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C-METHYLATION OF SUCROSE: SYNTHESIS OF 6- AND 6′-*C*-METHYLSUCROSE

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ABSTRACT

2,3,4,6,1′,3′,4′-Hepta-*O*-benzylsucrose, obtained by acid-catalysed hydrolysis of the 6′-*O*-trityl derivative, was oxidised with the Pfitzner–Moffatt reagent and the product was alkylated with methylmagnesium iodide. Removal of the protecting groups then gave a mixture of diastereomers, namely 7-deoxy-β-D-*altro*- and -α-L-*galacto*-hept-2-ulofuranosyl α-D-glucopyranoside. Application of this reaction sequence to 2,3,4,1′,3′,4′,6′-hepta-*O*-benzylsucrose afforded β-D-fructofuranosyl 7-deoxy-DL-*glycero*-α-D-*gluco*-heptopyranoside.

INTRODUCTION

The study of structure–activity relationships in sweet-tasting substances is important in the design of new structures having predictable sensory characteristics. Sweeteners with a higher intensity of sweetness and lower degree of cariogenicity than sucrose have obvious advantages in the food industry. The replacement of certain hydroxyl groups of sucrose by chlorine[1] or bromine[2] produces derivatives possessing a high intensity of sweetness. The enhanced sweetness of the halogenated sucroses was attributed to the presence of a Kier tripartite pharmacophore in these molecules[1], or as being due to hydrophobic interaction of the halogen and the protein of the receptor site[3]. In our studies of structure–sweetness relationships for sucrose derivatives, we required sucrose derivatives with *C*-methyl groups at positions 6 and 6′, and we now report the synthesis of two members of this hitherto unexemplified class of sucrose derivative.

RESULTS AND DISCUSSION

Because of the instability of acyl groups towards the organometallic reagents needed for alkylation[4], benzyl protecting-groups were used in the planned syn-

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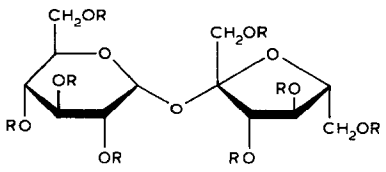
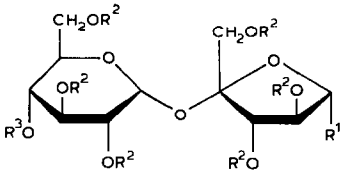


1 R = H
2 R = Bn



3 R^1 = CH_2OTr, R^2 = Ac, R^3 = H
4 R^1 = CH_2OTr, R^2 = R^3 = Bn
5 R^1 = CH_2OH, R^2 = R^3 = Bn
6 R^1 = CHO, R^2 = R^3 = Bn
7 R^1 = CH(Me)OH, R^2 = R^3 = Bn
8 R^1 = CH(Me)OAc, R^2 = R^3 = Ac
9 R^1 = CH(Me)OH, R^2 = R^3 = H

theses. The *tert*-butyldiphenylsilyl group (*t*BDPS), which has been used to block primary hydroxyl groups in sugar derivatives, was reported to be stable under benzylation conditions[5]. However, benzylation of the 6′-*t*BDPS ether of sucrose[6], either with benzyl chloride–methyl sulphoxide–sodium hydride or benzyl bromide–*N,N*-dimethylformamide–sodium hydride, resulted in hydrolysis and the formation of known[7] octa-*O*-benzylsucrose (**2**). Treatment of 2,3,6,1′,3′,4′-hexa-*O*-acetyl-6′-*O*-tritylsucrose[8] (**3**) with benzyl chloride–methyl sulphoxide–sodium hydride gave hepta-*O*-benzyl-6′-*O*-tritylsucrose (**4**).

Hydrolysis of **4** with aqueous 80% trifluoroacetic acid in chloroform at room temperature removed the trityl group in 20 min to provide the hepta-*O*-benzyl derivative **5**. Oxidation of **5** with the Pfitzner–Moffatt reagent (methyl sulphoxide–dicyclohexylcarbodi-imide–pyridinium phosphate) gave 60% of α-D-glucopyranosyl D-*lyxo*-5-hexosulofuranoside (**6**). It is of interest that, whereas methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside could be quantitatively oxidised to the corresponding aldehyde by methyl sulphoxide–SO_3–triethylamine, **5** was completely inert under these conditions[9].

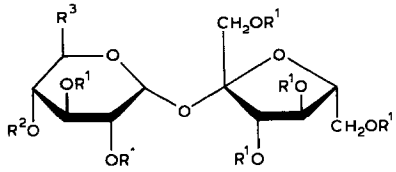
The aldehyde **6** was unstable under normal storage conditions (see Experimental) and was difficult to free from excess of reagents and *N,N′*-dicyclohexylurea. Treatment of **6** with ethereal methylmagnesium iodide gave **5** and the syrupy diastereomeric 6′-*C*-methylsucrose derivatives **7** which were isolated by column chromatography. Lemieux *et al.*[10] were able to separate the D and L isomers formed by the addition of methylmagnesium iodide to 1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-hexodialdo-1,5-pyranose by fractional crystallisation. However, the 6′-*C*-methylsucroses **7** failed to crystallise and attempts to determine the proportion of D and L isomers by using the chiral shift reagent Eu[hfc]$_3$ were not successful. Hough *et al.*[11] experienced difficulties in the conventional hydrogenolysis of benzylated sucrose derivatives and found it necessary to use a boiling mixture of Pd/C, ethanol, and cyclohexene for 5 days. Debenzylation of **7** was complete after stirring with 5% Pd/C in methanol for 18 h, but t.l.c. revealed at least four components in

TABLE I

^{13}C-N.M.R. CHEMICAL SHIFTS (P.P.M.)

Carbon atom	**2**[a]	**4**[a]	**5**[a]	**7**[a]	**11**[a]	**12**[a]	**14**[a]	**9**[b]	**16**[b]
C-2′	104.5	104.4	103.8	103.6	104.6	104.6	104.6	105.0	105.3
C-1	89.9	89.4	91.0	91.2	89.9	89.4	89.4	93.9	93.5
C-5′	83.8	83.9	83.6	84.6	84.3	83.8	83.6	85.1	82.7
C-3′	82.4	81.9	81.7	81.7	82.6	82.0	82.2	79.0	78.7
C-4′	81.9	81.5	81.2	83.6	82.2	81.0	80.7	76.4	75.9
C-3	79.8	80.0	79.4	79.4	80.6	80.1	80.2	73.9	75.9
C-2	79.5	79.5	79.5	79.4	79.5	79.5	79.7	72.5	74.5
C-5	68.4	68.3	67.9	67.9	71.0	70.4	69.8	73.9	75.9
C-4	77.2	77.2	77.3	77.3	78.0	78.1	79.2	70.6	74.5
C-6′	70.5	64.0	61.2	66.3	71.0	71.4	72.1	69.5	63.6
C-1′	71.3	70.6	71.3	71.5	71.4	72.0	71.9	63.2	63.4
C-6	71.2	70.7	71.2	71.4	62.5	62.1	67.0	61.5	68.5
C-7									17.6
C-7′				17.5			16.7	19.3	
OTr		89.4, 143.7			86.9, 144.2				

[a]In $CDCl_3$; Bn (138.9–138.2, 128.3–127.5, 77.5–72.2).[b]In $(CD_3)_2SO$.



10 R^1 = Ac, R^2 = H, R^3 = CH_2OTr
11 R^1 = R^2 = Bn, R^3 = CH_2OTr
12 R^1 = R^2 = Bn, R^3 = CH_2OH
13 R^1 = R^2 = Bn, R^3 = CHO
14 R^1 = R^2 = Bn, R^3 = CH(Me)OH
15 R^1 = R^2 = Ac, R^3 = CH(Me)OAc
16 R^1 = R^2 = H, R^3 = CH(Me)OH

addition to **9** which could have arisen by hydrolysis of **9** due to the presence of adsorbed acids on the catalyst surface[12]. Unsubstituted sucrose derivatives are markedly sensitive towards acids[13]. The product **9** was isolated as the hepta-acetate **8**. The stability of **7** towards hydrogenolysis could be markedly improved by *tert*-butyldimethylsilylation[9] of HO-6'. *O*-Deacetylation of **8** with sodium methoxide regenerated **9** as a syrup, the structure of which was confirmed by ^{13}C-n.m.r. spectroscopy (Table I).

By applying the above sequence of reactions to 2,3,1',3',4',6'-hexa-*O*-acetyl-6-*O*-tritylsucrose[14] (**10**), β-D-fructofuranosyl 7-deoxy-DL-*glycero*-α-D-*gluco*-heptopyranoside (**16**) was obtained. The ^{13}C-n.m.r. data for **11, 12, 14,** and **16** are given in Table I. Compound **16** and its hepta-acetate **15** could not be obtained crystalline.

Sensory analysis of **9** and **16** showed no noticeable enhancement of sweetness over that of sucrose.

The synthesis of branched-chain derivatives of sucrose, using the same approach as outlined here, is currently under investigation.

EXPERIMENTAL

Optical rotations were determined with an automatic Polarimeter P70-7 (1-dm tubes). T.l.c. was performed on Kieselgel 60 F_{254} (Merck) with detection by u.v. light or by charring with sulphuric acid. Column chromatography was carried out with Kieselgel 60 (Merck, 7734). Methyl sulphoxide, dried by storing over powdered calcium hydride, was distilled and stored over molecular sieves Type 4A. Pyridine, dried by boiling under reflux over barium oxide, was distilled, and stored over potassium hydroxide. Light petroleum refers to the fraction having b.p. 60–80°. ^{1}H-N.m.r. spectra (internal Me_4Si) were recorded with a Bruker WM-250 or a Varian 220-MHz spectrometer; ^{13}C-n.m.r. spectra (62.89 MHz) were recorded with a Bruker WM-250 spectrometer.

1,3,4-Tri-O-*benzyl*-6-O-*trityl*-β-D-*fructofuranosyl 2,3,4,6-tetra*-O-*benzyl*-α-D-

glucopyranoside (**4**). — A solution of 2,3,6,1′,3′,4′-hexa-*O*-acetyl-6′-*O*-trityl-sucrose[8] (**3**, 6 g) in dry methyl sulphoxide (40 mL) was added to a stirred mixture of powdered sodium hydride (2 g) and dry methyl sulphoxide (20 mL) under nitrogen. Stirring was continued for 40 min at room temperature, benzyl chloride (20 mL) was then added dropwise, and the mixture was stirred for a further 2 h and then poured into ice–water (500 mL). The crude product was extracted with ether (200 mL), and the extract was washed with water (2 × 50 mL), dried ($MgSO_4$), and concentrated. Column chromatography (light petroleum–ether, 4:1) of the resulting syrup gave **4** (7.8 g, 89%), $[\alpha]_D^{20}$ +25° (*c* 2, chloroform) (Found: C, 78.69; H, 6.38. $C_{79}H_{78}O_{11}$ calc.: C, 78.86; H, 6.49%).

1,3,4-Tri-O-*benzyl*-β-D-*fructofuranosyl* *2,3,4,6-tetra*-O-*benzyl*-α-D-*glucopyranoside* (**5**). — Aqueous 80% trifluoroacetic acid (6 mL) was added to a solution of **4** (6 g) in chloroform (100 mL). The solution was stirred at room temperature until t.l.c. (ether–light petroleum, 2:1) indicated complete disappearance of **4** (~20 min). The solution was then diluted with chloroform (50 mL), washed with saturated aqueous sodium hydrogencarbonate and water, dried ($MgSO_4$), and concentrated. The syrupy residue was adsorbed onto silica gel, and triphenylmethanol was eluted with light petroleum–ether (4:1). On further elution with a 1:1 solvent mixture, concentration of the appropriate fractions gave **5** as a syrup (3.8 g, 78%), $[\alpha]_D^{20}$ +46° (*c* 1.7, chloroform) (Found: C, 75.05; H, 6.23. $C_{61}H_{64}O_{11}$ calc.: C, 75.30; H, 6.58%).

1,3,4-Tri-O-*benzyl*-*7-deoxy*-(β-D-altro,α-L-galacto)-*hept*-*2*-*ulofuranosyl* *2,3,4,6-tetra*-O-*benzyl*-α-D-*glucopyranoside* (**7**). — Anhydrous, crystalline orthophosphoric acid (400 mg) in dry methyl sulphoxide (4 mL) was added to a solution of **5** (3 g) in anhydrous pyridine (0.6 mL), dicyclohexylcarbodi-imide (7.5 g), and dry methyl sulphoxide (30 mL). The mixture was stirred at room temperature until t.l.c. (ether–light petroleum, 2:1) indicated a maximal yield of the aldehyde **6** (~6 h). The *N,N′*-dicyclohexylurea was removed and a solution of oxalic acid (5 g) in methanol (15 mL) was added to the filtrate. The resulting suspension was stirred for 30 min at room temperature, then filtered, diluted with ethyl acetate (100 mL), washed with saturated aqueous sodium hydrogencarbonate and water, dried ($MgSO_4$), and concentrated. The aldehyde was unstable and t.l.c. (as above) showed the appearance of 3 faster moving spots after 2 h at room temperature; therefore, no characterisation was attempted. The residual syrup was dissolved in anhydrous ether (50 mL), *N,N′*-dicyclohexylurea was removed, and the filtrate was added to a stirred solution of methylmagnesium iodide (from 2 g of Mg and 6 mL of MeI in 50 mL of anhydrous ether). After stirring for 6 h at room temperature, the mixture was cooled in ice–water, and aqueous 20% ammonium chloride (50 mL) was added. Work-up in the usual manner, using ether as extractant, gave a syrup (2.5 g), column chromatography (ether–light petroleum, 1:1) of which gave **7** as a colourless syrup (1.5 g, 50%), $[\alpha]_D^{20}$ +33° (*c* 1, chloroform) (Found: C, 75.05; H, 6.60. $C_{62}H_{66}O_{11}$ calc.: C, 75.45; H, 6.69%).

1,3,4,6-Tetra-O-*acetyl*-*7-deoxy*-(β-D-altro,α-L-galacto)-*hept*-*2*-*ulofuranosyl*

2,3,4,6-tetra-O-*acetyl*-α-D-*glucopyranoside* (**8**). — A solution of **7** (1 g) in methanol (60 mL) was hydrogenated over 5% Pd/C (2 g) at room temperature and atmospheric pressure for 18 h. The reaction was monitored by t.l.c. (acetonitrile–water, 3:1) which revealed a single product with a mobility slightly greater than that of sucrose (**1**).

The catalyst was removed, and the filtrate was stirred with Amberlite IR-45 (HO^-) resin for 15 min, filtered, and concentrated. The residue was acetylated in the usual way with acetic anhydride–pyridine. Column chromatography (ether–light petroleum, 3:1) of the product gave **8** as a syrup (500 mg, 71%), $[\alpha]_D^{20}$ +49.5° (*c* 1, chloroform) (Found: C, 50.60; H, 5.72. $C_{29}H_{40}O_{11}$ calc.: C, 50.28; H, 5.78%). ^{1}H-N.m.r. data (220 MHz, $CDCl_3$): δ 4.32 (d, $J_{1,2}$ 4 Hz, H-1), 4.46 (t, $J_{4',5'}$ 5 Hz, H-4'), 4.50 (t, $J_{3,4}$ 10.0 Hz, H-3), 4.55 (d, $J_{3',4'}$ 5 Hz, H-3'), 4.82 (t, $J_{4,5}$ 10 Hz, H-4), 4.85 (m, H-6',6'), 5.06 (dd, $J_{2,3}$ 10 Hz, H-2), 5.98 (dd, $J_{5',6'}$ 6 Hz, H-5'), 7.74–8.00 (m, 24 H, 8 OAc), and 8.68 (d, $J_{6',7'}$ 6.5 Hz, H-7',7',7').

7-Deoxy-(β-D-altro,α-L-galacto)-*hept-2-ulofuranosyl* α-D-*glucopyranoside* (**9**). — Zemplén deacetylation of **8** (200 mg) was monitored by t.l.c. (acetonitrile–water, 3:1). When complete, the solution was neutralised with solid carbon dioxide and concentrated to yield **9** as a syrup (80 mg, 78%), $[\alpha]_D^{20}$ +33° (*c* 0.8, pyridine) (Found: C, 43.90; H, 6.68. $C_{13}H_{24}O_{11}$ calc.: C, 43.82; H, 6.74%).

1,3,4,6-Tetra-O-*benzyl*-β-D-*fructofuranosyl 2,3,4-tri*-O-*benzyl-6*-O-*trityl*-α-D-*glucopyranoside* (**11**). — 2,3,4,1',3',4'-Hexa-*O*-acetyl-6-*O*-tritylsucrose[14] (**10**) was benzylated as described above, to give **11** as a syrup (93%), $[\alpha]_D^{20}$ +32° (*c* 1, chloroform) (Found: C, 79.02; H, 6.20. $C_{79}H_{78}O_{11}$ calc.: C, 78.86; H, 6.49%).

1,3,4,6-Tetra-O-*benzyl*-β-D-*fructofuranosyl 2,3,4-tri*-O-*benzyl*-α-D-*glucopyranoside* (**12**). — Detritylation of **11** with aqueous trifluoroacetic acid, as described above, gave **12** (75%), $[\alpha]_D^{20}$ +42° (*c* 2, chloroform) (Found: C, 75.49; H, 6.32. $C_{61}H_{64}O_{11}$ calc.: C, 75.30; H, 6.50%).

1,3,4,6-Tetra-O-*benzyl*-β-D-*fructofuranosyl 2,3,4-tri*-O-*benzyl-7-deoxy*-DL-glycero-α-D-gluco-*heptopyranoside* (**14**). — Compound **12** was oxidised and alkylated as described above. Column chromatography of the product gave **14** (46%), $[\alpha]_D^{20}$ +51° (*c* 1, chloroform) (Found: C, 75.50; H, 6.82. $C_{62}H_{66}O_{11}$ calc.: C, 75.45; H, 6.69%).

1,3,4,6-Tetra-O-*acetyl*-β-D-*fructofuranosyl 2,3,4,6-tetra*-O-*acetyl-7-deoxy*-DL-glycero-α-D-gluco-*heptopyranoside* (**15**). — Compound **14** was hydrogenolysed as described above and the product was acetylated in the usual manner to give **15** as a syrup, $[\alpha]_D^{20}$ +48° (*c* 1, chloroform) (Found: C, 50.38; H, 5.86. $C_{29}H_{40}O_{11}$ calc.: C, 50.28; H, 5.78%). ^{1}H-N.m.r. data (250 MHz, $CDCl_3$): δ 4.32 (d, $J_{1,2}$ 3.7 Hz, H-1), 4.51 (d, $J_{3',4'}$ 5 Hz, H-3'), 4.53 (dd, $J_{3,4}$ 9 Hz, H-3), 4.64 (t, $J_{4',5'}$ 5 Hz, H-4'), 5.02 (dd, $J_{4,5}$ 10 Hz, H-4), 5.05 (m, H-6), 5.36 (dd, $J_{2,3}$ 10 Hz, H-2), 7.80–8.00 (m, 24 H, 8 OAc), and 8.75 (d, $J_{6,7}$ 6.3 Hz, H-7,7,7).

β-D-*Fructofuranosyl 7-deoxy*-DL-glycero-α-D-gluco-*heptopyranoside* (**16**). — Zemplén deacetylation of **15** gave amorphous **16**, $[\alpha]_D^{20}$ +41° (*c* 1, pyridine) (Found: C, 44.07; H, 6.92. $C_{13}H_{24}O_{11}$ calc.: C, 43.82; H, 6.74%).

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