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Concerning the phakellin substructure of palau'amine

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Abstract—The phakellin (**6**) subunit of palau'amine (**1**) has been synthesized and found to be devoid of antibacterial activity, resolving the question of whether **1** is simply an elaborate phakellin in terms of its antimicrobial properties.

Palau'amine (**1**, Fig. 1) and its relatives are distinctly structured and potently bioactive alkaloids.[1] As highlighted recently by Jacquot and Lindel,[2] the family presents a unique preparative challenge. Palau'amine synthesis, in particular, has been pursued unabated for a decade without success—despite numerous creative and insightful attempts.[3] We too are interested in preparing members of the series. As that effort continues,[4] we describe here experiments that distinguish palau'amine, in terms of its biological properties, from simpler phakellin-class compounds.

While initially characterizing palau'amine, Scheuer and Kinnel observed that the antimicrobial activities possessed by **1** were lacking in its co-occurring brominated congeners **2** and **3** (Fig. 1).[1b] Thirty years earlier Sharma had isolated the structural component of palau'amine termed phakellin (**4**) – yet only as brominated forms **5** and **6**.[5] He noted that while extracts of the producing organism displayed potent antibacterial activity, it was not due to halogenated phakellins. Given that precedent, Scheuer's 1998 article[1b] logically questioned whether Sharma's unidentified activity might simply have been due to phakellin (**4**) – reasoning by analogy to their palau'amine/bromopalau'amine findings. If true, and palau'amine's phakellin motif was necessary, perhaps sufficient for its antimicrobial activity, that information would influence justification for attempts at preparing **1**, an effort far more involved than phakellin synthesis.

Racemic dibromophakellin was synthesized according to Horne's modifications[6] of Büchi's original protocol.[7] Namely, dihydrooroidin (**7**) was oxidized with stoichiometric amounts of NBS in TFA solvent and the crude intermediate was treated with Et_3N to generate **6** (92%).[8] Sharma's hydrogenolysis procedure[5b] was subsequently employed to generate phakellin itself (**4**, 98%). Compound **4** is considerably more acid labile than **6**. Exposure of the former to 3 N HCl (23 °C, 36 h) affords nearly a quantitative yield of ketene aminal **8**.[5,9] Notably, **4**, **6**, and **8** are each found to be devoid of activity when screened against a panel of gram negative as well as gram positive bacteria, including multiple drug efflux pump mutant strains.[10] Assuming one enantiomer does not antagonize actions of the other while assaying these racemates,[11] **4** is not Sharma's missing activity and palau'amine is more than an elaborate phakellin in terms of its antibacterial properties.[12] We anticipate using synthetic materials to define this statement more precisely in the future, as well as to ascertain whether palau'amine's antimicrobial and immunosuppressive actions originate with common events at a molecular level.

Acknowledgments

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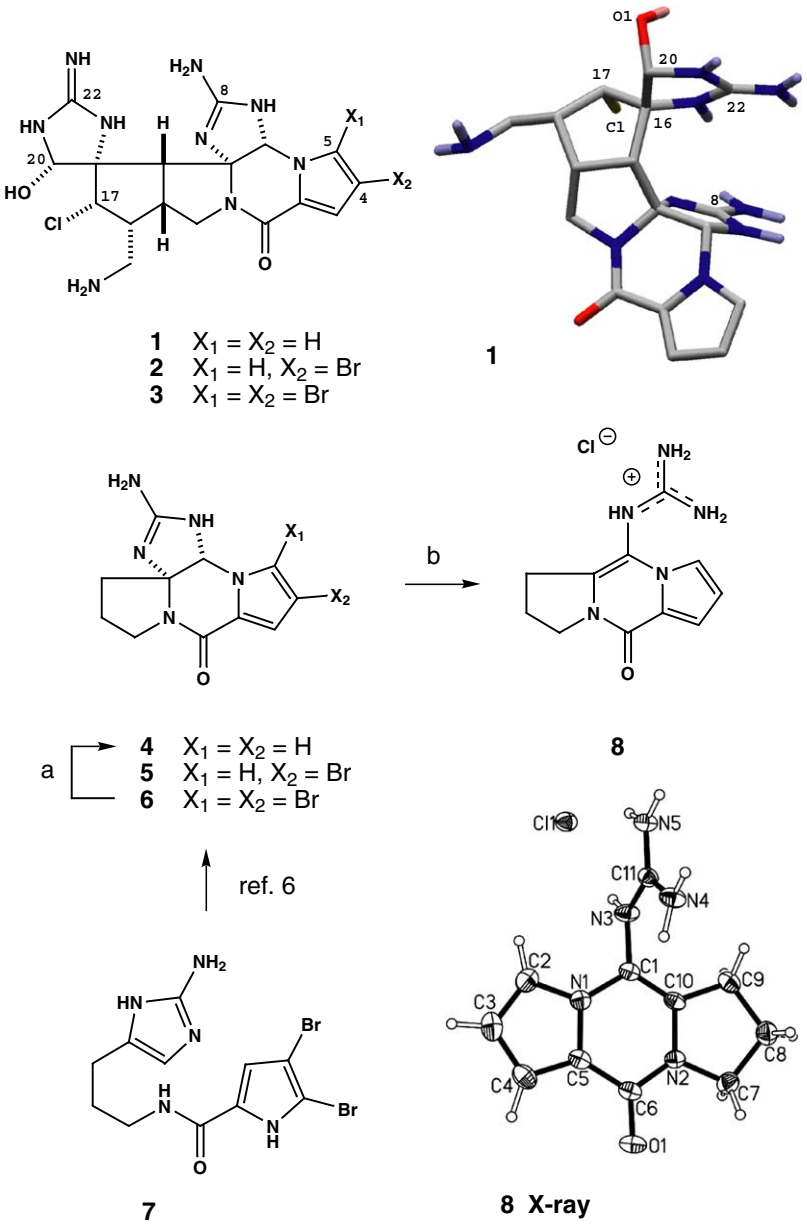

Figure 1. Palau'amine (**1**–**3**) and phakellin (**4**–**6**) structure. Tubes rendition of **1** generated using Macromodel v7.0 (geometry optimized structure). The crystal structure of **8** is shown as an ORTEP (50% probability thermal elipsoids). Reagents and conditions: (a) 2.5 equiv NaOAc, 10% Pd/C, 1 atm H_2, MeOH , rt (98%); (b) 3N HCl, rt, 36 h (>95%).

Supplementary data

Tabular survey of antibacterial assay results and ^{1}H NMR spectra of **4**, **6**, **7**, and **8**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.03.156.

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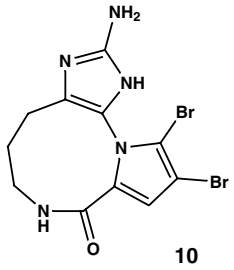
8. Dibromophakellin (**6**) can also be synthesized by treating tetra(fluoroaryl)borate salts of **7** with bis(diphenylphosphinyl) peroxide (CH_2Cl_2, −78 °C), followed by Et_3N (−78 °C→rt). However, the isolated yield of **6** in such experiments is moderate (35–50%), limited in part by competing unimolecular rearrangement of the oxidant [i.e., $Ph_2P(O)–O–O–(O)PPh_2 \rightarrow Ph_2P(O)–O–(O)P(OPh)-Ph$]. See: Dannley, R. L.; Waller, R. L.; Hoffman, R. V.; Hudson, R. F. *J. Org. Chem.* **1972**, *37*, 418–421, Known compounds **4**, **6**, and **7** were synthesized and purified by recrystallization. Data for each (^1H, ^{13}C NMR, melting points, mass spectra) were in full accord with that reported.
9. As reported by Sharma and confirmed by us, **6** is also decomposed in 3 N HCl to the corresponding dibrominated variant of **8**. However, this requires heating at 100 °C wherein three additional products form (in roughly equal amounts). Sharma characterized one of those as ring-expanded compound **10**. See: Sharma, G. *Drugs, Food, Sea, Myth, Reality [Intl. Symp. Proc.]* **1978**, 203–207.



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10. Antimicrobial assays were performed at Cumbre, Inc., 1502 Viceroy Dr., Dallas, TX 75235. See Supplementary data for a full tabular survey.
11. Dibromophakellin has been isolated from nature in both enantiomeric forms but not as a racemate. See Ref. 1b and De Nanteuil, G.; Ahond, A.; Guilhem, J.; Poupat, C.; Tran Huu Dau, E.; Potier, P.; Pusset, M.; Pusset, J.; Laboute, P. *Tetrahedron* **1985**, *41*, 6019–6033.
12. Palau'amine is reported 'active' against *Staphylococcus aureus* and *Bacillus subtilis* at 10 μg/disk. See Ref. 1a.