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Synthetic Studies of Amphotericin B. II.[1] A Facile Synthesis of the C-1—C-12 Segments of the Amphotericin B Aglycon†

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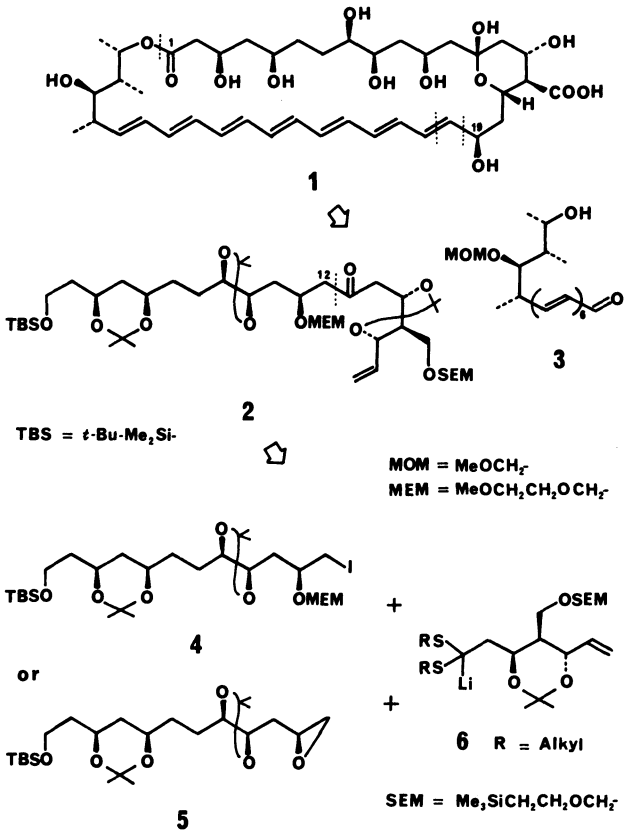
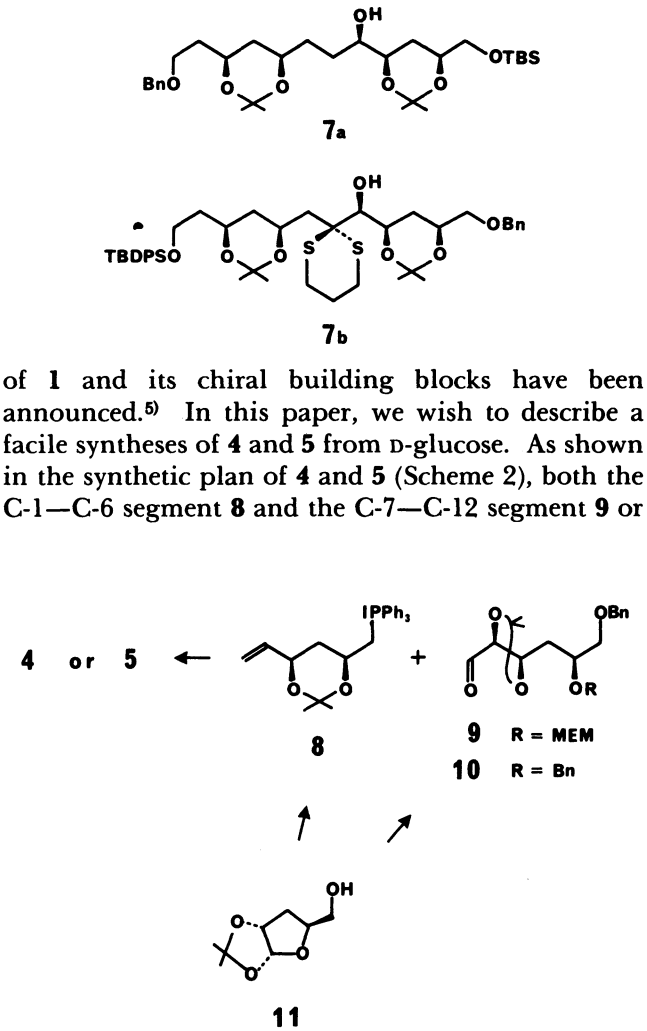
3-Deoxy-1,2-*O*-isopropylidene-α-D-*glycero*-D-*erythro*-pentofuranose (**11**) was stereoselectively converted into the Witting salt **8** corresponding to the C-1—C-6 portion of amphotericin B aglycon (**1**) in 57% overall yield in 8 steps. The aldehydic segment **9** or **10** corresponding to the C-7—C-12 portion of **1** was also derived in 6 steps from **11** in 53 or 38% overall yield, respectively. Wittig condensation of **8** with **9** or **10** followed by four-step conversion afforded the C-1—C-12 segment, (3*S*,5*R*,8*R*,9*R*,11*S*)-1-*O*-*t*-butyldimethylsilyl-12-iodo-3,5:8,9-di-*O*-isopropylidene-11-*O*-[(2-methoxyethoxy)methyl]-1,3,5,8,9,11-dodecanehexol (**4**) or (2*S*,4*R*,5*R*,8*R*,10*S*)-1,2-anhydro-12-*O*-*t*-butyldimethylsilyl-4,5:8,10-di-*O*-isopropylidene-1,2,4,5,8,10,12-dodecaneheptol (**5**) in 26 or 15% overall yield from **11**, respectively.

In our studies directed toward the total synthesis of amphotericin B,[2] a clinically valuable important member of the polyene macrolide antibiotics, our general synthetic plan[1] of its free aglycon **1** required two major segments, **2** and **3** corresponding to the C-1—C-19 and C-21—C-37 portions of **1**, respectively. The enantiospecific synthesis of the latter **3** from carbohydrate has already been accomplished in our laboratories.[1] The retrosynthetic examination of **2** revealed that a disconnection of the C-12—C-13 bond devided **2** into the C-1—C-12 segment **4** or **5** and the C-13—C-19 segment **6** (Scheme 1). The asymmetric synthesis of other kinds of C-1—C-12 segments, **7a**[3] and **7b**[4] have been reported. Recent synthetic efforts of **1** and its chiral building blocks have been announced.[5] In this paper, we wish to describe a facile syntheses of **4** and **5** from D-glucose. As shown in the synthetic plan of **4** and **5** (Scheme 2), both the C-1—C-6 segment **8** and the C-7—C-12 segment **9** or



Scheme 1.

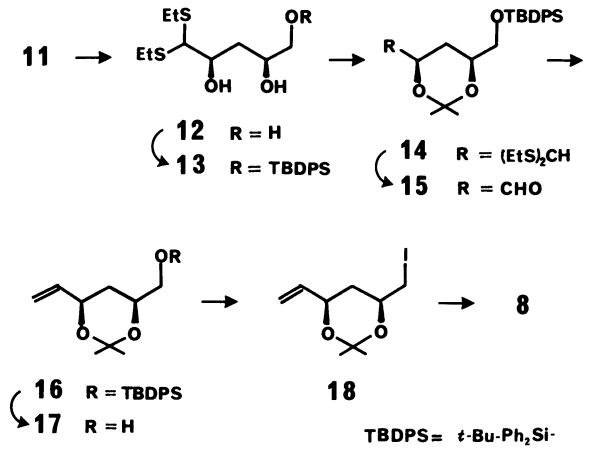


Scheme 2.

† A part of this paper was read at the 52nd National Meeting of the Chemical Society of Japan, Kyoto, April 1986, Abstr., No. 4N05.

10 would be derived from the common 3-deoxy-1,2-*O*-isopropylidene-α-D-*glycero*-D-*erythro*-pentofuranose (**11**)[6] which is obtainable from D-glucose. Wittig coupling of **8** with **9** or **10** followed by a sequence of reactions involving hydroboration and catalytic hydrogenation would give **4** or **5**.

Preparation of 8. Dithioacetalization of **11** with ethanthiol and boron trifluoride etherate afforded **12** which was regioselectively *t*-butyldiphenylsilylated[7] to give **13** in 92% overall yield from **11**. 2,4-*O*-Isopropylidenation of **13** with 2,2-dimethoxypropane (DMP) and a catalytic amount of H_2SO_4 in acetone afforded **14**, which was treated with 1:1 $HgCl_2$–HgO (red) in 80% aqueous acetone to give the aldehyde **15** in 94% overall yield from **13**. Wittig methylenation[8] of **15** with methylenetriphenylphosphorane in ether afforded **16** in 90% yield. Desilylation of **16** with tetrabutylammonium fluoride (TBAF) in THF gave **17** in 99% yield. Treatment[9] of **17** with triphenyl-

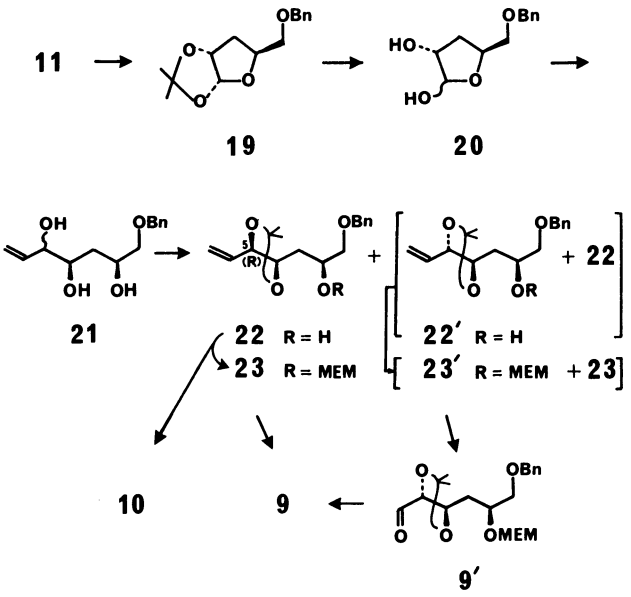


Scheme 3.

phosphine, imidazole, and iodine in benzene afforded the iodide **18** in 88% yield, which was allowed to react with triphenylphosphine in refluxed benzene to provide **8** in 88% yield. The overall yield of **8** from **11** was 57% in 8 steps.

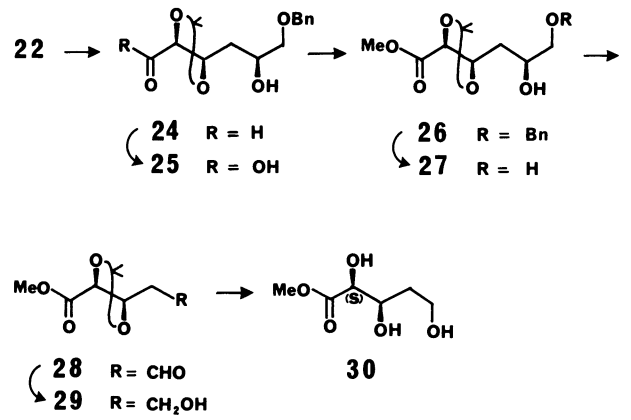
Preparation of 9 and 10. 5-*O*-Benzylation of **11** with sodium hydride and benzyl bromide in DMF afforded **19** in 97% yield. Hydrolysis of **19** with a 1:1 mixture of 3.2 M†† hydrochloric acid and dioxane gave **20** in 92% yield. Grignard reaction of **20** with large excess of vinylmagnesium bromide in THF afforded a ca. 3.5:1[10] syn/anti diastereomeric mixture **21** in 95% yield. Regioselective 4,5-*O*-isopropylidenation[11] of **21** with a catalytic amount of iodine in acetone gave a 54% yield of the major product **22** and a 24% yield of a mixture of **22** and its 3-epimer **22′** after chromatography. The chromatography also afforded a third fraction which consisted of **22**, **22′**, and a small amount of inseparable mixture of two epimeric 2,4-*O*-isopropylidene derivatives of **21**. Methoxyethoxy-

†† 1 M=1 mol dm^{-3}.



Scheme 4.

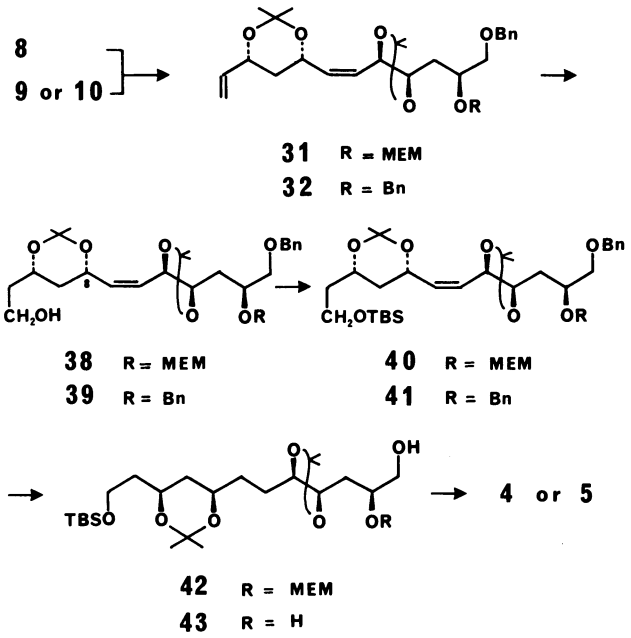
methylation of **22** with (2-methoxyethoxy)methyl chloride (MEM-Cl) and *N*,*N*-diisopropylethylamine gave **23** in 98% yield, which was oxidized with OsO_4–$NaIO_4$[12] to afford **9** in 92% yield. The mixture of **22** and **22′** was methoxyethoxymethylated to give in 94% yield a mixture of **23** and **23′**, which was oxidized with OsO_4–$NaIO_4$ to afford **9** and its epimer **9′** in 38 and 26% yields, respectively after chromatography. An isomerically pure sample of **22′** obtained by chromatographic separation of the aforesaid epimeric mixture was methoxyethoxymethylated and then oxidized to yield a mixture of **9** (20%) and **9′** (50%). Exposure of **9′** to methanolic K_2CO_3 at 23 °C for 4.5 h gave **9** in 68% yield. No starting **9′** was detected by ^{13}C NMR of the unpurified product. The total yield of the major product **9** from **11** amounted to 53%. The complete epimerization of **9** to **9′** indicated that the aldehyde **9** had presumably the desired 2,3-syn structure which would be thermodynamically more stable than the anti structure (in the basic conditions of epimerization). The structures of **22** and **22′** were thus presumed as depicted in Scheme 4. The (5R)-configuration of **22** was confirmed by the transformation of **22** into the (2*S*)-2-hydroxy ester **30** as shown in Scheme 5. Oxidation of **22** with OsO_4–$NaIO_4$ afforded the free aldehyde **24**. No hemiacetal structure was detected by ^1H NMR of the reaction product. This observation also supported the 2,3-syn structure of **24**. Oxidation of **24** with the periodite reagent (K_2CO_3, I_2, KI)[13] followed by treatment of the resulting carboxylic acid **25** with diazomethane gave **26** which was hydrogenolyzed over Pd-black to yield **27**. Periodate-oxidation of **27** followed by $NaBH_4$(0.5 molar) reduction of the resulting **28** afforded **29**. Finally, **29** was de-*O*-isopropylidenated to give **30**. Since the CD spectrum of **30** showed the (+)-CD Cotton effect which reflected



Scheme 5.

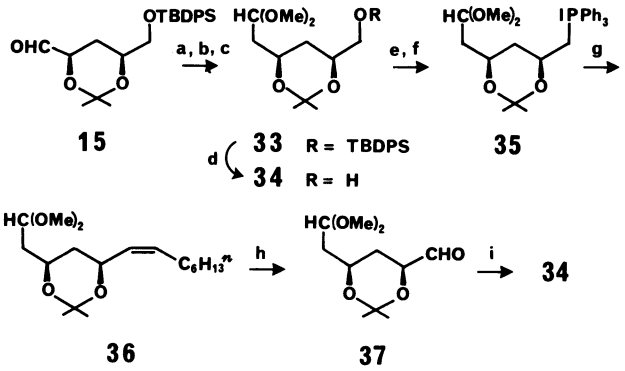
the (S)-configuration at the C-2 carbon atom,[14] the (5R)-configuration of **22** as depicted was confirmed. On the other hand, benzylation of **22** followed by OsO_4–$NaIO_4$ oxidation provided another C-7—C-12 segment **10** in 82% yield.

Preparation of 4 and 5. Wittig coupling between **8** and **9** or **10** was best achieved under the modified Secruist and Wu's conditions.[15] Treatment of 1 equivalent of **8** with 1 equivalent of butyllithium in 2:1 THF–HMPA at −70 °C under argon generated an orange-colored ylide which condensed with 0.9 equivalents of **9** or **10** at −50 °C to afford a single product **31** or **32** in 70 or 52% yield, respectively. The ^1H NMR examination showed both **31** and **32** to be the



Scheme 6.

isomerically pure (6Z)-olefines. The configurational integrity[15] of left half of the condensation product **31** or **32** was confirmed by the following experimental results (Scheme 7). The aforesaid aldehyde **15** was converted in 3 steps into its homologous aldehyde dimethyl acetal **33** according to the procedure developed in our laboratories.[16] The acetal **33** was transformed via the intermediate **34** into the Wittig salt **35**. Wittig reaction of **35** with heptanal was carried out by the same procedure as described for the reaction of **8** with **9** to afford only the condensation product **36** of (Z)-configuration. OsO_4–$NaIO_4$ oxidation of **36** followed by $NaBH_4$ reduction of the product **37** gave **34** which proved to be identical in all respects with a sample of the intermediate **34** derived from **15**, cleanly indicating that the (2S)-configuration of **35** was retained during the Wittig reaction.



(a) $MeOCH_2PPh_3Cl$, $NaCH_2SOMe$, ether; (b) NBS, MeOH; (c) *n*-Bu_3SnH, AIBN, PhMe; (d) TBAF, THF; (e) Ph_3P, DEAD, MeI; (f) Ph_3P, PhH, 84 °C, 4 d; (g) *n*-BuLi, 2:1 THF–HMPA; *n*-$C_6H_{13}CHO$; (h) OsO_4, $NaIO_4$, 3:1 dioxane–H_2O; (i) $NaBH_4$, MeOH.

Scheme 7.

The regioselective hydroboration of **31** or **32** with 1.8 equivalents of dicyclohexylborane in THF at 25 °C followed by treatment with alkaline hydrogen peroxide at 50 °C afforded **38** or **39** in 90 or 85% yield, respectively. The *t*-butyldimethylsilylation (TBS-Cl, Py, 23 °C) of **38** or **39** gave the silyl ether **40** or **41** in 95 or 90% yield, respectively. Simultaneous catalytic reduction of the double bond and benzyloxy group in **40** proceeded effectively with Raney Ni W-4 in ethanol to give **42** in 84% yield. Whereas the reduction of **40** with Pd-black in *t*-butyl alcohol provided a complex mixture involving the partially desilylated and de-*O*-isopropylidenated products. On the contrary, the catalytic reduction of **41** with Pd-black in *t*-butyl alcohol proceeded cleanly to afford the diol **43** in 98% yield. Iodination[17] of **42** with triphenylphosphine, diethyl azodicarboxylate (DEAD), and methyl iodide in benzene provided the segment **4** in 92% yield. One stage epoxidation[18] of **43** with triphenylphosphine, DEAD, and 3A molecular sieves in benzene afforded another segment **5** in 70% yield.

Experimental

Melting points were determined on a micro hot stage Yanaco MP-S3 and were uncorrected. Optical rotations

were measured on a Carl Zeiss photoelectric polarimeter and a JASCO DIP-360 photoerectric polarimeter in chloroform, and ^{1}H NMR spectra in $CDCl_3$ using TMS on either a Varian EM-390 or a Bruker WM 250 spectrometer. ^{13}C NMR spectra were measured on a JEOL FX 90A in $CDCl_3$, and IR spectra on a Hitachi Perkin-Elmer spectropotometer. High-performance liquid chromatography (HPLC) was carried out on a Waters 208 Compact Liquid Chromatograph, and TLC on Merck TLC plates (60F-254, 0.25 mm) and on Merck HPTLC plates (60F-254) for "HPTLC." Column chromatography was performed 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 the appropriate procedure, and evaporation and concentration were carried out under reduced pressure below 30 °C, unless otherwise noted.

(2*S*,4*R*)-5,5-Bis(ethylthio)-1,2,4-pentanetriol (12). To an ice-cooled solution of **11**[6] (8.05 g, 46.2 mmol) in ethanethiol (240 ml) was added boron trifluoride etherate (2.40 ml) and the mixture was stirred at room temperature for 2 h. The reaction mixture was neutralized (pH=7) with triethylamine and evaporated. The residue was chromatographed on silica gel (220 g) with 10:1 chloroform–methanol to afford **12** (10.5 g, 95%): colorless syrup, R_f=0.41 (10:1 chloroform–methanol); $[\alpha]_D^{35}$ +61.5° (*c* 1.05); IR ($CHCl_3$) 3440 cm^{-1}; ^{1}H NMR (90 MHz) δ=1.27 (6H, t, 2×MeCH$_2$S, *J*=7.0 Hz), 1.50—2.10 (2H, m, 2×H-3), 2.70 (4H, q, 2×MeCH$_2$S), and 3.40—4.10 (8H, m, 3×OH, 2×H-1, H-2, H-4, H-5).

Found: C, 45.04; H, 8.14%. Calcd for $C_9H_{20}O_3S_2$: C, 44.97; H, 8.39%.

(2*S*,4*R*)-1-*O*-(*t*-Butyldiphenylsilyl-5,5-bis(ethylthio)-1,2,4-pentanetriol (13). To an ice-cooled solution of **12** (2.02 g, 8.4 mmol) in DMF (20.2 ml) was added dropwise imidazole (744 mg, 10.9 mmol) and *t*-butyldiphenylsilyl chloride (2.62 ml, 10.8 mmol), and the mixture was stirred at 25 °C for 0.5 h. The reaction mixture was then poured into cold water (40 ml) and extracted with chloroform (3×40 ml). The extracts were washed with saturated aqueous NaCl, dried, and evaporated to a syrup which was chromatographed on silica gel (200 g) with 7:1 benzene–ethyl acetate to give a pure sample of **13** (3.69 g, 92%): coloreless syrup; R_f=0.60 (3:1 toluene–ethyl acetate); $[\alpha]_D^{25}$ +14.6° (*c* 1.64); IR($CHCl_3$) 3480, 1110 cm^{-1}; ^{1}H NMR (90 MHz) δ=1.13 (9H, s, *t*-Bu), 1.27 (6H, t, 2×MeCH$_2$S, *J*=7.0 Hz), 1.41—2.00 (2H, m, 2×H-3), 2.70 (4H, dd, 2×MeCH$_2$S), 2.85—3.20 (2H, brs, 2×OH), 3.63 (2H, d, 2×H-1, *J*=6.6 Hz), 3.76—4.13 (3H, m, H-2, H-4, H-5), and 7.20—7.81 (10H, m, 2×Ph).

Found: C, 62.80; H, 7.89%. Calcd for $C_{25}H_{38}O_3S_2Si$: C, 62.72; H, 8.00%.

(2*S*,4*R*)-1-*O*-(*t*-Butyldiphenylsilyl)-5,5-bis(ethylthio)-2,4-*O*-isopropylidene-1,2,4-pentanetriol (14). To an ice-cooled solution of **13** (11.9 g, 37.4 mmol) and 2,2-dimethoxypropane (9.2 ml, 74.8 mmol) in dry acetone (360 ml) was added 1.0% H_2SO_4 in acetone (1.8 ml). After being stirred at room temperature for 20 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 water and saturated aqueous NaCl, dried, and evaporated to afford an essentially pure sample of **14** (19.4 g, 100%) as a pale yellow syrup. An analytical sample was obtained after silica gel column chromatography with 10:1 hexane–ethyl acetate: R_f=0.80 (3:1 hexane–ethyl acetate); $[\alpha]_D^{32}$ −14.2° (*c* 1.00); IR ($CHCl_3$) 1110 cm^{-1}; ^{1}H NMR (90 MHz) δ=1.08 (9H, s, *t*-Bu), 1.28 (6H, t, 2×MeCH$_2$S, *J*=7.5 Hz), 1.40 (6H, s, CMe$_2$), 1.58—1.88 (2H, m, 2×H-3), 2.73 (4H, q, 2×SCH$_2$), 3.42—4.25 (5H, m, 2×H-1, H-2, H-4, H-5), and 7.21—7.90 (10H, m, 2×Ph).

(2*R*,4*S*)-6-*O*-(*t*-Butyldiphenylsilyl)-2,4-*O*-isopropylidene-2,4,5-trihydroxypentanal (15). A mixture of the aforesaid sample of **14** (19.1 g, ca. 36.8 mmol), aqueous 80% acetone, $HgCl_2$ (43.0 g, 162 mmol), and HgO(red)(35.1 g, 162 mmol) was stirred vigorously at room temperature for 20 min. The resulting 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 (3×40 ml) and extracts were washed with aqueous 10% KI (2×30 ml) and saturated aqueous NaCl, dried, and evaporated. The residue was chromatographed on silica gel (760 g) with 3:1 hexane–ethyl acetate to afford **15** (14.3 g, 94% from **13**): colorless syrup, R_f=0.34 (3:1 hexane–ethyl acetate); $[\alpha]_D^{26}$ +16.6° (*c* 1.06); IR($CHCl_3$) 1735, 1110 cm^{-1}; ^{1}H NMR (90 MHz) δ=1.10 (9H, s, *t*-Bu), 1.45 (6H, s, CMe$_2$), 1.66—2.00 (2H, m, 2×H-3), 3.43—4.57 (4H, m, H-2, H-4, 2×H-5), 7.10—7.91 (10H, m, 2×Ph), and 9.63 (1H, d-like, CHO).

(2*S*,4*R*)-1-*O*-(*t*-Butyldiphenylsilyl)-2,4-*O*-isopropylidene-5-hexene-1,2,4-triol (16). A 4 M solution of methylsulfinylmethanide anion in DMSO (5.0 ml, 20 mmol) prepared from sodium hydride and DMSO was added dropwise to a stirred suspension of methyltriphenylphosphonium bromide (7.1 g, 19.9 mmol) in dry ether (82 ml) under argon at 25 °C. The mixture was stirred at 25 °C for 25 min, and to the resulting yellow suspension of ylide, a solution of **15** (2.05 g, 4.97 mmol) in dry ether (41 ml) was added dropwise over a 5-min period. After being stirred at 25 °C for 20 min, the reaction mixture was poured into an ice-water (100 ml) and the mixture was extracted with ether(3×50 ml). The extracts were washed with saturated aqueous NaCl, dried, and evaporated. The residue was chromatographed on silica gel (100 g) with 15:1 hexane–ethyl acetate to afford **16** (1.84 g, 90%): colorless syrup, R_f=0.79 (4:1 hexane–ethyl acetate); IR($CHCl_3$) 1105 cm^{-1}; $[\alpha]_D^{25}$ +2.0°, $[\alpha]_{365}^{25}$ +10.0° (*c* 1.00); ^{1}H NMR (90 MHz) δ=1.04 (9H, s, *t*-Bu), 1.38 (6H, s, CMe$_2$), 1.50—1.90 (2H, m, H-3), 3.33—3.65 (2H, m, 2×H-1), 3.80—4.15 (1H, m, H-2), 4.20—4.50 (1H, m, H-4), 5.07 (1H, ddd, H-6*Z*, J_{gem}=$J_{6Z,4}$=ca. 1.2, $J_{6Z,5}$=9.3 Hz), 5.21 (1H, ddd, H-6*E*, $J_{6E,4}$=ca. 1.2, $J_{6E,5}$=15.9 Hz), 5.82 (1H, ddd, H-5, $J_{5,4}$=5.7 Hz), and 7.0—7.9 (10H, m, 2×Ph).

Found: C, 73.16; H, 8.25%. Calcd for $C_{25}H_{34}O_3Si$; C, 73.13; H, 8.35%.

(2*S*,4*R*)-1-Iodo-2,4-*O*-isopropylidene-5-hexene-2,4-diol (18). To a solution of **16** (10.9 g, 26.5 mmol) in THF (100 ml) was added dropwise a 1M solution of TBAF in THF (53 ml). After being stirred at 24 °C for 15 min, the mixture was poured into cold water (150 ml) and extracted with ethyl acetate (3×150 ml). The combined extracts were washed with saturated aqueous NaCl, dried, and evaporated to afford a syrup which was chromatographed on silica gel (230 g) with 1:1 hexane–ethyl acetate to give **17** (4.54 g, 99%) as a colorless syrup. A mixture of the alcohol **17** (4.33 g, 25.1 mmol), triphenylphosphine (13.2 g, 50.3 mmol), imidazole (3.46 g, 50.3 mmol), iodine (9.6 g, 37.7 mmol), and benzene (65 ml) was stirred at 60 °C for 45 min. The resulting mixture was then cooled to 0 °C and aqueous $Na_2S_2O_3$ and $NaHCO_3$ were added in sequence. After

vigorous stirring at 0 °C for 10 min, the reaction mixture was extracted with ethyl acetate (3×50 ml) and the extracts were washed with saturated aqueous NaCl, dried, and evaporated. The residue was chromatographed on silica gel (350 g) with 12:1 hexane–ether to give **18** (5.93 g, 84%) and a mixture of **18** and triphenylphosphine (2.3 g) which was separated by chromatography to afford an additional sample of **18** (0.28 g, 4%). The total yield of **18** was 6.21 g (88%): colorless syrup, R_f=0.84 (3:1 hexane–ethyl acetate); $[\alpha]_D^{33}$ +19.4° (*c* 1.04); ^{1}H NMR (90 MHz) δ=1.25 (1H, ddd, H-3, $J_{3,2}=J_{3,4}$=10.5, J_{gem}=12.0 Hz), 1.47 (6H, s, CMe_2), 1.90 (1H, ddd, H-3, $J_{3,2}=J_{3,4}$=3.3 Hz), 3.07—3.30 (2H, m, 2×H-1), 3.83—4.13 (1H, m, H-2), 4.27—4.57 (1H, m, H-4), 5.07 (1H, ddd, H-6Z, $J_{gem}=J_{6Z,4}$=ca. 1.5, $J_{6Z,5}$=9.3 Hz), 5.20 (1H, ddd, H-6E, $J_{6E,4}$=ca. 1.5, $J_{6E,5}$=15.9 Hz), and 5.86 (1H, ddd, H-5, $J_{5,4}$=5.7 Hz)

Found: C, 38.32; H, 5.24%. Calcd for $C_9H_{15}O_2I$: C, 38.32; H, 5.36%.

[[(4*S*,6*R*)-2,2-Dimethyl-6-vinyl-1,3-dioxan-4-yl]methyl]triphenylphosphonium Iodide (8). A mixture of **18** (5.57 g, 19.7 mmol), triphenylphosphine (13.0 g, 49.3 mmol), and benzene (30 ml) was stirred at 80 °C for 5 d. The resulting insoluble matter was collected by filtration and washed with hexane (100 ml) and benzene (200 ml), then dried over NaOH pellets under reduced pressure for 10 h to afford **8** (9.5 g, 88%) as a white powder. An analytical sample was obtained by column chromatography with 10:1 chloroform–methanol: mp 194—196 °C; R_f=0.52 (10:1 chloroform–methanol); $[\alpha]_D^{33}$ +32.0° (*c* 1.02); IR (KBr) 1435, 1108 cm^{-1}; ^{1}H NMR (90 MHz) δ=0.83, 1.13 (each 3H, each s, CMe_2), 1.21—2.10 (4H, m, 2×H-5, CH_2P), 3.50—4.00 (1H, m, H-4), 4.07—4.53 (1H, m, H-6), 5.08 (1H, ddd, CH=C$\underline{H}_2$ (*Z*), $J_{gem}=J_{Z,6}$=ca. 1.2, J_Z=10.2 Hz), 5.24 (1H, ddd, CH=C$\underline{H}_2$ (*E*), $J_{E,6}$=ca. 1.2, J_E=15.6 Hz), 5.79 (1H, ddd, C$\underline{H}$=CH_2, *J*=6.0 Hz), and 7.46—8.07 (15H, m, 3×Ph).

Found: C, 59.88; H, 5.63%. Calcd for $C_{27}H_{30}O_2PI$: C, 59.57; H, 5.55%.

5-*O*-Benzyl-3-deoxy-1,2-*O*-isopropylidene-α-D-*glycero*-D-*glycero*-pentofuranose (19). To a solution of **11**[6] (5.0 g, 28.7 mmol) in DMF (50 ml) was added 55% NaH (2.5 g, 57.4 mmol) at 0 °C. The mixture was stirred at 25 °C for 0.5 h, and benzyl bromide (5.12 ml, 43.0 mmol) was added dropwise at 0 °C. After being stirred at 25 °C for 0.5 h, the reaction mixture was poured into cold water (300 ml) which was extracted with ethyl acetate (3×150 ml). The extracts were washed with saturated aqueous NaCl, dried, and evaporated. The residue was chromatographed on silica gel (400 g) with 4:1 hexane–ethyl acetate to afford **19** (7.42 g, 97%): pale yellow syrup, R_f=4:1 (hexane–ethyl acetate); $[\alpha]_D^{28}$ −15° (*c* 1.00); ^{1}H NMR (90 MHz) δ=1.31, 1.50 (each 3H, each s, CMe_2), 1.70—2.25 (2H, m, 2×H-3), 3.50—3.80 (2H, m, 2×H-5), 4.20—4.55 (1H, m, H-4), 4.60 (2H, s, C$\underline{H}_2$Ph), 4.71 (1H, dd, H-2, $J_{2,1}=J_{2,3}$=4.0 Hz), 5.82 (1H, d, H-1), and 7.33 (5H, s, Ph).

Found: C, 68.43; H, 7.55%. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63%.

5-*O*-Benzyl-3-deoxy-D-*glycero*-D-*glycero*-pentofuranose (20). To an ice-cooled solution of **19** (7.39 g, 28.0 mmol) in dioxane (74 ml) was added dropwise 3.2M aqueous HCl (74 ml) over a 15-min period. After being stirred at 25 °C for 1.25 h, the reaction mixture was neutralized (pH=7) with solid $NaHCO_3$ (3.0 g). The insoluble matter was filtered and washed with dioxane. The combined filtrate and washings were evaporated. The residue was taken up in dioxane and the resulting precipitates were filtered and washed with dioxane (5×8 ml). The filtrate and washings were evaporated, and the residue was chromatographed on silica gel (63 g) with 1:4 toluene–ethyl acetate to give a pure sample of **20** (5.78 g, 92%): colorless syrup, R_f=0.21 (1:1 toluene–ethyl acetate); $[\alpha]_D^{26}$ −14° (*c* 1.03, EtOH after 2d); ^{1}H NMR (90 MHz, after addition of D_2O) δ=1.70—2.20 (2H, m, 2×H-3), 3.30—3.75 (2H, m, 2×H-5), 4.10—4.30 (1H, m, H-4), 4.30—4.70 (1H, m, H-2), 4.58 (2H, s, C$\underline{H}_2$Ph), 5.22 (ca. 0.6H, s, β-H-1), 5.32 (ca. 0.4H, α-H-1, *J*=4.0 Hz), and 7.34 (5H, s, Ph).

Found: C, 63.98; H, 7.21%. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19%.

(2*S*,4*R*,5*R*)-1-*O*-Benzyl-6-heptene-1,2,4,5-tetrol (21) and Its (5*S*)-Epimer (21′). To a solution of vinylmagnesium bromide in THF which was prepared from vinyl bromide (18.2 ml, 258 mmol) and magnesium (6.27 g, 258 mmol) in THF (125 ml), was added dropwise a solution of **20** (5.78 g, 25.8 mmol) in THF (52 ml) over a 7-min period. After being stirred at 25 °C for 3.5 h, the reaction was quenched by addition of $Na_2SO_4 \cdot 10H_2O$ (solid), and the resulting mixture was filtered through a Celite. The filter cake was washed with acetone (5×50 ml) and the combined filtrate and washings were evaporated. The residue was charged together with silica gel (15 g) on a column of silica gel (325 g) by using 15:1 chloroform–methanol and then eluted with the same solvent system to afford a mixture of **21** and its epimer **21′** (6.19 g, 95%): colorless syrup, R_f=0.36 (1:4 toluene–ethyl acetate); ^{1}H NMR (90 MHz) δ=1.50—1.80 (2H, m, 2×H-3), 3.17 (3H, s, 3×OH), 3.30—3.55 (2H, m, 2×H-1), 3.60—4.25 (3H, m, H-2, 4, 5), 4.55 (2H, s, C$\underline{H}_2$Ph), 5.10—5.45 (2H, m, 2×H-7), 5.65—6.10 (1H, m, H-6), and 7.33 (5H, s, Ph).

Found: C, 66.59; H, 8.06%. Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99%.

(2*S*,4*R*,5*R*)-1-*O*-Benzyl-4,5-*O*-isopropylidene-6-heptene-1,2,4,5-tetrol (22) and Its (5S)-Epimer (22′). A mixture of **21** (1.57 g, 6.24 mmol), acetone (78.7 ml), and iodine (475 mg, 1.87 mmol) was stirred at 25 °C for 2 h. To the reaction mixture was added saturated aqueous $Na_2S_2O_3$ (30 ml), and the mixture was extracted with chloroform (3×100 ml). The extracts were washed with saturated aqueous NaCl, dried, and evaporated. The residue (2.18 g) was flushchromatographed on silica gel (270 g) with 7:1 chloroform–ethyl acetate to afford a pure sample of **22** (622 mg), a mixture of **22** and **22′** (799 mg), and a mixture of **22**, **22′**, and two epimeric 2,4-acetonides (288 mg). The fraction containing **22** and **22′** (799 mg) was again flushchromatographed on silica gel (80 g) with 4:1 hexane–ethyl acetate to give a pure sample of **22** (363 mg) and a mixture of **22** and **22′** (435 mg). A total yield of **22** amounted to 985 mg (54%). **22**: colorless syrup, R_f=0.59 (6:1 chloroform–ethyl acetate, HPTLC); $[\alpha]_D^{27}$ −5.13°, $[\alpha]_{365}^{27}$ −27.4° (*c* 1.44); ^{1}H NMR (90 MHz) δ=1.35 (6H, s, CMe_2), 1.78 (2H, dd, 2×H-3, $J_{3,2}=J_{3,4}$=4.5 Hz), 2.77 (1H, br-s, OH), 3.45 (2H, d, H-1, $J_{1,2}$=5.4 Hz), 3.66—4.27 (3H, m, H-2, 4, 5), 4.56 (2H, s, C$\underline{H}_2$Ph), 5.23 (1H, ddd-like, H-7Z, J_{gem}=2.4, $J_{7Z,5}$<1.0, $J_{7Z,6}$=10.0 Hz), 5.37 (1H, ddd-like, H-7E, $J_{7E,5}$<1.0, $J_{7E,6}$=15.6 Hz), 5.82 (1H, ddd, H-6, $J_{6,5}$=6.9 Hz), and 7.35 (5H, s, Ph).

Found: C, 70.10; H, 8.22%. Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27%.

A pure sample of **22′** was obtained by flashchromatog-

raphy of a sample of ca. 1:1 mixture of **22** and **22′** in other experiment. **22′**: colorless syrup, R_f=0.48 (6:1 chloroform–ethyl acetate, HPTLC); $[\alpha]_D^{24}$ +4.0°, $[\alpha]_{365}^{24}$ +14.4° (*c* 0.96); ^{1}H NMR (90 MHz) δ=1.38, 1.51 (each 3H, each s, CMe_2), 1.65 (2H, dd, 2×H-3, *J*=6.0, 6.0 Hz), 3.03 (1H, br-s, OH), 3.46 (2H, d, 2×H-1, *J*=5.4 Hz), 3.80—4.20 (1H, m, H-2), 4.20—4.70 (2H, m, H-4, 5), 4.59 (2H, s, $C\underline{H}_2Ph$), 5.26 (1H, ddd-like H-7Z, J_{gem}=2.1, $J_{7Z,5}$<1.0, $J_{7Z,6}$=9.6 Hz), 5.31 (1H, ddd-like, H-7*E*, $J_{7E,5}$<1.0, $J_{7E,6}$=18.0 Hz), 5.82 (1H, ddd, H-6, $J_{6,5}$=8.1 Hz), and 7.38 (5H, s, Ph).

Found: C, 69.54; H, 8.24%. Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27%.

(2*S*,4*R*,5*R*)-1-*O*-Benzyl-4,5-*O*-isopropylidene-2-*O*-[(2-methoxyethoxy)methyl]-6-heptene-1,2,4,5-tetrol (23). To a cold solution of **22** (1.61 g, 5.50 mmol) in CH_2Cl_2 (16.1 ml) was added *N*,*N*-diisopropylethylamine(4.79 ml, 27.5 mmol) and then (2-methoxyethoxy)methyl chloride (MEM-Cl)(1.85 ml, 16.5 mmol). After being stirred at 40 °C for 1.5 h, the mixture was poured into cold water which was extracted with ethyl acetate (3×30 ml). The extracts were washed with saturated aqueous NaCl, dried, and evaporated. The residue was chromatographed on silica gel (105 g) with 4:1 hexane–acetone to give a pure sample of **23** (2.06 g, 98%): colorless syrup, R_f=0.40 (4:1 hexane–acetone); $[\alpha]_D^{27}$ +3.8°, $[\alpha]_{546}^{27}$ +4.3°, $[\alpha]_{437}^{27}$ +4.9° (*c* 1.27); ^{1}H NMR (90 MHz) δ=1.35, 1.40 (each 3H, each s, CMe_2), 1.56—2.07 (2H, m, 2×H-3), 3.37 (3H, s, OMe), 3.43—4.17 (9H, m, 2×H-1, H-2, 4, 5, $-OCH_2CH_2O-$), 4.57 (2H, s, $C\underline{H}_2Ph$), 4.83 (2H, s, $-OCH_2O-$), 5.24 (1H, ddd-like, H-7Z, J_{gem}=2.1, $J_{7Z,5}$<1.0, $J_{7Z,6}$=10.5 Hz), 5.39 (1H, ddd-like, H-7E, $J_{7E,5}$<1.0, $J_{7E,6}$=16.5 Hz), 5.83 (1H, ddd, H-6, $J_{6,5}$=6.0 Hz).

Found: C, 66.08; H, 8.32%. Calcd for $C_{21}H_{32}O_6$: C, 66.29; H, 8.48%.

(2*S*,3*R*,5*S*)-6-*O*-Benzyl-2,3-*O*-isopropylidene-5-*O*-[(2-methoxyethoxy)methyl]-2,3,5,6-tetrahydroxyhexanal (9). To a stirred solution of **23** (477 mg, 1.25 mmol) in 75% aqueous dioxane (19.1 ml) was added OsO_4. (15.9 mg, 0.063 mmol) at 23 °C. After 15 min to this mixture was added sodium periodate (powder, 802 mg, 3.75 mmol). After being stirred at 23 °C for 2.5 h, the mixture was filtered through a Celite and the filter cake was washed with dioxane. The filtrate and washings were concentrated and diluted with chloroform (20 ml). The mixture was washed with saturated aqueous $Na_2S_2O_3$ and NaCl, dried, and evaporated. The residue was chromatographed on silica gel (24 g) with 6:1 chloroform–acetone to afford **9** (439 mg, 91.5%): colorless syrup, R_f=0.41 (6:1 chloroform–acetone), $[\alpha]_D^{27}$ −3.3°, $[\alpha]_{365}^{27}$ −26.9° (*c* 1.04); IR($CHCl_3$) 1730 cm^{-1}; ^{1}H NMR (90 MHz) δ=1.34, 1.77 (each 3H, each s, CMe_2), 1.98 (2H, dd, 2×H-4, *J*=6.0, 6.0 Hz), 3.34 (3H, s, OMe), 3.34—3.83 (6H, m, $-OCH_2CH_2O-$, 2×H-6), 3.83-4.30 (3H, m, H-2, 3, 5), 4.52 (2H, s, CH_2Ph), 4.77 (2H, s, $-OCH_2O-$), 7.30 (5H, s, Ph), and 9.72 (ca. 0.6H, CHO, *J*=1.8 Hz); ^{13}C NMR (22.50 MHz) δ=25.99, 26.99 (each q, $C\underline{M}e_2$), 35.44 (t, C-4), 58.74 (q, OMe), 66.97, 71.57, 73.12, 73.44 (each t, $\underline{C}H_2Ph$, $-OCH_2O-$, $-OCH_2CH_2O-$), 71.82, 73.63 (each d, C-3, 5), 84.77 (dd, C-2), 94.82 (t, C-6), 110.77 (s, $\underline{C}Me_2$), 127.48, 127.54, 128.19 (each d, Ph), 138.05 (s, Ph), and 200.35 (d, CHO).

(2*R*)-Epimer 9′ of 9. By the method described in the preparation of **23**, the aforesaid mixture of **22** and **22′** (416 mg) was methoxyethoxymethylated to afford a mixture of **23** and **23′** (508 mg, 94%). This mixture was oxidized with OsO_4–$NaIO_4$ by the same procedure as described in the preparation of **9** to give a crude mixture of **9** and **9′** which was flashchromatographed on silica gel (51 g) with 7:1 chloroform–ethyl acetate to afford **9** (193 mg, 38%) and **9′** (182 mg, 36%). **9′**: colorless syrup, R_f=0.66 (6:1 chloroform–acetone); $[\alpha]_D^{24}$ −7.6°, $[\alpha]_{365}^{24}$ −47.2° (*c* 1.02); IR($CHCl_3$) 1730 cm^{-1}; ^{1}H NMR (90 MHz) δ=1.37, 1.57 (each 3H, each s, CMe_2), 1.73—2.10 (2H, m, 2×H-4), 3.36 (3H, s, OMe), 3.40—3.80 (6H, m , $-OCH_2CH_2O-$, 2×H-6), 3.80—4.20 (1H, m, H-5), 4.20—4.80 (2H, m, H-2, 3), 4.54 (2H, s, CH_2Ph), 4.79 (2H, s, $-OCH_2O-$), 7.30 (5H, s, Ph), and 9.63 (1H, d, CHO, *J*=3.0 Hz); ^{13}C NMR (22.50 MHz) δ=25.13, 27.48 (each q, $C\underline{M}e_2$), 31.57 (t, C-4), 58.74 (q, OMe), 67.01, 71.53, 73.05, 73.56 (each t, $\underline{C}H_2Ph$, $-OCH_2O-$, $-OCH_2CH_2O-$), 71.53, 75.05 (each d, C-3, 5), 81.69 (dd, C-2), 94.80 (t, C-6), 110.26 (s, $\underline{C}Me_2$), 127.49, 128.27 (each d, Ph), 138.00 (s, Ph), and 201.87 (d, CHO).

Epimerization of 9′ to 9. To a sample of **9′** (182 mg, 0.475 mmol) was added a solution of K_2CO_3 (20 mg, 0.143 mmol) in methanol (3.63 ml). After being stirred at 23 °C for 4.5 h, the reaction mixture was evaporated. The residue was partitioned between chloroform (10 ml) and water. The chloroform layer was separated and washed with saturated aqueous NaCl, dried, and evaporated. The residue was flushchromatographed on silica gel (18.2 g) with 7:1 chloroform–ethyl acetate to afford **9** (123 mg, 68%) whose TLC, ^{1}H and ^{13}C NMR spectra were identical with those of the aforesaid sample of **9** derived from **23**.

Methyl (2*S*,3*R*,5*R*)-6-*O*-Benzyl-2,3-*O*-isopropylidene-2,3,5-trihydroxyhexanoate (26). By the procedure described in the preparation of **9**, **22** (197 mg, 0.673 mmol) was oxidized with OsO_4–$NaIO_4$ to afford crude aldehyde **24** (192 mg, 97%). To a solution of this aldehyde in 70% aqueous dioxane (6.70 ml) was added a solution of K_2CO_3 (568 mg, 4.11 mmol) and $KHCO_3$ (411 mg, 4.11 mmol) in water (7.70 ml) and then added a solution of KI (649 mg, 3.91 mmol) and I_2 (248 mg, 0.978 mmol) in water (0.96 ml) dropwise under stirring. The mixture was stirred at 23 °C for 1.75 h, after which period $Na_2S_2O_3$ (960 mg) was added to the reaction mixture at 0 °C. This mixture was washed with ether (10 ml) and the aqueous layer was acidified (pH =2—3) with 10% aqueous H_2SO_4 at 0 °C. The mixture was immediately extracted with chloroform (3×10 ml). The extracts were washed with saturated aqueous NaCl, dried, and evaporated to give the crude acid **25** (161 mg, 77% from **22**) as white crystals. The crystalline **25** was dissolved in a solution of diazomethane in ether and then evaporated to afford a syrup which was flushchromatographed on silica gel (5.1 g) with 3:1 chloroform–ethyl acetate to give **26** (163 mg, 74% from **22**): colorless syrup, R_f=0.49 (1:1 toluene–ethyl acetate); IR ($CHCl_3$) 1750 cm^{-1}; $[\alpha]_D^{26}$ +9.3°, $[\alpha]_{365}^{26}$ +21.8° (*c* 1.23); ^{1}H NMR (90 MHz) δ=1.44 (6H, s, CMe_2), 1.70—2.15 (2H, m, 2×H-4), 2.3—2.90 (1H, br-s, OH), 3.47 (2H, d, 2×H-6, *J*=3.0 Hz), 3.78 (3H, s, COOMe), 3.90—4.40 (3H, m. H-2, 3, 5), 4.58 (2H, s, CH_2Ph), and 7.35 (5H, s, Ph).

Found: C, 62.95; H, 7.41%. Calcd for $C_{17}H_{24}O_6$: C, 62.95; H, 7.46%.

Methyl (2*S*,3*R*)-2,3,5-Trihydroxypentanoate (30). A mixture of **26** (289 mg, 0.89 mmol), Pd-black, and methanol (5.8 ml) was vigorously stirred at room temperature for 10 min under bubbling with H_2 gas, and then filtered. The filtrate was evaporated to a colorless syrup of **27** (209 mg,

100%). To a solution of this syrup in acetone (2.10 ml) was added a solution of $NaIO_4$ (381 mg, 1.78 mmol) in water (3.8 ml) under ice-cooling. After being stirred for 15 min, the precipitate was filtered and washed with acetone. The combined filtrate and washings were concentrated. The aqueous residue was extracted with dichloromethane 6 times. The extracts were dried and evaporated to afford a syrup of **28** (180 mg). To an ice-cold solution of this syrup (33 mg, 0.163 mmol) in methanol (0.33 ml) was added $NaBH_4$ (31 mg, 0.082 mmol). After being stirred at 0 °C for 10 min, the mixture was neutralized with CO_2 and then evaporated. The residue was pertitioned between ethyl acetate and saturated aqueous NaCl, and the aqueous layer was extracted with ethyl acetate three times. The organic layers were dried and evaporated to give a syrup which was chromatographed on silica gel (2.3 g) with 1:1 hexane–ethyl acetate to afford **29** (23.5 mg, 70% yield from **26**) as a syrup. A solution of **29** (23.5 mg) and *p*-toluenesulfonic acid (2.2 mg, 0.015 mmol) in methanol (0.23 ml) was stirred at 33 °C for 19 h. The reaction mixture was neutralized with Amberlite IR-45 (OH type) at 0 °C, and then filtered. The resin was washed with methanol, and the combined filtrate and washings were evaporated to afford a syrup (21 mg). This syrup was chromatographed on silica gel (1.0 g) with 5:1 chloroform–methanol to give **30** (16 mg, 84% yield from **29**): colorless syrup, R_f=0.42 (5:1 chloroform–methanol); IR ($CHCl_3$) 3370, 1735 cm^{-1}; $[\alpha]_D^{30}$ +17.9° (*c* 0.47); CD $[\theta]_{210}$ +4105 (*c* 0.10, H_2O); ^1H NMR (90 MHz) δ=1.77—2.17 (2H, m, 2×H-4), 2.57—2.93 (1H, br-s, OH), 3.17—4.47 (6H, m, 2×OH, H-2, 3, 2×H-5), and 3.87 (3H, s, COOMe).

(2*S*,3*R*,5*S*)-5,6-Di-*O*-benzyl-2,3-*O*-isopropylidene-2,3,5,6-tetrahydroxyhexanal (10). To an ice-cold solution of **22** (570 mg, 1.95 mmol) in DMF (3.3 ml) was added 55% NaH (255 mg, 5.85 mmol), and the mixture was stirred at 24 °C for 0.5 h, after which period TBAF (72 mg, 0.195 mmol) was added, and after 5 min, to the stirred mixture was added benzyl bromide (464 µl, 3.90 mmol) dropwise under ice-cooling. After being stirred at 24 °C for 3 h, the reaction mixture was poured into cold water (8.0 ml) and the mixture was extracted with ethyl acetate (3×8.0 ml). The extracts were washed with saturated aqueous NaCl, dried, and evaporated. The residue (1.12 g) was chromatographed on silica gel (75 g) with 8:1 hexane–acetone to afford a colorless syrup of the 2-*O*-benzyl derivative of **22** (710 mg, 95%). A sample (1.59 g, 4.17 mmol) of this benzyl derivative was oxidized with OsO_4–$NaIO_4$ by the procedure described in the preparation of **9**. The crude product was chromatographed on silica gel (80 g) with 2:1 hexane–ethyl acetate to give **10** (1.38 g, 86%): colorless syrup, R_f=0.21 (2:1 hexane–ethyl acetate); IR($CHCl_3$) 1730 cm^{-1}; $[\alpha]_D^{27}$ −3.6°, $[\alpha]_{365}^{27}$ −29.7° (*c* 0.99); ^1H NMR (90 MHz) δ=1.41, 1.45 (each 3H, each s, CMe_2), 2.00 (2H, dd, 2×H-4, $J_{4,3}$=$J_{4,5}$=5.4 Hz), 3.40—4.40 (ca. 5.5H, m, H-2, 3, 5, 2×H-6, H-1), 4.55 (2H, s, CH_2Ph), 4.52, 4.66 (2H, ABq, CH_2Ph, *J*=9.6 Hz), 7.37 (10H, s, 2×Ph), and 9.66 (ca. 0.5H, CHO, *J*=ca. 1.5 Hz).

(2*S*,4*R*,5*R*,8*S*,10*R*)-(6*Z*)-1-*O*-Benzyl-4,5:8,10-di-*O*-isopropylidene-2-*O*-[(2-methoxyethoxy)methyl]-6,11-dodecadiene-1,2,4,5,8,10-hexol (31). To a suspension of **8** (77.8 mg, 0.143 mmol) in 2:1 THF–HMPA (477 µl) was added a 1.56M butyllithium in hexane (92 µl, 0.143 mmol) at −70 °C under Ar, and the mixture was stirred at −70 °C for 22 min. To the yellow colored mixture was added a solution of **9** (48.4 mg, 0.127 mmol) in THF (149 µl), and the mixture was stirred at −70 °C for 0.5 h. The reaction mixture was allowed to warm to −50 °C and diluted with THF (1.2 ml). The reaction was quenched by addition of aqueous NH_4Cl at room temperature. This mixture was extracted with ethyl acetate (3×1.0 ml), and the extracts were washed with saturated aqueous NaCl, dried, and evaporated. The residue was chromatographed on silica gel (3.5 g) with 3:1 hexane–ethyl acetate to afford a pure sample of **31** (46.0 mg, 70%): colorless syrup, R_f=0.45 (3:1 hexane–ethyl acetate); $[\alpha]_D^{32}$ −8.5°, $[\alpha]_{365}^{32}$ −38.5° (*c* 1.20); ^1H NMR (250 MHz) δ=1.34, 1.40, 1.49, 1.53 (12H, each s, 2×CMe_2), 1.70—1.86, 1.92—2.05 (4H, each m, 2×H-3, 2×H-9), 3.36 (3H, s, OMe), 3.46—4.04 (8H, m, 2×H-1, H-2, 4, -OCH_2CH_2O-), 4.33—4.43 (1H, m, H-10), 4.38 (1H, dd, H-5, $J_{5,4}$=$J_{5,6}$=8.8 Hz), 4.47 and 4.59 (2H, ABq, CH_2Ph, *J*=11.25 Hz), 4.69—4.85 (1H, m, H-8), 4.80 (2H, s, -OCH_2O-), 5.13 (1H, ddd, H-12*Z*, J_{gem}=$J_{12Z,10}$=ca. 1.2, $J_{12Z,11}$=10.5 Hz), 5.25 (1H, ddd, H-12*E*, $J_{12E,10}$=ca. 1.2, $J_{12E,11}$=17.8 Hz), 5.45 (1H, dd, H-6, $J_{6,7}$=11.2 Hz), 5.62 (1H, dd, H-7, $J_{7,8}$=7.5 Hz), and 5.81 (1H, ddd, H-11, $J_{11,10}$=4.8 Hz).

Found: C, 66.95; H, 8.29%. Calcd for $C_{29}H_{44}O_8$: C, 66.90; H, 8.52%.

(2*S*,4*R*,5*R*,8*S*,10*R*)-(6*Z*)-1,2-Di-*O*-benzyl-4,5:8,10-di-*O*-isopropylidene-6,11-dodecadiene-1,2,4,5,8,10-hexol (32). By the procedure described in the preparation of **31**, the ylide generated from **8** (66.0 mg, 0.121 mmol) was allowed to react with **10** (42.4 mg, 0.110 mmol) to afford, after silica gel chromatography with 4:1 hexane–ethyl acetate, the coupling product **32** (30.1 mg, 52%): colorless syrup; R_f=0.75 (2:1 hexane–ethyl acetate $[\alpha]_D^{30}$ −19.4° (*c* 1.80), ^1H NMR (250 MHz) δ=1.37, 1.39, 1.44, 1.45 (each 3H, each s, 2×CMe_2), 1.50—1.60, 1.79—2.04 (each 2H, each m, 2×H-3, 2×H-9), 3.50—3.62 (2H, m, 2×H-1), 3.75—3.92 (2H, m, H-2, 4), 4.19—4.32 (1H, m, H-10), 4.53 (2H, s, CH_2Ph), 4.52 and 4.70 (2H, ABq, CH_2Ph, *J*=11.3 Hz), 4.42—4.79 (2H, m, H-5, 8), 5.12 (1H, ddd, H-12Z, J_{gem}=$J_{12Z,10}$=ca. 1.2, $J_{12Z,11}$=11.2 Hz), 5.23 (1H, ddd, H-12E, $J_{12E,11}$=17.5, $J_{12E,10}$=ca. 1.2 Hz), 5.41 (1H, dd, H-6, $J_{6,5}$=9.5, $J_{6,7}$=10.5 Hz), 5.58 (1H, dd, H-7, $J_{7,8}$=7.5 Hz), 5.78 (1H, ddd, H-11, $J_{11,10}$=5.0 Hz), and 7.20—7.45 (10H, m, 2×Ph).

Found: C, 73.36; H, 8.02%. Calcd for $C_{32}H_{42}O_6$: C, 73.53; H, 8.10%.

(2*S*,4*R*)-2,4-*O*-Isopropylidene-6,6-dimethoxy-1,2,4-hexanetriol (34). A 4M methylsulfinylmethanide anion in DMSO[8] (1.25 ml, 4.98 mmol) was added dropwise to a stirred suspension of (methoxymethyl)triphenylphosphonium chloride (1.71 g, 4.98 mmol) in ether under Ar at room temperature. The mixture was sirred for 20 min and then, to the resulting red suspension of the ylide, a solution of **15** (1.03 g, 2.49 mmol) in ether (20 ml) was added dropwise. After being stirred at room temperature for 10 min, the resulting suspension was poured into an ice-water, and the mixture was extracted with ethyl acetate (3×80 ml). The extracts were washed with saturated aqueous NaCl, dried, and evaporated. The residue was chromatographed on silica gel (100 g) with 6:1 hexane–ethyl acetate to a syrup (1.10 g, 96.5%) of methyl enol ether of the homologus aldehyde of **15**. To an ice-cold solution of the methyl enol ether (0.91 g, 2.07 mmol) in methanol (9.0 ml) were added solid $NaHCO_3$ (0.21 g, 2.48 mmol) and NBS (0.44 g, 0.248 mmol) successively. After being stirred at 0 °C for 0.5 h, the mixture was evaporated and the residue was extracted with ethyl acetate (20 ml). The extract was washed with water and saturated

aqueous NaCl, dried, and evaporated to a syrup which was chromatographed on silica gel (80 g) with 6:1 hexane–ethyl acetate to afford a syrup (1.10 g, 96.5%) of the bromo dimethyl acetal. A solution of this bromo acetal (1.10 g), tributylstannane (0.8 ml) and AIBN (66 mg) in toluene (17 ml) was stirred at 60 °C for 2 h and then evaporated. The residue was chromatographed on Kieselgel (50 g) with 10:1 toluene–ethyl acetate to give a syrup of **33** (0.78 g, 83%). A mixture of **33** (228 mg), THF (2.3 ml), and 1M TBAF in THF (0.96 ml) was stirred at 0 °C for 1.5 h and then poured into cold water (10 ml). The mixture was extracted with ethyl acetate (3×15 ml). The extracts were washed with saturated aqueous NaCl, dried, and evaporated. The residue was chromatographed on silica gel (4.5 g) with 1:2 hexane–ethyl acetate to afford **34** (88 mg, 78%): colorless syrup, R_f=0.52 (3:1 hexane–ethyl acetate); $[\alpha]_D^{26}$ −11°(*c* 0.97); ^{1}H NMR (90 MHz) δ=1.38, 1.45 (each 3H, each s, CMe_2), 1.03—1.60 (2H, m, 2×H-3), 1.73 (2H, dd-like 2×H-5, $J_{5,4}=J_{5,6}$=5.4 Hz), 1.96—2.26 (1H, br-s, OH), 3.36, 3.39 (each 3H, each s, 2×OMe), 3.41—3.66 (2H, m, 2×H-1), 3.76—4.22 (2H, m, H-2, 4), and 4.53 (1H, t, H-6).

Found: C, 56.14; H, 9.26%. Calcd for $C_{11}H_{22}O_5$: C, 56.39; H, 9.46%.

[[(4*R*,6*R*)-2,2-Dimethyl-6-(2,2-dimethoxyethyl)-1,3-dioxan-4-yl]]methyl]triphenylphosphonium Iodide (35). A solution of **34** (265 mg, 1.13 mmol), triphenylphosphine (889 mg, 3.39 mmol), and DEAD (0.53 ml, 3.39 mmol) in benzene (5.0 ml) was stirred at 0 °C and then methyl iodide (0.21 ml, 3.39 mmol) was added. The mixture was stirred at room temperature for 1 h and then evaporated. The residue was taken up in ethyl acetate (10 ml) which was washed successively with saturated aqueous $NaHCO_3$ (7.5 ml), $Na_2S_2O_3$ (7.5 ml), and NaCl, dried, and evaporated. The residue was chromatographed on silica gel (12 g) with 5:1 hexane–ethyl acetate to afford a syrup of iodide (276 mg, 71%). A solution of this syrup (235 mg) and triphenylphosphine (386 mg) in benzene (0.76 ml) was stirred at 84 °C for 5 d. The reaction mixture was evaporated and the residual solid was triturated with hexane (10×7.0 ml) to give the Wittig salt **35** (348 mg, 78%): colorless crystals, mp 200—201 °C (MeOH–ether); $[\alpha]_D^{15}$+14.6° (*c* 1.03); ^{1}H NMR (90 MHz) δ=0.77,1.09 (each 3H, each s, CMe_2), 3.28, 3.31 (each 3H, each s, 2×OMe), and 4.51 (1H, *t*, C<u>H</u>$(OMe)_2$, *J*=6.0 Hz).

Found: C, 57.08; H, 6.02; I, 20.62%. Calcd for $C_{29}H_{36}O_4PI$: C, 57.43; H, 5.98; I, 20.92%.

(3*R*,5*S*)-(6*Z*)-1,1-Dimethoxy-3,4-*O*-isopropylidene-5-tridecene-3,4-diol (36). By the procedure described in the preparation of **31**, the ylide generated from **35** (109 mg, 0.179 mmol) was condensed with heptanal (36.1 μl, 0.269 mmol) to afford, after silica-gel chromatography with 8:1 hexane–ethyl acetate and with 16:1 hexane–acetone, the condensation product **36** (18.2 mg, 32%): colorless syrup, R_f=0.35 (8:1 hexane–ethyl acetate); ^{1}H NMR (250 MHz) δ=0.89 (3H, t, 3×H-13, *J*=7.0 Hz), 1.20—1.85 (12H, m, 2×H-2, 2×H-4, -C<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>$_2$Me), 1.40, 1.50 (each 3H, each s, CMe_2), 2.0—2.2 (2H, m, 2×H-8), 3.34, 3.38 (each 3H, each s, 2×OMe), 4.0—4.1 (1H, m, H-3), 4.57 (1H, dd, H-1, $J_{1,2}$=4.5, 7.0 Hz), 4.69 (1H, ddd, H-5, $J_{5,4}$=2.8, 11.8 Hz, $J_{5,6}$=8.0 Hz), 5.35 (1H, approximately dd, dd after decoupled with 2×H-8 protons, H-6, $J_{6,7}$=11.8 Hz), and 5.4—5.6 (1H, m, d after decoupled with 2×H-8 protons, H-7).

Preparation of 34 from 36 via 37. By the procedure described in the preparation of **9**, a sample of **36** (103 mg) was oxidized with OsO_4–$NaIO_4$ to afford a crude syrup of the aldehyde **37** (30.4 mg, 40%): ^{1}H NMR (90 MHz) δ=1.45 (6H, s, CMe_2), 3.34, 3.35 (each 3H, each s, 2×OMe), and 9.61 (0.5H, s, CHO). To an ice-cold solution of the syrup (30 mg) in methanol (0.3 ml) was added $NaBH_4$ (10.0 mg). After being stirred at 0 °C for 2 h, the mixture was neutralized with CO_2 and treated successively with IR-45 and CG-50 resin. The resulting methanol solution was evaporated to a syrup which was purified by silica-gel chromatography with 1:1 hexane–ethyl acetate to afford **34** (19 mg) in 24% overall yield from **36**. This sample proved to be identical with the sample of **34** obtained from **15** by TLC, $[\alpha]_D$ and ^{1}H NMR.

(2*S*,4*R*,5*R*,8*S*,10*S*)-(6*Z*)-1-*O*-Benzyl-4,5:8,10-di-*O*-isopropylidene-2-*O*-[(2-methoxyethoxy)methyl]-6-dodecene-1,2,4,5,8,10,12-heptol (38). To a solution of dicyclohexylborane (0.854 mmol) in THF (0.48 ml) was added a solution of **31** (247 mg, 0.475 mmol) in THF (0.74 ml) at 0 °C under Ar, and the mixture was stirred at 25 °C for 25 min. The reaction was quenched by addition of water (1.22 ml). To this mixture was added 3M aqueous NaOH (0.284 ml) and 30% H_2O_2 (0.256 ml) at 0 °C. After being stirred at 5 °C for 1 h, the reaction mixture was extracted with chloroform (3×2.0 ml). The extracts were washed with saturated aqueous NaCl, dried, and evaporated. The residue was chromatographed on silica gel (13 g) with 1:3 hexane–ethyl acetate to afford a pure sample of **38** (229 mg, 90%): colorless syrup, R_f=0.48 (1:3 hexane–ethyl acetate); $[\alpha]_D^{30}$ −6.7°, $[\alpha]_{365}^{30}$−24.1° (*c* 1.77); ^{1}H NMR (250 MHz) δ=1.34, 1.37, 1.39, 1.48 (each 3H, each s, 2×CMe_2), 1.20—2.07 (7H, m, 2×H-3 2×H-9, 2×H-11, OH), 3.36 (3H, s, OMe), 3.43-3.63 (4H, m, -OCH_2CH_2O-), 3.63—4.21 (7H, m, 2×H-1, H-2, 4, 10, 2×H-12), 4.36 (1H, ddd-like, H-5, $J_{5,7}$<1.0, $J_{5,4}=J_{5,6}$=8.8 Hz), 4.46 and 4.61 (2H, ABq, CH_2Ph, *J*=12.5 Hz), 4.65-4.80 (1H, m, H-8), 4.80 (2H, s, -OCH_2O-), 5.45 (1H, dd, H-6, $J_{6,7}$=10.5 Hz), 5.62 (1H, dd, H-7, $J_{7,8}$=7.5 Hz), and 7.20—7.54 (5H, m, Ph).

Found: C, 64.65; H, 8.57%. Calcd for $C_{29}H_{46}O_9$: C, 64.66; H, 8.61%.

(2*S*,4*R*,5*R*,8*S*,10*S*)-(6*Z*)-1,2-Di-*O*-benzyl-4,5:8,10-di-*O*-isopropylidene-6-dodecene-1,2,4,5,8,10,12-heptol (39). By the procedure described in the preparation of **38**, the title compound **39** (24.9 mg, 85%) was obtained from **32** (28.2 mg) after silica-gel chromatography with 1:2 hexane–ethyl acetate: colorless syrup, R_f=0.55 (1:2 hexane–ethyl acetate); $[\alpha]_D^{29}$ −19.6° (*c* 1.43); ^{1}H NMR (90 MHz) δ=1.40, 1.46 (each 6H, each s, 2×CMe_2), 1.60—2.20 (6H, m, 2×H-3, 2×H-9, 2×H-11), 2.44 (1H, br-s, OH), 3.40—4.20 (7H, m, 2×H-1, H-2, 4, 10, 2×H-12), 4.30—4.93 (4H, m, H-5, 8, CH_2Ph), 4.55 (2H, s, CH_2Ph), 5.20—5.75 (2H, m, H-6, 7), and 7.36 (10H, s, 2×Ph).

Found: C, 71.08; H, 8.14%. Calcd for $C_{32}H_{44}O_7$: C, 71.08; H, 8.20%.

(2*S*,4*R*,5*R*,8*S*,10*S*)-(6*Z*)-1-*O*-Benzyl-12-*O*-*t*-butyldimethylsilyl-4,5:8,10-di-*O*-isopropylidene-2-*O*-[(2-methoxyethoxy)methyl]-6-dodecene-1,2,4,5,8,10,12-heptol (40). To an ice-cold solution of **38** (40 mg, 0.0613 mmol) in pyridine (0.33 ml) was added TBS-Cl (13.9 mg, 0.092 mmol). After being stirred at 23 °C for 2 h, the mixture was poured into cold water (1.0 ml) and the resulting mixture 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 (2.0 g) with 4:1

hexane-ethyl acetate to afford **40** (38.1 mg, 95%): colorless syrup, R_f=0.74 (1:2 hexane-ethyl acetate); $[\alpha]_D^{31}$ −10.9° (*c* 1.43); ^{1}H NMR (250 MHz) δ=0.89 (9H, s, *t*-Bu), 1.34, 1.35, 1.40, 1.45 (each 3H, each s, 2×CMe$_2$), 1.49—2.05 (6H, m, 2×H-3, 2×H-9, 2×H-11), 3.36 (3H, s, OMe), 3.47—3.58 (4H, m, -OCH$_2$CH$_2$O-), 3.59—4.13 (7H, m, 2×H-1, H-2, 4, 10, 2×H-12) 4.38 (1H, ddd-like, H-5, $J_{5,7}$<1.0, $J_{5,6}$=$J_{5,4}$=9.3 Hz), 4.46 and 4.60 (2H, ABq, CH$_2$Ph, *J*=11.8 Hz), 4.63—4.77 (1H, m, H-8), 4.80 (2H, s, -OCH$_2$O-), 5.44 (1H, dd, H-6, $J_{6,7}$=10.5 Hz), 5.62 (1H, dd, H-7, $J_{7,8}$=7.5 Hz), and 7.31 (5H, s, Ph).

Found: C, 64.64; H, 9.14%. Calcd for $C_{35}H_{60}O_9Si$: C, 64.38; H, 9.26%.

(2*S*,4*R*,5*R*,8*S*,10*S*)-(6*Z*)-1,2-Di-*O*-benzyl-12-*O*-*t*-butyldimethylsilyl-4,5:8,10-di-*O*-isopropylidene-6-dodecene-1,2,4,5,8,10,12-heptol (41). By the procedure described in the preparation of **40**, a sample of **39** (76.0 mg) was silylated to afford, after silica-gel chromatography with 6:1 hexane-ethyl acetate, **41** (82.6 mg, 90%): colorless syrup R_f=0.47 (5:1 hexane-ethyl acetate); $[\alpha]_D^{31}$ −18.7° (*c* 1.43); ^{1}H NMR (90 MHz) δ=0.94 (9H, s, *t*-Bu), 1.40 and 1.46 (each 6H, each s, 2×CMe$_2$), 1.40—2.20 (6H, m, 2×H-3, 2×H-9, 2×H-11), 3.40-4.20 (7H, m, 2×H-1, H-2, 4, 10, 2×H-12), 4.30—4.90 (6H, m, H-5, 8, 2×CH$_2$Ph), 5.20—5.80 (2H, m, H-6, 7), and 7.37 (10H, s, 2×Ph).

Found: C, 69.35; H, 8.75%. Calcd for $C_{38}H_{58}O_7Si$: C, 69.69; H, 8.93%.

(2*S*,4*R*,5*R*,8*R*,10*S*)-12-*O*-*t*-Butyldimethylsilyl-4,5:8,10-di-*O*-isopropylidene-2-*O*-[(2-methoxyethoxy)methyl]-1,2,4,5,8,10,12-dodecaneheptol (42). A solution of **40** (28.1 mg) in ethanol (0.56 ml) was stirred with a catalytic amount of Raney Ni W-4 for 2 h under bubbling with H_2 gas. The reaction mixture was filtered through a sintered-glass funnel and the catalyst was washed with ethanol. The combined filtrate and washings were evaporated, and the residue was chromatographed on silica gel (1.0 g) with hexane-ethyl acetate to afford **42** (20.5 mg, 84%): colorless syrup, R_f=0.34 (1:1 hexane-ethyl acetate); $[\alpha]_D^{33}$ +35.7° (*c* 0.74); ^{1}H NMR (90 MHz) δ=0.90 (9H, s, *t*-Bu), 1.38, 1.42 (each 6H, each s, 2×CMe$_2$), 1.17—2.10 (10H, m, 2×H-3, 2×H-6, 2×H-7, 2×H-9, 2×H-11), 2.90 (1H, br-s, OH), 3.40 (3H, s, OMe), 3.43—4.30 (13H, m, 2×H-1, H-2, 4, 5, 8, 10, 2×H-12, -OCH$_2$CH$_2$O-), and 4.81 (2H, s, -OCH$_2$O-).

Found: C, 59.84; H, 9.81%. Calcd for $C_{28}H_{56}O_9Si$: C, 59.54; H, 9.99%.

(2*S*,4*R*,5*R*,8*R*,10*S*)-12-*O*-*t*-Butyldimethylsilyl-4,5:8,10-di-*O*-isopropylidene-1,2,4,5,8,10,12-dodecaneheptol (43). A mixture of **41** (138 mg), Pd-black, and *t*-BuOH was vigorously stirred at 30 °C for 1 h under bubbling with H_2 gas, and then the suspension was filtered. The filtrate was evaporated to a syrup which was chromatographed on silica gel (5.0 g) with 1:2 hexane-ethyl acetate to afford **43** (99 mg, 98%): colorless syrup, R_f=0.52 (1:2 hexane-ethyl acetate); $[\alpha]_D^{28}$ +10.3° (*c* 0.66); ^{1}H NMR (90 MHz) δ=0.87 (9H, s, *t*-Bu), 1.32, 1.36, 1.38 (12H, each s, 2×CMe$_2$), 1.10—1.90 (10H, m, 2×H-3, 2×H-6, 2×H-7, 2×H-9, 2×H-11), and 2.70—4.20 (11H, m, 2×H-1, H-2, 4, 5, 8, 10, 2×H-12, 2×OH).

Found: C, 60.51; H, 9.69%. Calcd for $C_{24}H_{48}O_7Si$: C, 60.47; H, 10.15%.

(3*S*,5*R*,8*R*,9*R*,11*S*)-1-*O*-*t*-Butyldimethylsilyl-12-iodo-3,5:8,9-di-*O*-isopropylidene-11-*O*-[(2-methoxyethoxy)methyl]-1,3,5,8,9,11-dodecanehexol (4). To a cold (10 °C) solution of **42** (41.3 mg, 0.073 mmol) and triphenylphosphine (57.5 mg, 0.219 mmol) in benzene (0.83 ml) was added DEAD (0.045 ml, 0.219 mmol). After being stirred at 24 °C for 10 min, methyl iodide (0.0136 ml, 0.219 mmol) was added to the mixture at 10 °C. The mixture was stirred at 24 °C for 3 h and then water (1.5 ml) was added. The mixture was extracted with benzene (3×1.0 ml), and extracts were washed with saturated aqueous NaCl, dried, and evaporated. The residue was chromatographed on silica gel (2.4 g) with 4:1 hexane-ethyl acetate to afford **4** (45.1 mg, 92%): colorless syrup, R_f=0.43 (4:1 hexane-ethyl acetate); $[\alpha]_D^{26}$ +11.3° (c 1.28); ^{1}H NMR (250 MHz) δ=0.89 (9H, s, *t*-Bu), 1.36, 1.37 (each 6H each s, 2×CMe$_2$), 1.43—1.93 (10H, m, 2×H-2, 2×H-4, 2×H-6, 2×H-7, 2×H-10), 3.39 (3H, s, OMe), 3.30—4.22 (13H, m, 2×H-1, H-3, 5, 8, 9, 11, 2×H-12, -OCH$_2$CH$_2$O-), and 4.80 (2H, s, -OCH$_2$O-).

Found: C, 50.20; 8.04%. Calcd for $C_{28}H_{55}O_8SiI$: C, 49.84; H, 8.22%.

(2*S*,4*R*,5*R*,8*R*,10*S*)-1,2-Anhydro-12-*O*-*t*-butyldimethylsilyl-4,5:8,10-di-*O*-isopropylidene-1,2,4,5,8,10,12-dodecaneheptol (5). A mixture of **43** (24.2 mg, 0.051 mmol), triphenylphosphine (29.3 mg, 0.112 mmol), molecular sieves 3A powder (242 mg) and benzene (1.21 ml) was vigorously stirred at 85 °C for 10 min, and DEAD (17.6 μl, 0.112 mmol) was added dropwise to the mixture. After being stirred at 85 °C for 4 d, the cold reaction mixture was filtered through a sintered-glass funnel and filter cake was washed with benzene (5×1.0 ml). The combined filtrate and washings were evaporated. The residue was flushchromatographed on silica gel (2.3 g) with 4:1 hexane-ethyl acetate to give **5** (16.3 mg, 70%): colorless syrup, R_f=0.50 (4:1 hexane-ethyl acetate) $[\alpha]_D^{30}$ +8.4°, $[\alpha]_{365}^{30}$ +21.5° (*c* 1.05); ^{1}H NMR (90 MHz) δ=0.89 (9H, s, *t*-Bu), 1.36, 1.39 (each 6H, each s, 2×CMe$_2$), 1.20—2.00 (10H, m, 2×H-3, 2×H-6, 2×H-7, 2×H-9, 2×H-11), 2.53 (1H, dd, H-1, $J_{1,2}$=2.7 Hz, J_{gem}=5.1 Hz), 2.77 (1H, dd, H-1), 3.0—3.3 (1H, m, H-2), and 3.40—4.20 (6H, m, H-4,5,8,10).

Found: C, 62.89; H, 9.63%. Calcd for $C_{24}H_{46}O_6Si$: C, 62.84; H, 10.11%.

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