Rumphellatin D, a Novel Chlorinated Caryophyllane from Gorgonian Coral *Rumphella antipathies*

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The first chloride-containing caryophyllane-type sesquiterpenoid, designated as rumphellatin D (**1**), was isolated from gorgonian coral *Rumphella antipathies*. The structure of **1** was established by spectral-data analysis. Rumphellatin D (**1**) showed moderate inhibitory effects on elastase release by human neutrophils.

Previous chemical investigations of gorgonian coral *R. antipathies* have revealed a series of interesting caryophyllane derivatives, including kobusone,[1] isokobusone,[2] rumphellatins A–C,[3,4] and rumphellolides A–G.[5,6] Caryophyllane-type natural products exist widely in terrestrial plants, but are rarely found in marine organisms.[7–9]

We describe herein the isolation, structure determination, and bioactivity of an unprecedented sesquiterpenoid, rumphellatin D (**1**) (Chart 1), a chlorinated caryophyllane, from the further studies of *R. antipathies*.

Sliced bodies 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 hexane and 9:1 MeOH–H_2O; the MeOH–H_2O layer was diluted to 1:1 MeOH–H_2O and further partitioned against CH_2Cl_2. The CH_2Cl_2 layer was separated on a silica gel column and purified by normal phase HPLC to afford **1** (0.9 mg, acetone–hexane, 4:1).

Rumphellatin D (**1**), $[\alpha]_D^{25}$ −4 ($c = 0.05$, $CHCl_3$), was isolated as a colorless oil that gave a sodiated molecule $(M + Na)^+$ at m/z 309.1234 in the HRESIMS, indicating the molecular formula $C_{15}H_{23}{}^{35}ClO_3$ (calcd $C_{15}H_{23}ClO_3 + Na$, 309.1233) and implying four degrees of unsaturation. IR absorptions were observed at 3417 and 1709 cm^{-1}, suggesting the presence of hydroxy and ketone groups in **1**. The ^{13}C NMR and DEPT spectra of **1** (Table 1) showed that this compound has 15 carbons, including three methyls, five sp^3 methylenes (including a chlorinated methylene), three sp^3 methines (including an oxymethine), four quaternary carbons (including two oxygenated quaternary carbons and a ketone carbonyl). Thus, from the ^{13}C NMR data, one degree of unsaturation was accounted for, and **1** must be tricyclic. The presence of an epoxide containing a methyl substituent was confirmed from the signals of two oxygen-bearing carbons at δ 63.3 (s, C-4) and 62.8 (d, CH-3), and further supported by the proton chemical shifts of an oxymethine (δ 3.02, H-3) and a methyl singlet resonating at δ 1.65 (H_3-12). In addition, two germinal methyls, a pair of chlorinated methylene protons, four pairs of aliphatic methylene protons, and two

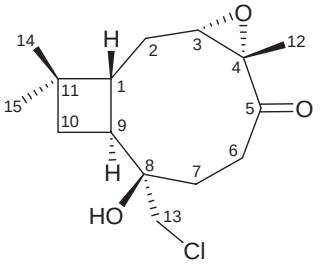

Chart 1.

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	2.20 ddd (12.8, 8.0, 1.6)[c]	40.1 (d)[d]	C-2, -8, -9
2α	1.13 ddd (14.8, 12.8, 9.2)	30.5 (t)	C-3, -4, -9, -11
β	2.15 ddd (14.8, 4.8, 1.6)		C-1, -3, -4, -11
3	3.02 dd (9.2, 4.8)	62.8 (d)	C-2
4		63.3 (s)	
5		206.9 (s)	
6	2.75 m	37.8 (t)	C-5, -7, -8
6′	2.30 m		C-5, -7, -8
7	2.82 dd (9.6, 3.2)	31.5 (t)	C-5, -6, -8, -9
7′	2.38 m		C-5, -6, -8, -13
8		83.1 (s)	
9	1.85 ddd (8.0, 8.0, 8.0)	41.3 (d)	C-1, -2, -8, -10, -13
10α	1.60 dd (10.4, 8.0)	35.3 (t)	C-1 -11, -15
β	1.92 dd (10.4, 8.0)		C-8, -9, -14, -15
11		33.4 (s)	
12	1.65 s	19.4 (q)	C-3, -4, -5
13	3.49 br s (2H)	65.2 (t)	C-7
14	1.04 s	29.1 (q)	C-1, -10, -11, -15
15	0.93 s	23.6 (q)	C-1, -10, -11, -14

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.

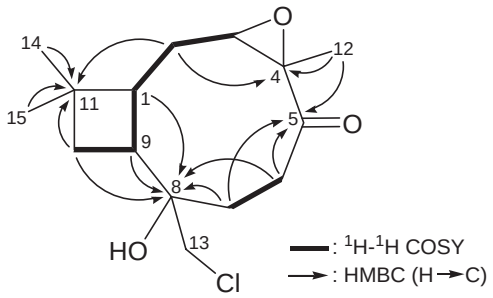

Figure 1. The ^{1}H–^{1}H COSY and selective HMBC correlations (protons and quaternary carbons) of **1**.

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** (Figure 1), it was possible to establish the spin systems that map out the proton sequences from H-1/H_2-2, H_2-2/H-3, H_2-6/H_2-7, H-9/H_2-10, and H-9/H-1. Based on these data and the HMBC correlations observed between H-1/C-2, -8, -9; H_2-2/C-1, -3, -4, -9; H-3/C-2; H_2-6/C-5, -7, -8; H_2-7/C-5, -6, -8, -9; and H-9/C-1, -2, -8 (Figure 1 and Table 1), the connectivity from C-1 to C-9 within the nine-membered ring was established. The presence of a methyl group attached at C-4 was confirmed by the HMBC correlations between H_3-12/C-3, -4, -5. A cyclobutane ring, which is fused to the nine-membered ring at C-1 and C-9, was elucidated by analyzing the HMBC correlations between H_2-2/C-11; H-9/C-10; and H_2-10/C-1, -8, -9. The ketone group positioned at C-5 was confirmed by the HMBC correlations between H_2-6, H_2-7, H_3-12, and the C-5 ketone carbonyl (δ 206.9, s). The methylene unit at δ 65.2 (t) was more shielded than would be expected for an oxygenated C-atom and was correlated to the methylene protons at δ 3.49 (2H, br s) in the HMQC spectrum. The latter methylene signals were ^3J-correlated with C-7 (δ 31.5, t), proving the attachment of a chloromethyl group at C-8 (Figure 1 and Table 1). Thus, the remaining hydroxy group had to be attached at C-8, an oxygenated quaternary carbon resonating at δ 83.1 (s).

The relative stereochemistry of five chiral centers at C-1, -3, -4, -8, and C-9 in **1** was elucidated by analysis of NOESY interactions (Figure 2) and vicinal ^{1}H–^{1}H coupling constants. The trans geometry of H-1 (δ 2.20, ddd, J = 12.8, 8.0, 1.6 Hz) and H-9 (δ 1.85, ddd, J = 8.0, 8.0, 8.0 Hz) is indicated by an 8.0 Hz coupling constant between these two ring juncture protons, and H-9 and H-1 were assigned as α- and β-oriented, respectively. It was found that H-9 showed correlations with H_2-13 but not with H-1, indicating that H_2-13 should be positioned on the α-face as well. A triple doublet coupling was found between H-1/H-9 (J = 8.0 Hz) and H-1/H-2α/β (J = 12.8, 1.6 Hz). By molecular modeling and dihedral angle analysis, the proton chemical shift appearing at δ 1.13 and 2.15 should be assigned as H-2α and H-2β, respectively. Furthermore, the

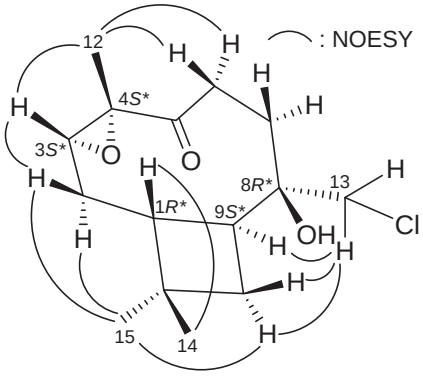

Figure 2. Selective NOESY correlations of **1**.

epoxy proton H-3 was found to interact with H-2β and H_3-12, revealing the cis geometry of trisubstituted epoxy group and this group should be α-oriented in the nine-membered ring. On the basis of the above findings, the structure of **1** was established and the configurations of the chiral centers of **1** were assigned as 1R*, 3S*, 4S*, 8R*, 9S*.

It is worth noting that rumphellatin D (**1**) is the first caryophyllane-type sesquiterpenoid possessing a chloride atom and this compound was found to show 27.2% inhibitory effects on human neutrophil elastase release at 10 μg/mL.

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