

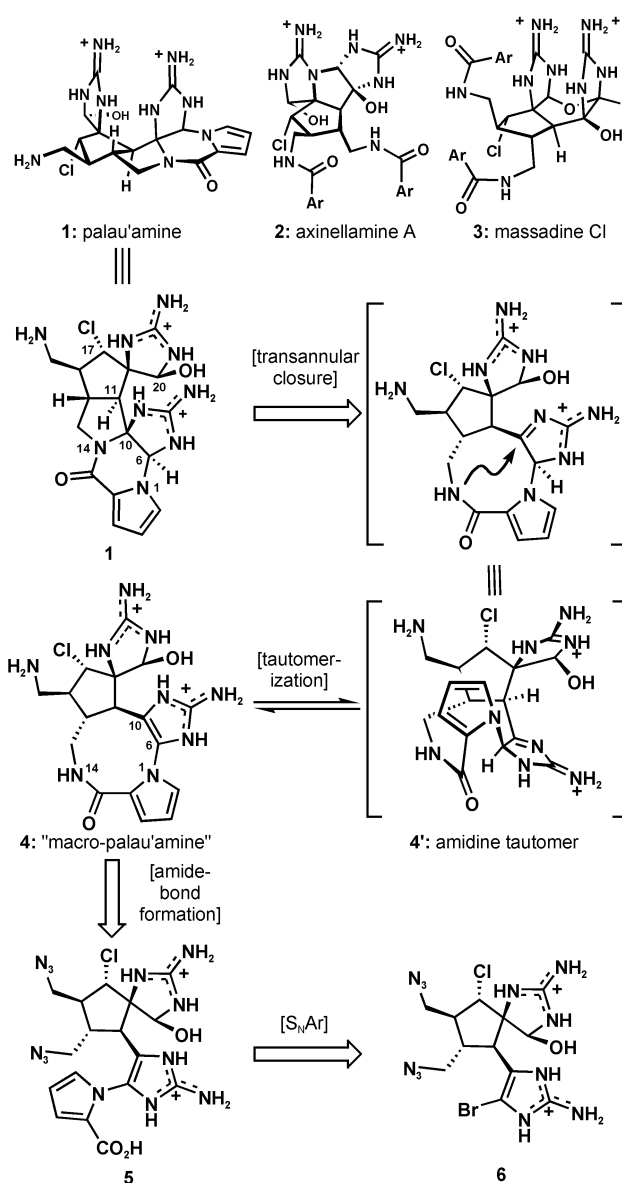
Total Synthesis of Palau'amine**

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Polycyclic dimeric pyrrole–imidazole alkaloids such as palau'amine (**1**, Scheme 1),^[1] axinellamine A (**2**),^[2] and massadine chloride (**3**)^[3] possess daunting structural and physical attributes, including nine or more nitrogen atoms, eight contiguous stereogenic centers, reactive (hemi)aminal moieties, oxidation-prone pyrroles, and highly polar, non-crystalline morphologies. Their unique structures have been the focus of numerous publications from many groups worldwide, and have led to notable advances in synthetic methodology.^[4] Among the more complex members of this class, only the axinellamines (e.g. **2**)^[5] and the massadines (e.g. **3**)^[6] have succumbed to total synthesis, aided by the invention of a highly chemoselective and controllable late-stage oxidation reaction.

Compared to its congeners (**2** and **3**), palau'amine (**1**) possesses a unique chemical challenge: one of the pyrrole–amide sidechains is embedded in an exquisite, hexacyclic core architecture which contains a highly strained *trans*-azabicyclo[3.3.0]octane substructure (unprecedented among natural products). This is undoubtedly a central reason why the synthesis of palau'amine (**1**) has thus far eluded organic chemists despite the dozens of Ph.D. theses^[7] and studies towards publications^[8] that have appeared since its isolation in 1993 and structural reassignment in 2007.^[1] Many well-founded and logical plans to secure the peculiar *trans*-5,5 core of **1** in our laboratory resulted in unfortunate outcomes. Presumably, the high degree of strain implicit in the hexacyclic architecture thwarted all attempts at a biomimetic closure (N14–C10 and N1–C6 simultaneously)^[4] or a stepwise closure (N14–C10 followed by N1–C6).^[9] The lessons learned during those initial attempts inspired an alternative strategy that ultimately led to the total synthesis of **1** presented herein.

As depicted in Scheme 1, our retrosynthetic analysis relied upon a speculation that hypothetical macrocycle **4**, dubbed “macro-palau'amine”, would be a kinetically stable isomer of **1**. It was predicted that an irreversible transannular ring–chain tautomerization would convert **4** into its constitutional isomer **1** through a dynamic equilibrium involving amidine tautomer **4'**. Handheld molecular models suggested that **4** might adopt a folded conformation wherein N14 and C10 would be in close proximity to facilitate such a ring



Scheme 1. Selected pyrrole–imidazole alkaloids, and retrosynthetic analysis of palau'amine (**1**). Ar = 2-(4,5-dibromopyrrole).

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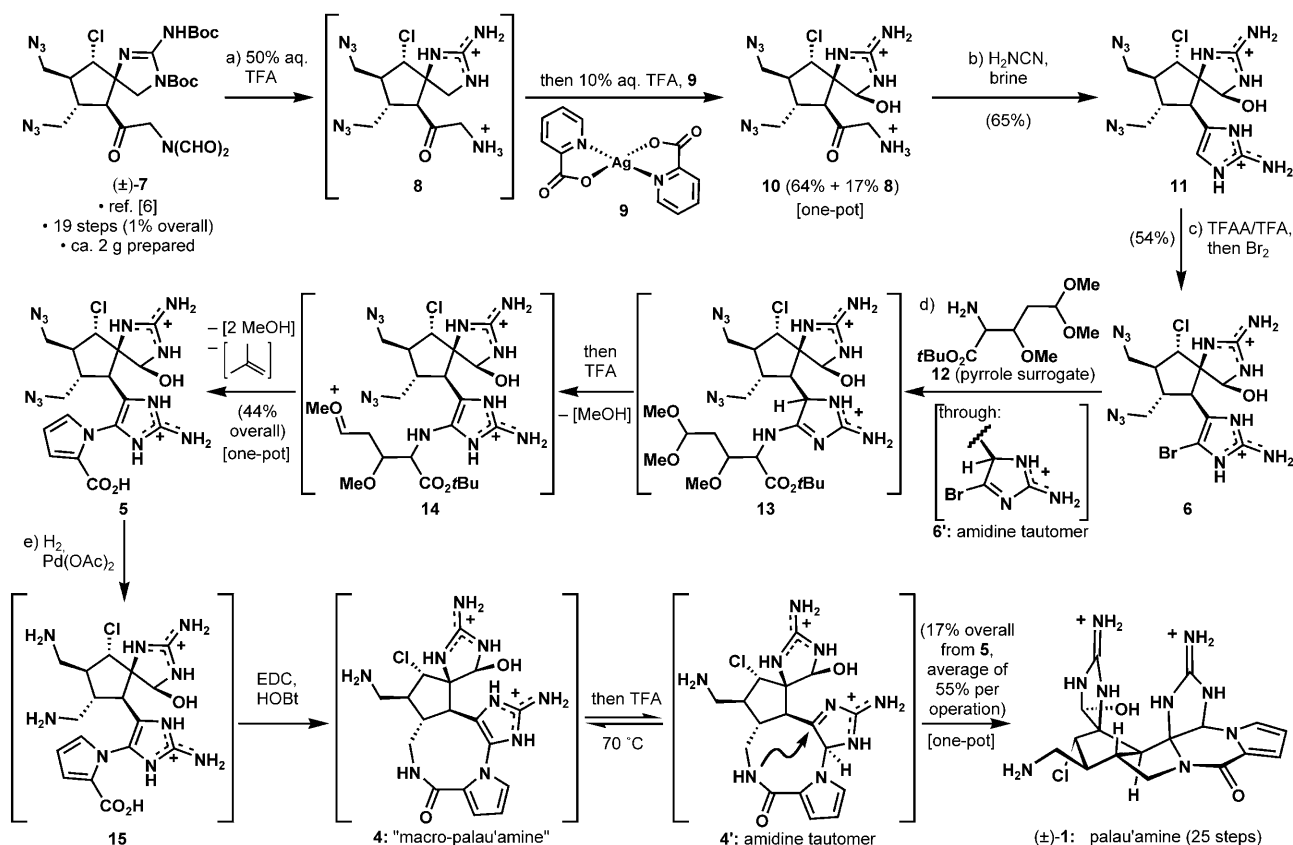
closure. A conceptually related late-stage shift of topology between constitutional isomers through dynamic equilibration was a key design element of our recent synthesis of the kapakahines.^[10] As with **1**, “macro palau’amine” (**4**) exhibits a high level of strain and was believed to be accessible through macrolactamization of the diamine derived from diazide **5**. This intermediate was envisioned to arise from the S_NAr of a pyrrole (or surrogate thereof) to the bromo-aminoimidazole **6**.

The total synthesis of **1**, outlined in Scheme 2, commences with the readily available cyclopentane core **7**, an intermediate enlisted in the synthesis of the massadines and available in 19 steps from commercially available materials in 1% overall yield.^[6] Treatment of **7** with aqueous TFA unveiled amino-guanidine **8**, which was directly converted in unprotected form to the hemiaminal **10** in 64% isolated yield (along with 17% recovered **8**, 130 mg scale)^[11] using silver(II)-picolinate (**9**). It is notable that this oxidation reaction takes place with precise position selectivity—no oxidation of the primary amine is observed under these acidic reaction conditions. Construction of the remaining 2-aminoimidazole took place in 65% yield (251 mg scale)^[11] to afford **11** using cyanamide in brine (sat. aq. NaCl), a solvent that minimizes displacement of the highly labile chlorine atom.^[3,6] Subsequent bromination

using Br_2 in a 1:1 mixture of TFA/TFAA delivered the desired 2-amino-4-bromoimidazole **6** in 54% yield (150 mg scale).^[11] The introduction of the pyrrole moiety proved challenging, as standard conditions to couple amines to aryl halides using transition metal catalysis failed to produce any detectable amounts of product (even on the Boc-protected 2-amino-4-bromoimidazole derivatives). In principle, the inherent ambiphilicity of the 2-aminoimidazole could lend itself to a unique reactivity pattern, one that would allow for uncatalyzed nucleophilic attack on the 2-amino-4-bromoimidazole as a possible direct route to the pyrrole-acid intermediate **5**.

In the event, the nucleophilic pyrrole surrogate **12**^[12] was reacted with 2-amino-4-bromoimidazole **6** buffered with AcOH, followed by treatment with TFA, to deliver the desired N-coupled pyrrole-2-carboxylic acid **5** in a one-pot operation in 44% yield (91 mg scale).^[11] Presumably, facile N–C bond formation is observed due to the high reactivity of its tautomeric amidine form (**6'**). This reaction appears to be general and its scope will be reported in the full account of this work. The pyrrole-forming step, mediated by TFA and traversing through oxonium **14**, involves no less than five chemical transformations occurring in tandem to deliver **5**.

In preparation for the key macrolactamization step, the azide groups of **5** were reduced to afford highly polar diamine



Scheme 2. Total synthesis of palau'amine (**1**). Counterions are $CF_3CO_2^-$ and are omitted for clarity. Reagents and conditions: a) TFA/ H_2O (1:1), 50 °C, 12 h, then silver(II)-picolinate (2.4 equiv), TFA/ H_2O (1:9), 23 °C, 5 min, 64% + 17% recovered **8**; b) H_2NCN (40 equiv), pH 5, brine, 70 °C, 4 h, 65%; c) TFAA/TFA (1:1), 1 h, then Br_2 (2.0 equiv), 1 h, then TFA/ H_2O (1:1) 1 h, 38 °C, 54%; d) AcOH (3.0 equiv), **12** (3.0 equiv), THF, 38 °C, 6 h, then TFA/DCM (1:30 to 1:1), 23 °C, 12 h, 44%; e) $Pd(OAc)_2$ (1.6 equiv), H_2 (bubbled through solution) TFA/ H_2O (1:9), 23 °C, then EDC (2.8 equiv), HOBT (2.8 equiv), DMF, 23 °C, 3 h, then TFA, 70 °C, 38 h, 17% from **5**. TFA = trifluoroacetic acid, TFAA = trifluoroacetic anhydride, THF = tetrahydrofuran, HOBT = *N*-hydroxybenzotriazole, EDC = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, DMF = *N,N*-dimethylformamide.

15 (4.0 mg scale). The synthesis of “macro-palau’amine” **4** was effected using EDC and HOBt. Heating of the crude reaction mixture in TFA (70°C) elicited the crucial trans-annular cyclization (presumably proceeding through amidine tautomer **4'**) that fastened the remaining two stereocenters and cemented the hallmark trans-5,5 ring system to deliver palau’amine (**1**) in 17% overall yield from **5** (one-pot, average of 55% per operation) after repeated purification with reverse phase HPLC (spectroscopically identical to that reported for **1** with the exception of optical rotation).^[13] Optimization and mechanistic investigation of this final sequence (**5**→**1**) is currently underway.^[9]

The journey to **1** (25 steps from commercial material, 0.015% overall yield with current procedures)^[9] has led not only to useful strategies and methods, but also to an empirical demonstration of numerous guiding principles for synthesis design at the frontiers of chemical complexity.^[14] Over six years ago our group embarked on the synthesis of dimeric pyrrole-imidazole alkaloids by methodically applying the logic of biosynthesis where appropriate during the syntheses of sceptrin, oxysceptrin, nakamuric acid, ageliferin, nagelamide, the axinellamines (e.g. **2**), and the massadines (e.g. **3**).^[5,6,15] The synthesis of **1** benefited from a tremendous amount of chemical reactivity learned during those endeavors. Our 2004 biosynthetic hypothesis^[15b] led us to pursue the true structure of **1** prior to the realization of its revised structure.^[1] In an effort to apply redox economic principles^[16] to this chemical synthesis program, a late-stage, chemo-selective, silver-mediated oxidation was invented to circumvent laborious routes to the key hemiaminal unit expressed in **1**–**3** (C-20, Scheme 1). Cascade reactions were incorporated to rapidly assemble complexity (e.g. **6**→**5**→**1**). Finally, innate reactivity was utilized so as to minimize the use of redundant and orthogonal protecting group operations,^[17] and instead maximize the discovery of interesting chemical reactivity such as the direct coupling of nucleophiles to unprotected 2-amino-4-bromoimidazoles. An enantioselective, scalable variant of the current synthesis, as well as a full account of this work will be forthcoming.

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