Structure Elucidation

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Unprecedented Stylissazoles A–C from *Stylissa carteri*: Another Dimension for Marine Pyrrole-2-aminoimidazole Metabolite Diversity**

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The pyrrole-2-aminoimidazole (P-2-AI) alkaloids have been exclusively reported to be isolated from marine sponges. The P-2-AIs are well known for their dense structures with a very low carbon/nitrogen (mainly $nxC_{11}N_5$) ratio.[1] Their intriguing dimeric polycyclic ring systems that were isolated during the last years revealed their elaborate structures and molecular diversity which arise from a variety of modes of dimerization and polycyclization. Structurally, it is assumed that these metabolites arise from the crucial intermediates clathrodin,[2] hymenidin,[3] or oroidin[4] through either an interesting intramolecular or intermolecular reaction occurring at ambident centers.[5] Although the biosynthesis of these intermediates is not clear, it is obvious that dipeptides involving proline and another amino acid residue such as ornithine or arginine constitute an interesting route for early biosynthetic precursors.[6–7] The reactivity of the monomers that give rise to the diversity of P-2-AI dimers isolated thus far is very intriguing. Biomimetic synthesis approaches toward several members of P-2-AIs reported by various groups have led to better understanding of the reactivity and the potential biosynthetic chemical pathways of the dimeric compounds.[8] The lack of biosynthetic studies using labeled precursors, necessitates the exhaustive isolation of the targeted P-2-AI metabolome. Research into the biosynthetic intermediates is crucial for the construction of the chemical pathway. Isolation of new intermediates helps to explore the ability of the corresponding phylogenetically related sponges to create newly targeted metabolomes. Specifically, we are interested in four families of marine sponges (Agelasidae, Axinellidae, Halichondriidae, and Dictyonellidae) that could afford additional P-2-AI metabolites.

We have investigated the methanolic extract of a Pacific *Stylissa carteri* which is known to yield compounds such as cyclopeptides,[9] oroidin, 4,5-dibromopyrrolecarboxamide, 4-dibromopyrrolecarboxamide and hanishin,[10] latonduine A and B,[7e] (*E*)- and (*Z*)-hymenialdisine, (*E*)- and (*Z*)-debromohymenialdisine, (*E*)- and (*Z*)-bromohymenialdisine, stevensine, debromostevensine, hymenin and debromohymenin,[11] dibromoisophakellin and ugibohlin,[12] carteramine A,[13] and hanishenol A and B.[14] We report herein the isolation of three unprecedented N–C bonded stylissazoles A–C (**1**—**3**; Figure 1), which fit well with our previous biosynthetic proposal[4a] and add another dimension to the diversity of marine P-2-AI metabolites. Consequently, the universal proposal is also updated.

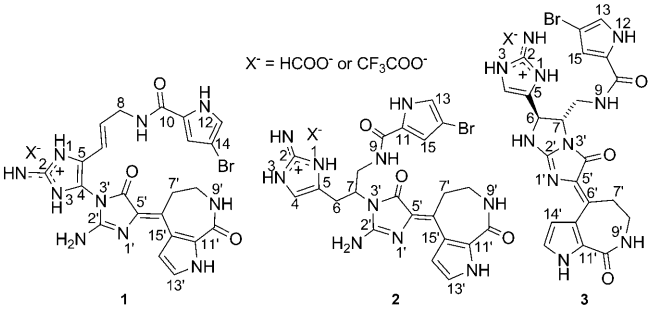

Figure 1. Structures of stylissazoles A–C (**1**–**3**) isolated from *Stylissa carteri*.

The sponge *Stylissa carteri* collected off the coast of the Solomon Islands was extracted with MeOH. *n*BuOH-soluble materials of this extract yielded the unprecedented N–C connected dimeric P-2-AI stylissazoles A–C (**1**—**3**, Figure 1).

The electrospray ionization (ESI) mass spectrum of **1** (10.5 mg, 0.0034 %, dry weight) showed the pseudomolecular ion peaks at *m*/*z* 552.9, 554.9 (1:1), indicating the presence of one bromine atom in the molecule. The molecular formula was revealed to be $C_{22}H_{21}{}^{79}BrN_{10}O_3$ by ESI-HRMS at *m*/*z* 553.1060 ($[M+H]^+$). The UV absorption at $\lambda_{max}=$ 269 nm ($\varepsilon=28000$) is indicative of a substituted pyrrole chromophore. The ^{13}C NMR spectrum (see Table 1 in the

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Supporting Information) showed 22 signals, representing 13 sp^2 quaternary, six sp^2 methine, and three sp^3 methylene carbon atoms. The ^{1}H NMR spectrum (see Table 1 in the Supporting Information) included eight deuterium exchangeable protons at $\delta = 11.95, 11.51, 8.40, 7.84, 6.94$ ppm (2H), and 5.80(2H). Comparison of the NMR data from ^{1}H-^{1}H COSY spectra, and ^{1}H-^{13}C and ^{1}H-^{15}N HMBC spectra with those of known monomeric bromopyrrole alkaloids clearly indicated the presence of hymenidin[3] and debromohymenialdisine[15] (see the Supporting Information for a detailed NMR spectroscopic analysis). The most important correlations are shown in Figure 2. Detailed analysis of the ^{1}H-^{1}H COSY,

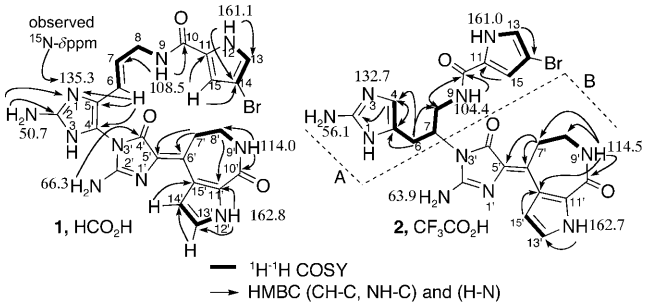


Figure 2. Selected NMR data for stylissazoles A and B.

HSQC, NOESY, ^{1}H-^{13}C and ^{1}H-^{15}N HMBC spectra disclosed connectivity between H9 and C6. The HMBC spectrum showed a correlation between H9 ($\delta = 8.4$ ppm) and C10 ($\delta =$ 159.8 ppm) indicating that the monobromopyrrolecarboxamide moiety (C10–N12) was attached to N9. The connection of the 4,5-disubstituted 2-aminoimidazole ring to C6 was deduced from HMBC correlations for H6 ($\delta = 6.22$ ppm) to the quaternary carbon atoms C5 ($\delta = 119.1$ ppm) and C4 ($\delta =$ 125.9 ppm). This segment corresponds to a hymenidin[3] moiety connected at C4 to the second part of the molecule.

The second set of protons at $\delta = 3.83$, 3.36, and 7.84 ppm (exchangeable) corresponds to the -NH-CH_2-CH_2- (C7′–N9′) system. Detailed analysis of the ^{1}H-^{1}H COSY, HSQC, NOESY, and ^{1}H-^{13}C and ^{1}H-^{15}N HMBC[16] spectra disclosed the aldisine moiety which is present in the (*Z*)-debromohymenaldisine.[15] The *Z* configuration was determined by a comparison of ^{13}C NMR values; in particular, C7′ appearing at $\delta = 30.2$ ppm. At this stage the connection between the quaternary carbon C4 ($\delta = 125.9$ ppm) of the hymenidin moiety and the debromohymenialdisine moiety had three N–C possibilities: C4–N1′, C4–N2′, or C4-N3′. The C4–N1' connection was immediately eliminated as a possibility because of the steric hindrance inflicted by the *Z* geometry of the hymenialdisine portion.[15b] Finally, the bonding of the two units was solved by ^{1}H NMR and ^{15}N NMR spectra that were recorded in [D_7]DMF (DMF = *N*,*N*-dimethylformamide). The presence of an exocyclic NH_2 group (a free amine), indicated by signals at $\delta = 6.94$ (2H) and 66.3 ppm (C2′–NH_2), suggests that there is no connection of C4 to this nitrogen atom. Therefore, the structure of stylissazole A was assigned as **1**, which possesses a debromohymenialdisine ring connected to hymenidin through a C4–N3′ bond (Figure 2).

The ESI mass spectrum of **2** (2.5 mg, 0.0008%, dry weight) showed the pseudomolecular ion peaks at *m*/*z* 555.0, 557.0 (1:1) ($[M+H]^+$), indicating the presence of one bromine atom in the molecule. The ESI-HRMS at *m*/*z* 555.1235 indicated the molecular formula $C_{22}H_{24}{}^{79}BrN_{10}O_3$. The ^{13}C NMR spectrum (see Table 2 in the Supporting Information) showed 22 signals representing twelve sp^2 quaternary, five sp^2 methine, four sp^3 methylene, and one sp^3 methine carbon atoms. The ^{1}H NMR spectrum included ten deuterium exchangeable protons ($\delta = 12.98, 12.74, 12.20, 11.81, 8.84, 8.18$ (2H), 8.12, and 7.26 ppm (2H)) attributed to amino or amide protons. Of the ten nitrogen atoms present, only seven were detected by ^{15}N NMR methods (see Table 2 in the Supporting Information). The ^{1}H NMR spectrum of **2** indicates the presence of two pyrroles having signals at $\delta = 7.74$, 7.09, 7.01, and 6.93 ppm. Examination of the ^{1}H NMR data revealed the presence of a 4-bromopyrrole-2-carboxamide moiety (NH9–C15), which showed very similar δ values to those of the above stylissazole A (**1**). A 2-aminoimidazole unit (N1–C5) was suggested by the ^{13}C NMR signals at $\delta = 148.8$ (C2), 124.3 (C5), and 110.5 ppm (C4). Detailed analysis of ^{1}H-^{1}H COSY, HSQC, and HMBC NMR experiments for **2** revealed the presence of a -CH_2-CH-CH_2- unit (C8–C6). The 2-aminoimidazole ring (N1–C5) connection to C6 was determined from HMBC correlations for H6 at $\delta = 3.37$ and 3.16 ppm to C5 ($\delta = 124.6$ ppm) and C4 ($\delta = 110.9$ ppm). With all these data, the partial structure **A** for **2** was identified (Figure 2). Additional analysis of the ^{1}H-^{1}H COSY, HSQC, NOESY, and ^{1}H-^{13}C and ^{1}H-^{15}N HMBC spectra of **2** disclosed the same moiety **B** (Figure 2) corresponding to debromohymenaldisine[15] found in stylissazole A (**1**). Assembling the two substructures **A** and **B** was not obvious. As for stylissazole A (**1**), the connection through C4–N1′ was ruled out because of the steric hindrance inflicted by the *Z* geometry of the hymenialdisine part. Discrimination between the remaining possible bonds C7–N3′ and C7–N1′ was not readily achieved by use of HMBC correlations. The ambiguity was solved by the observation of the presence of a free exocyclic NH_2 indicated by the shifts at $\delta = 7.26$ (2H) and 63.9 ppm (C2′-NH_2), in the ^{1}H and ^{13}C NMR spectra, respectively. Finally, the C7–N3′ bonded structure was assigned for **2** and named stylissazole B (**2**) (Figure 2).[17]

The positive ESI spectrum of stylissazole C (**3**; 5.8 mg, 0.0019% dry weight) showed the pseudomolecular ion peaks at *m*/*z* 552.9, 554.9 (1:1), indicating the presence of one bromine atom. The ESI-HRMS at *m*/*z* 522.9065 indicated the molecular formula $C_{22}H_{22}{}^{79}BrN_{10}O_3$. The ^{13}C NMR spectrum disclosed 22 signals representing twelve sp^2 quaternary, seven sp^2 methine, and three sp^3 methylene carbon atoms. The ^{1}H NMR spectrum included seven deuterium exchangeable protons at $\delta = 12.10$, 11.57, 8.62, 8.54, 7.80, 5.74 ppm (2H) attributed to the protons of amine and amide functions (see Table 3 in the Supporting Information).

Examination of the ^{1}H NMR data revealed the presence of a 4-bromopyrrole-2-carboxamide moiety (NH9–C15), which appears very similar to the values reported for the above compounds **1** and **2**. The ring (N1–C5) corresponding to 2-aminoimidazole unit was indicated by ^{13}C NMR signals at $\delta = 151.4$ (C2), 134.0 (C5), and 110.3 ppm (C4). A detailed

analysis of the ^{1}H NMR COSY, HSQC, and HMBC spectra revealed the presence of a -CH_2-CH-CH- unit corresponding to the C6–C7–C8 sequence. The connection of the 2-amino-imidazole to C6 was determined from HMBC correlations from H6 ($\delta = 5.07$ ppm) to C5 ($\delta = 134.0$ ppm) and C4 ($\delta =$ 110.3 ppm, Figure 3). Thus, the partial structure for **3** was identified as **A** (Figure 3). Additional NMR investigations, including ^{1}H-^{15}N two-dimensional spectra of **3**, disclosed the partial hymenidin structure (**B**; N1′–C15′) found in the above compounds **1** and **2** (Figure 3).

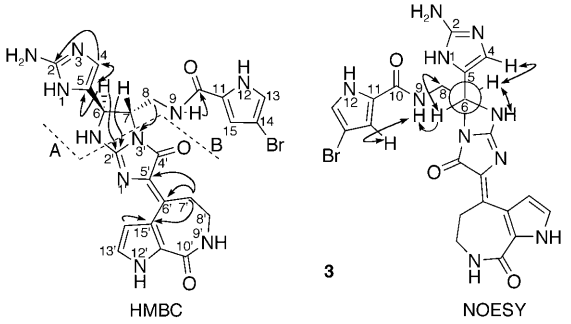
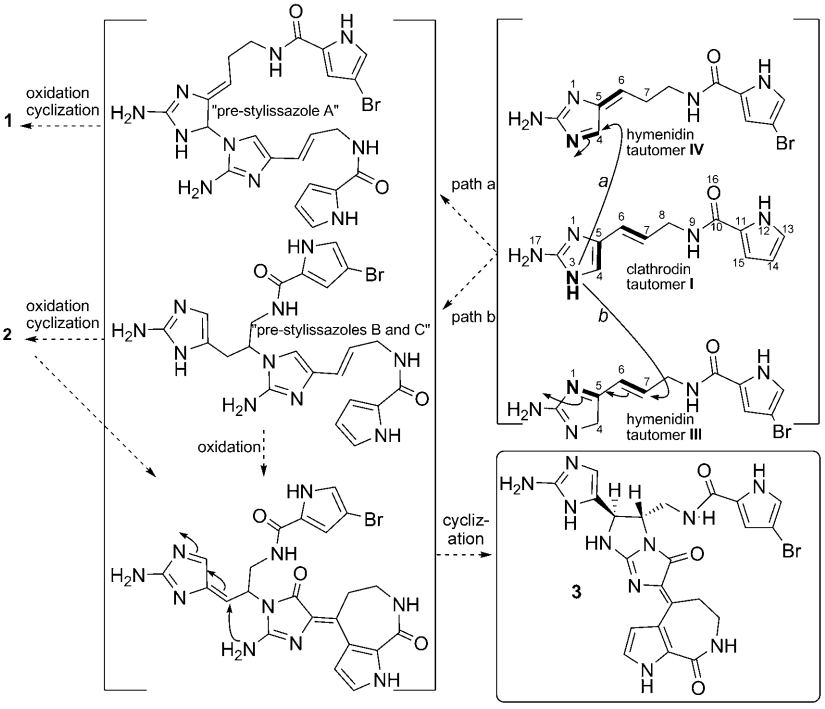


Figure 3. HMBC and NOESY correlations for stylissazole C.

Despite the indications given by the above substructures **A**/**B**, their assemblage to the final molecule was not obvious. The putative double connection involving two carbon atoms of segment **A** and two nitrogen atoms of segment **B** prompted us to take a look at the ^{1}H-^{15}N HMBC spectrum. There was an important correlation between H8 at $\delta = 3.86$–3.79 ppm and N3′ at $\delta = 152.2$ ppm indicating similar connection for C7–N3′ as found in stylissazole B (**2**). Additional analysis of ^{1}H-^{13}C HMBC spectra showed correlations for H6 ($\delta = 5.07$ ppm) and H7 ($\delta = 4.39$ ppm) with C2′ ($\delta = 160.6$ ppm). All these correlations indicated the connection of C6 to the exocyclic nitrogen of NH–C2′ and C7 to N3′, thereby connecting the substructures **A** and **B** (Figure 3). The relative configuration of the contiguous centers C6 and C7 was determined in [D_7]DMF by NOESY experiments which indicated correlations between H4 ($\delta =$ 6.68 ppm) and H7 ($\delta = 4.39$ ppm), and H6 ($\delta = 5.07$ ppm) with both H8 ($\delta = 3.86$–3.79 ppm) and H9 ($\delta = 8.54$ ppm) (Figure 3). The latter correlations together indicated that protons H6 and H7 were in a *trans* configuration. These data together with their comparison to the above compounds **1** and **2** were consistent with **3** being the first member of imidazo[1,2-a]imidazolone P-2-AI derivatives. The compound was named stylissazole C. Stylissazole C (**3**), similarly to stylissazole B (**2**), has no optical activity and the circular dichroic curve was completely flat. This lack of optical activity is probably a result of the interconversion of the configurationally unstable chiral carbons C6 and C7.

These new members of P-2-AI metabolites constitute an unprecedented example wherein the dimerization involves solely N–C bonds. Astonishingly, despite the high N/C ratio (ca. 0.5), the N–C dimerization mode was not discovered before. These first examples add another dimension to the molecular diversity of P-2-AI metabolites and additionally highlights the unique dual reactivity of the vinylogous 2-aminoimidazolic precursors.[5,18] The co-occurrence of stylissazoles A–C (**1**–**3**) provides biosynthetic insights into their new dimerization/oxidation sequence. Scheme 1 shows a proposed biosynthesis suggesting that the building blocks of the molecule are clathrodin and brominated hymenidin. The biosynthetic scheme also suggests that stylissazole C (**3**) might arise from stylissazole B (**2**) or from a common "pre-stylissazoles B and C" (Scheme 1). The chemical pathway would presumably start from clathrodin (tautomer **I**; see Scheme 2) and hymenidin (tautomer **IV** for **1** and tautomer **III** for **2** and **3**) undergoing a 1,2- or 1,4-aza-Michael reaction to produce the decisive N3′–C4 and N3′–C7 bounds (Scheme 1).

In a previous publication,[5] we postulated a universal chemical pathway for the formation of dimeric P-2-AI members known up to 2000. All the dimeric P-2-AI members isolated during the last decade fit into the general chemical pathway that we had suggested for their formation and relative stereochemical relationships. The correction of the relative configuration of palau′amine [13, 19] provided more evidence in support of the hypothesis. The universal chemical pathway is also in accordance with the conserved stereochemical relationships within the dimer subclass. Additional



Scheme 1. Plausible biosynthetic path for stylissazoles A–C (**1**—**3**, respectively).

development of the hypothesis and extension to the recently isolated P-2-AI dimeric members has been reported by Köck, Baran, and co-workers.[5b]

The first decisive C–C or N–C bonds establish the propensity for various cascades of cyclization reactions. The formation of the stylissazoles A–C (**1**–**3**) dimmers, connected through N–C bond, involves the formation of an N–C bond in the first step. Various modes of dimerization through C–C and N–C bond formations involve the joining of tautomers **I**–**IV** with each other (Scheme 2). Nucleophilic and electrophilic positions can vary with the tautomer engaged in the dimerization step.

The process leading to the selection of the reacting tautomers in nature is an interesting question to be answered. The dynamic hydrogen-bonding interaction of monomers like clathrodin with the host enzyme is probably an interesting biochemical catalytic system. The composition of the P-2-AI targeted metabolome which changes with the sponge species, should serve as the foundation for a significant proposal for biosynthetic chemical pathways. Additional metabolomic studies of various species of P-2-AI metabolite producing sponges are in progress.

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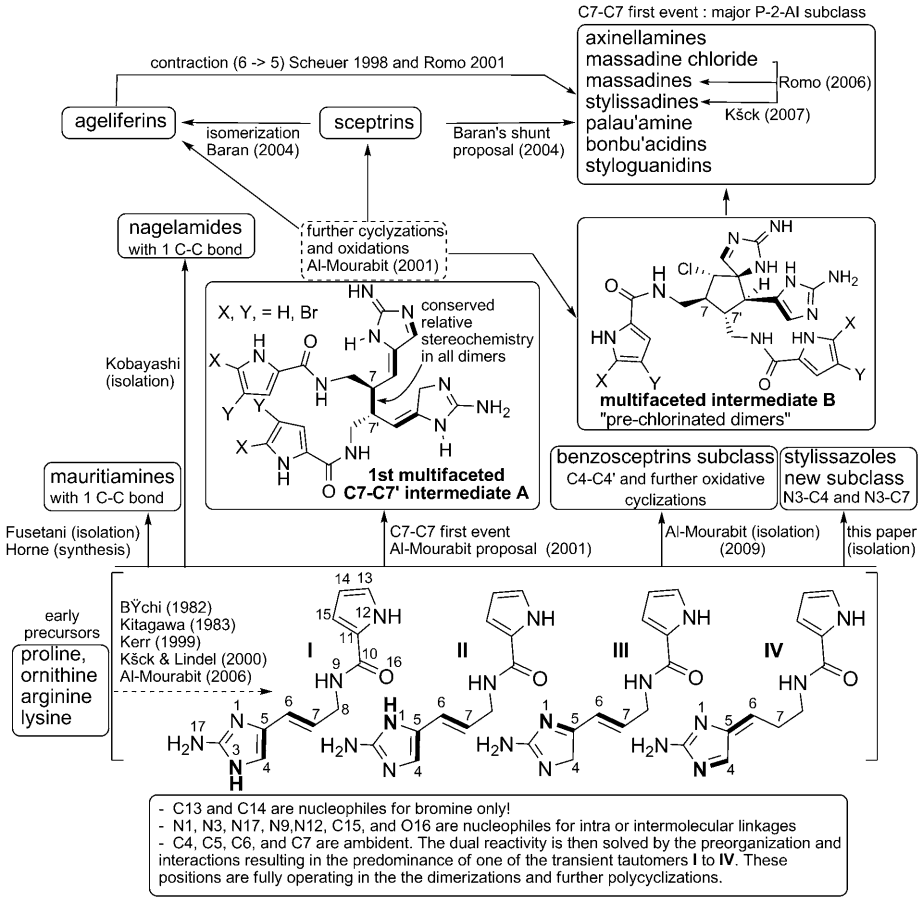

Scheme 2. Biosynthetic proposals summarized.

Keywords: alkaloids · biosynthesis · heterocycles · metabolites · structure elucidation

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