Synthetic Studies of Amphotericin B. III.[1] An Enantiospecific Synthesis of the C-1—C-19 Segment of the Amphotericin B Aglycon†

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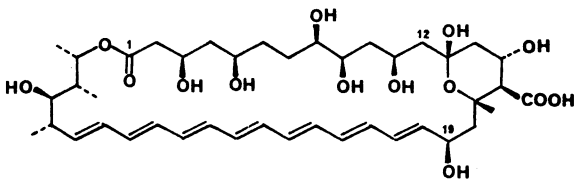
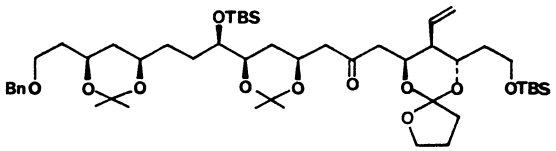
The title compound, (3*S*,4*S*,5*S*,9*S*,11*R*,12*R*,15*R*,17*S*)-4-[(*t*-butyldimethylsilyloxy)methyl]-1,3,5,9,11,12,15,17,19-nonahydroxy-3,5 : 11,12 : 15,17-tri-*O*-isopropylidene-19-*O*-(4-methoxybenzyl)-9-*O*-[(2-methoxyethoxy)methyl]-7-nonadecanone (**1**) was effectively synthesized through the coupling of (3*S*,5*R*,8*R*,9*R*,11*S*)-12-iodo-3,5 : 8,9-di-*O*-isopropylidene-1-*O*-(4-methoxybenzyl)-11-*O*-[(2-methoxyethoxy)methyl]-1,3,5,8,9,11-dodecanehexol (**2**) and (3*S*,4*R*,5*S*)-4-[(*t*-butyldimethylsilyloxy)methyl]-3,5-*O*-isopropylidene-1,1-bis(methylthio)-1-trimethylstannyl-6-heptene-3,5-diol (**36**). The C-13—C-19 segment **36** was enantiospecifically synthesized from 1,2 : 5,6-di-*O*-isopropylidene-α-D-*threo*-D-*glycero*-3-hexofuranosulose (**7**) via (2*S*,4*R*,5*S*)-5,6-epoxy-3-[(*t*-butyldimethylsilyloxy)-methyl]-1-hexen-3-ol (**6a**) in 11.6% overall yield.

Recently, the total syntheses of amphotericin B and its aglycon have been first achieved by Nicolaou et al.[2] The synthesis of key intermediate **A** corresponding to the C-1—C-19 portion of the aglycon has also been announced by Abiko et al.[3] In connection with our synthetic efforts[1] toward the aglycon of amphotericin B, we required access to the compound **1** which was considered to be practically useful as a C-1—C-19 synthetic segment for the construction of the aglycon. In this paper, we wish to describe an enantiospecific synthesis of **1**.

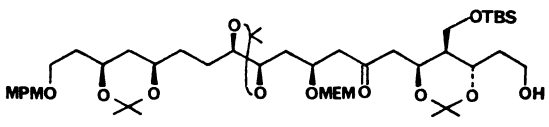
The synthetic plan is outlined in Scheme 1. The synthetic route to **1** through the intermediate **B** which is expected to be formed by the coupling of **2** and the dithioacetal compound **C** seems to be conventional and simple, whereas it may be rather interesting as a synthetic challenge because success of the coupling of **2** and **C** probably depends on the chemical stability of a lithiation derivative of **C**, which is now never precisely predictable (see Ref. 18). The C-1—C-12 segment **2** would be obtainable via **4** from **5**[1] which was previously prepared in our laboratory. The key intermediate **6a** useful for the preparation of various dithioacetal compounds **C** would be enantiospecifically synthesized via the compound **9** (see Scheme 2)



Amphotericin B Aglycon



A



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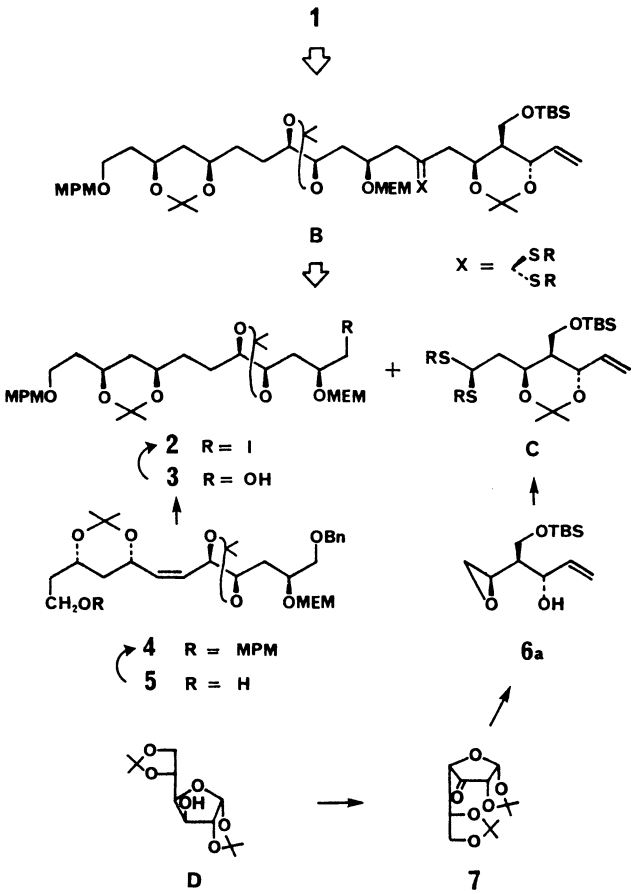

Scheme 1.

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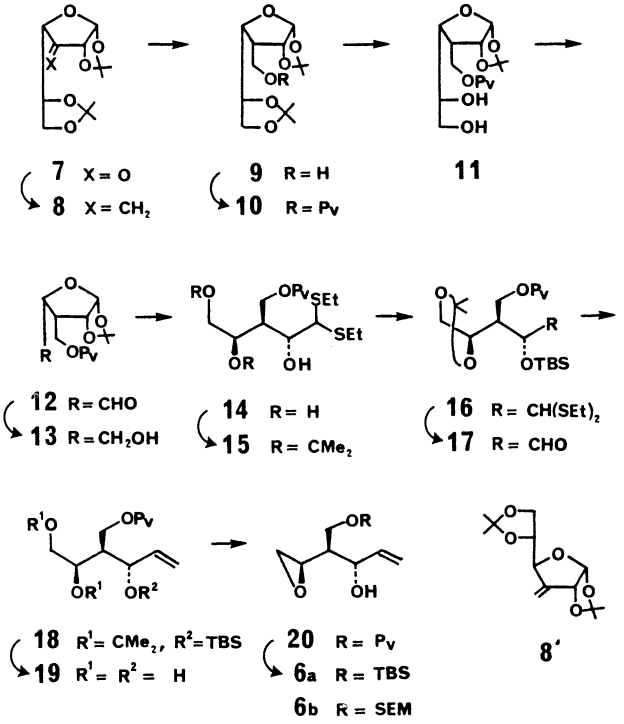
which will be stereoselectively prepared from the known compound **7**.[4] This plan was devised by considering that the absolute stereochemistry at C-2, C-3, and C-4 of **9** correlates to that of C-3, C-4, and C-5, respectively, of **6a**. The successful pursuit of the basic elements of this synthetic plan forms the topic of this report.

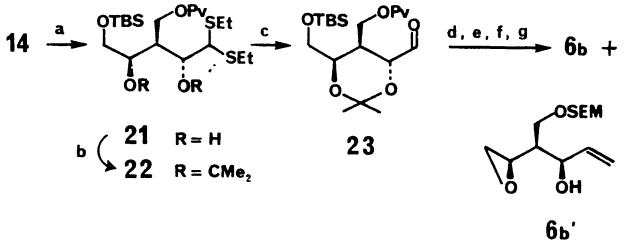
Preparation of 2. The alcohol **5**[1] was treated with 4-methoxybenzyl chloride (MPM-Cl) and NaH in THF to afford the O-MPM derivative **4** in 88% yield. Simultaneous catalytic reduction of the double bond and benzyloxy group in **4** proceeded effectively with Raney Ni W-4 (1 atm H_2, EtOH, 20 °C, 6 h) to give **3** in 86% yield. In this reduction, no cleavage of the O-MPM bond occurred.[5] In the last step, the iodination of the hydroxyl group at C-1 was carried out by treatment of **3** with triphenylphosphine, imidazole, and iodine in benzene to provide the segment **2** in 99% yield.

Synthesis of 6a. The synthesis of the key intermediate **6a** started with the known **7**[4] which was obtainable in 5 steps from commercially supplied 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**D**). Wittig methylenation of **7** with methylenetriphenylphosphorane[7] in benzene at 25 °C afforded an 84% yield of **8** and a 7% yield of the α-D-erythro epimer 8′.[8] Hydroboration of **8** with dicyclohexylborane followed by oxidation with alkaline H_2O_2 gave the alcohol **9** in 94% yield, which was *O*-pivaloylated to afford **10** in quantitative yield. Partial hydrolysis of **10** with 75% aqueous acetic acid yielded **11** (67% yield) and unchanged **10** (31% yield). Periodate-oxidation of **11** followed by sodium borohydride reduction of the aldehyde **12** afforded the alcohol **13** in 85% yield. Dithioacetalization of **13** with ethanethiol and boron trifluoride etherate gave **14** in 74% yield from **11**. Regioselective 1,2-*O*-isopropylidenation of **14** with 2,2-dimethoxypropane (DMP) in acetone containing a catalytic amount of H_2SO_4 gave **15** in 95% yield. *t*-Butyldimethylsilylation (TBSOTf, 2,6-lutidine) of **15** followed by dedithioacetalization of the silyl ether **16** (83% yield) with 1:1 $HgCl_2$–HgO (red) in 80% aqueous acetone afforded the aldehyde **17** which was immediately methylenated with methylenetriphenylphosphorane[7] in ether at 23 °C to give **18** in 80% yield from **16**. Treatment of **18** with 75% aqueous acetic acid at 50 °C afforded the triol **19** in 95% yield, which was directly subjected to the one stage epoxidation[9] of vicinal diol with triphenylphosphine, diethyl azodicarboxylate (DEAD), and 3A Molecular Sieves in refluxed benzene to give the epoxide **20** in 72% yield. One step conversion of **20** into **6a** was well-achieved in 81% yield by the treatment of **20** in THF with *n*-BuLi (3.5 equiv) at −50 °C and then with TBS-Cl (2.5 equiv) at −8 °C for 12 h. The overall yield of **6a** from **7** in 14 steps was 11.6%.

The direct conversion of **20** to the *O*-[2-(trimethylsilylethoxy)methyl] (O-SEM) derivative **6b** using *n*-BuLi and SEM-Cl was not practicable (42% yield) because of low regioselectivity of SEM-Cl. However, **6b** was obtainable in 84% yield by the sequence of reactions involving *O*-*t*-butyldimethylsilylation, one-stage exchange of pivaloyl and SEM groups, and selective de-*O*-*t*-butyldimethylsilylation. It is noteworthy that a sample of **6b** which was prepared via **23** from **14** through the alternative reaction sequence as shown in Scheme 3 was revealed to be a ca. 3:1 4-epimeric mixture by the ^{1}H NMR (400 MHz) examination. The

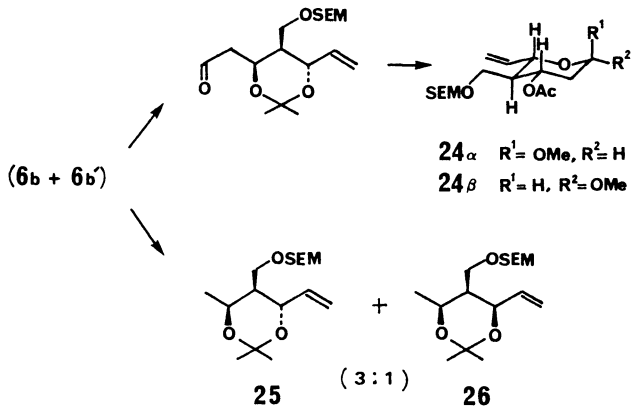


Scheme 2.



Scheme 3. (a) TBS-Cl, imidazole, DMF, 24 °C; (b) DMP, Me_2CO, cat. H_2SO_4, 25 °C; (c) $HgCl_2$, HgO, 80% Me_2CO–H_2O, 24 °C; (d) $(Ph_3PCH_3)Br$, $NaCH_2SOMe$, Et_2O; (e) 75% AcOH–H_2O, 50 °C; (f) Ph_3P, DEAD, PhH, MS 3A, 80 °C; (g) 1. TBS-Cl, imidazole, DMF, 25 °C, 3 h; 2. *n*-BuLi, THF (−60 °C, 15 min); SEM-Cl, THF, 0 °C, 16 h; 3. TBAF, THF, 0 °C, 4 h.

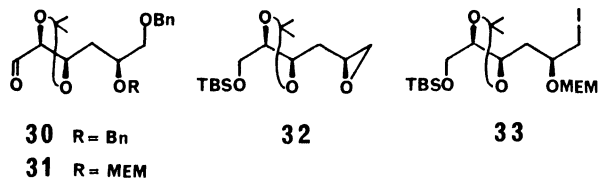
major and minor epimers proved to be **6b** and **6b′**, respectively, by the following fashions (Scheme 4): (a) The sample (**6b**+**6b′**) was converted into **24** (as an anomeric mixture) in 5 steps. The ^{1}H NMR spectrum of **24** showed signals in line with the depicted structure



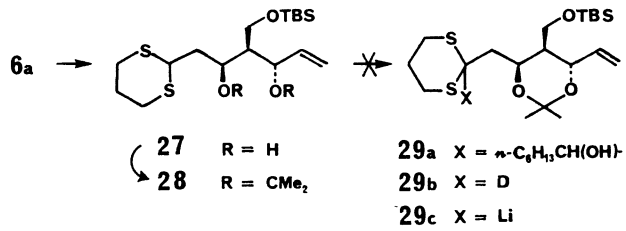
Scheme 4.

(see Experimental). (b) The sample (**6b**+**6b'**) was converted in two steps into a 3:1 mixture of **25** and **26**, whose structures were confirmed by ^{1}H NMR analysis (see Experimental). The formation of the epimer **6b'** in the route to **6b** via **23** from **14** may be ascribed to the epimerization that occurred at the C-4 carbon of the thermodynamically unstable 1,3-dioxane-4-carbaldehyde **23** during its Wittig methylenation using the ylide prepared from methyltriphenylphosphonium bromide by the Corey's method.[10]

Synthesis of C. For the construction of the target compound **1**, we first took account of the coupling of a dithiane derivative **28** (the segment **C**) with a model compound **32** or **33** which was obtained from the

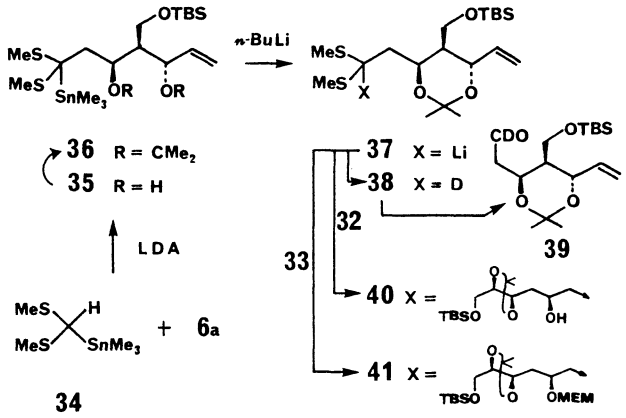


known **30** or **31**,[1] respectively. The treatment of the epoxide **6a** with 5 equivalents of 2-lithio-1,3-dithiane afforded the dithiane derivative **27** in 81% yield, which was subsequently isopropylidenated to give **28** in 92% yield. However, the attempted coupling of **28** with heptanal by the usual dithiane lithiation procedure[11] (*n*-BuLi, THF, −25 °C, 3 h) afforded no coupling product **29a**, recovering the reactants, **28** and heptanal. Even though the reaction mixture of lithiation was treated with D_2O instead of heptanal, no deuterio derivative **29b** could be detected. These facts suggested to us that the desired lithium derivative **29c** is very short-lived probably due to its unusually increased kinetic basicity[12] and it is practically impossible to generate **29c** from its conjugate acid **28**, which is far less acidic than 1,3-dithiane, by the lithiation using *n*-BuLi.[13] This suggestion prompted us to use the trimethylstannylated dimethyl dithioacetal compound **36** for the dithiane derivative **28**. The trimethylstannyl group in **36** would be instantaneously substituted by



Scheme 5.

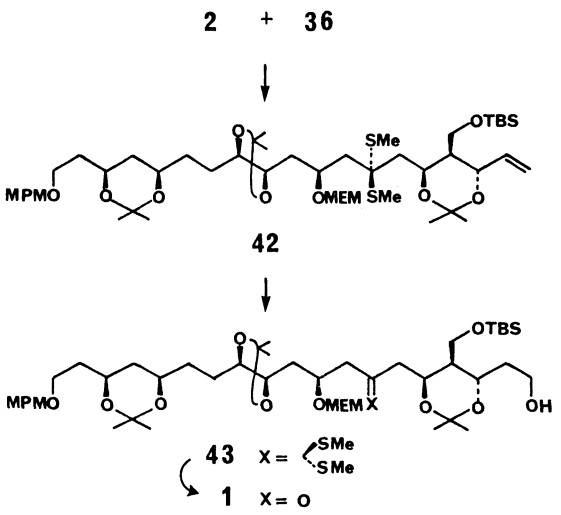
lithium on treatment with *n*-BuLi.[14] Moreover, it pleased us very much that in contrast to the H/Li-exchange, the Sn/Li-transmetallation should easily be detected by TLC. The validity of our choice was proved by the following sequence of reactions (Scheme 6). Lithiation of [bis(methylthio)methyl]trimethylstannane[15] (**34**) with lithium diisopropylamide (LDA)



Scheme 6.

in THF-HMPA followed by treatment with the epoxide **6a** afforded **35** in a ca. 70% yield, which was isopropylidenated with 2-methoxy-1-propene and pyridinium *p*-toluenesulfonate (PPTS) in dichloromethane to yield **36** in 62% yield from **6a**. Immediately the addition of *n*-BuLi (2 equiv) to a solution of **36** in THF-HMPA at −30 °C was complete, the reaction mixture was treated with D_2O to give the product **38** in 85% yield, which was carefully hydrolyzed to the deuterio aldehyde **39** in moderate yield (44%) by using *N*-bromosuccinimide (NBS) and $AgNO_3$ in 85% aqueous acetonitlile containing 2,4,6-trimethylpyridine.[16] Thus obtained sample of **39** showed a ca. 75—80% aldehydic deuterium content by ^{1}H NMR analysis. The reaction of the epoxide **32** with the lithium compound **37** generated from **36** (1.5 equiv) and *n*-BuLi (1.8 equiv) afforded a ca. 5:7 mixture of the coupling product **40** and the starting epoxide **32**. Whereas the iodo derivative **33** reacted more smoothly with **37** generated from **36** (1.43 equiv) and *n*-BuLi (1.71 equiv) to yield the coupling product **41** in 76% yield.

Synthesis of 1. In keeping with the successful results in the similar model coupling reactions using **36**, the coupling of the C-1—C-12 segment **2** with **36** was carried out to afford in 84% yield the desired prod-



Scheme 7.

uct **42** corresponding to the intermediate **B** (Scheme 7).[17] Hydroboration of **42** using dicyclohexylborane followed by treatment with alkaline H_2O_2 gave the alcohol **43** in 92% yield. Dedithioacetalization of **43** with 1 : 1 $HgCl_2$-HgO provided the target compound **1** in 82% yield.

Experimental

Melting points were determined on a micro hot stage Yanaco MP-S3 and were uncorrected. Optical rotations were measured on a JASCO DIP-360 photoelectric polarimeter in chloroform, and ^{1}H NMR spectra were recorded on a Varian EM-390 or a JEOL GX-400 spectrometer in $CDCl_3$ using TMS as internal standard unless stated otherwise. Mass spectra were measured on a Hitachi M-80 mass spectrometer. TLC was performed on Merck TLC plate (60F-254, 0.25 mm), and column chromatography on silica gel, Wakogel C-200 and Merck Kieselgel 60 (230—400 mesh) for "Flash Chromatography." In general, organic solvents were purified and dried by appropriate procedure, and evaporation and concentration were carried out under reduced pressure below 30°C, unless otherwise noted.

(2*S*,4*R*,5*R*,8*S*,10*S*)-(6*Z*)-1-*O*-Benzyl-4,5:8,10-di-*O*-isopropylidene-12-*O*-(4-methoxybenzyl)-2-*O*-[(2-methoxyethoxy)methyl]-6-dodecene-1,2,4,5,8,10,12-heptol (4). To an ice-cold solution of **5**[1] (321 mg, 0.597 mmol) in dry DMF (3.2 ml) was added 55% NaH suspension (65 mg, 1.49 mmol). After being stirred at 25 °C for 0.5 h, to this reaction mixture was added 4-methoxybenzyl chloride (130 µl, 0.90 mmol) at 0 °C. After being stirred at 25 °C for 15 h, the reaction mixture was poured into saturated aqueous $NaHCO_3$, which was extracted with benzene (3×5.0 ml). The extracts were washed with saturated aqueous NaCl, dried, and evaporated. The residue was chromatographed on silica gel (20 g) with 2 : 1 hexane-ethyl acetate to afford **4** (346 mg, 88%) as a colorless syrup: R_f=0.74 (1 : 1 hexane-ethyl acetate); $[\alpha]_D^{32}$ −12.7° (*c* 1.32); ^{1}H NMR (90 MHz) δ=1.34, 1.40, 1.43 (6H, 3H, 3H, each s, 2×CMe_2), 1.17—2.20 (6H, m, 2×H-3, 2×H-9, 2×H-11), 3.33 (3H, s, OMe of MEM), 3.30—4.63 (13H, m, OCH_2-CH_2O, 2×H-1, H-2, 4, 5, 8, 10, 2×H-12), 3.80 (3H, s, OMe of MPM), 4.43 (2H, s, OCH_2(MPM)), 4.53 (2H, s, OCH_2(Bn)), 4.80 (2H, s, OCH_2O), 5.30—5.77 (2H, m, H-6,7), 6.80—7.00 (2H, m, MPM), and 7.20—7.50 (7H, m, MPM, Ph).

Found: C, 67.77; H, 8.26%. Calcd for $C_{37}H_{54}O_{10}$: C, 67.45; H, 8.26%.

(2*S*,4*R*,5*R*,8*S*,10*S*)-4,5:8,10-Di-*O*-isopropylidene-12-*O*-(4-methoxybenzyl)-2-*O*-[(2-methoxyethoxy)methyl]-1,2,4,5,8,10,12-dodecaneheptol (3). A solution of **4** (346 mg) in ethanol (6.9 ml) was stirred with a catalytic amount of Raney Ni W-4 under bubbling with H_2 gas at 20 °C for 6 h. The reaction mixture was filtered and concentrated to a syrup which was chromatographed on silica gel (15 g) with 1 : 2 benzene-ethyl acetate to afford **3** (257 mg, 86%): colorless syrup; R_f=0.20 (1 : 1 hexane-ethyl acetate); $[\alpha]_D^{32}$ +31.4° (*c* 1.02); ^{1}H NMR (90 MHz) δ=1.37, 1.43 (12H, each s, 2×CMe_2), 1.10—2.00 (10H, m, 2×H-3, 2×H-6, 2×H-7, 2×H-9, 2×H-11), 3.40 (3H, s, OMe (MEM)), 3.40—4.20 (10H, m, OH, 2×H-1, H-2, 4, 5, 8, 10, 2×H-12), 4.43 (2H, s, OCH_2(MPM)), 4.80 (2H, s, OCH_2O), 6.80—7.00 and 7.20—7.40 (each 2H, each m, MPM).

Found: C, 62.95; H, 8.74%. Calcd for $C_{30}H_{50}O_{10}$: C, 63.14; H, 8.83%.

(3*S*,5*R*,8*R*,9*R*,11*S*)-12-Iodo-3,5:8,9-di-*O*-isopropylidene-1-*O*-(4-methoxybenzyl)-11-*O*-[(2-methoxyethoxy)methyl]-1,3,5,8,9,11-dodecanehexol (2). A mixture of **3** (42.3 mg, 0.0741 mmol), benzene (0.846 ml), imidazole (10.1 mg, 0.148 mmol), triphenylphosphine (38.9 mg, 0.148 mmol), and iodine (28.2 mg, 0.111 mmol) was stirred at 25 °C for 0.5 h and then cooled at 0 °C. To this mixture were added saturated aqueous $Na_2S_2O_3$ and $NaHCO_3$ in sequence under vigorous stirring. The mixture was then extracted with benzene (3×3 ml) and the extracts were washed with saturated aqueous NaCl, dried, and evaporated. The residue was chromatographed on silica gel (2.5 g) with 3 : 1 hexane-ethyl acetate to afford **2** (50.1 mg, 99.4%) as a colorless syrup: R_f=0.76 (1 : 1 hexane-ethyl acetate); $[\alpha]_D^{32}$ +11.7° (*c* 0.92); ^{1}H NMR (400 MHz) δ=1.16 (1H, ddd, H-4, $J_{4,3}\fallingdotseq J_{4,5}\fallingdotseq J_{gem}\fallingdotseq$12.5 Hz), 1.35, 1.36, 1.41 (3H, 6H, 3H, each s, 2×CMe_2), 1.43—1.90 (9H, m, 2×H-2, H-4, 2×H-6, 2×H-7, 2×H-10), 3.39 (3H, s, OMe (MEM)), 3.39 (1H, dd, *J*=4.8, 9.6 Hz), 3.46—3.59 (5H, m), 3.60—3.67 (3H, m), 3.72 (1H, ddd, *J*=3.5, 5.1, 11.2 Hz), 3.81 (3H, s, OMe(MPM)), 3.79—3.88 (2H, m), 3.94—4.05 (1H, m), 4.41 and 4.43 (2H, ABq, CH_2Ph, *J*=11.2 Hz), 4.80 (2H, s, OCH_2O), 6.88 and 7.25 (each 2H, ddd-like, MPM).

Found: C, 52.91; H, 7.17%. Calcd for $C_{30}H_{49}O_9I$; C, 52.94; H, 7.26%.

3-Deoxy-1,2 : 5,6-di-*O*-isopropylidene-3-*C*-methylene-α-D-*threo*-D-*glycero*-hexofuranose (8) and α-D-*erythro* Epimer (8′). To a suspension of freshly prepared methylenetriphenylphosphorane[7] (140 g, 507 mmol) in dry benzene (291 ml) was added a solution of **7**[4] (29.1 g, 113 mmol) in benzene (582 ml) dropwise at 25 °C in a 20-min period. After being stirred for 1.7 h, the reaction mixture was concentrated and diluted with ether (873 ml). The mixture was poured into cold water (800 ml), which was extracted with ether (3×700 ml). The extracts were washed with saturated aqueous NaCl, dried, and evaporated. The residue was chromatographed on silica gel (1450 g) with 5 : 2 hexane-ethyl acetate to afford **8** (24.1 g, 84%) and **8′** (2.02 g, 7%). **8**: R_f=0.68 (1 : 1 hexane-ethyl acetate); mp 49 °C; $[\alpha]_D^{34}$ −0.32°, $[\alpha]_{365}^{34}$ +1.94° (*c* 1.23); ^{1}H NMR (90 MHz) δ=1.32, 1.38, 1.44, 1.56 (each 3H, each s, 2×CMe_2), 3.7—4.1, 4.3—4.6 (each 2H, each m, H-4,5, 2×H-6), 4.83 (1H, dd-like, H-2, $J_{2,1}$=4.2, $J_{2,C=CH_2}\fallingdotseq$1.0 Hz), 5.28 5.48 (each 1H,

each dd-like, C=C$\underline{H}_2$, J_{gem}≒1.5 Hz), 5.81 (1H, d, H-1).

Found: C, 60.88; H, 7.81%. Calcd for $C_{13}H_{20}O_5$: C, 60.93; H, 7.87%.

8′: Colorless syrup; R_f=0.89 (1 : 1 hexane-ethyl acetate); $[\alpha]_D^{30}$ +99° (*c* 1.30) [lit, $[\alpha]_D$ +75° (*c* 1.0);[8a]) $[\alpha]_D^{22}$ +104° (*c* 2)[8b]]; ^{1}H NMR (90 MHz) δ=1.38, 1.45, 1.52 (6H, 3H, 3H, each s, 2×CMe_2), 3.85—4.40 (4H, m, H-4,5, 2×H-6), 4.70—5.70 (1H, m, H-2), 5.40—5.60 (2H, m, C=C$\underline{H}_2$), 5.80 (1H, d, H-1, $J_{1,2}$=4.2 Hz).

3-Deoxy-3-*C*-hydroxymethyl-1,2:5,6-di-*O*-isopropylidne-α-D-gulofuranose (9). To a solution of dicyclohexylborane (55.2 mmol) in THF (50.0 ml) was added a solution of **8** (7.00 g, 27.3 mmol) in THF (21.0 ml) at 0 °C under Ar, and the mixture was stirred at 25 °C for 100 min. The reaction was quenched by addition of water (70.9 ml). To the mixture was added 3M†† aqueous NaOH (18.4 ml) and 30% H_2O_2 (16.6 ml) at 0 °C. After being stirred at 50 °C for 1 h, the reaction mixture was extracted with ethyl acetate (5×100 ml). The extracts were evaporated and the residue was chromatographed on silica gel (400 g) with 1 : 4 hexane-ethyl acetate to afford **9** (7.14 g, 94%) as colorless crystals. Recrystallization from hexane-ethyl acetate gave a pure sample of **9**: mp 145 °C; R_f=0.41 (1 : 4 hexane-ethyl acetate); $[\alpha]_D^{31}$ −20.4° (*c* 1.08); ^{1}H NMR (90 MHz) δ=1.34, 1.38, 1.46, 1.59 (each 3H, each s, 2×CMe_2), 2.5—2.7 (1H, m, H-3), 3.0—3.2 (1H, m, OH), 3.4—4.3 (5H, m, H-5, 2×H-6, C$\underline{H}_2$OH), 4.4—4.6 (1H, m, H-4), 4.76 (1H, dd, H-2, $J_{2,1}$=4.8, $J_{2,3}$=5.7 Hz), 5.82 (1H, d, H-1).

Found: C, 56.98; H, 8.01%. Calcd for $C_{13}H_{22}O_6$: C, 56.92; H, 8.08%.

3-Deoxy-1,2 : 5,6-di-*O*-isopropylidene-3-*C*-[(pivaloyloxy)methyl]-α-D-gulofuranose (10). To a solution of **9** (7.14 g, 26.0 mmol) in dry CH_2Cl_2 (71.4 ml) were added 4-(dimethylamino)pyridine (DMAP) (6.36 g, 52.1 mmol) and pivaloyl chloride (4.76 ml, 39.1 mmol) in sequence at 0 °C. The mixture was stirred at 25 °C for 40 min and then diluted with ethanol (7.14 ml). After being stirred at 25 °C for 0.5 h, the mixture was evaporated. The residue was dissolved in ethyl acetate and the solution was washed with water and saturated aqueous NaCl, dried, and evaporated to give a crude sample of **10** (9.3 g, 100%). Recrystallization from ethyl acetate-hexane afforded an analytical sample: mp 127°C, R_f=0.60 (1 : 2 hexane-ethyl acetate; IR (KBr) 1720 cm^{-1}; $[\alpha]_D^{31}$ −23.9° (*c* 1.08); ^{1}H NMR (90 MHz) δ=1.23 (9H, s, *t*-Bu), 1.31, 1.37, 1.46, 1.57 (each 3H, each s, 2×CMe_2), 2.5—2.9 (1H, m, H-3), 3.4—4.8 (7H, m, H-2, 4, 5, 2×H-6, PvOC$\underline{H}_2$), 5.83 (1H, d, H-1).

Found: C, 60.18; H, 8.15%. Calcd for $C_{18}H_{30}O_7$: C, 60.32; H, 8.44%.

3-Deoxy-1,2-*O*-isopropylidene-3-*C*-[(pivaloyloxy)methyl]-α-D-gulofuranose (11). A solution of **10** (7.63 g) in 75% aqueous acetic acid (76.3 ml) was stirred at 30 °C for 4.5 h. The mixture was evaporated at 40 °C in a 2-h period. The residue was then chromatographed on silica gel (350 g) with 2 : 1 hexane-ethyl acetate to afford unchanged **10** (2.34 g, 30.7%) and **11** (4.54 g, 67% from **9**) as colorless crystals. **11**: R_f=0.37 (1 : 1 hexane-ethyl acetate); mp 63 °C; $[\alpha]_D^{31}$ −14.8° (*c* 1.03), ^{1}H NMR (90 MHz) δ=1.20 (9H, s, *t*-Bu), 1.30, 1.55 (each 3H, each s, CMe_2), 2.4—3.3 (3H, m, H-3, 2×OH), 3.4—4.7 (6H, m, H-4,5, 2×H-6, PvOC$\underline{H}_2$), 4.65 (1H, dd, H-2, $J_{2,1}$=4.2, $J_{2,3}$=5.7 Hz), 5.83 (1H, d, H-1).

†† 1M=1 mol dm^{-3}.

Found: C, 56.81; H, 8.19%. Calcd for $C_{15}H_{26}O_7$: C, 56.59; H, 8.23%.

3-Deoxy-1,2-*O*-isopropylidene-3-*C*-[(pivaloyloxy)methyl]-α-L-lyxofuranose (13). To a solution of **11** (11.5 g, 36.2 mmol) in 80% aqueous acetone (115 ml) was added a solution of $NaIO_4$ (11.6 g, 53.5 mmol) in water (116 ml) at 0 °C in a 15-min period. After being stirred at 25 °C for 35 min, the reaction mixture was evaporated. Ethyl acetate was added to the residue and the mixture was washed with water and saturated aqueous NaCl, dried, and evaporated to afford crystalline aldehyde **12** (11.6 g). To an ice cold solution of the aldehyde **12** (11.6 g) in methanol (116 ml) was added $NaBH_4$ (2.74 g, 72.4 mmol) and was stirred at 25 °C for 15 min. The reaction mixture was neutralized (pH=7) with CO_2 and evaporated. Ethyl acetate (550 ml) was added to the residue and the mixture was washed with water and saturated aqueous NaCl, dried, and evaporated to give crude **13** (8.92 g, 85% yield from **11**). An analytical sample was obtained after silica-gel column chromatography with 1 : 1 hexane-ethyl acetate: colorless crystals; R_f=0.54 (1 : 1 hexane-ethyl acetate); mp 81°C; $[\alpha]_D^{30}$ −14.1° (*c* 1.02); ^{1}H NMR (90 MHz) δ=1.21 (9H, s, *t*-Bu), 1.30, 1.55 (each 3H, each s, CMe_2), 2.42 (1H, br-s, OH), 2.5—2.9 (1H, m, H-3), 3.3—4.6 (5H, m, H-4, 2×H-5. PvOC$\underline{H}_2$), 4.68 (1H, dd, H-2, $J_{2,1}$=$J_{2,3}$=4.5 Hz), 5.84 (1H, d, H-1).

Found: C, 58.46; H, 8.28%. Calcd for $C_{14}H_{24}O_6$: C, 58.32; H, 8.39%.

(2*S*,3*R*,4*R*)-5,5-Bis(ethylthio)-3-[(pivaloyloxy)methyl]-1,2,4-heptanetriol (14). To a solution of the crude **13** (8.92 g, 30.9 mmol) in EtSH (268 ml) was added $BF_3 \cdot Et_2O$ (2.6 ml) at 0 °C. After being stirred at 25 °C for 0.5 h, the reaction mixture was neutralized with triethylamine (pH=7) at 0 °C, and was diluted with ethyl acetate (250 ml). The mixture was washed with water and saturated aqueous NaCl, dried, and evaporated. The residue was chromatographed on silica gel (550 g) with 2 : 3 hexane-ethyl acetate to afford **14** (8.09 g, 74% from **11**). **14**: Colorless syrup; R_f=0.29 (1 : 1 hexane-ethyl acetate); $[\alpha]_D^{30}$ +64.5° (*c* 1.01); ^{1}H NMR (90 MHz) δ=1.21 (9H, s, *t*-Bu), 1.26, 1.29 (each 3H, each t, 2×$SCH_2\underline{Me}$), 2.2—2.9 (6H, m, 2×$SC\underline{H}_2$, H-3, OH), 3.4—4.6 (9H, m, H-1, 2,4, 2×H-5, PvOC$\underline{H}_2$, 2×OH).

Found: C, 50.68; H, 8.35%. Calcd for $C_{15}H_{30}O_5S_2$: C, 50.82; H, 8.53%.

(2*S*,3*R*,4*R*)-5,5-Bis(ethylthio)-1,2-*O*-isopropylidene-3-[(pivaloyloxy)methyl]-1,2,4-heptanetriol (15). To a solution of **14** (1.82 g, 5.14 mmol), 2,2-dimethoxypropane (DMP) (1.26 ml, 10.3 mmol) in dry acetone (36.4 ml) was added 1% H_2SO_4-acetone (0.188 ml) at 0 °C. After being kept at 25 °C for 25 min, the mixture was neutralized with $NaHCO_3$ (pH=7) under ice-cooling, and evaporated. The residue was partitioned between ethyl acetate and water. The organic layer was separated and washed with saturated aqueous NaCl, dried, and evaporated to afford an essentially pure sample of **15** (1.93 g, 95%) as colorless crystals. An analytical sample of **15** was obtained after silica-gel column chromatograpy with 8 : 1 hexane-ethyl acetate: R_f=0.24 (8 : 1 hexane-ethyl acetate; mp 65°C; $[\alpha]_D^{37}$ −0.47°, $[\alpha]_{365}^{37}$ +7.49° (*c* 1.28); ^{1}H NMR (90 MHz) δ=1.20 (9H, s, Pv), 1.15—1.50 (6H, m, 2×$SCH_2\underline{Me}$), 1.33, 1.39 (each 3H, each s, CMe_2), 2.30—2.65 (2H, m, H-3, OH), 2.62, 2.73 (4H, q, 2×$SC\underline{H}_2$, *J*=6.3 Hz), 3.70—4.50 (7H, m, 2×H-1, H-2, 4, 5, C$\underline{H}_2$OPv).

Found: C, 54.86; H, 8.56%. Calcd for $C_{18}H_{34}O_5S_2$: C, 54.79; H, 8.68%.

(2*S*,3*R*,4*R*)-4-*O*-(*t*-Butyldimethylsilyl)-1,2-*O*-isopropylidene-3-[(pivaloyloxy)methyl]-1,2,4-heptanetriol (16). To a solution of **15** (1.93 g, 4.88 mmol) in dry CH_2Cl_2 (4.88 ml) were added 2,6-lutidine (1.71 ml, 14.6 mmol), TBSOTf (2.24 ml, 9.76 mmol) at 0 °C. After being stirred at 0 °C for 70 min, the reaction mixture was poured into ice-water, which was extracted with ethyl acetate (3×20 ml). The extracts were washed with saturated aqueous NaCl, dried, and evaporated. The residue was chromatographed on silica gel (250 g) with 12 : 1 hexane-ethyl acetate to afford **16** (2.06 g, 83%) as colorless syrup: R_f=0.54 (8 : 1 hexane-ethyl acetate); $[\alpha]_D^{35}$ −0.70°, $[\alpha]_{365}^{35}$ +7.72° (*c* 1.14); ^{1}H NMR (90 MHz) δ=0.90 (9H, s, *t*-BuSi), 1.20 (9H, s, Pv), 1.13—1.43 (12H, m, CMe_2, 2×$SCH_2\underline{Me}$), 2.1—2.48 (1H, m, H-3), 2.60, 2.68 (4H, 2×$SC\underline{H}_2$, *J*=4.5 Hz), 3.70—4.50 (7H, m, 2×H-1, H-2, 4, 5, $C\underline{H}_2OPv$).

Found: C, 56.89; H, 9.47%. Calcd for $C_{24}H_{28}O_5SiS_2$: C, 56.65; H, 9.51%.

(2*S*,3*R*,4*S*)-4-*O*-(*t*-Butyldimethylsilyl)-1,2-*O*-isopropylidene-3-[(pivaloyloxy)methyl]-5-hexene-1,2,4-triol (18). To a solution of **16** (2.06 g, 4.05 mmol) in 80% aqueous acetone (72.1 ml) were added in sequence HgO (3.86g, 17.8 mmol) and $HgCl_2$ (4.84 g, 17.8 mmol) at 25 °C with efficient stirring. After the addition, stirring was continued at 25 °C for 20 min. The reaction mixture was filtered through a Celite, and the filter cake was washed with acetone (5×5 ml). The filtrate and washings were evaporated, and to the residue was added chloroform. The mixture was washed with 10% aqueous KI and saturated aqueous NaCl, dried, and evaporated to give the aldehyde **17** (1.72 g). A solution of the crude aldehyde (1.72 g) in dry benzene (32.6 ml) was added to a solution of $Ph_3P{=}CH_2$ (5.03 g, 18.2 mmol) in dry benzene (16.3 ml) at 25 °C in a 5-min period. After being stirred at 25 °C for 20 min, the reaction mixture was evaporated. The residue was taken up in ether (40 ml) which was washed with water and then saturated aqueous NaCl, dried, and evaporated. The residual syrup was chromatographed on silica gel (130 g) with 15 : 1 hexane-ethyl acetate to afford **18** (1.30 g, 80% from **16**) as a colorless syrup: R_f=0.60 (8 : 1 hexane-ethyl acetate); $[\alpha]_D^{34}$ −1.20° $[\alpha]_{365}^{34}$ −11.3° (*c* 1.51); ^{1}H NMR (400 MHz, $CHCl_3$, δ=7.26) δ=0.02, 0.05 (each 3H, each s, $SiMe_2$), 0.89 (9H, s, *t*-BuSi), 1.19 (9H, s, Pv), 1.31 ,1.36 (each 3H, each s, CMe_2), 1.86 (1H, ddd, H-3), 3.70 (1H, dd, *J*=7.8, 7.8 Hz), 4.05 (1H, dd, *J*=5.9, 7.8 Hz), 4.13 (1H, dd, *J*=5.9, 11.2 Hz), 4.18—4.24 (2H, m), 4.26 (1H, dd, *J*=3.9, 11.2 Hz), 5.11 (1H, ddd, H-6, $J_{6,5}$=10.1 Hz), 5.15 (1H, ddd, H-6, $J_{6,5}$=17.3 Hz), 5.75 (1H, ddd, H-5, $J_{5,4}$=6.8 Hz).

Found: C, 63.32; H, 10.01%. Calcd for $C_{21}H_{40}O_5Si$: C, 62.96; H, 10.06%.

(2*S*,4*R*,5*S*)-5,6-Epoxy-3-[(pivaloyloxy)methyl]-1-hexen-3-ol (20). A solution of **18** (2.92 g, 7.29 mmol) in 75% aqueous acetic acid (58.4 ml) was stirred at 50 °C for 5 h. The reaction mixture was concentrated to give a syrup, which was chromatographed on silica gel (50 g) with 1 : 2 hexane-ethyl acetate to afford **19** (1.72 g, 95%). A mixture of **19** (1.71 g, 6.95 mmol), triphenylphosphine (2.19 g, 8.34 mmol), Molecular Sieves 3A powder (17.1 g), and dry benzene (85.6 ml) was vigorously stirred at 80 °C for 10 min, and DEAD (1.29 ml, 8.34 mmol) was added dropwise to the mixture. After being stirred at 80 °C for 14 h, the cold reaction mixture was filtered through a Celite, and the filter cake was washed with benzene (5×40 ml). The filtrate and washings were evaporated, and the residue was chromatographed on silica gel (170 g) with 2 : 1 hexane-ethyl acetate to give **20** (1.15 g, 72%) as a colorless syrup: R_f=0.56 (1 : 1 hexane-ethyl acetate); $[\alpha]_D^{32}$ −11.2° (*c* 1.39); ^{1}H NMR (90 MHz) δ=1.23 (9H, s, *t*-Bu), 1.50—2.00 (1H, m, H-3), 2.57 (1H, d, OH, *J*=2.7 Hz), 2.67 (1H, dd, H-1, $J_{1,2}$=2.7, J_{gem}=4.5 Hz), 2.85 (1H, dd, H-1, $J_{1,2}$=4.5 Hz), 3.10 (1H, ddd, H-2, $J_{2,3}$=8.7 Hz), 4.1—4.5 (3H, m, H-4, PvO$C\underline{H}_2$), 5.40 (1H, ddd-like, H-6, $J_{6,5}$=10.5 Hz), 5.50 (1H, ddd-like, H-6, $J_{6,5}$=17.4 Hz), 5.95 (1H, ddd, H-5, $J_{5,4}$=6.6 Hz).

Found: *m/z* 211.1336. Calcd for $C_{12}H_9O_3(M^+-OH)$: 211.1333.

(2*S*,4*R*,5*S*)-5,6-Epoxy-3-[(*t*-butyldimethylsilyloxy)methyl]-1-hexen-3-ol (6a). To a cold (−50°C) solution of **20** (153 mg, 0.67 mmol) in dry THF (1.53 ml) was added a 1.64 M solution of *n*-BuLi in hexane (1.43 ml, 2.35 mmol) under stirring, and stirring was continued at −50 °C for 1 h. To this mixture was added a solution of TBS-Cl (252 mg, 1.68 mmol) in dry THF (0.504 ml). After being stirred at 8 °C for 12 h, the mixture was neutralized (pH=7) with 0.12 M HCl under ice-cooling, and then extracted with ethyl acetate (3× 4.0 ml). The extracts were washed with saturated aqueous NaCl, dried, and evaporated. The residue was flushchromatographed on silica gel (10 g) with 30:1 chloroform-acetone to afford **6a** (140.4 mg, 81%) as a colorless syrup: R_f=0.43 (15 : 1 chloroform-acetone); $[\alpha]_D^{31}$ −2.7°, $[\alpha]_{365}^{31}$ −12.5° (*c* 0.83); ^{1}H NMR (90 MHz) δ=0.83 (9H, s, *t*-Bu), 1.20—1.50 (1H, m, H-3), 2.53 (1H, dd, H-l, J_{gem}=4.8, $J_{1,2}$=2.7 Hz), 2.77 (1H, dd, H-1, $J_{1,2}$=4.8 Hz), 2.90—3.20 (1H, m, H-2), 3.37 (1H, d-like, OH, *J*=3.6 Hz), 3.80—4.29 (2H, m, $SiOCH_2$), 4.30—4.60 (1H, m, H-4), 5.18 (1H, ddd, H-6, $J_{6,5}$=10.5 Hz), 5.28 (1H, ddd, H-6, $J_{6,5}$=18.0 Hz), 5.93 (1H, ddd, H-5, $J_{5,4}$=4.8 Hz).

Found: *m/z* 259.1733. Calcd for $C_{13}H_{27}O_3Si$: M^++1, 259.1728.

(2*S*,3*R*,4*R*)-1-*O*-*t*-Butyldimethylsilyl-5,5-bis(ethylthio)-3-[(pivaloyloxy)methyl]-1,2,4-pentanetriol (21). To a solution of **14** (8.09 g, 22.8 mmol) in dry DMF (80.9 ml) were added imidazole (3.73 g, 54.7 mmol) and TBS-Cl (6.88 g, 45.6 mmol) at 0 °C. After being stirred at 25 ° for 20 min, the mixture was poured into cold water, which was extracted with benzene (3×100 ml). The extracts were washed with saturated aqueous NaCl, dried, and evaporated. The residue was chromatographed on silica gel (540 g) with 5 : 1 hexane-ethyl acetate to afford **21** (8.71 g, 81.5%) as a colorless syrup: R_f=0.18 (8 : 1 hexane-ethyl acetate); $[\alpha]_D^{30}$ +33.1° (*c* 1.25); ^{1}H NMR(90 MHz) δ=0.93 (9H, s, *t*-BuSi), 1.22 (9H, s, Pv), 1.27, 1.30 (6H, each t, 2×$SCH_2\underline{Me}$, *J*=6.3 Hz), 2.4—2.6 (1H, m, H-3), 2.66, 2.70 (4H, each q, 2×$SC\underline{H}_2$), 3.09 (1H, d, OH, *J*=2.1 Hz), 3.56 (1H, d, OH, *J*=2.7 Hz), 3.6—4.4 (7H, m, 2×H-1, H-2,4,5, $C\underline{H}_2OPv$).

Found: C, 54.10; H, 9.11%. Calcd for $C_{21}H_{44}O_5SiS_2$: C, 53.81; H, 9.46%.

(2*S*,3*R*,4*R*)-1-*O*-*t*-Butyldimethylsilyl-5,5-bis(ethylthio)-2,4-*O*-isopropylidene-3-[(pivaloyloxy)methyl]-1,2,4-pentanetriol (22). To a solution of **21** (8.71 g, 18.6 mmol) and DMP (9.14 ml, 73.3 mmol) in dry acetone (174 ml) was added 1% H_2SO_4-acetone(0.87 ml) at 25 °C. After being kept at 25 °C for 21 min, the mixture was neutralized with $NaHCO_3$ (pH=7) at 0 °C, and evaporated. The residue was taken up in ethyl acetate (250 ml) which was washed with water and saturated aqueous NaCl, dried, and evaporated to crude **22** (9.36 g, 99%). An analytical sample was obtained after silica-gel chromatography with 10:1 hexane-ethyl acetate: R_f=0.73 (8 : 1 hexane-ethyl acetate); $[\alpha]_D^{30}$ −3.3°, $[\alpha]_{365}^{30}$ −11.3° (*c* 1.20); ^{1}H NMR (90 MHz) δ=0.93 (9H, s, *t*-BuSi), 1.25 (9H,

s, Pv), 1.2—1.5 (12H, m, 2×$SCH_2\underline{Me}$, CMe_2), 2.4—2.9 (5H, m, 2×$SC\underline{H}_2$, H-3), 3.6—4.3 (7H, m, 2×H-1, H-2, 4,5, $C\underline{H}_2OPv$).

Found: C, 56.66; H, 9.33%. Calcd for $C_{24}H_{48}O_5SiS_2$: C, 56.65; H, 9.51%.

Preparation of (6b+6b′) via 23 from 22. By the procedure described in the preparation of **17**, the aldehyde **23** (6.86 g, 91.7% from **21**) was obtained from **22** (9.36 g, 18.5 mmol) after silica-gel chromatography with 6:1 hexane-ethyl acetate ($[\alpha]_D^{30}$ +21.8° (*c* 1.24)). A 4 M solution of methylsulfinylmethanide anion in DMSO (17.0 ml, 68.2 mmol) prepared from NaH and DMSO[10] was added to a stirred suspension of methyltriphenylphosphonium bromide (24.4 g, 68.2 mmol) in dry ether (274 ml) under Ar at 25 °C. The mixture was stirred at 25 °C for 15 min, and to the resulting yellow suspension of ylide, a solution of **23** (6.86 g, 17.0 mmol) in dry ether (137 ml) was added dropwise in a 20-min period. After being stirred at 25 °C for 20 min, the reaction mixture was poured into ice-water (500 ml), and the mixture was extracted with ether (3×500 ml). The extracts were washed with saturated aqueous NaCl, dried, and evaporated. The residue was chromatographed on silica gel (340 g) with 12 : 1 hexane-ethyl acetate to afford the vinylic compound (5.51 g, 80.7%) as a colorless syrup which was treated with 75% aqueous acetic acid at 50 °C for 5 h to give a sample of **19** (3.39 g, 100%) after silica-gel chromatography with 1 : 2 hexane-ethyl acetate. By the procedure described in the preparation of **20**, the sample of **19** (349 mg) was epoxidated to afford a sample of **20** (230 mg, 71%) after silica-gel chromatography with 2 : 1 hexane-ethyl acetate. To a solution of the sample of **20** (42.7 mg, 0.187 mmol) in dry DMF (427 µl) were added imidazole (63.7 mg, 0.935 mmol) and TBS-Cl (113 mg, 0.748 mmol) at 0 °C. After being kept at 25 °C for 3 h, the reaction mixture was poured into ice-water which was extracted with ethyl acetate (3×1 ml). The extracts were washed with saturated aqueous NaCl, dried, and evaporated. The residue was chromatographed on silica gel (3.2 g) with 6 : 1 hexane-ethyl acetate to give a colorless syrup (70.2 mg). To a solution of this syrup (64.1 mg, 0.187 mmol) in dry THF (641 µl) was added 1.07 M *n*-BuLi in hexane (437 µl, 0.468 mmol) at −60 °C. After being stirred at −60 °C for 15 min, a solution of SEM-Cl (99.3 µl, 0.561 mmol) in dry THF (497 µl) was added to the reaction mixture, which was stored at 0 °C for 16 h. Saturated aqueous NH_4Cl (2.0 ml) was added to the reaction mixture, and was extracted with ethyl acetate (3×2.0 ml). The extracts were washed with saturated aqueous NaCl, dried, and evaporated. A mixture of the residual syrup (104 mg), dry THF (727 µl), and *n*-Bu_4NF (374 µl, 0.374 mmol) was stored at 0 °C for 4 h. The reaction mixture was poured into ice-water which was extracted with ethyl acetate (3×2.0 ml). The extracts were washed with saturated aqueous NaCl, dried, and evaporated. The residue was chromatographed on silica gel (1.5 g) with 5 : 2 hexane-ethyl acetate to afford an inseparable 3 : 1 mixture of **6b** and **6b′** (43.1 mg, 84% from **20**) as a colorless syrup: R_f=0.20 (3 : 1 hexane-ethyl acetate); ^1H NMR (400 MHz, $CHCl_3$, δ=7.26) δ=0.88—0.93 (2H, m, $SiCH_2$), 1.42—1.48 (0.25H, m, H-3), 1.53—1.61 (0,75H, m, H-3), 2.62 and 2.59—2.63 (1H, dd and m, H-1, $J_{1,2}$=3.0, J_{gem}=4.0 Hz), 2.81 (1H, dd, H-1, $J_{1,2}$=4.0 Hz), 2.87—2.94 and 2.97—3.02 (0.75H and 0.25H, br-s, OH), 3.05—3.39 (1H, m, H-2), 3.57—3.63 (2H, m, $SiCH_2C\underline{H}_2O$), 3.72 and 3.78 (1.5H, ABX , $SEMOC\underline{H}_2$, J_{AB}=9.6, J_{AX}=J_{BX}=4.5 Hz), 3.77 and 3.84 (0.5H, ABX, $SEMOC\underline{H}_2$, J_{AB}=9.6, J_{AX}=J_{BX}=4.5 Hz), 4.30—4.35 (0.25H, m, H-4), 4.37—4.42 (0.75H, m, H-4), 4.66 (2H, s, OCH_2O), 5.15—5.20 (1H, m, H-6), 5.28—5.35 (1H, m, H-6), 5.88 (0.25H, ddd, H-5, $J_{5,4}$=5.9, $J_{5,6}$=10.7, 16.6 Hz), 5.90 (0.75H, ddd, H-5, $J_{5,4}$=5.9, $J_{5,6}$=10.7, 16.6 Hz).

Conversion of (6b+6b′) into 24. To a solution of bis(methylthio)methane (173 µl, 1.73 mmol) in dry THF (1.73 ml) was added 1.53 M *n*-BuLi in hexane (1.13 ml, 1.73 mmol) at −40 °C. The mixture was stirred at −20 °C for 2 h, and a solution of (**6b+6b′**) (95.1 mg, 0.346 mmol) in dry THF (285 µl) was added to the mixture at −20 °C under stirring. After the mixture was stirred at −20 °C for 0.5 h, to this was added saturated aqueous NH_4Cl, and the mixture was extracted with ethyl acetate (3×4.0 ml). The extracts were washed with saturated aqueous NaCl, dried, and evaporated. The residue was chromatographed on silica gel with 3 : 1 hexane-ethyl acetate to give the dimethyl dithioacetal compound [122 mg, 93%, R_f=0.58 (2 : 1 hexane-ethyl acetate]. By the procedure described in the preparation of **36** from **35**, the dithioacetal (122 mg) was isopropylidenated to afford a sample of acetonide [123 mg, 91.4%, R_f=0.37 (10 : 1 hexane-ethyl acetate)] after chromatography. The acetonide (21.2 mg) was dedithioacetalized by the procedure described in the preparation of **39** from **36** to give a crude sample of aldehyde which was purified by silica-gel chromatography to afford pure aldehyde [7.2 mg, 42%, R_f=0.40 (5 : 1 hexane-ethyl acetate)] as a main product. A solution of the aldehyde (3.4 mg) in 0.02% methanolic HCl (60 µl, pH=4) was kept at 25 °C for 50 min. The mixture was neutralized (pH 7) with $NaHCO_3$ and filtered. The filtrate was evaporated and the residue was chromatographed on silica gel (0.5 g) with 2 : 1 hexane-ethyl acetate to give a cyclic methyl acetal derivative (2.6 mg, 83%) as a mixture of anomers [R_f=0.62, 0.56 (15 : 1 chloroform-methanol)]. Acetylation of this sample of acetal (2.6 mg) with Ac_2O (1.6 µl) and DMAP (3.0 mg) in CH_2Cl_2 (78 µl) at 25 °C for 17 min afforded the acetate **24** (2.9 mg) after chromatography (R_f=0.63, 8 : 1 benzene-acetone). This sample revealed to be a 6 : 4 mixture of **24α** and **24β** by its 400 MHz ^1H NMR spectrum ($CHCl_3$, δ=7.26): δ=0.017 (5.4H, s, Me_3Si of **24α**), 0.021 (3.6H, s, Me_3Si of **24β**), 0.86—0.94 (4H, m, $SiCH_2$), 1.45—1.68 (1.4H, m, H-4 and H-2 of **24β**), 0.66 (0.6H, dd, H-2 of **24α**, J_{gem}=12.8, $J_{2,1}$=3.4, $J_{2,3}$=11.5 Hz), 2.03 (1.8H, s, Ac of **24α**), 2.05 (1.2H, s, Ac of **24β**), 2.25 (0.6H, dd, H-2 of **24α**, $J_{2,1}$=ca. 1, $J_{2,3}$=4.8 Hz), 2.34 (0.4H, dd, H-2 of **24β**, $J_{2,1}$=2.0, $J_{2,3}$=5.8 Hz), 3.34 (1.8H, s, MeO of **24α**), 3.50 (1.2H, s, MeO of **24β**), 3.46—3.59 (4H, m, $SiCH_2$-$C\underline{H}_2OCH_2OC\underline{H}_2$), 3.98 (0.4H, dd, H-5 of **24β**, $J_{5,4}$=10.0, $J_{5,6}$=6.7 Hz), 4.28 (0.6H, dd, H-5 of **24α**, $J_{5,4}$=10.0, $J_{5,6}$=6.4 Hz), 4.43 (0.4H, H-1 of **24β**, $J_{1,2}$=10.0 Hz), 4.52 and 4.58 (0.8H, ABq, OCH_2O of **24β**, J_{gem}=6.4 Hz), 4.53 and 4.60 (1.2H, ABq, OCH_2O of **24α**, J_{gem}=6.4 Hz), 4.83 (0.6H, dd, H-1 of **24α**), 5.14 (0.4H, ddd, H-3 of **24β**, $J_{3,2}$=4.8, $J_{3,4}$=11.5 Hz), 5.28 (1H, ddd, H-7, $J_{7,6}$=9.6, J_{gem}=1.6, $J_{7,5}$=1.6 Hz), 5.35 (0.6H, ddd, H-3 of **24α**, $J_{3,4}$=11.5 Hz), 5.37 (1H, dd, H-7, $J_{7,6}$=17.9, $J_{7,5}$=0 Hz), 5.85 (0.4H, ddd, H-6 of **24β**, $J_{6,5}$=9.9 Hz), 5.88 (0.6H, ddd, H-6 of **24α**, $J_{6,5}$=9.9 Hz).

Conversion of (6b+6b′) into 25 and 26. To an ice-cooled solution of (**6b+6b′**) (140 mg, 0.51 mmol) in dry ether (4.2 ml) was added $LiAlH_4$ (29.1 mg, 0.765 mmol) and the mixture was stirred at 25 °C for 35 min. After water (0.1 ml), 3 M NaOH (0.1 ml), water (0.3 ml), and 3 M NaOH (0.3 ml) were added in sequence with vigorous stirring at 0 °C, the mixture was filtered through a Celite, and the filter cake was washed with ether (3×10 ml). The filtrate and washings were evapo-

rated and the residue was taken up in ethyl acetate (10 ml), which was washed with water and saturated aqueous NaCl, dried, and evaporated. The residue was chromatographed on silica gel (7.0 g) with 2:1 hexane-ethyl acetate to afford the diol (109 mg, 78%); R_f=0.32 (2:1 hexane-ethyl acetate). By the procedure described in the preparation of **36** from **35**, the diol (83.4 mg) was isopropylidenated to give an inseparable 3:1 mixture of **25** and **26** (78.5 mg, 82%) after silica-gel chromatography with 10:1 hexane-ethyl acetate: colorless syrup; ^{1}H NMR (400 MHz, $CHCl_3$, δ=7.26) δ=0.02 (9H, s, Me_3Si), 0.90—0.97 (2H, m, $SiCH_2$), 1.21 (2.25H, d, H-1 of **25**, $J_{1,2}$=6.8 Hz), 1.24 (0.75H, d, H-1 of **26**, $J_{1,2}$=6.8 Hz), 1.38 (4.5H, s, CMe_2 of **25**), 1.39 and 1.46 (1.5H, each s, CMe_2 of **26**), 1.54—1.58 (0.25H, m, H-3 of **26**), 1.88—1.96 (0.75, m, H-3 of **25**), 3.49 and 3.58 (1.5H, ABX, SEMOC$\underline{H}_2$ of **25**, J_{AX}=J_{BX}=5.1, J_{AB}=9.3 Hz), 3.57—3.64 (1.5H, OC$\underline{H}_2$CH$_2$Si of **25**), 3.65—3.72 (0.5H, m, OC$\underline{H}_2$CH$_2$Si of **26**), 3.66 and 3.75 (0.5H, ABX, SEMOC$\underline{H}_2$ of **26**, J_{AX}=J_{BX}=5.1, J_{AB}=9.3 Hz), 4.03 (0.75H, dddd, H-4 of **25**, $J_{3,4}$=$J_{4,5}$=6.7 Hz), 4.17 (1H, dq, H-2, $J_{2,3}$=6.7 Hz), 4.48 (0.25H, dddd, H-4 of **26**, $J_{4,3}$=2.2, $J_{4,5}$=4.8 Hz), 4.59—4.67 (2H, m, OCH_2O), 5.16 (0.25H, ddd, H-6 of **26**, $J_{6,5}$=11.2, $J_{6,4}$=J_{gem}=ca. 0.8 Hz), 5.17 (0.75H, ddd, H-6 of **25**, $J_{6,5}$=11.2, $J_{6,4}$=J_{gem}=ca. 0.8 Hz), 5.26 (0.25 H, ddd, H-6 of **26**, $J_{6,5}$=17.6, $J_{6,4}$=ca. 0.8 Hz), 5.28 (0.75H, ddd, H-6 of **25**, $J_{6,5}$=17.6, $J_{6,4}$=ca. 0.8 Hz), 5.87 (0.75H, ddd, H-5 of **25**), 5.94 (0.25H, ddd, H-5 of **26**).

(2*S*,3*R*,4*S*)-3-[(*t*-Butyldimethylsilyloxy)methyl]-1-(1,3-dithian-2-yl)-2,4-*O*-isopropylidene-5-hexene-2,4-diol (28). To a solution of 1,3-dithiane (47.3 mg, 0.390 mmol) in dry THF (473 ml) was added 1.64 M *n*-BuLi in hexane (237 µl, 0.390 mmol) at −40 °C. After being stirred at −20 °C for 2 h, to this mixture was added a solution of **6a** (20.2 mg, 0.078 mmol) in dry THF (60.6 µl) at −40 °C. After being stirred at −20 °C for 0.5 h, the reaction mixture was poured into cold water which was extracted with ethyl acetate (3×1 ml). The extracts were washed with saturated aqueous NaCl, dried, and evaporated. The residue was chromatographed on silica gel 30:1 chloroform-acetone to give **27** (23.9 mg, 81%). A sample of **27** (22 mg) was isopropylidenated by the procedure described in the preparation of **15** from **14** to afford **28** (22.4 mg, 92%) after silica-gel chromatography with 10:1 hexane-ethyl acetate: R_f=0.75 (3:1 hexane-ethyl acetate), $[\alpha]_D^{32}$ −1.22°, $[\alpha]_{546}^{32}$ −1.71° (*c* 0.82); ^{1}H NMR (90 MHz) δ=0.86 (9H, s, *t*-Bu), 1.32 and 1.36 (each 3H, each s, CMe_2), 1.6—2.1 (5H, m, 2×H-1,3, $SCH_2C\underline{H}_2$), 2.6—2.9 (4H, m, 2×SCH_2), 3.57 and 3.69 (2H, ABX, TBSOC$\underline{H}_2$, J_{AX}=J_{BX}=6.6, J_{AB}=9.9 Hz), 3.8—4.4 (3H, m, S-C$\underline{H}$-S, H-2,4), 5.0—5.4 (2H, m, 2×H-6), 5.95 (1H, ddd, H-5, $J_{5,4}$=5.7, $J_{5,6}$=9.9, 17.4 Hz).

Found: C, 57.20; H, 8.79%. Calcd for $C_{20}H_{38}O_3Si$: C, 57.37; H, 9.15%.

(3*S*,4*R*,5*S*)-4-[(*t*-Butyldimethylsilyloxy)methyl]-3,5-*O*-isopropylidene-1-trimethylstannyl-1,1-bis(methylthio)-6-heptene-3,5-diol (36). To a solution of diisopropylamine (0.931 ml, 6.64 mmol) in a 4:1 mixture of THF-HMPA (16.5 ml) was added 1.64 M *n*-BuLi in hexane (4.05 ml, 6.64 mmol) at 0 °C. After being stirred at 0 °C for 15 min, to this mixture was added rapidly with stirring under Ar a solution of [bis(methylthio)methyl]trimethylstannane (1.64 g, 6.04 mmol) in dry THF (3.3 ml) at −65 °C and stirring was continued at −40 °C for 0.5 h. A solution of **6a** (130 mg, 0.503 mmol) in dry THF (390 µl) was then introduced and the mixture was stirred at −40 °C for 23 min. Then saturated aqueous NH_4Cl was added to the mixture which was extracted with ethyl acetate (3×20 ml). The extracts were washed with saturated aqueous NaCl, dried, and evaporated. The oily residue was chromatographed on silica gel (40 g) with 8:1 hexane-ethyl acetate to afford **35** (190 mg, 71%) as a colorless syrup. To a solution of **35** (190 mg, 0.349 mmol) in dry CH_2Cl_2 (1.9 ml) was added 2-methoxy-1-propene (0.20 ml, 2.10 mmol) and PPTS (13.2 mg, 0.0524 mmol) at 0°C. After being stirred at 24 °C for 3 h, the reaction mixture was diluted with ethyl acetate (7.0 ml) and was washed with water and saturated aqueous NaCl, dried, and evaporated. The residue was chromatographed on silica gel (18.5 g) with 15:1 hexane-ethyl acetate to give **36** (173 mg, 87%) as a colorless syrup: R_f=0.70 (10:1 hexane-ethyl acetate); $[\alpha]_D^{30}$ +8.8°, $[\alpha]_{435}^{30}$ +11.0° (*c* 0.82); ^{1}H NMR (400 MHz, δ ($CHCl_3$)=7.26) δ=0.055, 0.063 (each 3H, each s, $SiMe_2$), 0.24 (9H, s, Me_3Sn), 0.90 (9H, s, *t*-BuSi), 1.33, 1.46 (each 3H, each s, CMe_2), 1.80 (1H, dddd-like, H-4), 1.99, 2.03 (each 3H, each s, 2×SMe), 2.26 (1H, dd, H-2, $J_{2,3}$=2,4, J_{gem}=15.1 Hz), 2.39 (1H, dd, H-2, $J_{2,3}$=10.3 Hz), 3.62 and 3.78 (2H, ABX, C$\underline{H}_2$OTBS, J_{AX}=J_{BX}=5.4, J_{AB}=10.3 Hz), 4.10 (1H, dddd-like, H-5, $J_{5,4}$=$J_{5,6}$=6.4 Hz), 4.22 (1H, ddd, H-3, $J_{3,4}$=3.9 Hz), 5.16 (1H, ddd, H-7, J_{gem}≒$J_{7,5}$≒1.5, $J_{7,6}$=10.7Hz), 5.23 (1H, ddd, H-7, $J_{7,5}$≒1.0, $J_{7,6}$=17.6 Hz), 5.99 (1H, ddd, H-6).

Found: C, 46.64; H, 7.92%. Calcd for $C_{22}H_{46}O_3SiS_2Sn$: C, 46.40; H, 8.14%.

Preparation of Deuterio Product 38. To a solution of **36** (29.2 mg, 0.0495 mmol) in a 3:1 mixture of dry THF-HMPA (117 µl) were added a 1.5 M solution of *n*-BuLi in hexane (66.0 µl, 0.0991 mmol) and immediately D_2O (1.0 ml) at −20 °C. The reaction mixture was warmed up to room temperature and extracted with ethyl acetate (3×1 ml). The extracts were washed with saturated aqueous NaCl, dried and evaporated. The residue was chromatographed on silica gel (1.6 g) with 12:1 hexane-ethyl acetate to afford **38** (17.1 mg, 84.7%) as a colorless syrup: R_f=0.67 (5:1 hexane-ethyl acetate).

Preparation of Deuterio Aldehyde 39. To a mixture of NBS (40.6 mg, 0.228 mmol), $AgNO_3$ (40.8 mg, 0.240 mmol), 2,4,6-trimethylpyridine (60.3 µl, 0.456 mmol), and 85% aqueous acetonitrile (0.62 ml) was added a solution of **38** (15.5 mg, 0.380 mmol) in acetonitrile (46.5 µl) at room temperature. After being stirred at room temperature for 20 min, to the stirred mixture were added in sequence saturated aqueous Na_2SO_3 (0.11 ml), saturated aqueous $NaHCO_3$ (0.11 ml), and saturated aqueous NaCl (0.11 ml) in each 1-min period. Then, this mixture was filtered and the filter cake was washed with acetonitrile (3×2.0 ml). The filtrate and washings were extracted with ethyl acetate (3×2.0 ml), and the extracts were washed with water, saturated aqueous K_2SO_4, $NaHCO_3$, and NaCl, dried, and evaporated. The residue was chromatographed on silica gel (1.7 g) with 5:1 hexane-ethyl acetate to afford **39** (5.0 mg, 43.6%) as a colorless syrup.

Formation of 40 by Coupling of 36 and 32. To a solution of **36** (18.4 mg, 0.0312 mmol) in dry 3:1 THF-HMPA (98.8 µl) was added 1.5 M *n*-BuLi in hexane (25.0 µl, 0.0375 mmol) at −30 °C, and immediately a solution of **32** (6.3 mg, 0.0208 mmol) in dry THF (18.9 µl) was added. After being stirred at 0 °C for 5 h, saturated aqueous NH_4Cl (1.0 ml) was added to the reaction mixture which was extracted with ethyl acetate (3×1.0 ml). The extracts were washed with saturated aqueous NaCl, dried, and evaporated. The residue was chromatographed on silica gel (1.5 g) with 8:1 hexane-ethyl acetate to afford a mixture of **40** and **32** (8.4 mg) as a colorless syrup

(R_f=0.44, 20 : 1 benzene-ethyl acetate). The ratio of **40** and **32** was determined to be 5 : 7 by ^{1}H NMR (90 MHz).

Preparation of 41 by Coupling of 36 and 33. To a solution of **36** (15.0 mg, 0.0254 mmol) in dry 3 : 1 THF-HMPA (60.0 μl) was added 1.5 M *n*-BuLi in hexane (20.3 μl, 0.0305 mmol) at −30 °C, and immediately a solution of **33** (9.2 mg, 0.0177 mmol) in dry THF (27.6 μl) was added. After being stirred at 25 °C for 40 min, saturated aqueous NH_4Cl (1.0 ml) was added to the reaction mixture which was extracted with ethyl acetate (3×1 ml). The extracts were washed with saturated aqueous NaCl, dried, and evaporated. The residue was chromatographed on silica gel (1.4 g) with 10 : 1 hexane-ethyl acetate to afford **41** (10.1 mg, 76%) as colorless syrup: R_f=0.44 (5 : 1 hexane-ethyl acetate); ^{1}H NMR (90 MHz) δ=0.92 (18H, s-like, 2×*t*-Bu), 1.33, 1.38, and 1.47 (total 12H, each s, 2×CMe_2), 1.4—2.3 (7H, m, H-10, 2×H-8, 2×H-6, 2×H-4), 1.97 and 2.03 (each 3H, each s, 2×SMe), 3.38 (3H, s, OMe), 3.4—4.3 and 4.4—4.6 (total 13H, each m, H-2,3,5,9,11, 2×H-1, $C\underline{H}_2OTBS$, $OC\underline{H}_2C\underline{H}_2O$), 4.74 and 4.88 (2H, ABq, $OC\underline{H}_2O$, *J*=6.9 Hz), 5.0—5.4 (2H, m, 2×H-13), 5.8—6.3 (1H, m, H-12).

(3*S*,5*R*,8*R*,9*S*,11*S*,15*S*,16*R*,17*S*)-16-*O*-[(*t*-Butyldimethylsilyloxy)methyl]-3,5 : 8,9 : 15,17-tri-*O*-isopropylidene-1-*O*-(4-methoxybenzyl)-11-*O*-[(2-methoxyethoxy)methyl]-13,13-bis(methylthio)-18-nonadecene-1,3,5,8,9,11,15,17-octol (42). To a stirred solution of **36** (24.7 mg, 0.0434 mmol) in a 3 : 1 mixture of dry THF and HMPA (91.4 μl) was added rapidly 1.64 M *n*-BuLi in hexane (32.0 μl, 0.0521 mmol) at −29 °C. Immediately, to the resulting brown colored mixture was added a solution of **2** (20.6 mg, 0.0304 mmol) in dry THF (61.8 μl) rapidly. Then, saturated aqueous NH_4Cl was added to the yellow reaction mixture which was extracted with ethyl acetate (5×1.0 ml). The extracts were washed with saturated aqueous NaCl, dried, and evaporated to a syrup, which was chromatographed on silica gel (2.9 g) with 3 : 1 hexane-ethyl acetate to afford **42** (24.3 mg, 84%) as a colorless syrup: R_f=0.55 (3 : 1 hexane-thyl acetate); $[\alpha]_D^{32}$ +11.1° (*c* 0.90); ^{1}H NMR (400 MHz, δ($CHCl_3$)=7.26) δ=0.055, 0.061 (each 3H, each s, $SiMe_2$), 0.90 (9H, s, *t*-BuSi), 1.15 (1H, ddd, H-4, $J_{4,3}\fallingdotseq J_{4,5}\fallingdotseq J_{gem}\fallingdotseq$11.5 Hz), 1.32, 1.33, 1.347, 1.355, 1.40, 1.47 (each 3H, each s, 3×CMe_2), 1.97, 2.03 (each 3H, each s, 2×SMe), 1.25—2.15 (14H, m, 2×H-2, H-4, 2×H-6, 2×H-7, 2×H-10, 2×H-12, 2×H-14, H-16), 3.37 (3H, s, MeO of MEM), 3.45—3.67 (7H, m), 3.80 (3H, s, MeO of MPM), 3.73—3.88 (4H, m), 3.97—4.10 (3H, m), 4.41 and 4.43 (2H, ABq, $OC\underline{H}_2Ar$, *J*=14.4 Hz), 4.45—4.51 (1H, m), 4.73 and 4.93 (2H, ABq, $OC\underline{H}_2O$ of OMEM, *J*=7.3 Hz), 5.16 (1H, ddd, H-19, $J_{19,18}$=10.7, $J_{gem}\fallingdotseq J_{19,17}\fallingdotseq$1.5 Hz), 5.25 (1H, ddd, H-19, $J_{19,18}$=17.6, $J_{19,17}\fallingdotseq$1.5 Hz), 5.97 (1H, ddd, H-18, $J_{18,17}$=5.9 Hz), 6.87, 7.25 (each 2H, each ddd-like, Ar).

Found: C, 61.26; H, 8.82%. Calcd for $C_{49}H_{86}O_{12}SiS_2$: C, 61.34; H, 9.03%.

(3*S*,4*S*,5*S*,9*S*,11*R*,12*R*,15*R*,17*S*)-4-[(*t*-Butyldimethylsilyloxy)methyl]-1,3,5,9,11,12,15,17,19-nonahydroxy-3,5 : 11,12 : 15,17-tri-*O*-isopropylidene-19-*O*-(4-methoxybenzyl)-9-*O*-[(2-methoxyethoxy)methyl]-7-nonadecanone (1). To a solution of dicyclohexylborane (0.406 mmol) in dry THF (0.228 ml) was added a solution of **42** (77.9 mg, 0.0812 mmol) in dry THF (0.234 ml) at 0 °C under Ar. After being stirred at 23 °C for 45 min, the reaction mixture was diluted with water (0.463 ml), and added in sequence 3 M aqueous NaOH (0.135 ml, 0.406 mmol) and 30% H_2O_2 (0.122 ml, 1.22 mmol) at 0 °C. After being stirred at 23 °C for 1 h, the reaction mixture was extracted with chloroform (3×1.0 ml). The extracts were washed with saturated aqueoud NaCl, dried, and evaporated. The residue was chromatographed on silica gel (7.9 g) with 2 : 1 hexane-ethyl acetate to afford **43** (73.2 mg, 92%) as a colorless syrup. To a solution of **43** (73.2 mg, 0.0749 mmol) in 80% aqueous acetone (2.6 ml) was added HgO (71.4 mg, 0.330 mmol) and $HgCl_2$ (89.5 mg, 0.330 mmol) at 23 °C. After being stirred at 23 °C for 25 min, the reaction mixture was filtered through a Celite and the filter cake was washed with acetone. The combined filtrate and washings were concentrated to remove acetone. The aqueous residue was extracted with chloroform (3×4.0 ml) and extracts were washed with aqueous 10% KI (2×5.0 ml), saturated aqueous NaCl, dried, and evaporated. The residue was chromatographed on silica gel (6.7 g) with 1 : 1 hexane-ethyl acetate to afford **1** (54.9 mg, 81.6%) as a colorless syrup: R_f=0.42 (1 : 1 hexane-ethyl acetate); $[\alpha]_D^{31}$ +6.5°, $[\alpha]_{435}^{31}$ +11.2° (*c* 0.68); IR($CHCl_3$) 1710 cm^{-1} (C=O); ^{1}H NMR 400 MHz, δ($CHCl_3$)= 7.26) δ=0.05, 0.055 (each 3H, each s, $SiMe_2$), 0.89 (9H, s, *t*-Bu), 1.15 (1H, ddd, H-16, $J_{16,17}\fallingdotseq J_{16,15}\fallingdotseq J_{gem}\fallingdotseq$11.0 Hz), 1.318, 1.324, 1.33, 1.34, 1.35, 1.40 (each 3H, each s, 3×CMe_2), 1.42—1.95 (12H, m, 2×H-2, H-4, 2×H-10, 2×H-13, 2×H-14, H-16, 2×H-18), 2.53 (1H, br-t-like, OH), 2.54 (1H, dd, *J*=3.8, 16.8 Hz), 2.68 (1H, dd, *J*=9.6, 16.8 Hz), 2.72 and 2.80 (each 1H, each dd, *J*=6.4 and 16.8 Hz), 3.38 (3H, s, MeO of MEM), 3.46—3.87 (10H, m), 3.80 (3H, s, MeO of MPM), 3.97—4.05 (1H, m), 4.24—4.31 (1H, m), 4.41 and 4.44 (2H, ABq, $OC\underline{H}_2Ar$, *J*=12.8 Hz), 4.43—4.49 (1H, m), 4.71 and 4.74 (2H, ABq, $OC\underline{H}_2O$ of MEM, *J*=6.4 Hz), 6.88 and 7.25 (each 2H, each ddd-like, Ar).

Found: C, 62.75; H, 8.79%. Calcd for $C_{47}H_{82}O_{14}Si$: C, 62.78; H, 9.19%.

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13) The coupling of heptanal and **28** using *t*-BuLi instead of *n*-BuLi was also unsuccessful, affording only a complex mixture of side products formed by the reaction of **28** and *t*-BuLi.

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17) Unfortunately, for the present, this procedure can not be adapted for large scale preparation of **42**. When the amount of **36** was greater than 25 mg, the yield of **42** sharply lowerd probably due to the short-lived characteristic of **37**.

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