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STEREOSELECTIVE TOTAL SYNTHESIS OF THE BLOOD GROUP I-ACTIVE BIANTENNARY *NEOLACTO*-GLYCODECAOSYL CERAMIDE[1]

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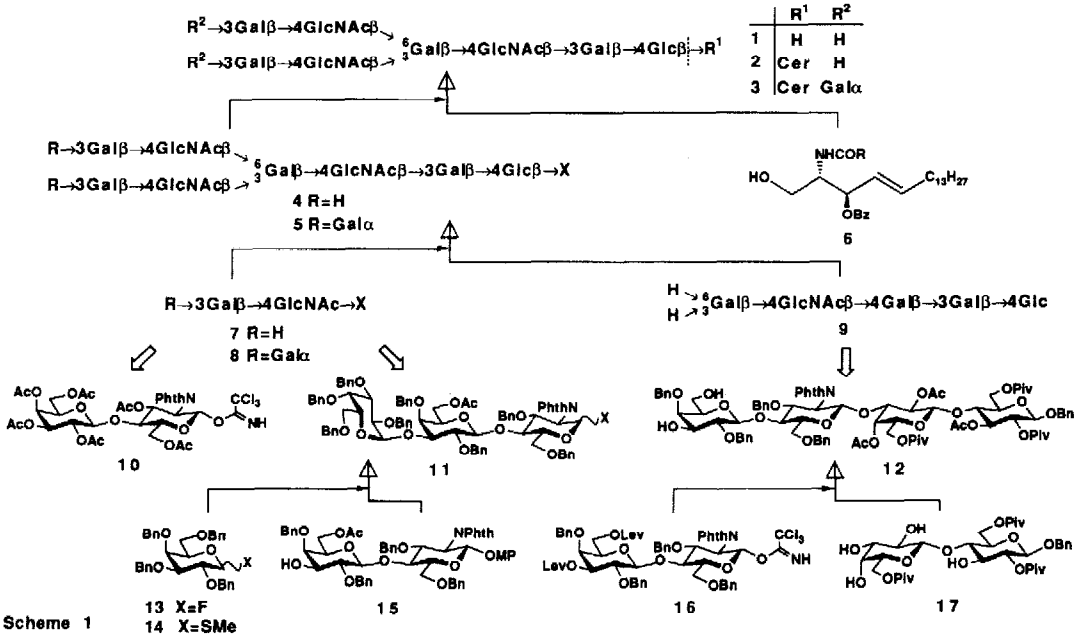
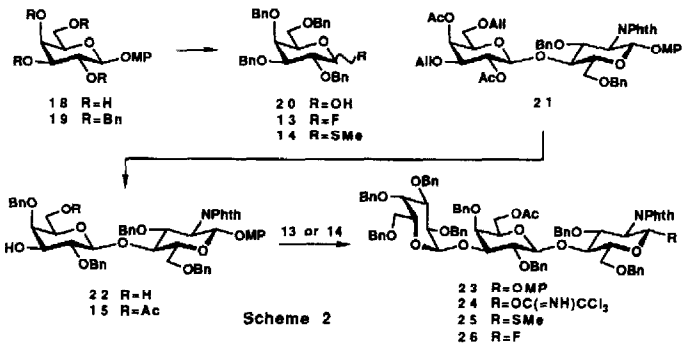
Abstract: A stereocontrolled total synthesis of biantennary *neolacto*-glycodecaosyl ceramide was achieved for the first time.

In 1981, Hanfland[2] et al. reported isolation and characterization of an I-active glycodecaosyl ceramide **3**. Because of the biological significance[3] as well as the structural diversity[4] of I-active glycosyl ceramides, we started our project on their synthesis and in 1986 reported the first synthesis[5] of the octasaccharide **1**. Both chemical[6] and enzymic[7] synthesis of closely related I-active hexasaccharide were reported independently in 1986. Here we describe for the first time a total synthesis of both glycooctaosyl ceramide **2** and glycodecaosyl ceramide **3**. Retrosynthetic analysis of **2** and **3** shown in scheme 1 led us to design two glycosyl donors **10**[8] and **11**, and a glycosyl acceptor **12**. The glycosyl donor **11** was synthesized from the coupling of either **13** or **14** with **15**, while the key glycotetraosyl glycosyl acceptor **12** designed as a common intermediate for the synthesis of both **2** and **3** was synthesized via the regioselective glycosylation of the tetraol **17** with the imidate **16**.

The fluoride **13**[9] was readily obtainable from **18**[10] via **19**[9] in three steps (*1* BnBr, NaH in DMF, *2* CAN[11] in 4:1 CH_3CN-H_2O, 0°, 30 min, *3* DAST[12] in $(ClCH_2)_2$, 0°, 30 min, 64% overall). The glycotriosyl donors **24-26** were prepared as follows. Compound **21**[13] was converted into **15**[9] via **22**[9] in 4 steps (*1* LiOH, 30% H_2O_2 in THF[14], *2* Ag_2O, KI, BnBr in DMF, *3* $[Ir(COD)(PMePh_2)_2]PF_6$ in THF[15], then I_2 in 4:1 THF-H_2O, *4* AcCl in Py at 0°, 43% overall). Glycosylation of **15** with fluoride **13** in the presence of $SnCl_2$[16], $AgClO_4$ and molecular sieve 4A (MS4A) in Et_2O at -20°~10° gave 80% of **23**[9] together with 12% of the β-anomer. Use of the thioglycoside **14**[17], however, improved

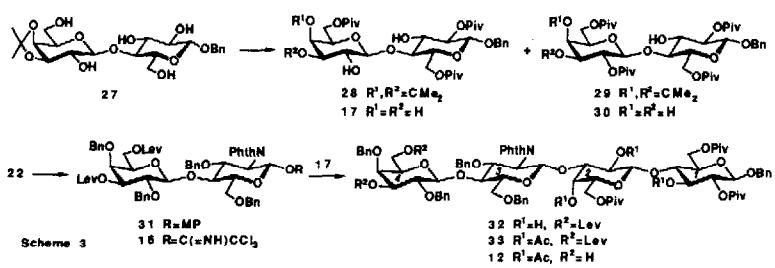


Scheme 1



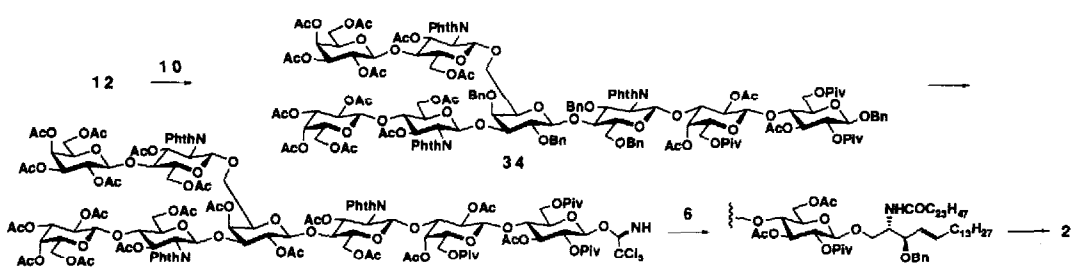
Scheme 2

the stereoselectivity. Reaction of **14**(β) with **15** in the presence of $CuBr_2$-nBu_4NBr-MS4A[18] in 5:1 $(ClCH_2)_2$-DMF gave 95% of **23** with the concomitant formation of only 2% of the β-anomer. Compound **23** was transformed into trichloroacetimidate **24**[9] in two steps (*1* CAN in 25:19:12 CH_3CN-MePh-H_2O, 25°, 20 min, *2* CCl_3CN[19] and DBU in $(ClCH_2)_2$, 0°, 50 min, overall 78%). Treatment of **24** with Bu_3SnSMe and BF_3•OEt_2 in $(ClCH_2)_2$ at -23° for 80 min gave 95% of thioglycoside **25**[9]. Conversion of **23** into fluoride **26**[9] was carried out in 2 steps as described in the preparation of **13** in 77% overall. Now glycosyl donors designed in scheme 1 being available, synthesis of key glycosyl acceptor **12** was performed as follows. Partial acylation of **27**[20] with ^tBuCOCl-DMAP-Et_3N in $(ClCH_2)_2$ at -5° afforded 51% of **28**[9] and 27% of **29**, which were treated with TsOH in 1:1 dioxane-MeOH at 50° afforded **17**[9] (92%) and **30**[9] (94%), respectively. The trichloracetimidate **16**[9] was prepared from **22** via **31** in 3 steps (*1* Lev_2O, DMAP in 4:3 Py-$(ClCH_2)_2$, *2* CAN in 4:3:2 CH_3CN-MePh-H_2O, 20°, 1h, *3* Cl_3CCN, DBU in $(ClCH_2)_2$, 0°, 1h, 82% overall). TMSOTf promoted glycosylation of **17** with **16** in 2:1 PhMe-$(ClCH_2)_2$ at -23° afforded 72% yield of the β1→3 linked compound **32**[9] as a main product along with 13% yield of the minor regioisomers. Conversion of **32** into **12**[9] was carried out via **33** in 2 steps (*1* Ac_2O in Py, *2* NH_2NH_2•AcOH in EtOH, 20°, 50 min, 81% overall).



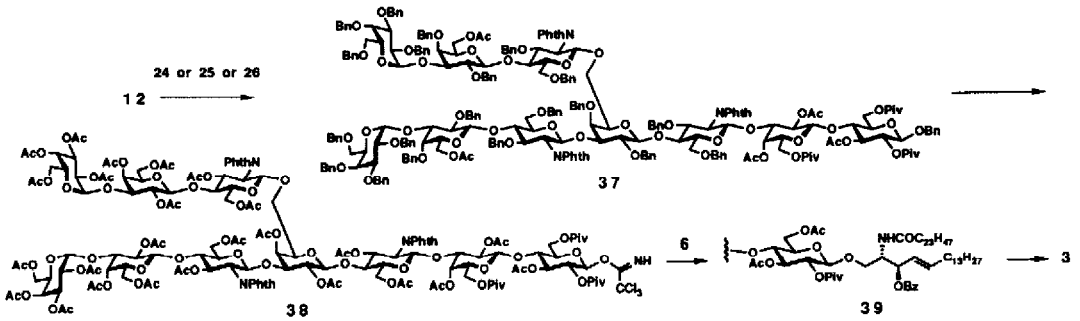
Scheme 3

TMSOTf promoted glycosylation of **12** with trichloroacetimidate **10** at -23° proceeded to give 63% of the desired compound **34**[9] which was subsequently converted to the glycooctaosyl donor **35**[9] in 4 steps (*1* $Pd(OH)_2$; H_2 in MeOH, *2* Ac_2O, DMAP in Py, *3* NH_2NH_2•AcOH in DMF, 50°, 20 min, *4* Cl_3CCN, DBU in $(ClCH_2)_2$, 71% overall). Coupling between **35** and **6**[21] in $CHCl_3$ in the presence of TMSOTf and MS4A afforded 59% of **36**[9] which was converted into glycooctaosyl ceramide **2**[9] in 3 steps (*1* 40% $MeNH_2$[22] in MeOH, 20°, 40h, *2* Ac_2O, DMAP in Py, 50°, 16h, *3* MeONa in 1:1 MeOH-THF, 65°, 16h; 73% overall). ^{1}H-nmr data for synthetic **2** was in complete agreement with that for natural sample[23].



Scheme 4

Next, we studied the coupling reactions of glycotriosyl donors **24**, **25**, and **26** with glycotetraosyl acceptor **12**. TMSOTf promoted glycosylation of **12** with trichloroacetimidate **24** in $(ClCH_2)_2$ at -23° gave only 23% of **37**[9]. Similarly glycosylation of **12** with thioglycoside **25** in the presence of $CuBr_2$-Bu_4NBr-AgOTf afforded only 16% of **37**. Best result was obtained by employing fluoride **26**, which was reacted with **12** in the presence of Cp_2HfCl_2[24] and AgOTf in $(ClCH_2)_2$ at -23° to give 88% of **37**. Conversion of **37** into **38**[9] was achieved as described for **35** in 4 steps in 58% overall. Crucial coupling between **38** and **6** was achieved in the presence of TMSOTf and MS4A in $CHCl_3$ at -23° to give 54% of **39**[9] which was further converted into the target molecule **3** as described for **2** in 3 steps in 56% overall yield. ^{1}H-nmr data for synthetic **3** were in complete agreement with those for natural **3** reported by Hanfland et al[2].



Scheme 5

In conclusion, l-active glycooctaosyl and glycodecaosyl ceramides **2** and **3** were synthesized for the first time by employing glycotetraosyl acceptor **12** as a key intermediate and trichloroacetimidates **35** and **38** as the glycosyl donors for the crucial coupling with ceramide derivative **6**.

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References and Notes

1 Part 84 in the series "Synthetic Studies on Cell-Surface Glycans". For part 83, see C. Murakata and T. Ogawa, *Carbohydr. Res.* submitted.

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9 Physical data for new compounds are given below, values of $[\alpha]_D$ and $\delta_{H,C}$ were measured at 25°±3° for solutions in $CHCl_3$ and $CDCl_3$, respectively, unless noted otherwise. **2**: R_F 0.34 in 6:4:1 $CHCl_3$-MeOH-H_2O; $[\alpha]_D$ +10.0° (c 0.1, py); δ_H (49:1:1 $DMSOd_6$-D_2O-CD_3OD, 60°) 1.828 (s, Ac), 1.846 (s, 2Ac), 4.180 (d, 7.7Hz, 1^1), 4.237 (d, 6.6Hz, 1^6 and $1^{6'}$), 4.285 (d, 7.0Hz, 1^2), 4.318 (d, 7.0Hz, 1^4), 4.434 (d, 8.1Hz, $1^{5'}$), 4.688 (d, 8.1Hz, 1^3 and 1^5), 5.380 (dd, 7.0 and 15.4Hz, 4^{Cer}), 5.563 (td, 7.0 and 15.4Hz, 5^{Cer}). **3**: R_F 0.32 in 6:4:1 $CHCl_3$-MeOH-H_2O; $[\alpha]_D$ +39.5° (c 0.1, py); δ_H (49:1:1 $DMSOd_6$-D_2O, 60°) 0.855 (t, 6.8Hz, 2Me), 1.831 (s, Ac), 1.850 (s, 2Ac), 4.175 (d, 7.3Hz, 1^1), 4.282 (d, 6.2Hz, 1^2), 4.308 (d, 7.3Hz, 1^4, 1^6, and $1^{6'}$), 4.432 (d, 7.3Hz, $1^{5'}$), 4.689 (d, 8.1Hz, 1^3 and 1^5), 4.855 (d, 3.3Hz, 1^7 and $1^{7'}$), 5.374 (dd, 7.0 and 15.4Hz, 4^{Cer}), 5.557 (td, 7.0 and 15.4Hz, 5^{Cer}). **12**: R_F 0.39 in

1:1 toluene-EtOAc; $[\alpha]_D$ +1.5° (c 0.1); δ_H 1.080, 1.190, and 1.217 (3s, 3Piv), 1.688, 1.900, and 2.091 (3s, 3Ac), 4.173 (d, 8.1Hz, 1^2), 5.121 (d, 8.4Hz, 1^3), 5.338 (d, 3.7Hz, 4^2). **13**: δ_H 5.166 (dd, 0.5H, 7.0 and 53.1Hz, 1β), 5.588 (dd, 2.5 and 53.5Hz, 1α), for the alternative synthesis see ref. 25. **15**: R_F 0.26 in 3:2 hexane-EtOAc; $[\alpha]_D$ +41.5° (c 1.0); δ_H 2.004 (s, Ac), 3.696 (s, OMe), 4.468 (d, 7. Hz, 1^2), 5.623 (d, 8.6Hz, 1^1). **16**: R_F 0.43 in 2:1 toluene-EtOAc; δ_H 2.147 and 2.184 (2s, 2Lev), 6.399 (d, 8.4Hz, 1^1), 8.533 (s, NH). **17**: R_F 0.40 in 10:1 $CHCl_3$-MeOH; $[\alpha]_D$ -11.2° (c 1.0); mp 124-125° (iPr_2O); δ_H 1.171, 1.184, and 1.240 (3s, 3Piv), 4.293 (d, 8.1Hz, 1^2), 4.476 (d, 8.1Hz, 1^1), 4.920 (dd, 8.1 and 9.9Hz, 2^1). **19**: R_F 0.60 in 3:1 hexane-EtOAc; $[\alpha]_D$ -17.6° (c 1.1); δ_H 3.738 (OMe). **22**: R_F 0.33 in 3:2 toluene-EtOAc, $[\alpha]_D$ +44.2° (c 1.3); δ_H 4.459 (d, 7.3Hz, 1^2), 5.638 (d, 8.2Hz, 1^1). **23**: R_F 0.33 in 4:1 toluene-EtOAc; $[\alpha]_D$ +50.7° (c 0.9); δ_H 1.955 (s, Ac), 3.684 (s, OMe), 4.465 (d, 7.7Hz, 1^2), 5.217 (d, 3.3 Hz, 1^3), 5.575 (d, 8.4 Hz, 1^1). **24**: R_F 0.53 in 4:1 toluene-EtOAc; $[\alpha]_D$ +56.4° (c 1.0); δ_H 1.962 (s, Ac), 5.202 (d, 3.3 Hz, 1^3), 6.363 (d, 7.8Hz, 1^1), 8.505 (s, NH). **25**: R_F 0.55 in 3:1 toluene-EtOAc; $[\alpha]_D$ +45.1° (c 1.1); δ_H 1.862 (s, SMe), 1.940 (s, Ac), 5.089 (d, 9.9Hz, 1^1), 5.209 (d, 2.9Hz, 1^3). **26**: R_F 0.56 in 4:1 toluene-EtOAc; δ_H 1.952 (s, Ac), 5.205 (d, 3.3Hz, 1^3), 5.600 (dd, 0.08H, 3.5 and 54.0 Hz, $1^1\alpha$), 5.800 (dd, 0.92H, 7.5 and 53.5 Hz, $1^1\beta$). **28**: R_F 0.42 in 2:1 toluene-EtOAc; $[\alpha]_D$ +5.6° (c 1.2); δ_H 1.175, 1.192, and 1.236 (3s, 3Piv), 1.335 and 1.510 (2s, CMe_2), 4.229 (d, 8.1Hz, 1^2), 4.451 (d, 8.1Hz, 1^1), 4.930 (dd, 8.1 and 9.5Hz, 2^1). **30**: R_F 0.45 in 1:1 toluene-EtOAc; $[\alpha]_D$ -8.1° (c 0.9); δ_H 1.175, 1.201, 1.217 and 1.235 (4s, 4Piv), 4.907 and 4.990 (2dd, 8.1 and 9.5Hz, 2^1 and 2^2). **31**: R_F 0.60 in 1:1 toluene-EtOAc; mp 112-113° (Et_2O-iPr_2O); $[\alpha]_D$ +47.9° (c 0.9); δ_H 2.146 and 2.192 (2s, 2Lev), 3.692 (s, OMe), 4.499 (d, 7.7Hz, 1^2), 4.854 (dd, 2.8 and 9.9Hz, 3^2), 5.609 (d, 8.1Hz, 1^1). **32**: R_F 0.40 in 1:1 toluene-EtOAc; $[\alpha]_D$ +20.2° (c 1.3); δ_H 1.132, 1.143, and 1.146 (3s, 3Piv), 2.157 and 2.184 (2s, 2Lev), 5.338 (d, 8.8Hz, 1^3). **34**: R_F 0.41 in 1:1 toluene-EtOAc; $[\alpha]_D$ -10.3° (c 1.1); δ_H 1.069, 1.171, and 1.191 (3s, 3Piv), 1.629, 1.860, 1.877, 1.901 1.918, 1.963, 1.981, 2.028, 2.029, 2.036, 2.051, 2.055, 2.128, 2.138, and 2.149 (15s, 15Ac), 5.449 (d, 8.4Hz, 1^5), 5.652 and 5.703 (2dd, 8.8 and 10.6 Hz, 3^5 and $3^{5'}$). **35**: R_F 0.60 in 1:3 toluene-EtOAc; $[\alpha]_D$ +23.8° (c 0.4); δ_H 1.089, 1.192, and 1.211 (3s, 3Piv), 1.693, 1.756, 1.771, 1.869, 1.885, 1.926, 1.943, 1.970, 1.973, 2.036, 2.040, 2.064, 2.083, 2.092, 2.098, 2.105, 2.134, 2.134, and 2.159 (18s, 19Ac), 5.416 (d, 8.4Hz, 1^5), 5.542, 5.636, and 5.653 (3dd, 8.5 and 10.0Hz, 3^3, 3^5, and $3^{5'}$), 6.441 (d, 3.7Hz, 1^1), 7.65-7.90 (m, 3Phth), 8.591 (s, NH). **36**: R_F 0.52 in 2:1 CCl_4-Me_2CO; $[\alpha]_D$ +9.8° (c 0.6); δ_H 0.878 (t, 7.0Hz, 2Me), 1.097, 1.129, and 1.218 (3s, 3Piv), 1.686, 1.740, 1.756, 1.869, 1.884, 1.906, 1.943, 1.970, 1.973, 2.036, 2.039, 2.063, 2.069, 2.083, 2.096, 2.104, 2.133, 2.134, and 2.159 (19s, 19Ac), 5.833 (td, 7.3 and 15.0Hz, 5^{Cer}), 7.40-8.00 (m, Bz and 3Phth). **37**: R_F 0.40 in 3:1 toluene-EtOAc; $[\alpha]_D$ +14.5° (c 1.4); δ_H 1.069, 1.168, and 1.184 (3s, 3Piv), 1.631, 1.845, 1.890, 1.903, and 2.026 (5s, 5Ac), 5.180 (d, 3.3Hz, 4^2), 5.217 (d, 3.3Hz, 1^7 and $1^{7'}$), 5.251 (d, 8.4Hz, 1^3 or ^{5}). **38**: R_F 0.47 in 1:3 toluene-EtOAc; δ_H 1.088, 1.194, and 1.211 (3s, 3Lev), 5.540, 5.625 and 5.645 (3dd, 8.5 and 10.5Hz, 3^3, $3^5$and $3^{5'}$), 6.441 (d, 3.7Hz, 1^1), 7.60-7.90 (m, 3Phth), 8.591 (s, NH). **39**: R_F 0.62 in 1:3 toluene-EtOAc; $[\alpha]_D$ +32.4° (c 0.6); δ_H 0.879 (t, 7.0Hz, 2Me), 1.098, 1.132, and 1.220 (3s, 3Piv), 5.834 (td, 7.0 and 15.0Hz, 5^{Cer}), 7.40-8.05 (m, Bz and 3Phth).

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