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STEREOCHEMISTRY OF APLIDIASPHINGOSINE AS PROPOSED BY THE ASYMMETRIC SYNTHESIS AND ^{13}C-NMR STUDY OF SPHINGOSINE RELATIVES

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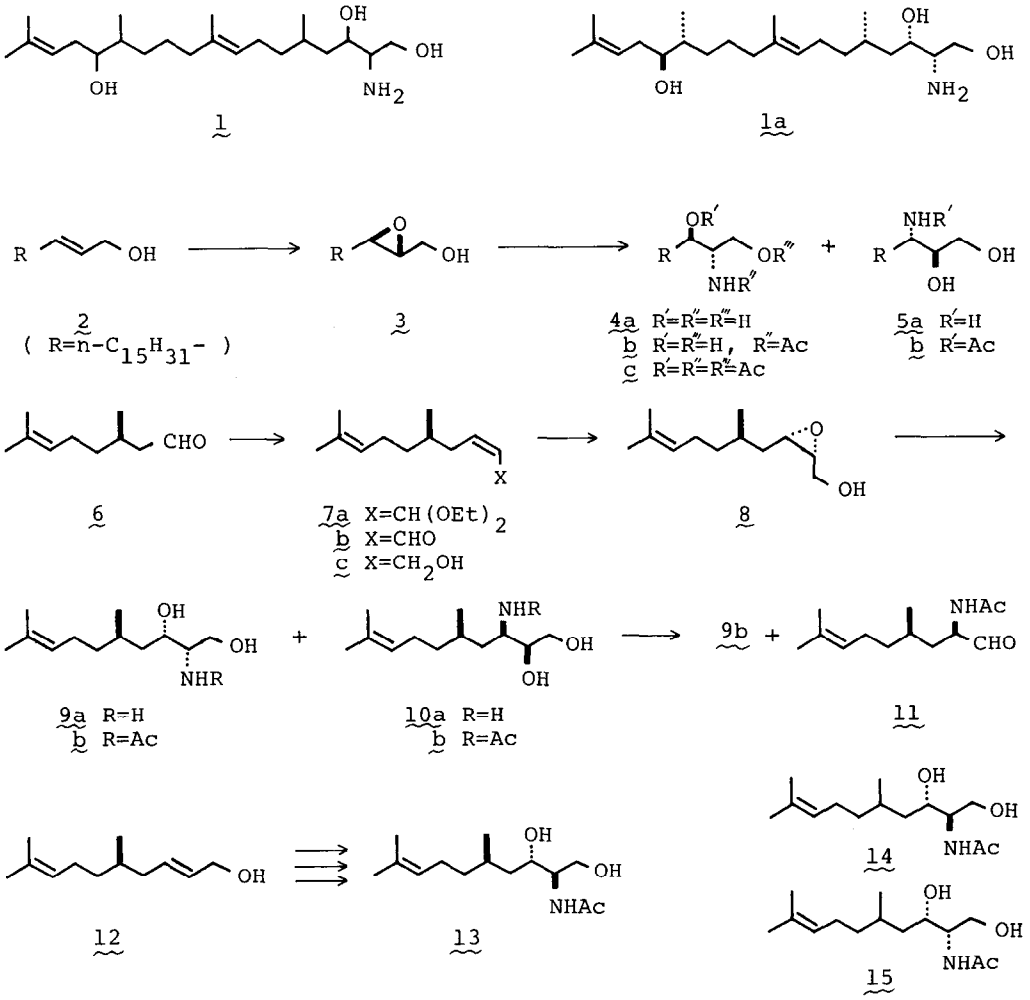
Abstract : The Sharpless asymmetric epoxidation was used for the synthesis of D-erythro-dihydrosphingosine triacetate and (2S, 3S, 5R)-2-acetamino-5,9-dimethyl-8-decene-1,3-diol, whose ^{13}C-NMR study coupled with biogenetic consideration enabled us to propose (2S, 3S, 5S, 13R, 14S)-stereochemistry for aplidiasphingosine.

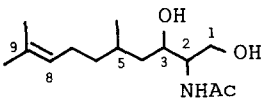
Our recently completed synthesis[2)] of diastereomeric mixtures of aplidiasphingosine 1, a bioactive marine terpenoid,[3)] made us to propose 2,3-threo- and 13,14-erythro-relative configurations for 1. Herein we report the elucidation of the stereochemical relationship between C-3 and C-5 of 1. This was made possible by the asymmetric synthesis and ^{13}C-NMR study of sphingosine relatives.

The Sharpless asymmetric epoxidation (2 → 3)[4)] can be regarded to be the key reaction in an asymmetric synthesis of sphingosine relatives, since the conversion of (±)-3 into (±)-erythro-dihydrosphingosine 4a is a known process.[5)] Indeed the synthesis of D-(+)-4c proceeded smoothly as follows. The known (E)-allylic alcohol 2[5)] was oxidized (t-BuOOH/Ti(Oi-Pr)$_4$/diethyl D-(-)-tartrate/CH_2Cl_2, -20°, 38 hr)[4)] to (2R, 3R)-epoxide 3 (75% yield after recrystallization from pet. ether), mp 78-79° ; $[\alpha]_D^{22}$ + 21.6° (c=0.49, $CHCl_3$).[6,7)] This was heated (100°, 7 days) with NH_3/MeOH to give a mixture of 4a and 5a (99% yield), mp 70-80°.[cf.5)] Ac_2O/MeOH converted the mixture into the corresponding N-acetates 4b and 5b (98%). Removal of the unwanted isomer 5b from the mixture was effected by treating it with HIO_4/MeOH.[5)] Trituration of the product with hot pet. ether gave 4b (18% yield after recrystallization from acetone), mp 115-117°. Acetylation (Ac_2O/C_5H_5N) of 4b yielded D-erythro-dihydrosphingosine triacetate 4c (73% yield after SiO_2 chromatography),[8)] mp 94-96°; $[\alpha]_D^{22}$ + 17.0° (c=1.1, $CHCl_3$) (lit.[9)] mp 97-98°; $[\alpha]_D^{19}$ + 17.4° (c=1.373, $CHCl_3$) for the natural product). The present synthesis of (+)-4c is much simpler than the previous one employing either optical resolution[10)] or a carbohydrate starting material.[11)]



We then turned our attention to the synthesis of an optically active sphingosine analog with a Me group at C-5 with known absolute configuration. For this purpose, optically pure (R)-(+)-citronellic acid was prepared from (R)-(+)-pulegone[cf.12] and converted to (R)-(+)-citronellal 6 in the conventional manner. This was treated with a Wittig reagent ($Ph_3P^+(CH=CHOEt)Br^-$-NaOEt/THF)[13] to give a (Z)-olefinic acetal 7a (57%), $[\alpha]_D^{23}$ -9.90° (c=0.52, $CHCl_3$). Mild hydrolysis (TsOH/An-H_2O, 0°, 15 min) of 7a yielded an aldehyde 7b.[14] Reduction of 7b (DIBALH/n-C_6H_{14}-C_6H_6, 0°, 30 min) gave an alcohol 7c (93% from 7a), bp 103-105°/0.25 mm; $[\alpha]_D^{22}$ -7.43°(c=0.54, $CHCl_3$). This was submitted to the Sharpless epoxidation (t-BuOOH/Ti(Oi-Pr)$_4$/diethyl D-tartrate/CH_2Cl_2, -20°, 18 hr). Chromatographic purification of the product (SiO_2) yielded an epoxy alcohol 8 (57%), $[\alpha]_D^{22}$ + 5.43° (c=0.6, $CHCl_3$).[7] Cleavage of the epoxy ring of 8 with ammonia (NH_3/MeOH, trace $HClO_4$, 100°, 2 days) gave a mixture of 9a and 10a (50.4%). This was acetylated (Ac_2O/EtOH, room

Table 1. ^{13}C-NMR Data of Stereoisomers of 2-Acetamino-5,9-dimethyl-8-decene-1,3-diol
(25 MHz, CD_2Cl_2-CD_3OD 2 : 1, δ, ppm)



Carbon No.	(±)-(2S*, 3R*)-erythro-14	(±)-(2S*, 3S*)-threo-15	(2S,3S,5R)-9b
C-1	62.0	63.0	63.0
2	55.9, 56.5	54.9, 55.9	55.9
3	70.4, 71.1	68.4, 68.8	68.4
5	29.5, 30.1	29.3, 29.7	29.3
8	125.4	125.3	125.3
9	131.6	131.5	131.5

Table 2. ^{13}C-NMR Data of Natural and (±)-2,3-threo-Aplidiasphingosines (25MHz, CD_2Cl_2 ; δ, ppm)

Carbon No.	Natural 1	Synthetic (±)-2,3-threo-1
C-2 (>CH-N<)	54.7	54.5, 55.4
3 (>CH-O-)	70.0	68.8, 69.4

temp, 16hr) to 9b and 10b. The mixture was treated with $NaIO_4$/THF-H_2O (room temp, 1.5hr) and the product was chromatographed to give (2S, 3S, 5R)-9b (30 %),[15] $[\alpha]_D^{22.5}$ -7.58° (c=0.88, $CHCl_3$), and 11 (66%), $[\alpha]_D^{22.5}$ -7.67° (c=0.86, $CHCl_3$). The desired product 9b contained about 10% of (2R, 3S, 5R)-erythro-isomer 13 derived from an (E)-allyl alcohol 12 contaminating in 7c. For the purpose of ^{13}C-NMR spectral comparison, diastereomeric mixtures of 2,3-erythro-14 and 2,3-threo-15 were synthesized from (±)-citronellal and 2-nitroethanol in the same manner as described in the preceding paper.[2]

The ^{13}C-NMR data of 14,15 and 9b are shown in Table 1. Comparison of the data of (±)-(2S,* 3S*)-threo-mixture 13 with those of (2S, 3S, 5R)-isomer 9b afforded a useful information : C-2 of (2S, 3S, 5R)-isomer 9b absorbed at an upfield than that of (2S,* 3S*, 5S*)-isomer, while C-3 of 9b absorbed at a downfield than that of (2S,* 3S,* 5S*)-isomer. In Table 2 a part of the ^{13}C-NMR data of natural[3] and synthetic[2] (±)-(2S,* 3S*)-aplidiasphingosine 1 is listed. As to the C-2 signals of the synthetic material, one with a smaller δ-value (54.5) than the other (55.4) coincided with the C-2 signal of natural

1. As to the C-3 signals of the synthetic material, on the other hand, one with a bigger δ-value (69.4) than the other (68.8) coincided with the C-3 signal of natural 1. This implied that the stereochemistry at C-2, C-3 and C-5 of natural 1 should be 2S*, 3S*, 5S*. (2S)-Configuration was favored considering the possible biogenetic role of (S)-serine as the building-block of C-1 to C-3 of 1 in analogy with sphingosine itself. Two secondary Me groups in natural 1 was thought to be with the same absolute configuration like other acyclic terpenoids.

In conclusion (2S, 3S, 5S, 13R, 14S)-stereochemistry as depicted in 1a is proposed for aplidiasphingosine. It is also possible that the stereochemistry is 2R, 3R, 5R, 13S, 14R, the antipode of 1a, if D-serine is used as the biogenetic precursor.

REFERENCES AND FOOTNOTES

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6) All new compounds were characterized by IR, NMR and combustion or MS analyses.

7) Neither the MTPA-ester method nor the NMR optishift reagent method was suc cessfully applicable for the direct determination of the optical purity of this epoxy alcohol.

8) ν_{max} ($CHCl_3$) 3380, 1725, 1660, 1500 cm^{-1}; ^{1}H-NMR δ($CDCl_3$, 100 MHz) 0.90 (3H, deformed t, J=6Hz), 1.1-2.0 [28H, 1.30 (s)] 2.05 (3H, s, NHCOMe), 2.12 (6H, s, OCOMe x 2), 4.0-4.8 (3H, m), 4.9-5.3 (1H, m), 6.20 (1H, br).

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14) Z/E-ratio of 7b was 92:8 as revealed by ^{1}H-NMR of 7b, δ 10.02 (0.92H, d, J=7Hz, CHO of (Z)-7b), 9.46 (0.08H, d, J=7Hz, CHO of (E)-7b).

15) ν_{max} ($CHCl_3$) 3440, 1660, 1520 cm^{-1} ; ^{1}H-NMR (CD_2Cl_2-CD_3OD 2:1, 60MHz) 0.6-2.3 [~19H, 0.91 (3H, d, J=6Hz), 1.61 (3H, s), 1.67 (3H, s), 2.02 (3H, s. NHCOMe)] 3.3-4.4 (7H), 5.18 (1H, t, J=7Hz).

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