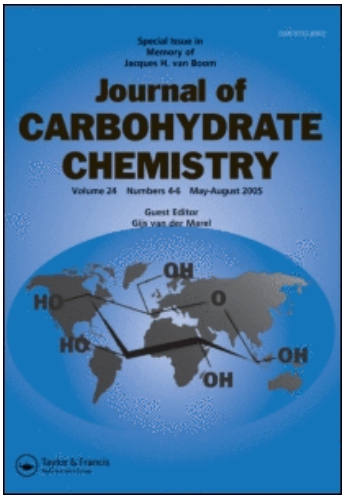

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NOVEL PARTIAL PROTECTIONS OF 1,6-ANHYDRO-β-LACTOSE

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ABSTRACT

1,6-Anhydro-β-lactose (3) was prepared as its peracetate (2) from lactose monohydrate via its pentachlorophenyl β-lactoside derivative in 49% overall yield. Treatment of the 4',6'-O-benzylidene derivative of 3 with 1.2 mol. equiv. of 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane gave two cyclic silyl ethers, the 2',3'-O-silyl and the 2,3:2',3'-di-O-silyl ethers, in the ratio of ca. 2:1. Cyclohexylidenation of 3 at 50 °C with excess of 1,1-dimethoxycyclohexane and trace of protic acid gave the 2',3':4',6'- and the 2,2':3',4'-di-O-cyclohexylidene derivatives, whereas a similar reaction at 90-110 °C resulted in the 3,2':3',4'-di-O-cyclohexylidene derivative.

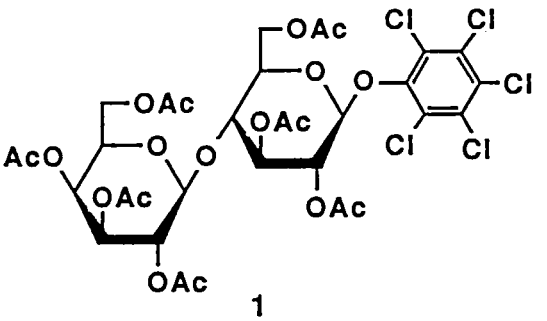
INTRODUCTION

In the course of our studies on chemical modifications[2] and transformations[3] of di- and tri-saccharides such as cellobiose, maltose, and maltotriose, we have developed several means for their regioselective protections. The first protection made in common for those oligosaccharides has been 1,6-anhydro ring formation,[4] which simultaneously protects hydroxyl groups on the anomeric and the sixth carbons of the reducing end. Those 1,6-anhydro derivatives have next been subjected to various protective reactions like cyclic acetal[5] and cyclic silyl ether formations.[5,6] Now we wish to describe the extended application of such methodology to partial protection of lactose and some novel features concerning the resulting derivatives.

RESULTS AND DISCUSSION

We have succeeded in preparing the 1,6-anhydro derivatives of cellobiose, maltose,[4] and maltotriose[5] *via* the corresponding crystalline pentachlorophenyl β-glycoside peracetates in better overall yields than those of the preceeding procedures.[7] In a similar way lactose monohydrate was successively treated with acetic anhydride-pyridine, HBr in acetic acid, and sodium pentachlorophenoxide without thorough purification of every intermediate. Unfortunately, the resulting pentachlorophenyl 2,3,6,2',3',4',6'-hepta-*O*-acetyl-β-lactoside (1) resisted crystallization, differing from the corresponding derivatives of other oligosaccharides previously prepared. Nevertheless, when the syrupy crude **1** was heated with aqueous KOH and then acetylated, the desired compound, 2,3,2',3',4',6'-hexa-*O*-acetyl-1,6-anhydro-β-lactose (2) was obtained as crystals. The overall yield of pure **2** after recrystallization was 49% on the basis of lactose monohydrate, which was much better than the overall yields of procedures reported previously.[8] Following literature procedures,[9] deacetylation and subsequent benzylidenation of **2** were performed, giving the known 1,6-anhydro-β-lactose (3) and its 4',6'-*O*-benzylidene derivative (4), respectively. Compound **4** was purified as the 2,3,2',3'-tetraacetate (5).[9]

It seemed quite interesting to examine what might be produced by the reaction between **4** and 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane. With the same reagent, the cellobiose and maltose derivatives corresponding to **4** were observed to undergo regioselective *O*-protection with a tetraisopropyldisiloxane-1,3-diyl group at the 2,3- and 2',3'-positions, respectively.[6] After deacetylation of **5**, regenerated **4** was soon treated with 1.2 mol. equiv. of 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane at 0 °C → room temperature in pyridine for 2 days and then with acetic anhydride, giving two compounds in the yields of 50% and 26%. The structures of these products were elucidated by comparison of their ^{1}H NMR spectra with that of **5**. The signals due to H-2' and H-3' of the major product appeared in the upper field compared to those of **5**, revealing that the silyl group attached to the 2'- and 3'-hydroxyl groups. On the other hand, in the minor product, the signals due to H-2, H-3, H-2', and H-3' appeared in the upper field region compared to those of **5**, suggesting



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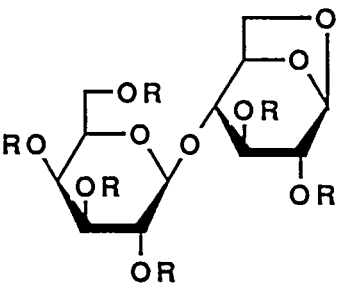

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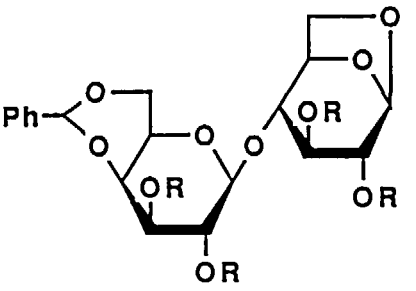
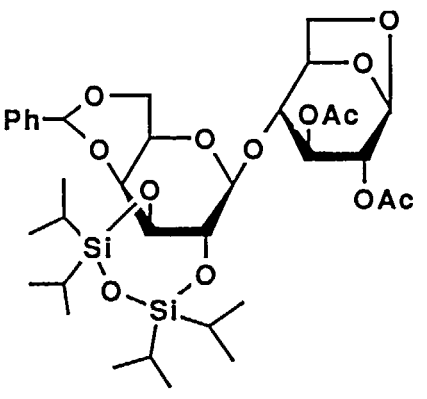
3 R=H



4 R=H
5 R=Ac

Ac = Acetyl
Ph = Phenyl



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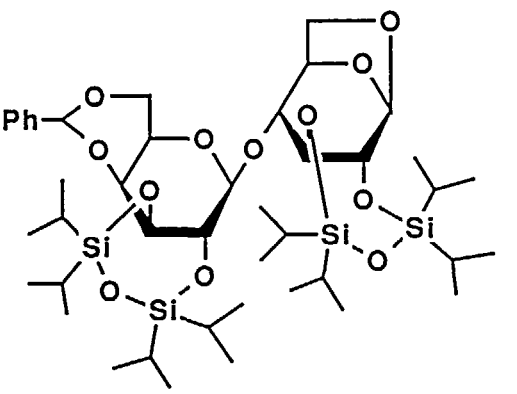


7

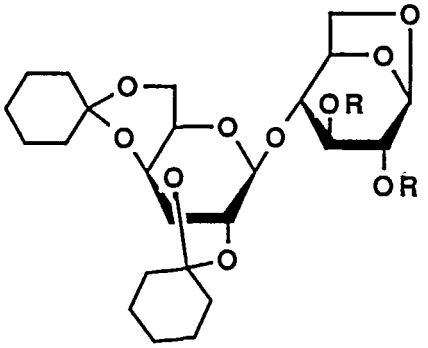
that both the 2,3- and the 2',3'-hydroxy pairs were silylated. Therefore, these major and minor products were elucidated as 2,3-di-O-acetyl-1,6-anhydro-4',6'-O-benzylidene-2',3'-O-(tetraisopropyldisiloxane-1,3-diyl)-β-lactose (6) and 1,6-anhydro-4',6'-O-benzylidene-2,3:2',3'-di-O-(tetraisopropyldisiloxane-1,3-diyl)-β-lactose (7), respectively. Chemical shift data from ^{1}H NMR spectra are summarized in Table 1. Thus, the disiloxolane reagent preferably reacts with the 2',3'-hydroxy pair of 4 although such selectivity is not very high. This contrasts with the selective silylation of the 2,3-hydroxy pair of the corresponding cellobiose derivative, which also belongs to β-linked disaccharides. Regioselectivity of the cyclic ether formation with a tetraisopropyldisiloxane-1,3-diyl group is probably dominated by the position of a hydroxyl group undergoing the first silylation. Thus, the 2-hydroxyl group should be the most reactive in the case of the cellobiose derivative; whereas the order of reactivities of the hydroxyl groups in 4 should be 3'>2> the other positions, with a little difference between the 3'- and 2-hydroxyl groups. This rationalizaton is supported by the experimental results which Tejima et al.[10,11] obtained when examining the reactivities of the hydroxyl groups of 4 in benzoylation and p-toluenesulfonylation reactions.

Our attention was next directed towards the role of cyclic acetals for partial protections of 3. In particular, the behavior of 3 toward cyclohexylidenation was of interest to us. Compound 3 was treated with several mol. equiv. of 1,1-dimethoxycyclohexane and a catalytic amount of d-10-camphorsulfonic acid at 50 °C for several hours during which time methanol generated was removed under reduced pressure. The reaction mixture was acetylated before products were isolated. TLC revealed that more than three compounds were produced, two of which moved much faster on TLC (toluene-ethyl acetate) than the other one. Those fast-moving compounds were isolated in yields of 34% and 24% on the basis of 3 when the reaction with 3.3 mol. equiv. of the cyclohexane reagent was carried out for 3.5 h. When 7.5 mol. equiv. of the reagent and 6 hours of the reaction period were employed, the yield of the major product was enhanced up to 49% with no change for the minor one. Similar to the cases of 6 and 7, structural elucidation of these products was achieved mainly by comparison of their ^{1}H NMR spectra with that of 2. The

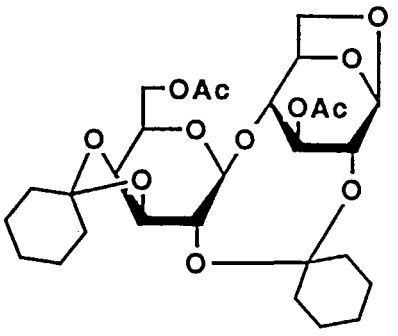
Table 1. ^{1}H NMR Data for 1,6-Anhydro-β-lactose Derivatives.

H-atom	Chemical Shift (δ) and Multiplicity								
	2	5	6	7	8	9	10	12	11
H-1	5.46s	5.48s	5.52s	5.28s	5.64s	5.27s	5.25s	5.37s	5.53s
H-2	5.16s	5.40s[a]	5.47s	3.52d	5.50s	3.85[a]	4.54d	3.42d	5.50s
H-3	4.55s	4.50s	4.49s	3.72t	4.53s	4.57s[a]	3.91dd	3.86m	4.53s[a]
H-4	4.00s[a]	3.58s	3.48s	3.60d	3.65s	3.74m	3.75[a]	3.69d	3.61s[a]
H-5	4.60d	4.62d	4.62d	4.62m	4.81d	4.59[a]	4.52d	4.69d	4.75d
H-6a	3.81dd	3.80dd	3.80dd[a]	3.7[a]	3.81dd	3.85[a]	3.78dd	3.72dd	3.8[a]
H-6b	4.0[a]	3.97d	3.95d[a]	3.7[a]	3.98d	4.05dd	3.74[a]	4.03d	4.10[a]
H-1'	4.80d	4.87d	4.58d	4.36d	4.87d	4.63d	4.43d	4.83d	4.52d[a]
H-2'	5.28t	5.41dd[a]	3.95t[a]	3.91dd	4.12t	3.95t	3.74[a]	4.00dd	3.8[a]
H-3'	5.04dd	4.98dd	3.80[a]	3.80dd	3.48dd	3.85[a]	4.08dd	3.59dd	3.60m[a]
H-4'	5.38d	4.35d	4.09d	4.08d	4.40s	4.38[a]	4.14m	4.49[a]	4.16d
H-5'	3.56s	3.61s	3.48s	3.34s	3.36s	3.40s	4.03m	3.44s	3.44s
H-6'a	4.06dd	4.03d	4.01dd	3.99dd	3.85d	4.38[a]	4.28dd	3.92d	3.8[a]
H-6'b	4.16dd	4.26dd	4.23dd	4.25dd	4.04dd	4.68dd	4.40dd	4.28dd	4.10d[a]

a. Overlapped.



8 R=Ac
10 R=H



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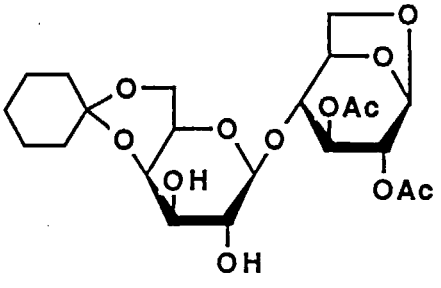

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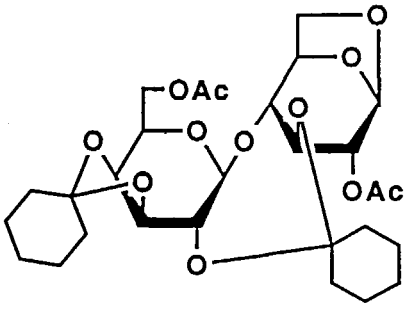

12

signals due to H-2', H-3', and H-4' of the major product appeared in the remarkably upper field region of the spectrum compared to those of 2, suggesting that this compound is 2,3-di-O-acetyl-1,6-anhydro-2',3':4',6'-di-O-cyclohexylidene-β-lactose (8). In the minor product the signals due to H-2, H-2', H-3', and H-4' appeared at an upper field compared to those of 2, suggesting that the minor product is 3,6'-di-O-acetyl-1,6-anhydro-2,2':3',4'-di-O-cyclohexylidene-β-lactose (9). Examination of the ^{1}H NMR spectrum of the fraction more polar than 8 and 9, which moved more slowly on TLC, strongly indicated that the fraction might be a mixture of monocyclohexylidene derivatives. As separation of the components in this fraction seemed to be greatly difficult, their isolation and characterization were never attemped. A couple of compounds having the versatility as substrates for further modifications

were derived from **8**. The acetyl groups were removed from the 2- and 3-positions of **8** by the Zemplen procedure, giving the crystalline 2,3-dihydroxy compound (**10**). The cyclohexylidene acetal group of **8**, trans-fused at the 2'- and 3'-positions, was selectively hydrolyzed under mildly acidic conditions giving the crystalline 2',3'-hydroxy compound (**11**) in good yield.

Several examples of cyclic acetals bridging two contiguous monosaccharide constituents of an oligosaccharide chain are known.[12] All such acetals have been limited to the 3, 2'-O-alkylidene or 6, 2'-O-alkylidene derivatives. To our best knowledge, formation of **9** constituted the first example of a 2, 2'-O-alkylidene derivative. However, we found that the usual 3, 2'-linked acetal was also obtainable through a reaction conducted at elevated temperature. Thus, treatment of **3** with 1,1-dimethoxycyclohexane-camphorsulfonic acid at 90-110 °C for 8 h followed by acetylation gave 2,6'-di-O-acetyl-1,6-anhydro-3,2':3',4'-di-O-cyclohexylidene-β-lactose (**12**) in 34% yield. As shown in Table 1, the ^{1}H NMR spectrum of **12** is compatible with the structure proposed. Under these reaction conditions, three unidentified compounds which moved faster on TLC than **12** were also produced as well as a trace of **8** and **9**.

Conformational analysis based on the coupling constants from the ^{1}H NMR spectrum (Table 2) suggests that the 1,6-anhydro-β-D-glucopyranose moiety of **12** does not adopt the typical $^1C_4$(D) conformation expected but rather a deformed conformation. Namely, in contrast to most 1,6-anhydro-β-D-glucopyranose derivatives which reveal signals due to H-2, H-3, H-4 as broad singlets owing to long range couplings, **12** reveals those protons as a couple of sharp doublets and one doublet of doublets. The observed coupling constants, $J_{2,3}$ = 7.6 Hz and $J_{3,4}$ = 6.4 Hz, have a close resemblance to those from the $B_{0,3}$ conformation of 3-amino-1,6-anhydro-3-deoxy-β-D-glucopyranose previously examined.[13] Judging from a similar coupling constants, $J_{2,3}$ = 7.0 Hz, $J_{3,4}$ = 7.0 Hz, the 1,6-anhydro-β-D-glucopyranose moiety of **7** also adopts the $B_{0,3}$ conformation.

In conclusion, our procedure for preparation of 1,6-anhydro oligosaccharides was also applicable to lactose. Cyclic silylation and/or cyclic acetalation of 1,6-anhydro-β-lactose gave several novel derivatives, some of which would be useful intermediates for syntheses of compounds with biological importance.

Table 2. ^{1}H NMR Data for 1,6-Anhydro-β-lactose Derivatives

	Proton-Proton Coupling Constant (Hz)								
	2	5	6	7	8	9	10	12	11
$J_{1,2}$	<2	<2	<2	<2	<2	<2	<2	<2	<2
$J_{3,4}$	<2	<2	<2	7.0	<2	<2	a	7.6	<2
$J_{3,4}$	<2	<2	<2	7.0	<2	a	a	6.4	<2
$J_{4,5}$	<2	<2	<2	<2	<2	a	a	a	a
$J_{5,6a}$	5.9	5.8	a	a	6.0	1.7	5.7	<2	a
$J_{5,6b}$	a	<2	a	a	<2	2.1	a	<2	a
$J_{6a,6b}$	7.6	7.6	7.3	a	7.6	12.8	7.3	7.9	8.1
$J_{1',2'}$	7.9	8.3	4.6	7.0	8.1	7.6	5.8	9.1	a
$J_{2',3'}$	10.4	10.4	a	9.1	8.6	7.2	9.6	8.0	a
$J_{3',4'}$	3.5	3.6	a	3.7	2.7	a	2.6	5.4	a
$J_{4',5'}$	<2	<2	a	<2	<2	a	a	2.8	a
$J_{5',6'a}$	6.6	1.9	1.7	<2	<2	a	2.0	6.9	a
$J_{5',6'b}$	6.3	1.5	1.4	<2	1.9	3.6	1.2	4.2	a
$J_{6'a,6'b}$	11.2	12.5	12.4	10.7	13.0	10.2	13.1	11.8	a

a : Coupling constant could not be determined.

EXPERIMENTAL

General Procedures. Melting points were determined with a Yamato micro melting point apparatus, and are uncorrected. Optical rotations were determined with a Perkin-Elmer Model 241MC polarimeter. ^{1}H NMR spectra were recorded at 400 MHz or 500 MHz with JEOL JNM-GX-400 or JEOL JNM-GX-500 spectrometers, using tetramethylsilane as internal standard. Reactions were monitored by TLC on a precoated plate of silica gel $60F_{254}$ (layer thickness, 0.25 mm; E. Merck, Darmstadt, Germany). Column chromatography was performed on silica gel 60 (230-400 mesh; E. Merck, Darmstadt, Germany) with the solvent system specified. Solvent extracts were dried with anhydrous sodium sulfate unless otherwise specified, and solutions were concentrated under diminished pressure.

2,3,2',3',4',6'-Hexa-O-acetyl-1,6-anhydro-β-lactose (2) via syrupy pentachlorophenyl 2,3,6,2',3',4',6'-hepta-O-acetyl-β-lactoside (1). To lactose monohydrate (205.2 g, 569.5 mmol) placed in a flask were added pyridine (600 mL) and acetic anhydride (800 mL) at 0 °C. The resulting slurry was stirred overnight at room temperature, poured into ice-cold water, and extracted with dichloromethane. The extract was washed with 2 **M** hydrochloric acid, aqueous sodium bicarbonate and water, dried, and concentrated to dryness; the resulting residue was dissolved in dichloromethane (800 mL). Hydrogen bromide in acetic acid (25%, 700 mL) was dropwise added to the solution at 0 °C over the period of 1.5 h. The mixture was stirred at room temperature for 5 h, poured into ice-cold water, and extracted with dichloromethane. The extract was washed with water, dried, and concentrated to dryness; the residue was dissolved in acetone (1 L). After sodium pentachlorophenoxide (purity 85%, 288.3 g) had been added to the solution, the mixture was heated under reflux for 7 h and concentrated; the resulting residue was extracted with dichloromethane. The extract was washed with water, dried, and concentrated to give syrupy **1**, which resisted crystallization. A solution of potassium hydroxide (571 g) in water (1.4 L) was added to the syrupy **1** and the mixture was heated at 100 °C for 24 h with stirring. After having been cooled, the resulting solution was adjusted to pH 5 with dilute 3.6 **M** sulfuric acid to give insoluble inorganic salt, which was filtered off. The filtrate was readjusted to pH 7 with solid sodium hydrogen carbonate and then

concentrated to dryness. The residue was suspended in a mixture of pyridine (350 mL) and acetic anhydride (350 mL) and the suspension was stirred at 70 °C for 3 h. The slurry was poured into ice-cold water and extracted with dichloromethane; the extract was washed with cold 2 **M** hydrochloric acid, aqueous sodium hydrogen carbonate, and water, dried (anhydrous magnesium sulfate), and concentrated. The resulting solid mass was recrystallized from ethanol-chloroform, giving **2** (159.3 g, 48.5% from lactose monohydrate); mp 205-206 °C, lit.[8] 208 °C.

2,3-Di-O-acetyl-1,6-anhydro-4',6'-O-benzylidene-2',3'-O-(tetraisopropyldisiloxane-1,3-diyl)-β-lactose (6) and 1,6-Anhydro-4',6'-O-benzylidene-2,3:2',3'-di-O-(tetraisopropyldisiloxane-1,3-diyl)-β-lactose (7). Methanolic sodium methoxide (5 **M**, 0.05 mL) was added to a solution of **5** (2.0 g, 3.45 mmol) in methanol (10 mL). The mixture was stirred overnight, neutralized with Dowex 50W-X8 (H^+ form), concentrated to dryness and the resulting residue was dissolved in pyridine (15 mL). 1,3-Dichlorotetraisopropyldisiloxane (1.21 mL, 3.84 mmol) was added to the solution at 0 °C and the mixture was stirred at room temperature for 2 days. After acetic anhydride (10 mL) had been added, the mixture was kept at room temperature for 5 h, poured into ice-cold water, and extracted with chloroform. The extract was washed with 2 **M** hydrochloric acid, aqueous sodium hydrogen carbonate, and water, dried, and concentrated. The residue was chromatographed with toluene-ethyl acetate (100:1 → 50:1 v/v) as the eluant, giving **7** (737 mg, 25.7% yield) and **6** (1.171 g, 49.5% yield). Compound **7** was recrystallized from methanol: mp 147-147.5 °C; $[\alpha]_D^{19}$ -35° (*c* 0.68, chloroform); for ^{1}H NMR data see Table 1 and 2.

Anal. Calcd for $C_{43}H_{76}O_{12}Si_4$: C, 57.55; H, 8.54. Found: C, 57.43; H, 8.51.

Compound **6** was recrystallized from ethanol-chloroform: mp 199-202 °C; $[\alpha]_D^{19}$ -20° (*c* 0.74, chloroform); for ^{1}H NMR data see Table 1 and 2.

Anal. Calcd for $C_{35}H_{54}O_{13}Si_2$: C, 56.89; H, 7.37. Found: C, 56.80; H, 7.35.

3,6'-Di-O-acetyl-1,6-anhydro-2,2':3',4'-di-O-cyclohexylidene-β-lactose (9) and 2,3-Di-O-acetyl-1,6-anhydro-2',3':4',6'-di-O-cyclohexylidene-β-lactose (8). A solution of **3** (1.10 g, 3.39 mmol), 1,1-dimethoxycyclohexane (1.61 g, 11.19 mmol, 3.39 mol. equiv. to **3**), and *d*-10-camphorsulfonic acid (30 mg) in *N,N*-dimethylformamide (30 mL)

was heated with stirring at 50 °C for 3.5 h under diminished pressure (ca. 6660 Pa). The mixture was neutralized by stirring with anhydrous sodium carbonate for 30 min and filtered. The filtrate was concentrated to dryness and the residue was dissolved in a mixture of pyridine (10 mL) and acetic anhydride (10 mL). After the solution was kept at room temperature overnight, it was poured into ice-cold water and extracted with dichloromethane. The extract was washed with 2 M hydrochloric acid, aqueous sodium hydrogen carbonate, and water, dried, and concentrated. The residue was chromatographed with toluene-ethyl acetate (7:1 → 5:1 v/v) as the eluant, giving 9 (467 mg, 24.2% yield) and 8 (650 mg, 33.4% yield). Compound 9: amorphous powder; $[\alpha]_D^{19}$ +12° (c 1.0, chloroform); for ^{1}H NMR data see Table 1 and 2.

Anal. Calcd for $C_{28}H_{40}O_{12}$: C, 59.15; H, 7.09. Found: C, 59.43; H, 7.30.

Compound 8: amorphous powder; $[\alpha]_D^{19}$ -36° (c 0.56, chloroform); for ^{1}H NMR data see Table 1 and 2.

Anal. Calcd for $C_{28}H_{40}O_{12}$: C, 59.15; H, 7.09. Found: C, 59.20; H, 7.09.

When a larger amount of 1,1-dimethoxycyclohexane (7.5 mol. equiv. to 3) and longer reaction time (6 h) were employed, the yield of 8 increased to 48.6% with no essential change in the yield of 9 (23.5%).

1,6-Anhydro-2',3':4',6'-di-O-cyclohexylidene-β-lactose (10). To a solution of 8 (568 mg, 1.0 mmol) in methanol (10 mL) was added 5 M methanolic solution of sodium methoxide (0.02 mL). The mixture was kept at room temperature for 5 h, neutralized with Dowex 50W-X8 (H^+ form) under stirring, and filtered. The filtrate was concentrated and the resulting mass was recrystallized from ethanol-chloroform, giving 10 (387 mg, 80% yield): mp 218-220 °C; $[\alpha]_D^{20}$ -58° (c 0.83, methanol); for ^{1}H NMR data see Table 1 and 2.

Anal. Calcd for $C_{24}H_{36}O_{10}$: C, 59.49; H, 7.49. Found: C, 59.48; H, 7.38.

2,3-Di-O-acetyl-1,6-anhydro-4',6'-O-cyclohexylidene-β-lactose (11). A solution of 8 (300 mg, 0.528 mmol) and d-10-camphorsulfonic acid (6 mg) in methanol (10 mL) was stirred at room temperature for 15 min, diluted with pyridine (10 mL), and concentrated. The residue was chromatographed with chloroform-methanol (95:5 v/v) as eluant to give 11 (220 mg, 85.4% yield), which was recrystallized from benzene-ethyl

acetate: mp 171.5-172 °C; $[\alpha]_D^{24}$ -52° (c 0.6, chloroform); for ^{1}H NMR data see Table 1 and 2.

Anal. Calcd for $C_{22}H_{32}O_{12}$: C, 54.09; H, 6.60. Found. C, 53.83; H, 6.55.

2,6'-Di-O-acetyl-1,6-anhydro-3,2':3',4'-di-O-cyclohexylidene-β-lactose (12). A solution of 3 (550 mg, 1.70 mmol), 1,1-dimethoxycyclohexane (1.46 g, 10.1 mmol), and d-10-camphorsulfonic acid (10 mg) in N,N-dimethylformamide (20 mL) was heated with stirring at 90-110 °C for 8 h under diminished pressure (10000-20000 Pa). The resulting mixture was worked up as described in the preparation of 9 and 8. TLC of the crude product showed several spots corresponding to 12, 9 (faint), and 8 (faint) as well as three unidentified compounds which moved faster than 12. The mixture was chromatographed with hexane-ethyl acetate (3:2 v/v) to give 12 (326 mg, 33.8% yield), which was recrystallized from chloroform: mp 210-211 °C; $[\alpha]_D^{20}$ +54° (c 0.76, chloroform); for ^{1}H NMR data see Table 1 and 2.

Anal. Calcd for $C_{28}H_{40}O_{12}$: C, 59.15; H, 7.09. Found: C, 59.19; H, 7.13.

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