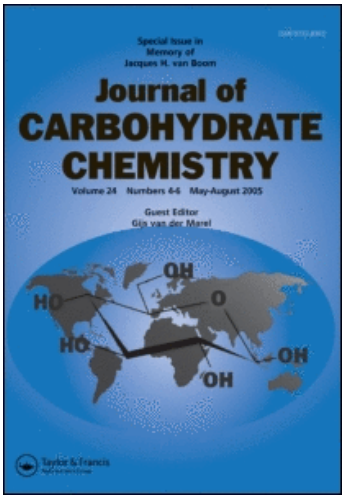

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Communication

AZIDE SUBSTITUTION AT MANNOSE DERIVATIVES. A POTENTIAL NEW ROUTE TO GLUCOSAMINE DERIVATIVES.

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Since the pioneering work of Paulsen et al.[1] on stereoselective coupling reactions of glucosamine derivatives, the azide function has found general application in carbohydrate chemistry as a non--participating masking group for amines. Although excellent results have been reported for the synthesis of α-coupled glucosamine derivatives, the preparation of the required 2-azido-2-deoxy-D--glucopyranose is often laborious.[1c]

One of the first attempts to shorten the route to 2-azido-2-deoxy--carbohydrates was the azidonitration of glycal in the presence of ceric ammonium nitrate (CAN) and sodium azide.[2] However, this procedure worked well for galactose, but practically not for glucose. Further, Bovin et al. described the addition of halogenazides to

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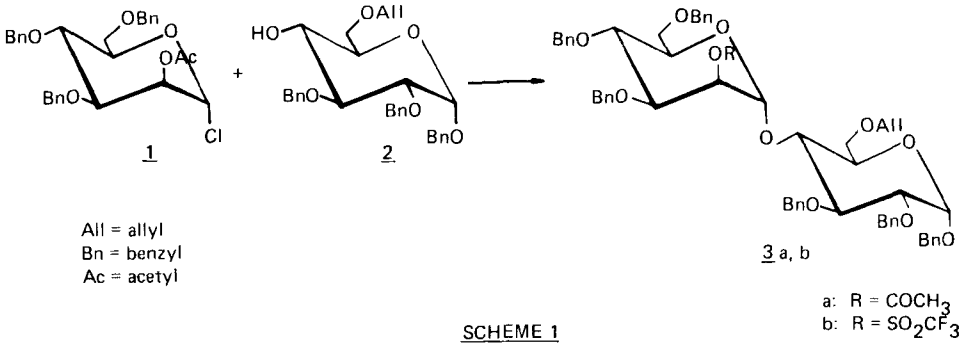
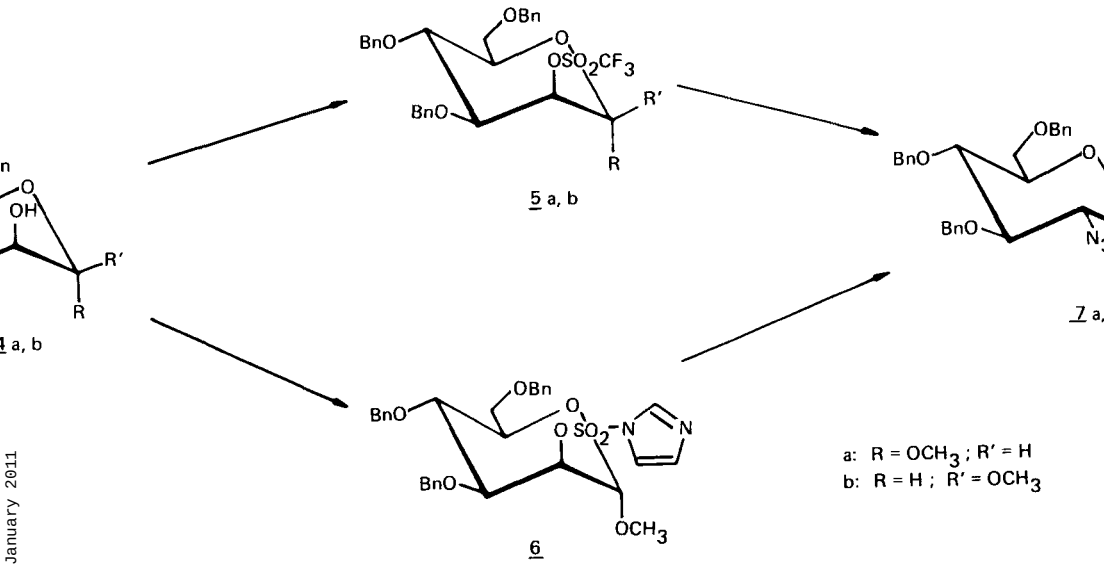
glycal to give 2-azido-2-deoxy-D-galactopyranosyl as well as glucopyranosyl derivatives.[3] Our attempts to facilitate the synthesis of carbohydrates containing α-coupled glucosamine derivatives were based on the observation of Ogawa et al.[4] that coupling of mannosylchloride 1 (Scheme 1) almost exclusively gives α-coupled products. As azide substitution at C-2 of mannose derivatives will proceed with Walden inversion, we reasoned that a very short synthetic route to α-coupled glucosamine derivatives could be realized.



SCHEME 1

In order to examine this route we performed some model experiments on the methyl-α-D-mannopyranosyl derivative 4a. An appropriate leaving group had to be introduced at the 2-hydroxyl function of the mannose compound 4a. Hanessian reported good yields for the azide substitution of carbohydrates containing the imidazolylsulphonyl leaving group.[5] However, azide substitution of 6 (Scheme 2) gave only trace amounts of the desired 2-azido-2--deoxy-D-glucopyranosyl derivative 7a.

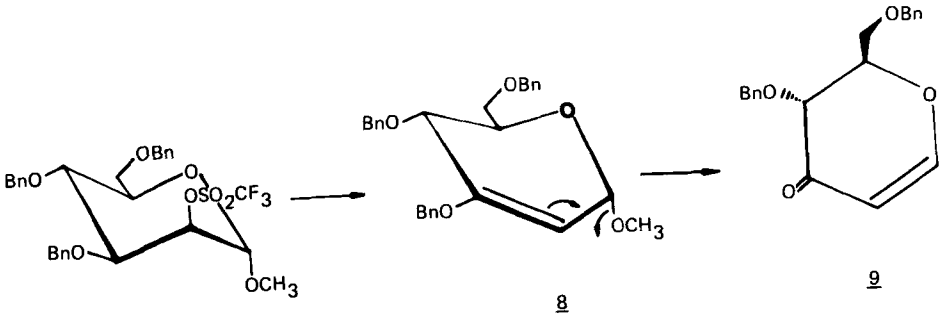
Better results were obtained by application of the trifluoromethanesulphonyl (triflate) leaving group (i.e. compound 5a in



SCHEME 2

Scheme 2). Treatment of 5a with excess of lithium azide in DMF afforded 2-azido-2-deoxy-D-glucopyranoside 7a in 27% isolated yield.

One has to take into account that dipolar interactions between the attacking azide anion and the anomeric oxygen hamper substitution considerably,[6] which explains the moderate yield. This in fact is the first example of a direct displacement of sulphonate at C-2 of an α-mannose derivative by an azide anion.[7] The major product isolated, however, is the α,β-unsaturated ketone 9,[8] the formation of which can be explained via the elimination product 8 (see Scheme 3).



5a 8 9

SCHEME 3

Having established that azide substitution at monosaccharide 5a is possible, it was of interest to see whether a similar substitution reaction could also be performed on disaccharides. Therefore, we tried the reaction of α-mannopyranosyl-glucopyranosyl derivative 3b with azide anion. It turned out that substitution at C-2 was also possible in this case albeit in lower yield (13% of isolated product). Again the α,β-unsaturated ketone 9 was the major reaction product.

On the other hand, dipolar interactions and torsion strain should be lower[6] for the azide substitution at the methyl-β-D-mannose derivative 5b. This compound was obtained after trifluoromethanesulphonic anhydride treatment of 4b in pyridine. As expected, substitution with lithium azide proceeded in excellent yield (90%), giving 2-azido-2-deoxy-β-D-glucopyranoside 7b. This method may provide 2-azido-2-deoxy-D-glucose building blocks in a more simple and faster way than via the existing procedures, especially when the anomeric β-methyl is replaced by a protecting group, which can be removed easily.

EXPERIMENTAL

Azide substitution at 2-trifluoromethanesulphonate-D-mannopyranosyl derivatives

In a typical experiment a solution of trifluoromethanesulphonic anhydride (243 mg, 144 µl, 0.86 mmol) in dry 1,2-dichloroethane (1 ml) was added to a stirred, precooled (-10°C) solution of pyridine (80 mg, 80 µl, 1 mmol) in dry 1,2-dichloroethane (4 ml). To this mixture, a solution of methyl 3,4,5-tri-O-benzyl-α-D--mannopyranoside 4a (200 mg, 0.43 mmol) in 1 ml of 1,2-dichloroethane was added and stirred for 1 h.

A 5% aq. $NaHCO_3$ solution (10 ml) was added and the mixture stirred for 20 min. Extraction with dichloromethane and washing with brine gave an organic layer which was dried ($MgSO_4$) and evaporated to dryness. The crude slightly yellow oil obtained (5a) was coevaporated with toluene and used directly in the next step.

R_f (SiO_2; dichloromethane/aceton 97:3 v/v) : 0.76.

^1H NMR ($CDCl_3$) δ : 4.90 (d, $J_{1,2}$ = 1.9 Hz, 1 H, H_1); 5.11 (dd, $J_{1,2}$ = 1.9 Hz, $J_{2,3}$ = 3.1 Hz, 1 H, H_2).

Crude 5a was dissolved in 5 ml of dry dimethylformamide and 255 mg (4.5 mmol) of lithium azide was added. The solution was heated overnight at 50°C, evaporated to dryness and the residue taken up in a water/dichloromethane mixture. The organic layer was washed with brine, dried over $MgSO_4$ and evaporated to dryness. The crude product was chromatographed over silica (eluent : dichloromethane), after which 56 mg of pure 7a (11.5 mmol; 27% yield) was obtained. R_f (SiO_2; dichloromethane/aceton 99:1 v/v) : 0.52.

^1H NMR ($CDCl_3$) δ: 4.82 (d, $J_{1,2}$ = 3.8 Hz, 1 H, H_1); 3.65 (dd, $J_{1,2}$ = 3.8 Hz, $J_{2,3}$ = 10.0 Hz, 1 H, H_2). ^{13}C NMR ($CDCl_3$) δ: 98.7 (C_1); 63.6 (C_2). IR (neat) 2110 cm^{-1} (νN_3).

Compound 3b was prepared from disaccharide 3a after deacetylation (KOtBu/MeOH/THF) analogous to the synthesis of 5a. Disaccharide 3a was prepared by reacting together compound 1 and 2 (see Scheme 1) in dichloromethane in the presence of silver trifluoromethanesulphonate and 1,1,3,3-tetramethylurea according to the method of Ogawa et al.[4] After stirring for 15 h at room temperature compound 3a was isolated after chromatography on silica in 85% yield. ^{13}C NMR of 3a ($CDCl_3$) δ: 95.3 (C_1); 99.2 (C'_1). R_f (SiO_2; toluene/ethylacetate 9:1 v/v) : 0.60.

Synthesis of methyl 3,4,6-tri-O-benzyl-β-D-mannopyranoside (4b)

According to the method of Ashry and Schuerch,[9] 1 g (2,22 mmol) of 3,4,6-tri-O-benzyl-α-D-mannopyranose[10] in 100 ml of dry methanol was stirred under reflux with 555 mg (2,22 mmol) dibutyltin oxide. After 1.5 h the methanol was evaporated and the residue coevaporated with dry toluene and dried under vacuo. The dibutylstannylene derivative obtained was dissolved in 10 ml of dry

dimethylformamide and heated overnight at 50°C with 1 ml (2,2 g; 15.2 mmol) methyl iodide. After evaporation to dryness, the residue was dissolved in dichloromethane, washed with water, dried over $MgSO_4$ and evaporated to dryness. There was obtained 850 mg (1.83 mmol; 83% yield) of 4b (oil).

The conversion of 4b to methyl 2-azido-2-deoxy-3,4,6-tri-O--benzyl-β-D-glucopyranoside 7b, via its 2-trifluoromethane sulphonate derivative 5b, was performed according to the synthesis of 7a from 4a, however, the substitution with lithium azide was complete after 1 h at room temperature.

R_f (SiO_2; toluene/ethylacetate 7:3 v/v) 0.75.
^1H NMR ($CDCl_3$) δ: 4.16 (d, $J_{1,2}$ = 7,6 Hz, 1 H, H_1). ^{13}C NMR ($CDCl_3$) δ: 103.0 (C_1); 66.4 (C_2). IR (neat) 2112 cm^{-1} (νN_3).

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7. The only precedent of a successful substitution at C-2 of compound 4a, is the bromination with tribromoimidazole and triphenylphosphine. See B. Classon, P.J. Garegg and B. Samuelsson, Can. J. Chem., 59, 339 (1981). The reversed substitution from the gluco to the manno configuration has been described by J. Ishido and N. Sakairi, Carbohydr. Res., 97, 151 (1981).

8. Compound 9 is a useful chiral synthon, which may find application in stereoselective reactions, for instance as a Michael acceptor. See : T.E. Goodwin, C.M. Crowder, R.B. White, J.S. Swanson et al., J. Org. Chem., 48, 376 (1983). ^{1}H NMR ($CDCl_3$) δ : 7.32 (d, $J_{1,2}$ = 6.0 Hz, 1 H, H_1); 5.38 (d, $J_{1,2}$ = 6.0 Hz, 1 H, H_2). IR (neat) 1690 cm^{-1} (νC=O). ^{13}C NMR ($CDCl_3$) δ : 162.4 (C_1); 105.3 (C_2).

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