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Note

Synthesis of partially-protected D-fructofuranoses and D-fructose-6-phosphates*

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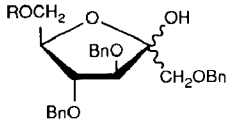
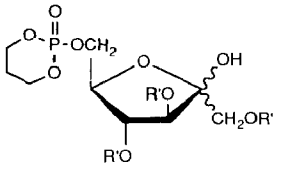
In connection with a program related to D-fructose 2,6-bisphosphate analogues[1], partially protected D-fructofuranose derivatives were prepared. We now report a new synthesis of 1,3,4,6-tetra-*O*-benzyl-D-fructofuranose (**1**, Scheme 1), an efficient synthesis of the novel compound 1,3,4-tri-*O*-benzyl-D-fructofuranose (**2**, Scheme 2), and conversion of the latter product to fructofuranose 6-phosphate derivatives **3** and **4** (Scheme 3).



1 R = Bn
2 R = H



3 R' = Bn
4 R' = H

Previously, sucrose, inulin, and fructose were used to prepare blocked fructofuranose intermediates. 1,2,3,4,6-Penta-*O*-acetyl[2] and -benzoyl[3], 1,3,4,6-tetra-*O*-benzyl[4], -acetyl[5], -benzoyl[6], -nicotinoyl[7], and -methyl[8] D-fructofuranoses have been reported. The addition of a hydroxymethylene equivalent to a protected γ-aldonolactone, as depicted in Scheme 1, constitutes a novel entry into the ketofuranose series. Treatment of 2,3,5-tri-*O*-benzyl-D-arabinonolactone (**5**) (ref. 9) with excess benzyloxymethyllithium[10] (prepared *in situ* from butyllithium and (benzyloxymethyl)tributylstannane at −78–0°) provided 1,3,4,6-tetra-*O*-benzyl-D-fructofuranose[4] (**1**, β:α, *ca.* 2:1 by n.m.r.) in 66% isolated yield.

An attempt to directly convert **1** to **2** gave non-selective deprotection and a poor yield of recovered products, owing to the lability of the ring structure. A separate, efficient synthesis of **2** was devised as shown in Scheme 2.

Silylation of sucrose under controlled conditions[11] provided the 6′-*O*-*tert*-bu-

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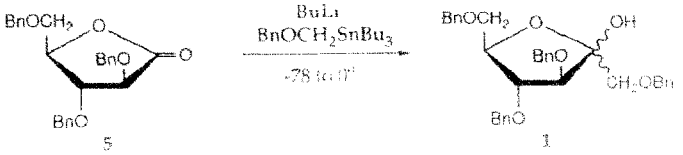
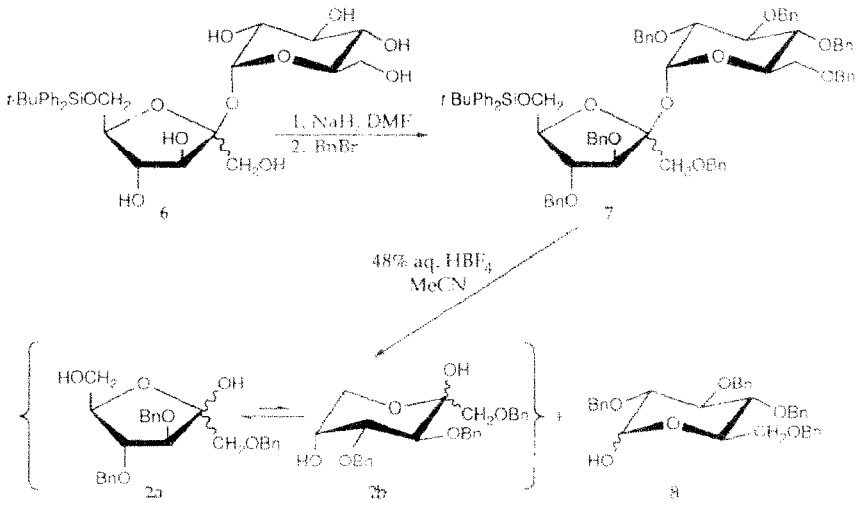


Scheme 1.

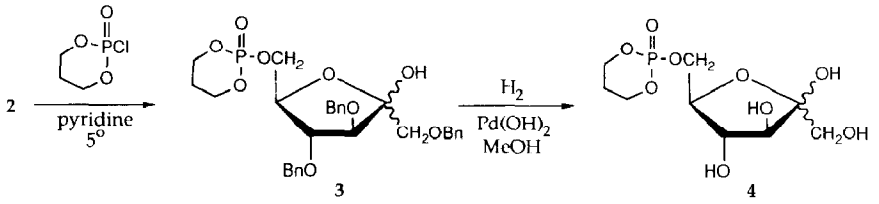


Scheme 2.

tyldiphenylsilyl derivative **6**. Perbenzylation of **6** with benzyl bromide and sodium hydride in *N*,*N*-dimethylformamide afforded 6′-*O*-*tert*-butyldiphenylsilyl-2,3,4,6,1′,3′,4′-hepta-*O*-benzylsucrose (**7**) in 50% yield, after chromatography. Hydrolysis of the latter intermediate with sulfuric acid in glacial acetic acid, as in the earlier preparation[4] of **1**, or with 88% aqueous formic acid in ether, resulted in decomposition of the fructofuranose portion and gave only the known[12] 2,3,4,6-tetra-*O*-benzyl-D-glucose (**8**). Hydrolysis of the glycosidic linkage of **7** and concomitant desilylation were best achieved by treatment of **7** with tetrafluoroboric acid in acetonitrile at ambient temperature. The crystalline tetrabenzylglucose **8** was filtered off, and the desired 1,3,4-tri-*O*-benzyl-D-fructofuranose (**2**) was isolated from the residue by chromatography in 80% yield as a mixture of isomers. Spectral analysis (^{13}C-n.m.r.) of the mixture revealed the presence of both furanose and pyranose forms (65% **2a** and 35% **2b**, respectively), with the β anomer predominating in each. Compound **2a** provides a versatile synthon for further functionalization, since the two primary hydroxyl moieties are differentiated, and the primary benzyl group can be selectively removed in the presence of secondary groups at a later stage. The previously known 1,3,4-tri-*O*-methyl-D-glucose[13] had been reported as a mixture with other methylated products from the methylation of sucrose, but it does not afford the possibility of mild deprotection, as does **2**.

The synthesis of the 6-phosphate **4**, illustrated in Scheme 3, is just one example of

the utility of this intermediate. Mixture **2** was phosphorylated with 2-chloro-1,3,2-dioxaphosphorinane 2-oxide[14] in pyridine solution at 5° to obtain fully-protected phosphate **3** in 60% yield after chromatography. Hydrogenation of **3** over $Pd(OH)_2$ catalyst at 74 p.s.i. afforded a quantitative yield of the fructofuranose 6-phosphate **4**, which was required for our biological studies.



Scheme 3.

EXPERIMENTAL

General methods. — Unless otherwise specified, products were separated by flash chromatography on Silica Gel 60 (230–400 mesh, 60 Å pore size, Baxter Healthcare/Scientific Products Div.). The purity of products was determined by t.l.c. on Silica Gel GF (250 μm, Analtech.). Preparative h.p.l.c. was performed on a Waters Prep LC/System 500A chromatograph fitted with two 6 × 33 cm silica gel columns. Melting points were obtained on a Mel-Temp apparatus and are uncorrected. Optical rotations were determined with a Perkin–Elmer Model 241 automatic polarimeter. Unless otherwise specified, n.m.r. spectra (300 MHz for ^1H and 75.46 MHz for ^{13}C) were obtained for $CDCl_3$ solutions (1% internal standard, Me_4Si) on a Nicolet/Oxford NT-300WB or a GE QE-300 spectrometer. Mass spectra were obtained on a Finnigan MAT-90 or a VG ZAB-SE spectrometer. Reactions requiring anhydrous conditions were performed under an argon atmosphere, using Aldrich solvents in Sure/Seal bottles. Organic solutions were dried over magnesium sulfate or sodium sulfate, and solvents were evaporated *in vacuo* with a rotary evaporator. Unless otherwise specified, products were obtained as oils.

*Preparation of 1,3,4,6-tetra-*O*-benzyl-*D*-fructofuranose* (**1**). — To a stirred solution of (benzyloxymethyl)tributylstannane[10] (10.3 g, 25 mmol) in anhydrous tetrahydrofuran (100 mL) at −78° was added butyllithium in hexane (2.5M, 9.6 mL) during 5 min. After an additional 5 min, a solution of 2,3,5-tri-*O*-benzyl-D-arabinonolactone (**5**) (8.37 g, 20 mmol) in tetrahydrofuran (20 mL) was added during 5 min at −78 to −60°. The solution was stirred for 30 min at −78°, warmed to 0° during 30 min, stirred for 10 min at 0°, and quenched with glacial acetic acid (2.8 mL). The mixture was then partitioned between ether and water. The organic layer was washed with sodium hydrogencarbonate solution, water, and brine, dried, and concentrated to give a mixture of two liquid phases. The tetrabutylstannane was removed by washing the mixture, adsorbed on silica gel (300 g), with hexane (1 L). The crude product (11.1 g) was removed by washing the silica gel with ethyl acetate (1 L), and the product was then

subjected to dry-column chromatography (3:1 heptane–EtOAc) to give compound **1** as a syrup (8.9 g, 66%, homogeneous on t.l.c.). The spectral properties of **1** were identical with those of a sample prepared indepedently, following the procedure of Ness *et al.*[4]: $[\alpha]_D^{26}$ +13° (*c* 1.43, chloroform); lit. (mutarotation observed) $[\alpha]_D^{20}$ +6.5 → +8.7° in 24 h; ^{1}H-n.m.r.: δ 7.45–7.15 (m, 20 H), 4.75–4.45 (m, 8 H), 4.25–4.05 (m, 4 H), and 3.75–3.45 (m, 4 H); ^{13}C-n.m.r.: δ 137.95–137.50 (m), 128.50–127.50 (m), 105.31 and 102.44 (C-2, α and β, respectively), *ca.* 1:2), 86.42, 83.68, 83.47, 82.77, 81.71, 79.94, 73.77, 73.57, 73.48, 73.24, 72.67, 72.06, 71.94, 71.84, 70.97, 70.64, and 70.08.

*2,3,4,6,1′,3′,4′-Hepta-*O*-benzyl-6′-*O*-tert-(butyldiphenylsilyl)sucrose* (**7**). — A solution of 6′-*O*-*tert*-(butyldiphenylsilyl)sucrose (**6**, 6.56 g, 11.3 mmol) in anhydrous *N*,*N*-dimethylformamide (60 mL) was added to a slurry of sodium hydride (5.7 g, 50% dispersion in oil, prewashed and dried, *ca.* 110 mequiv.) in *N*,*N*-dimethylformamide (60 mL). The mixture was stirred for 1.4 h at room temperature and then treated with benzyl bromide (32.0 mL, 269 mmol). Stirring was continued for 4 h at room temperature and for 1 h at 60°. Methanol (10 mL) was added to the cooled mixture, and the volatiles were removed, first at aspirator pressure, then at 0.1 torr to give a brown oil (18 g). Chromatographic separation (prep. h.p.l.c., hexane–EtOAc gradient of 14:1 to 10:1) afforded **7** (5.75 g, 42%): $[\alpha]_D^{26}$ +31° (*c* 0.7, chloroform); ^{1}H-n.m.r.: δ 7.69–7.63 and 7.37–7.10 (m, 45 H), 5.77 (d, *J* 3.58 Hz, 1 H), 4.81 (m, 2 H), 4.69–4.60 (m, 3 H), 4.58–4.42 (m, 8 H), 4.35–4.21 (m, 3 H), 4.08–3.23 (m, 11 H), and 1.046 (s, 9 H); ^{13}C-n.m.r.: δ 138.92–127.38 (multiplets), 104.55, 89.74, 84.16, 82.63, 81.97, 81.27, 79.88, 77.46, 75.51, 74.69, 73.38, 73.26, 73.06, 72.42, 72.06, 71.17, 70.51, 68.37, 64.97, 26.87, and 9.23.

Anal. Calc. for $C_{77}H_{82}O_{11}Si$: C, 76.33; H, 6.82; Si, 2.32. Found: C, 76.50; H, 6.81; Si, 1.88.

*1,3,4-Tri-*O*-benzyl-*D*-fructose* (**2**). — To a solution of **7** (1.55 g, 1.27 mmol) in acetonitrile (18.5 mL), aqueous 48% tetrafluoroboric acid (2.4 mL) was added over a period of 5 min. Stirring was continued for 50 min at room temperature, and the mixture was filtered. The white solid was washed with hexane, dried, and characterized as 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**8**, 60% yield)[4,12] by comparison of its t.l.c. and n.m.r. spectral properties with those of an authentic sample (Sigma Chemical Co.). The combined filtrate was treated with excess sodium hydrogencarbonate powder and refiltered after the effervescence had stopped. The volatiles were removed, and the residue was dissolved in ether and water. Ether work-up gave a yellow oil (1.1 g). Chromatography (2:1 hexane–EtOAc) provided a second portion of **8** (total 86%) and the desired pure **2** (450 mg, 79%): m.p. 70.0–71.5° (from hexane–EtOAc), $[\alpha]_D^{26}$ +10° (*c* 0.5, chloroform); ^{1}H-n.m.r.: δ 7.39–7.18 (m, 15 H), 5.00–4.40 (m, 6 H), 4.35–4.15 (m, 2 H), 4.15–3.90 (m, 2 H), and 3.84–3.35 (m, 5 H); ^{13}C-n.m.r.: δ 137.90–137.10 (m), 129.10–127.50 (m), 105.12 and 101.74 (C-2 of **2a**, α and β, respectively, 28:72), 97.91 and 97.11 (C-2 of **2b**, β and α, respectively, 84:16), 86.24, 83.81, 83.07, 82.08, 81.88, 81.63, 78.92, 75.32, 75.17, 73.79, 73.60, 72.83, 72.47, 72.24, 72.07, 72.01, 71.93, 71.69, 70.88, 67.17, 62.68, 62.54, and 62.44; m.s. (c.i., with NH_3): *m/z* 468 ($M + NH_4$), calc. for $C_{27}H_{34}O_6N$, 468.

Anal. Calc. for $C_{27}H_{30}O_6$: C, 71.98; H, 6.71. Found: C, 71.55; H, 6.75.

1,3,4-Tri-O-benzyl-6-O-(1,3-dioxa-2-phosphacyclohexane-2-yl)-D-fructofuranose 2'-oxide (**3**). — A cold (0–5°) solution of **2** (202 mg, 0.45 mmol) in anhydrous pyridine (1 mL) was treated with 2-chloro-1,3,2-dioxaphosphorinane 2-oxide[14] (84 mg, 0.54 mmol). Stirring was continued for 1 h at 5° and for 30 min at room temperature. Excess reagent was destroyed with two drops of methanol, and the volatiles were removed. Ether work-up provided the crude product, which was isolated by chromatography (1:1–1:2, hexane–EtOAc gradient) and characterized as **3** (166 mg, 64%); ^{1}H-n.m.r.: δ 7.50–7.10 (m, 15 H), 4.70–4.45 (m, 6 H), 4.45–3.85 (m, 10 H), 3.75–3.45 (m, 2 H), 2.30–1.98 (m, 2 H); ^{13}C-n.m.r.: δ 137.80–136.80 (m), 129.40–126.50 (m), 105.46 and 102.49 (α and β C-2, respectively), *ca.* 1:2), 86.23, 82.94, 82.40, 82.07, 81.10 and 78.92 (d, α and β C-5, J_{C-P} 6.9 Hz), 73.67, 73.43, 72.84, 72.20, 72.08, 72.02, 70.75, 69.00–68.35 (overlapped m, 5 lines), 66.69 and 66.01 (d, C-6 of β and α, respectively, J_{C-P} 5.7 Hz), 25.81 (d, J_{C-P} 6.0 Hz).

Anal. Calc. for $C_{30}H_{35}O_9P$: C, 63.15; H, 6.18; P, 5.43. Found: C, 62.97; H, 6.16; P, 5.46.

6-O-(1,3-dioxa-2-phosphacyclohexane-2-yl)-D-fructofuranose 2'-oxide (**4**). — A solution of compound **3** (163 mg, 0.28 mmol) in methanol (12 mL) and ethyl acetate (3 mL) was shaken in a Parr hydrogenator over Pearlman's catalyst (palladium hydroxide-on-carbon, 80 mg) for 8 h at 74 psi. The catalyst was filtered through Celite, and the solvent was evaporated. The gummy product (90 mg gum, 100%) was characterized as **4**; ^{1}H-n.m.r. ($CDCl_3$–CD_3OD): δ 4.83 (br s, 4 H), 4.65–3.45 (m, 11 H), 2.40–2.10 (m, 1 H), and 1.95–1.75 (br d, 1 H); ^{13}C-n.m.r. ($CDCl_3$–CD_3OD): δ 105.76 and 103.09 (α and β C-2, respectively, *ca.* 1:3), 83.50, 80.97 and 80.35 (d, α and β C-5, J_{C-P} 8.3 Hz), 77.90, 76.77, 76.14, 70.41 (m, 3 lines, J_{C-P} 6.3 Hz), 68.39 and 67.53 (d, β and α C-6, respectively, J_{C-P} 6.0 Hz), 64.04 and 64.23 (α and β C-1, respectively), 26.80 (d, J_{C-P} 6.5 Hz); f.a.b.-m.s.: *m/z* 301.0689 (M + H), calc. for $C_9H_{18}O_9P$, 301.0688.

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