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Note

Synthesis of 2-azido-2-deoxy-3,4:5,6-di-*O*-isopropylidene-*aldehydo*-D-mannose dimethyl acetal and 4-azido-4-deoxy-2,3:5,6-di-*O*-isopropylidene-*aldehydo*-D-galactose dimethyl acetal*

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In the course of recent investigations[1–4] in this series, we developed a one-flask synthesis of triacetalated, acyclic aldohexoses by use of 2,2-dialkoxypropanes or 1,1-dialkoxycyclohexanes in the presence of *p*-toluenesulfonic acid. As shown in a preceding paper[1], one of the triacetals obtained from D-glucose, *viz.*, 3,4:5,6-di-*O*-isopropylidene-*aldehydo*-D-glucose dibenzyl acetal, was readily convertible, *via* the trifluoromethanesulfonate[5] intermediate, into 2-azido-2-deoxy-3,4:5,6-di-*O*-isopropylidene-*aldehydo*-D-mannose, and then this gave 2-amino-2-deoxy-D-mannose derivatives.

When treated at 65° with 2,2-dimethoxypropane in 1,4-dioxane solution in the presence of *p*-toluenesulfonic acid, D-glucose gave[6] a mixture of 3,4:5,6- and 2,3:5,6-di-*O*-isopropylidene-*aldehydo*-D-glucose dimethyl acetal (**1** and **2**) in good yield. The chromatographically inseparable mixture of **1** and **2** was treated, without further purification, with trifluoromethanesulfonic anhydride. In the ^{1}H-n.m.r. spectrum of the product (**3** + **4**) in chloroform-*d*, at lowest field, the protons on the carbon atom (C-2 or C-4) bearing the sulfonyloxy group appeared as a doublet of doublets, at δ 4.92 and 5.16, and their intensity ratio was ~0.44 (for **3**) to 0.56 (for **4**). Ester **4** showed, in t.l.c., a slightly lower mobility than **3**, but chromatographic separation was extremely difficult because of the lability of the two compounds.

When the mixture (**3** + **4**) was treated with sodium azide in *N,N*-dimethylformamide[7,8] for 1 h at room temperature, only **4** underwent preferential SN2 displacement, to afford the corresponding 4-azido derivative[8] **6**. Compound **6** and the unchanged 3,4:5,6-di-*O*-isopropylidene-2-*O*-(trifluoromethylsulfonyl)-*aldehydo*-D-glucose dimethyl acetal (**3**) were then purified by chromatography on a column of silica gel. Complete replacement of the sulfonyloxy group in **3** with azide anion as just described, in contrast to **4**, required 24 h, even at 50°. Such a large

*The Behavior of Some Aldoses with Acetal-Exchange Reagents, Part XIV. For Part XIII, see ref. 1.

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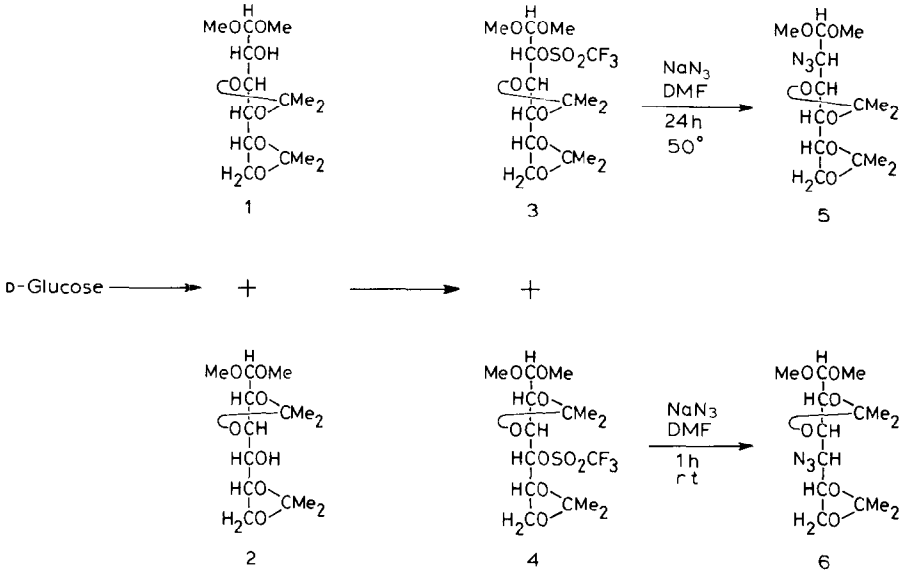
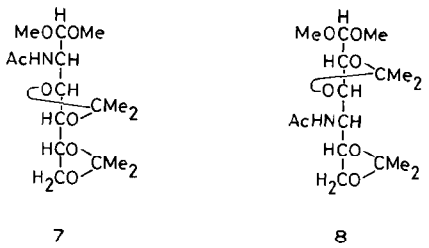


difference in reactivity was also observed[1] for the corresponding sulfonates of 2,3:5,6- and 3,4:5,6-di-*O*-isopropylidene-*aldehydo*-D-glucose dibenzyl acetal.

Reduction of the azide group in **5** and **6** was accomplished in methanol in the presence of 10% palladium–carbon catalyst, and the amino group formed was acetylated, to yield **7** and **8**, respectively.



EXPERIMENTAL

General methods. — See ref. 3.

Acetalation of D-*glucose with 2,2-dimethoxypropane.* — A stirred mixture of D-glucose (1 g) and *p*-toluenesulfonic acid monohydrate (150 mg) in dry 1,4-dioxane (10 mL) was heated to 65°, and then 2,2-dimethoxypropane (4 mL) was added; stirring was continued for 2 h at 65°. The mixture was cooled, and the acid was neutralized by addition of sodium hydrogencarbonate. The suspension was filtered, and the filtrate was evaporated to a residue that was chromatographed on a column of silica gel with (*a*) chloroform and (*b*) 500:1 chloroform–methanol.

Eluant *b* yielded a mixture (1.4 g; 83%) of 3,4:5,6- (**1**) and 2,3:5,6- (**2**) di-*O*-isopropylidene-*aldehydo*-D-glucose dimethyl acetal as a syrup that showed a single spot in t.l.c. The respective structures of **1** and **2** were confirmed by comparing the spectral features with those of the same compounds prepared alternatively by the procedure of Stevens[6]. As a minor product, methyl 2,3:4,6-di-*O*-isopropylidene-α-D-glucopyranoside (16%) was obtained from eluant *a*.

3,4:5,6-Di-O-isopropylidene-2-O-(trifluoromethylsulfonyl)-aldehydo-D-*glucose dimethyl acetal* (**3**) *and 2,3:5,6-di-O-isopropylidene-4-O-(trifluoromethylsulfonyl)*-aldehydo-D-*glucose dimethyl acetal* (**4**). — A solution of the mixture of **1** and **2** (1 g) in dry pyridine (5 mL) and dichloromethane (1 mL) was stirred at −15°, while trifluoromethanesulfonic anhydride (1.1 mL) in dichloromethane (5 mL) was added portionwise; the mixture was then stirred for 1.5 h at 0°. Ice was added, the mixture extracted with chloroform, and the extract washed successively with ice-cold M hydrochloric acid, water, M sodium carbonate, and water, dried, and evaporated, to give a mixture of **3** and **4** as a syrup (1.3 g; 91%); ν_{max}^{film} 1400 cm^{-1} (SO_3); n.m.r. data: δ 1.3–1.5 (m, 12 H, 2 Me_2C), 3.42, 3.45, 3.47, and 3.49 (4 s, 6 H, 2 OMe), 4.38 (d, $J_{1,2}$ 5 Hz, H-1 of **4**), 4.16 (d, 0.44 H, $J_{1,2}$ 7.5 Hz, H-1 of **3**), 4.92 (dd, 0.44 H, $J_{1,2}$ 7.5, $J_{2,3}$ 1.2 Hz, H-2 of **3**), and 5.16 (dd, 0.56 H, *J* 4 and 2.5 Hz, H-4 of **4**).

The mixture (1 g) of **3** and **4** was treated, without further purification, with sodium azide (990 mg) in *N,N*-dimethylformamide (3 mL) for 1 h at room temperature. The mixture was extracted with chloroform, and the extract was successively washed with water, 2M hydrochloric acid, and water, dried, and evaporated. The syrupy residue was chromatographed on a column of silica gel with (*a*) chloroform and (*b*) 1000:1 chloroform–methanol. Eluant *b* yielded **3** (300 mg) as needles, and **6** (400 mg) as a syrup. Compound **3** had m.p. 48–50°, $[\alpha]_D$ +6.9° (*c* 0.9, chloroform); ν_{max}^{Nujol} 1400 (SO_3), and 880 and 825 cm^{-1} (Me_2C); n.m.r. data: δ 1.31 (s, 3 H, 0.5 Me_2C), 1.37 (s, 9 H, 1.5 Me_2C), 3.47 and 3.49 (2 s, 6 H, 2 MeO), 4.61 (d, 1 H, $J_{1,2}$ 7.5 Hz, H-1), and 4.92 (dd, 1 H, $J_{1,2}$ 7.5, $J_{2,3}$ 1.2 Hz, H-2).

Anal. Calc. for $C_{15}H_{25}F_3O_9S$: C, 41.09; H, 5.75. Found: C, 40.87; H, 5.68.

2-Azido-2-deoxy-3,4:5,6-di-O-isopropylidene-aldehydo-D-*mannose dimethyl acetal* (**5**). — To a solution of **3** (823 mg) in *N,N*-dimethylformamide (2.8 mL) was added sodium azide (810 mg). The mixture was stirred for 24 h at 50°, cooled, and extracted with chloroform. The extract was washed successively with water, ice-cold 2M hydrochloric acid, and water, dried, and evaporated, to give a syrup that was chromatographed on a column of silica gel with (*a*) chloroform and (*b*) 1000:1 chloroform–methanol. Eluant *b* gave compound **5** (364 mg; 55%) as a syrup; $[\alpha]_D$ +8.44° (*c* 0.545, chloroform); ν_{max}^{film} 2120 (N_3), and 880 and 855 cm^{-1} (Me_2C); n.m.r. data: δ 1.35 and 1.42 (2 s, 12 H, 2 Me_2C), 3.40 and 3.47 (2 s, 6 H, 2 MeO), 3.73 (dd, 1 H, $J_{1,2}$ 6.8, $J_{2,3}$ 2.6 Hz, H-2), and 4.50 (d, 1 H, $J_{1,2}$ 6.8 Hz, H-1).

Anal. Calc. for $C_{14}H_{25}N_3O_6$: C, 50.74; H, 7.61; N, 12.68. Found: C, 50.95; H, 7.53; N, 12.76.

4-Azido-4-deoxy-2,3:5,6-di-O-isopropylidene-aldehydo-D-*galactose dimethyl*

acetal (**6**). — As described for **3** and **4**, when the mixture of **3** and **4** (1 g) was treated with sodium azide in *N,N*-dimethylformamide for 1 h at room temperature, only **4** underwent nucleophilic displacement by azide anion, to give compound **6** (400 mg). A small amount of impurity was removed by rechromatography on a column of silica gel with 1000:1 chloroform–methanol. Compound **6** was a syrup, $[\alpha]_D$ −18.4° (*c* 0.523, chloroform); ν_{max}^{film} 2120 (N_3), and 860 and 850 cm^{-1} (Me_2C); n.m.r. data: δ 1.36, 1.41, and 1.47 (3 s, 12 H, 2 Me_2C), 3.44 and 3.46 (2 s, 6 H, 2 MeO), 3.27–3.5 (m, 1 H, H-5), 3.32 (dd, 1 H, *J* 8 and 6.5 Hz, H-4), and 4.35 (d, 1 H, $J_{1,2}$ 5 Hz, H-1).

Anal. Calc. for $C_{14}H_{25}N_3O_6$: C, 50.74; H, 7.61; N, 12.68. Found: C, 51.04; H, 7.46; N, 12.36.

*2-Acetamido-2-deoxy-3,4:5,6-di-*O*-isopropylidene*-aldehydo-D-*mannose dimethyl acetal* (**7**). — To a solution of **5** (300 mg) in methanol was added 10% palladium–carbon catalyst (100 mg), and hydrogen was bubbled through for 2 h while the solution was stirred at room temperature. The catalyst was filtered off, and the filtrate was evaporated to a syrup of the amine that was acetylated with acetic anhydride (1 mL) and pyridine (2 mL). Compound **7** (quantitative), purified by chromatography on silica gel, was a syrup; $[\alpha]_D$ +37.4° (*c* 0.44, chloroform); ν_{max}^{film} 3300 (NH), 1680 and 1540 (amide), and 880 and 850 cm^{-1} (Me_2C); n.m.r. data: δ 1.32, 1.37, and 1.44 (3 s, 12 H, 2 Me_2C), 1.99 (s, 3 H, AcN), 3.39 and 3.47 (2 s, 6 H, 2 MeO), 4.31 (m, 1 H, H-2), 4.50 (d, 1 H, $J_{1,2}$ 2 Hz, H-1), and 5.78 (d, 1 H, NH).

Anal. Calc. for $C_{16}H_{29}NO_7$: C, 55.31; H, 8.41; N, 4.03. Found: C, 55.18; H, 8.31; N, 3.91.

*4-Acetamido-4-deoxy-2,3:5,6-di-*O*-isopropylidene*-aldehydo-D-*galactose dimethyl acetal* (**8**). — Reduction of the azide group of **6** (320 mg) was performed as just described, and then the amino group formed was acetylated. Compound **8** (quantitative) was crystalline, m.p. 109–110°, $[\alpha]_D$ +1.8° (*c* 0.504, chloroform); ν_{max}^{Nujol} 3240 (NH) 1640 and 1540 (amide), and 870 and 850 cm^{-1} (Me_2C); δ 1.35 and 1.42 (2 s, 12 H, 2 Me_2C), 1.99 (s, 3 H, AcN), 3.40 and 3.46 (2 s, 6 H, 2 MeO), 4.29 (d, 1 H, $J_{1,2}$ 4.8 Hz, H-1), and 5.75 (broad d, 1 H, NH). This compound was also synthesized by Paulsen *et al.*[9] *via* the tosylate of **2**; m.p. 110.5°, $[\alpha]_D$ −0.5°.

Anal. Calc for $C_{16}H_{29}NO_7$: C, 55.31; H, 8.41; N, 4.03. Found: C, 55.53; H, 8.46; N, 4.29.

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