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Sarcoglaucone A, a novel sarsolenane-related diterpenoid from the soft coral *Sarcophyton glaucum*

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Two sarsolenane-type diterpenoids, including a known compound, dihydrosarsolenone (**1**), and a novel metabolite, sarcoglaucone A (**2**), were isolated from the soft coral *Sarcophyton glaucum*, collected off the coast of Taiwan. The absolute configuration of dihydrosarsolenone (**1**) was determined by single-crystal X-ray difraction (SC-XRD) analysis for the first time in this study. The structure of sarsolenane **2** was established on the basis of spectroscopic analysis and further confirmed by SC-XRD analysis. One aspect of the stereochemistry of the known sarsolenanes **1** (dihydrosarsolenone) and methyl dihydrosarsolenoneate was revised. Sarsolenane **1** was found to exhibit activity in enhancing alkaline phosphatase (ALP) activity in human osteoblast-like cells (MG63).

1 Introduction

Octocorals of the genus *Sarcophyton* (phylum Cnidaria, subphylum Anthozoa, class Octocorallia, order Malacalcyonacea, family Sarcophytidae)[1] are widely distributed across shallow coral reefs throughout the Asia-Pacific region. These marine invertebrates have garnered considerable scientific interest due to their abundant and structurally diverse secondary metabolites, many of which exhibit noteworthy pharmacological potential.[2–4] Among these metabolites, sarsolenane-type diterpenoids constitute one of the predominant classes of chemical constituents in *Sarcophyton* species.[5–12] These compounds have been reported to display diverse biological activities, including anti-diabetic,[9] antiviral,[11] and ALP-modulating effects,[12] underscoring their potential as promising leads for drug discovery and biomedical research.

This study reports the isolation and characterization of secondary metabolites from the soft coral *Sarcophyton glaucum* (Quoy & Gaimard, 1833), collected from the coastal waters of Taiwan, a marine region renowned for its exceptional biodiversity arising from the convergence of the Kuroshio Current and the South China Sea surface currents. Two sarsolenane-type diterpenoids were obtained, including the known compound dihydrosarsolenone (**1**)[6] and a new structural analogue,

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designated sarcoglaucone A (**2**) (Fig. 1). Comprehensive spectroscopic analyses, supported by SC-XRD analysis, enabled unambiguous elucidation of their structures. In addition, the biological evaluation of these metabolites revealed potential anti-osteoporotic properties, as assessed through the enhancement of ALP activity in MG63 cells.

2 Results and discussion

Compound **1** was obtained as colorless prisms and exhibited a sodiated molecular ion peak at *m/z* 399.21411 $[M + Na]^+$ in the (+)-HRESIMS spectrum, corresponding to the molecular formula $C_{22}H_{32}O_5$ (calcd for $C_{22}H_{32}O_5$ + Na, 399.21420), indicating seven degrees of unsaturation. The ^1H and ^{13}C NMR chemical shifts and coupling constants of **1** were consistent with those previously reported for dihydrosarsolenone (Table 1).[6] Dihydrosarsolenone was originally isolated from the soft coral *Sarcophyton trocheliophorum* and assigned an absolute 1*R*,2*R*,7*R*,8*S* configuration.[6] However, our SC-XRD analysis, using Cu Kα radiation, of **1** (Fig. 2) revealed that the acetoxy and tertiary methyl substituents at C-7 and C-8, respectively, are oriented on the α-face. The ORTEP plot further confirmed the absolute configurations of the stereogenic centers in **1** as 1*R*,2*R*,7*S*,8*R* (absolute structure parameter $x = 0.02$).[13–15] Based on these findings, the previously reported stereochemical assignment of dihydrosarsolenone should be revised.[6,8,9,12]

Consistent with these findings, the ^1H and ^{13}C NMR data and the rotation value of the known sarsolenane derivative, methyl dihydro-sarsolenoneate ($[\alpha]_D$ + 59),[6] were found to be identical to those of the previously reported compound tortuosene A ($[\alpha]_D$ + 59) (Fig. 1 and Table 2), a sarsolenane-type diterpenoid isolated from the formosan soft coral *Sarcophyton tortuosum*.[7] Notably, the NMR chemical shifts of the key oxymethine CH-7 (δ_H 4.56/δ_C 75.6 for methyl dihydrosarsolenoneate; δ_H 4.56/δ_C 75.5 for tortuosene A), oxygenated quaternary carbon C-8 (δ_C 84.9 for methyl dihydrosarsolenoneate; δ_C 84.8 for tortuosene A), as well as that of the tertiary methyl Me-19 (δ_H 1.42/δ_C 20.2 for both compounds) attaching at C-8, are identical.[6,7] This further confirms that methyl dihydrosarsolenoneate and tortuosene A are identical compounds and share the same configuration. Moreover, in the known compound tortuosene A, the absolute configurations at stereogenetic centers C-7 and C-8 have been established as *R*- and *S*-configurations,[7] respectively, consistent with the configurations assigned to compound **1**. This strong correspondence supports that both compounds methyl dihydrosarsolenoneate and tortuosene A share the same stereochemical framework. Accordingly, the acetoxy and methyl substituents at C-7 and C-8, respectively, in methyl dihydrosarsolenoneate, are assigned to the α-face, aligned with the absolute configuration established for compound **1**.

In this context, it is worth noting that, in a previous study, Liang *et al.* employed a dihydrosarsolenone structure that has since been shown in the present work to be inaccurate as a reference for quantum-chemical calculations aimed at reassessing the stereochemical assignment of another compound, sarsolenone.[5,6] This observation suggests that the use of time-dependent density functional theory-electronic circular dichroism (TDDFT-ECD) calculations for determining absolute configurations may still benefit from further methodological

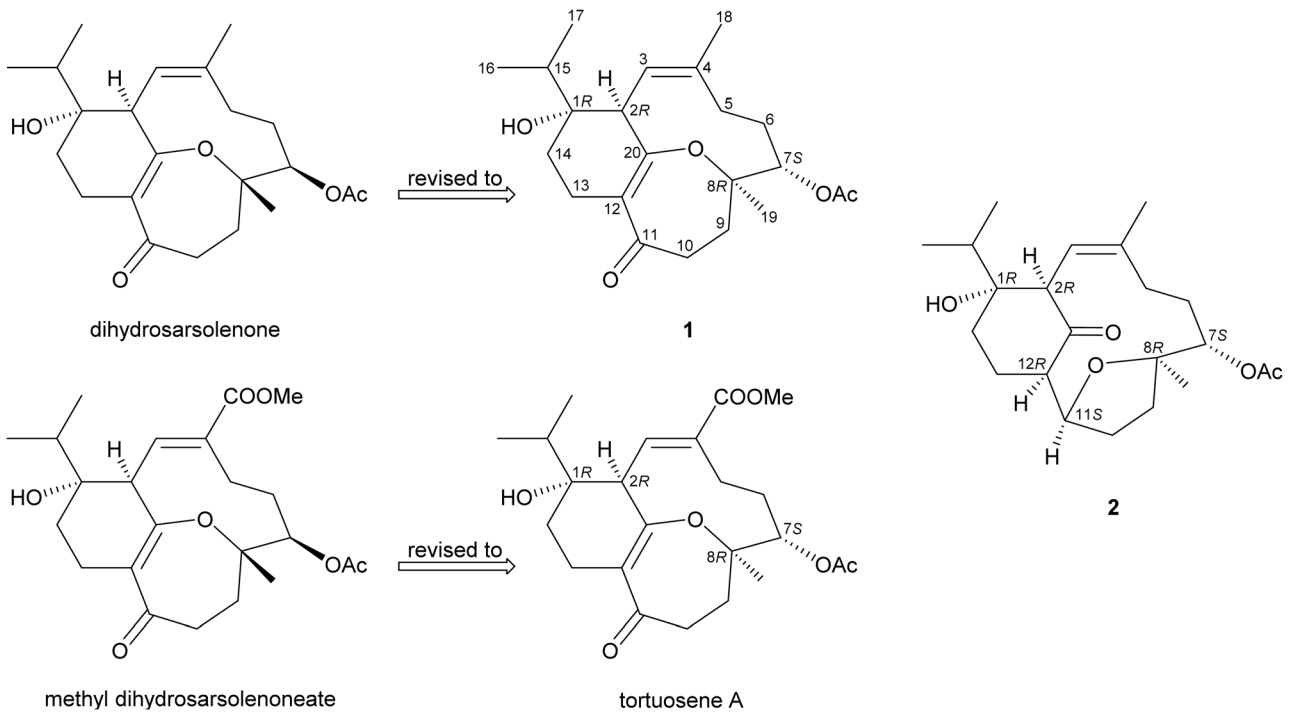


Fig. 1 Structures of dihydrosarsolenone and its revised structure **1**; methyl dihydrosarsolenoneate and its revised structure tortuosene A; and sarcoglaucone A (**2**).

Table 1 ^{1}H and ^{13}C NMR spectroscopic data for dihydrosarsolenone and its revised structure **1**; and sarcoglaucone A (**2**)

	Dihydrosarsolenone[a]		**1**		**2**	
Position	δ_H,[b] mult (J in Hz)	δ_C,[c] type	δ_H,[b] mult (J in Hz)	δ_C,[c] type	δ_H,[b] mult (J in Hz)	δ_C,[c] type
1		74.9, C[d]		74.8, C		77.0, C
2	3.07 d (7.5)	49.0, CH	3.07 d (7.6)	49.0, CH	3.19 br s	58.1, CH
3	5.01 d (7.5)	123.2, CH	5.02 dd (7.6, 0.8)	123.1, CH	5.10 d (1.6)	118.5, CH
4		138.1, C		138.0, C		139.1, C
5α	3.03 td (13.1, 5.6) 1.94 m	28.9, CH_2	3.06 ddd (12.8, 12.8, 5.2) 1.92 m	28.8, CH_2	2.87 ddd (13.6, 13.6, 4.4) 1.69 m	29.1, CH_2
β						
6α	1.80 m	26.5, CH_2	1.80 m	26.4, CH_2	1.57 m	28.6, CH_2
β	1.96 m		1.98 m		1.95 m	
7	4.68 dd (11.5, 2.7)	75.8, CH	4.69 dd (11.6, 2.8)	75.7, CH	4.67 dd (11.2, 1.6)	76.8, CH
8		84.6, C		84.5, C		83.6, C
9α	1.60 m	33.4, CH_2	1.96 m	33.3, CH_2	1.98 m	38.7, CH_2
β	1.91 m		1.62 m		1.62 m	
10α	2.55 dd (14.5, 7.4)	38.1, CH_2	2.66 ddd (15.6, 12.4, 1.2)	38.0, CH_2	2.06 m	26.1, CH_2
β	2.65 m		2.56 ddd (15.6, 7.6, 1.2)		1.74 m	
11		200.3, C		200.2, C	5.00 ddd (8.8, 5.2, 2.4)	77.8, CH
12		116.7, C		116.6, C	2.54 ddd (14.4, 5.2, 4.8)	50.0, CH
13α	2.25 dd (18.2, 6.6)	20.6, CH_2	2.40 ddd (18.0, 11.6, 7.2)	20.5, CH_2	1.65 m	18.0, CH_2
β	2.38 ddd (18.2, 11.5, 7.2)		2.26 ddd (18.0, 7.2, 1.2)		2.21 m	
14α	1.52 ddd (14.2, 11.6, 7.3)	25.6, CH_2	1.89 ddd (14.4, 7.2, 1.2)	25.5, CH_2	1.98 m	32.2, CH_2
β	1.86 m		1.53 ddd (14.4, 11.6, 7.2)		1.67 m	
15	1.73 m	32.8, CH	1.74 sept (6.8)	32.7, CH	2.08 m	34.1, CH
16	0.83 d (6.8)	15.7, CH_3	0.84 d (6.8)	15.6, CH_3	0.96 d (6.8)	15.3, CH_3
17	0.93 d (6.8)	16.0, CH_3	0.94 d (6.8)	15.9, CH_3	0.81 d (6.8)	15.7, CH_3
18	1.84 s	22.9, CH_3	1.84 d (0.8)	22.8, CH_3	1.80 d (1.6)	24.0, CH_3
19	1.41 s	20.5, CH_3	1.41 s	20.3, CH_3	1.14 s	19.7, CH_3
20		164.7, C		164.5, C		214.2, C
7-OAc	2.00 s	170.0, C	2.01 s	169.9, C	2.02 s	170.1, C
		21.4, CH_3		21.2, CH_3		21.4, CH_3

[a] Data reported by Liang *et al.*[6] [b] Spectrum recorded at 400 MHz in $CDCl_3$. [c] Spectrum recorded at 100 MHz in $CDCl_3$. [d] Attached protons were deduced by DEPT experiment.

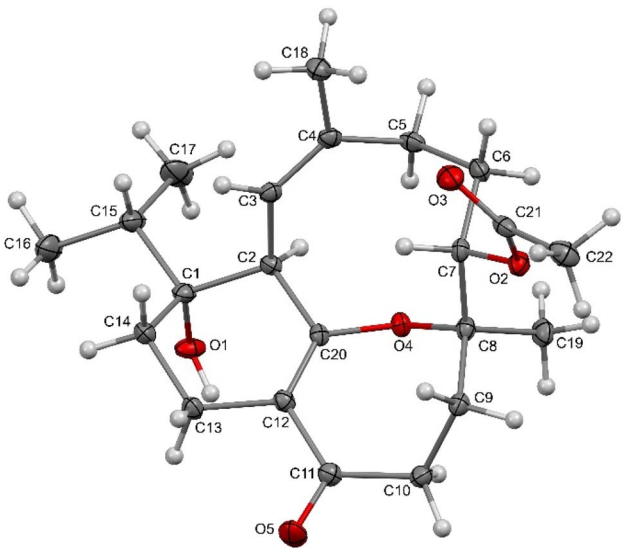


Fig. 2 The computer-generated ORTEP diagram of **1**.

refinement. Accordingly, the stereochemical assignment of sarsolenone may warrant further examination.[5,6]

Sarcoglaucone A (**2**) was isolated as colorless prisms and its molecular formula was determined to be $C_{22}H_{34}O_5$ (6 degrees of unsaturation) by the sodium adduct peak at m/z 401.22986 (calcd for $C_{22}H_{34}O_5$ + Na, 401.22985) in the (+)-HRESIMS spectrum. Comparison of the ^{1}H NMR, HSQC, and HMBC data with the molecular formula indicated that there must be an exchangeable proton, requiring the presence of a hydroxy group, and this deduction was supported by a broad absorption in the IR spectrum at 3453 cm^{-1}. The IR spectrum of **2** also showed strong bands at 1737 and 1717 cm^{-1}, consistent with the presence of ester and ketonic groups. The presence of a trisubstituted olefin was deduced from the signals of an sp^2 methine carbon at δ_C 118.5 (CH-3) and an sp^2 non-protonated carbon at δ_C 139.1 (C-4), further supported by an olefinic proton signal at δ_H 5.10 (1H, d, J = 1.6 Hz, H-3). Two carbonyl resonances at δ_C 214.2 (C-20) and 170.1, confirmed the presence of ketonic and ester groups. An acetate methyl (δ_H 2.02, 3H, s) was also observed. From the above NMR data (Table 1), the remaining three degrees of unsaturation must correspond to a tricyclic framework for **2**.

In addition, a tertiary methyl singlet (δ_H 1.14, 3H, s/δ_C 19.7, CH_3-19), a vinyl methyl (δ_H 1.80, 3H, d, J = 1.6 Hz/δ_C 24.0, CH_3-18), an isopropyl group (δ_H 0.96, 3H, d, J = 6.8 Hz/δ_C 15.3, CH_3-16; δ_H 0.81, 3H, d, J = 6.8 Hz/δ_C 15.7, CH_3-17; δ_H 2.08, 1H, m/δ_C 34.1, CH-15), six pairs of aliphatic methylenes (δ_H 2.87, 1H, ddd, J = 13.6, 13.6, 6.4 Hz; 1.69, 1H, m/δ_C 29.1, CH_2-5; δ_H 1.57, 1H, m;

Table 2 ^{1}H and ^{13}C NMR spectroscopic data for methyl dihydrosarsolenoneate and tortuosene A

	Methyl dihydrosarsolenoneate[a]		Tortuosene A[b]	
Position	δ_H,[c] mult (J in Hz)	δ_C,[d] type	δ_H,[c] mult (J in Hz)	δ_C,[d] type
1		74.7, C[e]		74.6, C
2	3.24 d (8.1)	49.6, CH	3.24 d (8.0)	49.5, CH
3	6.62 d (8.2)	138.1, CH	6.63 d (8.0)	138.1, CH
4		133.2, C		133.1, C
5α/β	2.96 dt (13.2, 5.3); 2.64 m	24.5, CH_2	2.97 td (13.2, 5.2); 2.64 m	24.4, CH_2
6α/β	1.90 m; 2.05 m	27.1, CH_2	1.89 m; 2.02 m	27.1, CH_2
7	4.56 dd (11.5, 2.7)	75.6, CH	4.56 d (10.4)	75.5, CH
8		84.9, C		84.8, C
9α/β	1.62 m; 1.94 m	33.0, CH_2	1.92 m; 1.60 m	33.0, CH_2
10α/β	2.58 dd (15.2, 6.9); 2.67 m	38.0, CH_2	2.65 m; 2.58 m	37.9, CH_2
11		199.7, C		199.7, C
12		118.6, C		118.6, C
13α/β	2.31 dd (18.3, 6.9); 2.44 ddd (18.3, 11.4, 7.3)	20.5, CH_2	2.43 m; 2.30 dd (18.0, 6.8)	20.5, CH_2
14α/β	1.69 m; 1.98 m	25.5, CH_2	1.96 m; 1.62 m	25.5, CH_2
15	1.71 m	33.2, CH	1.70 m	33.2, CH
16	0.82 d (6.8)	15.7, CH_3	0.82 d (6.8)	15.6, CH_3
17	0.96 d (6.8)	15.9, CH_3	0.96 d (6.8)	15.8, CH_3
18		167.0, C		166.9, C
19	1.42 s	20.2, CH_3	1.42 s	20.2, CH_3
20		161.6, C		161.6, C
7-OAc	1.97 s	169.6, C	1.97 s	169.5, C
		21.1, CH_3		21.0, CH_3
18-OMe	3.80 s	52.1, CH_3	3.80 s	52.0, CH_3

[a] Data reported by Liang *et al.*[6] [b] Data reported by Lin *et al.*[7] [c] Spectrum recorded at 400 MHz in $CDCl_3$. [d] Spectrum recorded at 100 MHz in $CDCl_3$. [e] Attached protons were deduced by DEPT experiment.

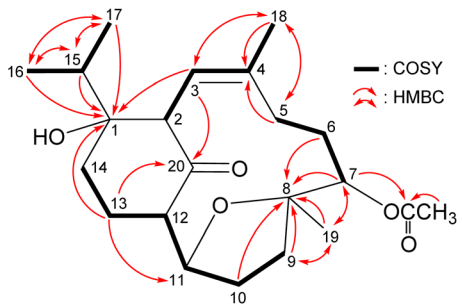


Fig. 3 Key COSY and HMBC correlations of **2**.

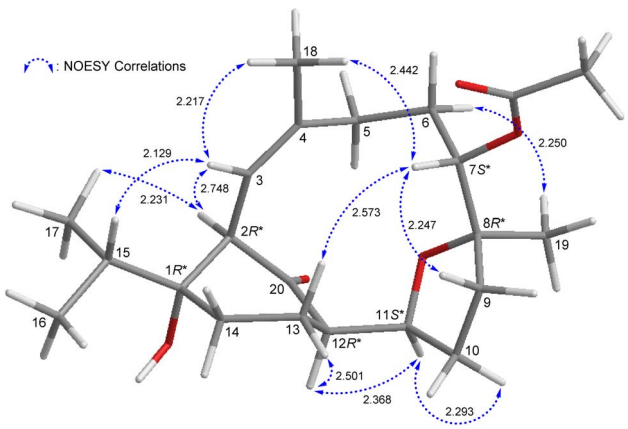


Fig. 4 Stereoview of **2** (from computer modelling) showing key NOESY correlations and selected proton distances (Å).

1.95, 1H, m/δ_C 28.6, CH_2-6; δ_H 1.98, 1H, m; 1.62, 1H, m/δ_C 38.7, CH_2-9; δ_H 2.06, 1H, m; 1.74, 1H, m/δ_C 26.1, CH_2-10; δ_H 1.65, 1H, m; 2.21, 1H, m/δ_C 18.0, CH_2-13; δ_H 1.98, 1H, m; 1.67, 1H, m/δ_C 32.2, CH_2-14), an aliphatic methine (δ_H 3.19, 1H, br s/δ_C 58.1, CH-2), and two oxymethines (δ_H 4.67, 1H, dd, J = 11.2, 1.6 Hz/δ_C 76.8, CH-7; δ_H 5.00, 1H, ddd, J = 8.8, 5.2, 2.4 Hz/δ_C 77.8, CH-11) were observed.

The gross structure of **2** was elucidated by 2D NMR analyses. ^{1}H–^{1}H COSY correlations identified the fragments C2–C3, C5–C6–C7, C9–C10–C11–C12–C13–C14, and C16–C15–C17, which were assembled with the aid of HMBC correlations (Fig. 3). Key HMBC correlations between protons and non-protonated carbons, including H-3, H_2-13, H-15, H_3-16, H_3-17/C-1; H_2-5, H_3-18/C-4; H_2-6, H-7, H_2-9, H_2-10, H_3-19/C-8; and H-3, H_2-13/C-20, defined the major carbon framework of **2**. A vinyl methyl at C-4 was confirmed by an allylic coupling between H_3-18 and H-3 (J = 1.6 Hz) and by HMBC correlations of H_3-18/C-3, C-4, C-5 and H-3, H_2-5/C-18. The ring-junction methyl C-19 was placed at the oxygenated quaternary carbon C-8, as supported by HMBC correlations of H_3-19/C-7, C-8, C-9 and H-7, H_2-9/C-19. The acetoxy group at C-7 was established from an HMBC correlation of H-7 (δ_H 4.67) with the acetate carbonyl (δ_C 170.1). Although no HMBC correlations were observed for H-11, the presence of an ether linkage between C-8 and C-11 forming a tetrahydrofuran (THF) ring was inferred from the

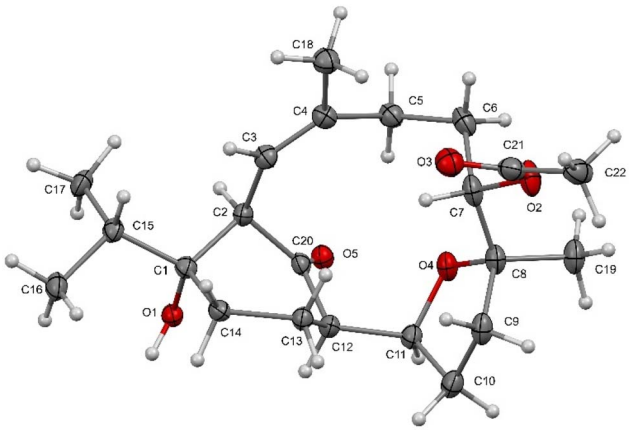


Fig. 5 The computer-generated ORTEP diagram of **2**.

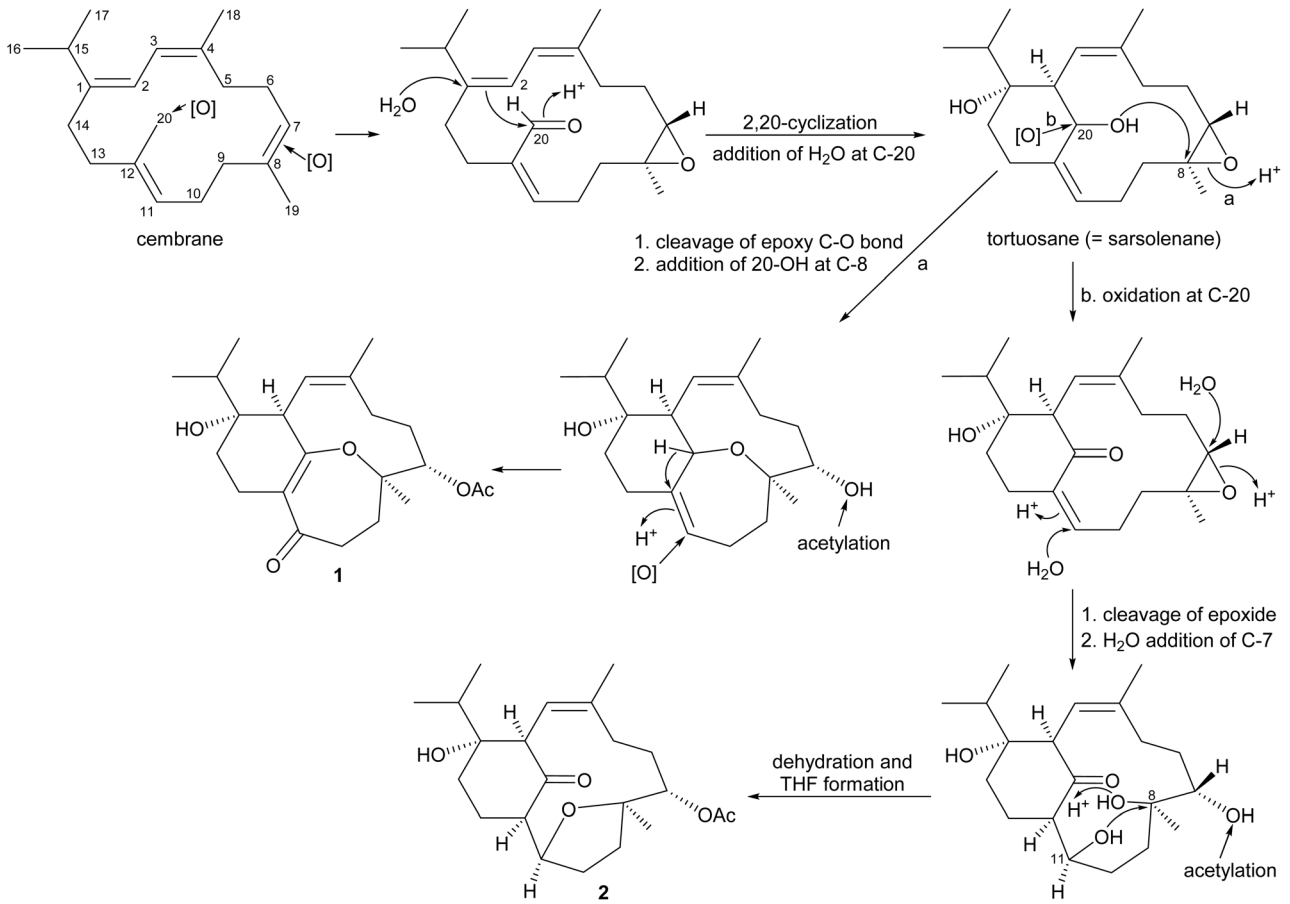
characteristic chemical shifts of the oxymethine CH-11 (δ_H 5.00/δ_C 77.8) and the oxygenated quaternary carbon C-8 (δ_C 83.6), which together satisfied the remaining degree of unsaturation. Among the five oxygen atoms in the molecular formula, four were assigned to the ketone, ether, and acetoxy groups, leaving a hydroxy group at C-1, supported by HMBC correlations of H-3, H_2-13, H-15, H_3-16, and H_3-17 with C-1, an oxygenated quaternary carbon resonating at δ_C 77.0.

Table 3 ALP activity in MG63 cells treated with **1** and **2** at 10 μM for 72 h

Compounds	ALP activity (%)	Cell viability
Control	100.00 ± 3.08	100.00 ± 1.10
1	120.41 ± 8.44*	94.86 ± 0.74***
2	110.60 ± 5.18**	90.63 ± 0.67***
Rutin[a]	113.64 ± 7.09***	81.35 ± 5.17**

[a] Rutin (100 μM) was used as the positive control. Results are shown as mean ± standard error of the mean (SEM) ($n = 3$), with one-way ANOVA used for statistics (*$p < 0.05$, **$p < 0.005$, ***$p < 0.001$ *vs.* control).

The relative stereochemistry of **2** was established from the analysis of NOESY correlations (Fig. 4) and vicinal ^1H–^1H coupling constants. In the NOESY spectrum, the correlation between H-12 and H-11 indicated that both protons are α-oriented. One of the C-13 methylene protons at δ_H 1.65, showed a correlation with H-12 and was thus assigned as H-13α, while the other (δ_H 2.21) was designated as H-13β. The correlation between H-13β and H-7 suggested that H-7 is β-oriented. One of the C-6 methylene protons (δ_H 1.57) showed a correlation with H_3-19 but not with H-7. This proton exhibited a large coupling constant ($J = 11.2$ Hz) with H-7, indicating an anti-relationship between H-7 and this proton. Accordingly, it was assigned as H-



Scheme 1 Proposed biosynthetic pathway for dihydrosarsolenone (**1**) and sarcoglaucone A (**2**).

6α, while the other methylene proton at δ_H 1.95 was designated as H-6β. Accordingly, the C-19 methyl group was deduced to be α-oriented. H-2 showed a correlation with H-3 but not with H-13β, and the absence of coupling between H-2 and H-3 indicated a dihedral angle close to 90°, supporting an α-orientation for H-2. The *Z* configuration of the Δ^3 double bond was confirmed by the correlation between H-3 and H_3-18. Furthermore, correlations of H-2/H_3-17 and H-3/H-15 suggested that the isopropyl group attached at C-1 is β-oriented. Notably, the six-membered ring in compound **2** adopts a twist-boat conformation, on the basis of the above findings.

Due to the conformational flexibility of the macrocyclic framework, the stereochemistry of the chiral centers at C-1, C-2, C-7, C-8, C-11, and C-12 of **2** was further investigated by SC-XRD analysis using Cu Kα radiation (λ = 1.54178 Å). The X-ray structure (Fig. 5) clearly reveals the presence of an ether bridge between C-8/11 within the macrocyclic ring. In addition, the six-membered ring adopts a twist-boat conformation, which is consistent with the NOESY correlations observed for **2** (Fig. 4). Based on the X-ray diffraction analysis, the relative configurations of the stereogenic centers in **2** were assigned as 1*R**,2*R**,7*S**,8*R**,11*S**, and 12*R** (absolute structure parameter $x = -0.4$). Taken together, these results allow the structure of **2** to be unambiguously elucidated.

The absolute configuration of dihydrosarsolenone was unambiguously established by SC-XRD analysis, as shown for structure **1**. On biosynthetic grounds, the newly identified sarsolenane-type diterpenoid sarcoglaucone A (**2**) is proposed to possess the same absolute configuration as compound **1**, since both metabolites were isolated from the same organism. Furthermore, all naturally occurring sarsolenane-type diterpenoids whose absolute configurations have been unequivocally determined are known to share an *R*-configuration at the C-2 stereogenic center.[6–8,10] Accordingly, sarcoglaucone A is assigned the absolute configuration depicted in structure **2**.

The biosynthetic pathways of dihydrosarsolenone (**1**) and sarcoglaucone A (**2**) are illustrated in Scheme 1. It is proposed that both metabolites originate from cembrane-type precursors commonly found in *Sarcophyton* species. The proposed cembranoidal precursor could undergo oxidation at C-20 and epoxidation at the C-7/C-8 double bond to form an aldehydocembrane, which could be cyclized from C-2 to C-20 *via* an acid-catalyzed nucleophilic attack of the C-1/C-2 double bond to the carbonyl group to give a tortuosane intermediate. This intermediate could further afford **1** by the acid-catalyzed epoxide-cleavage and the subsequent reaction sequence as shown in route a, or **2** as shown in route b. The shown formation of a six-membered ring could further increase the diversity of molecular framework, ultimately giving rise to the distinctive architectures of compounds **1** and **2**. This cascade of enzymatic transformations reflects the remarkable biosynthetic capability of *Sarcophyton* species in generating structurally complex and chemically diverse metabolites.

Previous studies have suggested that diterpenoids derived from *Sarcophyton* species may exhibit ALP-enhancing activity.[16,17] In the present study, compounds **1** and **2** were evaluated in MG63 cells. Preliminary results indicated that compound **1** exhibited a tendency to increase ALP activity (Table 3).

3 Conclusions

This study investigated the chemical constituents of the octocoral *S. glaucum*, leading to the isolation of a novel sarsolenane-related diterpenoid, sarcoglaucone A (**2**), along with its known analogue, dihydrosarsolenone (**1**).[6] The structures of **1** and **2** were confirmed by SC-XRD analysis. In the process, the configurational assignment of the previously reported compound, dihydrosarsolenone, was corrected, highlighting that computational approaches in chemical structure determination still have room for improvement. Notably, the six-membered ring in compound **2** adopts a rare twist-boat conformation, underscoring the structural diversity of natural products from *Sarcophyton* species. In terms of biological activity, compound **1** was found to enhance ALP activity in MG63 cells.

4 Experimental

4.1 General experimental procedures

Optical rotation values were measured using a JASCO P-1010 digital polarimeter (JASCO, Tokyo, Japan). IR spectra were obtained with a Thermo Scientific Nicolet iS5 FT-IR spectrophotometer (Thermo Fisher Scientific, MA, USA). NMR spectra were recorded on a 400 MHz Jeol ECZ NMR spectrometer (JEOL Ltd, Tokyo, Japan) using the residual $CHCl_3$ (δ_H 7.26 ppm) and $CDCl_3$ signals (δ_C 77.0 ppm) as internal standards for ^1H and ^{13}C NMR, respectively; coupling constants (*J*) are presented in hertz (Hz). The ESIMS and HRESIMS spectra were ascertained with Thermo Fisher orbitrap Exploris 120 mass spectrometer equipped with an ESI ion source in positive ionization mode. The extracted samples were separated *via* column chromatography (C.C.) with silica gel (Si) (particle size, 230–400 mesh; Merck). TLC was performed on plates precoated with silica gel 60 (DC-Fertigfolien Alugram Xtra SIL G/UV_{254}, layer thickness 0.20 mm; Macherey-Nagel, Düren, Germany), and visualization of the TLC plates was conducted using an aqueous solution of 10% H_2SO_4, subsequently to be heated to show the spots of signals. The separation process was conducted *via* a system that included an injection port (model 7725, Rheodyne, USA) paired with a semi-preparative normal-phase column (Supelco Ascentis Si, Catalog No.#: 581514-U, Sigma-Aldrich, USA) and a pump (model L-7110, Hitachi, Japan) for normal-phase high-performance liquid chromatography (NP-HPLC).

4.2 Animal material

A specimen of *S. glaucum* was manually collected by SCUBA diving off the southern coast of Taiwan at a depth of approximately 10–15 m in February 2024. A voucher specimen (NMMBA-SC-2024-1) was deposited at the National Museum of Marine Biology and Aquarium (NMMBA), Taiwan. Species identification was confirmed by comparing its morphological

features and microscopic characteristics of sclerites with published descriptions of *S. glaucum*.[1,18–21]

4.3 Extraction and isolation

The freeze-dried *S. glaucum* specimen (wet/dry weight = 1000/182 g) was minced and extracted with MeOH–CH_2Cl_2 (1 : 1, v/v) at room temperature to give a crude extract (29.7 g). The extract was partitioned between ethyl acetate (EtOAc) and water. The EtOAc layer was concentrated under reduced pressure to yield a residue (15.9 g), which underwent Si C.C. eluting with *n*-hexane-EtOAc mixtures of increasing polarity, to give 11 fractions F1–F11. Fraction F4 was purified by NP-HPLC (*n*-hexane-EtOAc, 5 : 1) to afford 12 subfractions F4A–F4L. Subfractions F4J and F4K were further purified by NP-HPLC (*n*-hexane-acetone, 3 : 1, flow rate = 3.0 mL min^{-1}), affording compounds **1** (4.0 mg, R_t = 11.0 min, ~0.00220% of dry weight) and **2** (1.5 mg, R_t = 25.0 min, ~0.00082% of dry weight), respectively.

4.4 Structural characterization of compounds 1 and 2

4.4.1 Dihydrosarsolenone (1). Colorless prisms (MeOH); mp 218–219 °C; $[\alpha]_{24}^{D}$ + 65 (*c* 0.40, EtOH) ref. 6 $[\alpha]_{23}^{D}$ + 56 (*c* 0.10, EtOH); IR (ATR) ν_{max} 3415, 1731, 1651 cm^{-1}; ^1H (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) data see Table 1; ESIMS: *m*/*z* 399 $[M + Na]^+$; HRESIMS: *m*/*z* 399.21411 (calcd for $C_{22}H_{32}O_5$ + Na, 399.21420).

4.4.2 Sarcoglaucone A (2). Colorless prisms (MeOH); mp 212–214 °C; $[\alpha]_{25}^{D}$ − 15 (*c* 0.15, EtOH); IR (ATR) ν_{max} 3453, 1737, 1717 cm^{-1}; ^1H (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) data see Table 1; ESIMS: *m*/*z* 401 $[M + Na]^+$; HRESIMS: *m*/*z* 401.22986 (calcd for $C_{22}H_{34}O_5$ + Na, 401.22985).

4.5 SC-XRD of dihydrosarsolenone (1)

The methanol solution was allowed to slowly evaporate to generate suitable colorless prisms of **1**. Diffraction intensity data were obtained on a Bruker D8 Venture diffractometer using graphite-monochromated Cu Kα radiation (λ = 1.54178 Å). Crystal data for this compound: $C_{22}H_{32}O_5$ (formula weight 376.47), approximately crystal size, 0.190 × 0.080 × 0.036 mm^3, monoclinic system, space group *C*2 (#5),[22] *T* = 100 (2) K, *a* = 18.2228 (7) Å, *b* = 5.8415 (2) Å, *c* = 18.7272 (7) Å, α = γ = 90°, β = 90.551 (2)°, *V* = 1993.39 (13) $Å^3$, *Z* = 4, D_{calcd} = 1.254 Mg m^{-3}, *F*(000) = 816. A total of 18 724 reflections were collected in the range of 2.359 < θ < 74.644°, with 4026 independent reflections [*R*(int) = 0.0786], completeness to theta was 99.6%; semi-empirical from equivalents absorption correction applied; refinement method: full-matrix least-square on F^2,[23,24] the data/restraints/parameters were 4026/1/251; goodness-of-fit on F^2 = 1.040; final *R* indices [*I* > 2 sigma (*I*)], R_1 = 0.0405; wR_2 = 0.1026; *R* indices (all data), R_1 = 0.0431, wR_2 = 0.1049, large difference peak and hole, 0.302 and −0.257 e $Å^{-3}$; absolute structure parameter, *x* = 0.02 (11).[13–15] Crystallographic data for the structure of dihydrosarsolenone (**1**) were submitted to the Cambridge Crystallographic Data Center (CCDC) with supplementary publication number CCDC 2496063.

4.6 SC-XRD of sarcoglaucone A (2)

The methanol solution was allowed to slowly evaporate to generate suitable colorless prisms of **2**. Diffraction intensity data were obtained on a Bruker D8 Venture diffractometer using graphite-monochromated Cu Kα radiation (λ = 1.54178 Å). Crystal data for this compound: $C_{22}H_{34}O_5$ (formula weight 378.49), approximately crystal size, 0.149 × 0.026 × 0.017 mm^3, orthorhombic system, space group $P2_12_12_1$ (#19),[22] *T* = 100 (2) K, *a* = 6.6754 (4) Å, *b* = 12.6299 (8) Å, *c* = 24.3212 (15) Å, α = β = γ = 90°, *V* = 2050.5 (2) $Å^3$, *Z* = 4, D_{calcd} = 1.226 Mg m^{-3}, *F*(000) = 824. A total of 28 706 reflections were collected in the range of 3.635 < θ < 66.599°, with 3586 independent reflections [*R*(int) = 0.1776], completeness to theta was 99.7%; semi-empirical from equivalents absorption correction applied; refinement method: full-matrix least-square on F^2,[23,24] the data/restraints/parameters were 3586/0/250; goodness-of-fit on F^2 = 1.042; final *R* indices [*I* > 2 sigma (*I*)], R_1 = 0.0638; wR_2 = 0.1229; *R* indices (all data), R_1 = 0.1207, wR_2 = 0.1448, large difference peak and hole, 0.162 and −0.220 e $Å^{-3}$; absolute structure parameter, *x* = −0.4 (5). Crystallographic data for the structure of sarcoglaucone A (**2**) were submitted to the CCDC with supplementary publication number CCDC 2496064.

4.7 ALP activity assay and cell viability assays

4.7.1 ALP assay. ALP activity was measured to assess the effects of the compounds on osteoblastic differentiation. MG63 cells (1 × 10^3 cells per well) were seeded in 96-well plates (200 μL per well) and incubated for 24 h. Cells were then treated with the test compounds (10 μM) or rutin (100 μM, positive control) and cultured for an additional 72 h. After treatment, cells were washed once with physiological saline and lysed with 1% Triton X-100. ALP activity was determined by incubating the cell lysates with 15 mM *p*-nitrophenyl phosphate (*p*NPP) at 37 °C for 1 h. The formation of *p*-nitrophenol was quantified by measuring absorbance at 405 nm. Total protein content was determined using the Pierce™ BCA Protein Assay Kit (Thermo Fisher Scientific, Waltham, MA, USA) according to the manufacturer's instructions, and ALP activity was normalized to protein content.[25]

4.7.2 Cell viability. Cell viability was evaluated using the MTT assay. MG63 cells were maintained in Alpha MEM (Gibco™, Thermo Fisher Scientific, Waltham, MA, USA) supplemented with 10% fetal bovine serum (FBS) at 37 °C in a humidified atmosphere containing 5% CO_2. Cells (1 × 10^3 cells per well) were seeded in 96-well plates (200 μL per well) and incubated for 24 h. The medium was then replaced with fresh medium containing the test compounds (10 μM) or rutin (100 μM, positive control), and the cells were further incubated for 72 h. After treatment, 20 μL of MTT solution (5 mg mL^{-1} in PBS) was added to each well, followed by incubation for 4 h at 37 °C. The medium was subsequently removed, and the formazan crystals were dissolved in 100 μL of DMSO. Absorbance was measured at 600 nm using a microplate reader to determine cell viability.[26]

4.7.3 Statistical analysis. Statistical analyses were performed using GraphPad Prism (San Diego, CA, USA). Data are

presented as mean ± S.E.M. from three biological replicates ($n = 3$), with all measurements conducted in triplicate within a single independent experiment. Group differences were analyzed by one-way analysis of variance (ANOVA), followed by appropriate *post hoc* comparisons against the control group. A p value of <0.05 was considered statistically significant.

Author contributions

Y.-W. Chuang, A. F. Ahmed, H.-L. Chung, Y.-W. Liu, Y.-C. Lin, C.-C. Liaw, Y.-J. Wu, J.-R. Weng, and Q. V. Pham: methodology, analysis, investigation, data curation, and draft preparation. S.-Y. Chien: analysis, investigation. J.-H. Su, J.-H. Sheu, and P.-J. Sung: conceptualization, resources, supervision, project administration, visualization, draft review & editing, and funding acquisition.

Conflicts of interest

The authors declare no conflicts of interest.

Data availability

CCDC 2496063 and 2496064 contain the supplementary crystallographic data for this paper.[27a,b]

The datasets supporting this article are provided in the supplementary information (SI). Supplementary information: the SI includes HRESIMS data, 1D and 2D NMR spectra, and X-ray crystallographic data for compounds **1** and **2**. See DOI: https://doi.org/10.1039/d5ra09073c.

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