Agelastatin E, Agelastatin F, and Benzosceptrin C from the Marine Sponge *Agelas dendromorpha*

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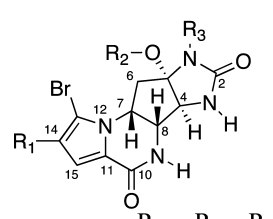
The study of the *n*-butanol extract of the New Caledonian sponge *Agelas dendromorpha* led to the isolation and identification of three new pyrrole-2-aminoimidazole (P-2-AI) alkaloids, named agelastatins E (**3**) and F (**4**) and benzosceptrin C (**5**), together with 10 known metabolites, agelastatin A (**1**), agelastatin D (**2**), sceptrin (**6**), manzacidin A, tauroacidin A, taurodispacamide A, nortopsentin D, thymine, longamide, and 4,5-dibromopyrrole-2-carboxamide. Their structures were assigned by spectroscopic data interpretation. All the compounds were tested for cytotoxic activity.

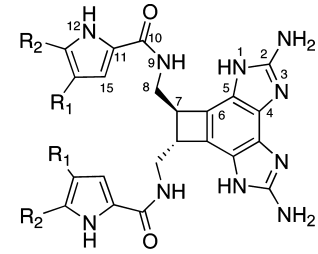
Marine alkaloids possessing a pyrrole-2-imidazole (P-2-AI) structure are known to be some of the most common and structurally intriguing metabolites isolated from marine sponges. Over the last 30 years, a number of molecules have been encountered that likely arise from clathrodin,[1] hymenidin,[2] and oroidin precursors.[3] Many of these compounds are reported to have interesting biochemical activities, such as blocking α-adrenoceptors,[4] serving as an antagonist of serotonergic receptors,[5] activating actomyosin ATPase,[6] and inhibiting kinase activity,[7] as well as antibacterial,[8] antifungal,[8] and antihistamine activities.[9] Among them, the immunosuppressive activity of palau'amine,[10] the kinase inhibition of debromohymenialdesin,[11] the antitumor activity of girolline,[12] and the cytotoxicity of agelastatin A[13] are remarkable. Agelastatin A (**1**), along with a minute quantity of agelastatin B, was first reported from the sponge *Agelas dendromorpha*.[13a] Later on, in addition to agelastatins A and B, the closely related compounds agelastatins C and D were isolated from the sponge *Cymbastela* sp.[13b]

During our search for bioactive substances from marine organisms, we have previously reported several pyrrole-2-aminoimidazole (P-2-AI) alkaloids, together with a proposal for their biogenesis and biomimetic synthesis.[14] In line with the pursuit of biological activities and the structure-guided isolation for biosynthetic investigations, we have recently carried out a chemical study of the New Caledonian sponge *Agelas dendromorpha* (Lévi, 1993) (order Agelasida, family Agelasidae). The freeze-dried sponge was extracted with MeOH, and the extract was partitioned between *n*-BuOH and H_2O. The *n*-BuOH fraction was subjected to silica gel column chromatography followed by preparative RP_{18} HPLC to yield three new minor compounds, agelastatin E (**3**), agelastatin F (**4**), and benzosceptrin C (**5**) together with a series of known alkaloids. These were agelastatin A (**1**),[13a] agelastatin D (**2**),[13b] sceptrin (**6**),[15] manzacidin A,[16] tauroacidin A,[17] taurodispacamide A,[18] nortopsentin D,[19] thymine, longamide,[20] and 4,5-dibromopyrrole-2-carboxamide.[21] The structures of the known metabolites were determined by comparison of their ^1H and ^{13}C NMR spectra with those reported in the literature. Here, we describe the isolation of the new compounds **3**, **4**, and **5**.

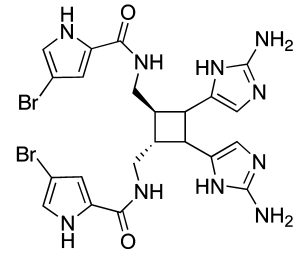
The ESI mass spectrum of agelastatin E (**3**) showed pseudomolecular ion peaks at *m*/*z* 353:355 (1:1) $[M + H]^+$, indicating the presence of one bromine atom in the molecule. The molecular formula of **3** was revealed as $C_{13}H_{15}{}^{79}BrN_4O_3$ by HRESIMS. The



	R_1	R_2	R_3
1	H	H	Me
2	H	H	H
3	H	Me	Me
4	Br	H	H



	R_1	R_2
5	Br	Br
7	H	H
8	Br	H



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UV absorption at λ_{max} 286 nm was attributed to a substituted pyrrole chromophore, while IR absorption at 3223, 1656, and 1642 cm^{-1} indicated the occurrence of NH and amide carbonyl functionalities. The ^1H and ^{13}C NMR spectra of compound **3** were similar to those of agelastatin A (**1**),[13a] except for an additional signal arising at δ_H 3.18 (s, 3H) for either an $-OCH_3$ or $-NCH_3$ group (Table 1). The position of the CH_3 with δ_H 3.18 (δ_C 50.8) was established as an $-OCH_3$ at C-5 on the basis of its HMBC correlation with δ_C 101.0 (C-5). The signal at δ_H 2.78 (3H, s) showed correlations with amide carbonyls at C-2 (δ_C 162.2) and 101.0 (C-5), confirming the presence of an NCH_3 group (Figure 1). The $^1H-^1H$ COSY spectrum showed the connectivities from H-6a/b (δ_H 2.66, dd, J = 12.9, 6.6 Hz/2.14, dd, J = 12.9 Hz) to H-7 (δ_H 4.62, dd, J = 12.6, 6.6 Hz); H-7 to H-8 (δ_H 4.11, d, J = 5.4 Hz); and H-14 (δ_H 6.32, d, J = 4.1 Hz) to H-15 (δ_H 6.91, d, J = 4.1 Hz) for a cyclopentane ring and a monobromopyrrole moiety, respectively. The pyrrole signals at δ_H 6.32 (d, J = 4.1 Hz, H-14) and δ_H 6.91 (d, J = 4.1 Hz, H-15) showed HMBC correlations at δ_C 124.2 (C-11), 107.5 (C-13), 116.2 (C-15) and δ_C 124.2 (C-11), 107.4 (C-13), 114.0 (C-

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Table 1. ^{1}H and ^{13}C NMR Data for Agelastatins E (**3**) and F (**4**) Recorded in CD_3OD (600 MHz)

	agelastatin E (**3**)				agelastatin F (**4**)			
position	δ_C	δ_H (*J* in Hz)	COSY	HMBC[b]	δ_C	δ_H (*J* in Hz)	COSY	HMBC[b]
1-NH								
2	162.2				162.8			
3-NH		7.3				7.3		
4	61.2	4.08, bs		2, 5, 7, 8	69.5	3.92, bs		2, 5, 7
5	101.0				93.3			
6a	39.3	2.66, dd (12.9, 6.6)	H-6b, H-7	5, 6a, 7	43.7	2.58, dd (12.9, 6.6)	H-6b, H-7	4, 5, 6, 7, 8
6b		2.14, bt (12.9)	H-6a, H-7	5, 6a, 7, 8		2.24, bt (12.9)	H-6a, H-7	5, 6, 7
7	53.9	4.62, m (12.6, 6.6)	H-8	6, 11, 13	55.8	4.74, m (12.6, 6.6)	H-8	6, 7, 11, 13
8	62.2	4.11, d (5.4)	H-7	4, 6	62.2	4.14, d (5.5)	H-7	4, 5, 6
9-NH		7.92				8.1		
10	161.2				160.2			
11	124.2				125.0			
12								
13	107.4				108.7			
14	114.0	6.32, d (4.1)	H-15	11, 13, 15	101.1			
15	116.2	6.91, d (4.1)	H-14	11, 13, 14	117.1	6.98, s		11, 14
N-Me	24.7	2.78, s		2, 5, 6				
O-Me	50.8	3.18, s		5				

[a] Shifts of D_2O exchangeable protons were detected in DMSO-d_6 at 500 MHz: δ_H 6.86, 6.39 for agelastatins E (**3**) and F (**4**); δ_H 5.7, 8.04, 8.34 for benzosceptrin C (**5**). [b] HMBC correlations are from the proton stated to the indicated carbon.

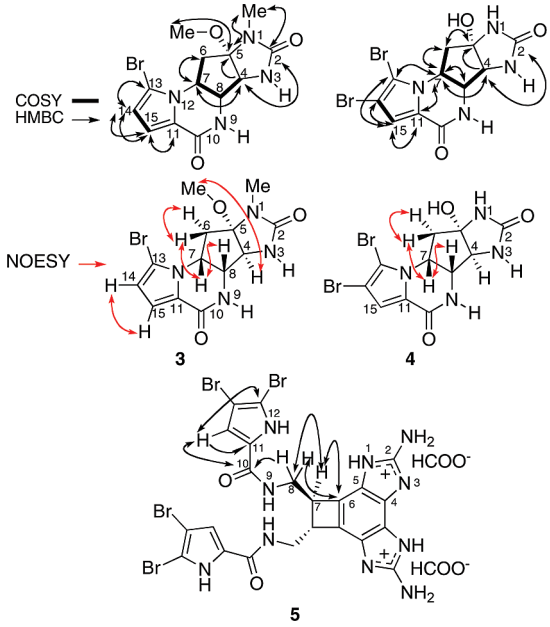

Figure 1. Key COSY, HMBC, and NOESY correlations of agelastatins E (**3**) and F (**4**) and benzosceptrin C (**5**).

14), respectively. The HMBC correlations of δ_H 4.62 (H-7) with δ_C 124.3 (C-11) and 107.4 (C-13) established the connection between the cyclopentane ring and the pyrrole moiety. Further analysis of the HMBC experiment established the connectivity of H-6 methylene protons at δ_H 2.66 (dd) and 2.14 (br t) to C-5, C-6, C-7 and C-5, C-6, C-7, C-8, respectively. The broad singlet at δ_H 4.08 (H-4) showed correlations with C-2, C-5, C-7, and C-8, while the doublet at δ_H 4.11 (H-8) showed correlations with C-4 and C-6. The quaternary carbon signals δ_C 162.2 (C-2), 101.0 (C-5), 124.3 (C-11), and 107.4 (C-13), invisible in the 1D ^{13}C NMR spectrum, have been confirmed by HMBC experiment. Taken together, the data and the very similar 1D ^{1}H NMR spectrum to that of agelastatin A (**1**) gave the structure **3** for this compound, which was named agelastatin E. NOESY experiments (Figure 1) showed correlations between the OMe group at position C-5 and H-4 on one hand and between H-7 and H-6/H-8 on the other hand, indicating the *cis*-fused cycles at C_4-C_5 and C_7-C_8. The relative configuration for **3** was revealed to be the same as for agelastatin A (**1**). Whether agelastatin E (**3**) is a naturally methylated derivative of agelastatin A (**1**) or just a result of its dehydration and methoxylation is an interesting question. The second process could occur during the purification process in the presence of MeOH.

Agelastatin F (**4**) was obtained as a white solid and was sparingly soluble in MeOH. The positive ESI-MS spectrum showed pseudomolecular ion peaks at *m/z* 405, 407, and 409 (1:2:1) for the presence of two bromine atoms in the molecule. The molecular formula of **4** was revealed as $C_{11}H_{10}{}^{79}Br_2N_4O_3$ by (−)-HRESIMS. The ^{1}H NMR spectrum of **4** was very similar to that of agelastatin D (**2**),[13b] but lacked a proton signal at δ_H 6.33 (H-14), which is replaced by a Br atom, as revealed by the molecular formula. The pyrrole signal at δ_H 6.98 showed HMBC correlations to the carbons at δ_C 125.03 (C-11), 108.7 (C-13), and 101.1 (C-14) (Table 1). There were HMBC correlations from H-7 to the pyrrolic C-11 and C-13. The H-15 (δ_H 6.98) bonded to C-15 (δ_C 117.1) showed strong HMBC correlations with C-11 and C-14, allowing for only the 13,14 bromine substitution pattern, positioning the hydrogen at C-15. The strongly down-shifted C-14 (δ_C 101.1) and the comparison with NMR spectra published for agelastatin B[13b,e] indicated that this position was brominated. The UV absorption at λ_{max} 288 nm was attributed to a substituted pyrrole chromophore. The IR spectrum showed absorption bands at 3254, 1681, and 1634 cm^{-1} for OH, NH, and amide carbonyl groups. All of the connections were established by HMBC and COSY experiments. The $^{1}H-^{1}H$ COSY spectrum showed the connectivities from H-6a/b to H-7 and H-7 to H-8 (Figure 1). The methylene protons (H-6) of the cyclopentane ring, δ_H 2.24 (br t) and 2.58 (dd), showed HMBC connections with δ_C 93.3 (C-5), 43.7 (C-6), 55.8 (C-7) and δ_C 69.5 (C-4), 93.3 (C-5), 43.7 (C-6), 55.8 (C-7), 62.2 (C-8), respectively. The singlet at δ_H 3.92 was connected to 162.8 (C-2), 93.3 (C-5), and 55.8 (C-7). The multiplet at δ_H 4.74 (H-7) and doublet at δ_H 4.14 (H-8) showed correlations with δ_C 93.3 (C-5) and δ_C 43.7 (C-6), 125.0 (C-11), 108.7 (C-14), respectively. As for compound **3**, NOESY experiments of **4** showed clear correlations between H-7 and H-6/H-8, while H-4 does not correlate with any proton. These observations together with the very similar 1D ^{1}H NMR spectra of **3** and **4** included in the Supporting Information indicate that the relative configuration of **4** must be the same as for **3**.

The ESI-MS of compound **5** displayed five pseudomolecular ion peaks at *m/z* 771, 773, 775, 777, and 779 $[M + H]^+$, which indicated the presence of four bromines in the molecule. The molecular formula of **5** was determined to be $C_{22}H_{18}{}^{79}Br_4N_{10}O_2$ by (−)-HRESIMS. The ^{1}H NMR spectrum displayed only a few protons at δ_H 3.43(m)/3.97(dd) for H-8, δ_H 3.71(dd, H-7), and δ_H 6.60(d, H-15), suggesting it to be a symmetric molecule. The comparison of the ^{1}H NMR spectrum of **5** with the data of

benzosceptrins A (**7**) and B (**8**), recently isolated in our group,[22] suggested it to be a benzosceptrin-type compound with the benzocyclobutane ring system. The ^{1}H NMR spectra were similar in the upfield region with the difference in the pyrrole proton region. Only a single pyrrole proton peak at δ_H 6.60 (2H, H-15) was observed. Thus, the molecule differs from benzosceptrins A (**7**) and B (**8**) in the degree of bromination. Interestingly, the chemical shifts of the remaining pyrrolic protons are not dramatically changed with the degree of bromination. Comparison of the chemical shifts of H-13 (δ_H 8.86), H-14 (δ_H 6.08), and H-15 (δ_H 6.61) in benzosceptrin A (**7**)[22] with H-13 (δ_H 8.86) and H-15 (δ_H 6.61) in the dibrominated benzosceptrin B (**8**) and the signal at δ_H 6.60 in **5** clearly show that it corresponds to H-15. Similar chemical shifts have been observed for debromosceptrin,[23] sceptrin, and dibromosceptrin.[24] The ^{13}C NMR spectrum gave the characteristic values for the brominated carbons at δ_C 100.3 (C-14) and 106.4 (C-13). The intense signal at δ_C 114.4 was attributed C-15. This was confirmed by the HMBC correlations of H-15 with C-10 at δ_C 162.1 and C-11 at δ_C 128.6. In fact, the HMBC correlations were simlar to those observed for benzosceptrin A (Figure 1).[22] The ^{1}H−^{1}H COSY spectrum showed correlations between δ_H 3.43 (m, H-8a), 3.97 (dd, H-7), and 3.71 (dd, H-8b). The ^{13}C NMR spectrum gave the corresponding carbon values at δ_C 49.7 (CH-7) and 43.7 (CH_2-8).

The specific rotation, $[\alpha]^{25}_D$ −22.7, showed the C7−C7′ *trans* configuration, indicating the preservation of the C_2 symmetry axis like for sceptrin (**6**) and benzosceptrins A and B. A *cis* configuration for C7−C7′ would give the achiral *meso* compound. This third remarkable and unique benzocyclobutane metabolite was named benzosceptrin C (**5**).[25]

For biogenetic considerations, we have previously suggested that the agelastatin skeleton could be derived from oroidin through subtle tautomerization and the dual reactivity induced by the 2-aminoimidazole portion of the structure.[14a] A preagelastatin motif like that we have proposed is clearly shown by the dimeric natural product nagelamide J, recently isolated by Kobayashi and co-workers.[26] A discussion regarding the mechanism for formation of the benzosceptrin skeleton has also been reported in our previous paper.[22]

The pure compounds were screened for cytotoxicity against the KB cell line,[27] and except for agelastatin A (**1**) (100% activity at 30 and 3 μM), all of the compounds lacked significant bioactivity at 30 μM. The pharmacological activities of agelastain A have been extensively studied.[28] The sharp difference between the high activity of agelastatin A compared to the natural derivatives agelastatins B−F reveals very little flexibility for synthetic analogues and structure−activity relationship studies.

In conclusion, the majority of the compounds isolated from *A. dendromorpha* are of the pyrrole-2-aminoimidazole type. In addition to the known cytotoxic compounds agelastatin A (**1**) and agelastatin D (**2**), which have already been isolated from the same sponge, we have isolated agelastatins E (**3**) and F (**4**). Benzosceptrin C (**5**) was also isolated as a new P-2-AI derivative. Moreover, metabolites having a substituted benzocyclobutane such as benzosceptrin C (**5**), described in this paper, and the benzosceptrins A and B,[22] which we have reported earlier, are completely new. Their significance for chemistry, biology, and chemical ecology is an interesting question. Accordingly, the presence of these compounds should stimulate considerable synthetic interest. It is noteworthy that there are very few examples of benzocyclobutane-containing natural products.

Experimental Section

General Experimental Procedures. Optical rotations were measured in MeOH on a Jasco P1010 polarimeter. The UV spectra were recorded on a Waters 996 photodiode array detector in the HPLC solvent. The IR spectra were measured (neat) on a Perkin-Elmer BX-FT-IR spectrometer. NMR spectra were recorded on Bruker Avance 600 MHz and DRX 500 MHz spectrometers. The chemical shifts were referenced to the residual solvent signal (CD_3OD, $\delta_H = 3.32$, $\delta_C = 49.0$). HRMS data were obtained with a hybrid linear trap/orbitrap mass spectrometer (LTQ-orbitrap, ThermoFisher) in electrospray ionization mode by direct infusion of the purified compounds. Preparative HPLC was performed on an autoprep system (Waters 600 controller and Waters 600 pump with a Waters 996 photodiode array detector). Samples were injected by a Waters 2700 sample manager.

Sponge Material. The sponge *Agelas dendromorpha* (order Agelasida, family Agelasidae) was collected during the research cruise Terrasses (October 2008) on a sea mount of the Norfolk rise (23°41′ S, 168°00′ E), New Caledonia, at a depth of 250 m. The voucher sample is preserved in Muséum National d'Histoire Naturelle in Paris under the accession number ORSTOM-R1569.

Extraction and Isolation. The lyophilized sponge *A. dendromorpha* (150 g) was extracted with MeOH (500 mL × 3). After removing the solvent *in vacuo*, the combined MeOH extract was partitioned between *n*-BuOH (200 mL × 3) and H_2O to afford an *n*-BuOH fraction (6.5 g). This *n*-BuOH fraction was chromatographed on a silica gel column (VersaPak, Sigma, 40−150 mm) with gradient elution of MeOH−CH_2Cl_2 to give 15 subfractions (B1−B15). The alkaloid-rich fractions B8−B15 were further purified on a preparative C18 HPLC (X-bridge column, 19−150 mm), flow rate 17 mL/min, MeOH−0.1% HCOOH and H_2O−0.1% HCOOH, UV detection at 270 nm. Further purification of the B8 fraction yielded thymine (1.6 mg, t_R 12.2 min), longamide (5.6 mg, t_R 33.1 min), and 4,5-dibromopyrrole-2-carboxamide (6.5 mg, t_R 35.7 min). Fractions B10 and B11 yielded a major compound, agelastatin A (**1**, 380 mg, t_R 31.0 min). The purification of fractions B12−15 afforded three new compounds along with several known compounds, agelastatin D (**2**, 2.0 mg, t_R 26.1 min), agelastatin E (**3**, 1.5 mg, t_R 34.4 min), agelastatin F (**4**, 20.9 mg, t_R 34.1 min), benzosceptrin C (**5**, 0.6 mg, t_R 35.1 min), sceptrin (**6**, 9.3 mg, t_R 17.8 min), manzacidin A (16.0 mg, t_R 29.5 min), tauroacidin A (16.9 mg, t_R 32.7 min), taurodispacamide (37.2 mg, t_R 32.7 min), and nortopsentin D (34.1 mg, t_R 35.7 min). The HPLC (LC-MS) of all the isolated compounds was carried out on an analytical column (Sunfire C18, 5 μm, 4.6−150 mm, flow rate 0.7 mL/min) with an isocratic gradient for 5 min using 98:2 (H_2O−0.1% HCOOH to MeOH−0.1% HCOOH) followed by a linear gradient to 100% MeOH−0.1% HCOOH in 45 min. The retention time, t_R, for all the isolated compounds is based on this analytical HPLC.

Agelastatin A (1): white solid; $[\alpha]^{25}_D$ −58.5 (*c* 0.21, MeOH) (lit.[13a] −84.3 (*c* 0.3, EtOH)).

Agelastatin D (2): white solid, $[\alpha]^{25}_D$ −12 (*c* 0.07, MeOH) (lit.[13b] not given).

Agelastatin E (3): white solid; $[\alpha]^{25}_D$ −28 (*c* 0.09, MeOH); UV (MeOH) λ_{max} (log ε) 232 (3.95), 286 (4.08); IR (neat) ν_{max} 3223, 2933, 1656, 1642, 1552, 1421, 1351, 1197, 1082, 1037 cm^{-1}; ^{1}H and ^{13}C NMR (CD_3OD, 600 MHz), Table 1; ESIMS *m/z* 355, 357 (1:1) $[M + H]^+$; HRESIMS *m/z* 353.0276 $[M - H]^-$ (calcd for $C_{13}H_{15}{}^{79}BrN_4O_3$, *m/z* 353.0255).

Agelastatin F (4): colorless, amorphous solid; $[\alpha]^{25}_D$ −34.3 (*c* 0.11, MeOH); UV (MeOH) λ_{max} (log ε) 208 (4.0), 238 (3.98), 288 (4.18); IR (neat) ν_{max} 3254, 1681, 1634, 1552, 1373, 1346, 1221, 1112, 1067 cm^{-1}; ^{1}H and ^{13}C NMR (CD_3OD, 600 MHz), Table 1; ESIMS *m/z* 405, 407, 409 $[M + H]^+$; HRESIMS *m/z* 402.9071 $[M - H]^-$ (calcd for $C_{11}H_{10}{}^{79}Br_2N_4O_3$, *m/z* 402.9048).

Benzosceptrin C (5): white solid; $[\alpha]^{25}_D$ −22.7 (*c* 0.13, MeOH); UV (MeOH) λ_{max} (log ε) 229 (4.04), 276 (3.90); IR (neat) ν_{max} 3156, 1679, 1577, 1565, 1555, 1347, 1228, 1096, 1038, 750, 613 cm^{-1}; ^{1}H NMR (CD_3OD, 600 MHz) 3.71 (dd, J = 6.7, 3.8 Hz), 3.97 (dd, J = 10.1, 3.9 Hz), 3.43 (m), 6.60 (s); ^{13}C NMR (CD_3OD, 150.8 MHz) 43.7 (C8, C8′), 49.7 (C7, C7′), 100.3 (C14, C14′), 106.4 (C13, C13′), 114.4 (C15, C15′), 120.2 (C6, C6′), 128.6 (C11, C11′), 154.5 (C2, C2′), 162.1 (C10, C10′), C4 and C5 were not detected; ESI-MS *m/z* 771, 773, 775, 777, 779; (−)-HRESIMS *m/z* 768.8301 $[M - H]^-$ (calcd for $C_{22}H_{18}{}^{79}Br_4N_{10}O_2$, *m/z* 768.8277).

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Supporting Information Available: NMR spectra of compounds **1**−**5** are available free of charge via the Internet at http://pubs.acs.org.

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