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Preliminary communication

Synthesis and stereochemistry of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosylidene acetals of α-diols and D-glucose derivatives

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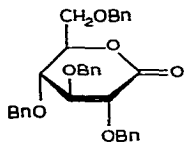
The unique type of acetal interlinkage between a glycosylidene (1-dehydroglycosyl) group and a glycose has been found in such oligosaccharide antibiotics as the evernomicins [1], flambamycin[2], hygromycin B (ref. 3), and the destomycins[4]. In these interlinkages in the field of carbohydrate chemistry, two modes are possible, depending on the *R* or *S* configuration of the orthoester carbon atom. However, no absolute configuration in these antibiotics has been determined, and no synthetic analogs have thus far been reported.

We now describe the synthesis of some analogs, and, from the results, discuss the configuration and conformation of the isomers. Because it is known that the orthoester linkage in these antibiotics is hydrolyzed under mildly acidic conditions to give the corresponding lactone and α-diol component, two methods usual for the synthesis of orthoesters were examined, using 2,3,4,6-tetra-*O*-benzyl-D-glucono-1,5-lactone (**1**).

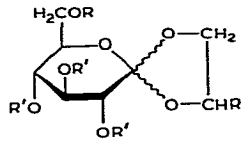
(i) Reaction of **1** *with epoxides*[5]. To a solution of equimolar amounts of **1** and boron trifluoride etherate in dichloromethane was added dropwise, with stirring, three equimolar proportions of 1-chloro-2,3-epoxypropane or 1,2-epoxypropane at 28–30°. The mixture was kept for 1 h, washed successively with 2.5M sodium hydroxide and water, and evaporated to a syrup which was purified on a silica gel column (eluant, 7:2 hexane–ethyl acetate), to give the corresponding spiro, cyclic orthoesters (**2** and **3**) as syrups in 45 and 65% yield, respectively. The presence of both of the isomers possible was indicated by the n.m.r. spectra of **2** and **3**, respectively.

A similar reaction of **1** with 5,6-anhydro-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-glucofuranose for 1 h gave only one of the two isomers possible, 1,2-*O*-isopropylidene-3-*O*-methyl-5,6-*O*-(2,3,4,6-tetra-*O*-benzyl-D-glucopyranosylidene)-α-D-glucofuranose (**4**), m.p. 63–64°, $[\alpha]_D^{22}$ +17° (*c* 0.62, $CHCl_3$), in 26% yield. The presence of the orthoester linkage in **4** was proved by the characteristic signal of carbon at δ 110.8 p.p.m. (from Me_4Si) in the ^{13}C-n.m.r. spectrum. However, this method was unsuccessful in the case of 1,2-epoxycyclohexane.

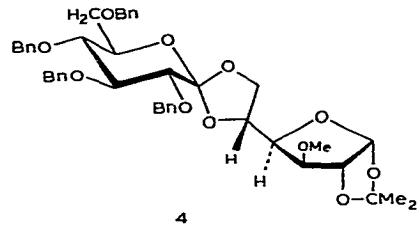
(ii) Dehydration between **1** *and α-diols*[6]. Azeotropic dehydration of a solution of equimolar amounts of **1** and ethylene glycol in benzene containing a catalytic amount of conc. sulfuric acid during 10 h and the usual processing of the reaction mixture after neutralization of the acid, gave, in 43% yield, the corresponding spiro, cyclic orthoester **5**



1



2 R = CH_2Cl, R' = Bn ($PhCH_2$)
3 R = Me, R' = Bn
5 R = H, R' = Bn
6 R = H, R' = Ac



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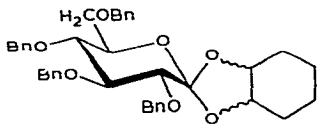
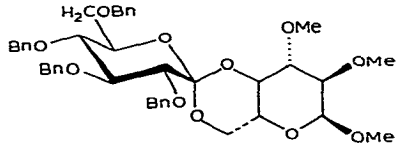


7a,b
8a,b



9

m.p. 51–52°, $[\alpha]_D^{22}$ +51° (*c* 1.0, $CHCl_3$); orthoester ^{13}C: δ 119.63. On continuation of the dehydration for 24 h, **1** disappeared, and the yield of **5** rose to 77%. Catalytic hydrogenation of **5** in methanol in the presence of palladium–charcoal and a few drops of acetic acid gave the *O*-debenzylated product as a syrup; this was acetylated with acetic anhydride in pyridine to give the corresponding tetraacetate **6** in 73% overall yield; m.p. 143–145°, $[\alpha]_D^{22}$ +51° (*c* 1.0, $CHCl_3$).

Similar dehydration of a mixture of **1** and *cis*-1,2-cyclohexanediol for 3 h gave a mixture of two isomers of the corresponding spiro, cyclic orthoesters (**7a** and **7b**), which were separated on a column of silica gel (eluant, 1:1 hexane–ether), to give **7a**, m.p. 98–103°, $[\alpha]_D^{22}$ +55° (*c* 1.1, $CHCl_3$), orthoester ^{13}C: δ 118.5; and **7b**, m.p. 58–60°, $[\alpha]_D^{22}$ +45° (*c* 0.90, $CHCl_3$); orthoester ^{13}C: δ 119.6, in 45 and 28% yield, respectively. Similar reaction of *trans*-1,2-cyclohexanediol for 37 h also gave two products; **8a**, m.p. 91–93°, $[\alpha]_D^{22}$ + 65° (*c* 0.8, $CHCl_3$), orthoester ^{13}C: δ 119.2; and **8b**, syrup, $[\alpha]_D^{22}$ +7.9° (*c* 0.5, $CHCl_3$), orthoester ^{13}C: δ 119.1, in 21 and 22% yield, respectively. Reaction of **1** and methyl 2,3-di-*O*-methyl-α-D-glucopyranoside for 8 h in a similar way gave only one of the two isomers possible, namely, methyl 2,3-di-*O*-methyl-4,6-*O*-(2,3,4,6-tetra-*O*-benzyl-D-glucopyranosylidene)-α-D-glucopyranoside (**9**), m.p. 131–132°, $[\alpha]_D^{22}$ +93° (*c* 0.92, $CHCl_3$); orthoester ^{13}C: δ 110.6, in 20% yield.

These results provide interesting problems in stereochemistry. The stereochemistry of five-membered, spiro, cyclic orthoesters is indicated in Fig. 1, in which the pyranosylidene ring is presented in a "Newman" projection. For **7**, the cyclohexane ring includes a → a′ bonds or b → b′ bonds, and the less-hindered, former compound, the (1*R*) isomer, will be the main product, **7a**. For **8**, the cyclohexane ring includes a → b′ bonds or b → a′ bonds. The ratio for formation of **8a** and **8b** indicates no significant difference in steric hindrance between them, but their ready separation suggests a new technique for

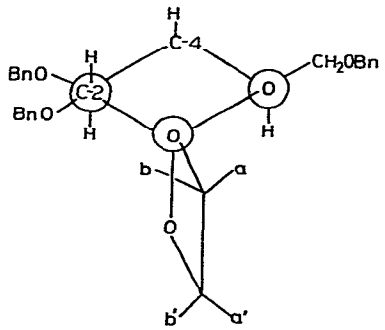


Fig. 1.

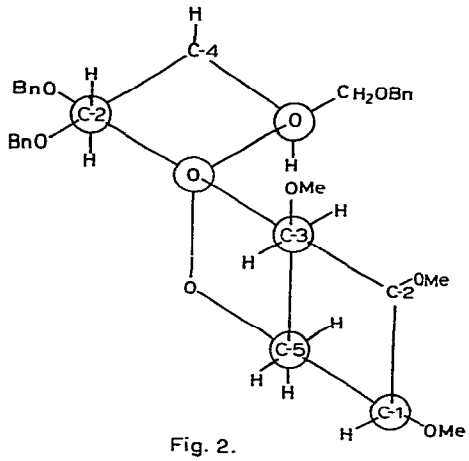


Fig. 2.

the resolution of the (1*R*, 2*R*)- and (1*S*, 2*S*)-*trans*-1,2-cyclohexanediols. In possible formulations of **4**, the bulky D-glucofuranose ring should be attached to either the b or the a′ position, and therefore, the latter, the (1*R*)-pyranosylidene isomer shown, will be much the more stable.

The "Newman" projection of the stable, (1*R*) isomer of **9**, having a six-membered, spiro, cyclic ring is presented in Fig. 2. It is obvious that the ring-oxygen side of the glycopyranosylidene moiety is the less hindered.

ACKNOWLEDGMENT

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