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Two Unprecedented Dibromotyrosine-Derived Alkaloids from the Brazilian Endemic Marine Sponge *Aplysina caissara*

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Two new bromotyrosine-derived alkaloids, caissarine A (**1**) and caissarine B (**2**), along with three known biogenetically related alkaloids, aeroplysinin-1, fistularin-3, and the artifact of isolation 2-(3,5-dibromo-4-dimethoxy-1-hydroxy-2,5-cyclohexadien-1-yl)ethanamide, have been isolated from *Aplysina caissara*, an endemic species of marine sponge from the Southeastern Brazilian coast. The alkaloids have been identified by analysis of spectroscopic data. While caissarine A has a 2-hydroxyagmatine moiety in its structure, caissarin B is the first naturally occurring compound encompassing the unprecedented 1,7-diamino-3-hydroxyheptane moiety.

Sponges belonging to the order Verongida are the richest source of naturally occurring bromine-containing alkaloids, biogenetically derived from tyrosine.[1] Although the first compound of this structural class was isolated almost 40 years ago,[2] Verongid sponges continue to provide new bromotyrosine-derived alkaloids. Such compounds have proven to be valuable chemotaxonomic markers,[3,4] and many of them display potent biological activities. Examples are aeroplysinin-1, a promising anticancer agent,[5] and the bastadins from *Ianthella basta*, which display potent cytotoxic,[6] inosine 5′-phosphate dehydrogenase inhibitory,[7] and open Ca^{2+} channel stabilizing activities.[8] Recent investigations on related sponges led to the isolation of completely new biologically active chemotypes, such as the antihistaminic archerine from *Aplysina archeri*,[9] and the cytotoxic ma'edamines A and B from *Suberea* species.[10] A recent study demonstrated that the Verongid sponge *Aplysina cavernicola* had a high assemblage of symbiotic bacteria.[11] Both *A. cavernicola* and *A. aerophoba* from the Mediterranean have associated bacteria that inhibit the growth of Gram-positive and Gram-negative bacteria, including antibiotic-resistant strains.[12]

During our ongoing search of new bioactive natural products from marine invertebrates,[13] we have noticed that the crude methanol extract of the sponge *Aplysina caissara* (Pinheiro and Hajdu, 2001) displayed mild cytotoxic and antibacterial activities. *A.* caissara is a recently described endemic Brazilian species of marine sponge.[14] A chemical investigation of the crude extract of *A. caissara* led to the isolation of three known compounds, aeroplysinin-1 (**4**),[15] fistularin-3 (**5**),[16] the artifact of isolation 2-(3,5-dibromo-4-ethoxy-1-hydroxy-4-methoxy-2,5-cyclohexadien-1-yl)ethanamide (**6**),[17] as well as two new dibromotyrosine-derived alkaloids, caissarins A (**1**) and B (**2**), whose isolation and structure elucidation are reported herein.

The frozen sponge was extracted with methanol, and the methanol extract was concentrated to an aqueous suspension, which was partitioned with hexanes and with ethyl acetate. The ethyl acetate fraction was subjected to C_{18} reversed-phase column chromatography and silica gel flash chromatography. The UV-absorbing fractions were further separated and purified by reversed-phase HPLC, to give, in increasing order of polarity, aeroplysinin-1, 1-acetamide-3,5-dibromo-4,4-dimethoxy-1-hydroxycyclohexa-2,5-diene, fistularin-3, caissarine B (**2**), and caissarine A (**1**).

The positive FABMS of caissarine A (**1**) displayed a molecular ion triplet at *m/z* 516, 518, and 520, indicating the presence of two bromine atoms in its structure. Analysis of the ^{1}H, ^{13}C, gHSQC, and gHMBC NMR spectra (Table 1) indicated the presence of the 7,9-dibromo-10-hydroxy-8-methoxy-1-oxa-2-aza-spiro[4.5]deca-2,6,8-trien-3-carboxamide moiety, typically found in most of the secondary metabolites isolated from Verongida sponges. Aditionally, we observed the presence of three methylene (δ_C 44.7, 25.7, and 40.2), one methine (δ_C 78.4), and a quaternary carbon (δ_C 157.5). Analysis of IR, gHSQC, ^{1}H−^{1}H gCOSY, and gHMBC indicated that the C-10 methylene (δ_C 44.7; δ_H 3.54) was attached to a carbinolic methine (C-11), in agreement with the ^{13}C (78.4) and ^{1}H (4.45) chemical shifts. Further ^{1}H−^{1}H and longe-range couplings observed between C-11 methine and the C-12 methylene (δ_C 25.7; δ_H 1.78 and 2.05), between the C-12 methylene and C-13 methylene (δ_C 40.2; δ_H 3.35), and between the C-13 methylene and the quaternary carbon (C-14) at δ 157.5 established the identity of the 2-hydroxyagmatine chain.

Considering the structure **1** proposed for caissarine A by analysis of the IR and NMR data, the *m/z* 518 peak could not be assigned to the structure established above. However, it was assigned to the deuterated form of caissarine A, in which the exchangeable hydrogens were replaced by deuterium atoms.[18] The presence of deuterium atoms in **1** was consistent with the fact that the sample submitted for mass spectra was recovered from MeOH-d_4. In the positive FABMS we also observed a small triplet at *m/z* 511, 513, and 515, possibly indicating the presence of two deuterium atoms in the place of two exchangeable hydrogens in **1**. A high-resolution measurement on the peak at *m/z* 518 indicated the formula $C_{15}H_7D_7Br_2N_5O_5$ (measd 518.20911) and that on the peak at *m/z* 513 indicated the formula

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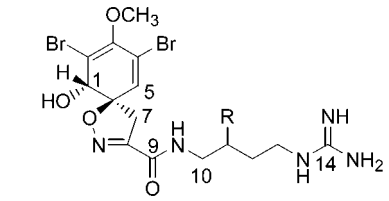

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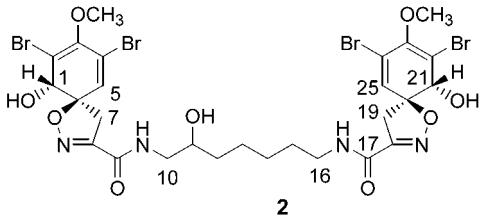

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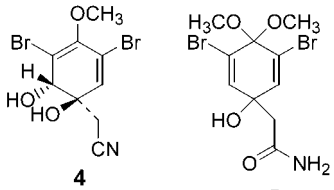

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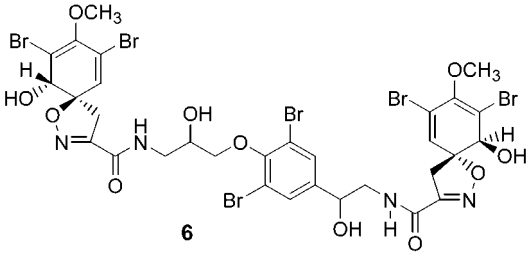

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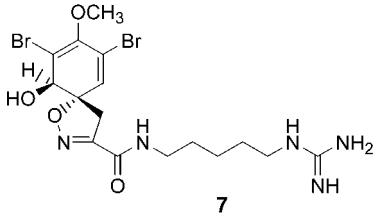

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$C_{15}H_{12}D_2Br_2N_5O_5$ (measd 513.17885), in agreement with ^1H and ^{13}C NMR data. Therefore, caissarine A presented seven exchangeable hydrogens and seven degrees of unsaturation. Dereplication with the MarinLit database[19] indicated that **1** had 16 mass units higher than purealidine L (**3**), previously isolated from the sponge *Psammaplysilla purea*.[20] Indeed, the ^1H and ^{13}C NMR data of caissarine A (see Table 1) are very similar to NMR data of purealidine L,[20] except for the 2-hydroxyagmatine chain. Several attempts to transform the guanidine group of **1** into its 2-amino-3,5-dimethylpyrimidine derivative were made, but we only obtained complex mixtures, probably due to the formation of degradation products as previously observed for aplysinamisine II (**7**).[21] It was not possible to obtain the value of specific rotation or the circular dichroism spectrum of **1** because the sample was lost after the NMR experiments. Nevertheless, we have been able to establish the relative stereochemistry of the bicyclic moiety of caissarine A by comparison of the ^1H and ^{13}C chemical shifts of H-1, H-5, and CH_2-7 with the literature data of related compounds.[22]

Caissarin B (**2**) was also isolated as a glassy solid. The low-resolution FABMS of caissarine B displayed a molecular ion cluster at *m/z* 867, 869, 871, 873, and 875. A high-resolution measurement on the peak at *m/z* 871 (measd 871.97930) indicated the formula $C_{27}H_{32}Br_4N_4O_9$. Considering the presence of only 17 signals in the ^{13}C NMR spectrum of **2**, we supposed that caissarine B had two chemically equivalent bicyclic moieties. This hypothesis was further supported by the fact that the intensity of the ^{13}C signals of the bicyclic spin system was more than 3-fold the intensity of the ^{13}C signals assigned to the 1,7-diamino-3-hydroxyheptane chain.

The assignment of ^1H and ^{13}C signals of the bicyclic moieties of caissarine B was established by comparison with data reported for dihydroxyaerothionin[23] and are presented in Table 1. Although no long-range correlations were observed in the gHMBC spectrum between the hydrogens of methylenes CH_2-10 (δ 3.08 and 3.15) and CH_2-16 (δ 3.15) with their respectively attached carbonyl carbons C-9 (δ 159.2) and C-17 (δ 159.2), or between the amide hydrogens with C-10 and C-16, the presence of the 1,7-diamino-3-hydroxyheptane chain was evident in the $^1H-^1H$ gCOSY spectrum. The resonances of the hydrogens in the 1,7-diamino-3-hydroxyheptane chain were poorly resolved, suggesting the occurrence of a conformational dynamic change. $^1H-^1H$ correlations have been observed between CH_2-10 (δ 3.08 and 3.15), CH-11 (δ 3.55 and 3.61), and CH_2-12 (δ 1.28 and 1.40), enabling us to establish the position of the hydroxyl group. The ^1H and ^{13}C chemical shifts of the methine carbinol group appeared as two signals at δ 3.55 and 3.61, certainly due to the presence of two amide rotamers in solution. Furthermore, one amide proton appeared as two triplets at δ 8.41 (major conformer) and δ 8.45 (minor conformer), and the other amide proton appeared as two triplets at δ 8.26 (major conformer) and δ 8.21 (minor conformer), providing additional evidence for the presence of two rotamers in DMSO-d_6. Further sequential $^1H-^1H$ couplings observed between CH_2-12 and CH_2-13 (δ 1.60 and 1.50), between CH_2-13 and CH_2-14 (δ 3.22 and 3.28), between CH_2-14 and CH_2-15 (δ 1.65 and 1.45), and finally between CH_2-15 with CH_2-16 (δ 3.15) completed the assignments of the 1,7-diamino-3-hydroxyheptane moiety of caissarine B. Aiming to confirm the structure of caissarine B, a second set of ^1H, ^{13}C, $^1H-^1H$ gCOSY, gHSQC, and gHMBC NMR experiments were obtained in MeOH-d_4 (see Experimental Section and Supporting Information), and the results confirm the planar structure of **2**. Particularly relevant were long-range couplings observed in the gHMBC spectrum between CH_2-10 (δ 3.38 and 3.26) and C-9 (δ 163.0), as well as between CH_2-13 (δ 1.65 and 1.73) and C-11 (δ 69.5 and 71.0). The ^1H spectrum of caissarine B in MeOH-d_4 is even less defined than in DMSO-d_6, indicating that the conformational dynamic change in solution is more pronounced in MeOH-d_4. As in the case of caissarine A, it was not possible to establish the absolute stereochemistry of the bicyclic moieties of caissarine B because the sample was lost after the NMR experiments. However, its relative stereochemistry was determined as shown by comparison with literature data.[22]

To solve the absolute stereochemistry of caissarines A and B by circular dichroism analysis, we collected additional samples of *A. caissara* in April 2000. Unexpectedly, the second sponge sample was devoid of both caissarine A and caissarine B. A third collection of this animal is envisaged in order to investigate if occurrence of **1** and **2**

Table 1. ^{1}H and ^{13}C NMR Data for Caissarine A (**1**) and Caissarine B (**2**)

1			**2**		
position	δ ^{13}C[a]	δ ^{1}H (mult, *J* in Hz)[a]	position	δ ^{13}C[b]	δ ^{1}H (mult, *J* in Hz)[b]
CH-1	76.4	4.10 (s)	CH-1 and CH-21	74.1	3.93 (s)
C-2	115.1		C-2 and C-22	113.5	
C-3	150.2		C-3 and C-23	147.6	
C-4	123.7		C-4 and C-24	121.2	
CH-5	133.2	6.40 (s)	CH-5 and CH-25	131.7	6.57 (s)
C-6	93.4		C-6 and C-20	90.7	7.47 (dd, 8.6 and 1.5)
CH_2-7	41.0	3.11 (d, 18) and 3.78 (d, 18)	CH_2-7 and CH_2-19	40.0	3.12 (d, 18) and 3.62 (d, 18)
C-8	156.0		C-8 and C-18	155.0	
C-9	162.8		C-9 and C-17	159.3	
CH_2-10	44.7	3.54 (d, 4)	CH_2-10	45.7	3.08 (m) and 3.15 (m)
CH-11	78.4	4.45 (m)	CH-11	67.4 and 68.9	3.55 (m) and 3.61 (m)
CH_2-12	25.7	1.78 (m) and 2.05 (m)	CH_2-12	32.3	1.28 (m) and 1.40 (m)
CH_2-13	40.2	3.35 (m)	CH_2-13	25.5	1.50 (m) and 1.60 (m)
C-14	157.5		CH_2-14	36.6	3.28 (m) and 3.22 (m)
OCH_3	61.3	3.72 (s)	CH_2-15	34.4	1.45 (m) and 1.65 (m)
			CH_2-16	39.4	3.15 (m)
			OCH_3	60.1	3.65 (s)
			N-H		8.41 (t, 6) and 8.45 (t, 5)
			N-H		8.27 (t, 6) and 8.21 (t, 5)
			O-H		6.36 (s)

[a] Taken in CD_3OD. [b] Taken in DMSO-d_6.

in *A. caissara* is seasonal and to determine the absolute stereochemistry of both compounds.

To the best of our knowledge, caissarine B is the first Verongid dibromotyrosine-derived alkaloid bearing a 1,7-diamino-3-hydroxyheptane chain, a diamine moiety that has no precedent among natural products. Structurally related to caissarine B are dihydroxyaerothionin from *Verongula rigida*,[23] areothionin and homoaerothionin, which have been isolated from diferent species of Verongid sponges,[24−27] and 11-hydroxyaerothionin from *Pseudoceratina durrissima*.[28]

Experimental Section

General Experimental Procedures. IR spectra were recorded on a FT-IR Bomem MB102 infrared spectrometer. NMR spectra were run either on a Bruker AC-4.7 T spectrometer, operating at 200.1 MHz for ^{1}H NMR and 50.3 MHz for ^{13}C NMR spectra, or on a Bruker DRX400 9.4 T instrument, operating at 400.35 MHz for ^{1}H and 100.10 MHz for ^{13}C channels, respectively. All the NMR spectra were obtained at 28 °C using tetramethylsilane as internal reference. High-resolution FAB mass spectra were obtained on hybrid Kratos concept IIHQ equipment. Solvents employed for extraction and column chromatography were glass distilled prior to use. TLC analysis were performed with Aldrich precoated TLC sheets of silica gel on polyester with 254 nm fluorescent indicator eluting with two eluents: 1:1 hexanes−ethyl acetate and 9:1 CH_2Cl_2−MeOH. Plates were developed by observing at 254 nm and subsequently by spraying with phosphomolybdic acid reagent in ethanol and further heating at 120 °C.

Animal Material. Samples of *A. caissara* were collected in the São Sebastião channel, during the summer of 1999. The animals were immediately frozen. Voucher specimens are deposited in the Porifera collection of the Museu Nacional da Universidade Federal do Rio de Janeiro [MNRJ 268 (paratype), 578 (paratype), 1673 (paratype), 1675 (paratype), 1988 (holotype), 1989 (paratype)].

Extraction and Isolation. The sponge *A. caissara* (900 g, wet wt) was blended in MeOH (3 L) and filtered, and the solid residue was re-extracted with MeOH (2 L). After filtration the methanol extract was evaporated in vacuo until the alcohol was removed. The final aqueous extract (ca. 500 mL) was partitioned against hexanes, then with EtOAc (3 × 700 mL), to give 9.55 g of a brown gum of the EtOAc extract. This material was divided in portions of ca. 1 g, which were subjected to a chromatography on a C_{18} reversed-phase Sep Pak (Waters) column, with a gradient of MeOH in H_2O. Four fractions were obtained, with UV-absorbing compounds concentrated in fractions 2 (3.5 g) and 3 (2.9 g). Both fractions were subjected to several separations by flash chromatography (gradient of MeOH in CH_2Cl_2), yielding fractions enriched in single components. Caissarine A (24 mg, 0.0026% wet wt) was obtained as a pure compound in the last fractions of these separations. Impure compounds were purified by C_{18} reversed-phase HPLC with a Whatman Partisil 10 ODS-3 column, using 70% MeOH for the purification of aeroplysinin-1 (340 mg) and 1-acetamide-3,5-dibromo-4,4-dimethoxy-1-hydroxycyclohexa-2,5-diene (249 mg) and 65% MeOH for the purification of fistularin-3 (25 mg) and caissarine B (25 mg, 0.0026% wet wt).

Caissarine A (1): colorless, glassy solid; UV (MeOH) λ_{max} 232 (ϵ 9100), 283 (ϵ 4250); IR (neat) ν_{max} 3500−3000, 2928, 2860, 1690−1630, 1405, 1100, 605 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz), see Table 1; ^{13}C NMR (DMSO-d_6, 400 MHz), see Table 1; FABMS (thioglycerol) *m*/*z* 518 [M + 7D − 7H]$^+$ (13), 513 [M + 2D − 2H]$^+$ (4), 496 (8), 478 (6), 295 (23), 279 (22), 157 (60), 71 (100); HRFABMS *m*/*z* found 518.20911 [M + 7D − 7H] $^+$, calcd for $C_{15}H_7D_7Br_2N_5O_5$ [M + 7D − 7H]$^+$ 518.20836.

Caissarine B (2): colorless, glassy solid; UV (MeOH) λ_{max} 234 (ϵ 9000), 283 (ϵ 4300); IR (neat) ν_{max} 3382, 2357, 1665, 1549, 1106, 603 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz), see Table 1; ^{13}C NMR (DMSO-d_6, 100 MHz), see Table 1; ^{1}H NMR (MeOH-d_4, 400 MHz) δ 6.42 (2H, m, H-5 and H-25), 4.10 (2H, m, H-1 and H-21), 3.79 (1H, m, H-11) and 3.72 (1H, m, H-11), 3.77 (2H, dd, 3.6, 20.8 Hz, CH_2-7 and CH_2-19) and 3.09 (2H, dd, 2.9, 20.8 Hz, CH_2-7 and CH_2-19), 3.72 (3H, s, OCH_3), 3.40 (2H, m, CH_2-14), 3.38 (1H, m, CH_2-10) and 3.26 (1H, m, CH_2-10), 3.30 (2H, m, CH_2-16), 1.73 (1H, m, CH_2-13) and 1.65 (1H, m, CH_2-13), 1.62 (2H, m, CH_2-15), 1.55 (1H, m, CH_2-12) and 1.43 (1H, m, CH_2-12); ^{13}C NMR (MeOH-d_4, 100 MHz) δ 163.0 (s, C-9 and C-17), 156.2 (s, C-8 and C-18), 149.9 (s, C-3 and C-23), 135.0 (d, C-5 and C-25), 123.5 (s, C-4 and C-24), 115.0 (C-2 and C-22), 93.5 (s, C-6 and C-20), 76.0 (d, C-1 and C-21), 71.0 and 69.5 (d, C-11), 61.0 (q, OCH_3), 47.5 (t, C-10), 40.6 (t, C-16), 40.5 (t, C-7 and C-9), 37.8 (t, C-14), 35.0 (t, C-15), 32.9 (t, C-12), 27.0 (t, C-13); FABMS (thioglycerol + MeOH) *m*/*z* 875 (1), 873 (2), 871 [M]$^+$ (4), 869 (2), 867 (1), 861 (1.5), 859 (3.5), 857 (5), 855 (3.5), 855 (1.5), 322 (1.5), 320 (2.5) 318 (1.5), 297 (2.5), 295 (4.5), 293 (2.5), 281 (18), 279 (37), 277 (18), 70 (100); HRFABMS *m*/*z* found 871.97930 [M]$^+$, calcd for $C_{27}H_{32}Br_4N_4O_9$ [M]$^+$ 871.97028.

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Supporting Information Available: This material is available free of charge via the Internet at http://pubs.acs.org.

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