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Chemical Modification of Maltose. IV.[1] Synthesis of 4-O-α-D-Altropyranosyl-D-glucopyranose[2]

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The new reducing disaccharide 4-O-α-D-altropyranosyl-D-glucopyranose (**12**) was synthesized by isomerization of secondary hydroxyl groups in the non-reducing part of maltose.

Treatment of 1,6-anhydro-4′,6′-O-benzylidene-2,2′-di-O-tosyl-β-maltose (**2**) with methanolic sodium methoxide at room temperature gave the corresponding monoepoxide (**3**) in 90% yield, in which the oxirane ring is located in the reducing part of maltose. When the reaction was performed at boiling temperature, the diepoxide (**5**) having α-D-mannopyranosyl-D-mannopyranose configuration was obtained in 77% yield. Compound **5** was also obtainable from **2** in 79% yield. Heating a mixture of **5** and excess potassium hydroxide resulted in *trans*-diaxial cleavage of both oxirane rings, and 2,3-di-O-acetyl-1,6-anhydro-4-O-(2,3-di-O-acetyl-4,6-O-benzylidene-α-D-altropyranosyl)-β-D-glucopyranose (**6**) was isolated in 81.4% yield after acetylation of the cleavage product. Compound **6** was also obtainable from **2** in 59% yield. The disaccharide **12** was prepared as a hygroscopic amorphous powder after removal of the protecting groups of **6** as follows; debenzylidenation, acetylation, acetolysis, and deacetylation.

Keywords——synthesis; new reducing disaccharide; maltose; maltosan; maltosan ditosylate; maltosan monoepoxide; maltosan diepoxide; Fuerst-Plattner rule; isomerization; altrose-containing disaccharide

We reported previously a synthesis of a new reducing disaccharide having an α-(1→4) glycosidic linkage, 4-O-α-D-galactopyranosyl-D-glucopyranose, through chemical modification of maltose.[3] As an extension of our program of chemical modification of maltose, we now describe a synthesis of 4-O-α-D-altropyranosyl-D-glucopyranose. The method is based on utilization of the latent α-glycosidic linkage in maltose derivatives, isomerization of both secondary hydroxyl groups in the non-reducing part of maltose, and finally, removal of the protecting groups.

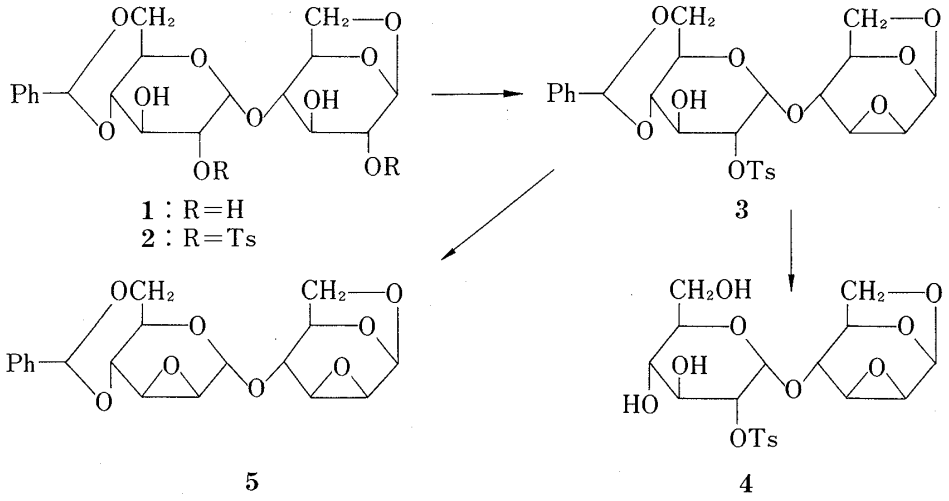
As D-altrose-containing reducing disaccharide, 4-O-β-D-galactopyranosyl-D-altrose (neolactose)[4] and 4-O-β-D-glucopyranosyl-D-altrose (celtrobiose)[5] are known. Both were chemically synthesized by isomerization of secondary hydroxyl groups in the reducing part of lactose and cellobiose, respectively. However, isomerization of maltose to a D-altrose-containing disaccharide has not yet been accomplished, as far as we know.

1,6-Anhydro-4′,6′-O-benzylidene-2,2′-di-O-tosyl-β-maltose (**2**) was the major product in selective tosylation of 1,6-anhydro-4′,6′-O-benzylidene-β-maltose (**1**) as reported in the previous paper[1]; it was isolated in 67.7% yield from **1**. In compound **2**, the tosyl and hydroxyl groups in the anhydroglucose residue are *trans*-diaxial because of the $^1C_4$-D-conformation, while those in the benzylideneglucose residue are *trans*-diequatorial. Thus, on treatment of **2** with alkali under mild conditions, such as treatment with 1.8 molar equivalents of 0.5 N methanolic sodium methoxide at room temperature, monoepoxide formation proceeded predominantly in the anhydroglucose residue of **1** to give 1,6: 2,3-dianhydro-4-O-(4,6-O-benzylidene-2-O-tosyl-α-D-glucopyranosyl)-β-D-mannopyranose (**3**) in 90% yield.

The structure of **3** was confirmed as follows. 1) In the infrared (IR) spectrum, absorption maxima due to hydroxyl and sulfonyloxy groups could be observed at 3490 and 1173 cm^{-1}, respectively. 2) In the proton magnetic resonance (^{1}H-NMR) spectrum, a new doublet having

a coupling constant of 3 Hz was recognized at 5.58 ppm, while the singlet at 5.29 ppm due to the anomeric proton (H-1) of the β-glucose residue in **2** disappeared. The doublet was assigned to H-1 of the newly introduced β-mannose residue, because the small coupling constant and the ^{1}H-NMR spectral data reported for 1,6: 2,3-dianhydro-β-D-mannopyranose[6] were consistent with this assignment. 3) Debenzylidenation of **3** gave a crystalline monotosyl-dianhydro-disacchacharide, 1,6: 2,3-dianhydro-4-O-(2-O-tosyl-α-D-glucopyranosyl)-β-D-mannopyranose (**4**), which consumed the theoretical amounts of periodate expected from the assigned structure.

Epoxide formation of the benzylideneglucose residue of **2** requires more severe conditions than those used for the anhydro-glucose residue, because of its *trans*-diequatorial $^4C_1$-conformation. A mixture of **3** and 5.3 molar equivalents of 0.5 N methanolic sodium methoxide was refluxed for 8 hours. From the mixture, white prisms (**5**) was isolated in 77% yield. The same product was also prepared in 78.7% yield directly from **2** by refluxing it with alkali. Compound **5** showed no IR absorption due to hydroxyl groups, but showed a purple color in the Ross test[7] due to the oxirane rings. In the ^{1}H-NMR spectrum, the H-1′ signal was observed as a singlet at 5.22 ppm. According to reports on the ^{1}H-NMR spectra of 2,3-anhydro-glycopyranosides and related compounds,[8] the H-1 of methyl 2,3-anhydro-4,6-O-benzylidene-α-D-mannopyranoside appeared as a singlet at 5.14 ppm . From the unequivocal synthetic route and properties of **5** mentioned above, **5** was assigned as 1,6: 2,3-dianhydro-4-O-(2,3-anhydro-4,6-O-benzylidene-α-D-mannopyranosyl)-β-D-mannopyranose.



Ph=phenyl, Ts=tosyl

Chart 1

As a next step, isomerization of secondary hydroxyl groups in the benzylideneglucose residue of **1** was investigated. Heating a mixture of **5** and excess aqueous potassium hydroxide for 28 hours caused the cleavage of both of the oxirane rings. The products were isolated as their acetate after neutralization and removal of the solvent, followed by acetylation of the residue. Thin-layer chromatogrophy (TLC) showed the formation of one major product (**6**) together with a trace of2,2′,3,3′-tetra-O-acetyl-1,6-anhydro-4′,6′-O-benzylidene-β-maltose.[3] Compound **6** was isolated by column chromatography as an amorphous powder in 81.4% yield. The same product was also obtainable in 59% yield from **2** by alkaline treatment, acetylation, and chromatography. The ^{1}H-NMR spectrum indicated the presence of a benzylidene acetal and four acetyl groups.

In compound **5**, each hexopyranose ring is rigidly fixed by a 1,6-anhydro or 4,6-O-benzylidene acetal ring. Therefore, both of the oxirane rings undergo scission by nucleophiles, leading to predominantly *trans*-diaxial substitution according to the Fuerst-Plattner rule.[9]

Thus, **6** was assigned as 2,3-di-O-acetyl-1,6-anhydro-4-O-(2,3-di-O-acetyl-4,6-O-benzylidene-α-D-altropyranosyl)-β-D-glucopyranose.

Debenzylidenation of **6** and subsequent acetylation gave the hexaacetate (**7**) as crystals. Deacetylation of **7** yielded a 1,6-anhydro-disaccharide (**8**). Each anomeric proton due to the reducing and non-reducing parts was assigned by ^{1}H-NMR spectroscopy and the chemical shifts of the anomeric carbons were measured by carbon 13-nuclear magnetic resonance (^{13}C-NMR) spectroscopy of **8**. The details of the ^{13}C-NMR spectrum will be reported in a separate paper.[10]

The 1,6-anhydro ring of **7** was cleaved by mild acetolysis to yield the octaacetate (**9**) as an anomeric mixture in 72% yield. The β-anomer was isolated from the earlier fractions on column chromatography, while the α-anomer was eluted from subsequent fractions of the same solvent. The α: β ratio in **9** was *ca.* 2: 1, as calculated from the specific rotations of **9** and the two anomers.

Deacetylation of **9** afforded the title sugar (**12**) as a hygroscopic amorphous powder in 83% yield. Since free D-altrose is extremely labile under acidic conditions, forming 1,6-anhydro-β-D-altrose,[11] usual hydrolytic conditions used for the component analysis of oligosaccharides cannot be applied in this case. Therefore, the disaccharide **12** was converted into its alditolacetate, which was acetolyzed. The acetolysate was deacetylated, and the products were examined by paper partition chromatography (PPC) and TLC on cellulose. Altrose was identified as a reducing monosaccharide together with glucitol and 4-O-altrosyl-glucitol. Thus, the structures of **6**—**12** were unequivocally determined.

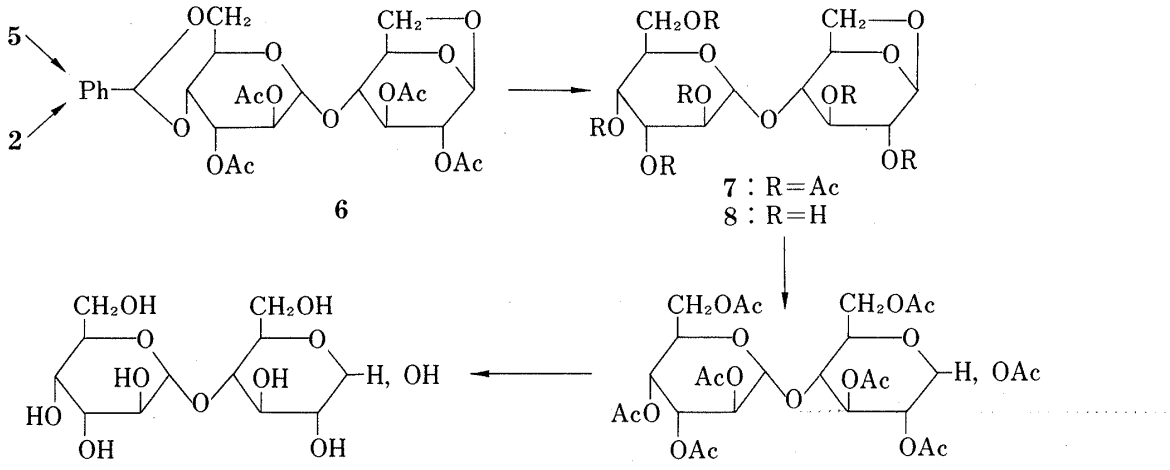


Chart 2

Experimental

Instruments used and conditions for chromatography were the same in Part III[1] unless otherwise indicated. ^{1}H-NMR spectra were recorded at 100 MHz with a JEOL JNM-MH-100 or JNM-FX-100 spectrometer. ^{13}C-NMR spectra were recorded at 25 MHz with a JEOL JNM-FX-100 spectrometer. Tetramethylsilane (TMS) was used as an internal (in $CDCl_3$ and pyridine-d_5) or external (in D_2O) standard. Chemical shifts are given in ppm from TMS. TLC was performed on Merck Kiesel Gel 60_{254} with the following solvent combinations (v/v): (A), CH_2Cl_2–acetone (9: 1); (B), CH_2Cl_2–acetone (1: 1); (C), benzene–ether (1: 3); (D), AcOEt–iso PrOH–H_2O (5: 7: 3).

1,6: 2,3-Dianhydro-4-O-(4,6-O-benzylidene-2-O-tosyl-α-D-glucopyranosyl)-β-D-mannopyranose (**3**)——A 0.5 N methanolic solution of MeONa (1.5 ml, 0.75 mmol) was added to a suspension of 1,6-anhydro-4′,6′-O-benzylidene-2,2′-di-O-tosyl-β-maltose (**2**)[1] (300 mg, 0.42 mmol) in MeOH (30 ml), and the mixture was stirred at room temperature overnight. The mixture was neutralized with AcOH in MeOH and concentrated

to a syrup, which was treated with CH_2Cl_2 (20 ml) and H_2O (15 ml) to effect dissolution. The organic layer was separated, washed with H_2O (10 ml×2), and dried (Na_2SO_4). Removal of the solvent and recrystallization of the residue from EtOH gave white needles (205 mg, 90%) which showed a pale red color in the Ross test,[7] mp 187—189°, $[\alpha]_D^{23}$ +68.8° (c=1.1, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 2.40 (3H, s, C<u>H</u>$_3$C$_6$H$_4$SO$_2$), 2.66 (1H, br. s, OH, exchangeable in D_2O), 5.26 (1H, d, J=4 Hz, H-1′, α-Glc), 5.43 (1H, s, C$_6$H$_5$C<u>H</u>), 5.58 (1H, d, J=3 Hz, H-1, β-Man). IR ν_{max}^{Nujol} cm^{-1}: 3490 (OH), 1596 (C=C bonds in tosyl), 1173 (SO_2). TLC: *Rf* 0.51 (solvent A), 0.50 (C). *Anal.* Calcd for $C_{26}H_{28}O_{11}S$: C, 56.93; H, 5.15. Found: C, 57.04; H, 5.21.

1,6: 2,3-Dianhydro-4-O-(2-O-tosyl-α-D-glucopyranosyl)-β-D-mannopyranose (4)——A suspension of **3** (300 mg, 0.55 mmol) in MeOH (60 ml) was hydrogenated with a Pd catalyst at room temperature under atmospheric pressure until absorption of H_2 ceased; the catalyst was freshly prepared[12] from $PdCl_2$ (150 mg). After removal of the catalyst and solvent, **4** was crystallized from AcOEt as white prisms (170 mg, 67.7%), mp 188—190°, $[\alpha]_D^{23}$ +94.6° (c=1.03, $CHCl_3$). IR ν_{max}^{Nujol} cm^{-1}: 3330 (OH), 1592 (C=C bonds in tosyl), 1175 (SO_2). TLC: *Rf* 0.01 (solvent A), 0.14 (B). *Anal.* Calcd for $C_{19}H_{24}O_{11}S$: C, 49.56; H, 5.25. Found: C, 49.52; H, 5.31. Periodate consumption[13] (mol) of **4** (54 mg) at room temperature was as follows: 0.17 (0.5 hr), 0.40 (2 hr), 0.71 (8 hr), and 1.12 (24 hr, constant).

1,6: 2,3-Dianhydro-4-O-(2,3-anhydro-4,6-O-benzylidene-α-D-mannopyranosyl)-β-D-mannopyranose (5)

——1) From Compound **3**: A mixture of **3** (155 mg, 0.28 mmol), 0.5 N methanolic MeONa (3 ml, 1.5 mmol), and MeOH (10 ml) was refluxed for 8 hr. The mixture was treated as described for the preparation of **3** to give **5** (82 mg, 77.1%). Recrystallization from AcOEt–hexane afforded white prisms showing a purple color in the Ross test,[7] mp 196—198°, $[\alpha]_D^{23}$ +76.4° (c=1.02, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 5.22 (1H, s, H-1′, α-Man), 5.53 (1H, s, C$_6$H$_5$C<u>H</u>), 5.65 (1H, d, J=3 Hz, H-1, β-Man). TLC: *Rf* 0.53 (solvent A), 0.47 (C). *Anal.* Calcd for $C_{19}H_{20}O_8$: C, 60.64; H, 5.36. Found: C, 60.51; H, 5.45.

2) From 1,6-Anhydro-4′,6′-O-benzylidene-2,2′-di-O-tosyl-β-maltose (**2**): A mixture of **2** (900 mg, 1.25 mmol) and 0.5 N methanolic MeONa (15 ml, 7.5 mmol) in MeOH (80 ml) was refluxed for 12 hr. The mixture was treated as described in method 1) to give **5** (370 mg, 78.7%).

2,3-Di-O-acetyl-1,6-anhydro-4-O-(2,3-di-O-acetyl-4,6-O-benzylidene-α-D-altropyranosyl)-β-D-glucopyranose (6)——1) From Compound **5**: A mixture of **5** (300 mg, 0.8 mmol) and 5% (w/v) KOH (30 ml, 26 mmol) was refluxed for 28 hr. After neutralization with ice-cold 6 N H_2SO_4, the solution was concentrated to dryness. The residue was acetylated with Ac_2O (4 ml) and pyridine (4 ml) at room temperature for 15 hr, poured into ice-H_2O (50 ml), and extracted with CH_2Cl_2 (20 ml×2). The extracts were successively washed with 10% H_2SO_4, aq. $NaHCO_3$, and H_2O. Desiccation (Na_2SO_4) and removal of the solvent provided a syrup, which was chromatographed on a column of silica gel with benzene–ether (2: 1, v/v). From the earlier fractions, **6** (380 mg, 81.4%), $[\alpha]_D^{23}$ +32.5° (c=0.80, $CHCl_3$), was isolated as an amorphous powder. ^{1}H-NMR ($CDCl_3$): 2.09, 2.13, 2.15, 2.18 (12H, all s, OAc×4), 5.44 (1H, s, H-1, β-Glc), 5.63 (1H, s, C$_6$H$_5$-C<u>H</u>). TLC: *Rf* 0.45 (solvent A), 0.36 (C). *Anal.* Calcd for $C_{27}H_{32}O_{14}$: C, 55.86; H, 5.56. Found: C, 55.59; H, 5.47. From subsequent fractions having *Rf* 0.28 (TLC, solvent C), a trace of 2,2′,3,3′-tetra-O-acetyl-1,6-anhydro-4′,6′-O-benzylidene-β-maltose[3] was isolated.

2) From Compound **2**: A suspension of **2** (200 mg, 0.25 mmol) in 5% KOH (20 ml, 7.8 mmol) was heated to reflux for 34 hr. After removal of insoluble material by filtration, the filtrate was treated as described in method 1) to give **6** (95 mg, 59%).

2,3-Di-O-acetyl-1,6-anhydro-4-O-(2,3,4,6-tetra-O-acetyl-α-D-altropyranosyl)-β-D-glucopyranose (7)——A mixture of **6** (980 mg, 1.69 mmol) in 80% (v/v) AcOH (30 ml) was stirred at 60° for 1 hr; complete debenzylidenation was confirmed by TLC with solvents A and B. The reaction mixture was concentrated to a syrup, which was acetylated with Ac_2O (15 ml) and pyridine (15 ml) at room temperature overnight. The mixture was treated as described for the preparation of **6** to yield **7** as an amorphous powder (880 mg, 90.7%), which crystallized from benzene–hexane. Recrystallization from the same solvent gave white prisms, mp 146—148°, $[\alpha]_D^{20}$ +31.8° (c=1.43, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 2.05, 2.07, 2.08, 2.10, 2.13, 2.15 (18H, all s, OAc×6), 5.39 (1H, s, H-1, β-Glc). TLC: *Rf* 0.35 (solvent A), 0.22 (C). *Anal.* Calcd for $C_{24}H_{32}O_{16}$: C, 50.00; H, 5.59. Found: C, 49.95; H, 5.60.

1,6-Anhydro-4-O-(α-D-altropyranosyl)-β-D-glucopyranose (8)——A 0.5 N methanolic MeONa (0.1 ml) was added to a solution of **7** (200 mg, 0.35 mmol) in MeOH (10 ml), and the mixture was stirred at room temperature for 2 hr under exclusion of moisture; complete deacetylation was confirmed by TLC with solvent A. After neutralization with Amberlite IR-120 (H^+) resin and removal of the solvent, **8** was obtained as a hygroscopic amorphous powder (104 mg, 92.5%), $[\alpha]_D^{23}$ +47.1° (c=0.67, H_2O). ^{1}H-NMR (D_2O): 5.44 (1H, s, H-1′, α-Alt), 5.96 (1H, s, H-1, β-Glc). ^{13}C-NMR (D_2O): 101.1 (C-1′, α-Alt), 102.5 (C-1, β-Glc). ^{13}C-NMR (pyridine-d_5): 102.8 (C-1′, α-Alt), 104.1 (C-1, β-Glc). TLC: *Rf* 0.37 (solvent D). *Anal.* Calcd for $C_{12}H_{20}O_{10}\cdot H_2O$: C, 42.11; H, 6.48. Found: C, 42.36; H, 6.51.

1,2,3,6-Tetra-O-acetyl-4-O-(2,3,4,6-tetra-O-acetyl-α-D-altropyranosyl)-D-glucopyranoses (9)——Sulfuric acid (0.1 ml) was added dropwise under stirring at 0° to a chilled solution of **7** (650 mg, 1.13 mmol) in Ac_2O (7 ml) and AcOH (3 ml), and stirring was continued below 10° for a further 1.5 hr. The mixture was poured into ice-H_2O (80 ml), and extracted with CH_2Cl_2 (20 ml×3). The extracts were washed with aq. $NaHCO_3$ and H_2O. Desiccation (Na_2SO_4) and removal of the solvent gave a syrup, which was chromatographed on a column of silica gel with benzene–ether (1: 1, v/v) to yield **9** as an amorphous powder (530 mg, 71.8%),

$[\alpha]_D^{23}$ +79.7° (c=1.07, $CHCl_3$). The α: β ratio in **9** was calculated as 67: 33 from the specific rotations of **9**, **10**, and **11**.

1,2,3,6-Tetra-O-acetyl-4-O-(2,3,4,6-tetra-O-acetyl-α-D-altropyranosyl)-β-D-glucopyranose (10)——The anomeric mixture (**9**, 210 mg) was chromatographed on a column of silica gel, eluting with benzene–ether (2: 1, v/v). From the earlier fractions, **10** (38 mg, 18%) was isolated as an amorphous powder, $[\alpha]_D^{20}$ +51.5° (c=0.74, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 2.02, 2.04, 2.08, 2.10, 2.12 (24H, all s, OAc×8), 5.75 (1H, d, J=8 Hz, H-1, β-Glc). TLC: *Rf* 0.38 (solvent A), 0.26 (C), 0.42 (solvent C, two elutions). *Anal.* Calcd for $C_{28}H_{38}O_{19}$: C, 49.56; H, 5.64. Found: C, 49.96; H, 5.76.

1,2,3,6-Tetra-O-acetyl-4-O-(2,3,4,6-tetra-O-acetyl-α-D-altropyranosyl)-α-D-glucopyranose (11)——Compound **11** (45 mg, 21.4%) was eluted in subsequent fractions from the column chromatography of **9**. The product was isolated as an amorphous powder, $[\alpha]_D^{20}$ +93.5° (c=0.62, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 2.01, 2.05, 2.10, 2.12, 2.13, 2.19 (24H, all s, OAc×8), 6.30 (1H, d, J=4 Hz, H-1, α-Glc). TLC: *Rf* 0.38 (solvent A), 0.24 (C), 0.38 (solvent C, two elutions). *Anal.* Calcd for $C_{28}H_{38}O_{19}$: C, 49.56; H, 5.64. Found: C, 50.03; H, 5.90.

4-O-α-D-Altropyranosyl-D-glucopyranose (12)——Deacetylation of **9** (430 mg, 0.63 mmol) in MeOH (15 ml) with 0.5 N methanolic MeONa (0.3 ml) was performed as described for the preparation of **8** to yield **12** (180 mg, 83%), as a hygroscopic amorphous powder, $[\alpha]_D^{23}$ +110.5° (c=1.17, H_2O). TLC: *Rf* 0.34 (solvent D). TLC on precoated microcrystalline cellulose plates 0.25 mm thick (Avicel SF, Funakoshi Yakuhin, Ltd., Tokyo) with AcOEt–pyridine–AcOH–H_2O (5: 5: 1: 3, v/v): *Rf* 0.27; detection was effected with alkaline silver nitrate reagent.[14] PPC with BuOH–pyridine–H_2O (6: 4: 3, v/v) or phenol–H_2O (5: 1, v/v): *Rf* 0.33. *Anal.* Calcd for $C_{12}H_{22}O_{11}\cdot 1.5H_2O$: C, 39.03; H, 6.82. Found: C, 38.94; H, 6.86.

Identification of the Component Monosaccharides in 12——Sodium borohydride (120 mg) was added to a solution of **12** (55 mg) in H_2O (10 ml), and the mixture was stirred at room temperature for 20 hr. After neutralization with Amberlite IR-120 (H^+) resin, the mixture was filtered and the filtrate was concentrated to dryness. The contaminating boric acid was then removed by repeated co-distillation with MeOH. The residue was dissolved in Ac_2O–AcOH (7: 3, v/v, 1.5 ml), H_2SO_4 (1 drop) was added, and then the mixture was stirred at room temperature for 20 hr to achieve acetolysis. The mixture was poured into ice-H_2O, and extracted with $CHCl_3$ (10 ml×2). The extracts were washed with aq. $NaHCO_3$ and H_2O. Desiccation (Na_2SO_4) and removal of the solvent provided a syrup, which was deacetylated with 0.5 N methanolic MeONa as described for the preparation of **12**, to give a syrup. The residue was dissolved in a small amount of H_2O and subjected to PPC or TLC on cellulose plates. Solvent combinations used for the analysis of **12** were applied. Detection was effected with alkaline silver nitrate or permanganate-periodate reagent.[15] TLC: *Rf* 0.48 (altrose[11]); 0.33 (glucitol); 0.24 (4-O-altropyranosyl-glucitol). *cf.* 0.35 (glucose). PPC with BuOH–pyridine–H_2O (6: 4: 3, v/v): *Rf* 0.53 (altrose); 0.40 (glucitol); 0.31 (4-O-altropyranosyl-glucitol). *cf.* 0.42 (glucose).

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References and Notes

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