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# SYNTHESIS OF BOTH 2,3-ERYTHRO- AND 2,3-THREO- ISOMERS OF APLIDIASPHINGOSINE, A BIOACTIVE MARINE TERPENOID

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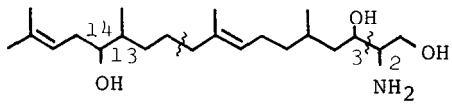
Abstract: 2,3-threo- and 13,14-erythro-Relative configurations were proposed for aplidiasphingosine by synthesizing both its 2,3-erythro- and 2,3-threo-isomers and examining their $^{13}C$-NMR spectra.

Aplidiasphingosine (1, 2-amino-5,9,13,17-tetramethyl-8,16-octadecadiene-1,3,14-triol) is an antimicrobial and antitumor terpenoid recently isolated from an Aplidium sp. (marine tunicate) by Carter and Rinehart, Jr.[2)] The presence of five chiral centers in 1 demands 32 stereoisomers. However, nothing was known concerning its stereochemistry with no available chiroptical data. Its obvious structural resemblance to sphingosine may suggest that the various bioactivities of 1 may be due to its interference with normal sphingosine functions. We therefore became interested in the synthesis of 1, so as to provide structural proof and stereochemical assignment as well as to obtain its bioactive analogs. The synthesis was achieved by dissecting the molecule into three parts, A, B and C and connecting them as described below.

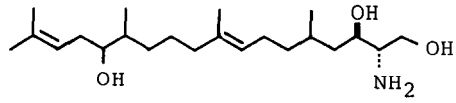
An aldehyde 2[3)] was added (-70°) to an anion derived from methyl propionate (LDA/THF) to give an aldol product 3a (77% yield) as an erythro-threo mixture.[4)] After protecting the OH group as an MEM ether 3b (97%),[5)] the thioacetal protecting group was removed (HgO, $BF_3$-ether/THF-$H_2O$)[6)] to give 4 (93%). The aldehyde 4 was converted to 5 (75%) by the inverse addition of a salt-free DME soln of $Me_2C{=}PPh_3$ to an ether soln of 4 (-78°, gradually raised -overnight- to room temp). The ester 5 was reduced (LAH/ether) to 6a, whose tosylate 6b was converted to an ester 6d (86% from 5) via a nitrile 6c. LAH reduction of the ester 6d yielded an alcohol 7a. The derived tosylate 7b was reacted with $NaSO_2C_6H_4Me$ (p) (4 eq in the presence of 3eq of LiI/DMF, room temp, 36hr) to give a p-tolylsulfone 7c in 65% overall yield from 6d. This completed the synthesis of the fragment A.

A chloride 8 (=the fragment B) was prepared from (±)-citronellol in 3 steps in 26% overall yield.[cf.7)] This was employed for the alkylation of the sulfone 7c (n-BuLi/THF) to give a sulfone 9 with the desired diterpenoid carbon skeleton in 83% yield.[cf.8)] Reduction of 9 with Li/$EtNH_2$ (-78°, 30 min) removed both the tolylsulfone and benzyl groups to give 10 (67%).[cf.8)] Oxidation of 10 with pyridinium dichromate (PDC) yielded an aldehyde 11 (63%).

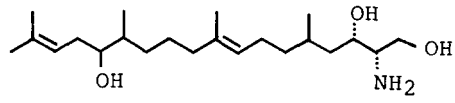


A B C

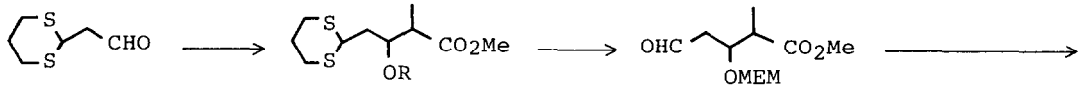
1



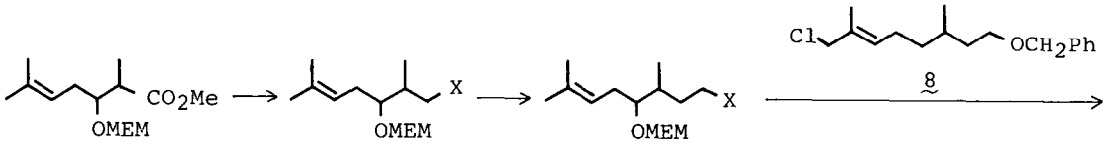
1a 2,3 - erythro



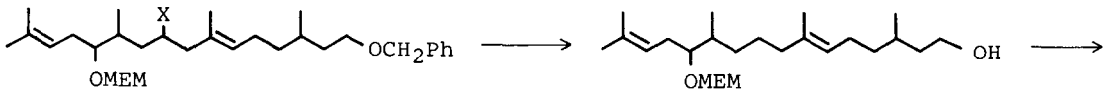
1b 2,3 - threo



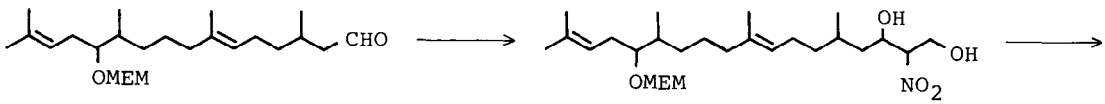
2 3a R=H, b R=MEM 4



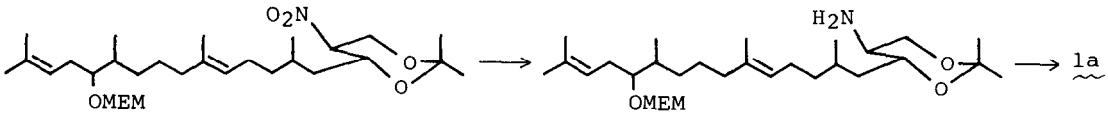
5 6a X=OH, b X=OTs, c X=CN, d X=$CO_2Me$ 7a X=OH, b X=OTs, c X=$SO_2C_6H_4CH_3$ 8



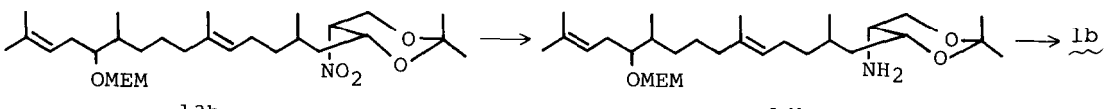
9 X=$SO_2C_6H_4CH_3$ 10



11 12



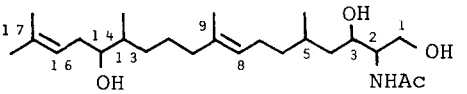
13a 14a 1a



13b 14b 1b

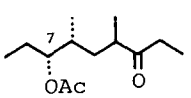
2-Nitroethanol served as the fragment C.[cf.9] Condensation of this with 11 was carried out in the presence of KF and n-$Bu_4NBr$ in MeCN (room temp, 2 days) affording 12 (90%) as a diastereomeric mixture. The separation of 2,3-erythro- and threo-isomers of 12 was effected by the conversion of 12 into the corresponding acetonides 13a and 13b ($Me_2C(OMe)_2$,PPTS.[10]/DMF, 75°, 3hr), which were separable by $SiO_2$ chromatography (Mallinckrodt CC7, n-hexane-EtOAc) The isomer 13a with lower Rf value was obtained in 40% yield and was reduced with Al-Hg[9] (ether-EtOH-$H_2O$, room temp, 2 days) to an amino acetonide 14a (51%), δ 2.60 (1H, ddd, J=5, 9, 9Hz, C<u>H</u>$NH_2$). The $^1$H-NMR data revealed the equatorial nature of the $NH_2$ group of 14a and hence that of $-NO_2$ in 13a. The other isomer 13b (55%) was similarly reduced with Al-Hg to the axial-$NH_2$ isomer 14b (45%), δ 2.47 (1H, m, J ≃ 2HZ). Finally the acetonide and MEM pro-

Table 1. $^{13}$C-NMR Data of Natural and Synthetic N-Acetylaplidiasphingosines ($CD_2Cl_2$, δ, ppm).

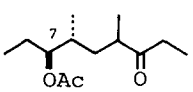



| Carbon (No.) | Natural | Synthetic (±)-2,3-erythro | (±)-2,3-threo |
|---|---|---|---|
| $-CH_2O-$ (C-1) | 64.6 (t) | 62.4 | 64.4 (t) |
| >CHN< (C-2) | 54.7 (d) | 55.0, 55.7 | 54.5, 55.4 (d) |
| >CHO- (C-3) | 70.0 (d) | 71.2, 71.7 | 68.8, 69.4 (d) |
| =CH- (C-8) | 125.5 (d) | 125.0 | 125.1 (d) |
| >C= (C-9(-17)) | 135.6 (s) | 135.3 | 135.3 (s) |
| >CHO- (C-14) | 76.5 (d) | 75.4, 76.2 | 75.4, 76.2 (d) |
| =CH- (C-16) | 121.8 (d) | 121.5 | 121.4 (d) |
| >C= (C-17 (-9)) | 135.0 (s) | 134.3 | 134.4 (s) |

cf. 1. Serricornin acetate.[13]

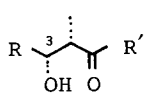



C-7; 77.80, 78.10

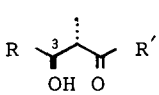



C-7; 78.92, 79.09

cf. 2. Some aldol products.[14]




C-3; 71.6-78.1




C-3; 74.0-82.5

tecting groups of 14a were removed (p-TsOH/MeOH, 45°)to give 1a (2,3-erythro-isomer, 54%).[11] Similarly 14b yielded 1b (2,3-threo-isomer, 44%).[12] This concluded the synthesis of aplidiasphingosine diastereomeric mixtures.

For the purpose of $^{13}$C-NMR spectral comparison with the natural product, our synthetic 1a and 1b were converted into the corresponding N-acetates by treatment with $Ac_2O$-EtOH. The $^{13}$C-NMR data are shown in Table 1. The chemical shifts of the signals due to C-1, C-2 and C-3 of the 2,3-threo-N-acetate were in good accord with those of the natural product except that additional signals were observable in the case of the synthetic product owing to the stereoisomerism at C-5. The chemical shift value (δ 76.5) of the signal due to C-14 of the natural product was very similar to the δ-value of one of the two signals (75.4 and 76.2) due to C-14 of the synthetic materials. The $^{13}$C-NMR data of serricornin acetate[13] and some aldol products[14] (see Table 1) indicate that the C-OR of the erythro-isomers absorbs at a downfield than that of the threo-isomer. Therefore 13,14-erythro-stereochemistry was assigned to the natural product. The assignment of the relative stereochemistry at C-3 and C-5 will be reported in the accompanying communication.

## REFERENCES AND FOOTNOTES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4) All new compounds were characterized by IR, NMR and combustion or MS analyses. The erythro-threo ratio of 3a was estimated to be ca. 1:1 by examining the $^1$H-NMR spectrum ($CHCH_3$) of 5.

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11) $n_D^{22}$ 1.4960; $\nu$max (film) ~3350 (br.s), ~1595 (br.m), 1050 (br.s)cm$^{-1}$; δ 0.90 (6H,d,J=6Hz), 1.53 (3H,s), 1.63 (3H,s), 1.71 (3H,s); MS : m/z 369 ($M^+$, 3%), 338 (4%), 308 (11%), 300 (7%), 282 (4%), 69 (60%), 60 (100%).

12) $n_D^{22}$ 1.4965; IR data were similar to those of 1a; MS:m/z 369.3286 ($M^+$= $C_{22}H_{43}O_3N$=369.59).

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