Excavatoids L—N, New 12-Hydroxybriaranes from the Cultured Octocoral *Briareum excavatum* (Briareidae)

Jui-Hsin Su,[a,b] Bo-Yuan Chen,[a,c] Tsong-Long Hwang,[d] Yung-Husan Chen,[a] I-Chu Huang,[a] Mei-Ru Lin,[a,e] Jih-Jung Chen,[f] Lee-Shing Fang,[g] Wei-Hsien Wang,[a,e] Jan-Jung Li,[a] Jyh-Horng Sheu,*[,e] and Ping-Jyun Sung*[,a,c,e]

[a] *National Museum of Marine Biology & Aquarium (NMMBA); Checheng, Pingtung 944, Taiwan:* [b] *Department of Biological Science and Technology, Meiho Institute of Technology; Pingtung 912, Taiwan:* [c] *Graduate Institute of Marine Biotechnology and Department of Life Science and Graduate Institute of Biotechnology, National Dong Hwa University (NDHU); Checheng, Pingtung 944, Taiwan:* [d] *Graduate Institute of Natural Products, Chang Gung University; Taoyuan 333, Taiwan:* [e] *Department of Marine Biotechnology and Resources and Asia-Pacific Ocean Research Center (APORC), National Sun Yat-sen University (NSYSU); Kaohsiung 804, Taiwan:* [f] *Department of Pharmacy, Tajen University; Pingtung 907, Taiwan: and* [g] *Department of Sport, Health, and Leisure, Cheng Shiu University; Kaohsiung 833, Taiwan.*
Received December 18, 2009; accepted February 4, 2010; published online February 24, 2010

Three new 12-hydroxybriarane diterpenoids, excavatoids L—N (1—3), have been isolated from the cultured octocoral *Briareum excavatum*. The structures of new briaranes 1—3 were elucidated by the interpretations of spectroscopic methods. Excavatoid L (1) displayed moderate inhibitory effects on superoxide anion generation and elastase release by human neutrophils.

Key words *Briareum excavatum*; cultured octocoral; excavatoid; briarane; human neutrophil

Previous studies on the chemical constituents of octocorals belonging to the genus *Briareum* (family Briareidae) have yielded over 273 interesting briarane-type diterpenoid derivatives (3,8-cyclized cembranoid).[1—3] In continuation of our search for new substances from the invertebrates originally collected off Taiwan waters, a series of new briarane analogues, including briaexcavatins I—Z,[4—8] excavatoids A, B, and E—K,[9—11] had been isolated from the cultured octocoral *Briareum excavatum*. Briarane-type natural products are found only in marine organisms and mainly from octocorals.[1—3] The compounds of this type are suggested to be originally synthesized by host corals,[12,13] and proven to possess various bioactivities.[1—3] We have further isolated three new 12-hydroxybriaranes, excavatoids L—N (**1**—**3**), from the cultured octocoral *B. excavatum*. In this paper, we describe the isolation, structure determination, and bioactivity of above new briaranes.

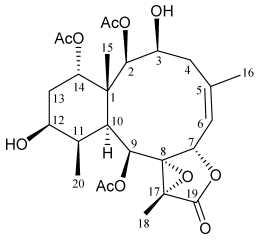
Results and Discussion

Excavatoid L (**1**) was isolated as a white powder. The molecular formula of **1** was established as $C_{26}H_{36}O_{11}$ (nine degrees of unsaturation) from a sodiated molecule at *m*/*z* 547 in the electrospray ionization (ESI)-MS spectrum and further supported by the HR-ESI-MS (*m*/*z* Calcd: 547.2155; Found: 547.2158, $[C_{26}H_{36}O_{11}Na]^+$). The IR spectrum of **1** showed bands at 3450, 1781, and 1734 cm^{-1}, consistent with the presence of hydroxy, γ-lactone, and ester carbonyl groups. The ^{13}C-NMR and distortionless enhancement by polarization transfer (DEPT) spectra of **1** showed that this compound has 26 carbons (Table 1), including seven methyls, two sp^3 methylenes, eight sp^3 methines, three sp^3 quaternary carbons, an sp^2 methine, and five sp^2 quaternary carbons. From the ^{13}C- and ^{1}H-NMR spectra (Tables 1, 2), **1** was found to possess three acetoxy groups (δ_H 2.31, 2.20, 2.17, each 3H×s; δ_C 173.1, 170.1, 169.4, each s; 21.4, 21.3, 21.3, each q), a γ-lactone moiety (δ_C 170.2, s, C-19), and a trisubstituted olefin (δ_C 142.1, s, C-5; 119.4, d, CH-6; δ_H 5.13, 1H, br s, H-6). The presence of a tetrasubstituted epoxide, containing a methyl substituent was established from the signals of two quaternary oxygenated carbons at δ_C 70.4 (s, C-8) and 61.9 (s, C-17), and further confirmed by the proton signal of a methyl singlet at δ_H 1.63 (3H, s, H_3-18). Thus, from the above NMR data, five degrees of unsaturation were accounted for, and **1** was identified as a tetracyclic compound.

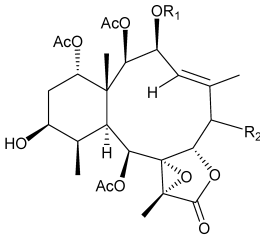
The gross structure of **1** was determined mainly using 2D-NMR studies. From the ^{1}H–^{1}H correlation spectroscopy (COSY) spectrum of **1** (Table 3), five different structural units, including C-3/-4, C-6/-7, C-9/-10/-11/-12/-13/-14, C-11/-20, and C-6/-16 (by allylic coupling), were identified. From these data and the heteronuclear multiple bond connectivity (HMBC) correlations (Table 4), the carbon skeleton of **1** could be established. A methyl at C-5 was confirmed by the allylic coupling between H_3-16/H-6 in the ^{1}H–^{1}H COSY spectrum of **1** and by the HMBC correlations between H_3-16/C-4, -5, -6. The ring junction C-15 methyl group was positioned at C-1 from the HMBC correlations between H-10/C-15 and H_3-15/C-1, -2, -10, -14. The hydroxy proton signal at δ_H 3.89 (1H, br s) was revealed by its ^{1}H–^{1}H COSY correlation to H-12 (δ_H 4.10, 1H, m) indicating its attachment to C-12. The remaining three acetate esters and a hydroxy group positioned at C-2, C-9, C-14, and C-3, as indicated by analysis of the ^{1}H–^{1}H COSY correlations and characteristic NMR signals analysis. These data, together with the HMBC correlations between H_3-18/C-8, -17, -19, established the mainly molecular framework of **1**.

Based on previous surveys, all the briaranes have the H-10 is *trans* to the C-15 methyl, and these two groups are assigned as α- and β-oriented in most briarane analogues.[1—3] The relative stereochemistry of **1** was established from the interactions observed in a nuclear Overhauser effect spectroscopy (NOESY) experiment and by geminal and vicinal ^{1}H–^{1}H coupling constants analysis. In the NOESY experiment of **1** (Fig. 1), the correlations between H-10 and H-3, H-11, H-12; and a correlation between H-3 and H-2, indicated that these

* To whom correspondence should be addressed. e-mail: pjsung@nmmba.gov.tw; sheu@mail.nsysu.edu.tw
© 2010 Pharmaceutical Society of Japan



1



2:R_1=C(O)$(CH_2)_2CH_3$, R_2=α-OH
3:R_1=C(O)$(CH_2)_2CH_3$, R_2=β-OH
4:R_1=Ac, R_2=α-OH

Table 1. ^{13}C-NMR Data for Diterpenoids **1**—**3**[a]

Carbon	**1**	**2**	**3**
1	43.2 (s)[b]	44.3 (s)	44.3 (s)
2	89.7 (d)	78.9 (d)	78.8 (d)
3	73.8 (d)	70.2 (d)	70.2 (d)
4	35.5 (t)	124.5 (d)	125.9 (d)
5	142.1 (s)	139.3 (s)	136.6 (s)
6	119.4 (d)	75.3 (d)	87.7 (d)
7	74.5 (d)	81.9 (d)	78.1 (d)
8	70.4 (s)	68.8 (s)	69.1 (s)
9	66.6 (d)	66.5 (d)	66.4 (d)
10	40.2 (d)	40.5 (d)	40.6 (d)
11	36.7 (d)	37.4 (d)	37.4 (d)
12	66.8 (d)	66.9 (d)	66.9 (d)
13	30.4 (t)	30.0 (t)	30.0 (t)
14	80.3 (d)	81.1 (d)	81.2 (d)
15	18.9 (q)	18.8 (q)	18.7 (q)
16	22.6 (q)	19.5 (q)	19.9 (q)
17	61.9 (s)	62.8 (s)	62.4 (s)
18	10.3 (q)	10.2 (q)	10.1 (q)
19	170.2 (s)	170.1 (s)	169.9 (s)
20	8.9 (q)	9.7 (q)	9.7 (q)
Acetate methyls	21.4 (q)	21.8 (q)	21.8 (q)
	21.3 (q)	21.8 (q)	21.7 (q)
	21.3 (q)	21.4 (q)	21.4 (q)
Acetate carbonyls	173.1 (s)	170.8 (s)	170.8 (s)
	170.1 (s)	170.2 (s)	170.2 (s)
	169.4 (s)	169.7 (s)	169.7 (s)
3-OC(O)$(CH_2)_2CH_3$		172.1 (s)	172.2 (s)
		36.0 (t)	36.0 (t)
		18.0 (t)	18.1 (t)
		13.6 (q)	13.6 (q)

a) Spectra measured at 100 MHz in $CDCl_3$ at 25 °C. *b*) Attached protons were deduced by DEPT and HMQC spectra.

protons (H-2, H-3, H-10, H-11, H-12) were situated on the same face; they were assigned as α protons, as C-15 methyl was β-oriented and H_3-15 did not show correlation with H-10. H-14 was found to exhibit an interaction 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 3.15) exhibited a large coupling constant (doublet, J=14.0 Hz) and no correlation was found between this proton and H-3. The large coupling constant is considered to be derived from a geminal coupling and indicating the dihedral angle between this proton and H-3 is approximately 90°. By molecular modeling analysis, this proton should be placed on the β face and assigned as H-4β, while the other one was denoted as H-4α (δ_H 1.69). A correlation between H-4β and H-7, reflected the β-orientation of H-7. H-9 (δ_H 5.33) exhibited a doublet coupling with H-10 (J=8.8 Hz) and only a weak correlation was found between H-9 and H-10. This coupling constant is considered to be derived from a vicinal coupling and indicating the dihedral angle between H-9 and H-10 is approximately 180°. Furthermore, H-9 was found to show responses with H-11, H_3-18, and H_3-20, but not with H_3-15. From modeling analysis, H-11 and H_3-20 were positioned at equatorial and axial directions in the cyclohexane ring, respectively, if H-9 was found to be close to H-11, H_3-18, and H_3-20, H-9 should be α-oriented in the ten-membered ring and H_3-18 was β-oriented in the γ-lactone moiety, respectively. Moreover, H_3-16 exhibited a correlation with H-6, suggesting the *Z*-configuration of C-5/6 double bond. Based on the above findings, the structure of **1** was established.

Table 2. ^{1}H-NMR Data for Diterpenoids **1**—**3**[a]

Proton	**1**	**2**	**3**
2	4.52 s	5.13 d (3.2)	5.15 d (3.2)
3	4.10 m	6.33 dd (10.8, 3.2)	6.32 dd (11.2, 3.2)
4α	1.69 m	6.14 dd (10.8, 1.2)	6.10 dd (11.2, 1.2)
β	3.15 d (14.0)[b]		
6	5.13 br s	4.00 d (8.0)	4.29 d (8.0)
7	5.13 br s	4.58 d (8.0)	4.63 d (8.0)
9	5.33 d (8.8)	5.23 d (8.4)	5.24 d (8.4)
10	2.72 dd (8.8, 5.2)	2.68 dd (8.4, 4.8)	2.46 dd (8.4, 4.8)
11	2.45 m	2.17 m	2.17 m
12	4.10 m	3.99 m	4.00 m
13α	1.74 m	1.95 m (2H)	1.95 m (2H)
β	2.00 m		
14	4.91 br s	4.86 dd (2.8, 2.8)	4.86 dd (2.8, 2.8)
15	0.97 s	0.86 s	0.85 s
16	1.93 s	2.14 d (1.2)	2.17 d (1.2)
18	1.63 s	1.63 s	1.63 s
20	1.06 d (7.2)	1.07 d (7.2)	1.07 d (7.2)
OH-12	3.89 br s	n.o.[c]	n.o.
Acetate methyls	2.31 s	2.35 s	2.34 s
	2.20 s	2.27 s	2.27 s
	2.17 s	2.17 s	2.17 s
n-Butyrate		0.90 t (7.6)	0.90 t (7.2)
		1.59 m	1.58 m
		2.16 t (7.6)	2.17 t (7.2)

a) Spectra measured at 400 MHz in $CDCl_3$ at 25 °C. *b*) J values (in hertz) in parentheses. *c*) n.o.=not observed.

Table 3. ^{1}H–^{1}H COSY Correlations for Diterpenoids **1**—**3**

Proton	**1**	**2**	**3**
H-2	n.o.[a]	H-3	H-3
H-3	H_2-4	H-2, H-4	H-2, H-4
H-4	H-3	H-3, H_3-16	H-3, H_3-16
H-6	H-7, H_3-16	H-7	H-7
H-7	H-6	H-6	H-6
H-9	H-10	H-10	H-10
H-10	H-9, H-11	H-9, H-11	H-9, H-11
H-11	H-10, H-12, H_3-20	H-10, H-12, H_3-20	H-10, H-12, H_3-20
H-12	H-11, H_2-13, OH-12	H-11, H_2-13	H-11, H_2-13
H-13	H-12, H-14	H-12, H-14	H-12, H-14
H-14	H_2-13	H_2-13	H_2-13
H-16	H-6	H-4	H-4
H-20	H-11	H-11	H-11
OH-12	H-12	n.o.	n.o.

a) n.o.=not observed.

Excavatoid M (**2**) had a molecular formula $C_{30}H_{42}O_{13}$ as deduced from HR-ESI-MS (*m*/*z* 633.2527, Calcd for $C_{30}H_{42}O_{13}Na$, 633.2523). Its IR spectrum exhibit broad OH

Table 4. HMBC Correlations (H→C) for Diterpenoids **1**—**3**

Position	**1**	**2**	**3**
H-2	C-3, -10	C-1, -3, -4, -10, -14, acetate carbonyl	C-1, -3, -4, -10, -14, acetate carbonyl
H-3	n.o.[a)]	C-4, -5, *n*-butyrate carbonyl	C-4, -5
H-4	C-6, -16	C-3, -6, -16	C-6, -16
H-6	n.o.	C-4, -5, -7, -16	C-4, -5, -7, -16
H-7	n.o.	C-6, -19	C-6, -19
H-9	C-8, -11	C-7, -8, -10, -11, -17, acetate carbonyl	C-7, -8, -10, -11, -17, acetate carbonyl
H-10	C-1, -8, -9, -11, -12, -15, -20	C-1, -2, -8, -9, -11, -15, -20	C-1, -8, -11, -12, -15, -20
H-11	n.o.	C-1, -10, -12, -13	C-1, -9, -10, -12, -13
H-12	n.o.	C-20	n.o.
H-13	n.o.	C-1, -11, -12, -14	C-11
H-14	n.o.	C-10, -12, acetate carbonyl	C-10, -12, acetate carbonyl
H-15	C-1, -2, -10, -14	C-1, -2, -10, -14	C-1, -2, -10, -14
H-16	C-4, -5, -6	C-4, -5, -6	C-4, -5, -6
H-18	C-8, -17, -19	C-8, -17, -19	C-8, -17, -19
H-20	C-10, -11, -12	C-10, -11, -12	C-10, -11, -12

a) n.o.=not observed.

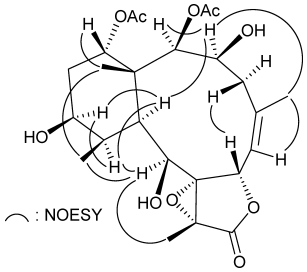


Fig. 1. Selective NOESY Correlations of **1**

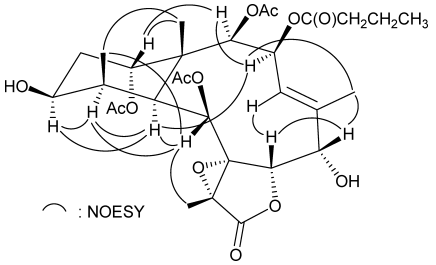


Fig. 2. Selective NOESY Correlations of **2**

stretch at 3460 cm^{-1}, γ-lactone at 1780 cm^{-1}, and ester carbonyls at 1736 cm^{-1}. Carbonyl resonances in the ^{13}C-NMR spectrum of **2** at δ_C 172.1, 170.8, 170.2, 170.1, and 169.7 (5×s), revealed the presence of a γ-lactone and four esters in **2** (Table 1). Three of the esters were identified as acetates by the presence of three acetyl methyl resonances in the ^{1}H-NMR spectrum of **2** at δ_H 2.35, 2.27, and 2.17 (each 3H×s) (Table 2). The other ester was found to be an *n*-butyroxy group based on ^{1}H-NMR studies, which revealed seven contiguous protons (δ_H 2.16, 2H, t, J=7.6 Hz; 1.59, 2H, m; 0.90, 3H, t, J=7.6 Hz). It was found that the 1D- and 2D-NMR data of **2** were similar with those of a known briarane analogue, fragilide A (**4**),[14)] except that the signals corresponding to an acetoxy group in **4** were replaced by an *n*-butyroxy group in **2**. From an HMBC correlation noticed the *n*-butyrate carbonyl carbon at δ_C 172.1 (s) and the proton at δ_H 6.33 (H-3), the *n*-butyroxy group should be attached at C-3 in **2** (Table 4). The other HMBC correlations observed fully supported the locations of functional groups, and hence excavatoid M (**2**) was assigned as the structure **2** with the same relative stereochemistry as in fragilide A (**4**) because for the chiral centers that **2** has in common with **4**, the ^{1}H- and ^{13}C-NMR chemical shifts and proton coupling constants match well, and further supported by a NOESY experiment (Fig. 2). Thus, excavatoid M (**2**) was found to be the 3-deacetoxy-3-*n*-butyroxy derivative of **4**.

Excavatoid N (**3**) was isolated as a white powder and had the same molecular formula $C_{30}H_{42}O_{13}$ as that of **2** on the basis of HR-ESI-MS (see Experimental). By detailed analysis, it was found that the spectral data of **3**, including 1D- and 2D-NMR data, were very similar to those of **2** (Tables 1—4). However, by comparison of the ^{1}H- and ^{13}C-NMR chemical shifts of C-6 oxymethine of **3** (δ_H 4.29, 1H, d, J=8.0 Hz; δ_C 87.7, d) with those of **2** (δ_H 4.00, 1H, d, J=8.0 Hz; δ_C 75.3, d), it was shown that the C-6 hydroxy group in **3** was β-oriented, and this compound should possess a structure as represented by formula **3**.

To the best of knowledge, only two briarane-type natural products, fragilide A and junceellolide L, which possessing a 6-hydroxy group in their structures, were isolated from the gorgonian coral *Junceella fragilis* belonging to the family Ellisellidae.[14,15)] Excavatoids M (**2**) and N (**3**) are the third and fourth examples which possessing a 6-hydroxy group in their structures. It is noteworthy to mention that the double bonds attached at C-4/5 as presented in briaranes **2** and **3** are also rarely found in briarane-type metabolites.[14,16,17)]

In the biological activity testing, excavatoid L (**1**) had displayed moderate inhibitory effects on superoxide anion generation and elastase release by human neutrophils and briaranes **2** and **3** were found to show weak inhibitory effects on above assays (Table 5).

Experimental

General Melting points were measured on a FARGO apparatus and were uncorrected. Optical rotation values were measured with a JASCO P-1010 digital polarimeter. IR spectra were obtained on a VARIAN DIGLAB FTS 1000 FT-IR spectrophotometer. NMR spectra were recorded on a VARIAN MERCURY PLUS 400 FT-NMR at 400 MHz for ^{1}H-NMR and 100 MHz for ^{13}C-NMR, respectively, in $CDCl_3$. Proton chemical shifts were referenced to the residual $CHCl_3$ signal (δ_H 7.26 ppm). ^{13}C-NMR spectra were referenced to the center peak of $CDCl_3$ at δ_C 77.1 ppm. ESI-MS and HR-ESI-MS data were recorded on a BRUKER APEX II mass spectrometer. Gravity column chromatography was performed on silica gel (230—400 mesh, Merck, Darmstadt, Germany). TLC was carried out on precoated

Table 5. Inhibitory Effects of Briaranes **1**—**3** on Superoxide Anion Generation and Elastase Release by Human Neutrophils in Response to fMet-Leu-Phe/Cytochalastin B

Compound	Superoxide anion generation IC_{50} (μM) or (inh.%)[a)]	Elastase release IC_{50} (μM) or (inh.%)[a)]
1	(42.44±2.38)**	(31.25±0.07)***
2	(14.85±3.66)*	(16.96±2.93)*
3	(10.90±0.50)***	(22.21±3.34)*
DPI[b)]	0.8±0.2	
Elastatinal[b)]		30.82±5.69

a) Percentage of inhibition at 10 μg/ml. Results are presented as means±S.E.M. (n=2—3). *p<0.05, **p<0.01, and ***p<0.001 compared with the control value. *b*) DPI (diphenylene indonium) and elastatinal were used as positive control.

Kieselgel 60 F_{254} (0.2 mm, Merck) and spots were visualized by spraying with 10% H_2SO_4 solution followed by heating. HPLC was performed using a system comprised of a HITACHI L-7100 pump, a HITACHI L-7455 photodiode array detector, and a RHEODYNE 7725 injection port. A semi-preparative reverse phase column (Hibar 250—10 mm, Purospher Star RP-18e, 5 μm) was used for HPLC.

Animal Material Specimen of the octocoral *B. excavatum* were collected off the coast of Pingtung, southern Taiwan, and transplanted to five 0.6-ton tanks equipped with a flow-through sea water system in December 2003. The cultured octocorals were harvested in December 2006. This organism was identified by comparison with previous descriptions.[18,19)]

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_2Cl_2 (1 : 1) at room temperature. The extract was partitioned between EtOAc and H_2O. The EtOAc layer was separated on Sephadex LH-20 and eluted using MeOH/CH_2Cl_2 (1 : 1) to yield fractions A—C. Fr. C was separated on silica gel and eluted using hexane/EtOAc (stepwise, 20 : 1-pure EtOAc) to yield Fr. C1—9. Fr. C7 was repurified by reverse phase HPLC, using the mixtures of MeOH, CH_3CN, and H_2O to afford briaranes **1** (0.9 mg, 44/1/55), **2** (3.7 mg, 44/1/55), and **3** (3.0 mg, 55/1/44).

Excavatoid L (**1**): White powder; mp 182—183 °C; $[\alpha]_D^{25}$ +103° (c=0.05, $CHCl_3$); IR (neat) ν_{max} 3450, 1781, 1734 cm^{-1}; ^{13}C-NMR ($CDCl_3$, 100 MHz) data, see Table 1; ^{1}H-NMR ($CDCl_3$, 400 MHz) data, see Table 2; ESI-MS m/z 547 $(M+Na)^+$; HR-ESI-MS m/z 547.2158 (Calcd for $C_{26}H_{36}O_{11}Na$, 547.2155).

Excavatoid M (**2**): White powder; mp 176—177 °C; $[\alpha]_D^{25}$ +65° (c=0.19, $CHCl_3$); IR (neat) ν_{max} 3460, 1780, 1736 cm^{-1}; ^{13}C-NMR ($CDCl_3$, 100 MHz) data, see Table 1; ^{1}H-NMR ($CDCl_3$, 400 MHz) data, see Table 2; ESI-MS m/z 633 $(M+Na)^+$; HR-ESI-MS m/z 633.2527 (Calcd for $C_{30}H_{42}O_{13}Na$, 633.2523).

Excavatoid N (**3**): White powder; mp 168—169 °C; $[\alpha]_D^{25}$ +45° (c=0.15, $CHCl_3$); IR (neat) ν_{max} 3426, 1787, 1740 cm^{-1}; ^{13}C-NMR ($CDCl_3$, 100 MHz) data, see Table 1; ^{1}H-NMR ($CDCl_3$, 400 MHz) data, see Table 2; ESI-MS m/z 633 $(M+Na)^+$; HR-ESI-MS m/z 633.2529 (Calcd for $C_{30}H_{42}O_{13}Na$, 633.2523).

Human Nuetrophil Superoxide Generation and Elastase Release Human neutrophils were obtained by means of dextran sedimentation and Ficoll centrifugation. Superoxide generation and elastase release were carried out according to the procedures described previoulsy.[20,21)] 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-Valp-nitroanilide as the elastase substrate.

Acknowledgements This research work was supported by grants from the NMMBA (981001101); NDHU; APORC, NSYSU (96C031702); and NSTPBP, National Science Council (NSC 98-2323-B-291-001 and 98-2320-B-291-001- MY3), Taiwan, awarded to P.-J.S.

References

1) Sung P.-J., Sheu J.-H., Xu J.-P., *Heterocycles*, **57**, 535—579 (2002).
2) Sung P.-J., Chang P.-C., Fang L.-S., Sheu J.-H., Chen W.-C., Chen Y.-P., Lin M.-R., *Heterocycles*, **65**, 195—204 (2005).
3) Sung P.-J., Sheu J.-H., Wang W.-H., Fang L.-S., Chung H.-M., Pai C.-H., Su Y.-D., Tsai W.-T., Chen B.-Y., Lin M.-R., Li G.-Y., *Heterocycles*, **75**, 2627—2648 (2008).
4) 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., *Tetrahedron*, **64**, 2596—2604 (2008).
5) Sung P.-J., Lin M.-R., Hwang T.-L., Fan T.-Y., Su W.-C., Ho C.-C., Fang L.-S., Wang W.-H., *Chem. Pharm. Bull.*, **56**, 930—935 (2008).
6) Hwang T.-L., Lin M.-R., Tsai W.-T., Yeh H.-C., Hu W.-P., Sheu J.-H., Sung P.-J., *Bull. Chem. Soc. Jpn.*, **81**, 1638—1646 (2008).
7) Sung P.-J., Lin M.-R., Chiang M. Y., *Chem. Lett.*, **38**, 154—155 (2009).
8) Sung P.-J., Lin M.-R., Chiang M. Y., Hwang T.-L., *Bull. Chem. Soc. Jpn.*, **82**, 987—996 (2009).
9) 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., *Tetrahedron*, **65**, 6918—6924 (2009).
10) Sung P.-J., Chen B.-Y., Lin M.-R., Hwang T.-L., Wang W.-H., Sheu J.-H., Wu Y.-C., *Mar. Drugs*, **7**, 472—482 (2009).
11) Sung P.-J., Chen B.-Y., Chiang M. Y., Hou C.-H., Su Y.-D., Hwang T.-L., Chen Y.-H., Chen J.-J., *Bull. Chem. Soc. Jpn.*, **83**, in press (2010).
12) Kokke W. C. M. C., Epstein S., Look S. A., Rau G. H., Fenical W., Djerassi C., *J. Biol. Chem.*, **259**, 8168—8173 (1984).
13) Sung P.-J., Fan T.-Y., Chen M.-C., Fang L.-S., Lin M.-R., Chang P.-C., *Biochem. Syst. Ecol.*, **32**, 111—113 (2004).
14) Sung P.-J., Lin M.-R., Chen W.-C., Fang L.-S., Lu C.-K., Sheu J.-H., *Bull. Chem. Soc. Jpn.*, **77**, 1229—1230 (2004).
15) Sheu J.-H., Chen Y.-P., Hwang T.-L., Chiang M. Y., Fang L.-S., Sung P.-J., *J. Nat. Prod.*, **69**, 269—273 (2006).
16) Anjaneyulu A. S. R., Rao, N. S. K., *J. Chem. Soc., Perkin Trans. 1*, **1997**, 959—962 (1997).
17) Guerriero A., D'Ambrosio M., Pietra F., *Helv. Chim. Acta*, **71**, 472—485 (1988).
18) Bayer F. M., *Proc. Biol. Soc. Wash.*, **94**, 902—947 (1981).
19) Benayahu Y., Jeng M.-S., Perkol-Finkel S., Dai C.-F., *Zool. Stud.*, **43**, 548—560 (2004).
20) Hwang T.-L., Su Y.-C., Chang H.-L., Leu Y.-L., Chung P.-J., Kuo L.-M., Chang Y.-J., *J. Lipid Res.*, **50**, 1395—1408 (2009).
21) Hwang T.-L., Li G.-L., Lan Y.-H., Chia Y.-C., Hsieh P.-W., Wu Y.-H., Wu Y.-C., *Free Radic. Biol. Med.*, **46**, 520—528 (2009).