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ACID-CATALYZED CONVERSION OF 2-*O*-(2-HYDROXYPROPYL)-D-GLUCOSE DERIVATIVES INTO 1,2-*O*-(1-METHYL-1,2-ETHANEDIYL)-D-GLUCOSE ACETALS. STUDIES RELATED TO *O*-(2-HYDROXYPROPYL)CELLULOSE

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ABSTRACT

The acid-catalyzed solvolysis of methyl 3,5,6-tri-*O*-benzyl-2-*O*-(2-hydroxypropyl)-α-D-glucofuranoside (**1**) in chloroform involves a neighboring-group attack on C-1 by the hydroxypropyl substituent, and opening of the furanoside ring to yield a diastereomeric pair of 3,5,6-tri-*O*-benzyl-1-*O*-methyl-1,2-*O*-(1-methyl-1,2-ethanediyl)-D-glucose acetals (**2** and **3**). The latter, which differ in configuration at C-8, represent a resolution of the enantiomeric forms of the original 2-*O*-(2-hydroxypropyl) group. In a succeeding reaction, the 1-methoxyl group of each acetal undergoes an intramolecular displacement by O-**4**, leading to the formation of the corresponding bicyclic acetals, *i.e.*, the two diastereomers (**4** and **5**) of 3,5,6-tri-*O*-benzyl-1,2-*O*-(1-methyl-1,2-ethanediyl)-α-D-glucofuranose. Solvolysis of **6**, the β anomer of **1**, proceeds in an analogous manner, although more rapidly, to yield a corresponding pair of acyclic-aldose acetals (**7** and **8**), as well as bicyclic acetals **4** and **5**. Similar results are observed for solvolysis in the 2-*O*-(2-hydroxyethyl) series, whereas the reaction of the 2-*O*-(2,3-epoxypropyl) counterpart of **1** (or **6**) with hydrogen chloride affords the corresponding chloromethyl analogs of **4** and **5**. In all of these series, one of each diastereomeric pair of products is more stable than the other, and reasons for this are considered. Evidence based on n.m.r.-spectral data and steric factors is presented to show that the configuration of the chiral center C-8 of **2**, **4**, and **7** is *(S)*, whereas it is *(R)* in **3**, **5**, and **8**. Also, conformational characteristics of the various solvolysis products are assessed, and mechanisms possibly involved in their formation are discussed.

INTRODUCTION

During the acid hydrolysis of *O*-(2-hydroxypropyl)cellulose, an intramolecular attack by single 2-*O*-(2-hydroxypropyl) groups upon the anomeric center of aldose residues being liberated leads to the formation of cyclic acetals[1]. The presence of these acetals in the hydrolyzate is of substantial value[1] in assessing the substitution pattern of the parent cellulose derivative. Some characteristics of this type of

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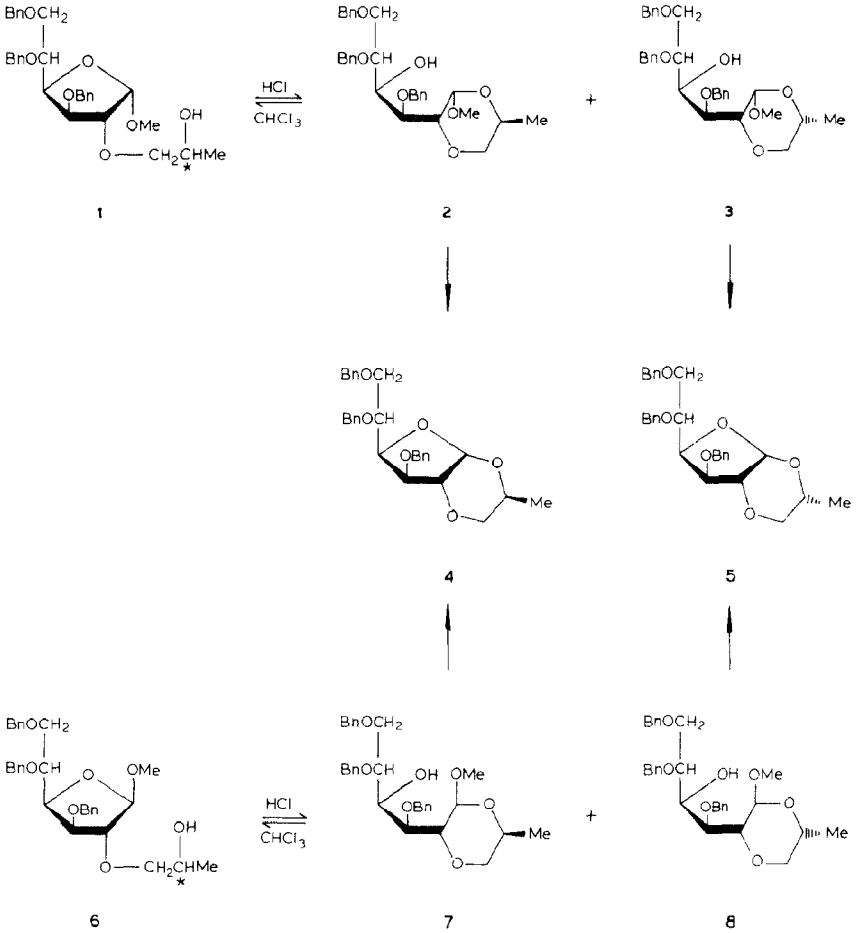
neighboring-group participation reaction have been reported[2] from studies on model glycosides containing the 2-*O*-(2-hydroxypropyl) substituent. We now give a fuller description of the model studies, as well as of some related reactions, and also deal with the stereochemistry of the reaction products.

RESULTS AND DISCUSSION

*Solvolysis of methyl 3,5,6-tri-*O*-benzyl-2-*O*-(2-hydroxypropyl)-α- and -β-*D*-glucofuranoside.* — When methyl 3,5,6-tri-*O*-benzyl-*O*-(2-hydroxypropyl)-α-D-glucofuranoside (**1**) was dissolved in chloroform containing 0.1% of hydrogen chloride, it yielded a mixture of at least four products (see Scheme 1) over a period of five days. Two of these (**2** and **3**) were detected by t.l.c. during the first 24 h as



Scheme 1. Solvolysis of methyl 3,5,6-tri-*O*-benzyl-2-*O*-(2-hydroxypropyl)-α- and -β-D-glucofuranoside (**1** and **6**, respectively).

compounds migrating ahead of **1**, compound **3** being formed in only traces. Subsequently, **2** and **3** were replaced by two other, less polar, compounds (**4** and **5**).

Solvolysis of the β anomer (**6**) followed a similar pattern, although it was far more facile than that of **1**. In 5 h at only 1/10th the concentration of hydrogen chloride (0.01%), results paralleling those with the α anomer were obtained, *i.e.*, two transient products, **7** and **8** (minor), having chromatographic properties close to those of **2** and **3** were detected at an early stage, and the end-products were indistinguishable from **4** and **5** obtained from **1**. By column chromatography on silica gel, products from both solvolysis reactions were isolated, and were characterized by n.m.r. spectroscopy and mass spectrometry.

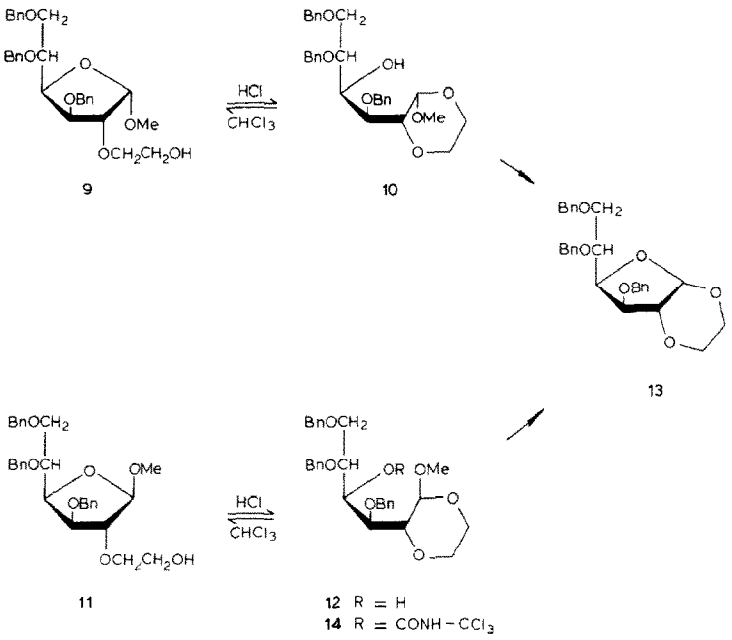
The observations just described are interpreted in the following way (see Scheme 1). During solvolysis, the anomeric carbon atom of glycoside **1** or **6** undergoes intramolecular, nucleophilic attack by the hydroxyl group of the 2-*O*-(2-hydroxypropyl) substituent, although less readily for **1** due to hindrance by the 1-methoxyl group. Instead of the latter being removed, the furanoside ring is opened, to yield an acyclic acetal intermediate possessing a 1,4-dioxane ring. Hence, each glycoside is rearranged into two diastereomeric species (**2** and **3**, or **7** and **8**) differing only in the configuration* of C-8, which constitutes a resolution of the enantiomeric forms of the original 2-*O*-(2-hydroxypropyl) group; in each series, one of the diastereomers (**2** or **7**) is more stable than the other. Ultimately, OH-4 of each acyclic-aldose acetal displaces the methoxyl group of the 1,4-dioxane moiety, thereby generating diastereomeric, bicyclic acetals (**4** and **5**) as end-products of the overall reaction.

*Solvolysis of 2-O-(2-hydroxyethyl) derivatives***. — A parallel series of observations was afforded by the corresponding solvolysis reactions of *O*-(2-hydroxyethyl) analogs, *i.e.*, of methyl 3,5,6-tri-*O*-benzyl-2-*O*-(2-hydroxyethyl)-α- and -β-D-glucofuranoside (**9** and **11**, respectively; see Scheme 2). By employing the same conditions as for **1** and **6**, it was found that only one monocyclic product appeared early in each reaction (**10** from the α anomer, and **12** from the β anomer), and that only one final product (**13**) was formed by both anomeric glycosides. Hence, these results conform exactly to expectation, as the absence of an 8-*C*-methyl group diminishes the number of diastereoisomeric possibilities in this series, relative to that of the *O*-(2-hydroxypropyl) derivatives.

Structures of monocyclic acetals **2**, **3**, **7**, **8**, **10**, and **12**. — The four *O*-(2-hydroxypropyl) diastereomers (**2**, **3**, **7**, and **8**) were differentiated in the following manner. Compounds **2** and **7** were found (in additional experiments) to yield the same bicyclic acetal (**4**; see Scheme 1) upon loss of the *O*-methyl group, showing

*Note that, in the 400-MHz, ^{1}H-n.m.r. spectrum (see Table I) and the 100-MHz, ^{13}C-n.m.r. spectrum (see Table II) of **1**, signals due to the individual, diastereomeric forms present in admixture are detectable.

**Related reactions have been observed[3] in the acid hydrolysis of 2-*O*-(2-hydroxyethyl) derivatives of some polysaccharides.



Scheme 2. Solvolysis of methyl 3,5,6-tri-*O*-benzyl-2-*O*-(2-hydroxyethyl)-α- and -β-D-glucofuranoside (**9** and **11**, respectively).

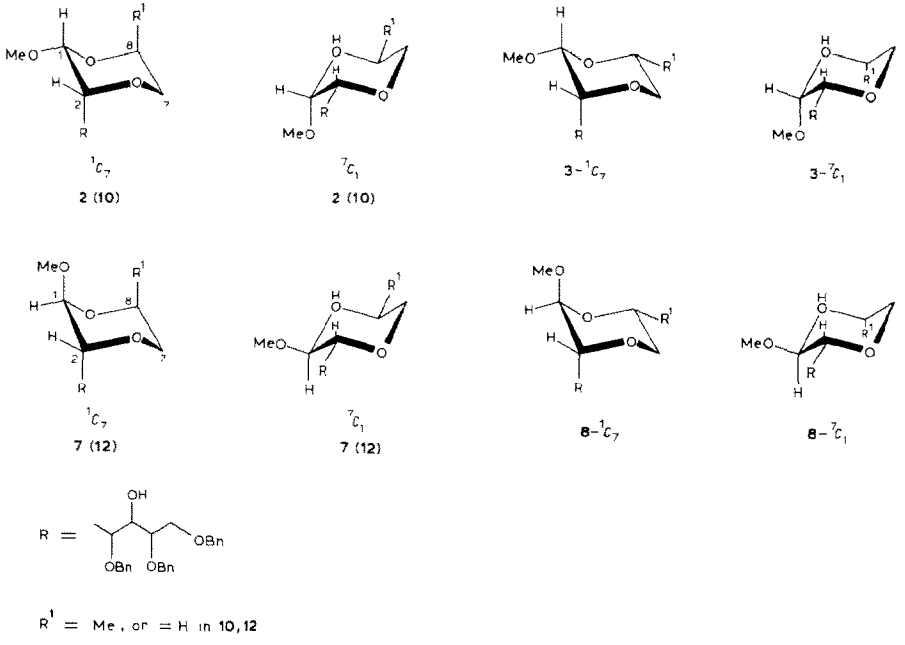


Fig. 1. Configurational assignments, and possible conformations, of acyclic-aldose acetals **2**, **3**, **7**, **8**, **10**, and **12**.

TABLE I

^{1}H-N.M.R. DATA[a] FOR METHYL 3,5,6-TRI-*O*-BENZYL-2-*O*-(2-HYDROXYALKYL)-D-GLUCOFURANOSIDES, AND ACYCLIC-ALDOSE ACETALS DERIVED FROM THEM

Proton	*Glycofuranosides*				*Acetals*					
	1	**6**	**9**	**11**	**2**	**7**	**8**	**10**	**12**	**14**
H-1	4.92	4.82	4.90	4.80	4.56	4.54	4.67	4.61	4.47	4.46
	4.90									
($J_{1,2}$)	(4.2)	(1.3)	(4.0)	(1.6)	(≤2)[b]	(7.73)	(5.8)	(≤2)[b]	(7.43)	(7.3)
H-9	1.08	1.06			1.07	1.12	1.20			
	1.06									
($J_{8,9}$)	(6.6)	(6.3)			(6.0)	(6.35)	(6.0)			
OCH_3	3.38	3.36	3.35	3.34	3.41	3.40	3.36	3.43	3.38	3.35
-OCH_2-	4.72	4.76	4.75	4.76	4.94	4.75	4.74	4.94	4.73	4.67
	4.51	4.49	4.40	4.49	4.47	4.49	4.43	4.45	4.47	4.61
(^2J)	(11.8)	(11.4)	(11.4)	(11.4)	(11.4)	(11.85)	(11.8)	(11.4)	(11.8)	(12.2)
-OCH_2-	4.54	4.58	4.52	4.57	4.72	4.54	4.70	4.72	4.56	4.57
					4.38		4.46	4.38		
(^2J)					(11.8)		(11.4)	(11.8)		
-OCH_2-	4.53	4.56	4.57	4.57	4.56	4.54	4.58	4.57	4.56	4.53[c]

[a]Chemical shifts (δ) and, in parentheses, spacing (Hz). [b]Broad singlet. [c]N–H, δ 8.35.

that they differ in configuration only at C-1. The same configurational relationship then applies for **3** and **8**, both of which must be converted into **5**.

Stereochemistry proposed for the monocyclic acetals is illustrated in Fig. 1. Therein, the configurations at C-8 are first designated, and on that basis, the various conformational possibilities are assessed, supported by the n.m.r. data in Table I.

As the 1,4-dioxane ring of each compound has two possible chair conformations, $^1C_7$ and $^7C_1$, depicted in Fig. 1, the intermediates formed in the solvolysis of **1** may be depicted in four ways, *i.e.*, two each for **2** and for **3**. Of these, the $^7C_1$ conformation of **2** and the $^1C_7$ conformation of **3** are expected to be the more stable, because they incorporate fewer destabilizing (axial, *syn*-diaxial) interactions between the substituents on the 1,4-dioxane ring. Additional stabilization of the $^7C_1$ (**2**) species should be derived through the anomeric effect of the axial methoxyl group. With respect to the chiral centers at C-8, it is to be noted that **2** and **7** are assigned the (*S*) configuration, whereas **3** and **8** are assigned the (*R*) configuration.

Consistent with the $^7C_1$ conformation proposed for **7** is the large coupling of 7.73 Hz between H-1 and H-2 (see Table I), which clearly shows that these protons are *anti*. Similarly, the intermediate size (5.8 Hz; see Table I) of $^3J_{1,2}$ for **8** indicates an interconversion between the two chair conformations, as already suggested. The depiction of **2** as a 1,2-*cis* isomer is supported by the coupling of <2 Hz between H-1 and H-2, which is of the order (1 to 1.8 Hz) observed[4] for vicinal *a,e* protons in 1,4-dioxanes. Although this does not differentiate between the two possible

TABLE II

^{13}C-CHEMICAL SHIFTS (δ) FOR METHYL 3,5,6-TRI-*O*-BENZYL-2-*O*-(2-HYDROXYALKYL)-D-GLUCOFURANOSIDES, AND ACYCLIC-ALDOSE ACETALS DERIVED FROM THEM

Compound	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*C-7*	*C-8*	*C-9*	*OMe*	*-OCH$_2$-*			*C-1' of C_6H_5*		
1	101.54	85.0	82.23	76 60	76.9	71.3	77.90	66.58	17.94	55.4	73.5	72.5	72.5	139.2	138.9	138.4
	101.22		81.97				77.20	65.67		55 4						
6	108.1	86 5	80.3	79.8	76.6	70.6	75.4	66.3	18.50	55 9	73 4	72.3	72.3	138.9	139.7	137.8
9	101.6	85.9	82.1	77.0	76.6	71.2	72 5	61.6		55.4	73 4	72.5	72.5	139 0	138.6	138 0
11	108.2	86.4	80.3	79.9	76 4	70.5	71.0	61 5		55.8	73.2	72.2	72.2	138 7	138.5	137 7
17	108.1	86.9	80 3	79.9	76.5	70.3	69.9	70.3	45.6	55 8	73.3	72.3	72 3	138.8	138.5	137.7
2	96.3	79.2	77.6	72.3	77.9	70.5	72.0	63.0	16 4	55.0	74.9	73.5	70.5	139.1	138.6	138.3
7	99.4	79.9	77.9	72.1	75.6	69.6	70.1	71.6	16.2	55.8	74.7	73.5	71.6	138 5	138.5	138.5
10	95.8	79.8	77.6	71.9	77.8	70.4	66.7	58.5		55.2	75.0	73.6	70 5	139.0	138.5	138.3
12	99 3	80.4	77.7	71.9	75 7	69 9	64.7	65.9		55.7	74.6	73.4	71.4	138.3	138.3	138.3
26	101.5	84.2	81.8	77 0	76 5	71.2	67.5	170 4	51.6 (OCH_3)	55.4	73.2	72.4	72.0	138.9	138.6	137 9
27	108.2	87 0	80 5	79.9	76.6	70.8	66 8	170.1	51 8	55.9	73 4	72 4	72.2	139.0	138.7	137 8

chair conformers, the $^1C_7$ conformation is obviously untenable. Corresponding n.m.r. data for **3** were not obtained, as it was never more than a trace component.

The ^{13}C-n.m.r. data (see Table II) provide additional evidence favoring the structures proposed for **2**, **3**, **7**, **8**, **10**, and **12**. Overall, the pattern of resonance signals for each of these is distinctly different from that of the corresponding parent glycoside and the bicyclic acetal. Most striking are the upfield shifts of the C-1 to C-4 resonances of the D-glucose moiety in these acyclic-aldose derivatives, such as are observed on comparing the spectra of (acyclic) alditols[5] with those of furanose derivatives[6]. The C-1 chemical shifts are in the region characteristic[6] of pyranosides (consistent with the position of the anomeric carbon atom within a six-membered ring). Furthermore, the fact that the C-1 chemical shifts for **2** and **10** are similar (δ 96.3 and 95.8, respectively), as well as being several p.p.m. upfield of those of **7** and **12** (δ 99.4 and 99.3, respectively), is consistent with the proposal (see Fig. 1) that the methoxyl group is preponderantly axial in the former pair, and equatorial in the latter.

A resonance, due to a methine carbon atom, at δ 71.9–72.3 in the spectra of **2**, **7**, **10**, and **12**, for which no counterpart is present in the spectra of the other series of compounds (see Table II), is assigned to C-4, as this carbon atom is free from the deshielding β-effect on ring closure, and hence, is analogous to methine carbon atoms of glucitol*. The three methine carbon signals at lower field, probably due to C-2, -3, and -5, are designated by attributing the β-effect of substitution to chemical-shift values for glucitol, assuming that the gross, electronic environments of C-2 and C-3 in all four compounds are similar. It is also worth mentioning that, whereas **2** and **10** each exhibits three distinct, phenyl C-1 resonances, in the spectra of **7** and **12** the corresponding signals are coincident, and also that the chemical shifts of the three benzylic methylene carbons (although not individually identified) are distinctive for each of these pairs**.

Structures of bicyclic acetals **4**, **5**, *and* **13**. — Ring closure to yield the bicyclic acetals (**4**, **5**, and **13**) as end products could result in the formation of *trans*- or *cis*-fused ring-systems. Although the *trans*-fused type is conformationally rigid (*t*, see Fig. 2), the *cis* isomer can exist in two potentially interconvertible forms in which the conformation of the six-membered ring is $^7C_1$ or $^1C_7$, and that of the furanose ring is $^2T_1$ or $^1T_2$ (see Fig. 2).

In general, because a *cis*-fused, 5,6-bicyclic compound is thermodynamically favored over its *trans* isomer[7], the stable end-products of solvolysis are expected to be *cis*-fused. The ^{1}H-n.m.r. results (see Table III) support this contention. Hence,

*Supplementary evidence for the presence of a secondary free hydroxyl group in molecules of this class was obtained from the reaction of **12** with trichloroacetyl isocyanate. An N–H singlet attributable to the resulting carbamate (**14**; see Table I) appeared at δ 8.35, and the H-4 resonance appeared as a doublet of doublets at δ 5.72. As this corresponds to a downfield shift of >1.0 p.p.m. relative to H-4 of **12**, the latter contains a secondary, rather than a primary, hydroxyl group.

**Analogously, the benzylic methylene protons exhibit patterns distinctive for each of the two pairs of isomers (see Table I).

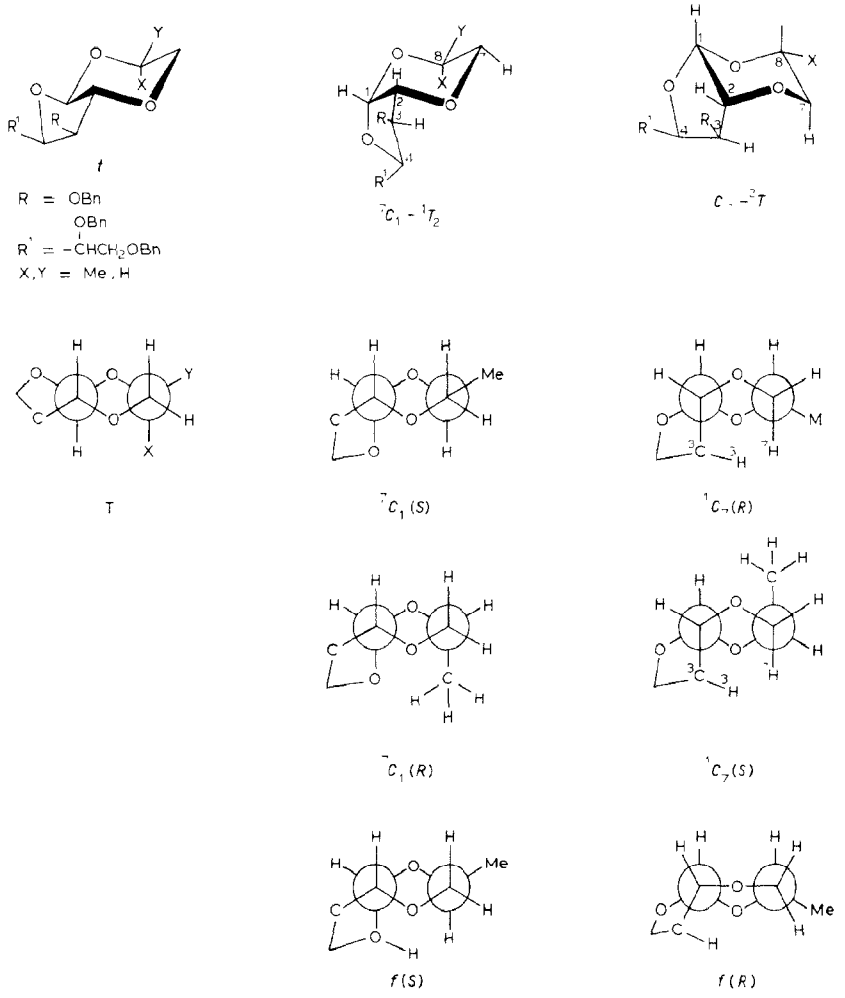


Fig. 2. Stereochemical representations of 3,5,6-tri-*O*-benzyl-1,2-*O*-(1-methyl-1,2-ethanediyl)-α-D-glucofuranose (**4**, **5**), and product **13** (X = Y = H).

$^3J_{1,2}$ is 2.20 Hz for **4** and **13**, and 3.42 Hz for **5**, values consistent with the *a,e, gauche* arrangement in a *cis*-fused structure. By contrast, as the *trans*-fused isomer (*t* or *T*) would incorporate an antiperiplanar arrangement of H-1 and H-2, much larger 1,2-coupling (7–8 Hz) would have to be observed. Of the two conformations depicted in Fig. 2 for the *cis*-fused system, the $^7C_1$-$^1T_2$ possibility should be favored (especially in the absence of a bulky group on C-8), because the $^1C_7$-$^2T_1$ conformation incorporates a strong destabilizing interaction between the axial C-7–H-7 bond and the C-3–H-3 bond. Hence, product **13** probably possesses the $^7C_1$-$^1T_2$ conformation. Diastereomeric products **4** and **5** differ in the configuration of C-8, however, and this suggests that they may also differ in conformation. This is more apparent in the "Newman" projections of the 1,4-dioxane moieties depicted in Fig. 2.

TABLE III

^{1}H-N.M.R DATA FOR 3,5,6-TRI-*O*-BENZYL-1,2-*O*(1-METHYL-1,2-ETHANEDIYL)- AND -1,2-*O*-(1,2-ETHANEDIYL)-α-D-GLUCOFURANOSE

Proton	**4**	**5**	**13**
H-1	5.43	5.23	5.38
($J_{1,2}$) (°)[a]	(2.20) (57.2°)	(3.42) (48.6°)	(2.20) (57.2°)
H-2	3.84	4.06	3.94
($J_{2,3}$)	(0.24) (103.8°)	(2.81) (124.9°)	(~0) (~90°)
H-3	4.05	4.25	4.07
($J_{3,4}$)	(3.30) (49.4°)	(5.01) (37.2°)	(3.66) (47.0°)
H-4	4.53	4.52	4.50
($J_{4,5}$)	(9.28) (~0° or ~180°)	(8.42) (~0° or ~180°)	(10.07) (~0° or 180°)
H-5	3.98	4.03	~4.0
($J_{5,6}$)	(1.95) (59.0° or 119.1°)	(2.20) (57.2° or 120.9°)	
H-6	3.94	3.58	~4.0
($J_{5,6'}$)	(5.86) (31.7° or 143.6°)	(6.10) (29.8° or 145.2°)	(5.83) (31.9° or 143.4°)
H-6′	3.73	3.70	3.73
($J_{6,6'}$)	(10.50)	(10.50)	(10.60)
H-7	3.62	3.58	
($J_{7,7'}$)	(11.72)	(11.72)	
H-7′	3.21	3.37	
($J_{7,8}$)	(1.95) (59.0°)	(2.93) (51.9°)	
H-8	4.09	3.75	
($J_{7',8}$)	(10.25) (~180°)	(5.86) (143.6°)	
H-9	1.06	1.22	
($J_{8,9}$)	(6.35) (27.8° or 147.8°)	(6.59) (25.8° or 148.4°)	
-OCH_2-	4.81	4.81	4.83
	4.48	4.50	4.52
(J)	(11.7)	(11.2)	(11.7)
-OCH_2-	4.56	4.64	4.62
	4.46	4.53	
(J)	(11.5)	11.7	
-OCH_2-[b]	4.58	4.56	4.62

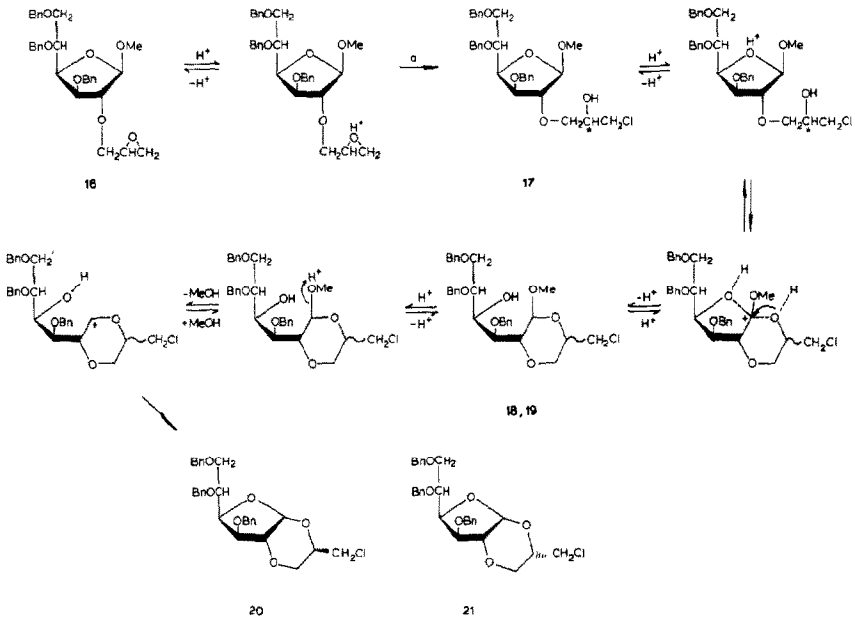
[a]Dihedral angles[8]: ($^3J_{H1,H2} = 8.5 \cos^2\phi - 0.3$ (0–90°); $^3J_{H1,H2} = 9.5 \cos^2\phi - 0.3$ (90–180°). [b]Of 6-*O*-benzyl group.

Assuming the (*S*) configuration of C-8 of acetal **4**, on the basis of its relationship to intermediate **2**, the $^1C_7(S)$ and $^7C_1(S)$ conformations are to be compared. As the former clearly incorporates stronger, overall destabilizing interactions, the $^7C_1(S)$ conformation should be favored by **4**. N.m.r. data support this possibility. Thus, the couplings of H-8 with H-7 and H-7′ are 1.95 and 10.25 Hz, respectively (see Table III), which are attributable to a *gauche* and an *anti* disposition with respect to these protons. Furthermore, the furanose counterpart of the $^7C_1$ conformation should possess an H-2, H-3 dihedral angle of ~90°, in good agreement with the small coupling ($^3J_{2,3}$ 0.2 Hz) observed. The corresponding angle for the $^1C_7(S)$ conformation, estimated at ~150°, would require a much larger splitting. It is noteworthy that this inconsistency would also apply to the furanose ring were **4** assigned the (*R*) configuration of C-8, because the corresponding $^1C_7(R)$ pyranose

TABLE IV

^{13}C-CHEMICAL SHIFTS (δ) FOR 3,5,6-TRI-*O*-BENZYL-1,2-*O*-(1-METHYL-1,2-ETHANEDIYL)- (**4**, **5**) AND -1,2-*O*-(1,2-ETHANEDIYL)- (**13**) α-D-GLUCOFURANOSE AND 1-CHLOROMETHYL ANALOGS (**20**, **21**)

Compound	*C-1*	*C-2*	*C-3*	*C-4*	*C-5*	*C-6*	*C-7*	*C-8*	*C-9*	*-OCH$_2$Ph*			*C-1' of C$_6$H$_5$*		
4	99.3	82.3	79.8	76.2	72.7	71.6	69.4	64.0	16.3	73.4	72.5	72.4	139.1	138.7	137.8
5	96.8	79.4	77.7	78.5	76.3	71.3	66.7	67.1	17.9	73.4	72.5	71.9	139.1	138.7	137.8
13	98.6	82.3	80.0	76.2	73.6	71.7	64.1	59.4		73.5	72.5	72.4	139.2	138.8	137.8
20	99.3	82.0	80.0	76.1	73.1	71.3	66.3	67.1	42.8	73.4	72.6	72.3	138.9	138.7	137.6
21	97.5	81.4	75.9	78.4	75.1	70.6	62.8	70.4	42.9	73.5	72.5	72.2	138.9	138.5	137.6



Scheme 3. Reaction between methyl 3,5,6-tri-*O*-benzyl-2-*O*-(2,3-epoxypropyl)-β-D-glucofuranoside (**16**) and hydrogen chloride in chloroform, showing possible intermediate steps in the formation of isolated products **17**, **18**, **20**, and **21**.

conformation would then have to be implicated in order to account for the couplings observed between H-7, -7′, and -8. Hence, the ^{1}H-n.m.r. data for **4** are consistent with both the (*S*) configuration and the $^7C_1$ conformation. Some contribution from a flexible form [*e.g.*, *f*(*S*); see Fig. 2] also seems possible.

Both the $^7C_1(R)$ and the $^1C_7(R)$ conformation envisaged for acetal **5** appear to incorporate comparably strong, nonbonded interactions, ensuring that neither is preponderant. Indeed, the value of 5.86 Hz for $^3J_{7',8'}$, as well as 2.93 Hz for $^3J_{7,8}$ (see Table III) is consistent with contributions from both species, although it is also possible that, in order to relieve steric crowding, the 1,4-dioxane ring favors a flexible form. Species *f*(*R*) (see Fig. 2) is a plausible representation, as it gives good agreement between several dihedral angles predicted with respect to the ^{1}H–^{1}H coupling observed: *i.e.*, $^3J_{2,3}$ corresponds to 125° (see Table III) as compared with ~130° in *f*, and $^3J_{7,8}$ and $^3J_{7',8}$ correspond respectively to angles of 52 and 144°, as compared with ~35 and 145°, respectively.

The ^{1}H-n.m.r. data for acetal **13** (see Table III), derived from the 2-*O*-(2-hydroxyethyl) glycosides, are closely similar to those for **4**. This strongly indicates that **13** also primarily adopts the $^7C_1$-$^1T_2$ conformation (X = Y = H; see Fig. 2), which is to be expected in view of the close proximity of H-3 and H-7 in the alternative form.

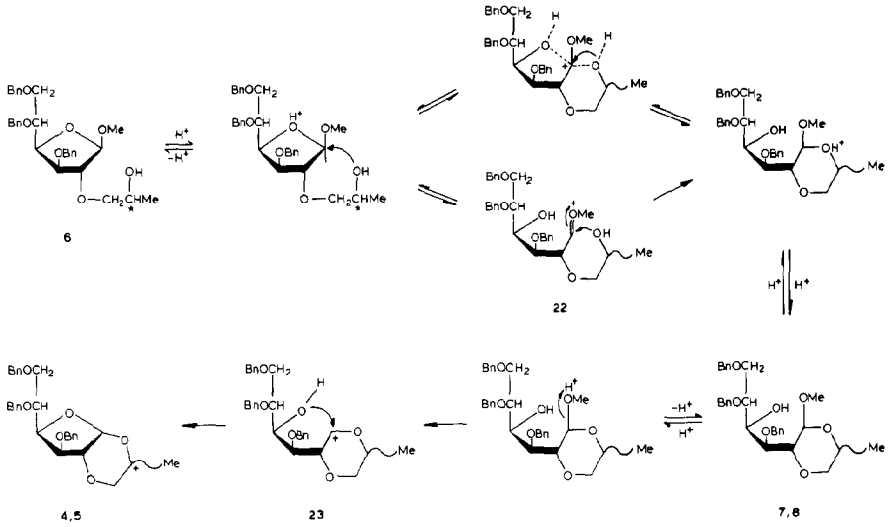
^{13}C-N.m.r. data for acetals **4** and **13** (see Table IV) again demonstrate a close

stereochemical analogy between the two, as most of the chemical shifts are virtually the same; those of C-7 and C-8 understandably differ, due to the presence of the 8-methyl group in **4** only.

Solvolysis of methyl 3,5,6-tri-O-benzyl-2-O-(2,3-epoxypropyl)-D-glucofuranosides with hydrogen chloride. — In an extension of the study on the solvolysis of the 2-*O*-(2-hydroxypropyl) derivatives, methyl 3,5,6-tri-*O*-benzyl-2-*O*-(2,3-epoxypropyl)-β-D-glucofuranoside (**16**) was dissolved in chloroform containing 1% of HCl, and the reaction was monitored by t.l.c. Opening of the epoxy ring gave mainly methyl 3,5,6-tri-*O*-benzyl-2-*O*-(3-chloro-2-hydroxypropyl)-β-D-glucofuranoside (**17**; see Scheme 3), although a minor product detected may have been the (2-chloro-3-hydroxypropyl) isomer. The formation of diastereomeric, acyclic-aldose acetals (**18** and **19**) then followed and, over a period of several days, the latter were largely converted into 1,2-*O*-(1-chloromethyl-1,2-ethanediyl)-D-glucofuranoses (**20** and **21**). At an appropriate stage of the overall reaction, column chromatography was employed in order to isolate the four major products present (*i.e.*, **17**, **18**, **20**, and **21**). A similar series of reactions was observed with the α anomer (**15**) which, however, required an overall reaction time of 1–2 weeks.

The foregoing conclusions were reached not only by analogy with the solvolysis of glycosides **1** and **6**, but also from the strikingly close similarities between the ^{1}H- and ^{13}C-n.m.r. spectra (see Tables III and IV) of the chloro analogs and the products from **1** and **6**, due allowance being made for the differences in shielding at the α, β, and γ positions caused by the introduction of a chlorine atom. For example, the ^{13}C spectrum of **20** is essentially the same as that of **4** (see Table IV), except for the resonances of the carbon atoms of the dioxane moiety which, as expected, experience deshielding by 26.5 p.p.m. of the α-carbon (C-9) and 3.1 p.p.m. of the β-carbon (C-8), and shielding by 3.1 p.p.m. of the γ-carbon (C-7). Only in comparing **21** with **5** are there differences in chemical shifts for C-1 to C-6 of more than 0.5 p.p.m., which suggests that the conformation of the furanose ring of **21** may be appreciably affected by the bulky 8-chloromethyl (as compared with the 8-methyl) group.

Reaction mechanism. — In general, the results obtained indicate that the acid-catalyzed solvolysis of glycosides **1** and **6**, and related compounds, entailed two consecutive, nucleophilic-substitution steps, uncomplicated by isomerization (as illustrated in Scheme 4 for the β anomer **6**). The β-furanoside yielded diastereomeric, bicyclic acetals **4** and **5** through the intermediacy of the isolable intermediates **7** and **8**. Moreover, when pure **7** was subjected to the same reaction conditions, it initially afforded some starting material (**6**) without anomerization to the α anomer (**1**), and subsequently gave a single, bicyclic product (**4**). The early stage of solvolysis was dependent on the configuration at C-8. That is, the monocyclic intermediate (**7**), possessing the (*S*) configuration, was formed far more rapidly from the (*S*) diastereomer of glycoside **6** than was **8** from **6**(*R*). However, the overall rates of formation of **4** and **5** were similar. Solvolysis of the α anomer **1** appeared to proceed in the same manner, although at a far lower rate, which indicates[9] that



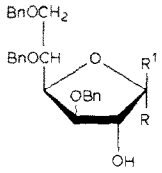
Scheme 4. Possible steps involved in the mechanism of the acid-catalyzed conversion of β-glycoside **6** into bicyclic acetals **4** and **5**.

anchimeric assistance is much more significant with the β-glycoside. Whereas the same bicyclic acetals (**4** and **5**) were obtained, the intermediates (**2** and **3**) were anomers of **7** and **8**, respectively.

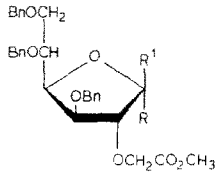
According to the structures deduced for **2**, **3**, **7**, and **8**, the attack by the hydroxyl group of the substituent on C-1 of the conjugate acid of the furanoside resulted in an inversion of configuration (see Scheme 4). As already noted[2], the conjugate acid of **6** meets the requirements of the bimolecular (A-2) mechanism proposed[10] for some solvolysis reactions of glycofuranosides. Although this suggests an SN2 type of transition state, a two-step process involving an oxonium-ion intermediate (**22**) is also plausible, provided that the succeeding step is much faster than rotation about the C-1–C-2 bond of **22**. Displacement of the 1-methoxyl group then occurred, and regeneration of the furanose ring was completed, to give bicyclic acetals **4** and **5**. As the latter were obtained from each anomer, and are both *cis*-fused acetals differing only in the configuration of C-8, a common intermediate (represented here by carbonium ion **23**) appears to be mandatory in order to account for the apparently stereospecific attack by OH-4 during closure of the furanose ring. If, however, the *trans*-bicyclic acetal were to be formed through kinetic control, it should readily rearrange to the *cis*-fused acetals actually obtained. The latter, it may be noted, conform to the requirements of the[11] "stereoelectronic effect", inasmuch as, in the $^{7}C_{1}$-$^{1}T_{2}$ and $^{1}C_{7}$-$^{2}T_{1}$ conformations (see Fig. 2), one of the two ring-oxygen atoms does not have a lone-pair orbital oriented antiperiplanar with respect to a neighboring C–H bond, whereas, in the

less stable, *trans*-bicyclic system, orbitals of both ring-oxygen atoms are so oriented.

Synthesis of glycosides **1**, **6**, **9**, **11**, **15***, *and* **16**. — *O*-Benzylation of 1,2-*O*-isopropylidene-α-D-glucofuranose, followed by methanolysis, afforded methyl 3,4,6-tri-*O*-benzyl-α- and -β-D-glucofuranoside (**24** and **25**)[12], which were separated



24 R = OMe, R^1 = H
25 R = H, R^1 = OMe



26 R = OMe, R^1 = H
27 R = H, R^1 = OMe

chromatographically. Each of these anomeric glycosides was converted into the corresponding 2-*O*-(2,3-epoxypropyl) derivative (**15*** and **16**, respectively) by reaction with 1-chloro-2,3-epoxypropane[13]. Hydrogenolysis of the oxiranes with lithium aluminum hydride gave the corresponding 2-*O*-(2-hydroxypropyl) glycosides **1** and **6**. Similarly, **24** and **25** were converted[14] into the corresponding 2-*O*-(methoxycarbonylmethyl) derivatives (**26** and **27**) by reaction with methyl bromoacetate, and this was followed by reduction of the esters with lithium aluminum hydride, to give the 2-*O*-(2-hydroxyethyl) glycosides (**9** and **11**, respectively).

EXPERIMENTAL

General methods. — Solutions were usually evaporated below 40° under diminished pressure. Column chromatography was performed by the procedure of Still *et al.*[15] with silica gel 60 (Merck; 40–63 μm). Thin-layer chromatography (t.l.c.) was performed on t.l.c. sheets precoated with silica gel 60F-254 (E. Merck; 0.2 mm thickness) on an aluminum support. Mass spectra were recorded with an LKB 9000 spectrometer at an ionization potential of 70 eV, or, by chemical ionization (isobutane), with an HP 5980A spectrometer. N.m.r. spectra (^{1}H and ^{13}C) were recorded with a Bruker WH-90, Varian XL-200, or Bruker WH-400 spectrometer. Chemical shifts (δ) are reported with reference to tetramethylsilane.

3,5,6-Tri-O-benzyl-1,2-O-isopropylidene-α-D-glucofuranose. — A solution of 1,2-*O*-isopropylidene-α-D-glucofuranose (10 g), sodium hydride (12 g), and tetrabutylammonium iodide (a few crystals) in dry *N*,*N*-dimethylformamide (100 mL) was cooled to 0°, and benzyl bromide (10 mL) was introduced dropwise. After 24 h, when t.l.c. showed that the reaction was complete, the mixture was filtered (without decomposing the sodium hydride remaining), the filtrate evaporated, and the residue purified by column chromatography, with 1:7 ethyl acetate–petroleum

*The α anomer of **16**; see Scheme 3

ether as the eluant, giving a colorless syrup; yield, 19.8 g (90%); ^{1}H-n.m.r. data ($CDCl_3$): δ 7.18–7.12 (m, 15 H, 3 C_6H_5), 5.78 (d, 1 H, H-1), 4.64 (s, 2 H, OCH_2), 4.58, 4.48 (2 d, AB, 2 H, OCH_2, J 11.3 Hz), 4.34 (dd, AB, 2 H, OCH_2, J 11.3 Hz), 4.19 (dd, 1 H, H-4), 4.00 (d, 1 H, H-2), 3.98 (m, 1 H, H-5), 3.82 (dd, 1 H, H-6), 3.57 (dd, 1 H, H-6'), 1.38 (s, 3 H, CH_3), and 1.21 (s, 3 H, CH_3); $^3J_{1,2}$ 3.9, $^3J_{3,4}$ 3.1, $^3J_{4,5}$ 9.3, $^2J_{6,6'}$ 1.8, and $^3J_{5,6}$ 5.6 Hz.

*Methyl 3,5,6-tri-*O*-benzyl-α-*D*-glucofuranoside* (**24**), *methyl 3,5,6-tri-*O*-benzyl-β-*D*-glucofuranoside* (**25**), *and 3,5,6-tri-*O*-benzyl-α,β-*D*-glucofuranose.* — A solution of the previous syrup (10 g) in methanol (150 mL) was boiled under reflux and stirred with Amberlite IR-120 (H^+) ion-exchange resin (60 mL) for 5 days. T.l.c. then showed that the starting material had disappeared completely, and that three products had been formed. The suspension was filtered, the filtrate evaporated, the residue dissolved in 1:1 petroleum ether–ethyl acetate, and the mixture separated by column chromatography, with 2:3 ethyl acetate–petroleum ether as the eluant, yielding **24** (4 g; colorless syrup, R_F 0.55), **25** (3.9 g; colorless syrup, R_F 0.45), and the mixed aldoses (1.1 g; colorless syrup, R_F 0.45); ^{1}H-n.m.r. data ($CDCl_3$): for **24**, δ 7.26–7.20 (m, 15 H, 3 C_6H_5), 5.02 (d, 1 H, H-1), 4.78, 4.54 (2 d, AB, 2 H, OCH_2, J 11.5 Hz), 4.70, 4.50 (2 d, AB, 2 H, OCH_2, J 11.7 Hz), 4.57 (s, 2 H, OCH_2, J 11.7 Hz), 4.57 (s, 2 H, OCH_2), 4.36 (dd, 1 H, H-4), 4.23 (m, 1 H, H-3), 4.04 (d, 1 H, H-2), 4.03 (m, 1 H, H-5), 3.87 (dd, 1 H, H-6), 3.69 (dd, 1 H, H-6'), and 3.46 (s, 3 H, OCH_3); $J_{1,2}$ 4.4, $J_{3,4}$ 4.4, $J_{4,5}$ 8.3, $J_{5,6}$ 1.9, $J_{5,6'}$ 5.6 Hz, and $J_{6,6'}$ 10.5 Hz. For **25**, δ 7.31–7.26 (m, 15 H, 3 C_6H_5), 4.79 (d, 1 H, H-1), 4.66 (dd, AB, 2 H, OCH_2), 4.61 (s, 2 H, OCH_2), 4.58 (s, 2 H, OCH_2), 4.41 (dd, 1 H, H-4), 4.18 (dd, 1 H, H-2), 4.10 (m, 1 H, H-5), 3.97 (dd, 1 H, H-3), 3.91 (dd, 1 H, H-6), 3.72 (dd, 1 H, H-6'), and 3.37 (s, 3 H, OCH_3); $J_{1,2}$ 1.9, $J_{3,4}$ 5.0, $J_{4,5}$ 8.7, $J_{5,6}$ 1.8, $J_{5,6'}$ 5.6, and $J_{6,6'}$ 10.7 Hz.

*Methyl 3,5,6-tri-*O*-benzyl-2-*O*-(2,3-epoxypropyl)-α- and -β-*D*-glucofuranoside* (**15** *and* **16**). — To a solution of **24** (0.1 g) in anhydrous ether (50 mL) were added sodium hydride (0.03 g), imidazole (0.01 g), and epichlorohydrin (0.15 mL). After 8 days, when t.l.c. showed that the reaction was complete, the suspension was filtered, the filtrate evaporated, and the product isolated by column chromatography, with 1:1 ethyl acetate–petroleum ether as the eluant, to afford a colorless syrup (**15**). The same procedure was used to obtain **16** from β anomer **25**. For **15**, yield 0.1 g (94%); for **16**, 0.1 g (95%); $[\alpha]_D$ of **15**, +33.6° (*c* 7.3, MeOH), and of **16**, −35.3° (*c* 10.4, $CDCl_3$); ^{1}H-n.m.r. data ($CDCl_3$): for **15**, δ 7.24–7.21 (m, 15 H, 3 C_6H_5), 4.97, 4.93 [2 d, 1 H, H-1(*R*) and (*S*)], 4.67, 4.59 (2 d, AB, 2 H, OCH_2, J 11.9 Hz), 4.55 (AB, 2 H, OCH_2), 4.52 (s, 2 H, OCH_2), 3.39 (s, 3 H, CH_3O), 3.11 (m, 1 H, H-8), 2.73 and 2.53 (m, 1 H, H-9); $J_{1,2}$ 3.7 Hz. For **16**, δ 7.24–7.21 (m, 15 H, 3 C_6H_5), 4.75 [dd, 1 H, H-1(*R*) and (*S*)], 4.62, 4.50 (2 d, AB, 2 H, OCH_2, J 11.2 Hz), 4.47 (s, 4 H, 2 OCH_2), 3.26 (s, 3 H, OCH_3), 2.94 (m, 1 H, H-8), 2.63 and 2.43 (m, 1 H, H-9); $J_{1,2}$ 2.0, $J_{8,9}$ 2.5, $J_{8,9'}$ 5.0, and $J_{9,9'}$ 4.0 Hz.

Anal. Calc. for $C_{31}H_{36}O_7$: mol. wt., 520. Found for **15**: *m/z* 489 (M − OCH_3, 0.4%). Found for **16**: *m/z* 489 (M − OCH_3, 0.1%).

*Methyl 3,5,6-tri-*O*-benzyl-2-*O*-(2-hydroxypropyl)-α- and -β-*D*-glucofuranoside* (**1** *and* **6**). — A solution of **14** or **25** (0.16 g) in diethyl ether (5 mL) was added dropwise to a suspension of lithium aluminum hydride (20 mg) in diethyl ether (20 mL); 2 h later, the suspension was filtered, the filtrate evaporated, and the syrupy product separated by column chromatography with 2:1 ethyl acetate–petroleum ether as the eluant; yield of **1**, 0.12 g (87%); $[\alpha]_D$ +10.6° (*c* 10.5, $CDCl_3$); yield of **6**, 0.16 g (96%); $[\alpha]_D$ −35.5° (*c* 11.9, MeOH). The ^{1}H- and ^{13}C-n.m.r. spectra are reported in Tables I and II, respectively.

Anal. Calc. for $C_{31}H_{38}O_7$: mol. wt., 522. Found (e.i.) for **1**: *m/z* 491 (M − OCH_3, 0.6%).

*3,5,6-Tri-*O*-benzyl-1-*O*-methyl-1,2-*O*-(1-methyl-1,2-ethanediyl)-*D*-glucose* (**2** *and* **3**) *and 3,5,6-tri-*O*-benzyl-1,2-*O*-(1-methyl-1,2-ethanediyl)-α-*D*-glucofuranose* (**4** *and* **5**). — Methyl 3,5,6-tri-*O*-benzyl-2-*O*-(2-hydroxypropyl)-α-D-glucoside (**1**; 0.54 g) was dissolved in chloroform (30 mL) containing hydrogen chloride (0.1%), and the solution was stirred for 5 days at room temperature. T.l.c. then showed that a substantial amount of **4** and **5** had been formed, together with some **2** and **3**. The acid was neutralized with barium carbonate, the precipitate was filtered off, and the filtrate was evaporated to a colorless syrup that was subjected to chromatography on a column of silica gel with 1:4 ethyl acetate–petroleum ether as the eluant. Yields: of **2**, 0.08 g (R_F 0.21); **3**, ≤0.002 g (R_F 0.15); **4**, 0.14 g (m.p. 75°, R_F 0.57); and **5**, 0.19 g (R_F 0.43); 0.05 g of **1** was recovered. $[\alpha]_D$ of **2**, −41.2° (*c* 5.3, MeOH); of **4**, −36.5° (*c* 11.6, MeOH); and of **5**, −5.4° (*c* 1.75, MeOH). The ^{1}H- and ^{13}C-n.m.r. data for **2** are respectively reported in Tables I and II, and for **4** and **5** in Tables III and IV, respectively.

Anal. Calc. for $C_{31}H_{38}O_7$: mol. wt., 522. Found for **2**: *m/z* 491 (M − OCH_3, 5.9%). Calc. for $C_{30}H_{34}O_6$: mol. wt., 490. Found for **4**: *m/z* 490 (M, 0.1%); for **5**: *m/z* 490 (M, 0.1%).

*3,5,6-Tri-*O*-benzyl-1-*O*-methyl-1,2-*O*-(1-methyl-1,2-ethanediyl)-*D*-glucose* (**7** *and* **8**) *and 3,5,6-tri-*O*-benzyl-1,2-*O*-(1-methyl-1,2-ethanediyl)-α-*D*-glucofuranose* (**4** *and* **5**). — A solution of methyl 3,5,6-tri-*O*-benzyl-2-*O*-(2-hydroxypropyl)-β-D-glucofuranoside (**6**; 0.3 g) in chloroform containing hydrogen chloride (0.01%) was stirred for 5 h at room temperature, and then processed as described in the preceding section. Yields: for **7**, 0.05 g (R_F 0.20); for **8**, ≤0.003 g (R_F 0.15); for **4**, 0.08 g (R_F 0.57); and for **5**, 0.11 g (R_F 0.43); $[\alpha]_D$ +4.1° (*c* 2.8, MeOH) for **7**. The ^{1}H- and ^{13}C-n.m.r. data for **7** and **8** are reported in Tables I and II, respectively, and for **4** and **5** in Tables III and IV, respectively.

Anal. Calc. for $C_{31}H_{38}O_7$: mol. wt., 522. Found for **7**: *m/z* 491 (M − OCH_3, 2.3%).

*Methyl 3,5,6-tri-*O*-benzyl-2-*O*-(methoxycarbonylmethyl)-α- and -β-*D*-glucofuranoside* (**26** *and* **27**). — To a stirred mixture of **24** (0.6 g) and sodium hydride (0.1 g) in ethyl ether (10 mL) were added imidazole (0.01 g) and tetrabutylammonium bromide (0.01 g), followed, 30 min later, by methyl bromoacetate (1 mL, dropwise). After 4 d, the mixture was filtered, and the filtrate was evaporated, giv-

ing an oil consisting of a mixture of **26** (major) and free acid (minor), which was separated by column chromatography (eluant, 1:2 ethyl acetate–petroleum ether). Yield of **26**, 0.5 g (72%) (R_F 0.35), $[\alpha]_D$ +37.2° (*c* 5.9, $CDCl_3$); ^{1}H-n.m.r. data ($CDCl_3$): δ 7.3–7.2 (m, 15 H, 3 C_6H_5), 4.96 (d, 1 H, H-1), 3.67 (s, 3 H, OCH_3), and 3.39 (s, 3 H, OCH_3); $J_{1,2}$ 4.4 Hz.

Analogously, a 75% yield of **27** was obtained from **25**.

Methyl 3,5,6-tri-O-*benzyl-2*-O-*(2-hydroxyethyl)-α- and -β*-D-*glucofuranoside* (**9** *and* **11**). — Methyl 3,5,6-tri-*O*-benzyl-2-*O*-(methoxycarbonylmethyl)-α-D-glucofuranoside (**26**; 0.32 g) was reduced with lithium aluminum hydride (0.04 g) in anhydrous ethyl ether for 2 h, the mixture filtered, the filtrate evaporated, and the residue subjected to column chromatography (eluant, 3:1 ethyl acetate–petroleum ether), to give **9**; yield, 0.26 g (85%); colorless syrup. Product **11** was obtained from **27** (3 g) by the same procedure, except that the eluant was 2:1 ethyl acetate–petroleum ether; yield, 2.59 g (91%), colorless syrup. The ^{1}H-n.m.r. data ($CDCl_3$) were, for **9**, δ 7.3–7.1 (m, 15 H, 3 C_6H_5), 4.90 (d, 1 H, H-1), 4.75, 4.48 (2 d, AB, 2 H, OCH_2, *J* 11.6 Hz), 4.52 (s, 2 H, OCH_2), and 3.35 (s, 3 H, OCH_3); $J_{1,2}$ 4.0 Hz. For **11**, δ 7.4–7.2 (m, 15 H, 3 C_6H_5), 4.80 (d, 1 H, H-1), 4.76, 4.49 (2 d, AB, 2 H, OCH_2, *J* 11.4 Hz), 4.57 (s, 4 H, 2 OCH_2), and 3.34 (s, 3 H, OCH_3); $J_{1,2}$ 1.6 Hz.

3,5,6-Tri-O-*benzyl-1*-O-*methyl-1,2*-O-*(1,2-ethanediyl)*-D-*glucose* (**10** *and* **12**) *and 3,5,6-tri*-O-*benzyl-1,2*-O-*(1,2-ethanediyl)*-α-D-*glucofuranose* (**13**). — Compounds **9** and **11** (0.13 and 1.5 g), respectively, were dissolved in chloroform containing hydrogen chloride, as employed earlier for the neighboring-group-participation reactions of **1** and **6**, respectively. Both **9** and **11** yielded the same product (**13**), through different, separable intermediates (**10** and **12**, respectively). The products were separated by column chromatography (eluant, 1:2 ethyl acetate–petroleum ether). Yields: **10**, 0.03 g (22%) (R_F 0.42), $[\alpha]_D$ −6.7° (*c* 2.4, MeOH); **13**, 0.07 g (60%) (R_F 0.75), $[\alpha]_D$ −55.2° (*c* 2.9, MeOH); and **12**, 0.32 g (21%) (R_F 0.49), $[\alpha]_D$ +24.1° (*c* 7.1, MeOH). The ^{1}H- and ^{13}C-n.m.r. data are given in Tables I–IV.

Anal. Calc. for $C_{30}H_{36}O_7$: mol. wt., 508. Found for **10**: *m/z* 477 (M − OCH_3, 11.7%); Found for **12**: *m/z* 477 (M − OCH_3, 8.0%). Calc. for $C_{29}H_{32}O_6$: mol. wt., 476. Found for **13**: *m/z* 476 (M, 0.2%).

3,5,6-Tri-O-*benzyl-1*-O-*methyl-1,2*-O-*(1,2-ethanediyl)-4*-O-*(trichlorocarbamyl)*-D-*glucose* (**14**). — Compound **12** (40 mg), dissolved in $CDCl_3$ in a 5-mm n.m.r. tube, was transformed into **14** by reaction with fresh trichloroacetyl isocyanate (0.1 mL). The ^{1}H-n.m.r. data ($CDCl_3$) are reported in Table I.

3,5,6-Tri-O-*benzyl-1,2*-O-[*1-chloromethyl)-(*R *and* S*)-1,2-ethanediyl*]-α-D-*glucofuranose* (**20** *and* **21**) *and 3,5,6-tri*-O-*benzyl-2*-O-*(1-chloromethyl-1,2-ethanediyl)-1*-O-*methyl*-D-*glucose* (**18** *and* **19**). — Methyl 3,5,6-tri-*O*-benzyl-2-*O*-(2,3-epoxypropyl)-β-D-glucofuranoside (**16**; 0.9 g) was dissolved in chloroform (50 mL) containing 1% of hydrogen chloride, and the reaction was monitored by t.l.c. After 2 weeks, an excess of barium carbonate was introduced, the suspension was filtered, the filtrate was evaporated, and the residue was subjected to column chro-

matography. The column was successively eluted with 1:5, 1:3, 1:2, and 1:1 ethyl acetate–petroleum ether, affording **19**, 0.13 g, R_F 0.35, δ 4.83 (H-1, $J_{1,2}$ 0.8 Hz); **18**, 0.04 g, R_F 0.45, δ 4.41 (H-1, $J_{1,2} \leq 1$ Hz); **20**, 0.11 g, R_F 0.80, δ 5.47 (H-1, $J_{1,2}$ 2.1 Hz); and **21**, 0.14 g, R_F 0.85, δ 5.31 (H-1, $J_{1,2}$ 2.5 Hz), all as colorless syrups.

Anal. Calc. for $C_{30}H_{33}ClO_6$: mol. wt., 524. Found for **20**: *m/z* 435 (^{37}Cl) (M $-$ $C_6H_5CH_2$, 1.1%), *m/z* 433 (^{35}Cl) (M $-$ $C_6H_5CH_2$, 3.4%). Calc. for $C_{30}H_{33}ClO_6$: mol. wt., 524. Found for **21**: *m/z* 435 (^{37}Cl) (M $-$ $C_6H_5CH_2$, 0.9%), *m/z* 433 (^{35}Cl) (M $-$ $C_6H_5CH_2$, 2.5%).

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