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Grob-Type Fragmentation Releases Paracyclophane Ring Strain in a Late-Stage Precursor of Haouamine A

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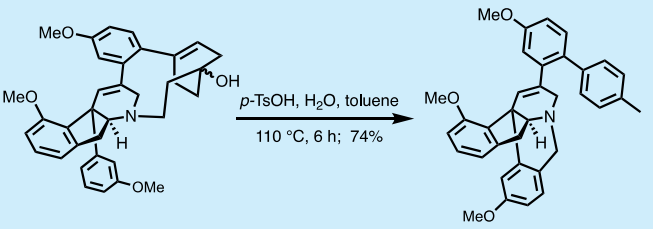
Supporting Information

ABSTRACT: A ketene [2 + 2]-addition, an intramolecular aldol reaction, a Suzuki−Miyaura coupling, and a chemoselective lactam reduction were used to prepare a late-stage precursor of haouamine A. Exposure to acid led to a Grob-type fragmentation of the strained 3-aza[7]paracyclophane ring, followed by a tandem Pictet−Spengler reaction of the intermediate iminium ion and conversion to a novel 1,4a-propanocyclopenta[*b*]pyridine. This cascade reaction might also be relevant for the mechanism of action of the natural product.



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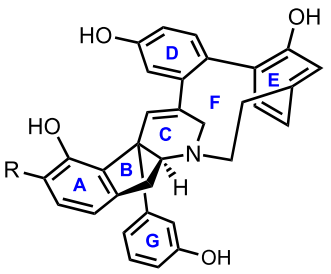
Since their discovery in 2003 from *Aplidium haouarianum*, isolated off the coast of Spain,[1] haouamines A and B have inspired organic chemists to design synthetic strategies to prepare the polycyclic ring system, in particular, the unique 3-aza[7]paracyclophane substructure, of these natural products (Figure 1).



Haouamine A (R=H)
Haouamine B (R=OH)

Figure 1. Revised structures of haouamines. Rings A−B−C form a *cis*-indenotetrahydropyridine fragment, and D−E−F constitute the 3-aza[7]paracyclophane.

Even the structure assignment of haouamines was the source of some controversy.[2] While the atropisomer in the D−E−F ring system is locked in the (*M*)-configuration, the piperidine C-ring undergoes a slow pyramidal inversion of the sp^3-nitrogen, complicating NMR spectra, and ring A in haouamine B was originally assigned as a resorcinol but then revised to a catechol on the basis of two total syntheses by Trauner et al. and Tokuyama et al.[3,4] Several other groups completed total syntheses,[5,6] formal syntheses,[7−9] and fragment syntheses of haouamines[10−13] or analyzed their biosynthetic pathway[14] and biological profile.[15] Initial assays in human lung carcinoma (A-549), human colon carcinoma (HT-29 and HCT-116), mice endothelial (MS-1), and human prostate carcinoma (PC-3) cell lines noted that haouamine A had selective activity against HT-29 cells with an IC_{50} = 0.1 μg/mL, while haouamine B was only slightly cytotoxic in MS-1 cells with an IC_{50} = 5 μg/mL.[1] However, subsequent analyses of synthetic material in a cell line panel including HT-29 detected only moderate (IC_{50} = ca. 30 μM) cytotoxicity for both (*M*)- and (*P*)-atropisomers of haouamine A in PC-3 cells and no effect below 75 μM for the two corresponding E-ring dihydro analogues.[5] While not unusual for early reports on natural products, where small impurities from the isolation can significantly alter biological data,[16,17] this discrepancy has yet to be resolved.

An attractive feature as well as a significant challenge for any total synthesis of haouamine lies in the assembly of the distorted E-ring. X-ray analyses of both the natural product[1] as well as the 3-aza[7]paracyclophane D−E−F substructure[11] demonstrated significant derivations from planarity for this arene (Figure 2). Specifically, the benzene ring forms a shallow boat with the substituted *para*-carbons lifted by about 15° (ϕ_1, ϕ_2) above the plane of the remaining four carbons in ring E. Furthermore, the *para*-carbons also suffer from a distortion of the sp^2 bond angles, with both benzylic bonds raised another 15°−17° (α_1, α_2) from planarity. Interestingly, there is essentially no difference between ϕ_1, ϕ_2, α_1, and α_2 in the untethered D−E−F substructure and the complete, fused ring system of the natural product, suggesting that the bridge formed by piperidine C, including the double bond exocyclic to the paracyclophane, do not further influence the ring strain. Calculations at the DFT/BRLYP/6-311+G**, MP2/6-31G*, DFT/M06/cc-pVTZ, and MP/RI-MP2/cc-pVTZ levels indicate a strain energy in the 3-aza[7]-paracyclophane of 14.0−

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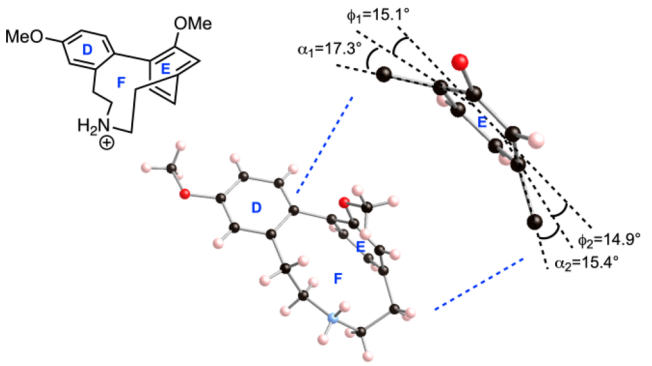
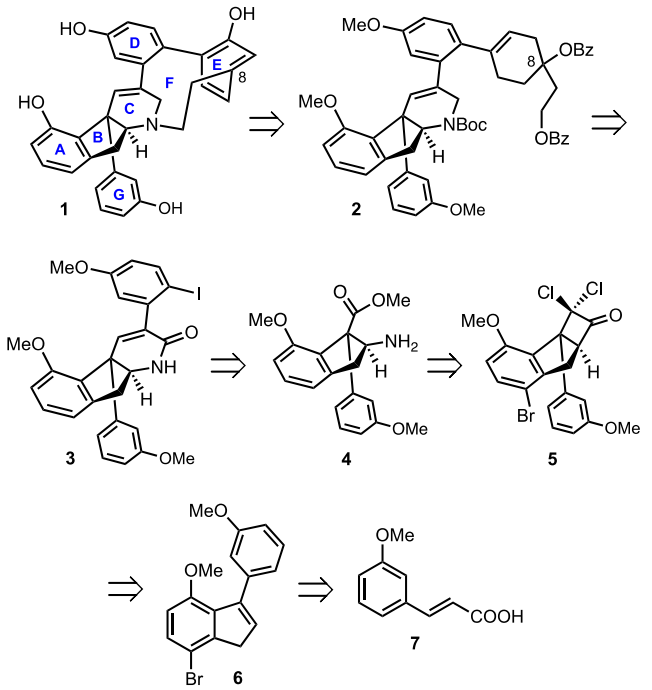


Figure 2. X-ray structure of the D–E–F 3-aza[7]paracyclophane moiety[11] highlighting the derivations from planarity at the E-ring.

15.6 kcal/mol, i.e., compensating for ca. 40% of the aromatic resonance energy.

We have previously reported the synthesis of the 3-aza[7]paracyclophane core of haouamines A and B based on a novel macrocyclization-aromatization protocol, allowing for a stepwise assembly of the perimeter of the F-ring, and leveraging the aromatic stabilization energy to compensate for the ring strain in the formation of the E-arene.[11] We have now relayed this strategy toward a retrosynthetic approach for haouamine A (Scheme 1).

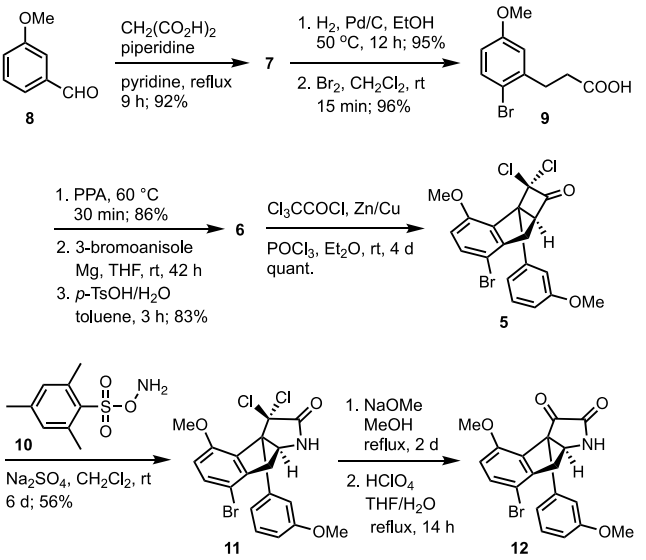
Scheme 1. Retrosynthetic Analysis of Haouamine A (1)



We envisioned that the formation of the 11-membered F-ring from **2** was facile as long as C(8) remained sp^3-hybridized.[18] A Suzuki–Miyaura coupling of iodide **3** with an E-ring alkene would give **2**. The *β*-amino ester **4** could be constructed from cyclobutanone **5** and serve as the scaffold for the attachment of the D-ring in **3**. Dichloroketene addition to indene **6** could be used as a regioselective approach to **5**, and after bromination of cinnamate **7**, a regioselective intramolecular Friedel–Crafts reaction followed by G-ring aryl Grignard 1,2-addition and alcohol elimination would provide indene **6**.

A Knoevenagel chain extension of 3-methoxybenzaldehyde (**8**) provided acid **7** in 92% yield (Scheme 2). The alkene was

Scheme 2. Preparation of Ketolactam Intermediate 12 from Aldehyde 8 by a Knoevenagel/Friedel–Crafts/Beckmann Rearrangement Sequence



reduced with Pd/C and hydrogen gas, and the 2-position on the arene was brominated in preparation for a regiocontrolled Friedel–Crafts reaction on **9**. Polyphosphoric acid (PPA) was used to close the indanone in 86% yield, and subsequent addition of the Grignard reagent derived from 3-bromoanisole and dehydration of the resulting tertiary alcohol led to indene **6** in 71% overall yield from **9**. We considered several strategies for the conversion of **6** to *β*-aminoester **4**.[19] Interestingly, this is a rare transformation in the literature. While an intermolecular alkene aminocarbonylation would be the most direct and attractive approach to effect this conversion, trisubstituted alkenes pose reactivity and stereoselectivity problems.[20] Accordingly, we resorted to a [2 + 2]-cycloaddition with in situ prepared dichloroketene, which proceeded in quantitative yield to give cyclobutanone **5**. Treatment with mesitylene sulfonyl hydroxylamine **10**[21,22] promoted the Beckmann rearrangement[23] and led to a regioselective insertion of a nitrogen atom into the C,C-bond distal from the chlorinated quaternary carbon to furnish dichlorolactam **11** with retention of configuration at the tertiary C.[24] The dichloro moiety was hydrolyzed to *α*-ketolactam **12** using a two-step methanolysis–hydrolysis sequence since basic or acidic conditions failed to promote a one-step hydrolysis to the ketone.

The Boc-protected *α*-keto lactam derived from **12** was subjected to an oxidative hydrolytic decarboxylation,[25] and the resulting carboxylate was immediately methylated to give the Boc-*β*-amino methyl ester **13** (Scheme 3). The aryl bromide in **13** was now reduced with Pd/C, and the Boc group was cleaved with TFA to give amine **4** in preparation for **C**-ring closure. After reduction of the ester with $LiAlH_4$, the amino alcohol was coupled with acid **14** in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) in CH_2Cl_2 to afford amide **15** in 56% yield from **4**. The primary alcohol

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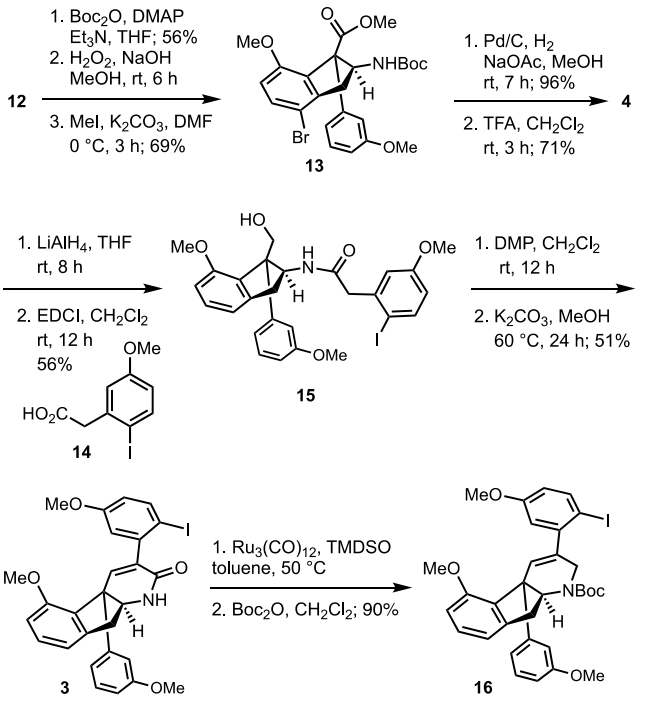
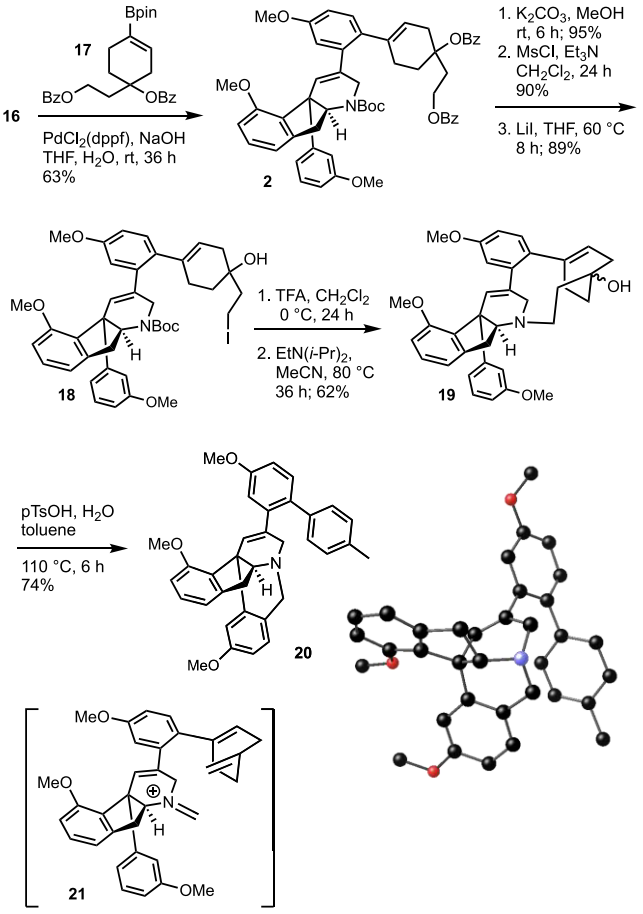
Scheme 3. Synthesis of β-Amino Ester 4 and Completion of C-Ring Synthesis



Scheme 4. Preparation of Late-Stage Intermediate 19, Grob Fragmentation, and Pictet–Spengler Reaction To Give Propanocyclopenta[*b*]pyridine 20



function in **15** was subsequently oxidized to the aldehyde with Dess–Martin periodinane (DMP), and an intramolecular aldol condensation gave lactam **3** in 51% yield over the two steps.[7] Reduction of **3** to the corresponding amine with 1,1,3,3-tetramethyldisiloxane (TMDS) in the presence of catalytic $Ru_3(CO)_{12}$ in toluene[26,27] was found to be highly chemoselective and avoid the undesired reduction of the aryl iodide. After Boc-protection of the amine, **16** was isolated in 90% yield. In an analogous synthetic sequence, the aryl bromide analog of **16** was obtained, thus intersecting with Baran's synthesis[5,7] and representing a formal total synthesis of (±)-haouamine A.[19] However, we were unable to obtain satisfactory yields in subsequent Suzuki–Miayura or related Stille cross-couplings with this bromide and, therefore, proceeded onward with **16** and the more reactive iodide substitution at the D-ring.[19]

Cross-coupling of iodide **16** with pinacolboronate **17** generated the styrene **2** in 63% yield as long as at least stoichiometric amounts of water were present in the reaction mixture (Scheme 4). The yield under strictly anhydrous conditions was ca. 30% lower.[28] Saponification of the bis-benzoate **2** followed by mesylation of the primary alcohol and conversion to the iodide **18** was followed by cleavage of the Boc group with TFA. Formation of the macrocyclic amine **19** succeeded in good overall yield in the presence of Hünig's base in acetonitrile at 80 °C.

When hydroxy cyclohexene **19** was heated at reflux with *p*-TSA in toluene (typical conditions for dehydration/aromatization of compounds containing a hydroxy cyclohexene moiety),[29] unexpectedly the fragmentation product **20** was generated in 74% yield.[30] The structural assignment of **20** was confirmed by an X-ray crystallographic analysis.

The formation of the interesting product **20** from γ-amino alcohol **19** is related to a Grob fragmentation,[31] and we suggest that its mechanism of formation involves iminium ion **21** as an intermediate in the cascade process prior to a Pictet–Spengler reaction. There is only limited precedence for this type of conversion. A mass spectrometry study of Chao et al. postulated this mechanism in the fragmentation of a variety of diterpenoid alkaloids using an electrospray ionization technique,[32] and Charette et al. were able to prepare 2,3,6-trisubstituted tetrahydropyridines from aza-bicyclo[2.2.2]-octenes bearing a γ-amino hydroxide moiety.[33]

In summary, starting from readily prepared indene **6**, we used a dichloroketene [2 + 2]-cycloaddition, a Beckmann rearrangement, and an intramolecular aldol reaction to introduce the C- and D-rings of haouamine. A Suzuki–Miyaura coupling added the E-ring, and an intramolecular amine alkylation closed the F-ring carbon tether to generate the late-stage intermediate **19**. An attempted acid-catalyzed elimination of the tertiary alcohol did not provide the dihydro analogue of the aromatic E-ring in haouamine A but instead led to a Grob-type fragmentation of the strained 3-aza[7]-paracyclophane ring and generated an intermediate iminium ion **21** that alkylated the electron-rich G-ring in high yield in a tandem Pictet–Spengler process. Isomerization of the exocyclic alkene and spontaneous air oxidation generated an untethered biphenyl substituent. The 1,4a-propanocyclopenta-[*b*]pyridine core structure of the resulting polycyclic product **20** is quite unprecedented in the literature, but the relatively facile formation of the iminium ion **21** could also be relevant for the biological mode of action of the highly strained,

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cytotoxic haouamines. For example, the mechanism of action of the ecteinascidin[34] and anthramycin[35] anticancer agents involves closely related iminium ions that alkylate guanine residues on DNA.[36] We plan to further investigate this mechanistic hypothesis after completion of the total synthesis of haouamine A using a slightly modified synthetic end game.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00424.

Experimental details and ^{1}H and ^{13}C NMR spectra for new synthetic intermediates and products (PDF)

Accession Codes

CCDC 1888421 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(30) In our model system,[11] aromatization of the E-ring was achieved by epoxidation of the cyclohexene moiety, epoxide opening under mild acidic conditions, oxidation of the allylic alcohol, and elimination. However, in the current approach toward the complete polycyclic system of haouamine A, the tertiary amine present in the C-ring led to the formation of *N*-oxide and decomposition products under a variety of conditions. In order to bypass this problem, we attempted several alternatives, including the epoxidation of the E-ring cyclohexene with a lactam present in the C-ring, which allowed for a repeat of the conditions from the model sequence, and successful aromatization. However, we were subsequently unable to reduce the amide to the desired allylic amine due to the extreme steric shielding in the C-ring after formation of the 3-aza[7]paracyclophane.[19]
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