

Article

Sarcophylides B–E, New Cembranoids from the Soft Coral *Sarcophyton elegans*

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Abstract: Four new cembrane-type diterpenoids, sarcophylides B–E (**1–4**), along with 11 known analogues were isolated from the soft coral *Sarcophyton elegans*. The structures of new compounds **1–4** were established on the basis of spectroscopic analysis and chemical conversion. The new cembranoids sarcophylides B (**1**) and lobocrasol were found to exhibit potent inhibition against A2780 human ovarian tumor cells.

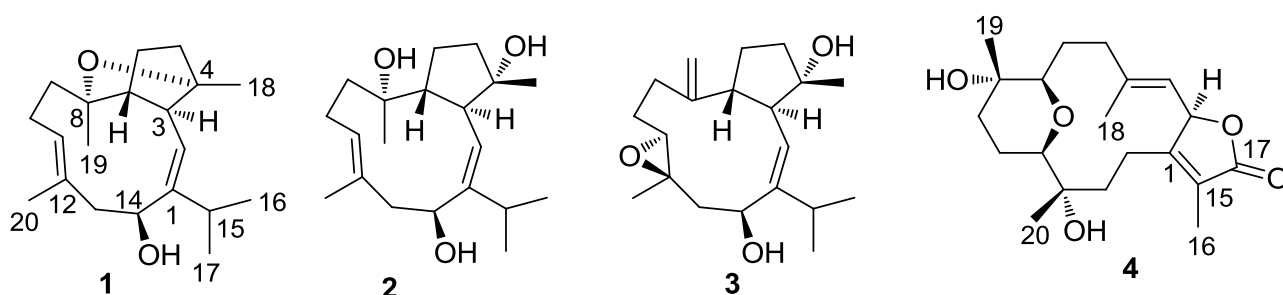
Keywords: soft coral; *Sarcophyton elegans*; sarcophylide; cembranoid; cytotoxicity

1. Introduction

Since the first cembranoid (+)-cembrene was reported five decades ago, numerous cembranoids have been isolated from marine organisms, plants, and insects [1–3]. Their basic structural patterns typically featured a common 14-membered carbocyclic nucleus and unconventional cembranoids

containing a 12-membered carbon skeleton or 13-membered variants. Some of the typical terpenoids are known as chemical defense tools to protect soft corals against natural predators, as feeding deterrents or act by virtue of their toxicity [4–6]. From a pharmaceutical point of view, cembranoids have been reported to exhibit various biological activities, such as having antitumor, ichthyotoxic, antiinflammatory, neuroprotective, antibacterial, antiangiogenic, antimetastatic, and antiosteoporotic properties [7–13]. Soft corals, belonging to the genus *Sarcophyton* (Alcyoniidae), are well recognized as a rich source of macrocyclic cembrane-type diterpenoids and biscembranoids. The structural patterns of cembranoids from the genus *Sarcophyton* vary notably due to geographic location and species differentiation [14]. It is a challenging work to uncover new natural products from known species of marine organisms distributed in new locations. In our continuing search for the chemical diversity from the soft corals inhabited in various locations of South China Sea, the specimen *Sarcophyton elegans* was collected. Primary HPLC-ESIMS and ^1H NMR examinations on the EtOAc extracts revealed the spectroscopic signals representing a diverse array of terpenoids. Further chromatographic separation and purification resulted in the isolation of four new cembranoids (Figure 1) in addition to 11 known analogues.

Figure 1. Structures of sarcophylolides B–E (1–4).



2. Results and Discussion

2.1. Structural Elucidation of New Compounds

Sarcophylolide B (**1**) was isolated as a colorless oil with the molecular formula of $\text{C}_{20}\text{H}_{32}\text{O}_2$ based on the high resolution electrospray ionization mass spectroscopy (HRESIMS) and nuclear magnetic resonance (NMR) data, implying five degrees of unsaturation. The IR absorptions at 3406 and 1604 cm^{-1} suggested the presence of hydroxy and olefinic groups. The ^1H NMR displayed the signals for five methyls, two olefinic protons at δ_{H} 5.26 (1H, d, $J = 11.5\text{ Hz}$, H-2) and 5.49 (1H, dd, $J = 3.0, 5.0\text{ Hz}$, H-11), a hydroxymethine δ_{H} 5.04 (1H, brd, $J = 9.0\text{ Hz}$, H-14), and a number of alkyl protons for methylene and methine groups. The ^{13}C NMR and distortionless enhancement by polarization transfer (DEPT) spectra exhibited a total of 20 carbon resonances, involving four olefinic carbons and three oxygen-bearing sp^3 carbons. Diagnostic NMR data (Tables 1 and 2) through COSY and heteronuclear multiple quantum coherence (HMQC) analyses indicated compound **1** to be a cembrane-based diterpenoid. The COSY relationships connected the protons to form three subunits from C-2 to C-7, C9 to C-11, and C-13 to C-14, in addition to an isopropyl group. The connectivity of the subunits was accomplished by the HMBC correlations. The observed HMBC interactions from the methyl protons of isopropyl group (δ_{H} 1.12

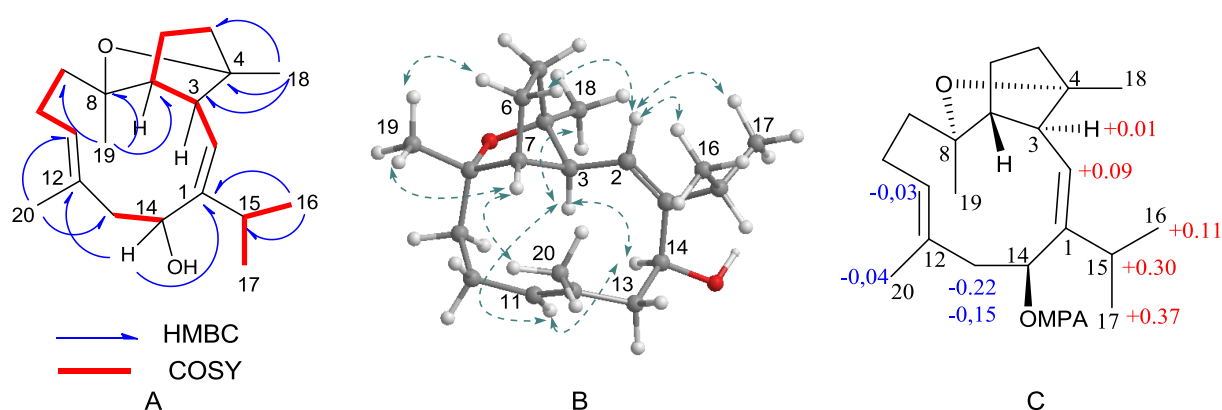
and 1.13, d) to an olefinic carbon at δ_C 150.6 (qC, C-1) and, in turn, the olefinic proton H-2 correlating to the methine carbon C-15 (δ_C 26.9, CH), indicated a double bond to be resided at C-1/C-2, while an isopropyl group is positioned at C-1. The HMBC relationships from H₃-18 (δ_H 1.19, s) to C-3 (δ_C 53.2, CH), C-4 (δ_C 87.6, qC), and C-5 (δ_C 32.8, CH₂); from H-3 (δ_H 3.11, brd, $J = 11.5$ Hz) to C-1, C-4, C-7, and C-8 (δ_C 82.8, qC); and from H-7 (δ_H 1.90) to C-4 and C-2 (δ_C 120.9, CH) revealed a capnosane-based cembranoid bearing a 3,7-cyclopentane ring [15], in which an oxygen atom and a methyl group were co-positioned at C-4. Additional HMBC relationships were conducted to assign the linkage of a methyl group H₃-19 (δ_H 1.23, s) at oxygenated carbon C-8, while the second olefinic group was resided at C-11/C-12 (Figure 2A). A hydroxy group was evident to be located at C-14 (δ_C 72.9, CH) according to the COSY relationship between a D₂O exchangeable proton at δ_H 4.60 (br) and H-14, while H-14 coupled to C-14 in HMQC. The above functional groups are accounted for four degrees of unsaturation, the remaining site is, thus, assumed to be contributed by an ether bridge across C-4 and C-8.

Table 1. ¹H NMR data for sarcophyolides B–E (1–4) in CDCl₃ (δ in ppm, J in Hz).

No.	1	2	3	4
2	5.26 d (11.5)	5.28 d (9.5)	5.09 d (10.4)	5.50 d (10.0)
3	3.11 brd (11.5)	2.64 dd (9.5, 10.5)	2.77 dd (10.4, 10.4)	5.00 d (10.0)
5	1.55 m	1.76 m	1.85 m	2.16 m
	1.74 m	1.78 m	1.80 m	2.20 m
6	1.68 m	1.35 m	1.70 m	1.43 m
	1.74 m	1.74 m	1.82 m	1.96 m
7	1.90 m	1.97 ddd (8.5, 10.0, 10.5)	2.50 m	3.02 brd (10.0)
9	1.90 m	1.62 ddd (3.0, 5.0, 14.0)	2.25 m	1.48 m
	1.92 m	1.82 brdd (10.0, 14.0)	2.20 m	1.46 m
10	2.00 m	2.05 m	2.45 m	1.34 m
	2.02 m	2.41 ddd (8.0, 10.0, 12.0)	1.40 m	1.67 m
11	5.49 dd (3.0, 5.0)	5.36 dd (4.5, 8.0)	2.88 dd (4.2, 9.8)	3.14 d (8.5)
13	2.00 dd (9.0, 11.5)	2.09 dd (11.5, 13.0)	2.13 d (13.3)	1.48 m
	2.62 brd (11.5)	2.50 dd (3.0, 13.0)	1.50 dd (10.7, 13.3)	1.73 m
14	5.04 brd (9.0)	4.86 dd (3.0, 11.5)	3.83 d (10.7)	1.93 m
				2.45 m
15	2.68 qq (7.0, 7.0)	2.56 qq (7.0, 7.0)	2.49 qq (6.8, 6.8)	
16	1.12 d (7.0)	1.09 d (7.0)	1.03 d (6.9)	
17	1.13 d (7.0)	1.15 d (7.0)	1.14 d (6.9)	1.73 s
18	1.19 s	1.11 s	1.17 s	1.78 s
19	1.23 s	1.15 s	4.96 brs	0.98 s
			4.91 brs	
20	1.60 s	1.73 s	1.49 s	0.98 s

Table 2. ^{13}C NMR data for sarcophyolides B–E (**1–4**) in CDCl_3 (δ in ppm, J in Hz).

No.	1	2	3	4
1	150.6 qC	149.8 qC	150.9 qC	165.8 qC
2	120.9 CH	126.2 CH	124.9 CH	80.1 CH
3	53.2 CH	49.7 CH	50.8 CH	120.0 CH
4	87.6 qC	81.5 qC	81.3 qC	144.2 qC
5	32.8 CH_2	39.7 CH_2	40.1 CH_2	36.2 CH_2
6	21.1 CH_2	24.4 CH_2	25.4 CH_2	24.7 CH_2
7	49.6 CH	56.3 CH	54.6 CH	83.9 CH
8	82.8 qC	74.7 qC	147.4 qC	68.8 qC
9	43.5 CH_2	34.2 CH_2	24.1 CH_2	40.8 CH_2
10	24.0 CH_2	23.4 CH_2	27.5 CH_2	23.4 CH_2
11	133.0 CH	129.9 CH	59.5 CH	80.5 CH
12	128.0 qC	131.0 qC	58.1 qC	71.8 qC
13	43.5 CH_2	43.0 CH_2	45.6 CH_2	37.3 CH_2
14	72.9 CH	70.8 CH	67.8 CH	20.6 CH_2
15	26.9 CH	26.4 CH	26.7 CH	121.7 qC
16	25.3 CH_3	24.7 CH_3	24.4 CH_3	9.0 CH_3
17	25.7 CH_3	26.4 CH_3	26.4 CH_3	174.9 qC
18	19.1 CH_3	23.0 CH_3	24.1 CH_3	16.7 CH_3
19	25.1 CH_3	31.7 CH_3	111.2 CH_2	20.5 CH_3
20	20.0 CH_2	18.8 CH_3	17.1 CH_3	23.9 CH_3

Figure 2. Key COSY, HMBC (A), NOE (B), and $\Delta\delta^{\text{RS}}$ values (C) of **1**.

The relative configuration of **1** was established on the basis of NOE relationships and J values. The NOE interactions between H-2 and H₃-16 and H₃-17 were assignable to 1*Z* geometry, whereas 11*E* was inferred from the NOE interactions between H-11 and H-13a (δ_{H} 2.62), and between H₃-20 and H₂-10. The NOE interactions between H-3 and H-14 and H₃-18 indicated that H-3 is spatially approximated to H-14 and H₃-18. Additional NOE relationships between H-2 and H-6a (δ_{H} 1.68), and between H₃-19 and H-6b (δ_{H} 1.74) and H-7 (Figure 2B), in association with the absence of NOE interaction between H-2 and H-3, allowed to establish the relative configurations of the stereogenic centers in cyclopentane ring and the orientation of ether bridge. The absolute configuration of C-14 in **1** was determined by Mosher's method. Esterification of **1** with (*R*)- and (*S*)-MPA yielded 14-(*R*)-MPA and 14-(*S*)-MPA esters, respectively. Based on MPA rules [16], the chemical shift difference

($\Delta\delta^{\text{RS}} = \delta^{\text{R}} - \delta^{\text{S}}$) reflected the absolute configuration of C-14. Analyses of the $\Delta\delta^{\text{RS}}$ values (Figure 2C) resulted in 14*S* configuration. Based on the established relative configurations of **1** and the NOE interaction of the protons related to H-14, the absolute configurations of the remaining chiral carbons were supposed to be 3*S*, 4*S*, 7*R*, and 8*R*.

The NMR data of sarcophylide C (**2**) closely resembled those of compound **1**, while 2D NMR data analysis established the structure of **2** to be a homolog of **1**. The major difference was found concerning the upfield-shifted C-4 (δ_{C} 81.5) and C-8 (δ_{C} 74.7) and the molecular weight of **2** having 18 amu more than that of **1**, while the degrees of molecular unsaturation in **2** are four instead of five, based on the HRESIMS data (m/z 345.2406 [$\text{M} + \text{Na}$] $^{+}$). These findings disclosed the structure of **2** to be a 4,8-dihydroxylated derivative of **1**. The closely similar NOE interactions of **2** and **1** in association with the chemical conversion from **1** to **2** under acidic solution (Figure 3) indicated the configurations of **2** to be the same as those of **1**.

The absolute configurations of the stereogenic centers in **1** and **2** were further proved by their single-crystal X-ray diffraction analysis using Flack's method (Figure 4).

Figure 3. Conversion of **1** to **2** under acidic condition.

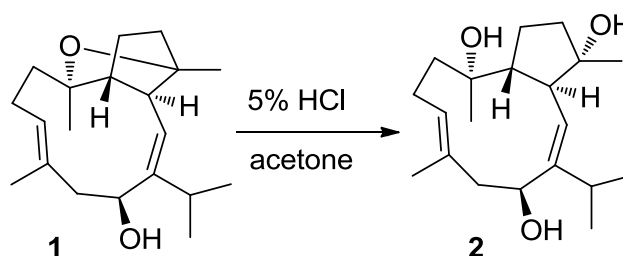
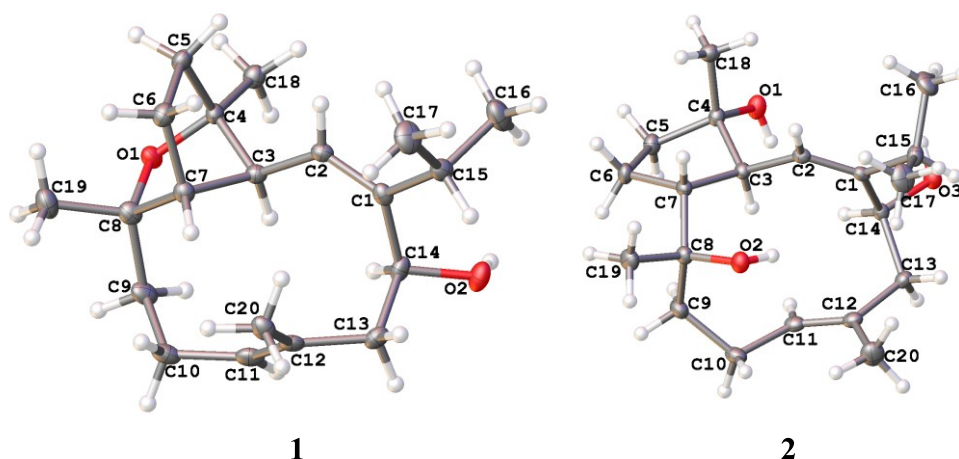


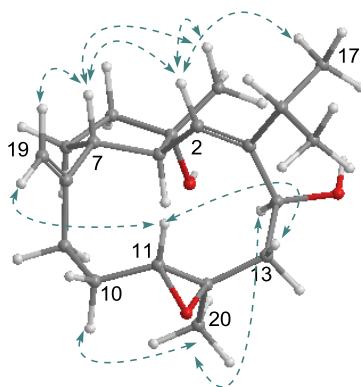
Figure 4. ORTEP depiction for X-ray crystal structures of **1** and **2**.



The HRESIMS data (m/z 343.2239 [$\text{M} + \text{Na}$] $^{+}$) of sarcophylide D (**3**) was in accordance with a molecular formula of $\text{C}_{20}\text{H}_{32}\text{O}_3$ with five degrees of unsaturation. The NMR data of compound **3** were compatible to those of sarcophytol L [15], except for the presence of two olefinic bonds instead of three bonds in the known analog. Analysis of ^{13}C NMR in association with 2D NMR data revealed **3** presenting two epoxy carbons (δ_{C} 58.1 and 59.5), residing at C-11 and C-12 according to the HMBC correlations of H₃-20 (δ_{H} 1.49, s) to C-11 (δ_{C} 59.5, CH), C-12 (δ_{C} 58.1, qC), and C-13 (δ_{C} 45.6, CH_2).

Thus, the structure of **3** was determined as an 11,12-epoxidated sarcophytol L. The relative configurations of the stereogenic centers in **3** from C-1 to C-7 were in agreement with those of sarcophytol L due to the similar NOE and NMR data. Additional NOE relationships from H-14 to H₃-20 and H-3, and from H-11 to H₃-16 and H-13a (Figure 5) assigned a *trans* geometry of the epoxy group, while H₃-20 is oriented in the same face as H-14.

Figure 5. Key NOE correlations of **3**.



The 2D NMR (COSY, HMQC, and HMBC) data analysis revealed the gross structure of sarcophyllide E (**4**) closely related to a known cembranoid derived from sarcophytolide through oxymercuration [17]. The only difference was due to C-12 in which a quaternary carbon (δ_C 71.8) of **4** was replaced by a methine carbon of the known analog. The hydroxylated C-12 was supported by its HMBC correlations with H₃-20 (δ_H 0.98, s) and a hydroxyl proton OH-12 (δ_H 4.46, s). The relative configurations of **4** were determined on the basis of NOE interactions. The NOE correlations between H-7 and H-11 and H₃-18, and between H₃-18 and H-2 informed a *cis*-geometry of the epoxy bond and 3*E* of the olefinic bond. In addition, the NOE interactions between H-7 and OH-8 (δ_H 4.40, s) and between H-11 and OH-12 in association with the absence of the interactions of H-11/H₃-20 and H-7/H₃-19 revealed the opposite orientation of H-7 and H-11 toward their vicinal methyl groups (Figure 6). Based on the CD rule for α,β -unsaturated- γ -lactone [18], the Cotton effects due to the $n \rightarrow \pi^*$ and $\pi^* \rightarrow \pi^*$ transitions of the α,β -unsaturated lactone chromophore correlated directly to the absolute configuration of the stereogenic center at C(γ). Thus, the positive Cotton effects for $n \rightarrow \pi^*$ (252 nm) and negative $\pi^* \rightarrow \pi^*$ (226 nm) of **4** (Figure 7) indicated that it follows *p*-helicity rule, demonstrating 2*R* configuration.

Figure 6. Key NOE correlation of **4**.

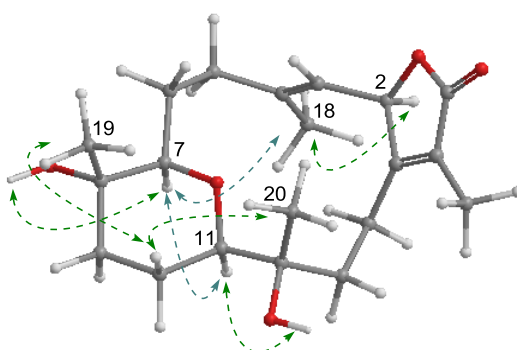
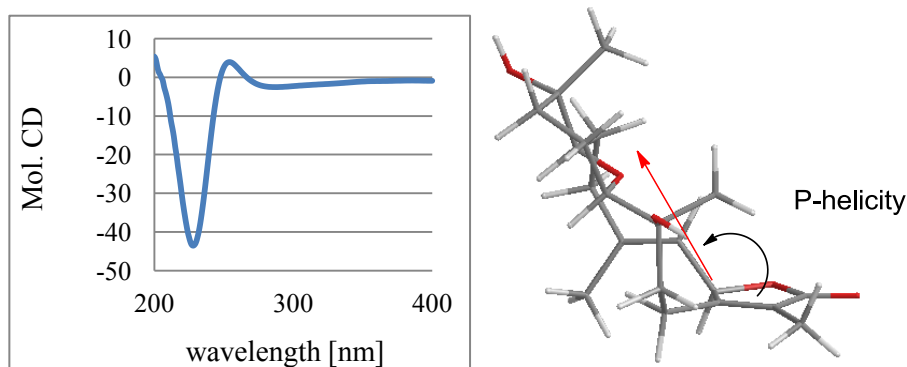


Figure 7. CD effects and P-helicity of **4**.

Based on the spectroscopic analyses and comparison of the NMR data with those reported in literature, 11 known cembranoids were identical to: sarcophytol L [19], 13 α -hydroxysarcophytol L [19], sarcophylide A [20], sarcophine [21], sarcophinone [22,23], 7 α -hydroxy- $\Delta^{8(19)}$ -deepoxysarcophine [24], 4 β -hydroxy- $\Delta^{2(3)}$ -sarcophine [24], 7 α ,8 β -dihydroxydeepoxysarcophine [25], 1,15 β -epoxy-2-*epi*-16-deoxysarcophine [3], sarcophytol Q [26], and lobocrasol [27]. Lobocrasol presented as a unique skeleton that was isolated from soft coral for the second time.

2.2. Cytotoxic Results

A bioassay guiding fractionation revealed the EtOAc extract showing selective inhibition against human ovarian carcinoma cell line A2780 (IC_{50} = 4.9 μ g/mL), but it exhibited weak inhibition against human lung adenocarcinoma epithelial cell line A549 (IC_{50} = 23.7 μ g/mL), human gastric carcinoma cell line BGC823 (IC_{50} = 20.4 μ g/mL), human hepatoma cell line Bel7402 (IC_{50} = 19.1 μ g/mL), and human colonic carcinoma cell line HCT-8 (IC_{50} = 19.5 μ g/mL). In the additional tests of the pure compounds, **1** and lobocrasol showed significant inhibition against A2780 with IC_{50} values of 2.92 and 3.37 μ M, respectively, whereas the other cembranoids exhibited weak activity (IC_{50} > 10 μ g/mL). Taxol was used as a positive control, which displayed the inhibition against A2780 with IC_{50} of 14.45 μ M.

3. Experimental Section

3.1. General

Optical rotations were measured on a Perkin-Elmer 243B polarimeter. IR spectra were recorded on a Thermo Nicolet Nexus 470 FTIR spectrometer. ^1H and ^{13}C NMR and 2D NMR spectra were measured on an Avance-500 FT 500 MHz NMR spectrometer using TMS as an internal standard, while δ values are expressed in parts per million (ppm), and J values are reported in Hertz (Hz). HRESIMS data were obtained from Bruker APEX IV instrument. Low pressure column chromatography was carried using silica gel (160–200 and 200–300 mesh). The GF₂₅₄ silica gel for TLC was provided by Qingdao Marine Chemistry Co., Ltd. (Qingdao, China).

3.2. Animal Material

The soft coral *Sarcophyton elegans* was collected from Xidao Island, Hainan, China, in 2002, and kept frozen until extraction. The specimen was identified by Dr. Leen van Ofwegen (National Museum of Natural History, Naturalis). The soft coral (HSE-17) was deposited at State Key Laboratory of Natural and Biomimetic Drugs, Peking University, China.

3.3. Extraction and Isolation

The frozen soft coral *Sarcophyton elegans* (3.5 kg, wet weight) was homogenized and extracted with EtOH. The concentrated extract was desalted through dissolving in MeOH to yield a residue (100 g) after evaporation. This residue was defatted by partitioning between H₂O and petroleum ether, and then the H₂O fraction was extracted with EtOAc. The EtOAc fraction (7.4 g) was subjected to Si gel column chromatography eluting with a gradient of petroleum ether (PE)-acetone to obtain eight subfractions (SF1–SF8). SF2 (1.2 g) was subsequently subjected to Si gel column chromatography eluting with PE–EtOAc (5:1) to yield **1** (9.0 mg), **3** (4.2 mg), and **2** (4.8 mg). SF3 (1.0 g) was treated by the same process as SF2 to yield **4** (2.3 mg). From SF7 (890 mg) and SF8 (320 mg) fractions, **5** (5.6), **15** (3.2 mg), **22** (8.6 mg), **6** (5.5 mg), **8** (7.2 mg), **7** (8.8 mg), **9** (2.3 mg), **10** (2.5 mg), **12** (4.5 mg), **11** (6.8 mg), **13** (3.2 mg), and **14** (5.4 mg) were separated upon semipreparative HPLC (C₁₈, 5 µm) using a mobile phase of MeOH–H₂O (65:35).

Sarcophyolide **B** (**1**). Colorless oil. $[\alpha]_D^{25} +16.7$ (*c* 6.0, CHCl₃). IR $\nu_{\max}$ (KBr) 3406, 2954, 2925, 1604, 1459, 1189, 1071 cm^{−1}; for ¹H and ¹³C NMR data, see Tables 1 and 2; HRESIMS *m/z* 305.2473 [M + H]⁺, 327.2292 [M + Na]⁺ (calcd for C₂₀H₃₂O₂Na, 327.2294).

Sarcophyolide **C** (**2**). Colorless oil. $[\alpha]_D^{25} -62.0$ (*c* 4.9, CHCl₃). IR $\nu_{\max}$ (KBr) 3386, 2958, 2927, 1604, 1189, 1079 cm^{−1}; ¹H and ¹³C NMR data, see Tables 1 and 2; HRESIMS *m/z* 345.2406 [M + Na]⁺ (calcd for C₂₀H₃₄O₃Na, 345.2400).

Sarcophyolide **D** (**3**). Colorless oil. $[\alpha]_D^{25} -2.5$ (*c* 2.9, CHCl₃). IR $\nu_{\max}$ (KBr) 3370, 2959, 2961, 2860, 1610, 1389, 1298, 1113, 1050 cm^{−1}; ¹H and ¹³C NMR data, see Tables 1 and 2; HRESIMS *m/z* 343.2239 [M + Na]⁺ (calcd for C₂₀H₃₂O₃Na, 343.2239).

Sarcophyolide **E** (**4**). Colorless oil. $[\alpha]_D^{25} +4.4$ (*c* 3.1, CHCl₃). IR $\nu_{\max}$ (KBr) 3464, 2964, 2937, 2253, 1725, 1673, 1443, 1378, 1103 cm^{−1}; ¹H and ¹³C NMR data, see Tables 1 and 2; HRESIMS *m/z* 373.1980 [M + Na]⁺ (calcd for C₂₀H₃₀O₅Na, 373.1980).

3.4. Cytotoxic Bioassays

The tetrazolium-based colorimetric assay (MTT assay) was used for *in vitro* assay of cytotoxicity from HCT-8, Bel-7402, BGC-823, A549, and A2780 tumor cell lines.

3.5. Mosher Reaction

Compound **1** (0.01 mmol), together with DMAP (4-dimethylaminopyridine, 0.01 mmol) and DCC (dicyclohexylcarbodiimide, 0.01 mmol), were dissolved in methylene dichloride (2 mL) at 0 °C, and

then (*R*)- or (*S*)-MPA (0.01 mmol) was added to the solution. After stirring at room temperature for 24 h, the mixture was evaporated under reduced pressure to obtain a residue, which was separated using a reversed phase semipreparative HPLC with 95% CH₃CN–H₂O as a mobile phase to yield (*R*)-MPA ester or (*S*)-MPA ester.

3.6. Chemical Conversion

To a solution of **1** (1 mg/mL) in acetone 5% HCl (0.2 mL) was added. After stirring for 2 h at room temp. the reaction mixture was extracted with EtOAc (0.5 mL). The organic layer was concentrated to yield a product **1a**. Specific rotations, ESIMS, R_f-values of TLC, and ¹H NMR data indicated the structure of **1a** to be identical to **2**.

1a. Colorless oil. [α]_D²⁵ −60.0 (*c* 0.32, CHCl₃). ¹H NMR δ (CDCl₃) 5.29 (1H, d, *J* = 9.5 Hz, H-2), 2.63 (1H, dd, *J* = 9.5, 10.0 Hz, H-3), 1.74, 1.76 (m, H₂-5), 1.33, 1.76 (m, H₂-6), 1.97 (1H, m, H-7), 1.62, 1.83 (m, H₂-9), 2.04, 2.40 (m, H₂-10), 5.35 (1H, dd, *J* = 4.5, 8.0 Hz, H-11), 2.08, 2.50 (m, H₂-13), 4.85 (1H, dd, *J* = 2.0, 10.0 Hz, H-14), 2.55 (1H, m, H-15), 1.08 (3H, d, *J* = 7.5 Hz, H₃-16), 1.15 (3H, d, *J* = 7.5 Hz, H₃-17), 1.10 (3H, s, H₃-18), 1.15 (3H, s, H₃-19), 1.72 (3H, s, H₃-20), ESIMS *m/z* 345.2 [M + Na]⁺.

4. Conclusions

Present work provided a number of new cembranoids, which enriched the cembranoid family. Capnosane-type cembranoids with 3,7-fused carbobicyclic skeleton are a group of uncommon derivatives, derived from soft corals, while the unique ether bridge across C-4/C-8 in **1** is reported for the first time. These findings implied that the species of genus *Sarcophyton* are potential sources, waiting for the discovery of structurally unique chemical diversity.

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Conflicts of Interest

The authors declare no conflict of interest.

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