A Modular Enantioselective Approach to Construction of the Macrolactone Core of Polycavernoside A

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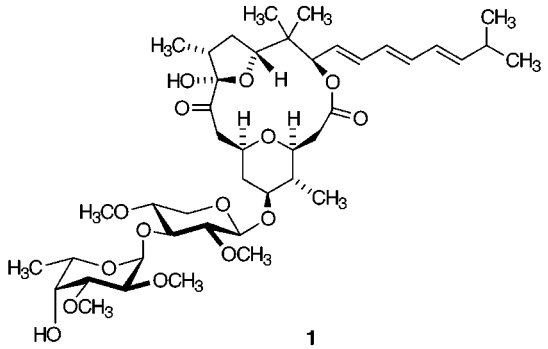
A program directed toward a total synthesis of polycavernoside A is described. The synthesis of five building blocks is detailed. The first of two electrophilic units, the lactone **3**, was prepared in four steps from the known enantiomerically pure oxirane **15**. Pyranyl aldehyde **5** was elaborated in turn from L-malic acid via **10**. While the route to **30** involved **3** as a starting material, dithiane **2** was obtained in a straightforward manner from **10** as well. The merging of the chiral sectors could not be accomplished by way of the lithiated dithianyl anions, presumably as a consequence of their heightened basicity. The strategic incorporation of the trienyl sector was accomplished, although no attempt was made to control the diastereoselectivity of the process.

The red alga *Polycavernosa tsudai* is a delicacy widely consumed in the Far East. When several Guam natives died suddenly following its ingestion in April 1991, immediate attempts were launched to identify the responsible toxin. Shortly thereafter, Yasumoto succeeded in characterizing polycavernoside A (**1**) as one of the principal risk factors.[1] Other structurally related metabolites originating from the same source were later reported.[2] Since the production of these toxins is seasonal and they are expressed in vanishingly small quantities, only planar representations of these architecturally unusual macrolide disaccharides were initially defined. Insufficient material was initially available with which to elucidate absolute stereochemistry.

Although the carbon backbone of **1** deviates from that resident in known macrocyclic lactones, some similarity with the smaller trioxadodecane subunit of the aplysiatoxins[3] has been noted.[1] Johnston, while working in this laboratory,[4] has pointed out the considerable structural homology between an "unraveled" view of polycavernoside A and the Celmer model of macrolide stereostructure[5] (Figure 1). We arrived at a working model for the absolute configuration of **1** (as shown) on this basis and



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have previously described an enantioselective synthesis of its disaccharide component.[6] The α-L- and β-D-glycosidic linkages were selected on the basis of their regular appearance in macrolide antibiotics.[7]

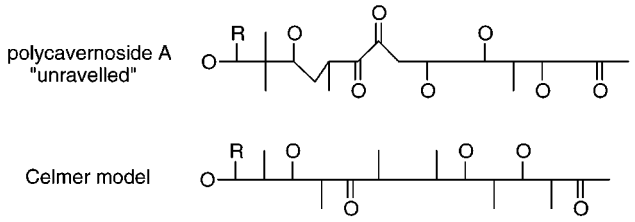

Figure 1.

These conclusions have been reinforced by the work of Murai, whose group has prepared several disaccharides[8] and concluded that this segment of **1** must be defined by a combination of D-xylose and L-fucose or the enantiomers thereof.[9] Their efforts have also extended to the tetrahydrofuran[10] and tetrahydropyran components[11] of the polycavernoside structure.[12]

Results and Discussion

As a continuation of our efforts directed toward the development of methodology relevant to the total synthesis of the polycavernoside toxins, we have addressed two retrosynthetic pathways defined as **A** and **B** in Scheme 1. The two routes share in common the expectations that the conjugated trienyl side chain will be amenable to incorporation by 1,2-addition to a suitable aldehyde precursor and that introduction of the disac-

(1) Yotsu-Yamashita, M.; Haddock, R. L.; Yasumoto, T. *J. Am. Chem. Soc.* **1993**, *115*, 1147.
(2) Yotsu-Yamashita, M.; Seki, T.; Paul, V. J.; Naoki, H.; Yasumoto, T. *Tetrahedron Lett.* **1995**, *36*, 5563.
(3) Kato, Y.; Scheuer, P. J. *J. Am. Chem. Soc.* **1974**, *96*, 2245.
(4) Johnston, J. N. Ph.D. Dissertation, The Ohio State University, 1997.
(5) Celmer, W. D. *Pure Appl. Chem.* **1971**, *28*, 413.
(6) Johnston, J. N.; Paquette, L. A. *Tetrahedron Lett.* **1995**, *36*, 4341. The stereochemistry depicted for **1** in this paper was that tentatively proposed by Yasumoto.[1]
(7) (a) Celmer, W. D. *J. Am. Chem. Soc.* **1965**, *87*, 1799. (b) Celmer, W. D. *J. Am. Chem. Soc.* **1965**, *87*, 1801.
(8) Fujiwara, K.; Amano, S.; Murai, A. *Chem. Lett.* **1995**, 191.
(9) Fujiwara, K.; Amano, S.; Murai, A. *Chem. Lett.* **1995**, 855.
(10) Hayashi, N.; Mine, T.; Fujiwara, K.; Murai, A. *Chem. Lett.* **1994**, 2143.
(11) Fujiwara, K.; Amano, S.; Oka, T.; Murai, A. *Chem. Lett.* **1994**, 2147.
(12) For additional synthetic work in this area, see: Robarge, L. A.; Wardrop, D. J.; White, J. D. *Abstracts of Papers*, 213th National Meeting of the American Chemical Society, San Francisco, CA; American Chemical Society: Washington, DC, 1997; Abstract 557.

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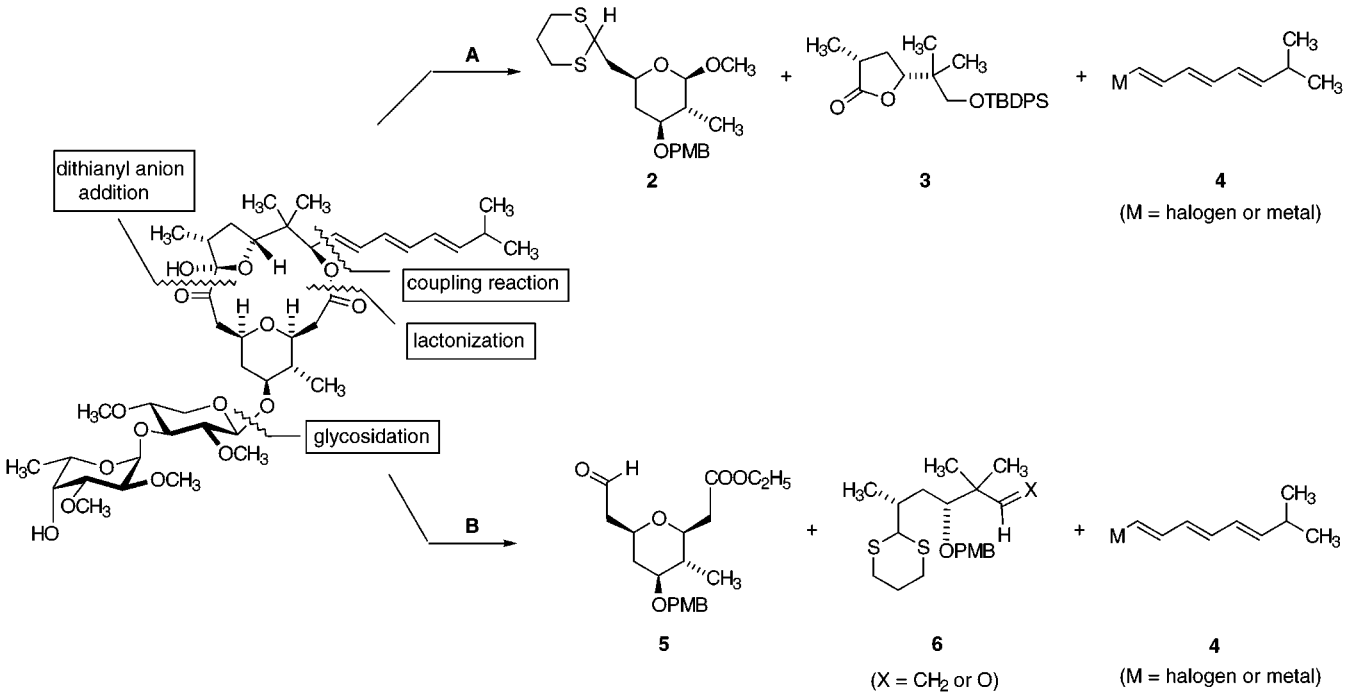
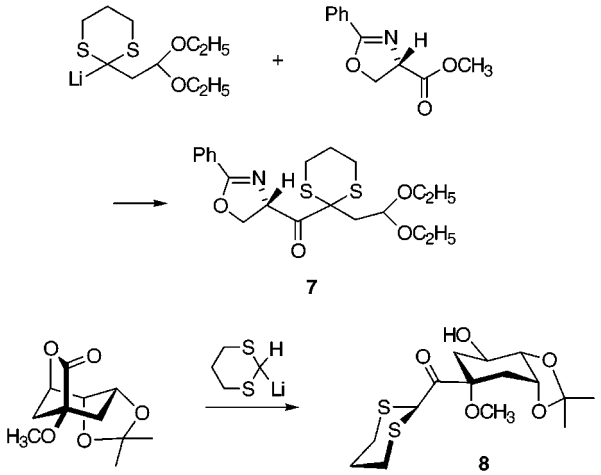
Scheme 1



charide unit via the preformed phenylthio derivative[6] will be serviceable. Beyond that, the building blocks **2** and **3** are distinguished from **5** and **6** in terms of their projected use as electrophilic or nucleophilic reaction partners. The anticipated successful conjoining of the major structural segments within **1** by the coupling of lithiodithianes to a carbonyl compound was founded on several literature reports.[13−15] The feasibility of directly producing α-keto thioacetals such as **7** and **8** by condensation with esters and lactones was of particular interest.

The general guidelines to be followed in plan **A** were to implement the coupling of **2** to **3** in advance of the introduction of an acetic acid moiety at the anomeric center and ensuing macrolactonization. For plan **B**, considerations based on functional group compatibility suggested that **5** might be constituted of the full complement of carbon atoms from the outset, although the opportunities for β-oxido elimination would be enhanced accordingly.

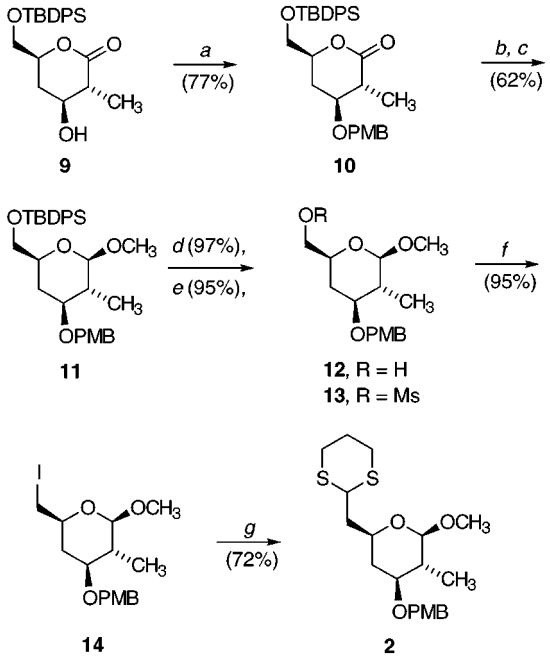


Synthesis of 2. The targeted precursor to **2** was lactone **9**, previously prepared in enantioselective fashion by Fukui and co-workers from L-malic acid.[16] When attempts to transform **9** into the *p*-methoxybenzyl-protected derivative **10** via base-promoted alkylation via the chloride could not be successfully implemented, recourse was made instead to use of the trichloroacetimidate under mildly acidic conditions (Scheme 2).[17] Arrival at **10** in this manner made possible chemoselective Dibal-H reduction to the lactol and protection as the methyl acetal. When the latter transformation was performed with silver(I) oxide and methyl iodide at the reflux temperature,[18] only the β-anomer **11** was isolated.[19] Since this stereoisomer does not conform to expectations based on the anomeric effect, this quite satisfactory route clearly operates under kinetic control. Following desilylation to give **12**, attempts were made to implement the one-step conversion of this alcohol to iodide **14** by employing the triphenylphosphine−iodine reagent. However, this protocol was accompanied by significant byproduct formation. For this reason, optimum yields and improved selectivity were realized by the two-step route involving S_N2 displacement by iodide ion on mesylate **13**. The intermediacy of **14** was warranted since its condensation with lithio 1,3-dithiane proceeded satisfactorily when promoted by Schlosser's base.[20] Comparable studies on mesylate **13** were not productive.

Arrival at 3. Synthesis of the lactone subunit **3** was initiated by structural modification of (*R*)-(−)-pantolac-

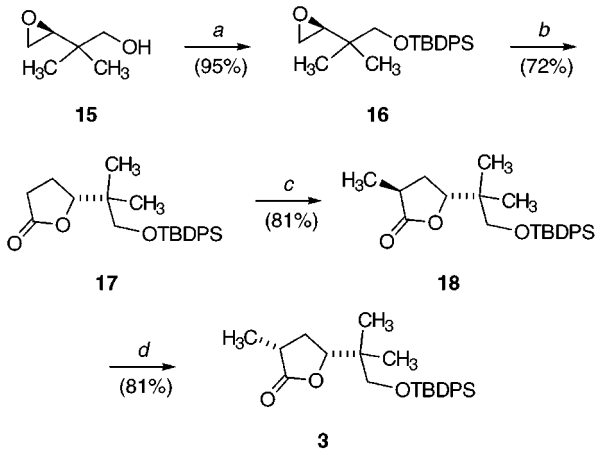
(13) Fujisawa, T.; Kojima, E.; Itoh, T.; Sato, T. *Chem. Lett.* **1985**, 1751.
(14) Flores-Parra, A.; Khuong-Huu, F. *Tetrahedron* **1986**, *42*, 5925.
(15) Blarer, S. J. *Tetrahedron Lett.* **1985**, *26*, 4055.
(16) Fukui, M.; Okamoto, S.; Sano, T.; Nakata, T.; Oishi, T. *Chem. Pharm. Bull. Jpn.* **1990**, *38*, 2890. We thank Dr. Tadashi Nakata of RIKEN for providing us with experimental details for this 10-step procedure.
(17) Nakajima, N.; Horita, K.; Abe, R.; Yonemitsu, O. *Tetrahedron Lett.* **1988**, *29*, 4139.
(18) Greene, A. E.; Le Drian, C.; Crabbé, P. *J. Am. Chem. Soc.* **1980**, *102*, 7583.
(19) This lactol proved unreactive to acidic methanol at room temperature. Warming of such solutions led to decomposition.
(20) Jones, A. B.; Villalobos, A.; Linde, R. G., II; Danishefsky, S. J. *J. Org. Chem.* **1990**, *55*, 2786.

Scheme 2[a]



[a] Key: (a) PMBOC(=NH)CCl_3, (TfOH), ether; (b) (*i*-Bu)$_2$AlH, CH_2Cl_2, −78 °C; (c) Ag_2O, CH_3I, reflux; (d) (*n*-Bu)$_4N^+$ F^-, THF; (e) CH_3SO_2Cl, Et_3N, CH_2Cl_2, −10 °C; (f) (*n*-Bu)$_4N^+$ I^-, C_6H_6, reflux; (g) 1,3-dithiane, 1:1 *n*-BuLi/KO-*t*-Bu, 2:1 THF/hexanes, −78 °C.

Scheme 3[a]



[a] Key: (a) TBDPSCl, imid, CH_2Cl_2; (b) CH_2=C(OLi)OLi (9 equiv), DME, reflux; H_3O^+; (c) LiHMDS, THF, −78 °C; CH_3I; (d) LDA, THF, −78 °C; NH_4Cl.

tone to give **15** as earlier described by Lavallée et al.[21] Silylation of this epoxy alcohol under conditions designed to generate a reasonably robust Si−O bond afforded **16** (Scheme 3). The structural features of this intermediate are particularly conducive to regiocontrolled nucleophilic attack by dilithioacetate.[22] This strongly basic reagent is tolerant of the *tert*-butyldiphenylsiloxy group, but not of the TBDMS equivalent. Beyond that, 1,2-dimethoxyethane is the solvent of choice. When THF was utilized, considerable decomposition was encountered and only 40% of **17** could be isolated.

In initial methylation experiments designed to complete the assembly of this building block, we recognized that attempts to achieve the complete consumption of **17** resulted in unwanted α,α-dimethylation. The compromise position was to allow monoalkylation to proceed to approximately the 80% level and to recycle the unconsumed **17**. The methylation step reveals a high level of stereocontrol in that only the *β*-isomer **18** is formed as a consequence of the presence of a bulky side chain at C-5. Advantage could be taken of this steric bias to orient the methyl on the α surface as in **3**. Formation of the lithium enolate and ensuing protonation with ammonium chloride was equally stereoselective and gave rise exclusively to **3**.

Preparation of 5. Following a series of preliminary experiments, the method of choice for stereocontrolled introduction of an acetic acid unit into **10** was considered to be that devised by Kishi,[23] despite accompanying loss of the *p*-methoxybenzyl protecting group. Thus, treatment of **10** with lithio ethyl acetate gave the aldol adduct **19** in 70% yield as a single major anomer (^{1}H NMR analysis) (Scheme 4). Reduction of **19** with triethylsilane and titanium tetrachloride in CH_2Cl_2 cleanly furnished **20** as a consequence of exclusive hydride delivery to the oxonium ion from the axial direction. No conditions were found that arrested the concomitant unmasking of the 4-hydroxy substituent. In light of this development, it proved somewhat more expeditious to advance to **20** via the preliminary trimethylsilation of **9**.

Following reintroduction of the PMB protecting group and liberation of the primary carbinol as in **22**, the stage was set to carry out the proper homologation of this side chain. Oxidation with the Dess−Martin periodinane[24] provided **23** without any evidence of epimerization. Equally uneventful was the subsequent Wittig olefination with (methoxymethyl)triphenylphosphorane.[25] Finally, liberation of the acetaldehyde unit as in **5** by hydrolysis with 1 M HCl in THF was accomplished in 45% overall yield.

The Route to 30. It was recognized that the configuration at C-3 in **3** and the relationship of this center to that at C-5 mapped well with the requirements of the two stereogenic centers in **30**. Successful implementation of a strategy that would lead from **3** to **30** would require reductive cleavage of the lactone ring, permutation of the terminal silyl ether to a vinyl group, and appropriate protecting group modification.

A satisfying resolution of these requirements began by Dibal-H reduction of **3** to *γ*-lactol **24** (Scheme 5). Application of the $TiCl_4$-mediated procedure for the dithioketalization[26] of this masked hydroxy aldehyde produced **25** efficiently (93%). Following chromatographic purification, the interchange of hydroxyl protection groups was achieved by conversion of **25** to diol **26**, formation of *p*-methoxybenzylidene acetal **27**, and reduction with Dibal-H.[27] With generation of **28** as the very major product, a primary hydroxyl group was made available for oxidation to aldehyde **29** under Swern conditions.[28]

(21) Lavallée, P.; Ruel, R.; Grenier, L.; Bissonnette, M. *Tetrahedron Lett.* **1986**, *27*, 679.

(22) Creger, P. L. *J. Org. Chem.* **1972**, *37*, 1907.

(23) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976.

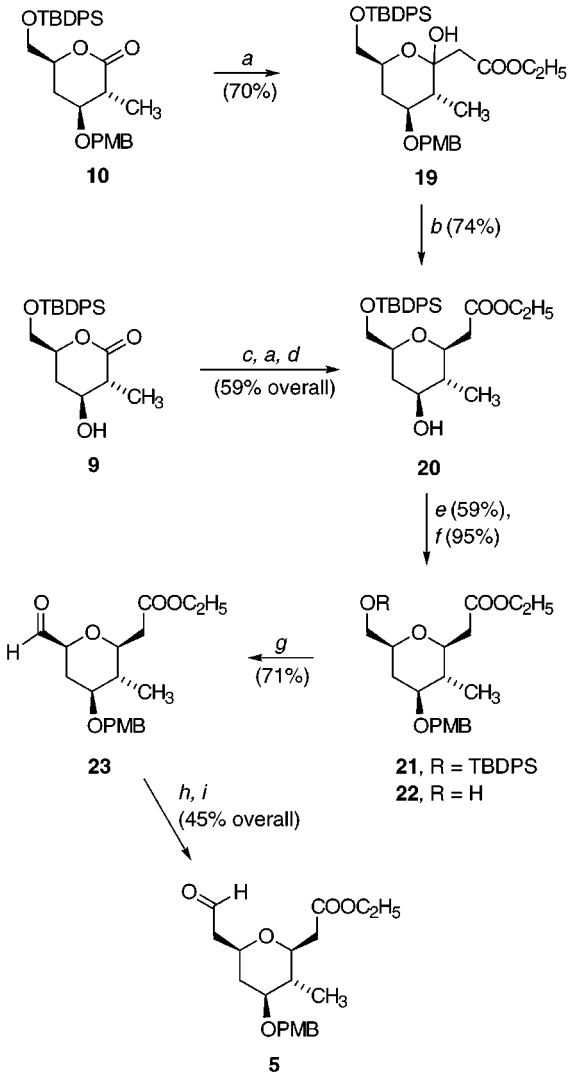
(24) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (b) Ireland, R. E.; Liu, L. B. *J. Org. Chem.* **1993**, *58*, 2899.

(25) (a) Wittig, G.; Schlosser, M. *Chem. Ber.* **1961**, *94*, 1373. (b) Wittig, G.; Böll, W.; Krück, K.-H. *Chem. Ber.* **1962**, *95*, 2514.

(26) Bulman-Page, P. C.; Roberts, R. A.; Paquette, L. A. *Tetrahedron Lett.* **1983**, *24*, 3555.

(27) Takano, S.; Akiyama, M.; Sato, S.; Ogasawara, K. *Chem. Lett.* **1983**, 1593.

Scheme 4[a]

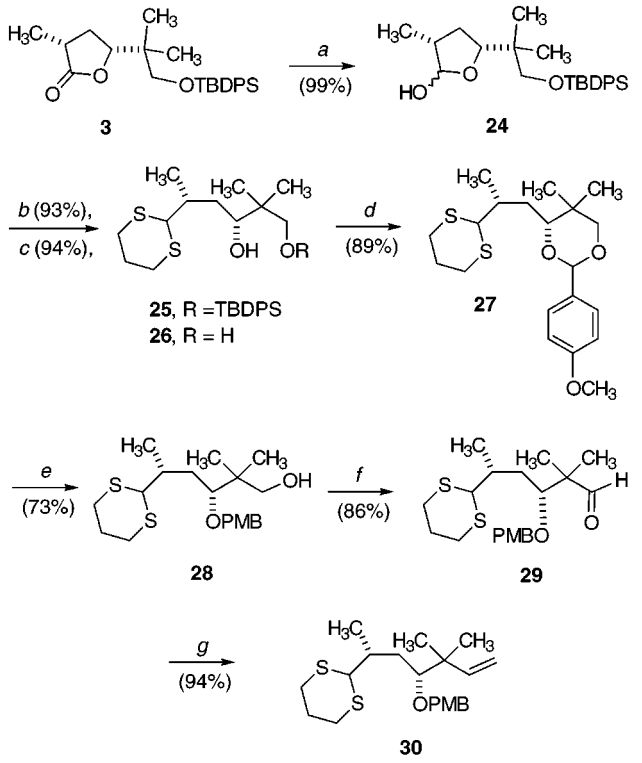


[a] Key: (a) $CH_2{=}C(OLi)OC_2H_5$, THF, −78 °C; (b) $(C_2H_5)_3SiH$, $TiCl_4$, CH_2Cl_2, −78 °C → rt; (c) $(Me_3Si)_2NH$, (Me_3SiCl), reflux; (d) $(C_2H_5)_3SiH$, $SnCl_4$, CH_2Cl_2, −78 °C → −20 °C; (e) PMBOC(=NH)CCl_3, (TfOH), ether; $(n\text{-}Bu)_4N^+ F^-$, THF; (g) Dess−Martin periodinane, CH_2Cl_2; (h) $Ph_3P{=}CHOCH_3$, THF, 0 °C; (i) 1 M HCl/THF (1:4).

After this, it proved possible to generate **30** in high yield by application of the Wittig olefination protocol.

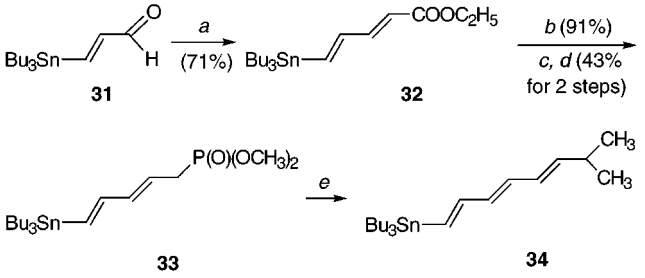
Acquisition of 34. The straightforward route developed for the purpose of obtaining the triene fragment **34** is outlined in Scheme 6. With the ready availability of *trans*-3-(tributylstannyl)-2-propenal (**31**),[29,30] its conversion to dienyl ester **32** under Wadsworth−Emmons conditions[31] could quickly be established to proceed satisfactorily under mild conditions. As has been established by other workers in a closely related context,[32] chemoselective reduction of the ester functionality and transformation of the resulting allylic alcohol into the rather sensitive bromide with carbon tetrabromide and triphenylphosphine[33] was immediately followed by a Michaelis−Becker reaction.[34] Formation of the halide

Scheme 5[a]



[a] Key: (a) $(i\text{-}Bu)_2AlH$, CH_2Cl_2, −78 °C; (b) $HS(CH_2)_3SH$, $TiCl_4$, C_6H_6; (c) $(n\text{-}Bu)_4N^+ F^-$, THF; (d) $p\text{-}CH_3OC_6H_4CHO$, (CSA), C_6H_6, reflux, Dean−Stark trap; (e) $(i\text{-}Bu)_2AlH$, CH_2Cl_2, 0 °C → rt; (f) $(COCl)_2$, DMSO, CH_2Cl_2; $(C_2H_5)_3N$; (g) $Ph_3P{=}CH_2$, THF.

Scheme 6[a]



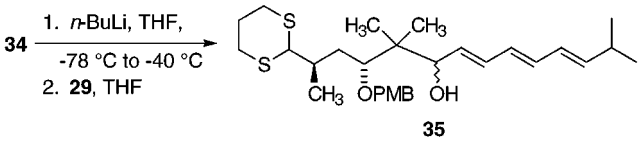
[a] Key: (a) LDA, $(C_2H_5O)_2P(O)CH_2COOC_2H_5$, THF, −40 °C; (b) $(i\text{-}Bu)_2AlH$ (excess), THF, −78 °C; (c) Ph_3P, CBr_4, CH_3CN; (d) $NaP(O)(OCH_3)_2$, THF; (e) *n*-BuLi, THF, −78 → −40 °C; *i*-PrCHO, −78 °C.

and its ensuing treatment with the sodium salt of dimethyl phosphite in THF proceeded in 43% overall yield. The ultimate elaboration of **34** was accomplished by metalation of **33** with *n*-butyllithium and condensation with isobutyraldehyde. The all-trans geometry was assigned to **34** on the strength of extensive precedent.

Attempts to Achieve Subunit Assembly. With **34** in hand, its practical coupling to aldehyde **29** was initially scrutinized. Transmetalation of **34** with *n*-butyllithium in THF at −78 to −40 °C proved to be uncomplicated. When generation of the trienyllithium reagent in this manner was followed by the introduction of **29**, conver-

(28) Mancuso, A. J.; Brownfain, D. S.; Swern, D. *J. Org. Chem.* **1979**, *44*, 4148.
(29) Johnson, C. R.; Kadow, J. F. *J. Org. Chem.* **1987**, *52*, 1493.
(30) Jung, M. E.; Light, L. A. *Tetrahedron Lett.* **1982**, *23*, 3851.
(31) Wadsworth, W. S., Jr. *Org. React.* **1977**, *25*, 73.
(32) Evans, D. A.; Gage, J. R.; Leighton, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 9434.
(33) (a) Axelrod, E. H.; Milne, G. M.; van Tamelen, E. E. *J. Am. Chem. Soc.* **1970**, *92*, 2139. (b) Hayashi, H.; Nakanishi, K.; Brandon, C.; Marmur, J. *J. Am. Chem. Soc.* **1973**, *95*, 8749. (c) Shue, Y.-K.; Carrera, G. M., Jr.; Nadzan, A. M. *Tetrahedron Lett.* **1987**, *28*, 3225.
(34) Michaelis, A.; Becker, T. *Chem. Ber.* **1897**, *30*, 1003.

sion to **35** was accomplished in 83% yield. Although the efficiency of this C−C bond-forming step is considered acceptable, the 2:1 diastereoselectivity is not. However, further work on the stereocontrol of this reaction was not pursued in light of the developments described below.



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At this juncture, the focus of our attention turned to proper identification of a method for conjoining **2** with **3** or, alternatively, **30** with **5**. Williams and Sit have demonstrated that 2-substituted 1,3-dithianes readily attack epoxides once they are lithiated.[35] However, deprotonation of **30** under their conditions (*t*-BuLi, THF−HMPA (9:1), −78 °C, 5 min) followed by the introduction of **5** resulted predominantly in recovery of unreacted dithiane. At somewhat warmer temperatures (−60 °C → −50 °C → −65 °C), total degradation of the aldehyde was observed. The response of this reactant combination to various alternative base−solvent combinations[36−38] and a wide variety of time and temperature regimens was equally capricious.[39,40] Since there are many instances in the literature of dithianes that could not be deprotonated under standard or more elaborate conditions, and **30** could be plagued by competitive deprotonation at the benzylic position, deuteration studies were undertaken. Under the first set of conditions specified above, followed by quenching with D_2O after 5 and 15 min, 41% and 92% d_1 incorporation, respectively, was observed (^{1}H NMR analysis) exclusively at the dithiane site (doublet at δ 4.10). Some modest onset of degradation was noted at the longer reaction time.

Our second specific objective of bringing about the union of **2** and **3** proved likewise to be unrewarding. The highly oxygenated nature of **2**$^-$Li$^+$ could be responsible for an increase in kinetic basicity.[41,42] The partial epimerization of **3** witnessed on a number of occasions can be rationalized in these terms. Whatever the cause underlying the unwillingness of **2** to exhibit a capacity for favorable 1,2-addition to **3**, it has become clear that new protocols need to be uncovered to make operative the desired merging of these chiral segments. We hope to report on a workable solution to this assembly problem as well as a completed synthesis of polycavernoside A soon.

Experimental Section

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

(3*R*,4*S*,6*S*)-6-[(*tert*-Butyldiphenylsiloxy)methyl]tetrahydro-4-[(*p*-methoxybenzyl)oxy]-3-methyl-2*H*-pyran-2-one (10). A solution of **9**[16] (317 mg, 0.80 mmol) in ether (6 mL) and CH_2Cl_2 (1 mL) was treated sequentially with ethereal triflic acid (0.023 mL of 0.1 M in ether, 0.3 mol %) and a solution of *p*-methoxybenzyl trichloroacetamidate (337 mg, 0.80 mmol) in ether (1 mL) in dropwise fashion via syringe. The reaction mixture was allowed to stir overnight, taken up in ether (50 mL), washed in turn with 1 M NaOH solution, 1 M HCl, water, and brine, dried, and concentrated. Purification of the residue by chromatography on silica gel (elution with 30% ether in hexanes) furnished **10** as a colorless oil (316 mg, 77%): IR (film, cm^{-1}) 1732; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67−7.60 (m, 4 H), 7.46−7.32 (m, 6 H), 7.28−7.22 (m, 2 H), 6.91−6.85 (m, 2 H), 4.61 (d, J = 11.3 Hz, 1 H), 4.44 (d, J = 11.3 Hz, 1 H), 4.22 (dq, J = 11.4, 4.0 Hz, 1 H), 3.80−3.72 (m, 5 H), 3.46 (td, J = 3.6, 10.1 Hz, 1 H), 2.49 (dq, J = 9.7, 7.0 Hz, 1 H), 2.36 (dt, J = 13.3, 3.6 Hz, 1 H), 1.79 (dt, J = 13.2, 11.4 Hz, 1 H), 1.37 (d, J = 7.0 Hz, 3 H), 1.06 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 159.4, 135.6 (2 C), 135.5 (2 C), 133.1 (2 C), 132.8, 129.8, 129.7, 129.3 (2 C), 127.8 (4 C), 113.9 (2 C), 76.4, 76.3, 70.8, 65.6, 55.3, 43.4, 31.0, 26.8 (3 C), 19.2, 13.9; MS *m*/*z* (M^+ − *t*-Bu) calcd 461.1787, obsd 461.1767; [α] −38.2 (*c* 0.39, $CHCl_3$).

Anal. Calcd for $C_{31}H_{38}O_5Si$: C, 71.78; H, 7.39. Found: C, 71.86; H, 7.45.

***tert*-Butyldiphenyl[[(2*S*,4*S*,5*R*,6*R*)-tetrahydro-6-methoxy-4-[(*p*-methoxybenzyl)oxy]-5-methyl-2*H*-pyran-2-yl]methoxy]silane (11).** To a solution of **10** (570 mg, 1.10 mmol) in CH_2Cl_2 (20 mL) at −78 °C was added diisobutylaluminum hydride in hexanes (1.2 mL of 1 M, 1.2 mmol). The reaction mixture was stirred for 5 min, quenched with saturated sodium potassium tartrate solution (15 mL), and extracted with ether (3 × 5 mL). After drying and evaporation of the organic phase, the residue was eluted through a column of silica gel with 40% ether in hexanes, concentrated, dissolved in methyl iodide (10 mL), treated with silver oxide (509 mg, 2.20 mmol), and refluxed for 6 h. After dilution with ether (20 mL), the insoluble solids were separated by filtration, and the filtrate was evaporated. Purification of the product by chromatography (silica gel, elution with 15% ether in hexanes) provided 365 mg (62%) of **11** as a colorless oil: IR (film, cm^{-1}) 1613; ^{1}H NMR (300 MHz, C_6D_6) δ 7.86−7.82 (m, 4 H), 7.26−7.21 (m, 8 H), 6.83−6.80 (m, 2 H), 4.46 (d, J = 11.6 Hz, 1 H), 4.21 (d, J = 11.6 Hz, 1 H), 3.87 (dd, J = 5.9, 10.5 Hz, 1 H), 3.80 (d, J = 8.5 Hz, 1 H), 3.70 (dd, J = 4.5, 10.5 Hz, 1 H), 3.39 (s, 3 H), 3.39−3.31 (m, 1 H), 3.31 (s, 3 H), 2.95 (td, J = 11.6, 5.1 Hz, 1 H), 1.82−1.75 (m, 2 H), 1.27 (q, J = 11.6 Hz, 1 H), 1.21 (d, J = 7.0 Hz, 3 H), 1.20 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.7, 136.09 (2 C), 136.06 (2 C), 134.11, 134.06, 131.4, 130.0 (2 C), 129.3 (2 C) 128.1 (4 C), 114.0 (2 C), 106.3, 79.0, 72.8, 70.1, 67.4, 56.1, 54.8, 43.2, 33.4, 27.1 (3 C), 19.5, 12.9; MS *m*/*z* (M^+) calcd 534.2801, obsd 534.2751; [α] +13.0 (*c* 0.95, $CHCl_3$).

Anal. Calcd for $C_{32}H_{42}O_5Si$: C, 71.87; H, 7.92. Found: C, 71.83; H, 7.95.

(2*S*,4*S*,5*R*,6*R*)-Tetrahydro-6-methoxy-4-[(*p*-methoxybenzyl)oxy]-5-methyl-2*H*-pyran-2-methanol (12). A solution of **11** (309 mg, 0.58 mmol) in THF (20 mL) was treated with a 1.0 M solution of tetra-*n*-butylammonium fluoride in THF (0.75 mL, 0.75 mmol) and stirred for 8 h. Following solvent evaporation, the product was purified by chromatography on silica gel (elution with 75% ether in hexanes) to provide 166 mg (97%) of **10** as a colorless oil: IR (film, cm^{-1}) 3460 (br), 1613; ^{1}H NMR (300 MHz, C_6D_6) δ 7.24−7.20 (m, 2 H), 6.84−6.80 (m, 2 H), 4.43 (d, J = 11.5 Hz, 1 H), 4.15 (d, J

(35) Williams, D. R.; Sit, S.-Y. *J. Am. Chem. Soc.* **1984**, *106*, 2949.
(36) Lipshutz, B. H.; Garcia, E. *Tetrahedron Lett.* **1990**, *31*, 7261.
(37) Smith, A. B., III; Condon, S. M.; McCauley, J. A.; Leazer, J. L., Jr.; Leahy, J. W.; Maleczka, R. E., Jr. *J. Am. Chem. Soc.* **1997**, *119*, 947.
(38) Cerè, V.; De Angelis, S.; Pollicino, S.; Ricci, A.; Kishan Reddy, C.; Knochel, P.; Cahiez, G. *Synthesis* **1997**, 1174.
(39) Oppong, I.; Pauls, H. W.; Liang, D.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1986**, 1241.
(40) Kinoshita, M.; Taniguchi, M.; Morioka, M.; Takami, H.; Mizusawa, Y. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2147.
(41) Hanessian, S.; Pougny, J.-R.; Boessenkool, I. K. *Tetrahedron* **1984**, *40*, 1289.
(42) De Brabander, J.; Vandewalle, M. *Synthesis* **1994**, 855.

= 11.5 Hz, 1 H), 3.73 (d, J = 8.5 Hz, 1 H), 3.50 (m, 2 H), 3.32 (s, 3 H), 3.30 (s, 3 H), 3.16−3.08 (m, 1 H), 2.91 (dt, J = 4.7, 10.5 Hz, 1 H), 2.03 (br s, 1 H), 1.83−1.75 (m, 1 H), 1.59 (ddd, J = 1.8, 4.6, 12.4 Hz, 1 H), 1.28 (q, J = 11.6 Hz, 1 H), 1.17 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) δ 159.7, 131.3, 129.3 (2 C), 114.1 (2 C), 106.3, 78.8, 72.6, 70.1, 65.7, 56.2, 54.8, 43.1, 32.8, 12.8; MS m/z (M^+) calcd 296.1623, obsd 296.1617; [α] +31.1 (*c* 0.84, CH_2Cl_2).

Anal. Calcd for $C_{16}H_{24}O_5$: C, 64.84; H, 8.16. Found: C, 64.62; H, 8.64.

(2*S*,4*S*,5*R*,6*R*)-Tetrahydro-6-methoxy-4-[(*p*-methoxybenzyl)oxy]-5-methyl-2*H*-pyran-2-methanol Methanesulfonate (13). A cold (−10 °C) solution of **12** (22 mg, 0.073 mmol) and triethylamine (0.20 mL) in CH_2Cl_2 (2.5 mL) was treated with methanesulfonyl chloride (8.5 μL, 0.11 mmol). The reaction mixture was allowed to warm to room temperature, stirred for 1 h, and concentrated under reduced pressure. The product, purified by chromatography on silica gel (elution with 60% ether in hexanes), was a white solid: mp 98−99 °C (27 mg, 95%): IR (film, cm^{-1}) 1512, 1367, 1339; ^{1}H NMR (300 MHz, C_6D_6) δ 7.31−7.24 (m, 2 H), 6.94−6.85 (m, 2 H), 4.46 (d, J = 11.4 Hz, 1 H), 4.19 (d, J = 6.4 Hz, 1 H), 4.02−3.94 (m, 2 H), 3.67 (d, J = 8.6 Hz, 1 H), 3.38 (s, 3 H), 3.31 (s, 3 H), 3.26−3.12 (m, 1 H), 2.87 (dt, J = 4.6, 10.6 Hz, 1 H), 2.38 (s, 3 H), 1.82−1.68 (m, 2 H), 1.18 (d, J = 6.5 Hz, 3 H), 1.15 (q, J = 11.9 Hz, 1 H); ^{13}C NMR (75 MHz, C_6D_6) δ 159.8, 131.1, 129.3 (2 C), 114.1 (2 C), 106.1, 78.2, 71.6, 70.3, 69.7, 56.3, 54.8, 42.9, 37.0, 32.5, 12.6; MS m/z (M^+) calcd 374.1399, obsd 374.1387; [α] +24.8 (*c* 0.93, CH_2Cl_2).

Anal. Calcd for $C_{17}H_{26}O_7S$: C, 54.53; H, 7.00. Found: C, 54.37; H, 7.04.

(2*R*,3*R*,4*S*,6*S*)-Tetrahydro-6-(iodomethyl)-2-methoxy-4-[(*p*-methoxybenzyl)oxy]-3-methyl-2*H*-pyran (14). A mixture of **13** (90 mg, 0.24 mmol) and tetra-*n*-butylammonium iodide (622 mg, 1.68 mmol) in benzene (10 mL) was refluxed for 40 h, cooled, diluted with ether (20 mL), washed with water and brine, and then dried. After solvent evaporation, the residue was purified by chromatography on silica gel (elution with 30% ether in hexanes) to provide 93 mg (95%) of **14** as a white solid: mp 58 °C; IR (film, cm^{-1}) 1614; ^{1}H NMR (300 MHz, C_6D_6) δ 7.22−7.17 (m, 2 H), 6.84−6.78 (m, 2 H), 4.40 (d, J = 11.5 Hz, 1 H), 4.13 (d, J = 11.5 Hz, 1 H), 3.63 (d, J = 8.5 Hz, 1 H), 3.38 (s, 3 H), 3.33 (s, 3 H), 2.97−2.86 (m, 2 H), 2.86−2.73 (m, 2 H), 1.83−1.75 (m, 1 H), 1.75−1.66 (m, 1 H), 1.13 (d, J = 6.5 Hz, 3 H), 1.04−0.93 (m, 1 H); ^{13}C NMR (75 MHz, C_6D_6) δ 159.7, 131.2, 129.3 (2 C), 114.1 (2 C), 106.0, 78.5, 71.5, 70.3, 56.3, 54.8, 42.7, 36.5, 12.6, 8.5; MS m/z (M^+) calcd 406.0641, obsd 406.0657; [α] +37.8 (*c* 2.52, CH_2Cl_2).

Anal. Calcd for $C_{16}H_{23}IO_4$: C, 47.30; H, 5.71. Found: C, 47.17; H, 5.67.

(2*R*,3*R*,4*S*,6*S*)-6-(*m*-Dithian-2-ylmethyl)tetrahydro-2-methoxy-4-[(*p*-methoxybenzyl)oxy]-3-methyl-2*H*-pyran (2). To a slurry of potassium *tert*-butoxide (38 mg, 0.34 mmol) in hexanes (0.5 mL) cooled to 0 °C was added *n*-butyllithium in hexanes (0.19 mL of 1.6 M, 0.31 mmol). The mixture was stirred at room temperature for 1 h, cooled to −78 °C, and treated with a solution of 1,3-dithiane (37 mg, 0.31 mmol) in THF (0.5 mL). After 20 min of stirring at this temperature, a THF solution (0.5 mL) of **14** (25 mg, 0.06 mmol) was introduced, and the reaction was allowed to proceed for 10 min prior to an aqueous quench (1 mL) and extraction with ether (2 × 3 mL). The organic layers were washed with brine, dried, and evaporated. Chromatography of the residue (silica gel, elution with 30% ether in hexanes) furnished **2** as a colorless oil (18 mg, 72%): IR (film, cm^{-1}) 1614; ^{1}H NMR (300 MHz, C_6D_6) δ 7.22 (d of m, J = 8.7 Hz, 2 H), 6.82 (dm, J = 8.7 Hz, 2 H), 4.41 (d, J = 11.4 Hz, 1 H), 4.41−4.36 (m, 1 H), 4.13 (d, J = 11.4 Hz, 1 H), 3.80 (d, J = 8.6 Hz, 1 H), 3.62 (tm, J = 8.5 Hz, 1 H), 3.40 (s, 3 H), 3.31 (s, 3 H), 2.89 (dt, J = 4.7, 10.5 Hz, 1 H), 2.48−2.30 (m, 4 H), 2.17 (ddd, J = 4.6, 11.8, 14.1 Hz, 1 H), 1.90 (ddd, J = 3.4, 10.1, 14.1 Hz, 1 H), 1.84−1.80 (m, 1 H), 1.73 (ddd, J = 2.0, 4.7, 12.3 Hz, 1 H), 1.65−1.57 (m, 1 H), 1.50−1.42 (m, 1 H), 1.18 (d, J = 6.5 Hz, 3 H), 1.22−1.09 (m, 1 H); ^{13}C NMR (75 MHz, C_6D_6) δ 159.7, 131.5, 129.4 (2 C), 114.0 (2 C), 106.2, 79.1, 70.2, 67.8, 56.0, 54.8, 44.3, 43.0, 41.9, 37.0, 30.3, 30.0, 26.2, 12.8; MS m/z (M^+) calcd 398.1585, obsd 398.1617; [α] +19.5 (*c* 1.93, CH_2Cl_2).

Anal. Calcd for $C_{20}H_{30}O_4S_2$: C, 60.27; H, 7.59. Found: C, 60.06; H, 7.64.

***tert*-Butyl[(*S*)-3,4-epoxy-2,2-dimethylbutoxy]diphenylsilane (16).** A solution of **15**[21] (229 mg, 1.92 mmol) and imidazole (262 mg, 3.84 mmol) in CH_2Cl_2 (10 mL) was admixed with a solution of *tert*-butyldiphenylsilyl chloride (581 mg, 2.11 mmol) in CH_2Cl_2 (3 mL). After 2.5 h of stirring, the reaction mixture was diluted with ether (50 mL), washed with water (10 mL) and brine (10 mL), dried, and concentrated. Purification of the residue by chromatography on silica gel (elution with 3% ether in hexanes) gave **16** as a colorless oil (647 mg, 95%): IR (film, cm^{-1}) 1361, 1111; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71−7.67 (m, 4 H), 7.48−7.37 (m, 6 H), 3.54 (d, J = 9.7 Hz, 1 H), 3.44 (d, J = 9.7 Hz, 1 H), 2.99 (t, J = 3.5 Hz, 1 H), 2.68 (d, J = 3.5 Hz, 2 H), 1.09 (s, 9 H), 0.92 (s, 3 H), 0.89 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.6 (4 C), 133.6, 133.5, 129.6 (2 C), 127.6 (4 C), 70.6, 57.2, 44.0, 36.1, 26.8 (3 C), 20.2, 19.8, 19.4; MS m/z (M^+) calcd 354.2015, obsd 354.2030; [α] +9.0 (*c* 1.30, $CHCl_3$).

Anal. Calcd for $C_{22}H_{30}O_2Si$: C, 74.53; H, 8.53. Found: C, 74.27; H, 8.53.

(*R*)-5-[2-(*tert*-Butyldiphenylsiloxy)-1,1-dimethylethyl]-dihydro-2(3*H*)-furanone (17). To a solution of LDA, prepared by the addition of *n*-butyllithium (81.2 mL of 1.6 M in hexanes, 130 mmol) to diisopropylamine (14.6 g, 144 mmol) in DME (120 mL) cooled to −20 °C with a subsequent warming to 0 °C, was added acetic acid (3.89 g, 64.9 mmol). The reaction mixture was stirred at room temperature for 40 min and at +40 °C for 20 min to complete the metalation. This white suspension was treated with **16** (2.60 g, 7.22 mmol) in a small amount of DME, heated to reflux overnight, cooled, and diluted with water. The separated aqueous phase was acidified to pH 3 and extracted with ether, and the combined organic solutions were washed with 1 M HCl until the washes were acidic. The organic phase was refluxed for 4 h in order to complete the lactonization process and then evaporated. The product was chromatographed on silica gel (elution with 20% ether in petroleum ether) and obtained as a colorless oil (2.05 g, 72%): IR (film, cm^{-1}) 1778; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70−7.63 (m, 4 H), 7.47−7.37 (m, 6 H), 4.61 (dd, J = 7.1, 8.9 Hz, 1 H), 3.57 (d, J = 9.9 Hz, 1 H), 3.41 (d, J = 9.9 Hz, 1 H), 2.59−2.49 (m, 2 H), 2.15−2.00 (m, 2 H), 1.08 (s, 9 H), 0.95 (s, 3 H), 0.91 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.2, 135.6 (4 C), 133.3, 133.2, 129.7 (2 C), 127.6 (4 C), 84.1, 69.6, 38.9, 29.3, 26.9 (3 C), 22.7, 19.6, 19.3, 19.2; MS m/z (M^+ − *t*-Bu) calcd 339.1416, obsd 339.1427; [α] −17.8 (*c* 2.35, $CHCl_3$).

(3*S*,5*R*)-5-[2-(*tert*-Butyldiphenylsiloxy)-1,1-dimethylethyl]dihydro-3-methyl-2(3*H*)-furanone (18). A solution of **17** (1.05 g, 2.65 mmol) in cold (−78 °C) THF (10 mL) was treated with lithium hexamethyldisilazide (3.17 mL of 1.0 M in THF, 3.17 mmol), stirred for 1 h at this temperature, quenched with methyl iodide (0.3 mL), and diluted with ether prior to washing with saturated NH_4Cl solution and brine, drying, and concentration. Chromatographic purification of the residue on silica gel (elution with 15% ether in petroleum ether) afforded **18** as a colorless oil (2.15 g, 81%): IR (film, cm^{-1}) 1777; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68−7.60 (m, 4 H), 7.47−7.34 (m, 6 H), 4.61 (t, J = 7.4 Hz, 1 H), 3.53 (d, J = 9.9 Hz, 1 H), 3.39 (d, J = 9.9 Hz, 1 H), 2.65 (ddq, J = 9.5, 7.4, 5.4 Hz, 1 H), 2.28 (ddd, J = 13.1, 7.0, 9.5 Hz, 1 H), 1.79 (ddd, J = 13.1, 7.7, 5.4 Hz, 1 H), 1.29 (d, J = 7.4 Hz, 3 H), 1.07 (s, 9 H), 0.93 (s, 3 H), 0.88 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) δ 178.6, 136.02 (2 C), 135.99 (2 C), 133.8, 133.6, 130.13, 130.10, 128.14 (2 C), 128.11 (2 C), 80.6, 69.9, 39.3, 34.7, 30.1, 27.1 (3 C), 19.8, 19.6, 19.0, 16.5; MS m/z (M^+ − CH_3) calcd 395.2042, obsd 395.2038; [α] −25.7 (*c* 3.39, $CHCl_3$).

Anal. Calcd for $C_{25}H_{34}O_3Si$: C, 73.13; H, 8.35. Found: C, 73.13; H, 8.43.

(3*R*,5*R*)-5-[2-(*tert*-Butyldiphenylsiloxy)-1,1-dimethylethyl]dihydro-3-methyl-2(3*H*)-furanone (3). A solution of LDA (9.39 mmol) in THF (10 mL), prepared in the predescribed

manner, was cooled to −78 °C, treated with a solution of **18** (772 mg, 1.88 mmol) in THF (1 mL), stirred for 2 h at −78 °C, and quenched with saturated NH_4Cl solution. The product was extracted into ether, washed with brine, dried, evaporated, and purified chromatographically (silica gel, elution with 35% ether in hexanes). There was obtained 741 mg (96%) of **3** as a colorless oil: IR (film, cm^{-1}) 1770; ^1H NMR (300 MHz, $CDCl_3$) δ 7.66−7.60 (m, 4 H), 7.46−7.35 (m, 6 H), 4.45 (dd, J = 5.6, 11.1 Hz, 1 H), 3.55 (d, J = 9.9 Hz, 1 H), 3.40 (d, J = 9.9 Hz, 1 H), 2.67 (ddq, J = 7.0, 8.6, 12.5 Hz, 1 H), 2.23 (ddd, J = 5.6, 8.6, 12.5 Hz, 1 H), 1.68 (q, J = 12.2 Hz, 1 H), 1.26 (d, J = 7.0 Hz, 3 H), 1.07 (s, 9 H), 0.93 (s, 3 H), 0.89 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.5, 135.6 (4 C), 133.4, 133.3, 129.7 (2 C), 127.7 (4 C), 81.6, 69.7, 38.5, 36.0, 31.9, 26.9 (3 C), 19.6, 19.4, 19.2, 14.9; MS m/z (M^+) calcd 410.2277, obsd 410.2316; [α] −8.3 (*c* 3.95, $CHCl_3$).

Anal. Calcd for $C_{25}H_{34}O_3Si$: C, 73.13; H, 8.35. Found: C, 72.72; H, 8.44.

Ethyl (3*R*,4*S*,6*S*)-6-[(*tert*-Butyldiphenylsiloxy)methyl]-tetrahydro-2-hydroxy-4-[(*p*-methoxybenzyl)oxy]-3-methyl-2*H*-pyran-2-acetate (19). A solution containing 0.77 mmol of LDA in THF (2 mL) was cooled to −78 °C, treated during 10 min with dry ethyl acetate (0.073 mL, 0.75 mmol), and stirred for 10 min prior to the introduction of **10** (100 mg, 0.19 mmol) dissolved in THF (1 mL). The reaction mixture was agitated for an additional 10 min, quenched with saturated NH_4Cl solution (1 mL), and extracted with ether. The combined organic layers were dried and concentrated to leave a residue that was purified chromatographically (silica gel, elution with 10% ether in petroleum ether). There was isolated 82 mg (70%) of **19** as a colorless oil: IR (film, cm^{-1}) 3443, 1713; ^1H NMR (300 MHz, C_6D_6) δ 7.82−7.76 (m, 4 H), 7.29−7.19 (m, 8 H), 6.81 (dm, J = 8.7 Hz, 2 H), 5.56 (d, J = 1.8 Hz, 1 H), 4.44 (d, J = 11.3 Hz, 1 H), 4.40−4.18 (m, 1 H), 4.21 (d, J = 11.3 Hz, 1 H), 3.97−3.82 (m, 2 H), 3.78 (dd, J = 5.7, 10.5 Hz, 1 H), 3.72−3.63 (m, 2 H), 3.30 (s, 3 H), 2.51 (d, J = 15.3 Hz, 1 H), 2.37 (d, J = 15.3 Hz, 1 H), 2.02 (ddd, J = 2.3, 4.5, 12.2 Hz, 1 H), 1.58−1.40 (m, 1 H), 1.38−1.27 (m, 1 H), 1.21 (d, J = 6.5 Hz, 3 H), 1.19 (s, 9 H), 0.87 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 159.2, 135.7 (2 C), 135.6 (2 C), 133.8 (2 C), 130.9, 129.58, 129.56, 129.3 (2 C), 127.6 (4 C), 113.8 (2 C), 98.8, 76.2, 70.7, 69.1, 66.9, 60.9, 55.3, 45.2, 42.3, 33.8, 26.8 (3 C), 19.3, 14.1, 12.4; MS m/z ($M^+ - C_4H_9 - H_2O$) calcd 531.2203, obsd 531.2216; [α] +36.3 (*c* 1.84, $CHCl_3$).

Anal. Calcd for $C_{35}H_{46}O_7Si$: C, 69.28; H, 7.64. Found: C, 69.28; H, 7.66.

Ethyl (2*S*,3*R*,4*S*,6*S*)-6-[(*tert*-Butyldiphenylsiloxy)methyl]tetrahydro-4-hydroxy-3-methyl-2*H*-pyran-2-acetate (20). A. By Ionic Reduction of 19. A solution of **19** (15 mg, 0.025 mmol) in CH_2Cl_2 (1 mL) at 0 °C was treated sequentially with titanium tetrachloride (0.025 mL of 1 M in CH_2Cl_2, 0.025 mmol) and triethylsilane (6 mg, 0.050 mmol), allowed to warm to room temperature, washed with water and brine, dried, and evaporated. Purification of the residue by chromatography on silica gel (elution with 30% ether in petroleum ether) furnished 9 mg (74%) of **20** as a colorless oil: IR (film, cm^{-1}) 3471, 1738; ^1H NMR (300 MHz, $CDCl_3$) δ 7.67−7.65 (m, 4 H), 7.44−7.27 (m, 6 H), 4.15−4.05 (m, 2 H), 3.71−3.60 (m, 1 H), 3.57−3.41 (m, 4 H), 2.62 (dd, J = 3.3, 15.1 Hz, 1 H), 2.41 (dd, J = 8.9, 15.1 Hz, 1 H), 2.07 (dd, J = 4.3, 11.6 Hz, 1 H), 1.57 (br s, 1 H), 1.39−1.23 (m, 2 H), 1.20 (t, J = 7.1 Hz, 3 H), 1.04 (s, 9 H), 1.00 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 135.63 (2 C), 135.60 (2 C), 133.6 (2 C), 129.6 (4 C), 127.6 (2 C), 77.8, 76.0, 73.3, 66.6, 60.4, 43.8, 39.2, 37.6, 26.8 (3 C), 19.2, 14.2, 12.8; FAB MS m/z (M^+ + H) calcd 471.26, obsd 471.32; [α] −17.8 (*c* 0.54, $CHCl_3$).

Anal. Calcd for $C_{27}H_{38}O_5Si$: C, 68.90; H, 8.14. Found: C, 68.78; H, 8.22.

B. Alternate Route from 9. A solution of **9** (100 mg, 0.25 mmol), hexamethyldisilazane (2 mL), and chlorotrimethylsilane (1 drop) was refluxed for 2 h, cooled, and freed of solvent under reduced pressure. In a separate flask, a THF solution containing 1.76 mmol of LDA was cooled to −78 °C, treated with ethyl acetate (155 mg, 1.76 mmol), and stirred for 1 h at −78 °C prior to introduction of the silylated lactone. The reaction mixture was stirred for 5 min, quenched with saturated NH_4Cl solution (1 mL), diluted with ether (50 mL), washed with 1 M HCl, dried, and concentrated. The resulting material was dissolved in CH_2Cl_2 (2 mL), cooled to −78 °C, treated with triethylsilane (292 mg, 2.51 mmol) and then tin tetrachloride (0.25 mL of 1 M in CH_2Cl_2, 0.25 mmol), allowed to warm during 1 h to −20 °C, and stirred at this temperature for an additional 30 min before being quenched with water (2 mL). The product was extracted into ether and purified in the predescribed manner to deliver 69 mg (59% for 3 steps) of **20**.

Ethyl (2*S*,3*R*,4*S*,6*S*)-6-[(*tert*-Butyldiphenylsiloxy)methyl]tetrahydro-4-[(*p*-methoxybenzyl)oxy]-3-methyl-2*H*-pyran-2-acetate (21). A solution of **20** (594 mg, 1.26 mmol) in dry ether (20 mL) was treated with triflic acid (0.037 mL of 0.1 M in ether, 0.3 mol %) followed immediately by *p*-methoxybenzyl trichloroacetimidate (535 mg, 1.89 mmol) dissolved in ether (1 mL). The reaction mixture was stirred for 20 min, washed with water and saturated $NaHCO_3$ solution, dried, and concentrated. Chromatography of the residue on silica gel (elution with 15% ether in petroleum ether) gave 437 mg (59%) of **21** as a colorless oil: IR (film, cm^{-1}) 1738; ^1H NMR (300 MHz, $CDCl_3$) δ 7.71−7.68 (m, 4 H), 7.46−7.36 (m, 6 H), 7.28 (dm, J = 8.6 Hz, 2 H), 6.90 (dm, J = 8.6 Hz, 2 H), 4.60 (d, J = 11.2 Hz, 1 H), 4.39 (d, J = 11.2 Hz, 1 H), 4.17−4.06 (m, 2 H), 3.81 (s, 3 H), 3.74 (dd, J = 5.2, 10.0 Hz, 1 H), 3.62−3.50 (series of m, 3 H), 3.18 (td, J = 4.5, 10.6 Hz, 1 H), 2.63 (dd, J = 3.2, 15.1 Hz, 1 H), 2.42 (dd, J = 9.1, 15.1 Hz, 1 H), 2.23−2.18 (m, 1 H), 1.50−1.41 (m, 1 H), 1.35−1.25 (m, 1 H), 1.21 (t, J = 7.1 Hz, 3 H), 1.07 (s, 9 H), 0.98 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 159.2, 135.68 (2 C), 135.65 (2 C), 133.7 (2 C), 130.7, 129.6 (2 C), 129.4 (2 C), 127.6 (4 C), 113.8 (2 C), 80.0, 78.2, 76.1, 70.2, 66.9, 60.4, 55.3, 41.9, 39.4, 33.6, 26.8 (3 C), 19.3, 14.2, 13.1; FAB MS m/z (M^+ + H) calcd 591.31, obsd 591.42; [α] +23.3 (*c* 1.22, $CHCl_3$).

Anal. Calcd for $C_{35}H_{46}O_6Si$: C, 71.15; H, 7.85. Found: C, 71.04; H, 7.82.

Ethyl (2*S*,3*R*,4*S*,6*S*)-Tetrahydro-6-(hydroxymethyl)-4-[(*p*-methoxybenzyl)oxy]-3-methyl-2*H*-pyran-2-acetate (22). To a solution of **21** (486 mg, 0.82 mmol) in THF (5 mL) was added tetra-*n*-butylammonium fluoride (1.07 mL of 1 M in THF, 1.07 mmol). The reaction mixture was stirred for 1.5 h, diluted with ether (50 mL), washed with water and brine, dried, and concentrated. Purification of the residue by chromatography (silica gel, gradient elution with 30−70% ethyl acetate in petroleum ether) provided 275 mg (95%) of **22** as a colorless oil: IR (film, cm^{-1}) 3454, 1732; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25 (dm, J = 8.5 Hz, 2 H), 6.87 (dm, J = 8.5 Hz, 2 H), 4.58 (d, J = 11.1 Hz, 1 H), 4.36 (d, J = 11.1 Hz, 1 H), 4.41 (q, J = 7.1 Hz, 2 H), 3.80 (s, 3 H), 3.61−3.42 (m, 4 H), 3.17 (td, J = 4.6, 10.6 Hz, 1 H), 2.64 (dd, J = 3.4, 15.1 Hz, 1 H), 2.40 (dd, J = 9.1, 15.1 Hz, 1 H), 2.11−1.46 (m, 2 H), 1.51−1.44 (m, 1 H), 1.43−1.29 (m, 1 H), 1.25 (t, J = 7.1 Hz, 3 H), 0.96 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 159.1, 130.4, 129.2 (2 C), 113.7 (2 C), 79.2, 78.0, 75.8, 70.1, 65.7, 60.4, 55.2, 41.8, 39.2, 32.7, 14.1, 12.9; FAB MS m/z (M^+ + H) calcd 353.20, obsd 353.21; [α] +48.9 (*c* 2.22, $CHCl_3$).

Anal. Calcd for $C_{19}H_{28}O_6$: C, 64.75; H, 8.01. Found: C, 64.47; H, 8.08.

Ethyl (2*S*,3*R*,4*S*,6*S*)-6-Formyltetrahydro-4-[(*p*-methoxybenzyl)oxy]-3-methyl-2*H*-pyran-2-acetate (23). A solution of **22** (264 mg, 0.75 mmol) in CH_2Cl_2 (10 mL) was treated with the Dess−Martin periodinane (508 mg, 1.20 mmol), stirred for 1 h, and subjected directly to chromatography on silica gel. Elution with 50% ether in petroleum ether provided 187 mg (71%) of **23** as a colorless oil: IR (film, cm^{-1}) 1732; ^1H NMR (300 MHz, $CDCl_3$) δ 9.61 (s, 1 H), 7.24 (dm, J = 8.5 Hz, 2 H), 6.87 (dm, J = 8.5 Hz, 2 H), 4.61 (d, J = 11.1 Hz, 1 H), 4.36 (d, J = 11.1 Hz, 1 H), 4.16 (q, J = 7.1 Hz, 2 H), 3.84−3.79 (m, 1 H), 3.80 (s, 3 H), 3.61 (td, J = 3.3, 9.7 Hz, 1 H), 3.18 (td, J = 4.4, 10.3 Hz, 1 H), 2.67 (dd, J = 3.3, 15.3 Hz, 1 H), 2.49 (dd, J = 9.0, 15.3 Hz, 1 H), 2.36 (ddd, J = 2.5, 4.4, 12.6 Hz, 1 H), 1.54−1.49 (m, 1 H), 1.47−1.32 (m, 1 H), 1.26 (t, J = 7.1 Hz, 3 H), 0.97 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.2, 171.3, 159.3, 130.1, 129.4 (2 C), 113.9 (2 C), 79.6, 78.7,

78.4, 70.3, 60.6, 55.3, 41.6, 39.1, 31.6, 14.2, 12.9; FAB MS *m*/*z* ($M^+ + H$) calcd 351.18, obsd 351.17; [α] +17.5 (*c* 1.50, $CHCl_3$).

Ethyl (2*S*,3*R*,4*S*,6*S*)-6-(Formylmethyl)tetrahydro-4-[(*p*-methoxybenzyl)oxy]-3-methyl-2*H*-pyran-2-acetate (5). A magnetically stirred suspension of (methoxymethyl)triphenylphosphonium chloride (94 mg, 0.37 mmol) in THF (2 mL) was cooled to 0 °C, treated with potassium hexamethyldisilazide (0.55 mL of 0.5 M in toluene, 0.27 mmol), and stirred for 15 min in advance of the addition of **23** (32 mg, 0.091 mmol) dissolved in THF (0.5 mL). The reaction mixture was stirred at 0 °C for 30 min, quenched with saturated NH_4Cl solution, and extracted with ether. The combined organic phases were dried, concentrated, and passed through a pad of silica gel (elution with 30% ether in petroleum ether). The resulting enol ether was dissolved in THF (1 mL), treated with 1 M HCl (0.25 mL), stirred for 5 h, diluted with ether, and washed with water and saturated $NaHCO_3$ solution prior to drying, concentration, and chromatography on silica gel (elution with 50−60% ether in petroleum ether) to furnish 15 mg (45%) of **5** as a colorless oil: IR (film, cm^{-1}) 1731; ^1H NMR (300 MHz, $CDCl_3$) δ 9.70 (m, 1 H), 7.24 (dm, *J* = 8.6 Hz, 2 H), 6.87 (dm, *J* = 8.6 Hz, 2 H), 4.57 (d, *J* = 11.1 Hz, 1 H), 4.36 (d, *J* = 11.1 Hz, 1 H), 4.11 (q, *J* = 7.1 Hz, 2 H), 3.92−3.83 (m, 1 H), 3.79 (s, 3 H), 3.52 (td, *J* = 3.2, 9.7 Hz, 1 H), 3.17 (td, *J* = 4.5, 10.3 Hz, 1 H), 2.65−2.57 (m, 2 H), 2.45 (ddd, *J* = 1.7, 4.7, 16.4 Hz, 1 H), 2.35 (dd, *J* = 9.5, 14.9 Hz, 1 H), 2.15 (ddd, *J* = 1.8, 4.5, 12.4 Hz, 1 H), 1.48−1.39 (m, 1 H), 1.36−1.24 (m, 1 H), 1.23 (t, *J* = 7.1 Hz, 3 H), 0.95 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.8, 171.4, 159.2, 133.8 (2 C), 130.3, 129.3 (2 C), 79.1, 78.3, 70.7, 70.3, 60.5, 55.2, 49.2, 41.5, 39.2, 36.8, 14.1, 12.9; FAB MS *m*/*z* ($M^+ + H$) calcd 365.20, obsd 365.27; [α] +41.3 (*c* 1.21, $CHCl_3$).

(3*R*,5*R*)-5-[2-(*tert*-Butyldiphenylsiloxy)-1,1-dimethylethyl)-tetrahydro-3-methyl-2-furanol (24). Lactone **3** (247 mg, 0.60 mmol) was dissolved in CH_2Cl_2 (5 mL), cooled to −78 °C, treated with diisobutylaluminum hydride (0.72 mL of 1 M in CH_2Cl_2, 0.72 mmol), stirred for 10 min, quenched with saturated sodium potassium tartrate solution (2 mL), and partitioned between ether (10 mL) and water (10 mL). The aqueous phase was extracted with ether (3 × 10 mL), and the combined organic solutions were processed as described earlier. Passage through a short silica gel column (elution with 30% ether in hexanes) afforded 245 mg (99%) of **24** as a colorless oil: IR (film, cm^{-1}) 3409; ^1H NMR (300 MHz, C_6D_6) (major anomer) δ 7.88−7.79 (m, 4 H), 7.30−7.25 (m, 6 H), 4.93 (m, 1 H), 4.26 (dd, *J* = 5.9, 10.3 Hz, 1 H), 3.69 (d, *J* = 9.5 Hz, 1 H), 3.61 (d, *J* = 9.5 Hz, 1 H), 3.11 (br s, 1 H), 1.78−1.52 (m, 1 H), 1.28 (m, 1 H), 1.23 (s, 9 H), 1.15−1.00 (m, 1 H), 1.00−0.87 (2 singlets (3H each) and a doublet (3H)—overlapping with minor anomer); ^{13}C NMR (75 MHz, C_6D_6) δ (136.2, 136.1, 4 C), (134.23, 134.10, 134.17, 2 C), 129.9 (4 C), 128.2 (2 C), (104.9, 98.8), (84.3, 82.2), (71.0, 70.9), (41.4, 39.5), (38.73, 38.66), (34.2, 31.8), 27.2 (3 C), 19.7, (21.3, 20.9), (19.9, 19.8), (17.5, 12.9); MS *m*/*z* ($M^+ - OH$) calcd 395.2406, obsd 395.2438; [α] +1.3 (*c* 1.38, $CHCl_3$).

Anal. Calcd for $C_{25}H_{36}O_3Si$: C, 72.77; H, 8.79. Found: C, 72.84; H, 8.83.

(α*R*,γ*R*)-α-[2-(*tert*-Butyldiphenylsiloxy)-1,1-dimethylethyl]-γ-methyl-*m*-dithiane-2-propanol (25). A solution of **24** (78 mg, 0.19 mmol) and 1,3-propanedithiol (41 mg, 0.38 mmol) in benzene (2 mL) was treated with titanium tetrachloride (0.19 mL of 1.0 M in CH_2Cl_2, 0.19 mmol), stirred for 30 min, and diluted with ether (7 mL) and water (5 mL). The organic phase was washed with brine, dried, and evaporated to leave a residue that was purified by chromatography on silica gel (elution with 15% ether in petroleum ether) to give 89 mg (93%) of **25** as a colorless oil: IR (film, cm^{-1}) 3500; ^1H NMR (300 MHz, $CDCl_3$) δ 7.71−7.63 (m, 4 H), 7.48−7.40 (m, 6 H), 4.20 (d, *J* = 3.9 Hz, 1 H), 3.59−3.49 (m, 1 H), 3.56 (d, *J* = 9.9 Hz, 1 H), 3.44 (d, *J* = 9.9 Hz, 1 H), 3.17 (br s, 1 H), 2.97−2.81 (m, 4 H), 2.37−2.28 (m, 1 H), 2.16−2.06 (m, 1 H), 1.93−1.78 (m, 1 H), 1.70 (ddd, *J* = 3.2, 11.1, 13.9 Hz, 1 H), 1.50−1.42 (m, 1 H), 1.13 (d, *J* = 6.8 Hz, 3 H), 1.07 (s, 9 H), 0.88 (s, 3 H), 0.86 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.7 (2 C), 135.6 (2 C), 132.7, 132.6, 129.84, 129.80, 127.8 (4 C), 75.9, 73.0, 56.8, 38.9, 36.3, 35.0, 31.0, 30.8, 26.9 (3 C), 26.4, 22.4, 19.5, 19.1, 16.3; MS *m*/*z* (M^+) calcd 502.2395, obsd 502.2391; [α] +29.5 (*c* 1.47, $CHCl_3$).

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

(3*R*,5*R*)-5-*m*-Dithian-2-yl-2,2-dimethyl-1,3-hexanediol (26). A solution of **25** (188 mg, 0.37 mmol) in THF (5 mL) was reacted with tetra-*n*-butylammonium fluoride (0.45 mL of 1.0 M in THF, 0.45 mmol) as described previously to give after chromatography (silica gel, gradient elution with 50 → 80% ether in petroleum ether) 93 mg (94%) of **26** as a colorless oil: IR (film, cm^{-1}) 3408; ^1H NMR (300 MHz, $CDCl_3$) δ 4.19 (d, *J* = 3.9 Hz, 1 H), 3.58−3.42 (series of m, 3 H), 2.95−2.77 (series of m, 6 H), 2.23−2.05 (m, 2 H), 1.90−1.75 (m, 1 H), 1.65 (ddd, *J* = 3.8, 10.5, 14.0 Hz, 1 H), 1.49 (ddd, *J* = 1.8, 9.8, 14.0 Hz, 1 H), 1.09 (d, *J* = 6.8 Hz, 3 H), 0.87 (s, 3 H), 0.86 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 76.5, 71.8, 56.3, 38.2, 36.3, 35.1, 30.9, 30.6, 26.1, 22.4, 18.7, 16.3; FAB MS *m*/*z* ($M^+ + H$) calcd 265.13, obsd 265.11; [α] +27.8 (*c* 1.44, $CHCl_3$).

Anal. Calcd for $C_{12}H_{24}O_2S_2$: C, 54.50; H, 9.15. Found: C, 54.23; H, 9.14.

(4*R*)-4-[(2*R*)-2-*m*-Dithian-2-ylpropyl]-2-(*p*-methoxyphenyl)-5,5-dimethyl-*m*-dioxane (27). A mixture of **26** (773 mg, 2.92 mmol), *p*-methoxybenzaldehyde (418 mg, 3.07 mmol), and camphorsulfonic acid (10 mg) was refluxed under a modified Dean−Stark trap filled with 4 Å molecular sieves for 6 h. The cooled reaction mixture was concentrated and the residue was purified by chromatography on silica gel (elution with 15% ether in petroleum ether) to furnish 993 mg (89%) of **27** as a white solid: mp 144−145 °C (from ether−hexanes): IR ($CHCl_3$, cm^{-1}) 1615, 1249, 1106; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42 (dm, *J* = 8.7 Hz, 2 H), 6.88 (dm, *J* = 8.7 Hz, 2 H), 5.41 (s, 1 H), 4.17 (d, *J* = 3.8 Hz, 1 H), 3.80 (s, 3 H), 3.71 (d, *J* = 11.0 Hz, 1 H), 3.58 (d, *J* = 11.5 Hz, 1 H), 3.51 (dd, *J* = 1.6, 10.7 Hz, 1 H), 2.94−2.80 (m, 4 H), 2.26−2.20 (m, 1 H), 2.08 (dm, *J* = 13.6 Hz, 1 H), 1.87−1.73 (m, 2 H) 1.48 (ddd, *J* = 1.7, 10.2, 13.9 Hz, 1 H), 1.13 (s, 3 H), 1.11 (d, *J* = 6.9 Hz, 3 H), 0.76 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.7, 131.3, 127.2 (2 C), 113.4 (2 C), 101.5, 82.5, 78.9, 56.4, 55.2, 34.5, 33.8, 32.6, 31.1, 30.7, 26.2, 21.3, 18.6, 16.1; MS *m*/*z* (M^+) calcd 382.1636, obsd 382.1647; [α] +29.6 (*c* 1.08, $CHCl_3$).

Anal. Calcd for $C_{20}H_{30}O_3S_2$: C, 62.79; H, 7.90. Found: C, 62.89; H, 7.92.

(γ*R*,ε*R*)-γ-[(*p*-Methoxybenzyl)oxy]-β,β,ε-trimethyl-*m*-dithiane-2-pentanol (28). A cold (0 °C), magnetically stirred solution of **27** (106 mg, 0.277 mmol) in CH_2Cl_2 (2 mL) was treated with Dibal-H (0.42 mL of 1.0 M in hexanes, 0.42 mmol), stirred for 1 h at 0 °C and 30 min at room temperature, quenched with saturated sodium potassium tartrate solution (5 mL), and extracted with ether (3 × 20 mL). The combined organic layers were dried and concentrated, and the residue was purified chromatographically (silica gel, elution with 30% ether in petroleum ether) to give **28** (79 mg, 73%) as a white solid: mp 46 °C; IR (film, cm^{-1}) 3477, 1613; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27 (dm, *J* = 8.5 Hz, 2 H), 6.86 (dm, *J* = 8.5 Hz, 2 H), 4.56 (s, 2 H), 4.14 (d, *J* = 3.8 Hz, 1 H), 3.78 (s, 3 H), 3.62 (d, *J* = 10.8 Hz, 1 H), 3.37 (dd, *J* = 1.8, 9.5 Hz, 1 H), 3.31 (d, *J* = 10.8 Hz, 1 H), 2.93−2.78 (m, 4 H), 2.70 (br s, 1 H), 2.17−2.04 (m, 2 H), 1.92−1.75 (m, 2 H), 1.52 (dd, *J* = 2.0, 10.5 Hz, 1 H), 1.11 (d, *J* = 6.8 Hz, 3 H), 1.02 (s, 3 H), 0.85 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 130.4, 129.3 (2 C), 113.8 (2 C), 84.5, 74.6, 70.4, 56.5, 55.2, 39.8, 36.3, 35.8, 31.0, 30.7, 26.2, 23.2, 20.8, 16.7; MS *m*/*z* (M^+) calcd 384.1793, obsd 384.1762; [α] +7.0 (*c* 1.51, $CHCl_3$).

Anal. Calcd for $C_{20}H_{32}O_3S_2$: C, 62.46; H, 8.39. Found: C, 62.46; H, 8.43.

(β*R*,δ*R*)-β-[(*p*-Methoxybenzyl)oxy]-α,α,δ-trimethyl-*m*-dithiane-2-valeraldehyde (29). A solution of oxalyl chloride (0.136 mL, 1.56 mmol) in CH_2Cl_2 (3 mL) was cooled to −78 °C, treated dropwise with a solution of DMSO (244 mg, 3.12 mmol) in CH_2Cl_2 (1 mL), and stirred for 15 min in the cold prior to the dropwise addition of **28** (500 mg, 1.30 mmol) dissolved in CH_2Cl_2 (1 mL). After 15 min at this temperature, triethylamine (1.08 mL, 7.8 mmol) was introduced followed by warming to −40 °C during 40 min. The reaction mixture

was poured into water, extracted with CH_2Cl_2, washed with brine, dried, and concentrated. The residue was chromatographed on silica gel (elution with 25% ether in petroleum ether) to furnish **29** (428 mg, 86%) as a white solid: mp 63 °C; IR (film, cm^{-1}) 1724, 1612; ^1H NMR (300 MHz, $CDCl_3$) δ 9.62 (s, 1 H), 7.23 (dm, J = 8.7 Hz, 2 H), 6.86 (dm, J = 8.7 Hz, 2 H), 4.49 (s 2 H), 4.11 (d, J = 3.9 Hz, 1 H), 3.79 (s, 3 H), 3.61 (dd, J = 2.1, 9.7 Hz, 1 H), 2.92−2.87 (m, 4 H), 2.17−2.04 (m, 2 H), 1.91−1.77 (m, 2 H), 1.61−1.39 (m, 1 H), 1.13 (s, 3 H), 1.11 (d, J = 6.8 Hz, 3 H), 1.05 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.0, 159.2, 130.3, 129.2 (2 C), 113.8 (2 C), 80.8, 74.1, 56.2, 55.2, 51.2, 36.2, 35.5, 31.0, 30.7, 26.2, 19.4, 17.6, 16.6; FAB MS m/z (M^+ + H) calcd 383.17, obsd 383.25; [α] −1.5 (c 0.88, $CHCl_3$).

Anal. Calcd for $C_{20}H_{30}O_3S_2$: C, 62.79; H, 7.90. Found: C, 62.64; H, 7.89.

2-[(1*R*,3*R*)-3-[(*p*-Methoxybenzyl)oxy]-1,4,4-trimethyl-5-hexenyl]-*m*-dithiane (30). A suspension of methyltriphenylphosphonium iodide (110 mg, 0.271 mmol) in dry THF (1 mL) was treated with potassium hexamethyldisilazide (542 μL of 0.5 M in toluene, 0.271 mmol) at 0 °C and stirred for 0.5 h prior to the addition of **29** (35 mg, 0.090 mmol) dissolved in THF (2 mL) via cannula. After 20 min, the reaction mixture was quenched with saturated NH_4Cl solution (10 mL) and extracted several times with ether. The combined organic phases were dried, filtered, and concentrated to leave a residue, chromatography of which on silica gel (elution with 20% ethyl acetate in hexanes) provided **30** (33 mg, 94%) as a colorless oil: IR (film, cm^{-1}) 1534; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, J = 8.9 Hz, 2 H), 6.96 (d, J = 8.9 Hz, 2 H), 5.86 (dd, J = 17.8, 10.5 Hz, 1 H), 5.00 (m, 2 H), 4.58 (d, J = 10.6 Hz, 1 H), 4.51 (d, J = 10.6 Hz, 1 H), 4.10 (d, J = 3.8 Hz, 1 H), 3.79 (s, 3 H), 3.13 (dd, J = 10.0, 2.0 Hz, 1 H), 2.87−2.80 (m, 4 H), 2.15−1.40 (m, 5 H), 1.06 (d, J = 6.5 Hz, 3 H), 1.06 (s, 3 H), 1.04 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.0 (2 C), 131.2, 129.1 (2 C), 113.7, 111.9, 99.9, 84.6, 74.8, 56.6, 55.3, 42.4, 36.7, 35.5, 31.1, 30.7, 26.3, 24.0, 22.9, 16.5; MS m/z (M^+) calcd 308.1844, obsd 308.1847; [α] +13.1 (c 0.99, $CHCl_3$).

Ethyl (2*E*,4*E*)-5-(Tributylstannyl)-2,4-pentadienoate (32). A solution of LDA in THF (1.74 mmol) was cooled to −60 °C, treated with triethyl phosphonoacetate (338 mg, 1.51 mmol), and allowed to warm to −40 °C, at which point **31**[29] (400 mg, 1.16 mmol) dissolved in THF (3 mL) was introduced. The reaction mixture was brought to room temperature during 2 h, diluted with an equal volume of ether, washed with water and brine, dried, and concentrated. Chromatographic purification of the residue on silica gel (elution with 1% ether in petroleum ether) furnished 340 mg (71%) of **32** as a colorless oil: IR (film, cm^{-1}) 1716, 1626; ^1H NMR (300 MHz, $CDCl_3$) δ 7.18 (dd, J = 10.0, 15.4 Hz, 1 H), 6.81 (d, J = 18.7 Hz, 1 H), 6.64 (dd, J = 10.0, 18.7 Hz, 1 H), 5.79 (d, J = 15.4 Hz, 1 H), 4.20 (q, J = 7.1 Hz, 2 H), 1.55−1.41 (m, 6 H), 1.36−1.24 (series of m, 9 H), 1.03−0.85 (series of m, 15 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.4, 147.2, 146.3, 144.2, 119.9, 60.2, 29.0 (3 C), 27.2 (3 C), 14.3, 13.6 (3 C), 9.6 (3 C); MS m/z (M^+) calcd 416.1737, obsd 416.1693.

Dimethyl [(2*E*,4*E*)-5-(Tributylstannyl)-2,4-pentadienyl]-phosphonate (33). A solution of **32** (301 mg, 725 mmol) in THF (5 mL) was cooled to −78 °C and treated dropwise with Dibal-H (2.17 mL of 1 M in hexanes, 2.17 mmol). After 20 min, saturated sodium potassium tartrate solution was introduced, vigorous stirring was maintained for 2, and the separated aqueous layer was extracted with ether. The combined organic layers were dried and concentrated to leave a residue that was purified chromatographically (silica gel, elution with 25% ether in petroleum ether) to furnish 247 mg (91%) of the primary alcohol as a colorless oil: IR (film, cm^{-1}) 3330; ^1H NMR (300 MHz, $CDCl_3$) δ 6.54 (dd, J = 9.8, 18.7 Hz, 1 H), 6.28−6.19 (m, 2 H), 5.79 (dt, J = 5.8, 15.4 Hz, 1 H), 4.19 (dt, J = 0.9, 5.7 Hz, 2 H), 1.59−1.24 (series of m, 13 H), 0.98−0.77 (series of m, 15 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.9, 135.0, 134.6, 130.7, 63.3, 29.1 (3 C), 27.2 (3 C), 13.7 (3 C), 9.5 (3 C); MS m/z ($M^+ - C_4H_9$) calcd 317.0927, obsd 317.0896.

Anal. Calcd for $C_{17}H_{34}OSn$: C, 54.72; H, 9.18. Found: C, 54.85; H, 9.25.

A solution of the above alcohol (911 mg, 2.44 mmol) and carbon tetrabromide (1.62 g, 4.88 mmol) in acetonitrile (10 mL) was treated with triphenylphosphine (1.28 g, 4.88 mmol) in portions during 30 min. The reaction mixture was poured into saturated $NaHCO_3$ solution (50 mL), extracted with a 1:10 mixture of ether and petroleum ether (2 × 50 mL), dried, and concentrated. The solid was rinsed with petroleum ether, and the filtrate was concentrated prior to rapid elution through silica gel with 5% ether in petroleum ether. After solvent evaporation, there remained 957 mg (91%) of the bromide.

A solution of sodium dimethyl phosphite was prepared by the addition of dimethyl phosphite (660 mg, 6.00 mmol) to a suspension of sodium hydride (144 mg, 6.00 mmol) in dry THF (22 mL), and the mixture was warmed with a heat gun until a clear solution was obtained. The above bromide was dissolved in THF (5 mL), added to the anion solution, and stirred for 2 h during which time sodium bromide precipitated. The mixture was diluted with ether and water, and the organic phase was dried, concentrated, and chromatographed on silica gel (elution with ether) to provide 491 mg (43% for two steps) of **33** as a colorless oil: IR (film, cm^{-1}) 1032; ^1H NMR (300 MHz, $CDCl_3$) δ 6.49 (dd, J = 9.8, 18.9 Hz, 1 H), 6.22−6.10 (m, 2 H), 5.64−5.51 (m, 1 H), 3.75 (d, J = 10.8 Hz, 6 H), 2.64 (ddd, J = 1.1, 7.6, 22.4 Hz, 2 H), 1.52−1.40 (m, 6 H), 1.36−1.20 (m, 6 H), 1.00−0.15 (series of m, 15 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.8 (d, J = 4.3 Hz), 138.5 (d, J = 14.6 Hz), 134.4 (d, J = 3.9 Hz), 120.4 (d, J = 12.3 Hz), 52.7 (d, J = 7.1 Hz, 2 C), 29.6 (d, J = 139.4 Hz), 29.1 (3 C), 27.3 (3 C), 13.7 (3 C), 9.5 (3 C); MS m/z ($M^+ - C_4H_9$) calcd 409.0954, obsd 409.0989.

Anal. Calcd for $C_{19}H_{39}O_3PSn$: C, 49.06; H, 8.45. Found: C, 48.56; H, 8.36.

Tributyl [(1*E*,3*E*,5*E*)-7-Methyl-1,3,5-octatrienyl]stannane (34). A cold (−78 °C) solution of **33** (152 mg, 326 mmol) in dry THF (1 mL) was treated with *n*-butyllithium (0.24 mL of 1.5 M in hexanes, 0.36 mmol), stirred for 5 min, and treated with isobutyraldehyde (24 mg, 0.33 mmol). After 10 min at −78 °C, the reaction mixture was placed in an ice bath for 30 min, diluted with ether, washed with water and brine, dried, and concentrated. The residue was chromatographed on silica gel (elution with petroleum ether) to provide **34** (83 mg, 62%) as a colorless oil: ^1H NMR (300 MHz, C_6D_6) δ 6.81 (ddd, J = 1.9, 7.2, 18.7 Hz, 1 H), 6.30−6.20 (m, 2 H), 6.05 (ddd, J = 1.0, 9.3, 15.3 Hz, 1 H), 5.61 (d, J = 6.9 Hz, 1 H), 5.59 (dd, J = 6.9, 15.0 Hz 1 H), 2.24−2.17 (m, 1 H), 1.63−1.51 (m, 6H), 1.50−1.27 (m, 6 H), 1.08−0.87 (series of m, 21 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.0, 142.9, 133.7, 133.4, 132.2, 127.4, 31.3, 29.1 (3 C), 27.3 (3 C), 22.3 (2 C), 13.7 (3 C), 9.6 (3 C); MS m/z ($M^+ - C_4H_9$) calcd 355.1448, obsd 355.1422.

Coupling of 34 to 29. A solution of **34** (90 mg, 0.219 mmol) in dry THF (0.7 mL) was cooled to −78 °C, treated dropwise with *n*-butyllithium in hexanes (0.160 mL of 1.5 M, 0.241 mmol), allowed to warm to −40 °C during 70 min, and cooled back to −78 °C. A solution of **29** (59 mg, 0.15 mmol) in THF (0.5 mL) was introduced via cannula, and the reaction mixture was allowed to warm to 0 °C, diluted with ether, washed with water and brine, dried, and concentrated. The residue was passed down a column of silica gel (elution with 30% ether in petroleum ether) to furnish 64 mg (83%) of a 2:1 diastereomeric mixture of **35**. Partial separation could be achieved by MPLC (silica gel, elution with 10:1:14 dichloromethane−acetone−hexanes). For the major alcohol: ^1H NMR (300 MHz, $CDCl_3$) δ 7.26 (dm, J = 8.6 Hz, 2 H), 6.86 (dm, J = 8.6 Hz, 2 H), 6.26−6.18 (m, 1 H), 6.17−6.15 (m, 2 H), 6.13−6.01 (m, 1 H), 5.98−5.62 (m, 2 H), 4.57 (s, 2 H), 4.19−4.16 (m, 1 H), 4.13 (d, J = 3.9 Hz, 1 H), 3.79 (s, 3 H), 3.64 (br s, 1 H), 3.39 (dd, J = 1.6, 9.5 Hz, 1 H), 2.88−2.80 (m, 4 H), 2.47−2.30 (m, 1 H), 2.15−1.75 (series of m, 4 H), 1.68−1.55 (m, 1 H), 1.10 (d, J = 6.8 Hz, 3 H), 1.00 (s, 3 H), 0.99 (d, J = 6.7 Hz, 6 H), 0.81 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 142.4, 133.0, 132.2, 131.9, 130.5, 130.2, 129.3 (2 C), 127.3, 113.9 (2 C), 86.0, 78.7, 74.9, 56.5, 55.3, 42.2, 36.2, 35.9, 31.2, 31.1, 30.7, 26.3, 22.3 (2 C), 20.5, 17.1, 16.7; FAB MS m/z (M^+ + H) calcd 505.2810, obsd 505.2825.

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Supporting Information Available: NMR spectra of **30** (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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