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SYNTHESIS OF 4-*O*-α-D-GALACTOPYRANOSYL-L-RHAMNOSE AND 4-*O*-α-D-GALACTOPYRANOSYL-2-*O*-β-D-GLUCOPYRANOSYL-L-RHAMNOSE USING DIOXOLANE-TYPE BENZYLIDENE ACETALS AS TEMPORARY PROTECTING-GROUPS

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ABSTRACT

The halide ion-catalysed reaction of benzyl *exo*-2,3-*O*-benzylidene-α-L-rhamnopyranoside with tetra-*O*-benzyl-α-D-galactopyranosyl bromide and hydrogenolysis of the *exo*-benzylidene group of the product **2** gave benzyl 3-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl)-α-L-rhamnopyranoside (**6**). Compound **2** was converted into 4-*O*-α-D-galactopyranosyl-L-rhamnose. The reaction of **6** with tetra-*O*-acetyl-α-D-glucopyranosyl bromide and removal of the protecting groups from the product gave 4-*O*-α-D-galactopyranosyl-2-*O*-β-D-glucopyranosyl-L-rhamnose.

INTRODUCTION

The synthesis of complex oligosaccharides involves a suitable agent for glycosylation and a suitable aglycon derivative. Glycosylating agents have been widely studied[1–4], but the synthesis of aglycons suitable for the synthesis of branched oligosaccharides has been relatively neglected. The introduction of allyl ethers[5] and the application of "persistent" and "temporary" protecting-groups[6] seem to be generally useful[7]. Such methods as the partial hydrolysis of ortho esters[8], acyl migration[9], or partial acylation[10] have produced remarkable results, but they cannot be considered as general.

The stereoselective hydrogenolysis[11,12] of dioxolane-type benzylidene acetals to give *O*-benzyl derivatives opens convenient routes for the synthesis of 2,4-di-*O*-glycosylpyranosides from the easily available *exo*-2,3- or -3,4-*O*-benzylidene acetals of L-rhamno-, D-manno-, D- and L-arabino-, D- and L-fuco-, and D-galacto-pyranosides.

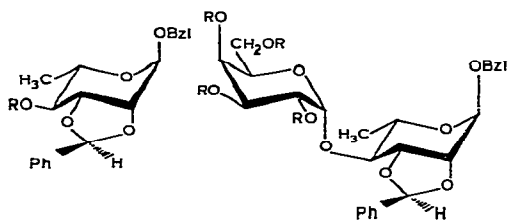
Analogous reactions of dioxane-type benzylidene acetals have been reported[13] for the synthesis of branched trisaccharides.

We now report on the synthesis of 4-*O*-α-D-galactopyranosyl-2-*O*-β-D-glucopyranosyl-L-rhamnose, the carbohydrate moiety[14,15] of Saponaside D.

RESULTS AND DISCUSSION

The halide ion-catalysed[1] reaction of benzyl *exo*-2,3-*O*-benzylidene-α-L-

rhamnopyranoside[16] (**1**) with 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl bromide[17] gave the crystalline disaccharide derivative **2** (85%). The ^{1}H-n.m.r. signal (δ 6.12) for the benzylidene acetal proton of **2** confirmed the *exo* configuration. That the interglycosidic bond was α was shown by the ^{13}C-resonance for C-1′ at 99.0 p.p.m. ($J_{C\text{-}1',H\text{-}1'}$ 167 Hz). For methyl 2,3,4,6-tetra-*O*-benzyl-α- (**3**) and -β-D-galactopyranoside (**4**), the corresponding data were 98.9 (168.7 Hz) and 105.2 p.p.m. (156 Hz), respectively.

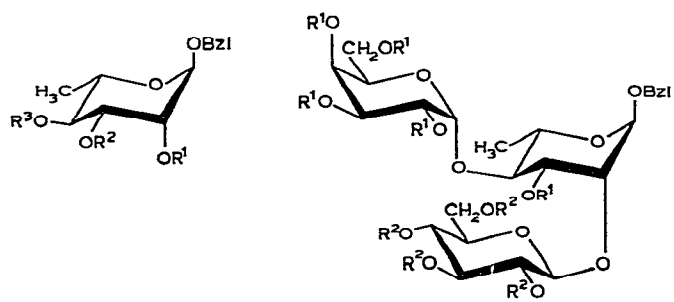


1 R = H **2** R = Bzl **3** R^1=OMe; R^2= H; R^3= Bzl **6** R = Bzl

5 R = Bzl **4** R^1= H; R^2= OMe; R^3= Bzl

The assignment of signals in the ^{13}C-spectrum of **2** was based on a comparison of the spectra of **1**, the 4-*O*-benzyl derivative[16] (**5**) of **1**, and **3**. Thus, benzylation resulted in a positive shift of 5.8 p.p.m. for the C-4 signal, whereas glycosylation was accompanied by a positive α-shift of 4.4 p.p.m. The chemical shifts of the 2,3,4,6-tetra-*O*-benzyl-D-galactopyranosyl part of **2** and methyl 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranoside (**3**) are similar. There is a large difference (6.2 p.p.m.) between the chemical shift of C-1′ of **2** and C-1 of **4**. These findings and the $^1J_{C,H}$ coupling constant of **2** proved the interglycosidic bond of **2** to be α. The identity of configuration[18] at the benzylidene acetal carbon in **1** and **2** is also indicated by the data in Table I.

The reaction of **2** with the $LiAlH_4$–$AlCl_3$ reagent gave the disaccharide derivative **6**, the ^{13}C-n.m.r. spectrum of which, in comparison with those of benzyl 3,4-[16] (**7**) and 2,4-di-*O*-benzyl-α-L-rhamnopyranoside[16] (**8**), confirmed that **6** was the 2-hydroxy-3-*O*-benzyl derivative. Benzylation of HO-2 of rhamnopyranoside deriva-



7 R^1= H; R^2= R^3=Bzl **9** R^1= Bzl; R^2= Ac

8 R^1=R^3= Bzl; R^2= H **10** R^1= Bzl; R^2= H

TABLE I

^{13}C-N.M.R. CHEMICAL SHIFTS (P.P.M.) AND COUPLING CONSTANTS (Hz)

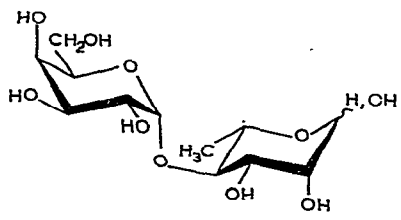
Carbon atom	*Compound*																
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**[a]		**12**		**13**		**14**
											α	β	α	β	α	β	
Rhamnose																	
C-1	96.6	96.5			96.5	98.4	98.7	96.5	99.2	97.9	94.0	93.9	94.3	94.1	93.35	93.26	91.8
		164					169		168						171.9	161.5	
C-2	75.6	76.0			75.8	68.2	68.7	78.9	76.2	76.3	82.1	82.4	71.8	72.0	81.9	82.5	79.2
C-3	79.8	79.4			79.9	79.1	80.2	71.8	79.2	78.3	70.9	74.3	69.6	72.4	69.4	72.4	71.2
C-4	72.2	76.6			78.0	79.0	80.2	82.4	79.2	79.2	73.5	73.2	82.1	81.6	81.8	81.4	82.3
C-5	65.9	65.3			64.6	67.9	67.8	67.6	68.6	68.8	69.3	73.8	68.1	72.3	68.2	72.4	67.4
C-6	17.5	17.4			17.9	18.3	18.1	18.1	18.2	18.5	17.9	17.9	17.9	17.9	17.9	17.9	18.1
Ph-CH	103.1	102.8			102.9												
Ph-CH_2-1	69.4	69.2			69.3	69.1	69.1	69.0	69.2	69.5							
Ph-CH_2-2								73.1									73.1
Ph-CH_2-3						71.7	72.0		71.7	72.9							
Ph-CH_2-4					73.0		75.2	74.9									74.9
Galactose																	
C-1		99.0	98.9	105.2		98.5			98.5	98.6			100.5		100.5		
		167	168.7	156											170.2		
C-2		78.4	79.1	82.4		77.5			78.9	78.2			69.2		69.3		
C-3		76.8	76.8	79.7		77.0			77.0	77.0			69.6		70.1[b]		
C-4		75.1	75.6	75.1		75.4			75.3	75.7			69.9		69.9[b]		
C-5		69.4	69.5	69.1		69.8			69.7	69.9			70.0		71.4		
C-6		68.6	69.2	73.1		69.1			68.9	69.2			61.6		61.5		
OCH_3			55.2	56.8													
Glucose																	
C-1									101.7	105.4	105.3	104.6			104.9	104.4	
—									162							159.7	
C-2									72.7	74.2	74.5	73.2			74.3	74.1	
C-3									72.9	76.9	77.0	77.2			76.7	76.9	
C-4									68.8	70.1	70.5				70.3	70.2	
C-5									71.3	76.6	76.7	76.6			76.5	76.4	
C-6									61.9	62.2	61.7				61.5	61.4	

[a]Chemical shifts for **11** are taken from ref. 21. [b]Assignments may be reversed.

tives results in a strong, negative β-shift (1.5–2.0 p.p.m.) at C-1, and the lack of this β-shift for **6** proves the structure. T.l.c. showed that only traces of the 2-*O*-benzyl-3-hydroxy analogue were formed.

The reaction of **6** with tetra-*O*-acetyl-α-D-glucopyranosyl bromide in benzene–nitromethane in the presence of $Hg(CN)_2$ afforded the trisaccharide derivative **9** (45%). The low yield reflects the decreased reactivity[19,20] of HO-2. The β configuration of the new glycosidic bond in **9** was indicated by the ^{13}C-chemical shift (101.7 p.p.m.) of C-1″ and the low coupling-constant (162 Hz). This assignment was proved also by the C-1″ resonance (105.4 p.p.m.) of **10**, obtained from **9** by Zemplén deesterification. The chemical shifts of the carbon atoms of the glucose moiety were in good agreement with those of the corresponding carbon atoms of 2-*O*-β-D-glucopyranosyl-L-rhamnose[21] (**11**).

Palladium-catalysed hydrogenolysis of **2** and **10** gave 4-*O*-α-D-galactopyranosyl-L-rhamnose (**12**) and 4-*O*-α-D-galactopyranosyl-2-*O*-β-D-glucopyranosyl-L-rhamnose (**13**), respectively.



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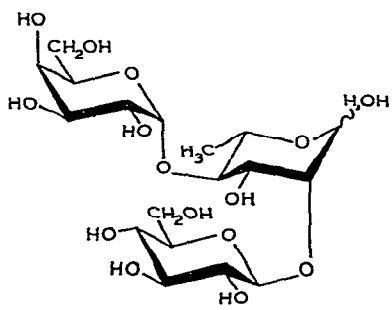

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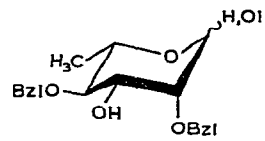

14

In the ^{13}C-n.m.r. spectrum of **12**, the signals for the L-rhamnose moiety, except that for C-6, were doublets reflecting the ratio of the α and β anomers. At C-4, glycosylation α-shifts of 9.4 and 8.9 p.p.m. were observed relative to α,β-L-rhamnopyranose[21]. Since the αβ-ratio for the reducing L-rhamnopyranose moiety of **13** was ~1.5, it can be inferred that the resonances at 82.5, 81.9, 81.8, and 81.4 p.p.m. correspond to C-2β, C-2α, C-4α, and C-4β, respectively. For the assignment of the signals of the carbon atoms of the rhamnopyranose and α-D-galactopyranosyl moieties, the spectral data[22,23] of 2,4-di-*O*-benzyl-L-rhamnopyranose (**14**) and D-galactopyranosyl derivatives were considered.

Inversion of configuration at C-1 in glycosyl-(1→2)-glycoses induces[24] a large chemical shift of C-1′. A similar effect occurs[21] with 2-*O*-β-D-glucopyranosyl-L-rhamnopyranose, for which the C-2,3,5 signals of the β-D-glucopyranosyl part were reported to be doublets.

In the ^{13}C-n.m.r. spectrum of **13**, each signal of the β-D-glucopyranosyl residue is a doublet reflecting the αβ-anomeric ratio. The following chemical-shift differences

for the β-D-glucopyranosyl moiety reflect the α or β character of the rhamnopyranose moiety: C-1′ +0.49, C-2′ +0.16, C-3′ −0.20, C-4′ +0.13, C-5′ +0.10, and C-6′ +0.10 p.p.m. The two $^1J_{C\text{-}1',H\text{-}1'}$ values were 159.7 Hz, and the other $^1J_{C,H}$ values were C-1α 171.9, C-1β 161.5, and C-1″α 170.2 Hz. The observed value (4 Hz) of $^3J_{C\text{-}1'',H\text{-}4'}$ is characteristic for a staggered interglycosidic linkage[25].

Double signals for the carbon atoms of the α-D-galactopyranosyl moiety, reflecting the αβ-ratio of the reducing-end, as reported by Lemieux *et al.*[8] for 3-*O*-α-D-galactopyranosyl-α,β-D-galactopyranose, were not observed for **12** or **13**.

EXPERIMENTAL

General methods. — Melting points (uncorrected) were determined with a Kofler apparatus. T.l.c. and column chromatography were performed on Kieselgel G; detection was effected in t.l.c. by charring with sulphuric acid. Optical rotations were measured with a Perkin–Elmer 241 automatic polarimeter; equilibrium values are given for **12–14**. ^{13}C-N.m.r. spectra were recorded with a Varian XL-100-15 FT spectrometer for solutions in $CDCl_3$ (internal Me_4Si) or D_2O (internal 1,4-dioxane).

Benzyl exo-*2,3-O-benzylidene-4-O-(2,3,4,6-tetra-O-benzyl-α-D-galactopyranosyl)-α-L-rhamnopyranoside* (**2**). — To a mixture of benzyl *exo*-2,3-*O*-benzylidene-α-L-rhamnopyranoside[16] (**1**, 1.03 g), tetraethylammonium bromide (1.26 g), ethyl diisopropylamine (1 ml), and powdered molecular sieve 4 A (5 g) in dry dichloromethane (5 ml) was added a solution of 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl bromide (freshly prepared[17] from 4.13 g of *p*-nitrobenzoate) in dry dichloromethane (10 ml). The mixture was stirred for 3 days at room temperature, and then diluted with chloroform, filtered, washed with water (3 × 50 ml), dried, and concentrated. The residue was eluted from a column (250 g) of silica gel with light petroleum–ether (4:1), to remove u.v.-fluorescent by-products, and then with 4:1 light petroleum–ethyl acetate to give **2** (2.22 g, 85%), which, after recrystallisation from chloroform–hexane, had m.p. 88–89°, $[\alpha]_D$ +15.5° (*c* 2.1, chloroform), R_F 0.33 (light petroleum–ethyl acetate, 4:1).

Anal. Calc. for $C_{54}H_{56}O_{10}$: C, 74.98; H, 6.52. Found: C, 75.10; H, 6.61.

Benzyl 3-O-benzyl-4-O-(2,3,4,6-tetra-O-benzyl-α-D-galactopyranosyl)-α-L-rhamnopyranoside (**6**). — To a stirred suspension of $LiAlH_4$ (0.38 g) in dry dichloromethane–ether (1:1, 20 ml) were added a solution of $AlCl_3$ (1.33 g) in ether (20 ml) and then a solution of **2** (1.29 g) in the former solvent mixture (20 ml). The solution was boiled for 15 min and then cooled, and the excess of reagent was decomposed by the addition of water. The precipitate was collected, and extracted with ether (3 × 50 ml), and the combined extracts were washed with water, dried, and concentrated. The residue was eluted from a column of silica gel (120 g) with light petroleum–ethyl acetate (7:3), to give **6** (0.82 g, 64%) as a syrup, R_F 0.20 (light petroleum–ethyl acetate, 7:3), $[\alpha]_D$ +3°, $[\alpha]_{365}$ −1° (*c* 1, chloroform).

Anal. Calc. for $C_{54}H_{58}O_{10}$: C, 74.80; H, 6.74. Found: C, 75.08; H, 6.81.

Benzyl 3-O-benzyl-2-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-4-O-(2,3,4,6-tetra-O-benzyl-α-D-galactopyranosyl)-α-L-rhamnopyranoside (**9**). — To a solution of **6** (0.73 g) in benzene–nitromethane (1:1, 30 ml) was added $Hg(CN)_2$ (0.26 g), and 20 ml of the solvent was distilled off at atmospheric pressure. After cooling, tetra-*O*-acetyl-α-D-glucopyranosyl bromide (*X*) (0.42 g) was added to the mixture, which was then stirred at 45°. After 12 and 20 h, more $Hg(CN)_2$ (0.13 g) and *X* (0.21 g) were added and stirring was continued for 20 h. The mixture was then concentrated, diluted with chloroform (200 ml), washed with 5% aqueous potassium iodide (3 × 50 ml) and water (50 ml), dried (Na_2SO_4), and concentrated. The residue was eluted from a column of silica gel (250 g) with chloroform–ethyl acetate (7:3), to obtain amorphous **9** (0.45 g, 45%), $[\alpha]_D$ +6° (*c* 1.9, chloroform), R_F 0.52 (chloroform–ethyl acetate, 9:1).

Anal. Calc. for $C_{68}H_{76}O_{19}$: C, 68.21; H, 6.40. Found: C, 68.17; H, 6.46.

Benzyl 3-O-benzyl-2-O-β-D-glucopyranosyl-4-O-(2,3,4,6-tetra-O-benzyl-α-D-galactopyranosyl)-α-L-rhamnopyranoside (**10**). — To a solution of **9** (0.45 g) in methanol (20 ml) was added 2M methanolic sodium methoxide (0.2 ml). The solution was kept at room temperature for 2 h, neutralised with Amberlite IR-120 (H^+) resin, filtered, and concentrated, to give amorphous **10** (0.36 g, 93%), $[\alpha]_D$ −0.7° (*c* 0.96, chloroform), R_F 0.26 (benzene–methanol, 9:1).

Anal. Calc. for $C_{60}H_{68}O_{15}$: C, 70.02; H, 6.66. Found: C, 70.18; H, 6.72.

4-O-α-D-Galactopyranosyl-L-rhamnose (**12**). — A mixture of **2** (0.42 g) and 10% palladium-on-carbon (0.2 g) in ethanol (16 ml) and acetic acid (4 ml) was hydrogenated at room temperature and atmospheric pressure, filtered, and eluted from a column of charcoal–Celite (1:1, 6 g) with an ethanol–water gradient (ethanol, 2.5% initially). The disaccharide **12** (0.12 g, 76%) was eluted at 10% ethanol and had $[\alpha]_D$ +114° (*c* 0.93, water), R_F 0.37 (t.l.c., cellulose, 1-butanol–acetic acid–water, 2:2:1).

Anal. Calc. for $C_{12}H_{22}O_{10}$: C, 44.17; H, 6.80. Found: C, 44.25; H, 6.88.

4-O-α-D-Galactopyranosyl-2-O-β-D-glucopyranosyl-L-rhamnose (**13**). — A solution of **10** (0.34 g) in acetic acid (40 ml) was hydrogenated in the presence of 10% palladium-on-carbon (0.4 g) at room temperature for 24 h, and then filtered and concentrated. The residue was eluted from a column of Kieselgel G (15 g) with 1-butanol–methanol–water (3:1:1), to give amorphous **13** (91 mg, 56.9%), $[\alpha]_D$ +74.5° (*c* 1.2, water), R_F 0.38 (1-butanol–methanol–water, 3:1:1).

Anal. Calc. for $C_{18}H_{32}O_{15}$: C, 44.26; H, 6.60. Found: C, 44.48; H, 6.54.

2,4-Di-O-benzyl-L-rhamnose (**14**). — Compound **7** (0.13 g) was hydrolysed with a mixture of acetic acid–water (4:1, 3 ml) and M hydrochloric acid (1 ml) at 100° for 20 h. The cooled mixture was concentrated, water and then toluene were distilled from the residue, and column chromatography with toluene–methanol (85:15) then yielded syrupy **13** (83 mg, 83%), R_F 0.52 and 0.54 (toluene–methanol, 85:15), $[\alpha]_D$ +7° (*c* 1.5, chloroform).

Anal. Calc. for $C_{20}H_{24}O_5$: C, 69.75; H, 7.02. Found: C, 69.89; H, 7.10.

REFERENCES

1 R. U. LEMIEUX, K. B. HENDRIKS, R. V. STICK, AND K. JAMES, *J. Am. Chem. Soc.*, 97 (1975) 4056–4062.
2 B. HELFERICH, W. M. MÜLLER, AND S. KARBACH, *Justus Liebigs Ann. Chem.*, (1974) 1514–1521.
3 H. PAULSEN AND W. STENZEL, *Angew. Chem. Int. Ed. Engl.*, 14 (1975) 558–559.
4 J. R. POUGNY, J.-C. JACQUINET, M. NASSR, D. DUCHET, M. L. MILAT, AND P. SINAŸ, *J. Am. Chem. Soc.*, 99 (1977) 6762–6763.
5 J. GIGG AND R. GIGG, *J. Chem. Soc., C*, (1966) 82–86.
6 P. J. PFÄFFLI, S. H. HIXSON, AND L. ANDERSON, *Carbohydr. Res.*, 23 (1972) 195–206.
7 J.-C. JACQUINET AND P. SINAŸ, *J. Org. Chem.*, 42 (1977) 720–724.
8 R. U. LEMIEUX AND H. DRIGUEZ, *J. Am. Chem. Soc.*, 97 (1975) 4069–4075.
9 F. SZTARICSKAI, A. LIPTÁK, I. F. PELYVÁS, AND R. BOGNÁR, *J. Antibiot.*, 29 (1976) 626–631.
10 H. PAULSEN AND C. KOLÁR, *Angew. Chem.*, 90 (1978) 823–824.
11 A. LIPTÁK, *Tetrahedron Lett.*, (1976) 3551–3554.
12 A. LIPTÁK, P. FÜGEDI, AND P. NÁNÁSI, *Carbohydr. Res.*, 51 (1976) c19–c21.
13 A. LIPTÁK AND P. NÁNÁSI, *Tetrahedron Lett.*, (1977) 921–924.
14 V. YA. CHIRVA AND P. K. KINTYA, *Khim. Prir. Soedin.*, 6 (1970) 214–218; *Chem. Abstr.*, 73 (1970) 88123.
15 R. TSCHESCHE AND G. WULFF, *Fortschr. Chem. Org. Naturst.*, 30 (1973) 461–606.
16 A. LIPTÁK, P. FÜGEDI, AND P. NÁNÁSI, *Carbohydr. Res.*, 65 (1978) 209–217.
17 F. J. KRONZER AND C. SCHUERCH, *Carbohydr. Res.*, 33 (1974) 273–280.
18 A. LIPTÁK, P. FÜGEDI, P. NÁNÁSI, AND A. NESZMÉLYI, *Tetrahedron*, 35 (1979) 1111–1119.
19 R. R. KING AND C. T. BISHOP, *Carbohydr. Res.*, 32 (1974) 239–249.
20 C. LAFFITE, A. M. NGUYEN PHUOC DU, F. WINTERNITZ, R. WYLDE, AND F. PRATVIEL-SOSA, *Carbohydr. Res.*, 67 (1978) 91–103.
21 P. COLSON AND R. R. KING, *Carbohydr. Res.*, 47 (1976) 1–13.
22 T. E. WALKER, R. E. LONDON, T. W. WHALEY, R. BARKER, AND N. A. MATWIYOFF, *J. Am. Chem. Soc.*, 98 (1976) 5807–5813.
23 D. D. COX, E. K. METZNER, L. W. CARY, AND E. J. REIST, *Carbohydr. Res.*, 67 (1978) 23–31.
24 T. USUI, N. YAMAKOA, K. MATSUDA, K. TUZIMURA, H. SUGIYAMA, AND S. SETO, *J. Chem. Soc., Perkin Trans. 1*, (1973) 2425–2432.
25 A. PARFONDRY, N. CYR, AND A. S. PERLIN, *Carbohydr. Res.*, 59 (1977) 299–309.