Fasciospongides A, B, and C, New Manoalide Derivatives from the Sponge Fasciospongia sp.

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FASCIOSPONGIDES A, B, AND C, NEW MANOALIDE DERIVATIVES FROM THE SPONGE *FASCIOSPONGIA* SP.

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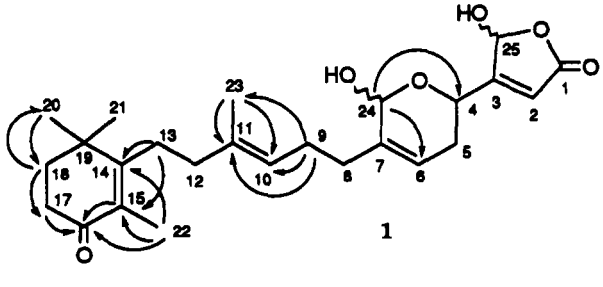
ABSTRACT.—Three new manoalide-related sesterterpenes, fasciospongides A [**1**], B [**2**], and C [**3**], have been isolated from the sponge *Fasciospongia* sp. and their structures elucidated by spectral methods.

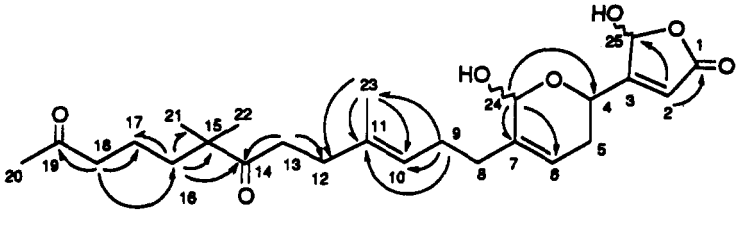
In the course of our search for biologically active compounds from New Caledonian marine organisms, we have isolated from the CH_2Cl_2 extract of the sponge *Fasciospongia* sp. (family Thorectidae) three new sesterterpenes named fasciospongides A [**1**], B [**2**], and C [**3**]. The structures of the new products were closely related to the known marine sesterterpene manoalide [**4**] (1) and secomanoalide [**5**] (2), which have also been isolated in the present study. Manoalide is well known for its biological properties, since it demonstrates some antimicrobial activity (3), potent anti-inflammatory properties and irreversible inhibition of phospholipase A_2 (3,4). In addition, the two C-25 epimeric monocetates of manoalide [**6ab**], previously prepared from manoalide by de Silva and Scheuer (1), were also found in the sponge. One of these acetates has also been isolated from the sponge *Thorectandra excavatus* (5).

The EtOH extract of the lyophilized organism was partitioned between CH_2Cl_2 and H_2O. The CH_2Cl_2 extract was subjected to Si gel cc with CH_2Cl_2/MeOH. The fractions showing antimicrobial activity were further purified by reversed-phase hplc, to give compounds **1–6**.

Fasciospongide [**1**] was obtained as a colorless oil, $[\alpha]_D$ +46°. The eims showed a molecular peak at *m/z* 430. The molecular ion peak was very weak, as in the case of manoalide, and was accompanied by a relatively intense $[M-18]^+$ peak due to the loss of H_2O. These data together with ^{13}C-nmr data suggested the molecular



1



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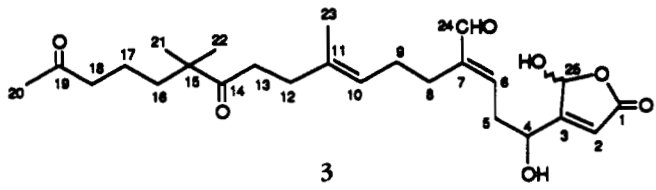

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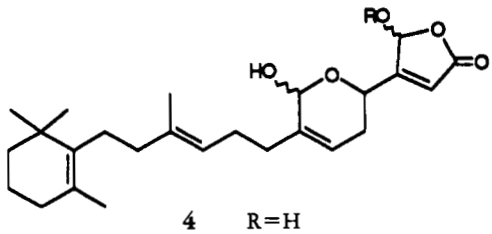
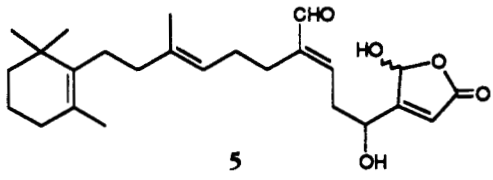


4 R=H
6ab R=Ac



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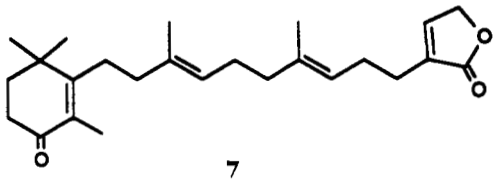

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formula of $C_{25}H_{34}O_6$, which was confirmed by hr fabms (*m/z* 453.2244, $[M+Na]^+$, Δ 0.9 mmu). The uv spectrum disclosed a maximum at 244 nm (ϵ 7800) attributed to the γ-hyroxybutenolide terminus. The ir spectrum exhibited bands at 3580, 1790 (sh), and 1762 cm^{-1}, typical of a γ-hydroxybutenolide, together with an absorption at 1649 cm^{-1} supporting the presence of an α,β-unsaturated ketone. The ^{13}C-nmr ($CDCl_3$) signals of **1** (Table 1) and **4** were very similar to those assigned to the C_1-C_{13} region of manoalide, with, in particular, diagnostic peaks at δ 98.3 (C-24) and δ 91.4 (C-25). The spectrum of **1** lacked the signals of the cyclohexene part of manoalide. Instead, it showed resonances similar to those of the cyclohexenone moiety of a related sesterterpene **7**, previously isolated from the sponge *Fascalinopsis reticulata* (6). Hence, the spectrum showed the characteristic signals of an α,β-unsaturated ketone at δ 199.5 (C-18), δ 130.8 (C-15) and δ 165.4 (C-14) and of a deshielded methyl group at δ 11.5 (C-22). These data suggested structure **1** for fasciospongide A, which was entirely supported by COSY, HMQC and HMBC (see arrows in the structure of **1**) experiments.

TABLE 1. ^{13}C-(62.5 MHz) and ^{1}H-(400 MHz) Nmr Data for Fasciospongides A [**1**], B [**2**] and C [**3**].[a]

Position	1		2		3	
	δ C	δ H (*J*, Hz)	δ C	δ H (*J*, Hz)	δ C	δ H (*J*, Hz)
1	171.5		171.3		171.0	
2	117.6	6.08[b]	117.3	6.06[b]	118.7	6.12[b]
3	168.2		167.8		170.3	
4	62.7	4.89[b]	59.6	4.88[b]	67.1	4.80[b]
5[c]	28.9[b]	[d]	29.2[b]	[d]	34.9	2.80[b]
6	120.8	5.68[b]	121.1	5.68[b]	147.7	6.62[b]
7	137.3		137.6		148.2	
8[c]	25.9	2.15 m	26.2	2.15 m	24.5	2.30 m
9[c]	32.4	2.15 m	32.4	2.15 m	26.6	2.15 m
10	124.1	5.18[b]	124.4	5.13[b]	123.8	5.31[b]
11	135.3		134.8		136.3	
12	38.4	2.10 m	33.6	2.20 m	33.5	2.20 m
13	30.0	2.30 m	35.6	2.56 t (7)	35.4	2.57 t (7)
14	165.4		215.4		215.4	
15	130.8		47.7		47.9	
16	199.5		39.3	1.45 m	39.3	1.45 m
17	34.1	2.46 t (7)	19.1	1.45 m	19.0	1.45 m
18	37.4	1.80 t (7)	44.0	2.42 t (7)	43.9	2.44 t (7)
19	36.3		209.6		208.8	
20	26.8	1.16 s	30.0	2.13 s	27.0	2.15 s
21	26.8	1.16 s	24.5	1.15 s	24.5	1.16 s
22	11.5	1.76 s	24.5	1.15 s	24.5	1.11 s
23	15.9	1.67 s	16.3	1.60 s	16.3	1.55 s
24	91.4	5.32[b]	91.5	5.31[b]	194.9	9.40 s
25	98.4	6.21[b]	97.9	6.12[b]	97.9	6.20[b]

[a]For compounds **1** and **2**, the data are based on COSY, HMQC and HMBC experiments.

[b]Broad signal due to the presence of a mixture of epimers at C-25 (and at C-24 for **1** and **2**).

[c]For manoalide [**3**], the earlier ^{13}C-nmr assignments (1) of δ 33.1 to C-5 and δ 28.5 to C-9 should be reversed (7); for seco-manoalide [**4**], the earlier ^{13}C-nmr assignment (2) of δ 28.0 to C-5 should be corrected to δ 35.1.

[d]The signal of this CH_2 group could not be assigned.

[e]The earlier ^{13}C-nmr assignments (1,2) for manoalide (δ 40.9) and for seco-manoalide (δ 35.2) should be corrected to δ 26.1 and δ 24.7 respectively.

Fasciospongide B [**2**] was also isolated as an oil, $[\alpha]_D$ +54°. The cims and fabms showed no molecular peak, but only an $[MH-18]^+$ ion at *m/z* 431. However, an $[M-H]^-$ peak at *m/z* 447 was obtained using electrospray mass spectrometry (esms) in the negative-ionization mode. In the positive mode, the esms exhibited an $[M+Na]^+$ ion at *m/z* 471 together with a $[MH-18]^+$ peak. The molecular formula was established as $C_{25}H_{38}O_7$ by hr fabms (*m/z* 431.2428, $[M-H_2O+H]^+$, Δ 0.6 mmu). Ir bands at 3580, 1790 (sh) and 1762 cm^{-1} were assigned to a γ-hydroxybutenolide moiety. An additional ir band at 1702 cm^{-1} indicated the presence of saturated carbonyl groups. The ^{13}C-nmr spectrum showed resonances similar to the C_1–C_{11} region of manoalide, and the signals of the cyclohexene ring were absent as in the case of **1**. The presence of two carbonyls at δ_C 209.6 and 215.4 and a MeCO group (Me δ_C 30.0 and δ_H 2.13) in the nmr spectrum implied the existence of an open-chain dicarbonyl sub-structure, which could be derived from an oxidative opening of the cyclohexene ring of manoalide, thus suggesting structure **2** for fasciospongide B. This structure was fully supported by 2D nmr techniques, namely, COSY, HMQC, and HMBC. The COSY spectrum aided

by HMQC helped identify two spin systems of two and three CH_2 units, respectively, with one CH_2 of each adjacent to a carbonyl group as deduced from the observed chemical shifts (δ_H 2.56, CH_2-13 and 2.42, CH_2-18). The HMBC spectrum (see arrows in the structure of **2**) allowed unambiguous assignment of the position of the quarternary carbons in the aliphatic chain. Particularly diagnostic were the correlations between CH_3-23 and C-12, H-13 and C-12, and H-13 and H-14, indicating the C-11 to C-14 connectivity. The cross-peaks H-18/C-19, H-18/C-17, H-16/C-15, and H-16/C-14 further supported the connectivity chain C_{14}–C_{19}.

Fasciospongide C [**3**] was related to secomanoalide as fasciospongide B is related to manoalide. The spectral data were in accordance with an α,β-unsaturated aldehyde with *E*-geometry about the olefinic double bond, a γ-hydroxybutenolide moiety and an δ-diketone chain.

Numerous manoalide-type compounds have been previously isolated, but only a few of them contain the δ-lactol moiety of manoalide and fasciospongide A [**1**] and B [**2**] or the chain tautomer form of this lactol, which is present in secomanoalide [**5**] and fasciospongide C [**3**]. Furthermore, fasciospongides B and C possess a new oxidized variant of the cyclohexene part of manoalide.

The fasciospongides are very minor manoalide-type components of the sponge extract isolated in minute quantities and could not be tested in the present study for the interesting antiinflammatory activity previously found for this series of compounds.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Optical rotations at 20° were taken on a Perkin-Elmer 241 polarimeter. Spectra were recorded on: uv, Shimadzu UV-161 uv-visible spectrophotometer; ir, Nicolet 205 Ft-ir spectrometer; eims (70 eV), Kratos MS 50; cims, Kratos MS 9; fabms, Kratos MS 80; hr fabms, VG-Zab-Seq spectrometer; esms, Fisons Instruments Trio 2000; nmr, Bruker AC 250 (^{1}H- and ^{13}C-nmr spectra), AM 400 (2D spectra). Uv spectra were recorded in MeOH. Cc was performed using Si gel Merck H 60 and prep. hplc over a Waters Delta prep. 3000 apparatus.

ANIMAL MATERIAL.—The sponge *Fasciospongia* sp. (order Dictyoceratida; family Thorectidae) was collected at Récif de Beautemps Beaupré, Ouvéa, New Caledonia, under the aegis of the CNRS-ORSTOM program "Substances Marines d'Intérêt Biologique" (SMIB). The sponge was massive, of an irregular, cushion-like shape. It has a dark-brown conulose, alveolar surface and a yellow brown interior. Conules were 2 mm high. The primary fibers were cored with sand, slightly fasciculous, 100 μm wide, pith 40 μm. The secondary fibers were clear of detritus, numerous and 20–50 μm wide. Samples (ref. R1542) were identified by Prof. Lévi of the Muséum d'Histoire Naturelle de Paris, France and conserved at ORSTOM, Nouméa, New Caledonia.

EXTRACTION AND PURIFICATION.—The freeze-dried animal material (50 g) was extracted with 80% EtOH (3×0.5 liter) at room temperature. After filtration, the pooled solutions were concentrated *in vacuo* to an aqueous suspension, which was extracted with CH_2Cl_2. The organic layer was evaporated to give a crude residue (4.5 g), which was subjected to Si gel cc with CH_2Cl_2 containing increasing concentrations of MeOH as eluent. The fractions eluted with CH_2Cl_2-MeOH (96:4), which showed antibacterial activity (MIC ca. 10 μg/ml toward *Staphylococcus aureus*), were further purified by reversed-phase hplc [Delta-pak C-18 (100 Å, 15 mm), 47×300; MeOH-H_2O (85:15), (70:30), (60:40); flow rate 50 ml/min; ri and uv (230 nm) detection] to give [MeOH-H_2O (85:15)] manoalide [**4**] (220 mg), seco-manoalide [**5**] (23 mg) and manoalide monoacetates [**6ab**] (32 mg), [MeOH-H_2O (70:30)] fasciospongide A [**1**] (17 mg), [MeOH-H_2O (60:40)] and fasciospongides B [**2**] (10 mg) and C [**3**] (7 mg).

Fasciospongide A [**1**].—[α]D +46° (*c*=1, $CHCl_3$); uv λ max 244 (ε 7800) nm; ir ν max ($CHCl_3$) 3580, 1790 (sh), 1762 cm^{-1}; eims *m/z* 430 (<1), 412 $[M-H_2O]^+$ (10), 366 (12), 152 (100), 147 (60); nmr, see Table 1.

Fasciospongide B [**2**].—[α]D +20° (*c*=1, $CHCl_3$); ir ν max ($CHCl_3$) 3580, 1790 (sh), 1762, 1702 cm^{-1}; cims *m/z* 431 $[MH-H_2O]^+$ (77), 385, (100), 127 (44); fabms *m/z* 431 $[MH-H_2O]^+$; esms *m/z* 447 $[M-H]^-$, 429 $[M-H-H_2O]^-$, 471 $[M+Na]^+$, 431 $[MH-H_2O]^+$; nmr, see Table 1.

Fasciospongide C [**3**].—[α]D +54° (*c*=1, $CHCl_3$); ir ν max ($CHCl_3$) 3580, 1790 (sh), 1762, 1709, 1696 cm^{-1}; eims *m/z* 430 $[M-H_2O]^+$ (13), 384 (52), 127 (30), 43 (100); nmr, see Table 1.

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