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Chemical Modification of Lactose. VII.[1] Synthesis of 4-O-β-D-Idopyranosyl-D-glucopyranose

The title new reducing disaccharide (**10**) was synthesized starting from 1,6-anhydro-4′,6′-O-benzylidene-β-lactose (**1**) *via* selective benzoylation, epoxide formation, alkaline cleavage of the epoxide, and removal of the blocking groups. This is the first reported example of isomerization of the secondary hydroxyl groups in the D-galactopyranosyl moiety of lactose.

Reducing disaccharides having structures in which the secondary hydroxyl groups in the D-glucose moiety of lactose are isomerized have been synthesized for a long time. For example, when lactal is oxidized with perbenzoic acid, 4-O-β-D-galactopyranosyl-D-mannopyranose is produced in good yield.[2] The product, later designated epi-lactose, was synthesized by condensation of 1,6-anhydro-2,3-O-isopropylidene-β-D-mannopyranose with acetobromo-D-galactopyranose, followed by removal of the blocking groups.[3] Neolactose, 4-O-β-D-galactopyranosyl-D-altropyranose, was also synthesized by Hudson, *et al.*[4] However, isomerization of those in the D-galactose moiety has not yet been reported in the literature.

In this communication, we wish to report a facile synthesis of the title new reducing disaccharide by a simultaneous isomerization of both 2′- and 3′-OH of lactose.

Selective benzoylation of 1,6-anhydro-4′,6′-O-benzylidene-β-lactose (**1**),[1] using 4 molar equivalents of benzoyl chloride in pyridine at −20°, afforded 1,6-anhydro-2,3,3′-tri-O-benzoyl-4′,6′-O-benzylidene-β-lactose (**2**)[1] (yield 41%). Sulfonylation of **2** yielded the corresponding 2′-sulfonates (**3** and **4**). 2′-Methanesulfonate (**3**) (yield 90%), mp 245—246°, $[\alpha]_D^{26}$ +92° (c=0.9, $CHCl_3$). NMR ($CDCl_3$) δ: 2.96 (3H, s, OMs), 7.00—8.40 (20H, m, aromatic protons). *Anal.* Calcd. for $C_{41}H_{38}O_{15}S$: C, 61.34; H, 4.77. Found: C, 61.25; H, 4.67. 2′-*p*-Toluenesulfonate (**4**) (yield 88%), mp 126—128°, $[\alpha]_D^{24}$ +133° (c=1.1, $CHCl_3$). NMR ($CDCl_3$) δ: 2.13 (3H, s, $C_6H_4C\underline{H}_3$), 6.70—8.40 (24H, m, aromatic protons). *Anal.* Calcd. for $C_{47}H_{42}O_{15}S$: C, 64.23; H, 4.82. Found: C, 64.02; H, 4.70.

Treatment of **3** or **4** with 1.1 molar equivalents of sodium methoxide in boiling MeOH for 3 hr afforded 1,6-anhydro-4-O-(2,3-anhydro-4,6-O-benzylidene-β-D-talopyranosyl)-β-D-glucopyranose (**5**) (yield 50 or 66%, respectively), mp 235—237°, $[\alpha]_D^{25}$ −101° (c=1.1, pyridine). *Anal.* Calcd. for $C_{19}H_{22}O_9$: C, 57.87; H, 5.62. Found: C, 57.69; H, 5.60.

Acetylation of **5** with Ac_2O and pyridine gave the corresponding 2,3-diacetate (**6**) (yield 91%), mp 189—190°, $[\alpha]_D^{24}$ −76.5° (c=1, $CHCl_3$). NMR ($CDCl_3$) δ: 2.10, 2.14 (6H, s, 2AcO), 7.20—7.60 (5H, m, aromatic protons). *Anal.* Calcd. for $C_{23}H_{26}O_{11}$: C, 57.74; H, 5.48. Found: C, 57.54; H, 5.32.

A mixture of **5** with excess aqueous KOH was heated for 3 hr at 100°. After neutralization with glacial AcOH and evaporation of the solvent, the residue was acetylated to afford 2,3-di-O-acetyl-1,6-anhydro-4-O-(2,3-di-O-acetyl-4,6-O-benzylidene-β-D-idopyranosyl)-β-D-glucopyranose (**7**) (yield 84%), mp 217—218°, $[\alpha]_D^{25}$ −57° (c=1.1, $CHCl_3$). NMR ($CDCl_3$) δ: 2.11, 2.13 (12H, s, 4AcO), 7.20—7.70 (5H, m, aromatic protons). *Anal.* Calcd. for $C_{27}H_{32}O_{14}$: C, 55.86; H, 5.56. Found: C, 55.99; H, 5.37.

Compound **7** clearly differed from 2,2′,3,3′-tetra-O-acetyl-1,6-anhydro-4′,6′-O-benzylidene-β-lactose[5] with respect to mp, $[\alpha]_D$, infrared (IR) and nuclear magnetic resonance (NMR)

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3) W.T. Haskins, R.M. Hann, and C.S. Hudson, *J. Am. Chem. Soc.*, **64**, 1490, 1852 (1942).
4) A. Kunz and C.S. Hudson, *J. Am. Chem. Soc.*, **48**, 1978, 2435 (1926); N.K. Richtmyer and C.S. Hudson, *ibid.*, **57**, 1716 (1935).
5) T. Chiba, M. Haga, and S. Tejima, *Chem. Pharm. Bull.* (Tokyo), **23**, 1283 (1975).

spectra. Therefore, the epoxide ring of **5** cleaved *trans*-diaxially according to the Fürst-Plattner rule.

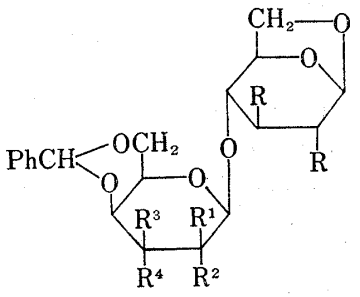
Catalytic hydrogenation of **7** over Pd catalyst, followed by acetylation, afforded crystalline 2,3-di-O-acetyl-1,6-anhydro-4-O-(2,3,4,6-tetra-O-acetyl-β-D-idopyranosyl)-β-D-glucopyranose (**8**) (yield 85%), mp 146—147°, $[\alpha]_D^{25}$ −72° (*c*=1.2, $CHCl_3$). NMR ($CDCl_3$) δ: 2.04, 2.11, 2.13, 2.14 (18H, s, 6AcO). *Anal.* Calcd. for $C_{24}H_{32}O_{16}$: C, 50.00; H, 5.59. Found: C, 50.08; H, 5.67.

Reflux of **8** with titanium tetrachloride in $CHCl_3$, followed by treatment of the product with mercuric acetate in order to replace the chlorine atom introduced by an acetoxyl group, afforded 1,2,3-tri-O-acetyl-4-O-(2,3,4,6-tetra-O-acetyl-β-D-idopyranosyl)-β-D-glucopyranose (**9**) (yield 50%), mp 173—175°, $[\alpha]_D^{22}$ −33° (*c*=1.1, $CHCl_3$). IR ν_{max}^{Nujol} cm^{-1}: 3485 (OH). NMR ($CDCl_3$) δ: 2.03, 2.08, 2.10, 2.12 (21H, s, 7AcO). *Anal.* Calcd. for $C_{26}H_{36}O_{18}$: C, 49.06; H, 5.70. Found: C, 48.89; H, 5.65.

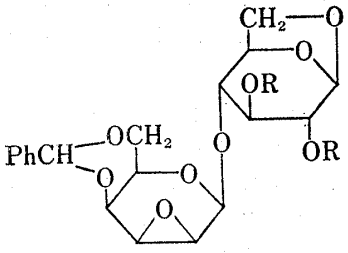
Deacetylation of **9** with sodium methoxide in MeOH yielded the title compound (**10**) (yield 95%) as a hygroscopic, hardly sweet, amorphous powder, $[\alpha]_D^{24}$ +31° (*c*=1.1, H_2O). Paper partition chromatography (PPC) by the ascending method: *Rf* 0.43 with 6:4:3 (v/v) *n*-BuOH–pyridine–H_2O, *Rf* 0.24 with 25:6:25 *n*-BuOH–AcOH–H_2O, and *Rf* 0.13 with 4:1:1 *n*-BuOH–EtOH–H_2O. *Anal.* Calcd. for $C_{12}H_{22}O_{11}\cdot 1/2H_2O$: C, 41.03; H, 6.60. Found: C, 41.07; H, 6.95.

Reflux of a mixture of **10** and one molar equivalent of *p*-toluenesulfonylhydrazide in EtOH for 45 min afforded a hygroscopic crystalline *p*-toluenesulfonylhydrazone (yield 66%), mp 138—139° (decomp.), $[\alpha]_D^{19}$ −31° (*c*=1, pyridine).

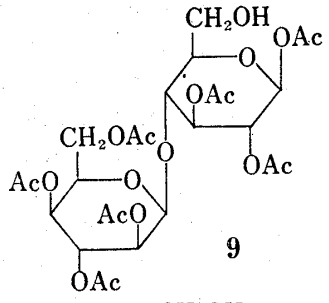
Acidic hydrolysis of **10** gave glucose and idose[6] which were identified with authentic samples by PPC (the ascending method): *Rf* 0.42 (glucose) and 0.55 (idose) with 6:4:3 (v/v) *n*-BuOH–pyridine–H_2O, *Rf* 0.26 (glucose) and 0.34 (idose) with 25:6:25 *n*-BuOH–AcOH–H_2O, *Rf* 0.20 (glucose) and 0.30 (idose) with 4:1:1 *n*-BuOH–EtOH–H_2O.



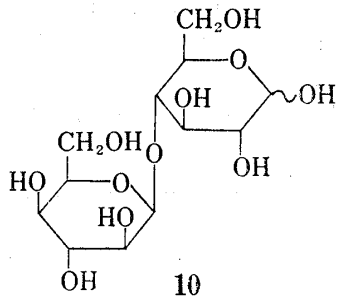
1: R=R²=R³=OH, R¹=R⁴=H
2: R=R³=OBz, R¹=R⁴=H, R²=OH
3: R=R³=OBz, R¹=R⁴=H, R²=OMs
4: R=R³=OBz, R¹=R⁴=H, R²=OTs
7: R=R¹=R⁴=OAc, R²=R³=H



5: R=H
6: R=Ac



9



10

Ac=acetyl, Bz=benzoyl, Ms=mesyl, Ph=phenyl, Ts=tosyl

Chart 1

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