A Total Synthesis Prompts the Structure Revision of Haouamine B

Matveenko, M.; Liang, G.; Lauterwasser, E. M. W.; Zubía, E.; Trauner, D.


1. **Introduction**

1.1. **Haouamines**

- Haouamines (*Figure 1*) are alkaloids from *Aplidium haouarianum*, which display cytotoxic effects.\(^1\)
- The Baran group reported the total synthesis of haouamine A, and its structure was firmly secured.\(^2\)
- In contrast, only the synthesis of the core of the molecule was reported for haouamine B.\(^3\)
- The structure of haouamine B was assigned from nature-derived haouamine B peracetate.\(^1\)
- Its isomerization through nitrogen inversion, coupled with a conformational reorganization, leads to the complexity of the NMR spectra.

1.2. **This Work**

- First total synthesis of the structure assigned to haouamine B (2) was reported.
- The structure of haouamine B was reassigned through the disagreement of spectral data.

1.3. **Strategy**

- For haouamine A, the total synthesis was achieved via late-aromatization step to form the *p*-cyclophane macrocycle (*Scheme 1*).\(^2\)
- The biosynthesis route of this macrocycle is unknown yet.\(^4\)
- The authors proposed a *o,p*-phenol oxidative radical coupling as a biosynthetic way to construct this macrocycle (*Scheme 2*).

*Scheme 1*. Reported synthesis of the *p*-cyclophane moiety of haouamine A (1).\(^2\)

*Scheme 2*. Mechanism of the proposed oxidative phenol coupling toward *p*-cyclophane moiety.
2. Results and Discussion

2.1. Synthesis of the indeno-tetrahydropyridine core of Haouamine B

The indeno-tetrahydropyridine core 17 was synthesized (Scheme 3).


- The synthesis was started from N-Boc-L-serine.
- Through the Friedel-Crafts triflation of 16, the core was afforded without loss of optical purity.

2.2. Oxidative Phenol Coupling towards $p$-cyclopane macrocycle

To focus on the oxidative phenol coupling, amine 18, bisphenol 19, amide 20 were prepared from 17 (Scheme 4) as a substrate.

- Biomimetic oxidative conditions (horseradish peroxidase/H$_2$O$_2$) did not give any identifiable products.
- Neither the electrochemical oxidation nor the use of chemical oxidants gave useful outcomes.
- Heating with radical initiator resulted in complete recovery of starting material.

The authors suggest that:
- Oxidative phenol coupling might not proceed without enzymatic assistance.
- The formation of this $p$-cyclopane macrocycle might take place before the formation of indeno-tetrahydropyridine core.
2.3. Total synthesis of the proposed structure of haouamine B

To form this p-cyclopane moiety, a late-stage aromatization strategy, which was pioneered by Baran, was adapted.

- Total synthesis of compound 2 was achieved (Scheme 5).

Scheme 5. Total synthesis of the proposed structure of haouamine B (2) and its peracetate (37).

- The stereocenter of 28 allows single biaryl atropisomer of 34.
- Peracetate of 2 (37) was finally obtained and its structure was ensured by spectral and physical data.

2.4. Structural Reassignment of Haouamine B

The spectral data of 37 did not fully match those reported for nature-derived haouamine B peracetate (Figure 2).1

- In the originally published data, signals of H-20 and H-22 were overlapped with other signals at δ 7.08 (obtained at 400 MHz).
- For compound 37, two meta-coupled protons could be clearly observed at δ 6.83 and 6.76.
- Structure of haouamine B needed to be revised.

Figure 2. NMR signals of H-20 and H-22. Signals are of its major isomer.
For detailed analysis, NMR spectra of the nature-derived haouamine B were recorded at 600 MHz.

- The two protons on ring A of the major isomer were still overlapped; those of the minor isomer were resolved enough to two ortho-coupled signals at δ 7.25 and 7.27.
- From the HMBC spectrum, the proton at δH 7.25 showed correlations with carbons C-18 and C-24, while the proton at δH 7.27 showed with C-19 and C-23.
  - These protons are located in position 20 and 21 (Figure 3).
  - The molecular structure of this compound must be reassigned to 38 (Figure 3).

The structure of the natural product haouamine B should be revised from 2 to 39 (Figure 3).

![Figure 3. Revised structure of haouamine B peracetate (38) and haouamine B (39). NMR signals of 38 are of its minor isomer.](image)

### 3. Conclusions
- Concise total synthesis of the structure originally assigned to haouamine B was developed.
- Through the re-examination in the nature-derived haouamine B peracetate, the structure of haouamine B was reassigned to 39.

### 4. References