Pergamon

Tetrahedron Letters, Vol. 37, No. 15, pp. 2613-2614, 1996

0040-4039/96 $15.00 + 0.00

S0040-4039(96)00383-8

A Facile Preparation of the Methyl 2-Thioglycoside of N-Glycolylneuraminic Acid, An Efficient Donor of NeuGc

Tetsuji Sugata and Ryuichi Higuchi*

Faculty of Pharmaceutical Sciences, Kyushu University,
Maidashi 3-1-1, Higashi-ku, Fukuoka, 812-82, Japan.

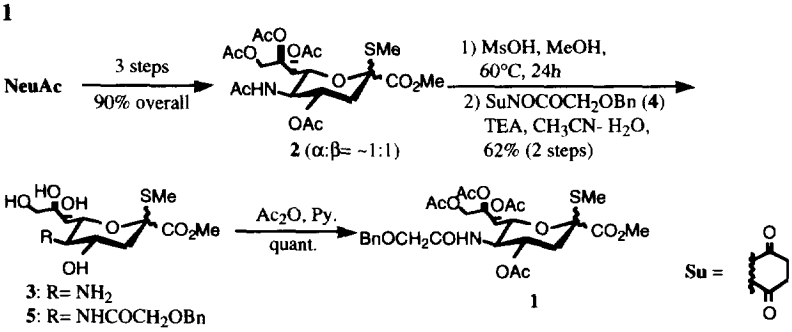
Abstract: The methyl 2-thioglycoside of N-glycolylneuraminic acid (SMe-NeuGc, **1**), which is an efficient donor of NeuGc in the preparation of sialosyl glycoconjugates, was synthesized from N-acetylneuraminic acid (NeuAc) in 6 steps in good yield. **1** could be glycosylated with two lactose acceptors to give sialosyl oligosaccharides **8**, **9** and **10** in high yields. Copyright © 1996 Elsevier Science Ltd

Recently, gangliosides, sialic acid-containing glycosphingolipids, have received much attention due to their biological functions[1]. NeuAc and NeuGc are two major sialic acids in animals, and their relative amounts depend on the species, tissues, and cell lines. NeuGc-containing glycoconjugates are not observed in normal chicken and man[2], but a significant amount of NeuGc residues are present in a variety of their cancer cells[3]. For instance, hematoside, NeuGcα(2-3)Galβ(1-4)Glcβ(1-1)Cer, has been identified as the antigens for human Hanganutziu-Deicher heterophile antibodies which are detected in sera from patients with various cancer cells[4]. In spite of these interesting biological phenomena, only few synthetic studies of NeuGc have been reported[5]. One of the reasons for this seems to be due to the low availability of NeuGc. In previous studies, these glycoconjugates were synthesized using either NeuGc itself[5a,c] or the exchange of N-substitution of NeuAc containing oligosaccharides[5b], which seems to be a disadvantage for the synthesis of the aminosugar-containing one.

In this paper, we describe the facile preparation of the methyl 2-thioglycoside of NeuGc **1**, an efficient donor of NeuGc, from NeuAc, and its application for the synthesis of the sugar moieties of hematoside and its position isomer.

Thioglycosides have been known to be good glycosyl donors and stable in many organic operations, therefore, we first introduced the methylthio group at the anomeric position, followed by exchange of N-substitution. The methylthioglycoside of NeuAc **2**, which was prepared from NeuAc in 3 steps[6], was N, O-deacetylated with methanesulfonic acid in MeOH for 24h at 60°C, and then N-glycolylation of the amine **3** with benzylglycolic acid N-hydroxysuccinimide ester **4** in the presence of triethylamine gave the N-glycolyl derivative **5** in 62% overall yield (Scheme 1). The acetylation of **5** gave SMe-NeuGc **1** in quantitative yield as an anomeric mixture[7].

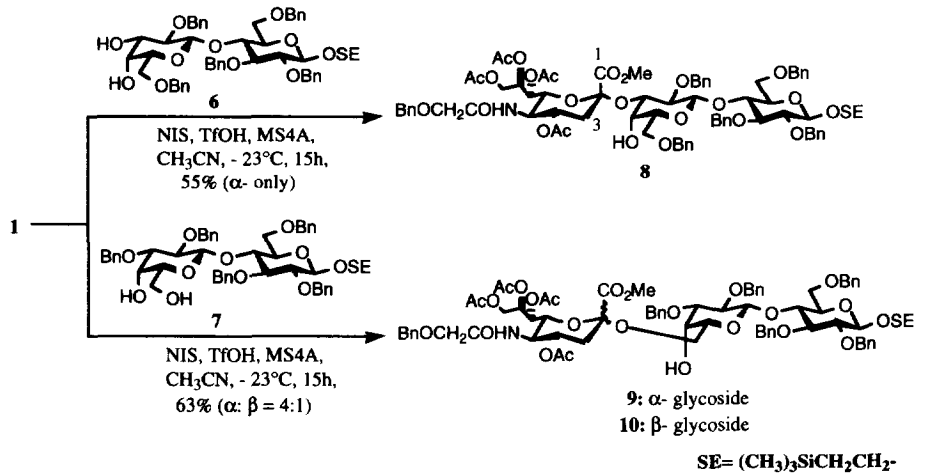
Scheme 1



For examination of its donor property, **1** was glycosylated with two 2-(trimethylsilyl)ethyl lactoside derivatives **6**[8] or **7**[9] in CH_3CN in the presence of N-iodosuccinimide(NIS), trifluoromethanesulfonic acid(TfOH)[10] and powdered molecular sieves 4A for 15h at -23°C (Scheme 2). Glycosylation of **1** with **6** gave α-sialoside **8** in 55% yield and neither the β-glycoside nor any position isomers were isolated. The structure of

8 was confirmed as follows; namely, acetylation of **8** with Ac_2O, pyridine and DMAP showed a 3-O-linked[11], and a large long-range $J_{C(1)\text{-}H(3ax)}$ coupling constant (168.4ppm, J=7.1Hz)[12] indicated the α-configuration of the NeuGc residue. The glycosylation of **1** with **7** afforded **9** and **10** as a 4:1 mixture in 63% yield, and the structure was confirmed in the same way as **8**[13].

Scheme 2



In conclusion, NeuGc donor **1** was synthesized in 56% overall yield from NeuAc and gave NeuGc-containing oligosaccharides in good yields. This NeuGc donor **1** must be useful for the synthesis of the biologically active ganglioside with NeuGc, such as neuritogenically active GAA-7[1d].

Acknowledgement: The authors thank Nissin Food Products Co., Ltd. for providing NeuAc. Thanks are also due to Dr. R. Isobe, Mr. Y. Tanaka and Miss Y. Soeda of the Faculty of Pharmaceutical Sciences, Kyushu University, for providing the MS and NMR data.

References and Notes

1. (a) H. Wiegandt (Ed.), *Glycolipids, New Comprehensive Biochemistry*, Vol. 10, Elsevier, Amsterdam, **1985**, pp.199-260; (b) E. C. Bremor, J. Schlessinger and S. Hakomori, *J. Biol. Chem.*, **1986**, *261*, 2434-2440; (c) S. Tsuji, T. Yamakawa, M. Tanaka and Y. Nagai, *J. Neurochem.*, **1988**, *50*, 414-423; (d) R. Higuchi, K. Inukai, J. X. Jhou, M. Honda, T. Komori, S. Tsuji and Y. Nagai, *Liebigs Ann. Chem.*, **1993**, 359-366; (e) K. Kitajima, H. Nomoto, Y. Inoue, M. Iwasaki and S. Inoue, *Biochemistry*, **1984**, *23*, 310-316; (f) T. Yamakawa and S. Suzuki, *J. Biochem.*, **1951**, *38*, 199-212.
2. T. Kawai, A. Kato, H. Higashi, S. Kato and M. Naiki, *Cancer Res.*, **1991**, *51*, 1242-1246
3. S. Hara, Y. Takemori, M. Yamaguchi, M. Nakamura and Y. Ohkura, *Anal. Biochem.*, **1987**, *164*, 138-145
4. H. Higashi, Y. Hirabayashi, Y. Fukui, M. Naiki, M. Matsumoto, S. Ueda and S. Kato, *Cancer Res.*, **1985**, *45*, 3796-3802
5. (a) M. Numata, M. Sugimoto, S. Shibayama and T. Ogawa, *Carbohydr. Res.*, **1988**, *174*, 73-85; (b) T. Yamamoto, T. Teshima, U. Saitoh, M. Hoshi and T. Shiba, *Tetrahedron Lett.*, **1994**, *35*, 2701-2704, (c) A. Hasegawa, A. Uchimura, H. Ishida and M. Kiso, *Biosci. Biotech. Biochem.*, **1995**, *59*, 1091-1094
6. A. Hasegawa, H. Ohki, T. Nagahama, H. Ishida and M. Kiso, *Carbohydr. Res.*, **1991**, *212*, 277-281
7. ^{1}H- NMR data of **1** (270MHz, $CDCl_3$, δ ppm, J Hz); **1a**: 7.43-7.31 (m, 5H, Ph), 6.33 (d, 1H, J=10.6 Hz, NH), 4.61, 4.55 (2d, 2H, $PhCH_2$), 3.98-3.83 (m, 3H, H-6, CH_2CO), 3.82 (s, 3H, CO_2Me), 2.77 (dd, 1H, J= 4.6, 12.7Hz, H-3e), 2.18, 2.13, 2.12, 2.01, 2.00 (5s, 15H, 4Ac, SMe),; **1b**: 7.42-7.32 (m, 5H, Ph), 6.45 (d, 1H, J=10.6Hz, NH), 4.61, 4.53 (2d, 2H, $PhCH_2$), 3.94-3.84 (m, 2H, CH_2CO), 3.82 (s, 3H, CO_2Me), 2.58 (dd, 1H, J=5.0, 13.9Hz, H-3e), 2.13, 2.07, 2.04, 2.02, 1.99 (5s, 15H, 4Ac, SMe),
8. K. Jansson, S. Ahlfors, T. Frejd, J. Kihlberg and G. Magnusson, *J. Org. Chem.*, **1988**, *53*, 5629-5647
9. Compound **7** was prepared from 2-(trimethylsilyl)ethyl lactoside[8] in 3 steps (40% overall yield): (a) $PhCH(OMe)_2$, *p*-TsOH• H_2O, DMF; (b) BnBr, NaH, DMF; (c) TFA, CH_2Cl_2
10. G. H. Veeneman, S. H. van Leeuwen and J. H. van Boom, *Tetrahedron Lett.*, **1990**, *31*, 1331-1334
11. Protone chemical shift for Gal H-4 of **8** was shifted downfield by acetylation at 500 MHz in $CDCl_3$.(δ 3.82→5.04 ppm)
12. α-anomer gave a doublet C-1 signal (J=~6Hz) while the β gave a singlet (J=~0Hz). H. Hori, T. Nakajima, Y. Nishida, H. Ohrui and H. Meguro, *Tetrahedron Lett.*, **1988**, *29*, 6317-6320
13. **9**: $J_{C(1)\text{-}H(3ax)}$= 5.9Hz, Gal H-4 (δ 4.06→5.49ppm), **10**: $J_{C(1)\text{-}H(3ax)}$ = 0Hz, Gal H-4 (δ 4.15→5.49 ppm)

(*Received in Japan* 1 *February* 1996; *revised* 19 *February* 1996; *accepted* 23 *February* 1996)