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Note

The acetonation of methyl 5-*C*-methoxy-β-D-galactopyranoside[1] with 2,2-dimethoxypropane

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Abstract

The acetonation of methyl 5-*C*-methoxy-β-D-galactopyranoside (**1a**), masked bis-glycoside form of L-*arabino*-hexos-5-ulose, with a large excess of 2,2-dimethoxypropane and catalytic amounts of *p*-toluenesulfonic acid gives a mixture of five acetonides. The most abundant isolated product was the mixed acetal methyl 6-*O*-(1–methoxy-1-methylethyl)-3,4-*O*-isopropylidene-5-*C*-methoxy-β-D–galactopyranoside (44% yield). © 1998 Elsevier Science Ltd. All rights reserved

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Methyl 5-*C*-methoxy-β-D-galactopyranoside (**1a**) is one of the four 1,5-bis-glycopyranoside anomers of L-*arabino*-hexos-5-ulose hydrate. It was easily obtained in a highly diastereoselective manner through epoxidation-methanolysis of methyl 2,6-di-*O*–benzyl-α-L-*threo*-4-hexenopyranoside, followed by hydrogenolytic removal of the benzyl protecting groups [1] and was quantitatively converted by mild acid hydrolysis into the parent L-*arabino*-hexos–5-ulose [1]. With the purpose of extending this approach to other diastereomeric hexos-5-uloses [2] such the as yet unreported *ribo* forms, we needed a 3,4,6-protected derivatives of **1a**. The most direct approach to such type of derivatives appeared to be the extension to **1a** of the acid catalyzed acetonation reaction with 2,2–dimethoxypropane (DMP) under conditions favoring equilibration of products (Scheme 1). This was developed in our laboratory some time ago [3] for the high-yield conversion of methyl β-D–galactopyranoside (**1b**) into its 6-*O*-(1-methoxy-1-methylethyl)–3,4-*O*-isopropylidene derivative **2b**, but no data were available on the use of this type of protection on 5-*C*-substituted aldopyranosides. We are reporting here the results of the above reaction, and comparing them with those of the corresponding reaction of the parent D-galactopyranoside **1b**.

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[1] The nomenclature for these bis-glycosides is still somewhat ambiguous, since the introduction of a substituent at C-5, according to the Cahn, Ingold, Prelog rules, may invert its absolute configuration. We have preferred to use the Fischer nomenclature, since it is simpler and directly correlated with the name of the base compound, which undergoes a substitution of a hydrogen atom with a MeO group. This nomenclature has been previously used by us and by other authors, and is reported without change in Chemical Abstract. According to the more recent rules, the name would be methyl (5*R*)-5-methoxy-α-L-*arabino*-hexopyranoside.

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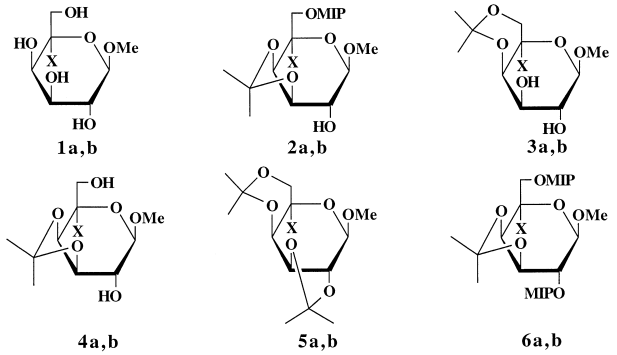

When **1a** was dissolved in a large excess of DMP (0.05 *M*) and treated at room temperature with a catalytic amount of TsOH, TLC revealed a rapid disappearance of **1a**, and a slower phase during which several intermediates were present and evolved to a final equilibrium mixture of five less polar products after 24 h. The components of the above mixture were separated by a flash chromatographic procedure and the structure of the products established by NMR analysis on the basis of the Buchanan rules [4] for the identification of dioxolane and dioxane isopropylidene acetal systems fused to pyranose rings, and by comparison with the data for the analogous D-galactopyranoside derivatives [5].

Although the most abundant acetonation product was the expected mixed diacetonide **2a**, its isolated yield was lower (44%) with respect to that reported [3] for the D-galactopyranoside analogue **2b** (>95%). The isolated yields of the other components **3a–5a** were higher with respect to those of the corresponding compounds formed only in trace amounts in the acetonation of **1b** [3]. The two cyclic monoacetonides **3a** and **4a** were isolated in equivalent amounts of about 13%, whereas the tricyclic diacetonide **5a**, containing the 2,3-trans-fused dioxolane system, and the mixed triacetonide **6a**, formed by transacetalation both at OH-6 and OH-2 and previously found only in the α-D-galactopyranoside series [3], were isolated in small amounts, respectively, of 6 and 3%.

The differences in the distribution of the acetonation products between the D-galacto and the 5-*C*-methoxy-D-galacto series could be attributed, in the first instance, to some differences in the relative thermodynamic stability of the various bi- and tricyclic fused ring systems induced by conformational deviations due to the presence of the axial 5-*C*-methoxy substituent. A comparison of the vicinal proton coupling constants, although limited to H-1, H-2, H-3 and H-4 protons, speaks against this hypothesis. The experimental values found for the same type of acetonide are, in fact, practically identical for the two series of compounds (see Table 1), proving that the introduction of the 5-*C* substituent has little effect on the pyranose ring conformation.

It appears more likely that the smaller tendency of 6-OH in **4a** to undergo methoxyisopropylation with respect to **4b**, is due to the fact that the former is in a structure isosteric with that of a neopentyl alcohol, with a consequent significant reduction in reactivity. An appreciable reduction of the reactivity of the primary alcoholic function of **4a** has been found for some other irreversible reactions aimed at its regioselective protection, which will be presented in a forthcoming paper.

1. Experimental

General methods are those reported in ref [6]. **1a** was prepared as previously described [1]. Commercially available DMP (Aldrich) was used without further purification.

Acetonation of methyl 5-C-methoxy-β-D-galactopyranoside (**1**).—A magnetically stirred solution of **1a** (1.030 g, 4.59 mmol) in DMP (90 mL) was treated, at room temperature and under argon, with previously dried TsOH (30 mg), the disappearance of **1a** (9:1 EtOAc–MeOH, R_f 0.47) and the evolution to products being followed by TLC. After 28 h the distribution of the reaction products was constant. An excess of triethylamine (1.0 mL) was added to the reaction mixture and, after 30 min of additional stirring, evaporated under reduced pressure and repeatedly co-evaporated with toluene (3×50 mL). The crude reaction product (1.392 g) was directly applied to a

Table 1
Comparison between the vicinal proton coupling constants (CD_3CN) of different isopropylidene (IPR) acetal systems

	3,4-*O*-IPR			4,6-*O*-IPR		2,3:4,6-di–*O*-IPR	
	4b[a]	**2a**	**4a**	**3b**[b]	**3a**	**5b**[c]	**5a**
$J_{1,2}$	8.16	8.33	8.37	7.65	7.90	7.7	7.70
$J_{2,3}$	7.20	7.43	7.44	9.33	9.89	9.5	9.73
$J_{3,4}$	5.53	5.17	5.26	3.95	3.60	2.6	2.64

[a] Ref. [5b].
[b] Ref. [5c].
[c] Ref. [5a].

flash-chromatographic column of silica gel and eluted first with 1:1 hexane–EtOAc + 0.1% Et_3N, then with 1:4 hexane–EtOAc + 0.1% Et_3N and, finally, with EtOAc + 0.1% Et_3N. The following products were collected in the order.

Methyl 3,4-O-*isopropylidene-5*-C-*methoxy-2,6-di*-O-*(1-methoxy-1-methylethyl)*-β-D-*galactopyranoside* (**6a**). 64 mg, (3.4% yield), syrup, R_f 0.68 (1:1 hexane–EtOAc), $[\alpha]_D$ −30.19 (*c* 1.5, $CHCl_3$); ^1H NMR (CD_3CN) δ: 1.25, 1.28, 1.30, 1.31, 1.32, 1.43 (6 s, each 3 H, dioxolane CMe_2 and 2×MIP CMe_2); 3.15 and 3.17 (2 s, each 3 H, 2×MIP OMe); 3.28 (s, 3 H, 5-OMe); 3.42 (s, 3 H, 1-OMe); 3.53 (m, 1 H, H-2); 3.68 (s, 2 H, 2×H-6); 4.01 and 4.08 (m, 2 H, H-3 and H-4); 4.33 (d, 1 H, $J_{1,2}$ = 7.97 Hz, H-1). ^{13}C NMR (CD_3CN) δ: 24.44, 24.52, 25.97, 26.28, 26.41 and 28.01 (dioxolane C*Me*$_2$ and 2×MIP C*Me*$_2$); 49.17 and 49.82 (2×MIP OMe); 48.43 (5-OMe); 57.56 (1-OMe); 58.43 (C-6); 73.59 (C-2); 75.33 (C-4); 79.32 (C-3); 99.32 (C-1); 101.24 (C-5); 99.64 and 102.39 (2×MIP *C*Me$_2$); 110.02 (dioxolane *C*Me$_2$). Anal. Calcd. for $C_{19}H_{36}O_9$: C, 55.87; H, 8.88. Found: C, 56.01; H, 8.65.

Methyl 2,3:4,6-di-O-*isopropylidene-5*-C-*methoxy*-β-D-*galactopyranoside* (**5a**). 86 mg, (6.1% yield), syrup, R_f 0.54 (1:1 hexane–EtOAc), $[\alpha]_D$ −51.3 (*c* 1.1, $CHCl_3$); ^1H NMR (CD_3CN) δ: 1.31 and 1.41 (2 s, each 3 H, dioxane CMe_2), 1.33 and 1.35 (2 s, each 3 H, dioxolane CMe_2); 3.24 (s, 3 H, 5-OMe); 3.49 (s, 3 H, 1-OMe); 3.73 (dd, 1 H, $J_{1,2}$ = 7.70 Hz, $J_{2,3}$ = 9.73 Hz, H-2); 3.84 (dd, 1 H, $J_{3,4}$ = 2.64 Hz, H-3); 3.87 (s, 2 H, 2×H-6); 4.27 (d, 1 H, H-4); 4.69 (d, 1 H, H-1). ^{13}C NMR (CD_3CN) δ: 19.33 and 28.29 (dioxane C*Me*$_2$); 26.60 and 26.60 (dioxolane C*Me*$_2$); 49.07 (5-OMe); 56.99 (1-OMe); 65.21 (C-6); 69.80 (C-4); 73.29 (C-2); 75.38 (C-3); 94.96 (C-5); 101.33 (C-1); 100.3 (dioxane *C*Me$_2$); 111.65 (dioxolane *C*Me$_2$). Anal. Calcd. for $C_{14}H_{24}O_7$: C, 55.25; H, 7.95. Found: C, 55.50; H, 8.05.

Methyl 3,4-O-*isopropylidene-5*-C-*methoxy-6*-O-*(1-methoxy–1-methylethyl)*-β-D-*galactopyranoside* (**2a**). 678 mg, (43.9% yield), syrup, R_f 0.30 (1:1 hexane–EtOAc), $[\alpha]_D$ −36.7 (*c* 1.9, $CHCl_3$); ^1H NMR (CD_3CN) δ: 1.27, 1.29, 1.31, 1.42 (4 s, each 3 H, dioxolane CMe_2 and MIP CMe_2); 317 (s, 3 H, MIP OMe); 3.28 (s, 3 H, 5-OMe); 3.45 (s, 3 H, 1-OMe); 3.33 (dd, 1 H, $J_{1,2}$ = 8.33 Hz, $J_{2,3}$ = 7.43 Hz, H-2); 3.46 and 3.54 (AB system, 2 H, $J_{6,6'}$ = 10.21 Hz, H-6a and H-6b); 3.98 (ddd, 1 H, $J_{3,4}$ = 5.17 Hz, $J_{3,6}$ = 0.26 Hz, H-3); 4.07 (d, 1 H, H-4); 4.33 (d, 1 H, H-1). ^{13}C NMR (CD_3CN) δ: 24.51, 24.59, 26.46, and 28.41 (dioxolane C*Me*$_2$ and MIP C*Me*$_2$); 49.15 (MIP OMe); 48.33 (5-OMe); 57.35 (1-OMe); 58.47 (C-6); 72.99 (C-2); 75.45 (C-4); 78.93 (C-3); 99.47 (C-1); 101.11 (C-5); 100.12 (MIP *C*Me$_2$); 110.15 (dioxolane *C*Me$_2$). Anal. Calcd. for $C_{15}H_{28}O_8$: C, 53.56; H, 8.39. Found: C, 53.35; H, 8.40.

Methyl 3,4-O-*isopropylidene-5*-C-*methoxy*-β-D-*galactopyranoside* (**4a**). 162 mg, (13.4% yield), colourless solid, m.p. 118–119 °C (hexane–EtOAc) R_f 0.11 (1:1 hexane–EtOAc), $[\alpha]_D$ −57.2 (*c* 1.3, $CHCl_3$); ^1H NMR (CD_3CN) δ: 1.29 and 1.42 (2 s, each 3 H, CMe_2); 3.28 (s, 3 H, 5-OMe); 3.44 (s, 3 H, 1-OMe); 3.32 (dd, 1 H, $J_{1,2}$ = 8.37 Hz, $J_{2,3}$ = 7.44 Hz, H-2); 3.49 and 3.70 (AB system, 2 H, $J_{6a,6b}$ = 12.20 Hz, H-6 and H-6′); 4.01 (ddd, 1 H, $J_{3,4}$ = 5.26 Hz, $J_{3,6}$ = 0.28 Hz, H-3); 4.08 (d, 1 H, H-4); 4.32 (d, 1 H, H-1). ^{13}C NMR (CD_3CN) δ: 26.55, and 28.32 (C*Me*$_2$); 48.28 (5-OMe); 57.44 (1-OMe); 59.07 (C-6); 72.77 (C-2); 75.25 (C-4); 78.69 (C-3); 99.29 (C-1); 100.42 (C-5); 110.48 (*C*Me$_2$). Anal. Calcd. for $C_{11}H_{20}O_7$: C, 49.99; H, 7.63. Found: C, 49.95; H, 7.56.

Methyl 4,6-O-*isopropylidene-5*-C-*methoxy*-β-D-*galactopyranoside* (**3a**). 160 mg, (13.2% yield), syrup, R_f 0.05 (1:1 hexane–EtOAc), $[\alpha]_D$ −48.8 (*c* 1.4, $CHCl_3$); ^1H NMR (CD_3CN) δ: 1.32, 1.39 (2 s, each 3 H, CMe_2); 3.24 (s, 3 H, 5-OMe); 3.48 (s, 3 H, 1-OMe); 3.48 (dd, 1 H, $J_{1,2}$ = 7.90 Hz, $J_{2,3}$ = 9.89 Hz, H-2); 3.72 (dd, 1 H, $J_{3,4}$ = 3.60 Hz, H-3); 3.76 and 3.82 (AB system, 2 H, $J_{6a,6b}$ = 11.96 Hz, H-6 and H–6′); 3.92 (d, 1 H, H-4); 4.31 (d, 1 H, H-1). ^{13}C NMR (CD_3CN) δ: 19.23, and 28.51 (C*Me*$_2$); 48.78 (5-OMe); 57.46 (1-OMe); 65.10 (C-6); 69.66 (C-4); 71.12 (C-2); 71.84 (C-3); 94.03 (C-5); 100.34 (*C*Me$_2$); 101.40 (C-1). Anal. Calcd. for $C_{11}H_{20}O_7$: C, 49.99; H, 7.63. Found: C, 48.26; H, 7.10.

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