Novel Caryophyllane-Related Sesquiterpenoids with Anti-Inflammatory Activity from *Rumphella antipathes* (Linnaeus, 1758)

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**Abstract:** Two previously undescribed caryophyllane-related sesquiterpenoids, antipacids A (1) and B (2), with a novel bicyclo[5.2.0] core skeleton, and known compound cleyane-2β,9α-diol (3), along with rumphellolide L (4), an esterified product of 1 and 3, were isolated from the organic extract of octocoral *Rumphella antipathes*. Their structures, including the absolute configurations...
were elucidated by spectroscopic and chemical experiments. In vivo anti-inflammatory activity analysis indicated that antipacid B (2) inhibited the generation of superoxide anions and the release of elastase by human neutrophils, with IC₅₀ values of 11.22 and 23.53 μM, respectively, while rumphellolide L (4) suppressed the release of elastase with an IC₅₀ value of 7.63 μM.

**Keywords:** *Rumphella antipathes*; antipacid; caryophyllane; clovane; rumphellolide; superoxide anion; elastase

1. **Introduction**

*Rumphella* (family Gorgoniidae) is a genus of soft coral consisting of four species, *R. aggregata*, *R. antipathes*, *R. suffrutiicosa*, and *R. torta*, the center of marine diversity of this genus being found in the Indo-Pacific Ocean. Corals were described by Shi-Zhen Li in his ancient herbal Compendium of Chinese Materia Medica, published in 1596, as “sweet, neutral and non-toxic; used to remove eye vision obstruction; clear abiding static blood; blow the powder to nose to stop nose bleeding; brighten the eye and calm the spirit; stop epileptic seizure; apply to the eye to improve floater.” Previous studies showed that the *Rumphella* genus exhibited extensive bioactivities, including antiproliferative [1], cytotoxic [2–4], antifungal [5], antibacterial [6–9], and anti-inflammatory [10–18] activities. Studies of the chemical constituents of octocorals of the *Rumphella* genus have led to the isolation of a series of compounds, including caryophyllanes [2,6–12,16–22], clovanes [13–15,23], steroids [3–5,24,25], glycerols [5], and fatty acids and lipids [25–29]. Our continuing studies of the constituents of the same extract from *R. antipathes* (Figure 1) resulted in the isolation of two novel caryophyllane-related sesquiterpenoids, antipacids A (1) and B (2), featuring a bicyclo[5.2.0] carbon core; a known sesquiterpenoid, clovane-2β,9α-diol (3); and rumphellolide L (4), an esterified product of 1 and 3 (Figure 1). This paper describes the isolation, structure determination, biosynthetic pathway analysis, and anti-inflammatory properties of sesquiterpenoids 1–4.

![Figure 1. Structures of antipacids A (1) and B (2), clovane-2β,9α-diol (3), and rumphellolide L (4), and an image of Rumphella antipathes.](image)

2. **Results and Discussion**

Antipacid A (1) was obtained as a colorless colloid, showing an electrospray ionization mass spectrum (ESIMS) quasimolecular ion peak at *m/z* 253, and was found to have the molecular formula
C_{15}H_{24}O_{3} by analysis of $^{13}$C and $^1$H NMR data (Table 1); this conclusion was confirmed by a positive-mode high-resolution-ESIMS ([+]-HRESIMS) peak at m/z 253.1792 [M + H]$^+$ (calcd. for C_{15}H_{24}O_{3} + H, 253.1789), with four indexes of hydrogen deficiency. The IR spectrum showed absorption bands at 3600–2400 (carboxyl group) and 1708 cm$^{-1}$ (ketonic carbonyl). From the $^{13}$C NMR data of 1 (Table 1), ketonic ($\delta \approx 212.8$, C-4) and carboxyl ($\delta \approx 179.1$, C-5) groups were deemed present. Thus, 1 was identified as a bicyclic compound. $^1$H–$^1$H correlation spectroscopy (COSY) enabled identification of two spin systems, H$_2$-10/H-9/H-1/H$_2$-2/H$_2$-3 and H$_2$-6/H$_2$-7 (Figure 2). These findings, together with the $^1$J$^{'-}$ H and $^3$J$^{'-}$ H–$^{13}$C long-range correlations between protons and non-protonated carbons, such as H$_2$-3, H$_2$-12/C-4; H$_2$-6, H$_2$-7/C-5; H$_2$-6, H$_2$-7, H-9, H-10, H$_2$-12, H$_3$-13/C-8; and H-1, H-10, H$_2$-14, H$_3$-15/C-11 in the heteronuclear multiple-bond coherence (HMBC) experiment (Figure 2), permitted elucidation of the main carbon skeleton of 1.

### Table 1. $^1$H (400 MHz, CDCl$_3$) and $^{13}$C (100 MHz, CDCl$_3$) NMR data of 1 and 2.

|   | 1            | 2            |
|---|--------------|--------------|
| C/H| $\delta$ (J in Hz) | $\delta$ (J in Hz) | $\delta$ (J in Hz) |
| 1  | 1.77 ddd (10.4, 10.4, 3.6) | 45.3, CH | 1.81 ddd (10.8, 10.8, 3.6) | 44.9, CH |
| 2a/b | 1.70 m; 1.64 m | 23.7, CH$_3$ | 1.71 m; 1.62 m | 23.7, CH$_3$ |
| 3a/b | 2.48 m; 2.41 m | 43.8, CH$_3$ | 2.49 m | 43.7, CH$_3$ |
| 4  | - | 212.8, C | - | 212.5, C |
| 5  | - | 179.1, C | - | - |
| 6  | 2.27 m | 29.3, CH$_3$ | - | 176.0, C |
| 7a/b | 1.72 m; 1.53 m | 36.5, CH$_3$ | 2.29 d (13.6); 2.28 d (13.6) | 44.7, CH$_3$ |
| 8  | - | 35.0, C | - | 34.9, C |
| 9  | 1.87 ddd (10.4, 10.4, 8.0) | 46.3, CH | 1.98 ddd (10.8, 10.8, 8.4) | 46.2, CH |
| 10a/b | 1.57 dd (10.4, 8.0); 1.49 dd (10.4, 10.4) | 35.5, CH$_3$ | 1.56 dd (10.8, 8.4); 1.48 dd (10.8, 10.8) | 34.9, CH$_3$ |
| 11 | - | 34.4, C | - | 33.9, C |
| 12a/b | 2.35 d (11.2); 2.30 d (11.2) | 54.8, CH$_3$ | 2.60 d (11.2); 2.49 d (11.2) | 54.1, CH$_3$ |
| 13 | 0.92 s | 20.5, CH$_3$ | 1.08 s | 21.2, CH$_3$ |
| 14 | 1.01 s | 30.1, CH$_3$ | 1.02 s | 30.1, CH$_3$ |
| 15 | 1.01 s | 22.1, CH$_3$ | 1.01 s | 22.1, CH$_3$ |

**Figure 2.** (A) Key COSY (---), HMBC (----), and (B) NOESY (-----) correlations of 1.

The relative configuration of 1 was assigned from the results of a nuclear Overhauser effect spectroscopy (NOESY) experiment (Figure 2) and vicinal coupling constants. The *trans* geometries of H-9 ($\delta$ 1.87) and H-1 ($\delta$ 1.77) were indicated by a large coupling constant ($J = 10.4$ Hz) between these two ring juncture protons, and H-9 and H-1 were $\alpha$- and $\beta$-oriented, respectively. H-1 exhibited a correlation with H$_3$-13, setting Me-13 at C-8 on the $\beta$ face. Based on the above findings, the stereogenic
carbons of 1 were elucidated as (1R*,8S*,9S*). Antipacid A (1) and B (2) were isolated along with natural products rumphellaone A, a novel 4,5-secocaryophyllane [2], and (8R,9R)-isocaryolane-8,9-diol [21,30] (the numbering system used in reference [30] was different to that in this study) from the same target organism, *R. antipathes* [2,21]. The structures, including the absolute configurations, of rumphellaone A [31–33] and (8R,9R)-isocaryolane-8,9-diol [30], were confirmed by synthetic methods. Based on these findings and previous studies [2,6–12,16–22], all marine-origin naturally occurring caryophyllane-type sesquiterpenoids have the H-9 *trans* to H-1, which are assigned as α- and β-oriented, respectively. Therefore, it is reasonable on biogenetic grounds to suggest that 1 and 2 have the same absolute configuration as rumphellaone A and (8R,9R)-isocaryolane-8,9-diol, tentatively, and the configurations of the stereogenic carbons of 1 can be elucidated as (1R,8S,9S) (Supplementary Materials, Figures S1–S7).

Antipacid B (2) was isolated as a colorless colloid that showed a sodiated adduct ion peak in (+)-HRESIMS at *m/z* 261.1468 [M + Na]*, which accounted for the molecular formula, C_{14}H_{22}O_{3} (calcd. for C_{14}H_{22}O_{3} + Na, 261.1467), with 4 degrees of unsaturation. The spectroscopic data of 2 resembled those of 1 (Table 1). The one-dimensional (1D) and two-dimensional (2D) NMR spectra revealed that the signals corresponding to the propanoic acid moiety in 1 were replaced by those of an acetic acid in 2 (Figure 3). Therefore, 2 was assigned as having a structure with the same stereochemistry as 1 because of the stereogenic carbons that 2 had in common with 1 by correlations observed in the NOESY spectrum (Figure 3); therefore, the configurations of the stereogenic carbons of 2 were elucidated as (1R,8S,9S) (Supplementary Materials, Figures S8–S14).

**Figure 3.** Key COSY ( ), HMBC ( ), and NOESY ( ) correlations of 2.

Compound 3 was identified by comparison of its spectroscopic data with those of clovane-2β,9α-diol, which had been previously isolated from terrestrial plants *Dipterocarpus pilosus* [34], *Salvia canariensis* [35], *Viguiera excelsa* [36], *Viguiera linearis* [37], and *Sindora sumatrana* [38]. This was the first occasion in which this metabolite was obtained from a marine source. Clovane 3 was treated with (R)-(−)- and (S)-(−)-MTPA chloride to yield (S)- and (R)-MTPA esters 3a and 3b, respectively. A comparison of the 1H NMR chemical shifts of 3a and 3b (∆δ values shown in Figure 4) led to the assignment of the S-configuration at C-2 (Supplementary Materials, Figures S15–S16). Therefore, the absolute configurations of the stereogenic centers of 3 were determined as (15,25,5S,8R,9R).
Rumphellolide L (4) was isolated as a colorless colloid that showed a sodiated adduct ion peak [M + Na]+ at m/z 495.3447 in (+)-HRESIMS. The result revealed that this compound had a molecular formula of C30H48O4 (calcld. for C30H44O4 + Na, 495.3450), with 7 degrees of unsaturation. Strong bands at 3485, 1731, and 1704 cm⁻¹ in the IR spectrum indicated the presence of hydroxy, ester, and ketonic groups. The ¹³C NMR and distortionless enhancement by polarization transfer (DEPT) spectra revealed that 4 had 30 carbons (Table 2), including six methyls, twelve methylenes, five methines (including two oxymethines), five sp³ quaternary carbons, an ester carbonyl, and a ketonic carbonyl. Therefore, 4 was identified as having five rings.

From the ¹H–¹H COSY spectrum, the data differentiated the spin systems H2-10/H-9/H-1/H-2/H-3, H-6/H-7, H-2'/H-3', H-5'/H-6'/H-7', and H-9'/H-10'/H-11' (Figure 5), and these findings together with the results of key HMBC correlations shown in Figure 5 confirmed the carbon skeleton of 4. An HMBC correlation between H-2' (δH 4.83), an oxymethine proton, and the C-5 ester carbonyl carbon (δC 173.6) was found, which proved the existence of an ester linkage in 4. It was found that the NMR data were similar to those of 1 and 3, and this compound was proven to be the dehydrated product of 1 and 3. Due to the absolute configurations of 1 and 3 having been determined, the absolute configurations of the stereogenic carbons of 4 were assigned as (1R,8S,9S,1'S,2'S,5'S,8'R,9'R) (Supplementary Materials, Figures S17–S23).

Table 2. ¹H (400 MHz, CDCl₃) and ¹³C (100 MHz, CDCl₃) NMR data for 4.

| C/H   | δH (J in Hz) | δC, Type | C/H   | δH (J in Hz) | δC, Type |
|-------|--------------|----------|-------|--------------|----------|
| 1     | 1.77 m       | 45.2, CH | 1     |              | 44.5, C  |
| 2     | 1.64 m       | 23.6, CH₃| 2     | 4.83 dd (8.8, 6.0) | 82.1, CH |
| 3a/b  | 2.48 ddd (12.4, 7.6, 4.0); 2.39 m | 43.7, CH₃| 3'a/b | 1.78 dd (12.0, 6.0); 1.51 m | 44.3, CH₂ |
| 4     | -            | 212.2, C | 4'    | -            | 38.0, C  |
| 5     | -            | 173.6, C | 5'    | 1.48 m       | 50.3, CH |
| 6     | 2.21 t (7.6) | 29.8, CH₂| 6'    | 1.46 m       | 20.8, CH₁ |
| 7     | 1.73 m       | 36.7, CH₂| 7'    | 1.40 m       | 33.0, CH₂ |
| 8     | -            | 35.1, C  | 8'    | -            | 34.6, C  |
| 9     | 1.87 ddd (10.8, 10.8, 8.4) | 46.4, CH | 9'    | 3.31 br s    | 74.9, CH |
| 10    | 1.54 m       | 35.5, CH₂| 10'a/b| 2.00 m; 1.65 m | 26.3, CH₁ |
| 11    | -            | 34.4, C  | 11'   | 1.58 m       | 27.3, CH₂ |
| 12    | 2.31 s       | 54.9, CH₂| 12'a/b| 1.53 m; 1.01 m | 35.4, CH₂ |
| 13    | 0.90 s       | 20.5, CH₃| 13'   | 1.05 s       | 31.4, CH₃ |
| 14    | 1.02 s       | 30.1, CH₃| 14'   | 0.91 s       | 25.3, CH₂ |
| 15    | 1.00 s       | 22.1, CH₃| 15'   | 0.94 s       | 28.2, CH₂ |
The proposed biogenetic pathway of sesquiterpenoids 1–4 is outlined in Scheme 1. The ring-opening reaction might be rationally derived from (8R,9R)-isocaryolane-8,9-diol [30] (the numbering system used in reference [30] was different to that in this study), which had also been isolated from R. antipathes [21], and might subsequently, under oxidation, produce the carbon skeletons of 1 and 2.

The in vitro anti-inflammatory effects of 1–4 were assessed (Table 3). Antipacid B (2) displayed inhibitory effects on the generation of superoxide anions and the release of elastase by human neutrophils (IC50 = 11.22 and 23.53 μM, respectively). Antipacid A (1) did not show activity, implying that the presence of a large substituent at C-8 weakens the activity in comparison with the structure and anti-inflammatory activities of 2. Although 1 and 3 were not active, rumphellolide L (4), the dehydrated product of 1 and 3 with esterification, showed activity in inhibiting the release of elastase (IC50 = 7.63 μM).
Table 3. Inhibitory effects of sesquiterpenoids 1–4 on superoxide anion generation and elastase release by human neutrophils in response to N-Formyl-t-methionyl-t-leucyl-t-phenylalanine/Cytochalasin B (fMLF/CB).

| Compound | IC50 (μM) | Inh % | IC50 (μM) | Inh % |
|----------|-----------|-------|-----------|-------|
| 1        | -         | 11.89 ± 5.13 | - | 13.69 ± 2.33 * |
| 2        | 11.22     | -     | 23.53 | - |
| 3        | -         | 22.92 ± 4.27 * | - | 35.33 ± 6.40 * |
| 4        | -         | 19.57 ± 3.69 ** | 7.63 | - |

* Concentration necessary for 50% inhibition (IC50). b Percentage of inhibition (Inh %) at 10 μg/mL. Results are presented as means ± S.E.M (standard error of the mean) (n = 3). * p < 0.05, ** p < 0.01 compared with the control (solvent, dimethyl sulfoxide-DMSO).

3. Materials and Methods

3.1. General Experimental Procedures

Optical rotations were recorded on a JASCO-P1010 polarimeter (Japan Spectroscopic Corporation, Tokyo, Japan). IR spectra were obtained on a Varian Diglab FTS 1000 FT-IR spectrometer (Varian Inc., Palo Alto, CA, USA). NMR spectra were recorded on a Varian Mercury Plus 400 spectrometer (400 MHz for 1H and 100 MHz for 13C) (Varian Inc.) using the residual CHCl3 (δH 7.26 ppm) and CDCl3 (δC 77.1 ppm) signals as internal references for 1H and 13C NMR, respectively.

Chemical shifts are shown in δ (ppm) and coupling constants (J) are given in Hz. ESIMS and HRESIMS data were recorded using a Bruker APEX II FTMS system (Bremen, Germany). Silica gel (230–400 mesh, Merck, Darmstadt, Germany) was used for column chromatography. Thin-layer chromatography (TLC) was performed on plates precoated with Kieselgel 60 F254 (0.25-mm-thick, Merck), then sprayed with 10% H2SO4 solution followed by heating to visualize the spots. Normal-phase HPLC (NP-HPLC) (Hitachi L-7100 series using a L-7455 photodiode array detector, Hitachi Ltd., Tokyo, Japan; and a semi-preparative Hibar 250 mm × 10 mm, LiChrospher Si 60, 5 μm column, Merck) was employed.

3.2. Animal Material

The octocoral _R. antipathes_ (Linnaeus, 1758) was collected by hand by self-contained underwater breathing apparatus (SCUBA) divers off the coast of South Taiwan in May 2004. The samples were stored in a −20 °C freezer until used for extraction. Identification of the species of this organism was performed by comparison as described in previous studies [39,40]. A voucher specimen (no.: NMMA-TWGC-010) was deposited in the National Museum of Marine Biology and Aquarium, Taiwan.

3.3. Extraction and Isolation

_R. antipathes_ (wet/dry weight = 402/144 g) was sliced and then extracted with a solvent mixture of MeOH and dichloromethane (DCM) (1:1). The extract was partitioned between ethyl acetate (EtOAc) and H2O. The EtOAc layer (1.23 g) was then applied on silica gel column and eluted with gradients of hexanes/EtOAc (from 25:1 to 100% EtOAc) to furnish 29 subfractions. Fraction 18 was purified by NP-HPLC using a solvent mixture of n-hexane/EtOAc (5:1; at a flow rate = 3.0 mL/min) to yield 4 (3.5 mg, 5:1). Fraction 22 was separated by NP-HPLC using a mixture of DCM and EtOAc (10:1; at a flow rate = 5.0 mL/min) to afford 2 (3.5 mg). Fraction 24 was separated by NP-HPLC using a mixture of n-hexane and EtOAc (1:1; at a flow rate = 5.0 mL/min) to afford 1 (5.8 mg) and 3 (60.1 mg), respectively.

_Antipacid A_ (1): Colorless colloid; [α]D20 = −9.2 (c 0.29, CHCl3); IR (neat) νmax 3600–2400 (broad), 1708 cm⁻¹; 1H and 13C NMR data, see Table 1; ESIMS: m/z 253 [M + H]+; HRESIMS: m/z 253.1792 [M + H]+ (calcld. for C15H24O3 + H, 253.1789).

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Antipacid B (2): Colorless colloid; [α]_25° = −9.4 (c 0.18, CHCl3); IR (neat) ν_max 3600–2600 (broad), 1710 cm⁻¹; ¹H and ¹³C NMR data, see Table 1; ESIMS: m/z 261 [M + Na]+; HRESIMS: m/z 261.1468 [M + Na]+ (calcd. for C₁₂H₂₆O₆ + Na, 261.1467).

Clovane-2β,9α-diol (3): Amorphous powder; [α]_25° = +3.5 (c 1.82, CHCl3) (ref. [38] [α]_25° = +3.19 (c 2.27, CHCl3)); IR (neat) ν_max 3378 cm⁻¹; ¹H (400 MHz, CDCl3) and ¹³C (100 MHz, CDCl3) NMR data were found to be in complete agreement with a previous report [37]; ESIMS: m/z 261 [M + Na]+.

Rumphellolide L (4): Colorless colloid; [α]_25° = −7.5 (c 0.18, CHCl3); IR (neat) ν_max 3485, 1731, 1704 cm⁻¹; ¹H and ¹³C NMR data, see Table 2; ESIMS: m/z 495 [M + Na]+; HRESIMS: m/z 495.3447 [M + Na]+ (calcd. for C₉H₆O₆ + Na, 495.3450).

3.4. (S)- and (R)-MTPA Esters of 3

To a solution of 3 (10.0 mg) in pyridine (0.4 mL) (−)-α-methoxy-α-(trifluoromethyl)-phenylacetyl (MTPA) chloride was added (25.0 µL) at 25 °C for 4–5 h. The mixture was dried and purified by a silica gel column with n-hexane/EtOAc (10:1) to give (S)-MTPA ester 3α (8.5 mg). The (R)-MTPA ester 3b (0.2 mg) was prepared from (+)-MTPA chloride by the same method (10 mg compound 3 was used). Selected ΔΔ values are shown in Figure 4.

3.5. Superoxide Anion Generation and Elastase Release by Human Neutrophils

The proinflammatory suppression assay was employed to assess the activities of isolated compounds 1–4 against the generation of superoxide anions and the release of elastase by human neutrophils according to the protocols described in the literature [41].

4. Conclusions

The current work illustrated the anti-neutrophilic inflammatory properties of caryophyllane-related sesquiterpenoids, and two metabolites with novel structures, antipacids A and B (1 and 2), clovane-2β,9α-diol (3), and rumphellolide L (4), an esterified product of 1 and 3, were isolated from R. antipathes. Compound 2 displayed inhibitory effects on the generation of superoxide anions and the release of elastase, and 4 showed activity in suppressing the release of elastase. These results indicated a structural-dependent specificity of C-8 in 1, 2, and 4 in neutrophilic targets, which will motivate future research examining this specificity, as well as clarify the mechanisms of the active leads.

Supplementary Materials: The following are available online at www.mdpi.com/1660-3397/18/11/554/s1, Figure S1: HRESIMS spectrum of 1; Figures S2–S7: ¹H NMR (400 MHz), ¹³C NMR (100 MHz), HMQC, ¹H−¹H COSY, HMBC and NOESY Spectrum of 1 in CDCl₃; Figure S8: HRESIMS spectrum of 2; Figures S9–S14: ¹H NMR (400 MHz), ¹³C NMR (100 MHz), HMQC, ¹H−¹H COSY, HMBC and NOESY Spectrum of 2 in CDCl₃; Figure S15: ¹H NMR (S)-MTPA ester of 3 in CDCl₃; Figure S16: ¹H NMR (R)-MTPA ester of 3 in CDCl₃; Figure S17: HRESIMS spectrum of 4; Figures S18–S23: ¹H NMR (400 MHz), ¹³C NMR (100 MHz), HMQC, ¹H−¹H COSY, HMBC and NOESY Spectrum of 4 in CDCl₃.

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