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8-O-Sialylation of Derivatives of Neuraminic Acid 1,7-Lactone Unusual Stereoselectivity

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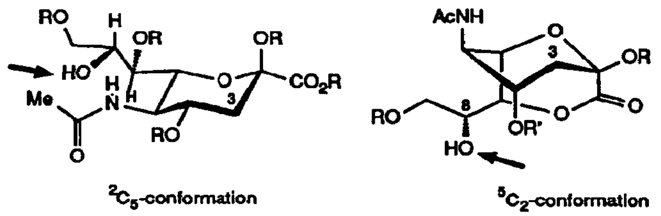
Abstract: Reaction of 8-O-unprotected Neu5Ac-1,7-lactone derivatives **3a-c**, which were readily obtained from Neu5Ac, gave with sialyl donor **4** exclusively β(2-8)-linked disaccharides **5a-c** in good yields. The lactone ring in disaccharides **5a-c** was readily cleaved, thus **5c** afforded Neu5Acβ(2-8)Neu5Ac derivative **6**.

The disaccharide sequence Neu5Acα(2-8)Neu5Ac is a principal constituent of a number of glycoconjugates including a series of gangliosides. They were found to play an important role in numerous biological phenomena being, for example, tumor-associated antigens[1,2] or receptors for bacterial toxins and viruses[2,3].

Successful syntheses of this disaccharide linkage were based on the use of sialyl donors bearing at C-3 an additional function, namely OH[4] or SPh[5], which can control the stereochemistry of substitution at the anomeric center and prevent elimination. On the other hand, attempts to prepare the target disaccharide directly, using conventional nonmodified sialyl donors such as thioglycoside[6] or phosphite[7,8], gave thus far only very low yields.

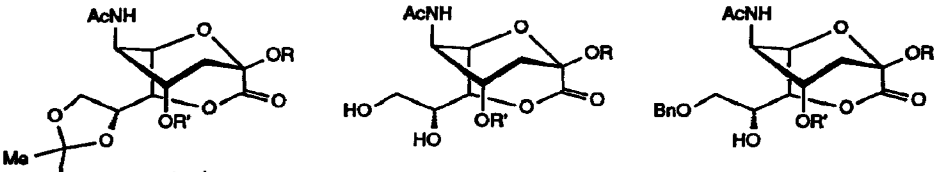
Scheme 1



It was assumed that the low reactivity of the 8-OH group in the derivatives of Neu5Ac possessing $^2C_5$ conformation (Scheme 1, see arrow) is caused by its interaction with the 5-acetamido group (or, alternatively, with the ring oxygen) via the formation of hydrogen bonds. In order to avoid this undesirable interaction, we have decided to apply derivatives of the Neu5Ac 1,7-lactone[9] as sialyl acceptors. In these derivatives, due to the rigid $^5C_2$ conformation, the 8-OH group and the 5-acetamido group are remote, thus preventing the interaction between them.

Treatment of Neu5Ac with 2,2-dimethoxypropane in the presence of p-TsOH in DMF afforded the 8,9-O-isopropylidene derivative which was subjected, without isolation, to lactonisation with pivaloyl chloride in pyridine to give the lactone **1a** in 67% yield (Scheme 2). Deisopropylidenation of **1a** (80% AcOH, 60°C → 89% of **2a**) followed by selective Bu_2SnO-mediated 9-O-benzylation with benzyl bromide afforded the acceptor **3a**[10] in 62% yield.

Scheme 2

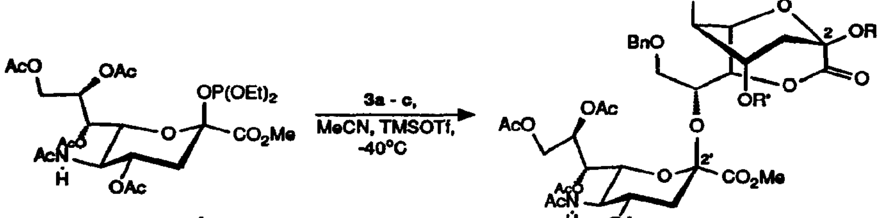


1a-d **2a-c** **3a-c**

a R = R' = Piv; **b** R = Me, R' = Piv; **c** R = Me, R' = Ac; **d** R = Me, R' = H

Sialylation of **3a** with the phosphite **4**[11,12] under the conditions (MeCN, -40°C, 0.1 equivalents of TMSOTf), which were shown to provide a high degree of α-stereoselectivity[11,12], gave unexpectedly 68% of the β-linked disaccharide **5a**[10] (Scheme 3). The formation of the corresponding α-anomer was not detected. The known empirical ^{1}H-NMR rules for the assignment of the anomeric configuration of Neu5Ac glycosides[6], namely the chemical shift of H-4' (5.31 ppm), the $J_{7',8'}$ value (4.6 Hz) and the Δδ/H 9'a - H 9'b/ value (0.89 ppm) clearly indicated the β-configuration for the glycosylating Neu5Ac residue in **5a**. The near to 0 $^3J_{C'1,H\,3'a}$ value in the ^{13}C NMR spectrum of **5a** also confirmed the β-configuration[13].

Scheme 3

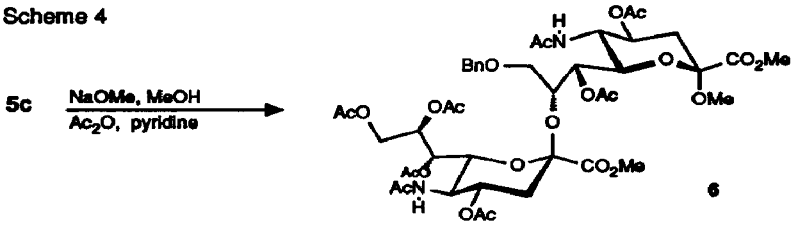


4 **5a-c**

The unusual β-selectivity in the sialylation could be due to the presence of two sterically demanding pivaloyl groups in **3a**. In order to examine the effect of protective groups, the acceptors **3b,c** were synthesized in which the pivaloyl groups were successively replaced by methyl and acetyl groups. **3b,c** were prepared starting from methyl N-acetyl-β-neuraminoside[14] which was subjected to acetonation followed by lactonisation with pivaloyl chloride in pyridine to give the lactones **1b** and **1d** in 51 and 21% yields, respectively. The latter compound is more conveniently obtained using as lactonisating agent DCC in the presence of catalytic amounts of DMAP. The yield of **1d** was in this case 65%. Conventional acetylation of **1d** with Ac_2O-pyridine afforded **1c**. Deisopropylidenation of **1b,c** and subsequent regioselective 9-O-benzylation of the diols **2b,c** obtained gave the target acceptors **3b,c**[10] in 45 and 48% yields, respectively. Sialylation of **3b,c** with **4** resulted again in the formation of β-disaccharides **5b,c**[10] in 51 and 54% yields, respectively. These results allow to conclude that not the character of protective groups in the acceptor but the bicyclic lactone structure itself determines the observed β-selectivity in the sialylation reaction.

The lactones 5 could easily be converted into the corresponding methyl esters on treatment with methanolic sodium methoxide. For example, reaction of 5c with sodium methanolate in methanol followed by acetylation with acetic anhydride in pyridine afforded 61% of the disaccharide 6[10] (Scheme 4). The described highly stereoselective synthesis of Neu5Acβ(2-8)Neu5Ac disaccharides could find useful application in the preparation of unnatural analogues of gangliosides.

Scheme 4



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10. **3a**: $[\alpha]_D$ + 19.5° (c = 1, chloroform). ¹H-NMR (250 MHz, $CDCl_3$, δ ppm, J Hz): 1.19, 1.21 (2 s, 18 H, 2 Piv), 2.04 (s, 3 H, NAc), 2.18 (dd, 1 H, $J_{3a,4}$ = 3.8 Hz, $J_{3a,3e}$ = 14.6 Hz, 3a-H), 2.25 (dd, 1 H, $J_{3e,4}$ = 1.7 Hz, 3e-H), 2.97 (br.s, 1 H, OH), 3.73 (dd, 1 H, $J_{9a,8}$ = 3.5 Hz, $J_{9a,9b}$ = 9.9 Hz, 9a-H), 3.89 (dd, 1 H, $J_{9b,8}$ = 3.4 Hz, 9b-H), 4.14 (br.d, 1 H, $J_{5,NH}$ = 8.3 Hz, 5-H), 4.26 (m, 1 H, 8-H), 4.48 (d, 1 H, $J_{7,8}$ = 8.2 Hz, 7-H), 4.58 (d, 1 H, J = 11.8, PhCH_2), 4.61 (d, 1 H, PhCH_2), 4.70 (s, 1 H, 6-H), 5.13 (m, 1 H, 4-H), 6.27 (d, 1 H, NH), 7.30-7.38 (m, 5 H, aromatic). **3b**: $[\alpha]_D$ + 48.9° (c = 1, chloroform). ¹H-NMR (selected data): 1.17 (s, 9 H, Piv), 2.04 (s, 3 H, NAc), 3.36 (s, 3 H, OMe), 4.41 (d, 1 H, $J_{7,8}$ = 9.0 Hz, 7-H), 4.58 (s, 2 H, PhCH_2), 4.69 (s, 1 H, 6-H), 5.11 (m, 1 H, 4-H). **3c**: $[\alpha]_D$ + 50.8° (c = 0.7, chloroform). ¹H-NMR (selected data): 2.02 (s, 6 H, OAc, NAc), 3.34 (s, 3 H, OMe), 4.41 (d, 1 H, $J_{7,8}$ = 9.0 Hz, 7-H), 4.60 (s, 2 H, PhCH_2), 4.67 (s, 1 H, 6-H), 5.08 (m, 1 H, 4-H). **5a**: $[\alpha]_D$ + 13.2° (c = 1, chloroform). ¹H-NMR: 1.12, 1.24 (2 s, 18 H, 2 Piv), 1.79 (dd, 1 H, $J_{3'a,4'}$ = 12.5 Hz, $J_{3'a,3'e}$ = 13.2 Hz, 3'a-H), 1.89, 1.98, 2.00 x 2, 2.10, 2.14 (5 s, 18 H, 4 OAc, 2 NAc), 2.20 (dd, 1 H, $J_{3a,4}$ = 4.0 Hz, $J_{3a,3e}$ = 15.4 Hz, 3a-H), 2.27 (dd, 1 H, $J_{3e,4}$ = 2.6 Hz, 3e-H), 2.62 (dd, 1 H, $J_{3'e,4'}$ = 4.8, 3'e-H), 3.34 (dd, 1 H, $J_{9a,8}$ = 4.3 Hz, $J_{9a,9b}$ = 11.3 Hz, 9a-H), 3.45 (dd, 1 H, $J_{9b,8}$ = 2.8 Hz, 9b-H), 3.61 (s, 3 H, OMe), 4.02 (dd, 1 H, $J_{9'a,8}$ = 7.7 Hz, $J_{9'a,9'b}$ = 12.3 Hz, 9'a-H), 4.07 (br.d, 1 H, $J_{5,NH}$ = 7.6 Hz, 5-H), 4.16 (ddd, 1 H, $J_{4',5'}$ ~ $J_{5',6'}$ ~ $J_{5',NH'}$ ~ 10.4 Hz, 5'-H), 4.39 (dd, 1 H, $J_{6',7'}$ = 1.9 Hz, 6'-H), 4.44 (s, 2 H, PhCH_2), 4.66

(ddd, 1 H, 8-H), 4.90 (m, 3 H, 6,7,9'b-H), 5.18 (m, 1 H, 4-H), 5.31 (ddd, 1 H, 4'-H), 5.43 (dd, 1 H, $J_{7',8'}$ = 4.6 Hz, 7'-H), 5.56 (ddd, 1 H, 8'-H), 6.27 (d, 1 H, NH), 6.51 (d, 1 H, NH'), 7.30-7.40 (m, 5 H, aromatic). **5b**: $[\alpha]_D$ + 16.8° (c = 2, chloroform). ^{1}H-NMR (selected data): 1.17 (s, 9 H, Piv), 1.83 (dd, 1 H, $J_{3'a,4'}$ = 12.0 Hz, $J_{3'a,3'e}$ = 13.5 Hz, 3'a-H), 1.89, 1.95, 2.01, 2.04, 2.09, 2.14 (6 s, 18 H, 4 OAc, 2 NAc), 2.66 (dd, 1 H, $J_{3'e,4'}$ = 4.8 Hz, 3'e-H), 3.37 (s, 3 H, OMe), 3.60 (s, 3 H, CO_2Me), 4.10 (dd, 1 H, $J_{9'a,8'}$ = 9.1 Hz, $J_{9'a,9'b}$ = 12.1 Hz, 9'a-H), 4.46 (d, 1 H, J = 12.0 Hz, PhCH_2), 4.55 (d, 1 H, PhCH_2), 4.95 (dd, 1 H, $J_{9'b,8'}$ = 2.2 Hz, 9'b-H), 5.34 (t, 1 H, $J_{7',6'}$ ~ $J_{7',8'}$ ~ 2.1 Hz, 7'-H), 5.37 (ddd, 1 H, $J_{4',5'}$ = 10.0, 4'-H). **5c**: $[\alpha]_D$ + 20.4° (c = 2, chloroform). ^{1}H-NMR (selected data): 1.83 (dd, 1 H, $J_{3'a,4'}$ = 11.7 Hz, $J_{3'a,3'e}$ = 13.5 Hz, 3'a-H), 1.88, 1.97, 2.01, 2.03, 2.06 x 2, 2.14 (6 s, 21 H, 5 OAc, 2 NAc), 2.64 (dd, 1 H, $J_{3'e,4'}$ = 4.9 Hz, 3'e-H), 3.38 (s, 3 H, OMe), 3.64 (s, 3 H, CO_2*Me*), 4.10 (dd, 1 H, $J_{9'a,8'}$ = 9.0 Hz, $J_{9'a,9'b}$ = 12.4 Hz, 9'a-H), 4.48 (d, 1 H, J = 12.0 Hz, PhCH_2), 4.54 (d, 1 H, PhCH_2), 4.92 (dd, 1 H, $J_{9'b,8'}$ = 2.4 Hz, 9'b-H), 5.34 (ddd, 1 H, $J_{4',5'}$ = 10.0 Hz, 4'-H), 5.35 (t, 1 H, $J_{7',6'}$ ~ $J_{7',8'}$ ~ 2.4 Hz, 7'-H). **6**: $[\alpha]_D$ - 15.2° (c = 2, chloroform), 1.79 (dd, 1 H, $J_{3a,4}$ = 11.8 Hz, $J_{3a,3e}$ = 13.5 Hz, 3a-H), 1.94 (t, 1 H, $J_{3'a,4'}$ ~ $J_{3'a,3'e}$ ~ 13.3 Hz, 3'a-H), 1.84, 1.90, 2.02 x 2, 2.06, 2.12, 2.15, 2.18 (7 s, 24 H, 6 OAc, 2 NAc), 2.49 (dd, 1 H, $J_{3'e,4'}$ = 5.0 Hz, 3'e-H), 2.57 (dd, 1 H, $J_{3e,4}$ = 4.8 Hz, 3e-H), 3.24 (s, 3 H, OMe), 3.44, 3.75 (2 s, 6 H, 2 CO_2Me), 3.45 (dd, 1 H, $J_{9a,8}$ = 7.4 Hz, $J_{9a,9b}$ = 11.0 Hz, 9a-H), 4.09 (dd, 1 H, $J_{9'a,8'}$ = 8.5 Hz, $J_{9'a,9'b}$ = 12.1 Hz, 9'a-H), 4.11 (ddd, 1 H, $J_{5,6}$ ~ $J_{5,4}$ ~ $J_{5,NH}$ ~ 10.0 Hz, 5-H), 4.19 (m, 3 H, 5',6,9b-H), 4.38 (d, 1 H, J = 12.0 Hz, PhCH_2), 4.45 (d, 1 H, PhCH_2), 4.49 (dd, 1 H, $J_{6',5'}$ = 10.5 Hz, $J_{6',7'}$ = 2.5 Hz, 6'-H), 4.52 (m, 1 H, 8-H), 4.99 (dd, 1 H, $J_{9'b,8'}$ = 2.4 Hz, 9'b-H), 5.09 (ddd, 1 H, 4'-H), 5.22 (ddd, 1 H, 4-H), 5.30 (ddd, 1 H, 8'-H), 5.35 (t, 1 H, $J_{7',8'}$ = 2.5 Hz, 7'-H), 5.47 (dd, 1 H, $J_{7,6}$ = 1.6 Hz, $J_{7,8}$ = 3.1 Hz, 7-H), 6.19 (d, 1 H, NH), 6.36 (br.d, 1 H, NH'), 7.23-7.30 (m, 5 H, aromatic).

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