Six New Spongian Diterpenes from the Sponge *Spongia matamata*

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Received September 16, 1998

Chemical investigation of the sponge *Spongia matamata* collected in Yap, Micronesia, has resulted in the isolation of six new spongian diterpenoids, **2**−**7**, along with the known compound, spongia-13(16),-14-dien-19-oic acid (**1**). The structures were determined by spectroscopic methods.

Spongian diterpenoids are a small family of tetracyclic diterpenoid compounds that have been isolated from marine sponges, a typical example being dihydroxyspongia-13(16),14-dien-2-one.[1] Spongian diterpenoids have also been isolated from nudibranchs,[2] which obtain them from their sponge diets and use them to deter predation. The members of the spongian family vary primarily in the extent and pattern of oxidation. Some of the metabolites have undergone oxidative cleavage of ring A to give lactones,[3,4] while other members of this group display further oxidation on rings B, C, or D.[5−7] Some of the spongians have displayed antiviral and cytotoxic activities.[4,8] In connection with our studies on biologically active compounds from marine invertebrates, we have isolated the known spongian **1**[9] and six new spongian diterpenes, **2**−**7**, from the sponge *Spongia matamata* de Laubenfels (order Dictyoceratida, family Spongiidae), collected at Yap Island. All of these diterpenes possess a carboxylic acid functionality at C-19 and either ring D lactones or other oxygenation in ring D.

Earlier,[10] we reported several new diterpene lactones from *S. matamata*, but subsequent histological work has indicated that this material is closer to *Spongia zimocca* Schmidt *sensu* de Laubenfels 1954, a species characterized by thicker, more abundant primary fibers, and a more irregular secondary skeleton. *S. zimocca sensu* de Laubenfels occurs in much shallower water and is common on intertidal reef flat environments in Micronesia. This species forms low undulating encrustations and is often silt covered. The sponge is very tough, and the interior is often bright rust colored from the deposition of ferrous oxide granules on the fibers.

Results and Discussion

The CH_2Cl_2-soluble portion of the combined MeOH and MeOH−CH_2Cl_2 extracts of *S. matamata* were toxic to brine shrimp at 5 ppm. A flash Si gel chromatography of this extract afforded the major component, **1**, and fractions containing minor compounds. These fractions were further purified by reversed-phase HPLC to yield compounds **2**−**7**.

The identity of the compound **1** was established by comparison of its spectral properties with those reported.[9] Molecular formulas of all the new compounds were established from HRFABMS data (see Experimental Section),

Table 1. Pyridine-Induced Solvent NMR Shifts $\Delta\delta^a$ for Compounds 2−7

compound	H-18	H-20	H-17
2	0.10	0.19	−0.002
3	0.10	0.20	0.01
4	0.13	0.19	−0.08
5	0.13	0.35	0.30
6	0.11	0.24	0.05
7	0.26	0.25	−0.07

[a] $\Delta\delta = \delta_{\text{pyridine}-d_5} - \delta_{CDCl_3}$ (ppm).

and they were consistent with ^{1}H and ^{13}C NMR data. Comparison of the ^{1}H and ^{13}C NMR data of **2**−**7** with those of **1** revealed that these compounds all belonged to the same class, and all had identically substituted rings A and B. Confirmation of the A and B ring stereochemistry was obtained from pyridine-induced solvent NMR shifts (Table 1).[9,11] Compared with the chemical shifts taken in $CDCl_3$, the ^{1}H signals for H-20 and H-18 in each of the new compounds shifted downfield dramatically, while the H-17 signals (except for the signal in **5**) shifted little. This confirmed that all these metabolites share a common A/B ring structure of the spongian diterpene skeleton, with C-19 being oxidized to a carboxylic acid. Hence, the structural differences were confined to rings C and D.

The molecular formula of compound **2**, $C_{21}H_{30}O_5$, indicated seven degrees of unsaturation. Besides the signals for three tertiary methyl groups and a carboxyl group (δ 182.25), compound **2** showed in its NMR spectra signals for an additional carbonyl at δ 169.52, a tetrasubstituted double bond (δ 156.67 and 139.30), a methoxy group (δ 3.51), and an acetal moiety (δ 102). IR absorption at 1737 cm^{-1}, UV absorption at 220 nm, and the low field shift of one of the double-bond carbons were all consistent with the presence of an α,β-unsaturated γ-lactone. This was confirmed by HMBC correlations between signals for the acetal proton (H-16) and the carbonyl carbon, the δ 139.3 resonance, and the OMe. The H-17 signal was also correlated (HMBC) with the δ 139.3 signal, and, hence, the regiochemistry of the lactone was confirmed as shown in **2**. Both H-12 allylic proton signals (δ 2.08 and 2.44) showed HMBC correlations to C-13 and C-14. The well-resolved signal at δ 2.44 was assigned to H-12β (equatorial) by virtue of its coupling pattern (dd, J = 18.5, 5.0 Hz). Therefore, the signal at δ 2.08 (overlapped with other signals) must be H-12α. In the NOESY experiment, the signal of H-16 showed a cross-peak with the signal for H-12α; hence, H-16 is α-oriented.

Compound **3** has the same molecular formula as **2**, and the ^{13}C NMR data for the two compounds were nearly

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10.1021/np9803981 CCC: $18.00
Published on Web 12/22/1998

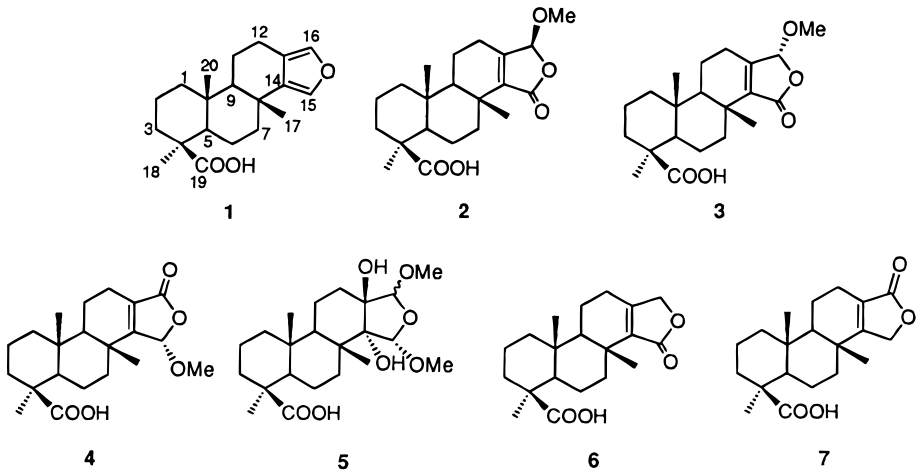

Table 2. ^{13}C NMR Data for 1−7 ($CDCl_3$)

position	**1**	**2**[a]	**3**[b]	**4**[b]	**5**[b]	**6**[b]	**7**[b]
1	37.7	40.03 t	39.92 t	39.90 t	40.05 t	39.98 t	39.71 t
2[c]	18.3	17.16 t	16.99 t	17.18 t	17.97 t	17.23 t	16.93 t
3	41.0	38.87 t	37.79 t	37.66 t	37.63 t	37.73 t	37.75 t
4	43.8	43.65 s	43.68 s	43.70 s	43.66 s	43.72 s	43.34 s
5	55.5	57.05 d	56.95 d	56.90 d	56.08 d	57.09 d	56.68 d
6[c]	20.7	18.36 t	18.90 t	18.87 t	18.90 t	18.88 t	18.68 t
7	40.1	35.67 t	36.16 t	36.29 t	35.01 t	35.92 t	37.27 t
8	34.1	35.16 s	35.19 s	37.50 s	40.09 s	35.05 s	36.70 s
9	57.2	55.95 d	55.82 d	54.79 d	48.00 d	56.16 d	54.82 d
10	38.1	38.00 s	37.96 s	38.12 s	37.98 s	37.94 s	37.80 s
11[c]	18.9	18.91 t	19.37 t	19.32 t	19.35 t	19.34 t	19.34 t
12	20.1	24.28 t	24.56 t	21.50 t	29.72 t	25.46 t	21.22 t
13	119.7	156.67 s	156.23 s	127.90 s	78.01 s	158.97 s	122.95 s
14	137.3	139.30 s	139.24 s	165.89 s	80.81 s	135.57 s	171.64 s
15	134.9	169.52 s	169.10 s	101.85 d	102.76 d	172.38 s	68.46 t
16	136.7	102.00 d	102.25 d	171.51 s	112.03 d	70.57 t	175.27 s
17	25.8	20.95 q	20.76 q	22.56 q	17.18 q	20.75 q	21.30 q
18	28.8	28.72 q	28.72 q	28.75 q	28.81 q	28.70 q	28.55 q
19	184.8	182.25 s	183.05 s	183.64 s	183.99 s	184.07 s	180.05 s
20	13.8	13.99 q	13.96 q	14.03 q	14.04 q	13.91 q	13.79 t
MeO-15				56.72 q	56.46 q		
MeO-16		56.51 q	56.74 q		56.57 q		

[a] Multiplicities are consistent with HMQC data. [b] Multiplicities were assigned from DEPT experiments. [c] Chemical shifts for C-2, C-6, and C-11 are interchangeable.

identical (Table 2). Only slight differences could be seen in their ^1H NMR spectra. HMBC data for the two compounds were also essentially the same. These findings led to the conclusion that compound **3** has the same gross structure as compound **2**. Because the stereochemistry of rings A and B was confirmed for both compounds by pyridine-induced solvent shifts (Table 1), the difference between **2** and **3** must be due to the configuration of the acetal chiral center. Therefore, the methoxy group in **3** was assigned the α orientation. The signals for the two allylic protons at C-12 overlapped in all solvents used (pyridine-d_5, C_6H_6-d_6, and $CDCl_3$). Hence, the stereochemistry at C-16 could not be resolved by NOE.

Compound **4** also has the same molecular formula as compounds **2** and **3** and showed UV absorption at 222 nm like **2** and **3**, thus indicating the presence of the α,β-unsaturated γ-lactone. The NMR signal for H-17 correlated in the HMBC experiment with the double-bond carbon signal at δ 165.89 (C-14). This indicated the carbonyl (δ 171.51) must be at C-16, forming a five-membered lactone with the acetal functionality (δ 5.70 and 101.85). This acetal structure was confirmed by the HMBC correlation between the methoxy signal (δ 3.52) and the acetal carbon signal at δ 101.85. Irradiation of the H-17 signal caused an NOE enhancement of the acetal proton signal (H-15); therefore, the methoxy is assigned the α configuration.

The molecular formula of compound **5** was confirmed as $C_{22}H_{36}O_7$ by HRFABMS. Besides the signals for a carboxylic acid and three methyls (H-17, H-18, and H-20), compound **5** showed in its NMR spectra signals for two methoxy groups (δ 3.42, 3.46, each 3H, s), two acetal partial structures (δ 4.68, 4.86 and δ 102.76, 112.03), and two tertiary oxygenated carbons (δ 78.01, 80.81). Both methoxy groups were shown to be part of the acetal structures, as each methoxy signal showed HMBC correlation to a different acetal carbon signal. Hence, two tertiary hydroxyl groups were postulated to account for the two tertiary oxygenated carbons. Because the structure for rings A and B could be confirmed by comparison of spectroscopic data with **1**−**4**, the two acetal functionalities must be located on the D ring, and the two tertiary hydroxyls must be located on C-13 and C-14. The presence of this D ring was evident from the HMBC correlations of H-15/C-16 (δ 4.68/112.03) and H-16/C-15 (δ 4.86/102.76). The HMBC experiment showed the correlation from H-17 to the tertiary carbon signal at δ 80.81 (C-14) as well. A NOESY experiment showed a cross-peak between the H-17 and the H-15 signals, indicating that the methoxy group at C-15 is α-oriented; therefore, the hydroxy group at C-14 is also α-oriented. The ^1H NMR spectrum of **5** taken in pyridine-d_5 showed a sharp downfield shift for the H-17 signal (Δδ = 0.29 ppm) compared with the signal when taken in

$CDCl_3$. This deshielding effect proved that the hydroxy group at C-13 is β-oriented, forming an 1,3-diaxial relationship with the methyl (C-17). The configuration of C-16 could not be resolved.

Compounds **6** and **7** have the same molecular formula, $C_{20}H_{28}O_4$, and the ^{13}C NMR data for carbons 1−12 and 17−20 for each corresponded closely to those of **1**−**5**, thus confirming the presence of the common A/B ring structure along with carbons 11 and 12 of ring C. The remaining four carbons of the formula were assigned to α,β-unsaturated γ-lactone structures as in **2**−**4** to satisfy the carbon NMR chemical shifts (Table 2), the UV absorption at ca. 220 nm, and IR absorptions at 1732−1740 cm^{-1}. In the HMBC experiments, both compounds showed cross-peaks between the H-17 and C-14 signals. The much lower field position of C-14 in **7** confirmed that this carbon is the β-carbon of the unsaturated γ-lactone system, and this established the regiochemistry of ring D in **7**. The opposite regiochemistry was, therefore, assigned to **6**.

Compounds **2**−**7** all differ from **1** by various modifications of the furan ring, for example, CH_3OH or H_2O addition and oxidation. Hence, they may be artifacts from reaction during two years' storage in methanol. However, in our recent work on the metabolites of *S. zimocca* (incorrectly identified as *S. matamata*) also collected in Yap in 1995 and stored under identical conditions, we did not detect similar ring-modified products among the five spongian furanoditerpenoids isolated. Hence, we consider that **2**−**7** are natural products, while realizing they might be artifacts.

The brine shrimp lethality test was carried out for the purified compounds **1** and **3**−**7**. The new compounds **3**−**7** were inactive, and compound **1** showed mild toxicity, with an LC_{50} value between 10 and 100 μg/mL.

Experimental Section

General Experimental Procedures. IR spectra were measured on a Bio-Rad FT Win-IR instrument (film). UV spectra were obtained on a Hewlett−Packard 8452A diode array spectrometer. NMR spectra were measured on a Varian VXR-500 instrument at 500 MHz (^1H) and 125 MHz (^{13}C), except for the HMBC experiment, which was performed on a Varian INOVA-600 spectrometer. FABMS were obtained on a VG ZAB E instrument and optical rotations on a Rudolph Autopol III Automatic Polarimeter. Preparative HPLC was performed using a Phenomenex C_{18} column (250 × 10 mm) with a refractive index detector. Flash chromatography was carried out on Si gel 60-H (230−400 mesh).

Animal Material. The sponge was collected from Goofnuw Channel, Yap Island, Federated States of Micronesia, on August 5, 1995, from a depth of 10 m. It consists of a hemispherical mass composed of spherical lobes, each with an apical oscule. The color in life is dark brownish black with a beige interior, and the texture is highly compressible and springy. The sponge is closely comparable to *S. matamata* de Laubenfels 1954. A specimen has been deposited in the Natural History Museum (BMNH 1998.6.30.1), and a voucher is maintained in the Department of Chemistry, University of Oklahoma (16-YA-95).

Extraction and Isolation. Sponges were frozen for shipment to Oklahoma and then stored in MeOH at 5 °C until workup. The material (wet wt 165 g) was extracted twice with MeOH and twice with CH_2Cl_2−MeOH (1:1). The extracts were concentrated and combined to give a residue that was dissolved in 300 mL of 10% aqueous MeOH. The solution was partitioned against hexane (3 × 300 mL), and the resulting aqueous solution was diluted to 30% H_2O in MeOH and partitioned against CH_2Cl_2 (3 × 300 mL). The aqueous MeOH phase was concentrated in vacuo, and the aqueous concentrate was extracted with *n*-BuOH (3 × 120 mL). Only the residue from the CH_2Cl_2 extract (2.9 g) showed brine shrimp lethality, and this was, therefore, fractionated on an open Si gel column using increasing amounts of EtOAc in hexane as eluent. The first fraction (eluted by hexane−EtOAc 5:1) was evaporated and gave 1.3 g pure compound **1**. The fourth fraction (hexane−EtOAc 2:1 → 1:1) contained mixtures of minor components (87.5 mg) and was further purified by reversed-phase HPLC using either MeOH−H_2O or MeCN−H_2O mixtures as eluents to furnish isolated new compounds **2** (1.9 mg), **3** (1.2 mg), **4** (3.6 mg), **5** (9.5 mg), **6** (9.9 mg), and **7** (8.7 mg).

16β-Methoxy-15-oxospongi-13-en-19-oic acid (2): white powder; $[\alpha]_D$ +62.5° [*c* 0.16, $CHCl_3$−MeOH (1:1)]; IR (film) ν_{max} 3500−3100 (br, OH), 1737, 1704, 1692 cm^{-1}; UV (MeOH) λ_{max} 220 nm (ϵ 3500); ^1H NMR ($CDCl_3$) δ 5.46 (1H, s, H-16), 3.51 (3H, s, MeO-16), 2.64 (1H, dt, J = 13.5, 3.0 Hz, H-7_{eq}), 2.44 (1H, dd, J = 18.5, 5.0 Hz, H-12_{eq}), 1.23 (3H, s, H-18), 1.17 (3H, s, H-17), 0.81 (3H, s, H-20); ^{13}C NMR data, see Table 2; FABMS *m/z* 363 $[M + H]^+$, 385 $[M + Na]^+$; HRFABMS *m/z* 363.2176 $[M + H]^+$, calcd for $C_{21}H_{31}O_5$, 363.2171.

16α-Methoxy-15-oxospongi-13-en-19-oic acid (3): white powder; $[\alpha]_D$ −92.6° [*c* 0.108, $CHCl_3$−MeOH (1: 1)]; IR (film) ν_{max} 3500−3200 (br, OH), 1735, 1716, 1691 cm^{-1}; UV (MeOH) λ_{max} 222 nm; ^1H NMR ($CDCl_3$) δ 5.45 (1H, s, H-16), 3.52 (3H, s, MeO-16), 2.60 (1H, dt, J = 12.5, 4.0 Hz, H-7_{eq}), 2.29−2.19 (2H, m, H-12), 2.13 (1H, br d, J = 13.5 Hz, H-3_{eq}), 1.78 (1H, br d, J = 12.5 Hz, H-1_{eq}), 1.24 (1H, td, J = 12.5, 3.0 Hz, H-7_{ax}), 1.13 (1H, dd, J = 13.0, 3.0 Hz, H-5), 1.10 (1H, br d, J = 11.0 Hz, H-9), 1.00 (1H, td, J = 13.5, 4.0 Hz, H-3_{ax}), 0.87 (1H, td, J = 12.5, 4.0 Hz, H-1_{ax}), 1.22 (3H, s, H-18), 1.15 (3H, s, H-17), 0.80 (3H, s, H-20); ^{13}C NMR data, see Table 2; FABMS *m/z* 363 $[M + H]^+$; HRFABMS *m/z* 363.2156 $[M + H]^+$, calcd for $C_{21}H_{31}O_5$, 363.2171.

15α-Methoxy-16-oxospongi-13-en-19-oic acid (4): white powder; $[\alpha]_D$ +45° [*c* 0.225, $CHCl_3$−MeOH (1: 1)]; IR (film) ν_{max} 3200−3050 (br, OH), 1768, 1692, 1681 cm^{-1}; UV (MeOH) λ_{max} 222 nm; ^1H NMR ($CDCl_3$) δ 5.70 (1H, s, H-15), 3.52 (3H, s, MeO-15), 2.37 (1H, d, J = 17.5 Hz, H-12_{eq}), 1.23 (3H, s, H-18), 1.19 (1H, d, J = 12.0 Hz, H-9), 1.15 (3H, s, H-17), 1.12 (1H, dd, J = 12.5, 3.0 Hz, H-5), 1.01 (1H, td, J = 13.5, 4.0 Hz, H-3_{ax}), 0.90 (1H, td, J = 13.0, 4.0 Hz, H-1_{ax}), 0.81 (3H, s, H-20); ^{13}C NMR data, see Table 2; FABMS *m/z* 363 $[M + H]^+$; HRFABMS *m/z* 363.2152 $[M + H]^+$, calcd for $C_{21}H_{31}O_5$, 363.2171.

13β,14α-Dihydroxy-15α,16ξ-dimethoxyspongian-19-oic acid (5): white powder; $[\alpha]_D$ +137.3° [*c* 0.383, $CHCl_3$−MeOH (1: 1)]; IR (film) ν_{max} 3580−3360 (br, OH), 1697 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.86 (1H, s, H-16), 4.68 (1H, s, H-15), 3.47 (3H, s, MeO-15), 3.42 (3H, s, MeO-16), 1.22 (3H, s, H-18), 1.03 (3H, s, H-17), 0.78 (3H, s, H-20); ^{13}C NMR data, see Table 2; FABMS *m/z* 435 $[M + Na]^+$, 413 $[M + H]^+$; HRFABMS *m/z* 413.2609 $[M + H]^+$, calcd for $C_{22}H_{37}O_7$, 413.2639; 435.2359 $[M + Na]^+$, calcd for $C_{22}H_{36}O_7Na$, 435.2359.

15-Oxospongi-13-en-19-oic acid (6): white crystals, mp 280−282 °C; $[\alpha]_D$ −289.8° [*c* 1.0, $CHCl_3$−MeOH (1: 1)]; IR (film) ν_{max} 3370−3110 (br, OH), 1732, 1717, 1699 cm^{-1}; UV (MeOH) λ_{max} 220 nm (ϵ 12 776); ^1H NMR ($CDCl_3$) δ 4.56 (1H, d, J = 13.5 Hz, H-16), 4.51 (1H, d, J = 13.5 Hz, H-16), 2.65 (1H, br d, J = 13.5 Hz, H-7_{eq}), 2.35 (1H, dd, J = 19.0, 5.5 Hz, H-12_{eq}), 1.22 (3H, s, H-18), 1.14 (3H, s, H-17), 1.15 (1H, dd, J = ∼ 15.0, 3.0 Hz, H-5, partially overlapped with H-17), 1.08 (1H, br d, J = 11.5 Hz, H-9), 0.99 (1H, td, J = 14.0, 4.0 Hz, H-3_{ax}), 0.88 (1H, td, J = 13.5, 3.0 Hz, H-1_{ax}), 0.80 (3H, s, H-20); ^{13}C NMR data, see Table 2; FABMS *m/z* 355 $[M + Na]^+$, 333 $[M + H]^+$; HRFABMS *m/z* 333.2066 $[M + H]^+$, calcd for $C_{20}H_{29}O_4$, 333.2066.

16-Oxospongi-13-en-19-oic acid (7): white crystals, mp 273−275° C $[\alpha]_D$ −378.8° [*c* 0.625, $CHCl_3$−MeOH (1: 1)]; IR (film) ν_{max} 3337−3140 (br, OH), 1740, 1693, 1685 cm^{-1}; UV (MeOH) λ_{max} 220 nm (ϵ 13 240); ^1H NMR ($CDCl_3$) δ 4.65 (1H, d, J = 17.0 Hz, H-15), 4.55 (1H, d, J = 17.0 Hz, H-15), 1.07 (3H, s, H-18), 1.06 (3H, s, H-17), 1.04 (1H, br d, J = 10.5 Hz, H-5), 1.00 (1H, br d, J = 10.5 Hz, H-9), 0.88 (1H, td, J = 13.0, 3.0 Hz, H-3_{ax}), 0.78 (1H, td, J = 13.0, 3.0 Hz, H-1_{ax}), 0.72 (3H,

s, H-20); ^{13}C NMR data, see Table 2; FABMS *m*/*z* 333 $[M + H]^+$; HRFABMS *m*/*z* 333.2061 $[M + H]^+$, calcd for $C_{20}H_{29}O_4$, 333.2066.

Acknowledgment. This work was supported by Department of Commerce, NOAA, Sea Grant Project NA66RG0172. We thank the Coral Reef Research Foundation for assistance in collection and the Government of Yap, Federated States of Micronesia for permission to collect specimens in their waters. We also gratefully acknowledge the National Science Foundation (BIR-9512269), the Oklahoma State Regents for Higher Education, the W.M. Keck Foundation, and Conoco, Inc. for funds to purchase the Oklahoma Statewide Shared 600 MHz NMR spectrometer.

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NP9803981