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A GENERAL METHOD FOR THE PREPARATION OF 2,6-DI-O-GLYCOSYL-HEXOPYRANOSES. SYNTHESIS OF O-β-D-GALACTOPYRANOSYL-(1→2)-O-[α-L-RHAMNOPYRANOSYL-(1→6)]-D-GALACTOPYRANOSE DECAACETATE

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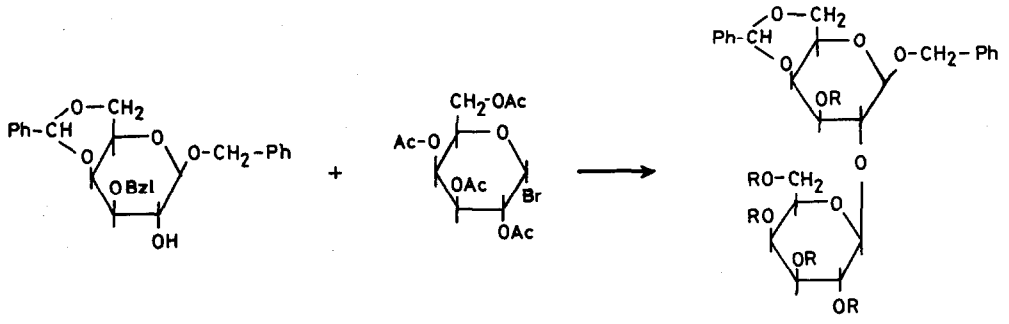
Branched chain oligosaccharides can often be found among the degradation products of heteropolysaccharides, immune agents and glycolipids. There is no generally applicable method available for the preparation of these compounds. In the preparation of the few chemically synthesized branched chain trisaccharides use was made of the partial acetylation[1], partial hydrolysis of orthoesters[2] or the "temporary" properties of the allyl groupings[3].

In this communication we now report a general method for the preparation of 2,6-di-O-glycosyl-hexopyranoses. This method is based on the stereoselective hydrogenolysis of 4,6-O-benzylidene-hexopyranosides[4,5], which was extended to disaccharides, too[6]. The key compounds of these syntheses may be the 3-O-acyl, 3-O-benzyl or 3-O-allyl derivatives of 4,6-O-benzylidene-hexopyranosides.

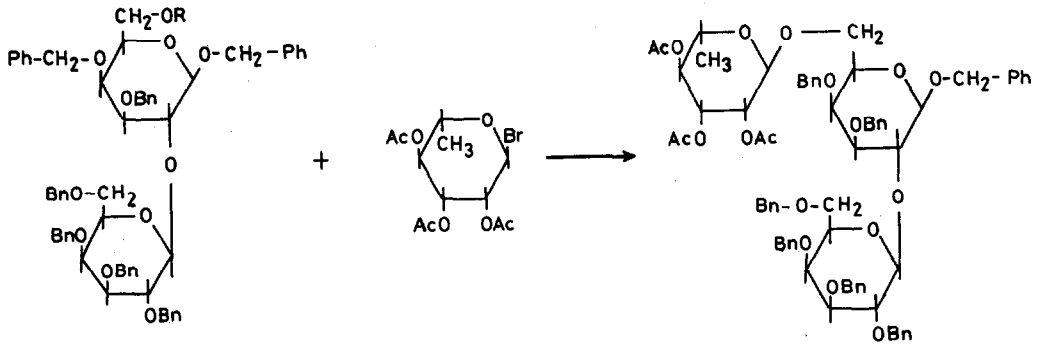
The starting compound of the trisaccharide, synthesized by us, was benzyl 3-O-benzoyl-4,6-O-benzylidene-β-D-galactopyranoside[7] (1) which was condensed with α-acetobromo-D-galactose (2) in benzene-nitromethane (1:1) in the presence of $Hg(CN)_2$ catalyst, to yield a disaccharide derivative. Saponification of this amorphous product was followed, without isolation, by acetylation in 1:1 pyridine-acetic anhydride to give crystalline benzyl 3-O-acetyl-4,6-O-benzylidene-2-O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-β-D-galactopyranoside (3, 48 %, mp: 123-124° C, $[\alpha]_D = +8.7°$, δ_{CH-Ph} : 5.48 ppm, $\nu_{C=O}$: 1745 cm^{-1}). 3 was deacetylated (Zemplén) and benzylated, without isolation, with benzyl chloride at 105-110° C in the presence of KOH. Both IR and NMR spectra proved that the crystalline benzyl 3-O-benzyl-4,6-O-benzylidene-2-O-(2,3,4,6-tetra-O-benzyl-β-D-galactopyranosyl)-β-D-galactopyranoside (4, 61 %, mp: 102-104° C, $[\alpha]_D = +14.1°$, δ_{CH-Ph} : 5.90 ppm) is a fully protected derivative. The presence of the benzylidene ring, playing a crucial role in the subsequent steps, was also indicated. No migration[9] or hydrolysis of this group during glycosylation, saponification or benzylation occured.

Fig. 1.



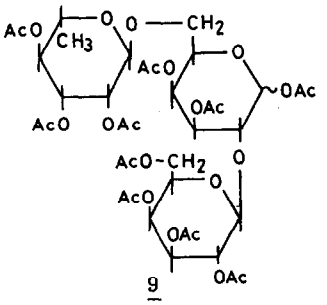
1 2 3 R = Ac

4 R = Bn



5 R = H 7 8

6 R = OCH_3



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Ac = Acetyl
Bzl = Benzoyl
Bn = Benzyl

Hydrogenolysis of 4 by $LiAlH_4$-$AlCl_3$ yielded a C_6-OH, C_4-O-benzyl derivative, benzyl 3,4-di-O-benzyl-2-O-(2,3,4,6-tetra-O-benzyl-β-D-galactopyranosyl)-β-D-galactopyranoside (5, 79 %, mp: 60-61° C, $[\alpha]_D$ = -12.5°). The structure of 5 was proved by an intense absorption, in its IR spectrum, of the OH group in the range of 3200-3400 cm^{-1} and the lack, in its NMR spectrum, of the singlet characteristic of the benzylidene proton. Upon methylation[10], 5 yielded 6, the NMR spectrum of which revealed only one OCH_3 signal(δ : 3.42 ppm). Catalytic hydrogenation and acid hydrolysis followed by $NaBH_4$ reduction and acetylation gave a 1:1 mixture of 1,2,3,4,5-penta-O-acetyl-6-O--methyl-D-galactitol and hexa-O-acetyl-galactitol (GLC examination).

The benzylidene group of 4 can be considered as a "temporary" protecting group which, upon hydrogenolysis, yields a free hydroxyl group and is transformed to the "persistent" benzyl protecting group[11-12].

Reaction of 5 with α-acetobromo-L-rhamnose (7) in 1:1 benzene-nitromethane, in the presence of $Hg(CN)_2$, gave a crystalline trisaccharide derivative (8, 76 %, mp : 52° C, $[\alpha]_D$ = -34.1°, $\nu_{C=O}$: 1740 cm^{-1}, δ_{CH_3CO} : 2.09, 2.02, 1.97 ppm, $\delta_{CH_3\text{-}CH}$: 1.09 ppm, J = 6.5 Hz).

The NMR spectrum of 8 supports its postulated structure. The anomeric configurations of the interglycosidic linkages could, however, not be determined on the basis of this spectrum. The α-L-rhamnopyranosyl configuration is supported by the optical rotation value and the stereoselectivity of the glycosylation reaction. 8 was fully debenzylated by catalytic hydrogenation (H_2/Pd on carbon). The product of this reaction was directly acetylated in pyridine-acetic anhydride to yield crystalline title compound (9, 84 %, mp : 102-103° C, $[\alpha]_D$ = -33.7°).

The route of the synthesis is shown in Figure 1.

It appears that the benzylidene derivatives of glycopyranosides containing only one free hydroxyl function may be new precursors in the synthesis of branched chain oligosaccharides. Our investigations on the exo and endo isomers of the dioxolane derivatives of cis axial-equatorial hydroxyl groups are in progress.

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13 Optical rotations were measured in chloroform with a Bendix automatic polarimeter. NMR spectra were recorded on a Jeol MH-100 in $CDCl_3$, using Me_4Si as internal standard. GLC determinations were performed on a Hewlett-Packard 5830 A gas chromatograph using a UCCW-982 (10 %) column.