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Note

Synthesis of 1,2-anhydro-3,4,6-tri-*O*-benzyl-β-D-mannopyranose

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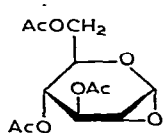
Although sugar derivatives with an epoxide ring linked to the anomeric center have potential utility as synthetic intermediates, few examples are reported in the literature. These include Brigl's anhydride[1] [1,2-anhydro-3,4,6-tri-*O*-acetyl-α-D-glucopyranose (**1**)], a related compound based on maltose[2] [1,2-anhydro-3,6-di-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-α-D-glucopyranose (**2**)] and the analogous mannopyranose derivative, and 2,3-anhydro-1,4,6-tri-*O*-nitrofructo-β-D-furanose[3] (**3**). We now report the synthesis of a new member of this class, a crystalline compound, 1,2-anhydro-3,4,6-tri-*O*-benzyl-β-D-mannopyranose (**4**).

The difficulties involved in the synthesis of compounds of this class can be understood by considering attempted and successful syntheses of related sugar derivatives and model compounds. Two compounds that can be considered models for 1,2-anhydroglycofuranoses are 2,6-dioxabicyclo[3.1.0]hexane (2,3-epoxytetrahydrofuran; 2,3-epoxyoxolane) (**5**) first synthesized by Decor and Descotes[4] and 5-methyl-



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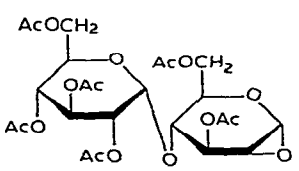

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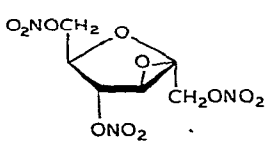

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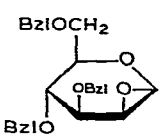

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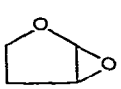

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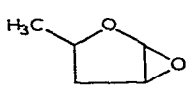

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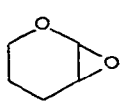

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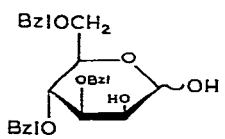
*In ref. 3, compound **3** was shown as the α-L derivative.

2,6-dioxabicyclo[3.1.0]hexane (2,3-epoxy-5-methyltetrahydrofuran; 2,3-epoxy-5-methyloxolane) (**6**) synthesized by Birkofer and Drutz[5]. A model for 1,2-anhydroglycopyranoses is 2,7-dioxabicyclo[4.1.0]heptane (2,3-epoxytetrahydropyran) (**7**) first synthesized by Wakselman and Wartski[6].

One method of synthesis, applicable to sugar derivatives, is the epoxidation of a cyclic vinyl ether, or in the sugar series, a glycal. Wood and Fletcher[7] found, however, that treatment of 1,5-anhydro-2-deoxy-D-*lyxo*-hex-1-enitol with peroxybenzoic acid yielded 1-*O*-benzoyl-α-D-talopyranose in low yield together with an amorphous (presumably oligomeric) material which on hydrolysis gave D-talose and benzoic acid. The peroxidation was apparently stereoselective, but the formed epoxide was sensitive to acid, and ring opening and polymerization occurred. A number of similar reactions on glycals and substituted glycals were reviewed, and similar results have been observed on **7** by Barker *et al.*[8] (See also ref. 6.). On the other hand, Arita *et al.*[2] reported the synthesis of **2** in poor yield and with poor stereoselectivity by a similar method using 3-chloroperbenzoic acid. Simple model compounds have been prepared from cyclic vinyl ethers with atomic oxygen[9], but this reagent gives little promise of useful application in the sugar series.

Conventional syntheses of ethylene oxide (oxirane) and propylene oxide (2,3-epoxypropane), and successful syntheses of **1**, **5**, **6**, and **7** have been effected by substitution processes involving a hydroxyl group on one carbon and a leaving group on the adjacent carbon atom. In the synthesis of **1**, the leaving group is Cl-1 in β configuration, whereas in the synthesis of **5** and **7** the halogeno group is vicinal to C-1, which bears a hydroxyl group. Similarly, 1,4-anhydro sugars have been prepared both by reaction of OH-4 with C-1 bearing a fluoride group[10], and by reaction of OH-1 with O-4 bearing a tosyl group[11]. A 1,6-anhydro-D-mannose derivative has also been prepared by a method analogous to the latter reaction[12]. Clearly, ring closure of the SN2 type is the best method of synthesis, but the preferred position and nature of the leaving group requires selection.

In our case, the selection of D-mannose as the parent sugar was dictated by our objective, to synthesize oligosaccharides and polysaccharides containing (1→2)-α-D-mannopyranosyl sequences that are important antigenic determinants of yeast mannan[13,14]. Benzyl ethers were chosen as removable blocking groups for OH-3, OH-4, and OH-6, because ester functions were previously shown to interfere in the polymerization of Brigl's anhydride[15] (**1**), and because the classical synthesis of sucrose[16] from the same compound gave poor yields. The most obvious method of introducing a



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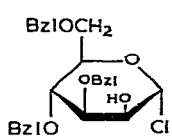

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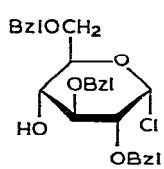

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leaving group at C-2 is the tosylation of a glycoside derived from 3,4,6-tri-*O*-benzyl-D-mannopyranose (**8**), followed by hydrolysis, but this route is not available because 2-*O*-tosyl glycosides are not readily hydrolyzed[17–19]. This resistance is also characteristic[20] of glycosides having other electronegative substituents at C-2. In preliminary experiments in this laboratory, ditosylation followed by hydrolysis also gave complex product mixtures[21].

We, therefore, attempted to convert OH-1 into a leaving group; the key intermediate in the synthesis of Brigl's anhydride (**1**) contains a 2-*O*-trichloroacetyl and a 1-β-D-chloride group, but its method of preparation is not suitable for D-mannose. Preliminary experiments indicated that elimination of a C-1 ester group by hydrogen halide from the 1,2-di-*O*-di- and -trichloroacetyl derivatives of **8** was possible but unattractive[21].

Finally, a more direct preparation of the desired 3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl chloride (**9**) was achieved by a modification of the method of Micheel and Kreutzer[22]. These authors prepared 2,3,6-tri-*O*-benzyl-α-D-glucopyranosyl chloride (**10**) by treatment of 2,3,6-tri-*O*-benzyl-D-glucopyranose with hydrogen chloride in ether, a most useful method inadequately reported in the literature. The desired compound **9** is substantially more reactive than **10**, and removal of hydrogen chloride in a stream of dry nitrogen tended to reverse the equilibrium and re-form the diol **8**. As soon as the bulk of the hydrogen chloride was removed, even in the presence of molecular sieves, it was necessary to proceed directly to the ring closure. The latter reaction is mechanistically straightforward, as the substituents at C-1 and C-2 of **9** are in a *trans*-diaxial relationship. However, the selection of the reagent caused concern because the prior literature has frequently postulated carbohydrate epoxyacetals as reaction intermediates in base-catalyzed reactions at the anomeric center, *e.g.*, in the alkaline conversion of phenyl β-D-glucopyranoside to 1,6-anhydro-β-D-glucopyranose[23] and in the conversion of 2-*O*-methylsulfonyl-D-arabinose to D-ribose[24–26]. Furthermore, the treatment of 3-chloro-2-hydroxyoxolane with aqueous alkali to form the corresponding diol was postulated to proceed through a bicyclic epoxyacetal[6], and the successful synthesis of **7** required the use of sodium hydride dispersion in anhydrous medium[6]. However, the use of anhydrous ammonia in benzene was successful, as in the case of Brigl's anhydride (**1**).

Compound **4** was obtained in crystalline form by ring closure and concentration of the benzene solution, and with relatively little purification could be obtained with the proper carbon and hydrogen analysis and a specific rotation $[\alpha]_D^{25} \sim +8$ to 10°. This material could be purified further to $[\alpha]_D^{25} +4.5°$ by careful recrystallization as described later. Analysis of the mother liquors by high pressure liquid chromatography on polyvinyl acetate in toluene showed the presence of materials that are probably dimeric and oligomeric. Under these conditions, compounds bearing hydroxyl groups have long retention times[27] and were usually present only as minor by-products. The major impurities appear to be cyclic dimers or oligomers free of hydroxyl groups.

The ^{1}H-n.m.r. spectrum is consistent with the assigned structure and specifically with the presence of an oxirane ring involving C-1 and C-2. The signals of protons at

both C-1 and C-2 are moved remarkably upfield. No peak between δ 5 and 6, where the signals for H-1 of mannopyranose and mannopyranoside derivatives are expected, was observed, but a doublet at δ 4.95 and a doublet of doublets at δ 3.3, which are assigned to H-1 and H-2 by decoupling experiments, are present. The δ 3.3 peak is farther upfield than usually seen in carbohydrates but corresponds to a similar broad doublet in the spectrum of **1** at δ 3.0–3.1.

The ^{13}C-n.m.r. spectrum is also unusual. The signals of C-1 of mannose derivatives are usually found between 90 and 105 p.p.m. Except for aromatic carbons, the peak farthest downfield is at 79.3 p.p.m., and a peak at 54.3 p.p.m., 15 p.p.m. farther upfield than any mannose ring-carbon observed by us, is also present. The latter peak appears as a doublet in off-resonance spectrum and corresponds probably to C-2.

EXPERIMENTAL

Methods and materials. — Instrumentation used was as described in ref. 12, except for the n.m.r. spectra which were recorded with a Varian XL100-15 spectrometer, in Fourier transform-mode, for 25% solutions in chloroform-*d* with Me_4Si as internal standard in 5-mm (o.d.) tubes. All values are in p.p.m. downfield of the Me_4Si signal. Protons were assigned on the basis of chemical shifts and decoupling experiments. In the ^{13}C-n.m.r. spectra[18], methylene and methine atoms were identified by an off-resonance experiment, and the peak assignments are based on chemical shifts.

Mallinkrodt anhydrous ether, and spectral-grade benzene and chloroform were used. Ethanol was first removed from chloroform by filtration through a column of neutral alumina. All operations, insofar as possible, were carried out under an inert atmosphere of nitrogen. The reaction vessel was a 250-mL, round-bottomed flask with a 24/40 outer joint and a side arm equipped with a stopcock leading to a T-tube with two 14/20 outer joints; one of the joints was protected by a serum cap for introduction of gases or liquids through a syringe, and the second joint served as a vent and was protected with a drying tube. The reaction vessel was opened only under a stream of nitrogen. Filtrations were made through a coarse, sintered-glass funnel equipped with 24/40 joints at both ends and a vacuum take-off. Crystallizations were carried out in a small column equipped with a medium-sintered-glass frit and having a stopcock in the bottom and ground joint in the top; two pressure-equalizing addition funnels holding solvent and nonsolvent were attached through a Y tube with ground-glass connections. Solvent and nonsolvent were kept under nitrogen, and the solution was maintained on the surface of the sintered glass during crystallization by a positive nitrogen pressure.

*1,2-Anhydro-3,4,6-tri-*O*-benzyl-β-*D*-mannopyranose* (**4**). — 3,4,6-Tri-*O*-benzyl-D-mannopyranose[28] (2.0 g) was dissolved in pure chloroform (10 mL) in the reaction vessel and anhydrous ether (50 mL) was added with a syringe under nitrogen. The solution was saturated with hydrogen chloride while being cooled in an ice bath. The reaction vessel was closed and stored for 2 days at 0°. It was then allowed to return to

room temperature (with release of pressure) and benzene (50 mL) was added. The hydrogen chloride was removed from the solution by a stream of nitrogen for a period of 0.5 h. Powdered Linde 3-Å molecular sieves (10 mL) was added, and the nitrogen flow continued for another 0.5 h. The solution was filtered under vacuum into another reaction vessel containing molecular sieves (10 mL), and a Teflon-coated, magnetic stirring-bar. The first flask and sieves were washed with benzene, and the wash liquors were added to the second flask by vacuum filtration. A second portion of benzene (50 mL) was added directly to the second flask, and a drying tube was attached. Ammonia was added steadily for 3 h with stirring and cooling in a salt–ice bath. The sieves and ammonium chloride were filtered off, and the clear solution was evaporated to dryness on a rotary evaporator under vacuum. The solid crystalline residue was transferred to the crystallization apparatus, dissolved in benzene (~5 mL), and hexane (13.5 mL) was added, just prior to the cloud point. The solution was cautiously cooled with salt and ice. Nitrogen pressure was controlled to maintain the solution on the surface of the sintered-glass without bubbling. When crystallization was complete, vacuum was applied and the crystals dried under vacuum. The mother liquors were retained for g.l.c. analysis. The crystals were stored in a sealed bottle in a desiccator under inert atmosphere (yield ~1.4 g), m.p. 89.5–90.0°, $[\alpha]_D^{25}$ +4.5 ± 0.2° (*c* 1, chloroform); ^{1}H-n.m.r.: δ 7.55–7.15 (m, 15 H, aromatic H), 4.94–4.91 (d, 1 H, $J_{1,2}$ 2.8 Hz, H-1), 4.87–4.43 (m, 6 H, CH_2 of Bzl) 3.97–3.91 (q, 1 H, H-3), 3.90 (broad s, 1 H, H-5), 3.78–3.64 (m, 1 H, H-4), 3.64 (broad s, 2 H, H-6), and 3.31–3.27 (q, 1 H, $J_{2,3}$ 1.7 Hz, H-2); ^{13}C-n.m.r.: 138.2, 128.5, 127.9 (arom.), 79.3, 78.7, 78.2, 76.1, 54.3 (=CH–), and 75.1, 73.6, 72.0, 68.8 p.p.m. (–CH_2–).

Anal. Calc. for $C_{27}H_{28}O_5$: C, 74.98; H, 6.53. Found: C, 74.60: H, 6.74.

ACKNOWLEDGMENTS

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