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

 Yue-Wen Chuang,^{†ab} Atallah F. Ahmed,^{id}†^{cd} Hsiao-Ling Chung,^{ab} Yueh-Wen Liu,^e Su-Ying Chien,^f Yu-Chi Lin,^{id}^g Chia-Ching Liaw,^{id}^{ghijk} Yu-Jen Wu,^l Jing-Ru Weng,^{id}^a Quoc Vu Pham,^m Jui-Hsin Su,^{id}^{*abn} Jyh-Horng Sheu^{*ao} and Ping-Jyun Sung^{id}^{*abhpqrs}

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 diffraction (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).

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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,

^aDepartment of Marine Biotechnology and Resources, National Sun Yat-sen University, Kaohsiung 804201, Taiwan. E-mail: sheu@mail.nsysu.edu.tw

^bNational Museum of Marine Biology and Aquarium, Pingtung 944401, Taiwan. E-mail: pjsung@nmmba.gov.tw; x2219@nmmba.gov.tw

^cDepartment of Pharmacognosy, College of Pharmacy, King Saud University, Riyadh 11451, Saudi Arabia

^dDepartment of Pharmacognosy, Faculty of Pharmacy, Mansoura University, Mansoura 35516, Egypt

^eDepartment of Cosmetics and Fashion Styling, Cheng Shiu University, Kaohsiung 833301, Taiwan

^fX-Ray Laboratory, The Institute of Chemistry, Academia Sinica, Taipei 115201, Taiwan

^gNational Research Institute of Chinese Medicine, MOHW, Taipei 112026, Taiwan

^hGraduate Institute of Natural Products, Kaohsiung Medical University, Kaohsiung 807378, Taiwan

ⁱDepartment of Pharmacy, College of Pharmaceutical Sciences, National Yang Ming Chian Tung University, Taipei 112304, Taiwan

^jSchool of Chinese Medicine, College of Medicine, National Yang Ming Chian Tung University, Taipei 112304, Taiwan

^kDepartment of Biochemical Science and Technology, National Chiayi University, Chiayi 600355, Taiwan

^lYu Jun Biotechnology Co., Ltd, Donggang, Pingtung 928003, Taiwan

^mGraduate Institute of Pharmacognosy, College of Pharmacy, Taipei Medical University, Taipei 110301, Taiwan

ⁿGraduate Institute of Marine Biology, National Dong Hwa University, Pingtung 944401, Taiwan

^oDepartment of Medical Research, China Medical University Hospital, China Medical University, Taichung 404327, Taiwan

^pChinese Medicine Research and Development Center, China Medical University Hospital, China Medical University, Taichung 404327, Taiwan

^qPhD Program in Pharmaceutical Biotechnology, Fu Jen Catholic University, New Taipei City 242062, Taiwan

^rDepartment of Biochemistry and Molecular Medicine, National Dong Hwa University, Hualien 974301, Taiwan

^sSchool of Medicine, Kaohsiung Medical University, Kaohsiung 807378, Taiwan

† These authors have contributed equally to this work.



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 $1R,2R,7R,8S$ configuration.⁶ However, our SC-XRD analysis, using Cu $K\alpha$ 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 $1R,2R,7S,8R$ (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 stereogenic 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

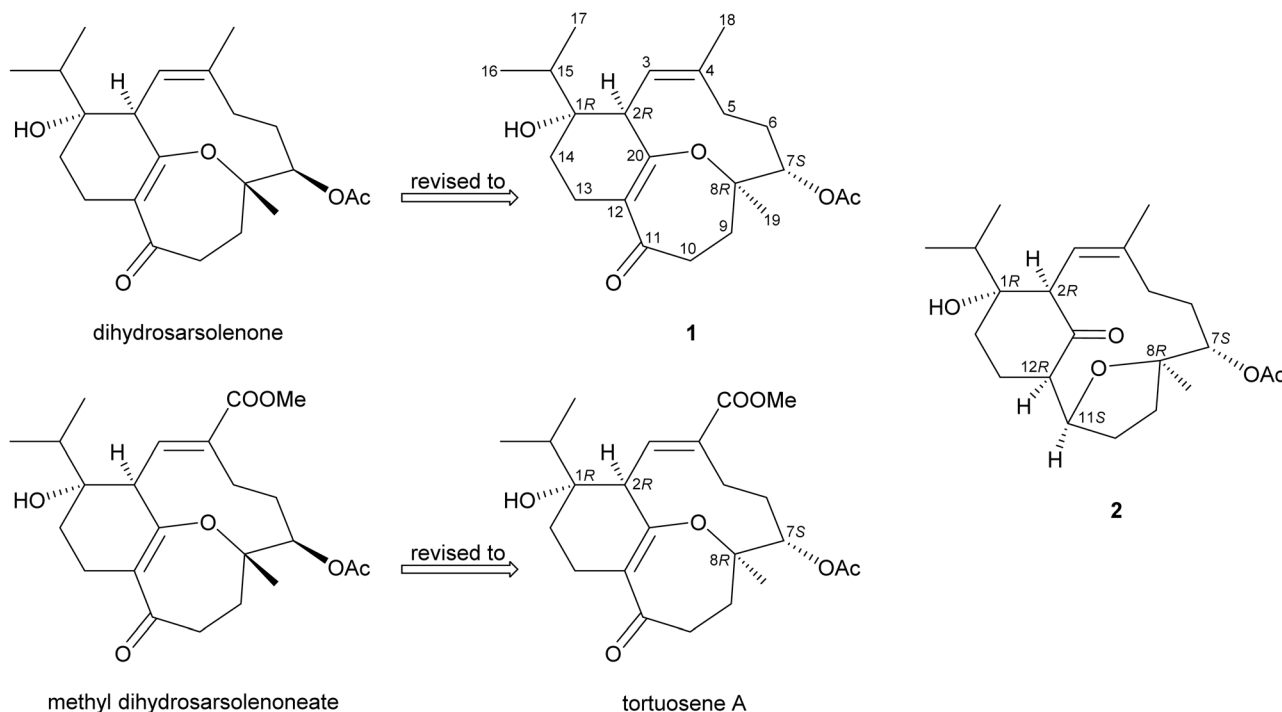
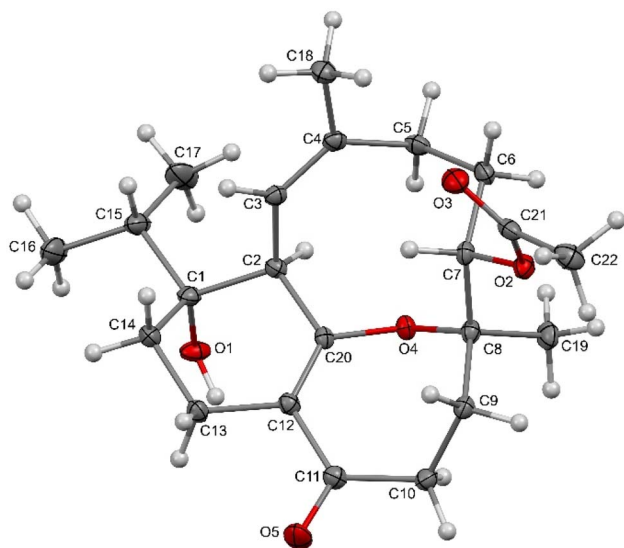


Fig. 1 Structures of dihydrosarsolenone and its revised structure **1**; methyl dihydrosarsolenoneate and its revised structure tortuosene A; and sarcoglaucone A (**2**).

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

Position	Dihydrosarsolenone ^a		1		2	
	$\delta_{\text{H}},^b$ mult (J in Hz)	$\delta_{\text{C}},^c$ type	$\delta_{\text{H}},^b$ mult (J in Hz)	$\delta_{\text{C}},^c$ type	$\delta_{\text{H}},^b$ mult (J in Hz)	$\delta_{\text{C}},^c$ 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
5 α	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						
6 α	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
9 α	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	
10 α	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
13 α	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	
14 α	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 CDCl₃. ^c Spectrum recorded at 100 MHz in CDCl₃. ^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 C₂₂H₃₄O₅ (6 degrees of

unsaturation) by the sodium adduct peak at m/z 401.22986 (calcd for C₂₂H₃₄O₅ + Na, 401.22985) in the (+)-HRESIMS spectrum. Comparison of the ^1H 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 sp² methine carbon at δ_{C} 118.5 (CH-3) and an sp² 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, CH₃-19), a vinyl methyl (δ_{H} 1.80, 3H, d, J = 1.6 Hz/ δ_{C} 24.0, CH₃-18), an isopropyl group (δ_{H} 0.96, 3H, d, J = 6.8 Hz/ δ_{C} 15.3, CH₃-16; δ_{H} 0.81, 3H, d, J = 6.8 Hz/ δ_{C} 15.7, CH₃-17; 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, CH₂-5; δ_{H} 1.57, 1H, m;



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

Position	Methyl dihydrosarsolenoneate ^a		Tortuosene A ^b	
	$\delta_{\text{H}},^c$ mult (J in Hz)	$\delta_{\text{C}},^d$ type	$\delta_{\text{H}},^c$ mult (J in Hz)	$\delta_{\text{C}},^d$ 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
5 α/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
6 α/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
9 α/β	1.62 m; 1.94 m	33.0, CH ₂	1.92 m; 1.60 m	33.0, CH ₂
10 α/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
13 α/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
14 α/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 CDCl₃. ^d Spectrum recorded at 100 MHz in CDCl₃. ^e Attached protons were deduced by DEPT experiment.

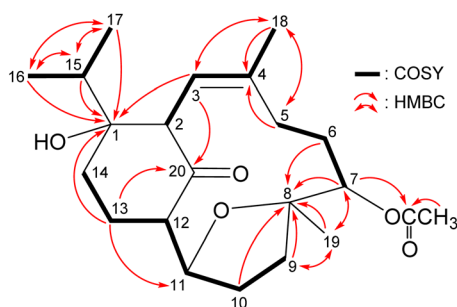


Fig. 3 Key COSY and HMBC correlations of 2.

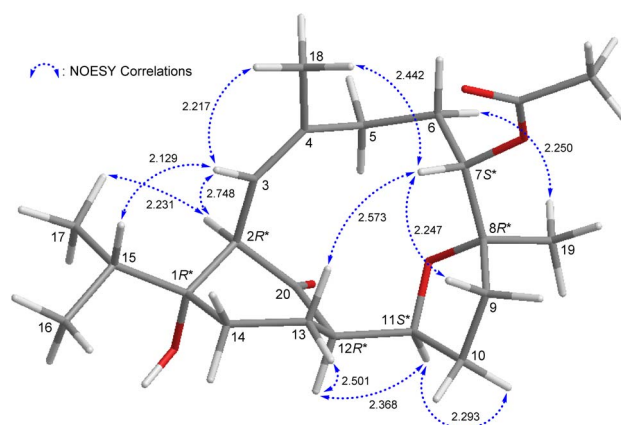


Fig. 4 Stereoview of 2 (from computer modelling) showing key NOESY correlations and selected proton distances (Å).

1.95, 1H, m/δ_{C} 28.6, CH₂-6; δ_{H} 1.98, 1H, m ; 1.62, 1H, m/δ_{C} 38.7, CH₂-9; δ_{H} 2.06, 1H, m ; 1.74, 1H, m/δ_{C} 26.1, CH₂-10; δ_{H} 1.65, 1H, m ; 2.21, 1H, m/δ_{C} 18.0, CH₂-13; δ_{H} 1.98, 1H, m ; 1.67, 1H, m/δ_{C} 32.2, CH₂-14), an aliphatic methine (δ_{H} 3.19, 1H, $br\ s/\delta_{\text{C}}$ 58.1, CH-2), and two oxymethines (δ_{H} 4.67, 1H, $dd, J = 11.2, 1.6\text{ Hz}/\delta_{\text{C}}$ 76.8, CH-7; δ_{H} 5.00, 1H, $ddd, J = 8.8, 5.2, 2.4\text{ Hz}/\delta_{\text{C}}$ 77.8, CH-11) were observed.

The gross structure of 2 was elucidated by 2D NMR analyses. ^1H - ^1H 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, H₂-13, H-15, H₃-16, H₃-17/C-1; H₂-5, H₃-18/C-4; H₂-6, H-7, H₂-9, H₂-10, H₃-19/C-8; and H-3, H₂-13/C-20, defined the major carbon framework of 2. A vinyl methyl at

C-4 was confirmed by an allylic coupling between H₃-18 and H-3 ($J = 1.6\text{ Hz}$) and by HMBC correlations of H₃-18/C-3, C-4, C-5 and H-3, H₂-5/C-18. The ring-junction methyl C-19 was placed at the oxygenated quaternary carbon C-8, as supported by HMBC correlations of H₃-19/C-7, C-8, C-9 and H-7, H₂-9/C-19. The acetate 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



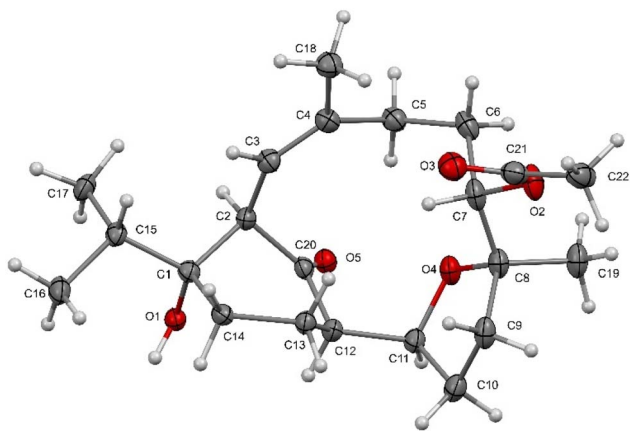


Fig. 5 The computer-generated ORTEP diagram of 2.

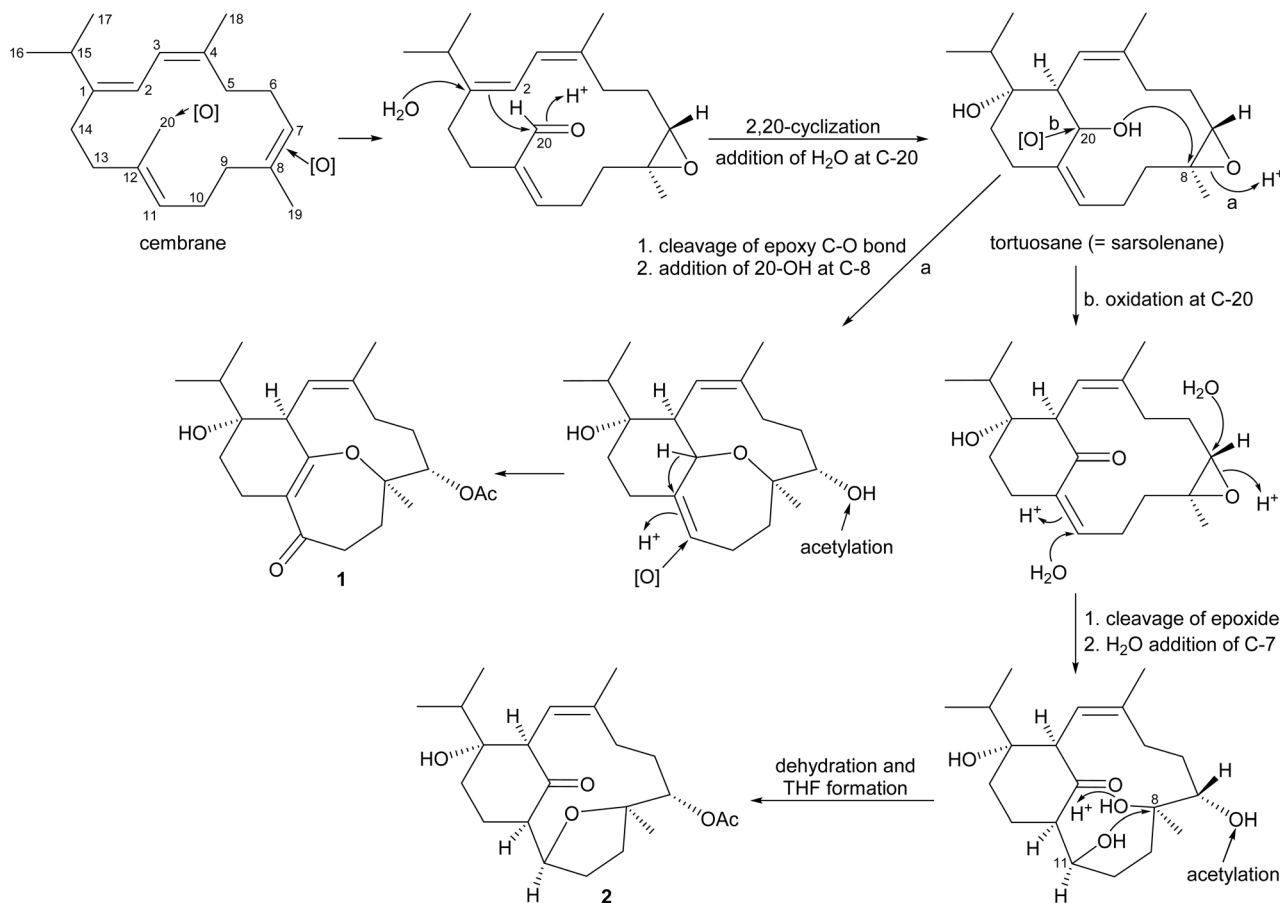
characteristic chemical shifts of the oxymethine CH-11 (δ_{H} 5.00/ δ_{C} 77.8) and the oxygenated quaternary carbon C-8 (δ_{C} 83.6), which together satisfied the remaining degree of unsaturation. Among the five oxygen atoms in the molecular formula, four were assigned to the ketone, ether, and acetoxy groups, leaving a hydroxy group at C-1, supported by HMBC correlations of H-3, H₂-13, H-15, H₃-16, and H₃-17 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 \pm 3.08	100.00 \pm 1.10
1	120.41 \pm 8.44*	94.86 \pm 0.74***
2	110.60 \pm 5.18**	90.63 \pm 0.67***
Rutin ^a	113.64 \pm 7.09***	81.35 \pm 5.17**

^a Rutin (100 μM) was used as the positive control. Results are shown as mean \pm 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-13 α , while the other (δ_{H} 2.21) was designated as H-13 β . The correlation between H-13 β 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 H₃-19 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-6 β . Accordingly, the C-19 methyl group was deduced to be α -oriented. H-2 showed a correlation with H-3 but not with H-13 β , 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 H₃-18. Furthermore, correlations of H-2/H₃-17 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 K α radiation ($\lambda = 1.54178 \text{ \AA}$). 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 $1R^*, 2R^*, 7S^*, 8R^*, 11S^*$, and $12R^*$ (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 cembranoid 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 CHCl₃ (δ_{H} 7.26 ppm) and CDCl₃ signals (δ_{C} 77.0 ppm) as internal standards for ¹H and ¹³C 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/UV₂₅₄, layer thickness 0.20 mm; Macherey-Nagel, Düren, Germany), and visualization of the TLC plates was conducted using an aqueous solution of 10% H₂SO₄, 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–CH₂Cl₂ (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; [α]_D²⁴ + 65 (*c* 0.40, EtOH) ref. 6 [α]_D²³ + 56 (*c* 0.10, EtOH); IR (ATR) ν_{\max} 3415, 1731, 1651 cm^{−1}; ¹H (400 MHz, CDCl₃) and ¹³C NMR (100 MHz, CDCl₃) data see Table 1; ESIMS: *m/z* 399 [M + Na]⁺; HRESIMS: *m/z* 399.21411 (calcd for C₂₂H₃₂O₅ + Na, 399.21420).

4.4.2 Sarcoglaucone A (2). Colorless prisms (MeOH); mp 212–214 °C; [α]_D²⁵ − 15 (*c* 0.15, EtOH); IR (ATR) ν_{\max} 3453, 1737, 1717 cm^{−1}; ¹H (400 MHz, CDCl₃) and ¹³C NMR (100 MHz, CDCl₃) data see Table 1; ESIMS: *m/z* 401 [M + Na]⁺; HRESIMS: *m/z* 401.22986 (calcd for C₂₂H₃₄O₅ + 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 K α radiation (λ = 1.54178 Å). Crystal data for this compound: C₂₂H₃₂O₅ (formula weight 376.47), approximately crystal size, 0.190 × 0.080 × 0.036 mm³, monoclinic system, space group *C2* (#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) Å³, *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 K α radiation (λ = 1.54178 Å). Crystal data for this compound: C₂₂H₃₄O₅ (formula weight 378.49), approximately crystal size, 0.149 × 0.026 × 0.017 mm³, orthorhombic system, space group *P2₁2₁2₁* (#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) Å³, *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 × 10³ cells per well) were seeded in 96-well plates (200 μ L per well) and incubated for 24 h. Cells were then treated with the test compounds (10 μ M) or rutin (100 μ M, 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% CO₂. Cells (1 × 10³ cells per well) were seeded in 96-well plates (200 μ L per well) and incubated for 24 h. The medium was then replaced with fresh medium containing the test compounds (10 μ M) or rutin (100 μ M, positive control), and the cells were further incubated for 72 h. After treatment, 20 μ L 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 μ L 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 \pm 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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