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PATAGONICOL: A DITERPENOID FROM THE CHINESE SOFT CORAL *ALCYONIUM PATAGONICUM*

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ABSTRACT.—Patagonicol [1], a diterpenoid with a eunicellin skeleton, was isolated from the soft coral *Alcyonium patagonicum*. The structure of 1 was determined by X-ray diffraction, and detailed ^1H and ^{13}C assignments were made via 1D and 2D nmr experiments.

A number of diterpenoids (1–7), mostly cembranoids (1–6), and sesquiterpenoids (8–10) have been reported from soft corals of the genus *Alcyonium*, family Alcyoniidae. One of the diterpenoids (7) has the eunicellin skeleton. We report here another eunicellin-type diterpenoid 1 from *Alcyonium patagonicum* (May) collected off the Xisha Islands in the South China Sea in 1988.

The concentrated EtOH extract of *A. patagonicum* (dry wt 3.5 kg) was partitioned between EtOAc and H_2O to give 30 g of crude organic extract, which exhibited quite good antifungal activity (87% inhibition at 100 μg/ml) against *Candida pseudotropicalis*. Flash chromatography of the extract on a Si gel column afforded fractions from which colorless needles of patagonicol [1] (20 mg) were deposited (Me_2CO).

Patagonicol, mp 172.5–174.0°, [α]D +7.5 (c=0.0042/ml), was confirmed to have the formula $C_{22}H_{38}O_4$ by hrms analysis. The structure of patagonicol was elu-

cidated by single crystal X-ray diffraction and found to be that shown by structure 1. Patogonicol is thus the C-6 ethyl ether of sclerophytin F [2]. It is likely that 1 is an artifact resulting from opening of a C-6, -7 epoxide during extraction of the dried specimens with EtOH. However, the location of the ethoxy group is not consistent with a solvolytic opening of such an epoxide, a reaction that would be expected. On the other hand an S_N2 opening of this epoxide would yield 1. Interestingly, the X-ray analysis reveals that the conformation of 1 is nearly identical to that of sclerophytin C [3], which has an additional hydroxyl substituent at C-8.

The ^1H- and ^{13}C-nmr assignments (Table 1) were made from the combined information obtained from difference decoupling, COSY, TOCSY, HETCOR, HMQC, and selective INEPT experiments. Only the signals for C-3 and C-6 were not directly confirmed. The ^{13}C signal for C-16 was very small and broad in both $CDCl_3$ and C_6D_6 at ambient temperature, but the signal sharpened noticeably when the spectrum was taken at 55° in C_6D_6. There is a large difference in the ^1H chemical shift of H-15 in C_6D_6 (0.80 ppm) vs $CDCl_3$ (1.15 ppm). The ^{13}C signal for C-15 in C_6D_6 occurs at lower field (29.9 ppm) than that reported for C-15 in sclerophytin F [2] in $CDCl_3$ (23.2 ppm). Nmr analyses were carried out in C_6D_6 at elevated temperature because this solvent/temperature combination
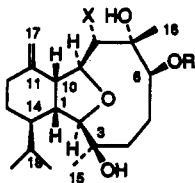
1 X=H, R=Et
2 X=H, R=H
3 X=OH, R=H

TABLE 1. ^{1}H- and ^{13}C-nmr Data for Patagonicol [1].[a]

Position	^{1}H[b]	^{13}C
1	2.03 (bdd, ca. 10, ca. 7.5)	45.3 (d)
2	3.52 (s)	91.1 (d)
3		74.4 (s)[c]
4	1.54, ca. 1.60 (m)	40.9 (t)
5	ca. 1.5, ca. 1.9 (m)	27.2 (t)
6	4.46 (m)	88.4 (d)
7		76.1 (s)[c]
8	1.94, 2.30 (dd, 14.5, 11)	45.1 (t)
9	4.47 (m)	78.6 (d)
10	3.06 (dd, ca. 7.5; ca. 7.5)	53.8 (d)
11		148.4 (s)
12	2.14, 1.97	31.9 (t)
13	0.98 dq (3, ca. 12), 1.54 (m)	25.2 (t)
14	1.28 (dddd, ca. 11, ca. 11, 3.5, 3)	44.0 (d)
15	0.80 (s)	29.9 (q)
16	1.37 (s)	24.8 (q)
17	4.71 (m), 4.75 (brd, 3)	109.2 (t)
18	1.66 (m)	29.3 (d)
19	0.69 (d, 7.0)	15.7 (q)
20	0.91 (d, 7.0)	22.1 (q)
21	3.35, 3.56 (dq, 9.5, 7.0)	64.8 (t)
22	1.11 (t, 7.0)	15.3 (q)

[a]Data recorded in C_6D_6 at 500 MHz (^{1}H) and 125 MHz (^{13}C) at 55°. Carbon multiplicities were determined through a DEPT experiment.
[b]Multiplicity and J in Hz.
[c]These resonances can be interchanged.

TABLE 2.   Atomic Parameters. ESDs are in parentheses.

Atom	x	y	z	Ueq[a]
O-1	0.3403 (2)	0.00000	0.2994 (1)	0.0179 (3)
O-2	−0.1841 (2)	−0.0188 (1)	0.3171 (1)	0.0225 (4)
O-3	0.2073 (2)	0.1615 (1)	0.0220 (1)	0.0260 (4)
O-4	0.4064 (2)	0.0025 (1)	0.0136 (1)	0.0275 (4)
C-1	0.2097 (3)	−0.0966 (1)	0.4307 (2)	0.0189 (5)
C-2	0.2105 (3)	−0.0017 (1)	0.3956 (1)	0.0182 (5)
C-3	−0.0258 (3)	0.0424 (1)	0.3717 (2)	0.0192 (5)
C-4	−0.0201 (3)	0.1244 (1)	0.2977 (2)	0.0227 (5)
C-5	−0.0454 (3)	0.1171 (2)	0.1658 (2)	0.0231 (6)
C-6	0.1743 (3)	0.0997 (1)	0.1096 (2)	0.0201 (5)
C-7	0.1806 (3)	0.0128 (1)	0.0481 (2)	0.0212 (5)
C-8	0.1373 (3)	−0.0633 (1)	0.1241 (2)	0.0205 (5)
C-9	0.3011 (3)	−0.0776 (1)	0.2332 (1)	0.0180 (5)
C-10	0.2024 (3)	−0.1437 (1)	0.3131 (2)	0.0199 (5)
C-11	0.3233 (4)	−0.2291 (2)	0.3161 (2)	0.0257 (6)
C-12	0.5446 (4)	−0.2342 (2)	0.3942 (2)	0.0311 (7)
C-13	0.4997 (4)	−0.2089 (2)	0.5156 (2)	0.0290 (6)
C-14	0.4214 (3)	−0.1158 (1)	0.5184 (2)	0.0215 (5)
C-15	−0.0997 (4)	0.0676 (2)	0.4880 (2)	0.0258 (6)
C-16	0.0020 (4)	0.0101 (2)	−0.0588 (2)	0.0278 (6)
C-17	0.2333 (5)	−0.2951 (2)	0.2554 (2)	0.0409 (8)
C-18	0.3765 (3)	−0.0857 (2)	0.6395 (2)	0.0249 (6)
C-19	0.2206 (4)	−0.1462 (2)	0.6966 (2)	0.0326 (7)
C-20	0.5975 (4)	−0.0712 (2)	0.7196 (2)	0.0361 (7)
C-21	0.2898 (4)	0.2418 (2)	0.0663 (2)	0.0358 (7)
C-22	0.3814 (5)	0.2917 (2)	−0.0271 (3)	0.0400 (8)

[a]Ueq$=(\frac{1}{3})\Sigma_i\Sigma_j U_{ij}a_i^*a_j^*(\bar{a}_i\cdot\bar{a}_j)$.

gave the best signal dispersion, thus facilitating signal assignments.

Patagonicol proved not to be the source of the antifungal activity, as it was inactive against *Candida albicans*. In a test for toxicity to P388 murine leukemia cells, patagonicol was also inactive.

X-RAY ANALYSIS OF PATAGONICOL.—The final atomic parameters of the non-hydrogen atoms are listed in Table 2. An ORTEP plot of a single molecule of patagonicol is shown in Figure 1. The X-ray structure showed the basic eunicellin skeleton consisting a six-membered and a ten-membered ring cis-fused at C-1 and C-10 and an ether bridge between C-2 and C-9. The presence of an ethoxy group at C-6 is uncommon. The six-membered ring is in a distorted chair conformation with significant flattening near the bridging bond, C-1—C-10, and puckering at C-12 and C-13.

in other eunicellins with C-2/C-9 ether bridging (11–13) with root mean square deviation of 0.49 Å for the 14 ring atoms from the least-squares plane.

The molecules are packed in unending chains along the *a*-axis where neighboring molecules are linked through an intermolecular O-H...O hydrogen bond between the C-3 hydroxyl with the ether oxygen, O-2-H...O-1 $(x-1,y,z)=2.791$ (2) Å.
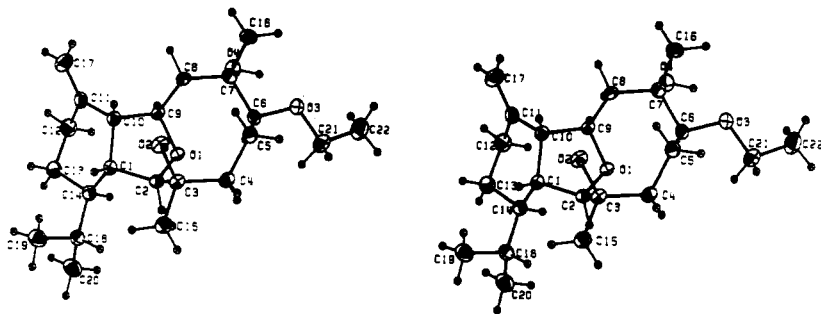
EXPERIMENTAL

FIGURE 1.   A stereoview of an ORTEP plot of a single molecule of patagonicol.

Patagonicol [1] was assigned the same configuration as sclerophytin C [3] whose absolute configuration was determined by X-ray diffraction (11). The geometrical features of the six- and the ten-membered rings of patagonicol are almost identical with those of sclerophytin C. The difference in bond distances and bond angles are within experimental error. The mean difference in the endocyclic torsion angle between the two molecules is 2.8° with a maximum of 5.0° for C-11–C-1–C-10–C-14, despite differences in their substitution patterns. The molecular backbone is relatively flat as observed

ISOLATION.—Specimens of *A. patagonicum* were collected off the Xisha Islands in the South China Sea in 1988. A voucher specimen (No. 88-28) is held at Zhongshan University. The chopped, sun-dried specimens (3.5 kg) were extracted with EtOH at room temperature. The EtOH extract was evaporated in vacuo, and the residue was partitioned between EtOAc and H₂O. The organic phase was concentrated in vacuo to give a syrup (30 g), which was chromatographed on Si gel, eluting with EtOAc/petroleum ether with gradually increasing amounts of EtOAc. The fraction that was eluted with 15% EtOAc in petroleum ether was further subjected to flash cc. The eluates with EtOAc-petroleum ether (3:7) gave crude patagonicol [1] (20 mg), which crystallized from Me₂CO: mp 172.5–174.0°; ir (KBr), ν max 3450, 3410 (OH), 3100, 2930, 1649, 1400, 1370,

1100 (ether), 900, 890 (exocyclic methylene) cm^{-1}; ^{1}H nmr and ^{13}C nmr see Table 1; eims m/z [M]$^+$ 366, [M−H$_2$O]$^+$ 348, [M−H$_2$O−Me]$^+$ 333, [M−H$_2$O−OCH$_2$CH$_3$]$^+$ 303, 237, 223, 149, 147, 129, (100), hr fabms m/z (3-nitrobenzyl alcohol) 366.2744 (calcd for C$_{22}$H$_{38}$O$_4$, 366.2770), [M−H]$^+$ 365.2666 (calcd for C$_{22}$H$_{37}$O$_4$, 365.2692), [M−OH]$^+$ 349.2772 (calcd for C$_{22}$H$_{37}$O$_3$, 349.2743). SINEPT results (J=6 Hz, C$_6$D$_6$, room temperature) (irradiated proton→observed carbon signal): 4.71 (H-17)→148.6 (C-11), 31.9 (C-12); 3.52 (H-2)→78.6 (C-9), 53.8 (C-10), 45.3 (C-1), 44.0 (C-14); 3.06 (H-10)→148.6 (C-11), 109.2 (C-17), 78.6 (C-9), 45.3 (C-1), 44.0 (C-14), 31.9 (C-12); 1.37 (H-16)→88.4 (C-6), 76.1 (C-7).

X-ray diffraction.—Patagonicol [1] was crystallized from Me$_2$CO. A prismatic crystal of size 0.27×0.13×0.13 mm was selected for all crystallographic measurements. Cell dimensions were obtained by least-squares fit to ± 2θ values of 48 reflections measured at 138K using CuKα$_1$ radiation. All X-ray measurements were carried out on an Enraf-Nonius CAD-4 diffractometer equipped with a liquid N$_2$ low-temperature device.

Crystal data[1].—C$_{22}$H$_{38}$O$_4$, MW=366.6, monoclinic, $P2_1$, a=5.8720 (6), b=15.624 (1), c=11.743 (1) Å, β=96.84 (1)°, V=1069.7 Å^3, Z=2, D$_x$=1.138 g·cm^{-3}, F(000)=404, λ(CuKα)=1.54178 Å, μ(CuKα)=5.3 cm^{-1}.

The intensity data of all the unique reflections within 2θ range 0–150° were collected at 138±2K using CuKα radiation and employing θ–2θ scan technique with a variable scan width of (0.90+0.20 tan θ)° and horizontal aperture of (3.0+0.86 tan θ) mm. Three standard reflections were monitored every 2 h of X-ray exposure, and they showed maximum variation of 2.5%. The crystal orientation was checked regularly by three control reflections. A total of 2283 unique reflections were recorded, of which 2125 reflections were considered observed on the basis, I≥2σ(I). The intensities were corrected for Lorentz and polarization factors, but no absorption correction was made. The structure was solved by direct methods and the use of program MULTAN80 (14) and refined by a full-matrix least-squares routine SHELX76 (15) in which the quantity, $\Sigma\omega(F_o-F_c)^2$ is minimized, where $\omega=1/\sigma^2(F_o)$. All the hydrogen atoms were located from a difference Fourier map and hydrogen parameters were refined isotropically. In the final stages of refine-

ment, non-hydrogen atoms were given anisotropic thermal parameters. The refinement converged to a final R=0.029, R$_w$=0.034 for 2125 observed reflections, S=1.3, Δ/σ=0.08, electron density in the final difference map ±0.2 e/Å^3.

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[1]Atomic coordinates, bond distances and angles torsion angles, and thermal parameters for this compound have been deposited at the Cambridge Crystallographic Data Centre and can be obtained from Dr. Olga Kennard, University Chemical Laboratory, 12 Union Road, Cambridge CB2 1EZ, UK.