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SYNTHESIS AND STEREOCHEMISTRY OF AGELASPHIN-9b

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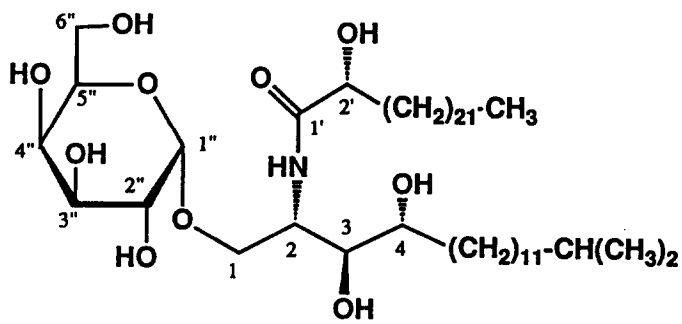
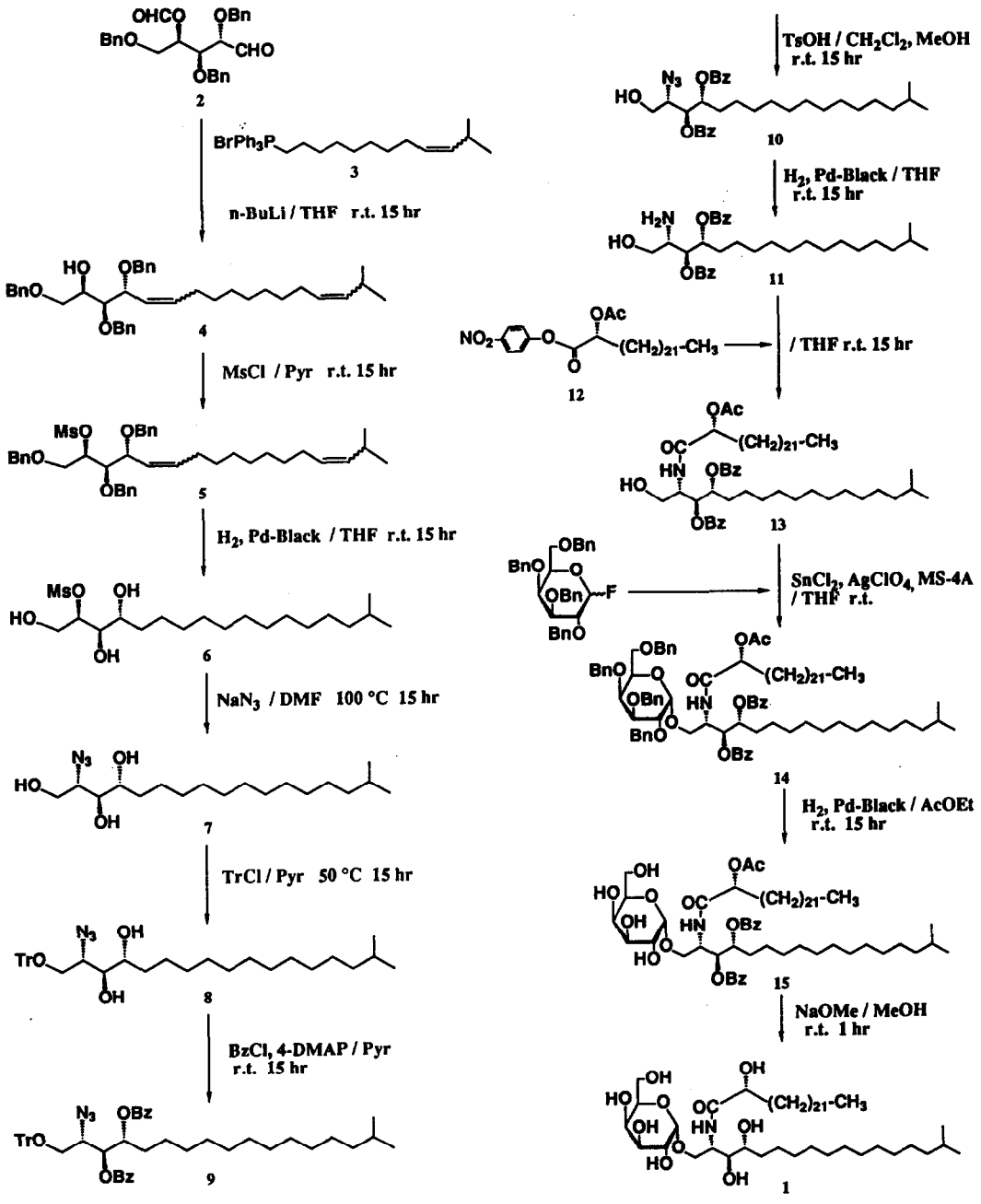
Abstract: Agelasphin-9b, one of the α-galactosylceramides from an Okinawan marine sponge, was synthesized, and the absolute stereochemistry was determined.

In the preceding paper we described the isolation and the structures of agelasphins, the first naturally occurring α-galactosylceramides.[1] However, the absolute stereochemistry of these cerebrosides remained undetermined. We herein report a total synthesis of agelasphin-9b (1) and the absolute stereochemistry.

Since known 4-hydroxylated cerebrosides occurring in nature possess (2*S*, 3*S*, 4*R*, 2'*R*)-stereochemistry,[2] we designed our target molecule possessing the same stereochemistry.



Agelasphin-9b (1)



Scheme 1 Synthetic Route of Agelasphin-9b (1)

An aldehyde (2)[3] was treated with a phosphonium salt (3), prepared by Wittig reaction of isobutylidene-triphenylphosphorane and 9-bromononanal followed by triphenylphosphonium salt formation, to afford a mixture of geometrically isomeric alcohols (4) in 68% yield, accompanied with hydrolysis of a formic ester. Mesylation (MsCl / Pyr) of 4 followed by hydrogenation accompanied with hydrogenolysis (H_2 / Pd-Black) gave a tetraol monomesylate (6) in 94% overall yield from 4. The mesylate (6) was convertible to an azide (7) (NaN_3, 72% yield), the primary hydroxyl group of which was tritylated (TrCl / Pyr, 84% yield) to give 8. Then, benzoylation (BzCl / Pyr - DMAP) of 8 followed by selective deprotection (TsOH / CH_2Cl_2 - MeOH) gave an alcohol (10) in 80% overall yield. The reduction of 10 (H_2 / Pd-Black) afforded an amine (11), which was acylated with *p*-nitrophenylester (12), prepared from (*R*)-2-acetoxytetracosanoic acid[4] and *p*-nitrophenol, to give a protected ceramide (13) in 40% overall yield.

The reaction of 13 with galactosyl fluoride under Mukaiyama's glycosidation condition[5] gave an α–galactoside (14) as a single product in 36% yield along with 40% recovery of 13. Deprotection [(i) H_2 / Pd-Black, (ii) NaOMe] of 14 afforded our target molecule (1). All of the spectral data of this product were identical with those of the natural 1. Thus, it is concluded that natural agelasphin-9b possesses the (2*S*, 3*S*, 4*R*, 2'*R*)-stereochemistry.

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References and Notes

1. T. Natori, Y. Koezuka, and T. Higa, preceding paper.
2. S. Sugiyama, M. Honda, R. Higuchi, and T. Komori, *Liebigs Ann. Chem.*, 349 (1991).
3. K. Koike, Y. Nakahara, and T. Ogawa, *Agric. Biol. Chem.*, 54, 663(1990).,
4. T. Sugai and H. Ohta, *Tetrahedron Lett.*, 32(48), 7063(1991).
5. T. Mukaiyama, Y. Murai, and S. Shoda, *Chem. Lett.*, 431 (1981).
6. Selected physical data of the compounds described in text are shown below.
   4: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20-7.35 (15H, m), 5.71 (1H, m), 5.44 (1H, dd, *J* = 9.5, 10.7 Hz), 5.37 (1H, m), 5.11 (1H, m), 4.30-4.70 (6H, m), 4.42 (1H, dd, *J* = 5.8, 9.5 Hz), 4.06 (1H, m), 3.55 (1H, dd, *J* = 3.0, 5.8 Hz), 3.50 (2H, d, *J* = 6.1 Hz), 2.99 (1H, m), 1.85-2.00 (2H, m), 1.51 (1H, m), 1.1-1.4 (12H, m), 0.85 (3H, d, *J* = 6.1 Hz), and 0.84 (3H, d, *J* = 6.1 Hz).
   5: FDMS *m/z* 663 [$(M+H)^+$]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25-7.40 (15H, m), 5.79 (1H, m), 5.48 (1H, t like, *J* = 10.4 Hz), 5.36 (1H, m), 5.00-5.12 (2H, m), 4.75 (1H, d, *J* = 11.6 Hz), 4.35-4.55 (6H, m), 3.76 (1H, m), 3.66 (1H, dd, *J* = 6.7, 10.7 Hz), 3.50 (1H, dd, *J* = 3.0, 10.7 Hz), 2.93 (3H, s), 1.90-2.10 (4H, m), 1.51 (1H, m), 1.10-1.40 (10H, m), 0.85 (3H, d, *J* = 6.7 Hz), and 0.84 (3H, d, *J* = 6.7 Hz).
   6: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.04 (1H, m), 4.04 (2H, m), 3.61 (2H, bs), 3.20 (3H, s), 1.5 (1H, m), 1.10-1.40(22H, m), and 0.87 (6H, d, *J* = 6.7 Hz).
   7: $[\alpha]_D^{24}$ +17.7° (*c* 1.30, $CHCl_3$); mp 63.0-64.0 °C; FDMS *m/z* 344 [$(M+H)^+$]; IR (cm^{-1}, KBr) 3320, 2910,

2830, 2100, 1460, 1250, 1055, and 1010; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.97 (1H, dd, *J* = 4.9, 11.6 Hz), 3.90 (1H, dt, *J* = 4.3, 11.6 Hz), 3.77 (2H, m), 3.62 (1H, m), 1.52 (1H, m), 1.1-1.4 (22H, m), and 0.86 (6H, d, *J* = 6.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 74.6 (d), 72.5 (d), 63.1 (d), 61.7 (t), 39.1 (t), 31.9 (t), 29.9 (t), 29.71 (t), 29.67 (t), 29.60 (t), 29.55 (t), 28.0 (d), 27.4 (t), 25.8 (t), and 22.7 (q).

9: FDMS *m/z* 794 [$(M+H)^+$]; IR (cm^{-1}, film) 2910, 2840, 2090, 1725, 1445, 1250, and 1090; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (2H, bd, *J*=8.5 Hz), 7.79 (2H, bd, *J* = 8.6 Hz), 7.57 (1H, t, *J* = 7.9 Hz), 7.55 (1H, t, *J*=7.9 Hz), 7.14-7.47 (19H, m), 5.47 (1H, dt, *J* = 4.3, 7.9 Hz), 5.42 (1H, dd, *J* = 4.3, 6.7 Hz), 3.90 (1H, dt, *J* = 3.1, 7.9 Hz), 3.49 (1H, dd, *J* = 3.1, 9.8 Hz), 3.36 (1H, dd, *J* = 8.2, 10.1 Hz), 1.77 (2H, m), 1.51 (1H, m), 1.10-1.42 (20H, m), and 0.85 (6H, d, *J* = 6.1 Hz).

10: $[\alpha]_D^{23}$ +15.8° (*c* 1.14, $CHCl_3$); mp 52.5-54.0 °C; FDMS *m/z* 552 [$(M+H)^+$]; IR (cm^{-1}, KBr) 3360, 2880, 2810, 2080, 1715, 1700, 1595, 1575, 1455, 1445, 1240, 1170, and 1100; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (2H, d, *J* = 7.3 Hz), 7.98 (2H, d, *J* = 6.7 Hz), 7.60 (1H, t, *J* = 7.3 Hz), 7.55 (1H, t, *J* = 7.6 Hz), 7.46 (2H, t, *J* = 7.6 Hz), 7.41 (2H, t, *J* = 7.9 Hz), 5.51-5.56 (2H, m), 3.98 (1H, m), 3.79 (2H, m), 2.41 (1H, m), 1.85-1.98 (2H, m), 1.51 (1H, m), 1.10-1.5 (20H, m), and 0.84 (6H, d, *J* = 6.7 Hz).

13: FDMS *m/z* 935 [$(M+H)^+$]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (2H, d, *J* = 7.3 Hz) 7.96 (2H, d, *J* = 7.3 Hz), 7.64 (1H, t, *J* = 7.3 Hz), 7.54 (1H, t, *J* = 7.6 Hz), 7.50 (2H, t, *J* = 7.9 Hz), 7.39 (2H, t, *J* = 7.9 Hz), 7.05 (1H, d, *J* = 9.2 Hz), 5.45 (1H, dd, *J* = 2.4, 9.1 Hz), 5.38 (1H, dt, *J* = 3.1, 9.8 Hz), 5.20 (1H, t, *J* = 6.1 Hz), 4.36 (1H, m), 3.55-3.70 (2H, m), 2.70 (1H, m), 2.22 (3H, s), 2.03 (2H, m), 1.92 (2H, m), 1.51 (1H, m), 1.10-1.50 (60H, m), 0.89 (3H, t, *J* = 6.7 Hz), and 0.86 (6H, d, *J* = 6.7 Hz).

14: FDMS *m/z* 1456 [$(M+H)^+$]; ^{1}H NMR (500 MHz, $CDCl_3$), δ 8.02 (2H, d, *J* = 7.9 Hz) 7.90(2H, d, *J* = 7.9 Hz), 7.74 (1H, m), 7.59 (1H, t, *J* = 6.4 Hz), 7.50 (1H, t, *J* = 6.4 Hz), 7.45 (2H, t, *J* = 7.6 Hz), 7.16-7.35 (22H, m), 5.78 (1H, dd, *J* = 2.6, 9.8 Hz), 5.39 (1H, m), 5.09 (1H, dd, *J* = 5.2, 7.6 Hz), 4.87 (1H, d, *J* = 11.3 Hz), 4.732 (1H, d, *J* = 4.3 Hz), 4.73 (1H, d, *J* = 11.3 Hz), 4.66 (1H, d, *J* = 11.3 Hz), 4.63 (1H, d, *J* = 11.3 Hz), 4.58 (1H, d, *J* = 11.3 Hz), 4.55 (1H, d, *J* = 11.3 Hz), 4.48 (1H, d, *J* = 11.3 Hz), 4.40 (1H, d, *J* = 11.3 Hz), 4.07 (1H, t, *J* = 7.2 Hz), 3.98 (1H, dd, *J* = 3.3, 10.4 Hz), 3.92 (1H, m), 3.87 (1H, dd, *J* = 2.4, 11.9 Hz), 3.81 (1H, dd, *J* = 2.4, 9.8 Hz), 3.59 (1H, dd, *J* = 2.3, 12.1 Hz), 3.52 (1H, dd, *J* = 6.4, 8.9 Hz), 3.45 (1H, dd, *J* = 6.7, 9.2 Hz), 2.02 (3H, s), 1.88 (4H, m), 1.50 (1H, m), 1.10-1.42 (60H, m), 0.88 (3H, t, *J* = 7.0 Hz), and 0.85 (6H, d, *J* = 6.7 Hz).

1: $[\alpha]_D^{25}$ +56.3° (*c* 0.27, Pyr); mp 221.0-222.5 °C; negative FABMS *m/z* 844 [$(M-H)^-$]; IR (cm^{-1}, KBr) 3400, 2950, 2870, 1645, 1625, 1535, 1475, 1270, and 1080; ^{1}H NMR (500 MHz, C_5D_5N) δ 8.50 (1H, d, *J* = 8.5 Hz, NH), 6.70 (1H, m, OH), 6.09 (1H, m, OH), 5.60 (1H, d, *J* = 3.7 Hz, H1"), 5.29 (1H, m, H2), 4.65 (2H, m, H2', H2"), 4.59 (1H, m, H1a), 4.54 (1H, m, H4"), 4.49 (2H, m, Gal-H5, H3"), 4.40 (1H, m, H3), 4.36 (2H, m, H1b, H6"a), 4.33 (1H, m, H6"b), 4.28 (1H, m, H4), 2.30 (1H, m), 2.20 (1H, m), 2.00 (1H, m), 1.89 (2H, m), 1.76 (1H, m), 1.68 (2H, m), 1.48 (2H, m), 1.12-1.43 (55H, m), 0.874 (3H, t, *J* = 6.7 Hz), 0.871 (6H, d, *J* = 6.7 Hz); ^{13}C NMR (125 MHz, C_5D_5N) δ 174.9 (s, C1'), 101.2 (d, C1"), 76.5 (d, C3), 73.0 (d, C5"), 72.4 (d, C2'), 72.3 (d, C4), 71.5 (d, C3"), 70.9 (d, C4"), 70.1 (d, C2"), 68.1 (t, C1), 62.6 (t, C6"), 50.4 (d, C2), 39.2 (t), 35.5 (t), 34.4 (t), 32.0 (t), 30.3 (t), 30.2 (t), 30.1 (t), 30.0 (t), 29.9 (t), 29.5 (d), 28.1 (t), 27.6 (t), 26.3 (t), 25.8 (t), 22.8 (t), 22.7 (q), 14.2 (q).

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