Scabrolides A−D, Four New Norditerpenoids Isolated from the Soft Coral *Sinularia scabra*

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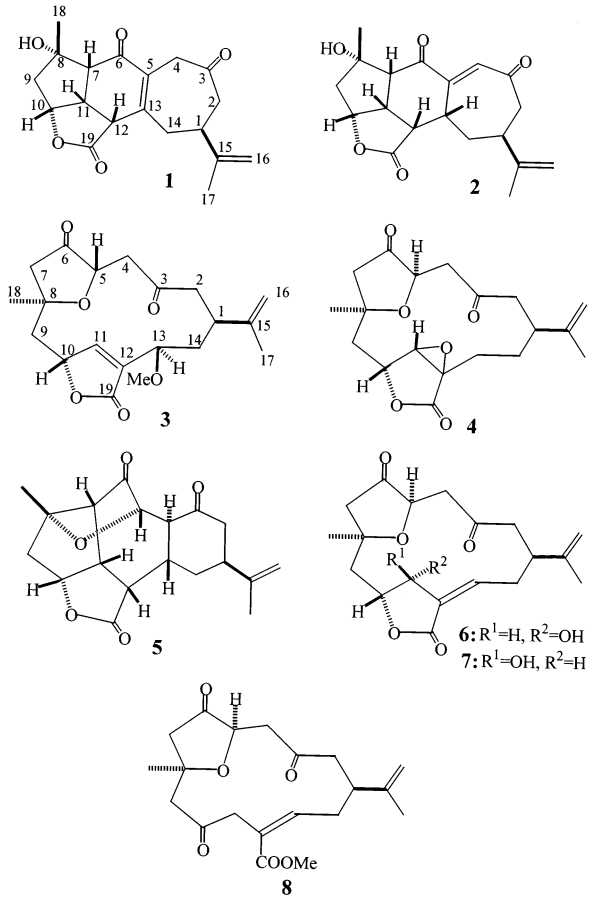
Four new norditerpenoids, scabrolides A−D (**1**−**4**), along with four known ones, **5**−**8**, have been isolated from the dichloromethane extract of the Taiwanese soft coral *Sinularia scabra*. The structures of **1**−**4** were elucidated on the basis of extensive spectroscopic analyses, while the relative configurations were determined by the NOESY experiments. The epimeric metabolites **6** and **7** have been shown to exhibit strong cytotoxic activity against KB and Hepa59T/VGH cancer cell lines.

Soft corals, including those belonging to genus *Sinularia* (Alcyoniidae), have been found to be a rich source of structurally unique and biologically active diterpenoids.[1] Since the first report of a C-4 norcembranoid, **6**, isolated from *Sinularia lepoclados* by an Australian group,[2] several skeletons of the related norditerpenoids have been discovered during the investigation of other *Sinularia* species.[1,3−11] As a part of our continuing investigation on the bioactive chemical constituents of Taiwanese soft corals,[12−16] four new norditerpenoids, scabrolides A−D (**1**−**4**), along with four known metabolites, **5**−**8**, have been isolated from *Sinularia scabra* (Tixier-Durivault, 1970), a species that has been not investigated previously. Herein, we wish to describe the isolation and structure elucidations of these four new norditerpenoids. Cytotoxicity of the isolated metabolites is also reported.



Results and Discussion

The sliced red bodies of *S. scabra* were exhaustively extracted with MeOH. The organic extract was subsequently partitioned between dichloromethane and aqueous methanol. The combined dichloromethane layers were evaporated under vacuum to afford an oily residue. The residue was triturated with *n*-hexane. Metabolites **1**−**8** were isolated from the *n*-hexane-insoluble residue by recrystallization and extensive chromatographic separations (see Experimental Section).

Scabrolide A (**1**) was obtained as a white powder. Its HREIMS spectrum exhibited a molecular ion peak at *m*/*z* 330.1467, consistent with the molecular formula $C_{19}H_{22}O_5$ and nine degrees of unsaturation. The mass spectrum of **1** exhibited a peak at *m*/*z* 312 $[M - H_2O]^+$, suggesting the presence of a hydroxy group in **1**. The ^{13}C NMR spectrum measured in $CDCl_3$ showed signals of 19 carbon atoms. The DEPT spectrum of **1** revealed the presence of two methyls, four sp^3 methylenes, one sp^2 methylene, five sp^3 methines, and seven quaternary carbons (Table 1). The quaternary carbon signals appearing at δ 208.3, 193.1, and 173.7 were attributable to carbonyl carbons of a normal ketone, an α,β-conjugated ketone, and a lactone, respectively. The signal appearing at δ 82.9 (s) was due to an oxygenated carbon. Furthermore, the four carbon signals appearing at δ 151.7 (s), 147.1 (s), 132.7 (s), and 110.8 (t) designate the presence of tetrasubstituted and 1,1-disubstituted carbon−carbon double bonds in the molecular structure of **1**. Thus, **1** was suggested to be a tetracyclic norditerpene containing two olefinic bonds and three carbonyl groups. By comparison of the ^{13}C NMR spectral data of **1** with those of yonarolide (**9**)[6] (Table 1), it was found that both compounds have very similar carbon shifts except the signals of the 7,8-tetrasubstituted double bond of **9** (δ 126.5, s and 150.7, s) had been replaced by signals of a methine (δ 54.5, d) and an oxygenated tertiary carbon (δ 82.9, s) in **1**. Therefore,

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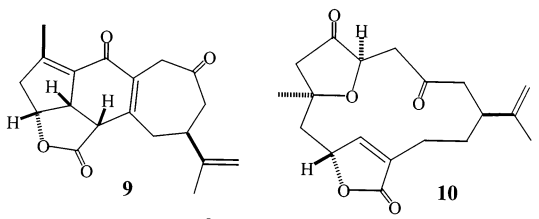
Table 1. ^{13}C NMR Chemical Shifts of Compounds **1**−**4** and **9**

	1[a]	**2**[b]	**3**[c]	**4**[d]	**9**[e,6]
1	41.6 (d)[f]	38.9 (d)	36.9 (d)	40.8 (d)	41.4 (d)
2	46.3 (t)	45.0 (t)	50.4 (t)	48.3 (t)	47.1 (t)
3	208.3 (s)	202.2 (s)	207.7 (s)	207.6 (s)	207.8 (s)
4	39.5 (t)	130.5 (d)	44.2 (t)	44.8 (t)	39.5 (t)
5	132.7 (s)	150.8 (s)	77.9 (d)	75.0 (d)	134.1 (s)
6	193.1 (s)	202.5 (s)	212.4 (s)	213.8 (s)	183.3 (s)
7	54.5 (d)	62.4 (d)	51.1 (t)	49.4 (t)	126.5 (s)
8	82.9 (s)	81.3 (s)	79.5 (s)	79.1 (s)	150.7 (s)
9	47.4 (t)	47.4 (t)	42.1 (t)	42.4 (t)	45.7 (t)
10	82.2 (d)	79.5 (d)	79.4 (d)	75.9 (d)	80.9 (d)
11	40.9 (d)	45.3 (d)	154.9 (d)	62.7 (d)	50.1 (d)
12	44.6 (d)	45.3 (d)	132.0 (s)	60.7 (s)	47.5 (d)
13	151.7 (s)	41.6 (d)	71.3 (d)	21.3 (t)	149.1 (s)
14	37.2 (t)	30.5 (t)	35.9 (t)	26.4 (t)	38.5 (t)
15	147.1 (s)	146.4 (s)	145.4 (s)	145.8 (s)	149.9 (s)
16	110.8 (t)	112.7 (t)	112.9 (t)	112.7 (t)	111.0 (t)
17	21.3 (q)	21.8 (q)	18.6 (q)	18.7 (q)	21.4 (q)
18	26.1 (q)	30.0 (q)	27.9 (q)	25.6 (q)	15.7 (q)
19	173.7 (s)	175.9 (s)	178.5 (s)	174.0 (s)	172.4 (s)
OMe			56.7 (q)		

[a] Spectra recorded at 100 MHz in $CDCl_3$ at 25 °C. [b]Spectra recorded at 75 MHz in $CDCl_3$ at 25 °C. [c]Spectra recorded at 125 MHz in $CDCl_3$ at 25 °C. [d] Spectra recorded at 100 MHz in $CDCl_3$ at 25 °C. [e]Spectra recorded at 100 MHz in $CDCl_3$ at 25 °C, see ref 6. [f]Multiplicity deduced by DEPT and indicated by usual symbols. The values are in ppm downfield from TMS.

metabolite **1** was suggested to be a 7,8-hydrated derivative of **9**. This could be further proven by the upfield shift of H_3-18 (δ 1.49, 3H, s) of **1** (^1H NMR spectral data, see Table 2), in comparison with that of **9** (δ 2.09, 3H, s). Thus the hydroxy group had to be positioned at C-8. On the basis of the above observations and by the assistance of 2D NMR ($^1H-^1H$ COSY, HMQC, and HMBC) spectra, it was possible to establish the planar structure of **1**, as illustrated in Figure 1.



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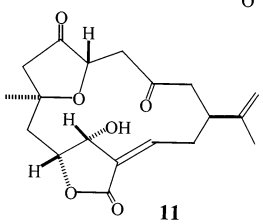
10



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The relative stereochemistries of the six chiral centers in **1** were determined on the basis of the NOE correlations observed in a NOESY spectrum (Figure 2). The NOE interactions between H-11 and each of H-7, H-10, and H-12 in **1** indicated the protons positioned at C-7, C-10, C-11, and C-12 should be *syn* to each other and were assigned arbitrarily to be β-oriented. Furthermore, the significant NOE interactions between H_3-18 and H-7 indicated that the methyl substituent at C-8 should be located on the β-face. Finally, the β-configuration of the isopropenyl group at C-1 was determined on the basis of NOE correlations observed from H-14β to both H_3-17 and H-12. On the basis of the above findings, the structure of scabrolide A (**1**) was unambiguously established as shown in formula **1**.

Metabolite **2** was obtained as a white powder. On the basis of its HREIMS (*m*/*z* 330.1464, M^+) and ^1H and ^{13}C NMR spectral data, the molecular formula of **2** also was established as $C_{19}H_{22}O_5$. As in the case of **1**, compound **2** revealed the presence of one hydroxyl (IR ν_{max} 3482 cm^{-1} and EIMS *m*/*z* 312 $[M - H_2O]^+$). Inspection of the ^{13}C NMR spectral data (Table 1) of **2**, by the assistance of a DEPT spectrum, indicated the presence of 19 carbon signals of a norditerpenoid. These signals were ascribable to carbons of two methyls, three sp^3 methylenes, one sp^2 methylene, six sp^3 methines, and one sp^2 methine. The remaining six carbon signals appearing in the broad-band spectrum were due to the quaternary carbons of two ketone carbonyls (δ 202.5 and 202.2), an ester carbonyl (δ 175.9), an oxygenated tertiary carbon (δ 81.3), and two olefinic carbons (δ 150.8 and 146.4). On the basis of the above observations and by comparison of the ^{13}C NMR spectral data of **2** with those of **1**, scabrolide B was considered to be a structurally similar isomer of **1**. In fact, the ^1H NMR spectral data of **2** were found to be very similar to those of **1**, except that the signals of H_2-4 of **1** disappeared and were replaced by signals of a vinylic proton (δ 6.34, 1H, d, J = 3 Hz) and a methine proton (δ 2.75, 1H, m). Therefore, **2** was considered to be a positional isomer of **1**. This could be further supported by the careful investigation of the COSY spectrum of **2**, where it was found that, unlike **1**, the sequential proton spin systems were extended from both H-7 and H-10 through H-11 into H_2-2 (Figure 1). The presence of the 4,5-double bond was further confirmed by an HMBC experiment, which showed key correlations of the vinylic H-4 to C-5 (δ 150.8, s), C-6 (δ 202.5, s), C-3 (δ 202.2, s), and C-13 (δ 41.6, d) (Figure 1).

Careful investigation of the NOESY spectrum of **2** revealed that **2** possesses the same relative stereochemistries at C-1, C-7, C-8, C-10, C-11, and C-12 as those of **1**. Moreover, the additional chiral center at C-13 was found to possess a ring-juncture proton, which showed NOE interactions with both H-11 and H-12. Thus H-13 should be on the same face as H-12, H-11, H-10, and H-7 (Figure 2). Therefore, the structure of scabrolide B (**2**) was fully established as described in formula **2**.

The third metabolite **3** was obtained as a white solid with a molecular formula $C_{20}H_{26}O_6$ and eight units of unsaturation, as indicated by the HREIMS (*m*/*z* 362.1730, M^+) and the NMR spectral data. The ^{13}C NMR spectral data of **3** accounted for the presence of 20 carbon signals, which were assigned by the assistance of a DEPT spectrum to three methyls (including one methoxy methyl), six methylenes, five methines, and six quaternary carbons. Furthermore, trisubstituted (δ 154.9, d and 132.0, s) and 1,1-disubstituted (δ 145.4, s and δ 112.9, t) carbon−carbon double bonds, two ketones (δ 207.7, s and δ 212.4, s), and one lactone carbonyl (δ 178.5, s) were also identified. From the above findings, metabolite **3** should be a methoxylated tricyclic norcembranoid. In the ^1H NMR spectrum of **3** (in $CDCl_3$, see Table 2), the 3H singlets appearing at δ 1.33, 1.83, and 3.26 were assigned as the signals of a tertiary methyl attached to C-8, an olefinic methyl, and a methoxy group, respectively. Also, the $^1H/^{13}C$ long-range correlations observed in the HMBC spectrum of **3** (Figure 3) indicated that protons of the three oxymethines, which showed signals at δ 4.03 (1H, dd, J = 11.5, 3.0 Hz), 4.50 (1H, d, J = 10.5 Hz), and 5.27 (1H, br s) in the ^1H NMR spectrum, were attributable to H-13, H-5, and H-10, respectively. Moreover, the vinylic proton signal appearing at δ 7.56 (s) exhibited $^1H/^{13}C$ long-range correlations with the lactonic carbonyl carbon (C-19) and both oxymethine carbons, C-10 and C-13, and was assigned as H-11. Comparison of the ^{13}C NMR spectral data of **3** with those of the known

Table 2. ^{1}H NMR Chemical Shifts of Compounds **1**−**4**

	1[a]	**2**[b]	**3**[c]	**4**[a]
H-1	3.07 q (6.4)[d]	2.81 m	2.44 tt (11.0, 2.5)	2.61 m
H-2α	2.63 m	2.90 ddd (16.0, 4.0, 2.5)	2.33 dd (11.0, 11.0)	2.20 d (11.6)
H-2*β*	2.63 m	2.60 dd (16.0, 6.0)	2.51 dd (11.0, 2.5)	2.52 dd (11.6, 2.4)
H-4α	3.42 d (17.2)	6.34 d (3.0)	2.64 dd (14.5, 11.0)	3.09 dd (16.4, 4.0)
H-4*β*	3.70 d (17.2)		2.55 d (14.0)	2.73 dd (16.4, 6.0)
H-5			4.50 d (10.5)	4.19 t (4.0)
H-7α			2.39 d (17.0)	2.49 d (18.4)
H-7*β*	2.62 d (10.0)	2.93 d (7.2)	2.52 d (17.0)	2.63 d (18.4)
H-9α	2.30 d (15.2)	3.36 dd (16.0, 2.5)	2.58 d (15.0)	2.12 dd (15.2, 6.4)
H-9*β*	1.92 dd (15.2, 5.6)	2.21 ddd (16.0, 9.0, 1.5)	2.24 dd (15.0, 3.5)	2.30 dd (15.2, 6.4)
H-10	5.11 t (6.4)	4.98 td (9.0, 2.5)	5.27 br s	4.74 t (6.0)
H-11	3.62 dd(11.2, 6.4)	3.45 t (10.5)	7.56 s	3.95 s
H-12	3.51 d (11.2)	3.14 dt (10.5, 7.8)		
H-13α			4.03 dd (11.5, 3.0)	2.21 dd (11.6, 3.2)
H-13*β*		2.75 m		1.76 dd (11.6, 3.8)
H-14α	2.86 m	1.71 tdd (10.0, 5.0, 1.2)	1.83 ddd (13.5, 11.5, 3.0)	1.33 dd (11.6, 3.2)
H-14*β*	2.88 m	3.30 dtd (10.0, 4.0, 2.5)	2.01 ddd (13.5, 11.5, 3.0)	1.67 dd (11.6, 3.8)
H-16	4.85 s	4.95 s	4.89 s	4.93 s
	4.83 s	4.72 s	4.78 s	4.86 s
17-Me	1.82 3H, s	1.83 3H, s	1.83 3H, s	1.68 3H, s
18-Me	1.49 3H, s	1.63 3H, s	1.33 3H, s	1.46 3H, s
OMe			3.26 3H, s	

[a] Spectra recorded at 400 MHz in $CDCl_3$ at 25 °C. [b] 300 MHz in $CDCl_3$ at 25 °C. [c] 500 MHz in $CDCl_3$ at 25 °C [d] The *J* values are in Hz in parentheses.

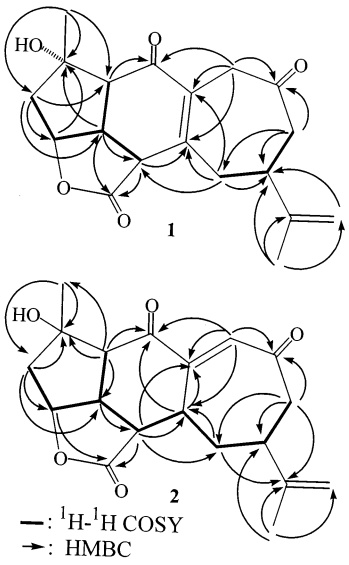

Figure 1. ^{1}H−^{1}H COSY and key HMBC correlations for **1** and **2**.

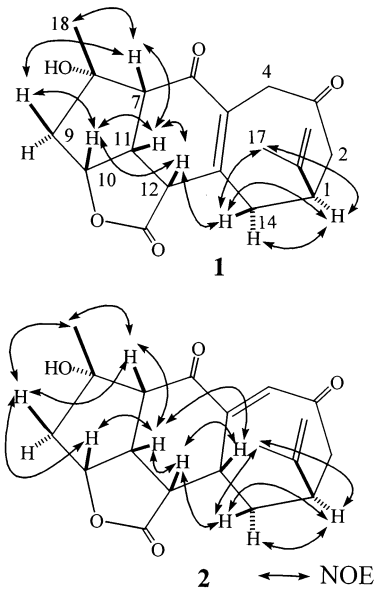

Figure 2. Key NOESY correlations of **1** and **2**.

compound **10**[3] revealed high similarity in chemical shift for most carbons; however, the C-13 methylene (*δ* 27.5, t) in **10** was replaced by an oxygenated methine (*δ* 71.3, d) in **3**. The HMBC correlations observed between the signal at *δ* 3.26 (3H, s) and the oxymethine carbon C-13 (*δ* 71.3, d) further established the C-13 location of the methoxy group. This was further confirmed by the assistance of the ^{1}H−^{1}H COSY correlations observed between the consequent proton sets H-13 to H_2-14, and H_2-14 to H_2-2 through H-1 (Figure 3). Thus, the gross structure of scabrolide C could be established.

The relative stereochemistries of chiral centers at C-1, C-5, C-8, C-10, and C-13 of **3** were determined by the NOE interactions observed in the NOESY spectrum (Figure 4). Assuming the α-orientation of H_3-18, it was found that H_3-18 exhibited NOE correlations with H-7α (*δ* 2.39, 1H, d, *J* = 17.0 Hz) and H-9α (*δ* 2.58, 1H, d, *J* = 15.0 Hz), but neither with H-7*β* (*δ* 2.52, 1H, d, *J* = 17.0 Hz) nor H-9*β* (*δ* 2.24, 1H, dd, *J* = 15.0, 3.5 Hz). H-10 exhibited NOE interactions with H-9*β* and the vinylic proton H-11, implying the *β*-orientation of H-10 and the upper face orientation of H-11. H-5 did not exhibit NOE with H_3-18, but showed a weak NOE response with H-11. Thus, H-5 was assumed to be *β*-oriented, and consequently C-5 is *S**-configured. This was further supported by the apparent downfield shifts of C-5 (*δ* 77.9, d), C-3 (*δ* 207.7, s), and C-18 (*δ* 27.9, q), in comparison to those of **6** (C-5, *δ* 75.8; C-3, *δ* 205.8; and C-18, 26.1)[10] and its related derivatives possessing 5*R**-configuration.[3] Also, the chemical shift of the above-mentioned carbons of **3** were found to be very similar to those of **11**[10] and the 5*S**-configured monomeric moiety of a norcembranoid dimer, singardin.[11] Thus, the relative configuration of C-5 was determined. The NOE interactions observed between H-5*β* with H-4*β*, and H-4α with H-1, revealed the α-orientation of H-1 and consequently the *β*-orientation of the isopropenyl group. One of the C-14 protons (*δ* 1.83, ddd, *J* = 13.5, 11.5, 3.0 Hz) exhibited NOE responses with H-1 and the vinylic proton H-11 and was assigned as H-14α. H-13 was found to show NOE interactions with H-16 (*δ* 4.78, s) and H-14*β* (*δ* 2.01, ddd *J* = 13.5, 11.5, 3.0 Hz), but not with H-11, indicating that it should

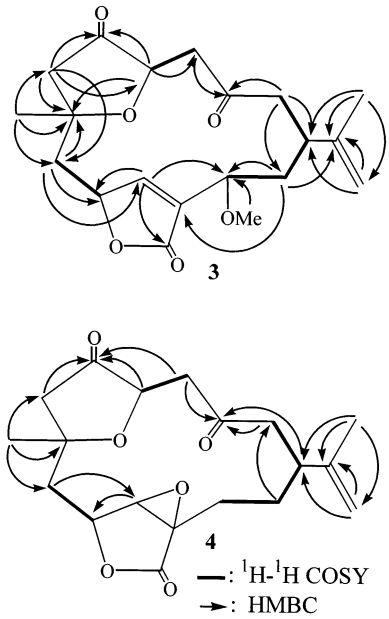

Figure 3. ^{1}H−^{1}H COSY and HMBC correlations for **3** and **4**.

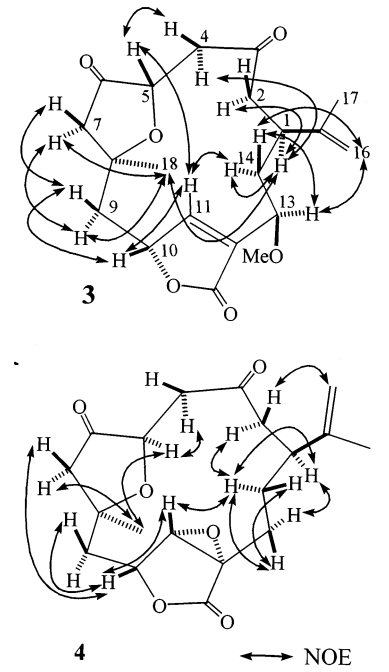

Figure 4. Key NOESY correlations of **3** and **4**.

be *syn* to the isopropenyl group and positioned on the α-face, as suggested by examining a molecular model of **3**. Thus, the relative configuration of **3** was unambiguously established.

The new metabolite **4** was separated as a white solid. The HREIMS spectrum of **4** (*m*/*z* 348.1570, M^+) was in accordance with a molecular formula $C_{19}H_{24}O_6$ and eight degrees of unsaturation. Its ^{13}C NMR spectrum revealed the presence of 19 carbons, characteristic for a norditerpene. The DEPT spectrum of **4** exhibited signals of two methyls, six methylenes, one exomethylene, and four methines, including three bonded to an oxygen, and six quaternary carbons. The carbon signals appearing at δ 213.8 (s), 207.6 (s), 174.0 (s), 145.8 (s), and 112.7 (t) were assigned to carbons of two normal ketones, one lactonic carbonyl, and one 1,1-disubstituted carbon−carbon double bond, respectively. Therefore, the molecule of **4** is a tetracyclic norcembranoid. From the ^{1}H NMR spectrum of **4**, the signals of one 1,1-disubstituted double bond (δ 4.93, 1H, s and 4.86, 1H, s), three oxymethines (δ 4.74, 1H, t, J = 6.0 Hz, 4.19, 1H, t, J = 4.0 Hz, and 3.95, 1H, s), one olefinic methyl (δ 1.68, 3H, s), and one tertiary methyl (δ 1.46, 3H, s) were recognized. Moreover, the two signals appearing at 62.7 (d) and 60.7 (s) in the ^{13}C NMR spectrum of **4** revealed the presence of an epoxy functionality. Comparison of the ^{13}C NMR spectral data of **4** with those of **3** (Table 1) suggested that both compounds have the same carbon skeleton from C-1 to C-10, including the attached tertiary methyl and the isopropenyl group. The remaining two methylene groups (δ 21.3, t and 26.4, t) were assigned to be those of C-13 and C-14, respectively, as H_2-14 showed ^{1}H−^{1}H COSY correlations with H_2-13, and H_2-13 with H-1 (Figure 3). Thus, the remaining oxygen atom has to be located at C-11 and C-12 to form an epoxy group. On the basis of above observations and by the assistance of HMBC correlations (Figure 3), the molecular framework of **4** could be established.

Table 3. Cytotoxicity of the Nor-cembranoids **1** and **3**−**8**[a]

compound	cell line ED_{50} (μg/mL) KB	Hepa59T/VGH
1	>20	>20
3	11.9	17.8
4	>20	>20
5	>20	>20
6	2.5	2.6
7	2.3	2.4
8	>20	17.5

[a] Standard = doxourbicine, ED_{50} = 0.3 μg/mL

The relative stereochemistry of **4** was resolved by careful investigation of the NOE interactions of **4**. Similar to those of **3**, H-1 and H_3-18 of **4** were found to be placed on the α-face, whereas H-10 was positioned on the β-face (Figure 4). Furthermore, the NOE responses observed between H-11 and the β-oriented H-10 revealed the α-orientation of the epoxy ring. H-5 was found to be α-oriented on the basis of the NOE correlation observed with H_3-18. This was further proven by the chemical shifts induced at C-5 and C-18 similar to those of **6**[2] and other 5*R**-related norcembranoids.[3,9−11] Therefore, the structure of scabrolide D was unambiguously established as described by formula **4**.

Compounds **5**−**8**, which were also isolated from *S. scabra*, were found to be identical to the previously reported norditerpenoids isolated from other *Sinularia* species, by comparison of the physical (mp and $[\alpha]_D$) and spectral (MS, ^{1}H and ^{13}C NMR) data.[2,3,5,8,9]

The cytotoxicity of metabolites **1** and **3**−**8** against the growth of KB and Hepa59T/VGH cancer cells was studied (Table 3). The known epimeric metabolites **6** and **7** were found to show significant cytotoxicity against both cell lines (ED_{50}'s 2.3−2.6 μg/mL). Compound **3** exhibited a weak activity against KB cells, while both **3** and **8** were found to display weak activity against Hepa 59T/VGH cells, too. The remaining metabolites were shown to be inactive (ED_{50} >20 μg/mL) to both cell lines.

Experimental Section

General Experimental Procedures. Optical rotations were measured on a Jasco DIP-1000 digital polarimeter. IR spectra were recorded on a Hitachi I-2001 infrared spectrophotometer. The NMR spectra were recorded on a Bruker AMX-300/5 FT-NMR at 300 MHz for ^{1}H and 75 MHz for ^{13}C or on a Bruker AMX-400 FT-NMR at 400 MHz for ^{1}H and 100 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 and FABMS were obtained

with a VG Quattro GC/MS spectrometer. Si gel (Merck, 230−400 mesh) was used for column chromatography. Precoated Si gel plates (Merck, Kieselgel 60 F-254, 0.2 mm) were used for analytical TLC.

Organism. *S. scabra* (Tixier-Durivault, 1970) was collected by hand via scuba at the coast of Kenting, Taiwan, in Febrauary 2001, at a depth of 10−15 m, and stored in a freezer until extraction. A voucher sample was deposited at the Department of Marine Resources, Sun Yat-Sen University (specimen no. SC39).

Extraction and Separation. The sliced red bodies of *S. scabra* (1.2 kg, wet wt) were exhaustively extracted with MeOH. The organic extract was concentrated under vacuum and subsequently partitioned between dichloromethane and aqueous methanol. The dichloromethane layers were combined and evaporated under vacuum to afford an oily residue (23.83 g). The residue was triturated with *n*-hexane, leaving an *n*-hexane-insoluble dark red oily residue (4.83 g) with crystalline deposit. The crystalline mass was removed and recrystallized from CH_2Cl_2−MeOH (4:1) to afford needle-shaped crystals of **6** (740 mg). The remaining liquid portion of the dichloromethane extract was subjected to column chromatography on Si gel 60, using *n*-hexane−CH_2Cl_2−MeOH (stepwise, 1:1:0 to 0:1:0 to 0:9:1) to yield 14 fractions. Fractions 4 and 5, eluted with CH_2Cl_2−MeOH (9:1), were chromatographed separately by normal-phase HPLC using *n*-hexane−EtOAc (gradient, 7:3 to 1:1) to yield **4** (1.3 mg) and **5** (1.5 mg) from fraction 4, and **8** (7.3 mg), **2** (1.9 mg), and **3** (4.0 mg) from fraction 6. Fraction 6, eluted with CH_2Cl_2−MeOH (9:1), was triturated with *n*-hexane−CH_2Cl_2 (2:1) to afford crude **1** (soluble part) and an epimeric mixture of **6** and **7** (insoluble part). Crude **1** was purified by normal-phase MPLC using *n*-hexane−EtOAc (1:1) to afford **1** (1.5 mg). A preparative TLC separation of the epimeric mixture using *n*-hexane−EtOAc (1:1) yielded **6** (5 mg) and **7** (9 mg).

Scabrolide A (1): white solid, mp 92−93 °C; $[\alpha]^{29}_D$ −104.0° (*c* 0.48, $CHCl_3$); IR (neat) ν_{max} 3462, 2920, 2361, 2338, 1757, 1699, 1651, 1373, 1088 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) and ^{13}CNMR ($CDCl_3$, 100 MHz), see Tables 1 and 2, respectively; EIMS (70 eV) *m*/*z* 330 (7.0, $[M]^+$), 312 (38.3, $[M - H_2O]^+$), 267 (12.6), 239 (9.2), 215 (7.1), 173 (8.0), 105 (27.6); HREIMS *m*/*z* 330.1467, calcd for $C_{19}H_{22}O_5$, 330.1468.

Scabrolide B (2): white solid, mp 110−111 °C; $[\alpha]^{29}_D$ −80.0° (*c* 0.33, $CHCl_3$); IR (neat) ν_{max} 3482, 2956, 2336, 1765, 1699, 1667, 1375, 1053 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) and ^{13}CNMR ($CDCl_3$, 75 MHz), see Tables 1 and 2, respectively; EIMS (70 eV) *m*/*z* 330 (2.5, $[M]^+$), 312 (6.5, $[M - H_2O]^+$), 267 (1.1), 215 (4.0), 173 (5.6), 105 (8.1); HREIMS *m*/*z* 330.1464, calcd for $C_{19}H_{22}O_5$, 330.1468.

Scabrolide C (3): white solid, mp 81−82 °C; $[\alpha]^{29}_D$ −16.7° (*c* 0.60, $CHCl_3$); IR (neat) ν_{max} 3016, 2934, 1757, 1712, 1655, 1379, 1094 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) and ^{13}CNMR ($CDCl_3$, 125 MHz), see Tables 1 and 2, respectively; EIMS (70 eV) *m*/*z* 362 (0.8, $[M]^+$), 331 (1.8, $[M - OMe]^+$), 139 (41.3), 126 (3.0), 111 (100.0); HREIMS *m*/*z* 362.1730, calcd for $C_{20}H_{26}O_6$, 362.1730.

Scabrolide D (4): white solid, mp 83−84 °C; $[\alpha]^{25}_D$ −58.3° (*c* 0.24, $CHCl_3$); IR (neat) ν_{max} 2932, 1761, 1751, 1666, 1381, 1090 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) and ^{13}CNMR ($CDCl_3$, 100 MHz), see Tables 1 and 2, respectively; EIMS (70 eV) *m*/*z* 348 (11.5, $[M]^+$), 267 (30.6), 134 (49.9), 109 (51.5); HREIMS *m*/*z* 348.1570, calcd for $C_{19}H_{24}O_6$, 348.1573.

Norditerpene 5: white solid, mp 187−188 °C; $[\alpha]^{25}_D$ +48.5° (*c* 0.68, $CHCl_3$); IR (neat) ν_{max} 2967, 2361, 1757, 1707, 1645, 1377, 1321, 1066 cm^{-1}; MS, ^1H and ^{13}C NMR spectral data were found to be in full agreement with those reported previously.[8]

Norditerpene 6: colorless needles, mp 226−227 °C; $[\alpha]^{25}_D$ −93.0° (*c* 1.00, $CHCl_3$); IR (neat) ν_{max} 3684, 3029, 2942, 1757, 1715, 1674, 1207, 1180, 1099 cm^{-1}; MS, ^1H and ^{13}C NMR spectral data were found to be in full agreement with those reported previously.[2,9]

Norditerpene 7: white powder, mp 210−211 °C; $[\alpha]^{25}_D$ +20.0° (*c* 0.60, $CHCl_3$); IR (neat) ν_{max} 3688, 3023, 2940, 2361, 1757, 1713, 1672, 1217, 1180, 1097 cm^{-1}; MS, ^1H and ^{13}C NMR spectral data were found to be in full agreement with those reported previously.[3,5]

Norditerpene 8: white solid, mp 180−181 °C; $[\alpha]^{25}_D$ −47.9° (*c* 0.48, $CHCl_3$); IR (neat) ν_{max} 3028, 3015, 2974, 2361, 1759, 1718, 1670, 1290, 1064 cm^{-1}; MS, ^1H and ^{13}C NMR spectral data were found to be in full agreement with those reported previously.[3,9]

Cytotoxicity Testing. Hepa59T/VGH and KB cells were purchased from the American Type Culture Collection (ATCC). Cytotoxicity assays of the test compounds **1** and **3**−**8** were performed using the MTT [3-(4,5-dimethylthiazole-2-yl)-2,5-diphenyltetrazolium bromide] colorimetric method.[17,18]

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