New Cadinene Sesquiterpenoids from the Formosan Soft Coral *Xenia puerto-galerae*

Chang-Yih Duh,^{*,†} Shih-Chao Chien,[†] Pei-Ying Song,[†] Shang-Kwei Wang,[‡] Ali Ali H. El-Gamal,[†] and Chang-Feng Dai[§]

Department of Marine Resources, National Sun Yat-sen University, Kaohsiung, Taiwan, Department of Microbiology, Kaohsiung Medical University, Kaohsiung, Taiwan, and Institute of Oceanography, National Taiwan University, Taipei, Taiwan, Republic of China

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Six new cadinene sesquiterpenoids, xenitorins A–F (**1**–**6**), were isolated from the methylene chloride solubles of the Formosan soft coral *Xenia puerto-galerae*. The structures were elucidated by 1D and 2D NMR spectral analysis, and their cytotoxicity against selected cancer cells was measured in vitro.

The soft corals of the genus *Xenia* are rich in terpenoids^{1–19} and steroids.²⁰ As part of our search for bioactive substances from marine organisms, the Formosan soft coral *Xenia puerto-galerae* Roxas (family Xenidiidae) was studied because CH₂Cl₂ extracts showed significant cytotoxicity values to A549 (human lung adenocarcinoma), HT-29 (human colon adenocarcinoma), and P-388 (mouse lymphocytic leukemia) cell cultures as determined by standard procedures.^{21,22} Bioassay-guided fractionation resulted in the isolation of six new cadinene sesquiterpenoids, xenitorins A–F (**1**–**6**). Xenitorins A–B and xenitorins D–F contain an oxygen functionality at C-8, which is a previously unrecognized site of oxidation in cadinene sesquiterpenoids. Xenitorin A exhibited cytotoxicity against A-549 cells. Xenitorin E showed cytotoxicity against P-388 and A-549 cells.

Results and Discussion

Xenitorin A (**1**) was isolated as a colorless oil. HREIMS, ¹³C NMR, and DEPT spectra established the molecular formula of **1** as C₁₅H₂₄O. Thus, four degrees of unsaturation were determined for **1**. The presence of a secondary hydroxyl group in **1** was indicated by IR (3400 cm⁻¹) and NMR data (δ_H 3.92 br s; δ_C 64.5 d). The presence of four sp²-hybridized carbon atoms in the molecule, as deduced from the ¹³C and DEPT NMR spectra (Table 2), corresponding to two carbon–carbon double bonds as the only multiple bonds, indicated compound **1** to be bicyclic. The ¹³C NMR singlet at δ 141.8 and a doublet at δ 122.7 that was correlated in the HMBC experiment (Figure 1) with the ¹H NMR signal at δ 5.66 (dq, *J* = 1.0, 3.0 Hz, 1H) together with the vinylic methyl signals at δ 1.71 (d, *J* = 1.0 Hz, 3H) in the ¹H NMR spectrum and at δ 20.9 (q) in the ¹³C NMR spectrum were assigned to a *Z*-trisubstituted double bond bearing a methyl group. HMQC correlation of δ_H 4.71 (s, 1H) and 5.11 (s, 1H) with δ_C 113.4 (t) as well as HMBC correlation of these two protons with δ_C 144.8 (s), 24.1 (q), and 53.0 (d) indicated that **1** contained an isopropenyl group. NMR also showed the presence of a secondary methyl (δ_H 0.98 d; δ_C 18.3), three methylenes (δ_C 24.4, 32.4, 35.6), and four methines (δ_C 27.8, 53.0, 47.1, 30.2). Measurement of the ¹³C–¹³C homonuclear shift correlation 2D spectrum (INADEQUATE) of **1** together with COSY (Figure 1), HMQC, and HMBC experiments established its chemical structure and enabled also the assignment of all resonances in the NMR spectra. The relative stereochemistry of **1** was deduced from a 2D NOESY experiment (Figure 2), which indicated that Me-11, H-6, H-2β, and Me-14 were on one side of the molecule, while H-1, H-3α, H-5α, H-7, and H-8 were on the opposite side of the molecule. From the aforementioned data, xenitorin A can be formulated as **1**.

Xenitorin B (**2**) was isolated as a colorless amorphous solid, whose molecular formula, C₁₅H₂₂O, was revealed by HREIMS and NMR spectra. The IR and UV spectra showed the presence of an α,β-unsaturated ketone (1657 cm⁻¹; 239 nm) moiety. The ¹³C NMR features (Table 2) of **2** were closely related to those of **1** except in the vicinity of the carbonyl in **2**. The only difference was the secondary hydroxyl at C-8 in **1** was replaced by a ketone in **2**. HMBC correlations from H-7 to C-8, C-6, C-1, C-14 and from H-15 to C-9, C-10, C-1 confirmed the position of the ketone in **2**. The relative stereochemistry of **2** was deduced from 2D NOESY experiment (Table 4), which indicated that Me-

* To whom correspondence should be addressed. Tel: 886-7-525-2000, ext. 5036. Fax: 886-7-525-5020. E-mail: yihduh@mail.nsysu.edu.tw.

[†] National Sun Yat-sen University.

[‡] Kaohsiung Medical University.

[§] National Taiwan University.

Table 1. ^1H NMR Data^a of **1–6**

H	1	2	3	4	5	6
1	1.59 br d (13.0)	2.03 m	1.17 m	1.30 m		
2 α	1.84 m	1.98 m	1.79 m	1.80 dq (13.0, 2.8)	1.88 dt (14.0, 2.6)	1.72 dt (4.8, 14.0)
2 β	1.26 m	2.38 m	1.62 m	1.44 qd (4.0, 12.5)	1.64 td (14.0, 4.8)	1.90 br d (14.0)
3 α	1.56 m	1.65 m	1.56 m	1.58 m	1.95 dt (14.0, 4.8)	1.54 br d (13.0)
3 β	1.58 m	1.66m	1.58 m	1.60 m	1.48 dq (14.0, 2.6)	1.26 m
4	2.04 m	2.08 m	1.98 m	2.01 m	2.08 m	1.63 m
5 α	1.06 dt (4.0, 13.0)	1.30 m	1.10 dt (4.5, 12.5)	1.55 br d (14.0)	1.69 td (13.5, 4.5)	1.64 m
5 β	1.84 m	2.03 m	1.71 m	1.02 m	1.27 m	1.20 m
6	1.80 td (13.1, 3.0)	1.49 br d (14.0)	1.65 m	1.61 m	2.20 td (12.6, 3.0)	2.90 br d (14.0)
7	1.99 dd (3.5, 12.0)	2.70 d (12.5)	2.38 dt (9.5, 2.0)	1.73 br d (8.5)	3.07 d (12.6)	3.26 d (14.0)
8	3.92 br s		5.49 dd (2.0, 10.0)	4.04 dt (8.5, 4.2)		
9	5.66 dq (3.0, 1.0)	5.92 q (1.0)	5.70 dd (2.0, 10.0)	3.24 d (5.5)	5.87 q (1.0)	5.95 s
11	0.98 d (7.0)	0.98 d (7.0)	0.97 d (7.5)	0.98 d (7.5)	1.00 d (7.0)	0.90 d (6.5)
13 _Z	4.71 s	4.78 s	4.74 d (1.5)	4.69 s	4.83 s	4.87 s
13 _E	5.11 s	5.03 s	4.80 d (1.0)	4.94 s	5.05 s	5.08 s
14	1.79 s	1.59 s	1.60 s	1.76 s	1.57 s	1.66 s
15	1.71 d (1.0)	1.93 d (1.0)	1.26 s	1.33 s	1.99 d (1.0)	2.05 s
OH-1						2.35 t (7.5)
OH-8				2.12 d (8.5)		

^a Recorded in CDCl_3 at 500 MHz.**Table 2.** ^{13}C NMR Spectral Data^a (δ) of **1–6** in CDCl_3

	1	2	3	4	5	6
1	47.1	45.7	47.6	47.2	84.0	70.1
2	24.4	23.6	18.9	21.9	29.1	29.4
3	32.4	31.8	31.4	32.0	29.8	26.3
4	27.8	26.8	27.2	27.6	25.1	26.1
5	35.6	36.7	37.0	36.1	31.7	31.1
6	30.2	36.6	29.4	26.2	36.7	37.9
7	53.0	62.3	52.7	53.7	57.1	56.4
8	64.5	198.8	132.6	67.0	197.6	198.6
9	122.7	127.3	134.6	62.6	128.5	127.9
10	141.8	164.0	68.6	62.5	164.9	161.6
11	18.3	17.8	17.6	18.1	22.1	17.3
12	144.8	141.3	146.6	144.4	140.7	140.4
13	113.4	116.7	112.8	114.2	117.1	117.4
14	24.1	18.5	18.9	22.5	18.3	18.4
15	20.9	21.5	27.3	20.5	18.0	18.6

^a Recorded in CDCl_3 at 75 MHz (assigned by DEPT, COSY, HSQC, and HMBC experiments). **Figure 1.** COSY and HMBC correlations of **1**. **Figure 2.** Selected NOESY correlations of **1**.

11, H-6, H-2 β , and Me-14 were on one side of the molecule, while H-1, H-3 α , and H-5 α were on the opposite side of the molecule. From the aforementioned data, xenitorin B can be formulated as **2**.

Xenitorin C (**3**) was isolated as a colorless oil and analyzed for $\text{C}_{15}\text{H}_{24}\text{O}$ by HREIMS and NMR spectral data (Tables 1 and 2). Spectroscopic data of **3** were analogous to those of **1** with the exception that the resonances for the methyl-bearing trisubstituted olefin and the secondary hydroxyl were replaced by a disubstituted olefin and a methyl-bearing tertiary hydroxyl. HMBC correlations (Table 3) from H-15 to C-1, C-9, and C-10; from H-9 to C-8 and C-7; and from H-8 to C-7 and C-9 clearly positioned the disubstituted olefin and the tertiary hydroxyl. The relative stereochemistry of **3** was deduced from a 2D NOESY experiment (Figure 3), which indicated that Me-11, H-6, H-2 β , and Me-14 were on one side of the molecule, while Me-15, H-1, H-3 α , H-5 α , and H-7 were on the opposite side of the molecule. The structure of xenitorin C is thus formulated as **3**.

Xenitorin D (**4**) was isolated as a colorless oil of molecular formula $\text{C}_{15}\text{H}_{24}\text{O}_2$, as indicated by HREIMS and ^{13}C NMR (Table 2) spectral methods. The NMR features of **4** were also analogous to those of **1**. Analyses of 2D NMR data revealed that **4** possessed the same carbocyclic skeleton as **1**. However, there was a significant difference that indicated the presence of a methyl-bearing trisubstituted epoxide [δ_{C} 20.5 (q), 62.5 (s), 62.6 (d)] in **4** instead of a methyl-bearing trisubstituted olefin in **1**. HMBC correlations (Table 3) between H-15 and C-1, C-9, and C-10 and between H-9 and C-15, C-10, C-8 clearly positioned the methyl-bearing trisubstituted epoxide. The relative stereochemistry of **4** was deduced from a 2D NOESY experiment (Figure 4), which indicated that Me-11, H-6, H-2 β , OH-8, and Me-14 were on one side of the molecule, while Me-15, H-1, H-3 α , H-5 α , H-8, H-9, and H-7 were on the opposite side of the molecule. The structure of xenitorin D is thus formulated as **4**.

Xenitorin E (**5**) was analyzed for $\text{C}_{15}\text{H}_{22}\text{O}_2$ by HREIMS and NMR spectral data. The IR and UV spectra showed the presence of an α,β -unsaturated ketone (1650 cm^{-1} ; 237 nm) and hydroxyl (3400 cm^{-1}) moieties. Spectroscopic data of **5** were analogous to those of **2** with the exception that the resonances for the C-1 methine [δ_{C} 45.7 d] were replaced by a tertiary hydroxy at C-1 [δ_{C} 70.1 s], which was proved by HMBC correlations (Table 3) between H-15 and C-1, C-9, C-10; H-9 and C-1, C-15; and H-7 and C-8, C-6, C-1. The relative stereochemistry of **5** was deduced from a 2D NOESY experiment (Table 4), which indicated that Me-11, H-6, H-2 β , and Me-14 were on one side of the

Table 3. HMBC Correlations of **1–6**

H	1	2	3	4	5	6
1			C-2, 6			
2 α	C-1, 3, 10	C-1, 4, 6		C-1, 4, 6		
2 β	C-1, 3, 10	C-1, 6				
3 α	C-4, 5, 11	C-1, 4, 5	C-2			C-2
3 β	C-4, 5, 11	C-1, 4, 5				C-2
4	C-5					
5 α	C-1, 4, 7	C-1	C-6		C-4, 6, 11	
5 β	C-1, 4, 7	C-1, 6	C-6			
6	C-7			C-5		
7	C-1, 8, 12, 13, 14	C-1, 6, 8, 12, 13, 14	C-1, 6, 9, 12, 13, 14	C-12, 13, 14	C-1, 6, 8, 12, 13, 14	C-6, 8, 12, 13, 14
8	C-7, 9		C-6, 7, 9, 12			
OH-8				C-8, 9		
9	C-15		C-1, 7, 8, 10, 15	C-7, 8, 10	C-1, 15	C-1, 7, 15
11	C-3, 4, 5	C-3, 4, 5	C-3, 4, 5	C-3, 4, 5	C-3, 4, 5	C-3, 4, 5
13 $_Z$	C-7, 12	C-7, 12	C-12	C-7, 12, 14	C-7, 12, 14	C-7, 14
13 $_E$	C-7, 8, 12, 14	C-12, 14	C-7, 14	C-7, 14	C-7, 14	C-7, 14
14	C-7, 8, 12, 13	C-7, 12, 13	C-7, 12, 13	C-7, 12, 13	C-7, 12, 13	C-7, 12, 13
15	C-1, 9	C-1, 9, 10	C-1, 6, 9, 10	C-1, 9, 10	C-1, 9, 10	C-1, 9, 10

Table 4. NOESY Correlations of **1–6**

H	1	2	3	4	5	6
1	H-3 α , 5 α	H-3 α	H-3 α , 5 α , 15	H-3 α , 5 α , 15		
2 α				H-2 β , 15		H-2 β
2 β	H-6, 11	H-11	H-11	H-2 α , 11	H-2 β , 3 α , 15	H-2 α
3 α	H-5 α	H-1, 5 α	H-1	H-1	H-3 β	H-3 β
3 β					H-2 β , 3 α	H-2 β , 3 α
4				H-5 α , 5 β , 11	H-5 α	H-7
5 α	H-1, 3 α	H-3 α		H-1, 4, 7	H-4, 5 α	H-4 α , 5 β , 6
5 β	H-6	H-6, 11	H-6	H-4, 11	H-4, 5 α , 6, 11	H-5 α , 6, OH-1
6	H-2 β , 5 β , 11	H-5 α , 11	H-5 β , 11	H-11, OH-8	H-2 β , 5 β , 11	H-5 α , 5 β , 14
7	H-8	H-13 $_Z$		H-5 α , 8, 13 $_Z$	H-13 $_Z$, 5 α	H-4, 13 $_Z$
8	H-7, 9		H-9, 14	H-7, 9		
9	H-8, 15	H-15	H-8, 15	H-8, 15	H-15	H-15
11	H-2 β , 6	H-2 β , 5 β , 6	H-2 β , 6	H-2 β , 5 β , 4, 6	H-2 β , 5 β , 6	H-3 β , 5 α , 5 β
13 $_Z$	H-7, 13 $_E$	H-7, 13 $_E$	H-7, 13 $_E$	H-7, 13 $_E$	H-7, 13 $_E$	H-7, 13 $_E$
13 $_E$	H-13 $_Z$, 14	H-13 $_Z$, 14	H-13 $_Z$, 14	H-13 $_Z$, 14	H-13 $_Z$	H-13 $_Z$, 14
14	H-13 $_E$	H-13 $_E$	H-8	H-13 $_E$		H-6
15	H-9	H-9	H-1, 9	H-1, 2 α , 9	H-2 α , 9	H-9
OH-1						H-3 β , 5 β
OH-8				H-6

Figure 3. Selected NOESY correlations of **3**. **Figure 4.** Selected NOESY correlations of **4**.

molecule, while OH-1, H-3 α , H-5 α , and H-7 were on the opposite side of the molecule. The structure of xenitorin E is thus formulated as **5**.

Xenitorin F (**6**) has the molecular formula $C_{15}H_{24}O_2$, as determined by HREIMS and NMR spectral data (Tables 1 and 2). The IR and UV spectra showed the presence of an α,β -unsaturated ketone (1655 cm^{-1} ; 239 nm) and hydroxyl (3365 cm^{-1}) moieties. The NMR spectra of **6** were analogous

Figure 5. Selected NOESY correlations of **6**.

to those of **5** except that the ^{13}C NMR chemical shifts for the tertiary hydroxyl and Me-11 were upfield shifted by 13.9 and 4.8 ppm, respectively. An HMBC experiment proved the planar structure to be identical with **5**. In the NOESY experiment (Figure 5), NOESY correlations from H-4 to H-7 and the absence of NOESY correlations from H-6 to Me-11 proved the *cis* A/B ring junction and equatorial (β) position of Me-11. The structure of xenitorin F is thus formulated as **6**. An attempt at nonenzymatic air oxidation of **2** failed to provide a mixture of **5** and **6**.

Xenitorin A exhibited cytotoxicity against A-549 cells with an ED_{50} of $0.79\text{ }\mu\text{g/mL}$. Xenitorin E showed cytotoxicity against P-388 and A-549 cells with ED_{50} 's of 3.69 and $1.86\text{ }\mu\text{g/mL}$, respectively. ED_{50} 's of xenitorins B–D and xenitorin F against P-388 and A-549 were higher than $50\text{ }\mu\text{g/mL}$.

Experimental Section

General Experimental Procedures. Melting points were determined using a Yanagimoto micromelting point apparatus and are reported uncorrected. Optical rotations were determined on a JASCO DIP-181 polarimeter. UV spectra were obtained on a Shimadzu UV-160A spectrophotometer, and IR spectra were recorded on a Hitachi 26-30 spectrophotometer. The NMR spectra were recorded on a Bruker Avance 300 NMR spectrometer at 300 MHz for ^1H and 75 MHz for ^{13}C or on a Varian Unity INOVA 500 FT-NMR at 500 MHz for ^1H and 125 MHz for ^{13}C , respectively, in CDCl_3 using TMS as internal standard. EIMS spectra were obtained with a JEOL JMS-SX/SX 102A mass spectrometer at 70 eV. Si gel 60 (Merck, 230–400 mesh) was used for column chromatography; precoated Si gel plates (Merck, Kieselgel 60 F_{254} , 0.25 mm) were used for TLC analysis.

Animal Material. The soft coral *X. puerto-galerae* was collected at Green Island, off Taiwan, in March 2001, at a depth of 6 m and was stored for 1 month in a freezer until extraction. A voucher specimen, NSUGN-044, was deposited in the Department of Marine Resources, National Sun Yat-sen University, Taiwan.

Extraction and Isolation. The bodies of the soft coral *X. puerto-galerae* were freeze-dried to give 0.45 kg of a solid, which was extracted with CH_2Cl_2 (1.0 L $\times$ 3). After removal of solvent in vacuo, the residue (25 g) was chromatographed over Si gel 60 using *n*-hexane and *n*-hexane– CH_2Cl_2 mixtures of increasing polarity. Elution by *n*-hexane– CH_2Cl_2 (1:3) afforded fractions containing **1**–**4**. Elution by *n*-hexane– CH_2Cl_2 (1:5) afforded fractions containing **5** and **6**. Compound **1** was further purified by Si gel column chromatography, by eluting with *n*-hexane–EtOAc (20:1). Compound **2** was further purified by Si gel column chromatography, by eluting with *n*-hexane–EtOAc (100:7). Compound **3** was further purified by Si gel column chromatography, by eluting with *n*-hexane–EtOAc (12:1). Compound **4** was further purified by Si gel column chromatography, by eluting with *n*-hexane–EtOAc (9:1). Compound **5** was obtained by a C_{18} HPLC column, by using MeOH– H_2O (67:33) as solvent system. Compound **6** was obtained by Si gel column chromatography, by eluting with *n*-hexane–EtOAc (12:1).

Xenitorin A (1): colorless oil (15 mg); $[\alpha]_D^{25}$ –39° (*c* 0.21, CHCl_3); UV (MeOH) λ_{max} (log ϵ) 206 (3.6) nm; IR (KBr) ν_{max} 3400 cm^{-1} ; ^1H NMR, see Table 1; ^{13}C NMR, see Table 2; EIMS m/z 220 $[\text{M}]^+$ (27), 203 (12), 187 (32), 175 (71), 162 (39), 149 (79), 136 (40), 123 (64), 109 (100); HREIMS m/z 220.1830 (calcd for $\text{C}_{15}\text{H}_{24}\text{O}$, 220.1821).

Xenitorin B (2): colorless amorphous solid (10 mg); $[\alpha]_D^{25}$ –5.7° (*c* 0.20, CHCl_3); UV (MeOH) λ_{max} (log ϵ) 239 (3.9) nm; IR (KBr) ν_{max} 1657 cm^{-1} ; ^1H NMR, see Table 1; ^{13}C NMR, see Table 2; EIMS m/z 218 $[\text{M}]^+$ (100), 203 (57), 175 (20), 161 (18), 147 (13), 133 (10), 107 (22), 95 (17); HREIMS m/z 218.1671 (calcd for $\text{C}_{15}\text{H}_{22}\text{O}$, 218.1665).

Xenitorin C (3): colorless oil (38 mg); $[\alpha]_D^{25}$ –5.1° (*c* 0.12, CHCl_3); UV (MeOH) λ_{max} (log ϵ) 206 (3.3) nm; IR (KBr) ν_{max} 3436 cm^{-1} ; ^1H NMR, see Table 1; ^{13}C NMR, see Table 2; EIMS m/z 220 $[\text{M}]^+$ (4), 205 (24), 187 (13), 177 (30), 162 (43), 109 (100); HREIMS m/z 220.1831 (calcd for $\text{C}_{15}\text{H}_{24}\text{O}$, 220.1821).

Xenitorin D (4): colorless oil (6 mg); $[\alpha]_D^{25}$ –39° (*c* 0.16, CHCl_3); UV (MeOH) λ_{max} (log ϵ) 209 (3.7) nm; IR (KBr) ν_{max} 3405 cm^{-1} ; ^1H NMR, see Table 1; ^{13}C NMR, see Table 2; EIMS m/z 236 $[\text{M}]^+$ (3), 221 (23), 207 (18), 189 (47), 161 (100), 133 (70); HREIMS m/z 236.1781 (calcd for $\text{C}_{15}\text{H}_{24}\text{O}_2$, 236.1770).

Xenitorin E (5): colorless oil (1 mg); $[\alpha]_D^{25}$ –10° (*c* 0.18, CHCl_3); UV (MeOH) λ_{max} (log ϵ) 237 (3.6) nm; IR (KBr) ν_{max} 3450, 1650 cm^{-1} ; ^1H NMR, see Table 1; ^{13}C NMR, see Table 2; EIMS m/z 234 $[\text{M}]^+$ (7), 219 (16), 189 (32), 179 (100), 133 (32), 123 (36), 107 (45); HREIMS m/z 234.1626 (calcd for $\text{C}_{15}\text{H}_{22}\text{O}_2$, 234.1614).

Xenitorin F (6): colorless oil (2 mg); $[\alpha]_D^{25}$ +65° (*c* 0.22, CHCl_3); UV (MeOH) λ_{max} (log ϵ) 239 (3.9) nm; IR (KBr) ν_{max} 3365, 1702, 1650 cm^{-1} ; ^1H NMR, see Table 1; ^{13}C NMR, see Table 2; EIMS m/z 234 $[\text{M}]^+$ (22), 218 (38), 204 (15), 192 (23), 180 (100), 168 (84); HREIMS m/z 234.1614 (calcd for $\text{C}_{15}\text{H}_{22}\text{O}_2$, 234.1614).

Cytotoxicity Testing. P-388 cells were kindly supplied by J. M. Pezzuto, Department of Medicinal Chemistry and Pharmacognosy, University of Illinois at Chicago; A549 and HT-29 were purchased from the American Type Culture Collection. Cytotoxic assays were carried out according to the procedure described previously.²²

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