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

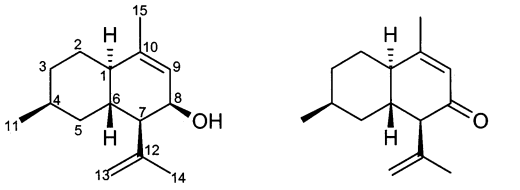
Chang-Yih Duh,*,† Shih-Chao Chien,† Pei-Ying Song,† Shang-Kwei Wang,‡ Ali Ali H. El-Gamal,† and Chang-Feng Dai§

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

Received July 18, 2002

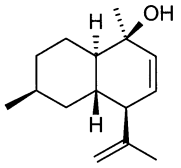
Six new cadinene sesquiterpenoids, xenitorins A−F (**1**−**6**), were isolated from the methylene chloride solubles of the Formosan soft coral *Xenia puerto-galerae*. The structures were elucidated by 1D and 2D NMR spectral analysis, and their cytotoxicity against selected cancer cells was measured in 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 Xeniidae) was studied because CH_2Cl_2 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 cytotoxicty against P-388 and A-549 cells.

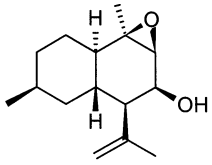


1

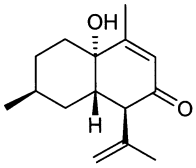
2



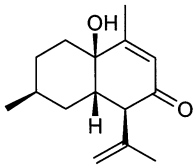
3



4



5



6

Results and Discussion

Xenitorin A (**1**) was isolated as a colorless oil. HREIMS, ^{13}C NMR, and DEPT spectra established the molecular formula of **1** as $C_{15}H_{24}O$. 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 sp^2-hybridized carbon atoms in the molecule, as deduced from the ^{13}C 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 ^{13}C 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 ^{13}C 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 $^{13}C-^{13}C$ 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, $C_{15}H_{22}O$, 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 ^{13}C 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.

10.1021/np0203281 CCC: $22.00
Published on Web 10/31/2002

Table 1. ^{1}H 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		
2α	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)
3α	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
5α	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).

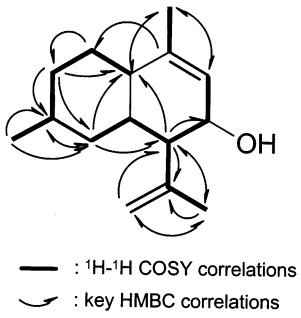


Figure 1. COSY and HMBC correlations of **1**.

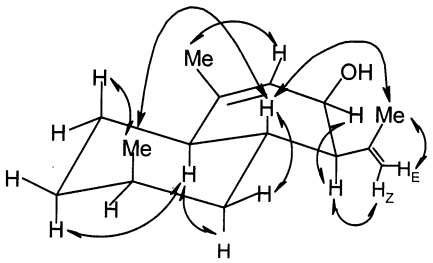


Figure 2. Selected NOESY correlations of **1**.

11, H-6, H-2*β*, and Me-14 were on one side of the molecule, while H-1, H-3α, and H-5α 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 $C_{15}H_{24}O$ 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-3α, H-5α, 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 $C_{15}H_{24}O_2$, 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-3α, H-5α, 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 $C_{15}H_{22}O_2$ 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			
2α	C-1, 3, 10	C-1, 4, 6		C-1, 4, 6		
2β	C-1, 3, 10	C-1, 6				
3α	C-4, 5, 11	C-1, 4, 5	C-2			C-2
3β	C-4, 5, 11	C-1, 4, 5				C-2
4	C-5					
5α	C-1, 4, 7	C-1	C-6		C-4, 6, 11	
5β	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, 14
13_E	C-7, 8, 12, 14	C-12, 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-3α, 5α	H-3α	H-3α, 5α, 15	H-3α, 5α, 15		
2α				H-2β, 15	H-2β, 3α, 15	H-2β
2β	H-6, 11	H-11	H-11	H-2α, 11	H-2α, 6, 11	H-2α
3α	H-5α	H-1, 5α	H-1	H-1	H-3β	H-3β
3β					H-2β, 3α	H-2β, 3α
4				H-5α, 5β, 11	H-5α	H-7
5α	H-1, 3α	H-3α		H-1, 4, 7	H-4, 5α	H-4α, 5β, 6
5β	H-6	H-6, 11	H-6	H-4, 11	H-4, 5α, 6, 11	H-5α, 6, OH-1
6	H-2β, 5β, 11	H-5α, 11	H-5β, 11	H-11, OH-8	H-2β, 5β, 11	H-5α, 5β, 14
7	H-8	H-13_Z		H-5α, 8, 13_Z	H-13_Z, 5α	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-2β, 6	H-2β, 5β, 6	H-2β, 6	H-2β, 5β, 4, 6	H-2β, 5β, 6	H-3β, 5α, 5β
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, 2α, 9	H-2α, 9	H-9
OH-1						H-3β, 5β
OH-8				H-6		

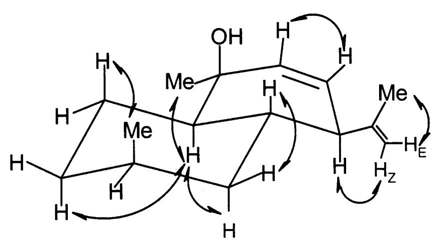


Figure 3. Selected NOESY correlations of **3**.

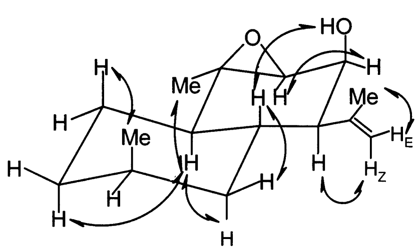


Figure 4. Selected NOESY correlations of **4**.

molecule, while OH-1, H-3α, H-5α, 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

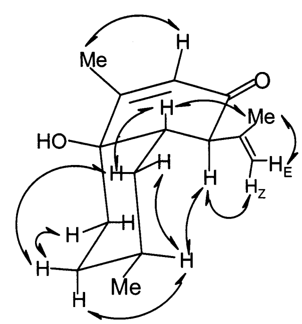


Figure 5. Selected NOESY correlations of **6**.

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 μg/mL. Xenitorin E showed cytotoxicty against P-388 and A-549 cells with ED_{50}'s of 3.69 and 1.86 μg/mL, respectively. ED_{50}'s of xenitorins B−D and xenitorin F against P-388 and A-549 were higher than 50 μg/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 ^{1}H and 75 MHz for ^{13}C or on a Varian Unity INOVA 500 FT-NMR at 500 MHz for ^{1}H 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 × 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); $[\alpha]^{25}_D$ −39° (*c* 0.21, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 206 (3.6) nm; IR (KBr) ν_{max} 3400 cm^{-1}; ^{1}H NMR, see Table 1; ^{13}C NMR, see Table 2; EIMS *m*/*z* 220 $[M]^+$ (27), 203 (12), 187 (32), 175 (71), 162 (39), 149 (79), 136 (40), 123 (64), 109 (100); HREIMS *m*/*z* 220.1830 (calcd for $C_{15}H_{24}O$, 220.1821).

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

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

Xenitorin D (4): colorless oil (6 mg); $[\alpha]^{25}_D$ −39° (*c* 0.16, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 209 (3.7) nm; IR (KBr) ν_{max} 3405 cm^{-1}; ^{1}H NMR, see Table 1; ^{13}C NMR, see Table 2; EIMS *m*/*z* 236 $[M]^+$ (3), 221 (23), 207 (18), 189 (47), 161 (100), 133 (70); HREIMS *m*/*z* 236.1781 (calcd for $C_{15}H_{24}O_2$, 236.1770).

Xenotorin E (5): colorless oil (1 mg); $[\alpha]^{25}_D$ −10° (*c* 0.18, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 237 (3.6) nm; IR (KBr) ν_{max} 3450, 1650 cm^{-1}; ^{1}H NMR, see Table 1; ^{13}C NMR, see Table 2; EIMS *m*/*z* 234 $[M]^+$ (7), 219 (16), 189 (32), 179 (100), 133 (32), 123 (36), 107 (45); HREIMS *m*/*z* 234.1626 (calcd for $C_{15}H_{22}O_2$, 234.1614).

Xenitorin F (6): colorless oil (2 mg); $[\alpha]^{25}_D$ +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}; ^{1}H NMR, see Table 1; ^{13}C NMR, see Table 2; EIMS *m*/*z* 234 $[M]^+$ (22), 218 (38), 204 (15), 192 (23), 180 (100), 168 (84); HREIMS *m*/*z* 234.1614 (calcd for $C_{15}H_{22}O_2$, 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]

Acknowledgment. We thank J. M. Pezzuto, Department of Medicinal Chemistry and Pharmacognosy, College of Pharmacy, University of Illinois at Chicago, for the provision of P-388 cell lines. This work was supported by grants from the National Science Council of Taiwan awarded to C.-Y.D.

References and Notes

(1) Kashman, Y.; Groweiss, A. *J. Org. Chem.* **1980**, *45*, 3814−3824.
(2) Groweiss, A.; Kashman, Y. *Tetrahedron* **1983**, *39*, 3385−3396.
(3) Bowden, B. F.; Coll, J. C.; Ditzel, E.; Michell, S. J.; Robinson, W. T. *Aust. J. Chem.* **1982**, *35*, 907−1002.
(4) Kitagawa, I.; Kobayashi, M.; Zheng, C.; Kiyota, Y.; Ohnishi, M. *Chem. Pharm. Bull.* **1986**, *34*, 4590−4596.
(5) Kitagawa, I.; Zheng, C.; Yang, C.; Kobayashi, M.; Kyogohu, Y.; Ohnishi, M. *Chem. Pharm. Bull.* **1986**, *34*, 4641−4652.
(6) Bowden, B. F.; Coll, J. C.; Engelhardt, L. M.; Heaton, A.; White, A. H. *Aust. J. Chem.* **1987**, *40*, 1483−1489.
(7) Bowden, B. F.; Coll, J. C.; Ditzel, E.; Willis, R. H. *Aust. J. Chem.* **1986**, *39*, 1717−1722.
(8) Iwagawa, T.; Kawasaki, J.; Hase, T.; Yu, C.; Walter, J. A.; Wright, J. L. C. *J. Chem. Soc., Chem. Commun.* **1994**, *18*, 2073−2074.
(9) Kashman, Y.; Saltoun, M.; Rudi, A.; Benayahu, Y. *Tetrahedron Lett.* **1994**, *35*, 8855−8858.
(10) Iwagawa, T.; Amano, Y.; Hase, T.; Shiro, M. *Tetrahedron* **1995**, *51*, 11111−11118.
(11) Iwagawa, T.; Amano, Y.; Hase, T.; Shiro, M. *Chem. Lett.* **1995**, *8*, 695−696.
(12) Iwagawa, T.; Amano, Y.; Nakatani, M.; Hase, T. *Bull. Chem. Soc. Jpn* **1996**, *69*, 1309−1312.
(13) Iwagawa, T.; Masuda, T.; Okamura, H.; Nakatani, M. *Tetrahedron* **1996**, *52*, 13121−13128.
(14) Iwagawa, T.; Kawasaki, J.; Hase, T., Wright, J. L. C. *Tetrahedron* **1997**, *53*, 6809−6816.
(15) Iwagawa, T.; Kawasaki, J.; Hase, T. *J. Nat. Prod.* **1998**, *61*, 1513−1515.
(16) Kawasaki, J.; Amano, Y.; Okamura, H.; Nakatani, M.; Hase, T. *Heterocycles* **1996**, *43*, 1271−1278.
(17) Iwagawa, T.; Nakamura, K.; Hirose, T.; Okamura, H.; Nakatani, M. *J. Nat. Prod.* **2000**, *63*, 468−472.
(18) Miyaoka, H.; Nakano, M.; Iguchi, K.; Yamada, Y. *Tetrahedron* **1999**, *55*, 12977−12982.
(19) Miyaoka, H.; Mitome, H.; Nakano, M.; Yamada, Y. *Tetrahedron* **2000**, *56*, 7737−7740.
(20) Kobayashi, M.; Zheng, C.; Yang, C.; Kyogohu, Y.; Kitagawa, I. *Chem. Pharm. Bull.* **1986**, *34*, 4641−4652. Kobayashi, M.; Zheng, C.; Yang, C.; Kyogohu, Y.; Kitagawa, I. *Chem. Pharm. Bull.* **1986**, *34*, 4641−4652.
(21) Geran, R I.; Greenberg, N. H.; MacDonald, M. M.; Schumacher, A. M.; Abbott, B. J. *Cancer Chemother. Rep.* **1972**, *3*, 1−91.
(22) Hou, R.-S.; Duh, C.-Y.; Chiang, M. Y.; Lin, C.-N. *J. Nat. Prod.* **1995**, *58*, 1126−1130.

NP0203281