Regioselective Reductive Ring Opening of 4-Methoxybenzylidene Acetals of Hexopyranosides. Access to a Novel Protective Group Strategy

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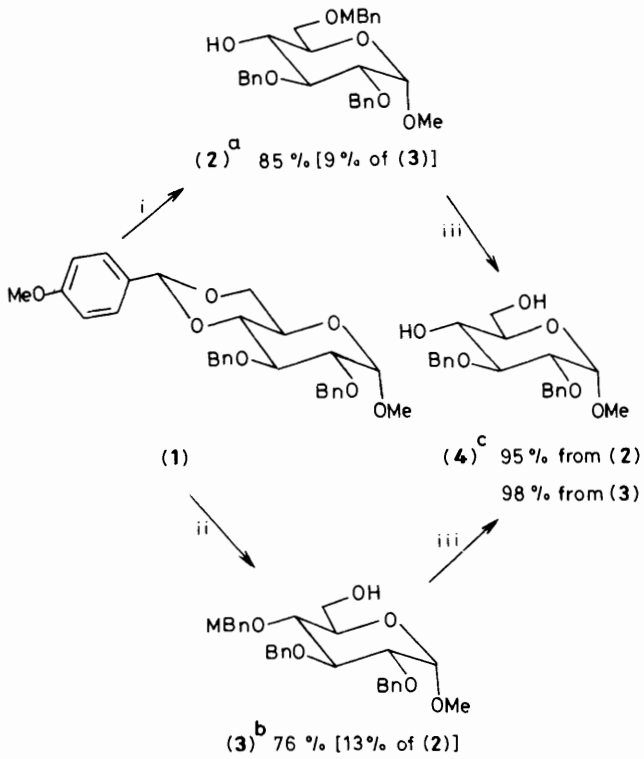
Reduction of fully protected 4,6-*O*-(4-methoxybenzylidene)hexopyranosides with sodium cyanoborohydride–trifluoroacetic acid in *N,N*-dimethylformamide, or with trimethylsilyl chloride in acetonitrile, gives the 6- and 4-*O*-(4-methoxybenzyl) ethers, respectively, in good yields and with good regioselectivity; 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.

Recently the versatility of the 4-methoxybenzyl group for hydroxy protection was highlighted.[1] In the present communication we report on the regioselective introduction of the 4-methoxybenzyl group by reductive ring cleavage of the 1,3-dioxane ring of 4-methoxybenzylidene acetals of carbohydrates. The general type of reaction is well known, and in particular the reductive cleavage of benzylidene acetals using $LiAlH_4$–$AlCl_3$[2] or $NaCNBH_3$–HCl[3] has been extensively studied. In the only report on a stereoselective reductive cleavage of a 4-methoxybenzylidene acetal, methyl 4,6-*O*-(4-methoxybenzylidene)-2,3-di-*O*-methyl-α-D-glucopyranoside was cleaved using $LiAlH_4$–$AlCl_3$ giving exclusively the 4-*O*-(4-methoxybenzyl) ether.[4]

Compounds (**1**) {m.p. 143–144 °C; $[\alpha]_D^{22}$ −22° (*c* 1.0, chloroform)}, (**5**) {m.p. 239—245 °C; $[\alpha]_D^{22}$ 37° (*c* 1.3, pyridine)}, and (**8**) {m.p. 100—102 °C; $[\alpha]_D^{22}$ 77° (*c* 1.8, chloroform)} were prepared by treating the corresponding unprotected hexopyranoside with 4-methoxybenzaldehyde dimethyl acetal in *N,N*-dimethylformamide (DMF) containing a catalytic amount of toluene-*p*-sulphonic acid, and continuously distilling off methanol at room temperature *in vacuo*. Conventional benzylation of the remaining hydroxy groups, followed by crystallization from ethanol or ethanol–water, furnished (**1**), (**5**), and (**8**) in good overall yields.

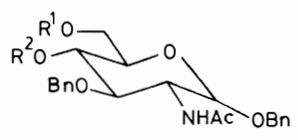
Good regioselectivity in the reductive cleavage of (**1**), (**5**), and (**8**), yielding the 6-*O*-(4-methoxybenzyl) ethers (**2**), (**6**), and (**9**), was attained using sodium cyanoborohydride–trifluoroacetic acid in DMF. To a solution of the (4-methoxybenzylidene) acetal (1 mmol) and sodium cyanoborohyride (5 mmol) in DMF (8 ml) containing powdered 3 Å molecular sieves, was added trifluoroacetic acid (10 mmol) dissolved in DMF (6 ml). When t.l.c. indicated complete reaction (7—18 h), the products were isolated in a conventional manner. The results are given in Scheme 1 and Table 1.

Reversed regioselectivity, giving the 4-*O*-(4-methoxybenzyl) regio-isomers (**3**) and (**7**) or (**10**), was observed when trimethylsilyl chloride was used as electrophile and acetonitrile as solvent. To a solution of the (4-methoxybenzylidene) acetal (1 mmol) and sodium cyanoborohydride (6 mmol) in acetonitrile (20 ml), containing 3 Å molecular sieves, was added dropwise a solution of trimethylsilyl chloride (6 mmol) in acetonitrile (16 ml) at 0 °C. The reaction went to completion in 0.5—18 h (trimethylsilylated product was desilylated during workup). The results are shown in Scheme 1 and Table 1.

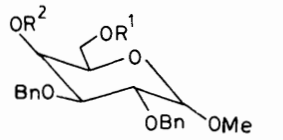


Scheme 1. *Reagents:* (i) $NaCNBH_3$–CF_3CO_2H, DMF; (ii) $NaCNBH_3$–Me_3SiCL, acetonitrile; (iii) cerium(IV) ammonium nitrate, acetonitrile–water (9:1). [a] Oil, $[\alpha]_D^{22}$ 7.7° (*c* 1.0, chloroform); [b] Oil that solidified on standing, $[\alpha]_D^{22}$ 19.3° (*c* 1.0, chloroform); [c] $[\alpha]_D^{22}$ 18.5° (*c* 2.1, chloroform) (lit.,[5] $[\alpha]_D^{18}$ 18.8°).

MBn = *p*-$MeOC_6H_4CH_2$–; Bn = $PhCH_2$–.



(**5**) R^1, R^2 = *p*-$MeOC_6H_4CH<$
(**6**) R^1 = MBn, R^2 = H
(**7**) R^1 = H, R^2 = MBn



(**8**) R^1, R^2 = *p*-$MeOC_6H_4CH<$
(**9**) R^1 = MBn, R^2 = H
(**10**) R^1 = H, R^2 = MBn

Table 1

Starting material	Product	Reagent[e]	% Isolated yield
(**5**)	(**6**)[a]	(i)	84
(**5**)	(**7**)[b]	(ii)	73
(**8**)	(**9**)[c]	(i)	89[f]
(**8**)	(**10**)[d]	(ii)	83[g]

[a] M.p. 123—127 °C, $[\alpha]_D^{22}$ 127° (*c* 1.2, pyridine). [b] M.p. 185—189 °C, $[\alpha]_D^{22}$ 79° (*c* 0.95, pyridine). [c] Oil, $[\alpha]_D^{22}$ 33° (*c* 2.0, chloroform). [d] Oil, $[\alpha]_D^{22}$ −3.8° (*c* 0.9, chloroform). [e] See Scheme 1. [f] + 10% of (**10**). [g] + 8% of (**9**).

The versatility of the (4-methoxybenzyl) ether as a protection group is reflected in the mildness and selectivity of its removal. Thus, the (4-methoxybenzyl) ether in (**2**) and (**3**) (1 mmol) was cleaved by cerium(IV) ammonium nitrate (2 mmol; 30 min) in acetonitrile–water (9 : 1; 4 ml), to give (**4**) in 95 and 98% yield respectively.

The structures of all isolated compounds were in agreement with their ^{1}H and ^{13}C n.m.r. spectra, and elemental analysis.

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