Notes

New Furanoterpenoids from the Sponge *Spongia officinalis*

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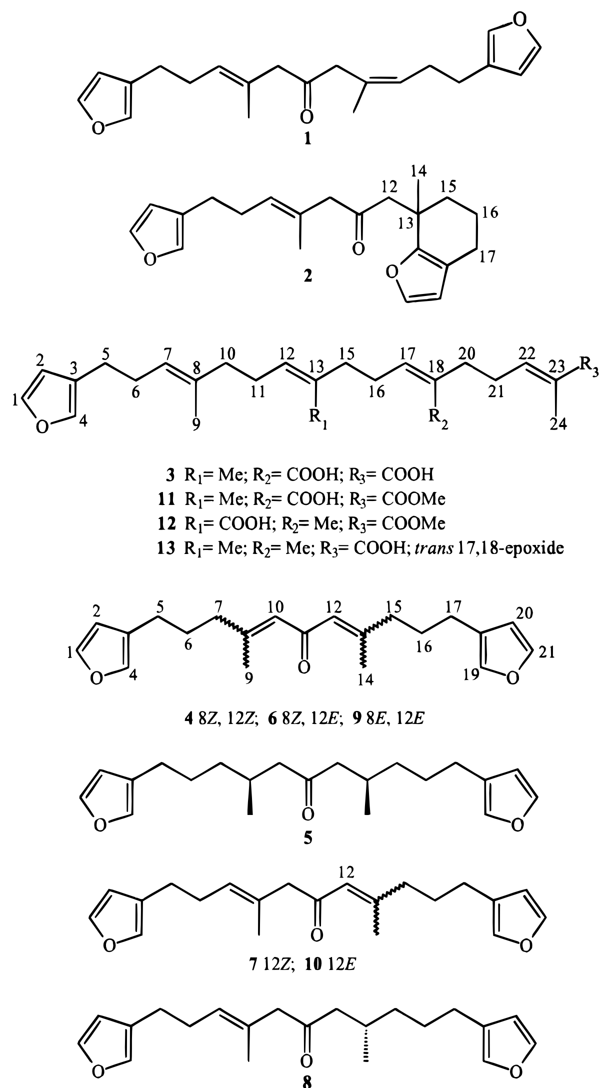
The sponge *Spongia officinalis* from La Caleta, Cádiz, Spain, contains the new C-21 furanoterpenes furospongin-5 (**1**) and cyclofurospongin-2 (**2**) and the new furanosesterterpene demethylfurospongin-4 (**3**), in addition to the known terpenoids **4**–**11**. The structures of compounds **1**–**3** were elucidated by interpretation of spectral data and chemical interconversions. Furospongin-5 (**1**) was weakly cytotoxic against the P-388 cell line (ED_{50} = 5 μg/mL).

It is well known that sponges of the order Dictyoceratida are the source of a group of terpenoids characterized by possessing 21 carbon atoms and two terminal furan rings. These C-21 furanoterpenoids have been isolated from several genera of the Spongiidae and Thorectidae families[1–12] and, occasionally, from nudibranchs that prey on them.[13] Dictyoceratidae sponges of these two families and some of their predators have given rise, in addition, to linear furanosesterterpenes containing a single ring, an otherwise uncommon group of terpenoids.[2,14–17]

As a part of our research project aimed at the discovery of new bioactive compounds from marine organisms of the southern coast of Spain, we obtained a specimen of the sponge *Spongia officinalis* Linné (Spongiidae) collected in the infralitoral zone of La Caleta, Cádiz, Spain. *S. officinalis* had been extensively studied, affording furanosesterterpenes and C-21 furanoterpenes among its constituents.[1–3,10,12] Our specimen contained two new C-21 furanoterpenes (**1**, **2**), and a new linear furanoserterterpene (**3**), together with the known C-21 furanoterpenes **4**–**10**, and the furanosesterterpene **11**.

The specimen of *S. officinalis* (62.2 g dry wt) was collected by hand and immediately frozen. The less polar material of an Me_2CO extract was chromatographed on Si gel. Final purification of selected fractions using HPLC allowed isolation of the following compounds in order of increasing polarity: isomer 1 of furospongin-2 (**4**, 0.003% dry wt), cyclofurospongin-2 (**2**, 0.005% dry wt), tetrahydrofurospongin-2 (**5**, 0.016% dry wt), isomer 2 of furospongin-2 (**6**, 0.015% dry wt), isofurospongin-2 (**7**, 0.015% dry wt), dihydrofurospongin-2 (**8**, 0.018% dry wt), furospongin-5 (**1**, 0.003% dry wt), isomer 3 of furospongin-2 (**9**, 0.040% dry wt), furospongin-2 (**10**, 0.029% dry wt), furospongin-4 (**11**, 0.003% dry wt), and demethylfurospongin-4 (**3**, 0.048% dry wt). Compounds **4**,[18] **5**,[3] **6**,[18] **7**,[3] **8**,[3,6] **9**,[18] **10**,[3,6] and **11**[2] were identified by comparison of ^{1}H-NMR, UV, IR, and MS spectroscopic data with those reported in the literature. ^{13}C-NMR data of compounds **5**, **7**, and **11** had not been previously reported and are listed in Table 1. It is worth noting that significant differences were observed between the ^{13}C-NMR data of compounds **4**, **6**, and **9** (Table 1) with respect to those previously reported.[18]



Furospongin-5 (**1**) was isolated as a colorless oil. The molecular formula, $C_{21}H_{26}O_3$, was obtained from the

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Table 1. ^{13}C-NMR Data of Compounds **1**–**11**[a]

C no.	**1**	**2**	**3**[b]	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
1	142.7	142.6	142.5	142.6	142.6	142.6	142.6	142.7	142.8	142.6	142.5
2	111.0	111.0	111.1	111.0	110.9	111.0	111.0[c]	110.9	110.8	111.0	111.1
3	124.6	124.7	125.0	125.0	125.0	125.0	124.7[d]	124.6	124.5	124.7	125.0
4	138.9	138.9	138.8	138.9	138.7	138.9[c]	138.9	138.8[c]	138.9	138.9[c]	138.8
5	24.7	24.7	25.0	24.9	24.8	24.9	24.7	24.7[d]	24.3	24.7	25.0
6	28.9[c]	28.5	28.4	28.5	27.4	28.5	28.5	28.5	27.8	28.5	28.4[c]
7	129.0	128.8	123.8	*33.2*	36.5	*33.3*	128.7	128.9	40.7	128.6	123.8
8	129.7	129.8	135.7	*157.5*	28.9	*157.9*[d]	130.4	129.7	*157.5*	130.4	135.7
9	16.4	16.4	16.0[c]	*25.3*	19.8	*25.4*	16.5	16.5	19.1	19.2	16.1[d]
10	53.1	55.1	39.6	126.7	50.8	126.6	55.4	54.5	125.9	55.4	39.6
11	206.8	208.5	26.6	*190.7*	210.7	*191.2*	198.8	209.4	*191.6*	199.4	26.6
12	45.4	50.5	125.0	126.7	50.8	125.9	123.1	49.0	125.9	122.5	125.1
13	129.2	35.0	134.0	*157.5*	28.9	*157.3*[d]	159.5	28.8	*157.5*	158.7	134.0
14	24.1	26.0	15.8[c]	*25.3*	19.8	19.1	25.5	19.8	19.1	16.5	15.8[d]
15	128.2	36.1	38.9	*33.2*	36.5	40.7	33.6	36.4	40.7	40.6	39.0
16	28.5[c]	20.3	28.0	28.5	27.4	27.9	28.5	27.4	27.8	27.7	28.2[c]
17	24.9	22.4	144.5	24.9	24.8	24.3	25.0	24.8[d]	24.3	24.2	146.1[e]
18	124.6	116.5	131.3[d]	125.0	125.0	124.5	124.6[d]	125.0	124.5	124.4	129.8[f]
19	138.9	155.1	174.1[e]	138.9	138.7	138.8[c]	138.9	138.7[c]	138.9	138.8[c]	171.0[g]
20	111.0	110.4	33.2	111.0	110.9	110.8	110.9[c]	110.9	110.8	110.8	33.5
21	142.7	140.3	30.5	142.6	142.6	142.8	142.6	142.7	142.8	142.9	28.5[c]
22			143.6								141.1[e]
23			128.1[d]								128.2[f]
24			11.7								12.4
25			173.5[e]								168.6[g]
OMe											51.7

[a] Assignments were aided by APT experiments. [b] Assignments were aided by a HETCOR experiment. [c–g] Values with the same superscript in the same column may be interchanged. Italic values indicate rectifications of previous data.[18]

high-resolution mass measurement. In general, the NMR data of **1** resembled those reported[3,6] for furospongin-2 (**10**). The IR spectrum contained a nonconjugated carbonyl band at 1718 cm^{-1}, while the ^{13}C-NMR spectrum (Table 1) showed the carbonyl signal at δ 206.8 (s). The ^{13}C-NMR signals at δ 142.7 (d), 138.9 (d), 124.6 (s), and 111.0 (d) were assigned to β-substituted furan carbons, and the signals at δ 129.7 (s), 129.2 (s), 129.0 (d), and 128.2 (d) indicated the presence of two trisubstituted olefinic bonds. The ^{1}H-NMR signals at δ 3.10 (2H, br s) and 3.04 (2H, br s) were assigned to the α,α' methylene groups of a β,γ-β',γ'-diunsaturated ketone moiety. Because the ^{13}C NMR contained the vinylic methyl signals at δ 24.1 (q) and 16.4 (q), the stereochemistry of the double bonds was defined as *Z* and *E*, respectively,[19] and therefore structure **1** was proposed for furospongin-5.

A series of NOE difference spectroscopy experiments provided confirmation of the proposed structural assignments. Irradiation of the H-7 signal at δ 5.28 caused enhancement on the H-10 methylene proton signal at δ 3.04, whereas irradiation of the H-15 vinylic proton signal at δ 5.40 enhanced the H-14 methyl proton signal at δ 1.69, allowing unambiguous assignment of the H-7, H-9, H-10, H-12, H-14, and H-15 proton signals, and providing confirmation of the stereochemistry of the double bonds.

Cyclofurospongin-2 (**2**) was isolated as an optically active oil. The molecular formula, $C_{21}H_{26}O_3$, indicated that **2** was an isomer of furospongin-5 (**1**). The IR, ^{1}H-NMR and ^{13}C-NMR spectra clearly indicated that compound **2** possessed an (*E*)- furylmethylpentenyl side chain linked to a central ketone as its isomer **1**.

In addition the ^{13}C-NMR (Table 1) signals at δ 155.1 (s), 140.3 (d), 116.5 (s), and 110.4 (d) together with the ^{1}H-NMR signals at δ 7.22 (1H, d, $J = 2.0$ Hz) and 6.16 (1H, d, $J = 2.0$ Hz) indicated the presence of an α,β-disubstituted furan ring. This ring, along with the fragment mentioned above, accounted for eight of the nine degrees of unsaturation of the molecule. A singlet at δ 1.32 (3H, s) in the ^{1}H-NMR spectrum and the ^{13}C-NMR signal at δ 26.0 (q) were assigned to a methyl on a quaternary carbon of a cyclohexene ring fused to the disubstituted furan ring,[9,20,21] accounting for the remaining unsaturation of the molecule. The sp^3 carbon signals of the six-membered ring appeared at δ 36.1 (t), 35.0 (s), 22.4 (t), and 20.3 (t), indicating the presence of three methylene groups. Finally, the ^{1}H-NMR signals at δ 2.69 (1H, d, $J = 14.7$ Hz) and 2.65 (1H, d, $J = 14.7$ Hz) were assigned to the protons of an isolated methylene that linked the ketone to the methyltetrahydrobenzofuran moiety. These spectral features were in agreement with the proposed structure for cyclofurospongin-2 (**2**).

It has been demonstrated that the cyclic furospongins can be obtained from acyclic precursors by acid-catalyzed cyclization.[9] Acid treatment of furospongin-2 (**10**) yielded ($\pm$)-cyclofurospongin-2 as expected. Because the natural product isolated from *S. officinalis* is optically active, it seems unlikely that compound **2** arose from an acyclic precursor such as furospongin-2 (**10**) through an acid-catalyzed cyclization during the isolation process.

The major and most polar component isolated from *S. officinalis*, demethylfurospongin-4 (**3**), had the molecular formula $C_{25}H_{34}O_5$. The IR spectrum contained bands at 3100–2600 cm^{-1} and 1692 cm^{-1} while the ^{13}C-NMR spectrum contained two singlets (Table 1) at δ 174.1 and 173.5 assigned to the carbons of two α,β-unsaturated carboxyl groups. The ^{13}C-NMR signals at δ 142.5 (d), 138.8 (d), 125.0 (s), and 111.1 (d) indicated the presence of a β-substituted furan, and the signals at δ 144.5 (d), 143.6 (d), 135.7 (s), 134.0 (s), 131.3 (s), 128.1 (s), 125.0 (d), and 123.8 (d) were assigned to four trisusbtituted olefinic bonds. The olefinic proton triplets in the ^{1}H-NMR spectrum at δ 6.93, 6.00, 5.17, and 5.12 indicated that the double bonds were joined to four methylene groups and that, in addition, two of them

were conjugated with the carboxyl groups. Finally, the ^{1}H-NMR signals at δ 1.79 (3H, br s) and 1.59 (6H, br s) indicated that the three methyl groups present in the structure of **3** must be vinylic. These spectral features, together with a comparison with the data described for a mixture of the linear sesterterpenes furospongin-3 (**12**) and -4 (**11**),[2] clearly indicated that the dicarboxylic acid **3** was a demethyl derivative of one of these two isomers. Assignment of the olefinic carbon signals C-8 at δ 135.7 (s) and C-13 at δ 134.0 (s), made by comparison with the data described by Searle and Molinski[17] for the epoxyfuranosesterterpene carboxylic acid **13**, was consistent with a similar substitution pattern at C-13 in **3** as that of **13**. It was concluded that the second carboxylic group was located at C-18 and that compound **3** was therefore the demethyl derivative of furospongin-4 (**11**).

The new compounds isolated from *Spongia officinalis* were tested against P-388 mouse lymphoma, A-549 human lung carcinoma, HT-29 human colon carcinoma, and MEL-28 human melanoma to detect in vitro cytotoxicity. In general, the new compounds **1**−**3** exhibited low cytotoxicity with ED_{50} values over 10 μg/mL in all cases with the exception of furospongin-5 (**1**), which showed a mild cytotoxicity against the P-388 cell line (ED_{50} = 5 μg/mL).

Experimental Section

General Experimental Procedures. IR spectra were recorded on a Perkin-Elmer 881 spectrophotometer. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian 400 at 400 MHz and 100 MHz, respectively, using $CDCl_3$ as solvent. The resonances of residual $CHCl_3$ at δ_H 7.26 and δ_C 77.0 were used as internal reference for ^{1}H-NMR and ^{13}C-NMR spectra, respectively. An asterisk means interchangeable signals. Mass spectra were measured on a VG 12250 or on a Kratos MS 80RFA spectrometer. In HPLC separations LiChrosorb Si-60 was used in normal-phase mode using a differential refractometer. All solvents were distilled from glass prior to use.

Collection, Extraction, and Isolation Procedures. The specimen of *S. officinalis* (62.2 g dry wt) was collected by hand in La Caleta, Cádiz, Spain, and immediately frozen. A voucher is deposited at Departamento de Biología Animal, Biología Vegetal y Ecología, Universidad de Cádiz. The material was chopped into small pieces and extracted with Me_2CO at room temperature. The solution was filtered, and the solvent was evaporated under reduced pressure to obtain a residue that was partitioned between H_2O and Et_2O. The Et_2O solution was dried over anhydrous Na_2SO_4 and the solvent removed to afford a dark brown oil (1.8 g). The organic extract was subjected to SiO_2 column separation eluting with mixtures of increasing polarity from hexane to Et_2O. Selected fractions were further separated using HPLC as follows. Fractions eluted with hexane−Et_2O (97:3) afforded, after purification by HPLC (LiChrosorb 10 μm, 10 mm × 25 cm; hexane−EtOAc, 99:1), compound **4** (2 mg, 0.003% dry wt). Fractions eluted with hexane−Et_2O (93:7) were grouped in four fractions A, B, C, and D according to TLC analyses. Fraction A was further separated by HPLC (LiChrosorb 10 μm, 10 mm × 25 cm; hexane−EtOAc, 97:3) to afford compounds **2** (3 mg, 0.005% dry wt) and **5** (10 mg, 0.016% dry wt). Fraction B was further separated by HPLC (LiChrosorb 10 μm, 10 mm × 25 cm; hexane−EtOAc, 97:3) to afford compounds **6** (9 mg, 0.015% dry wt), **7** (9 mg, 0.015% dry wt), and **8** (11 mg, 0.018% dry wt). Fraction C was further separated by HPLC (LiChrosorb 10 μm, 10 mm × 25 cm; hexane−EtOAc, 96:4) to afford compound **1** (2 mg, 0.003% dry wt). Fraction D afforded compounds **9** (25 mg, 0.040% dry wt) and **10** (18 mg, 0.029% dry wt) upon HPLC separation (LiChrosorb 10 μm, 10 mm × 25 cm; hexan−EtOAc, 95:5). A more polar fraction of the general chromatography eluted with hexane−Et_2O (1:1) afforded, after purification by HPLC (LiChrosorb 10 μm, 10 mm × 25 cm; $CHCl_3$−MeOH, 99:1) compound **11** (2 mg, 0.003% dry wt). Finally, fractions eluted with hexane−Et_2O (3:7) were further separated using HPLC (LiChrosorb 10 μm, 10 mm × 25 cm; $CHCl_3$−MeOH, 98:2) to afford compound **3** (30 mg, 0.048% dry wt).

Furospongin-5 (1): colorless oil; UV (MeOH) λ_{max} (ϵ) 204 (11543) nm; IR (dry film) ν_{max} 1718 (C=O), 1671 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34 (2H, dd, J = 1.7, 1.6 Hz, H-1 and H-21), 7.21 (2H, dd, J = 1.6, 0.8 Hz, H-4 and H-19), 6.27 (1H, br s, H-2)*, 6.26 (1H, br s, H-20)*, 5.40 (1H, br t, J = 6.9 Hz, H-15), 5.28 (1H, tq, J = 7.0, 1.2 Hz, H-7), 3.10 (2H, br s, H-12), 3.04 (2H, br s, H-10), 2.47 (2H, t, J = 7.5 Hz, H-5), 2.46 (2H, t, J = 7.5 Hz, H-17), 2.29 (2H, td, J = 7.5, 7.0 Hz, H-6), 2.23 (2H, td, J = 7.5, 6.9 Hz, H-16), 1.69 (3H, d, J = 1.2 Hz, H-14), 1.60 (3H, d, J = 1.2 Hz, H-9); ^{13}C NMR ($CDCl_3$, 100 MHz), see Table 1; EIMS (70 eV) m/z [M$^+$] 326 (1), 245 (2), 177 (11), 149 (29), 135 (48), 134 (38), 95 (16), 81 (100), 67 (5); HREIMS m/z 326.1900, calcd for $C_{21}H_{26}O_3$ 326.1882.

Cyclofurospongin-2 (2): colorless oil; $[\alpha]^{25}_D$ −6.0 (c 0.1, $CHCl_3$); UV (MeOH) λ_{max} (ϵ) 207 (18452) nm; IR (dry film) ν_{max} 1720 (C=O), 1670 (C=C) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.33 (1H, dd, J = 1.7, 1.6 Hz, H-1), 7.22 (1H, d, J = 2.0 Hz, H-21), 7.20 (1H, dd, J = 1.6, 0.9 Hz, H-4), 6.27 (1H, dd, J = 1.7, 0.9 Hz, H-2), 6.16 (1H, d, J = 2.0 Hz, H-20), 5.18 (1H, tq, J = 7.1, 1.2 Hz, H-7) 2.88 (1H, d, J = 15.2 Hz, H-10), 2.82 (1H, d, J = 15.2 Hz, H-10′), 2.69 (1H, d, J = 14.7 Hz, H-12), 2.65 (1H, d, J = 14.7 Hz, H-12′), 2.47 (2H, t, J = 7.5 Hz, H-5), 2.39 (2H, t, J = 6.0 Hz, H-17), 2.27 (2H, td, J = 7.5, 7.1 Hz, H-6), 1.89 (2H, m, H-15), 1.72 (2H, m, H-16), 1.55 (3H, br s, H-9), 1.32 (3H, s, H-14); ^{13}C NMR ($CDCl_3$, 100 MHz), see Table 1; EIMS (70 eV) m/z [M$^+$] 326 (3), 136 (23), 135 (100), 134 (29), 81 (13); HREIMS m/z 326.1885, calcd for $C_{21}H_{26}O_3$ 326.1882.

Demethylfurospongin-4 (3): colorless oil; UV (MeOH) λ_{max} (ϵ) 207 (13174) nm; IR (dry film) ν_{max} 3100−2600 (OH), 1692 (C=O), 1649 (C=C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.33 (1H, dd, J = 1.7, 1.6 Hz, H-1), 7.20 (1H, dd, J = 1.6, 0.9 Hz, H-4), 6.93 (1H, br t, J = 7.8 Hz, H-22), 6.27 (1H, dd, J = 1.9, 0.9 Hz, H-2), 6.00 (1H, br t, J = 7.3 Hz, H-17), 5.17 (1H, tq, J = 7.0, 1.2 Hz, H-7), 5.12 (1H, tq, J = 6.9, 1.1 Hz, H-12), 2.53 (2H, td, J = 7.3, 7.3 Hz, H-16), 2.50 (2H, t, J = 7.0 Hz, H-20), 2.45 (2H, br t, J = 7.5 Hz, H-5), 2.36 (2H, dt, J = 7.8, 7.0 Hz, H-21), 2.24 (2H, td, J = 7.5, 7.0 Hz, H-6), 2.08 (2H, td, J = 7.3, 6.9 Hz, H-11), 2.07 (2H, t, J = 7.3 Hz, H-15), 1.99 (2H, br t, J = 7.3 Hz, H-10), 1.79 (3H, br s, H-24), 1.59 (6H, br s, H-9 and H-14); ^{13}C NMR ($CDCl_3$, 100 MHz), see Table 1; EIMS (70 eV) m/z [M$^+$] 414 (1),

399 (2), 315 (5), 217 (19), 203 (12), 201 (25), 135 (47), 95 (16), 93 (57), 81 (100), 67 (16); HREIMS *m/z* 414.2421, calcd for $C_{25}H_{34}O_5$ 414.2406.

Cyclization of Furospongin-2 (10) to (±)-Cyclofurospongin-2. To furospongin-2 (**10**, 5 mg) in dioxane (0.4 mL) was added 60 μL of an aqueous solution of $HClO_4$ (0.5 M), and the resulting solution was maintained at 25 °C for 12 h. The reaction mixture was neutralized with NaOH (0.1 M) and extracted with Et_2O. The organic layer was washed with H_2O, dried over anhydrous Na_2SO_4, and the solvent evaporated to obtain an oil (3 mg). The crude reaction was purified on HPLC (LiChrosorb 10 μ, 10 mm × 25 cm; hexane−EtOAc, 96:4) to afford the optically inactive (±)-cyclofurospongin-2 (2.1 mg, 31% yield).

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