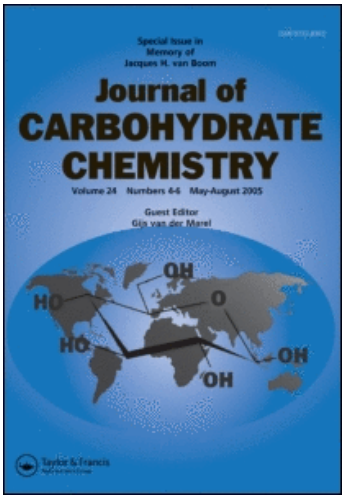

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AN IMPROVED SYNTHESIS AND NMR SPECTRA OF BENZYLATED GLYCALS

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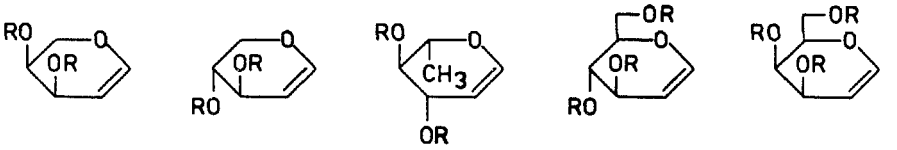
Benzylated glycals, unlike their acylated congeners which easily undergo allylic rearrangement, are frequently employed as reactive enol ether type substrates in a variety of electrophilic addition reactions.[1-4] Although these compounds are considered to be readily available substrates, reported procedures for their syntheses involve some steps of limited efficiency, chromatographic separations or costly reagents,[5-7] and experimental requirements not amenable for large scale preparations. In view of the recent applications of benzylated glycals to syntheses of *O*-glycosides,[1,2] *C*-glycosyl compounds,[3] and *β*-lactams,[4] we have undertaken a study aimed at efficient one step benzylation procedures applicable to pyranoid 1-enitols as well as to their acylated derivatives. This goal was eventually achieved by employing a catalytic phase transfer alkylation system with

benzyl chloride and sodium hydroxide as the principal reagents. Additionally, enhancement of hydroxide ion transfer to an organic phase was sought by introduction of a tertiary alcohol to the reaction mixture. Such a co-solvent has been shown to transport measurable quantities of titratable base into an organic layer in a typical two phase system containing a quaternary ammonium salt as catalyst.[8] This modification, combined with controlled addition of benzyl chloride allowed us to reduce the alkylating agent to sugar substrate ratio and consequently led to considerable decrease in dibenzyl ether formation, which in turn greatly facilitated the isolation procedure. Thus, in a typical example (Procedure B) the entire course of reactions starting from hexopyranose and ending with the corresponding benzylated glycal could be carried out without isolation of intermediate compounds, on a molar scale, affording good yield of crystalline product, without recourse to chromatography.

The stereochemistry of glycals has evoked considerable interest and their conformations in solution were deduced from ^{1}H NMR spectra of acetylated species,[9] while solid state geometry has been determined, for representative examples, by X-ray diffraction.[10]



R=Ac 1 2 3 4 5

TABLE 1. Chemical Shifts (ppm) and Coupling Constants (Hz) Obtained From ^1H NMR Spectra of Benzylated Glycals

	6	7	8	9	10
H-1	6.37 $J_{1,2}$ = 6.0 $J_{1,3}$ = 0.5	6.54 $J_{1,2}$ = 6.2	6.34 $J_{1,2}$ = 6.1 $J_{1,3}$ = 1.1	6.41 $J_{1,2}$ = 6.1 $J_{1,3}$ = 1.1	6.36 $J_{1,2}$ = 6.3 $J_{1,3}$ = 1.7
H-2	4.84 $J_{2,3}$ = 5.3	4.92 $J_{2,3}$ = 4.6 $J_{2,4}$ = 1.4	4.84 $J_{2,3}$ = 2.5	4.86 $J_{2,3}$ = 2.7	4.85 $J_{2,3}$ = 2.9 $J_{2,4}$ = 1.4
H-3	3.99 $J_{3,4}$ = 3.8 $J_{3,5}$ = 1.5	3.84 $J_{3,4}$ = 2.0 $J_{3,5}$ = 1.5	4.20 $J_{3,4}$ = 6.5	4.20 $J_{3,4}$ = 6.0	4.18 $J_{3,4}$ = 4.0
H-4	3.72 $J_{4,5}$ =10.4 $J_{4,5'}$ = 3.8	3.66 $J_{4,5}$ = 4.1 $J_{4,5'}$ = 2.0	3.47 $J_{4,5}$ = 9.1	3.86 $J_{4,5}$ = 8.7	3.94 $J_{4,5}$ = 2.6
H-5	4.04 $J_{5,5'}$ =10.3	4.09 $J_{5,5'}$ =11.7	3.93 $J_{5,6}$ = 6.5	4.05 $J_{5,6}$ = 3.0 $J_{5,6'}$ = 5.1	4.18 $J_{5,6}$ = 5.1 $J_{5,6'}$ = 7.2
H-5'	3.95	3.95	-	-	-
H-6	-	-	1.36	3.75 $J_{6,6'}$ =11.0	3.64 $J_{6,6'}$ =10.1
H-6'	-	-	-	3.80	3.78

Since conformational equilibria of the two half-chair forms ($^4H_5$ and $^5H_4$) of acetylated glycals are characterized by a low energy interconversion barrier and because stereoelectronic factors governing the position of equilibria are not fully understood, we have decided to record high field ^1H NMR spectra of the obtained benzylated

TABLE 2. ^{13}C NMR Chemical Shifts for Benzylated Glycals (ppm)

Compound	6	7	8	9	10
C-1	146.51	146.64	144.77	144.71	144.15
C-2	98.81	98.99	100.13	99.95	99.95
C-3	66.89	69.30	76.47	76.80	75.71
C-4	73.37	72.90	79.57	74.46	71.45
C-5	63.26	64.00	73.94	75.74	70.78
C-6	-	-	17.48	68.58	68.44
CH_2Ph	71.06	71.26	70.46	70.43	70.89
	70.84	69.99	73.97	73.49	73.28
				73.68	73.38

glycals for comparison with available spectral data. (TABLE 1)

^{13}C NMR Spectra were also recorded and assignments presented in TABLE 2 were confirmed by HETCOR experiments. Examination of the coupling constants between pyranoid ring protons leads to the conclusion that compounds **6**, **7**, and **8** in deuteriochloroform solutions mainly exist in an $^5H_4$ conformation. On the other hand for glucal **9** and galactal **10**, equilibria in which the $^4H_5$ forms preponderate should be postulated. In general, conformational preferences found for benzylated glycals coincide with those determined for acetylated derivatives. Comparison of the two sets of ^1H NMR data allows us to conclude, that the "allylic effect" of the benzyloxy substituent at C-3 plays a minor role in influencing the position of conformational equilibria, which in turn support arguments favouring a polar origin of this effect.

EXPERIMENTAL

Melting points were determined on a Koefler type apparatus and are uncorrected. Optical rotations were measured with an IASCO DIP-360 digital polarimeter. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AM 500 spectrometer. Assignments of ^{13}C signals were confirmed in HETCOR experiments. TLC was performed on silica gel plates (Merck DC Alufolien Kieselgel $60F_{254}$) in benzene - ethyl acetate solution.

Procedure A. To a solution of an acetylated glycal (10 mmol) in benzene (20 mL) were added concentrated (ca 50%) aqueous sodium hydroxide (20 mL), *tert*-butyl alcohol (0.5 mL) and tetra n-butylammonium hydrogen sulfate (0.64 g, 2 mmol). The mixture was warmed to 50°C and benzyl chloride (2 equivalents for each acetoxyl group) in benzene (5 mL) was added very slowly (4-6 h) with vigorous stirring. Throughout addition of the alkylating agent and then during the next four h the temperature of the reaction mixture was mantained between 50-55 °C. Progress of the reaction was conveniently monitored by TLC. After cooling the reaction mixture, layers were separated, and the aqueous layer was extracted with benzene (2 x 20 mL), and than the combined organic layers were washed with water (2 x 50 mL), dried with anhydrous magnesium sulfate and concentrated. The benzylated glycal crystallizes from the oily residue and can be separated by filtration followed by washing with a small amount of cold pentane.

Procedure B. The crude reaction mixture, obtained in the standard glycal preparation,[11] was subjected was exhaustive extraction with toluene without prior removal of the zinc suspension. Easily separated toluene layers are combined, washed, dried and concentrated to a small volume. This residue is treated as a substrate solution in procedure A.

1,5-Anhydro-3,4-di-O-benzyl-2-deoxy-L-erythro-pent-1-enitol (6). Procedure A. Yield 79%; oil; $[\alpha]_D^{25}$ -294.3° (*c*

1, CH_2Cl_2); $[\alpha]_D^{23}$ -210.2° (*c* 1.1, $CHCl_3$). lit.[12] $[\alpha]_D^{23}$ -192.8° (*c* 1.03, $CHCl_3$).

Anal. Calcd for $C_{19}H_{20}O_3$: C, 76.99; H, 6.82. Found: C, 77.10; H, 6.75.

1,5-Anhydro-3,4-di-O-benzyl-2-deoxy-D-threo-pent-1--enitol (7). Procedure A. Yield 73%; mp 30-32 °C; $[\alpha]_D^{25}$ -239.9° (*c* 1, CH_2Cl_2); $[\alpha]_D^{23}$ -156.5° (*c* 1, $CHCl_3$) lit.[13] $[\alpha]_D^{23}$ -148.6° (*c* 1.5, $CHCl_3$). Anal. Calcd for $C_{19}H_{20}O_3$: C, 76.99; H, 6.82. Found: C, 76.83; H, 7.23.

1,5-Anhydro-3,4-di-O-benzyl-2,6-dideoxy-L-arabino-hex--1-enitol. (8). Procedure A. Yield 84% mp 27-29 °C; $[\alpha]_D^{25}$ 63.6° (*c* 1, CH_2Cl_2); $[\alpha]_D^{23}$ 44.1° (*c* 1, $CHCl_3$). lit.[14] for D-enantiomer $[\alpha]_D$ -33°.

Anal. Calcd $C_{20}H_{22}O_3$: C, 77.4; H, 7.1. Found: C, 77.52; H, 6.99.

1,5-Anhydro-3,4,6-tri-O-benzyl-2-deoxy-D-arabino-hex--1-enitol (9). Procedure B. Yield 70%, (calculated on D-glucose); mp 53-55 °C, lit.[5] 55°C $[\alpha]_D$-2.7° (*c* 10, $CHCl_3$). lit.[5] $[\alpha]_D^{22}$ -2.7° (*c* 16.5, $CHCl_3$).

1,5-Anhydro-3,4,6-tri-O-benzyl-2-deoxy-D-lyxo-hex-1--enitol (10). Procedure B . Yield 70% (calculated from D-galactose), mp 52-54 °C; $[\alpha]_D$ -41.7° (*c* 1, CH_2Cl_2); $[\alpha]_D^{23}$ -48.4 (*c* 1, $CHCl_3$)

Anal. Calcd for $C_{27}H_{28}O_4$: C, 77.86; H, 6.78. Found: C, 78.08; H, 6.94.

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