A Convenient Synthesis of Carbohydrate Methylene Acetals

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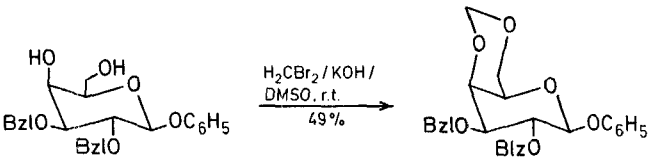
Acetalization is one of the most useful reactions in carbohydrate chemistry for the synthesis of partially blocked derivatives[1,2]. While the acid-catalyzed acetalization and trans-acetalization[3] reactions are the most common procedures for the preparation of different acetals, these reactions result only in very poor yield in the case of methylene derivatives[4]. Several attempts have been made to produce the desired derivatives under alkaline conditions; Brimacombe et al.[5] used sodium hydride/dibromo- or dichloromethane in dimethylformamide and isolated dioxolane derivatives involving vicinal *cis*- and *trans*-diols. Hanessian et al.[6,7], and more recently Munavu[8], used dimethyl sulfoxide/*N*-bromosuccinimide or dimethyl sulfoxide/bromine systems for the preparation of methylene acetals utilizing the Pummerer rearrangement of an initially formed bromosulfonium ion to give an α-alkoxy sulfoxide intermediate. Phase-transfer catalysis also proved to be a very useful method for the methylenation of catechol[9], and this procedure was applied by Cesare and Gross[10], as well, in the field of carbohydrates for obtaining *cis*-fused methylene derivatives. The preparation of *trans*-fused methylene acetals under phase-transfer conditions was successfully achieved by Kim and Szarek[11].

Oligosaccharide antibiotics[12,13] of the orthosomycin family contain 2,3-*O*-methylene-aldonolactones of different configurations and this finding has initiated new efforts for the synthesis of suitable methylene acetals[14].

We now describe a convenient procedure for the synthesis of different carbohydrate methylene acetals using dibromomethane as the reagent in dimethyl sulfoxide in the presence of fine powdered potassium hydroxide. Application of this system has been found particularly useful for the alkylation of carbohydrate derivatives[15].

Our procedure covers the methylenation of 2,3-di-*O*-alkylhexopyranosides **(1a–d)** in the 4,6-positions and the pentofuranoside **(1e)** in the 3,5-positions to give dioxane-type methylene derivatives **(2a–e)**. The *trans-diequatorial* hydroxy groups in compounds **1f** and **1g**, and the *cis-axial-equatorial* hydroxy groups in compounds **1h–1j** are transformed into dioxolane-type methylene acetals **(2f–j)** in the methylenation reaction.



1a (Ref.[16]) **2a**

In all reaction mixtures the different isomers of the dimers could be also detected by T.L.C., but their quantity did not exceed 5–8%, so we did not attempt their isolation. The I.R. spectra of the compounds did not show hydroxy-stretching frequencies, confirming their entire protection. On the basis of the ^{1}H-N.M.R. spectra, the compounds can be divided into three groups. In the spectra of the dioxane-type methylene derivatives **(2a–e)** the *axial* proton of the dioxane ring resonates at a lower field than the *equatorial* one, and the value of the geminal coupling constant is about 6.5 Hz. In the case of the dioxolane-type methylene derivatives, involving *trans-diequatorial* hydroxy groups **(2f, g)**, the two hydrogens of the methylene group give one sharp singlet[11], whereas two distinct singlets were observed for the methylene protons of those dioxolane derivatives **(2h–j)** which are formed from *cis-axial-equatorial* hydroxy groups. The low-field signals can be assigned to the *endo*-hydrogens, and the high-field signals belong to the *exo* ones.

Optical rotations were measured with a Perkin-Elmer Model 241 automatic polarimeter at room temperature. I.R. spectra were recorded on a Perkin-Elmer 700 spectrophotometer. ^{1}H-N.M.R. spectra were obtained on a JEOL-MH-100 (100 MHz) instrument with TMS as the internal standard. T.L.C. examination was carried out on DC-Alurolle Kieselgel 60F 254 (Merck) layer, and the detection with 50% sulfuric acid.

Phenyl 2,3-Di-*O*-benzyl-4,6-*O*-methylene-β-D-galactopyranoside (2a); Typical Procedure:

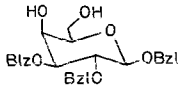
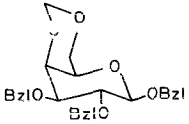
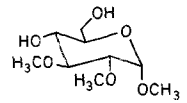
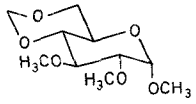
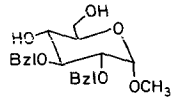
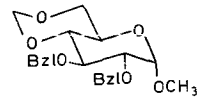
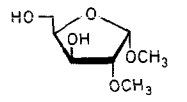
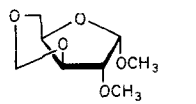
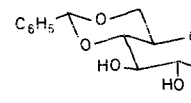
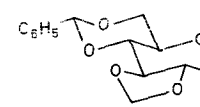
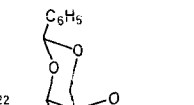
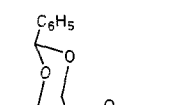
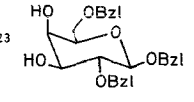
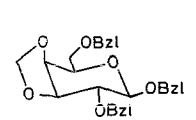
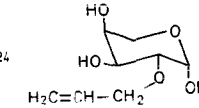
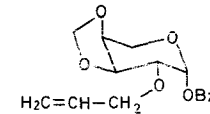
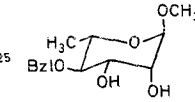
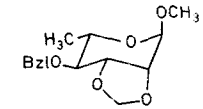
A mixture of phenyl 2,3-di-*O*-benzyl-β-D-galactopyranoside[16] (**1a**; 2.18 g, 0.005 mmol), finely powdered potassium hydroxide (2.24 g, 0.04 mol) and dibromomethane (1.74 g, 0.01 mol) is suspended in dry dimethyl sulfoxide (10 ml) and the mixture is stirred at room temperature. The reaction is monitored by T.L.C., performed on Kieselgel layer with 95 : 5 dichloromethane/acetone as eluent. After the starting material has disappeared (1–2 h) the reaction mixture is diluted with dichloromethane (50 ml), filtered, the filtrate is washed with water (5 × 20 ml), dried with sodium sulfate, and the solvent removed under reduced pressure. The residue is crystallized from ethyl acetate/cyclohexane: yield: 1.10 g (49%); m.p. 178–180°C; $[\alpha]_D$: −44.3° (*c* 0.60, chloroform); R_f: 0.81.

$C_{27}H_{28}O_6$	calc.	C 72.30	H 6.29
(448.5)	found	72.41	6.35

^{1}H-N.M.R. ($CDCl_3$/TMS): δ = 4.68 [d, 1H, J = 6.5 Hz, O—CH_2(*eq*)—O]; 4.72 (s, 2H, CH_2—C_6H_5); 4.80 (dd, 2H, CH_2—C_6H_5); 4.96 (d, 1H, J = 9.0 Hz, H-1); 5.14 [d, 1H, J = 6.5 Hz, O—CH_2(*ax*)—O]; 7.0–7.4 ppm (m, 15 H_{arom}).

0039-7881/82/0532-0421 $ 03.00

Table. Methylene Acetals **2b–j** of Carbohydrates **1b–j** prepared

Substrate (Reference)	Product	Yield [%]	m.p. [°C] (solvent)	$[\alpha]_D$ (*c*, $CHCl_3$)	R_F (solvent)	Molecular Formula[a]	^{1}H-N.M.R. ($CDCl_3$/TMS) δ [ppm]
1b[17] 	**2b** 	37	118–119° (*c*-C_6H_{12})	−58.4° (0.63)	0.56 (9:1 CH_2Cl_2/C_2H_5OAc)	$C_{28}H_{36}O_6$ (462.5)	3.43 (dd, H-3, J = 10.1 Hz, 3.7 Hz); 3.90 (dd, H-2, J = 8.0 Hz, 10.1 Hz); 4.45 (d, H-1, J = 8.0 Hz); 4.68 [d, 1H, J = 6.4 Hz, OCH_2(*eq*)O]; 5.18 [d, 1H, J = 6.4 Hz, OCH_2(*ax*)O]; 7.3 (m, 15 H_{arom})
1c[18] 	**2c** 	44[b]	87° (C_2H_5OH)	+143.4° (0.61)	0.61 (9:1 CH_2Cl_2/acetone)	$C_{10}H_{18}O_6$ (234.2)	3.43, 3.53, 3.62 (3s, 9H, OCH_3); 4.14 (dd, H-2, J = 3.6 Hz, 10.0 Hz); 4.59 [d, 1H, J = 6.4 Hz, OCH_2(*eq*)O]; 4.82 (d, H-1, J = 4.0 Hz); 5.07 [d, 1H, J = 6.4 Hz, OCH_2(*ax*)O]
1d[19] 	**2d** 	48	syrup	+29.3° (1.08)	0.76 (97:3 CH_2Cl_2/acetone)	$C_{22}H_{26}O_6$ (386.4)	3.31 (s, 3H, OCH_3); 3.5 (m, H-6,6′); 3.7 (m, H-5); 3.94 (t, H-3); 4.08 (dd, H-2); 4.52 [d, 1H, J = 6.0 Hz, OCH_2(*eq*)O]; 4.58 (d, H-1, J = 1.9 Hz); 4.7 (m, $CH_2C_6H_5$); 4.80 (s, $CH_2C_6H_5$); 5.03 [d, 1H, J = 6.0 Hz, OCH_2(*ax*)O]; 7.2–7.4 (m, 10 H_{arom})
1e[20] 	**2e** 	72	119–120° (*c*-C_6H_{12})	+97° (0.69)	0.60 (8:2 CH_2Cl_2/acetone)	$C_8H_{14}O_5$ (190.2)	3.49, 3.52 (2s, 6H, OCH_3); 4.65 [d, 1H, J = 6.5 Hz, OCH_2(*eq*)O]; 5.09 [d, 1H, J = 6.5 Hz, OCH_2(*ax*)O]; 5.32 (d, H-1, J = 4.5 Hz)
1f[21] 	**2f** 	48	106–107° (*c*-C_6H_{12}/C_2H_5OAc)	+118.9° (0.82)	0.79 (9:1 CH_2Cl_2/C_2H_5OAc)	[c]	3.48 (s, 3H, OCH_3); 5.10 (d, H-1, J = 3.0 Hz); 5.16 (s, OCH_2O); 5.58 (s, CHC_6H_5); 7.4 (m, 5 H_{arom})
1g[22] 	**2g** 	36[b]	181–182° (*c*-C_6H_{12}/C_2H_5OAc)	−47.1° (1.34)	0.70 (9:1 CH_2Cl_2/C_2H_5OAc)	$C_{21}H_{22}O_6$ (370.4)	3.4 (m, H-5); 3.39 (dd, H-3, J = 2.4 Hz, 10.0 Hz); 4.00 (dd, H-2, J = 10.0 Hz, 8.0 Hz); 4.10 (dd, H-6, J = 12.8 Hz, 2.0 Hz); 4.40 (dd, H-6′, J = 12.8 Hz, 2.0 Hz); 4.50 (dd, H-4, J = 2.4 Hz, 1.4 Hz); 4.80 (d, H-1, J = 8.0 Hz); 4.9 (m, $CH_2C_6H_5$); 5.10 (s, OCH_2O); 5.55 (s, CHC_6H_5); 7.2–7.4 (m, 10 H_{arom})
1h[23] 	**2h** 	89	96° (*c*-C_6H_{12})	~0° (0.70)	0.70 (95:5 CH_2Cl_2/C_2H_5OAc)	$C_{28}H_{30}O_6$ (462.5)	3.40 (dd, H-3, J = 9.0 Hz, 5.8 Hz); 3.7–3.9 (m, H-5,6,6′); 4.22 (dd, H-4); 4.40 (dd, H-2, J = 8.5 Hz, 9.0 Hz); 4.56 (s, $CH_2C_6H_5$); 4.8 (m, 4H, $CH_2C_6H_5$); 4.93 (d, H-1, J = 8.5 Hz); 4.97 [s, 1H, OCH_2(*exo*)O]; 5.06 [s, 1H, OCH_2(*endo*)O]; 7.4–7.5 (m, 15 H_{arom})
1i[24] 	**2i** 	76[b]	syrup	+232.2° (0.88)	0.82 (95:5 CH_2Cl_2/C_2H_5OAc)	$C_{16}H_{20}O_5$ (292.3)	3.44 (dd, H-3, J = 7.8 Hz, 4.1 Hz); 3.8–4.1 (m, 5H, H-4,5,5′ + CH_2—CH=); 4.32 (dd, H-2, J = 2.9 Hz, 7.8 Hz); 4.7 (m, $CH_2C_6H_5$); 4.93 (d, H-1, J = 2.9 Hz); 4.96 [s, 1H, OCH_2(*exo*)O]; 5.17 [s, 1H, OCH_2(*endo*)O]; 5.2 (m, =CH_2); 5.9 (m, —CH=); 7.3–7.4 (m, 5 H_{arom})
1j[25] 	**2j** 	44[b]	syrup	−66.3° (1.69)	0.78 (95:5 CH_2Cl_2/C_2H_5OAc)	$C_{15}H_{20}O_5$ (280.3)	1.28 (d, CH_3, J = 6.5 Hz); 3.13 (dd, H-4, J = 6.9 Hz, 9.5 Hz); 3.35 (s, OCH_3); 3.7 (m, H-5); 3.88 (dd, H-2, J = ~1 Hz, 5.6 Hz); 4.31 (dd, H-3, J = 5.6 Hz, 6.9 Hz); 4.8 (m, $CH_2C_6H_5$); 4.90 (s, H-1); 4.99 [s, 1H, OCH_2(*exo*)O]; 5.14 [s, 1H, OCH_2(*endo*)O]; 7.2–7.4 (m, 5 H_{arom})

[a] Satisfactory microanalyses obtained: C ±0.34, H ±0.16.

[b] Purified by column chromatography.

[c] Lit.[15], m.p. 118–119°C (ethanol); $[\alpha]_D$: +123° (*c* 0.23, $CHCl_3$); Lit.[11], m.p. 104–105°C (ether); $[\alpha]_D$: +122.9° (*c* 0.21, $CHCl_3$).

Compounds **2b–j** were prepared similarly and purified by crystallization or chromatography on a Kieselgel G column using the short column technique and eluting with the same solvent as for the T.L.C. analysis (Table).

Received: November 10, 1981

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0039-7881/82/0532-0423 $ 03.00