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BASE-CATALYSED EQUILIBRATION AND CONFORMATIONAL ANALYSIS OF SOME METHYL 2,3- AND 3,4-ANHYDRO-6-DEOXY-β-D-HEXOPYRANOSIDES*

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ABSTRACT

Methyl 2,3-anhydro-6-deoxy-β-D-mannopyranoside (**6**) and methyl 3,4-anhydro-6-deoxy-β-D-altropyranoside (**8**) have been prepared from methyl 3,4-di-*O*-acetyl-6-deoxy-2-*O*-toluene-*p*-sulphonyl-β-D-glucopyranoside (**5**). At equilibrium, in alkaline solution, the anhydromannoside is preferred by 2:1. Methyl 3,4-anhydro-6-deoxy-β-D-galactopyranoside (**14**) and methyl 2,3-anhydro-6-deoxy-β-D-gulopyranoside (**16**) have been prepared by the action of base on methyl 2,3-di-*O*-acetyl-6-deoxy-4-*O*-toluene-*p*-sulphonyl-β-D-glucopyranoside (**13**) and also from methyl 2-*O*-acetyl-6-deoxy-3-*O*-toluene-*p*-sulphonyl-β-D-galactopyranoside (**25**). At equilibrium, the anhydrogalactoside preponderates in the ratio 9:1. Nuclear magnetic resonance spectroscopy has been employed to define the conformations of the anhydro compounds and hence to rationalise the results of the base-catalysed equilibrations.

INTRODUCTION

As part of a study of epoxide migration[1,2], we wished to examine the methyl anhydro-6-deoxy-β-D-hexopyranosides. By determining the preponderant conformation of each compound in solution and measuring the concentration of each under conditions of alkaline equilibration, it was hoped to augment the earlier conclusions regarding conformational stability in the anhydroglycopyranoside series[2,3]. 6-Deoxy derivatives were selected for study, rather than the anhydrohexopyranosides themselves, because of the relative simplicity of the n.m.r. signal for the methyl group. It is known that the methyl and hydroxymethyl groups differ very little in their conformational properties[4].

The compounds of interest to us were the anhydromannoside **6**, anhydroaltroside **8**, anhydrogalactoside **14**, and anhydroguloside **16**. Of these, only **14** was previously known[5]; it has also been prepared since the completion of this work[6].

*Dedicated to Dr. Horace S. Isbell, in honour of his 75th birthday.
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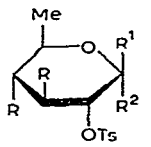
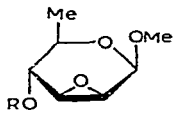
RESULTS AND DISCUSSION

Preparation of anhydroglycosides, and their equilibration

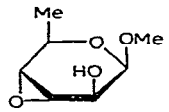
Methyl 6-deoxy-2-*O*-toluene-*p*-sulphonyl-α-D-glucopyranoside[7] (**1**) was selected as a suitable starting material for the anhydromannoside **6** and anhydroaltroside **8**. Acetolysis of **1** gave an analytically pure mixture of acetates **2** and **3**. The derived bromide **4** was converted into the glycoside **5** by reaction with methanol and lead carbonate. In the n.m.r. spectrum of **5**, $J_{1,2}$ was 7.7 Hz, showing that the anomeric linkage was β, as expected[8,9].



1 R = OH, R¹ = H, R² = OMe
2 R = R² = OAc, R¹ = H
3 R = R¹ = OAc, R² = H
4 R = OAc, R¹ = H, R² = Br
5 R = OAc, R¹ = OMe, R² = H



6 R = H
7 R = Ac



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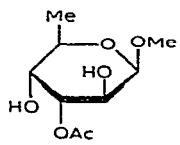

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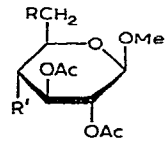
Treatment of the sulphonate **5** with sodium methoxide in methanol resulted in the formation of the anhydromannoside **6** and anhydroaltroside **8**. T.l.c. indicated that epoxide migration had begun before all of the deacetylated sulphonate had disappeared. The structures of the two epoxides were assigned initially on the basis that the first one to be formed, clearly the anhydromannoside **6**, had the lower R_F value. The two components were separated, by chromatography on silica gel, to yield the crystalline anhydromannoside **6** and syrupy anhydroaltroside **8**.

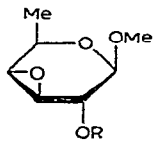
The anhydromannoside **6** afforded a crystalline acetate **7** which, on hydrolysis with 80% acetic acid at 100°, yielded, as the sole product, the syrupy monoacetate **9**, which did not reduce sodium periodate. The formation of the expected axial acetate[10] **9**, *via* neighbouring-group participation[11], effectively confirmed the structure **6**. The structure **8** follows from many well-authenticated cases of epoxide migration[3].

The anhydrogalactoside **14** was prepared from the diacetate **10**[12] which had been obtained by acid hydrolysis of its 4,6-*O*-benzylidene derivative. Treatment of the diacetate **10** with toluene-*p*-sulphonyl chloride yielded the 4,6-disulphonate **11**[12]. When heated with sodium iodide in *N*,*N*-dimethylformamide at 110°, **11** gave the primary iodide **12**[12], from which the 6-deoxy compound **13** was obtained by hydrogenolysis. The anhydrogalactoside **14** was isolated in 83% yield when the sulphonate **13** was treated with sodium methoxide in methanol, very little of the anhydro-

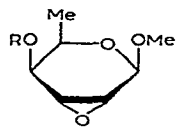
guloside **16** being formed. The epoxide **14** afforded a crystalline acetate **15**, which, on acid hydrolysis, gave a crystalline diol that was not oxidisable by periodate and whose n.mr. spectrum at 100 MHz showed $J_{1,2}$ 8 Hz, $J_{2,3}$ and $J_{3,4}$ 4 Hz, in agreement with structure **19**. It should be noted that **19** is an axial acetate[10].



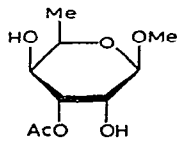
10 R = R' = OH
11 R = R' = OTs
12 R = I · R' = OTs
13 R = H R' = OTs



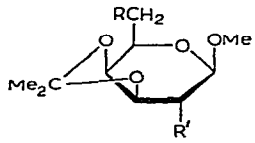
14 R = H
15 R = Ac



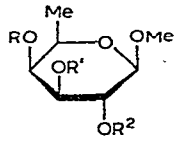
16 R = H
17 R = THP
18 R = Ac



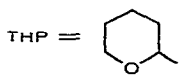
19



20 R = R' = OH
21 R = OTs, R' = OAc
22 R = I, R' = OAc
23 R = H, R' = OAc



24 R = R^1 = H, R^2 = Ac
25 R = H, R^1 = Ts, R^2 = Ac
26 R = THP, R^1 = Ts, R^2 = Ac
27 R = Ac, R^1 = R^2 = H



Because of the strong preference at equilibrium for the anhydrogalactoside **14** over the anhydroguloside **16**, the latter could not be obtained in reasonable amount by this method. Instead, methyl β-D-galactopyranoside was converted into its 3,4-*O*-isopropylidene derivative[13] **20** and then into the sulphonate **21**. Iodide displacement then yielded the iodo compound **22**, which was converted into the 6-deoxy compound **23** by hydrogenolysis and then by deacetonation into **24**, monotoluene-*p*-sulphonylation of which gave the equatorial 3-sulphonate **25** in 60% yield. All the compounds in this series were crystalline.

Treatment of the sulphonate **25** with sodium methoxide in methanol yielded the epoxides **14** and **16**, but at no time was the first-formed epoxide, the anhydroguloside **16**, present in high yield. T.l.c. indicated that **16**, once formed, rapidly equilibrated with the more-favoured anhydrogalactoside **14**. Attempts to use a basic ion-exchange resin for the conversion of **25** into **16** without epoxide migration were disappointing[14]. The problem was solved by converting **25** into a derivative containing an alkali-stable, acid-labile group on O-4. The sulphonate **25**, when treated with 2,3-dihydropyran and toluene-*p*-sulphonic acid in *p*-dioxane solution, gave a crystalline mixture of diastereoisomeric tetrahydropyranyl ethers **26**. Treatment of **26** with methanolic sodium methoxide yielded the epoxide **17** as a mixture of diastereoisomers. Acid hydrolysis of **17** with 80% acetic acid gave the crystalline anhydro-

guloside **16**. The structure of **16** was confirmed by treatment with alkali, when the anhydrogalactoside **14** was obtained in good yield. The acetate **18** was prepared by acetylation of **16** and subjected to acid hydrolysis. The crystalline, axial acetate **27** was isolated, in accordance with the expected participation of the 4-*O*-acetyl group of **18** in the hydrolysis[10,11].

Our original intention to use polarimetry[1] to study the equilibration of **6** and **8**, and **14** and **16** was thwarted by the small differences in specific rotation. We have therefore used g.l.c. of the trimethylsilyl ethers[15] of the epoxides to determine the ratios at equilibrium. Each epoxide was dissolved in aqueous sodium hydroxide (0.1M) and allowed to equilibrate. The ratios found were 2:1 for **6** and **8**, and 9:1 for **14** and **16**.

It may be noted that Kaufmann[5] treated the anhydride **14** with alkaline reagents to yield the derivatives of methyl 6-deoxy-β-D-gulopyranoside. The possibility of epoxide migration was not considered.

N.m.r. spectra and conformations of the anhydrohexosides

Studies on compounds of this type have indicated that the conformation of the pyranoid ring is essentially a half-chair[2,16,17]. Two methods of determination of conformation by n.m.r. spectroscopy were employed in the present work, *viz.* the determination of vicinal coupling constants and a study of the chemical shift of H-1 as a guide to its conformation. The data, derived by first-order analysis of the spectra, are given in Tables I–IV.

TABLE I

N.M.R. CHEMICAL SHIFTS (τ) FOR COMPOUNDS **6**, **8**, **14** AND **16** (D_2O; 100 MHz)

Compound	*H-1*	*H-2*	*H-3*	*H-4*	*H-5*	*OMe*	*Me-5*
6	5.01	←— complex between 6.40 and 6.70 —→				6.44	8.74
8	5.54	5.92	6.52	6.74	5.82	6.52	8.56
14	5.86	6.45	complex between 6.70 and 6.75		5.81	6.55	8.70
16	5.15	(6.64?)	—	6.10	—	6.43	8.82

TABLE II

N.M.R. COUPLING CONSTANTS (±0.3 Hz) OF METHINE PROTONS OF COMPOUNDS **6**, **8**, **14** AND **16** (D_2O)

Compound	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,Me}$
6	0.0	—	—	—	6.0
8	2.0	2.0	4.0	0.5	6.5
14	7.5	0.0	—	0.3	6.5
16	0.5	(4.0?)	2.0	2.0	6.5

TABLE III

N.M.R. CHEMICAL SHIFTS (τ) FOR COMPOUNDS **5–8, 15, 18, 19, 25,** AND **27** ($CDCl_3$; 100 MHz)

Compound	*H-1*	*H-2*	*H-3*	*H-4*	*H-5*	*OMe*	*Me-5*
5	5.72	4.82	5.22	5.46	6.48	6.74	8.79
6	5.21	6.81	6.74	6.44	6.72	6.45	8.68
7	5.18	6.82 (coincident)	6.82	5.34	6.56	6.45	8.76
8	5.61	5.97	6.56	6.96	5.92	6.52	8.56
15	5.76	5.26	7.00	6.88	5.94	6.56	8.61
18	5.30	6.80	6.70	4.96	6.32	6.44	8.85
19	5.54	—	4.72	—	—	6.46	8.72
25	5.70	4.84	5.38	6.08	6.35	6.58	8.67
27	5.84	—	—	4.86	—	6.46	8.81

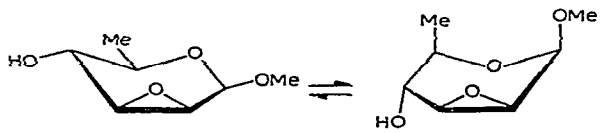
TABLE IV

N.M.R. COUPLING CONSTANTS (±0.3 Hz) OF METHINE PROTONS OF COMPOUNDS **5–8, 15, 18, 19, 25,** AND **27** ($CDCl_3$)

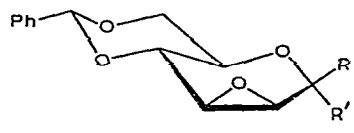
Compound	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,Me}$
5	7.7	9.0	9.0	9.0	6.0
6	0.0	4.0	0.0	8.5	7.0
7	0.0	—	<0.3	8.5	6.5
8	2.0	2.0	4.0	0.0	7.0
15	7.5	0.0	4.0	0.0	6.2
18	0.5	3.5	2.5	2.5	6.5
19	8.0	4.0	4.0	—	7.0
25	8.0	9.0	3.6	<1.0	6.0
27	7.5	—	<3.5	<3.5	6.0

The anhydromannoside **6** is capable of existing in two half-chair conformations $^{o}H_5$ (**28**) and $^{5}H_o$ (**29**)[18]. Its n.m.r. spectrum in deuterium oxide was only partially resolved, but the signal for H-1 showed clearly as a singlet at τ 5.01. The spectrum of **6** in chloroform-*d* was better resolved. It showed H-1 as a singlet (τ 5.21), and $J_{4,5}$ was large (8.5 Hz), corresponding to the diaxial arrangement in **28** rather than that in **29**. There was no evidence that **6** had substantially different conformations in deuterium oxide and chloroform-*d*.

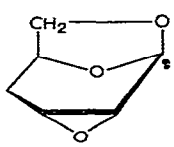
Guthrie and his co-workers[19] have found that, in methyl 2,3-anhydro-4,6-*O*-benzylidene-β-D-mannopyranoside, which is restricted to the $^{o}H_5$ conformation **30** as its only half-chair form, H-1 appears in the n.m.r. spectrum as a sharp singlet at τ 5.15 (chloroform-*d*). They quote the generalisation[16,20] that, for oxiranes fused to 6-membered rings, the *epi*-hydrogens show a coupling (J ~2.5–4.5 Hz) with their *cis* neighbours, and conclude that the anhydromannoside may not have the ideal half-chair conformation **30**. Although in 2,3-anhydroglycopyranosides[2,16,20] the coupling constant $J_{1,2}$ is never large, it is still probably related to the dihedral angle in



28 29



30 R = OMe, R' = H
31 R = H, R' = OMe



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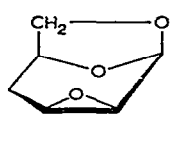

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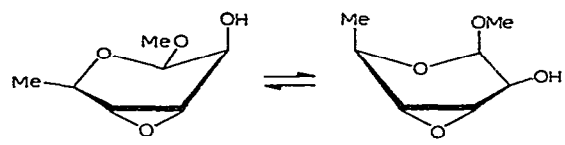


34 35

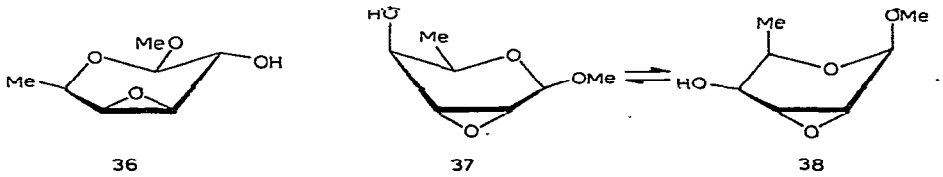
a relationship of the Karplus type[21,22]. In most of the published examples of 2,3-anhydroglycosides having H-1 and H-2 in a *cis*-relationship, the dihedral angle is ~10–20° (inspection of Dreiding models), and the coupling constant $J_{1,2}$ is ~2.5 Hz[2,16,20,23]. On the other hand, the dihedral angles in **28** and **30** are ~55° and 45°, respectively, and it is reasonable to expect that the coupling constants should be appreciably lower than 2.5 Hz. This is borne out in the dianhydride **32** whose n.m.r. spectrum shows H-1 as a "singlet", $J_{1,2}$ 1.0 Hz[24], corresponding to a dihedral angle of ~45°. The fact that the signals for H-1 in the anhydromannoside **30**[19] and its α anomer **31**[16,20] both appear as singlets is therefore not surprising.

The alternative half-chair conformation **29** has a dihedral angle of ~10° for H-1 and H-2. The H-1 signal for this conformation should resemble that of the dianhydride **33**, *viz.* a doublet with $J_{1,2}$ ~3.3 Hz[24] (dihedral angle ~5°), in contrast with the singlet actually observed. This confirms the earlier conclusion that **28** represents the preponderant conformation of **6**.

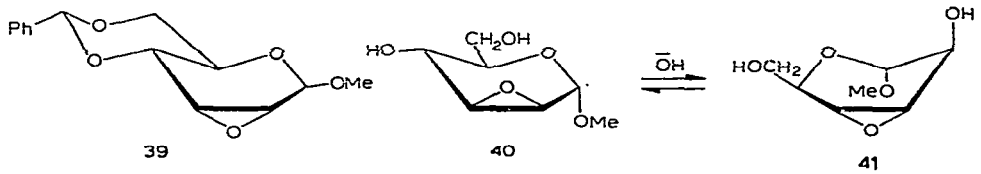
The n.m.r. data for the anhydroaltroside **8** in deuterium oxide are given in Tables I and II. It is difficult to distinguish between the $^{\circ}H_1$ (**34**) and $^{1}H_0$ (**35**) conformations from vicinal coupling constants in this case, since $J_{1,2}$ would be expected to be small in both conformations. However, the relative magnitudes of $J_{2,3}$ and $J_{4,5}$, together with the high field of the chemical shift for H-1 (τ 5.54) indicate that **8** exists largely in the $^{\circ}H_1$ conformation **34**.

The n.m.r. spectrum of **14** in deuterium oxide shows a high value for $J_{1,2}$ (7.5 Hz) and a low value for $J_{4,5}$ (<0.3 Hz), corresponding to the $^{\circ}H_1$ conformation **36**. The chemical shift of H-1 is also noteworthy, being at higher field than any other epoxide we have examined[2]. This indicates that **14** must be almost exclusively in conformation **36** in deuterium oxide, having H-1 axial.

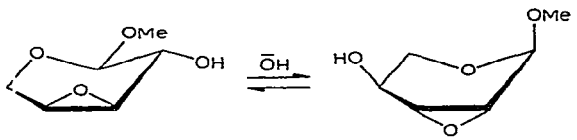
For the anhydroguloside **16** in deuterium oxide, the H-1 signal in the n.m.r. spectrum is a broad singlet, but this does not distinguish between the $^{\circ}H_5$ and $^{5}H_0$ conformations **37** and **38**. In **37**, the dihedral angle between H-1 and H-2 is ~105°, which should lead to a low value for $J_{1,2}$, in agreement with observations on the



36 37 38



39 40 41



42 43

anhydroalloside **39** (dihedral angle, ~95°; H-1 signal, a broad singlet[19]). The dianhydride **32** is a 4-deoxy derivative of **16** whose conformation resembles **38**; it too shows the H-1 signal as a "singlet", $J_{1,2}$ 1 Hz[24]. Measurements on **32** would predict a value of ~0.3 Hz for $J_{3,4}$, the dihedral angle in **38** being ~90°. The observed value, 2.0 Hz, is much more in keeping with conformation **37** in which the dihedral angle is ~65°. We conclude that **16** is mainly in the $^{\circ}H_5$ conformation **37**. Benzyl 2,3-anhydro-4-*O*-methanesulphonyl-β-L-gulopyranoside gives an n.m.r. spectrum (chloroform-*d*) having many features in common with that of **16**, and a conformation corresponding to **37** has been assigned[25]. The 4-deoxy analogue of **16** shows H-1 as a singlet in its n.m.r. spectrum[23].

It might be argued that the chemical shift of H-1 in **16** (τ 5.15), at higher field than that of the corresponding α anomer (τ 4.98)[2], is further evidence in favour of the axial character of H-1 in **16**, *i.e.*, in favour of conformation **37**. The same argument does not hold for **6** (H-1, τ 5.01) [α anomer (H-1, τ 5.08)[2]], and it should be noted that the H-1 signal in all of the 2,3-epoxides is at relatively low field due, probably, to diamagnetic anisotropy of the oxirane ring[26].

The conclusion to be drawn from the n.m.r. study is that, in all of the epoxides **6**, **8**, **14**, and **16**, the preponderant conformation in solution is that in which both the *C*-methyl group (C-6) and the glycosidic methoxyl group are equatorial. In this way, the 1,3-diaxial interaction, which would occur in the opposite half-chair conformation, is avoided[2]. We cannot rule out the presence of an appreciable proportion of other, non-chair, conformations.

Epoxide migrations: factors influencing the point of equilibrium

Even when the conformations of the equilibrating epoxides are known, it is not easy to explain the positions of equilibrium in absolute, quantitative terms. It does appear, however, that the results are those expected from the earlier work[2].

Considering first the equilibration of **6** and **8** (ratio 2:1), it was found previously in the α series that the *manno* isomer **40** was strongly preferred (9:1) over the *altro* isomer **41**, due mainly to the interaction between the axial methoxyl group and the oxirane ring oxygen in the anhydroaltroside **41**. This major effect is relieved in the β-glycoside **8**, but may be replaced by the Reeves "Δ2 effect" of the ring oxygen, HO-2, and glycosidic methoxyl group in close proximity[27]. The Δ2 effect may also be present in the β-anhydromannoside **6**, as shown by the fact that in aqueous solutions of 2,3-anhydro-D-mannose the α-pyranose anomer is preferred over the β by ~3:1[9,27]. The results of the change in configuration at C-1 should, on balance, be to increase the relative amount of *altro* isomer at equilibrium, as was found.

In the equilibrium of **14** and **16**, we have to consider the relative energies of the two conformations **36** and **37**. It is of interest to compare this system with the anhydro-α-L-arabinoside **42** and anhydro-α-L-lyxoside **43**, whose enantiomers were shown to exist in the ratio 7:3 at equilibrium under conditions of epoxide migration[1]. The conformations shown in **42** and **43** are derived from n.m.r. studies on the enantiomers[2]. The two systems are related by the presence or absence of a C-5 methyl group. Conformations **36** and **42** are the same ($^{o}H_1$), and the two compounds differ in energy only by the additional, pseudoequatorial methyl group in **36**.

On the other hand, conformations **37** and **43** are different ($^{o}H_5$ and $^{5}H_o$, respectively), and **37** is of appreciably higher energy. Not only is there the additional, equatorial methyl group (*cf.* **36** and **42**) but also the glycoside methoxyl group is pseudoequatorial, thereby losing the benefit of the anomeric effect[28]*.

On the basis of these arguments, it would be expected that the energy difference between **14** and **16** (*i.e.*, between **36** and **37**) would be greater than that existing[2] between **42** and **43** (0.5 kcal.mole^{-1}) by an amount due to the anomeric effect. If this amount is 0.8 kcal.mole^{-1}, a not unreasonable figure[28], the total energy difference is 1.3 kcal.mole^{-1}, corresponding to an isomer ratio of 9:1, in agreement with that observed.

EXPERIMENTAL

Evaporations were carried out under diminished pressure with a bath temperature below 40°. Melting points are uncorrected. Optical rotations were measured with a Thorn-Bendix TBL-NPL Polarimeter type 143D and a cell of 1-cm path-length. "80% Acetic acid" refers to acetic acid–water (4:1, v/v). Quantitative periodate oxidations were performed by the spectrophotometric method[29].

*The conformational form of **16** related to **43** ($^{5}H_o$) is **38**, and this would have even higher energy due to the 1,3-diaxial interaction of methyl and methoxyl groups.

N.m.r. spectra were measured for 10% solutions in chloroform-*d* (unless otherwise stated) on a Perkin–Elmer R12 spectrometer operating at 60 MHz, or a Varian HA-100D spectrometer operating at 100 MHz.

Chromatographic methods. — Adsorption chromatography was carried out with silica gel (Merck), and t.l.c. with Kieselgel G (Merck). Compounds were detected with anisaldehyde–sulphuric acid[30], and toluene-*p*-sulphonates with diphenylamine[31]. Paper chromatography was by the descending technique, using Whatman No. 1 paper, and water-saturated butanone as solvent. Vicinal glycols were detected by periodate and Schiff's reagent[32], and vicinal epoxides by sodium iodide and Methyl Red[11]. The latter spray was also used on t.l.c.

G.l.c. of the trimethylsilyl ethers[15] was performed on a Perkin–Elmer F11 gas chromatograph, using a 2-m column of Silicon OV1 on Chromosorb G, with an inlet pressure of 15 p.s.i. and a column temperature of 120°. The component ratio was determined by cutting out and weighing the individual peaks.

*Acetolysis of methyl 6-deoxy-2-*O*-toluene-*p*-sulphonyl-α-*D*-glucopyranoside* (**1**). — The glycoside **1**[7] (0.5 g) was treated with a mixture of acetic acid (1 ml), acetic anhydride (1 ml), and conc. sulphuric acid (0.1 ml) overnight at room temperature. Isolation using chloroform yielded a crystalline mixture of acetates **2** and **3** (0.4 g, 60%), as shown by t.l.c. (benzene–ether, 4:1). The n.m.r. spectrum ($CDCl_3$; 60 MHz) showed no signal in the region τ 6.5 corresponding to the original glycoside, but there were 3 3-proton singlets at τ 7.88, 7.98, and 8.12, corresponding to AcO-1, AcO-3, and AcO-4, respectively (Found: C, 50.8; H, 5.4. $C_{19}H_{24}O_{10}S$ calc.: C, 51.35; H, 5.4%).

*3,4-Di-*O*-acetyl-6-deoxy-2-*O*-toluene-*p*-sulphonyl-α-*D*-glucopyranosyl bromide* (**4**). — The mixture of triacetates **2** and **3** (0.05 g) in dichloromethane (0.4 ml was treated with hydrogen bromide in acetic acid (45% w/v; 1 ml) at room temperature overnight. After evaporation of solvent *in vacuo*, the product was crystallised from light petroleum, yielding **4** (35 mg, 61%), m.p. 116°; **4** was unstable and could not be stored for more than 12 h without decomposition. N.m.r. data ($CDCl_3$; 60 MHz): τ 3.65 (*d*, 1 proton, $J_{1,2}$ 4 Hz, H-1); 5.55 (*q*, 1 proton, $J_{2,1}$ 4, $J_{2,3}$ 9 Hz, H-2); 4.60 (*t*, 1 proton, *J* 9 Hz, H-3 or H-4); 5.22 (*t*, 1 proton, *J* 9 Hz, H-4 or H-3); ~5.88 (*m*, H-5); 8.80 (*d*, 3 protons, *J* 6 Hz, Me-5).

*Methyl 3,4-di-*O*-acetyl-6-deoxy-2-*O*-toluene-*p*-sulphonyl-β-*D*-glucopyranoside* (**5**). — The bromide **4** (1.0 g) was stirred overnight with methanol (10 ml) and anhydrous lead carbonate (3 g). The solution was filtered, and the solvent evaporated to give the crystalline glycoside **5**. Recrystallised from ethanol, **5** (0.8 g, 89%) had m.p. 136°, $[\alpha]_D$ +10.7° (*c* 1.40, chlorcform) (Found: C, 51.85; H, 5.7. $C_{18}H_{24}O_9S$ calc.: C, 51.9; H, 5.8%). N.m.r. data are given in Tables III and IV.

*Treatment of methyl 3,4-di-*O*-acetyl-6-deoxy-2-*O*-toluene-*p*-sulphonyl-β-*D*-gluco-pyranoside* (**5**) *with sodium methoxide.* — The sulphonate **5** (3 g) was treated with methanolic sodium methoxide [30 ml, from sodium (0.35 g)] at room temperature for 16 h. T.l.c. (ether) then indicated that none of the deacetylated sulphonate remained. Solid carbon dioxide was added and the solution was evaporated *in vacuo*. The residue

was extracted with hot benzene (2 × 10 ml). Evaporation of the extracts yielded a syrup (0.9 g), which was chromatographed on a column of silica gel (35 g). Benzene–ether (19:1) eluted first methyl 3,4-anhydro-6-deoxy-β-D-altropyranoside (**8**; 0.245 g, 21%) as a syrup, which was purified by distillation (85°/10^{-1} mmHg), $[\alpha]_D$ −27.7° (*c* 0.36, water) (Found: C, 52.3; H, 7.4. $C_7H_{12}O_4$ calc.: C, 52.5; H, 7.55%). N.m.r. data are given in Tables I–IV.

Further elution with benzene–ether (19:1) gave methyl 2,3-anhydro-6-deoxy-β-D-mannopyranoside (**6**); when crystallised from light petroleum, **6** (0.45 g, 40%) had m.p. 72–74°. After sublimation at 80°/10^{-1} mmHg, **6** had m.p. 76°, $[\alpha]_D$ −27.5° (*c* 0.4, water) (Found: C, 52.4; H, 7.6. $C_7H_{12}O_4$ calc.: C, 52.5; H, 7.55%). N.m.r. data are given in Tables I–IV.

Methyl 4-O-acetyl-2,3-anhydro-6-deoxy-β-D-mannopyranoside (**7**). — The epoxide **6** (0.10 g) was treated with acetic anhydride (0.5 ml) in pyridine (1 ml) for 6 h at room temperature. Isolation of the product using chloroform yielded **7** (0.11 g, 87%), m.p. 56–58°. After sublimation (80°/10^{-1} mmHg), **7** had m.p. 60°, $[\alpha]_D$ −9.6° (*c* 1.25, chloroform). N.m.r. data are given in Tables III and IV.

Hydrolysis of **7** *with acetic acid.* — The acetate **7** (0.2 g) was heated at 100° for 20 min with 80% acetic acid (2 ml). Evaporation yielded **9** as a chromatographically homogeneous syrup, $[\alpha]_D$ −45.5° (*c* 1.45, chloroform) (Found: C, 49.0; H, 7.55. $C_9H_{16}O_6$ calc.: C, 49.1; H, 7.3%); **9** did not reduce sodium periodate.

Methyl 2,3-di-O-acetyl-4,6-di-O-toluene-p-sulphonyl-β-D-glucopyranoside (**11**). — Methyl 2,3-di-*O*-acetyl-β-D-glucopyranoside[12] (**10**) (2.0 g) in pyridine (15 ml) was added to a solution of toluene-*p*-sulphonyl chloride (4.2 g, 3 mol. equiv.) in pyridine (15 ml). After 30 h at room temperature, isolation using chloroform yielded **11**, which crystallised from ethanol. Recrystallised from ethanol, **11** (3.6 g, 85%) had m.p. 162°, $[\alpha]_D$ −13.3° (*c* 1.5, chloroform) (Found: C, 51.3; H, 5.1. $C_{25}H_{30}O_{12}S_2$ calc.: C, 51.2; H, 5.2%).

Methyl 2,3-di-O-acetyl-6-deoxy-6-iodo-4-O-toluene-p-sulphonyl-β-D-glucopyranoside (**12**). — The disulphonate **11** (2.0 g) was heated in *N*,*N*-dimethylformamide (20 ml) with sodium iodide (1.0 g) at 110° for 2 h. Isolation using chloroform yielded the iodide **12**, m.p. 149–151°. Recrystallised from methanol, **12** (1.5 g, 80%) had m.p. 153°, $[\alpha]_D$ −21° (*c* 1.0, chloroform) (Found: C, 40.05; H, 4.1. $C_{18}H_{23}IO_9S$ calc.: C, 39.9; H, 4.25%).

Methyl 2,3-di-O-acetyl-6-deoxy-4-O-toluene-p-sulphonyl-β-D-glucopyranoside (**13**). — The iodide **12** (1.3 g) in methanol (15 ml) containing sodium acetate trihydrate (0.5 g) was hydrogenated over 5% palladium-on-charcoal (0.5 g) for 2 h. Isolation using chloroform (15 ml) yielded crystalline **13** (0.75 g, 75%), m.p. 148–150°, $[\alpha]_D$ −62.8° (*c* 1.05, chloroform) (Found: C, 52.3; H, 5.8. $C_{18}H_{24}O_9S$ calc.: C, 51.9; H, 5.8%).

Treatment of sulphonate **13** *with sodium methoxide.* — Compound **13** (1.0 g) was treated with methanolic sodium methoxide [10 ml, from sodium (0.11 g)]. T.l.c. (ether) indicated that no deacetylated **13** remained after 1 h, and that equilibrium between the epoxides **14** and **16** was reached after 14 h. After addition of solid carbon

dioxide, the solution was evaporated to dryness and the residue extracted with hot benzene (2 × 20 ml). On evaporation of the extracts, methyl 3,4-anhydro-6-deoxy-β-D-galactopyranoside (**14**) crystallised. Recrystallisation from ethyl acetate–light petroleum yielded **14** (0.32 g, 83%), m.p. 97–98°. After sublimation, **14** had m.p. 102°, $[\alpha]_D$ −116.3° (*c* 0.55, water) (Found: C, 52.4; H, 7.4. $C_7H_{12}O_4$ calc.: C, 52.5; H, 7.55%); lit.: m.p. 114–115°, $[\alpha]_D$ −64.6° (methanol)[5]; m.p. 108–109°, $[\alpha]_D$ −132° (methanol)[6]. N.m.r. data are given in Tables I and II.

Methyl 2-O-acetyl-3,4-anhydro-6-deoxy-β-D-galactopyranoside (**15**). — The epoxide **14** (0.1 g) in pyridine (1 ml) was treated with acetic anhydride (1 ml) for 1 h at room temperature. Isolation using chloroform yielded the acetate **15**, which crystallised on standing. Recrystallisation from ethyl acetate–light petroleum gave **15** (0.11 g., 88%), m.p. 136°, raised to 137° by sublimation, $[\alpha]_D$ −117° (*c* 0.85, chloroform) (Found: C, 53.7; H, 6.8. $C_9H_{14}O_5$ calc.: C, 53.5; H, 7.0%). N.m.r. data are given in Tables III and IV.

Acid hydrolysis of **15** *with acetic acid.* — The acetate **15** (0.14 g) was heated at 100° for 20 min with 80% acetic acid (2 ml). Evaporation *in vacuo* yielded a syrup which crystallised on standing. Recrystallisation from ethyl acetate yielded methyl 3-*O*-acetyl-6-deoxy-β-D-gulopyranoside (**19**) (0.11 g, 72%), m.p. 129°, $[\alpha]_D$ −73.3° (*c* 0.6, chloroform) (Found: C, 49.0; H, 7.4. $C_9H_{16}O_6$ calc.: C, 49.1; H, 7.3%); **19** consumed no sodium periodate during 20 h. N.m.r. data are given in Tables III and IV.

Methyl 2-O-acetyl-3,4-O-isopropylidene-6-O-toluene-p-sulphonyl-β-D-galactopyranoside (**21**). — Methyl 3,4-*O*-isopropylidene-β-D-galactopyranoside[13] (**20**) (0.1 g) in pyridine (1 ml) was treated with toluene-*p*-sulphonyl chloride (0.09 g) at 0° for 10 min, and then at room temperature for 1 h. Acetic anhydride (0.5 ml) was then added and the mixture left at room temperature overnight. Isolation using chloroform yielded **21** as a syrup which crystallised from ethanol. Recrystallised from ethanol, **21** (0.14 g, 76%) had m.p. 135°, $[\alpha]_D$ +4.5° (*c* 1.65, chloroform) (Found: C, 53.0; H, 6.2. $C_{19}H_{26}O_9S$ calc.: C, 53.0; H, 6.1%).

Methyl 2-O-acetyl-6-deoxy-6-iodo-3,4-O-isopropylidene-β-D-galactopyranoside (**22**). — The sulphonate **21** (0.1 g) in *N*,*N*-dimethylformamide (1 ml) was heated with sodium iodide (0.15 g) at 110° for 4 h. Isolation using chloroform yielded a syrup which crystallised from light petroleum to give **22** (68 mg, 76%), m.p. 92°, $[\alpha]_D$ +32° (*c* 0.75, chloroform) (Found: C, 37.6; H, 4.9. $C_{12}H_{19}IO_6$ calc.: C, 37.4; H, 4.9%).

Methyl 2-O-acetyl-6-deoxy-β-D-galactopyranoside (**24**). — The iodo-compound **22** (0.2 g) in methanol (5 ml) containing sodium acetate trihydrate (0.1 g) was hydrogenated over 5% palladium-on-charcoal for 1 h. Isolation using chloroform gave a crystalline residue of **23**, which was heated in 80% acetic acid at 100° for 10 min. Evaporation left a crystalline solid which, recrystallised from ethyl acetate, afforded **24** (75 mg, 66%), m.p. 135°, $[\alpha]_D$ −15.2° (*c* 1.45, chloroform) (Found: C, 49.0; H, 7.5. $C_9H_{16}O_6$ calc.: C, 49.1; H, 7.3%).

Methyl 2-O-acetyl-6-deoxy-3-O-toluene-p-sulphonyl-β-D-galactopyranoside (**25**). — The acetate **24** (0.2 g) in pyridine (2 ml) was treated with toluene-*p*-sulphonyl chloride (0.2 g) at room temperature for 15 h. Isolation using chloroform yielded a

syrup which crystallised from ethyl acetate–light petroleum. Recrystallised from ethyl acetate, the sulphonate **25** (0.2 g, 60%) had m.p. 135°, $[\alpha]_D$ +33.9° (*c* 1.15, chloroform) (Found: C, 51.55; H, 6.0. $C_{16}H_{22}O_8S$ calc.: C, 51.3; H, 5.85%). N.m.r. data are given in Tables III and IV.

Treatment of sulphonate **25** *with sodium methoxide.* — Compound **25** (0.01 g) was treated with methanolic sodium methoxide [0.1 ml, from sodium (3 mg)]. T.l.c. (ether) indicated that no sulphonate remained after 6 h, but that the first-formed oxide **16** rapidly reached equilibrium with the oxide **14**, the latter being strongly preferred.

*Methyl 2,3-anhydro-6-deoxy-β-*D*-gulopyranoside* (**16**). — The sulphonate **25** (0.5 g) in *p*-dioxane (5 ml) was stirred for 1.5 h at room temperature with freshly distilled dihydropyran (1 ml) and toluene-*p*-sulphonic acid (5 mg). After neutralisation isolation using chloroform yielded a syrup (0.6 g) which crystallised from benzene–light petroleum. T.l.c. [benzene–ether (4:1)] indicated that the crystals consisted of two compounds, presumably the diastereoisomers of **26**.

The crystalline mixture (0.35 g) was treated with methanolic sodium methoxide [4 ml, from sodium (35 mg)] at room temperature for 36 h. Solid carbon dioxide was added to the solution, and the product was isolated using chloroform. The resulting syrup (0.12 g) was purified by chromatography on aluminium oxide, and elution with benzene yielded the diastereoisomers **17** as a syrup (0.1 g).

The syrupy epoxide **17** (0.5 g) was treated with 80% acetic acid (5 ml) at room temperature for 30 min. Evaporation yielded a syrup which crystallized from light petroleum (0.25 g, 76%); m.p. 90–91°. Sublimation yielded **16** as needles, m.p. 93°, $[\alpha]_D$ −101° (*c* 0.55, water) (Found: C, 52.7; H, 7.8. $C_7H_{12}O_4$ calc.: C, 52.5; H, 7.55%). N.m.r. data are given in Tables I and II.

Conversion of anhydroguloside **16** *into anhydrogalactoside* **14**. — The epoxide **16** (0.1 g) was dissolved in 0.08M methanolic sodium methoxide (10 ml). T.l.c. indicated that equilibrium with **14** was established after 15 h, and that **14** was strongly preferred. The solution was treated with solid carbon dioxide and evaporated to dryness. The residue was extracted with hot benzene (2 × 10 ml). Evaporation of the extracts yielded crude, crystalline **14**. Recrystallisation from ethyl acetate–light petroleum yielded **14** (70 mg, 70%), m.p. 101–102°, undepressed on admixture with an authentic sample.

*Methyl 4-*O*-acetyl-2,3-anhydro-6-deoxy-β-*D*-gulopyranoside* (**18**). — The epoxide **16** (80 mg) in pyridine (1 ml) was acetylated with acetic anhydride (0.1 ml) overnight. Isolation using chloroform yielded the syrupy acetate **18** (80 mg, 80%), $[\alpha]_D$ −133° (*c* 0.6, chloroform). N.m.r. data are given in Tables III and IV.

Acid hydrolysis of **18** *with acetic acid.* — The acetate **18** (80 mg) was heated at 100° for 10 min with 80% acetic acid (0.5 ml). Evaporation yielded the crystalline acetate **27** (80 mg), m.p. 138–140°. Recrystallized from ethyl acetate, the product (70 mg, 80%) had m.p. 141°, $[\alpha]_D$ −35° (*c* 0.4, chloroform) (Found: C, 49.3; H, 7.2. $C_9H_{16}O_6$ calc.: C, 49.1; H, 7.3%). N.m.r. data are given in Tables III and IV.

Deacetylation of **27** with sodium methoxide yielded only methyl 6-deoxy-

β-D-galactopyranoside, as shown by paper chromatography. The acetate **27** consumed sodium periodate (0.98 mol. equiv.) during 20 h.

Equilibration of the epoxides in aqueous sodium hydroxide. — The epoxides **6**, **8**, **14**, and **16** (0.02 g) were each dissolved in 0.1M sodium hydroxide (2 ml) and kept at room temperature (~25°) in a tightly stoppered flask. After 16–20 h, t.l.c. indicated that equilibrium had been reached. Each solution was treated with solid carbon dioxide, the solvent evaporated, and the residue extracted with hot ethanol. After evaporation, the extracts were examined by g.l.c. of the trimethylsilyl ethers[15]. The retention times found for the TMS ethers of **6**, **8**, **14**, and **16** were 20.5, 10.5, 18.0, and 21.5 min, respectively. The equilibrium ratios found were 2:1 for **6** and **8**, and 9:1 for **14** and **16**.

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