Bromopyrrole Carboxamide Biosynthetic Products from the Caribbean Sponge *Agelas dispar*

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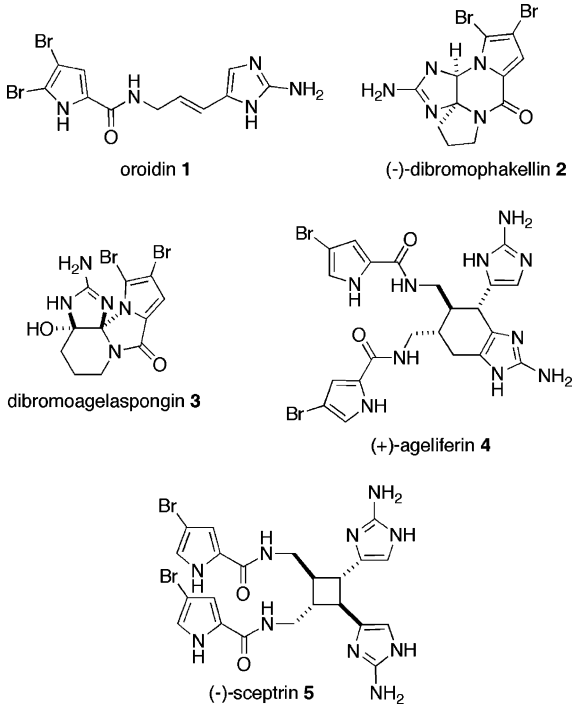
Two new bromopyrrole alkaloids, dispyrin (**6**) and dibromoagelaspongin methyl ether (**12**), were isolated from the Caribbean sponge *Agelas dispar*, collected near the Venezuelan island La Blanquilla, and their structures were elucidated from spectroscopic data analysis. Dispyrin (**6**) contains a novel bromopyrrole tyramine motif that has no precedent in marine natural products chemistry and represents a notable variation from the oroidin class compounds consistently produced by species of *Agelas* in general. Compounds isolated from Caribbean *Agelas* species were found to possess a unique biogeographical bromination trend.

Interest in the biology and chemistry of sponges that belong to the genus *Agelas* continues despite years of study devoted to this taxa. The members of this group are found throughout the world's tropical coral reefs, and knowledge of its species continues to expand. For example, in 1992 it was noted that 12 species of *Agelas* were well documented,[1] while today the taxonomic record shows that there are 33 such species.[2] Surprisingly, the natural history of Caribbean species of *Agelas*, which are extremely well described,[3−10] is as rich as that of those from the Indo-Pacific because 55% of the known taxa are found in the former source.[2] From a chemodiversity viewpoint, the chemistry of *Agelas* described in the literature is quite broad. Many of its metabolites are of mixed biogenetic origin, as illustrated by sesquiterpenoid derivatives of hypotaurocyamine (i.e., agelasidines),[10−12] diterpene adenine derivatives (i.e., agelines and agelasines),[13−16] polycyclic bromopyrrole-imidazole alkaloids that range from monomers (headed by oroidin (**1**))[17,18] to fused polycyclic monomers, such as dibromophakellin (**2**)[19] and dibromoagelaspongin (**3**),[20] and dimers, such as ageliferin (**4**)[21] and sceptrin (**5**).[22]

We consider the congeners of the oroidin class of alkaloids to be of particular value in further chemical biological investigations of *Agelas*. Two recent milestone discoveries include the following: (1) In 2003, the Richelle-Maurere group reported that oroidin (**1**) (and sceptrin (**5**)) are directly biosynthesized by the sponge (Caribbean *A. conifera* (Schmidt, 1870)), not the associated bacteria, and these compounds are localized in the spherulous cells.[23] (2) In 2004, the UCSC group presented an analysis of the stereostructural and optical relationships among the oroidin structures that can be obtained from Indo-Pacific sponges.[24] As a prelude to beginning biosynthetic-based research, our attention turned to identifying Caribbean taxa that could be a reliable source of bromopyrrole carboxamide-containing products. The species *A. dispar* was chosen for this project even though past reports on its chemistry between 1975 and 2000 seemed variable.[3−5,16,25,26]

Results and Discussion

This project focused on a specimen collected in 2001 near the Venezuelan island La Blanquilla. We were successful in finding both known and new brominated indole compounds in this sponge. The five known compounds all contained the bromopyrrole carboxamide unit. This biosynthetic moiety was also present in a new compound, dispyrin (**6**), along with a novel brominated tyramine motif. The latter is reminiscent of a variety of brominated tyrosine-derived compounds, including ma'edamine A (**7**)[27] and aplysamine-2 (**8**),[28] isolated from marine sponges, including *Pseudoceratina verrucosa*,[29] *Psammaplysilla purpurea*,[30−33] and *Suberea* species.[27,34]



In addition to dispyrin (**6**), known compounds dibromophakellin (**2**),[19] (−)-monobromophakellin (**9**),[19] (−)-dibromoisophakellin (**10**),[35] (−)-monobromoisophakellin (**11**),[8] and dibromoagelaspongin (**3**)[20] were isolated from *A. dispar*, showing for the first time that this sponge possesses biosynthetic enzymes to produce many members of the oroidin class. A second new compound, dibromolagelaspongin methyl ether (**12**), also isolated from *A. dispar*, is likely an artifact of workup, as exhaustive extraction was performed in methanol. Side-by-side comparison of NMR chemical shifts of dibromoagelaspongin methyl ether (**12**) with dibromoagelaspongin (**3**) showed that all ^{13}C shifts were nearly identical in MeOH-d_4, but an additional resonance indicated the presence of the methyl ether (Supporting Information, Table S1).

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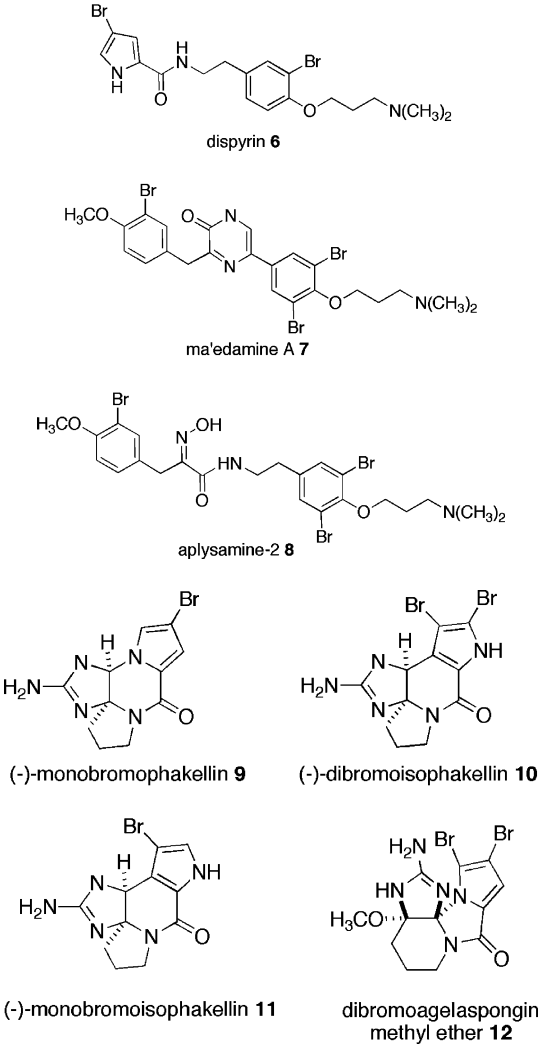


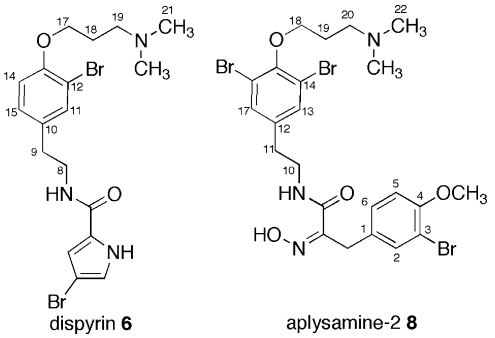
The molecular formula of dispyrin (**6**) was established as $C_{18}H_{23}N_3O_2Br_2$ by HRESIMS $[M + H]^+$ *m*/*z* 472.0241 (calculated *m*/*z* 472.0229). The data in Table 1 summarize the ^{13}C resonances observed for 17 carbons, which, when compared to C_{18} in the molecular formula, indicated the presence of two symmetrical carbons. The 3-bromopyrrole carboxamide moiety was recognized by the signals at δ 6.86 (d, 2.0 Hz, 1H) and 6.68 (d, 2.0 Hz, 1H) in the ^1H NMR spectrum (MeOH-d_4) and by the diagnostic pattern of ^{13}C NMR resonances (δ_C 127.6, C-2; δ_C 113.1, C-3; δ_C 96.2, C-4; δ_C 122.7, C-5; δ_C 163.5, C-6), which were very similar to the values reported in the literature for other *Agelas* 3-bromopyrrole alkaloids.[4,5,8,9,21,22,25,36] In addition, the ^{13}C NMR data showed resonances due to five sp^3 methylenes at δ_C 41.9 (C-8), 35.3 (C-9), 67.5 (C-17), 25.6 (C-18), and 57.2 (C-19) and two isochronous *N*-methyl groups at δ_C 43.8 (C-20, C-21). The HMBC correlations from H-17 (δ 4.14) to C-18 and C-19 and from H-19 (δ_H 3.35) to C-21 together with $^1H-^1H$ COSY couplings H-17 (δ 4.14) to H-18 (δ 2.24) and H-18 (δ 2.24) to H-19 (δ 3.35) defined the $O-CH_2$-(17)$-CH_2$(18)$-CH_2$(19)$-N-Me_2$(20, 21) system outlined in Figure 1. The HMBC correlations from H-9 (δ_H 2.77) to C-8, C-10, and C-15, together with COSY correlation from H-8 to H-9, also support assignment of $-NH-CH_2$(8)$-CH_2$(9)$-$Ar. Furthermore, the HMBC correlation from the methylene (C-8) to the carbonyl C-6 (δ_C 163.5) established connectivity to the bromopyrrole carboxamide subunit. The only possible location for the remaining bromine atom was on the aromatic ring.

Establishing the substitution pattern of the aromatic ring was the next step to defining the additional four units of unsaturation. The $^3J_{14,15}$ = 8.0 Hz and $^4J_{11,15}$ = 2.0 Hz indicated a 1,2,4-trisubstited aromatic ring, with six possible arrangements for the three substituents, consisting of a 3-oxy-*N*,*N*-dimethylpropan-1-amine, a Br, and an ethylene group linked to the bromopyrrole carboxamide residue. The HMBC correlation from H-9 to C-10 and to C-15 placed the ethylene adjacent to C-15. The requirement for a vicinal relationship between H-14 and H-15 ruled out two possible structures, and the *meta* coupling noted above to H-15 ruled out two others. The HMBC correlations from H-14 (δ 6.96 attached to δ_C = 118) and from H-15 (δ 7.16 attached to δ_C = 130) to C-13 (δ 155.0) firmly established the location and assignment of the latter carbon with the attached phenol oxygen. These data further dictated that C-14 was *ortho* to C-13 and that C-15 was *meta* to C-13, which ruled out the fifth possibility and was consistent with the final structure of dispyrin (**6**) shown in Figure 1.

A final test in further support of structure **6** involved comparing its aromatic ^{13}C shifts to similar portions of the mono- and dibrominated phenol rings of aplysamine-2 (**8**).[28] Shown in Table 1 is a side-by-side comparison of these data, and there is excellent agreement in the shifts at C-15 of dispyrin (**6**) and at C-6 of the monobrominated portion of aplysamine-2 (**8**). Further evidence for the tyrosine ether-derived substructure was the nearly identical shifts of C-11 of dispyrin (**6**) and C-13 of aplysamine-2 (**8**) and similar shifts at C-17 to C-21 of **6** versus that at C-18 to C-22 of **8**.

An interesting biogeographical trend emerges from a comparison of the numerous Caribbean *Agelas*-derived natural products, such

Table 1. NMR Spectroscopic Data (500 MHz for ^1H and 125.7 MHz for ^{13}C, MeOH-d_4) for Dispyrin (**6**)



dispyrin (**6**)				aplysamine-2 (**8**)	
position	δ_H	DEPT	δ_C	position	δ_C
2	6.86 (d, 2.0 Hz)	CH	122.7		
3		C	96.2		
4	6.68 (d, 2.0 Hz)	CH,	113.1		
5		C	127.6[a]		
6		C	163.5		
8	3.46 (t, 7.5 Hz)	CH_2	41.9	10	41.4
9	2.77 (t, 7.5 Hz)	CH_2	35.3	11	35.2
10		C	135.3	12	140.3
11	7.44 (d, 2.0 Hz)	CH	134.6	13	134.4
12		C	113.1	14	118.7
13		C	155.0[a]	4	155.8
14	6.96 (d, 8.0 Hz)	CH	114.8	5	112.1
15	7.16 (dd, 8.0, 2.0 Hz)	CH	130.3	6	131.7
17	4.14 (t, 5.5 Hz)	CH_2	67.5	18	71.7
18	2.24 (m)	CH_2	25.6	19	26.4
19	3.35 (t, 7.0 Hz)	CH_2	57.2	20	56.9
21, 20	2.93 (s)	CH_3	43.8	22	43.6

[a] Observed in HMBC.

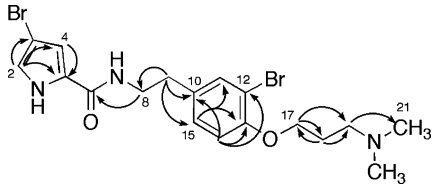
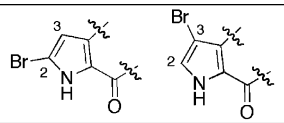


Figure 1. g-HMBC correlations of dispyrin (**6**).

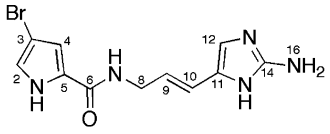
Table 2. Divergent Biosynthetic Pathway of Monobromopyrrole Carboxamide-Containing Natural Products from Caribbean *Agelas* Species



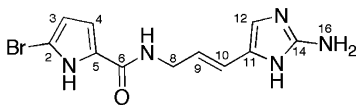
compound	location	source	bromination pattern	
nagelamide E[a]	Indo-Pacific	*Agelas* sp.		X
mukanadins A-C[b]	Indo-Pacific	*Agelas nakamurai*		X
slagenins A-C[c]	Indo-Pacific	*Agelas nakamurai*		X
agelastatin A[d]	Indo-Pacific	*Agelas dendromorpha*	X	
5-bromopyrrole-2-carboamide[e]	Indo-Pacific	*Agelas nakamurai*	X	
hymenidin[f]	Caribbean	*Agelas* sp.		X
keramidine[g]	Caribbean	*Agelas dispar*		X
ageliferin[h]	Caribbean	*Agelas conifera*		X
monobromoisophakellin (**11**)[i]	Caribbean	*Agelas dispar*		X
sceptrin[j]	Caribbean	*Agelas sceptrum*		X
bromosceptrin[k]	Caribbean	*Agelas conifera*		X
dispacamide B[l]	Caribbean	*Agelas dispar*		X
dispacamide D[l]	Caribbean	*Agelas longissima*		X
dispyrin (**6**)	Caribbean	*Agelas dispar*		X
monobromophakellin (**9**)[i]	Caribbean	*Agelas dispar*		X
clathramides A & B[m]	Caribbean	*Agelas clathrodes*		X
clathramides C & D[n]	Caribbean	*Agelas clathrodes*		X

[a] Endo, T.; Tsuda, M.; Okada, T.; Mitsuhashi, S.; Shima, H.; Kikuchi, K.; Mikami, Y.; Fromont, J.; Kobayashi, J. *J. Nat. Prod.* **2004**, *67*, 1262−1267. [b] Uemoto, H.; Tsuda, M.; Kobayashi, J. *J. Nat. Prod.* **1999**, *62*, 1581−1583. [c] Tsuda, M.; Uemoto, H.; Kobayashi, J. *Tetrahedron Lett.* **1999**, *40*, 5709−5712. [d] Dambrosio, M.; Guerriero, A.; Debitus, C.; Ribes, O.; Pusset, J.; Leroy, S.; Pietra, F. *J. Chem. Soc., Chem. Commun.* **1993**, 1305−1306. [e] Iwagawa, T.; Kaneko, M.; Okamura, H.; Nakatani, M.; van Soest, R. W. M. *J. Nat. Prod.* **1998**, *61*, 1310−1312. [f] Bickmeyer, U.; Drechsler, C.; Kock, M.; Assmann, M. *Toxicon* **2004**, *44*, 45−51. [g] Cafieri, F.; Fattorusso, E.; Mangoni, A.; Taglialatela-Scafati, O. *Tetrahedron Lett.* **1996**, *37*, 3587−3590. [h] Keifer, P. A.; Schwartz, R. E.; Koker, M. E. S.; Hughes, R. G.; Rittschof, D.; Rinehart, K. L. *J. Org. Chem.* **1991**, *56*, 2965−2975. [i] Assmann, M.; Kock, M. *Z. Naturforsch.* **2002**, *57c*, 153−156. [j] Walker, R. P.; Faulkner, D. J.; Vanengen, D.; Clardy, J. *J. Am. Chem. Soc.* **1981**, *103*, 6772−6773. [k] Assmann, M.; Kock, M. *Z. Naturforsch.* **2002**, *57c*, 157−160. [l] Cafieri, F.; Carnuccio, R.; Fattorusso, E.; Taglialatela-Scafati, O.; Vallefuoco, T. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2283−2288. [m] Cafieri, F.; Fattorusso, E.; Mangoni, A.; Taglialatela-Scafati, O. *Tetrahedron* **1996**, *52*, 13713−13720. [n] Fattorusso, E.; Taglialatela-Scafati, O. *J. Nat. Prod.* **1998**, *61*, 122−125.

as monobrominated hymenidin (**13**),[37] the hypothetical 2-bromooroidin (**14**), and dispyrin (**6**). Monobromination in Caribbean *Agelas* appears to occur exclusively at the 3-position, evidenced by the large number of monobrominated natural products isolated with bromine relegated to the 3-position, as shown in Table 2. Caribbean *Agelas* species contain a functional biogenetic network for production of hymenidin (**13**)-type compounds but do not appear to be able to biosynthesize 2-bromooroidin (**14**), the presumed, but not yet isolated, monobrominated precursor to 2-bromopyrrole carboxamide-containing compounds. Monobrominated pyrrole carboxamide natural products isolated from the Indo-Pacific do not show specificity in the bromination trend, as compounds with bromine in the 2- or the 3-position are abundant. These data suggest that the biogenetic pathways of Indo-Pacific and Caribbean *Agelas* species have distinct differences that result in production of only the 3-bromo chemotype in Caribbean specimens.



hymenidin **13** (*Agelas*- Caribbean)



2-bromo oroidin **14** (*not isolated*)

Dispyrin (**6**) represents a unique marine natural product discovery because, unlike alkaloids discovered in *Agelas* specimens thus far, it is not biosynthetically derived from oroidin (**1**). Derivatives of oroidin (**1**) include more than 75 compounds that have been isolated from *Agelas* and other sponges. Simple conversions, such as oxidation at C-12, gives dispacamide (**19**). Cyclization of oroidin (**1**) can occur at different locations and in different orientations to afford fused heterocycles isolated in this study, including (−)-dibromophakellin (**2**), dibromoagelaspongin (**3**), and (−)-dibromoisophakellin (**10**), as depicted in Figure 2. Likewise, the biogenesis of dispyrin (**6**) can be envisioned as a parallel path to that of oroidin (**1**) in which 5-bromopyrrole carboxylic acid (**15**) forms an amide bond with a tyrosine-derived compound, much like purpurealidin E (**18**). Similarly, peptide bond formation between 4,5-dibromopyrrole-2-carboxylic acid (**16**) and 3-amino-1-(2-aminoimidazolyl)prop-1-ene (**17**) results in the formation of oroidin (**1**), a biosynthesis supported by isotope-labeled feeding experiments in *Teichaxinella morchellla*, a confirmed producer of oroidin class compounds.[38]

Conclusions

The novel compounds dispyrin (**6**) and dibromoagelaspongin methyl ether (**12**) from *A. dispar* add to the immense diversity of bromopyrrole carboxamide-containing compounds isolated and characterized. Our work with Caribbean *A. dispar* established a novel bromopyrrole tyramine motif that has no precedent in natural products research. The 3-bromopyrrole functionality observed in dispyrin (**6**) is consistent with the biogenetic trend observed for compounds isolated from Caribbean species of *Agelas*. We consider dispyrin (**6**) to be a parallel biosynthetic product to oroidin (**1**) and hope to discover more complex dispyrin-derived compounds in future work with Caribbean species of *Agelas*. Finally, we consider *A. dispar* to be an ideal target organism for further study of the process responsible for pyrrole ring mono- and dibromination.

Experimental Section

General Experimental Procedures. The NMR spectra were recorded at 500 MHz for ^{1}H and 125.7 MHz for ^{13}C. Multiplicities of

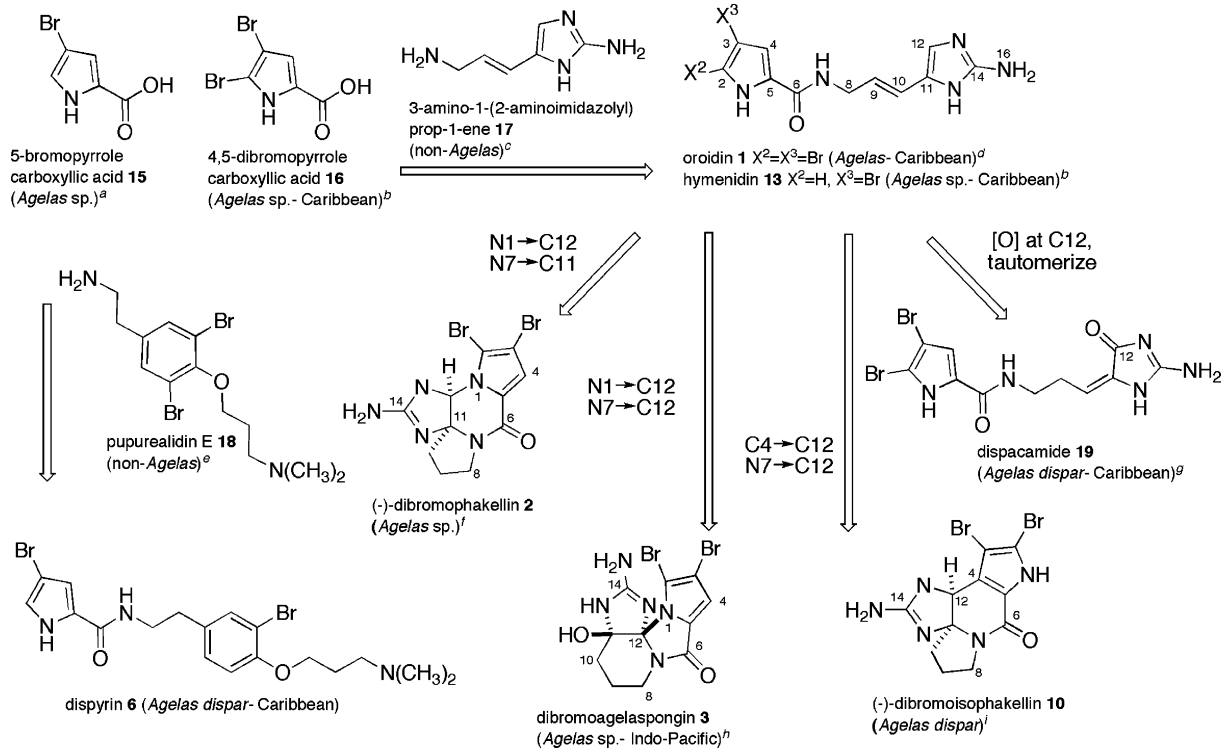


Figure 2. Overview of selected bromopyrrole carboxamide-containing natural products. [a]This compound was isolated in our lab from an unidentified *Agelas* sponge. Unpublished result. [b]Bickmeyer, U.; Drechsler, C.; Kock, M.; Assmann, M. *Toxicon* **2004**, *44*, 45−51. [c]Wright, A. E.; Chiles, S. A.; Cross, S. S. *J. Nat. Prod.* **1991**, *54*, 1684−1686. [d]Walker, R. P.; Faulkner, D. J.; Vanengen, D.; Clardy, J. *J. Am. Chem. Soc.* **1981**, *103*, 6772−6773. [e]Tilvi, S.; Rodrigues, C.; Naik, C. G.; Parameswaran, P. S.; Wahidhulla, S. *Tetrahedron* **2004**, *60*, 10207−10215. [f]Sharma, G.; Magdofffairchild, B. *J. Org. Chem.* **1977**, *42*, 4118−4124. [g]Cafieri, F.; Fattorusso, E.; Mangoni, A.; TaglialatelaScafati, O. *Tetrahedron Lett.* **1996**, *37*, 3587−3590. [h]Fedoreyev, S. A.; Ilyin, S. G.; Utkina, N. K.; Maximov, O. B.; Reshetnyak, M. V.; Antipin, M. Y.; Struchkov, Y. T. *Tetrahedron* **1989**, *45*, 3487−3492. [i]Fedoreyev, S. A.; Utkina, N. K.; Ilyin, S. G.; Reshetnyak, M. V.; Maximov, O. B. *Tetrahedron Lett.* **1986,** *27*, 3177−3180.

^{13}C NMR were determined from DEPT data and HMQC (500 MHz). LC-MS was performed on a reversed-phase analytical column (4.6 × 250 mm, 5 μm) using photodiode array (PDA) and evaporative light-scattering detectors (ELSD) with an electrospray time-of-flight (ESITOF) mass spectrometer. High-resolution mass measurements were obtained on a benchtop ESITOF mass spectrometer. Preparative and semipreparative HPLC were carried out on a C18 column (22 × 250 mm, 10 μm or 10 × 250 mm, 4 μm).

Collection and Identification. The sponge was collected by scuba near the Venezuelan island La Blanquilla in 2001 (coll. no. 01009) (400 g dry weight). The fresh sponge was preserved, transported to our lab, and extracted as previously described.[39] The sponge, found growing on ledges, had a massive encrusting form 0.5−1.0 cm thick and was bright orange in life. The sponge surface was irregular and characterized by amorphous protuberances and depressions, with round and key-hole-shaped oscules. The texture was compressible. The skeleton was a fibrous reticulation of spongin echinated by acanthostyles with verticillate spining. The sponge was identified by Dr. M. C. Diaz (UCSC) as *Agelas dispar* Duchassaing & Michelotti, 1864 (order Agelasida; family Agelasidae). An underwater photograph and a voucher sample (coll. no. 01009) are available from P.C. (UCSC).

Extraction and Isolation. The dried sponge material was extracted with MeOH to afford a brown-colored crude extract that was partitioned between H_2O and CH_2Cl_2. The aqueous layer was extracted with *sec*-butanol. The concentrated *sec*-butanol fraction (01009WB, 1.4 g) was chromatographed using Sephadex LH-20, eluting with 100% MeOH, to yield eight fractions. A single fraction (01009WBS4) was rechromatographed via reversed-phase HPLC and yielded the known compounds (−)-dibromophakellin (**13**),[19] (−)-monobromophakellin (**17**),[19] (−)-dibromoisophakellin (**15**),[35] (−) monobromoisophakellin (**18**),[8] and dibromoagelaspongin (**14**)[20] and the new compounds dispyrin (**6**) (4.5 mg) and dibromoagelaspongin methyl ether (**12**) (21.7 mg).

Dispyrin (6): ^{1}H NMR (500 MHz, MeOH-d_4) and ^{13}C NMR (125.7 MHz, MeOH-d_4), see Table 1; LRESIMS *m/z* 472/474/476 (1:2:1) $[M + H]^+$; HRESMS *m/z* 472.0241 $[M + H]^+$ (calcd for $C_{18}H_{24}N_3O_2Br_2$, 472.0229).

Dibromoagelaspongin methyl ether (12): ^{1}H NMR (500 MHz, MeOH-d_4) and ^{13}C NMR (125.7 MHz, MeOH-d_4), see Table 1; LRESIMS showed a typical cluster for a dibromo compound at *m/z* 418/420/422 $[M + H]^+$; HRESIMS *m/z* 417.9517 $[M + H]^+$ (calcd for $C_{12}H_{14}N_5O_2Br_2$, 417.9509).

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Supporting Information Available: The ^{1}H, ^{13}C, g-HMQC, g-HMBC, and g-COSY NMR spectra for **6** and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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