Tetrahedron Letters,Vol.31,No.3,pp385-388, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

A STEREOCONTROLLED TOTAL SYNTHESIS OF A *GANGLIO*-GANGLIOSIDE GM1b, IV^{3}NeuAcαGgOse$_4$Cer[1]

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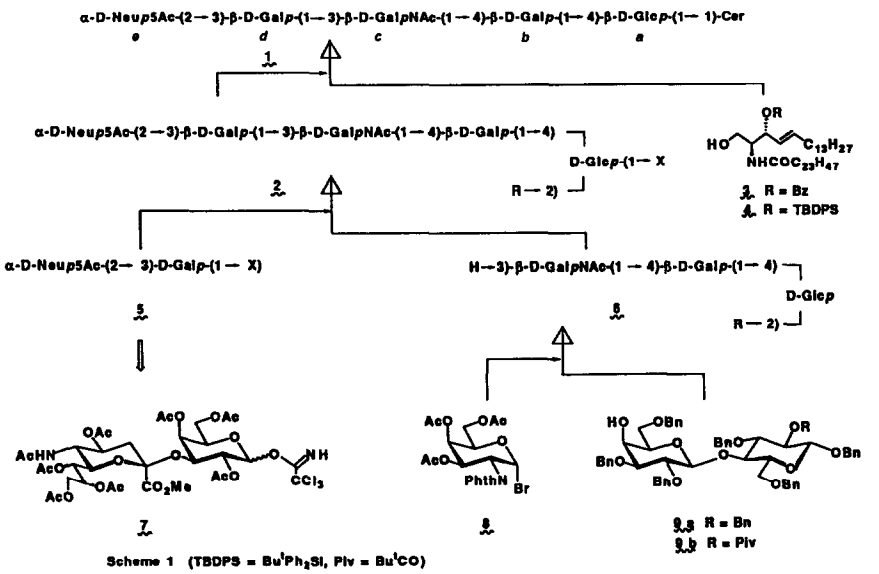
Abstract: A first total synthesis of *ganglio* ganglioside GM1b, α-D-Neu*p*5Ac-(2→3)-β-D-Gal*p*-(1→3)-β-D-Gal*p*NAc-(1→4)-β-D-Gal*p*-(1→4)-β-D-Glc*p*-(1→1)-Cer, was achieved in a stereocontrolled manner.

In 1973, biotransformation of gangliotetraosylceramide asialo GM1b into GM1b **1** was reported by Yip[2] and the structure was determined in 1975 by Stoffyn et al[3]. Subsequently GM1b was isolated from human erythrocyte membranes[4], rat tumor cells[5], mouse myeloid leukemia cells[6], mouse spleen[7], human brain[8], and murine T lymphoblast[9].

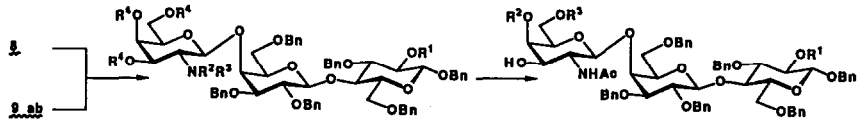


Scheme 1 (TBDPS = Bu^tPh_2Si, Piv = Bu^tCO)

As part of our project[10] on the synthesis of *ganglio* gangliosides, we now describe a first total synthesis of GM1b **1**, which clearly demonstrates the efficiency of O-2a pivaloyl group in **19b** over acetyl group in **19a** as an auxiliary[11] to achieve coupling between a glycan of *ganglio* series and a ceramide part.

Synthetic plan was delineated in scheme 1. A glycopentaosyl donor **2** armed with an auxiliary at O-2a is designed as a key glycosyl donor along with two kinds of known ceramide derivatives **3**[12] and **4**[13] as key glycosyl acceptors. The donor **2** was disconnected into a glycobiosyl donor **5** and a glycotriosyl acceptor **6**. A readily available[14] imidate **7** was chosen as an equivalent to the donor **5**. A glycosyl acceptor **6** may be designed as **13ab** and prepared as follows. $Sn(OTf)_2$[15] And powdered molecular sieves 4A (MS4A) promoted glycosylation of **9a**[16]

and **9b**[17] with **8**[18] in CH_3CN gave **10ab**[19] (a 67%; b 72%), which were further converted into glycosyl acceptors **13ab**[19] in 4 steps via **11ab**[19] and **12ab**[19] (1 $NH_2NH_2 \cdot H_2O$ in EtOH at 80°, 2 1:10 Ac_2O-MeOH, 3 $PhCH(OMe)_2$ and $TsOH \cdot H_2O$ in CH_3CN, 4 BH_3NMe_3-$AlCl_3$ in THF[20], a 36%; b 50% overall).

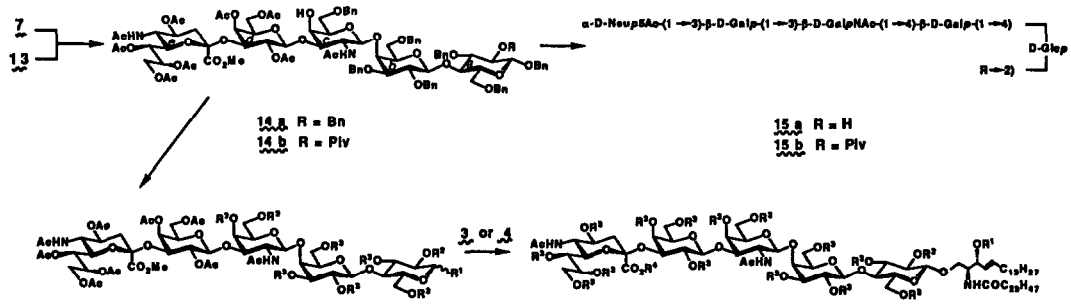


	R^1	R^2	R^3	R^4
10 a	Bn	Phth		Ac
10 b	Piv	Phth		Ac
11 a	Bn	H, Ac		Ac
11 b	Piv	H, Ac		Ac

	R^1	R^2	R^3
12 a	Bn	PhCH	
12 b	Piv	PhCH	
13 a	Bn	H	Bn
13 b	Piv	H	Bn

Scheme 2

Crucial couplings between **13ab** and **7** were achieved in $(CH_2Cl_2)_2$ by use of $BF_3 \cdot OEt_2$ as a promotor in the presence of MS4A to afford **14**[19] (a 50%, b 59%) whose configurations at newly introduced glycosidic linkages at C-1d were assigned as β-D by ^1H n.m.r. data after convertion into deblocked derivatives **15ab**[19] in 3 steps (1 NaOMe-MeOH, 2 NaOH-aq. MeOH, 3 10% Pd-C and H_2 in 8:2 MeOH-H_2O, a 63%; b 67% overall). Having determined the structures, **14ab** were smoothly converted into the key glycopentaosyl donors **19ab**[19] in a conventional manner in 4 steps (1 10% Pd-C and H_2 in MeOH, 2 Ac_2O in Py, 3 $NH_2NH_2 \cdot AcOH$ in DMF for 5 min at 50°[21], 4 Cl_3CCN and DBU[22] in $(CH_2Cl)_2$, a 36%; b 62%).



14 a R = Bn
14 b R = Piv

15 a R = H
15 b R = Piv

	R^1	R^2	R^3
16 a	OH	H	H
16 b	OH	Piv	H
17 a	OAc	Ac	Ac
17 b	OAc	Piv	Ac
18 a	OH	Ac	Ac
18 b	OH	Piv	Ac
19 a	$OCNHCCl_3$	Ac	Ac
19 b	$OCNHCCl_3$	Piv	Ac

	R^1	R^2	R^3	R^4
20 a	Bz	Ac	Ac	Me
20 b	Bz	Piv	Ac	Me
21 a	TBDPS	Ac	Ac	Me
1	H	H	H	Na

Scheme 3

Having necessary key intermediates **3**, **4** and **19ab** in our hands, the coupling experiments were performed employing $BF_3 \cdot OEt_2$ in the presence of MS4A at 20° under Ar. Reaction of the donor **19a** with the acceptor **3** in $CHCl_3$ and **4** in $(CH_2Cl)_2$ afforded 15.4 and 17.4% yield of the desired product **20a** and **21a**, respectively. On the other hand, the donor **19b** armed with pivaloyl auxiliary at O-2a upon reaction with the acceptor **3** did afford a 32% yield of the coupled

product **20b**, showing clearly the efficacy of pivaloyl over acetyl auxiliary at O-2a in the coupling between a ceramide equivalent and a *ganglio* series glycosyl donor. The result is in harmony with our previous experiments on *lacto*[23] and *globo*[24] series glycosyl donors. Both of the fully protected glycosphingolipids **20ab** were converted into the target molecule GM1b **1** in 2 steps (1 NaOMe in 1:1 MeOH-THF, 2 NaOH in 1:1:1 MeOH-THF-H_2O, finally purified by Sephadex LH-20 in 12:6:1 $CHCl_3$-MeOH-H_2O **a** and **b**: 78%).

In summary, a first total synthesis of GM1b was achieved in a stereocontrolled manner. ^1H-N.m.r. data recorded in 49:1 $(CD_3)_2SO$-D_2O for both synthetic **1** and human brain[8] GM1b were found in complete agreement.

Acknowledgment. We thank Dr. J. Uzawa and Mrs. T. Chijimatsu for recording and measuring the NMR spectra and Mrs. M. Yoshida and her staff for the elemental analyses. We also thank Ms. A. Takahashi and Ms. K. Moriwaki for their technical assistance.

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19 Physical data for key compounds are given below. Values of $[\alpha]_D$ and $\delta_{H,C}$ were recorded for

solutions in $CHCl_3$ and $CDCl_3$, respectively, at 23±3°, unless noted otherwise. **1**: δ_H (49:1 $(CD_3)_2SO$-D_2O, 24°) 4.513 (d, 7.0 Hz, 1c), 4.232 (d, 8.1 Hz, 1d), 4.191 (d, 7.7 Hz, 1b), 4.159 (d, 7.7 Hz, 1a), 2.771 (dd, 4.0, 12.5 Hz, 3eeq), 1.888 and 1.794 (2 s, 2NAc); **10a**: $[\alpha]_D$ +2.6° (c 1.1); δ_H 6.149 (dd, 3.3 and 11.4 Hz, 3c), 5.554 (d, 3.7 Hz, 4c), 5.381 (d, 8.4 Hz, 1c); δ_C 102.6 (1a), 102.1 (1b), 99.8 (1c), and 51.6 (2c); **10b**: $[\alpha]_D$ -12.5° (c 2.0); δ_H 6.157 (dd, 3.3 and 11.4 Hz, 3c), 5.558 (d, 3.3 Hz, 4c), 5.340 (d, 8.4 Hz, 1c), 1.219 (s, Bu^t); δ_C 102.2 (1b), 99.8 (1a) and 99.8 (1c), 51.6 (2c); **11a**: $[\alpha]_D$ +10.3° (c 1.0); δ_H 1.478 (s, Ac); δ_C 103.0 (1c), 102.6 (1a), 102.4 (1b), 62.5 (6c), 56.5 (2c); **11b**: $[\alpha]_D$ -9.7° (c 1.4); δ_H 5.119 (dd, 7.7 and 9.2 Hz, 2a), 1.499 (s, Ac), 1.165 (s, Bu^t); **12a**: $[\alpha]_D$ +24.5° (c 1.0); δ_H 5.595 (s, CHPh), 1.612 (s, Ac); δ_C 103.0 (1c), 102.6 (1ab), 101.3 (*C*HPh), 55.2 (2c); **12b**: $[\alpha]_D$ +1.2° (c 1.2); δ_H 5.583 (s, CHPh), 5.113 (dd, 8.1 and 9.2 Hz, 2a), 4.475 (d, 8.1 Hz, 1a), 4.482 (d, 7.7 Hz) and 4.428 (d, 7.3 Hz, 1bc); δ_C 103.1 (1c), 102.9 (1b), 101.4 (*C*HPh), 99.9 (1a), 55.2 (2c); **13a**: $[\alpha]_D$ +7.7° (c 1.2); δ_H 1.524 (s, Ac); δ_C 102.8, 102.6 and 102.4 (1abc), 56.4 (2c); **13b**: $[\alpha]_D$ -9.4° (c 0.7); δ_H 5.130 (dd, 7.7 and 9.2 Hz, 2a), 4.489 (d, 7.7 Hz, 1a), 1.537 (s, Ac), 1.164 (s, tBu); δ_C 102.8 and 102.5 (1bc), 99.9 (1a), 56.4 (2c); **14a**: $[\alpha]_D$ +16.6° (c 2.3); δ_H 7.40-7.15 (m, 8Ph), 3.837 (s, OMe); **14b**: $[\alpha]_D$ +6.6° (c 0.5); δ_H 7.40-7.15 (m, 7Ph), 3.841 (s, OMe); **15a**: δ_H (D_2O, $TMSCD_2CD_2CO_2Na$, 24°) 5.227 (d, 0.5 H, 4.0 Hz, 1aα), 4.714 and 4.709 (2d, 8.4 Hz, 1cαβ), 4.675 (d, 0.5 H, 8.1 Hz, 1aβ), 4.526 (d, 7.7 Hz, 1d), 4.494 (d, 8.1 H, 1b), 2.761 (dd, 4.8 and 12.8 Hz, 3eeq), 2.051, 2.049, and 2.037 (3s, 3Ac), 1.797 (t, 12.1 Hz, 3eax), **15b**: δ_H (D_2O, ^{t}BuOH 24° and 60°*) 5.315* (d, 0.5 H, 3.7 Hz, 1aα), 4.824* (d, 0.5 H, 8.1 Hz, 1aβ), 4.731* and 4.718* (2 d, 8.0 Hz, 1cαβ), 4.691* (dd, 0.5 H, 3.7 and 10.3 Hz, 2aα), 4.655* (dd, 0.5 H, 8.4 and 10.3 Hz, 2aβ), 4.504 (d, 7.7 Hz, 1d), 4.450 and 4.440 (2 d, 7.7 Hz, 1bαβ), 2.739 (dd, 4.8 and 12.8 Hz, 3eeq), 2.031, 2.027, and 2.016 (3 s, 3Ac), 1.776 (t, 12.1 Hz, 3eax); **16a**: $[\alpha]_D$ +6.2° (c 2.7, MeOH); δ_H (CD_3OD) 3.858 (s, OMe), 2.575 (dd, 4.5 and 12.2 Hz, 3eeq); **16b**: $[\alpha]_D$ +2.0° (c 1.0, MeOH); δ_H (CD_3OD) 3.864 (s, OMe), 2.585 (dd, 4.8 and 12.7 Hz, 3eeq), 1.544 (t, 12.1 Hz, 3eax), 1.228 (s, tBu); **17a** (α:β=1:1): δ_H 6.274 (d, 0.5 H, 3.7 Hz, 1aα), 5.665 (d, 0.5 H, 8.4 Hz, 1aβ), 3.841 (s, OMe), 2.585 (dd, 4.6 and 12.0 Hz, 3eeq); **17b** (α:β=1:1): δ_H 6.308 (d, 0.5 H, 3.7 Hz, 1aα), 5.703 (d, 0.5 H, 8.4 Hz, 1aβ), 3.842 (s, OMe), 2.577 (dd, 4.7 and 12.5 Hz, 3eeq), 1.701 (t, 12.5 Hz, 3eax); **18a**: δ_H 3.842 (s, OMe), 2.578 (dd, 4.8 and 12.8 Hz, 3eeq); **18b**: δ_H 3.840 (s, OMe), 2.578 (dd, 4.7 and 12.2 Hz, 3eeq); **19a**: $[\alpha]_D$ +31.0° (c 1.3); δ_H 6.499 (d, 3.7 Hz, 1a), 3.843 (s, OMe), 2.579 (dd, 4.5 and 12.4 Hz, 3eeq); δ_C 100.7, 100.0, 98.2, 96.8, 92.9 (5 anomeric C), 90.7 (CCl_3), and 37.6 (3e); **19b**: $[\alpha]_D$ +31.0° (c 2.5); δ_H 2.580 (dd, 4.8 and 12.8 Hz, 3eeq); **20a**: $[\alpha]_D$ +15.4° (c 0.3); δ_H 8.008 (d, 2 H, 8.4 Hz, Ph), 7.548 (t, H, 8.1 Hz, Ph), 7.439 (t, 2 H, 8.1 Hz, Ph), 5.869 (dt, 15.4 and 7.0 Hz, 5cer), 4.694 (d, 7.7 Hz, 1d), 4.427 (d, 7.7 Hz, 1a), 4.372 (d, 8.0 Hz, 1b), 2.578 (dd, 4.8 and 12.5 Hz, 3eeq), 1.694 (t, 12.5 Hz, 3eax), 0.879 (t, 7.0 Hz, $2CH_2CH_3$); δ_C 100.5, 100.5, 100.1, 98.2, 96.9 (5 anomeric C); **20b**: δ_H 2.577 (dd, 4.4 and 12.8 Hz, 3eeq), 0.880 (t, 6.6 Hz, $2CH_2CH_3$); **21a**: $[\alpha]_D$ +4.8° (c 0.3); δ_H (HOHAHA) 7.7-7.3 (m, aromatic), 5.269 (dd, 7.7 and 14.3 Hz, 4cer), 4.688 (d, 7.7 Hz, 1d), 4.411 (d, 8.1 Hz, 1a), 4.375 (d, 7.7 Hz, 1b), 3.843 (s, OMe), 2.579 (dd, 4.8 and 12.8 Hz, 3eeq), 1.005 (s, tBu), 0.883 (t, 7.0 Hz, CH_2CH_3), 0.879 (t, 7.0 Hz, CH_2CH_3).

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(Received in Japan 26 October 1989)