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## Note

# The synthesis of some 4-deoxy-4-fluoro and 4,6-dideoxy-4,6-difluoro derivatives of sucrose*

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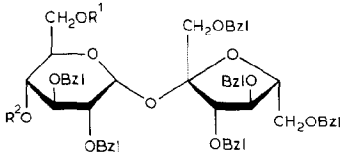
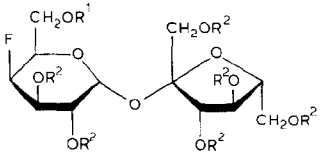
In our search for sweeter and non-metabolisable alternatives to sucrose, we have described[1] several of its monofluorinated derivatives and now report on further fluorinated derivatives.

Selective reaction of 2,3-di-*O*-benzyl-α-D-glucopyranosyl 1,3,4,6-tetra-*O*-benzyl-β-D-fructofuranoside[1] (**1**) with trityl chloride in pyridine followed immediately by treatment *in situ* with methanesulphonyl chloride afforded the syrupy 4-mesylate **2** (61% overall yield). Treatment of **2** with tetrabutylammonium fluoride in boiling acetonitrile for 3 days gave 65% of the 4-fluoride **3**. Subsequent deprotection of **3** by catalytic transfer hydrogenation[2], using 20% palladium hydroxide-on-charcoal in boiling ethanol containing cyclohexene, afforded 4-deoxy-4-fluoro-*galacto*-sucrose (**4**) as a syrup, which was also converted into the syrupy hepta-acetate **5**.




**1** $R^1 = R^2 = H$
**2** $R^1 = Tr, R^2 = Ms$




**3** $R^1 = Tr, R^2 = Bzl$
**4** $R^1 = R^2 = H$
**5** $R^1 = R^2 = Ac$

The $^{19}$F-n.m.r. spectrum of **5** showed a single resonance which appeared as a double triplet, as would be expected for a 4-deoxy-4-fluorogalactopyranoside[3] (Table I); in particular, the values (31 Hz) of the coupling constants for $J_{F\text{-}4,H\text{-}3}$ and $J_{F\text{-}4,H\text{-}5}$ were consistent with an antiperiplanar relationship of F-4 and its vicinal hydrogens. Furthermore, the mass spectrum of **5** contained ions at *m/z* 331 (Fru*f*Ac$_4^+$) and 291 (Glc*p*Ac$_3$F$^+$), resulting from the cleavage of the two glycosidic bonds. The

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TABLE I

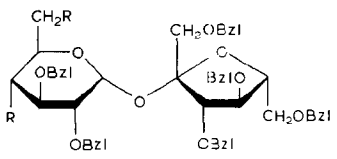
$^{19}$F-N.M.R. DATA ($CDCl_3$)[a]

| | 3 | 5 | 8 | 7 |
|---|---|---|---|---|
| F-6 | | | 63.9 | 67.8 |
| $J_{F\text{-}6,H\text{-}6}$ | | | 45.1 | 50.1 |
| $J_{F\text{-}6,H\text{-}5}$ | | | 20.0 | 25.0 |
| F-4 | 52.1 | 53.05 | 51.6 | 28.2 |
| $J_{F\text{-}4,H\text{-}5}$ | 31.3 | 30.8 | 28.8 | 3.0 |
| $J_{F\text{-}4,H\text{-}4}$ | 48.9 | 48.9 | 50.1 | 53.0 |
| $J_{F\text{-}4,H\text{-}3}$ | 31.3 | 30.8 | 28.8 | 14.0 |

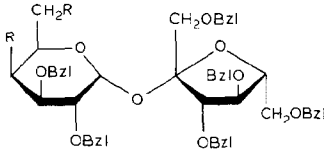
[a]Chemical shifts (p.p.m. to high field of external hexafluorobenzene) and coupling constants (Hz) at 56.4 MHz.

ion *m/z* 291 then fragmented in the manner characteristic of a hexopyranosyl moiety, namely, by the successive loss of acetic acid (→ *m/z* 231), ketene (→ *m/z* 189), hydrogen fluoride (→ *m/z* 169), carbon monoxide (→ *m/z* 141), and acetic acid (→ *m/z* 81).

When 2,3-di-*O*-benzyl-4,6-*O*-methanesulphonyl-α-D-glucopyranosyl 1,3,4,6-tetra-*O*-benzyl-β-D-fructofuranoside (**6**) was similarly treated with tetrabutylammonium fluoride in boiling acetonitrile for 3 days, it gave 65% of the syrupy 4,6-difluoride **8**. Treatment of **6** with potassium fluoride in boiling ethane-1,2-diol gave 43% of **8** together with several minor products that were not isolated.




6 R = OMs
7 R = F




8 R = F 10 R = OH
9 R = OBz 11 R = OMs

The $^{19}$F-n.m.r. spectrum of **8** showed two resonances separated by ~12 p.p.m. (Table I). The resonance at higher field appeared as a triplet of doublets with splittings of 45, 45, and 20 Hz, which was consistent with F-6 of a galactopyranoside, and that due to F-4 appeared as a double triplet with splittings of 29, 29, and 50 Hz. The values of the vicinal couplings to H-5 and H-3 indicated that each of these hydrogens was antiperiplanar to F-4.

The synthesis of 4,6-dideoxy-4,6-difluorosucrose required a 4,6-di-*O*-methanesulphonyl-*galacto*-sucrose derivative, but it was anticipated that the synthesis of such a derivative by nucleophilic displacement of the axial 4-*O*-methanesulphonyloxy group would be difficult because of the antiperiplanar relationship between MsO-4 and H-3 and H-5, which favours elimination in reactions involving nucleophilic displacements with such weak nucleophiles as the fluoride

anion[4]. The appropriate derivative of *galacto*-sucrose, namely **11**, was synthesised from 2,3-di-*O*-benzyl-4,6-di-*O*-methanesulphonyl-α-D-glucopyranosyl 1,3,4,6-tetra-*O*-benzyl-β-D-fructofuranoside (**6**) in 85% yield by reaction with sodium benzoate in hexamethylphosphoric triamide, followed by *O*-debenzoylation and methanesulphonylation. Reaction of **11** with tetrabutylammonium fluoride in acetonitrile for 4 days then gave a mixture of two products of very similar chromatographic mobilities.

The faster-moving component was isolated by column chromatography in 47% yield as a syrup, and was shown to be the 4,6-difluoride **7** by its $^{19}$F-n.m.r. spectrum, which showed two resonances due to a primary and secondary fluorine. The resonance at lower field was due to F-4 and appeared as a poorly resolved double double-doublet with splittings of ~53, 14, and 3 Hz which were consistent with *gauche* relationships between F-4/H-3 and F-4/H-5. The rather small $J_{F\text{-}4,H\text{-}5}$ coupling is probably due to a large electronegativity effect associated with the antiperiplanar relationships of H-5/F-6 and F-4/O-5, and which has been observed in other 4,6-dideoxy-4,6-difluoro-α-D-glucopyranosides[3,5]. The higher-field resonance was due to the primary fluorine and appeared as a triplet of doublets with splittings of 50, 50, and 25 Hz. The large $J_{F\text{-}6,H\text{-}5}$ coupling was characteristic of a 6-deoxy-6-fluoro-α-D-glucopyranoside in which the coupled atoms are antiperiplanar[6]. The slower-moving component was not isolated pure, but was probably a product of elimination.

## EXPERIMENTAL

*2,3-Di-O-benzyl-4-O-methanesulphonyl-6-O-trityl-α-D-glucopyranosyl 1,3,4,6-tetra-O-benzyl-β-D-fructofuranoside* (**2**). — To a solution of the hexabenzyl ether[1] **1** (2.4 g) in pyridine (25 mL) was added chlorotriphenylmethane (2.4 g), and the mixture was heated under reflux for 20 h, when t.l.c. (ether–light petroleum, 1:2) indicated that the reaction was complete. The mixture was then cooled to −5° and methanesulphonyl chloride (2 mL) was added. The mixture was kept overnight at room temperature, and then diluted with chloroform, washed well with water, dilute hydrochloric acid, aqueous sodium hydrogencarbonate, and water, dried ($MgSO_4$), and concentrated to dryness. The residue was purified by column chromatography on silica gel with ether–light petroleum (1:5), to afford **2** as a chromatographically pure syrup (2 g, 61%), $[\alpha]_D$ +41° (*c* 1, chloroform) (Found: C, 74.2; H, 6.2. $C_{74}H_{74}O_{13}S$ calc.: C, 73.9; H, 6.2%).

*2,3-Di-O-benzyl-4-deoxy-4-fluoro-6-O-trityl-α-D-galactopyranosyl 1,3,4,6-tetra-O-benzyl-β-D-fructofuranoside* (**3**). — To a solution of **2** (2 g) in dry acetonitrile (15 mL) was added anhydrous tetrabutylammonium fluoride (4 g), and the solution was heated under reflux for 3 days, when t.l.c. (ether–light petroleum, 2:1) indicated that the reaction was complete and that one major product had been formed. Concentration of the reaction mixture afforded a dark-brown syrup which was purified by column chromatography (silica gel; ether–light petroleum, 9:1), to

give **3** (1.2 g, 65%) as a chromatographically homogeneous syrup, $[\alpha]_D$ +18° (*c* 1, chloroform) (Found: C, 78.6; H, 6.9. $C_{73}H_{71}FO_{11}$ calc.: C, 76.7; H, 6.3%).

*2,3,6-Tri-*O*-acetyl-4-deoxy-4-fluoro-α-*D*-galactopyranosyl 1,3,4,6-tetra-*O*-acetyl-β-*D*-fructofuranoside* (**5**). — To a solution of **3** (500 mg) in ethanol (10 mL) and cyclohexene (10 mL) was added 20% palladium hydroxide-on-charcoal (500 mg), and the mixture was heated under reflux for 7 days, after which t.l.c. (chloroform–methanol, 2:1) indicated that the reaction was complete and that one major product had been formed. The mixture was filtered and concentrated to dryness, and the residue was subjected to column chromatography (silica gel). Elution with chloroform–methanol (15:1) removed impurities, and elution with a 9:1 mixture of the same solvents then afforded **4** as a syrup that was acetylated in the usual way (acetic anhydride–pyridine) to give **5** (0.15 g, 54%), $[\alpha]_D$ +65° (*c* 1, chloroform) (Found: C, 47.5; H, 5.4. $C_{26}H_{35}FO_{17}$ calc.: C, 48.9; H, 5.5%). Mass spectrum: *m/z* 331 (4%), 291 (7), 231 (12), 211 (9), 189 (1), 169 (6), 141 (0.3), 109 (8), 81 (2), and 43 (100). $^1$H-N.m.r. data ($CDCl_3$): δ 5.78 (d, 1 H, $J_{1,2}$ 3.0 Hz, H-1), 5.52 (d, 1 H, $J_{3',4'}$ 6.6 Hz, H-3'), 5.41 (t, 1 H, $J_{4',5'}$ 6.6 Hz, H-4'), 5.2–5.4 (m, H-2,3), 4.97 (dd, 1 H, $J_{F\text{-}4,H\text{-}4}$ 50, $J_{3,4}$ 3, $J_{4,5}$ ~1 Hz, H-4), 4.1–4.5 (m, remaining resonances), 2.15, 2.14, 2.135, 2.13, 2.11 (× 2), and 2.10 (6 s, 7 OAc).

*2,3-Di-*O*-benzyl-4,6-di-*O*-methanesulphonyl-α-*D*-glucopyranosyl 1,3,4,6-tetra-*O*-benzyl-β-*D*-fructofuranoside* (**6**). — Methanesulphonyl chloride (1 mL) was added to a cold solution of **1** (2.4 g) in anhydrous pyridine (20 mL). The solution was then stored at room temperature overnight, after which t.l.c. (light petroleum–ethyl acetate, 2:1) indicated the formation of a single product. The mixture was poured into ice and water, and extracted with chloroform in the usual way. The extract was washed well with dilute hydrochloric acid, aqueous sodium hydrogencarbonate, and water, dried ($MgSO_4$), and concentrated to dryness. The dark-brown syrup was then purified by column chromatography (silica gel; light petroleum–ethyl acetate, 9:1), to give amorphous **6** (2.7 g, 95%), $[\alpha]_D$ +95° (*c* 1.5, chloroform) (Found: C, 64.25; H, 6.2. $C_{56}H_{62}O_{15}S_2$ calc.: C, 64.75; H, 5.95%).

*2,3-Di-*O*-benzyl-4,6-dideoxy-4,6-difluoro-α-*D*-galactopyranosyl 1,3,4,6-tetra-*O*-benzyl-β-*D*-fructofuranoside* (**8**). — (*a*) A solution of **6** (1 g) in anhydrous acetonitrile (10 mL) containing tetrabutylammonium fluoride (4 g) was boiled under reflux for 3 days. T.l.c. then indicated the formation of a faster-moving major product and the absence of **6**. The mixture was concentrated to dryness, and a solution of the gummy residue in chloroform was washed well with water, dried ($MgSO_4$), and concentrated to dryness. The syrupy residue was purified by column chromatography (silica gel; light petroleum–ethyl acetate, 9:1), to give **8** as a syrup (0.55 g, 65%), $[\alpha]_D$ +40° (*c* 1, chloroform) (Found: C, 72.6, H, 6.45. $C_{54}H_{56}F_2O_9$ calc.: C, 73.15; H, 6.3%).

(*b*) A solution of **6** (1 g) in ethane-1,2-diol (5 mL) containing potassium fluoride (2 g) was boiled under reflux for 1 h. T.l.c. (light petroleum–ethyl acetate, 3:1) indicated that **8** had been formed together with several slower-moving minor components. The cooled solution was diluted with chloroform, washed well with

water, dried ($MgSO_4$), and concentrated to dryness. Column chromatography of the residue as in (*a*) gave **8** (0.4 g, 43%).

*4,6-Di-*O*-benzoyl-2,3-di-*O*-benzyl-α-*D*-galactopyranosyl 1,3,4,6-tetra-*O*-benzyl-β-*D*-fructofuranoside* (**9**). — To a solution of **6** (3.6 g) in hexamethylphosphoric triamide (20 mL) was added sodium benzoate (2 g), and the mixture was heated at 100° for 4 days; t.l.c. (light petroleum–ethyl acetate, 3:1) then indicated that the reaction was complete. The mixture was diluted with ethyl acetate, washed several times with water, dried ($MgSO_4$), and concentrated to dryness. The resulting syrup was eluted from a short column of silica gel with light petroleum–ethyl acetate (9:1), to give **9** as a syrup (3.2 g, 85%), $[\alpha]_D$ +29° (*c* 1, chloroform) (Found: C, 75.25; H, 6.3. $C_{68}H_{66}O_{13}$ calc.: C, 74.85; H, 6.05%).

*2,3-Di-*O*-benzyl-4,6-di-*O*-methanesulphonyl-α-*D*-galactopyranosyl 1,3,4,6-tetra-*O*-benzyl-β-*D*-fructofuranoside* (**11**). — To a solution of **9** (2 g) in dry methanol (30 mL) was added methanolic M sodium methoxide (0.3 mL) so that the pH was 9–10. The mixture was kept overnight at room temperature and t.l.c. (ether) then indicated completion of the reaction. The mixture was filtered through a pad of silica gel in order to remove the sodium methoxide, and then concentrated to dryness to give a syrupy diol, a solution of which in pyridine (10 mL) at −10° was treated with methanesulphonyl chloride (1.5 mL). The mixture was kept at room temperature for 16 h and worked up as described above to give a syrupy product that was purified by column chromatography (silica gel; light petroleum–ethyl acetate, 5:1), to afford **11** as a syrup (1.4 g, 68%), $[\alpha]_D$ +48° (*c* 1, chloroform) (Found: C, 65.1; H, 6.05. $C_{56}H_{62}O_{15}S_2$ calc.: C, 64.75; H, 5.95%).

*2,3-Di-*O*-benzyl-4,6-dideoxy-4,6-difluoro-α-*D*-glucopyranosyl 1,3,4,6-tetra-*O*-benzyl-β-*D*-fructofuranoside* (**7**). — To a solution of **11** (1 g) in anhydrous acetonitrile (10 mL) was added anhydrous tetrabutylammonium fluoride (3 g), and the mixture was boiled under reflux for 4 days. T.l.c. (light petroleum–ethyl acetate, 5:1) then indicated that two components with very similar mobilities had been formed. The mixture was processed as described above, and column chromatography (silica gel; light petroleum–ethyl acetate, 20:1) afforded the faster-moving component **7** as a chromatographically homogeneous syrup (0.4 g, 47%), $[\alpha]_D$ +33° (*c* 1, chloroform) (Found: C, 70.8; H, 6.25. $C_{54}H_{56}F_2O_9$ calc.: C, 73.15; H, 6.3%).

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