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Preliminary communication

Stereocontrolled synthesis of GD_2 *

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Ganglioside GD_2 (**1**) was first isolated in 1964 from human brain[2] and was later chemically characterized[3]. GD_2 was then identified as a human neuroectodermal tumor antigen OFA-I-2 (ref 4) as well as a human melanoma antigen Leo Mel 3 (ref 5). As part of our synthetic studies[6] on gangliosides, we describe herein a first synthesis of GD_2. The overall synthetic strategy is depicted in Scheme 1. The putative glycopentaosyl donor **2** that should be coupled with ceramide derivative **3** (ref 7) was expected to be synthesized from Gal*p*NAc donor **4**, Neu*p*5Ac-α-(2 → 8)-Neu*p*5Ac donor **5** and lactose derivative **6**.

The disodium salt of Neu*p*5Ac-α-(2 → 8)-Neu*p*5Ac, readily obtainable[8] from colomic acid, was converted into thioglycoside **5** {$[\alpha]_D$ −37° (*c* 0.5); the values of $[\alpha]_D$ and $\delta_{H,C}$ were measured for solutions in $CHCl_3$ and $CDCl_3$ at 23 ± 3°C, respectively, unless noted otherwise; R_f 0.31 in 1:1 $CHCl_3$–THF; δ_H 3.849 and 3.800 (2 s, 2 × OMe), 2.708 and 2.536 (2 dd, *J* 4.5 and 13.0 Hz, 2 × H-3_{eq})} in three steps (44% overall yield) via **7** by the following reactions: (i) MeI in Me_2SO, 3 h at 25°C, (ii) Ac_2O and DMAP in pyridine, and (iii) $MeSSnBu_3$ and $SnCl_4$ in $(ClCH_2)_2$ (ref 9). Peracetate **7** was obtained as a 5:1 mixture of β and α acetates {**7**(β), $[\alpha]_D$ −18° (*c* 0.5); R_f 0.25 in 20:1 $CHCl_3$–MeOH; δ_H 5.348 and 4.886 (2 ddd, 2 × H-5). **7**(a), R_f 0.30 in 20:1 $CHCl_3$–MeOH; δ_H 4.983 and 4.886 (2 ddd, 2 × H-5)}. Glycosylation of **6** (ref 10) with **5** (0.5 equiv.) in MeCN (ref 11) in the presence of PhSeOTf (ref 12) at −40°C afforded a 27% yield of the α-(2 → 3) linked compound **8** {$[\alpha]_D$ −6.1° (*c* 0.8); R_f 0.42 in 20:1 $CHCl_3$–MeOH}, as well as a 9% yield of its β isomer {$[\alpha]_D$ −14° (*c* 0.4); R_f 0.35}. The stereochemistry of **8** and the β isomer was deduced from ^1H NMR data, which contained two signals

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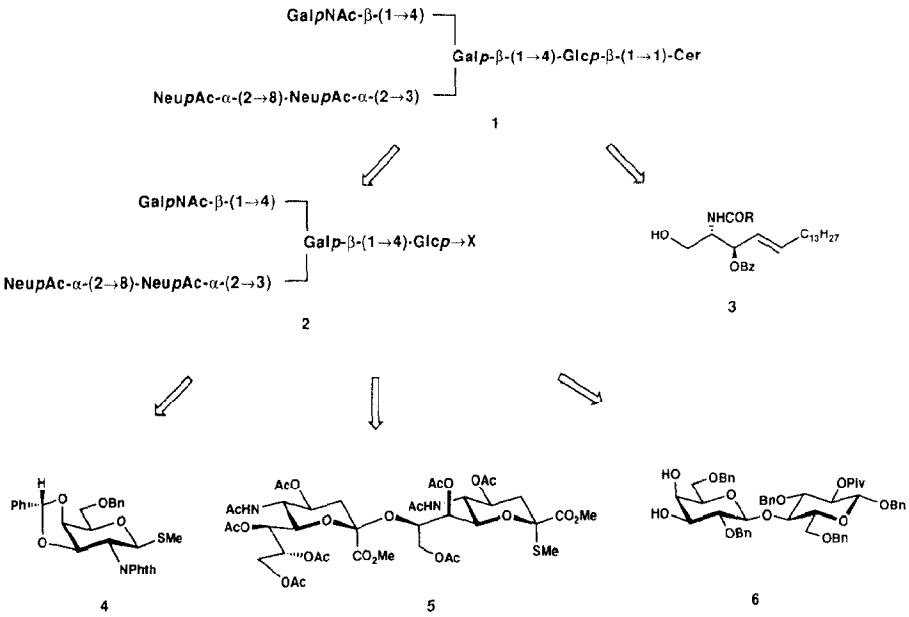
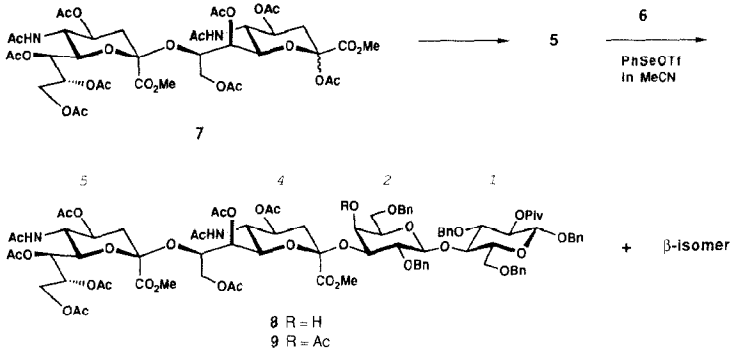


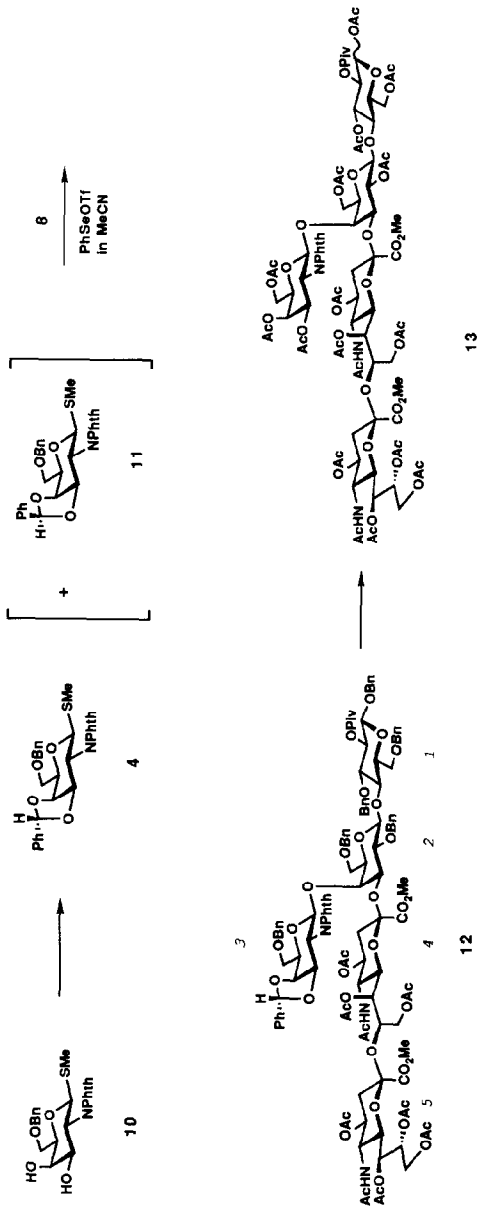
Scheme 1.

for H-4[4] and H-4[5] at δ 4.931 and 4.886 as two multiplets for compound **8**, while the corresponding signals at 5.662 and 4.925 were for the β isomer. The regiochemistry of newly introduced glycosidic linkage of **8** was deduced by converting **8** into acetate **9** {$[\alpha]_D$ −21° (*c* 0.1); R_f 0.37 in 5:3 Me_2CO–hexane}, which showed in the ^1H NMR spectrum a deshielded signal for H-4[2] at d 5.127 as a doublet of *J* 3.0 Hz.

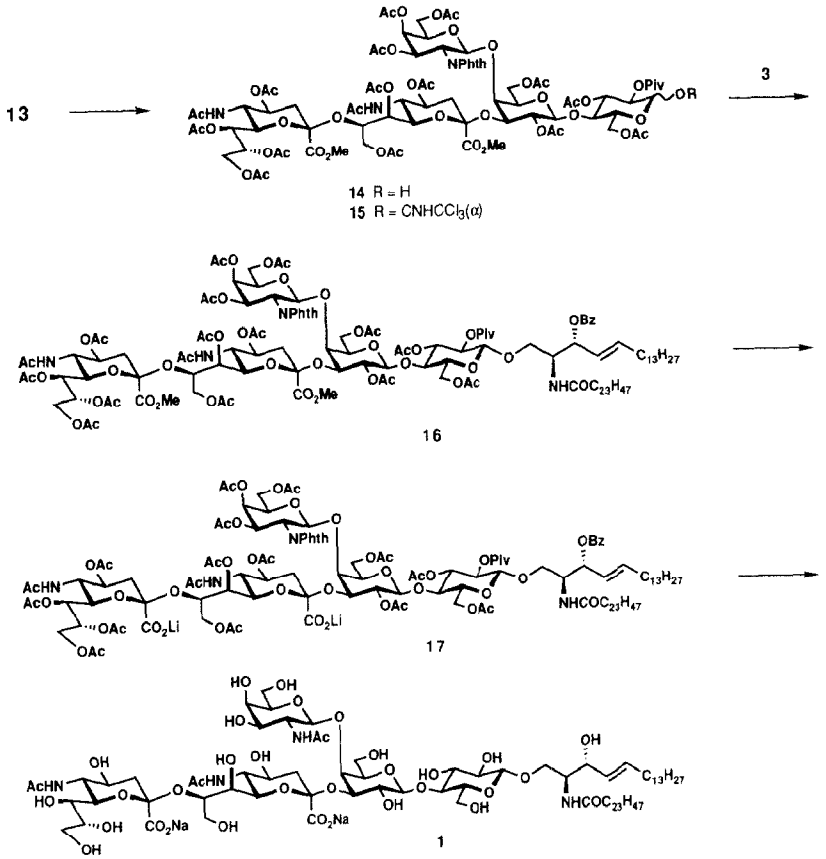
Treatment of thioglycoside **10** (ref 13) with $PhCH(OMe)_2$ and $TsOH \cdot H_2O$ in MeCN gave **4** {50%; $[\alpha]_D$ +49° (*c* 1.2); R_f 0.40 in 2:1 hexane–EtOAc}, and the *endo* isomer **11** {(37%) $[\alpha]_D$ +91° (*c* 0.7); R_f 0.32}, which showed in the ^1H NMR



Scheme 2.



Scheme 3.



Scheme 4.

spectrum signals for the benzylidene proton at d 6.323 and 5.927, respectively, in agreement with the structural assignment[14]. PhSeOTf-promoted glycosylation of **8** with *exo* isomer **4** in MeCN at −38°C afforded an 89% yield of **12** {$[\alpha]_D$ +6.7° (*c* 0.6); R_f 0.43 in 20:1 $CHCl_3$–MeOH}; however, with the *endo* isomer **11**, the glycosyl acceptor **8** was quantitatively recovered under the same reaction conditions. The anomeric configuration of newly introduced Gal*p*NAc residue of **12** was confirmed by ^{1}H NMR spectroscopy that revealed a signal for H-1^3 at d 5.306 as a doublet of *J* 8.8 Hz. Conversion of **12** into the completely acylated glycopentaose **13** was carried out in two steps in 65% overall yield: (i) 20% $Pd(OH)_2$ and H_2 in 10:5:3 MeOH–EtOAc–H_2O and (ii) Ac_2O and DMAP in pyridine. Compound **13** was obtained as a 1:1 mixture of α and β anomers at C-1^1 [R_f 0.51 in 16:1 $CHCl_3$–MeOH; δ_H 3.872 and 3.814 (2 s, 2 × OMe), 5.667 (d, 8.1 Hz, H-1$^1\beta$) and 6.247 (d, 3.7 Hz, H-1$^1\alpha$)].

Compound **13** was then treated with piperidinium acetate[15] in THF at 48°C to chemoselectively cleave the anomeric acetate to give a 49% yield of hemiacetal **14** [R_f 0.40 in 2:1 Me_2CO–toluene], which was immediately treated with CCl_3CN

(ref 16) and DBU in $(ClCH_2)_2$ to give trichloroacetimidate **15** in 93% yield [R_f 0.48 in 2:1 Me_2CO–toluene; δ_H 6.483 (d, 3.6 Hz, H-1^I), 3.875 and 3.819 (2 s, 2 × OMe), 2.929 and 2.709 (2 dd, H-3^4 and H-3^5)].

Crucial coupling between **15** and **3** was achieved in $CHCl_3$ in the presence of powdered 4A molecular sieves and Me_3SiOTf at −23°C (ref 17) to give a 48% yield of the desired product **16**, {$[\alpha]_D$ +19.0° (*c* 0.6); R_f 0.39 in 6:5 Me_2CO–toluene}. The structure of **16** was confirmed by ^1H NMR spectroscopy, which showed signals for two CO_2Me groups at d 3.822 and 3.868 as two singlets, as well as three anomeric protons at d 5.345, 4.380, and 4.290 for H-1^3, H-1^I, and H-1^2 as three doublets of *J* 8.4, 8.1, and 8.1 Hz, respectively. Deprotection of **16** to give **1** was executed in four steps via compound **17**. Compound **16** was refluxed for 2.5 h with a large excess of LiI in dry pyridine[18]. Purification of the product by gel filtration through Sephadex LH-20 in 1:1 $CHCl_3$–MeOH gave an 83% yield of the diacid dilithium salt **17** [R_f 0.27 in 35:10:1 $CHCl_3$–MeOH–AcOH]. Subsequent treatment of **17** with (i) 40% NH_2Me in MeOH[19], (ii) Ac_2O in MeOH, and (iii) NaOH in aq MeOH, afforded the target compound **1** {$[\alpha]_D$ −3.3° (*c* 0.2); R_f 0.36 in 6:4:1 $CHCl_3$–MeOH–H_2O; ESIMS $(M + O)^-$ 1803} in 57% overall yield, after purification of the crude product by preparative TLC in 6:4:1 $CHCl_3$–MeOH–H_2O, and then by gel filtration through Sephadex LH-20 in 6:4:1 $CHCl_3$–MeOH–H_2O. ^1H NMR (in 99:1 Me_2SO-d_6–D_2O, 60°C) of synthetic **1** was found to be indentical with that of the natural sample.

In summary, a stereocontrolled synthetic route to the ganglioside GD_2 was exploited for the first time by use of glycopentaosyl trichloroacetimidate **15** as a key glycosyl donor.

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