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Synthetic Studies toward the Haouamines

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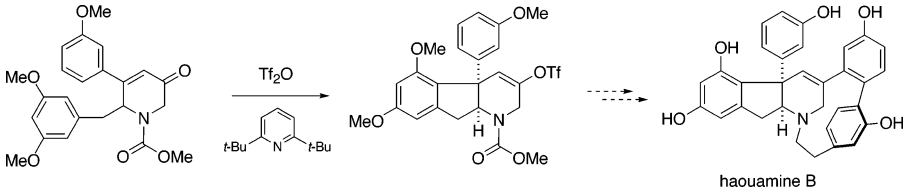
ABSTRACT



A concise synthetic approach toward the haouamines based on Stork–Danheiser alkylation and Friedel–Crafts chemistry is described. A novel electrophilic aromatic substitution with concomitant formation of an enol triflate is reported.

The haouamines are a pair of structurally intriguing alkaloids recently isolated from the ascidian *Aplidium haouarianum*.[1] In cytotoxicity tests against five cancer cell lines, haouamine A was found to strongly inhibit growth of human colon carcinoma cells HT-29 and haouamine B displayed moderate activity against mice endothelial MS-1 cells.

Structurally, both alkaloids feature an indeno tetrahydropyridine moiety that contains a diaryl quaternary center and an *anti*-Bredt double bond. The tetrahydropyridine ring is fused to a highly strained 11-membered cyclophane ring system. In addition, the molecules show interesting dynamic behavior, existing as an equilibrating mixture of isomers that could stem from atropisomerism of the cyclophane moiety or from nitrogen inversion. These features, in combination with the presence of a basic amine and multiple phenolic hydroxy groups, make the haouamines a formidable synthetic challenge.

Molecules as complex and unprecedented as the haouamines are sure to attract the attention of the synthetic community. Indeed, very recently Rawal has reported an approach to haouamine A that hinges on an intramolecular Friedel−Crafts alkylation (Scheme 1).[2]

This report prompted us to give an account of our own studies, which although distinct bear some strategic similarities. In particular, one of our approaches to haouamine B also relies on an intramolecular Friedel−Crafts reaction to establish the diaryl quaternary center of the alkaloid. The tertiary allylic alcohol employed as a substrate, however, is a regioisomer of Rawal's type and is assembled using a Stork−Danheiser alkylation sequence.

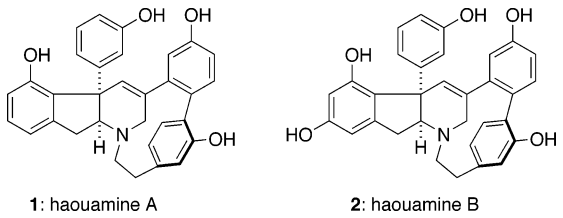


Figure 1. The haouamines.

Our general approach to the haouamines starts with readily available 3,5-dimethoxypyridine (**5**),[3] which was converted into the vinylogous ester **6** in three straightforward steps (Scheme 2).[4] Deprotonation and alkylation of **6** with either

(1) Garrido, L.; Zubia, E.; Ortega, M. J.; Salva, J. *J. Org. Chem.* **2003**, *68*, 293.

(2) Smith, N. D.; Hayashida, J.; Rawal, V. J. *Org. Lett.* **2005**, *7*, 4309.

(3) Testaferri, L.; Tiecco, M.; Tingoli, M.; Bartoli, D.; Massoli, A. *Tetrahedron* **1985**, *41*, 1373.

(4) Phillips, S. T.; Rezac, M.; Abel, U.; Kossenjans, M.; Bartlett, P. A. *J. Am. Chem. Soc.* **2002**, *124*, 58.

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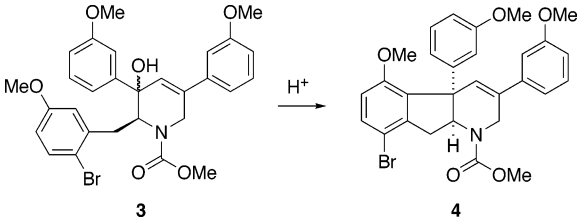
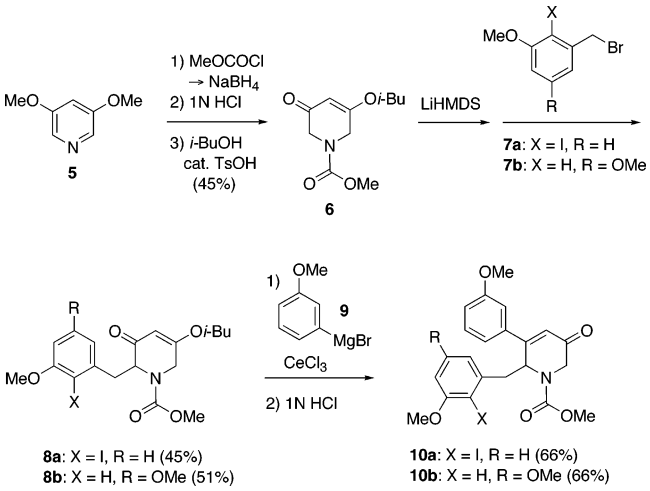
Scheme 1. Rawal's Approach toward Haouamine A



iodomethoxy benzyl bromide **7a** or dimethoxy benzyl bromide **7b** gave **8a** and **8b**, respectively, as the only isolated regioisomers. The regiochemical outcome of these reactions

Scheme 2. Preparation of Precursors **10a** and **11**



was confirmed by an X-ray structure of **8a** (Figure 2). Cerium chloride mediated addition of Grignard reagent **9** to **8a** or **8b**, followed by hydrolysis with concomitant elimination, afforded aryl enones **10a** and **10b**, which correspond to haouamines A and B, respectively.

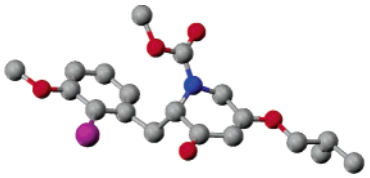
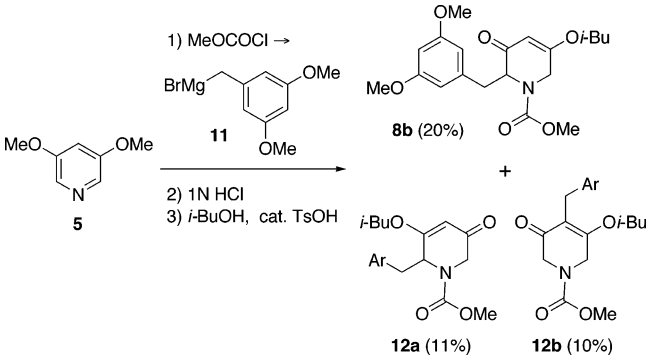


Figure 2. X-ray structure of **8a**.

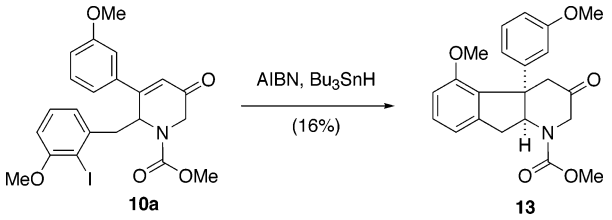
A more direct, alternative approach to piperidinone **8b** was briefly explored (Scheme 3). Addition of Grignard reagent **11** to the acyl pyridium salt formed from **5** and methyl chloroformate was followed by hydrolysis of the resultant crude product and formation of the vinylogous ester. Unfortunately, **8b** was formed as a mixture with its regioisomers **12a** and **12b** under these conditions, thus offering no advantage over the alkylation strategy.

Scheme 3. Alternative Preparation of **8b**



With **10a** and **10b** at hand, the stage was set to explore various modes of cyclization that would yield the indeno tetrahydropyridine moiety and set the biaryl quaternary stereocenter of the haouamines. So far, attempts to achieve this key bond formation with **10a** using organometallic or radical chemistry have been moderately successful. For instance, radical cyclization of **10a** afforded the desired product **13**, albeit in very low yield (Scheme 4).

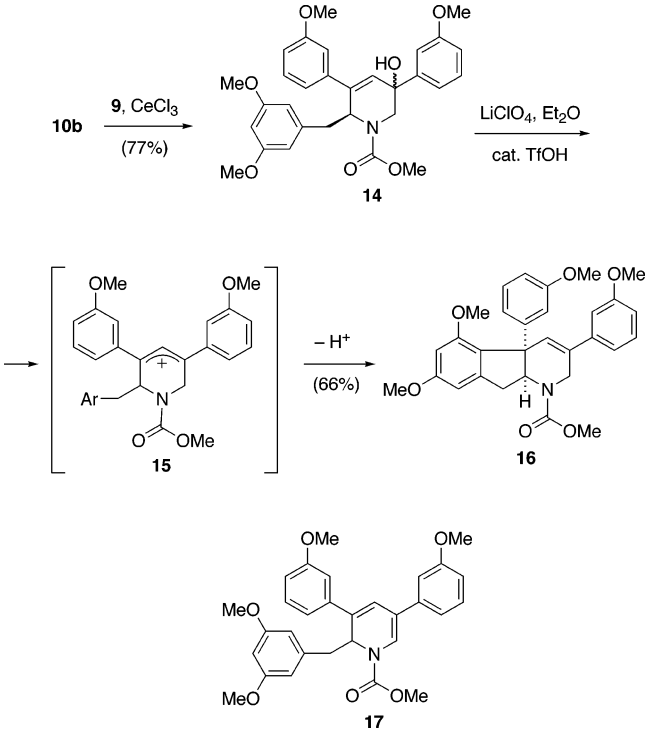
Scheme 4. Radical Cyclization Approach



By contrast, our approach to haouamine B based on intramolecular Friedel−Crafts chemistry proved to be more satisfying (Scheme 5). To this end, **10b** was reacted with aryl Grignard **9** to afford the tertiary allylic alcohol **14**. Dissolution of this compound in 4 M ethereal lithium perchlorate followed by addition of catalytic amounts of triflic acid resulted in the formation of indeno piperidine **16** in 66% yield. This reaction presumably proceeds through the intermediacy of stabilized carbocation **15**, which undergoes the cyclization with a high degree of regio- and stereoselectivity. Importantly, the choice of reaction conditions proved to be crucial for the success of this reaction. Under less polar and acidic conditions, simple elimination of the tertiary alcohol was observed to afford dihydropyridine **17**. This *N*-acyl dienamine apparently fails to undergo protonation (→ **15**) followed by cyclization (→ **16**).

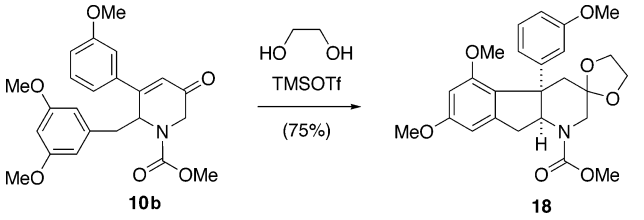
Alternative modes of Friedel−Crafts chemistry involving the electrophilic activation of an enone were investigated as

Scheme 5. Friedel−Crafts Approach



well. For instance, treatment of enone **10b** with ethylene glycol in the presence of trimethyl silyl triflate afforded dioxolane **18** in good yield (Scheme 6).

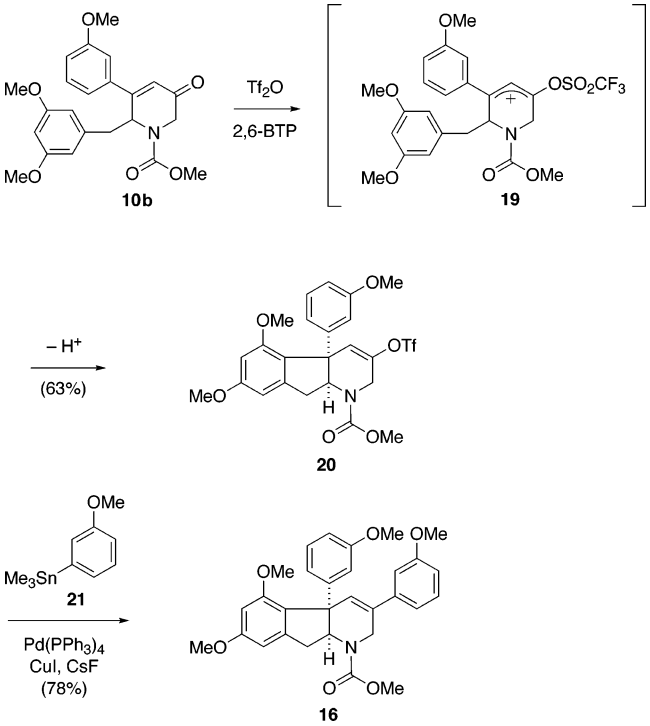
Scheme 6. Friedel−Crafts Cyclization with Concomitant Formation of an Ethylene Ketal



Our most advanced compound, **16**, was also prepared using a novel electrophilic aromatic substitution that generates a strategically positioned enol triflate directly (Scheme 7). Treatment of **10b** with triflic anhydride in the presence of 2,6-bis-*tert*-butyl pyridine (2,6-BTP) resulted in the formation of compound **20**.[5] This reaction presumably involves trifloxy allylic cation **19**, which undergoes intramolecular nucleophilic attack by the electron-rich arene at a faster rate than deprotonation.

Enol triflate **20** is set up to undergo transition metal catalyzed cross-coupling to install the trisubstituted double bond of the haouamines. Indeed, Stille coupling of **20** with

Scheme 7. Friedel−Crafts Cyclization with Concomitant Formation of an Enol Triflate



stannane **21** (prepared in one step from **9**) afforded **16**, which proved to be identical in all respects to the material obtained previously (see Scheme 5).

In summary, we have achieved the synthesis of a substantial portion of the haouamines following concise synthetic strategies that could be readily rendered asymmetric.[6] Future directions will be aimed at the completion of the synthesis of haouamine B and the further exploration of transition metal catalyzed cyclizations of substrates of type **10a**. The systematic exploration of Friedel−Crafts reactions involving activated enones is also under investigation.

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Note Added after ASAP Publication. There was an MeO substituent missing in the abstract graphic in the version posted ASAP December 13, 2005; the corrected version posted December 15, 2005.

Supporting Information Available: Spectroscopic and analytical data for compounds **6**, **8a**, **8b**, **10a**,**b** **12a**,**b**, **13**, **14**, **16**, and **18**−**20**, including a CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) For related examples of electrophilic activation with triflic anhydride, see: (a) Corey, E. J.; Tian, Y. *Org. Lett* **2005**, *7*, 5535. (b) Baraznenok, I. L. Nenajdenko, V. G.; Balenkova, E. S. *Synthesis* **1997**, 465.

(6) For an example of asymmetric Stork-Danheiser alkylations, see: Dudley, G. B.; Takaki, K. S.; Cha, D. D.; Danheiser, R. L. *Org. Lett.* **2000**, *21*, 3407.