Two New Cembrane-type Diterpenoids from Okinawan Soft Coral of the Genus, *Sarcophyton*

Hiroaki Miyaoka, Shouta Taira, Hidemichi Mitome, Kazuo Iguchi,# Keita Matsumoto,† Chihiro Yokoo,† and Yasuji Yamada*
School of Pharmacy, Tokyo University of Pharmacy and Life Science, Horinouchi, Hachioji, Tokyo 192-03
†*Research Center, Taisho Pharmaceutical Co., Ltd., 1-403 Yoshino-cho, Omiya, Saitama 330*

(Received December 14, 1995)

Two new cembrane-type diterpenoids, sarcodiol (**1**) and 3,4-epoxysarcophytonin (**4**), were isolated from Okinawan soft coral of the genus, *Sarcophyton*. Their structures were determined from spectroscopic measurements, X-ray analysis and chemical reaction.

Various natural products have been isolated from marine invertebrates. Many of these, isolated from soft corals, are considerable interest from the unique structural features and biological activity.[1] In the couse of our studies on the chemical constituents of Okinawan marine invertebrates,[2] we isolated two new cembrane-type diterpenoids sarcodiol (**1**) and 3,4-epoxysarcophytonin (**4**) from soft coral of the genus, *Sarcophyton*, along with (-)-sarcophytonin-A (**5**).[3] Their structures were elucidated on the basis of spectroscopic data, X-ray analysis and chemical transformation. Sarcodiol (**1**) is the first example of cembrane-type diterpenoid possessing a tetrahydropyran system between C-3 and C-7 positions.

Specimens of soft coral (wet wt 1.9 kg), from the coral reef of Ishigaki Island, Okinawa, Japan, in May 1992, were immersed successively in MeOH and EtOAc. The MeOH and EtOAc extracts were combined and partitioned between EtOAc and H_2O. The EtOAc-soluble portion (61.1 g) was repeatedly chromatographed on a silica gel column to give sarcodiol (**1**) (0.16% yield based on the EtOAc-soluble portion), 3,4-epoxysarcophytonin (**4**) (0.29% yield), and (-)-sarcophytonin-A (**5**) (5.8% yield).

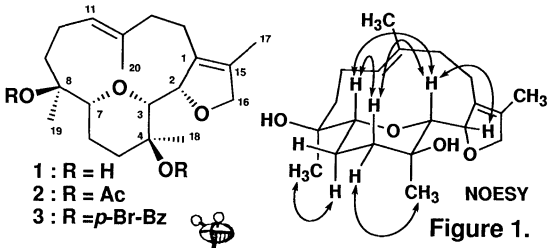


Figure 1.

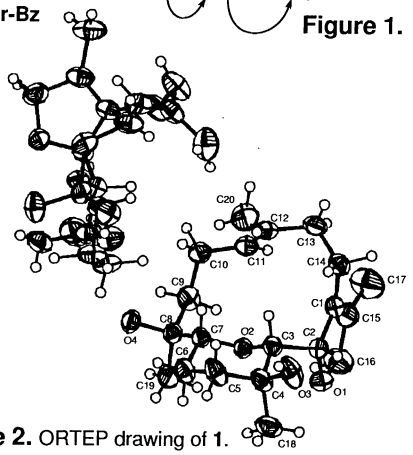


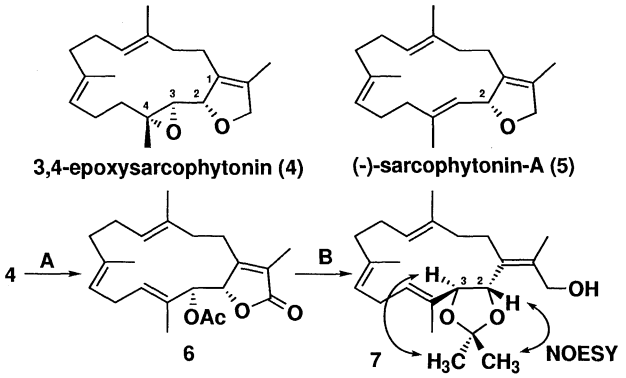
Figure 2. ORTEP drawing of **1**.

Sarcodiol (**1**)[4] was shown to have the molecular formula $C_{20}H_{32}O_4$ based on the high resolution mass measurement. The IR spectrum of **1** showed absorption at 3412 cm^{-1} due to hydroxyl group. All twenty carbons appeared in the ^{13}C NMR spectrum and DEPT spectrum indicated the presence of four methyls, seven methylenes, three sp^3 methines, one sp^2 methine, two sp^3 quaternary carbons and three sp^2 quaternary carbons. ^1H and ^{13}C NMR correlations were indicated by the two-dimensional HMQC spectrum. ^1H and ^{13}C NMR data indicated a tetrasubstituted olefin [δ_C 129.9 (C), 130.0 (C)], a trisubstituted olefin [δ_H 4.99 (1H, br d, 11.0 Hz), δ_C 128.2 (C), 129.6 (CH)], two olefinic methyl groups [δ_H 1.69 (3H, br s), 1.71 (3H, br s), δ_C 17.4 (CH_3), 10.9 (CH_3)], two tertiary hydroxyl groups [δ_C 70.0 (C), 73.7 (C)], three oxygenated methine groups [δ_H 2.79 (1H, s), 3.06 (1H, m), 4.86 (1H, d, 5.3 Hz), δ_C 83.2 (CH), 78.8 (CH), 85.7 (CH)] and one oxygenated methylene group [δ_H 4.33 (1H, d, 11.0 Hz), 4.51 (1H, dd, 5.1, 11.0 Hz), δ_C 79.8 (CH_2)]. The presence of two tertiary hydroxyl groups was confirmed by acetylation. Treatment of **1** with acetic anhydride in pyridine at 80 °C gave diacetate **2** [δ_H 1.98 (3H, s), 1.99 (3H, s), δ_C 81.3 (C), 84.9 (C)]. The partial structures of -O-CH-CH-O- (from C-2 to C-3), $-CH_2-CH_2-CH-O-$ (from C-5 to C-7) and $-CH_2-CH_2-CH=C-CH_3$ (from C-9 to C-12, 20) were surmised based on ^1H coupling constants and decoupling experiments. The small coupling constant (about 0 Hz) was observed between H-2 and H-3 suggesting the dihedral angle of approximately 90° between these protons. Connection of the partial structures of **1** was made based on two-dimensional HMBC spectrum to give a tricyclic plane structure involving the dihydrofuran and the tetrahydropyran system for sarcodiol (**1**).

Relative configurations of five chiral centers (C-2, -3, -4, -7 and -8) were indicated by NOESY measurement (Figure 1) and confirmed by X-ray single-crystal analysis (Figure 2).[5] The absolute configuration of **1** was determined by CD measurement[6] of di-*p*-bromobenzoate **3** obtained by reaction of **1** with *p*-bromobenzoyl trifluoromethanesulfonate[7] and pyridine. The CD spectrum of **3** showed a negative Cotton effect at 253 nm ($\Delta\varepsilon$ -66.4) and positive Cotton effect at 237 nm ($\Delta\varepsilon$ +76.3), indicating negative chirality between the two chromophores (two *p*-bromobenzoyl groups). The CD data disclosed 4*S* and 8*S* configurations at C-4, and -8 in **3**, thus indicating absolute configurations of five chiral centers in **1** to be 2*S*, 3*R*, 4*S*, 7*R* and 8*S*.

3,4-Epoxysarcophytonin (**4**)[8] was found to have the molecular formula $C_{20}H_{30}O_2$ from high resolution mass measurement. A dihydrofuran group was shown to present by ^1H NMR [δ_H 4.43 (1H, d, 11.8 Hz), 4.53 (1H, dd, 5.1, 11.8 Hz), 4.80 (1H, m)] and ^{13}C NMR [δ_C 78.7 (CH_2), 85.0 (CH), 129.2 (C), 131.4 (C)]. ^1H and ^{13}C NMR spectra showed signals due to two trisubstituted olefins [δ_H 5.04 (1H, m), δ_C

125.0 (CH), 134.7 (C), δ_H 5.04 (1H, m), δ_C 124.6 (CH), 134.6 (C)] and an epoxide group [δ_H 2.70 (1H, d, 5.4 Hz), δ_C 64.2 (CH), 61.1 (C)]. The ^1H and ^{13}C NMR spectra of **4** were closely related to those of (-)-sarcophytonin-A (**5**)[3] the presence of signals of the epoxide group instead of those of the 3,4-trisubstituted olefin in **5**, suggesting the structure of 3,4-epoxysarcophytonin to be **4**. The plane structure of **4** was confirmed by two-dimensional ^1H-^1H COSY, HMQC and HMBC spectral data.



Scheme 1. *Reagents*: A. i) LDA, THF, 0 °C, 76%; ii) Ac_2O, pyridine, DMAP, 85%; iii) CrO_3, 3,5-dimethylpyrazole, CH_2Cl_2, -20 °C to 0 °C, 57%; **B**. i) $LiAlH_4$, Et_2O-THF, 0 °C, 43%; ii) $CuSO_4$, cat. PPTS, acetone, r.t., 83%.

The relative configurations of three chiral centers, C-2, -3, and -4, were determined from NOESY measurement and chemical conversion. The configuration of epoxide (C-3 and -4) was assigned based on NOE correlations between H-2 (δ_H 4.80) and Me-18 (δ_H 1.43) and between H-3 (δ_H 2.70) and H-5 (δ_H 1.33). The configuration of C-2 was determined by NOESY measurement of **7** derived from **4** (Scheme 1). 3,4-Epoxysarcophytonin (**4**) was converted to lactone **6** in three steps: 1) cleavage of epoxide with LDA, 2) acetylation of the hydroxy group and 3) oxidation of the dihydrofuran group with CrO_3 in the presence of 3,5-dimethylpyrazole.[9] Reduction of lactone in **6**, followed by protection of 1,2-diol gave acetonide **7**. The configuration of the acetonide (C-2 and C-3) in **7** was assigned by NOE correlations between H-3 (δ_H 4.30) and an acetonide methyl (δ_H 1.48) and between H-2 (δ_H 4.12) and another acetonide methyl (δ_H 1.51). The absolute configuration of **4** was determined by chemical conversion. Reduction of **4** with a zinc-copper couple in EtOH for 3 days gave (-)-sarcophytonin-A, $[\alpha]_D$ -84.0° (*c* 0,10, $CHCl_3$). Physical data for (-)-sarcophytonin-A obtained above were in agreement with those of the corresponding natural (-)-sarcophytonin-A (**5**), $[\alpha]_D$ -92° (*c* 2.3, $CHCl_3$),[3a] whose absolute configuration was determined previously.[3b] The absolute configurations of three chiral centers in **4** were thus determined as 2*S*, 3*S* and 4*R*.

References and Notes

Present address: *School of Life Science, Tokyo University of Pharmacy and Life Science.*

1 D. J. Faulkner, *Nat. Prod. Rep.*, **12**, 223 (1995), and previous papers in this series.

2 Recent examples: K. Iguchi, H. Shimura, S. Taira, C. Yokoo, K. Matsumoto, and Y. Yamada, *J. Org. Chem.*, **59**, 7499 (1994); K. Iguchi, K. Kajiyama, and Y. Yamada, *Tetrahedron Lett.*, **36**, 8807 (1995), and references cited therein.

3 a) M. Kobayashi, T. Nakagawa, and H. Mitsuhashi, *Chem. Pharm. Bull.*, **27**, 2382 (1979). b) B. F. Bowden, J. C. Coll, A. Heaton, and G. König, *J. Nat. Prod.*, **50**, 650 (1987).

4 **1**: colorless rods; m.p. 133-135 °C; $[\alpha]_D$ +48.4° (*c* 0.55, $CHCl_3$); IR (KBr) 3412, 2942, 1681 cm^{-1}; HREIMS: Found: 336.2293, Calcd for $C_{20}H_{32}O_4$ (M^+) 336.2301; ^1H NMR (500 MHz, $CDCl_3$) δ 1.12 (3H, s, Me-19), 1.35 (3H, s, Me-18), 1.50 (1H, m, H-5β), 1.51 (1H, m, H-6α), 1.62 (2H, m, H-9), 1.69 (3H, br s, Me-20), 1.71 (3H, br s, Me-17), 1.72 (1H, m, H-6β), 1.85 (1H, m, H-5α), 1.88 (1H, m, H-10), 2.06 (1H, m, H-14), 2.10 (1H, m, H-14), 2.25 (1H, m, H-10), 2.36 (1H, m, H-13), 2.55 (1H, m, H-10), 2.79 (1H, s, H-3), 3.06 (1H, m, H-7), 4.33 (1H, d, J=11.0 Hz, H-16), 4.51 (1H, dd, J=5.3, 11.0 Hz, H-16), 4.86 (1H, d, J=5.3 Hz, H-2), 4.99 (1H, br d, J=11.0 Hz, H-11); ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.9 (q, C-17), 17.4 (q, C-20), 21.0 (t, C-10), 22.7 (q, C-18), 22.8 (t, C-14), 23.5 (t, C-6), 23.7 (q, C-19), 35.2 (t, C-13), 40.4 (d, C-9), 41.2 (t, C-5), 70.0 (s, C-4), 73.7 (s, C-8), 78.8 (d, C-7), 79.8 (t, C-16), 83.2 (d, C-3), 85.7 (d, C-2), 128.2 (s, C-12), 129.6 (d, C-11), 129.9 (s, C-1), 130.1 (s, C-15); HMBC correlation (H/C) 2/1, 3/1, 3/4, 3/5, 3/7, 3/18, 5/3, 5/4, 5/6, 5/7, 5/18, 6/4, 6/5, 6/7, 7/3, 7/5, 7/6, 7/8, 7/19, 9/7, 9/8, 9/10, 9/11, 9/19, 10/8, 10/9, 10/11, 10/12, 11/13, 11/20, 13/1, 13/12, 13/14, 14/1, 14/12, 14/15, 16/1, 16/2, 16/15, 17/1, 17/15, 17/16, 18/3, 18/4, 18/5, 19/7, 19/8, 20/11, 20/12, 20/13.

5 The crystals consisted of two different conformers. Crystal data for **1**: orthorhombic, space group $P2_12_12_1$, a=14.402 (4) Å, b=19.969 (7) Å, c=13.497 (6) Å, Z = 8, Dc = 1.18 g/cm^3, V = 3882 (2) $Å^3$, crystal size = 0.45 x 0.50 x 0.40 mm^3, R = 0.055, R_W = 0.072.

6 N. Harada, S. L. Chen, and K. Nakanishi, *J. Am. Chem. Soc.*, **97**, 5345 (1975).

7 K. Jaworski and L. L. Smith, *J. Org. Chem.*, **53**, 545 (1988).

8 **4**: colorless oil; $[\alpha]_D$ -52.8° (*c* 0.38, $CHCl_3$); IR (KBr) 3412, 2942, 1681 cm^{-1}; HREIMS: Found: 302.2238, Calcd for $C_{20}H_{30}O_2$ (M^+) 302.2264; ^1H NMR (500 MHz, $CDCl_3$) δ 1.33 (1H, m, H-5), 1.43 (3H, s, Me-18), 1.52 (3H, br s, Me-19), 1.63 (3H, br s, Me-17), 1.65 (3H, br s, Me-20), 1.90 (1H, m, H-14), 1.92 (1H, dd, J=6.8, 13.6 Hz, H-13), 2.03 (1H, dd, J=3.1, 7.7 Hz, H-5), 2.07 (2H, m, H-10), 2.12 (1H, m, H-13), 2.21 (2H, m, H-6), 2.51 (1H, dd, J=6.5, 13.9 Hz, H-14), 2.70 (1H, d, J=5.4 Hz, H-3), 4.43 (1H, d, J=11.8 Hz, H-16), 4.53 (1H, dd, J=5.1, 11.8 Hz, H-16), 4.80 (1H, m, H-2), 5.04 (1H, m, H-7), 5.04 (1H, m, H-11); ^{13}C NMR (125 MHz, $CDCl_3$) δ 9.7 (q, C-17), 15.5 (q, C-19), 16.6 (q, C-20), 17.9 (q, C-18), 24.06 (t, C-14), 24.08 (t, C-10), 24.14 (t, C-6), 37.6 (t, C-13), 38.7 (t, C-5), 39.0 (t, C-9), 61.1 (s, C-4), 64.2 (d, C-3), 78.7 (t, C-16), 85.0 (d, C-2), 124.6 (d, C-7), 125.0 (d, C-11), 129.2 (s, C-15), 131.4 (s, C-1), 134.7 (s, C-7), 134.6 (s, C-12).

9 W. G. Salmond, M. A. Barta, and J. L. Havens, *J. Org. Chem.*, **43**, 2057 (1978).