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Bioactive Cembranoids from the Coral *Sarcophyton trocheliophorum* of Ximao Island

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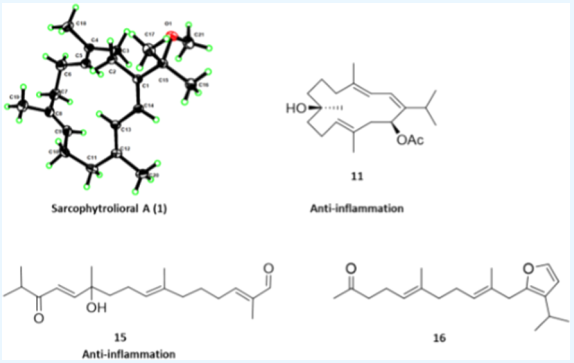
ABSTRACT: Eight new cembranoids (sarcophytembranoids A−H, **1**−**8**) and 10 known terpenoids (**9**−**18**) were obtained from the soft coral *Sarcophyton trocheliophorum* of Ximao Island. Notably, **11**, **15**, and **16** were obtained from a natural source for the first time. The structures of the new isolates were elucidated by extensive spectroscopic analysis, optical rotatory dispersion, and X-ray diffraction experiments. Although the isolated compounds did not show significant activity against the tested tumor cell lines, compounds **3**, **7**, **8**, and **10**−**15** exhibited anti-inflammatory activities at 10 μM, and compounds **17** and **18** showed moderate protein tyrosine phosphatase 1B inhibition activities with the minimum inhibitory concentrations of 22.19 and 11.26 μM, respectively.



Terpenoids are the most structurally diverse[1] compounds to be isolated from all kingdoms of life. To date, over 80,000 terpenoids have been isolated[2] with a variety of biological activities,[3] for instance, antitumor, antibacterial, anti-inflammation, anti-dementia, antimalaria, and so forth. The 14-membered carbocyclic cembranoids are diterpenoids linking one isopropyl and three methyl groups, and the isopropyl group is often oxidized to carboxylic acids or hydroxymethyls. Various functions, including epoxide, ester, furan, lactone, and so forth, were frequently found among these compounds.[4−6] Cembranoids are biologically synthesized from the C20 precursor geranylgeranyl diphosphate (GGPP).[1,7] The biological activities of cembranoids have made them fascinating candidates for drug development and chemical synthesis.[8] Over the past decades, nearly 1500 cembranoids have been discovered[2] from various organisms, especially soft corals.[9,10] Corals of the genus *Sarcophyton* are renowned for the production of a wide variety of bioactive terpenoids, especially cembranoids.[11−20] More than 90 cembranoids have been isolated from *Sarcophyton trocheliophorum* in the past decades.[13,14,16] In the course of our ongoing program toward the isolation of biologically active second metabolites from Chinese marine invertebrates, several geographically distinct soft coral *S. trocheliophorum* were chemically investigated, affording 33 new cembranoids from *S. trocheliophorum* collected off the Yalong Bay[18,21−25] and Ximao Island.[26] Among the isolates, sarcophytonolide N, sarcrassin E, 4*Z*,12*Z*,14*E*-sarcophytolide, sartrolide H, cembrene-C, and ketoemblide showed potential to moderate inhibitory activities against the human protein tyrosine phosphatase 1B (PTP1B) enzyme,[18,22] which plays a major role in the dephosphorylation of the insulin receptor and the insulin receptor substrate (IRS-1) protein, representing a promising drug target for the treatment of type-II diabetes and obesity.[27]

Inspired by our and other research groups' continuous isolation of bioactive and structurally diverse cembranoids from *S. trocheliophorum*, we chemically examined the soft coral *S. trocheliophorum* from Ximao Island. The current efforts let us identify 16 macrocyclic/linearized terpenoids, including 8 new cembranoids, sarcophytembranoids A−H (**1**−**8**), 8 known cembranoids **9**−**14** and **17**−**18**, and 2 known linearized terpenoids **15** and **16** as shown in Chart 1. It is worth mentioning that compounds **11**, **15**, and **16** were isolated from a natural source for the first time. In addition, several isolates exhibited anti-inflammation or PTP1B inhibition activities. In this paper, the isolation, structure determination, and biological evaluation of the isolates are reported.

RESULTS AND DISCUSSION

The specimen of *S. trocheliophorum* was extracted using Me_2CO in an ultrasonic bath. The ether-soluble portion of the Me_2CO extract was subjected to silica, Sephadex LH-20, and reversed-phase high-performance liquid chromatography (RP-HPLC), affording 16 compounds **1**−**16**, including 8 new cembranoids **1**−**8**, 3 first-time isolated known compounds **11**, **15**, and **16**, and 5 other compounds **9**, **10**, and **12**−**14**. The 8

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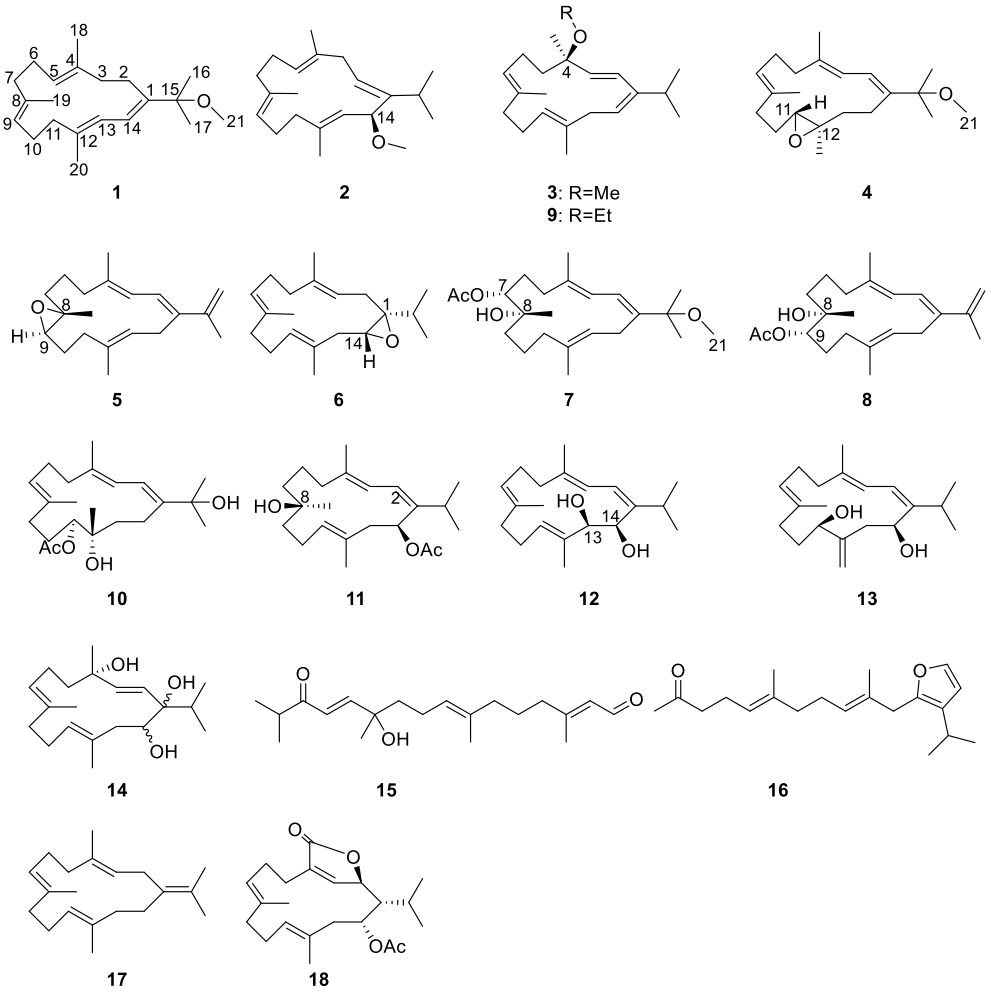
Chart 1. Chemical Structures of the Isolated Compounds



known compounds **9**−**16** were readily identified as (4*R*,1*E*,3*Z*,6*E*,10*E*)-14-ethoxy-3-isopropyl-6,10,14-trimethylcyclotetradeca-1,3,6,10-tetraene (**9**),[28] sarcomililatol A (**10**),[29] (1*R*,2*Z*,4*E*,7*Z*,9R,12*E*)-9-hydroxy-2-isopropyl-5,9,13-trimethylcyclotetradeca-2,4,7,12-tetraen-1-yl acetate (**11**),[30] sarcophytol B (**12**),[31] sarcophytol I (**13**),[32] sarcophytol Q (**14**),[28] (2*E*,7*E*,12*E*)-11-hydroxy-2,7,11,15-tetramethyl-14-oxohexadeca-2,7,12-trienal (**15**),[30] (5*E*,9*E*)-11-(3-isopropylfuran-2-yl)-6,10-dimethylundeca-5,9-dien-2-one (**16**),[30] (*E*,*E*,*E*)-1-isopropenyl-4,8,12-trimethylcyclotetradeca-3,7,11-triene (**17**),[22] and sacrophytonolide I (**18**).[33] We included the extensive structure elucidations of the new compounds below.

Sarcophytembranoid A (**1**) was isolated as a colorless crystal with a chemical formula of $C_{21}H_{34}O$ as assigned by high-resolution electrospray ionization mass spectroscopy (HRESIMS) *m*/*z*: 325.2492 ($[M + Na]^+$ calcd for $C_{21}H_{34}ONa^+$, 325.2502). Its ultraviolet (UV) (λ_{max} 286 and 204 nm) and infrared (IR) (ν_{max} 1710 cm^{-1}) spectra showed typical absorptions for a conjugated polyene pattern. The NMR spectra (Figures S2 and S3) of **1** revealed 21 carbon signals, including 5 methyls, 1 methoxy group, 6 sp^3 methylenes, 4 sp^2 methines, and 5 quaternary carbons. As only four trisubstituted double bonds could be found, as assigned by the following signals: δ_C 135.4 (qC), δ_H 4.99 (1H, t, J = 6.1 Hz)/δ_C 125.3 (CH); δ_C 134.2 (qC), δ_H 5.00 (1H, t, J = 5.3 Hz)/δ_C 126.1 (CH); δ_C 138.5 (qC), δ_H 5.92 (1H, d, J = 11.2 Hz)/δ_C 120.6 (CH); δ_C 144.0 (qC), δ_H 6.25 (1H, d, J = 11.2 Hz)/122.1 (CH), one monocyclic ring could be deduced, fitting the limit of five degrees of unsaturation. Further 2D NMR experiments helped establish the planar structure of **1** as a 14-membered cembrane. Briefly, the correlated spectroscopy (COSY) spectrum of **1** implicated four fragments: (i), H_2-2 (δ_H 2.15, 2.22)/H_2-3 (δ_H 2.10, 2.16); (ii), H-5 (δ_H 4.99)/H_2-6 (δ_H 2.12, 2.25)/H_2-7 (δ_H 2.09, 2.17); H-5 (δ_H 4.97)/H_2-6 (δ_H 2.12, 2.25)/H_2-7 (δ_H 2.09, 2.17); (iii), H-9 (δ_H 5.00)/H_2-10 (δ_H 2.15, 2.22)/H_2-11 (δ_H 2.09, 2.17); and (iv), H-13 (δ_H 5.92)/H-14 (δ_H 6.25). Further heteronuclear multiple bond correlation (HMBC) analysis established the connectivity of the four fragments, as evidenced by the following HMBC cross-peaks: from H_3-18 to C-3/C-4/C-5, from H_3-19 to C-7/C-8/C-9, from H_3-20 to C-11/C-12/C-13, from H_3-16 to C-1/C-15/C-17, from H_3-17 to C-1/C-15/C-16, and from H-14 to C-2/C-15. The known compound sarcophytol V is a close analogue to sarcophytembranoid A, only different at the C-15 and C-16 positions. At C-15, our compound has a methoxy group (δ_C 50.4; δ_H 3.03, s) (C-15: δ_C 78.4, s); sarcophytol V has a hydroxy group (C-15: δ_C 76.4, s). At C-16, our compound has a methyl group (δ_C 26.3; δ_H 1.32, s); sarcophytol V has a $-CH_2OH$ group (δ_C 69.3; δ_H 3.43, d, 11.0 Hz/δ_H 3.63, d, 11.0 Hz).[34]

To determine the stereochemistry of the four double bonds, namely, Δ^4, Δ^8, Δ^{12}, and $\Delta^{1(14)}$, in **1**, nuclear overhauser effect (NOE) analysis was implemented. The NOE correlations of H-6a/CH_3-18, H-10a/CH_3-19, H-11a/H-13, and H-14/H_3-16

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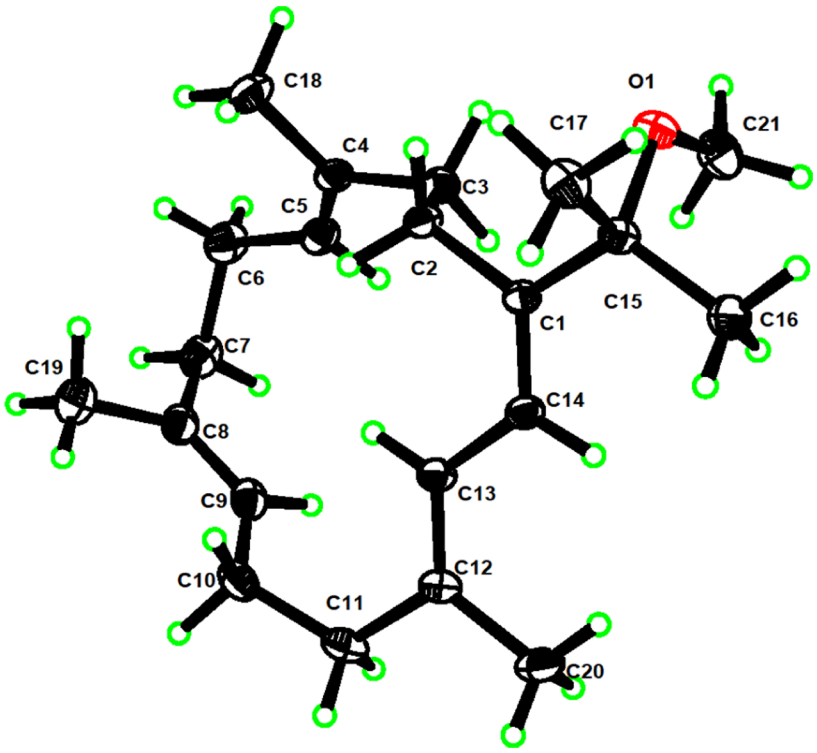

Figure 1. Perspective ORTEP drawing of the X-ray structure of **1**.

Table 1. ^{1}H NMR Data (δ_H in ppm, J in Hz) for Compounds 1−8 in $CDCl_3$

no.	1	2	3	4	5	6	7	8
2a	2.22, m	5.52, dd (9.1, 6.5)	5.94, d (16.6)	6.15, d (10.1)	6.28, d (11.0)	2.78, m	6.30, d (11.0)	6.42, d (11.0)
2b	2.15, m					1.83, m		
3a	2.16, m	2.79, dd (16.7, 9.1)	5.72, d (16.6)	5.83, d (10.1)	5.98, d (11.0)	5.16, t (7.8)	6.16, d (11.0)	6.43, d (11.0)
3b	2.10, m	2.56, dd (16.7, 6.5)						
5a	4.99, t (5.3)	5.01, t (5.8)	1.85, ddd (12.9, 9.7, 3.0)	2.18, m	2.23, m	2.12, m	2.20, m	2.27, m
5b			1.66, ddd (12.9, 9.7, 3.0)	2.11, m	2.18, m	2.07, m	1.67, m	2.27, m
6a	2.25, m	2.09, m	2.03, m	2.27, m	2.25, m	2.20, m	1.93, m	2.95, m
6b	2.12, m	2.09, m	2.22, m	2.17, m	2.18, m	2.20, m	1.67, m	2.25, m
7a	2.17, m	2.19, m	4.91, t (6.2)	5.30, m	2.06, m	4.97, t (6.3)	5.05, d (9.0)	1.81, m
7b	2.09, m	2.00, m			1.51, m			1.66, m
9a	5.00, t (5.3)	4.94, t (5.5)	2.03, m	2.28, m	2.86, t (6.1)	2.12, m	2.20, m	5.12, m
9b			2.03, m	2.12, m		2.07, m	1.67, m	
10a	2.22, m	2.26, m	2.14, m	2.00, m	1.69, m	2.20, m	2.56, m	1.97, m
10b	2.15, m	2.18, m	2.14, m	1.46, m	1.63, m	2.15, m	2.10, m	1.53, m
11a	2.17, m	2.19, m	4.80, t (6.6)	2.91, dd (9.2, 3.5)	2.28, m	5.22, t (6.9)	2.19, m	2.09, m
11b	2.09, m	2.00, m			2.15, m		1.81, m	1.81, m
13a	5.92, d (11.2)	5.26, d (9.2)	2.67, m	2.10, m	5.24, m	2.15, m	5.18, m	5.17, m
13b			2.67, m	1.35, m		2.05, m		
14a	6.25, d (11.2)	4.34, d (9.2)	5.47, t (8.0)	2.12, m	2.39, m	3.05, dd (9.3, 3.4)	2.20, m	2.27, m
14b				2.05, m	2.22, m			2.12, m
15		2.70, m	2.56, m			1.62, m		
16a	1.32, s	0.94, d (7.0)	1.08, d (6.8)	1.31, s	5.02, s	1.09, d (6.9)	1.35, s	5.07, s
16b					4.96, s			5.04, s
17	1.32, s	1.08, d (7.0)	1.08, d (6.8)	1.31, s	1.92, s	0.96, d (6.9)	1.35, s	1.94, s
18	1.62, s	1.63, s	1.23, s	1.75, s	1.79, s	1.58, s	1.78, s	1.81, s
19	1.55, s	1.55, s	1.48, s	1.67, s	1.25, s	1.59, s	1.13, s	1.06, s
20	1.78, s	1.66, s	1.61, s	1.27, s	1.60, s	1.66, s	1.54, s	1.48, s
21	3.03, s	3.24, s	3.16, s	3.04, s			3.07, s	
22								2.11, s
23							2.12, s	

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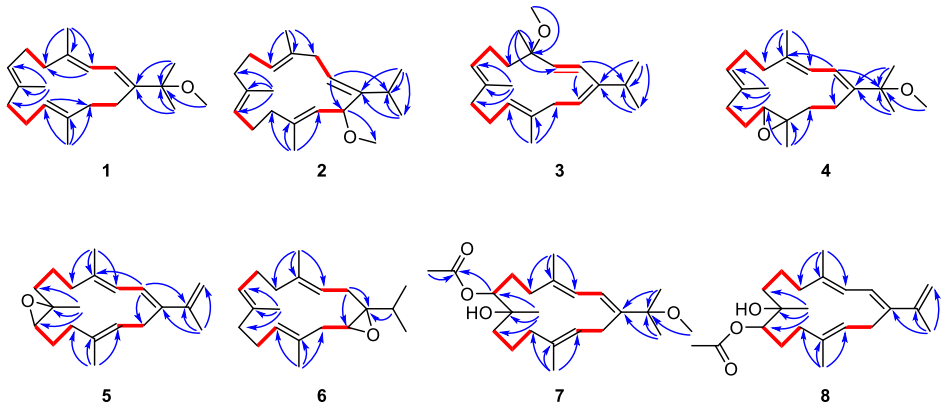

Figure 2. Key COSY (red) and HMBC (blue) correlations of **1**−**8**.

Table 2. ^{13}C NMR Data (δ_C in ppm) for Compounds 1−8 in $CDCl_3$

no.	1	2	3	4	5	6	7	8
1	144.0, C	146.6, C	145.6, C	143.0, C	139.7, C	67.2, C	142.1, C	142.6, C
2	24.8, CH_2	124.2, CH	125.9, CH	122.4, CH	122.6, CH	31.0, CH_2	123.2, CH	124.2, CH
3	42.0, CH_2	35.4, CH_2	134.6, CH	120.3, CH	121.8, CH	120.8, CH	121.9, CH	122.9, CH
4	135.4, C	133.3, C	78.1, C	138.9, C	139.6, C	135.7, C	139.0, C	141.3, C
5	125.3, CH	122.8, CH	40.9, CH_2	38.3, CH_2	39.1, CH_2	39.3, CH_2	39.7, CH_2	40.4, CH_2
6	25.9, CH_2	23.7, CH_2	23.6, CH_2	25.1, CH_2	25.5, CH_2	24.9, CH_2	27.1, CH_2	22.1, CH_2
7	39.2, CH_2	39.5, CH_2	127.0, CH	127.3, CH	36.8, CH_2	126.3, CH	75.7, CH	36.9, CH_2
8	134.2, C	134.1, C	133.0, C	133.6, C	61.1, C	133.6, C	75.0, C	75.2, C
9	126.1, CH	126.3, CH	39.7, CH_2	37.0, CH_2	60.1, CH	38.7, CH_2	38.6, CH_2	74.0, CH
10	24.4, CH_2	25.0, CH_2	24.9, CH_2	24.5, CH_2	24.7, CH_2	24.4, CH_2	22.4, CH_2	26.2, CH_2
11	38.7, CH_2	39.2, CH_2	124.8, CH	61.4, CH	36.9, CH_2	124.2, CH	34.2, CH_2	34.9, CH_2
12	138.5, C	135.5, C	133.7, C	61.4, CH	133.8, C	131.7, C	134.6, C	133.8, C
13	120.6, CH	128.0, CH	37.1, CH	38.9, CH_2	126.9, CH	36.3, CH_2	126.0, CH	126.4, CH
14	122.1, CH	77.6, CH	121.3, CH	23.1, CH_2	22.1, CH_2	62.5, CH	25.7, CH_2	26.3, CH_2
15	78.4, C	27.8, CH	32.3, CH	78.1, C	143.5, C	30.9, CH	78.5, C	139.4, C
16	26.3, CH_3	21.8, CH_3	22.6, CH_3	25.9, CH_3	112.3, CH_2	18.3, CH_3	26.3, CH_3	113.3, CH_2
17	26.3, CH_3	21.8, CH_3	22.7, CH_3	26.4, CH_3	21.4, CH_3	19.2, CH_3	26.6, CH_3	21.6, CH_3
18	15.7, CH_3	18.5, CH_3	21.9, CH_3	18.3, CH_3	17.7, CH_3	15.6, CH_3	17.2, CH_3	16.8, CH_3
19	15.7, CH_3	15.1, CH_3	14.9, CH_3	15.1, CH_3	18.5, CH_3	16.2, CH_3	24.0, CH_3	23.4, CH_3
20	18.2, CH_3	16.4, CH_3	17.5, CH_3	17.4, CH_3	15.1, CH_3	18.2, CH_3	16.8, CH_3	15.8, CH_3
21	50.4, CH_3	55.7, CH_3	50.0, CH_3	50.5, CH_3			50.1, CH_3	170.7, C
22							170.9, C	21.4, CH_3
23							21.4, CH_3	

indicated that the four double bonds in **1** are all *E*-configured. The structure of **1** was also unambiguously confirmed by X-ray crystallography, as observed by Cu Kα radiation (Figure 1).

Sarcophytembranoid B (**2**) has a molecular formula of $C_{21}H_{34}O$ based on HRESIMS (*m*/*z*: 325.2499 $[M + Na]^+$, calcd for 325.2502). The signals of proton, carbon, and heteronuclear single quantum coherence spectra (Table 1) indicated the presence of four trisubstituted olefinic bonds: (i) [δ_H 5.52 (1H, dd, *J* = 9.1, 6.5 Hz)/δ_C 124.2 (CH), 146.6 (qC); (ii) δ_H 5.01 (1H, t, *J* = 5.8 Hz)/δ_C 122.8 (CH), δ_C 133.3 (qC); (iii) δ_H 4.94 (1H, d, *J* = 5.5 Hz)/δ_C 126.3 (CH), δ_C 134.1 (qC); and (iv) δ_H 5.26 (1H, d, *J* = 9.2 Hz)/δ_C 128.0(CH), δ_C 135.5 (qC)]. Extensive analysis of the $^1H-^1H$ COSY spectrum of compound **2** revealed four fragments: a−d (Figure 2) based on the evident correlations of H-2(δ_H 5.52)/H_2-3(δ_H 2.56, 2.79) (a); H-5 (δ_H 5.01, t, *J* = 5.8 Hz)/H_2-6 (δ_H 2.09, 2.09)/H-7 (δ_H 2.00, 2.19) (b); H-9 (δ_H 4.94, d, *J* = 5.5 Hz)/H_2-10 (δ_H 2.18, 2.26)/H-11 (δ_H 2.00, 2.19) (c); and H-13 (δ_H 5.26, d, *J* = 9.2 Hz)/H-14 (δ_H 4.34, d, *J* = 9.2 Hz) (d). We then determined the planar macrocyclic structure by HMBC from H-2 to C-14/C-15, from H_3-16 to C-1/C-15/C-17, from H_3-17 to C-1/C-15/C-16, H_3-18 to C-3/C-4/C-5, from H_3-19 to C-7/C-8/C-9, from H_3-20 to C-11/C-12/C-13, and from H_3-21 to C-14. NOE data (Figure 4) revealed the geometries of four double bonds in **2**, namely, Δ^1, Δ^4, Δ^8, and Δ^{12}, as *E*-configured, which is supported by the smaller chemical shifts of three methyl groups, CH_3-18/19/20 (Table 2).

Optical rotatory dispersion (ORD) is a powerful method for determining absolute configuration by comparison of the experimental and calculated spectra.[35,36] The specific rotation of **2** at the Na D-line (589 nm) is moderately large, $[\alpha]_D^{20}$ +60.0 (*c* 0.20, MeOH), making the ORD comparison and the speculation of the absolute configuration more definitive. We calculated the specific rotations of 26 conformers of **2** (Figure S64) and averaged them by their relative abundance in the gas phase at 4 wavelengths (589, 546, 436, and 405 nm) at the 6-311+G(d) level. There is a satisfactory agreement of the overall patterns between the experimental and calculated data for 14*S*-**2** (Figure 3), suggesting that the structure of compound **2** is as shown (Chart 1).

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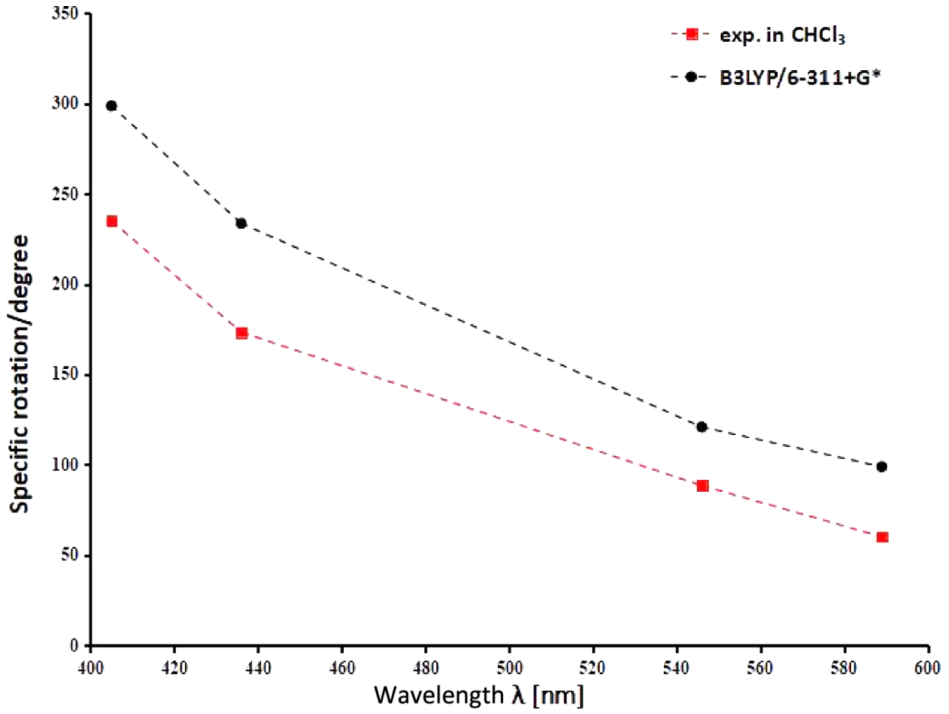

Figure 3. Experimental ORD spectrum of **2** (red) and calculated ORD spectrum of 4*S*-**2** (black) at different wavelengths.

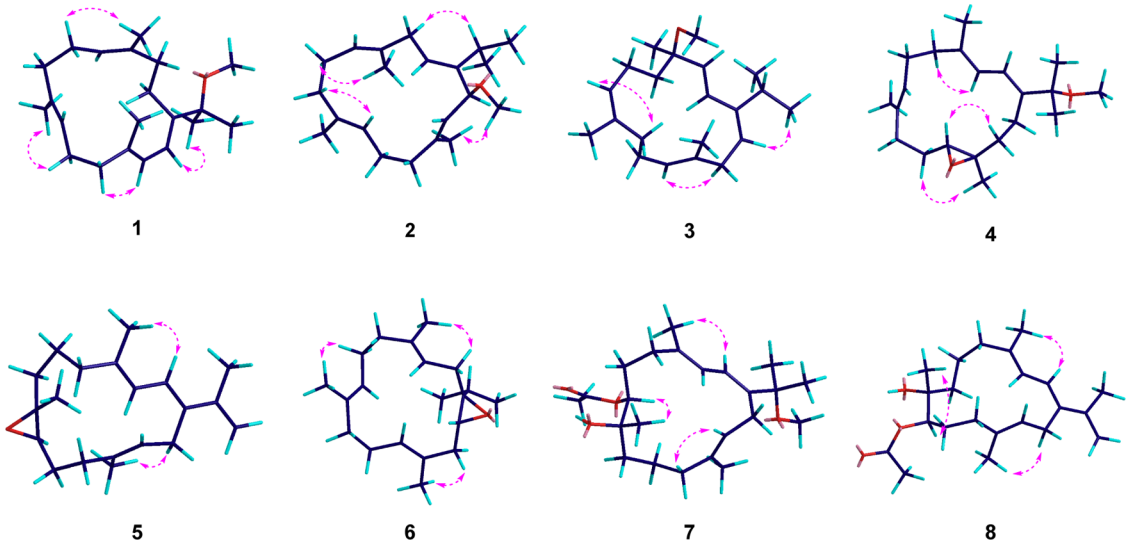

Figure 4. Key NOESY correlations of **1**−**8**.

Sarcophytembranoid C (**3**) possessed a molecular formula of $C_{21}H_{34}O$ inferred from high-resolution electron ionization mass spectrometry (HREIMS) data *m*/*z*: 303.2620 ([M]$^+$, calcd for 302.2604). **9** is an analogue of **3**, with the only difference at the C-4 position. Through detailed comparison, we found that **9** contains an ethoxy group (OCH_2−Me: δ_H 3.36, 2H, q, *J* = 7.0 Hz) in place of the methoxy group (OMe: δ_H 3.16, 3H, s) in **3**. We further performed the electron capture dissociation (ECD) calculation to determine the stereochemistry of C-4 in **3** but did not achieve a satisfying result. As the NMR spectra of **9** and **3** are highly similar and considering that they should have the same biosynthetic precursors, the absolute configuration of **3** was thus tentatively assigned as the same as that of **9** (4*R*).

The HRESIMS ion peak at *m*/*z*: 341.2453 ([M + Na]$^+$, calcd 341.2451) of sarcophytembranoid D (**4**) displayed a protonated molecule consistent with a molecular formula of $C_{21}H_{34}O_2$. The NMR data of compound **4** highly matched those of **1** except for C-11 and C-12. Further comparison analysis revealed that the double bond $\Delta^{11,12}$ of **1** was oxidized to an epoxide to become **4**. Then, the NOE experiment was conducted to elucidate the relative configuration of C-11 and C-12. The NOE correlations between H_3-20/H-10 and H-11/H-13 and no prominent NOE cross-peaks between H_3-20 (δ_H 1.27) and H-11(δ_H 2.91) indicated the trans-configuration between H_3-20 and H-11. The relative configuration was then presumably identified as 11*S**, 12*R**.

The molecular formula of sarcophytembranoid E (**5**) was established as $C_{20}H_{30}O$ by HRESIMS at *m*/*z*: 287.2365 ([M +

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H]$^+$, calcd 287.2369). Detailed analysis of the ^{1}H−^{1}H COSY spectrum of compound **5** revealed the connectivity of four fragments: H-1 (δ_H 6.28)/H-2 (δ_H 5.97) (i); H_2-5 (δ_H 2.18, 2.23)/H_2-6 (δ_H 2.18, 2.25)/H_2-7 (δ_H 1.51, 2.06) (ii); H-9 (δ_H 2.85)/H_2-10 (δ_H 1.63, 1.69)/H_2-11 (δ_H 2.15, 2.28) (iii); and H-13 (δ_H 5.24)/H_2-14 (δ_H 2.22, 2.39) (iv). Then, the HMBC correlations from H_3-18 to C-3/C-4/C-5, from H_3-19 to C-7/C-8/C-9, from H_3-20 to C-11/C-12/C-13, from H_3-16 to C-1/C-15/C-17, from H_3-17 to C-1/C-15/C-16, and from H-2 to C-14/C-15 built the planar structure. Furthermore, the clear NOE correlations of H-2 (δ_H 6.28)/H_3-18 (δ_H 1.79), H_3-20 (δ_H 1.60)/H-14b (δ_H 2.22), and H-3 (δ_H 5.98)/H_2-14a (δ_H 2.39) suggested *E*-geometry for Δ^1, Δ^3, and Δ^{12}. Considering that H_3-19 (δ_H 1.25) and H-9 (δ_H 2.86) have no NOE correlation, the relative configuration of **5** was assigned as 8*S**, 9*R**. The absolute configuration of the epoxide was not determined due to the low yield of this compound.

Sarcophytembranoid F (**6**) was obtained as a colorless oil. Its molecular formula was determined according to the HRESIMS ion peak at *m*/*z*: 289.2527 ([M + H]$^+$, calcd 289.2526). The NMR data of compound **6** was quite similar to that of **1** but with three differences: compound **6** contained an epoxide between C-1 and C-14, but **1** lacked an epoxide (i); **1** had a double bond between C-1 and C-2, but **6** did not (ii); there was a methoxy group at the C-15 position of **1**, but not **6** (iii). The NOE interactions of H_3-18 (δ_H 1.58)/H-2a (δ_H 2.78), H_3-19 (δ_H 1.59)/H-6a (δ_H 2.20), and H_3-20 (δ_H 1.66)/H-10b (δ_H 2.15) indicated that the double bonds Δ^3, Δ^7, and Δ^{11} are all *E*-configured. No NOE correlations were found between H-15 (δ_H 1.62) and H-14 (δ_H 3.05). Thus, the relative configuration was roughly determined as 1*S**, 14*R**.

Sarcophytembranoid G (**7**) was isolated as a colorless oil with a molecular formula of $C_{23}H_{38}O_4$ deduced by the HRESIMS ion peak at *m*/*z*: 401.2660 ([M + Na]$^+$, calcd 401.2662). The NMR data of **7** were similar to those of **4**, except for C-7, C-8, and C-11 to C-13. Further analysis revealed that the original double bond Δ^7 in the cembrane core of **4** is replaced in **7** with an acetoxy group at C-7 and a hydroxyl group at C-8. Additionally, the epoxide between C-11 and C-12 in compound **4** is replaced in **7** with a $\Delta^{12,13}$ double bond and full saturation at C-11. NOE correlations of H-2 (δ_H 6.30)/H_3-16 (δ_H 1.35), H-2 (δ_H 6.30)/H_3-18 (δ_H1.78), and H-11a (δ_H 2.19)/H-13 (δ_H 5.18) support *E*-geometry of Δ^1, Δ^3, and Δ^{12}. Furthermore, C-11/12 in compound **10** shares the same chemical environment as C-7/8 in compound **7**, which bears vicinal acetoxy and hydroxyl groups. By analyzing the chemical shifts, coupling constants, and peak patterns between two compounds, we reasoned that the relative configurations of C-7 and C-8 in **7** are probably all *R**, as are C-11 and C-12 in **10**.

Sarcophytembranoid H (**8**) has a molecular formula of $C_{22}H_{34}O_3$ based on HREIMS data *m*/*z*: 346.2490 ([M]$^+$, calcd for 346.2502). The NMR data of **8** partially matched those of **5**, except for an additional acetyl signal in **8**. Further analysis indicated that the chemical environment of C-8 and C-9 is the same as that of the hydroxy- and acetoxy-bearing carbons in compounds **7** and **10**. Therefore, we did a similar chemical analysis for compound **8** as for compound **7** to determine the stereochemistry and concluded that the absolute configuration of **8** was most likely 1*S*, 2*S*. Furthermore, the NOE interactions of H-2 (δ_H 6.42)/H_2-16 (δ_H 5.05), H-2 (δ_H 6.42)/H_3-17 (δ_H 1.94), H-2 (δ_H 6.42)/H_3-18(δ_H 1.81), and H-14a (δ_H 2.27)/H_3-20 (δ_H 1.48) indicated the *E*-geometry of the double bonds Δ^1, Δ^3, and Δ^{12} in compound **8**.

It also should be noted that although Masaru Kobayashi et al.[30] had chemically synthesized compounds **11**, **15**, and **16**, we isolated them from a natural source for the first time, highlighting the unlimited synthetic abilities among living organisms.

As the isolated compounds share a typical cembranoid skeleton, a plausible biosynthetic pathway was proposed (Figure S67). In brief, the cyclization of GGPP formed three different cembranoid scaffolds resulting from three deprotonations, forming double bonds: Δ^1, $\Delta^{1(14)}$, and $\Delta^{1(15)}$. The isolated natural products would then be readily generated following a series of simple enzymatic reactions, for example, oxidation, acetylation, and methylation.

All the isolated compounds were screened for biological activities, including cytotoxicity, anti-inflammation, and PTP1B inhibition. Although no evident cytotoxic activity was found, compounds **3**, **7**, **8**, and **10**−**15** displayed anti-inflammatory activities in 10 μM tests. Notably, compounds **7**, **8**, and **10** all exhibit anti-inflammatory activities and contain adjacent acetoxy and hydroxyl groups, suggesting that an epoxide ring-opening step could be essential to anti-inflammatory activity. In addition, it is worth mentioning that these compounds exhibited no evident cytotoxicity against BV-2 cells, suggesting that they are potential human-friendly lead compounds for anti-inflammation. Furthermore, compounds **17** and **18** showed moderate PTP1B inhibition activities with minimum inhibitory concentrations of 22.19 and 11.26 μM, respectively. However, cembranoids barely exhibit PTP1B inhibition activities. Despite rare exampled cembranoids being PTP1B inhibitors, the finding would provide new types of candidate leads in drug development for treating type II diabetes and obesity.

Previously reported cembranoids displaying PTP1B inhibition activities,[22,37] for instance, sarcophytonolide N,[22] sarcrassin E,[22] ketoemblide,[22] and jatrophainolides A−C,[37] all have the methyl ester group or formyl group at C-18 (Figure S67), indicating that the oxidation of the methyl group at C-4 would probably significantly increase the PTP1B inhibitory activity. In addition, compounds **17** and cembrene-C[22] showed moderate PTP1B inhibition activities, while their oxidized derivatives **1**−**14** did not, suggesting that oxidation at other positions may decrease the inhibitory activity.

CONCLUSIONS

In conclusion, 8 new cembranoids, sarcophytembranoid A−H (**1**−**8**), and 10 known compounds **9**−**18**, including 3 previously chemically synthesized but not isolated from a natural source **11**, **15**, and **16**, were isolated from the soft coral *S. trocheliophorum* collected from Ximao Island, China. In bioassays, compounds **3**, **7**, **8**, and **10**−**15** displayed significant anti-inflammatory activities, and compounds **17** and **18** exhibited moderate PTP1B inhibition activities.

However, the biosynthesis of the diverse and bioactive cembranoids remains elusive. Recent reports on the identifications of terpene synthases, including cembrane synthase, from marine invertebrates,[38−41] have proved that marine animals contain functional genes responsible for the biosynthesis of bioactive terpenoids, which are likely used as a "chemical weapon" against predators.[5,42] These previous reports have opened the door to elucidate the biosynthesis of bioactive, soft coral-derived cembranoids. Because these

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compounds are often found in extremely low yield, understanding their biosynthetic pathways could allow for their overproduction in genetically engineered systems to assist downstream drug development of cembranoids and to assist efforts in chemical ecology to protect coral ecosystems.

EXPERIMENTAL SECTION

General Experimental Procedures. 1D and 2D NMR spectra were acquired in $CDCl_3$ with a Bruker AVANCE III 400, Bruker AVANCE III 500, or Bruker AVANCE III 600 spectrometer (Bruker Biospin AG, Fällanden, Germany) with residual $CDCl_3$ (δ_H 7.26 ppm, δ_C 77.16 ppm) as the internal standard. HRESIMS spectra were measured using an Agilent G6520 Q-TOF mass spectrometer. A Nicolet 6700 spectrometer (Thermo Scientific, Waltham, MA, USA) was used to obtain the IR spectra. Circular dichroism spectra were measured using a JASCO 810 spectrometer. UV spectra were acquired using a Varian Cary 50 Bio spectrophotometer. Optical rotations were obtained on a PerkinElmer 241MC polarimeter. Column chromatography (CC) was performed using commercial silica gel (Sinopharm Chemical Reagent Co., Ltd., 200−300 and 300−400 mesh) and Sephadex LH-20 gel (GE Healthcare). Thin-layer chromatography was performed on precoated silica gel plates [Merck Chemicals (Shanghai) Co., Ltd., G60 F-254]. RP-HPLC was performed on an Agilent 1260 series liquid chromatography system (Agilent, Santa Clara, CA, USA) equipped with a DAD G1315D detector at 210 nm and an Agilent semi-preparative XDB-C18 column (5 μm, 250 × 9.4 mm). All solvents used for CC were of analytical grade (Shanghai Chemical Reagent Co., Ltd.) and for HPLC were of chromatographic grade (Dikma Technologies Inc).

Biological Material. The title animal, *S. trocheliophorum*, was collected from the coast of Ximao Island (stored in a −20 °C freezer until extraction), Hainan Province, China, and identified by Prof. Xiu-Bao Li (Hainan University). A voucher specimen (no. 18XD-19) is available for inspection at the Shanghai Institute of Materia Medica, CAS.

Extraction and Isolation. The soft coral (800 g, dry weight) of *S. trocheliophorum* was cut into pieces and extracted exhaustively with Me_2CO at room temperature in an ultrasonic bath (4 × 5.0 L). The organic extract was evaporated to give a brown residue and then partitioned between Et_2O and H_2O. The upper layer was concentrated under reduced pressure to give a Et_2O portion (21.0 g). The resulting residue was separated into five fractions (A−E) by gradient silica-gel CC (200−300 mesh, 0 → 50% Et_2O) in petroleum ether (PE). Fraction B was then fractionated into subfractions (B1−B3) using a Sephadex LH-20 column ($PE/CH_2Cl_2/MeOH$ = 2:1:1). Subfraction B1 was further purified by HPLC (100% CH_3CN, 2.5 mL/min), yielding compounds **5** (3.0 mg), **6** (5.0 mg), **7** (2.0 mg), and **17** (3.0 mg). Fraction C was further isolated as compound **1** (2.0 mg), **2** (1.5 mg), **3** (3.0 mg), **8** (2.0 mg), **9** (1.0 mg), and **16** (0.7 mg) by Sephadex LH-20 CC ($PE/CH_2Cl_2/MeOH$, 2:1:1) and RP-HPLC (100% CH_3CN, 2.5 mL/min). Fraction E was fractionated into subfractions E1−E3 using a Sephadex LH-20 column eluted with $PE/CH_2Cl_2/MeOH$ (2:1:1). Subfraction E1 was further purified by HPLC (80% CH_3CN, 2.5 mL/min) to give compound **4** (2.0 mg) and **11** (2.2 mg). Subfraction E2 was further purified by HPLC (80% CH_3CN, 2.5 mL/min) to give compound **15** (1.5 mg). Subfraction E3 was further purified by HPLC (75% CH_3CN, 2.5 mL/min) to give compound **12** (5.1 mg), **13** (2.1 mg), **14** (2.0 mg), and **18** (5.4 mg).

Sarcophytembranoid A (**1**): colorless crystals, mp 120.2−120.5 °C; IR (KBr) ν_{max}: 3426, 2934, 1710, 1453, 1376, 1072 cm^{-1}; UV (MeOH): λ_{max} (log ε) 248.5 (4.35) nm; ECD (CH_3CN): λ_{max} ($\Delta\varepsilon$) 395.0 (+0.01), 246.5 (−0.33) nm; ^1H and ^{13}C NMR data see Tables 1 and 2; HRESIMS *m*/*z*: 325.2492 $[M + Na]^+$ (calcd for $C_{21}H_{34}NaO$, 325.2502).

Sarcophytembranoid B (**2**): colorless solid, $[\alpha]_D^{20}$ +50.0 (*c* 0.15, MeOH); IR (KBr) ν_{max}: 2959, 2923, 1443, 1383, 1260, 1087, 1031, 865, 803 cm^{-1}; UV (MeOH): λ_{max} (log ε) 217.0 (4.65) nm;^1H and ^{13}C NMR data see Tables 1 and 2; HRESIMS *m*/*z*: 325.2499 $[M + H]^+$ (calcd for $C_{21}H_{34}NaO$, 325.2502).

Sarcophytembranoid C (**3**): colorless solid; $[\alpha]_D^{20}$ +6.1 (*c* 0.30, MeOH); IR (KBr) ν_{max}: 2959, 2928, 1434, 1381, 1155, 1080, 971, 860 cm^{-1}; UV (MeOH): λ_{max} (log ε) 232.0 (4.24) nm; ECD (CH_3CN): λ_{max} ($\Delta\varepsilon$) 238 (+0.02), 200(−0.20) nm; ^1H and ^{13}C NMR data, see Tables 1 and 2; HREIMS *m*/*z*: 302.2620 $[M]^+$ (calcd for $C_{21}H_{34}O$, 302.2604).

Sarcophytembranoid D (**4**): colorless solid; $[\alpha]_D^{20}$ −12.4 (*c* 0.20, MeOH); IR (KBr) ν_{max}: 2958, 2926, 1448, 1379, 1247, 1156, 1073, 826 cm^{-1}; UV (MeOH): λ_{max} (log ε) 248.5 (4.13) nm; ECD (CH_3CN): λ_{max} ($\Delta\varepsilon$) 275.5 (−0.01), 246 (−0.20) nm; ^1H and ^{13}C NMR data, see Tables 1 and 2; HRESIMS *m*/*z*: 341.2453 $[M + Na]^+$ (calcd for $C_{21}H_{34}NaO_2$, 341.2451).

Sarcophytembranoid E (**5**): colorless solid; $[\alpha]_D^{20}$ +3.3 (*c* 0.30, MeOH); IR (KBr) ν_{max}: 2960, 2930, 2871, 1711, 1454, 1383, 1250, 1119, 980 cm^{-1}; UV (MeOH): λ_{max} (log ε) 216.0 (4.60) nm; ECD (CH_3CN): λ_{max} ($\Delta\varepsilon$) 222.5 (−0.05), 210.5 (−2.79) nm; ^1H and ^{13}C NMR data, see Tables 1 and 2; HRESIMS *m*/*z*: 287.2365 $[M + H]^+$ (calcd for $C_{20}H_{31}O$, 287.2369).

Sarcophytembranoid F (**6**): colorless solid; $[\alpha]_D^{20}$ +6.0 (*c* 0.50, MeOH); IR (KBr) ν_{max}: 2963, 2919, 1435, 1384, 1091, 1033 cm^{-1}; UV (MeOH): λ_{max} (log ε) 214.0 (4.83) nm; ^1H and ^{13}C NMR data, see Tables 1 and 2; HRESIMS *m*/*z*: 289.2527 $[M + H]^+$ (calcd for $C_{20}H_{33}O$, 289.2526).

Sarcophytembranoid G (**7**): colorless solid; $[\alpha]_D^{20}$ +7.5 (*c* 0.20, MeOH); IR (KBr) ν_{max}: 3451, 2976, 2930, 2856, 1732, 1448, 1373, 1242, 1143, 1072, 1023 cm^{-1}; UV (MeOH): λ_{max} (log ε) 249.0 (4.37) nm; ECD (CH_3CN): λ_{max} ($\Delta\varepsilon$) 224.5 (−0.09), 215 (+3.50) nm; ^1H and ^{13}C NMR data, see Tables 1 and 2; HRESIMS *m*/*z*: 401.2660 $[M + Na]^+$ (calcd for $C_{23}H_{38}NaO_4$, 401.2662).

Sarcophytembranoid H (**8**): colorless solid; $[\alpha]_D^{20}$ −5.0 (*c* 0.20, MeOH); IR (KBr) ν_{max}: 3440, 2973, 2932, 2870, 1732, 1668, 1448, 1374, 1241, 1029, 802 cm^{-1}; UV (MeOH): λ_{max} (log ε) 249.0 (4.35) nm; ECD (CH_3CN): λ_{max} ($\Delta\varepsilon$) 233.0 (+0.02), 210 (−0.91) nm; ^1H and ^{13}C NMR data, see Tables 1 and 2; HR-EIMS *m*/*z*: 346.2490 $[M]^+$ (calcd for $C_{22}H_{34}O_3$, 346.2502).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c05687.

Detailed HRESIMS or HREIMS, 1D NMR, 2D NMR, and IR spectra of compounds **1**−**8** and biological activity evaluation (PDF)

Sarcophytembranoid A (CIF)

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The manuscript was written with the contributions of all authors. All authors have given approval for the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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