An Enantiospecific Synthesis of the C-21–C-37 Segment of the Aglycon of Amphotericin B†

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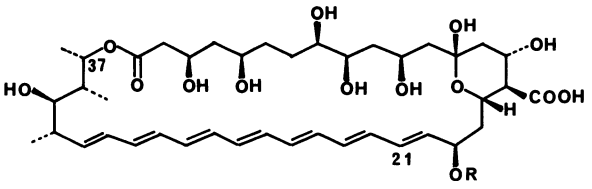
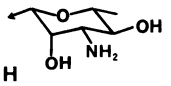
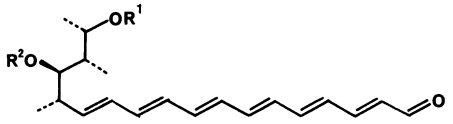
3-Deoxy-1,2-*O*-isopropylidene-3-*C*-methyl-α-D-allofuranose was stereoselectively converted into 3,5-dideoxy-4-*O*-(methoxymethyl)-3,5-di-*C*-methyl-6-*O*-pivaloyl-L-talose ethylene dithioacetal (**31**) via 3,5-dideoxy-4-*O*-(methoxymethyl)-3,5-di-*C*-methyl-L-talopyranuro-6,2-lactone ethylene dithioacetal (**24**) in 10 steps (23.6% overall yield). Desulfurization [Raney Ni W-4, 92% yield] of **31** followed by three-step transformation (91% yield) afforded 2,4,6-trideoxy-5-*O*-(diethylisopropylsilyl)-3-*O*-(methoxymethyl)-2,4-di-*C*-methyl-L-altrose, which was olefinated by using methyl (2*E*,4*E*)-6-(dimethoxyphosphinyl)-2,4-hexadienoate twice to give the target compound, all-*trans*-hexaenal **4** (12 steps, 38.6% overall yield from **31**).

Amphotericin B (**1**),[1] produced by *Streptomyces nodosus*, is the only member of the polyene antibiotic group which is widely used for treatment of the "deep seated" systemic fungal infections and the only polyene macrolide whose absolute structure is firmly established by X-ray crystallographic analysis.[2] Though the extremely difficult problem to isolate the free type of aglycon **2** from natural amphotericin B still remains unsolved, many synthetic approaches toward construction of such aglycon molecule have so far been reported.[3] The preparation in a protected



1, R = 

2, R = H



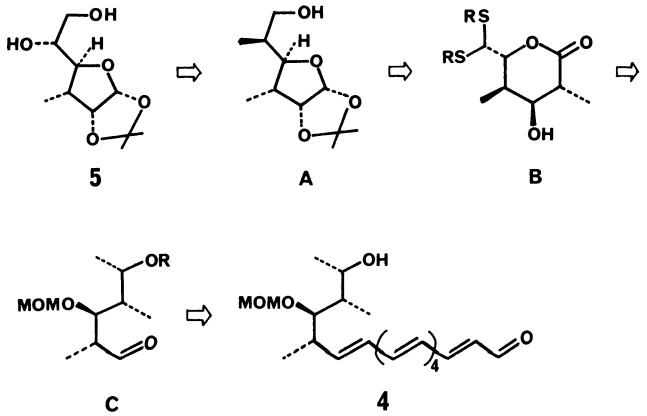
3a R¹ = TES, R² = TBS
3b R¹ = MEM, R² = TBS
3c R¹ = H, R² = TBS
4 R¹ = H, R² = MOM

TBS = *t*-Bu-Si(Me)(Me)-, TES = Et_3Si-, MEM = $MeOCH_2CH_2OCH_2$-
MOM = $MeOCH_2$-

form of **2** (or its C-13 epimer) from naturally derived C-1–C-20 and C-21–C-37 segments has recently been announced by Nicolaou et al.[4] As can be seen in some of these synthetic approaches, the C-21–C-37 segments **3a**,[3l] **3b**,[3m] and **3c**[4] have already been enantiospecifically synthesized from chiral carbon sources other than carbohydrates. In our studies directed toward the total synthesis of amphotericin B (**1**), general plan for synthesis of the free aglycon **2** which was considered to be a synthetic precursor of **1**, required **4** as the C-21–C-37 synthetic segment of **2** (Scheme 1). This strategic segment was expected to be synthesized enantiospecifically from carbohydrate. In this paper, we wish to describe a synthesis of **4** from D-glucose.

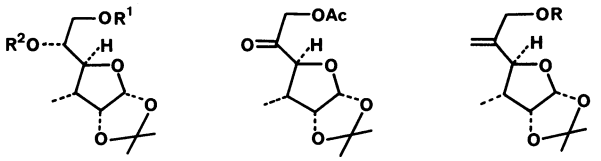
The synthetic plan as broadly outlined in Scheme 1 was devised by considering that the key intermediate **B** (whose absolute stereochemistry at C-2, C-3, and C-4 correlates to that at C-17, C-16, and C-15, respectively, of **4**) is obtainable from the known sugar derivative **5**,[5] and the formation of a new chiral center (corresponding to C-14, the last asymmetric carbon atom in **4**) on C-5 of **B** should be possible by asymmetric conversion[6] of **5** into **A** which is a precursor of **B**. The synthetic route to **C** via the lactone **B** from **A** should be indispensable for the regioselective *O*-methoxymethylation toward the C-3 hydroxyl group of **C**. The successful pursuit of the basic elements of this synthetic plan forms the topic of this report.

The starting diol **5**,[5] which was obtainable in large scale from 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose in 41% yield, was acetylated with acetic anhydride and triethylamine in dichloromethane to afford an 85% yield of a ca. 10:1 mixture of the monoacetates **6a** and **6b**, and a 6.4% yield of the diacetate **6c** after chromatographic isolation through a



Scheme 1.

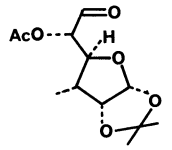
† A part of this paper was read at the 52nd National Meeting of the Chemical Society of Japan, Kyoto, April 1986, Abstr., No. 4N06.



5 $R^1 = R^2 = H$
6a $R^1 = Ac$, $R^2 = H$
6b $R^1 = H$, $R^2 = Ac$
6c $R^1 = R^2 = Ac$

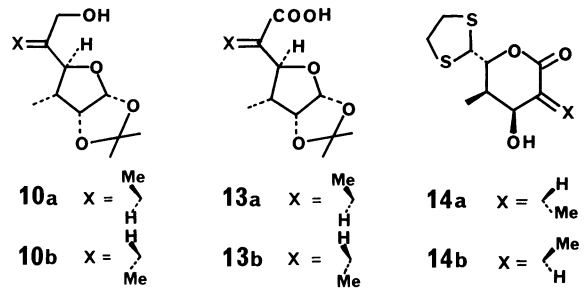
7a

8 R = Ac
9 R = H



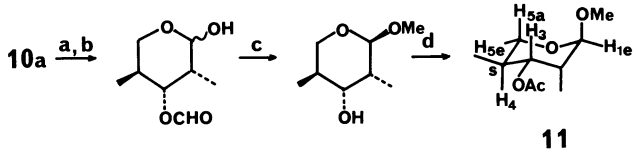
7b

short silica-gel column. Since the preparative separation of the desired acetate **6a** from the minor regioisomer **6b** by column chromatography was impracticable, the mixture was directly oxidized with pyridinium chlorochromate (PCC) and molecular sieves 3A powder[7] to give the chromatographically separable ketone **7a** and the aldehyde **7b** in 87.9 and 8.9% yields, respectively. Wittig methylenation[8] of **7a** with methylenetriphenylphosphorane in ether afforded a 71.5% yield of **8** and 5.4% yield of **9**. Treatment of **8** with methanolic sodium hydroxide provided **9** in 97% yield; the total yield of **9** from **5** amounted to 55.8%. Homogeneous hydrogenation of **9** with 0.2 molar equivalents of tris(triphenylphosphine)chlororhodium (I) in benzene gave a 2.3 : 1 mixture of **10a** and **10b** in 95% yield. Because the preparative separation of **10a**



10a X = Me/H
10b X = H/Me
13a X = Me/H
13b X = H/Me
14a X = H/Me
14b X = Me/H

from its epimer **10b** was not practicable in this stage, the separation had to be carried over to the later synthetic step. The isomeric ratio was assumed based on the intensities of the double-doublet signals due to the H-4 protons at δ 3.91 (**10a**) and δ 3.72 (**10b**) in the 250 MHz ^{1}H NMR spectrum of the mixture. The configuration at C-5 of the isolated major isomer **10a** was assigned as (*S*) by the following fashions: (a) The product **10a** was converted into **11** in four steps (Scheme 2). The ^{1}H NMR spectrum of **11** showed



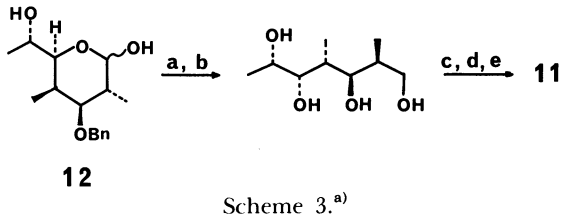
Scheme 2.[a]

a) (a) 1 M HCl, rt, 5 h, 91%; (b) $NaIO_4$, 1:1 Me_2CO–H_2O, rt, 1 h, ca. 100%; (c) 0.15 M HCl–MeOH, rt, 1 h, α-anomer (68%); (d) Ac_2O, DMAP, py, rt, 1 h, 97%.

signals in line with the depicted structure with 4(*S*) configuration (see Experimental section). (b) The compound **11** proved to be identical spectroscopically and chromatographically with an authentic sample of **11** which was derived from the known sugar derivative **12**[9] by the sequence of reactions shown in Scheme 3.

The low stereoselectivity (**10a** : **10b**=2.3 : 1) in the hydrogenation of **9** may suggest that the difference in free energy between the possible transition states **I** and **II** (Scheme 4) corresponding to **10a** and **10b** should be very small. This result prompted us to examine the homogeneous hydrogenation of the 1,6-anhydro-derivative **15** whose rigid conformation in the ground state may be similar to that in the transition state **I**. The compound **15** could be obtained by exposure of **9** to 50% aqueous trifluoroacetic acid[6b] in 13% yield. Though direct hydrogenation of **15** could not be accomplished, its silyl ether **16** was smoothly hydrogenated with rhodium catalyst to afford **17** as a sole reduction product, which was identical with a sample of **17** derived from **10a** via **18**. This highly stereoselective hydrogenation process, however, could not be utilized in the asymmetric conversion of **9** into **B**(**14a**), because of the low yield of **15** and of undesired elongation of the synthetic route by this process.

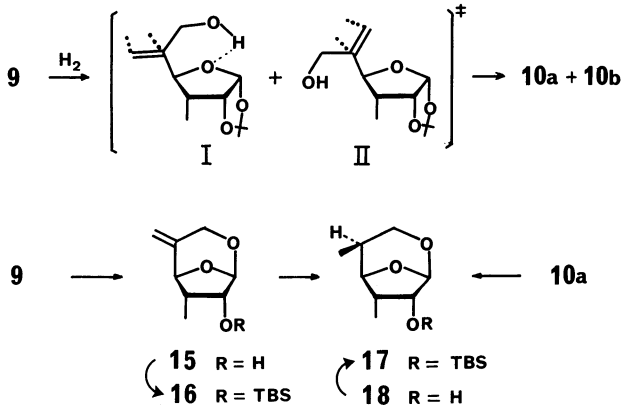
Chromium trioxide oxidation[10] of the mixture of **10a** and **10b** provided in 98.5% yield a mixture of the carboxylic acids **13a** and **13b**, which were quite difficult to separate each other. Dithioacetalization of the mixture with 1,2-ethanedithiol and boron trifluoride etherate afforded the chromatographically separable epimeric lactones **14a** and **14b** in 46.9 and 23.4% yields, respectively. The major lactone **14a** proved to correspond to **10a** by transformation of the isolated **10a** into **14a**.



12

Scheme 3.[a]

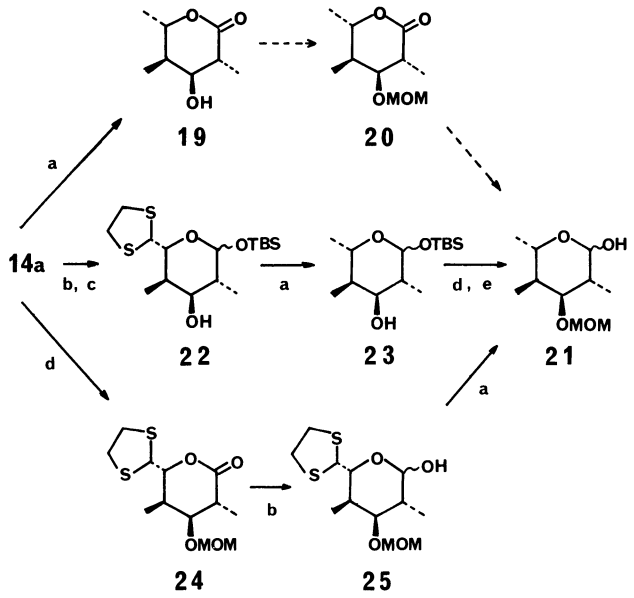
a) (a) H_2/Pd, MeOH; (b) $NaBH_4$, H_2O, rt, 1 h; (c) $NaIO_4$, 1:1 Me_2CO–H_2O, rt, 0.5 h; (d) 0.15 M HCl–MeOH, rt, 15 min, α:β=10:1; (e) Ac_2O, Py, rt.



15 R = H
16 R = TBS
17 R = TBS
18 R = H

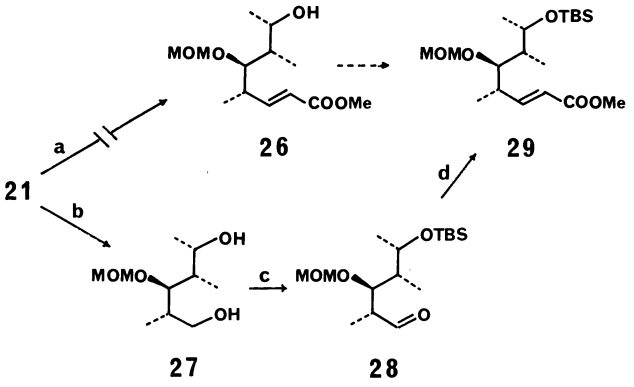
Scheme 4.

Direct desulfurization of the thioacetal group of **14a** with Raney Ni W-4 in methanol yielded only a 20% yield of **19**. Therefore, the first route to **21** via **20** from **14a** was not practicable (Scheme 5). The second route to **21** from **14a** was successful as follows. Reduction of **14a** with diisobutylaluminium hydride (DIBAL) followed by selective *t*-butyldimethylsilylation gave **α-22** (α-anomer) and **β-22** (β-anomer) in 34.8 and 43.5% yields, respectively. Desulfurization of **α-22** and **β-22** with Raney Ni W-4 in methanol afforded smoothly the corresponding **α-23** and **β-23** in 89.8 and 85.1% yields. Methoxymethylation of **α-23** and **β-23** followed by desilylation gave **21** in 96 and 99% yields, respectively. In the third route to **21**, methoxymethylation of **14a** afforded in 98% yield **24** which was treated with DIBAL to give **25** in good yield. However, desulfurization of **25** provided **21** in unsatisfactory yield (44%). The desulfurization reactions of **14a**, **22**, and **25** were carried out with irradiation in the water bath of an ultrasound laboratory cleaner. The TLC inspection of the reaction mixtures showed that, in all cases, no starting material could be detected in the supernatant layer after ultrasonic irradiation for 0.5—1 h, while at that time, only the spot of desulfurized product was observed. The precipitated nickel residue was thoroughly extracted with methanol in twenty times to provide an additional amount of product in almost pure state. The reason the desulfurizations of **14a** and **25** resulted in low yields is now indefinable.



Scheme 5.[a)]

a) (a) Raney Ni W-4, MeOH; (b) DIBAL, PhMe, −78°C; (c) TBSCl, imidazole, DMF; (d) MOMCL, *i*-Pr_2NEt, DMF; (e) *n*-Bu_4NF, THF.

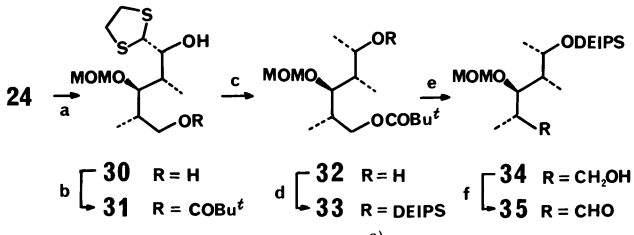


Scheme 6.[a)]

a) (a) Ph_3P=CHCOOMe, PhMe, 90°C, 24 h, (b) $NaBH_4$, 2:1 MeOH-H_2O, rt, 0.5 h, ca. 100%; (c) (1) *t*-BuCOCl, py, rt, 20 h, 69%; (2) TBSCl, imidazole, DMF, 35°C, 1 h, 99%; (3) MeLi, ether, rt, 0.5 h, 92%; (4) $(COCl)_2$, CH_2Cl_2, DMSO (−60°C), Et_3N (−25°C), 98%; (d) Ph_3P=CHCOOMe, PhMe, 90°C, 1 h, 90%.

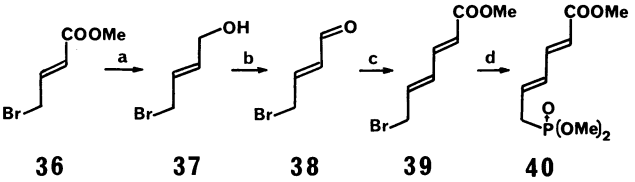
Having thus prepared the hemiacetal **21** which contains entire chiral sequence of **4** in the proper absolute configuration, we turned our attention to the facile transformation of **21** into **4**. The first attempt to convert **21** through direct Wittig olefination into a model intermediate **29** failed, because the condensation of **21** and (methoxycarbonylmethylene)triphenylphosphorane (or trimethyl phosphonoacetate) afforded no desired product **26**. The compound **29**, therefore, had to be prepared from **21** via the diol **27** and the free aldehyde **28** (Scheme 6). The overall yield of **28** from **14a** was 40.9%.

In keeping with these experimental results, the last and more facile synthetic route to **35** (equivalent to **28**) from **24** was pursued (Scheme 7). Lithium aluminium hydride reduction of **24** afforded the alcohol **30** in almost quantitative yield, which was selectively 6-*O*-pivaloylated to give **31** in 96.5% yield. Desulfurization of **31** with Raney Ni W-4 in methanol yielded **32** in 91.6% yield. *O*-Silylation of **32** with diethylisopropylsilyl chloride[11] in the presence of imidazole followed by depivaloylation of the resulting **33** with methyllithium in ether, afforded **34** in almost quantitative yield, which was subjected to Swern oxidation[12] to give the aldehyde **35** in 92% yield. The overall yield of **35** from



Scheme 7.[a)]

a) (a) $LiAlH_4$, THF, rt, 1 h; (b) *t*-BuCOCl, Py, rt, 3 h; (c) Raney Ni W-4, MeOH, 0.5 h; (d) DEIPSCl, imidazole, DMF, rt, 0.5 h; (e) MeLi, ether, rt, 0.5 h; (f) $(COCl)_2$, CH_2Cl_2, DMSO, Et_3N.



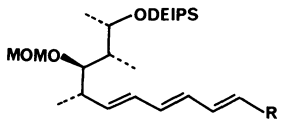
Scheme 8.[a)]

a) (a) DIBAL, PhMe, −78°C, 0.5 h, ca. 100%; (b) MnO_2, CH_2Cl_2, rt, 1 h, 88%; (c) Ph_3P=CHCOOMe, PhMe, 90°C, 2 h, 70.5%; (d) $(MeO)_3P$, 120—130°C, 3 h, 88%.

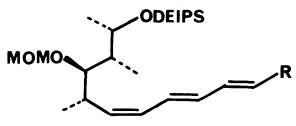
14a was 79.2%.

Having effectively arrived at the key intermediate **35**, the task remained to complete a synthesis of **4** was effective elaboration of **35** to all-*trans*-hexaenal **49**. After many unsuccessful attempts, the effective construction of **49** from **35** was achieved by the repeated Wittig-type olefination procedure using methyl (2*E*,4*E*)-6-(dimethoxyphosphinyl)-2,4-hexadienoate (**40**). The preparation of **3c** by the similar olefination procedure using ethyl (2*E*,4*E*)-6-(diethoxyphosphinyl)-2,4-hexadienoate instead of **40**, have recently been reported by Nicolaou et al.[4] after our work had been completed.

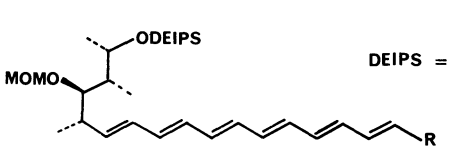
A facile preparation of the reagent **40** starting from methyl 4-bromocrotonate (**36**) was first accomplished as detailed in Scheme 8. Condensation of **35** with the lithio derivative of **40** which was prepared by treatment of **40** with lithium diisopropylamide(LDA) in THF afforded a 1:2 mixture of the (2*E*,4*E*,6*E*)-trienoic ester **41** and its (6*Z*)-isomer **42** in 99.7% yield. The mixture was then isomerized[13] with 0.01 molar equivalent of iodine in dichloromethane to give a ca. 8:1 mixture of **41** and **42** in almost quantitative yield. Reduction of this mixture with DIBAL followed by oxidation of the resulting mixture of the allylic alcohol **43** and its (6*Z*)-isomer **44** with manganese dioxide, afforded after chromatographic isomeric separation, the (2*E*,4*E*,6*E*)-trienal **45** and its (6*Z*)-isomer **46** in 70 and 13% overall yields from **35**, respectively. The olefinic structures of **41**, **42**, **45**, and **46** were confirmed by ^{1}H NMR spectroscopy. It is noteworthy that the iodine-catalyzed isomerization of **46** to **45** is not practicable, because the reaction proceeds with considerable decomposition of both **45** and **46**.



41 R = COOMe
43 R = CH_2OH
45 R = CHO

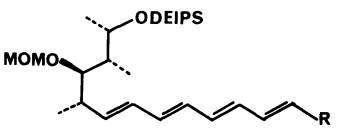


42 R = COOMe
44 R = CH_2OH
46 R = CHO



DEIPS = i-Pr-Si(Et)-Et

47 R = COOMe
48 R = CH_2OH
49 R = CHO



50 R = COOMe
51 R = CHO

The isolated **45** was again coupled with lithium derivative of **40** to give the pure all-*trans*-hexaenoic ester **47** in 96.2% yield as the only detectable product. DIBAL reduction of **47** followed by manganese dioxide oxidation of the resulting allylic alcohol **48** afforded the all-*trans*-hexaenal **49** in 73.5% overall yield. Finally, exposure of **49** to a 1M[††] solution of tetrabutylammonium fluoride in THF led to **4** in 96.8% yield. The *O*-diethylisopropylsilyl protecting group in **49** could be removed more smoothly than the *O*-*t*-butyldimethylsilyl group. The structures of **49** and **4** were confirmed[14] by their 250 MHz ^{1}H NMR spectra.

Experimental

Melting points were determined on a micro hot-stage Yanaco MP-S3 and were uncorrected. IR spectra were recorded on a Hitachi Perkin-Elmer 225 spectrometer, UV spectra on a JAS·CO UVIDEC-1 spectrometer, and ^{1}H NMR spectra in $CDCl_3$ using TMS as the internal standard on either a Varian EM-390 or a Bruker WM 250 spectrometer. Optical rotations were measured on a JAS·CO DIP-360 photoelectric polarimeter in chloroform. TLC was carried out on Merck TLC plates (60F-254, 0.25 mm). 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.

Acetylation of Diol 5. A mixture of **5**[5] (10.1 g, 46.4 mmol), acetic anhydride (5.30 ml, 55.6 mmol), and triethylamine (7.80 ml, 55.6 mmol) in dichloromethane (101 ml) was stirred at room temperature for 4 h, after which period ethanol (3.30 ml) was added and stirring was continued for 0.5 h. The reaction mixture was then evaporated and the residue was coevaporated with ether to a yellow syrup (18.3 g), which was chromatographed on silica gel (600 g) with 2:1 toluene-ethyl acetate to afford a mixture of **6a** and **6b** (10.2 g, 85%) and **6c** (0.90 g, 6.4%) as syrups. The mixture of **6a** and **6b** was used for the next step without further purification. Pure samples of **6a** (0.27 g) and **6b** (0.02 g) were obtained from a sample of the mixture (0.42 g) by flash chromatography on silica gel (42 g) with 2:3 toluene-ethyl acetate.

6a: R_f=0.36 (1:1 toluene-ethyl acetate); $[\alpha]_D^{27}$ +32° (*c* 1.00); IR($CHCl_3$) 1740 and 1230 cm^{-1}; ^{1}H NMR (90 MHz) δ=1.17 (3H, d, 3-Me, *J*=6.6 Hz), 1.36 and 1.53 (each 3H, each s, CMe_2), 1.7—2.0 (1H, m, H-3), 2.12 (3H, s, OAc), 2.53 (1H, d, OH, *J*=3.9 Hz), 3.8—4.3 (4H, m, H-4,5, 2×H-6), 4.57 (1H, t, H-2, *J*=3.9 Hz), and 5.78 (1H, d, H-1, *J*=3.9 Hz).

Found: C, 55.23; H, 7.71%. Calcd for $C_{12}H_{20}O_6$: C, 55.37; H, 7.74%.

6b: R_f=0.33 (1:1 toluene-ethyl acetate); ^{1}H NMR(90 MHz) δ=1.13 (3H, d, 3-Me, *J*=6.6 Hz), 1.33 and 1.51 (each 3H, each s, CMe_2), 2.12 (3H, s, OAc), 1.8—2.4 (2H, m, H-3, OH), 3.8—4.1 (3H, m, H-4 and 2×H-6), 4.55 (1H, t, H-2, *J*=4.5 Hz), 4.8—5.1 (1H, m, H-5), and 5.79 (1H, d, H-1, *J*=4.5 Hz).

6c: R_f=0.67 (1:1 toluene-ethyl acetate); $[\alpha]_D^{17}$ +53° (*c* 0.99); IR ($CHCl_3$) 1740 and 1230 cm^{-1}; ^{1}H NMR (90 MHz) δ=1.12 (3H, d, 3-Me, *J*=6.0 Hz), 1.31 and 1.50 (each 3H, each s, CMe_2), 1.7—2.0 (1H, m, H-3), 2.03 and 2.08 (each 3H, each s, 2×OAc), 3.91 (1H, dd, H-4, *J*=5.1 and 9.6 Hz), 4.20 (1H,

[††] 1 M=1 mol dm^{-3}.

dd, H-6, J=7.2, 12.0 Hz), 4.43 (1H, dd, H-6′, J=4.2, 12.0 Hz), 4.53 (1H, t, H-2, J=4.2 Hz), 5.1—5.3 (1H, m, H-5), and 5.75 (1H, d, H-1, J=4.2 Hz).

Found: C, 55.36; H, 7.30%. Calcd for $C_{14}H_{22}O_7$: C, 55.62; H, 7.33%.

6-*O*-Acetyl-3-deoxy-1,2-*O*-isopropylidene-3-*C*-methyl-α-D-*ribo*-5-hexulofuranose (7a) and 5-*O*-Acetyl-3-deoxy-1,2-*O*-isopropylidene-3-*C*-methyl-α-D-allodialdo-1,4-furanose (7b). To a stirred mixture of PCC (22.3 g, 0.10 mol), molecular sieves 3A powder (34.5 g), and dichloromethane (86 ml) was added a solution of the mixture of **6a** and **6b** (8.98 g, 34.5 mmol) in dichloromethane (50 ml) at room temperature over a period of 15 min. After being stirred at room temperature for 1 h, the reaction mixture was diluted with ether (140 ml) and filtered through a column filled with silica gel (230 g). Evaporation of the eluates left a syrupy residue (8.90 g) which was chromatographed on silica gel (600 g) with 2:1 toluene-ethyl acetate to afford **7a** (7.83 g, 87.9%) and **7b** (0.75 g, 8.4%).

7a: Colorless plates, mp 72—74 °C (ethyl acetate-hexane); R_f=0.66 (3:2 toluene-ethyl acetate); $[\alpha]_D^{27}$ −40° (c 1.01); IR (KBr) 1760, 1730, and 1240 cm^{-1}; ^{1}H NMR (90 MHz) δ=1.19 (3H, d, 3-Me, J=6.6 Hz), 1.35 and 1.51 (each 3H, each s, CMe_2), 2.16 (3H, s, OAc), 2.0—2.4 (1H, m, H-3), 4.20 (1H, d, H-4, J=10.8 Hz), 4.58 (1H, t, H-2, J=3.3 Hz), 4.77 and 5.07 (2H, ABq, 2×H-6, J=18.0 Hz), and 5.90 (1H, d, H-1, J=3.3 Hz).

Found: C, 55.52; H, 6.91%. Calcd for $C_{12}H_{18}O_6$: C, 55.81; H, 7.02%.

7b: Pale yellow syrup, R_f=0.46 (3:2 toluene-ethyl acetate); ^{1}H NMR (90 MHz) δ=1.11 (3H, d, 3-Me, J=6.9 Hz), 1.33 and 1.54 (each 3H, each s, CMe_2), 2.21 (3H, s, OAc), 1.9—2.5 (1H, m, H-3), 4.14 (1H, dd, H-4, J=3.6, 11.1 Hz), 4.53 (1H, t, H-2, J=4.5 Hz), 5.05 (1H, d-like, H-5), 5.72 (1H, d, H-1, J=4.5 Hz), and 9.53 (0.4H, s-like, CHO).

6-*O*-Acetyl-3,5-dideoxy-1,2-*O*-isopropylidene-3-*C*-methyl-5-*C*-methylene-α-D-*ribo*-hexofuranose (8) and 3,5-Dideoxy-1,2-*O*-isopropylidene-3-*C*-methyl-5-*C*-methylene-α-D-*ribo*-hexofuranose (9). A 4 M solution of methylsulfinylmethanide anion in DMSO (9.87 ml, 39.5 mmol) prepared from sodium hydride and DMSO,[8] was added dropwise to a stirred suspension of methyltriphenylphosphonium bromide (14.1 g, 39.5 mmol) in dry ether (188 ml) under argon at room temperature. The mixture was stirred at room temperature for 10 min and then to the resulting yellow suspension of ylide was added dropwise a solution of **7a** (4.08 g, 15.8 mmol) in dry ether (94 ml). After the mixture had been stirred at room temperature for 0.5 h, the reaction mixture was poured into an ice-water mixture, which was extracted with ether (3×250 ml). The organic layer was washed with saturated aqueous NaCl, dried, and evaporated. The residue (8.71 g) was chromatographed on silica gel (600 g) with 3:1 hexane-ethyl acetate to afford **8** (2.89 g, 71.5%) and **9** (0.22 g, 5.4%).

8: R_f=0.57 (3:2 hexane-ethyl acetate); IR ($CHCl_3$) 3010, 1740, 1210, and 1020 cm^{-1}; $[\alpha]_D^{25}$ +17° (c 0.99); ^{1}H NMR (90 MHz) δ=1.05 (3H, d, 3-Me, J=7.2 Hz), 1.34 and 1.52 (each 3H, each s, CMe_2), 2.07 (3H, s, OAc), 1.8—2.1 (1H, m, H-3), 4.20 (1H, d, H-4, J=10.8 Hz), 4.53 (1H, t, H-2, J=4.2 Hz), 4.60 (2H, s, 2×H-6), 5.2—5.3 (2H, m, $=CH_2$), and 5.77 (1H, d, H-1, J=4.2 Hz).

Found: C, 60.65; H, 7.63%. Calcd for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87%.

Preparation of 9 from 8. To a solution of **8** (2.71 g, 10.6 mmol) in methanol (32 ml) was added a solution of NaOH (0.64 g) in methanol (16 ml), and stirred at room temperature for 1 h. After being neutralized (pH 7) with CO_2 gas, the reaction mixture was dilluted with water (30 ml), and extracted with chloroform (3×30 ml). The organic layers were washed with a saturated aqueous NaCl solution, dried, and evaporated. The residue (2.62 g) was chromatographed on silica gel (150 g) with 3:2 hexane-ethyl acetate to afford **9** (2.20 g, 97%) as a syrup.

9: R_f=0.28 (3:2 hexane-ethyl acetate); $[\alpha]_D^{27}$ +7.5° (c 0.99); IR ($CHCl_3$) 3510, 3010, and 1020 cm^{-1}; ^{1}H NMR (90 MHz) δ=1.04 (3H, d, 3-Me, J=6.6 Hz), 1.35 and 1.54 (each 3H, each s, CMe_2), 1.8—2.3 (2H, m, H-3, OH), 4.1—4.4 (3H, m, H-4, 2×H-6), 4.60 (1H, t, H-2, J=4.2 Hz), 5.16 and 5.27 (each 1H, each s, $=CH_2$), and 5.84 (1H, d, H-1, J=4.2 Hz).

Found: C, 61.80; H, 8.24%. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47%.

3,5-Dideoxy-1,2-*O*-isopropylidene-3,5-di-*C*-methyl-α-L-talofuranose (10a) and D-allo Epimer (10b). A solution of **9** (2.30 g, 10.7 mmol) and tris(triphenylphosphine)chlororhodium(I) (1.99 g, 2.15 mmol) in benzene (115 ml) was stirred under an atmospheric pressure of hydrogen at room temperature for 4 h. The reaction mixture was then evaporated and the residue was passed through Florisil (100—200 mesh, 160 g) with ether to afford a pale yellow syrup after evaporation of the solvent, a mixture of **10a** and **10b** (2.20 g, 95%). This sample was utilized without further purification in the subsequent transformation. Part of this syrup was flash chromatographed on silica gel with 1:1 hexane-ethyl acetate to give pure **10a** and **10b**.

10a: R_f=0.49 (1:1 hexane-ethyl acetate); $[\alpha]_D^{26}$ +45° (c 0.54); ^{1}H NMR (90 MHz) δ=0.90 and 1.04 (each 3H, each d, 3 and 5-Me, J=6.9 and 7.2 Hz), 1.32 and 1.49 (each 3H, each s, CMe_2), 1.7—2.0 (2H, m, H-3, 5), 2.52 (1H, br-s, OH), 3.64 (2H, d, after addition of D_2O, 2×H-6, J=6.0 Hz), 3.91 (1H, dd, H-4, $J_{4,5}$=2.4, $J_{4,3}$=9.9 Hz), 4.51 (1H, t, H-2, $J_{2,1}$=$J_{2,3}$= 3.6 Hz), and 5.72 (1H, d, H-1).

Found: C, 60.90; H, 9.17%. Calcd for $C_{11}H_{20}O_4$: C, 61.09; C, 9.32%.

10b: R_f=0.47 (1:1 hexane-ethyl acetate); $[\alpha]_D^{27}$ +12° (c 1.00); ^{1}H NMR (90 MHz) δ=1.06 and 1.10 (each 3H, each d, 3 and 5-Me, J=7.2, 6.9 Hz), 1.33 and 1.51 (each 3H, each s, CMe_2), 1.7—2.1 (2H, m, H-3,5), 2.5—2.7 (1H, m, OH), 3.63 (2H, d, 2×H-6, J=4.8 Hz), 3.72 (1H, dd, H-4, $J_{4,5}$=5.1, $J_{4,3}$=9.9 Hz), 4.54 (1H, t, H-2, $J_{2,1}$=$J_{2,3}$=3.9 Hz), and 5.76 (1H, d, H-1).

Found: C, 61.17; H, 9.15%. Calcd for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32%.

Methyl 3-*O*-Acetyl-2,4-dideoxy-2,4-di-*C*-methyl-α-L-lyxopyranoside (11). (A) From **12**: A solution of **12**[9] (70.8 mg) in methanol (1.4 ml) was stirred with Pd-black under bubbling with H_2 gas at 25 °C for 2.5 h, and the suspension was filtered. The filtrate was evaporated to a colorless syrup (52 mg) of debenzylation product, which was treated with $NaBH_4$ (10 mg) in water (0.52 ml) at room temperature for 1 h. The reaction mixture was neutralized with CO_2 gas and evaporated. The residue was chromatographed on silica gel (5 g) with 3:1 chloroform-methanol to afford the crystalline tetrol (30.5 mg). To a solution of the tetrol (30.5 mg) in acetone (0.61 ml) was added a solution of $NaIO_4$ (32.4 mg) in water (0.72 ml) and the mixture allowed to stand at room temperature for 0.5 h. The mixture was extracted with

chloroform three times and then with ethyl acetate seven times. The combined extracts were dried and evaporated to give crude crystals of 2,4-dideoxy-2,4-di-*C*-methyl-L-lyxose (31 mg). A solution of the crystals (24.7 mg) in a 0.15M methanolic hydrogen chloride (0.49 ml) was allowed to stand at room temperature for 15 min. The reaction mixture was neutralized with saturated aqueous $NaHCO_3$, concentrated, and extracted with ethyl acetate. The dried extracts were evaporated to a syrup which was chromatographed on silica gel (2.7 g) with 8:1 benzene-acetone to afford the major anomer of methyl 2,4-dideoxy-2,4-di-*C*-methyl-L-lyxopyranoside [R_f=0.28 (8:1 benzene-acetone), 10.1 mg] and the minor anomer [R_f=0.37 (8:1 benzene-acetone), 0.9 mg]. The major anomer (9 mg) was acetylated with Ac_2O in dry pyridine and worked up by the usual way to give a crude syrup of **11**, which was chromatographed on silica gel (1 g) with 3:1 hexane-ethyl acetate to afford a pure sample of **11**: Colorless syrup, R_f=0.81 (1:1 hexane-ethyl acetate); $[\alpha]_D^{26}$ −35° (*c* 0.65); ^{1}H NMR (250 MHz) δ=0.85 and 0.97 (each 3H, each d, 2- and 4-Me, J=6.6 and 6.9 Hz), 1.9—2.3 (2H, m, H-2,4), 2.06 (3H, s, OAc), 3.36 (3H, s, OMe), 3.46 (1H, dd, H-5a, $J_{5a,4}$=10.0, $J_{5a,5e}$=11.5 Hz), 3.61 (1H, dd, H-5e, $J_{5e,4}$=5.0 Hz), 4.45 (1H, d, H-1, $J_{1,2}$=2.7 Hz), and 4.95 (1H, dd, H-3, $J_{2,3}$=4.8, $J_{3,4}$=9.0 Hz). (B) From **10a**: A solution of **10a** (166 mg) in 1M hydrochloric acid (1.7 ml) was allowed to stand at room temperature for 5 h. The reaction mixture was neutralized with saturated aqueous $NaHCO_3$, diluted with acetone, and evaporated. The residue was chromatographed on silica gel (17 g) with 5:1 chloroform-methanol to afford 3,5-dideoxy-3,5-di-*C*-methyl-L-idofuranose (123 mg, 91.2%). To a solution of the free sugar (19.2 mg) in acetone (0.38 ml) was added a solution of $NaIO_4$ (35 mg) in water (0.35 ml) and the mixture was stirred at room temperature for 1 h. The reaction mixture was extracted with ethyl acetate (3×2 ml). The extracts were washed with saturated aqueous NaCl, dried, and evaporated to a syrup (21.3 mg). The syrup (19.0 mg) was dissolved in 0.15M methanolic HCl (0.38 ml) and the solution was allowed to stand at room temperature for 1 h. The reaction mixture was neutralized (pH 8) with saturated aqueous $NaHCO_3$ and evaporated. The residue was taken with ethyl acetate (2.0 ml), which was washed with saturated aqueous NaCl, dried, and evaporated to a pale yellow syrup (30 mg). This syrup was chromatographed on silica gel (2.0 g) with 8:1 benzene-acetone to afford two syrupy anomers of methyl 2,4-dideoxy-2,4-di-*C*-methyl-L-lyxopyranoside: Major anomer [R_f=0.28 (8:1 benzene-acetone)], 11.9 mg; minor anomer [R_f=0.37 (8:1 benzene-acetone)], 5.3 mg. The major anomer (8.6 mg) was acetylated with Ac_2O (6.1 µl), DMAP (0.66 mg) in dry pyridine (86 µl) at room temperature for 1 h, and worked-up to afford a syrup which was chromatographed on silica gel (1 g) with 3:1 hexane-ethyl acetate to give a colorless syrup of **11** (10.5 mg); R_f=0.81 (1:1 hexane-ethyl acetate). This sample was identical in all respects with the sample of **11** described in (A).

1,6-Anhydro-3,5-dideoxy-3-*C*-methyl-5-*C*-methylene-β-D-*ribo*-hexofuranose (15). A solution of **9** (24.1 mg) in 50% aqueous trifluoroacetic acid (TFA)(0.24 ml) was kept at room temperature for 50 h and then neutralized with Amberlite IRA-45 resin. The resin was filtered and washed with methanol (3×5.0 ml). The combined filtrates were evaporated and the residue was chromatographed on silica gel (1.8 g) with 1:1 benzene-ethyl acetate to afford **15** (2.2 mg, 13%): mp 219—224 °C; R_f=0.40 (1:1 benzene-ethyl acetate); $[\alpha]_D^{25}$ −84° (*c* 0.39); ^{1}H NMR (90 MHz) δ=1.00 (3H, d, 3-Me, J=6.6 Hz), 1.58 (1H, br-s, OH), 2.5—2.8 (1H, m, H-3), 3.70 (1H, d, H-6, $J_{6,6'}$=9.0 Hz), 4.02 (1H, d, H-4, $J_{4,3}$=4.2 Hz), 4.35 (1H, d, H-6′), 4.90 (1H, d, H-2, $J_{2,3}$=9.3 Hz), 4.91 (1H, s, H-1), and 5.07 and 5.25 (each 1H, each s, $=CH_2$).

2-*O*-*t*-Butyldimethylsilyl Derivative (16). To a stirred solution of **15** (5.0 mg) in DMF (50 µl) was added imidazole (8.7 mg) and TBSCl (14.5 mg) at 0 °C. After being stirred at room temperature for 2 h, the reaction mixture was poured into cold water, which was extracted with ethyl acetate (3×1.0 ml). The extracts were washed with saturated aqueous NaCl, dried, and evaporated to a syrup (24.1 mg), which was chromatographed on silica gel (0.9 g) with 2:1 hexane-ethyl acetate to give colorless needles of **16** (8.3 mg, 95.8%): mp 139—144 °C; R_f=0.56 (20:1 benzene-ethyl acetate); $[\alpha]_D^{26}$ −29° (*c* 0.40); ^{1}H NMR (90 MHz) δ=0.8—1.0 (12H, m, *t*-Bu, 3-Me), 2.4—2.7 (1H, m, H-3), 3.63 (1H, d, H-6, $J_{6,6'}$=9.3 Hz), 3.93 (1H, d, H-4, $J_{4,3}$=3.9 Hz), 4.31 (1H, d, H-6′), 4.73 (1H, s, H-1), 4.84 (1H, d, H-2, $J_{2,3}$=9.6 Hz), and 5.03 and 5.20 (each 1H, each s, $=CH_2$).

1,6-Anhydro-3,5-dideoxy-3,5-di-*C*-methyl-α-L-talofuranose (18) and Its 2-*O*-*t*-Butyldimethylsilyl Derivative (17). A solution of **10a** (33.2 mg) in 75% aqueous TFA (0.33 ml) was kept at room temperature for 1 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ containing solid $NaHCO_3$. The mixture (pH=8) was saturated with NaCl and extracted with ethyl acetate. The extracts were dried and evaporated to a syrup which was chromatographed on silica gel (1.2 g) with 1:1 benzene-ethyl acetate to afford **18** (18.5 mg, 76.2%) as a colorless syrup; ^{1}H NMR (90 MHz) δ=0.70 (3H, d, 5-Me, J=6.9 Hz), 1.11 (3H, d, 3-Me, J=7.2 Hz), 1.62 (1H, br-s, OH), 2.2—2.5 (2H, m, H-3, 5), 3.25 (1H, dd, H-6, $J_{5,6}$=$J_{6,6'}$=10.8 Hz), 3.81 (1H, dd, H-6′, $J_{5,6'}$=6.3 Hz), 3.8—4.0 (1H, m, H-4), 4.37 (1H, d, H-2, $J_{2,3}$=7.5 Hz), and 5.15 (1H, s, H-1).

By the procedure described for the silylation of **15**, **18** (8.0 mg) obtained above was silylated to give **17** (11.6 mg, 84.4%) as a colorless syrup; R_f=0.47 (20:1 benzene-ethyl acetate); $[\alpha]_D^{27}$ −9.5° (*c* 0.37); ^{1}H NMR (90 MHz) δ=0.68 (3H, d, 5-Me, J=6.6 Hz), 0.91 (9H, s, *t*-Bu), 1.04 (3H, d, 3-Me, J=7.8 Hz), 2.1—2.5 (2H, m, H-3, 5), 3.24 (1H, dd, H-6, $J_{5,6}$=$J_{6,6'}$=11.7 Hz), 3.79 (1H, dd, H-6′, $J_{5,6'}$=6.3 Hz), 3.8—4.0 (1H, m, H-4), 4.35 (1H, d, H-2, $J_{2,3}$=7.2 Hz), and 5.03 (1H, s, H-1).

Homogeneous Hydrogenation of 16. By the procedure described for hydrogenation of **9**, **16** (4.5 mg) was hydrogenated with $(Ph_3P)_3RhCl$ (3.1 mg), to afford **17** (3.2 mg, 70.6%) after silica-gel column chromatography, by which no isomeric product was detected in the reduction product. The product **17** was identical with the sample of **17** derived from **10a** via **18** by TLC and ^{1}H NMR.

3,5-Dideoxy-1,2-*O*-isopropylidene-3,5-di-*C*-methyl-L-talofuranuronic Acid (13a) and D-allo Epimer (13b). Chromium trioxide (5.0 g, 49.9 mmol) was dissolved in a 30:1 mixture of acetic acid and pyridine (155 ml). This chromium oxidation reagent (142 ml, 45.8 mmol) was added to the aforesaid mixture of **10a** and **10b** (1.65 g, 7.63 mmol). After being stirred at room temperature for 15 h, the reaction mixture was poured into cold water (300 ml) which was extracted with chloroform (3×200 ml). The extracts were washed with saturated aqueous NaCl, dried, and evaporated. The residue was co-evaporated with ether repeatedly to a

syrup (2.60 g), which was chromatographed on silica gel (200 g) with 150:5:1 chloroform-methanol-acetic acid to afford a mixture of **13a** and **13b** (1.73 g, 98.5%). Analytical samples of **13a** and **13b** were obtained from pure samples of **10a** and **10b** by the procedure described above.

13a: Colorless syrup, R_f=0.53 (100:10:1 chloroform-methanol-acetic acid) $[\alpha]_D^{31}$ +18° (*c* 0.58); IR ($CHCl_3$) 3080 and 1710 cm^{-1}; ^1H NMR (90 MHz) δ=1.09 and 1.22 (each 3H, each d, 3 and 5-Me, *J*=7.2 and 7.8 Hz), 1.34 and 1.53 (each 3H, each s, CMe_2), 1.7—2.1 (1H, m, H-3), 2.5—2.7 (1H, m, H-5), 4.10 (1H, dd, H-4, *J*=5.4, 10.5 Hz), 4.54 (1H, t, H-2, *J*=3.6 Hz), 5.76 (1H, d, H-1, *J*=3.6 Hz), and 9.67 (1H, br-s, COOH).

Found: C, 57.12; H, 7.77%. Calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88%.

13b: Colorless needles, R_f=0.53 (100:10:1 chloroform-methanol-acetic acid); mp 110—114 °C (ethyl acetate-hexane); $[\alpha]_D^{30}$ +43° (*c* 0.84); IR(KBr) 3200 and 1730 cm^{-1}; ^1H NMR (90 MHz) δ=1.11 and 1.29 (each 3H, each d, 3-and 5-Me, *J*=7.2 and 7.8 Hz), 1.34 and 1.53 (each 3H, each s, CMe_2), 1.9—2.3 (1H, m, H-3), 2.6—2.9 (1H, m, H-5), 4.00 (1H, dd, H-4, *J*=4.5, 9.6 Hz), 4.57 (1H, t, H-2, *J*=3.6 Hz), 5.80 (1H, d, H-1, *J*=3.6 Hz), and 10.2 (1H, br-s, COOH).

Found: C, 57.28; H, 7.69%. Calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88%.

3,5-Dideoxy-3,5-di-*C*-methyl-L-talopyranurono-6,2-lactone Ethylene Dithioacetal (14a) and D-allo Epimer (14b). To an ice-cooled solution of a mixture of **13a** and **13b** (1.96 g, 8.51 mmol) in 1,2-ethaneditiol (19.6 ml) was added boron trifluoride etherate (0.59 ml) and the mixture was stirred at room temperature for 1 h. The reaction mixture was neutralized (pH 7) with 10% aqueous K_2CO_3, and extracted with ethyl acetate (3×50 ml). The extracts were washed with saturated aqueous NaCl, dried, and evaporated. The residue was chromatographed on silica gel (100 g) with 1:1 benzene-ethyl acetate to afford the mixture of **14a** and **14b** (1.52 g, 71.9%). The mixture was separated by flash chromatography on silica gel (200 g) with 3:2 benzene-ethyl acetate to give **14a** (0.87 g, 46.9%) and **14b** (0.49 g, 23.4%).

14a: Colorless plates, mp 113—114 °C (ethyl acetate-hexane); R_f=0.43 (1:1 hexane-ethyl acetate); $[\alpha]_D^{30}$ −42° (*c* 0.51); IR (KBr) 3400, 1700, and 1210 cm^{-1}: ^1H NMR (90 MHz) δ=1.13 and 1.36 (each 3H, each d, 3-and 5-Me, each *J*=6.9 Hz), 1.9—2.3 (1H, m, H-3), 2.72 (1H, dq, H-5, *J*=3.3 and 6.9 Hz), 2.73 (1H, br-s, OH), 3.1—3.7 (4H, m, SCH_2CH_2S), 3.76 (1H, t after addition of D_2O, H-4, *J*=3.0 Hz), 4.51 (1H, dd, H-2, $J_{2,1}$=1.8, $J_{2,3}$=9.0 Hz), and 4.73 (1H, d, H-1).

Found: C, 48.34; H, 6.50%. Calcd for $C_{10}H_{16}O_3S_2$: C, 48.36; H, 6.49%.

14b: Colorless needles, mp 115—119 °C (ethyl acetate-hexane); R_f=0.49 (1:1 hexane-ethyl acetate) $[\alpha]_D^{25}$ −36° (*c* 1.01); IR (KBr) 3460, 1710, and 1200 cm^{-1}; ^1H NMR (90 MHz) δ=1.17 and 1.33 (each 3H, each d, 3- and 5-Me, each *J*=6.9 Hz), 1.8—2.2 (1H, m, H-3), 2.23 (1H, br-s, OH), 2.63 (1H, dq, H-5, *J*=2.4 and 7.2 Hz), 3.0—3.6 (4H, m, SCH_2CH_2S), 3.83 (1H, br-s, H-4), 4.52 (1H, dd, H-2, $J_{2,1}$=1.8, $J_{2,3}$=10.2 Hz), and 4.74 (1H, d, H-1).

Found: C, 48.06; H, 6.40%. Calcd for $C_{10}H_{16}O_3S_2$: C, 48.36; H, 6.49%.

2,4,6-Trideoxy-3-*O*-(methoxymethyl)-2,4-di-*C*-methyl-L-altropyranose (21). To a cooled (−78 °C) solution of **14a** (171 mg, 0.689 mmol) in dry toluene (1.7 ml) was added a 1M solution of DIBAL in toluene (1.38 ml, 1.38 mmol) and stirred at −78 °C for 0.5 h. A 50% aqueous acetic acid solution (0.28 ml) was added to the reaction mixture which was stirred at −78 °C for 5 min and then warmed to room temperature. The mixture was filtered through a Celite and washed with acetone (3×5.0 ml). The organic layer was evaporated to afford a colorless syrup (175 mg). A mixture of this syrup (57.6 mg), TBSCl (52.0 mg), imidazole (31.3 mg), and dry DMF (0.58 ml) was stirred at room temperature for 3 h, and the mixture was poured into cold water, which was extracted with ethyl acetate (3×3.0 ml). The extracts were washed with saturated aqueous NaCl, dried, and evaporated to a syrup, which was chromatographed on silica gel (8.5 g) with 7:1 hexane-ethyl acetate to **α-22** (α-anomer, 29.2 mg), **β-22** (β-anomer, 36.5 mg), and di-*O*-TBS derivative (18.6 mg). A suspension of Raney Ni W-4 (0.3 g) in a solution of **α-22** (44.8 mg) in methanol (1.1 ml) was irradiated in the water bath of an ultrasound laboratory cleaner (65W, 48KHz) for 1 h. The supernatant layer was separated and the precipitate was extracted with methanol (20×0.5 ml). The combined extracts were evaporated to a colorless syrup (48 mg), which was chromatographed on silica gel (2.4 g) with 7:1 hexane-ethyl acetate to afford **α-23** (30.3 mg, 89.8%) as a colorless syrup. By the same way, **β-23** (31.6 mg, 81.1%) was obtained from **β-22** (49.3 mg). A mixture of **α-23** (31.8 mg), methoxymethyl chloride (70.4 μl), *N,N*-diisopropylethylamine (242 μl), and DMF (0.32 ml) was stirred at 50 °C for 6 h. The reaction mixture was poured into cold water, which was extracted with ethyl acetate (3×2.0 ml). The extracts were worked up to give a brown syrup, which was chromatographed on silica gel (2.6 g) with 6:1 hexane-ethyl acetate to afford the 3-*O*-methoxymethyl derivative of **α-23** (35.4 mg, 95.8%). By the same way, the corresponding β-anomer (30.1 mg, 98.6%) was obtained from **β-23** (26.3 mg). The combined α- and β-anomeric 3-*O*-methoxymethyl derivatives (65.1 mg) were treated with 2 equivalents of n-Bu_4NF in THF, and worked up to a syrup, which was chromatographed on silica gel (3.3 g) with 1:1 benzene-ethyl acetate to afford **21** (39 mg): Colorless syrup, ^1H NMR (90 MHz) δ=0.8—1.3 (9H, m, 3×Me), 1.5—1.9 (1H, m, H-4), 2.0—2.3 (1H, m, H-2), 3.40 (0.8H, s, β-OMe), 3.44 (2.2H, s, α-OMe), 3.5—3.7 (1H, m, H-3), 3.8—4.0 (0.3H, m, β-OH), 3.8—4.1 (1H, m, H-5), 4.59 and 4.74 (0.7H, ABq, OCH_2O (β), *J*=6.9 Hz), 4.63 and 4.77 (1.3H, ABq, OCH_2O (α), *J*=6.3 Hz), 4.84 (0.7H, d, H-1(α), *J*=9.9 Hz), 5.06 (0.7H, d, α-OH, *J*=9.9 Hz), and 5.1—5.3 (0.3H, m, H-1(β)).

3,5-Dideoxy-4-*O*-(methoxymethyl)-3,5-di-*C*-methyl-L-talopyranurono-6,2-lactone Ethylene Dithioacetal (24). To a solution of **14a** (248 mg, 0.99 mmol) in DMF (2.50 ml) was added *N,N*-diisopropylethylamine (0.87 ml, 4.99 mmol) and methoxymethyl chloride (0.30 ml, 3.99 mmol) at 0 °C. After being stirred at 60 °C for 10 h, the reaction mixture was poured into an ice-water mixture, which was extracted with ethyl acetate (3×5 ml). The extracts were washed with saturated aqueous NaCl, dried, and evaporated to a syrup (520 mg), which was chromatographed on silica gel (11 g) with 2:1 benzene-ethyl acetate to afford **24** (271 mg, 98.3%) as a colorless syrup: R_f=0.72 (1:1 benzene-ethyl aceta); $[\alpha]_D^{27}$ −25.9° (*c* 0.99); IR ($CHCl_3$) 1725 and 1030 cm^{-1}; ^1H NMR (90 MHz) δ=1.11 (3H, d, 3-Me, *J*=6.9 Hz), 1.34 (3H, d, 5-Me, *J*=7.5 Hz), 1.9—2.3 (1H, m, H-3), 2.84 (1H, dq, H-5, *J*=3.3, 7.5 Hz), 3.1—3.6 (4H, m, SCH_2CH_2S), 3.35 (3H, s, OMe), 3.59 (1H, t, H-4, *J*=3.3 Hz), 4.43 (1H, dd, H-2, *J*=2.1, 9.3 Hz), and 4.6—4.8 (3H, m, H-1, OCH_2O).

Found: C, 49.03; H, 6.87%. Calcd for $C_{12}H_{20}O_4S_2$: C, 49.29, H, 6.89%.

3,5-Dideoxy-4-*O*-(methoxymethyl)-3,5-di-*C*-methyl-L-talose Ethylene Dithioacetal (30). To a solution of **24** (288 mg, 1.04 mmol) in dry THF (4.30 ml) was added lithium aluminium hydride (790 mg, 2.08 mmol) at 0 °C. After being stirred at room temperature for 1 h, saturated aqueous NaCl was added to the reaction mixture until bubbling was stopped. Then, the mixture was filtered through a Celite and the filter cake was washed with acetone (5×7 ml). The filtrate and washings were evaporated and the residue was chromatographed on silica gel (20 g) with 1 : 1 benzene-ethyl acetate to afford **30** (297 mg, ca. 100%) as a colorless syrup: R_f=0.18 (1 : 1 benzene-ethyl acetate); $[\alpha]_D^{28}$ +34° (*c* 0.93); IR($CHCl_3$) 3460 and 1020 cm^{-1}; ^1H NMR (90 MHz) δ=0.89 and 1.00 (each 3H, each d, 3- and 5-Me, *J*=6.6 and 6.9 Hz), 1.8—2.4 (3H, m, H-3, H-5, OH), 2.8—3.1 (1H, m, OH), 3.2—3.4 (4H, m, SCH_2CH_2S), 3.43 (3H, s, OMe), 3.4—3.7 (3H, m, H-2, 2×H-6), 3.91 (1H, dd, H-4, *J*=3.3, 7.5 Hz), 4.65 and 4.79 (2H, ABq, OCH_2O , *J*=6.6 Hz), and 4.90 (1H, d, H-1, *J*=5.7 Hz).

Found: C, 48.67; H, 8.13%. Calcd for $C_{12}H_{24}O_4S_2$: C, 48.62; H, 8.16%.

6-*O*-Pivalate (31) of 30. To a solution of **30** (184 mg, 0.655 mmol) in dry pyridine (5.50 ml) was added pivaloyl chloride (121 μl, 0.982 mmol) at room temperature. After being stirred at room temperature for 3 h, the reaction mixture was diluted with ethyl acetate (6.0 ml) and washed with saturated aqueous K_2SO_4 (2×5.0 ml), $NaHCO_3$ (2×5.0 ml), and NaCl, dried, and evaporated. The residual syrup (350 mg) was chromatographed on silica gel (8.0 g) with 3 : 1 benzene-ethyl acetate to afford **31** (230 mg, 96.5%) as a colorless syrup: R_f=0.75 (1 : 1 benzene-ethyl acetate); $[\alpha]_D^{28}$ +6.5°, $[\alpha]_{365}$=+17° (*c* 0.99); IR ($CHCl_3$) 3500, 1720, 1280, 1150, and 1020 cm^{-1}; ^1H NMR (90 MHz) δ=0.95 and 0.98 (each 3H, each d, 3- and 5-Me, *J*=6.6 and 7.2 Hz); 1.21 (9H, s, O-Bu^t), 2.0—2.4 (2H, m, H-3, H-5), 3.1—3.4 (4H, m, SCH_2CH_2S), 3.37 (3H, s, OMe), 3.4—3.7 (1H, m, H-2), 3.74 (1H, dd, H-4, *J*=3.0, 6.9 Hz), 3.91 and 3.99 (each 1H, each s, 2×H-6), 4.59 and 4.67 (2H, ABq, OCH_2O, *J*=6.3 Hz), and 4.86 (1H, d, H-1, *J*=6.3 Hz).

Found: C, 53.67; H, 8.48%. Calcd for $C_{17}H_{32}O_5S_2$: C, 53.65; H, 8.48%.

2,4,6-Trideoxy-3-*O*-(methoxymethyl)-2,4-di-*C*-methyl-1-*O*-pivaloyl-L-altritol (32). A flask containing a solution of **31** (480 mg, 1.3 mmol) in methanol (4.80 ml) in the presence of Raney Ni W-4 (3.0 g) was ultrasonificated for 40 min. The organic layer was separated from insoluble matter which was washed with methanol (10×5.0 ml). The combined organic layers were concentrated to a crude syrup of **32** (525 mg) contaminated with a small amount of impurity. The crude syrup was chromatographed on silica gel (30 g) with 2 : 1 benzene-ethyl acetate to afford **32** (350 mg, 91.6%) as a colorless syrup: R_f=0.36 (2 : 1 benzene-ethyl acetate); $[\alpha]_D^{29}$ +11° (*c* 1.01); ^1H NMR (90 MHz) δ=0.83 and 0.96 (each 3H, each d, 2 and 4-Me, *J*=6.9 and 7.2 Hz), 1.17 (3H, d, 3×H-6, *J*=4.8 Hz), 1.23 (9H, s, Bu^t), 1.5—2.2 (2H, m, H-2, H-4), 2.83 (1H, s, OH), 3.43 (3H, s, OMe), 3.4—3.6 (1H, m, H-5), 3.7—4.1 (3H, m, 2×H-1 and H-3), and 4.68 (2H, s, OCH_2O).

Found: C, 62.10; H, 10.15%. Calcd for $C_{15}H_{30}O_5$: C, 62.04; H, 10.41%.

2,4,6-Trideoxy-5-*O*-(diethylisopropylsilyl)-3-*O*-(methoxymethyl)-2,4-di-*C*-methyl-1-*O*-pivaloyl-L-altritol (33). To a solution of **32** (134 mg, 0.462 mmol) in DMF (1.34 ml) were added at 0 °C imidazole (62.9 mg, 0.924 mmol) and diethylisopropylsilyl chloride[11] (129 μl, 0.693 mmol). After being stirred at room temperature for 0.5 h, the reaction mixture was poured into an ice-water mixture, which was extracted with ethyl acetate (3×2.0 ml). The extracts were washed with saturated aqueous NaCl, dried, and evaporated. The residual syrup (326 mg) was chromatographed on silica gel (5.8 g) with 10 : 1 hexane-ethyl acetate to afford **33** (192 mg, 99.1%) as a colorless syrup: R_f=0.69 (5 : 1 hexane-ethyl acetate); $[\alpha]_D^{26}$ +7.1°, $[\alpha]_{365}$+22° (*c* 1.02); IR ($CHCl_3$) 1720, 1290, 1160, and 1030 cm^{-1}; ^1H NMR (90 MHz) δ=0.5—1.2 (26H, m, 2-, 4-, and 5-Me, $SiEt_2Pr^i$), 1.21 (9H, s, Bu^t), 1.5—2.3 (2H, m, H-2, H-4), 3.3—3.5 (4H, m, H-3, -OMe), 3.96 and 4.04 (each 1H, each d, 2×H-1, *J*=1.8, 3.3 Hz), 4.19 (1H, dq, H-5, *J*=3.3 Hz), and 4.61 (2H, s, OCH_2O).

Found: C, 63.00; H, 10.79%. Calcd for $C_{22}H_{46}O_5Si$: C, 63.11; H, 11.07%.

2,4,6-Trideoxy-5-*O*-(diethylisopropylsilyl)-3-*O*-(methoxymethyl)-2,4-di-*C*-methyl-L-altritol (34). To a solution of **33** (213 mg, 0.506 mmol) in ether (2.13 ml) was added at 0 °C 0.5M methyllithium in ether (2.02 ml, 1.01 mmol). After being stirred at room temperature for 10 min, to the reaction mixture was added saturated aqueous NH_4Cl (3.0 ml). The mixture was extracted with ether (3×3.0 ml), and the extracts were washed with saturated aqueous NaCl, dried, and evaporated. The crude syrup (254 mg) was chromatographed on silica gel (8.5 g) with 2 : 1 hexane-ethyl acetate to afford **34** (171 mg, almost quantitative yield) as a colorless syrup: R_f=0.38 (5 : 1 hexane-ethyl acetate); $[\alpha]_D^{30}$ +50° (*c* 1.02); ^1H NMR (90 MHz) δ=0.4—1.2 (26H, m, 2-, 4-, and 5-Me, $SiEt_2Pr^i$), 1.7—2.1 (2H, m, H-2, H-4), 2.7—3.0 (1H, m, OH), 3.44 (3H, s, OMe), 3.4—3.6 (3H, m, 2×H-1 and H-3), 4.11 (1H, dq, H-5, *J*=3.0, 6.3 Hz), and 4.65 (2H, s, OCH_2O).

Found: C, 61.11; H, 11.10%. Calcd for $C_{17}H_{38}O_4Si$: C, 61.03; H, 11.45%.

2,4,6-Trideoxy-5-*O*-(diethylisopropylsilyl)-3-*O*-(methoxymethyl)-2,4-di-*C*-methyl-L-altrose (35). To a solution of oxalyl dichloride (70.1 μl, 0.803 mmol) in dry dichloromethane (374 μl) was added a mixture of dry DMSO (114 μl, 1.61 mmol) and dry dichloromethane (449 μl) at −60 °C. After being stirred at −60 °C for 0.5 h, a solution of **34** (150 mg, 0.446 mmol) in dichloromethane (446 μl) was added, and the mixture was stirred at −60 °C for 1 h. Triethylamine (311 μl, 2.23 mmol) was added to the reaction mixture, which was stirred at −40 °C for 1 h. The mixture was diluted with ether (1.50 ml) and poured into an ice-water mixture, which was extracted with ether (3×2.0 ml). The extracts were washed with saturated aqueous NaCl, dried, and evaporated to give a syrup (143 mg), which was chromatographed on silica gel (7.5 g) with 3 : 1 hexane-ethyl acetate to afford **35** (137 mg, 91.9%) as a colorless syrup: R_f=0.66 (3 : 1 hexane-ethyl acetate); $[\alpha]_D^{26}$ −43° (*c* 0.95); IR ($CHCl_3$) 2966, 1720, and 1030 cm^{-1}: ^1H NMR (90 MHz) δ=0.5—1.3 (26H, m, 2,4, and 5-Me, $SiEt_2Pr^i$), 1.7—2.1 (1H, m, H-4), 2.49 (1H, dq, H-2, *J*=2.1, 6.9 Hz), 3.28 (1H, s, OMe), 3.95 (1H, dd, H-3, *J*=2.1, 9.6 Hz), 4.15 (1H, dq, H-5, *J*=3.6, 6.0 Hz), 4.50 and 4.57 (2H, ABq, OCH_2O, *J*=6.3 Hz), and 9.77 (1H, s, CHO).

Found: C, 61.62; H, 10.65%. Calcd for $C_{17}H_{36}O_4Si$: C, 61.40; H, 10.91%.

Methyl (2*E*,4*E*)-6-(Dimethoxyphosphinyl)-2,4-hexadienoate (40). To a solution of methyl 4-bromocrotonate (**36**) (1.00 g, 5.59 mmol) in toluene (20.0 ml) was added dropwise a 1M solution of DIBAL in hexane (14.0 ml, 14.0 mmol) at

−78 °C. After being stirred at −78 °C for 0.5 h, 50% aqueous acetic acid (1.60 ml, 14.0 mmol) was added and the mixture was warmed to room temperature. The resulting insoluble material was removed by filtration through a Celite, and the filter cake was washed with acetone (5×10 ml). The filtrate and washings were evaporated to give a yellow syrup of allylic alcohol **37** (0.97 g). A mixture of **37** (0.73 g, 4.82 mmol), MnO_2 (12.6 g, 145 mmol), and dichloromethane (36.0 ml) was stirred at room temperature for 1 h. The insoluble material was filtered through a column filled with silica gel (2.0 g) with ethyl acetate. The filtrate was evaporated to give a syrup of crude aldehyde **38** (0.63 g, 88%). To a solution of the crude **38** (72.3 mg) in toluene (1.0 ml) was added (methoxycarbonylmethylene)triphenylphosphorane (206 mg, 0.615 mmol). The mixture was stirred at 90 °C for 2 h, and then evaporated. The residue was chromatographed on silica gel (20 g) with 5 : 1 hexane-ethyl acetate to afford **39** (70 mg, 70.5%) as a pale yellow liquid. A sample of **39** (116 mg, 0.567 mmol) was added dropwise to trimethyl phosphite (62.8 μl, 0 536 mmol) at 120—130 °C. After being stirred at 120—130 °C for 3 h, the reaction mixture was chromatographed on silica gel (7.5 g) with 10 : 1 chloroform-methanol to afford **40** (111 mg, 88%) as a pale yellow syrup: R_f=0.61 (10:1 chloroform-methanol); IR ($CHCl_3$) 3000, 2950, 2850, 1710, 1250, and 1030 cm^{-1}; UV(EtOH) 257 nm (log ε=4.45); ^1H NMR (90 MHz) δ=2.59 and 2.84 (each 1H, each d, 2×H-6, J=6.9 Hz), 3.69 , 3.74, and 3.83 (each 3H, each s, 3×OMe), 5.84 (1H, d, H-2, $J_{2,3}$=15.6 Hz), 6.08 (1H, dd, H-5, $J_{4,5}$=14.4, $J_{5,6}$=6.9 Hz), 6.29 (1H, dd, H-4, $J_{3,4}$=9.9 Hz), and 7.25 (1H, dd, H-3).

Found: C, 46.18; H, 6.38%. Calcd for $C_9H_{15}O_5P$: C, 46.16; H, 6.46%.

Methyl (8*S*,9*R*,10*R*,11*S*)-(2*E*,4*E*,6*E*)-11-[(Diethylisopropylsilyl)oxy]-9-(methoxymethoxy)-8,10-dimethyl-2,4,6-dodecatrienoate (41) and (6*Z*)-Isomer (42). To a stirred solution of *N*,*N*-diisopropylamine (32.1 μl, 0.229 mmol) in dry THF (153 μl) was added a 1.37 M solution of butyllithium in hexane (167 μl, 0.229 mmol) at −60 °C. After being kept at −60 °C for 1 h, to this solution was added a solution of **40** (50.0 mg, 0.191 mmol) in dry THF (0.50 ml). The reaction mixture was stirred at −60 °C for 0.5 h. A solution of **35** (31.7 mg, 0.0953 mmol) in dry THF (0.32 ml) was added at −60 °C and stirring was continued at −60—−40 °C for 1 h. Saturated aqueous NH_4Cl (1.5 ml) was added to the reaction mixture, which was warmed to room temperature and extracted with ethyl acetate (3×1.5 ml). The extracts were washed with saturated aqueous NaCl, dried, and evaporated. The residue (93.7 mg) was chromatographed on silica gel (1.3 g) with 4 : 1 hexane-ethyl acetate to afford a 1 : 2 mixture of **41** and **42** (41.9 mg, 99.7%) as a pale yellow syrup. The R_f-values (200 : 20 : 1 hexane-ethyl acetate-methanol) of **41** and **42** were 0.42 and 0.46, respectively. The mixture (40.0 mg, 0.0908 mmol) was dissolved in a solution of iodine (0.23 mg, 9.08×10^{-4} mmol) in dry dichloromethane (1.20 ml) and the resulting mixture was stirred at room temperature for 8 h without shading the light. Then saturated aqueous $Na_2S_2O_3$ (1.5 ml) was added to the reaction mixture, which was extracted with ethyl acetate (3×2.0 ml). The extracts were washed with saturated aqueous NaCl, dried, and evaporated to give a 8 : 1 mixture of **41** and **42** (40.0 mg, almost quantitative) as a pale yellow syrup. This syrup was used for the next reaction without further purification. A pure sample of **41** was obtained by flash chromatography of the isomerized product: $[\alpha]_D^{26}$ −4.6°, $[\alpha]_{577}$ −5.1°, $[\alpha]_{546}$ −5.2°, $[\alpha]_{435}$ −2.7° (*c* 0.78); IR ($CHCl_3$) 2950, 1700, and 1615 cm^{-2}; UV (EtOH) 304 nm (log ε=4.54); ^1H NMR (250 MHz) δ=0.60 (4H, q, 2×$SiCH_2CH_3$, J=8.5 Hz), 0.87 (3H, d, 10-Me, J=7.0 Hz), 1.9—1.1 (13H, m, 2×$SiCH_2CH_3$, *i*-Pr), 1.06 (3H, d, 8-Me, J=7.0 Hz), 1.07 (3H, d, 11-Me, J=6.3 Hz), 1.8—2.0 (1H, m, H-10), 2.54 (1H, ddq, H-8, J=3.8, 7.0 Hz), 3.31 (1H, dd, H-9, J=3.8, 8.3 Hz), 3.35 (3H, s, OCH_2OMe), 3.74 (3H, s, COOMe), 4.13 (1H, dq, H-11, J=4.0, 6.3 Hz), 4.54 and 4.57 (2H, ABq, OCH_2O, J=7.0 Hz), 5.85 (1H, d, H-2, $J_{2,3}$=15.0 Hz), 5.99 (1H, dd, H-7, $J_{7,8}$=7.0, $J_{7,6}$=15.0 Hz), 6.16 (1H, dd, H-6, $J_{6,5}$=10.5 Hz), 6.25 (1H, dd, H-4, $J_{4,3}$=11.5, $J_{4,5}$=15.0 Hz), 6.54 (1H, dd, H-5), and 7.30 (1H, dd, H-3).

Found: C, 65.57; H, 9.89%. Calcd for $C_{24}H_{44}O_5Si$: C, 65.41; H, 10.06%.

(8*S*,9*R*,10*R*,11*S*)-(2*E*,4*E*,6*E*)-11-[(Diethylisopropylsilyl)oxy]-9-(methoxymethoxy)-8,10-dimethyl-2,4,6-dodecatrienal (45) and (6*Z*)-Isomer (46). To a stirred solution of the 8 : 1 mixture of **41** and **42** (40.4 mg) in dry toluene (1.20 ml) was added dropwise a 1 M solution of DIBAL in hexane (229 μl) at −78 °C. After being stirred at −78 °C for 10 min, 50% aqueous acetic acid (262 μl) was added to the mixture, which was warmed to room temperature. The resulting insoluble matter was removed by filtration through a Celite, and the filter cake was washed with acetone (5×3.0 ml). The filtrate and washings were evaporated to give a yellow syrup (40.2 mg), which was chromatographed on silica gel (3.8 g) with 1 : 1 hexane-ethyl acetate to afford a mixture of the allylic alcohol **43** and its isomer **44** (35.4 mg, 93.6%) as a yellow syrup [R_f=0.17 (4 : 1 hexane-ethyl acetate)]. To this syrup (35.4 mg, 0.0858 mmol) was added dichloromethane (1.42 ml) and MnO_2 (423 mg, 4.87 mmol), and the mixture was stirred at room temperature for 0.5 h. The insoluble material was removed by filtration through a column filled with silica gel (0.35 g). The filtrate was evaporated to give an orange syrup (35.1 mg), which was flash-chromatographed on silica gel (7.0 g) with 140 : 20 : 1 hexane-ethyl acetate-methanol to afford **45** (27.5 mg) and **46** (5.1 mg) in 71 and 13% overall yields from **35**, respectively. **45**: Pale yellow syrup, R_f=0.41 (4 : 1 hexane-ethyl acetate); $[\alpha]_D^{25}$ −14.3° (*c* 0.48); IR ($CHCl_3$) 2960, 1725, 1670, and 1610 cm^{-1}; UV (EtOH) 319 nm (log ε=4.75); ^1H NMR (250 MHz) δ=0.61 (4H, q, 2×$SiCH_2Me$, J=7.8 Hz), 0.87 (3H, d, 10-Me, J=7.3 Hz), 0.9—1.1 (13H, m, 2×$SiCH_2CH_3$, *i*-Pr), 1.07 (6H, d, 8-and 11-Me, J=7.0 Hz), 1.88 (1H, m, H-10), 2.57 (1H, ddq, H-8, J=3.3, 7.0 Hz), 3.33 (1H, dd, H-9, J=3.3, 8.3 Hz), 3.36 (3H, s, OMe), 4.13 (1H, dq, H-11, J=4.5, 7.0 Hz), 4.54 and 4.58 (2H, ABq, OCH_2O, J=7.0 Hz), 6.10 (1H, dd, H-7, $J_{7,8}$=7.0, $J_{7,6}$=15.0 Hz), 6.14 (1H, dd, H-2, $J_{2,1}$=8.3, $J_{2,3}$=15.3 Hz), 6.21 (1H, dd, H-6, $J_{6,5}$=9.8 Hz), 6.37 (1H, dd, H-4, $J_{4,3}$=11.3, $J_{4,5}$=15.0 Hz), 6.66 (1H, dd, H-5), 7.12 (1H, dd, H-3, $J_{3,2}$=15.3 Hz), and 9.56 (1H, d, CHO, J=8.3 Hz).

Found: C, 67.45; H, 10.11%. Calcd for $C_{23}H_{42}O_4Si$: C, 67.27; H, 10.31%.

46: R_f=0.47 (4 : 1 hexane-ethyl acetate), ^1H NMR (250 MHz) δ=2.9—3.1 (1H, m, H-8), 5.77 (1H, dd, H-7, $J_{7,6}$=$J_{7,8}$=10.8 Hz), 6.10 (1H, dd, H-6, $J_{6,5}$=$J_{6,7}$=10.8 Hz), 6.17 (1H, dd, H-2, $J_{2,1}$=7.3, $J_{2,3}$=15.0 Hz), 6.44 (1H, dd, H-4, $J_{4,3}$=10.8, $J_{4,5}$=14.5 Hz), 6.65 (1H, dd, H-5), 7.17 (1H, dd, H-3), and 9.58 (1H, d, CHO).

Methyl (14*S*,15*R*,16*R*,17*S*)-(2*E*,4*E*,6*E*,8*E*,10*E*,12*E*)-17-[(Diethylisopropyl)oxy]-15-(methoxymethoxy)-14,16-dimethyl-2,4,6,8,10,12-octadecahexaenoate (47). To a stirred solution

of LDA in THF prepared from *N,N*-diisopropylamine (15.0 μl, 0.107 mmol) by the procedure described in the preparation of **41** was added a solution of **40** (23.4 mg, 0.0892 mmol) in dry THF (234 μl) at −60 °C and the mixture was stirred at −60 °C for 0.5 h. A solution of **45** (18.3 mg, 0.0446 mmol) in dry THF (183 μl) was added and stirred at −30 °C for 2 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (1.0 ml), and extracted with ethyl acetate (3×1.0 ml). The extracts were washed with saturated aqueous NaCl, dried, and evaporated. The residue (53.3 mg) was chromatographed on silica gel (2.0 g) with 40 : 1 chloroform-ethyl acetate to afford **47** (21.4 mg, 92.6%) as a yellow plates: R_f=0.45 (5 : 1 hexane-ethyl acetate); mp 154—157 °C; $[\alpha]_D^{25}$ +2.5°, $[\alpha]_{577}$ +4.1°, $[\alpha]_{546}$ +7.1° (*c* 0.42); IR (KBr) 1710, 1615, 1010 cm^{-1}; UV (EtOH), nm (log ε) 224 (4.07), 282 (4.10), 381 (4.90); ^1H NMR (250 MHz) δ=0.61 (4H, q, 2×SiC$\underline{H_2}$Me, *J*=7.3 Hz), 0.85 (3H, d, 16-Me, *J*=6.8 Hz), 0.9—1.1 (19H, m, 14- and 17-Me, 2×SiCH$_2\underline{Me}$, *i*-Pr), 1.8—1.9 (1H, m, H-16), 2.4—2.6 (1H, m, H-14), 3.29 (1H, dd, H-15, *J*=4.0, 8.8 Hz), 3.36 (3H, s, $CH_2O\underline{Me}$), 3.74 (3H, s, COOMe), 4.34 (1H, dq, H-17, *J*=4.3, 6.5 Hz), 4.54 and 4.58 (2H, ABq, OCH_2O, *J*=7.5 Hz), 5.83 (1H, dd, H-13, $J_{13,14}$=7.3, $J_{13,12}$=15.0 Hz), 5.88 (1H, d, H-2, $J_{2,3}$=15.3 Hz), 6.0—6.7 (9H, m, H-4,5,6,7,8,9,10,11,12), and 7.32 (1H, dd, H-3, $J_{3,4}$=11.3 Hz).

Found: C, 69.41; H, 9.52%. Calcd for $C_{30}H_{50}O_5Si$: C, 69.45; H, 9.71%.

(14*S*,15*R*,16*R*,17*S*)-(2*E*,4*E*,6*E*,8*E*,10*E*,12*E*)-17-[(Diethylisopropylsilyl)oxy]-15-(methoxymethoxy)-14,16-dimethyl-2,4,6,8,10,12-octadecahexaenal (49). By the procedure described in the preparation of **45** from **41**, above obtained **47** (49.3 mg) was transformed via the allylic alcohol **48** into **49** (33.2 mg, 73.5%).

49: Orange crystals; R_f=0.39 (5 : 1 hexane-ethyl acetate); mp 146—149 °C; $[\alpha]_D^{28}$ +3.5°, $[\alpha]_{577}$ +4.1°, $[\alpha]_{546}$ +9.4°(*c* 0.34); IR (KBr) 1665, 1600, 1550, 1005 cm^{-1}; UV (EtOH) nm (log ε) 228 (4.18), 288 (4.20), 408 (4.99); ^1H NMR (250 MHz) δ=0.61 (4H, q, 2×SiC$\underline{H_2}$Me, *J*=8.3 Hz), 0.87 (3H, d, 16-Me, *J*=7.0 Hz), 0.9—1.1 (13H, m, 2×SiCH$_2\underline{Me}$, *i*-Pr), 1.05 and 1.06 (each 3H, each d, 14- and 17-Me, *J*=6.5 Hz), 1.87 (1H, m, H-16), 2.52 (1H, ddq, H-14, *J*=3.3, 6.8 Hz), 3.30 (1H, dd, H-15, *J*=3.3, 7.8 Hz), 3.36 (3H, s, OMe), 4.15 (1H, dq, H-17, *J*=4.3, 7.0 Hz), 4.54 and 4.58 (2H, ABq, OCH_2O, *J*=7.0 Hz), 5.85 (1H, dd, H-13, $J_{13,14}$=6.8, $J_{13,12}$=15.0 Hz), 6.15 (1H, dd, H-2, $J_{2,1}$=3.4, $J_{2,3}$=15.3 Hz), 6.0—6.8 (9H, m, H-4,5,6,7,8,9,10,11,12), 7.15 (1H, dd, H-3, $J_{3,4}$=11.3 Hz), and 9.57 (1H, d, CHO).

Found: C, 71.24; H, 9.73%. Calcd for $C_{29}H_{48}O_4Si$: C, 71.26; H, 9.90%.

(14*S*,15*R*,16*R*,17*S*)-(2*E*,4*E*,6*E*,8*E*,10*E*,12*E*)-17-Hydroxy-15-(methoxymethoxy)-14,16-dimethyl-2,4,6,8,10,12-octadecahexaenal (4). To a solution of **49** (19.6 mg, 0.04 mmol) in dry THF (0.39 ml) was added a 1 M solution of *n*-Bu_4NF in THF (80.2 μl, 0.08 mmol) at 0 °C. After being stirred at 0 °C for 15 h, the reaction mixture was poured into an ice-water mixture which was extracted with ethyl acetate (3×1.0 ml). The extracts were washed with saturated aqueous NaCl, dried, and evaporated. The residue (23.4 mg) was chromatographed on silica gel (2.2 g) with 2 : 3 hexane-ethyl acetate to afford **4** (14.0 mg, 96.8%) as orange crystals: R_f=0.15 (7 : 3 hexane-ethyl acetate); mp 105—114 °C; IR (KBr) 3340, 1670, 1550, and 1010 cm^{-1}; UV (EtOH) nm (log ε) 288 (4.01), 406 (4.73); ^1H NMR (250 MHz) δ=0.88 (3H, d, 16-Me, *J*=7.0 Hz), 1.08 (3H, d, 17-Me, *J*=6.8 Hz), 1.17 (3H, d, 14-Me, *J*=6.3 Hz), 1.76 (1H, q-like, H-16, *J*=7.0 Hz), 2.5—2.7 (1H, m, H-14), 3.3—3.5 (2H, m, H-15, OH), 3.40 (3H, s, OMe), 3.83 (1H, dq, H-17, *J*=6.8 Hz), 4.65 and 4.67 (2H, ABq, OCH_2O, *J*=7.5 Hz), 5.82 (1H, dd, H-13, $J_{13,14}$=7.5, $J_{13,12}$=14.5 Hz), 6.16 (1H, dd, H-2, $J_{2,1}$=8.0, $J_{2,3}$=15.0 Hz), 6.1—6.8 (9H, m, H-4,5,6,7,8,9,10,11,12), 7.14 (1H, dd, H-3, $J_{3,4}$=11.5 Hz), and 9.56 (1H, d, CHO).

Found: C, 73.02; H, 8.65%. Calcd for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95%.

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References

1) J. Vandeputte, J. L. Wachtel, and E. T. Stiller, *Antibiot. Annu.*, **1956**, 587.

2) W. Mechliuski, C. P. Schaffner, P. Ganis, and G. Avitabile, *Tetrahedron Lett.*, **1970**, 3873; P. Ganis, G. Avitabile, W. Mechlinski, and C. P. Schaffner, *J. Am. Chem. Soc.*, **93**, 4560 (1971).

3) a) D. M. Floyed and A. W. Fritz, *Tetrahedron Lett.*, **22**, 2847 (1981); b) D. W. Brooks and R. P. Kellogg, *ibid.*, **23**, 4991 (1982); c) S. Masamune, T. Kaiho, and D. S. Garvey, *J. Am. Chem. Soc.*, **104**, 5521 (1982); d) P. Ma, V. S. Martin, S. Masamune, K. B. Sharpless, and S. M. Viti, *J. Org. Chem.*, **47**, 1378 (1982); e) K. C. Nicolaou and J. Venishi, *J. Chem. Soc., Chem. Commun.*, **1982**, 1292; f) M. Hirama and M. Vie, *Tetrahedron Lett.*, **23**, 5307 (1982); g) B. H. Lipshutz and J. A. Kozlowski, *J. Org. Chem.*, **49**, 1149 (1984); h) S. Masamune, P. Ma, H. Okamoto, J. W. Ellingboe, and Y. Ito, *J. Org. Chem.*, **49**, 2843 (1984); i) D. Liang, H. W. Pauls, and B. Fraser-Reid, *J. Chem. Soc., Chem. Commun.*, **1984**, 1123; j) M. A. Blanchette, W. Choy, J. T. Davis, A. P. Essenfeld, S. Masamune, W. R. Roush, and T. Sakai, *Tetrahedron Lett.*, **25**, 2183 (1984); k) J. M. Williams and G. J. McGarvey, *ibid.*, **26**, 4891 (1985); l) D. Boschell, T. Takemasa, Y. Nishitani, and S. Masamune, *ibid.*, **26**, 5239 (1985); m) G. J. McGarvey, J. M. Williams, R. N. Hiner, Y. Matsubara, and T. Oh, *J. Am. Chem. Soc.*, **108**, 4943 (1986); J. M. Williams and G. J. McGarvey , *Tetrahedron Lett.*, **26**, 4891 (1985).

4) K. C. Nicolaou, T. K. Chakraborty, R. A. Daines, and N. S. Simpkins, *J. Chem. Soc., Chem. Commun.*, **1986**, 413.

5) M. Kinoshita and S. Mariyama, *Bull. Chem. Soc. Jpn.*, **48**, 2081 (1975); A. Rosenthal and M. Spinze, *Can. J. Chem.*, **47**, 3941 (1969).

6) a) H. Redlich and H.-J. Neumann, *Chem. Ber.*, **114**, 2029 (1981); b) M. Kinoshita, N. Ohsawa, and S. Gomi, *Carbohydr. Res.*, **109**, 5 (1982).

7) J. Herscovici and K. Antonakis, *J. Chem. Soc., Chem. Commun.*, **1980**, 561.

8) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **84**, 866 (1962); M. Nakata, Y. Ikeyama, H. Takao, and M. Kinoshita, *Bull. Chem. Soc. Jpn.*, **53**, 3252 (1980).

9) M. Nakata, H. Takao, Y. Ikeyama, T. Sakai, K. Tatsuta, and M. Kinoshita, *Bull. Chem. Soc. Jpn.*, **54**, 1749

(1981).

10) J. C. Sheehan, H. G. Zachan, and W. B. Lawson, *J. Am. Chem. Soc.*, **80**, 3349 (1958).

11) K. Toshima, K. Tatsuta, and M. Kinoshita, *Tetrahedron Lett.*, **27**, 4741 (1986).

12) A. J. Mancuso, S.-L. Huang, and D. Swern, *J. Org. Chem.*, **33**, 2480 (1978).

13) I. Ernest, A. J. Main, and R. Menassé, *Tetrahedron Lett.*, **23**, 167 (1982).

14) Direct ^{1}H NMR spectroscopic confirmation of the (6E)-configuration of **47** and **49** was impossible, because, in their spectra, the signals of the H-6 and 7 protons were found in a complex multiplet due to nine olefinic protons. Therefore, their (6E)-configuration was indirectly confirmed. The reaction of **45** with (methoxycarbonylmethylene)triphenylphosphorane afforded the all-*trans*-tetraenoic ester **50** in 89% yield: ^{1}H NMR (90 MHz) δ=5.88 (1H, d, H-2, $J_{2,3}$=15.6 Hz), 6.0—6.7 (6H, m, H-4,5,6,7,8,9), and 7.37 (1H, d, H-3, $J_{3,4}$=10.8 Hz). The ester **50** was converted , by the procedure described in the preparation of **45**, into the all-*trans*-tetraenal **51** in 43.3% yield: ^{1}H NMR (90 MHz) δ=6.17 (1H, dd, H-2, $J_{2,1}$=8.1, $J_{2,3}$=15.3 Hz), 6.0—6.8 (6H, m, H-4,5,6,7,8,9), 7.16 (1H, dd, H-3, $J_{3,4}$=9.9 Hz), and 9.62 (1H, d, CHO). The reaction of **51** with methyl (*2E*)-4-(dimethoxyphosphinyl)-2-butenoate (THF, LDA, −60 °C, 0.5h) provided in almost quantitative yield the hexaenoic ester **47**, which proved to be identical in all respects with a sample of **47** obtained by the reaction of **45** and **40**.