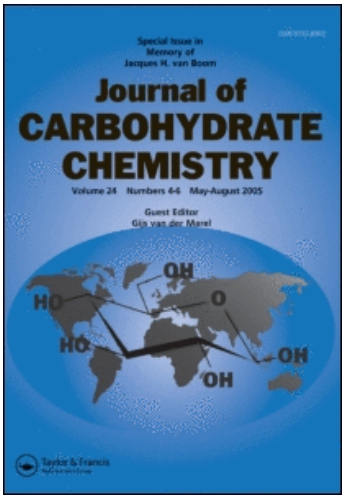


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# Selective Reactions of the Free Hydroxyl Groups of 2,3,4,3',4'-Penta-*O*-Benzylsucrose

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# SELECTIVE REACTIONS OF THE FREE HYDROXYL GROUPS OF 2,3,4,3',4'-PENTA-*O*-BENZYLSUCROSE

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## ABSTRACT

Selective transformations of the free hydroxyl groups in 2,3,4,3',4'-penta-*O*-benzylsucrose (**1**) were studied. Oxidation of **1** with the Swern reagent followed by reaction with $Ph_3P$=CH-COOMe gave 2,3,4,3',4'-penta-*O*-benzyl-1',6,6'-tris-(*E*)(*C*-carbomethoxymethylene)sucrose (**2**) in ca. 40% as the single product. Reaction of **1** with *p*-nitrobenzoic acid under Mitsunobu conditions gave 6,6'-di-*O*-*p*-nitrobenzoyl-2,3,4,3',4'-penta-*O*-benzylsucrose (**3**) which was easily converted into 2,3,4,3',4'-penta-*O*-benzyl-1'-methoxymethylsucrose (**5**). Reaction of **1** with one equivalent of pivaloyl chloride gave monoprotected 2,3,4,3',4'-penta-*O*-benzyl-6'-*O*-pivaloylsucrose (**6**) [30% with triethylamine or 45% yield in the presence of $(Bu_3Sn)_2O$] together with a small amount of diprotected 2,3,4,3',4'-penta-*O*-benzyl-6,6'-di-*O*-pivaloylsucrose (**7**).

## INTRODUCTION

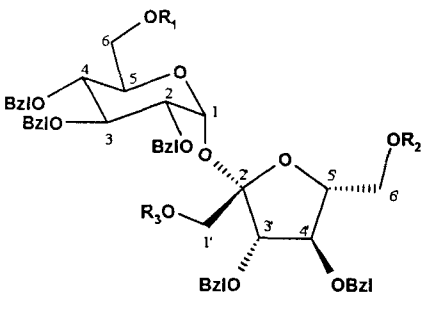
Selective monoacylation of sucrose, with eight free hydroxyl groups, is a significant challenge,[1,2] and only differentiation between primary and secondary hydroxyl groups is

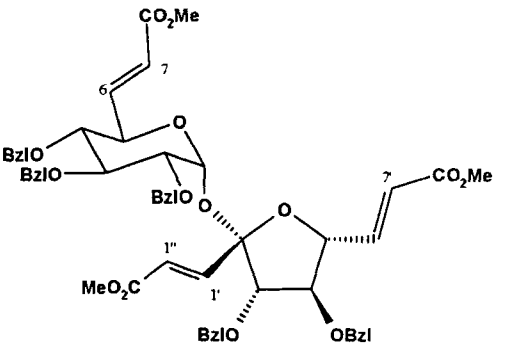
straightforward; for example reaction of sucrose with a large excess of trityl chloride affords 6,6',1'-tri-*O*-tritylsucrose in good yield.[3,4] Also, the glycosidic linkage in sucrose is very sensitive towards acids.[1,2] Nevertheless, some synthetic protocols have been proposed for selective protection of one or more hydroxyl groups of sucrose.[1,2,5-7]

## RESULTS AND DISCUSSION

As a part of our program for conversion of sucrose into useful chiral synthons we elaborated a convenient method for the preparation of 2,3,4,3',4'-penta-*O*-benzylsucrose (1) in which all secondary hydroxyl groups are protected as the easily removable benzyl ethers (50% overall from sucrose).[8] Some methods for selective transformation of the remaining free primary hydroxyl groups will now be presented.






1. $R_1 = R_2 = R_3 = H$
3. $R_1 = R_2 = p\text{-}NO_2C_6H_4CO\text{-}$, $R_3 = H$
4. $R_1 = R_2 = p\text{-}NO_2C_6H_4CO\text{-}$, $R_3 = MOM$
5. $R_1 = R_2 = H$, $R_3 = MOM$
6. $R_1 = R_3 = H$, $R_2 = Piv$
7. $R_1 = R_2 = Piv$, $R_3 = H$

**2**

Triol **1** was oxidized under Swern conditions[9] to a trialdehyde which upon treatment with (methoxycarbonyl)methylenetriphenylphosphorane furnished (in 40% overall yield)

2,3,4,3',4'-penta-*O*-benzyl-1',6,6'-tris-*C*-carbomethoxymethylene)sucrose (**2**) with *trans* configuration of the double bonds.

To differentiate the free primary hydroxyl groups triol **1** was treated with *a.* triphenylphosphine, diethylazodicarboxylate, and *p*-nitrobenzoic acid and *b.* bulky pivaloyl chloride ($Me_3CCOCl$).

Treatment of triol **1** with an excess of the Mitsunobu reagent (*p*-nitrobenzoic acid\ $Ph_3P$\DEAD)[10] gave 73% of the monoalcohol **3** (*C*-1') having protected (as *p*-nitrobenzoates) at primary hydroxyl groups *C*-6 and *C*-6'. This structure was verified by the high resolution $^1$HNMR spectrum in which the only high field AB pattern at δ: 3.63 and 3.53 ppm (characteristic for not esterified $CH_2OH$ group) could be assigned to unprotected $C(1')H_2OH$. Protection of this alcohol function as a methoxymethyl ether and subsequent hydrolysis of the ester blocks in **4** afforded 2,3,4,3',4'-penta-*O*-benzyl-1'-methoxymethylsucrose (**5**) in overall yield 28% (from **1**), with free OH groups at positions *C*-6 and *C*-6'. When the same sequence of reactions (**1** → **3** → **4** → **5**) was performed without purification of the intermediates (**3** and **4**) the overall yield of **5** increased to 58%.

Selective monoprotection of 2,3,4,3',4'-penta-*O*-benzylsucrose (**1**) was achieved by action of 1 equivalent of the bulky pivaloyl chloride in the presence of triethylamine. Under these conditions 2,3,4,3',4'-penta-*O*-benzyl-6'-*O*-pivaloylsucrose (**6**) was obtained in 30% yield. When the hydroxyl groups were activated with tributyltin oxide[11] ***before*** addition of acylating agent the yield of **6** increased to 45%. In both cases, a small amount of a less polar product, identified as 2,3,4,3',4'-penta-*O*-benzyl-6,6'-di-*O*-pivaloylsucrose (**7**), was isolated.

From these experiments the following reactivity pattern (towards acylation) could be assigned for primary hydroxyl groups in 2,3,4,3',4'-penta-*O*-benzylsucrose (**1**):

$$C\text{-}6'\text{-OH} > C\text{-}6\text{-OH} >> C\text{-}1'\text{-OH}$$

Further studies on the conversion of 2,3,4,3',4'-penta-*O*-benzylsucrose (**1**) into the useful chiral synthons are in progress.

## CONCLUSION

Derivatives of sucrose with the free hydroxyl group(s) at *C*-1' (**3** and **7**), *C*-6 and *C*-6' (**5**), and *C*-6 and *C*-1' (**6**) were prepared by selective protection of 2,3,4,3',4'-penta-*O*-benzylsucrose (**1**).

## EXPERIMENTAL

**General methods.** $^1$HNMR spectra were recorded with a Bruker AM 500 spectrometer for solutions in $CDCl_3$ (internal $Me_4Si$). Mass spectra (LSIMS; *m*-nitrobenzyl alcohol was used as a matrix to which sodium acetate was added) were recorded with a AMD-604 apparatus. Column chromatography was performed on silica gel (Merck, 70-230 mesh). Organic solutions were dried over anhydrous magnesium sulfate.

**2,3,4,3',4'-Penta-*O*-benzyl-1',6,6'-tris-(*E*)(*C*-carbomethoxymethylene)sucrose (2).** To a cooled (-78 °C) solution of oxalyl chloride (3 mL) in methylene chloride (50 mL) DMSO (8 mL) was added dropwise followed by triol **1** (1.59 g, 2.0 mmol in 20 mL of $CH_2Cl_2$). The mixture was stirred for 30 min. at -78 °C, triethylamine (7 mL) was added, stirring was continued at -78 °C for another 15 min and the temperature was gradually raised to 20 °C. Water (30 mL) was added, the organic layer was separated, dried and concentrated. The residue was dissolved in dry benzene (50 mL) to which carbomethoxymethylene-triphenylphosphorane ($Ph_3P$=CH-$CO_2Me$) was added (3.1 g, 9.0 mmol, 1.5 equiv) and the mixture was stirred for 2 days at room temperature. Crude material was purified by column chromatography (hexane - ethyl acetate, 5:1 to 3:1) to afford triester **2** (770 mg, 0.81 mmol, 40.5%) as an oil. $^1$HNMR (for numbering of protons see Scheme) δ 7.10 (d, 1H, $J_{1'1''}$ = 15.6 Hz, H-1'), 6.99 (dd, 1H, $J_{6,7}$ = 15.8 Hz, $J_{5,6}$ = 4.8 Hz, H-6), 6.83 (dd, 1H, $J_{6',7'}$ = 15.7 Hz, $J_{5',6'}$ = 5.7 Hz, H-6'), 6.35 (d, 1 H, H-1''), 6.05 (dd, 1H, $J_{5,7}$ = 1.7 Hz, H-7), 6.03 (dd, 1H, $J_{5',7'}$ = 15.7 Hz, $J_{5',6'}$ = 1.5 Hz, H-7'), 5.22 (d, 1H, $J_{1,2}$ = 3.4 Hz, H-1), 4.06 (dd, 1H, $J_{3,4}$ = 9.1 Hz, $J_{4,5}$ = 9.4 Hz, H-4), 3.99 (d, 1H, $J_{3,4}$ = 7.7 Hz, H-3'), 3.75, 3.70, and 3.66 (3s, 9H, 3 OMe), 3.50 (dd, 1H, $J_{2,3}$ = 9.7 Hz, H-2), 3.22 (dd, 1H, H-3). Mass spectrum *m/z*: 977.3721 [M($C_{56}H_{58}O_{14}$)+$Na^+$ Calcd: 977.3724, 2.5%], 451 (28), 217 (20), 181 (100).

**2,3,4,3',4'-Penta-*O*-benzyl-6,6'-di-*O*-*p*-nitrobenzoylsucrose (3).** To a solution of 2,3,4,3',4'-penta-*O*-benzylsucrose (**1**) (1.18 g, 1.5 mmol) in pyridine (20 mL), triphenyl-phosphine (1.68 g, 6.4 mmol) and *p*-nitrobenzoic acid (840 mg, 5.0 mmol) were added followed by diethyl azodicarboxylate (4.8 mL of ca. 40% solution in toluene). The mixture was stirred at room temperature for 3 h, the solvent was evaporated and the residue was purified by column chromatography (hexane - ethyl acetate, 4:1 to 3:2) to afford alcohol **3** as an oil (1.2 g, 1.1 mmol, 73%). $^1$HNMR δ ca. 8.1 (m, 8H, two *p*-nitrobenzoyl groups), 5.40 (d, 1 H, $J_{1,2}$ = 3.5 Hz, H-1), 3.63 (d, 1H, $J_{1'1'}$ = 12.5 Hz, H-1'), 3.59 (dd, 1H, $J_{3,4}$ = 9.1 Hz,

$J_{4,5}$ = 9.8 Hz, H-4), 3.53 (d, 1 H, second H-1'). Mass spectrum *m/z*: 1113 [M($C_{61}H_{58}O_{17}N_2$)+$Na^+$, 19.5%], 603 (8), 519 (16), 355 (97), 293 (33), 271 (100).

**2,3,4,3',4'-Penta-*O*-benzyl-1'-methoxymethyl-6,6'-di-*O*-*p*-nitrobenzoylsucrose (4).** To a solution of the above prepared **3** (205 mg, 0.188 mmol) in methylene chloride (10 mL), diisopropylethylamine (0.5 mL) was added followed by methoxymethyl chloride (0.3 mL) and the mixture was stirred for 4 h at room temperature. Water was added, the organic layer was separated, washed with water, dried and concentrated, and the residue was subjected to column chromatography (hexane - ethyl acetate, 5:1 to 3:1) to afford protected sucrose **4** as an oil (134 mg, 0.118 mmol, 63%). $^1$HNMR δ ca. 8.1 (m, 8H, both *p*-nitrobenzoyl groups), 5.69 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1), 4.0 (dd, 1H, $J_{2,3}$ = 9.3 Hz, $J_{3,4}$ = 9.0 Hz, H-3), 3.81 and 3.66 [AB pattern of C(1')$H_2$-OMOM, J = 11.2 Hz], 3.56 (dd, 1H, $J_{4,5}$ = 9.8 Hz, H-4), 3.55 (s, 3 H, $CH_2OCH_3$). Mass spectrum *m/z*: 1157 [M($C_{63}H_{62}O_{18}N_2$)+$Na^+$, 26%], 607 (11), 536 (6), 414 (8), 315 (100), 293 (6), 261 (29), 181 (59), 145 (45).

**2,3,4,3',4'-Penta-*O*-benzyl-1'-methoxymethylsucrose (5).** To a solution of **4** (790 mg, 0.7 mmol) in tetrahydrofuran/methanol (1:1 v/v, 15 mL) sodium methoxide (1 mL of ca. 15% solution in methanol) was added and the mixture was stirred at room temperature for 3 h. Toluene (30 mL) and water (15 mL) were added and THF/methanol were distilled off *under vacuum*. The organic layer was separated, dried and concentrated, and the crude product was purified by column chromatography (hexane - ethyl acetate, 2:1 to 1:2) to afford diol **6** as an oil (360 mg, 0.43 mmol, 61.5%). $^1$HNMR δ 5.48 (d, 1H, $J_{1,2}$ = 3.5 Hz, H-1), 4.15 (ddd, 1H, $J_{4,5}$ = 10.1 Hz, $J_{5,6}$ = 1.9 and 5.1 Hz, H-5), 4.00 (dd, 1H, $J_{2,3}$ = 9.7 Hz, $J_{3,4}$ = 9.2 Hz, H-3), 3.94 [dt, 1 H, $J_{4',5'}$ = 8.0, $J_{5',6'}$ = 2.2 Hz (both), H-5'], 3.65 and 3.57 [AB pattern of C(1')$H_2$-OMOM, $J_{AB}$ = 11.2 Hz], 3.65 (dd, 1 H, $J_{6,6}$ = 12.2 Hz, $J_{5,6}$ = 5.1 Hz, one of H-6), 3.57 (d, 1H, $J_{6',6'}$ = 12.6 Hz, $J_{5',6'}$ = 2.2 Hz, H-6'), 3.52 (dd, 1H, H-2), 3.45 (dd, 1H, H-4), 3.30 (s, 3 H, $OCH_3$). Mass spectrum *m/z*: 859.3674 [M($C_{49}H_{56}O_{12}$)+$Na^+$ Calcd: 859.3669, 29%], 355 (9.8), 307 (6), 181 (100).

In a separate experiment, **1** (2.50 g, 3.17 mmol) was converted into **5** as described above in 58% overall yield but, without purification of the intermediates **3** and **4**.

**2,3,4,3',4'-Penta-*O*-benzyl-6'-*O*-pivaloylsucrose (6).** *Method a* To a solution of triol **1** (1.19 g, 1.5 mmol) in dry toluene (10 mL), triethylamine (0.5 mL) and pivaloyl chloride (0.25 mL, 2.1 mmol) were added and the mixture was stirred for 4 days at room

temperature. After usual work-up the crude material was subjected to column chromatography (hexane - ethyl acetate, 3:1 to 3:2) to afford:

2,3,4,3',4'-penta-*O*-benzyl-6,6'-di-*O*-pivaloyl-sucrose (**7**): (85 mg, 0.09 mmol, 6%), $^1$HNMR δ 5.39 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1), 3.60 and 3.49 [AB pattern for C(1')$H_2$OH, $J_{AB}$ = 12.3 Hz), 3.54 (dd, 1H, $J_{2,3}$ = 9.7 Hz, H-2), 1.18 and 1.11 (2s, 2x9H, 2xCMe$_3$). Mass spectrum *m/z*: 983.4550 [M($C_{57}H_{68}O_{13}$)+$Na^+$ Calcd: 983.4557, 17.5%], 767 (10.6), 583 (54.1), 427 (31.2), 335 (47.1), 319 (100), 291 (86.5), 235 (95.3), 229 (87.0), 211 (62.4);

diol **6**: (0.4 g, 0.46 mmol, 30.7% or 53% based on consumed triol **1**). $^1$HNMR data (the assignment is based on the $^1$H-$^1$H COSY spectrum) δ 5.23 (d, 1H, $J_{1,2}$ = 3.5 Hz, H-1), 4.30 and 4.05 [AB pattern for C(6')$H_2$-OPiv, $J_{AB}$ = 11.2 Hz, $J_{5',6'}$ = 6.8 and 6.1 Hz], 3.81 and 3.64 [AB pattern for C(6)$H_2$OH, $J_{AB}$ = 12.1 Hz, $J_{5,6}$ = 2.3 and 4.5 Hz], 3.62 [d, 1 H, $J$ = 12.5 Hz, one of C(1')$H_2$OH], 3.51 (dd, 1 H, $J_{2,3}$ = 9.3 Hz, H-2), 1.13 (s, 9 H, CMe$_3$). Mass spectrum *m/z*: 899 [M($C_{52}H_{60}O_{12}$)+$Na^+$, 10%], 427 (9), 181 (70), 91 (100);

unreacted triol **1** (0.5 g, 0.63 mmol).

*Method b* To a solution of triol **1** (550 mg, 0.69 mmol) in toluene (15 mL) tri-*n*-butyltin oxide (250 mg, 0.51 mmol) was added and the mixture was boiled under reflux with azeotropic removal of water for 8 h. After the solution was cooled to room temperature, pivaloyl chloride (0.1 mL, 0.84 mmol) was added, the mixture was stirred for 2 days at room temperature and then concentrated. The crude material was purified by column chromatography (as in *method a*) to give: **7** (45 mg, 0.047 mmol, 6.8%), **6** (270 mg, 0.31 mmol, 45%, or 53% calculated on consumed **1**) and unreacted **1** (80 mg, 0.1 mmol).



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