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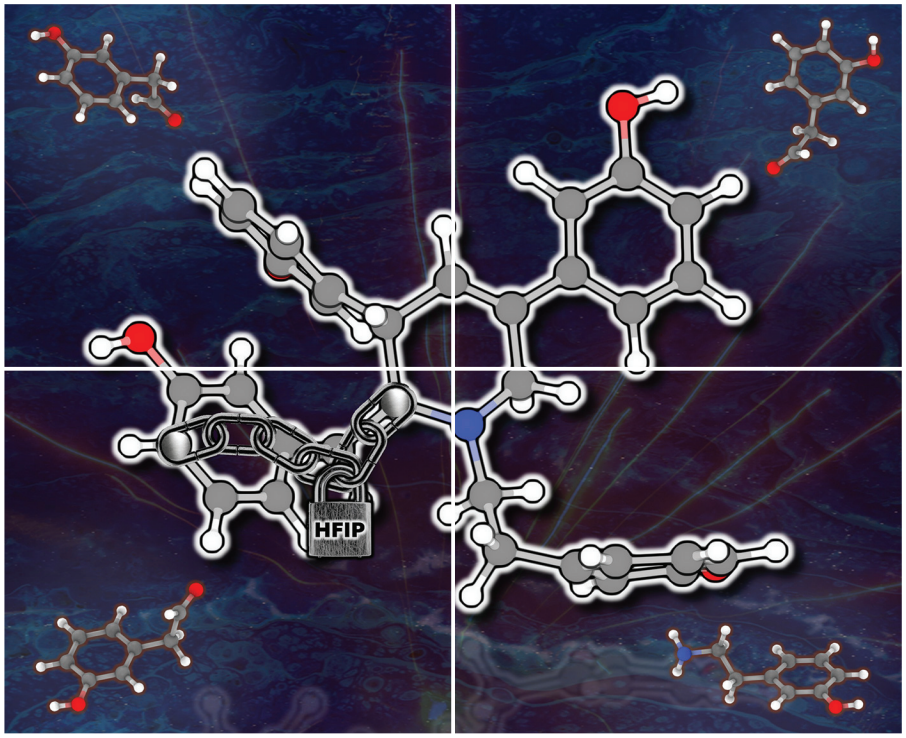

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Bypassing the abnormal Chichibabin reaction dead-end provides a biomimetic access to *pre*-haouamine

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Haouamines are highly constrained marine alkaloids possessing a unique in nature skeleton. The high degree of complexity of such alkaloids raises questions about their chemical assembly. This is addressed in this paper in which we propose a biomimetic scenario corroborated experimentally by a fine study of the classical Chichibabin pyridine synthesis, especially in its "abnormal" *oxidative* version. Finely tuned *reductive* conditions and mechanistic investigations permit the concise obtention of an advanced and challenging intermediate that we coined "*pre*-haouamine".

Introduction

Haouamines A and B (**1** and **2**, Fig. 1), two representatives of a new family of complex polycyclic alkaloids were isolated in 2003 by Zubía and co-workers from *Aplidium haouarianum*, an ascidian collected off Tarifa Island (Cádiz, Spain).[1] The structure of haouamine B (**2**) was later revised by Zubía, Trauner and co-workers.[2] and confirmed by a total synthesis of the new proposed structure by Tokuyama and co-workers in 2014.[3] The molecular complexity of haouamines, including an indeno-tetrahydropyridine ring system and a strained aza-paracyclophane moiety bearing a "bent" aromatic ring,[4] makes them highly challenging targets for organic chemists. Thus, several approaches toward the construction of the indeno-tetrahydropyridine core were reported[5] leading to the total synthesis of **1**, successfully achieved by Baran and Burns in 2006[6] with later insightful works.[7] This was followed by Tsukamoto and co-workers.[8] accompanied by several formal total syntheses[9] and also synthetic approaches (see Discussion S1).[10] While the biosynthetic pathway to haouamines remains a totally unanswered question, a synthetic route, that could mimic the biochemical processes explaining the emergence of such a unique scaffold, is addressed in this paper.

From a practical standpoint, in the absence of biochemical data or genomics studies demonstrating the "true" origin of **1** and **2** (whether from the sea slug or its associated microbiome), a "retrobiosynthetic" analysis combined with a "biomimetic" approach remains one of the few viable strategies for initiating the investigation of the biosynthetic pathway. Biologically relevant disconnections have been proposed by some of us[11] and are detailed as follows in accordance to the "metabolome consistency" concept (Scheme 1, see also Discussion S2).[12] Instinctively, two bonds C8–C9 and C24–C26, which are formed through phenolic couplings (we will discuss this point later), can be the first to be disconnected leading to

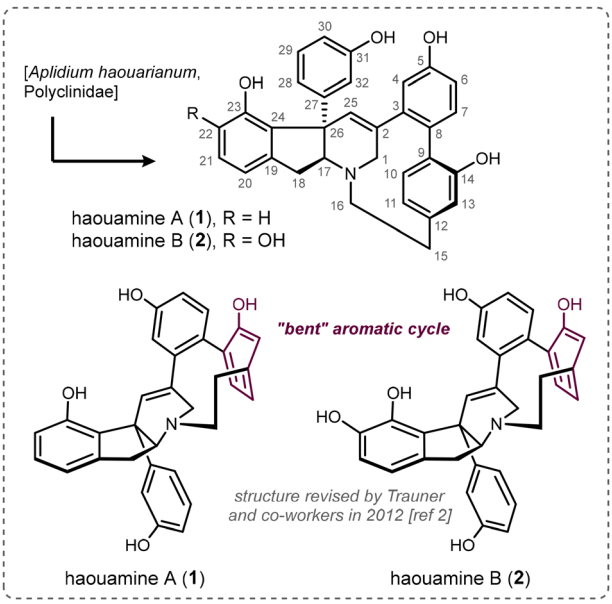

Fig. 1 Structures of haouamines A and B (**1** and **2**).

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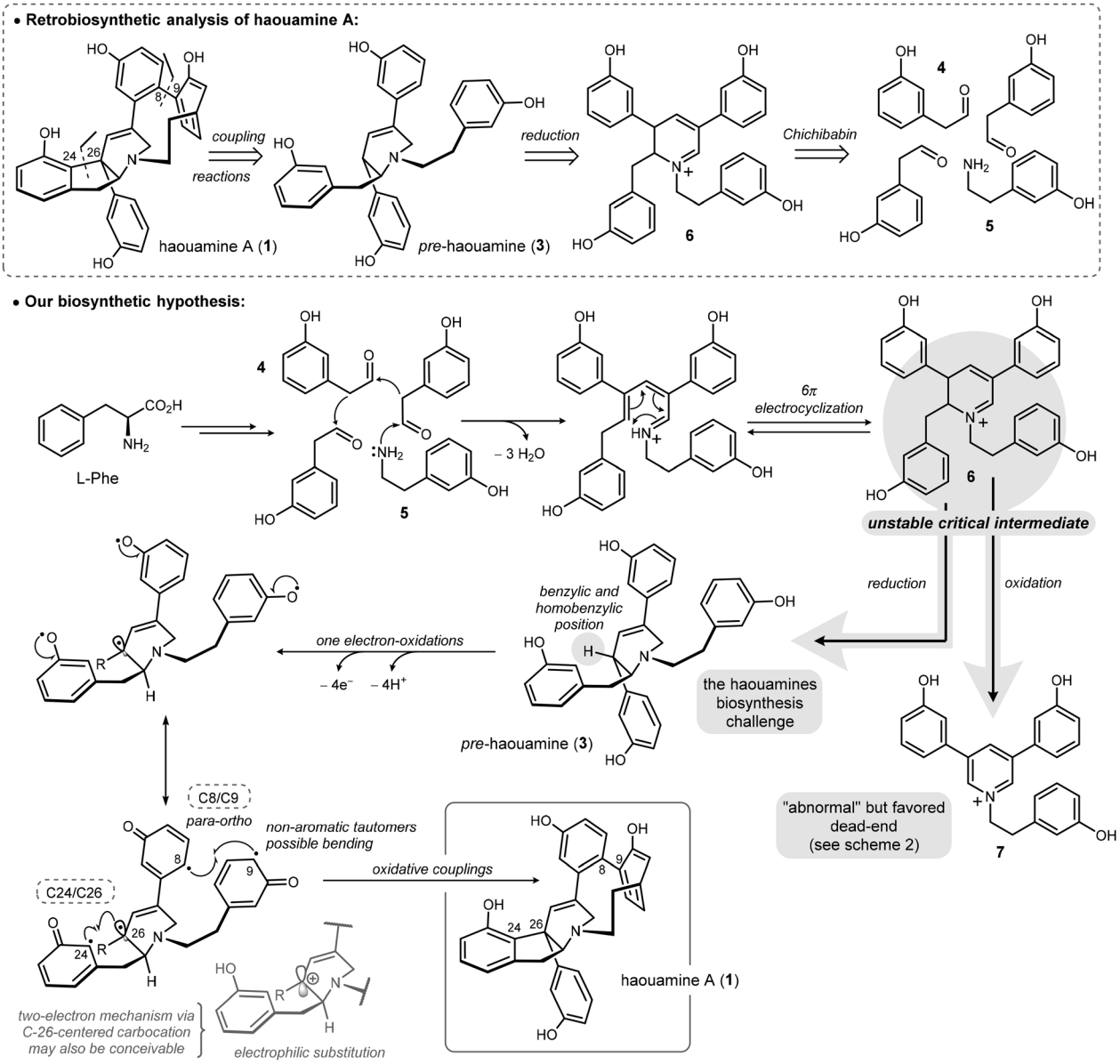
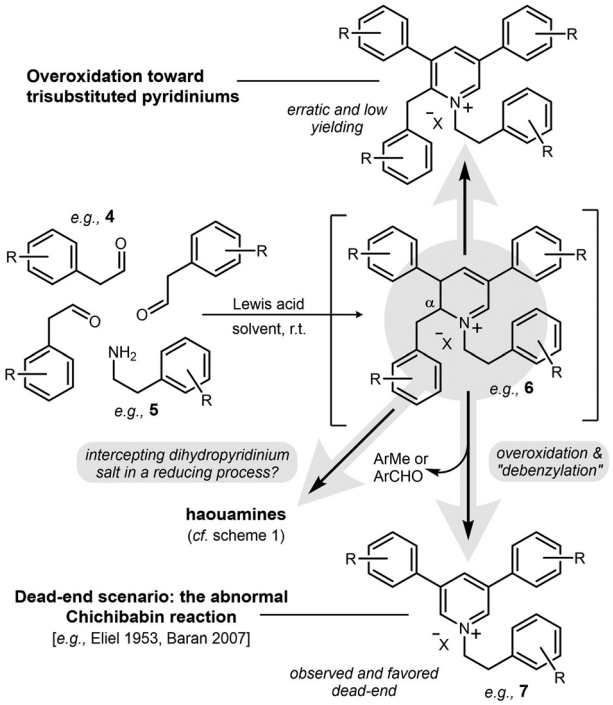


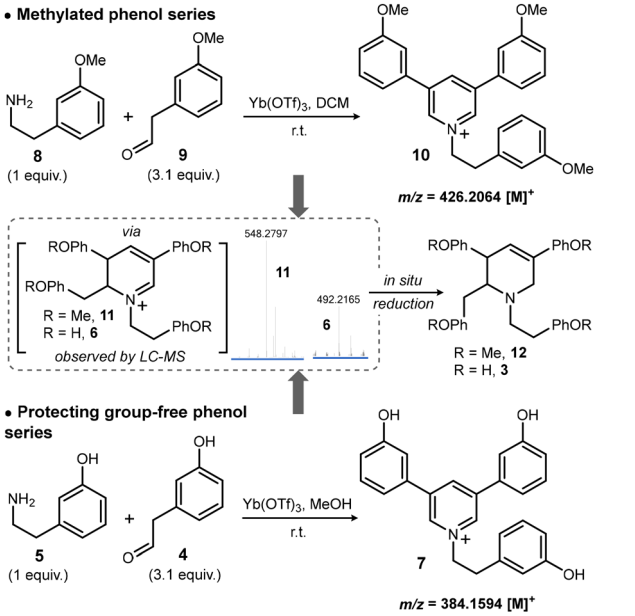
Scheme 1 Retrobiosynthetic analysis of haouamine A (**1**) and proposed biosynthetic hypothesis.

tetrahydropyridine **3** (Scheme 1). This key intermediate, that we propose to name "*pre*-haouamine", is the main focus of our article. The chemical assembly of this latter could be easily explained by a sequence of reactions inspired by the century-old Chichibabin pyridine synthesis (Scheme 1).[13] Starting from two reactive units, the benzylic aldehyde **4** and the primary amine **5**, presumably derived from L-phenylalanine but with an uncommon *meta*-phenol pattern,[14] the classical Chichibabin reaction mechanism would involve a dihydropyridinium salt such as **6** as the first intermediate possessing the full C_5N central cycle (which upon *oxidation* provides the desired pyridine or pyridinium salt in the Chichibabin reaction). In the case of haouamines, the *reductive* interception of intermediate **6** could provide *pre*-haouamine (**3**, Scheme 1). Finally, one-electron oxidative couplings (although an alternative two-electron mechanism could be put forward for C24–C26 bond formation) would easily explain the final steps of the proposed biosynthetic assembly scheme.

Back to the Chichibabin pyridine synthesis step, representing an immediate challenge for the formation of *pre*-haouamine (**3**) in terms of reactivity. Indeed, it is known that, especially from phenylacetaldehyde derivatives (*i.e.*, aldehydes bearing a benzylic position), an "abnormal" Chichibabin reaction is observed (limited or inexistent with aliphatic aldehydes[15]). This unexpected spontaneous reactivity was described by Eliel and co-workers in the 1950s[15] and consists of a loss of substituent at position α to the nitrogen upon oxidation (Scheme 2) which was also foreseen by Chichibabin



Scheme 2 Abnormal Chichibabin reaction observed in an attempt to construct the tetrahydropyridine core of haouamine A (**1**).



Scheme 3 Detected masses during the Chichibabin pyridinium salt synthesis reaction.

himself in the aliphatic series.[13] Isolation of the awaited trisubstituted pyridines[15] or pyridinium salts is possible but usually from erratically reproducible and low-yielding procedures. Given these dead-end outcomes, the spontaneous formation of pyridinium **7**, as per our biosynthetic proposal (Scheme 1), could pose significant challenges. From biosynthetic considerations, this suggests that fine control is required if this reaction occurs in the biosynthesis of natural products.

In the present work, according to our biosynthetic hypothesis, we herein report a finely tuned strategy to bypass the abnormal Chichibabin reaction dead-end and provide concise access to *pre*-haouamine (**3**) showing the chemical feasibility of the scenario.

Results and discussion

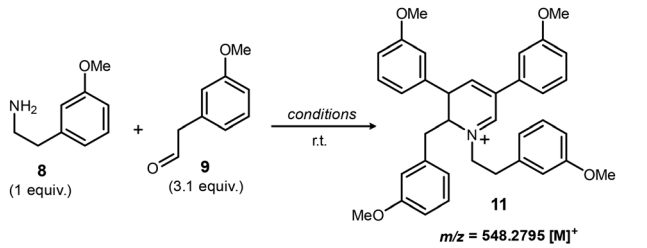
Abnormal Chichibabin reaction: statement with the haouamine scenario

First, we decided to re-investigate the Chichibabin pyridine synthesis outcomes based on a thorough LC-MS analyses of the various masses detected during the reaction. In this way, we applied conditions known to promote the Chichibabin reaction, especially in its abnormal version. Indeed, according to literature, Lewis acids and more precisely lanthanide-based Lewis acids are known to yield the resulting pyridinium salts.[7a,11] Thus, amine **8** and aldehyde **9**, as well as their protecting group-free versions **5** and **4** respectively (*i.e.*, the "biochemical" units of our proposed scenario, Scheme 1), were reacted in the presence of ytterbium triflate ($Yb(OTf)_3$) (Scheme 3). Previously synthesized pyridinium salts **7** and **10** (see Experimental procedure S4), were used as LC-MS analytical reference materials to confirm their formation in the reaction mixtures (Experimental procedure S1). As expected, both pyridiniums were easily identified according to their analytical read-outs (Scheme 3), underlining the predisposition of dihydropyridinium salt intermediates – through the abnormal Chichibabin reaction – to lead to a synthetic dead-end. Despite these expected outcomes and examination of the other detected masses revealed the presence of two mass-to-charge ratios (m/z) that could match dihydropyridinium unstable intermediates **11** (548.2797 $[M]^+$) and **6** (492.2165 $[M]^+$) as shown in Scheme 3 (see Experimental procedure S1). This promising observation raised the possibility of intercepting such intermediates through an *in situ* reduction, leading to the corresponding tetrahydropyridines **12** and **3**, respectively (Scheme 3).

Intercepting the dihydropyridinium intermediate

Methylated phenol series: reaction conditions screening and LC-MS monitoring. Based on the detection by LC-MS of m/z ratios matching with dihydropyridinium salts, we decided to further investigate the course of the reaction and find conditions under which dihydropyridiniums **11** and **6** could be traced and, why not, intercepted before overoxidation and α-deletion. Therefore, several conditions were screened and monitored by LC-MS (Table 1 and Fig. 2, see also Experimental procedure S2). A mixture of H_2O/1,4-dioxane was selected as it had been already used by Baran and co-workers in a previous work related to haouamine A.[7a] In order to increase the reactiv-

Table 1 Reaction conditions screening – methylated phenol series



Entry	Solvent[a]	Catalyst[b]
1	H_2O/1,4-dioxane (1 : 1)	—
2	MeOH	—
3	MeOH	$Yb(OTf)_3$
4	HFIP	—
5	MeOH/HFIP (10 : 1)	—

[a] Conditions: **8** (21.2 mg, 0.14 mmol, 1.0 equiv.), **9** (66.1 mg, 0.44 mmol, 3.1 equiv.), solvent (5.5 mL). [b] Amount set at 50 mol%.

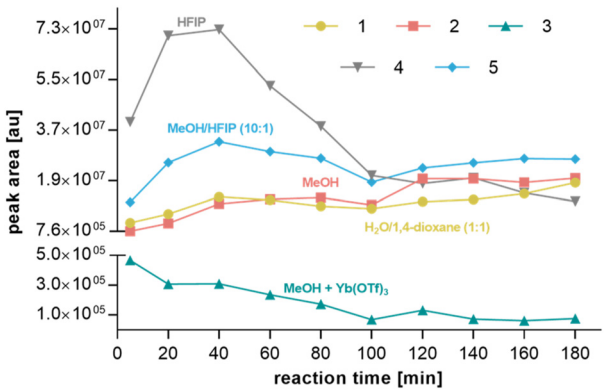


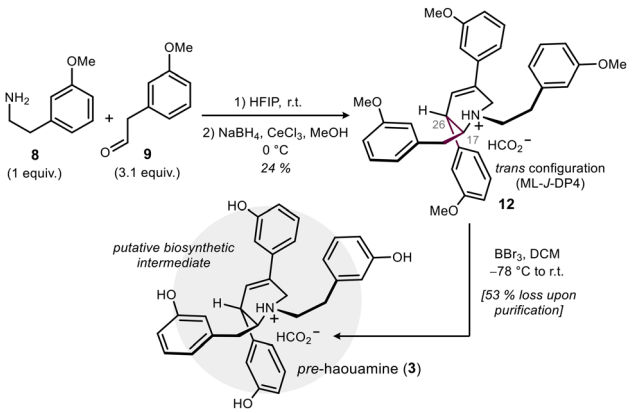
Fig. 2 LC-MS monitoring of dihydropyridinium salt **11**. Legend numbers correspond to Table 1 entries.

ity of carbonyls and intermediate imines, MeOH, hexafluoroisopropanol (HFIP), and $Yb(OTf)_3$ were also considered. According to this study, HFIP provided crucial assistance in dihydropyridinium **11** formation (entries 4 and 5, Table 1 and Fig. 2),[16] especially when it is used as solvent rather than an additive (entry 4). After approximately 40 minutes of reaction, a sharp decline occurs. As HFIP was described to have a wide range of interesting features,[17] some arguments may be put forward to explain this remarkable outcome. Indeed, due to its hydrogen-bond-donating ability and its acidic properties, HFIP can activate, as aforementioned, carbonyl compounds such as **9** and intermediate imines involved in the Chichibabin reaction cascade. In addition, HFIP is known to stabilize radicals and positively charged species, which could explain the accumulation of dihydropyridinium **11** in the reaction mixture at some point. From a "biomimetic" point of view, HFIP could mimic the ability of certain enzymes to stabilize highly reactive intermediates.[18] Finally, the repeatability of our results with neat HFIP was confirmed by performing reactions in triplicate (Fig. S8).

***In* situ reduction provides advanced intermediate *pre*-haouamine.** The identification of HFIP as a suitable solvent to promote dihydropyridinium salt **11** formation paved the way for the next biomimetic step: the needed reduction of compound **11** into tetrahydropyridine **12** (the methylated counterpart of presumed biosynthetic intermediate **3**, Scheme 4). Satisfyingly, through a one-pot fashion from amine **8** and aldehyde **9**, the *in situ* reduction of dihydropyridinium **11** under Luche conditions[19] after 30 minutes of reaction provided tetrahydropyridine **12** with an appreciable yield of 24% (Scheme 4). The structure of compound **12** was assigned by NMR and a *trans* configuration at C17 and C26 was assigned using the ML-*J*-DP4 approach (see Experimental procedure S5, Fig. S13).[20] Finally, demethylation of compound **12** with boron tribromide led to *pre*-haouamine (**3**, Scheme 4), which corresponds to the putative central biosynthetic intermediate involved in our biosynthetic pathway proposal for haouamine A (**1**, Scheme 1).

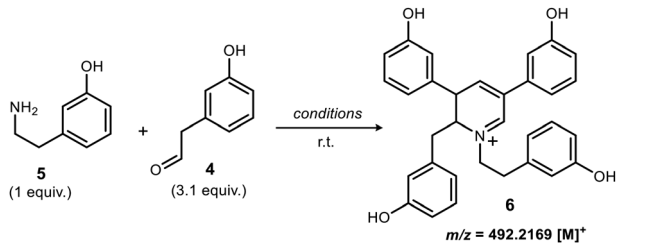
Challenging the scenario with native biochemical units

Everything was in place to accurately assess the chemical feasibility of our proposed scenario for the biosynthesis of haouamine A (**1**). In this purpose, protecting group-free biochemical units **4** and **5** were used "as they stand" and reacted under different conditions accompanied by LC-MS monitoring (Table 2 and Fig. 3), inspired by our previous study on the methylated phenol series (*cf.* Table 1 and Fig. 2). A mass-to-charge ratio m/z = 492.2169 $[M]^+$ corresponding to the expected dihydropyridinium salt **6** was tracked (see Experimental procedure S3). Unlike our previous study, neat HFIP unexpectedly gave poor results (entry 4, Table 2 and Fig. 3). However, HFIP was found to promote the formation of dihydropyridinium salt **6**, albeit to a moderate extent, when used as an additive in MeOH (entry 5, see also Fig. S11 for repeatability assessment). This contrast between the methylated and non-methylated phenol series highlights, in our case, a significant solvent effect affecting the formation of dihydropyridinium salts through the Chichibabin pyridine synthesis reaction.



Scheme 4 One-pot synthesis of tetrahydropyridine **12** and deprotection into *pre*-haouamine (**3**).

Table 2 Reaction conditions screening – protecting group-free phenol series



Entry	Solvent[a]	Catalyst[b]
1	H_2O/1,4-dioxane (1 : 1)	—
2	MeOH	—
3	MeOH	$Yb(OTf)_3$
4	HFIP	—
5	MeOH/HFIP (10 : 1)	—

[a] Conditions: **5** (19.2 mg, 0.14 mmol, 1.0 equiv.), **4** (60.0 mg, 0.44 mmol, 3.1 equiv.), solvent (5.5 mL). [b] Amount set at 50 mol%.

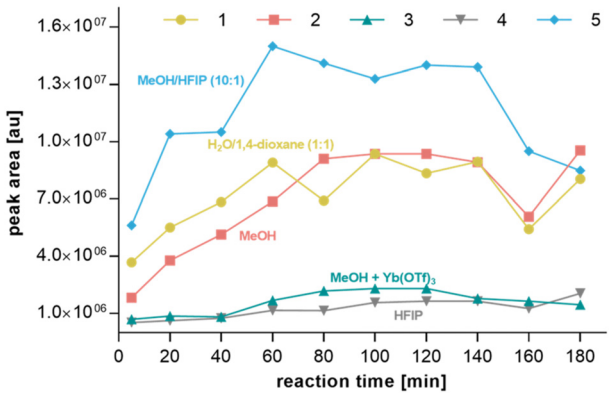
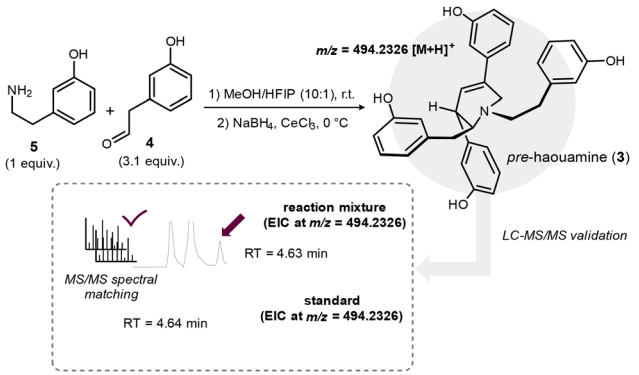


Fig. 3 LC-MS monitoring of dihydropyridinium salt **6**. Legend numbers correspond to Table 2 entries.

The tracking of highly reactive biosynthetic intermediates is an uncommon approach to the validation of biosynthetic hypotheses. But in the present case and based on our biosynthetic hypothesis, LC-MS monitoring of compound **6** provided consistent clues for a formally similar scenario *in vivo*. Finally, a biomimetic reduction was carried out and provided clear evidence of the formation of **3** from our "as in nature" reaction (*i.e.*, from free phenols) (Scheme 5, see Experimental procedure S6). Despite obvious issues related to the use of hydrides in the presence of free phenol functions, we were able to observe a product that satisfyingly matched the high-resolution mass-to-charge ratio, retention time, and MS/MS spectrum of authentic **3** (synthesized through the demethylation of **12**, *vide supra*) which was used as a reference material.

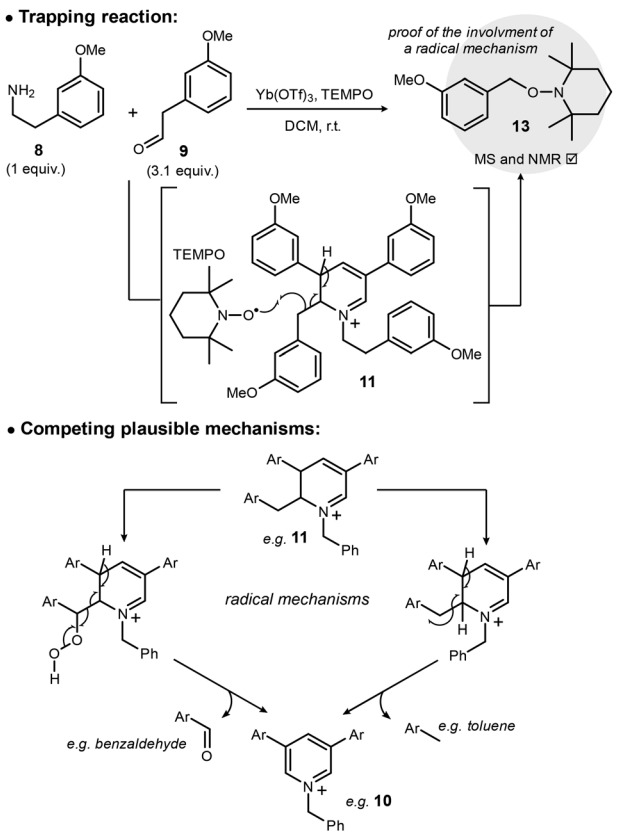
Mechanistic investigation

Since the work of Eliel and co-workers, very few experimental observations have contributed to the study of the mechanisms



Scheme 5 One-pot synthesis of *pre*-haouamine (**3**) and validation of its formation by LC-MS/MS. EIC = extracted ion chromatogram, RT = retention time.

behind the "abnormal" spontaneous evolution of the Chichibabin reaction.[15] Experimentally, toluene was isolated by Eliel and co-workers[15] as well as benzaldehyde in Baran and co-workers' work,[7a] suggesting at least two competitive mechanisms and implying probable radical intermediates and oxidative processes (Scheme 6, see also Discussion S3). To confirm such intermediates, we were able to run reactions, known to promote the expected dead-end outcome, in the



Scheme 6 Radical trapping experiment with TEMPO led to the isolation of compound **13**.

presence of (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO). Satisfyingly, compound **13**, derived from a radical trapping, was detected by LC-MS analysis, and successfully isolated from the reaction mixture (Scheme 6). Validation of its structure by NMR gave, for the first time, a strong clue for the implication of radical intermediates in the abnormal loss of substituents upon oxidation.

Conclusion

From a thorough LC-MS monitoring of unstable dihydropyridinium salt intermediates **6** and **11**, we were able to develop a biomimetic strategy and find optimal reaction conditions involving HFIP, to bypass the "abnormal" Chichibabin reaction dead-end. These remarkable results allowed us to achieve the synthesis of challenging tetrahydropyridine **12** in a one-pot fashion and finally access to tetrahydropyridine **3**. The latter key intermediate, that we named "*pre*-haouamine", strengthen our proposed biosynthetic scenario for haouamines and paves the way toward haouamine A (**1**). Indeed, the structural predisposition of tetrahydropyridine **3** should favor the two phenol couplings needed to complete the construction of the aza-paracyclophane moiety and the indeno-tetrahydropyridine ring system that give haouamines their unique architecture. Our work also provides a framework for future genome mining of putative biosynthetic gene clusters and enzymes related to challenging marine natural product biosynthesis elucidation (whether the compounds are produced by the invertebrate or its associated microorganisms).[21] Furthermore, a mechanistic investigation has pinpointed the involvement of a possible radical mechanism for the abnormal Chichibabin reaction contributing to its understanding.

Author contributions

The manuscript was written through contributions of all authors.

Conflicts of interest

There are no conflicts to declare.

Data availability

Discussions and full experimental details have been included as part of the SI: NMR data (FID) have also been uploaded on Zenodo. See DOI: **https://doi.org/10.1039/d5qo01111f**.

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