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A TOTAL SYNTHESIS OF PARA-FORSSMAN GLYCOLIPID ISOLATED FROM HUMAN ERYTHROCYTE MEMBRANE[1)]

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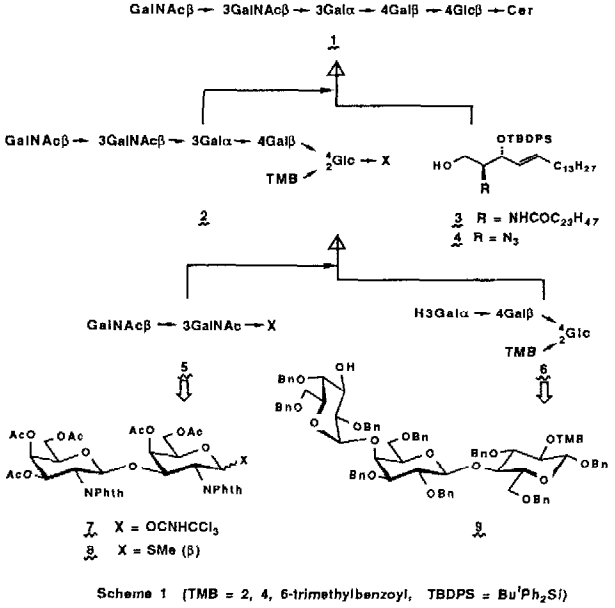
Abstract: A first total synthesis of Para-Forssman glycolipid, GalNAcβ1→3GalNAcβ1→3Galα1→4Galβ1→4Glcβ1→1Cer, is described to provide an unambiguous evidence for the proposed structure of the natural product.

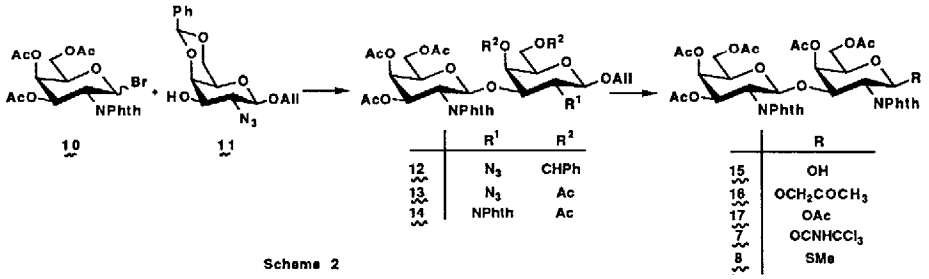
A novel globopentaosyl ceramide **1** was isolated from human red blood cells in 1982 and chemically characterized. **1** showed a precipitin reaction with anti-Globoside I antibody but no reaction with anti-Forssman antibody and was named Para-Forssman glycolipid[2]. We describe here a first total synthesis of **1**, which has provided a synthetic evidence for the proposed structure **1**.



Scheme 1 (TMB = 2, 4, 6-trimethylbenzoyl, TBDPS = Bu^tPh_2Si)

Based on a retrosynthetic analysis of **1**, a glycopentaosyl glycosyl donor **2** with trimethylbenzoyl auxiliary[3] at O-2a, and two glycosyl acceptors **3**[4] and **4**[5] as a ceramide equivalents were designed. The donor **2** was further disconnected into a glycobiosyl glycosyl donor **5** and a glycotriosyl glycosyl acceptor **6**, which were designed as either an imidate **7** or a thioglycoside **8**, and a readily available **9**[3], respectively.

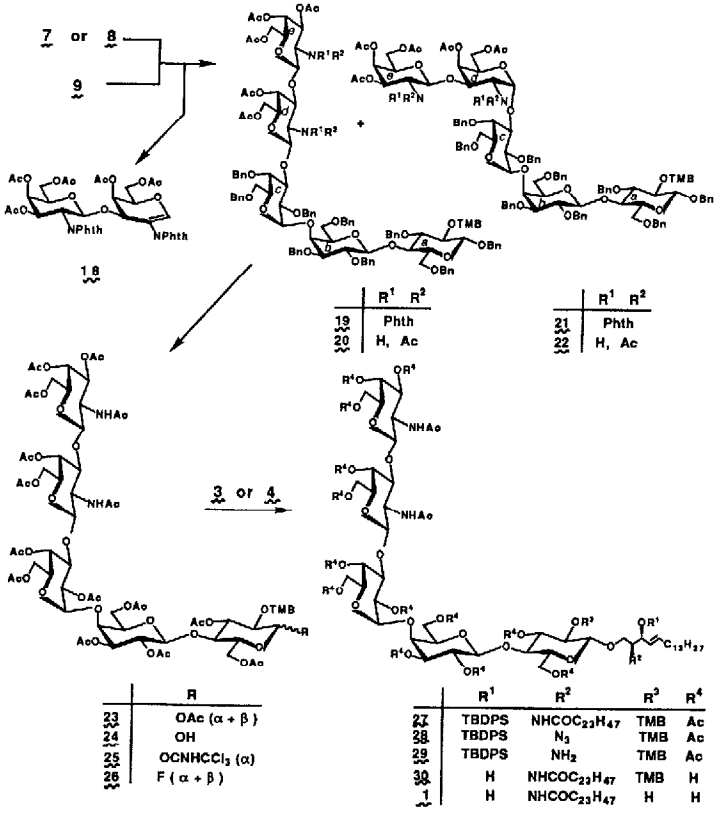
A practical route to the glycosyl donors **7** and **8** was developed as follows. Silver triflate and powdered molecular-sieves 4A (MS4A) promoted glycosylation of alcohol **11**[6] with bromide **10**[6] in $(CH_2Cl)_2$ gave stereoselectively a 94% yield of **12**[7], which was converted into **14**[7] via **13**[7] in 5 steps (1 4:1 AcOH-H_2O at 80°, 2 Ac_2O in Py, 3 MeONa in MeOH, 4 $HS(CH_2)_3SH$-Et_3N in MeOH[8], 5 phthalic anhydride-Et_3N-Py then Ac_2O at 75°, 39% overall). Deallylation of **14** by treatment with $(Ph_3P)_3RhCl$-DABCO in 7:3:1 EtOH-PhH-H_2O[9] and then $HgCl_2$-HgO in 9:1 Me_2CO-H_2O gave a 51% yield of **15**[7]. Removal of allyl group was achieved more efficiently in the presence of 3:1 $PdCl_2$-$(Ph_3P)_3RhCl$ in 5:1 AcOH-H_2O and crude **15** was acetylated to give a 70% yield of **17**[7] along with a 27% yield of **16**[7] as a by-product. In this specific case addition of $(Ph_3P)_3RhCl$ is essential to increase the yield of **17** and in the absence of added $(Ph_3P)_3RhCl$ a 1:1 mixture of **16** and **17** was obtained in 80% yield. Treatment of hemiacetal **15** with Cl_3CCN-DBU[10] in $(ClCH_2)_2$ at -15° afforded a 2:1 mixture of α- and β-trichloroacetimidates **7** in 68% yield. Another glycosyl



Scheme 2

donor **8** was also obtained in 93% yield from **17** by treatment[11] with $MeSSnBu_3$ and $SnCl_4$ in $(ClCH_2)_2$.

Crucial couplings between either glycobiosyl donors **7** or **8** and a glycotriosyl acceptor **9** were next examined. TMSOTf-MS4A promoted[12] glycosylation of **9** with **7** in $(ClCH_2)_2$ proceeded quickly at -20° to give a 31% yield of the desired product **19** stereoselectively together with a 65% recovery of **9**. Alternatively, $(Bu_4N)_2CuBr_4$-AgOTf-MS4A promoted[13] glycosylation of **9** with **8** in CH_3NO_2 proceeded at 20° to give an 8:1 mixture of **19** and **21** in 65% yield, and recovered **9** (31%). Use of $(ClCH_2)_2$ instead of CH_3NO_2 as a solvent deteriorated this reaction to afford a glycal **18**[7] (72%) as a major product. The inseparable 8:1 mixture of **19** and **21** was separated after convertion into **20** and **22** in 55 and 7% yield, respectively, from **9** in two steps (1 $NH_2NH_2 \cdot H_2O$ in EtOH for 14 h at 80°, 2 Ac_2O-DMAP in Py). Hydrogenolysis of **20** in the presence of 10% Pd-C in 7:3 MeOH-H_2O followed by acetylation gave an 1:1 mixture of **23**[7] α and β in 94% yield. Treatment of **23** with $NH_2NH_2 \cdot AcOH$ in DMF[14] afforded a 99% yield of **24**[7], which was further converted into glycosyl donors **25** (92%) and **26** (75%, α : β=1:5) by treatment with CCl_3CN-DBU in $(ClCH_2)_2$ and DAST in $(ClCH_2)_2$[15], respectively.



Scheme 3

Crucial glycosylation of **3** with a glycosyl donor **25** was performed in the presence of TMSOTf-MS4A in $(ClCH_2)_2$ but the formation of desired product **27** could not be detected by tlc examination. Use of a fluoride **26** in the presence of $SnCl_2$-AgOTf[16]-MS4A in $(ClCH_2)_2$, however, did afford a 6% yield of **27**[7]. In order to enhance the efficiency of this crucial coupling, an another glycosyl acceptor **4** was next examined.

$SnCl_2$-AgOTf-MS4A promoted glycosylation of **4** with **26** augmented the yield of the coupled product **28** to 43%. Slightly higher yield of 50% was attained by using Cp_2ZrCl_2-AgOTf-MS4A as a promotor according to Suzuki et al[17]. **28** was converted via **29** into **27** in two steps (1 Ph_3P in 1000:1 PhH-H_2O[18] at 45°, 2 $C_{23}H_{47}COOH$ and 2-chloro-1-methylpyridinium iodide in 1:1 Bu_3N-$(ClCH_2)_2$[19], 98% overall), which was further deprotected to afford the target glycolipid **1** via **30**[7] in three steps (1 Bu_4NF in THF, 2 2:1 0.1*M* MeONa in MeOH-THF at 20°, 3 2:1 0.25*M* MeONa in MeOH-THF at 60°, overall 88%). ^{1}H-N.m.r. data for synthetic **1** were in full agreement with those[20] for the natural glycolipid.

In conclusion, a stereo-controlled total synthesis of Para-Forssman glycolipid, globopentaosyl ceramide **1**, was achieved for the first time by employing glycopentaosyl fluoride **26** as a key glycosyl donor and the proposed structure **1** was eventually confirmed.

Acknowledgments. We are grateful to Dr. Susumu Ando for kindly sending us the 500 MHz ^{1}H-n.m.r. data of natural 1 taken in 49:1 $(CD_3)_2SO$-D_2O at 60°. We thank Dr. J. Uzawa, Mrs. T. Chijimatsu, and Mr. K. Fujikura for recording and measuring the NMR spectra and Ms. M. Yoshida and her staff for the elemental analyses. We also thank Ms. A. Takahashi and Ms. K. Moriwaki for their technical assistance.

Reference and Notes

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7) Physical data for new compounds are compatible with the assigned structures and are given below. Values of $[\alpha]_D$ and $\delta_{H,C}$ were measured for the solution in $CHCl_3$ and $CDCl_3$, respectively, at 25°± 3° unless noted otherwise. **1**: $[\alpha]_D$ -8.0° (c 0.1 py); δ_H (49:1 $(CD_3)_2SO$-D_2O, 60°) 5.544 (td, 6.7 and 15.3 Hz, 5cer), 5.363 (dd, 6.4 and 15.3 Hz, 4cer), 4.820 (d, 3.6 Hz, 1c), 4.560 (d, 8.6 Hz, 1d), 4.483 (d, 8.3 Hz, 1e), 4.267 (d, 7.7 Hz, 1b), 4.163 (d, 7.9 Hz, 1a), 1.834 and 1.844 (2s, 2NAc), and 0.884 (t, 6.7 Hz, 2Me); 7(α): $[\alpha]_D$ +49.0° (c 1.4); δ_H 8.464 (s, NH), 6.293 (d, 3.6 Hz, 1a); 7(β): $[\alpha]_D$ +30.40° (c 1.3); δ_H 8.490 (s, NH), 6.260 (d, 8.8 Hz, 1a); **8**: $[\alpha]_D$ +24.4° (c 1.2); δ_H 5.339 (d, 8.2 Hz, 1b), 5.029 (d, 10.4 Hz, 1a), 2.182, 2.180, 2.082, 2.077, 2.067, and 1.723 (6s, Ac x 5 and SMe); δ_C 98.0 (1b), 80.8 (1a); **12**: $[\alpha]_D$ -1.7° (c 1.2); δ_H 5.536 (s, CHPh), 5.512 (d, 8.6 Hz, 1b), 4.255 (d, 7.8 Hz, 1a); δ_C 101.2 (1a), 100.8 (*C*HPh), 100.4 (1b); **13**: $[\alpha]_D$ +9.0° (c 1.1); 5.454 (d, 2.2 Hz, 4b), 5.447 (d, 8.3 Hz, 1b), 5.319 (d, 2.2 Hz, 4a), 4.213 (d, 7.3 Hz, 1a); **14**: $[\alpha]_D$ +17.8° (c 1.4); δ_H 5.508 (d, 2.4 Hz, 4b), 5.354 (d, 3.1 Hz, 4a), 5.347 (d, 8.5 Hz, 1b), 5.015 (d, 8.5 Hz, 1a), 4.796 (dd, 3.4 and 11.2 Hz, 3a);

15: $[\alpha]_D$ +34.8° (c 0.8); **16**: $[\alpha]_D$ -5.0° (c 1.0); δ_H 5.355 (d, 8.3 Hz, 1b), 4.972 (d, 8.5 Hz, 1a), 4.110 and 4.041 (2d, 17.4 Hz, OCH_2CO), 2.188, 2.178, 2.076, 2.072, 1.908, and 1.726 (6s, 6Ac); **17**: $[\alpha]_D$ +27.7° (c 1.6); δ_H 6.148 (d, 8.8 Hz, 1a), 5.360 (d, 8.2 Hz, 1b), 2.193, 2.178, 2.078, 2.071, 1.875, and 1.722 (6s, 6Ac); δ_C 98.0 (1b) and 90.4 (1a); **18**: $[\alpha]_D$ +1.7° (c 1.0); δ_H 6.556 (s, 0.9 Hz, 1a), 5.321 (d, 8.3 Hz, 1b), 2.191, 2.163, 2.101, 2.074, and 1.718 (5s, 5Ac). A mixture of **19** and **21**: δ_H 5.530 (dd, 3.4 and 11.3 Hz, 3e of **19**) and 5.660 (dd, 3.4 and 11.3 Hz, 3e of **21**); **20**: $[\alpha]_D$ +12.5° (c 0.6); δ_H 5.406 (dd, 7.9 and 9.5 Hz, 2a), 5.318 (d, 2.8 Hz, 4e), 5.223 (d, 2.7 Hz, 4d), 5.212 (dd, 3.3 and 11.3 Hz, 3e), 4.954 (d, 3.3 Hz, 1c), 2.270 (s, PhMe), 2.082 (s, 2PhMe), 2.136, 2.033, 2.033, 1.975, 1.889, 1.880 and 1.553 (7s, 7Ac); δ_C 102.9($^1J_{CH}$ 163 Hz, 1b), 100.7 ($^1J_{CH}$ 160 Hz, 1d), 100.2 ($^1J_{CH}$ 163 Hz, 1e), 99.9 ($^1J_{CH}$ 160 Hz, 1a) and 99.7 ($^1J_{CH}$ 168 Hz, 1c); **22**: $[\alpha]_D$ +39.3° (c 0.4); δ_H 5.380 (dd, 7.8 and 9.5 Hz, 2a), 2.244 (s, PhMe), 2.089 (s, 2PhMe), 2.079, 2.036, 2.029, 2.001, 1.925, 1.817 and 1.608 (7s, 7Ac); δ_C 103.4 ($^1J_{CH}$ 160 Hz, 1b), 99.8 ($^1J_{CH}$ 160 Hz, 1a), 98.5 ($^1J_{CH}$ 160 Hz, 1e), 97.1 ($^1J_{CH}$ 168 Hz, 1c), and 92.6 ($^1J_{CH}$ 170 Hz, 1d); **23**α and β: δ_H 6.471 (d, 3.7 Hz, 1aα) and 5.704 (d, 8.2 Hz, 1aβ); **24**: $[\alpha]_D$ +65.8° (c 0.7); **25**: $[\alpha]_D$ +54.6° (c 0.8); δ_H 8.750 (s, C=NH), 6.836 (s, 2PhH), and 6.698 (d, 3.4 Hz, 1a); **26**: α:β=1:5, δ_H 6.869 (s, 2PhH), 5.893 (dd, 2.4 and 53.4 Hz, 1aα), 5.489 (dd, 5.2 and 52.5 Hz, 1aβ), 5.016 (d, 8.0 Hz, 1cβ), 4.989 (d, 8.3 Hz, 1eα); **27**: $[\alpha]_D$ +36.6° (c 0.2); δ_H 6.820 (s, 2PhH), 5.012 (d, 8.2 Hz, 1d), 4.946 (d, 3.9 Hz, 1c), 4.790 (d, 8.3 Hz, 1e), 1.009 (s, tBu), and 0.880 (t, 6.7 Hz, 2Me); **28**: $[\alpha]_D$ +32.3° (c 0.6); δ_H 6.831 (s, 2PhH), 5.601 (d, 3.1 Hz, 4c), 5.396 (d, 2.9 Hz, 4d), 5.307 (d, 3.1 Hz, 4e), 4.995 (d, 8.2 Hz, 1d), 4.934 (d, 3.6 Hz, 1c), 4.771 (d, 8.0 Hz, 1e), 4.764 (dd, 1.8 and 11.0 Hz, 2c), 1.051 (s, tBu), and 0.881 (t, 6.7 Hz, Me); **30**: $[\alpha]_D$ +14.2° (c 0.1); δ_H (49:1 $(CD_3)_2SO$-D_2O, 60°) 6.854 (s, 2PhH), 5.518 (td, 7.1 and 15.4 Hz, 5cer), 5.352 (dd, 6.7 and 15.4 Hz, 4cer), 4.849 (dd, 8.6 and 9.0 Hz, 2a), 4.807 (d, 3.6 Hz, 1c), 4.556 (d, 8.5 Hz, 1d), 4.540 (d, 7.9 Hz, 1a), 4.479 (d, 7.6 Hz, 1e), 4.298 (d, 7.6 Hz, 1b), 2.234 (s, 3PhMe), 1.827 (s, 2Ac), and 0.844 (t, 6.7 Hz, 2Me).

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