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Note

Synthesis of 4-*C*-methyl and 4-*C*-allyl derivatives of sucrose*

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In pursuit of structure–activity studies[1,2] on sucrose-based sweeteners, we have investigated the synthesis of 4-*C*-branched-chain analogues of *galacto*-sucrose by the reaction of Grignard reagents with suitable derivatives of 4-ketosucrose. Selective tritylation of 2,3-di-*O*-benzyl-α-D-glucopyranosyl 1,3,4,6-tetra-*O*-benzyl-β-D-fructofuranoside[3] (**1**) with trityl chloride in *N*,*N*-dimethylformamide containing 4-dimethylaminopyridine gave the 6-*O*-trityl derivative **2** in high yield. Oxidation of **2** with acetic anhydride and methyl sulphoxide gave 80% of the corresponding 4-ulose **3**. However, as with similar benzylated "oxo" sugars[2], **3** was unstable so that the crude product was used for subsequent reactions.

The attack of organometallic reagents on uloses is highly stereoselective when the reaction is carried out at −78°, giving, in many instances, one isomer only[4]. The configuration at the newly formed quaternary carbon atom is usually assigned on the basis of the chemical shifts of the ^{13}C signals of the *C*-methyl carbon atoms[5]. Thus, treatment of **3** with methylmagnesium iodide at room temperature for 2 h, followed by conventional work-up of the reaction mixture, gave a mixture of the branched-chain derivatives (**4** and **5**) in the ratio ~1:2 (t.l.c.). The high-field region of the ^{13}C-n.m.r. spectrum of the mixture contained two signals due to the branching methyl group (δ 14.5 and 21.4, respectively) indicative of the *gluco* (**4**) and *galacto* (**5**) configurations. Repetition of the reaction *at* −78° gave only **5** as revealed by t.l.c. ^{13}C-N.m.r. spectroscopy confirmed the proposed structure since the resonance for the *C*-methyl group appeared at 21.4 p.p.m. (Table I).

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TABLE I

^{13}C-N.M.R. CHEMICAL SHIFTS (P.P.M.; $CDCl_3$, INTERNAL Me_4Si)

Atom	**1**[a]	**2**[a]	**5**[a]	**9**[a]	**10**[b]	**11**[b]	**12**[b]
C-2′	104.5	104.4	104.4	102.6	103.9	102.6	103.4
C-1	89.2	89.6	89.4	89.3	90.5	89.7	90.3
C-5′	83.5	83.9	84.0	78.1	79.1	78.5	78.7
C-3′	81.2	82.2	82.2	76.5	74.8	74.8	75.1
C-4′	80.9	81.4	81.5	74.4	74.3	73.8	74.4
C-3	79.4	79.6	80.2	73.4	73.7	73.4	74.0
C-5	70.0	70.4	70.5	71.9	73.7	71.9	70.2
C-2	79.1	79.4	79.3	70.6	72.4	71.7	69.5
C-4	71.7	71.3	72.1	177.4	69.5	68.7	69.1
C-6′	70.4	71.1	71.0	64.3	62.1	64.9	64.7
C-1′	71.4	71.6	71.7	63.3	65.1	63.2	63.1
C-6	62.5	63.6	62.3	61.4	62.1	62.5	62.6
Ph_3C	—	86.5	86.1				
Ph_3C	—	143.8	143.8				
Me_3C–COO	—	—	—	177.4	177.7	177.3	177.1
Me_3C–COO	—	—	—	38.7	38.8	38.8	38.8
Me_3C–COO	—	—	—	21.7	27.1	27.1	27.2
4-CH_3	—	—	21.4	—	15.5	21.4	—
–CH_2–CH=CH_2	—	—	—	—	—	—	131.0
–CH_2–CH=CH_2	—	—	—	—	—	—	120.67

[a]At 62.89 MHz [Bn (139.0–138.1, 128.3–127.5, 77.5–72.2)]. [b]At 15.08 MHz.

Hydrogenolysis (Pd/C) of **5** effected both *O*-detritylation and *O*-debenzylation, giving the octa-ol **6** as a syrup which was characterised as its octa-acetate **7**. The complete acetylation of **6** proceeded with difficulty, even in the presence of 4-dimethylaminopyridine, undoubtedly due to the presence of the tertiary 4-hydroxyl group. The ^{1}H-n.m.r. spectrum of **7** was in complete accord with the proposed structure as a derivative of 4-*C*-methyl-*galacto*-sucrose (Table II).

2,3,6,1′,3′,4′,6′-Hepta-*O*-pivaloylsucrose (**8**) was considered to be a more convenient starting-material of 4-substituted sucrose derivatives, since it is obtained directly from sucrose by selective pivaloylation[6]. Oxidation of **8** with methyl sulphoxide–acetic anhydride[7,8] was complete in 36 h at ambient temperature and gave 61% of the 4-ulose **9**. The mass spectrum of **9** contained peaks for two major fragment ions at *m/z* 499 and 413, as expected from cleavage of the interglycosidic bond; the ^{1}H-n.m.r. spectrum confirmed the loss of H-4. In order to avoid methylthiomethyl ether and other impurities, the oxidation of **8** with pyridinium dichromate–acetic anhydride in dichloromethane[9] was investigated. The reaction was complete in 1 h at room temperature, giving 88% of the syrupy **9**.

Treatment of **9** with an excess of methylmagnesium iodide in ether for 2 h gave two products in yields of 38 and 43% after chromatography. The mass spectra revealed that these products were isomeric 4-*C*-methyl derivatives (**10** and **11**), with

fragment ions at *m/z* 499 (Fru*f*.Pv_4) and at 429 (Glc*p*.Pv_3.CH_3). The 200-MHz ^{1}H-n.m.r. spectrum (Table II) of the faster moving isomer had an H-2 resonance that was 0.3 p.p.m. upfield of that of the slower isomer, suggesting that the former was the *gluco*-isomer **10** and the latter the *galacto*-isomer **11** with an axial HO-4. The ^{13}C-n.m.r. spectra of **10** and **11** confirmed these structural assignments, since the 4-*C*-methyl resonances appeared at 15.5 and 21.4 p.p.m., respectively (Table I).

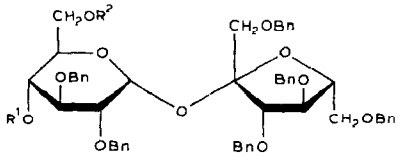
A solution of **9** in tetrahydrofuran reacted with allylmagnesium iodide to

TABLE II

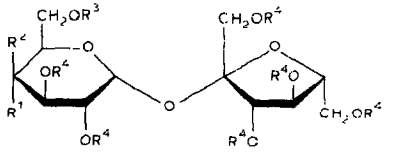
FIRST-ORDER ^{1}H-N.M.R. DATA (δ AND Hz)

Atom	**9**[a,c]	**7**[a,b]	**10**[a,b]	**11**[a,b]	**12**[b,d]
H-1	5.94d	5.70d	5.57d	5.68d	5.65d
H-2	5.51dd	5.15dd	4.93dd	5.22dd	5.26dd
H-3	5.98d	5.30d	5.47d	5.30d	5.43d
H-1a					4.03d
H-1b					3.93d
H-3′	5.89d	5.50d	5.54d	5.54d	5.53d
H-4′	5.72t	5.35d	5.34t	5.38t	5.32t
$J_{1,2}$	3.3	3.5	3.9	3.1	3.9
$J_{2,3}$	11.0	10.5	10.9	10.0	10.4
$J_{1a,1b}$				11.9	11.7
$J_{3',4'}$	7.2	5.0	7.3	7.9	7.5
$J_{4',5'}$	7.6	5.0	7.5	7.9	7.1

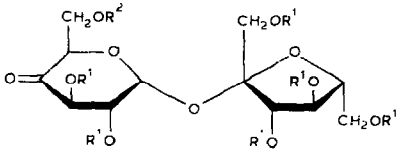
[a]At 200 MHz. [b]In $CDCl_3$ at room temperature. [c]In C_6D_6 at room temperature. [d]At 250 MHz; allyl resonances at δ 5.77 (m, H-2″), 5.16 (dd, H-3″a), and 5.11 (dd, H-3″b).



1 R^1 = R^2 = H
2 R^1 = H, R^2 = Tr



4 R^1 = OH, R^2 = Me, R^3 = Tr, R^4 = Bn
5 R^1 = Me, R^2 = OH, R^3 = Tr, R^4 = Bn
6 R^1 = Me, R^2 = OH, R^3 = R^4 = H
7 R^1 = Me, R^2 = OAc, R^3 = R^4 = Ac
8 R^1 = OH, R^2 = H, R^3 = R^4 = $COCMe_3$
10 R^1 = OH, R^2 = Me, R^3 = R^4 = $COCMe_3$
11 R^1 = Me, R^2 = OH, R^3 = R^4 = $COCMe_3$
12 R^1 = $CH_2CH{=}CH_2$, R^2 = OH, R^3 = R^4 = $COCMe_3$



3 R^1 = Bn, R^2 = Tr
9 R^1 = R^2 = $COCMe_3$

yield one major product (61%). The mass and n.m.r. spectra confirmed that it was the expected 4-*C*-allyl derivative **12**, and the low-field resonance in the 200-MHz ^{1}H-n.m.r. spectrum due to H-2 (δ 5.26) was consistent with the *galacto* configuration. Allylmagnesium iodide was therefore more stereospecific than methylmagnesium iodide in the Grignard reaction with **9** to give the product (**12**) with the 4-allyl substituent equatorial.

EXPERIMENTAL

Optical rotations were measured in 1-dm tubes at 589 nm on either an Optical Activity Automatic p70-7 or a Perkin–Elmer 141 polarimeter. T.l.c. was performed on Kieselgel 60 F_{254} (Merck) with detection by u.v. light or charring with sulphuric acid. Column chromatography was carried out with Kieselgel 60 (7734, Merck). Methyl sulphoxide, dried by storing over powdered calcium hydride, was distilled and stored over molecular sieves (type 4A, B.D.H.) Pyridine, dried by refluxing 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 Nicolet NT-200, Bruker WM-250, or Varian 220-MHz spectrometer; ^{13}C-n.m.r. spectra were recorded with a Bruker WM-250 (62.89 MHz) or WP-60 F.t. (15.08 MHz) spectrometer. Mass spectra were recorded with A.E.I. MS-30 and MS-35 spectrometers at 70 eV with a DS50 data processing system.

*2,3-Di-*O*-benzyl-6-*O*-trityl-α-*D*-glucopyranosyl 1,3,4,6-tetra-*O*-benzyl-β-*D*-fructofuranoside* (**2**). — A solution of **1** (ref. 3) (4 g), trityl chloride (1.4 g, 1.1 mol), triethylamine (1.2 mL), and 4-dimethylaminopyridine (40 mg) in dry *N,N*-dimethylformamide (40 mL) was stirred at room temperature for 18 h. T.l.c. (ether–light petroleum, 1:1) then showed a single product. The mixture was poured into ice–water (200 mL) and extracted with ether (2 × 50 mL), and the combined extracts were washed with saturated aqueous ammonium chloride and water, dried ($MgSO_4$), and concentrated to dryness. Elution of the residue from silica gel with light petroleum–ether (3:2) gave **2**, isolated as a syrup (4.6 g, 90%), $[\alpha]_D$ +31° (*c* 1.2, chloroform) (Found: C, 77.75; H, 6.25. $C_{73}H_{72}O_{11}$ calc.: C, 77.95; H, 6.4%).

*2,3-Di-*O*-benzyl-4-*C*-methyl-6-*O*-trityl-α-*D*-galactopyranosyl 1,3,4,6-tetra-*O*-benzyl-β-*D*-fructofuranoside* (**5**). — A solution of **2** (2 g) in acetic anhydride–methyl sulphoxide (30 mL, 3:2) was stirred, with exclusion of moisture, at 70° for 3 h. The mixture was allowed to cool to room temperature, cold water (100 mL) was added, and the mixture was stirred for 30 min. The aqueous phase was decanted and a solution of the residue in ether (50 mL) was washed with saturated aqueous sodium hydrogencarbonate and water, dried ($MgSO_4$), and concentrated. The residue was further dried by distillation of toluene therefrom, and then a solution in anhydrous ether (40 mL) was added to a solution of methylmagnesium iodide at −78° prepared from magnesium (2 g), methyl iodide (7 mL), and ether (40 mL). The mixture was stirred at −78° until t.l.c. (ether–light petroleum, 1:1) showed the

disappearance of **2** and the formation of a single product (~2 h). The mixture was allowed to attain room temperature and then treated with aqueous 80% ammonium chloride (200 mL). The ether layer was separated, washed with water, dried ($MgSO_4$), and concentrated. Elution of the residue from silica gel with light petroleum–ether (2:1) gave **5**, isolated as a syrup (1.6 g, 80%), $[\alpha]_D$ +39° (*c* 1, chloroform) (Found: C, 77.9; H, 6.7. $C_{74}H_{74}O_{11}$ calc.: C, 78.05; H, 6.5%).

*2,3,4,6-Tetra-*O*-acetyl-4-*C*-methyl-α-*D*-galactopyranosyl 1,3,4,6-tetra-*O*-acetyl-β-*D*-fructofuranoside* (**7**). — Compound **5** (0.6 g) was hydrogenated over 5% Pd/C (1.2 g) in methanol (30 mL) at room temperature and atmospheric pressure for 18–24 h, when t.l.c. (acetonitrile–water, 3:1) revealed a single product. The catalyst was removed, the filtrate was neutralised with Amberlite IR-45 (HO^-) resin, filtered, and concentrated, and the resulting syrup was treated with acetic anhydride–pyridine (10 mL), 1:4) in the presence of 4-dimethylaminopyridine (100 mg). After stirring at 50° for 36 h, the mixture was processed in the usual way, using chloroform as extractant. Chromatography (ether–light petroleum, 3:1) of the product gave **7**, isolated as a syrup (30 mg, 8% based on **5**), $[\alpha]_D$ +83° (*c* 0.8, chloroform) (Found: C, 50.4; H, 5.85. $C_{29}H_{40}O_{19}$ calc.: C, 50.3; H, 5.8%).

*2,3,6-Tri-*O*-pivaloyl-α-*D*-xylo-hexopyranosyl-4-ulose 1,3,4,6-tetra-*O*-pivaloyl-β-*D*-fructofuranoside* (**9**). — (*a*) A solution of 2,3,6,1′,3′,4′,6′-hepta-*O*-pivaloylsucrose[7] (**8**; 1.5 g, 1.6 mmol) in methyl sulphoxide (20 mL) was stirred with acetic anhydride (10 mL) at ambient temperature for 36 h, when t.l.c. (ether–light petroleum, 1:1) indicated total conversion of **8** into a major faster-moving product and some minor components. The mixture was poured into ice–water and extracted with ether. The etheral layer was concentrated to a syrup, chromatography (ether–light petroleum, 1:10) of which gave **9** (0.9 g, 62%, $[\alpha]_D$ +53° (*c* 1, chloroform) (Found: C, 61.5; H, 8.5. $C_{47}H_{76}O_{18}$ calc.: C, 61.8; H, 8.45%). Mass spectrum: *m/z* 413 and 499.

(*b*) To a solution of **8** (8 g, 8.6 mmol) in dichloromethane (100 mL) at 0° was added crystalline pyridinium dichromate (12.8 g, 34.4 mmol). After 5 min, the mixture was stirred with acetic anhydride (34.4 mmol) at room temperature for 1 h. T.l.c. (ether–light petroleum, 1:2) then indicated a single fast-moving product and the absence of **8**. The reaction was stopped by cooling in an ice-bath and by the addition of water (5 mL). Further addition of ether (100 mL) promoted rapid precipitation of the chromium complexes. The mixture was then filtered (Hyflo-supercel) and concentrated to dryness to give a crude brown syrup, which on column chromatography (ether–light petroleum, 1:8) afforded **9** (7 g, 88%).

Reaction of **9** *with methylmagnesium iodide in ether.* — To a solution of methylmagnesium iodide, prepared from methyl iodide (1.2 mL, 8.4 mmol), magnesium (0.2 g, 8.4 mmol), and sodium-dried ether (50 mL), cooled in an ice-bath, a solution of **9** (1.2 g, 1.3 mmol) in sodium-dried ether (20 mL) was added dropwise. After 5 min, the mixture was stirred at room temperature for 2 h. T.l.c. (ether–light petroleum, 1:2) indicated that two major products had been formed together with some de-esterified slower-moving components. The reaction was

stopped by the addition of cold aqueous 10% hydrochloric acid (300 mL), the products were extracted with ether, and the extract was washed with saturated aqueous sodium hydrogencarbonate and water, dried ($MgSO_4$), and concentrated. The syrupy residue was treated with pivaloyl chloride (10 mL) and pyridine (20 mL). After 24 h, t.l.c. (ether–light petroleum, 1:2) revealed two major products and the absence of starting material. The mixture was worked-up by ether extraction, and column chromatography (ether–light petroleum, 1:6) of the product yielded, as the faster-moving component, 4-*C*-methyl-2,3,6-tri-*O*-pivaloyl-α-D-glucopyranosyl 1,3,4,6-tetra-*O*-pivaloyl-β-D-fructofuranoside (**10**; 0.47 g, 38%), $[\alpha]_D$ +59° (*c* 0.6, chloroform). Mass spectrum: *m/z* 499 (Fru*f*Pv_4^+) and 429 (Glc*p*Pv_3Me^+) (Found: C, 61.4; H, 8.35. $C_{48}H_{80}O_{18}$ calc.: C, 61.0; H, 8.5%).

Further elution with ether–light petroleum (1:4) yielded 4-*C*-methyl-2,3,6-tri-*O*-pivaloyl-α-D-galactopyranosyl 1,3,4,6-tetra-*O*-pivaloyl-β-D-fructofuranoside (**11**; 0.53 g, 43%), $[\alpha]_D$ +48° (*c* 0.7, chloroform). Mass spectrum: *m/z* 499 (Fru*f*Pv_4^+) and 429 (Gal*p*Pv_3Me^+) (Found: C, 61.05; H, 8.45. $C_{48}H_{80}O_{18}$ calc.: C, 61.0; H, 8.5%).

*4-C-Allyl-2,3,6-tri-*O*-pivaloyl-α-*D*-galactopyranosyl 1,3,4,6-tetra-*O*-pivaloyl-β-*D*-fructofuranoside* (**12**). — To an ice-cold solution of freshly prepared allylmagnesium iodide (23 mmol) in dry tetrahydrofuran (60 mL) was added dropwise a solution of **9** (1.0 g, 1.08 mmol) in dry tetrahydrofuran (10 mL). The mixture was stirred at ambient temperature for 3 h, and t.l.c. (ether–light petroleum, 1:2) then indicated a single slow-moving product with some de-esterified components. The mixture was then cooled, treated with water (3 mL), filtered through Hyflo-supercel, and concentrated. The resulting crude syrup was treated with pivaloyl chloride (10 mL) and pyridine (25 mL) for 18 h. T.l.c. (ether–light petroleum, 1:2) showed a major product with a trace of **9**. The mixture was worked-up in the usual way and column chromatography (ether–light petroleum, 1:6) of the product yielded **12** (0.64 g, 61%), $[\alpha]_D$ +36° (*c* 0.5, chloroform). Mass spectrum: *m/z* 499 and 455 (Found: C, 62.1; H, 8.25. $C_{50}H_{82}O_{18}$ calc.: C, 61.9; H, 8.45%).

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