Tetrahedron Vol. 46, No. 17, pp. 6125-6132, 1990
Printed in Great Britain

0040-4020/90 $3.00+.00

NEW XENICANE DITERPENES FROM THE BROWN ALGAE OF *DICTYOTACEAE*

Manuel Norte, A.G. González, Patricia Arroyo, Miguel Zárraga, Cirilo Pérez, Matias L. Rodríguez, Catalina Ruiz-Perez and Luis Dorta

Centro de Productos Naturales Orgánicos Antonio González. Instituto Universitario de Química Bio-orgánica. Universidad de La Laguna. 38206 La Laguna. Spain.

(*Received in UK* 2 *April* 1990)

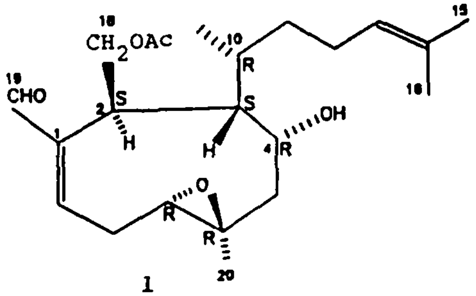
Summary: Two new xenicane diterpenes have been isolated from the brown algae of the **Dictyotaceae** family, and their structures and absolute configurations have been elucidated on the basis of their spectral and X-ray diffraction analyses.

Brown algae of the **Dictyotaceae** family are characterized by the production of diterpenoids with different carbon frameworks[1]. Among the diterpenes found in this family of seaweeds, one of the most intriguing groups are the xenicanes, some of them with a significant cytotoxic activity[2], which have been isolated not only from alga but also from soft corals and gorgonians[3,4]. Structurally these compounds are characterized as being composed of a cyclononane skeleton, which is rarely found in other natural products.

In this paper, we wish to describe the structures of two new xenicane derivatives isolated during the comparative study of the brown algae communities from the Atlantic and Pacific shores. Thus, we have collected at Valparaiso (Chile) the brown alga **Glossophora kuntii** from which we have isolated the xenicane derivative **2**. On the other hand, the diterpene **1** was isolated from the brown alga Dictyota sp collected at Tenerife in the Canary Islands.

Compound 1, $(\alpha_D) = -80.7^{\circ}$ (c, 0.29, $CHCl_3$), was isolated as a crystalline compound (m.p. 53-54 ºC). Its molecular formula was established as $C_{22}H_{34}O_5$ on the basis of its HRMS (m/z 378.2397). Absorptions in the I.R. spectrum at 3435, 1730 and 1760 cm^{-1} were due to the presence of an hydroxyl, acetate and α,β-unsaturated carbonyl groups, this last one being confirmed by a band in the UV spectrum at 225 nm. Moreover, the NMR spectra established the presence of an acetoxymethyl group (^{13}C: δ, 63.8; ^{1}H: δ, 4.63 and 4.73); a trisubstituted epoxy ring (^{13}C: δ, 60.09 and 63.32; ^{1}H: δ, 2.88 and 1.5), a secondary hydroxyl group (^{13}C: δ, 68.21; ^{1}H: δ, 4.16) and a disubstituted α,β-unsaturated aldehyde group (^{13}C: δ, 189.8, 152.41, 100.67; ^{1}H: δ, 6.82 and 9.32). The NMR spectra, together with the presence of the fragmentations at m/z 109 and 69 in the MS spectrum, also revealed that the 6 methyl-5-hepten-2-yl group, the typical side chain in the **Dictyotaceae** diterpenes, was present.

The assignments of the chemical shifts of compound 1 (Table I) were made by using mono- and bidimensional, homo- and heteronuclear NMR experiments. Comparison of these data with those published for fukurinolal[5] or hydroxyacetyldictyolal[6] 3, which was published in two independent works as a metabolite of **Dilophus okamurai** and **Dictyota dichotoma** respectively, indicated that compound 1 was the 6,7-epoxy derivative of 3.



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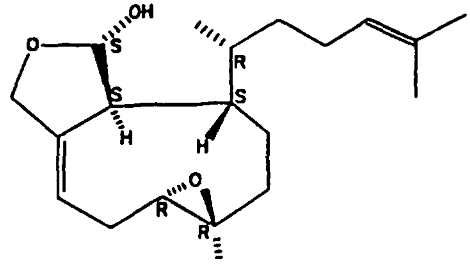

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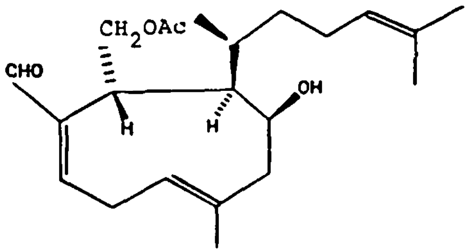

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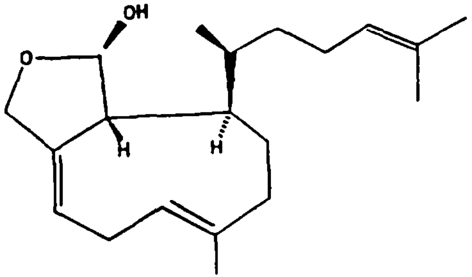

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The structure of compound 2, $(\alpha_D) = +6.81^{\circ}$ (c, 0.088. $CHCl_3$), $C_{20}H_{32}O_3$ (m/z 320.3241), isolated from **Glossophora kunti** collected at Valparaiso (Chile), was deduced in essentially the same manner. Its spectral properties (Table I) confirmed that compound 2 also possesses a 6,7-epoxy xenicane skeleton, in which the presence of a hemiacetal moiety was evident: IR: 3500cm^{-1}; NMR: ^{13}C: δ, 100.3 and 71.1; ^{1}H: δ, 4.39, 5.67. In fact the comparison of the ^{13}C-NMR signals of 2 with those of isodictyohemicetal 4, metabolite isolated from D. **dichotoma**[6], showed that the obvious difference was the absence of the C(6) and C(7) olefinic signals at δ 134.6 and 124.7, and the presence of signals from a trisubstituted epoxy ring at δ 60.4 and 63.9. Thus we can conclude that 2 is the 6,7-epoxy isodictyohemicetal.

The structures of these compounds were confirmed by X-ray diffraction analysis. Compound 1 crystallized in the orthorhombic space group $P2_12_12_1$ with one molecule of composition $C_{22}H_{34}O_5$ in the asymmetric unit. Cell constants were a = 9.423(1), b = 10.236(1) and c = 22.675(1) Å. All unique diffraction maxima with $3 \leq 2\theta \leq 128^{\circ}$ were collected on a computer-controlled Siemens AED four-circle diffractometer using graphite monochromated CuKα (1.54178 Å) radiation and a

Table I: NMR Spectral data of compounds 1 and 2

C	1	2	H	1	2
1	150.67	146.6	1		
2	38.76	44.9	2	3.25 dd, 10;6.5	2.56 bs
3	49.12	53.8	3	1.80 bs	-
4	68.21	27.9	4	4.16 dd, 7.1;3.5	-
5	47.66	39.8	5 5	1.06 dd, 14.1;7.1 2.42 dd, 14.1;3.5	- -
6	60.01	60.4	6	-	-
7	62.32	63.9	7	2.90 d, 10	3-03 dd, 1.9;10.8
8	26.65	26.1	8 8	2.91 dd, 9.1;16 2.45 ddd, 3.5;10;16	2.65 ddd, 1.9;8.4;10.8 2.33 ddd, 1.9;10.8;16.2
9	152.41	116.6	9	6.82 dd, 9.1;3.5	5.64 dd, 1.6;8.4
10	32.12	31.9	10	2.41 m	1.88 m
11	38.38	38.1	11	1.15 m	1.16 m
12	26.13	26.6	12	1.79 m	1.92 m
13	124.56	124.4	13	5.07 bt, 7	5.03 bt, 7
14	131.56	131.4	14	-	-
15	17.85	17.6	15	1.61	1.65
16	25.77	25.5	16	1.51	1.58
17	17.74	17.3	17	1.00 d, 7	0.98
18	63.80	100.2	18 18	4.61 t, 10 4.71 dd, 6.5;10	5.67 bs
19	189.80	71.1	19	9.42 d, 1.9	4.39 bs
20	20.3	17.0	20	1.61	1.40
(C=O)	170.84				
Me(OAc)	21.05			1.93	

a) Assignments made by heteronuclear COSY, b) assignments made by homonuclear decoupling and homonuclear COSY

ω:θ scan. After correction for Lorentz, polarization and background effects, only 1897 (99%) of the 1912 reflections surveyed were considered observed ($I \geq 3\sigma(I)$).

A phasing model was arrived at using a multisolution weighted tangent formula approach using magic integers[7]. The best model from this approach showed all non-hydrogen atoms. The structure was anisotropically refined by block-diagonal least squares (on F)[8]. Scattering factors were taken from International Tables for X-Ray Crystallography[9]. All H-atoms were located on a difference electron density map. An appropriate weighting scheme to normalize $<\omega\Delta^2F>$ vs. $<Fo>$ and $<\sin\theta/\lambda>$ was carried out[10]. A final weighted anisotropic full-matrix refinement (fixed isotropic contribution for H atoms) gave for the correct enantiomer the discrepancy indices R= 0.055 (Rw= 0.060).

The absolute configuration of 1 was determined by comparison of 30 Bijvoet pairs with Fo $>5\sigma$(Fo), which are in the range 5.< Fc < 50. and 0.2 < ($\sin\theta/\lambda$) < 0.4 Å^{-1}. The averaged Bijvoet differences

ATOM	X/A	Y/B	Z/C	Ueq
O1	0.0323(1)	0.0621(1)	0.7595(1)	835(10)
O2	0.2973(1)	0.0342(1)	0.8599(1)	662(7)
O3	-0.1367(1)	-0.1990(1)	1.0218(1)	772(9)
O4	0.0452(1)	0.2087(1)	0.9929(1)	580(7)
O5	0.4182(1)	0.0914(1)	0.9383(1)	1273(17)
C1	0.0239(1)	-0.0678(1)	0.8482(1)	562(9)
C2	0.0541(1)	0.0419(1)	0.8921(1)	476(8)
C3	-0.0818(1)	0.1245(1)	0.9075(1)	452(7)
C4	-0.0900(1)	0.1587(1)	0.9739(1)	499(8)
C5	-0.1406(1)	0.0484(1)	1.0148(1)	589(9)
C6	-0.0585(1)	-0.0780(1)	1.0094(1)	567(9)
C7	-0.1021(1)	-0.1663(1)	0.9615(1)	632(10)
C8	-0.0035(1)	-0.2486(1)	0.9247(1)	750(13)
C9	0.0045(1)	-0.1934(1)	0.8634(1)	688(12)
C10	-0.1105(1)	0.2438(1)	0.8672(1)	481(8)
C11	-0.2712(1)	0.2685(1)	0.8629(1)	552(9)
C12	-0.3140(1)	0.3659(1)	0.8154(1)	674(11)
C13	-0.4707(1)	0.3961(1)	0.8161(1)	656(11)
C14	-0.5280(1)	0.5094(1)	0.8015(1)	779(13)
C15	-0.6836(2)	0.5337(2)	0.8060(1)	1348(29)
C16	-0.4440(2)	0.6218(1)	0.7792(1)	1081(20)
C17	-0.0343(1)	0.3703(1)	0.8854(1)	615(10)
C18	0.1818(1)	0.1244(1)	0.8735(1)	561(9)
C19	0.0208(1)	-0.0423(1)	0.7836(1)	705(12)
C20	0.0893(1)	-0.0806(1)	1.0355(1)	657(11)
C21	0.4061(1)	0.0257(1)	0.8963(1)	586(10)
C22	0.5069(1)	-0.0787(1)	0.8779(1)	816(14)

$$U_{eq} = \left(\tfrac{1}{3}\right)\cdot\sum\left(U_{ij}\cdot\vec{a}^{*}_{i}\cdot\vec{a}^{*}_{j}\cdot\vec{a}_{i}\cdot\vec{a}_{j}\cdot\cos(\vec{a}_{i},\vec{a}_{j})\right)\cdot 10^{4}$$

Table II.- Atomic coordinates (A) and equivalent isotropic temperature factors (A^2 x 10^3) for compound 1 with e.s.d.'s. in ( ).

O1	- C19	1.205 (5)	C4	- C5	1.538 (4)
O2	- C18	1.460 (4)	C5	- C6	1.512 (5)
O2	- C21	1.319 (4)	C6	- C7	1.472 (5)
O3	- C6	1.468 (4)	C6	- C20	1.513 (5)
O3	- C7	1.444 (5)	C7	- C8	1.506 (5)
O4	- C4	1.438 (4)	C8	- C9	1.502 (6)
O5	- C21	1.172 (6)	C10	- C11	1.539 (4)
C1	- C2	1.528 (4)	C10	- C17	1.537 (4)
C1	- C9	1.344 (5)	C11	- C12	1.522 (5)
C1	- C19	1.488 (5)	C12	- C13	1.509 (5)
C2	- C3	1.574 (4)	C13	- C14	1.320 (6)
C2	- C18	1.529 (4)	C14	- C15	1.491 (8)
C3	- C4	1.548 (4)	C14	- C16	1.484 (7)
C3	- C10	1.549 (4)	C21	- C22	1.490 (5)

C18	- O2	- C21	119.2 (3)	C7	- C6	- C20	122.2 (3)
C6	- O3	- C7	60.7 (2)	O3	- C7	- C6	60.4 (2)
C9	- C1	- C19	114.8 (3)	C6	- C7	- C8	125.5 (3)
C2	- C1	- C19	121.1 (3)	O3	- C7	- C8	122.3 (3)
C2	- C1	- C9	124.1 (3)	C7	- C8	- C9	109.4 (3)
C1	- C2	- C18	111.9 (2)	C1	- C9	- C8	127.2 (3)
C1	- C2	- C3	112.8 (2)	C3	- C10	- C17	115.1 (2)
C3	- C2	- C18	113.9 (2)	C3	- C10	- C11	109.8 (2)
C2	- C3	- C10	115.7 (2)	C11	- C10	- C17	109.8 (2)
C2	- C3	- C4	112.2 (2)	C10	- C11	- C12	114.4 (3)
C4	- C3	- C10	112.7 (2)	C11	- C12	- C13	112.7 (3)
O4	- C4	- C3	109.1 (2)	C12	- C13	- C14	125.2 (4)
C3	- C4	- C5	115.8 (5)	C13	- C14	- C16	123.2 (5)
O4	- C4	- C5	110.8 (2)	C13	- C14	- C15	122.1 (4)
C4	- C5	- C6	114.9 (3)	C15	- C14	- C16	114.7 (5)
O3	- C6	- C5	116.7 (3)	O2	- C18	- C2	107.2 (2)
C5	- C6	- C20	117.0 (3)	O1	- C19	- C1	126.8 (4)
C5	- C6	- C7	116.3 (3)	O2	- C21	- O5	123.1 (3)
O3	- C6	- C20	111.9 (3)	O5	- C21	- C22	125.3 (4)
O3	- C6	- C7	58.8 (2)	O2	- C21	- C22	111.6 (3)

Table III.- Interatomic distances (A) and angles (º) of compound 1 with e.s.d.'s. in ( ).

are 0.274 for the correct enantiomer vs 0.348 for the wrong one. The final positional and equivalent isotropic thermal parameters are given in Table II. A drawing of the final X-ray model less hydrogens is given in Fig.1. Bond lengths and bond angles are listed in Table III.

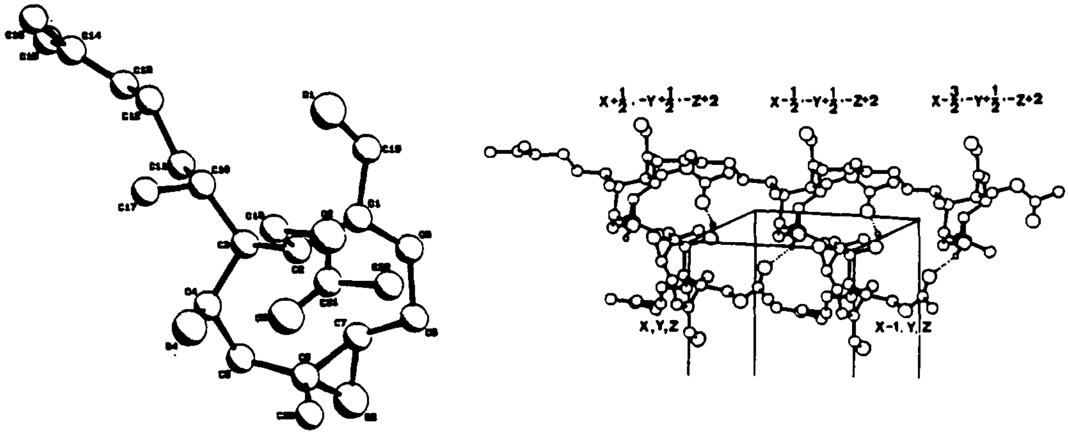

Fig. 1.- Perspective view of the structure of 1, showing atomic labelling and packing diagram

Molecules interact in the crystal through a hydrogen bond, with hydroxyl group O(4) as donor and the O(5) of a molecule related by x-1/2, -y+1/2, -z+2 as acceptor. Geometrical parameters of this hydrogen bond are O▪▪▪O: 2.838(5), H▪▪▪O: 1.91 (1) and O-H▪▪▪O: angle 155.5 (2)º. The chains formed by these interactions are depicted in Fig.1. No other intermolecular interactions shorter than 3.35P between non-hydrogen atoms exist.

Compound 2 ($C_{20}H_{32}O_3$) crystallized in the monoclinic space group C(2). The cell constants were a= 16.687(1), b= 6.260(1), c= 21.230(1) P, ß= 120.4(2)º. All unique diffraction maxima with also 3 \ 2h \ 128º were collected in the manner described for 1 and 1298 (83%) of the 1554 reflections were judged observed. The structure was solved using direct methods[12] and subsequent Fourier analysis. Blocked full-matrix least-squares refinement on F. Some H atoms were introduced at calculated positions with C-H = 1.08Å, and refined riding on their carrier atoms with a general isotropic thermal parameter. In the final cycles of the refinement positional and individual anisotropic thermal parameters for the non-H atoms, positional parameters for H-atoms, their isotropic thermal parameter and an overall scale factor were varied. For 2 the final R value was 0.043, Rw= 0.050, w= $1/[\sigma^2(Fo) + 0.0011(Fo)^2]$ The refinement calculation were performed with SHELX76[13]. The absolute configuration was fixed by comparison of 65 Bijvoet pairs with Fo $\leq 5\sigma$(Fo), which are in the ranges 5. $\leq$ Fo $\leq$ 50. and .2 $\leq \sin\theta/\lambda \leq$ .4Å^{-1} [11]. The averaged Bijvoet differences are 0.427 for the correct enantiomer vs 0.491 for the wrong one. Fig. 2 shows the molecular configuration and the

ATOM	X/A	Y/B	Z/C	Ueq
O1	0.1792(2)	0.2796(*)	0.4002(2)	59(1)
O2	0.4997(2)	0.3183(8)	0.3110(2)	64(2)
O3	0.5240(2)	0.5845(8)	0.3964(2)	63(1)
C1	0.4159(2)	0.1963(9)	0.3656(2)	47(2)
C2	0.3776(2)	0.4127(9)	0.3315(2)	45(2)
C3	0.2821(2)	0.3968(9)	0.2569(2)	46(2)
C4	0.2100(3)	0.5610(10)	0.2530(2)	56(2)
C5	0.1540(3)	0.4845(10)	0.2895(2)	55(2)
C6	0.2149(2)	0.4344(9)	0.3688(2)	46(2)
C7	0.2530(3)	0.2165(9)	0.3861(2)	47(2)
C8	0.3483(3)	0.1559(10)	0.4482(2)	53(2)
C9	0.4077(2)	0.0914(9)	0.4156(2)	51(2)
C10	0.2898(3)	0.4079(10)	0.1868(2)	54(2)
C11	0.2126(3)	0.2682(11)	0.1269(2)	59(2)
C12	0.2211(4)	0.2345(15)	0.0591(3)	85(3)
C13	0.1489(4)	0.0844(13)	0.0047(3)	78(3)
C14	0.0768(4)	0.1370(12)	-0.0589(3)	76(3)
C15	0.0100(4)	-0.0293(14)	-0.1091(4)	104(3)
C16	0.0549(5)	0.3572(15)	-0.0882(5)	121(4)
C17	0.2858(4)	0.6330(11)	0.1582(3)	75(3)
C18	0.4610(3)	0.4980(10)	0.3271(2)	56(2)
C19	0.4789(3)	0.1285(10)	0.3372(3)	60(2)
C20	0.2600(4)	0.6207(10)	0.4190(3)	61(2)

Table V.- Atomic coordinates (A) and equivalent isotropic temperature factors (A^2 x 10^3) for compound 2 with e.s.d.'s. in ( ).

O1 - C6	1.476 (9)		C5 - C6	1.504 (7)	
O1 - C7	1.452 (9)		C6 - C7	1.465 (10)	
O2 - C18	1.413 (10)		C6 - C20	1.510 (10)	
O2 - C19	1.439 (11)		C7 - C8	1.511 (7)	
O3 - C18	1.430 (8)		C8 - C9	1.498 (11)	
C1 - C2	1.525 (9)		C10 - C11	1.542 (9)	
C1 - C9	1.318 (10)		C10 - C17	1.540 (11)	
C1 - C19	1.499 (12)		C11 - C12	1.532 (13)	
C2 - C3	1.575 (6)		C12 - C13	1.512 (13)	
C2 - C18	1.530 (10)		C13 - C14	1.319 (9)	
C3 - C4	1.536 (11)		C14 - C15	1.510 (12)	
C3 - C10	1.563 (10)		C14 - C16	1.473 (14)	
C4 - C5	1.550 (11)				

C6 - O1 - C7	60.0(4)	O1 - C7 - C6	60.8(4)
C18 - O2 - C19	109.2(7)	C6 - C7 - C8	125.1(6)
C9 - C1 - C19	124.0(6)	O1 - C7 - C8	121.8(5)
C2 - C1 - C19	106.1(5)	C7 - C8 - C9	109.1(5)
C2 - C1 - C9	129.6(6)	C1 - C9 - C8	126.3(6)
C1 - C2 - C18	98.9(5)	C3 - C10 - C17	113.4(5)
C1 - C2 - C3	113.1(6)	C3 - C10 - C11	109.2(5)
C3 - C2 - C18	116.7(5)	C11 - C10 - C17	110.1(5)
C2 - C3 - C10	114.8(5)	C10 - C11 - C12	114.5(7)
C2 - C3 - C4	112.2(5)	C11 - C12 - C13	112.8(7)
C4 - C3 - C10	112.1(5)	C12 - C13 - C14	125.8(9)
C3 - C4 - C5	115.7(6)	C13 - C14 - C16	124.3(9)
C4 - C5 - C6	111.9(6)	C13 - C14 - C15	120.7(9)
O1 - C6 - C5	116.5(6)	C15 - C14 - C16	115.0(8)
C5 - C6 - C20	116.7(6)	O3 - C18 - C2	106.8(6)
C5 - C6 - C7	116.4(5)	O2 - C18 - C2	106.8(6)
O1 - C6 - C20	111.0(5)	O2 - C18 - O3	110.9(6)
O1 - C6 - C7	59.2(4)	O2 - C19 - C1	106.0(6)
C7 - C6 - C20	123.2(5)		

Table IV.- Interatomic distances (A) and angles (º) of compound 2 with e.s.d.'s. in ( )

atomic numbering, together with the crystal packing along the a axis. In Tables IV and V bond lengths and angles, and final positional and equivalent isotropic thermal parameters respectively are reported. They compare well with 1 and those observed in other related marine diterpenes[14]. Bond distances and angles are normal. The five-membered ring shows an envelope conformation. Four of the five ring atoms are almost coplanar (as defined by the C(18)-O(2)-C(19)-C(1) dihedral angle of 4.6(8)º), while the fifth atom C(2) lies 0.431Å above this plane.

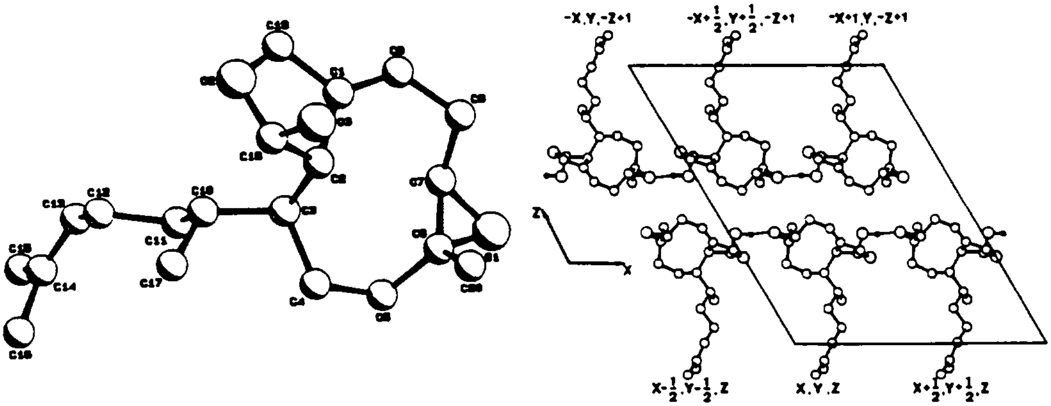

Fig. 2.- Perspective view of the structure of 2, showing atomic labelling and packing diagram.

The crystalline cohesion is ensured by a hydrogen bond between the hydroxyl group O(3) as donor and the O(1) of the epoxide of a molecule related by x + 12, y + 1/2, z, as acceptor. The HO(3)▪▪▪O(1) bond length is 2.819(7)Å and the angle of this bond is 159.1(1)º. Other intermolecular distances are in the normally expected range for nonbonded contacts.

The interest of different marine chemistry research groups in this type of compounds has been due not only to their pharmacological activity but also to their structural features. Thus, for compounds 1 and 2, we can infer that, in solution, the preferred conformation of the nine-membered ring is that in which the dihedral angles between the carbon protons C(2) and C(3); C(3) and C(10) for 1 and 2, together with those between C(3) and C(4) for 1 and between C(2) and C(18) for 2 are 90º. In this conformation can be explained, as advanced by Matsumoto[6], the deshielding effect observed in the NMR chemical shifts in compound 1 for the methyl group C(20).

On the other hand, the absolute configuration of some marine diterpenes from brown algae possessing a xenicane skeleton, has recently been published[15]. In our case, the results also confirmed the advanced conclusion that the absolute configuration of the xenicane diterpenes from Dictyotaceae algae are opposite to that of xenicin, isolated from soft corals[16].

EXPERIMENTAL PART

Infrared spectra were recorded on a Perkin-Elmer Mod. 257. Optical rotations were determined for solution in chloroform with a Perkin-Elmer Mod. 241 polarimeter. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker Mod. WP-200 SY (200 MHz), chemical shifts are reported relative to Me_4Si(d 0) and coupling constants are given in hertz. The 2D-NMR spectra were obtained using Bruker's microprograms. Low and high resolution mass spectra were obtained from VG micromass ZAB-2F spectrophotometer. Silica gel chromatography was performed on silica gel 60 G, TLC and PLC obtained from Merck products. The tlc plates were developed by spraying with 6N sulphuric acid and heating. Sephadex LH-20 obtained from Pharmacia was used for gel filtration chromatography. All solvents were purified by standard techniques. Anhidrous sodium sulfate was used for driying solution.

Collection, extraction and chromatographic separation.

Dictyota sp was collected at -10 m deep at Güimar (Tenerife, Canary Islands) in November 1987. The air-dried alga (8 kg) was extracted with acetone and diethyl ether and the solvents were evaporated in vacuo to yield 220 gr of extract. **Glossophora kuntii** was collected in shallow water at low tide near Valparaiso (Chile) in January 1986 and treated as above to yield 150 gr of crude extract. The chromatographic treatment of both extracts were identical. First, flash chromatography on silica gel column eluted with mixtures of n-hexane/ethyl acetate of increasing polarity. The fractions eluted with n-Hex./EtOAc 70:30 were combined to yield, after solvent evaporation, compound **1** in the crude extract of **Dictyota sp** and compound **2** in those of **G. kuntii.** These extracts were submitted to repeated chromatographies on silica and finally purified by chromatography on a Sephadex LH-20 column with $CHCl_3$:MeOH:n-Hex (1:1:2) as eluent to give pure compounds **1** and **2**.

Compound 1: solid (m.p. 53-54º C), (a_D= -80.7º (c, 0.29, $CHCl_3$). UV_{max}: 225 nm (e= 5333). IR: 3435, 2900, 1720, 1670, 1440, 1360and 1020 cm^{-1}. HRMS: M^+ at m/z 378.2397 (Calc. 378.2406). MS: m/z 378 (M^+), 360, 332, 318, 109, 69. NMR spectra: see Table I.

Compound 2: solid (m.p. 90-92 ºC), (a_D)= +6.81º (c, 0.88, $CHCl_3$). UV_{max}: 208 nm (e= 2831). IR: 3550, 2950, 1750, 1350, 1050 cm^{-1}. HRMS: M^+ at m/z 320.2341 (Calc. 320.2331). MS: m/z 320 (M^+), 302, 284, 259, 231, 109, 69. NMR spectra: see Table I.

Acknowledgments: We acknowledge financial support from Plan Nacional de Investigacion FAR 88-0500. P.A. and M.Z. acknowledge Instituto de Cooperación Iberoamericana (ICI) and Banco Central de España respectively for a fellowship. The authors acknowledge to Dr. Patricio Rivera (University of Chile) for collection of **G. kuntii.**

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