Natural Product Synthesis

DOI: 10.1002/anie.201407686

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

*Yuichi Momoi, Kei-ichiro Okuyama, Hiroki Toya, Kenji Sugimoto, Kentaro Okano, and Hidetoshi Tokuyama**

Dedicated to Professor Amos B. Smith, III on the occasion of his 70th birthday

Abstract: *The enantiocontrolled total synthesis of (−)-haouamine B pentaacetate was accomplished via an optically active indane-fused β-lactam, which was prepared by a newly developed Friedel–Crafts reaction. Subsequent cleavage of the β-lactam and an intramolecular McMurry coupling reaction provided the core indane-fused tetrahydropyridine, which led to the elucidation of the structure, as proposed by Trauner and Zubía.*

Haouamines were isolated from a tunicate, *Aplidium haouarianum*, at the southern coast of Spain by Zubía and co-workers in 2003.[1] They exhibit highly specific and strong cytotoxicity against the HT-29 human colon carcinoma cell line (haouamine A; $IC_{50} = 200$ nM). Structurally, haouamines have unique features, such as the *cis*-fused indeno-tetrahydropyridine and 3-aza-[7]-paracyclophane containing a bent aromatic ring. The intriguing structure of haouamine A was elucidated by X-ray crystallographic analysis[1] and through total synthesis by Baran and Burns.[2a] The structure of haouamine B (**1**) was also determined by Zubía in 2003 using 2D NMR data. Very recently, however, Trauner and Zubía reported an inconsistency between the ^{1}H NMR spectra of the natural compound and that of their synthetically obtained haouamine B.[3] After careful inspection of the ^{1}H NMR spectra of the synthetic **1** and natural haouamine B, they concluded that the initially proposed structure of haouamine B, **1**, should be revised to **2** (Figure 1).

The total synthesis of this newly proposed structure of haouamine B (**2**) should end the argument regarding the structure, but this has not been achieved despite considerable synthetic endeavors to construct the indeno-tetrahydropyridine core and cyclophane moiety in the haouamine family of compounds.[4,5] Herein we describe the first enantiocontrolled synthesis of natural haouamine B (**2**), based on the development of a mild Friedel–Crafts alkylation of the azetidium ion for the construction of the sterically hindered dihydroxyindeno-tetrahydropyridine and confirm the newly proposed structure by Trauner and Zubía.

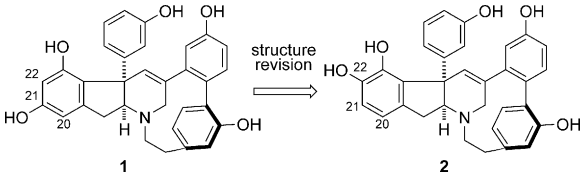

Figure 1. Revision of the structure of haouamine B. **1**: initially proposed structure, **2**: newly proposed structure by Trauner and Zubía.

The retrosynthetic analysis of structure **2** is depicted in Scheme 1. Considering the utilization of Baran's protocol,[2c] we set indane-fused dihydropyridone **3** as a key intermediate for **2**. On the basis of our preliminary synthetic studies on the initially proposed structure **1**,[5b] the dihydropyridone would be formed through an intramolecular McMurry coupling[6] of **4**, which should be derived through the ring-opening of β-lactam **5**. The *cis*-fused β-lactam **5** should be accessible from mesylate **8** by an intramolecular Friedel–Crafts alkylation of the cationic species **7**. The cyclization should proceed at the hindered C2b position to form the 1,2,3,4-tetrasubstituted aromatic ring. Therefore, mesylate **8** should have a removable substituent R, such as a halogen atom or a pseudohalogen moiety, at the less-hindered C6 position. Mesylate **8** would be derived from β-aminoester **9**, which we planned to prepare by Ellman's diastereoselective Mannich reaction using optically active sulfinimine **10** and glycolate **11**.[7]

We started the synthesis by preparing sulfinimine **17** from the known allylbenzene derivative **13**, which was readily available from 3,4-dimethoxyphenol (**12**) (Scheme 2).[8] Dihydroxylation of alkene **13** afforded diol **14** in 96% yield over four steps. After the oxidative cleavage of diol **14**, dehydrative condensation of the resultant aldehyde **15** and optically active sulfinamide **16**[7] provided the corresponding sulfinimine **17**. Using **17**, we then examined the diastereoselective Mannich reaction. Thus, treatment of **17** with a lithium enolate, prepared from *O*-Boc glycolate **11**,[9] provided β-aminoester **18** as a single isomer in 86% yield. Interestingly, unlike in the

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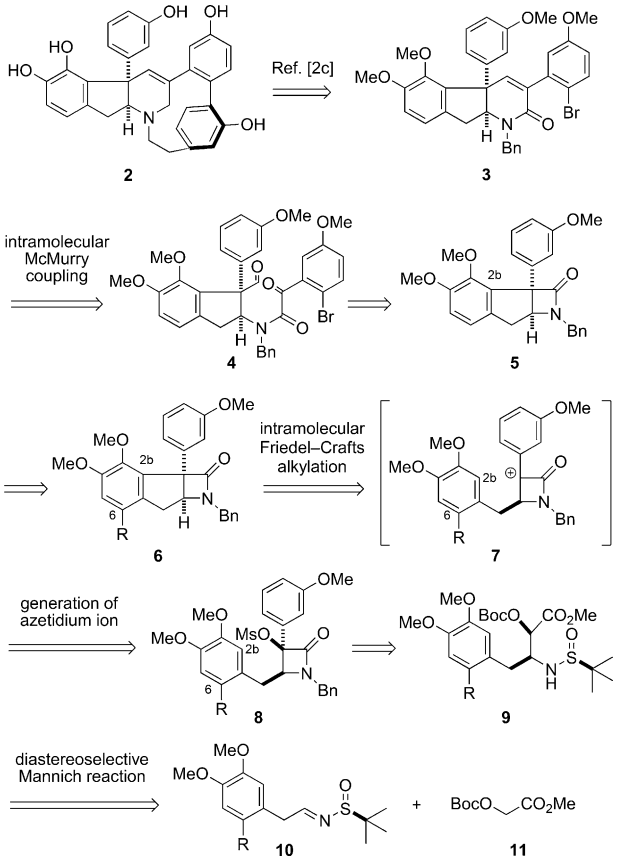
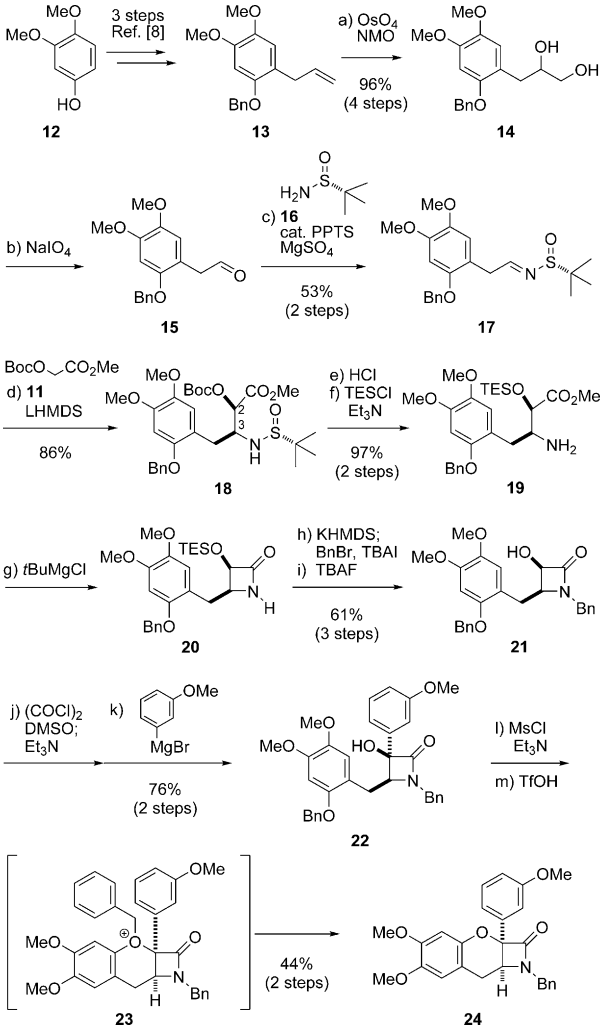
[**] This work was financially supported by the Cabinet Office, Government of Japan, through its "Funding Program for Next Generation World-Leading Researchers" (LS008), the JSPS KAKENHI, a Grant-in-Aid for Scientific Research (B) (20390003) and Scientific Research (A) (26253001), the Nagase Science and Technology Foundation for H.T., a Grant-in-Aid for Young Scientists (B) (19790004) for K.S., and JSPS predoctoral fellowship for Y.M. We thank Prof. D. Trauner for his valuable suggestions on the formation of the aza-paracyclophane, and Professors H. Ishibashi and T. Taniguchi (Kanazawa Univ.) for their valuable discussions on the reduction of the unsaturated lactam.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201407686.



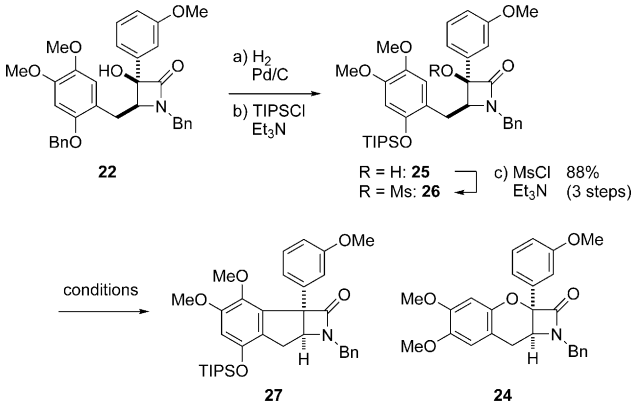
Scheme 1. Retrosynthetic analysis of haouamine B (**2**).



Scheme 2. Preparation of the optically active β-aminoester **18**. Reagents and conditions: a) OsO_4 (1 mol%), NMO, THF/*t*BuOH/H_2O, RT, 96% (over 4 steps); b) $NaIO_4$, MeOH/H_2O, RT; c) **16**, cat. PPTS, $MgSO_4$, CH_2Cl_2, RT, 53% (over 2 steps); d) **11**, LHMDS, THF, −78 °C, 86% (sole isomer); e) HCl, MeOH/1,4-dioxane, 0 °C→RT; f) TESCl, Et_3N, CH_2Cl_2, 0 °C→RT, 97% (over 2 steps); g) *t*BuMgCl, THF, 0 °C; h) KHMDS, THF, −78 °C, then BnBr, TBAI, −78→0 °C; i) TBAF, THF, 0 °C, 61% (over 3 steps); j) $(COCl)_2$, DMSO, CH_2Cl_2, −78→−45 °C, then Et_3N, −45→0 °C; k) 3-methoxyphenyl magnesium bromide, THF, 0 °C, 76% (over 2 steps); l) MsCl, Et_3N, CH_2Cl_2, 0 °C; m) TfOH, CH_3CN, −40 °C→RT, 44% (over 2 steps). NMO = *N*-methylmorpholine oxide, PPTS = pyridinium *p*-toluenesulfonate, LHMDS = lithium hexamethyldisilazide, TES = triethylsilyl, KHMDS = potassium hexamethyldisilazide, TBAI = tetra-*n*-butylammonium iodide, TBAF = tetra-*n*-butylammonium fluoride, DMSO = dimethylsulfoxide.

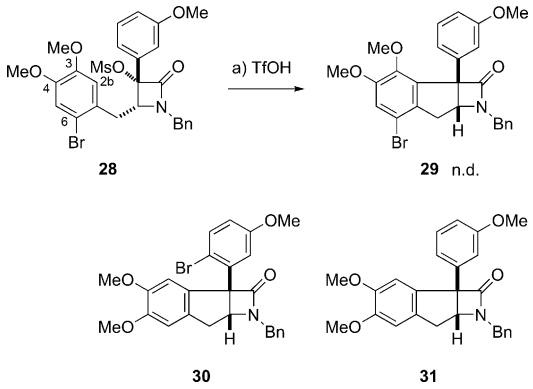
related report by Qin and co-workers, who used an arylsulfinimine,[9] the absolute configuration of the C2 and C3 positions was 2*R* and 3*S*, which was determined by comparison of specific rotations after transformation of **18** to a known compound.[10] Having successfully constructed the consecutive stereogenic centers, we then focused on the intramolecular Friedel–Crafts alkylation of the tertiary alcohol **22**.[5b] After manipulation of protecting groups, the resultant compound **19** was subjected to the Merck protocol[11] to provide β-lactam **20**. *N*-Benzylation and subsequent removal of the TES group gave the secondary alcohol **21**, which was converted to substrate **22** for the key Friedel–Crafts alkylation through Swern oxidation and diastereoselective 1,2 addition of an aryl Grignard reagent to the azetidin-2,3-dione.[12] Conversion of the tertiary alcohol to its mesylate,[13] which was treated with TfOH,[5b] unexpectedly afforded chromane **24** in 44% yield. The reaction proceeded through a nucleophilic attack of the oxygen atom of the benzyl ether to form the six-membered oxonium intermediate **23** followed by the removal of the benzyl cation.[14]

To circumvent the undesired cyclization, we switched the benzyl group to the more bulky TIPS group with the intention of reducing the nucleophilicity of the oxygen atom and investigated a variety of Brønsted/Lewis acids (Scheme 3). After hydrogenolysis of the benzyl ether, introduction of the TIPS group followed by mesylation of the tertiary alcohol afforded substrate **26** for the Friedel–Crafts alkylation. Treatment of **26** with TfOH in acetonitrile provided chromane **24** in 36% yield (Scheme 3, entry 1). In this case, the TIPS ether was primarily deprotected, and subsequent cyclization to the carbocation from the generated phenolic hydroxy group provided chromane **24**. Next, we examined a variety of Lewis acids for preventing the undesired protodesilylation and found that $Sc(OTf)_3$[15] was a superior acid to selectively afford indeno-β-lactam **27**, albeit in low yield (Scheme 3, entry 2). Speculating that the low yield was attributed to the in situ generation of TfOH, we performed



Entry	Solvent	Reagents	*T* (°C)	**27** (%)	**24** (%)
1	CH_3CN	TfOH	–40 to RT	–	36
2	CH_2Cl_2	$Sc(OTf)_3$	0 to RT	14	trace
3	CH_2Cl_2	$Sc(OTf)_3$, DTBPy	0 to RT	80	–

Scheme 3. Successful intramolecular Friedel–Crafts alkylation. Reagents and conditions: a) H_2 (1 atm), Pd/C (20 mol%), EtOAc/EtOH, RT; b) TIPSCl, Et_3N, DMF, 0°C; c) MsCl, Et_3N, CH_2Cl_2, 0°C, 88% (over 3 steps). TIPS = tri-*iso*-propylsilyl, DTBPy = 2,6-di-*tert*-butylpyridine.

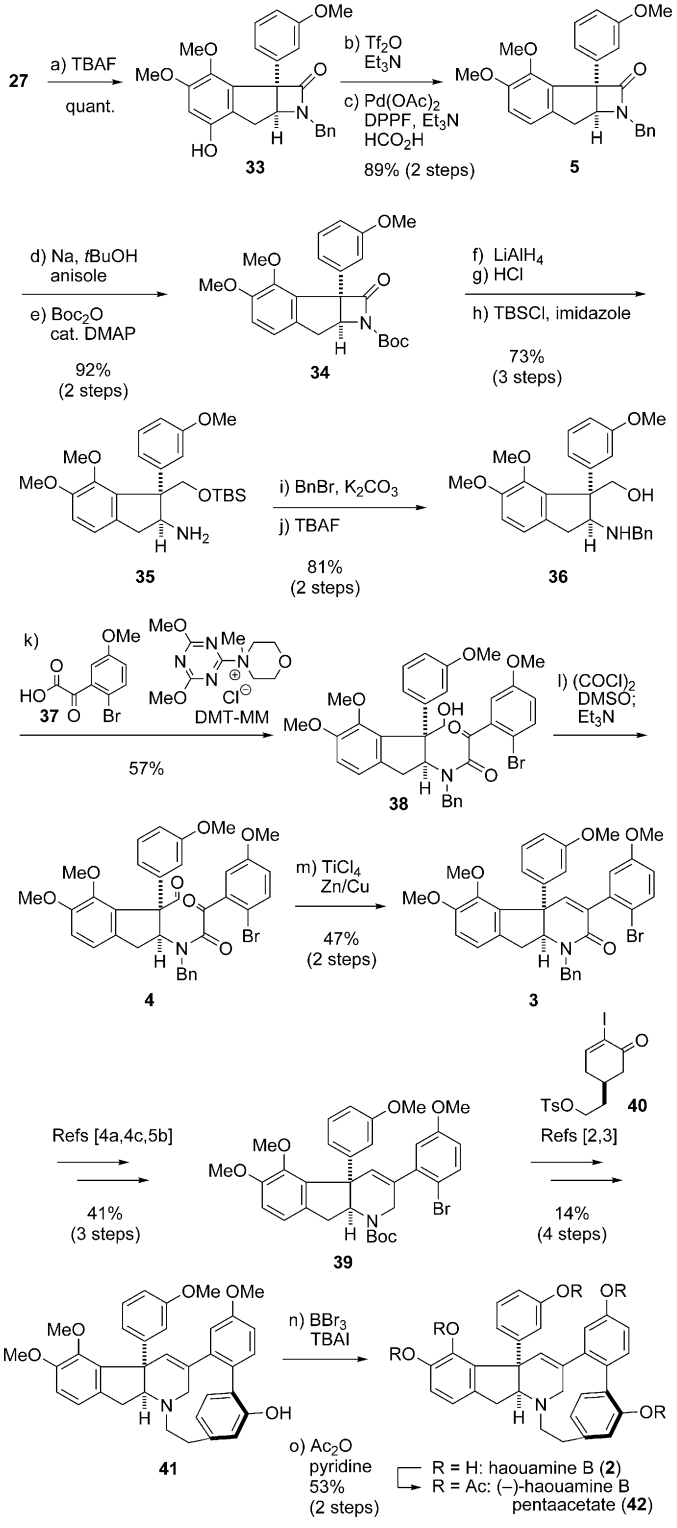


Scheme 4. Preliminary trials in the Friedel–Crafts alkylation. Reagents and conditions: a) TfOH, CH_3CN, −40°C→RT or TfOH, CH_2Cl_2, −40°C→RT. n.d. = not detected.

Scheme 5. Total synthesis of (−)-haouamine B pentaacetate (**42**). Reagents and conditions: a) TBAF, THF, 0°C, quant.; b) Tf_2O, Et_3N, CH_2Cl_2, 0°C; c) $Pd(OAc)_2$, DPPF, HCO_2H, DMF, 80°C, 89% (over 2 steps); d) Na, *t*BuOH, anisole, liq. NH_3/THF, −78°C; e) Boc_2O, DMAP, CH_2Cl_2, 0°C, 92% (over 2 steps); f) $LiAlH_4$, THF, 0°C; g) HCl, CH_2Cl_2/1,4-dioxane, 0°C→RT; h) TBSCl, imidazole, CH_2Cl_2/DMF, RT, 73% (over 3 steps); i) BnBr, K_2CO_3, CH_3CN, 0°C→RT; j) TBAF, THF, 60°C, 81% (over 2 steps); k) **37**, DMT-MM, THF, RT, 57%; l) $(COCl)_2$, DMSO, CH_2Cl_2, −78→−45°C, then Et_3N, −45→0°C; m) $TiCl_4$, Zn/Cu, DME, 0°C→reflux, 47% (over 2 steps); n) BBr_3, TBAI, CH_2Cl_2, 0°C; o) Ac_2O, pyridine, 0°C→RT, 53% (over 2 steps). TBAF = tetra-*n*-butylammonium fluoride, Tf = trifluoromethanesulfonyl, DPPF = 1,1′-*bis*(diphenylphosphino)ferrocene, DMAP = *N*,*N*-dimethyl-4-aminopyridine, TBS = *tert*-butyldimethylsilyl, DMF = *N*,*N*-dimethylformamide, DMT-MM = 4-(4,6-dimethoxy[1,3,5]triazin-2-yl)-4-methylmorpholium chloride, DMSO = dimethylsulfoxide, DME = 1,2-dimethoxyethane, TBAI = tetra-*n*-butylammonium iodide, Ac_2O = acetic anhydride.

the reaction in the presence of 2,6-di-*tert*-butylpyridine (DTBPy). As expected, the desired compound **27** was obtained in 80% yield with the labile TIPS group intact (Scheme 3, entry 3).

The silyloxy blocking group was essential for the Friedel–Crafts alkylation (Scheme 4). We first tested substrate **28**[16] with a bromo group in accordance with Rawal's synthesis of



haouamine A,[4e] providing not only the desired compound **29**, but also the unexpected indeno-β-lactam **30** in 37% yield (in dichloromethane) and the debrominated compound **31** in 34% yield (in acetonitrile).[17]

We then focused on the construction of the indenotetrahydropyridine core (Scheme 5). Initially, the OTIPS group was reductively removed via the corresponding triflate to give key intermediate **5**. The β-lactam was reductively cleaved after switching the benzyl group to the Boc group to enhance the electrophilicity of the carbonyl group. Thus, the benzyl group was removed by Birch reduction in the presence of excess anisole to prevent over-reduction of the aromatic ring.[18] Reduction of *N*-Boc-β-lactam **34** with $LiAlH_4$ proceeded to give the primary alcohol. Subsequent removal of the Boc group and protection of the hydroxy group provided primary amine **35**, which was converted to ketoamide **38** through condensation of **36** and α-keto acid **37** using DMT-MM.[19] The sterically hindered alcohol was smoothly converted by Swern oxidation to aldehyde **4**, which was treated with $TiCl_4$ and Zn/Cu in refluxing DME to give the *cis*-fused indeno-dihydropyridone **3** in 47% yield over two steps.[6] The stage was set for the synthesis of **2**, the newly proposed structure of haouamine B by Trauner and Zubía. According to Ishibashi's conditions,[4c] we transformed lactam **3** to tetrahydropyridine **39** in a three-step sequence. Following Baran's protocol,[2c] we conducted Suzuki–Miyaura cross-coupling of borylated compound **39** and iodocyclohexenone **40**,[2c,20] followed by oxidation of the resulting cyclohexenone to provide aza-paracyclophane **41**.[21] Finally, cleavage of all methyl ethers in **41** by a combination of BBr_3 and TBAI[22] followed by acetylation of the resulting phenolic hydroxy groups provided (−)-haouamine B pentaacetate (**42**) (1.2 mg).[23] Its ^1H and ^{13}C NMR spectra and analytical data were identical to those of pentaacetylated haouamine B from isolated natural haouamine B (**2**) [derived from natural haouamine B by Zubía: $[\alpha]_D^{20} = -27.1$ ($c = 0.14$, $CHCl_3$),[1] synthetic: $[\alpha]_D^{30} = -28$ ($c = 0.17$, $CHCl_3$)].

In summary, we have put an end to the arguments concerning the structure of natural haouamine B by the enantiocontrolled total synthesis of the newly proposed structure of (−)-haouamine B pentaacetate (**42**) from commercially available 3,4-dimethoxyphenol (**12**) in 40 steps in 0.055% overall yield with an average 83% chemical yield for each step. Our synthesis features Ellman's diastereoselective Mannich reaction to generate β-aminoester and the $Sc(OTf)_3$-mediated intramolecular Friedel–Crafts alkylation to construct the unusual indane-fused β-lactam **27**, which was converted to (−)-haouamine B pentaacetate (**42**) through an intramolecular McMurry coupling.

Received: July 28, 2014
Published online: October 3, 2014

Keywords: alkaloids · aromatic substitution · cross-coupling · cyclization · total synthesis

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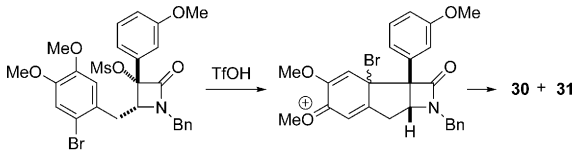
[16] In our early experiments, we examined the reaction with substrate **28**, which has opposite configurations to those of natural haouamine B.

[17] These compounds would be generated via *ipso*-substituted intermediate **32** and subsequent intramolecular transfer or trapping of the bromine atom with a nucleophile to give the

compounds **30** or **31**.



28 32

Compounds **30** and **31** were also obtained by utilizing $Sc(OTf)_3$ and 2,6-di-*tert*-butylpyridine in dichloromethane in 34% and 26% yields, respectively (for details, see the Supporting Information). The structure of compound **30** was determined by the synthesis of **30** using another approach and comparison of ^{1}H NMR spectra. The structure of **31** was determined by X-ray diffraction analysis. CCDC 981399 (**31**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[18] In the absence of anisole, the desired product was obtained in a low yield because of the concomitant over-reduction of the 3-methoxyphenyl group. The excess amount of anisole suppressed the undesired reduction of the 3-methoxyphenyl group, and thus is essential for the high-yielding process.

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[23] We attempted the deacetylation of (−)-haouamine pentaacetate (**42**) to obtain haouamine B (**2**) according to Trauner's protocol in their synthesis of isohaouamine B.[3] Monitoring of the reaction by ESI-MS analysis of aliqots taken from the reaction mixture indicated a progress of smooth deacetylation to mainly provide haouamine B. Disappointingly, however, we failed to isolate haouamine B (**2**) using potassium carbonate in methanol. Treatment of (−)-haouamine pentaacetate (**42**) with 10% NH_4OH in methanol provided a product whose *m*/*z* (ESI mass spectrometry) was corresponding to that of haouamine B (**2**). For details, see the Supporting Information.

