The Application of Unsaturated Carbohydrates to Glycoside Syntheses: 6-*O*-α-D-Mannopyranosyl-, 6-*O*-α-D-Altropyranosyl-, and 6-*O*-(3,6-Anhydro-α-D-glucopyranosyl)-D-galactose

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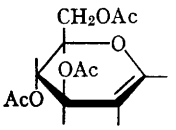
A NEW approach to the important problem of glycoside synthesis is based on the preparation of 2,3-unsaturated glycosides from glycal esters and subsequent hydroxylations of the double bonds, and has the advantages of permitting the use of glycosylating agent and aglycone in equimolar proportions, and of proceeding with high stereoselectivity at the anomeric centre. Until now the use of such a method has been precluded by the absence of satisfactory synthetic routes to the 2,3-unsaturated intermediates.

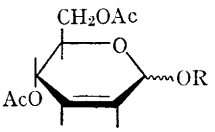
With suitable nucleophiles, and in the absence of strong protonic acids (which cause addition reactions), glycal esters undergo attack at C(1) and allylic displacement of the C(3) ester function.[1] Phenols, for example, react smoothly with 3,4,6-tri-*O*-acetyl-D-glucal (I) to give the 2,3-unsaturated glycosides (II; R = aryl) under convenient conditions; alcohols, however, require high temperatures and pressures to cause them to react.[2] The stereoselectivity of this reaction is not high, and in the case of the methyl compounds (II; R = Me) the α- and β-anomers are produced in the ratio 1·5 : 1, presumably under kinetic control.[2] We now report that such reactions are catalysed at room temperatures and in inert solvents by boron trifluoride etherate, and will proceed satisfactorily with stoicheiometric amounts of alcohols. Further, anomerisation occurs and the stereoselectivity of the reaction is appreciably enhanced, so that the methyl compounds are obtained in the ratio 10 : 1, and from the ethyl analogues (II; R = Et) the crystalline α-anomer can be isolated by simple procedures in 70% yield. With the

high temperature method this compound may be obtained in 25% yield,[2] and even this represents an improvement on the ethylation of the free unsaturated sugar which is normally used for the preparation.[3] Other aliphatic alcohols react in similar fashion, although the main products do not normally crystallise as readily as the α-ethyl derivative, and complex hydroxyl-containing compounds may be employed.

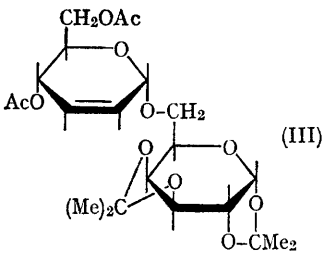
cis-Hydroxylations have been carried out on glycosides of this series (II; R = Et, aryl; α-



(I)



(II)



(III)

isomers) and, as would be expected on steric grounds, mainly α-mannoside derivatives are obtained.[3c, d, 4] Therefore the development now reported renders this route to α-mannopyranosyl compounds practicable. *trans*-Hydroxylations of 2,3-unsaturated glycosides have, alternatively, not been reported, and we find that the benzonitrile–hydrogen peroxide reagent[5] causes smooth conversions to mixed epoxides which hydrolyse mainly to mixtures of altropyranosyl and 3,6-anhydroglucopyranosyl derivatives.

Application of these procedures is illustrated by the syntheses of the disaccharides named in the title. Equimolecular proportions of tri-*O*-acetyl-D-glucal (I) and 1,2 : 3,4-di-*O*-isopropylidene-α-D-galactopyranose reacted within 15 min. at room temperature in benzene solution (*ca.* 5% with respect to each reactant), and in the presence of boron trifluoride etherate (0·4%), and from the products 6-*O*-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosyl)-1,2 : 3,4-di-*O*-isopropylidene-α-D-galactopyranose (III), m.p. 136—137°, $[\alpha]_D$ + 10° (benzene), was readily isolated in 60% yield. It afforded a dihydro-derivative {88%, m.p. 94—95°, $[\alpha]_D$ + 18° (benzene)}, and on hydroxylation (4 g.) with neutral permanganate in aqueous acetone followed by deacetylation and partial acid hydrolysis gave a syrup (1·8 g), 1·0 g. of which was resolved on a column of cellulose to afford 6-*O*-α-D-mannopyranosyl-α-D-galactose (0·2 g.) m.p. 166—168°, $[\alpha]_D$ + 115°—> + 96° (in H_2O). On hydrolysis the disaccharide gave galactose and mannose, and on oxidation of the derived polyol with periodate 3·8 mol. and 5·8 mol. of the reagent were reduced when it was employed at 0·4 mM and 40 mM concentrations respectively. In each case formaldehyde (0·95 mol.) was liberated which confirms the 6-*O*-glycosidic linkage,[6] and since the product of complete periodate oxidation of the disaccharide had [α] + 89° the α-configuration can be assigned.[7]

Epoxidation[5] of the double bond of the unsaturated compound (III) (4 g.) and re-acetylation of the hydroxyl groups liberated during the process gave a sharp-melting, epoxide-containing product 3·5 g., 84%, m.p. 140—141° $[\alpha]_D$ + 20° ($CHCl_3$), 1·1 g. of which on saponification afforded two readily resolved products (i) 6-*O*-(α-D-altropyranosyl)-1,2 : 3,4-di-*O*-isopropylidene-α-D-galactose, 0·38 g., 40%, $[\alpha]_D$ + 13° (EtOH) and (ii) 6-*O*-(3,6-anhydro-α-D-glucopyranosyl)-1,2 : 3,4-di-*O*-isopropylidene-α-D-galactose, 0·52 g., 57%, $[\alpha]_D$ − 17° (EtOH). These on partial acidic hydrolysis gave the altropyranosylgalactose 0·20 g. $[\alpha]_D$ + 100° (H_2O) and the 3,6-anhydroglucopyranosylgalactose 0·05 g. $[\alpha]_D$ + 75° (H_2O), which were isolated after cellulose-column chromatography. Each hydrolysed to the appropriate free sugars with acid, but the altrosyl derivative gave, in addition, very small amounts of glucose.

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