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A Total Synthesis Prompts the Structure Revision of Haouamine B

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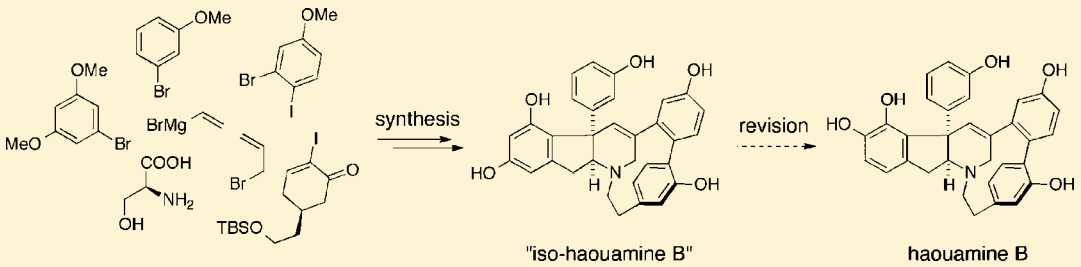
Supporting Information



ABSTRACT: A concise asymmetric approach to the indeno-tetrahydropyridine core of the unusual alkaloid haouamine B allowed for an investigation of a biomimetic oxidative phenol coupling as a proposed biosynthetic step, and ultimately provided access to the published structure of the natural product. As a consequence of our synthetic studies, the structure of haouamine B has been revised.

INTRODUCTION

Alkaloids continue to surprise with unusual and unexpected structures that have motivated advances in synthetic methodology and strategy. A case in point are the haouamines, a pair of intriguing alkaloids from the ascidian *Aplidium haouarianum* that display cytotoxic effects.[1] Structurally, these alkaloids feature an indeno-tetrahydropyridine moiety that contains a diaryl quaternary center and an anti-Bredt double bond (Figure 1). The tetrahydropyridine ring is fused to a highly strained 11-membered *p*-cyclophane ring system, which contains a stereogenic biaryl axis. The complexity of the NMR spectra of the haouamines, however, does not arise from two interconverting biaryl atropisomers but rather from an equilibrating mixture of two isomers formed through nitrogen inversion coupled with a conformational reorganization around the tetrahydropyridine ring.[2]

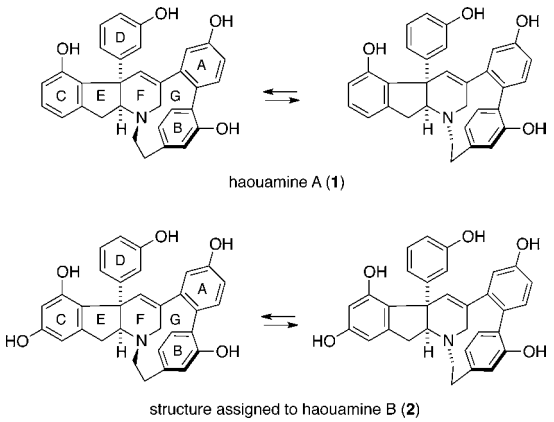


Figure 1. The haouamines.

Haouamine A has received considerable attention in the synthetic community, with several approaches to the assembly of the tetrahydropyridine core[3] and a model study of the macrocycle[4] having been reported. The Baran group has made a significant contribution to this body of work by virtue of their synthesis of racemic haouamine A and two subsequent total syntheses of the non-natural enantiomer of the natural product, involving two distinct methods for construction of the *p*-cyclophane moiety.[5,2b] Through this work, the structure of haouamine A (**1**) has been firmly secured, in contrast with the less abundant and more unstable haouamine B, which differs from haouamine A through oxygenation pattern of ring C and was given the structure **2** on the basis of the characterization of its peracetylated derivative.[1] No total synthesis of haouamine B has been disclosed to date, with only two reports of the synthesis of the core of the molecule.[6] Herein, we describe the first total synthesis of enantiomerically pure compound **2** and report that the physical and spectral data derived from our synthetic material do not correspond to the structure suggested for haouamine B. As a consequence of our synthetic studies, the molecular structure of haouamine B has been reassigned.

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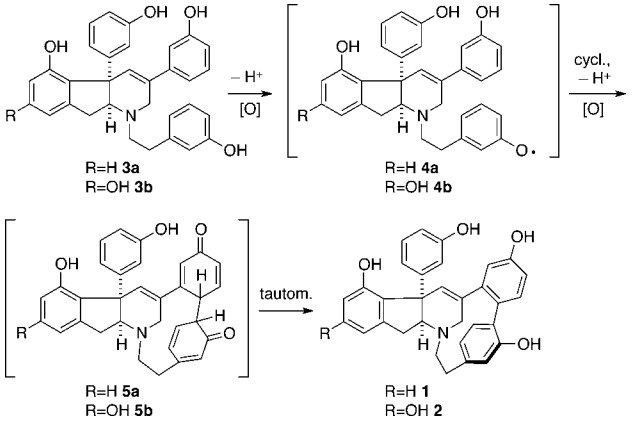
While the biosynthetic origin of the haouamines remains a mystery,[5b] it is reasonable to propose that an *o*,*p*-phenol oxidative radical coupling is involved in the construction of the *p*-cyclophane macrocycle (Scheme 1). Oxidation of phenols **3a** or **3b** would yield phenoxyl radicals (e.g., **4a**,**b**) which would undergo further cyclization and oxidation to afford *bis*-cyclohexadienones **5a**,**b**. Due to the presence of an sp^3-hybridized carbon, these are considerably less strained than the corresponding cyclophanes **1** or **2**, which are subsequently formed through rearomatization. Presumably, the enzymatic machinery of the native host ensures that this reaction proceeds in a regio- and stereoselective manner. Whether the oxidative phenol coupling takes place at the stage indicated in Scheme 1, rendering **3a** and **3b** real biosynthetic intermediates, however, remains unknown.

Scheme 1. Biosynthesis of the Haouamines Could Involve an Oxidative Phenol Coupling of the Proposed Intermediates 3a/3b

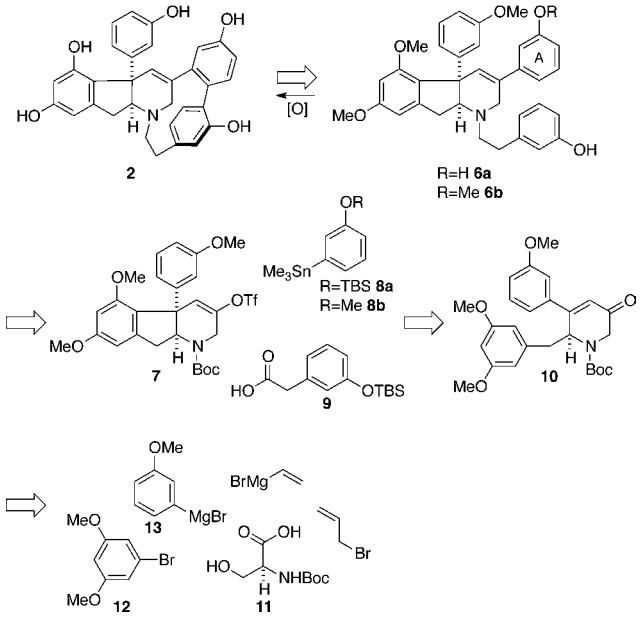


RESULTS AND DISCUSSION

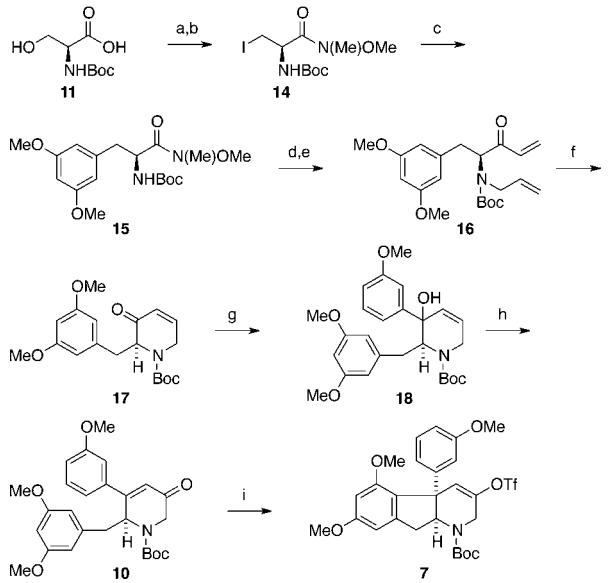
Our initial synthetic approach to compound **2** centered around the hypothesized ortho,para-coupling of the appropriately protected biphenol substrate **6a** (Scheme 2), or the methylated congener **6b**. The phenoxyl radical available from the latter compound represents an electrophilic species,[7] and thus could be attacked by the electron-rich methyl phenol of ring A within substrate **6b**. We reasoned that both of these compounds could be accessed from enol triflate **7**. This last intermediate, in racemic form, had previously been identified by us as a useful entry into the synthesis of haouamine B and was obtained via an electrophilic aromatic substitution of enone **10** with concomitant formation of an enol triflate ("Friedel–Crafts Triflation").[8,6a] We envisaged that dihydropyridone **10**, in turn, could be obtained from *tert*-butyloxycarbonyl-protected L-serine **11** and phenol ethers **12** and **13**, using advanced organometallic methodology.

Our total synthesis of **2** commenced with a palladium-catalyzed cross-coupling of an organozinc compound derived from iodinated *N*-Boc-serine derivative **14** with dimethoxy bromobenzene **12** (Scheme 3).[9] Subsequent *N*-allylation of the ensuing material, followed by a reaction with vinyl magnesium bromide, afforded diene **16** that underwent a clean RCM reaction to furnish enone **17**. The latter was subjected to 1,2-nucleophilic attack by Grignard reagent **13**, and the resulting tertiary allylic and benzylic alcohol immediately underwent Dauben oxidation[10] mediated by pyridinium chlorochromate (PCC) to give dihydropyridone **10**. In the critical step of the sequence, enone **10** underwent the Friedel–Crafts triflation reaction to afford the indeno-tetrahydropyridine core **7**, importantly without loss of optical purity (see Supporting Information for details).

Scheme 2. Retrosynthetic Analysis of Compound 2



Scheme 3. Synthesis of Indeno-tetrahydropyridine Core 7[a]



[a](a) EDCI, NH(Me)OMe·HCl, *N*-methylmorpholine, CH_2Cl_2, −15 °C;[11] (b) PPh_3, imidazole, I_2, CH_2Cl_2, 0 °C → room temperature, 83% in two steps; (c) Zn, cat. I_2, DMF, then **12**, $Pd(OAc)_2$, SPhos, 60 °C, 78%; (d) NaH, DMF, 0 °C, then allyl bromide, 0 °C, 92%; (e) vinyl magnesium bromide, THF, 0 °C; (f) Grubbs second-generation catalyst, CH_2Cl_2, 83% in two steps; (g) **13**, THF, 0 °C → room temperature, 75%; (h) PCC, 3 Å MS, CH_2Cl_2, 78%; (i) trifluoromethanesulfonic anhydride, 2,6-di-*tert*-butylpyridine, $MeNO_2$, 3 Å MS, −20 °C, 55%. EDCI = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, SPhos = 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl, PCC = pyridinium chlorochromate, MS = molecular sieves.

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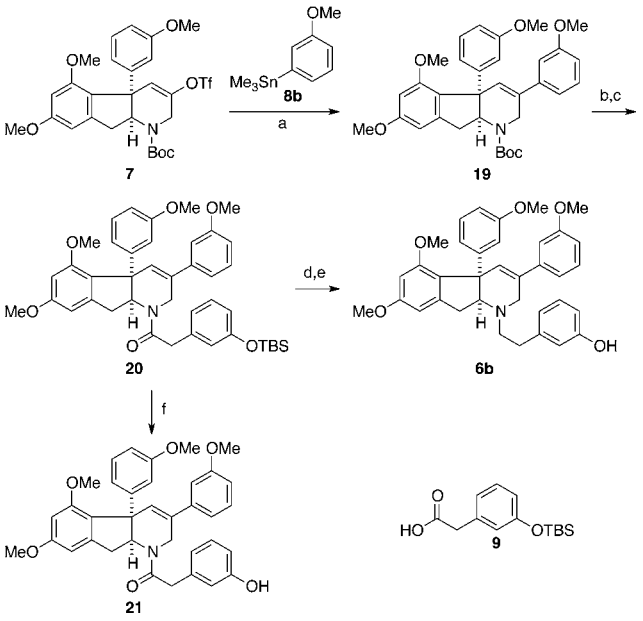
The synthesis of **6b**, one of our substrates for oxidative phenol coupling, is shown in Scheme 4, and begins with a Stille

Scheme 4. Synthesis of Oxidative Phenol Coupling Substrates: Amine 6b and Amide 21[a]

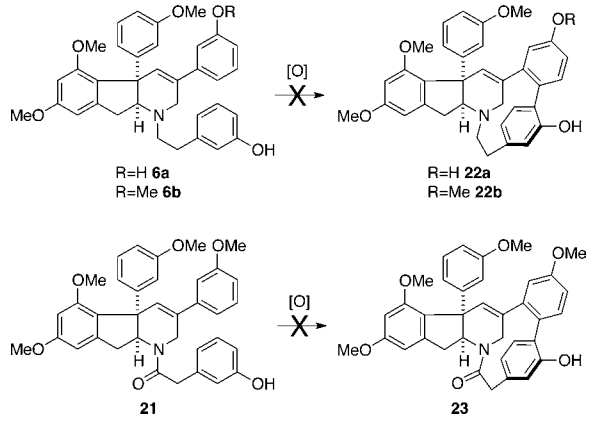


[a](a) $Pd(PPh_3)_4$, CuI, CsF, DMF, 45 °C, 88%; (b) TFA, CH_2Cl_2; (c) CDI, **9**, DMF, 85% in two steps; (d) $LiAlH_4$, $AlCl_3$, THF, 90%; (e) NH_4F, MeOH, 57%; (f) NH_4F, MeOH, 97%. TFA = trifluoroacetic acid, CDI = 1,1′-carbonyldiimidazole.

cross-coupling of enol triflate **7** with stannane **8b**. The ensuing arylated compound **19** was treated with TFA to remove the BOC group. Condensation of the resulting free secondary amine with a mixed anhydride of the known acid **9**[12] followed by reduction of the ensuing amide and subsequent cleavage of the OTBS group afforded amine **6b**. The bisphenol **6a** was prepared in an analogous fashion (see Supporting Information for details). Compounds **6a** and **6b** represent a reduced form of the haouamine skeleton and, in deprotected form, could even be biosynthetic intermediates. Amide **21** was also available through this sequence and was to serve as the deactivated counterpart of tertiary amine **6b**. We were intrigued to see if these substrates could engage in the envisaged oxidative process.

With the three substrates (**6a**, **6b**, and **21**) in hand, efforts were focused toward the key oxidative processes (Scheme 5). Clearly, in the absence of enzymatic control, oxidative coupling reactions of each of these compounds were expected to result in mixtures of atrop- and regioisomers. Fortunately, all but the ortho,ortho-regioisomeric products were predicted to be impossibly strained on the basis of preliminary calculations. Initial experiments under enzymatic conditions (horseradish peroxidase/H_2O_2), however, failed to yield any identifiable products of substrate **6a** under a variety of reaction conditions including various enzyme sources. Similar findings were observed for electrochemical approaches. Specifically, under anodic oxidation conditions (Pt or boron-doped diamond (BDD) anode, various electrolytes, solvents and temperatures),[7] both amine **6b** and amide **21** were recovered unchanged, even under increasingly high current density and total electric current applied. No useful outcomes were

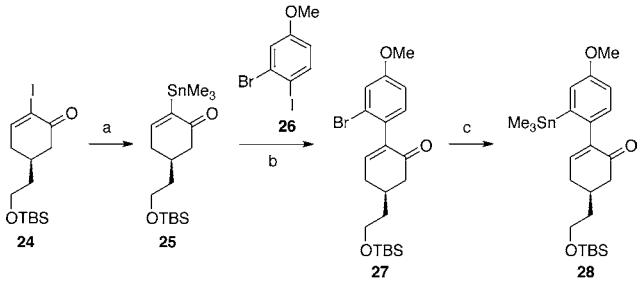
Scheme 5. Attempted Oxidative Phenol Couplings of Amines 6a/6b and Amide 21



obtained using chemical oxidants, such as hypervalent iodine reagents, silver salts, vanadium oxyhalides as well as iron and copper reagents. Despite extensive experimentation, we were unable to identify the sought-after compounds in useful amounts. In an experiment that demonstrates the stubbornness of these substrates, heating bisphenol **6a** to 132 °C in the presence of 2 equiv of di-*tert*-butyl peroxide (DTBP) as a radical initiator for several hours resulted in complete recovery of starting material. Our findings suggest that the proposed oxidative phenol coupling does not proceed without enzymatic assistance or that a substrate might be involved in the biosynthesis wherein the indeno-tetrahydropyridine system is not yet formed.

Since our biomimetic approaches were met with so many difficulties, we resolved to adapt a late-stage aromatization strategy that had been pioneered by Baran in his second-generation total synthesis of haouamine A.[2b] To make our synthesis more convergent, however, we decided to develop an enantiomerically pure phenyl cyclohexenone building block that could be coupled with our enol triflate **7** (Scheme 6). To

Scheme 6. Synthesis of the Reduced Eastern Half[a]



[a](a) $Pd(PPh_3)_4$, Me_6Sn_2, toluene, 70 °C, 80%; (b) PEPPSI-IPr, LiCl, DMF, 50 °C, 63%; (c) Me_6Sn_2, Ag_2O, $Pd(Pt\text{-}Bu_3)_2$, toluene, 100 °C, 46%. PEPPSI-IPr = [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride.

that end, the (*R*)-enantiomer of vinyl iodide **24**, which had been known as a racemate,[2b] was prepared, starting from cyclohexenone (see Supporting Information).[13,2b] This compound was then converted into the corresponding vinyl stannane **25**, which underwent a chemoselective Stille cross-coupling reaction with the known bromo-iodoarene **26**.[14] The resultant bromide **27** had to be subsequently activated toward a cross-coupling reaction with enol triflate **7** and therefore was

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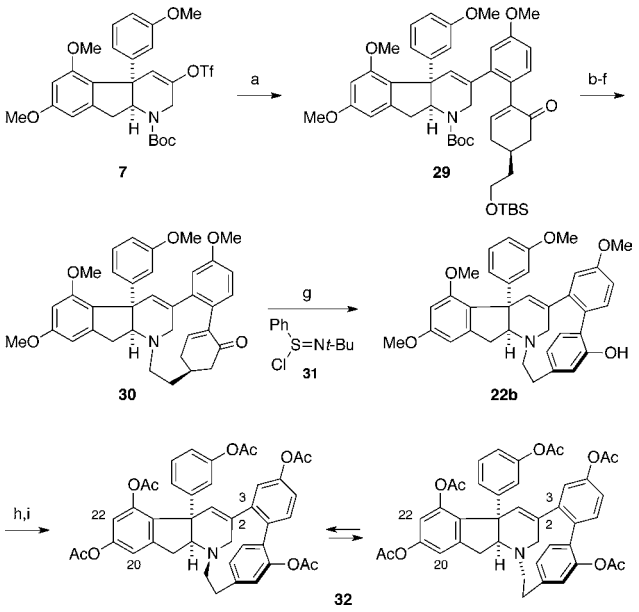
transformed into aryl stannane **28**. This compound embodies A,B-rings of compound **2** with the configuration of the biaryl axis ultimately derived from the sole stereocenter on **28**.

The stage was now set to bring the two halves of our target molecule together via Stille cross-coupling (Scheme 7). We

Scheme 7. Total Synthesis of the Proposed Structure of Haouamine B Peracetate[a]



[a](a) **28**, $Pd(PPh_3)_4$, $Ph_2PO_2NBu_4$, CuI, DMF, 45 °C, 85%; (b) HF·pyridine, pyridine, THF, 100%; (c) MsCl, Et_3N, CH_2Cl_2; (d) NaI, acetone, 96% in two steps; (e) TFA, CH_2Cl_2, 7 °C; (f) DIPEA, CH_3CN, 82 °C, 76% in two steps; (g) LiCl, LDA, THF, −78 °C, then **31**, −78 °C, 67%; (h) BBr_3, $CH_2Cl_2/CHCl_3$, 0 °C → room temperature; (i) Ac_2O, pyridine, 70% in two steps. MsCl = methanesulfonyl chloride, TFA = trifluoroacetic acid, DIPEA = *N*,*N*-diisopropylethylamine, LDA = lithium diisopropylamide, Ac_2O = acetic anhydride.

were pleased to find that heating triflate **7** and stannane **28** in deoxygenated DMF in the presence of $Pd(PPh_3)_4$, CuI, and tetra-*n*-butylammonium diphenylphosphinate[15] afforded compound **29** in 85% yield. Installation of a primary iodide, subsequent cleavage of the *tert*-butyloxycarbonyl protecting group, and heating the ensuing secondary amine in the presence of diisopropylethylamine lead to a clean conversion into macrocycle **30**. Subjection of this material to LDA-promoted kinetic dienolate formation, followed by treatment with *N*-*tert*-butylbenzenesulfinimidoyl chloride **31**,[16] provided phenol **22b** in 67% yield, following careful optimization of workup conditions. As expected, the defined stereocenter on the cyclohexenone ring translated to a single biaryl atropisomer. In the final phase of the synthesis, tetramethyl ether **22b** was subjected to a large excess of boron tribromide, followed by global acetylation of partially purified polyphenol to afford the target pentaacetate **32**.

The spectral and physical data obtained for this compound were in complete agreement with the assigned structure, but they did not fully match those reported for the nature-derived haouamine B peracetate.[1] A careful comparison of the ^1H and ^{13}C NMR data of both compounds showed that discrepancies were focused on the signals of ring C. Thus, in the ^1H NMR spectrum of compound **32** (600 MHz, $CDCl_3$) the two meta-coupled protons H-20 and H-22 of ring C (major isomer) were clearly observed at δ 6.83 (m) and 6.76 (d, J = 2.1 Hz), respectively, while the two protons of ring C of haouamine B peracetate (400 MHz, $CDCl_3$) appeared overlapped with other protons in a signal centered at δ 7.08 for the major isomer and in a signal obscured by the solvent signal (δ 7.26) for the minor isomer. The signals of C-20 and C-22 in the ^{13}C NMR spectrum of compound **32** were consistent with the resorcinol-type substitution of ring C, appearing at δ 116.1 and 115.5 (major isomer), respectively, while the methines of ring C of haouamine B peracetate gave rise to signals at δ 123.0 and 123.1 (major isomer). All these data indicated that the substitution pattern described for ring C of haouamine B needed to be revised.

Indeed, a re-examination of the original 400 MHz spectra of haouamine B peracetate revealed the possible misinterpretation of some of the HMBC correlations observed for ring C. To find additional data, new NMR spectra at 600 MHz were recorded and analyzed (see Supporting Information). In the ^1H NMR spectrum registered in $CDCl_3$, the proton signals of ring C of the major isomer were still overlapped with other signals, but the signals of the protons of ring C of the minor isomer were resolved enough to show an AB system attributable to two ortho-coupled protons at δ 7.27 (d, J = 8.1 Hz) and δ 7.25 (d, J = 8.3 Hz). The HMBC correlations of the proton at δ_H 7.25 with carbons C-18 (δ_C 34.6) and C-24 (δ_C 138.2) confirmed that this proton was located at the position 20, as originally established.[1] Taking into account the ortho relationship between the protons of ring C herein disclosed, the second proton on the ring (δ 7.27) must be reassigned to the position 21, and consequently, the oxygenated functions must be at C-22 and C-23. The signals corresponding to these carbons were identified at δ_C 141.7 and 139.7, respectively. In the HMBC spectrum, the proton at δ 7.27 exhibited correlations attributable to the interactions with C-19 and C-23 that were consistent with the position 21 for this proton. These new data obtained for the minor isomer of haouamine B peracetate indicated that the structure of this compound must be reassigned to **33** (Figure 2), displaying the two acetoxy groups of ring C at C-22 and C-23.

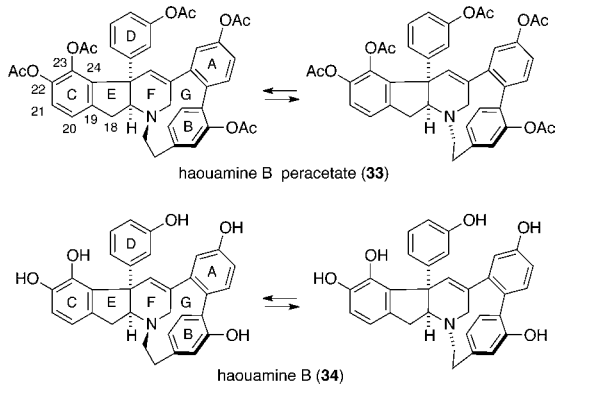


Figure 2. Revised structures of haouamine B and its peracetate.

The structural reassignment of haouamine B peracetate was further supported by the NMR data obtained at 600 MHz in $(CD_3)_2CO$ (see Supporting Information). Analysis of the COSY, HSQC, and HMBC spectra allowed the complete assignment of the ^1H and ^{13}C resonances and led to identifying the signals due to protons of ring C of the major isomer at δ_H

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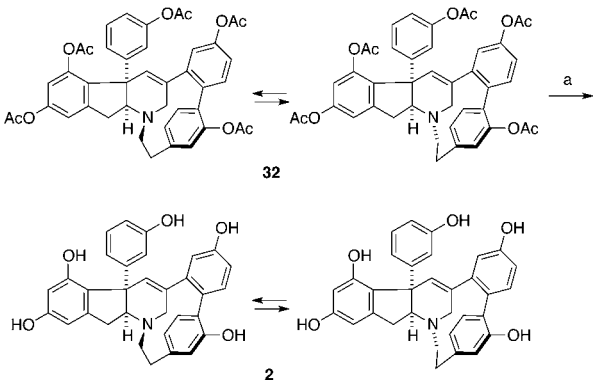
7.12 (H-20, d, J = 8.3 Hz) and δ_H 7.09 (H-21, d, J = 8.3 Hz), while those of the minor isomer could be identified at δ_H 7.35 (H-20, overlapped with other signals) and δ_H 7.28 (H-21, d, J = 8.1 Hz). The HMBC correlations H-20/C-18,C-24 and H-21/C-23 observed for the major isomer, together with the correlations H-20/C-18,C-22,C-24 and H-21/C-19,C-23 for the minor isomer, were in full agreement with the presence of protons at positions 20 and 21. Following these results, the structure of the natural product haouamine B must be revised from **2** to **34**, displaying two hydroxyl groups at C-22 and C-23 and not at C-21 and C-23, as previously reported.[1] This reassignment points to a biosynthesis that could involve L-DOPA, which is more in line with alkaloids than the resorcinol pattern usually associated with type II polyketides.

Scheme 8. Exposure of "Iso-haouamine B" (2)[a]



[a](a) K_2CO_3, MeOH, 71%.

With the structure of naturally occurring haouamine B clarified, we turned to obtaining pure samples of a synthetic member of the haouamine family, viz. compound **2**. Hydrolysis of acetate **32**, mediated by potassium carbonate in methanol, afforded "iso-haouamine B", **2**, as an amorphous solid (Scheme 8). To date, over 100 mg of this compound have been prepared, making it available for extensive biological testing.

CONCLUSIONS

In summary, we have developed a concise, total synthesis of the structure originally assigned to haouamine B. Our fast approach to the core of the molecule allowed for the detailed investigation of a hypothesized oxidative phenol coupling and eventually led to the proposed structure of the alkaloid. The true structure of haouamine B was revised in accord with our findings and has been reassigned to the catechol **34**. In principle, our total synthesis could be adapted to reach **34**, but with limited time and resources we have decided to resist this temptation and focus on the further evaluation of iso-haouamine B (**2**). The biological activity of **2** and a number of synthetic intermediates and derivatives is currently under investigation and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

Experimental details and spectra of all new synthetic compounds and of haouamine B peracetate (**33**). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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