Regioselective Reductive Ring-opening of 4-Methoxybenzylidene Acetals of Hexopyranosides. Access to a Novel Protecting-group Strategy. Part 1.

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Reduction of fully protected 4,6-*O*-(4-methoxybenzylidene) hexopyranosides with sodium cyanoborohydride–trifluoroacetic acid in *NN*-dimethylformamide, or trimethylsilyl chloride in acetonitrile, gives the 6- and 4-*O*-(4-methoxybenzyl) ethers, respectively, in good yield and good regioselectivity. The 4-methoxybenzyl ether linkage in products containing benzyl ethers or other protective groups is selectively cleaved upon treatment with cerium(IV) ammonium nitrate in aqueous acetonitrile.

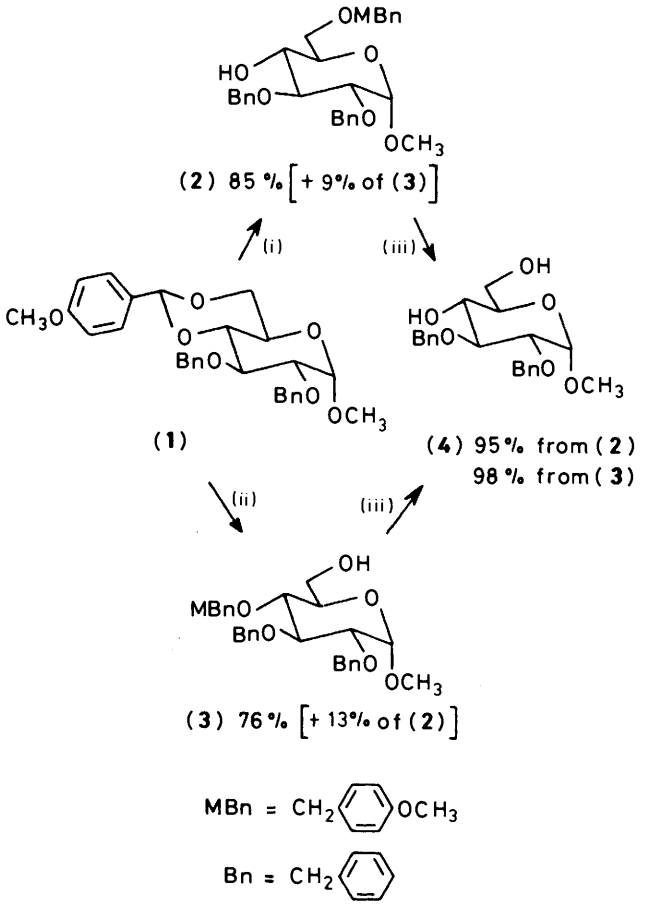
There is an increasing need for new protective groups and protective group strategies as the chemical syntheses of highly complex molecules evolve. Selectivity in introduction and removal under mild conditions in high yields are essential requirements.

Recently the versatility of the 4-methoxybenzyl group for hydroxy-group protection was highlighted.[1,2] It was demonstrated that this group could be cleaved in a selective fashion using 2,3-dichloro-5,6-dicyanobenzoquinone in the presence of other protective groups, including benzyl ethers. We have recently shown that 4-methoxybenzyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranoside could be cleaved with cerium(IV) ammonium nitrate (CAN) in acetonitrile–water (9:1) to give 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranose in 88% yield.[3] This procedure using CAN was, in our hands, found to give better yields than that with 2,3-dichloro-5,6-dicyanobenzoquinone. In the present work the 4-methoxybenzyl ethers methyl 2,3-di-*O*-benzyl-6-*O*-(4-methoxybenzyl)-α-D-glucopyranoside (**2**) and methyl 2,3-di-*O*-benzyl-4-*O*-(4-methoxybenzyl)-α-D-glucopyranoside (**3**) having two benzyl groups in the molecule were selectively cleaved using the CAN procedure to afford compound (**4**) in 95 and 98% yield respectively (Scheme). The 4-methoxybenzyl group, like the benzyl group is generally introduced by etherification using the appropriate benzyl halide and *e.g.* sodium hydride in an *NN*-dimethylformamide (DMF) solution. A regioselective reductive ring-opening of 4-methoxybenzylidene acetals offers an alternative route to 4-methoxybenzyl ethers. and such a report has appeared in the literature.[4] The reductive cleavage of methyl 4,6-*O*-(4-methoxybenzylidene)-2,3-di-*O*-methyl-α-D-glucopyranoside using lithium aluminium hydride–aluminium chloride gave exclusively the 4-*O*-(4-methoxybenzyl) ether.[4]

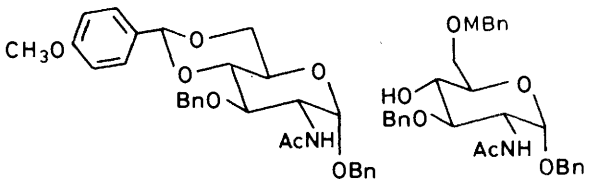
The reductive cleavage of benzylidene acetals of carbohydrates has been extensively studied using the lithium aluminium hydride–aluminium chloride reagent.[5–8] In a series of 4,6-*O*-benzylidene-D-hexopyranosides, reductive cleavage of the 1,3-dioxane ring gave regioselectively the corresponding 4-*O*-benzyl derivative (minor amounts of the 6-*O*-benzyl regioisomers were also formed). The regioselection from this reaction has been associated with the steric bulk exerted by the substituent at O-3 giving kinetic control of the reaction, or 'steric-approach control' of the electrophile.[7]

Recently the sodium cyanoborohydride–hydrogen chloride system has been shown to give the opposite regioselectivity for 4,6-*O*-benzylidene-D-hexopyranosides, giving mainly the 6-*O*-benzyl regioisomer.[9–12] This difference in regioselectivity was explained by assuming that the steric bulk of the electrophile H^+ is small and thus favours thermodynamic protonation of O-4 rather than O-6.[11,12]

We have found that, by suitable choice of solvent and electrophile, the product distribution of regioisomers can be controlled. As 4-methoxybenzylidene acetals are considerably more acid sensitive than benzylidene acetals a polar solvent is necessary in order to stabilize the intermediate 4-methoxybenzylic cation formed in the reaction and avoid hydrolysis. In DMF, a polar and slightly basic solvent, good stereoselectivity and overall yields were obtained using sodium cyanoborohydride–trifluoroacetic acid. Thermodynamic protonation of O-4 by trifluoroacetic acid followed by reduction gives the corresponding 6-*O*-(4-methoxybenzyl) ether (**2**), (**6**), or (**9**).



Scheme. *Reagents:* (i) $Na[B(CN)H_3]$–CF_3CO_2H, DMF; (ii) $Na[B(CN)H_3]$–$(CH_3)_3SiCl$, CH_3CN; (iii) cerium(IV) ammonium nitrate, CH_3CN–water (9:1).



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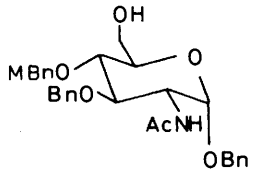

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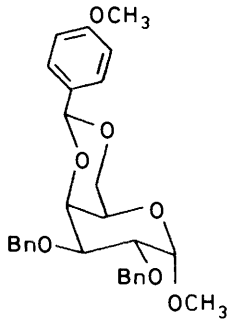

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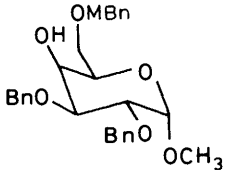

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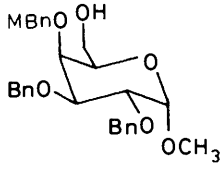

(10)

Table.

Substrate	Reagent[a]	Product	Isolated yield (%)
(5)	(i)	(6)	84
	(ii)	(7)	73
(8)	(i)	(9)	89
		(10)	10
	(ii)	(9)	8
		(10)	83

[a] (i) Sodium cyanoborohydride–trifluoroacetic acid, PMF; (ii) sodium cyanoborohydride–trimethylsilyl chloride, CH_3CN.

Stabilization of the intermediate benzylic cation by DMF is so effective that almost no hydrolysis is observed.

Trimethylsilyl chloride, on the other hand, is a sterically more demanding electrophile than is a proton, thus giving preference for activation of O-6, resulting in the formation of the corresponding 4-*O*-(4-methoxybenzyl) ether (**3**), (**7**), or (**10**). With acetonitrile as solvent this regioselectivity is good, whereas with DMF a *ca.* 1:1 mixture of regioisomers is obtained. The results obtained are summarized in the Scheme and the Table.

Experimental

General Methods.—These were the same as those reported elsewhere.[13] Light petroleum was in the b.p. range 60—80 °C.

4-*Methoxybenzaldehyde Dimethyl Acetal.*—A solution of 4-methoxybenzaldehyde (275 ml, 2.26 mol), trimethyl orthoformate (272 ml, 2.49 mol) and toluene-*p*-sulphonic acid monohydrate (2.15 g, 11.3 mmol) was stirred at room temperature for 18 h. Sodium carbonate (2.4 g, 22.6 mmol) was added and the mixture was stirred for an additional 1 h. The residue was filtered and the methyl formate was distilled off at aspirator pressure without external heating. Distillation of the residue gave the title compound (320 ml, 83%), b.p. *ca.* 100 °C at 7 mmHg; *d* 1.06 g ml^{-1}; n_D^{21} 1.5064.

Methyl 4,6-O-(4-*Methoxybenzylidene*)-α-D-*glucopyranoside*.[14]—A solution of methyl α-D-glucopyranoside (10.0 g, 51.5 mmol), 4-methoxybenzaldehyde dimethyl acetal (14.0 g, 76.8 mmol), and toluene-*p*-sulphonic acid monohydrate (97 mg, 0.48 mmol) in DMF (50 ml) was rotated under aspirator pressure at 50 °C for 2.5 h. The temperature was raised to 70 °C and solvent was distilled off until about 20 ml remained, and the solution was poured onto a stirred mixture of ice (25 g), saturated aqueous sodium hydrogen carbonate (50 ml), and diethyl ether (50 ml). After 0.5 h the solid residue was filtered off, washed successively with light petroleum and water, and dried to give the title compound (12.3 g, 76%). An aliquot was crystallized from ethyl acetate to give an *analytically pure sample*, m.p. 194 °C; $[\alpha]_D^{22}$ +97.4° (*c* 1.0, in DMF) (Found: C, 57.8; H, 6.2. $C_{15}H_{20}O_7$ requires C, 57.7; H, 6.45%); δ_C [$(CD_3)_2SO$; 50 °C] 54.71, 55.05, 62.36, 68.16, 69.96, 72.50, 81.32, 100.52, 100.76, 113.24, 127.57, 130.20, and 159.49 p.p.m.

Methyl 4,6-O-(4-*Methoxybenzylidene*)-α-D-*galactopyranoside*.—A solution of methyl α-D-galactopyranoside (5.0 g, 25.7 mmol), 4-methoxybenzaldehyde dimethyl acetal (12.0 g, 65.8 mmol), and toluene-*p*-sulphonic acid monohydrate (10 mg) in DMF (10 ml) was stirred under aspirator pressure at 50 °C overnight. The mixture was poured into a stirred solution of cold water (100 ml) containing sodium hydroxide (10 mg). After 1 h, the mixture was put in a refrigerator (5 °C) and kept for 24 h. The crystals which had formed were filtered off, washed successively with cold water (10 × 25 ml) and light petroleum (5 × 25 ml), and dried *in vacuo* to give the title compound (5.9 g, 73%). An aliquot was crystallized from ethanol–water, m.p. 139—141 °C; $[\alpha]_D^{22}$ +120° (*c* 1.0 in $CHCl_3$) (Found: C, 55.2; H, 6.4. $C_{15}H_{20}O_7 \cdot 3/4\ H_2O$ requires C, 55.3; H, 6.65%); δ_C[$(CD_3)_2SO$] 54.51, 54.65, 61.96, 67.71, 68.15, 68.15, 68.49, 75.66, 100.03, 100.03, 112.55, 126.98, 130.00, and 159.14 p.p.m.

Benzyl 2-*Acetamido*-2-*deoxy*-4,6-O-(4-*methoxybenzylidene*)-α-D-*glucopyranoside*.—A solution of benzyl 2-acetamido-2-deoxy-α-D-glucopyranoside (3.1 g, 10 mmol), 4-methoxybenzaldehyde dimethyl acetal (4.0 ml, 24 mmol), and toluene-*p*-sulphonic acid monohydrate (5 mg) in DMF (10 ml) was stirred under reduced pressure (30 mmHg) at 70 °C for 16 h. The mixture was poured into ice–water (60 g) containing sodium hydroxide (5 mg) and left in a refrigerator for 24 h. The crystals which formed were filtered off, washed successively with water (5 × 25 ml) and light petroleum (5 × 25 ml), and dried *in vacuo* to give the title compound (4.3 g, 100%). An aliquot was crystallized from DMF–H_2O, m.p. 266—269 °C; $[\alpha]_D^{22}$ +71.6° (*c* 1.05 in pyridine) (Found: C, 62.4; H, 6.2; N, 3.1. $C_{23}H_{27}NO_7 \cdot 3/4\ H_2O$ requires C, 62.3; H, 6.49; N, 3.16%).

Methyl 2,3-*Di*-O-*benzyl*-4,6-O-(4-*methoxybenzylidene*)-α-D-*glucopyranoside* (**1**).—Benzyl bromide (13.8 ml, 115 mmol) was added dropwise to a stirred solution of methyl 4,6-*O*-(4-methoxybenzylidene)-α-D-glucopyranoside (15.0 g, 48.0 mmol) and sodium hydride (4.6 g, 192 mmol) [sodium hydride (50% in oil; 9.2 g) was washed with light petroleum] in DMF (300 ml). After 2 h the reaction was complete and methanol (40 ml) was added dropwise to the mixture. The mixture was diluted with ethyl acetate (600 ml) and washed with water (3 × 200 ml). The combined aqueous phases were extracted with diethyl ether (200 ml) and the combined organic phases were dried ($MgSO_4$),

filtered, and evaporated to dryness. The residue was crystallized from ethanol (500 ml) to give *compound* (**1**) (19.4 g, 82%) in a single crop, m.p. 143—144 °C; $[\alpha]_D^{22}$ −22° (*c* 1.0 in $CHCl_3$) (Found: C, 70.6; H, 6.5. $C_{29}H_{32}O_7$ requires C, 70.7; H, 6.54%); δ_C [$(CD_3)_2SO$; 50 °C] 54.66, 55.05, 62.16, 68.01, 71.86, 73.52, 77.56, 79.17, 81.03, 98.08, 100.37, and 113.34 p.p.m.

Methyl 2,3-*Di*-O-*benzyl*-6-O-(4-*methoxybenzyl*)-α-D-*glucopyranoside* (**2**).—A solution, at 0 °C, of trifluoroacetic acid (10 mmol) in DMF (6 ml) was added dropwise to a stirred mixture containing compound (**1**) (1 mmol), sodium cyanoborohydride (5 mmol), and 3 Å molecular sieves in DMF (8 ml). After 7 h the mixture was filtered through Celite and poured into ice-cold saturated aqueous sodium hydrogen carbonate. The aqueous phase was repeatedly extracted with dichloromethane. The combined extracts were washed with saturated aqueous sodium hydrogen carbonate, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography on silica gel using toluene–ethyl acetate (2:1) as eluant to yield *compound* (**2**) (85%) as a syrup, $[\alpha]_D^{22}$ +7.7° (*c* 1.0 in $CHCl_3$) (Found: C, 70.1; H, 7.0. $C_{29}H_{34}O_7$ requires C, 70.4; H, 6.93%); $\delta_C(CDCl_3)$ 55.14, 55.14, 69.18, 69.91, 70.83, 73.03, 73.12, 75.27, 79.56, 81.41, 98.08, and 113.72 p.p.m. The substitution pattern was confirmed by ^1H n.m.r. homonuclear decoupling experiments on compound (**2**) and on the corresponding 4-*O*-^2H and 4-*O*-Ac derivatives. Regioisomer (**3**) was also obtained (9%).

Methyl 2,3-*Di*-O-*benzyl*-4-O-(4-*methoxybenzyl*)-α-D-*glucopyranoside* (**3**).—A solution, kept at 0 °C, of trimethylsilyl chloride (6 mmol) in acetonitrile (6 ml) was added dropwise to a stirred mixture containing compound (**1**) (1 mmol), sodium cyanoborohydride (6 mmol), and 3 Å molecular sieves in acetonitrile (20 ml). The reaction mixture was stirred for 5 h at room temperature and worked up as described for (**2**) to yield *compound* (**3**) (76%) as a syrup which solidified with time, $[\alpha]_D^{22}$ +19.3° (*c* 1.0 in $CHCl_3$) (Found: C, 70.3; H, 6.9%); $\delta_C(CDCl_3)$ 55.14, 55.14, 61.67, 70.78, 73.27, 74.59, 75.61, 77.17, 80.00, 81.90, 98.08, and 113.82 p.p.m. The substitution pattern was confirmed by ^1H n.m.r. homonuclear decoupling experiments on compound (**3**) and on the corresponding 6-*O*-^2H and 6-*O*-Ac derivatives. Regioisomer (**2**) was also obtained (13%).

Methyl 2,3-*Di*-O-*benzyl*-α-D-*glucopyranoside* (**4**).[15]—A solution of (**2**) or (**3**) (200 mg, 0.40 mmol) and CAN (443 mg, 0.81 mmol) in acetonitrile–water (9:1, 2 ml) was stirred for 30 min at room temperature. The reaction mixture was diluted with dichloromethane (50 ml). The organic phase was washed with saturated aqueous sodium hydrogen carbonate (25 ml), and the aqueous phase was extracted with dichloromethane. The combined organic phases were dried ($MgSO_4$), filtered, concentrated, and subjected to silica gel column chromatography using water-saturated ethyl acetate as eluant to give compound (**4**) [144 mg, 95% from (**2**); 150 mg, 98% from (**3**)], $[\alpha]_D^{22}$ +18.5° (*c* 2.1 in $CHCl_3$) lit.,[15] $[\alpha]_D^{18}$ +18.8°). The ^{13}C n.m.r. spectrum of compound (**4**) was identical with that from an authentic sample.

Benzyl 2-*Acetamido*-3-O-*benzyl*-2-*deoxy*-4,6-O-(4-*methoxybenzylidene*)-α-D-*glucopyranoside* (**5**).—Benzyl bromide (0.30 ml, 2.5 mmol) was dropwise added to a stirred mixture of benzyl 2-acetamido-2-deoxy-4,6-*O*-(4-methoxybenzylidene)-α-D-glucopyranoside (0.43 g, 1.0 mmol), barium hydroxide octahydrate (0.73 g, 2.3 mmol), and 3 Å molecular sieves (1.0 g) in DMF (10 ml). The mixture was stirred for 16 h, diluted with dichloromethane (20 ml), and filtered through Celite. The Celite was washed with dichloromethane (20 ml) and the combined organic phases were washed with water, dried ($MgSO_4$), and evaporated to dryness. The residue was crystallized from ethanol–water to give pure *compound* (**5**) (0.40 g, 77%), m.p. 239—245 °C; $[\alpha]_D^{22}$ +36.6° (*c* 1.3 in pyridine) (Found: C, 69.2; H, 6.4; N, 2.6. $C_{30}H_{33}NO_7$ requires C, 69.3; H, 6.40; N, 2.70%); δ_C[$(CD_3)_2SO$] 22.05, 52.17, 54.46, 62.31, 68.01, 68.98, 73.17, 73.81, 81.80, 97.00, 100.27, and 112.75 p.p.m.

Benzyl 2-*Acetamido*-3-O-*benzyl*-2-*deoxy*-6-O-(4-*methoxybenzyl*)-α-D-*glucopyranoside* (**6**).—Compound (**5**) was treated for 24 h, as described in the synthesis of (**2**), to give the *product* (**6**) (84%), m.p. 123—127 °C; $[\alpha]_D^{22}$ +127° (*c* 1.2 in pyridine) (Found: C, 68.7; H, 6.8; N, 2.8 $C_{30}H_{35}NO_7$ requires C, 69.1; H, 6.76; N, 2.69%); $\delta_C(CDCl_3)$ 23.41, 51.97, 55.34, 69.71, 70.05, 70.59, 72.39, 73.42, 73.90, 79.95, 97.25, and 113.97 p.p.m.

Benzyl 2-*Acetamido*-3-O-*benzyl*-2-*deoxy*-4-O-(4-*methoxybenzyl*)-α-D-*glucopyranoside* (**7**).—Compound (**5**) was treated for 16 h, as described for the synthesis of (**3**), to give the *product* (**7**) (73%), m.p. 185—189 °C; $[\alpha]_D^{22}$ +79° (*c* 0.95 in pyridine) (Found: C, 68.9; H, 6.8; N, 2.7%); $\delta_C(CDCl_3)$ 23.41, 52.80, 55.38, 61.82, 69.81, 71.96, 74.93, 74.93, 78.10, 80.24, 97.35, and 114.11 p.p.m.

Methyl 2,3-*Di*-O-*benzyl*-4,6-O-(4-*methoxybenzylidene*)-α-D-*galactopyranoside* (**8**).—Methyl 4,6-*O*-(4-methoxybenzylidene)-α-D-galactopyranoside (3.0 g, 9.6 mmol) was benzylated as described for (**1**). The crude product was crystallized from ethanol–water to give *pure compound* (**8**) (3.8 g, 81%), m.p. 100—102 °C; $[\alpha]_D^{22}$ +77.3° (*c* 1.8 in $CHCl_3$) (Found: C, 70.4; H, 6.6. $C_{29}H_{32}O_7$ requires C, 70.7; H, 6.54%); $\delta_C(CDCl_3)$ 55.14, 55.38, 62.35, 69.23, 71.95, 73.66, 74.54, 75.41, 75.95, 99.34, 100.81, and 113.38 p.p.m.

Methyl 2,3-*di*-O-*benzyl*-6-O-(4-*methoxybenzyl*)-α-D-*galactopyranoside* (**9**).—Compound (**8**) was treated for 6 h, as described for the synthesis of (**2**), to give the *product* (**9**) (89%) as a syrup, $[\alpha]_D^{22}$ +33° (*c* 2.0 in $CHCl_3$) (Found: C, 69.9; H, 6.9. $C_{29}H_{34}O_7$ requires C, 70.4; H, 6.93%); $\delta_C(CDCl_3)$ 54.90, 54.99, 67.76, 68.35, 69.13, 72.34, 72.93, 73.12, 75.61, 77.46, 98.32, and 113.53 p.p.m. Compound (**10**) was also obtained (10%).

Methyl 2,3-*Di*-O-*benzyl*-4-O-(4-*methoxybenzyl*)-α-D-*galactopyranoside* (**10**).—Compound (**8**) was treated for 30 min, as described for the synthesis of (**3**), to give the *product* (**10**) (83%) as a syrup, $[\alpha]_D^{22}$ −3.8° (*c* 0.9 in $CHCl_3$) (Found: C, 70.1; H, 6.85%); $\delta_C(CDCl_3)$ 55.33, 55.43, 62.50, 70.40, 73.66, 73.66, 74.10, 74.78, 76.63, 79.22, 98.91, and 113.97 p.p.m. Compound (**9**) was also obtained (8%).

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