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SYNTHESIS OF N-ACETYLSUGAR-ß-*trans*-GLYCOSIDES: FACILE ONE-POT TRANSGLYCOSYLATION OF EPOXYPENTYL TRI-O-ACETYL N-ACETYLGLUCOSAMINE

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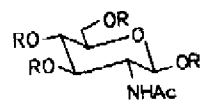
Abstract - Glycosides 10 and 11 were prepared from epoxypentyl ß-D-N-acetylglucosamine 8 under mild conditions, using TMS triflate as the promotor. Presumably, this novel reaction proceeds *via in situ* activation of the intermediate oxazoline 9.

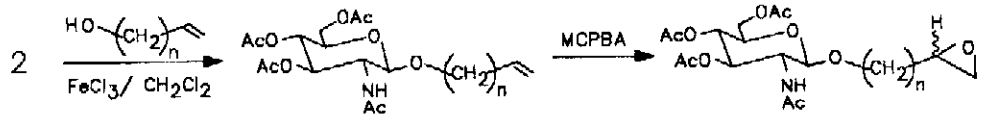
Glycosidically linked 2-acetamido-2-deoxy-glucose (N-acetylglucosamine)(1) is an important component of many glycoproteins and some polysaccharides. Glycosides of 1 are synthesized usually by treating a suitably protected glycosyl halide or acetate with a heavy metal promotor.[1,2] This leads, under neighboring group participation, eventually to an oxazoline which, in a second step, is activated by an acid[3] or Lewis acid[4,5] in order to allow nucleophilic attack by a glycosyl acceptor. Alternatively, 2-azido-2-deoxy- or 2-deoxy-2-phthalimidoglucose derivatives are used; their preparation, however, requires rather lengthy procedures. Recently, Fraser-Reid et al.[6], in extension of their elegant work on glycoside synthesis,[7] reported on the iodonium ion mediated transformation of n-pentenyl 2-deoxy-2-phthalimido and 2-anisylimino-2-deoxy-D-glucopyranosides into disaccharides. It should be noted that this reaction does not proceed to an appreciable extent when the glycosyl donor bears a 2-acylamino group.[6] We have found now that 4',5'-epoxypentyl 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-ß-D-glucopyranoside (8) which is reminiscent of a halonium ion,[6,7] is a useful glycoside



1: R = H
2: R = Ac

donor for the preparation of ß-*trans*-glycosides of N-acetyl-glucosamine in a one step transglycosylation reaction.

During ongoing investigations of inhibitors of endoglycosidases,[8,9] we have prepared the epoxyalkyl N-acetylglucosamine derivatives 6-8 by epoxidation of alkenyl glycosides 3-5 with MCPBA (scheme 1; *cf.*[5,10,11])[12]. The ß-configuration in 3-5 is proven by NMR spectroscopy ($CDCl_3$) (doublets at δ = 4.68 ± 0.2 ppm; J = 8.4 Hz). Quite interestingly, the anomeric protons of the epoxyalkyl glycosides appear in the diastereomeric pairs of 6-8 always in the form of two doublets, each showing J = 8.9 Hz which again consistently proves the ß-configuration.

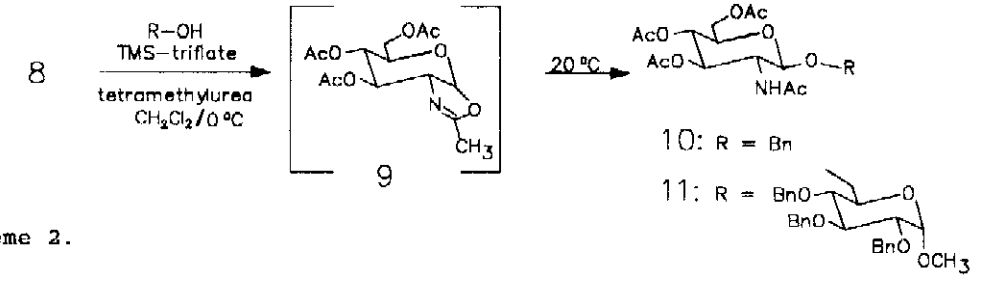


3: n = 1 (79%)
4: n = 2 (56%)
5: n = 3 (69%)

6: n = 1 (71%)
7: n = 2 (77%)
8: n = 3 (94%)

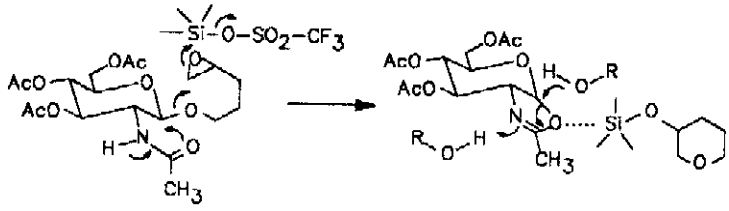
Scheme 1.

When TMS triflate and tetramethylurea (1.2 fold excess each) are added at 0°C to a solution of 8 in CH_2Cl_2, TLC reveals disappearance of the epoxide within 2 h and concomitant formation of oxazoline 9 (scheme 2). In presence of a primary alcohol, the oxazoline is converted overnight at 20°C into a ß-glycoside which is isolated by usual workup and column chromatography. Thus, reaction of 8 in the presence of allyl alcohol reconverts 8 into 3. Similarly, the benzyl glycoside 10 results from reaction of 8 with benzyl alcohol, whereas reaction with methyl 2,3,4-tri-O-benzyl-α-D-glucopyranoside leads to the protected disaccharide ßDGlcNAc(OAc)$_3$p-6αDGlc(OBn)$_3$p-OMe (11).[13] In a preliminary experiment, we have also prepared, albeit in low yield, ßDGlcNAc(OAc)$_3$p-4αDMan(OBn)$_3$p-OMe from 8 and methyl 2,3,6-tri-O-benzyl-α-D-mannopyranoside.



Scheme 2.

The reaction mechanism (scheme 3) apparently involves opening of epoxide 8 with simultaneous intramolecular attack of the glycosidic oxygen and oxazoline formation. This intermediate is activated *in situ* presumably by 3-tetrahydropyranyl TMS ether. Addition of the alcohol then leads to the glycoside. The epoxypropyl and epoxybutyl glycosides 6 and 7, respectively, also rapidly disappear upon addition of TMS triflate. However, decomposition ensues and no glycoside is formed from 6 in the presence of primary alcohols, whereas traces of glycosides are detectable in TLC of reaction mixtures containing 7 and primary alcohol.



Scheme 3.

Another interesting aspect of epoxypentyl glycoside reactivity is seen in enzyme chemistry. It was noted previously[11] that epoxypentyl cellobioside is a powerful covalent inhibitor of cellulase whereas the epoxide of 4-methylenecyclohexyl cellobioside is ineffective. In view of the mechanism depicted in scheme 3, this result may be explained by a rate acceleration of epoxide opening by intramolecular attack of the glycosidic oxygen which is not possible in the conformationally more restricted cyclohexyl derivative. This also raises the intriguing question whether glycosidase inhibition by epoxypentyl glycosides is accompanied by glycosylation of the enzyme, in addition to alkylation.

Typical experimental procedure for transglycosylation:

TMS triflate (1.2 mmol) is added at 0°C to a stirred solution of epoxypentyl glycoside 8 (1 mmol), tetramethylurea (1.2 mmol) and the acceptor alcohol (2-4 mmol) in CH_2Cl_2 (40 ml). Stirring is continued for 2 h at 0°C, and for another 10-14 h at 20°C. Dilution with 60 ml CH_2Cl_2 is followed by washing (2 x 20 ml sat. aq. $NaHCO_3$, 2 x 20 ml H_2O), drying ($MgSO_4$), evaporation and column chromatography [silica gel, $CHCl_3$/acetone (3:1)].

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12. **4**: m.p. = 130-1°C; $[\alpha]_D^{20}$ -15.6 ($CHCl_3$, c = 1); **5**: m.p. = 123-4°C; $[\alpha]_D^{20}$ -10.9 ($CHCl_3$, c = 1); **7**: m.p. = 145-6°C; $[\alpha]_D^{20}$ -14.2 ($CHCl_3$, c = 1); **8**: m.p. = 120-1°C; $[\alpha]_D^{20}$ -19.5 ($CHCl_3$, c = 1). Details of the NMR-spectra will be reported elsewhere.
13. Yields: **3** (from **8**): 49% (*cf.*[10b]); **10**: 46 % (*cf.*[5]); **11**: 49% (*cf.*[14]). The yields are not optimized; they are always calculated from the amount of donor **8** used. All compounds gave correct analytical data (m.p.; $[\alpha]_D$; NMR spectra).
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