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Rumphellaone A, a novel caryophyllane-related derivative from the gorgonian coral *Rumphella antipathies*

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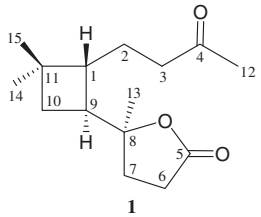
ABSTRACT

A novel 4,5-*seco*-caryophyllane sesquiterpenoid derivative, rumphellaone A (**1**), which was found to possess an unprecedented γ-lactone moiety, was isolated from the gorgonian coral *Rumphella antipathies*. The structure of **1** was elucidated by spectroscopic method. A plausible biosynthetic pathway of compound **1** was proposed.

Previous chemical investigations on gorgonian coral *Rumphella antipathies* have yielded a series of interesting caryophyllane- and clovane-related sesquiterpenoid derivatives, including kobusone,[1] isokobusone,[2] rumphellatins A–D,[3–5] rumphellolides A–I,[6–9] and rumphellclovane A[10] and the compounds of these types are rarely found in marine organisms. In our continuing studies on the chemical constituents of *R. antipathies*, a novel 4,5-*seco*-caryophyllane sesquiterpenoid derivative, rumphellaone A (**1**), was isolated. In this Letter, we describe the isolation, structure characterization, plausible biosynthetic pathway, and bioactivity of compound **1**, which was found to feature with a new carbon skeleton.

Sliced bodies of *R. antipathies* (wet weight 402 g, dry weight 144 g) were extracted with a mixture of MeOH and DCM (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–pureEtOAc) to yield 29 fractions. Fraction 19 was purified by normal-phase HPLC, using the mixtures of DCM and EtOAc as a mobile phase to afford compound **1** (0.9 mg, 10:1).



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Rumphellaone A (**1**), $[\alpha]_D^{25}$ +257 (*c* 0.014, $CHCl_3$), was isolated as a colorless oil that gave a pseudomolecular ion $(M+Na)^+$ at *m*/*z* 275.1622 in the HRESIMS, indicating the molecular formula $C_{15}H_{24}O_3$ (calcd for $C_{15}H_{24}O_3$ + Na, 275.1623) and implying four degrees of unsaturation. IR absorptions were observed at 1714 and 1769 cm^{-1}, suggesting the presence of ketone and γ-lactone groups in **1**. The ^{13}C NMR and DEPT spectra of **1** (Table 1) showed that this compound has 15 carbons, including four methyls, five methylenes, two methines, and four quaternary carbons (including an oxygenated quaternary carbon, an ester carbonyl, and a ketone carbonyl). From the ^{13}C NMR data, two degrees of unsaturation were accounted for and **1** must be a bicyclic compound.

From the ^1H–^1H COSY experiment of **1** (Table 1), it was possible to establish the spin systems that map out the proton sequences from H-1/H_2-2/H_2-3; H_2-6/H_2-7; H-9/H_2-10 and H-1/H-9, which were assembled with the assistance of an HMBC experiment (Table 1). The HMBC correlations between protons and quaternary carbons of **1**, such as H_2-3, H_3-12/C-4; H_2-6, H_2-7/C-5; H-1, H_2-6, H-7β, H-9, H_2-10, H_3-13/C-8; H-1, H_2-10, H_3-14, H_3-15/C-11 permitted elucidation of the main carbon skeleton. The tertiary methyls at C-4 and C-8 were confirmed by the HMBC correlations between H_3-12/C-3, -4 and H_3-13/C-7, -8, -9, respectively. Moreover, two tertiary methyls at C-11 were elucidated by the HMBC correlations between H_3-14/C-1, -10, -11, -15 and H_3-15/C-1, -10, -11, -14. The linkage between the fragments cyclobutane and γ-lactone was established by the HMBC correlations between H-1, H-9, H_2-10/

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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]	COSY	HMBC (H→C)
1	1.91 ddd (10.0, 9.2, 5.6)[c]	44.5 (d)[d]	H_2-2, H-9	C-3, -8, -9, -11, -14, -15
2	1.67 m (2H)	25.1 (t)	H-1, H_2-3	C-1, -9
3	2.37 t (8.0) (2H)	42.0 (t)	H_2-2	C-1, -2, -4
4		208.6 (s)		
5		177.0 (s)		
6α	2.63 ddd (18.0, 9.6, 8.8)	29.2 (t)	H-6β, H_2-7	C-5, -7, -8
β	2.54 ddd (18.0, 10.0, 4.8)		H-6α, H_2-7	C-5, -8
7α	1.84 m	30.6 (t)	H_2-6, H-7β	C-5, -6, -13
β	2.01 m		H_2-6, H-7α	C-5, -8, -9, -13
8		87.2 (s)		
9	2.06 ddd (10.4, 10.0, 10.0)	44.3 (d)	H-1, H_2-10	C-1, -2, -8, -10, -11, -13
10α	1.57 dd (10.0, 10.0)	33.6 (t)	H-9, H-10β	C-1, -8, -9, -11, -14, -15
β	1.42 dd (10.4, 10.0)		H-9, H-10α	C-1, -8, -9, -11, -14, -15
11		33.0 (s)		
12	2.13 s	29.9 (q)		C-3, -4
13	1.31 s	24.9 (q)		C-7, -8, -9
14	1.03 s	22.5 (q)		C-1, -10, -11, -15
15	1.07 s	30.9 (q)		C-1, -10, -11, -14

[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.

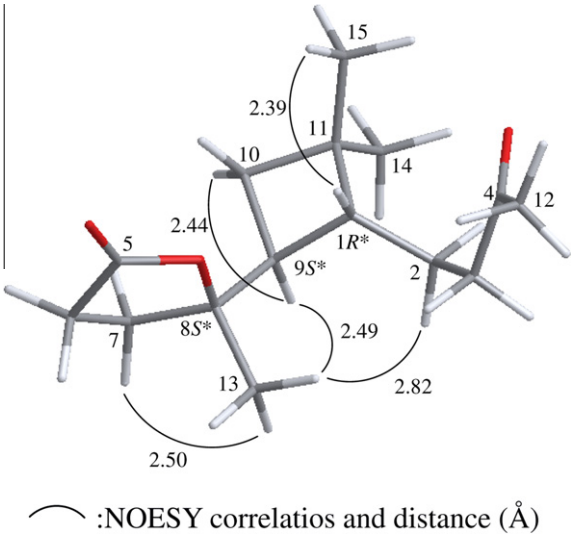
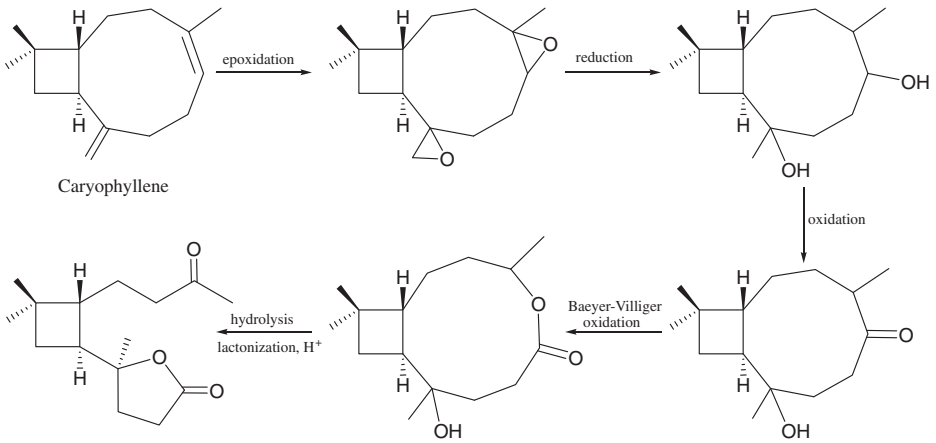


Figure 1. Selective NOESY correlations of **1**.

C-8 and H-1, H-7β, H_3-13/C-9. Based on the consideration of molecular formula, an oxygen atom had to be placed between C-5 and C-8 to form a γ-lactone moiety.

The relative configuration of **1** was established by an analysis of interactions that were found in the NOESY experiment and by vicinal ^{1}H–^{1}H coupling constant analysis. Due to the α-orientation of H-9, a large coupling constant was found between H-9 and H-1 (J = 10.0 Hz), indicating that H-1 has a β-orientation. H-1 showed a correlation with the tertiary methyl Me-15 suggesting that H-1 and H_3-15 are located on the same face. One of the methylene protons at C-10 (δ_H 1.57) exhibited a correlation with H-9 and was assigned as H-10α, while the other was denoted as H-10β (δ_H 1.42). Moreover, Me-13 showed interactions with H-9, one proton of C-7 methylene (δ_H 1.84, H-7α), and C-2 methylene protons (δ_H 1.67). By molecular modeling analysis and minimum energy calculation for compound **1**, all the key correlations and calculated distances between the key protons fit the configuration of **1** as that we presented in Figure 1, indicating that Me-13 was α-oriented at C-8 and the chiral center C-8 existed in S^* configuration. Based on the above findings, the structure of **1** was elucidated and the chiral centers for **1** were assigned as $1R^*$, $8S^*$, and $9S^*$.



Scheme 1. Possible biogenetic pathway for compound **1**.

We also propose a biogenetic pathway to account for the plausible formation of **1** (Scheme 1). Caryophyllene was lactonized to **1** by epoxidation, reduction, oxidation, Baeyer–Villiger oxidation, and esterification reactions. To the best of our knowledge, caryophyllane-type derivatives like **1** containing a γ-lactone moiety have not been found previously. Rumphelloane A (**1**) is also the first 4,5-*seco*-caryophyllane analog.

Compound **1** was found to show moderate cytotoxicity toward CCRF-CEM (human T-cell acute lymphoblastic leukemia) tumor cells (IC_{50} = 12.6 μg/mL).

Acknowledgments

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