

Total Synthesis of (±)-Hauouamine 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 hauouamine 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 ($IC_{50} = 0.1 \mu\text{g/mL}$) 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 hauouamine 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 nitron **7**. It was reasoned that a subsequent reduction of the nitron 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 considerations⁶ 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 nitron **7** as an inconsequential mixture of two diastereomers, (2) immediate reduction with NaBH₄ 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 reduction⁷ of the crude *N*-hydroxypiperidine using In⁰ 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

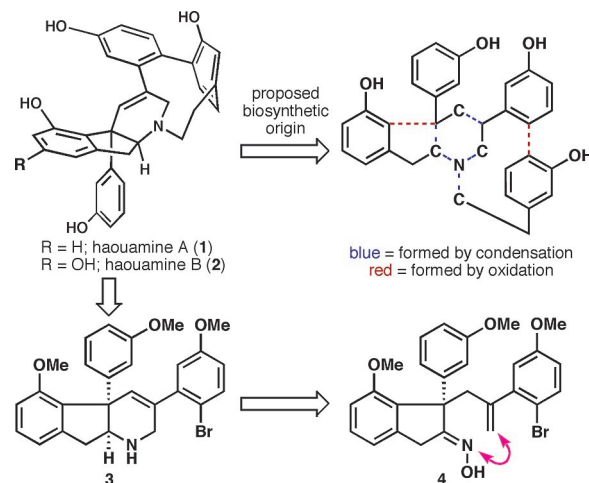


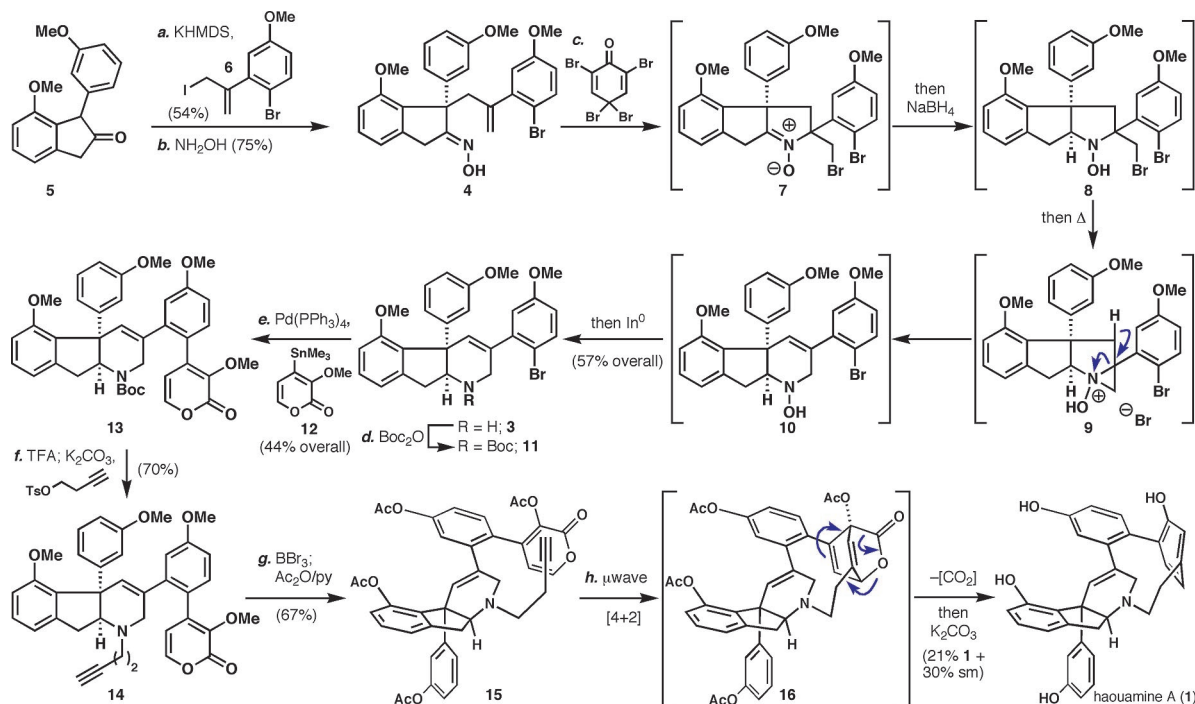
Figure 1. Retrosynthetic analysis of hauouamine A (**1**).

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

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 reaction¹⁰ fits these criteria since it leads to a cyclohexadiene having a boat configuration and an embedded leaving group (CO₂). 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 BBr₃ 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 (K₂CO₃, MeOH) acetate hydrolysis. The use of fully acetylated precursor **15** was essential to minimize thermal decomposition of **1**. Remarkably, the macrocyclization event proceeded with high atropselectivity in favor of **1** (10:1, separable by HPLC).¹² Synthetic (±)-hauouamine 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 hauouamine has been met in eight steps from readily available indanone **5** (prepared in two steps from commercially

Scheme 1. Short Total Synthesis of **1**^a

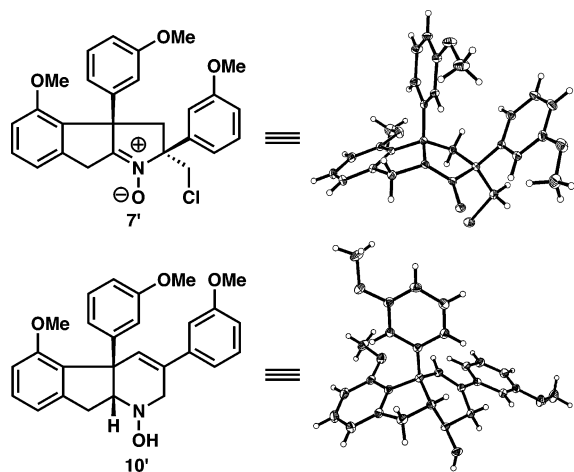
assistance. We are grateful to Biotage for a generous donation of microwave process vials used in this study. Financial support for this work was provided by The Scripps Research Institute, Amgen, AstraZeneca, BMS, DuPont, Eli Lilly, GlaxoSmithKline, Roche, and the Searle Scholarship Fund.

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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- 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 atropisomerization would be geometrically and sterically forbidden.

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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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