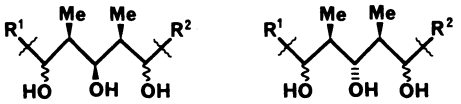
Stereoselective Syntheses of 1,3,5-Trihydroxy-2,4-dimethylpentane Equivalents from Methyl α-Mannopyranosides

Kuniaki TATSUTA,* Yoshihito KOGUCHI, and Motohiro KASE
Department of Applied Chemistry, Faculty of Science and Technology, Keio University, Hiyoshi, Kohoku, Yokohama 223
(Received February 12, 1988)

The optically active 1,3,5-trihydroxy-2,4-dimethylpentane equivalents: methyl 2,4-dideoxy-2,4-di-*C*-methyl-α-D-ido- and talopyranosides and their enantiomers, which should be suitable for the syntheses of propionate-derived natural products, were stereo- and regioselectively prepared from methyl α-D- and L-mannopyranosides through the reactions of the 3,4-anhydro-2-*O*-mesyl- and 3,4-anhydro-2-*C*-methyl-altropyranoside derivatives with methylmagnesium bromide and methylmagnesium chloride.

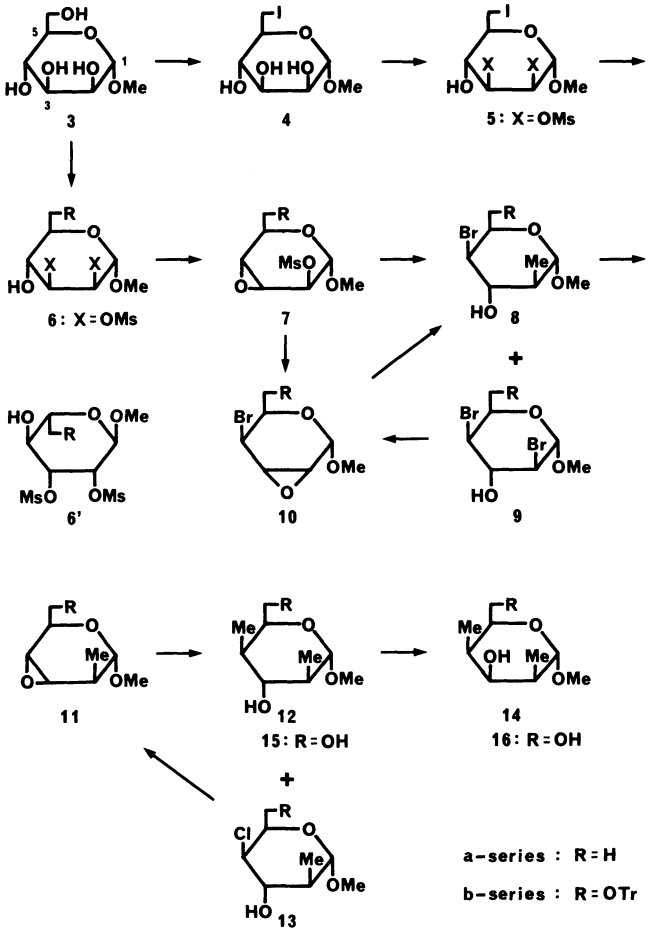
In recent years an impressive number of natural products have been synthesized from carbohydrate derivatives.[1] The syntheses have required fragments with the correct relative and absolute configurations, together with functionality which allows them to be incorporated into the synthetic schemes. Especially, such chiral fragments as 1,3,5-trihydroxy-2,4-dimethylpentane units **1** and **2** can be found in the structures of biologically active natural products including erythromycin A,[2] monensin,[3] rifamycin S,[4] ionomycin,[5] and tirandamycin.[6] Several methods have been developed to affect these stereoselective syntheses by mainly using 1,6-anhydro-β-D-glucopyranose[7] as a chiral source, although alternative strategies including aldol type reactions[8] have been recently reported.



In this paper, we report the novel stereoselective syntheses of such fragment equivalents (**12ab**, **14ab**, **15**, and **16**) and their enantiomers from readily and enantiomerically available methyl α-mannopyranoside derivatives. Repeated alkylation of the intermediary epoxides with methylmagnesium bromide–*t*-butyl bromide and methylmagnesium chloride–CuCl[7c] reagents results in the stereo- and regiospecific introduction of *C*-methyl groups through the trans diaxial opening of their epoxide rings.

The study commenced with the synthesis of the 6-deoxy derivatives **12a** (in the a-series, R=H) and **14a** from methyl α-D-mannopyranoside (**3**). Methyl α-D-mannopyranoside (**3**) was converted by the published procedure[9] into the corresponding 6-iodo compound **4**, which was mesylated to give exclusively the 2,3-di-*O*-mesyl derivative **5** in a quantitative yield. The compound **5** was dehalogenated by tributylstannane to methyl 6-deoxy-2,3-di-*O*-mesyl-α-D-mannopyranoside (**6a**).

The corresponding L-enantiomer (**6'a**) of **6a** could be directly obtained by mesylation of methyl α-L-rhamnopyranoside[10] in a 90% yield for the L-series.



The compound **6a** was treated with sodium methoxide to give methyl 3,4-anhydro-6-deoxy-2-*O*-mesyl-α-D-altropyranoside (**7a**) in an 86% yield. Treatment of the 3,4-epoxide **7a** in dichloromethane with an ethereal methylmagnesium bromide solution and *t*-butyl bromide gave methyl 4-bromo-2,4,6-trideoxy-2-*C*-methyl-α-D-idopyranoside (**8a**) and methyl 2,4-dibromo-2,4,6-trideoxy-α-D-idopyranoside (**9a**) in 56 and 29% yields, respectively, both of which could be reasonably formed by the following sequence: (i) an attack of the Br anion on the C-4 position with the first diaxial opening of the epoxide; (ii) an adjacent attack of the intermediary hydroxide anion on the C-2 position with the *O*-mesyl group leaving to give the

2,3-epoxide **10a**; (iii) an attack of the methyl anion or Br anion on the C-2 position with the second diaxial opening of the epoxide to give **8a** and **9a**. This epoxide-swinging reaction could be traced by the stepwise reactions as follows. The compound **7a** reacted with LiBr to give the same methyl 2,3-anhydro-4-bromo-4,6-dideoxy-α-D-gulopyranoside (**10a**) in an 80% yield, which was converted into the compounds **8a** and **9a** in 62 and 24% yields by the aforesaid conditions using methylmagnesium bromide and *t*-butyl bromide. Then, the by-product **9a** was selectively led to the 2,3-epoxide **10a** by treatment with sodium methoxide in an 83% yield and recycled to the desired compound **8a**.

In the transformation of **7a** into **8a**, other couples[7] of organometallic reagents (methylmagnesium iodide, methylmagnesium bromide, methylmagnesium chloride, lithium dimethylcuprate(I) and methyllithium) and additives (tetrabutylammonium bromide, LiBr, CuI, CuBr, CuCl, $MgBr_2$, Li_2CuCl_4, phenylmagnesium iodide, phenylmagnesium chloride, *t*-butyl bromide, and trimethylsilyl bromide) were investigated in several solvents (ether, dichloromethane, dibromomethane, THF, and dioxane), but they gave **8a** only in lower yields.

The compound **8a** was converted by NaH into the 3,4-epoxide, methyl 3,4-anhydro-2,6-dideoxy-2-*C*-methyl-α-D-altropyranoside (**11a**) in an 85% yield, which was treated with methylmagnesium chloride and CuCl in THF to give methyl 2,4,6-trideoxy-2,4-di-*C*-methyl-α-D-idopyranoside **12a** and methyl 4-chloro-2,4,6-trideoxy-2-*C*-methyl-α-D-idopyranoside **13a** in 60 and 28% yields, respectively, as results of the diaxial opening of the epoxide. Also, in the latter reaction, a large number of variables[7] including reagents, additives and solvents were assayed as mentioned above, but in vain. The by-product **13a** was recycled to **12a** through **11a**, which was obtained by treatment with NaH.

The stereochemistry of **12a** was confirmed by the ^1H NMR analysis. In the $CDCl_3$ solution, the spectrum showed $J_{1,2}$=4.0 Hz, $J_{2,3}=J_{3,4}$=5.5 Hz, and $J_{4,5}$=4.5 Hz, supporting that the idopyranoside **12a** could exist in the C_1^4 chair form[11] (Fig. 1) due to an intramolecular hydrogen-bond between the C-1 and C-3 position, as suggested by Lemieux and Levine,[12] rather than other possible conformations including the C_4^1 chair form.[11] However, in the deuterated acetone solution, the spectrum showed $J_{1,2}$=7.4 Hz, $J_{2,3}=J_{3,4}$=9.1 Hz, and $J_{4,5}$=5.6 Hz, indicating that **12a** existed in the C_4^1 form as shown in Fig. 1.[12]

Inversion of the stereochemistry at the C-3 position of **12a** was cleanly achieved by oxidation to the corresponding ketone with pyridinium chlorochromate followed by borohydride reduction to give methyl 2,4,6-trideoxy-2,4-di-*C*-methyl-α-D-talopyranoside (**14a**) in an 82% yield with a little of **12a**. The coupling constants ($J_{1,2}$=3.5 Hz, $J_{2,3}=J_{3,4}$=4.8 Hz, and $J_{4,5}$=4.2 Hz) in the $CDCl_3$ solution supported that **14a** was favoured in the C_1^4 chair form spread by a strong repulsion between the C-2 and C-4 methyl groups. Consequently, **12a** and **14a** are equivalent to the pentane units **1** and **2**, respectively.

The corresponding L-isomers of **12a** and **14a**, which are equivalent to the antipodes of **1** and **2**, were derived from methyl α-L-rhamnoside through **6'a** by the same conditions as described above.

On the other hand, the 6-hydroxy derivatives **15** and **16** were also synthesized from methyl α-D-mannopyranoside (**3**) by the similar manner with the aforesaid sequences.

Tritylation of **3** followed by mesylation afforded methyl 2,3-di-*O*-mesyl-6-*O*-trityl-α-D-mannopyranoside (**6b**: in the b-series, R=OTr), which was converted into the 3,4-epoxide (**7b**) in a 73% overall yield. The epoxide **7b** was treated with methylmagnesium bromide and *t*-butyl bromide to give methyl 4-bromo-2,4-dideoxy-2-*C*-methyl-6-*O*-trityl-α-D-idopyranoside (**8b**) and methyl 2,4-dibromo-2,4-dideoxy-6-*O*-trityl-α-D-idopyranoside (**9b**) in 55 and 27% yields, respectively. The latter product **9b** was recycled into **8b** through **10b** in a 54% overall yield as described in the recovery of **8a** through **10a**. Reaction of **8b** with NaH afforded the 3,4-epoxide **11b** in an 89% yield, which was treated with methylmagnesium chloride and CuCl to give methyl 2,4-dideoxy-2,4-di-*C*-methyl-6-*O*-trityl-α-D-idopyranoside (**12b**) and methyl 4-chloro-2,4-dideoxy-2-*C*-methyl-6-*O*-trityl-α-D-idopyranoside (**13b**) in 60 and 29% yields. The by-product **13b** was also recycled to **12b** through **11b**. The compound **12b** was transferred into the C-3 epimer **14b** by pyridinium chlorochromate oxidation and borohydride reduction. Removal of *O*-trityl group in **12b** and **14b** by acidic conditions did not give the desired products **15** and **16**, but the

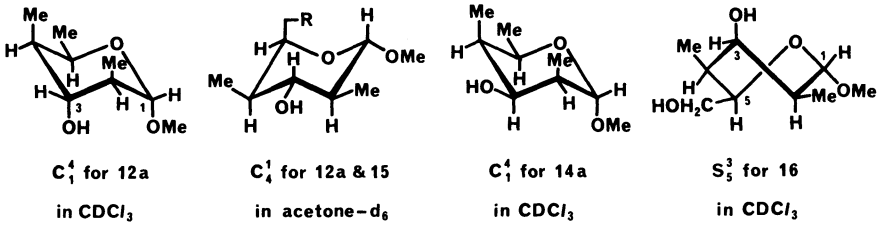


Fig. 1. Preferred conformations of **12a**, **14a**, **15**, and **16** in $CDCl_3$ or acetone-d_6.

corresponding 1,6-anhydro derivatives. Then, by hydrogenolysis with palladium hydroxide, methyl 2,4-dideoxy-2,4-di-*C*-methyl-α-D-ido- and talopyranosides (**15** and **16**) were obtained in 75 and 87% yields, respectively.

The stereochemistry of **15** and **16** was confirmed by their ^{1}H NMR spectra, the coupling constants (see the Experimental section) of which revealed that **15** existed in the C_4^1 chair form in the deuterated acetone solution and **16** in the S_5^3-like skew conformation[11] in the $CDCl_3$ solution as shown in Fig. 1. Hence, **15** and **16** are equivalent to the chiral units **1** and **2**, respectively.

The enantiomers of **15** and **16** could be reasonably derived from methyl α-L-mannopyranoside by the same reaction sequences to generate the antipode units of **1** and **2**.

In conclusion, an efficient, stereo- and regiospecific preparation of synthetic equivalents of the structural fragments **1** and **2** and their enantiomeric fragments have been developed, starting from methyl α-D- and L-mannopyranosides.

Experimental

Melting points were determined on a micro hot-stage Yanaco MP-S3 and were uncorrected. Optical rotations were measured with a JASCO DIP-360 photoelectric polarimeter in chloroform unless otherwise stated. IR spectra were recorded on a Hitachi Perkin-Elmer 225 spectrometer, and ^{1}H NMR spectra on a Varian EM-390, a Bruker WM 250 or a JEOL GX-400 spectrometer in $CDCl_3$ using TMS as internal standard unless otherwise noted. Mass spectra were measured with a Hitachi M-80 mass spectrometer or a Hitachi RMU-6M mass spectrometer. TLC was carried out on Merck TLC plates (60F-254, 0.25 mm). Column chromatography was performed on silica gel, Wakogel C-200. In general, organic solvents were purified and dried by the appropriate procedures, and evaporation and concentration were carried out under reduced pressure below 35 °C, unless otherwise noted.

Methyl 6-Deoxy-6-iodo-2,3-di-*O*-mesyl-α-D-mannopyranoside (5). The starting methyl 6-deoxy-6-iodo-α-D-mannopyranoside (**4**) was prepared from methyl α-D-mannopyranoside (**3**) according to the reported procedure.[9]

To a stirred and ice-cooled solution of **4** (88.8 g) in pyridine (620 ml) were added 4-dimethylaminopyridine (17.8 g) and mesyl chloride (68 ml), and stirring was continued at room temperature for 24 h. After addition of ethanol (52 ml), the mixture was evaporated and co-evaporated with toluene to a residue, which was partitioned between ethyl acetate and a saturated aqueous $NaHCO_3$ solution. The combined layers were evaporated to a residue, which was chromatographed on silica gel (670 g) with 2:1 benzene–ethyl acetate to give an amorphous solid of **5** (130.8 g, 97%): R_f 0.36 (2:1 benzene–ethyl acetate); $[\alpha]_D^{31}$ +29° (*c* 0.60); IR (KBr): 1350 cm^{-1} (OMs); ^{1}H NMR (400 MHz): δ=2.79 (1H, d, OH-4, $J_{4,OH}$=4.5 Hz), 3.15 and 3.17 (each 3H, s, Ms), 3.37 (1H, dd, H-6, $J_{5,6}$=7.7 Hz, $J_{6,6'}$=10.9 Hz), 3.48 (3H, s, OMe), 3.56 (1H, ddd, H-5, $J_{4,5}$=9.5 Hz, $J_{5,6'}$=2.9 Hz), 3.63 (1H, dd, H-6′), 3.82 (1H, dt, H-4, $J_{3,4}$=9.5 Hz), 4.92 (1H, d, H-1, $J_{1,2}$=1.6 Hz), 4.92 (1H, dd, H-3, $J_{2,3}$=3.5 Hz), and 4.96 (1H, dd, H-2); MS *m/z* 460 (M$^+$).

Methyl 6-Deoxy-2,3-di-*O*-mesyl-α-D-mannopyranoside (6a). A solution of **5** (58.2 g) in toluene (466 ml) was stirred with tributylstannane (51.2 ml) and α,α′-azobis(isobutyronitrile) (2.08 g) at 90 °C for 3 h under argon. The resulting solution was evaporated and co-evaporated with ethyl acetate to a solid, which was recrystallized from ethyl acetate–hexane to give a solid of **6a** (36.7 g, 87%), which was used for the next step.

An analytically pure sample was obtained by chromatography on silica gel with 3:2 benzene–ethyl acetate followed by recrystallization from ether to afford cubes of **6a**: R_f 0.31 (2:1 benzene–ethyl acetate); mp 143—145 °C; $[\alpha]_D^{34}$ +6.9° (*c* 0.94); IR (KBr): 1347 cm^{-1} (OMs); ^{1}H NMR (400 MHz): δ=1.38 (3H, d, Me-5, $J_{5,Me}$=6.0 Hz), 2.64 (1H, d, OH-4, $J_{4,OH}$), 3.15 and 3.17 (each 3H, s, Ms), 3.41 (3H, s, OMe), 3.66 (1H, dt, H-4, $J_{3,4}$=9.4 Hz, $J_{4,5}$=9.4 Hz), 3.74 (1H, dq, H-5), 4.83 (1H, d, H-1, $J_{1,2}$=1.6 Hz), 4.85 (1H, dd, H-3, $J_{2,3}$=3.0 Hz), and 4.92 (1H, dd, H-2).

Found: C, 32.50; H, 5.32%. Calcd for $C_9H_{18}O_9S_2$: C, 32.33; H, 5.43%.

Methyl 6-Deoxy-2,3-di-*O*-mesyl-α-L-mannopyranoside (6′a). A solution of methyl α-L-rhamnopyranoside[10] (0.94 g) in pyridine (9.4 ml) was stirred with mesyl chloride (0.86 ml) at room temperature for 4 h. After addition of ethanol (1 ml), the resulting mixture was evaporated and co-evaporated with toluene to a residue, which was chromatographed on silica gel with 15:1 chloroform–methanol followed by recrystallization from ether to give cubes of **6′a** (1.61 g, 90%): mp 142—145 °C; $[\alpha]_D^{30}$ −6.9° (*c* 1.0). The physicochemical properties were identical with those of **6a** except for the sign of the optical rotation.

Methyl 3,4-Anhydro-6-deoxy-2-*O*-mesyl-α-D-altropyranoside (7a). A solution of **6a** (7.93 g) in chloroform (79 ml) was stirred with a 28% methanolic sodium methoxide solution (6.0 ml) at room temperature for 48 h. The reaction mixture was partitioned between chloroform and water, and the combined organic layers were dried and evaporated to a residue. This was chromatographed on silica gel (85 g) with 4:1 benzene–ethyl acetate followed by recrystallization from ethyl acetate–hexane to give plates of **7a** (4.85 g, 86%): R_f 0.55 (2:1 benzene–ethyl acetate); mp 88—90 °C; $[\alpha]_D^{33}$ +64° (*c* 0.98); IR (KBr): 1345 cm^{-1} (OMs); ^{1}H NMR (400 MHz): δ=1.45 (3H, d, Me-5, $J_{5,Me}$=7.2 Hz), 3.09 (1H, d, H-4, $J_{3,4}$=3.5 Hz, $J_{4,5}$=0 Hz), 3.12 (3H, s, OMs), 3.42 (3H, s, OMe), 3.44 (1H, d, H-3, $J_{2,3}$=0 Hz), 4.31 (1H, q, H-5), 4.56 and 4.63 (each 1H, d, H-1 and H-2, vice versa, $J_{1,2}$=4.2 Hz).

Found: C, 40.34; H, 5.86%. Calcd for $C_8H_{14}O_6S$: C, 40.33; H, 5.92%.

Methyl 4-Bromo-2,4,6-trideoxy-2-*C*-methyl-α-D-idopyranoside (8a) and Methyl 2,4-Dibromo-2,4,6-trideoxy-α-D-idopyranoside (9a). A) From 7a: To a stirred and ice-cooled solution of **7a** (105 mg) in dichloromethane (0.53 ml) were added *t*-butyl bromide (0.149 ml) and dropwise a 3 M† ethereal methylmagnesium bromide solution (1.48 ml) under argon, and stirring was continued at the same temperature for 15 min and then at room temperature for 2.5 h. After the reaction was quenched with a saturated aqueous NH_4Cl solution (1.5 ml), the reaction mixture was extracted with ethyl acetate (1.5 ml×3). The combined

† 1 M=1 mol dm^{-3}.

extracts were dried and evaporated to a residue, which was chromatographed on silica gel (10 g) with 6:1 benzene–ethyl acetate to give **8a** (59 mg, 56%) and **9a** (39 mg, 29%) having the R_f-values of 0.35 and 0.48 (6:1 benzene–ethyl acetate) respectively.

8a: Needles from ether–hexane; mp 116—118 °C; $[\alpha]_D^{34}$ +114° (*c* 0.93); ^{1}H NMR (400 MHz): δ=1.28 (3H, d, Me-2, $J_{2,Me}$=7.4 Hz), 1.37 (3H, d, Me-5, $J_{5,Me}$=6.7 Hz), 1.95 (1H, m, H-2), 3.33 (1H, d, OH, $J_{3,OH}$=8.0 Hz), 3.41 (3H, s, OMe), 3.92 (1H, dt, H-3, $J_{2,3}$=$J_{3,4}$=4.8 Hz), 4.04 (1H, dd, H-4, $J_{4,5}$=3.5 Hz), 4.28 (1H, dq, H-5), 4.51 (1H, d, H-1, $J_{1,2}$=3.5 Hz).

Found: C, 40.02; H, 6.16%. Calcd for $C_8H_{15}O_3Br$: C, 40.19; H, 6.32%.

9a: Needles from ether–hexane; mp 95—97 °C; $[\alpha]_D^{27}$ +72° (*c* 0.67); ^{1}H NMR (400 MHz): δ=1.48 (3H, d, Me-5, $J_{5,Me}$=7.0 Hz), 2.88 (1H, broad d, OH, $J_{3,OH}$=3.8 Hz), 3.49 (3H, s, OMe), 3.76 (1H, dd, H-2, $J_{1,2}$=7.4 Hz, $J_{2,3}$=8.6 Hz), 4.07 (1H, dd, H-4, $J_{3,4}$=8.6 Hz, $J_{4,5}$=5.4 Hz), 4.12 (1H, dt, H-3), 4.37 (1H, dq, H-5), 4.80 (1H, d, H-1).

Found: C, 27.93; H, 3.97%. Calcd for $C_7H_{12}O_3Br_2$: C, 27.66; H, 3.98%.

B) From 10a: To a stirred and ice-cooled solution of **10a** (3.80 g) in dichloromethane (19 ml) was added dropwise a 3 M ethereal methylmagnesium bromide solution (42 ml) under argon, and stirring was continued at room temperature for 2 h. After the reaction was quenched with a saturated aqueous NH_4Cl solution (38 ml), the mixture was partitioned between ethyl acetate and water. The combined organic layers were dried and evaporated to a residue, which was chromatographed on silica gel (133 g) with 7:1 benzene–ethyl acetate to give **8a** (2.52 g, 62%) and **9a** (1.23 g, 24%).

Methyl 2,3-Anhydro-4-bromo-4,6-dideoxy-α-D-gulopyranoside (10a). A) From 7a: A solution of **7a** (4.29 g) in 1,4-dioxane (43 ml) was stirred with LiBr (3.13 g) under argon at 100 °C for 68 h. The salt was filtered and washed with dichloromethane. The filtrates and washings were combined and partitioned between dichloromethane and water. The combined organic layers were dried and evaporated to a residue, which was chromatographed on silica gel (80 g) with 4:1 hexane–ethyl acetate to give a solid of **10a** (3.20 g, 80%), which was used for the next step.

An analytically pure sample was obtained by distillation under reduced pressure (bath temp 85 °C/4 mmHg††) as a syrup which was changed into cubes of **10a**: R_f 0.60 (5:1 benzene–ethyl acetate); mp 56 °C; $[\alpha]_D^{32}$ −14° (*c* 1.0); ^{1}H NMR (90 MHz): δ=1.30 (3H, d, Me-5, $J_{5,Me}$=7 Hz), 3.60 (1H, m, H-3), 3.65 (3H, s, OMe), 3.82 (1H, dd, H-2, $J_{1,2}$=3.3 Hz, $J_{2,3}$=2.7 Hz), 4.16 (1H, dq, H-5, $J_{4,5}$=2 Hz), 4.41 (1H, t, H-4, $J_{3,4}$=2 Hz), and 5.17 (1H, d, H-1).

Found: C, 37.42; H, 4.86%. Calcd for $C_7H_{11}O_3Br$: C, 37.69; H, 4.97%.

B) From 9a: A solution of **9a** (6.47 g) in 1,4-dioxane (97 ml) was stirred with a 28% methanolic sodium methoxide solution (5.2 ml) at room temperature for 1 h. The reaction mixture was partitioned between chloroform and water, and the combined organic layers were dried and evaporated to a residue. This was chromatographed on silica gel (145 g) with 5:1 hexane–ethyl acetate to give a solid of **10a** (3.94 g, 83%).

Methyl 3,4-Anhydro-2,6-dideoxy-2-*C*-methyl-α-D-altropyranoside (11a). A) From 8a: A solution of **8a** (3.06 g) in 1,2-dimethoxyethane (46 ml) was stirred with a 55% oily NaH powder (670 mg) at room temperature for 30 min. After addition of ethanol (1 ml), the resulting mixture was partitioned between ethyl acetate and a saturated aqueous NaCl solution, and the combined organic layers were dried and evaporated under atmospheric pressure to give a residue. This was purified by distillation under reduced pressure (bath temp 86 °C/2—3 mmHg) to give a syrup of **11a** (1.71 g, 85%): R_f 0.32 (6:1 benzene–ethyl acetate); bp ca. 66 °C (2 mmHg); $[\alpha]_D^{32}$ +122° (*c* 0.54); ^{1}H NMR (90 MHz): δ=1.17 (3H, d, Me-2, $J_{2,Me}$=7.5 Hz), 1.44 (3H, d, Me-5, $J_{5,Me}$=7.2 Hz), 2.27 (1H, dq, H-2, $J_{1,2}$=3.0 Hz, $J_{2,3}$=0 Hz), 3.11 (2H, apparently s, H-3 and H-4, $J_{3,4}$=4 Hz), 3.50 (3H, s, OMe), 4.38 (1H, q, H-5, $J_{4,5}$=0 Hz), and 4.43 (1H, d, H-1). MS *m/z* 127 (M^+−31).

B) From 13a: A sample of **13a** (611 mg) was treated by the procedure described in the preparation from **8a** and then worked up to give a syrup of **11a** (432 mg, 87%).

Methyl 2,4,6-Trideoxy-2,4-di-*C*-methyl-α-D-idopyranoside (12a) and Methyl 4-Chloro-2,4,6-trideoxy-2-*C*-methyl-α-D-idopyranoside (13a). A 3 M methylmagnesium chloride solution (37 ml), which was prepared in situ from magnesium (2.7 g) and a large excess of methyl chloride in THF, was added dropwise to a suspension of **11a** (1.60 g) with CuCl (400 mg) in THF (8 ml) with stirring at 5 °C under argon, and then stirring was continued at room temperature for 18 h. After the reaction was quenched with a saturated aqueous NH_4Cl solution (50 ml), the resulting mixture was partitioned between ethyl acetate and water. The combined organic layers were dried and evaporated to a residue, which was chromatographed on silica gel (88 g) with 5:2 benzene–ethyl acetate to give **12a** (1.05 g, 60%) and **13a** (0.55 g, 28%) having the R_f-values of 0.19 and 0.36 (3:1 hexane–ethyl acetate) respectively.

12a: Needles from ethyl acetate–hexane; mp 102—104 °C; $[\alpha]_D^{35}$ +111° (*c* 1.04); ^{1}H NMR (400 MHz): δ=1.00 and 1.08 (each 3H, d, Me-2 and Me-4, vice versa, *J*=7.0 and 7.4 Hz), 1.17 (3H, d, Me-5, $J_{5,Me}$=6.8 Hz), 1.77 (2H, m, H-2 and H-4), 2.62 (1H, d, OH, $J_{3,OH}$=8.2 Hz), 3.40 (1H, dt-like, H-3, $J_{2,3}$=$J_{3,4}$=5.5 Hz), 3.40 (3H, s, OMe), 4.23 (1H, dq, H-5, $J_{4,5}$=4.5 Hz), and 4.40 (1H, d, H-1, $J_{1,2}$=4.0 Hz); ^{1}H NMR (400 MHz, acetone-d_6): δ=0.93, 1.01, and 1.12 (each 3H, d, Me-2, Me-4, and Me-5, vice versa, *J*=7.2 Hz, *J*=6.7 Hz, and *J*=6.7 Hz), 1.44 (1H, m, H-2), 1.68 (1H, m, H-4), 2.80 (1H, broad s, OH), 3.10 (1H, t, $J_{2,3}$=$J_{3,4}$=9.1 Hz), 3.32 (3H, s, OMe), 4.08 (1H, dq, H-5, $J_{4,5}$=5.6 Hz, $J_{5,Me}$=6.7 Hz), and 4.22 (1H, d, H-1, $J_{1,2}$=7.4 Hz).

Found: C, 61.84; H, 10.23%. Calcd for $C_9H_{18}O_3$: C, 62.04; H, 10.41%.

13a: Needles from ether–hexane: mp 93—94 °C; $[\alpha]_D^{32}$ +117° (*c* 0.91); ^{1}H NMR (400 MHz): δ=1.25 (3H, d, Me-2, $J_{2,Me}$=7.5 Hz), 1.34 (3H, d, Me-5, $J_{5,Me}$=6.5 Hz), 1.97 (1H, m, H-2), 3.40 (3H, s, OMe), 3.43 (1H, d, OH, $J_{3,OH}$=8.0 Hz), 3.85 (1H, m, H-3), 3.91 (1H, dd, H-4, $J_{3,4}$=3.5 Hz, $J_{4,5}$=3.0 Hz), 4.40 (1H, dq, H-5), and 4.56 (1H, d, H-1, $J_{1,2}$=2.3 Hz).

Found: C, 49.09; H, 7.58%. Calcd for $C_8H_{15}O_3Cl$: C, 49.36; H, 7.77%.

Methyl 2,4,6-Trideoxy-2,4-di-*C*-methyl-α-D-talopyranoside (14a). To a stirred and ice-cooled solution of **12a** (22.4 mg)

†† 1 mmHg≅133.322 Pa.

in dichloromethane (0.45 ml) were added Molecular Sieves 3A powder (193 mg) and pyridinium chlorochromate (111 mg), and stirring was continued at room temperature for 1 h. The mixture was diluted with ether and passed through a silica-gel column (1.0 g) with ether to give a crude syrup (23 mg) of the keto compound.

The syrup was stirred with $NaBH_4$ (9.7 mg) in methanol (0.49 ml) at room temperature for 1 h. The reaction mixture was neutralized with Amberlite CG-50 (H type), filtered and then evaporated to a residue, which was chromatographed on silica gel (2.2 g) with 3:1 hexane–ethyl acetate to afford **14a** (18 mg, 82%) and the starting **12a** (2.2 mg, 10%) having R_f-values of 0.24 and 0.19 (3:1 hexane–ethyl acetate) respectively.

14a: syrup; $[\alpha]_D^{31}$ +107° (*c* 0.69); ^{1}H NMR (400 MHz): δ=0.97 and 1.05 (each 3H, d, Me-4 and Me-2, $J_{4,Me}=J_{2,Me}$=7.2 Hz), 1.22 (3H, d, Me-5, $J_{5,Me}$=6.7 Hz), 1.51 (1H, broad s, OH), 1.90 (2H, m, H-2 and H-4), 3.36 (3H, s, OMe), 3.99 (1H, t, H-3, $J_{2,3}=J_{3,4}$=4.8 Hz), 4.04 (1H, dq, H-5, $J_{4,5}$=4.2 Hz), and 4.51 (1H, d, H-1, $J_{1,2}$=3.5 Hz). HRMS Found: *m/z* 174.1229. Calcd for $C_9H_{18}O_3$: M, 174.1255.

Methyl 3,4-Anhydro-2-*O*-mesyl-6-*O*-trityl-α-D-altropyranoside (7b). To a stirred and ice-cooled solution of **3** (40.4 g) in pyridine (400 ml) were added 4-dimethylaminopyridine (1.26 g) and trityl chloride (63.2 g), and stirring was continued at room temperature for 24 h. After cooling again, mesyl chloride (33.7 ml) was added, and the resulting mixture was allowed to stand with stirring at room temperature for 8 h. After addition of ethanol (23 ml), the mixture was evaporated and co-evaporated with toluene to a residue, which was partitioned between ethyl acetate and a saturated aqueous $NaHCO_3$ solution. The combined organic layers were washed with a saturated aqueous NaCl solution, dried, and evaporated to give a crude syrup of **6b** (approximately 150 g): R_f 0.28 (6:1 benzene–ethyl acetate).

To an ice-cooled solution of the crude syrup in chloroform (750 ml) was added dropwise a 28% methanolic sodium methoxide solution (65.7 ml) with stirring, and the mixture was stirred at room temperature for 14 h and then partitioned between chloroform and water. The combined organic layers were washed with water, dried and evaporated to a residue, which was chromatographed on silica gel (1 kg) with 10:1 benzene–ethyl acetate followed by recrystallization from benzene–ethyl acetate to give cubes of **7b** (75.4 g. 73% overall yield from **3**): R_f 0.30 (20:1 benzene–ethyl acetate); mp 150—151 °C; $[\alpha]_D^{31}$ +17° (*c* 1.0); IR (KBr): 1367 and 1176 cm^{-1} (OMs); ^{1}H NMR (400 MHz): δ=3.09 (3H, s, Ms), 3.27 (1H, d, H-4, $J_{3,4}$=3.5 Hz, $J_{4,5}$=0 Hz), 3.37 (3H, s, OMe), 3.47 (1H, dd, H-6, $J_{5,6}$=4.3 Hz, $J_{6,6'}$=10.3 Hz), 3.51 (1H, dd, H-6′, $J_{5,6'}$=4.3 Hz), 3.53 (1H, d, H-3, $J_{2,3}$=0 Hz), 4.22 (1H, t, H-5), 4.65 (1H, d, H-1, $J_{1,2}$=4.5 Hz), 4.82 (1H, d, H-2), and 7.24—7.47 (15H, m, Tr).

Found: C, 65.10; H, 5.60%. Calcd for $C_{27}H_{28}O_7S$: C, 65.31; H, 5.68%.

Methyl 4-Bromo-2,4-dideoxy-2-*C*-methyl-6-*O*-trityl-α-D-idopyranoside (8b) and Methyl 2,4-Dibromo-2,4-dideoxy-6-*O*-trityl-α-D-idopyranoside (9b). A) From 7b: A sample of **7b** (1.26 g) was treated by the procedure described in the preparation of **8a** and **9a** from **7a**, and then worked up to give amorphous solids of **8b** (694 mg, 55%) and **9b** (386 mg, 27%) having the R_f-values of 0.41 and 0.47 (20:1 benzene–ethyl acetate) respectively.

8b: $[\alpha]_D^{27}$ +25° (*c* 1.0); ^{1}H NMR (400 MHz): δ=1.27 (3H, d, Me-2, $J_{2,Me}$=7.2 Hz), 1.99 (1H, m, H-2), 3.24 (1H, dd, H-6, $J_{5,6}$=4.8 Hz, $J_{6,6'}$=9.8 Hz), 3.43 (3H, s, OMe), 3.44 (1H, d, OH, $J_{3,OH}$=8.0 Hz), 3.52 (1H, dd, H-6′, $J_{5,6'}$=6.7 Hz), 3.91 (1H, dt, H-3, $J_{2,3}=J_{3,4}$=3.2 Hz), 4.02 (1H, t, H-4, $J_{4,5}$=3.2 Hz), 4.14 (1H, m, H-5), 4.57 (1H, broad s, H-1, $J_{1,2}$=0 Hz), and 7.22—7.49 (15H, m, Tr); MS *m/z* 498 and 496 (M$^+$).

9b: $[\alpha]_D^{31}$ +37° (*c* 1.0); ^{1}H NMR (400 MHz): δ=2.96 (1H, d, OH, $J_{3,OH}$=5.2 Hz), 3.49 (3H, s, OMe), 3.52 (1H, dd, H-6, $J_{5,6}$=3.8 Hz, $J_{6,6'}$=10.7 Hz), 3.63 (1H, dd, H-6′, $J_{5,6'}$=5.4 Hz), 3.78 (1H, dd, H-2, $J_{1,2}$=6.4 Hz, $J_{2,3}$=7.5 Hz), 4.04 (1H, dd, H-4, $J_{3,4}$=7.5 Hz, $J_{4,5}$=4.6 Hz), 4.15 (1H, m, H-5), 4.37 (1H, dt, H-3), 5.10 (1H, d, H-1), and 7.23—7.49 (15H, m, Tr); MS *m/z* 564, 562, and 560 (M$^+$), and 482 (M$^+$—Br).

B) From 10b: A sample of **10b** (172 mg) was treated by the procedure described in the preparation of **8a** and **9a** from **10a**, and then worked up to give **8b** (114 mg, 64%) and **9b** (54 mg, 27%).

Methyl 2,3-Anhydro-4-bromo-4-deoxy-6-*O*-trityl-α-D-gulopyranoside (10b). A sample of **9b** (294 mg) was treated by the procedure described in the preparation of **10a** from **9a**, and then worked up to give a syrup of **10b** (213 mg, 85%): R_f 0.58 (20:1 benzene–ethyl acetate); $[\alpha]_D^{31}$ −31° (*c* 0.99); ^{1}H NMR (400 MHz): δ=3.04 (1H, dd, H-6, $J_{5,6}$=5.8 Hz, $J_{6,6'}$=9.3 Hz), 3.39 (1H, dd, H-6′, $J_{5,6'}$=6.4 Hz), 3.45 (1H, dd, H-2, $J_{1,2}$=2.9 Hz, $J_{2,3}$=3.9 Hz), 3.50 (3H, s, OMe), 3.62 (1H, dd, H-3, $J_{3,4}$=2.0 Hz), 4.09 (1H, m, H-5), 4.41 (1H, t, H-4, $J_{4,5}$=2.0 Hz), 4.98 (1H, d, H-1), and 7.21—7.45 (15H, m, Tr); MS *m/z* 482 and 480 (M$^+$).

Methyl 3,4-Anhydro-2-deoxy-2-*C*-methyl-6-*O*-trityl-α-D-altropyranoside (11b). A) From 8b: A sample of **8b** (1.32 g) was treated by the procedure described in the preparation of **11a** from **8a**, and then worked up to give an amorphous solid of **11b** (987 mg, 89%): R_f 0.33 (20:1 benzene–ethyl acetate); $[\alpha]_D^{30}$ +44° (*c* 1.1); ^{1}H NMR (400 MHz): δ=1.15 (3H, d, Me-2, $J_{2,Me}$=8.0 Hz), 2.20 (1H, dq, H-2, $J_{1,2}$=2.4 Hz, $J_{2,3}$=0 Hz), 3.05 and 3.20 (each 1H, d, H-3 and H-4, vice versa, $J_{3,4}$=4.5 Hz, $J_{4,5}$=0 Hz), 3.33 (3H, s, OMe), 3.36 (1H, dd, H-6, $J_{5,6}$=4.8 Hz, $J_{6,6'}$=9.5 Hz), 3.43 (1H, dd, H-6′, $J_{5,6'}$=4.8 Hz), 4.13 (1H, t, H-5), 4.37 (1H, d, H-1), and 7.22—7.49 (15H, m, Tr); MS *m/z* 417 (M$^+$+1).

B) From 13b: A sample of **13b** (1.01 g) was treated by the procedure described in the preparation of **11a** from **8a** or **13a**, and then worked up to give **11b** (931 mg, 99%).

Methyl 2,4-Dideoxy-2,4-di-*C*-methyl-6-*O*-trityl-α-D-idopyranoside (12b) and Methyl 4-Chloro-2,4-dideoxy-2-*C*-methyl-6-*O*-trityl-α-D-idopyranoside (13b). A sample of **11b** (1.88 g) was treated by the procedure described in the preparation of **12a** and **13a** from **11a**, and then worked up to give amorphous solids of **12b** (1.17 g, 60%) and **13b** (587 mg, 29%) having the R_f-values of 0.25 and 0.44 (3:1 hexane–ethyl acetate) respectively.

12b: $[\alpha]_D^{33}$ +25° (*c* 1.1); ^{1}H NMR (400 MHz): δ=0.80 and 1.06 (each 3H, d, Me-2 and Me-4, vice versa, *J*=7.2 Hz), 1.75—1.92 (2H, m, H-2 and H-4), 2.91 (1H, dull d, OH, $J_{3,OH}$=7.8 Hz), 3.02 (1H, dd, H-6, $J_{5,6}$=4.5 Hz, $J_{6,6'}$=9.8 Hz), 3.33 (1H, dd, H-6′, $J_{5,6'}$=6.9 Hz), 3.42 (1H, m, H-3), 3.49 (3H, s, OMe), 4.26 (1H, dt, H-5, $J_{4,5}$=4.5 Hz), 4.52 (1H, d, H-1, $J_{1,2}$=2.7 Hz), and 7.20—7.50 (15H, m, Tr); MS *m/z* 433 (M$^+$+1).

13b: $[\alpha]_D^{33}$ +23° (*c* 0.69); ^{1}H NMR (400 MHz): δ=1.22 (3H, d, Me-2, $J_{2,Me}$=7.8 Hz), 1.99 (1H, ddq, H-2, $J_{1,2}$=1 Hz,

$J_{2,3}$=2.5 Hz), 3.28 (1H, dd, H-6, $J_{5,6}$=4.9 Hz, $J_{6,6'}$=10.0 Hz), 3.43 (3H, s, OMe), 3.46 (1H, d, OH, $J_{3,OH}$=8.3 Hz), 3.52 (1H, dd, H-6', $J_{5,6'}$=6.4 Hz), 3.82 (1H, ddd, H-3, $J_{3,4}$=2.9 Hz), 3.95 (1H, t, H-4, $J_{4,5}$=2.9 Hz), 4.26 (1H, m, H-5), 4.58 (1H, broad s, H-1), and 7.21—7.49 (15H, m, Tr); MS *m/z* 453 and 452 (M^+).

Methyl 2,4-Dideoxy-2,4-di-*C*-methyl-6-*O*-trityl-α-D-talopyranoside (14b). A sample of **12b** (99 mg) was treated by the successive procedure in the preparation of **14a** through the keto compound, and then worked up to give **14b** (83 mg, 84%) and the starting **12b** (7.7 mg, 7.6%) having the R_f-values of 0.30 and 0.25 (3:1 hexane–ethyl acetate) respectively.

14b: syrup; $[\alpha]_D^{33}$ +59° (*c* 0.30); ^{1}H NMR (400 MHz): δ=0.73 (3H, d, Me-4, $J_{4,Me}$=7.4 Hz), 1.04 (3H, d, Me-2, $J_{2,Me}$=7.0 Hz, 1.88 (1H, m, H-2), 1.96 (1H, d, OH, $J_{3,OH}$=6.2 Hz), 2.04 (1H, m, H-4), 3.16 (1H, dd, H-6, $J_{5,6}$=4.2 Hz, $J_{6,6'}$=10.2 Hz), 3.29 (1H, dd, H-6', $J_{5,6}$=6.4 Hz), 3.49 (3H, s, OMe), 3.89 (1H, dt, H-3, $J_{2,3}$=$J_{3,4}$=4.4 Hz), 4.03 (1H, dt, H-5, $J_{4,5}$=4.2 Hz), 4.65 (1H, d, H-1, $J_{1,2}$=4.1 Hz), and 7.21—7.51 (15H, m, Tr); MS *m/z* 433 (M^++1).

Methyl 2,4-Dideoxy-2,4-di-*C*-methyl-α-D-idopyranoside (15). A solution of **12b** (152 mg) in ethanol (3.6 ml) was shaken with palladium hydroxide on carbon and 3-atm hydrogen at room temperature for 38 h, filtered and evaporated to give a residue. This was chromatographed on silica gel (8 g) with ethyl acetate followed by recrystallization from ethyl acetate to give needles of **15** (49.8 mg, 75%): R_f 0.33 (ethyl acetate); mp 149—150 °C; $[\alpha]_D^{31}$ +99° (*c* 1.0); ^{1}H NMR (400 MHz): δ=1.00 and 1.11 (each 3H, d, Me-2 and Me-4, vice versa, *J*=7.2 Hz), 1.81—1.96 (3H, m, H-2, H-4, and OH-3), 2.99 (1H, broad signal, OH-6), 3.42 (1H, m, H-3), 3.42 (3H, s, OMe), 3.58 (1H, dd, H-6, $J_{5,6}$=3.6 Hz, $J_{6,6'}$=11.2 Hz), 3.76 (1H, dd, H-6', $J_{5,6'}$=9.0 Hz), 4.19 (1H, dt, H-5, $J_{4,5}$=3.6 Hz), and 4.51 (1H, d, H-1, $J_{1,2}$=2.9 Hz); ^{1}H NMR (400 MHz, acetone-d_6): δ=0.99 (3H, d, Me-4, $J_{4,Me}$=6.8 Hz), 1.02 (3H, d, Me-2, $J_{2,Me}$=6.8 Hz), 1.55 (1H, m, H-2), 1.77 (1H, m, H-4), 3.17 (1H, dt, H-3, $J_{2,3}$=8.8 Hz, $J_{3,4}$=$J_{3,OH}$=6.8 Hz), 3.35 (3H, s, OMe), 3.47 (1H, dd, OH-6, $J_{6,OH}$=6.4 Hz, $J_{6',OH}$=4.4 Hz), 3.57 (1H, ddd, H-6, $J_{5,6}$=4.9 Hz, $J_{6,6'}$=11.2 Hz), 3.67 (1H, d, OH-3), 3.70 (1H, ddd, H-6', $J_{5,6'}$=7.3 Hz), 3.99 (1H, dt, H-5, $J_{4,5}$=4.9 Hz), and 4.35 (1H, d, H-1, $J_{1,2}$=6.8 Hz).

Found: C, 56.63; H, 9.25%. Calcd for $C_9H_{18}O_4$: C, 56.82; H, 9.54%.

Methyl 2,4-Dideoxy-2,4-di-*C*-methyl-α-D-talopyranoside (16). A sample of **14b** (97.5 mg) was treated by the procedure described in the preparation of **15**, and then worked up to give a syrup of **16** (37.3 mg, 87%): R_f 0.40 (ethyl acetate); $[\alpha]_D^{32}$ +106° (*c* 1.0); ^{1}H NMR (400 MHz): δ=0.99 (3H, d, Me-2, $J_{2,Me}$=7.1 Hz), 1.05 (3H, d, Me-4, $J_{4,Me}$=7.2 Hz), 1.82 (1H, ddq, H-2, $J_{1,2}$=5.8 Hz, $J_{2,3}$=3.6 Hz), 2.13 (1H, m, H-4), 2.25—2.50 (2H, broad signal, OH-3 and OH-6), 3.43 (3H, s, OMe), 3.67 (1H, dd, H-6, $J_{5,6}$=3.3 Hz, $J_{6,6'}$=11.2 Hz), 3.85 (1H, dd, H-6', $J_{5,6'}$=6.6 Hz), 3.87 (1H, dd, H-3, $J_{2,3}$=3.6 Hz, $J_{3,4}$=7.4 Hz), 3.99 (1H, ddd, H-5, $J_{4,5}$=5.3 Hz), and 4.63 (1H, d, H-1); MS *m/z* 190 (M^+).

We are grateful to Prof. Sumio Umezawa, Institute of Bioorganic Chemistry, and the late Prof. Hamao Umezawa, Institute of Microbial Chemistry for their generous support of our program. Financial support by the Ministry of Education, Science and Culture (Grant-in-Aid for Scientific Research) is gratefull acknowledged.

References

1) K. Tatsuta, Y. Amemiya, S. Maniwa, and M. Kinoshita, *Tetrahedron Lett.*, **21**, 2837 (1980); K. Tatsuta, Y. Amemiya, Y. Kanemura, and M. Kinoshita, *Tetrahedron Lett.*, **22**, 3997 (1981); S. Hanessian, *Acc. Chem. Res.*, **12**, 159 (1979); I. Paterson and M. M. Mansuri, *Tetrahedron*, **41**, 3569 (1985).

2) D. R. Harris, S. G. McGeachin, and H. H. Mills, *Tetrahedron Lett.*, **1965**, 679; M. Kinoshita, M. Arai, K. Tomooka, and M. Nakata, *Tetrahedron Lett.*, **27**, 1811, 1815 (1986) and references cited therein; H. Tone, T. Nishi, Y. Oikawa, M. Hikota, and O. Yonemitsu, *Tetrahedron Lett.*, **28**, 4569 (1987).

3) A. G. Agtarap, J. W. Charnberlain, M. Pinkerton, and L. Steinrauf, *J. Am. Chem. Soc.*, **89**, 5737 (1967); T. Fukuyama, K. Akasaka, D. S. Karanewsky, C.-L. J. Wang, G. Schmid, and Y. Kishi, *ibid.*, **101**, 259 (1979).

4) W. Oppolzer and V. Prelog, *Helv. Chim. Acta.*, **56**, 2287 (1973); H. Nagaoka, W. Rutsch, G. Schmid, H. Iio, M. R. Johnson, and Y. Kishi, *J. Am. Chem. Soc.*, **102**, 7962 (1980); M. Nakata, S. Wada, K. Tatsuta, and M. Kinoshita, *Bull. Chem. Soc. Jpn.*, **58**, 1801 (1985).

5) B. K. Toeplitz, A. I. Cohen, P. T. Funke, W. L. Parker, and J. Z. Gougoutas, *J. Am. Chem. Soc.*, **101**, 3344 (1979).

6) D. J. Duchamp, A. R. Branfman, A. C. Button, K. L. Rinehart, Jr., *J. Am. Chem. Soc.*, **95**, 4077 (1973).

7) a) S. Challenger and G. Procter, *Tetrahedron Lett.*, **27**, 391 (1986); b) T. Ogawa, N. Takasaka, and M. Matsui, *Carbohydr. Res.*, **60**, C4 (1978); c) A. G. Kelly and J. S. Roberts, *J. Chem. Soc., Chem. Commun.*, **1980**, 228; d) N. K. Kochetkov, A. F. Sviridov, and M. S. Ermolenko, *Tetrahedron Lett.*, **22**, 4315 (1981); e) A. F. Sviridov, G. E. Berdimbetova, and N. K. Kochetkov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, **1982**, 2572; *Chem. Abstr.*, **98**, 179765b (1983); f) L. Magdzinski, B. Cweiber, and B. Fraser-Reid, *Tetrahedron Lett.*, **24**, 5823 (1983); g) M. P. Edwards, S. V. Ley, S. G. Lister, and B. D. Palmer, *J. Chem. Soc., Chem. Commun.*, **1983**, 630; h) P. J. Hodges and G. Procter, *Tetrahedron Lett.*, **26**, 4111 (1985); i) T. Wakamatsu, H. Nakamura, Y. Nishikimi, K. Yoshida, T. Noda, M. Taniguchi, and Y. Ban, *Tetrahedron Lett.*, **27**, 6071 (1986).

8) S. Masamune, T. Sato, B. M. Kim, and T. A. Wollman, *J. Am. Chem. Soc.*, **108**, 8279 (1986); W. R. Roush and A. D. Palkowitz, *ibid.*, **109**, 953 (1987).

9) P. J. Garegg and B. Samuelsson, *J. Chem. Soc., Chem. Commun.*, **1979**, 978.

10) K. Tatsuta, K. Akimoto, M. Annaka, Y. Ohno, and M. Kinoshita, *Bull. Chem. Soc. Jpn.*, **58**, 1699 (1985).

11) L. Hough and A. C. Richardson, "Conformational Analysis of The Monosaccharides," in "Rodd's Chemistry of Carbon Compounds," ed by S. Coffey, Elsevier Publishing Co., Amsterdam (1967), pp. 87—124.

12) R. U. Lemieux and S. Levine, *Can. J. Chem.*, **42**, 1473 (1964).