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Total Synthesis of (±)-Haouamine A

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Structurally unique natural products have historically served as conduits to mend gaps in the science of synthesis.[1] Recently, Zubía and co-workers discovered the structurally unprecedented alkaloids haouamine A and B (**1** and **2**, Figure 1) from a tunicate (*Aplidium haouarianum*) residing off the southern coast of Spain.[2] Their heptacyclic framework of mysterious biosynthetic origin exists as an inseparable mixture of two interconverting isomers that accommodate a congested indeno-tetrahydropyridine ring system, an unusual oxygenation pattern, and a highly strained aza-paracyclophane with a *bent* aromatic ring. These architectural features combined with exquisitely selective anticancer activity in human colon carcinoma cells (IC_{50} = 0.1 μg/mL) make **1** a particularly attractive target for total synthesis.[3] Herein, we describe a short and efficient total synthesis of **1** facilitated by the invention of a powerfully simplifying annulation method to access the indeno-tetrahydropyridine ring system and a new method for macrocyclization leading to the bent aromatic ring.

Initial forays into the haouamine problem were guided by our postulated biosynthesis put forth in Figure 1 wherein the key C−C and C−N bonds would be formed through simple oxidation and condensation events of ammonia and four *meta*-hydroxylated phenylacetaldehydes. The final retrosynthetic analysis (Figure 1) was derived from an amalgamation of empirical intelligence gained from "failures" in attempting to reduce this plan to practice. Thus, the indeno-tetrahydropyridine **3** was chosen as an ideal intermediate from which to evaluate strategies for forging the unusual aza-paracyclophane, which in turn was envisioned as arising from oxime **4** *via* a cascade annulation sequence designed exclusively for this ring system.

The synthesis commenced with alkylation of the thermodynamic potassium enolate of readily available **5**[4] with allylic iodide **6**[4] in 54% yield followed by oxime formation to furnish **4** in 75% yield (Scheme 1). On the basis of the precedent set by Grigg and co-workers,[5] exposure of **4** to an electrophilic halogen source was expected to elicit a 5-*exo*-*trig* cyclization to nitrone **7**. It was reasoned that a subsequent reduction of the nitrone would occur stereoselectively to produce **8**, which, in principle, could cyclize to the unprecedented *N*-hydroxyaziridinium species **9**. Assuming that this new chemical entity can even be formed, orbital considerations[6] allow one to predict a subsequent position selective fragmentation to the desired *N*-hydroxypiperidine **10** in preference to the alternate *N*-hydroxyl enamine. Chemoselective reduction of the N−O bond (in the presence of the aryl bromide and olefin) could then lead to the key intermediate **3**. This designed cascade could be reduced to practice by executing the following sequence: (1) treatment of **4** with 2,4,4,6-tetrabromo-2,5-cyclohexadienone at 0 °C to furnish the intermediate nitrone **7** as an inconsequential mixture of two diastereomers, (2) immediate reduction with $NaBH_4$ at 50 °C to the cis-fused hydroxy pyrrolidine **8**, (3) continued heating for 1 h to elicit hydroxyaziridinium formation and subsequent ring expansion to **10**, and (4) selective reduction[7] of the crude *N*-hydroxylpiperidine using In^0 to furnish **3** in 57% overall yield (corresponding to an average yield of 90% per transformation). The structures of the stable intermediates **7** and **10** were secured spectroscopically by intercepting the cascade and by X-ray crystallographic analysis (Figure 2) of related intermediates **7′** (prepared from debromo-**4** using *t*-BuOCl) and **10′** (debromo-**10**).[4] Although the *N*-hydroxyaziridinium species **9** was not spectroscopically observable, it is logical to invoke such an intermediate by analogy to the chemistry of related pyrrolidine systems lacking an *N*-hydroxyl.[8]

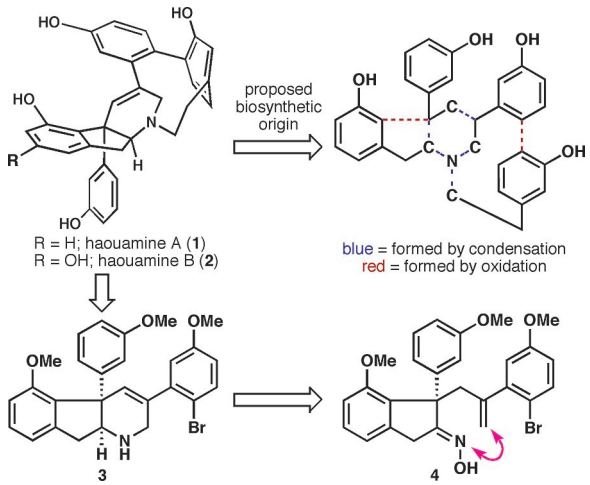

Figure 1. Retrosynthetic analysis of haouamine A (**1**).

With gram-scale access to the core indeno-tetrahydropyridine ring system in only three steps, attention turned to construction of the hallmark aza-paracyclophane sector. The pseudo-boat configuration adopted by one of the phenols clearly posed a challenge to the current state of the art in macrocyclization methodology. Not surprisingly, several standard approaches such as transition metal-based biaryl synthesis, Witkop photocyclization,[9] and intramolecular alkylation all failed. *A new strategy for this type of cyclization was conceived of on the premise that a nonaromatic conformational mimic of the bent aromatic ring might serve as a viable precursor if it were able to undergo subsequent aromatization*. The pyrone-alkyne Diels−Alder reaction[10] fits these criteria since it leads to a cyclohexadiene having a boat configuration and an embedded leaving group (CO_2). To the best of our knowledge, such a strategy for macrocyclization is unknown.

Implementation of this approach commenced with a Stille coupling of pyrone **12**[4,11] with Boc-protected piperidine **11** to afford the pyrone−piperidine conjugate **13**. Subsequent Boc removal and alkylation delivered **14** in 70% yield. Global demethylation using BBr_3 and peracetylation afforded **15** in 67% yield and set the stage for the key macrocyclization event. After extensive experimentation, **15** was converted into **1** upon microwave irradiation of **15** in dichlorobenzene at 250 °C for 10 h followed by basic (K_2CO_3, MeOH) acetate hydrolysis. The use of fully acetylated precursor **15** was essential to minimize thermal decomposion of **1**. Remarkably, the macrocyclization event proceeded with high atropselectivity in favor of **1** (10:1, separable by HPLC).[12] Synthetic (±)-haouamine A (**1**), isolated in 21% yield along with 30% of recovered **15** (separated by PTLC prior to deacetylation), was spectroscopically identical to a natural sample kindly provided by Professor Zubía.

The synthetic challenge posed by the ornate molecular architecture of haouamine has been met in eight steps from readily available indanone **5** (prepared in two steps from commercially

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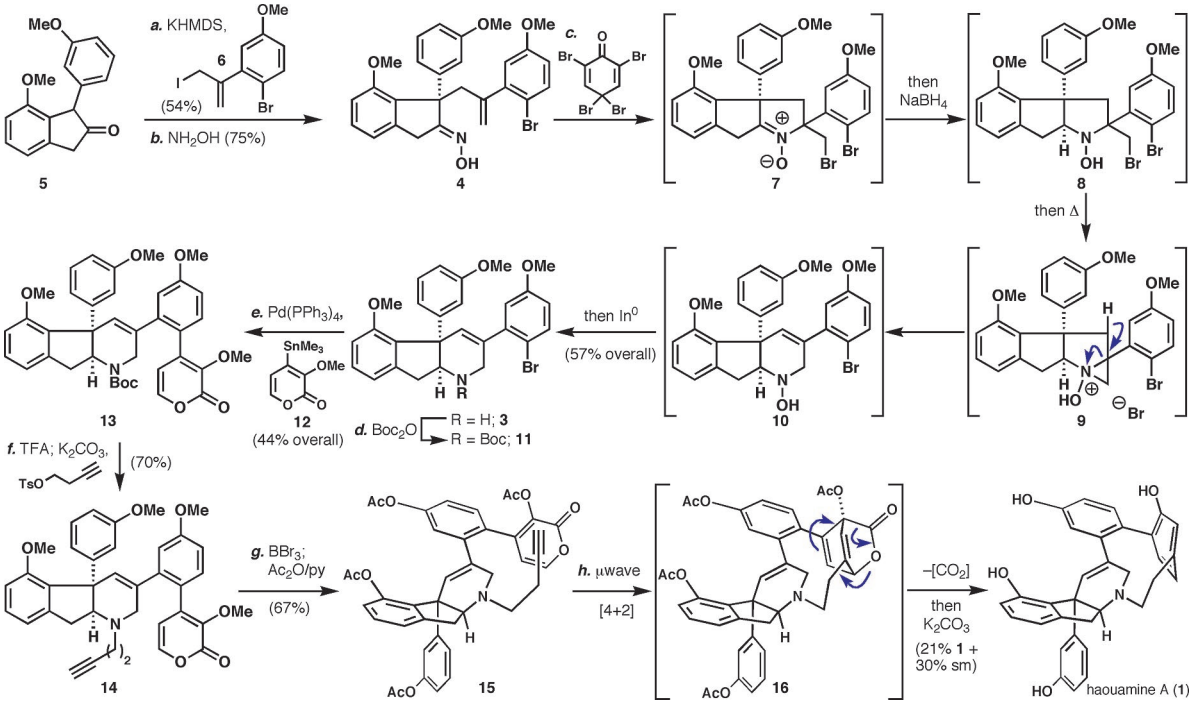
Scheme 1. Short Total Synthesis of **1**[a]



[a] Reagents and conditions: (a) KHMDS (1.1 equiv), 5:1 THF/DMPU, 0 °C, 30 min; **6** (1.5 equiv), −78 to 23 °C, 54%; (b) $NH_2OH{\cdot}HCl$ (20 equiv), NaOAc (15 equiv), EtOH, reflux, 24 h, 75%; (c) 2,4,4,6-tetrabromo-2,5-cyclohexadienone (2.2 equiv), DCE, 0 °C, 30 min, then $NaBH_4$ (5.0 equiv), EtOH, 50 °C, 1 h; In powder (2.0 equiv), 2:1 EtOH/saturated aqueous NH_4Cl, reflux, 3.5 h, 57% overall; (d) Boc_2O (1.2 equiv), DCM, 30 min; (e) **12** (1.6 equiv), $Pd(PPh_3)_4$ (0.1 equiv), CuI (0.2 equiv), toluene, reflux, 12 h, 44% overall; (f) 10:1 DCM/TFA, 3 h; 4-tosyloxybutyne (5.0 equiv), K_2CO_3 (2.5 equiv), CH_3CN, reflux, 6 h, 70%; (g) BBr_3 (10.0 equiv), DCM, −78 to 23 °C, 1:1 Ac_2O/pyr, 3 h, 67%; (h) DCB (0.001 M), 250 °C, BHT (7.7 equiv), 10 h; PTLC; K_2CO_3 (4.0 equiv), MeOH, 30 min, 21% **1** + 30% **15**. BHT = 2,6-di-*tert*-butylmethyl phenol; DCE = 1,2-dichloroethane; KHMDS = potassium hexamethyldisilazide; DCB = *o*-dichlorobenzene.

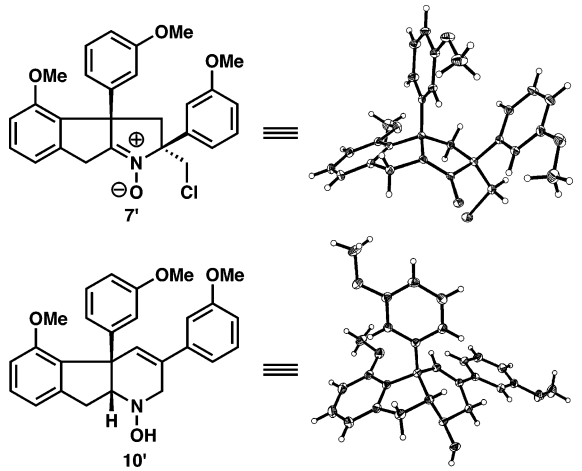


Figure 2. X-ray crystal structures of **7′** and **10′**.

available material). Brevity of the sequence and complete control of chemo-, position-, and stereoselectivity (both planar and axial chirality) was possible through the invention of chemistry specifically tailored for the problems at hand, namely a cascade annulation proceeding via a hitherto unknown chemical entity for the indenotetrahydropyridine ring system as well as a pyrone-assisted stitching of the daunting bent aromatic ring. Studies are underway to render the alkylation of **5** enantioselective, apply the current strategy to the total synthesis of **2**, and probe the medicinal properties of **1**.

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Supporting Information Available: Detailed experimental procedures, copies of all spectral data, and full characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) The minor atropisomer of **1** is tentatively assigned on the basis of its similarity to **1** in the crude ^1H NMR spectra prior to HPLC separation. On the basis of this, and as implied in ref 2, **1** exists as a mixture of isomers due to slow inversion at nitrogen as opposed to atropisomerism. Molecular models indicate that atropoisomerization would be geometrically and sterically forbidden.

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