DIOXOLANE CONFIGURATION IN DIASTEREOISOMERIC 1,2-*O*- AND 1,2:4,6-DI-*O*-ALKYLIDENE-α-D-GLUCOPYRANOSE DERIVATIVES BY N.M.R. SPECTROSCOPY*.

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ABSTRACT

Three related pairs of diastereoisomers, the previously unknown 3,4,6-tri-*O*-acetyl-1,2-*O*-ethylidene- and 3-*O*-acetyl-1,2:4,6-di-*O*-ethylidene-α-D-glucopyranoses, and the known 3,4,6-tri-*O*-acetyl-1,2-*O*-benzylidene-α-D-glucopyranose, were prepared by reduction of intermediate dioxolenium chloride ions with sodium borohydride. Each pair of isomers was separated into its components by preparative t.l.c. Four correlations of n.m.r. parameters with dioxolane configuration were used to assign the structure of each isomer of a diastereoisomeric pair: (*1*) Deshielding of the 2′-substituent when *endo*: (*2*) deshielding of H-2 or H-5 by bulky *exo* or *endo* 2′-substituents; (*3*) larger values of $J_{2,3}$ and $J_{3,4}$ when a bulky 2′-substituent has an *exo* orientation; and (*4*) the presence of long-range (^4J) coupling of H-2 and H-4 of the pyranose ring only in molecules with a bulky 2′-substituent in an *endo* orientation. The degree to which the pyranose ring is distorted by the *cis*-fusion of a dioxolane ring in such derivatives, as well as by *endo* phenyl, methyl, and proton substituents, is evaluated.

INTRODUCTION

Two factors affecting distortion of the pyranose ring of 1,2-*O*-alkylidene-α-D-glucose derivatives are *cis*-fusion of the dioxolane ring and steric interactions between H-5 and bulky *endo* 2′-substituents[1–7]. Evaluation of these two distortional effects is complicated by lack of general agreement as to the actual degree of distortion of the pyranose ring[1,2]. Nevertheless, several correlations have been reported[3,4].

For a series of orthoacetates of D-glucopyranose, Lemieux and Morgan[3] showed that conformation of the pyranose ring is independent of the bulk of *exo* 2′-alkoxyl substituents. However, the type and bulk of *endo* 2′-substituents do influence the pyranose-ring conformation. An *endo tert*-butyl or methoxyl group imposes greater distortion than an *endo* methyl group[3], and n.m.r. data reported by Rees *et al.*[5] indicate equivalent distortional effects for *endo* methyl and ethyl groups.

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The effect of a bulky, planar *endo* substituent (such as phenyl) is not well understood, as contradictory dioxolane-ring configurations have been reported for diastereoisomers of 3,4,6-tri-*O*-acetyl-1,2-*O*-benzylidene-α-D-glucopyranose[4,5]. However, space-filling models indicate that linear or planar (such as ethyl or phenyl) *endo* substituents can relieve steric interactions with H-5 by simple rotations about the C–C bond at C-2′ and that globular (*tert*-butyl) substituents cannot. If so, the reported similarity of pyranose-ring distortions caused by *endo* phenyl and tert-butyl substituents are questionable, and a configurational assignment partially based on the similarity needs to be reexamined.

To find n.m.r. parameters appropriate to assign configuration of the dioxolane moiety for the general class of 1,2-*O*- and 1,2:4,6-di-*O*-alkylidene-α-D-glucopyranose derivatives, and to assess the degree to which the pyranose ring is distorted by *endo* phenyl, methyl, or proton substituents at the C-2′ dioxolane position, two pairs of previously unknown diastereoisomeric ethylidene derivatives, and a series of analogous reference compounds were prepared and studied by 100-MHz n.m.r. spectroscopy.

RESULTS AND DISCUSSION

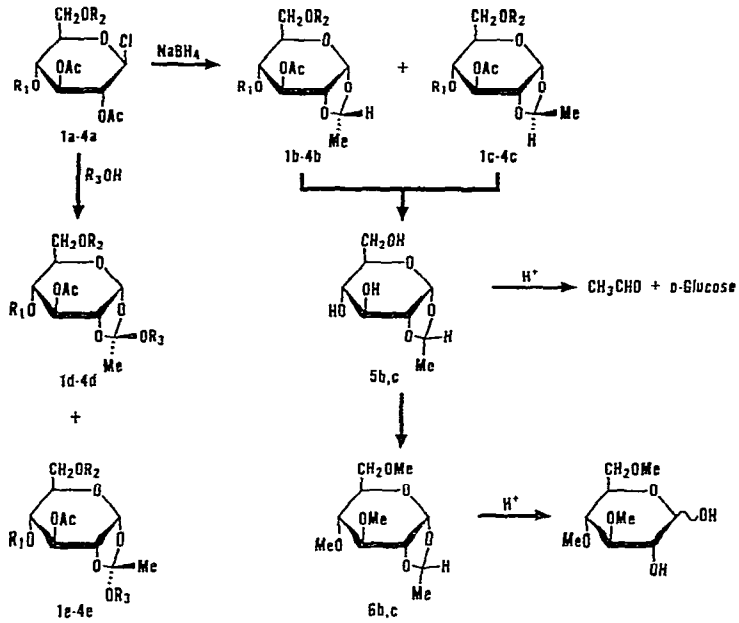
Although a number of diastereoisomeric acetals of D-glucose have been prepared by acid-catalyzed condensation, such condensations with derivatives of acetaldehyde have yielded only the well-known 4,6-*O*-ethylidene form[8], or poorly characterized mono- and di-*O*-ethylidene product mixtures[9–12].

The desired ethylidene derivatives were synthesized by direct reduction of an intermediate acetoxonium ion[13,14], one of several techniques that can generate a dioxolane ring under conditions that do not give mixtures of pyranose and furanose forms and that avoid multiple condensations (oxidodiethylidene)[15–18]. The reduction technique, first used with steroid derivatives[19] and later adapted to monosaccharides[13,14], was further modified and simplified for derivatives that readily form acetoxonium ions in solution, namely the *O*-acetyl-β-D-glucopyranosyl chlorides.

Solutions of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl chloride (**1a**) and 2,3-di-*O*-acetyl-4,6-*O*-ethylidene-β-D-glucopyranosyl chloride (**2a**) in *N*,*N*-dimethylformamide (DMF), 1,2-dimethoxyethane, or pyridine rapidly formed acetoxonium chlorides which were converted by added sodium borohydride into diastereoisomeric mixtures of 3,4,6-tri-*O*-acetyl-1,2-*O*-ethylidene-α-D-glucopyranose (**1b**, **1c**) and 3-*O*-acetyl 1,2:4,6-di-*O*-ethylidene-α-D-glucopyranose (**2b**, **2c**).

The 1,2-*O*-ethylidene substituent in **1b** and **1c** was confirmed by deacetylation, methylation, and hydrolysis of a mixture of the two diastereoisomers. The hydrolysis products were identified as acetaldehyde and 3,4,6-tri-*O*-methyl-D-glucopyranose (**7**).

Although the yield of ethylidene derivatives was 80–90% in each reaction mixture, the ratio of diastereoisomers was solvent-dependent. The selectivity was greater in 1,2-dimethoxyethane than in pyridine. Solutions in DMF were least selective; each isomer was formed in nearly equal amounts. Similar solvent-effects



1, $R_1 = R_2$ = Ac, R_3 = Et
2, $R_1 + R_2$ = CH_3—CH
3, $R_1 + R_2$ = Ph—CH, R_3 = Me
4, R_1 = Tetra-*O*-acetyl-α-D-glucopyranosyl, R_2 = Ac, R_3 = Me

SCHEME 1

were noted when the reduction technique was extended to ions derived from 2,3-di-*O*-acetyl-4,6-*O*-benzylidene-β-D-glucopyranosyl chloride (**3a**) and hepta-*O*-acetyl-β-maltosyl chloride (**4a**). The ratios, as determined by g.l.c. or n.m.r. spectroscopy, are shown in Table I.

TABLE I

RATIOS OF ALKYLIDENE DIASTEREOISOMERS FORMED BY SODIUM BOROHYDRIDE SOLUTIONS[a]

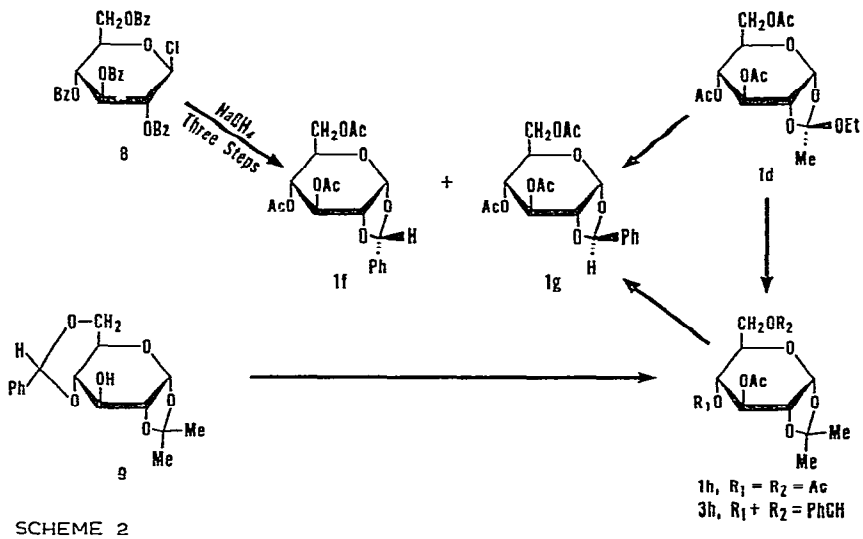
Solvent	*Relative proportions of isomers formed*									
	1b	**1c**	**1f**	**1g**	**2b**	**2c**	**3b**	**3c**	**4b**	**4c**
N,N-Dimethylformamide	45	55	64	36	55	45	54	46	65	35
1,2-Dimethoxyethane	79	21			80	20	81	19	87	13
Pyridine	73	27			74	26	67	33	86	14

[a]Average of values determined by g.l.c. and n.m.r.

The configuration of each dioxolane isomer was determined by n.m.r. spectroscopy. For each selective solvent, the preponderant isomer was the one having the proton substituent *exo* (*trans* to the pyranoid ring). These results fulfil the prediction that the *exo* surface of the 2′-carbon in a dioxolenium ion is less sterically hindered for nucleophilic attack (as by hydride ion) than the *endo* surface[14–20]. Selective

formation of *exo* alkoxy orthoacetates is known in alcoholic solutions of pyridine or its substituted derivatives[3,21].

Application of the reduction technique to 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl chloride (**8**) for the direct synthesis of 3,4,6-tri-*O*-benzoyl-1,2-*O*-benzylidene-α-D-glucose, with subsequent conversion to the tri-*O*-acetyl analog (**1f, 1g**), gave much lower yields than reduction of **1a** and **2a**. Solutions of **8** in DMF gave 1,2-*O*-benzylidene diastereoisomers in 30% yield, whereas reaction in 1,2-dimethoxyethane gave none at all. Bulk preparations of **1f** and **1g** were based on acetal exchange[4,5].



SCHEME 2

Individual diastereoisomers were isolated from each of the three pairs, **1b, 1c**; **1f, 1g**; and **2b, 2c**, by preparative t.l.c. For each of these pairs, and for the ortho esters indicated in the scheme, the isomer having an *endo* methyl or phenyl group had a lower R_F or R_T value than the opposite form.

The six individual *O*-ethylidene or *O*-benzylidene isomers isolated were examined by n.m.r. spectroscopy, and their spectral data were compared with those obtained from reference *O*-isopropylidene and orthoacetyl derivatives. Four n.m.r. properties were correlated with the bulk and orientation of the 2′-substituent of the dioxolane ring: the 2′-substituent is deshielded when *endo*; H-2 or H-5 are deshielded by bulky *exo* or *endo* 2′-substituents; values of $J_{2,3}$ and $J_{3,4}$ are larger when a bulky 2′-substituent is *exo* than when it is *endo*; and long-range (^4J) coupling of H-2 and H-4 of the pyranoid ring is present only in molecules having a bulky *endo* 2′-substituent.

The first correlation is well established for a number of carbohydrate derivatives[5,13,21–23], including 3,4,6-tri-*O*-acetyl-1,2-*O*-(methoxyethylidene)-α-D-glucopyranose[3]. Later investigations with 2,4-di- and 2,4-*cis*-5-trialkyl-1,3-dioxolanes show that when a C-2 alkyl group (equivalent to our C-2′) is *cis* to alkyl substituents

at C-4 and C-5, the chemical shift of the C-2 group is invariably downfield from the corresponding signal of the *trans* isomer[24,25]. These findings agree with our observation that for each pair of diastereoisomers examined, whether in pure form or as crude mixtures, the derivative whose formation is favored in pyridine or 1,2-dimethoxyethane has the 2′-methyl-group resonance shifted to lower field and the 2′-proton or -alkoxyl group resonances shifted to higher field than the corresponding signals of the minor forms. Assignments of the major isomeric structures as **1b**, **1d**, **1f**, **2b**, **3b**, **3d**, **4b**, and **4d**, wherein the configuration[26] of the ethylidene and benzylidene dioxolane rings is *R* and that of the orthoacetates is *S*, are consistent with the first correlation and supported by other data in Table II.

The deshielding of one or more pyranoid-ring protons by a bulky, proximal 2′-substituent forms the basis of the second correlation. The deshielding of H-5 in **1b**, **1f**, and **2b** indicates an *endo* methyl or phenyl substituent in these isomers; conversely, deshielding of H-2 in the opposite isomers, **1c**, **1g**, and **2c**, supports an *exo* methyl or phenyl structure. Although the *exo* methyl and phenyl groups are also in close proximity to H-1, deshielding of H-1 was noted only in **1g**, presumably because the effects of the two oxygen atoms flanking C-1 mask the interactions of H-1 and the *exo* methyl group. The 2′-substituent is distant from H-3 and H-4 at all times, and the shifts seen for these protons in **2b** and **2c** are not attributed to proximity effects of the type just described.

The third and fourth correlations of n.m.r. parameters and dioxolane configuration are based on the expectation that the pyranose ring in such derivatives will assume a conformation more nearly that of a *C1* (D) chair in the isomers having the smaller 2′-substituent in an *endo* orientation. Even though contradictory conformations have been proposed for the pyranoid ring of certain 1,2-*O*-alkylidene-α-D-glucopyranoses[1,2], knowledge of the actual conformation is not needed to evaluate data in Table II on vicinal-proton coupling-constants.

A comparison of the coupling-constant data obtained from the three pairs of diastereoisomeric derivatives (**1b**, **1c**; **1f**, **1g**; **2b**, **2c**) with those from models suggests that the coupling constants, $J_{2,3}$ and $J_{3,4}$, can be used to gauge dihedral angles H-2–H-3 and H-3–H-4 and estimate the relative degree to which a pyranoid ring is distorted in a given isomer. Although the dihedral angles H-2–H-3 and H-3–H-4 cannot be unequivocally assigned as acute or obtuse in **1b** and **1f**, the notable increases in the magnitudes of $J_{2,3}$ and $J_{3,4}$ recorded for **1c**, **1g**, and **2c** are more likely to signal substantially increased dihedral angles than extremely diminished acute angles. Therefore, minimized steric interactions in the isomer having the smaller *endo* 2′-substituent (a proton) favors a slightly flattened, chair conformation for the pyranoid ring. On this basis, the *cis*-fusion of the dioxolane ring imposes only slight flattening of the *C1* (D) chair, and the bulk of the distortions seen in **1b**, **1d**, **1f**, **1h**, and analogous compounds results from steric interactions of the *endo* methyl or phenyl groups with H-5. The values of $J_{1,2}$ and $J_{4,5}$ remain constant, or nearly so, in each pair of diastereoisomers.

The extent to which the pyranoid ring in **1c**, **1g**, and **2c** approaches the *C1* (D)

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TABLE II

N.M.R. PARAMETERS FOR 1,2-*O*- AND 1,2:4,6-DI-*O*-ALKYLIDENE-α-D-GLUCOPYRANOSE DERIVATIVES[a]

Compound	*Chemical shift, τ*					*Dioxolane (1, 2-O-)*			*Dioxane (4,6-O-)*	
	H-1	*H-2*	*H-3*	*H-4*	*H-5*	*2'-H*	*2'-OR*	*2'-R*	*H*	*R*
1b	4.56d	6.15qd	4.62t	4.92m	5.79m	5.13q		8.62d		
1c	4.55d	5.94t	4.59t	4.91dd	6.04m	4.53q		8.84d		
1d	4.34d	5.67qd	4.54t	4.85qd	5.86m		6.66q, 8.96t	8.33s		
1f	4.55d	6.16qd	4.47t	4.85qd	5.72m	4.42s				
1g	4.47d	5.99t	4.45t	4.82dd	5.85m	3.72s				
1h	4.56d	5.97qd	4.53t	4.86m	5.75m			8.51s, 8.88s		
2b	4.67d	6.22dd	4.60dd	6.53dd	6.05m	5.17q		8.66d	5.54q	8.72d
2c	4.71d	6.06dd	4.47dd	6.81t	6.27m	4.76q		8.83d	5.64q	8.71d
3b	4.76d	6.30dd	4.46dd	6.40dd	5.92m	5.24q		8.70d	4.72s	
3d	4.36d	5.84dd	4.40dd	6.45t	6.08m		6.95s	8.40s	4.70s	
3h	4.59d	6.04t	4.37dd	6.45dd	5.90m			8.55s, 8.86s	4.71s	

Compound	*Chemical shift, τ*								*Dioxolane*		
	H-1	*H-1'*	*H-2*	*H-2'*	*H-3*	*H-3'*	*H-4*	*H-4'*	*2'-H*	*2'-OCH₃*	*2'CH₃*
4b	4.61d	4.26d	6.32m	4.95dd	4.67m	4.23t	6.21m	4.69t	5.22q		8.64d
4d	4.39d	4.25d	5.83m	4.98dd	4.73m	4.21t	6.22m	4.68t		7.03s	8.39s

Compound	*Coupling constants, J (Hz)*										
	$J_{1,2}$	$J_{1',2'}$	$J_{2,3}$	$J_{2',3'}$	$J_{3,4}$	$J_{3',4'}$	$J_{4,5}$	$J_{4',5'}$	$J_{2,4}$	J_{CH_3-CH-}	
										(*1,2*-O-	(*4,6*-O-)
1b	5		2.8		2.5		9.5		+0.9	5	
1c	5		5.2		6.5		9.5		0	5	
1d	5.1		3		3.1		9.1		+0.9		
1f	5		2.8		3		9.2		+0.9		
1g	4.8		4.5		5.2		9.3		0		
1h	4.8		3.2		3.2		9.5		+0.9		
2b	4.8		3.5		8		9.3		0	5.1	5.2
2c	4.8		6.1		9.7		9.6		0	4.9	5
3b	5		3.6		8		9.4			5	
3d	5		4.3		8.7		9				
3h	4.5		4.5		8.7		9				
4b	5	4	2.8	10		10	9	9.5	[b]	4.9	
4d	5.5	4	2.8	10		10		9.5	[b]		

[a] 100 MHz in benzene-d_6; d = doublet, dd = doublet of doublets, m = multiplet, q = quartet, qd = quartet of doublets, s = singlet, t = triplet. [b] Present, magnitude undetermined.

chair conformation, when 2′-*endo* substituent–H-5 interactions are minimized, also depends on the effect of other pyranoid-ring substituents. When the vicinal-proton coupling-constants of **2b** and **2c** are compared with those of **1b**, **1c** or **1f**, **1g**, the *trans*-fused 4,6-*O*-ethylidene ring forces a pyranose conformation, judging from the magnitudes of $J_{2,3}$ and $J_{3,4}$, which is more nearly that of a *C1* (D) chair than for any of the four monoalkylidene isomers. The resistance imposed by a 4,6-*O*-alkylidene ring against distortional effects induced by the *cis*-fusion of a dioxolane ring was noted by Coxon[7] in a series of 1,2:4,6-di-*O*-benzylidene-α-D-glucopyranose derivatives of uncertain dioxolane configuration. A comparison of his vicinal-proton coupling-constants for the 3-*O*-acetyl derivative with those of **2b** and **2c** suggests that his compound, as with **2c**, has the *S* configuration (*exo* phenyl).

The dioxolane substituents that alter the conformation of the pyranoid ring also determine whether or not long-range (^4J) coupling will be observed between H-2 and H-4. An isomer with ^4J coupling is assumed to adopt a pyranoid-ring conformation much less like a *C1* (D) chair than an isomer that does not show such coupling, because the H-2 and H-4 protons, normally in a 1,3-diaxial relationship on a *C1*(D) chair, must achieve a nearly coplanar "W" relationship to be appreciably coupled[27,28]. Vicinal-proton coupling-constant data in Table II support this premise. When ^4J coupling is absent, as in **1c**, **1g**, and **2c**, the data are consistent with the dihedral angles of a slightly flattened *C1*(D) chair. However, when ^4J coupling is present, as in **1b**, **1d**, **1f**, and **1h**, the vicinal-proton coupling-constants fit either of two conformers; the half-chair[1] and the skew-boat[2]. Application of selective-decoupling techniques showed the sign of $J_{2,4}$ to be positive for each, a condition reported to indicate a 1,3-diequatorial relationship for the coupled protons[29,30]. The "virtual coupling" limits of Musher and Corey[31] were exceeded for each derivative.

Regardless of the actual conformation, the data of Table II clearly demonstrate that the extent to which the pyranoid ring is distorted away from a *C1* (D) chair depends far more on the degree to which an *endo* substituent interacts with H-5 than upon the *cis*-fusion of the dioxolane ring itself. Additionally, when these data are compared to those published for *endo* ethyl[5] or *tert*-butyl[3] analogs, it is apparent that the extent to which an *endo* substituent interacts with H-5 does not depend solely upon the actual size of the substituent. Since the effective bulk of *endo* methyl, ethyl, and phenyl groups appears to be equivalent, as judged by a comparison of vicinal-proton coupling-constants, and less than that of an *endo* tert-butyl analog, we suggest that ethyl and phenyl groups adopt an orientation that minimizes interactions with H-5 by simple C–C rotation at the 2′ site. However, a globular *endo* substituent, such as a *tert*-butyl group, cannot adopt such a noninterfering orientation; it causes substantially more pyranoid-ring distortion than the ethyl or phenyl groups.

On the basis of the four correlations, the n.m.r. parameters for each pair of diastereoisomers and for the single isomers **3b**, **3d**, **4b**, and **4d** are consistent with the structures assigned in Schemes I and II. Applications of these four correlations should prove useful for assignments of dioxolane configurations to diastereoisomers of D-glucose derivatives having structures similar to those in the schemes.

EXPERIMENTAL

General. — N.m.r. spectra were measured at 100 MHz on a Varian* HA-100 spectrometer with tetramethylsilane ($\tau = 10.0$) as the internal standard. Chemical shifts and coupling constants are first-order, measured directly from spectral spacings. An F and M research chromatograph, Model 700 equipped with a Disc integrator, was employed for g.l.c. Hydroxyl compounds were converted into trimethylsilyl ethers approximately 18 h before injection. Columns of 1/8-in. o.d. stainless-steel tubing were packed as follows: 3% HI-EFF 8BP (cyclohexanedimethanol succinate–Applied Science Labs) on Chromosorb W (80–100 mesh) for (A) 10 ft, (B) 8 ft, (C) 6 ft, and (D) 4 ft; 3% JXR (dimethyl silicone) on Gas Chrom Q (80–100 mesh) for (E) 6 ft; 15% Carbowax 20M on Gas Chrom Q (80–100 mesh) for (F) 5 ft. Column programming was isothermal with helium as the carrier gas and with flame-ionization detection.

Melting points were determined in capillary tubes and are corrected. Optical rotations were measured in a 1-dm tube. Pyridine was removed from organic phases by repeated washing with 5% aqueous cupric sulfate and acetic acid was removed with aqueous $NaHCO_3$. Solutions were evaporated below 40° under diminished pressure. Precoated plates of Silica Gel F-254 (E. Merck, Darmstadt, Germany) were used for t.l.c. Layer thicknesses were 0.25 and 2.0 mm for analytical and preparative separations, respectively. For column chromatography, Baker Analyzed Silica Gel (J. T. Baker Chemical Co., Phillipsburg, N. J.) was used without pretreatment. All solvents contained 0.1% pyridine and were proportioned on a *v/v* basis. Calcium hydride was used to dry pyridine, 1,2-dimethoxyethane, chloroform, and DMF.

O-Acetyl-β-D-glucopyranosyl chlorides. — Samples of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl chloride (**1a**), 2,3-di-*O*-acetyl-4,6-*O*-ethylidene-β-D-glucopyranosyl chloride (**2a**), 2,3-di-*O*-acetyl-4,6-*O*-benzylidene-β-D-glucopyranosyl chloride (**3a**), and hepta-*O*-acetyl-β-maltosyl chloride (**4a**) were prepared by published procedures[32,33].

Ortho esters. — *A.* Diastereoisomeric 3,4,6-tri-*O*-acetyl-1,2-*O*-(1′-ethoxyethylidene)-α-D-glucopyranose (**1d**, **1e**) and hexa-*O*-acetyl-1,2-*O*-(1′-methoxyethylidene)-α-maltose (**4d**, **4e**) were prepared by published procedures[20,32,34]. For n.m.r. data, see Table II.

B. 3-*O*-Acetyl-4,6-*O*-benzylidene-1,2-*O*-(*S*)-(1′-methoxyethylidene)-α-D-glucopyranose (**3d**) was prepared by an improved procedure. A mixture of **3a** (5 g) in 50 ml of methanol and 12.5 ml of 2,4,6-trimethylpyridine was shaken briefly and kept for 18 h at 25°. The mixture was evaporated to a low volume, taken up in ethyl acetate (500 ml), and washed twice with water. A crystalline mixture of **3d** and **3e** (4 g, 79%, 70:30 by n.m.r.) was obtained from ether–petroleum ether; m.p. 147–149° (lit. 148–149°)[32]. Preparative t.l.c. (methyl cyclopentane–acetone 4:1 or toluene–ether

*The mention of firm names or trade products does not imply that they are endorsed or recommended by the Department of Agriculture over other firms or similar products not mentioned.

7:3, two ascents) gave pure **3d** after crystallizations from ether and methanol; m.p. 151–152°. For n.m.r. data, see Table II.

*3,4,6-Tri-*O*-acetyl-1,2-*O*-isopropylidene-α-*D*-glucopyranose* (**1h**). — Crude **1h** was prepared by the method of Lemieux and Detert[4]. Separation on a column of silica gel (chloroform–acetone 9:1) gave pure **1h**, as judged by g.l.c. (column B, 180°), which spontaneously crystallized at −5° after distillation (160°, 0.1 mtorr). Recrystallization from methanol gave m.p. 87–88°, a value that agrees with the literature[4,5].

*4,6-*O*-Benzylidene-1,2-*O*-isopropylidene-α-*D*-glucopyranose* (**9**). — A reaction mixture, which contained 4,6-*O*-benzylidene-α,β-D-glucopyranose (4 g) in a previously prepared solution of *p*-toluenesulfonic acid (0.1 g) and 2,2-dimethoxypropane (5 ml) in 25 ml of DMF, was kept for 36 h at 25° and then was neutralized with barium methoxide (0.35M, 1 ml) in methanol. The mixture was evaporated at 70° and the residue was chromatographed on a silica gel column (chloroform–acetone 9:1). Pure **9** (1.0 g) was crystallized from 2-propanol; m.p. 144–145°, $[\alpha]_D^{20}$ +85° (*c* 1, chloroform); n.m.r. data (benzene-d_6): τ 4.63 (doublet, $J_{1,2}$ 4.5 Hz, H-1), 4.74 (singlet, benzylidene methine), 7.39 (doublet, OH), 8.65, 8.85 (two singlets, isopropylidene C-methyl).

Anal. Calc. for $C_{16}H_{20}O_6$: C, 62.3; H, 6.5. Found: C, 62.5; H, 6.7.

The structure of a compound (m.p. 152–153°, $[\alpha]_D^{20}$ +25.8° in chloroform) previously reported[3,5] to be **9** is unknown.

*3-*O*-Acetyl-4,6-*O*-benzylidene-1,2-*O*-isopropylidene-α-*D*-glucopyranose* (**3h**). — A 0.5-g sample of **9** was acetylated for 48 h in a mixture of pyridine (10 ml) and acetic anhydride (5 ml) kept at 25°. Crystallization of the product from ethanol gave **3h**; m.p. 159–160°, $[\alpha]_D^{20}$ +77.5° (*c* 1.3, chloroform). For n.m.r. data, see Table II.

Anal. Calc. for $C_{18}H_{22}O_7$: C, 61.7; H, 6.3. Found: C, 61.4; H, 6.4.

*3,4,6-Tri-*O*-acetyl-1,2-*O*-benzylidene-α-*D*-glucopyranose* (**1f**, **1g**). — Large-scale preparations of **1f** and **1g** were accomplished by two acetal-exchange procedures[4,5], reported previously, and by a method that applied the techniques of Rees and coworkers[5] to a more readily available starting compound, **1d**. Each method produced the diastereoisomeric mixture (**1f**:**1g**) in overall yields of 40–50%. The ratio of isomers in each mixture was 65:35 (±1%), as determined by g.l.c. (column C, 230°). Separation of each isomer by preparative t.l.c. (methylcyclopentane–acetone 4:1 or toluene–ether 2:1, two ascents) gave **1f** as a colorless syrup after distillation [210°, 0.1 mtorr; $[\alpha]_D^{20}$ +56° (*c* 1, chloroform)] and crystalline **1g** [m.p. 112–113°; $[\alpha]_D^{20}$ +48° (*c* 0.9 chloroform)]. Constants recorded for **1g** agree with literature values[5,36]. See Table II for n.m.r. data of each diastereoisomer.

Reactions of dioxolenium chloride ions with sodium borohydride. — *A*. A series of 1-g samples of **1a**, **2a**, **3a**, or **4a** was dissolved in 10-ml portions of 1,2-dimethoxyethane, pyridine, or DMF; protected from moisture; and treated with 0.3-g portions of sodium borohydride after 10-15 min. Intermittent cooling with an ice bath kept the reaction temperature below 30° for the first 60 min; thereafter all samples were kept for 48 h at 25°. Each sample was cooled to 0°, treated with methanol (20 ml), and then with glacial acetic acid (2 ml) after 15 min. Methanol and other volatiles (not

DMF) were evaporated off. All samples were dissolved in mixtures of acetic anhydride (10 ml) and pyridine (25 ml) and kept for 48 h at 25°. Excess anhydride was decomposed with cold methanol, and each sample was taken up in ethyl acetate and freed of water-soluble materials. Extensive quantities of pyridine–diborane complex were noted in samples derived from pyridine–sodium borohydride solutions. The ratio of the diastereoisomers in each reaction mixture was determined by n.m.r. spectroscopy or by g.l.c. [**1b**, **1c**–columns A (190°), C (180°), D (170°); **2b**, **2c**–column B (125°) as 3-trimethylsilyl ether]. See Table I.

B. **1b** *and* **1c**. Each of three solutions containing 3 g of **1a** in 30 ml of 1,2-dimethoxyethane, pyridine, or DMF was protected from moisture, treated with a 0.7-g portion of sodium borohydride, and kept for 48 h at 25°. Extensive deacetylation was noted by t.l.c. (chloroform–acetone 9:1) before workup. Residual borohydride was destroyed as described for reaction *A*, and each sample was isolated after a 48-h acetylation in a mixture of pyridine and acetic anhydride. G.l.c. analysis (column A, 190°; column E, 180°) showed that **1b** and **1c** formed 85–90% of each sample and that two unknown components and penta-*O*-acetyl-α,β-D-glucopyranose were the major byproducts. The diastereoisomers were formed in ratios equivalent (±1%) to the values given in Table I. The final sample from pyridine weighed 3.1 g and contained pyridine–diborane complex; the other samples weighed 2.8 g each. Samples of **1b** and **1c** were isolated by preparative t.l.c. (toluene–ether 7:3 or methylcyclopentane–acetone 4:1, two ascents) from product mixtures isolated from 1,2-dimethoxyethane or DMF, respectively. Each sample was distilled before analysis. See Table II for n.m.r. data.

3,4,6-Tri-*O*-acetyl-1,2-*O*-(*R*)-ethylidene-α-D-glucopyranose (**1b**), syrup, $[\alpha]_D^{20}$ +25° (*c* 0.7, chloroform).

Anal. Calc. for $C_{14}H_{20}O_9$: C, 50.6; H, 6.1. Found: C, 50.8; H, 6.3.

3,4,6-Tri-*O*-acetyl-1,2-*O*-(*S*)-ethylidene-α-D-glucopyranose (**1c**), syrup, $[\alpha]_D^{20}$ +74° (*c* 1.1, chloroform).

Anal. Calc. for $C_{14}H_{20}O_9$: C, 50.6; H, 6.1. Found: C, 50.9; H, 6.4.

C. **1f** *and* **1g**. A crude, syrupy preparation[37] of **8** (19 g), isolated from a chloroform (200 ml) solution in which penta-*O*-benzoyl-β-D-glucopyranose (20 g) was stirred with titanium tetrachloride (15 ml) at 25° for 8 min, was dissolved in DMF (300 ml) and protected from moisture. After 15 min, 3 g of sodium borohydride was added, with swirling, and the reaction was kept for 30 min. Addition of another 3 g of sodium borohydride caused the reaction mixture to form a stiff gel, which was kept for 48 h at 25°. Excess borohydride was converted into trimethyl borate and sodium acetate, as described in reaction A, and the entire mixture was poured into ethyl acetate and freed of water-soluble materials.

The product syrup (15 g) was dissolved in 500 ml of sodium methoxide in methanol (0.2M), kept overnight at +5°, and then neutralized with acetic acid, and evaporated. G.l.c. analysis (column E, 150°, 180°) showed that the diastereoisomeric 1,2-*O*-benzylidene-α-D-glucopyranose derivatives formed 30–35% of the total carbohydrate fraction and were present in an *R*–*S* ratio of 64:36. D-Glucose and

D-glucitol (10–15% total) were identified in the complex carbohydrate byproducts. The crude benzylidene products were extracted with hot acetone and separated from byproducts on an Avicel PH-101 column irrigated with ethyl acetate–pyridine–water 10:4:3. The product (2.5 g, 33%) was a syrup. Acetylation gave a mixture of **1f** and **1g**, as judged by g.l.c. and n.m.r. spectroscopy.

D. **2b** *and* **2c**. Two solutions containing 7 g of **2a** in 75 ml of 1,2-dimethoxyethane or DMF were reacted with 2.5-g portions of sodium borohydride for 48 h in the manner described for reaction A. Each sample was worked up, acetylated, and isolated from ethyl acetate as described for **1b** and **1c**, a process that yielded 6–7 g of thin syrup from each sample that spontaneously crystallized. One recrystallization from 2-propanol gave 4 g of mixed diastereoisomers from each product. Equal portions were pooled and analyzed.

Anal. Calc. for $C_{12}H_{18}O_7$: C, 52.6; H, 6.6. Found: C, 52.6; H, 6.8.

Samples of the individual diastereoisomers were obtained by preparative t.l.c. (methylcyclopentane–acetone 4:1 or toluene–ether 7:3, two ascents), and purified by sublimation (100°/250 torr) and a final crystallization from ethanol (**2b**) or 2-propanol (**2c**); **2b**, m.p. 105–106.5°, $[\alpha]_D^{20}$ +45° (*c* 1, chloroform), n.m.r. data, Table II; **2c**, m.p. 114–115.5°, $[\alpha]_D^{20}$ +100° (*c* 0.7, chloroform), n.m.r. data, Table II.

E. **3b**. A 7-g sample of **3a** was dissolved in a mixture of 1,2-dimethoxyethane (50 ml) and pyridine (5 ml) and treated with sodium borohydride (1.5 g) for 24 h at 25°. The crude product was worked up, acetylated, and isolated as described for **1b** and **1c**. Purification on a column of silica gel (benzene–ethyl acetate 3:2) gave 4.9 g of mixed, crystalline **3b** and **3c**. Preparative t.l.c. (methylcyclopentane–acetone 4:1 or toluene–ether 7:3, two ascents) gave pure **3b**; m.p. 147–149°, $[\alpha]_D^{20}$ +43.6° (*c* 0.5, chloroform); n.m.r. data, see Table II.

Anal. Calc. for $C_{17}H_{20}O_7$: C, 60.7; H, 6.0. Found: C, 60.9; H, 6.2.

F. **4b** *and* **4c**. The reaction of a solution containing 6 g of **4a** in 50 ml of 1,2-dimethoxyethane with 1 g of sodium borohydride followed the procedure described in reaction *A*. Acetylation was omitted, and the residue obtained after evaporation was taken up in 500 ml of ethyl acetate and washed three times with water. The syrupy product (4 g) was chromatographed on a silica gel column (ethyl acetate–benzene 1:1), a process that yielded 3.2 g of a crystalline mixture of **4b** and **4c**. Purification of a 1-g sample of the mixture by preparative t.l.c. (methylcyclopentane–acetone 7:3 or toluene–ether 1:2, two ascents) gave 0.7 g of **4b** after crystallization from ethanol; m.p. 145–146.5°, $[\alpha]_D^{20}$ +108° (*c* 1, chloroform), for n.m.r. data, see Table II.

Anal. Calc. for $C_{26}H_{36}O_{17}$: C, 50.3; H, 5.9. Found: C, 50.2; H, 6.0.

1,2-O-Ethylidene-α-D-glucopyranose (**5b**, **5c**). — A 30-g composite sample of **1b** and **1c** was dissolved in 300 ml of 0.2M sodium methoxide in methanol, kept overnight at −5°, and then neutralized with solid carbon dioxide. Chromatography on a silica gel column (ethyl acetate–methanol 5:1) gave 15 g of mixed **5b** and **5c** (two overlapping peaks by g.l.c. column E, 125°; column F, 160°) as a syrup.

Hydrolysis of **5b**, **5c**. — Sweeping with nitrogen was used to remove volatile hydrolysis products formed when the mixture of **5b** and **5c** (5 g) was heated for 1 h at

100° in a mixture of methanol (10 ml), water (80 ml), and conc. HCl (5 ml). All volatiles were collected in a trapping solution of 2,4-dinitrophenylhydrazine (2,4-DNP, 2.5 g), conc. sulfuric acid (7 ml), and methanol (170 ml). Chromatography of the contents of the trapping solution on a silica gel column (benzene) yielded the 2,4-dinitrophenylhydrazone of acetaldehyde; 0.3 g, m.p. 147–150° (lit. 147°, 168°)[38].

1,2-O-Ethylidene-3,4,6-tri-O-methyl-α-D-glucopyranose (**6b**, **6c**). — A 2.5-g portion of sodium hydride was added to a solution, under nitrogen, that contained 10 g of **5b**, **5c** in 130 ml of DMF and 70 ml of 1,2-dimethoxyethane. The mixture was stirred for 0.5 h, treated with an additional 2.5 g of hydride, and then kept for 18 h at 25°. The gelatinous mass that resulted was treated with 10 ml of methyl iodide and cooled to maintain the reaction temperature below 30°. After 1 h, a second 10-ml portion of methyl iodide was added and the reaction was then kept 4 h longer at 25° and filtered. The filtrate was diluted with ether (800 ml) before filtering again, and all solvents were evaporated off. Chromatography of the residue on a silica-gel column (hexane–acetone 3:1) gave a mixture of **6b** and **6c** as a syrup (9 g). G.l.c. (column E, 130°) showed the sample to be pure, and the syrup was not examined further.

Hydrolysis of **6b**, **6c**. — Hydrolysis of mixed **6b** and **6c** (4 g) in 90% aqueous trifluoroacetic acid (40 ml) was complete[39] within 15 min at 25°. The solvent was evaporated, with the aid of three 50-ml portions of benzene, and the dark residue was chromatographed on a silica gel column (ethyl acetate). The g.l.c. characteristics of the syrupy product (3 g) were identical with those of standard 3,4,6-tri-*O*-methyl-D-glucose (column E, 120°), and, after treatment with methanolic HCl, with standard methyl 3,4,6-tri-*O*-methyl D-glucoside (column E, 110°; column F, 150°).

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