Notes

New Furanoterpenoids from the Sponge *Spongia officinalis*

Leda Garrido, Eva Zubía, María J. Ortega, and Javier Salvá*

Departamento de Química Orgánica, Facultad de Ciencias del Mar, Universidad de Cádiz, Apdo. 40, Puerto Real, 11510 Cádiz, Spain

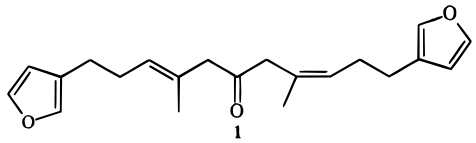
Received March 7, 1997[⊗]

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).

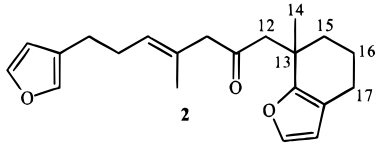
It is well known that sponges of the order Dictyoceratida are the source of a group of terpenoids characterized by possessing 21 carbon atoms and two terminal furan rings. These C-21 furanoterpenoids have been isolated from several genera of the Spongiidae and Thorectidae families[1−12] and, occasionally, 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**.

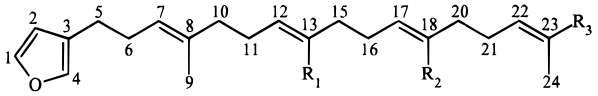
The specimen of *S. officinalis* (62.2 g dry wt) was collected by hand and immediately frozen. The less polar material of an Me_2CO extract was chromatographed on Si gel. Final purification of selected fractions using HPLC allowed isolation of the following compounds in order of increasing polarity: 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]



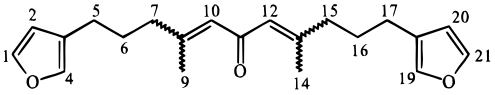
1



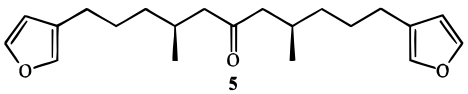
2



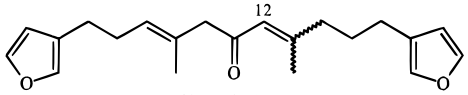
3 R_1= Me; R_2= COOH; R_3= COOH
11 R_1= Me; R_2= COOH; R_3= COOMe
12 R_1= COOH; R_2= Me; R_3= COOMe
13 R_1= Me; R_2= Me; R_3= COOH; *trans* 17,18-epoxide



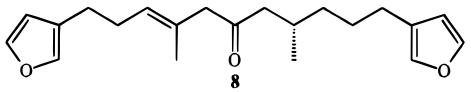
4 8*Z*, 12*Z*; **6** 8*Z*, 12*E*; **9** 8*E*, 12*E*



5



7 12*Z*; **10** 12*E*



8

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

* To whom correspondence should be addressed. Phone: 3456-470855. FAX: 3456-470811. E-mail: javier.salva@uca.es.

[⊗] Abstract published in *Advance ACS Abstracts,* July 1, 1997.

S0163-3864(97)00160-2 CCC: $14.00 © 1997 American Chemical Society and American Society of Pharmacognosy

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 (±)-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; [α]$^{25}_D$ −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).

Acknowledgment. The sponge was identified by Dr. J. Luis Carballo, Laboratorio de Biología Marina, Universidad de Sevilla. This research was supported by grants from C. I. C. Y. T. (research project SAF94-1383) and Junta de Andalucía (PAI 1081). Cytotoxicity assays were performed through a cooperative agreement with Instituto Biomar S. A.

References and Notes

(1) Cimino, G.; De Stefano, S.; Minale, L.; Fatorusso, E. *Tetrahedron* **1971**, *27*, 4673−4679.
(2) Cimino, G.; De Stefano, S.; Minale, L. *Tetrahedron* **1972**, *28*, 5983−5991.
(3) Cimino, G.; De Stefano, S.; Minale, L.; Fatorusso, E. *Tetrahedron* **1972**, *28*, 267−273.
(4) Kazlauskas, R.; Murphy, P. T.; Quinn, R. J.; Wells, R. J.; Why, D. *Tetrahedron Lett.* **1976**, 1333−1334.
(5) Capon, R. J.; Ghisalberti, E. L.; Jefferies, P. R. *Experientia* **1982**, *38*, 1444−1445.
(6) Guella, G.; Amade, P.; Pietra, F. *Helv. Chim. Acta* **1986**, *69*, 726−733.
(7) Tanaka, J.; Higa, T. *Tetrahedron*, **1988**, *44*, 2805−2810.
(8) Kobayashi, M.; Chavakula, R.; Murata, O.; Sharma, N. S. *J. Chem. Res. (S)* **1992**, 366−367.
(9) Kobayashi, M.; Chavakula, R.; Murata, O.; Sarma, N. S. *Chem. Pharm. Bull.* **1992**, *40*, 599−601.
(10) Kobayashi, J.; Shinonaga, H.; Shigemori, H.; Sasaki, T. *Chem. Pharm. Bull* **1993**, *41*, 381−382.
(11) Fontana, A.; Albarella, L.; Scognamiglio, G.; Uriz, M.; Cimino, G. *J. Nat. Prod.* **1996**, *59*, 869−872.
(12) Lenis, L. A.; Núñez, L.; Jiménez, C.; Riguera, R. *Nat. Prod. Lett.* **1996**, *8*, 15−23.
(13) Cimino, G.; De Rosa, S.; De Stefano, S.; Morrone, R.; Sodano, G. *Tetrahedron* **1985**, *41*, 1093−1100.
(14) Cimino, G.; De Stefano, S.; Minale, L. *Tetrahedron* **1972**, *28*, 1315−1324.
(15) Walker, R. P.; Thompson, J. E.; Faulkner, D. J. *J. Org. Chem.* **1980**, *45*, 4976−4979.
(16) Thompson, J. E.; Walker, R. P.; Wratten, S. J.; Faulkner, D. J. *Tetrahedron*, **1982**, *37*, 1865−1873.
(17) Searle, P. A.; Molinski, T. F. *Tetrahedron* **1994**, *50*, 9893−9908.
(18) De Giulio, A.; De Rosa, S.; Di Vincenzo, G.; Zavodnik, N. *J. Nat Prod.* **1989**, *52*, 1258−1262.
(19) Breitmeier, E.; Voelter, W. *Carbon-13 NMR Spectroscopy*; VCH: New York, 1990; 3rd ed., p 192.
(20) Kobayashi, J.; Ohizumi, Y.; Nakamura. H.; Hirata, Y. *Tetrahedron Lett.* **1986**, *27*, 2113−2116.
(21) Shoji, N.; Umeyama, A.; Kishi, K.; Arihara, S.; Ohizumi, Y.; Kobayashi, J. *Aust. J. Chem.* **1992**, *45*, 793−795.

NP970160X