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A STEREOCONTROLLED SYNTHESIS OF (2R,3R,5R,13S,14R)-(+)-APLIDIASPHINGOSINE, A MARINE TERPENOID

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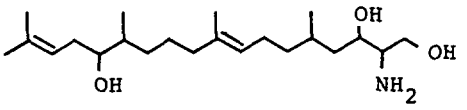
Abstract : (2R,3R,5R,13S,14R)-(+)-Aplidiasphingosine was synthesized starting from (R)-(+)-citronellic acid.

Aplidiasphingosine (1, 2-amino-5,9,13,17-tetramethyl-8,16-octadecadiene-1,3,14-triol) is an antimicrobial and antitumor terpenoid isolated from an Aplidium sp. of marine tunicate by Carter and Rinehart, Jr.[1] The presence of five chiral centers in the gross structure 1 proposed by them[1] demands 32 stereoisomers. We recently reported a synthesis of the both of its 2,3-*erythro*- and 2,3-*threo*-isomers[2] and proposed (2S,3S,5S,13R,14S)-or (2R,3R,5R,13S,14R)-stereochemistry to aplidiasphingosine 1a on the basis of ^{13}C-NMR studies coupled with a stereocontrolled synthesis of an optically active model compound .[3] Herein we describe a stereocontrolled synthesis of (2R,3R,5R,13S,14R)-aplidiasphingosine 1a from (R)-(+)-citronellic acid.[4]

The left-hand fragment of the target molecule was constructed from 100% optically pure methyl (R)-(+)-citronellate 2[5,6] as shown in the Scheme. Ozonolysis of 2 was followed by the Jones oxidation to give the known half ester 3, $[\alpha]_D^{25}$ + 6.92° ($CHCl_3$).[7] This was oxidatively decarboxylated [$Pb(OAc)_4$, $Cu(OAc)_2$, C_6H_6, reflux][8] and the resulting ester was hydrolyzed (10% KOH) to give an acid 4 (43% yield from 3), bp 81∿ 82°/2.5 mm, $[\alpha]_D^{25}$ +17.5° ($CHCl_3$).[9] Iodolactonization of 4 according to Bartlett (I_2, MeCN, -20°, 3 days)[10] yielded 5 (75%), $[\alpha]_D^{25}$ + 18.4° ($CHCl_3$), after chromatographic (SiO_2) purification.[9] Treatment of 5 with Na_2CO_3 in MeOH[10] gave an epoxy ester 6 (80% yield), b.p. 87∿ 89°/18mm. The Me_2C=CH unit was attached to 6 (Me_2C=CHMgBr, 10 mol % CuBr, THF, -20°)[11] to give a lactone 7.[12] This, without further purification, was reduced with LAH to give a diol 8a (68% from 6), $[\alpha]_D^{25}$ + 8.97° ($CHCl_3$), after chromatographic (SiO_2) purification.[13] After



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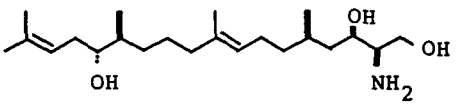
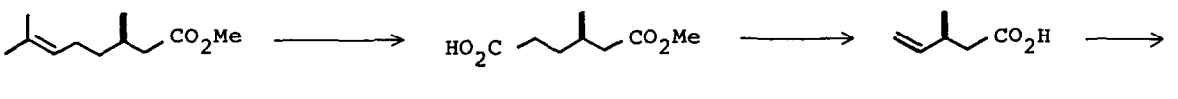


(2R,3R,5R,13S,14R)-1a



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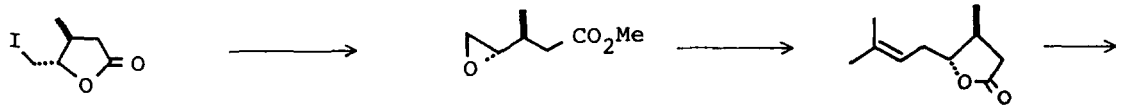

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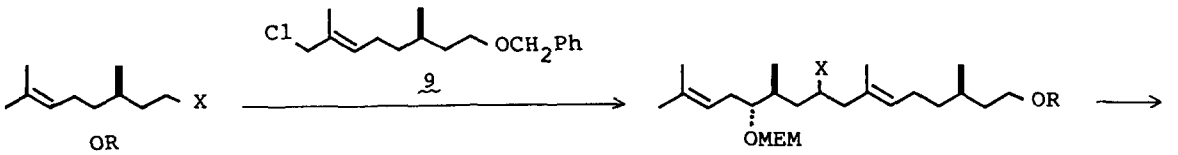
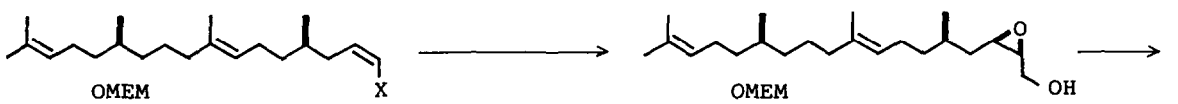


8a R=H,X=OH
b R=MEM,X=OH
c R=MEM,X=$SO_2C_6H_4Me$

10a R=CH_2Ph,X=$SO_2C_6H_4Me$
b R=H,X=H



11a X=CH(OEt)$_2$
b X=CHO
c X=CH_2OH

12

13a R=H
b R=Ac

14a R=H
b R=Ac

1a R=H
b R=Ac

15

protecting the primary OH group of 8a as trityl ether ($TrBr/C_5H_5N$), the secondary OH group was converted to MEM ether ($MEMCl/i\text{-}Pr_2NEt$). Subsequent deprotection of the primary OH group (80% AcOH) gave 8b (62% from 8a), $[\alpha]_D^{27}$ -26.0° ($CHCl_3$). This was tosylated ($TsCl/C_5H_5N$) and the resulting tosylate was converted ($NaSO_2C_6H_4Me$, LiI, DMF, r.t. 42 hr) to a p-tolylsulfone 8c (60% yield), $[\alpha]_D^{27}$ -29.2° ($CHCl_3$).

The central fragment 9, $[\alpha]_D^{27}$ + 3.94° ($CHCl_3$), of aplidiasphingosine was prepared from optically pure (R)-(+)-citronellol in 21% overall yield in the conventional manner.[2,cf.14] Alkylation of 8c with 9 (n-BuLi/THF, -20°, 9, -78∿0°)[cf.15] gave 10a (73% yield), $[\alpha]_D^{27}$ -20.5° ($CHCl_3$), with the desired diterpenoid skeleton.[cf.15] Reduction of 10a with $Li/EtNH_2$ (-78°, 30 min)[cf. 15] removed both the p-tolylsulfone and benzyl groups to give 10b (70% yield), $[\alpha]_D^{27}$ -5.65° ($CHCl_3$), MS : m/z 398 (M^+). This was oxidized ($CrO_3 \cdot 2C_5H_5N/CH_2Cl_2$, r.t. 2 hr)[16] to a crude aldehyde (92% yield), which was immediately treated with a Wittig reagent [$Ph_3P^+(CH{=}CHOEt)Br^-$, NaOEt/THF, r.t.][17] to give a (Z)-olefinic acetal 11a (83% yield), $[\alpha]_D^{27}$ -11.9° ($CHCl_3$). Mild hydrolysis of 11a (TsOH/An-H_2O, 0°, 15 min) gave 11b (quantitative yield) with the full carbon skeleton of 1a.[18] Reduction of 11b (DIBALH/n-C_6H_{14}-C_6H_6, 0°, 1hr) yielded 11c (93%), $[\alpha]_D^{26.5}$ -11.5° ($CHCl_3$). This was submitted to the Sharpless asymmetric epoxidation [t-BuOOH-Ti(Oi-Pr)$_4$-diethyl L-(+)-tartrate/CH_2Cl_2, -20°, 20hr][19] to give an epoxy alcohol 12 (80% yield), $[\alpha]_D^{26.5}$ -8.90° ($CHCl_3$). Cleavage of the epoxy ring of 12 with ammonia (NH_3/MeOH, trace $HClO_4$, 100°, 30 hr) gave a mixture of 13a and 14a (85% combined yield). This was acetylated (Ac_2O-MeOH, r.t. 3 hr) to 13b and 14b. The mixture was treated with $NaIO_4$/THF-H_2O (r.t. 2 hr) and the product was separated by SiO_2 chromatography to give 13b (24%) and 15 (75%). Alkaline hydrolysis of 13b (KOH/MeOH-H_2O, reflux, 5 hr) was followed by acid treatment (TsOH/i-PrOH, 40∿45°, 25 hr) to afford (2R,3R,5R,13S,14R)-(+)-aplidiasphingosine 1a (44% yield from 13b), $[\alpha]_D^{20}$ + 10.2° (c=0.49, MeOH) ; MS : m/z 369.3300 ($C_{22}H_{43}O_3N$). The stereochemical homogeneity of our synthetic product was ascertained by examining the ^{13}C-NMR spectrum of its N-acetyl derivative 1b, $[\alpha]_D^{20}$ + 14.5° (c=0.41, MeOH) ; MS : m/z 411.3375 ($C_{24}H_{45}O_4N$), in which only 24 signals were observable.[20] Our ^{13}C-NMR data were in good agreement with those reported for N-acetyl aplidiasphingosine[1,21]

For the establishment of the absolute stereochemistry of natural aplidiasphingosine, direct comparison of spectral and chiroptical data such as $[\alpha]_D$ values of the natural and synthetic products was absolutely necessary. In their paper reporting the structure determination of aplidiasphingosine,[1] Carter and Rinehart, Jr. recorded no chiroptical data (neither $[\alpha]_D$ nor ORD) of the natural 1a and 1b. We therefore repeatedly requested to Prof. Rinehart, Jr. to send us such data as a comparison sample and a copy of ^{13}C-NMR spectrum of N-acetyl aplidiasphingosine. Until now we are unable to have

them. Therefore, in spite of the present synthesis of (2R,3R,5R,13S,14R)-1a, the absolute stereochemistry of aplidiasphingosine remains obscure.[22]

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4) This work was presented at the 24th Natural Products Symposium (Osaka, October 1981) as well as in seminars at the Institute of Organic Chemistry, University of Vienna, and at the Institute of Natural Products Chemistry, CNRS, Gif-sur-Yvette (November, 1981).

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12) The lactone 7 with unknown absolute stereochemistry was recently isolated as the pheromone of African sugar cane borer, Eldana saccharina [G. Kunesch, P. Zagatti, J.Y. Lallemand, A. Debal and J.P. Vigneron, Tetrahedron Letters, 22, 5271 (1981)]. In a separate full paper we will describe details of the synthesis of both enantiomers of 7(K. Mori, T. Uematsu and T. Umemura, to be submitted).

13) The purified diol 8a was a single stereoisomer judging from its ^{13}C-NMR data : δ($CDCl_3$, 22.6 MHz) 134.4, 120.8, 75.7, 60.3, 36.0, 35.7, 33.3, 25.9, 18.0, 16.6 ; ten signals only.

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18) This aldehyde 11b seems to be pure on the basis of its ^{1}H-NMR spectrum: δ 10.07, d, J=8Hz, (Z)-CHO > 0.95H ; δ 9.50, d, J=8Hz, (E)-CHO, < 0.05H.

19) T. Katsuki and K.B. Sharpless, J. Am. Chem. Soc., 102, 5974 (1980).

20) Spectral data of (2R, 3R, 5R, 13S, 14R)-(+)-1b : IR($CHCl_3$) ν_{max} 3440, 1660, 1515 cm^{-1} ; ^{13}C-NMR (CD_2Cl_2, 50.3 MHz) δ 171.5, 135.3, 134.7, 125.0, 121.4, 76.1, 69.7, 64.4, 54.5, 41.9, 40.2, 38.5, 36.9, 33.0, 31.5, 29.0, 26.0, 25.6, 25.4, 23.4, 20.4, 18.1, 15.9, 15.8.

21) ^{13}C-NMR data of the natural N-acetyl aplidiasphingosine (only 8 signals were recorded in the literature)[1] : δ(CD_2Cl_2) 135.6, 135.0, 125.5, 121.8, 76.5, 70.0, 64.6, 54.7.

22) All new compounds reported in this paper gave correct spectral and analytical data. Experimental part of this work was taken from the doctoral dissertation of T.U. (The University of Tokyo).

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