Erratum

Carbohydrate Research 306 (1998) 579–585

The following paper originally appeared in *Carbohydrate Research* 304 (1997) 187–189 without the relevant figures. The Publisher wishes to apologise for this error and the paper appears here in its entirety.

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Carbohydrate Research 306 (1998) 581–585

CARBOHYDRATE RESEARCH

Erratum

First total synthesis of ganglioside GT1aα[1]

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Received 7 July 1997; accepted 7 August 1997

Abstract

A first total synthesis of ganglioside GT1aα ($IV^3III^6II^3$Neu5AcGg4Cer) is described. The suitably protected sialyl α-(2→6) ganglioside was glycosylated with the phenylthio glycoside of sialic acid in the presence of *N*-iodosuccinimide-(NIS)-trimethylsilyl trifluoromethanesulfonate (TMSOTf), followed by further glycosylation with the methyl thioglycoside promoted by dimethyl(methylthio)sulfonium triflate (DMTST), to give the heptasaccharide. The oligosaccharide obtained was converted into the title ganglioside by the introduction of ceramide and then complete deprotection. © 1998 Elsevier Science Ltd. All rights reserved

Keywords: Myelin-associated glycoprotein; Chol-1 ganglioside

It has been widely recognized that sialoglycoconjugates, so-called gangliosides and glycoproteins, have important roles in biological processes such as cell growth, differentiation, adhesion, and oncogenesis [2–5]. In addition, the functions of these molecules as receptors for viruses [6] and bacteria [7] and as ligands of animal lectins [8,9] have drawn much attention in connection with infections or inflammatory diseases. Myelin-associated glycoprotein (MAG), a quantitatively minor protein constituent of the myelin of both the central and peripheral nervous systems, is a member of a group of immunoglobulin-like adhesion molecules termed the 'sialoadhesin family' or 'I-type lectins' [10,11]. It has also been found that MAG binds best to 2,3-linked sialic acid on a β-D-Gal-(1→3)-β-D-GalNAc core structure [10], which is often carried on gangliosides in the nervous system. In our continuing efforts on the chemical synthesis, biological function and structural determination of carbohydrate ligands of cell-adhesion molecules, we have reported the total synthesis of ganglioside GQ1bα [12], which is known as the cholinergic neuron-specific antigen and termed 'chol-1' ganglioside [13], and the extremely high potency of GQ1bα as ligands of MAG [14], which is nearly 10-fold higher than that of GT1b.

In view of these facts, we describe herein the first total synthesis of ganglioside GT1aα, which is another member of chol-1 gangliosides [15].

For the synthesis of GT1aα (**17**), we selected the suitably protected sialyl α-(2→6) gangliotriose **1** as a key glycosyl acceptor, which had served as the intermediate for GQ1bα (**18**) [12]. It is noteworthy that the acceptor was glycosylated with the dimeric sialyl donor **2** in the presence of *N*-iodosuccinimide (NIS)–trifluoromethanesulfonic acid (TfOH) [16,17] in 44% yield (Table 1, Entry 1), while only

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[1] Synthetic studies of Sialoglycoconjugates, Part 100. For Part 99 see ref 1.

[2] Deceased 10 October 1996.

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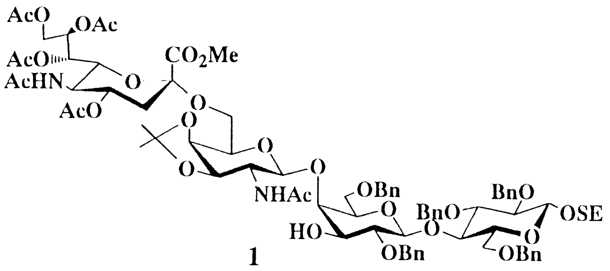
PII S0008-6215(98)00009-3

Table 1
α-Glycosylation of tetrasaccharide derivative with sialyl donors

Entry	Donor	Promoter	Yield (%)[a]
1 [11]	2	NIS–TfOH	44
2	3	NIS–TfOH	7
3	3	NIS–TMSOTf	10
4	3	DMTST	34
5	4	NIS–TfOH	26
6	4	NIS–TMSOTf	40
7	5	DMTST	10
8	6	NIS–TfOH	—

[a] All reactions were performed at -15 °C in CH_3CN.

in 26% yield with the monomeric sialyl donor **4** under the same reaction conditions. To improve the yield of the glycosylation, we varied the leaving and protecting groups of the glycosyl donors **(3–6)**, as well as the glycosyl promoters. As summarized in Table 1, the glycosylation of the acceptor with the per-*O*-acetylated phenyl thioglycoside of sialic acid (**4**) [18,19] promoted by NIS–trimethylsilyl trifluoromethanesulfonate (TMSOTf) [20] gave the best result (Entry 5; 40%).



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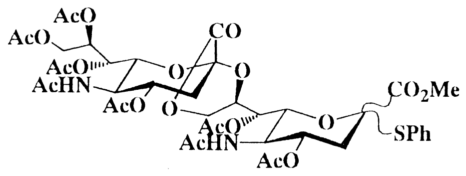

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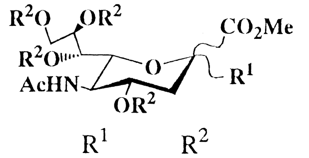

	R^1	R^2
3	SMe	Ac
4	SPh	Ac
5	SMe	Bz
6	SPh	Bz

The glycosylation of 2-(trimethylsilyl)ethyl(methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonate)-(2→6)-2-acetamido-2-deoxy-3,4-*O*-isopropylidene-β-D-galactopyranosyl-(1→4)-2,6-di-*O*-benzyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (**1**) [12] with methyl (phenyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-2-thio-D-*glycero*-D-*galacto*-2-nonulopyranosid)onate (**4**) [18,19] in acetonitrile for 72 h at -15 °C in the presence of NIS–TMSOTf and powdered 3Å molecular sieves (MS-3Å) gave the desired α-glycoside **7**[3] $\{[\alpha]_D + 2.8°$ (c 0.7, $CHCl_3$)$\}$ in 40% yield, showing in its ^1H NMR spectrum a one-proton doublet of doublets at δ 2.56 (dd, J_{gem} 12.7, $J_{3eq,4}$ 4.6 Hz, H-3deq) and 2.72 (dd, J_{gem} 13.5, $J_{3eq,4}$ 4.3 Hz, H-3eeq) characteristic of the α sialyl linkage [21]. Removal of the isopropylidene group from **7** with aq 80% acetic acid for 3 h at 40 °C gave the glycosyl acceptor **8** $\{[\alpha]_D - 7.2°$ (c 0.6, $CHCl_3$)$\}$ in 85% yield. Glycosylation of **8** with methyl (methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonate)-(2→3)-2,4,6-tri-*O*-benzoyl-1-thio-β-D-galactopyranoside (**9**) [22] in dichloromethane for 24 h at 0 °C in the presence of dimethyl(methylthio)sulfonium triflate (DMTST) and MS-4Å, gave the protected GT1aα oligosaccharide **10** $\{$amorphous mass, $[\alpha]_D + 0.4°$ (c 0.6, $CHCl_3$)$\}$ in 95% yield.

Hydrogenolytic removal of the benzyl groups in **10** over $Pd(OH)_2$ in 9:1 ethanol–acetic acid for 72 h at 30 °C, followed by acetylation of the free hydroxyls with acetic anhydride and pyridine for 24 h at 40 °C, affords the fully acylated oligosaccharide **11** $[\alpha]_D$ $-12.5°$ (c 0.6, $CHCl_3$)$\}$ in 81% yield. For the selective removal of the 2-(trimethylsilyl)ethyl group, the fully acylated oligosaccharide **11** was treated [23,24] with trifluoroacetic acid in dichloromethane for 3 h at room temperature to give the 1-hydroxy compound **12** a in 92% yield, which upon further treatment [25] with trichloroacetonitrile in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dichloromethane for 0.5 h at 0 °C, gave the trichloroacetimidate **13** $\{[\alpha]_D$ $-1.4°$ (c 0.6, $CHCl_3$)$\}$ in 65% yield. The ^1H NMR spectrum of the trichloroacetimidate contained a one-proton doublet at δ 6.51 ($J_{1,2}$ 3.67 Hz, H-1) and a one-proton singlet at δ 8.7 (C=NH), showing the imidate to be the α anomer.

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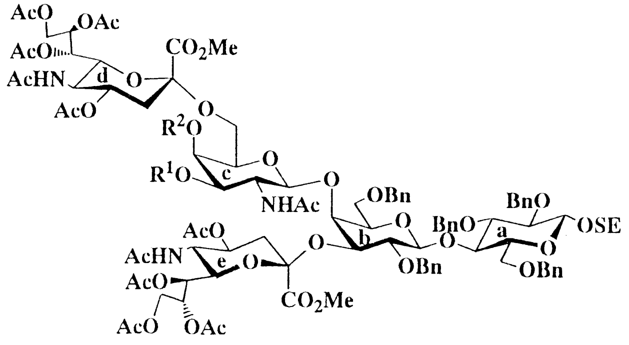
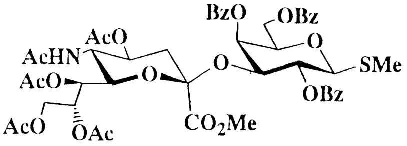
[3] All new compounds were fully characterized by elemental analyses, IR and ^1H NMR spectroscopy.

Glycosylation of (2*S*,3*R*,4*E*)-2-azido-3-*O*-(*tert*-butyldiphenylsilyl)-4-octadecene-1,3-diol (**14**) [26] was carried out in the presence of TMSOTf and MS-4Å (AW300) for 45 h at 0 °C to give the desired β-glycoside **15** {$[\alpha]_D$ −14.3° (*c* 0.8, $CHCl_3$ in 62% yield. Selective reduction [27] of the azido group in **14** with triphenylphosphine in 5:1 benzene–water gave the amine, which on condensation with stearic acid using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (WSC) in



7 R^1 , R^2 = isopropylidene
8 $R^1 = R^2 = H$



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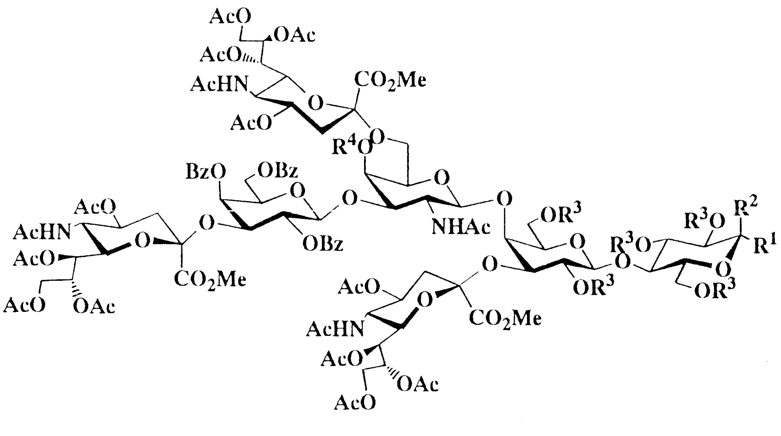
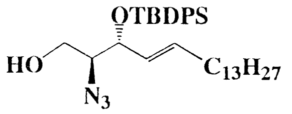
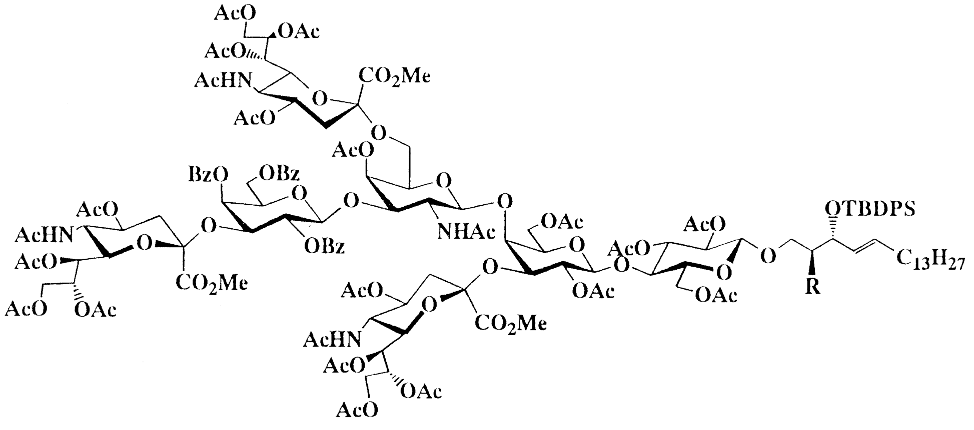


	R^1	R^2	R^3	R^4
10	OSE	H	Bn	H
11	OSE	H	Ac	Ac
12	OH , H		Ac	Ac
13	H	OC(=NH)CCl_3	Ac	Ac

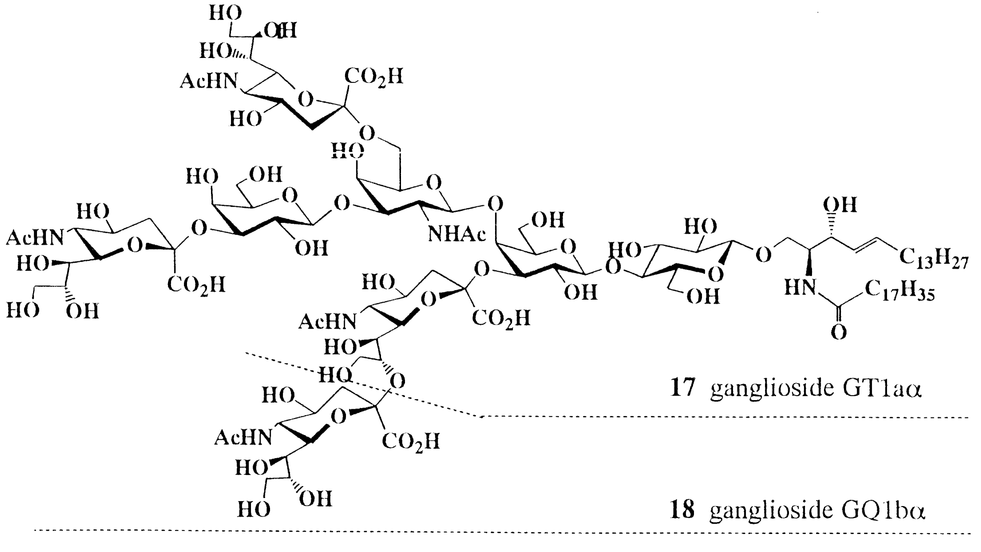


TBDPS = *tert*-butyldiphenylsilyl

14



15 R = N_3
16 R = $NHCOC_{17}H_{35}$



17 ganglioside GT1aα

18 ganglioside GQ1bα

dichloromethane, gave the fully protected ganglioside GT1a*α* **16** {[*α*]$_D$ −2.2° (*c* 1.2, $CHCl_3$)} in 76% yield.

Finally, removal [26] of the *tert*-butyldiphenylsilyl group in **16** with 1.0 M tetrabutylammonium fluoride in acetonitrile, *O*-deacetylation of **16** with sodium methoxide in methanol for 48 h at 40 °C, and subsequent saponification of the methyl ester group afforded ganglioside GT1a*α* as an amorphous mass in quantitative yield, after chromatography on a column of Sephadex LH-20 with 5:5:1 $CHCl_3$–MeOH–H_2O. The ^1H NMR data of the product thus obtained are consistent with the structure assigned.

Acknowledgements

This work was supported in part by Grants-in-Aid for Scientific Research on Priority Areas (No. 09240101) from the Ministry of Education, Science and Culture of Japan.

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