Abstract: New four eunicellin-based diterpenoids, krempfielins J–M (1–4) were isolated from the organic extract of a Taiwanese soft coral *Cladiella krempfi*. The structures of the new metabolites were elucidated on the basis of extensive spectroscopic analysis. The structure of compound 2 is rare due to the presence of the highly oxygenated pattern. Anti-inflammatory activity of 1–6 to inhibit the superoxide anion generation and elastase release in FMLP/CB-induced human neutrophils was also evaluated, and 2 and 4 were shown to possess the ability to inhibit the elastase release.

Keywords: *Cladiella krempfi*; eunicellin-based diterpenoid; elastase; anti-inflammatory agent
1. Introduction

Many recent studies about the discovery of versatile structures and bioactivities of eunicellin-type compounds isolated from soft corals have been reported [1–15]. The soft coral Cladiella krempfi has been found to generate several types of metabolites including eunicellin-type diterpenoids [16,17] and pregnane-type steroids [18–20]. Our previous study on the bioactive secondary metabolites of a Taiwanese soft coral Cladiella krempfi also resulted in the isolation of a series of new eunicellin-based diterpenoids, krempfielins A–I [21,22]. In this paper, we further report the discovery of four new eunicellin-based diterpenoids, krempfielins J–M (1–4), along with two known diterpenoids sclerophytin F (5) [23] and litophynol B (6) [24] (Chart 1). The ability of these compounds to inhibit the superoxide anion generation and elastase release in FMLP/CB-induced human neutrophils was also evaluated. The results showed that at 10 μM compounds 2 and 4 effectively inhibited the elastase release in FMLP/CB-induced human neutrophils.

Chart 1. Structures of metabolites 1–6.

2. Results and Discussion

Krempfielin J (1) showed the pseudomolecular ion peak [M + Na]^+ at m/z 417.2616 in the HRESIMS and the molecular formula was determined as C_{23}H_{38}O_{5}. NMR spectroscopic data of 1 (Table 1) showed the presence of one acetoxy group (δ_{C} 169.6 and 22.4; δ_{H} 2.12, s, 3H) and one methoxyl group (δ_{C} 57.0 and δ_{H} 3.34, 3H, s). The NMR data of 1 was found to be similar to the known compound, 7 [22,25] (Chart 1). Comparison of the NMR data of them revealed that the only difference between both compounds arises from the replacement of the n-butyryloxy group at C-3 in 7 by one acetoxy group in 1. The stereochemistry of 1 was confirmed by comparison of the NMR data and NOE correlations of both 7 and 1.
### Table 1. $^{13}$C and $^1$H NMR data for compounds 1–4.

|    | $\delta$C | $\delta$H |    | $\delta$C | $\delta$H |    | $\delta$C | $\delta$H |    | $\delta$C | $\delta$H |
|----|-----------|-----------|----|-----------|-----------|----|-----------|-----------|----|-----------|-----------|
| 1  | 45.6, CH  | 2.20 dd   | 37.8, CH | 3.24 m  | 44.2, CH  | 2.31 t (8.0) | 44.2, CH | 3.69 br s  | 902, CH  | 3.69 d (2.0) |
| 2  | 92.1, CH  | 3.59 br s | 80.9, CH | 3.58 m  | 90.4, CH  | 3.69 br s  | 902, CH | 3.69 br s  | 902, CH  | 3.69 d (2.0) |
| 3  | 86.6, C   | 1.75 m  | 83.8, C  | 1.92 m  | 86.6, C  | 1.94 m  | 86.6, C | 1.94 m  | 1.92 m |
| 4  | 36.8, CH$_2$ | 2.61 dd (14.4, 9.2) | 28.8, CH$_2$ | 2.90 dd (14.8, 7.0) | 34.6, CH$_2$ | 2.48 m | 34.9, CH$_2$ | 2.52 dd (14.8, 8.8) |
| 5  | 26.8, CH$_2$ | 1.33 m | 19.9, CH$_2$ | 1.50 m | 30.4, CH$_2$ | 1.42 m | 30.5, CH$_2$ | 1.45 m | 1.68 m |
| 6  | 90.6, CH  | 4.12 d (6.0) | 70.1, CH | 3.68 m  | 79.0, CH  | 4.57 d (8.4) | 79.1, CH | 4.58 d (7.2) |
| 7  | 75.9, C   | 1.82 m  | 79.0, CH | 3.62 m  | 46.0, CH$_2$ | 1.85 m | 45.9, CH$_2$ | 1.83 m |
| 8  | 45.0, CH$_2$ | 4.18 dd (14.8, 7.2) | 69.9, CH | 4.39 t (8.0) | 79.4, CH | 4.53 m | 78.8, CH | 4.40 m |
| 9  | 78.5, CH  | 2.95 t (7.2) | 50.0, CH | 2.51 br s | 51.0, CH | 2.86 m | 51.4, CH | 2.93 dd (7.2, 6.0) |
| 10 | 53.9, CH  | 2.04 m | 71.6, CH | 5.29 m  | 70.7, CH | 4.37 s  | 72.5, CH | 5.44 dd (5.6, 2.8) |
| 11 | 147.6, C  | 145.3, C | 148.0, C | 1.70 m | 1.00 m | 1.58 m | 31.9, CH$_2$ | 1.46 m | 29.0, CH$_2$ | 1.42 m |
| 12 | 31.5, CH$_2$ | 1.26 m | 40.1, CH | 1.48 m  | 36.5, CH | 1.82 m  | 37.2, CH | 1.70 m |
| 13 | 24.6, CH$_3$ | 1.26 m | 31.9, CH$_2$ | 1.46 m | 31.2, CH$_2$ | 1.84 m | 29.0, CH$_2$ | 1.90 m |
| 14 | 44.0, CH  | 1.85 s  | 26.3, CH$_3$ | 1.56 s | 23.2, CH$_3$ | 1.48 s | 23.2, CH$_3$ | 1.47 s |
| 15 | 23.1, CH$_3$ | 1.19 s | 13.7, CH$_3$ | 1.99 s | 22.6, CH$_3$ | 1.17 s | 22.8, CH$_3$ | 1.18 s |
| 16 | 23.6, CH$_3$ | 4.64 s | 105.0, CH$_2$ | 5.04 s | 111.8, CH$_2$ | 4.87 s | 114.9, CH$_2$ | 4.97 s |
| 17 | 109.4, CH$_2$ | 4.68 s | 37.5, CH$_2$ | 2.22 m | 37.5, CH$_2$ | 2.22 m | 37.5, CH$_2$ | 2.22 m |
| 18 | 29.1, CH  | 1.72 m  | 28.3, CH | 2.03 m  | 29.0, CH | 1.80 m  | 28.9, CH | 1.80 m |
| 19 | 15.6, CH$_3$ | 0.79 d (6.8) | 21.5, CH$_3$ | 1.06 d (6.5) | 16.4, CH$_3$ | 0.85 d (6.4) | 16.2, CH$_3$ | 0.83 d (6.8) |
| 20 | 21.9, CH$_3$ | 0.97 d (6.8) | 21.5, CH$_3$ | 1.09 d (6.5) | 21.9, CH$_3$ | 1.00 d (6.4) | 21.8, CH$_3$ | 0.96 d (6.8) |
| 3-n-butrate | | | | | | | | |
| 3-OAc | 169.6, C | 169.5, C | 169.4, C | 22.4, CH$_3$ | 22.4, CH$_3$ | 22.4, CH$_3$ | 22.4, CH$_3$ | 22.4, CH$_3$ | 22.4, CH$_3$ |
| 6-OMe | 57.0, CH$_3$ | 3.34 s | 18.6, CH$_2$ | 1.64 m | 13.8, CH$_3$ | 0.95 t (7.5) | 18.6, CH$_2$ | 1.64 m |
| 6-OAc | | | | | | | | |
| 8-OAc | | | | | | | | |
| 12-OAc | 170.0, C | 21.2, CH$_3$ | 2.14 s | 170.3, C | 21.5, CH$_3$ | 2.06 s |

$^a$ $^{13}$C and $^1$H spectra recorded at 100 and 400 MHz in CDCl$_3$; $^b$ $^{13}$C and $^1$H spectra recorded at 125 and 500 MHz in CDCl$_3$; $^c$ Deduced from DEPT; $^d$ $J$ values (Hz) in parentheses; $^e$ Broad signal.
The new metabolite krempfielin K (2) was found to have the molecular formula C_{26}H_{42}O_{8} and six degrees of unsaturation, as indicated from the HRESIMS. The IR absorptions at $\nu_{\text{max}}$ 3444 and 1732 cm$^{-1}$ revealed the presence of hydroxy and ester carbonyl functionalities. The $^{13}$C carbons spectral data (Table 1) were assigned by the assistance of DEPT spectrum to six methyls (including one acetate methyl $\delta_{C}$ 21.2), five $sp^3$ methylenes, one $sp^2$ methylene, nine $sp^3$ methines (including five oxymethines), two $sp^3$ and three $sp^2$ quaternary carbons (including two ester carbonyls). The NMR spectroscopic data of 2 (Table 1) showed the presence of one 1,1-disubstituted double bond ($\delta_{C}$ 105.0, CH$_2$ and 145.3, C; $\delta_{H}$ 5.23, s and 5.04, s, each 1H). Two ester carbonyls ($\delta_{C}$ 172.6 and 170.0) were assigned from the $^{13}$C NMR spectrum and were HMBC correlated with the methylene ($\delta_{H}$ 2.30 m and 2.22 m, each 1H) of an $n$-butyrate and those of an acetate methyl ($\delta_{H}$ 2.14, s, 3H), respectively. Therefore, the remaining three degrees of unsaturation identified compound 2 as a tricyclic molecule. $^1$H-$^1$H COSY and HMBC correlations (Figure 1) were further used to establish the molecular skeleton of 2. The COSY experiment assigned five isolated consecutive proton spin systems. Above evidences and HMBC correlations from H-2 and H-6 ($\delta_{H}$ 3.58 and 3.68) to C-6 and C-2 ($\delta_{C}$ 70.1 and 80.9), respectively, implied the presence of an ether linkage between C-2 and C-6, and suggested that 2 is an 2,6-ether linked eunicellin-based diterpenoid [1,26]. Furthermore, the acetoxy group attaching at C-12 was confirmed from the HMBC correlations from H-12 ($\delta_{H}$ 5.29) and acetate methyl protons ($\delta_{H}$ 2.14) to the carbonyl carbon appearing at 170.0 (C). Thus, the remaining one $n$-butyryloxy group had to be positioned at C-3, an oxygen-bearing quaternary carbon resonating at $\delta$ 83.8 ppm. On the basis of above analysis, the planar structure of 2 was established. The relative structure of 2 was elucidated by the analysis of NOESY correlations, as shown in Figure 2. The observation of the NOE interactions between H-1 and H-6, H-8 and H-10; H-10 and both H-8 and H-12, revealed that they are all $\beta$-oriented. Also, the correlations between H-2 and H-9, H-14 and H$_3$-15; H-9 and H$_3$-16 suggested that of all of H-2, H-9, H-14, H$_3$-15 and H$_3$-16 are $\alpha$-oriented. The relative configuration of 2 was thus established. The highly oxygenated pattern of 2 at C-2, C-3, C-6, C-7, C-8, C-9 and C-12 is rare in known eunicellins.

**Figure 1.** Selected $^1$H-$^1$H COSY (→) and HMBC (→) correlations of 2–4.

Krempfielin L (3) showed the molecular ion peak [M + Na]$^+$ at m/z 419.2407 in the HRESIMS and established a molecular formula of C$_{25}$H$_{36}$O$_6$, implying five degrees of unsaturation. The IR absorptions at $\nu_{\text{max}}$ 3419 and 1734 cm$^{-1}$ revealed the presence of hydroxy and ester carbonyl functionalities. The $^{13}$C NMR spectrum of 3 showed signals of 22 carbons (Table 1), which were characterized by the DEPT spectrum as five methyls (including one acetate methyl), five methylenes (including one $sp^2$ methylene),
eight methines (including four oxygenated carbons), and four quaternary carbons (including one ester carbonyl and one sp² quaternary carbon of an olefin). The ¹H and ¹³C NMR spectral data of 3 (Table 1) also showed the presence of one acetoxy group (δ_H 2.07, s, 3H; δ_C 22.4, CH₃ and 169.5, C). The remaining three degrees of unsaturation again identified 3 as a tricyclic diterpenoid. The molecular framework was established by ¹H-¹H COSY and HMBC correlations (Figure 1). Comparison of the NMR data of 3 with those of the known compound sclerophytin E [27] revealed that 3 is the C-12 hydroxylated derivative of sclerophytin E. The stereochemistry of compound 3 was determined by the NOESY spectrum as shown in Figure 2.

**Figure 2.** Key NOESY correlations for 2 and 3.

The HRESIMS (m/z 461.2518 [M + Na]⁺) of kremphielin M (4) established the molecular formula of C$_{24}$H$_{38}$O$_7$. The ¹H and ¹³C NMR spectral data of 4 (Table 1) revealed that the structure of metabolite 4 should be similar to that of 3, as the ¹H NMR spectral data of 4 are almost identical with those of 3 except for the presence of one additional acetyl group (δ_H 2.06, s, 3H) in 4. Furthermore, the placement of an acetoxy group at C-12 was established by the HMBC experiment which showed correlations from an oxymethine (δ_H 5.44, H-12) and acetate methyl (δ_H 2.06) to the ester carbonyl carbon appearing at δ_C 170.3 (C) (Figure 1). The NOE correlations of 4 also showed that the stereochemistry of this metabolite is identical with that of 3. Thus the structure of metabolite 4 was determined.

The *in vitro* anti-inflammatory effects of the diterpenoids 1–6 were tested by examining the inhibitory activity of these compounds toward the release of elastase in N-formyl-methionyl-leucyl-phenylalanine/cytochalasin B (FMLP/CB)-induced human neutrophils cells (Table 2). At a concentration of 10 µM, all of these compounds could not significantly reduce the expression of superoxide anion, relative to the control cells stimulated with FMLP/CB only. At the same concentration, compounds 2 and 4 were found to effectively inhibit the elastase release (45.51 ± 2.69% and 27.30 ± 5.42% inhibition, respectively) in the same FMLP/CB-stimulated cells.
Table 2. Effect of pure compounds on elastase release in FMLP/CB-induced human neutrophils.

| Compound | Elastase Inh% | IC₅₀ (μM) |
|----------|---------------|-----------|
| 1        | 19.42 ± 7.89  | >10       |
| 2        | 45.51 ± 2.69  | >10       |
| 3        | 18.67 ± 5.75  | >10       |
| 4        | 27.30 ± 5.42  | >10       |
| 5        | −0.32 ± 0.81  | >10       |
| 6        | 6.15 ± 3.42   | >10       |

Percentage of inhibition (Inh%) was measured at 10 μM. Results are presented as mean ± S.E.M. (n = 3 or 4); * p < 0.05, ** p < 0.01 and *** p < 0.001 compared with the control value.

3. Experimental Section

3.1. General Experimental Procedures

Melting point was determined using a Fisher-Johns melting point apparatus. Optical rotations were measured on a JASCO P-1020 polarimeter. IR spectra were recorded on a JASCO FT/IR-4100 infrared spectrophotometer. ESIMS were obtained with a Bruker APEX II mass spectrometer. The NMR spectra were recorded either on a Varian UNITY INOVA-500 FT-NMR and a Varian 400MR FT-NMR. Silica gel (Merck, 230–400 mesh) was used for column chromatography. Precoated silica gel plates (Merck, Kieselgel 60 F254, 0.2 mm) were used for analytical thin layer chromatography (TLC). High performance liquid chromatography was performed on a Hitachi L-7100 HPLC apparatus with an octadecylsilane (ODS) column (250 × 21.2 mm, 5 μm).

3.2. Animal Material

_C. krempfi_ was collected by hand using scuba off the coast of Penghu islands of Taiwan in June 2008, at a depth of 5–10 m, and stored in a freezer until extraction. A voucher sample (specimen No. 200806CK) was deposited at the Department of Marine Biotechnology and Resources, National Sun Yat-sen University.

3.3. Extraction and Separation

The octocoral (1.1 kg fresh wt) was collected and freeze-dried. The freeze-dried material was minced and extracted exhaustively with EtOH (3 × 10 L). The EtOH extract of the frozen organism was partitioned between CH₂Cl₂ and H₂O. The CH₂Cl₂-soluble portion (14.4 g) was subjected to column chromatography on silica gel and eluted with EtOAc in n-hexane (0%–100% of EtOAc, stepwise) and then further with MeOH in EtOAc with increasing polarity to yield 41 fractions. Fraction 28, eluted with n-hexane–EtOAc (1:2), was rechromatographed over a reversed-phase column (RP-18) using acetone–H₂O (10:1) as the mobile phase to afford six subfractions (A1–A6). Subfraction A3 was repeatedly separated by reverse phase HPLC (CH₃CN–H₂O, 1.4:1.1) to afford compound 1 (2.6 mg). Fraction 31, eluted with n-hexane–EtOAc (1:10), was rechromatographed over a silica gel
open column using n-hexane–acetone (3:1) as the mobile phase to afford eight subfractions (B1–B8). Subfraction B5 separated by reverse phase HPLC (CH<sub>3</sub>CN–H<sub>2</sub>O, 1:1 to 1:1.6) to afford compounds 2 (5.1 mg), 3 (2.8 mg), 5 (52.3 mg) and 6 (13.4 mg). Subfraction B6 by reverse phase HPLC (CH<sub>3</sub>CN–H<sub>2</sub>O, 1:1.5) to afford compounds 4 (8.4 mg).

3.3.1. Krempfielin J (1)

Colorless oil; [α]<sup>23</sup> <sub>D</sub> = +52 (c 0.85, CHCl<sub>3</sub>); IR (neat) ν<sub>max</sub> 3479, 2958, 2930, 2872, 1737, 1644, 1463, 1369, 1244, and 1100 cm<sup>−1</sup>; <sup>13</sup>C and <sup>1</sup>H NMR data, see Table 1; ESIMS m/z 417 [M + Na]<sup>+</sup>; HRESIMS m/z 417.2616 [M + Na]<sup>+</sup> (calcd. for C<sub>23</sub>H<sub>38</sub>O<sub>3</sub>Na, 417.2617).

3.3.2. Krempfielin K (2)

White powder; mp 162–163 °C; [α]<sup>25</sup> <sub>D</sub> = −58 (c 1.5, CHCl<sub>3</sub>); IR (neat) ν<sub>max</sub> 3444, 2963, 1731, 1651, 1464, 1380, 1240, 1177, 1087, and 1045 cm<sup>−1</sup>; <sup>13</sup>C and <sup>1</sup>H NMR data, see Table 1; ESIMS m/z 505 [M + Na]<sup>+</sup>; HRESIMS m/z 505.2780 [M + Na]<sup>+</sup> (calcd. for C<sub>26</sub>H<sub>42</sub>O<sub>6</sub>Na, 505.2777).

3.3.3. Krempfielin L (3)

Colorless oil; [α]<sup>25</sup> <sub>D</sub> = +26 (c 0.8, CHCl<sub>3</sub>); IR (neat) ν<sub>max</sub> 3419, 2958, 1734, 1457, 1369, 1246, 1063 and 1026 cm<sup>−1</sup>; <sup>13</sup>C and <sup>1</sup>H NMR data, see Table 1; ESIMS m/z 419 [M + Na]<sup>+</sup>; HRESIMS m/z 419.2407 [M + Na]<sup>+</sup> (calcd. for C<sub>22</sub>H<sub>38</sub>O<sub>6</sub>Na, 419.2409).

3.3.4. Krempfielin M (4)

Colorless oil; [α]<sup>25</sup> <sub>D</sub> = +24 (c 2.4, CHCl<sub>3</sub>); IR (neat) ν<sub>max</sub> 3452, 2960, 1736, 1435, 1370, 1243, 1199, 1075, and 1024 cm<sup>−1</sup>; <sup>13</sup>C and <sup>1</sup>H NMR data, see Table 1; ESIMS m/z 461 [M + Na]<sup>+</sup>; HRESIMS m/z 461.2518 [M + Na]<sup>+</sup> (calcd. for C<sub>24</sub>H<sub>38</sub>O<sub>7</sub>Na, 461.2515).

3.4. In Vitro Anti-Inflammatory Assay—Superoxide Anion Generation and Elastase Release by Human Neutrophils

Human neutrophils were obtained by means of dextran sedimentation and Ficoll centrifugation. Measurements of superoxide anion generation and elastase release were carried out according to previously described procedures [28,29]. LY294002, a phosphatidylinositol-3-kinase inhibitor, was used as a positive control for inhibition of superoxide anion generation and elastase release with IC<sub>50</sub> values of 1.88 ± 0.45 and 4.12 ± 0.92 μM, respectively. 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 [30].

4. Conclusions

New eunicellin-based diterpenoids were isolated together with known ones from the soft coral *Cladiella krempfi*. Compounds 2 and 4 could significantly inhibit the release of elastase in
FMLP/CB-induced human neutrophils. Thus, compounds 2 and 4, in particular 2, could be promising anti-inflammatory agents and may warrant further biomedical investigation.

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