Scabrolides E−G, Three New Norditerpenoids from the Soft Coral *Sinularia scabra*

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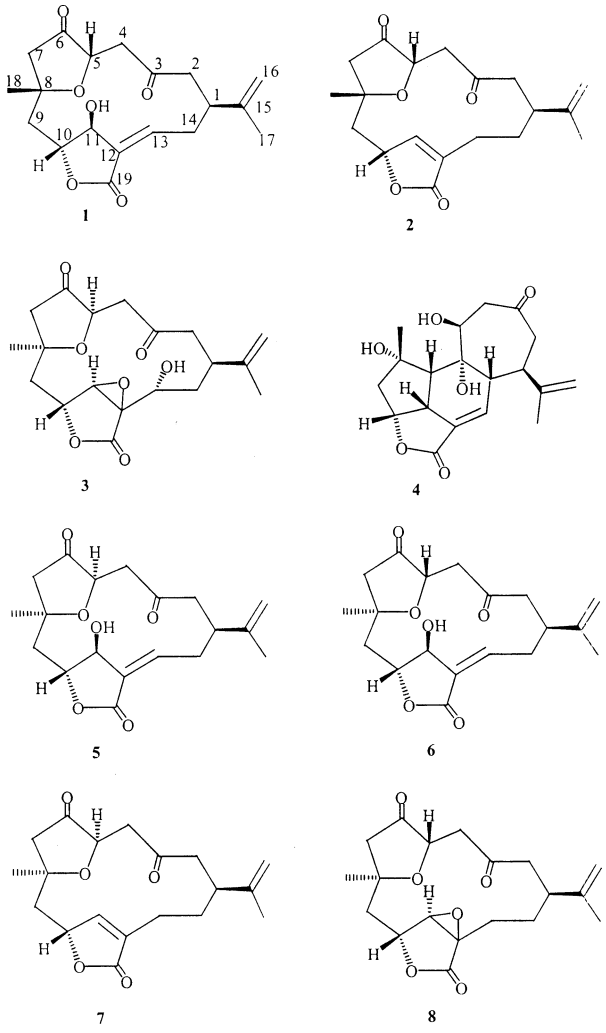
Three new norditerpenoids, scabrolides E−G (**1**−**3**), and dissectolide A (**4**) have been isolated from the organic extract of a Taiwanese soft coral *Sinularia scabra*. The structures of **1**−**3** were determined on the basis of extensive spectroscopic analyses and by comparison of their spectral data with those of the known related metabolites. Metabolite **1** was found to exhibit significant cytotoxicity against the growth of Hepa59T/VGH and KB cell lines.

During the course of our investigation on the chemical constituents from marine invertebrates of the Taiwanese waters, several C-4 norcembranoids with varying structures have been isolated from soft corals of the genus *Sinularia* (family Alcyoniidae), among which some of these metabolites have been shown to exhibit cytotoxic activity against cancer cells.[1,2] Our continuing chemical investigation on *Sinularia scabra* Tixier-Durivault[1] had led to the isolation and identification of three new norcembranoids, scabrolides E−G (**1**−**3**), in addition to dissectolide A (**4**).[3] In contrast to the related (5*R**,8*S**)-[1−8] and (5*S**,8*S**)[2,8]-norcembranoids, scabrolides E (**1**) and F (**2**) represent two newly discovered (5*S**,8*R**)-derivatives of this series. In this report, we describe the structure elucidation of these new norditerpenoids (**1**−**3**). Moreover, **1** has been shown to exhibit significant cytotoxic activity against the growth of KB (human oral epidermoid carcinoma) and Hepa59T/VGH (human liver carcinoma) cell lines.

The methanol extract of *S. scabra* was partitioned between dichloromethane and aqueous methanol. The combined dichloromethane layer was evaporated to yield a viscous oil, which was triturated with *n*-hexane. The *n*-hexane-insoluble portion was further separated to afford new compounds **1**−**3** and a known compound **4**.[3]

Scabrolide E (**1**) was obtained as a white powder. Its HREIMS spectrum exhibited a molecular ion peak at *m/z* 348.1573, consistent with a molecular formula $C_{19}H_{24}O_6$ and eight degrees of unsaturation. The ^{13}C NMR spectrum measured in $CDCl_3$ showed signals of 19 carbon atoms (Table 1), which were found to be analogous with those of 5-*epi*-sinuleptolide (**5**)[1−8] and sinuleptolide (**6**),[2,8] also isolated previously from the same coral and other *Sinularia* species.[1−8] The ^1H NMR spectrum of **1** displayed signals (Table 2) for an isopropenyl group (δ 1.79, 4.82, and 4.85), a tertiary non-olefinic methyl group (δ 1.40, H_3-18), a 12,13-trisubstituted double bond (δ 6.48, H-13), three oxymethines (δ 4.25, H-5; 4.58, H-10; 5.09, H-11), an allylic methylene (δ 3.44 and 2.08, H_2-14), and a non-oxygenated methine (δ 3.21, H-1). The gross structure of **1** was confirmed by the observed $^1H-^1H$ COSY and HMBC correlations (Figure 1). Thus, **1** was elucidated as an isomer of metabolites **5** and **6**.[1−8]



Previous reports revealed that C-4 norcembranoids with *cis*-oriented H-5 and H_3-18 could be distinguished from their *trans*-epimers, by the diagnostic upfield chemical shifts ($\Delta\delta$ −1.0 to −3.0 ppm) observed at C-5 and C-18 in the ^{13}C NMR spectra,[1−8] as exemplified by the ^{13}C data of **5** and **6** (Table 1). Therefore, the upfield shifts at C-5 (δ 75.1) and C-18 (δ 27.8) in **1**, relative to those of **6** (δ 77.5 and 29.6, respectively), indicated the *cis*-orientation for H-5 and H_3-18 in **1** as in the case of **5**.[1−8]

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Table 1. ^{13}C NMR Chemical Shifts of Compounds **1**–**3** and **5**–**8**

C#	**1**[a]	**2**[b]	**3**[b]	**5**[a,1,2,4]	**6**[a,2]	**7**[c,5]	**8**[d,2]
1	42.2 (CH)[e]	41.2 (CH)	38.0 (CH)	39.8 (CH)	41.9 (CH)	42.9 (CH)	39.8 (CH)
2	47.2 (CH_2)	48.8 (CH_2)	48.0 (CH_2)	43.3 (CH_2)	48.2 (CH_2)	40.5 (CH_2)*	49.9 (CH_2)
3	206.3 (C)	206.7 (C)	207.9 (C)	205.5 (C)	208.2 (C)	207.8 (C)	208.4 (C)
4	44.4 (CH_2)	44.2 (CH_2)	44.8 (CH_2)	46.3 (CH_2)	44.5 (CH_2)	46.5 (CH_2)	43.9 (CH_2)
5	75.1 (CH)	76.0 (CH)	76.7 (CH)	75.0 (CH)	77.5 (CH)	74.7 (CH)**	78.1 (CH)
6	215.1 (C)	214.5 (C)	212.6 (C)	214.6 (C)	212.9 (C)	212.9 (C)	211.9 (C)
7	49.0 (CH_2)	49.8 (CH_2)	49.9 (CH_2)	51.4 (CH_2)	51.9 (CH_2)	48.0 (CH_2)	51.0 (CH_2)
8	79.5 (C)	78.6 (C)	79.1 (C)	79.3 (C)	79.4 (C)	78.6 (C)	79.5 (C)
9	42.0 (CH_2)	48.8 (CH_2)	42.4 (CH_2)	43.4 (CH_2)	42.3 (CH_2)	45.4 (CH_2)*	40.5 (CH_2)
10	84.2 (CH)	78.0 (CH)	75.9 (CH)	83.3 (CH)	83.8 (CH)	78.4 (CH)**	78.2 (CH)
11	73.4 (CH)	151.7 (CH)	64.9 (CH)	75.2 (CH)	75.6 (CH)	151.1 (CH)	63.1 (CH)
12	133.4 (C)	131.4 (C)	61.4 (C)	132.5 (C)	131.8 (C)	130.6 (C)	62.1 (C)
13	144.8 (CH)	20.4 (CH_2)	68.0 (CH)	145.2 (CH)	145.2 (CH)	20.7 (CH_2)	21.2 (CH_2)
14	31.9 (CH_2)	28.7 (CH_2)	34.8 (CH_2)	28.6 (CH_2)	31.7 (CH_2)	27.5 (CH_2)	25.5 (CH_2)
15	147.7 (C)	145.2 (C)	148.2 (C)	147.2 (C)	148.0 (C)	145.8 (C)	145.3 (C)
16	110.8 (CH_2)	113.1 (CH_2)	111.5 (CH_2)	110.5 (CH_2)	110.3 (CH_2)	112.8 (CH_2)	113.1 (CH_2)
17	20.7 (CH_3)	18.3 (CH_3)	19.8 (CH_3)	21.7 (CH_3)	21.1 (CH_3)	18.0 (CH_3)	18.7 (CH_3)
18	27.8 (CH_3)	25.9 (CH_3)	25.7 (CH_3)	26.6 (CH_3)	29.6 (CH_3)	25.2 (CH_3)	28.5 (CH_3)
19	168.2 (C)	173.5 (C)	170.4 (C)	168.5 (C)	169.6 (C)	174.0 (C)	172.3 (C)

[a] Spectra recorded at 75 MHz in $CDCl_3$ at 25 °C [b] Spectra recorded at 125 MHz in $CDCl_3$ at 25 °C. [c] Spectra recorded at 50 MHz in $CDCl_3$. See ref 4. [d] Spectra recorded at 100 MHz in $CDCl_3$. See ref 1. [e] Multiplicity deduced by DEPT and indicated by usual symbols. The values are in ppm downfield from TMS.

Table 2. ^1H NMR Chemical Shifts of Compounds **1**–**3**

	1[a]	**2**[b]	**3**[b]
H-1	3.21 br dddd (10.5, 10.5, 5.0, 1.5)[c]	2.33 dddd (10.5, 10.5, 2.5, 2.5)	3.04 m
H-2α	2.42 dd (15.3, 1.5)	2.47 dd (12.0, 2.5)	2.46 dd (13.0, 3.0)
H-2*β*	2.61 dd (15.3, 10.5)	2.32 dd (12.0, 10.5)	2.38 dd (13.0, 10.0)
H-4α	2.97 dd (18.6, 7.8)	2.75 dd (17.5, 10.5)	3.03 dd (15.0, 3.5)
H-4*β*	2.78 dd (18.6, 3.0)	2.66 dd (17.5, 2.5)	2.68 dd (15.0, 7.0)
H-5	4.25 dd (7.5, 3.0)	4.61 dd (10.5, 2.5)	4.20 dd (7.0, 3.5)
H-7α	2.89 d (18.0)	2.60 d (19.0)	2.54 2H, s
H-7*β*	2.37 d (18.0)	2.50 d (19.0)	
H-9α	2.22 dd (15.3, 7.2)	2.59 dd (13.5, 5.5)	2.10 dd (15.0, 5.5)
H-9*β*	2.16 dd (15.3, 4.8)	1.51 m	2.40 dd (15.0, 6.5)
H-10	4.58 dd (7.2, 4.8)	5.13 br dd (5.0, 2.5)	4.79 dd (6.5, 5.5)
H-11	5.09 s	7.57 s	4.07 s
H-13α		2.19 m	
H-13*β*	6.48 dd (9.0, 8.1)	2.35 ddd (17.0, 5.5, 2.5)	3.78 br dd (11.0, 5.5)
H-14α	3.44 ddd (12.6, 9.0, 5.1)	1.75 m	1.98 ddd (15.0, 5.0, 5.0)
H-14*β*	2.08 ddd (12.6, 10.8, 8.1)	1.65 m	2.13 dd (15.0, 6.0)
H-16	4.82 s	4.72 s	4.86 s
	4.85 s	4.83 s	4.91 s
17-Me	1.79 3H, s	1.65 3H, s	1.83 3H, s
18-Me	1.40 3H, s	1.52 3H, s	1.50 3H, s

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

Finally, the relative stereochemistry of **1** was established by the detailed analyses of correlations observed in the NOESY spectrum of **1** (Figure 2). Assuming the α-orientation of H-1, it was found that both a proton attaching at C-2 (*δ* 2.42) and one attaching at C-14 (*δ* 3.44) exhibited strong NOE correlations with H-1 and were assigned as H-2α and H-14α, respectively. H-2*β* (*δ* 2.61) exhibited NOE response with H-4*β* (*δ* 2.78), which further interacted with H-5. Thus, H-5 should be positioned on the *β*-face. NOE correlations were also detected between H-5 and H_3-18, H_3-18 and H-11, and H-11 and H-5, revealing the *β*-orientation of H_3-18 and the α-orientation of H-11, as suggested by a molecular model of **1**. One of the C-9 protons, resonating at *δ* 2.16, exhibited NOE responses with H_3-18 and H-10, revealing the *β*-orientations of these protons. Furthermore, the *Z* configuration of the 12,13-double bond was established on the basis of an NOE correlation between H-11 and H-13. The molecular model of **1** also revealed that the unprecedented (5*S**,8*R**)-configuration in **1** could bring H-11α closer to the oxygen atom of the 5,8-ether ring than that of **5** or **6**. This phenomenon was clearly observed by the significant downfield shift of H-11 observed in the ^1H NMR spectrum of **1** (*δ* 5.09) relative to those of **5** (*δ* 4.61)[4–6] and **6** (*δ* 4.61).[2] In C_5D_5N, it was also observed that the H-11 of **1** (*δ* 5.61) is more downfield shifted in comparison with those of **5** (*δ* 4.96)[2,8] and **6** (*δ* 4.92).[2,8] Thus, **1** was the C-5 and C-8 epimer of **5** and was assigned as (1*S**,5*S**,8*R**,10*R**,11*S**)-11-hydroxy-1-isopropenyl-8-methyl-3,6-dioxo-5,8-epoxycyclotetradec-12*Z*-ene-10,12-carbolactone.

Scabrolide F (**2**) was obtained as a white powder. On the basis of its HREIMS (*m/z* 332.1615, M^+) and NMR spectral data (Tables 1 and 2), the molecular formula of **2** was established as $C_{19}H_{24}O_5$. Similar to that of **1**, the IR spectrum of **2** showed the presence of both lactone and ketone functionalities (ν_{max} 1757 and 1712 cm^{-1}). However, the absorption band of the hydroxyl group was absent. The NMR spectral data of **2** showed the appearance of only two oxymethine groups (^{13}C NMR: *δ* 76.0, CH and 78.0, CH; ^1H NMR: *δ* 4.61, dd, *J* = 10.5, 2.5 Hz and 5.13, br dd, *J* = 5.0, 2.5 Hz), instead of three in **1**. By careful analyses of the ^1H and ^{13}C spectral data and 2D correlations observed

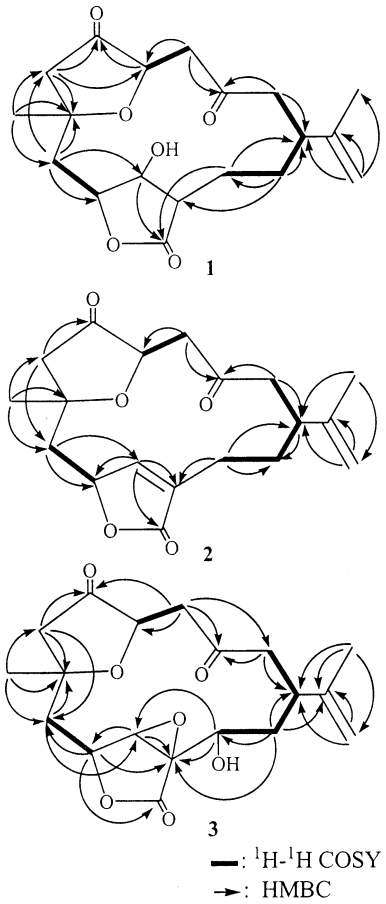

Figure 1. ^{1}H−^{1}H COSY and HMBC correlations for **1**−**3**.

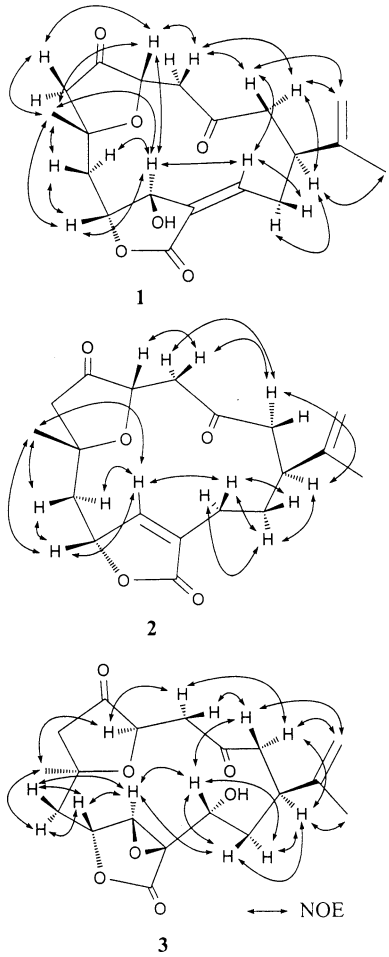

Figure 2. Key NOESY correlations of **1**−**3**.

(Figure 1) from the ^{1}H−^{1}H COSY and HMBC spectra, the gross structure of **2** was established. Thus, **2** is a stereoisomer of **7**, which was isolated previously from an unidentified *Sinularia* species.[5]

Compound **2** showed a characteristic downfield shift at H-11 (δ 7.57), when measured in benzene-d_6, relative to that of **7** (δ 6.88)[5] in the same solvent, a phenomenon that was previously observed in **1** relative to **5** or **6**. This suggested the (5*S**,8*R**)-configuration of **2** as in case of **1**. Furthermore, the NOE correlations displayed in the NOESY spectrum of **2** (Figure 2) also revealed the (1*S**,5*S**,8*R**,10*R**)-configuration. On the basis of the above findings, the structure of scabrolide F was established as described by formula **2**.

Scabrolide G (**3**) was obtained as a white solid with the molecular formula $C_{19}H_{24}O_7$, as indicated by the HREIMS (*m*/*z* 364.1525) and the NMR spectral data. The ^{13}C NMR spectrum of **3** also revealed the presence of 19 carbon signals, characteristic for a C-4 norcembranoid (Table 1). However, it was found that **3** displayed signals of a trisubstituted epoxide (δ 61.4, C and 64.9, CH), instead of a trisubstituted double bond, as was present in **1** or **2**. By comparison of the ^{13}C NMR spectral data of **3** with those of the known metabolite **8**, isolated previously from *Sinularia leptoclados*,[2] it was found that one methylene in **8** was oxidized to an oxymethine (δ 68.0, CH). The ^{1}H−^{1}H COSY spectrum of **3** revealed that the signal of this oxymethine proton (δ 3.78) showed correlations with H_2-14, which further correlated with H-1. Thus, **3** is a 13-hydroxynorcembranoid. The above findings, together with other correlations observed in the COSY and HMBC spectra (Figure 1), further established the planar structure of **3**.

The relative stereochemistry at C-1, C-5, C-8, C-10, C-11, C-12, and C-13 was well resolved by careful interpretation of the NOE correlations (Figure 2) and through comparison of NMR spectral data with those of **8**. In the ^{13}C NMR spectrum of **3**, the upfield shifted signals for C-5 (δ 76.7) and C-18 (δ 25.7) relative to those of **8**[2] (δ 78.1 and 28.5, respectively) assigned the *syn* orientation of H-5 and methyl group at C-8.[2] This phenomenon could be seen also from the NOE interactions between H-5 (δ 4.20) and H_3-18 (δ 1.50). One of the C-2 methylene protons, H-2α (δ 2.46), showed strong NOE interaction with H-1α, while the other one (δ 2.38) was correlated with H-13. Thus, H-13 is β-oriented and the hydroxy group at C-13 should be position on the α-face. H-4α was found to interact with H-2α and H-5. Thus, H-5 should be positioned on the α-face. The NOE correlations observed for H-13 with H-11, H-11 with H-10, and H-11 with a proton attaching at C-9 (δ 2.10), which did not give NOE response with H_3-18 and was assigned as H-9β, indicated the relative stereochemistry at C-8 and C-10 to be 8*S** and 10*R**, respectively, as revealed by a molecular model of **3**. On the basis of the above observations, the structure of **3** was established.

Although many (5*R**,8*S**)- and (5*S**,8*S**)-norcembranoids[1−8] such as **5** and **6**, respectively, have been isolated and identified from soft corals of the genus *Sinularia*, this study represents the first discovery of their (5*S**,8*R**)-epimers. Diagnostic signals in the ^{1}H and ^{13}C NMR spectra in connection with key NOE correlations were essential tools in the structure determination for epimers of this type, e.g., scarbrolides E and F.

The in vitro cytotoxic activity of metabolites **1** and **4** revealed that the tricyclic scabrolide E (**1**) showed strong cytotoxicity against the growth of Hepa 59T/VGH and KB cells (ED_{50}'s 0.5 and 0.7 μg/mL, respectively), while the polycyclic dissectolide A (**4**) was inactive against these two cell lines.

Experimental Section

General Experimental Procedures. Melting points were determined using a Fisher-Johns melting point apparatus and were uncorrected. Optical rotations were measured on a Jasco DIP-1000 digital polarimeter. Ultraviolet spectra were recorded on a Hitachi U-3210 UV spectrophotometer, and IR spectra were recorded on a Jasco FT/IR-5300 infrared spectrophotometer. The NMR spectra were recorded on a Bruker AVANCE DPX300 FT-NMR, a Bruker AMX-400 FT-NMR, or a Varian Unity INOVA 500 FT-NMR, in $CDCl_3$ using TMS as internal standard, unless otherwise indicated. EIMS was obtained with a VG Quattro GC/MS spectrometer. HRMS spectra were recorded on a Finnigan MAT-95XL mass 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.

Collection, Extraction, and Separation. Frozen specimens of *S. scabra* (1.2 kg, wet wt), collected at a depth of 10−15 m off the coast of the southernmost tip of Taiwan in 2001, were sliced and then exhaustively extracted with MeOH. The *n*-hexane-insoluble fraction of the dichloromethane layer, which was obtained from partition between dichloromethane and an aqueous mixture of the methanol extract, was subjected to column chromatography on silica gel after removal of the deposited crystals of **5**, and elution was performed as previously described to afford 14 fractions.[1] After the isolation of eight norcembranoids from fractions 4−6,[1] the remaining portion of fraction 5 was further separated by normal-phase HPLC using *n*-hexane−EtOAc (gradient, 8:2 to 1:1) to yield **2** (1.5 mg) and **3** (1.2 mg). The remaining portion of fraction 6 was chromatographed by normal-phase HPLC using *n*-hexane−acetone (gradient, 3−20% acetone in hexane) to afford crude **1**, which was purified by preparative silica TLC plates, developed twice by *n*-hexane−EtOAc (1:1), to afford **1** (8.0 mg). Fraction 9 eluted with CH_2Cl_2−MeOH (19:1) was rechromatographed by RP-18 MPLC using H_2O−MeOH (gradient, 25−75% MeOH), and the fraction resulting from the elution with 25% MeOH was further purified by normal-phase HPLC using *n*-hexane−EtOAc (1:2) to yield **4** (8.2 mg).

Scabrolide E (1): white solid, mp 225−226 °C; $[\alpha]^{27}_D$ −3.2° (*c* 0.95, $CHCl_3$); IR (neat) ν_{max} 3600, 3020, 2970, 2935, 1757, 1712, 1668, 1645, 1379, 1269, 1182, 1109 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz), see Table 2; ^1H NMR (C_5D_5N, 300 MHz) δ 6.68 (1H, dd, J = 10.3, 7.2 Hz, H-13), 5.61 (1H, s, H-11), 4.94 (1H, dd, J = 9.2, 6.6 Hz, H-10), 4.80 (1H, s, H-16), 4.73 (1H, s, H-16), 4.40 (1H, dd, J = 4.2, 4.2 Hz, H-5), 3.76 (1H, ddd, J = 12.0, 10.3, 5.0 Hz, H-14α), 3.28 (1H, dd, J = 10.5, 5.0 Hz, H-1), 3.24 (1H, dd, J = 13.5, 4.2 Hz, H-4α), 3.18 (1H, dd, J = 13.5, 4.2 Hz, H-4β), 2.85 (1H, d, J = 18.3 Hz, H-7α), 2.72 (1H, dd, J = 16.0, 10.5 Hz, H-2β), 2.53 (1H, d, J = 18.3 Hz, H-7β), 2.28 (1H, d, J = 16.0 Hz, H-2α), 2.20 (1H, dd, J = 15.0, 9.2 Hz, H-9α), 2.14 (1H, dd, J = 15.0, 6.6 Hz, H-9β), 2.00 (1H, ddd, J = 12.0, 10.5, 7.2 Hz, H-14β), 1.64 (3H, s, H_3-17), 1.37 (3H, s, H_3-18); ^{13}C NMR ($CDCl_3$, 75 MHz), see Table 1; ^{13}C NMR (C_5D_5N, 75 MHz) δ 214.9 (C, C-6), 206.7 (C, C-3), 169.5 (C, C-19), 148.7 (C, C-15), 142.8 (CH, C-13), 134.2 (C, C-12), 110.1 (CH_2, C-16), 84.9 (CH, C-10), 79.5 (C, C-8), 76.3 (CH, C-5), 72.8 (CH, C-11), 49.8 (CH_2, C-7), 46.1 (CH_2, C-2), 45.8 (CH_2, C-4), 44.0 (CH_2, C-9), 43.1 (CH, C-1), 31.6 (CH_2, C-14), 26.6 (CH_3, C-18), 20.4 (CH_3, C-17); EIMS (30 eV) *m/z* 348 (0.1, $[M]^+$), 330 (0.2, $[M - H_2O]^+$), 255 (0.3), 217 (1.0), 199 (1.5), 173 (8.0), 149 (6.6), 124 (15.0), 109 (19.3), 97 (61.7); HREIMS *m/z* 348.1573 (calcd for $C_{19}H_{24}O_6$, 348.1573).

Scabrolide F (2): white solid, mp 119−120 °C; $[\alpha]^{27}_D$ −6.3° (*c* 0.48, $CHCl_3$); IR (neat) ν_{max} 3020, 2970, 2941, 2359, 1757, 1712, 1662, 1440, 1383, 1087, 1022 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz), see Table 2; ^1H NMR (C_6D_6, 300 MHz) δ 6.99 (1H, s, H-11), 4.80 (1H, s, H-16), 4.77 (1H, s, H-16), 4.39 (1H, dd, J = 8.4, 4.5 Hz, H-5), 4.30 (1H, m, H-10), 2.41 (1H, m, H-1), 2.14−2.18 (2H, m, H_2-4), 2.04 (1H, m, H-14), 2.01 (1H, d, J = 18.4 Hz, H-7), 1.92 (1H, m, H-2), 1.87 (1H, m, H-2), 1.87 (1H, d, J = 18.4 Hz, H-7), 1.80 (1H, m, H-13), 1.65 (1H, m, H-13), 1.56 (1H, dd, J = 14.0, 3.0 Hz, H-9), 1.45 (1H, m, H-14), 1.42 (3H, s, H_3-17), 0.79 (1H, dt, J = 14.0, 10.0 Hz, H-9), 0.68 (3H, s, H_3-19); ^{13}C NMR ($CDCl_3$, 125 MHz), see Table 1; EIMS (30 eV) *m/z* 332 (0.1, $[M]^+$), 289 (0.3), 243 (0.3), 135 (9.0), 124 (45.0), 109 (30.0); HREIMS *m/z* 332.1615 (calcd for $C_{19}H_{24}O_5$, 332.1624).

Scabrolide G (3): white solid, mp 180−182 °C; $[\alpha]^{27}_D$ +37.5° (*c* 0.08, $CHCl_3$); IR (neat) ν_{max} 3445, 2956, 2916, 2851, 2359, 2329, 1734, 1714, 1377, 1080 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) and ^{13}C NMR ($CDCl_3$, 125 MHz), see Tables 2 and 1, respectively; EIMS (30 eV) *m/z* 364 (0.1, $[M]^+$), 346 (0.4, $[M - H_2O]^+$), 331 (0.1), 267 (0.3), 257 (0.3), 163 (3.0), 149 (4.0), 135 (7.0), 111 (19.4), 97 (29.6); HREIMS *m/z* 364.1525 (calcd for $C_{19}H_{24}O_7$, 364.1522).

Dissectolide (4): white needles, mp 255−256 °C; $[\alpha]^{27}_D$ +87.5° (*c* 0.24, C_5H_5N) [lit.[3] +91.0° (*c* 0.50, C_5H_5N)]; IR (KBr) ν_{max} 3391, 3293, 2930, 2893, 1745, 1716, 1674, 1645, 1383, 1246, 1109, 1084 cm^{-1}; EIMS (70 eV) *m/z* 348 (0.2, $[M]^+$), 330 (1.0, $[M - H_2O]^+$), 312 (1.0, $[M - 2H_2O]^+$), 284 (1.0), 267 (3.0), 239 (3.4), 111 (51.2); ^1H and ^{13}C NMR spectral data were found to be in full agreement with those reported previously.[3]

Cytotoxicity Testing. Hepa59T/VGH and KB cells were purchased from the American Type Culture Collection (ATCC). Cytotoxicity assays of the test compounds **1** and **4** were performed using the MTT [3-(4,5-dimethylthiazole-2-yl)-2,5-diphenyltetrazolium bromide] colorimetric method.[9,10]

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