Carbohydrate Research, 96 (1981) 41–58
Elsevier Scientific Publishing Company, Amsterdam – Printed in The Netherlands

SYNTHESIS AND SOME REACTIONS OF 1,3:4,6-DI-*O*-BENZYLIDENE-D-*threo*-2,5-HEXODIULOSE

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(Received February 24th, 1977; accepted for publication in revised form, March 23rd, 1981)

ABSTRACT

Oxidation of 1,3:4,6-di-*O*-benzylidene-D-mannitol in ethyl acetate with ruthenium tetraoxide gave the corresponding diketone as its hydrate, which was dehydrated to the free diketone. These compounds were treated with a variety of reagents containing hydride, oxygen, nitrogen, and carbon nucleophiles. Only in reactions with methylmagnesium iodide and with diazomethane was the symmetrical bis-adduct obtained. In all other cases, the reactivity of the two carbonyl groups was different. Hydride addition occurred with opposite stereoselectivity at each carbonyl group. With oxygen and nitrogen nucleophiles, cyclic adducts were obtained, arising from bridging across the two carbonyl groups by one molecule of nucleophilic reagent. The configurations of the ring fusions were deduced by p.m.r spectroscopy, and the *cis,cis*-structure was preferred in compounds containing one five- and two six-membered rings. In the reactions with other carbon nucleophiles, complex mixtures were obtained due, at least in the case of the reaction with phenylmagnesium bromide, to elimination reactions.

INTRODUCTION

In connection with another investigation, a range of 2,5-disubstituted derivatives of 1,3:4,6-di-*O*-benzylidene-D-mannitol (**1**) containing branched-chain and amino functions at positions 2 and 5 was required. The synthetic utility of ketone intermediates in the synthesis of derivatives in these classes has been amply demonstrated[1] and therefore a strategy was devised involving 1,3:4,6-di-*O*-benzylidene-D-*threo*-2,5-hexodiulose, which could be reacted with a range of carbon or nitrogen nucleophiles.

Of the available methods for oxidation of secondary hydroxyl groups in carbohydrates, those using dimethyl sulphoxide–acetic anhydride[2] and ruthenium dioxide–potassium periodate[3] were selected as being potentially most suitable.

RESULTS AND DISCUSSION

Oxidation of **1** (ref. 4) with dimethyl sulphoxide–acetic anhydride gave three products, and structures were assigned, on the basis of the analytical and spectroscopic data, by analogy with previous results[5] and assuming no migration of benzylidene acetal groups and no configurational inversion. The major product was a methylthiomethyl ether (p.m.r. peaks at τ 5.31 and 7.89) of a dibenzylidenehexulose, and, because of the symmetry of the substrate, it follows that this is 1,3:4,6-di-*O*-benzylidene-5-*O*-(methylthiomethyl)-D-fructose.

The second product was shown by its elemental analysis and simple p.m.r. spectrum to be a symmetrical hydrate of a dibenzylidenehexodiulose which is assumed to have retained the 1,3:4,6-arrangement of the acetal groups, and the D-*threo* configuration. Two diastereoisomeric structures are possible for this hydrate, which differ in the configuration of the ring fusions. This aspect of the structure will be discussed later.

The third product was a syrup; the spectroscopic data were consistent with its being 1,3:4,6-di-*O*-benzylidene-2,5-di-*O*-(methylthiomethyl)-D-mannitol, but satisfactory analytical data could not be obtained.

The formation of methylthiomethyl ethers in competition with oxidation is analogous with previous results using unhindered secondary alcohols[5], and attention was turned to ruthenium tetraoxide[6,7] as oxidant. Carbon tetrachloride or dichloromethane is the best solvent for this type of oxidation[8], but **1** is only slightly soluble in these solvents. Although **1** is more soluble in dichloroethane, oxidation failed to occur in this solvent. Ether, benzene, and pyridine were excluded because of their explosive reaction[9] with ruthenium tetraoxide, leaving acetone and ethyl acetate as the only common solvents in which **1** is reasonably soluble. The use of acetone as solvent has previously given[8] disappointing results, and oxidation of **1** in wet acetone overnight at room temperature gave only 4% of the diketone hydrate **2**, together with another compound which appeared to be a monoketone, most probably 1,3:4,6-di-*O*-benzylidene-D-fructose (**3**).

With ethyl acetate as solvent and potassium periodate as oxidant, **1** was converted efficiently into the diketone hydrate **2** (73% yield by direct crystallisation). Attempted oxidation of **1** using sodium hypochlorite[10] in ethyl acetate gave a complex mixture of products (t.l.c.) from which **2** could not be isolated by crystallisation.

Crystallisation of **2** from dry methanol yielded the methanolate **4**, from which the acetate **5** was obtained. The hydrate **2** was converted into the crystalline diketone **6** using a type 5A molecular sieve.

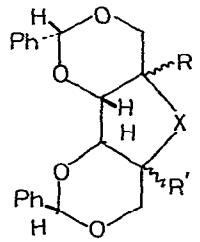
Stereoisomeric structures are possible for **2**, **4**, and **5**, involving *cis,cis*-, *cis,trans*-, and *trans,trans*-fusions of the rings. For **2**, only one *cis,trans* isomer is possible, but for **4** and **5**, there are two possible *cis,trans* isomers.

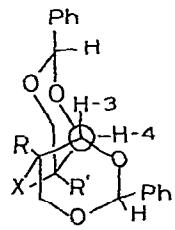
Consideration of the structures of 1,3:4,6-di-*O*-benzylidene-2-hexuloses, in which the stereometry at one of the ring fusions in the cyclic hemiacetal form is determined by the configuration, gives information about the relative stabilities of

cis- and *trans*-fusions in this particular heterocyclic system. The i r. absorption at 1740 cm^{-1} shows that 1,3:4,6-di-*O*-benzylidene-D-fructose (**3**) exists as the free ketone; an internal hemiacetal would have a *trans*-fusion of five- and six-membered rings. The occurrence[11] of the internal hemiacetal, with two *cis*-fusions between five- and six-membered rings, in 1,3:4,6-di-*O*-benzylidene-β-L-sorbofuranose (**7**) indicates that the *cis*-fusion between five- and six-membered rings is more stable than the *trans*-fusion in these oxygen heterocycles. The *cis*-fusion is more stable in other heterocycles[12].

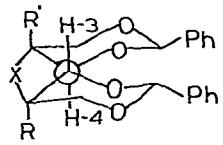
The relatively simple p.m.r. spectrum for the hydrate **2** suggests a symmetrical structure and, because of the expected greater stability of the *cis*-fusion, the (2*S*,5*S*)-2,5-anhydro-1,3:4,6-di-*O*-benzylidene-2,5-di-*C*-hydroxy-D-*threo*-hexitol structure can be assigned. Replacement of the hydroxyl group in **7** by a methoxyl group, to give methyl 1,3:4,6-di-*O*-benzylidene-β-L-sorbofuranoside (**8**), caused only a small change in optical rotation[11], and therefore, because of the similarity in optical rotation of **2**, **4**, and **5**, the *cis,cis*-structure may be assigned to each compound.

Inspection of molecular models reveals that the torsion angle between H-3 and H-4 is close to 90° in a *cis,cis*-fused structure and close to 180° in a *trans,trans*-fused structure, so that a significant difference in the coupling constant between these protons would be expected[13]. Because of the symmetry of the hydrate **2**, H-3 and H-4 are stereochemically equivalent and therefore isochronous, so that no coupling is observed; in the methanolate **4** and its acetate **5**, separate singlet peaks were observed for H-3 and H-4. The absence of coupling indicates[14] that the torsion angle is close to 90° and confirms that the compounds have *cis,cis*-fusion of the rings.





a *cis,cis*-fusion



b *trans,trans*-fusion

2 R = R′ = OH, X = O

4 R = OH, R′ = OMe, X = O

5 R = OAc, R′ = OMe X = O

7 R = OH, R′ = H X = O (ref.11)

8 R = OMe, R′ = H X = O (ref 11)

11 R = R′ = OH, X = N–NH_2 or 

13 R = R′ = OH, X = NNHPh

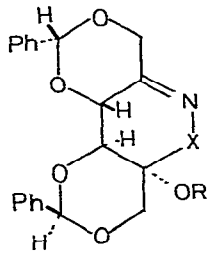
14 R = R′ = OH, X = 

19 R = R′ = OH, X = NPh

24 R = OH, R′ = dithianyl, X = O

There are three 1,3:4,6-di-*O*-benzylidenehexitols, having D-*manno*, D-*gluco*, or L-*ido* configurations, which may be obtained from reduction of the symmetrical diketone **6**. Only the D-*manno* isomer is known[4].

Reduction of **6** with lithium aluminium hydride, or of the hydrate **2** with

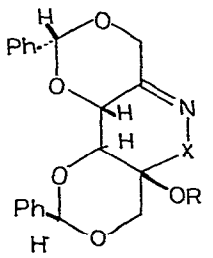


a *cis*-fusion

10 R = H, X = NH

16 R = H, X = O

18 R = Ac, X = O



b *trans*-fusion

12 R = H, X = NH

15 R = H, X = O

17 R = Ac, X = O

sodium borohydride, gave the same product, which was unsymmetrical and must therefore be 1,3:4,6-di-*O*-benzylidene-D-glucitol (**9**). Thus, the two initially identical carbonyl groups have been reduced with opposite selectivity. However, this identity is lost when one carbonyl group is reduced and it is therefore not surprising that the second is reduced with opposite selectivity to the first. For 1,4-diketones, it has been suggested[15] that the second carbonyl group is reduced intramolecularly by the alkoxy-metal hydride formed in the intermolecular reduction of the first carbonyl group, thus accounting for the opposite stereoselectivity observed.

The reaction of a diketone with hydrazine could give a mono- or bis-hydrazine adduct. A cyclic monohydrazine adduct of the diketone **6** may have five- or six-membered rings, but if elimination of one or two molecules of water occurs, the structure must contain a six-membered ring.

The reaction of the hydrate **2** with hydrazine hydrate gave three products, one of which (**10**) was shown by elemental analysis to be a hydrated azine. The p.m.r. spectrum of **10** showed two singlets attributed to H-3 and H-4, indicating a torsion angle close to 90° and therefore a *cis*-fusion of the ring. The major product **11** was apparently symmetrical, because of its simple p.m.r. spectrum when freshly dissolved, and the presence of OH and NH groups was suggested by the i.r. spectrum. However, the elemental analysis was intermediate between those for a di- and a mono-hydrate. The spectroscopic data for **11** do not indicate whether the rings are *cis*- or *trans*-fused, nor whether the two carbonyl groups are bridged through a single nitrogen atom or through two nitrogen atoms. When a cooled solution of **11** was stored for 7 days, a third crystalline substance (**12**) was obtained. Satisfactory elemental analysis figures could not be obtained for **12**, but the i.r. and p.m.r. spectra suggested it to be a mono-hydrate of the azine. The $J_{3,4}$ value of ~9 Hz in the p.m.r. spectrum of **12** indicated an *anti*-disposition of H-3 and H-4, and therefore a *trans*-fused ring system can be tentatively assigned to this compound.

The major product obtained on treatment of **11** with sodium borohydride still contained one C=N group, was unaffected by sodium borohydride, and had a $J_{3,4}$ value of ~9 Hz, indicating that the rings were *trans*-fused.

The reaction of the hydrate **2** with phenylhydrazine gave two isomeric adducts resulting from replacement of the water of hydration by one phenylhydrazine molecule without further elimination of water. It is possible for a phenylhydrazine molecule to bridge the two carbonyl groups through one nitrogen atom (**13**) or through two nitrogen atoms (**14**); in each case, *cis*- or *trans*-fusion of the rings must be considered, so that there may be three isomers of **13** (assuming, as is likely[16], that nitrogen inversion and bond rotation are both rapid) and four isomers of **14**.

In the five-membered ring structures **13**, assuming that bond rotation and nitrogen inversion are rapid on the n.m.r. time-scale, both *cis,cis*- and *trans,trans*-structures are symmetrical and should therefore show relatively simple p.m.r. spectra; the observation of complex spectra excludes these structures. The *cis,trans*-fused structure **13** is also unlikely, because of the relative instability of a *trans*-fusion of five- and six-membered heterocycles.

Inspection of molecular models shows that, of the structures (**14**) containing three six-membered rings, only the *cis,cis*- and *trans,trans*-structures allow all three rings to adopt chair conformations and hence are the most likely[17] for the two products obtained. In the all-chair *trans,trans*-structure **14b**, the torsion angle between H-3 and H-4 is 180°, whereas it is 60° for the all-chair *cis,cis*-structure **14a**. Furthermore, a conformation with a 90° torsion angle between H-3 and H-4 can readily be obtained for **14a** (but not for **14b**) by partial flattening of the chair rings.

The p.m.r. spectrum of the less-soluble phenylhydrazine adduct showed two singlets attributed to H-3 and H-4, and therefore this compound can be assigned the *cis,cis*-structure **14a**; the more-soluble isomer is tentatively assigned the *trans,trans*-structure **14b**. The i.r. spectrum of each compound in dilute solution in carbon tetrachloride contained peaks attributed to intramolecularly bonded OH groups, but the information does not allow structural assignments to be made[18]. Attempts to make acetate derivatives were unsuccessful.

The reaction of hydroxylamine with the hydrate **2** gave two mono-oximes (A and B) which had no i.r. absorption for carbonyl, indicating that cyclisation analogous to hemiacetal formation had taken place between the oxime OH and the remaining C–O group. Each product gave an acetate.

Two structures are possible for these oximes, which differ in the configuration of the fusion of the "hemiacetal" ring to the 1,3-dioxane ring; the *trans* isomer **15** has a torsion angle of ~180° between H-3 and H-4, whereas in *cis* isomer **16**, a torsion angle of 90° is possible when the rings are somewhat flattened to accommodate the C=N double bond. The p m.r. spectra of oxime A (crystallised from ethyl acetate) and its acetate both showed $J_{3,4}$ to be ~9 Hz, consistent with the *trans*-configuration **15** and **17**. The p.m.r. data for oxime B (crystallised from ethanol) were inconclusive, because of accidental equivalence of peaks, but that for the acetate revealed singlets for H-3 and H-4 consistent with the *cis*-configuration **18** and **16**.

The reaction of aniline with either the hydrate **2** or the free diketone **6** gave the same monoaniline derivative, which had no i.r. absorption for carbonyl and a simple p.m.r. spectrum, suggesting a symmetrical, bridged structure **19**, which is a nitrogen

analogue of that for the hydrate **2**. By analogy with **2**, **19** can be assigned the *cis,cis*-structure **19a**. Acetylation of **19** caused decomposition and yielded acetanilide.

Thus, in reactions of the diketone **6** or its hydrate **2** with reagents of the type NH_2–XH, the initial adduct cyclises by interaction of XH with the second carbonyl group, thereby preventing further reaction with NH_2–XH. If a reagent of the type NH_2R is used, cyclisation involving a five-membered ring occurs. Furthermore, the acetyl derivatives contained the group O–C–OAc, and compounds of the type =N–C–OAc were not obtained, presumably because the =N–C–OH group would be attacked preferentially at nitrogen, leading to decomposition.

The reactions of carbonyl compounds with Grignard reagents or organolithium reagents can proceed with opposite[19,20] stereoselectivities. The reaction of each type of reagent with the diketone **6** was investigated. The reactions of methylmagnesium iodide with the hydrate **2** gave two products arising by the addition of one methyl and two methyl groups, respectively. The chemical shifts of the p.m.r. signals for methyl groups in these compounds were similar (τ 8.49 and 8.42) and consequently they can be assigned the same configuration at the tertiary-alcohol centres. The mono-*C*-methyl adduct had i.r. absorptions for hydroxyl and carbonyl groups, indicating that internal hemiacetal formation had not occurred, and it can therefore be assigned the structure 1,3:4,6-di-*O*-benzylidene-5-*C*-methyl-D-fructose (**20**). It follows that the di-*C*-methyl adduct is 1,3:4,6-di-*O*-benzylidene-2,5-di-*C*-methyl-D-mannitol (**21**).

The reaction of methylmagnesium iodide with the methanolate **4** gave **21** in low yield, whereas the ketone **6** gave **21** in 46% yield together with 3% of another bis-adduct. The unsymmetrical nature of the latter compound was indicated by the two p.m.r. signals (τ 8.48 and 8.83) for *C*-methyl groups and therefore it must have the (2*R*,5*S*)- or D-*gluco*-configuration **22**. Axial Me-5 groups in 1,3-dioxane derivatives generally resonate to lower field than equatorial[21] Me-5 groups, so that the p.m.r. signals at τ 8.48 and 8.83 for **22** are due to axial and equatorial methyl groups, respectively. The p.m.r. signals at τ 8.42 for **20** and at τ 8.49 for **21** can be assigned to axial methyl groups.

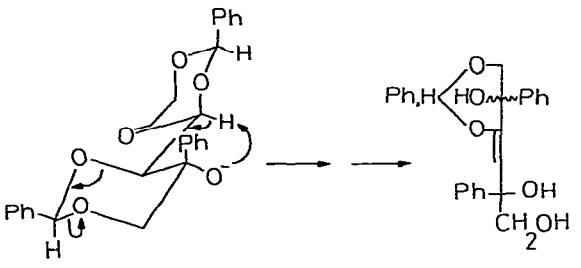
The hydrate **2** and the methanolate **4** were not significantly affected by methyllithium, but the diketone **6** gave a complex mixture (t.l.c.).

In the subsequent reactions, the diketone **6** was used rather than the hydrate **2** or the methanolate **4**, in view of the higher yields obtained in reactions with methylmagnesium iodide.

The reaction of **6** with phenylmagnesium bromide gave 15% of a product tentatively identified as a 1,3-*O*-benzylidene-4-deoxy-2,5-di-*C*-phenylhex-3-enitol (**23**); the configuration at C-2 and C-5 was not assigned. Such a product could arise by β-elimination prior to addition to the second carbonyl group. Attempted acetylation of **23** gave a product for which satisfactory analytical figures could not be obtained, but which appeared to be a di-acetate; it had two p.m.r. signals for OAc groups and i.r. absorption for hydroxyl.

The reactions of **6** with benzylmagnesium chloride and ethylmagnesium bromide gave complex mixtures (t.l.c.).

Consideration of the structure of the intermediate product suggests a possible reason for the difference in reactivity with various Grignard reagents. Assuming that the Grignard reagent adds into the axial position in all cases, addition of the alkoxide group to the carbonyl group is precluded, because this would involve a *trans*-fusion of five- and six-membered rings. In the conformation of the intermediate which has a planar, zigzag carbon-chain, the alkoxide group is ideally arranged for abstraction of a proton and antiperiplanar elimination, as shown in Scheme 1. The other possible fate of the intermediate is to undergo addition of a second equivalent of Grignard reagent. Apparently, attack of the second molecule of Grignard reagent is the major route for the relatively small, methyl Grignard reagent, whereas elimination occurs with the more bulky, phenyl Grignard reagent



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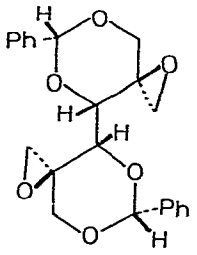
Scheme 1

The reaction of **6** with 2-lithio-1,3-dithiane produced a complex mixture of products from which 1,3-dithiane (61%) was recovered, suggesting that the reagent reacted as a base, rather than as a nucleophile, and abstracted protons. Extensive chromatography of the remainder gave a chromatographically homogeneous syrup which appeared to be 1,3:4,6-di-*O*-benzylidene-5-*C*-(1,3-dithian-2-yl)-β-L-sorbofuranose (**24**). It had i r. absorption for hydroxyl, but not for carbonyl, and the n.m.r. spectrum indicated two different benzylidene groups, one dithiane residue, and one hydroxyl group. The peaks attributed to H-3 and H-4 were singlets, suggesting a torsion angle close to 90° and a *cis,cis*-fusion of rings. Structure **24** could arise by addition of the dithianyl group to the less hindered, equatorial position followed by cyclisation of the alkoxide group onto the carbonyl group. Previous results[22] indicate addition into the less hindered position.

The reactions of **6** with diazoalkanes were also explored. Diazoalkanes generally react with ketones to give mixtures of epoxides and homologous carbonyl compounds; epoxides preponderate if electron-withdrawing groups are present α to the carbonyl group[23]. Carbohydrate ketones have given epoxides[24] and also ring-expansion products[25].

The reaction of **6** with diazomethane gave mainly a bis-epoxide, which was reduced by lithium aluminium hydride to the same compound as obtained by the addition of methylmagnesium iodide to **6**. Thus, the bis-epoxide was 2,2^1:5,5^1-dianhydro-1,3:4,6-di-*O*-benzylidene-2,5-di-*C*-hydroxymethyl-D-mannitol (**25**). Two

minor products were also obtained from the reaction: one was a mono-epoxide resulting from addition of one diazomethane molecule, and the second had the elemental analysis for a bis-epoxide, showing that addition of two methylene groups had occurred, and i.r. absorption for carbonyl, suggesting ring expansion. The structure (**26**) for this product was deduced from its p.m.r. spectrum; the peaks assigned to the methylene group gave an ABX pattern, showing that the methylene group was adjacent to one other hydrogen and was therefore not adjacent to either terminal position. In both the bis-epoxide and the product of methylene insertion, a long-range coupling, with J 2 Hz, was observed between the lower-field epoxide peaks and the lower-field terminal protons. This observation was taken to indicate similarity of constitution of the epoxide rings in the two compounds and therefore that methylene insertion had taken place in the ring without the epoxide group.



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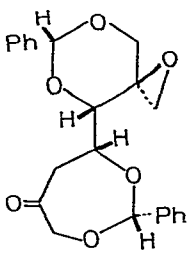

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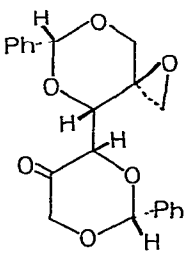

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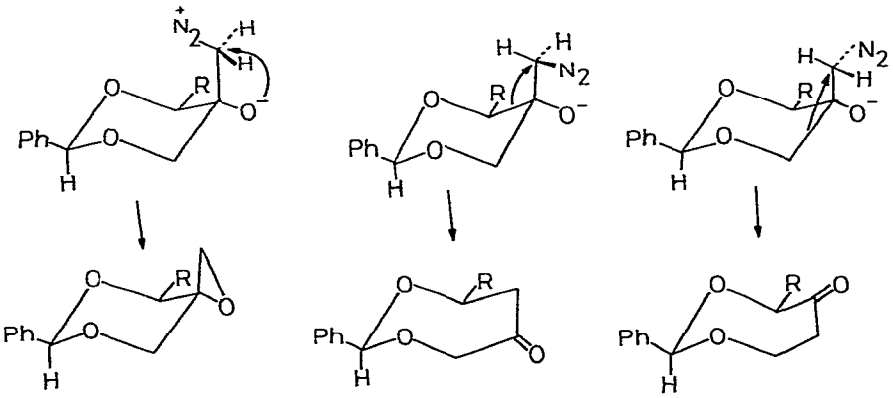
The formation of these products is consistent with the previously proposed mechanism[26]. Following axial addition of diazomethane to the carbonyl group, three staggered conformations are possible (Scheme 2). In one, the N_2^+ group is favourably placed, both sterically and electrostatically, above the ring-oxygen atoms, and antiperiplanar-elimination of nitrogen would give the epoxide. The remaining rotamers may be designated *exo* and *endo*, with the N_2^+ group directed either away from or towards the rest of the molecule. The *exo* rotamer should be the more



Scheme 2

favoured, and loss of nitrogen with participation by the electrons in the antiperiplanar bond would give insertion of the methylene group into the internal bond.

Some support for the notion that the configuration of the monoepoxide (**27**) is the same as in the other two products comes from the observation of similar, long-range coupling in their p.m.r. spectra.

The reaction of the hydrate **2** with diazomethane gave the same three products as were obtained from **6**, which was also recovered unchanged after six days in contact with diazo(diphenyl)methane[27].

Epoxides with either axial or equatorial methylene groups can be obtained by reaction of cyclic carbohydrate ketones with dimethylsulphoxonium methylide[28], whereas non-carbohydrate ketones give products having equatorial methylene groups. The reaction of **6** with dimethylsulphoxonium methylide did not give a bis-epoxide, and the only product had the formula $C_{21}H_{20}O_6$ and must have resulted from the addition of one methylene group to the substrate $C_{20}H_{18}O_6$. However, it had i.r. absorption for hydroxyl (3420 cm^{-1}), but not for carbonyl, and is therefore not a simple mono-epoxide or homologous ketone.

The foregoing data indicate that the two equivalent carbonyl groups in 1,3:4,6-di-*O*-benzylidene-D-*threo*-2,5-hexodiulose do not generally undergo identical reactions with nucleophilic reagents. Whereas symmetrical bis-adducts were obtained from reactions with methylmagnesium iodide and with diazomethane, the reactions with hydride, oxygen, nitrogen, and other carbon nucleophiles did not give symmetrical bis-adducts This behaviour can be interpreted as an intermolecular reaction of either of the identical carbonyl groups with the nucleophilic reagent, followed by intramolecular reactions leading to cyclisation or elimination.

EXPERIMENTAL

General methods. — Concentrations were effected *in vacuo* below 40°. Melting points are uncorrected. T.l.c. was performed on Silica Gel (Merck, 7731) with detection by iodine vapour or vanillin–sulphuric acid. Column chromatography was conducted on Silica Gel (Merck, 7734). I.r. spectra were recorded for liquid films or Nujol mulls with a Pye Unicam SP 200G instrument, and for dilute solutions with a Perkin–Elmer 125 instrument. Optical rotations were determined with a Perkin–Elmer 141 automatic polarimeter (1-dm tube) at 21°. N.m.r. spectra (internal Me_4Si) were recorded at 100 MHz with a Perkin–Elmer R14 spectrometer. Chemical shifts are given in p.p.m., and the couplings given are first-order spacings.

Oxidation of 1,3:4,6-di-O-benzylidene-D-mannitol (**1**) *with ruthenium tetraoxide* — (*A*) To a stirred solution of **1** (1 g) in alcohol-free acetone (30 ml) and water (20 ml) were added potassium carbonate (93 mg), potassium periodate (1.68 g), and ruthenium dioxide (20 mg). After 20 h, t.l.c revealed that all of **1** had reacted, giving two products. Propan-2-ol (10 ml) was added, and, after 30 min, the mixture was filtered, the acetone was evaporated, and the product (0.73 g) was isolated by extraction with chloroform (100 ml). Elution from silica gel (50 g) with tetrachloromethane–

ethyl acetate (1:1) gave, first, 1,3:4,6-di-*O*-benzylidene-D-*threo*-2,5-hexodiulose hydrate (**2**), m.p. 144–145°, $[\alpha]_D$ +58.5° (*c* 1.04, 1:1 chloroform–methanol), ν_{max}^{Nujol} 3320 cm^{-1} (OH). P.m.r. data ($CDCl_3$): τ 2 6 (m, 10 H, 2 Ph), 4.43 (s, 2 H, 2 PhC*H*), 5.57 (s, 2 H, H-3,4), 5.64 and 5.98 (ABq, 4 H, J_{gem} 12 Hz, H-1,1',6,6'), and 6.04 (s, 2 H, OH) (Found: C, 64.7: H, 5.4. $C_{20}H_{20}O_7$ calc.: C, 64.5; H, 5.4%).

Eluted second was 1,3:4,6-di-*O*-benzylidene-D-fructose (180 mg), m p. 171–172°, $[\alpha]_D$ −62° (*c* 0.75, chloroform), ν_{max}^{Nujol} 3480 (OH) and 1740 cm^{-1} (C=O). P.m.r. data [$(CD_3)_2CO$]: τ 2.6 (m. 10 H, 2 Ph), 3.78 and 4.40 (2 s, 2 H, 2 PhC*H*), 4.91 (s, 1 H, H-3), 5.36 and 5.58 (ABq. 2 H. J_{gem} 16 Hz, H-1,1'), and 5.65–6.40 (m, 4 H, H-4,5,6,6') (Found: C, 67.1: H, 5.8. $C_{20}H_{20}O_6$ calc.: C, 67.4; H, 5.7%).

(*B*) A solution of **1** (2 g) in ethyl acetate (30 ml) was stirred, and water (30 ml) followed by anhydrous potassium carbonate (186 mg), potassium periodate (3.36 g), and ruthenium dioxide (40 mg) were added. The reaction was monitored by t.l.c., which showed that the same two spots as in (*A*) were present after 24 h. Potassium periodate (3.36 g) and potassium carbonate (186 mg) were added and, after a further 24 h, the oxidation was complete (t.l.c.). Propan-2-ol (10 ml) was added and, after stirring for 30 min, the mixture was filtered, and the ethyl acetate layer was washed with water (20 ml), dried ($MgSO_4$), and concentrated. The residue was crystallised from ethanol, to give **2** (1.46 g, 70%), m.p. 144–145°.

(*C*) When oxidations were attempted with 1,2-dichloroethane as solvent, or ethyl acetate as solvent and sodium hypochlorite as oxidant, a mixture of products was obtained (t.l.c.).

Oxidation of **1** *with dimethyl sulphoxide and acetic anhydride.* — A solution of **1** (5 g) in dimethyl sulphoxide (80 ml) and acetic anhydride (40 ml) was stored at room temperature overnight and then concentrated to dryness. Benzene was twice evaporated from the residue, which was then eluted from silica gel (200 g) with tetrachloromethane–ethyl acetate (4:1), to give three homogeneous fractions (in addition to mixtures): (*1*) a syrup (272 mg); p m r. data ($CDCl_3$): τ 2 55 (m, 10 H, 2 Ph), 4.46 (s, 2 H, 2 PhC*H*), 5.28 (s, 4 H. 2 OCH_2S), 7.85 (s, 6 H, 2 SMe), and 5.36–6.40 (m, 8 H, hexitol chain); (*2*) **2** (375 mg); (*3*) 1,3:4,6-di-*O*-benzylidene-5-*O*-(methylthiomethyl)-D-fructose (0.93 g), m.p. 132–133°, $[\alpha]_D$ −63° (*c* 1.06, chloroform), ν_{max}^{Nujol} 1740 cm^{-1} (C=O). P.m.r. data ($CDCl_3$): τ 2.6 (m, 10 H, 2 Ph), 4.02 and 4.50 (2 s, 2 H, 1,3- and 4,6-*O*-benzylidene methines, respectively), 5.31 (s, 2 H, OCH_2S), 7.89 (s, 3 H, SMe), and 5.12–6.40 (m, 7 H, skeleton protons) (Found: C, 63.6; H, 5.5; S, 7.9. $C_{22}H_{24}O_6S$ calc.: C, 63.45; H, 5.8; S, 7.7%).

*1,3:4,6-Di-*O*-benzylidene-*D-threo-*2,5-hexodiulose.* — A solution of **2** (1 g) in dry benzene (100 ml) was heated under reflux and the condensed solvent was percolated through molecular sieve type 5A in a Soxhlet thimble. Aliquots of the solution were withdrawn at intervals and examined by n.m.r. spectroscopy. After 3 days, when the signals for the hydrate had been replaced by signals for a new component, the solution was cooled, dry light petroleum (b.p. 60–80°) was added, and the title compound was collected; m.p. 195–196°, $[\alpha]_D$ −93° (*c* 1.7, chloroform), ν_{max}^{Nujol} 1730 cm^{-1} (C=O). P.m.r. data ($CDCl_3$): τ 2.60 (m, 10 H, 2 Ph), 4.05 (s, 2 H, 2

PhC*H*), 4.87 (s, 2 H, H-3,4), 5.38 and 5.47 (ABq, 4 H, J_{gem} 17 Hz, 2 CH_2) (Found: C, 68.0; H, 5.2. $C_{20}H_{18}O_6$ calc.: C, 67.8; H, 5.1%).

(*2S,5S*)-*2,5-Anhydro-1,3:4,6-di*-O-*benzylidene-2*-C-*hydroxy-5*-C-*methoxy*-D-threo-*hexitol* (**4**). — Two recrystallisations of **2** or **6** from dry methanol gave **4** (80%), m.p. 173–174°, $[\alpha]_D$ +71° (*c* 1.1, chloroform), ν_{max}^{Nujol} 3500 cm^{-1} (OH). P.m.r. data ($CDCl_3$ or C_6D_6): τ 2.50 or 2.75 (m, 10 H, 2 Ph); 4.38, 4.40 or 4.72, 4.85 (2 s, 2 H, 2 PhC*H*); 6.15 or 6.10 (s, 1 H, OH); 6.50 or 6.70 (s, 3 H, OMe), 5.47, 5 57 or 5.61, 5.74 (2 s, 2 H, $J_{3,4}$ 0 Hz, H-3,4); 5.39 and 5.94, 5 60 and 5.94, or 5.54 and 6.07, 5.60 and 6.36 (2 ABq, 4 H, J_{gem} 12 Hz, 2 CH_2) (Found: C, 65.8; H, 5.6. $C_{21}H_{22}O_7$ calc.: C, 65.3; H, 5.7%).

(*2R,5S*)-*2*-C-*Acetoxy-2,5-anhydro-1,3:4,6-di*-O-*benzylidene-5*-C-*methoxy*-D-threo-*hexitol*. — A solution of **4** (0.5 g) in acetic anhydride (8 ml) and pyridine (10 ml) was stored at 0° for 18 h and then poured into ice–water (50 ml) The product was collected, and recrystallised from ethanol to give the title compound (0.41 g, 74%), m.p. 108–109°, $[\alpha]_D$ +34° (*c* 1, chloroform), ν_{max}^{Nujol} 1745 cm^{-1} (C=O). P.m r. data ($CDCl_3$): τ 2.6 (m, 10 H, 2 Ph), 4.36, 4.45 (2 s, 2 H, 2 PhC*H*), 5.18 and 5.63, 5.56 and 6.01 (2 ABq, 4 H, J_{gem} 12 Hz, 2 CH_2), 5.58, 5.20 (2 s, 2 H, H-3,4), 6.51 (s, 3 H, OMe), and 8.10 (s, 3 H, Ac) (Found: C, 64.8; H, 5 8. $C_{23}H_{24}O_8$ calc : C, 64.5; H, 5.65%).

Reactions of 1,3:4,6-di-O-*benzylidene*-D-threo-*2,5-hexodiulose hydrate* (**2**). — (*A*) *With phenylhydrazine*. A solution of **2** (5 g) in ethanol (150 ml) containing phenylhydrazine (3 g) was stirred for 30 min and then cooled to 0° for 30 min. The resulting solid (5.1 g, 85%) was collected, and then fractionally crystallised from ethanol. The less soluble derivative **14a** had m.p. 157–158°, $[\alpha]_D$ +122° (*c* 1, chloroform), $\nu_{max}^{CCl_4}$ (*c* 0.01M) 3552 (OH) and 3339 cm^{-1} (NH_2). P.m.r. data (C_6D_6). τ 2.8 (m, 15 H, 3 Ph), 4.86 and 4.93 (2 s, 2 H, 2 PhC*H*), 5.30 and 6.06 (ABq, 2 H, J_{gem} 13 Hz, H-1,1′), 5.56 and 6.14 (ABq, 2 H, J_{gem} 12 Hz, H-6,6′), 5.74 and 5.82 (2 s, 2 H, H-3,4), 5.91 (s, 1 H, NH), and 4.50 and 4.78 (2 s, 2 H, 2 OH); shaking the solution with D_2O removed the peaks at τ 4.50 and 4.78, and diminished the peak at τ 5.91. P.m.r. data ($CDCl_3$): *inter alia*, τ 5.54 and 6.09 (2 s, 2 H, H-3,4) (Found· C, 67.8; H, 5.8; N, 6.0. $C_{26}H_{26}N_2O_6$ calc.: C, 67.5; H, 5.7; N, 6.1%).

The more soluble derivative **14b** had m.p. 165–166°, $[\alpha]_D$ +115° (*c* 1, chloroform), $\nu_{max}^{CCl_4}$ (*c* 0.01M) 3564, 3572 (sh), and 3517 (OH), 3351 cm^{-1} (NH). P.m.r. data (C_6D_6): τ 2.7 (m, 15 H, 3 Ph), 4.50 and 4.90 (2 s, 2 H, 2 PhC*H*), 5.82 (s, 2 H, H-3,4). 5.38 and 6.30 (ABq, 2 H, J_{gem} 12 Hz, H-1,1′), 5.94 and 6.36 (ABq, 2 H, J_{gem} 12 Hz, H-6,6′), 4.15 (s, 1 H, NH), and 6.40 and 6.61 (2 s, 2 H, 2 OH); shaking the solution with D_2O removed the peaks at τ 6.40 and 6 61, and diminished the peak at τ 4.15 (Found: C, 67.2; H, 5.6; N, 6 4. $C_{26}H_{26}N_2O_6$ calc.: C, 67.5; H, 5.7; N, 6.1%).

(*B*) *With hydroxylamine*. A solution of **2** (2 g) in a solution of hydroxylamine hydrochloride (1 g) and sodium hydroxide (0.5 g) in ethanol (80 ml) and water (10 ml) was stirred at room temperature for 1 5 h and then poured into ice–water (300 ml). The resulting solid (1.7 g, 86%) was collected, and eluted from silica gel (100 g) with tetrachloromethane–ethyl acetate (2:1). Fractions containing material

with R_F 0.75 were combined and concentrated to a syrup which was shown to be a mixture by p.m.r. spectroscopy in acetone-d_6. The syrup was crystallised from ethanol to give oxime **16**, m.p. 222–223°. P.m.r. data [$(CD_3)_2CO$]: τ 2.56 (m, 10 H, 2 Ph), 3.94 and 4.20 (2 s, 2 H, 2 PhC*H*), 5.67 (s, 2 H, H-3,4), 5.13 and 5.40 (ABq, 2 H, J_{gem} 14 Hz, H-1,1'), and 5.68 and 5.96 (ABq, 2 H, J_{gem} 14 Hz, H-6,6'). After 24 h in solution, a spectrum similar to that of the original, syrupy mixture was obtained.

Crystallisation of the syrup from ethyl acetate gave oxime **15**, m.p. 117–120°. P.m.r. data [$(CD_3)_2CO$]: τ 2.56 (m, 10 H, 2 Ph), 3.98 and 4.10 (2 s, 2 H, 2 PhC*H*), 5.87 (s, 2 H, H-1,1'), 4.99 and 5.56 (ABq, 2 H, $J_{3,4}$ 9.0 Hz, H-3,4), and 5.18 and 5.43 (ABq, 2 H, J_{gem} 14 Hz, H-6,6'). A solution of a mixture of **15** and **16** (1 g) in pyridine (20 ml) and acetic anhydride (16 ml) was made up at 0°, stored at 5° overnight and then at room temperature for 3 h, and poured into ice–water (200 ml). The resulting solid was collected, and eluted from silica gel (100 g) with carbon tetrachloride–ethyl acetate (1:1) to give, first, the acetate **18** (320 mg), m.p. 159–160°, $[\alpha]_D$ −151° (*c* 1, chloroform), R_F 0.88 (tetrachloromethane–ethyl acetate, 2:1), ν_{max} 1758 cm^{-1} (C=O). P.m.r. data ($CDCl_3$): τ 2.57 (m, 10 H, 2 Ph), 4.21 and 4.30 (2 s, 2 H, 2 PhC*H*), 5.30 (s, 2 H, H-1,1'), 5.35 and 5.80 (2 s, 2 H, H-3,4), 5.11 and 5.57 (ABq, 2 H, J_{gem} 13 Hz, H-6,6'), and 7.99 (s, 3 H, Ac) (Found: C, 64.0; H, 5.3; N, 3.1. $C_{22}H_{21}NO_7$ calc.: C, 64.2; H, 5.15; N, 3.4%).

Eluted second was the acetate **17** (37 mg), m.p. 233–234°, $[\alpha]_D$ −198.5° (*c* 0.75, chloroform), R_F 0.80 (tetrachloromethane–ethyl acetate, 2:1), ν_{max} 1755 cm^{-1} (C=O). P.m.r. data ($CDCl_3$): τ 2.56 (m, 10 H, 2 Ph), 4.18 and 4.24 (2 s, 2 H, 2 PhC*H*), 5.24 and 5.41 (ABq, 2 H, J_{gem} 13 Hz, H-1,1'), 5.06 and 5.63 (ABq, 2 H, $J_{3,4}$ 9 Hz, H-3,4), 4.68 and 6.00 (ABq, 2 H, J_{gem} 13 Hz, H-6,6'), and 7.84 (s, 3 H, Ac) (Found: C, 64.0; H, 5.0. $C_{22}H_{21}NO_7$ calc.: C, 64.2; H, 5.15%).

The oxime **16** was acetylated as described above, and the reaction was monitored by t.l.c. The major product was the faster-moving acetate **18**, R_F 0.88 (tetrachloromethane–ethyl acetate, 2:1).

(*C*) *With aniline.* A mixture of **2** (1 g), benzene (30 ml), and aniline (0.6 g) was heated under reflux for 24 h, and then cooled and concentrated. The syrupy residue was crystallised from benzene–light petroleum to give the mono-aniline adduct **19a** (240 mg), m.p. 165–166°, $[\alpha]_D$ +103.5° (*c* 1, chloroform), R_F 0.88 (benzene–ether, 9:1), ν_{max}^{Nujol} 3530 cm^{-1} (OH). P.m.r. data ($CDCl_3$): τ 2.53 (m, 15 H, 3 Ph), 4.33 (s, 2 H, 2 PhC*H*), 5.51 (s, 2 H, H-3,4), 5.56 and 6.03 (ABq, 4 H, J_{gem} 13 Hz, 2 CH_2), and 6.31 (s, 2 H, 2 OH).

A similar reaction of the anhydrous diketone **6** (1 g) with aniline (0.6 g) also gave **19a** (430 mg, 34%), m.p. 165–166°.

(*D*) *With hydrazine.* A mixture of **2** (1.75 g), ethanol (10 ml), and hydrazine hydrate (0.25 g) was stirred for 1 h at room temperature. The white solid was collected, and recrystallised from ethanol to give a mixture (1.5 g, 86%), m.p. 125–127°, which was extracted with chloroform (20 ml). Insoluble material was filtered off, to give the azine **10** (66 mg), m.p 146–147°, $\nu_{max}^{CCl_4}$ (*c* mM) 3610, 3575, 3422 (OH), 3390, and 3303 cm^{-1} (NH). P.m.r. data [$(CD_3)_2SO$]: τ 2.6 (m, 10 H, 2 Ph), 4.08 and 4.39

(2 s, 2 H, 2 PhC*H*), 4.69 and 5.90 (2 s, 2 H, H-3,4), 5.85 (s, 1 H, NH), 5.32 and 5.69 (ABq, 2 H, J_{gem} 14 Hz, H-1,1'), and 5.98 and 6.28 (ABq, 2 H, J_{gem} 13 Hz, H-6,6') (Found: C, 64.9; H, 5.2; N, 7.4. $C_{20}H_{20}N_2O_5$ calc.: C, 65.2; H, 5.5; N, 7.6%).

Light petroleum (50 ml) was added to the chloroform extract, to give the azine **11**, m.p. 116–117°, ν_{max}^{Nujol} 3410 (OH) and 3350 cm^{-1} (NH) P.m.r. data [$(CD_3)_2$-SO]: τ 2.6 (m, 10 H, 2 Ph), 4.48 (s, 2 H, 2 PhC*H*), 5.01 (s, 2 H, 2 OH), 5.24 (s, 1 H, NH), 6.08 (s, 2 H, H-3,4), and 6.26 (s, 4 H, 2 CH_2) (Found: C, 63.9; H, 5.9; N, 7.2. $C_{20}H_{22}N_2O_6$ calc.: C, 62.2; H, 5.7; N, 7.25%).

A solution of **11** in chloroform was maintained at −5° for 7 days, crystals formed. Light petroleum (30 ml) was added, and, after 1 day, the crystals were collected, to give the azine **12**, $\nu_{max}^{CCl_4}$ (*c* mM) 3618, 3566 (sh) (OH), and 3385 cm^{-1} (NH). P.m.r. data [$(CD_3)_2SO$]: τ 2.6 (s, 10 H, 2 Ph), 4.11, 4.23 (2 s, 2 H, 2 PhC*H*), 4.32 (s, 1 H, NH), 5.23 and 5.75 (ABq, 2 H, $J_{3,4}$ 9 Hz, H-3,4), 5.37 and 5.67 (ABq, 2 H, J_{gem} 12 Hz, H-6,6'), and 6.09 (s, 2 H, H-1,1').

Reduction of hydrazine derivative **11** *with sodium borohydride.* — To a solution of **11** (1 g) in ethanol (50 ml) was added sodium borohydride (0.5 g). The mixture was stirred overnight and then concentrated under diminished pressure. The resulting solid was partitioned between saturated, aqueous ammonium chloride (50 ml) and chloroform (50 ml). The chloroform layer was washed with water, dried ($MgSO_4$), and concentrated under diminished pressure to a syrup (770 mg) which contained several components (t.l.c.). The syrup was eluted from silica gel (50 g) with benzene–ether (4:1), to give a product, m.p. 189–190°, ν_{max}^{Nujol} 3260 cm^{-1} (NH). P.m.r. data ($CDCl_3$): τ 2.6 (m, 10 H, 2 Ph), 4.30 (2 s, 2 H, 2 PhC*H*), 5.30 (d, 1 H, $J_{3,4}$ 8 Hz, H-3), 5.52 (s, 2 H, H-1,1'), 5.80 (dd, 1 H, $J_{3,4}$ 8, $J_{4,5}$ 11 Hz, H-4), 5.85 (dd, 1 H, $J_{5,6e}$ 5, J_{gem} 11 Hz, H-6*e*), 6.20 (t, 1 H, $J_{5,6a} = J_{gem} = 11$ Hz, H-6*a*), and 6.78 (dt, 1 H, $J_{5,6e}$ 5, $J_{4,5} = J_{5,6a} = 11$ Hz, H-5) (Found: C, 67.9; H, 5.6; N, 7.6. $C_{20}H_{20}N_2O_4$ calc.: C, 68.2; H, 5.7; N, 7.9%)

*Reactions of 1,3:4,6-di-*O*-benzylidene-*D-threo-*2,5-hexodiulose* (**6**), *its hydrate* **2**, *and its methanolate* **4**. — (*A*) *With methylmagnesium iodide.* (*i*) A solution of **6** (6 g) in dry benzene (150 ml) was added to a solution of Grignard reagent made from magnesium (1.95 g) and iodomethane (11.4 g) in dry ether (100 ml). The mixture was heated under reflux for 1.5 h, and then poured into ice–water (200 ml), filtered, and extracted with ethyl acetate (2 × 100 ml). The extract was dried ($MgSO_4$), and concentrated under diminished pressure, and the syrupy residue was crystallised from chloroform–light petroleum to give (2*R*,5*R*)-1,3:4,6-di-*O*-benzylidene-2,5-di-*C*-methyl-D-*threo*-hexitol (**21**; 1.8 g, 28%), m.p. 117–118°, $[\alpha]_D$ −66° (*c* 1.1, chloroform). P.m.r. data ($CDCl_3$): τ 2.5 (m, 10 H, 2 Ph), 4.48 (s, 2 H, 2 PhC*H*), 6.10 (s, 2 H, H-3,4), 6.68 (s, 2 H, 2 OH), 6.13 and 6.34 (ABq, 4 H, J_{gem} 10 Hz, H-1,1',6,6'), and 8.49 (s, 6 H, 2 Me) (Found: C, 68.3; H, 6.7. $C_{22}H_{26}O_6$ calc : C, 68.4; H, 6.8%).

The mother liquid was concentrated to a syrup (4.1 g) which was eluted from silica gel (150 g) with tetrachloromethane–ethyl acetate (4:1), to give **21** (1.0 g, 15%) and (2*R*,5*S*)-1,3:4,6-di-*O*-benzylidene-2,5-di-*C*-methyl-D-*threo*-hexitol (**22**; 180 mg, 3%), m.p. 150–152°, $[\alpha]_D$ +28° (*c* 1, chloroform). P.m.r. data ($CDCl_3$):

τ 2.65 (m, 10 H, 2 Ph), 4.45 (s, 2 H, 2 PhC*H*), 5.89 and 6.01 (s, 2 H, H-3,4), 6.09 and 6.27 (ABq, 2 H, J_{gem} 12 Hz, H-6,6'), 6.16 and 6.34 (ABq, 2 H, J_{gem} 11 Hz, H-1,1'), 8.48 (s, 3 H, axial Me), 8.83 (s, 3 H, equatorial Me), and 6.32 (s, 2 H, 2 OH) (Found: C, 67.9; H, 6.7. $C_{22}H_{26}O_6$ calc.: C, 68.4; H, 6.8%).

(*ii*) A solution of the hydrate **2** (4 g) in dry tetrahydrofuran (100 ml) was added to a solution of Grignard reagent made from magnesium (1.1 g) and iodomethane (6.5 g) in dry ether (200 ml). The mixture was stirred overnight at room temperature, and then heated under reflux for 30 min. poured into ice–water (200 ml), filtered, and extracted with ether (2 × 100 ml). The combined extracts were dried ($MgSO_4$), and concentrated under diminished pressure to give a red syrup (2.75 g). Crystallisation from tetrachloromethane gave a solid which was a mixture (t.l.c.; ethyl acetate–tetrachloromethane, 1:1). Fractional recrystallisation from benzene and light petroleum gave the more soluble component 1,3:4,6-di-*O*-benzylidene-5-*C*-methyl-D-*threo*-2-hexulose (**20**), m.p. 124–126°, $[\alpha]_D$ −78° (*c* 1, chloroform), ν_{max}^{Nujol} 1750 (C=O) and 3470 cm^{-1} (OH). P.m.r. data ($CDCl_3$): τ 2.6 (m, 10 H, 2 Ph), 4.01 and 4.52 (2 s, 2 H, 2 PhC*H*), 5.15 and 5.74 (ABq, 2 H, $J_{3,4}$ 3 Hz, H-3,4), 5.51 and 5.66 (ABq, 2 H, J_{gem} 12 Hz, H-1,1'), 6.12 and 6.33 (ABq, 2 H, J_{gem} 12 Hz, H-6,6'), 8.42 (s, 3 H, Me), and 7.8 (bs, 1 H, OH) (Found: C, 67.8; H, 5.7. $C_{21}H_{22}O_6$ calc.: C, 68.1; H, 6.0%).

Other fractions of the product were combined, and eluted from silica gel (200 g) with tetrachloromethane–ethyl acetate (4:1), to give the di-*C*-methyl derivative **21** (271 mg), m.p. 117–118°, $[\alpha]_D$ −66° (*c* 1.1, chloroform).

(*iii*) A solution of the methanolate **4** (1.5 g) in dry tetrahydrofuran (150 ml) was added to the Grignard reagent made from magnesium (0.37 g) and iodomethane (2.21 g) in dry ether (150 ml). The reaction mixture was processed essentially as for that from **2**, to give a syrup (1.29 g, 87%), which, after chromatography, gave **2** (425 mg) and **21** (128 mg), m.p. 117–118°.

(*B*) *With methyl-lithium.* (*i*) A solution of ketone **6** (2.2 g) in dry benzene (100 ml) at 0° was stirred while a solution of methyl-lithium [made from lithium (1 g) and iodomethane (10 g) in dry ether (60 ml)] was added, keeping the temperature below 5°. The mixture was then heated under reflux for 1 h, poured into ice–water (100 ml), filtered, and extracted with ethyl acetate (2 × 100 ml) The dried ($MgSO_4$) extracts were concentrated to a red syrup which was a complex mixture (t.l.c.; tetrachloromethane–ethyl acetate, 1:1). Elution from silica gel (120 g) with this solvent failed to give any pure fractions.

A solution of the hydrate **2** (1.5 g) in dry ether (150 ml) was added to a solution of methyl-lithium [made from lithium (1 g) and iodomethane (10 g) in dry ether (60 ml)]. The mixture was stirred overnight at room temperature, heated under reflux for 2 h, poured into ice–water (100 ml), and extracted with ether. Crystallisation of the product from chloroform–light petroleum gave **2** (1.2 g, 80%).

When the methanolate **4** (1.4 g) was treated with methyl-lithium as for **2**, the only product isolated was **2**.

(*C*) *With phenylmagnesium bromide.* A solution of **6** (5 g) in dry benzene

(200 ml) was added to a solution of Grignard reagent made from magnesium (1.96 g) and bromobenzene (12.6 g) in dry ether (100 ml). The mixture was heated under reflux for 3 h, and then poured into ice–water (100 ml), filtered, and extracted with ethyl acetate (2 × 100 ml). The combined and dried ($MgSO_4$) extracts were concentrated to a syrup, which was eluted from silica gel (170 g) with benzene–ether (9:1) to give, in addition to several unidentified components, 1,3-*O*-benzylidene-4-deoxy-2,5-di-*C*-phenylhex-3-enitol (**23**; 732 mg, 13%), m.p. 169–170°, $[\alpha]_D$ +153° (*c* 1, acetone), ν_{max} 3460, 3360, 3180 (OH), and 1660 cm^{-1} (C=C). P.m.r. data [$(CD_3)_2$-CO]: τ 2.7 (m, 15 H, 3 Ph), 4.20 (s, 1 H, H-4), 4.28 (s, 1 H, PhC*H*), 5.78 and 6.01 (ABq, 2 H, J_{gem} 11 Hz, H-1,1'), and 6.15 and 6.28 (ABq, 2 H, J_{gem} 12 Hz, H-6,6') (Found: C, 74.1; H, 6.1. $C_{25}H_{24}O_5$ calc.: C, 74.2; H, 6.0%).

Treatment of **23** (50 mg) with acetic anhydride (8 ml) and pyridine (10 ml) in the usual way, gave a diacetate (40 mg), m.p. 111–112°, ν_{max} 3550 (OH), 1740 (C=O), and 1650 cm^{-1} (C=C). P.m.r. data ($CDCl_3$): τ 2.8 (m, 15 H, 3 Ph), 4.01 (s, 1 H, H-4), 4.18 (s, 1 H, PhC*H*), 5.04 and 5.76 (ABq, 2 H, J_{gem} 11 Hz, H-1,1'), 5.82 and 5.95 (ABq, 2 H, J_{gem} 13 Hz, H-6,6'), 5.93 (s, 1 H, OH), and 7.89 and 7.97 (2 s, 6 H, 2 Ac). Satisfactory analysis figures were not obtained for this compound.

(*D*) *Other Grignard reagents.* In separate reactions, **6** (5 g) was treated with Grignard reagents made from benzyl chloride or ethyl bromide. Syrupy products were obtained which could not be purified by column chromatography

*Reaction of diazomethane with 1,3:4,6-di-*O*-benzylidene-*D-threo-*2,5-hexodiulose* (**6**). — A solution of diazomethane in ether, prepared from *N*-methyl-*N*-nitroso-toluene-4-sulphonamide (10.75 g) in ether (80 ml), was added to a stirred solution of **6** (5 g) in dry benzene (200 ml) at 0–5°. The mixture was allowed to attain room temperature, and stirring was continued overnight. The yellow colour had then disappeared, and the solvents were evaporated under diminished pressure. The resulting, colourless syrup (4.8 g) was eluted from silica gel (150 g) with benzene–ether (19:1) to give, first, $2,2^1$:$5,5^1$-dianhydro-1,3:4,6-di-*O*-benzylidene-2,5-di-*C*-hydroxymethyl-D-mannitol (**25**; 2.76 g, 54%), m.p. 154–155°, $[\alpha]_D$ −35° (*c* 1, chloroform). P.m.r. data ($CDCl_3$): τ 2.7 (m, 10 H, 2 Ph), 4.37 (s, 2 H, 2 PhC*H*), 5.80 (q, 2 H, J_{gem} 12, $^4J_{HH}$ 2 Hz, 2 H, H-1,6), 5.87 (s, 2 H, H-3,4), 6.28 (d, 2 H, J_{gem} 12 Hz, H-1',6'), 6.73 (q, 2 H, J_{gem} 4, $^4J_{HH}$ 2 Hz, 2 epoxide-H), and 7.18 (d, 2 H, J_{gem} 4 Hz, 2 epoxide-H) (Found: C, 69.4; H, 5.9. $C_{22}H_{22}O_6$ calc.: C, 69.1; H, 5.8%).

Eluted second was (6*R*)-$6,6^1$-anhydro-1,4:5,7-di-*O*-benzylidene-3-deoxy-6-*C*-hydroxymethyl-D-*threo*-2-heptulose (**26**; 649 mg, 13%), m.p. 136–138°, $[\alpha]_D$ −42° (*c* 1, chloroform), ν_{max} 1720 cm^{-1} (C=O). P.m.r. data (C_6D_6): τ 2.8 (m, 10 H, 2 Ph), 4.59 and 4.80 (2 s, 2 H, 2 PhC*H*), 6.02 and 6.35 (ABq, 2 H, J_{gem} 18 Hz, H-1,1'), 6.23 (dd, 1 H, J_{gem} 12, $^4J_{HH}$ 2 Hz, H-6), 6.50 (dd, 1 H, J_{gem} 12 Hz, H-6'), 7.10 and 7.45 (AB part of ABX system, J_{AB} 15, J_{AX} 8, J_{BX} 4 Hz, H-3,3'), 7.16 (dd, 1 H, J_{gem} 4, $^4J_{HH}$ 2 Hz, epoxide-H), and 7.79 (d, 1 H, J_{gem} 4 Hz, epoxide-H') (Found: C, 68.9; H, 5.8. $C_{22}H_{22}O_6$ calc.: C, 69.1; H, 5.8%).

Eluted third was (5*R*)-$5,5^1$-anhydro-1,3:4,6-di-*O*-benzylidene-5-*C*-hydroxymethyl-D-*threo*-2-hexulose (148 mg, 3%), m.p. 173–175°, $[\alpha]_D$ −97° (*c* 1, benzene),

ν_{max} 1720 cm^{-1} (C=O). P.m.r. data (C_6H_6): τ 2.6 (m, 10 H, 2 Ph), 4.63 and 4.79 (2 s, 2 H, 2 PhC*H*), 5.80 and 5.94 (2 s. 2 H, H-3,4), 5.70 and 6.25 (ABq, 2 H, J_{gem} 12 Hz, H-1,1'), 6.02 and 6.39 (ABq, 2 H, J_{gem} 12 Hz, H-6,6'), and 6.84 and 7.54 (2 bs, 2 H, 2 epoxide-H) (Found: C, 68.1; H, 5.5. $C_{21}H_{20}O_6$ calc.: C, 68.5; H, 5.5%).

Reduction of (2R,5R)-*2,2*^{1}:*5,5*^{1}-*dianhydro-1,3*:*4,6-di*-O-*benzylidene-2,5-di*-C-*hydroxymethyl*-D-threo-*hexitol*. — (*A*) A solution of the title compound (376 mg) in dry ether (50 ml) was added to a stirred suspension of lithium aluminium hydride (100 mg) in dry ether (20 ml). The mixture was heated under reflux for 0.5 h, water (5 ml) was added, and the product was extracted with ether, to give 1,3:4,6-di-*O*-benzylidene-2.5-di-*C*-methyl-D-mannitol (325 mg, 86%), m.p. and mixture m.p. 117–118°, $[\alpha]_D$ —66° (*c* 1, chloroform).

(*B*) A solution of the title compound (500 mg) in ethanol (50 ml) containing a suspension of 10% palladium-on-charcoal (250 mg) was shaken under a slight overpressure of hydrogen. After 73 ml of hydrogen (25% excess over that calculated for hydrogenolysis of the benzylidene groups) had been absorbed, the catalyst was removed and the filtrate was evaporated to a syrup which contained at least three components (t.l.c.). Elution from silica gel (30 g) gave, first, 1,3:4,6-di-*O*-benzylidene-2.5-di-*C*-methyl-D-mannitol (34.6 mg), m.p. and mixture m.p. 117–118°.

The other two compounds were not characterised, but each had peaks in their n.m.r. spectra attributable to C-Me groups and no peaks attributable to epoxide groups.

Reduction of 1,3:*4,6-di*-O-*benzylidene*-D-threo-*2,5-hexodiulose* (**6**) *and its hydrate* (**2**). — (*A*) A solution of **6** (1 g) in dry benzene (50 ml) was added to a stirred suspension of lithium aluminium hydride (0.2 g) in dry ether (50 ml). After 2 h, the mixture was poured into water (10 ml), filtered, and extracted with ethyl acetate (2 × 50 ml). The combined extracts were dried ($MgSO_4$) and concentrated, and the syrupy residue (348 mg, 34%) was crystallised from chloroform–light petroleum to give 1,3:4,6-di-*O*-benzylidene-D-glucitol, m.p. 154–155°, $[\alpha]_D$ —34.5° (*c* 1, chloroform). P.m.r. data ($CDCl_3$): τ 2.55 (m, 10 H, 2 Ph), 4.32 and 4.45 (2 s, 2 H, 2 PhC*H*), and 5.65–6.60 (m, 8 H, hexitol chain) (Found: C, 66.7; H, 6.25. $C_{20}H_{22}O_6$ calc.: C, 67.0; H, 6.2%).

(*B*) To a solution of **2** (1.0 g) in ethanol (50 ml) was added sodium borohydride (0.5 g), and the mixture was stirred overnight. The solvent was evaporated and the residue was partitioned between chloroform (2 × 50 ml) and saturated, aqueous ammonium chloride (100 ml). Concentration of the dried ($MgSO_4$) organic layer gave a residue which was crystallised from ethanol to give a product (543 mg, 56%), m.p. 154–155°, which was identical to the product in (*A*).

Action of 2-lithio-1,3-dithiane on 1,3:*4,6-di*-O-*benzylidene*-D-threo-*2,5-hexodiulose* (**6**). — To a solution of 1,3-dithiane (3.53 g) in dry tetrahydrofuran (30 ml) at —80° was added butyl-lithium (29mM) in hexane (11.1 ml), and the solution was stirred for 1.5 h at —80°. A solution of **6** (5 g) in dry tetrahydrofuran (100 ml) was added dropwise, and the mixture was stirred for 0.5 h at —80° and then allowed to attain room temperature. After 2 h, the dark-red solution was poured into water (200 ml)

and extracted with ethyl acetate (2 × 100 ml) to give a red syrup which was eluted from silica gel (250 g) with benzene to give 1,3-dithiane (2.16 g, 61%). Elution with benzene–ether (9:1) gave a mixture (2.49 g), a portion (600 mg) of which was eluted from silica gel (100 g) with carbon tetrachloride–ethyl acetate (19:1), to give a chromatographically homogeneous syrup (41 mg, 2.8%), $[\alpha]_D$ +46° (*c* 1, chloroform), ν_{max} 3540 cm^{-1} (OH). P.m.r. data ($CDCl_3$): τ 2.6 (m, 10 H, 2 Ph), 4.40, 4.47 (2 s, 2 H, 2 PhC*H*), 4.85 (s, 1 H, SCHS), 4.95, 5.53 (2 s, 2 H, H-3,4), 5.49 (s, 2 H, H-1,1'), 5.61 and 5.97 (ABq, 2 H, J_{gem} 12 Hz, H-6,6'), 7.2 and 8.0 [2 m, 6 H, $S(CH_2)_3S$], and 6.09 (s, 1 H, OH). The singlet at τ 6.09 was removed by shaking the solution with D_2O. Satisfactory analysis figures could not be obtained for this syrup.

A second product (147 mg), m.p. 165–167°, $[\alpha]_D$ +106° (*c* 1, chloroform), was isolated, but not characterised.

*Action of dimethylsulphoxonium methylide on 1,3:4,6-di-*O*-benzylidene-*D*-threo-2,5-hexodiulose* (**6**). — Trimethylsulphoxonium iodide (11 g) and sodium hydride (1.25 g) were stirred together under a nitrogen atmosphere, and dry dimethyl sulphoxide (50 ml) was slowly added. A solution of **6** (6 g) in dry dimethyl sulphoxide (100 ml) was then added. The resulting, red solution was stirred overnight at room temperature, poured into water (200 ml), and extracted with ether (3 × 100 ml), and the combined, dried ($MgSO_4$) extracts were concentrated. The syrupy residue (6.0 g) was eluted from silica gel (150 g) with benzene–ether (9:1) to give a product (1.86 g, 31%) having m.p. 176–178°, $[\alpha]_D$ −27° (*c* 0.98, chloroform), ν_{max} 3420 cm^{-1} (OH). P m.r. data ($CDCl_3$): τ 2 6 (m, 10 H, 2 Ph), 4.37, 4.51 (2 s, 2 H, 2 PhC*H*), 5.55 and 6.01, 5.56 and 6.07 (2 ABq, 2 H, J_{gem} 13 Hz, 2 CH_2), 5.86 and 6.45 (2 bs, 2 H), 5.59 (s, 1 H), and 7.50 (s, 1 H, OH; removed with D_2O) (Found: C, 68.4; H, 5.8. $C_{21}H_{20}O_6$ calc.: C, 68.5; H, 5.5%).

ACKNOWLEDGMENT

We thank the S.R.C. for a studentship (to P.S.).

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