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Note

Improved synthesis of 2,3:4,6-di-*O*-isopropylidene-D-glucopyranose and -D-galactopyranose

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Abstract

2,3:4,6-Di-*O*-isopropylidene-D-glucopyranose and -D-galactopyranose acetals are conveniently prepared by hydrogenolysis of benzyl 2,3:4,6-di-*O*-isopropylidene-β-D-glucopyranose and -β-D-galactopyranose in almost quantitative yields in 3 h. This result is in contrast with the sluggish reaction observed (48 h) when the hydrogenolysis was carried out on either anomeric α,β mixtures or on the corresponding α anomers.

Keywords: 2,3:4,6-Di-*O*-isopropylidene-D-glucopyranose; 2,3:4,6-Di-*O*-isopropylidene-D-galactopyranose; Benzyl glycosides; Hydrogenolysis; Carbohydrate acetals

As part of a synthetic program aimed at the preparation of carbasugars [1–3], we needed gram amounts of 2,3:4,6-di-*O*-isopropylidene acetals of D-mannose (**1**) [2], D-glucose (**2**) [3], and D-galactose (**3**) [3]. Kinetically controlled acetonation of D-mannose, according to Gelas and Horton [4], is the method of choice for the preparation of **1**. On the other hand, the products of kinetic acetonation of D-glucose and D-galactose are 4,6-*O*-isopropylidene-D-glucopyranose (**5**) and 4,6-*O*-isopropylidene-D-galactopyranose (**10**), respectively, owing to the strain associated with the formation of the trans-fused 1,3-dioxolanes at positions C-2 and C-3 of their pyranose ring [5,6]. A survey of the literature showed just one procedure for the preparation of **2** and **3** [7–9]. The method involves acetonation under kinetic control [10] of an anomeric mixture of the corresponding benzyl gluco- **6** [11] or galactopyranoside **11** [12] to furnish the corresponding 2,3:4,6-di-*O*-isopropylidene derivatives **7** [7] and **12** [7], respectively, followed by hydrogenolysis of the anomeric benzyl groups. Although in our hands, hydrogenation of **7** afforded **2** in good yield, we were concerned about the long reaction times (48 h), and/or the presence of variable amounts of unreacted starting material in the resulting reaction mixtures. Hydrogenation of **7** (starting anomeric mixture: α-**7**:β-**7** = 1.6:1, ^{1}H NMR, 300 MHz) under the conditions reported by Toma and co-workers [7] afforded, in our hands, hemiacetal **2** (12%) along with unreacted starting material **7** (86%, α-**7**:β-**7** = 2.5:1, ^{1}H NMR, 300 MHz). On the other hand, forcing conditions for the hydro-

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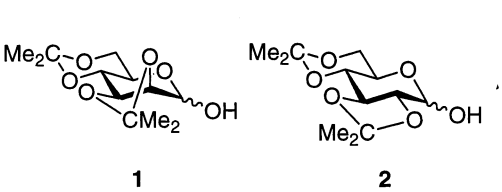
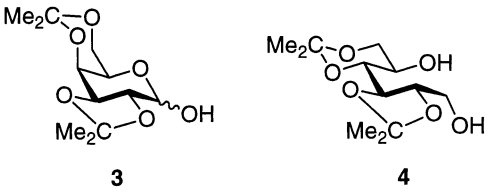
genation of **7** (35 psi, room temperature, 7:1 EtOH:Et_3N, 10% Pd/C, 20% w/w, 36 h) trying to drive the reaction to completion, resulted in the formation of the D-glucitol diacetonide **4** (78%) [7] along with **2** (13%). Along this line, Krohn and co-workers [9] reported that **2** was better prepared when the hydrogenation of benzyl D-glucopyranosides **7** was stopped at an 80% conversion level (72% yield of **2** after chromatography). Analogously, in our hands, hydrogenation of benzyl galactosides **12** also required prolonged reaction times and usually did not go to completion. We have searched for improved reaction conditions for the preparation of **2** and **3**, and we now report on these results.

A careful study of the reaction mixture resulting from the hydrogenation of **7** (starting anomeric mixture: α-**7**:β-**7** = 1.6:1, ^1H NMR, 300 MHz) (5 psi, room temperature, 7:1 EtOH:Et_3N, 10% Pd/C, 10% w/w, 48 h) showed the presence of the desired hemiacetal **2** (85%) along with residual benzyl 2,3:4,6-di-*O*-isopropylidene-α-D-glucopyranoside (α-**7**) (12%). The persistence of α-**7** in the anomeric hydrogenation mixture seemed to indicate a different hydrogenation rate for each anomer. In order to test this hypothesis, pure samples of α-**7** and β-**7** were prepared by kinetic acetonation (2-methoxypropene, Sikkon, 0 °C, *p*TsOH, DMF, 5 h) of α-**6** [13] and β-**6** [13]. It turned out that while β-**7** was hydrogenolyzed in 3 h (25 psi, room temperature, 7:1 EtOH:Et_3N, 10% Pd/C, 10% w/w) to give **2** in 91% yield, its corresponding anomer, α-**7**, had not reacted completely even after 24 h. Complete hydrogenation of α-**7** required the addition of more catalyst (40 mg/mmol) and 48 h of reaction. Similar results were obtained with pure samples of benzyl galactosides β-**12** [14] and α-**12**. Then, while hydrogenation of β-**12** (25 psi, room temperature, 7:1 EtOH:Et_3N, 10% Pd/C, 10% w/w) was completed in 3 h to yield **3** (89%), α-**12** required 48 h to be hydrogenolyzed (Scheme 1).

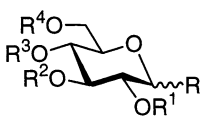
Based on the above-mentioned results, compounds **2** and **3** can be conveniently prepared by hydrogenation of benzyl 2,3:4,6-di-*O*-isopropylidene-β-D-glycopyranosides β-**7** and β-**12**, respectively, preparation of which is shown in Scheme 2. Benzyl β-D-glucopyranoside tetraacetate (**9**) [15], which was obtained from commercially available D-glucose pentaacetate (**8**) by treatment with benzyl alcohol ($SnCl_4$, CH_2Cl_2, 84%), was easily correlated with compound β-**7** by deacetylation (NaOMe, MeOH, then Amberlyst 89%) followed by kinetic acetonation (75%). In a similar manner, benzyl β-D-galactopyranoside tetraacetate (**14**) [16], which was prepared

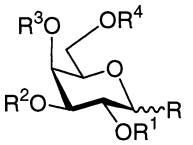


1 **2**



3 **4**

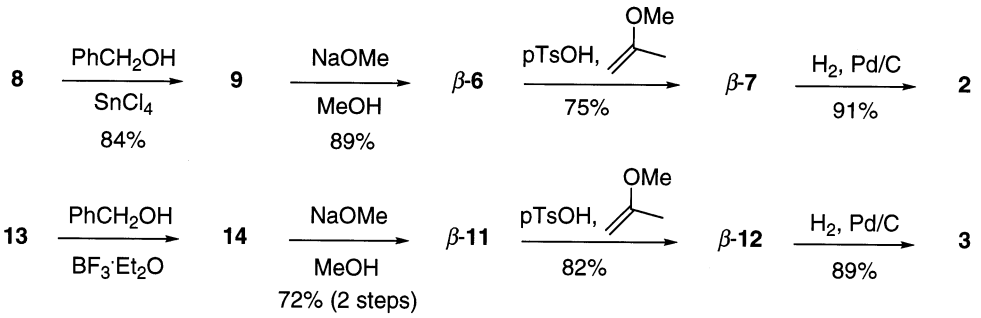




	R	R^1	R^2	R^3	R^4
5	OH	H	H	—CMe_2—	
6	OBn	H	H	H	H
7	OBn	—CMe_2—		—CMe_2—	
8	OAc	Ac	Ac	Ac	Ac
9	β-OBn	Ac	Ac	Ac	Ac

	R	R^1	R^2	R^3	R^4
10	OH	H	H	—CMe_2—	
11	OBn	H	H	H	H
12	OBn	—CMe_2—		—CMe_2—	
13	β-OAc	Ac	Ac	Ac	Ac
14	β-OBn	Ac	Ac	Ac	Ac

Scheme 1.



Scheme 2.

from commercially available β-D-galactose pentaacetate (**13**) ($PhCH_2OH$, $BF_3{\cdot}Et_2O$, CH_2Cl_2) [17], was deacetylated (NaOMe, MeOH, then Amberlyst, 72% yield, two steps) to give β-**11**, which when submitted to kinetic acetonation afforded β-**12** (82%).

Although, to the best of our knowledge, no systematic study has been carried out on the rate of hydrogenolysis of anomeric benzyl glycosides, the experimental results obtained in this work seem to be in agreement with some previous reports found in the literature: (i) Bieg and Szeja reported that benzyl 2,3,4-tri-*O*-benzyl-α-L-arabinopyranoside (BnO-1 equatorial) was converted into 2,3,4-tri-*O*-benzyl-L-arabinopyranose within 30 min (ammonium formate, 10% Pd–Al_2O_3, MeOH), whereas the reaction of the corresponding β-glycoside (BnO-1 axial) was much slower (only 8% conversion after 30 min) [18]; (ii) Suárez and co-workers also reported on the impossibility of hydrogenolyzing (Pd/C or $Pd(OH)_2$/C) the axial anomeric benzyl acetal in benzyl 6-*O*-(*tert*-butyldiphenylsilyl)-3,4-dideoxy-2-*O*-methyl-α-D-*erythro*-hexopyranoside [19]. In our opinion, and although some more data will be needed to assess the generality of this observation, a tentative explanation for the large difference in the rate of hydrogenolysis between axial and equatorial anomers may lie in adverse steric effects in the case of the axial anomers, which would hinder the optimal coordination of the aromatic ring on the palladium surface [20].

1. Experimental

General methods.—Melting points were determined in capillary tubes and are uncorrected. Optical rotations were determined at the sodium D line. ^1H NMR spectra were recorded at 200, 300 or 500 MHz; chemical shifts (δ) are relative to residual non-deuterated solvent as internal reference. Thin-layer chromatography (TLC) was conducted in precoated Kieselgel 60 F_{254}. Detection was first by UV (254 nm) then charring with a solution of ammonium molybdate(VI) tetrahydrate (12.5 g), and cerium(IV)sulfate tetrahydrate (5.0 g) in 10% aq H_2SO_4 (500 mL). Column chromatography was carried out on Kieselgel (230–400 mesh) and, unless otherwise stated, mixtures of hexane–EtOAc were used as eluant. All reactions were conducted under an argon atmosphere. Anhydrous $MgSO_4$ or Na_2SO_4 was used to dry the organic solutions during work-ups and the removal of the solvents was done under vacuum with a rotavapor. Unless otherwise noted, materials were obtained from commercially available sources and used without further purification. Solvents were dried and purified using standard methods. Benzyl glycosides **6**, **11** [13], diacetonides **7**, **12** [7], and benzyl β-D-galactopyranoside tetraacetate (**14**) [17], were prepared according to published procedures.

General procedure for the hydrogenation of benzyl glycopyranosides.—The benzyl glycosides (**7** or **12**, respectively, 1 mmol) were dissolved in EtOH (14 mL) in the presence of Et_3N (2 mL) and hydrogenated in a Parr hydrogenator with 10% Pd/C (10% w/w) at 25 psi. After the reaction reached completion (48, 3, 48 and 3 h for compounds α-**7**, β-**7**, α-**12**, and β-**12**, respectively), the catalyst was filtered off and the filtrate evaporated under reduced pressure to afford crude **2** and **3**.

Compound **7** (338 mg, α-**7**:β-**7** = 1.6:1) was submitted to hydrogenation (6 h) under the conditions reported by Toma [7], after which time the reaction mixture was divided into two halves. The first half was filtered and separated by chromatography to yield compound **2** (15 mg, 12%) along with recovered **7** (146 mg, α-**7**:β-**7** = 2.5:1, 86%). The second half was treated with a second amount of catalyst as before and resubmitted to hydrogenation (42 h) to afford, after flash chromatography, hemiacetal **2** (106.3 mg, 85%) and α-**7** (20 mg, 12%).

Benzyl 2,3:4,6-di-O-*isopropylidene*-α-D-*glucopyranoside* (α-**7**).—(238 mg, 68%), $[\alpha]_D$ + 90.8° (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.26–7.37 (m, 5 H, Ph), 5.25 (d, 1 H, $J_{1,2}$ 2.6 Hz, H-1), 4.78 and 4.65 (2d, 2 H, *J* 12.4 Hz, OCH_2Ph), 4.11 (t, 1 H, *J* 9.2 Hz, H-3), 3.90 (t, 1 H, *J* 9.5 Hz, H-4), 3.81 (m, 2 H, 2H-6), 3.36 (m, 2 H, H-2, H-5), 1.54 (s, 3 H, Me), 1.49 (s, 3 H, Me), 1.46 (s, 3 H, Me), 1.43 (s, 3 H, Me); ^{13}C NMR ($CDCl_3$): δ 137.1, 128.3, 127.7, 127.5, 111.4, 99.6, 97.3, 76.8, 73.9, 73.7, 69.9, 65.1, 62.2, 28.9, 26.8, 26.3, 19.1. Anal. Calcd for $C_{19}H_{26}O_6$: C, 65.13; H, 7.48. Found: C, 64.89; H, 7.35.

Benzyl 2,3:4,6-di-O-*isopropylidene*-β-D-*glucopyranoside* (β-**7**).—(262 mg, 75%), mp 124–125 °C, $[\alpha]_D$ − 62.5° (*c* 1.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.25–7.38 (m, 5 H, Ph), 4.90 and 4.69 (2d, 2 H, *J* 11.8 Hz, OCH_2Ph), 4.77 (d, 1 H, $J_{1,2}$ 7.8 Hz, H-1), 3.85–3.98 (m, 3 H, H-3, H-4, H-6), 3.63 (t, 1 H, *J* 9.2 Hz, H-6′), 3.46 (t, 1 H, *J* 8.4 Hz, H-2), 3.25 (dt, 1 H, J_d 6.2, J_t 9.2 Hz, H-5), 1.53 (s, 3 H), 1.45 (s, 6 H, 2Me), 1.43 (s, 3 H, Me), 1.43 (s, 3 H, Me); ^{13}C NMR ($CDCl_3$): δ 136.5, 128.3, 128.1, 127.9, 112.1, 101.1, 99.7, 77.8, 77.5, 72.6, 70.7, 69.6, 62.1, 28.9, 26.6, 26.4, 19.0. Anal. Calcd for $C_{19}H_{26}O_6$: C, 65.13; H, 7.48. Found: C, 65.39; H, 7.55.

Benzyl 2,3:4,6-di-O-*isopropylidene*-α-D-*galactopyranoside* (α-**12**).—(262 mg, 75%), $[\alpha]_D$ + 114.1° (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.25–7.35 (m, 5 H, Ph), 5.39 (d, 1 H, $J_{1,2}$ 2.7 Hz, H-1), 4.71 (s, 2 H, OCH_2Ph), 4.46 (m, 1 H, H-4), 4.01–4.21 (m, 3 H, H-2, H-3 H-6), 3.81 (dd, 1 H, *J* 1.5, *J* 12.9 Hz, H-6′), 3.28 (m, 1 H, H-5), 1.47 (s, 9 H, 3 Me), 1.44 (s, 3 H); ^{13}C NMR ($CDCl_3$): δ 137.5, 128.2, 128.1, 127.5, 110.1, 98.3, 97.8, 72.6, 71.1, 70.1, 67.2, 62.9, 62.7, 29.1, 26.4, 18.2. Anal. Calcd for $C_{19}H_{26}O_6$: C, 65.13; H, 7.48. Found: C, 65.22; H, 7.57.

Benzyl 2,3:4,6-di-O-*isopropylidene*-β-D-*galactopyranoside* (β-**12**).—(287 mg, 82%), mp 125–127 °C, lit 128–130 °C [14], $[\alpha]_D$ − 51.6° (*c* 1.0, $CHCl_3$), lit − 52° (*c* 1.0, $CHCl_3$) [14]; ^{1}H NMR ($CDCl_3$): δ 7.25–7.38 (m, 5 H), 4.96 and 4.59 (2d, 2 H, *J* 12.0 Hz, OCH_2Ph), 4.68 (d, 1 H, $J_{1,2}$ 7.8 Hz, H-1), 4.41 (m, 1 H, H-4), 3.97–4.17 (m, 3 H, 2H-6, H-2), 3.51 (dd, 1 H, *J* 2.8, *J* 9.5 Hz, H-3), 3.29 (m, 1H, H-5), 1.48 (s, 3 H, Me), 1.47 (s, 3 H, Me), 1.43 (s, 3 H, Me), 1.38 (s, 3 H, Me); ^{13}C NMR ($CDCl_3$): δ 137.0, 128.1, 127.8, 127.5, 110.8, 100.8, 98.4, 78.0, 72.6, 69.8, 67.2, 66.1, 62.7, 28.8, 26.5, 26.3, 18.5. Anal. Calcd for $C_{19}H_{26}O_6$: C, 65.13; H, 7.48. Found: C, 64.81; H, 7.32.

2,3:4,6-Di-O-*isopropylidene*-D-*glucopyranose* (**2**).—(272 mg, 91% yield), $[\alpha]_D$ − 32.3° (*c* 1.0, $CHCl_3$), lit − 34° (*c* 1.6, $CHCl_3$) [7]; (3:2 hexane:EtOAc) ^{1}H NMR ($CDCl_3$): δ (selected peaks) 1.25–1.50 (cluster of singlets, 12 H), 3.4–5.0 (m, 7 H), 9.77 (d, 0.10 H, *J* 1.5 Hz, CHO).

2,3:4,6-Di-O-*isopropylidene*-D-*galactopyranose* (**3**).—(245 mg, 89% yield), $[\alpha]_D$ − 10.7° (*c* 1.0, $CHCl_3$), lit − 8° (*c* 2.0, $CHCl_3$) [7]; (3:2 hexane:EtOAc) ^{1}H NMR ($CDCl_3$): δ (selected peaks) 1.30–1.50 (cluster of singlets, 12 H), 3.4–5.1 (m, 7 H), 9.64 (d, 0.10 H, CHO).

2,3:4,6 - Di - O - *isopropylidene* - D - *glucitol* (**4**).—Hydrogenation of **7** (159 mg) was carried out at 35 psi using a 20% w/w proportion of 10% Pd/C during 36 h, to yield after column chromatography D-glucitol diacetonide (**4**) (93 mg, 78%).$[\alpha]_D$ − 17.3 (*c* 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 4.18–4.24 (m, 2 H), 3.59–3.92 (m, 6 H), 3.21 (d, 1 H, *J* 2.4 Hz, OH), 2.45 (t, 1 H, *J* 5.7 Hz, OH), 1.43 (s, 3 H, Me), 1.41 (s, 3 H, Me), 1.39 (s, 3 H, Me), 1.35 (s, 3 H, Me); ^{13}C NMR ($CDCl_3$): δ 109.4, 99.0, 77.3, 76.6, 72.0, 64.0, 63.5, 62.7, 28.0, 27.0, 26.6, 19.2. Anal. Calcd for $C_{12}H_{22}O_6$: C, 54.95; H, 8.45. Found: C, 54.78; H, 8.23. Compound **2** (16 mg, 13.5%) was also isolated.

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