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Formal Total Synthesis of Haouamine A

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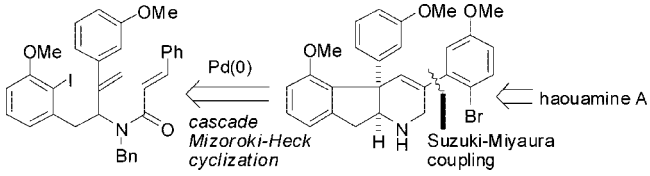


A synthesis of the indenotetrahydropyridine unit of haouamine A is described. The construction of a diaryl quaternary center and tricyclic framework of this compound was achieved by an intramolecular cascade Mizoroki−Heck reaction.

Haouamines A (**1**) and B (**2**) are a new class of cytotoxic alkaloids isolated from the marine ascidian *Aplidium haouarianum* collected off the coast of southern Spain (Figure 1).[1]

Haouamine A exhibits strong and selective anticancer activity in the human colon carcinoma cell line HT-29 ($IC_{50} = 0.1$ μg/mL). In addition to the bioactivity of haouamines A and B, their heptacyclic framework composed of an indenotetrahydropyridine unit and a highly strained 11-membered paracyclophane moiety has attracted much attention from organic chemists.[2−6]x After Baran's first total synthesis of haouamine A,[2] Weinreb and co-worker achieved a formal synthesis of haouamine A using an intramolecular 1,3-dipolar cycloaddition of nitrone,[5a] and Fürstner and co-worker reported a formal synthesis of haouamine A using a transition-metal-catalyzed reaction.[5b] Herein we describe a concise construction of the indenotetrahydropyridine **14**,

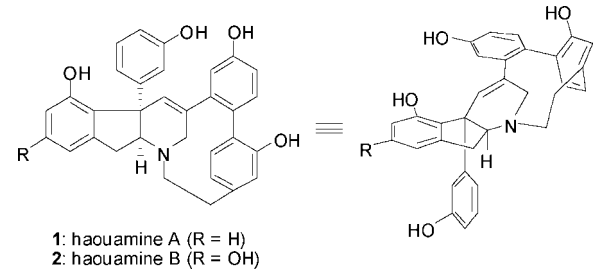
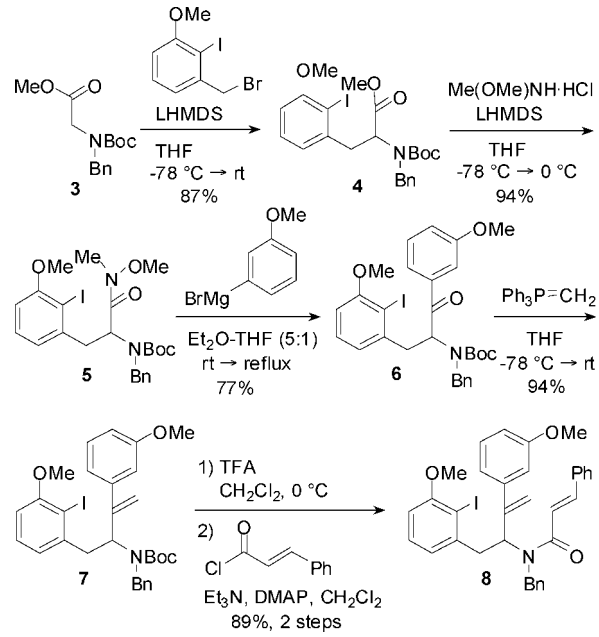


FIGURE 1. Haouamines A and B.

SCHEME 1. Synthesis of Cyclization Precursor 8



Baran's intermediate for the synthesis of haouamine A,[2] using an intramolecular cascade Mizoroki−Heck reaction as the key step.[7−9]

Synthesis of **14** was begun by alkylation of compound **3**,[10] which was readily prepared from glycine methyl ester, with 2-iodo-3-methoxybenzyl bromide[11] to give ester **4** (Scheme 1). After transformation of ester **4** into Weinreb amide **5**, addition of 3-methoxyphenylmagnesium bromide afforded ketone **6** in good yield. Wittig olefination of ketone **6** with $Ph_3P{=}CH_2$ gave alkene **7**, and subsequent removal of the Boc group followed

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(2) For the total synthesis of (±)-haouamine A, see: Baran, P. S.; Burns, N. Z. *J. Am. Chem.Soc.* **2006**, *128*, 3908.

(3) For the total synthesis of (+)-haouamine A, see: Baran, P. S.; Burns, N. Z. *Angew. Chem., Int. Ed.* **2008**, *47*, 205. This paper also corrected the biosynthesis proposed in ref 4.

(4) For a study of biosynthesis of haouamines, see: Gravel, E.; Poupon, E.; Hocquemiller, R. *Chem. Commun.* **2007**, 719.

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(6) For synthetic studies toward haouamines, see: (a) Smith, N. D; Hayashida, J.; Rawal, V. H. *Org. Lett.* **2005**, *7*, 4309. (b) Grundl, M. A.; Trauner, D. *Org. Lett.* **2006**, *8*, 23. (c) Wipf, P.; Furegati, M *Org. Lett.* **2006**, *8*, 1901.

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(8) For reviews on palladium-catalyzed reactions involving the Mizoroki−Heck reaction, see: (a) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945. (b) Tietze, L. E.; Ila, H.; Bell, H. P. *Chem. Rev.* **2004**, *104*, 3453. (c) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442.

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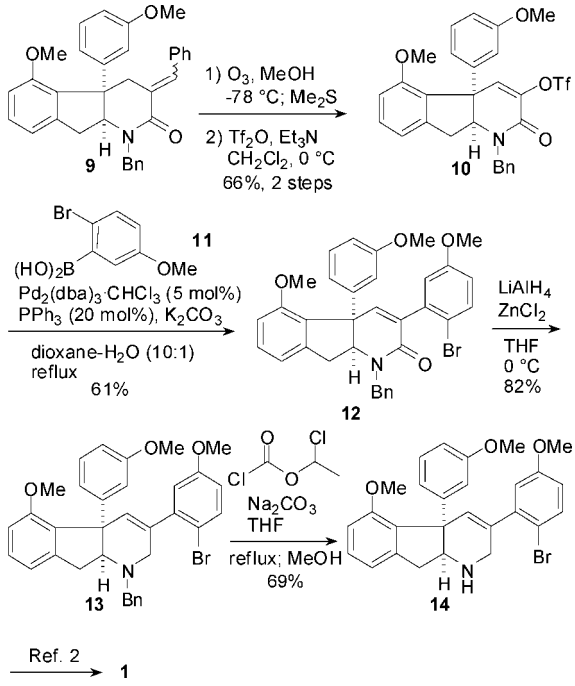
TABLE 1. Cascade Mizoroki−Heck reaction of 8

entry	[Pd]	amine	time (h)	yield (%)
1[a]	$Pd(OAc)_2$	Et_3N	24	60
2[a]	$Pd(OAc)_2$	*i*-Pr_2NEt	12	77
3[b]	$Pd_2(dba)_3 \cdot CHCl_3$	*i*-Pr_2NEt	2.5	99

[a] 20 mol % of PPh_3 was employed. [b] 40 mol % of PPh_3 was employed.

SCHEME 2. Formal Synthesis of Haouamine A



by acylation with cinnamyl chloride afforded compound **8** in good yield.[12]

Next, cascade Mizoroki−Heck cyclization of **8** was examined (Table 1). Treatment of **8** with a catalytic amount of $Pd(OAc)_2$ (10 mol %) in the presence of PPh_3 (20 mol %) and Et_3N (2 equiv) in DMF at 100 °C for 24 h afforded desired tricyclic system **9** in moderate yield (60%) (entry 1). Using *i*-Pr_2NEt in place of Et_3N improved the yield (77%) (entry 2). A combination of a catalytic amount of $Pd_2(dba)_3 \cdot CHCl_3$ (10 mol %) with *i*-Pr_2NEt (2 equiv) gave almost quantitative yield of **9** (entry 3).

Ozonolysis of compound **9** and subsequent treatment with trifluoromethanesulfonic anhydride in the presence of Et_3N afforded compound **10** (Scheme 2). A 2-bromo-5-methoxyphenyl group was readily introduced to compound **10** by Suzuki−Miyaura coupling[13] using boronic acid **11**[14] to give α,β-unsaturated lactam **12**. Reduction of lactam **12** by $LiAlH_4/ZnCl_2$ afforded amine **13** in good yield.

Finally, *N*-debenzylation of **13** was examined. The usual hydrogenolysis with $H_2/Pd-C$ was unsuccessful because of competitive reduction of the olefin and debromination. Acylation with α-chloroethoxylcarbonyl chloride[16] followed by treatment with methanol afforded compound **14**. This compound is Baran's intermediate for the synthesis of haouamine A (**1**). Our spectral data were in accordance with the literature values.[2]

In conclusion, we have achieved a concise synthesis of the indenotetrahydropyridine unit **14** of haouamine A (**1**). Our strategy, based on an intramolecular cascade Mizoroki−Heck reaction, is efficient in terms of simplicity and flexibility. Further investigations directed toward the asymmetric synthesis of **14** based on the use of optically pure aminoester **4** and the total synthesis of haouamine A are now in progress in our laboratory.

Experimental Section

Typical Procedure for the Cascade Mizoroki−Heck Cyclization. A mixture of **8** (1.1 g, 1.75 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (181 mg, 0.175 mmol), triphenylphosphine (184 mg, 0.699 mmol), and diisopropylethylamine (452 mg, 3.49 mmol) in DMF (10 mL) was heated at 100 °C for 2.5 h. The reaction mixture was diluted with water and extracted with Et_2O, and the organic layer was washed with brine. After drying ($MgSO_4$), the mixture was concentrated and chromatographed on silica gel (hexane/AcOEt, 4:1) to give **9** (871 mg, 99%, *E*/*Z* = 14:1) as a colorless amorphous solid: IR ($CHCl_3$) ν 1603, 1628 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, for a major isomer) δ 2.85 (1H, dd, J = 14.4, 2.2 Hz), 3.11 (1H, dd, J = 16.7, 7.1 Hz), 3.22 (1H, d, J = 12.9 Hz), 3.46 (1H, d, J = 12.7 Hz), 3.65 (3H, s), 3.72 (3H, s), 4.136 (1H, dd, J = 6.6, 4.2 Hz), 4.139 (1H, d, J = 14.6 Hz), 5.23 (1H, d, J = 14.6 Hz), 6.43 (1H, s), 6.56−6.80 (5H, m), 7.06−7.35 (12H, m); ^{13} CNMR (125 MHz, $CDCl_3$, for a major isomer) δ 38.9, 41.2, 48.2, 54.9, 55.0, 58.5, 69.4, 109.3, 111.6, 112.6, 117.5, 118.7, 127.35, 127.40, 127.7, 128.2, 128.6, 128.8, 129.2, 129.7, 130.4, 131.0, 135.9, 136.3, 137.6, 142.9, 146.5, 156.6, 159.5, 166.8; HRMS calcd for $C_{34}H_{31}NO_3$ 501.2304, found 501.2298.

1-Benzyl-5-methoxy-4a-(3-methoxyphenyl)-2-oxo-1,4a,9,9a-tetrahydroindeno[2,1-*b*]pyridin-3-yl Trifluoromethanesulfonate (10). A solution of **9** (530 mg, 1.06 mmol) in MeOH (20 mL) was cooled to −78 °C, and then a stream of ozone was passed through for 10 min. After excess ozone was removed by purging with nitrogen, dimethyl sulfide (328 mg, 5.29 mmol) was slowly added at −78 °C, and the mixture was stirred at room temperature for 1 h. The mixture was concentrated to give a brown oil. To the mixture of the crude material and triethylamine (160 mg, 1.59 mmol) in CH_2Cl_2 (10 mL) was added trifluoromethanesulfonic anhydride (358 mg, 1.27 mmol) at 0 °C, and the mixture was further stirred at room temperature for 1.5 h. The reaction mixture was diluted with saturated $NaHCO_3$ solution and extracted with CH_2Cl_2, and the organic layer was washed with brine. After drying ($MgSO_4$), the mixture was concentrated and chromatographed on silica gel (hexane/AcOEt, 4:1) to give **10** (390 mg, 66%) as colorless crystals: mp 138−139 °C (hexane−AcOEt); IR ($CHCl_3$) ν 1142, 1226, 1426, 1481, 1601, 1647, 1678 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.85 (1H, dd, J = 15.6, 9.8 Hz), 3.22 (1H, dd, J = 15.6, 8.1 Hz), 3.54 (3H, s), 3.72 (3H, s), 3.90 (1H, dd, J = 9.8, 8.1 Hz), 4.36 (1H, d, J = 14.6 Hz), 4.85 (1H, d, J = 14.6 Hz), 6.49 (1H, s), 6.60−6.64 (2H, m), 6.74−6.79 (2H, m), 6.84 (1H, d, J = 7.6 Hz), 6.95−6.97

(12) The cinnamyl group in compound **8** was chosen so as to avoid the isomerization of *exo* olefin into *endo* olefin after the cyclization of **8**.

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(2H, m), 7.07−7.15 (4H, m), 7.25−7.28 (1H, m); ^{13} CNMR (125 MHz, $CDCl_3$) δ 38.9, 49.8, 54.1, 55.1, 55.2, 68.3, 110.3, 111.5, 112.9, 117.3, 118.0, 118.6 (q, $J_{C,F}$ = 320 Hz), 127.4, 127.6, 128.0, 128.3, 128.4, 129.5, 130.2, 135.8, 139.2, 142.2, 143.7, 156.2, 157.4, 159.8. Anal. Calcd for $C_{28}H_{24}F_3NO_6S$: C, 60.10; H, 4.32; N, 2.50. Found: C, 59.98; H, 4.32; N, 2.55.

1-Benzyl-3-(2-bromo-5-methoxyphenyl)-5-methoxy-4a-(3-methoxyphenyl)-1,4a,9,9a-tetrahydroindeno[2,1-*b*]pyridin-2-one (12). The mixture of **10** (320 mg, 0.572 mmol), 2-bromo-5-methoxyphenylboronic acid (**11**) (200 mg, 0.858 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (30 mg, 28.6 μmol), triphenylphosphine (33 mg, 0.114 mmol), and potassium carbonate (154 mg, 1.11 mmol) in dioxane (6 mL) and water (0.6 mL) was heated at 100 °C for 1.5 h. The reaction mixture was diluted with water and extracted with Et_2O, and the organic layer was washed with brine. After drying ($MgSO_4$), the mixture was concentrated and chromatographed on silica gel (hexane/AcOEt, 3:1) to give **12** (208 mg, 61%) as colorless crystals: mp 209−210 °C (AcOEt−MeOH); IR ($CHCl_3$) ν 1267, 1481, 1601, 1655 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.17 (2H, AB, J = 8.9 Hz), 3.50 (3H, s), 3.72 (3H, s), 3.81 (3H, s), 3.97 (1H, td, J = 8.9, 1.5 Hz), 4.51 (1H, d, J = 14.6 Hz), 4.75 (1H, d, J = 14.6 Hz), 6.45 (1H, d, J = 1.5 Hz), 6.69−6.84 (6H, m), 7.03−7.22 (8H, m), 7.44 (1H, d, J = 8.8 Hz); ^{13} CNMR (125 MHz, $CDCl_3$) δ 38.9, 49.9, 54.6, 55.0, 55.2, 55.6, 69.2, 110.0, 111.9, 112.5, 114.3, 114.8, 117.1, 117.2, 118.8, 127.1, 128.20, 128.23, 129.1, 129.5, 129.8, 132.9, 135.8, 137.0, 137.2, 139.5, 143.0, 144.9, 156.3, 158.8, 159.6, 161.9. Anal. Calcd for $C_{34}H_{30}BrNO_4$: C, 68.46; H, 5.07; N, 2.35. Found: C, 68.21; H, 5.13; N, 2.26.

1-Benzyl-3-(2-bromo-5-methoxyphenyl)-5-methoxy-4a-(3-methoxyphenyl)-2,4a,9,9a-tetrahydro-1*H*-indeno[2,1-*b*]pyridine (13). To a suspension of zinc chloride (35.0 mg, 0.252 mmol) in THF (1 mL) was added lithium aluminum hydride (19.0 mg, 0.503 mmol) at 0 °C. After the mixture was stirred at 0 °C for 10 min, a solution of **12** (50 mg, 83.3 μmol) in THF (1.0 mL) was added, and the mixture was further stirred at the same temperature for 20 min. The reaction mixture was continuously treated with water (0.02 mL), 15% NaOH solution (0.02 mL), and water (0.06 mL) at 0 °C and filtered. The solids were thoroughly washed with Et_2O, and the filtrate was concentrated. The residue was chromatographed on silica gel (hexane/AcOEt, 7:1) to give **13** (40.0 mg, 82%) as a colorless amorphous solid: IR ($CHCl_3$) ν 1480, 1590 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.82 (1H, dd, J = 15.1, 7.8 Hz), 3.23 (1H, dd, J = 15.1, 9.8 Hz), 3.42 (2H, AB, J = 9.0 Hz), 3.50 (3H, s), 3.68−3.77 (3H, m), 3.73 (3H, s), 3.79 (3H, s), 5.95 (1H, s), 6.62−6.69 (2H, m), 6.73 (1H, d, J = 2.9 Hz), 6.78 (1H, dd, J = 8.3, 2.7 Hz), 6.84 (1H, d, J = 10.5 Hz), 6.94 (1H, d, J = 7.6 Hz), 7.07−7.20 (8H, m), 7.37 (1H, d, J = 8.8 Hz); ^{13} CNMR (125 MHz, $CDCl_3$) δ 49.8, 55.0, 55.3, 55.52, 55.54, 56.3, 59.4, 70.2, 109.4, 111.3, 113.2, 113.3, 114.1, 116.4, 117.8, 119.9, 126.7, 127.8, 128.0, 128.1, 128.2, 128.7, 132.5, 133.2, 136.8, 138.9, 143.2, 143.3, 148.8, 156.3, 158.7, 159.1; HRMS calcd for $C_{34}H_{32}{}^{79}BrNO_3$ 581.1566, found 581.1558.

3-(2-Bromo-5-methoxyphenyl)-5-methoxy-4a-(3-methoxyphenyl)-2,4a,9,9a-tetrahydro-1*H*-indeno[2,1-*b*]-pyridine (14). A mixture of **13** (30.0 mg, 51.5 μmol), α-chloroethoxylcarbonyl chloride (53.2 mg, 0.515 mmol), and sodium carbonate (546 mg, 5.16 mmol) in THF (2 mL) was heated at reflux for 24 h. After MeOH (2 mL) was added, the mixture was heated at reflux for 1.5 h. The reaction mixture was filtered, and the filtrate was concentrated. The residue was diluted with 10% NaOH solution and extracted with CH_2Cl_2, and the organic layer was washed with brine. After drying ($MgSO_4$), the mixture was concentrated and chromatographed on silica gel (hexane/AcOEt, 1:1) to give **14** (17.5 mg, 69%) as a colorless amorphous solid: IR ($CHCl_3$) ν 1266, 1289, 1466, 1480, 1590, 2932 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.75 (1H, br s), 2.93 (1H, dd, J = 16.1, 4.6 Hz), 3.16 (1H, dd, J = 16.1, 7.1 Hz), 3.52 (1H, d, J = 17.6 Hz), 3.63 (3H, s), 3.67 (1H, dd, J = 7.1, 4.6 Hz), 3.76 (3H, s), 3.77 (3H, s), 3.80 (1H, d, J = 17.6 Hz), 6.35 (1H, s), 6.69 (1H, dd, J = 8.8, 3.2 Hz), 6.73−6.77 (4H, m), 6.83 (1H, t, J = 2.1 Hz), 6.95 (1H, d, J = 7.3 Hz), 7.17 (1H, t, J = 7.8 Hz), 7.26 (1H, t, J = 7.8 Hz), 7.43 (1H, d, J = 8.8 Hz); ^{13} CNMR (125 MHz, $CDCl_3$) δ 36.1, 45.3, 55.16, 55.21, 55.51, 55.53, 66.6, 109.6, 111.3, 112.9, 113.1, 114.2, 116.0, 117.8, 119.5, 128.99, 129.00, 130.0, 132.6, 133.2, 139.4, 143.7, 143.8, 147.5, 157.5, 158.9, 159.6; HRMS calcd for $C_{27}H_{26}{}^{79}BrNO_3$ 491.1096, found 491.1088.

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Supporting Information Available: Expermental procedures for **4**−**8** and ^{1}H and ^{13} CNMR spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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