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Note

Some aspects of the synthesis of allyl β-D-fructopyranoside

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The specific synthesis of glycosides of D-fructose is not readily achieved. The Fischer-type glycosidation procedures frequently lead to complicated mixtures of furanosides and pyranosides, which require chromatographic separation [1–7].

We have recently reported [8] the synthesis of the ω′-halogenoalkyl β-D-fructopyranosides **1–4** from D-fructose, sucrose, and inulin by a previously described [9] procedure. They were required as potential intermediates for the synthesis of some new amphiphilic alkoxyalkyl and acyloxyalkyl derivatives. During some preliminary studies involving displacement reactions, compound **3** was treated *inter alia* with sodium 1-butoxide in 1-butanol. One of the products of this reaction was identified as the hitherto unknown allyl β-D-fructopyranoside (**5**). It was shown subsequently that **5** was available directly from D-fructose under simple conditions. Some aspects of these reactions are now described.

When a suspension of **3** in 0.1 M sodium 1-butoxide in 1-butanol was heated at 110°C for 36 h, analysis (TLC) demonstrated the presence of two products, in addition to significant amounts of material with low mobility, probably resulting from base-catalysed intermolecular substitution of **3**. Processing of the mixture, followed by acetylation and column chromatography, yielded allyl β-D-fructopyranoside 1,3,4,5-tetraacetate (**6**, 2.6%), and the spiro-anhydride **7** (4.4%) which were identified [9] by ^{1}H and ^{13}C NMR spectroscopy. No other products could be detected in the mixture.

The formation of **7** was not unexpected since it is known [9] that the corresponding 2′-chloroethyl derivative **1** readily undergoes base-induced intramolecular

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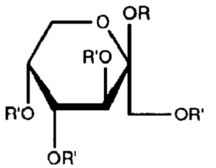
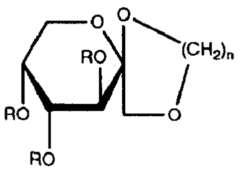


1 $R = CH_2CH_2Cl, R' = H$
2 $R = CH_2CH_2Br, R' = H$
3 $R = CH_2CH_2CH_2Cl, R' = H$
4 $R = CH_2CH_2CH_2CH_2Cl, R' = H$
5 $R = CH_2CH{=}CH_2, R' = H$
6 $R = CH_2CH{=}CH_2, R' = Ac$
9 $R = CH_2CH{=}CH_2, R' = Bz$
10 $R = CH_2CH_2CH_3, R' = H$
11 $R = CH_2CH_2CH_2OCH_3, R' = Ac$
12 $R = CH_2CH_2CH_2OCH_3, R' = H$



7 $n = 3, R = Ac$
8 $n = 2, R = H$

cyclisation to give the 6-membered spiro-anhydride **8** in high yield. The formation of the 7-membered ring in **7** obviously occurs much less readily.

When a solution of **3** in *N,N*-dimethylformamide was treated with potassium *tert*-butoxide in a similar manner, compound **6** became a major product (48%).

Deacetylation of the tetraacetate in methanolic potassium cyanide [10] yielded the crystalline fructoside **5** which was characterised as the tetrabenzoate **9**. Catalytic hydrogenation over palladised charcoal yielded the known propyl β-D-fructopyranoside **10**, thereby substantiating its structure.

Treatment of **3** with boiling 1 M methanolic sodium methoxide, followed by acetylation, did not yield **6**. The major product (26%) of this reaction was identified simply as the 3-methoxypropyl glycoside **11** resulting from direct substitution, together with the anhydride **7** (3%). Compound **11** on deacetylation yielded crystalline **12**.

The crystalline nature of **5** and its relatively low solubility in ethanol suggested that it might be available directly from D-fructose. Thus, treatment of D-fructose with allyl alcohol containing ca. 1% hydrogen chloride at room temperature gave **5** in 49% yield. The mixture remained heterogeneous throughout the reaction period; after ca 16 h, the crystals of D-fructose were replaced by a precipitate of **5**. The addition of further D-fructose to the filtrate of this reaction yielded additional **5** (31%).

It is noteworthy that treatment of sucrose or inulin in a similar manner failed to yield crystalline **5**. Treatment of D-fructose with propargyl alcohol also failed to give a crystalline fructoside.

The chemistry of D-fructose has not developed at a rate comparable with the other common monosaccharides. This is due mainly to a lack of suitably protected derivatives, especially glycosides. The easy availability of compound **5** should significantly broaden this scope.

1. Experimental

Optical rotations were determined on 1% solutions at 20°C with a Perkin–Elmer model 241 polarimeter. TLC was performed on Kieselgel 60 (Merck) with 4:1 CH_2Cl_2–MeOH and detection by charring with 3% H_2SO_4 in EtOH. Column chromatography (1:1 hexane–EtOAc) was performed on Silica Gel 60 (Merck). NMR spectra were recorded with a Bruker AM 400 spectrometer operating at 400 MHz for ^1H spectra, on solutions in $CDCl_3$ (internal standard, Me_4Si) or D_2O, and at 100.6 MHz for ^{13}C spectra, on solutions in $CDCl_3$ (internal standard, Me_4Si) or D_2O (external standard, 1,4-dioxane at 67.8 ppm).

*Reaction of 3-chloropropyl β-*D*-fructopyranoside* (**3**).–*(a) With sodium 1-butoxide.* A stirred suspension of **3** (1.0 g, 3.9 mmol) in 0.1 M sodium 1-butoxide in 1-butanol (30 mL) was heated at 110°C for 36 h. The cooled mixture was filtered, the inorganic material washed with 1-butanol, and the combined filtrate and washings concentrated in vacuo. A solution of the residue in water (20 mL) was percolated through columns (21 × 3 cm) of Amberlite IRA-400 (HCO_3^- form) and IR-120 (H^+ form) ion-exchange resins, and the combined eluates and washings were concentrated in vacuo. The residue was treated with pyridine (3.5 mL) and Ac_2O (0.9 mL), and then processed in the usual manner. Column chromatography of the resultant syrup (0.3 g) gave allyl 1,3,4,5-tetra-*O*-acetyl-β-D-fructopyranoside (**6**; 40 mg, 2.6%); $[\alpha]_D$ −127.5° ($CHCl_3$). ^1H NMR data ($CDCl_3$): δ 5.92 (m, 1 H, H-2′), 5.55 (d, 1 H, $J_{3,4}$ 10.4 Hz, H-3), 5.38–5.31 (m, 3 H, H-3′a, 4, 5), 5.22 (d, 1 H, $J_{2',3'b}$ 10.5, $J_{3'a,3'b}$ < 1.5 Hz, H-3′b), 4.29 (d, 1 H, $J_{1a,1b}$ − 11.9 Hz, H-1a), 4.08 (d, 1 H, $J_{1a,1b}$ − 11.9 Hz, H-1b), 4.15–4.05 (m, 2 H, H-1′a, 1′b, 1b), 3.88 (d, 1 H, $J_{6ax,6eq}$ −13.1 Hz, H-6*eq*), 3.81 (dd, 1 H, $J_{5,6ax}$ 1.4 Hz, H-6*ax*) 2.17, 2.10, 2.08, 1.99 (4 s, each 3H, acetyl CH_3). ^{13}C NMR data ($CDCl_3$): δ 170.3, 170.1, 170.0, 169.9 (4 C=O), 133.6 (C-2′), 118.8 (C-3′), 99.2 (C-2), 68.8, 68.3, 67.4 (C-3, C-4, C-5), 62.8, 62.5, 62.0 (C-1, C-6, C-1′), 20.9, 20.7, 20.6 (3 CH_3).

Further elution gave 1,2-*O*-trimethylene-β-D-fructopyranose 3,4,5-triacetate (**7**; 60 mg, 4.4%); mp 119–121°C (from isopropyl ether); $[\alpha]_D$ −161° ($CHCl_3$). ^1H NMR data: δ 5.32 (br s, 3 H, H-3,4,5), 4.02–3.96 (m, 4 H, H-1′a,3′a, H-1a,6eq), 3.84 (dd, 1 H, *J* 2.7, *J* −12.6 Hz, H-1′b or H-3′b), 3.72 (dd, 1 H, $J_{5,6ax}$ 1.4, $J_{6ax,6eq}$ −12.8 Hz, H-6*ax*), 3.55 (d, 1 H, $J_{1a,1b}$ −13.8 Hz, H-1b), 3.47 (ddd, 1 H, *J* −11.9, *J* 3.6 Hz, H-3′b or H-1′b), 2.14, 2.08, 1.97 (3 s, each 3 H, acetyl CH_3), 2.14–2.07 (m, 1 H, H-2′a), 1.74–1.69 (m, 1 H, H-2′b). ^{13}C NMR data ($CDCl_3$): δ 170.5, 170.3, 170.0 (3 C=O), 100.1 (C-2), 76.2 (C-6), 73.2 (C-1), 70.4, 69.0, 68.0 (C-3, C-4, C-5), 61.7, 61.3 (C-1′ and C-3′), 32.6 (C-2′), 20.9, 20.7, 20.6 (3 CH_3). Anal. Calcd for $C_{15}H_{22}O_9$: C, 52.02; H, 6.40. Found: C, 51.81; H, 6.20%.

(b) With potassium tert*-butoxide.* A stirred mixture of **3** (2.0 g, 7.8 mmol) and potassium *tert*-butoxide (0.87 g, 7.8 mmol) in DMF (50 mL) was heated at 80°C for 3 h and then set aside at room temperature for a further 16 h. The inorganic material was removed by filtration and washed with DMF (10 mL), and the combined filtrate and washings concentrated in vacuo. A cooled (0°C) solution of the residue (2.82 g) in pyridine (15 mL) was treated with Ac_2O (10 mL), stored at

room temperature overnight, and then processed in the usual manner. Column chromatography of the residue gave **6** (1.47 g, 48%); $[\alpha]_D$ −127.5° ($CHCl_3$).

Further elution gave **7** (0.41 g, 15%); mp 118–120°C (from isopropyl ether); $[\alpha]_D$ −160° ($CHCl_3$).

(c) With 1 M methanolic sodium methoxide. A stirred solution of **3** (4.8 g, 19 mmol) in 1 M methanolic NaOMe (50 mL) was heated under reflux for 16 h. The cooled mixture was treated with water (50 mL) and then percolated through columns (21 × 3 cm) of Amberlite IR-45 (HO^- form) and IR-120 (H^+ form) ion-exchange resins. The combined eluates and washings were concentrated in vacuo, and a cooled (0°C) solution of the residue (3.4 g) in pyridine (20 mL) was treated with Ac_2O (12 mL), set aside at room temperature overnight, and processed in the usual manner. Column chromatography of the syrupy crude product (4.53 g) gave 3-methoxypropyl 1,3,4,5-tetra-*O*-acetyl-β-D-fructopyranoside (**11**; 2.04 g, 26%); $[\alpha]_D$ −123° ($CHCl_3$). ^1H NMR data ($CDCl_3$): δ 5.51 (d, 1 H, $J_{3,4}$ 10.3 Hz, H-3), 5.36 (m, 1 H, H-5), 5.33 (dd, 1 H, $J_{4,5}$ 3.4 Hz, H-4), 4.30 (d, 1 H, $J_{1a,1b}$ −11.8 Hz, H-1a), 4.10 (d, 1 H, H-1b), 3.90 (dd, 1 H, $J_{6ax,6eq}$ −13.1, $J_{5,6eq}$ 1.1 Hz, H-6*eq*), 3.80 (dd, 1 H, $J_{5,6ax}$ 1.6 Hz, H-6*ax*), 3.66 (m, 1 H, H-1′a or H-3′a), 3.58–3.44 (m, 3 H, H-1′b, 3′b and H-1′a or H-3′a), 3.34 (s, 3 H, OCH_3), 2.16, 2.11, 2.06, 1.98 (4 s, each 3 H, acetyl CH_3), 1.89 (m, 2 H, H-2′a and H-2′b). ^{13}C NMR data ($CDCl_3$): δ 170.4, 170.2, 170.1, 169.9 (4 C=O), 98.9 (C-2), 69.0 (C-5), 68.4 (C-3), 67.5 (C-4), 62.8 (C-1), 61.9 (C-6), 58.6 (OCH_3), 58.4 (C-1′ and C-3′), 29.7 (C-2′), 21.0, 20.7 (acetyl CH_3).

A solution of **11** (160 mg) in MeOH (20 mL) containing KCN (5 mg) was stirred at room temperature for 18 h, and then filtered through a layer (3 × 3.5 cm) of Silica Gel 60. The inorganic material was washed with MeOH (60 mL) and the combined filtrate and washings were concentrated in vacuo to give 3-methoxypropyl β-D-fructopyranoside (**12**; 50 mg, 52%); mp 111–114°C (from EtOH); $[\alpha]_D$ −127° (MeOH). ^1H NMR data (D_2O): δ 3.94–3.50 (m, 11 H, H-1a, 1b, 3, 4, 5, 6*ax*, 6*eq* and H-1′a, 1′b, 3′a, 3′b), 3.00 (s, 3 H, OCH_3), 1.80 (m, 2 H, H-2′a, 2′b). ^{13}C NMR data (D_2O): 101.7 (C-2), 70.9, 70.4, 69.6 (C-3, C-4, C-5), 70.6, 65.1, 62.5, 58.9 (C-1, C-6, C-1′, C-3′), 60.0 (OCH_3), 30.1 (C-2′). Anal. Calcd for $C_{10}H_{20}O_7$: C, 47.61; H, 7.99. Found: C, 47.37; H, 7.78%.

Allyl β-D-fructopyranoside (**5**).—*(a) From* **6**. A stirred solution of **6** (0.55 g, 1.4 mmol) in MeOH (30 mL) containing KCN (5 mg) was set aside at room temperature for 16 h and processed as described above, to give **5** (0.203 g, 65%); mp 159–161°C (from EtOH); $[\alpha]_D$ −147° (MeOH). ^1H NMR data (D_2O) δ 5.95–5.85 (m, 1 H, H-2′), 5.28 (dd, 1 H, $J_{2',3'a}$ 17.3, $J_{3'a,3'b}$ 1.5 Hz, H-3′a), 5.15 (dd, 1 H, $J_{2',3'b}$ 10.5 Hz, H-3′b), 4.08–3.29 (m, 9 H, H-1a, 1b, 3, 4, 5, 6*ax*, 6*eq* and H-1′a, 1′b). ^{13}C NMR data (D_2O) δ 135.6 (C-2′), 117.8 (C-3′), 102.1 (C-2), 70.9, 70.4, 69.4 (C-3, C-4, C-5), 65.2, 63.1, 62.6 (C-1, C-6, C-1′). Anal. Calcd for $C_9H_{16}O_6$: C, 49.09; H, 7.32. Found: C, 48.46; H, 7.10%.

(b) From D*-fructose.* D-Fructose (20 g, 0.11 mol) was added to a stirred mixture of allyl alcohol (100 mL) and AcCl (2 mL) and then set aside at room temperature for 16 h. The solid material thus produced was collected by filtration, washed with

cold EtOH and ether, and recrystallised from EtOH containing a few drops of aq 25% NH_3 to give **5** (12.43 g, 49%); mp 162–164°C; $[\alpha]_D$ −149.9° (MeOH).

The original filtrate, not mixed with the washings, was treated with D-fructose (20 g) to yield a further crop of **5** (7.88 g, 31%).

A solution of the foregoing product (1.0 g, 4.35 mmol) in pyridine (10 mL) was treated with benzoyl chloride (2.1 mL, 18.3 mmol) and processed in the usual manner to give **9** (2.58 g, 89%); mp 133–135°C (from EtOH); $[\alpha]_D$ −169° ($CHCl_3$). ^1H NMR data ($CDCl_3$): δ 8.08–7.22 (m, 20 H, arom. H), 6.38 (d, 1 H, $J_{3,4}$ 10.5 Hz, H-3), 6.07–6.00 (m, 1 H, H-2′), 5.48 (dd, 1 H, $J_{2',3'a}$ 17.2, $J_{3'a,3'b}$ 1.5 Hz, H-3′a), 5.28 (dd, 1 H, $J_{2',3'b}$ 10.5 Hz, H-3′b), 4.82 (d, 1 H, $J_{1a,1b}$ −11.8 Hz, H-1a), 4.33 (d, 1 H, H-1b), 4.34–4.24 (m, 2 H, H-1′a, 1′b), 4.16 (dd, 1 H, $J_{5,6eq}$ 1.2, $J_{6ax,6eq}$ −13.1 Hz, H-6*eq*), 4.09 (dd, 1 H, $J_{5,6ax}$ 1.8 Hz, H-6*ax*). ^{13}C NMR data ($CDCl_3$): δ 165.7, 165.6 (benzoyl, C=O), 133.8 (C-2′), 133.2, 133.1, 129.7, 129.2, 129.0, 128.3, 128.2 (arom. C), 116.8 (C-3′), 99.7 (C-2), 70.0, 69.5, 68.3 (C-3, C-4, C-5), 62.7, 62.6, 62.1 (C-1, C-6, C-1′). Anal. Calcd for $C_{37}H_{32}O_{10}$: C, 69.80; H, 5.07. Found: C, 69.73; H, 4.95.

Propyl β-D-fructopyranoside (**10**).—A solution of **5** (2.0 g, 9 mmol) in water (50 mL) containing Et_3N (0.1 mL) and Pd–C (5%, 100 mg) was hydrogenated (1 atm) at room temperature for 5 h. The mixture was filtered, the inorganic material washed with water, and the combined filtrate and washings concentrated in vacuo. Recrystallisation of the residue from EtOH gave **10** (1.71 g, 86%); mp 160–163°C, $[\alpha]_D$ −151° (MeOH); lit. [7] mp 157–158°C, $[\alpha]_D$ −142°; lit. [8] mp 161–163°C, $[\alpha]_D$ −151°.

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