A New *N*-Acetylneuraminic Acid Donor for Highly Stereoselective α-Sialylation

Teddy Ercegovic and Göran Magnusson*

Organic Chemistry 2, Chemical Center, The Lund Institute of Technology, University of Lund, PO Box 124, 221 00 Lund, Sweden

The new sialyl donor **6** (prepared from *N*-acetylneuraminic acid in 44% yield over six steps) effects clean α-sialylation of 2-(trimethylsilyl)ethyl 2,3,6,2′,4′,6′-hexabenzyl-β-D-lactoside in 67% yield.

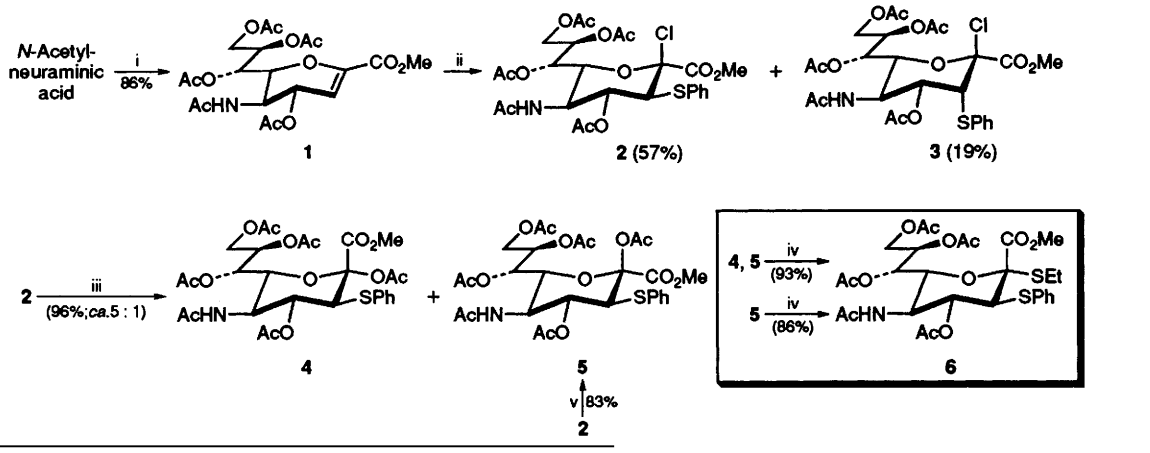
Sialylation in high yield and stereoselectivity is difficult.[1,2] Hindered glycosyl acceptors are particularly troublesome, causing a substantial fraction of the sialic acid-derived donor to undergo elimination to the corresponding glycal; yields obtained with such acceptors are consequently modest. However, yields may be increased with donors (*e.g.* **7**[3] and **8**[4]) carrying sulfur-containing leaving groups, and especially when the acceptors have several hydroxy groups unprotected (*e.g.* HO-2,3,4 in galactose residues). In order to improve the α:β-ratio in the sialylation reaction and also reduce glycal formation, an auxiliary participating 3-PhS-group has been introduced in 2-halogeno-sialic acid donors.[5] However, the most effective donors carry *O*-benzyl protecting groups and their syntheses require *ca.* six steps, which furnish the desired donor in 20–50% overall yield,[5,6] starting from the glycal **1**.

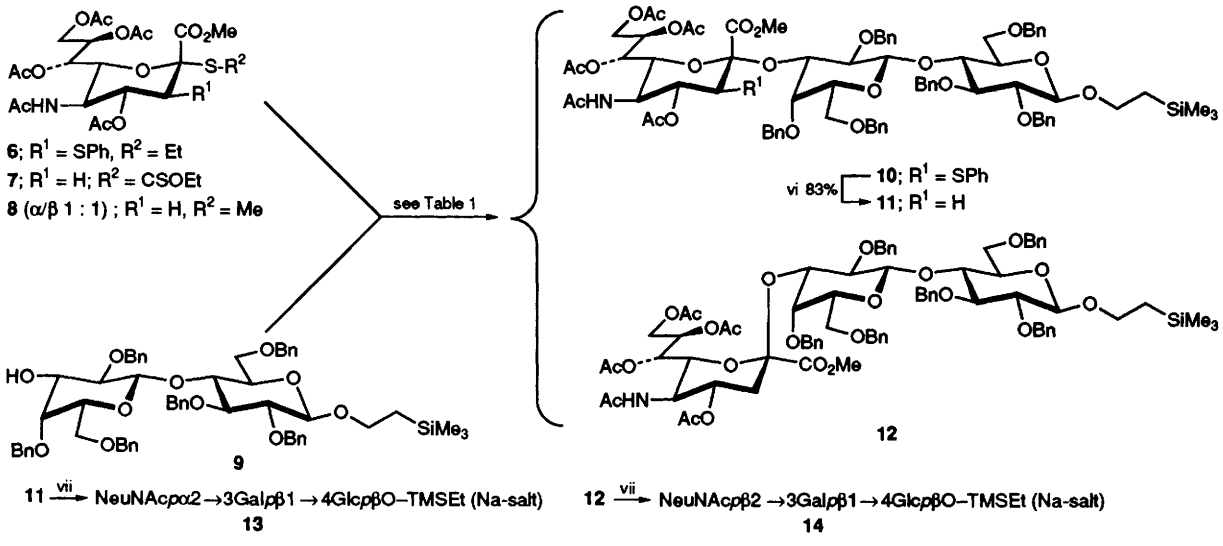
We now report the new sialyl donor **6**: (*i*) its synthesis

Table 1 Sialylation of lactoside acceptor **9** (0.15–0.50 mmol) with the sialic acid donors **6–8**

Donor	Mol. ratio[a]	P1,P2[a]	Reaction conditions[b]	Product	Yield[c] (%)	α:β
6	1.0:1.0:1.1:1.1	MSB–AgOTf	MeCN, −40 °C	**10**	54	>99:1
6	1.0:1.5:1.6:1.6	MSB–AgOTf	MeCN, −40 °C	**10**	67	>99:1
6	1.0:1.5:1.7:0.5	NIS–TfOH	MeCN, −40 °C	**10**	57	>99:1
7	1.0:1.5:1.3:1.2	MSB–AgOTf	MeCN, CH_2Cl_2, −60 °C	**11** + **12**	36 + 4	90:10
8	1.0:1.5:1.5:0.7	NIS–TfOH	MeCN, −40 °C	**11** + **12**	29 + 4	88:12

[a] Donor/acceptor/promotor 1 (P1)/promotor 2 (P2). [b] The concentration of **9** was ~0.10 mol dm^{-3}. [c] Based on the donor (**6–8**).





Scheme 1 *Reagents and conditions*: i, MeOH, Dowex-H^+, then Ac_2O, pyridine, then TMSOTf, MeCN, 0 °C, 6 h; ii, PhSCl, CH_2Cl_2, 20 °C, 7 days, Ar; iii, $Hg(OAc)_2$, AcOH–Ac_2O 10:1, 40 °C, 18 h. iv, EtSH, BF_3Et_2O, CH_2Cl_2, 20 °C, 18 h; v, $HgBr_2$, $Hg(CN)_2$, $ClCH_2CH_2Cl$–H_2O 100:1, reflux, 3.5 h, then Ac_2O, pyridine, DMAP, 20 °C, 1 h; vi, Ph_3SnH, AIBN, toluene, reflux, 14 h. vii, Pd/C, AcOH, 20 °C, overnight, then MeONa, MeOH, 20 °C, 2 h, then NaOH, H_2O, 20 °C, 0.5 h

Table 2 Anomeric configuration (NeuNAc residue) based on NMR analysis of compounds **2**, **4–6**, **10–14**

Compound	$JC(1)$–$H(3)_{ax}$/Hz[a]	$JH7,8$/Hz	$\delta H(3)_{eq}$/ppm	$\Delta\delta$ H(9)–H(9′)/ppm	Configuration[b]
2	1.7	8.0	—	0.28	β
4	5.9	6.5	—	0.32	α
5	1.4	4.0	—	0.38	β
6	7.5	7.9	—	0.21	α
10	6.3	8.1	—	0.34	α
11	7.4[c]	8.4	2.45	0.34	α
12	1.1	n.d.	2.71	~1.0[d]	β
13	5.8	n.d.	2.75	n.d.	α
14	1.0	n.d.	2.45	n.d.	β

[a] Identified by long-range HECTOR and measured according to ref. 21. [b] Anomeric (non-carboxyl) substituent. [c] $JC(1)$–$H(3)_{eq}$ = 1.1 Hz. [d] Estimated from COSY spectrum.

requires only three steps (*ca.* 50% overall yield) from glycal **1**; (*ii*) it is a stable, pure α-thioglycoside; (*iii*) it carries a 3-PhS auxiliary group; (*iv*) unreacted **1** and the potentially useful byproduct **3** can be rescued from the reaction mixture; (*v*) **6** is an efficient α-sialyl donor, even with sterically congested aceptors such as **9**[7] (Table 1).

The glycal **1**[8,9] was synthesised (Scheme 1) by treatment of fully acetylated neuraminic acid methyl ester[10,11] (9.3 mmol) with 2 equiv.[12,6] (not 0.2[13]) of fresh (to reduce 4,5-oxazoline[14,15] formation) trimethylsilyl trifluoromethanesulfonate.

Addition of fresh phenyl sulfenyl chloride (23 mmol) to **1** (8.55 mmol) in dichloromethane (30 ml) gave the diastereoisomers **2** (57%) and **3** (19%),[16] and unreacted **1** (10%) after chromatography (chloroform–acetone gradient 40 : 1 → 3 : 1).

Acetolysis of **2** (0.58 mmol) with $Hg(OAc)_2$ (0.71 mmol) in acetic acid–acetic anhydride (2.76 ml; 10 : 1) followed by chromatography (toluene–acetone gradient 4 : 1 → 3 : 1) gave pure **4** and a mixture of **4** and **5** in a total yield of 96% (**4** : **5** *ca.* 5 : 1). Hydrolysis of **2** (1.6 mmol) followed by acetylation of the intermediate β-hemiacetal[17] gave pure **5** (83%).

Treatment of the **4–5** mixture (0.53 mmol) with ethanethiol (1.05 mmol) and boron trifluoride etherate ($BF_3{\cdot}Et_2O$, 2.7 mmol) in dichloromethane (2.5 ml) gave, after chromatography (toluene–acetone 3 : 1) pure **6** in 93% yield; no β-anomer was detected. Similar treatment of **5** gave **6** in 86% yield.

A comparative glycosylation of the hexabenzyl lactoside **9**[7] was performed (Table 1) with donors **6**, **7**[3] and **8**[4] using either methyl sulfenyl bromide–silver trifluoromethanesulfonate[18] or *N*-iodosuccinimide–trifluoromethanesulfonic acid[4] as promoters.

The new donor **6** gave the GM_3-trisaccharide **10** in good yield and very high stereoselectivity, with both the methods used for anomeric activation. Note also the high yield obtained when **6** and **9** were used in a molar ratio of 1 : 1.

The donors **7**[3] and **8**[4] have been used extensively for sialylation of the 3-position of galactose residues; good yields (60–80%) have been reported with acceptors having two or three hydroxy groups unprotected.[4,19,20] However, sialylation of the sterically congested acceptor **9** with **7** and **8** proceeded in only 30–40% yield of GM_3-saccharide **11** (Table 1) and with concomitant formation of the corresponding β-glycoside **12**.

The auxiliary PhS-group was removed by treatment of **10** (0.12 mmol) with triphenyltin hydride (1.2 mmol)–AIBN (0.09 mmol), thus giving **11** (83%) and unreacted **10** (12%) after chromatography (toluene–MeCN gradient 4 : 1 → 2 : 1). We found that triphenyltin hydride is superior to tributyltin hydride, which gave **11** in low yield.

De-*O*-benzylation, de-*O*-acetylation, and hydrolysis of the methyl ester of **11** and **12** gave the TMSEt glycosides **13** and **14** (as the sodium salts) in 98 and 96% yields, respectively.

The anomeric configuration of the sialic acid residues of **2**, **4–6**, **10–14** were determined by measuring the long-range $JC(1)$–$H(3)_{ax}$ coupling constant.[21] As seen in Table 2, all sialic acid residues having an axial carboxyl (ester) group (as in α-glycosides) show couplings in the range 5.8–7.5 Hz, whereas the corresponding equatorial carboxyl compounds show couplings in the range 1.0–1.7 Hz.

Values of $\delta H(3)_{eq}$ have been suggested to be smaller for β- than for α-glycosides.[22] Data in Table 2 serve as a caveat in this respect, since the chemical shift order is reversed in the protected pair **11–12** as compared to the unprotected pair **13–14**.

$JH_{7,8}$ has also been used as an anomeric configuration probe (*ca.* 2 and >7 Hz indicating β and α configuration).[23] In addition, the chemical-shift difference between the two hydrogens at position 9 [$\Delta\delta$ H(9)–H(9′)] is reported to depend on the anomeric configuration, $\Delta\delta$ being *ca.* 1 for β glycosides and <0.5 for α glycosides.[23] However, these empirical rules do not apply for the 2-chloro and 2-*O*-acetyl compounds **2** and **5** (Table 2).

We are grateful to Ulf Nilsson for valuable participation in the NMR analyses. This work was supported by the Swedish Natural Science Research Council.

Received, 9th December 1993; Com. 3/07284C

References

1 K. Okamoto and T. Goto, *Tetrahedron*, 1990, **46**, 5835.
2 G. Magnusson, *Adv. Drug Deliv. Rev.*, 1993, in the press.
3 A. Marra and P. Sinaÿ, *Carbohydr. Res.*, 1990, **195**, 303.
4 A. Hasegawa, H. Ohki, T. Nagahama, H. Ishida and M. Kiso, *Carbohydr. Res.*, 1991, **212**, 277.
5 Y. Ito and T. Ogawa, *Tetrahedron*, 1990, **46**, 89.
6 K. C. Nicolaou, C. W. Hummel and Y. Iwabuchi, *J. Am. Chem. Soc.*, 1992, **114**, 3126; supplementary material.
7 A. Kameyama, H. Ishida, M. Kiso and A. Hasegawa, *Carbohydr. Res.*, 1989, **193**, C1.
8 P. Meindl and H. Tuppy, *Montash. Chem.*, 1969, **100**, 1295.
9 K. Okamoto, T. Kondo and T. Goto, *Bull. Chem. Soc. Jpn.*, 1987, **60**, 631.
10 R. Kuhn, P. Lutz and D. L. MacDonald, *Chem. Ber.*, 1966, **99**, 611.
11 A. Marra and P. Sinaÿ, *Carbohydr. Res.*, 1989, **190**, 317.
12 W. Schmidt, R. Christian and E. Zbiral, *Tetrahedron Lett.*, 1988, **29**, 3643.
13 A. Claesson and K. Luthman, *Acta Chem. Scand. Ser. B*, 1982, **36**, 719.
14 V. Kumar, J. Kessler, M. E. Scott, B. H. Patwardhan, S. W. Tanenbaum and M. Flashner, *Carbohydr. Res.*, 1981, **94**, 123.
15 E. Schreiner, E. Zbiral, R. G. Kleineidam and R. Schauer, *Liebigs Ann. Chem.*, 1991, 129.
16 T. Kondo, H. Abe and T. Goto, *Chem. Lett.*, 1988, 1657.
17 K. Ikeda, Y. Nagao and K. Achiwa, *Carbohydr. Res.*, 1992, **224**, 123.
18 F. Dasgupta and P. J. Garegg, *Carbohydr. Res.*, 1988, **177**, C13.
19 H. Lönn and K. Stenvall, *Tetrahedron Lett.*, 1992, **33**, 115.
20 A. K. Ray, U. Nilsson and G. Magnusson, *J. Am. Chem. Soc.*, 1992, **114**, 2256.
21 H. Hori, T. Nakajima, Y. Nishida, H. Ohrui and H. Meguro, *Tetrahedron Lett.*, 1988, **29**, 6317.
22 U. Dabrowski, R. Brossmer, M. Supp and H. Friebolin, *Tetrahedron Lett.*, 1979, **48**, 4637.
23 K. Okamoto, T. Kondo and T. Goto, *Bull. Chem. Soc. Jpn.*, 1987, **60**, 637.