Cytotoxic Xenia Diterpenoids from the Soft Coral *Xenia umbellata*[⊥]

Ali A. H. El-Gamal,[†,‡] Shang-Kwei Wang,[§] and Chang-Yih Duh*[,†]

Department of Marine Biotechnology and Resources, National Sun Yat-sen University, Kaohsiung, Taiwan, Republic of China, Faculty of Pharmacy, Mansoura University, Egypt, and Department of Microbiology, Kaohsiung Medical University, Kaohsiung, Taiwan, Republic of China

Received August 10, 2005

Eleven new xenia diterpenoids, umbellacins A−G (**1**−**7**), 14,15-epoxy-xeniolide H (**8**), 3-acetyl-14,15-epoxy-xeniolide H (**9**), and umbellacins H and I (**10**, **11**), were isolated from a methylene chloride-soluble fraction of the soft coral *Xenia umbellata.* The structures were elucidated by extensive spectroscopic analysis, and their cytotoxicity against selected cancer cells was measured in vitro.

Soft corals belonging to the genus *Xenia* (order Alcyonacea, family Xeniidae) have proved to be rich sources of terpenoids and have afforded several types of bioactive diterpenoids.[1] As part of a search for bioactive substances from marine organisms, the soft coral *Xenia umbellata* Lamarck was studied because the CH_2Cl_2-soluble extract showed significant cytotoxicity to A549 (human lung adenocarcinoma), HT-29 (human colon adenocarcinoma), and P-388 (mouse lymphocytic leukemia) cell cultures, as determined by standard procedures.[2,3] Bioassay-guided fractionation resulted in the isolation of 11 new xenia diterpenoids, umbellacins A−G (**1**−**7**), 14,15-epoxy-xeniolide H (**8**), 3-acetyl-14,15-epoxy-xeniolide H (**9**), and umbellacins H and I (**10**, **11**).

Results and Discussion

The IR spectrum of **1** exhibited absorptions due to hydroxyl (3450 cm^{-1}) and carbonyl (1730 cm^{-1}) groups. HRESIMS and NMR data (Tables 1 and 2) of **1** suggested a molecular formula of $C_{20}H_{30}O_5$. The carbon resonances at δ_C 194.8 (qC), 134.4 (qC), 150.5 (CH), 121.4 (CH), and 153.4 (CH) in the ^{13}C NMR and DEPT spectra showed the presence of an $\alpha,\beta,\gamma,\delta$-unsaturated aldehyde. The ^1H NMR spectrum confirmed this functionality, since signals were observed at δ_H 9.26, 6.73, 6.85, and 6.36. Resonances due to two methyl groups carrying a hydroxyl group at δ 1.41 (6H, s) were assigned to H_3-16 and H_3-17. The presence of a bicyclic [4.3.1] ring system, containing two hydroxyl groups at C-8 and C-11, was assumed from the resonances due to methyl protons at C-18 (δ 1.02, 3H, s), as well as the isolated methylene protons at C-19 (δ 1.62, 1.32), and a broad singlet at C-8 (δ 3.42, 1H).[5,6] The NMR spectroscopic data of **1** were similar to those of florlide A,[4] except that the lactone function was replaced by two aldehydes (δ_H 9.67, 9.26; δ_C 207.0, 194.8). The geometry of the olefinic bond between C-4 and C-12 was concluded to be *E* on the basis of a strong NOESY correlation between H-4a (δ 3.52, m) and H-13. The configuration of all chiral centers was elucidated from NOESY experiments of **1**. NOESY correlations from H_2-19 (δ 1.62, 1.32) to H-11a (δ 3.95) and H_3-18 and from H-11a to H_2-3 showed that these protons occur on the β face of the ring system. The large coupling constant (J = 12.0 Hz) between H-4a (δ 3.52 m) and H-11a suggested that they have a configuration opposite each other.[5−7] The α-configuration of H-8 was assumed from the signal pattern (broad singlet) as for the floridicins.[5,6] Therefore, the structure of umbellacin A was assigned as **1** on the basis of the above results.

The IR spectrum of **2** indicated absorption bands due to hydroxyl (3480 cm^{-1}) and ester carbonyl (1740 cm^{-1}) functionalities. The molecular formula of $C_{23}H_{36}O_7$ was obtained from the HRESIMS and NMR data. The NMR features of compound **2** were analogous to those of **1**, with the exception that a secondary hydroxyl group [δ_H 4.15 (1H, t, J = 6.0 Hz); δ_C 73.8 (CH)] appeared at C-14, a terminal methylene [δ_H 4.89 (1H, s), 5.01 (1H, s); δ_C 111.0 (CH_2)] appeared at C-15, and the aldehydes were replaced by a carbomethoxy group [δ_H 3.64, 3H, s; δ_C 51.7 (CH_3); 173.5 (qC)] and an acetoxymethyl group [δ_H 4.51 (1H, br d, J = 12.3 Hz), 4.58 (1H, d, J = 12.3 Hz); δ_C 65.1 (CH_2)]. $^1H-^1H$ COSY cross-peaks between H_2-13 and H-12/H-14, as well as HMBC correlations between H_2-17 and C-15/C-16/C-14, between H_2-3 and C-4/C-4a, and between H-11a and C-1/C-4a/C-11/C-10, confirmed these assignments. The *E*-geometry of the $\Delta^{4(12)}$ olefinic bond was determined by NOESY correlations from H_2-3 to H-12 and from H-4a to H_2-13. The relative stereochemistry of the ring system was also established by a NOESY experiment. NOESY correlations from H_2-19 to H-11a and H_3-18 and from H-11a to H_2-3 showed that these protons occur on the β face of the ring system. The large coupling constant (J = 12.0 Hz) between H-4a and H-11a suggested that they have a configuration opposite one another.[5−7] From these results, the structure of umbellacin B was formulated as **2**.

The IR spectrum of **3** exhibited absorptions due to hydroxyl (3460 cm^{-1}) and carbonyl (1735 cm^{-1}) groups. HRESIMS and NMR data of **3** suggested a molecular formula of $C_{20}H_{28}O_4$. The NMR features of compound **3** closely resembled those of florlide A,[4] except that a trisubstituted olefin [δ_H 5.92 (1H, d, J = 7.5 Hz); δ_C 123.9 (CH), 136.7 (qC)] at C-10/C-11 replaced the tertiary hydroxyl of florlide A. HMBC correlations between H-11a and C-11, C-10, C-19, C-5, and C-4a and between H-9 and C-11, C-10, C-7, and C-8 positioned the trisubstituted olefin at C-10 and C-11. The relative stereochemistry of **3** was established by a NOESY experiment. NOESY correlations from H_2-19 (δ 1.68) to H-11a (δ 3.18) and H_3-18 and from H-11a to H_2-3 showed that these protons occur on the β face of the ring system. The large coupling constant (J = 11.5 Hz) between H-4a (δ 2.30 m) and H-11a (δ 3.18) suggested that the configuration of H-4a was α-oriented.[6] Therefore, the structure of umbellacin C was determined as **3**.

Compound **4** analyzed for $C_{23}H_{36}O_7$ from its HRESIMS and NMR spectroscopic data. The NMR features of compound **4** were analogous to those of umbellatol B,[8] except that a secondary hydroxyl group appeared at C-14, and the aldehyde functions of umbellatol B were replaced by carbomethoxy and acetoxymethyl groups. $^1H-^1H$ COSY cross-peaks between H-13 and H-12/H-14, as well as HMBC correlations between H_2-3 and C-4 and C-4a and between H-11a and C-1, C-4a, C-11, and C-10, supported these assignments. The relative stereochemistry of the ring system was established by comparison of NOESY data with those of umbellatols

[⊥] Dedicated to Dr. Norman R. Farnsworth of the University of Illinois at Chicago for his pioneering work on bioactive natural products.

* 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.

[‡] Mansoura University.

[§] Kaohsiung Medical University.

10.1021/np058093r CCC: $33.50
Published on Web 10/28/2005

Chart 1

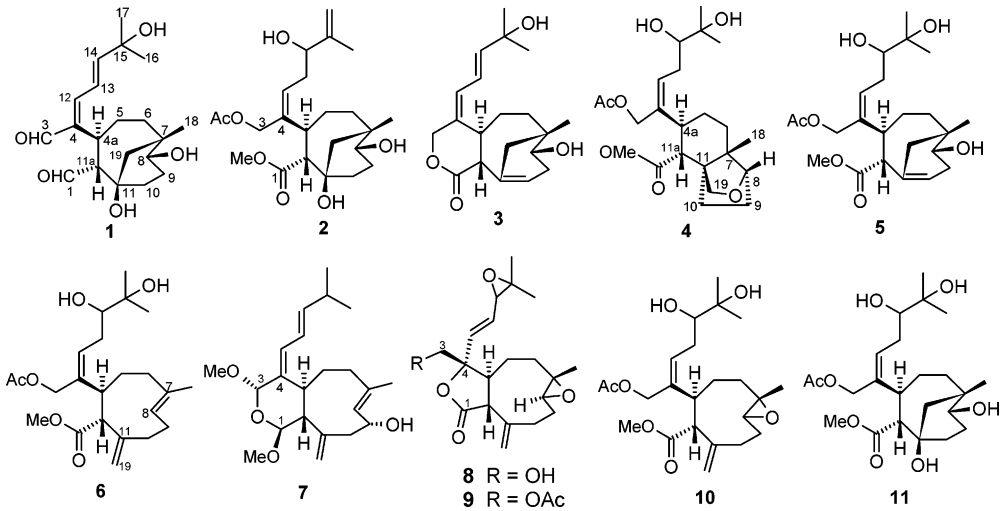

Table 1. ^{1}H NMR Data of Compounds **1**−**6**

H	**1**[a]	**2**[a]	**3**[b]	**4**[a]	**5**[a]	**6**[a]
1	9.67 br s					
3	9.26 s	4.51 d (12.3)[c]	4.45 d (12.0)	4.51 d (12.3)	4.54 br s	4.53 br s
		4.58 d (12.3)	4.93 d (12.0)	4.58 d (12.3)		
4a	3.52 m	3.08 br t (12.0)	2.30 br t (11.5)	3.21 dt (3.9, 10.8)	2.83 m	3.30 m
5	2.80 m	1.55 m	1.72 m	1.58 m	1.76 m	1.64 m
	2.98 m	1.92 m	2.04 m		2.18 m	1.39 m
6	1.82 m	1.97 m	1.11 m	1.50 m	1.14 m	2.00 m
			1.55 m		1.35 m	
8	3.42 br s	3.42 br s	3.49 t (3.3)	3.83 s	3.46 m	5.38 br d (9.0)
9	1.42 m	1.68 m	2.05 m	1.80 m	2.91 m	2.10 m
	1.76 m	2.17 m	2.95 dt (16.5, 7.5)	2.14 m		2.40 m
10	1.32 m	1.36 m	5.92 br d (7.5)	1.23 m	5.59 br d (7.2)	2.22 m
	1.62 m	1.64 m				2.43 m
11a	3.95 d (12.0)	2.74 d (12.0)	3.18 d (12.0)	2.69 d (10.8)	3.32 d (11.1)	3.12 d (11.4)
12	6.73 d (11.4)	5.46 t (6.6)	6.06 d (11.5)	5.75 t (7.2)	5.66 t (7.2)	5.57 t (6.6)
13	6.85 dd (11.4,14.4)	2.43 m	6.26 dd (11.5, 15.5)	2.49 ddd (15.0, 7.2, 3.0)	2.26 m	2.32 m
				2.27 ddd (15.0, 7.2, 1.0)	2.48 m	2.56 m
14	6.36 d (14.4)	4.15 t (6.0)	5.88 d (15.5)	3.52 dd (9.0, 3.0)	3.44 m	3.55 m
16	1.41 s	1.76 s	1.34 s	1.23 s	1.22 s	1.23 s
17	1.41 s	4.89 s	1.34 s	1.27 s	1.26 s	1.30 s
		5.01 s				
18	1.02 s	1.03 s	1.04 s	1.12 s	1.01 s	1.55 s
19	1.73 m	1.78 m	1.68 m	3.41 d (7.2)	1.56 m	5.04 s
	2.03 m		2.22 d (13.0)	3.64 d (7.2)	1.70 m	5.11 s
OC*H*$_3$		3.64 s		3.61 s	3.64 s	3.56 s
OCOC*H*$_3$		2.06 s		2.04 s	2.06 s	2.06 s

[a] Recorded in $CDCl_3$ at 300 MHz. [b] Recorded in $CDCl_3$ at 500 MHz. The values are ppm downfield from TMS, and assignments were made by COSY, NOESY, HMQC, and HMBC experiments. [c] *J* values (in Hz) in parentheses.

A and B. The *E*-geometry of the olefinic bond $\Delta^{4(12)}$ was determined by NOESY correlations from H_2-3 to H-12 and from H-4a to H_2-13.

Compound **5** analyzed for $C_{23}H_{36}O_7$ from its HRESIMS and NMR spectroscopic data. The NMR features of compound **5** were similar to those of **3** except that a secondary hydroxyl group [δ_H 3.44 m; δ_C 77.9 (CH)] appeared at C-14 in **5** and the lactonic function of **3** was replaced by a carbomethoxy group [δ_H 3.64, 3H, s; δ_C 51.8 (CH_3); 173.2 (qC)] and an acetoxymethyl [δ_H 4.54 br s; δ_C 64.7 (CH_2)] in **5**. ^{1}H−^{1}H COSY cross-peaks between H-13 and H-12/H-14 as well as HMBC correlations between H_2-3 and C-4 and C-4a and between H-11a and C-1, C-4a, C-11, and C-10 suggested these assignments. NOESY correlations from H_2-3 to H-12 and from H-4a to H_2-13 established the *E*-geometry of the olefinic bond $\Delta^{4(12)}$.

Compound **6** gave a molecular formula of $C_{23}H_{36}O_6$, as indicated by its HRESIMS and NMR spectroscopic data. The NMR features of compound **6** were analogous to those of compound **5** with the exception that the isolated aliphatic methylene (C-19) signal was replaced by an exo-methylene at C-11 and a trisubstituted olefin resonance appeared at C-7. COSY correlations between H-9 and H-8/H-10 and HMBC correlations between H_3-18 and C-6/C-8 and between H_2-19 and C-11/C-11a/C-10 confirmed the positions of the trisubstituted olefin and the exo-methylene.

HRESIMS and NMR spectroscopic data revealed **7** to have a molecular formula of $C_{22}H_{34}O_5$. The NMR features of compound **7** (Tables 2 and 3) closely resembled those of xenibecin,[7] with the exception of an additional secondary hydroxyl group [δ_H 4.75 br s; δ_C 68.2 (CH)] at C-9 in **7**. A COSY correlation between H-9 and H-8/H-10 and HMBC correlations between H-8 and C-9/C-10/C-18/C-6 confirmed the location of the secondary hydroxyl at C-9. The relative configuration of **7** was established by a NOESY experiment. NOESY correlations from H-11a to H-3 and Me-18 and from H-9 to Me-18 showed that these protons occurred on the same face on the ring system (β). A NOESY correlation from H-4a to H-8 showed that these protons also occurred on the same face of the ring system (α).

Compound **8** proved to have a molecular formula of $C_{20}H_{28}O_5$ by its HRESIMS and NMR spectroscopic data. The NMR features of compound **8** were similar to those of xeniolide H with the

Table 2. ^{13}C NMR Data of Compounds **1**−**11**

C	**1**[a]	**2**[a]	**3**[b]	**4**[a]	**5**[a]	**6**[a]	**7**[a]	**8**[b]	**9**[b]	**10**[a]	**11**[a]
1	207.0	173.5	172.2	173.1	173.2	173.2	104.3	176.0	174.3	172.8	173.7
3	194.8	65.1	73.1	66.7	64.7	66.0	99.6	65.3	64.2	65.5	65.1
4	134.4	139.1	134.3	136.8	138.2	139.5	139.4	87.5	85.5	138.4	138.8
4a	34.5	39.9	50.5	34.8	47.7	37.8	44.2	47.8	43.1	37.9	39.5
5	29.6	29.9	29.5	26.1	28.0	32.3	35.8	27.5	25.5	29.1	29.8
6	29.1	27.6	39.8	28.8	38.6	39.9	39.7	38.7	38.3	38.3	38.5
7	37.2	37.2	40.5	48.8	40.4	136.0	132.8	59.0	58.9	59.7	37.2
8	73.6	73.4	74.8	83.4	74.1	124.6	130.5	64.3	64.3	63.7	73.8
9	27.9	28.6	34.9	28.	33.9	28.9	68.2	28.7	28.8	27.3	27.5
10	38.6	38.6	123.9	28.3	119.7	30.9	45.6	27.6	27.5	26.1	28.3
11	74.9	74.4	136.7	47.7	137.9	144.2	149.6	143.6	141.6	143.1	73.4
11a	59.1	61.0	51.3	43.4	53.4	61.4	56.3	59.1	57.9	60.7	61.0
12	150.5	127.2	128.7	131.5	130.2	126.7	124.6	127.1	128.0	128.2	128.3
13	121.4	33.2	120.9	30.3	30.2	30.8	121.2	132.1	130.7	30.7	30.2
14	153.4	73.8	144.8	77.8	77.9	77.3	144.2	63.0	62.7	77.3	77.3
15	71.2	146.6	70.8	73.0	73.0	73.0	71.1	60.9	61.6	72.9	73.1
16	29.8	18.5	29.8	24.2	24.1	24.0	29.6	18.6	18.7	24.0	23.9
17	29.8	111.0	29.8	26.5	26.4	26.5	29.6	25.4	24.5	26.5	26.4
18	29.6	29.8	23.3	15.2	22.5	18.6	18.2	18.1	18.2	18.8	29.8
19	44.4	43.8	39.8	76.3	38.2	120.3	111.0	121.8	122.7	121.3	43.9
$OCOCH_3$		21.2		21.1	21.2	21.2			20.7	21.2	21.3
$OCOCH_3$		170.7		170.6	170.8	170.9			170.2	170.8	171.0
OCH_3		51.7		51.5	51.8	51.7	55.8			51.9	51.6
							57.1				

[a] Recorded in $CDCl_3$ at 75 MHz. [b] Recorded in $CDCl_3$ at 125 MHz. The values are ppm downfield from TMS, and assignments were made by COSY, NOESY, HMQC, and HMBC experiments.

Table 3. ^1H NMR Data of Compounds **7**−**11**

H	**7**[a]	**8**[b]	**9**[b]	**10**[a]	**11**[a]
1	4.34 d (9.0)[c]				
3	5.26 m	3.76 d (12.0)	4.23 m	4.53 br s	4.52 d (12.3)
		3.95 d (12.0)			4.59 d (12.3)
4a	2.92 br d (14.1)	2.60 m	2.77 td (7.0, 7.0)	3.30 m	3.09 br t (12.3)
5	2.19 m	2.08 dq (15.0, 4.0)	2.00 dq (15.5, 3.0)	1.55 m	1.54 m
	1.90 m	1.88 m	1.58 m	1.74 m	1.88 m
6	1.55 m	2.21 dt (13.0, 3.0)	2.17 dt (13.0, 2.4)	1.22 m	1.32 m
	2.20 m	1.10 dq (13.0, 4.5)	1.06 tt (13.0, 2.4)	2.02 m	1.62 m
8	5.26 m	2.85 dd (11.5, 3.0)	2.81 br d (11.5)	3.03 d (11.4)	3.40 br s
9	4.75 br s	2.25 m	2.26 br d (11.5)	2.18 m	1.72 m
		1.20 m	1.40 m	1.42 m	2.18 m
10	2.32 br d (13.8)	2.60 m	1.79 br t (13.5)	2.38 m	1.60 m
	2.55 dd (13.8, 6.6)		2.70 br d (13.5)		2.20 m
11a	1.72 m	3.76 d (12.5)	3.16 d (12.5)	3.26 d (11.1)	2.73 d (12.3)
12	6.40 d (10.2)	5.85 d (15.5)	5.88 d (15.5)	5.61 t (7.2)	5.57 t (7.2)
13	6.49 dd (10.2, 15.3)	5.85 dd (15.5, 5.5)	5.88 dd (15.5, 5.5)	2.29 m	2.26 m
				2.46 m	
14	5.98 d (15.3)	3.22 d (5.5)	3.27 d (5.5)	3.50 dd (8.4, 2.7)	3.41 m
16	1.35 s	1.26 s	1.27 s	1.22 s	1.21 s
17	1.35 s	1.38 s	1.39 s	1.26 s	1.25 s
18	1.79 s	1.18 s	1.13 s	1.15 s	1.05 s
19	4.75 s	5.22 s	5.22 s	5.11 s	1.77 m
	4.91 s	5.25 s	5.23 s	5.31 s	
OCH_3	3.40 s			3.59 s	3.60 s
	3.56 s				
$OCOCH_3$			2.11 s	2.05 s	2.06 s

[a] Recorded in $CDCl_3$ at 300 MHz. [b] Recorded in $CDCl_3$ at 500 MHz. The values are ppm downfield from TMS, and assignments were made by COSY, NOESY, HMQC, and HMBC experiments. [c] *J* values (in Hz) in parentheses.

exception that a trisubstituted epoxy group [δ_H 3.22 d; δ_C 63.0 (CH), 60.9 (qC)] replaced the olefin at C-14/C-15 in xeniolide H.[7] COSY correlations between H-13 and H-14/H-12 and a HMBC correlation from H-16/H-17 to C-15/C-14 confirmed the location of the epoxy group.

Compound **9** was assigned a molecular formula of $C_{22}H_{30}O_6$, as shown by the HRESIMS and NMR spectroscopic data. The NMR features of compound **9** closely resembled those of **8**, with the exception that the hydroxyl group at C-3 was replaced by an acetoxyl [δ_H 2.11, 3H, s; δ_C 20.7 (CH_3), 170.2 (qC)] in **9**. HMBC correlations between H_2-3 and C-4/C-4a/C-12/CH_3COO permitted the placement of the secondary acetoxyl at C-3.

Compound **10** proved to have a molecular formula of $C_{23}H_{36}O_7$ from its HRESIMS and NMR spectroscopic data. The NMR features of compound **10** resembled those of **6**, with the exception that a trisubstituted epoxy group [δ_H 3.03 d; δ_C 63.7 (CH), 59.7 (qC)] replaced the olefin at C-7/C-8 in **6**. A COSY NMR correlation between H-8 and H-9 and a HMBC correlation between H_3-18 and C-6/C-7/C-8 confirmed the location of the epoxy group at C-7/C-8.

Compound **11** analyzed for $C_{23}H_{38}O_8$ by HRESIMS and NMR spectroscopic data. The NMR features of compound **11** were similar to those of **2**, except that a methyl group replaced the exo-methylene at C-15 and the secondary hydroxyl was shifted to C-14. $^1H-^1H$

COSY cross-peaks between H-14 and H_2-13, as well as HMBC correlations between H_3-16/17 and C-15, C-14, supported these assignments.

Compounds **2**, **4**, **5**, **6**, **10**, and **11** exhibited cytotoxicity against murine P-388 lymphocytic leukemia with ED_{50} values of 1.6, 4.2, 3.8, 3.7, 3.4, and 3.6 μg/mL, respectively. All of these cytotoxic isolates contain carbomethoxy and acetoxymethyl functionalities. However, none of the isolates were cytotoxic to A549 (human lung adenocarcinoma) and HT-29 (human colon adenocarcinoma) cell lines (IC_{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, using $CDCl_3$ with TMS as internal standard. ESIMS were obtained with a Bruker APEX II mass spectrometer. Silica gel 60 (Merck, 230−400 mesh) was used for column chromatography; precoated silica gel plates (Merck, Kieselgel 60 F_{254}, 0.25 mm) were used for TLC analysis.

Animal Material. The soft coral *X. umbellata* was collected at Green Island, off Taiwan, in June 2004, at a depth of 3−4 m and was stored for 3 months in a freezer until extraction. A voucher specimen, NSUGN068, identified by Dr. C.-F. Dai (Institute of Oceanography, National Taiwan University), was deposited in the Department of Marine Biotechnology and Resources, National Sun Yat-sen University, Taiwan.

Extraction and Isolation. The bodies of the soft coral *X. umbellata* were freeze-dried to give 800 g of a solid, which was extracted with CH_2Cl_2 (3.0 L × 3). After removal of solvent in vacuo, the residue (60 g) was chromatographed over silica gel 60 using *n*-hexane and *n*-hexane−EtOAc mixtures of increasing polarity. Elution by *n*-hexane−EtOAc (9:1) afforded fractions containing compound **9**. Elution by *n*-hexane−EtOAc (5:1) afforded fractions containing compound **8**. Elution by *n*-hexane−EtOAc (4:1) afforded fractions containing compound **1**. Elution by *n*-hexane−EtOAc (2:1) afforded fractions containing compounds **6**, **10**, and **11**. Elution by *n*-hexane−EtOAc (3:2) afforded fractions containing compound **5**. Elution by MeOH−EtOAc (98:2) afforded fractions containing compounds **3** and **7**. Elution by MeOH−EtOAc (95:5) afforded fractions containing compounds **2** and **4**. Compound **1** (6 mg, 0.001%) was further purified by HPLC (RP-18) eluting with MeOH−H_2O (65:35). Compound **2** (3 mg, 0.0005%) was further purified by HPLC (RP-18), eluting with MeOH−H_2O (60:40). Compound **3** (3 mg, 0.0005%) was further purified by HPLC (RP-18) by eluting with MeOH−H_2O (70:30). Compounds **4** (2 mg, 0.00003%) and **5** (3 mg, 0.0005%) were further purified by HPLC (RP-18) eluting with MeOH−H_2O (60:40). Compounds **6** (2 mg, 0.0003%), **10** (4 mg, 0.0006%), and **11** (3 mg, 0.0005%) were further purified by HPLC (RP-18) eluting with MeOH−H_2O (68:32). Compound **7** (2 mg, 0.0003%) was further purified by HPLC (RP-18) eluting with MeOH−H_2O (67:33). Compound **8** (2 mg, 0.00003%) was further purified by HPLC (RP-18) eluting with MeOH−H_2O (73:27). Compound **9** (2 mg, 0.00003%) was further purified by HPLC (RP-18) eluting with MeOH−H_2O (82:18).

Umbellacin A (1): oil; $[\alpha]^{25}_D$ −36° (*c* 0.2, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 235 (4.26) nm; IR (neat) ν_{max} 3450, 1730 cm^{-1}; ^{1}H NMR, see Table 1; ^{13}C NMR, see Table 2; HRESIMS *m*/*z* 373.1991 (calcd for $C_{20}H_{30}O_5Na$, 373.1990).

Umbellacin B (2): amorphous solid; $[\alpha]^{25}_D$ −28° (*c* 0.3, $CHCl_3$); IR (neat) ν_{max} 3480, 1740, 1610 cm^{-1}; ^{1}H NMR, see Table 1; ^{13}C NMR, see Table 2; HRESIMS *m*/*z* 447.2358 (calcd for $C_{23}H_{36}O_7Na$, 447.2356).

Umbellacin C (3): oil; $[\alpha]^{25}_D$ +12° (*c* 0.2, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 228 (4.12) nm; IR (neat) ν_{max} 3460, 1735 cm^{-1}; ^{1}H NMR, see Table 1; ^{13}C NMR, see Table 2; HRESIMS *m*/*z* 355.1886 (calcd for $C_{20}H_{28}O_4Na$, 355.1885).

Umbellacin D (4): amorphous solid; $[\alpha]^{25}_D$ +36° (*c* 0.1, $CHCl_3$); IR (neat) ν_{max} 3448, 1736 cm^{-1}; ^{1}H NMR, see Table 1; ^{13}C NMR, see Table 2; HRESIMS *m*/*z* 447.2357 (calcd for $C_{23}H_{36}O_7Na$, 447.2356).

Umbellacin E (5): amorphous solid; $[\alpha]^{25}_D$ +32° (*c* 0.2, $CHCl_3$); IR (neat) ν_{max} 3450, 1738 cm^{-1}; ^{1}H NMR, see Table 1; ^{13}C NMR, see Table 2; HRESIMS *m*/*z* 447.2358 (calcd for $C_{23}H_{36}O_7Na$, 447.2356).

Umbellacin F (6): amorphous solid; $[\alpha]^{25}_D$ −30° (*c* 0.1, $CHCl_3$); IR (neat) ν_{max} 3420, 1730, 1620 cm^{-1}; ^{1}H NMR, see Table 1; ^{13}C NMR, see Table 2; HRESIMS *m*/*z* 431.2406 (calcd for $C_{23}H_{36}O_6Na$, 431.2407).

Umbellacin G (7): amorphous solid; $[\alpha]^{25}_D$ +36° (*c* 0.3, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 224 (3.8) nm; IR (neat) ν_{max} 3460, 1610 cm^{-1}; ^{1}H NMR, see Table 3; ^{13}C NMR, see Table 2; HRESIMS *m*/*z* 401.2304 (calcd for $C_{22}H_{34}O_5Na$, 401.2302).

14,15-Epoxy-xeniolide H (8): amorphous solid; $[\alpha]^{25}_D$ +26° (*c* 0.2, $CHCl_3$); IR (neat) ν_{max} 3400, 1760, 1600 cm^{-1}; ^{1}H NMR, see Table 3; ^{13}C NMR, see Table 2; HRESIMS *m*/*z* 371.1836 (calcd for $C_{20}H_{28}O_5Na$, 371.1834).

3-Acetyl-14,15-epoxy-xeniolide H (9): amorphous solid; $[\alpha]^{25}_D$ +22° (*c* 0.1, $CHCl_3$); IR (neat) ν_{max} 1760, 1740, 1620 cm^{-1}; ^{1}H NMR, see Table 3; ^{13}C NMR, see Table 2; HRESIMS *m*/*z* 413.1937 (calcd for $C_{22}H_{30}O_6Na$, 413.1939).

Umbellacin H (10): amorphous solid; $[\alpha]^{25}_D$ +46° (*c* 0.1, $CHCl_3$); IR (neat) ν_{max} 3409, 1733 cm^{-1}; ^{1}H NMR, see Table 3; ^{13}C NMR, see Table 2; HRESIMS *m*/*z* 447.2354 (calcd for $C_{23}H_{36}O_7Na$, 447.2356).

Umbellacin I (11): amorphous solid; $[\alpha]^{25}_D$ −30° (*c* 0.2, $CHCl_3$); IR (neat) ν_{max} 3490, 1742 cm^{-1}; ^{1}H NMR, see Table 3; ^{13}C NMR, see Table 2; HRESIMS *m*/*z* 465.2464 (calcd for $C_{23}H_{38}O_8Na$, 465.2461).

Cytotoxicity Testing. P-388 cells were kindly supplied by Dr. J. M. Pezzuto, formerly of the Department of Medicinal Chemistry and Pharmacognosy, University of Illinois at Chicago; A549 and HT-29 cells were purchased from the American Type Culture Collection. Cytotoxic assays were carried out according to previously described procedures.[3]

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

References and Notes

(1) Blunt, J. W.; Copp, B. R.; Munro, M. H. G.; Northcote, P. T.; Prinsep, M. R. *Nat. Prod. Rep.* **2005**, *22*, 15−61, and references therein.
(2) Geran, R I.; Greenberg, N. H.; MacDonald, M. M.; Schumacher, A. M.; Abbott, B. J. *Cancer Chemother.* Rep. **1972**, *3* (3), 1−91.
(3) Hou, R.-S.; Duh, C.-Y.; Chiang, M. Y.; Lin, C.-N. *J. Nat. Prod.* **1995**, *58*, 1126−1130.
(4) Iwagawa, T.; Kawasaki, J.; Hase, T. *J. Nat. Prod.* **1998**, *61*, 1513−1515.
(5) Iwagawa, T.; Nakamura, K.; Hirose, T.; Okamura, H.; Nakatani, M. *J. Nat. Prod.* **2000**, *63*, 468−472.
(6) Iwagawa, T.; Kawasaki, J.; Hase, T.; Wright, J. L. C. *Tetrahedron* **1997**, *53*, 6809−6816.
(7) Duh, C.-Y.; El-Gamal, A. A. H.; Chiang, C.-Y.; Chu, C.-J.; Wang, S.-K.; Dai, C.-F. *J. Nat. Prod.* **2002**, *65*, 1882−1885.
(8) El-Gamal, A. A. H.; Wang, S.-K.; Duh, C.-Y. *Org. Lett.* **2005**, *7*, 2023−2025.

NP058093R