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The Purification of Glucose Type Glycosyl Nitrate and the Synthesis of Spacer-armed *N*-Acetyllactosamines and Their Dimers

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Abstract: 3, 6-di-O-acetyl-4-O-(2, 3, 4, 6-tetra-O-acetyl-β-D-galactopyranosyl)-2-azido-2-deoxy-β-D-glucoppyranosyl nitrate could be separated from its mannose type isomer by glycosylation according to the reactivity difference of these two compounds. The pure glucose type nitrate can be converted to corresponding trichloroacemidate, which reacted with spacer arms in solution of CH_2Cl_2 with $BF_3{\cdot}Et_2O$ as promoters to give desired glycosides and dimers.

Keywords: Glycosyl nitrate, glycosyl trichloroacemidate, spacer-armed dimer.

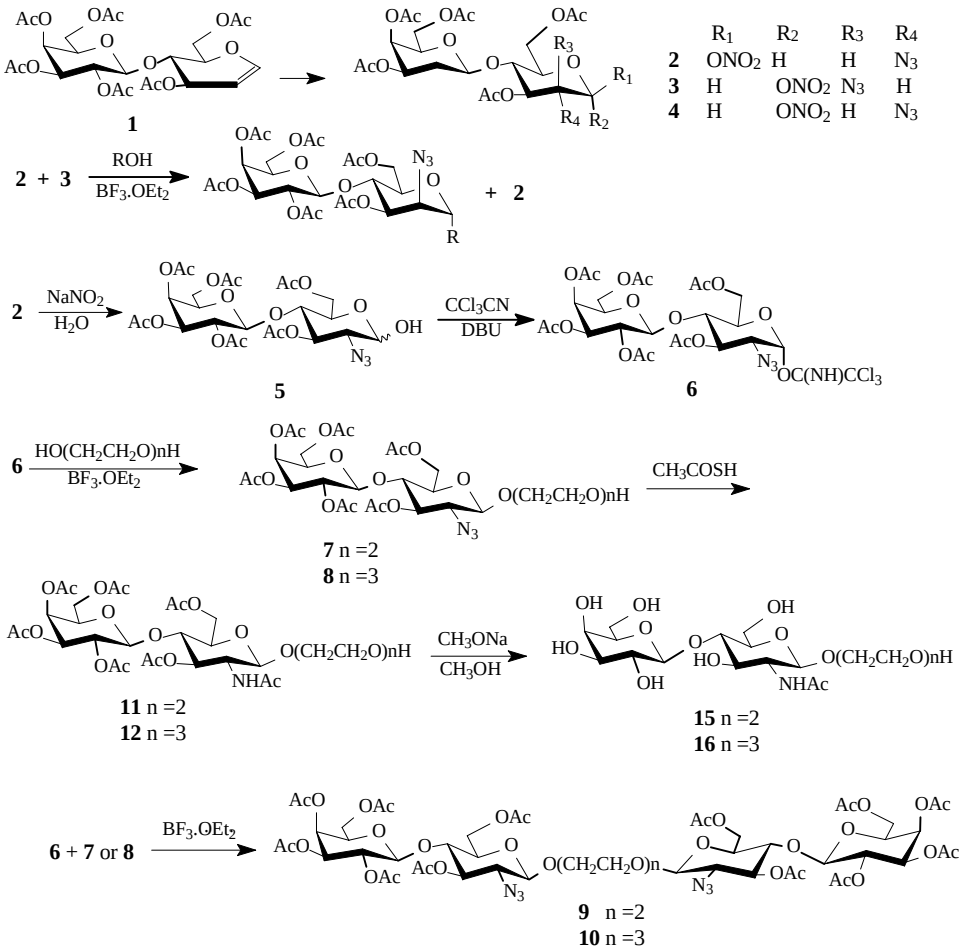
Our previous paper[1,2]reported the results of selective synthesis of mannose type glycosides and their dimers in our attempt to synthesize derivatives of *N*-acetyllactosamine, which could have potential activity of anti-metastasis[3]. Further studies on the glycosylation of the accepters exploiting glycosyl nitrate instead of the acetate as donor showed interesting chemoselectivity between the two kinds of donor, namely, the glucose type and the mannose type. The reactivity difference of the two glycosyl nitrates led to a practical separation method of the nitrates mixture, which were prepared from azidonitration of the corresponding lactal, and were not likely to be separated in conventional methods[4]. In addition, the synthesis of spacer-armed glucose type glycosides and their dimers will be involved in this paper.

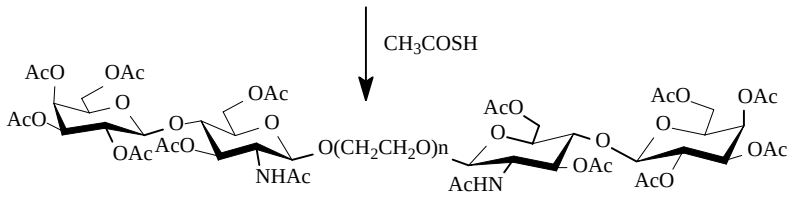
The azidonitration of lactal **1** would usually give three main products: two glucose type nitrates **2**, **4** and a mannose type compound **3**. **2** and **3** are difficult to be separated because of their very close polarity in most solvent systems. However, the mixture of **2** and **3** reacted with accepters in the presence of $BF_3{\cdot}Et_2O$ to give only the mannose type glycosides and the glucose type nitrate **2** keep intact and can be recovered from the mixture[4]. After purifying and treating with $NaNO_2$ and H_2O in the solution of 1, 4-dioxane at 80°C and then with trichloroacetonitrile, **2** was converted to trichloroacetimidate **6**, which reacted readily with di- and triethylene glycol (r.t. CH_2Cl_2, $BF_3{\cdot}Et_2O$ or TMSOTf as promoter, 20 h) to afford glycoside **7** or **8** in the yield of 70% and 65% respectively. Further glycosylation with **6** in the presence of $BF_3{\cdot}Et_2O$ gave corresponding dimers **9** or **10** in the yield of 42% or 40% respectively.

The aforementioned facts indicated that glucose type nitrate, the precursor of *N*-acetyllactosamine obtained from the azidonitration of lactal could be purified by glyco-

sylation according to the reactivity difference of this compound and its mannose type isomer and was used in the synthesis of spacer-armed *N*-acetyllactosamine and their dimers.

Treatment of **7**, **8**, **9** and **10** with thioacetic acid for 36 h at room temperature gave the protected spacer-armed *N*-acetyllactosamine and their dimers in the yield of 60%~85%, which then were deacetylated with CH_3ONa/CH_3OH to afford the target compounds **15**, **16**, **17** and **18** which will be used in the studies on anti-metastasis. All the first reported compounds were confirmed by related spectral analyses, such as 1D and 2D NMR, MS, and elemental analysis.





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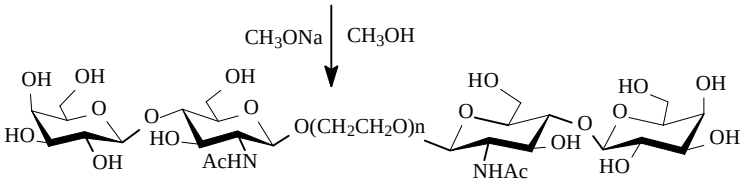
14 n =3



17 n =2
18 n =3

Acknowledgments

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References and Notes

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4. Q. Li, H. Li, B. Su, X. B. Meng, M. S. Cai, Z. J. Li, *J Peking Univ(Health Sci)*, **2001**, *33*, 270.
5. Physical data of the target compounds **15**, **16**, **17** and **18**:
Compound 15: $[\alpha]_D$ -83.9 (*c* 0.62, H_2O). ^{1}HNMR (D_2O, δppm): 4.64 (d, 1H, $J_{1,2}$=8.10Hz, H-1), 4.52 (d, 1H, $J_{1',2'}$=7.50Hz, H-1′), 4.06~3.69 (m, 20H, H-2, 3, 4, 5, 6a, 6b, H-2′, 3′, 4′, 5′, 6a′, 6b′, -CH_2O-), 2.09 (s, 3H, -NHCOCH_3). ^{13}CNMR (D_2O, δppm) 171.5 (-NHCO-), 99.9 (C-1′), 97.9 (C-1), 75.6 (C-4), 72.4, 71.8, 69.6, 69.5, 68.8, 67.9, 66.6, 66.0, 57.4 (9C, C-3, C-5, C-2′, C-3′, C-5′, -CH_2O-), 65.6 (C-4′), 58.0 (C-6), 57.2 (C-6′), 52.1 (C-2), 19.2 (CH_3CONH-).
Compound 16: $[\alpha]_D$ -105.3 (*c* 0.76, H_2O). ^{1}HNMR (D_2O, δppm) 4.58 (d, 1H, $J_{1,2}$=7.80Hz, H-1), 4.46 (d, 1H, $J_{1',2}$=7.50Hz, H-1′), 3.96~3.64 (m, 24H, H-2, 3, 4, 5, 6a, 6b, H-2′, 3′, 4′, 5′, 6a′, 6b′, -CH_2O-), 2.03 (s, 3H, -NHCOCH_3). ^{13}CNMR (D_2O, δppm) 171.2 (-NHCO-), 99.3 (C-1′), 97.5 (C-1), 75.7 (C-4), 72.7, 71.9, 70.7, 69.8, 68.5, 68.0, 66.6, 66.3, 64.9, 57.8, 57.3 (11C, C-3, C-5, C-2′, C-3′, C-5′, -CH_2O-), 64.9 (C-4′), 57.8 (C-6), 57.1 (C-6′), 52.3 (C-2), 19.7 ($\underline{C}H_3$CONH-).
Compound 17: $[\alpha]_D$ +26.7 (*c* 1.20, H_2O). ^{1}HNMR (CD_3OD, δppm) 4.51 (d, 1H, $J_{1,2}$=8.00Hz, H-1), 4.38 (d, 1H, $J_{1',2}$=7.50Hz, H-1′), 3.97~3.48 (m, 16H, H-2, 3, 4, 5, 6a, 6b, H-2′, 3′, 4′, 5′, 6a′, 6b′, -CH_2O-), 2.02 (s, 3H, -NHCOCH_3). ^{13}CNMR (CD_3OD, δppm) 174.0 (-NHCO-), 105.1 (C-1′), 102.6 (C-1), 81.6 (C-4), 77.2 (C-5′), 74.9 (C-3′), 72.6 (C-2′), 72.3, 71.5, 71.2, 70.4 (4C, C-3, C-5, -CH_2O-), 68.2 (C-4′), 62.5 (C-6), 62.0 (C-6′), 55.1(C-2), 22.5 (CH_3CONH-).
Compound 18: $[\alpha]_D$ +21.7 (*c* 0.92, H_2O). ^{1}HNMR (CD_3OD, δppm) 4.53 (d, 1H, $J_{1,2}$= 8.00 Hz, H-1), 4.39 (d, 1H, $J_{1',2}$=7.50Hz, H-1′), 3.96~3.54 (m, 18H, H-2, 3, 4, 5, 6a, 6b, H-2′, 3′, 4′, 5′, 6a′, 6b′, -CH_2O-), 1.99 (s, 3H, -NHCOCH_3). ^{13}CNMR (CD_3OD, δppm) 174.2 (-NHCO-), 104.8 (C-1′), 102.6 (C-1), 81.0 (C-4), 76.9 (C-5′), 74.5 (C-3′), 72.5 (C-2′), 72.2, 71.4, 71.1, 70.1, 69.9 (5C, C-3, C-5, -CH_2O-), 68.1 (C-4′), 62.4 (C-6), 61.8 (C-6′), 56.6 (C-2), 23.2 (CH_3CONH-).

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