Total Synthesis of (–)-Haouamine B Pentaacetate and Structural Revision of Haouamine B

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In the last few decades, developments in NMR techniques have significantly advanced the structure elucidation of organic compounds, even for samples in sub-milligram quantities. NMR techniques are indispensable in current organic chemistry, especially for the identification of scarce complex natural products. However, analysis of NMR spectra of a natural product with similar structural subunits might cause misassignment of overlapping or close signals, leading to an incorrect structural determination.

Haouamines A and B (Scheme 1, i), isolated from a marine tunicate by Zubía and co-workers,[1] are structurally unique alkaloids possessing strong cytotoxicity against the HT-29 human colon carcinoma cell line (haouamine A; IC_{50} = 200 nM). Although haouamine A (**1**) was synthesized by Baran in 2006,[2] no total synthesis of haouamine B (**2**) has been reported. In 2012, Trauner and Zubía[3] reported that the initially proposed haouamine B (**2**) should be revised to **3** based on careful analysis of the ^{1}H NMR spectra of natural haouamine B pentaacetate. However, this was not the end of the 'haouamine saga'. In fact, the group of Professor Hidetoshi Tokuyama at Tohoku University (Japan) just recently settled the matter by means of the first total synthesis of (–)-haouamine B pentaacetate.

In 2011, Tokuyama's group reported the synthesis of indeno-dihydropyridone **4**,[4] as a partial structure of the initially proposed haouamine B (**2**) (Scheme 1, ii). Professor Tokuyama said: "This was the first project undertaken since I moved to Tohoku University. We were excited that a quite unusual intramolecular Friedel–Crafts reaction via an azetidium carbocation **5** was promoted by TfOH, which facilitated smooth construction of the quaternary carbon center." According to Professor Tokuyama, of interest was the observation that the stereochemistry of the key intermediate **6** was opposite to that predicted by Ellman's report[5] for the stereocontrolled synthesis of β-lactam **7**.

Professor Tokuyama and co-workers focused on the synthesis of the 1,2,3,4-tetrasubstituted benzene ring in the revised haouamine B (**3**) (Scheme 1, iii). However, treatment of compound **8** under the established conditions did not give the desired compound **9**. Instead, the unexpected indeno-β-lactam **10** in 37% yield (in dichloromethane), or the debrominated compound **11** in 34% yield (in acetonitrile) were obtained. "The unexpected reaction outcomes would be caused by the additional methoxy group, reducing nucleophilicity of C2b carbon by the steric repulsion and the electron-withdrawing effect (*meta* to the C2b position) of the methoxy group," explained Professor Tokuyama.

The Japanese researchers then switched the bromine atom to a benzyloxy group to suppress the *ipso* substitution (Scheme 2); however, reaction of **12** provided the undesired chromane **13** in 44% yield, presumably via oxonium ion **14** by nucleophilic addition of the ethereal oxygen atom to the carbocation. Finally, Professor Tokuyama and co-workers found that the triisopropylsilyl (TIPS) group was effective for promoting the desired conversion. In this case, the authors established very mild conditions [$Sc(OTf)_3$ and 2,6-di-*tert*-butylpyridine] to avoid the undesired formation of chromane **13** through acidic removal of the TIPS group. After palladium-catalyzed removal of the TIPSO group, the indane-fused β-lactam **15** was converted into indeno-dihydropyridone **16**.

While facing the problem of constructing the paracyclophane skeleton in 2011, the Tokuyama group members were among those in Japan who suffered from the Great East Earthquake in Sendai. Professor Tokuyama said: "Our research facilities were severely damaged, and I realized we had to stop our research for several months. Fortunately, Professors Dirk Trauner (University of Munich) and Oliver Reiser (University of Regensburg) offered us an opportunity to send my graduate student Mr. Yuichi Momoi to Professor Trauner's laboratories at the University of Munich for three months to learn the detailed protocol for the paracyclophane skeleton. Finally, we synthesized the revised structure of haouamine B pentaacetate (**17**) and confirmed its absolute configuration."

Professor Tokuyama said: "We greatly appreciate their warm support and kind cooperation. We also received invaluable information on the formation of aza-paracyclophane from Professor Trauner and Dr. Maria Matveenko. We appreciate financial support from the Alexander von Humboldt Foundation, the German Chemical Society, for Mr. Momoi's stay," concluded Professor Tokuyama.

Matteo Zanda

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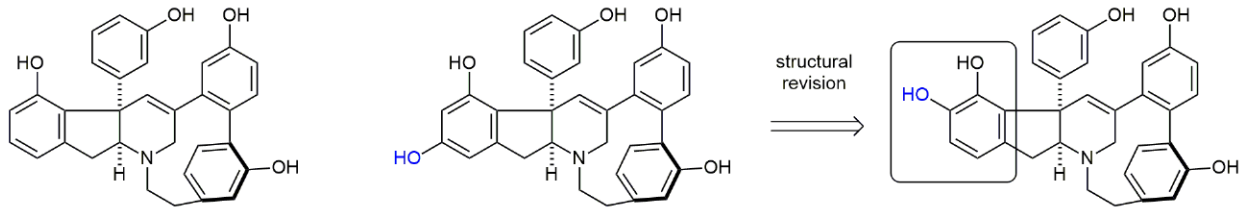
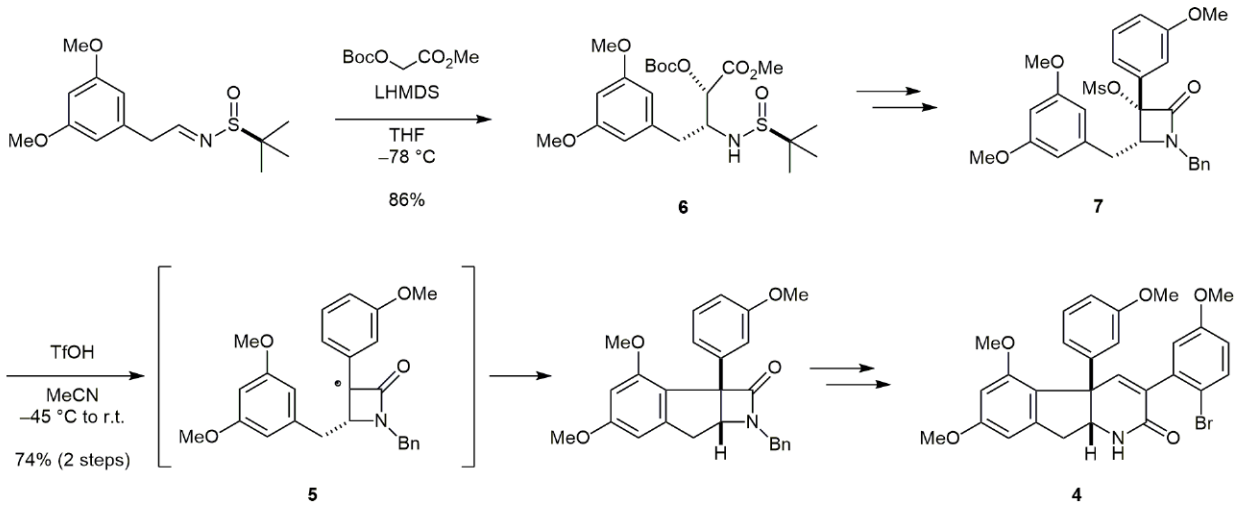
(i) Structural revision of haouamine B (Trauner and Zubía, *J. Am. Chem. Soc.* **2012**, *134*, 9291.)



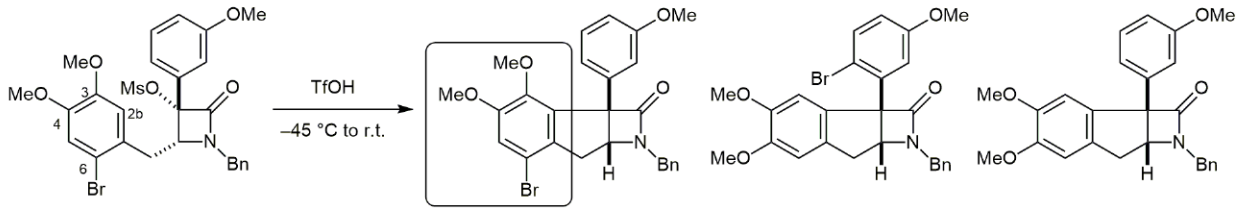
(–)-haouamine A (**1**) | initially proposed structure of haouamine B (**2**) | revised structure of haouamine B (**3**)

(ii) Previous work (Tokuyama, *Synlett* **2011**, 73.)



6 | **7** | **5** | **4**

(iii) Unexpected cyclization (this work)



8 | **9** not detected | **10** 37% (in CH_2Cl_2) | **11** 34% (in MeCN)

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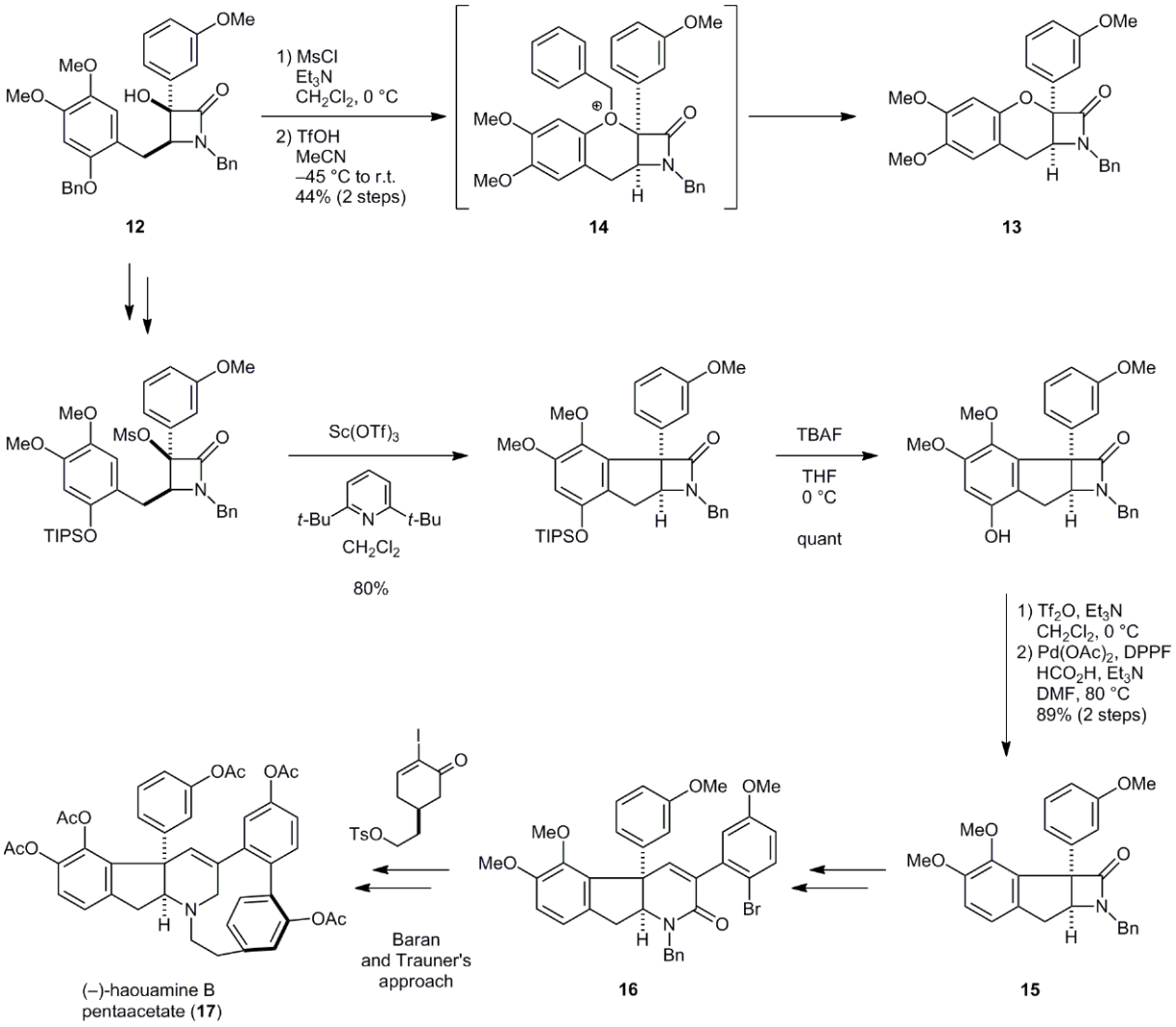

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(5) T. P. Tang, J. A. Ellman *J. Org. Chem.* **2002**, *67*, 7819.

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About the authors

Prof. H. Tokuyama

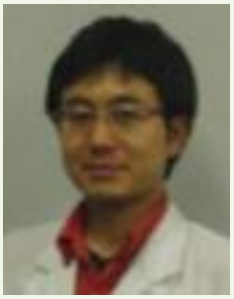
Hidetoshi Tokuyama was born in Yokohama (Japan) in 1967. He received his PhD in 1994 from the Tokyo Institute of Technology (Japan) under the direction of Professor Ei-ichi Nakamura. He spent one year (1994–1995) at the University of Pennsylvania (USA) as a JSPS postdoctoral fellow with Professor Amos B. Smith, III. He joined the group of Professor Tohru Fukuyama at the University of Tokyo in 1995 and was appointed associate professor in 2003. In 2006, he moved to Tohoku University (Japan), where he is currently a professor of pharmaceutical sciences. His research interests include the development of synthetic methodologies and the total synthesis of natural products.

Prof. K. Okano

Kentaro Okano was born in Tokyo (Japan) in 1979. He received his BS degree in 2003 from Kyoto University (Japan) under the supervision of Professor Tamejiro Hiyama. He then moved to the laboratories of Professor Tohru Fukuyama at The University of Tokyo (Japan) and started his PhD research on synthetic studies toward the antitumor antibiotic yatakemycin using a copper-mediated aryl amination strategy. In 2007, he joined the faculty at Tohoku University (Japan), where he is currently an assistant professor in Professor Hidetoshi Tokuyama's group. In 2014, he visited Professor Amir Hoveyda's laboratories at Boston College (USA) as a visiting researcher. His current research interest focuses on natural product synthesis based on the development of new synthetic methodologies.

Prof. K. Sugimoto

Kenji Sugimoto completed his PhD in 2005 under the guidance of Professor Masataka Ihara at Tohoku University (Japan) and spent a year in the same group as a research assistant. He then joined the research group of Professor Hidetoshi Tokuyama at Tohoku University as an assistant professor. In 2010, he moved to University of Toyama (Japan) as an assistant professor in the research group of Professor Yuji Matsuya and was promoted to the position of associate professor in 2012. His research interests are the development of novel domino reactions, their applications in total synthesis, and the synthesis of biologically active compounds.



Y. Momoi

Yuichi Momoi completed his undergraduate studies in the research group of Professor Hidetoshi Tokuyama (Tohoku University, Japan) in 2010. He then continued on in the same laboratory to pursue his PhD studies. He stayed at the research group of Professor Dirk Trauner (Ludwig Maximilians University Munich, Germany) for three months in 2011.

K. Okuyama

Keiichiro Okuyama received his BS degree in 2006 from Tohoku Pharmaceutical University (Japan), where he carried out undergraduate research under the supervision of Professor Tadashi Kato. He then moved to the laboratories of Professor Hidetoshi Tokuyama, Tohoku University and began his PhD research on synthetic studies toward haouamine B. In 2011, he received his PhD, and is currently working for Astellas Pharma Inc. as a drug discovery researcher.

H. Toya

Hiroki Toya received his PhD in 2012 under the guidance of Professor Hidetoshi Tokuyama at Tohoku University (Japan). Now, he works for Astellas Pharma Inc. (Japan) as a medicinal chemist.

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