Natural Products

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On the Origin of the Haouamine Alkaloids**

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The haouamines (**1** and **2**, Figure 1) are some of the most fascinating natural products to be isolated as of late.[1] Their topologically unique carbon skeleton, exotic oxygenation pattern, and mysterious biosynthesis render them interesting

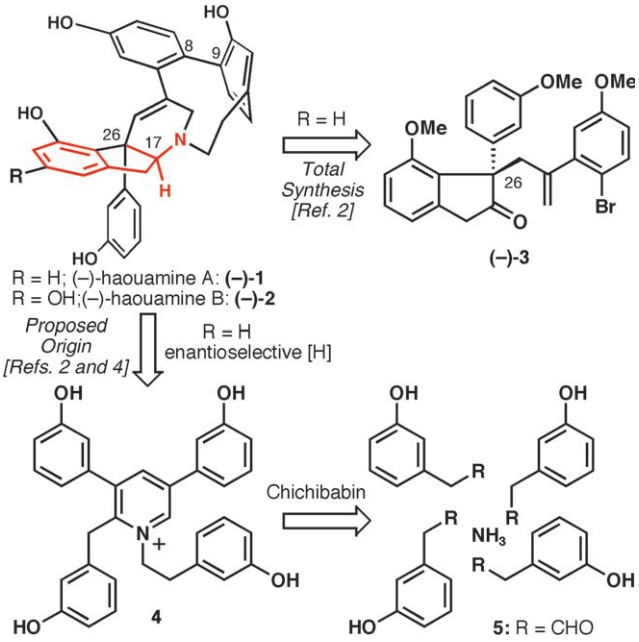

Figure 1. Paths to the haouamine alkaloids.

targets from both synthetic and biochemical vantage points.[2,3] This Communication sheds light on the latter aspect of these alkaloids through a detailed chemical inquiry resulting in: 1) compelling evidence against a seemingly logical tetramerization pathway to **1** and **2**,[2,4] 2) amelioration of erroneous literature reports dealing with the classic Chichibabin pyridine synthesis,[4,5] 3) discovery and mechanistic exploration of a mild variant of the "abnormal" Chichibabin pyridine synthesis, and 4) a simple, enantioselective synthesis of **1** that illuminates its absolute configuration and points towards a phenylalanine-based biosynthesis.

In 2006, we reported a total synthesis of haouamine A from racemic ketone **3** (Figure 1).[2] Although an "abiotic" strategy was employed to complete the synthesis, a theory was presented to explain the origin of the haouamine skeleton as arising from the merger of four equivalents of a *meta*-hydroxylated phenylacetaldehyde (**5**) and one equivalent of ammonia (Figure 1). A similar view of pseudosymmetric biological assembly was later published by Poupon and co-workers.[4] The idea that the haouamines could arise in nature from a 2,3,5-trisubstituted pyridine species (such as pyridinium **4**) is logical, for the Chichibabin pyridine synthesis[6] is well known to produce such appropriately functionalized heterocycles in a single operation. Although nearly all examples of this reaction in the literature are performed with aliphatic aldehydes, a promising example by Wang and co-workers[5] came to our attention. Therein, phenylacetaldehyde reacted with benzylammonium chloride in the presence of ytterbium triflate in water to produce the requisite 2-benzyl-3,5-diphenylpyridinium salt **6** (Scheme 1 A). Surprisingly, however, attempts to reproduce this identical reaction gave a compound that matched the published spectrum but seemed inconsistent with the proposed structure. Despite the lack of a clear mechanistic explanation, the 3,5-diphenylpyridinium salt **7** uniformly matched the acquired data. The structure was confirmed synthetically by simple benzylation of 3,5-diphenylpyridine (**8**) and reaction with silver triflate to exchange counterions. Submitting other substituted phenylacetaldehydes to the identical reaction conditions produced the same results, regardless of the electronic nature of the aldehyde component (Scheme 1 B). As confirmed by X-ray crystallography, *meta*-methoxy (**9**), *para*-bromo (**10**), *meta*-trifluoromethyl (**11**), and *ortho*-methyl (**12**) substitution is tolerated under the reaction conditions. The products of this reaction correspond to those of the "abnormal" Chichibabin pyridine synthesis—a variant that, until now, was not synthetically useful.[7] This approach represents the first mild one-pot route to such 3,5-diarylpyridine systems (known bioactive agents[8]) that does not require prefunctionalized heterocycles.

Labeling experiments carried out as shown in Scheme 2 A clearly pinpoint the fate of the reactants in this transformation. Thus, the trideuterated and bisdeuterated pyridinium species **13** and **14** were prepared using aldehyde **15** and amine **16**, respectively. Furthermore, aldehyde **17** afforded the expected pyridinium **18** along with the nonvolatile substituted benzaldehyde **19**. Taken together, these results point to a plausible mechanism outlined in Scheme 2 B. The critical step

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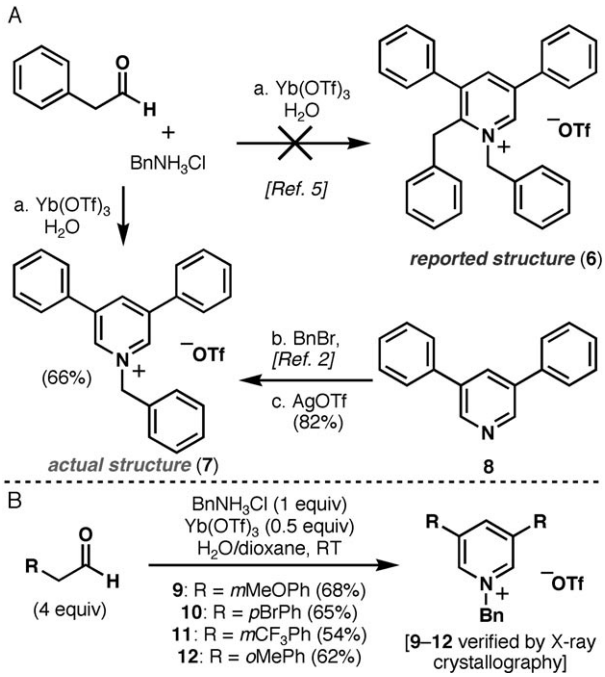
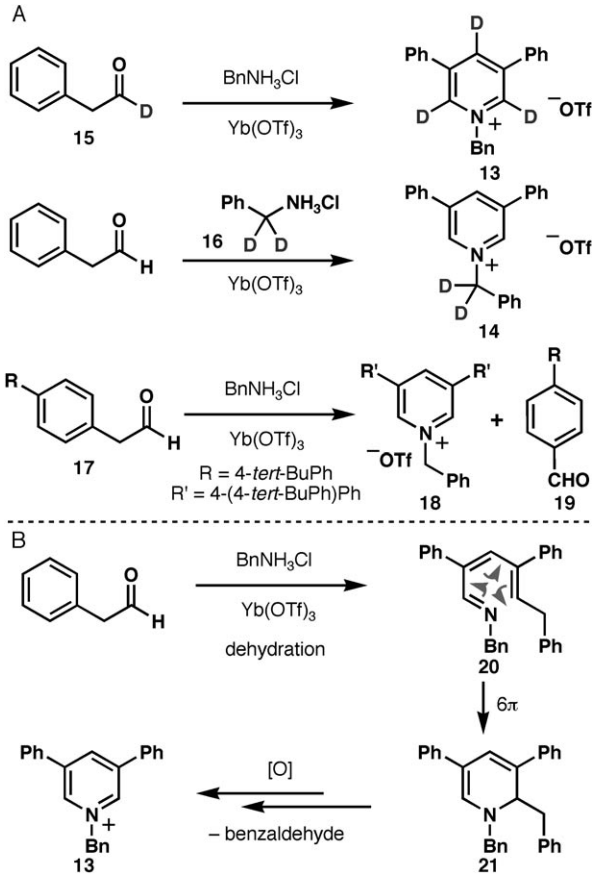


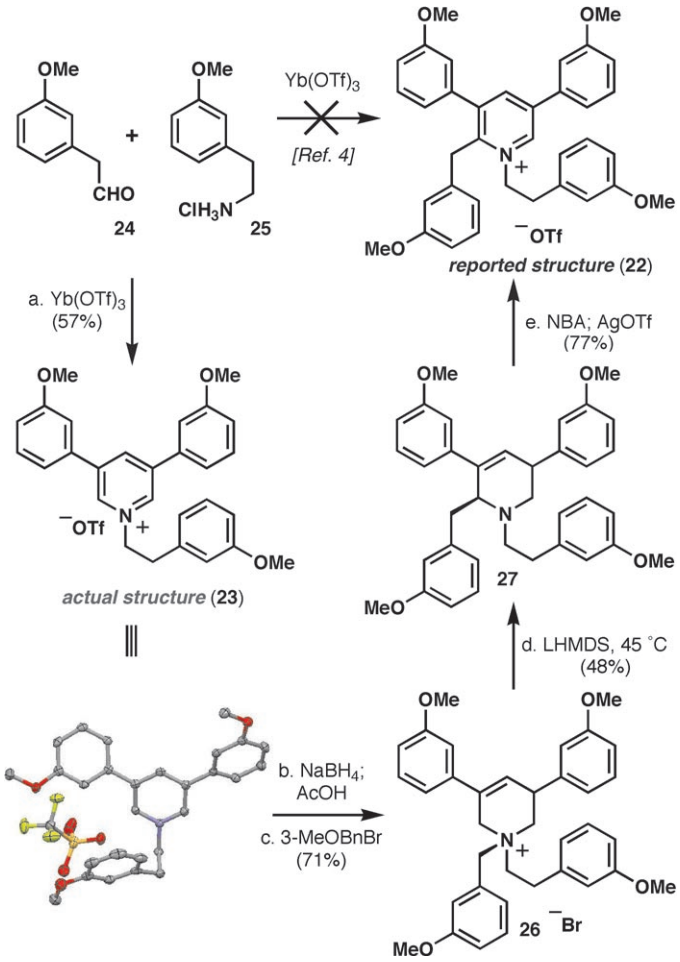
Scheme 1. Discovery of a mild "abnormal" Chichibabin pyridine synthesis. Reagents and conditions: a) phenylacetaldehyde (4.0 equiv), benzylammonium chloride (1.0 equiv), $Yb(OTf)_3$ (0.5 equiv), H_2O, 23 °C, 66%; b) BnBr, acetone, 60 °C; c) AgOTf (1.1 equiv), CH_2Cl_2, 23 °C, 82% overall. Bn = benzyl, Tf = triflate.



Scheme 2. Deuterium labeling and mechanistic explanation.

of this transformation involves a molecular oxygen coupled oxidative de-alkylation of dihydropyridine **21** to expel benzaldehyde.[9]

It was therefore surprising to us when Poupon and coworkers[4] reported the synthesis of 2,3,5-trisubstituted pyridine derivative **22** (Scheme 3), also en route to the haouamines, under conditions that should produce the "abnormal"



Scheme 3. Connection to the haouamine problem. Reagents and conditions: a) **24** (4.0 equiv), **25** (1.0 equiv), $Yb(OTf)_3$ (0.5 equiv), H_2O, 23 °C, 57%; b) $NaBH_4$, $CeCl_3$, 0 °C; AcOH, 72%; c) 3-MeOBnBr, acetone, 60 °C, 99%; d) LHMDS, THF, 45 °C, 5 min, 48%; e) NBA (2.2 equiv), CH_2Cl_2, 23 °C; AgOTf (1.1 equiv), CH_2Cl_2, 23 °C, 77%. LHMDS = lithium hexamethyldisilazanide, NBA = *N*-bromoacetamide.

Chichibabin product **23**. Indeed, the $Yb(OTf)_3$-catalyzed condensation of *meta*-methoxyphenylacetaldehyde (**24**) with 2-(*meta*-methoxyphenyl)ethylammonium chloride (**25**) actually produces the 3,5-diarylpyridinium **23** (confirmed by X-ray) rather than **22**.[10]

To unambiguously demonstrate that **22** is not produced in this reaction, it was synthesized from **23** by the following sequence: 1) reduction ($NaBH_4$ and acetic acid) to the tetrahydropyridine and alkylation with 3-methoxybenzyl bromide to afford **26** (71% yield), 2) Stevens rearrangement[11] to furnish **27** (LHMDS, 48% yield, ca. 7:3 d.r.), and 3)

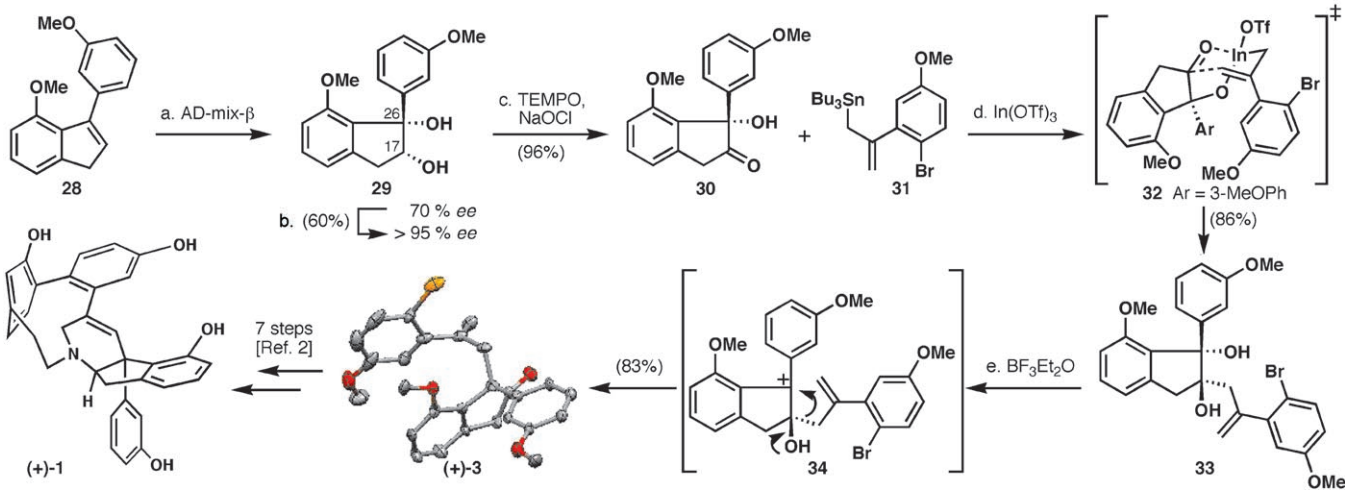
oxidation (*N*-bromoacetamide) and salt exchange (from bromide to triflate) using AgOTf (77% yield). Examination of the crude reaction mixture of **24** + **25** showed no detectable amounts of **22** by ^{1}H NMR spectroscopy (see Supporting Information).

Molecular models and MM2 calculations suggest that 2,3,5-substituted pyridiniums such as **22** (and **4**, see Figure 1) possess a destabilized architecture that forces the 3-aryl substituent out of planarity with the pyridine core. In contrast, simple alkyl aldehydes furnish the expected 2,3,5-substituted products and have been implicated in natural product biosynthesis.[12] The striking finding that pyridinium intermediates such as **22** (or **4**) resist formation under such conditions may point to a prebiotic barrier for the direct tetramerization route to **1** and **2** (Figure 1), precluding the utilization of molecular machinery.[13]

To ascertain whether naturally configured L-amino acids might be involved in the biosynthesis of the haouamines, an enantioselective route to **1** was required since its absolute configuration was unknown (Scheme 4). Our original synthesis (10 steps from commerically available 7-methoxyindanone or 12 steps from phenol)[2] relied on a conventional enolate alkylation to produce ketone **3** with its all-carbon quaternary center. Although it would seem that an asymmetric route to these molecules would amount to an enantioselective alkylation, such strategies were not successful.[14]

In principle, a diastereoselective pinacol rearrangement could set the stereochemistry of C-26 via a fleetingly stereogenic C-17 center (haouamine numbering). Thus, as depicted in Scheme 4, Sharpless asymmetric dihydroxylation[15] on aryl indene **28** achieved moderate levels of enantioselectivity yielding optically active diol **29** in 70% *ee* (determined by ^{1}H NMR analysis of the monoester derived from the (*R*)-Mosher acid). The 30% of racemic diol within this mixture was selectively crystallized (see Supporting Information for X-ray), leaving the enantiopure diol in solution (isolated in 60% overall yield from **28**). According to the Sharpless mnemonic[15] the diol produced should have the 17*R*,26*S* absolute configuration as shown in **29**. Subsequent chemoselective oxidation (other oxidants lead to diol cleavage) with TEMPO/NaOCl[16] afforded α-hydroxy ketone **30**, poised for incorporation of an appropriate allyl nucleophile. Allyl Grignard, silane, and boronate reagents were not competent nucleophiles either because of a lack of reactivity or interference of the aryl bromide. After considerable exploration, the allylindium species formed by transmetalation of an organotin reagent with an indium(III) species[17] was found to be both highly active and selective. Exposure of tributylallyltin **31**[18] to **30** in the presence of indium(III) triflate gave the desired addition product **33** in 86% yield. Treatment of this fully functionalized diol with a stoichiometric amount of BF_3Et_2O intercepted ketone (+)-**3** through a pinacol rearrangement[19] in 83% yield.[20] The absolute stereochemical assignment of (+)-**3** (26*R*) was verified by X-ray crystallographic analysis (Scheme 4, m.p. 88–90 °C, colorless cubes). Gratifyingly, there was no loss of stereochemical information throughout this sequence, as confirmed by diastereoselective reduction of ketone (+)-**3** to the alcohol and ^{1}H NMR analysis of the ester derived from the (*R*)-Mosher acid.

The optically active ketone was then carried through our previous synthetic sequence[2] to produce (+)-(8:9*S*,17*R*,26*R*)-haouamine A ((+)-**1**; $[\alpha]_D = +45.8$ deg cm^3 g^{-1} dm^{-1} (MeOH, $c = 0.05$ g cm^{-3})). Circular dichroism spectra were obtained (Figure 2) of this synthetic material as well as that of a natural sample of (−)-haouamine A ((−)-**1**; $[\alpha]_D = -52.0$ deg cm^3 g^{-1} dm^{-1} (MeOH, $c = 0.4$ g cm^{-3}))[1] kindly provided by Professor Zubía which showed that the unnatural enantiomer had been synthesized and thus proving the configuration of natural haouamine A to be 8:9*R*,17*S*,26*S*. As the configuration of C-17 in (−)-**1** correlates to the natural configuration of an amino acid, it is likely that L-phenylalanine[21] is incorporated in a biosynthetic route to (−)-haouamine A ((−)-**1**), specifically where highlighted in red in Figure 1.



Scheme 4. Reagents and conditions: a) AD-mix-β, $MeSO_2NH_2$ (5 equiv), 1:1 *t*BuOH/H_2O, 5 °C, 44 h; b) crystallization, 60% overall; c) TEMPO (0.05 equiv), NaOCl (2.0 equiv), KBr (0.05 equiv), CH_2Cl_2/sat. aq $NaHCO_3$ (2.6:1), 0 °C, 30 min, 96%; d) **31** (2.0 equiv), $In(OTf)_3$ (1.2 equiv), THF, 0–23 °C, 86%; e) BF_3Et_2O (1.1 equiv), CH_2Cl_2, 0 °C, 10 min, 83%. TEMPO = 2,2,6,6-tetramethylpiperidinyl-1-oxy.

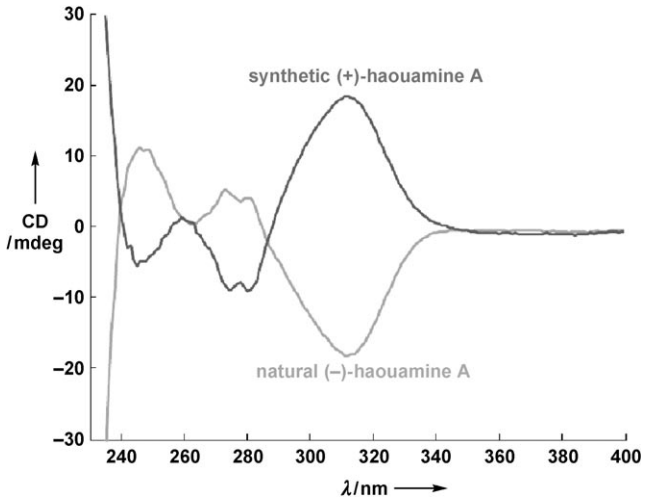


Figure 2. Circular dichroism spectrum.

While it may not be possible to pin down the precise synthetic route that nature uses for **1** and **2**, this line of inquiry has been enlightening. Reinvestigation of the venerable Chichibabin pyridine synthesis in this context has revealed that products of the "abnormal" variant are now readily accessible using lanthanide catalysis. Labeling studies point to a plausible mechanism of this intriguing reaction and have aided in the correction of structural misassignments.

These findings suggest that, in the absence of enzymatic intervention, **1** is unlikely to originate through a seemingly logical tetramerization route via **4** (Figure 1). Finally, an enantioselective synthesis of **1** is highlighted by a mild and selective indium-mediated allylation and stereoselective pinacol shift to secure its absolute configuration and support the proposition that **1** originates from a natural amino acid. Further studies into a biologically inspired route to **1** will be forthcoming in a full account of this work.

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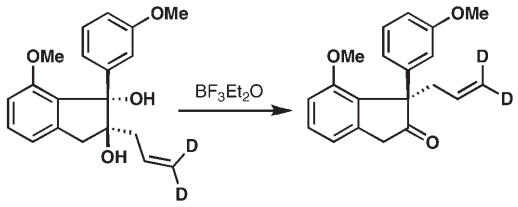

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