Rumphellolide G, a New Caryophyllane-type Tetrahydropyran Norsesquiterpenoid from the Gorgonian Coral *Rumphella antipathies* (Gorgoniidae)

Ping-Jyun Sung,*[1,2] Li-Fan Chuang,[1,2,3] Tung-Yung Fan,[1,4] Hong-Nong Chou,[3] Jimmy Kuo,[1,2] Lee-Shing Fang,[4,5] and Wei-Hsien Wang[1,6]

[1]*National Museum of Marine Biology and Aquarium, Checheng, Pingtung 944, Taiwan*
[2]*Institute of Marine Biotechnology, National Dong Hwa University, Checheng, Pingtung 944, Taiwan*
[3]*Institute of Fisheries Science, National Taiwan University, Taipei 106, Taiwan*
[4]*Institute of Marine Biodiversity and Evolution, National Dong Hwa University, Checheng, Pingtung 944, Taiwan*
[5]*Department of Sport, Health, and Leisure, Cheng Shiu University, Niaosong, Kaohsiung 833, Taiwan*
[6]*Department of Marine Biotechnology and Resources, National Sun Yat-sen University, Kaohsiung 804, Taiwan*

(Received August 6, 2007; CL-070844; E-mail: pjsung@nmmba.gov.tw)

A new caryophyllane-type tetrahydropyran norsesquiterpenoid, rumphellolide G (**1**), has been isolated from the gorgonian coral *Rumphella antipathies*, collected off southern Taiwan coast. The structure of caryophyllane **1** was elucidated by the interpretation of spectral data.

We recently reported several interesting caryophyllane-type natural products featuring with a bicyclo[2.7.0] carbon skeleton, including kobusone,[1] rumphellatin A,[2] and rumphellolides A–F,[3] from the gorgonian coral *Rumphella antipathies* (phylum Cnidaria, order Gorgonacea, family Gorgoniidae).[4] In continuation of our search to exploit structural diversity of Taiwanese marine invertebrates, we have discovered a series of terpenoid derivatives from the octocorals, including *Briareum* sp.,[5] *B. excavatum*,[6] *Ellisella robusta*,[7] *Junceella fragilis*,[8] and *J. juncea*.[8c,9] In this paper, we wish to report the isolation and structure determination of a new caryophyllane-type norsesquiterpenoid with a tetrahydropyran moiety, rumphellolide G (**1**) (Chart 1), from *R. antipathies*. The structure, including the relative configuration for this compound, was elucidated by spectroscopic methods.

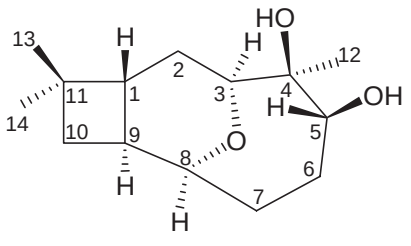
Specimens of the gorgonian coral *R. antipathies* (wet weight 402 g), collected off southern Taiwan coast, were minced and extracted with a mixture of MeOH and CH_2Cl_2 (1:1). The extract was further partitioned between hexane and 9:1 MeOH–H_2O; the MeOH–H_2O layer was diluted to 1:1 MeOH–H_2O and partitioned against CH_2Cl_2. The CH_2Cl_2 layer was separated on silica gel and purified by HPLC to afford norsesquiterpenoid **1** (hexane–acetone, 6:1).

Caryophyllane **1** was obtained as a colorless oil, 2.1 mg, $[\alpha]_D^{25} - 38$ ($c = 0.03$, $CHCl_3$). The molecular formula for metabolite **1** was determined to be $C_{14}H_{24}O_3$ (three degrees of unsaturation) by analysis of ^{1}H and ^{13}C NMR data (Table 1) in conjunction with DEPT results, and this conclusion was further confirmed by HRESIMS ($C_{14}H_{24}O_3$ + Na: m/z found, 263.1625; calcd.: 263.1623). Comparison of the ^{1}H NMR and DEPT data with the molecular formula indicated that there must be two exchangeable protons, requiring the presence of two hydroxy groups and this deduction was supported by a broad absorption in the IR spectrum at 3404 cm^{-1}. From the ^{13}C NMR data of **1**, there are no olefinic carbon and carbonyl groups were observed. Thus, from above observations, rumphellolide G (**1**) must be tricyclic. In the ^{13}C NMR spectrum of **1**, the signals for an oxygen-bearing quaternary carbon (δ 81.9, s, C-4) and three oxymethines (δ 79.0, d, CH-3; 69.8, d, CH-5; 70.6, d, CH-8) were observed, along with ten additional sp^3 signals (a quaternary carbon, two methines, four methylenes, and three methyl groups) in the ^{13}C NMR spectrum. The ^{1}H NMR spectrum showed that all three methyl groups are isolated (δ 1.29, 3H, s, H_3-12; 1.04, 3H, s, H_3-13; 1.03, 3H, s, H_3-14). In addition, four pairs of aliphatic methylene protons (δ 1.56, 1H, m, H-2α; 2.10, 1H, m, H-2β; 1.65, 1H, m, H-6α; 1.71, 1H, m, H-6β; 1.95, 1H, m, H-7α; 1.62, 1H, m, H-7β; 1.49, 1H, dd, $J = 10.4$, 7.6 Hz, H-10α; 1.22, 1H, dd, $J = 10.4$, 10.4 Hz, H-10β), two aliphatic methine protons (δ 2.08, 1H, ddd, $J = 10.8$, 10.8, 7.6 Hz, H-1; 2.21, 1H, dddd, $J = 10.8$, 10.4, 7.6, 4.4 Hz, H-9), three oxygenated methine protons (δ 3.90, 1H, m, H-3; 4.17, 1H, m, H-5; 4.00, 1H, ddd, $J = 10.4$, 4.4, 4,4 Hz, H-8) were observed in the ^{1}H NMR spectrum of **1**.

Table 1. ^{1}H and ^{13}C NMR Data and HMBC Correlations for **1**

C/H	^{1}H[a]	^{13}C[b]	HMBC (H→C)
1	2.08 ddd (10.8, 10.8, 7.6)[c]	39.6 (d)[d]	C-3, 11
2α/β	1.56 m; 2.10 m	34.9 (t)	C-1, 3, 4
3	3.90 m	79.0 (d)	C-1, 4, 5, 8, 12
4		81.9 (s)	
5	4.17 m	69.8 (d)	C-3, 7, 12
6α/β	1.65 m; 1.71 m	24.2 (t)	C-4, 5, 7, 8
7α/β	1.95 m; 1.62 m	21.7 (t)	C-5, 6, 8, 9
8	4.00 ddd (10.4, 4.4, 4.4)	70.6 (d)	C-6, 7
9	2.21 dddd (10.8, 10.4, 7.6, 4.4)	43.0 (d)	C-1
10α	1.49 dd (10.4, 7.6)	35.0 (t)	C-8, 9, 11, 13, 14
β	1.22 dd (10.4, 10.4)		
11		36.4 (s)	
12	1.29 s	23.0 (q)	C-3, 4, 5
13	1.04 s	30.2 (q)	C-1, 10, 11, 14
14	1.03 s	21.1 (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.



Rumphellolide G (**1**)

Chart 1.

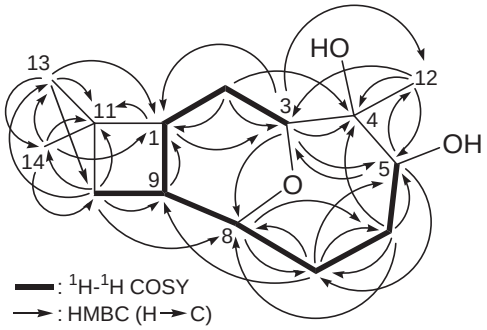


Figure 1. The ^{1}H–^{1}H COSY and HMBC correlations of **1**.

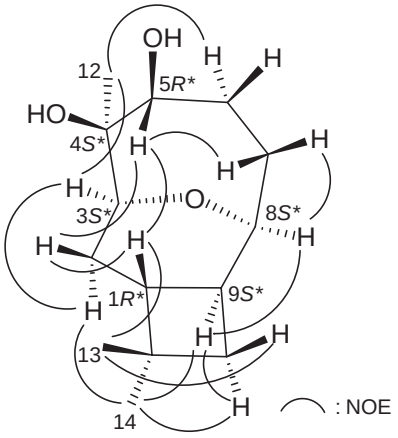


Figure 2. The selective NOESY correlations of **1**.

The gross structure of **1** and all of the ^{1}H and ^{13}C NMR data associated with the molecule was determined by 2D NMR studies, including ^{1}H–^{1}H COSY, HMQC, and HMBC experiments. From the ^{1}H NMR coupling information in the ^{1}H–^{1}H COSY spectrum of **1** enabled identification of the C1–C2–C3, C5–C6–C7–C8–C9–C10, and C9–C1 units (Figure 1). These data, together with the HMBC correlations between H-1/C-3; H_2-2/C-1, C-3, C-4; H-3/C-1, C-4, C-5; H-5/C-3, C-7; H_2-6/C-4, C-5, C-7, C-8; H_2-7/C-5, C-6, C-8, C-9; H-8/C-6, C-7; and H-9/C-1 (Table 1 and Figure 1), established the connectivity from C-1 to C-9 within the nine-membered ring. A methyl attached at C-4 was confirmed by the HMBC correlations between H_3-12/C-3, C-4, C-5, H-3/C-12, and H-5/C-12. The cyclobutane ring, which is fused to the nine-membered ring at C-1 and C-9, was elucidated by the key HMBC correlations between H-1/C-11; and H_2-10/C-8, C-9. The cyclic ether ring between C-3 and C-8 was established by a strong HMBC correlation between the proton of C-3 oxymethine (δ_H 3.90) and the C-8 oxymethine carbon (δ_C 70.6). Thus, the remaining hydroxy groups should be positioned at C-4 and C-5, as indicated by the key ^{1}H–^{1}H COSY correlations and characteristic NMR signals analysis, although the hydroxy protons for OH-4 and OH-5 were not observed in the ^{1}H NMR spectrum of **1**.

The stereochemistry of **1** was elucidated from the NOE interactions observed in an NOESY experiment (Figure 2) and by the vicinal ^{1}H–^{1}H coupling constants. The trans geometry of H-9 (δ 2.21, dddd, J = 10.8, 10.4, 7.6, 4.4 Hz) and H-1 (δ 2.08, ddd, J = 10.8, 10.8, 7.6 Hz) is indicated by a 10.8 Hz coupling constant between these two ring juncture protons, and H-9 and H-1 were assigned as α- and β-oriented protons, respectively, in the structure of **1**. In the NOESY experiment, H-9 exhibited strong NOE correlations with H-8 (δ 4.00), H-10α (δ 1.49), and H_3-14 (δ 1.03), indicating that these protons (H-8, H-9, H-10α, and H_3-14) are located on the same face and assigned as α protons, since H-1 is β-oriented and H-9 did not show correlation with H-1. Furthermore, H-3 showed NOE interactions with one proton of C-2 methylene (δ 1.56, H-2α) and H_3-12 (δ 1.29), but not with H-1; and H-1 exhibited strong NOE response with H-5 (δ 4.17), suggesting the hydroxy groups attached at C-4 and C-5 were placed on the β- and α-orientation of **1**, respectively. On the basis of above findings, the structure including the relative stereochemistry of **1** was established and the configurations of all chiral centers of **1** were assigned as 1*R**, 3*S**, 4*S**, 5*R**, 8*S**, 9*S**.

It is noteworthy to mention that rumphellolide G (**1**) represents the first example of caryophyllane-type natural products possessing a cyclic ether bridge between C-3 and C-8 (a tetrahydropyran ring). The antibacterial activity of **1** toward the Gram-positive bacterium *Staphylococcus aureus* and the Gram-negative bacteria *Escherichia coli* and *Pseudomonoas aeruginosa*, was assayed. It was found that **1** was inactive toward the above bacteria. The other biological activities of **1** will be assayed in the future.

This research work was supported by grants from the funding from the National Museum of Marine Biology and Aquarium and the National Science Council, Taiwan (grant no.: NSC 95-2320-B-291-001-MY2), awarded to P.-J. Sung.

References

1 L.-F. Chuang, T.-Y. Fan, J.-J. Li, P.-J. Sung, *Biochem. Syst. Ecol.* **2007**, *35*, 470.
2 P.-J. Sung, L.-F. Chuang, J. Kuo, T.-Y. Fan, W.-P. Hu, *Tetrahedron Lett.* **2007**, *48*, 3987.
3 P.-J. Sung, L.-F. Chuang, J. Kuo, J.-J. Chen, T.-Y. Fan, J.-J. Li, L.-S. Fang, W.-H. Wang, *Chem. Pharm. Bull.* **2007**, *55*, 1296.
4 F. M. Bayer, *Proc. Biol. Soc. Wash.* **1981**, *94*, 902.
5 P.-J. Sung, W.-P. Hu, L.-S. Fang, T.-Y. Fan, J.-J. Wang, *Nat. Prod. Res.* **2005**, *19*, 689.
6 a) P.-J. Sung, W.-P. Hu, S.-L. Wu, J.-H. Su, L.-S. Fang, J.-J. Wang, J.-H. Sheu, *Tetrahedron* **2004**, *60*, 8975. b) P.-J. Sung, C.-H. Chao, Y.-P. Chen, J.-H. Su, W.-P. Hu, J.-H. Sheu, *Tetrahedron Lett.* **2006**, *47*, 167. c) P.-J. Sung, Y.-P. Chen, T.-L. Hwang, W.-P. Hu, L.-S. Fang, Y.-C. Wu, J.-J. Li, J.-H. Sheu, *Tetrahedron* **2006**, *62*, 5686. d) Y.-P. Chen, S.-L. Wu, J.-H. Su, M.-R. Lin, W.-P. Hu, T.-L. Hwang, J.-H. Sheu, T.-Y. Fan, L.-S. Fang, P.-J. Sung, *Bull. Chem. Soc. Jpn.* **2006**, *79*, 1900.
7 P.-J. Sung, W.-T. Tsai, M. Y. Chiang, Y.-M. Su, J. Kuo, *Tetrahedron* **2007**, *63*, 7582.
8 a) P.-J. Sung, T.-Y. Fan, *Heterocycles* **2003**, *60*, 1199. b) P.-J. Sung, T.-Y. Fan, L.-S. Fang, S.-L. Wu, J.-J. Li, M.-C. Chen, Y.-M. Cheng, G.-H. Wang, *Chem. Pharm. Bull.* **2003**, *51*, 1429. c) P.-J. Sung, T.-Y. Fan, M.-C. Chen, L.-S. Fang, M.-R. Lin, P.-C. Chang, *Biochem. Syst. Ecol.* **2004**, *32*, 111. d) P.-J. Sung, M.-R. Lin, L.-S. Fang, *Chem. Pharm. Bull.* **2004**, *52*, 1504. e) P.-J. Sung, M.-R. Lin, W.-C. Chen, L.-S. Fang, C.-K. Lu, J.-H. Sheu, *Bull. Chem. Soc. Jpn.* **2004**, *77*, 1229. f) J.-H. Sheu, Y.-P. Chen, T.-L. Hwang, M. Y. Chiang, L.-S. Fang, P.-J. Sung, *J. Nat. Prod.* **2006**, *69*, 269. g) P.-J. Sung, L.-S. Fang, Y.-P. Chen, W.-C. Chen, W.-P. Hu, C.-L. Ho, S.-C. Yu, *Biochem. Syst. Ecol.* **2006**, *34*, 64. h) P.-J. Sung, Y.-P. Chen, Y.-M. Su, T.-L. Hwang, W.-P. Hu, T.-Y. Fan, W.-H. Wang, *Bull. Chem. Soc. Jpn.* **2007**, *80*, 1205.
9 P.-J. Sung, T.-Y. Fan, L.-S. Fang, J.-H. Sheu, S.-L. Wu, G.-H. Wang, M.-R. Lin, *Heterocycles* **2003**, *61*, 587.

Published on the web (Advance View) October 6, 2007; doi:10.1246/cl.2007.1322