HETEROCYCLES, Vol. 83, No. 9, 2011, pp. 2149 - 2155. © The Japan Institute of Heterocyclic Chemistry
Received, 9th May, 2011, Accepted, 1st July, 2011, Published online, 11th July, 2011
DOI: 10.3987/COM-11-12251

CYTOTOXIC EUNICELLIN-TYPE DITERPENES FROM THE SOFT CORAL *LITOPHYTON VISCUDIUM*

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Abstract – Five new eunicellin-type diterpenes were isolated from the soft coral *Litophyton viscudium*. The structures of the compounds were elucidated mainly on the basis of extensive spectroscopic analysis. Compounds exhibited cytotoxic activity against HL-60 with IC_{50} values of 4.2–50 μM.

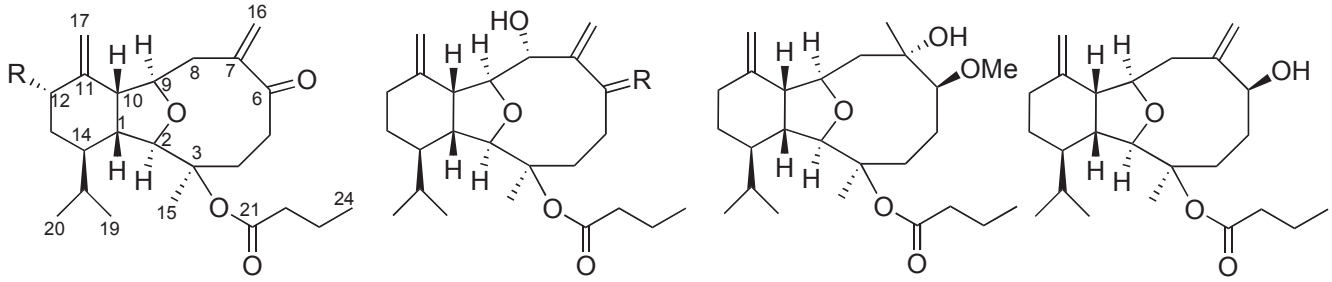
The soft coral *Litophyton* species is known to produce a sesquiterpene,[1] cembranes,[1] eunicellin-based diterpenes,[2-5] and sterols[6] possessing biological activities, such as antiproliferative activity against the cell lines L-929 and K-562, cytotoxicity against HeLa cells,[1] and hemolytic,[2] molluscicidal,[3] repellent,[4] insect growth inhibitory,[5] brine shrimp lethality,[6] and antileukemic[7] activities. As a continuation of our survey on bioactive compounds from marine organisms,[8] the CH_2Cl_2-soluble portion (23 g) of a MeOH extract of the soft coral *L. viscudium* (5.3 kg, wet wt.), collected in the area of Otsuki Town area, Kochi Prefecture, Japan, showed moderate cytotoxic activity (IC_{50} = 6.9 μg/mL) against the proliferation of human promyelocytic leukemia cells (HL-60). Further investigation of this CH_2Cl_2 fraction has led to the

isolation of five new eunicellin-type diterpenes: (**1** (3.7 mg), **2** (2.0 mg), **3** (1.8 mg), **4** (3.7 mg), and **5** (11.7 mg)) and a known compound, litophynin F (**6**)[5(a)] (7.3 mg). The isolates exhibited moderate cytotoxic activity against HL-60 cells. In this paper, we describe the isolation and structure elucidation of these new compounds.

Compound **1** was isolated as an amorphous powder and had a molecular formula of $C_{24}H_{36}O_5$, which was determined by HRFABMS [*m/z* 405.2629, $(M + H)^+$, calcd *m/z* (405.2641)]. The IR spectrum showed absorptions characteristic of a hydroxy group at 3426 cm^{-1}, an ester carbonyl at 1732 cm^{-1}, and a conjugated carbonyl at 1688 cm^{-1}. The molecular formula implied seven degrees of unsaturation and the presence of one carbonyl, one ester carbonyl, and four olefinic carbons in the ^{13}C NMR spectrum (Table 1) indicated that compound **1** had a tricyclic structure. Resonances due to *i*-propyl protons at C-14, methyl protons at C-3, and two terminal methylene protons in the ^1H NMR spectrum (Table 1) were observed along with signals due to two oxygenated methine carbons at δ_C 90.7 and 80.1 that were correlated to the signals δ 3.77 (s, H-2) and 4.47 (m, H-9), respectively, in an HMQC experiment. This suggested that compound **1** was a eunicellin-based diterpenoid, which is commonly found as a chemical constituent of the *Litophyton* genus.[2-6] The ^1H NMR spectrum further indicated the presence of another oxygenated methine proton (δ 4.45, br s, $W_{1/2}$ = 8.4 Hz) and an *n*-butyroxyl group at C-3 (δ 0.95, 1.63, 2.20). The gross structure was elucidated on the basis of ^1H–^1H COSY and HMBC experiments (Figure 1). HMBC correlations of both H_2-5 (δ 2.47, 2.73) and H_2-16 (δ 5.23, 5.39) to C-6 (δ 206.0) and C-7 (δ 147.6) indicated that the carbonyl group was located at C-6. Another terminal methylene and the hydroxy group were determined to be attached to C-11 and C-12, respectively, on the basis of the correlations of H-10 (δ 3.06), H-12 (δ 4.45) and the methylene protons (δ 4.87, 5.12) to C-11 (δ 146.2). Correlations of Me-15 (δ 1.53) to C-2 (δ 90.7), C-3 (δ 84.1), and C-4 (δ 31.9) indicated that C-3 was attached to C-2 and C-4, and the chemical shift of C-3 suggested the presence of the *n*-butyroxyl group at C-3.

The relative stereochemistry was determined on the basis of NOESY analysis (Figure 2). NOESY correlation of H-1 to H-10, Me-19, and Me-20; H-10 to H-16_b (δ 5.23) and H-17_b (δ 4.87); H-16_b to H-17_b, and H-12 to H-17_a (δ 5.12) suggested that H-1, H-10, H-12, and the *i*-propyl moiety were on the same face (β) of the ring. The configuration of H-12 was also indicative of a pseudo-equatorial orientation (β) based on the half-height width, $W_{1/2}$ = 8.4 Hz, of this proton. H-2 showed NOE's to H-9, H-14, and Me-15, and H-9 gave an NOE to H-14, confirming α-orientations for H-2, H-9, H-14, and Me-15. Thus, compound **1** has the relative structure corresponding to the 6-oxo derivative of litophynin H.

Absorptions of compound **2**, $C_{26}H_{38}O_6$, in the IR spectrum indicated the presence of an ester carbonyl at 1736 cm^{-1} and a conjugated carbonyl at 1692 cm^{-1}. The ^1H NMR spectrum was similar to that of **1**, except for resonances due to additional acetyl protons (δ 2.00, 3H, s). The position of the acetyl group was determined to be located at C-12 based on the downfield shift of H-12 (δ 5.48, 1H, m) by 1.03 ppm when



1 R = OH **3** R = O **5** **6**

2 R = OAc **4** R = α-OH

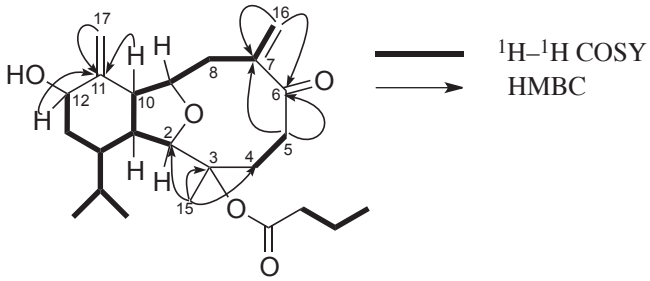


Figure 1. Selected 2D NMR correlations of **1**

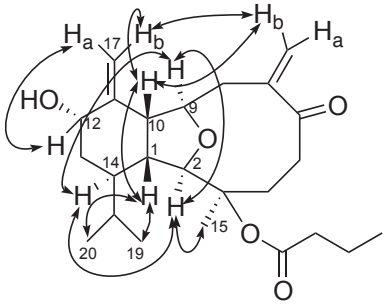


Figure 2. Selected NOE correlations of **1**

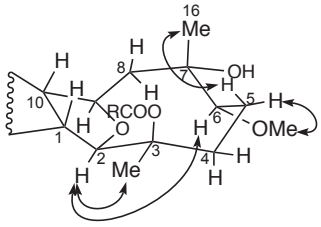


Figure 3. Seclected NOE correlations of **5**

compared with that of **1**. The β-configuration of H-12 was supported by the observation of NOE's between H-12 and H-10. Therefore, compound **2** is the 12-*O*-acetyl analogue of **1**.

Compound **3**, $C_{24}H_{36}O_5$, was isomeric with **1**, and the presence of a hydroxy group, an ester carbonyl, and a conjugated carbonyl was observed in the IR spectrum similar to the case of **1**. The NMR spectra were essentially similar to those of **1**; however, the chemical shifts corresponding to C-8 (δ 79.9) and C-12 (δ 31.3) in the ^{13}C NMR spectrum were shifted downfield by 43.0 ppm and upfield by 40.2 ppm, respectively when compared with those of **1**. This suggested that the hydroxy group was attached to C-8. The configuration was inferred to be α-oriented from NOE correlations of H-8 (δ 4.26) to H-16$_b$ (δ 5.44) and H-17$_b$ (δ 4.68), the latter of which was also correlated to H-10. The relative configurations of the remaining chiral centers in **3** were deduced from the similarity of their coupling patterns and chemical shifts in the NMR spectra and NOE correlations to those of **1**. Thus, compound **3** has the relative structure corresponding to the keto derivative of litophynol A.[2]

Table 1. NMR Spectroscopic Data for **1**–**4** in $CDCl_3$[a]

	1		**2**		**3**		**4**		**5**	
position	δ_C	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)
1	44.6	2.25, m	44.3	2.77, m	45.2	2.23, m	44.4	2.23, m	45.6	2.17, dd (11.0, 7..3)
2	90.7	3.77, s	90.8	3.75, s	91.6	3.75, s	91.3	3.77, s	92.3	3.59, br s
3	84.1		84.1		83.9		84.4		86.4	
4a	31.9	2.73, m	31.4	2.38, 2H, br t (11.7)	31.3	2.31, 2H, m		2.25[b]	37.0	1.75, m
b		2.47, m						1.86[b]		2.72, dd (15.5, 8.5)
5a	38.4	2.73, m	38.2	2.73, td (11.3, 2.2)	39.0	2.71[b]	28.9	2.16[b]	26.8	1.34, m
b		2.47, m		2.45, br t (11.4)		2.47[b]		1.57[b]		1.58, dd (15.5, 8.9)
6	206.0		206.0		208.4		81.4	5.07, dd (11.4, 3.4)	90.7	4.11, d (6.1)
7	147.6		147.5		145.5		148.2		76.0	
8	36.9	2.31, d (14.2)	36.9	3.21, dd (13.3, 5.4)	79.9	4.26, br d (8.0)	77.1	4.22, s	45.1	1.82, m 2H
		3.23, dd (14.2, 5.7)		2.30[b]						
9	80.1	4.47 m	79.6	4.29, ddd (10.7, 5.8, 2.1)	84.3	4.17, d (11.2)	83.3	4.20, d (10.9)	78.5	4.17, dd (14.6, 7.3)
10	46.9	3.06, dd (10.1, 7.8)	47.3	3.09, dd (10.3, 7.6)	48.6	2.84, dd (11.0, 7.4)	48.1	2.86, dd (10.9, 7.9)	53.9	2.97, t (7.3)
11	146.2		141.4		145.5		145.9		147.6	
12α	71.5	4.45, br s, $W_{1/2}$ = 8.4	73.1	5.48, m, $W_{1/2}$ = 10.2	31.3	2.12[b]	31.5	2.13[b]	31.5	2.04, br t (12.9)
β						2.31, m		2.30, m		2.26, m
13α	31.1	1.90, dt (2,6, 3.4)	29.0	1.96, dt (14,3, 3.1)	25.2	1.77[b]	25.3	1.77, dd (12.9, 3.1)	24.7	1.02, m
β		2.34, m		1.30, dt (2.5, 13.7)		1.05, m		1.05, ddd (13.0, 13.0, 2.8)		1.71[b]
14	35.1	1.84, m	36.2	1.69, br t (12.6)	43.1	1.32, m	44.0	1.31, m	44.0	1.27, m
15	22.6	1.53, s	22.6	1.52, s	22.7	1.49, s	22.5	1.59, s	23.2	1.39, s
16a	117.2	5.39, br s	117.5	5.41, br s	119.3	5.52, br s	119.3	5.54, br s	23.6	1.11, s
b		5.23, br s		5.23, br s		5.44, br s		5.37, br s		
17a	116.0	5.12, br s	119.2	5.30, d (1.1)	111.7	4.85, br s	111.6	4.83, br s	109.4	4.68, br s
b		4.87, br s		5.00, br s		4.68, br s		4.67, br s		4.64, br s
18	27.1	1.88, m	27.1	1.87, m	27.7	1.77[b]	27.5	1.85, m	29.1	1.74[b]
19	21.7	0.98, d (7.2)	21.6	0.94, d (7.0)	21.9	0.97 d (6.8)	21.9	0.97, d (6.9)	21.9	0.96, d (6.9)
20	15.2	0.77 d (6.8)	15.1	0.76, d (6.8)	15.3	0.76 d (6.7)	15.5	0.75, d (6.8)	15.5	0.78, d (6.8)
21	172.6		172.5		172.6		172.6		172.3	
22	37.4	2.20, t (7.3)	37.3	2.21, m	37.3	2.23 m	37.4	2.14[b]	37.4	2.30, m, 2.37 m
23	18.5	1.63, hex (7.5)	18.5	1.63, sex (7.5)	18.4	1.63 m	18.5	1.59[b]	18.4	1.68, m
24	13.6	0.95, t (8.1)	13.6	0.96, t (7.5)	13.7	0.97 t (7.0)	13.6	0.92, t (7.4)	13.7	0.99, t (7.4)
MeOCO			170.0							
MeOCO			21.5	2.00 s						
MeO									56.9	3.34, s

[a]For ^{1}H, 600 MHz; ^{13}C, 150 MHz. [b] Overlapped signals. $W_{1/2}$: width at half-height in Herz.

The IR spectrum of compound **4**, $C_{24}H_{38}O_5$, indicated the presence of hydroxy groups at 3366 cm^{-1}, an ester carbonyl at 1732 cm^{-1}, and olefins at 1645 cm^{-1}. However, unlike that observed for **1**–**3**, absorption due to a conjugated carbonyl was not observed. A resonance due to H-6 (δ 5.07, 1H, dd, *J* = 11.4, 3.4 Hz) in the ^{1}H NMR spectrum suggested that the carbonyl group in **3** was reduced to a hydroxy group in **4**. The remaining resonances were similar to those of **3**. The configuration of the hydroxy group was found to be the α-oriented based on an NOE correlation between H-6 and H-10. Therefore, the relative structure of 4 is as same as that of the 6-*epi* litophynol A.[2]

The molecular formula of compound **5**, $C_{25}H_{42}O_5$, indicated that the MW of **5** was 16 mass units higher than **4**. The presence of a hydroxy group at 3495 cm^{-1} and an ester carbonyl at 1736 cm^{-1} was indicated by

the IR spectrum. The ^{1}H NMR spectrum was essentially similar to that of **4**, except for the presence of signals extra side chains on the 10-membered ring. Thus, unique resonances due to an additional methoxy group at δ 3.34 (3H, s) and a methyl group at δ 1.11 (3H, s) bearing an oxygenated carbon were observed instead of the terminal methylene protons in **4**. The positions of the methoxy and the hydroxy groups were confirmed to be C-6 and C-7, respectively, by interpretation of HMBC correlations between the methoxy protons and C-6 (δ 90.7) and between the methyl protons and C-7 (δ 76.0). The relative configuration of chiral carbons on the five-membered ring and six-membered ring was determined by the similarity of the NOESY data for **4** compared with those of **3** and **5**. Regarding the configurations of C-3, C-6, and C-7, NOESY correlations of Me-15 to H-2 and H-6 indicated a β-orientation of the methoxy group, while an α-orientation of the hydroxy group was suggested from NOESY correlations between the methoxy protons and H-5*exo* (δ 1.58, 1H, dd, 15.5, 8.9 Hz) and between Me-16 and H-5*endo* (δ 1.34, 1H, m), as shown in Figure 3. This meant that C-3, C-6, and C-7 had relative configurations as shown in Figure 5. Therefore, the relative structure of **5** is identical with that of the 6-methyl ether of litophynol B.[2] However, compound **5** may well be an artifact of the methanol extraction method used, because a hydroxy substituent at C-7 that could form hydrogen bond with the 6-hydroxy would facilitate nucleophilic attack at the 6-position by methanol.

The cytotoxicity of compounds **1**–**5** and litophynin F (**6**) in human promyelocytic leukemia cells was determined by an MTT assay. Compounds **1**–**6** exhibited activity with the following IC_{50} values: **1** (20 μM), **2** (20 μM), **3** (5.7 μM), **4** (4.2 μM), **5** (50 μM), and **6** (18 μM). Compounds **1** and **2**, possessing a hydroxy group or acetoxy group at C-12 exhibited moderate cytotoxic activity with an IC_{50} = 20 μM, while compounds **3** having an additional hydroxy group at C-8 and its reduced compound **4** showed significant cytotoxic activity with an IC_{50} = 4.2–5.7 μM. The C-6 methoxy and C-7 hydroxy groups apparently reduced the toxicity of compound **5**. Compound **6** with the absence of a hydroxy group at C-8 and the presence of a β-hydroxy group at C-6 displaying less cytoxocic activity with an IC_{50} = 18 μM than that of **4**.

EXPERIMENTAL

Optical rotations were measured at 25 °C on a JASCO DIP-370S polarimeter. UV spectra were measured using a Hitachi U-2001 double-beam spectrophotometer. IR spectra were recorded on a MASCO FT/IR 5300. NMR spectra were recorded with a Bruker AVANCE 600 MHz NMR instrument using $CDCl_3$ as a solvent. Chemical shifts are given on a δ (ppm) scale (^{1}H, 7.26 ppm; ^{13}C, 77.0 ppm as the internal standard). MS spectra were obtained with a JEOL JMS XD-303 instrument. VCC separation was performed with silica gel 60H (Merck, 90% < 45 μm). Column chromatography was carried out on silica gel 60 (Merck, 70—230 μm). Silica gel 60F (Merck, 0.25 mm thick) was used for TLC. HPLC was

performed using a Waters 501 HPLC pump with a Shodex UV-41 detector. A Develosil ODS-UG-5 C_{18} column (10 mm× 250 mm) was used for HPLC.

Soft Coral Material. The soft coral *Litophyton viscudium* (collection number 253) was collected in the Otsuki Town area, Kochi Prefecture, Japan (32°44'10"N, 132°43'56"E), on June 15th 2004 and was identified by Dr. F. Iwase. A voucher specimen has been deposited at Faculty of Science, Kagoshima University (voucher specimen: 253).

Extraction and Isolation. The organism (wet weight: 5.3 kg, dry weight: 748 g) was chopped into small pieces and extracted with MeOH several times. The dried MeOH extract was suspended in H_2O and extracted with CH_2Cl_2. The CH_2Cl_2 extract (23 g) was subjected to vacuum column chromatography on silica gel. Fractions of 300 mL were collected as follows: 1—3 (CH_2Cl_2/*n*-hexane, 4:1), 4—6 (CH_2Cl_2), 7—11 (MeOH/CH_2Cl_2, 1:49), 12—18 (MeOH/CH_2Cl_2, 1:19), 19—21 (MeOH/CH_2Cl_2, 1:9), 22—25 (MeOH/CH_2Cl_2, 1:4), 26—28 (MeOH). Fractions 15—18 (5.4 g) were subjected to silica gel column chromatography with n-hexane/CH_2Cl_2 (4:1) and then MeOH/CH_2Cl_2 of increasing polarity. Fractions eluted with MeOH/CH_2Cl_2 (1:49 to 1:4) were chromatographed on silica gel successively with acetone/CH_2Cl_2 (3:97 to 1:9) and then MeOH/CH_2Cl_2 (1:49) followed by reversed-phase HPLC with CH_3OH/H_2O (7:3 to 3:2) to yield compounds (**2**) (2.0 mg) and (**3**) (1.8 mg). Compounds (**4**) (3.7 mg), (**5**) (11.7 mg), and (**6**) (7.3 mg) were isolated from the fractions eluted with acetone/CH_2Cl_2 (1:49 to 1:9) followed by reversed-phase HPLC using MeCN/H_2O (3:2 to 1:1). Fractions eluted slowly with acetone/CH_2Cl_2 (1:9) were subjected to reversed-phase HPLC with MeCN/H_2O (1:1) afforded compound (**1**) (3.7 mg).

Compound (1): amorphous powder; $[\alpha]^{25}_{D}$ -22.4 (*c* 0.11, MeOH); TLC R_f 0.41 (3:97, MeOH/CH_2Cl_2); UV (MeOH) λ_{max} (log ε) 216 (3.41) nm; IR (NaCl) ν_{max} 3426, 1732, 1688 cm^{-1}; ^1H NMR and ^{13}C NMR, see Table 1; HRFABMS *m/z* 405.2629 $[M + H]^+$ (calcd for $C_{24}H_{37}O_5$, 405.2641).

Compound (2): amorphous powder; $[\alpha]^{25}_{D}$ -9.6 (*c* 0.06, MeOH); TLC R_f 0.36 (3:17, EtOAc/*n*-hexane); UV (MeOH) λ_{max} (log ε) 216 (3.54) nm; IR (NaCl) ν_{max} 1736, 1692 cm^{-1}; ^1H NMR and ^{13}C NMR, see Table 1; HRFABMS *m/z* 447.2745 $[M + H]^+$ (calcd for $C_{26}H_{39}O_6$, 447.274 7).

Compound (3): amorphous powder; $[\alpha]^{25}_{D}$ -5.0 (*c* 0.06, MeOH); TLC R_f 0.25 (3:17, EtOAc/*n*-hexane); UV (MeOH) λ_{max} (log ε) 215 (3.58) nm; IR (NaCl) ν_{max} 3451, 1736, 1686 cm^{-1}; ^1H NMR and ^{13}C NMR, see Table 1; HRFABMS *m/z* 405.2647 $[M + H]^+$ (calcd for $C_{24}H_{37}O_5$, 405.2641).

Compound (4): amorphous powder; $[\alpha]^{25}_{D}$ +25.0 (*c* 0.06, MeOH); TLC R_f 0.29 (3:97, MeOH/CH_2Cl_2); IR (NaCl) ν_{max} 3366, 1732, 1645 cm^{-1}; ^1H NMR and ^{13}C NMR, see Table 1; HRFABMS *m/z* 407.2764 $[M + H]^+$ (calcd for $C_{24}H_{39}O_5$, 407.2797).

Compound (5): amorphous powder; $[\alpha]^{25}_{D}$ +33.4 (*c* 0.35, MeOH); TLC R_f 0.55 (3:97, MeOH/CH_2Cl_2);

IR (NaCl) ν_{max} 3495, 1736, 1645 cm^{-1}; ^1H NMR and ^{13}C NMR, see Table 1; HRFABMS *m/z* 445.2917 [M + Na]$^+$ (calcd for $C_{25}H_{42}O_5Na$, 445.2920), *m/z* 421.2958 [M – H]$^+$ (calcd for $C_{25}H_{41}O_5$, 421.2954).

Litophynin F (6): amorphous powder; $[\alpha]^{25}_D$ +12.4 (*c* 0.28, MeOH); TLC R_f 0.28 (1:99, MeOH/CH_2Cl_2); ν_{max} 3614, 1734, 1644 cm^{-1}; HRFABMS *m/z* 391.2845 [M + H]$^+$ (calcd for $C_{24}H_{39}O_4$, 391.2848).

Cell lines. Human leukemia HL-60 cells were maintained in RPMI1640 containing 10% fetal calf serum, 2 mM glutamine and the antibiotic/antimycotic solution at 37 °C in a 5 % CO_2 humidified atmosphere.

ACKNOWLEDGEMENT

This study was supported in part by the Kagoshima Science Scholarship Foundation and JSPS via Grants-in-Aid for Scientific Research (No. 22510236).

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