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Novel Sulfated Sesterterpene Alkaloids from the Marine Sponge *Fasciospongia* sp.

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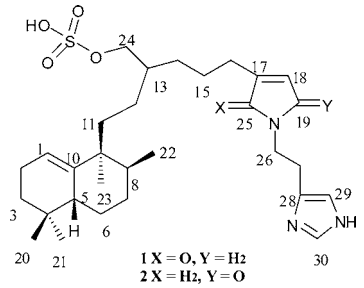
ABSTRACT



Fasciospongines A (1) and B (2), two unusual sulfated sesterterpene alkaloids of an unprecedented structural class, have been isolated from the marine sponge *Fasciospongia* sp. The structures were elucidated on the basis of spectroscopic analysis. Compounds 1 and 2 displayed potent inhibitory activity to *Streptomyces* 85E in the hypha formation inhibition (HFI) bioassay.

Sesterterpenoids[1] are the smallest and therefore rarest group of all subclasses of terpenoids, and have been isolated from fungi, lichens, higher plants, insects, and various marine organisms. Marine organisms, mainly marine sponges, have provided a large number of sesterterpenoids with novel carbon skeletons,[2] which are different from those in terrestrial species. Among these sesterterpenoids, sulfated sesterterpenoids are rare, only 25 sulfated sesterterpenoids[3,4] have been discovered from natural sources so far. These sulfated sesterterpenoids exhibited antimicrobial activity,[4g] cytotoxicity against P388, A-549, HT-29, MEL-28, and HeLa cells,[3b,4a] and inhibitory effects on phospholipase A_2,[4g] serine protease,[4c] PMA-induced inflammation,[4g] and cell division of sea urchin eggs.[3a,4g]

During the course of our search for novel protein kinase inhibitors from marine invertebrates, we isolated two unusual sulfated sesterterpene alkaloids (**1**−**2**) of an unprecedented structural class from the marine sponge *Fasciospongia* sp. (order Dictyoceratida). The sponge genus of *Fasciospongia* has yielded sesterterpenoids,[5] macrolides,[6] sesquiterpenes,[7] ceramides,[8] steroids,[9] trisnorditerpenoids,[10] and merosesquiterpenoids.[11] We report herein the isolation, structural elucidation, postulated biogenetic formation, and biological

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activity of **1**−**2**. To the best of our knowledge, this is the first isolation of sulfated sesterterpene alkaloids.

The sponge *Fasciospongia* sp. (1732 g) was collected in Palau on December 7, 2003 and was extracted with water at 4 °C. The mixture was centrifuged, and the solution was lyophilized to give an aqueous extract which was extracted with MeOH/CH_2Cl_2 (1:1) and then with MeOH. The combined organic extract (10.0 g) was subjected to medium-pressure liquid chromatography (MPLC) eluting with a gradient of hexane/acetone, and then CH_2Cl_2/MeOH, to afford 35 fractions. The fraction FS-31 was fractionated via Si gel MPLC by eluting with $CHCl_3$/MeOH/H_2O (14:1:0.1) to give two major fractions. Each fraction was further chromatographed over Sephadex LH-20 (MeOH) and then Si gel MPLC to afford compounds **1** (10.5 mg) and **2** (5.6 mg), respectively (Figure 1).

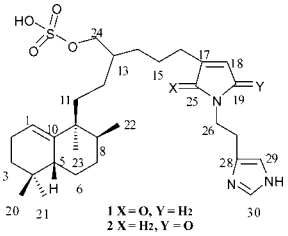

Figure 1. Structures of fasciospongine A (**1**) and B (**2**).

Fasciospongine A (**1**)[12] was obtained as a colorless oil, with the molecular formula of $C_{30}H_{47}N_3O_5S$ determined from HR-ESIMS (*m/z* 584.3141 $[M+Na]^+$; calcd, 584.3134) indicating nine degrees of unsaturation. The IR spectrum of **1** showed the presence of a hydroxyl (3448 cm^{-1}), α,β-unsaturated lactam carbonyl (1672 cm^{-1}), and sulfate functionality (1250, 1221 cm^{-1}). The ^1H NMR spectrum of fasciospongine A (**1**) in chloroform-*d* showed two broad singlet peaks at δ_H 13.83 and δ_H 13.55 at lower field; however, these two peaks disappeared when the solvent was changed to methanol-d_4, which led to these two peaks being ascribed to two exchangeable protons. The ^1H NMR spectrum (Table 1) in methanol-d_4 showed the signals for four olefinic protons (δ_H 8.06, br.s, 1H; 7.00, br. s, 1H; 6.84, t, J = 1.5 Hz, 1H; 5.34, dd, J = 2.3, 4.8 Hz, 1H), three tertiary methyl groups (δ_H 1.01, s, 3H; 0.90 s, 3H; 0.85, s, 3H), and

Table 1. ^1H (500 MHz) and ^{13}C NMR (125 MHz) Assignments of **1** and **2** in CD_3OD

	1		**2**	
no.	δ_H (mult, J, Hz)	δ_C	δ_H (mult, J, Hz)	δ_C
1	5.34 dd (2.3, 4.8)	118.0 d	5.34 dd (2.3, 4.8)	118.1 d
2α	1.98 m	24.4 t	1.98 m	24.4 t
2β	2.07 m		2.07 m	
3α	1.39 m	32.5 t	1.39 m	32.5 t
3β	1.09 m		1.09 m	
4		32.4 s		32.4 s
5β	1.64 dd (2.5, 13.0)	44.9 d	1.64 m	45.0 d
6α	1.08 m	31.6 t	1.08 m	31.6 t
6β	1.83 dddd (11.7, 3.9, 3.9, 3.5)		1.84 dddd (11.7, 3.9, 3.9, 3.5)	
7α	1.53 m	32.6 t	1.54 m	32.6 t
7β	1.51 m		1.52 m	
8α	1.25 m	46.3 d	1.25 m	46.3 d
9		43.8 s		43.8 s
10		147.8 s		147.7 s
11a	1.75 m	29.3 t	1.75 m	29.5 t
11b	1.05 m		1.05 m	
12a	1.10 m	26.2 t	1.10 m	26.6 t
12b	1.04 m		1.04 m	
13	1.59 m	39.9 d	1.59 m	39.8 d
14a	1.44 m	32.0 t	1.44 m	32.1 t
14b	1.29 m		1.31 m	
15	1.57 m	25.9 d	1.61 m	25.8 d
16a	2.24 dd (15.0, 7.0)	26.8 t	2.48 dd (15.0, 7.0)	30.7 t
16b	2.19 dd (15.0, 7.5)		2.42 dd (15.0, 7.5)	
17		140.1 s		164.3 s
18	6.84 t (1.5)	138.3 d	5.76 s	122.0 d
19	3.89 d (1.5)	52.5 t		174.6 s
20	0.90 s	28.3 q	0.90 s	28.5 q
21	0.85 s	28.5 q	0.86 s	28.2 q
22	0.86 d (7.0)	16.9 q	0.87 d (7.0)	16.9 q
23	1.01 s	23.9 q	1.02 s	23.9 q
24a	3.94 dd (5.0, 9.5)	71.7 t	3.99 dd (4.0, 9.5)	71.5 t
24b	3.81 dd (6.8, 9.5)		3.81 dd (7.0, 9.5)	
25a		174.0 s	4.08 d (20.5)	55.7 t
25b			4.02 d (20.5)	
26a	3.77 dd (14.0, 7.0)	43.0 t	3.75 dd (13.8, 6.8)	42.1 t
26b	3.72 dd (14.0, 6.5)		3.70 dd (13,8, 7.0)	
27	2.94 t (6.8)	26.3 t	3.02 t (6.8)	25.3 t
28		134.7 s		133.3 s
29	7.00 br. s	118.0 d	7.25 br. s	118.1 d
30	8.06 br. s	135.8 d	8.55 br. s	135.2 d

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(12) Fasciospongine A (**1**): colorless oil; $[\alpha]^{23}_D$ −51.5 (*c* 0.26, MeOH); UV (MeOH) λ_{max} (log ϵ) 205 (4.28) nm, 230 (sh); IR (AgCl, film) ν_{max} 3448, 3142, 2939, 2921, 2864, 1672, 1635, 1460, 1382, 1250 (strong), 1221 (strong), 1061, 988, 813, 628, 585 cm^{-1}; ^1H and ^{13}C NMR see Table 1; HR-ESIMS *m/z* 584.3141 $[M + Na]^+$ (calcd for $C_{30}H_{47}N_3NaO_5S$, 584.3134).

a secondary methyl group (δ_H 0.86, d, J = 7.0 Hz, 3H). The ^{13}C NMR and DEPT spectra revealed 30 carbon signals due to one amide carbonyl, four methyls, thirteen methylenes, three sp^3 and four sp^2 methines, and three sp^2 and two quaternary carbons. Among them, one methylene (δ_C 71.7, δ_H 3.81 and 3.94) was ascribed to that bearing an oxygen atom, while two methylenes (δ_C 52.5, δ_H 3.89, 2H; δ_C 43.0, δ_H 3.77 and 3.72) were ascribed to those bearing nitrogen atoms. An amide carbonyl and four double bonds account for five degrees of unsaturation, and the remaining four degrees of unsaturation required the presence of four rings in **1**.

The gross structure of **1** was deduced from extensive analyses of the 2D NMR data, including the ^{1}H-^{1}H COSY, HMQC, and HMBC in CD_3OD (Figure 2). The ^{1}H-^{1}H COSY

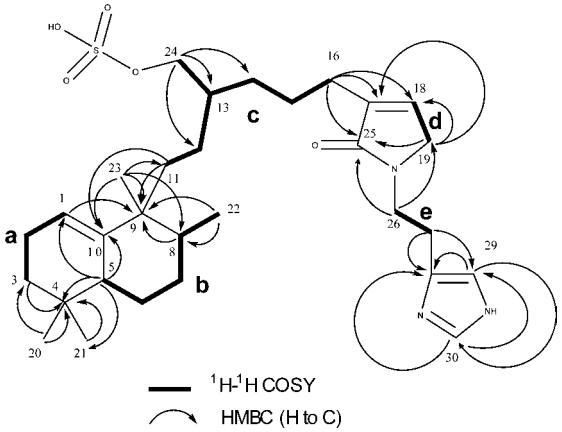

Figure 2. Selected two-dimensional NMR correlations for fasciospongine A (**1**).

spectrum of **1** revealed connectivities of five partial structures, **a** (C-1∼C-3), **b** (C-5∼C-8, C-22), **c** (C-11∼C-16, C-24), **d** (C-18∼C-19), and **e** (C-26∼C-27), as shown in Figure 2. In the decalin moiety, the connectivity of partial structures **a** and **b** was analyzed by the HMBC spectrum. HMBC correlations from H_2-3, H-5, H_3-20, and H_3-21 to quaternary carbon C-4 (δ_C 32.4), H_2-3, H_3-20, and H_3-21 to C-5 (δ_C 44.9), H-5, H_3-20, and H_3-21 to C-3 (δ_C 32.5), and H_2-3 and H-5 to C-20 (δ_C 28.3) and C-21 (δ_C 28.5) established the connection among C-3, C-4, C-5, C-20, and C-21. HMBC cross-peaks of H-5 to C-1 (δ_C 118.0) and C10 (δ_C 147.8), of H_2-6 to C-5 and C10 (δ_C 147.8), and of H-1 to C-5 indicated the connection of C-5 to C-10. HMBC cross-peaks of H-1, H-8, H_2-11, H_3-22, and H_3-23 to quaternary carbon C-9 (δ_C 43.8), and of H-8, H_2-11, and H_3-23 to C-10 constructed the connection of C-8, C-10, C-11, and C-23 to C-9. Accordingly, partial structure **c** was connected to partial structures **a** and **b** through C-9. HMBC correlations of H_2-16 and H_2-19 with C-17 (δ_C 140.1), C-18 (δ_C 138.3), and C-25 (δ_C 174.0) indicated that partial structure **c** was connected to amide carbonyl C-25 and partial structure **d** through C-17. Moreover, several significant HMBC correlations were observed for H-19 to C-25 (δ_C 174.0) and C-26 (δ_C 43.0) and H_2-26 to C-19 (δ_C 52.5) and C-25, suggesting that C-19, C-25, and C-26 were connected to each other through a nitrogen atom. The presence of an imidazole ring[13] was deduced from the molecular formula, the ^{13}C NMR chemical shift of C-28 (δ_C 134.7), C-29 (δ_C 118.0), and C-30 (δ_C 135.8), the ^{1}H NMR chemical shift of H-29 (δ_H 7.0, br. s), H-30 (δ_H 8.06, br. s) in methanol-d_4 and NH (δ_H 13.55, br. s) in $CDCl_3$, as well as HMBC correlations of H-29 to C-28 and C-30 and H-30 to C-28 and C-29. Furthermore, the cross-peaks of H-27 to C28 and C-29 suggested that partial structure **d** was connected to the imidazole ring. In addition, a sulfate group was placed at C-24 on the basis of the low-field resonance of H-24 (δ_H 3.94, dd, J = 5.0, 9.5 Hz; 3.81, dd, J = 6.8, 9.5 Hz) and C-24 (δ_C 71.7). The HMBC correlations of H_2-24 with C-13 (δ_C 39.9), C-14 (δ_C 32.0), and C-12 (δ_C 26.2) located the sulfate ester group at C-13 of the side chain.

The relative stereochemistry in the bicyclic portion of **1** was deduced from analysis of its NOESY spectrum (Figure 3). The NOESY correlations among H-5 (δ_H 1.64, dd, J =

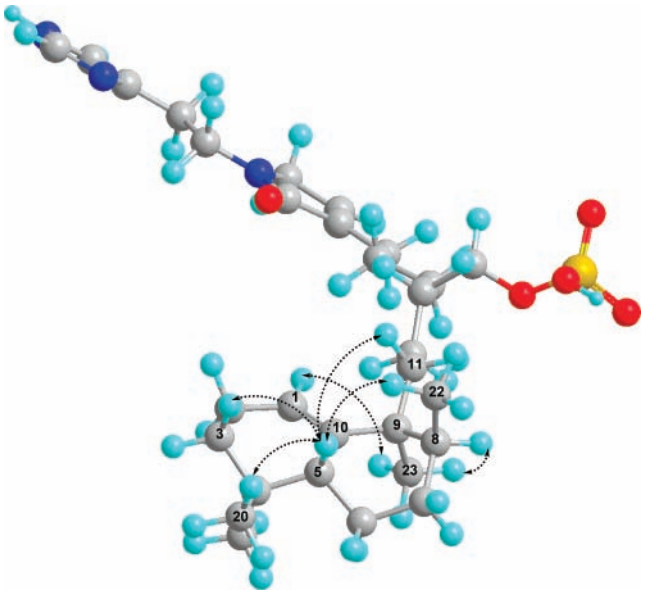

Figure 3. Key NOESY correlations (dotted arrow) and relative configurations of fasciospongine A (**1**).

2.5, 13.0 Hz), H-7β (δ_H 1.51 m), and H-11a (δ_H 1.75 m) suggested the β-orientations for both H-5 and C-11 to the cyclohexane ring. H-8 (δ_H 1.25 m) and H-1 (δ_H 5.34, dd, J = 2.3, 4.8 Hz) displayed NOESY cross-peak correlations with H_3-23 (δ_H 1.01, s), which indicated the α-orientations for both H-8 and H_3-23. Accordingly, C-22 should possess the β-orientation, and the NOESY correlation of H-5 and H-11a to H_3-22 (δ_H 0.86, d, J = 7.0 Hz) further supported the above deduction. In addition, the NOESY correlation of

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H-5 with H_3-20 (δ_H 0.90, s) indicated their syn relationship. The key NOESY correlations of compound **1** are shown in Figure 3.

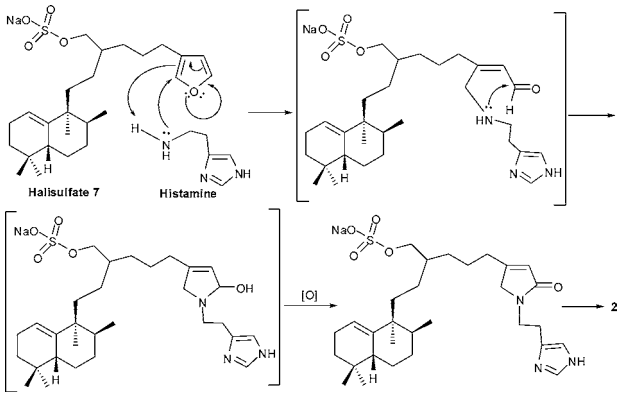
On the basis of the above evidence, the structure of compound **1** was determined as a sulfated sesterterpene alkaloid containing a decalin moiety, named fasciospongine A.

Fasciospongine B (**2**),[14] a colorless oil, was shown to have a molecular formula of $C_{30}H_{47}N_3O_5S$ by HR-ESIMS (*m*/*z* 584.3120; calcd for $[M+Na]^+$, 584.3134). The same molecular formula of compounds **2** and **1** indicated they were isomers. The ^1H NMR and ^{13}C NMR data of **2** were very similar to those of **1**; the major differences were that H-18 (δ_H 5.76, s) and C-18 (δ_C 122.0) in **2** were shifted to a higher field than those in **1** (δ_H 6.84, t, $J = 1.5$ Hz, δ_C 138.3), while C-17 (δ_C 164.3) in **2** was shifted to a lower field than that in **1** (δ_C 140.1), which suggested that the C-25 carbonyl carbon in **1** moved to C-19 in **2**. HMBC correlation of H-16 to C-25 (δ_C 55.7) further supported the above deduction. ^1H-^1H COSY, HMQC, HMBC, and NOESY experiments allowed the complete assignment for structure **2**.

Sesterterpene alkaloids are rare in nature. To date, only 5 tetracarbocyclic sesterterpene alkaloids[15] and 13 linear sesterterpene alkaloids[16] have been reported from natural sources. Interestingly, these two kinds of sesterterpene alkaloids were only discovered from marine sponges of the order Dictyoceratida. The isolation of fasciospongine A and B from *Fasciospongia* sp. reinforces the importance of sesterterpenes alkaloids as useful chemotaxonomic biomarkers for the marine sponges order of Dictyoceratida. In addition, two linear pyrroloseterterpenes, palinurines A and B, had been artificially generated from a furanosesterterpene through fungal biotransformation.[17] As far as we know, this is the first report of sulfated sesterterpene alkaloids, although sesterterpene alkaloids and sulfated sesterterpenes have been discovered.

The structure of fasciospongine is notable on two counts. First, it represents a new subclass of sesterterpene alkaloids with a dicarbocyclic decalin carbon skeleton. A second and unusual feature is the presence of sulfate functionality. One possible biogenetic pathway to fasciospongine B (**2**) is presented in Scheme 1.[17]

Scheme 1. Plausible Biogenetic Pathway for **2**



The plausible precursors are the sulfated sesterterpene, halisulfate 7,[3b,c] and histamine. In an enzyme-catalyzed reaction, the nucleophilic attack of histamine to C-5 of the furan ring would be followed by furan-ring fission and formation of an intermediate with an aldehyde at C-2. Subsequent cyclization and oxidation would result in the formation of the more stable *N*-2′-imidazolylethyldehydro-3-enepyrrolidin-2-one derivative (fasciospongine B, **2**).

Compounds **1** and **2** were evaluated for their inhibitory activities against *Streptomyces* 85E in the hyphae formation inhibition assay, according to an established protocol.[18] Compounds **1** and **2** exhibited potent activity and gave a 14 mm and 15 mm clear zone of inhibition, respectively, at the concentration of 2.5 μg/disk.

Acknowledgment. We are grateful to J. Davies for providing the strain of *Streptomyces* 85E and G. Cragg, D. Newman, and E. Brown for providing extracts from the NCI Natural Products Open Repository. This work was supported, in part, by an American Society of Pharmacognosy Research Starter Grant and Tackling Interdisplinary Research Roadblocks (TIRR) Grants from University of Minnesota Chemical Biology Initiative (L.C.C).

Supporting Information Available: Hyphae formation inhibition bioassay, ESI-MS, IR, UV, NMR spectral data tables and complete 2D NMR spectra for **1** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Fasciospongine B (**2**): colorless oil; $[\alpha]^{23}_D$ −52.4 (*c* 0.255, MeOH); UV (MeOH) λ_{max} (log ϵ) 205 (4.27) nm, 230 (sh); IR (AgCl, film)ν_{max} 3134, 2937, 1670, 1634, 1457, 1382, 1259 (strong), 1210 (strong), 1057, 989, 802, 629, 582 cm^{-1}; ^1H and ^{13}C NMR see Table 1; HR-ESIMS *m*/*z* 584.3120 $[M + Na]^+$ (calcd for $C_{30}H_{47}N_3NaO_5S$, 584.3134).

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