Rumphellolide I, a Novel Caryophyllane-related Tetrahydropyran Norsesquiterpenoid from Gorgonian Coral *Rumphella antipathies*

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A novel caryophyllane-related norsesquiterpenoid, rumphellolide I (**1**), which possessing an unprecedented cyclic ether bridge between C-4 and C-8, was isolated from the gorgonian coral *Rumphella antipathies*. The structure of **1** was established by spectral data analysis and this compound showed moderate inhibitory effects on elastase release by human neutrophils.

In our continuing search for bioactive natural products from marine invertebrates collected off Taiwanese waters as part of the National Science and Technology Program for Biotechnology and Pharmaceuticals (NSTPBP), Taiwan,[1] we study the organic extracts from a gorgonian coral *R. antipathies*, in the hope of identifying chemical constituents that exhibit meaningful signals in NMR studies and interesting bioactivity.

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 hexane and 9:1 MeOH–H_2O; the MeOH–H_2O layer was diluted to 1:1 MeOH–H_2O and further partitioned against DCM. The DCM layer was separated on a silica gel column and purified by HPLC to afford **1** (0.9 mg, hexane–acetone, 5:1) (Chart 1).

Rumphellolide I (**1**), $[\alpha]_D^{24}$ −2 ($c = 0.05$, $CHCl_3$), was isolated as a colorless oil that gave a sodiated molecule $[M + Na]^+$ at m/z 261.1470 in the HRESIMS, indicating the molecular formula $C_{14}H_{22}O_3$ (calcd $C_{14}H_{22}O_3$ + Na, 261.1467) and implying four degrees of unsaturation. The presence of hydroxy and ketone groups in **1** was evidenced by IR absorptions at 3431 and 1696 cm^{-1}. The ^{13}C NMR data (Table 1) showed that **1** had a ketone carbonyl group appearing at δ 216.3 (s, C-3), and this compound must be tricyclic to account for the remaining degrees of unsaturation. In addition, the signals for an oxygenated quaternary carbon (δ 85.6, s, C-4), two oxymethines (δ 72.1, d, CH-8; 67.6, d, CH-5) along with ten aliphatic sp^3 signals (a quaternary carbon, four methylenes, two methines, and three methyls) were observed in the ^{13}C NMR spectrum. The ^1H NMR spectrum showed that all three methyls are isolated (δ 1.27, 3H, s, H_3-12; 1.10, 3H, s, H_3-14; 1.07, 3H, s, H_3-13) (Table 1). Moreover, four pairs of aliphatic methylene protons (H-2α/β, H_2-6, H_2-7, and H-10α/β), two aliphatic methine protons (H-1 and H-9), and two oxymethine protons (H-5 and H-8) were observed in the ^1H NMR spectrum of **1**.

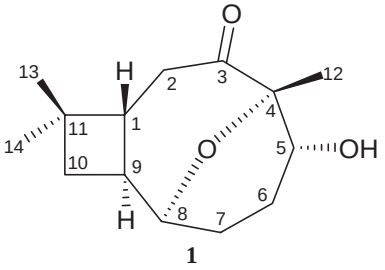

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Chart 1.

Table 1. ^1H and ^{13}C NMR data and HMBC correlations for **1**

C/H	$^1H^a/\delta$	$^{13}C^b/\delta$	HMBC (H→C)
1	1.65 ddd (13.2, 8.4, 1.2)[c]	42.1 (d)[d]	C-3, -8, -9, -11, -13, -14
2α	2.75 dd (13.2, 11.6)	44.8 (t)	C-1, -3, -9
β	2.37 dd (11.6, 1.2)		C-1, -3, -4, -9, -11
3		216.3 (s)	
4		85.6 (s)	
5	4.00 dd (3.2, 3.2)	67.7 (d)	n.o.[e]
6α	1.73 m	26.2 (t)	n.o.
β	1.76 m		C-7
7/7′	2.09 m; 1.60 m	15.8 (t)	C-5, -6, -8, -9
8	4.15 dd (8.8, 4.4)	72.1 (d)	C-1, -4, -6, -7
9	2.52 dddd (10.0, 8.4, 4.4, 3.2)	45.5 (d)	C-1, -7, -8, -10
10α	1.68 dd (10.0, 3.2)	36.4 (t)	C-1, -8, -9, -11, -13, -14
β	1.43 dd (10.0, 10.0)		C-1, -8, -9, -11, -13, -14
11		37.3 (s)	
12	1.27 s	24.0 (q)	C-3, -4, -5
13	1.07 s	30.1 (q)	C-1, -10, -11, -14
14	1.10 s	20.0 (q)	C-1, -10, -11, -13

Spectra recorded at [a]400 and [b]100 MHz in $CDCl_3$ at 25 °C. respectively. [c]J values (in Hz) in parentheses. [d]Multiplicity deduced by DEPT and indicated by usual symbols. [e]n.o. = not observed.

The ^1H NMR coupling information in the ^1H–^1H COSY spectrum of **1** enabled identification of the C1–C2, C5–C6–C7–C8–C9–C10, and C9–C1 units (Figure 1), which were assembled with the assistance of an HMBC experiment (Table 1 and Figure 1). Key HMBC correlations between H-1/C-3, -8, -9, -11; H_2-2/C-1, -3, -4, -9, -11; H_2-6/C-7; H_2-7/C-5, -6, -8, -9; H-8/C-1, -4, -6, -7; H-9/C-1, -7, -8, -10; H_2-10/C-1, -8, -9, -11, established the connectivity from C-1 to C-11. A methyl attached at C-4 was confirmed by the HMBC correlations between H_3-12/C-3, -4, -5. The ketone group positioned at C-3 was deduced by the HMBC correlations between H-1, H_2-2, H_3-12,

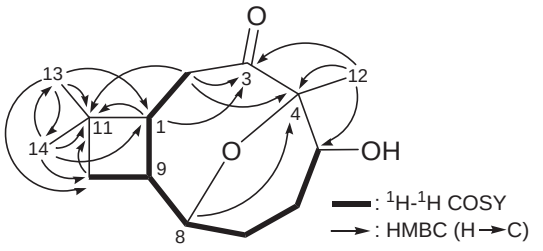

Figure 1. The ^{1}H–^{1}H COSY and selective key HMBC correlations of **1**.

and the C-3 ketone carbonyl (δ 216.3, s). The cyclic ether ring between C-4 and C-8 was established by a key HMBC correlation between the proton of C-8 oxymethine (δ_H 4.15) and the C-4 oxygenated quaternary carbon (δ_C 85.6). Thus, the remaining hydroxy group should be positioned at C-5, an oxygenated methine resonating at δ 67.7 (d), as indicated by key ^{1}H–^{1}H COSY correlations and characteristic NMR signals analysis, although the hydroxy proton for OH-5 was not observed in the ^{1}H NMR spectrum of **1**.

The relative configurations of five chiral centers at C-1, C-4, C-5, C-8, and C-9 in **1** were elucidated by analysis of NOESY interactions (Figure 2) and vicinal ^{1}H–^{1}H coupling constants. The trans geometry of H-1 and H-9 is indicated by an 8.4 Hz coupling constant and no correlation was found between these two ring juncture protons. Thus, H-9 and H-1 were assigned as α- and β-oriented, respectively. It was found that H-9 showed correlations with H-8, one proton of the C-2 methylene, one proton of the C-10 methylene, and H_3-14, but not with H-1, indicating that these protons (H-2α, H-8, H-9, H-10α, and H_3-14) should be positioned on the α-face in **1**. Also, H-5 was found to interact with H-1, H_2-6, and H_3-12; and one proton of the C-6 methylene (δ_H 1.76, H-6β) correlated with H-1, suggesting H-5 and C-12 methyl should be β-oriented and C-12 methyl having an equatorial direction in the tetrahydropyran ring by molecular modeling analysis. A doublet doublet coupling pattern was found between H-5 and H_2-6 (J = 3.2, 3.2 Hz) also supported the observations. Based on the above findings, the structure of **1** was established and the configurations of the chiral centers of **1** were assigned as 1R*, 4R*, 5R*, 8S*, and 9S*.

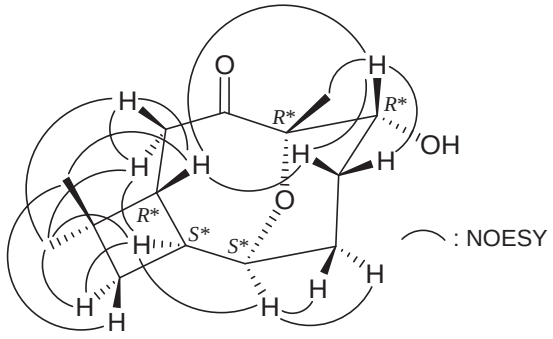

Figure 2. Selective NOESY correlations of **1**.

Previous studies of the chemical constitutens of *R. antipathies* have resulted in isolation of a series of interesting caryophyllane-type natural products.[2] Compounds of this type are rarely found in marine organisms.[3–6] It is worth noting that rumphellolide I (**1**) is the first natural 14C caryophyllane-type norsesquiterpenoid possessing a C-4/C-8 ether bridge moiety (a tetrahydropyran ring) and this compound was found to show 32.3% inhibitory effects on human neutrophil elastase release at 10 μg/mL.

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References and Notes

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