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HYDROGENOLYSIS OF BENZYLIDENE ACETALS OF 1,6-ANHYDRO-β-D-GALACTOPYRANOSE DERIVATIVES WITH THE $LiAlH_4$–$AlCl_3$ REAGENT

CARMEN SUBERO, LUIS FILLOL, AND MANUEL MARTÍN-LOMAS
Instituto de Química Orgánica General, CSIC, Juan de la Cierva, 3, Madrid-6 (Spain)
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ABSTRACT

Benzylidenation of 1,6-anhydro-β-D-galactopyranose (**1**) and its 2-*O*-acetyl (**2**) and 2-*O*-allyl (**3**) derivatives under various conditions afforded mixtures of 1,6-anhydro-*exo*- and -*endo*-3,4-*O*-benzylidene-β-D-galactopyranose (**4** and **5**) and the 2-*O*-acetyl (**6** and **7**) and 2-*O*-allyl (**8** and **9**) derivatives, respectively. Hydrogenolysis of the *exo* (**4** and **8**) or the *endo* (**5** and **9**) derivatives with the $LiAlH_4$–$AlCl_3$ reagent gave only the 3-*O*-benzyl derivatives (**10** and **11**).

INTRODUCTION

1,6-Anhydrohexose derivatives have been used as aglycons in the synthesis of oligosaccharides. Partially acetylated[1,2], and benzylated[3] derivatives of 1,6-anhydro-β-D-galactopyranose have been used in the synthesis of galactosylgalactoses[3–5]. Hydrogenolytic cleavage of the benzylidene ring in 3,4-*O*-benzylidene derivatives of D-galacto-, D-arabino-, and D-fuco-pyranoside[6] and 2,3-*O*-benzylidene derivatives of D-manno- and L-rhamno-pyranoside[7,8] with the $LiAlH_4$–$AlCl_3$ reagent[9] depends on the configuration of the acetal carbon atom. The *exo* isomers gave mainly derivatives containing equatorial *O*-benzyl groups, and the *endo* isomers yielded derivatives having axial *O*-benzyl groups. Similar results have been obtained for 3,4-*O*-benzylidene derivatives of benzyl α-D-galactopyranoside[10]. In order to prepare benzyl derivatives of 1,6-anhydro-β-D-galactopyranose (**1**) suitable for oligosaccharide synthesis, we have studied the reaction of the 3,4-*O*-benzylidene derivatives of 1,6-anhydro-β-D-galactopyranose with the $LiAlH_4$–$AlCl_3$ reagent. In contrast to previously reported results[6–8,10], both the *exo* and the *endo* isomers afforded products containing axial benzyl groups.

RESULTS AND DISCUSSION

Treatment of 1,6-anhydro-β-D-galactopyranose (**1**) with benzaldehyde–zinc chloride gave a mixture of products from which the *endo*-3,4-*O*-benzylidene derivative (**5**) was crystallised in 35% yield and converted into the 2-acetate (**7**) and 2-*O*-allyl derivative (**9**). The reaction of 2-*O*-acetyl-1,6-anhydro-β-D-galactopyranose (**2**)

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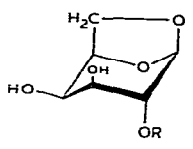
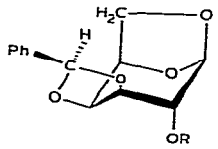
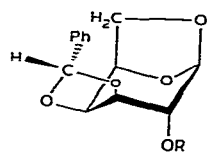
with benzaldehyde under similar conditions also gave a mixture of products, from which the *exo* isomer (**6**) was crystallised in 44% yield. Deacetylation of **6** gave 1,6-anhydro-*exo*-3,4-*O*-benzylidene-β-D-galactopyranose (**4**) from which the 2-*O*-allyl derivative (**8**) was obtained. The reaction of **1**, **2**, and 2-*O*-allyl-1,6-anhydro-β-D-galactopyranose (**3**) with benzaldehyde or its dimethyl acetal under various conditions afforded mixtures of the *exo*- and *endo*-3,4-*O*-benzylidene derivatives (**4–9**) in various yields.



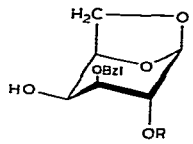
1 R = H
2 R = Ac
3 R = Allyl



4 R = H
6 R = Ac
8 R = Allyl



5 R = H
7 R = Ac
9 R = Allyl



10 R = H
11 R = Allyl

The configuration at the benzylidene acetal carbon atom of **4–9** was determined by ^{1}H- and ^{13}C-n.m.r. spectroscopy. The ^{1}H and ^{13}C chemical shifts are given in Tables I and II, respectively. The benzylidene proton (H-7) in the *exo* isomer resonates[11] at a lower field than that of the corresponding *endo* isomer. On the other hand, the acetal carbon (C-7) in the *exo* isomer resonates[12,13] at higher field than that in the *endo* isomer. Also, the aromatic carbon attached to C-7 resonates at lower field for the *exo* isomers than for the *endo* isomers, and the $\Delta\delta$ value for the signals of C-7 and the quaternary aromatic carbon atom is greater (>35.4 p.p.m.) in the *exo* than in the *endo* isomer (<33.8 p.p.m.). From the ^{1}H-n.m.r. data (Table I), the configuration of **4–9** could be assigned as shown. The ^{13}C resonances of the quaternary carbon atoms and the $\Delta\delta$ values are also in agreement with the proposed configuration (Table II). These results do not agree well with the previous data[12,13] on the chemical shifts of C-7 in the *exo* and *endo* isomers.

TABLE I

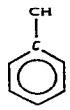
^{1}H-N.M.R., FIRST-ORDER CHEMICAL-SHIFT DATA (p.p.m.) FOR BENZYLIDENE ACETALS OF 1,6-ANHYDRO-β-D-GALACTOPYRANOSE DERIVATIVES

Compound	*H-1*	*H-2*	*H-3*	*H-4*	*H-5*	*H-6*endo	*H-6*exo	*H-7*[a]	*Ph*
4	5.39	3.94	4.57		3.94	4.10	3.52	6.32	7.38
5	5.41	4.03	4.54		4.21	4.10	3.52	5.83	7.43
6	5.40	5.02	4.60		3.72	4.16	3.70	6.35	7.39
7	5.41	5.08	4.57			4.11	3.52	5.82	7.44
8	5.46	3.64	4.60			4.05	3.70	6.30	7.38
9	5.46	3.72	4.57			4.09	3.49	5.80	7.43

[a]Benzylidene proton.

TABLE II

^{13}C-N.M.R. CHEMICAL-SHIFT DATA (p.p.m., Cl_3CD) FOR BENZYLIDENE ACETALS OF 1,6-ANHYDRO-β-D-GALACTOPYRANOSE DERIVATIVES

Compound	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*C-7*[a]		*Δδ*
4	100.9	72.7	70.1	69.6	75.0	64.0	103.7	138.9	35.2
5	101.0	72.5	69.8	69.3	75.7	63.7	103.0	135.4	32.5
6	98.7	72.3	70.5	69.9	72.9	63.8	103.5	138.7	35.2
7	99.0	72.3	70.9	69.5	75.3	63.6	103.0	135.4	32.3
8	99.5	76.5	72.2	70.2	72.9	63.5	103.4	139.0	35.6
9	99.6	76.0	71.9	69.5	75.2	63.1	102.6	135.4	32.7

[a]Acetal carbon atom.

Hydrogenolysis of 1,6-anhydro-*endo*-3,4-*O*-benzylidene-β-D-galactopyranose (**5**) with the $LiAlH_4$–$AlCl_3$ reagent gave the expected 1,6-anhydro-3-*O*-benzyl-β-D-galactopyranose (**10**). The product was not attacked by sodium metaperiodate, and its ^{13}C-n.m.r. spectrum showed a peak assignable to C-3 at 77.9 p.p.m. (70.8 p.p.m. in the spectrum of **1**) and those for C-2 and C-4 at 68.1 and 64.2 p.p.m., respectively (71.9 and 64.9 p.p.m. in the spectrum of **1**), as expected for the introduction of a benzyl group at position 3. Hydrogenolysis of the *exo* isomer (**4**) was more difficult and, surprisingly, also gave **10**. Similarly, 2-*O*-allyl-1,6-anhydro-*endo*-3,4-*O*-benzylidene-β-D-galactopyranose (**9**) reacted with the $LiAlH_4$–$AlCl_3$ reagent to give the expected 2-*O*-allyl-1,6-anhydro-3-*O*-benzyl-β-D-galactopyranose (**11**), the ^{13}C-n.m.r. spectrum of which showed peaks attributable to C-3 at 74.8 p.p.m. and for C-2 and C-4 at 75.9 and 64.7 p.p.m., respectively. Under similar conditions, the *exo* isomer **8** gave **11**. In the above reactions, the $LiAlH_4$–$AlCl_3$ reagent attacked O-4 (equatorial) in both the *exo* (**4**,**8**) and *endo* (**5**,**9**) isomers, leading to 3-*O*-benzyl derivatives. It could be argued that *exo*→*endo* isomerisation took place before the hydrogenolytic cleavage of the *exo* derivatives to give the 3-benzyl ether[14]. Although this possibility cannot be completely discounted, no evidence was obtained either of the greater thermodynamic stability of the *endo* isomer or of any isomerisation during the reduction reaction. The 1,6-anhydro-β-D-galactopyranose derivatives are rigidly held in the $^1C_4$ conformation, and attack of the $LiAlH_4$–$AlCl_3$ reagent on O-3 could be sterically hindered, thereby deflecting attack to O-4 with the *exo* isomers reacting more slowly than, but in the same direction as, the *endo* isomers.

EXPERIMENTAL

Melting points were measured on a Kofler hot-stage and are uncorrected. T.l.c. was performed on silica gel $60F_{254}$ (Merck) with detection by charring with sulphuric

acid. Column chromatography was performed on silica gel (Merck, 60–230 mesh). I.r. spectra were recorded for KBr discs with a Perkin–Elmer 457 spectrometer. ^{1}H- (90 MHz) and ^{13}C-n.m.r. spectra (25.2 MHz) were recorded for solutions in $CDCl_3$ (internal Me_4Si) with Varian EM-390 and XL-100 spectrometers, respectively. Optical rotations were determined with a Perkin–Elmer 141 polarimeter.

1,6-Anhydro-endo-*3,4*-O-*benzylidene*-β-D-*galactopyranose* (**5**). — A mixture of 1,6-anhydro-β-D-galactopyranose (**1**, 1 g), freshly fused zinc chloride (1 g), and freshly distilled benzaldehyde (5 ml) were stirred for 24 h and then poured into ice–water (250 ml) with stirring. The resulting syrup was washed with hexane and crystallised from ethanol, to give **5** (0.53 g, 35%), m.p. 186–189°, $[\alpha]_D$ +8° (*c* 1.6, chloroform).

Anal. Calc. for $C_{13}H_{14}O_5$: C, 62.40; H, 5.60. Found: C, 62.59; H, 5.79.

The 2-acetate (**7**) of **5** had m.p. 123–125° (from ethanol), $[\alpha]_D$ +40° (*c* 0.8, chloroform).

Anal. Calc. for $C_{15}H_{16}O_6$: C, 61.63; H, 5.51. Found: C, 61.84; H, 5.75.

2-O-*Allyl-1,6-anhydro*-endo-*3,4*-O-*benzylidene*-β-D-*galactopyranose* (**9**). — A mixture of **5** (0.19 g), sodium hydride (0.1 g), allyl bromide (0.2 ml), and *N,N*-dimethylformamide (6 ml) was stirred for 2 h. Methanol and water were added successively, the solution was extracted with chloroform, and the extracts were washed with water, dried ($MgSO_4$), and concentrated *in vacuo*, to give **9** (0.12 g) as a chromatographically homogeneous syrup (t.l.c.; hexane–ethyl acetate, 7:3), $[\alpha]_D$ −9° (*c* 0.1, chloroform).

Anal. Calc. for $C_{16}H_{18}O_5$: C, 66.19; H, 6.25. Found: C, 66.44; H, 6.50.

2-O-*Acetyl-1,6-anhydro*-exo-*3,4*-O-*benzylidene*-β-D-*galactopyranose* (**6**). — A mixture of 2-*O*-acetyl-1,6-anhydro-β-D-galactopyranose (**2**, 1 g), freshly fused zinc chloride (1 g), and freshly distilled benzaldehyde (5 ml) was stirred at room temperature for 24 h and then concentrated *in vacuo*. Crystallisation of the residue from ethanol gave **6** (0.59 g, 44%), m.p. 182–183°, $[\alpha]_D$ −49.5° (*c* 0.3, chloroform).

Anal. Calc. for $C_{15}H_{16}O_6$: C, 61.63; H, 6.60. Found: C, 61.62; H, 5.57.

1,6-Anhydro-exo-*3,4*-O-*benzylidene*-β-D-*galactopyranose* (**4**). — A solution of **6** (0.25 g) in methanol (10 ml) was treated with methanolic M sodium methoxide (1 ml) for 4 h, and then neutralised with Amberlite IR-120(H^+) resin, filtered, and concentrated *in vacuo*. The residue was crystallised from ethanol–water, to give **4** (0.20 g), m.p. 119–121°, $[\alpha]_D$ −28.5° (*c* 0.6, chloroform).

Anal. Calc. for $C_{13}H_{14}O_5$: C, 62.40; H, 5.60. Found: C, 62.07; H, 5.30.

2-O-*Allyl-1,6-anhydro*-exo-*3,4*-O-*benzylidene*-β-D-*galactopyranose* (**8**). — Allylation of **4** (0.7 g), as described above for **5**, and crystallisation of the product from 2-propanol gave **8** (0.5 g), m.p. 120–121°, $[\alpha]_D$ −75° (*c* 2.1, chloroform).

Anal. Calc. for $C_{16}H_{18}O_5$: C, 66.19; H, 6.21. Found: C, 66.23; H, 6.32.

The ^{1}H- and ^{13}C-n.m.r. data for **4**–**9** are given in Tables I and II.

Hydrogenolyses. — (*a*) *1,6-Anhydro*-endo-*3,4*-O-*benzylidene*-β-D-*galactopyranose* (**5**). To a boiling mixture of **5** (0.7 g), dichloromethane–ether (1:3, 100 ml), and $LiAlH_4$ (1.5 g) was added a solution of $AlCl_3$ (3 g) in ether, and boiling was

continued for 20 min. The mixture was cooled, ethyl acetate (100 ml) and water (100 ml) were added, the organic layer was separated, and the aqueous layer was extracted with ether (3 × 50 ml). The combined extracts were washed with water, dried ($MgSO_4$), and concentrated *in vacuo*, and the resulting syrup was eluted from a small column of silica gel with hexane–ethyl acetate (7:3), to give 1,6-anhydro-3-*O*-benzyl-β-D-galactopyranose (**10**). ^{1}H-N.m.r. data: δ 5.30 (t, 1 H, $J_{1,2} \simeq J_{1,3} \simeq 1.5$ Hz, H-1), 4.30 (t, 1 H, $J_{4,5} \simeq J_{3,4} = 4.5$ Hz, H-4), 4.16 (d, 1 H, $J_{5,6endo}$ 0, $J_{6endo,6exo}$ 7.8 Hz, H-6*endo*), 4.00 (t, 1 H, $J_{5,6exo}$ 4.5 Hz, H-5), 3.80 (t, 1 H, $J_{2,3}$ 1.5 Hz, H-2), 3.60 (m, 1 H, H-3), and 3.56 (m, 1 H, H-6*exo*). ^{13}C-N.m.r. data: 100.9 (C-1), 77.9 (C-3), 74.7 (C-5), 68.1 (C-2), 62.2 (C-4), and 63.5 p.p.m. (C-6).

Anal. Calc. for $C_{13}H_{16}O_5$: C, 61.89; H, 6.39. Found: C, 62.21; H, 6.59.

(*b*) *1,6-Anhydro*-exo-*3,4*-O-*benzylidene*-β-D-*galactopyranose* (**4**). A mixture of **4** (0.5 g) and dichloromethane–ether (1:1, 100 ml) was treated, as in (*a*), with $LiAlH_4$ (1.3 g) and $AlCl_3$ (2.6 g) in ether for 5 h, to give **10** (0.32 g, 65%), which was identical with the product from (*a*).

(*c*) *2*-O-*Allyl-1,6-anhydro*-endo-*3,4*-O-*benzylidene*-β-D-*galactopyranose* (**9**). A mixture of **9** (0.13 g) and dichloromethane–ether (1:1) was treated for 2 h with $LiAlH_4$ (0.2 g) and $AlCl_3$ (0.6 g) in ether, as in (*a*), to give 2-*O*-allyl-1,6-anhydro-3-*O*-benzyl-β-D-galactopyranose (**11**; 0.1 g, 75%) as a syrup, $[\alpha]_D$ −62°. ^{1}H-N.m.r. data: δ 7.30 (s, 5 H, Ph), 5.80 (m, 1 H, =C*H*-), 5.36 (t, 1 H, $J_{1,2} \simeq J_{1,3} \simeq 1.5$ Hz), 5.20 (m, 2 H, $=CH_2$), 4.52 (q, 2 H, PhCH_2), 4.35 (t, 1 H, $J_{4,5} \simeq J_{3,4} \simeq 4.5$ Hz, H-4), 4.15 (d, 1 H, $J_{5,6endo}$ 0, $J_{6endo,6exo}$ 7.8 Hz, H-6*endo*), 4.03 (t, 1 H, $J_{5,6exo}$ 4.5 Hz, H-5), 3.97 (m, 1 H, $J_{2,3}$ 1.5 Hz, H-3), 3.66 (m, 1 H, H-6_{exo}), and 3.50 (d, 1 H, H-2). ^{13}C-N.m.r. data: 99.7 (C-1), 75.9 (C-2), 74.8 (C-3), 74.4 (C-5), 72.7 (PhCH_2), 71.2 (-CH_2-CH=), 64.7 (C-4), and 63.2 p.p.m. (C-6).

Anal. Calc. for $C_{16}H_{20}O_5$: C, 65.73; H, 6.89. Found: C, 65.85; H, 7.03.

(*d*) *2*-O-*Allyl-1,6-anhydro*-exo-*3,4*-O-*benzylidene*-β-D-*galactopyranose* (**8**). A mixture of **8** (0.43 g) in dichloromethane–ether (1:1, 100 ml) was treated, as in (*a*), with $LiAlH_4$ (0.98 g) and $AlCl_3$ (1.97 g) in ether for 2 h, to give **11** (0.35 g, 71%), which was identical with the product from (*c*).

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