A Rare Prostaglandin from the Soft Coral *Sarcophyton crassocaule* of the Indian Ocean

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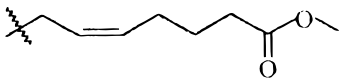
The rare prostaglandin methyl (5*Z*)-9,15-dioxoprosta-5,8(12)-dien-1-oate (**1**), hitherto unreported as a natural product, has been isolated from the Indian Ocean soft coral *Sarcophyton crassocaule*. Its structure was elucidated using detailed spectral (^{1}H and ^{13}C NMR, DEPT, H−H COSY, C−H COSY, HRMS, and HMBC) analysis.

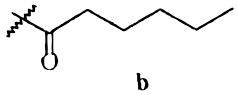
Isolation of PGA_2 from the gorgonian *Pseudoplexaura homomalla*,[1] initiated a fascinating era in the field of marine natural products research. Since then, a great many prostanoids have been isolated from marine animals.[2] It is the role of these compounds in the marine environment, their biological activities, and their structural similarity to the mammalian substances that provide the primary interest in marine-derived prostanoids. Some of them have not been isolated from mammalians and are exclusively marine. These include punaglandins,[3] which contain a 10-chloro substituent, and clavulones.[4] However, to the best of our knowledge, there has been no report wherein the 15-hydroxyl group has been oxidized except as in urinary metabolites.

In our continuing program on the secondary metabolites of soft corals of the Indian Ocean,[5] we undertook the chemical examination of *Sarcophyton crassocaule* (family Alcyoniidae). An Australian specimen of this soft coral was reported to contain cembrenoid diterpenes,[6] which have not been found in the Indian sample. Chromatography of the ethyl acetate extract of the soft coral resulted in the isolation of two novel epoxy sterols,[5a] 17β,20β-epoxy-23,24-dimethylcholest-5-ene-3β,22-diol and its diacetate; four new hippurin derivatives;[5e] and two prostglandins, PGB_2 acid and its methyl ester, in addition to other known compounds. We report herein the isolation and characterization of a rare prostanoid (**1**) with high occular hypotensive activity[7] from the same extract.

The rare prostanoid **1** was obtained as a pale yellow oil, and its molecular formula was fixed as $C_{21}H_{32}O_4$ by HREIMS, indicating six double-bond equivalents. ^{1}H and ^{13}C NMR data accounted for five double-bond equivalents (two keto carbonyls, an ester carbonyl, and two double bonds), and therefore the compound had to be monocyclic. An APT spectrum indicated that there were two methyls, five quaternary carbons, and 14 methylenes in the molecule. A triplet in the NMR spectrum at δ 0.82 indicated the presence of a terminal methyl. Similarly, the methoxyl signal at δ 3.62 showed a coupling to a carbonyl carbon (174.09) in the HMBC spectrum and, therefore, had to be at the end of another chain. The presence of a methyl ester was also supported by the mass spectrum, which indicated a successive loss of methoxyl and ketene from the molecular ion. A detailed examination of the H−H COSY, C−H COSY, and HMBC spectra revealed the chain fragments **a** and **b**.

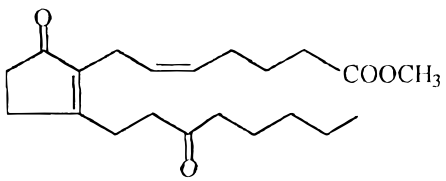


a



b

The C-7 methylene group in partial structure **a** (doublet at δ = 2.88, J = 3 Hz) had to be attached to a quaternary carbon atom because it showed couplings only with C-5/C-6 in the COSY spectrum. Furthermore, the UV data (λ_{max} = 237 nm) and the ^{13}C NMR data indicated the presence of a ketone in conjugation with a tetrasubstituted double bond. According to long-range couplings (see Table 1), these fragments and the remaining two CH_2-CH_2 groups could be assembled only in a single way, revealing the structure of compound **1** as methyl (5*Z*)-9,15-dioxoprosta-5,8(12)-dien-1-oate, assuming the stereochemistry of the 5,6-double bond as *Z*, as in PGB_2 acid and its methyl ester,[5a] in view of the close ^{13}C and ^{1}H chemical sifts of C-5 and C-6 and the respective protons in these compounds.



1

Compound **1** has been obtained previously by microbial transformation[8] of PGA2. To the best of our knowledge, this is the first report of a prostaglandin with a C-15 keto function from natural sources.

Experimental Section

General Experimental Procedures. UV and IR spectra were measured on a Perkin-Elmer lambda 15 UV/vis spectrophotometer and a Perkin-Elmer 1600 Series FTIR spectrometer, respectively. EIMS and HREIMS were recorded on a

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Table 1. ^{1}H, ^{13}C, and HMBC Spectral Data of Compound **1** in $CDCl_3$

C	δ ^{13}C[a]	δ ^{1}H[b]	HMBC
1	174.09		
2	33.47	2.38 (t, J = 4.5 Hz)	C-1
3	24.72	1.72 (p, J = 4.5 Hz)	C-1, C-2, C-4, C-5
4	26.62	2.18 (q, J = 4.5 Hz)	C-5, C-6
5	126.62	5.33 m	C-7
6	129.82	5.35 m	C-4
7	21.34	2.88 (d, J = 3 Hz)	C-5, C-6, C-8, C-9, C-12
8	139.69		
9	209.13		
10	24.99	2.70 m	C-8
11	39.74	2.62 m	C-9, C-12
12	172.32		
13	42.81	2.36 m	C-8
14	34.13	2.42 m	C-12
15	208.92		
16	29.12	2.40 (t, J = 4.5 Hz)	C-15
17	23.53	1.52 (p, J = 4 Hz)	C-15
18	22.44	1.22 m	
19	31.38	1.20 m	
20	13.91	0.82 (t, J = 4 Hz)	C-18, C-19
21	51.49	3.62	C-1

[a] 75.5 MHz. [b] 300.1 MHz.

Finnigan MAT 95 (70 eV) instrument. NMR spectra were measured on Varian Unity 300 and Bruker AMX 300 instruments with TMS as internal standard. 2D spectra were run on a Bruker AMX 300 instrument using a 5-mm inverse probe.

Animal Material. The soft coral specimen (5.0 kg dry wt) was collected at Rutland Island (12° 09′ N, 93° 48′ E) of the Andaman and Nicobar archipelago of the Indian Ocean in March 1994, from the intertidal regions and was hand picked. It was cut into small pieces and stored in methanol at room temperature till extraction. It was identified as *Sarcophyton crassocaule* by Dr. V. Jaya Sree, Scientist, NIO, Goa, and Dr. P. A. Thomas, Scientist, Vizinjam Research Centre, CMFRI, Trivendrum. The voucher specimens were preserved at the above museums, and the School of Chemistry, Andhra University, Visakhapatnam, as AU1−120.

Extraction and Isolation. Methanol used for storing the specimen was decanted, and fresh MeOH was added and the specimen percolated for 3 days. The extract (10 L in total) was filtered and concentrated. This procedure was repeated eight times. The combined methanolic extracts were concentrated under reduced pressure, and the residue was extracted into ethyl acetate, which was concentrated under reduced pressure to leave a gummy residue (90 g). A part of the above residue (35 g) was chromatograhped on a Si gel column (100−200 mesh, Acme) with an increasing gradient, starting from hexane and progressing through EtOAc to MeOH. Full experimental details were reported.[5a] One of the fractions from the Si gel column on preparative TLC over Si gel yielded methyl (5*Z*)-9,15-dioxoprosta-5,8(12)-dien-1-oate (**1**, 15 mg) as a pale yellow oil: R_f = 0.73 (hexane/EtOAc 4:6); UV ($CHCl_3$) λ_{max} 237 nm; IR (KBr) ν_{max} 3050, 2950, 2820, 1735, 1698, 1438 cm^{-1}; ^{1}H NMR and ^{13}C NMR ($CDCl_3$), see Table 1; EIMS m/z 348 $[M]^+$ (22), 317 [M − OMe], 275 [M − CH_2COOMe] (8), 217 (100); HREIMS m/z 348.2285 (calcd for $C_{21}H_{32}O_4$, 348.2300).

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References and Notes

(1) Weinheimer, A. J.; Spraggins, R. L. *Tetrahedron Lett.* **1969**, 5185−5188.
(2) (a) Gerwick, W. H. *Chem. Rev.* **1993**, *93*, 1807−1823. (b) Faulkner, D. J. *Nat. Prod. Rep.* **2000**, *17*, 7−55, and the earlier references therein.
(3) Baker, B. J.; Scheuer, P. J. *J. Nat. Prod.* **1994**, *57*, 1346−1353.
(4) Iwashima, M.; Okamoto, K.; Konno, F.; Iguchi, K. *J. Nat. Prod.* **1999**, *62*, 352−354.
(5) (a) Anjaneyulu, A. S. R.; Krishna Murthy, M. V. R.; Gowri, P. M. *J. Nat. Prod.* **2000**, *63*, 112−118. (b) Anjaneyulu, A. S. R.; Gowri, P. M.; Krishna Murthy, M. V. R. *J. Nat. Prod.* **1999**, *62*, 1600−1604. (c) Anjaneyulu, A. S. R.; Venugopal, M. J. R. V.; Sarada, P.; Rao, G. V.; Lobkovsky, E.; Clardy, J. *Tetrathedron Lett.* **1998**, *39*, 135−138. (d) Anjaneyulu, A. S. R.; Krishna Murthy, M. V. R.; Rao, G. V. *Tetrahedron* **1997**, *53*, 9301−9312. (e) Anjaneyulu, A. S. R.; Krishna Murthy, M. V. R.; Rao, N. S. K. *J. Chem. Res.* (*S*) **1997**, 450−451, and *J. Chem. Res.* (*M*) **1997**, 2743.
(6) Bowden, B. F.; Coll, J. C.; Mitchell, S. J. *Aust. J. Chem.* **1980**, *33*, 879.
(7) (a) Ryuzo, U.; Ruizi, U.; Tomio, O. Eur. Pat. Appl. EP 308,135; *Chem. Abstr.* **1990**, *112*, 48, 817. (b) Charles, H. F.; James, J.; Seth, M. S.; U.S. Patent 3,788,947, 1972; *Chem. Abstr.* **1974**, *81*, 24, 194.
(8) James, J.; Charles, H. F.; Seth, M. S. *Dev. Ind. Microbiol.* **1974**, *15*, 345−352.

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