Synthesis and Reduction of Carbohydrate Benzylidene Hemithioacetal Diastereomers with $LiAlH_4$–$AlCl_3$

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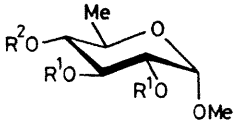
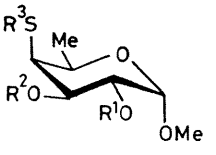
Summary Reduction of methyl 2-*O*-benzyl-*endo*- (**11**) and -*exo*-3-*O*-4-*S*-benzylidene-4,6-dideoxy-4-thio-α-D-galactopyranoside (**12**) gives the same *S*-benzyl derivative (**6**), but with very different reaction rates, indicating that the configuration of the acetal carbon considerably influences the reactivity of the acetal oxygen atoms

THE reduction of carbohydrate benzylidene acetals with $LiAlH_4$–$AlCl_3$ proved to be a useful regioselective benzylation procedure.[1–3] Hydrogenolysis of *cis*-fused dioxolan-type benzylidene acetals takes place *via* two different pathways depending on the configuration of the acetal carbon, the *exo*- and *endo*-isomers giving rise to equatorial and axial *O*-benzyl derivatives, respectively, which are accompanied by small amounts of the other isomer.[2–5] Since the reductive cleavage of non-carbohydrate 1,3-oxathiolans gives sulphides,[6] we have investigated the scope of this reaction in the carbohydrate field.

Compounds (**9**)—(**12**) which, as far as we are aware, are the first representatives of carbohydrate benzylidene hemithioacetals, were synthesized from (**1**)[7] as follows. Tosylation of (**1**) gave (**2**), from which the benzyl groups were readily removed by hydrogenation in acetic acid at atmospheric pressure (Pd on charcoal) to yield (**3**). Acetylation to (**4**), followed by nucleophilic displacement with KSAc in dimethylformamide (DMF) then gave the thio-derivative (**5**) [overall yield (**2**) → (**5**) 71%]. Compound (**5**) was deacetylated and the benzylidene acetal derivatives were subsequently obtained (αα-dimethoxytoluene, DMF, *p*-TsOH) as a mixture of the isomers (**9**) and (**10**), in a ratio of *ca.* 1·5 : 1, which was then separated by column chromatography [yields: (**9**) 53%, (**10**) 32%]. Conventional benzylation of (**9**) and (**10**) afforded (**11**) and (**12**), respectively.



	R^1	R^2
(**1**)	Bn	H
(**2**)	Bn	Ts
(**3**)	H	Ts
(**4**)	Ac	Ts

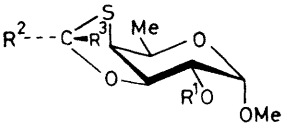


	R^1	R^2	R^3
(**5**)	Ac	Ac	Ac
(**6**)	Bn	H	Bn
(**7**)	Bn	Bn	Ac
(**8**)	Bn	Bn	H

Bn = $PhCH_2$; Ts = *p*-$MeC_6H_4SO_2$

The similar chemical shifts of the benzylidene protons[8] [δ 6·20 for (**9**) and 6·23 for (**10**)] did not permit an unambiguous assignment of the configuration of the acetal carbon. However, the ^3J coupling constants [$J_{2,3}$ 6·9 Hz, $J_{3,4}$ 6·3 Hz for (**9**) and $J_{2,3}$ 8·8 Hz, $J_{3,4}$ 5·8 Hz for (**10**)] showed the same differences as found for the oxygen analogues, in agreement with the tendency of the *endo*-isomers to have a more flattened chair form than the *exo*-isomers, thus making the assignment unambiguous. The significant differences in the ^{13}C n.m.r. spectra of (**9**) and (**10**) [for example δ (C-7) 87·0 for (**9**) and 84·2 p.p.m. for (**10**)] confirmed this assignment by a comparison with the chemical shift values found by us[9] and others[10] for the oxygen analogues.

Reduction with $LiAlH_4$–$AlCl_3$ of the *endo*-benzylidene acetal (**11**) in ether–dichloromethane was complete in less than 5 min at room temperature, while the same reaction of (**12**) required 48 h to go to completion at reflux temperature. Both reactions gave the same *S*-benzyl derivative (**6**), no *O*-benzyl isomer (**8**) [synthesized *via* (**2**) → (**7**) → (**8**)] being detected by g.l.c. or t.l.c. No isomerised acetal (**12**) was detected, either, in the hydrogenolysis of (**11**) These findings thus provide a method for the selective *S*-benzylation of *cis*-SH and -OH groups in glycopyranosides.



	R^1	R^2	R^3
(**9**)	H	H	Ph
(**10**)	H	Ph	H
(**11**)	Bn	H	Ph
(**12**)	Bn	Ph	H

Bn = $PhCH_2$; Ts = *p*-$MeC_6H_4SO_2$

Since no complexation of the Lewis acid takes place at the sulphur atom[6] under the reaction conditions used, the >500-fold enhancement of the reaction rates of (**11**) with respect to (**12**) reflects the very different reactivity of the acetal oxygen atoms upon changing the configuration of the acetal carbon. This observation may explain the high regioselectivity in the hydrogenolysis of dioxolan-type benzylidene acetals.[2–5] Experiments to establish whether this difference derives from the preferred complexation of the Lewis acid on the axial oxygen atoms in the *exo*-benzylidene isomers and on the equatorial oxygen in the *endo*-isomers, or from the preferred formation of one of the possible oxocarbonium ions[11] from the *exo*-isomers and the other ion from the *endo*-isomers, are under way in our laboratory.

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