Acta Chemica Scandinavica B 28 (1974) 381—384

Synthesis and Configurational Assignment of the Two Stereoisomeric Methyl 3,4-*O*-Ethylidene-β-D-galactopyranosides

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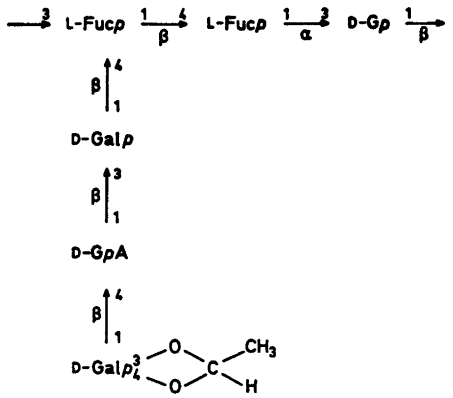
The two stereoisomers of methyl 3,4-*O*-ethylidene-β-D-galactopyranoside have been prepared. Their configurations have been assigned from an X-ray crystallographic structural determination of one of them and correlated with the observed chemical shift of the ethylidene methine proton for each of the stereoisomers.

Previous structural studies on the extracellular M-antigen which can be isolated from the mutant *Salmonella typhimurium* 395 MRO-M1 have demonstrated the following polysaccharide frame-work.[1,2]



The configuration at the asymmetric acetal carbon of the ethylidene group linked to the terminal D-galactose residues is so far not known.

In the present paper, we report the synthesis of the two stereoisomeric methyl 3,4-*O*-ethylidene-β-D-galactopyranosides. These were required as reference compounds for the determination of the configuration at the above 3,4-*O*-ethylidene groups. We have determined the configuration of the ethylidene group in one of these acetals by X-ray crystallography. This has made it possible for us to correlate the NMR chemical shifts of the acetal methine protons with the structures of the two possible stereoisomers.

We have recently reported a method of benzylidenation, whereby the appropriate diol is treated with a benzal halide in pyridine at reflux temperature. The method is applicable in the presence of acetyl or trityl groups on other positions of a pyranose ring.[3,4] It therefore gives easy access to methyl 3,4-*O*-benzylidene-β-D-galactopyranoside (I),[4] which was the starting material in the present synthetic work. Benzylation of I produced II, the stereoisomers of which (IIa and IIb) were obtained by chromatography. Removal of the benzylidene group from II under mild acidic conditions produced methyl 2,6-di-*O*-benzyl-β-D-galactopyranoside III. This, on treatment with excess 1,1-dimethoxyethane and a catalytic amount of sulphuric acid afforded the 3,4-*O*-ethylidene acetal IV, the stereoisomers of which, IVa and IVb, were obtained by chromatographic separation. Catalytic hydrogenation of IVa and IVb yielded the stereoisomeric methyl 3,4-*O*-ethylidene-β-D-galactopyranosides Va and Vb, respectively.

The assignments of configuration at the asymmetric benzylidene acetal carbons for compounds Ia, Ib, IIa, and IIb described in the experimental part, are based on the observations of Baggett and co-workers that the benzylic proton in a dioxolane ring fused to a

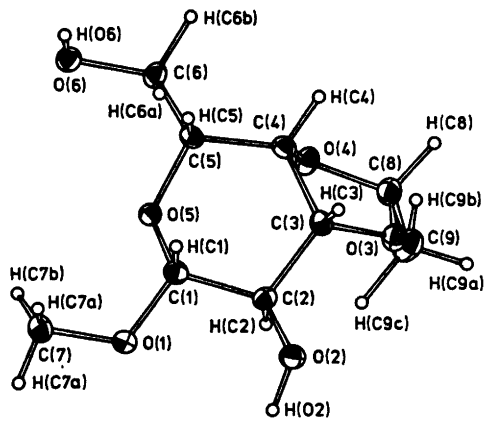


Fig. 1. Molecular structure of methyl 3,4-*O*-ethylidene-β-D-galactopyranoside, isomer Vb.

pyranoside (of Ia and Ib) has different chemical shifts depending on the configuration. An *exo*-benzylidene proton resonates at a higher field than does an *endo* one, and this was used in the structural assignment of benzylidene acetals previously described.[5,6] By similar reasoning the ethylidene acetals IVa and Va have an *endo* acetalic hydrogen and IVb and Vb correspondingly an *exo* one. In view of the fact that such correlations for pyranoside ethylidene acetals do not seem to have been made, we decided to determine the structure of one of the acetals, Vb, by X-ray crystallography. The molecular structure is shown in Fig. 1. Intramolecular distances and angles are listed in Table 1. Having thus determined the configuration at the ethylidene carbon in Vb, the corresponding configuration in Va, IVa, and IVb follows. The results (*cf.* Table 2) clearly indicate the possibility of applying the NMR correlations of Baggett and co-workers (for the configuration of benzylidene acetals) to ethylidene acetals. However, no such correlation for the chemical shift of the methyl protons of the ethylidene group with the configuration at the ethylidene acetal carbon was found.

EXPERIMENTAL

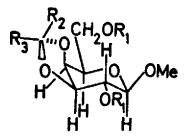
General methods were the same as those described in a previous paper.[4] Unless otherwise stated, chemical shifts are measured in ppm downfield from tetramethylsilane (internal).

Methyl 2,6-di-O-benzyl-3,4-O-benzylidene-β-D-galactopyranoside (IIa, IIb). Methyl 3,4-*O*-benzylidene-β-D-galactopyranoside (Ia, m.p. 139–141°, 530 mg) was converted into the 2,6-di-*O*-benzyl ether by treatment with benzyl bromide (3.25 g) and sodium hydride (from 0.91 g 50 % suspension in oil, thoroughly washed with light

Table 1. Intramolecular nonhydrogen bond distances (Å) and angles (°) for methyl 3,4-*O*-ethylidene-β-D-galactopyranoside, isomer Vb. Estimated standard deviations are given in parentheses.

C(1)–C(2)	1.515 (6)	C(1)–C(2)–C(3)	110.6 (4)
C(2)–C(3)	1.530 (6)	C(2)–C(3)–C(4)	113.4 (4)
C(3)–C(4)	1.530 (7)	C(3)–C(4)–C(5)	115.8 (4)
C(4)–C(5)	1.510 (7)	C(4)–C(5)–O(5)	110.7 (4)
C(5)–C(6)	1.505 (6)	C(5)–O(5)–C(1)	110.6 (3)
C(8)–C(9)	1.495 (9)	C(5)–C(1)–C(2)	109.3 (4)
C(1)–O(1)	1.393 (6)	C(4)–C(5)–C(6)	113.2 (4)
C(7)–O(1)	1.421 (7)	O(5)–C(5)–C(6)	108.1 (4)
C(2)–O(2)	1.429 (6)	C(5)–C(6)–O(6)	112.1 (4)
C(3)–O(3)	1.420 (5)	C(1)–O(1)–C(7)	113.5 (4)
C(4)–O(4)	1.441 (6)	C(1)–C(2)–O(2)	110.9 (4)
C(1)–O(5)	1.423 (5)	C(3)–C(2)–O(2)	108.3 (4)
C(5)–O(5)	1.442 (6)	C(2)–C(3)–O(3)	111.1 (4)
C(6)–O(6)	1.426 (6)	C(4)–C(3)–O(3)	102.9 (3)
C(8)–O(3)	1.439 (6)	C(2)–C(1)–O(1)	109.1 (4)
C(8)–O(4)	1.416 (6)	C(5)–C(1)–O(1)	107.9 (4)
		C(3)–C(4)–O(4)	101.4 (4)
		C(5)–C(4)–O(4)	111.3 (4)
		C(3)–C(8)–O(4)	106.3 (4)
		O(3)–C(8)–C(9)	111.5 (4)
		O(4)–C(8)–C(9)	110.4 (5)
		C(3)–O(3)–C(8)	108.6 (3)
		C(4)–O(4)–C(8)	104.4 (4)

Table 2. Chemical shifts for benzylidene or ethylidene methine protons in compound I – V.



	R_1	R_2	R_3	δ
I a	H	H	Ph	6.15[a]
I b	H	Ph	H	5.97[a]
II a	CH_2Ph	H	Ph	5.98[a]
II b	CH_2Ph	Ph	H	5.92[a]
IV a	CH_2Ph	H	CH_3	5.25[a]
IV b	CH_2Ph	CH_3	H	5.13[a]
V a	H	H	CH_3	5.45[b]
V b	H	CH_3	H	5.25[b]

[a] In ppm downfield from TMS. [b] In ppm downfield from sodium 3-(trimethylsilyl)propanesulphonate.

petroleum) in dry dimethylformamide (30 ml), essentially as described by Brimacombe and co-workers.[7] Excess benzyl bromide was converted into benzyl methyl ether by adding methanol (15 ml) and continuing the reaction at room temperature for 3 h. The product was partitioned between benzene and water and concentrated. The resulting syrup was purified by TLC to yield syrupy II (580 mg) $[\alpha]_D$ +11° (*c* 0.9, $CHCl_3$). (Found: C 72.5; H 6.37. $C_{28}H_{30}O_6$ requires: C 72.7; H 6.54).

An NMR spectrum showed that although the starting material contained one stereoisomer only (Ia), the product contained approximately equal quantities of the isomers IIa and IIb. A small-scale benzylation of Ia with benzyl bromide and silver oxide in dimethyl formamide essentially as described by Kuhn and co-workers,[8] however yielded pure IIa. Benzylation of a mixture of Ia and Ib (4.2 g) with benzyl bromide and sodium hydride in dimethyl formamide as described above afforded an 80 % yield of a stereoisomeric mixture of IIa and IIb, used in the subsequent synthesis. A small quantity of this mixture was separated by TLC ($CHCl_3$ – Et_2O 9:1) yielding pure, syrupy, IIa (faster-moving isomer), $[\alpha]_D$ +10° (*c*, 0.6, $CHCl_3$) and IIb, $[\alpha]_D$ +13° (*c* 0.3, $CHCl_3$). (Found: IIa: C 72.6; H 6.36. IIb: C 72.9; H 6.69. $C_{28}H_{30}O_6$ requires: C 72.7; H 6.54). NMR, IIa ($CDCl_3$): δ 3.60 (s and broad one-proton signal, 4 H), methoxyl and one ring proton; δ 4.62 (2 H) and 4.90 (2 H), benzylic protons; δ 5.98 (s, 1 H), benzylidene proton. NMR, IIb ($CDCl_3$): δ 3.57 (s and broad one-proton signal, 4 H), methoxyl and one ring proton; δ 4.67 (2 H) and 4.75 (2 H), benzylic protons; δ 5.92 (s, 1 H), benzylidene proton.

Methyl 2,6-O-benzyl-β-D-galactopyranoside (III). A mixture of the stereoisomers IIa and IIb (9.2 g) was treated with 85 % aqueous trifluoroacetic acid (100 ml) at room temperature for 15 min. The solution was concentrated and the product purified on a silica gel column, ($CHCl_3$, $CHCl_3$ – Et_2O 9:1 and 1:1, EtOAc in sequence), to yield III (4.7 g), which after recrystallization from cyclohexane had m.p. 78 – 80°, $[\alpha]_D$ +10° (*c* 0.4, $CHCl_3$). (Found: C 67.1; H 7.16. $C_{21}H_{26}O_6$ requires: C 67.4; H 7.00). NMR ($CDCl_3$): δ 3.54 (s, 3 H), methoxyl protons; δ 4.58 (2 H) and 4.73, 4.87 (2 H), benzylic protons.

Methyl 2,6-di-O-benzyl-3,4-O-ethylidene-β-D-galactopyranoside (IVa, IVb). The dibenzyl ether II (100 mg) in 1,1-dimethoxyethane (1.5 ml) containing sulphuric acid (1 drop) was allowed to stand at room temperature for 15 min. Excess chloroform was added and the resulting solution was shaken with aqueous sodium bicarbonate. The chloroform layer was dried (Na_2SO_4), filtered, and concentrated to a syrup (IVa and IVb, 78 mg) $[\alpha]_D$ +19° (*c* 0.5, $CHCl_3$). (Found: C 69.8, H 6.91, $C_{23}H_{28}O_6$ requires: C 70.0; H 7.05). The syrup was subsequently fractionated by TLC (light petrol (40 – 60°) – Et_2O – EtOAc 5:2:1) to yield IVa (minor component), $[\alpha]_D$ +13° (*c* 0.3, $CHCl_3$), and IVb (major component), $[\alpha]_D$ +12° (*c* 0.3, $CHCl_3$). These substances were not quite pure and tended to decompose on standing which may account for the rotations being lower than that recorded above for the mixture. NMR, IVa, ($CDCl_3$): δ 1.33 (d, J = 5 Hz, 3 H), ethylidene methyl protons; δ 3.58 (s, 3 H), methoxyl protons; δ 4.65 (2 H) and 4.83 (2 H), benzylic protons; δ 5.25 (q, J = 5 Hz, 1 H), ethylidene methine proton. NMR IVb, ($CDCl_3$): δ 1.30 (d, J = 5 Hz, 3 H), ethylidene methyl protons; δ 3.54 (s, 3 H), methoxyl protons; δ 4.62 (2 H) and 4.82 (2 H), benzylic protons; δ 5.13 (q, J = 5 Hz, 1 H), ethylidene methine proton.

Methyl 3,4-O-ethylidene-β-D-galactopyranoside (Va, Vb). The above dibenzylated ethylidene acetals, IVa and IVb, were hydrogenated in ethanol using 5 % palladium on charcoal as catalyst to give, in quantitative yields, respectively, Va, $[\alpha]_D$ +13° (*c*, 0.3, H_2O), m.p. 169 – 171° (recrystallized from ethanol), and Vb, $[\alpha]_D$ +8° (*c*, 0.3, H_2O), m.p. 193 – 196° (recrystallized from ethanol). (Found, Va: C 49.2; H 7.48. Vb: C 49.0; H 7.27. $C_9H_{16}O_6$ requires: C 49.1; H 7.32). NMR, Va (D_2O, δ values in ppm downfield from sodium 3-(trimethylsilyl)-propane sulphonate: δ 1.35 (d, J = 5 Hz, 3 H), ethylidene methyl protons; δ 3.57 (s, 3 H), methoxyl protons; δ 5.45 (q, J = 5 Hz, 1 H), ethylidene methine proton. NMR, Vb (D_2O, δ values in ppm downfield from sodium 3-(trimethylsilyl)propane sulphonate: δ 1.45 (d, J = 5 Hz, 3 H), ethylidene methyl protons; δ 3.58 (s, 3 H), methoxyl protons; δ 5.25 (q, J = 5 Hz, 1 H), ethylidene methine proton.

Crystallography. Vb crystallized in space groups $P2_12_12_1$, $a=16.678$ (1), $b=12.828$ (2), $c=4.9165(9)$, $Z=4$. The X-ray data were collected using a Philips PW 1100 computer-controlled single-crystal diffractometer with graphite monochromatized Cu$K\alpha$ radiation. The determination of the phases were carried out by a computerized application of direct methods using the weighted phase-sum formula described by Norrestam.[9]

Several cycles of full-matrix least-squares refinements (anisotropic non-hydrogen and fixed isotropic hydrogen temperature parameters) gave an R-value of 0.052. Full details of the X-ray diffraction investigation will be published elsewhere.[10]

Acknowledgements. The authors are indebted to Professor Peder Kierkegaard and to Professor Bengt Lindberg for their interest. The investigation received financial support from Riksbankens Jubileumsfond, Hierta Retzius stipendiefond and Statens Naturvetenskapliga Forskningsråd.

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Received December 11, 1973.