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# SYNTHESIS OF TRIANTENNARY BLOOD GROUP I ANTIGENS: *NEOLACTO*-GLYCOPENTADECAOSYL CERAMIDE[1]

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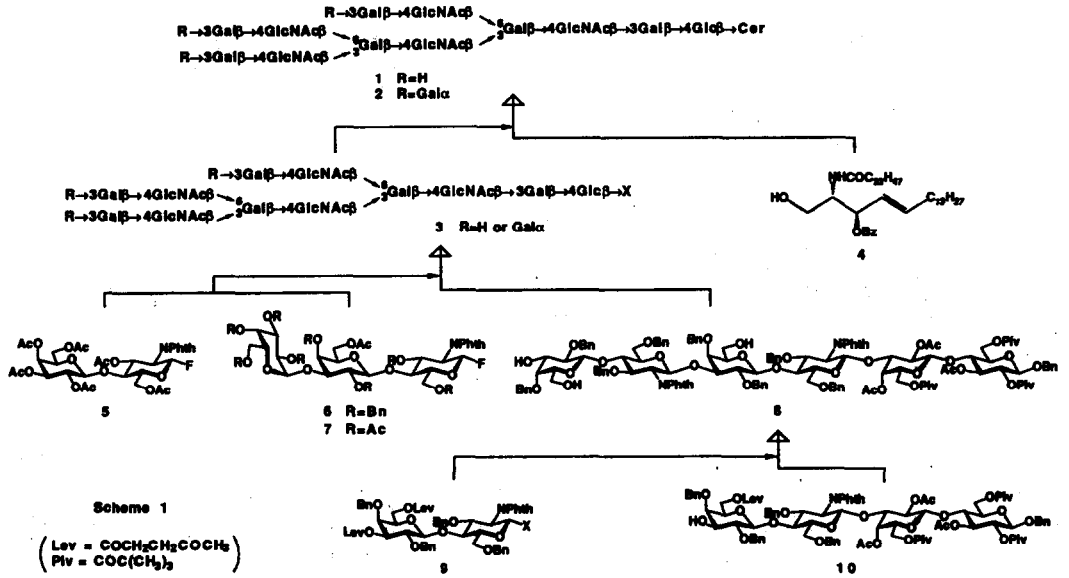
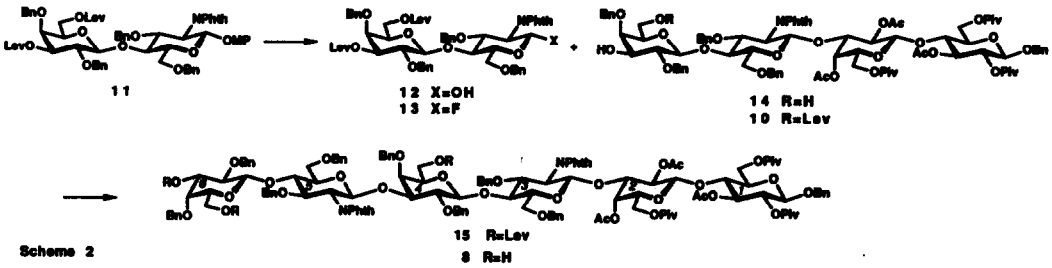
**Abstract:** A stereocontrolled total synthesis of triantennary *neolacto*-glycopentadecaosyl ceramide was achieved for the first time.

Branched poly-N-acetyl-lactosamine type structures that are expressed on the cell surface of embryonic and transformed cells have significant biological functions in terms of cell-cell recognition and differentiation[2]. Synthetic studies on the poly-N-acetyl-lactosamine type glycosyl ceramides have so far been focussed mainly for linear[3] and biantennary[4] *neolacto* series. Interested by the isolation and characterization of triantennary poly-N-acetyl-lactosamine type glycosyl ceramide **2** from rabbit erythrocyte membranes[5] as well as of other related structures from human placenta[6], we have studied a reasonable synthetic approach toward the triantennary structures **1** and **2**. The retrosynthetic analysis shown in scheme 1 led us to design a glycosyl donor **3** and a ceramide derivative **4**. The former may be further disconnected into glycosyl donors **5** and **6**[4] (or **7**), and a glycohexaosyl acceptor **8**. The key intermediate **8** may be reconstructed from glycosyl donor **9** and glycotetraosyl acceptor **10**.



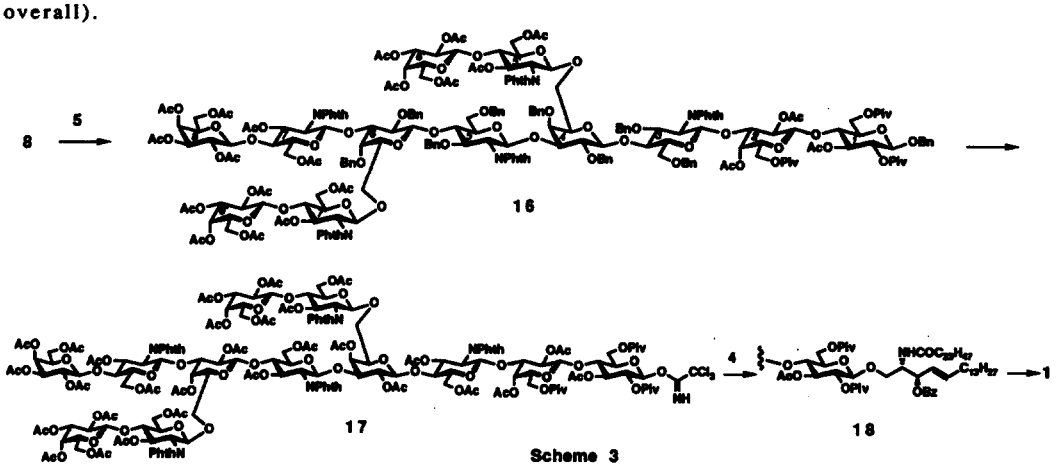

The glycohexaosyl acceptor **8** was synthesized as follows. The known compounds **11**[4] was converted in two steps into fluoride **13**[7] via **12**[7] (*1* CAN[8] in 4:3:2 $CH_3CN$-toluene-$H_2O$, 2 DAST[9] in $(ClCH_2)_2$, 89% overall). Selective protection of diol **14**[4] was carried out by treatment with LevOH, 2-chloro-1-methylpyridinium iodide (CMPI) and DABCO[10] in $(ClCH_2)_2$ for 40 min at 25° to give nearly quantitative yield of **10**[7]. Glycosylation of **10** with **13** in the presence of $Cp_2HfCl_2$[11],

AgOTf and powdered molecular sieve 4A (MS4A) in $(ClCH_2)_2$ for 3.5h at -23° afforded 96% of 15[7]. Three levuloyl groups in 15 was easily removed by $NH_2NH_2$•AcOH in 3:1 EtOH-THF to give 94% of the designed key intermediate triol 8[7].



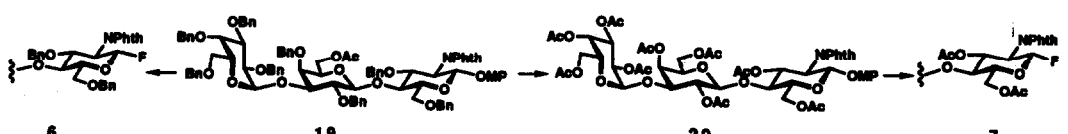

Scheme 2

Having prepared compound 8, synthesis of glycododecaosyl ceramide 1 was first studied. $Cp_2Hf(OTf)_2$ promoted[11] coupling of 8 with 2.7 equivalents of 5 that was readily available from corresponding hemiacetal[12] by treatment with DAST afforded 92% of glycododecaoside 16[7]. Conversion of 16 into trichloroacetimidate 17 was achieved in 4 steps (*1* 10% $Pd(OH)_2$-C and $H_2$ in 16:1 MeOH-EtOAc, *2* $Ac_2O$ and DMAP in Py at 45° for 18h, *3* $NH_2NH_2$•AcOH[13] in DMF at 50° for 25min, *4* $CCl_3CN$[14], DBU in $(ClCH_2)_2$ at -5° for 1h, 56% overall). TMSOTf promoted coupling of 17 with ceramide derivative 4[15] in $CHCl_3$ at -23° afforded 45% of 18 which was further converted into 1 in 3 steps (*1* 40% $MeNH_2$[16] in MeOH, *2* $Ac_2O$ and DMAP in Py, *3* NaOMe in 7:4 MeOH-THF, 54% overall).



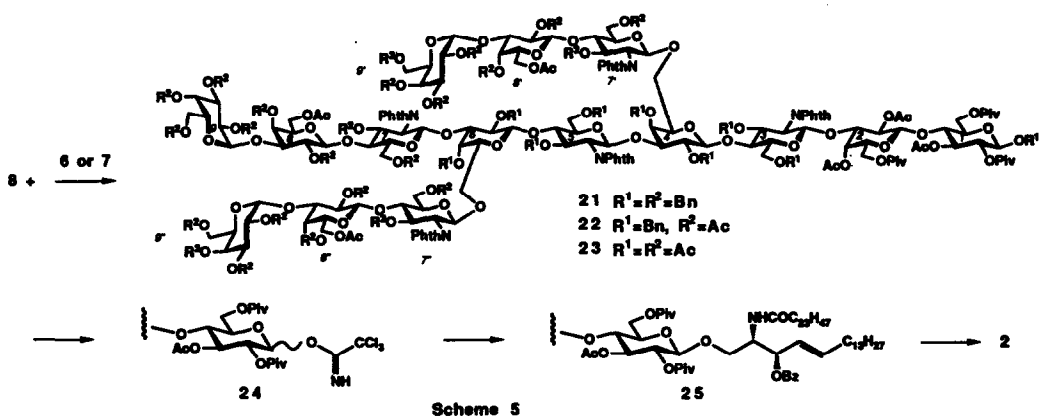

Scheme 3

In studying the synthesis of 2 the known glycosyl donor 6 readily obtainable[4] from 19 was first employed. $Cp_2Hf(OTf)_2$ promoted glycosylation of 8 with 2.7 equivalents of 6 in $(ClCH_2)_2$ at -23° afforded 90% of desired compound 21 which, however, could be converted into 23 only with difficulty mainly due to the sluggish hydrogenolytic removal of 33 benzyl groups in 21. In




Scheme 4

order to decrease the number of benzyl groups in the pentadecaoside **21** we designed a completely acylated donor **7**. Compound **19**[4] was converted into **7**[7] via **20**[7] in 4 steps (*1* 10% Pd-C and $H_2$ in 10:5:1 MeOH-EtOAc-$H_2O$, *2* $Ac_2O$ and DMAP in Py, *3* CAN in 50:38:25 $CH_3CN$-toluene-$H_2O$, *4* DAST in $(ClCH_2)_2$, 79% overall). With 2.1 equivalents of the glycotriosyl donor **7** $Cp_2Hf(OTf)_2$ promoted glycosylation of **8** in $(ClCH_2)_2$ at -23° gave 71% of **22**, which was to our delight smoothly converted into **23** in two steps (*1* 10% Pd-C and $H_2$ in 16:1 MeOH-EtOAc, *2* $Ac_2O$ and DMAP in Py, 60% overall). Conversion of **23** into **25** in 19% overall yield was carried out in 3 steps via trichloracetimidate **24** as described for **18**. Finally, conversion of **25** into the target molecule **2** was executed in 3 steps as described for **1**(*1* 40% $MeNH_2$ in MeOH for 3 days at 25°, *2* $Ac_2O$ and DMAP in Py for 23h at 58°, *3* NaOMe in 7:4 MeOH-THF, 41% overall). The $^1$H-nmr data for synthetic **1** and **2** were in good agreement with those for natural samples[5], thus confirming the assigned structure for both **1** and **2**.




Scheme 5

In summary, by employing a key glycohexaosyl acceptor **8** and acetylated glycosyl donors **5** and **7**, a versatile synthetic route to triantennary poly-N-acetyl-lactosamine type *neolacto*-glycosyl ceramide **1** and **2** was developed.

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## References and Notes

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7 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. Signal assignment such as $1^3$ stands for a proton at C-1 of sugar residue *3*. **1**: $R_F$ 0.26 in 55:45:12 $CHCl_3$-MeOH-$H_2O$; $[\alpha]_D$ -1.3° (c 0.1, py); $\delta_H$ (49:1:1 DMSO$d_6$-$D_2O$-$CD_3OD$, 60°) 0.845 (t, 6.4Hz, 2Me), 4.173 (d, 8.1Hz, $1^1$), 4.233 (d, 7.0Hz, $1^{8,8',8''}$), 4.276 (d, 7.3Hz, $1^2$), 4.306 (d, 6.6Hz, $1^{4,6}$), 4.428 (d, 8.4Hz, $1^{7',7''}$), 4.667 (d, 8.4Hz, $1^{3,5,7}$), 5.364 (dd, 7.0 and 15.6Hz, $4^{Cer}$), 5.557 (td, 7.0 and 15.0Hz, $5^{Cer}$). **2**: $R_F$ 0.19 in 65:35:8 $CHCl_3$-MeOH-$H_2O$; $\delta_H$ (49:1:1 DMSO$d_6$-$D_2O$-$CD_3OD$, 60°) 0.858 (t, 7.0Hz, 2Me), 4.182 (d, 8.1Hz, $1^1$), 4.286 (d, 7.3Hz, $1^2$), 4.315 (d, 7.3Hz, $1^{4,6,8,8',8''}$), 4.438 (d, 8.4Hz, $1^{7',7''}$), 4.690 (d, 8.4Hz, $1^{3,5,7}$), 4.864 (d, 3.7Hz, $1^{9,9',9''}$), 5.378 (dd, 7.0 and 15.4Hz, $4^{Cer}$), 5.565 (td, 7.0 and 15.0Hz, $5^{Cer}$). **5**: $R_F$ 0.48 in 1:1 toluene-EtOAc; $\delta_H$ 1.924, 1.969, 2.048, 2.074, 2.139, and 2.166 (6s, 6Ac), 6.108 (dd, 8.0 and 52.6Hz, $1^1$). **7**: $R_F$ 0.41 in 2:3 toluene-EtOAc; $\delta_H$ 1.915, 1.947, 2.051, 2.057, 2.066, 2.134 x 2, 2.153, and 2.159 (8s, 9Ac), 5.779 (dd, 8.2 and 10.4Hz, $3^1$), 6.102 (dd, 8.0 and 52.4Hz, $1^1$). **8**: $R_F$ 0.36 in 1:1 toluene-EtOAc; $[\alpha]_D$ -1.4° (c 1.4); $\delta_H$ 1.069, 1.166, and 1.194 (3s, 3Piv), 1.623, 1.874, and 2.045 (3s, 3Ac), 5.232 (d, 3.7Hz, $4^2$), 5.391 (d, 8.4Hz, $1^5$). **10**: $R_F$ 0.39 in 1:1 hexane-EtOAc; $[\alpha]_D$ +2.4° (c 1.1); $\delta_H$ 1.079, 1.188, and 1.214 (3s, 3Piv), 1.685, 1.898, and 2.079 (3s, 3Ac), 2.173 (s, Lev), 5.112 (d, 8.4Hz, $1^3$), 5.333 (d, 3.7Hz, $4^2$). **12**: $R_F$ 0.36 in 1:1 toluene-EtOAc, $[\alpha]_D$ +46.9° (c 1.3); $\delta_H$ 2.155 and 2.181 (2s, 2Lev), 5.285 (d, 0.9H, 8.4Hz, $1^1\beta$), 5.319 (d, 0.1H, 3.7Hz, $1^1\alpha$). **13**: $R_F$ 0.56 in 1:1 toluene-EtOAc; $\delta_H$ 5.626 (dd, 0.15H, 2.6 and 54.2Hz, $1^1\alpha$), 5.836 (dd, 0.85H, 7.7 and 53.9Hz, $1^1\beta$). **15**: $R_F$ 0.35 in 3:2 toluene-EtOAc; $[\alpha]_D$ +2.8° (c 1.0); $\delta_H$ 1.068, 1.165, and 1.194 (3s, 3Piv), 1.628, 1.871, and 2.026 (3s, 3Ac), 2.121, 2.126, and 2.153 (3s, 3Lev), 4.928 (d, 8.4Hz, $1^3$), 5.225 (d, 3.7Hz, $4^2$), 5.386 (d, 8.4Hz, $1^5$). **16**: $R_F$ 0.28 in 2:3 toluene-EtOAc; $[\alpha]_D$ -13.6° (c 0.9); $\delta_H$ 1.065, 1.159, and 1.179 (3s, 3Piv), 1.754, 1.864, 1.872, 1.885, 1.889, 1.897, 1.960, 1.963, 1.984, 2.017, 2.020, 2.032 x 3, 2.047, 2.052, 2.131, 2.137 x 2, 2.153, and 2.170 (18s, 21Ac), 5.708-5.634 (3dd, $3^{5'}$, $3^7$, and $3^{7'}$). **17**: $R_F$ 0.45 in 1:3 toluene-EtOAc; $\delta_H$ 1.088, 1.190, and 1.209 (3s, 3Piv), 6.440 (d, 3.3Hz, $1^1$), 7.70-7.90 (m, 5Phth), 8.588 (s, NH). **18**: $R_F$ 0.58 in 1:3 toluene-EtOAc; $[\alpha]_D$ +9.4° (c 0.5); $\delta_H$ 0.878 (t, 7Hz, 2Me), 1.097, 1.127, and 1.253 (3s, 3Piv), 1.676-2.172 (28s, 29Ac), 5.831 (td, 6.6 and 15.0Hz, $5^{Cer}$), 7.35-8.00 (m, 5Phth and Bz). **20**: $R_F$ 0.23 in 1:1 toluene-EtOAc; $\delta_H$ 1.923-2.156 (9s, 9Ac), 3.725 (s, OMe), 5.833 (d, 8.4Hz, $1^1$). **21**: $R_F$ 0.44 in 3:1 toluene-EtOAc; $[\alpha]_D$ +13.6° (c 1.2); $\delta_H$ 1.067, 1.166, and 1.180 (3s, 3Piv), 1.626, 1.824, 1.866, 1.874, 1.903, and 2.014 (6s, 6Ac). **22**: $R_F$ 0.36 in 2:5 toluene-EtOAc; $[\alpha]_D$ +20.1° (c 1.3); $\delta_H$ 1.066, 1.162, and 1.180 (3s, 3Piv), 1.767-2.221 (23s, 30Ac). **23**: $R_F$ 0.23 and 0.25 in 1:3 toluene-EtOAc; $\delta_H$ 6.227 (d, 3.7Hz, $1^1$), 7.60-7.95 (m, 5Phth). **24**: $R_F$ 0.46 in 1:4 toluene-EtOAc; $\delta_H$ 1.088, 1.190, and 1.208 (3s, 3Piv), 6.439 (d, 3.7Hz, $1^1$), 7.65-7.95 (m, 5Phth), 8.590 (s, NH). **25**: $R_F$ 0.55 in 1:4 toluene-EtOAc; $[\alpha]_D$ +38.9° (c 0.3); $\delta_H$ 0.878 (t, 6.8Hz, 2Me), 1.097, 1.128 and 1.216 (3s, 3Piv), 1.679-2.177 (24s, 38Ac), 5.832 (td, 7.3 and 15.0Hz, $5^{Cer}$), 7.30-7.98 (m, 5Phth and Bz).
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