Crystal and Molecular Structure of Sclerophytin F Methyl Ether from the Soft Coral Cladiella krempfi

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J. Nat. Prod., **1993**, 56 (11), 1977-1980• DOI: 10.1021/np50101a017 • Publication Date (Web): 01 July 2004

Journal of Natural Products
Vol. 56, No. 11, pp. 1977-1980, November 1993

CRYSTAL AND MOLECULAR STRUCTURE OF SCLEROPHYTIN F METHYL ETHER FROM THE SOFT CORAL *CLADIELLA KREMPFI*

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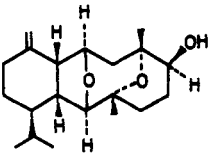
ABSTRACT.—A new cembranoid diterpene was isolated from the soft coral *Cladiella krempfi* from Minicoy Island (India), and its structure was established by X-ray crystallography to be sclerophytin F methyl ether [**2**] with the *R* absolute configuration at all six epimeric centers, assuming a configuration similar to that of sclerophytin C. Compound **2** may be an artifact of the isolation process.

Novel sterols, prostaglandins, and especially cembranoid diterpenes have been reported from alcyonarian soft corals and gorgonians of the phylum Coelenterata. Natural products produced by biosynthetic internal cyclization of cembranoids are illustrated by eunicellin (1), cladiellin (2), and briarein (3). There are, to our knowledge, 21 cladiellanes reported so far (4), including sclerophytin A [**1**] which is cytotoxic against L_{1210} cell line even at 1×10^{-6} mg/ml (5). The Lakshadweep group of islands (India) are characterized by placid lagoons in the eastern sea facing the Indian mainland and the turbulent Arabian sea on the west. A variety of organisms occur selectively on either side of the islands; algae, hard corals, and sea cucumbers prefer the lagoon habitat while sponges, zoanthids, and soft corals prefer the turbulent sea. We report herein the isolation of a sclerophytin derivative **2** from a soft coral species collected at Minicoy Island, India.

From the EtOAc extract of *Cladiella krempfi* (Hickson) (registered as NTM C11545 in the Northern Territory Museum of Arts and Sciences, Darwin, Australia) compound **2** was obtained as colorless prisms after cc. Its ^{13}C nmr showed 21 carbons, of which two were sp^2 [147.9, C-11; 109.1, C-20, being part of an exomethylene (ir at 895 cm^{-1})], and six were oxygenated sp^3 carbons (90.5, C-2 and C-6; 76.1, C-3; 78.1, C-9; 74.9, C-7; and 57.0, C-21). The last of these was methoxyl carbon; the corresponding protons appeared at δ 3.32 s (ether) and the oxymethine proton at δ 4.08 m in the ^1H-nmr spectrum. The ms of compound **2** showed highest *m/z* at 334.246 $[M-H_2O]^+$, analyzing for $C_{21}H_{34}O_3$ with five double bond equivalents.

X-ray analysis of **2** was carried out to determine its structure. Crystal data were as follows: $C_{21}H_{36}O_4$, M=352.51, monoclinic, a=5.911 (1), b=14.427 (1), c=11.947 (1) Å, β=97.41 (2), V=1010.2



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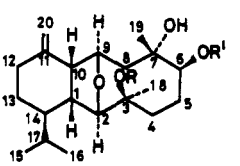

2 R=H, R^1=Me
3 R=Ac, R^1=H
4 R=R^1=H

TABLE 1. Fractional Atomic Coordinates and Equivalent Isotropic Thermal Parameters ($\times 10^4$) of Nonhydrogen Atoms of Sclerophytin F Methyl Ether [2] (with the ESDs in parentheses).

Atom	x/a	y/b	z/c	U(A^2)
O-1	0.9037 (3)	0.2826 (2)	0.7630 (2)	287 (3)
C-2	0.8681 (4)	0.1962 (3)	0.6994 (3)	308 (4)
C-3	0.7723 (5)	0.1256 (3)	0.7773 (3)	358 (3)
C-4	0.7803 (4)	0.1784 (3)	0.8925 (3)	304 (3)
C-5	0.7774 (4)	0.2809 (3)	0.8571 (2)	280 (4)
C-6	0.5405 (4)	0.3279 (3)	0.8307 (3)	302 (4)
C-7	0.5477 (5)	0.4140 (3)	0.7561 (3)	379 (3)
C-8	0.5223 (4)	0.4035 (3)	0.6269 (3)	405 (4)
C-9	0.7405 (4)	0.3873 (3)	0.5716 (3)	367 (4)
C-10	0.7539 (4)	0.2920 (3)	0.5148 (3)	395 (4)
C-11	0.7072 (4)	0.2102 (3)	0.5902 (3)	341 (3)
C-12	0.8916 (5)	0.0346 (3)	0.7791 (3)	434 (4)
C-13	1.1151 (5)	0.0297 (3)	0.8537 (3)	527 (4)
C-14	1.0710 (5)	0.0567 (3)	0.9749 (3)	482 (4)
C-15	0.9920 (4)	0.1588 (3)	0.9786 (3)	349 (4)
C-16	0.4688 (5)	0.3568 (3)	0.9454 (3)	416 (4)
O-17	0.3832 (3)	0.2601 (2)	0.7775 (2)	373 (3)
O-18	0.7589 (4)	0.4532 (3)	0.4839 (2)	537 (3)
C-19	0.8379 (6)	0.5415 (4)	0.5263 (4)	731 (4)
O-20	0.9814 (4)	0.2816 (3)	0.4868 (2)	536 (4)
C-21	0.5833 (5)	0.2832 (4)	0.4067 (3)	569 (3)
C-22	0.8060 (5)	−0.0379 (4)	0.7220 (4)	1043 (4)
C-23	0.9490 (5)	0.1892 (3)	1.0971 (3)	417 (4)
C-24	1.1737 (5)	0.1994 (4)	1.1768 (3)	569 (4)
C-25	0.7945 (5)	0.1233 (4)	1.1529 (3)	621 (3)

(2) Å^3 (by least squares refinement of angles of 25 automatically centered reflections), $\lambda(CuK_\alpha)=1.5418$ Å. Space group $p2_1$; $Z=2$, $D_x=1.16$ g/cm^3; colorless crystals; crystal dimensions $0.5\times0.2\times0.3$ mm; $\mu(CuK_\alpha)=5.87$ cm^{-1}. The atomic coordinates for nonhydrogen atoms are given in Table 1, and a view of the molecule is given in Figure 1. On the basis of the absolute configuration

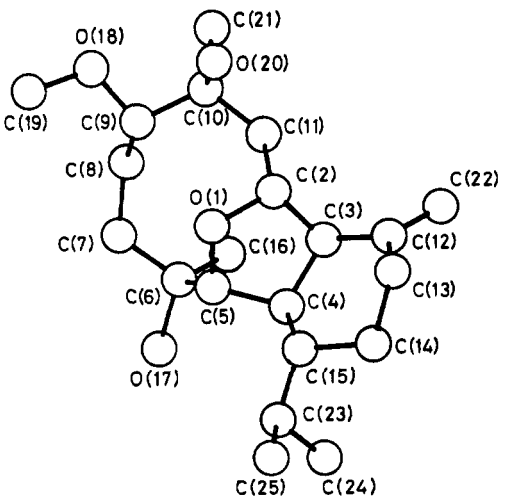

FIGURE 1. X-ray structure of **2**.

TABLE 2. Important Torsion Angles (°) of Sclerophytin F Methyl Ether [2] and Sclerophytin C [3].

Angle	Compound	
	2	3
C-15–C-4–C-5–C-6	−146.1 (2)	−145.3
C-4–C-5–C-6–C-16	82.0 (3)	−159.8
C-5–C-6–C-7–C-8	85.7 (3)	83.3
C-6–C-7–C-8–C-9	−88.6 (4)	−86.1
C-7–C-8–C-9–C-10	114.3 (3)	115.0
C-8–C-9–O-18–O-19	78.4 (3)	−54.3
C-9–C-10–C-11–C-2	−61.5 (4)	−56.0
C-10–C-11–C-2–C-3	167.8 (3)	162.8
C-11–C-2–C-3–C-12	105.5 (3)	104.2

of sclerophytin C [3] (6), the absolute configuration of sclerophytin F methyl ether [2] has been derived by comparing the signs of the torsion angles as given in Table 2. The configuration at C-2 is reversed with respect to that in sclerophytin C [3], and this is due to the absence of substitution at C-11. Consequently, the title compound will have an all-*R* configuration. The six-membered ring (C-3, C-4, C-15, C-14, C-13, C-12) is in the chair conformation and is fused to the ten-membered ring C-1–C-10 (Figure 1).

The methylether compound is new, but there may be some doubt about its occurrence as a natural product. Sclerophytin F [4] was obtained as a gummy residue, preventing an X-ray study (6). Sclerophytins C and E are 18-oxyacetates, claimed by Alam *et al.* (6) to be natural products even though EtOAc was used during their extraction and hplc purification procedures. These authors also used MeOH for extraction and hplc separation procedures in the same way as was done in this report. They did not report the isolation of any methylether. On this basis sclerophytin F methylether may not be an artifact, and may indeed be a true natural product.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Melting points were determined on a Fisher-Johns apparatus and were uncorrected. Nmr spectra were recorded on Jeol GX-400 nmr spectrometer (400 MHz for ^{1}H nmr, 100 MHz for ^{13}C nmr), with $CDCl_3$ as solvent and internal standard ($CHCl_3$, 7.25 ppm; $CDCl_3$, 77.0 ppm). The hrms was obtained on a Finnigan model 1020 mass spectrometer equipped with Incos data system and operating at 70 eV. The ir spectra were recorded on a Perkin-Elmer model 841 spectrometer. The collection of X-ray data was by CAD4 diffractometer, w/2θ mode, graphite monochromated Cu-K_α radiation, 1743 reflections measured, 1548 unique, giving 1533 with $I > 3\sigma(I)$ which were used in the least squares refinement without absorption correction. The structure analysis and refinement was done by direct methods (7), full-matrix least squares refinement with all non-hydrogen atoms anisotropic and all hydrogens isotropically refined. All hydrogen atoms were located by difference Fourier, except H-2 which could not be located. The weighting scheme, $W=1/[\sigma^2(F_0)+0.00544 F_0^2]$, gave satisfactory agreement analysis. Final R and R_w values were 0.057 and 0.071, respectively. The atomic scattering factors were taken from the "International Tables for X-ray Crystallography" (8). The program package SHELX 86 (7) was used to solve the structure and SHELX 76 (9) for the refinement of the structure. The molecular diagram was drawn using PLUTO 78 (10).[1]

ISOLATION OF SCLEROPHYTIN F METHYL ETHER.—The title organism (dry wt 4 kg) was collected when it was exposed at low tide on the rocks at the southern tip of Minicoy Island, India (Arabian Sea side), in December 1989, and a voucher specimen is kept at the School of Chemistry, Andhra University, Visakhapatnam, India. The organism was stored in MeOH. The residue from the MeOH (Soxhlet) extract was partitioned

[1]Atomic coordinates for this structure are deposited with the Cambridge Crystallographic Data Centre and can be obtained on request from Dr. Olga Kennard, University Chemical Laboratory, 12 Union Road, Cambridge CB2 1EZ, UK.

into EtOAc to give a gummy mass (60 gm) that was adsorbed on SiO_2 gel (130 gm) and chromatographed over the same gel (300 gm), set in *n*-C_6H_{14}. By gradient elution with *n*-C_6H_{14}/EtOAc mixtures, compound **2** was obtained in fractions (500 ml each) 55–57 in the 20% EtOAc eluents. Compound **2** (410 mg): colorless prisms; mp 202–203° (MeOH); R_f 0.52 (30% EtOAc in *n*-C_6H_{14}); ir ($CHCl_3$) cm^{-1} 3683, 2964, 1643, 1532, 1500, 1461, 1083, 994, 895 cm^{-1}; ^1H nmr ($CDCl_3$) δ 4.61 (t, J=0.5 Hz, H_A-20), 4.59 (s, H_B-20), 4.11 (ddd, J=12, 6, 4 Hz, H-9), 4.08 (m H-6), 3.60 (s, H-2), 3.32 (s, 21-OMe), 2.95 (t, J=7 Hz, H-10), 2.36–2.44 (m, H_A-4), 2.16–2.44 (m, H_2-12), 1.90–2.05 (m, H-1, H_A-8, H_B-4), 1.76–1.82 (m, H_2-5), 1.64–1.72 (m, H_B-8, H_2-13), 1.22–1.30 (m, H-17), 1.14 (s, Me-18), 1.12 (s, Me-19), 0.94–1.4 (m, H-14), 0.92 (d, J=6.5 Hz, Me-16), 0.75 (t, J=6.5 Hz, Me-15); ^{13}C nmr ($CDCl_3$) δ 15.9 (q, C-15), 22.0 (q, C-16), 23.9 (q, C-18), 24.9 (t, C-13), 25.9 (q, C-19), 29.0 (d, C-17), 30.0 (t, C-5), 31.6 (t, C-12), 41.0 (t, C-4), 43.7 (d, C-14), 44.6 (d, C-1), 45.1 (t, C-8), 53.0 (d, C-10), 57.0 (q, C-21), 74.9 (s, C-7), 76.1 (s, C-3), 78.1 (d, C-9), 90.5 (d, C-2, C-6), 109.1 (t, C-20), 147.9 (s, C-11); ms *m/z* $[M-H_2O]^+$334 (10.6%), 335 (3.53), $[M-18]^+$302 (8.8) $[M-18-isopropyl]^+$291 (15.9), $[M-18-isopropyl-Me]^+$276 (15.9), 237 (17.69), 219 (18.58), 209 (70), 150 (37), 149 (81), 115 (100), 86 (81), 59 (70.8), 55 (69).

ACKNOWLEDGMENTS

The authors acknowledge financial assistance by the Department of Science and Technology, Government of India, New Delhi (SP/SI/G15/86), in the form of research project (to NSS), and the CSIR, New Delhi for a fellowship (to RK). They also thank Dr. P. Alderslade, Curator of Coelenterates of the Northern Territory Museum of Arts and Sciences, Darwin, Australia for identification of the organism.

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Received 11 February 1993