Excavatoids E and F: Discovery of Two New Briaranes from the Cultured Octocoral *Briareum excavatum*

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**Abstract:** Two new briarane-related diterpenoids, designated as excavatoids E (1) and F (2), were isolated from the cultured octocoral *Briareum excavatum*. The structures of compounds 1 and 2 were established on the basis of extensive spectral data analysis. Briaranes 1 and 2 were found to exhibit moderate inhibitory effects on elastase release by human neutrophils.

**Keywords:** excavatoid; briarane; octocoral; *Briareum excavatum*; human neutrophil

**1. Introduction**

In our continuing research on chemical constituents of marine invertebrates collected in Taiwan waters, a series of interesting and complex briarane-type diterpenoid derivatives (3,8-cyclized...
cembranoids), have been isolated from the octocorals belonging to the genus *Briareum* [1–21], *Ellisella* [18,22–25], and *Junceella* [16,26–38], and the compounds of this type were proven to possess various interesting bioactivities [39–41]. Because of its interesting and potential chemical constituents and a series of new briarane metabolites, including briaexcavatins I-Z [16–20] and excavatoids A-D [21] (Figure 1), the octocoral *B. excavatum* was transplanted to the National Museum of Marine Biology & Aquarium (NMMBA), Taiwan. We report herein the isolation, structure determination, and bioactivity of two new briaranes, excavatoids E (1) and F (2) (Figure 2), resulting from further studies on the chemical constituents of cultured *B. excavatum*. The structures of compounds 1 and 2 were established by extensive spectroscopic methods and these two metabolites have displayed moderate inhibitory effects on elastase release by human neutrophils.

![Figure 1. The Structures of Excavatoids A-D.](image)

![Figure 2. The Structures of Excavatoids E (1) and F (2).](image)

2. Results and Discussion

Excavatoid E (1) was obtained as a white powder and the molecular formula of 1 was determined to be C_{28}H_{38}O_{9} by analysis of 13C- and 1H-NMR data, in conjunction with DEPT results (Table 1); this conclusion was further confirmed by HRESIMS with m/z 541.2415 (calcd. for C_{28}H_{38}O_{9}Na, 541.2413). This showed that 1 contained 10 degrees of unsaturation. Comparison of the 1H and DEPT data with the molecular formula indicated that there must be an exchangeable proton, requiring the presence of a hydroxy group, and this deduction was supported by a broad band in the IR spectrum at 3,463 cm\(^{-1}\). The IR absorptions of 1 also showed the presence of α,β-unsaturated γ-lactone (1,743 cm\(^{-1}\)) and ester (1,740 cm\(^{-1}\)) groups. From the 13C-NMR spectrum (Table 1), compound 1 was found to possess an n-butyryloxy group (δC: 13.6, q; 18.0, t; 35.9, t; 172.3, s); two acetoxy groups (δC: 21.2, q; 20.9, q;
a γ-lactone moiety (δC 173.9, s, C-19), a tetrasubstituted olefin (δC 160.8, s, C-8; 127.6, s, C-17), and two disubstituted olefins (δC 141.9, s, C-5; 123.9, d, CH-6; 130.5, s, C-11; 123.4, d, CH-12). Thus, from the above data, seven degrees of unsaturation were accounted for, and compound 1 must be tricyclic.

### Table 1. $^1$H and $^{13}$C-NMR data for Diterpenoids 1 and 2.

| Position | $^1$H$^a$ | $^{13}$C$^b$ | $^1$H$^a$ | $^{13}$C$^b$ |
|----------|-----------|-------------|-----------|-------------|
| 1        | 41.7 (s)$^d$ |            |           | 46.3 (s)    |
| 2        | 5.45 d (2.4)$^c$ | 74.9 (d) | 5.03 d (7.2) | 75.3 (d)    |
| 3α       | 4.98 dd (6.0, 2.4) | 72.2 (d) | 1.69 m | 32.5 (t)    |
| β        | 2.04 d (15.6) | 34.4 (t) | 1.97 m | 28.7 (t)    |
| 4α       | 3.46 dd (15.6, 6.0) |          | 2.50 m |            |
| 5        | 141.9 (s) |            |           | 146.2 (s)   |
| 6        | 5.21 d (8.8) | 123.9 (d) | 5.25 d (9.2) | 117.6 (d)   |
| 7        | 6.07 d (8.8) | 79.2 (d) | 5.32 d (9.2) | 74.9 (d)    |
| 8        | 160.8 (s) |            |           | 70.6 (s)    |
| 9        | 4.98 br s | 68.4 (d) | 5.86 d (2.0) | 67.8 (d)    |
| 10       | 3.25 br s | 45.2 (d) | 2.20 d (2.0) | 47.8 (d)    |
| 11       | 130.5 (s) |            |           | 75.7 (s)    |
| 12       | 5.58 br s | 123.4 (d) | 4.90 dd (11.6, 5.2) | 73.1 (d) |
| 13α      | 2.15 m | 28.0 (t) | 1.89–1.97 m (2H) | 25.6 (t) |
| β        | 2.57 br d (18.4) |          |           |            |
| 14       | 5.08 dd (6.0, 6.0) | 75.6 (d) | 4.87 dd (4.8, 2.0) | 75.6 (d) |
| 15       | 1.36 s | 16.7 (q) | 1.30 s | 15.6 (q)    |
| 16       | 1.85 s | 23.0 (q) | 2.02 s | 27.0 (q)    |
| 17       | 127.6 (s) |          |           | 64.5 (s)    |
| 18       | 2.01 s | 10.2 (q) | 1.73 s | 10.3 (q)    |
| 19       | 173.9 (s) |          |           | 170.9 (s)   |
| 20       | 1.64 s | 22.1 (q) | 1.24 s | 27.9 (q)    |
| 2-OAc    | 169.1 (s) |          |           | 170.5 (s)   |
| 9-OAc    | 2.12 s | 20.9 (q) | 2.00 s | 21.3 (q)    |
| 12-OAc   |            |          |           | 168.1 (s)   |
| 14-OAc   |            |          |           | 21.5 (q)    |
| 3-OCOPr  | 172.3 (s) |          |           | 169.5 (s)   |
| 9.0-Ac   |            |          |           | 21.1 (q)    |
| 12-OAc   |            |          |           | 170.6 (s)   |
| 14-OAc   | 1.99 s | 21.2 (q) | 2.05 s | 21.3 (q)    |
| 3-OCOPr  |            |          |           | 172.3 (s)   |
| 2.22 t (7.6) | 35.9 (t) |          |           | 170.4 (s)   |
| 1.61 m   | 18.0 (t) |          |           | 170.4 (s)   |
| 0.94 t (7.6) | 13.6 (q) |          |           | 172.3 (s)   |

$^a$ Spectra were recorded at 400 MHz at 25 °C. $^b$ Spectra were recorded at 100 MHz at 25 °C. $^c$ J values (in Hz) in parentheses. $^d$ Multiplicity deduced by DEPT and HMQC spectra and indicated by usual symbols.
Moreover, a methyl singlet (δ\textsubscript{H} 1.36, 3H, s, H\textsubscript{3}-15), three vinyl methyls (δ\textsubscript{H} 2.01, 3H, s, H\textsubscript{3}-18; 1.85, 3H, s, H\textsubscript{3}-16; 1.64, 3H, s, H\textsubscript{3}-20), two pairs of methylene protons (δ\textsubscript{H} 3.46, 1H, dd, J = 15.6, 6.0 Hz; 2.04, 1H, d, J = 15.6 Hz, H\textsubscript{2}-4; 2.57, 1H, br d, J = 18.4 Hz; 2.15, 1H, m, H\textsubscript{2}-13), an aliphatic methine proton (δ\textsubscript{H} 3.25, 1H, br s, H-10), five oxymethine protons (δ\textsubscript{H} 6.07, 1H, d, J = 8.8 Hz, H-7; 5.45, 1H, d, J = 2.4 Hz, H-2; 5.08, 1H, dd, J = 6.0, 6.0 Hz, H-14; 4.98, 1H, br s, H-9; 4.98, 1H, dd, J = 6.0, 2.4 Hz, H-3), two olefin protons (δ\textsubscript{H} 5.58, 1H, br s, H-12; 5.21, 1H, d, J = 8.8 Hz, H-6), and two acetyl methyls (δ\textsubscript{H} 2.12, 3H, s; 1.99, 3H, s) were observed in the 1H-NMR spectrum of 1. An n-butyryl group (δ\textsubscript{H} 0.94, 3H, t, J = 7.6 Hz; 1.61, 2H, m; 2.22, 2H, t, J = 7.6 Hz) was also observed in the 1H-NMR spectrum and further confirmed by the 1H-1H COSY correlations and coupling constant analysis.

**Table 2.** The 1H-1H COSY and HMBC (H→C) Correlations for Diterpenoids 1 and 2.

| Position | 1H-1H COSY | HMBC | 1H-1H COSY | HMBC |
|----------|------------|------|------------|------|
| H-2      | H-3        | C-1, -3, -4, -14, -15, acetate carbonyl | H-3 | C-1, -3, -4, -10, -14, -15, acetate carbonyl |
| H-3      | H-2, H\textsubscript{2}-4 | C-1 | H-2, H-4 | C-1, -4 |
| H-4      | H-3        | C-3, -5, -6, -16 | H-3, H-6 | C-5, -6 |
| H-6      | H-7, H\textsubscript{3}-16 | C-4, -16 | H-4, H-7, H\textsubscript{3}-16 | C-4 |
| H-7      | H-6        | C-5, -6, -8 | H-6 | C-5, -6, -19 |
| H-9      | H-10       | C-1, -8 | H-10 | C-1, -7, -8, -10, -17, acetate carbonyl |
| H-10     | H-9        | C-9, -11 | H-9 | C-1, -2, -8, -9, -11, -14, -15 |
| H-12     | H\textsubscript{2}-13, H\textsubscript{3}-20 | n.o.\textsuperscript{a} | H\textsubscript{2}-13 | acetate carbonyl |
| H-13     | H\textsubscript{12}, H\textsubscript{14} | n.o. | H\textsubscript{12}, H\textsubscript{14} | C-1, -11, -14 |
| H-14     | H\textsubscript{2}-13 | C-1, -2, -13, -15, acetate carbonyl | H\textsubscript{2}-13 | C-10, acetate carbonyl |
| H-15     | H\textsubscript{2}-13 | C-1, -2, -10, -14 | C-1, -2, -14 |
| H-16     | H\textsubscript{6} | C-4, -5, -6 | H\textsubscript{6} | C-4, -5, -6 |
| H-18     | H\textsubscript{8}, -17, -19 | C-8, -17, -19 | C-8, -17, -19 |
| H-20     | H-12       | C-10, -11, -12 | C-10, -11, -12 |

\textsuperscript{a} n.o. = not observed.

The gross structure of 1 was elucidated with the assistance of 2D NMR studies. From the 1H-1H COSY experiment of 1 (Table 2), it was possible to establish the separate spin systems that map out the proton sequences from H-2/3/4, H-6/7, and H-9/10. These data, together with the HMBC correlations between H-2/C-1, -3, -4; H-3/C-1; H-2/C-3, -5, -6; H-6/C-4; H-7/C-5, -6, -8; H-9/C-1, -8; and H-10/C-9, established the connectivity from C-1 to C-10 in the 10-membered ring (Table 2). The vinyl methyl groups attached at C-5 and C-11 were confirmed by the HMBC correlations between H\textsubscript{3}-16/C-4, -5, -6; and H\textsubscript{3}-20/C-10, -11, -12, and further supported by the allylic couplings between H-6/H\textsubscript{3}-16 and H-12/H\textsubscript{2}-20, respectively. The vinyl methyl group attached at C-17 was also established by the HMBC correlations between H\textsubscript{3}-18 and C-8, -17, -19. The methylocyclohexene ring, which is fused to the 10-membered ring at C-1 and C-10, was elucidated by the 1H-1H COSY correlations between H\textsubscript{12}/H\textsubscript{2}-13/H-14 and by the HMBC correlations between H-2/C-14; H-10/C-11;
H-14/C-1, -2; and H_3-20/C-10. The ring junction C-15 methyl group was positioned at C-1 from the HMBC correlations between H-2/C-15; H-14/C-15; and H_3-15/C-1, -2, -10, -14. In addition, the HMBC correlations also revealed that two acetates should attach at C-2 and C-14, respectively. The remaining n-butyryloxy and hydroxy groups were positioned at C-3 and C-9 as indicated by analysis of H-1H-COSY correlations and characteristic NMR signals analysis, although no HMBC correlation was observed between H-3 and the n-butyrate carbonyl.

Based on previous studies, all naturally occurring briarane-type diterpenoids have the C-15 methyl group trans to H-10, and these two groups are assigned as β- and α-oriented, respectively, as shown in most briarane derivatives [42–44]. The relative stereochemistry of 1 was established from a NOESY experiment (Figure 3), in which the NOE correlations of H-10 with H-3 and H-9; and H-3 with H-2, indicated that these protons are situated on the same face and were assigned as α protons since the C-15 methyl is the β-substituent at C-1. H-14 was found to exhibit a correlation with H_3-15 but not with H-10, revealing the β-orientation of this proton. One of the C-4 methylene protons (δ_H 3.46) exhibited a correlation with H_3-15 and was assigned as H-4β, while the other was denoted as H-4α (δ_H 2.04). A correlation observed between H-4β and H-7, reflected the β-orientation of H-7. The NOESY spectrum showed correlations of H-6/H_3-16 and H-12/H_3-20, revealing the Z geometry of C-5/6 and C-11/12 double bonds in 1.

Figure 3. Selected NOE Correlations of 1.

The molecular formula of excavatoid F (2) was determined as C_{28}H_{38}O_{12} by its HRESIMS (m/z 589.2257, calcd. for C_{28}H_{38}O_{12}Na, 589.2261). The IR spectrum showed bands at 3,487, 1,779, and 1,737 cm^{-1}, consistent with the presence in 2 of hydroxy, γ-lactone, and ester groups. From the 13C-NMR data of 2 (Table 1), a trisubstituted olefin was deduced from the signals of two carbons at δ_C 146.2 (s, C-5) and 117.6 (d, CH-6). A methyl-containing tetrasubstituted epoxy group was confirmed from the signals of two quaternary oxygenated carbons at δ_C 70.6 (s, C-8) and 64.5 (s, C-17), and from the chemical shifts of a tertiary methyl group (δ_H 1.73, 3H, s, H_3-18; δ_C 10.3, q, CH_3-18) (Table 1). Moreover, five carbonyl resonances appeared at δ_C 170.9 (s, C-19), 170.6, 170.5, 169.5, and 168.1 (4 × s, ester carbonyls), confirming the presence of a γ-lactone and four esters in 2. All the esters were identified as acetates by the presence of methyl resonances in the 1H-NMR spectrum at δ_H 2.19, 2.07, 2.05, and 2.00 (each 3H × s).
The planar structure of 2 was determined mainly by 2D NMR studies. The coupling information in the $^1$H-$^1$H COSY spectrum of 2 enabled identification of the proton sequences H-2/3/4, H-4/6 (by allylic coupling), H-6/7, H-6/H-16 (by allylic coupling), H-9/10, and H-12/13/14 (Table 2). These data, together with the correlations observed in an HMBC experiment of 2 (Table 2), the molecular framework of 2 could be further established. The HMBC correlations also indicated that the acetoxy groups should attach at C-2, -9, -12, and C-14. Thus, the remaining hydroxy group has to be positioned at C-11, as indicated by characteristic NMR signal analysis. The relative stereochemistry of 2 was elucidated from the NOE interactions observed in a NOESY experiment (Figure 4). In the NOESY spectrum of 2, correlations were observed between H-10 with H-2, -9, -12, and H-13-20, indicating that these protons should be positioned on the $\alpha$ face in 2 and Me-20 was positioned on the equatorial direction in the methylcyclohexane ring of 2. One proton attaching at C-3 ($\delta$H 2.65) was found to exhibit a correlation with H-15 and was assigned as H-3$\beta$ proton. H-7 showed a correlation with H-3$\beta$, confirming the $\beta$-orientation for this proton. Furthermore, H-18 was found to show correlations with H-9, H-20, and H-7, and from molecular models, was found to be reasonably closed to H-9, H-20, and H-7; therefore, H-18 should be placed on the $\beta$ face in the $\gamma$-lactone ring of 2. The Z-configuration of the C-5/C-6 double bond was elucidated by an interaction between H-6 ($\delta$H 5.25) and H-16 ($\delta$H 2.02). On the basis of the above results, the structure of 2, including the relative configuration, was elucidated.

Table 3. Inhibitory Effects of Compounds 1 and 2 on Elastase Release and Superoxide Anion Generation by Human Neutrophils in Response to fMet-Leu-Phe/Cytochalasin B.

| Compound | Elastase Inh.% | Superoxide Anion Inh.% |
|----------|---------------|------------------------|
| 1        | 26.22 ± 0.50 *** | 12.95 ± 6.99           |
| 2        | 30.63 ± 4.68 *  | 2.57 ± 1.11            |

Percentage of inhibition (Inh.%) at 10 $\mu$g/mL concentration. Results are presented as mean ± S.E.M. ($n$ = 2-3). * $P < 0.05$, ** $P < 0.01$, and *** $P < 0.001$ compared with the control value.
In previous study, several diterpenoid derivatives of potential medical interest were isolated from a cultured gorgonian coral *Erythropodium caribaeorum* [45]. Because all corals are claimed to be threatened species, we wanted to maintain and culture these interesting specimens as sources of new and interesting natural products in our continuing search for novel substances from marine organisms originally collected in Taiwan waters, in the hope of identifying extracts that exhibit bioactivity. Briaranes 1 and 2 displayed moderate inhibitory effects on elastase release by neutrophils, and briarane 1 exhibited weak inhibitory effects on superoxide anion generation by human neutrophils at 10 $\mu$g/mL, respectively (Table 3). Furthermore, these two compounds were not cytotoxic toward the CCRF-CEM (human T-cell acute lymphoblastic leukemia) and DLD-1 (human colon adenocarcinoma) cells (ED$_{50}$ > 40 $\mu$g/mL). The possible bioactivity for these two compounds will be further studied if we can obtain enough material from the cultured *B. excavatum* in the future.

3. Experimental Section

3.1. General Experimental Procedures

Melting points were determined on a Fargo apparatus and were uncorrected. Optical rotation values were measured with a JASCO P-1010 digital polarimeter at 25 °C. Infrared spectra were obtained on a Varian Digilab FTS 1000 FT-IR spectrometer. The NMR spectra were recorded on a Varian Mercury Plus 400 FT-NMR at 400 MHz for $^1$H and 100 MHz for $^{13}$C, in CDCl$_3$, respectively. Proton chemical shifts were referenced to the residual CHCl$_3$ signal ($\delta$ 7.26 ppm). $^{13}$C-NMR spectra were referenced to the center peak of CDCl$_3$ at $\delta$ 77.1 ppm. ESIMS and HRESIMS data were recorded on a Bruker APEX II mass spectrometer. Column chromatography was performed on silica gel (230-400 mesh, Merck, Darmstadt, Germany). TLC was carried out on precoated Kieselgel 60 F$_{254}$ (0.25 mm, Merck) and spots were visualized by spraying with 10% H$_2$SO$_4$ solution followed by heating. HPLC was performed using a system comprised of a Hitachi L-7100 pump, a Hitachi photodiode array detector L-7455, and a Rheodyne 7725 injection port. A semi-preparative reverse phase column (Hibar 250 × 10 mm, LiChrospher 100 RP-18e, 5 $\mu$m, Merck) was used for HPLC.

3.2. Animal Material

Specimens of the octocoral *Briareum excavatum* were collected and transplanted to a 0.6-ton cultivating tank located in the NMMBA, Taiwan, in December 2003, and the material for this research work was collected from the tank in December 2006. This organism was identified by comparison with previous descriptions [46–48]. A voucher specimen was deposited in the National Museum of Marine Biology & Aquarium, Taiwan (NMMA-CSC-001).

3.3. Extraction and Isolation

The freeze-dried and minced material of *B. excavatum* (wet weight 672 g, dry weight 270 g) was extracted with a mixture of MeOH and CH$_2$Cl$_2$ (1:1) at room temperature. The residue was partitioned between EtOAc and H$_2$O. The EtOAc layer was separated on Sephadex LH-20 and eluted using
MeOH/CH₂Cl₂ (2:1) to yield three fractions A-C. Fraction C was separated on silica gel and eluted using hexane/EtOAc (stepwise, 20:1-pure EtOAc) to yield fractions 1-9. Fraction C7 was separated by reverse phase HPLC, using the mixtures of MeOH, CH₃CN, and H₂O to afford briaranes 1 (2.9 mg, 65/1/34) and 2 (1.2 mg, 62/1/37).

Excavatoid E (1): white powder; mp 192-193 °C; [α]_25^D + 2 (c 0.15, CHCl₃); IR (neat) ν_max 3,463, 1,743, 1,737 cm⁻¹; ¹³C-NMR (CDCl₃, 100 MHz) and ¹H-NMR (CDCl₃, 400 MHz) data, see Table 1; ESIMS m/z 541 (M + Na)^⁺; HRESIMS m/z 541.2415 (calcd. for C₂₈H₃₈O₉Na, 541.2413).

Excavatoid F (2): white powder; mp 164-165 °C; [α]_25^D -16 (c 0.06, CHCl₃); IR (neat) ν_max 3,487, 1,779, 1,737 cm⁻¹; ¹³C-NMR (CDCl₃, 100 MHz) and ¹H-NMR (CDCl₃, 400 MHz) data, see Table 1; ESIMS m/z 589 (M + Na)^⁺; HRESIMS m/z 589.2257 (calcd. for C₂₈H₃₈O₁₂Na, 589.2261).

3.4. Human Neutrophil Superoxide Anion Generation and Elastase Release

Human neutrophils were obtained by means of dextran sedimentation and Ficoll centrifugation. Superoxide generation was carried out according to the procedures described previously [49,50]. Briefly, superoxide anion production was assayed by monitoring the superoxide dismutase-inhibitable reduction of ferricytochrome c. Elastase release experiments were performed using MeO-Suc-Ala-Ala-Pro-Val-p-nitroanilide as the elastase substrate.

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References

1. Sheu, J.-H.; Sung, P.-J.; Huang, L.-H.; Lee, S.-F.; Wu, T.; Chang, B.-Y.; Duh, C.-Y.; Fang, L.-S.; Soong, K.; Lee, T.-J. New cytotoxic briarane diterpenes from the Formosan gorgonian *Briareum* sp. *J. Nat. Prod.* 1996, 59, 935–938.

2. Sheu, J.-H.; Sung, P.-J.; Cheng, M.-C.; Liu, H.-Y.; Fang, L.-S.; Duh, C.-Y.; Chiang, M.Y. Novel cytotoxic diterpenes, excavatolides A-E, isolated from the Formosan gorgonian *Briareum excavatum*. *J. Nat. Prod.* 1998, 61, 602–608.

3. Sung, P.-J.; Su, J.-H.; Wang, G.-H.; Lin, S.-F.; Duh, C.-Y.; Sheu, J.-H. Excavatolides F-M, new briarane diterpenes from the gorgonian *Briareum excavatum*. *J. Nat. Prod.* 1999, 62, 457–463.

4. Sheu, J.-H.; Sung, P.-J.; Su, J.-H.; Wang, G.-H.; Duh, C.-Y.; Shen, Y.-C.; Chiang, M.Y.; Chen, I.-T. Excavatolides U-Z, new briarane diterpenes from the gorgonian *Briareum excavatum*. *J. Nat. Prod.* 1999, 62, 1415–1420.

5. Sheu, J.-H.; Sung, P.-J.; Su, J.-H.; Liu, H.-Y.; Duh, C.-Y.; Chiang, M.Y. Briaexcavatolides A-J, new diterpenes from the gorgonian *Briareum excavatum*. *Tetrahedron* 1999, 55, 14555–14564.

6. Sung, P.-J.; Su, J.-H.; Duh, C.-Y.; Chiang, M.Y.; Sheu, J.-H. Briaexcavatolides K-N, new briarane diterpenes from the gorgonian *Briareum excavatum*. *J. Nat. Prod.* 2001, 64, 318–323.
1. Wu, S.-L.; Sung, P.-J.; Chiang, M.Y.; Wu, J.-Y.; Sheu, J.-H. New polyoxygenated briarane diterpenoids, briaexcavatolides O-R, from the gorgonian *Briareum excavatum*. *J. Nat. Prod.* 2001, 64, 1415–1420.

2. Wu, S.-L.; Sung, P.-J.; Su, J.-H.; Sheu, J.-H. Briaexcavatolides S-V, four new briaranes from a Formosan gorgonian *Briareum excavatum*. *J. Nat. Prod.* 2003, 66, 1252–1256.

3. Wu, S.-L.; Sung, P.-J.; Su, J.-H.; Wang, G.-H.; Sheu, J.-H. Briaexcavatolide W, a new diterpenoid from *Briareum excavatum*. *Heterocycles* 2004, 63, 895–898.

4. Sung, P.-J.; Hu, W.-P.; Wu, S.-L.; Su, J.-H.; Fang, L.-S.; Wang, J.-J.; Sheu, J.-H. Briaexcavatolides X-Z, three new briarane-related derivatives from the gorgonian coral *Briareum excavatum*. *Tetrahedron* 2004, 60, 8975–8979.

5. Sung, P.-J.; Hu, W.-P.; Fang, L.-S.; Fan, T.-Y.; Wang, J.-J. Briarenol A, a new diterpenoid from a gorgonian *Briareum* sp. (Briareidae). *Nat. Prod. Res.* 2005, 19, 689–694.

6. Sung, P.-J.; Chao, C.-H.; Chen, Y.-P.; Su, J.-H.; Hu, W.-P.; Sheu, J.-H. Briaexcavatins A and B, novel briaranes from the octocoral *Briareum excavatum*. *Tetrahedron Lett.* 2006, 47, 167–170.

7. Sung, P.-J.; Chen, Y.-P.; Hwang, T.-L.; Hu, W.-P.; Fang, L.-S.; Wu, Y.-C.; Li, J.-J.; Sheu, J.-H. Briaexcavatins C-F, four new briarane-related diterpenoids from the Formosan octocoral *Briareum excavatum* (Briareidae). *Tetrahedron* 2006, 62, 5686–5691.

8. Chen, Y.-P.; Wu, S.-L.; Su, J.-H.; Lin, M.-R.; Hu, W.-P.; Hwang, T.-L.; Sheu, J.-H.; Fan, T.-Y.; Fang, L.-S.; Sung, P.-J. Briaexcavatins G and H, two new briaranes from the octocoral *Briareum excavatum*. *Bull. Chem. Soc. Jpn.* 2006, 79, 1900–1905.

9. Su, J.-H.; Sung, P.-J.; Kuo, Y.-H.; Hsu, C.-H.; Sheu, J.-H. Briarenolides A-C, briarane diterpenoids from the gorgonian coral *Briareum* sp. *Tetrahedron* 2007, 63, 8282–8285.

10. Sung, P.-J.; Lin, M.-R.; Su, Y.-D.; Chiang, M. Y.; Hu, W.-P.; Su, J.-H.; Cheng, M.-C.; Hwang, T.-L.; Sheu, J.-H. New briaranes from the octocorals *Briareum excavatum* (Briareidae) and *Juncella fragilis* (Ellisellidae). *Tetrahedron* 2008, 64, 2596–2604.

11. Sung, P.-J.; Lin, M.-R.; Hwang, T.-L.; Fan, T.-Y.; Su, W.-C.; Ho, C.-C.; Fang, L.-S.; Wang, W.-H. Briaexcavatins M-P, four new briarane-related diterpenoids from cultured octocoral *Briareum excavatum* (Briareidae). *Chem. Pharm. Bull.* 2008, 56, 930–935.

12. Hwang, T.-L.; Lin, M.-R.; Tsai, W.-T.; Yeh, H.-C.; Hu, W.-P.; Sheu, J.-H.; Sung, P.-J. New polyoxygenated briaranes from octocorals *Briareum excavatum* and *Ellisella robusta*. *Bull. Chem. Soc. Jpn.* 2008, 81, 1638–1646.

13. Sung, P.-J.; Lin, M.-R.; Chiang, M.Y. The structure and absolute stereochemistry of briaexcavatin U, a new chlorinated briarane from a cultured octocoral *Briareum excavatum*. *Chem. Lett.* 2009, 38, 154–155.

14. Sung, P.-J.; Lin, M.-R.; Chiang, M.Y.; Hwang, T.-L. Briaexcavatins V-Z, discovery of new briaranes from a cultured octocoral *Briareum excavatum*. *Bull. Chem. Soc. Jpn.* 2009, 82, 987–996.

15. Sung, P.-J.; Su, Y.-D.; Li, G.-Y.; Chiang, M. Y.; Lin, M.-R.; Huang, I.-C.; Li, J.-J.; Fang, L.-S.; Wang, W.-H. Excavatoids A-D, new polyoxygenated briaranes from the octocoral *Briareum excavatum*. *Tetrahedron* 2009, 65, 6918–6924.
22. Sung, P.-J.; Tsai, W.-T.; Chiang, M.Y.; Su, Y.-M.; Kuo, J. Robustolides A-C, three new briarane-type diterpenoids from the female gorgonian coral Ellisella robusta (Ellisellidae). Tetrahedron 2007, 63, 7582–7588.

23. Su, Y.-M.; Fan, T.-Y.; Sung, P.-J. 11,20-Epoxybriaranes from the gorgonian coral Ellisella robusta (Ellisellidae). Nat. Prod. Res. 2007, 21, 1085–1090.

24. Sung, P.-J.; Chiang, M.Y.; Tsai, W.-T.; Su, J.-H.; Su, Y.-M.; Wu, Y.-C. Chlorinated briarane-type diterpenoids from the gorgonian coral Ellisella robusta (Ellisellidae). Tetrahedron 2007, 63, 12860–12865.

25. Sung, P.-J.; Tsai, W.-T.; Lin, M.-R.; Su, Y.-D.; Pai, C.-H.; Chung, H.-M.; Su, J.-H.; Chiang, M.Y. Robustolides H and I, chlorinated briaranes from the gorgonian coral Ellisella robusta (Ellisellidae). Chem. Lett. 2008, 37, 88–89.

26. Sung, P.-J.; Wu, S.-L.; Fang, H.-J.; Chiang, M.Y.; Wu, J.-Y.; Fang, L.-S.; Sheu, J.-H. Junceellolides E-G, new briarane diterpenes from the West Pacific Ocean gorgonian Junceella fragilis. J. Nat. Prod. 2000, 63, 1483–1487.

27. Sung, P.-J.; Fan, T.-Y. 9-O-Deacetylumbraculolide A, a new diterpenoid from the gorgonian Junceella fragilis. Heterocycles 2003, 60, 1199–1202.

28. Sung, P.-J.; Fan, T.-Y.; Fang, L.-S.; Sheu, J.-H.; Wu, S.-L.; Wang, G.-H.; Lin, M.-R. Juncin N, a new briarane-type diterpenoid from the gorgonian coral Junceella juncetia. Heterocycles 2003, 61, 587–592.

29. Sung, P.-J.; Fan, T.-Y.; Fang, L.-S.; Wu, S.-L.; Li, J.-J.; Chen, M.-C.; Cheng, Y.-M.; Wang, G.-H. Briarane derivatives from the gorgonian coral Junceella fragilis. Chem. Pharm. Bull. 2003, 51, 1429–1431.

30. Sung, P.-J.; Lin, M.-R.; Fang, L.-S.; Lin, M.-R.; Chang, P.-C. Junceellin and praelolide, two briaranes from the gorgonian corals Junceella fragilis and Junceella juncetia (Ellisellidae). Biochem. Syst. Ecol. 2004, 32, 111–113.

31. Sung, P.-J.; Lin, M.-R.; Fang, L.-S. Briarane diterpenoids from the Formosan gorgonian coral Junceella fragilis. Chem. Pharm. Bull. 2004, 52, 1504–1506.

32. Sung, P.-J.; Lin, M.-R.; Chen, W.-C.; Fang, L.-S.; Lu, C-K.; Sheu, J.-H. Fragilide A, a novel diterpenoid from Junceella fragilis. Bull. Chem. Soc. Jpn. 2004, 77, 1229–1230.

33. Sheu, J.-H.; Chen, Y.-P.; Hwang, T.-L.; Chiang, M.Y.; Fang, L.-S.; Sung, P.-J. Junceellolides J-L, 11,20-epoxybriaranes from the gorgonian coral Junceella fragilis. J. Nat. Prod. 2006, 69, 269–273.

34. Sung, P.-J.; Chen, Y.-P.; Su, Y.-M.; Hwang, T.-L.; Hu, W.-P.; Fan, T.-Y.; Wang, W.-H. Fragilide B, a novel briarane-type diterpenoid with a s-cis diene moiety. Bull. Chem. Soc. Jpn. 2007, 80, 1205–1207.

35. Sung, P.-J.; Pai, C.-H.; Su, Y.-D.; Hwang, T.-L.; Kuo, F.-W.; Fan, T.-Y.; Li, J.-J. New 8-hydroxy-briarane diterpenoids from the gorgonians Junceella juncetia and Junceella fragilis (Ellisellidae). Tetrahedron 2008, 64, 4224–4232 (corrigendum in Tetrahedron 2008, 64, 9150).

36. Sung, P.-J.; Pai, C.-H.; Hwang, T.-L.; Fan, T.-Y.; Su, J.-H.; Chen, J.-J.; Fang, L.-S.; Wang, W.-H.; Sheu, J.-H. Junceols D-H, new polyoxygenated briaranes from sea whip gorgonian coral Junceella juncetia (Ellisellidae). Chem. Pharm. Bull. 2008, 56, 1276–1281.
37. Sung, P.-J.; Li, G.-Y.; Chen, Y.-P.; Huang, I.-C.; Chen, B.-Y.; Wang, S.-H.; Huang, S.-K. Fragilide E, a novel chlorinated 20-acetoxybriarane from the gorgonian coral Junceella fragilis. Chem. Lett. 2009, 38, 454–455.

38. Sung, P.-J.; Wang, S.-H.; Chiang, M.Y.; Su, Y.-D.; Chang, Y.-C.; Hu, W.-P.; Tai, C.-Y.; Liu, C.-Y. Discovery of new chlorinated briaranes from Junceella fragilis. Bull. Chem. Soc. Jpn. 2009, 82, in press.

39. Blunt, J.W.; Copp, B.R.; Hu, W.-P.; Munro, M.H.G.; Northcote, P.T.; Prinsep, M.R. Marine natural products. Nat. Prod. Rep. 2009, 26, 170–244, and references cited therein.

40. Berrue, F.; Kerr, R.G. Diterpenes from gorgonian corals. Nat. Prod. Rep. 2009, 26, 681–710, and references cited therein.

41. Hanson, J.R. Diterpenoids. Nat. Prod. Rep. 2009, 26, 1156–1171, and references cited therein.

42. Sung, P.-J.; Sheu, J.-H.; Xu, J.-P. Survey of briarane-type diterpenoids of marine origin. Heterocycles 2002, 57, 535–579.

43. Sung, P.-J.; Chang, P.-C.; Fang, L.-S.; Sheu, J.-H.; Chen, W.-C.; Chen, Y.-P.; Lin, M-R. Survey of briarane-type diterpenoids-Part II. Heterocycles 2005, 65, 195–204.

44. Sung, P.-J.; Chang, P.-C.; Fang, L.-S.; Sheu, J.-H.; Chen, W.-C.; Chen, Y.-P.; Lin, M-R. Survey of briarane-type diterpenoids-Part III. Heterocycles 2008, 75, 2627–2648.

45. Taglialetela-Scafati, O.; Deo-Jangra, U.; Campbell, M.; Roberge, M.; Andersen, R.J. Diterpenoids from cultured Erythropodium caribaeorum. Org. Lett. 2002, 4, 4085–4088.

46. Bayer, F.M. Key to the genera of octocorallia exclusive of Pennatulacea (Coelenterata: anthozoa), with diagnoses of new taxa. Proc. Biol. Soc. Wash. 1981, 94, 902–947.

47. Benayahu, Y.; Jeng, M.-S.; Perkol-Finkel, S.; Dai, C.-F. Soft corals (Octocorallia: Alcyonacea) from southern Taiwan. II. Species diversity and distribution patterns. Zool. Stud. 2004, 43, 548–560.

48. Fabricius, K.; Alderslade, P. Soft Corals and Sea Fans–A comprehensive guide to the tropical shallow-water genera of the Central-West Pacific, the Indian Ocean and the Red Sea, 1st ed.; Australian Institute of Marine Science: Queensland, Australia, 2001; pp. 55, 154–157.

49. Hwang, T.-L.; Li, G.-L.; Lan, Y.-H.; Chia, Y.-C.; Hsieh, P.-W.; Wu, Y.-H.; Wu, Y.-C. Potent inhibitors of superoxide anion production in activated human neutrophils by isopedicin, a bioactive component of the Chinese medicinal herb Fissistigma oldhamii. Free Radic. Biol. Med. 2009, 46, 520–528.

50. Hwang, T.-L.; Su, Y.-C.; Chang, H.-L.; Leu, Y.-L.; Chung, P.-J.; Kuo, L.-M.; Chang, Y.-J. Suppression of superoxide anion and elastase release by C18 unsaturated fatty acids in human neutrophils. J. Lipid Res. 2009, 50, 1395–1408.

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