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Synthesis of the 3-Aza-[7]-paracyclophane Core of Haouamine A and B

Peter Wipf* and Markus Furegati

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260
pwipf+@pitt.edu

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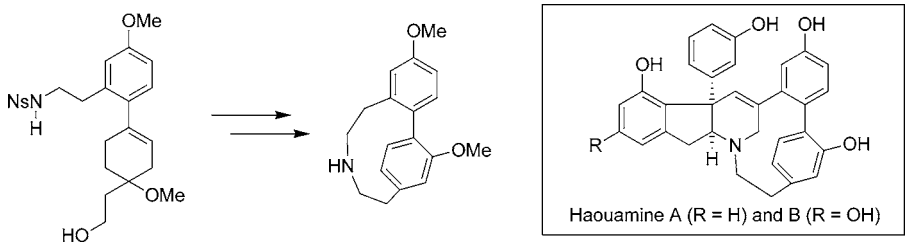
ABSTRACT



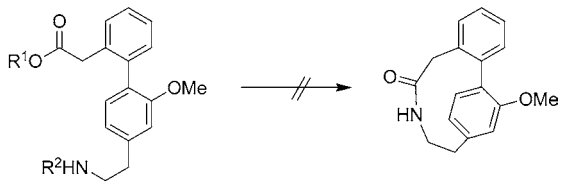
The synthesis of the highly strained 3-aza-[7]-paracyclophane core of haouamines A and B is based on a macrocyclization–aromatization protocol, allowing for a stepwise increase in ring strain and establishing the oxygenation pattern of the natural products.

Haouamines A and B are members of a novel class of alkaloids recently isolated from the ascidian *Aplidium haouarianum*.[1] Biological tests against several cell lines revealed that haouamine A exhibits high and selective activity against the human colon carcinoma HT-29 with an IC_{50} = 0.1 μg/mL (200 nM), whereas haouamine B shows only weak cytotoxicity against the MS-1 cell line with an IC_{50} = 5 μg/mL. Both compounds display dynamic behavior in the NMR and exist at room temperature as a mixture of interconverting isomers. Zubía and co-workers assigned these properties to either a restricted bond rotation or to a slow pyramidal inversion of the tertiary amine in the 3-aza-[7]-paracyclophane moiety.

The structural features combined with the biological activity of these polycyclic alkaloids attracted immediate attention in the chemical community. Recently, two syntheses of the racemic indenotetrahydro-pyridine moiety were reported,[2a,b] in addition to a successful total synthesis by Baran and Burns.[2c] In the former approaches, the formation of the [7]-paracyclophane ring was postponed to the end of the synthesis, whereas the Baran and Burns route accomplished this challenging task by an intramolecular pyrone-alkyne Diels−Alder reaction.[2c]

As part of a convergent synthetic approach toward haouamine A we encountered difficulties forming the strained 3-aza-[7]-paracyclophane ring with standard coupling methodologies. In particular, we were not able to effect direct ring closure of the amino acid HCl salt **2a** or the Cbz-protected activated ester **2b** under various macrolactamization conditions (Scheme 1).[3]

Scheme 1



2a: R^1 = H, R^2 = H•HCl
2b: R^1 = PFP, R^2 = Cbz

The application of a recently published protocol for the synthesis of medium-ring biaryl compounds by organocu-

(1) Garrido, L.; Zubia, E.; Ortega, M. J.; Salvá, J. *J. Org. Chem.* **2003**, *68*, 293−299.
(2) (a) Smith, N. D.; Hayashida, J.; Rawal, V. H. *Org. Lett.* **2005**, *7*, 4309−4312. (b) Grundl, M. A.; Trauner, D. *Org. Lett.* **2006**, *8*, 23−25. (c) Baran, P. S.; Burns, N. Z. *J. Am. Chem. Soc.* **2006**, *128*, 3908−3909.

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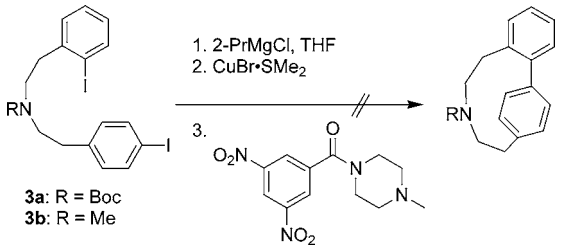
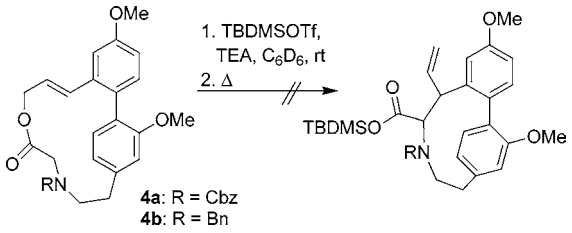
Scheme 2



prate oxidation also failed (Scheme 2).[4] Subjecting the model compound **3a** or **3b** to the reaction conditions gave no cyclization product detectable by mass spectrometry.

We also attempted to construct the strained ring system by a ring contraction strategy.[5a] Formation of the silyl ketene acetals derived from macrolactones **4a** and **4b** followed by a [3,3] sigmatropic rearrangement[5b] upon heating was thought to overcome the deterrent of the ring strain (Scheme 3).[5c−e]

Scheme 3



The formation of the silyl ketene acetals could conveniently be observed by ^{1}H NMR and took place within 2 days. Heating of the Claisen precursors with or without prior purification in a microwave reactor up to 220 °C, however, did not lead to the desired rearrangement.

As can be seen from the X-ray diffraction analysis of haouamine A,[1] the 3-aza-[7]-paracyclophane ring is extremely strained (Figure 1). The six carbon atoms of ring B are not aligned in a plane, but rather arranged in a boatlike geometry. Analysis[6] of the B-ring of haouamine A revealed large deviation angles $\Phi_{1,2}$ of the benzene ring from planarity as well as unusual out-of-plane angles $\alpha_{1,2}$, which include the adjacent substituents C(8) and C(15), respectively. These

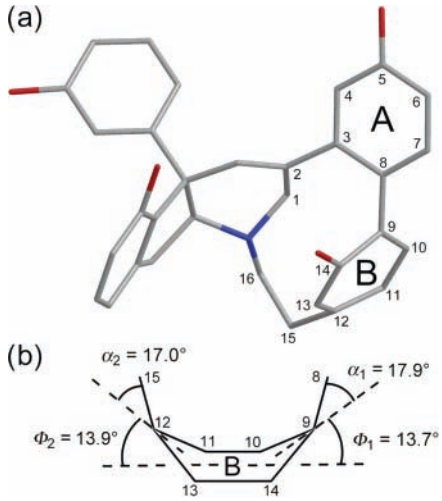
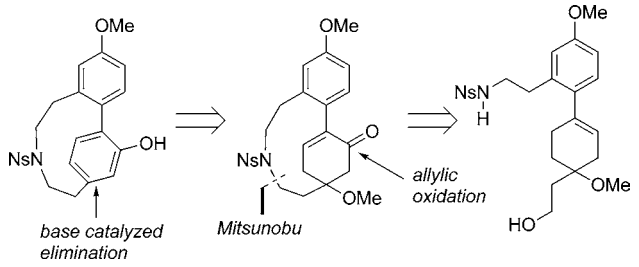


Figure 1. (a) X-ray structure of haouamine A (with the original atom and ring numbering); (b) noteworthy derivations from planarity in ring B.

carbon atoms are located significantly out of the plane of the distorted benzene ring B.

As an alternative to the more traditional strategies for overcoming the kinetic barriers of ring closure, we envisioned the preparation of a macrocyclic ring composed of a tetrahydro derivative and subsequently an introduction of the ring strain by altering the hybridization of C(12) from sp^3 to sp^2 by elimination of methanol. Tautomerization to the phenol would result in the formation of the biaryl system (Scheme 4).

Scheme 4



For the synthesis of precursor **8** we converted 2-iodo-5-methoxyphenylacetic acid (**5**), readily available in 66% yield by iodination of 3-methoxyphenylacetic acid,[7] to the corresponding amide (Scheme 5). Borane reduction, followed by stepwise conversion of the primary amine **6** with 2-nitrobenzenesulfonyl chloride,[8] and then Boc_2O/DMAP gave the fully protected imide **7**. The boronic ester **8** was obtained via palladium-catalyzed reaction with pinacolborane[9] in 56% overall yield (5 steps).

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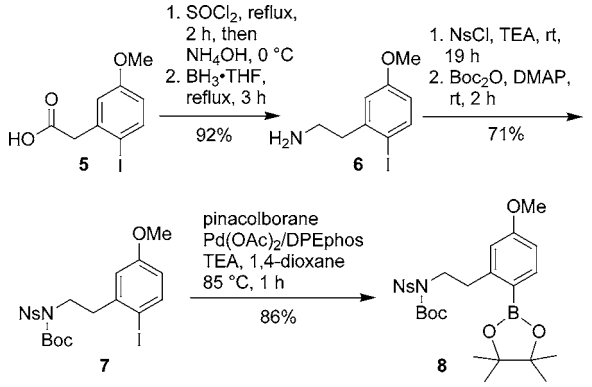
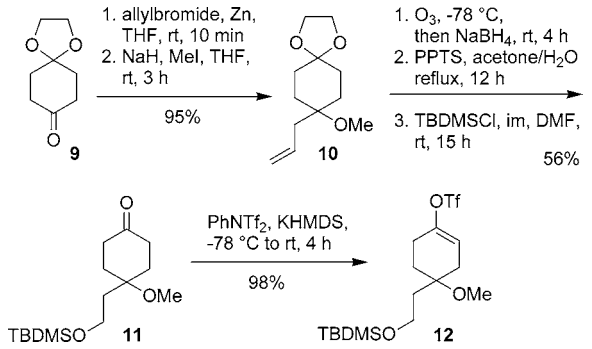
(8) Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373−6374.

Scheme 5. Preparation of Precursor **8**



The preparation of precursor **12** started with commercially available 1,4-cyclohexanedione monoethylene acetal (**9**) (Scheme 6). Allylation using Zn and allylbromide[10] gave the

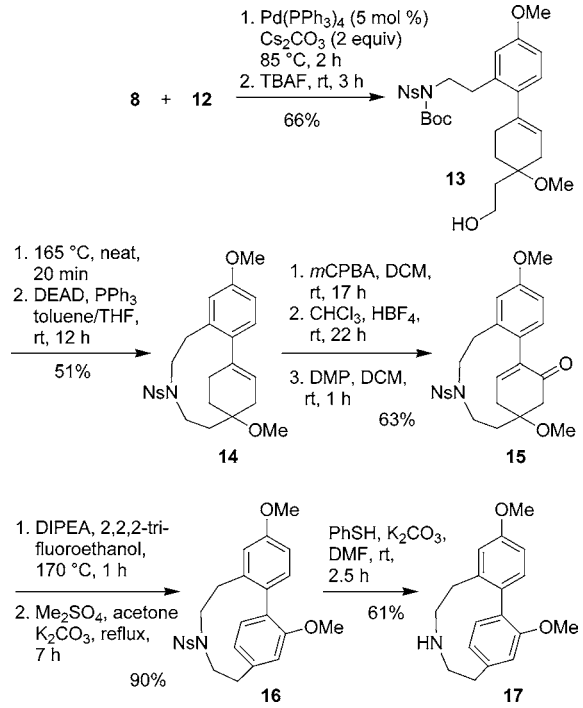
Scheme 6. Preparation of Precursor **12**



tertiary alcohol,[11] which was methylated with MeI. Ozonolysis of **10** followed by a reductive workup using $NaBH_4$ gave the primary alcohol. The ketal was cleaved with PPTS[12] in acetone/H_2O, and the alcohol was protected as the TBDMS-ether.[13] Formation of the vinyltriflate using $PhNTf_2$/KHMDS[14] resulted in the formation of **12** in 52% overall yield (6 steps).

Suzuki−Miyaura reaction[15] of a 1:1 mixture of **8** and **12** afforded the coupling product **13** in 66% yield after TBDMS removal (Scheme 7). Cleavage of the Boc group was facilitated by the nosyl substituent and occurred thermally at 165 °C in 90% yield.[16] The macrocyclization to the 11-

Scheme 7



membered **14** was accomplished by an intramolecular Mitsunobu reaction with the 2-nitrobenzenesulfonamide as the internal nucleophile in 57% yield.[17] Treatment of macrocycle **14** with *m*CPBA gave the benzylic epoxide, which rearranged quantitatively to the allylic alcohol in chloroform in the presence of 1 mol % HBF_4. Subsequent oxidation with Dess−Martin periodinane[18] resulted in the

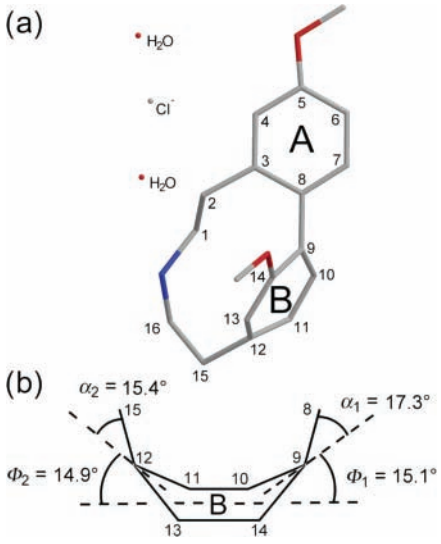


Figure 2. (a) X-ray structure of **17**·HCl (with atom and ring numbering based on haouamine A; the structure also contains two water molecules and a chloride, which are labeled separately); (b) characteristic angles in ring B.

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(10) Chen, C.; Dai, W.-C.; Chang, H.-G. *Org. Prep. Proc. Int.* **2002**, *34*, 507−511.
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formation of the α,β-unsaturated ketone **15** in 63% (3 steps). Treatment of **15** with a 1:1 mixture of DIPEA and 2,2,2-trifluoroethanol in a pressure tube at 170 °C for 1 h followed by O-methylation of the crude product with dimethyl sulfate resulted in the formation of the nosyl-protected 3-aza-[7]-paracyclophane **16**. Removal of the nosyl substituent[8] gave the secondary amine **17** in 61% yield.

X-ray analysis of the hydrochloride salt of **17** provided convincing evidence that ring distortion and folding of this subunit are a close match of the natural product (Figure 2).

In conclusion, we have demonstrated a new approach toward the synthesis of the unique and highly strained 3-aza-[7]-paracyclophane core of the haouamine alkaloids in 21 steps (22 steps from commercially available materials). The overall yield for the longest linear sequence was 12% (16 steps); the average yield for the 21 steps was 86%. Highlights of our strategy are the use of a Mitsunobu reaction to close an 11-membered ring and the formation of the paracyclophane moiety from a partly saturated precursor followed by stepwise aromatization.[19]

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Supporting Information Available: Experimental procedures and spectral data for all new compounds, including CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

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