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Note

Stereoselective preparation of dioxolane-type *endo*-benzylidene acetals by kinetically controlled reactions *,†

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Dioxolane-type benzylidene acetals of pyranoid carbohydrates are readily produced from *cis*(axial/equatorial)-diols in the form of two diastereoisomeric products. The preparative importance of such acetals was increased significantly by the observation that they can be stereoselectively cleaved into monohydroxy benzyl ethers[1].

The conventional procedure for the preparation of dioxolane-type benzylidene acetals (benzaldehyde and zinc chloride) and the method described by Evans[2] (α,α-dimethoxytoluene, *p*-toluenesulfonic acid, DMF, 50–70°C, several hours) afford mixtures of the corresponding *exo* and *endo* isomers in almost equal quantities[3–6]. The synthesis of dioxolane-type benzylidene acetals by the treatment of diols with benzal halides in pyridine at reflux temperature[7] also results in a ca. 1:1 mixture of the *exo* and *endo* acetals. Consequently, the diastereoisomeric products must be separated prior to application in the next synthetic step. In most cases, the *exo* isomer can be easily isolated from the mixture by crystallization in yields of 28–66%[3–6]. In this paper, we report a convenient procedure to synthesize *endo*-benzylidene acetal derivatives of various sugars with high stereoselectivity.

Compounds carrying 2,3- or 3,4-*cis* hydroxyl groups were treated with neat α,α-dimethoxytoluene in the presence of *p*-toluenesulfonic acid (5–10% of DMF was added when the solubility of the starting sugar in α,α-dimethoxytoluene was low). Under such conditions, the acetalation reaction proceeded with high stereoselectivity to afford the *endo*-benzylidene derivatives **1–10** (see Table I). The reaction times were between 5–10 min at room temperature, and the corresponding *exo* isomers could not be detected by TLC, indicating a kinetic control

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TABLE I

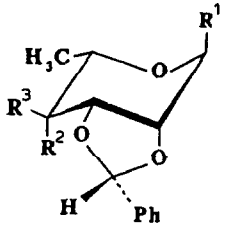
Selected data for compounds **1–10**

Compound [a]	^{1}H NMR [b]	$[\alpha]_D$ [c]	Mp (°C)	R_f [d]	Yield (%)	Ref
p-Nitrophenyl 4-*O*-benzyl-*endo*-2,3-*O*-benzylidene-6-deoxy-α-L-talopyranoside (**1**)	5.91	−76° (*c* 0.31)	syrup	0.46 (*A*)	78	
p-Nitrophenyl 4-*O*-benzyl-*endo*-2,3-*O*-benzylidene-α-L-rhamnopyranoside (**2**)	5.99	−133° (*c* 0.11)	syrup	0.60 (*A*)	81	
Benzyl 4-*O*-benzyl-*endo*-2,3-*O*-benzylidene-6-deoxy-α-L-talopyranoside (**3**)	5.79	−48° (*c* 1.0)	76	0.48 (*B*)	83	8
Methyl 4-*O*-benzyl-*endo*-2,3-*O*-benzylidene-α-L-rhamnopyranoside (**4**)	5.91	−33° (*c* 0.9)	syrup	0.55 (*B*)	77	3
Phenyl 4-*O*-benzyl-*endo*-2,3-*O*-benzylidene-1-thio-α-L-rhamnopyranoside (**5**)	5.87	+12° (*c* 0.25)	101	0.42 (*A*)	76	
Methyl *endo*-3,4-*O*-benzylidene-2-*O*-methyl-1-thio-β-L-fucopyranoside (**6**)	5.93	+17° (*c* 0.99)	syrup	0.74 (*C*)	76	9
Ethyl *endo*-3,4-*O*-benzylidene-2-*O*-methyl-1-thio-β-L-fucopyranoside (**7**)	5.92	+37° (*c* 0.42)	78	0.48 (*A*)	82	
p-Nitrophenyl *endo*-3,4-*O*-benzylidene-6-deoxy-α-L-talopyranoside (**8**)	5.78	−106° (*c* 0.68)	glass	0.39 (*D*)	78	9
Benzyl 2-*O*-benzyl-*endo*-3,4-*O*-benzylidene-β-L-arabinopyranoside (**9**)	5.88	+150° (*c* 0.75)	75	0.30 (*B*)	81	5
Benzyl 2,6-di-*O*-benzyl-*endo*-3,4-*O*-benzylidene-β-D-galactopyranoside (**10**)	5.86	+14° (*c* 0.57)	64	0.47 (*A*)	84	6

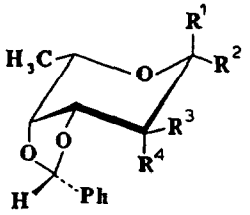
[a] New compounds gave satisfactory elemental analyses. [b] δ Values of benzal protons in $CDCl_3$ (Me_4Si internal standard). [c] In $CHCl_3$. [d] *A*, 7:3 hexane–EtOAc; *B*, 8:2 hexane–EtOAc; *C*, 9:1 CH_2Cl_2–EtOAc; *D*, 1:1 hexane–EtOAc.

operating under these reaction conditions. For dioxolane-type benzylidene acetals[10], the kinetic phase of acetal formation gives the *endo*-phenyl derivative, which gradually equilibrates with the *exo*-phenyl analogue. It appears that the isomerization of the initially formed *endo* isomers is slow under these conditions, and the $t_{1/2}$ values for the isomerization of the benzylidene ring in compounds **1–10** must be greater than 15–30 min. In previous studies[11], the rate of isomerization of the isomeric dioxolane-type benzylidene acetals in CH_2Cl_2 solution catalyzed by $AlCl_3$ has been extensively investigated, and the results showed that substitution of the hydroxyl groups vicinal to the benzylidene ring increases the $t_{1/2}$ values by at least one order of magnitude. These results are in good agreement with our observations: namely, in the case of methyl α-L-rhamnopyranoside[12], the present procedure (in the presence of 10% DMF, 15 min) afforded a 1:1 mixture (GLC) of methyl *endo*/*exo*-2,3-*O*-benzylidene-α-L-rhamnopyranoside[3], but benzylidenation of methyl 4-*O*-benzyl-α-L-rhamnopyranoside[13] (10% DMF, 10 min) yielded compound **4** stereoselectively (*endo*/*exo* = 96:4, determined by GLC). The $t_{1/2}$ values ($AlCl_3$ reaction) for methyl *endo*-2,3-*O*-benzylidene-α-L-rhamnopyranoside and for methyl 4-*O*-benzyl-*endo*-2,3-*O*-benzylidene-α-L-rhamnopyranoside were 4 and 27 min, respectively[11].

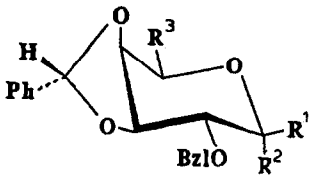
The most welcome result was obtained when *p*-nitrophenyl 6-deoxy-α-L-



1 R^1 = OPNP ; R^2 = OBzl ; R^3 = H
2 R^1 = OPNP ; R^2 = H ; R^3 = OBzl
3 R^1 = OBzl ; R^2 = OBzl ; R^3 = H
4 R^1 = OMe ; R^2 = H ; R^3 = OBzl
5 R^1 = SPh ; R^2 = H ; R^3 = OBzl



6 R^1 = H ; R^2 = SMe
R^3 = OMe ; R^4 = H
7 R^1 = H ; R^2 = SEt
R^3 = OMe ; R^4 = H
8 R^1 = OPNP ; R^2 = H
R^3 = H ; R^4 = OH



9 R^1 = H ; R^2 = OBzl ; R^3 = H
10 R^1 = OBzl ; R^2 = H ;
R^3 = CH_2OBzl

PNP = *p*-Nitrophenyl

talopyranoside[9] was benzylidenated according to this new procedure, furnishing *p*-nitrophenyl *endo*-3,4-*O*-benzylidene-6-deoxy-α-L-talopyranoside[9] (**8**), in a regio- and stereo-selective manner, in 78% (isolated) yield. This compound was then successfully applied for the synthesis of the antigenic tetrasaccharide of *Mycobacterium avium* serovariant 20[9].

In a typical procedure, *p*-toluenesulfonic acid (10 mg) was added to a solution of the sugar (1 mM) in α,α-dimethoxytoluene (2–4 mL). If the solubility of the sugar necessitated, as in the case of the preparation of **4** and **8**, DMF (0.2–0.4 mL) was also added. The mixture was stirred at room temperature for 5–15 min (except for the preparation of **8**, where the reaction time was between 50 min–3 h in different experiments). The mixture was diluted with CH_2Cl_2, and the organic layer was washed with aq $NaHCO_3$ and water, dried (Na_2SO_4), filtered, and concentrated. Column chromatography of the residue then yielded compounds **1–10** (for physical data, see Table I). The structure of the products was proved by ^1H NMR spectroscopy and by direct comparison with authentic samples.

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