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Preliminary communication

Synthesis of α- and β-(2→9)-linked disialylglycerolipids*

TOMOYA OGAWA** and MAMORU SUGIMOTO
RIKEN (The Institute of Physical and Chemical Research), Wako-shi, Saitama, 351 (Japan)

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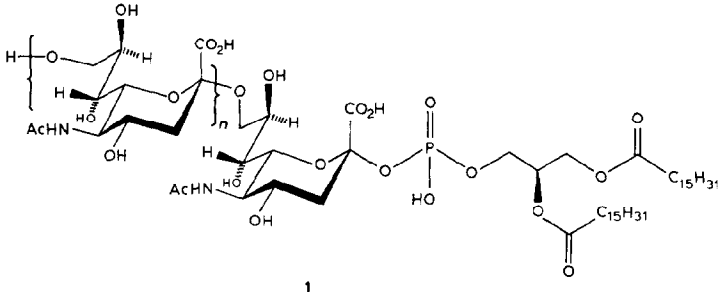
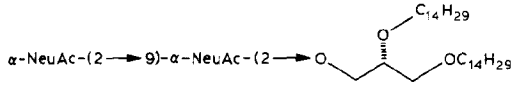
Oligosialyl structures[2] have been reported to occur in glycoproteins, glycolipids, and bacterial polysaccharides. In surface antigens of pathogenic bacteria, two types of sialic acid-containing polymers are known: α-(2→8)- and α-(2→9)-linked sialic acid[3]. In 1981, the α-(2→9)-linked polysialyl phospholipid structure 1 was proposed for the group C meningococcal polysaccharide[4].

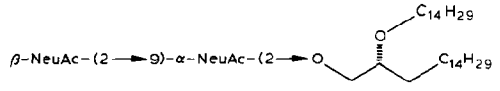
As part of a project on the synthesis of glyceroglycolipids[5], we report here a regioselective synthesis of the α- and β-(2→9)-linked disialyl glycerolipids 2 and 3 as model glycolipids for **1**.



1



2



3

*Synthetic Studies on Cell-surface Glycans, Part XXVIII. For Part XXVII, see ref. 1.
**To whom enquiries should be addressed.

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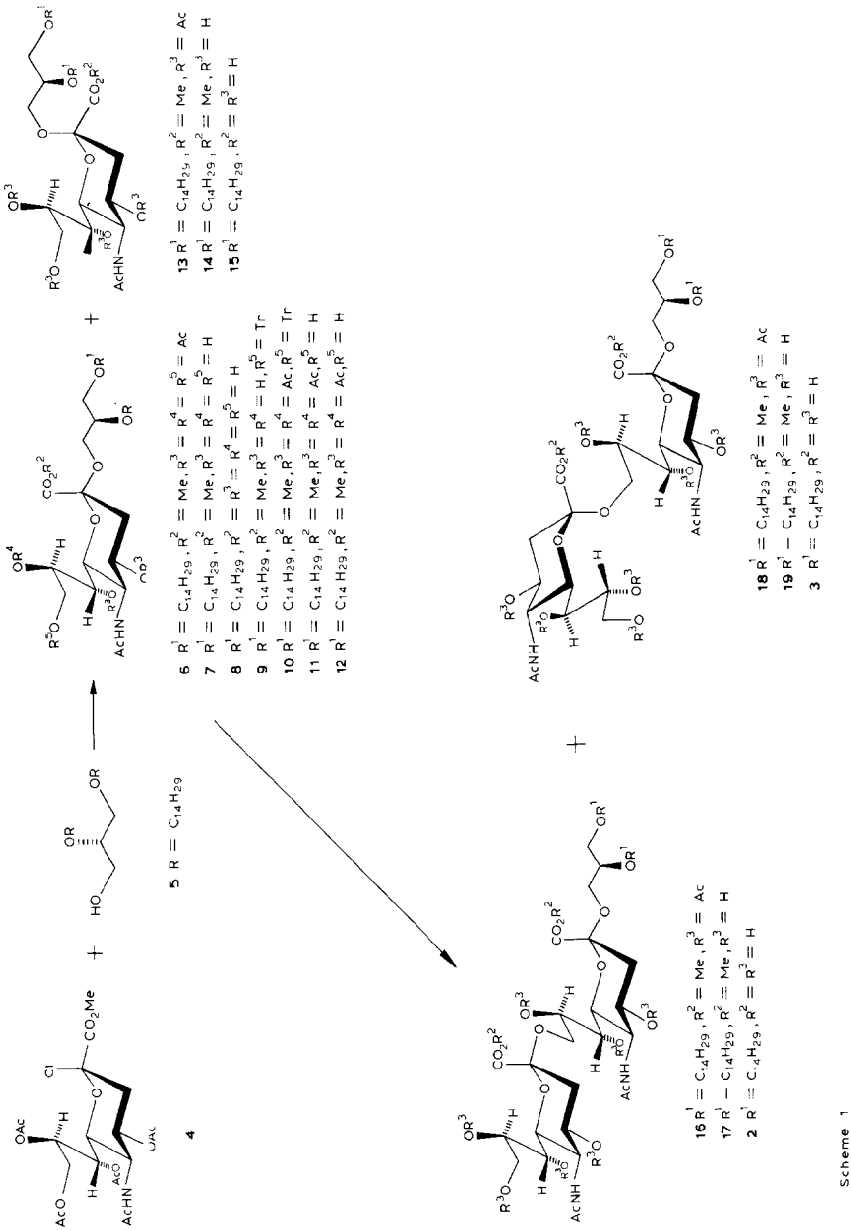

4

5 R = $C_{14}H_{29}$

6 $R^1 = C_{14}H_{29}$, $R^2 = Me$, $R^3 = R^4 = R^5 = Ac$
7 $R^1 = C_{14}H_{29}$, $R^2 = Me$, $R^3 = R^4 = R^5 = H$
8 $R^1 = C_{14}H_{29}$, $R^2 = R^3 = R^4 = R^5 = H$
9 $R^1 = C_{14}H_{29}$, $R^2 = Me$, $R^3 = R^4 = H$, $R^5 = Tr$
10 $R^1 = C_{14}H_{29}$, $R^2 = Me$, $R^3 = R^4 = Ac$, $R^5 = Tr$
11 $R^1 = C_{14}H_{29}$, $R^2 = Me$, $R^3 = R^4 = Ac$, $R^5 = H$
12 $R^1 = C_{14}H_{29}$, $R^2 = Me$, $R^3 = R^4 = Ac$, $R^5 = H$

13 $R^1 = C_{14}H_{29}$, $R^2 = Me$, $R^3 = Ac$
14 $R^1 = C_{14}H_{29}$, $R^2 = Me$, $R^3 = H$
15 $R^1 = C_{14}H_{29}$, $R^2 = R^3 = H$

16 $R^1 = C_{14}H_{29}$, $R^2 = Me$, $R^3 = Ac$
17 $R^1 = C_{14}H_{29}$, $R^2 = Me$, $R^3 = H$
2 $R^1 = C_{14}H_{29}$, $R^2 = R^3 = H$

18 $R^1 = C_{14}H_{29}$, $R^2 = Me$, $R^3 = Ac$
19 $R^1 = C_{14}H_{29}$, $R^2 = Me$, $R^3 = H$
3 $R^1 = C_{14}H_{29}$, $R^2 = R^3 = H$

Scheme 1

Glycosidation of the di-*O*-alkylated glycerol **5** (ref. 6) with the glycosyl donor **4** (ref. 7) in the presence of 1:1:2 $Hg(CN)_2$–$HgBr_2$–powdered molecular sieves 4A in $Cl(CH_2)_2Cl$ for 48 h at 20° gave a mixture of the anomers. Separation by flash chromatography[8] over silica gel C-300 in toluene–EtOAc afforded **6** and **13** in 37 and 24% yield, respectively: **6**, $[\alpha]_D$* −9.3° (*c* 1.04); R_F 0.26 in 1:1 toluene–EtOAc; δ_H ($CDCl_3$): 4.85 (m, 1 H, H-4), 2.60 (q, 1 H, *J* 4.80 and 13.10 Hz, H-3*e*), and 1.97 (t, 1 H, *J* 12.8 Hz, H-3*a*); **13**, $[\alpha]_D$ −13.0° (*c* 1.00); R_F 0.36 in 1:1 toluene–EtOAc; δ_H ($CDCl_3$): 5.23 (m, 1 H, H-4), 2.45 (q, 1 H, *J* 4.8 and 12.5 Hz, H-3*e*), and 1.90 (t, 1 H, *J* 12.2 Hz, H-3*a*).

The anomeric configurations of **6** and **13** were assigned by the presence in the ^{1}H-n.m.r. spectrum of the more deshielded signal for H-4 of **13** compared with that of **6**, according to the observation reported by Paulsen and Tietz[9].

Deprotection of **6** and **13** [(*i*) NaOMe–MeOH, (*ii*) 0.1M NaOH–THF] afforded **8** and **15** in 43 and 58% overall yield, respectively, *via* **7** and **14**: **8**, R_F 0.51 in 2:1:1 BuOH–EtOH–H_2O; δ_H (CD_3OD): 2.75 (q, 1 H, *J* 4.4 and 12.7 Hz, H-3*e*), 2.00 (s, 3 H, Ac), and 1.71 (t, 1 H, *J* 12.5 Hz, H-3*a*); **15**, R_F 0.67 in 2:1:1 BuOH–EtOH–H_2O; δ_H (CD_3OD): 2.40 (bm, 1 H, H-3*e*) and 2.02 (s, 3 H, Ac).

In order to synthesize the target disialyl glycerolipids **2** and **3**, compound **7** {$[\alpha]_D$ −5;30° (*c* 1.0); R_F 0.26 in 1:9 MeOH–EtOAc} was transformed into acetate **11** in 52% overall yield, in 3 steps: (*i*) TrCl–pyridine, (*ii*) Ac_2O–pyridine, (*iii*) 90% aq. AcOH for 2 h at 50–60°; **9**: $[\alpha]_D$ −5.20° (*c* 1.0); R_F 0.17 in 1:1 toluene–EtOAc; δ_H ($CDCl_3$): 7.5–7.1 (m, 15 H, CPh_3), 3.76 (s, 3 H, OMe), and 1.94 (s, 3 H, Ac); δ_C ($CDCl_3$): 98.79 (C-2) and 86.60 (CPh_3). Compound **10**: $[\alpha]_D$ +2.92° (*c* 1.20); R_F 0.48 in 1:1 toluene–EtOAc; δ_H ($CDCl_3$): 2.59 (q, 1 H, *J* 4.7 and 12.7 Hz, H-3*e*), and 1.90 (t, 1 H, *J* 12.4 Hz, H-3*a*); δ_C ($CDCl_3$): 98.64 (C-2) and 86.51 (CPh_3). Compound **11**: $[\alpha]_D$ −17.2° (*c* 0.50); R_F 0.52 in 20:1 EtOAc–MeOH; δ_H ($CDCl_3$): 5.17 (m, 1 H, H-8), 5.10 (bd, 1 H, *J* 9.8 Hz, H-7), 3.31 (q, 1 H, *J* 5.6 and 10.3 Hz, H-9), 3.00 (q, 1 H, *J* 4.8 and 10.3 Hz, H-9′), 2.60 (q, 1 H, *J* 4.5 and 12.7 Hz, H-3*e*), and 2.00 (t, 1 H, *J* 12.5 Hz, H-3*a*). Besides **11**, a product of acetyl migration was also isolated in 14% yield, and the structure was assigned to be **12** {$[\alpha]_D$ −12.3° (*c* 0.61); R_F 0.62 in 20:1 EtOAc–MeOH} according to the ^{1}H-n.m.r. data, which showed a deshielded signal at δ 5.14 for H-7, but not for H-8 (ref. 10).

Glycosidation of **11** with **4**, as for **5**, afforded a mixture of **16** and **18** in 41% yield. Flash chromatography of the product on silica gel C-300 in 5:3 CCl_4–acetone gave **16** and **18** in 17.1 and 9.2% yield, respectively; **16**, $[\alpha]_D$ −13.14° (*c* 1.41); R_F 0.47 in 1:1 CCl_4–acetone; δ_H 4.88 (oct, 1 H, H-4), 4.84 (oct, 1 H, H-4′), 3.80 (s, 6 H, 2 MeO), 2.60 (q, 1 H, *J* 4.6 and 12.7 Hz, H-3*e*), 2.57 (q, 1 H, *J* 4.6 and 12.7 Hz, H-3′*e*), 1.96 (t, 1 H, *J* 12.6 Hz, H-3*a*), and 1.93 (t, 1 H, *J* 12.4 Hz, H-3′*a*); **18**, $[\alpha]_D$ −4.26° (*c* 0.47); R_F 0.56 in 1:1 CCl_4–acetone; δ_H ($CDCl_3$): 5.09 (sex, 1 H, H-4b), 4.88 (oct, 1 H, H-4a), 3.80 (s, 3 H, MeO), 3.79 (s, 3 H, MeO), 2.60 (q, 1 H, *J* 4.6 and 12.9 Hz, H-3a-*e*), 2.45 (q, 1 H, *J* 4.9 and 12.9 Hz, H-3b-*e*), 1.95 (t, 1 H, *J* 12.7 Hz, H-3a-*a*), and 1.82 (q, 1 H, *J* 11.7 and 12.9 Hz, H-3b-*a*).

Finally, both **16** and **18** were deacetylated (MeONa–MeOH) and saponified (NaOH–aq. MeOH), to give **2** and **3**, respectively, *via* **17** (R_F 0.57 in 2:1:1 BuOH–EtOH–

*Values of $[\alpha]_D$ were measured for $CHCl_3$ solutions at 25°, unless noted otherwise. Compounds having $[\alpha]_D$ recorded gave satisfactory data for elemental analyses.

H_2O) and **19** (R_F 0.67 in 2:1:1 BuOH–EtOH–H_2O); **2**: $[\alpha]_D$ +2.22° (*c* 0.45, MeOH); R_F 0.50 in 2:1:1 BuOH–EtOH–H_2O; δ_H (CD_3OD): 2.80 (bq, 2 H, *J* 4.7 and 12.0 Hz, 2 H-3*e*). 2.01 (s, 3 H, Ac), and 2.00 (s, 3 H, Ac); **3**: $[\alpha]_D$ −8.5° (*c* 0.34, MeOH); R_F 0.54 in 2:1:1 BuOH–EtOH–H_2O; δ_H (CD_3OD): 2.73 (q, 1 H, *J* 4.5 and 12.0 Hz, H-3a-*e*), 2.41 (q, 1 H, *J* 4.5 and 12.1 Hz, H-3b-*e*), and 2.01 (s, 6 H, 2 Ac).

In conclusion, by use of a stepwise approach, the disialylglycerolipids **2** and **3** were synthesized, and their ^{1}H-n.m.r. data were in good agreement[11] with the anomeric configurations assigned.

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