 1.2 mL of 15% aqueous DMF. The reaction mixture was stirred overnight under an atmosphere of oxygen, water was added, and the mixture was extracted with ether. After usual processing and purification by column chromatography, 1.21 g (85%) of the ketone was obtained: $[\alpha]^{25}_D$ 8.3° (*c* 1.65,

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$CHCl_3$), together with 113 mg (8%) of starting material.

Reduction of the ketone with L-selectride at −78 °C gave a mixture of epimeric alcohols (90%), $[\alpha]^{25}_D$ −8.06° (*c* 1.23, $CHCl_3$), which was treated with *tert*-butyldimethylsilyl chloride and DMAP in dichloromethane containing triethylamine. The resulting silyl ether derivative was dissolved in 15 mL of liquid ammonia containing 2 mL of ethanol. The solution was treated with 100-mg portions of sodium metal three times, and the reaction was quenched with ammonium chloride. Usual processing afforded the title compound as an oil (530 mg, 86%): $[\alpha]^{25}_D$ −14.4° (*c* 1.645, $CHCl_3$); ^1H NMR (300 MHz) δ 0.02 (s, 6 H, Me_2Si, 1.8–1.89 (m, 12 H, Me, *tert*-butyl), 1.93 (d, *J* = 7 Hz, 3 H, Me), 1.02 (d, *J* = 7 Hz, 3 H, Me), 1.37–1.72 (m, 4 H, CH, CH_2), 3.32–3.4 (m, 1 H, CH, CH_2OTr), 3.47–3.53 (m, 1 H, CH, CH_2OTr), 3.6–3.7 (m, 1 H, CH, C*H*-OH); ^{13}C NMR (75 MHz) δ 71.76, 67.95, 37.77, 36.72, 33.31, 25.86, 19.11, 18.07, 17.94, 15.29, −4.43, −4.78.

Lactone 9 as *E*/*Z* Isomers. The preceding compound **7** was oxidized to the corresponding aldehyde as follows. To a solution of oxalyl chloride (0.23 mL, 2.6 mmol) in 3 mL of dichloromethane was added 0.37 mL (5.2 mmol) of DMSO at −78 °C. To this mixture was added 530 mg (2.03 mmol) of **7** in 2 mL of dichloromethane. The resulting slurry was stirred at −78 °C for 30 min, and then 1.1 mL of triethylamine was added. After warming to 0 °C, water was added, the solution was extracted with ether, the extracts were processed, and the final residue was purified by flash column chromatography (10% EtOAc–hexanes) to give the aldehyde (445 mg, 85%): $[\alpha]^{25}_D$ −22.95° (*c* 2.11, $CHCl_3$); M^+ calcd for $C_{14}H_{30}O_{25}$ 258.2016, found 258.1987.

A solution of LiHMDS was prepared by adding 0.53 mL of 2 M *n*-BuLi to 0.23 mL (1.1 mmol) of hexamethyldisilazane in 2 mL of THF at 0 °C. After 15 min, 450 mg (1.05 mmol) of the lactone **8** was added in 2 mL of THF at −78 °C. After stirring at −78 °C for 1 h, the aldehyde prepared from **7** was added (242 mg, 0.936 mmol) in 2 mL of THF. The reaction mixture was allowed to warm to 0 °C, and it was stirred overnight. Saturated ammonium chloride was added, followed by ether, and the mixture was processed as usual. Purification of the crude product by flash column chromatography (5% EtOAc–hexanes) gave 419 mg (75%) of the *E* and *Z* mixture (~4:1) of lactone **9**: $[\alpha]^{25}_D$ 25.1° (*c* 1.8, $CHCl_3$); *E* isomer, ^1H NMR (300 MHz) δ 0.03 (d, *J* = 3 Hz, (Me_2Si), 0.83 (d, *J* = 7 Hz, Me), 0.85 (d, *J* = 6 Hz, Me), 0.88 (s, *tert*-butyl), 1.01 (s, *tert*-butyl) 1.05 (d, *J* = 7 Hz, Me), 1.1–1.2 (m, CH of CH_2), 1.3–1.4 (m, CH), 1.45–156 (m, CH of CH_2), 2.35–2.5 (m, allylic CH), 2.8–2.9 (m, CH_2), 3.55–3.65 (m, CH), 3.77 (ab quartet, CH_2OSi), 4.62 (dd, lactone CH, *J* = 5 Hz), 6.48 (dt, *J* = 12 Hz, *J* = 3 Hz, vinyl H), 7.35–7.8 (m, Ar-H); ^{13}C NMR 75 MHz) δ 145.6, 135.6, 135.5, 133.1, 132.6, 129.8, 127.8, 125.2, 72.1, 65.3, 39.3, 38.3, 32.9, 27.1, 26.7, 25.9, 20.4, 19.7, 19.2, 18.1, 15.1, −4.3, −4.8.

Lactone 10. The above obtained mixture of lactones (180 mg, 0.3 mmol) and 75 mg of rhodium on alumina in 3 mL of ethyl acetate was stirred under an atmosphere of hydrogen overnight. The catalyst was removed by filtration through a pad of Celite, and the filtrate was concentrated to an oil which was purified by flash column chromatography (5% EtOAc–hexanes) affording 172 mg (95%) of the title compound which was >98% cis isomer: $[\alpha]^{25}_D$ 12.8° (*c*, 1.12, $CHCl_3$); IR_{max} 1780 cm^{-1} (C=O); ^1H NMR (300 MHz) δ 0.04 (d, *J* = 2 Hz, (Me_2Si), 0.87 (d, *J* = 7 Hz, Me), 0.89 (s, *tert*-butyl), 0.95 (d, *J* = 7 Hz, Me), 1.02 (d, *J* = 7 Hz, Me), 1.07 (s, *tert*-butyl), 1.15 (2.0, m, CH_2, CH), 2.3–2.4 (m, CH), 2.6–2.71 (m, CHC=O), 3.62–3.7 (m, CHOSi), 3.79 (ab quartet, CH_2OSi), 4.4–4.51 (m, CH of lactone), 7.35–7.7 (m, Ar-H); ^{13}C NMR (75 MHz) δ 179.0, 135.7, 135.6, 133.1, 132.9, 129.8, 127.8, 78.1, 71.3, 64.8 (CH_2), 40.0 (CH_2), 38.5, 38.3 (CH_2), 37.6, 31.4 (CH_2), 28.9, 26.8, 25.9, 21.0, 19.3, 19.0, 15.3, −4.4, −4.7. Anal. Calcd for $C_{35}H_{56}O_4Si_2$: C, 69.94; H, 9.99. Found: C, 69.81; H, 9.77.

(2*R*,4*S*,6*R*,8*S*,9*R*,*S*)-9-[(*tert*-Butyldimethylsilyl)oxy]-1-[(*tert*-butyldiphenylsilyl)oxy]-6,8-dimethyl-4-(hydroxymethyl)-2-decanol (11). The above lactone (336 mg, 0.56 mmol) in 2 mL of THF was treated with 2 M borane–dimethyl sulfide complex, and the resulting solution was stirred overnight at room temperature. Methanol was added, and the solution was concentrated to give an oil which was purified by flash column chromatography affording 297 mg (88%) of the title diol: $[\alpha]^{25}_D$ −18.7° (*c* 1.1, $CHCl_3$); ^1H NMR (300 MHz) δ 0.03 (d, *J* = 2 Hz, (Me_2Si), 0.82 (d, *J* = 7 Hz, Me), 0.89 (s, *tert*-butyl), 0.89 (d, *J* = 7 Hz, Me). 0.99 (d, *J* = 7 Hz, Me), 1.09 (s, *tert*-butyl), 1.2–1.8 (m, CH_2), 3.3–3.72 (m, CH_2OSi, CHOSi, CH_2OH), 3.8–3.9 (m, C*H*-OH), 7.4–7.71 (m, Ar-H); ^{13}C NMR (75 MHz) δ 135.5, 133.1, 133.05, 129.9, 127.8, 71.6, 68.4 (CH_2), 66.3 (CH_2), 41.1 (CH_2), 4.01 (CH_2), 37.8 (CH_2), 37.5; 37.4, 27.9, 26.9, 25.9, 20.9, 19.2, 18.96, 18.1, 14.97, −4.4, −4.7. Anal. Calcd for $C_{35}H_{60}O_4Si_2$: C, 69.94; H, 10.06. Found: 69.89, H, 9.98.

Methyl (4*S*,6*S*,8*S*)-4,6,8-Trimethyl-9-oxodecanoate (13). To a solution containing 66 μL (0.266 mmol) of tri-*n*-butylphosphine and 41 mg (0.19 mmol) of diphenyl disulfide in 1 mL of THF was added 80 mg (0.133 mmol) of the preceding compound **11** at 0 °C. The solution was stirred overnight at 0 °C, and then an additional 132 μL (0.53 mmol) of the phosphine and 116 mg (0.53 mmol) of diphenyl disulfide were added. The mixture was heated at reflux for 8 h, then solvent was removed by evaporation, and the resulting oil was purified by flash chromatography (1% EtOAc–hexanes) to give 70 mg (76%) of the bisphenylthio derivative **12**, and 27 mg of the monosulfide which could be reacted again (88% yield). Raney-nickel desulfurization of **12** (100 mg, 0.27 mmol) in ethanol (4 h, 25 °C) followed by filtration and evaporation gave an oil. Treatment with excess aqueous HF in acetonitrile at 0 °C for 1 h, followed by addition of water, extraction with ethyl acetate, and usual processing left an oil. Purification by flash chromatography (10% EtOAc–hexanes) gave 21 mg (78%) of the expected diol: $[\alpha]^{25}_D$ −47.1° (*c* 1.0, $CHCl_3$).

A solution of the above prepared compound (19 mg, 87.8 μmmol) in 1 mL of acetone was treated with 0.12 mL of a 2.6 M Jones reagent. After 30 min at 0 °C, 2-propanol was added, followed by excess sodium bicarbonate. Filtration through a pad of Celite and usual processing of the filtrate gave an oil which was dissolved in ether and treated with excess diazomethane. Evaporation followed by column chromatography (10% EtOAc–hexanes) gave 15 mg (71%) of the keto ester **11**, $[\alpha]^{25}_D$ −34.7° (*c* 1.0, $CHCl_3$). The ^1H and ^{13}C NMR spectra were identical with data published by Evans and Dow[13] who reported $[\alpha]^{25}_D$ −35.8° (*c* 1.22, $CHCl_3$).

(2*R*,3*R*,4*S*)-5-[(*tert*-Butyldiphenylsilyl)oxy]-2-hydroxy-3-methyl-4-pentanolide (16). A solution of 5.25 g (14 mmol) of lactone **15** in 50 mL of THF was treated with 48 mL of 0.5 M KHMDS at −78 °C, and then 9 g (4.14 mmol) of MoOPH[37] was added. The mixture was warmed to −30 °C gradually. Saturated sodium sulfite was added, the layers were separated, and the organic layer was washed with saturated sodium sulfite. The aqueous layers were extracted with ether, and the ether extracts were processed as usual to give an oil which was purified by column chromatography (30% EtOAc–hexanes) providing 4.25 g (78%) of hydroxylactone **16**, mp 96–97 °C: $[\alpha]^{25}_D$ 90.6° (*c* 4.5, $CHCl_3$); IR_{max} (KBr) 1775 cm^{-1} (C=O); ^1H NMR (400 MHz) δ 1.03 (s, 9 H, *tert*-butyl), 1.35 (d, *J* = 7 Hz, 3 H, Me), 2.62–2.72 (m, 1 H, CH), 3.29 (br s, 1 H, OH), 3.71 (dd, *J* = 12 Hz, *J* = 1.4 Hz, 1 H, CH_2OSi), 3.88 (dd, *J* = 12 Hz, *J* = 2.6 Hz, 1 H, CH_2OSi), 4.43 (ddd, *J* = 8.6 Hz, *J* = 2.6 Hz, *J* = 1.4 Hz, 1 H, CH), 4.56 (d, *J* = 10.6 Hz, 1 H, CH), 7.24–7.67 (m, Ar-H); ^{13}C NMR (75 MHz): δ 177.9, 135.53, 133.40, 132.39, 131.69, 129.92, 129.88, 128.13, 127.8, 80.09, 72.85, 62.13, 40.69, 26.63, 18.87, 12.13. Anal. Calcd for $C_{22}H_{28}O_4Si$: C, 68.71; H, 7.34. Found: C, 68.68; H, 7.21.

(2*R*,3*S*)-[(*tert*-Butyldiphenylsilyl)oxy]-2-methyl-1,3-butanediol (17). A solution of 4.19 g (10.89 mmol) of **16** in 20 mL of 75% aqueous THF was treated with 4.12 g (109 mmol) of sodium borohydride. After 1 h, 10% HCl was added until the pH was ~7. The THF was removed by evaporation, and 20 mL of MeOH was added. The mixture was cooled to 0 °C, and then 4.65 g (21.8 mmol) of sodium metaperiodate was added. The mixture was stirred at 0 °C for 6 h, and then 2 g (54 mmol) of sodium borohydride was carefully added. After 1 h, 10% HCl was added, and the dark mixture was extracted with ethyl acetate. The organic layers were processed as usual, and the resulting oil was purified by flash column chromatography (30% EtOAc–hexanes) yielding 3.63 g (93%) of **17**: $[\alpha]^{25}_D$ 1.98° (*c* 1.97, $CHCl_3$). Anal. Calcd for $C_{21}H_{30}O_3Si$: C, 70.34; H, 8.43. Found: C, 70.31; H, 8.41.

(2*R*,3*R*)-1,2-Epoxy-3-methyl-4-[(triphenylsilyl)oxy]butane (18). A solution of 2.64 g (7.36 mmol) of **15**, 2.26 g (8.09 mmol) of trityl chloride, 124 mL (8.9 mmol) of triethylamine, and 90 mg (0.74 mmol) of DMAP in 10 mL of CH_2Cl_2 was stirred for 6 h. Water was added, and the mixture was extracted with ether. The organic layers were processed as usual to give an oil. Purification by flash column chromatography (4% EtOAc–hexanes) gave 4.16 g (94%) of the trityl ether: $[\alpha]^{25}_D$ 1.5° (*c* 1.01, $CHCl_3$).

A solution of the above compound (5.1 g, 8.49 mmol), 0.72 mL (9.34 mmol) of methanesulfonyl chloride, and 1.5 mL (11.0 mmol) of triethylamine in 10 mL of CH_2Cl_2 at 0 °C was stirred for 30 min. Water was added, and the mixture was extracted with ether. The organic layers were processed in the usual manner to leave an oil. This was dissolved in 10 mL of THF, and 20 mL of 1 M *n*-Bu_4NF in THF was added. The solution was stirred overnight at room temperature. Sodium methoxide (2 mL of a 35 wt % solution) was added, and after 0.5 h the mixture was diluted with water, and extracted with ether. Processing the organic layer gave an oil which was purified by flash column chromatography (4% EtOAc–hexanes) giving 2.66 g (91%) of the epoxide **18**: $[\alpha]^{25}_D$ 3.11° (*c* 1.67, $CHCl_3$); ^1H NMR (300 MHz) δ 1.01 (d, *J* = 7 Hz, 3 H, Me), 1.7–1.75 (m, 1 H, CH), 2.85, 2.53 (dd, *J* = 5 Hz, *J* = 2.7 Hz, 1 H, CH), 2.75 (dd, *J* = 5 Hz, *J* = 4 Hz, 1 H, CH), 2.96–3.01 (m, 1 H), 3.17 (dd, *J* = 5.5 Hz, *J* = 1 Hz, 2 H, CH_2OTr), 7.22–7.51 (m, Ar-H); ^{13}C NMR (75 MHz) δ 144.23, 128.74, 127.72, 126.89, 86.5, (CH), 65.84 (CH_2),

54.35 (CH), 45.49 (CH_2), 36.85 (CH), 13.12 (Me); M^+ calcd for $C_{24}H_{24}O_2$ 344.271, found 344.177.

(4*S*,5*R*)-5-Methyl-6-[(triphenylmethyl)oxy]-2-hexen-4-olide (19). To a solution of 1.99 g (9.27 mmol) of α-(phenylseleno)acetic acid in 15 mL of THF at 0 °C was added 4.7 mL of 1.95 M *n*-BuLi in hexanes. After 0.5 h, 2.66 g (7.7 mmol) of epoxide **18** in 7 mL of THF was added. The mixture was stirred overnight at room temperature, acidified with 10% HCl, and then extracted with ether. Removal of solvent left an oil which was dissolved in 15 mL of dichloromethane and treated with ethyl((dimethylamino)propyl)carbodiimide hydrochloride (1.73 g, 9.0 mmol) and 110 mg (0.9 mmol) of DMAP. The dark mixture was stirred 30 min at 0 °C. Water was added, and the mixture was extracted with ether. The organic layers were processed as usual leaving an oil which was purified by flash column chromatography (15% EtOAc–hexanes) yielding an epimeric mixture of selenides. The purified product was dissolved in 15 mL of CH_2Cl_2 and cooled to 0 °C, and 30% hydrogen peroxide (8 mL) was added. The biphasic solution was vigorously stirred for 30 min, water was added, and the mixture was extracted with ether. The organic layers were processed to give an oil which was purified by flash column chromatography (20% EtOAc–hexanes) yielding 2.22 g (75%) of the lactone **19**: $[\alpha]^{25}_D$ −69.45° (*c*, 1.27, $CHCl_3$); ^1H NMR (300 MHz) δ 0.92 (d, *J* = 7 Hz, 3 H, Me), 2.29–2.40 (m, 1 H, CH), 3.07 (dd, *J* = 7.5 Hz, *J* = 7 Hz, 1 H, CH_2OTr), 3.33 (dd, *J* = 5 Hz, *J* = 10 Hz, 1 H, CH_2OTr), 5.25 (br d, *J* = 3 Hz, 1 H, CH), 6.06 (dd, *J* = 2 Hz, *J* = 3 Hz, 1 H, CH), 7.23–7.51 (m, Ar-H, vinyl H); ^{13}C NMR (75 MHz) δ 172.80, 154.75, 143.68, 128.47, 127.79, 127.05, 121.91, 86.76, 84.70, 64.44 (CH_2), 37.09 (CH, 11.70 (Me); M^+ calcd for $C_{26}H_{24}O_3$ 384.170, found 384.170.

3,5-Dimethyl-6-[(triphenylmethyl)oxy]-4-hexanolide (20). To a slurry of 2.4 g (12.8 mmol) of CuI in 15 mL of ether at 0 °C was added 18.3 mL of 1.4 M MeLi·LiBr in ether. The pale yellow colored solution was cooled to −30 °C, and 1.64 g (4.26 mmol) of **19** in 7 mL of ether was added. The mixture was stirred 1 h at −20 °C, and then saturated ammonium chloride and ether were added. The layers were separated, and the organic layer was washed with ammonium hydroxide. The blue aqueous layers were back extracted with ether. The organic layers were processed to give an oil which was purified by flash column chromatography (15% EtOAc–hexanes) affording 1.65 g (97%) of lactone **20**: $[\alpha]^{25}_D$ 9.08° (*c* 1.53, $CHCl_3$); IR (film) 1780, 1740, 1600 cm^{-1}; ^1H NMR (300 MHz) δ 1.00 (d, *J* = 7 Hz, 3 H, Me), 1.09 (d, *J* = 7 Hz, 3 H, Me), 2.04–2.15 (m, 1 H, CH), 2.12 (dd, *J* = 8 Hz, *J* = 17 Hz, 1 H, CH_2), 2.31–2.49 (m, 1 H, CH), 2.61 (dd, *J* = 9 Hz, *J* = 17 Hz, 1 H, CH_2), 3.1–3.23 (m, 2 H, CH_2OTr), 4.17 (t, 5.6 H, 1 H, CH), 7.2–7.5 (m, Ar-H); ^{13}C NMR (75 MHz) δ 176.31, 143.99, 128.59, 127.75, 126.98, 88.65, 86.73, 64.52 (CH_2), 37.52 (CH), 37.08 (CH_2), 31.87 (CH), 19.22 (Me), 13.56 (Me); M^+ calcd for $C_{27}H_{28}O_3$ 400.204, found 400.2035.

Hydroxylation of 20. To a solution of 1.2 g (3 mmol) of **20** in 10 mL of THF was added 9.6 mL of 0.5 M KHMDS in toluene at −78 °C. The solution was stirred 0.5 h at −78 °C, and then 1.82 g (4.2 mmol) of MoOPH was added. The mixture was gradually warmed to −30 °C, and then saturated sodium sulfite and ether were added. The organic layer was washed with aqueous sodium sulfite. The organic layers were processed in the conventional way to give an oil which was purified by flash column chromatography (20% EtOAc–hexanes) providing 387 mg (31%) of the hydroxylactone **21** and 658 mg (53%) of the hydroxylactone **22**: for **21**, $[\alpha]^{25}_D$ 19.2° (*c*, 1.245, $CHCl_3$); IR (film) ν 1780, 1600 cm^{-1}; ^1H NMR (300 MHz) δ 1.00 (d, *J* = 7 Hz, 3 H, Me), 1.08 (d, *J* = 7 Hz, 3 H, Me), 1.93–2.02 (m, 1 H, CH), 2.47–2.59 (m, 1 H, CH), 3.0–3.23 (m, 3 H, CH_2OTr, OH), 4.25 (dd, *J* = 3 Hz, *J* = 7 Hz, 1 H, CH), 4.36 (dd, *J* = 3 Hz, *J* = 8 Hz, 1 H, CH), 7.22–7.47 (m, Ar-H); ^{13}C NMR (75 MHz) δ 177.23, 143.93, 128.60, 127.79, 127.03, 87.49, 86.80, 69.36, 64.51 (CH_2), 37.26 (CH), 35.69 (CH), 13.64 (Me), 12.70 (Me); M^+ calcd for $C_{27}H_{28}O_4$ 416.202, found 416.2030. For **22**: ^1H NMR (300 MHz) δ 1.00 (d, *J* = 7 Hz, 3 H, Me), 1.14 (d, *J* = 7 Hz, 3 H, Me), 2.11–2.33 (m, 2 H, CH), 3.05–3.25 (m, 2 H, CH_2OTr), 3.45 (br d, *J* = 3 Hz, OH), 4.03 (dd, *J* = 3.6 Hz, *J* = 11 Hz, 1 H, CH), 4.11–1.47 (m, 1 H, CH), 7.2–7.5 (m, Ar-H).

(2*R*,3*R*,4*R*,5*R*)-6-[(Triphenylmethyl)oxy]-3,5-dimethylhexane-1,2,4-triol (23). To a solution containing 490 mg (1.17 mmol) of **21**, in 3 mL of THF at room temperature, was added 3.0 mL of 1 M lithium aluminum hydride in THF. The solution was stirred 4 h, and then 120 μL of H_2O, 120 μL of 75% NaOH, and 360 μL of H_2O were added in succession. The salts were filtered off and washed well with ether. The solvent was removed, and the oil as well as the dried aluminum salts were loaded on a silica gel column (75% EtOAc–hexanes) yielding 460 mg (93%) of tetrol **23**: $[\alpha]^{25}_D$ 1.22° (*c* 1.80, $CHCl_3$); ^1H NMR (300 MHz) δ 0.68 (d, *J* = 7 Hz, 3 H, Me), 1.24 (d, *J* = 7 Hz, 3 H, Me), 1.41–1.52 (m, 1 H, CH), 1.95–2.06 (m, 1 H, CH), 2.9 (m, OH), 3.31 (dd, *J* = 3 Hz, *J* = 2 Hz, 2 H, CH_2OTr), 3.40–3.52 (m, 2 H, CH_2OH), 3.58–3.67 (m, 2 H, CH), 4.2, 4.5 (m, 2 H, OH), 7.2–7.5 (m, 15 H, Ar-H); ^{13}C NMR (75 MHz) δ 143.37, 128.48, 127.97, 127.21, 87.47, 81.02, 75.92, 65.31 (CH_2), 64.65 (CH_2), 38.59 (CH), 35.15 (CH), 15.62 (Me), 13.44 (Me). Anal. Calcd for $C_{27}H_{32}O_4$: C, 77.11; H, 7.67. Found: C, 77.03; H, 7.61.

(2*R*,3*R*,4*R*,5*R*)-2,4-Dihydroxy-3,5-dimethyl-6-[(triphenylmethyl)-oxy]hexyl Pivalate (24). Pivaloyl chloride (135 mg, 1.12 mmol) was added dropwise to a cooled (0 °C) solution of tetrol **23** (262 mg, 0.623 mmol) in pyridine (0.3 mL). The mixture was stirred for 1 h at 0 °C followed by 1 h at room temperature, poured into water, and extracted with ethyl acetate. The combined extracts were washed with saturated copper sulfate, and the organic layer was concentrated to dryness under reduced pressure. The residue was purified by flash chromatography (20% EtOAc–hexanes) to afford **24** (278 mg, 88%) as a colorless oil: $[\alpha]^{25}_D$ −14.4° (*c* 1.15, $CHCl_3$); ^1H NMR (300 MHz) δ 0.77 (d, *J* = 7 Hz, 3 H, Me), 1.17 (d, *J* = 7 Hz, 3 H, Me), 121 (s, 9 H, *tert*-butyl), 1.54–1.64 (sextet *J* = 6 Hz, 1 H, CH), 1.95–2.06 (m, 1 H, CH), 3.29 (s, *J* = 6 Hz, 2 H, CH_2OTr), 3.45–3.51 (m, 1 H, CH), 3.81–3.90 (m, 1 H, CH), 3.92 (br s, 1 H, OH), 4.12–4.23 (m, 2 H, CH_2OPiv), 7.21–7.5 (m, Ar-H); ^{13}C NMR (75 MHz) δ 178.38, 143.15, 128.15, 127.55, 126.78, 87.10, 80.46, 73.58, 67.20 (CH_2), 65.42 (CH_2), 38.49 (CH), 38.42 (CH), 26.81 (Me), 15.2 (Me), 13.37 (Me).

Acetonide of (2*R*,3*R*,4*R*,5*R*)-2,4-Dihydroxy-3,5-dimethyl-6-[(triphenylmethyl)oxy]hexanal (25). A solution of **24** (163 mg, 0.32 mmol), 37 mg (0.16 mmol) of camphorsulfonic acid in 2 mL of acetone, and 2 mL of 2,2-dimethoxypropane was stirred for 2 min. Saturated $NaHCO_3$ was added, and the mixture was extracted with ether. The ether layers were processed as usual to give an oil which was dissolved in 3 mL of THF, and 0.5 mL of 1 M lithium aluminum hydride in THF was added at 0 °C. After 30 min, 20 μL of H_2O, 20 μL of 15% NaOH, and 60 μL of H_2O were added in succession. The aluminum salts were removed by filtration, and the filtrate was concentrated to an oil which was purified by flash column chromatography (10% EtOAc–hexanes) providing 105 mg (75%) of the acetonide derivative: $[\alpha]^{25}_D$ −8.9° (*c* 0.95, $CHCl_3$); ^1H NMR (300 MHz) δ 0.73 (d, *J* = 7 Hz, 3 H, Me), 0998 (d, *J* = 7 Hz, 3 H, Me), 1.29 (s, 3 H, Me), 1.38 (s, 3 H, Me), 1962–1.74 (m, 1 H, CH), 2.02–2.11 (m, 1 H, CH), 3.01 (dd, *J* = 6.6 Hz, *J* = 6.0 Hz, 1 H, CH_2OTr), 3.28 (dd, *J* = 6 Hz, *J* = 5 Hz, 1 H, CH_2OTr), 3.40–3.54 (m, 3 H, CH_2OH, CH), 3.66–3.72 (m, 1 H, CH), 7.20–7.48 (m, Ar-H); ^{13}C NMR (75 MHz) δ 144.55, 128.80, 127.63, 126.78, 89.12, 86.71, 77.44, 75.19, 64.04, 63.78, 34.75, 31.74, 29.88, 19.49, 15.92, 11.96.

To a solution containing 63 μL (0.716 mmol) of oxalyl chloride in 1 mL of dichloromethane was added 102 μL (1.43 mmol) of DMSO at −78 °C. The mixture was stirred 5 min at −78 °C, and then 220 mg (0.477 mmol) of the preceding compound was added in 1.5 mL of dichloromethane. The mixture was stirred 0.5 h at −78 °C, and then 0.35 mL (2.5 mmol) of triethylamine was added. The slurry was warmed rapidly to ~10 °C, water was added, and the mixture was extracted with ether. The ether layers were processed as usual to give an oil which was purified by flash column chromatography (5% EtOAc–hexanes) to give 187 mg (85%) of the aldehyde **25** as a solid, mp 96–99 °C: $[\alpha]^{25}_D$ 26.1° (*c* 1.87, $CHCl_3$); IR (film) 1780, 1600 cm^{-1}; ^1H NMR (300 MHz) δ 0.84 (d, *J* = 7 Hz, 3 H, Me), 0.99 (d, *J* = 7 Hz, 3 H, Me), 1.82–1.95 (m, 1 H, CH), 2.05–2.15 (m, 1 H, CH), 3.04 (dd, *J* = 6 Hz, *J* = 6.6 Hz, 1 H, CH_2OTr), 3.30 (dd, *J* = 6.6 Hz, *J* = 6 Hz, 1 H, CH_2OTr), 3.49 (dd, *J* = 9 Hz, *J* = 1.5 Hz, 1 H, CH), 3.75 (dd, *J* = 9 Hz, *J* = 2.4 Hz, 1 H, CH), 7.20–7.48 (m, Ar-H), 9.44 (d, *J* = 2.4 Hz, 1 H, CHO); ^{13}C NMR (75 MHz) δ 200.18 (C=O), 144.36, 128.72, 127.64, 126.83, 98.27, 86.77, 79.18, 63.88, 34.62, 30.48, 29.60, 19.36, 15.69, 11.34. Anal. Calcd for $C_{30}H_{34}O_4$: C, 78.58; H, 8.90. Found for a partial hydrate 0.3 H_2O: C, 77.37; H, 7.69.

The 2-epimeric lactone **22** was subjected to a similar series of transformations as for **21** to give the tetrol derivative **26**, which was converted into the aldehyde **27**. Equilibration with methanol containing 5% potassium carbonate at room temperature afforded **25** (87%).

(2*R*,3*S*)-3,4-Epoxy-3-methyl-2-butanol (29). A stirred suspension of powdered activated 4Å molecular sieves (7.6 g, 22 wt % based on alcohol) in dry dichloromethane (1.4 L) was cooled to −10 °C. (D)-(−)-Diisopropyl tartrate (16.4 g, 70 mmol) and freshly distilled titanium(IV) isopropoxide (16.5 g, 58 mmol) were added sequentially. After cooling to −20 °C a solution of anhydrous *tert*-butyl hydroperoxide (35.2 mL of a 5.6 M solution, 197 mmol) in dichloromethane was added, and the mixture was stirred at −20 °C for 10 min. A solution of (*R*,*S*)-3-methyl-3-buten-2-ol, **28** (38 g, 440 mmol), in dichloromethane (30 mL) was added dropwise over 10 min. The resultant suspension was stored in a freezer (−20 °C). After 30 h at −20 °C, gas–liquid chromatography analysis (5% oviol; 25 psi nitrogen carrier gas) indicated a 60:40 mixture of olefin to epoxide **26**. Dimethyl sulfide (12.43 g, 200 mmol) was added, and the reaction was kept at −20 °C for an additional 3 h, whereupon a solution of triethanolamine (105 mL of a 1 M solution, 105 mmol) in dichloromethane was added, and the solution was stirred for 30 min at 0 °C. The solution was filtered through 150 g of silica gel in a sintered

glass funnel and eluted with ether. The filtrate was concentrated by distillation through a 20-cm vigreux column at atmospheric pressure. The residue was fractionally distilled at reduced pressure with the collecting flasks cooled to −30 °C, to afford (2*R*,3*S*)-3,4-epoxy-3-methyl-2-butanol (**29**) as a colorless oil (14.0 g, 62% based on R-alcohol), bp 75–80 °C at 50 mmHg: $[\alpha]^{25}_D$ −29.9° (*c* 1.90 in $CHCl_3$); (400 MHz) δ 1.24 (3 H, d *J* = 4.9 Hz, C_1-H), 1.35 (3 H, s, C_2-Me), 2.11 (1 H, d, *J* = 1.0 Hz, OH), 2.60 (1 H, d, *J* = 4.7 Hz, C_4-H), 2.91 (1 H, d, *J* = 4.7 Hz, C_4-H), and 3.83 (1 H, qd, *J* = 4.9, *J* = 1.0 Hz); ^{13}C NMR (75 MHz) δ 17.5 (q, Me), 18-2 (q, Me), 50.0 (t, C_4), 60.0 (s, C_3), and 67.2 (d, C_2); *m/e* (Cl, isobutane) 103 (MH^+, 90%), 101 (M^+ − H, 42), 85 (M^+ − H_2O, 100), 75 (55), and 71 (60); MS calcd for $C_5H_{10}O_2$, M^+, 102.0681, found 102.0678.

A 300 MHz ^{1}H NMR analysis of the Mosher ester (derived from (+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride) in chloroform-*d* indicated an optical purity of 95%.

(*E*)-3,7-Dimethyl-2,6-octadienyl Phenyl Sulfone (30). This was prepared following a scheme described by Marshall and Andrews.[25] To a stirred solution of geraniol (5 g, 32.4 mmol) in diethyl ether (100 mL) cooled to 0 °C was added phosphorus tribromide (3.51 g, 13.0 mmol) dropwise. The resultant yellow solution was stirred at 0 °C, under light-free conditions for 2 h. The solution was poured into saturated $NaHCO_3$ solution and extracted with ether. The combined ether extracts were washed with saturated $NaHCO_3$, dried ($MgSO_4$), and concentrated to afford (*E*)-1-bromo-3,7-dimethylocta-2,6-diene (7.1 g, 100%) as a golden oil: IR_{max}, 1660 cm^{-1} (C=C).

The crude bromide (7.1 g, 32 mmol) was dissolved in DMF (5 mL) and sodium phenyl sulfinate (8.0 g, 48.6 mmol) was added. The resultant suspension was stirred at room temperature for 18 h. The mixture was poured into 10% aqueous solution of $NaHCO_3$ (300 mL) and extracted with ethyl acetate. The combined extracts were processed as usual to give an oil which was purified by "dry flash" chromatography (30% EtOAc–hexanes) to afford the title compound (7.4 g, 82%) as a golden brown oil: IR_{max} 1340, 1320 (SO_2Ph), 1150 cm^{-1} (SO_2); ^{1}H NMR (300 MHz) δ 1.32 (3 H, d, *J* = 1.1 Hz, C_3-Me), 1.59 (3 H, br s, C_8-H), 1.69 (3 H, br s, C_7-Me), 2.00 (4 H, m, C_4-H and C_5-H), 3.81 (2 H, d, *J* = 8.1 Hz, C_1-H), 5.03 (1 H, m, C_6-H), 5.19 (1 H, tq *J* = 8.1 Hz, *J* = 1.1 Hz, C_2-H), 7.50–7.56 (2 H, m, Ar-H), 7.61–7.66 (1 H, m, Ar-H) 7.86–7.89 (2 H, m, Ar-H); (75 MHz) δ 16.1 (q, C_3-Me), 17.5 (q, C_8), 25.5 (q, C_7-Me), 26.2 (t, allylic CH_2), 39.6 (t, allylic CH_2), 56.1 (t, C_1), 110.4 (d, C_2), 123.4 (d, C_6), 128.5 (d, Ar-CH), 128.8 (d, Ar-CH), 131.9 (s, C=CR, R_2), 133.3 (d, Ar-CH), 139.0 (s, C=CR, R_2), and 146.2 (s, Ar-C); *m/e* (EI) 279 (MH^+, 40%), 243, 205, 153, 137 (100), 95, 81; MS (EI) calcd for $C_{16}H_{23}O_2S$, MH^+, 279.1419, found 279.1412.

(6*E*,2*R*,3*S*,5*RS*)-5-(Phenylsulfonyl)-3,7,11-trimethyl-6,10-dodecadiene-2,3-diol (31A and 31B). To a stirred solution of phenyl sulfone **30** (7.3 g, 26 mmol) in 16 mL of THF and HMPA (4 mL) cooled to −78 °C under argon was added a solution of *n*-butyllithium (22 mL of a 1.2 M solution, 26.5 mmol) in hexanes dropwise. The resultant red solution was stirred for 30 min at −78 °C, and a solution of ethyl magnesium bromide (20.25 mL of a 1.19 molar solution, 24 mmol) in ether was added dropwise according to Marshall and Andrews.[25] In a separate vessel, a solution of epoxide **29** (2.56 g, 25 mmol) in THF (16 mL) and HMPA (4 mL) was cooled to −78 °C. The resulting slurry of magnesium salt was stirred at −78 °C for 10 min. The mixture was warmed rapidly to 0 °C and added dropwise via a cannula to the stirred solution of **29** at −78 °C. The mixture was stirred at −78 °C for 1 h and then warmed slowly to room temperature. After the mixture was stirred at room temperature for 18 h, it was quenched by addition of methanol (10 mL) and saturated aqueous ammonium chloride (5 mL). The mixture was poured into water and extracted with ether, and the combined organic layers were processed as usual to give a residue which was purified by flash chromatography (80% ether–hexanes) to afford two isomeric sulfones, A and **B**.

The first to be eluted, isomer A (3.9 g, 41%), showed mp 64–65 °C (ether–hexanes): $[\alpha]^{25}_D$ +33.7° (*c* 0.83, $CHCl_3$); IR_{max} (CCl_4), 1305 (SO_2Ph), 1295 cm^{-1} (SO_2Ph); ^{1}H NMR δ (300 MHz) δ 1.12 (3 H, d, *J* = 6.5 Hz, 1 H), 1.13 (3 H, s, C_3-Me), 1.14 (3 H, d, *J* = 1.0 Hz, C_7-Me), 1.55 (3 H, m, 12 H), 1.64 (3 H, M, C_{11}-Me), 1.95 (5 H, br m, C_4-H, C_8-H, and C_9-H), 2.17 (1 H, d, *J* = 4.6 Hz, C_2-OH), 2.36 (1 H, dd, *J* = 14.6 Hz, *J* = 3.5 Hz, C_4-H), 2.52 (1 H, br s, C_3-OH), 3.63 (1 H, qd, *J* = 6.5, *J* = 4.6 Hz, C_2-H), 4.17 (1 H, ddd, *J* = 10.4 Hz, *J* = 8.6 Hz, *J* = 3.5 Hz, C_5-H), 5.00 (1 H, m, C_{10}-H), 5.04 (1 H, dd, *J* = 10.4 Hz, *J* = 1 Hz, C_6-H), 7.48 (2 H, m, Ar-H), 7.57 (1 H, m, Ar-H), and 7.79 (2 H, m, Ar-H); ^{13}C NMR (75 MHz) δ 16.1 (q, C_7-Me), 17.0 (q, C_1), 17.5 (q, C_{12}), 23.7 (q, C_3-Me), 25.4 (q, C_{11}-Me), 25.8 (t, C=$CRCH_2$), 34.0 (t, C_4), 39.4 (t, C=$CRCH_2$), 61.1 (d, C_5) 78.7 (d, C_2), 73.9 (s, C_3), 118.7 (d, C_6), 123.3 (d, C_{10}), 128.5 (d, Ar-CH), 129.2 (d, Ar-CH), 132.1 (s, C=CR_1R_2), 133.3 (d, Ar-CH), 137.4 (s, C=CR_1R_2), and 144.7 (s, Ar-C); *m/e* (EI) 381 (M^+ + H, 24%), 363 (M^+ − OH), 239 (M^+ − SO_2Ph), 221 (M^+ − SO_2Ph − H_2O), 203, 151, 89, and 69 (100); found M^+ + H, 381.2079; $C_{21}H_{33}O_4S$ requires M^+, 381.2091.

The second isomer, B, to be eluted (2.85 g, 30%) was a colorless oil: $[\alpha]^{25}_D$ −33.2° (*c* 4.20, $CHCl_3$); IR_{max} (film), 1660 cm^{-1} br (C=C); ^{1}H NMR (300 MHz) δ 1.07 (3 H, s, C_3-Me), 1.15 (3 H, d, *J* = 1.0 Hz, C_7-Me), 1.21 (3 H, d, *J* = 6.6 Hz, C_1-H), 1.59 (3 H, s, C_{12}-H), 1.64 (1 H, m, C_4-H), 1.68 (3 H, s, C_{11}-Me), 1.98 (4 H, br m, C_8-H and C_9-H), 2.31 (1 H, br s, 20 H), 2.68 (1 H, dd, *J* = 14.5 Hz, *J* = 2.8 Hz, C_4-H), 2.79 (1 H, br s, C_3-OH), 3.65 (1 H, q, *J* = 6.6 Hz, C_2-H), 4.23 (1 H, ddd, *J* = 10.4 Hz, *J* = 8.0 Hz, *J* = 2.8 Hz, C_5-H), 5.05 (1 H, br m, C_{10}-H), 5.08 (1 H, dd, *J* = 10.4 Hz, *J* = 1 Hz, C_6-H), 7.52 (2 H, m, Ar-H), 7.61 (1 H, m, Ar-H), and 7.84 (2 H, m, Ar-H); ^{13}C NMR (75 MHz) δ 16.1 (q, C_7-Me), 17.4 (q, C-1), 17.5 (q, C_{12}), 23.4 (q, C_3-Me), 25.5 (q, C_{11}-Me), 25.9 (5, C=$CRCH_2$), 32.9 (t, C_4), 39.5 (t, C=$CRCH_2$), 60.8 (d, C_5), 73.8 (s, C_3), 74.6 (d, C_2), 119.3 (d, C_6), 123.4 (d, C_{10}), 128.5 (d, Ar-CH), 129.26 (d, Ar-CH), 131.86 (s, C=CR_1R_2), 133.3 (d, Ar-CH), 137.4 (s, C=CR_1R_2), 133.3 (d, Ar-CH), 137.4 (s, C=CR_1R_2), and 144.51 (s, Ar-C); MS (EI), Me 381 (M^+ + H, 55%), 363 (M^+ − OH, 15), 239 (M^+ − SO_2Ph, 56), 221 (M^+ − SO_2Ph − H_2O, 67), 203 (58), 151 (100), 89 (88), and 69 (95); found (M^+ + H), 381.2073; $C_{21}H_{33}O_4S$ requires M^+, 381.2091.

(2*R*,3*S*,5*RS*,6*E*)-2-[(*tert*-Butyldimethylsilyl)oxy]-5-(phenylsulfonyl)-3,7,11-trimethyl-6,10-dodecadien-3-ol (32A and 32B). To a solution of **31** (isomer A) (3.6 g, 9.46 mmol) and 2,6-lutidine (2.03 g, 18.9 mmol) in dichloromethane (11 mL) cooled to 0 °C under argon was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (3.25 g, 12.3 mmol) dropwise. After stirring the mixture for 1 h at 0 °C, the mixture was poured into a saturated solution of $NaHCO_3$ and extracted with dichloromethane. The combined extracts were processes as usual to give a residue which was purified by flash column chromatography (15% ethyl acetate–hexanes) to afford **32** (isomer A) (3.91 g, 84%) as a colorless oil: $[\alpha]^{25}_D$ −8.6° (*c* 1.25 in $CHCl_3$); ^{1}H NMR (300 MHz) δ 0.05 (3 H, s, Si-Me), 0.08 (3 H, s, Si-Me), 0.88 (9 H, s, *tert*-butyl), 1.12 (3 H, s, C_3-Me), 1.13 (3 H, d, *J* = 6.4 Hz, C_1-H), 1.18 (3 H, d, *J* = 1.4 Hz, C_7-Me), 1.59 (3 H, s, C_{12}-H), 1.69 (3 H, s, C_{11}-Me), 1.93 (5 H, m, C_4-H, C_8-H), and C_9-H), 2.19 (1 H, s, C_3-OH), 2.34 (1 H, dd, *J* = 14.3 Hz, *J* = 2.4 Hz, C_4-H), 3.60 (1 H, q, *J* = 6.4 Hz, C_2-H), 4.00 (1 H, ddd, *J* = 10.3 Hz, *J* = 8.8 Hz, *J* = 4.4 Hz, C_5-H), 5.05 (2 H, m, C_6-H and C_{10}-H), 7.51 (2 H, m, Ar-H), 7.61 (1 H, m, Ar-H), and 7.85 (2 H, m, Ar-H); ^{13}C NMR (75 MHz) δ −5.1 (q, Si-Me), −4.1 (q, Si-Me), 16.2 (q, C_7-Me), 17.5 (q, C_{12}), 17.8 [2C, q and s, C_1 and *tert*-butyl], 22.6 (q, C_3-Me), 25.5 (q, C_{11}-Me), 25.7 (q, *tert*-butyl), 26.1 (t, allylic CH_2), 33.7 (t, C_4), 39.6 (t, allylic, CH_2), 61.3 (d, C_5), 74.2 (d, C_2), 75.2 (s, C_3), 119.3 (d, C_6), 123.6 (d, C_{10}), 128.5 (d, Ar-CH), 129.3 (d, Ar-CH), 131.9 (d, Ar-CH), 133.2 (s, C=CR_1R_2), 137.8 (s, C=CR_1R_2), and 143.9 (s, Ar-C); MS (EI, *m/e*) 495 (M^+ + H, 67%), 477 (M^+ − OH, 59), 437 (M^+ − *tert*-Bu, 23), 353 (M^+ − SO_2Ph, 55), 335 (72), 203 (100), 151 (98), and 69 (88); found: (M^+ + H), 495.2952; $C_{27}H_{47}O_4SSi$ requires M^+, 495.2964.

By using the above described procedure, sulfone isomer **31B** was converted to **32B** in 83% yield.

(4*E*,6*RS*,8*S*,9*R*)-9-[(*tert*-Butyldimethylsilyl)oxy]-4,8-dimethyl-4-dodecaene-1,9-diol (33). A solution of **32A** (3.71 g, 7.50 mmol) in methanol (130 mL) was cooled to −78 °C, and a stream of ozone gas was passed through the stirred solution. The progress of the reaction was monitored by TLC (40% EtOAc–hexanes). After only a trace of diene could be detected (<1 h) by TLC, the ozone flow was discontinued, and argon was bubbled through the solution (2 min). Solid sodium borohydride (2.5 g, 66 mmol) was added in one portion, and the mixture was allowed to warm to room temperature. After stirring at room temperature for an additional 1 h, the methanol was removed under reduced pressure, ethyl acetate (300 mL) and brine (50 mL) were added, and the aqueous phase was extracted with ethyl acetate. The combined organic extracts were processed, and the residue was purified by flash chromatography (40% EtOAc–hexanes) to afford the expected diol (3.06 g, 87%) as a colorless oil: $[\alpha]^{25}_D$ 17.3° (*c* 1.08, $CHCl_3$); MS for $C_{24}H_{43}O_5Si$, MH^+, 471.2601, found 471.2604.

The same procedure was followed for the isomeric sulfone **32B** to give the corresponding diol in 78% yield: $[\alpha]^{25}_D$ −48.9° (*c* 0.95, $CHCl_3$).

Anhydrous ammonia (~75 mL) was condensed into a reaction vessel containing a solution of the preceding diols individually (2.0 g, 4.25 mmol) in ethanol (20 mL). The resultant mixture was maintained under reflux (−33 °C), while sodium (1.5 g, 65.2 mmol) was added portionwise over 3 h. Once all the sodium had dissolved and the blue color had discharged, granular ammonium chloride (3.74 g, 70.0 mmol) was added, and the liquid ammonia was allowed to evaporate (approximately 3 h). Ethyl acetate (200 mL) and water (20 mL) were added, and the mixture was extracted with ethyl acetate. The combined organic extracts were processed as usual, and the residue was purified by flash column chromatography (gradient elution: 10–40% EtOAc–hexanes) to afford **34**

(630 mg, 40%) and **33** (410 mg, 29%). An analytical sample of **34** was obtained by preparative HPLC (Waters 500, silica, 4% EtOAc–hexanes): $[\alpha]^{25}_D$ −13.5° (*c* 1.08, $CHCl_3$), MS calcd for $C_{20}H_{41}O_4Si$, MH^+ 373.2774, found 373.2744. An analytical sample of **33** was obtained by preparatory HPLC (20% EtOAc–hexanes): $[\alpha]^{25}_D$ −15.1° (*c* 1.04, $CHCl_3$); MH^+ calcd for $C_{18}H_{39}O_3Si$, MH^+, 331.2668, found, 331.2664.

Acetylation of **33**, with acetic anhydride in dichloromethane in the presence of DMAP and triethylamine, 0 °C, 30 min, afforded **34**, in 93% yield contaminated (~7%) with the 4(*Z*)-olefinic isomer.

(1″*R*,2′*R*,4*S*,5′*S*)-4-Hydroxy-4-[5′-[1″-[(*tert*-butyldimethylsilyl)oxy]ethyl]-2′,3′,4′,5′-tetrahydro-5′-methylfuran-2′-yl]pentyl Ethanoate (35). Vanadyl acetylacetonate (150 mg, 0.57 mmol, 15 mol %) was added to a stirred solution of **34** (1.4 g, 3.76 mmol) in anhydrous hexanes (25 mL), and the resulting suspension was stirred for 15 min at room temperature. Powdered activated 3Å molecular sieves (280 mg, 20 wt % based on **31**) were added, and the green heterogeneous mixture was stirred for an additional 10 min, whereupon an anhydrous solution of *tert*-butyl hydroperoxide (1.35 mL of a 5.6 molar solution, 7.56 mmol) in dichloromethane was added dropwise. The resulting deep red suspension was stirred for 36 h at room temperature whereby a light yellow solution was obtained. Additional vanadyl acetylacetonate (150 mg, 0.57 mmol) and *tert*-butyl hydroperoxide (1.35 mL of a 5.6 molar CH_2Cl_2 solution, 7.56 mmol) were added after 12 and 24 h resulting in a reappearance of the red color. Acetic acid (1 mL) and water (0.5 mL) were added, and the reaction was stirred for 3 h at room temperature. Ethyl acetate (200 mL) was added, and the resulting mixture was filtered through a pad of Celite. The filtrate was processed as usual, and the residue was purified by flash column chromatography (gradient elution to 10–15% ethyl acetate–hexanes) to afford a 9:1 mixture of **35** and its trans isomer (1.02 g, 70%).

An analytical sample of pure **35** was prepared by preparative TLC: $[\alpha]^{25}_D$ −8.5°, (*c* 1.06 in $CHCl_3$); ^1H NMR (300 MHz) δ 0.06 (3 H, s, Si-Me), 0.08 (3 H, s, Si-Me), 0.88 (9 H, s, *tert*-butyl), 1.12 (3 H, s, C_5-Me), 1.13 (3 H, d, *J* = 6.3 Hz, $C_{2''}$-H), 1.19 (3 H, s, C_5-H), 1.37 (1 H, m, C_3-H), 1.50 (1 H, m, C_3-H), 1.58 (1 H, m, C_4-H), 1.68 (1 H, m, C_2-H), 1.75 (1 H, m, C_2-H), 1.83 (2 H, m, C_3-H), 1.99 (1 H, m, C_4-H), 2.05 (3 H, s, COMe), 2.21 (1 H, s, OH), 3.66 (1 H, q, *J* = 6.3 Hz, $C_{1''}$-H), 3.81 (1 H, dd, *J* = 7.3 Hz, *J* = 7.2 Hz, $C_{2'}$-H), and 4.07 (2 H, m, C_1-H); ^{13}C NMR (75 MHz) δ −4.7 (1, Si-Me), −4.3 (q, Si-Me), 17.8 (s, *tert*-butyl), 18.6 (q, $C_{2''}$), 20.3 (q, $C_{5''}$-Me), 20.7 (q, COMe), 22.8 (t, C_2), 23.9 (q, C_5), 25.2 (t, $C_{3'}$), 25.7 (q, *tert*-butyl), 33.8 (t, C_3), 34.3 (t, $C_{4'}$), 64.8 (t, C_1), 72.5 (s, C_4), 72.9 (d, $C_{1''}$), 84.2 (d, $C_{2'}$), 85.4 (s, $C_{5'}$), and 170.8 (s, CO); *m/e* (CI; isobutane) 389 (M^+ + 1, 32%). Anal. Calcd for $C_{20}H_{40}O_5Si$: C, 61.80; H, 10.4. Found: C, 61.60; H, 10.3.

(1″*R*,2′*R*,4*S*,5′*S*)-4-[[(Diphenylisopropoxy)silyl]oxy]-4-[5′-[1″-[(*tert*-butyldimethylsilyl)oxy]ethyl]-2′,3′,4′,5′-tetrahydro-5′-methylfuran-2′-yl]pentyl Ethanoate (36). To a stirred solution of **35** [(0.924 g, 2.38 mmol, 90% (2′*R*,4*S*) isomer] and triethylamine (0.49 g, 4.88 mmol) in DMF (10 mL) was added diphenylisopropoxysilyl chloride[64] (1.63 g of 81% pure silyl chloride, 4.76 mmol) dropwise. The solution was stirred for 20 h at room temperature. Ether and saturated $NaHCO_3$ solution were added, and the mixture was extracted with ether. The combined etheral layers were processed, and the residue was purified by flash column chromatography (5% EtOAc–hexanes) to afford a 9:1 mixture of **36** and its trans isomer **36A** (1.40 g, 94%).

An analytical sample of pure **36** was prepared by preparative TLC: $[\alpha]^{25}_D$ −2.53° (*c* 0.99 in $CHCl_3$); ^1H NMR (300 MHz) δ 0.01 (3 H, s, Si-Me), 0.04 (3 M, s, Si-Me), 0.88 (9 H, s, *tert*-butyl), 1.07 (3 H, s, C_5-Me), 1.11 (3 H, d, *J* = 6.2 Hz, $C_{2''}$-H), 1.15 (3 H, d, *J* = 6.1 Hz, $OCHMe_2$), 1.18 (3 H, d, *J* = 6.1 Hz, $OCHMe_2$), 1.20 (3 H, s, C_5-H), 1.45 (1 H, m, C_3-H), 1.64 (2 H, m, C_3-H and C_4-H), 1.66–1.80 (3 H, m, C_2-H and C_4-H), 1.88 (2 H, m, C_3-H), 2.02 (3 H, s, COMe), 3.55 (1 H, q, *J* = 6.2 Hz, $C_{1''}$-H), 3.92 (2 H, m, C_1-H), 3.99 (1 H, dd, *J* = 7.1 Hz, *J* = 7.0 Hz, $C_{2'}$-H), 4.19 (1 H, septet, *J* = 6.1 Hz, $OCHMe_2$), 7.32–7.44 (6 H, m, Ar-H), and 7.64–7.67 (4 H, m, Ar-H); ^{13}C NMR (75 MHz) δ −5.0 (q, Si-Me), −4.1 (q, Si-Me), 17.8 (s, *tert*-butyl), 18.3 (q, $C_{2''}$), 18.8 (q, $C_{5''}$-Me), 20.8 (q, COMe), 22.8 (q, C_5), 23.0 (t, C_2), 25.5 (q, $OCHMe_2$) 25.7 (q, *tert*-butyl), 26.1 (t, $C_{3'}$), 36.1 (t, $C_{4'}$), 36.5 (t, C_3), 65.0 (t, C_1), 65.7 (d, $OCHMe_2$), 73.6 (d, $C_{1''}$), 78.3 (s, C-4), 82.8 (d, $C_{2'}$), 85.3 (s, $C_{5'}$), 127.4 (d, Ar-CH), 129.6 (d, Ar-CH), 135.0 d, Ar-CH), 135.58 (s, Ar-C), 135.62 (s, Ar-C), and 170.9 (s, COMe); *m/z* (EI) *m/e* 551 ($M^+ - C_6H_5$, 2%), 469 (76), 409 (75), 385 (100), 325 (80), 241 (98), 199 (89), and 85 (76). Anal. Calcd for $C_{35}H_{56}O_6Si_2$: C, 66.80; H, 9.0. Found: C, 67.1; H, 9.0.

(1″*R*,2′*R*,4*S*,5′*S*)- and (1″*R*,2′*S*,4*R*,5′*S*)-4-[[(Diphenylisopropoxy)silyl]oxy]-4-[5′-[1″-[(*tert*-butyldimethylsilyl)oxy]ethyl]-2′,3′,4′,5′-tetrahydro-5′-methylfuran-2′-yl]-1-pentanol (37 and 37A). A solution of lithium aluminum hydride (1.60 mL of a 1 M solution, 1.60 mmol) in ether was added dropwise to a cooled (−25 °C), stirred solution of acetates **36** and **36A** and (1.36 g, 2.16 mmol, 9:1 mixture) in 20 mL of ether. The mixture was stirred for 20 min at −25 °C. Sodium sulfate decahydrate (1 g) was added, and the mixture was allowed to warm to room temperature. Ether (100 mL) was added, and the mixture was processed as usual. The residue was purified by flash column chromatography (gradient **5** to 10% EtOAc–hexanes) to afford two compounds.

The first to be eluted was the (1″*R*,2′*S*,4*R*,5′*S*) minor trans isomer **37A** (120 mg, 10%): $[\alpha]^{25}_D$ −7.0° (*c* 1.06, $CHCl_3$). The second compound to be eluted was the expected cis isomer **37**, (1.09 g, 86%): $[\alpha]^{25}_D$ −1.5° (*c* 1.00, $CHCl_3$); ^1H NMR (300 MHz) δ −0.04 (3 H, s, Si-Me), 0.02 (3 H, s, Si-Me), 0.86 (9 H, s, *tert*-butyl), 1.07 (3 H, s, C_5-Me), 1.09 (3 H, d, *J* = 6.2 Hz, $C_{2'}$-H), 1.14 (3 H, d, *J* = 6.0 Hz, $OCHMe_2$), 1.17 (3 H, d, *J* = 6.0 Hz, $OCHMe_2$), 1.18 (3 H, s, C_5-H), 1.42–1.72 (6 H, br m, C_2-H, C_3-H, C_4-H, and OH), 1.73–1.99 (3 H, br m, C_3-H and C_4-H), 3.47 (2 H, m, C_1-H), 3.54 (1 H, q, *J* = 6.2 Hz, $C_{1''}$-H), 4.02 (1 H, dd, *J* = 7 Hz, $C_{2'}$-H), 4.16 (1 H, septet, *J* = 6.0 Hz, $OCHMe_2$), 7.31–7.44 (6 H, br m, Ar-H), and 7.62–7.65 (4 H, m, Ar-H); ^{13}C NMR (75 MHz) δ −5.0 (q, Si-Me), −4.1 (q, Si-Me), 17.8 (s, *tert*-butyl), 18.3 (q, $C_{2'}$), 18.8 (q, $C_{5''}$-Me), 22.9 (q, C_5), 25.5 (q, $OCHMe_2$), 25.7 (q, *tert*-butyl), 26.0 (t, $C_{3'}$), 26.8 (t, C_2), 36.0 (t, $C_{4'}$), 36.3 (t, C_3), 63.3 (t, C_1), 65.7 (d, $OCHMe_2$), 73.6 (d, $C_{1''}$), 78.5 (5, C_4), 82.7 (d, C-Z′), 85.4 (s, $C_{5'}$), 127.4 (d, Ar-CH), 129.7 (d, Ar-CH), 135.50 (d, Ar-CH), 135.52 (s, Ar-C), and 135.6 (s, Ar-C); *m/e* (EI) 527 ($M^+ - O - i$-Pr, 7%), 469 ($M^+ - O - i$-Pr − *t*-Bu, 3, 427 (20) 367 (96), 309 (15), 283 (100), 265 (71), 241 ($SiPh_2O$-*i*-Pr, 62), 199 (87), 183 (47), and 169 (67); found: $M^+ - O - i$-Pr (EI), 527.3042; $C_{30}H_{47}O_4Si_2$ requires M^+, 527.3012.

(1″*R*,2*S*,2′*R*,5′*S*)-2-[[(Diphenylisopropoxy)silyl]oxy]-5-iodo-2-[5′-[1″-[(*tert*-butyldimethylsilyl)oxy]ethyl]-2′,3′,4′,5′-tetrahydro-5′-methylfuran-2′-yl]pentane, (38). To a stirred solution of triphenylphosphine (209 mg, 0.80 mmol) in THF (3 mL) and acetonitrile (2.5 mL) was added imidazole (109 mg, 1.60 mmol) followed by iodine (203 mg, 0.80 mmol). The resulting dark brown solution was stirred for 20 min at room temperature, whereupon a solution of alcohol **37** (123 mg, 0.27 mmol) in THF (2 mL) was added dropwise. After stirring for a further 4 h, the mixture was poured into saturated sodium thiosulfate solution and extracted with ether. The ether extract was concentrated to dryness under reduced pressure, and the residue was preabsorbed onto florisil (2 g) and purified by flash column chromatography (5% EtOAc–hexanes) to afford **38** (140 mg, 91%) as a colorless oil: $[\alpha]^{25}_D$ 1.6° (*c* 1.10, $CHCl_3$); ^1H NMR (300 MHz) δ −0.01 (3 H, s, Si-Me), −0.02 (3 H, s, Si-Me), 0.86 [9 H, s, Si-C(Me)$_3$], 1.05 (3 H, s, C_5-Me), 1.10 (3 H, d, *J* = 6.2 Hz, $C_{2''}$-H), 1.14 (3 H, d, *J* = 6.1 Hz, Si-$OCHMe_2$), 1.166 (3 H, s, C_1-H), 1.170 (3 H, d, *J* = 6.1 Hz, Si-$OCHMe_2$), 1.45 (1 H, m, C_3-H), 1.56–1.71 (2 H, m, C_3-H and C_4-H), 1.72–2.00 (5 H, C_3-H, C_4-H, and C_4-H), 1.95 (2 H, m, C_5-H), 3.53 (1 H, q, *J* = 6.2 Hz, $C_{1''}$-H), 3.94 (1 H, dd, *J* = 7 Hz, 2′-H), 4.19 (1 H, septet, *J* = 6.1 Hz, Si-$OCHMe_2$), 7.34–7.41 (6 H, m, Ar-H), and 7.60–7.65 (4 H, m, Ar-H); ^{13}C NMR (75 MHz) δ −5.0 (q, Si-Me), −4.1 (q, Si-Me), 7.2 (t, C_5), 17.8 (s, *tert*-butyl), 18.3 (q, $C_{2''}$), 18.7 (q, $C_{5''}$-Me), 22.9 (q, C_1), 25.5 (q, $OCHMe_2$), 25.7 (q, *tert*-butyl), 26.1 (t, $C_{3'}$), 28.2 (t, C_4), 36.1 (t, $C_{4'}$), 41.3 (t, C_3), 65.7 (d, $OCHMe_2$), 73.6 (d, $C_{1''}$), 78.2 (s, C_2), 82.9 (d, $C_{2'}$), 85.4 (s, $C_{5'}$), 127.4 (d, Ar-CH), 127.5 (d, Ar-CH), 129.7 (d, Ar-CH), 134.9 (d, Ar-CH), 135.0 (d, Ar-CH), 135.4 (s, Ar-C), and 135.5 (s, Ar-C); *m/e* (CI; isobutane) 696 (M^+, 7%), 695 (M^+ − H, 14), 681 (M^+ − Me, 9) 637 ($M^+ - OC_3H_7$, 48), 569 (M^+ − I, 44), 537 (39), 511 ($M^+ - i$-Pr, 36), 439 (56), 313 (53), and 57 (100); found M^+ + H (FAB), 697.2433; $C_{33}H_{54}O_4Si_2I$ requires M^+, 697.2607.

(1″*R*,4*S*,2′*R*,5′*S*)-Triphenyl-[4-[[(diphenylisopropoxy)silyl]oxy]-4-[5′-[1″-[(*tert*-butyldimethylsilyl)oxy]ethyl]-2′,3′,4′,5′-tetrahydro-5′-methylfuran-2′-yl]pentyl]phosphonium Iodide (39). Iodide **38** (381 mg, 0.55 mmol) was dried by coevaporation with anhydrous toluene (5 × 3 mL). To the residue was added dry triphenylphosphine (172 mg, 0.66 mmol) and anhydrous toluene (3 mL), and the resulting solution was concentrated to dryness on a rotary evaporator. The residue was dissolved in anhydrous acetonitrile (0.85 mL) and stirred under an argon atmosphere. Anhydrous diisopropylethylamine (70 mg, 0.55 mmol) was added, and the mixture was stirred at 90 °C for 20 h. The mixture was cooled to room temperature, then concentrated to dryness under reduced pressure, and dired under high vacuum (0.05 mmHg) for 1 h. The residue was washed with anhydrous hexanes (5 × 5 mL), and dried by coevaporation with anhydrous toluene (5 × 5 mL). The residual solvents were removed under high vacuum (0.05 mmHg, 2 h) to afford the crude phosphonium iodide **39** (495 mg, 94%) as a white foam which was used immediately in the next step.

Wittig Coupling of 25 and 39—Olefins 40 and 41. A solution of crude phosphonium iodide **39** (495 m, 0.52 mmol) in anhydrous toluene (10 mL) was cooled to −78 °C under argon. A solution of sodium bis(trimethylsilyl)amide (364 μL of a 1.0 M solution, 0.36 mmol) in THF was added dropwise over 5 min. The resultant bright orange solution of ylid was stirred for an additional 15 min at −78 °C whereupon, a cooled solution of aldehyde **25** (139 mg, 0.30 mmol) in toluene (totally volume

of 2 mL including rinsing of flask) was added dropwise via a canula.[13] The resulting pale yellow solution was stirred at −78 °C for 1 h and then allowed to warm to room temperature (2 h). After stirring for an additional 1 h at room temperature, the reaction mixture was diluted with ether and filtered through a Celite pad. The filtrate was concentrated to dryness under reduced pressure. The residues were dissolved in dichloromethane (5 mL), preabsorbed onto florisil (4 g), and purified by flash column chromatography (4% ether–hexanes) to afford a mixture *Z* and *E* olefins **40** [≤95% *Z* olefin by ^{1}H NMR] (280 mg, 91%): $[\alpha]^{25}_D$ + 9.3° (*c* 1.11 in $CHCl_3$); ^{1}H NMR (300 MHz) δ 0.02 (3 H, s, Si-Me), 0.05 (3 H, s, Si-Me), 0.05 (3 H, s, Si-Me), 0.64 (3 H, d, *J* = 6.6 Hz, C_4-Me), 0.89 (9 H, s, *tert*-butyl), 1.02 (3 H, d, *J* = 7.0 Hz, C_2-Me), 1.09 (3 H, s, C_{14}-Me), 1.12 (3 H, d, *J* = 6.2 Hz, C_{16}-H), 1.15 (3 H, d, *J* = 6.0 Hz, $OCHMe_2$), 1.19 (3, d, *J* = 6.0 Hz, $OCHMe_2$), 1.20 (3 H, s, C_{10}-Me), 1.28 (3 H, s, $OOCMe_2$), 1.30 (3 H, s, $OOCMe_2$), 1.34–1.58 (2 H, m, C_9-H), 1.59–1.72 (2 H, m, C_4-H and C_{13}-H), 1.74–2.00 (3 H, br m, C_{12}-H and C_{13}-H), 2.07 (1 H, m, C_2-H), 2.22 (2, m, C_8-H), 3.00 (1 H, dd, *J* = 9.3 Hz, *J* = 6.8 Hz, C_1-H), 3.31 (1 H, dd, *J* = 9.3 Hz, *J* = 5.9 Hz, C_1-H), 3.38 (1 H, dd, *J* = 8.8 Hz, *J* = 1.7 Hz, C_3-H), 3.55 (1 H, q, *J* = 6.2 Hz, C_{15}-H), 4.03 (1 H, dd, *J* = 7.1 Hz, *J* = 7.1 Hz, C_{11}-H), 4.16 (2 H, m, C_5-H) and $OCHMe_2$), 5.16 (1 H, dd, *J* = 10.8 Hz, *J* = 9.1 Hz, C_6-H), 5.45 (1 H, ddd, *J* = 10.8 Hz, *J* = 7.4 Hz, *J* = 7.4 Hz, C_7-H), 7.20–7.50 (21 H, br m, Ar-CH), and 7.64–7.66 (4 H, m, Ar-CH); ^{13}C NMR (75 MHz) δ −5.0 (q, Si-Me), −4.0 (q, Si-Me), 12.1 (q, C_4-Me), 15.9 (q, C_2-Me), 17.7 [s, *tert*-butyl), 18.3 (q, C_{16}), 18.7 (q, C_{14}-Me), 19.2 (q, $OOCMe_2$), 22.4 (t, C_8), 22.8 (q, C_{10}-Me), 25.5 (q, $OCHMe_2$), 25.7 (q, *tert*-butyl), 26.1 (t, C_{12}), 30.0 (q, $OOCMe_2$), 34.9 (d, C_2), 35.8 (d, C_4), 36.2 (t, C_{13}), 39.6 (t, C_9), 64.0 (t, C_1), 65.6 (d, $CHMe_2$), 70.7 (d, C_5), 73.6 (d, C_{15}), 77.3 (d, C_3), 78.2 (s, C_{10}), 82.5 (d, C_{11}), 85.2 (s, C_{14}), 86.6 (s, CPh_3), 97.8 (d, $OOCMe_2$), 126.6 (d, trityl-CH), 127.37 (d, Si-Ar-CH), 127.41 (d, SiAr-CH), 127.49 (d, trityl-CH), 128.7 (d, trityl-CH), 128.8 (d, C_6), 129.6 (d, SiAr-CH), 134.4 (d, C_{76}), 134.9 (d, SiAr-CH), 135.5 (s, SiAr-C), and 144.5 (s, trityl-C).

Treatment of **40** (381 mg, 0.38 mmol) in THF (3 mL) with 1 M tetra-*n*-butylammonium fluoride gave **41** (210 mg, 72%), $[\alpha]^{25}_D$ 7.0° (*c* 1.03, $CHCl_3$), and the corresponding dihydroxy compound resulting from deprotection of the TBDMS group (36 mg, 14%): $[\alpha]^{25}_D$ 8.33° (*c* 0.54, $CHCl_3$). The latter could be selectively silylated to give **41** (80%).

Bis-THF Trityl Ether 42. A stirred solution of (*Z*)-hydroxyalkene **41** (121 mg, 156.7 μmol) in THF (1.26 mL) and water (0.79 mL), in an open-top vessel, was cooled to 0 °C. Mercury trifluoroacetate (134 mg, 313.4 μmol) was added in one portion, and the resulting heterogeneous mixture was stirred at 0 °C for 2 h. A solution of 10% aqueous NaOH (160 μL, 400 μmol) was added dropwise, and the resulting yellow heterogeneous mixture was stirred for a further 30 min at 0 °C. A solution of sodium borohydride (300 mg) in 10% aqueous sodium hydroxide solution (2.7 mL) was prepared, and 121 μL of this solution was added dropwise to the reaction mixture (30 sec). The resulting grey mixture was stirred at 0 °C for a further 5 min, and then poured into water and extracted with ether. The combined extracts were processed as usual, and the residue was purified by flash chromatography (5% EtOAc–hexanes and then 10% EtOAc–hexanes to elute the starting material). The first compound to be eluted was a mixture of (7*S* and 7*R*)-bis-THF trityl ethers **42** (>95%) and the trans isomer (≤5%) as a colorless oil (98 mg; 81%): $[\alpha]^{25}_D$ −21.0° (*c* 1.02, $CHCl_3$); ^{1}H NMR (300 MHz) δ 0.04 (3 H, s, Si-Me), 0.06 (3 H, s, Si-Me), 0.71 (3 H, d, *J* = 6.5 Hz, C_4-Me), 0.88 (9 H, s, *tert*-butyl), 0.96 (3 H, d, *J* = 7.0 Hz, C_2-Me), 1.10 (3 H, s, Me), 1.11 (3 H, d, *J* = 6.2 Hz, C_{16}-H), 1.12 (3 H, s, Me), 1.22 (3 H, s, $OOCMe_2$), 1.32 (3 H, s, $OOCMe_2$), 1.42–1.72 (6 H, br m, C_4-H, C_6-H, C_8-H, C_9-H, C_{12}-H, and C_{13}-H), 1.73–1.96 (5 H, br m, C_6-H, C_8-H, C_9-H, C_{12}-H, and C_{13}-H), 2.04 (1 H, m, 2-H), 2.97 (1 H, dd, *J* = 9.3 Hz, *J* = 6.5 Hz, C_1-H), 3.26 (1 H, dd, *J* = 9.3 Hz, *J* = 6.0 Hz, C_1-H), 3.37 (2 H, br m, C_3-H and C_5-H), 3.61 (1 H, q, *J* = 6.2 Hz, C_{15}-H), 3.90 (1 H, dd, *J* = 7.6 Hz, *J* = 6.6 Hz, C_{11}-M), 4.09 (1 H, m, H-H), 7.19–7.31 (9 H, br m, Ar-H), and 7.43–7.46 (6 H, m, Ar-H); ^{13}C NMR (75 MHz) δ −4.9 (q, Si-Me), −4.0 (q, Si-Me), 12.1 (q, C_4Me), 16.0 (q, C_2-Me), 17.8 (s, *tert*-butyl), 18.2 (q, Me), 19.1 (q, $OOCMe_3$), 19.3 (q, Me), 23.8 (q, C_{16}), 25.7 (q, *tert*-butyl), 26.9 (t, C_{12}), 29.9 (q, $OOCMe_2$), 31.2 (t, C_8), 34.3 (t, C_{13}), 34.9 (d, C_{20}, 35.9 (C_2, t and d, C_4 and C_9), 39.2 (t, C_6), 64.2 (t, C_1), 72.3 (d, C_5), 73.3 (d, C_{150}), 77.0 (d, C_7), 77.5 (d, C_3), 83.4 (s, C_{10}), 84.3 (d, C_{11}), 85.3 (s, C_{14}), 86.3 (s, CPh_3), 97.4 (s, $OOCMe_2$), 126.6 (d, Ar-CH), 127.5 d, (d, Ar-CH), 128.7 (d, Ar-CH), and 144.5 (s, Ar-C).

The second compound to be eluted was unreacted (*Z*)-hydroxyalkene **41** (11 mg, 9%).

Bis-THF Alcohol 43. Anhydrous ammonia (approximately 10 mL) was condensed into a two-necked, round-bottomed flask containing a solution of bis-THF trityl ethers **42** and its minor isomer [70.0 mg, 90.7 μmol; approximately 95% (7*S*): 5% (7*R*)] in THF (1.5 mL). The resulting solution was stirred under reflux −33 °C. Sodium (<5 mg, sufficient to maintain a blue color) was added, and the resulting deep blue solution was stirred under reflux (−33 °C) for 15 min. Ethanol (100%) was added dropwise until the deep blue color discharged. Sodium (<5 mg, sufficient to reestablish a blue color) was added, and the blue solution was stirred for a further 15 min. The reaction was then quenched with the minimum amount of ethanol, and the above sequence was repeated for a total of four additions of sodium. After the final ethanol quench, the colorless solution was stirred for an additional 5 min at −33 °C, then ammonium chloride (1 g) was added, and the liquid ammonia was allowed to evaporate (3 h). Water was added, the mixture was extracted with ethyl acetate, and the combined extracts were dried and processed. The residue was purified by flash column chromatography (gradient elution 10–20% EtOAc–hexanes) to afford **43** as a colorless oil (42 mg, 87%): $[\alpha]^{25}_D$ −20.9° (*c* 0.604, $CHCl_3$); ^{1}H NMR (300 MHz) δ 0.04 (3 H, s, Si-Me), 0.05 (3 H, s, Si-Me), 0.77 (3 H, d, *J* = 6.6 Hz, 4-Me), 0.87 (9 H, s, *tert*-butyl), 1.10–1.14 (12 H, br m, C_2-Me, C_{10}-Me, C_{14}-Me, and C_{16}-H), 1.34 (3 H, s, $OOCMe_2$), 1.37 (3 H, s, $OOCMe_2$), 1.50–1.74 (6 H, br m, C_4-H, C_8-H, C_9-H, C_{12}-H, and C_{13}-H), 1.78–2.04 (6 H, br m, C_2-H, C_6-H, C_8-H, C_9-H, C_{12}-H, and C_{13}-H), 2.85 (1 H, br s, OH), 3.42–3.56 (3 H, m, C_1-H, C_3-H, and C_5-H), 3.90 (1 H, q, *J* = 6.2 Hz, C_{15}-H), 3.89–4.00 (2 H, m, C_1-H and C_{11}-H), and 4.14 (1 H, m, C_7-H); ^{13}C NMR (75 MHz) δ −4.9 (q, Si-Me), −4.0 (q, Si-Me), 12.0 (q, C_4-Me), 15.2 (q, C_2-Me), 17.8 (s, *tert*-butyl), 18.2 (q, Me), 18.8 (q, $OOCMe_2$), 19.3 (q, Me), 24.0 (q, C_{16}), 25.7 (q, *tert*-butyl), 27.0 (t, C_{12}), 30.1 (q, $OOCMe_2$), 31.4 (t, C_8), 34.0 (t, C_{13}), 34.2 (d, C_2), 35.8 (t, C_9), 36.2 (d, C_4), 39.0 (t, C_6), 63.5 (t, C_1), 72.1 (d, C_5), 73.2 (d, C_{15}), 76.7 (d, C_7), 80.0 (d, C_3), 83.5 (s, C_{10}), 84.3 (d, C_{11}), 85.4 (s, C_{14}), and 98.0 (s, $OOCMe_2$); MS (FAB) 551 (M^+ + Na, 4%), 529 (M^+ + H), 471 (M^+ + *tert*-butyl) 423, 369, 328, 327, 199, and 73; found: M^+ + Na (FAB), 551.3660; $C_{29}H_{56}O_6Si$ Na, requires M^+, 551.3744.

Oxidation of 43. To a solution of oxalyl chloride (14.5 mg, 114.6 μmol) in dichloromethane (220 μL) cooled to −78 °C was added DMSO (17.0 mg, 218 μmol). The mixture was stirred 5 min at −78 °C and then added to a solution of **43** (30 mg, 56.7 μmol) in dichloromethane (0.44 mL) via a cannula. The mixture was stirred 0.5 h at −78 °C, and then triethylamine (34.8 mg, 344 μmol) was added. The white slurry was stirred for 15 min at −78 °C, then a pH 7 buffer solution was added at −78 °C, and the mixture was extracted with ether. The combined extracts were dried and concentrated under reduced pressure. The residue was purified by flash column chromatography (10% EtOAc–hexanes) to afford the aldehyde derived from **43** (26.8 mg, 90%) as a colorless oil: $[\alpha]^{25}_D$ −12.3° (*c* 0.675, $CHCl_3$); IR_{max} (CCl_4 solution) 1725 cm^{-1} (CO); ^{1}H NMR (300 MHz) δ 0.04 (3 H, s, Si-Me), 0.06 (3 H, s, Si-Me), 0.80 (3 H, d, *J* = 6.6 Hz, C_4-Me), 0.87 (9 H, s, *tert*-butyl), 1.10–1.13 (9 H, br m, C_{10}-Me, C_{14}-Me, and C_{16}-H), 1.18 (3 H, d, *J* = 7.0 Hz, C_2-Me), 1.33 (3 H, s, $OOCMe_2$), 1.40 (3 H, s, $OOCMe_2$), 1.50–1.72 (6 H, br m, C_4-H, C_6-H, C_8-H, C_9-H, C_{12}-H, and C_{13}-H), 1.78–2.02 (5 H, br m, C_6-H, C_8-H, C_9-H, C_{12}-H, and C_{13}-H), 2.52 (1 H, m), 2.0, 3.51 (1 H, m, C_5-H), 3.61 (1 H, q, *J* = 6.3 Hz, C_{15}-H), 3.58 (2 H, dd, *J* = 10.8 Hz, *J* = 1.8 Hz, C_3-H), 3.92 (1, dd, *J* = 7.4 Hz, *J* = 6.7 Hz, C_{11}-H), 4.13 (1 H, m, C_7-H), and 9.77 (1 H, d, *J* = 2.2 Hz, C_1-H); ^{13}C NMR (75 MHz) δ −5.0 (q, Si-Me), −4.0 (q, Si-Me), 11.4 (q, C_2-Me), 11.9 (q, C_4-Me), 17.8 (s, *tert*-butyl), 18.2 (q, Me), 18.9 (q, $OOCMe_2$), 19.3 (q, Me), 24.0 (q, C_{16}), 25.7 (q, *tert*-butyl), 27.0 (t, C_{12}), 29.8 (q, $OOCMe_2$), 31.4 (t, C_8), 33.9 (t, C_{13}), 35.8 (t, C_9), 36.3 (d, C_4), 38.8 (t, C_6), 47.4 (d, C_2), 72.0 (d, C_5), 73.2 (d, C_{15}), 76.7 (d, C_7), 76.9 (d, C_3), 83.5 (s, C_{10}), 84.3 (d, C_{11}), 85.3 (s, C_{14}), 97.9 (s, $OOCMe_2$), and 204.5 (d, C_1).

(2*R*,4*S*)-2,4-Dimethyl-6-(phenylsulfonyl)-1-[(triphenylmethyl)oxy]-hexane (44). To a solution of thioether **5** (264 mg, 0.55 mol) in 2 mL of dichloromethane was added 237 mg (1.1 mmol) of *m*-chloroperbenzoic acid at 0 °C. After 3 h, the solution was treated with sodium thiosulfate, and the mixture was processed to give 231 mg of the sulfone **44**: $[\alpha]^{25}_D$ 6.09° (*c* 1.29, $CHCl_3$). Anal. Calcd for $C_{33}H_{36}O_3S$: C, 77.31; H, 7.08. Found: C, 76.93; H, 7.47.

Julia Coupling of 43 and 44.[13] To a cooled (−78 °C), stirred solution of sulfone **44** (78.0 mg, 152 μmol) in THF (400 μL) was added a solution of *n*-butyllithium (75 μL of 1.60 M solution; 120 μmol) in hexanes. The resulting yellow solution was stirred at −78 °C for 15 min. In a second reaction vessel a solution of the aldehyde obtained from **46** (20.3 mg, 38.5 μmol) in THF (200 mL) was cooled to −78 °C with stirring. The cooled solution of sulfone anion was added via a cannula to the cooled (−78 °C) solution of aldehyde (about 15 s). The resulting yellow solution was stirred for an additional 1 h at −78 °C, whereupon acetic anhydride (16 μL, 169 μmol) was added, and the reaction mixture was warmed to room temperature. The reaction was stirred for a further 90 min at room temperature, then saturated NH_3Cl, aqueous solution was added, and the mixture was extracted with dichloromethane, dried, and concentrated to dryness. The resulting yellow oil was employed in the next reaction without further purification. To a cooled (−30 °C), stirred solution of the diastereomeric β-acetoxysulfones prepared above in anhydrous

methanol (0.9 mL) and anhydrous ethyl acetate (0.4 mL) was added freshly ground sodium amalgam (820 mg of 6% Na by weight) in a glove bag under argon. The reaction was vigorously stirred at −50 °C to −30 °C for 17 h. Ethyl acetate was added, and the liquid phase was decanted off. The solid residue was washed with ethyl acetate. The combined ethyl acetate washings were dried and concentrated to dryness under reduced pressure. The residue was purified by flash column chromatography (4% EtOAc–hexanes) to afford a 13:1 mixture of *E* and *Z* olefins **45** (17.6 mg, 52%): $[\alpha]^{25}_D$ −21.4° (*c* 1.02, $CHCl_3$). Repetition of the reaction twice gave essentially the same yield: ^{1}H NMR (300 MHz) δ 0.04 (3 H, s, Si-Me), 0.05 (3 H, s, Si-Me), 0.69 (3 H, d, *J* = 6.5 Hz, C_{10}-Me), 0.77 (3, d, *J* = 6.4 Hz, C_8-Me), 0.88 (7 H, s, Si-Me_3), 0.96 (3 H, d, *J* = 6.7 Hz, C_2-Me or C_4-Me), 1.00 (3 H, d, *J* = 6.9 Hz, C_4-Me or C_2-Me), 1.11 (3 H, s, C_{10}-Me or C_{20}-Me), 1.12 (3 H, s, C_{20}-Me or C_{16}-Me), 1.12 (3 H, d, *J* = 6.2 Hz, C_{22}-H), 1.32 (3 H, s, Me), 1.36 (3 H, s, Me), 0.80–2.04 (17 H, m, C_2-H, C_3-H, C_4-H, C_6-H, C_{10}-H, C_{12}-H, C_{14}-H, C_{15}-H), C_{18}-H, C_{19}-H), 2.22–2.40 (1 H, m, C_8-H), 2.83 (1 H, dd, J_{gem} = 8.8 Hz, $J_{1,2}$ = 6.6 Hz, C_1-H), 2.97 (1 H, dd, J_{gem} = 8.8 Hz, $J_{1,2}$ = 5.1 Hz, C_1-H′), 3.30 (1 H, dd, $J_{9,10}$ = 10.1 Hz, $J_{9,8}$ = 2.2 Hz, C_9-H), 3.47 (1 H, m, C_{11}-H), 3.61 (1 H, q, *J* = 6.2 Hz, C_{21}-H), 3.92 (1 H, dd, $J_{17,18}$ = 7.1 Hz, $J_{17,18'}$ = 7.1 Hz, C_{17}-H), 4.12 (1 H, m, C_{13}-H), 5.26 (1 H, m, C_6-H), 5.41 (1 H, dd, $J_{7,8}$ = 8.6 Hz, $J_{7,6}$ = 15.6 Hz, C_7-H), 7.20–7.32 (9 H, m, Ar-CH), 7.44–7.47 (6 H, m, Ar-H); ^{13}C NMR (75 MHz) δ −4.9 (q, Si-Me), −4.0 (q, Si-Me), 11.5 (q, C_{10}-Me), 17.8 (s, *tert*-butyl), 18.2 (2C, q, 2 × Me), 18.4 (q, $OOCMe_2$), 19.2 (q, Me), 19.9 (q, Me), 23.9 (q, C_{22}), 25.7 (q, *tert*-butyl), 26.9 (b C_{18}), 30.0 (q, $OOCe_2$), 30.4 (d, CH), 31.2 (t, C_{14}), 31.4 (d, CH), 34.3 (t, C_{19}), 35.9 (t, C_{15}), 36.3 (d, C_{10}), 38.4 (d, CH), 39.2 (t, C_{12}), 39.9 (t, CH_2), 41.3 (t, CH_2), 68.3 (t, C_1), 71.9 (d, C_{11}), 73.3 (d, C_{21}), 77.1 (d, C_{13}), 77.7 (d, C_9), 83.4 (s, C_{16}), 84.3 (d, C_{17}), 85.3 (s, C_{20}), 86.1 (s, C Ph_3), 97.4 (s, $OOCMe_2$), 126.7 (d, Ar-CH), 127.5 (d, Ar-CH), 128.7 (d, Ar-CH), 129.5 (d, C=CH), 132.3 (d, C=CH), and 144.6 (s, Ar-C). Anal. Calcd for $C_{56}H_{84}O_6Si$: C, 76.31; H, 9.60. Found: C, 75.98; H, 9.47.

Detritylation of 45. Anhydrous ammonia (approximately 10 mL) was condensed into a two-necked, round-bottomed flask containing a solution of **42** (19.5 mg, 22.1 μmol) in THF (1.5 mL). To the resulting heterogeneous mixture was added a minimum amount of sodium sufficient to maintain a blue color. The mixture was stirred under reflux (−33 °C) for 15 min. Ethanol was added dropwise until the color discharged. The process was repeated three times, and then ammonium chloride (1 g) was added slowly. The ammonia was allowed to evaporate (1.5 h). Water was added, and the mixture was extracted with ethyl acetate. The combined extracts were processed as usual, and the residue was purified by flash column chromatography (hexanes–EtOAc, 7:1) to give **46** (11.5 mg, 18.0 μmol, 81%) and the corresponding *Z* isomer (0.9 mg, 1.4 μmol, 6%). For the major isomer **46**: $[\alpha]^{25}_D$ −28.8° (*c* 0.67, CH_2Cl_2); reported[13] $[\alpha]^{25}_D$ −27.5° (*c* 0.3, CH_2Cl_2); MS (FAB) calcd for $C_{37}H_{71}O_6Si$ (M + H) 639.5022, found 639.4997.

Oxidation of 46.[13] To a solution of oxalyl chloride (10.0 μL, 115 μmol) in dry dichloromethane (200 μL) cooled to −70 °C was added DMSO (16 μL, 225 μmol). The mixture was stirred 5 min at −70 °C. The resulting solution was added via cannula to a cooled (−70 °C) solution of **46** (11.0 mg, 17.2 μmol) in dichloromethane (200 μL). The mixture was stirred for 30 min at −70 °C, and then triethylamine (65 μL, 466 μmol) was added. The mixture was stirred for 20 min at −70 °C, and then pH 7 aqueous phosphate buffer was added. The mixture was extracted with ether, and the combined extracts were washed with saturated NaCl, dried, and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexanes–EtOAc, 1:10) to give the aldehyde as a colorless oil (10.0 mg, 15.7 μmol, 91): $[\alpha]^{25}_D$ −36.4° (*c* 0.98, $CHCl_3$). The same oxidation was repeated on three different batches: ^{1}H NMR (300 MHz, C_6D_6) δ 0.065 (3 H, s, Si-Me), 0.070 (3 H, s, Si-Me), 0.65 (3, d, *J* = 6.6 Hz, C_{10}-Me), 0.76 (6 H, d. *J* = 6.9 Hz, C_2-Me, C_4-Me), 0.97 (9 H, s, *tert*-butyl), 1.20 (3 H, d, *J* = 6.3 Hz, C_8-Me), 1.22 (3 H, s, C_{16}-Me or C_{20}-Me), 1.28 (3 H, s, C_{20}-Me or C_{16}-Me), 1.29 (3 H, d, *J* = 6.2 Hz, C_{22}-H), 1.33 (3 H, s, $OOCMe_2$), 1.51 (3 H, s, $OOCMe_2$), 0.75–2.13 (17 H, m, C_2-H, C_3-H, C_4-H, C_5-H, C_{10}-H, C_{12}-H, C_{14}-H, C_{15}-H, C_{18}-H, C_{19}-H), 2.36 (1 H, m, (C_8-H), 3.29 (1 H, dd, $J_{9,10}$ = 10.2 Hz, $J_{9,8}$ = 2.3 Hz, C_9-H), 3.55 (1 H, ddd, *J* = 10.2 Hz, *J* = 8.4 Hz, *J* = 2.5 Hz, C_{11}-H), 3.77 (1 H, q, $J_{21,22}$ = 6.2 Hz, C_{21}-H), 3.967 (1 H, dd, $J_{17,18a}$ = 7.3 Hz, $J_{17,18b}$ = 7.3 Hz, C_{17}-H), 4.39 (1 H, m, C_{13}-H), 5.28 (1 H, ddd, $J_{6,7}$ = 15.5 Hz, $J_{6,5a}$ = 7.2 Hz, $J_{6,5b}$ = 7.6 Hz, C_6-H), 5.70 (1″, dd, $J_{7,6}$ = 15.5 Hz, $J_{7,8}$ = 9.3 Hz, C_7-H), 9.32 (1 H, d, *J* = 2.2 Hz, CHO); ^{13}C NMR (75 MHz, C_6D_6) δ −4.70, −3.81, 11.65, 14.05, 18.15, 18.68, 18.92, 19.44, 19.64, 19.75, 14.07, 16.07, 17.06, 30.46, 30.89, 31.81, 35.47, 36.47, 36.71, 37.74, 38.92, 39.98 (two carbons), 44.09, 72.31, 74.06, 77.40, 78.24, 83.55, 85.71, 85.51, 97.87, 128.93, 133.42, 203.17.

Aldol Coupling of 13. Following the protocol of Evans and Dow,[13] to a solution of ketone **13** (19.2 mg, 79.2 μmol) in dichloromethane (900 μL) cooled to −78 °C was added dibutylboron triflate (1.0 M solution in CH_2Cl_2) (103 μmol, 3.9 equiv) and diisopropylethylamine (231.3 μL) successively. The mixture was stirred at −78 °C for 30 min. The resulting solution was added via cannula to a cooled (−78 °C) solution of the aldehyde obtained from **46** (29.1 mg, 45.6 μmol) in dichloromethane (300 μL). The mixture was stirred for 1 h at −78 °C, then warmed up slowly to 0 °C (1 h), and stirred for a further 2 h at 0 °C. A pH 7 phosphate buffer solution (1.5 mL) was added to the reaction mixture followed by addition of methanol (6.0 mL). A solution of 30% H_2O_2 in MeOH (30% H_2O_2/MeOH = 1:4, 3.0 mL) was added, and the resulting mixture was stirred for 1 h at 0 °C. The mixture was poured into CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl. The CH_2Cl_2 layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was filtered through a short silica gel column (eluting with hexanes–EtOAc, 2:10) and employed in the next reaction without further purification. A small amount of the sample was purified for analytical purpose (silica gel column chromatography; hexanes–EtOAc, 1:6). The product was a 1:1 diastereomeric mixture, and it was used as such in the next step.

Collins Oxidation of the Aldol Proudct.[13] To a slurry of Celite (610 mg) in dichloromethane (6.0 mL) was added pyridine (150 μL) and chromium trioxide (96 mg, 960 μmol). The resulting mixture was stirred at room temperature for 30 min (chromium trioxide was crushed in the slurry by using a glass rod so that it dissolved easily). A solution of the aldol product obtained by the previous reaction in dichloromethane (1 mL) was added to the slurry, and the mixture was stirred at room temperature for 10 min. The heterogeneous mixture was poured into ether and washed with 2% hydrochloric acid.

The aqueous layer was extracted with ether. The combined extracts were filtered through a short Florisil column to give a colorless solution. After evaporation of the solvent, the residue was purified by silica gel column chromatography (hexanes–EtOAc, 15:1) to give **43** (25.4 mg, 300 μmol, 66%) as a colorless oil: $[\alpha]^{25}_D$ −29.3° (*c* 0.27, CH_2Cl_2); MS (FAB), calcd for $C_{51}H_{92}O_9Si$ + Na 899.6411, found 899.6245.

Ionomycin Methyl Ester. To a solution of the preceding compound (16.5 mg, 18.81 μmol) in acetonitrile (3 mL) was added 40% aqueous HF (ca. 10 drops) at room temperature. The mixture was stirred for 1 h. A pH 7 phosphate buffer solution was added, and the resulting mixture was extracted with dichloromethane. The combined extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexanes–EtOAc, 2:1 then AcOEt/$CHCl_3$/MeOH, 8:8:1) to give the ester (10.5 mg, 77%): $[\alpha]^{25}_D$ −11.5° (*c* 0.5, CH_2Cl_2); reported[13] $[\alpha]^{25}_D$ −12.3° (*c* 0.43, CH_2Cl_2); MS, calcd for $C_{24}H_{75}O_9$, M + H, 723.5414, found 723.5369; ^{13}C NMR (75 MHz, C_6D_6) δ −4.69, −3.80, 11.69, 18.16, 18.69, 18.85, 18.98, 19.18, 19.46, 19.62, 19.66, 24.06, 26.09, 27.07, 28.30, 29.92, 30.48, 31.33, 31.81, 31.87, 32.88, 35.49, 36.48, 36.73, 38.99, 40.00, 40.50, 40.68, 41.36, 32.54, 44.81, 50.91, 72.34, 74.06, 77.43, 78.24, 83.53, 84.72, 85.51, 97.55, 97.87, 129.3, 133.26, 173.42, 198.50, 198.93.

Ionomycin and Ionomycin Ca Salt. To a dimethoxyethane solution (1.5 mL) of ionomycin methyl ester (6.0 mg, 8.31 μmol) was added 555 μL of a 1.5% LiOH aqueous solution.[13] The mixture was stirred at room temperature for 1 h, and 0.1 N HCl (9.0 μL) was added. The cloudy mixture was extracted with dichloromethane and dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure to give an oil which was dissolved in dichloromethane (3.0 mL). A pH 9.7 $CaCl_2$ buffer solution (6.0 mL) was added, and the mixture was stirred vigorously at room temperature for 6 h. The mixture was extracted with dichloromethane, and the combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give crystalline ionomycin Ca salt (4.8 mg, 6.42 μmol, 77%); mp 199–200 °C; $[\alpha]^{25}_D$ 27.5° (*c* 0.36, MeOH). Commercial ionomycin Ca salt (Calbiochem, lot no. 810311) showed mp 188–196 °C: $[\alpha]^{25}_D$ 25.5° (*c* 0.20, MeOH); reported[6] mp 205–206 °C; $[\alpha]^{25}_D$ 33° (*c* 0.4, MeOH); mp 196–197 °C; $[\alpha]^{25}_D$ 31.5° (*c* 0.232, MeOH), R. L. Dow, Harvard, Ph.D. Thesis, 1985;[13] found M^+ (EI), 746.4641; $C_{41}H_{70}O_9Ca$ requires 746.4646; ^{1}H NMR (300 MHz, C_6D_6) δ 0.58 (3 H, *J* = 6.8 Hz), 0.96 (3 H, s), 1.06 (3 H, s), 1.07 (3 H, d, *J* = 5.1 Hz), 1.1 (3 H, d, *J* = 6.5 Hz), 1.13 (3 H, d, *J* = 6.4 Hz), 1.17 (3 H, *J* = 6.5 Hz), 1.19 (3 H, d, *J* = 6.4 Hz), 1.24 (3 H, d *J* = 6.4 Hz), 1.25 (3 H, d, *J* = 6.7 Hz), 1.25 (3 H, d, *J* = 6.7 Hz), 0.74–2.63 (m), 3.22 (1 H, dd, *J* = 10.4 Hz, *J* = 2.1 Hz), 3.35 (1 H, dd, *J* = 10.6 Hz, *J* = 5.5 Hz), 3.55 (1 H, m), 3.80 (1 H, m), 4.77 (1 H, q, *J* = 6.4 Hz), 5.40 (1 H, s), 5.60 (1 H, dd, *J* = 15 Hz, *J* = 9.1 Hz), 5.72 (1 H, ddd, *J* = 15.8 Hz, *J* = 6.9 Hz, *J* = 6.9 Hz); ^{13}C NMR (75 MHz, C_6D_6) δ 12.21, 18.81, 19.56, 19.80, 20.18, 21.39, 21.50, 22.15, 23.54, 26.41, 26.46, 28.26, 28.73, 29.02, 32.29, 33.52, 33.86, 34.16, 36.97, 39.61, 40.11, 40.39, 40.89, 41.89, 42.09, 42.29, 43.44, 47.58, 69.88, 76.82, 80.93,1 82.80, 84.33, 87.70, 101.40, 131.40, 131.91, 182.85, 193.77, 195.46; IR_{max} ($CHCl_3$) cm^{-1} 3340 (br), 2970, 2930, 2880, 2850, 1720 (br), 1610.

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Supplementary Material Available: Selected ^1H NMR and ^{13}C NMR spectra are listed (30 pages). Ordering information is given on any current masthead page.

Total Synthesis of the Polyether Antibiotic Ionomycin

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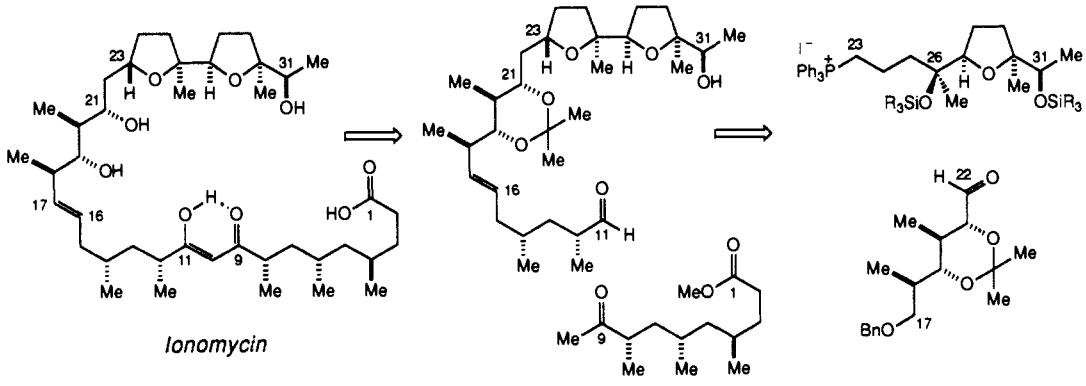
Abstract: A convergent asymmetric synthesis of the calcium ionophore ionomycin has been achieved through a route that is outlined below. The four illustrated subunits, which comprise the C_1–C_{10}, C_{11}–C_{16}, C_{17}–C_{22}, and C_{23}–C_{32} portions of ionomycin,



were constructed through the use of chiral enolate bond constructions wherein 9 of the 14 stereogenic centers were created. The remaining chirality at C_6, C_{21}, C_{26}, C_{30}, and C_{31} was incorporated through internal asymmetric induction. In the assemblage process, the ylide derived from the C_{23}–C_{32} synthon was coupled with the C_{17}–C_{22} aldehyde. The C_{23}–C_{26} tetrahydrofuranyl ring and associated C_{23} stereocenter were then established through intramolecular oxymercuration, which proceeded in a highly diastereoselective manner (≥93:7) with the desired stereochemical outcome. The C_{16}–C_{17} double bond was constructed through a Julia trans olefination sequence. The union of the C_1–C_{10} keto ester with the assembled C_{11}–C_{32} aldehyde was achieved through an aldol bond construction. Subsequent oxidation of the C_{11} alcohol afforded the fully protected ionomycin structure. Final deprotection provided synthetic ionomycin whose absolute configuration is in full agreement with that determined by X-ray crystallography.

Over the last three decades a large class of molecules, collectively known as polyether antibiotics, have been isolated from various strains of Streptomyces organisms.[3] It is now well appreciated that these unique structures, which characteristically contain a carboxylate group as well as from two to five additional oxygen ligands, are highly effective in the complexation of inorganic cations. Complexes generated from these "ionophores" are exceptionally hydrophobic and, as a result, facilitate the translocation of ions across membrane barriers. Membrane transport mechanisms provided by the polyether antibiotics induce a range of biological responses, which include ruminant growth promotion,[4] coccidiostatic activity,[5] and mammalian cardiovascular effects.[6] An excellent monograph provides an in-depth summary of the biology of this family of natural products.[7]

In 1978 Meyers and co-workers reported the isolation of the polyether antibiotic ionomycin, as its hexane-soluble calcium complex, from the organism *Streptomyces conglobatus*.[8] Subsequent competitive ion-binding studies have shown that the antibiotic exhibits a high propensity for divalent versus monovalent ions. The following hierarchy has been documented for the alkaline earth cations: $Ca^{2+} > Mg^{2+} \gg Sr^{2+}$ and Ba^{2+}.[9] The binding stoichiometry for these divalent ions was determined to be 1:1. The only other ionophore to exhibit similar selectivity for divalent cations is the "tridentate" ionophore calcimycin,[10,11] which shows little differentiation between calcium and magnesium as its 2:1 ligand/metal complex.

In 1979 the X-ray structure and absolute stereochemistry of both the calcium and cadmium complexes of ionomycin were

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