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Chemical Modification of Lactose. V.[1] Synthesis of 6′-Acetamido-6′-deoxy-α-lactose

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Benzylidenation of 1,6-anhydro-β-lactose afforded 1,6-anhydro-4′,6′-O-benzylidene-β-lactose (2) in 81% yield. Acylation of 2 yielded tetra-O-acyl-1,6-anhydro-4′,6′-O-benzylidene-β-lactose [acyl=acetyl (3), benzoyl (4)]. Reflux of 3 with N-bromosuccinimide and $BaCO_3$ in CCl_4 and 1,2-dichloroethane gave crystalline tetra-O-acetyl-1,6-anhydro-4′-O-benzoyl-6′-bromo-6′-deoxy-β-lactose (5) in 52% yield. Catalytic dehydrobromination of 5 afforded crystalline tetra-O-acetyl-1,6-anhydro-4′-O-benzoyl-6′-deoxy-β-lactose (6). Deacylation of 5 and successive reacetylation yielded 2,2′,3,3′,4′-penta-O-acetyl-1,6-anhydro-6′-bromo-6′-deoxy-β-lactose (7). Dehydrobromination of 7 gave penta-O-acetyl-1,6-anhydro-6′-deoxy-β-lactose (8). Heating of 7 and sodium azide in hexamethylphosphoric triamide afforded a mixture of crystalline penta-O-acetyl-1,6-anhydro-6′-azido-6′-deoxy-β-lactose (9) (36%) and sirupy 2,3-di-O-acetyl-1,6-anhydro-4-O-(2,3,4-tri-O-acetyl-α-L-arabino-hex-5-eno-pyranosyl)-β-D-glucopyranose (10) (34%). Compound 10 was also prepared by treatment of 7 in dry pyridine with silver fluoride. Acetolysis of 9, reduction of the azido group in the acetolysis product (11), N-acetylation, and finally de-O-acetylation afforded the title compound (13) as hydroscopic crystals, $[\alpha]_D^{24}$ +80°→+66.7°.

In catalytic hydrogenation of 10 over Pd catalyst, 8 was the sole product in 90% yield. Over Pt oxide or Raney Ni catalyst, a low yield of 8 was effected with fairly amounts of unidentified sirup.

In the preceding paper of this series, the primary hydroxyl group in the reducing part in lactose was modified by the authors. As further extension of our program aimed at the chemical studies on reducing disaccharides, modifications at the primary hydroxyl group in the non-reducing part, the C-6′ position in lactose, was designed. Now, starting from 1,6-anhydro-β-lactose (**1**), the title compound and several 6′-modified lactose derivatives were synthesized. The title compound (**13**) is another structural isomerism of 6-acetamido-6-deoxy-lactose, 4′-acetamido-4′-deoxy-α-lactose, and 6′-acetamido-6′-deoxy-α-cellobiose, and the first syntheses of which have been reported in Part II[3] or III[4] of this series. We report here the details leading to the synthesis of the title compound and also discuss briefly about differences in reactivities between C-6 and C-6′ positions in lactose.

Benzylidenation of **1** with benzaldehyde in the presence of zinc chloride afforded, after treatment of the reaction product with repeated acetone extraction, monobenzylidene compound in 81% yield as a hygroscopic, amorphous powder. The product consumed two molar equivalents of sodium metaperiodate with no concomitant formation of formic acid, therefore, the structure was tentatively assigned to 1,6-anhydro-4′,6′-O-benzylidene-β-lactose (**2**). Acetylation of **2** gave crystalline tetraacetate (**3**). When the product was recrystallized from ethanol, **3** contained one mole of ethanol of crystallization; the ethanol was eliminated by heating under vacuum. From the correlation of the structure of **2**, compound **3** was assigned to 2,2′,3,3′-tetra-O-acetyl-1,6-anhydro-4′,6′-O-benzylidene-β-lactose. Benzoylation of **2** afforded crystalline tetrabenzoate, 1,6-anhydro-2,2′,3,3′-tetra-O-benzoyl-4′,6′-O-benzylidene-β-lactose (**4**).

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[1] Part IV: T. Chiba, M. Haga, and S. Tejima, *Chem. Pharm. Bull.* (Tokyo), **22**, 398 (1974).

[2] Location: *Tanabe-dori, Mizuho-ku, Nagoya.*

[3] S. Tejima and T. Chiba, *Chem. Pharm. Bull.* (Tokyo), **21**, 546 (1973).

[4] Y. Okamori, M. Haga, and S. Tejima, *Chem. Pharm. Bull.* (Tokyo), **21**, 2538 (1973).

Introduction of bromine atom in the C-6′ position in **3** was smoothly performed by application of the Hanessian's procedure⁵⁾ which was reported in selective bromination at the C-6 position in methyl 4,6-O-benzylidene-α-D-glucopyranoside. Reflux of a mixture of **3**, N-bromosuccinimide, and barium carbonate in carbon tetrachloride and dichloroethane for 2.5 hr afforded, after column chromatography, crystals (**5**) in 52% yield. According to the nuclear magnetic resonance (NMR) spectroscopy and the elemental analysis, **5** had a composition of a tetraacetyl-1,6-anhydro-monobenzoyl-monobromo-monodeoxy-disaccharide. Reductive dehydrobromination of **5** over Raney nickel catalyst at room temperature under atmospheric pressure gave crystals (**6**) in 62% yield. After recrystallization from methanol, **6** contained one mole of methanol of crystallization. The NMR spectroscopy showed signals corresponding to an aryl, a methyl (τ 6.54, three proton singlet), four acetyls, and a methyl (τ 8.75, three proton doublet, $J=6.5$ Hz); the former methyl was assigned to that in methanol and the latter to that at C-5′. Therefore, **6** was assigned to 2,2′,3,3′-tetra-O-acetyl-1,6-anhydro-4′-O-benzoyl-6′-deoxy-β-lactose monomethanolate. Compound **5**, the precursor of **6**, was assigned to 2,2′,3,3′-tetra-O-acetyl-1,6-anhydro-4′-O-benzoyl-6′-bromo-6′-deoxy-β-lactose.

Efforts to substitute the bromine atom in **5** with azido group under different conditions were failed. The bulky benzoyloxy group at C-4′ presumably hinders approach of sodium azide, but recovers the starting bromide. Consequently, the authors changed the benzoyl to acetyl group. Concomitant debenzoylation and deacetylation of **5** were performed using methanolic sodium methoxide. After neutralization, without separation of the resulting deacylated product, it was reacetylated to give pentaacetyl-1,6-anhydro-6′-bromo-6′-deoxy-β-lactose (**7**) in 88% yield. Reductive dehydrobromination of **7** afforded pentaacetyl-1,6-anhydro-6′-deoxy-β-lactose (**8**) in 96% yield. Starting from **6**, after deacylation followed by reacetylation, **8** was also obtainable in 94% yield. The NMR spectrum of **8** showed a signal corresponding to the methyl at C-5′ (τ 8.80, three proton doublet, $J=6.5$ Hz). These results and periodate consumption mentioned before confirmed the structure of **2**, in which the benzylidene acetal attached to C-4′ and 6′.

Substitution of the bromine atom in **7** with azido group was effected by heating of a mixture of **7** and sodium azide in hexamethylphosphoric triamide (HMPA) at 100° for 5 hr. In the reaction mixture two products were identified as judged by thin-layer chromatography (TLC). After treatment of the mixture with the usual manner, an easily crystallizable compound was separated in 36% yield. The infrared (IR) spectrum showed an absorption corresponding to azido group. The product was assigned to 2,2′,3,3′,4′-penta-O-acetyl-1,6-anhydro-6′-azido-6′-deoxy-β-lactose (**9**). The filtrate, from which **9** had been separated, was chromatographed on a column of silica gel. From the faster moving eluate, an amorphous powder was isolated in 34% yield and assigned to 2,3-di-O-acetyl-1,6-anhydro-4-O-(2,3,4-tri-O-acetyl-α-L-arabino-hex-5-enopyranosyl)-β-D-glucopyranose (**10**) by comparison with an authentic sample; the preparation will be mentioned later. The yields of **9** (36%) and **10** (34%) were almost equal amounts, and **10** was more mobile than **9** on TLC plate. Consequently, concomitant elimination reaction occurred during azido substitution to give unsaturated sugar (**10**) which decreased the yield of azido sugar (**9**). While in azido substitution in benzyl or methyl 2,2′,3,3′,4′,6′-hexa-O-acetyl-6-O-mesyl-β-lactoside, as it has been reported in Part II of this series, merely gave substitution product with no elimination product. Whether the difference comes from that in reactivities between C-6 and C-6′, or different substituents in the individual starting materials is not yet uncertain. According to the literature, normal alkyl bromides are found to undergo dehydrobromination in HMPA at *ca.* 200°, giving alkyl-1-ene in good yield.⁶⁾ Whatever the detailed process, it is interesting to describe that the procedure mentioned above presents a novel preparative method for the synthesis of 5′,6′-unsaturated compound.

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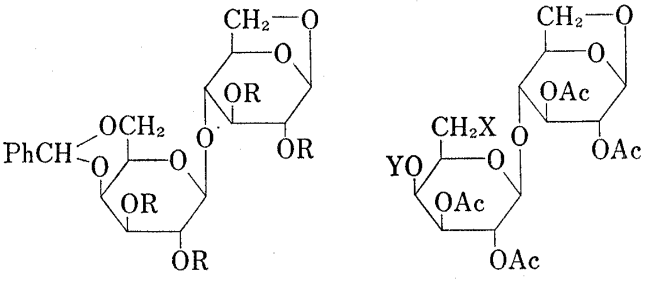
5) S. Hanessian, *Carbohyd. Res.*, 2, 86 (1966); W.A. Szarek, "Advances in Carbohydrate Chemistry and Biochemistry," Vol. 28, Academic Press, New York and London, 1973, p. 225.

6) R.S. Monson, *J. Chem. Soc. Commun.*, **1971**, 113.

Authentic sample of **10** was synthesized by treatment of **7** with silver fluoride in pyridine; synthesis of 5,6-unsaturated compound by this method has been effected in Part IV of this series. After column chromatography, **10** was isolated in 49% yield. The IR spectrum in chloroform indicated a signal at 1668 cm^{-1} corresponding to the C-C double bond.

Acetolysis of **9** effected opening of the 1,6-anhydro ring, during which the specific rotation changed from minus to plus, while the azido group was intact, and yielded heptaacetyl-6′-azido-6′-deoxy-α-lactose (**11**) in 67% yield. The NMR spectrum showed signals corresponding to seven acetyls and one proton doublet (τ 3.77, J=3.5 Hz). As the latter could not be found in **9**, we assigned it to the anomeric proton. Catalytic reduction of **11** and successive acetylation afforded, after column chromatography, heptaacetyl-6′-acetamido-6′-deoxy-α-lactose (**12**) in 89% yield as an amorphous powder. Deacetylation of **12** with methanolic sodium methoxide yielded the title compound (**13**) as a very hygroscopic, amorphous powder. Compound **13**, the Tollen's test-positive, mutarotated in water from +80° to +66.7° for 24 hr. After hydrochloric acid hydrolysis, two spots, *Rf* 0.21 and 0.40, were identified by paper partition chromatography (PPC), and other spot could not be identified. The less mobile spot, ninhydrin- and the Tollen's test-positive, was assigned to 6-amino-6-deoxy-D-galactose hydrochloride in comparison with an authentic product which was synthesized according to the procedure reported by Saeki, *et al.*⁷⁾ The more mobile spot was assigned to glucose.



2 : R=H
3 : R=Ac
4 : R=Bz
Ac=acetyl, Bz=benzoyl
Me=methyl, Ph=phenyl

5 : X=Br, Y=Bz
6 : X=H, Y=Bz·MeOH
7 : X=Br, Y=Ac
8 : X=H, Y=Ac
9 : X=N$_3$, Y=Ac

Chart 1

In Part IV of this series,¹⁾ the authors reported that in catalytic hydrogenation of 1,2,3-tri-O-acetyl-4-O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-β-D-xylo-hex-5-eno-pyranose (**14**), regardless of the catalysts, a stereospecific hydrogenation proceeded in such a way that the 6-deoxy-L-ido isomer was overwhelmingly predominant than the 6-deoxy-D-gluco isomer; the result was the reverse with that reported in unsaturated monosaccharide series. Therefore, from the correlation of the preceding work, we investigated about catalytic hydrogenation of **10**.

When palladium was used as the catalyst, a stereospecific hydrogenation proceeded in such a way that the 6′-deoxy-D-galacto isomer, 2,2′,3,3′,4′-penta-O-acetyl-1,6-anhydro-6′-deoxy-β-lactose (**8**) was the sole product. With Raney nickel catalyst, **8** (55%) and unidentified sirup were separated. With platinum oxide catalyst complex result was obtained; more than three spots were identified on TLC plate. From the reaction mixture, **8** was separated in a low yield (22%). Therefore, the hydrogenation products varied with the catalysts used and stereospecific hydrogenation could not be observed.

It is not unreasonable to assume that in **14**, as a bulky acetylated galactopyranosyl group is located with β-glycosidic linkage under the C-4 of the reducing part, approach of reagents under C-5 must be strongly hindered. Therefore, stereospecific hydrogenation proceeds such a way as giving the 6-deoxy-L-ido isomer. In compound **10**, although the two acetoxyl groups at the C-3′ and C-4′ are located over the non-reducing part, the acetoxyls are not so bulky as strongly interfere the approach of reagents over C-5′, consequently, non-stereospecific hydrogenation occurrs in **10**.

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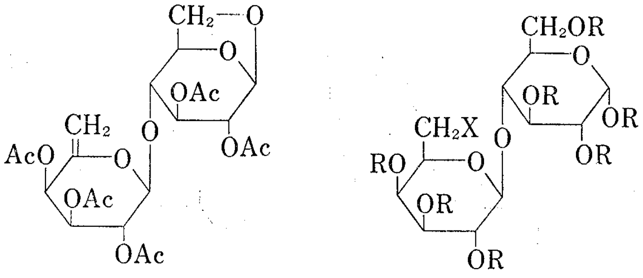
7) H. Saeki, T. Iwashige, E. Ohki, K. Furuya, and M. Shirasaka, *Ann. Sankyo Res. Lab.*, **19**, 139 (1967).

Among the three very common 1,4-linked reducing disaccharides, easily available from natural products, chemical modifications of the C-6′ position in maltose or cellobiose series have already been performed with several investigators. For example, Dutton and Slessor,8) Melton and Slessor,9) and Sleeter and Sinclair10) reported the syntheses of 6′-substituted maltose derivatives. Recently, introduction of azido and acetamido groups in C-6′ position in methyl β-maltoside11) has also been reported from the Hough's laboratory. In cellobiose, the analogous investigations have been performed by Lindberg and Selleby,12) Roy and Timell,13) and the authors.4) According to their data, in maltose and cellobiose, C-6′ position is more reactive than C-6.

In lactose, so far the authors are aware of, no paper has been reported on such modifications. Presumably, in lactose or lactosides, owing to presence of the axial hydroxyl at C-4′ and the β-glycosidic linkage at the anomeric center in the non-reducing part, selective sulfonylation or triphenylmethylation at C-6′ is hindered,14) which may be the main reason why modifications have not yet been accomplished in lactose. In this paper the first syntheses of 6′-substituted lactose derivatives were described and differences of reactivities between C-6 and C-6′ positions were discussed briefly. However, further accumulation of data needs to draw exact conclusion. It is also noteworthy to describe that 1,6-anhydro-4′,6′-O-benzylidene-β-lactose (**2**) having only four secondary hydroxyls, will become a versatile key intermediate for chemical modifications of lactose.



10

11 : X=N_3, R=Ac
12 : X=NHAc, R=Ac
13 : X=NHAc, R=H

Chart 2

Experimental

Melting points were determined on a Yanagimoto melting point apparatus and uncorrected. Solutions were evaporated in a rotary evaporator below 40° under vacuum. Optical rotations were measured with a Yanagimoto Model OR-10 polarimeter in a 0.5 dm cell. IR spectra were recorded with a Jasco Model IR-S spectrometer. NMR spectra were recorded at 100 MHz with a Jeol Model JNM-MH-100 spectrometer. Tetramethylsilane was used as the internal standard in $CDCl_3$. Chemical shifts are given on the τ scale. TLC on Silica gel GF_{254} (E. Merck, Darmstadt, Germany) activated at 110° was performed with solvent systems (A) 9:1 (v/v) CH_2Cl_2–acetone, (B) 2:1 ether–benzene, (C) ether, and (D) 2:1 70% iso-PrOH–AcOEt. Detection was effected with H_2SO_4 or UV light (short wave length). Column chromatography was performed on a column of Wako-gel C-200 as the adsorbent, with 1 g of the mixture to be separated per 20 g of adsorbent. PPC was performed on Toyo Filter Paper No. 50 by the ascending method with 6:4:3 (v/v) *n*-BuOH–pyridine–H_2O by the procedure of Ueda15) and detection was effected with (A) 0.2% ninhydrin solution dissolved in H_2O–saturated *n*-BuOH,16) and (B) Tollen's reagent.17)

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9) L.D. Melton and K.N. Slessor, *Can. J. Chem.*, **51**, 327 (1973).
10) R.T. Sleeter and H.B. Sinclair, *J. Org. Chem.*, **35**, 3804 (1970).
11) P.L. Durette, L. Hough, and A.C. Richardson, *J. Chem. Soc. Perkin I*, **1974**, 97.
12) B. Lindberg and L. Selleby, *Acta Chem. Scand.*, **14**, 1051 (1960).
13) N. Roy and T.E. Timell, *Carbohyd. Res.*, **6**, 475 (1968).
14) D. Beith-Halahmi, H.M. Flowers, and D. Shapiro, *Carbohyd. Res.*, **5**, 25 (1967).
15) M. Ueda, *Yakugaku Zasshi*, **90**, 1322 (1970).
16) D. Aminoff and W.T.J. Morgan, *Nature*, **162**, 579 (1948); A.R. Patton and P. Chism, *Anal. Chem.*, **23**, 1683 (1951).
17) W.E. Trevelyan, D.P. Procter, and J.S. Harrison, *Nature*, **166**, 444 (1950).

1,6-Anhydro-β-lactose (1)——To a suspension of hexa-O-acetyl-1,6-anhydro-β-lactose (lactosan hexaacetate[3]) (50 g) in dry MeOH (500 ml) was added methanolic 0.5 N sodium methoxide (50 ml) at room temperature and the mixture was stirred, with exclusion of moisture, for 1 hr; complete deacetylation was judged by TLC. Dry Amberlite IR-120 (H^+) resin was added, and the suspension was stirred for 30 min, and then filtered. The filtrate was concentrated to dryness to give a hygroscopic amorphous powder which completely desiccated in a vacuum desiccator over $CaCl_2$. The product (26.7 g, 95%) had $[\alpha]_D^{26}$ −49.1° (c=1.06, H_2O). (lit.[18] mp 140—144°, $[\alpha]_D^{20}$ −53.5°). TLC: *Rf* 0.49 (solvent D).

1,6-Anhydro-4′,6′-O-benzylidene-β-lactose (2)——A mixture of 1 (25 g, 77.2 mmole), powdered $ZnCl_2$ (25 g, 183.4 mmole), and freshly distilled benzaldehyde (250 ml, 2.46 mole) was shaken overnight at room temperature. After addition of H_2O (250 ml) and MeOH (25 ml), the excess benzaldehyde was extracted with petr. ether (3 × 100 ml), and the organic layers were discarded. To the aqueous layer was added Na_2CO_3 (25 g, 235.8 mmole) by portions under stirring. After 1 hr, the resulting precipitate was removed by filtration and the residue was washed with H_2O. The combined filtrate and washings were concentrated to dryness and the residue was extracted with dry acetone (8 × 200 ml). The combined extracts were concentrated to dryness to give a hygroscopic amorphous powder (25.8 g, 81%), $[\alpha]_D^{25}$ −63.7° (c=1.13, H_2O). TLC: *Rf* 0.66 (solvent D). *Anal.* Calcd. for $C_{19}H_{24}O_{10}\cdot 1/2H_2O$: C, 54.16; H, 5.98. Found: C, 54.29; H, 5.88.

Periodate consumption of 2 (80.5 mg) was estimated according to the procedure of Okui.[19] The $NaIO_4$-consumption (mole) at room temperature was as follows: 0.38 (2.5 hr), 0.70 (5 hr), 0.96 (7.5 hr), 1.15 (10 hr), 1.79 (25 hr), 1.92 (30 hr, constant); no concomitant formation of H·COOH was observed.

2,2′,3,3′-Tetra-O-acetyl-1,6-anhydro-4′,6′-O-benzylidene-β-lactose (3)——Compound 2 (15 g) was acetylated with Ac_2O (80 ml) and pyridine (80 ml) for 24 hr at room temperature. The mixture was evaporated to dryness by repeated co-distillation with toluene. The residue was triturated with ice-H_2O to afford a solid, filtered, and air-dried. Recrystallization from AcOEt gave pure 3 (18.1 g, 85%), mp 232—233°, $[\alpha]_D^{26}$ +9.7° (c=1.03, $CHCl_3$). *Anal.* Calcd. for $C_{27}H_{32}O_{14}$: C, 55.86; H, 5.56. Found: C, 55.57; H, 5.62.

Recrystallization of 3 from EtOH afforded crystals, mp 228—229°, $[\alpha]_D^{25}$ +10° (c=1, $CHCl_3$). The product contained one mole of EtOH of crystallization; the EtOH was completely removed by heating at 120° under vacuum overnight. *Anal.* Calcd. for $C_{27}H_{32}O_{14}\cdot C_2H_5OH$: C, 55.59; H, 6.11. Found: C, 55.43; H, 5.87. NMR ($CDCl_3$) τ: 2.50—2.80 (5H, m, aryl), 7.88, 7.90, 7.94, 7.97 (12H, s, 4 × Ac), 8.78 (3H, t, J=7 Hz, CH_3 in EtOH). TLC: *Rf* 0.51 (solvent A).

1,6-Anhydro-2,2′,3,3′-tetra-O-benzoyl-4′,6′-O-benzylidene-β-lactose (4)——To a chilled solution of 2 (1 g, 2.4 mmole) in dry pyridine (10 ml) was dropwise added benzoyl chloride (3 ml, 25.6 mmole) at 0° and the mixture was stirred, with exclusion of moisture, for 1 hr. After the mixture was kept overnight at 0°, a few piece of ice was added to decompose excess benzoyl chloride. The mixture was poured into ice-H_2O (50 ml), extracted with CH_2Cl_2 (3 × 20 ml); the combined extracts were washed with cold dil. H_2SO_4, saturated $NaHCO_3$, and H_2O, dried ($CaCl_2$), and evaporated to dryness which crystallized from AcOEt (1.77 g, 88%), mp 228—230°, $[\alpha]_D^{25}$ +113.5° (c=1.11, $CHCl_3$). TLC: *Rf* 0.89 (solvent A), 0.65 (B), 0.79 (C). *Anal.* Calcd. for $C_{47}H_{40}O_{14}$: C, 68.11; H, 4.86. Found: C, 68.39; H, 4.94.

2,2′,3,3′-Tetra-O-acetyl-1,6-anhydro-4′-O-benzoyl-6′-bromo-6′-deoxy-β-lactose (5)——To a suspension of 3 (5 g, 8.6 mmole) in CCl_4 (200 ml) and 1,2-dichloroethane (30 ml) were added N-bromosuccinimide (1.7 g, 9.6 mmole) and $BaCO_3$ (1.9 g, 9.6 mmole). The mixture was refluxed with efficient stirring for 2.5 hr, filtered, and the filtrate was evaporated to dryness. The residue was dissolved in ether, washed with a small volume of H_2O to remove succinimide, dried ($CaCl_2$), and evaporated to a colorless sirup which showed two spots, *Rf* 0.46 (main) and 0.17 (minor), on TLC (solvent C). The sirup was dissolved in CH_2Cl_2 and the solution chromatographed on a column of silica gel with 20 : 1 (v/v) CH_2Cl_2–acetone as eluant. Evaporation of the solvent from the faster moving eluate afforded a sirup which crystallized from MeOH by scratching the insides of the flask. Recrystallization from MeOH gave pure 5 (2.95 g, 52%), mp 166—167°, $[\alpha]_D^{25}$ −3.4° (c=1.19, $CHCl_3$). NMR ($CDCl_3$) τ: 1.80—2.64 (5H, m, aryl), 7.86, 7.88, 7.95, 8.06 (12H, s, 4 × Ac). TLC: *Rf* 0.65 (solvent A), 0.38 (B), 0.46 (C). *Anal.* Calcd. for $C_{27}H_{31}O_{14}Br$: C, 49.18; H, 4.74. Found: C, 49.14; H, 4.61.

2,2′,3,3′-Tetra-O-acetyl-1,6-anhydro-4′-O-benzoyl-6′-deoxy-β-lactose Monomethanolate (6)——Compound 5 (0.5 g, 0.76 mmole) was dissolved in AcOEt (10 ml) and MeOH (10 ml) containing triethylamine (0.3 g, 3 mmole). The mixture was hydrogenated over freshly prepared Raney nickel catalyst at room temperature under atmospheric pressure. After 6 hr, the catalyst was removed by filtration and washed with MeOH. The combined filtrate and washings were concentrated to dryness. The residue was dissolved in CH_2Cl_2 (20 ml), successively washed with 1 N HCl and aq. $NaHCO_3$, and H_2O, dried ($CaCl_2$) and then concentrated to a sirup which crystallized by addition of MeOH. Recrystallization from MeOH gave crystals (288 mg, 62%), mp 104—106°, $[\alpha]_D^{25}$ −6.8° (c=1.17, $CHCl_3$), which contained one mole of MeOH of crystallization. NMR ($CDCl_3$) τ: 1.80—2.66 (5H, m, aryl), 6.54 (3H, s, CH_3 in MeOH), 7.86, 7.88, 7.96, 8.06 (12H,

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19) S. Okui, *Yakugaku Zasshi*, **75**, 1262 (1955).

s, 4×Ac), 8.75 (3H, d, $J_{5',6'}=6.5$ Hz, C_5'-CH_3). TLC: *Rf* 0.58 (solvent A), 0.32 (B), 0.36 (C). *Anal.* Calcd. for $C_{27}H_{32}O_{14}\cdot CH_3OH$: C, 54.90; H, 5.92. Found: C, 55.01; H, 6.01.

2,2′,3,3′,4′-Penta-O-acetyl-1,6-anhydro-6′-bromo-6′-deoxy-*β*-lactose (7)——To a chilled suspension of **5** (2 g) in dry MeOH (50 ml) was added methanolic 0.5 N sodium methoxide (1 ml) at 0°. The mixture was similarly treated as for **1** to afford a crystalline residue which acetylated with Ac_2O (10 ml) and pyridine (10 ml) for 24 hr at room temperature. The mixture was evaporated by repeated co-distillation with toluene to afford a sirup which crystallized from EtOH. Recrystallization from EtOH gave pure **7** (1.60 g, 88%), mp 173—174°, $[\alpha]_D^{25}$ $-32.1°$ ($c=1.12$, $CHCl_3$). TLC: *Rf* 0.54 (solvent A), 0.30 (B), 0.33 (C). *Anal.* Calcd. for $C_{22}H_{29}O_{14}Br$: C, 44.23; H, 4.89. Found: C, 43.96; H, 4.93.

2,2′,3,3′,4′-Penta-O-acetyl-1,6-anhydro-6′-deoxy-*β*-lactose (8)——1) From Compound **6**: To a suspension of **6** (200 mg) in dry MeOH (5 ml) was added methanolic 0.5N sodium methoxide (0.1 ml) at room temperature. The mixture was similarly treated as for **1** to afford an amorphous powder which acetylated with Ac_2O (5 ml) and pyridine (5 ml) for 24 hr at room temperature. The sirup, obtained by repeated co-distillation with toluene, was dissolved in CH_2Cl_2 and, after treatment with charcoal, the solvent was evaporated to afford an amorphous powder (159 mg, 94%), $[\alpha]_D^{25}$ $-45.7°$ ($c=1.05$, $CHCl_3$). NMR ($CDCl_3$) τ: 7.84, 7.86, 7.88, 7.96, 8.02 (15H, s, 5×Ac), 8.80 (3H, d, $J_{5',6'}=6.5$ Hz, C_5'–CH_3). TLC: *Rf* 0.47 (solvent A), 0.23 (B), 0.26 (C). *Anal.* Calcd. for $C_{22}H_{30}O_{14}$: C, 50.97; H, 5.83. Found: C, 51.07; H, 5.65.

2) From Compound **7**: Compound **7** (100 mg, 0.17 mmole) was dissolved in AcOEt (6 ml) containing triethylamine (100 mg, 0.99 mmole). The mixture was hydrogenated over freshly prepared Raney Ni catalyst at room temperature under atmospheric pressure for 4 hr. The mixture was similarly treated as for **6** to afford an amorphous powder (83 mg, 96%). The product was indistinguishable with sample prepared by method 1) (IR).

2,2′,3,3′,4′-Penta-O-acetyl-1,6-anhydro-6′-azido-6′-deoxy-*β*-lactose (9) and 2,3-Di-O-acetyl-1,6-anhydro-4-O-(2,3,4-tri-O-acetyl-*α*-L-*arabino*-hex-5-eno-pyranosyl)-*β*-D-glucopyranose (10)——A mixture of **7** (1.5 g, 2.5 mmole) and NaN_3 (810 mg, 12.5 mmole) in HMPA (15 ml) was heated under stirring in an oil bath at 100° for 5 hr. After cooling to room temperature, the mixture was diluted with H_2O (50 ml) and extracted with AcOEt (3×20 ml). The combined extracts were washed with H_2O, dried ($MgSO_4$), and evaporated to a sirup which crystallized from EtOH. Recrystallization from EtOH gave pure **9** (506 mg, 36%), mp 172—173°, $[\alpha]_D^{25}$ $-48.8°$ ($c=0.86$, $CHCl_3$). IR ν_{max}^{Nujol} cm^{-1}: 2120 (N_3). TLC: *Rf* 0.54 (solvent A), 0.29 (B), 0.35 (C). *Anal.* Calcd. for $C_{22}H_{29}O_{14}N_3$: C, 47.23; H, 5.22; N, 7.51. Found: C, 46.98; H, 5.06; N, 7.32.

The filtrate showed two spots, Rf 0.38 (main) and 0.14 (minor), on TLC (solvent C). After evaporation of the solvent, the residue was dissolved in CH_2Cl_2 and chromatographed on a column of silica gel with ether as eluant. Evaporation of the solvent from the faster moving eluate afforded an amorphous powder (441 mg, 34%). The product was indistinguishable (IR and TLC) with **10** mentioned below.

2,3-Di-O-acetyl-1,6-anhydro-4-O-(2,3,4-tri-O-acetyl-*α*-L-*arabino*-hex-5-eno-pyranosyl)-*β*-D-glucopyranose (10)——Dry silver fluoride (1 g, 7.9 mmole) was added to a solution of **7** (1 g, 1.7 mmole) in dry pyridine (10 ml) and the suspension was shaken, with exclusion of light, for 20 hr at room temperature. After dilution of the resulting black product with CH_2Cl_2 (50 ml), it was poured into H_2O (100 ml) under stirring, filtered, and the organic layer was separated. The layer was successively washed with 5% H_2SO_4, aq. $NaHCO_3$, and H_2O, dried ($CaCl_2$), and concentrated to afford a black residue which showed three spots, *Rf* 0.58 (minor), 0.38 (major), and 0.14 (minor) on TLC (solvent C). The residue was dissolved in CH_2Cl_2 and chromatographed on a column of silica gel with 20:1 (v/v) CH_2Cl_2–acetone as eluant. Evaporation of the solvent from the second effluent afforded an amorphous powder (421 mg, 49%), $[\alpha]_D^{23}$ $-63.5°$ ($c=1.04$, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1668 (C=C), TLC: *Rf* 0.62 (solvent A), 0.35 (B), 0.38 (C). *Anal.* Calcd. for $C_{22}H_{28}O_{14}$: C, 51.16; H, 5.46. Found: C, 50.86; H, 5.27.

1,2,2′,3,3′,4′,6-Hepta-O-acetyl-6′-azido-6′-deoxy-*α*-lactose (11)——Compound **9** (500 mg) was dissolved in acetolysis mixture (10 ml, 1:70:30, v/v, H_2SO_4–Ac_2O–AcOH). After stirring for 2 hr at room temperature, the solution was poured into ice-H_2O (300 ml). The resulting precipitate was filtered, air-dried, and recrystallized from EtOH to afford pure **11** (396 mg, 67%), mp 177—178°, $[\alpha]_D^{24}$ $+55°$ ($c=1$, $CHCl_3$). IR ν_{max}^{Nujol} cm^{-1}: 2120 (N_3). NMR ($CDCl_3$) τ: 3.77 (1H, d, $J_{1,2}=3.5$ Hz, H-1), 7.83, 7.88, 7.92, 8.00, 8.04 (21H, s, 7×Ac). TLC: *Rf* 0.62 (solvent A), 0.32 (B), 0.39 (C). *Anal.* Calcd. for $C_{26}H_{35}O_{17}N_3$: C, 47.20; H, 5.33; N, 6.35. Found: C, 47.21; H, 5.36; N, 6.23.

1,2,2′,3,3′,4′,6-Hepta-O-acetyl-6′-acetamido-6′-deoxy-*α*-lactose (12)——A solution of **11** (300 mg) in MeOH (10 ml) was hydrogenated over freshly prepared Raney Ni catalyst for 5 hr at room temperature under atmospheric pressure. Removal of the catalyst and evaporation to dryness gave a sirup which acetylated with Ac_2O (3 ml) and pyridine (3 ml) for 24 hr at room temperature. The solvent was removed by repeated co-distillation with toluene to afford a sirup which contaminated with some impurities as judged by TLC (solvent A). The CH_2Cl_2–solution was chromatographed on a column of silica gel with 10:1 (v/v) CH_2Cl_2–acetone as eluant. An amorphous powder (273 mg, 89%), $[\alpha]_D^{23}$ $+53.3°$ ($c=0.3$, $CHCl_3$), was obtained after evaporation of the solvent. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3430 (NH), 1675 (CONH). TLC: *Rf* 0.16 (solvent A). *Anal.* Calcd. for $C_{28}H_{39}O_{18}N$: C, 49.63; H, 5.80; N, 2.07. Found: C, 48.93; H, 5.70; N, 2.17.

6′-Acetamido-6′-deoxy-α-lactose (13)——To a solution of **12** (150 mg) in dry MeOH (5 ml) was added methanolic 0.05N sodium methoxide (0.5 ml) at room temperature. The mixture was similarly treated as for **1** to afford a sirup which was dissolved in a small amount of MeOH. Crystallization was induced after addition of ether and kept for 24 hr in a refrigerator. The crystals were collected by rapid filtration and dried in a vacuum desiccator. The crystals (57 mg, 67%) were very hydgroscopic and had $[\alpha]_D^{24}$ +80° (5 min) → +66.7° (24 hr) (c=0.3, H_2O). IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 3600—3040 (OH, NH), 1636 (CONH). TLC: *Rf* 0.34 (solvent D). *Anal.* Calcd. for $C_{14}H_{25}O_{11}N$: C, 43.86; H, 6.57. Found: C, 43.61; H, 6.92.

PPC of Acid Hydrolyzate of Compound 13——Authentic 6-amino-6-deoxy-D-galactose hydrochloride, *Rf* 0.21, was prepared according to the method of Saeki, *et al.*[7]

A mixture of **13** (50 mg), *Rf* 0.27, and 1N HCl (2 ml) in a sealed tube was heated at 110° for 3 hr. After treatment with charcoal, the mixture was evaporated to dryness and a trace of HCl was completely removed by repeated co-distillation with EtOH, followed by storage overnight in a desiccator over NaOH. The residue was dissolved in a small amount of H_2O, in which glucose (*Rf* 0.40) and 6-amino-6-deoxy-D-galactose hydrochloride (*Rf* 0.21) were identified by PPC.

Catalytic Reduction of Compound 10——1) Reduction over Platinum Oxide Catalyst: To a solution of **10** (200 mg) in MeOH (10 ml) was added platinum oxide catalyst (100 mg). On vigorous stirring at room temperature under atmospheric pressure, the mixture absorbed theoretical amount of hydrogen in 2 min and the reaction was stopped by passing nitrogen. After removal of the catalyst, the solution was concentrated to a sirup which showed three spots, *Rf* 0.47 (major), 0.37 (minor), and 0.23 (major), on TLC (solvent B). The sirup was dissolved in CH_2Cl_2 and chromatographed on a column of silica gel with 1:3 (v/v) ether-benzene as eluant. Evaporation of the solvent from the last effluent afforded an amorphous powder (44 mg, 22%) which was indistinguishable with **8** (IR, NMR, and TLC).

From the first effluent, an unidentified sirup (74 mg), *Rf* 0.47, was separated.

2) Reduction over Palladium Catalyst: Instead of platinum oxide, Pd catalyst[20] was adopted and hydrogenation of **10** (200 mg) was similarly performed as for 1). After column chromatography **8** (180 mg, 90%) was isolated as the sole product.

3) Reduction over Raney Nickel Catalyst: In this case the hydrogenation mixture showed three spots, *Rf* 0.43 (major), 0.37 (minor), and 0.23 (major) by TLC (solvent B). Starting from **10** (200 mg), after column chromatography, **8** (110 mg, 55%), *Rf* 0.23, and an unidentified sirup (46 mg), *Rf* 0.43, were isolated.

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[20] O.T. Schmidt and W. Starab, *Chem. Ber.*, **87**, 393 (1954).