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THE STRUCTURE OF PACIFIGORGIOL, AN ICHTHYOTOXIC SESQUITERPENOID FROM THE PACIFIC GORGONIAN CORAL PACIFIGORGIA CF. ADAMSII

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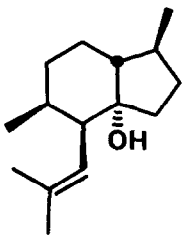
Summary. An ichthyotoxic sesquiterpenoid of unusual structure, pacifigorgiol, has been isolated from the Pacific gorgonian coral Pacifigorgia adamsii. The structure of pacifigorgiol, with relative stereochemistry only, has been defined by a combination of spectral and x-ray crystallographic techniques.

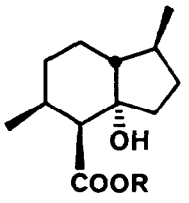
Our interest in the natural products chemistry of the gorgonian soft-corals (the sea fans and whips) found along subtropical Pacific Mexico is generated, in part, by the high levels of biological activity observed in the extracts of these animals.[1] In addition, since these animals lack the endosymbiotic algae (zooxanthellae) very frequently found in gorgonians, the synthesis of secondary metabolites must result from animal metabolism. In this paper we wish to report the isolation and structure elucidation of a moderately-potent ichthyotoxic terpenoid, pacifigorgiol, from the sea fan Pacifigorgia cf. adamsii. Pacifigorgiol possesses an unprecedented irregular terpenoid skeleton and shows toxicity toward the reef-dwelling fish Eupomacentrus leucostictus at the 1 μg/ml level.[2]

P. adamsii was collected subtidally using SCUBA at Bahia Los Frailes, Baja California Sur in January 1979, and immediately preserved in ethanol. The animals were subsequently repeatedly extracted with $CHCl_3$/MeOH (2 to 1) and the combined extracts were condensed to a viscous oil (8.2% dry wt). Silica gel flash and high-performance liquid chromatography resulted in the successful purification of the sole terpenoid component of the extract, pacifigorgiol (1, 2.3% ext.). Pacifigorgiol showed $[\alpha]_D$ +41° (c 1.02, $CHCl_3$) and analyzed for $C_{15}H_{26}O$ by HRMS and ^{13}C NMR. Infrared absorption at 3584 cm^{-1} (film), coupled with an off-resonance singlet at 83.9 ppm in the ^{13}C NMR spectrum of 1 confirmed pacifigorgiol as a tertiary alcohol. Further ^{13}C NMR bands at 121.2 (d) and 134.4 (s) showed the compound to contain only one olefin. This information in conjunction with the molecular formula showed the alcohol to possess a bicyclic skeleton.

The ^1H NMR spectrum of 1, with appropriate spin-decoupling experiments, and under Eu(fod)$_3$-induced shift conditions,[3] gave sufficient information to propose the final structure of this metabolite. Since two olefinic methyl groups were present (δ 1.74 and 1.60, 3 H, s, each), and both were allylically coupled ($J \leq 1$ Hz) to the lone olefinic proton at δ 5.07, pacifigorgiol was recognized to contain an isobutenyl constellation. Beginning with the proton in this group at

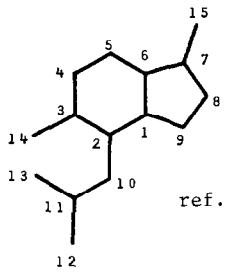


1



2, R=H

3, R=CH_3



ref. 8

4

C-10, each of the ring protons in the sequence C-2 through C-9 were interrelated through spin-decoupling. The methine protons at C-3 and C-7 were also coupled to the remaining methyl groups, thus placing C-14 and C-15 at these positions. Although each proton could be assigned by these techniques, thus allowing both the ring system and its substituents to be defined, the complexity of the numerous couplings made unambiguous analysis of many coupling constants difficult. Hence only partial stereochemical assignments were concluded based upon these experiments.

Ozonolysis of pacifigorgiol, followed by oxidative work-up, yielded the corresponding acid $\underline{2}$[4] in reasonable yield. Treatment with diazomethane in ether gave a smooth conversion to the corresponding methyl ester $\underline{3}$. The ^{1}H and ^{13}C NMR features of $\underline{3}$[5] confirmed that ozonolysis had eliminated a C_3 fragment without affecting the saturated bicyclic portion of the molecule.

The structure of pacifigorgiol was securely established by an x-ray diffraction experiment on the acid $\underline{2}$. Preliminary x-ray photographs displayed orthohombic symmetry and lattice constants of a = 12.472(2), b = 13.516(2) and c = 14.785(2)Å were obtained from a least squares analysis of fifteen diffractometer measured 2θ-values. Systematic extinctions and density considerations were uniquely accommodated by space group $P2_12_12_1$ with two molecules of $C_{12}H_{20}O_3$ forming the asymmetric unit. All unique diffraction maxima with $2\theta \leq 114°$ were recorded using a 1° ω-scan and graphite monochromated $CuK\bar{\alpha}$ radiation (1.54178Å). After correction for Lorentz, polarization and background effects, 1823 (97%) of the 1886 reflections were considered observed ($|F_o| \geq 3\sigma(F_o)$). A phasing model was achieved by a multisolution weighted tangent formula approach and the resulting E-synthesis was interpreted without difficulty.[7] Full matrix least-squares refinements with anisotropic temperature factors for carbon and oxygen and fixed isotropic temperature factors for hydrogen have converged to a final unweighted crystallographic residual of 0.051 for the observed reflections.

Figure 1 is a computer generated perspective drawing of the final x-ray model. The x-ray analysis did not define the absolute stereochemistry and the enantiomer shown represents an arbitrary choice. Both molecules in the asymmetric unit have the same structure and conformation. There is a hydrogen bonding network along each of the screw axes: O(1)-O(1'), 2.75 (z); O(3)-O(2'), 2.67 (x); O(3')-O(1), 2.64 (y). The basic structure is a trans-perhydroindane. The cyclohexane ring is in a chair conformation with the bridgehead hydroxyl and the carboxyl group at C(2) in axial positions. The methyl at C(3) is equatorial and the methyl at C(7) is cis to the bridgehead hydrogen at C(6). Bond distances and angles agree with generally accepted values.[8]

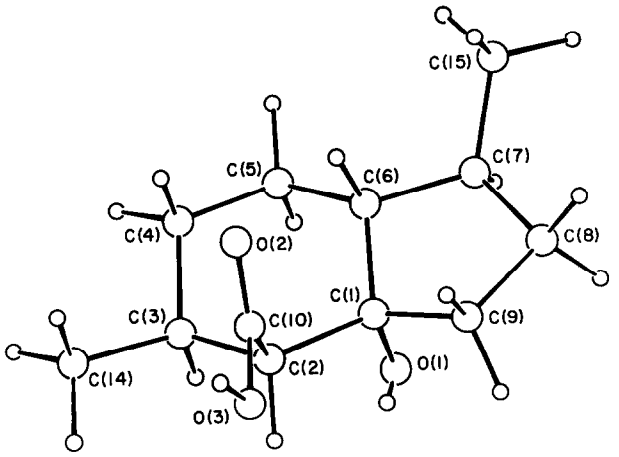


Figure 1, the computer-generated perspective drawing for acid 3. The enantiomer shown is an arbitrary choice.[6,7]

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2. Details of the fish toxicity bioassay have appeared elsewhere, see V.J. Paul, O.J. McConnell and W. Fenical, J. Org. Chem. 1980, 45, 3401.

3. For 1, waxy solid, $[\alpha]_D$ +41 (c 1.02, $CHCl_3$), IR (film): 3584, 2915, 1452, 1375, 1008, 910, 848 cm^{-1}; MS: M^+ m/z = 222 for $C_{15}H_{26}O$; ^1H NMR (220 MHz, $CDCl_3$): δ 5.07 (1 H, d, J = 10.5) C-10; δ 2.54 (1 H, dd, J = 10.5, 4 Hz) C-2; 2.06 (1 H, m) C-8α; 2.06 (1 H, m, J = 7, 4 Hz) C-3; 1.97 (1 H, m) C-9α; 1.97 (1 H, m) C-7; 1.74 (3 H, s) C-12; 1.60 (3 H, s) C-13; 1.60 (1 H, m) C-9β; 1.61 (1 H, m, J = 12, 12, 5) C-5α; 1.43 (1 H, m, J = 12, 12) C-6; 1.33 (1 H, m, J = 12, 2) C-5β; 1.22 (1 H, m, J = 5) C-4β; 1.07 (1 H, m) C-4α; 1.07 (1 H, m) C-8β; 0.97 (3 H, d, J = 6) C-15; 0.77 (3 H, d, J = 7) C-14; ^{13}C NMR (20 MHz, $CDCl_3$): 83.9 (s, C-1); 47.8 (d, C-2); 29.6 (d, C-3); 34.9 (t, C-4); 24.0 (t, C-5); 49.4 (d, C-6); 30.3 (d, C-7); 34.9 (t, C-8); 30.3 (t, C-9); 121.2 (d, C-10); 134.4 (s, C-11); 26.3 (q, C-12); 18.4 (q, C-13); 19.4 (19.0)(q, C-14); 19.0 (19.4) (q, C-15).

4. For 2, mp. 187-189°; IR (KBr): 3497, 3333, 2994, 2924, 1400, 1200, 1156 and 913 cm^{-1}; MS: m/z = 197, 194 and 183; ^1H NMR (220 MHz, $CDCl_3$): δ 2.82 (1 H, d, J = 4.9 Hz); 2.20 (2 H, m); 1.70 (8 H, m); 1.20 (3 H, m); 1.00 (6 h, d, J = 6.4 Hz).

5. For 3, mp. 56.8-57.5°, IR (CCl_4): 2967, 1733, 1453, 1374, 1196, 1145, 1004 and 915 cm^{-1}; MS: m/z = 211, 208, 197, 194, 179, 167; ^1H NMR (220 MHz, $CDCl_3$): δ 3.73 (3 H, s); 2.88 (1 H, d, J = 4 Hz); 0.96 (3 H, d, J = 6.1 Hz); 0.91 (3 H, d, J = 7.2 Hz); ^{13}C NMR (20 MHz, $CDCl_3$): 80.2 (s, C-1); 55.4 (d, C-2); 34.6 (d, C-3); 29.5 (t, C-4); 23.2 (t, C-5); 48.7 (d, C-6); 30.6 (d, C-7); 35.9 (t, C-8); 30.0 (t, C-9); 173.2 (s, C-10); 50.9 (q, OMe); 19.3 (18.9) (q, C-14); 18.9 (19.3) (q, C-15).
6. All crystallographic calculations were performed on a PRIME 400 computer operated by the Materials Science Center and the Department of Chemistry, Cornell University. The principal programs used were REDUCE and UNIQUE, data reduction programs, Leonowicz, M.E., Cornell University, 1978; BLS78A, anisotropic block-diagonal least squares refinement, Hirotsu, K. and Arnold, E., Cornell University, 1980; XRAY76, the X-ray System of Crystallographic Programs, edited by Stewart, J.M., University of Maryland, Technical Report, TR-445, March, 1976; ORTEP, crystallographic illustration program, Johnson, C.K., Oak Ridge, ORNL-3794; BOND, molecular metrics program, Hirotsu, K., Cornell University, 1978; MULTAN-68, "A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data." University of York, England. Principal author P. Main. For literature description of MULTAN see: Germain, G.; Main, P.; Woolfson, M.M.; Acta Crystallogr. Sect B 1970, 26, 274-285 and Woolfson, M.M. Acta Crystallogr., Sect A 1977, 33, 219-225.
7. Fractional coordinates and thermal parameters have been deposited with the Cambridge Crystallographic Data Centre.
8. We suggest the name pacifigorgiane for this new skeleton and the numbering scheme shown in 4.

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