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PREPARATION AND MASS-SPECTRAL ANALYSIS OF *O*-HYDROXYETHYL DERIVATIVES OF D-GLUCOSE

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ABSTRACT

Various hydroxyethyl ethers of D-glucose have been prepared in good yield by treating D-glucose derivatives with 2-bromoethyl tetrahydropyranyl ether in the presence of sodium hydride. The derived *O*-(hydroxyethyl)-D-glucitol acetates exhibited characteristic mass-spectral fragments. The furanose and pyranose forms of 1,2-*O*-ethylene-D-glucose derived from 2-*O*-(2-hydroxyethyl)-D-glucose were identified by mass-spectral analysis.

INTRODUCTION

Several gas–liquid chromatographic (g.l.c.) methods have been used to analyze hydrolyzates of *O*-(hydroxyethyl)starch and *O*-(hydroxyethyl)cellulose, compounds used medically as plasma-volume expanders and in industry as coating agents, thickeners or glues[1–3]. These methods are of poor quantitative value and generate multiple peaks because aldoses form *O*-trimethylsilyl (Me_3Si) derivatives of either or both anomers of the pyranose and furanose tautomers. In addition, 1,2-*O*-ethylene-D-glucose derivatives, into which these acid hydrolyzates are partially converted, are not separated satisfactorily by g.l.c. as Me_3Si derivatives of the derived oximes[3]. We recently reported a g.l.c. method, using alditol acetates formed from such hydrolyzates, which resulted in single peaks instead of multiple peaks from the different anomers of each sugar[4]. Identification of the individual peaks was accomplished by reference to authentic standards and/or by mass-spectral analysis.

This paper describes the preparation and mass spectra of *O*-(hydroxyethyl)-D-glucose derivatives needed as reference compounds for this g.l.c. method. The *O*-hydroxyethyl ethers of D-glucose were synthesized in high yield by a novel method involving reaction of glucose derivatives, containing appropriate free

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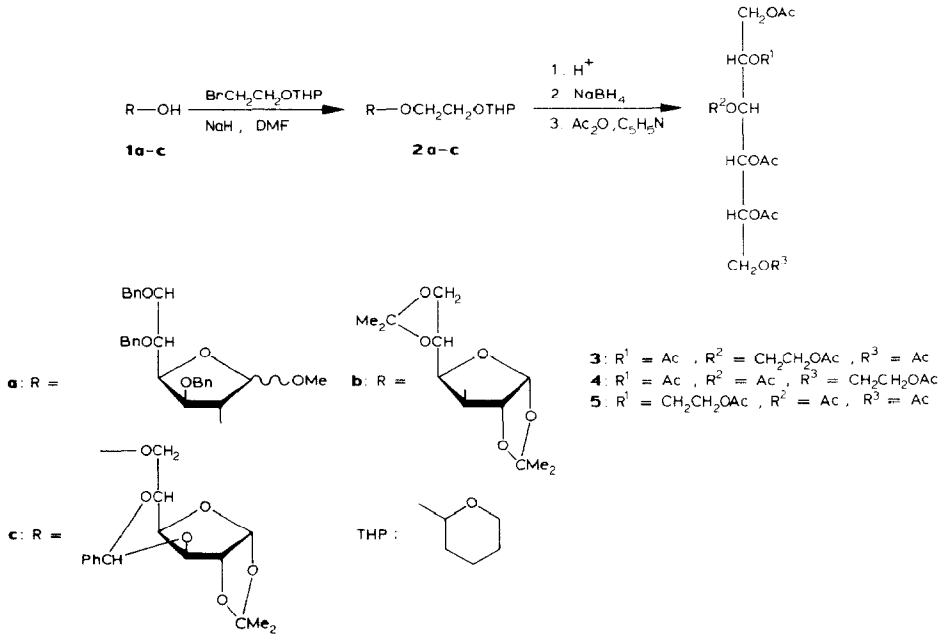
hydroxyl groups, with 2-bromoethyl tetrahydropyranyl ether in the presence of sodium hydride. The *O*-hydroxyethyl-D-glucitols were then obtained by reduction with $NaBH_4$. The mass spectra of the *O*-hydroxyethyl-D-glucitol acetates revealed characteristic, position-dependent fragments. Further, the furanose and pyranose forms of 1,2-*O*-ethylene-D-glucose derived from 2-*O*-hydroxyethyl-D-glucose were differentiated by mass-spectral analysis.

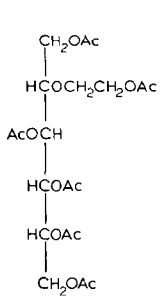
RESULTS AND DISCUSSION

Preparation of O-hydroxyethyl-D-glucose derivatives. — *O*-Hydroxyethyl derivatives of D-glucose have been prepared by several methods[5–7], but these methods give low yields and extensive byproducts. 2-Bromoethyl tetrahydropyranyl ether[8] was used here as a hydroxyethylating agent in the presence of NaH in *N,N*-dimethylformamide (DMF) for the preparation of 2-*O*-, 3-*O*-, and 6-*O*-hydroxyethyl-D-glucose (Scheme 1). Thus, when methyl 3,5,6-tri-*O*-benzyl-D-



Scheme 1

glucofuranose (**1a**) was treated with 2-bromoethyl tetrahydropyranyl ether and NaH in DMF in a nitrogen atmosphere, the 2-*O*-hydroxyethyl-D-glucose derivative **2a** was obtained in 91% yield. Compounds **2b,c** were similarly prepared from **1b,c** in 95 and 90% yields, respectively. Removal of blocking groups from **2b,c**, reduction of the *O*-(hydroxyethyl)glucoses with $NaBH_4$, and acetylation produced the alditol acetates **3** and **4**, respectively. 2-*O*-Hydroxyethyl-D-glucose has been



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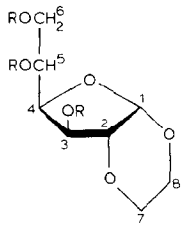
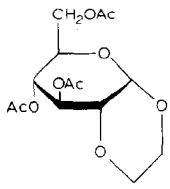


6: R = Bn
7: R = H
8: R = Ac



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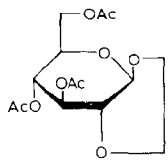

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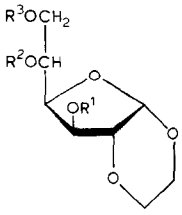
observed to undergo partial conversion into 1,2-*O*-ethylene-glucose (furanose and pyranose forms) during the acid hydrolysis of *O*-(hydroxyethyl)-starch and -cellulose[9–11]. The 1,2-*O*-ethylene-D-glucose derivatives **8** (furanose) and **9** (pyranose) were prepared as follows. Treatment of **2a** with 1% methanolic HCl in $CHCl_3$ afforded **6** in 75% yield. Debenzylation and subsequent acetylation of **6** gave the acetate **8**. Successive glycosidation of D-glucose with 2-bromoethanol, cyclization in alkaline ethanol, and acetylation gave compound **9**. The positive specific rotation of **9** and its $^1J_{CH}$ value of 170.19 Hz indicate the α-glycosidic configuration.

Preparation of disubstituted O-(hydroxyethyl)glucose derivatives and 2-O-(2-hydroxyethoxy)ethyl-D-glucitol peracetate. — The 2,3-diether **13** was prepared in four steps from **7**. Compound **7** was isopropylidenated at C-5 and C-6 and then treated with 2-bromoethyl tetrahydropyranyl ether. The resulting compound (**12**) was converted into the peracetate **13** by acid hydrolysis and subsequent acetylation. Similarly, the 2,6-diether **18** was prepared by starting from **7**. Successive tritylation

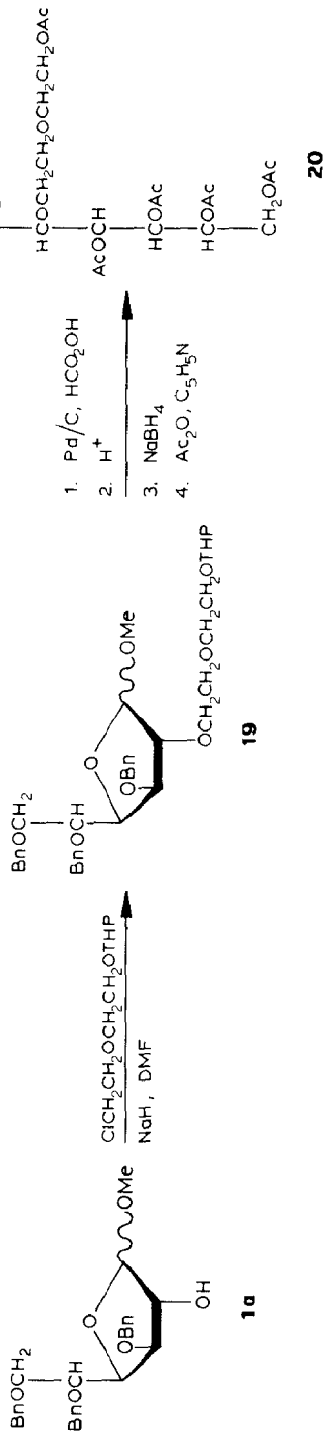


11: R^1 = H, R^2, R^3 = Me_2C
12: R^1 = CH_2CH_2OTHP, R^2, R^3 = Me_2C
13: R^1 = CH_2CH_2OAc, R^2 = R^3 = Ac

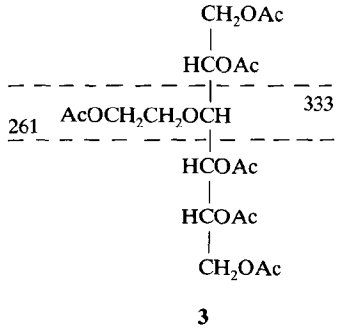
14: R^1 = R^2 = H, R^3 = Tr
15: R^1 = R^2 = Bn, R^3 = Tr
16: R^1 = R^2 = Bn, R^3 = H
17: R^1 = R^2 = Bn, R^3 = CH_2CH_2OTHP
18: R^1 = R^2 = Ac, R^3 = CH_2CH_2OAc

of **7**, benzylation of **14**, acid hydrolysis of **15**, treatment of **16** with 2-bromoethyl tetrahydropyranyl ether, catalytic hydrogenolysis of the benzyl ether of **17**, and acetylation gave compound **18**. 2-*O*-[(2-Hydroxyethoxy)ethyl-D-glucitol acetate (**20**) was prepared in five steps from **1a** (Scheme 2). Thus, treatment of **1a** with 2-(2-chloroethoxy)ethyl tetrahydropyranyl ether[12] in DMF in the presence of NaH gave compound **19** in 89% yield. Compound **19** was converted into alditol acetate **20** by successive catalytic hydrogenolysis, acid hydrolysis, reduction, and acetylation.

Mass spectra of alditol acetates **3**, **4**, *and* **20**. — For investigation by mass spectrometry, numerous mono- and oligo-saccharide derivatives have been


BnOCH2
BnOCH
OBn
OMe
OH
1a
ClCH2CH2OCH2CH2OTHP
NaH, DMF
OCH2CH2OCH2CH2OTHP
19
1. Pd/C, HCO2OH
2. H+
3. NaBH4
4. Ac2O, C5H5N
CH2OAc
HCOCH2CH2OCH2CH2OAc
AcOCH
HCOAc
HCOAc
CH2OAc
20

described[13,14]. The partially methylated alditol acetates show very characteristic mass spectra, especially for methylation analysis[15]. Lindberg *et al.*[16] reported that the fragmentation of methylated *O*-(hydroxyethyl)glucitol acetates in e.i.–m.s. follows the general principles for partially methylated alditol acetates in the analysis of the distribution of substituents in *O*-(hydroxyethyl)cellulose, using the Hakomori methylation procedure[17]. Position-dependent, characteristic fragments were observed for *O*-(hydroxyethyl)glucitol acetates. Molecular ions were not observed in the mass spectra of those alditol acetates, although [M + 1] peaks of low intensity were observed. The base peak in the spectra of these compounds was the acetylium ion, *m/z* 43. Primary ions were formed from alditol acetates by elimination of an acetoxy group, or by cleavage of the alditol chain. From 3-*O*-(hydroxy-



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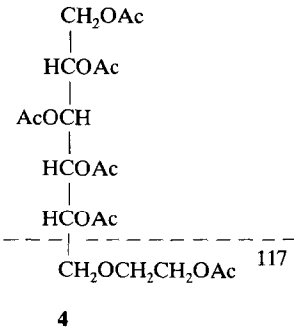

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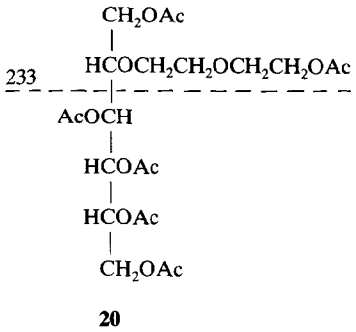

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ethyl)glucitol acetate (**3**) intense peaks at *m/z* 333 and 261 might arise from C-2–C-3 and C-3–C-4 cleavage, respectively. Prominent mass fragments observed in the mass spectrum of 6-*O*-hydroxyethyl-D-glucitol acetate (**4**) were similar to those of hexa-*O*-acetyl-D-glucitol, but the peak at *m/z* 117 which might result from cleavage between C-5 and C-6 was characteristic for **4**. Similarly, from 2-*O*-(2-hydroxyethoxy)ethyl-D-glucitol acetate (**20**), the peak arising from the fission between C-2 and C-3 was observed at *m/z* 233.

*Mass spectra of 1,2-*O*-ethylene-D-glucose derivatives* **8** *and* **9**. — In the mass spectra of the 1,2-*O*-ethylene-D-glucose derivatives **8** and **9**, molecular ions were

not observed, although low-intensity [M + 1] peaks were present. 1,2-*O*-Ethylene-D-glucose derivatives underwent fragmentation in a manner analogous to per-acetylated glycosides[18]. The base peak was *m/z* 43 (Ac), and the fragments were degraded by elimination of acetic acid (CH_3CO_2H, 60), or ketene (CH_2CO, 42). In the mass spectrum of the furanose **8**, prominent fragments were observed at *m/z* 273, 212, 187, 170, 127, 73, and 43. These fragments are anticipated to result from single or consecutive eliminations of acetic acid or ketene. The pyranose **9** also showed a characteristic mass spectrum with prominent fragments at *m/z* 272, 259, 230, 199, 170, 157, 86, 73, and 43. The fragment ion at *m/z* 259, resulting from the fission of the molecule into a fragment retaining C-1–C-5 and elimination of acetic acid, gives a fragment ion at *m/z* 199, that loses ketene to give *m/z* 157. In another fragmentation, the molecular ion is degraded into fragments at *m/z* 272, 230, and 170 by consecutive loss of acetic acid and ketene. Furthermore, the ion at *m/z* 170 gives a fragment ion at *m/z* 86 by elimination of two molecule of ketene. These

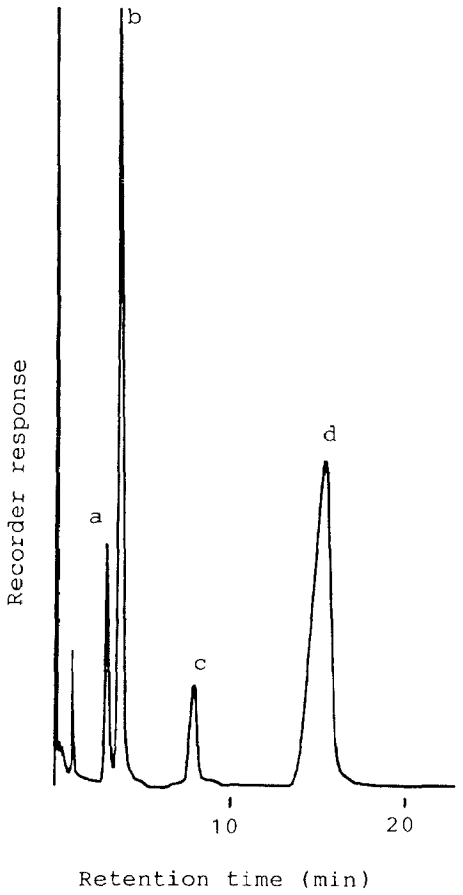


Fig. 1. G.l.c. of the acetates derived from acid hydrolyzates of 1,2-*O*-ethylene-α-D-glucofuranose.

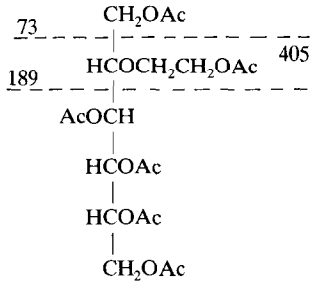
TABLE I

M.S. OF THE ACETATES DERIVED FROM ACID HYDROLYZATES OF 1,2-*O*-ETHYLENE-α-D-GLUCOFURANOSE

Peak numbers (compd. no.)	*Prominent fragments* (m/z)
a (**8**)	43, 73, 127, 170, 187, 212, 273
b (**9**)	43, 73, 86, 157, 170, 199, 230, 259, 272
c (**10**)	43, 73, 86, 157, 170, 199, 230, 259, 272
d (**5**)	43, 73, 87, 189, 375, 405

results suggest that characteristic fragmentations of the furanose and pyranose may be used to determine the ring size in 1,2-*O*-ethylene-D-glucoses.

G.l.c.–m.s. analysis of acid hydrolyzates of 1,2-O-ethylene-α-D-glucofuranose (**7**). — Other isomers of 2-*O*-hydroxyethylglucose were determined by g.l.c.–m.s. of hydrolyzates of 1,2-*O*-ethylene-α-D-glucofuranose (**7**). Compound **7** was successively hydrolyzed, reduced and acetylated. The g.l.c. trace is shown in Fig. 1, and Table I gives the prominent mass fragments of the components of the peaks in Fig. 1. By reference to the retention time of prepared standards (**8, 9**) and mass-spectral analysis, peak (*a*) in Fig. 1 was identified as 1,2-*O*-ethylene-α-D-glucofuranose (**8**) and peak (*b*) was 1,2-*O*-ethylene-α-D-glucopyranose (**9**). Prominent fragments of peak (*c*) were observed at *m/z* 272, 259, 230, 199, 170, 157, and 86 which are characteristic of 1,2-*O*-ethylene-D-glucopyranose triacetate, suggesting that peak (*c*) is 1,2-*O*-ethylene-β-D-glucopyranose triacetate (**10**). Peak (*d*) was identified as 2-*O*-hydroxyethyl-D-glucitol pentaacetate (**5**) by the mass fragment at



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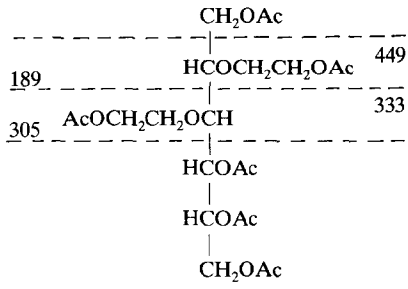

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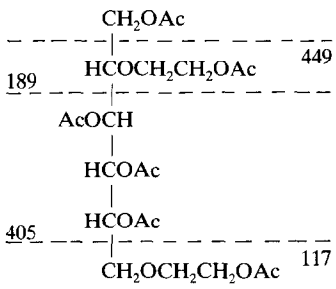

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TABLE II

PROMINENT FRAGMENTS (m/z) IN MASS SPECTRA OF HYDROXYETHYLGLUCITOL ACETATES

O-hydroxyethyl glucitol peracetates[a]	m/z																							
	43	*73*	*86*	*87*	*115*	*117*	*127*	*157*	*170*	*187*	*189*	*199*	*212*	*230*	*233*	*259*	*261*	*272*	*273*	*305*	*333*	*375*	*405*	*449*
1,2-*O*-etn-α-D-Glc*f* (**8**)	+	+					+		+	+			+						+					
1,2-*O*-etn-α-D-Glc*p* (**9**)	+	+	+					+	+			+		+		+		+						
1,2-*O*-etn-β-D-Glc*p* (**10**)	+	+	+					+	+			+		+		+		+						
1,2-*O*-etn-6-*O*-he-α-D-Glc*f* (**18**)	+	+		+			+			+														
1,2-*O*-etn-3-*O*-he-α-D-Glc*f* (**13**)	+	+		+			+		+				+					+						
6-*O*-he-Glc (**4**)	+			+	+	+																+		
2-*O*-he-Glc (**5**)	+	+		+	+						+											+	+	
3-*O*-he-Glc (**3**)	+			+	+												+				+	+		
2,6-*O*-dihe-Glc (**22**)	+	+		+	+	+																+	+	+
2,2-*O*-dihe-Glc (**20**)[b]	+	+		+	+										+							+		+
2,3-*O*-dihe-Glc (**21**)	+	+		+							+									+		+		+

[a]Ethylene = etn; hydroxyethyl = he. [b]2,2-*O*-dihe-Glc = 2-*O*-(2-acetoxyethoxy)ethyl-D-glucitol 1,3,4,5,6-pentaacetate.

m/z 405 resulting from C-1–C-2 cleavage, and at *m/z* 189 from cleavage between C-2 and C-3. Similarly, 2,3-di-*O*- and 2,6-di-*O*-(2-hydroxyethyl)-D-glucitol peracetates (**21** and **22**) were identified by g.l.c.–m.s. of the alditol acetates formed from the acid hydrolyzates of 1,2-*O*-ethylene-3-*O*-hydroxyethyl- and 1,2-*O*-ethylene-6-*O*-hydroxyethyl-α-D-glucofuranose. 2,3-Di-*O*-hydroxyethyl-D-glucitol peracetate (**21**) was identified by characteristic mass fragments at *m/z* 449, from C-1–C-2 cleavage, at *m/z* 333 and 189 from C-2–C-3 cleavage, and at *m/z* 305 from cleavage between C-3 and C-4. 2,6-Di-*O*-hydroxyethyl-D-glucitol peracetate (**22**) was also identified by the mass fragments at *m/z* 449 resulting from C-1–C-2 fission and at *m/z* 189 from C-2–C-3 fission, and at *m/z* 405, 117 from C-5–C-6 cleavage.

Table II gives the prominent mass-spectral fragments of these *O*-(hydroxyethyl)glucose derivatives. The fragment ion at *m/z* 87 was observed only in the case of compounds having hydroxyethyl groups that do not engage the glycosidic linkage (cyclic acetal). This result suggests that the *m/z* 87 fragment is characteristic of the acetoxyethyl group ($CH_3CO_2CH_2CH_2$, 87).

The characteristic mass-spectral fragments of these *O*-(hydroxyethyl)glucose derivatives as shown in Table II are useful for the characterization of acid hydrolyzates of *O*-(hydroxyethyl)-starch and -cellulose[4].

EXPERIMENTAL

General methods. — Evaporations were conducted under diminished pressure with bath temperatures not exceeding 40°. Column chromatography was performed with silica gel (Wako gel C-200, Wako Pure Chemical Industries, Ltd., Osaka, Japan). Thin layer chromatography (t.l.c.) was performed on t.l.c. sheets precoated with silica gel 60F-254 (Merck; 0.2-mm thickness) on an aluminum support, with the column-chromatographic solvent, unless otherwise specified. Specific rotations were measured with a Jasco DIP-4 automatic polarimeter. G.l.c. was performed with a Shimadzu 4CM chromatograph fitted with a flame-ionization detector. Peak retention times and areas were measured by use of a Shimadzu Chromatopac C-R3A integrator. Mass spectrometry and g.l.c.–m.s. were conducted with a JEOL JMS-D 300 instrument at an ionization potential of 30 eV. N.m.r. spectra were recorded with a JEOL JNM-GX270 instrument; chemical shifts are expressed in ppm (δ) relation to Me_4Si as the internal standard. Elemental analyses were not secured for the products; proposed structures are supported by n.m.r. and m.s. data on chromatographically homogeneous products.

*Methyl 3,5,6-tri-*O*-benzyl-2-*O*-(2-tetrahydropyranyloxyethyl)-α- and -β-*D*-glucofuranoside* (**2a**), *1,2;5,6-di-*O*-isopropylidene-3-*O*-(2-tetrahydropyranyloxyethyl)-α-*D*-glucofuranose* (**2b**), *and 3,5-*O*-benzylidene-1,2-*O*-isopropylidene-6-*O*-(2-tetrahydropyranyloxyethyl)-α-*D*-glucofuranose* (**2c**). — A mixture of methyl 3,5,6-tri-*O*-benzyl-α-D-glucofuranoside[19] (1.38 g), NaH (0.42 g), Bu_4NI (5 mg) and imidazole (5 mg) in dry DMF (20 mL) was stirred for 1 h at room temperature under nitrogen. 2-Bromoethyl tetrahydropyranyl ether[8] (2 mL) was added dropwise

TABLE III

^{1}H-N.M.R. DATA[a] FOR *O*-HYDROXYETHYL-D-GLUCOFURANOSE DERIVATIVES

Proton	**2a** (*α anomer*)	**2a** (*β anomer*)	**2b**	**2c**	**19** (*β anomer*)
H-1	4.98	4.87	5.86	6.03	4.86
($J_{1,2}$)	(3.85)	(~0)	(3.43)	(3.85)	(~0)
H-2	4.02	3.89	4.59	4.63	3.87
($J_{2,3}$)	(4.28)	(5.13)	(~0)	(~0)	(5.12)
H-3	4.22	4.05	3.94	4.57	3.98
($J_{3,4}$)	(5.98)	(4.70)	(2.93)	(2.43)	(4.58)
H-4	4.33	4.30	4.14	4.22	4.29
($J_{4,5}$)	(6.84)	(8.98)	(7.33)	(~0)	(8.99)
H-5	4.02	4.09	4.34	4.37	4.04
($J_{5,6}$)	(5.59)	(5.56)	(6.35)	(3.85)	(5.56)
H-6	3.86	3.91	4.09	4.00	3.85
($J_{5,6}$)	(2.14)	(2.14)	(5.86)	(3.85)	(2.14)
H-6	3.70	3.71	4.00	3.91–3.84	3.70
($J_{6,6}$)	(10.69)	(10.69)	(8.30)	(10.52)	(10.69)
$-OCH_2CH_2O-$	3.88–3.76(2H)	3.87–3.75(2H)	3.86–3.82(2H)	3.94–3.78(2H)	3.99–3.45(8H)
	3.76–3.55(2H)	3.66–3.54(2H)	3.81–3.75(2H)	3.72–3.63(2H)	
$-OCH_2-$	4.78, 4.56	4.77, 4.51			4.75, 4.50
	(11.54)	(11.54)			(11.54)
$-OCH_2-$	4.55	4.59			4.58
$-OCH_2-$	4.55	4.59			4.58
H-2 of THP ring	4.62	4.58	4.63	4.63	4.64
H-6 of THP ring	3.55–3.43	3.54–3.41	3.59–3.48	3.60, 3.52	3.55–3.44
H-3,4,5 of THP ring	1.89–1.39	1.89–1.40	1.81–1.52	1.86–1.44	1.80–1.50
$-OCH_3$	3.41	3.38			3.37
$-CCH_3$ (1,2)			1.50, 1.43	1.53, 1.34	
$-CCH_3$ (5,6)			1.35, 1.31		
$-CHC_6H_5$				6.07	
$-CHC_6H_5$				7.46–7.26	
$-C_6H_5$	7.32–7.24	7.36–7.24			8.06–7.26

[a]Chemical shifts (δ and, in parentheses, spacing (Hz). The assignments are based on the data in ref. 21.

and the mixture was stirred at room temperature for 4 days. After evaporation of the solvent, the residue was chromatographed on a column of silica gel (3:1 hexane–EtOAc), to give **2a** (α anomer) as 1.42 g (80.8%) of colorless syrup. This compound was homogeneous by t.l.c. (R_F 0.40); $[\alpha]_D^{20}$ +34.1° (*c* 0.51, $CHCl_3$); ^{1}H-n.m.r. data ($CDCl_3$) see Table III. Calc. for $C_{35}H_{44}O_8$: mol. wt., 592. Found for **2a** (α anomer): *m/z* 592 [M].

The β anomer was prepared from methyl 3,5,6-tri-*O*-benzyl-β-D-glucofuranoside (1.68 g) by the same procedure, giving 1.94 g (90.9%) of **2a** (β anomer) as a colorless syrup, homogeneous by t.l.c. (R_F 0.38); $[\alpha]_D^{20}$ −36.8° (*c* 0.13, $CHCl_3$); ^{1}H-n.m.r. data ($CDCl_3$) see Table III. Calc. for $C_{35}H_{44}O_8$: mol. wt., 592. Found for **2a** (β anomer): *m/z* 592 [M].

Compound **2b** was prepared from 1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranose (300 mg) by the same procedure as just described, as 425.3 mg (95.0%) of colorless, syrupy **2b**, homogeneous by t.l.c. (R_F 0.28, 2:1 hexane–EtOAc); $[\alpha]_D^{20}$

−38.2° (*c* 0.32, $CHCl_3$); ^{1}H-n.m.r. data ($CDCl_3$) see Table III. Calc. for $C_{19}H_{32}O_8$: mol. wt., 388. Found for **2b**: *m/z* 388 [M].

Compound **2c** was prepared from 3,5-*O*-benzylidene-1,2-*O*-isopropylidene-α-D-glucofuranose[20] (200 mg) by the same procedure, giving 255.4 mg (90.2%) of colorless crystals of **2c**, homogeneous by t.l.c. (R_F 0.33, 2:1 hexane–EtOAc); m.p. 102–103° $[\alpha]_D^{20}$ +7.0° (*c* 0.10, $CHCl_3$); ^{1}H-n.m.r. data ($CDCl_3$) see Table III. Calc. for $C_{23}H_{32}O_8$: mol. wt., 436. Found for **2c**: *m/z* 436 [M].

3-O-(2-Acetoxyethyl)glucitol 1,2,4,5,6-pentaacetate (**3**) *and 6-O-(2-acetoxyethyl)glucitol 1,2,3,4,5-pentaacetate* (**4**). — Compound **2b** (45.4 mg) was hydrolyzed in 10 mL of 2M CF_3CO_2H in a sealed tube for 5 h at 100°. The hydrolyzate was evaporated, and traces of CF_3CO_2H in the syrupy residue were removed by repeated evaporation (3 times) with water (3 mL). The residue was dissolved in water (10 mL) and reduced with $NaBH_4$ (50 mg) for 3 h at room temperature, and then passed through a column of Amberlite CG-120 (H^+) resin. The eluate was evaporated to dryness and boric acid in the residue was removed by repeated evaporation with methanol. The dried residue was acetylated with 1:1 Ac_2O–pyridine (1 mL) for 2 h at 95°. The solution was evaporated and the residue subjected to g.l.c.[4] on a column (0.3 cm × 1.5 m) packed with 2% EGSS-X on Chromosorb W AW DMCS (60–80 mesh) at 215° at a nitrogen pressure of 1.2 kg/cm^2. The retention time of **3** relative to hexa-*O*-acetylglucitol is 3.89; mass data are already described.

Compound **4** was prepared from **2c** (40.2 mg) by the same procedure, and analyzed by g.l.c. under the same condition as described. The retention time of **4** relative to hexa-*O*-acetylglucitol is 2.97; mass data are already given.

3,5,6-Tri-O-benzyl-1,2-O-ethylene-α-D-glucofuranose (**6**). — To a solution of compound **2a** (α anomer, 1.42 g) in $CHCl_3$ (63 mL) was added 10% HCl–MeOH (7 mL) and the solution was boiled under reflux for 3 h. The cooled solution was made neutral with $BaCO_3$. The mixture was filtered and the filtrate evaporated. The residue was chromatographed on a column of silica gel (3:1 hexane–EtOAc) to give 856 mg (75.0%) of colorless syrupy **6**, homogeneous by t.l.c. (R_F 0.48); $[\alpha]_D^{20}$ −61.7° (*c* 0.12, $CHCl_3$); ^{1}H-n.m.r. data ($CDCl_3$) see Table IV. Calc. for $C_{29}H_{32}O_6$: mol. wt., 476. Found for **6**: *m/z* 476 [M].

1,2-O-Ethylene-α-D-glucofuranose 3,5,6-triacetate (**8**). — Compound **6** (754 mg) was dissolved in MeOH (60 mL) containing 10% of formic acid. Palladium on carbon (10%, 2.25 g) was added slowly to the solution. The mixture was stirred at room temperature overnight, filtered, the filtrate evaporated, and the residue recrystallized from methanol to give 1,2-*O*-ethylene-α-D-glucofuranose (**7**). Compound **7** (5 mg) was dissolved in 1:1 Ac_2O–pyridine (0.5 mL) and heated for 2 h at 95°. The mixture was evaporated and the residue recrystallized from EtOH to give 6.53 mg (81.0%) of colorless crystalline **8**; m.p. 93–95°, $[\alpha]_D^{20}$ −40.7° (*c* 0.11, $CHCl_3$); ^{1}H-n.m.r. data ($CDCl_3$) see Table IV; mass data are described earlier.

1,2-O-Ethylene-α-D-glucopyranose 3,4,6-triacetate (**9**). — To a suspension of D-glucose (1.0 g) in 2-bromoethanol (18 mL) was added CF_3CO_2H (0.4 mL) and

TABLE IV

^{1}H-N.M.R. DATA[a] FOR 1,2-*O*-ETHYLENE-D-GLUCOFURANOSE DERIVATIVES

Proton	**6**	**8**	**11**	**12**	**13**
H-1	5.38	5.38	5.43	5.31	5.33
($J_{1,2}$)	(2.11)	(1.79)	(2.14)	(2.10)	(1.71)
H-2	3.92	3.81	3.86	3.91	3.90
($J_{2,3}$)	(~0)	(~0)	(~0)	(~0)	(~0)
H-3	4.04	5.30	4.25	3.88–3.79	3.82
($J_{3,4}$)	(2.99)	(3.42)	(2.57)	[b]	(3.85)
H-4	4.55	4.66	4.33–4.28	4.41–4.48	4.59
($J_{4,5}$)	(8.52)	(9.83)	[b]	[b]	(8.55)
H-5	3.99	5.16	4.25–4.31	4.28	5.20
($J_{5,6}$)	(5.98)	(5.56)	[b]	(5.98)	(5.13)
H-6	3.94	4.63	4.17	4.09	4.64
($J_{5,6}$)	(5.55)	(2.14)	(5.98)	(5.98)	(2.56)
H-6	3.73	4.15	4.05	4.06	4.19
($J_{6,6}$)	(10.68)	(12.39)	(8.12)	(8.12)	(12.39)
H-7	4.09–4.03(2H)	4.05, 3.73	4.11–4.01(1H)	4.03–3.97(1H)	4.11–3.98(1H)
	3.70–3.66(2H)		3.69(2H)	3.78–3.62(2H)	3.77–3.68(2H)
H-8	3.50(1H)	3.68, 3.54	3.50(1H)	3.61–3.44(1H)	3.52(1H)
$-OCH_2CH_2O-$				3.94–3.76(2H)	4.17–4.12(2H)
				3.76–3.65(2H)	3.66–3.56(2H)
$-OCH_2-$	4.81, 4.48				
	(11.54)				
$-OCH_2-$	4.59				
$-OCH_2-$	4.59				
H-2 of THP ring				4.63	
H-6 of THP ring				3.61–3.44	
H-3,4,5 of THP ring				1.80–1.54	
–Ac		2.05			2.07
$-CCH_3$ (5,6)			1.43, 1.35	1.42, 1.34	
$-C_6H_5$	7.37–7.26				

[a]Chemical shifts (δ) and, in parentheses, spacing (Hz). The assignments are based on the data in ref. 21.
[b]Signal not resolved.

the mixture was stirred for a week at room temperature. The solvent was evaporated and the thick syrupy residue of 2-*O*-bromoethyl-D-glucoside was dissolved in 0.12M NaOH–EtOH (1:1, 30 mL) and boiled under reflux for 2 days. The mixture was made neutral with 0.5M H_2SO_4 and filtered. The filtrate was evaporated and the dried residue was acetylated with 1:1 Ac_2O–pyridine (10 mL) for 2 h at 95°. The mixture was evaporated and the residue recrystallized from EtOH to yield colorless crystals of **9**; 986 mg (62.2%); m.p. 115–116° $[\alpha]_D^{20}$ +107.4° (*c* 0.50, $CHCl_3$); ^{1}H-n.m.r. data ($CDCl_3$) for **9**, 5.79 (dd, 1 H, H-3, 9.83), 5.06 (dd, 1 H, H-4, 9.83), 5.01 (d, 1 H, H-1, 3.42), 4.29 (dd, 1 H, H-6, 4.27, 12.40), 4.18 (ddd, 1 H, H-5, 1.71, 4.27, 9.83), 4.08 (dd, 1 H, H-6, 1.71, 12.40), 3.98 (dd, 2 H, H-7 or H-8, 11.97), 3.90 (dd, 1 H, H-7 or H-8, 2.57, 11.97), 3.76 (dd, 1 H, H-2, 3.42, 9.83), 3.41 (dd, 1 H, H-7 or H-8, 2.57, 11.97), 2.09 (s, 3 H, Ac), 2.08 (s, 3 H, Ac), and 2.04 (s, 3 H, Ac); mass spectral data already recorded.

1,2-O-Ethylene-5,6-O-isopropylidene-α-D-glucofuranose (**11**). — To a solution of 1,2-*O*-ethylene-α-D-glucofuranose (**7**, 200 mg) in dry acetone (4 mL) was added 2,2-dimethoxypropane (4 mL) and *p*-toluenesulfonic acid (3 mg). After stirring overnight at room temperature, the solution was made neutral with $BaCO_3$, the mixture filtered, and the filtrate evaporated. The residue was chromatographed on a column of silica gel (2:1 hexane–EtOAc) and crystallized from MeOH to give 214 mg (89.6%) of colorless crystals of **11**; m.p. 128° $[\alpha]_D^{20}$ +13.3° (*c* 0.02, $CHCl_3$); ^{1}H-n.m.r. data ($CDCl_3$) see Table IV. Calc. for $C_{11}H_{18}O_6$: mol. wt., 246. Found for **11**: *m/z* 246 [M].

1,2-O-Ethylene-5,6-O-isopropylidene-3-O-(2-tetrahydropyranyloxyethyl)-α-D-glucofuranose (**12**) — A mixture of compound **11** (75.7 mg), NaH (43 mg), Bu_4NI (1 mg) and imidazole (1 mg) in dry DMF (3 mL) was stirred for 1 h under nitrogen. 2-Bromoethyl tetrahydropyranyl ether (0.3 mL) was added dropwise with stirring. The mixture was stirred at room temperature overnight and then evaporated. The residue was chromatographed on a column of silica gel (2:1 hexane–EtOAc) to give 102.4 mg (89.0%) of colorless syrupy **12**, homogeneous by t.l.c. (R_F 0.59, 1:1 hexane–EtOAc); $[\alpha]_D^{20}$ −50.5° (*c* 0.11, $CHCl_3$); ^{1}H-n.m.r. data ($CDCl_3$) see Table IV. Calc. for $C_{18}H_{30}O_8$: mol. wt., 374. Found for **12**: *m/z* 374 [M].

3-O-(2-Acetoxyethyl)-5,6-di-O-acetyl-1,2-O-ethylene-α-D-glucofuranose (**13**). — Compound **12** (79.8 mg) was dissolved in 1:1 MeOH–0.8% H_2SO_4 (1 mL) and the solution was stirred overnight at room temperature. The solution was made neutral with $BaCO_3$, the mixture filtered, and the filtrate evaporated and the residue further acetylated with 1:1 Ac_2O–pyridine (2 mL) for 2 h at 95°. The mixture was evaporated and the residue chromatographed on a column of silica gel (3:1 hexane–EtOAc) to give 76.5 mg (95.3%) of **13** as a slightly yellow syrup, homogeneous by t.l.c. (R_F 0.48, 1:1 hexane–EtOAc); $[\alpha]_D^{20}$ −31.1° (*c* 0.24, $CHCl_3$); ^{1}H-n.m.r. data ($CDCl_3$) see Table IV. Calc. for $C_{16}H_{24}O_{10}$: mol. wt., 376. Found for **13**: *m/z* 317 [M − OAc].

1,2-O-Ethylene-6-O-trityl-α-D-glucofuranose (**14**). — Compound **7** (150 mg), chlorotriphenylmethane (230 mg) and *N,N*-dimethylaminopyridine (100 mg) were dissolved in pyridine (8 mL), and the solution was stirred for 5 days at 60°. The mixture was evaporated and the residue chromatographed on a column of silica gel (1:1 hexane–EtOAc) to give 255 mg (78.2%) of colorless syrupy **14**, homogeneous by t.l.c. (R_F 0.46); $[\alpha]_D^{20}$ −36.0° (*c* 0.08, $CHCl_3$); ^{1}H-n.m.r. data ($CDCl_3$) see Table V. Calc. for $C_{27}H_{28}O_6$: mol. wt. 448. Found for **14**: *m/z* 448 [M].

3,5-Di-O-benzyl-1,2-O-ethylene-6-O-trityl-α-D-glucofuranose (**15**). — Compound **14** (160 mg) was benzylated with NaH (160 mg), benzyl bromide (0.4 mL) and Bu_4NI (2 mg) in the same manner as already described. The residue was chromatographed on a column of silica gel (3:1 hexane–EtOAc) to give 217.5 mg (96.6%) of **15** as a slightly pale-yellow syrup, homogeneous by t.l.c. (R_F 0.40); $[\alpha]_D^{20}$ −41.7° (*c* 0.22, $CHCl_3$); ^{1}H-n.m.r. data ($CDCl_3$) see Table V. Calc. for $C_{41}H_{40}O_6$: mol. wt., 628. Found for **15**: *m/z* 385 [M − Tr].

3,5-Di-O-benzyl-1,2-O-ethylene-α-D-glucofuranose (**16**). — To a solution of

TABLE V

^{1}H-N.M.R. DATA[a] FOR 1,2-*O*-ETHYLENE-D-GLUCOFURANOSE DERIVATIVES

Proton	**14**	**15**	**16**	**17**	**18**
H-1	5.41	5.30	5.39	5.37	5.37
($J_{1,2}$)	(2.10)	(2.13)	(2.13)	(2.03)	(2.44)
H-2	3.80	3.90	3.94	3.91	3.80
($J_{2,3}$)	(~0)	(~0)	(~0)	(~0)	(~0)
H-3	4.24	4.04	4.04	4.02	5.29
($J_{3,4}$)	(3.14)	(3.42)	(3.85)	(2.88)	(3.42)
H-4	4.34	4.66	4.58	4.65	4.71
($J_{4,5}$)	(7.05)	(9.40)	(9.12)	(8.24)	(9.77)
H-5	4.07	3.86	3.93–3.87	3.96–3.82	5.11
($J_{5,6}$)	(5.56)	(5.13)	[b]	[b]	(5.37)
H-6	3.41	3.53	3.90–3.77	3.96–3.82	3.85–3.75
($J_{5,6}$)	(3.63)	(2.14)	[b]	[b]	(2.44)
H-6	3.32	3.42	3.90–3.77	3.96–3.82	3.85–3.75
($J_{6,6}$)	(9.83)	(10.26)	[b]	[b]	[b]
H-7	4.02–3.91(1H)	4.09–3.98(1H)	4.11–4.02(1H)	4.09–4.01(1H)	4.05(1H)
	3.62(2H)	3.71–3.63(2H)	3.71–3.67(2H)	3.79–3.61(2H)	3.73–3.62(2H)
H-8	3.50(1H)	3.47(1H)	3.49(1H)	3.57–3.46(1H)	3.53(1H)
$-OCH_2CH_2O-$				3.98–3.81(2H)	4.31(1H), 4.21(1H)
				3.79–3.57(2H)	3.85–3.75(2H)
$-OCH_2-$		4.74, 4.48	4.61, 4.48	4.86, 4.47	
		(11.54)	(11.54)	(11.54)	
$-OCH_2-$		4.57, 4.38		4.57, 4.49	
		(11.54)		(11.54	
H-2 of THP ring				4.64	
H-6 of THP ring				3.57–3.46	
H-3,4,5 of THP ring				1.89–1.42	
–Ac					2.04
$-C_6H_5$	7.49(6H)	7.53–7.49(6H)			
$-C_6H_5$	7.33–7.21(9H)	7.34–7.17(19H)	7.32–7.23	7.27–7.24	

[a]Chemical shifts (δ) and, in parentheses, spacing (Hz). The assignments are based on the data in ref. 21. [b]Signal not resolved.

compound **15** (210.0 mg) in MeOH (3 mL) was added 10% HCl–MeOH (0.3 mL). The solution was stirred for 1 h at room temperature, made neutral with $BaCO_3$, evaporated, and chromatographed on a column of silica gel (1:1 hexane–EtOAc) to give 107.7 mg (83.7%) of slightly pale-yellow syrupy **16**, homogeneous by t.l.c. (R_F 0.35); $[\alpha]_D^{20}$ −64.3° (*c* 0.47, $CHCl_3$); ^{1}H-n.m.r. data ($CDCl_3$) see Table V. Calc. for $C_{22}H_{26}O_6$: mol. wt., 386. Found for **16**: *m/z* 386 [M].

*3,5-Di-*O*-benzyl-1,2-*O*-ethylene-6-*O*-(2-tetrahydropyranyloxyethyl)-α-*D*-glucofuranose* (**17**). — A mixture of compound **16** (23.3 mg), NaH (8.5 mg) and Bu_4NI (1 mg) in dry DMF (1 mL) was stirred for 30 min under nitrogen. 2-Bromoethyl tetrahydropyranyl ether (0.06 mL) was added dropwise with stirring and the mixture was stirred for 5 days at room temperature. The solvent was evaporated and the residue chromatographed on a column of silica gel (1:1 hexane–EtOAc) to give 27.7 mg (89.3%) of **17** as a slightly pale-yellow syrup, homogeneous by t.l.c. (R_F 0.23); $[\alpha]_D^{20}$ −50° (*c* 0.03, $CHCl_3$); ^{1}H-n.m.r. ata ($CDCl_3$) see Table V. Calc. for $c_{29}H_{38}O_8$: mol. wt., 514. Found for **17**: *m/z* 429 [M − THP].

*6-*O*-(2-Acetoxyethyl)-3,5-di-*O*-acetyl-1,2-*O*-ethylene-α-*D*-glucofuranose* (**18**). — Debenzylation of compound **17** (25.6 mg) was accomplished as described for compound **8**. After acetylation of the residue with 1:1 Ac_2O–pyridine (0.5 mL) for 2 h at 95°, the solvent was evaporated and the residue chromatographed on a column of silica gel (1:1 hexane–EtOAc) to give 15.5 mg (82.8%) of **18** as a colorless syrup, homogeneous by t.l.c. (R_F 0.31); $[\alpha]_D^{20}$ −23.5° (*c* 0.17, $CHCl_3$); ^{1}H-n.m.r. data ($CDCl_3$) see Table V. Calc. for $C_{16}H_{24}O_{10}$: mol. wt., 376. Found for **18**: *m/z* 317 [M − OAc].

*Methyl 3,5,6-tri-*O*-benzyl-2-*O*-(2-tetrahydropyranyloxyethoxy)ethyl-β-*D*-glucofuranose* (**19**). — A mixture of methyl 3,5,6-tri-*O*-benzyl-β-D-glucofuranoside[19] (667.3 mg), NaH (200 mg), Bu_4NI (5 mg) and imidazole (5 mg) in dry DMF (13 mL) was stirred for 2 h at room temperature under nitrogen. 2-Chloroethoxyethyl tetrahydropyranyl ether[12] (1.3 mL) was introduced dropwise with stirring, and stirring was continued at room temperature for 5 days. The solvent was evaporated and the residue was chromatographed on a column of silica gel (3:1 hexane–EtOAc) to give 857.1 mg (93.7%) of colorless syrupy **19**, homogeneous by t.l.c. (R_F 0.57, 1:1 hexane–EtOAc); $[\alpha]_D^{20}$ −24.7° (*c* 0.46, $CHCl_3$); ^{1}H-n.m.r. data see Table III. Calc. for $C_{37}H_{48}O_9$: mol. wt., 636. Found for **19**: *m/z* 429 [M − OMe − THP − Bn].

*2-*O*-(2-Acetoxyethoxy)ethyl-*D*-glucitol 1,3,4,5,6-pentaacetate* (**20**). — Compound **19** (20.7 mg) was debenzylated with 10% Pd/C (48 mg) in 10% methanolic formic acid (1.1 mL) as described for compound **8**. The residue was reduced with $NaBH_4$ and acetylated with 1:1 Ac_2O–pyridine (0.5 mL) as described for compound **3**. The resulting material was subjected to g.l.c. as already described. The retention time of **20** relative to hexa-*O*-acetyl-glucitol was 8.67. Mass-spectral data are already described.

*G.l.c.–m.s. analysis of acid hydrolyzates of 1,2-*O*-ethylene-α-*D*-glucofuranose* (**7**). — 1,2-*O*-Ethylene-α-D-glucofuranose (5 mg) was hydrolyzed with 90% formic

acid (1.5 mL) for 4 h at 100°. The solution was evaporated, whereupon the residue was dissolved in 2M CF_3CO_2H (1 mL) and heated for 4 h at 100°. The acidic solution was evaporated to dryness with repeated (three times) addition of water (1 mL). Reduction ($NaBH_4$, 5 mg) and acetylation (1:1 Ac_2O–pyridine, 0.5 mL) of the residue as described for compound **3** was followed by analysis by g.l.c.–m.s. on a column (0.2 cm × 1 m) packed with 2% EGSS-X on Chromosorb W AW DMCS (60–80 mesh) at 205°, at a pressure of helium of 1.2 kg/cm^2. The mass spectra were recorded at an ionizing potential of 70 eV, an ionizing current of 50 μA, and an ion-source temperature of 220°. The data are given in Table I.

*G.l.c.–m.s. analysis of 2,3-di-*O*- and 2,6-di-*O*-(2-hydroxyethyl)-glucitol peracetates* (**21** *and* **22**). — 1,2-*O*-Ethylene-3-*O*-hydroxyethyl-α-D-glucofuranose (5 mg) and 1,2-*O*-ethylene-6-*O*-hydroxyethyl-α-D-glucofuranose (5 mg) were successively hydrolyzed, reduced, and acetylated by the procedure already described. G.l.c.–m.s. was performed on the same column under the same conditions. The retention times of **21** and **22** relative to hexa-*O*-acetyl-D-glucitol were 10.58 and 8.12, respectively. The prominent fragments in m.s. of **21** and **22** are listed in Table II.

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