Biogenetic hypothesis and first steps towards a biomimetic synthesis of haouamines†

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A detailed hypothesis for the biogenesis of haouamines is reported herein, supported by experiments headed towards biomimetic synthesis of these compounds.

Marine organisms belonging to the Ascidiacea class are a rich source of structurally unique secondary metabolites. Among the most remarkable of these, Haouamines A **1** and B were isolated by E. Zubía and co-workers in 2002 from *Aplidium haouarianum* collected off Tarifa Island (Spain).[1] Haouamines A and B belong to a new family of complex polycyclic alkaloids (Fig. 1).

The molecular complexity of **1** constitutes an intellectual challenge for organic chemists. In fact, several groups have disclosed their own approaches to the construction of haouamines.[2–4] These efforts culminated in a total synthesis by the Baran team in early 2006,[5] soon followed by a formal total synthesis by Weinreb and co-workers.[6] We wish to report in this communication the first biomimetically inspired approach to haouamine A featuring an expeditious assembly of an advanced intermediate towards the total synthesis of **1**.

The combination of ring systems into a single and small architectural unit like haouamine A leads one to wonder how such structures can be assembled in nature. The tetrahydropyridine center ring suggests that the biogenetic origin is likely to be an assembly of simple L-phenylalanine derived units which can be traced four times in the final structure of **1**. Baran and colleagues suggested a condensation of four *meta*-hydroxylated phenylacetaldehyde molecules with ammonia as the nitrogen source followed by oxidative events. They also reported they had failed to take advantage of that route. We suggest a modified hypothesis. Central in our proposals is the formation of the tetrahydropyridine core through a natural Chichibabin-like pyridine synthesis reaction involving three aldehydes and a primary amine as the nitrogen source, all units being presumably derived from the aforementioned amino-acid.

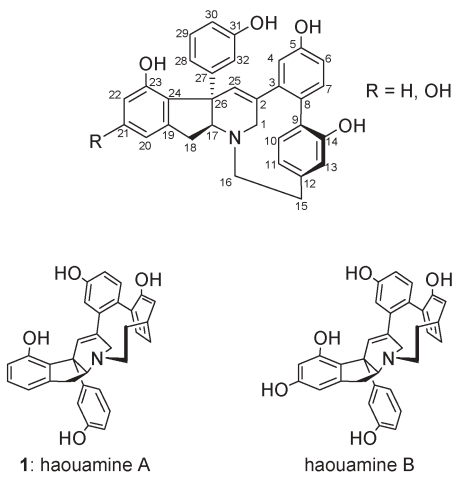
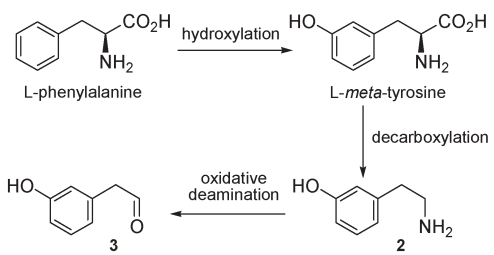


Fig. 1 Structures of haouamines.

Based on the fact that, in nature, amines can be transformed into aldehydes through an oxidative deamination process, we can assume that from L-phenylalanine, through hydroxylation to L-*m*-tyrosine[7,8] and decarboxylation, amine **2** can be obtained and then undergo oxidative deamination to give rise to *meta*-hydroxylated phenylacetaldehyde **3** (Scheme 1). The condensation of **2** and three molecules of **3** will lead to the formation of dihydropyridinium **4** (that already contains all atoms of the final molecule) which can then be reduced to compound **5**. The formation of the C_8–C_9 bond can be seen as the result of an *ortho*–*para* coupling[9] that occurs under oxidative conditions‡ to yield intermediate **6**. Such conditions might as well lead to the oxidation of C_{26} and generate an allylic hydroxyle group (**7**). It has been reported by Rawal and co-workers that under acidic conditions, the remaining bond (C_{24}–C_{26}) is then easily formed, *via* carbocation formation,[2] completing the biosynthesis of haouamine A **1** (Scheme 2).

Biomimetic investigations were performed with this possible biosynthetic route taken into consideration, and it was decided to study the outcome of the condensation reaction of 3-methoxyphenethylamine **8** with 3-methoxyphenylacetaldehyde **9**. The two species were reacted together (in a 1 : 3 ratio) along with catalytic quantities of ytterbium triflate in different solvents, at room temperature. After 20 hours, pyridinium **11**§ was found as the major product, whatever the solvent was, with yields of 60 to 75%



Scheme 1 Formation of precursors **2** and **3** from L-phenylalanine.

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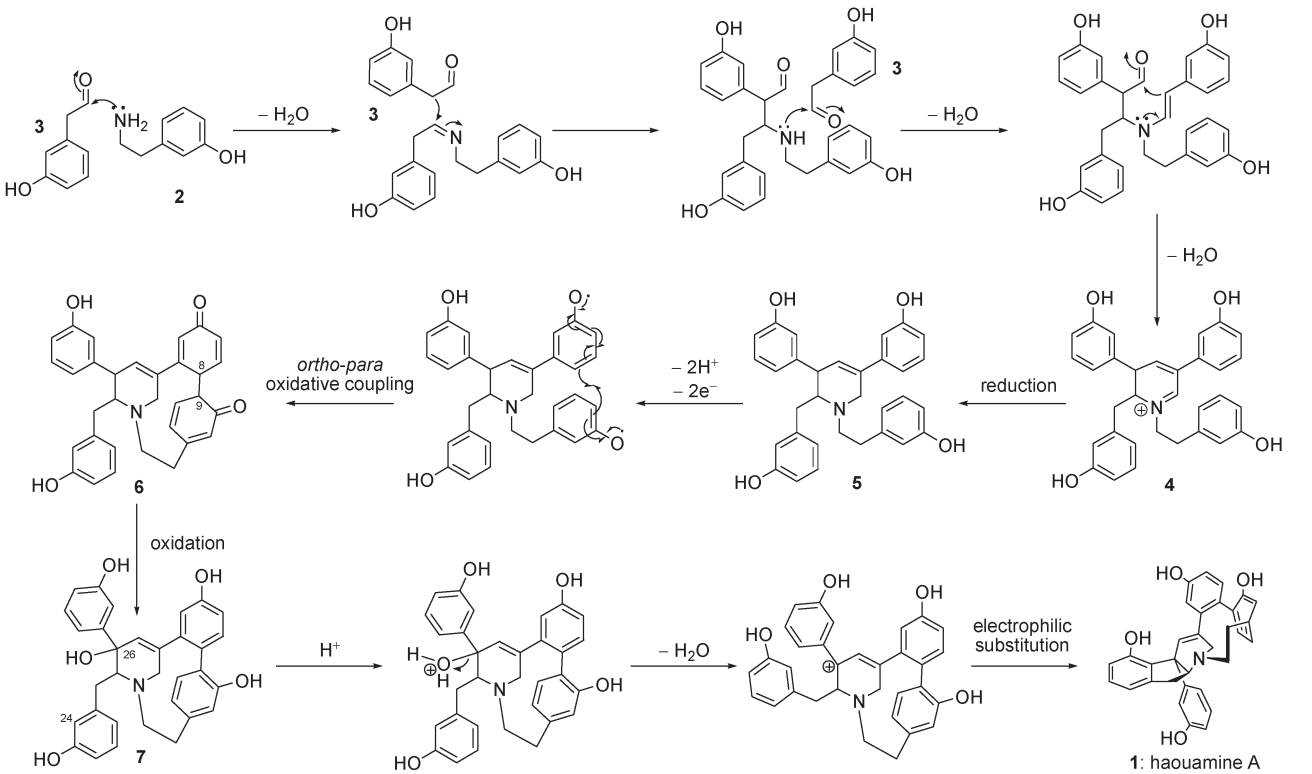
† Electronic supplementary information (ESI) available: Experimental procedures as well as copies of ^{1}H and ^{13}C NMR spectra are provided for compounds **11**, **12** and **14**. See DOI: 10.1039/b613737g

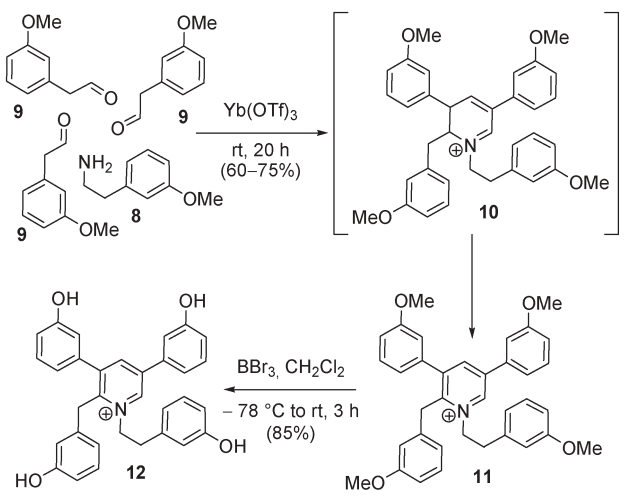


Scheme 2 Proposed biogenetic hypothesis for haouamine A **1**.

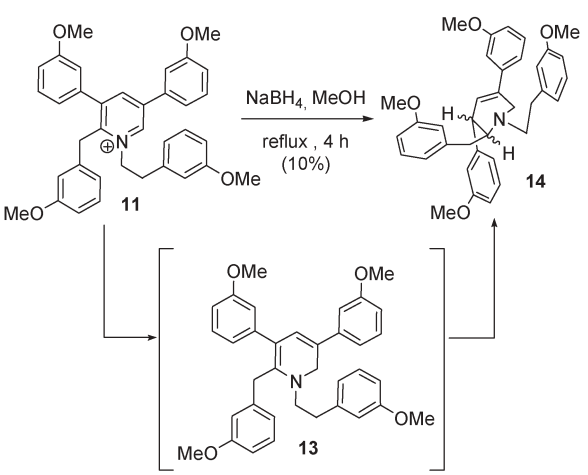
(Scheme 3). The reaction involves a cascade of reactions similar to the ones depicted on Scheme 2 (up to product **4**). Results highlight the great interest of rare earth-metal triflate catalyzed reactions in organic synthesis: the reaction takes place in very mild conditions instead of high temperatures and/or pressures historically required for the Chichibabin pyridine synthesis reaction.[10] Ytterbium triflate plays the role of a Lewis acid[11] and probably activates both aldehyde and imine groups of the reactants and intermediates. It should be noted that no traces of dihydropyridinium salt **10** (the logical outcome of the reaction) were detected in the crude reaction mixture. Spontaneous oxidations of dihydropyridinium salts into pyridinium salts have previously been observed with Chichibabin-like reactions,[12] and appear to be especially prominent when condensations are carried out with phenylacetaldehydes.

Compound **11** was then easily transformed into **12**¶ by reaction with tribromoborane (4.1 equiv.) in methylene chloride. The addition was performed at −78 °C and the mixture was allowed to slowly warm up to room temperature within the next three hours. Compound **12** was obtained in very good yield without any column purification needed.

Our initial plan was to perform reduction of **11** with sodium borohydride but the reaction only gave very limited quantities of the desired product **14**‖ as a mixture of *cis*/*trans* isomers



Scheme 3 Biomimetic self-assembly of pyridinium **11** followed by phenol deprotection to yield compound **12**.



Scheme 4 Reduction of **11** into tetrahydropyridine **14**.

(Scheme 4). The reason for such low yields is yet under investigation in our laboratory but it is likely to be an issue of pseudo-dimerisations through Diels–Alder type cycloadditions involving **14** and its direct precursor **13**.[13]

With compound **14** obtained in too little amounts, it was decided to try out different types of oxidative conditions applied to product **12** in order to see if the desired C_8–C_9 coupling can take place despite high constraint resulting from the pyridinium's planarity. The outcome of such reactions is still under investigation in our laboratory.

In conclusion, we have proposed a new detailed biogenetic hypothesis for haouamines that has led us to successfully achieve the first steps of the first biomimetic total synthesis of haouamine A. An advanced biomimetic precursor of that compound has been obtained through a convenient and efficient multicomponent reaction and the final two bonds that are needed to complete the synthesis are currently being investigated in our laboratory. The described biosynthetic hypothesis can serve as a useful framework from which to develop a coherent and straightforward synthetic plan towards haouamines (as well as close analogs such as compounds **11**, **12**, **14**) that competes with other synthetic approaches. This example also contributes to demonstrate the power of biomimetically inspired strategies in total synthesis.[14]

Notes and references

‡ It is interesting to note that oxidative conditions under which radicals can be generated on phenols to make phenolic couplings possible may also generate free hydroxyl radicals responsible for the formation of L-*meta*-tyrosine involved in our biogenetic proposal.

§ Compound **11**: orange oil; R_f = 0.40 (silica gel, CH_2Cl_2–MeOH 9 : 1); IR (film, $CHCl_3$): ν_{max} = 2937, 1585, 1260, 1030 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 1.25 (2 H, s), 3.27 (2 H, t, J = 6.5 Hz), 3.67 (6 H, s), 3.86 (6 H, s), 5.15 (2 H, t, J = 6.5 Hz), 6.55–7.45 (16 H, m), 8.47 (1 H, s), 8.75 (1 H, s); ^{13}C NMR (100 MHz, $CDCl_3$), δ 29.6, 37.8, 55.1, 55.7, 63.5, 112.5, 113.5, 114.2, 116.6, 118.2, 119.6, 121.1, 122.6, 130.2, 130.8, 134.0, 136.9, 139.8, 140.5, 141.3, 160.2, 160.6; MS (ES) m/z 546 (M^+), 440 (10), 426 (100); HRMS (ES) calcd for $C_{36}H_{36}NO_4^+$: 546.2639, found: 546.2642.

¶ Compound **12**: brown varnish; R_f = 0.30 (silica gel, CH_2Cl_2–MeOH 85 : 15); IR (film, CH_3OH): ν_{max} = 3061, 2926, 1589, 1029 cm^{-1}; ^1H NMR (400 MHz, CD_3OD), δ 1.25 (2 H, s), 3.35 (2 H, t partially hidden by CD_3OD signal, $J \sim$ 6.6 Hz), 4.97 (2 H, t, J = 6.6 Hz), 6.55–7.45 (16 H, m), 8.78 (1 H, s), 8.88 (1 H, s); ^{13}C NMR (100 MHz, CD_3OD), δ 30.8, 38.4, 64.4, 115.4, 115.6, 117.0, 117.2, 118.4, 119.7, 121.1, 121.3, 131.3, 131.9, 136.0, 138.5, 141.5, 141.9, 142.8, 159.3, 159.8; MS (ES) m/z 490 (M^+), 398 (10), 384 (100); HRMS (ES) calcd for $C_{32}H_{28}NO_4^+$: 490.2013, found: 490.2015.

‖ Compound **14**: yellow varnish; R_f = 0.70 (silica gel, CH_2Cl_2–MeOH 95 : 5); IR (film, $CHCl_3$): ν_{max} = 3010, 1579, 1300, 1108 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ 2.52 (2 H, d, J = 12 Hz), 2.75–3.10 (7 H, m), 3.25 (1 H, d, J = 14.5 Hz), 3.82 (12 H, m), 6.26 (1 H, s), 6.75–7.30 (16 H, m); ^{13}C NMR (100 MHz, $CDCl_3$), δ 30.2, 39.5, 40.1, 55.3, 58.9, 62.6, 66.0, 111.2, 111.4, 113.2, 114.4, 117.4, 117.8, 117.9, 128.5, 129.4, 129.7, 139.8, 141.3, 141.4, 159.8; MS (ES) m/z 550 ([M + H]$^+$), 444 (100); HRMS (ES) calcd for $C_{36}H_{39}NO_4H^+$: 550.2919, found: 550.2921.

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