Two New Subergane-Based Sesquiterpenes from a Taiwanese Gorgonian Coral *Subergorgia suberosa*

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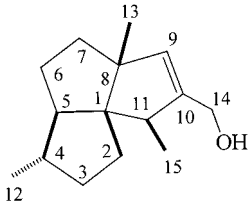
Received December 28, 2001

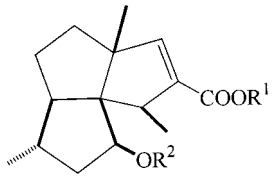
Chemical investigation of the ethyl acetate extract of the Taiwanese Gorgonian coral *Subergorgia suberosa* has resulted in the isolation of two new subergane-based sesquiterpenes, subergorgiol (**1**) and 2β-acetoxysubergorgic acid (**2**), along with four known compounds, subergorgic acid methyl ester (**3**), 2β-acetoxy methyl ester of subergorgic acid (**4**), 2β-hydroxysubergorgic acid (**5**), and subergorgic acid (**6**). The structures of the new metabolites **1** and **2** were determined on the basis of extensive spectral analyses. Subergorgiol (**1**) may be the biosynthetic precursor of **2**−**6**. Compound **3** was found to exhibit moderate cytotoxicity against the growth of HeLa cancer cells.

Previous investigations on the chemical constituents of gorgonian corals during the last fifteen years have discovered a large variety of structurally novel metabolites including sesquiterpenoids, diterpenoids, and steroids. Many of these metabolites were found to be cytotoxic or possess other biological activities.[1] Our continuous efforts in discovering biologically active metabolites from the Taiwanese gorgonian corals including a *Briareum* sp.,[2] *Briareum excavatum*,[3−8] *Junceella fragilis*,[9] and *Isis hippuri*,[10,11] also have resulted in the isolation of a series of novel terpene metabolites. A literature survey revealed that *Subergorgia suberosa* is a gorgonian coral that has been extensively investigated by different research groups. These investigations have resulted in the isolation of several sesquiterpenes of subergane,[12,13] quadrone,[14] and β-caryophyllene[14] types, in addtition to several 9,11-secosteroids.[15,16] Our recent chemical investigation on the ethyl acetate extract of a *S. suberosa* also has led to the isolation of four new sesquiterpenes, suberosols A−D.[17] Further studies on the more polar fractions of the same extract have yielded two new subergane-based sesquiterpenes, subergorgiol (**1**) and 2β-acetoxysubergorgic acid (**2**), along with four known related compounds, subergorgic acid methyl ester (**3**), 2β-acetoxy methyl ester of subergorgic acid (**4**), 2β-hydroxysubergorgic acid (**5**), and subergorgic acid (**6**). This paper deals with the isolation and structure elucidations of these two new subergane-based sesquiterpenes. Also, the full assignments of ^{1}H NMR spectral data for these subergane-based metabolites were achieved for the first time by the assistance of extensive 2D NMR experiments (^{1}H−^{1}H COSY, HMQC, HMBC, and NOESY). Cytotoxicity of metabolites **1**−**6** against KB (human nasalpharyngeal carcinoma) and HeLa (cervix carcinoma) cancer cells also is reported.

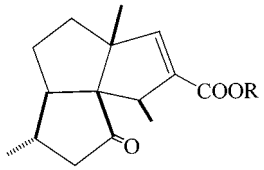
Subergorgiol (**1**) was isolated as a colorless oil. Its HREIMS spectrum exhibited a molecular ion peak at *m*/*z* 220.1827, which was coupled with ^{1}H and ^{13}C NMR spectral data to establish the molecular formula $C_{15}H_{24}O$. Thus, **1** possesses four degrees of unsaturation. The absorption band appearing at ν_{max} 3330 cm^{-1} in the IR spectrum and



1



2: R^1 = H, R^2 = Ac
4: R^1 = Me, R^2 = Ac
5: R^1 = R^2 = H



3: R = Me
6: R = H

the ion peak shown at *m*/*z* 202 [M − H_2O]$^+$ in the EIMS spectrum of **1** suggested the existence of a hydroxyl functional group in **1**. The ^{1}H NMR spectrum of **1** (Table 1) showed the signals of one tertiary (δ 1.00, 3H, s) and two secondary (δ 0.97 and 0.99, 3 H, d, J = 7.0 Hz for each signal) methyl groups and one olefinic (δ 5.27) and three methine protons (δ 1.33, 1H, m; 1.49, 1H, m; and 2.52, 1H, q, J = 7.5 Hz). These signals are the diagnostic signals for the subergane-based compounds.[12,13] The full assignments of all protons in **1** (Table 1) were accomplished by the assistance of DEPT and 2D NMR (^{1}H−^{1}H COSY, HMQC, and HMBC) experiments. The ^{13}C NMR spectrum of **1** (Table 1) showed the presence of 15 carbons. Furthermore, the DEPT experiments of **1** showed signals of three methyl, four high-field methylene, one oxygenated methylene (δ

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10.1021/np0106586 CCC: $22.00
Published on Web 06/01/2002

Table 1. ^{1}H and ^{13}C NMR Chemical Shifts of Compounds **1** and **2**

	1		**2**	
C/H	^{1}H[a]	^{13}C[b]	^{1}H[c]	^{13}C[d]
1		64.1 (s)[f]		66.9 (s)
2α	1.75 ddd (13.0, 5.5, 2.0)[e]	28.9 (t)	5.37 br d (2.5)	79.1 (d)
2β	1.26 td (12.5, 5.5)			
3α	1.08 dd (11.0, 5.5))	35.8 (t)	1.43 td (12.0, 3.3)	42.7 (t)
3β	1.69 dd (11.5, 5.5, 2.5)		1.94 m	
4	1.33 m	39.7 (d)	1.86 m	39.9 (d)
5	1.49 m	64.9 (d)	1.71 dd (17.0, 7.5)	63.9 (d)
6α	1.51 m	29.9 (t)	1.43 m	30.1 (t)
6β	1.21 dd (11.0, 5.5)		1.61 m	
7α	1.59 dd (11.0, 5.5)	37.6 (t)	1.83 m	39.9 (t)
7β	1.44 dd (11.0, 6.0)		1.94 m	
8		57.3 (s)		59.2 (s)
9	5.27 s	134.0 (d)	6.56 s	155.5 (d)
10		146.7 (s)		136.5 (s)
11	2.52 q (7.5)	50.9 (d)	2.77 q (7.0)	50.7 (d)
12	0.99 d (7.0)	20.0 (q)	1.04 d (6.4)	20.0 (q)
13	1.00 s	22.9 (q)	1.22 s	21.8 (q)
14	4.19 q (14.0)	61.3 (t)		168.6 (s)
15	0.97 d (7.0)	17.7 (q)	1.18 d (7.1)	17.6 (q)
OAc			2.06 s	21.7 (q)
				170.3 (s)

[a] Spectra recorded at 500 MHz in $CDCl_3$ at 25 °C. [b] Spectra recorded at 125 MHz in $CDCl_3$ at 25 °C. [c] Spectra recorded at 300 MHz in $CDCl_3$ at 25 °C. [d] Spectra recorded at 75 MHz in $CDCl_3$ at 25 °C. [e] J values (in Hz) in parentheses. [f] Multiplicity deduced by DEPT and indicated by usual symbols. The values are in ppm downfield from TMS.

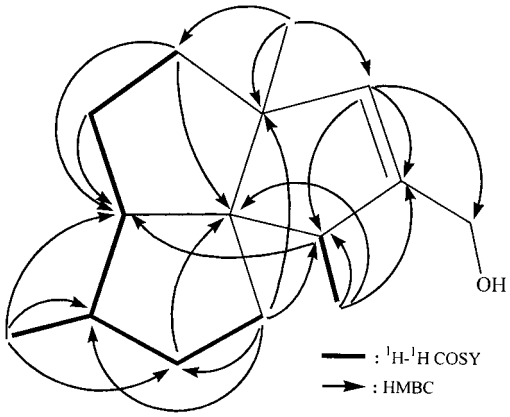

Figure 1. ^{1}H−^{1}H COSY and HMBC correlations for **1**.

61.3, t), one trisubstituted double bond (δ 134.0, d; 146.7, s), and three sp^3 methine carbons. Thus, **1** should contain two additional quaternary carbons. From the ^{1}H−^{1}H COSY spectrum of **1**, it was possible to establish the contiguous proton sets from H-2 to H-7, H-4 to H-12, and H-11 to H-15 (Figure 1). From the above findings, the four degrees of unsaturation required by the molecular formula of **1** should come from a tricyclic sesquiterpene containing a trisubstituted double bond. In comparison of the ^{1}H NMR spectral data of **1** with those of subergorgic acid (**6**),[12] it was found that **1** exhibited an additional signal which appeared as an AB quartet (2H, J = 14.0 Hz) at δ 4.19 ppm. Also, the carbon signals of **6**[12] appearing at δ 217.8 (C-2) and 169.6 ppm (C-14) disappeared and had been replaced by signals appearing at δ 28.9 (t) and 61.4 (t) in **1**, respectively. These observations suggested that the ketone and carboxylic acid functional groups of subergorgic acid have been reduced to the corresponding methylene and allylic hydroxymethyl moieties in **1**, respectively. On the basis of the above results and by the assistance of ^{1}H−^{1}H COSY and HMBC experiments (Figure 1), the molecular framework of **1** could be established. The relative stereochemistry of **1** was further established on the basis of the results of the NOESY experiment (Figure 2). It was found that H_3-13 showed strong NOE interaction with H-2β, whereas H_3-12 exhibited significant NOE with H-2α, suggesting that the C-12 methyl should be α oriented, since the C-13 methyl was placed on the β face. Furthermore, NOE interactions could be observed between H-9 and H_2-14, H_2-14 and H_3-15, and H_3-15 and H-2α. These observations indicated that **1** should possess the same relative configurations at chiral centers C-1, C-4, C-5, C-8, and C-11, in comparison with those of **6** and its analogues.[12,13] Thus, the structure of **1** was established unambiguously, as described by formula **1**.

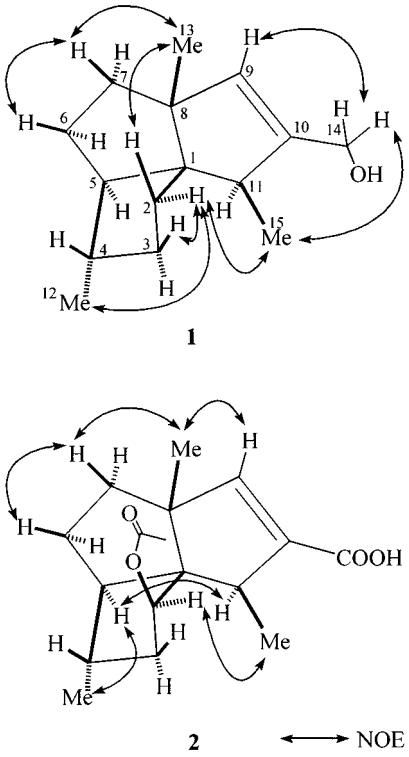

Figure 2. Observed NOESY correlations of **1** and **2**.

Compound **2** also was isolated as a colorless oil. Its molecular formula of $C_{17}H_{24}O_4$ was established by the HRFABMS experiment. Accordingly, six degrees of unsaturation were determined for **2**. The IR spectrum showed strong absorptions at ν_{max} 3100 (br), 1737, and 1714 cm^{-1}, and the FABMS showed the elimination of acetic acid, suggesting the presence of an acetoxyl group and a carboxylic acid functionality in the molecule of compound **2**. The ^{13}C NMR spectrum of **2** (Table 1) showed the presence of 17 carbons, including a trisubstituted olefinic bond (δ 155.5, d; 136.5, s) conjugating with a carboxylic acid. The chemical shifts of 15 carbons of **2** are very close to those of the known compound **5**,[13] while the two additional carbon signals of **2** appearing at δ 21.7 (q) and 170.3 (s) could be attributed to an acetyl group. Moreover, the proton signals of **2** (Table 1) were found to be very similar in chemical shifts and splitting patterns to those of **5**, except for the presence of an additional 3H singlet at δ 2.06, attributed to the methyl group of an acetate. On the basis of the above findings and with the assistance of ^{1}H−^{1}H COSY, HMQC, HMBC, and NOESY spectral data, the structure of compound **2** was unambiguously established as 2β-acetoxysubergorgic acid.

The known compounds, methyl ester of subergorgic acid (**3**),[13] 2β-acetoxy methyl ester of subergorgic acid (**4**),[13] 2β-

Table 2. ^{1}H NMR Chemical Shifts of Compounds **3**−**6**

	3[a]	**4**[a]	**5**[a]	**6**[a]
2		5.34 d (2.7)	4.38 br s	
3α	2.02 dd (16.6, 6.8)[b]	1.42 dd (12.5, 3.3)	1.46 dd (12.5, 3.3)	2.02 dd (16.7, 12.5)
3*β*	2.36 dd (16.6, 4.2)	1.91 dd (13.6, 4.0)	1.81 m	2.35 dd (16.7, 6.7)
4	1.65 m	1.90 dd (9.9, 2.2)	1.94 m	1.64 m
5	2.08 m	1.71 m	1.65 m	2.08 m
6α	1.63 m	1.37 m	1.35 m	1.64 m
6*β*	1.65 m	1.61 m	1.61 m	1.64 m
7α	1.55 m	1.78 dd (12.1, 6.7)	1.78 m	1.62 m
7*β*	1.78 m	1.95 dd (12.1, 3.8)	1.97 m	1.80 m
9	6.24 s	6.40 s	6.59 s	6.41 s
11	3.02 q (7.0)	2.75 q (7.1)	2.69 q (7.1)	3.00 q (7.1)
12	1.11 d (6.2)	1.01 d (6.4)	1.05 d (6.6)	1.10 d (6.4)
13	1.20 s	1.16 s	1.40 s	1.20 s
15	1.12 d (6.2)	1.13 d (7.1)	1.14 d (7.1)	1.11 d (7.1)
OAc		2. 03 s		
OMe	3.73 s	3.71 s		

[a] Spectra recorded at 300 MHz in $CDCl_3$ at 25 °C. [b] *J* values (in Hz) in parentheses.

hydroxysubergorgic acid (**5**),[13] and subergorgic acid (**6**),[12] also isolated in the present investigation, were identified by comparison of the spectral (IR, MS, and NMR) data with those published previously. The full assignments of ^{1}H NMR spectral data for known compounds **3**−**6** were accomplished (Table 2) for the first time by extensive analyses of a series of 2D NMR (^{1}H−^{1}H COSY, HMQC, HMBC, and NOESY) spectral data. Biosynthetically, metabolites **2**−**6** might arise from the further oxidation of **1** at C-2 and C-14.

The cytotoxicity of metabolites **1**−**6** against the growth of KB and HeLa cancer cells was evaluated, and the results showed that metabolites **1**, **2**, and **4**−**6** are not cytotoxic toward both cells (ED_{50} >10 *μ*g/mL). Compound **3** was found to exhibit a moderate cytotoxicity against the growth of HeLa cells with an ED_{50} of 4.3 *μ*g/mL, but inactive against the growth of KB cells.

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. EIMS and FABMS were obtained with a VG Quattro GC/MS spectrometer. 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 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. Si gel 60 (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 analyses.

Animal Material. The gorgonian coral *S. suberosa* was collected by hand via scuba along the coast of Green Island, Taiwan, in July 1998, at a depth of 10−15 m and was stored in a freezer until extraction. A voucher specimen was deposited at the Department of Marine Resources, National Sun Yat-Sen University, Taiwan (specimen no. GISC-103).

Extraction and Isolation. The tissues of *S. suberosa* (1.4 kg, wet wt) were freeze-dried and then exhaustively extracted with EtOAc. The EtOAc extract was then filtered and concentrated under vacuum to provide a brownish semisolid crude extract (24.8 g). The extract was subjected to column chromatography on Si gel. Elution was performed with EtOAc−*n*-hexane (stepwise, 0−100% EtOAc) to yield 18 fractions. Fraction 6 eluted with EtOAc−*n*-hexane (1:10) was further chromatographed by normal-phase HPLC, using EtOAc−*n*-hexane (1:5) to yield compunds **3** (5.0 mg) and **4** (131.0 mg). Similarly, fraction 7 eluted with EtOAc−*n*-hexane (1:4) was further chromatographed by normal-phase HPLC, using EtOAc−*n*-hexane (1:3) to yield compounds **1** (2.4 mg) and **5** (73.7 mg). Finally, fraction 9 eluted with EtOAc−*n*-hexane (2:5) was further chromatographed by HPLC using EtOAc−*n*-hexane (1:2) to yield compounds **6** (73.7 mg) and **2** (4.1 mg).

Subegorgiol (1): colorless oil; $[\alpha]^{31}_D$ 0° (*c* 0.12, $CHCl_3$); IR (neat) ν_{max} 3330, 2947, and 1012 cm^{-1}; EIMS *m*/*z* 220 (8.0, M^+), 205 (2.0), 202 (1.0), and 205 (2.0); HREIMS *m*/*z* 220.1827 (calcd for $C_{15}H_{24}O$, 220.1828).

2*β*-Acetoxysubergorgic acid (2): colorless oil; $[\alpha]^{31}_D$ −40° (*c* 0.21, $CHCl_3$); IR (neat) ν_{max} 3100 (br), 2953, 1737, 1714, 1633, and 1222 cm^{-1}; FABMS *m*/*z* 293 [2.0, $(M + H)^+$] and 233 (23.0); HRFABMS *m*/*z* 293.1750 (calcd for $C_{17}H_{24}O_4$ + H, 293.1754).

Methyl ester of subergorgic acid (3): colorless oil. $[\alpha]^{31}_D$ −55° (*c* 0.25, $CHCl_3$); IR (neat) ν_{max} 2953, 1724 (br), 1639, 1439, and 1251 cm^{-1}; EIMS *m*/*z* 262 (15.0, M^+), 247 (2.0), and 203 (2.2,); ^{1}H NMR spectral data, see Table 2; ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 217.8 (s, C-2), 165.0 (s, C-14), 149.6 (d, CH-9), 137.0 (s, C-10), 68.5 (s, C-1), 62.8 (d, CH-5), 61.7 (s, C-8), 52.0 (q, OMe), 51.4 (d, CH-11), 50.0 (t, CH_2-3), 38.4 (t, CH_2-7), 33.4 (d, CH-4), 28.4 (t, CH_2-6), 23.6 (q, CH_3-13), 20.0 (q, CH_3-12), 17.9 (q, CH_3-15); spectral data of **3** were found to be in full agreement with those previously reported.[13]

2-*β*-Acetoxy methyl ester of subergorgic acid (4): colorless oil; $[\alpha]^{31}$ −107° (*c* 0.24, $CHCl_3$); IR (neat) ν_{max} 2953, 1735, 1718, 1633, and 1456 cm^{-1}; FABMS *m*/*z* 307 [0.7, $(M + H)^+$]; ^{1}H NMR spectral data, see Table 2; ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 170.3 (s, acetate carbonyl), 165.3 (s, C-14), 152.8 (d, CH-9), 137.0 (s, C-10), 79.1 (d, CH-2), 66.8 (s, C-1), 63.9 (d, CH-5), 58.9 (s, C-8), 51.4 (d, CH-11), 50.9 (q, OMe), 42.7 (t, CH_2-3), 39.8 (t, CH_2-7), 39.8 (d, CH-4), 30.1 (t, CH_2-6), 21.8 (q, CH_3-13), 21.7 (q, acetate methyl), 20.0 (q, CH_3-12), 17.6 (q, CH_3-15); spectral data of **4** were found to be in full agreement with those previously reported.[13]

2-*β*-Hydroxysubergorgic acid (5): white powder; mp 146−147 °C; $[\alpha]^{28}_D$ −14° (*c* 0.1, $CHCl_3$); IR (neat) ν_{max} 3435 (br), 2926, 1728, 1682, 1456, and 1269 cm^{-1}; EIMS *m*/*z* 250 (2.0, M), 232 (4.0), 204 (2.0), and 186 (2.0); ^{1}H NMR spectral data, see Table 2; ^{13}C NMR (75 MHz, $CDCl_3$) 169.8 (s, C-14), 156.4 (d, CH-9), 136.7 (s, C-10), 68.0 (s, C-1), *δ* 76.0 (d, CH-2), 63.7 (d, CH-5), 59.3 (s, C-8), 50.4 (d, CH-11), 45.6 (t, CH_2-3), 40.0 (t, CH_2-7), 39.7 (d, CH-4), 30.3 (t, CH_2-6), 22.3 (q, CH_3-13), 20.4 (q, CH_3-12), 17.5 (q, CH_3-15); spectral data of **5** were found to be in full agreement with those previously reported.[13]

Subergorgic acid (6): white powder; mp 177−178 °C; $[\alpha]^{28}_D$ −61° (*c* 0.1, MeOH); IR (neat) ν_{max} 3100 (br), 2935, 1726, 1682, 1643, 1446, and 1284 cm^{-1}; FABMS *m*/*z* 249 [0.9, $(M + H)^+$]; ^{1}H NMR spectral data, see Table 2; ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 217.8 (s, C-2), 169.4 (s, C-14), 152.3 (d, CH-9), 136.7 (s, C-10), 68.6 (s, C-1), 62.8 (d, CH-5), 61.8 (s, C-8), 51.7 (d, CH-11), 49.9 (t, CH_2-3), 38.3 (t, CH_2-7), 33.4 (d, CH-4), 28.4 (t, CH_2-6), 23.4 (q, CH_3-13), 19.9 (q, CH_3-12), 17.7 (q, CH_3-15); spectral data of **6** were found to be in full agreement with those previously reported.[12]

Cytoxicity Testing. KB and Hela cells were purchased from the American Type Culture Collection (ATCC). Cytotoxicity assays of the test compounds **1**−**6** were performed using the MTT [3-(4,5-dimethylthiazole-2-yl)-2,5-diphenyltetrazolium bromide] colorimetric method.[18,19]

Acknowledgment. This work was supported by a grant from the National Science Council of the Republic of China (Contract No. NSC-89-2113-M-110-025) awarded to J.-H.S.

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NP0106586