Note

Sucrochemistry
Part V[1]. Synthesis of 4-sulphonate derivatives of sucrose and their conversion into α-D-galactopyranosyl β-D-fructofuranoside

R. KHAN

Tate and Lyle Research Centre, Westerham Road, Keston, Kent BR2 6HJ (Great Britain)

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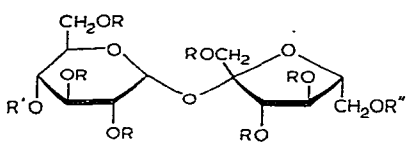
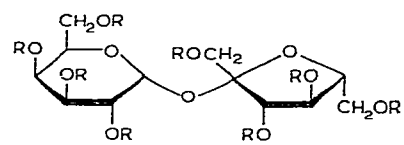
S_N2 displacement reactions of 4-sulphonates of α-D-glucopyranosides in aprotic solvents, with such nucleophiles as benzoate, azide, and thiocyanate, have been reported[2,3] to give products with inversion of configuration at C-4. Hough *et al.*[4,5] have shown that azide displacement of the 4-*O*-sulphonyl group in derivatives of sucrose also occurs with inversion of configuration. As part of a study of the chemistry of sucrose, the synthesis of the 4-*O*-sulphonyl derivatives of sucrose and their conversion into α-D-galactopyranosyl β-D-fructofuranoside[6] (**8**) have been investigated. An enzymic synthesis of **8** has been reported by the use of raffinose as D-fructosyl donor to D-galactose in a levansucrase enzyme system[6].

Detritylation of 6,6′-di-*O*-tritylsucrose hexa-acetate[7] in boiling, aqueous acetic acid occurred, with the expected O-4→O-6 migration of the acetyl group[8–10], to give 1′,2,3,3′,4′,6-hexa-*O*-acetylsucrose as the major product which was purified by column chromatography on silica gel. Retritylation of the hexa-acetate with trityl chloride in pyridine at 90°, followed by chromatography on silica gel, gave 6,6′-di-*O*-tritylsucrose hexa-acetate[7] in 12% and 6′-*O*-tritylsucrose hexa-acetate (**1**) in 66% yield. The hexa-acetate **1** with HO-4 free is an intermediate suitable for the synthesis of the 4-*O*-sulphonyl derivatives of sucrose.





1 R = Ac, R′ = H, R″ = Tr
2 R = Ac, R′ = Ms, R″ = Tr
3 R = Ac, R′ = Ts, R″ = Tr
4 R = Ac, R′ = Ms, R″ = H
5 R = Ac, R′ = Ts, R″ = H
6 R = R″ = Ac, R′ = Ms
7 R = R″ = Ac, R′ = Ts
8 R = H
9 R = Ac
10 R = Bz

Reaction of **1** with mesyl chloride in pyridine at room temperature gave 4-*O*-mesyl-6′-*O*-tritylsucrose hexa-acetate (**2**), whereas tosylation of **1** at room temperature was slow and incomplete even after 72 h. However, a good yield of 4-*O*-tosyl-6′-*O*-

tritylsucrose hexa-acetate (**3**) was obtained by carrying out the reaction at 80° for 8 h. Detritylation of **2** and **3**, using hydrogen bromide in acetic acid at 0°, gave 4-*O*-mesylsucrose hexa-acetate (**4**) and 4-*O*-tosylsucrose hexa-acetate (**5**). Conventional treatment of **4** and **5** with acetic anhydride in pyridine afforded the corresponding hepta-acetate derivatives **6** and **7**. The derived first-order coupling constants ($J_{1,2}$ 3.5, $J_{2,3}$ 10.3, $J_{3,4}$ 9.0, and $J_{4,5}$ 9.0 Hz for **6**; and $J_{1,2}$ 3.7, $J_{2,3}$ 10.3, $J_{3,4}$ 8.8, and $J_{4,5}$ 10.0 Hz for **7**) confirmed the *gluco* configuration and the C_1^4 conformation for the D-glucose moiety in **6** and **7**.

Replacement of the sulphonate group in **6** and **7** with sodium benzoate in hexamethylphosphoric triamide gave a product, with inversion of configuration at C-4, which on catalytic de-esterification afforded crystalline α-D-galactopyranosyl β-D-fructofuranoside[7] (**8**) in 62% yield. The structure of **8** was confirmed by acid hydrolysis to give D-galactose and D-fructose, and by p.m.r. spectroscopy of the octa-acetate **9**. The derived first-order coupling constants ($J_{1,2}$ 3.4, $J_{2,3}$ 10.5, $J_{3,4}$ 3.0, $J_{4,5}$ 3.0 Hz) indicated an *eq,ax,ax,eq* arrangement of H-4, H-3, H-2, and H-1, respectively, in agreement with the α-D-*galacto* configuration in **9**. Compound **8**, on treatment with benzoyl chloride in pyridine, gave the crystalline octabenzoate **10**.

EXPERIMENTAL

The general experimental data are as described in Part I[4].

1′,2,3,3′,4′,6-Hexa-O-*acetyl-6′*-O-*tritylsucrose* (**1**). — A solution of *6,6′*-di-*O*-tritylsucrose hexaacetate[7] (18 g) in glacial acetic acid (450 ml) and water (9 ml) was heated at 110° for 50 min. T.l.c. (ether) showed a slow-moving, major product. The solution was concentrated with co-distillation of toluene. Elution of the residue from a column of silica gel (200 g), using ether–light petroleum (4:1), gave a syrupy product (8 g, 81%), a portion (3 g) of which was treated with trityl chloride (4 g) in pyridine (20 ml) at 90° for 3 h. T.l.c. (ether–light petroleum, 5:1) revealed a minor, fast-moving product which co-chromatographed with 6,6′-di-*O*-tritylsucrose hexaacetate, and a slow-moving, major product. The reaction mixture was diluted with methylene chloride, washed with water, concentrated with co-distillation of toluene, and dried *in vacuo* overnight at 30°. The product was eluted from a column of silica gel (50 g), using methylene chloride–light petroleum (3:1) to give 6,6′-di-*O*-tritylsucrose hexaacetate[7] (650 mg, 12%) and **1** as a syrup (2.8 g, 67%), $[\alpha]_D$ +19.9° (*c* 3.47, chloroform) (Found: C, 62.0; H, 6.0. $C_{43}H_{48}O_{17}$ calc.: C, 61.7; H, 5.7%).

1′,2,3,3′,4′,6-Hexa-O-*acetyl-4*-O-*mesyl-6′*-O-*tritylsucrose* (**2**). — To a ccooled (0°) solution of **1** (4 g) in pyridine (30 ml), methanesulphonyl chloride (2 ml) was added, dropwise, over a period of 0.5 h. The reaction mixture was stored at room temperature for 52 h. T.l.c. (ether–light petroleum, 6:1) showed a fast-moving, major product. The solution was then poured into ice–water, and the precipitate was collected, washed well with water, and dried *in vacuo* overnight at 30°. Elution of the residue from a column of silica gel (50 g), using ether–light petroleum (2:1), afforded a syrup. Crystallization from aqueous ethanol gave **2** (3.5 g, 80%), m.p. 85–87°,

$[\alpha]_D$ +29.4° (*c* 2.19, chloroform) (Found: C, 57.9; H, 5.8; S, 3.4. $C_{44}H_{50}O_{19}S$ calc.: C, 57.8; H, 5.5; S, 3.5%). N.m.r. data ($CDCl_3$): τ 4.33 (*d*, 1 proton, $J_{1,2}$ 3.75 Hz, H-1), 5.28 (*q*, 1 proton, $J_{2,3}$ 10.0 Hz, H-2), 4.53 (*t*, 1 proton, $J_{3,4}$ 9.3 Hz, H-3), 5.24 (*t*, 1 proton, $J_{4,5}$ 9.3 Hz, H-4), 4.64–4.78 (*m*, H-3′ and H-4′), 7.26 (*s*, 3 protons, CH_3SO_2), 7.9–8.01 (18 protons, 6Ac), 2.5–2.8 (15 protons, Tr).

1′,2,3,3′,4′,6-Hexa-O-*acetyl-4*-O-*tosyl-6′*-O-*tritylsucrose* (**3**). — A solution of **1** (2 g) in pyridine (15 ml) was treated with toluene-*p*-sulphonyl chloride (1.5 g) in pyridine at 0°. The reaction mixture was then heated at 80° for 8 h. T.l.c. (ether–light petroleum, 6:1) showed a fast-moving, major product. The reaction was worked up as described previously, to give a syrupy mixture, which on elution from a column of silica gel (30 g), using ether–light petroleum (2:1), gave **3** (1.6 g, 68%) which, after crystallisation from aqueous ethanol, had m.p. 82–84°, $[\alpha]_D$ +31.3° (*c* 1.98, chloroform) (Found: C, 60.5; H, 5.7; S, 4.0. $C_{50}H_{54}O_{19}S$ calc.: C, 60.6; H, 5.5; S, 3.2%). N.m.r. data: τ 4.38 (*d*, 1 proton, $J_{1,2}$ 3.5 Hz, H-1), 5.24 (*q*, 1 proton, $J_{2,3}$ 10.3 Hz, H-2), 4.57 (*q*, $J_{3,4}$ 9.5 Hz, H-3), 5.17 (*t*, 1 proton, $J_{4,5}$ 9.5 Hz, H-4), 4.68 (*d*, 1 proton, $J_{3',4'}$ 4.3 Hz, H-3′), 4.7 (*t*, 1 proton, $J_{4',5'}$, 4.3 Hz, H-4′); 7.6 (*s*, 3 protons, Ts-CH_3); 7.9–8.02 (18 protons, 6Ac), 2.32–2.82 (19 protons, Tr and tosyl C_6H_4).

1′,2,3,3′,4′,6-Hexa-O-*acetyl-4*-O-*mesylsucrose* (**4**). — A solution of **2** (2.4 g) in glacial acetic acid (14 ml) and chloroform (4 ml) was treated with hydrobromic acid in acetic acid (1.5 ml, 45%) at 0° for 10 min. The reaction mixture was poured into ice–aqueous sodium acetate and extracted with methylene chloride. The extract was dried (Na_2SO_4) and concentrated, and the syrupy residue was eluted from silica gel (25 g), using ether–light petroleum (2:1), to give **4** as a syrup (1.3 g, 74%), $[\alpha]_D$ +22.1° (*c* 1.46, chloroform) (Found: C, 44.8; H, 5.6; S, 4.6. $C_{25}H_{36}O_{19}S$ calc.: C, 44.6; H, 5.4; S, 4.8%).

1′,2,3,3′,4′,6-Hexa-O-*acetyl-4*-O-*tosylsucrose* (**5**). — A solution of **3** (2 g) in glacial acetic acid (8 ml) and chloroform (5 ml) was treated with hydrobromic acid in acetic acid (2 ml, 45%) at 0° for 10 min. The reaction mixture was worked up as described previously to give a syrupy product which, after chromatography from silica gel (25 g), afforded **5** (1.1 g, 73%) as a syrup, $[\alpha]_D$ +20.6° (*c* 2.34, chloroform) (Found: C, 49.9; H, 5.7; S, 4.7. $C_{31}H_{40}O_{19}S$ calc.: 49.7; H, 5.3; S, 4.3%).

1′,2,3,3′,4′,6,6′-Hepta-O-*acetyl-4*-O-*mesylsucrose* (**6**). — A solution of **4** (1.5 g) in pyridine (10 ml) was treated with acetic anhydride (1 ml) at room temperature for 24 h, and t.l.c. (ether–light petroleum, 6:1) then showed a fast-moving product. The solution was concentrated, with co-distillation of toluene, to afford a syrup which was crystallised from ethanol to give **6** (1.5 g, 94%), m.p. 94–95°, $[\alpha]_D$ +25.2° (*c* 1.26, chloroform) (Found: C, 45.4; H, 5.5; S, 4.4. $C_{27}H_{38}O_{20}S$ calc.: C, 45.4; H, 5.3; S, 4.5%). N.m.r. data: τ 4.3 (*d*, 1 proton, $J_{1,2}$ 3.5 Hz, H-1), 5.16 (*q*, 1 proton, $J_{2,3}$ 10.3 Hz, H-2), 4.45 (*q*, 1 proton, $J_{3,4}$ 9.0 Hz, H-3), 5.2 (*t*, 1 proton, $J_{4,5}$ 9.0 Hz, H-4), 4.58 (*d*, 1 proton, $J_{3',4'}$ 5.0 Hz, H-3′), 4.68 (*q*, 1 proton, $J_{4',5'}$ 4.3 Hz, H-4′), 6.93 (*s*, 3 protons, CH_3SO_2), 7.8–7.98 (21 protons, 7 Ac).

1′,2,3,3′,4′,6,6′-Hepta-O-*acetyl-4*-O-*tosylsucrose* (**7**). — Conventional acetylation of **5** (1 g) with acetic anhydride (1 ml) in pyridine (10 ml) at room temperature for

24 h gave the heptaacetate **7** (1 g, 95%) as a syrup, $[\alpha]_D$ +24.5° (*c* 2.48, chloroform) (Found: C, 50.4; H, 5.6; S, 4.0. $C_{33}H_{42}O_{20}S$ calc.: C, 50.1; H, 5.3; S, 4.0%). N.m.r. data: τ 4.34 (*d*, 1 proton, $J_{1,2}$ 3.7 Hz, H-1), 5.16 (*q*, 1 proton, $J_{2,3}$ 10.0 Hz, H-2), 4.45 (*q*, 1 proton, $J_{3,4}$ 8.5 Hz, H-3), 5.13 (*q*, 1 proton, $J_{4,5}$ 10.0 Hz, H-4), 4.6 (*d*, 1 proton, $J_{3',4'}$ 5.3 Hz, H-3'), 4.72 (*q*, 1 proton, $J_{4',5'}$ 4.8 Hz, H-4'), 7.55 (*s*, 3 protons, Ts–CH_3), 7.83–8.04 (21 protons, 7 Ac).

α-D-Galactopyranosyl β-D-fructofuranoside[6] (**8**). — (*a*) A solution of compound **6** (1 g) in hexamethylphosphoric triamide (5 ml) containing sodium benzoate (1 g) was heated at 85° for 72 h. The reaction mixture was diluted with pyridine (20 ml) and treated with acetic anhydride (2 ml) at room remperature for 24 h. The solution was then poured into ice–water, and the precipitate was collected, washed well with water, and dried *in vacuo* overnight at 30°. T.l.c. (ether–light petroleum, 10:1) showed a fast-moving, major product. Elution of the residue from silica gel (25 g), using ether–light petroleum (1:1), gave a syrup. A solution of this product in dry methanol was treated with a catalytic amount of sodium methoxide. After standing at room temperature for 24 h, compound **8** crystallised; yield 350 mg (62%), m.p. 177–179°, $[\alpha]_D$ +82.3° (*c* 0.63, water); lit.[6] m.p. 179° (with sintering at 170°), $[\alpha]_D^{20}$ +81.5° (*c* 1.02, water).

(*b*) A mixture of **7** (1 g) and sodium benzoate (1 g) in hexamethylphosphoric triamide (5 ml) was heated at 85° for 72 h. The reaction mixture was re-acetylated and worked up as described in (*a*) to give a syrupy product. T.l.c. (ether–light petroleum, 6:1) showed a fast-moving, major product. The residue was eluted from a column of silica gel (25 g), using ether–light petroleum (1:1), to give a syrup which, on de-esterification in the usual way, gave **8**; yield 300 mg (57%), m.p. and mixed m.p. 176–178°.

2,3,4,6-Tetra-O-acetyl-α-D-galactopyranosyl 1',3',4',6'-tetra-O-acetyl-β-D-fructofuranoside (**9**). — Conventional acetylation of **8** (100 mg), with acetic anhydride (1 ml) in pyridine (5 ml) at room temperature for 24 h, gave the octa-acetate **9** (12.0 mg, 86%) as a syrup, $[\alpha]_D$ +52.6° (*c* 0.47, chloroform) (Found: C, 50.5; H, 5.7. $C_{28}H_{38}O_{19}$ calc.: C, 49.6; H, 5.6%). N.m.r. data: τ 4.27 (*d*, 1 proton, $J_{1,2}$ 3.4 Hz, H-1), 4.87 (*q*, 1 proton, $J_{2,3}$ 10.5 Hz, H-2), 4.75 (*q*, 1 proton, $J_{3,4}$ 3.0 Hz, H-3), 4.53 (*t*, 1 proton, $J_{4,5}$ 3.0 Hz, H-4), 4.51 (*d*, 1 proton, $J_{3',4'}$ 5.5 Hz, H-3'), 4.64 (*t*, 1 proton, $J_{4',5'}$ 5.5 Hz, H-4'), 7.75–8.04 (24 protons, 8 Ac).

2,3,4,6-Tetra-O-benzoyl-α-D-galactopyranosyl 1',3',4',6'-tetra-O-benzoyl-β-D-fructofuranoside (**10**). — A solution of **8** (100 mg) in pyridine was treated with benzoyl chloride (0.5 ml) at 0°. After standing at room temperature for 24 h, the reaction mixture was poured into ice–water, the precipitate formed was collected, washed well with water, and taken up in methylene chloride. The organic layer was washed with aqueous sodium hydrogen carbonate and water, dried (Na_2SO_4), and concentrated to a syrup. Crystallisation from ethanol gave **10** (200 mg, 83%), m.p. 79–81° $[\alpha]_D$ +52.6° (*c* 0.72, chloroform) (Found: C, 69.5; H, 4.6. $C_{68}H_{54}O_{19}$ calc.: C, 69.5; H, 4.6%).

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