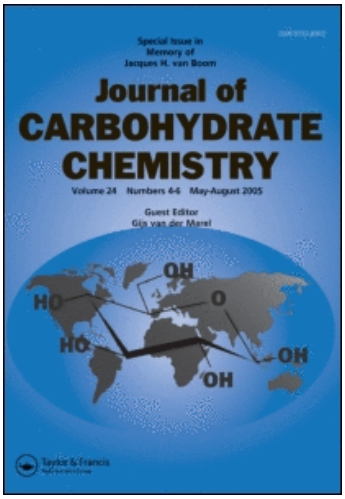

Journal of Carbohydrate Chemistry

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

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To cite this Article Hasegawa, Akira , Nagahama, Takao , Ohki, Hitoshi , Hotta, Kenji , Ishida, Hideharu and Kiso, Makoto(1991) 'Communication: Synthetic Studies on Sialoglycoconjugates 25: Reactivity of Glycosyl Promoters in α-Glycosylation of N-Acetyl-Neuraminic Acid with the Primary and Secondary Hydroxyl Groups in the Suitably Protected Galactose and Lactose Derivatives', Journal of Carbohydrate Chemistry, 10: 3, 493 — 498

To link to this Article: DOI: 10.1080/07328309108543925

URL: http://dx.doi.org/10.1080/07328309108543925

J. CARBOHYDRATE CHEMISTRY, 10(3), 493-498 (1991)

COMMUNICATION

SYNTHETIC STUDIES ON SIALOGLYCOCONJUGATES 25: REACTIVITY OF GLYCOSYL PROMOTERS IN α-GLYCOSYLATION OF N-ACETYL-NEURAMINIC ACID WITH THE PRIMARY AND SECONDARY HYDROXYL GROUPS IN THE SUITABLY PROTECTED GALACTOSE AND LACTOSE DERIVATIVES

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Received December 20, 1990 - Final form February 28, 1991

Development of an efficient α-glycoside synthesis of sialic acids is critically significant for the syntheses of sialoglycoconjugates, especially gangliosides which carry important biological functions[1] in biological systems. Previously, we demonstrated[2] a new α-glycosylation of sialic acids by use of dimethyl(methylthio)sulfonium triflate (DMTST)[3] as the glycosyl promoter, the suitably protected glycosyl acceptors and the methyl 2-thioglycoside 1 of N-acetylneuraminic acid (Neu5Ac) as the donor in acetonitrile under kinetically controlled conditions, and accomplished[4] the syntheses of a variety of gangliosides and their analogs.

Recently, N-iodosuccinimide (NIS)-trifluoromethanesulfonic acid (TfOH) was introduced[5,6] as a powerful glycosyl promoter for the thioglycosides and n-pentenyl glycosides as the donors. Now we report here on reactivity of DMTST and NIS in regio- and α-stereoselective glycosylation of Neu5Ac with the suitably protected galactose and lactose derivatives. Methyl (methyl 5-acetamido-4,7,8,9-tetra-O-acetyl-3,5-dideoxy-D-glycero-D-galacto-2-nonulopyranosid)onate[4b] (1) as the donor, and 2-(trimethylsilyl)ethyl 6-O-benzoyl-ß-D-galactopyranoside[7] (2), 2-(trimethylsilyl)ethyl 3-O-benzoyl-ß-D-galactopyranoside[7] (3), 2-(trimethylsilyl)ethyl 3-O-benzyl-ß-D-galacto-

pyranoside[7] (4), and 2-(trimethylsilyl)ethyl O-(2,6-di-O-benzyl-ß-D-galacto-pyranosyl)-(1-4)-2,3,6-tri-O-benzyl-ß-D-glucopyranoside[8] (5) as the suitably protected glycosyl acceptors were selected for this purpose.

The results in Table show that, when NIS-TfOH is applied as the promoter in acetonitrile, less reactive secondary hydroxyl groups (entries 2 and 12) and a hindered primary hydroxyl group (entry 5) are glycosylated regio- and α-stereoselectively in high yields, respectively. However with a less hindered primary hydroxyl group in acceptor 4 (entry 8) an anomeric mixture of disaccharides 9 and 10 (α : ß = 2 : 1) results. A similar regio- and α-stereoselective glycosylation (entries 1, 4, 7, and 11) has been observed in DMTST-promoted reactions in acetonitrile, indicating an analogous reaction mechanism of both of the thiophilic promoters. On the contrary, when dichloromethane (entries 6 and 9) in the place of acetonitrile is used as solvent, substantial amounts of the ß-glycoside are formed, and the rate (α:ß = 32:50) of thermodynamically stable ß-glycoside of Neu5Ac is increased with rise of the reaction temperature (entry 10).

A reasonable reaction mechanism for affording the thermodynamically unfavorable α-glycoside of Neu5Ac stereoselectively, by use of the methyl 2-thioglycoside 1 of Neu5Ac and the thiophilic promoters in acetonitrile, is rationalised as follows (Scheme); when the donor 1 is treated with the promoters in acetonitrile at low temperature, acetonitrium ions[9,10] (d and e) are formed, via intermediates a, b, and c, and the equilibrium lies so far to ß-acetonitrium ion d, that S_N2 displacement undergoes at the anomeric center, to form the α-glycoside of Neu5Ac. In this respect it has been demonstrated that use of acetonitrile as solvent in low-temperature glycosylation of the methyl 2-thioglycoside of Neu5Ac using the thiophilic glycosyl promoters leads to enhanced α-selectivity.

On the other hand, the reactive alcohol (entries 7 and 8) can attack the intermediates a and c or b and c, along with d and e, consequently the increased amount of ß-glycoside of Neu5Ac is formed. In addition, using dichloromethane as the solvent (entries 6, 9, and 10), nucleophile will react with the intermediates b and c, to give an anomeric mixture of glycoside non-stereoselectively.

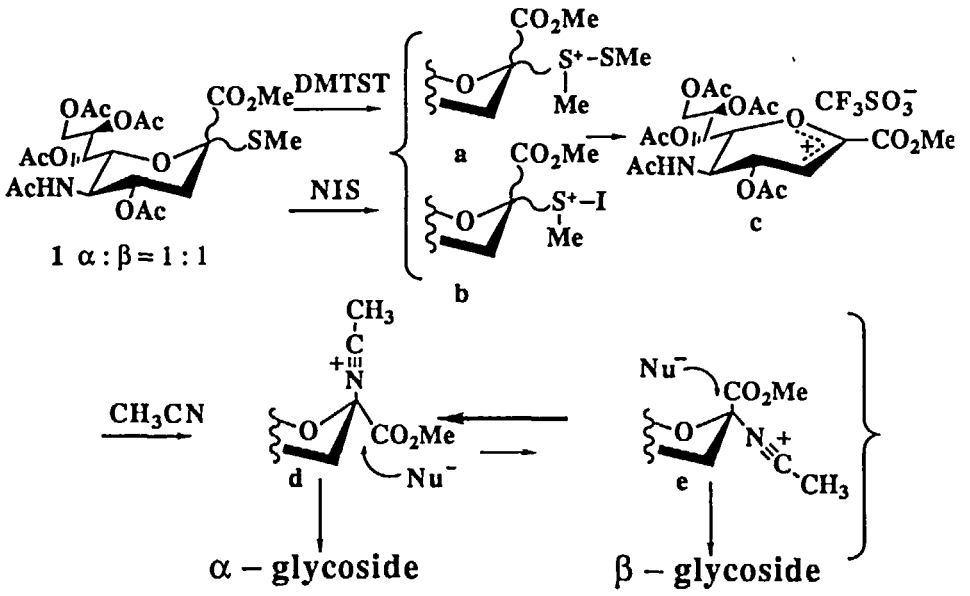
In conclusion, it is noteworthy that regio- and α-stereoselective glycosylation of Neu5Ac with the sterically hindered and less reactive hydroxyl groups in galactose and lactose derivatives was achieved in high yield by using an anomeric mixture (α:ß = 1:1) of the methyl 2-thioglycoside 1 of Neu5Ac and the suitably protected acceptors, with the thiophilic promoters (NIS and DMTST) in acetonitrile under kinetically controlled

Table

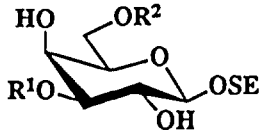
NIS-TfOH and DMTST Promoted Glycosylation[a] of Neu5Ac Using the Methyl 2-Thioglycoside 1 of Neu5Ac

Entry	Acceptor	Promoter	Solvent	Product	Yield[b](%)	
					α	β
1[c]	2	DMTST	CH_3CN	**6**	52	0
2	2	NIS	CH_3CN	**6**	61	0
3	2	NIS	CH_2Cl_2	**6**	16	0
4[c]	3	DMTST	CH_3CN	**7**	70	0
5	3	NIS	CH_3CN	**7**	59	0
6	3	NIS	CH_2Cl_2	**7,8**	49	25
7	4	DMTST	CH_3CN	**9,10**	50	15
8	4	NIS	CH_3CN	**9,10**	51	26
9	4	NIS	CH_2Cl_2	**9,10**	43	45
10	4	NIS	CH_2Cl_2	**9,10**	32	50
11	5	DMTST	CH_3CN	**11**	30	8
12	5	NIS	CH_3CN	**11**	59	10

[a] Reactions were performed at -40 °C, except entry 10 (-20 °C).
[b] Isolated yields.
[c] Ref. 2b.



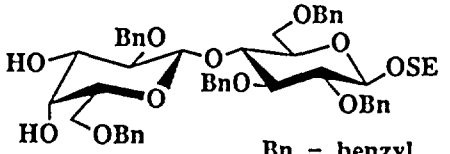
Scheme



2 R^1 = H , R^2 = Bz

3 R^1 = Bz , R^2 = H

4 R^1 = Bn , R^2 = H

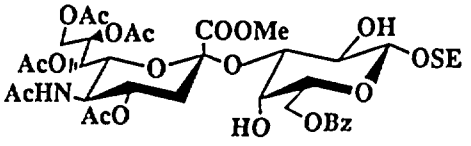


5

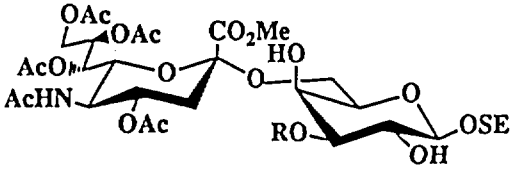
Bn = benzyl

Bz = benzoyl

SE = 2-(trimethylsilyl)ethyl

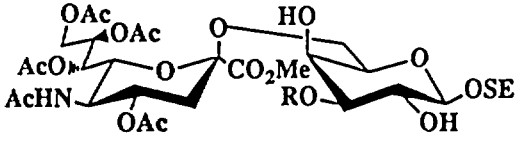


6[7]



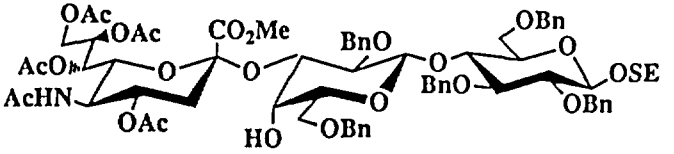
7[7] R = Bz

9[11] R = Bn



8 R = Bz

10 R = Bn



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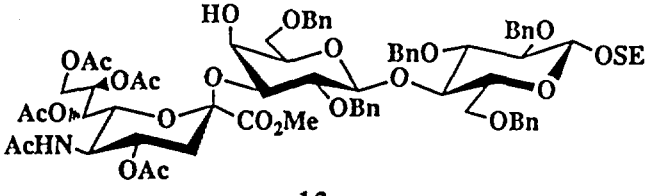

12

Figure

conditions. On efficacy of the glycosyl promoters, NIS-TfOH seems to be superior to DMTST in the case of glycosylation of Neu5Ac with the less-reactive hydroxyl acceptors. Compounds 6, 7, and 11 obtained here in good yields, have been widely used[4,7,11] for the ganglioside syntheses.

The new compounds[12] synthesized gave elemental analyses, IR and NMR data in agreement with structures assigned.

General glycosylation procedure:

A) DMTST-promoted glycosylation

To a solution of donor (5.2 mmol) and acceptor (2.6 mmol) in dry acetonitrile (20 mL) was added powdered molecular sieves 3A (3 g), and the mixture was stirred for 5 h at room temperature, and then cooled to -40 °C. To the cooled mixture was added DMTST (15 mmol), and the mixture was stirred for 17 h at -15 °C. The precipitate was filtered off, and washed with dichloromethane. The filtrate and washings were combined, and successively washed with M sodium carbonate and water, dried (Na_2SO_4), and concentrated. The product was purified by silica gel column chromatography.

B) NIS-TfOH-promoted glycosylation

To a solution of donor (3.2 mmol) and acceptor (1.9 mmol) in dry acetonitrile (or dichloromethane)(15 mL) was added powdered molecular sieves 3A (2.3 g), and the mixture was stirred for 5 h at room temperature, and then cooled to -40 °C. To the cooled mixture were added NIS (6.4 mmol) and TfOH (0.64 mmol), and the mixture was stirred for 2 h at -40 °C. A similar work-up as described above gave the product.

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12. Specific rotations were determined with a Union PM-201 polarimeter at 25 °C in chloroform. ^{1}H NMR spectra were recorded at 270 MHz with a JEOL JNM-GX270 spectrometer. Peracetylated 8: $[\alpha]_D$ -14.7°; ^{1}H NMR ($CDCl_3$) Gal unit δ 0.91 (m, 2H, $Me_3Si\underline{CH_2}CH_2$), 4.57 (d, 1H, $J_{1,2}$ = 7.7 Hz, H-1); Neu5Ac unit δ 1.81 (s, 3H, AcN), 2.41 (dd, 1H, J_{gem} = 12.9 Hz, $J_{3e,4}$ = 4.9 Hz, H-3e), 3.80 (s, 3H, MeO), 4.69 (dd, 1H, $J_{8,9}$ = 2.4 Hz, J_{gem} = 12.5 Hz, H-9), 5.03-5.40 (m, 3H, H-4,7,8). 10: $[\alpha]_D$ -10.5°; ^{1}H NMR ($CDCl_3$) Gal unit δ 0.98 (m, 2H, $Me_3Si\underline{CH_2}CH_2$), 2.41 (d, 1H, $J_{4,OH}$ = 1.8 Hz, 4-OH), 3.21 (d, 1H, $J_{2,OH}$ = 2.9 Hz, 2-OH), 4.22 (d, 1H, $J_{1,2}$ = 7.7 Hz, H-1), and 7.35-7.50 (m, 5H, Ph); Neu5Ac unit δ 1.84 (s, 3H, AcN), 2.45 (dd, 1H, J_{gem} = 12.8 Hz, $J_{3e,4}$ = 4.9 Hz, H-3e), 3.79 (s, 3H, MeO), 3.93 (ddd, 1H, $J_{4,5}$ = $J_{5,6}$ = $J_{5,NH}$ = 10.0 Hz, H-5), 4.17 (dd, 1H, J_{gem} = 12.6 Hz, H-9), 4.37 (dd, 1H, $J_{6,7}$ = 2.1 Hz, H-6), 4.74 (dd, 1H, $J_{8,9'}$ = 2.2 Hz, H-9'), 5.27-5.42 (m, 3H, H-4,7,8), and 5.73 (d, 1H, NH). 11: $[\alpha]_D$ +4.3°; ^{1}H NMR ($CDCl_3$) Lac unit δ 1.00 (m, 2H, $Me_3Si\underline{CH_2}CH_2$), 7.18-7.38 (m, 25H, 5Ph); Neu5Ac unit δ 1.85 (s, 3H, AcN), 1.87, 1.96, 1.99, 2.07 (4s, 12H, 4AcO), 2.48 (dd, 1H, J_{gem} = 13.0 Hz, $J_{3e,4}$ = 4.8 Hz, H-3e), 3.83 (s, 3H, MeO), 4.86 (m, 1H, H-4), 5.25 (d, 1H, $J_{5,NH}$ = 7.2 Hz, NH), 5.28 (dd, 1H, $J_{6,7}$ = 1.6 Hz, $J_{7,8}$ = 7.0 Hz, H-7), and 5.36 (ddd, 1H, H-8). 12: $[\alpha]_D$ -4.7°; ^{1}H NMR ($CDCl_3$) Lac unit δ 1.03 (m, 2H, $Me_3Si\underline{CH_2}CH_2$), 7.19-7.37 (m, 25H, 5Ph); Neu5Ac unit δ 1.72 (s, 3H, AcN), 1.94, 1.96, 2.07, 2.08 (4s, 12H, 4AcO), 2.53 (dd, 1H, J_{gem} = 13.3 Hz, $J_{3e,4}$ = 4.6 Hz, H-3e), 3.60 (s, 3H, MeO), 5.16 (m, 1H, H-4), 5.18 (dd, 1H, H-7), and 5.26 (m, 1H, H-8).