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Revised structure of palau'amine

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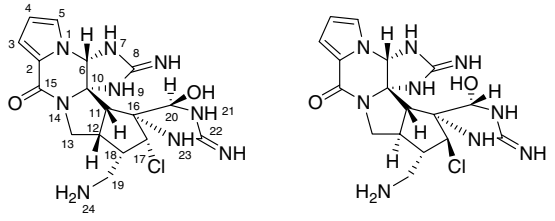
Abstract—The structure of palau'amine, a bioactive hexacyclic pyrrole–imidazole alkaloid, from the sponge *Stylotella aurantium* was revised by detailed analysis of its 2D ROESY and 1D NOESY data.

Palau'amine, isolated from the sponge *Stylotella aurantium* by Scheuer and co-workers,[1] exhibits antifungal, antitumor and immunosuppressive activities.[2] The structure was elucidated as shown in **1** (Fig. 1), a hexacyclic pyrrole–imidazole alkaloid containing a continuous chain of eight chiral centers. Since its initial report in a preliminary paper in 1993,[3] its challenging structure and interesting biological activity have attracted the attention of several synthesis research groups,[4] including those of Romo,[5] Overman,[6] Harran,[7] Lovely,[8] and Austin.[9] However, despite many creative and insightful attempts the total synthesis of palau'amine has not yet been achieved. During 2004–2005 we conducted a natural product high-throughput screening (HTS) campaign to discover selective $P2X_7$ receptor antagonists for the treatment of inflammatory diseases.[10] The marine sponge, *Stylissa flabellata* yielded the tetrameric pyrrole–imidazole alkaloids stylissadines A and B[11] as the specific bioactive constituents. Among the non-specific bioactive constituents was the dibromo analogue of palau'amine. NMR spectral analysis of 4,5-dibromopalau'amine led us to revise its structure and by analogy the structure of palau'amine. Furthermore, recently in reports discussing tetrabromostyloguanidine (carteramine A) the groups of Köck[12] and Matsunaga[13] have suggested the need for structural revision of palau'amine based on NMR data and molecular modeling of related compounds. In order to confirm the proposed revised structure, we undertook the isolation of palau'amine itself from *S. flabellata*. We report here the revised structure of palau'amine (**2**) (Fig. 1), by detailed analysis of its 2D ROESY and 1D NOESY data.



(1) **(2)**

Figure 1. Previously assigned structure (**1**) and revised structure (**2**) for palau'amine.

The marine sponge *S. flabellata* (51.8 g) was collected at the Swain Reefs, Great Barrier Reef, Queensland, Australia, in February 2001. The dichloromethane/methanol (4:1) extract (13.6 g) was purified by several C_{18} HPLC steps using 1% TFA/H_2O/methanol to give 17.8 mg of palau'amine (trifluoroacetate salt) as a white amorphous solid (HRESIMS calcd for $C_{17}H_{23}ClN_9O_2$ [M+H]: 420.165771; found: 420.166442, Δ +1.6 ppm). The isolated palau'amine had circular dichroism {299 nm, (θ +527), 269 nm, (θ +7723), 242 nm, (0) and 206 nm (θ −34,000)} and optical rotation {$[\alpha]_D$ −18.9 (MeOH, *c* 0.1)} data comparable to the literature reports.[1,14] The ^1H and ^{13}C NMR chemical shifts in DMSO-d_6 and D_2O compared accurately with those reported, indicating that they must be the same compound. Analysis of the 2D NMR data confirmed that the isolated compound had planar structure identical to that of palau'amine. However, the 2D ROESY and 1D NOESY data (Table 1) for the isolated compound contradicted the relative stereochemistry published for palau'amine. There were NOEs from H18 to H11 and H13β, which placed these protons on the same face of the octahydrocyclopenta[*c*]pyrrole and correlations

Keywords: Palau'amine; Revised structure; Bioactive natural product; Hexacyclic pyrrole–imidazole alkaloid; 2D ROESY NMR; 1D NOESY NMR.
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Table 1. 2D ROESY and 1D NOESY NMR data for palau'amine in DMSO-d_6

Position	δ_H (mult, J Hz)	NOE (H no.)
3	6.75 (dd, 3.8, 1.7)	4
4	6.35 (dd, 3.8, 2.8)	3, 5
5	7.19 (dd, 2.8, 1.7)	4, 6, 7
6	6.21 (br d, 1.0)	5, 7, 11, 20-OH
7(N)	9.93 (br s)	5, 6
11	3.05 (d, 14.4)	6, 13β, 18
12	2.53 (dddd, 14.6, 10.2, 9.0, 7.2)	13α, 17
13	4.05 (dd, 10.2, 7.2)α	12, 13β
	3.14 (t, 10.2)β	13α, 11, 18,
17	4.42 (d, 9.0)	12, 19a, 19b, 23
18	2.24 (qd, 9.0, 5.0)	11, 13β
19	3.15 (m)a	17, 19b
	2.94 (m)b	17, 19a
20	5.75 (br dd, 5.2, 1.0)	21, 20-OH
20-OH	7.71 (d, 5.2)	6, 20
21(N)	9.38 (br s)	20
23(N)	8.94 (br s)	17

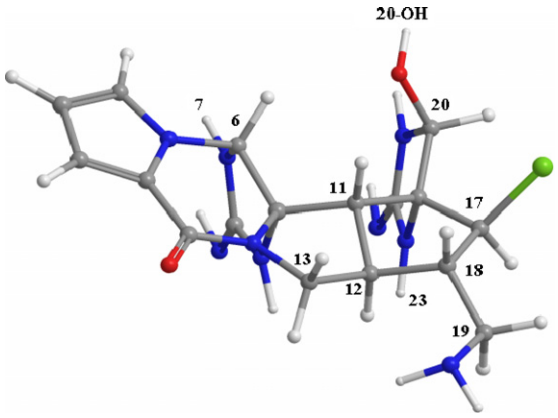

Figure 2. MM2 optimized structure of palau'amine.

from H12 to H17 and H13α, which placed these protons on the other face. There were also NOEs from H6 to 20-OH and H11, and from H17 to H23. Therefore, the octahydrocyclopenta[*c*]pyrrole ring system must be trans-fused (11*S*,12*R*) and have *S* stereochemistry at both C17 and C20. An MM2 optimized structure of isolated palau'amine is shown in Figure 2. However, the published structure for palau'amine depicted a cis-fused octahydrocyclopenta[*c*]pyrrole (11*S*,12*S*) and *R* stereochemistry at both C17 and C20. In the original isolation and structure elucidation paper,[1] the stronger ROESY correlations published for palau'amine would also fit for the isolated compound; however, most of the weak published correlations would not fit. Taking a look at the ROESY spectrum for palau'amine, included in the Supplementary data, suggested it may have been hard to interpret with some difficulty in distinguishing between noise and real correlations. Moreover, despite the dihedral angle between H11 and H12 being stated as 0.1° for palau'amine, there was no mention of a ROESY correlation between these two protons. The above evidence suggests that the relative stereochemistry published for palau'amine was incorrect and should be revised to 12*R*, 17*S*, 20*S*. Proton coupling data (Table 1) is in complete agreement with this stereochemistry.

Palau'amine has been isolated from *S. flabellata*, and its correct structure shown to be **2** (Fig. 1), using 2D ROESY and 1D NOESY NMR spectroscopy. This information is clearly important to the research groups pursuing the first total synthesis of palau'amine. It is also relevant to future biological studies.

Acknowledgements

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Supplementary data

^{1}H, ^{13}C, gCOSY and gHMBC NMR data in DMSO-d_6 and D_2O for palau'amine. Figures giving ^{1}H and ^{13}C NMR spectra for palau'amine in DMSO-d_6 and D_2O. 2D ROESY spectrum and 1D NOESY spectra for palau'amine. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.04.128.

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14. The optical rotation for the isolated compound had a smaller leavorotatory value than that reported {$[\alpha]_D^{24}$ −45.2 (MeOH, *c* 3.0)}.[1] We obtained consistent results when repeating the optical rotation three times on separate purified fractions: $[\alpha]_D^{27}$ −18.9 (MeOH, *c* 0.10), $\sigma = 0.3$; $[\alpha]_D^{19}$ −15.0 (MeOH, *c* 0.12), $\sigma = 1.0$; $[\alpha]_D^{19}$ −17.9 (MeOH, *c* 0.08), $\sigma = 0.7$.