Formal total synthesis of (−)-haouamine A†‡

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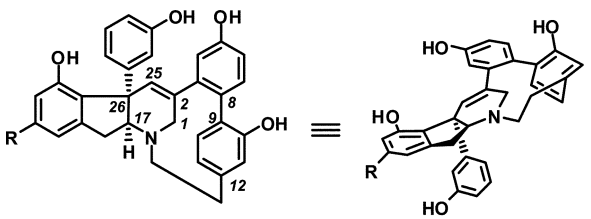
A largely catalysis based approach to optically active haouamine A (−)-1 is presented, which provides the hexacyclic compound 25 previously used to construct this cytotoxic marine alkaloid.

Haouamine A (**1**) and B (**2**) isolated from the marine ascidian *Aplidium haouarianum* collected off the coast of southern Spain represent an unorthodox new class of alkaloids.[1] They consist of a congested indeno-tetrahydropyridine unit fused to an 11-membered paracyclophane moiety which is so strained that one of its phenol rings is forced out of planarity to adopt a pseudo-boat conformation. The synthetic challenges posed by this intricate topology are further increased by an anti-Bredt double bond contained within the heptacyclic framework as well as by the all-carbon quaternary chiral center at C-26. **1** exhibits significant and selective cytotoxicity against the human colon carcinoma cell line HT-29 with an IC_{50} of 0.1 μg mL^{-1}.[1]

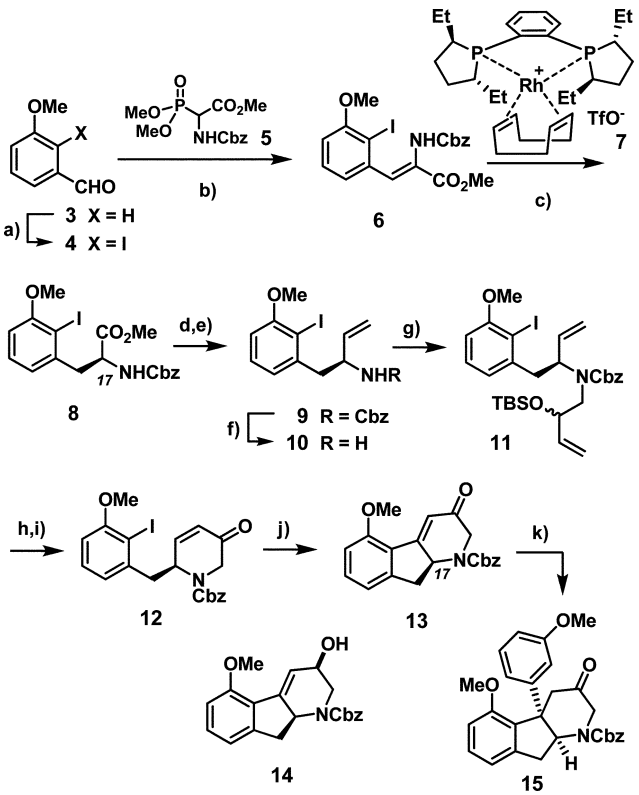


1 *Haouamine A* (R = H)
2 *Haouamine B* (R = OH)

Although several elegant approaches toward the haouamines have been reported in the literature,[2] it was only through a cleverly designed alkyne/pyrone Diels–Alder cycloaddition that Baran and coworkers were able to overcome the deterrent ring strain of these targets;[3–5] more conventional attempts to forge the bent aza-cyclophane motif invariably failed.[2,3] We now disclose a largely catalysis based approach to Baran's hexacyclic key intermediate **25** in optically pure form, which therefore represents a formal total synthesis of the naturally occurring enantiomer (−)-**1**.

Our synthesis commenced with 3-methoxybenzaldehyde **3**, which was selectively iodinated by following a literature route.[6] Reaction of **4** with phosphonate **5**[7] in the presence of DBU gave product **6** in good yield and high diastereoselectivity ($Z : E > 9 : 1$, Scheme 1), which underwent an asymmetric hydrogenation in the presence of the rhodium catalyst **7**[8] to set the directing stereocenter at C-17 exquisitely well (97% > 96% ee, >16 g scale). Slow addition of Dibal-H to a solution of this compound in toluene at −78 °C afforded the corresponding aldehyde which was subjected to a Wittig olefination to give product **9** in good yield without loss of optical purity (97% ee), provided that preformed $Ph_3P{=}CH_2$ was used as the reagent in toluene at 0 °C.[9]

Amine **10** released upon cleavage of the N-Cbz group in **9** underwent a smooth Petasis-type three-component coupling reaction[10] on exposure to formaldehyde and the functionalized allylborane **19**.[11] The latter was best prepared from O-silylated propargyl alcohol **16** *via* hydroboration with pinacolborane in the presence of catalytic amounts of $Cp_2Zr(H)Cl$,[12] followed



Scheme 1 *Reagents and conditions*: (a) ref. 6; (b) **5**, DBU, CH_2Cl_2, 86%; (c) complex **7** (1 mol%), H_2 (20 atm), EtOAc, 97% (>96% ee); (d) Dibal-H, toluene, −78 °C, 90%; (e) $Ph_3P{=}CH_2$, toluene, 0 °C, 84%; (f) HBr–HOAc, CH_2Cl_2, 0 °C, 94%; (g) (i) $[CH_2O]_n$, borane **19**, toluene, 90 °C, 69% (ii) CbzCl, K_2CO_3, EtOAc–H_2O, 94%; (h) (i) second-generation Grubbs catalyst (5 mol%), toluene, 80 °C; (ii) TBAF, THF, 89% (over both steps); (i) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 85%; (j) $Pd(OAc)_2$ (20 mol%), PPh_3 (20 mol%), Ag_2CO_3, MeCN, 65 °C, 75%; (k) CuI, 3-$MeOC_6H_4MgBr$, THF, 0 °C, 61–78%.

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† Dedicated to Prof. Andrew B. Holmes on the occasion of his 65th birthday.

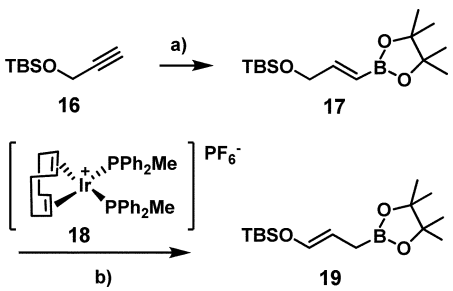
‡ Electronic supplementary information (ESI) available: Experimental part including analytical and spectroscopic data of all new compounds and the crystallographic summary (CCDC 683071). For ESI and crystallographic data in CIF or other electronic format see DOI:10.1039/b805295f

by an iridium catalyzed double bond isomerization (Scheme 2).[11] Borane **19** is sufficiently nucleophilic to intercept the imine primarily formed from **10** and formaldehyde in toluene at 90 °C to give product **11** as a mixture of diastereomers after reprotection with CbzCl under standard conditions. Subsequent ring closing olefin metathesis (RCM) with the aid of the second-generation Grubbs catalyst,[13] followed by oxidation furnished ketone **12** in excellent overall yield and set the stage for an intramolecular Heck reaction[14] to complete the core section of haouamine A.

The Heck cyclization, however, required careful optimization. Only in the presence of Ag_2CO_3 (≥ 1 eq.), which turned out to be the best amongst various silver additives investigated, could this palladium catalyzed C–C-bond formation be reliably effected.[15] The integrity of the resulting tricyclic product **13** was confirmed by X-ray structure analysis of the derived *endo*-configured alcohol **14** which turned out to be a nicely crystalline compound (Fig. 1).

The stereochemical course of the subsequent 1,4-addition of 3-methoxyphenylmagnesium bromide to enone **13** was determined by the adjacent stereocenter such that the required *cis*-annulated ring system was exclusively formed. This reaction was accomplished with the aid of purified CuI[16] and freshly prepared 3-$MeOC_6H_4MgBr$,[17] whereas the use of other copper sources and/or the corresponding lithium donor suffered from lower yields, turned out to be less reproducible, and was even plagued by competing 1,2- rather than 1,4-addition to the hindered enone functionality of **13**.

Next, the regioselective conversion of ketone **15** into the corresponding enol triflate was investigated as the prelude to the final act of the formal total synthesis of **1** (Scheme 3). In line with previous observations reported by Garst and coworkers,[18] treatment of **15** with various bases (KHMDS, NaH, Et_3N *etc.*) and different triflate sources invariably led to enolization toward nitrogen with formation of **20** as the major isomer. This undesirable outcome, however, could be easily rectified by replacement of the N-Cbz group by the 3-butynyl chain that is required for the envisaged intramolecular alkyne/pyrone Diels–Alder cycloaddition. The lone pair on the now basic nitrogen atom in **22** is thought to destabilize the enolate formed upon deprotonation at C-1; hence, equilibration upon warm-up to 0 °C afforded the desired enol triflate **23** as the only observed product upon treatment with 2-pyridyl–NTf_2.[19]



Scheme 2 *Reagents and conditions*: (a) pinacolborane, $Cp_2Zr(H)Cl$ (0.5 mol%), CH_2Cl_2, 0 °C → RT, 70%; (b) complex **18** (1 mol%, pre-activated with H_2, 1 atm), THF, 80%.

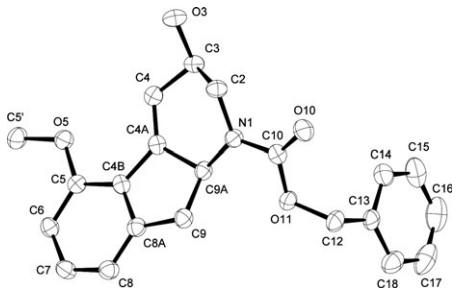
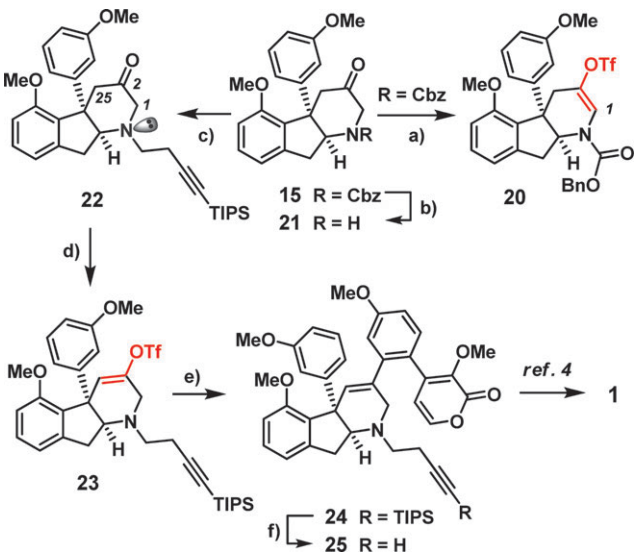


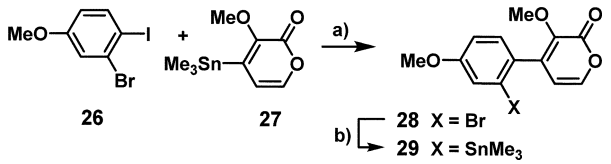
Fig. 1 Molecular structure of **14** from single-crystal X-ray structure determination.‡ Anisotropic displacement parameters are drawn at 50% probability and hydrogen atoms are omitted for clarity.

As expected, the palladium catalyzed reaction of the known stannane **27**[3] exclusively engaged the C–I bond of 1,2-dihalobenzene **26** in cross coupling (Scheme 4).[20,21] Product **28** was then stannylated to provide **29** as a suitably functionalized building block for the completion of the formal total synthesis of **1**.[22]

The Stille coupling of the sterically encumbered partners **23** and **29**, however, was far from trivial (Scheme 3). Attempts to induce coupling with catalytic $[Pd(PPh_3)_4]$ alone engendered rapid decomposition, and even the use of different copper additives,[2b,21,23] which are known to enhance the efficiency of problematic Stille reactions, led to unacceptably low yields of the desired compound. Therefore we were particularly pleased to see that the combination of $[Pd(PPh_3)_4]$ (5 mol%), copper thiophene-2-carboxylate (CuTC)[23a] and the phosphinate salt $[Ph_2PO_2][NBu_4]$[24] in DMF at ambient temperature resulted in a remarkably clean formation of product **24**. The scope of this protocol, which has also served our group well in other complex natural product syntheses,[25] is described in more detail in the accompanying Communication.[26]



Scheme 3 *Reagents and conditions*: (a) *cf.* Text; (b) Pd/C, H_2 (1 atm), MeOH, 94%; (c) $TIPSC{\equiv}C(CH_2)_2I$, $KHCO_3$, MeCN, 90 °C (sealed tube), 70%; (d) KHMDS, THF, −78 °C → 0 °C, then 2-pyridyl–NTf_2, 67% (86% based on recovered starting material); (e) stannane **29**, $Pd(PPh_3)_4$ (5 mol%), CuTC (1.5 eq.), $[Ph_2PO_2][NBu_4]$ (1.5 eq.), DMF, 65% (86% based on recovered substrate); (f) TBAF, aq. THF, 68%.



Scheme 4 *Reagents and conditions*: (a) $Pd(PPh_3)_4$ (5 mol%), CuI (10 mol%), CsF, DMF, 40 °C, 53%; (b) $Me_3SnSnMe_3$, $Pd(PPh_3)_4$ (5 mol%), toluene, reflux, 31%.

Fluoride induced cleavage of the silyl group in product **24** thus formed gave the terminal alkyne **25**. As this compound was identical in all respects to the key intermediate used by Baran and co-workers in their approach to **1**,[3,4] a total synthesis of this intricate alkaloid in optically active form has been accomplished.[27] Despite a somewhat higher step count, our catalysis based route is similarly productive and compares favorably in terms of its inherent flexibility.[28]

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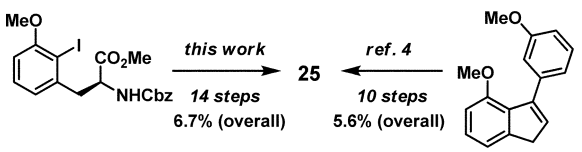
27. Attempts to reproduce the end game did afford the desired product but the yields were much lower than those reported in the literature, despite considerable experimentation. However, the small amounts of product allowed us to confirm the absolute configuration assigned to (−)-**1** by comparison with an authentic sample.
28. The two known asymmetric syntheses of the key intermediate **25** compare as follows:



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