Xenia Diterpenoids from the Formosan Soft Coral *Xenia blumi*

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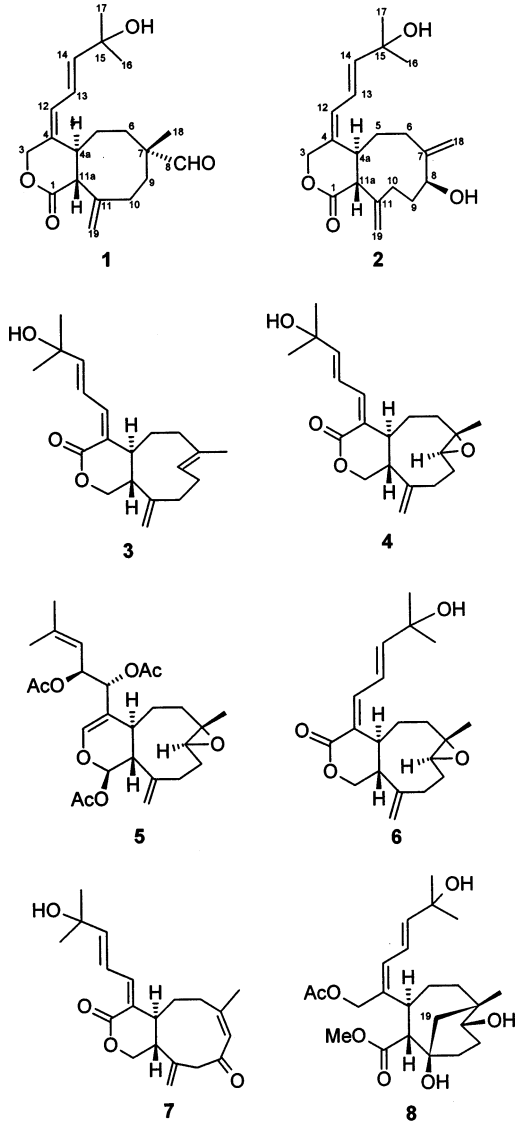
Eight new xenia diterpenoids, blumiolide-A (**1**) (novel carbon skeleton), blumiolide-B (**2**), 9-deoxy-isoxeniolide-A (**3**), 9-deoxy-7,8-epoxy-isoxeniolide-A (**4**), 9-deacetoxy-7,8-epoxy-13-epi-xenicin (**5**), 9-deoxy-7,8-epoxy-xeniolide-A (**6**), blumiolide-C (**7**), and blumicin-A (**8**), were isolated from the methylene chloride solubles of the Formosan soft coral *Xenia blumi.* Their 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 a rich sources of terpenoids and have afforded several types of bioactive diterpenoids.[1] As part of our search for bioactive substances from marine organisms, the Formosan soft coral *Xenia blumi* Roxas was studied because the CH_2Cl_2 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 fractionations of this extract resulted in the isolation of eight new xenia diterpenoids, blumiolide-A (**1**) (novel carbon skeleton), blumiolide-B (**2**), 9-deoxy-isoxeniolide-A (**3**), 9-deoxy-7,8-epoxy-isoxeniolide-A (**4**), 9-deacetoxy-7,8-epoxy-13-epi-xenicin (**5**), 9-deoxy-7,8-epoxy-xeniolide-A (**6**), blumiolide-C (**7**), and blumicin-A (**8**).

Results and Discussion

Compound **1** was isolated as a colorless oil, $[\alpha]^{25}_D$ +18° (*c* 0.4, $CHCl_3$). The IR spectrum of **1** exhibited absorptions due to hydroxyl (3419 cm^{-1}) and carbonyl (1735 cm^{-1}) groups. HRFABMS and NMR data of **1** suggested a molecular formula of $C_{20}H_{28}O_4$. The structure of **1** was completely solved by a combination of 1D and 2D NMR methods. The carbon resonances at δ_C 134.7 (qC), 128.4 (CH), 120.5 (CH), and 145.3 (CH) in the ^{13}C NMR and DEPT spectra (Table 2) suggested the presence of a diene, while the quaternary carbon signal at δ_C 143.9 along with the methylene olefinic carbon signal at δ_C 118.4 indicated the presence of an *exo* methylene double bond. Furthermore, the presence of two oxygenated carbons was deduced from the carbon signals at δ_C 71.3 (qC) and 70.9 (CH_2). Three methylene groups were inferred from four carbon signals at δ_C 29.5, 29.8, 31.2, and 33.3, a lactone carbonyl at δ 172.5, an aldehyde carbonyl at δ 205.9, and, finally, two methyl signals at δ_C 29.8 and 29.9. The ^1H NMR spectrum (Table 1) confirmed the presence of an *exo* methylene double bond by two singlet signals at δ_H 5.07 and 5.34. In addition, one oxygenated methylene was observed at δ_H 4.91 and 4.43. Two intense singlet signals are also observed at δ_H 1.38 and 1.39 (s, 3H each), and these correspond to two methyl groups. In this manner the seven degrees of unsaturation present in **1** were established.



Three spin systems (see **a**−**c** in Figure 1) were deduced from combined use of $^1H-^1H$ COSY and HMQC spectra of **1**. These substructures were connected through HMBC correlations between the protons H_2-3 (δ_H 4.43 and 4.91) and the carbons C-1 (δ_C 172.5), C-4 (δ_C 134.7), C-12 (δ_C 128.4), and C-4a (δ_C 43.5), between the proton H-11a (δ_H 3.16) and the carbons C-1 (δ_C 172.5) and C-10 (δ_C 33.3),

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Table 1. ^{1}H NMR Data of **1**−**7**

H	**1**[a]	**2**[b]	**3**[a]	**4**[a]	**5**[b]	**6**[b]	**7**[b]
1α			3.60 t (12.0)	3.67 t (11.5)	5.97 d (1.8)	3.67 t (12.6)	4.01 t (11.5)
1*β*			4.08 dd (12.0, 5.5)	4.18 dd (11.5, 5.5)		4.16 dd (12.6, 5.4)	4.19 dd (11.5, 4.2)
3α	4.43 d (12.0)[c]	4.42 d (12.0)			6.52 br s		
3*β*	4.91 d (12.0)	4.89 d (12.0)					
4a	2.88 m	3.16 m	2.57 dt (10.0, 3.0)	2.64 dd (8.5, 3.0)	2.37 m	3.13 m	2.55 m
5	2.08 m 1.48 m	2.09 m 1.91 m	1.62 m	1.83 m	2.13 m 1.69 m	1.69 m	1.72 m
6	2.24 m 1.80 m	2.23 m 2.40 m	2.21 m 2.21 m	1.20 m 2.24 m	2.25 m 1.22 m	2.23 m 1.37 m	2.24 m 3.05 dt (4.2, 13.5)
8	9.57 s	4.30 t (4.5)	5.38 t (7.5)	2.93 dd (11.0, 4.5)	2.99 dd (10.5, 8.3)	3.02 dd (10.5, 3.9)	5.97 s
9	1.74 m 2.04 m	2.03 m 2.12 m	2.49 m 2.24 m	2.30 m	2.30m 1.50 m	2.33 m 1.50m	
10	2.45 m 2.36 m	2.49 m 2.34 m	2.33 m	2.52 m	2.43 m	2.45 m 2.29 m	3.45 d (14.1) 3.52 d (14.1)
11a	3.16 d (11.0)	3.42 d (9.6)	2.10 m	2.44 m	2.43 m	2.52 m	2.53 m
12	6.08 d (11.5)	6.07 d (11.1)	6.35 d (11.0)	6.38 d (11.0)	5.30 d (6.3)	6.99 d (11.4)	6.32 d (11.1)
13	6.30 dd (11.5, 15.0)	6.36 dd (11.1, 15.0)	6.84 dd (15.5, 11.0)	6.88 dd (15.5, 11.0)	5.69 dd (9.0, 6.3)	6.46 dd (11.4, 15.0)	6.91 dd (11.1, 15.6)
14	5.95 d (15.0)	5.94 d (15.0)	6.07 d (15.5)	6.09 d (15.5)	5.15 d (9.0)	6.27 d (15.0)	6.09 d (15.6)
16	1.38 s	1.36 s	1.38 s	1.38 s	1.75 s	1.37 s	1.36 s
17	1.39 s	1.36 s	1.37 s	1.37 s	1.75 s	1.37 s	1.36 s
18	1.04 s	a: 5.14 s b: 5.33 s	1.71 s	1.38 s	1.32 s	1.37 s	1.92 s
19a	5.07 s	5.03 s	4.88 s	5.02 s	4.90 s	5.15 s	5.13 s
19b	5.34 s	5.26 s	4.95 s	5.16 s	5.03 s	5.01 s	4.94 s
OCOC*H*$_3$					2.08 s 2.03 s 2.01 s		

[a] Recorded in $CDCl_3$ at 500 MHz. [b] Recorded in $CDCl_3$ at 300 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.

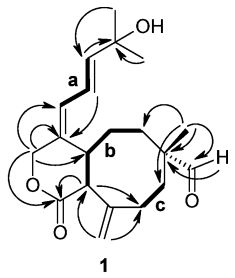


Figure 1. Key COSY and HMBC correlations of **1** and **2**.

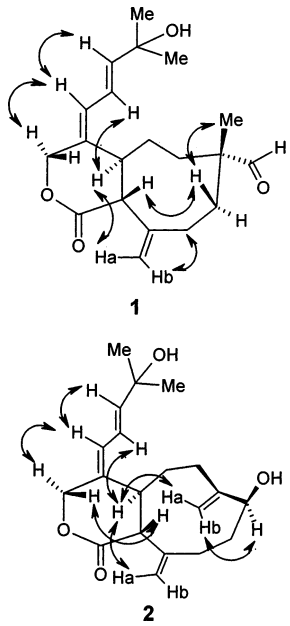


Figure 2. Key NOESY correlations of **1** and **2**.

between the methyl proton Me-18 (δ_H 1.04) and carbons C-6 (δ_C 29.5), C-7 (δ_C 49.3), C-8 (δ_C 205.9), and C-9 (δ_C 31.2), between the aldehydic proton H-8 (δ_H 9.57) and carbon C-7 (δ_C 49.3), and between the *exo* methylene protons H_2-19 (δ_H 5.07 and 5.34) and carbons C-11a (δ_C 48.2) and C-10 (δ_C 33.3). These relationships are represented in Figure 1. All these data allowed us to identify compound **1** as a new diterpenoid with a novel skeleton.

The relative stereochemistry of compound **1** was established from NOESY correlations (Figure 2) and by comparison of its spectroscopic data to those of xeniolide analogues.[4−15] The *E* geometry was assigned to the $\Delta^{4,12}$ double bond on the basis of the observation of NOESY correlations between H-3α and H-12 and between H-4a and H-13. The *E* geometry of the $\Delta^{13,14}$ double bond was established by the large coupling constant observed between H-13 and H-14 (J = 15.0 Hz). The coupling constant (J = 11.0 Hz) between H-4a and H-11a suggested a *trans* ring junction, which implied that H-4a was α-oriented.[4−15] NOESY correlations from H-11a to H-9*β* and H-3*β* and from H-9*β* to Me-18 were observed. This suggests that H-11a and Me-18 are on the same face (*β*) of the ring.

The IR spectrum of **2** indicated absorption bands due to hydroxyl (3450 cm^{-1}) and ester carbonyl (1736 cm^{-1}) functionalities. The molecular formula, $C_{20}H_{28}O_4$, was obtained by the HRFABMS. The NMR spectral data of **2** revealed a ring A and the side chain similar to those of **1**. Resonances due to two methyl groups on a carbon carrying a hydroxyl group at δ_H 1.36 (6H, s) were assigned to H-16 and H-17. The resonance due to H-13 (δ_H 6.36, 1H, dd, J = 11.1, 15.0 Hz) showed that H-13 was coupled to H-12 (δ_H 6.07, 1H, d, J = 11.1 Hz) and H-14 (1H, δ_H 5.94, d, J = 15.0 Hz). An AB system at δ_H 4.42 (1H, d, J = 12.0 Hz) and 4.89 (1H, d, J = 12.0 Hz) was due to H_2-3. Two coupled methines at δ_H 3.16 and 3.42 were due to two methine protons at the ring junction. The ^{13}C NMR resonances at δ_C 114.8 (CH_2) and 118.1 (CH_2) indicated the presence of two *exo* methylene double bonds, which were confirmed by the observation of four singlet signals at δ_H 5.14, 5.33, 5.03, and 5.26 in the ^1H NMR spectrum. In addition, the presence of an oxygenated methine was deduced from the carbon signal at δ_C 75.7 (CH) and the proton signal at δ_H 4.30. Four methylene signals (two allylic) were observed at δ_C 28.7, 30.7, 35.1, and, 35.6 and, finally, two methyl signals at δ_C 29.9 and 30.0.

Analysis of $^1H-^1H$ COSY and HSQC on **2** enabled us to distinguish three spin systems (see **d**−**f** in Figure 1). These substructures were connected through HMBC correlations between the protons H_2-3 (δ_H 4.42 and 4.89) and the carbons C-1 (δ_C 173.2), C-4 (δ_C 135.1), C-12 (δ_C 128.1), and C-4a (δ_C 38.1), between the proton H-11a (δ_H 3.42) and the carbons C-1 (δ_C 173.2), C-11 (δ_C 146.6), and C-19 (δ_C 118.1), between the *exo* methylene protons H_2-18 (δ_H 5.14 and 5.33) and carbons C-6 (δ_C 28.7), C-7 (δ_C 152.4), and C-8 (δ_C 75.7), and between the *exo* methylene protons H_2-19 (δ_H 5.03 and 5.26) and carbons C-11a (δ_C 50.7) and C-10 (δ_C 30.7). These relationships are represented in Figure 1. All these data allowed us to identify compound **2** as a new xeniolide diterpenoid.

The relative stereochemistry of compound **2** was deduced from NOESY correlations (Figure 2) and by comparison of its spectroscopic data with those of xeniolide analogues. The *E* geometry was assigned to the $\Delta^{4,12}$ double bond on the basis of the observation of NOESY correlations between H-3α and H-12 and between H-4a and H-13. The *E* geometry of the Δ^{13} double bond was established by the large coupling constant observed between H-13 and H-14 (J = 15.0 Hz). The coupling constant (J = 9.6 Hz) between H-4a and H-11a suggested a *trans* ring junction, which implied that H-4a was α-oriented.[4−15] NOESY correlations from H-4a to Ha-18 and Ha-19 and from H-18b to H-8 were observed. This suggests that two *exo* methylenes are perpendicular to the ring and H-4a, H_2-18, H_2-19, and H-8 are on the same face (α) of the ring.

Compound **3** had a molecular formula of $C_{20}H_{28}O_3$, as indicated by HRFABMS and NMR spectral data. The NMR features of compound **3** were analogous to those of 9-deoxyxeniolide-A[16] with the exception of the stereochemistry at C-12. The *Z* geometry was assigned to the $\Delta^{4,12}$ double bond on the basis of the resonances due to H-13 (δ_H 6.84, 1H, dd, J = 11.0, 15.5 Hz), H-12 (δ_H 6.35, 1H, d, J = 11.5 Hz), and H-14 (1H, δ_H 6.07, d, J = 15.5 Hz) as well as the observation of NOESY correlations between H-4a and H-12. The relative stereochemistry of the ring system, which was similar to that of 9-deoxyxeniolide-A, was established by a NOESY experiment.

Compound **4** had a molecular formula of $C_{20}H_{28}O_4$, as indicated by HRFABMS and NMR spectral data. The NMR features of compound **4** were analogous to those of compound **3** with the exception that the resonances for the methyl-bearing *E*-trisubstituted olefin were replaced by those of a methyl-bearing trisubstituted epoxide [δ_H 1.38 s, 2.93 dd; δ_C 16.3 (CH_3), 59.0 (qC), 62.1 (CH)]. Cross-peaks in the $^1H-^1H$ COSY spectrum showed couplings between the epoxide methine proton at C-8 and methylene protons at C-9. HMBC correlations between H-8 and C-6, C-7, C-9, and C-10 and between Me-18 and C-6, C-7, and C-8 positioned the methyl-bearing trisubstituted epoxide at C-7, C-8, and C-18. The relative stereochemistry of **4** was established by a NOESY experiment. NOESY correlations from H-11a to H-1β (δ 4.18) and Me-18 showed that these protons occurred on the same face of the ring system (β). The coupling constant (J = 8.5 Hz) between H-4a and H-11a suggested a *trans* ring junction, which implied that H-4a was α-oriented.[4−15] A NOESY correlation from H-4a to H-8 showed that these protons occurred on the α face of the ring system.

Compound **5** was analyzed for $C_{26}H_{36}O_8$ by HRFABMS and NMR spectral data. The NMR features of compound **5** were analogous to those of 9-desacetyl-7,8-epoxy-13-epi-xenicine[17] except the absence of the hydroxyl group at C-9, and this was confirmed by $^1H-^1H$ COSY cross-peaks between the epoxide methine proton at δ 2.99 (dd, H-8) and methylene protons at δ 2.30 and 1.50 as well as HMBC correlations between H-18 and C-6, C-7, C-9, and C-10. The relative stereochemistry of the ring system, which is similar to **4**, was established by a NOESY experiment. The relative stereochemistry of the side chain was determined as 12*R**, 13*S** by comparison of the ^1H and ^{13}C NMR chemical shifts and coupling constants of **5** with those of 13-epi-9-deacetylxenicin.[6]

Compound **6** had a molecular formula of $C_{20}H_{28}O_4$, as shown by HRFABMS and NMR spectral data. The NMR features of compound **6** closely resembled those of compound **4** with the exception of the stereochemistry at C-12. The *E* geometry was assigned to the $\Delta^{4,12}$ double bond on the basis of the observation of NOESY correlations between H-3α and H-12 and between H-4a and H-13. The relative stereochemistry of the ring system, which was similar to that of **4**, was established by a NOESY experiment.

Compound **7** exhibited a molecular formula of $C_{20}H_{26}O_4$ by HRFABMS and NMR spectral data. The NMR features of compound **7** were analogous to those of compound **3** except the methylene at C-9 was oxidized to a ketone, and this was confirmed by HMBC correlations from Me-18 to C-6/C-7/C-8 and from H_2-10 to C-9/C-10/C-19/C-11a. The *Z*-trisubstituted olefin at C-7 was established by the NOESY correlation between H_3-18 and H-8, and the relative stereochemistry of the ring system was decuced from the NOESY experiment.

Compound **8** was shown to have a molecular formula of $C_{23}H_{36}O_7$ by HRFABMS and NMR spectral data. The presence of the 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), isolated methylene protons at C-19 (δ 1.76), and a broad singlet at C-8 (δ 3.50, 1H).[18] Resonances due to two methyl protons on a carbon carrying a hydroxyl group at δ 1.36 (6H, s) were assigned to H-16 and H-17. The resonance due to H-13 (δ 6.48, 1H, dd, J = 10.5, 15.6 Hz) showed that H-13 was coupled to H-12 (δ 6.02, 1H, d, J = 10.5 Hz) and H-14 (1H, δ 5.88, d, J = 15.6 Hz). An AB system at δ 4.56 (1H, br d, J = 12.0 Hz) and 4.63 (1H, d, J = 12.0 Hz) was due to H_2-3. The acetoxy was placed at C-3 on the basis of a HMBC correlation from H_2-3 to the acetoxy carbonyl carbon. The remaining carbomethoxy group (δ_H 3.58, 3H,

Table 2. ^{13}C NMR Data of **1**−**8**

carbon	**1**[a]	**2**[b]	**3**[a]	**4**[a]	**5**[c]	**6**[a]	**7**[a]	**8**[b]
1	172.5	173.2	71.2	71.6	91.0	71.1	69.1	173.0
3	70.9	71.7	169.2	168.5	140.0	170.4	168.5	65.0
4	134.7	135.1	133.4	132.5	113.3	132.4	133.0	142.2
4a	43.5	38.1	51.5	50.7	36.8	42.3	47.0	40.3
5	29.8	35.1	37.8	36.3	29.6	36.4	36.0	30.0
6	29.5	28.7	40.0	39.7	39.1	39.7	30.7	38.5
7	49.3	152.4	135.5	59.0	60.2	59.1	142.8	37.2
8	205.9	75.7	124.3	62.1	62.6	62.7	130.4	73.8
9	31.2	35.6	24.8	25.0	24.2	25.5	200.6	27.8
10	33.3	30.7	34.9	29.7	29.6	31.8	52.5	28.0
11	143.9	146.6	152.1	141.8	142.4	148.9	149.7	73.6
11a	48.2	50.7	49.9	48.9	48.8	49.1	45.4	60.7
12	128.4	128.1	135.5	136.9	75.1	137.3	139.1	130.0
13	120.5	120.8	122.6	122.5	69.6	119.7	122.4	121.4
14	145.3	145.1	147.4	148.3	119.6	151.4	149.0	144.0
15	71.3	71.0	70.9	70.9	140.5	71.2	71.0	71.0
16	29.8	29.9	29.4	29.4	24.6	29.9	29.4	29.8
17	29.9	30.0	29.3	29.3	17.4	29.9	29.5	29.8
18	24.1	114.8	16.3	16.3	15.1	16.8	25.0	29.6
19	118.4	118.1	113.0	114.9	113.5	115.9	116.2	44.8
OCO*C*H$_3$					19.8			21.2
					19.5			
					19.4			
O*C*OCH$_3$					170.3			171.0
					170.0			
					169.6			
O*C*H$_3$								51.8

[a] Recorded at 125 MHz in $CDCl_3$. [b] Recorded at 75 MHz in $CDCl_3$. [c] Recorded at 75 MHz in d_4-methanol. The values are in ppm downfield from TMS, and assignments were made by DEPT, COSY, HMQC, and HMBC experiments.

Table 3. Cytotoxicity[a] of **1**−**8**

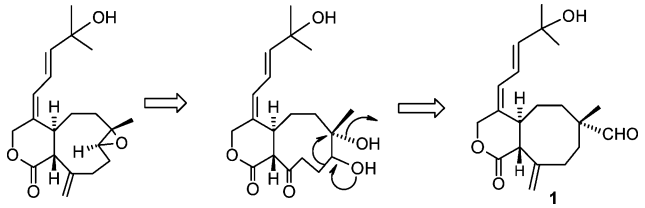
	cell lines ED_{50} (μg mL^{-1})	
compound	HT-29	P-388
1	4.6	3.3
2	4.9	3.7
3	8.7	>20
4	5.6	4.7
5	>20	>20
6	8.6	6.9
7	0.5	0.2
8	>20	>20

[a] For significant activity of pure compounds, an ED_{50} of ≤4.0 μg/mL is required.

s; δ_C 51.8, q; δ_C 173.0, s) to be assigned was deduced to be located at C-11a by a HMBC correlation from H-11a to C-1. The *E* geometry of the double bond at C-13 was determined by the coupling constant (J = 15.6 Hz) between H-13 and H-14. 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 3.22, m) and H-13. The stereochemistry of all chiral centers was elucidated from NOESY experiments of **8**. NOESY corralations from H-19 (δ 1.76) to H-11a (δ 2.74) and H-18 and from H-11a to H-3 showed that these protons occur on the β face of the ring system. The large coupling constant (J = 12.6 Hz) between H-4a (δ 3.22 m) and H-11a (δ 2.74) suggested that the configuration of H-4a was α-oriented.[18] The α-configuration of H-8 was assumed from the signal pattern (broad singlet) as for floridicins.[18] Therefore, the structure of blumicin-C was assigned as **8** on the basis of the above results.

The cytotoxicity of compounds **1**−**8** is shown in Table 3. Compound **7** exhibited potent cytotoxicity against P-388 and HT-29 cells. Compounds **1** and **2** exhibited moderate cytotoxicity against P-388 cells. A plausible biogenetic pathway of **1** was proposed as shown in Scheme 1.

Scheme 1. Plausible Biogenetic Pathway of **1**



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-NMT at 500 MHz for ^1H and 125 MHz for ^{13}C, using $CDCl_3$ with TMS as internal standard. FABMS spectra were obtained with a JEOL JMS-SX/SX 102A 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. blumi* was collected at Green Island, off Taiwan, in May 2002, at a depth of 3−4 m and was stored for 2 months in a freezer until extraction. A voucher specimen, NSUGN-4751, was deposited in the Department of Marine Resources, National Sun Yat-sen University, Taiwan.

Extraction and Isolation. The bodies of the soft coral *X. blumi* were freeze-dried to give 0.55 kg of a solid, which was extracted with CH_2Cl_2 (4.0 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 (5:1) afforded fractions containing compound **5**. Elution by *n*-hexane−EtOAc (4:1) afforded fractions containing compound **3**. Elution by *n*-hexane−EtOAc (3:1) afforded fractions containing compound **4**. Elution by *n*-hexane−EtOAc (7:3) afforded fractions containing compound **8**. Elution by *n*-hexane−EtOAc (5:2) afforded fractions containing compounds **6** and **7**. Elution by *n*-hexane−EtOAc (3:2) afforded fractions containing compounds **1** and **2**. Compounds **1** and **2** were further purified by silica gel column chromatography, by eluting with CH_2Cl_2−acetone (20:1). Compound **3** was further purified by HPLC (Si 60) by eluting with *n*-hexane−acetone (3:1). Compounds **5**−**8** were further purified by HPLC (RP-18) by eluting with MeOH−H_2O (82:18), MeOH−H_2O (70:30), MeOH−H_2O (67:33), and MeOH−H_2O (65:35), respectively.

Blumiolide-A (1): oil; $[\alpha]^{25}_D$ +18° (*c* 0.4, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 226 (3.6) nm; IR (neat) ν_{max} 3419, 1735, 1650 cm^{-1}; ^1H NMR, see Table 1; ^{13}C NMR, see Table 2; HRFABMS *m/z* 333.2054 (calcd for $C_{20}H_{29}O_4$, 333.2058).

Blumiolide-B (2): oil; $[\alpha]^{25}_D$ +33° (*c* 0.4, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 225 (3.8) nm; IR (neat) ν_{max} 3450, 1736, 1660 cm^{-1}; ^1H NMR, see Table 1; ^{13}C NMR, see Table 2; HRFABMS *m/z* 333.2064 (calcd for $C_{20}H_{29}O_4$, 333.2058).

9-Deoxy-isoxeniolide-A (3): oil; $[\alpha]^{25}_D$ +36° (*c* 0.6, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 265 (4.1) nm; IR (neat) ν_{max} 3420, 1720, 1642 cm^{-1}; ^1H NMR, see Table 1; ^{13}C NMR, see Table 2; HRFABMS *m/z* 317.2117 (calcd for $C_{20}H_{29}O_3$, 317.2109).

9-Deoxy-7,8-epoxy-isoxeniolide-A (4): oil; $[\alpha]^{25}_D$ +26° (*c* 0.2, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 261 (3.9) nm; IR (neat) ν_{max} 3450, 1718, 1650 cm^{-1}; ^1H NMR, see Table 1; ^{13}C NMR, see Table 2; HRFABMS *m/z* 333.2056 (calcd for $C_{20}H_{29}O_4$, 333.2058).

9-Deacetoxy-7,8-epoxy-13-epi-xenicin (5): oil; $[\alpha]^{25}_D$ +35° (*c* 0.6, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 233 (3.5) nm; IR (neat) ν_{max} 3441, 1722, 1645 cm^{-1}; ^1H NMR, see Table 1; ^{13}C NMR, see Table 2; HRFABMS *m/z* 477.2476 (calcd for $C_{26}H_{37}O_8$, 477.2478).

9-Deoxy-7,8-epoxy-xeniolide-A (6): oil; $[\alpha]^{25}_{D}$ +28° (*c* 0.3, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 258 (3.9) nm; IR (neat) ν_{max} 3400, 1722, 1660 cm^{-1}; ^1H NMR, see Table 1; ^{13}C NMR, see Table 2; HRFABMS *m/z* 333.2056 (calcd for $C_{20}H_{29}O_4$, 333.2058).

Blumiolide-C (7): oil; $[\alpha]^{25}_{D}$ +66° (*c* 0.4, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 256 (4.2) nm; IR (neat) ν_{max} 3460, 1720, 1640 cm^{-1}; ^1H NMR, see Table 1; ^{13}C NMR, see Table 2; HRFABMS *m/z* 331.1905 (calcd for $C_{20}H_{27}O_4$, 331.1902).

Blumicin-A (8): oil; $[\alpha]^{25}_{D}$ −23° (*c* 0.1, $CHCl_3$); UV (MeOH) λ_{max} (log ϵ) 235 (4.23) nm; IR (neat) ν_{max} 3520, 1740, 1705 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.02 (3H, s, Me-18), 1.31 (1H, m, H-6), 1.36 (6H, s, Me-16, 17), 1.38 (1H, m, H-5), 1.56 (1H, m, H-10), 1.64 (1H, m, H-6), 1.76 (2H, m, H_2-19), 1.96 (1H, m, H-5), 2.08 (3H, s, OAc), 2.74 (1H, d, J = 12.6 Hz, H-11a), 3.22 (1H, m, H-4a), 3.50 (1H, br s, H-8), 3.58 (3H, s, OMe), 4.56 (1H, d, J = 12.6 Hz, H-3), 4.63 (1H, d, J = 12.6 Hz, H-3), 5.88 (1H, d, J = 15.6 Hz, H-14), 6.02 (1H, d, J = 10.5 Hz, H-12), 6.48 (1H, dd, J = 15.6, 10.5 Hz, H-13); ^{13}C NMR, see Table 2; HRFABMS *m/z* 447.2362 (calcd for $C_{23}H_{36}O_7Na$,447.2359).

Cytotoxicity Testing. The P-388 cell line was 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 previously described procedures.[3,19]

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