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N,N-Diacetyl-Glucosamine and -Galactosamine Derivatives as Glycosyl Donors

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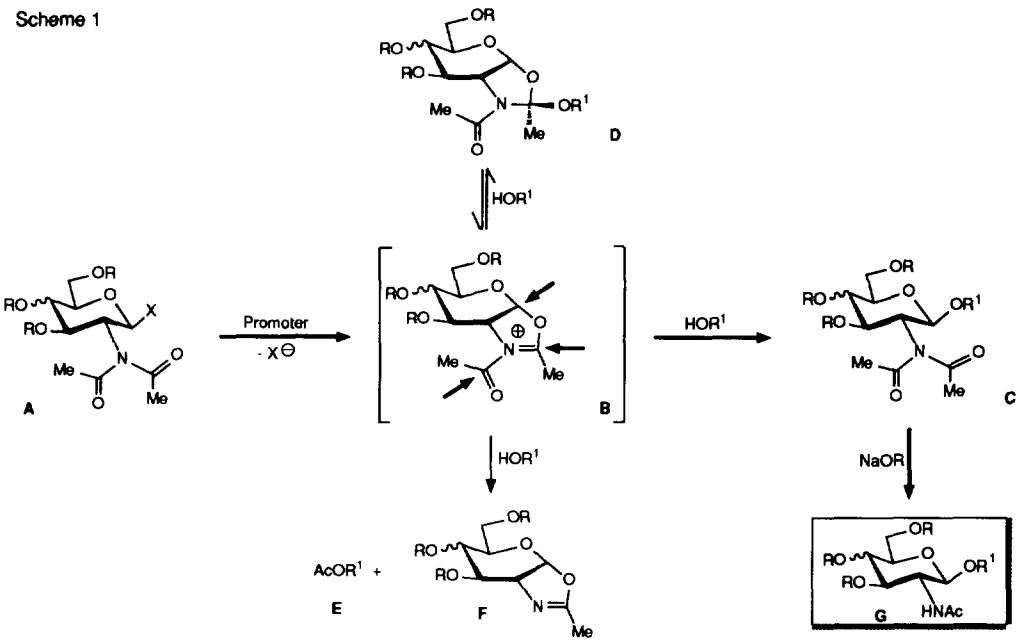
Abstract: N-Acetyl-glucosamine and N-acetyl-galactosamine were converted into the O-acetyl protected 1-methylthio-derivatives **1A,B** which were then transformed into N,N-diacetyl derivatives **2A** and **2B**, respectively. Activation of **2A,B** with DMTST afforded good glycosyl donors for the generation of β-linkages; thus, reaction with acceptors **3a,b** gave oligosaccharides **4Aa** and **4Ba** in high and **4Ab** and **4Bb** in good yields. Mono-N-deacetylation could be performed with NaOMe/MeOH in quantitative yield, thus concluding a convenient procedure for the formation of β-linked GlcNAc and GalNAc glycosides.

Glucosamine and galactosamine are frequently occurring as constituents of glycoconjugates[1]. Generally they are N-acetylated and N-acetylglucosamine is mainly found in β-glycosidic linkage. Glycoside bond formation with glycosyl donors from the N-acetyl derivatives results via neighboring group participation first in oxazoline formation[1,2]. However, even under strong acid catalysis these intermediates do not exert strong glycosyl donor properties because methyl substituted N-protonated oxazolinium systems are rather stable. Therefore, various donors having modified or latent amino functionalities have been investigated for this endeavour[1-12], amongst which the phthalimido group[2,3] and the azido group[1,2,4] gained wide use. The azido group serves as an excellent latent amino group and, for instance in combination with trichloroacetimidate activation, reactive donors for the generation of α- and β-glycosidic linkages are available[4,5]. However, the preparation of the required azido sugars is still not very economical[4]. The N-phthalimido sugars can be readily obtained from the aminosugars and in combination with trichloroacetimidate activation good glycosyl donors are available for β-glycoside bond formation via reactive N-acylated oxazolinium intermediates[4]. However, phthalimido group cleavage requires basic conditions which often results in partial product decomposition[6]. Therefore, N-tetrachlorophthalimido (TCP)-protected glycosyl donors were recently employed[10,11], which exhibit high glycosyl donor properties and permit removal of the TCP group under very mild nonbasic conditions[10,12].

The intermediate generation of free amino groups in all the above discussed methodologies is quite frequently disadvantageous[13]; therefore, methods retaining the N-acetyl functionality in the activated species are of great interest. A convenient solution of this problem would be formation of N,N-diacetyl derivatives of amino sugars (**A** in Scheme 1), which could lead upon anomeric activation to highly reactive N-acetyl-oxazolinium intermediates **B**; reaction with the acceptor HOR[1] at the anomeric center will then provide via stereocontrolled β-attack the desired β-linked glycoside **C**, which can be transformed into the target molecule **G** under very mild basic conditions.

Scheme 1



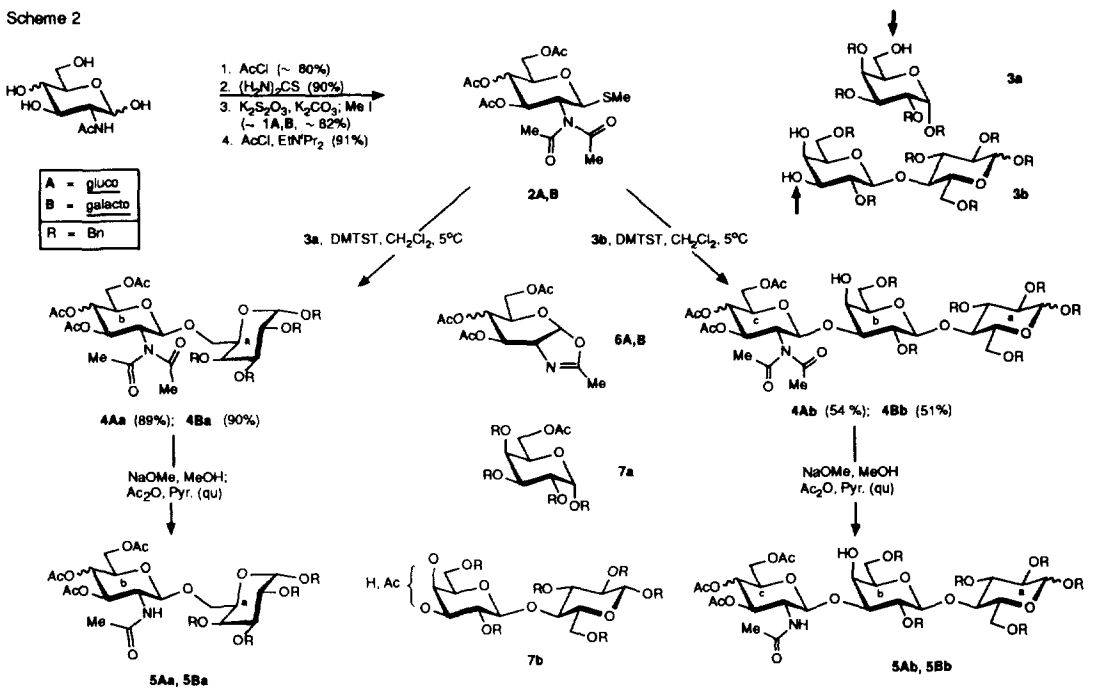
Obviously, under the reaction conditions, besides reaction of the acceptor at the oxazolinium carbon leading to reversible amide acetal **D** formation, attack at the N-acetyl group as competing reaction can take place; thus, undesired O-acetylated acceptor **E** and oxazoline **F** would be formed. The results of our investigations are exhibited below[12]. The previously reported N-allyloxycarbonyl substituted N-acyl-aminosugars obviously lead to additional byproducts, thus limiting their importance as glycosyl donors[2b].

For the investigation of N,N-diacetyl-glucosamine and -galactosamine derived glycosyl donors thio group activation at the anomeric center[4,14] was envisaged. To this aim N-acetyl-glucosamine was transformed in three highyielding steps into known O-acetyl protected 1-methylthio derivative **1A**[15] (Scheme 2); reaction with acetyl chloride in the presence of Hünig's base (EtN^iPr_2) afforded readily glycosyl donor **2A**. Similarly, from N-acetyl-galactosamine known **1B**[15] was obtained, which gave under the same conditions glycosyl donor **2B** in very high yield.

For the glycosylation with donor **2A** relatively reactive 6-O-unprotected galactose derivative **3a**[16] was chosen as acceptor, because GlcNAcβ(1-6)Gal-linkages occur frequently in nature[1,2,4]. Activation of **2A** with dimethyl(methylthio)sulfonium trifluoromethanesulfonate (DMTST) as promoter (4 eq) in CH_2Cl_2 at 5 °C afforded the desired β-linked disaccharide **4Aa** in 89% yield; only very small amounts of oxazoline **6A** and 6-O-acetyl-galactose **7a** (6%) could be isolated. Similar results were obtained for **2B** as donor and **3a** as acceptor: under the same conditions disaccharide **4Ba** was isolated in 90% yield. The β-linkage could be readily confirmed by the ^{1}H-NMR data: **4Aa**: $J_{1b,2b}$ = 9.5 Hz; **4Ba**: $J_{1b,2b}$ = 9.4 Hz. Because also GlcNAcβ(1-3)Galβ(1-4)Glc trisaccharides occur frequently in nature, 3,4-O-unprotected lactose **3b**[17] was investigated as acceptor for **2A,B**. Activation of donor **2A** with DMTST as promoter afforded under the same conditions the desired β-linked trisaccharide **4Ab** in 54% yield (^{1}H-NMR: 1c-H, δ = 5.20, $J_{1c,2c}$ = 10.1 Hz); because of the lower reactivity of **3b** more oxazoline **6A** and O-acetyl-lactose **7b** (15%) was isolated. The regioselective attack of **2A** at the 3b-OH group of **3b** could be readily derived from the ^{1}H-NMR data of the 4b-O-acetyl-product **5Ab**,

which exhibited for 4b-H the expected downfield shift (Table 1). Again, similar results were obtained with **2B** as donor and **3b** as acceptor furnishing trisaccharide **4Bb** in 51% yield (^{1}H-NMR: 1c-H, δ = 5.49, $J_{1c,2c}$ = 10.1 Hz).

Scheme 2



Removal of one of the N-acetyl groups in saccharides **4Aa**, **4Ab**, **4Bax**, and **4Bb** could be quantitatively performed with NaOMe in MeOH; ensuing per-O-acetylation with acetic anhydride in pyridine afforded compounds **5Aa**, **5Ab**, **5Ba**, and known **5Bb**[18], respectively. The ^{1}H-NMR data[19] support the structural assignments.

In conclusion, N,N-diacetylglucosamine and -galactosamine donors **2A,B** are readily available; they give β-linked glycosides with reactive acceptors in very high yields. Removal of one of the N-acetyl groups can be performed with NaOMe in MeOH, thus leading directly to N-acetylglucosamine and -galactosamine glycosides, respectively. For less reactive glycosyl acceptors, variations in the leaving group or in the protective groups should lead to decreased N-deacetylation of the donor by the acceptor.

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19. Selected physical data of new compounds: R_f (PE/EA, 2:1), $[\alpha]_D^{20}$ ($CHCl_3$, c = 1), ^{1}H-NMR ($CDCl_3$, TMS). **2A**: R_f 0.88, $[\alpha]_D^{20}$ -39.0; δ_H = 5.85 (dd, $J_{2,3} \approx J_{3,4} \approx$ 10.1 Hz, 1 H, 3 H), 5.51 (d, $J_{1,2}$ = 10.3 Hz, 1 H, 1-H), 5.11 (dd, $J_{3,4} \approx J_{4,5}$ = 10.3 Hz, 1 H, 4-H), 4.31 (m, 1 H, 6a-H), 4.15 (m, 1 H, 6b-H), 3.79-3.93 (m, 2 H, 2-H + 4-H), 2.41 (s, 3 H, NAc), 2.39 (s, 3 H, NAc), 2.22 (s, 3 H, SCH_3), 2.00-2.12 (3 s, 9 H, 3 OAc). **2B**: R_f 0.90, $[\alpha]_D^{20}$ -41.0; δ_H = 5.83 (dd, $J_{2,3}$ = 9.9 Hz, $J_{3,4}$ = 1.5 Hz, 1 H, 3-H), 5.50 (d, $J_{1,2}$ = 10.1 Hz, 1 H, 1-H), 5.50 (dd, $J_{3,4}$ = 1.5 Hz, $J_{4,5}$ = 1.3 Hz, 1 H, 4-H), 4.00-4.30 (m, 4 H, 2-H, 4-H, 6a-H, 6b-H), 2.39 (s, 3 H, NAc), 2.37 (s, 3 H, NAc), 2.23 (s, 3 H, SCH_3), 2.15, 2.11, 1.98 (3 s, 9 H, 3 OAc). **4Aa**: R_f 0.75, $[\alpha]_D^{20}$ -40.0; δ_H = 5.82 (dd, $J_{2,3} \approx J_{3,4} \approx$ 10.0 Hz, 1 H, 3b-H), 5.27 (d, $J_{1,2}$ = 9.8 Hz, 1 H, 1b-H), 5.08 (dd, $J_{3,4} \approx J_{4,5} \approx$ 10.1 Hz, 1 H, 4b-H), 4.42 (d, $J_{1,2}$ = 1.2 Hz, 1 H, 1a-H), 3.94 (dd, $J_{1,2}$ = 1.2 Hz, $J_{2,3}$ = 8.9 Hz, 1 H, 2a-H), 3.81 (dd, $J_{3,4} \approx$ 1.3 Hz $\approx J_{4,5}$, 1 H, 4a-H), 3.70 (dd, $J_{2,3}$ = 8.9 Hz, $J_{3,4}$ = 1.3 Hz, 1 H, 3a-H). **4Ab**: R_f 0.45, $[\alpha]_D^{20}$ -59.0; δ_H = 5.79 (dd, $J_{2,3} \approx J_{3,4} \approx$ 10.1 Hz, 1 H, 3c-H), 5.30 (d, $J_{1,2}$ = 10.1 Hz, 1 H, 1c-H), 5.03 (dd, $J_{3,4} \approx J_{4,5} \approx$ 10.1 Hz, 1 H,4c-H), 4.70 (d, $J_{1,2}$ = 9.5 Hz, 1 H, 1b-H), 3.84 (dd, $J_{2,3}$ = 8.9 Hz, $J_{3,4}$ = 1.8 Hz, 1 H, 3b-H), 3.72-3.80 (m, 3 H, 2c-H, 4b-H, 2b-H), 3.40-3.65 (m, 3 H, 5b-H, 2 x 6b-H). **4Ba**: R_f 0.80, $[\alpha]_D^{20}$ -38.0; δ_H = 5.80 (dd, $J_{2,3}$ = 10.0 Hz, $J_{3,4}$ = 1.5 Hz, 1 H, 3b-H), 5.54 (d, $J_{1,2}$ = 10.1 Hz, 1 H, 1b-H), 5.42 (dd, $J_{3,4}$ = 1.5 Hz, $J_{4,5}$ = 1.3 Hz, 1 H, 4b-H), 4.40 (d, $J_{1,2}$ = 1.2 Hz, 1 H, 1a-H), 3.94 (dd, $J_{1,2}$ = 1.2 Hz, $J_{2,3}$ = 8.9 Hz, 1 H, 2a-H), 3.81 (dd, $J_{3,4}$ = 1.3 Hz = $J_{4,5}$, 1 H, 4a-H), 3.70 (dd, $J_{2,3}$ = 8.9 Hz, $J_{3,4}$ = 1.3 Hz, 1 H, 3a-H). **4Bb**: R_f 0.50, $[\alpha]_D^{20}$ -53.0; δ_H = 5.77 (dd, $J_{2,3}$ = 10 Hz, $J_{3,4}$ = 1.8 Hz, 1 H, 3c-H), 5.49 (d, $J_{1,2}$ = 10.1 Hz, 1 H, 1c-H), 5.41 (dd, $J_{3,4}$ = 1.8 Hz, $J_{4,5}$ = 1.4 Hz, 1 H, 4c-H), 4.68 (d, $J_{1,2}$ = 9.5 Hz, 1 H, 1b-H), 3.86 (dd, $J_{2,3}$ = 9.0 Hz, $J_{3,4}$ = 2 Hz, 1 H, 3b-H), 3.70-3.82 (m, 3 H, 2c-H, 4b-H, 2b-H), 3.40-3.67 (m, 3 H, 5b-H, 2 x 6b-H). **5Aa**: R_f 0.50, $[\alpha]_D^{20}$ -20.0; δ_H = 5.52 (d, 1 H, NH), 5.10 (dd, $J_{2,3}$ = 9.5 Hz, $J_{3,4}$ = 9.2 Hz, 1 H, 3b-H), 4.90 (d, $J_{1,2}$ = 9.5 Hz, 1 H, 1b-H), 4.88 (dd, $J_{3,4}$ = 9.2 Hz, $J_{4,5}$ = 9.8 Hz, 1 H, 4b-H), 4.45 (d, $J_{1,2}$ = 0.9 Hz, 1 H, 1a-H), 3.97 (dd, $J_{1,2}$ = 1.2 Hz, $J_{2,3}$ = 9 Hz, 1 H, 2a-H), 3.94 (m, 1 H, 2b-H), 3.78 (dd, $J_{3,4} \approx J_{4,5} \approx$ 1.4 Hz, 1 H, 4a-H), 3.72 (dd, $J_{2,3}$ = 9.0 Hz, $J_{3,4}$ = 1.4 Hz, 1 H, 3a-H. **5Ab**: R_f 0.46, $[\alpha]_D^{20}$ +1.3; δ_H = 5.53 (d, 1 H, NH), 5.25 (dd, $J_{2,3}$ = 9.6 Hz, $J_{3,4}$ = 9.4 Hz, 1 H, 3c-H), 4.75 (d, $J_{1,2}$ = 9.4 Hz, 1 H, 1c-H), 5.20 (dd, $J_{3,4}$ = 0.6 Hz, $J_{4,5}$ = 0.8 Hz, 1 H, 4b-H), 5.10 (dd, $J_{3,4}$ = 9.4 Hz, $J_{4,5}$ = 9.6 Hz, 1 H, 4c-H), 4.43 (d, $J_{1,2}$ = 9.3 Hz, 1 H, 1b-H), 3.90 (dd, $J_{2,3}$ = 8.9 Hz, $J_{3,4}$ = 0.6 Hz, 1 H, 3b-H), 3.70-3.80 (m, 3 H, 2c-H, 4b-H, 2b-H), 3.40-3.65 (m, 3 H, 5b-H, 2 x 6b-H). **5Ba**: R_f 0.55, $[\alpha]_D^{20}$ -18.0; δ_H = 5.52 (d, 1 H, NH), 5.13 (dd, $J_{2,3}$ = 9.6 Hz, $J_{3,4}$ = 0.6 Hz, 1 H, 3b-H), 4.98 (d, $J_{1,2}$= 9.4 Hz, 1 H, 1b-H), 4.95 (dd, $J_{3,4}$ = 0.6 Hz, $J_{4,5}$ = 0.8 Hz, 1 H, 4b-H), 4.40 (d, $J_{1,2}$ = 0.8 Hz, 1 H, 1a-H), 3.95 (dd, $J_{1,2}$ = 1.2 Hz, $J_{2,3}$ = 9.0 Hz, 1 H, 2a-H), 3.93 (m, 1 H, 2b-H), 3.78 (dd, $J_{3,4} \approx J_{4,5} \approx$ 1.4 Hz, 1 H, 4a-H), 3.72 (dd, $J_{2,3}$ = 9.2 Hz, $J_{3,4}$ = 1.4 Hz, 1 H, 3a-H). **5Bb**: R_f 0.48, $[\alpha]_D^{20}$ +3.3 (+3.1; ref. 18); δ_H = 5.50 (d, 1 H, NH), 5.45 (dd, $J_{3,4} \approx J_{4,5}$ = 2.8 Hz, 1 H, 4c-H), 5.41 (dd, $J_{3,4} \approx J_{4,5}$ = 3.0 Hz, 1 H, 4b-H), 5.30 (dd, $J_{3,4}$ = 2.8 Hz, $J_{2,3}$ = 8.9 Hz, 1 H, 3c-H), 4.71 (d, 1 H, $J_{1,2}$ = 8.6 Hz, 1c-H), 4.46 (d, 1 H, $J_{1,2}$ = 8.1 Hz, 1b-H).

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