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Glycosylation with Sialic Acid at HO-3 of Three Different O-Protected D-Galactosides in Acetonitrile/Dichloromethane at Low Temperature

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Key Words: Sialic acid; glycosylation; different acceptors; α-selectivity; low temperature.

Summary: Three different O-protected D-galactosides have been compared as acceptors in α-sialoside synthesis using glycosyl donor **1**, methylsulfenyl triflate as promoter, and acetonitrile/dichloromethane as solvent at-70 °C. The 6-O-benzylated acceptor **2** was the most efficient, the α(2-3) sialoside **5** was obtained in 39% isolated yield.

Chemical synthesis of sialosides is a progressing area in carbohydrate chemistry, the subject has recently been reviewed[2]. We have recently submitted for publication[3] the effect of temperature in the glycosylation with the Neu5Ac derivative **1** of the 6-OH position at galactose. When **1** was activated with methylsulfenyl triflate in various nitriles the α-selectivity increased at lower temperatures and the proportion of competing elimination product 7 decreased.

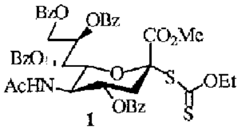
We are now reporting an investigation of the glycosylation with **1** in the 3-position of D-galactose. A Neu5Acα(2-3)Gal unit thus formed is an important structural element of gangliosides and glycoproteins. Three different glycosylacceptors **2**,**3** and **4** were investigated with **1** as glycosyl donor using the conditions producing the highest α-selectivity in the formation of α(2-6) bonds reported by us[3].

A mixture of glycosyl acceptor **2**[4], **3**[5] or **4**[6] (0.1 mmol), glycosyl donor **1** (0.12 mmol), powdered molecular sieves (3 Å, 200 mg) in acetonitrile/dichloromethane (3:2, 3 mL) was stirred at room temperature for 1 h, then silver triflate (0.12 mmol) was added, the mixture was flushed with dry nitrogen, sealed and cooled to -70 °C. Methylsulfenyl bromide[7] (0.12 mmol, 4.7 M) in 1,2-dichloroethane was then injected in one portion. After 1 h (tlc showed that **1** was consumed) diisopropylamine (25 µL) was injected and stirring was continued for 1h, and the reaction mixture was then filtered, concentrated, and purified by silica gel chromatography. The yields were as follows:

Acceptor	Products[a] and yields		
2	**5** (39 %)	**6** (9 %)	**7** (17 %)
3	**8** (15 %)	**9** [b]	**7** (31 %)
4	**10** (18 %)	**11** [b]	**7** (17%)

[a] Analytical data see note 8. [b] These compounds have not been isolated, but they are indicated to be present in the range of 2 - 5 %, by NMR from unresolved fractions.

As seen from above, among the three tested glycosyl acceptors, **2** was the most efficient for the formation of a Neu5Acα(2-3)Gal unit. Condensation of **1** with **2** gave α-sialoside **5** in 39 % isolated yield, which is among the best reported so far[9].



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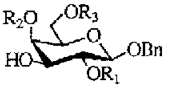
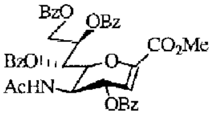


2 R_1= H, R_2= H, R_3= Bn
3 R_1= Bz, R_2= H, R_3= Bz
4 R_1= H, R_2, R_3= PhCH



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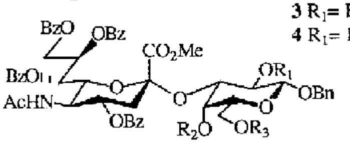
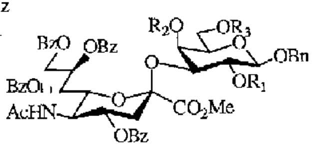


5 R_1= H, R_2= H, R_3= Bn
8 R_1= Bz, R_2= H, R_3= Bz
10 R_1= H; R_2, R_3= PhCH



6 R_1= H, R_2= H, R_3= Bn
9 R_1= Bz, R_2= H, R_3= Bz
11 R_1= H; R_2, R_3= PhCH

Acknowledgment

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References and Notes

1. Present address HL: Symbicom AB, IDEON, S-223 70 Lund, Sweden.
2. K. Okamato, and T. Goto, *Tetrahedron*, **1990**,*46*, 5835-5857.
3. W. Birberg, and H. Lönn, *Tetrahedron Lett.*, in press.
4. S. David, A. Thieffry, and A. Veyrières, *J. Chem. Soc. Perkin Trans 1*, **1981**, 6, 1796-1801.
5. Prepared from benzyl β-D-galactopyranoside: 1. Dimethoxypropane/HOTs. 2. Benzoylchloride in pyridine. 3. HOAc-H_2O, 80 °C. Analytical data for **3**: $[\alpha]_D$ -55° (c 0.5, chloroform); ^{13}C NMR ($CDCl_3$,125MHz) ∂ 62.9 (C-6), 68.6, 70.1, 72.2, 72.8, 74.3, (C-2-5,OCH_2Ph), 98.8 (C-1), 166.5, 167.2 (PhCO).
6. J. R. Turvey, and T.P. Williams, *J. Chem. Soc.*, **1962**, 2119-2122.
7. F. Dasgupta, and P. J. Garegg, *Carbohydr. Res.*, **1988**, *177*, C13-C17.
8. Analytical data for **5**: $[\alpha]_D$ +44° (c 0.5, chloroform); ^{13}C NMR ($CDCl_3$, 125 MHz) ∂ 23.2 ($NHCOCH_3$), 37.8 (C-3'), 50.4 (C-5') 53.0 (OCH_3), 63.2, (C-9'), 68.5, 68.6, 69.0, 69.3, 69.5, 70.2, 70.7, 73.0, 73.2, 77.1 (C-2-6,4',6'-8'; OCH_2Ph), 98.1 (C-2'), 102.3(C-1), 168.3 (C-1',$J_{C-1',H-3'ax}$ 7.5 Hz determined as described by: H. Hori, T. Nakajima, Y. Nishida, H. Ohrui, and H. Meguro, *Tetrahedron Lett.*, **1988**, *29(48)*, 6317-6320; M. F. Czarniecki, and E. R. Thornton, *J. Amer. Chem. Soc.*, **1977**, *99*, 8273-8279).

   Analytical data for **8**: $[\alpha]_D$ +30° (c 0.2, chloroform); ^{13}C NMR ($CDCl_3$, 125 MHz) ∂ 23.1 ($NHCOCH_3$), 37.1 (C-3'), 49.7 (C-5'), 53.0 (OCH_3), 63.2, 63,3 (C-6,9'), 68.1, 68.4, 69.4, 69.6, 70.0, 70.4, 72.1, 73.2, 74.0 (C-2-5,4',6'-8'; OCH_2Ph), 98.5 (C-2'), 99.6 (C-1), 168.2 (C-1', $J_{C-1',H-3'ax}$ 6.7 Hz).

   Analytical data for **10**: $[\alpha]_D$ +34° (c 0.2, chloroform); ^{13}C NMR ($CDCl_3$, 125 MHz) ∂ 23.3 ($NHCOCH_3$), 38.5 (C-3'), 50.7 (C-5'), 52.9 (OCH_3), 63.2 (C-9'), 66.4, 68.6, 68.7, 68.7, 69.3, 69.9, 70.4, 72.8, 74.6, 75.5 (C-2-6,4',6'-8', OCH_2Ph), 97.8 (C-2'), 101.0, 101.9 (C-1, CHPh), 168.3(C-1', $J_{C-1',H-3'ax}$ 6.2 Hz).
9. A. Marra, and P. Sinaÿ, *Carbohydr. Res.*, **1990**, *195*, 303-308, and references therein.

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