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STUDIES ON MARINE NATURAL PRODUCTS. IV
THE STEREOCHEMISTRY OF 13-MEMBERED CARBOCYCLIC CEMBRANOLIDE DITERPENES FROM THE SOFT CORAL LOBOPHYTUM PAUCIFLORUM (EHRENBERG)

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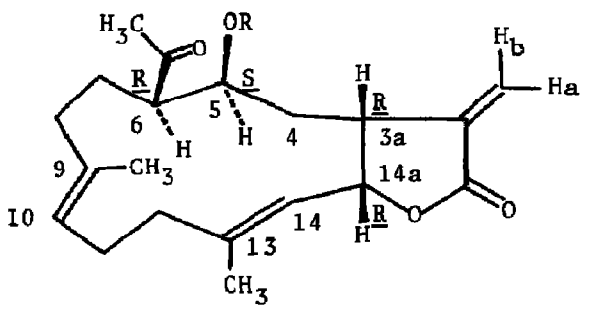
Summary : The relative and absolute stereochemistry of two 13-membered carbocyclic cembranolides was determined as shown in 1 and 2 on the basis of NMR spectral evidence.

A number of marine cembranolide diterpenes have been recently found in soft coral,[1] and in some cases these diterpenes have been reported to have interesting biological properties,[2] such as an anticancer activity. Most of these diterpenes possess a 14-membered carbocyclic ring system, to which a γ- or δ-lactone moiety is attached in many cases. We have already described the isolation and the planar structures of two cembranolide diterpenes, (1) and (2) from the Japanese soft coral Lobophytum pauciflorum (Ehrenberg)(Coelenterata, Anthozoa, Alcyonaria, Alcyonacea), each of which contains a unique 13-membered carbocyclic ring system.[3] The stereochemistry of two trisubstituted carbon-carbon double bonds have been assigned as E-type geometry from the ^{13}C-NMR chemical shifts of the olefin methyl carbons. We now wish to describe evidence for the stereochemistry of the chiral centers at C-3a, 5, 6 and 14a as depicted in 1 and 2.

The absolute configuration of the secondary hydroxyl group at C-5 in (2) was determined by applying a ^{1}H-NMR lanthanide induced shifts(LIS) method[4] and Mosher's ^{19}F-NMR configuration-correlation method[5] for the diastereomeric α-methoxy-α-trifluoromethylphenylacetyl(MTPA) esters. Acylation of (2) with R-(+)-



1 R = Ac
2 R = H
3 R = -CO-C(OCH3)(Ph)(CF3) (R-(+)-MTPA ester)
4 R = -CO-C(Ph)(OCH3)(CF3) (S-(-)-MTPA ester)

and S-(-)-MTPA chlorides gave the diastereomeric esters (3) and (4), respectively. The LIS values of OMe and ^{19}F-NMR chemical shifts of CF_3 in the pair of the diastereomeric esters are shown in Table I. The negative sign of the ΔLIS_{OMe} value[4] for MTPA esters suggests that the secondary hydroxyl group at C-5 in 2 has the S configuration. In addition, Mosher's model[5] predicts that the S-(-)-MTPA ester (4) will show CF_3 resonance downfield relative to the same resonance in the R-(+)-MTPA ester (3) if the secondary hydroxyl group has the S configuration. Alternatively, in the case of the R configuration, the prediction will be reversed. The data on the CF_3 resonance in Table I revealed that the secondary hydroxyl group at C-5 has the S configuration. Application of Horeau's method[6] to the secondary alcohol (2) also showed the configuration at C-5 to be S : observed rotation, $[\alpha]_D^{24°}$ -1.1°(c 2.54, C_6H_6); optical yield, 18 %. Since the compound (1) was obtained by acetylation of (2) with acetic anhydride in pyridine,[3] the absolute configuration of C-5 in 1 and 2 was thus established to be S.

Table I. LIS values of OMe and fluorine chemical shifts of CF_3 for MTPA esters

Compound	LIS_{OMe} [a]	Δ LIS_{OMe} [b]	CF_3 [c]
3	1.27	- 0.55	8.48
4	1.82		9.08

a) determined at a molar ratio of Eu(fod)$_3$/ester of 1.7:1 in CCl_4 at 60 MHz. b) The value represents the difference in two LIS_{OMe} for MTPA esters; LIS_{OMe}(3)-LIS_{OMe}(4). c) Fluorine shifts (in ppm) are downfield from external TFA in $CDCl_3$ at 56.4 MHz.

The stereochemistry of the other chiral centers at C-6, 3a and 14a were determined by relating to the configuration of C-5 as follows. The 360 MHz ^{1}H-NMR spectrum of 1(Fig.1) gave clear separation of all of the overlapping signals observed for the protons at C-6, 5, 4, 3a, 14a and 14 positions in the 100 MHz spectrum, and exact coupling constant values between the protons at those positions were obtained by decoupling experiments as listed in Table II.[7] Similar coupling constants for the protons of the same positions in 2 were observed by measuring the 360 MHz ^{1}H-NMR spectrum. Therefore, both compounds (1) and (2) were suggested to have a similar conformation, especially in the neighborhood of the chiral centers at C-6, 5, 3a and 14a.

A remarkable shifts for both H-5 and H-3a were observed in going from the alcohol (2) to the acetate (1) : H-5 downfield shift from 3.72 to 5.17 ppm; H-3a upfield shift from 3.52 to 3.01 ppm (Table II). The upfield shift of H-3a of 1 can be explained by the anisotropic effect of the acetoxyl group,[8] and the proton on C-3a is presumed to be extremely close proximity to the acetoxyl on C-5 as depicted in Fig.2. This arrangement was supported by the observation of the

Table II. 360 MHz ^{1}H-NMR data[a] of 1 and 2

Compound	1	2
H-3a	3.01 (m)	3.52 (m)
H-4	1.76 (ddd,J=15.3,11.2,2.1)	
	1.82 (ddd,J=15.3,10.4,4.3)	1.68 (ddd,J=15.1,11.0,3.0)
H-5	5.17 (ddd,J=10.4,3.0,2.1)	3.72 (tt,J=10.9,2.3)
H-6	2.35 (m)	2.34 (m)
H-10	5.07 (brt,J=8.0)	5.06 (brt,J=8.0)
H-14	5.06 (brd,J=10.0)	5.11 (brd,J=10.0)
H-14a	5.37 (dd,J=10.0,8.4)	5.32 (dd,J=10.0,8.0)
Ha	6.22 (d,J=3.2)	6.21 (d,J=3.0)
Hb	5.48 (d,J=2.9)	5.52 (d,J=2.5)
$COCH_3$	2.19 (s)	2.20 (s)
OAc	2.14 (s)	———
OH	———	3.38 (d,J=10.9)
C-9 Me	1.58 (brs)[b]	1.63 (brs)[b]
C-13 Me	1.86 (brs)[b]	1.76 (brs)[b]

a) Chemical shifts are given in δ units with tetramethylsilane as an internal standard in $CDCl_3$(J in Hz). b) These assignments may be reversed.

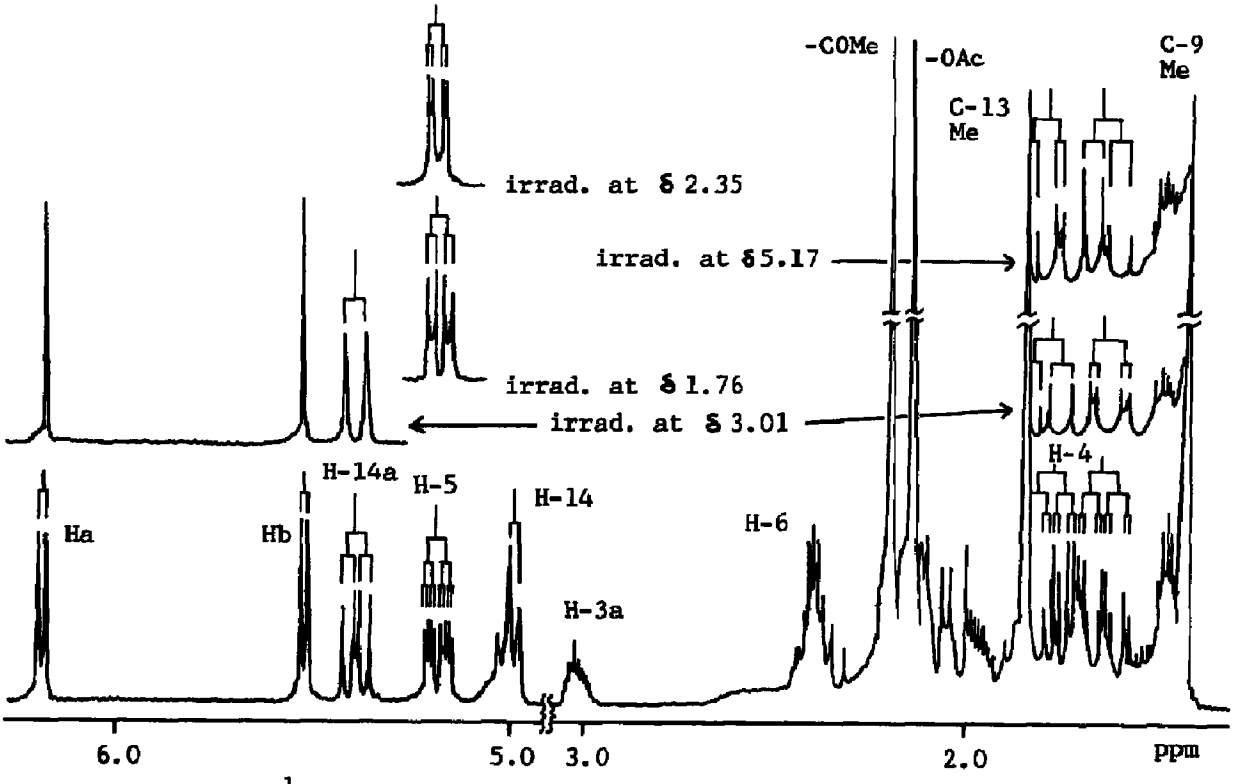


Fig.1 360 MHz ^{1}H-NMR spectra and decoupling experiments of 1

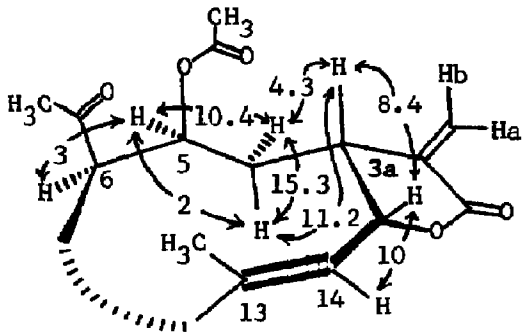


Fig.2 Coupling constant assignments for 1 (J in Hz)

coupling constants between H-5, H-4 and H-3 in 1. Furthermore, the coupling constant between H-3a and H-14a ($J_{3a,14a}$ =8.4 Hz) is consistent with cis relationship.[9] Accordingly, from the consideration described above, the configuration of C-5, 3a and 14a in 1 were assinged as shown in Fig.2. Determination of remaining chirality at C-6 which is shown in Fig.2, was based on the vicinal coupling constant ($J_{5,6}$ =3 Hz) between H-5 and H-6 in 1, and also on the presence of strong IR bands (ν_{max}3400, 168 cm^{-1}) due to the intramolecular hydrogen bonding of the hydroxyl and methyl ketone in 2. This was also supported by hydrog bonding induced downfield shift[10] for the carbonyl carbon of the methyl ketone i ^{13}C-NMR spectrum of 2 (211.0 ppm) from its position in 1 (208.8 ppm).[3]

Thus, the stereochemistry of both compounds (1) and (2) was established to have same absolute configuration of 3aR, 14aR, 5S and 6R as depicted in 1 and 2.

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7) Fig.1 shows a summary of decoupling experiments of 1 as follows :

irradiated proton(δ, ppm)	observed protons and changes(J in Hz)
H-3a (3.01)	H-4(1.76,ddd)⟶dd,J=15.3,2.1; H-4(1.82, ddd)⟶dd,J=15.3,10.4; Ha(5.48,d)⟶s; Hb(6.22,d)⟶s; H-14a(5.37,dd)⟶d,J=10
H-5(5.17)	H-4(1.76,ddd)⟶dd,J=15.3,11.2; H-4(1.82,ddd)⟶dd,J=15.3,4.3
H-4(1.76)	H-5(5.17,ddd)⟶dd,J=10.4,3.1
H-6(2.35)	H-5(5.17,ddd)⟶dd,J=10.4,2.1

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