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Note

Synthesis of 4,6,4′,6′- and 3,6,3′,6′-dianhydro-(α-D-galactopyranosyl α-D-galactopyranoside)

AVRAHAM LIAV

Department of Molecular and Cellular Biology, National Jewish Hospital and Research Center, Denver, Colorado 80206 (U.S.A.)

AND MAYER B. GOREN*

Department of Molecular and Cellular Biology, National Jewish Hospital and Research Center, Denver, Colorado 80206 (U.S.A.) and Department of Microbiology and Immunology, University of Colorado Health Sciences Center, Denver, Colorado (U.S.A.)

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As part of our studies to synthesize cord factors and pseudo cord factors in order to evaluate their biological activities (see ref. 1 and references cited therein), we have recently described the synthesis of 6,6′-di-*O*-mycoloyl- and -corynomycoloyl- (α-D-galactopyranosyl α-D-galactopyranoside)[1]. These were prepared from the appropriate potassium carboxylates and 2,3,2′,3′-tetra-*O*-benzyl-6,6′-di-*O*-*p*-tolylsulfonyl-(α-D-galactopyranosyl α-D-galactopyranoside) (**1**). The reactions also gave rise to the formation of by-products to which the tentative structure 4,6-anhydro-2,3,2′,3′-tetra-*O*-benzyl-6′-*O*-mycoloyl-(or -corynomycoloyl)-(α-D-galactopyranosyl α-D-galactopyranoside) was assigned. This assignment was based on our earlier finding that treatment of 6,6′-di-*O*-*p*-tolylsulfonyl- α,α-trehalose with potassium corynomycolate gave the desired 6,6′-diester and also a 3,6-monoanhydro derivative[2,3]. Since in **1** OH-3 is blocked by a benzyl group, in the absence of rearrangement the postulated by-product is expected to have the structure of a 4,6-anhydride.

In order to study the regioselectivity of dianhydride formation from 6,6′-di-*O*-*p*-tolylsulfonyl-(α-D-galactopyranosyl α-D-galactopyranoside), we have undertaken the synthesis of the 4,6,4′,6′- and 3,6,3′,6′-dianhydro-(α-D-galactopyranosyl α-D-galactopyranoside) derivatives **4** and **5**. Treatment of the di-*O*-tosyl derivative **1** with sodium methoxide in boiling methanol gave the 2,3,2′,3′-tetra-*O*-benzyl-4,6,4′,6′-dianhydride **3** as the sole product. Field-desorption, mass spectrometry confirmed that the molecular weight was as anticipated (666). Moreover, a principal peak (*m/z* 325) was in accord with that expected for the primary oxonium fragment

*To whom correspondence should be addressed.

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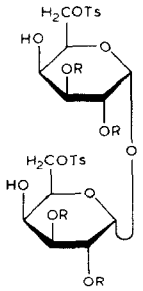

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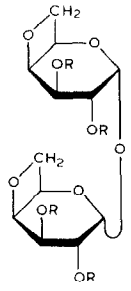
2 R = H



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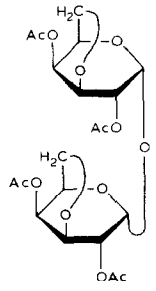
4 R = Ac



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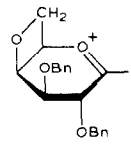

m/z 325

6

6. In order to simplify its complex ^{1}H-n.m.r. spectrum, **3** was converted into the corresponding tetraacetate **4** by catalytic hydrogenolysis and subsequent acetylation. The high-field, ^{1}H-n.m.r. spectrum (360 MHz) of **4** in $CDCl_3$ (Table I) is in agreement with the dianhydride structure. However, the interpretation of the spectrum is somewhat ambiguous owing to the overlapping of the H-1,1′ and H-4,4′ signals. A more conclusive assignment of the ^{1}H-n.m.r. signals was achieved when the spectrum was recorded for a solution in ($^2H_6$)benzene (see Table I and Fig. 1). In this case, the signals for H-1,1′ and H-4,4′ were well separated; H-1,1′ appeared

TABLE I

CHEMICAL SHIFTS AND COUPLING CONSTANTS FOR COMPOUNDS **4** AND **5**

Chemical shifts δ	*Compound*		
	4 *in* $CDCl_3$	**4** *in* C_6D_6	**5** *in* $CDCl_3$
H-1,1′	5.32	5.41	5.28
H-2,2′	5.49	5.81	5 19
H-3,3′	5.10	5.35	4.40
H-4,4′	5.32	5.72	5.41
H-5,5′	4.45	4.11	4.46
$H\text{-}6,6'_{endo}$	4.76	4.15	4.15
$H\text{-}6,6'_{exo}$	4.72	3.92	3.98
Couplings constant (Hz)			
$J_{1,2}$	2.8	2.9	2.7
$J_{2,3}$	10.2	10.0	5.4
$J_{3,4}$	5.0	5.0	0
$J_{4,5}$	3.8	5.0	1.8
$J_{4,6}$	1.40	1.30	
$J_{5,6endo}$	3.8	4.2	0
$J_{5,6exo}$	1.4	1.3	2.9
$J_{6endo,6exo}$	7.4	7.1	10.4

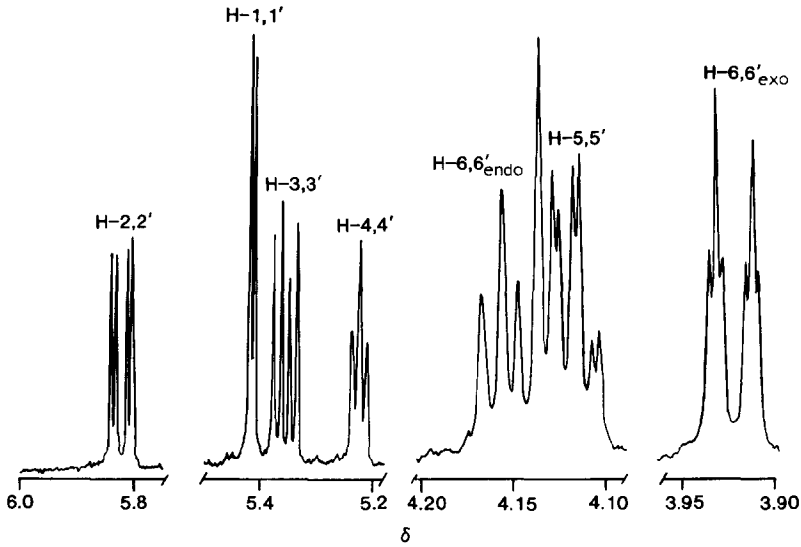

Fig. 1. Partial ^{1}H-n.m.r. spectrum of 2,3,2′,3′-tetra-*O*-acetyl-4,6,4′,6′-dianhydro-(α-D-galactopyranosyl α-D-galactopyranoside) (**4**) in C_6D_6 (at 360 MHz). See text and Table I.

as a doublet (δ 5.41) and H-4,4′ appeared as a broad triplet. The multiplicities of the remaining signals were identical with the signals that appeared in the $CDCl_3$ spectrum.

The H-6,6′$_{exo}$ signal appears as a doublet of triplets, which indicates that there is a long-range interaction ($J_{6,4}$ 1.3 Hz) in the spectrum. This interpretation was confirmed by a double-irradiation experiment; irradiation at H-4,4′ resulted in the collapse of the H-5,5′ and H-6,6′$_{exo}$ signals into a doublet of doublets. Long-range interactions have already been observed in sugar anhydrides[4–6]. The signals for H-2,2′ and H-3,3′ (both deshielded by an adjacent acetoxy group) appeared at low field as expected, and the remaining doublet of doublets (at δ 4.15) was assigned to H-6,6′$_{endo}$. Additional decoupling experiments confirmed the interpretation of the spectrum.

The coupling constants observed in the spectrum of **4** are similar to those described for methyl 4,6-anhydro-2,3-di-*O*-methyl-α-D-galactopyranoside[7]. The two pyranose rings in **4** probably exist in a slightly distorted $^4C_1$(D) conformation as previously described[7].

We suggest that the formation of a 4,6-anhydride is possible only under such unique circumstances as when OH-4 is in a suitable configuration (such as *galacto, talo, ido,* or *gulo*) for a nucleophilic attack to displace a leaving group at C-6 and, because of the steric restrictions to forming this strained structure, only if OH-3 is blocked by a stable substituent. Thus, as described earlier by Müller *et al.*[8], treatment of methyl 2,3,6-tri-*O*-acetyl-4-*O*-methylsulfonyl-β-D-galactopyranoside with sodium methoxide resulted only in deacetylation; the sulfonate group was not displaced. The requirement for blocking of OH-3 was ascertained by hy-

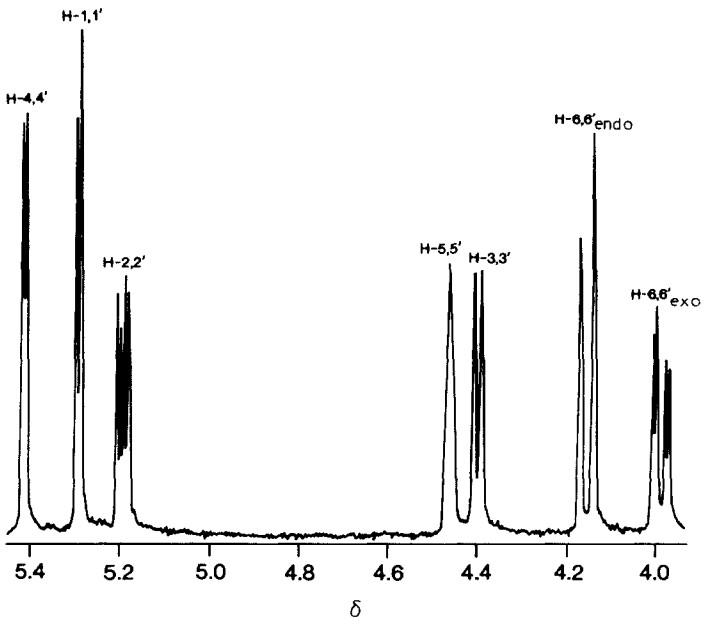

Fig. 2. Partial ^{1}H-n.m.r. spectrum of 2,4,2′,4′-tetra-*O*-acetyl-3,6,3′,6′-dianhydro-(α-D-galactopyranosyl α-D-galactopyranoside) (**5**) in $CDCl_3$ (at 360 MHz). See text and Table I.

drogenolysis of **1** to give 6,6′-di-*O*-*p*-tolylsulfonyl-(α-D-galactopyranosyl α-D-galactopyranoside) (**2**), which was treated with sodium methoxide in methanol and subsequently acetylated to give only one product, the more favored 3,6,3′,6′-dianhydro derivative **5**, which differed from the 4,6,4′,6′-dianhydride **4** in its optical rotation, mobility on t.l.c., and ^{1}H-n.m.r. spectrum.

In the ^{1}H-n.m.r. spectrum of **5** (Fig. 2 and Table I), the three low-field signals were attributed to H-2,2′, H-4,4′ (deshielded by the adjacent acetoxy groups), and H-1,1′. Irradiation at δ 5.19 caused the doublet at δ 5.28 to collapse into a singlet. Hence, this doublet belongs to H-1,1′ and the doublet of doublets (at δ 5.2) to H-2,2′. The narrow doublet at δ 5.41 p.p.m. (J 1.8 Hz) was assigned to H-4,4′. Irradiation at δ 5.19 (H-2,2′) also caused the collapse of the doublet at δ 4.40 into a singlet, which indicated that this doublet belongs to H-3,3′ and $J_{3,4}$ is 0 Hz. Also, irradiation at δ 4.40 (H-3,3′) did not change the H-4,4′ signal. The splitting of the H-4,4′ signal is probably due to H-5,5′. The H-5,5′ signal appeared as a broad singlet at δ 4.46. It is coupled to H-6,6′$_{exo}$ ($J_{5,6exo}$ 2.90 Hz) (confirmed by a double irradiation) but not to H-6,6′$_{endo}$ which appeared as a wide doublet ($J_{6endo,6exo}$ 10.4 Hz). The coupling constants observed in the spectrum of **5** are very similar to those reported for the analogous 3,6,3′,6′-dianhydro-α,α-trehalose[4] and in agreement with a slightly distorted $^1C_4$(D) conformation[4].

EXPERIMENTAL

General methods. — Optical rotations were determined with a Jasco DIP-140 polarimeter. Eastman Kodak plates were used for t.l.c. Chromatography columns were packed with silica gel (Baker #3405). Organic solutions were dried over Na_2SO_4. The n.m.r. spectra were recorded at 360 MHz with an NT 360 spectrometer with tetramethylsilane as the internal standard, and $CDCl_3$ or C_6D_6 as the solvent. Field desorption mass spectra (f.d.m.s.) were recorded with a combined FD/EI ion source at 8 kV on line to a LOGOS-II computer system[9]. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tennessee.

*4,6,4',6'-Dianhydro-2,3,2',3'-tetra-*O*-benzyl-(α-*D*-galactopyranosyl α-*D*-galactopyranoside)* (**3**). — A mixture of 2,3,2',3'-tetra-*O*-benzyl-6,6'-di-*O*-*p*-tolylsulfonyl-(α-D-galactopyranosyl α-D-galactopyranoside) (**1**, 116 mg) and M sodium methoxide (1 mL) in methanol (2 mL) was boiled under reflux for 2 h. The mixture was made neutral with acetic acid and evaporated. The residue was extracted with chloroform and the insoluble solid was filtered off and washed with chloroform. The organic solution was evaporated and the residue was chromatographed on silica gel. Elution with 3:2 hexane–ethyl acetate gave homogeneous **3** (51 mg, 67%), $[\alpha]_D^{23}$ + 189° (*c* 0.6, chloroform).

Anal. Calc. for $C_{40}H_{42}O_9$: C, 72.05; H, 6.35. Found: C, 72.21; H, 6.57.

*2,3,2',3'-Tetra-*O*-acetyl-4,6,4',6'-dianhydro-(α-*D*-galactopyranosyl α-*D*-galactopyranoside)* (**4**). — The dianhydride **3** (51 mg) was dissolved in 2:3 ethyl acetate–ethyl alcohol (50 mL) and hydrogenolyzed in the presence of 10% Pd–C (65 mg) at 340 kPa for 5 h. The catalyst was filtered off and washed with ethanol and the filtrate evaporated. The residue was acetylated with acetic anhydride and pyridine overnight at room temperature, and then evaporated. The residue was chromatographed on silica gel. Elution with 3:2 ethyl acetate–hexane removed a minor by-product. Continued elution with ethyl acetate–hexane 2:1 gave pure **4** (25 mg, 70%), $[\alpha]_D^{23}$ +193° (*c* 1.3, chloroform).

Anal. Calc. for $C_{20}H_{26}O_{13}$: C, 50.63; H, 5.52. Found: C, 50.51; H, 5.73.

*6,6'-Di-*O*-p-tolylsulfonyl-(α-*D*-galactopyranosyl α-*D*-galactopyranoside)* (**2**). — Compound **1** (312 mg) in 1:4 ethyl acetate–ethanol (50 mL) was hydrogenolyzed in the presence of 10% Pd–C (230 mg) at 340 kPa for 17 h. The catalyst was filtered off and washed with ethanol, and the filtrate evaporated. The residue was chromatographed on silica gel. Elution with 7:1 chloroform–methanol removed a trace amount of by-product. Continued elution with 5:1 chloroform–methanol gave **4** (110 mg, 55%), $[\alpha]_D^{23}$ +99° (*c* 1.0, 3:1 chloroform–methanol).

Anal. Calc. for $C_{26}H_{34}O_{15}S_2 \cdot 2\ H_2O$: C, 45.47; H, 5.58; S, 9.33. Found: C, 45.97; H, 5.41; S, 9.23.

*2,4,2',4'-Tetra-*O*-acetyl-3,6,3',6'-dianhydro-(α-*D*-galactopyranosyl α-*D*-galactopyranoside)* (**5**). — Compound **2** (72 mg) was treated with sodium methoxide solution in methanol as described for **3**. The crude dianhydride was acetylated with acetic anhydride and pyridine. The residue, obtained after evaporation and re-

moval of the insoluble solid, was chromatographed on silica gel. Elution with 2:1 ethyl acetate–hexane gave pure **5** (40 mg, 76%), $[\alpha]_D^{23}$ +69° (*c* 0.7, chloroform).

Anal. Calc. for $C_{20}H_{26}O_{15}$: C, 50.63; H, 5.52. Found: C, 50.58; H, 5.58.

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