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Scalable Total Synthesis and Biological Evaluation of Haouamine A and Its Atropisomer

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Haouamine A[1] (**1**, Figure 1) is a biologically active and architecturally unique alkaloid whose striking feature is a [7]-aza-paracyclophane macrocycle containing a highly deformed nonplanar aromatic ring. Somewhat mysteriously, **1** was discovered to exist as a mixture of two rapidly interconverting isomers in solution, a quality attributed to either atropisomerism of the bent arene or slowed pyramidal inversion at nitrogen. Recent computational work[2] supported a theory coupling the latter process with conformational reorganization of the tetrahydropyridine ring but could not rule out atropisomerism.[3] The total synthesis of **1** from this laboratory[4] also did not answer this question unequivocally due to an inability to control the atropisomer formed in the low-yielding cyclophane-forming step, which fortuitously favored the natural planar stereochemistry.[5,6]

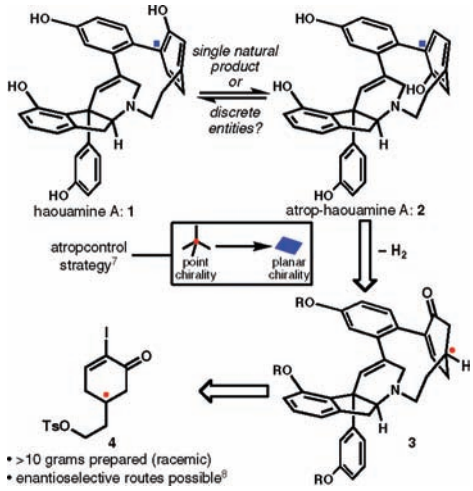
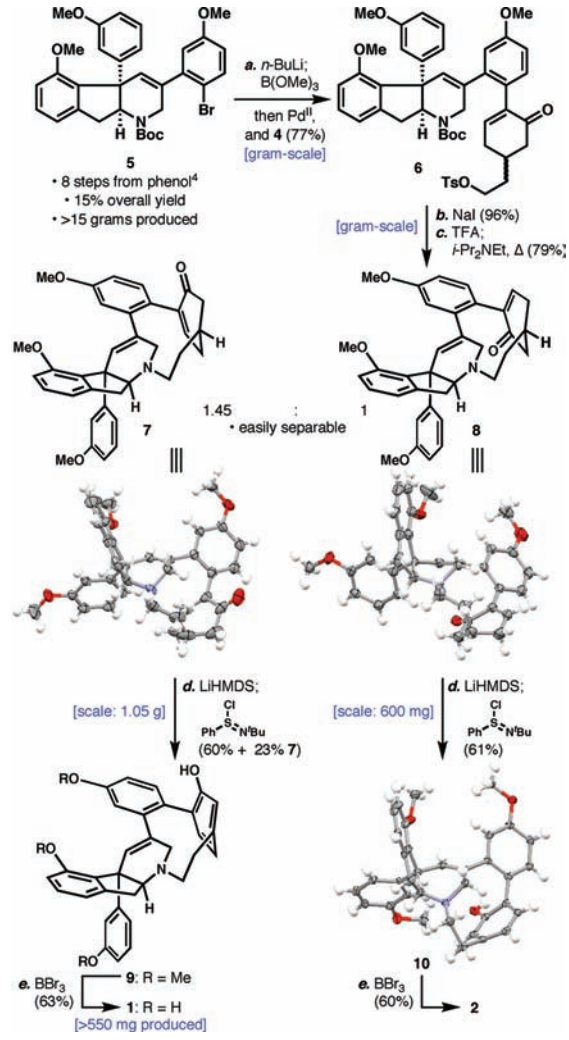


Figure 1. Synthetic strategy and an unanswered structural question.

Here, we report a scalable and controllable route to **1** and its atropisomer (**2**) that features point-to-planar chirality transfer[7] via a one-step, chemoselective cyclohexenone to phenol oxidation to introduce strain within the macrocycle, a reaction that may find future use in strained chiral cyclophane synthesis. We also demonstrate that the strained cyclophane in **1** is crucial for anticancer activity in PC3 cells.

To program planar chirality within the cyclophane macrocycle a reduced compound (**3**, Figure 1) was selected as the bent phenol precursor. Molecular models suggested that hybridization change of one of the *para* carbons of the cyclophane from sp^2 to sp^3 should significantly reduce the strain present within the macrocycle and thus make for an accessible intermediate[5c] (numerous attempts to form the macrocycle with a preinstalled phenol in this[4] and other[5,6] laboratories have all failed). Furthermore, it was surmised that the *point* chirality introduced by such a change in hybridization could be used to select for the *planar* chirality present in **1** and **2**. Saturated cyclophane **3** could then be traced

Scheme 1. Scalable, Programmed Syntheses of **1** and **2**[a]



[a] Reagents and conditions: (a) *n*-BuLi (1.1 equiv), THF, −78 °C, 10 min; $B(OMe)_3$ (2.0 equiv), −78 to 23 °C, 1 h; H_2O; **4** (1.0 equiv), $(PhCN)_2PdCl_2$ (0.1 equiv), Ph_3As (0.2 equiv), Ag_2O (1.6 equiv), 8:1 THF/H_2O, 23 °C, 18 h, 77%; (b) NaI (10.0 equiv), acetone, 23 °C, 7 h, 96%; (c) 20:1 CH_2Cl_2/TFA, 5 °C, 24 h; *i*-Pr_2NEt (10.0 equiv), CH_3CN (0.002 M), reflux, 26 h, 79%; (d) LiHMDS (2.0 equiv), LiCl (5.0 equiv), THF, −78 to 0 °C, 20 min; PhSClN*t*-Bu (1.3 equiv), −78 °C (for **7**) or −95 °C (for **8**), 1 min, 60% of **9** + 23% **7**, or 61% of **10**; (e) BBr_3 (7.0 equiv), CH_2Cl_2, −78 to 5 °C, 20 h, 63% for **1**, or 60% for **2**.

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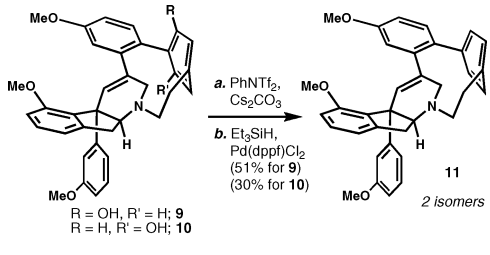
back to the simple functionalized cyclohexenone **4**, utilized as the racemate in this study.[8]

To commence this plan, racemic bromo-indeno-tetrahydropyridine **5**[4a] (Scheme 1) was cross-coupled with racemic tosyloxy-iodocyclohexenone **4**[9] in a one-step procedure involving lithium-halogen exchange, quenching with $B(OMe)_3$, addition of water, and direct transfer of the resulting boronic acid to **4** in the presence of palladium. The product **6** (77% yield on gram-scale) was isolated as an inseparable mixture of diastereomers that was converted to a mixture of primary iodides in high yield. *N*-Boc deprotection and heating of the unpurified amine-TFA salt (after removal of excess TFA) in dilute acetonitrile with Hünig's base then delivered macrocycles **7** and **8** (79% combined yield, gram-scale) as a 1.45:1 readily separable mixture (this ratio implies a small amount of selectivity in either the macrocyclization or the previous coupling step). Interestingly, each of these compounds was found to exist as two isomers in solution providing early evidence that **1** is not a mixture of atropisomers. X-ray crystallographic analysis of both **7** and **8** identified their correspondence to haouamine A (**1**) and atrop-haouamine A (**2**), respectively.

Efforts were then focused toward the key aromatization step. Initial attempts to oxidize the silyl dienol ether of **7** and **8** with palladium[10] or MnO_2[11] saw competitive oxidation of the indeno-tetrahydropyridine core. Several other attempts to oxidize the dienolate or cyclohexenone directly also failed.[9] Taking inspiration from the use of *N-tert*-butylbenzenesulfinimidoyl chloride by Mukaiyama[12] to introduce α,β-unsaturation to ketones in one step, it was discovered that treatment of the lithium dienolates of **7** and **8** with this reagent rapidly affected the desired oxidation to deliver the bent phenol macrocycles **9** and **10** as isomeric mixtures in respective 60% and 61% yield (23% of the starting material could be recovered in the reaction of **7** to **9**). This represents the first use of such a reagent to generate aromatic systems, and it should find future applicability to do so particularly in strained systems of this type due to its high oxidation potential and the possibility to introduce asymmetry into the starting cyclohexenone.[8] A low reaction temperature (−78 °C for **7** and −95 °C for **8**), the addition of lithium chloride, and a very short (1 min) reaction time were necessary to prevent subsequent reaction of the phenol product with the reagent. This transformation has proved to be highly practical and scalable, as it has been conducted on 1.05 g of **7** and 600 mg of **8** with no yield diminishment. BBr_3-mediated removal of the methyl ethers in **9** then delivered haouamine A (**1**) in 63% yield. As a testament to the practicality of this route, its utilization has allowed for the production of over 550 mg of (±)-**1** to date. Syntheses of enantiopure **1** and **2** (*ca*. 10 mg) have also been accomplished from enantiopure **5**.[4b,9]

Scheme 2. Reductive Convergence of **9** and **10** to **11**



X-ray crystallographic analysis of **10** secured its identity as the atropisomer of **9**. Interestingly, the isomer of **10** in this crystal structure displayed an inversion at nitrogen and an alternative tetrahydropyridine conformation as compared to the crystal structure of **1**[1] providing physical substantiation to computational results.[2] Ether cleavage then delivered atrop-haouamine A (**2**) whose solution isomeric behavior is similar to that of **1**. As a further confirmation of this phenomenon, both intermediates **9** and **10** were found to converge on cyclophane **11** (Scheme 2), a compound that also exists as two isomers.

While an initial bioassay was reported along with the isolation of **1**, the large amounts of material that are now made available with this chemistry have enabled a more thorough investigation into its bioactivity. Initial results have shown that **1** exhibits high activity against PC3 human prostate cancer cells with $IC_{50} = 29 \pm 2\ \mu M$. atrop-Haouamine A (**2**) also shows high activity ($IC_{50} = 32 \pm 3\ \mu M$); however, des-methyl **7** and des-methyl **8** (dihydro-**1** and dihydro-**2**) are much less active ($IC_{50} > 180\ \mu M$ and $IC_{50} > 75\ \mu M$, respectively) indicating that the presence of the cyclophane is necessary for activity in PC3 cells. Our findings on the biological activity of **1** are different than those reported by Zubía and co-workers.[1,9]

Thus, a scalable route to haouamine A (**1**) and atrop-haouamine A (**2**) has been developed, allowing for the synthesis of ample quantities of each. In the case of **1**, all steps (with the exception of the final methyl ether removal) have been conducted on gram-scale. This synthesis of **1** and **2** has put to rest the question of whether **1** exists as a mixture of atropisomers and was enabled by the development of a method for the chemoselective aromatization of cyclohexenones that allows for point-to-planar chirality transfer; application of this strategy to other chiral strained cyclophane-containing natural products is underway. As a result of this work, the haouamine material supply is no longer an issue, and extensive biological studies (including determination of the mechanism of action of **1**) are taking place and will be reported shortly.

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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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