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Discovery of novel sesquiterpenoids from a gorgonian *Menella* sp.

Shih-Yao Kao [a,b], Jui-Hsin Su [a,b,c], Tsong-Long Hwang [d], Jyh-Horng Sheu [c,e], Yin-Di Su [b,e], Chan-Shing Lin [c,e,f], Yu-Chia Chang [b,f], Wei-Hsien Wang [b,c,e], Lee-Shing Fang [g], Ping-Jyun Sung [a,b,c,e,h,*]

[a] *Graduate Institute of Marine Biotechnology, National Dong Hwa University, Pingtung 944, Taiwan*
[b] *National Museum of Marine Biology and Aquarium, Pingtung 944, Taiwan*
[c] *Division of Marine Biotechnology, Asia-Pacific Ocean Research Center, National Sun Yat-sen University, Kaohsiung 804, Taiwan*
[d] *Graduate Institute of Natural Products, Chang Gung University, Taoyuan 333, Taiwan*
[e] *Department of Marine Biotechnology and Resources, National Sun Yat-sen University, Kaohsiung 804, Taiwan*
[f] *Doctoral Degree Program in Marine Biotechnology, National Sun Yat-sen University and Academia Sinica, Kaohsiung 804, Taiwan*
[g] *Department of Sport, Health, and Leisure, Cheng Shiu University, Kaohsiung 833, Taiwan*
[h] *Department of Life Science and Institute of Biotechnology, National Dong Hwa University, Hualien 974, Taiwan*

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ABSTRACT

A novel sesquiterpenoid, menelloide A (**1**), which was found to possess a new carbon skeleton, and a new guaiane-type sesquiterpenoid, menelloide B (**2**), along with (+)-chloranthalactone B (**3**), an enantiomer of the known sesquiterpenoid, chloranthalactone B (**4**), were isolated from a gorgonian coral identified as *Menella* sp. The structures of sesquiterpenoids **1**–**3** were established by spectroscopic methods and by comparison of the data with those of related metabolites. Sesquiterpenoids **1** and **3** displayed inhibitory effects on the generation of superoxide anion by human neutrophils.

1. Introduction

The gorgonian corals have been proven to be rich sources of interesting and bioactive natural terpenoid derivatives.[1,2] In previous studies, various secondary metabolites including steroids,[3–5] guaiane lactones,[6,7] briarane diterpenoids,[5] menellin A (a highly oxygenated racemate with C8 skeleton),[5] picolinic acid *N*-methyl betaine,[3,8] *n*-hexadecanol,[3] 9*H*-purin-6-amino-*N*-9-dimethyl,[3] thymidine,[3] batyl alcohol,[3,9] and (−)-hydroxylindestrenolide,[10] had been isolated and reported from the gorgonian corals belonging to the genus *Menella*. As part of our ongoing investigation into the isolation of new natural substances from the marine invertebrates collected in Taiwan waters, the intersection point of Kuroshio current and the South China Sea surface current, the chemical constituents of a gorgonian identified as *Menella* sp. was studied for its organic extract, which displayed significant inhibitory effects on the generation of superoxide anion (inhibition rate 84.7%) and the release of elastase (inhibition rate 96.2%) at a concentration of 10 μg/mL by human neutrophils. Three new sesquiterpenoids were isolated, menelloide A (**1**), which was found to feature with a novel carbon skeleton; menelloide B (**2**), a new guaiane-type sesquiterpenoid; and (+)-chloranthalactone B (**3**), an enantiomer of the known sesquiterpenoid, chloranthalactone B (**4**). In this paper, we report the isolation, structure determination, and bioactivity of sesquiterpenoids **1**–**3**.

2. Results and discussion

Menelloide A (**1**) was isolated as a colorless oil and the molecular formula for this compound was determined using HRESIMS to be $C_{15}H_{20}O_3$ (6° of unsaturation) (*m*/*z* 271.1309 $[M+Na]^+$, calculated for 271.1310). The IR spectrum of **1** showed a band at 1767 cm^{-1}, consistent with the presence of ester group. The ^{13}C NMR data for **1** confirmed the presence of 15 carbon signals (Table 1), which were characterized by DEPT as three methyls, four sp^3 methylenes, two sp^2 methines, an sp^3 methine, and five sp^2 quaternary carbons. A suite of resonances at δ_C 171.9 (s, C-12), 154.0 (s, C-8), 130.3 (s, C-7), 101.0 (d, C-9), and 12.7 (q, C-13), could be assigned to the α,β-unsaturated-β-methyl-γ-lactone moiety. Two additional unsaturated functionalities were indicated by ^{13}C NMR resonances at δ_C 137.3 (s, C-4), 132.0 (d, C-1), 131.1 (s, C-11), and 121.4 (d, C-5), suggesting the

* Corresponding author. Tel.: +886 8 8825037; fax: +886 8 8825087; e-mail address: pjsung@nmmba.gov.tw (P.-J. Sung).

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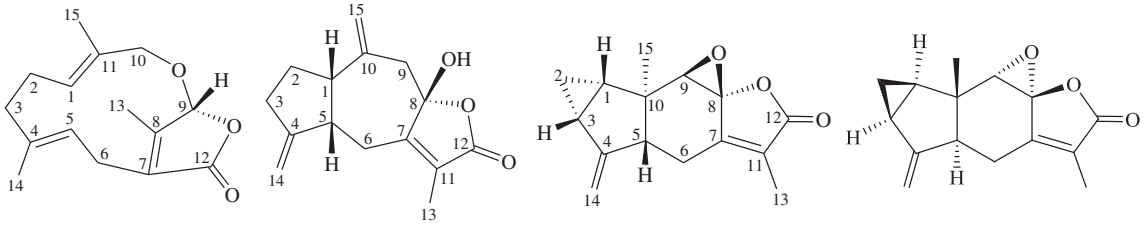

1 **2** **3** **4**

Table 1
^{1}H and ^{13}C NMR, ^{1}H–^{1}H COSY, and HMBC correlations for sesquiterpenoid **1**

C/H	δ_H[a]	δ_C[b]	^{1}H–^{1}H COSY	HMBC (H→C)
1	4.99 d (11.0)[c]	132.0 (d)[d]	H_2-2, H_3-15	n.o.[e]
2a/b	2.38 m; 2.02 br d (15.0)	26.4 (t)	H-1, H_2-3	n.o.
3	2.07 m	37.1 (t)	H_2-2	C-1, C-2, C-4, C-5, C-14
4		137.3 (s)		
5	5.27 dd (10.0, 5.0)	121.4 (d)	H_2-6, H_3-14	n.o.
6a/b	3.04 t (12.0); 2.83 br d (8.5)	22.6 (t)	H-5	C-4, C-5, C-7, C-12
7		130.3 (s)		
8		154.0 (s)		
9	5.82 s	101.0 (d)		C-7, C-10, C-12
10a/b	4.16 d (13.5); 3.90 d (13.5)	69.9 (t)		C-1, C-9, C-15
11		131.1 (s)		
12		171.9 (s)		
13	1.93 s	12.7 (q)		C-7, C-8, C-9
14	1.71 s	16.2 (q)	H-5	C-3, C-4, C-5
15	1.65 s	13.9 (q)	H-1	C-10, C-11

[a] Spectra measured at 500 MHz in $CDCl_3$ at 25 °C.
[b] Spectra measured at 125 MHz in $CDCl_3$ at 25 °C.
[c] *J* values (in hertz) in parentheses.
[d] Multiplicity deduced by DEPT and HMQC experiments and indicated by usual symbols.
[e] n.o.=not observed.

presence of two trisubstituted olefins. Thus, from the reported data, the proposed skeleton of **1** was suggested to be a sesquiterpenoid with two rings.

From the ^{1}H–^{1}H COSY spectrum of **1** (Table 1 and Fig. 1), it was possible to differentiate among the separate spin systems of H-1/H_2-2/H_2-3 and H-5/H_2-6, which was accomplished with the assistance of an HMBC experiment (Table 1 and Fig. 1). The key HMBC correlations between the protons and quaternary carbons of **1**, including H_2-3, H_2-6, H_3-14/C-4; H_2-6, H-9, H_3-13/C-7; H_3-13/C-8; H_3-15/C-11; and H-6, H-9/C-12, permitted the elucidation of the carbon skeleton. The vinyl methyls attached at C-4, C-8, and C-11 were confirmed by the HMBC correlations between H_3-14/C-3, C-4, C-5; H_3-13/C-7, C-8, C-9; and H_3-15/C-10, C-11, and further supported by the allylic couplings between H-1/H_3-15 and H-5/H_3-14, respectively. Furthermore, an HMBC correlation between H-9 (δ_H 5.82) and an oxygen-containing methylene at δ_C 69.9 (t, C-10) suggested the presence of a C-9/10 ether linkage in **1**. The methine unit at δ_C 101.0 (d, C-9) was more shielded than that expected for an oxygenated *C*-atom and correlated with the methine proton at δ_H 5.82 (H-9) in the HMQC spectrum, and this proton showed ^{3}J-correlations with C-7, C-10, and C-12, respectively, in the HMBC spectrum and concluded to be a part of a hemiketal constellation.

The relative configuration of **1** was elucidated on the basis of a NOESY experiment. In the NOESY experiment of **1** (Fig. 2), correlations were observed between H-1/H-5; H_2-2/Me-15; and H_2-6/Me-14; and no correlations were found between H-1/Me-15 and H-5/Me-14, reflected the *E* geometry of double bonds at C-1/11 and C-4/5. The *Z*-configuration of C-7/8 double bond was elucidated by a correlation between one proton of C-6 methylene (δ_H 3.04, H-6a) and C-13 vinyl methyl. However, because only a chiral center C-9 was found in **1**, the absolute configuration for **1** was not determined at this stage and the C-9 chiral center for **1** was assigned as *R**-

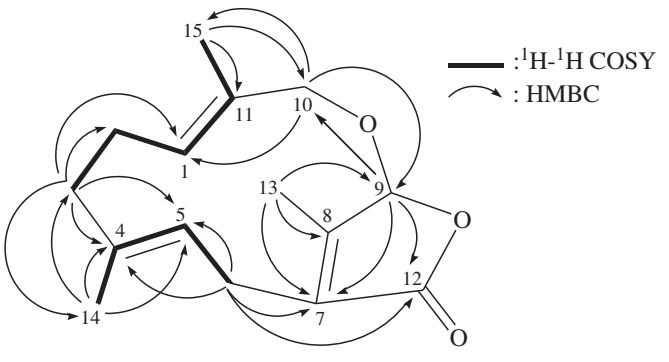

Fig. 1. The ^{1}H–^{1}H COSY and HMBC correlations of **1**.

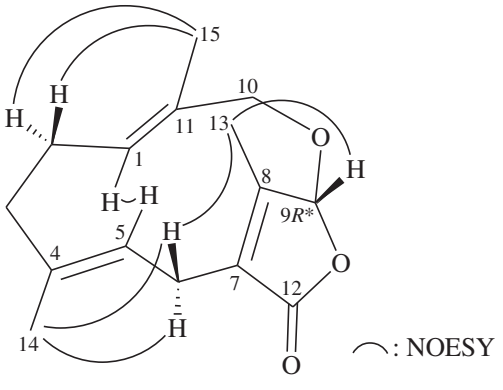

Fig. 2. Selective key NOESY correlations of **1**.

configuration by a correlation between H-9 and C-13 vinyl methyl. Based on the above findings, the structure of **1** was elucidated. To the best of our knowledge, the carbon skeleton as presented in **1** was not reported from any resources.

Sesquiterpenoid **2** (menelloide B), obtained as a colorless oil, showed the $[M+Na]^+$ signal at *m*/*z* 269.1152 in the HRESIMS, suggesting the molecular formula $C_{15}H_{18}O_3$ (calculated for $C_{15}H_{18}O_3$+Na, 269.1154), with 7° of unsaturation. Comparison of the ^{13}C NMR and DEPT spectral data with the molecular formula indicated that there must be an exchangeable proton, requiring the presence of a hydroxy group in **2**, and this deduction was supported by a broad absorption in the IR spectrum at 3369 cm^{-1}. The IR absorption at 1740 cm^{-1} also showed the presence of α,β-unsaturated γ-lactone group in **2**. From the ^1H and ^{13}C NMR spectra (Table 2), **2** was found to possess a γ-lactone moiety (δ_C 171.9, s, C-12), a tetrasubstituted olefin (δ_C 161.0, s, C-7; 123.5, s, C-11), and two exocyclic carbon–carbon double bonds (δ_H 5.09, 1H, s; 5.07, 1H, s, H_2-15; δ_C 142.8, s, C-10; 117.5, t, C-15; δ_H 5.05, 1H, br d, *J*=2.0 Hz; 4.96, 1H, br s, H_2-14; δ_C 155.3, s, C-4; 107.2, t, C-14). From the above data, 4° of unsaturation were accounted for and **2** must be tricyclic. In the ^1H NMR spectrum of **2**, a vinyl methyl (δ_H 1.86, 3H, s, H_3-13), four pairs of methylene protons (δ_H 2.94, 1H, d, *J*=13.2 Hz; 2.48, 1H, d, *J*=13.2 Hz, H_2-9; 2.51, 1H, dd, *J*=12.8, 2.8 Hz; 2.25, 1H, dd, *J*=12.8, 12.4 Hz, H_2-6; 2.50, 1H, m; 2.35, 1H, m, H_2-3; 2.00, 1H, m; 1.74, 1H, m, H_2-2), two methine protons (δ_H 2.82, 1H, m, H-1; 2.62, 1H, br t, *J*=9.6 Hz, H-5), and a hydroxy proton (δ_H 3.08, 1H, br s, OH-8), were observed.

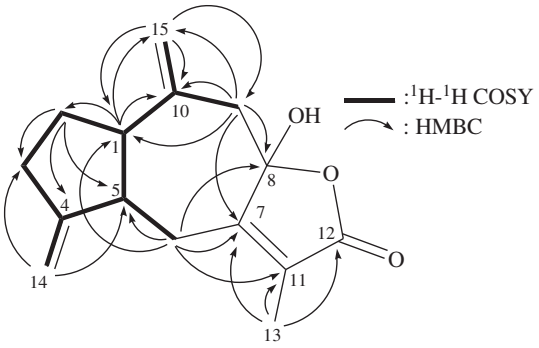

Fig. 3. The ^1H–^1H COSY and HMBC correlations of **2**.

The relative configuration of **2** was elucidated by analysis of NOESY correlations (Fig. 4). In the NOESY experiment of **2**, H-1 (δ_H 2.82), H-5 (δ_H 2.62), and C-8 hydroxy proton (δ_H 3.08) exhibited correlations with each other, indicating that these protons were situated on the same face and assigned as β protons. Based on the above findings, the structure of **2** was established and all the chiral centers for **2** (C-1, C-5, and C-8) were assigned as *S**-configuration, respectively.

Sesquiterpenoid **3** was isolated as a white powder, and the molecular formula of this compound was determined using HRESIMS to be $C_{15}H_{16}O_3$ (*m*/*z* 267.0998 $[M+Na]^+$, calculated for 267.0997). Thus, 8° of unsaturation were determined for **3**. Detailed

Table 2
^1H and ^{13}C NMR data, ^1H–^1H COSY, and HMBC correlations for sesquiterpenoid **2**

C/H	δ_H[a]	δ_C[b]	^1H–^1H COSY	HMBC (H→C)
1	2.82 m	49.5 (d)[d]	H_2-2, H-5, H_2-15	C-2, C-10, C-15
2a/b	2.00 m; 1.74 m	29.0 (t)	H-1, H_2-3	C-3, C-4, C-5
3a/b	2.50 m; 2.35 m	32.2 (t)	H_2-2, H_2-14	n.o.[e]
4		155.3 (s)		
5	2.62 br t (9.6)[c]	45.8 (d)	H-1, H_2-6, H_2-14	n.o.
6a/b	2.51 dd (12.8, 2.8); 2.25 dd (12.8, 12.4)	29.0 (t)	H-5	C-1, C-5, C-7, C-8, C-11
7		161.0 (s)		
8		103.6 (s)		
9a/b	2.94 d (13.2); 2.48 d (13.2)	45.1 (t)	H_2-15	C-1, C-7, C-8, C-10, C-15
10		142.8 (s)		
11		123.5 (s)		
12		171.9 (s)		
13	1.86 s	8.0 (q)		C-7, C-11, C-12
14a/b	5.05 br d (2.0); 4.96 br s	107.2 (t)	H_2-3, H-5	C-3, C-5
15a/b	5.09 s; 5.07 s	117.5 (t)	H-1, H_2-9	C-1, C-9, C-10
OH-8	3.08 br s			n.o.

[a] Spectra measured at 400 MHz in $CDCl_3$ at 25 °C.
[b] Spectra measured at 100 MHz in $CDCl_3$ at 25 °C.
[c] *J* values (in hertz) in parentheses.
[d] Multiplicity deduced by DEPT and HMQC experiments and indicated by usual symbols.
[e] n.o.=not observed.

From the ^1H–^1H COSY correlations of **2**, it was possible to identify the separate spin systems among H-1/H_2-2/H_2-3 and H-1/H-5/H_2-6 (Table 2 and Fig. 3). These data, together with the assistance of HMBC correlations between H-1/C-2, C-10; H_2-2/C-3, C-4, C-5; H_2-6/C-1, C-5, C-7, C-8, C-11; H_2-9/C-1, C-7, C-8, C-10, established the main carbon skeleton of **2** (Table 2 and Fig. 3). The exocyclic carbon–carbon double bonds at C-4 and C-10 were confirmed by the HMBC correlations between H_2-14/C-3, C-5; H-1, H_2-9/C-15; and H_2-15/C-1, C-9, C-10, and further supported by the allylic couplings between H_2-3/H_2-14, H-5/H_2-14, H-1/H_2-15, and H_2-9/H_2-15. The vinyl methyl group at C-11 was established by the HMBC correlations between Me-13/C-7, C-11, C-12. Thus, the remaining hydroxy group should be positioned at C-8 and be a part of a hemiketal constellation on the basis of a characteristic carbon signal at δ_C 103.6 (s, C-8). Therefore, the planar structure of **2** was established.

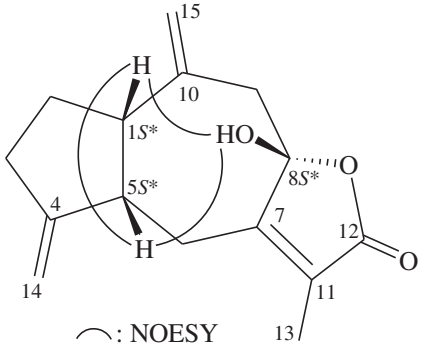

Fig. 4. Selective key NOESY correlations of **2**.

analysis of the NMR data showed that the data for **3** were in full agreement with those of a known lindenane-type sesquiterpenoid analogue, chloranthalactone B (**4**), which was isolated from the roots of *Chloranthus glaber* and *Chloranthus japonicus*, respectively.[11,12] However, the optical value of **3** ($[\alpha]_D^{25}$ +136 (*c* 0.05, $CHCl_3$)) was substantially different from that of **4** ($[\alpha]_{340}^{27}$ −130.3 (*c* 0.1, MeOH)),[12,13] indicating that sesquiterpenoid **3** is an enantiomer of **4** and should be designated as (+)-chloranthalactone B. Because of the absolute stereochemistry for chloranthalactone B (**4**) had been determined by chemical methods,[12] the absolute stereochemistry for the chiral centers of (+)-chloranthalactone B (**3**) should be assigned as 1*S*,3*R*,5*R*,8*R*,9*R*, and 10*R*, respectively. The ^1H and ^{13}C NMR data for **3** (Table 3) were assigned completely using 2D NMR data analysis and comparison to the NMR data of **4**.[11,12]

Table 3
^1H and ^{13}C NMR data, $^1H-^1H$ COSY, and HMBC correlations for sesquiterpenoid **3**

C/H	δ_H[a]	δ_C[b]	$^1H-^1H$ COSY	HMBC (H→C)
1	1.72 td (7.6, 3.6)[c]	23.9 (d)[d]	H_2-2, H-3	n.o.[e]
2a/b	0.91 ddd (9.2, 7.6, 5.6); 0.85 dt (5.6, 3.6)	16.9 (t)	H-1, H-3	C-4, C-10
3	2.01 m	22.9 (d)	H-1, H_{22}-2, H_{22}-14	n.o.
4		149.4 (s)		
5	3.39 ddt (13.2, 5.6, 2.8)	50.6 (d)	H_2-6, H_{22}-14	n.o.
6a/b	2.56 ddq (19.2, 5.6, 2.0); 2.12 ddq (19.2, 13.2, 2.0)	21.3 (t)	H-5, H_{32}-13	C-5, C-7, C-10
7		152.3 (s)		
8		87.9 (s)		
9	4.18 s	64.4 (d)		C-5, C-8, C-10
10		41.1 (s)		
11		129.1 (s)		
12		170.4 (s)		
13	1.90 t (2.0)	9.0 (q)	H_2-6	C-7, C-11, C-12
14a/b	5.04 m; 4.71 dd (2.8, 2.0)	106.8 (t)	H-3, H-5	C-3, C-5
15	0.65 s	16.8 (q)		C-1, C-5, C-9, C-10

[a] Spectra measured at 400 MHz in $CDCl_3$ at 25 °C.
[b] Spectra measured at 100 MHz in $CDCl_3$ at 25 °C.
[c] *J* values (in hertz) in parentheses.
[d] Multiplicity deduced by DEPT and HMQC experiments and indicated by usual symbols.
[e] n.o.=not observed.

The in vitro anti-inflammatory effects of sesquiterpenoids **1**–**3** were tested. Menelloide A (**1**) and (+)-chloranthalactone B (**3**) displayed weak inhibitory effects on the generation of superoxide anion by human neutrophils at a concentration of 10 μg/mL (Table 4).

Table 4
Inhibitory effects of sesquiterpenoids **1**–**3** on superoxide anion generation and elastase release by human neutrophils in response to FMLP/CB

Compounds	Superoxide anion		Elastase release
	Inh %[a]		Inh %
1	27.6±3.1	***	6.7±5.7
2	2.9±6.0		0.7±4.0
3	16.5±6.5		6.6±1.5

***$P<0.001$ compared with the control value.[14]
[a] Percentage of inhibition (Inh %) at 10 μg/mL concentration of **1**–**3**. Results are presented as mean±S.E.M. (n=3).

In our previous study, an eudesmane-type sesquiterpenoid, (−)-hydroxylindestrenolide, which displayed a weak inhibitory effect on the generation of superoxide anion by human neutrophils, was also isolated in this study material *Menella* sp.[10] As described in the introduction, the organic extract of *Menella* sp. displayed significant inhibitory effects on the generation of superoxide anion and the release of elastase. However, at this stage, the results showed that the compounds that we isolated only showed weak activity. We suggested that the active components are still existed in the other fractions and these fractions will be studied in the future.

3. Experimental

3.1. General experimental procedures

Optical rotations were measured on a Jasco P-1010 digital polarimeter. Infrared spectra were recorded on a Varian Diglab FTS 1000 FT-IR spectrometer; peaks are reported in cm^{-1}. The NMR spectra were recorded on Varian Mercury Plus 400 or Varian Inova 500 NMR spectrometers, using the residual $CHCl_3$ signal (δ_H 7.26 ppm) as an internal standard for ^1H NMR and $CDCl_3$ (δ_C 77.1 ppm) for ^{13}C NMR; coupling constants (*J*) are given in hertz. ^1H and ^{13}C NMR assignments were supported by $^1H-^1H$ COSY, HMQC, HMBC, and NOESY experiments. ESIMS and HRESIMS 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_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 injection port. Two normal phase columns (Hibar 250×10 mm, Merck, silica gel 60, 5 μm; Hibar 250×21.2 mm, Supelco, silica gel 60, 5 μm) were used for HPLC.

3.2. Animal material

Specimens of the gorgonian coral *Menella* sp. were collected by trawling off the coast of southern Taiwan in December 2004 at a depth of 100 m. A voucher specimen (NMMBA-TW-GC-005) was deposited in the National Museum of Marine Biology and Aquarium, Taiwan. This organism was identified by comparison with previous descriptions.[15]

3.3. Extraction and isolation

The freeze-dried and minced material of *Menella* sp. (wet weight 451 g, dry weight 411 g) was extracted with ethyl acetate (EtOAc) at room temperature. The EtOAc layer was separated on silica gel and eluted using *n*-hexane/EtOAc (stepwise) to yield fractions 1–16. Fraction 3 was separated by normal phase HPLC (NP-HPLC), using the mixtures of *n*-hexane and EtOAc (15:1-pure EtOAc) to yield the fractions 3A–3Z. Fractions 3I and 3J were combined and purified by NP-HPLC using the mixtures of *n*-hexane and EtOAc to afford **1**

(15:1). Fraction 3D was further separated by NP-HPLC (*n*-hexane/acetone, 25:1) to afford **3**. Compound **2** was obtained from fraction 6 by NP-HPLC (*n*-hexane/EtOAc, 6:1).

*3.3.1. Menelloide A (**1**).* Colorless oil (1.3 mg); $[\alpha]_D^{25}$ −9 (*c* 0.07, $CHCl_3$); IR (neat) ν_{max} 1767 cm^{-1}; ^1H ($CDCl_3$, 500 MHz) and ^{13}C ($CDCl_3$, 125 MHz) NMR data, see Table 1; ESIMS: *m*/*z* 271 $(M+Na)^+$; HRESIMS: *m*/*z* 271.1309 (calcd for $C_{15}H_{20}O_3$+Na, 271.1310).

*3.3.2. Menelloide B (**2**).* Colorless oil (1.5 mg); $[\alpha]_D^{25}$ −30 (*c* 0.1, $CHCl_3$); IR (neat) ν_{max} 3369, 1740 cm^{-1}; ^1H ($CDCl_3$, 400 MHz) and ^{13}C ($CDCl_3$, 100 MHz) NMR data, see Table 2; ESIMS: *m*/*z* 269 $(M+Na)^+$; HRESIMS: *m*/*z* 269.1152 (calcd for $C_{15}H_{18}O_3$+Na, 269.1154).

*3.3.3. (+)-Chloranthalactone B (**3**).* White powder (1.2 mg); mp 142–144 °C; $[\alpha]_D^{25}$ +136 (*c* 0.05, $CHCl_3$); IR (neat) ν_{max} 1793 cm^{-1}; ^1H ($CDCl_3$, 400 MHz) and ^{13}C ($CDCl_3$, 100 MHz) NMR data, see Table 3; ESIMS: *m*/*z* 267 $(M+Na)^+$; HRESIMS: *m*/*z* 267.0998 (calcd for $C_{15}H_{16}O_3$+Na, 267.0997).

3.4. Superoxide anion generation and elastase release by human neutrophils

Human neutrophils were obtained using dextran sedimentation and Ficoll centrifugation. Measurements of superoxide anion generation and elastase release were carried out according to previously described procedures.[16,17] 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.

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