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Rumphellclovane A, a novel clovane-related sesquiterpenoid from the gorgonian coral *Rumphella antipathies*

Hsu-Ming Chung [a,b], Yung-Husan Chen [b], Tsong-Long Hwang [c], Li-Fan Chuang [b,d,e], Wei-Hsien Wang [a,b,*], Ping-Jyun Sung [a,b,d,*]

[a] Department of Marine Biotechnology and Resources, Asia-Pacific Ocean Research Center (APORC), National Sun Yat-sen University (NSYSU), Kaohsiung 804, Taiwan
[b] National Museum of Marine Biology and Aquarium (NMMBA), Checheng, Pingtung 944, Taiwan
[c] Graduate Institute of Natural Products, Chang Gung University, Taoyuan 333, Taiwan
[d] Graduate Institute of Marine Biotechnology, Department of Life Science and Graduate Institute of Biotechnology, National Dong Hwa University (NDHU), Checheng, Pingtung 944, Taiwan
[e] Institute of Fisheries Science, National Taiwan University, Taipei 106, Taiwan

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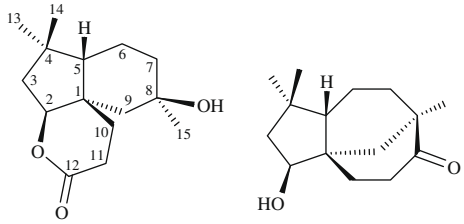
ABSTRACT

A novel clovane-related derivative, rumphellclovane A (**1**), which was found to possess a new carbon skeleton, and a new natural clovane, 2β-hydroxyclovan-9-one (**2**), were isolated from the gorgonian coral *Rumphella antipathies*. The structures of metabolites **1** and **2** were elucidated by spectroscopic analysis and by comparison of the spectral data with those of related clovane analogues. A plausible biosynthetic pathway of **1** was proposed.

Previous chemical investigations on the gorgonian coral *Rumphella antipathies* have yielded a series of interesting caryophyllane-related terpenoid derivatives.[1–9] In our continuing studies on *R. antipathies*, a novel clovane-related sesquiterpenoid derivative, rumphellclovane A (**1**), and a new natural clovane, 2β-hydroxyclovan-9-one (**2**),[10] were isolated. The compounds of clovane-related derivatives exist widely in terrestrial plants,[11] and could be obtained by microbiological transformation;[12] however, in previous studies, clovane-type natural products were shown to be not found in marine organisms. In this report, we wish to describe the isolation, structure characterization, and plausible biosynthetic pathway of **1**, which was found to feature with a new carbon skeleton, along with a new natural clovane 2β-hydroxyclovan-9-one (**2**) from *R. antipathies*.

Sliced boides of *R. antipathies* (wet weight 402 g, dry weight 144 g) were extracted with a mixture of MeOH and CH_2Cl_2 (1:1). The extract was partitioned between EtOAc and H_2O. The EtOAc layer was separated on silica gel and eluted using *n*-hexane/EtOAc (stepwise, 25:1–pure EtOAc) to yield 29 fractions. Fractions 22 and 19 were re-purified by normal-phase HPLC, using the mixtures of CH_2Cl_2 and EtOAc as a mobile phase to afford compounds **1** (2.7 mg, 10:1) and **2** (9.9 mg, 10:1), respectively.



1 **2**

Rumphellclovane A (**1**), $[\alpha]_D^{23}$ +11 (*c* 0.025, $CHCl_3$), was isolated as a colorless oil that gave a molecular ion $[M+Na]^+$ at *m/z* 275.1622 in the HRESIMS, indicating the molecular formula $C_{15}H_{24}O_3$ (calcd for $C_{15}H_{24}O_3Na$, 275.1623) and implying four degrees of unsaturation. IR absorptions were observed at 3453 and 1728 cm^{-1}, suggesting the presence of hydroxy and ester groups in **1**. The ^{13}C NMR and DEPT spectra showed that this compound has 15 carbons (Table 1), including three methyls, six methylenes, two methines (including an oxymethine), and four quaternary carbons (including an oxygenated quaternary carbon and an ester carbonyl). Thus, from the ^{13}C NMR data, a degree of unsaturation was accounted for, and **1** must be tricyclic. The ^1H NMR spectrum of **1** showed that all three methyl groups are isolated. In addition, six pairs of aliphatic methylene

* Corresponding authors. Tel.: +886 8 8825037; fax: +886 8 8825087 (P.-J.S.).
E-mail address: pjsung@nmmba.gov.tw (P.-J. Sung).

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Table 1
^{1}H and ^{13}C NMR data, ^{1}H–^{1}H COSY, and HMBC correlations for **1**

Position	δ_H[a]	δ_C[b]	^{1}H–^{1}H COSY	HMBC (H→C)
1		42.4 (s)[d]		
2	4.34 dd (6.8, 6.8)[c]	89.4 (d)	H_2-3	C-4, -5, -9, -10, -12
3α	2.06 dd (13.6, 6.8)	48.1 (t)	H-2, H-3β	C-1, -2, -4, -5, -13, -14
β	1.65 dd (13.6, 6.8)		H-2, H-3α	C-1, -2, -4, -5, -13, -14
4		39.7 (s)		
5	1.69 m	51.4 (d)	H_2-6	C-1, -2, -4, -6, -7, -9, -13, -14
6α	1.52 m	18.1 (t)	H-5, H-6β, H_2-7	C-1, -4, -5, -7, -8
β	1.87 m		H-5, H-6α, H_2-7	C-4, -8
7α	1.50 m	35.7 (t)	H_2-6, H-7β	C-5, -6, -8, -9, -15
β	1.61 m		H_2-6, H-7α	C-5, -15
8		70.1 (s)		
9α	1.31 d (14.8)	45.9 (t)	H-9β	C-1, -2, -8, -10, -15
β	1.79 d (14.8)		H-9α	C-1, -5, -7, -8, -10, -15
10α	2.21 m	32.4 (t)	H-10β, H_2-11	C-1, -2, -5, -9, -11, -12
β	1.95 m		H-10α, H_2-11	C-1, -2, -5, -9, -11, -12
11	2.39 m (2H)	27.6 (t)	H_2-10	C-1, -10, -12
12		173.7 (s)		
13	0.98 s	26.5 (q)		C-3, -4, -5, -14
14	1.09 s	31.3 (q)		C-3, -4, -5, -13
15	1.25 s	32.9 (q)		C-7, -8, -9

[a] Spectra measured at 400 MHz in $CDCl_3$ at 25 °C.
[b] Spectra measured at 100 MHz in $CDCl_3$ at 25 °C.
[c] *J* values (in hertz) in parentheses.
[d] Attached protons were deduced by DEPT and HMQC experiments.

protons and two aliphatic methine protons were observed in the ^{1}H NMR spectrum of **1** (Table 1).

From the ^{1}H–^{1}H COSY experiment of **1** (Table 1), it was possible to establish the spin systems that map out the proton sequences from H-2/H_2-3 and H-5/H_2-6/H_2-7. Based on these data and the HMBC correlations observed between H-2/C-4, -5, -9; H_2-3/C-1, -2, -4, -5; H-5/C-1, -2, -4, -6, -7, -9; H_2-6/C-1, -4, -5, -7, -8; H_2-7/C-5, -6, -8, -9; and H_2-9/C-1, -2, -5, -7, -8 (Table 1), established the connectivity from C-1 to C-9. The presence of a methyl group attached at C-8, an oxygenated quaternary carbon, was confirmed by the HMBC correlations between H_3-15/C-7, -8, -9; H_2-7/C-15; and H_2-9/C-15. A δ-lactone moiety, which is fused to the five-membered ring at C-1 and C-2, was elucidated by analyzing the HMBC correlations between H-2/C-10, -12; H_2-9/C-10; H_2-10/C-1, -2, -5, -9; and H_2-11/C-1. These data, together with the ^{1}H–^{1}H COSY correlations between H_2-10 and H_2-11 and the HMBC correlations between H_2-10/C-11, -12; H_2-11/C-12; H_2-3/C-13, -14; H-5/C-13, -14; H_3-13/C-3, -4, -5, -14; and H_3-14/C-3, -4, -5, -13, established the planar structure of **1**.

The relative stereochemistry of **1** was elucidated by analysis of a NOESY experiment (Fig. 1). Because of the β-orientation of H-5, and this proton was found to show correlations with H_3-14, one proton of C-6 methylene (δ 1.87), and one proton of C-10 methylene (δ 1.95), suggesting that these protons are located on the same face and could be assigned as β protons. H-2 was found to correlate with H_3-13 and H_2-9, indicating that this proton is α-oriented. Furthermore, H_3-15 exhibited correlations with H_2-7 and H_2-9, but not with H-2, H_2-10, and H_3-13. From consideration of molecular models, H_3-15 was found to be reasonably close to H_2-7 and H_2-9, when H_3-15 was α-oriented in **1** and the cyclohexane ring should be existed in chair form. Based on the above findings, the structure of **1** was established and the configurations of chiral centers of **1** were assigned as 1*S**, 2*S**, 5*S**, 8*R**.

Our present study has also led to the isolation of a new natural clovane **2**.[13] Clovane **2** has the molecular formula $C_{15}H_{24}O_2$ as determined by HRESIMS (*m/z* 259.1672, calcd for $C_{15}H_{24}O_2$ + Na, 259.1674). The IR spectrum of **2** indicated the presence of hydroxy (3349 cm^{-1}) and ketone (1701 cm^{-1}) groups. By detailed analysis, it was found that the spectral data (IR, ^{1}H, and ^{13}C NMR) and specific optical rotation of **2** are identical with those of a known synthetic compound 2β-hydroxylclovan-9-one that was prepared by Kikuchi's group.[10] However, to the best of our knowledge, clovane **2** has not been isolated previously from natural sources.

A plausible biosynthetic pathway for **1** from **2** was proposed as illustrated in Scheme 1. 2-Hydroxyclovan-9-one (**2**) was oxidized to the intermediate **3** by Baeyer–Villiger oxidation. The following

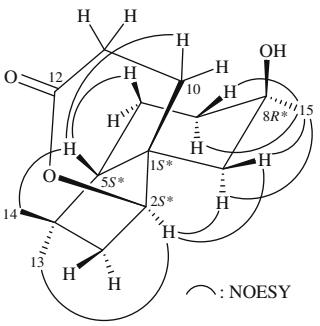
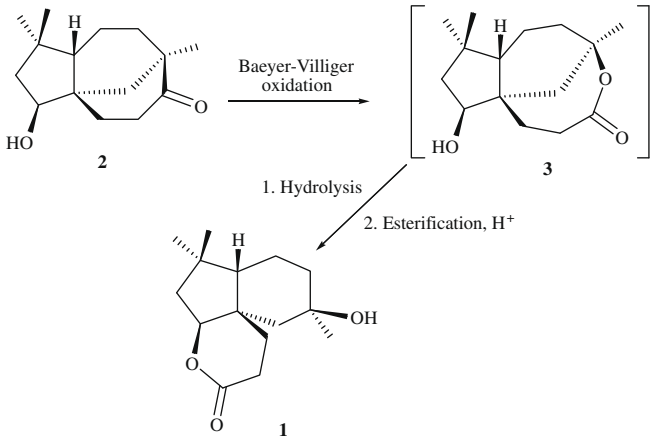


Figure 1. Selective NOESY correlations of **1**.



Scheme 1. Plausible biogenetic relationships for compounds **1** and **2**.

hydrolysis of the ε-lactone, and the subsequent esterification could lead to the formation of **1**. Also, to the best of our knowledge, clovane-type derivative like **1** containing the δ-lactone have not been found previously.

In the biological activity experiment, compounds **1** and **2** displayed 11.8% and 14.8% inhibitory effect on elastase release by human neutrophils at 10 μg/mL, respectively.

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