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ISOLATION OF 2,5-ANHYDRO-1,3-*O*-ISOPROPYLIDENE-6-*O*-TRITYL-D-GLUCITOL AND CONFORMATIONS OF ITS 4-*O*-SUBSTITUTED AND DEPROTECTED, ACYLATED DERIVATIVES*†

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ABSTRACT

Acidic dehydration of D-mannitol (**1**) gave a mixture of anhydrides (**2**) that was isopropylidenated and subsequently tritylated. A single component crystallized from the resulting mixture and was shown to be the novel 2,5-anhydro-1,3-*O*-isopropylidene-6-*O*-trityl-D-glucitol (**4**) by chemical and physical analysis and by comparison of its deprotected, dibenzoylated derivative (**10**) with authentic 2,5-anhydro-1,6-di-*O*-benzoyl-D-glucitol. Acid hydrolysis of **4** afforded pure 2,5-anhydro-D-glucitol (**9**) in better yield than by the previously reported route. The 4-*O*-acetyl (**5**), 4-*O*-chloroacetyl (**6**), 4-*O*-methyl (**7**), and 4-*O*-(methylsulfonyl) (**8**) derivatives of **4**, the tetra-*O*-acetyl (**11**) derivative of **9**, and the 3,4-di-*O*-acetyl (**12**) derivative of **10**, have been prepared and spectrally characterized. Complete proton-n.m.r. analysis yields first-order coupling constants that indicate the E_1(D) conformation for the tetrahydrofuran ring and the chair conformation for the 1,3-dioxane ring of **4**–**8**. Obtainable coupling constants suggest that **11** and **12** exist in the ^0E and/or $^0T_1$ conformations.

INTRODUCTION

For several years we[1–6] have explored the active site of the regulatory enzyme phosphofructokinase by use of synthetic analogues of D-fructose 6-phosphate. 2,5-Anhydro-D-glucitol 6-phosphate, an analogue of α-D-fructofuranose 6-phosphate, has proved to be an effective competitive inhibitor of the enzyme from both rabbit muscle[2] and the parasitic amoeba *Entamoeba histolytica*[6]. Initial enzymic studies with this analogue were conducted with material prepared via ATP-dependent, hexokinase phosphorylation. As enzymic O-6 phosphorylation of 2,5-anhydro-D-glucitol was presumptive, an unambiguous chemical synthesis of this analogue was desirable for comparison and proof of structure. The preparation of an intermediate having suitably protected hydroxyl groups was essential for such a chemical synthesis. Moreover, further studies of the β-D-fructofuranose 6-phosphate site of phospho-

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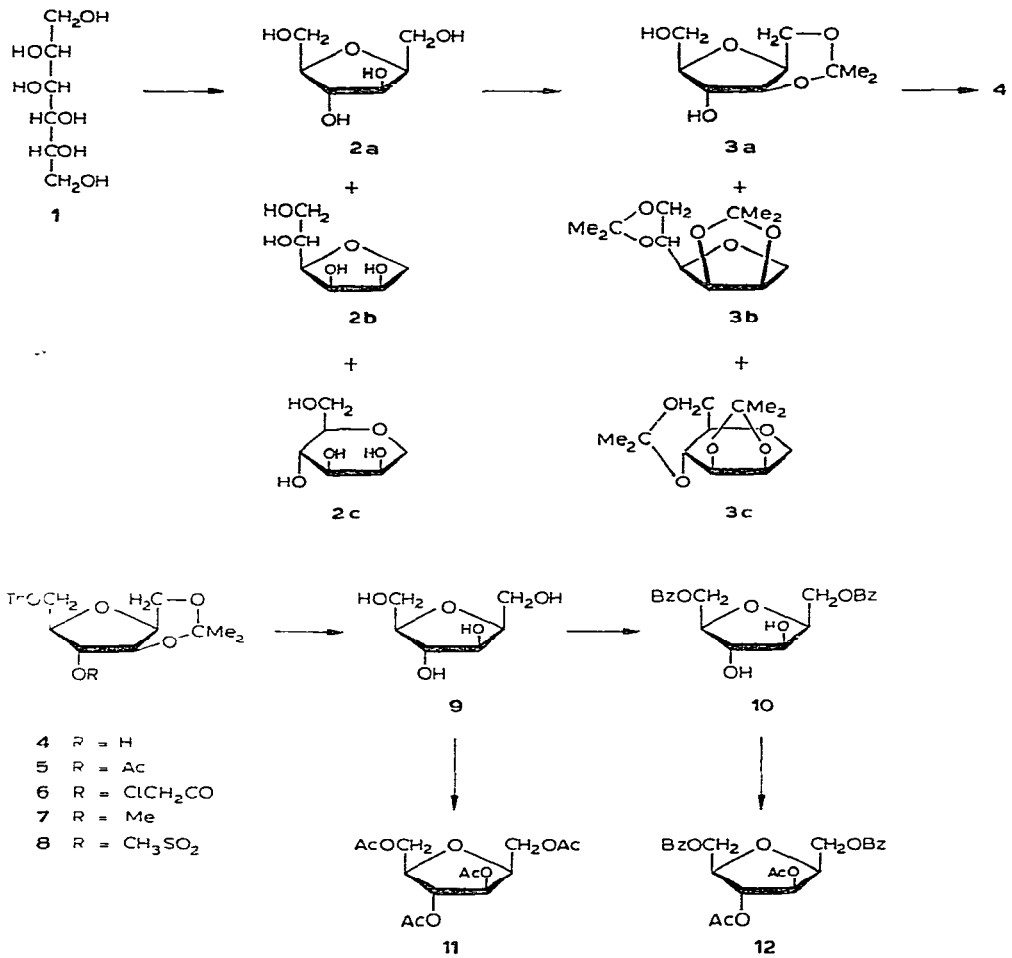
fructokinase have necessitated a synthetic route to 2,5-anhydro-D-glucitol (**9**) that affords higher yields and permits selective derivatization at O-4 of the anhydrohexitol. For these reasons, we have prepared 2,5-anhydro-1,3-*O*-isopropylidene-6-*O*-trityl-D-glucitol (**4**), four of its derivatives (**5**–**8**), and two acetylated derivatives (**11** and **12**) of 2,5-anhydro-D-glucitol. The structures and conformations of these compounds have been established unequivocally by classical and spectral analyses. 1,3,4,6-Tetra-*O*-acetyl-2,5-anhydro-D-mannitol (**13**) was also prepared for use in assignment of the proton resonances in the spectra of **11** and **12**.



RESULTS AND DISCUSSION

Isolation of **4** *and* **9**. — The traditional preparation[2,7–9] of 2,5-anhydro-D-glucitol (**9**), by acid-catalyzed dehydration of D-mannitol 1,6-dibenzoate and sub-

sequent saponification, gives low yields (less than 10%, based on **1**). Moreover, the only intermediate (**10**) in this synthesis that is suitable for derivatization possesses two chemically indistinguishable, secondary hydroxyl groups at C-3 and C-4. An industrial procedure[10,11] for the synthesis of **9** is contingent on an inconvenient, high-vacuum fractional-distillation of the crude mixture of hexitol anhydrides (**2**) and the isopropylidenated monoanhydrohexitol fraction (**3**). Recently, Barker[12] analyzed gas-chromatographically the acid-catalyzed dehydration products of D-mannitol (**1**) and concluded that, in the initial stage of the dehydration, the mixture contains 45% of 2,5-anhydro-D-glucitol (**2a**), 41% of 1,4-anhydro-D-mannitol (**2b**), and 14% of 1,5-anhydro-D-mannitol (**2c**). These findings suggested to us a convenient, alternative route to 2,5-anhydro-D-glucitol. As all primary hydroxyl groups in the components (**2**) of the anhydride mixture should be protected by isopropylidenation, except for the 6-hydroxyl group of **2a**, tritylation of the acetalation mixture (**3**) should lead to selective removal of the 2,5-anhydro-D-glucitol component (**3a**) as **4**. Acid hydrolysis of the product (**4**) obtained gave **9** in 32% yield, as based on the estimated[12] 45% yield of **2a** (and therefore **3a**), or 14%, if it is based on D-mannitol (**1**). Either calculation gives an improved yield over the traditional synthesis. However proof that **9** had, in fact, been obtained depended on establishing the structure of **4**.

Structure of **4**. — All possible anhydrohexitol structures must be considered in view of the constitutional and configurational isomerism possible during the harsh dehydration conditions used. Several erroneous structural assignments in the literature[8,13] attest to this premise.

From the elemental analysis and i.r. data, compound **4** is found to be a monotritylated, monoisopropylidenated monoanhydro-hexitol. From the stereochemistry of the ten parent hexitols[14], it follows that there are, *a priori*, ten 1,6-anhydrides, sixteen 1,5 or 2,6-anhydrides, sixteen 1,4 or 3,6-anhydrides, ten 2,5-anhydrides, forty-two oxiranes, and thirty-two oxetanes, so that a total of 126 possible structures must be considered for a monoanhydrohexitol.

Considering first the oxetane and oxiranes, it is known[15] that the anhydro rings of such structures are unstable to alcoholic base and dilute acid. As the initial dehydration was conducted in boiling, concentrated hydrochloric acid and as refluxing overnight with methanolic sodium methoxide left **4** unchanged, the possible oxetane and oxirane structures may be dismissed. Of the sixteen 1,6-anhydride structures, all lack primary hydroxyl groups and may be removed from consideration because **4** is tritylated.

By analogy with the formation[16] of the transoid, 4,6-*O*-isopropylidene ring from 1,5-anhydro-D-mannitol (**2c**) and of a cisoid 4,6-*O*-isopropylidene ring from methyl α-D-galactopyranoside[17], all sixteen 1,5(2,6)-anhydrides should form 4,6-isopropylidene acetals, as well as 2,3-isopropylidene acetals in the case of eight of them. Thus, no acetalated 1,5-anhydride should undergo tritylation, and all such anhydrides can be eliminated. Likewise, of the sixteen 1,4(3,6)-anhydrohexitols, four should form 5,6-acetals and four 2,3:5,6-diacetals and thus all should escape tritylation.

Thus, only the ten 2,5-anhydride structures need to be considered further

TABLE I

PROTON CHEMICAL-SHIFT DATA FOR COMPOUNDS **4**, **5**, **6**, **7**, AND **8** MEASURED AT 100 MHz IN CHLOROFORM-*d*

Compound	*C-4 Hydroxyl substituent* (R)	*Chemical shift* (δ)[a] *in chloroform-d*										
		H-1	*H-1'*	*H-2*	*H-3*	*H-4*	*H-5*	*H-6*	*H-6'*	*Ip*[b]	*R*[b]	*Ph*[c]
4	proton	~3.9	~3.9	~3.9	~4.1	~4.1[d]	~3.9	3.45	3.19	1.12 1.33	2.12(1)[e]	7.06–7.60
5	acetyl	3.98	3.97	3.84	4.17	5.12	4.13	3.49	3.26	1.12 1.33	2.02	7.04–7.60
6	chloroacetyl	3.99	3.98	3.84	4.21	5.21	4.13	3.49	3.27	1.12 1.34	4.00(2)	7.05–7.57
7	methyl	3.97	3.95	3.80	4.19	3.73	4.10	3.46	3.19	1.14 1.36	3.38	7.05–7.60
8	methylsulfonyl	3.97	3.95	3.86	4.42	5.03	4.19	3.51	3.31	1.14 1.36	2.99	7.06.7.60

[a]In the case of geminal protons, the one resonating at higher field is designated with a prime. [b]Three-proton singlets, unless otherwise indicated in parentheses. [c]5-Proton multiplets. [d]Approximate localization, shifted after D_2O-exchange of hydroxyl proton. [e]In methyl sulfoxide-d_6, appeared as a D_2O-exchangeable doublet at δ 5.25.

TABLE II

FIRST-ORDER PROTON COUPLING-CONSTANTS FOR **4**, **5**, **6**, **7**, AND **8** MEASURED AT 100 MHz IN CHLOROFORM-*d*

Compound	*C-4 Hydroxyl substituent*	*Coupling constants*[a] *(absolute values in Hz, estimated error ±0.2 Hz)*								
		$J_{1,1'}$	$J_{1,2}$	$J_{1',2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$	
4	proton	[b]	[b]	[b]	[b]	[b]	[b]	6.3	7.0	9.1	$J_{OH}<0.1$[c]
5	acetyl	<0.1	2.3	1.8	2.8	0.8	1.5	6.8	6.3	9.1	
6	chloroacetyl	<0.1	2.3	1.8	2.8	0.8	1.5	6.7	6.8	9.4	
7	methyl	<0.1	2.8	1.5	2.8	0.8	1.8	6.3	7.5	9.3	
8	methylsulfonyl	<0.1	2.8	1.5	2.8	0.8	1.5	5.8	8.5	9.3	

[a]In the case of geminal protons, the one resonating at higher field is designated with a prime. [b]Obscured due to overlapping. [c]In methyl sulfoxide-d_6, appeared as a D_2O-exchangeablet doublet ($J_{4,OH}$ 4.0 Hz).

for **4**. Based on the analogous reactions of D-lyxofuranose[18] and methyl α-D-lyxofuranoside[19] leading to *cis*-fused, 1,3-dioxolane acetals in preference to the possible 1,3-dioxane acetals, three of the possible 2,5-anhydride structures should form diacetals. Of the others, two should be dityrityl ethers and three dityrityl monoacetals. Thus, all 2,5-anhydride structures may be ruled out except for 2,5-anhydro-1,3-*O*-isopropylidene-6-*O*-trityl-D-glucitol and its enantiomer. Acid hydrolysis of **4** and benzoylation of the resulting alditol (**9**) gave the dibenzoate (**10**), whose optical rotation ($[\alpha]_D^{20}$ +2.3°) was of the same sign and approximate magnitude as those reported for the D enantiomer by Brigl and Gruner[7] ($[\alpha]_D$ +3.2°) and Vargha and Kuszmann[20] ($[\alpha]_D$ +1.2°). Thus, **4** is 2,5-anhydro-1,3-*O*-isopropylidene-6-*O*-trityl-D-glucitol.

Additional evidence supporting the structure assigned to **4** are: (*a*) the finding[6] that the 6-phosphate of **9** derived from **4** displays phosphofructokinase inhibition qualitatively and quantitatively identical to the enzymically prepared material, and (*b*) the proton-n.m.r. spectra of **4–8**.

Proton-n.m.r. studies. — The chemical shifts (δ) measured for **4–8** are given in Table I, and their first-order coupling-constants (*J*) in Table II. N.m.r. data for **9–13** are reported in the experimental section. A representative spectrum, that of 4-*O*-acetyl-2,5-anhydro-1,3-*O*-isopropylidene-6-*O*-trityl-D-glucitol (**5**), is shown in Fig. 1.

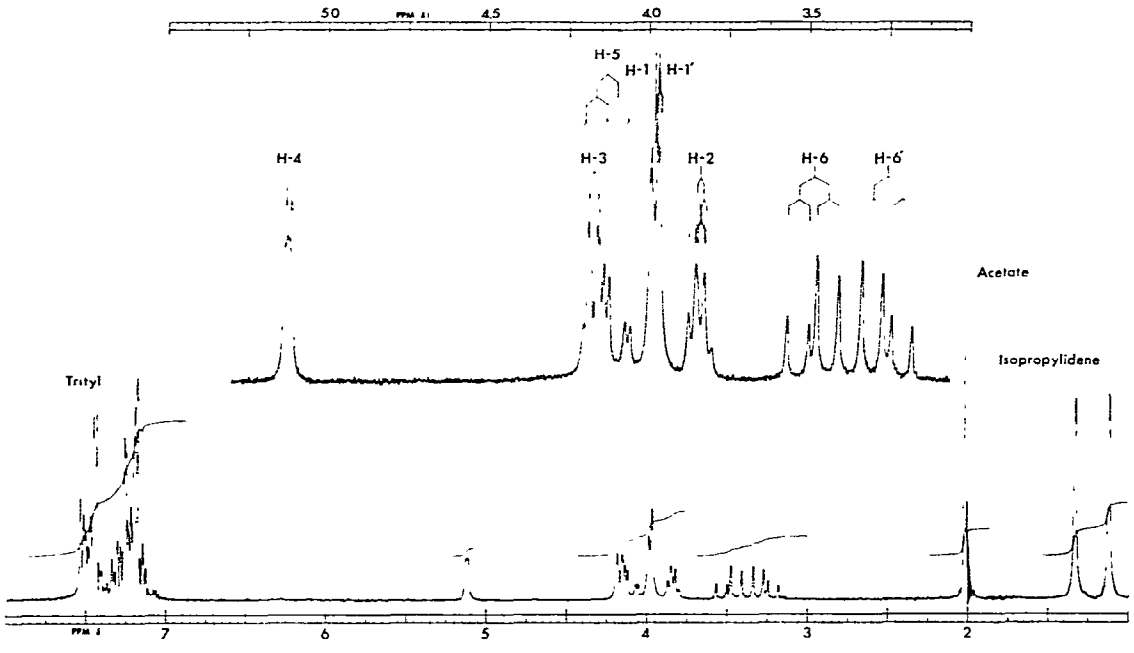


Fig. 1. Proton n.m.r. spectrum of **5** at 100 MHz in chloroform-*d*. The upper trace is an expansion of the signals from the methylene and methine protons attached to the anhydrohexitol skeleton.

The proton-n.m.r. spectra of **4** in chloroform-*d* manifests, at low field ($\delta \sim 7.3$), a 15-proton multiplet, as expected for the phenyl protons of a trityl ether, and at high field (δ 1.12 and 1.33) two 3-proton singlets, characteristic of the methyl protons of an isopropylidene monoacetal. Between these major signals, integration reveals nine protons in the region characteristic of the hydroxyl, methine, and methylene protons of the anhydrohexitol backbone. Of this group, only a 1-proton singlet at δ 2.12 and a symmetrical 8-line, 2-proton pattern (δ 3.1–3.5) are assignable. All other signals overlapped extensively in the region δ 3.8–4.2. Irradiation at δ 3.9–4.0 caused the 8-line pattern to collapse into a mutually-coupled (J 9.1 Hz) doublet-of-doublets, characteristic of an AB subspectrum. As the trityl group should cause shielding in nearby protons that are oriented above the plane of its phenyl rings[21,22], H-6 and H-6′ are assigned to this AB pattern. Exchange with deuterium oxide caused the disappearance of the singlet at δ 2.12, allowing the assignment of this signal to the hydroxyl proton. Examination of **4** in methyl sulfoxide-d_6, as suggested by Chapman and King[23], shifted the hydroxyl resonance downfield to δ 5.25 and resolved it into a doublet ($J_{4,OH}$ 4.0 Hz) because of slower exchange. Thus the free hydroxyl group of **4** is secondary, a finding consistent with the assigned structure.

The spectra of **5**–**8** in chloroform-*d* all showed patterns for trityl and isopropylidene groups almost identical with those for **4**. However, the deshielding influence of the 4-acyloxy groups in **5**, **6**, and **8** and the shielding influence of the 4-methoxyl group in **7** caused the dispersion of the overlapped methine and methylene envelope (δ 3.8–4.2) seen with **4**. The resulting chemical-shift difference is sufficient to allow a completely first-order analysis of all methine and methylene signals of the anhydrohexitol backbone. The results of this analysis are summarized here and in Tables I and II and Fig. 1. Assignments were verified by spin decoupling.

The 8-spin anhydroglucitol skeletons of **5**–**8** give rise to three subspectra. The first is an ABX system composed of the AB system (H-6, H-6′), first seen in the spectrum of **4** (see above), coupled to a downfield X portion at $\delta \sim 4.1$. This downfield signal is assigned to H-5, resolved as a doublet-of-doublets additionally coupled to a signal further downfield. Decoupling showed the latter signal to be the doublet-of-doublets at δ 5.0–5.2 for **5**, **6**, and **8** and at δ 3.73 for **7**. This signal is assigned to H-4. The H-4 signal, in turn, was observed to be additionally coupled to an upfield doublet-of-doublets at δ 4.2–4.4, assigned to H-3. Likewise, the H-3 resonance was observed to be coupled to a doublet-of-doublets-of-doublets at δ 3.8. The latter signal is assigned to H-2. Thus, H-5, H-4, H-3, and H-2 are seen to comprise the second subspectrum, a completely first-order AMRX system, the A portion (H-5) of which is the X-portion of the foregoing ABX system. The X portion of the AMRX system is observed to be part of the third subspectral system. This is another ABX system in which H-2 is the X portion and the closely-spaced pair of doublets near δ 4.0 (H-1 and H-1′) is the AB portion. The methyl or methylene signals of the substituents on the C-4 hydroxyl group of **5**–**8** are readily assigned (Tables I and II) as they are singlets having characteristic chemical shifts.

The poor dispersion of the methine and methylene resonances prevents the

complete analysis of the spectra of **10–12**. However, the available data are consistent with the assigned structures. Thus the spectrum of **10** in methyl sulfoxide-d_6 reveals the presence of two, secondary hydroxyl protons of similar chemical shift (δ 5.37 and 5.42) and identical spin-couplings (J 4.0 Hz). Moreover, acetylation of **9** and **10**, to form **11** and **12**, respectively, leads to a downfield shift of two, mutually coupled, methine protons. Taken together, these data indicate that **9–12** each contain an α-glycol or diacetylated α-glycol, a distinct fragment of **9–12**. The two methine protons of this α-glycol moiety are assigned to H-3 and H-4. On the basis of comparison of chemical shifts with the spectrum of 2,5-anhydro-D-mannitol tetraacetate (**13**), the upperfield signal was assigned to H-4, and the downfield signal to H-3. Finally, in the spectra of both **11** and **12**, the near-symmetry of the 2,5-anhydro-*gluco* structure is reflected in the appearance of a methylene multiplet (H-1, H-1′, H-6, and H-6′) and a methine multiplet (H-2 and H-5) slightly upfield. These two multiplets probably arise from the overlap of two ABX spin systems.

Conformation of **4–8**. — Conformational analysis is possible, based on the foregoing spin-coupling data, if initially certain assumptions are made, namely: (*a*) that each compound exists as one preponderant conformation in solution, (*b*) that the conformation is either an "envelope" (E) form[24] or a "twist" (T) form[25], and (*c*) that for the substituted tetrahydrofuran and 1,3-dioxane rings, coupling constants between protons on adjacent carbon atoms vary with the dihedral angle[26] (ϕ) in a manner similar to that of closely related 2-ketohexofuranose rings[27,28].

Determination of the conformation of **4** and its derivatives entails consideration of their component tetrahydrofuran and 1,3-dioxane rings. The conformation of the tetrahydrofuran ring of **5–8** may be deduced from consideration of the three vicinal coupling-constants between its four methine protons (Table II). The observation that $J_{3,4}$ is small (0.8 Hz) indicates that $60° < \phi_{3,4} < 120°$. This restriction is satisfied by only four conformations*, namely ${}^4E$, ${}^4T_0$, ${}^0T_1$, and ${}^0E_1$. Considering the first two, it is noted that they require $\phi_{2,3} \leq 20°$, for which $J_{2,3}$ should exceed 5 Hz. The fact that $J_{2,3}$ is 2.8 Hz, as well as steric considerations, lead to the exclusion of the ${}^4E$ and ${}^4T_0$ conformations. For the ${}^0T_1$ conformation, the idealized dihedral angles[29] are $\phi_{2,3} = 50°$, $\phi_{3,4} = 101°$, and $\phi_{4,5} = 139°$, and thus $J_{4,5}$ should exceed $J_{2,3}$. As $J_{2,3} > J_{4,5}$ this third conformation can be rules out. Thus assignment of the E_1 (D) conformation to the tetrahydrofuran ring of **5–8** is seen to be the most consistent with the spin-coupling data.

Construction of Dreiding models of **5–8** reveals that the E_1 conformation is adopted naturally by the models, because of the constraints of the fused 1,3-dioxane ring. Precise measurement of the actual dihedral angles from the models show $\phi_{2,3} = 50 \pm 5°$, $\phi_{3,4} = 95 \pm 5°$, and $\phi_{4,5} = 120 \pm 5°$. The values for the dihedral angles of an idealized, maximally puckered, E_1 conformation are $\phi_{2,3} = 60°$, $\phi_{3,4} = 83°$, and $\phi_{4,5} = 120°$. These values are in good agreement with those taken

*It should be noted that the numbering implicit in conformational symbols differs from the numbering of 2,5-anhydro-D-glucitol, thus C-2 of the alditol carbon chain is considered position one of the ring.

from the model. The fact that $J_{2,3}$ exceeds $J_{4,5}$ may be explained most simply by assuming that the tetrahydrofuran ring is not in a maximally puckered E_1 conformation. As C-2 approaches coplanarity with the other four atoms of the ring, $\phi_{2,3}$ decreases (60° → 50°), causing $J_{2,3}$ to increase (1.5 → 2.8 Hz). Moreover, relaxation of some puckering of C-2 would explain the increase in $\phi_{3,4}$ from 83 to 95°. It is possible, however, that there is some rapid equilibration with a small fraction of the ${}^0T_1$ conformation.

With the tetrahydrofuran ring set in the E_1 conformation, two conformations are possible for the 2,2-dimethyl-1,3-dioxane (isopropylidene) ring of **5–8**. In a skew form $\phi_{1,2} = 33°$ and $\phi_{1',2} = 155°$, and in a chair form $\phi_{1,2} = 60°$ and $\phi_{1',2} = 60°$. The fact that $J_{1,2}$ and $J_{1',2}$ are small (< 5 Hz) and of approximately the same value indicates that the 1,3-dioxane ring of **5–8** is disposed in the chair conformation. The angles measured from the Dreiding model are $\phi_{1,2} = 55 \pm 5°$ and $\phi_{1',2} = 65 \pm 5°$.

Having thus determined the conformations of both component rings, a complete stereochemical picture of **5–8** may be rendered (Fig. 2). As the isopropylidene and trityl groups are remote from the site of the 4-*O*-substitution, compound **4** should be conformationally identical to **5–8**.

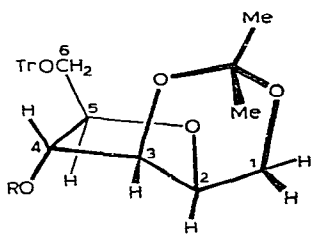


Fig. 2. The probable conformation of **4–8**. The tetrahydrofuran ring is shown disposed in an E_1(D) conformation and the 2,2-dimethyl-1,3-dioxane ring in a chair conformation. To be noted is the difference between the carbon numbering used in the conformational symbol (only ring carbon atoms are numbered) and the numbering system otherwise employed (shown above).

Conformation of **10–12**. — A rigorous conformational analysis, as reported for **5–8**, is not possible for **10–12** because the measurement of coupling from their proton n.m.r. spectra is incomplete. The spectrum of **10** yields no coupling constants. However, $J_{2,3}$, $J_{3,4}$, and $J_{4,5}$ may be estimated from the spectra of **11** and **12**. Using these data, we can attempt to deduce the conformation of **11** and **12**.

First, a modified Karplus curve[30] was constructed from the correlation of ϕ and J for **5–8**. This yields the function $J = J^0 \cos^2 \phi - 0.3$ Hz, for which $J^0 = J^{180} = 7.3$ Hz. With this function as a standard curve, the coupling constants of **11** were correlated with dihedral angles. Thus, $\phi_{2,3} = 45$ or 135°, $\phi_{3,4} = 60°$ or 120°, and $\phi_{4,5} = 47$ or 133° (all $\pm 5°$).

Systematic screening shows that only five conformations are consistent with $\phi_{3,4} = 60$ or 120°, namely ${}^0E$, ${}^0T_1$, ${}^2E$, E_3, and ${}^2T_3$. Construction of the Dreiding model of **11** reveals that the last three conformations all contain one or more axially

oriented, acetoxyl groups. Thus these three conformations seem improbable. This leaves only the ^0E and $^0T_1$ conformations consistent with the spin-coupling data and free of steric crowding. The values for the idealized, maximally puckered ^0E conformation are $\phi_{2,3} = 37°$, $\phi_{3,4} = 120°$, and $\phi_{4,5} = 157°$; those for the $^0T_1$ conformation are $\phi_{2,3} = 50°$, $\phi_{3,4} = 101°$, and $\phi_{4,5} = 133°$. Thus, either of these two conformations fits the data closely. Interestingly, however, an equimolar mixture of the two rapidly interconverting forms, $^0E \rightleftarrows {}^0T_1$, would yield the dihedral angles: $\phi_{2,3} = 44°$, $\phi_{3,4} = 111°$, and $\phi_{4,5} = 145°$. Such values are even closer to the experimental ones, and indicate that the ^0E and $^0T_1$ conformations of **11** may coexist. A similar argument indicates that **12** probably exists in the ^0E and/or $^0T_1$ conformations.

EXPERIMENTAL

General methods. — Melting points were measured with a Thomas–Hoover "Unimelt" oil-bath apparatus and are corrected. Solutions were evaporated *in vacuo*. Optical rotations were determined with a Jasco J-20 recording spectropolarimeter and a 1.00-dm cell. T.l.c. was performed on glass plates coated with Merck Silica Gel F-254. Sample migration was detected under u.v. light or in iodine vapor. I.r. spectra were obtained with a Perkin–Elmer Model 137 i.r. spectrometer and KBr pellets. N.m.r. spectra were recorded at 60 and 100 MHz at probe temperature (~32°) with a Varian A-60A or HA-100 spectrometers. Spectra were obtained in the field-sweep mode for integration and in the frequency-sweep mode for decoupling, by using 20% (w/v) sample solutions containing 1–5% (v/v) of tetramethylsilane as the lock signal and internal standard.

Isopropylidene acetals (**3**) *of mixed anhydrides of* D-*mannitol.* — To the desiccated, syrupy mixture of anhydrides (**2**) resulting from acid-catalyzed dehydration[31] of 150 g (824 mmol) of D-mannitol (**1**) was added dry acetone (1000 ml), 2,2-dimethoxypropane (1000 ml) and dry, acetone-washed Dowex 50W-X8 resin (H^+ form, 150 g). After stirring for 24 h at room temperature, the mixture was filtered. The filtrate was decolorized with charcoal (Norite A), evaporated, and dried to constant mass over phosphorus pentaoxide and paraffin; yield 150 g of a yellow, viscous syrup (**3**).

*2,5-Anhydro-1,3-*O*-isopropylidene-6-*O*-trityl-*D*-glucitol* (**4**). — To a solution of desiccated **3** (150 g) in anhydrous pyridine (500 ml), chlorotriphenylmethane (120 g, 430 mmol) was added. After stirring for 100 h at room temperature, processing of aliquot samples of the mixture indicated no increase in product mass. The mixture was then poured into 10 liters of stirred ice–water. The resulting precipitate was collected by filtration, washed with water, and air dried. This crude product was taken up in warm chloroform and decolorized with charcoal. It crystallized upon addition of petroleum ether; yield 55 g (15% based on **1**) of large prisms, m.p. 183.5–184°, $[\alpha]_D^{20}$ −7.47 ±0.14° (*c* 2.0, chloroform); R_F 0.45 (diethyl ether); λ_{max} 7.25 and 7.30 (doublet, CMe_2), 12.75, 13.07, 13.27, 14.00, 14.15, and 14.35 μm (all six, Ph). For proton-n.m.r. data, see Tables I and II.

Anal. Calc. for $C_{28}H_{30}O_5$ (446.55): C, 75.31; H, 6.77. Found: C, 75.18; H, 6.71.

Stability of **4** *in base.* — A solution of sodium methoxide (210mM) and **4** (500 mg, 11.0mM) in dry methanol (20 ml) was boiled vigorously for 30 h under reflux. At 18 and 30 h, t.l.c. (diethyl ether) indicated that only **4** was present; it was isolated and then crystallized from chloroform–hexane; yield 451 mg (90%); m.p., $[\alpha]_D^{20}$, and elemental analysis identical with those of **4**.

*4-O-Acetyl-2,5-anhydro-1,3-O-isopropylidene-6-O-trityl-*D*-glucitol* (**5**). — To a stirred solution of **4** (2.0 g, 4.48 mmol) in anhydrous pyridine (8 ml) at 0° acetic anhydride (4 ml, 44 mmol) was added. After 10 min, the mixture was kept for ~20 h at room temperature, and was then slowly poured into ice–water (125 ml). The resulting, fine precipitate was stirred for 20 min, collected by filtration, washed with water, and dried *in vacuo*. Several slow crystallizations of the crude product from boiling hexane gave long, thin plates; yield 1.89 g (86%), m.p. 130.0–130.5°, $[\alpha]_D^{20}$ +3.87 ±0.14° (*c* 2.0, chloroform); R_F 0.64 (diethyl ether); λ_{max} 5.73 (C=O of acetate), 7.25 and 7.30 (doublet, CMe_2), 12.80, 13.00, 13.35, 14.10, and 14.30 μm (all five, Ph). For proton-n.m.r. data, see Tables I and II and Fig. 1.

Anal. Calc. for $C_{30}H_{32}O_6$ (488.59): C, 73.75; H, 6.60. Found: C, 73.71; H, 6.69.

*2,5-Anhydro-4-O-chloroacetyl-1,3-O-isopropylidene-6-O-trityl-*D*-glucitol* (**6**). — A solution of chloroacetyl chloride (0.45 ml, 5.6 mmol) in 5 ml of dry ether was added, dropwise with stirring, to an ice-cold solution of **4** (0.50 g, 1.12 mmol) in 100 ml of dry ether containing 0.45 ml of anhydrous pyridine. After 4 h at room temperature, t.l.c. showed that **4** had been completely converted into a single, faster-moving product. The mixture was then taken up in 100 ml of diethyl ether and extracted thrice with ice-cold water, once with 100 ml of ice-cold M hydrochloric acid, and finally with 100 ml of saturated sodium hydrogencarbonate solution. After drying (sodium sulfate), the ether layer was evaporated to a viscous oil. Several crystallizations from chloroform–petroleum ether yielded stout plates; yield 484 mg (83%), m.p. 131.5–132.0°, $[\alpha]_D^{20}$ +4.31 ±0.10° (*c* 2.0, chloroform); R_F 0.68 (diethyl ether); i.r. data: λ_{max} 5.75 (C=O of chloroacetate), 7.28 and 7.33 (doublet, CMe_2), 7.65 and 12.45 (both CH_2Cl), 12.90, 13.05, 13.37, 14.15, and 14.35 μm (all five, Ph). For proton-n.m.r. data, see Tables I and II.

Anal. Calc. for $C_{30}H_{31}ClO_6$ (523.03): C, 68.89; H, 5.97. Found: C, 68.75; H, 6.03.

*2,5-Anhydro-1,3-O-isopropylidene-4-O-methyl-6-O-trityl-*D*-glucitol* (**7**). — To a stirred suspension of hexane-washed sodium hydride (7.0 g) in *N*,*N*-dimethylformamide at 0° was added dropwise a solution of **4** (6.10 g, 13.7 mmol) in *N*,*N*-dimethylformamide (25 ml). After further stirring for one h at room temperature, the mixture was again cooled to 0° and methyl iodide (10 ml, 160 mmol) was added to it dropwise. T.l.c. monitoring showed the reaction to be complete after one h, at which time methanol (10 ml) was carefully added dropwise to decompose the excess of reagents. After one h, the mixture was poured in a thin stream into well-stirred ice–water (1 liter). The precipitated product was collected by filtration, washed with water,

decolorized with charcoal, and crystallized from abs. ethanol; yield 5.03 g (80%) of fine needles, m.p. 108–108.5°, $[\alpha]_D^{20}$ −17.46 ±0.13° (*c* 2.0, chloroform); R_F 0.67 (diethyl ether); i.r. data: λ_{max} 7.25 and 7.30 (doublet, CMe_2), 12.80, 13.00, 13.25, 14.10 and 14.30 μm (all five, Ph), For proton-n.m.r. data, see Tables I and II.

Anal. Calc. for $C_{29}H_{32}O_5$ (460.58): C, 75.63; H, 7.00. Found: C, 75.21; H, 7.10.

2,5-Anhydro-1,3-O-isopropylidene-4-O-(methylsulfonyl)-6-O-trityl-D-glucitol (**8**). — To a stirred solution of **4** (1.00 g, 2.24 mmol) in dry pyridine (10 ml) at 0° was added dropwise methanesulfonyl chloride (0.40 ml, 5.12 mmol). After 24 h at 5°, the mixture was poured in a thin stream into well-stirred ice–water (800 ml). The precipitated product was collected by filtration, washed with water, air-dried, and crystallized from chloroform–hexane; yield 975 mg (83%) of long needles, m.p. 104–105°, $[\alpha]_D^{20}$ −8.49 ±0.10° (*c* 2.0, chloroform); R_F 0.56 (diethyl ether). For proton-n.m.r. data, see Tables I and II.

Anal. Calc. for $C_{29}H_{32}O_7S$ (524.64): C, 66.39; H, 6.15; S, 6.12. Found: C, 66.35; H, 6.29; S, 5.96.

2,5-Anhydro-D-glucitol (**9**). — To 80% aqueous acetic acid (50 ml), compound **4** (1.40 g, 3.13 mmol) was added. The resulting clear solution was stirred for 10 min at 70°, and then overnight at room temperature. After addition of water (50 ml), precipitated triphenylmethanol was removed by filtration and the filtrate concentrated to a semisolid residue. After suspending the residue in water (50 ml) and filtering again, the aqueous filtrate was treated with mixed-bed ion-exchange resin (Amberlite MB-3), evaporated, and dried over phosphorus pentaoxide at 60° under vacuum. The resulting clear syrup crystallized when seeded and scratched; yield 515 mg (96%); the physical constants obtained. m.p. 56–57°, $[\alpha]_D^{20}$ +23.10 ±0.17° (*c* 2.0, water) are in agreement with those of LeMaistre as reported by Defaye[3,2] and Koerner *et al.*[2], but in disagreement with those mistakenly assigned to 2,5-anhydro-D-glucitol[13].

Anal. Calc. for $C_6H_{12}O_5$ (164.16): C, 43.90; H, 7.37. Found: C, 43.97; H, 7.28.

2,5-Anhydro-1,6-O-benzoyl-D-glucitol (**10**). — To a stirred solution of **9** (463 mg, 2.82 mmol) in dry pyridine (5 ml) at −20° benzoyl chloride (0.70 ml, 6.02 mmol) was added. After ~18 h at room temperature, the mixture was added dropwise to vigorously stirred ice–water (300 ml). The resulting precipitate was collected by filtration, washed with water, dried, and crystallized from warm benzene; yield 840 mg (80%) of short needles, m.p. 135.5–138.5°, $[\alpha]_D^{20}$ +2.31 ±0.11° (*c* 2.0, abs. ethanol), lit.[7,20]: m.p. 135.5–138.0°, $[\alpha]_D$ +3.2°, +1.2° (*c* 2 and 1.8 respectively, ethanol); R_F 0.30 diethyl ether), R_F 0.29 (ethyl acetate–benzene, 3:2 by volume) both identical to authentic material[2,7–9]; λ_{max} 5.85 and 5.95 (C=O of benzoate), 6.95 (CH_2), 9.00 (C–CH_2–O of benzoylated primary hydroxyl group), 13.98, and 14.10 μm (both, Ph); proton-n.m.r. data (methyl sulfoxide-d_6, Me_4Si, 60 MHz): δ 4.00–4.20 (2-proton multiplet, H-3 and H-4), 4.10–4.75 (2-proton multiplet, H-2 and H-5), 4.40–4.55 (4-proton multiplet, H-1, H-1′, H-6, and H-6′), 5.37 and 5.42 (two 1-proton doublets, D_2O-exchangeable, C-3 and C-4 hydroxyl protons, $J_{3,OH} = J_{4,OH}$ 4.0 Hz), and 7.30–8.20 (10-proton multiplet, 2 benzoate phenyls). Both the proton n.m.r. and i.r. spectra of **10** were identical with those of an authentic sample.

Anal. Calc. for $C_{20}H_{20}O_7$ (372.38): C, 64.51; H, 5.41. Found: C, 64.27; H, 5.45.

1,3,4,6-Tetra-O-acetyl-2,5-anhydro-D-glucitol (**11**). — To 201 mg (1.22 mmol) of 2,5-anhydro-D-glucitol (**9**) in 7.7 ml of dry pyridine at 0° was added with stirring 4.6 ml (48.8 mmol, 10-fold excess) of acetic anhydride. After 0.5 h at 0° and 46 h at room temperature, the clear mixture was poured in a thin stream into 200 ml of vigorously stirred ice–water. The resulting, aqueous solution was stirred for 0.5 h and then transferred to a separatory funnel and extracted thrice with 70 ml of chloroform. The chloroform extracts were combined, extracted with 100 ml of 0.5M sulfuric acid, and then 100 ml of saturated sodium hydrogencarbonate solution, dried (anhydrous sodium sulfate), and finally evaporated. The resulting syrup was dried overnight under vacuum over paraffin shavings and phosphorus pentaoxide to yield 348 mg (86%) of a viscous, yellow syrup that was homogeneous by t.l.c. (R_F 0.55, diethyl ether). Proton-n.m.r. data (chloroform-*d*; Me_4Si, 60 and 100 MHz): δ 2.02, 2.04, 2.06, and 2.08 (all four, each a 3-proton singlet, 4 acetate methyl groups), 3.92–4.09 (2-proton multiplet, H-2 and H-5), 4.10–4.42 (4-proton multiplet, H-1, H-1′, H-6, and H-6′), 4.98 (1-proton doublet of doublets, H-4, $J_{3,4}$ 1.6 Hz, $J_{4,5}$ 3.1 Hz), and 5.28 (1-proton doublet of doublets, H-3, $J_{3,4}$ 1.6 Hz, $J_{2,3}$ 3.5 Hz).

Anal. Calc. for $C_{14}H_{20}O_9$ (332.31): C, 50.60; H, 6.07. Found: C, 50.51; H, 6.22.

3,4-Di-O-acetyl-2,5-anhydro-1,6-di-O-benzoyl-D-glucitol (**12**). — To 244 mg (0.656 mmol) of thrice recrystallized **10** in 10 ml of dry pyridine at 0° was added with stirring 1.24 ml (13.12 mmol) of acetic anhydride. After 0.25 h at 0°C and 8.3 h at room temperature, the clear mixture was poured in a thin stream into 150 ml of vigorously stirred ice–water. The resulting emulsion was stirred for 10 min and then kept overnight (~12 h) at room temperature. The upper aqueous layer was then decanted from the precipitated oil. This oil was taken up in 100 ml of chloroform, washed with 100 ml of 0.5M sulfuric acid and 100 ml of saturated sodium hydrogencarbonate solution, dried (sodium sulfate), and finally concentrated *in vacuo*. The resulting oil was dried overnight under vacuum over paraffin shavings and phosphorus pentaoxide to yield 248 mg (83%) of a viscous, yellow oil. Proton n.m.r. data (chloroform-*d*, Me_4Si, 60 MHz): δ 2.00 and 2.04 (two 3-proton acetate methyl groups), 4.00—4.40 (2-proton multiplet, H-2 and H-5), 4.45–4.80 (4-proton multiplet, H-1, H-1′, H-6, and H-6′), 5.21 (1-proton doublet of doublets, H-4, $J_{3,4}$ 1.5 Hz, $J_{4,5}$ 3.5 Hz), 5.48 (1-proton multiplet, H-3), and 7.20–8.20 (10-proton multiplet, benzoate phenyl groups).

Anal. Calc. for $C_{24}H_{24}O_9$ (456.45): C, 63.15; H, 5.30. Found: C, 62.92; H, 5.61.

Tetra-O-acetyl-2,5-anhydro-D-mannitol (**13**). — To a stirred solution of 2,5-anhydro-D-mannitol[33] (200 mg, 1.22 mmol) in dry pyridine (7.7 ml) at 0° was added acetic anhydride (4.6 ml, 48.8 mmol). After 0.5 h at 0° and 46 h at room temperature, the mixture was processed as for **11** to yield a viscous, yellow syrup (363 mg, 90%); R_F 0.50 (diethyl ether); $[\alpha]_D^{20}$ +27.1 ±0.5° (*c* 4.2, chloroform), lit.[34] $[\alpha]_D$ +27.3°.

Proton-n.m.r. data (chloroform-*d*, Me_4Si, 60 and 100 MHz): δ 1.89 (12-proton singlet, four 3-proton acetate methyl groups), 4.04 (6-proton broad singlet, H-1, H-1', H-2, H-5, H-6, and H-6'), and 4.95 (2-proton broad singlet, H-3 and H-4). It should be noted that these assignements differ slightly from those previously reported[34].

Anal. Calc. for $C_{14}H_{20}O_9$ (332.31): C, 50.60; H, 6.07. Found: C, 50.49; H, 6.18.

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