Isomeric Furanosesquiterpenes from the Portuguese Marine Sponge *Fasciospongia* sp.

Helena Gaspar,*[,†,‡] Susana Santos,[‡] Marianna Carbone,[§] Ana Sofia Rodrigues,[‡] Ana Isabel Rodrigues,[†] Maria J. Uriz,[⊥] Sónia Murta Savluchinske Feio,[†] Dominique Melck,[§] Madalena Humanes,[‡] and Margherita Gavagnin[§]

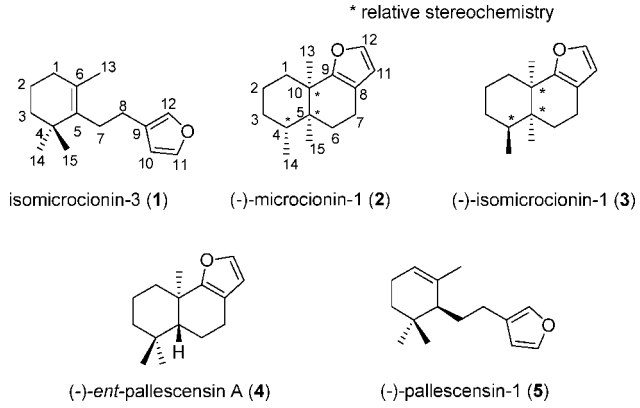
Instituto Nacional de Engenharia, Tecnologia e Inovação (INETI), Estrada do Paço do Lumiar, Edifício F, 1649-038 Lisboa, Portugal, Centro de Química e Bioquímica, DQB, Faculdade de Ciências da Universidade de Lisboa (FCUL), 1749-016 Lisboa, Portugal, Istituto di Chimica Biomolecolare, CNR, Via Campi Flegrei 34, 80078 Pozzuoli (Naples), Italy, and Centre d'Estudis Avançats de Blanes (CEAB-CSIC), Accés a la Cala St Francesc, 14, 17300 Blanes (Girona), Spain

Received June 11, 2008

This paper reports the chemical study of a sample of *Fasciospongia* sp. collected along the Atlantic Portuguese coast. Three new isomeric furanosesquiterpenes, isomicrocionin-3 (**1**), (−)-microcionin-1 (**2**), and (−)-isomicrocionin-1 (**3**), were isolated along with the known (−)-*ent*-pallescensin A (**4**) and (−)-pallescensin-1 (**5**) from the ethyl acetate-soluble portion of the methanolic extract. The structures of the new compounds were elucidated by extensive spectroscopic studies. (−)-Microcionin-1 (**2**) tested positive against several Gram-negative bacteria.

Marine benthic invertebrates, mainly sponges, have been proved to be a rich source of natural products with unique structures[1] and interesting biological properties.[1,2] Despite the large number of studies on secondary metabolites of benthic invertebrates from European littorals, there are very few chemical reports in the literature on organisms collected along the Portuguese coast.[3−6] In the course of our chemical investigation on marine benthic invertebrates from the Atlantic Ocean we examined the sponge *Fasciospongia* sp. (order Dictyoceratida, family Thorectidae) from Berlenga Island (Portugal). Sponges of this genus have been reported to contain macrolides (e.g., laulimalide),[7] sesterterpenes (e.g., cacospongionolide), [8,9] and sesquiterpenes (e.g., microcionins).[6,10]

Our study, which is the first chemical investigation of a *Fasciospongia* sponge from the Portuguese coast, led to the isolation of three new isomeric furanosesquiterpenes, isomicrocionin-3 (**1**), (−)-microcionin-1 (**2**), and (−)-isomicrocionin-1 (**3**), along with the known (−)-*ent*-pallescensin A (**4**) and (−)-pallescensin-1 (**5**).



The sponge *Fasciospongia* sp. was collected and extracted as described in the Experimental Section. The bioactive EtOAc extract (1.89 g) was fractionated by successive chromatographic steps using SiO_2 flash column chromatography, $AgNO_3-SiO_2$ open column chromatography, and HPLC to afford pure compounds **1**−**5**, with **2** being the main metabolite (0.032% of sponge dry weight).

A preliminary ^{1}H NMR analysis revealed that the isolated metabolites were furanosesquiterpenes with a bicyclic or a tricyclic skeleton, whereas MS analysis showed the same molecular peak for all molecules, thus indicating that compounds **1**−**5** were isomers.

Compounds **2**, **4**, and **5** were identified as (−)-microcionin-1,[6,10] (−)-*ent*-pallescensin A,[11−13] and (−)-pallescensin-1,[12,14,15] respectively.

This is the first occurrence of (−)-microcionin-1 (**2**), which showed opposite $[\alpha]_D$ value and CD curve with respect to its dextrorotatory enantiomer, already isolated from the marine sponge *Fasciospongia cavernosa* (erroneously reported as *Microciona toxystila*).[6,10,16] The absolute stereochemistry of **2** was however not defined.

ent-Pallescensin A (**4**), the absolute configuration of which has been established by stereospecific synthesis,[12] was first found in the Australian sponge *Dysidea* sp.[13] and further reported also from mollusks.[3,17]

Pallescensin-1 was previously isolated from *Dysidea pallescens*,[14] but as no optical activity data were reported in that study, it cannot be concluded if the (−)-enantiomer **5** that we found is the same as that already described.[14] The absolute stereochemistry of **5** has been assigned by comparing the $[\alpha]_D$ value with those reported in the literature[12] for the synthetic enantiomers.

The structures of the new compounds **1** and **3**, both having the molecular formula $C_{15}H_{22}O$, were determined by spectroscopic methods as described below. The NMR data of compound **1**, named isomicrocionin-3, were strongly reminiscent of those of the co-occurring (−)-pallescensin-1 (**5**), indicating the presence of a 4,4-dimethylcyclohexene ring and the terminal furan moiety as in **5**. In fact, the ^{1}H NMR spectrum of **1** contained signals attributed to two tertiary methyls [δ 1.02 (6H, s, H_3-14 and H_3-15)] and a vinyl methyl [δ 1.64 (3H, br s, H_3-13)] along with the typical ABX system [δ 7.36 (1H, br s, H-11), 7.24 (1H, br s, H-12), and 6.31 (1H, br s, H-10)] due to the protons of a β-substituted furan, as in (−)-pallescensin-1 (**5**). The main difference between the ^{1}H NMR spectra of compounds **1** and **5** was in the lack of the olefinic signal H-1 in the spectrum of **1**, according to the presence of a tetrasubstituted double bond. This was confirmed by analysis of the ^{13}C NMR spectrum of **1**, which contained two quaternary sp^2 carbons at δ 127.6 (C-6) and 136.9 (C-5) in addition to the one from the furan moiety at δ 125.7 (C-9). On the basis of these data, compound **1** was suggested to be the $\Delta^{1(5)}$ isomer of **5**. This hypothesis was supported by 2D-NMR experiments (^{1}H−^{1}H COSY, HSQC, and HMBC), which allowed the assignment of the structure as depicted in formula **1**, and of all carbon and proton resonances (Table 1).

* Author for correspondence. E-mail: helena.gaspar@ineti.pt. Phone: +351210924741. Fax: +35121716810.
† Instituto Nacional de Engenharia, Tecnologia e Inovação.
‡ Centro de Química e Bioquímica.
§ Istituto di Chimica Biomolecolare.
⊥ Centre d'Estudis Avançats de Blanes.

10.1021/np800346c CCC: $40.75
Published on Web 11/14/2008

Table 1. NMR Data of Isomicrocionin-3 (**1**) and Isomicrocionin-1 (**3**)

	isomicrocionin-3 (**1**)			isomicrocionin-1 (**3**)		
position	δ_C, mult.[b]	δ_H (J in Hz)[c]	HMBC	δ_C, mult.[b]	δ_H (J in Hz)[c]	HMBC
1	32.8, CH_2	1.93, m		37.7, CH_2	1.67, m	
2	19.5, CH_2	1.57, m	H_2-1	22.1, CH_2	1.51, m	
3	39.8, CH_2	1.44, m	H_3-15; H_3-14; H_2-1	30.6, CH_2	1.41, m; 1.26 m	H_3-14; H_2-2; H_2-1
4	35.0, qC		H_3-15; H_3-14; H_3-2	37.0, qC	1.74, m	H_3-15; H_3-14
5	136.9, qC		H_3-15; H_3-14; H_3-13; H_2-8; H_2-1	38.5, qC		H_2-7
6	127.6, qC		H_3-13; H_2-7; H_2-2; H_2-1	23.8, CH_2	1.89, m; 1.41, m	H_3-15; H_2-7
7	29.5, CH_2	2.23, m		18.7, CH_2	2.39, m	
8	25.6, CH_2	2.46, m		112.6, qC		H-12; H-11; H_2-7; H_2-6
9	125.7, qC		H-12; H-11; H-10; H_2-8	159.1, qC		H_3-13; H-12; H-11; H_2-7
10	110.9, CH	6.31, br s	H-11; H_2-8	38.1, qC		H-4
11	142.6, CH	7.36, br s	H-12; H-10	109.9, CH	6.14, d (1.5)	H-12
12	138.4, CH	7.24, br s	H-11; H-10; H_2-8	140.1, CH	7.22, d (1.5)	H-11
13	19.8, CH_3	1.64, s		16.6, CH_3	1.26, s	
14	28.6, CH_3	1.02, s		16.6, CH_3	0.88, d (6.5)	
15	28.6, CH_3	1.02, s		21.1, CH_3	0.87, s	H_2-6

[a] Bruker DPX 300, AVANCE 400, and DRX 600 MHz spectrometers, $CDCl_3$, chemical shifts (ppm) referred to $CHCl_3$ (δ 7.26) and to $CDCl_3$ (δ 77.0). [b] By DEPT, HSQC, and HMBC (J = 10 Hz) experiments. [c] By $^1H-^1H$ COSY and HSQC experiments.

Analysis of the NMR spectra of compound **3**, named isomicrocionin-1, revealed the presence of a tricyclic skeleton including a fused furan ring. The ^{13}C NMR spectrum contained only four sp^2 carbon signals at δ 159.1 (qC, C-9), 140.1 (CH, C-12), 112.6 (qC, C-8), and 109.9 (CH, C-11) due to the furan moiety. The remaining two unsaturation degrees indicated by the molecular formula were therefore attributed to two rings. The ^1H NMR spectrum of compound **3** displayed characteristic signals attributable to the protons of an α,β-disubstituted furan ring [δ 7.22 (1H, d, J = 1.5 Hz, H-12) and 6.14 (1H, d, J = 1.5 Hz, H-11)], two tertiary methyls [δ 1.26 (3H, s, H_3-13) and 0.87 (3H, s, H_3-15)], and one secondary methyl [δ 0.88 (3H, d, J = 6.9 Hz, H_3-14)] along with several complex high-field signals, assigned to five methylene and one methine group by the HSQC experiment. Comparison of the carbon and proton values with those reported in the literature[6,10,12] for tricyclic furan sesquiterpenes strongly suggested a structural similarity of compound **3** with the co-occurring microcionin-1 (**2**). In particular, careful analysis of $^1H-^1H$ COSY, HSQC, and HMBC spectra led us to determine that the planar structure of **3** was the same as **2**. Thus the difference between the two compounds was ascribed to a different relative stereochemistry of one of the three chiral centers. This stereochemical aspect was investigated by analysis of both proton coupling constants and NOE difference experiments as well as by comparison of the carbon chemical shift values with those of **2**. We started from the axial position of H-4 that was deduced by the *trans*-diaxial coupling constant with H-3_{ax}, determined by decoupling the geminal methyl H_3-14 ($J_{H4ax-H3ax}$ = 12.5 Hz, $J_{H4ax-H3eq}$ = 3.7 Hz). The irradiation on H-4 resulted in the enhancement of the signals of both angular methyl groups at C-10 and C-5 that pointed in the same orientation as H-4, H_3-13, and H_3-15 and consequently to the 5,10-*cis*-junction, as in microcionin-1. This implied that **3** differed from **2** only in the relative stereochemistry at C-4, a deduction also supported by comparison of the ^{13}C NMR values of the two compounds. Assuming a chair conformation for ring A as well as the axial orientation of H-4, the angular methyl groups H_3-13 and H_3-15 in **3** had to be axially and equatorially oriented, respectively, whereas in microcionin-1 (**2**) they had the opposite orientation (δ_{C-13} 16.6 in **3**, 25.9 in **2**; δ_{C-15} 21.1 in **3**, 14.6 in **2**). This stereochemical arrangement was further confirmed by a series of NOE effects as depicted in Figure 1. All proton and carbon values of isomicrocionin-1 (**3**) were assigned by 2D-NMR experiments (Table 1). The absolute stereochemistry of **3** remained undetermined even though the configuration of the junction chiral centers C-5 and C-10 should be the same as microcionin-1 (**2**), as suggested by the similar CD profiles obtained for both compounds.

In conclusion, the secondary metabolite pattern of the Portuguese sponge *Fasciospongia* sp. was found to be similar to that of

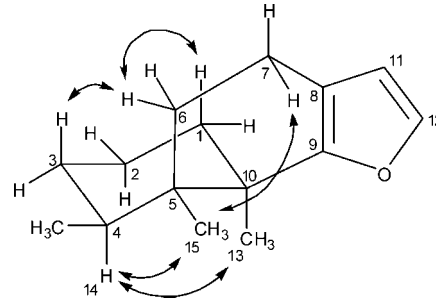


Figure 1. Significant NOE effects observed for isomicrocionin-1 (**3**).

Mediterranean *Fasciospongia cavernosa*.[6,10] Sponges of the genus *Fasciospongia* could be difficult to identify, so the chemistry may represent a valid tool for their taxonomic classification. This is more relevant in the present work due to the fact that *Fasciospongia* sp. here described is most likely a new species. Its secondary metabolite content was dominated by (−)-microcionin-1 (**2**), which is the optical antipode of the metabolite isolated from the Mediterranean specimen, and co-occurred with related isomeric bicyclic and tricyclic furanosesquiterpenes **1** and **3**−**5**. The finding of isomicrocionin-3 (**1**) is noteworthy because it provides additional information on the biogenetic pathway of sponge furanosesquiterpenes. In fact, the formation of an intermediate with the same structure of isomicrocionin-3 (**1**) was proposed by Butler and Capon[12] to explain the co-occurrence of sesquiterpenes of both *ent*-pallescensin and drimane series in Australian sponge *Dysidea* sp. A hypothetical biogenetic correlation could also be suggested for Portuguese *Fasciospongia* sesquiterpenes as depicted in Figure 2.

(−)-Microcionin-1 (**2**) showed low antibacterial activity against several Gram-positive bacteria with MIC values ranging from 6 to 50 μg/mL: *Micrococcus luteus* (6 μg/mL), *Staphylococcus aureus* (50 μg/mL), *Staphylococcus epidermidis* (25 μg/mL), *Streptococcus faecium* (50 μg/mL), *Mycobacterium smegmatis* (25 μg/mL), and *Lysteria monocytogenes* (50 μg/mL). (–)-Isomicrocionin-1 (**2**) and isomicrocionin-3 (**1**) were inactive against *Escherichia coli* (MIC > 200 μg/mL) and *Candida albicans* (MIC > 200 μg/mL).

Experimental Section

General Experimental Procedures. Optical rotations were measured on a Jasco DIP 370 digital polarimeter. ^1H NMR spectra were acquired in $CDCl_3$ (δ values are reported referenced to $\underline{CH}Cl_3$ at 7.26 ppm) on a Bruker Avance-400 or a Bruker DRX-600. $^{13}\underline{C}$ NMR spectra were recorded on a Bruker DPX-300 or Bruker DRX-600 operating respectively at 75 or 150 MHz (δ values are reported to $CDCl_3$, 77.0 ppm). EIMS were determined at 70 eV on a HP-GC 5890 series II

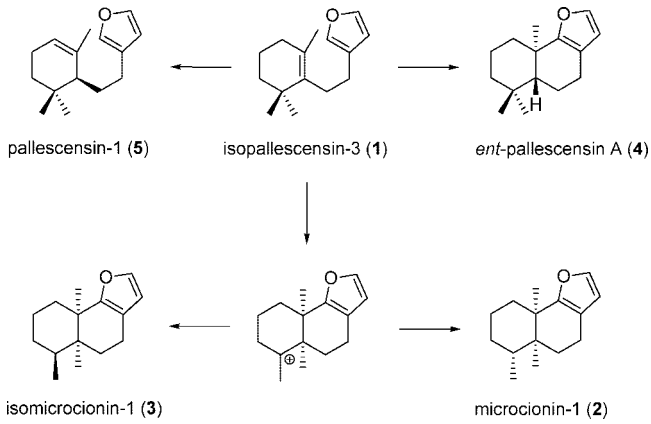


Figure 2. Hypothetical biogenetic correlations for Portuguese *Fasciospongia* sesquiterpenes.

mass spectrometer. HREIMS and ESIMS were recorded on a Finnigan FT/MS 2001-DT mass spectrometer, and HRESIMS (positive mode) was recorded on an Apex-Qe FTICR mass spectrometer, from Bruker Daltonics. Silica gel chromatography was performed using precoated Merck F_{254} plates and Merck Kieselgel 60 powder. HPLC purification was carried out on a Dionex liquid chromatograph equipped with a Dionex UVD340U detector.

Biological Material. A sample of *Fasciospongia* sp. was collected by scuba diving at Berlengas Islands (western coast of Portugal) in 1999, at a depth of 4 m, and kept at −20 °C until processed. A voucher specimen preserved in absolute EtOH has been deposited at the Porifera Collection of the Centre d'Estudis Avançats de Blanes CEAB-CSIC, under the name CEAB.POR.BIO.217, Spain.

Faciospongia sp. is a massive keratose sponge (order Dictyoceratida, family Thorectidae) with an irregularly conulose surface and a thick collagenous ectosome, which covers large subectosomal cavities. The skeleton consists of primary fasciculate and reticulated spongin fibers (133−400 μm thick) and weak, secondary fibers (33−97 μm thick), both strongly laminated. Primary fibers have a distinct medulla, 40−67 μm thick, and include foreign debris. The skeleton is weaker or even completely absent in the inner part of the sponge. This species shows the diagnostic characteristics of *Faciospongia*.[18] However, the genus *Faciospongia* was described by Burton[19] from the Indo-Pacific and was unknown up to now from the Atlantic. In contrast, two species have been recorded in the Mediterranean Sea: *Faciospongia cavernosa* (Schmidt) and *F. caerulea* Vacelet.[18] This author, however, expressed some doubts on the relationship of the Mediterranean species to the Indo-Pacific genus *Faciospongia*, although she could not examine enough material to establish definite conclusions. All these considerations suggest that the present specimen may correspond to a new species of *Faciospongia* from the Atlantic and not to the Mediterranean *F. cavernosa*, which is tubular in shape (instead of massive), covered by large surface conules (3−4 mm high) instead of the 1−2 mm high conules of our specimen and with narrower primary fibers (up to 250 μm vs 400 μm in the Portuguese specimen). *F. caerulea* can be distinguished from *F. cavernosa* because of its massive instead of tubular habit and especially by its armored surface, which incorporates large amounts of sand grains.[20] Although its growth habit is closer to the Portuguese specimen (massive), its thick external sandy layer, which is absent from our specimen, prevents us from considering that it belongs to *F. caerulea*.

Extraction and Isolation Procedures. A freeze-dried sponge sample (dry weight 233.0 g) of *Fasciospongia* sp. was extracted with MeOH (3 × 350 mL), and the combined extracts were concentrated to give a residue that was extracted with EtOAc (3 × 250 mL). The EtOAc extract (dark brown oil, 1.89 g) was flash chromatographed on a SiO_2 column using a gradient of *n*-hexane/Et_2O as eluent. Fractions 8−15 eluted with *n*-hexane afforded pure compound **2** (60 mg). Fractions 17−29, eluted with *n*-hexane, which showed similar TLC behavior (Erlich positive spots at R_f 0.4−0.6, *n*-hexane), were combined (80.5 mg) and purified by HPLC [Phenomenex-Kromasil column (3.6 μm, 100A, 150 × 4.60 mm); *n*-hexane (flow 0.5 mL/min)] to yield compounds **2** (14.5 mg), **3** (2.1 mg), and **4** (2.0 mg) and a mixture of **1** and **5** (42 mg), in order of increasing retention time. An aliquot (12 mg) of this latter mixture was submitted to a Pasteur pipet−$AgNO_3$-SiO_2 column (*n*-hexane/Et_2O, 99:01) to afford pure compounds **1** (7 mg) and **5** (3 mg). Compounds **1**−**5** accounted for 0.010%, 0.032%, 0.001%, 0.001%, and 0.004%, respectively, of the dry weight of the *Fasciospongia* sample.

Isomicrocionin-3 (1): colorless oil; ^{1}H and ^{13}C NMR, see Table 1; ESIMS *m/z* (%) 219 $[M + H]^+$ (100), 201(65), 145 (32), 137 (78), 125 (35) 95 (16), 81 (5); HREIMS *m/z* 218.16652 $[M]^+$ (calcd for $C_{15}H_{22}O$, 218.166516).

(−)-Microcionin-1 (2): colorless oil; $[\alpha]^{25}_D$ −61.4 (*c* 3.4, $CHCl_3$); CD $[\theta]_{225}$ (EtOH) +660; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (1H, d, J = 1.8 Hz, H-12), 6.16 (1H, d, J = 1.8 Hz, H-11), 2.37 (2H, dd, J = 2.2, 7.0 Hz, H_2-7), 2.16 (1H, dt, J = 13.6 Hz, H_2-1_{eq}), 1.74 (1H, qt, J = 7.2, 12.2 Hz, H_2-6_{ax}), 1.63 (1H, dd, J = 2.4, 5.4 Hz, H-4), 1.59 (1H, m, H_2-6_{eq}), 1.52 (1H, m, H_2-1_{ax}), 1.47 (1H, m, H_2-2_{ax}), 1.28 (1H, m, H_2-3_{eq}), 1.24 (1H, ddd, J = 12.4, 12.2, 3.2 Hz, H_2-3_{ax}), 1.10 (3H, s, H_3-13), 1.05 (1H, dt, J = 13.0; 4.2 Hz, H_2-2_{eq}), 0.87 (3H, d, J = 6.5 Hz, H_3-14), 0.88 (3H, s, H_3-15); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.7 (C-9), 140.2 (C-12), 115.1 (C-8), 110.7 (C-11), 40.1 (C-10), 39.1 (C-5), 32.3 (C-1), 31.9 (C-4), 30.7 (C-3), 29.3 (C-6), 25.9 (C-13), 23.7 (C-2), 18.6 (C-7), 16.7 (C-14), 14.6 (C-15); EIMS *m/z* (%) 218 (M^+, 19), 203 (100), 147 (13), 133 (17), 95 (5), 91 (9), 69 (6); HRESIMS *m/z* 219.17469 $[M + H]^+$ (calcd for $C_{15}H_{23}O$, 219.17434).

Isomicrocionin-1 (3): colorless oil; $[\alpha]^{25}_D$ −5.4 (*c* 0.1, $CHCl_3$); CD $[\theta]_{226}$ (EtOH) +645; ^{1}H and ^{13}C NMR, see Table 1; EIMS *m/z* (%) 218 (M^+, 6), 203 (13), 149 (16), 123 (11), 109 (16), 57 (92), 69 (98) 43 (100); HRESIMS *m/z* 219.17424 $[M + H]^+$ (calcd for $C_{15}H_{23}O$, 219.17434).

(−)-Pallescensin A (4): colorless oil; $[\alpha]^{25}_D$ −9.7 (*c* 0.43, $CHCl_3$); EIMS *m/z* (%) 218 (M^+, 28), 203 (100), 147 (24), 135 (14), 123 (11), 69 (31), 41 (18); HRESIMS *m/z* 219.17459 $[M + H]^+$ (calcd for $C_{15}H_{23}O$, 219.17434).

(−)-Pallescensin-1 (5): colorless oil; $[\alpha]^{25}_D$ −23.5 (*c* 0.07, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (1H, br s, H-11), 7.21 (1H, br s, H-12), 6.27 (1H, br s, H-10), 5.31 (1H, br s, H-1), 2.46 (2H, m, H_2-8), 1.97 (2H, m, H_2-2), 1.71 (1H, m, H_2-7a), 1.68 (3H, s, H_3-13), 1.55 (1H, m, H_2-7b), 1.47 (1H, m, H-5), 1.45 (1H, m, H_2-3a), 1.15 (1H, m, H_2-3b), 0.95 (3H, s, H_3-14), 0.88 (3H, s, H_3-15); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.2 (C-11), 139.2 (C-12), 136.2 (C-6), 125.6 (C-9), 120.1 (C-1), 110.6 (C-10), 49.0 (C-5), 32.6 (C-4), 31.6 (C-3 and C-7), 27.4 (C-14 and C-15), 25.5 (C-8), 23.5 (C-13), 23.1 (C-2); ESIMS *m/z* (%) 219 $[M + H]^+$ (100), 203 (43), 161 (4), 125 (2), 95 (<1), 81 (<1).

Biological Activity. Antimicrobial activity was determined against *Micrococcus luteus* (CCMI 322), *Staphylococcus aureus* (CCMI 335), *Staphylococcus epidermidis* (ATTCC 29641), *Streptococcus faecium* (CCMI 338), *Mycobacterium smegmatis* (CCMI 690), *Lysteria monocytogenes* (CCMI 1106), *Escherichia coli* (CCMI 270), and *Candida albicans* CCMI 209. Strains were obtained from the Culture Collection of Industrial Microorganisms (CCMI), Laboratório de Microbiologia Industrial, Lisbon, Portugal, except for *S. epidermidis*. The minimum inhibitory concentration (MIC) of compound **2** was determined at least twice in DMSO by the broth dilution method.[21] Rifampicin was used as antibiotic positive control for bacteria and 5-fluorocytosine for yeast.

Acknowledgment. We thank P. Madeira of FCUL and the staff of "ICB NMR Service" for HRMS and NMR experiments, respectively. We are deeply grateful to GRICES and MARBEF for financial support of the team missions.

References and Notes

(1) Blunt, J. W.; Copp, B. R.; Hu, W.-P.; Munro, M. H. G.; Northcote, P. T.; Prinsep, M. R. *Nat. Prod. Rep* **2008**, *25*, 35–94, and previous articles in this series.
(2) Mayer, A. M. S.; Rodríguez, A. D.; Berlinck, R. G. S.; Hamann, M. T. *Comp. Biochem. Physiol. Part C: Toxicol. Pharmacol.* **2007**, *145*, 553–581.
(3) Gavagnin, M.; Mollo, E.; Calado, G.; Fahey, S.; Ghiselin, M.; Ortea, J.; Cimino, G. *Chemoecology* **2001**, *11*, 131–136.
(4) Gavagnin, M.; Mollo, E.; Castelluccio, F.; Ghiselin, M. T.; Calado, G.; Cimino, G. *Tetrahedron* **2001**, *57*, 8913–8916.
(5) Fontana, A.; Tramice, A.; Cutignano, A.; d'Ippolito, G.; Gavagnin, M.; Cimino, G. *J. Org. Chem.* **2003**, *68*, 2405–2409.
(6) Gaspar, H.; Gavagnin, M.; Calado, G.; Castelluccio, F.; Mollo, E.; Cimino, G. *Tetrahedron* **2005**, *61*, 11032–11037.
(7) Jefford, C. W.; Bernardinelli, G.; Tanaka, J.; Higa, T. *Tetrahedron Lett.* **1996**, *37*, 159–162.

(8) De Rosa, S.; De Stefano, S.; Zavodnik, N. *J. Org. Chem.* **1988**, *53*, 5020–5023.
(9) De Rosa, S.; Crispino, A.; De Giulio, A.; Iodice, C.; Amodeo, P.; Tancredi, T. *J. Nat. Prod.* **1999**, *62*, 1316–1318.
(10) Cimino, G.; De Stefano, S.; Guerriero, A.; Minale, L. *Tetrahedron Lett.* **1975**, *16*, 3723–3726.
(11) Cimino, G.; De Stefano, S.; Guerriero, A.; Minale, L. *Tetrahedron Lett.* **1975**, *16*, 1425–1428.
(12) Matsumoto, T.; Usui, S. *Chem. Lett.* **1978**, 105–108.
(13) Butler, M. S.; Capon, R. *J. Aust. J. Chem* **1993**, *46*, 1255–1267.
(14) Cimino, G.; De Stefano, S.; Guerriero, A.; Minale, L. *Tetrahedron Lett.* **1975**, *17*, 1417–1420.
(15) Full assignments of ^{1}H and ^{13}C NMR NMR data of pallescensin-1 (**5**), not included in ref 12, are reported in this work (see section 4).
(16) The $[\alpha]^{25}_{D}$ value and CD curve of (+)-microcionin-1 were measured in this work on a freshly purified sample obtained from Mediterranean *F. cavernosa* according to ref 6. $[\alpha]^{25}_{D}$ +56.5 (*c* 4.0, $CHCl_3$); CD $[\theta]_{226}$ (EtOH)−604.
(17) Spinella, A.; Alvarez, L. A.; Avila, C.; Cimino, G. *Tetrahedron Lett.* **1994**, *35*, 8665–8668.
(18) Cook, S. C.; Bergquist, P. R. *Systema Porifera: A Guide to the Classification of Sponges*; 2002; pp 1021−1050.
(19) Burton, M. *Sci. Rep. Great Barrier Reef Expedition 1928−29* **1934**, *4*, 513–621.
(20) Vacelet, J. *Recl. Trav. St. Mar. Endoume.* **1959**, *16*, 39–101.
(21) Muroi, H.; Kubo, I. *J. Appl. Bacteriol.* **1996**, *80*, 387–394.

NP800346C