Further Highly Oxygenated Guaiane Lactones from the South China Sea Gorgonian *Menella* sp.

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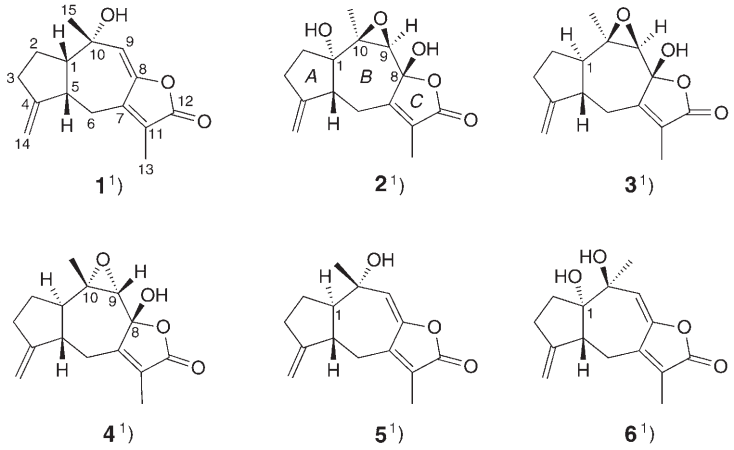
Four new highly oxygenated guaiane lactones, 1-epimenverin B (**1**), menverin F (**2**), 1-deoxymenverin F (**3**), and menverin G (**4**), together with the two known related analogues menverins B (**5**) and C (**6**), were isolated from the South China Sea gorgonian *Menella* sp. Their structures and relative configuration were elucidated by analysis of spectroscopic data and by comparison with those of known related compounds.

Introduction. – Gorgonian corals of the genus *Menella* (family Paramuriceidae, order Gorgonacea, class Anthozoa) is widespread in the South China Sea, but chemical studies on these animals were relatively rare. Our previous work on Hainan gorgonian *Menella verrucosa* (BRUNDIN) revealed that guaianolides [1] and polyoxygenated steroids [2] are common metabolites of this genus of gorgonian.

As part of our ongoing research with the purpose of discovering bioactive substances from Chinese marine invertebrates [3–6], we recently made a collection of the gorgonian coral *Menella* sp. off the Lingshui Bay, Hainan Province, China. Chemical investigation of the Et_2O-soluble fraction from the acetone extract of this animal led to the isolation of four new highly oxygenated guaiane-type sesquiterpene lactones, 1-epimenverin B (**1**), menverin F (**2**), 1-deoxymenverin F (**3**), and menverin G (**4**), all containing a conjugated α-methyl-substituted, α,β-unsaturated γ-lactone moiety and an exocyclic methylene group, together with the two known related analogues menverins B (**5**) and C (**6**), which were recently described [1]. The present work deals with isolation and structural elucidation of these new compounds.

Results and Discussion. – Freshly collected specimen of *Menella* sp. were immediately chilled to $-20°$ and kept frozen until their extraction with acetone. The acetone extract was then partitioned between Et_2O and H_2O, and BuOH and H_2O, respectively. The Et_2O-soluble portion was fractionated by silica gel and *Sephadex LH-20* column chromatography followed by reversed-phase HPLC purification giving six guaianolactones, of which four, namely 1-epimenverin B (**1**), menverin F (**2**),

1-deoxymenverin F (**3**), and menverin G (**4**) were determined as new compounds[1]). The known ones were identified as menverins B (**5**) and C (**6**) [1] by analysis of their NMR spectra and by comparison with the reported data.



1[1]) **2**[1]) **3**[1])

4[1]) **5**[1]) **6**[1])

All six isolates exhibited very similar spectroscopic properties. The UV spectra of compounds **2**–**4** showed a maximum absorption at *ca.* 220 nm (log ε 4.0) indicative of an α,β-unsaturated γ-lactone moiety within these molecules, whereas the λ_{max} shifts to 273 nm (for compounds **1**, **5**, and **6**) implied the extension of a conjugation of the same chromophore. The IR spectra displayed intense absorptions for OH groups (*ca.* 3430 cm^{-1}), an ester moiety (*ca.* 1712 cm^{-1}), and a terminal CH_2 group (*ca.* 957 cm^{-1}). In particular, the NMR spectra of **1** (*Tables 1* and *2*) showed strong structural analogies with the co-occurring compounds **5** and **6**, possessing a common conjugated α-methyl-substituted, α,β-unsaturated γ-lactone moiety. Comparison of the ^{1}H- and ^{13}C-NMR data (*Tables 1* and *2*) of compounds **2**–**4** with those of **5** and **6** [1] confirmed the presence of the same C-skeleton with differences mainly due to the oxidative patterns.

The 1-epimenverin B (**1**) is an optically active colorless oil. The molecular formula, $C_{15}H_{18}O_3$, indicating seven degrees of unsaturation, was established by HR-ESI-MS (*m*/*z* 269.1142 ($[M+Na]^+$)). Analysis of 1D- and 2D- (^{1}H,^{1}H-COSY, HMQC, HMBC, and ROESY) NMR spectra (*Tables 1* and *2*, *Fig. 1*) readily allowed to recognize a typical guaiane-type sesquiterpene lactone framework with an exocyclic methylene group at C(4) and an OH group at C(10). The above-mentioned structural features of **1** were strongly reminiscent of those of menverin B (**5**), and the data established that compound **1** is the 1-epimer of **5**.

Careful comparison of the ^{13}C-NMR data (*Table 2*) of compounds **1** and **5** revealed main differences at C(1), C(6)–C(9), and Me(15). The δ (C) values of C(6) and Me(15) were particularly diagnostic: the former was upfield shifted by -7.3 ppm according to the major interaction with the protons at C(2), whereas the latter was significantly downfield shifted (by $+10.3$ ppm) according to the different orientation of C(2). Both shifts supported the inversion of the configuration at C(1). Furthermore, β-orientation of H–C(1) was also supported by the ROESY experiment. Clear NOE cross-peaks (*Fig. 1*)

[1]) Trivial atom numbering and relative configuration; for systematic names, see *Exper. Part.*

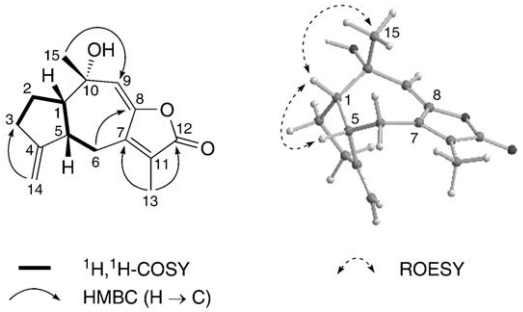


Fig. 1. *Selected two-dimensional NMR correlations for* **1**

Table 1. *^{1}H-NMR Data* (400 MHz) *of Compounds* **1**–**4**[1]). δ in ppm, J in Hz.

	1[a])	**2**[a])	**3**[a])	**4**[a])
H–C(1)	2.75 (*ddd*, J = 7.7, 10.6, 11.3)		2.02–2.07 (*m*)	2.24–2.28 (*m*)
H_a–C(2)	1.81–1.85 (*m*)	2.50–2.52 (*m*)	1.62–1.67 (*m*)	1.75–1.79 (*m*)
H_b–C(2)	1.24–1.28 (*m*)	2.53–2.56 (*m*)	1.73–1.78 (*m*)	1.70–1.76 (*m*)
H_a–C(3)	2.23–2.26 (*m*)	1.99–2.01 (*m*)	2.34–2.35 (*m*)	2.20–2.25 (*m*)
H_b–C(3)	2.27–2.29 (*m*)	2.01–2.04 (*m*)	2.36–2.41 (*m*)	2.31–2.37 (*m*)
H–C(5)	3.11–3.20 (*m*)	2.51–2.54 (*m*)	2.42–2.43 (*m*)	2.25–2.29 (*m*)
H_a–C(6)	2.96 (*dd*, J = 4.0, 15.1)	2.21–2.24 (*m*)	2.30–2.37 (*m*)	2.48–2.55 (*m*)
H_b–C(6)	3.46–3.55 (*m*)	2.79 (*dd*, J = 3.4, 15.2)	2.51–2.56 (*m*)	2.84–2.31 (*m*)
H–C(9)	5.69 (*s*)	3.42 (*s*)	3.32 (*s*)	3.33 (*s*)
Me(13)	1.92 (*d*, J = 1.6)	1.87 (*s*)	1.90 (*s*)	1.82 (*s*)
H_a–C(14)	4.87 (*d*, J = 1.5)	5.07 (*d*, J = 2.3)	4.99 (*d*, J = 2.0)	4.95 (*d*, J = 2.0)
H_b–C(14)	4.63 (*d*, J = 1.5)	4.94 (*d*, J = 2.3)	4.86 (*d*, J = 2.0)	4.84 (*d*, J = 2.0)
Me(15)	1.53 (*s*)	1.50 (*s*)	1.41 (*s*)	1.39 (*s*)

[a]) In $CDCl_3$, referred to the residual $CHCl_3$ (δ(H) 7.26), J in Hz. Assignments made by ^{1}H,^{1}H-COSY, HMQC, HMBC, and ROESY experiments.

between H–C(1), H–C(5), and Me(15) suggested that all of them are orientated on the same face (β) of the molecule according to the drawn structure **1**, that displays the relative configuration.

Menverin F (**2**) was also obtained as optically active colorless oil, and had the molecular formula $C_{15}H_{18}O_5$, deduced from its HR-ESI-MS exhibiting the pseudomolecular ion at m/z 579.2189 ($[2M + Na]^+$). Analysis of the spectroscopic data of **2** revealed that it was also an α-methyl-substituted, α,β-unsaturated γ-lactone-containing guaiane-type sesquiterpenoid. The structure of menverin F was established as depicted in **2** by its ^{1}H- and ^{13}C-NMR (*Tables 1* and *2*), ^{1}H,^{1}H-COSY, HMQC, HMBC, and ROESY data, by comparison with the known menverin C (**6**) [1], and by its CD spectrum; however, the configuration at C(1), C(5), C(9), and C(10) is relative.

The ^{1}H- and ^{13}C-NMR spectra of **2** displayed characteristic signals assignable to a hemiacetal C-atom at δ 105.9 (C(8)), a trisubstituted oxirane moiety at δ(H) 3.42 (H–C(9)) and δ(C) 65.4 (C(9)) and

Table 2. *^{13}C-NMR Data* (100 MHz) *of Compounds* **1**–**6**[1]). δ in ppm.

	1[a])	**2**[a])	**3**[a])	**4**[a])	**5**[a])	**6**[a])
C(1)	53.9 (*d*)	83.7 (*s*)	48.8 (*d*)	48.8 (*d*)	56.5 (*d*)	85.2 (*s*)
C(2)	29.5 (*t*)	35.8 (*t*)	28.3 (*t*)	30.1 (*t*)	27.1 (*t*)	34.2 (*t*)
C(3)	33.7 (*t*)	28.3 (*t*)	29.3 (*t*)	30.8 (*t*)	32.6 (*t*)	29.8 (*t*)
C(4)	154.1 (*s*)	152.6 (*s*)	155.1 (*s*)	154.1 (*s*)	155.3 (*s*)	154.2 (*s*)
C(5)	40.9 (*d*)	46.8 (*d*)	46.3 (*d*)	43.6 (*d*)	41.5 (*d*)	42.8 (*d*)
C(6)	26.3 (*t*)	28.2 (*t*)	26.7 (*t*)	28.4 (*t*)	33.6 (*t*)	26.4 (*t*)
C(7)	150.1 (*s*)	156.9 (*s*)	158.2 (*s*)	158.7 (*s*)	148.3 (*s*)	148.3 (*s*)
C(8)	153.2 (*s*)	105.9 (*s*)	107.0 (*s*)	105.8 (*s*)	146.4 (*s*)	149.2 (*s*)
C(9)	116.0 (*d*)	65.4 (*d*)	65.5 (*d*)	66.6 (*d*)	121.9 (*d*)	116.3 (*d*)
C(10)	73.1 (*s*)	62.5 (*s*)	63.3 (*s*)	62.0 (*s*)	70.9 (*s*)	73.5 (*s*)
C(11)	126.1 (*s*)	126.2 (*s*)	122.9 (*s*)	123.6 (*s*)	127.4 (*s*)	127.6 (*s*)
C(12)	170.8 (*s*)	171.0 (*s*)	171.0 (*s*)	171.0 (*s*)	169.9 (*s*)	169.9 (*s*)
Me(13)	8.6 (*q*)	8.7 (*q*)	8.2 (*q*)	8.5 (*q*)	8.9 (*q*)	8.9 (*q*)
CH_2(14)	104.3 (*t*)	107.3 (*t*)	107.0 (*t*)	105.8 (*t*)	106.4 (*t*)	107.1 (*t*)
Me(15)	33.2 (*q*)	19.7 (*q*)	30.6 (*q*)	22.9 (*q*)	22.9 (*q*)	26.1 (*q*)

[a]) In $CDCl_3$, referred to the residual $CHCl_3$ (δ(C)77.0).

62.5 (C(10)), and an OH-bearing tertiary C-atom at δ 83.7 (C(1)). The gross structure of **2** was completed by detailed analysis of the 1D- and 2D- (^{1}H,^{1}H-COSY, HMQC, HMBC) NMR spectra. In particular, the location of the OH groups at C(1) and C(8) was secured by the ^{13}C,^{1}H long-range correlations C(1)/CH_2(3) and CH_2(6), Me(15)/H–C(9), and C(8)/CH_2(6) and H–C(9), observed in the HMBC plot. The position of the oxirane moiety was also established by the ^{1}H,^{13}C-HMBC H–C(9)/C(1), C(7), and C(15) and Me(15)/C(9). The relative configuration at the oxirane moiety of **2** was presumed to be *cis* due to the observed ROESY correlation H–C(9)/Me(15). Further, the absence of an NOE H–C(5)/Me(15) implied that the oxirane O-atom is pointing to the same side (β) as H–C(5), as depicted in structure **2** that represents a relative configuration. The configuration of OH–C(1) was tentatively assigned to be α by comparison of the ^{13}C-NMR data of **2** with those of the co-occurring menverin C (**6**). In fact, a substantial similarity of the δ(C) values of segments C(1)–C(4), C(6), and C(14) between **2** and **6** was observed. The configuration of OH–C(8) was assigned β (*R*) because a negative π-π* *Cotton* effect in the region λ 205–235 nm was observed in its CD spectrum ($[\theta]_{203} = +4849.02$ and $[\theta]_{224} = -3437.94$ in MeOH, $c = 0.6$ mg/ml) [7].

The 1-deoxymenverin F (**3**) was obtained as an UV-active colorless oil. The molecular formula $C_{15}H_{18}O_4$ was established by HR-ESI-MS (*m*/*z* 285.1078 ($[M + Na]^+$), which accounts for 16 mass units less than that of **2**. The UV, IR, ^{1}H- and ^{13}C-NMR spectra (*Tables 1* and *2*) of **3** closely resembled those of **2**. In fact, **3** differs from **2** only by the functionality at C(1) where the OH substituent is absent. The loss of the OH group significantly upfield shifted the ^{13}C-NMR resonance of C(1) (from δ 83.7 to 48.8). Further detailed analysis of the 2D-NMR spectra (*Fig. 2*) allowed the unambiguous definition of the structure of **3**. Analogously to **2**, a negative π-π* *Cotton* effect was observed in the CD spectrum of **3** supporting the β-orientation of the OH group at C(8).

Menverin G (**4**) had a molecular formula $C_{15}H_{18}O_4$, identical to that of **3** as indicated by HR-ESI-MS (*m*/*z* 285.1078 ($[M + Na]^+$)). ^{1}H,^{1}H-COSY and HMBC Experiments led to the same proton sequence and framework as those of **3**. The

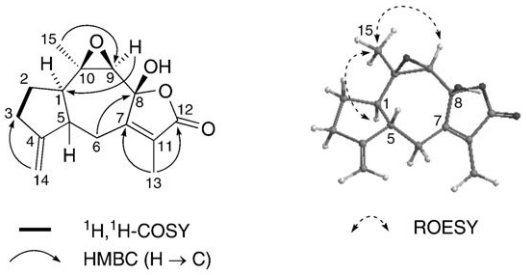


Fig. 2. *Selected two-dimensional NMR correlations for* **3**

^{13}C-NMR spectrum of **4** was also very similar to that of **3**, except for the ^{13}C-NMR resonance of Me(15) that was significantly upfield shifted (by −7.7 ppm) with respect to that of **3**. The different configuration at C(10) of **4** was supported by an analogous difference in the chemical shift of Me(15) of the pair menverin B (**5**) and its C(10) epimer menverin A [1] δ 22.9 *vs.* 29.9. On the other hand, in the ROESY studies, the interactions Me(15)/H–C(9) and H–C(5) were observed, whereas no NOE cross-peak H–C(1)/Me(15) and H–C(5) was detected. Thus, menverin G (**4**) is an epimer at C(9) and C(10) of 1-deoxymenverin F (**3**). Once again, a negative π-π* *Cotton* effect in the CD spectrum of **4** suggested that the configuration of the OH–C(8) was the same as that in **3**.

Many guaiane sesquiterpenoids have been isolated from natural sources [8]. However, they are infrequent in marine organisms [9][10]. Gorgonians contain the majority of marine guaiane analogs [11–22]. The discovery of new compounds **1**–**4** has added to an extremely diverse and complex array of marine guaiane sesquiterpenoids which is rapidly expanding. Unfortunately, high instability of these sesquiterpenoids prevented full characterization of their absolute configurations. Further studies should be conducted to test their bioactivities as well as to understand their real biological/ecological role in the life cycle of the animal.

The research work was financially supported by the *National Marine '863' Project* (Nos. 2006AA09Z412 and 2007AA09Z447), the *Natural Science Foundation of China* (Nos. 20721003, 30730108, 20572116, and 40776073), and *STCSM Projects* (Nos. 07XD14036, 054307062, and 06DZ22028) and partially funded by the *MEC Program for New Century Excellent Talents in University* (No. NCET-05-0600) and the *MEC Cultivation Fund of the Key Scientific and Technical Innovation Project* (No. 706038).

Experimental Part

General. Column chromatography (CC): commercial silica gel (*Qing Dao Hai Yang Chemical Group Co.*; 200–300 mesh) and *Sephadex LH-20* (*Amersham Biosciences*). TLC: precoated silica gel plates (*Yan Tai Zi Fu Chemical Group Co.*; *G60*, *F-254*). Optical rotation: *Perkin-Elmer 341* polarimeter. UV Spectra: *756-CRT* spectrophotometer; λ_{max} (log ε) in nm. CD Spectra: *Jasco J-810* spectropolarimeter; $\lambda([\theta])$ in nm. IR Spectra: *Nicolet Magna-FT-IR-750* spectrophotometer; ν_{max} in cm^{-1}. ^{1}H- and ^{13}C-NMR Spectra: *Varian Mercury-400* spectrometer; at 400 (^{1}H) and 100 MHz (^{13}C); chemical shifts δ in ppm, with residual $CHCl_3$ (δ(H) 7.26; δ(C) 77.0) as internal standard, coupling constant *J* in Hz. ESI-MS and HR-ESI-MS: *Q-TOF-Micro* LC-MS-MS spectrometer in *m*/*z*.

Animal Material. Specimens of the gorgonian *Menella* sp. were collected by Dr. *Ernesto Mollo* off the Lingshui Bay, Hainan Province, China, in July 2004, at a depth of −20 m, and were frozen immediately after collection. The animal was subsequently identified by Associate Prof. *H. Huang* of the South China Sea Institute of Oceanology, Chinese Academy of Sciences. A voucher sample (No. LS-208) is available for inspection at the Shanghai Institute of Materia Medica, Chinese Academy of Sciences.

Extraction and Isolation. The frozen specimen (264 g, dry weight) were cut into pieces and extracted exhaustively with acetone at r.t. (4 × 1.5 l). The org. extract was concentrated to give a residue, which was partitioned between Et_2O and H_2O. The Et_2O soln. was evaporated to give a dark brown residue (5.2 g). The residue was fractionated by CC (silica gel, 0 → 100% acetone/petroleum ether) yielding three fractions showing interesting yellow TLC spots (R_f 0.55, 050, and 0.45, resp.) on TLC ($CHCl_3$/MeOH 95:5) after spraying with H_2SO_4. These fractions were purified by CC (*Sephadex LH-20*, petroleum ether/$CHCl_3$/MeOH 2:1:1) followed by reversed-phase HPLC (semi-prep. *ODS HG-5* (5 μm, 250 × 10 mm), MeOH/H_2O gradient, 2 ml/min): **1** (2.5 mg; MeOH/H_2O 72:28, t_R 15.4 min), **2** (3.1 mg; MeOH/H_2O 60:40, t_R 15.1 min), **3** (1.7 mg; MeOH/H_2O 69:31, t_R 13.6 min), **4** (1.9 mg; MeOH/H_2O 69:31, t_R 14.5 min), **5** (4.5 mg; MeOH/H_2O 72:28, t_R 16.9 min), and **6** (5.0 mg; MeOH/H_2O 60:40, t_R 13.0 min).

1-Epimenverin B (= rel-*(4a*R,*7a*R,*8*R*)-4a,5,6,7,7a,8-Hexahydro-8-hydroxy-3,8-dimethyl-5-methyleneazuleno[5,6-*b*]furan-2(4*H*)-one*; **1**): Colorless oil. $[\alpha]_D^{22} = -12$ ($c = 0.18$, $CHCl_3$). UV (MeOH): 273 (4.0). ^{1}H- and ^{13}C-NMR: *Tables 1* and *2*. ESI-MS: 269 ($[M+Na]^+$). HR-ESI-MS: 269.1142 ($[M+Na]^+$; calc. 269.1154).

Menverin F (= rel-*(1a*R,*1b*R,*5a*R,*8a*S,*8b*S*)-1a,5,5a,6,7,8,8a,8b-Octahydro-1b,8a-dihydroxy-4,8b-dimethyl-6-methyleneoxireno[7,8]azuleno[5,6-*b*]furan-3(1b*H*)-one*; **2**): Colorless oil. $[\alpha]_D^{22} = +12$ ($c =$ 0.13, $CHCl_3$). UV (MeOH): 214 (3.9). CD (MeOH, $c = 0.6$ mg/ml): 203 (+4849.02), 224 (−3437.94). ^{1}H- and ^{13}C-NMR: *Tables 1* and *2*. ESI-MS: 579 ($[2M+Na]^+$). HR-ESI-MS: 579.2189 ($[2M+Na]^+$; calc. 579.2206).

1-Deoxymenverin F (= rel-*(1a*R,*1b*R,*5a*S,*8a*R,*8b*R*)-1a,5,5a,6,7,8,8a,8b-Octahydro-1b-hydroxy-4,8b-dimethyl-6-methyleneoxireno[7,8]azuleno[5,6-*b*]furan-3(1b*H*)-one*; **3**): Colorless oil: $[\alpha]_D^{22} = +22$ ($c =$ 0.10, $CHCl_3$). UV (MeOH): 214 (3.9). CD (MeOH, $c = 0.9$ mg/ml): 204 (+5420.52), 224 (−4333.93). ^{1}H- and ^{13}C-NMR: *Tables 1* and *2*. ESI-MS: 285 ($[M+Na]^+$). HR-ESI-MS: 285.1078 ($[M+Na]^+$; calc. 285.1103).

Menverin G (= rel-*(1a*R,*1b*S,*5a*R,*8a*S,*8b*R*)-1a,5,5a,6,7,8,8a,8b-Octahydro-1b-hydroxy-4,8b-dimethyl-6-methyleneoxireno[7,8]azuleno[5,6-*b*]furan-3(1b*H*)-one*; **4**): Colorless oil. $[\alpha]_D^{22} = +19$ ($c = 0.09$, $CHCl_3$). UV (MeOH): 214 (3.9). CD (MeOH, $c = 1.3$ mg/ml): 203 (+15741.69), 224 (−7658.46). ^{1}H- and ^{13}C-NMR: *Tables 1* and *2*. ESI-MS: 285 ($[M+Na]^+$). HR-ESI-MS: 285.1078 ($[M+Na]^+$; calc. 285.1103).

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Received August 20, 2007