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The *p*-Methoxybenzyl Group as Protective Group of the Anomeric Centre. Selective Conversions of Hydroxy Groups into Bromo Groups in *p*-Methoxybenzyl 2-Deoxy-2-phthalimido-β-D-glucopyranoside

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Selective conversions of hydroxy-groups into bromo-groups in *p*-methoxybenzyl 2-deoxy-2-phthalimido-β-D-glucopyranoside by the triphenylphosphine-tribromoimidazole system are described, as well as new procedures for the removal of the *p*-methoxybenzyl hydroxyl-protecting group.

Selective transformation of polyhydroxy compounds has gained importance with the widespread use of carbohydrates as a cheap and readily available chiral pool.

The reactivity and selectivity of the triphenylphosphine-tri-bromoimidazole system has been demonstrated for carbohydrates.[1] One of the most intriguing results was the high selectivity obtained for substitution in methyl α-D-glucopyranoside, yielding almost exclusively methyl 3,6-dibromo-3,6-dideoxy-α-D-allopyranoside (isolated in 74 % yield). A reasonable explanation for this selectivity is that a cyclic phosphorane intermediate involving O-2 and O-4 is formed, with the molecule in the $^1C_4$ conformation. 1,3-Diaxial steric strain between the methoxy group at C-1 and incoming bromide at C-3 is thus relieved and bromination at C-6 and C-3 takes place *via* phosphonium intermediates at these positions. As the phosphorane cannot be formed for 2-substituted derivatives of glucose, it was of interest to examine the pattern of selectivity for a derivative of this type. Monobromination of *p*-methoxybenzyl 2-deoxy-2-phthalimido-β-D-glucopyranoside (*3*) followed by acetylation gave the corresponding 6-bromo derivative *5* in 76 % yield. Dibromination of *3* gave, after acetylation, 89 % of a 7:3 mixture of the corresponding 4,6-dibromo *6* and 3,6-dibromo derivative *7*. No special selectivity in dibrominations was thus observed for this type of derivative.

The usefulness of *p*-methoxybenzyl as a hydroxyl protecting group for carbohydrates has been demonstrated.[2] This group was readily removed using 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in moist dichloromethane. Preparation and/or cleavage of *p*-methoxybenzyl glycosides are not described in this work. These can easily be prepared using regular Koenigs-Knorr type glycosidation procedures. Cleavage of this group by DDQ was not as straightforward as expected, and usually resulted in incomplete cleavage even in the presence of excess DDQ. Hydride abstraction at the benzylic position is probably less efficient here due to the low electron density at the adjacent anomeric centre. A radical oxidation procedure was thus examined to effect this cleavage. Using either bromine. *N*-bromosuccinimide, or ceric ammonium nitrate (CAN) in dichloromethane-water (9:1), the *p*-methoxybenzyl group of *2* was cleaved with retention of configuration at C-1 to give *4* in about 90 % yield. It was also possible to obtain the β-bromide *1* directly from the *p*-methoxygly-

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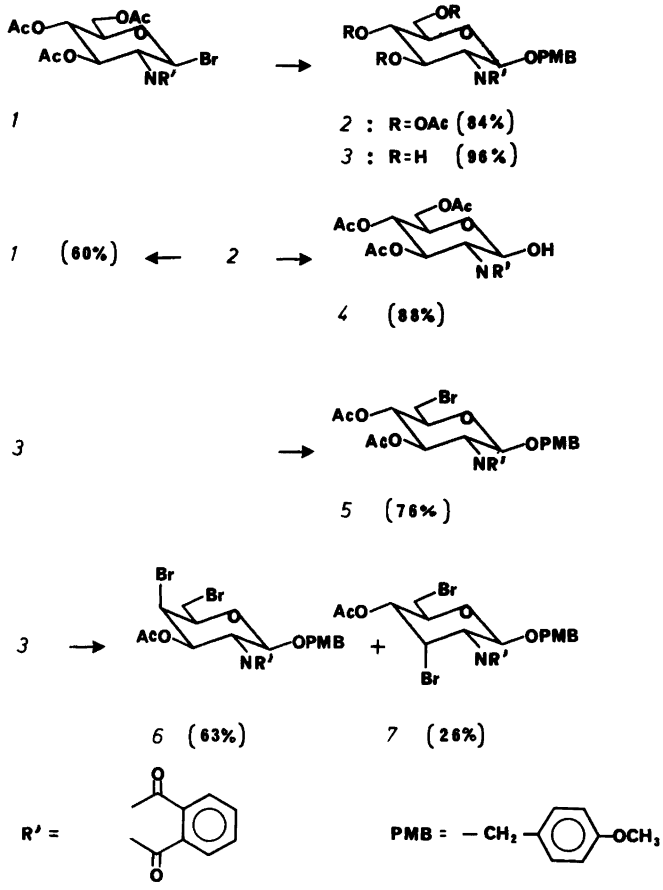
coside *2* using bromine or *N*-bromosuccinimide (NBS) in dry dichloromethane. An (α-bromo-4-methoxy)benzyl glycoside was formed as an intermediate and detected as the corresponding α-hydroxy compound on TLC, disappearing as the reaction went to completion. The β-bromide *1* was separated from *p*-methoxybenzaldehyde by column chromatography and isolated in 60 % yield. Presumably some material was lost during this separation as TLC of the reaction mixture showed little by-product.

The *p*-methoxybenzyl group can thus be used as a temporary protection group at the anomeric centre.

EXPERIMENTAL

General methods were the same as those published elsewhere.[1] p-*Methoxybenzyl 3,4,6-tri-O-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranoside* (2). A solution of 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl bromide (*1*)[3] (7.50 g, 15.1 mmol) in dichloromethane (15 ml) was added dropwise to a cooled (−30 °C), stirred solution of *p*-methoxybenzyl alcohol (2.76 g, 20.0 mmol), silver trifluoromethanesulfonate (5.14 g, 20.0 mmol) and 2,4,6-trimethylpyridine (2.42 g, 20.0 mmol) in dichloromethane (15 ml). During 2 h the temperature was gradually raised to room temperature, after which the reaction was complete. The mixture was diluted with dichloromethane (100 ml), filtered, washed with cold water, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was crystallized from diethyl ether yielding 7.02 g (84 %) of the title compound *2*, m.p. 155 °C, $[\alpha]_D^{22}$ −9.0° (*c* 1, chloroform). Anal. $C_{28}H_{29}NO_{11}$:C,H,N. δ_H (100 MHz, $CDCl_3$): 1.85, 2.02, 2.13 (3s, 9H, OAc); 3.70 (s, 3H, OCH_3); 3.82 (m, 1H, H-5); 4.24 (t, 2H, H-6); 4.34 (dd, 1H, H-2); 5.17 (dd, 1H, H-4);



5.35 (d, 1H, H-1); 5.79 (dd, 1H, H-3). $J_{1,2}$ 8.3, $J_{2,3}$ 10.7, $J_{3,4}$ 8.8, $J_{4,5}$ 9.8 Hz.

p-*Methoxybenzyl 2-deoxy-2-phthalimido-β-*D*-glucopyranoside* (3). *2* (4.6 g, 8.23 mmol) was de-*O*-acetylated overnight in methanol containing a catalytic amount of sodium methoxide. The reaction mixture was neutralized with Dowex 50 (H^+), filtered and concentrated to dryness. The residue was crystallized from ethanol to yield 3.4 g (96 %) of the title compound, m.p. 183 °C, $[\alpha]_D^{22}$ −40° (*c* 1, methanol). Anal. $C_{22}H_{23}NO_8$:C,H,N. δ_H (100 MHz, DMSO-d_6): 5.03 (d, $J_{1,2}$ 8.3 Hz, 1H, H-1).

p-*Methoxybenzyl 3,4-di-*O*-acetyl-6-bromo-2,6-dideoxy-2-phthalimido-β-*D*-glucopyranoside* (5). A mixture of *3* (500 mg, 1.16 mmol), triphenylphosphine (611 mg, 2.33 mmol), tribromoimidazole (426 mg, 1.40 mmol) and imidazole (80 mg, 1.16 mmol) in toluene-pyridine (9:1, 10 ml) was stirred at 70 °C for 1 h and then at 90 °C for 4 h. The reaction mixture was allowed to cool to room temperature and concentrated to dryness at reduced pressure. The residue was acetylated with pyridine-acetic anhydride at room temperature for 2 h. The mixture was concentrated to dryness and purified by silica gel column chromatography with toluene−ethyl acetate (4:1) as eluent to yield 510 mg (76 %) of the title compound, m.p. 142 °C (crystallized from ethanol); $[\alpha]_D^{22}$ −3° (*c* 1, chloroform). Anal. $C_{26}H_{26}BrNO_9$ C,H,Br,N. δ_H (100 MHz, $CDCl_3$): 3.48 (m, 2H, H-6); 3.89 (m, 1H, H-5); 4.34 (dd, 1H, H-2); 5.04 (dd, 1H, H-4); 5.35 (d, 1H, H-1); 5.78 (dd, 1H, H-3). $J_{1,2}$ 8.8, $J_{2,3}$ 10.3, $J_{3,4}$ 8.9, $J_{4,5}$ 9.3 Hz.

p-*Methoxybenzyl 3-*O*-acetyl-4,6-dibromo-2,4,6-trideoxy-2-phthalimido-β-*D*-galactopyranoside* (6) and p-*methoxybenzyl-4-*O*-acetyl-3,6-dibromo-2,3,6-trideoxy-2-phthalimido-β-*D*-allopyranoside* (7). A mixture of *3* (1.00 g, 2.30 mmol), triphenylphosphine (1.84 g, 7.01 mmol) and tribromoimidazole (1.60 g, 5.26 mmol) in toluene (20 ml) was stirred at 90 °C for 4.5 h. The reaction mixture was cooled to room temperature, concentrated and the residue acetylated in pyridine-acetic anhydride. Concentration followed by silica gel column chromatography with toluene−ethyl acetate (4:1) as eluent gave compounds *6* and *7*. *Compound 6* (868 mg, 62 %) had m.p. 124 °C, $[\alpha]_D^{22}$ −12° (*c* 1, chloroform). Anal. $C_{24}H_{23}NBr_2O_7$:C,H,Br,N. δ_H (100 MHz, $CDCl_3$): 3.60 (m, 2H, H-6); 3.90 (m, 1H, H-5); 4.65 (dd, 1H, H-2); 4.89 (dd, 1H, H-4); 5.24 (d, 1H, H-1); 5.64 (dd, 1H, H-3). $J_{1,2}$ 8.8, $J_{2,3}$ 10.7, $J_{3,4}$ 3.9, $J_{4,5}$ 0.9 Hz. *Compound 7* (372 mg, 27 %) was a syrup, $[\alpha]_D^{22}$ +5° (*c* 1, chloroform). Anal. $C_{24}H_{23}NBr_2O_7$: C,H,Br,N. δ_H (100 MHz, $CDCl_3$): 3.5 (m, 2H, H-6); 4.3 (m, 1H, H-5); 4.43 (dd, 1H, H-2); 4.86 (dd, 1H, H-4); 5.04 (dd, 1H, H-3); 6.6 (d, 1H, H-1). $J_{1,2}$ 8.3, $J_{2,3}$ 3.4, $J_{3,4}$ ~0, $J_{4,5}$ 4.6 Hz.

*3,4,6-Tri-*O*-acetyl-2-deoxy-2-phthalimido-β-*D*-glucopyranose* (4) A mixture of *2* (250 mg, 0.450 mmol) and (*a*) *N*-bromosuccinimide (176 mg, 0.99 mmol) in dichloromethane−water (9:1, 5 ml) *or (b)* bromine (158 mg, 0.99 mmol) in dichloromethane−water (9:1, 5 ml) *or (c)* ceric ammonium nitrate (CAN) (543 mg, 0.99 mmol) in acetonitrile−water (9:1, 5 ml), was stirred at room temperature for 1−3 h. The reaction was monitored by TLC using toluene−ethyl acetate (1:1) as eluent. After completion, the reaction mixture was diluted with dichloromethane and washed with water, aqueous sodium hydrogensulfite, aqueous sodium hydrogencarbonate and water. The organic phase was dried (Na_2SO_4), filtered and concentrated to dryness. The residue was crystallized from ethyl acetate-isooctane giving *for (a)* 155 mg in one crop. The mother liquor was concentrated and purified by silica gel chromatography giving an additional 15 mg of the title compound and a total yield of 170 mg (87 %). Procedure (*b*) similarly gave 172 mg (88 %), and procedure (*c*) 172 mg (88 %) of the title compound, m.p. 178 °C, $[\alpha]_D^{22}$+74° (*c* 0.5, chloroform). Anal. $C_{20}H_{21}NO_{10}$:C,H,N. δ_H (100 MHz, $CDCl_3$−D_2O). 4.01 (m, 1H, H-5); 4.25 (m, 2H, H-6); 4.27 (dd, 1H, H-2); 5.18 (dd, 1H, H-4); 5.64 (d, 1H, H-1); 5.85 (dd, 1H, H-3). $J_{1,2}$ 8.3, $J_{2,3}$ 10.8, $J_{3,4}$ 8.8, $J_{4,5}$ 9.5 Hz.

*3,4,6-Tri-*O*-acetyl-2-deoxy-2-phthalimido-β-*D*-glucopyranosyl bromide* (1)[3]. To a solution of *2* (250 mg, 0.45 mmol) in dichloromethane (2 ml) was added bromine (50 μl, 1 mmol) *or N*-bromosuccinimide (176 mg, 1 mmol). The mixture was stirred for 2 h at room temperature after which time TLC indicated that the reaction had gone to completion. The mixture was diluted with dichloromethane (20 ml), washed with aqueous sodium thiosulfate and sodium hydrogencarbonate, dried (Na_2SO_4), filtered and concentrated. The residue was purified by silica gel column chromatography using toluene-ethyl acetate (2:1) as eluent yielding 135 mg (60 %) of *1*, m.p. 122 °C, lit.[3] m.p. 122−123 °C.

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REFERENCES

1. Classon, B., Garegg, P. J. and Samuelsson, B. *Can. J. Chem. 59* (1981) 339.
2. Oikawa, Y., Yoshioka, T. and Yonemitsu, O. *Tetrahedron Lett. 23* (1982) 885.
3. Lemieux, R. U., Takeda, T. and Chung, B. Y. *Am. Chem. Soc. Symp. Ser. 39* (1976) 90.

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