New Scalarane-Based Sesterterpenes from the Sponge *Phyllospongia madagascarensis*

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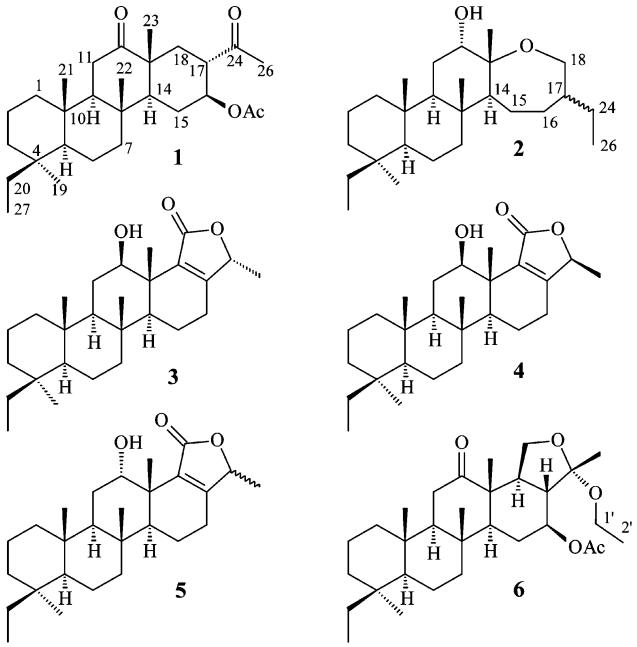
Two new natural scalaranes, 16β-acetoxy-20,24-dimethyl-12,24-dioxo-25-norscalarane (**1**) and 12β-hydroxy-20,24-dimethyl-13,18-oxa-25-norscalarane (**2**), were isolated from the Madagascaran sponge *Phyllospongia madagascarensis*, together with three previously decribed tetracyclic sesterterpenoids, phyllofolactones F (**3**), G (**4**), and B (**5**), and a new artifactual ethyl ether of scalaradisin B (**6**). Structure determinations were based on NMR and other spectral data. Compounds **1** and **2** represent new examples of 20,24-dimethyl-25-norscalarane sesterterpenes, and compound **2** has a seven-membered oxacycle that makes its skeletal system unique.

Scalarane-based metabolites occur in marine sponges belonging to the families Thorectidae and Spongiidae (the order Dictyoceratida)[1,2] and in mollusks feeding on them.[3−5] The scalarane-like skeletal systems can vary from the C_{24} norscalarane to the C_{27} bishomoscalarane types. Sponges of the genus *Phyllospongia* from the family Spongiidae have been studied extensively and have given rise to a great array of sesterterpenoids, especially 20,24-bishomoscalaranes.[6−17] Scalaranes have been reported to exhibit a wide spectrum of biological activities including cytotoxicity,[9,18−20] ichthyotoxicity,[21,22] and antiinflammatory,[23] antimicrobial,[24] antithrombocyte, and vasodilatory properties.[10]

In the course of our investigations directed to the search for new natural products from marine organisms, we have studied specimens of the sponge *Phyllospongia madagascarensis*. The acetone extract of the sponge was fractionated by silica gel flash chromatography. Compounds **1**−**5** and compound **6** were partially purified by Sephadex LH-20 chromatography using acetone and chloroform−ethanol as eluates, respectively. All substances were purified by preparative HPLC. A combination of 1D and 2D NMR spectroscopy and HREIMS was used to elucidate the structures of the new compounds **1** and **2** as described in the following paragraphs.



Results and Discussion

The molecular formula of compound **1** was deduced as $C_{28}H_{44}O_4$ using the HREIMS fragment ion at *m*/*z* 384.3045 (M^+ − AcOH) and ^{13}C NMR analysis (Table 1). The IR spectrum of **1** showed absorptions for acetoxyl (ν_{max} 1740 cm^{-1}) and two ketone functionalities (ν_{max} 1720 and 1708 cm^{-1}). Its ^{13}C NMR spectrum exhibited 28 signals including two carbonyl carbons (δ 214.7 and 208.7) and one carbonyl carbon of an acetate group (δ 170.0) (Table 1). Inspection of its 2D NMR data ($^1H-^1H$ COSY, HSQC, HMBC) allowed us to assemble the structure **1**. Stereochemistry at C-5, -9, and -14 followed from characteristic chemical shifts of CH_3-21, -22, and -23 in the ^{13}C NMR spectrum.[20,25] The β-configuration of the ethyl substituent at C-4 was established by comparison of chemical shifts of C-20 (δ 24.5) and C-19 (δ 28.5) with those of previosly reported scalarane derivatives.[6−17] The suggested structure was confirmed by EIMS fragmentation, especially by peaks at *m*/*z* 205, 219, and 287, characteristic for 20-methylscalaranes (see Figure S1, Supporting Information, for fragmentation). The orientation of the C-16 acetoxyl group was concluded to be β from coupling constants of the signal at δ 4.93 (H-16, dt, J = 5.2, 10.8 Hz) and a 1D NOE between H-16 and H-14 (δ 1.28 dd, J = 2.0, 13.0 Hz). The orientation of the proton at C-17 was concluded to be β from coupling constants of this signal at 2.76 (H-17, ddd, J = 4.0, 10.8, 13.5 Hz) and a NOE between H-17 and H_3-23 (δ 1.23 s). On the basis of these data, the structure of **1** was established as 16β-acetoxy-20,24-dimethyl-12,24-dioxo-25-norscalarane. A C-12 oxo functionality is rarely found in scalaranes, although 12-hydroxy compounds are reported in the literature.[6−11] Compound **1** is the first example of a 25-nor-12-oxo-scalarane.

The molecular formula of compound **2** was determined as $C_{26}H_{46}O_2$ by the molecular ion at *m*/*z* 390.3490 in the HREIMS and ^{13}C NMR analysis (Table 1). The IR spectrum of **2** showed absorptions for hydroxyl (ν_{max} 1461 cm^{-1}) and ether (ν_{max} 1088 cm^{-1}) functionalities. The ^{13}C NMR spectrum of **2** exhibited a total of 26 signals including one

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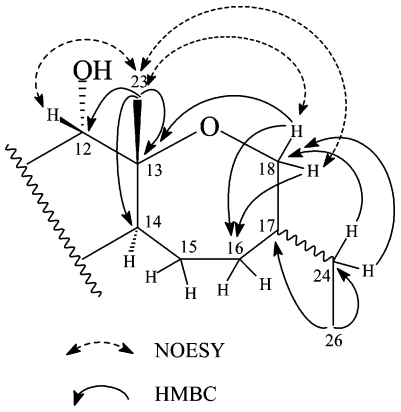
Table 1. NMR Data of Compounds **1** and **2** in $CDCl_3$

	1				**2**			
atom	δ_C mult.	δ_H (J, Hz)	HMBC (H/C)	NOESY (H/H)	δ_C mult.	δ_H (J, Hz)	HMBC (H/C)	NOESY (H/H)
1	39.8 CH_2	1.58 (m), 0.83 (m)			40.2 CH_2	0.92[a] (m) 1.65[e] (m)		11
2	18.2 CH_2				18.3 CH_2	1.34−1.57 (m)		
3	36.5 CH_2	0.85 (m), 1.66 (m)			36.7 CH_2	0.88[a] (m) 1.65[e] (m)		
4	36.2 C				36.2 C			
5	58.6 CH	0.89 (m)			58.5 CH	0.97 (m)		9
6	17.9 CH_2	1.44 (m), 1.53 (m)			18.4 CH_2	1.34−1.57 (m)		
7	41.4 CH_2	1.01 (m), 1.79 (m)			41.0 CH_2	1.03[a] (m) 1.86[e] (m)		22
8	37.7 C				38.7 C			
9	60.7 CH	1.21 (m)			50.9 CH	1.47 (m)	1	5
10	38.1 C				37.0 C			
11	34.8 CH_2	2.29 (dd, 2.6; 13.9) 2.62 (t, 13.9)			24.5 CH_2	1.48 (m) 1.83 (m)		1*e*
12	214.7 C				75.3 CH	3.67 (dd, 3.1; 2.5)	9	23
13	47.8 C				78.7 C			
14	55.3 CH	1.28 (dd, 2.0; 13.0)		16	52.7 CH	1.63 (m)		
15	25.2 CH_2	1.43 (m), 2.11 (m)			19.8 CH_2	1.48−1.62 (m)		
16	73.4 CH	4.93 (td, 10.8; 5.2)		14	32.2 CH_2	1.38 (m), 1.53 (m)		
17	51.0 CH	2.76 (ddd, 4.0; 10.8; 13.5)		23	41.0 CH	1.67 (m)		
18	37.6 CH_2	1.41 (t, 13.6) 1.97 (m)			67.0 CH_2	3.55 (dd, 7.6; 12.8) 3.63 (dd, 2.5; 12.6)	13, 16 13, 16	23 23
19	28.5 CH_3	0.79 (s)	3, 4, 5, 20		28.6 CH_3	0.79 (s)	4, 5, 20	2, 6
20	24.5 CH_2	1.17 (m), 1.53 (m)			24.6 CH_2	1.16 (m), 1.53 (m)		
21	16.7 CH_3	0.87 (s)	1, 5, 9, 10		17.0 CH_3	0.80 (s)	1, 5, 9, 10	
22	16.4 CH_3	1.00 (s)	7, 8, 9, 14		16.2 CH_3	0.72 (s)	7, 8, 9, 14	7*e*, 23
23	19.4 CH_3	1.23 (s)	12, 13, 14	17	21.1 CH_3	1.16 (s)	12, 13, 14	12, 18
24	208.7 C				26.1 CH_2	1.18 (m), 1.30 (m)	18, 18	
26	28.6 CH_3	2.14 (s)	24		11.9 CH_3	0.88 (t, 7.3)	17, 24	
27	8.7 CH_3	0.75 (t, 7.4)	4,20		8.7 CH_3	0.74 (t, 7.5)	4, 20	
OAc	170.0 C 21.2 CH_3	1.98 (s)	C(OAc)					

[a] Axial proton. [e] Equatorial proton.

hydroxymethine carbon (δ 75.3), one oxymethylene carbon (δ 67.0), and a quaternary oxygen-bonded carbon (δ 78.7). Analysis of the 2D NMR data ($^1H-^1H$ COSY, HSQC, HMBC) allowed us to assign all signals in the NMR spectra and revealed that **2** is based on a bishomo-25-norscalarane skeleton, having a modified ring D. The complete assignment of the NMR signals is given in Table 1. The suggested structure was confirmed by EIMS fragmentation (see Figure S1, Supporting Information, and Experimental Section for fragmentation). The chemical shifts of angular methyl groups (δ 16.2, 17.0, 21.1) suggested that all ring junctions were *trans*.[25] The absence of the cross-peak CH_3-22/H-14 in the NOESY and the closeness of the chemical shift of C-9 (δ 50.9), which must be sensitive to the ring junction, to those in spectra of other 12α-hydroxyscalaranes confirmed the C,D-*trans*-junction.[12,26] Small coupling constants of the signal at δ 3.67 (H-12, dd, J = 3.1, 2.5 Hz) indicated H-12 to be equatorial. The HMBC cross-peak between CH_3-23 and the quaternary oxygen-bonded carbon (δ 78.7) showed the attachment of an oxygen atom to C-13. The HMBC cross-peaks between two protons at C-18 (δ 3.55 dd, J = 7.6, 12.8 Hz and 3.63 dd, J = 2.5, 12.8 Hz) and C-13 indicated that C-13 and C-18 are connected with each other by an ether bond (Scheme 1). The fragment $-O-CH_2-$ was attached to the methine carbon (C-17, δ 41.0, CH; H-17, δ 1.67 m) through $^1H-^1H$ COSY cross-peaks (H-17/H-18, H-17/H-18′). The HMBC data (cross-peaks of H-26/C-24, H-26/C-17, and H-24/C-18) demonstrated the attachment of the fragment CH_3-CH_2- to C-17. The HMBC cross-peaks between H_2-18 and C-16 (δ 32.2) and the HMQC-TOCSY data (CH_3-26/C-24/C-17 and H-17/C-18) confirmed the partial structure of **2** at ring D. On the basis of these data, the structure of sesterterpenoid

Scheme 1. Key NOESY and HMBC Correlations for Ring D of **2**



2 was established as 12β-hydroxy-20,24-dimethyl-13,18-oxa-25-norscalarane. In addition to the unusual structure of ring D, the absence of any functional group at C-24 is an intriguing feature.

Compounds **3** and **4** have been identified as previously known sesterterpenoids described by Wan and co-workers from the sponge *Phylospongia foliascens*.[27] However, we have provided correct assignments of signals in their NMR spectra (see Table S1, Supporting Information). Compound **5** gave NMR spectra identical with those of phyllofolactone B.[12]

The IR spectrum of **6** showed absorptions for carbonyl (ν_{max} 1705 cm^{-1}) and ester (ν_{max} 1737 cm^{-1}) groups. Its ^{13}C NMR spectrum exhibited a total of 31 signals including resonances for a ketone (δ 215.2), an acetate group (δ 170.4

and 21.3), a ketal group (δ 103.8), and an oxymethine carbon (δ 72.6). The ^{1}H NMR spectrum also showed signals for a methyl of an acetoxyl group (δ 2.04 s), five angular methyls (δ 0.79, 0.87, 1.02, 1.12, and 1.37 s), and two methyls attached to methylene groups (δ 0.74 and 1.09 t). Analysis of its 2D NMR data (^{1}H−^{1}H COSY, HSQC, HMBC) revealed that **6** is based on a bishomoscalarane skeleton system with additional methylations at C-24 and C-20. Complete assignments of the ^{1}H and ^{13}C NMR data are given in the Experimental Section. The ethoxy group was placed at C-24 on the basis of the HMBC cross-peak between H_2-1′ (3.40 and 3.55 m) and the ketal type carbon (δ 103.8). The orientation of the ethoxy group was concluded to be α from a NOE between H-17 (δ 1.77 dd J = 10.7, 13.0 Hz) and H_3-26 (δ 1.37 s) and H_3-23 (δ 1.12 s). The orientation of the acetoxyl group was established as β from a NOE between H-16 (δ 4.84 m) and H-18 (δ 2.40 ddd, J = 8.7, 9.6, 13.0 Hz). On the basis of this evidence, we conclude that **6** is an artifactual ketal formed from scalaradisin B[10,28] as a result of its reaction with ethanol.

Experimental Section

General Experimental Procedures. Optical rotations were measured on a Perkin-Elmer model 343 polarimeter in $CHCl_3$. IR spectra were recorded on a Bruker IR-FT Vector 22 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker DPX-3003 spectrometer operating at 300 and 75.5 MHz, respectively, using TMS as an internal standard. HREIMS were obtained on a AMD-604S high-resolution mass spectrometer (Germany) with a UV-nitrogen laser (337 nm). GLC-MS analyses were performed on a Hewlett-Packard HP6890 GS system, using a HP-5MS capillary column (30.0 m × 250 μm × 0.25 μm) at 270 °C. The ionizing voltage was 70 eV. Helium was used as the carrier gas. Preparative HPLC was carried out on a Dupont-8800 chromatograph, using Ultrasphere-Si (5 μm, 250 × 10 mm) and Silasorb C_{18} (12 μm, 10 × 250 mm) columns with a RIDK-22 refractometric detector. TLC was performed on Sorbfil plates (Russia) in hexane−ethyl acetate and detected by spraying with sulfuric acid (100 °C, 5 min).

Animal Material. The sponge was collected from a depth of 5 m using scuba near the northwest coast of Madagascar during an expedition on board the research vessel "Academik Oparin" in November 1986 and identified as *Phyllospongia madagascarensis* (family Spongiidae, order Dictioceratida) by Dr. V. B. Krasokhin. The sponge was lyophilized immediately after collection and stored at −18 °C. The voucher sample is under storage at the Pacific Institute of Bioorganic Chemistry, Vladivostok (PIBOC O3-185).

Extraction and Isolation. The lyophilized specimens (370 g) were extracted with acetone (6 × 500 mL) by refluxing. The acetone extract concentrated in vacuo was sequentially separated by low-pressure column chromatography (35 × 2 cm column) on silica gel using hexane with increasing amounts of ethyl acetate to obtain three fractions. Fraction 3, containing compound **6**, was subjected to column chromatography (50 × 1 cm) on Sephadex LH-20 using chloroform−ethanol, 1:1. Compound **6** (3.5 mg, 9.4 × 10^{-4} % based on dry weight) was obtained from this fraction by HPLC using an Ultrasphere-Si column with hexane−ethyl acetate, 5:1. Fractions 1 and 2, containing compounds **1**−**5**, were purified in the same manner, but using acetone as eluent. Then fraction 1 was separated by HPLC on an Ultrasphere-Si column with hexane−ethyl acetate, 10:1, followed by Silasorb C_{18} column chromatography in acetone−water, 20:1, to give **2** (1.5 mg, 4.0 × 10^{-4} % based on dry weight). Fraction 2 was separated by HPLC on an Ultrasphere-Si column using hexane−ethyl acetate, 6:1, to give **1** and **3**−**5** (2.9 mg, 7.8 × 10^{-4}; 2.3 mg, 6.2 × 10^{-4}; 0.4 mg, 1.1 × 10^{-4}; 4.6 mg, 12.4 × 10^{-4} % based on dry weight, respectively). Compounds **1** and **4** were additionally purified by repeated HPLC using a Silasorb C_{18} column in the solvent system acetone−water, 10:1.

16β-Acetoxy-20,24-dimethyl-12,24-dioxo-25-norscalarane (1): amorphous solid; $[\alpha]_D^{25}$ 0° (*c* 0.03, $CHCl_3$); IR (CCl_4) ν_{max} 1740, 1720, 1708 cm^{-1}; NMR data, Table 1; EIMS *m/z* 384 [M − AcOH]$^+$ (100), 369 (60), 355 (18), 341 (27), 323 (30), 287 (8), 246 (10), 219 (6), 217 (18), 205 (45); HREIMS *m/z* 384.3045 (calcd for $C_{26}H_{40}O_2$, [M − AcOH]$^+$ 384.3028).

12β-Hydroxy-20,24-dimethyl-13,18-oxa-25-norscalarane (2): amorphous solid; $[\alpha]_D^{25}$ 35.0° (*c* 0.02, $CHCl_3$); IR (CCl_4) ν_{max} 1461, 1088 cm^{-1}; NMR data, Table 1; EIMS *m/z* 390 [M]$^+$ (100), 375 [M − CH_3]$^+$ (18), 372 [M − H_2O]$^+$ (10), 357 [M − CH_3 − H_2O]$^+$ (12), 343 [M − C_2H_5 − H_2O]$^+$ (16), 273 (12), 220 (15), 205 (53), 193 (35); HREIMS *m/z* 390.3490 (calcd for $C_{26}H_{46}O_2$, [M]$^+$ 390.3498).

Ethyl ether of scalaradisin B (6): amorphous solid; IR (CCl_4) ν_{max} 1737, 1705 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.82, 1.58 (1H each, m, H_2-1), 1.46, 1.41 (1H each, m, H_2-2), 0.84, 1.66 (each 1H, m, H_2-3), 0.87 (1H, m, H-5), 1.59, 1.55 (each 1H, m, H_2-6), 1.78, 1.05 (each 1H, m, H_2-7), 1.22 (1H, dd, J = 3.0, 14.0 Hz, H-9), 2.59 (1H, t, J = 13.8 Hz, H-11), 2.24 (1H, dd, J = 2.5, 13.6 Hz, H-11), 1.35 (1H, m, H-14), 1.37, 2.16 (each 1H, m, H_2-15), 4.84 (1H, m, H-16), 1.77 (1H, dd, J = 10.7, 13.0 Hz, H-17), 2.40 (1H, ddd, J = 8.7, 9.6, 13.0 Hz, H-18), 0.79 (3H, s, CH_3-19), 1.53, 1.17 (each 1H, m, H_2-20), 0.87 (3H, s, CH_3-21), 1.02 (3H, s, CH_3-22), 1.12 (3H, s, CH_3-23), 4.25 (1H, t, J = 8.7, Hz, H-25), 3.63 (1H, dd, J = 9.0, 9.6 Hz, H-25), 1.37 (3H, s, CH_3-26), 0.74 (3H, t, J = 7.4 Hz, CH_3-27), 2.04 (3H, s, $OCOCH_3$), 3.55, 3.40 (each 1H, m, H_2-1′), 1.09 (3H, t, J = 7.0 Hz, CH_3-2′); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 39.9 (CH_2-1), 18.2 (CH_2-2), 36.4 (CH_2-3), 36.1 (C-4), 58.6 (CH-5), 18.0 (CH_2-6), 41.8 (CH_2-7), 37.8 (C-8), 61.2 (CH-9), 38.2 (C-10), 34.9 (CH_2-11), 215.2 (C-12), 51.3 (C-13), 58.3 (CH-14), 26.3 (CH_2-15), 72.6 (CH-16), 51.9 (CH-17), 47.0 (CH-18), 28.6 (CH_3-19), 24.5 (CH_2-20), 16.4 (CH_3-21), 16.8 (CH_3-22), 13.7 (CH_3-23), 103.8 (C-24), 67.3 (CH_2-25), 22.1 (CH_3-26), 8.7 (CH_3-27), 170.1 ($OCOCH_3$), 21.3 ($OCOCH_3$), 56.1 (CH_2-1′), 15.8 (CH_3-2′); HMBC (H/C) H-11α/C-8, C-12; H-11β/C-8, C-9, C-12; H-17/C-13, C-26; H-25α/C-24; H-25β/C-24; Me-19/C-3, C-4, C-5, C-20; Me-21/C-1, C-9, C-10; Me-22/C-7, C-8, C-9, C-14; Me-23/C-12, C-13, C-18; Me-26/C-24, C-17; Me-27/C-4, C-20; Me(Ac)/C(Ac); H-1′α/C-2′, C-24; H-1′β/C-2′, C-24; Me-2′/C-1′; ^{1}D NOE (H/H) H-7β/Me-22; H-11β/Me-21, Me-22, Me-23; H-11α/H-1α; H-16α/H-18α; H-17β/Me-23, Me-26; Me-26/H-1′α, H-1′β; EIMS *m/z* 396 (100), 381 (30), 367 (7), 205 (50), 175 (20), 147 (50).

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Supporting Information Available: Mass spectral fragmentation of **1** and **2** and table of spectroscopic data for compounds **3**−**5**. This information is provided free of charge via the Internet at http://pubs.acs.org.

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