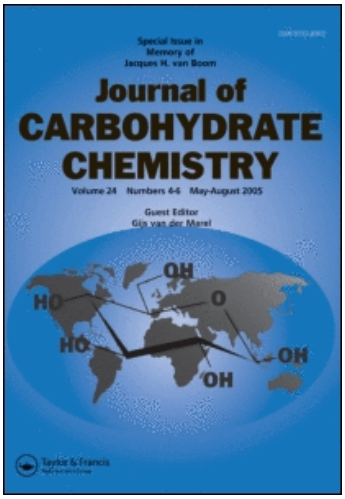

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COMMUNICATION

SYNTHETIC STUDIES ON SIALOGLYCOCONJUGATES 46 : A FACILE TOTAL SYNTHESIS OF GANGLIOSIDE GD_3

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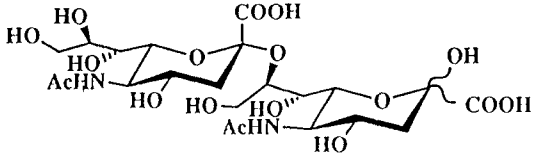
Sialic acids[1] are well known as constituents of cell membrane-glycoconjugates and involved in their various biological functions. As far as we know, sialic acids are linked in an α-configuration at C-3 and C-6 of the Gal unit, at C-6 of the GlcNAc and GalNAc units and at C-8 of the sialic acid residue in sialoglycoconjugates. We have developed[2-4] a facile α-stereoselective glycosylation of sialic acids by using 2-thioglycosides of sialic acids as glycosyl donors with suitably protected acceptors, using dimethyl(methylthio)sulfonium triflate (DMTST) or *N*-iodosuccinimide(NIS)-trifluoromethanesulfonic acid (or TMS triflate) as the glycosidation promoter in acetonitrile. A variety of gangliosides[5] and their analogs[6,7] have been synthesized in this way. As a part of our continuing studies on the systematic synthesis and structure-function relationship of gangliosides in connection with a novel approach for the systematic synthesis of polysialoglycolipids, we describe here a facile stereocontrolled synthesis of ganglioside GD_3 containing an α-sialyl-(2→8)-sialic acid residue in the molecule. Ganglioside GD_3 is well known as human melanoma associated antigen[9] and widely present in normal and pathogenic tissues. This ganglioside was first synthesized by Ogawa *et al.*[10] in multiple steps.

Treatment of *O*-(3-acetamido-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonic acid)-(2→8)-5-acetamido-3,5-dideoxy-D-*glycero*-D-*galacto*-2-nonulopyranosonic acid (**1**), easily prepared according to the procedure of Roy et al.,[11] with Amberlite IR-120 (H^+) resin in methanol at 40 °C, followed by acetylation, gave an anomeric mixture (α:β = 1:10) of the 2-acetate **2** in 84% yield. The replacement of the



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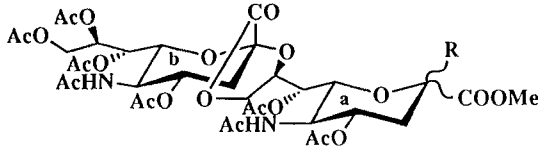
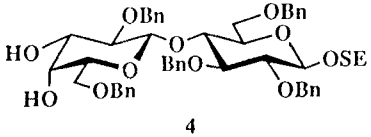


	R
2	OAc
3	SPh



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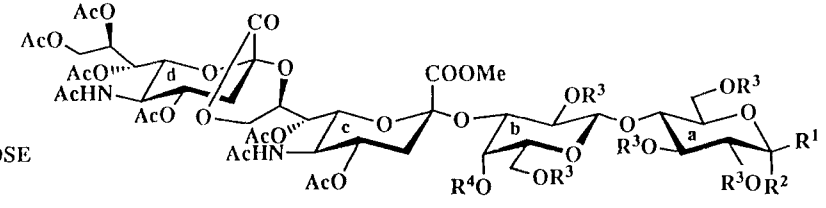
SE = 2-(trimethylsilyl)ethyl
Bn = benzyl

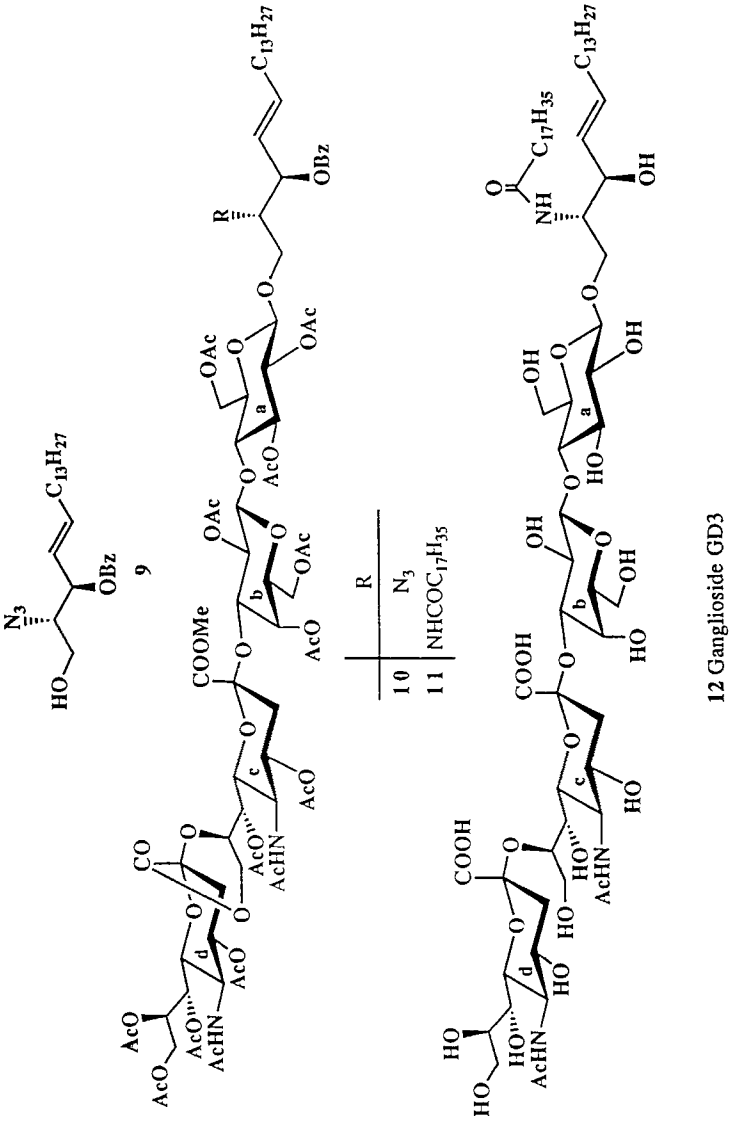


	R^1	R^2	R^3	R^4
5	OSE	H	Bn	H
6	OSE	H	Ac	Ac
7	OH , H		Ac	Ac
8	H	$OC(=NH)CCl_3$	Ac	Ac

anomeric acetoxy group in **2** with the phenylthio group by treatment with thiophenol in dichloromethane in the presence of boron trifluoride etherate at room temperature[12] gave the phenyl 2-thioglycoside **3** in 89% yield as a 1:3 anomeric mixture. The glycosylation of 2-(trimethylsilyl)ethyl 2,3,6,2',6'-penta-*O*-benzyl-β-lactoside[5] (**4**; 2.0 equiv relative to the donor) with **3** thus obtained, in acetonitrile for 48 h at -35 °C in the presence of NIS (2.0 equiv relative to the donor)-TfOH (0.2 equiv relative to the donor), gave the expected α-glycoside **5** at C-3' of the acceptor in 31% yield (based on the donor). The yield is quite appreciable, considering the bulkiness of the donor and the steric hindrance to glycosidation at C'-3 of the acceptor. Hydrogenolytic removal of the benzyl groups in **5** over 10% Pd-C in 1:1 methanol-acetic acid for 2 days at 45 °C and subsequent acetylation gave the fully acylated core oligosaccharide **6** {$[\alpha]_D$ -5° ($CHCl_3$)} in 90% yield. The structure of **6** was unambiguously proved from 500 MHz ^1H NMR data. Significant signals were two one-proton doublets of doublets at δ 2.52 and 2.54 due to H-3c*eq* and H-3d*eq*, a one-proton multiplet at δ 5.08 due to H-4c, and a one-proton doublet ($J_{6,7}$ = 2.5 Hz, $J_{7,8}$ = 8.5 Hz) at δ 5.19 due to H-7c, indicating[13] the newly formed glycosidic linkage to be α. The position of linkage of the α-Neu5Ac-(2→8)-Neu5Ac moiety to the acceptor was obtained from the ^1H NMR data of the galactose residue in **6**. The observed chemical shifts for H-3b (δ 4.32, $J_{2,3}$ = 10.0 Hz, $J_{3,4}$ = 3.5 Hz), H-2b (δ 4.95, $J_{1,2}$ = 8.0 Hz), and H-4 (δ 5.11) clearly indicated the linkage position to be C-3 of the galactose residue. Other ^1H NMR data are consistent with the structure assigned.

Selective removal of the 2-(trimethylsilyl)ethyl group in **6** by treatment with trifluoroacetic acid[14] at room temperature gave the 1-hydroxy compound **7** in 90% yield. Treatment[15] of **7** with trichloroacetonitrile in dichloromethane in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) for 2 h at 0 °C gave the α-trichloroacetimidate **8** in 86% yield after column chromatography. Characteristic signals in the ^1H NMR spectrum were at δ 6.55 (d, $J_{1,2}$ = 3.8 Hz, H-1a) and 8.73 (C=NH), indicating the imidate to be α.

Final glycosylation[16,17a] of (2*S*,3*R*,4*E*)-2-azido-3-*O*-benzoyl-4-octadecene-1,3-diol[17] (**9**) with **8** in dichloromethane in the presence of boron trifluoride etherate for 6 h at -20 °C afforded the desired β-glycoside **10** in 60% yield. A significant signal in the ^1H NMR spectrum of **10** was a one-proton triplet at δ 4.95 ($J_{1,2}$ = $J_{2,3}$ = 9.1 Hz, H-2a), showing the newly formed glycosidic linkage to be β. Selective reduction[17a,18] of the azido group in **10** with hydrogen sulfide in aqueous 83% pyridine for 60 h at 0 °C afforded the amine, and this on condensation with octadecanoic acid in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride in dichloromethane gave the



	R
10	N_3
11	$NHCOC_{17}H_{35}$

12 Ganglioside GD3

acylated ganglioside GD_3 (**11**) in 84% yield. *O*-Deacylation of **11** with sodium methoxide in methanol, and subsequent saponification of the methyl ester and lactone yielded the desired ganglioside GD_3 (**12**) in quantitative yield after Sephadex LH-20 column chromatography. The ^1H NMR data (400 MHz) of **12** in 1:1 CD_3OD - $CDCl_3$ included δ 1,93, 1.94 (2s, 6H, 2AcN), 2.52, 2.85 (2m, 2H, H-3c*eq*, H-3d*eq*), 4.20 (d, 1H, $J_{1,2}$ = 8.1 Hz, H-1a), 4.35 (d, 1H, $J_{1,2}$ = 7.7 Hz, H-1b), 5.35 (dd, 1H, $J_{3,4}$ = 7.7 Hz, $J_{4,5}$ = 15.4 Hz, H-4 of sphingosine) and 5.61 (dt, 1H, $J_{5,6} = J_{5,6'}$ = 6.6 Hz, H-5 of sphingosine), and were good agreement with the reported data.[19]

In summary a facile, stereocontrolled total synthesis of ganglioside GD_3 was accomplished. The work indicates that the phenyl 2-thioglycoside derivative **3** of α-sialyl-(2→8)-sialic acid (**1**) and the α-disialyl lactoside derivative **5** described herein could be used as intermediates suitable for polysialoganglioside synthesis, and they are also important as building units for glycoconjugate synthesis.

Elemental analyses, as well as IR as ^1H NMR data of all the new compounds reported here were satisfactory for the assigned structures.

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