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Facile Synthesis of the Indeno-Tetrahydropyridine Core of Haouamine A

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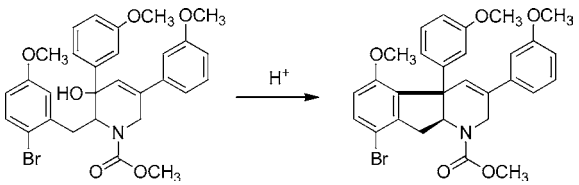
ABSTRACT



The tricyclic indeno-tetrahydropyridine core of haouamine A, containing five of the seven rings of the natural product, was constructed by a simple, concise route that features an acid-catalyzed Friedel–Crafts ring closure.

Two novel metabolites, haouamines A (**1**) and B (**2**), were recently isolated from the ascidian *Aplidium haouarianum*, collected off Tarifa Island in the south of Spain (Figure 1).[1] Belonging to an unprecedented class of alkaloids, these compounds are characterized by two constrained ring systems, the indeno-tetrahydropyridine moiety comprising the left half of the molecule and the strained aza-paracyclophane moiety comprising the right half. The strain in the cyclophane portion is evident from the reported X-ray crystal structure and molecular models, which show the para-disubstituted benzene ring to be nonplanar.[1]

The haouamines were tested for cytotoxic activity against several tumor cell lines, including the human lung carcinoma A-549, human colon carcinoma HT-29 and HCT-116, mice endothelial cells MS-1, and human prostate carcinoma PC-3. These studies showed haouamine A (**1**) to be very potent and selective for cytotoxic activity against the HT-29 cell line with an IC_{50} of 0.1 μg/mL. By comparison, haouamine B (**2**), with only an additional hydroxyl group, was much less cytotoxic, displaying an IC_{50} of 5 μg/mL against the MS-1 cell line.[1] The combination of interesting biological activity and novel chemical structures makes the haouamines attractive targets for synthesis. In this Letter, which represents the first publication on the synthesis of these natural products, we describe an efficient synthesis of the indeno-tetrahydropyridine ring system of haouamine A (**1**).

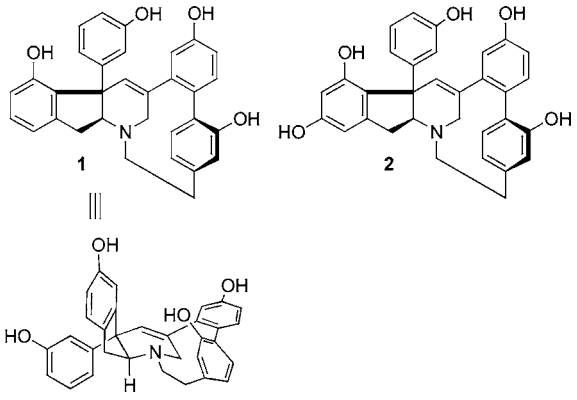


Figure 1. Haouamine A (**1**) and Haouamine B (**2**).

Our strategy to haouamine A (**1**) can be seen through the retrosynthetic analysis shown in Scheme 1. In principle, the paracyclophane can be constructed through cross-coupling or oxidative coupling of an appropriately functionalized precursor, **3**. We envisioned assembling the indeno-tetrahy-

(1) Garrido, L.; Zubia, E.; Ortega, M. J.; Salva, J. *J. Org. Chem.* **2003**, *68*, 293−299.

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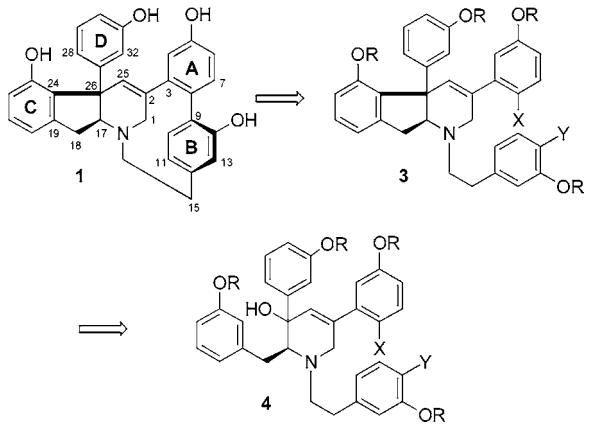
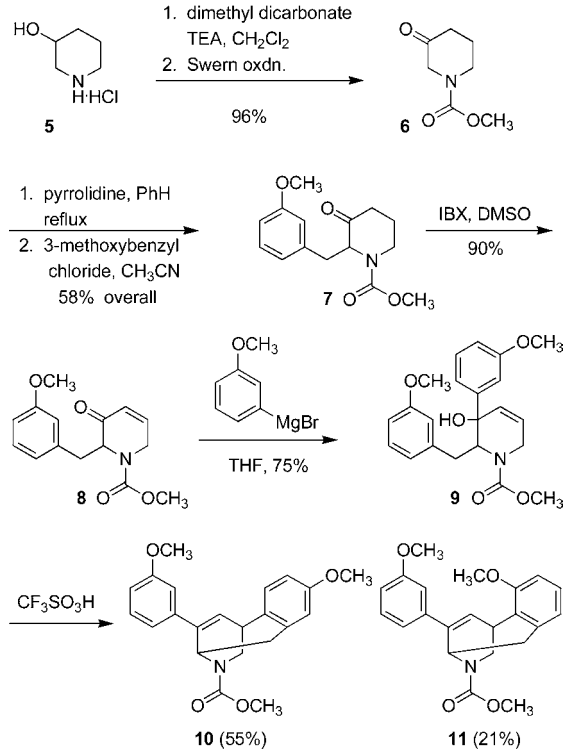
Scheme 1



dropyridine core of **3** by either a transition metal-catalyzed reaction or an acid-catalyzed reaction. The latter, a Friedel−Crafts reaction, was appealing for its simplicity.[2] The electron-rich C ring of **4** was expected to cyclize readily onto an allylic carbocation on the piperidine ring. From stereoelectronic and strain considerations, the cyclization was expected to produce the cis-fused product.

The feasibility of the Friedel−Crafts cyclization route was evaluated through a model system (Scheme 2). The commercially available HCl salt of 3-hydroxypiperidine (**5**) was reacted with dimethyl dicarbonate to afford the amino-protected piperidine in quantitative yield. The alcohol was oxidized under Swern conditions to yield ketone **6** in 96%

Scheme 2



yield. Transformation of the ketone into the pyrrolidine enamine and subsequent alkylation with 3-methoxybenzyl chloride afforded **7** in a 58% overall yield.[3] The double bond was next introduced utilizing the IBX protocol developed by Nicolaou et al.[4] to give α,β-unsaturated ketone **8** in 90% yield. The reaction of enone **8** with 3-methoxyphenylmagnesium bromide proceeded regioselectively to afford the 1,2-addition product, tertiary alcohol **9**, in 75% yield.[5]

With the tertiary alcohol in place, the acid-catalyzed cyclization was examined. Upon addition of a solution of the alcohol to a 1:1 mixture of $TfOH/CH_2Cl_2$, a smooth reaction took place to afford two closely related cyclization products. The major component, isolated in 55% yield, was determined by ^1H NMR and decoupling experiments to be bridged bicyclic compound **10**. The Friedel−Crafts reaction evidently took place such that the less hindered carbon of the putative allylic carbocation intermediate was intercepted by the aromatic ring at a position para to the methoxy group. The minor product (**11**) was formed in the same way but by attack of the aromatic ring at the position ortho to the methoxy group.

The above model study showed that although the Friedel−Crafts alkylation can take place readily, it does so to produce the less congested product: the reaction occurs primarily para to the methoxy group and exclusively at the less substituted carbon of the putative allylic carbocation intermediate. Fortunately, it was possible to address both of these regioselectivity issues.

Given the inherent preference for the undesired para-attack, we decided to install a blocking group at this position (Scheme 3). The para position of ketone intermediate **7** was selectively brominated using NBS in CH_3CN to afford **12** in 99% yield.[6] The brominated compound (**12**) was then subjected to the IBX protocol to install the double bond in 95% yield. Regioselective addition of 3-methoxyphenylmagnesium bromide to the carbonyl carbon of the resulting α,β-unsaturated ketone (**13**) afforded tertiary alcohol **14** in 76% yield.[5] The cyclization of this intermediate, carried out under the triflic acid conditions described above, proceeded cleanly and gave exclusively isomer **15**, resulting from attack by the ortho position of aromatic ring C. As before, the cyclization gave the bridged-bicyclic product rather than the desired indeno-tetrahydropyridine ring system.

With the ortho/para issue resolved, the next problem to address was the regioselectivity of the cyclization about the piperidinone ring. To determine if cyclization was even

(2) Friedel−Crafts cyclizations have been used extensively in the synthesis of alkaloids. For relevant examples, see: (a) Grewe, R.; Friedrichsen, W. *Chem. Ber.* **1967**, *100*, 1550−1558. (b) Rice, K. C.; Ripka, W. C.; Reden, J.; Brossi, A. *J. Org. Chem.* **1980**, *45*, 601−607. (c) Passarella, D.; Consonni, A.; Giardini, A.; Lesma, G.; Silvani, A. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1981−1983.

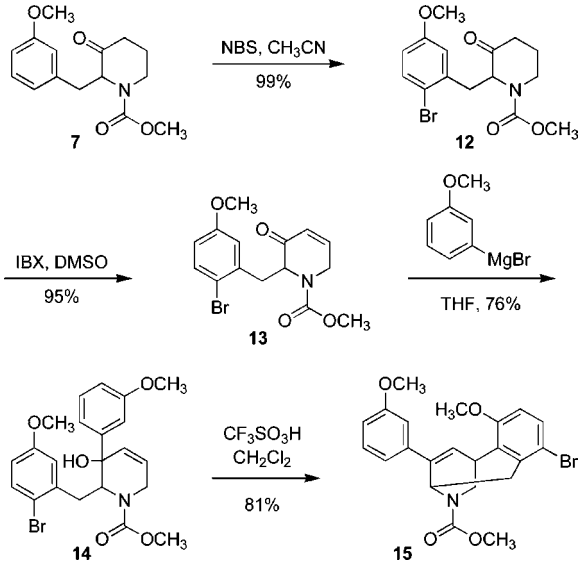
(3) (a) Masamune, T.; Hayashi, H.; Takasugi, M.; Fukuoka, S. *J. Org. Chem.* **1972**, *37*, 2343−2345. (b) Brubaker, A. N.; Colley, M. *J. Med. Chem.* **1986**, *29*, 1528−1531.

(4) (a) Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S. *J. Am. Chem. Soc.* **2000**, *122*, 7596−7597. (b) Nicolaou, K. C.; Montagnon, T.; Baran, P. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 993−996.

(5) 1,2-Addition product was obtained as a single diastereomer of as yet undetermined relative stereochemistry.

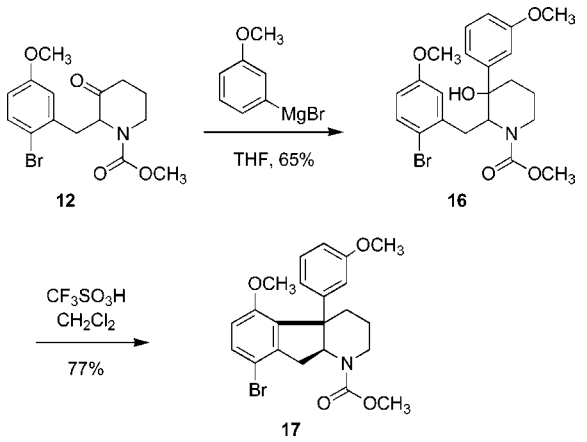
(6) Carreno, M. C.; Ruano, J. L. G.; Sanz, G.; Toledo, M. A.; Urbano, A. *J. Org. Chem.* **1995**, *60*, 5328−5331.

Scheme 3



possible at the sterically hindered tertiary center, we decided to prepare the alcohol precursor in which the double bond was absent. Cyclization onto the tertiary carbocation intermediate would necessarily produce the desired indeno-tetrahydropyridine ring system. Saturated ketone **12** was treated with 3-methoxyphenylmagnesium bromide to afford tertiary alcohol **16** in 65% yield (Scheme 4).[5] Treatment of

Scheme 4

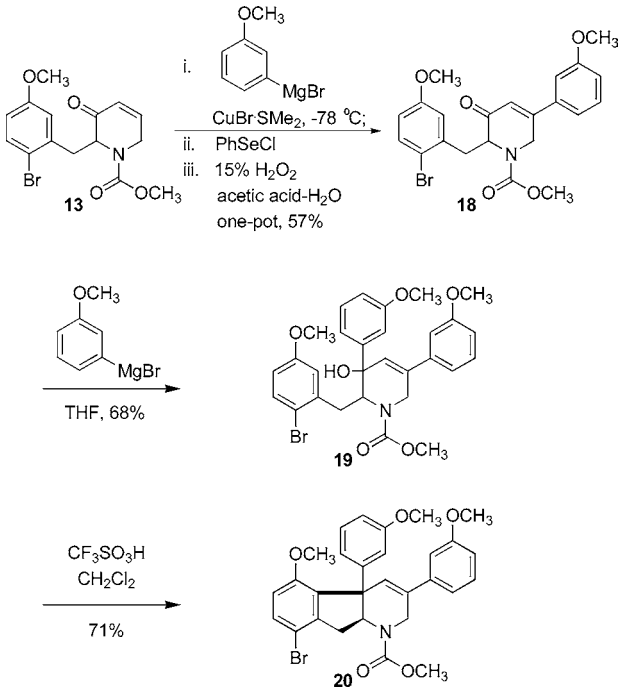


the tertiary alcohol with triflic acid promoted the desired cyclization and produced **17** in 77% yield.

The successful cyclization of the saturated pyrrolidinone intermediate confirmed the feasibility of forming the desired ring system through a Friedel−Crafts cyclization, despite the creation of a congested quaternary center. For the real system, it was imperative that the cyclization be carried out with the double bond in place, as it would be very difficult to install at a later point in the synthesis. The plan was to start with an enone precursor having an aromatic unit at the β-position. The aromatic ring would not only render the two reactive carbons sterically equivalent during the cyclization, but it would also put in place a ring that would be required for the natural product. Given the similar steric environment of the two electrophilic sites, the expectation was that the Friedel−Crafts cyclization would take to produce the desired five-membered ring over the bridged bicyclic product.

The route to the advanced model system is shown in Scheme 5. The aromatic ring on the β-position of the enone

Scheme 5



was installed conveniently through a one-pot sequence. Conjugate addition of 3-methoxyphenylmagnesium bromide to the brominated α,β-unsaturated ketone **13** (Scheme 5) was promoted with CuBr, and the intermediate enolate was trapped with phenylselenyl chloride. Oxidation of the selenoketone with H_2O_2 in the presence of acetic acid was accompanied by selenoxide elimination to produce the substituted α,β-unsaturated ketone (**18**) in 57% overall yield from ketone **13**.[7] The addition of 3-methoxyphenylmagnesium bromide to the carbonyl carbon of ketone **18** produced tertiary alcohol **19** in 68% yield.[5] Finally, on treatment with triflic acid, alcohol **19** cyclized to afford exclusively the desired indeno-tetrahydropyridine **20** in 71% isolated yield. Compound **20** possesses five of the seven rings of haouamine A.

In summary, the indeno-tetrahydropyridine core of haouamine A (**1**) has been synthesized in eight steps from commercially available 3-hydroxypiperidine. The key step is a simple, acid-catalyzed Friedel−Crafts cyclization, which assembles the desired cis-fused indeno-tetrahydropyridine. Studies aimed at the application of this strategy to the total synthesis of haouamine A (**1**) are currently under way.

(7) Reich, H. J.; Reich, I. L.; Regna, J. M. *J. Am. Chem. Soc.* **1973**, *95*, 5813−5815.

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Supporting Information Available: Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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