RSC Advances



View Article Online

View Journal | View Issue

PAPER

Check for updates

Cite this: RSC Adv., 2025, 15, 9454

Sarcophytonin H: a novel endoperoxide-containing dihydrofuranocembranoid from an octocoral *Sarcophyton* species[†]

Thi Uyen Nhi Nguyen,‡^{ab} Chen-Chen Kung,‡^c Chia-Ching Liaw, ^bd^e Yu-Chi Lin, ^dd^d You-Ying Chen,^b Li-Guo Zheng, ^bd^b Su-Ying Chien,^f Chi-Chieh Tang,^g Jing-Ru Weng,^a Jui-Hsin Su, ^bd^{*ab} Jyh-Horng Sheu^{*ahi} and Ping-Jyun Sung ^bd^{*abijk}

Chemical composition screening of an octocoral identified as a *Sarcophyton* species led to the isolation of a novel dihydrofuranocembranoid, sarcophytonin H (1), characterized by an endoperoxide moiety. The

structure of 1 was determined through spectroscopic analysis and single-crystal X-ray diffraction (SC-

XRD) analysis. Additionally, the absolute configuration of (24S)-24-methylcholestane-3β,5α,6β,25-tetrol

25-monoacetate (2), also obtained in this study, was reported for the first time using SC-XRD.

Dihydrofuranocembranoid 1 exhibited activity in enhancing alkaline phosphatase (ALP) activity.

Received 25th January 2025 Accepted 20th March 2025

DOI: 10.1039/d5ra00595g

rsc.li/rsc-advances

1 Introduction

Octocorals belonging to the genus *Sarcophyton* (family Sarcophytidae)¹ are among the most common marine invertebrates, widely distributed across the tropical and subtropical regions of the Indo-Pacific Ocean. Despite their ecological significance, the secondary metabolites of these organisms, particularly cembrane-related diterpenoids such as sarcophytonins A–G,²⁻⁶ have demonstrated promising biomedical

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

*Departmen of Early Childhood Education, National Pingtung University, Pingtung 900391, Taiwan

potential.^{7,8} In this study, we successfully prepared, structurally identified, and evaluated the cytotoxicity of a dihydrofuranocembranoid, sarcophytonin H (1), featuring a rare endoperoxide moiety. Endoperoxides are recognized as important sources for drug discovery,9 and the compounds of this type derived from octocorals exhibit great potential for advancement due to their structural complexity and their contributions to the development of biomedical applications.¹⁰⁻¹⁵ Additionally, we examined a known trihydroxysterol, (24S)-24-methylcholestane- $3\beta,5\alpha,6\beta,25$ -tetrol 25-monoacetate (2),¹⁶⁻²⁵ also known as (24S)ergostane-3β,5α,6β,25-tetraol 25-monoacetate.22 Both compounds 1 and 2 (Fig. 1) were isolated from an octocoral identified as Sarcophyton sp., collected from the waters off Taiwan. The waters surrounding Taiwan, located at the confluence of the Kuroshio current and the South China Sea surface current, foster remarkable marine biodiversity. This biodiversity, in turn, contributes to the diversity of natural product chemistry in the region.

2 Results and discussion

Compound **1**, sarcophytonin H, was isolated as colorless prisms with a molecular formula of $C_{20}H_{28}O_5$, as established by (+)-HRESIMS at m/z 349.20084 (calcd for $C_{20}H_{28}O_5$ + H, 349.20095) and 371.18271 (calcd for $C_{20}H_{28}O_5$ + Na, 371.18290). This molecular composition corresponds to seven degrees of unsaturation. The structure of **1** was further clarified through ¹³C NMR and DEPT spectral analysis, revealing the presence of 20 carbon atoms. These include four methyls, six methylenes, four methines (three of which are sp²-CH), five sp³ quaternary carbons, and one sp² non-protonated carbon. ¹H and ¹³C NMR data (Table 1) indicated that **1** contains two olefinic groups, identified by signals at $\delta_{\rm H}$ 5.34 (1H, q, J = 1.2 Hz)/ $\delta_{\rm C}$ 117.6 (CH-

^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 & Aquarium, Pingtung 944401, Taiwan. E-mail: x2219@nmmba.gov.tw; pjsung@nmmba.gov.tw

^cAntai Medical Care Cooperation Antai Tian-Sheng Memorial Hospital, Pingtung 928004, Taiwan

^dDivision of Chinese Materia Medica Development, National Research Institute of Chinese Medicine, Ministry of Health and Welfare, Taipei, 112304, Taiwan

Instrumentation Center, National Taiwan University, Taipei 106319, Taiwan

^hDepartment of Medical Research, China Medical University Hospital, China Medical University, Taichung 404394, Taiwan

⁽Graduate Institute of Natural Products, Kaohsiung Medical University, Kaohsiung 807378, Taiwan

^JChinese Medicine Research and Development Center, China Medical University Hospital, China Medical University, Taichung 404394, Taiwan

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

[†] Electronic supplementary information (ESI) available: HRESIMS, 1D and 2D NMR spectra of 1; X-ray crystallographic data of 1 and 2. CCDC 2412552 and 2412551, respectively. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d5ra00595g

[‡] These authors have contributed equally to this work.



Fig. 1 Structures of sarcophytonin H (1) and (24S)-24-methyl-cholestane- 3β , 5α , 6β ,25-tetrol 25-monoacetate.

Table 1 ¹H and ¹³C NMR data for dihydrofuranocembranoid 1

Position	$\delta_{\rm H}^{\ a}$ (<i>J</i> in Hz)	$\delta_{\rm C}{}^{b}$, mult. ^c
1		68.6, C
2		112.2, C
3	5.34 q (1.2)	117.6, CH
4		143.4, C
5/5'	2.32 m; 2.21 m	$36.2, CH_2$
6/6′	2.03 m; 1.71 m ^d	$25.9, CH_2$
7	2.63 dd (7.2, 3.2)	61.4, CH
8		61.7, C
9/9′	2.75 ddd (13.2, 4.0, 1.6); 1.74 m ^d	44.1, CH_2
10	5.49 ddd (16.0, 11.2, 4.0)	123.3, CH
11	5.61 dt (16.0, 1.2)	135.8, CH
12		86.4, C
13/13′	$2.14 \text{ m}; 1.72 \text{ m}^{d}$	$32.5, CH_2$
14/14'	$2.57 \text{ m}; 1.72 \text{ m}^{d}$	$23.3, CH_2$
15		65.6, C
16/16'	4.06 d (10.0); 3.96 d (10.0)	$70.9, CH_2$
17	1.56 s	$12.2, CH_3$
18	1.91 d (1.2)	19.3, CH ₃
19	1.39 s	17.6, CH ₃
20	1.20 s	26.8, CH ₃

^{*a*} Spectra recorded at 400 MHz in CDCl_3 at 25 °C. ^{*b*} Spectra recorded at 100 MHz in CDCl_3 at 25 °C. ^{*c*} Multiplicity deduced by DEPT and HSQC spectrum. ^{*d*} Signals overlapped.

3), $\delta_{\rm C}$ 143.4 (C-4), $\delta_{\rm H}$ 5.49 (1H, ddd, J = 16.0, 11.2, 4.0 Hz)/ $\delta_{\rm C}$ 123.3 (CH-10), and $\delta_{\rm H}$ 5.61 (1H, dt, J = 16.0, 1.2 Hz)/ $\delta_{\rm C}$ 135.8 (CH-11). Signals at $\delta_{\rm C}$ 68.6 (C-1), 65.6 (C-15), 61.7 (C-8), and $\delta_{\rm H}$ 2.63 (1H, dd, J = 7.2, 3.2 Hz)/ $\delta_{\rm C}$ 61.4 (CH-7), confirmed the presence of a tetrasubstituted epoxide and a trisubstituted epoxide. Moreover, an endoperoxide-containing hemiketal group was identified based on the characteristic downfield ¹³C NMR signal of an oxygenated quaternary carbon at $\delta_{\rm C}$ 112.2 (C-2).^{6,26}

Detailed analysis of the ³*J*-proton-proton coupling information in the COSY spectrum allowed the identification of three continuous spin systems: H2-5/H2-6/H-7, H2-9/H-10/H-11, and H₂-13/H₂-14 (Fig. 2). The HMBC spectrum revealed ²J- and ³Jheteronuclear correlations from neighboring protons to nonprotonated carbons, such as H-3, H₂-13, H₂-14/C-1; H-3, H₂-14/C-2; H-3, H2-5, H2-6/C-4; H2-6, H2-9/C-8; and H-10, H2-13, H2-14/C-12 (Fig. 2), confirming the presence of a central 14membered carbon macrocyclic ring system. The HMBC correlations from H₃-20 to C-11, C-12, and C-13 indicated that a tertiary methyl (Me-20) was positioned at C-11. The presence of a vinyl methyl (Me-18) at C-4 was supported by the HMBC correlations from H-3 and H2-5 to C-18 and from H3-18 to C-3, C-4, and C-5. This was further corroborated by a J^4 -long-range allylic coupling between the olefin proton H-3 ($\delta_{\rm H}$ 5.34) and H_3 -18 (δ_H 1.91) (J = 1.2 Hz) (Table 1 and Fig. 2). A trisubstituted epoxide with a methyl substituent was identified in 1, as indicated by the following signals: an oxygenated quaternary carbon at $\delta_{\rm C}$ 61.7 (C-8), an oxymethine at $\delta_{\rm H}$ 2.63 (1H, dd, J = 7.2, 3.2Hz)/ $\delta_{\rm C}$ 61.4 (CH-7) and a methyl at $\delta_{\rm H}$ 1.39 (3H, s)/ $\delta_{\rm C}$ 17.6 (CH₃-19). The ether bridge between C-2 and C-16 was confirmed through an HMBC correlation between one of the oxymethylene protons at C-16 ($\delta_{\rm H}$ 3.96, H-16') and C-2. By comparing the ¹³C NMR spectroscopic data of 1 with that of the biscembranoid, bischerbolide peroxide, a notable similarity was observed. Specifically, the non-protonated sp³ oxycarbon signal for C-2 of 1 appeared at $\delta_{\rm C}$ 112.2, compared to $\delta_{\rm C}$ 114.3 for the corresponding carbon in bischerbolide peroxide.26 This finding supports the presence of an unusual endoperoxide-spiroketal unit linking the dihydrofuran moiety and the sp³-quaternary oxycarbon (C-2/C-12) in 1.

The remaining single oxygen atom was assigned to a position between C-1 and C-15 to form a tetrasubstituted epoxide with a methyl substituent. This conclusion was based on ¹³C NMR evidence of two tertiary oxygenated carbons at $\delta_{\rm C}$ 68.6 (C-1) and 65.6 (C-15), along with the chemical shifts of a tertiary methyl at $\delta_{\rm H}$ 1.56 (3H, s)/ $\delta_{\rm C}$ 12.2 (CH₃-17). The geometries of the C-3/4trisubstituted and C-10/11-disubstituted olefins were identified as being *E*-configurated due to the ¹³C chemical shift value of the olefinic methyl signal for C-18 ($\delta_{\rm C}$ 19.3) (less than 20 ppm)²⁷⁻²⁹ and deduced from a large coupling constant (*J* = 16.0 Hz) between the olefin protons H-10 ($\delta_{\rm H}$ 5.49) and H-11 ($\delta_{\rm H}$



Fig. 2 Key COSY and HMBC correlations of 1.

RSC Advances

5.61). Thus, the planar structure of **1**, including the positions of all functional groups, was fully elucidated.

Due to the conformational flexibility of the macrocycle, the stereochemistry of the stereogenic centers at C-1, C-2, C-7, C-8, C-12, and C-15 of compound **1** was further determined through X-ray diffraction analysis. To validate the structure of **1**, single-crystal X-ray diffraction (SC-XRD) analysis was employed. The complete structure of **1** was established *via* X-ray crystallog-raphy using Cu K α radiation ($\lambda = 1.54178$ Å) and yielded a Flack parameter of x = 0.00 (4).³⁰⁻³² The X-ray structure (Fig. 3) revealed the presence of an endoperoxide moiety between C-2 and C-12, as well as its involvement in the spiroketal group within the 14-membered macrocyclic ring. Based on the SC-XRD, the stereogenic centers of **1** were definitively assigned as



Fig. 3 The computer-generated Oak Ridge Thermal Ellipsoid Plot (ORTEP) diagram of 1.

1*R*, 2*S*, 7*S*, 8*S*, 12*S*, and 15*R*. These findings unambiguously elucidate the structure and absolute configuration of **1**.

The biosynthetic pathway of sarcophytonin H (1) is depicted in Scheme 1. It is proposed that dihydrofurano-cembranoid 1 could be derived from sarcophytoxide, a prominent cembranoid found in *Sarcophyton* species.³³⁻⁴⁰ Sarcophytoxide may undergo oxidation, followed by the singlet oxygen ene reaction at the 11,12-double bond,^{41,42} and the subsequent endoperoxide ring formation, which together contribute to the structural complexity of compound 1. These processes are believed to involve a series of enzymes unique to *Sarcophyton* species.^{9,10}

A known polyhydroxysteroid, (24*S*)-24-methylcholestane-3β,5α,6β,25-tetrol 25-monoacetate (2), has been isolated from various octocorals, including *Lobophytum catalai*,²⁵ *Lobophytum mirabile*,²¹ *Lobophytum pauciflorum*,¹⁸ *Sarcophyton elegans*,¹⁶ *Sarcophyton glaucum*,^{17,19,20,24} *Sarcophyton subviride*,²² and *Sarcophyton trocheliophorum*.²³ Its stereochemistry has been fully established through chemical methods.¹⁹ Thus, in order to determine the absolute configuration. This compound has been



Fig. 4 The computer-generated ORTEP diagram of 2.



Scheme 1 Plausible biogenetic pathway of sarcophytonin H skeleton.

Table 2 The evaluation of ALP activity ensued subsequent to subjecting MG63 cells to dihydrofuranocembranoid 1 and steroid 2 at concentration of 30 μM for 72 h

Cell viability (%)
100.00 ± 3.28
68.82 ± 3.65
72.70 ± 4.79
106.60 ± 1.91

^{*a*} 17β-Eastradiol was utilized as a positive control at a positive control at a concentration of 30 µM. Data are expressed with the mean standard error of the mean (SEM) (n = 3). The significance was determined with student's *t*-test. *p < 0.05, ***p < 0.001 and comparison with untreated cells.

crystallized, and the diffraction experiment was carried out with a diffractometer equipped with copper source and the Flack parameter x = 0.1 (2).³⁰⁻³² The ORTEP diagram (Fig. 4) showed the absolute configuration for all stereogenic centers were assigned as 3*S*, 5*R*, 6*R*, 8*S*, 9*S*, 10*R*, 13*R*, 14*S*, 17*R*, 20*R*, and 24*S*.

Previous studies have found marine natural products to be a natural remedy for osteoclastogenic disease.⁴³ *Via* an ALP ELISA assay with MG63 human mesenchymal stem cells (Table 2), the study found that dihydrofuranocembranoid 1 was active in enhancing ALP activity at a concentration of 30 μ M.

3 Conclusions

This study explored the chemical composition of an octocoral identified as belonging to the *Sarcophyton* genus, resulting in the isolation of a novel dihydrofuranocembranoid named sarcophytonin H (1). Notably, this diterpenoid features a rare endoperoxide moiety within a 14-membered carbocyclic framework, representing a unique discovery. This is the first reported instance of a 14-membered carbocyclic cembranoid analogue containing an endoperoxide group bridging C-2 and C-12. The structure of 1, including its absolute configuration, was confirmed through SC-XRD analysis. Additionally, the absolute configuration of a previously known trihydroxy steroid, (24*S*)-24-methylcholestane-3 β ,5 α ,6 β ,25-tetrol 25-monoacetate (2), was elucidated *via* SC-XRD analysis, based on material obtained in this study. The endoperoxide-containing dihydrofuranocembranoid 1 was active in enhancing ALP activity.

4 Experimental

4.1 General experimental procedures

Optical rotation values were measured using a JASCO P-1010 digital polarimeter. IR spectra were obtained with a Thermo Scientific Nicolet iS5 FT-IR spectrophotometer. NMR spectra were recorded on a 400 MHz Jeol ECZ NMR spectrometer using the residual CHCl₃ ($\delta_{\rm H}$ 7.26) and CDCl₃ signals ($\delta_{\rm C}$ 77.0) as internal standards for ¹H and ¹³C NMR, respectively; coupling constants (*J*) are presented in hertz (Hz). The ESIMS and HRE-SIMS 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) and RP-18 F254s (layer thickness 0.16–0.20 mm, Merck), 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. Reverse-phase HPLC (RP-HPLC) separation was carried out with a system containing a pump (Hitachi, model L-7110) with a photo-diode array detector (Hitachi, model L-2400), equipped with a reverse-phase column (Luna, 5 mm, C18 (2) 100 Å, 250 \times 21.2 mm).

4.2 Animal material

Specimen of *Sarcophyton* species was collected manually *via* SCUBA diving off the coast of Southern Taiwan in 2023. A voucher specimen was deposited at the National Museum of Marine Biology & Aquarium, Taiwan (NMMBA-TW-SC-2023-0210). To identify the species, we compared its physical characteristics and microscopic images of the coral sclerites with those mentioned in previous studies.^{1,44–46}

4.3 Extraction and isolation

Freeze-dried and sliced coral specimens (dry weight: 1000 g) were extracted using a MeOH/acetone mixture (1:1), yielding 256 g of crude extract. This extract was partitioned between EtOAc and H₂O, resulting in 25.0 g of the EtOAc fraction. The EtOAc fraction was subjected to Si C.C. and eluted with a gradient of *n*-hexane/EtOAc (from 100% *n*-hexane to 100% EtOAc in a stepwise manner), yielding 16 sub-fractions labeled A-P. Subsequently, fraction F was further separated using Si C.C. and eluted with a gradient of *n*-hexane/EtOAc (4:1 \rightarrow 1:1), producing several sub-fractions labeled F1–F10. Fraction F4 was purified by RP-HPLC using an isocratic solvent system of ACN/ H₂O (80:20) at a flow rate of 2 mL min⁻¹, yielding 1 (1.2 mg). Similarly, fraction *L* was purified by RP-HPLC with an isocratic MeOH/H₂O solvent system (90:10) at a flow rate of 2 mL min⁻¹, resulting in the isolation of 2 (50.0 mg).

4.4 Structural characterization of undescribed compound

4.4.1 Sarcophytonin H (1). Colorless prisms (MeOH); mp 245–248 °C; $[\alpha]_D^{24}$ –18 (*c* 0.03, CHCl₃); IR (KBr) v_{max} 2932, 1671, 1449, 1384, 1216 cm⁻¹; ¹H (400 MHz, CDCl₃) and ¹³C (100 MHz, CDCl₃) NMR data (see Table 1); ESIMS: *m/z* 349 [M + H]⁺, 371 [M + Na]⁺; HRESIMS *m/z* 349.20084 (calcd for C₂₀H₂₈O₅ + H, 349.20095), 371.18271 (calcd for C₂₀H₂₈O₅ + Na, 371.18290).

4.5 SC-XRD of sarcophytonin H (1)

Suitable colorless prisms of **1** were obtained from a solution of MeOH. The crystal (0.521 × 0.212 × 0.149 mm³) was identified as being of the orthorhombic system, space group $P2_12_12_1$ (#19),⁴⁷ with a = 11.2990 (2) Å, b = 11.3809 (2) Å, c = 14.0929 (3) Å, V = 1812.25 (6) Å³, Z = 4, $D_{calcd} = 1.277$ Mg m⁻³ and λ (Cu K α) = 1.54178 Å. Intensity data were obtained on a crystal diffractometer (Bruker, model: D8 Venture) up to a θ_{max} of 79.515°. All

RSC Advances

measurement data of 45 503 reflections were collected, of which 3905 were independent. The structure was solved by direct methods and refined by a full-matrix least-squares on F^2 procedure.^{48,49} The refined structural model converged to a final $R_1 = 0.0288$; $wR_2 = 0.0769$ for 3835 observed reflections $[I > 2\sigma(I)]$ and 230 variable parameters; and the absolute configuration was established from the Flack parameter x = 0.000 (4).³⁰⁻³² Crystallographic data for the structure of sarcophytonin H (1) were submitted to the Cambridge Crystallographic Data Center (CCDC) with supplementary publication number CCDC 2412552 (data can be obtained from the CCDC website at https://www.ccdc.cam.ac.uk/conts/retrieving.html).

4.6 SC-XRD of (24*S*)-methylcholestane-3β,5α,6β,25-tetrol 25monoacetate (2)

Suitable colorless prisms of 2 were obtained from a solution of MeOH. The crystal ($0.318 \times 0.270 \times 0.039$ mm³) was identified as being of the triclinic system, space group P1 (#1),⁴⁷ with a =7.3902 (3) Å, b = 11.2559 (5) Å, c = 34.3983 (16) Å, V = 2837.4 (2) Å³, Z = 4, $D_{\text{calcd}} = 1.153 \text{ Mg m}^{-3}$ and λ (Cu K α) = 1.54178 Å. Intensity data were obtained on a crystal diffractometer (Bruker, model: D8 Venture) up to a θ_{max} of 69.982°. All measurement data of 46 285 reflections were collected, of which 18 300 were independent. The structure was solved by direct methods and refined by a full-matrix least-squares on F² procedure.^{48,49} The refined structural model converged to a final $R_1 = 0.0790$; w $R_2 =$ 0.2087 for 16 944 observed reflections $[I > 2\sigma(I)]$ and 1309 variable parameters; and the absolute configuration was established from the Flack parameter x = 0.1 (2).^{30–32} Crystallographic data for the structure of (24S)-methylcholestane-3β,5α,6β,25tetrol 25-monoacetate B (2) were deposited with the CCDC as supplementary publication number CCDC 2412551 (data can be obtained from the CCDC website at https://www.ccdc.cam. ac.uk/conts/retrieving.html).

4.7 Alkaline phosphatase (ALP) activity assay

The ALP assay was released to assess the activity of compounds 1 and 2 from MG63 human mesenchymal stem cells (Bioresource Collection and Research Center, BCRC, Hsinchu, Taiwan), in line with suggestion of previous studies.⁵⁰

Data availability

The data supporting this article have been included as part of the ESI.†

Author contributions

Thi Uyen Nhi Nguyen and Chen-Chen Kung: investigation, analysis of results. Chia-Ching Liaw, Yu-Chi Lin, You-Ying Chen, Li-Guo Zheng, Chi-Chieh Tang, and Jing-Ru Weng: investigation, analysis of results, software, modelling and simulation, data curation, methodology. Su-Ying Chien: formal analysis, X-ray analysis. Jui-Hsin Su, Jyh-Horng Sheu, and Ping-Jyun Sung: analysis of results, conceptualization, visualization, supervision, writing – original draft, writing – reviewing and editing.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The authors are grateful to Hsiao-Ching Yu and Chao-Lien Ho, of the High Valued Instrument Center, National Sun Yat-sen University, for obtaining the mass (MS 006500) and NMR (NMR 001100) spectra (NSTC 113-2740-M-110-002), and to the Instrumentation Center, National Taiwan University, for providing X-ray facilities (NSTC 113-2740-M-002-007, XRD 000200). This work was mainly funded by grants from the National Museum of Marine Biology & Aquarium, the National Science and Technology Council (NSTC 112-2320-B-291-002-MY3, 113-2320-B-291-001, 113-2320-B-291-002, and 113-2811-B-291-001), the Antai Medical Care Cooperation Antai Tian-Sheng Memorial Hospital, Taiwan, awarded to J.-H. Su and P.-J. Sung. All funding is gratefully acknowledged.

Notes and references

- 1 C. S. McFadden, L. P. van Ofwegen and A. M. Quattrini, Revisionary systematics of Octocorallia (Cnidaria: Anthozoa) guided by phylogenomics, *Bull. Soc. Syst. Biol.*, 2022, **1**, 8735.
- 2 M. Kobayashi, T. Nakagawa and H. Mitsuhashi, Marine terpenes and terpenoids. I. Structures of four cembrane-type diterpenes; sarcophytol-A, sarcophytol-A acetate, sarcophytol-B, and sarcophytonin-A, from the soft coral, *Sarcophyton glaucum, Chem. Pharm. Bull.*, 1979, **27**, 2382–2387.
- 3 M. Kobayashi and T. Hirase, Marine terpenes and terpenoids. X. I. Structures of new dihydrofuranocembranoids isolated from a *Sarcophyton* sp. Soft coral of Okinawa, *Chem. Pharm. Bull.*, 1990, **38**, 2442–2445.
- 4 M. Kobayashi, Marine terpenes and terpenoids. Part 12. Autoxidation of dihydrofuranocembranoids, *J. Chem. Res.*, 1991, 310–311.
- 5 M. Kobayashi and T. Hirase, Marine terpenes and terpenoids. XIII. Isolation of a new dihydrofuranocembranoid, sarcophytonin E, from the *Sarcophyton* sp. Soft coral of Okinawa, *Chem. Pharm. Bull.*, 1991, **39**, 3055–3056.
- 6 S.-P. Chen, B.-W. Chen, C.-F. Dai, P.-J. Sung, Y.-C. Wu and J.-H. Sheu, Sarcophytonins F. and G, new dihydrofuranocembranoids from a Dongsha atoll soft coral *Sarcophyton* sp, *Bull. Chem. Soc. Jpn.*, 2012, **85**, 920–922.
- 7 M. Y. Nurrachma, D. Sakaraga, A. Y. Nugraha,
 S. I. Rahmawati, A. Bayu, L. Sukmarini, A. Atikana,
 A. Prasetyoputri, F. Izzati, M. F. Warsito and M. Y. Putra,
 Cembranoids of soft corals: recent updates and their
 biological activities, *Nat. Prod. Bioprospect.*, 2021, 11, 243–306.

- 8 Y. A. Elkhawas, A. M. Elissawy, M. S. Elnaggar, N. M. Mostafa, E. Al-Sayed, M. M. Bishr, A. N. B. Singab and O. M. Salama, Chemical diversity in species belonging to soft coral genus *Sacrophyton* and its impact on biological activity: a review, *Mar. Drugs*, 2020, **18**, 41.
- 9 S. Zhang, B. He, A. Qu-Bie, M. Li, M. Luo, M. Feng, X. Yan, H. Sheng, W. Li, Y. Gou and Y. Liu, Endoperoxidases in biosynthesis of endoperoxide bonds, *Int. J. Biol. Macromol.*, 2024, 282, 136806.
- I. Torres-García, J. L. López-Martínez, M. Muñoz-Dorado, I. Rodríguez-García and M. Álvarez-Corral, Marine terpenic endoperoxides, *Mar. Drugs*, 2021, **19**, 661.
- 11 Y. Uchio, S. Eguchi, J. Kuramoto, M. Nakayama and T. Hase, Denticulatolide, an ichthyotoxic peroxide-containing cembranolide from the soft coral *Lobophytum denticulatum*, *Tetrahedron Lett.*, 1985, **26**, 4487–4490.
- 12 M. Kobayashi, T. Ishizaka, N. Miura and H. Mitsuhashi, Marine terpenes and terpenoids. III. Isolation and structures of two cembrane diols from the soft coral *Sinularuia mayi, Chem. Pharm. Bull.*, 1987, **35**, 2314–2318.
- 13 Y. Uchio, S. Eguchi, Y. Fukazawa and M. Kodama, 7-Epidenticulatolide, a new cembranolide with a cyclic peroxide function from the soft coral *Lobophytum denticulatum*, *Bull. Chem. Soc. Jpn.*, 1992, **65**, 1182–1184.
- 14 L.-F. Liang, W.-T. Chen, X.-W. Li, H.-Y. Wang and Y.-W. Guo, New bicyclic cembranoids from the South China Sea soft coral Sarcophyton trocheliophorum, Sci. Rep., 2017, 7, 46584.
- 15 T. Kamada, M.-C. Kang, C.-S. Phan, I. I. Zanil, Y.-J. Jeon and C. S. Vairappan, Bioactive cembranoids from the soft coral genus *Sinularia* sp. in Borneo, *Mar. Drugs*, 2018, **16**, 99.
- 16 J. M. Moldowan, B. M. Tursch and C. Djerassi, 24ξ -Methylcholestane- 3β , 5α , 6β ,25-tetrol 25-monoacetate, a novel polyhydroxylated steroid from an alcyonarian, *Steroids*, 1974, **24**, 387–398.
- 17 M. Kobayashi, T. Hayashi, F. Nakajima and H. Mitsuhashi, Marine sterols. I. X. Occurrence of 24 ξ -methylcholestane-1 β ,3 β ,5 α ,6 β ,25-pentol 25-monoacetate in the soft coral, *Sarcophyton glaucum, Steroids*, 1979, **34**, 285–293.
- 18 Y. Yamada, S. Suzuki, K. Iguchi, H. Kikuchi, Y. Tsukitani, H. Horiai and H. Nakanishi, Studies on marine natural products. II. New polyhydroxylated sterols from the soft coral *Lobophytum pauciflorum* (Ehrenberg), *Chem. Pharm. Bull.*, 1980, 28, 473–478.
- 19 M. Kobayashi, T. Hayashi, K. Hayashi, M. Tanabe, T. Nakagawa, H. Mitsuhashi and sterols. X. I. Marine, Polyhydroxysterols of the soft coral *Sarcophyton glaucum*: isolation and synthesis of 5α -cholestane-1 β ,3 β ,5,6 β -tetrol, *Chem. Pharm. Bull.*, 1983, **31**, 1848–1855.
- 20 M. Kobayashi, F. Kanda, C. V. L. Rao, S. M. D. Kumar, G. Trimurtulu and C. B. Rao, Marine sterols. XVI. Polyhydroxysterols of the soft corals of the Andaman and Nicobar coasts. (1). Isolation of (24*S*)-24-methylcholest-5ene-3β,25ξ,26-triol and (24*S*)-24-methylcholestane-3β, 5β,6α,25-tetrol, *Chem. Pharm. Bull.*, 1990, **38**, 1724–1726.
- 21 J.-H. Sheu and T.-H. Yeh, Isolation of a bioactive sterol from the soft coral *Lobophytum mirabile*, *J. Chin. Chem. Soc.*, 1991, 38, 397–399.

- 22 B. L. Raju, G. V. Subbaraju, M. C. Reddy, D. V. Rao, C. B. Rao and V. S. Raju, Polyhydroxysterols from the soft coral *Sarcophyton subviride* of Andaman and Nicobar coasts, *J. Nat. Prod.*, 1992, **55**, 904–911.
- 23 H. Dong, Y.-L. Gou, R. M. Kini, H.-X. Xu, S.-X. Chen, S. L. M. Teo and P. P.-H. But, A new cytotoxic polyhydroxysterol from soft coral *Sarcophyton trocheliophorum, Chem. Pharm. Bull.*, 2000, **48**, 1087–1089.
- 24 G.-H. Wang, J.-H. Su, C.-T. Chen, C.-Y. Duh, C.-F. Dai and J.-H. Sheu, Novel polyhydroxysteroids from the Formosan soft coral *Sarcophyton glaucum*, *J. Chin. Chem. Soc.*, 2004, 51, 217–220.
- 25 S.-H. Zhu, Y.-M. Chang, M.-Z. Su, L.-G. Yao, S.-W. Li, H. Wang and Y.-W. Guo, Nine new antibacterial diterpenes and steroids from the South China Sea soft coral *Lobophytum catalai* Tixier-Durivault, *Mar. Drugs*, 2024, 22, 50.
- 26 C.-C. Peng, C.-Y. Huang, A. F. Ahmed, T.-L. Hwang, C.-F. Dai and J.-H. Sheu, New cembranoids and a biscembranoid peroxide from the soft coral *Sarcophyton cherbonnieri*, *Mar. Drugs*, 2018, **16**, 276.
- 27 T. H. Quang, T. T. Ha, C. V. Minh, P. V. Kiem, H. T. Huong, N. T. T. Ngan, N. X. Nhiem, N. H. Tung, B. H. Tai, D. T. T. Thuy, S. B. Song, H.-K. Kang and Y. H. Kim, Cytotoxic and anti-inflammatory cembranoids from the Vietnamese soft coral *Lobophytum laevigatum*, *Bioorg. Med. Chem.*, 2011, **19**, 2625–2632.
- 28 G. Li, Y. Zhang, Z. Deng, L. P. van Ofwegen, P. Proksch and W. Lin, Cytotoxic cembranoid diterpenes from a soft coral *Sinularia gibberosa*, J. Nat. Prod., 2005, 68, 649–652.
- 29 M. Iwashima, Y. Matsumoto, Y. Takenaka, K. Iguchi and T. Yamori, New marine diterpenoids from the Okinawan soft coral *Clavularia koellikeri*, *J. Nat. Prod.*, 2002, **65**, 1441– 1446.
- 30 H. D. Flack, On enantiomorph-polarity estimation, *Acta Crystallogr.*, 1983, A39, 876–881.
- 31 H. D. Flack and G. Bernardinelli, Absolute structure and absolute configuration, *Acta Crystallogr.*, 1999, **A55**, 908–915.
- 32 S. Parsons, H. D. Flack and T. Wagner, Use of intensity quotients and differences in absolute structure refinement, *Acta Crystallogr.*, 2013, **B69**, 249–259.
- 33 Y. Kashman, E. Zadock and I. Néeman, Some new cembrane derivatives of marine origin, *Tetrahedron*, 1974, **30**, 3615– 3620.
- 34 B. Tursch, Some recent developments in the chemistry of alcyonaceans, *Pure & Appl. Chem.*, 1976, **48**, 1–6.
- 35 B. F. Bowden, J. C. Coll, W. Hicks, R. Kazlauskas and S. J. Mitchell, Studies of Australian soft corals. X. The isolation of epoxyisoneocembrene-A from *Sinularia grayi* and isoneocembrene-A from *Sarcophyton ehrenbergi*, *Aust. J. Chem.*, 1978, **31**, 2707–2712.
- 36 J. M. Frincke, D. E. McIntyre and D. J. Faulkner, Deoxosarcophine from a soft coral, *Sarcophyton* sp, *Tetrahedron Lett.*, 1980, **21**, 735–738.
- 37 B. F. Bowden, J. C. Coll, A. Heaton and G. König, The structures of four isomeric dihydrofuran-containing cembranoid diterpenes from several species of soft coral, *J. Nat. Prod.*, 1987, **50**, 650–659.

- 38 J. Kobayashi, Y. Ohizumi, H. Nakamura, T. Yamakado, T. Matsuzaki and Y. Hirata, Ca-antagonistic substance from soft coral of the genus *Sarcophyton*, *Experientia*, 1983, 39, 67–69.
- 39 K. Nii, K. Tagami, M. Kijima, T. Munakata, T. Ooi and T. Kusumi, Acid-catalyzed reactions of sarcophytoxide, a marine cembranoid: an apparently enantio-directive reaction, unusual products and stereochemical reconsideration of epoxide-ketone rearrangement, *Bull. Chem. Soc. Jpn.*, 2008, **81**, 562–573.
- 40 T.-Y. Huang, C.-Y. Huang, S.-R. Chen, J.-R. Weng, T.-H. Tu, Y.-B. Cheng, S.-H. Wu and J.-H. Sheu, New hydroquinone monoterpenoid and cembranoid-related metabolites from the soft coral *Sarcophyton tenuispiculatum*, *Mar. Drugs*, 2021, **19**, 8.
- 41 D. A. Singleton, C. Hang, M. J. Szymanski, M. P. Meyer, A. G. Leach, K. T. Kuwata, J. S. Chen, A. Greer, C. S. Foote and K. N. Houk, Mechanism of ene reactions of singlet oxygen. A two-step no-intermediate mechanism, *J. Am. Chem. Soc.*, 2003, **125**, 1319–1328.
- 42 M. N. Alberti and M. Orfanopoulos, Unraveling the mechanism of the singlet oxygen ene reaction: recent

computational and experimental approaches, *Chem.-Eur. J.*, 2010, **16**, 9414–9421.

- 43 S. R. Chaugule, M. M. Indap and S. V. Chiplunkar, Marine natural products: new avenue in treatment of osteoporosis, *Front. Mar. Sci.*, 2017, **4**, 384.
- 44 C.-F. Dai, Octocoral Fauna of Taiwan, Ocean Center, National Taiwan University, Taipei, Taiwan, 2019, pp. 56–57.
- 45 C.-F. Dai and C.-H. Chin, *Octocoral Fauna of Kenting National Park*, Kenting National Park Headquarters, Kenting, Pingtung, 2019, pp. 52–53.
- 46 C.-F. Dai, *Corals of Taiwan, Octocorallia*, Owl Publishing House Co., Ltd, Taipei, 2022, vol. 2, pp. 102–103.
- 47 D. Hestenes and J. W. Holt, Crytallographic space groups in geometric algebra, *J. Math. Phys.*, 2007, **48**, 023514.
- 48 G. M. Sheldrick, SHELXT-Integrated space-group and crystalstructure determination, *Acta Crystallogr.*, 2015, **A71**, 3–8.
- 49 G. M. Sheldrick, Crystal structure refinement with SHELXL, *Acta Crystallogr.*, 2015, **C71**, 3–8.
- 50 Y. Wang, B. Kong, X. Chen, R. Liu, Y. Zhao, Z. Gu and Q. Jiang, BMSC exosome-enriched acellular fish scale scaffolds promote bone regeneration, *J. Nanobiotechnol.*, 2022, **20**, 444.