Carbohydrate Research, 116 (1983) 49–60
Elsevier Science Publishers B.V., Amsterdam – Printed in The Netherlands

SYNTHESIS OF SOME MONOACETALS OF 1,4-ANHYDRO-D-MANNITOL*

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(Received November 8th, 1982; accepted for publication, November 29th, 1982)

ABSTRACT

The known 2,3- and 3,5-benzylidene acetals of 1,4-anhydro-D-mannitol have been shown to have the (*R*) and (*S*) configurations, respectively. The related 2,3-(*S*), 3,5-(*R*), 5,6-(*R*), and 5,6-(*S*) acetals have also been obtained and their configurations assigned by n.m.r. spectroscopy. The reaction of 1,4-anhydro-D-mannitol with acetone under kinetic-control conditions afforded the previously unknown 5,6-isopropylidene acetal.

INTRODUCTION

During studies of the stereochemistry of acetal formation and migration, the acid-catalysed rearrangement of 1,4-anhydro-3,5-*O*-benzylidene-D-mannitol (**1**) to the corresponding 2,3-(*R*)-acetal was examined[1]. This rearrangement was first described by Reeves[2], although he did not establish the identity of the 3,5-acetal and the stereochemistry of the 2,3-acetal. In the re-examination of the rearrangement, the n.m.r. method[3] was used to assign the configurations of the acetals. Reliable application of the n.m.r. method requires the availability of pairs of diastereoisomers, and we now describe the preparation of three pairs of diastereoisomeric monobenzylidene acetals of 1,4-anhydro-D-mannitol required for the arrangement studies. In addition, some derivatives of the monobenzylidene acetals and the hitherto unknown 5,6-isopropylidene acetal are described.

DISCUSSION

At the commencement of this work, two monobenzylidene acetals of 1,4-anhydro-D-mannitol were known, but only the 2,3-acetal obtained by Reeves[2] had been characterised. The other isomer had been prepared by a route in which acidic treatment of 1,6-di-*O*-benzoyl-D-mannitol gave[4,5] a 1,4-anhydro-D-mannitol diben-

*Studies of Cyclic Acetals, Part I.
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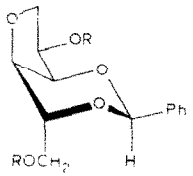
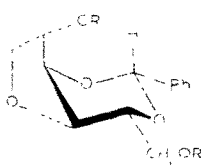
0008-6215/83/$ 03.00

zoate (**2**) from which the acetal was obtained[5] by benzylidenation followed by debenzoylation. Reeves[2] concluded that this acetal did not contain a vicinal diol group and therefore could not have the previously proposed[5] 5,6-acetal structure. This conclusion is confirmed by the present work, in which the acetal is identified as 1,4-anhydro-3,5-*O*-(*S*)-benzylidene-D-mannitol (**1**).

3,5-Acetals. — In our synthesis of **1**, the dibenzoate **2** used by Reeves was prepared by direct treatment of 1,4-anhydro-D-mannitol with 2 molar proportions of benzoyl chloride in pyridine, and this constitutes a more convenient route than the literature procedure. Although the good yield (59%) of the 2,6-dibenzoate **2** (for proof of structure, see below) obtained in the direct benzoylation may reflect its more rapid formation, the operation of thermodynamic control seems to be a more probable explanation. This would involve migration of benzoyl groups, which is known to occur under a variety of conditions[6]. This view is supported by the observation that treatment of 1,4-anhydro-5,6-di-*O*-benzoyl-D-mannitol with pyridine hydrochloride in pyridine resulted in rearrangement to **2**, which is therefore identified as the most stable dibenzoate of 1,4-anhydro-D-mannitol.





1 R = H
3 R = Bz
4 R = Ts

5 R = Bz
6 R = H
7 R = Ts

Treatment of **2** with benzaldehyde–zinc chloride gave the monobenzylidene acetal **3** which was debenzoylated with sodium methoxide to give **1**, the structure of which was established as follows. With an excess of tosyl chloride in pyridine, **1** gave the disulphonate **4** which, on treatment with sodium benzoate in *N,N*-dimethylformamide, afforded 40% of the 2,6-dibenzoate of 1,4-anhydro-3,5-*O*-(*S*)-benzylidene-D-glucitol[7]; the (*S*)-configuration at the benzylidene carbon atom in this compound has been assigned[8] by n.m.r. spectroscopy. Since the displacement of a secondary sulphonate group by benzoate ion proceeds with inversion of configuration[9], the conversion of a 1,4-anhydro-D-mannitol disulphonate into a 1,4-anhydro-D-glucitol derivative establishes that the ester groups are located at positions 2 and 6. Hence, the benzylidene ring occupies the 3,5-position in both the D-mannitol and D-glucitol series of compounds, and **1** is identified as 1,4-anhydro-3,5-*O*-(*S*)-benzylidene-D-mannitol. This identification means that the dibenzoate **2**, which is identical with the compound used by Reeves[2], is 1,4-anhydro-2,6-di-*O*-benzoyl-D-mannitol, and that the acetal {m.p. 162–163°, $[\alpha]_D$ +39.8° (chloroform)} studied by Reeves has the 3,5-(*S*) structure **1**.

When 1,4-anhydro-2,6-di-*O*-benzoyl-3,5-*O*-(*S*)-benzylidene-D-mannitol (**3**)

was treated in chloroform solution with hydrogen chloride, rearrangement occurred to give an equilibrium mixture of **3** and an isomeric acetal **5** in the ratio 3:2, as determined by n.m.r. spectroscopy. Acetal **5** was isolated by fractional crystallisation and then debenzoylated to give an acetal that did not reduce periodate and is therefore assigned the expected 1,4-anhydro-3,5-*O*-(*R*)-benzylidene-D-mannitol structure (**6**). Other periodate-resistant structures for **6** would require migration of a benzoyl group and the formation of unfavourable 7- and 8-membered acetal rings. Since 1,4-anhydro-3,5-*O*-(*S*)-benzylidene-D-mannitol (**1**) readily rearranges to the 2,3-(*R*) acetal (see below), it is concluded that the absence of 2,3-acetals in the rearrangement product of the 3,5-acetal 2,6-dibenzoate **3** indicates that there had been no migration of ester or acetal groups during this reaction, and this accords with the already described stability of the 2,6-dibenzoate **2**. Sulphonic esters show little tendency for migration, and further support for the 3,5-acetal structure of **6** was obtained when its ditoluene-*p*-sulphonate was found to be identical with the new disulphonate (**7**) isolated from the 1:1 equilibrium mixture of acetals obtained by acid treatment of the 3,5-(*S*)-acetal ditoluene-*p*-sulphonate (**4**).

The 3:2 equilibrium ratio for the 3,5-acetals **3** and **5** indicates that they have similar stabilities and this is consistent with the expected behaviour of these acetals. Six-membered cyclic acetals of alditols may have a *β*, *β-erythro,* or *β-threo* ring structure, of which the first two are usually more stable[10]. For the *β* and *β-erythro* acetals, one configurational isomer has all the substituents on the acetal ring in equatorial positions and is expected to be the product of a thermodynamically controlled reaction at equilibrium[11]. The isomer having an axial substituent at the acetal carbon atom or a flexible conformation of the acetal ring would be appreciably less stable[11]. However, for acetals containing a *β-threo* ring in a chair conformation, at least one of the substituents must be axial and, if there is no marked preference for one particular group to adopt the equatorial position, formation of both diastereoisomeric acetals may be expected[11]. This situation obtains with the 3,5-acetals **3** and **5**, in which the acetal ring in each isomer can adopt a chair form having an equatorial phenyl group.

An alternative way to describe these isomers is to indicate the conformation of the trioxabicyclo[4.3.0]nonane framework using the "O-inside" and "H-inside" terminology[11] for substituted tetraoxabicyclo[4.4.0]decanes. Thus, the 3,5-(*S*)-acetal **1** contains an axial hydroxymethyl group (C-6) and an "O-inside" conformation of the trioxabicyclo[4.3.0]nonane framework, whereas the 3,5-(*R*)-acetal **6** contains an axial hydroxymethylene group (C-1 of the anhydro ring) and an "H-inside" conformation. In these acetals, the benzylidene proton is *cis* to the respective axial group, and, because of this similarity in environment, it is not possible to assign configuration by simple, empirical correlation of the chemical shifts of the benzylidene protons. Moreover, there is no marked preference for one isomer in the acid-catalysed equilibration of the dibenzoates (**3** and **5**)and disulphonates (**4** and **7**), and it is therefore not possible to assign configurations by application of the principles of conformational analysis. However, the configurational correlation of

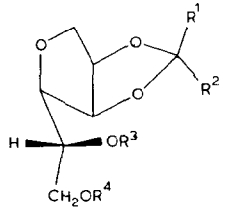
the 3,5-(*S*)-acetal **1**, *via* its disulphonate **4**, with 1,4-anhydro-3,5-*O*-(*S*)-benzylidene-D-glucitol permits confident assignment of the (*S*)-configuration to **1** and **4**, since the conversion should proceed with retention of configuration at the acetal centre.

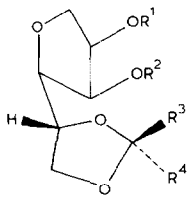
Because of the similar stabilities of the acetals **3** and **5**, it might at first seem surprising that the 3,5-(*S*) acetal (**3**) is obtained in ~70% yield by the zinc chloride-catalysed benzylidenation of dibenzoate **2**. However, the yields of acetals in preparative reactions do not necessarily reflect the thermodynamic stabilities, but, as pointed out by Mills[11], may result from kinetic control or preferential crystallisation.

Selective tosylation of the primary hydroxyl-group in the 3,5-(*R*)-acetal **6** occurred readily, but could not be achieved with the 3,5-(*S*)-acetal **1**; only disulphonate and starting material were isolated in the latter case. Examination of molecular models of **1** shows that, in an "O-inside" conformation with equatorial phenyl group, HO-2 occupies an *endo*-position close to the ring oxygen atoms and is structurally analogous to the hydroxyl-groups in 1,4:3,6-dianhydro-D-mannitol[12] and *cis*-2-phenyl-1,3-dioxan-5-ol[13], both of which show enhanced reactivity towards acid chlorides in pyridine. A similar situation for HO-2 is not observed for **6** in the "H-inside" conformation with equatorial phenyl group, so that the observed differences in selectivity during tosylation can be taken as support for the configurational assignment made above for these diastereoisomers. Selective tosylation of the primary group in 1,4-anhydro-3,5-*O*-(*S*)-benzylidene-D-glucitol has been reported[7]; in this case, HO-2 is in the *exo*-position and is not expected to be activated.

2,3-Acetals. — The 2,3-benzylidene acetal described by Reeves[2] has now been prepared in 64% yield by treatment of 1,4-anhydro-3,5-*O*-(*S*)-benzylidene-D-mannitol (**1**) with glacial acetic acid. The n.m.r. spectra of this acetal (**8**) and its dibenzoate **9** showed single benzylidene proton signals, suggesting that these compounds were single diastereoisomers. To obtain the isomeric 2,3-acetal (**10**), **8** was treated with toluene-*p*-sulphonic acid in *N*,*N*-dimethylformamide, and the resulting, slow rearrangement was monitored by n.m.r. spectroscopy. After 7 days, the ratio for **8**:**10** was 2:1, as determined by integration of the benzylidene proton signals, and **10** was isolated (25%) by column chromatography. Confirmation of the 2,3-acetal structure was obtained by periodate-oxidation analysis, in which **10** reduced 1 mol. of oxidant with liberation of ~1 mol. of formaldehyde. The configurations at the benzylidene carbon atoms in **8** and **10** were assigned from the relative positions of the benzylidene-proton signals in their p.m.r. spectra. Thus the (*R*)-configuration was assigned to **8** having the higher field signal (δ 5.68), and the (*S*)-configuration to **10** (δ 5.87).

The 2,3-acetals (**8** and **10**) each gave a crystalline 6-toluene-*p*-sulphonate (**11** and **12**) and a crystalline 5,6-dimethyl ether (**13** and **14**). In agreement with the configurational assignments given above, the benzylidene-proton signals for the derivatives of the (*R*)-isomer **8** occurred at higher field than those for the derivatives





8 R^1 = Ph, R^2 = R^3 = R^4 = H
9 R^1 = Ph, R^2 = H, R^3 = R^4 = Bz
10 R^2 = Ph, R^1 = R^3 = R^4 = H
11 R^1 = Ph, R^2 = R^3 = H, R^4 = Ts
12 R^2 = Ph, R^1 = R^3 = H, R^4 = Ts
13 R^1 = Ph, R^2 = H, R^3 = R^4 = Me
14 R^1 = H, R^2 = Ph, R^3 = R^4 = Me
16 R^1 = R^2 = Me, R^3 = R^4 = H

15 R^1 + R^2 = >C=O, R^3 = R^4 = Me
17 R^1 = R^2 = H, R^3 = R^4 = Me
18 R^1 = R^2 = R^3 = H, R^4 = Ph
19 R^1 = R^2 = R^4 = H, R^3 = Ph
20 R^1 + R^2 = >C=O, R^3 = H, R^4 = Ph
21 R^1 + R^2 = >C=O, R^3 = Ph, R^4 = H

of the (*S*)-isomer **10**. Acid-catalysed rearrangement of either of the dimethyl ethers **13** and **14** gave the same 1:1 mixture of the two, showing that these diastereomers have similar thermodynamic stabilities, as observed with other diastereomeric 2-phenyl-1,3-dioxolanes[14].

5,6-Acetals. — These acetals were prepared by an acetal-exchange reaction with 1,4-anhydro-5,6-*O*-isopropylidene-D-mannitol 2,3-(cyclic carbonate) (**15**). This route was chosen because a simpler pattern of products results from acetonation of 1,4-anhydro-D-mannitol than from benzylidenation. Thus, the acid-catalysed reaction of 1,4-anhydro-D-mannitol with acetone in *N,N*-dimethylformamide could be monitored by n.m.r. spectroscopy and halted before appreciable amounts of the known[15] diacetal had been formed. Chromatographic fractionation of the resulting product gave the known[15] 2,3-isopropylidene acetal (**16**) and, as the major product, 1,4-anhydro-5,6-*O*-isopropylidene-D-mannitol (**17**). In agreement with the assigned structure, **17** reduced 1 mol. of periodate. The preferred formation of the terminal 5,6-acetal accords with previous observations[16] for acetonation reactions. To protect the 2,3-positions during acetal exchange, **17** was converted into the 2,3-(cyclic carbonate) (**15**, 56%) by treatment with phosgene in pyridine. Replacement of the isopropylidene group in **15** was then readily effected by use of benzaldehyde and hydrogen chloride in chloroform; a similar acetal-exchange reaction has been used [17] to prepare methylene acetals. After the resulting ~1:1 mixture of 5,6-benzylidene acetals had been fractionated on silica gel, the carbonate groups were removed with sodium hydroxide to give 1,4-anhydro-5,6-*O*-(*R*)-benzylidene-D-mannitol (**18**) and the (*S*)-isomer (**19**). The assignments of configuration for these acetals [and for their 2,3-(cyclic carbonates)] were based on the positions of the benzylidene proton signals, which occur at higher field in **18** and its carbonate (**20**) than in **19** and its carbonate (**21**). In accord with the assigned 5,6-acetal structures, **18** and **19** each reduced 1 mol. of periodate.

EXPERIMENTAL

General methods. — *N,N*-Dimethylformamide was shaken with potassium hydroxide pellets and then with calcium oxide, decanted, and distilled on to calcium hydride for storage. Light petroleum refers to the fraction having b.p. 60–80°. Evaporations were effected under diminished pressure. Melting points are uncorrected. Davison silica gel 950 (60–200 mesh) was used for column chromatography. ^{1}H-N.m.r. spectra were recorded with a Varian A-60 instrument for solutions in deuteriochloroform, unless stated otherwise, with tetramethylsilane as internal standard.

*1,4-Anhydro-2,6-di-O-benzoyl-*D*-mannitol* (**2**). — Benzoyl chloride (10.6 g) was added dropwise, with stirring, to a cooled (0°) solution of 1,4-anhydro-D-mannitol[7] (6.15 g) in dry pyridine (60 mL) which was then allowed to attain ambient temperature overnight. Water (1.5 mL) was added and, after 25 min, the mixture was poured into ice–water (250 mL) which was then stirred for 4 h at ~0°. The resulting solid (11 g) was filtered off, washed with water, and dried. Recrystallisation from ethyl acetate gave **2** (9.3 g, 65%), m.p. 147–148°, $[\alpha]_D^{31}$ −3° (*c* 1, chloroform); lit.[2] m.p. 147–149°, $[\alpha]_D$ −2° (chloroform).

*1,4-Anhydro-2,6-di-O-benzoyl-3,5-O-(S)-benzylidene-*D*-mannitol* (**3**). — A mixture of the dibenzoate **2** (5.0 g), benzaldehyde (60 mL), and zinc chloride (6.0 g) was shaken for 7 days, and the resulting solution was then shaken with a mixture of water and light petroleum. The resulting solid was filtered off, washed with water and light petroleum, dried, and recrystallised from ethyl acetate to give the (*S*)-acetal **3** (4.4 g, 71%), m.p. 163–164°, $[\alpha]_D^{31}$ +40° (*c* 1, chloroform); n.m.r.: δ 5.89 (s, 1 H, PhC*H*); lit.[2] m.p. 162–163°, $[\alpha]_D^{25}$+39.8° (chloroform).

*1,4-Anhydro-2,6-di-O-benzoyl-3,5-O-(R)-benzylidene-*D*-mannitol* (**5**). — Dry hydrogen chloride was bubbled for 1 s into a solution of the 3,5-(*S*)-acetal **3** (3.8 g) in dry chloroform (32 mL), and the n.m.r. spectrum was recorded at intervals. The original signal at δ 5.89 diminished and a new signal appeared at δ 6.06; no further change occurred after 1.5 h when the two signals were in the ratio of 3:2. The solvent was then evaporated and the acid removed by co-distillation three times with dry chloroform. The solid residue was triturated with ethyl acetate–light petroleum (2:3), the soluble portion was retained, and the less-soluble residue was subjected to rearrangement and trituration as above. The final less-soluble residue was recrystallised from ethyl acetate, to give **3** (1.3 g, 34%), m.p. 163–164°. The more-soluble portions were combined and evaporated, and the resulting syrup (2.45 g) was crystallised from ethyl acetate–light petroleum, to give **5** (2.3 g, 61%), m.p. 101–102°, $[\alpha]_D^{28}$ −40° (*c* 1, chloroform); n.m.r.: δ 6.06 (s, 1 H, PhC*H*) (Found: C, 70.7; H, 5.1. $C_{27}H_{24}O_7$ calc.: C, 70.4; H, 5.2%).

*1,4-Anhydro-3,5-O-benzylidene-*D*-mannitol.* — (*a*) (R)-*Isomer* (**6**). A solution of sodium methoxide (1.1 g) in methanol (10 mL) was added to a solution of **5** (600 mg) in methanol (30 mL); the mixture was warmed to promote dissolution. After 1 h at room temperature, t.l.c. showed that debenzoylation was complete.

Water (3 mL) was then added, carbon dioxide was bubbled into the mixture, the solvents were evaporated, and the dry residue was extracted with hot acetone. The acetone extract was evaporated, and the residue was crystallised from ethyl acetate–light petroleum, to give **6** (305 mg, 92%), m.p. 96–97°, $[\alpha]_D^{28}$ +32° (*c* 1, chloroform); n.m.r.: δ 6.04 (s, 1 H, PhC*H*) (Found: C, 61.85; H, 6.45. $C_{13}H_{16}O_5$ calc.: C, 61.9; H, 6.35%).

(*b*) (S)-*Isomer* (**1**). In a similar manner, **3** was debenzoylated to give **1** (76%), m.p. 143°, $[\alpha]_D^{28}$ +32° (*c* 0.3, water); lit.[2] m.p. 143°, $[\alpha]_D^{25}$+32° (water); n.m.r.: δ 5.89 (s, 1 H, PhC*H*).

Toluene-p-*sulphonylation of 1,4-anhydro-3,5-*O*-benzylidene*-D-*mannitol.* — (*a*) (S)-*Isomer* (**1**). (*i*) Toluene-*p*-sulphonyl chloride (3.41 g, 3 mol.) was added to an ice-cold, stirred solution of **1** (1.5 g) in dry pyridine (20 mL), and the mixture was stored at room temperature overnight. Water (5 mL) was then added and, after 45 min, the mixture was poured into ice–water (50 mL) and stored at 0° overnight. The resulting solid was recrystallised from aqueous ethanol, to yield 1,4-anhydro-3,5-*O*-(*S*)-benzylidene-2,6-di-*O*-toluene-*p*-sulphonyl-D-mannitol (**4**) (2.54 g, 88%), m.p. 144–145°, $[\alpha]_D^{31}$ +55° (*c* 1, chloroform); ν_{max} 1375 and 1180 cm^{-1} (sulphonyl); n.m.r.: δ 5.90 (s, 1 H, PhC*H*) (Found: C, 57.8; H, 5.0; S, 11.2. $C_{27}H_{28}O_9S_2$ calc.: C, 57.8; H, 5.0; S, 11.4%).

(*ii*) A solution of toluene-*p*-sulphonyl chloride (0.76 g, 1 mol.) in dry pyridine (5 mL) was added slowly during 45 min to a cooled (0°), stirred solution of **1** (1 g) in dry pyridine (10 mL), which was then stored at room temperature overnight. Water (2 mL) was added and, after 10 min, the solution was poured into ice–water (50 mL). The mixture was extracted with chloroform (3 × 50 mL), the dried ($MgSO_4$) extract was evaporated, and the residue was fractionated on a column of silica gel (30 g), to give the disulphonate **4** (0.26 g, 12%; eluted with 1:1 carbon tetrachloride–chloroform) and the diol **1** (0.48 g, 48%; eluted with 9:1 ether–acetone), together with small amounts of materials of intermediate mobility (eluted with 19:1 chloroform–ether) which did not crystallise.

Monitoring of a similar reaction by t.l.c. showed that **4** was present after 5 min and that the components having mobilities intermediate between those of **1** and **4** did not reach significant proportions at any stage of the reaction.

(*b*) (R)-*Isomer* (**6**). Toluene-*p*-sulphonyl chloride (400 mg, 1.8 mol.) was added to an ice-cold solution of **6** (300 mg) in dry pyridine (4.5 mL), and the mixture was stored at 0° for 1.5 h. Water (a few drops) was then added and, after 15 min, the solution was poured into ice–water, the mixture was extracted with chloroform, the dried extract was evaporated, and the residue was fractionated on silica gel. Elution with 4:1 benzene–ether gave the disulphonate **7** (15 mg, 3%), and subsequent elution with 3:2 benzene–ether gave 1,4-anhydro-3,5-*O*-(*R*)-benzylidene-6-*O*-toluene-*p*-sulphonyl-D-mannitol (245 mg, 51%), m.p. 116–117° (from chloroform–light petroleum), $[\alpha]_D^{28}$ +44° (*c* 1, chloroform); ν_{max} 3420 (OH), 1373 and 1180 cm^{-1} (sulphonyl); n.m.r.: δ 6.04 (s, 1 H, PhC*H*) (Found: C, 58.7; H, 5.5; S, 8.2. $C_{20}H_{22}O_7S$ calc.: C, 59.1; H, 5.4; S, 7.9%).

*1,4-Anhydro-3,5-*O*-(*R*)-benzylidene-2,6-di-*O*-toluene-*p*-sulphonyl-*D*-mannitol* (**7**). — Dry hydrogen chloride was bubbled for 2 s into a solution of the (*S*)-disulphonate **4** (560 mg) in dry chloroform (4 mL), and the n.m.r. spectrum was recorded at intervals. The original signal at δ 5.89 diminished while a new signal appeared at δ 6.04; the rearrangement was complete in 1 h when the two signals were of comparable area. After 4 h, the solvent and acid were removed by evaporation and the residue was fractionally crystallised, to give **4** (100 mg, 18%), m.p. 143–144° (from chloroform); and **7** (130 mg, 23%), m.p. 120–121° (from chloroform–light petroleum), $[\alpha]_D^{32}$ +40° (*c* 1, chloroform); ν_{max} 1379 and 1180 cm^{-1} (sulphonyl); n.m.r.: δ 6.04 (s, 1 H, PhC*H*) (Found: C, 58.0; H, 4.7; S, 11.6. $C_{27}H_{28}O_9S_2$ calc.: C, 57.85; H, 5.0; S, 11.4%).

*1,4-Anhydro-2,6-di-*O*-benzoyl-3,5-*O*-benzylidene-*D*-glucitol.* — (*a*) (S)-*Isomer.* A solution of the (*S*)-2,6-disulphonate **4** (560 mg) in *N*,*N*-dimethylformamide (5 mL) was boiled under reflux for 16 h in the presence of sodium benzoate (780 mg). The cooled mixture was diluted with ice–water (50 mL), and the grey precipitate was collected by filtration and recrystallised from ethanol, to give the title compound (500 mg, 40%), m.p. 165° alone or in admixture with authentic material synthesised from 1,4-anhydro-D-glucitol[8], $[\alpha]_D^{27}$ +64° (*c* 2, chloroform); lit.[8] m.p. 163°, $[\alpha]_D$ +64.3° (chloroform); n.m.r.: δ 5.98 (s, 1 H, PhC*H*) (Found: C, 70.7; H, 5.2. $C_{27}H_{24}O_7$ calc.: C, 70.4; H, 5.25%).

(*b*) (R)-*Isomer.* Similar treatment of the (*R*)-2,6-disulphonate **7** (150 mg) with sodium benzoate gave the corresponding D-glucitol derivative (40 mg, 33%); n.m.r.: δ 6.06 (s, 1 H, PhC*H*); which was identical (t.l.c.; n.m.r. and i.r. data) with an authentic specimen[8].

*1,4-Anhydro-2,3-*O*-benzylidene-*D*-mannitol.* — (*a*) (R)-*Isomer* (**8**). The rearrangement of the 3,5-(*S*)-acetal **1** in glacial acetic acid[2] gave **8** (64%), m.p. 94–95°, $[\alpha]_D^{28}$ −96° (*c* 0.5, water); lit.[2] m.p. 94–96°, $[\alpha]_D^{25}$ −88° (water); n.m.r.: δ 5.68 (s, 1 H, PhC*H*).

(*b*) (S)-*Isomer* (**10**). A solution of **8** (1 g) and dry toluene-*p*-sulphonic acid (1 g) in dry *N*,*N*-dimethylformamide (25 mL) was stored at 37°, and the n.m.r. spectrum was recorded at intervals. The signal at δ 5.46 for the benzylidene proton slowly diminished and a new signal appeared at δ 5.65. After 7 days, when there was no further change in the spectrum and the ratio of the signals at δ 5.46 and 5.65 was ~2:1, sodium hydrogencarbonate was added to the reaction solution. The solvent was then evaporated, the residue was extracted with hot acetone, the extract was concentrated, and the resulting material was fractionated on a column of silica gel (50 g). Elution with 2:1 ether–ethyl acetate gave **10** (250 mg, 25%), m.p. 111–112° (from ethyl acetate), $[\alpha]_D^{30}$ −40° (*c* 0.7, water); n.m.r.: δ 5.87 (s, 1 H, PhC*H*) (Found: C, 61.9; H, 6.5. $C_{13}H_{16}O_5$ calc.: C, 61.9; H, 6.4%).

*1,4-Anhydro-5,6-di-*O*-benzoyl-2,3-*O*-(*R*)-benzylidene-*D*-mannitol* (**9**). — Benzoyl chloride (1 mL) was added dropwise, with stirring, to a cooled solution of the (*R*)-acetal **8** (0.4 g) in dry pyridine (15 mL). The solution was kept overnight at room temperature, water (1 mL) was then added, and, after 15 min, the mixture

was poured into ice–water (200 mL). The resulting solid was filtered off, and recrystallised from ethyl acetate–light petroleum to give **9** (0.53 g, 72%), m.p. 96–97 °, $[\alpha]_D$ −26° (*c* 1, chloroform) (Found: C, 70.65; H, 5.05. $C_{27}H_{24}O_7$ calc.: C, 70.4; H, 5.25%).

*1,4-Anhydro-5,6-di-*O*-benzoyl-*D*-mannitol.* — A solution of **9** (0.4 g) in methanol (100 mL) was hydrogenated using 5% palladium-on-charcoal (0.4 g) as catalyst. After 3 days, **9** could no longer be detected by t.l.c., and the catalyst was filtered off and washed with chloroform. Evaporation of the combined solutions gave a syrup that crystallised from benzene–ether–light petroleum, to give the title compound (0.26 g, 83%), m.p. 74–75°, $[\alpha]_D^{30}$ −13° (*c* 1, chloroform); ν_{max} 3400 (OH) and 1715 cm^{-1} (C=O) (Found: C, 64.4; H 5.5. $C_{20}H_{20}O_7$ calc.: C, 64.5; H, 5.4%).

*Rearrangement of 1,4-anhydro-5,6-di-*O*-benzoyl-*D*-mannitol.* — Dry hydrogen chloride was bubbled for 2 s into dry pyridine (2.5 mL), which was then mixed with a solution of the 5,6-dibenzoate (60 mg) in dry pyridine (1 mL). After being kept at room temperature for 24 h, the solution was poured into ice–water. After a further 24 h, the crystals were filtered off, washed with water, dried, and recrystallised from ethyl acetate, to yield **2** (40 mg, 67%), m.p. 148–149° alone or in admixture with authentic material.

*1,4-Anhydro-2,3-*O*-benzylidene-6-*O*-toluene-*p*-sulphonyl-*D*-mannitol.* — (*a*) (R)-*Isomer* (**11**). A solution of the 2,3-(*R*)-acetal **8** (0.26 g) in dry pyridine (3 mL) was treated with toluene-*p*-sulphonyl chloride (0.2 g, 1 mol.) at 0° for 30 min. Water (3 drops) was then added, and, after 30 min, the mixture was poured into ice–water. The resulting solid was filtered off, and recrystallised from chloroform–light petroleum to give **11** (0.17 g, 40%), m.p. 121°, $[\alpha]_D^{27}$ −24° (*c* 1, chloroform); ν_{max} 3480 (OH), 1375 and 1168 cm^{-1} (sulphonyl); n.m.r.: δ 5.68 (s, 1 H, PhC*H*) and 2.40 (s, 3 H, PhCH_3) (Found: C, 59.35; H, 5.7; S, 8.2. $C_{20}H_{22}O_7S$ calc.: C, 59.1; H, 5.4; S, 7.9%).

(*b*) (S)-*Isomer* (**12**). In a similar way, the (*S*)-acetal **10** (0.15 g) was sulphonylated to give **12** (128 mg, 53%), m.p. 115°, $[\alpha]_D^{28}$ ~0° (*c* 1, chloroform); ν_{max} 3488 (OH), 1376 and 1182 cm^{-1} (sulphonyl); n.m.r.: δ 5.87 (s, 1 H, PhC*H*) and 2.40 (s, 3 H, PhCH_3) (Found: C, 59.4; H, 5.6; S, 8.2%).

*1,4-Anhydro-2,3-*O*-benzylidene-5,6-di-*O*-methyl-*D*-mannitol.* — (*a*) (R)-*Isomer* (**13**). An ice-cooled and stirred solution of the 2,3-(*R*)-acetal **8** (0.45 g) in dry *N,N*-dimethylformamide (30 mL) was treated with sodium hydride (0.25 g). After 30 min, methyl iodide (8 mL) was added and the mixture was stored overnight at room temperature. Methanol was then added, and, after 4 h, the solvents were evaporated and the residue was partitioned between chloroform and water. The chloroform solution was washed with water and concentrated, to yield a syrup that crystallised from ether–light petroleum, to give **13** (395 mg, 75%), m.p. 65–66°, $[\alpha]_D^{29}$ −63° (*c* 1, chloroform); n.m.r.: δ 5.68 (s, 1 H, PhC*H*), 3.37 and 3.31 (2 s, 6 H, 2 OMe) (Found: C, 64.7; H, 7.3. $C_{15}H_{20}O_5$ calc.: C, 64.3; H, 7.1%).

(*b*) (S)-*Isomer* (**14**). In a similar way, the (*S*)-acetal **10** (0.2 g) was methylated

to give **14** (0.2 g, 90%), m.p. 35–36° (from light petroleum), $[\alpha]_D^{32}$ −32° (*c* 1, chloroform); n.m.r.: δ 5.87 (s, 1 H, PhC*H*), 3.43 and 3.32 (2 s, 6 H, 2 OMe) (Found: C, 64.1; H, 7.0%).

*1,4-Anhydro-3,5-O-(S)-benzylidene-2,6-di-O-methyl-*D*-mannitol* — The methylation of the 3,5-(*S*)-acetal **1** (0.2 g) was carried out by the procedure described above, to give the title compound (0.12 g, 54%), m.p. 53–54% (from ether–hexane), $[\alpha]_D^{31}$ +93° (*c* 1, chloroform); n.m.r. (CCl_4): δ 5.90 (s, 1 H, PhC*H*), 3.44 and 3.40 (2 s, 6 H, 2 OMe) (Found: C, 64.4; H, 7.2. $C_{15}H_{20}O_5$ calc.: C, 64.3; H, 7.1%).

Acid-catalysed rearrangement of **13** *and* **14**. — (*a*) Dry hydrogen chloride gas was bubbled for 2 min into a solution of **13** (75 mg) in dry chloroform (0.6 mL), and the n.m.r. spectrum was recorded at intervals. During 30 min, the original signal at δ 5.68 decreased in intensity and a new signal at δ 5.87 (characteristic of **14**) developed until the two signals were of equal area.

(*b*) In a similar way, the acetal **14** was rearranged; the final n.m.r. spectrum was identical to that obtained above.

*1,4-Anhydro-5,6-O-isopropylidene-*D*-mannitol* (**17**). — To a solution of 1,4-anhydro-D-mannitol (0.5 g) in *N,N*-dimethylformamide (10 mL) were added toluene-*p*-sulphonic acid (50 mg) and acetone (4 mL), and the n.m.r. spectrum of the solution was recorded at intervals. Two signals near δ 1.4 appeared almost immediately and increased steadily during 2.5 h, after which time a second pair of signals was just visible. The reaction was stopped at this stage by the addition of sodium hydrogencarbonate, the solvents were removed by evaporation, and the residue was extracted with chloroform. The dried ($MgSO_4$) extract was evaporated, and the syrupy residue was fractionated on a column of silica gel. Elution with benzene–ether (1:9) gave **17** (230 mg, 37%), m.p. 46–47° (from ether–light petroleum), $[\alpha]_D^{28}$ −20° (*c* 1, chloroform); n.m.r.: δ 1.39 and 1.34 (2 s, 6 H, CMe_2) (Found: C, 53.0; H, 7.4. $C_9H_{16}O_5$ calc.: C, 52.9; H, 7.8%).

Elution of the column with ether gave 1,4-anhydro-2,3-*O*-isopropylidene-D-mannitol (**16**; 56 mg, 9%), m.p. 82–83°, $[\alpha]_D$ −57.5° (*c* 1.4, water), lit.[15] m.p. 83–84°, $[\alpha]_D$ −59.1° (water); n.m.r.: δ 1.34 and 1.50 (2 s, 6 H, CMe_2).

*1,4-Anhydro-5,6-O-isopropylidene-*D*-mannitol 2,3-carbonate* (**15**). — A solution of phosgene in dry toluene (10 mL, 40% w/v) was slowly added to an ice-cooled, stirred solution of **17** (0.65 g) in dry pyridine (10 mL), and the semi-solid mixture was stored at room temperature overnight. After careful addition of sufficient water to dissolve the precipitate, the mixture was poured into ice–water and then extracted with chloroform, and the extract was washed with dilute hydrochloric acid at 0°, saturated sodium hydrogencarbonate, and water. The dried ($MgSO_4$) solution was evaporated and the residue was twice recrystallised from chloroform–light petroleum, to give **15** (0.42 g, 56%), m.p. 118–119°, $[\alpha]_D^{28}$ −94° (*c* 1, chloroform); ν_{max} 1770 cm^{-1} (C=O), no absorption for OH; n.m.r.: δ 1.42 and 1.37 (2 s, 6 H, CMe_2) (Found: C, 52.5; H, 6.1. $C_{10}H_{14}O_6$ calc.: C, 52.2; H, 6.1%).

*1,4-Anhydro-5,6-O-benzylidene-*D*-mannitol 2,3-carbonate* (**20** and **21**). —

Benzaldehyde (2.5 g) and the 5,6-isopropylidene acetal **15** (2.5 g) were dissolved in dry chloroform (5 mL), dry hydrogen chloride was bubbled into the solution for 5 s, and the n.m.r. spectrum was recorded at intervals. During 1 h, the signals at δ 1.42 and 1.37 for the isopropylidene group disappeared and two new signals at δ 5.85 and 5.66 due to the benzylidene group appeared. The solvents and acid were then evaporated, and the crude product was fractionated on a column of silica gel. Elution with benzene–ether (4:1) gave the (*R*)-isomer **20** (1.42 g, 47%), m.p. 130° (from chloroform–light petroleum), $[\alpha]_D^{28}$ −96° (*c* 1, chloroform); ν_{max} 1770 cm^{-1} (C=O); n.m.r.: δ 5.66 (s, 1 H, PhC*H*) (Found: C, 60.7; H, 5.1. $C_{14}H_{14}O_6$ calc.: C, 60.4; H, 5.0%).

Continued elution of the column with the same solvent gave the (*S*)-isomer **21** (1.22 g, 40%), m.p. 125° (from chloroform–light petroleum), $[\alpha]_D^{28}$ −60° (*c* 1, chloroform); ν_{max} 1770 cm^{-1} (C=O); n.m.r.: δ 5.85 (s, 1 H, PhC*H*) (Found: C, 60.2; H, 5.0%).

*1,4-Anhydro-5,6-O-benzylidene-*D*-mannitol.* — (*a*) (R)-*Isomer* (**18**). Aqueous sodium hydroxide (20 mL, 20%) was added to a solution of the (*R*)-carbonate **20** (1.1 g) in methanol (50 mL). After 5 h, more methanol (25 mL) was added, and carbon dioxide was bubbled through the mixture for 30 min. The mixture was then evaporated to dryness, the residue was extracted with chloroform, and the extract was concentrated. Addition of light petroleum then gave **18** (0.9 g, 92%), m.p. 62°, $[\alpha]_D^{29}$ −28° (*c* 1, chloroform); n.m.r.: δ 5.46 (s, 1 H, PhC*H*) (Found: C, 62.2; H, 6.6. $C_{13}H_{16}O_5$ calc.: C, 61.9; H, 6.35%).

(*b*) (S)-*Isomer* (**19**). In a similar way, the (*S*)-carbonate **21** gave **19** (70%), m.p. 110–111° (from chloroform–light petroleum), $[\alpha]_D^{29}$ +26° (*c* 1, chloroform); n.m.r.: δ 5.66 (s, 1 H, PhC*H*) (Found: C, 61.9; H, 6.3%).

ACKNOWLEDGMENT

The Commonwealth Scholarship Commission in the United Kingdom is thanked for financial support (to M.M.).

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