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Note

Preparative acetonation of pyranoid, vicinal *trans*-glycols under kinetic control: methyl 2,3:4,6-di-*O*-isopropylidene-α- and -β-D-glucopyranoside

JEAN-LOUIS DEBOST, JACQUES GELAS, DEREK HORTON, AND OLE MOLS
Ensemble Scientifique des Cézeaux (École Nationale Supérieure de Chimie), Université de Clermont-Ferrand, 63170 Aubière (France); and Department of Chemistry, The Ohio State University, Columbus, Ohio 43210 (U.S.A.)

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Previous papers in this series have documented[1] the value of 2-alkoxypropenes for kinetically controlled acetonation of sugars. Aldohexoses are readily converted into the corresponding 4,6-*O*-isopropylidenealdohexopyranoses[2]; those aldohexoses having O-2 and O-3 *cis*-disposed may be preparatively transformed by a larger proportion of the reagent into 2,3:4,6-di-*O*-isopropylidenealdohexopyranoses[1,3].

Vicinal *trans*-glycols in simple pyranoid rings do not generally undergo appreciable conversion into isopropylidene acetals (*trans*-fused 1,3-dioxolanes) under conventional reaction-conditions[4]. Formation of a *trans*-fused, 1,3-dioxolane ring tends to decrease the dihedral angle between the C–O bonds on adjacent carbon atoms, and thereby increase the puckering of the pyranose chair. Even slight distortion in this sense entails a steep energy-barrier, because of aggravation of 1,3-diaxial interactions. Because of this added energy, this type of ring fusion does not generally result under thermodynamically controlled conditions of acetonation. However, kinetically controlled acetalation offers potential for effective formation of 1,3-dioxolane rings *trans*-fused to pyranoid rings. In this paper it is shown, with methyl α- and β-D-glucopyranosides (**1** and **5**) as the examples, that acetonation with 2-alkoxypropenes affords initially, and predictably[5], the 4,6-isopropylidene acetals (**2** and **6**, respectively). Use of an excess of the reagent permits conversion of these glycosides in high yields into the respective 2,3:4,6-diisopropylidene acetals (**4** and **8**) in which the dioxolane ring (2,3-acetal) spans the *trans*-glycol group at C-2 and C-3. Detailed n.m.r.-spectral comparisons of the 4,6-acetals (**2** and **6**), their 2,3-diacetates (**3** and **7**), and the 2,3:4,6-diacetals (**4** and **8**) suggest that the $^4C_1$(D) conformation of the parent aldopyranosides (**1** and **5**) does not undergo major distortion by introduction of the vicinal, *trans*-acetal bridge.

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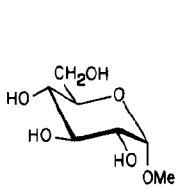

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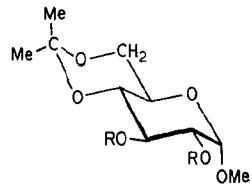

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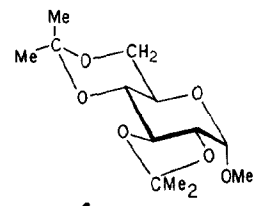

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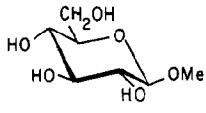

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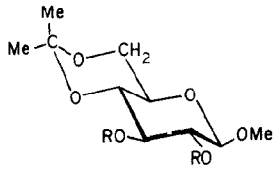

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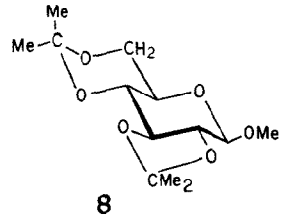
7 R = Ac



8

Acetonation of the α-glucoside **1** was performed essentially under the standard conditions described in the original report[5] with 2 mol of 2-methoxypropene at 0° in *N,N*-dimethylformamide in the presence of a trace of *p*-toluenesulfonic acid. The crystalline methyl 4,6-*O*-isopropylidene-α-D-glucopyranoside (**2**) thus prepared in 90% yield was converted into its crystalline 2,3-diacetate **3**, to provide a reference compound for the n.m.r. studies. Further acetonation of the monoacetal **2** with a 2.5-molar excess of 2-methoxypropene gave the 2,3:4,6-diacetal **4**, isolated crystalline in 70–75% yield; the yield of crude product was almost quantitative. The product had a m.p. and specific rotation essentially identical with the values reported by Evans *et al.*[6], who obtained **4** in 1.5–14% yield as a side-product upon treating the glycoside **1** with 2,2-dimethoxypropane in *N,N*-dimethylformamide in the presence of *p*-toluenesulfonic acid. The diacetal **4** could also be prepared, in good yield, directly from **1** and a suitable excess of 2-methoxypropene, but the procedure by way of the monoacetal **2** (used without purification) was more satisfactory.

In a similar manner, the β-glucoside **5** was converted by the action of a 2-molar excess of 2-methoxypropene into the 4,6-isopropylidene acetal **6**, isolated crystalline in 75% yield; it was identical with the product obtained in 36% yield by Parrish *et al.* [7], by acetonation of **5** with 2,2-dimethoxypropane. The crystalline diacetate (**7**) of **6** was prepared conventionally. Treatment of the monoacetal **7** with a 2.5-molar excess of 2-methoxypropene gave the corresponding, crystalline 2,3:4,6-diacetal **8** in ~65% yield; the yield of crude product was practically quantitative. It gave an acceptable elemental analysis, and could likewise be obtained directly from the glycoside **5**, although preparation *via* the monoacetal **6** was superior.

As indicated earlier, cyclic acetals engaging vicinal *trans*-diols in pyranoid systems have been encountered only rarely[4]. Methylene acetals of *trans*-diols are

TABLE I

PROTON CHEMICAL-SHIFT AND SPIN-COUPLING DATA AT 300 MHz FOR METHYL *O*-ISOPROPYLIDENE-D-GLUCOPYRANOSIDE DERIVATIVES **2–4** AND **6–8**

Compound	*Solvent*	*Chemical shifts (δ)*										
		H-1	*H-2*	*H-3*	*H-4*	*H-5*	*H-6*	*H-6'*	OCH_3	CMe_2	*OAc*	*OH*
2	$CDCl_3$	4.76	3.6	3.77	3.52	3.62	3.88	3.75	3.43	1.52, 1.44		2.60, 2.17
3	$(CD_3)_2CO$	4.89	4.81	5.33	3.82	3.64	3.84	3.78	3.38	1.49, 1.30	1.99, 1.98	
4	C_6D_6	4.82	3.50	4.31	~3.9	~3.7	~3.9	3.74	3.00	1.46, 1.39 1.38, 1.23		
6	$CDCl_3$	4.27	3.44	3.67	3.57	3.27	3.94	3.79	3.56	1.51, 1.44		2.78, 2.68
7[a]	$CDCl_3$	4.45	4.92	5.13	3.73	3.34	3.97	3.79	3.49	1.47, 1.38	2.05, 2.04	
8	$CDCl_3$	4.62	3.39	3.66	3.90	3.28	3.98	3.90	3.57	1.55, 1.47 1.47, 1.44		
		Spin couplings (Hz)										
		$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$				
2	$CDCl_3$	3.9	9.0	9.0	9.0	5.2	9.9	10.4				
3	$(CD_3)_2CO$	3.7	9.7	9.7	9.6	5.8	9.6	10.4				
4	C_6D_6	3.0	9.2	9.2	~9	—	~10	~10				
6	$CDCl_3$	7.7	9.3	9.3	9.3	5.4	10.3	10.3				
7[a]	$CDCl_3$	7.7	9.3	9.3	9.3	5.5	9.9	10.8				
8	$CDCl_3$	7.8	9.3	9.3	8.9	5.5	10.0	10.7				

[a]At 200 MHz.

TABLE II

CARBON-13 CHEMICAL-SHIFT[a] AND $^{13}C-^{1}H$ COUPLING DATA AT 50.3 MHz FOR METHYL *O*-ISOPROPYLIDENE-D-GLUCOPYRANOSIDE DERIVATIVES **2–4** AND **6–8**

Compound	Solvent	*Chemical shifts in δ (one-bond $^{13}C-^{1}H$ couplings, Hz, in parentheses)*															
		C-1	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*OCH_3*	*CMe_2*				*CMe_2*	*$COCH_3$*		*$COCH_3$*	
2	$CDCl_3$	99.89 (169.5)	73.08 (147.2)	71.18 (148.2)	73.55 (144.5)	63.29 (147.0)	62.31 (146.8)	55.36 (143.2)	28.95 (127.9)			18.97 (126.6)	99.80				
3	$(CD_3)_2CO$	98.79 (172.4)	72.55 (148.7)	70.17 (151.0)	72.96 (144.0)	64.63 (144.7)	62.94 (148)	55.57 (143.2)	29.41 (127.0)			19.43 (123.8)	100.51	20.66 (129.4)	20.50 (129.4)	170.76	170.27
4[b]	C_6D_6	99.19 (169.7)	77.30 (145.9)	74.14 (150.2)	74.43 (144.5)	65.27 (148.8)	62.42 (144.2)	54.81 (142.9)	28.95 (127.3)	26.70 (126.5)	26.11 (124.6)	18.64 (126.6)	110.75	99.27			
6	$CDCl_3$	104.31 (158.8)	74.67 (147.5)	73.61 (151.1)	73.27 (146.0)	67.31 (146.0)	62.03 (136.0, 145.1	57.25 (143.5)	28.86 (127.3)			18.93 (126.9)		99.88			
7	$CDCl_3$	102.31 (159.2)	72.48 (151.4)	72.41 (151.7)	71.36 (142.8)	67.34 (141.4)	62.02 (139.7, 151.2)	56.99 (143.7)	28.79 (124.4)			18.78 (126.1)		99.82	20.58 (129.7)	20.58 (129.7)	170.39	169.85
8	$CDCl_3$	103.32 (162.4)	77.85 (147.2)	77.63 (154.1)	72.82 (151.5)	69.80 (146.1)	62.19 (146.1)	56.79 (143.9)	28.82 (127.1)	26.50 (125.4)	26.25 (125.3)	18.98 (126.7)	112.24	99.79			

[a]Assignments were made by selective, heteronuclear decoupling experiments, differential isotope-shifts were also used for **2**. Shifts in $CDCl_3$ are relative to $CDCl_3$ = 77.0 p.p.m., in $(CD_3)_2CO$ to $(CD_3)_2CO$ = 29.80 p.p.m., and in C_6D_6 to C_6D_6 = 128.0 p.p.m. [b]Buchanan *et al.*[11] reported 20-MHz data in $CDCl_3$ for the CMe_2 signals that are in good general agreement with the data given here.

accessible by using irreversible conditions (dichloromethane and strong alkali[8]). The action of 2,2-dimethoxypropane on methyl α-D-xylopyranoside under acid catalysis has recently been shown[9] to give 39% of the 2,3- and 13% of the 3,4-isopropylidene acetal. The same reagent converted[10] 5-thio-D-glucose into 2,3:4,6-di-*O*-isopropylidene-5-thio-D-glucopyranose; the sulfur atom may significantly enhance the stability of the pyranose ring in this vicinal, *trans*-fused acetal which, nevertheless, is less stable than the thermodynamic acetonation-product, the conventional furanoid 1,2:5,6-diacetal.

The structures assigned to the products were firmly consolidated by detailed ^{1}H- (Table I) and ^{13}C- (Table II) n.m.r.-spectral studies at high field, with complete assignment of proton and carbon signals. The ^{1}H spectra were essentially all first-order, except for the H-4,5,6,6′ signals in **4**. The 4,6-monoacetal derivatives (**2**, **3**, **6**, and **7**) showed characteristic[11] ^{13}C resonances at δ ~100 for C-2 of the 1,3-dioxane ring, together with resonances at δ ~29 and ~19 for the equatorial and axial *C*-methyl groups, respectively. The diacetals **4** and **8** displayed, near δ ~111, the resonance[11] for C-2 of the 1,3-dioxolane ring, and the methyl groups attached to this carbon atom resonated at δ ~26, namely, between the signals of the axial and equatorial methyl groups at C-2 of the 1,3-dioxane ring. It is clear from these results, in conjunction with the detailed studies by Buchanan *et al.*[11] and the tables of Bock and Pedersen[12], that ^{13}C-n.m.r. spectroscopy is established as a powerful tool for identifying acetonation products from other sugars and glycosides.

The proton–proton spin-coupling data (see Table I) showed uniformly large (9.0–9.7 Hz) $J_{2,3}$ and $J_{4,5}$ values for the four monoacetal and two diacetal derivatives; likewise, the $J_{1,2}$ values fall in the classic ranges (3–4 Hz for α-, 7–8 Hz for β-glucosides) expected. This consistency, also evident for other spin-couplings in the series (see Table I), and for the tetraacetate[13] of **1**, is indicative of conformational uniformity, suggesting that bridging of O-2 and O-3 by the acetal group causes little distortion of the $^4C_1$(D) conformation of the glucosides, at least within the limits of the (somewhat insensitive) n.m.r. technique. This behavior contrasts with that for acetal-bridging of vicinal *cis*-diols, which introduces extensive conformational perturbation of pyranose ring-systems[14]. Hughes and co-workers[10] have noted, from the X-ray crystal-structure of 2,3:4,6-di-*O*-isopropylidene-5-thio-α-D-glucopyranose, that the 2,3-acetal bridge introduces little distortion of the $^4C_1$(D) pyranose ring in their example.

EXPERIMENTAL

General methods. — For these, see previous papers in this series[1,15]. N.m.r. spectra were recorded with Bruker WP-200 and WM-300 MHz spectrometers. 2-Methoxypropene was stored in small vials over Linde 4A molecular sieves in a refrigerator. Before use, a vial was allowed to reach room temperature, and the entire contents were then used in the experiments.

Methyl 4,6-O-isopropylidene-α-D-glucopyranoside (**2**). — The method previ-

ously described[5] for acetonation of methyl α-D-glucopyranoside (1.9 g) was modified slightly by conducting the reaction at 0°. The crude monoacetal **2**, yield 2.1 g (90%), was used in further experiments.

Methyl 2,3-di-O-acetyl-4,6-O-isopropylidene-α-D-glucopyranoside (**3**). — The crude monoacetal **2** (1.17 g, 5 mmol) was conventionally acetylated with acetic anhydride (5 mL) and pyridine (50 mL) for 12 h at 0°. The product crystallized from aqueous methanol; yield 1.46 g (92%); m.p. 73–75°, $[\alpha]_D$ 106° (*c* 0.1, chloroform).

Anal. Calc. for $C_{14}H_{22}O_8$: C, 52.83; H, 6.92; O, 40.25. Found: C, 52.81; H, 6.88; O, 40.18.

Methyl 2,3:4,6-di-O-isopropylidene-α-D-glucopyranoside (**4**). — To a solution of the crude monoacetal **2** (2.3 g, 10 mmol) in dry *N,N*-dimethylformamide (30 mL) at 0° was added desiccant (Sikkon, 5 g) followed by 2-methoxypropene (1.8 g, 25 mmol) in dry *N,N*-dimethylformamide (10 mL) and a catalytic amount (5 mg) of *p*-toluenesulfonic acid, and the mixture was agitated vigorously by magnetic stirring for 4 h at 0° with exclusion of moisture. Sodium carbonate (5 g) was added, and the mixture was further stirred for 1 h at room temperature. After filtration and evaporation of the filtrate, the crude product was obtained amorphous in almost quantitative yield. It could be used directly for further transformations.

Crystallization of the product from hexane gave **4** as plates (1.9 g, 73%); m.p. 84–85°, $[\alpha]_D$ +95° (*c* 0.1, chloroform) (lit.[6] m.p. 85°, $[\alpha]_D^{25}$ +99° in benzene).

The same product could be obtained by direct acetonation of **1** (1.9 g, 10 mmol) with 2-methoxypropene (2.9 g, 40 mmol) under essentially the same conditions, but the net yield of **4** was lower (~65%) than that attained by the two-stage procedure.

Methyl 4,6-O-isopropylidene-β-D-glucopyranoside (**6**). — To a solution of methyl β-D-glucopyranoside (**5**; 3.9 g, 20 mmol) in dry *N,N*-dimethylformamide (50 mL) at 0° were added desiccant (Sikkon, 5 g), *p*-toluenesulfonic acid (100 mg), and, dropwise, a solution of 2-methoxypropene (2.9 g, 40 mmol) in dry *N,N*-dimethylformamide (20 mL). The mixture was stirred for 6 h at 0°, and the product isolated essentially by the general procedure used for **2**. The product (**6**) crystallized from ethyl acetate–petroleum ether as a powder, yield 3.5 g (75%); m.p. 131°, $[\alpha]_D$ −85° (*c* 0.1, water) (lit.[7] m.p. 128–128.5°, $[\alpha]_D^{25}$ −72° in water).

Methyl 2,3-di-O-acetyl-4,6-O-isopropylidene-β-D-glucopyranoside (**7**). — Conventional acetylation of **6** (0.7 g, 3 mmol) with acetic anhydride (2 mL) and pyridine (20 mL), and crystallization of the product from methanol–water, gave **7** as a powder, yield 0.8 g (84%); m.p. 149°, $[\alpha]_D$ −65° (*c* 0.1, chloroform).

Anal. Calc. for $C_{14}H_{22}O_8$: C, 52.83; H, 6.92; O, 40.25. Found: C, 52.77; H, 7.01; O, 40.31.

Methyl 2,3:4,6-di-O-isopropylidene-β-D-glucopyranoside (**8**). — The crude monoacetal **6** (2.3 g, 10 mmol) was acetonated by exactly the procedure described for the conversion of **2** into **4**. The crude product (yield, almost quantitative) showed essentially (~95%) one spot, and could be directly used for further trans-

formations. The product (**8**) crystallized from hexane as needles, yield 1.8 g (65%); m.p. 71–73°, $[\alpha]_D^{20}$ −60.5°(*c* 0.1, chloroform).

Anal. Calc. for $C_{13}H_{22}O_6$: C, 56.93; H, 8.03; O, 35.04. Found: C, 56.87; H, 7.99; O, 35.09.

The same product (**8**) could be obtained by direct acetonation of **5** with 2-methoxypropene (4 equiv.), but in lower (40%) overall yield.

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