A Total Synthesis Prompts the Structure Revision of Haouamine B

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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]

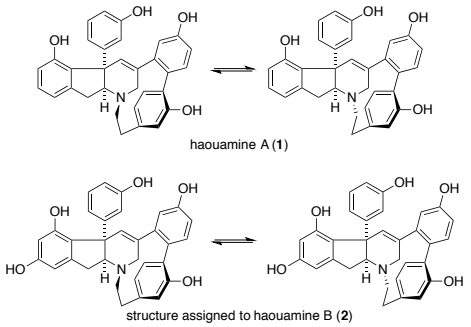


Figure 1. The haouamines.

- Its isomerization through nitrogen inversion, coupled with a conformational reorganization, leads to the complexity of the NMR spectra.

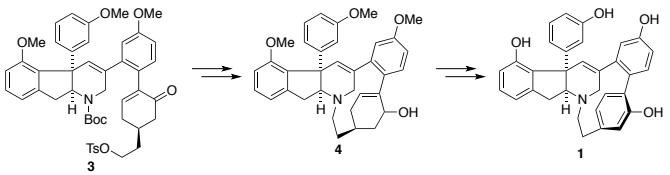
1.2. This Work

- 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

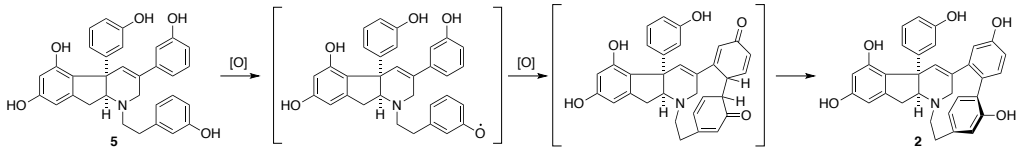
- For haouamine A, the total synthesis was achieved via late-aromatization step to form the *p*-cyclophane macrocycle (*Scheme 1*).[2]
- The biosynthesis route of this macrocycle is unknown yet.[4]

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



- The authors proposed a *o*,*p*-phenol oxidative radical coupling as a biosynthetic way to construct this macrocycle (*Scheme 2*).

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

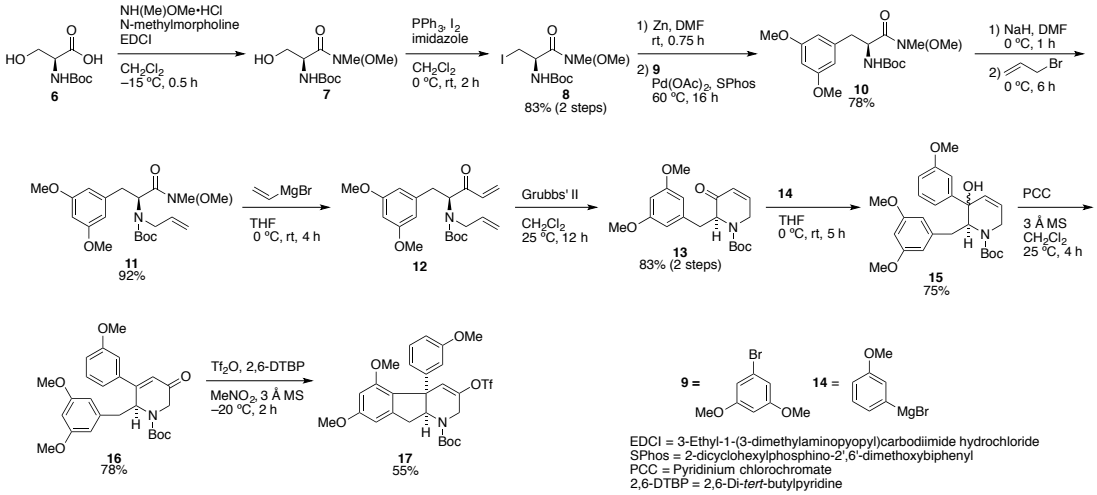


2. Results and Discussion

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

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

Scheme 3. Synthesis of indeno-tetrahydropyridine core **17**.



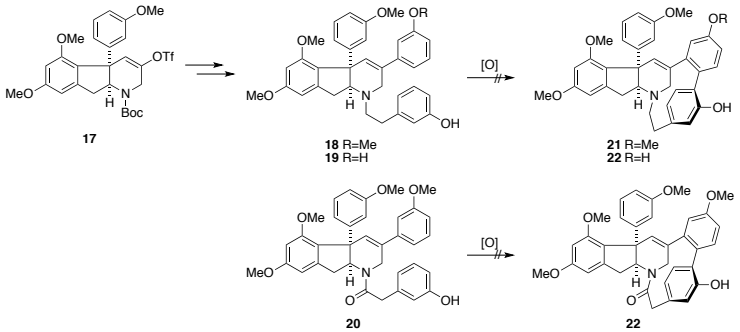
- The synthesis was started from *N*-Boc-L-serine.
- Through the Friedel-Crafts triflation of **16**, the core was afforded without loss of optical purity.

2.2. Oxidative Phenol Coupling towards *p*-cyclophane 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_2O_2) did not gave 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.

Scheme 4. Oxidative phenol couplings of substrates **18**, **19**, **20**.



The authors suggest that:

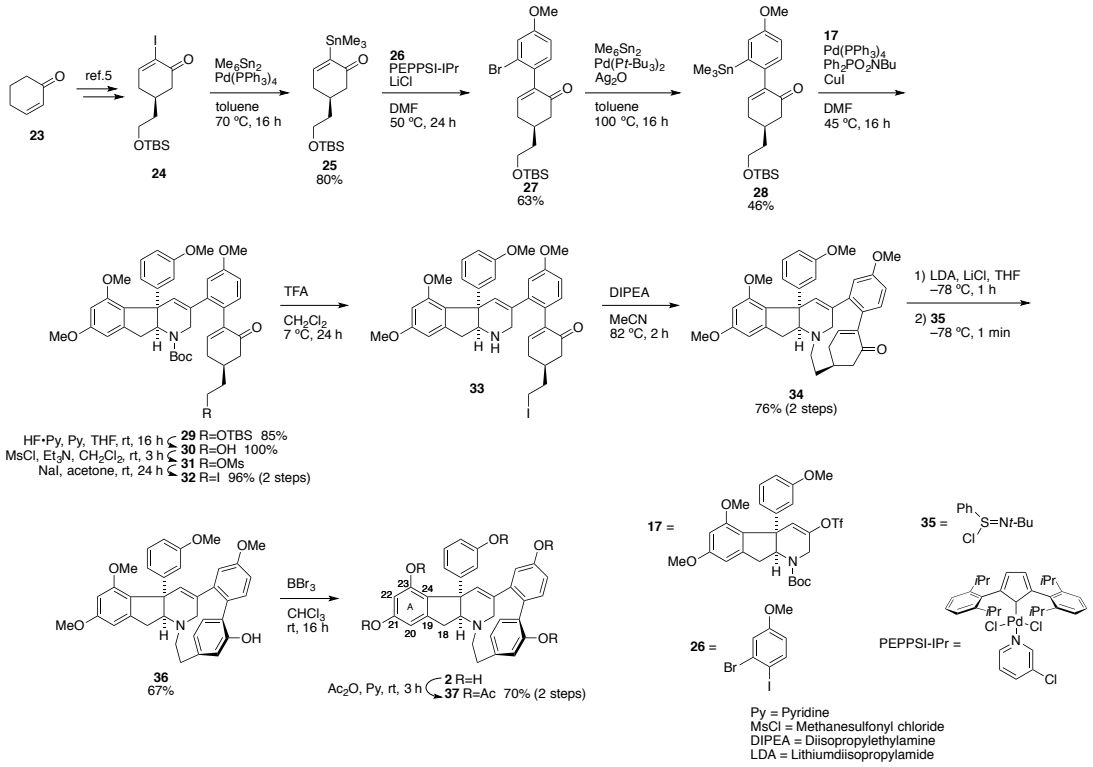
- Oxidative phenol coupling might not proceed without enzymatic assistance.
- The formation of this *p*-cyclophane macrocycle might take place before the formation of indeno-tetrahydropyridine core.

2.3. Total synthesis of the proposed structre of haouamine B

To form this *p*-cyclophane moiety, a late-stage aromatization strategy, which was pioneered by Baran,[2] 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.

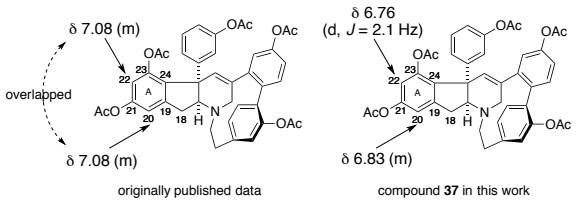


Figure 2. NMR signals of H-20 and H-22. Signals are of its major isomer.

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 δ_H 7.25 showed correlations with carbons C-18 and C-24, while the proton at δ_H 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*).

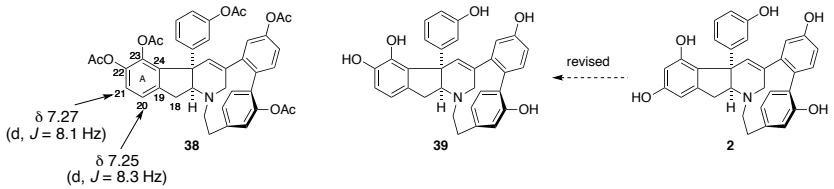


Figure 3. Revised structure of haouamine B peracetate (**38**) and haouamine B (**39**). NMR signals of **38** are of its minor isomer.

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

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