Synthetic Studies toward Haouamine B: Construction of Indenotetrahydropyridone Skeleton

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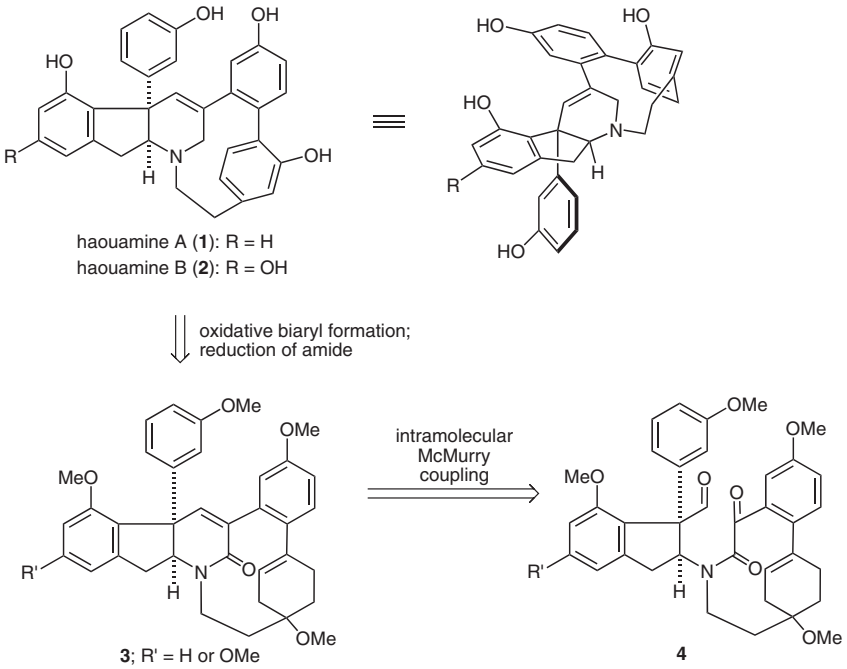
Abstract: Synthetic studies on haouamine B are described. The characteristic indenotetrahydropyridone skeleton was constructed by intramolecular Friedel–Crafts alkylation of mesyloxy β-lactam derivative and intramolecular McMurry coupling as key processes.

Key words: Friedel–Crafts reaction, β-lactam, McMurry coupling, natural products

Haouamines, a family of marine alkaloids, were isolated from a tunicate, *Aplidium haouarianum*, in the southern coast of Spain by Zubía and co-workers.[2] Among them, haouamine A (**1**) exhibits highly specific and strong cytotoxicity against HT-29 human colon carcinoma cell line (IC_{50} = 200 nM). In addition to the significant biological activity, haouamines have the unique structural features such as *cis*-fused indenotetrahydropyridine and highly strained 3-aza[7]paracyclophane containing bent aromatic ring. Therefore, many synthetic efforts have been directed toward these compounds.[3] However, only one total synthesis of haouamine A (**1**) by Baran and co-workers has so far been reported due to its highly strained structure.[4] Regarding haouamine B (**2**), there has been no report on total synthesis and the absolute stereochemistry.

We planned to construct tetrahydropyridine ring in the central part of these molecules by intramolecular McMurry coupling[5] of the advanced intermediate such as **3** having indane segment and macrolactam ring (Scheme 1). After formation of six-membered lactam, reduction of amide function[3d] and oxidative conversion to biaryl structure would lead to haouamines. In this context, we chose compound **5** as a model compound to examine the proposed intramolecular McMurry coupling as well as a possible intermediate for the synthesis of haouamine B, and carried out its synthetic investigations.

Scheme 2 illustrates our retrosynthetic analysis of the substrate **6** for the key reaction. β-Amino aldehyde **6** possessing *cis* stereochemistry would be derived from indane-fused tetracyclic β-lactam **7**. We planned to construct this unusual β-lactam **7** by Friedel–Crafts alkylation of β-lactam derivative **8**, which would be accessible from



Scheme 1 Haouamine A (**1**) and B (**2**), and synthetic strategy

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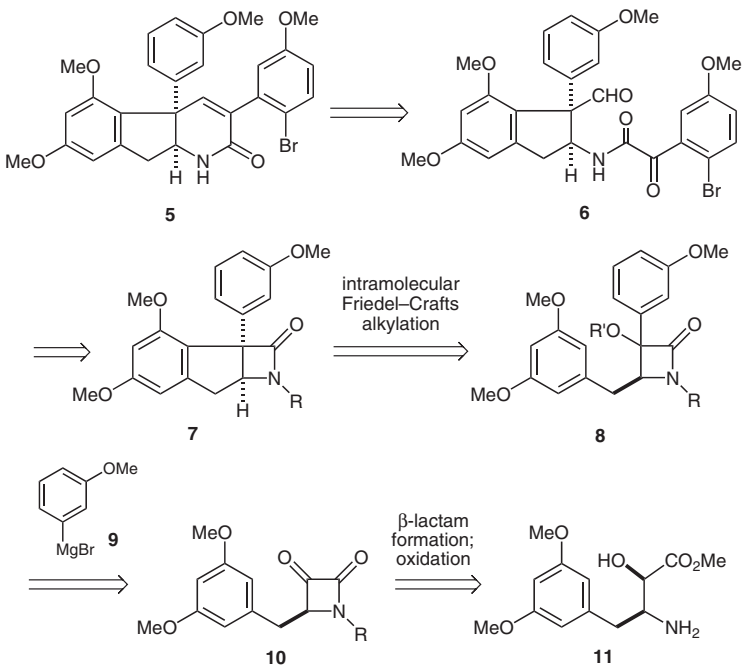


Scheme 2 Retrosynthetic analysis

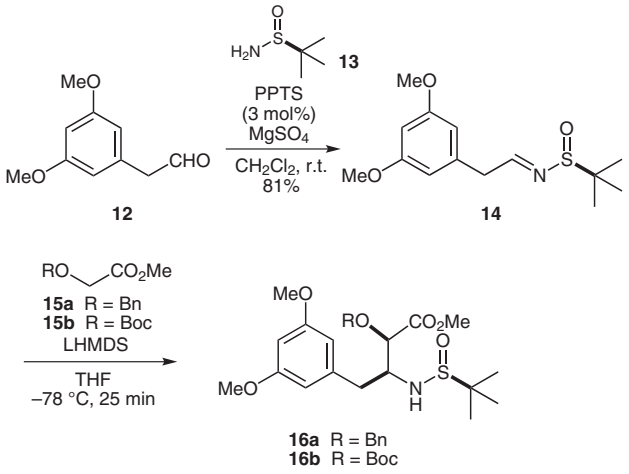
α-hydroxy-β-amino ester **11** by β-lactam formation and 1,2-addition of anisyl Grignard **9** to azetidine-2,3-dione derivative **10**.

Our research commenced with the asymmetric preparation of α-hydroxy-β-amino acid derivative **11** by application of Ellman's diastereoselective Mannich reaction using chiral sulfinamide.[6] Commercially available phenylacetaldehyde derivative **12** was condensed with chiral sulfinamide **13** to give the corresponding sulfinyl imine **14**, which was subjected to Mannich reaction conditions with glycolates **15**. The diastereoselectivity was strongly dependent on the choice of R group on the glycolates oxygen. Thus, reaction of benzyl ether **15a** provided an inseparable mixture of four diastereomers (Table 1, entry 1). In contrast, Qin's modification[7] utilizing Boc-protected compound **15b** gave the desired **16b** as a single product (entry 2).[8]

Having prepared α-hydroxy-β-amino acid derivative **16b** as a single diastereomer, we focused our efforts on construction of the β-lactam-fused indane skeleton (Scheme 3). Acidic removal of *tert*-butylsulfinyl and Boc groups[7] provided the corresponding aminoalcohol hydrochloride **17**. Construction of β-lactam was carried out according to the conventional method[9] to give the *N*-TES-β-lactam, which was then treated with KF to provide **18** in 96% ee.[10] After N-benzylation and conversion to azetidine 2,3-dione in two steps, *m*-anisyl group was introduced by Grignard addition to give the tertiary alcohol **21** as a single isomer.[11] The stage was set for the construction of indane ring by Friedel–Crafts-type cyclization. We found that conversion to the corresponding mesylate **22** and acidic treatment were crucial to promote smooth cyclization.[12] Thus, upon treatment of **22** with triflic acid in acetonitrile, the desired indane-fused β-lactam **23** was obtained in 74% yield from tertiary alcohol **21**.[13] This methodology was effective to construct the β-lactam-fused indane skeleton having a quaternary carbon.[14]

We next turned our attention to examine the McMurry coupling strategy for the construction of indenotetrahydropyridone ring. After removal of benzyl group under Birch conditions, indane-fused β-lactam **23** was activated with the Boc group to give **24**. $LiAlH_4$ reduction gave

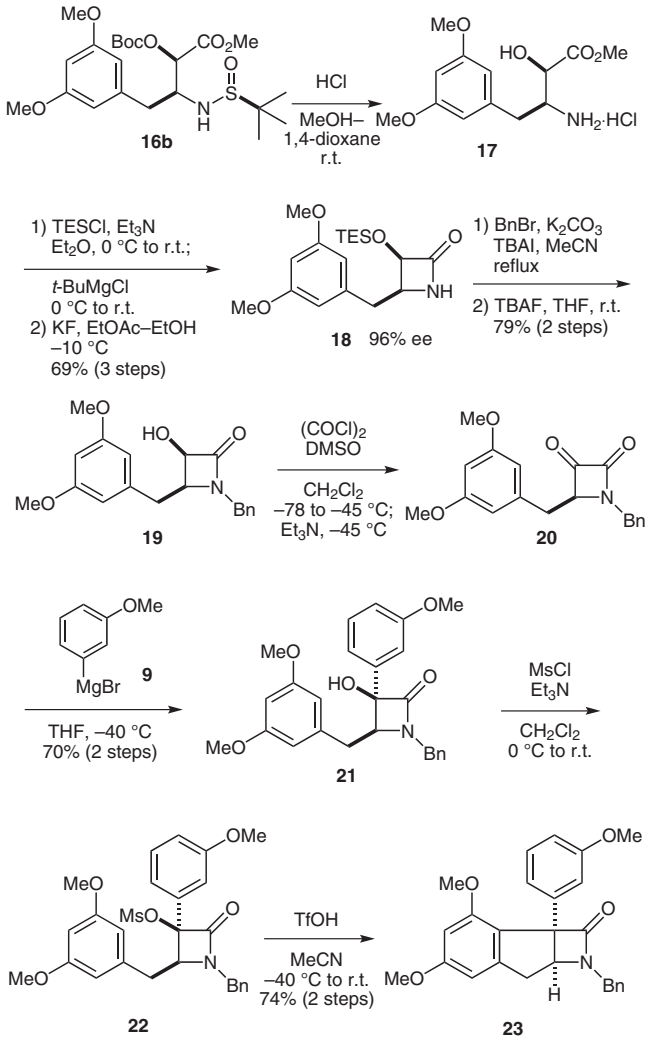
Table 1 Diastereoselective Mannich Reaction



Entry	R	Yield (%)[a]	dr[b]
1	Bn	82	6:2:2:1[c]
2	Boc	80	–[d]

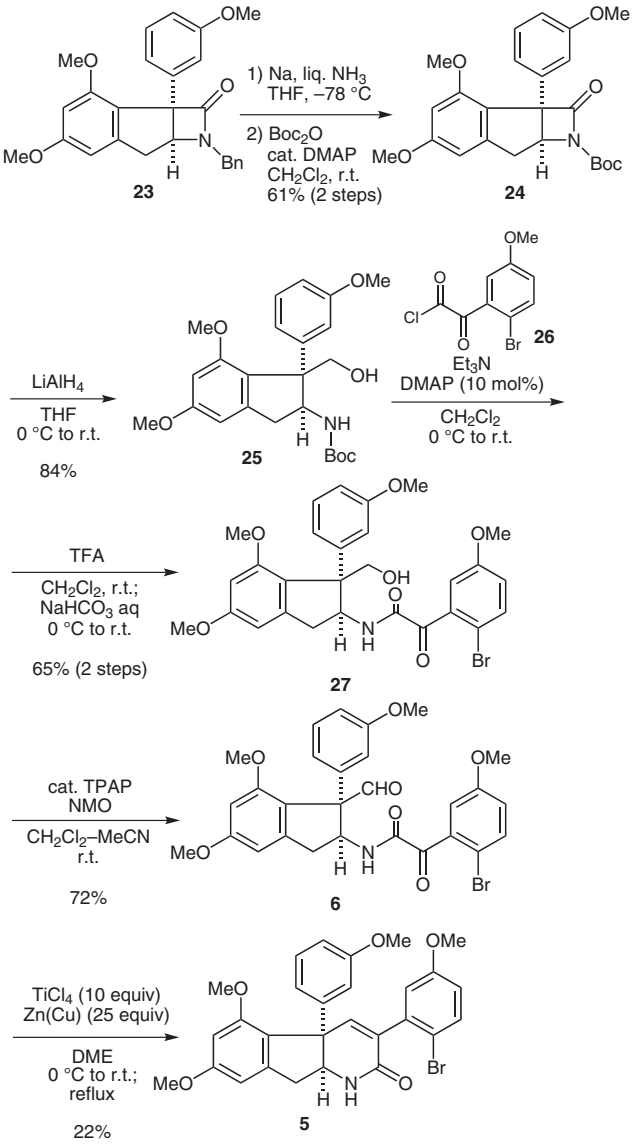
[a] Isolated yields.
[b] Determined by ^{1}H NMR of the crude material.
[c] The stereoselectivity of the diastereomers was not determined.
[d] Single diastereomer.

amino alcohol **25**, which was condensed with acyl chloride **26**. O-Acylation, followed by intramolecular acyl migration gave amide **27** after deprotection of Boc group. Finally, TPAP oxidation gave aldehyde **6**, a substrate for the McMurry coupling reaction. To our delight, upon subjection of aldehyde **6** to reductive conditions using a combination of titanium tetrachloride and zinc–copper couple in DME, the expected intramolecular McMurry coupling took place to give the desired lactam derivative,[15–17] although the yield was unsatisfactory (Scheme 4).



Scheme 3 Construction of indane-fused β-lactam skeleton

In conclusion, synthetic studies on haouamine B were carried out. Indenotetrahydropyridone derivative **5**, which would also be a potential intermediate of haouamine B based on the Baran's synthesis, was stereoselectively constructed through the quite unique indane-fused β-lactam **23**, by highly diastereoselective Mannich reaction of sulfinyl imine derivative, unprecedented Friedel–Crafts cyclization on the β-lactam ring, and intramolecular McMurry coupling. Further extensive optimization of the McMurry coupling and construction of the right-hand segment consisting 3-aza[7]paracyclophane are currently under investigation.



Scheme 4 Synthesis of indenotetrahydropyridone **5** utilizing McMurry coupling

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(8) The relative stereochemistry was determined after derivatization to β-lactam **18**. The absolute stereochemistry was tentatively assigned according to the Qin's proposed transition state (ref. 7).

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(10) The ee was determined by HPLC (Daicel CHIRALCEL OD-H, flow rate: 0.50 mL/min, hexane-*i*-PrOH = 80:20, t_R = 10.0, 13.1 min).

(11) The stereochemistry was tentatively assigned as described based on the general reactivity of 4-substituted azetidine 2,3-dione. For a typical example, see: Kant, J.; Schwartz, W. S.; Fairchild, C.; Gao, Q.; Huang, S.; Long, B. H.; Kadow, J. F.; Langley, D. R.; Farina, V.; Vyas, D. *Tetrahedron Lett.* **1996**, *37*, 6495.

(12) We found that the hydroxyl group should be activated as a mesylate for the smooth and high-yielding process. The O-methylated substrate has a low reactivity, and degradation of the starting material was observed. On the contrary, The O-triflated substrate was found to be unstable.

(13) **Procedure for the Intramolecular Friedel–Crafts Alkylation**: A 30-mL round-bottomed flask equipped with a magnetic stirrer bar and an inlet adapter with three-way stopcock was charged with tertiary alcohol **21** (740 mg, 1.62 mmol). The flask was evacuated and backfilled with argon gas. To the flask was added anhyd CH_2Cl_2 (6.0 mL), and the resulting solution was cooled to 0 °C. To the solution were added Et_3N (0.70 mL, 5.0 mmol) and methanesulfonyl chloride (0.25 mL, 3.2 mmol) at 0 °C, respectively. The reaction mixture was then warmed to r.t. and stirred for 8 h, after which time TLC (hexanes–EtOAc, 1:1) indicated complete consumption of the starting alcohol. The reaction was quenched with sat. aq NH_4Cl, and the mixture was extracted with CH_2Cl_2 (3 ×). The combined organic extracts were washed with brine, dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure to give a crude mesylate (1.1 g), which was used for the next reaction. A 30-mL round-bottomed flask equipped with a magnetic stirrer bar and an inlet adapter with three-way stopcock was charged with the crude mesylate (1.1 g). The flask was evacuated and backfilled with argon gas. To the flask was added anhyd MeCN (20 mL), and the resulting solution was cooled to –40 °C. To the solution was added TfOH (0.70 mL, 7.9 mmol) at –40 °C. The reaction mixture was warmed to r.t. and stirred for 3 h, after which time TLC (hexanes–EtOAc, 3:2) indicated complete consumption of the starting mesylate. After cooling to 0 °C, the reaction mixture was treated with sat. aq $NaHCO_3$, and the mixture was extracted with EtOAc (3 ×). The combined organic extracts were concentrated under reduced pressure to give the crude material, which was purified by column chromatography on silica gel to provide the title compound **23** (495 mg, 1.19 mmol, 74% over 2 steps) as a pale yellow amorphous solid; $[\alpha]_D^{23}$ –67.8 (*c* = 1.15, $CHCl_3$). IR (neat): 2939, 2835, 1747, 1601, 1489, 1456, 1339, 1151, 1078, 1047, 910, 733, 698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.20–7.37 (m, 6 H), 6.88–6.95 (m, 2 H), 6.76–6.81 (m, 1 H), 6.31–6.35 (m, 2 H), 4.66 (d, 1 H, *J* = 15.2 Hz), 4.23 (d, 1 H, *J* = 15.2 Hz), 4.02 (d, 1 H, *J* = 6.4 Hz), 3.79 (s, 3 H), 3.76 (s, 3 H), 3.63 (s, 3 H), 2.99 (dd, 1 H, *J* = 17.6, 6.4 Hz), 2.87 (d, 1 H, *J* = 17.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.8, 161.9, 159.5, 158.3, 144.9, 139.0, 136.0, 129.2, 128.7, 128.1, 127.6, 120.8, 119.1, 112.5, 112.4, 102.0, 98.1, 75.4, 65.3, 55.7, 55.5, 55.1, 43.7, 32.8. HRMS (ESI^+): *m*/*z* [M + Na^+] calcd for $C_{26}H_{25}NO_4Na$: 438.1681; found: 438.1674.

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(15) **Procedure for the Intramolecular McMurry Coupling Reaction**: A 10-mL test tube equipped with a magnetic stirrer bar and an inlet adapter with three-way stopcock was charged with Zn/Cu (6.2 mg, 95 μmol). The flask was flame-dried and backfilled with argon gas. To the flask was added degassed anyhd 1,2-dimethoxyethane (0.18 mL), and the resulting suspension was cooled to 0 °C. To the suspension was added $TiCl_4$ (4.0 μL, 36 μmol), and the mixture was heated at 90 °C for 1.5 h. After the flask was cooled to 0 °C, substrate **6** (2.0 mg, 3.5 μmol) in 1,2-dimethoxyethane (50 μL) was added to the flask. The reaction mixture was warmed to r.t. over 30 min and then heated at 90 °C for 2 h, after which time TLC (hexanes–EtOAc, 1:1) indicated complete consumption of the starting material. After cooling to r.t., the mixture was diluted with EtOAc and filtered through a celite pad. The filtrate was concentrated under reduced pressure to give the crude material, which was purified by preparative TLC providing the title compound **5** (0.42 mg, 0.78 μmol, 22%) as a colorless film. IR (neat): 3302, 2934, 1674, 1599, 1470, 1337, 1290, 1207, 1150, 754 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.45 (d, 1 H, *J* = 8.8 Hz), 7.21–7.26 (m, 1 H), 6.91 (d, 1 H, *J* = 2.4 Hz), 6.78–6.86 (m, 3 H), 6.75 (dd, 1 H, *J* = 8.8, 3.2 Hz), 6.66 (s, 1 H), 6.48 (d, 1 H, *J* = 2.0 Hz), 6.36 (d, 1 H, *J* = 2.0 Hz), 5.66 (s, 1 H), 4.14–4.21 (m, 1 H), 3.83 (s, 3 H), 3.79 (s, 3 H), 3.76 (s, 3 H), 3.59 (s, 3 H), 3.33 (dd, 1 H, *J* = 16.0, 7.6 Hz), 3.08–3.16 (m, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.4, 161.7, 159.8, 158.8, 157.2, 145.1, 143.9, 141.1, 138.9, 134.0, 133.0, 129.3, 122.3, 119.1, 117.2, 115.0, 114.4, 112.9, 112.0, 101.2, 98.3, 77.2, 64.6, 55.6, 55.5, 55.2, 55.1, 41.2. HRMS (ESI^+): *m*/*z* [M + Na^+] calcd for $C_{28}H_{26}{}^{79}BrNO_5Na$: 558.0892; found: 558.0873.

(16) Reduction of the amide is reported using a similar compound by Weinreb (ref. 3d).

(17) Chemical shifts of ^1H NMR and ^{13}C NMR of **5** were in excellent agreement with those of the analogous compound reported by Weinreb (ref. 3d).