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Chemical Modification of Lactose. X.[1] Syntheses of 4-O-(3-O-Methyl-β-D-idopyranosyl)-D-glucopyranose and 4-O-(3-Deoxy-β-D-*lyxo*-hexopyranosyl)-D-glucopyranose

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The titled new reducing disaccharides were synthesized from a derivative of lactose. When 1,6-anhydro-4-O-(2,3-anhydro-4,6-O-benzylidene-β-D-talopyranosyl)-β-D-glucopyranose (**2**) was treated with boiling methanolic sodium methoxide, or $LiAlH_4$ in boiling tetrahydrofuran, the *trans*-diaxial cleavage of the epoxide ring proceeded predominantly according to the Fürst-Plattner rule. This agreed with the result obtained by treatment of **2** with KOH, reported previously [T. Chiba and S. Tejima, *Chem. Pharm. Bull.* (Tokyo), **25**, 1049 (1977)]. After acetylation, the major and minor cleavage products of epoxide were isolated by column chromatography on silica gel. The structural assignments of individual products were described. The titled disaccharides were respectively prepared from the individual major product *via* a series of the following reactions: debenzylidenation, acetylation, opening of the 1,6-anhydro ring, and removal of the acetyl groups.

Keywords——synthesis; new reducing disaccharide; lactosan; nucleophilic cleavage; epoxide ring; 1,6-anhydro ring; NMR

Many higher oligosaccharides in human milk have structures conjugating amino oligosaccharides at the C-3′ hydroxyl group in lactose.[3] Among the several secondary hydroxyl groups in lactose derivatives, the hydroxyl group at C-3′ is the most reactive. This has been shown by detailed studies on the selective benzoylation of methyl β-lactoside[4] and 1,6-anhydro-4′,6′-O-benzylidene-β-lactose (**1**),[5] and by selective *p*-toluenesulfonylation of **1**.[6] Thus, the C-3′ position should be a remarkable one from chemical or biological viewpoint.

In Part VII of this series,[7] we reported a synthesis of 4-O-β-D-idopyranosyl-D-glucopyranose. This was the first example of isomerization of the secondary hydroxyl groups in the D-galactopyranosyl moiety of lactose. We pointed out in the paper that 1,6-anhydro-4-O-(2,3-anhydro-4,6-O-benzylidene-β-D-talopyranosyl)-β-D-glucopyranose (**2**) should be a useful key intermediate for chemical modification of lactose. We now report the syntheses of the titled new reducing disaccharides having 1,2-*cis* internal glycosidic linkage. The synthetic routes are based on nucleophilic cleavage of the epoxide ring in **2**, debenzylidenation, acetylation, opening of the 1,6-anhydro ring, and removal of the acetyl groups. This paper also describes another example of modification of the secondary hydroxyl groups in the D-galactopyranosyl moiety of lactose.

A mixture of **2**[7] with excess methanolic sodium methoxide was refluxed for 3 hr. After neutralization and removal of the solvent, the residue was acetylated to afford a sirup which showed two spots, *Rf* 0.36 (major) and 0.28 (minor), on thin-layer chromatography (TLC). It was chromatographed through a column of silica gel to afford a crystal (**3**, 85%) of *Rf* 0.36 and an amorphous powder (**9**, 4%) of *Rf* 0.28, both of which had the same elemental composi-

1) Part IX: T.G. Chung, H. Ishihara, and S. Tejima, *Chem. Pharm. Bull.* (Tokyo), **26**, 2147 (1978).
2) Location: *Tanabe-dori, Mizuho-ku, Nagoya, 467, Japan.*
3) A. Kobata, *Metabolism and Desease*, **13**, 575 (1976).
4) R.S. Bhatt, L. Hough, and A.C. Richardson, *J. Chem. Soc. Perkin I*, **1977**, 2001.
5) T. Chiba, M. Haga, and S. Tejima, *Carbohyd. Res.*, **45**, 11 (1975).
6) T. Takamura and S. Tejima, *Chem. Pharm. Bull.* (Tokyo), **26**, 1117 (1978).
7) T. Chiba and S. Tejima, *Chem. Pharm. Bull.* (Tokyo), **25**, 1049 (1977).

tion. They were assumed to be a pair of isomeric tri-O-acetyl-mono-O-methyl derivatives of 1,6-anhydro-4′,6′-O-benzylidene-β-disaccharide as indicated by the synthetic route and the nuclear magnetic resonance (NMR) spectra.

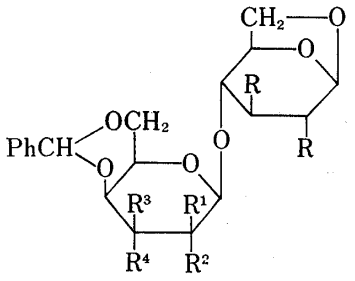
The position of the methoxyl group in **3** or **9** was determined as follows. Debenzylidenation of **3** by palladium-catalyzed hydrogenolysis yielded a crystalline 1,6-anhydro-tri-O-acetyl-mono-O-methyl-β-disaccharide (**4**). Deacetylation of **4** afforded a hygroscopic, amorphous monomethyl ether (**5**). Compound **5** consumed almost one molar equivalent of sodium metaperiodate without concomitant formation of formic acid.

On the other hand, deacetylation of **9** and successive benzoylation of the deacetylated **9**, afforded a crystalline tribenzoate (**10**). It was identified as the known 1,6 anhydro-2,3-di-O-benzoyl-4-O-(3-O-benzoyl-4,6-O-benzylidene-2-O-methyl-β-D-galactopyranosyl)-β-D-glucopyranose (1,6-anhydro-2,3,3′-tri-O-benzoyl-4′,6′-O-benzylidene-2′-O-methyl-β-lactose) by comparison with an authentic sample.[7] Therefore, **9** must be 2,3-di-O-acetyl-1,6-anhydro-4-O-(3-O-acetyl-4,6-O-benzylidene-2-O-methyl-β-D-galactopyranosyl)-β-D-glucopyranose (2,3,3′-tri-O-acetyl-1,6-anhydro-4′,6′-O-benzylidene-2′-O-methyl-β-lactose).

Since **3** and **9** are positional isomers of methoxyl group, **3** must be 2,3-di-O-acetyl-1,6-anhydro-4-O-(2-O-acetyl-4,6-O-benzylidene-3-O-methyl-β-D-idopyranosyl)-β-D-glucopyranose. The above results of the glycol oxidation of **5** were consistent with the assigned structure of **3**. The validity of the structure is also supported from analogy with the reaction reported in part VII.

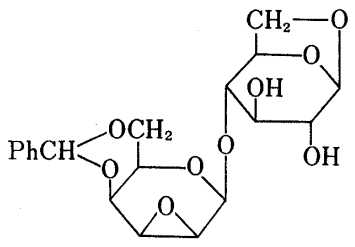
Thus, **4** and **5** were assigned to the structures, 2,3-di-O-acetyl-1,6-anhydro-4-O-(2-O-acetyl-3-O-methyl-β-D-idopyranosyl)-β-D-glucopyranose (**4**) and 1,6-anhydro-4-O-(3-O-methyl-β-D-idopyranosyl)-β-D-glucopyranose (**5**), respectively.

From these results, it is quite reasonable to assume that the *trans*-diaxial opening of the epoxide ring of **2** proceeded predominantly to afford **3** as the major product (85%). But the *trans*-diequatorial opening took place simultaneously, and small amounts of **9** were formed as the minor product (4%). Further studies on **9** were not done, because of the low yield.



1 : R=R²=R³=OH, R¹=R⁴=H
3 : R=R¹=OAc, R²=R³=H, R⁴=OMe
9 : R=R³=OAc, R¹=R⁴=H, R²=OMe
10 : R=R³=OBz, R¹=R⁴=H, R²=OMe

Ac=acetyl, Bz=benzoyl
Me=methyl, Ph=phenyl



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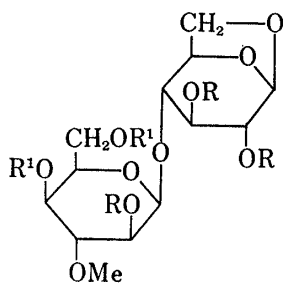
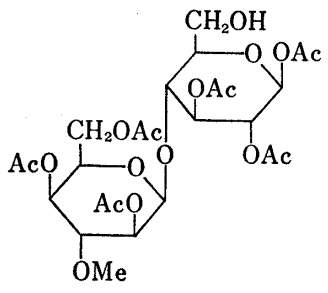


4 : R=Ac, R¹=H
5 : R=R¹=H
6 : R=R¹=Ac



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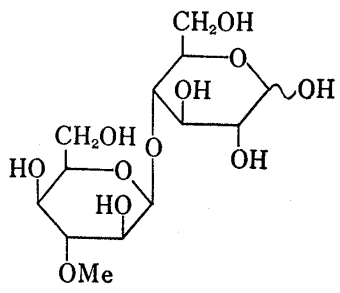

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Chart 1

Acetylation of **4** afforded a crystalline pentaacetate (**6**). Cleavage of the 1,6-anhydro ring in **6** by acetolysis failed: a considerable cleavage of the glycosidic linkage occurred simultaneously. According to the review[8] on acid-catalyzed hydrolysis of glycosides, methyl α-D-idopyranoside is six times faster hydrolyzed than methyl α-D-galactopyranoside. Therefore, refluxing of **6** in chloroform with titanium tetrachloride, followed by treatment of the product with mercuric acetate to replace the chlorine atom by an acetoxyl group, afforded a β-acetate. After purification through a column of silica gel, crystalline 1,2,3-tri-O-acetyl-4-O-(2,4,6-tri-O-acetyl-3-O-methyl-β-D-idopyranosyl)-β-D-glucopyranose (**7**) was isolated in 46% yield together with 7% of the starting material (**6**) unchanged. In the NMR spectrum of **7**, the anomeric proton appeared at δ 5.71 as a doublet with $J_{1,2}$=8 Hz.

Deacetylation of **7** afforded the former of the titled compounds, *i.e.* **8**, as a hygroscopic, amorphous powder, $[\alpha]_D^{21}$ +23.3°. On acidic hydrolysis of **8**, glucose was identified by paper partition chromatography (PPC) as the sole reducing sugar produced. Since idose forms readily a 1,6-anhydride,[9] 3-O-methylidose in **8** might change to a 1,6-anhydride during acidic hydrolysis of **8**. Presumably, this was the reason why 3-O-methylidose was undetected by the alkaline silver nitrate reagent.[10]

Next we describe the synthesis of the latter of the titled compounds, *i.e.* **19**. Stirring a mixture of **2** with lithium aluminum hydride ($LiAlH_4$) in boiling tetrahydrofuran (THF) for 15 hr resulted in a reductive cleavage of the epoxide ring in **2**: the 1,6-anhydro ring remained unchanged. Successive acetylation of the product afforded a sirup which showed two spots, *Rf* 0.60 (minor) and 0.19 (major) on TLC. The mixture was chromatographed through a column of silica gel. From the faster effluent, the minor product (**11**) was isolated in a yield of 4%. From the successive effluent of the same solvent, the major product (**13**) was isolated as a crystal in a yield of 73%. Compounds **11** and **13** had the same elemental compositions and their structures were established as 2,3-di-O-acetyl-1,6-anhydro-4-O-(3-O-acetyl-4,6-O-benzylidene-2-deoxy-β-D-*lyxo*-hexopyranosyl)-β-D-glucopyranose (**11**) and 2,3-di-O-acetyl-1,6-anhydro-4-O-(2-O-acetyl-4,6-O-benzylidene-3-deoxy-β-D-*lyxo*-hexopyranosyl)-β-D-glucopyranose (**13**), respectively, by the following experiments.

Deacetylation of **13** and successive benzoylation of the deacetylated product afforded a crystalline tribenzoate (**14**). The structure, 1,6-anhydro-2,3-di-O-benzoyl-4-O-(2-O-benzoyl-4,6-O-benzylidene-3-deoxy-β-D-*lyxo*-hexopyranosyl)-β-D-glucopyranose, was tentatively assigned to compound **14**.

On the other hand, debenzylidenation of **13** yielded a crystalline tri-O-acetyl-monodeoxy derivative (**15**). Successive deacetylation of **15** afforded a crystalline mono-deoxy derivative (**16**). Compound **16** consumed one molar equivalent of sodium metaperiodate with no concomitant formation of formic acid. The glycol oxidation and the unequivocal synthetic routes of **13**, **15**, and **16** indicated that the position of the deoxy group in **13** was C-3′. But further structural assignment was performed by the NMR spectrum of **14** and by the identification of deoxy monosaccharide obtained after acidic hydrolysis of the final product.

In the NMR spectrum of **14**, the geminal protons on H-3′ were identified at 2.12 ppm as a sextet and at 2.48 ppm as a multiplet with an observed spacing, $J_{3'a,3'e}$=16 Hz. If **14** has the assigned structure mentioned above, the relationships between H-3′a and H-2′, or H-3′a and H-4′ are axial–equatorial, but those between H-3′e and H-2′, or H-3′e and H-4′ are diequatorial. The observed spacing at 2,12 ppm, $J_{2',3'a}$=4 Hz and $J_{3'a,4'}$=4 Hz, were large, but those at 2.48 ppm were almost zero Hz. The values of these coupling constants, which were determined by irradiation of the H-4′ or H-2′ proton, are definitive evidence for validity of the structure for **14**.

8) J.N. BeMiller, *Advan. Carbohyd. Chem.*, **22**, 25 (1967).
9) L.F. Wiggins, *Methods Carbohyd. Chem.*, **1**, 140 (1962).
10) W.E. Trevelyan, D.P. Procter, and J.S. Harrison, *Nature* (London), **166**, 444 (1950).

Therefore, the structures of **15** and **16** must be 2,3-di-O-acetyl-1,6-anhydro-4-O-(2-O-acetyl-3-deoxy-β-D-*lyxo*-hexopyranosyl)-β-D-glucopyranose (**15**) and 1,6-anhydro-4-O-(3-deoxy-β-D-*lyxo*-hexopyranosyl)-β-D-glucopyranose (**16**), respectively.

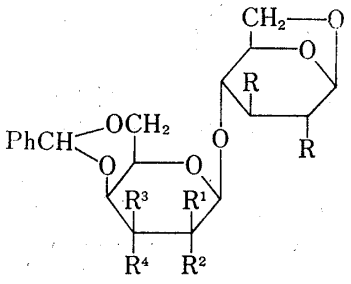
Acetylation of **15** gave a crystalline acetate (**17**). Attempt to cleave the 1,6-anhydro ring in **17** by acetolysis failed. In acid-catalyzed hydrolysis of glycosides, a considerable increase of hydrolysis was observed on removal of the hydroxyl group on C-3 in methyl α-aldohexopyranosides.[8] Probably, the internal glycosidic linkage in **17** is more susceptible to hydrolysis than the parent disaccharide.

Thus, the opening of the 1,6-anhydro ring in **17** and successive treatment of the product with mercuric acetate were performed as described above for **7** to afford 1,2,3-tri-O-acetyl-4-O-(2,4,6-tri-O-acetyl-3-deoxy-β-D-*lyxo*-hexopyranosyl)-β-D-glucopyranose (**18**) in 41% yield together with 30% of the starting material (**17**) unchanged. In the NMR spectrum of **18**, the anomeric proton appeared at δ 5.69 as a doublet with $J_{1,2}=8$ Hz.

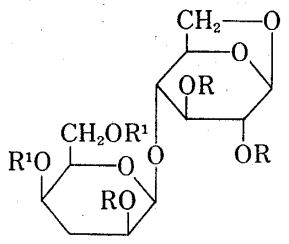
Deacetylation of **18** with sodium methoxide afforded the latter of the titled compounds, *i.e.* **19**, as a hygroscopic, amorphous powder. After acidic hydrolysis of **19**, glucose and 3-deoxy-*lyxo*-hexose[11] were the reducing sugars identified. In the hydrolyzate, 2-deoxy-*lyxo*-hexose[12] was not found. The component sugars were identified by PPC with samples synthesized according to the reported methods.[11,12]

The minor product (**11**) in the reductive cleavage of the epoxide ring in **2** is assumed to be a positional isomer of **13** as indicated by elemental analysis and the NMR spectrum. Deacetylation of **11** and successive benzoylation of deacetylated **11** afforded a tribenzoate (**12**). The compounds **11** and **12** were assigned to the structures, 2,3-di-O-acetyl-1,6-anhydro-4-O-(3-O-acetyl-4,6-O-benzylidene-2-deoxy-β-D-*lyxo*-hexopyranosyl)-β-D-glucopyranose(**11**)and 1,6-anhydro-2,3-di-O-benzoyl-4-O-(3-O-benzoyl-4,6-O-benzylidene-2-deoxy-β-D-*lyxo*-hexopyranosyl)-β-D-glucopyranose (**12**), respectively.

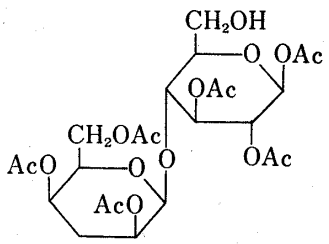
The NMR spectrum of **12** was consistent with the assigned structure. Namely, the geminal protons were identified at 2.52 ppm as a sextet and at 2.15 ppm as a multiplet with an observed spacing, $J_{2'a,2'e}=12$ Hz. The signal for H-1′ appeared at 5.10 ppm as a double-



11 : R=R³=OAc, R¹=R²=R⁴=H
12 : R=R³=OBz, R¹=R²=R⁴=H
13 : R=R¹=OAc, R²=R³=R⁴=H
14 : R=R¹=OBz, R²=R³=R⁴=H



15 : R=Ac, R¹=H
16 : R=R¹=H
17 : R=R¹=Ac



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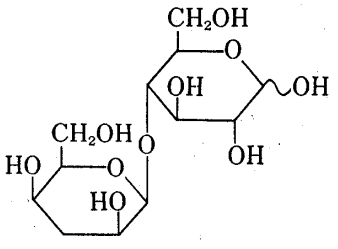

19

Chart 2

11) H. Huber and T. Reichstein, *Helv. Chim. Acta*, **31**, 1645 (1948).
12) F. Schafizadeh, *Methods Carbohyd. Chem.*, **1**, 190 (1962).

doublet with observed spacings, $J_{1',2'a}$=10 Hz and $J_{1',2'e}$=2 Hz, which changed from a double-doublet into a singlet by irradiation of the geninal protons. The larger value (10 Hz) is ascribed to the coupling with H-2'a and the smaller one (2 Hz) is the coupling with H-2'e. Further studies on **11** were not done, because of the low yield.

In conclusion, when **2** was treated with $LiAlH_4$, the *trans*-diaxial ring opening of the epoxide occurred predominantly to give **13** (73%) with small amounts of the *trans*-diequatorial opening product, **11** (4%). This result agreed with that obtained by treatment of **2** with potassium hydroxide[7] or sodium methoxide.

Experimental

Instruments used in the experimental section and the conditions for chromatography were the same as before,[6] unless otherwise indicated. TLC on Kieselgel GF_{254} (5×20 cm) (E. Merck, Darmstadt, Germany) was performed with solvent combination (v/v): (A), $CHCl_3$-acetone (3:1); (B), $CHCl_3$–acetone (6:1); (C), benzene–ether (1:1); (D), 70% 2-PrOH–AcOEt (2:1). PPC was performed on Toyo Filter Paper No. 50 (Toyo Roshi Kaisha, Ltd., Tokyo), by the ascending method with BuOH–pyridine–H_2O (6:4:3, v/v) by the procedure of Ueda,[13] and detection was effected with the alkaline silver nitrate reagent.[10]

2,3-Di-O-acetyl-1,6-anhydro-4-O-(2-O-acetyl-4,6-O-benzylidene-3-O-methyl-β-D-idopyranosyl)-β-D-glucopyranose (3) and 2,3-Di-O-acetyl-1,6-anhydro-4-O-(3-O-acetyl-4,6-O-benzylidene-2-O-methyl-β-D-galactopyranosyl)-β-D-glucopyranose (2,3,3'-Tri-O-acetyl-1,6-anhydro-4',6'-O-benzylidene-2'-O-methyl-β-lactose) (9)——To a suspension of 2[7] (5 g, 12.7 mmol) in dry MeOH (50 ml), methanolic 1 M sodium methoxide (50 ml, 50 mmol) was added, and the mixture was refluxed for 3 hr with stirring. After cooling to room temperature, the solution was neutralized with glacial acetic acid and concentrated to dryness. The residue was acetylated with Ac_2O (30 ml) and pyridine (30 ml) for 24 hr at room temperature. The mixture was evaporated by repeated co-distillation with toluene to afford a sirup which was dissolved in CH_2Cl_2 (100 ml). The CH_2Cl_2-solution was successively washed with H_2O, 10% H_2SO_4, H_2O, aq.$NaHCO_3$, and H_2O, dried ($CaCl_2$), and concentrated to a sirup which showed two spots, *Rf* 0.36 (major) and 0.28 (minor), on TLC (solvent B). The sirup was dissolved in CH_2Cl_2 and the solution chromatographed through a column of silica gel with $CHCl_3$–acetone (20:1, v/v) as eluent. Evaporation of the solvent from the faster moving fraction afforded an amorphous powder which crystallized from EtOH. Recrystallization from EtOH gave colorless leaflets (5.96 g, 85%) of **3**, mp 140—141°, $[\alpha]_D^{24}$ −59.4° (*c*=1.07, $CHCl_3$). NMR ($CDCl_3$) δ: 2.08, 2.11, 2.15 (9H, s, 3×OAc), 3.54 (3H, s, OMe), 7.20—7.60 (5H, m, aromatic protons). TLC: *Rf* 0.47 (solvent A), 0.36 (B), 0.17 (C). *Anal.* Calcd. for $C_{26}H_{32}O_{13}$: C, 56.52; H, 5.84. Found: C, 56.36; H, 5.79.

Removal of the solvent from the successive effluent of the same solvent yielded an amorphous powder (0.30 g, 4%) of **9**, $[\alpha]_D^{22}$ −10.5° (*c*=0.76, $CHCl_3$). NMR ($CDCl_3$) δ: 2.12, 2.14 (9H, s, 3×OAc), 3.60 (3H, s, OMe), 7.20—7.60 (5H, m, aromatic protons). TLC: *Rf* 0.40 (solvent A), 0.28 (B), 0.12 (C). *Anal.* Calcd. for $C_{26}H_{32}O_{13}$: C, 56.52; H, 5.84. Found: C, 56.18; H, 5.90.

2,3-Di-O-acetyl-1,6-anhydro-4-O-(2-O-acetyl-3-O-methyl-β-D-idopyranosyl)-β-D-glucopyranose (4)——To a suspension of **3** (5 g) in dry MeOH (100 ml), Pd catalyst,[14] prepared from $PdCl_2$ (1 g), was added. The mixture was hydrogenated with stirring at room temperature and under atmospheric pressure. Theoretical amount of hydrogen was absorbed in 3 hr. The mixture was filtered and concentrated to give a sirup which crystallized from EtOH. Recrystallization from EtOH gave colorless prisms (3.47 g, 83%) of **4**, mp 154—156°, $[\alpha]_D^{27}$ −87.1° (*c*=1.13, $CHCl_3$). IR ν_{max}^{Nujol} cm^{-1}: 3540, 3440 (OH). NMR ($CDCl_3$) δ: 2.14, 2.16, 2.18 (9H, s, 3×OAc), 3.53 (3H, s, OMe). TLC: *Rf* 0.08 (solvent A), 0.62 (D). *Anal.* Calcd. for $C_{19}H_{28}O_{13}$: C, 49.14; H, 6.08. Found: C, 49.12; H, 6.20.

1,6-Anhydro-4-O-(3-O-methyl-β-D-idopyranosyl)-β-D-glucopyranose (5)——To a solution of **4** (380 mg) in dry MeOH (10 ml), methanolic 0.5 M sodium methoxide (0.1 ml) was added at room temperature. The mixture was stirred for 1 hr under exclusion of moisture, with monitoring of the deacetylation by TLC (solvent A). Dry Amberlite IR-120 (H^+) resin was added, and the suspension was stirred for 30 min. After filtration, the filtrate was concentrated to dryness to give a hygroscopic, amorphous powder (262 mg, 95%) of **5**, $[\alpha]_D^{25}$ −54.1° (*c*=1.25, H_2O). TLC: *Rf* 0.51 (solvent D). *Anal.* Calcd. for $C_{13}H_{22}O_{10}\cdot 1/2H_2O$: C, 44.96; H, 6.68. Found: C, 44.89; H, 6.75.

Periodate consumption of **5** (124.6 mg) was estimated according to the procedure of Okui.[15] The $NaIO_4$-consumption (mol) at 28° was as follows: 0.34 (0.5 hr), 0.51 (1 hr), 0.61 (2 hr), 0.68 (3 hr), 1.15 (24 hr, constant); no concomitant formation of formic acid was observed.

2,3-Di-O-acetyl-1,6-anhydro-4-O-(2,4,6-tri-O-acetyl-3-O-methyl-β-D-idopyranosyl)-β-D-glucopyranose (6)——Compound **4** (3 g) was acetylated with Ac_2O (15 ml) and pyridine (15 ml) for 24 hr at room temperature.

13) M. Ueda, *Yakugaku Zasshi*, **90**, 1322 (1970).
14) O. Th. Schmidt and W. Staab, *Chem. Ber.*, **87**, 388 (1954).
15) S. Okui, *Yakugaku Zasshi*, **75**, 1262 (1955).

The mixture was treated in the usual way to give a sirup which crystallized from EtOH. Recrystallization from EtOH gave white needles (3.05 g, 86%) of **6**, mp 137—138°, $[\alpha]_D^{25}$ −70.5° (c=1.12, $CHCl_3$). NMR ($CDCl_3$) δ: 2.05, 2.11, 2.12, 2.14 (15H, s, 5×OAc), 3.56 (3H, s, OMe). TLC: *Rf* 0.41 (solvent A), 0.30 (B), 0.11 (C). *Anal.* Calcd. for $C_{23}H_{32}O_{15}$: C, 50.37; H, 5.88. Found: C, 50.28; H, 5.87.

1,2,3-Tri-O-acetyl-4-O-(2,4,6-tri-O-acetyl-3-O-methyl-β-D-idopyranosyl)-β-D-glucopyranose (7)——To a chilled solution of **6** (2 g) in dry $CHCl_3$ (40 ml) and EtOH (0.2 ml) was added titanium tetrachloride (4 ml). The mixture, protected from moisture, was refluxed for 4 hr with stirring and cooled. The mixture was poured into ice-H_2O (200 ml) with the aid of small amounts of $CHCl_3$ and ice-H_2O. The $CHCl_3$-layer was separated, washed with ice-H_2O (60 ml×3), dried (Na_2SO_4), and evaporated to dryness. The residue was dissolved in a solution of mercuric acetate (2 g) in glacial acetic acid (20 ml), and the solution was kept overnight at room temperature, poured into ice-H_2O (120 ml), and the mixture was extracted with CH_2Cl_2 (20 ml×4). The extracts were combined, washed successively with H_2O, aq. $NaHCO_3$, and H_2O, dried (Na_2SO_4), and evaporated to dryness to afford crude **7** which was contaminated by a trace of **6** and by-product as shown by TLC ($CHCl_3$–acetone, 20: 1, v/v, three-fold development).

It was dissolved in CH_2Cl_2 and the solution was chromatographed through a column of silica gel with $CHCl_3$–acetone (20: 1) as eluent. Evaporation of the solvent from the faster moving eluate afforded an amorphous powder which crystallized from EtOH. Recrystallization from EtOH gave white needles (144 mg, 7%), mp 136—137°, which was identified with **6** by mixed mp, IR, and TLC.

Removal of the solvent from the successive effluent of the same solvent afforded an amorphous powder which crystallized from EtOH. Recrystallization from EtOH gave white needles (1.03 g, 46%) of **7**, mp 156—157°, $[\alpha]_D^{24}$ −31.2° (c=0.95, $CHCl_3$). IR ν_{max}^{Nujol} cm^{-1}: 3480 (OH). NMR ($CDCl_3$) δ: 2.03, 2.10 (18H, s, 6×OAc), 3.53 (3H, s, OMe), 5.71 (1H, d, $J_{1,2}$=8 Hz, H-1). TLC: *Rf* 0.34 (solvent A), 0.19 (B), 0.09 (C). *Anal.* Calcd. for $C_{25}H_{36}O_{17}$: C, 49.34; H, 5.96. Found: C, 49.26; H, 5.68.

4-O-(3-O-Methyl-β-D-idopyranosyl)-D-glucopyranose (8)——To a suspension of **7** (500 mg) in dry MeOH (10 ml), methanolic 0.5 M sodium methoxide (0.2 ml) was added at room temperature. The mixture was treated in a manner similar to that for **5** to give a hygroscopic, amorphous powder (278 mg, 95%) of **8**, $[\alpha]_D^{21}$ +23.3° (c=0.80, H_2O). TLC: *Rf* 0.33 (solvent D). PPC: *Rf* 0.46. *Anal.* Calcd. for $C_{13}H_{24}O_{11}\cdot 1/2H_2O$: C, 42.74; H, 6.90. Found: C, 42.84; H, 7.18.

PPC of Acid Hydrolyzate of 8——A mixture of **8** (50 mg) and 0.5 M H_2SO_4 (2 ml) was heated at 98° for 2 hr. The hydrolyzate was neutralized with $BaCO_3$, filtered, and after treatment with charcoal, concentrated to a thin sirup, in which glucose (*Rf* 0.38) was identified as the sole reducing sugar by PPC.

1,6-Anhydro-2,3-di-O-benzoyl-4-O-(3-O-benzoyl-4,6-O-benzylidene-2-O-methyl-β-D-galactopyranosyl)-β-D-glucopyranose (1,6-Anhydro-2,3,3′-tri-O-benzoyl-4′,6′-O-benzylidene-2′-O-methyl-β-lactose) (10)——To a solution of **9** (250 mg) in dry MeOH (10 ml), methanolic 0.5 M sodium methoxide (0.5 ml) was added at room temperature. The mixture was treated as described above for **5** to give a deacetylated sirup which was benzoylated with benzoyl chloride (0.4 ml) and pyridine (5 ml) for 24 hr at room temperature. Ice was added to the mixture to decompose excess benzoyl chloride and the mixture was concentrated to dryness by repeated co-distillation with toluene. The residue was dissolved in CH_2Cl_2 (20 ml), successively washed with H_2O, 10% H_2SO_4, H_2O, aq. $NaHCO_3$, and H_2O, dried ($CaCl_2$), and then concentrated to a sirup which crystallized from EtOH. Recrystallization from EtOH gave colorless needles (248 mg, 74%) of **10**, mp 225—226°, $[\alpha]_D^{22}$ +73.9° (c=0.23, $CHCl_3$). It was indistinguishable (mixed mp, IR, and TLC) from the authentic sample.[7]

2,3-Di-O-acetyl-1,6-anhydro-4-O-(3-O-acetyl-4,6-O-benzylidene-2-deoxy-β-D-*lyxo*-hexopyranosyl)-β-D-glucopyranose (11) and 2,3-Di-O-acetyl-1,6-anhydro-4-O-(2-O-acetyl-4,6-O-benzylidene-3-deoxy-β-D-*lyxo*-hexopyranosyl)-β-D-glucopyranose (13)——To a suspension of **2** (5 g, 12.7 mmol) in freshly distilled THF (100 ml), $LiAlH_4$ (2 g, 52.7 mmol) was carefully added during 10 min. The mixture was refluxed for 15 hr with stirring and allowed to cool. After decomposition of excess $LiAlH_4$ by careful addition of H_2O, the inorganic precipitate was filtered and washed several times with hot THF in a hood. The combined filtrate and washings were evaporated to dryness and the residue was acetylated with Ac_2O (30 ml) and pyridine (30 ml) for 24 hr at room temperature. The mixture was treated in the manner described above for preparation of **3** and **9** to afford a sirup which showed two spots, *Rf* 0.60 (minor) and 0.19 (major), on TLC (solvent B). It was dissolved in CH_2Cl_2 and the solution was chromatographed through a column of silica gel with $CHCl_3$–acetone (20: 1, v/v) as eluent. Evaporation of the solvent from the faster moving eluate afforded an amorphous powder (0.29 g, 4%) of **11**, $[\alpha]_D^{24}$ −18.2° (c=1.11, $CHCl_3$). NMR ($CDCl_3$) δ: 2.08, 2.10, 2.12 (9H, s, 3×OAc), 7.20—7.60 (5H, m, aromatic protons). TLC: *Rf* 0.60 (solvent A), 0.60 (B), 0.50 (C). *Anal.* Calcd. for $C_{25}H_{30}O_{12}$: C, 57.47; H, 5.79. Found: C, 57.54; H, 5.66.

Removal of the solvent from the successive effluent of the same solvent afforded an amorphous powder which crystallized from EtOH. Recrystallization from EtOH gave colorless needles (4.86 g, 73%) of **13**, mp 222—223°, $[\alpha]_D^{25}$ −55.8° (c=1, $CHCl_3$). NMR ($CDCl_3$) δ: 2.08, 2.10, 2.14 (9H, s, 3×OAc), 7.20—7.60 (5H, m, aromatic protons). TLC: *Rf* 0.29 (solvent A), 0.19 (B), 0.05 (C). *Anal.* Calcd. for $C_{25}H_{30}O_{12}$: C, 57.47; H, 5.79. Found: C, 57.47; H, 5.65.

1,6-Anhydro-2,3-di-O-benzoyl-4-O-(3-O-benzoyl-4,6-O-benzylidene-2-deoxy-β-D-*lyxo*-hexopyranosyl)-β-D-glucopyranose (12)——Deacetylation and sequential benzoylation of **11** (160 mg) as described above for **10**

gave an amorphous powder which crystallized from MeOH. Recrystallization from MeOH–AcOEt gave colorless needles (130 mg, 60%) of **12**, mp 206—208°, $[\alpha]_D^{21}$ +56.5° (c=0.93, $CHCl_3$). NMR ($CDCl_3$) δ: 2.15 (1H, m, H-2'e), 2.52 (1H, sex, $J_{2'a,2'e}$=12 Hz, $J_{1',2'a}$=10 Hz, $J_{2'a,3'}$=12 Hz, H-2'a), 5.10 (1H, dd, $J_{1',2'a}$=10 Hz, $J_{1',2'e}$=2 Hz, H-1'), 5.30 (1H, m, H-3'), 5.52 (1H, s, $C_6H_5C\underline{H}$), 7.00—8.30 (20H, m, aromatic protons). TLC: *Rf* 0.60 (solvent A), 0.59 (B), 0.47 (C). *Anal.* Calcd. for $C_{40}H_{36}O_{12}$: C, 67.79; H, 5.12. Found: C, 67.68; H, 5.12.

1,6-Anhydro-2,3-di-O-benzoyl-4-O-(2-O-benzoyl-4,6-O-benzylidene-3-deoxy-β-D-*lyxo*-hexopyranosyl)-β-D-glucopyranose (14)——Deacetylation and successive benzoylation of **13** (200 mg) as described above for **12** afforded an amorphous powder which crystallized from EtOH. Recrystallization from EtOH gave colorless needles (183 mg, 67%) of **14**, mp 181—182°, $[\alpha]_D^{23}$ −34.5° (c=1.04, $CHCl_3$). NMR ($CDCl_3$) δ: 2.12 (1H, sex, $J_{3'a,3'e}$=16 Hz, $J_{2',3'a}$=4 Hz, $J_{3'a,4'}$=4 Hz, H-3'a), 2.48 (1H, m, H-3'e), 3.93 (1H, m, H-4'), 5.30 (1H, m, H-2'), 5.42 (1H, s, $C_6H_5C\underline{H}$), 7.00—8.30 (20H, m, aromatic protons). TLC: *Rf* 0.51 (solvent A), 0.46 (B), 0.28 (C). *Anal.* Calcd. for $C_{40}H_{36}O_{12}$: C, 67.79; H, 5.12. Found: C, 67.62; H, 5.36.

2,3-Di-O-acetyl-1,6-anhydro-4-O-(2-O-acetyl-3-deoxy-β-D-*lyxo*-hexopyranosyl)-β-D-glucopyranose (15)——Debenzylidenation of **13** (3 g) as described above for **4** afforded an amorphous powder which crystallized from EtOH. Recrystallization from EtOH gave colorless prisms (2.13 g, 85%) of **15**, mp 142—143°, $[\alpha]_D^{24}$ −85.3° (c=1.05, $CHCl_3$). IR ν_{max}^{Nujol} cm^{-1}: 3510 (OH). NMR ($CDCl_3$) δ: 2.14, 2.16 (9H, s, 3×OAc). TLC: *Rf* 0.05 (solvent A), 0.53 (D). *Anal.* Calcd. for $C_{18}H_{26}O_{12}$: C, 49.77; H, 6.03. Found: C, 50.01; H, 6.08.

1,6-Anhydro-4-O-(3-deoxy-β-D-*lyxo*-hexopyranosyl)-β-D-glucopyranose (16)——Deacetylation of **15** (1 g) as described above for **5** afforded an amorphous powder which crystallized from EtOH. Recrystallization from EtOH gave white needles (620 mg, 87%) of **16**, mp 150—152°, $[\alpha]_D^{19}$ −72.3° (c=1.09, $CHCl_3$). TLC: *Rf* 0.36 (solvent D). *Anal.* Calcd. for $C_{12}H_{20}O_9$: C, 46.75; H, 6.54. Found: C, 46.90; H, 6.76.

The $NaIO_4$-consumption (mol) of **16** (125 mg) at 19°, according to the procedure of Okui,[15] was as follows: 0.12 (0.5 hr), 0.15 (1 hr), 0.22 (2 hr), 0.31 (3 hr), 0.37 (4 hr), 0.40 (5 hr), 0.93 (24 hr, constant); no concomitant formation of formic acid was observed.

2,3-Di-O-acetyl-1,6-anhydro-4-O-(2,4,6-tri-O-acetyl-3-deoxy-β-D-*lyxo*-hexopyranosyl)-β-D-glucopyranose (17)——Acetylation of **15** (2 g) as described above for **6** afforded an amorphous powder which crystallized from EtOH. Recrystallization from EtOH gave rhombic prisms (2 g, 84%) of **17**, mp 153—154°, $[\alpha]_D^{22}$ −85° (c=1.08, $CHCl_3$). NMR ($CDCl_3$) δ: 2.01, 2.06, 2.09, 2.11 (15H, s, 5×OAc). TLC: *Rf* 0.30 (solvent A), 0.19 (B), 0.05 (C). *Anal.* Calcd. for $C_{22}H_{30}O_{14}$: C, 50.97; H, 5.83. Found: C, 51.09; H, 5.90.

1,2,3-Tri-O-acetyl-4-O-(2,4,6-tri-O-acetyl-3-deoxy-β-D-*lyxo*-hexopyranosyl)-β-D-glucopyranose (18)——To a chilled solution of **17** (1 g) in dry CH_2Cl_2 (12 ml) and EtOH (0.2 ml) was added titanium tetrachloride (2 ml). The mixture, protected from moisture, was refluxed for 6 hr with stirring and cooled. Similar treatment of the mixture as described above for **7** gave a sirup which showed two spots, *Rf* 0.19 (minor) and 0.11 (major), and small amounts of by-product as shown by TLC (solvent B). After chromatography through a column of silica gel with $CHCl_3$–acetone (20: 1, v/v) as eluent, **17** (0.3 g, 30%), *Rf* 0.19, was recovered from the faster moving fraction. From the successive eluate of the same solvent, **18** (460 mg, 41%) was isolated as an amorphous powder, $[\alpha]_D^{14}$ −39.6° (c=1.03, $CHCl_3$), IR ν_{max}^{Nujol} cm^{-1}: 3520 (OH). NMR ($CDCl_3$) δ: 2.03, 2.07, 2.10 (18H, s, 6×OAc), 5.69 (1H, d, $J_{1,2}$=8 Hz, H-1). TLC: *Rf* 0.21 (solvent A), 0.11 (B), 0.05 (C). *Anal.* Calcd. for $C_{24}H_{34}O_{16}$: C, 49.83; H, 5.92. Found: C, 49.78; H, 5.92.

4-O-(3-Deoxy-β-D-*lyxo*-hexopyranosyl)-D-glucopyranose (19)——Deacetylation of **18** (200 mg) as described above for **8** gave a hygroscopic, amorphous powder (107 mg, 95%) of **19**, $[\alpha]_D^{18}$ −6.4° (c=0.56, H_2O). It tastes slightly sweet. TLC: *Rf* 0.28 (solvent D). PPC: *Rf* 0.39. *Anal.* Calcd. for $C_{12}H_{22}O_{10}$: C, 44.17; H, 6.80. Found: C, 44.30; H, 6.70.

PPC of Acid Hydrolyzate of 19——Acidic hydrolysis of **19** (50 mg) and treatment of the hydrolyzate were effected as those of **8**, in which glucose (*Rf* 0.38) and 3-deoxy-*lyxo*-hexose (*Rf* 0.58) were identified by PPC.

Authentic 2-deoxy-D-*lyxo*-hexose (*Rf* 0.51) and 3-deoxy-D-*lyxo*-hexose (*Rf* 0.58) were synthesized according to the method of Shafizadeh[12] and Huber and Reichstein,[11] respectively.

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