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Sławomir Jarosz^a

^a Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44\52, 01-224, Warszawa Published online: 22 Aug 2006.

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

Sławomir Jarosz

Institute of Organic Chemistry, Polish Academy of Sciences Kasprzaka 44\52, 01-224 Warszawa

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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-Obenzylsucrose (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 (Bu₃Sn)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

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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.



Triol 1 was oxidized under Swern conditions⁹ 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 (Me₃CCOCl).

Treatment of triol 1 with an excess of the Mitsunobu reagent (*p*-nitrobenzoic acid Ph₃P\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 ¹HNMR spectrum in which the only high field AB pattern at δ : 3.63 and 3.53 ppm (characteristic for not esterified CH₂OH group) could be assigned to unprotected C(1')H₂OH. 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 $(1 \rightarrow 3 \rightarrow 4 \rightarrow 5)$ 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 oxide¹¹ 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):

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 <u>C-1</u>' (3 and 7), <u>C-6 and C-6</u>' (5), and <u>C-6 and C-1</u>' (6) were prepared by selective protection of 2,3,4,3',4'-penta-O-benzylsucrose (1).

EXPERIMENTAL

General methods. ¹HNMR spectra were recorded with a Bruker AM 500 spectrometer for solutions in CDCl₃ (internal Me₄Si). 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 CH₂Cl₂). 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 carbomethoxymethylenetriphenylphosphorane (Ph₃P=CH-CO₂Me) 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. ¹HNMR (for numbering of protons see Scheme) δ 7.10 (d, 1H, J₁₁₁ = 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, $J_{3,4} = 1.5$ Hz, $J_{5',7'} = 15.7$ 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, $J_{3,4} = 1.5$ Hz, $J_{5',7'} = 1.5$ Hz, $J_{5,7} = 1.5$ Hz, $J_{5,7}$ 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 $[M(C_{56}H_{58}O_{14})+Na^{\dagger} Calcd: 977.3724, 2.5\%], 451 (28), 217 (20), 181 (100).$

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%). ¹HNMR 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(C₆₁H₅₈O₁₇N₂)+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%). ¹HNMR 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')H₂-OMOM, J = 11.2 Hz], 3.56 (dd, 1H, J_{4,5} = 9.8 Hz, H-4), 3.55 (s, 3 H, CH₂OCH₃). Mass spectrum *m/z*: 1157 [M(C₆₃H₆₂O₁₈N₂)+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%). ¹HNMR 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')H₂-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, OCH₃). Mass spectrum *m*/z: 859.3674 [M(C₄₉H₅₆O₁₂)+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). <u>Method a</u> 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%), ¹HNMR δ 5.39 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1), 3.60 and 3.49 [AB pattern for C(1')H₂OH, J_{AB} = 12.3 Hz), 3.54 (dd, 1H, $J_{2,3}$ = 9.7 Hz, H-2), 1.18 and 1.11 (2s, 2x9H, 2xCMe₃). Mass spectrum m/z: 983.4550 [M(C₅₇H₆₈O₁₃)+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). ¹HNMR data (the assignment is based on the ¹H-¹H 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')H₂-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)H₂OH, 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')H₂OH], 3.51 (dd, 1 H, $J_{2,3}$ = 9.3 Hz, H-2), 1.13 (s, 9 H, CMe₃). Mass spectrum *m/z*: 899 [M(C₅₂H₆₀O₁₂)+Na⁺, 10%], 427 (9), 181 (70), 91 (100);

unreacted triol 1 (0.5 g, 0.63 mmol).

<u>Method b</u> 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 <u>method a</u>) 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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