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TOTAL SYNTHESIS OF A LACTO-GANGLIO SERIES GLYCOSPHINGOLIPID, M1⁻XGL-1[1)]

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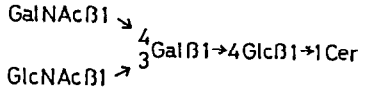
Abstract: First total synthesis of a novel "lacto-ganglio series" glycosphingolipid M1⁻XGL-1 was achieved regio- and stereoselectively.

Recently a change in glycolipid composition at the cell surface associated with differentiation or oncogenesis of cells attracted much attention[2)]. In 1984, Hakomori et al. isolated novel glycolipids M1⁻XGL-1 **1** and M1⁻XGL-3 **2** from murine leukemia cell line in an undifferentiated state (M1⁻cells)[3)]. These glycolipids are unique in having a branching pattern at II-galactose residue, with both features of lacto (GlcNAcβ1→3Gal) and ganglio (GalNAcβ1→4Gal) series. Described herein is the synthesis of hexatetraosyl ceramide M1⁻XGL-1 **1** in a regio- and stereochemically defined manner which gives a secure confirmation of the structure proposed by Hakomori et al[3)].



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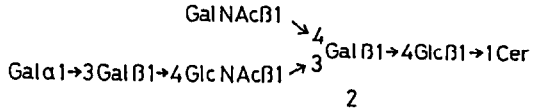

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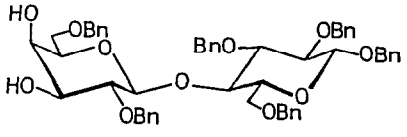

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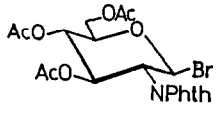

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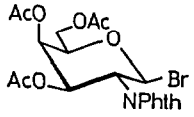
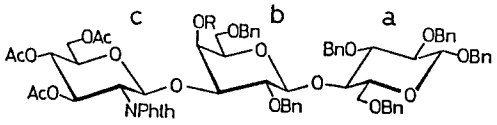


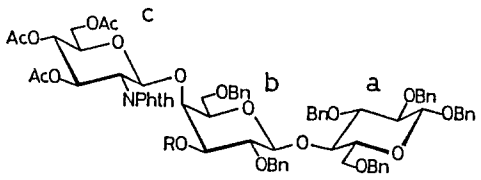
5

Retrosynthetic analysis reveals that the oligosaccharide portion of **1** would be constructed by sequential glycosylation of disaccharide acceptor **3**[4)] with monosaccharide donors **4**[5)] and **5**[6)]. Since we had observed that 3'-OH of **3** was more reactive than 4'-OH toward glycosylations[4)], first we examined the glycosylation of **3** with **4**. The acceptor **3** was reacted with 1.6 equiv. of the glycosyl donor **4** in the presence of silver triflate (2.0 equiv.), 2,4,6-collidine (2.0 equiv.) and molecular sieves 4A in nitromethane at -23°C to give a 72% of **6**, $[\alpha]_D^{20}$+20.6° (c 0.79, $CHCl_3$); R_f 0.60 (n-hexane : AcOEt = 1:1) and a 23% yield of **7**, $[\alpha]_D^{20}$+3.3° (c 0.75, $CHCl_3$); R_f 0.38 (n-hexane : AcOEt = 1:1). Regiochemistry of trisaccharides **6** and **7** was determined by NMR analysis of corresponding acetates **8** and **9**, respectively[7)]. Regioselectivity of this reaction is found to be in agreement with the

observation reported recently by Paulsen and coworkers[8].



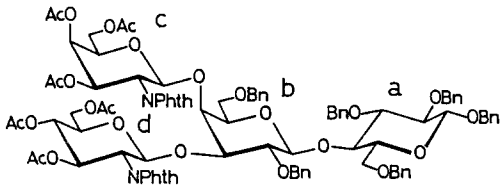
6: R = H
8: R = Ac



7: R = H
9: R = Ac

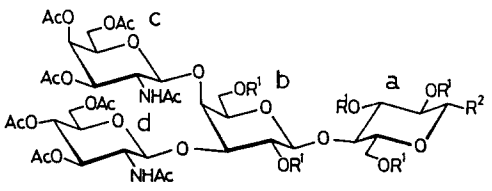
Second glycosylation with the glycosyl donor 5 (2.2 equiv.) was performed in the presence of silver silicate[9] and molecular sieves 4A in 1,2-dichloroethane to afford a 76% of tetrasaccharide 10[7], $[\alpha]_D^{20}$+32.3° (c 0.63, $CHCl_3$); R_f 0.52 (n-hexane : AcOEt = 5:6). Silver triflate was also effective for this reaction, but the yield was inferior (~50%). 10 was then subjected to reductive dephthaloylation procedure [1. $NaBH_4$, aq.i-PrOH; 2. AcOH] recently reported by Ganem et al.[10] and acetamide 11, $[\alpha]_D^{20}$-18.2° (c 0.73, $CHCl_3$); R_f 0.25 (Et_2O : AcOEt = 5:2) was obtained in 95% yield after acetylation [Ac_2O, DMAP, pyridine]. Debenzylation by catalytic hydrogen transfer [HCO_2H, Pd-C, MeOH][11], base treatment [K_2CO_3, MeOH][12] and acetylation gave peracetate 12[7], R_f 0.44 (CH_2Cl_2 : acetone = 3:2) as a 3:4 mixture of α- and β-anomers in 94% yield. 12 was selectively deacetylated [NH_2NH_2·AcOH, DMF][13] to give 13, R_f 0.26 (CH_2Cl_2 : acetone = 3:2) (84%) and 13 was then converted to fluoride 14[7] (α:β=1:4; 96% based on 79% conversion), R_f 0.41 and 0.36 (CH_2Cl_2 : acetone = 3:2) by DAST[14] in DME[15].

3 + 6 ⟶



10

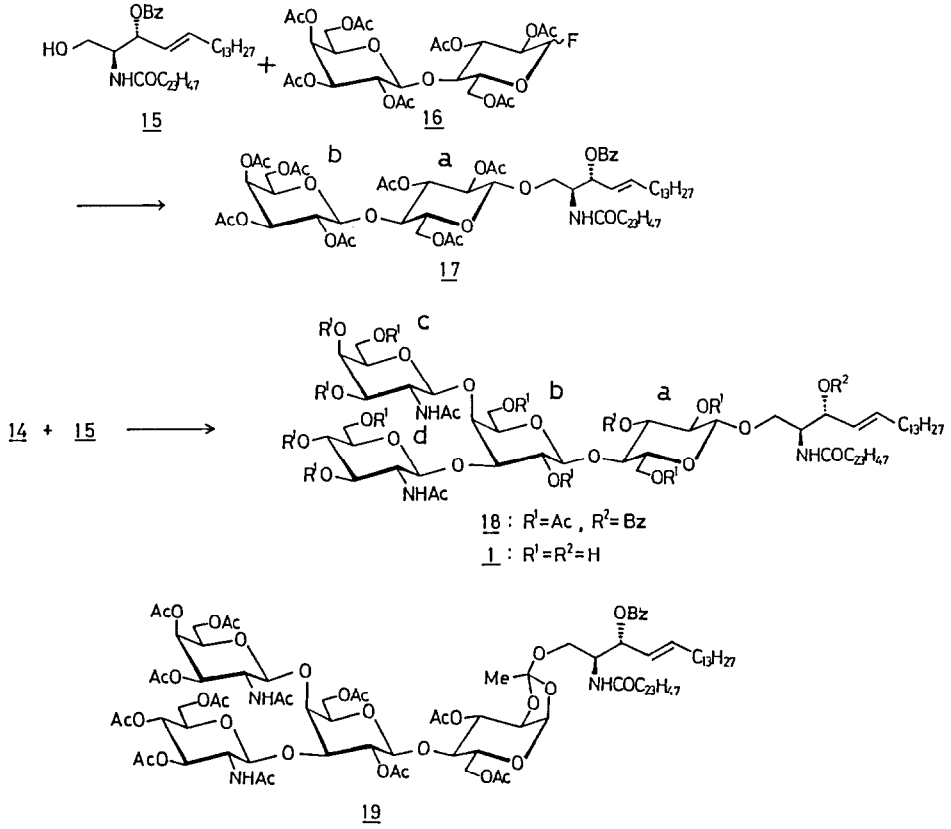
10 ⟶



11 R^1=Bn, R^2=OBn
12 R^1=Ac, R^2=OAc
13 R^1=Ac, R^2=OH
14 R^1=Ac, R^2=F

Before performing the key glycosylation with monobenzoylceramide 15[16], we examined the

reactivity of **15** toward glycosyl fluoride by using lactosyl fluoride **16** as a model compound. Coupling of **15** and **16** was accomplished in the presence of stannous chloride (2.3 equiv.), silver perchlorate (2.2 equiv.) and molecular sieves 4A[17] in $CHCl_3$ and protected lactosylceramide **17**[7], $[\alpha]_D^{23}$+4.2° (c 0.67, $CHCl_3$); R_f 0.29 (toluene : AcOEt = 2:1) was obtained in 71% yield. Then we tried the coupling reaction by using hexatetraosyl fluoride **14** under the same condition as above. In this case, however, only the formation of labile product, R_f 0.74 (CH_2Cl_2 : acetone = 3:2) which is readily hydrolysed back to **13** after aqueous work up was observed on TLC. Assuming that orthoester **19** is exclusively formed, trimethylsilyl triflate (2.0 equiv.)[18] was added to the reaction mixture after standard operation [2.8 equiv. $AgClO_4$ and 3.1 equiv. $SnCl_2$] in $CHCl_3$-DME (1:1). By following this procedure, coupled product **18**, $[\alpha]_D^{22}$-7.2° (c 0.36, $CHCl_3$); R_f 0.66 (CH_2Cl_2 : acetone = 3:2) was obtained in 22% yield.



Finally, deprotection of **18** [NaOMe, MeOH, THF] gave glycolipid M1-XGL-1] **1**. NMR data (400 MHz) of this compound was identical with the one reported by Hakomori et al[3].

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Chijimatsu for recording and measuring the NMR spectra and Dr. H. Honma and his staff for the elemental analyses. We also thank Ms. A. Takahashi and Ms. K. Moriwaki for their technical assistance.

References and Notes

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7) ^{1}H-NMR data of key compounds are given below (400 MHz, $CDCl_3$, ppm); **8**: 5.54 (d, 8.3 Hz, H-1c), 5.04 (d, 3.7 Hz, H-4b); **9**: 5.28 (d, 8.3 Hz, H-1c), 4.72 (dd, 10.3, 2.4 Hz, H-3b); **10**: 6.11 (dd, 11.6, 3.4 Hz, H-3c), 5.96 (d, 8.5 Hz, H-1c), 5.62 (d, 7.9 Hz, H-1d), 5.59 (t, 9.6 Hz, H-3d), 5.56 (d, 3.4 Hz, H-4c), 5.30 (t, 9.6 Hz, H-4d); **12**: 6.26 (d, 3.7 Hz, H-1a, α-anomer), 5.65 (d, 8.2 Hz, H-1a, β-anomer), 5.21 (d, 8.6 Hz, H-1d), 5.06 (d, 9.5 Hz, H-1c); **14**: 5.64 (dd, 53, 2 Hz, H-1a, α-anomer), 5.28 (dd, 50, 5.4 Hz, H-1a, β-anomer), 5.18 (d, 8.6 Hz, H-1d), 5.03 (d, 9.5 Hz, H-1c), 4.73 (d, 8.3 Hz, H-1b), 4.48 (dd, 9.7, 3 Hz, H-3b); **17**: 5.87 (dt, 15.1, 7.1 Hz, H-5'), 5.54 (t, 7.3 Hz, H-3'), 5.46 (dd, 15.1, 7.3 Hz, H-4'), 5.35 (d, 3 Hz, H-4b), 5.18 (t, 9.5 Hz, H-3a), 5.09 (dd, 10.5, 7.8 Hz, H-2b), 4.95 (dd, 10.5, 3 Hz, H-3b), 4.90 (dd, 9.5, 7.8 Hz, H-2a), 4.45 (2d, 7.8 Hz, H-1a and H-1b); **18**: 5.87 (dt, 15, 7 Hz, H-5'), 5.40 (d, 3 Hz, H-4c), 5.20 (d, 8.5 Hz, H-1d), 4.42 (d, 7 Hz, H-1a)
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