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Late-stage and strain-accelerated oxidation enabled synthesis of haouamine A†

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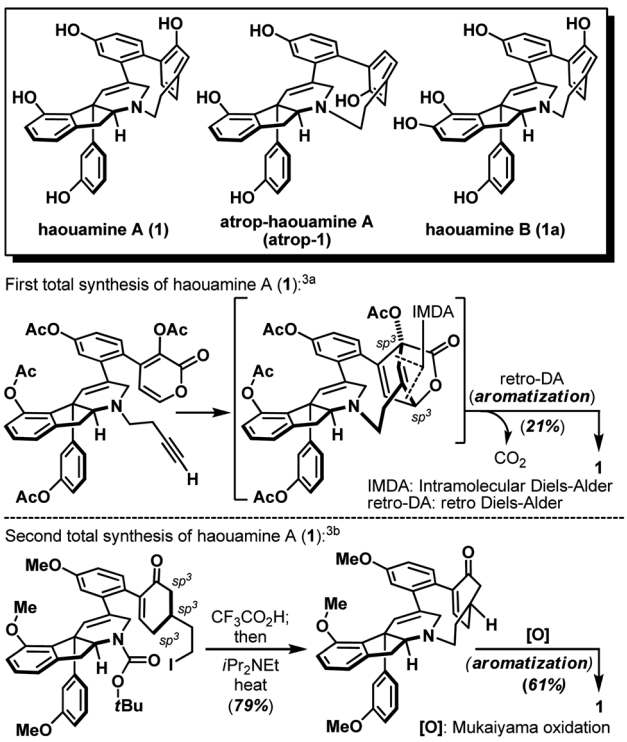
Herein we report a new synthetic entry to the strained cyclophane alkaloid natural product, haouamine A. The successful strategy featured a rhodium-catalyzed diazo-insertion reaction to install the all-carbon quaternary center and a rhodium-catalyzed intramolecular aziridination reaction to establish the nitrogen-bearing stereocenter, of the target molecule. Most notably, a late-stage, site-selective and strain-accelerated oxidation of a "deoxygenated" macrocyclic intermediate was successfully implemented, and in doing so provided a novel solution to the infamous biphenol cyclophane system of haouamine A.

Introduction

Strained cyclophanes are intriguing structural motifs with unusual physical properties, chemical reactivities, and methods for their preparation.[1] Due to the strain imposed by the macrocyclic framework, the constituent aryl ring(s) within the cyclophane often experiences stress that leads to a distortion from planarity. Consequently, one of the most common tactics for the construction of strained cyclophanes exploits a conformational flexible "masked" aryl precursor bearing sp^3 hybridized carbon center(s) for the macrocyclization event, followed by an aromatization-driven generation of the aryl ring(s) to render the targeted strained cyclophane system. In two instructive examples, Baran and co-workers disclosed contrasting approaches in their first syntheses of the indenotetrahydropyridine natural product, haouamine A (**1**, Scheme 1).[2] In their first-generation synthesis,[3a] an intramolecular [4 + 2] cycloaddition followed by an enthalpic and entropic driven retro-[4 + 2]/aromatization event successfully delivered the strained cyclophane system of haouamine A for the first time. A second-generation synthesis followed shortly after where an intramolecular *N*-alkylation of a cyclohexenone precursor bearing sp^3 hybridized carbon centers, followed by oxidative aromatization, rendered a more practical solution.[3b] In view of this state of affairs,[4] we hypothesized a "late-stage" oxidation[5] of a "deoxygenated" macrocyclic precursor (**2**) may provide an alternative solution to the biphenol cyclophane system of haouamine A (Scheme 2a). While this strategic maneuver benefits from greatly simplified synthetic precursors and broadens the selection of synthetic transformations for their preparation, site-selectivity of this unprecedented late-stage oxidation/oxygenation is expected to pose a serious challenge. Furthermore, we also envisaged the application of two rhodium-catalyzed processes ((a) diazo-insertion[6] and (b) intramolecular aziridination;[7] Scheme 2b) starting from two readily accessible building blocks **4** and **5** to provide a novel



Scheme 1 Structures of haouamine A (**1**), atrop-haouamine A (**atrop-1**), haouamine B (**1a**) and reported syntheses of the strained cyclophane.

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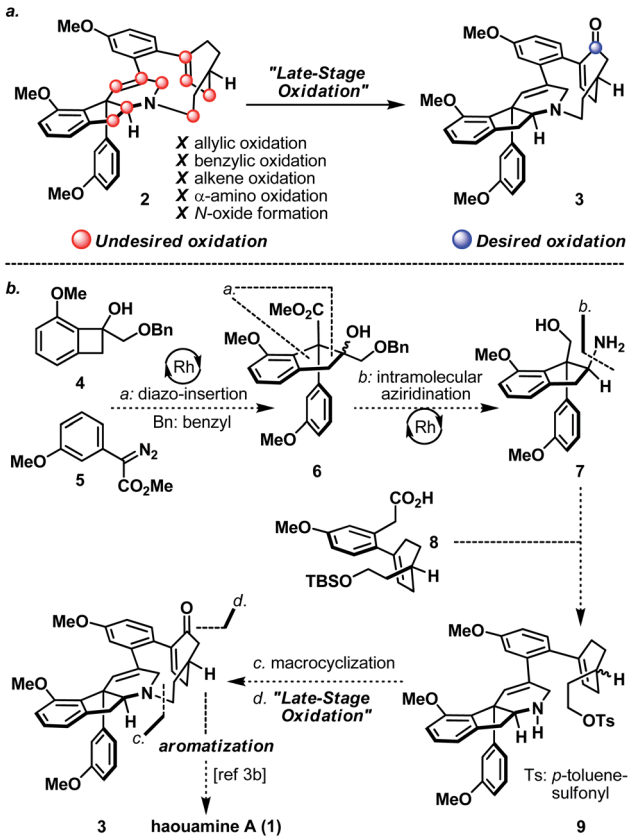


Scheme 2 (a) Desired and undesired oxidation of "Deoxygenated" macrocycle **2**; (b) proposed synthesis of haouamine A (**1**) in this work from building blocks **4**, **5**, and **8**.

and practical synthetic entry to the indeno-tetrahydropyridine core of haouamine A *via* amino-alcohol **7**.[4d,k]

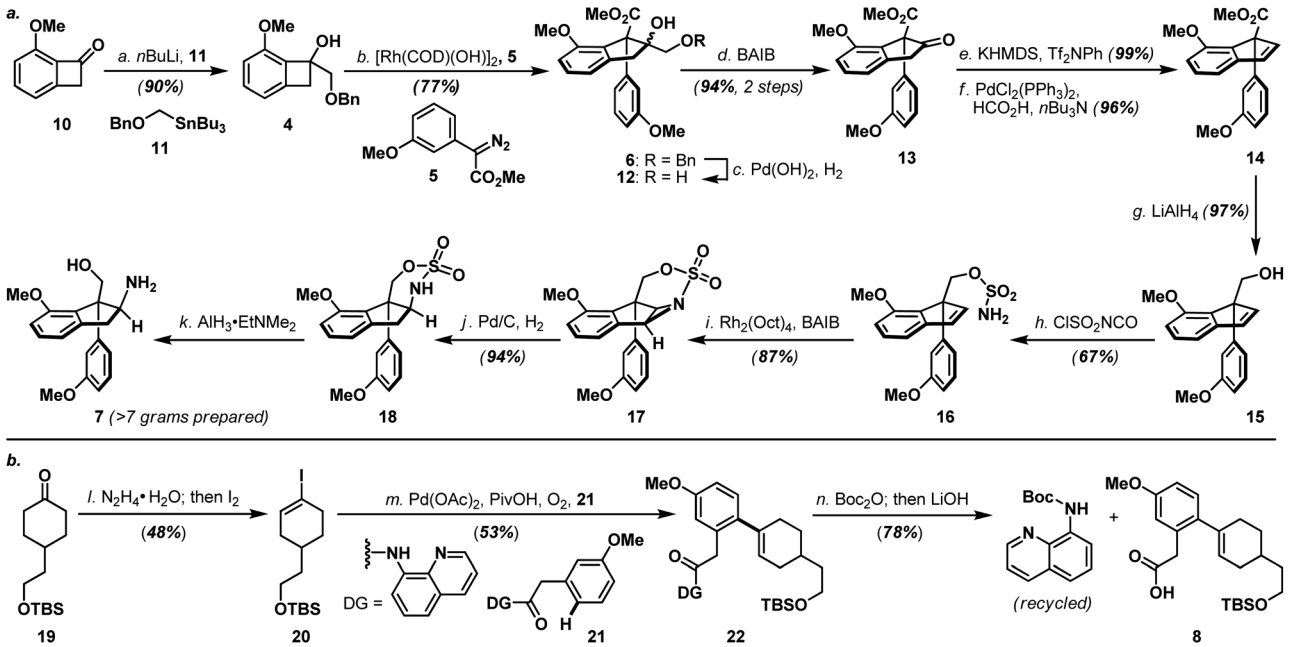
Results and discussion

As shown in Scheme 3a, the synthesis of haouamine A (**1**) commenced with the preparation of amino-alcohol **7**. Inspired by the protocol originally developed by Wang and co-workers,[6] rhodium-catalyzed diazo-insertion reaction engaging benzocyclobutanol **4** (ref. 8) and diazoester **5** (ref. 9) proceeded smoothly to afford tertiary alcohol **6** in good yield. Notably, this reaction took place with significantly improved yield at room temperature instead of the elevated temperature (100 °C) initially reported by Wang, and was routinely performed on multi-gram scale with further reduced catalyst loading (2 mol% to 0.8 mol%). In preparation for the ensuing intramolecular aziridination (**16** to **17**), hydroxy methyl ester **6** was elaborated to alkenyl alcohol **15** *via* oxidative cleavage of diol **12**, a two-step deoxygenation of keto ester **13** and reduction of alkenyl methyl ester **14**. On treatment with chlorosulfonyl isocyanate, primary alcohol **15** was converted to sulfamate **16** in readiness for the intramolecular aziridination. Analogous to the reaction conditions originally developed by the Du Bois laboratory,[7] rhodium-catalyzed intramolecular aziridination of **16** took place at a slightly elevated temperature (40 °C) to furnish aziridine **17** in high yield as the sole product (*e.g.* nitrene CH-insertion product(s) was not observed). Sequential reductive transformations on **17** that involved rupture of its aziridine (Pd/C, H_2) and cleavage of the sulfamate ($AlH_3 \cdot EtNMe_2$) yielded amino-alcohol **7** with spectroscopic data in full accordance with literature reports,[4d] thereby validated our developed reaction sequence. Furthermore, practicality of the developed sequence has been demonstrated in generating multi-gram quantities (>7 grams. For details, see ESI†) of amino-alcohol **7** for the ensuing synthetic investigations.

The synthesis of bicyclic carboxylic acid **8** is outlined in Scheme 3b. Inspired by the recent advances in CH-functionalization of phenylacetic acid derivatives, $Pd(OAc)_2$-catalyzed cross-coupling between quinolinamide **21** (ref. 10) and cyclohexanone **19** (ref. 11) derived vinyl iodide **20** under the aerobic *ortho*-alkenylation conditions described by Chen and co-workers[12] smoothly delivered bicycle **22** as the only detectable product. Hydrolytic amide-bond cleavage through the Boc derivative of quinolinamide **22** completed the synthesis of carboxylic acid **8** together with recovered 8-aminoquinoline directing group.[13]

Annulation of the tetrahydropyridine domain of haouamine A onto amino-alcohol **7** was realized through an adaptation of the reaction sequence described by Weinreb[4d] and Wipf groups,[4k] through the intermediacy primary alcohol **23** and intramolecular aldol-condensation of aldehyde **24**, to deliver lactam **25** uneventfully (Scheme 4).[14] In preparation for the macrocyclization event and the completion of macrocycle **2**/**2a**, TBS ether **25** was converted to its corresponding tosylate **27** followed by a Ru-catalyzed amide reduction[15] to afford amine **9**. Intramolecular *N*-alkylation of amino-tosylate **9** under high-dilution conditions[3,4a–c] (where the inclusion of NaI proved crucial) proceeded smoothly to deliver macrocycle **2**/**2a** as a mixture of diastereoisomers (Scheme 4). Notably, diastereoisomeric amino-tosylates (**9**, d.r. 1 : 1) exhibited different rate of macrocyclization that resulted the formation of diastereoisomerically enriched macrocycle (**2** : **2a** ∼ 2.8 : 1) together with unreacted and diastereoisomerically enriched amino-iodide intermediate (which could be re-subjected to the macrocyclization condition to afford additional supply of macrocycle **2**/**2a**) after 16 hours at 90 °C. On the other hand, inspired by the recently reported palladium-catalyzed intramolecular cross-coupling[16] featured in the herquline syntheses,[17] macrocyclic Suzuki reaction of boronic ester-aryl bromide **29** was also attempted but failed to deliver macrocycle **2**/**2a** (Scheme 5a). Notwithstanding the conformational and mechanistic differences between intramolecular *N*-alkylation and Suzuki cross-coupling, these results appear to substantiate the importance of site selection for a successful macrocyclization event. This finding is particularly noteworthy and path-pointing for future synthetic investigations in this field since it demonstrated for the first time that by simply replacing a constituent aromatic ring of the haouamine biphenol cyclophane system with a sp^3 hybridized "masked" aryl precursor may not guarantee the desired ring closure to take place.

With macrocycle **2**/**2a** in hand, the highly anticipated site-selective oxidation was pursued in earnest (Scheme 4). Having

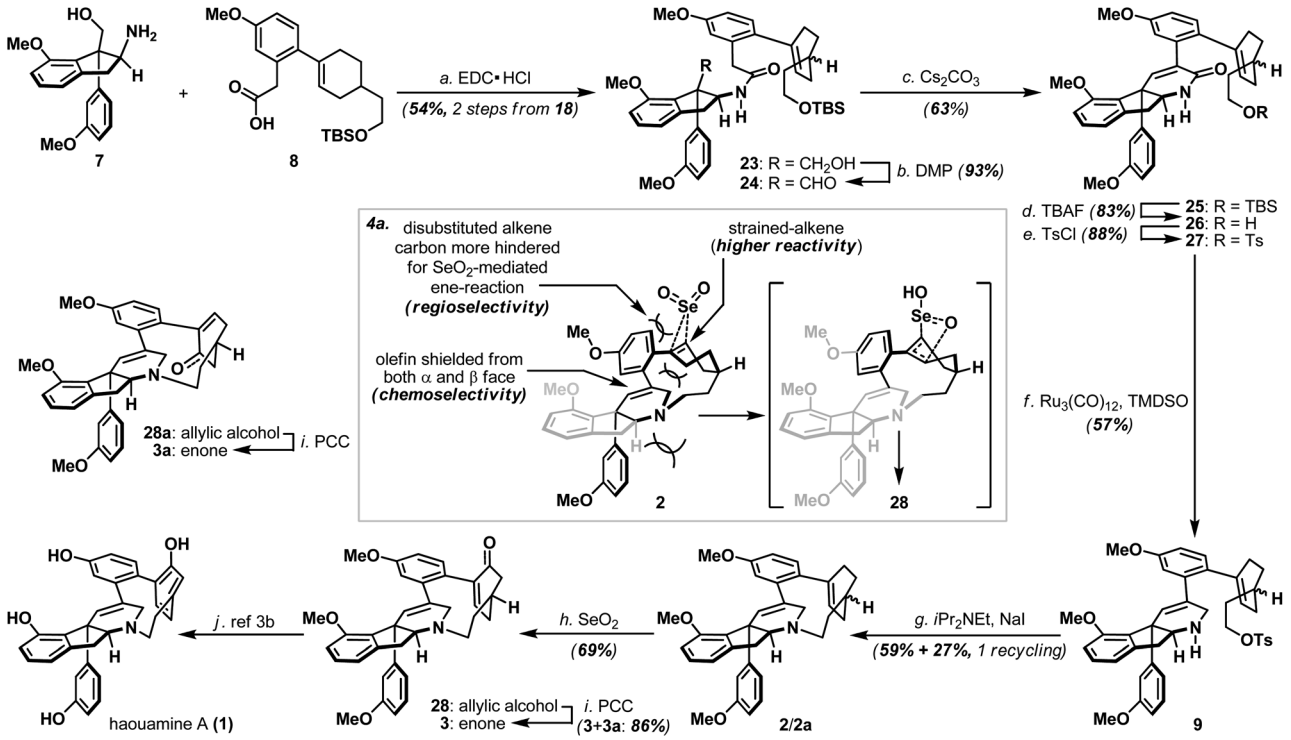


Scheme 3 (a) Preparation of amino-alcohol **7**; (b) preparation of bicyclic carboxylic acid **8**. Reagents and conditions: (a) **11** (1.05 equiv.), *n*BuLi (2.5 M in hexanes, 1.05 equiv.), THF, −78 °C, 50 min, 90%; (b) **5** (1.05 equiv.), $[Rh(COD)(OH)]_2$ (0.008 equiv.), toluene, 0 to 25 °C, 3 h, 77%; (c) $Pd(OH)_2$ (5 wt% on carbon, 18% wt/wt), H_2 (1 atm, balloon), MeOH, 25 °C, 15 h; (d) BAIB (1.0 equiv.), CH_2Cl_2, 25 °C, 3.5 h, 94% over 2 steps; (e) KHMDS (0.7 M in toluene, 1.1 equiv.), Tf_2NPh (1.3 equiv.), THF, −78 °C, 2 h, 99%; (f) $PdCl_2(PPh_3)_2$ (0.05 equiv.), nBu_3N (3.0 equiv.), HCO_2H (2.0 equiv.), DMF, 60 °C, 1.5 h, 96%; (g) $LiAlH_4$ (1.1 equiv.), Et_2O, 0 to 25 °C, 1.5 h, 97%; (h) $ClSO_2NCO$ (2.5 equiv.), HCO_2H (2.5 equiv.), pyridine (2.5 equiv.), CH_3CN/DMA (7 : 9), 25 °C, 7.5 h, 67%; (i) $Rh_2(Oct)_4$ (0.02 equiv.), MgO (2.3 equiv.), BAIB (1.2 equiv.), CH_2Cl_2, 25 to 40 °C, 4 h, 87%; (j) Pd/C (10 wt% on carbon, 45% wt/wt), H_2 (1 atm, balloon), EtOAc, 25 °C, 3 h, 94%; (k) $AlH_3 \cdot EtNMe_2$ (0.5 M in toluene, 6.0 equiv.), toluene, 25 to 110 °C, 6 h; (l) $N_2H_4 \cdot H_2O$ (4.0 equiv.), MeOH, 25 °C, 14 h; then I_2 (2.0 equiv.), Et_3N (10.0 equiv.), Et_2O, 0 to 25 °C, 25 min, 48% over 2 steps; (m) **20** (1.5 equiv.), **21** (1.0 equiv.), $Pd(OAc)_2$ (0.1 equiv.), PivOH (0.2 equiv.), $KHCO_3$ (2.0 equiv.), 1,2-dichloroethane, O_2, 100 °C, 14 h, 53% (2 cycles); (n) Boc_2O (3.0 equiv.), DMAP (0.5 equiv.), CH_3CN, 60 °C, 16 h; then $LiOH \cdot H_2O$ (8.5 equiv.), THF/H_2O (3 : 1), 25 to 60 °C, 2 h, 78% over 2 steps. BAIB = (diacetoxyiodo)benzene; COD = cyclooctadienyl; DMA = *N*,*N*′-dimethylacetamide; DMAP = *N*,*N*′-dimethylaminopyridine; DMF = *N*,*N*′-dimethylformamide; EtOAc = ethyl acetate; KHMDS = potassium bis(trimethylsilyl)amide; $Rh_2(Oct)_4$ = rhodium(II) octanoate, dimer; Tf_2NPh = *N*-phenyl-bis(trifluoromethanesulfonimide).

conducted an exhaustive study of conventional oxidation protocols (osmium-catalyzed dihydroxylation, peracid-mediated epoxidation, hydroboration–oxidation, metal-catalyzed and SeO_2-mediated allylic oxidation. For details, see ESI†), and recognizing the possibility to directly access the previously reported enone intermediate **3**/**3a**,[3b] we opted the SeO_2-mediated allylic oxidation as the focal point of our investigations on macrocycle **2**/**2a**. After extensive experimentations, we discovered that while prolonged treatment with SeO_2 at elevated temperature (100 °C) indeed generated analytically detectable amounts of enones **3** and **3a**, this condition proved highly capricious and difficult to obtain chromatographically pure material. Alternatively, performing the reaction at 45 °C for 5 hours cleanly afforded the allylic alcohol intermediate (**28** and **28a**) that could be easily isolated, and subsequent oxidation with PCC smoothly delivered a readily separable mixture of enones **3** and **3a**. It is worth-noting that allylic oxidation of model substrate **22a** under the identical reaction condition only proceeded in ~25% conversion (Scheme 5b), suggesting the enhanced reactivity of olefin **2**/**2a** may be a consequence of its strained macrocyclic system.[18] This mechanism-based selection of oxidation/oxygenation protocol proved crucial to achieve the overall selectivity for this challenging late-stage transformation (Scheme 4a).[19] Furthermore, conversion of allylic alcohols **28**/**28a** to enones **3**/**3a** was ineffective under Dess–Martin periodinane, Swern, and MnO_2 oxidation conditions. Enones **3** and **3a** exhibited spectroscopic data in complete accordance to those reported in the literature, and their conversion to haouamine A and atrop-haouamine A, respectively, have been reported.[3b] Finally, optically active alkenyl alcohol **15** could be conveniently obtained through a resolution process to provide an asymmetric entry to haouamine A (Scheme 5c).

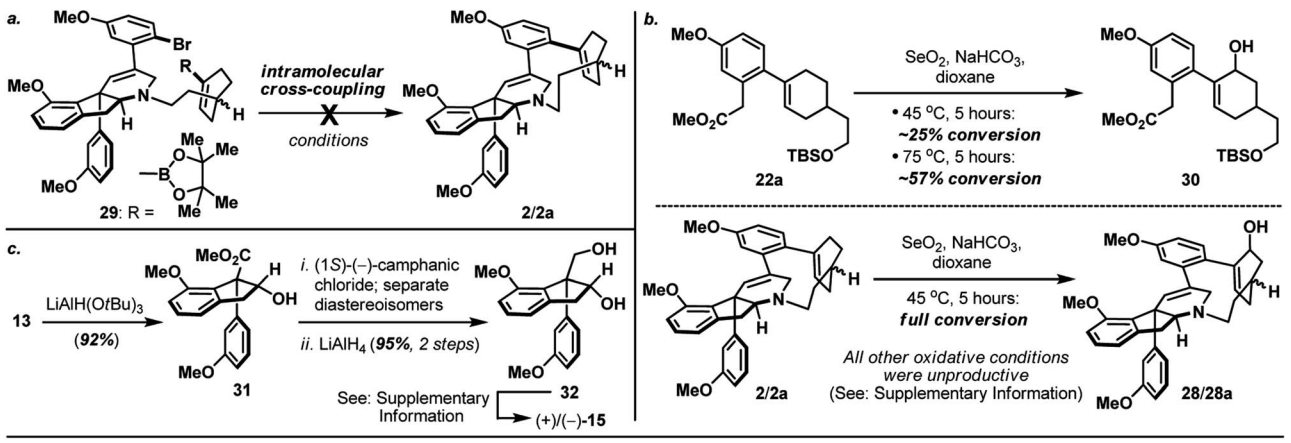
Conclusions

In conclusion, a new synthetic entry to the cyclophane alkaloid natural product haouamine A (**1**) has been realized. Most notably, a late-stage, site-selective, and strain-accelerated oxidation/oxygenation of macrocycle **2** was successfully implemented to render a novel solution to the biphenol cyclophane domain of haouamine A. In doing so, a simplified precursor has been identified for the first time to facilitate future chemical investigations of the haouamines by the synthetic community. The construction of the indeno-tetrahydropyridine core of haouamine A (**1**) developed herein also showcased two highly efficient and practical rhodium-



Scheme 4 Late-stage oxidation enabled synthesis of haouamine A (**1**); (a) 3-dimensional rendering and hypothetical transition-state structure to rationalize the highly effective late-stage oxidation/oxygenation of macrocycle **2**. Reagents and conditions: (a) EDC·HCl (1.1 equiv.), iPr_2NEt (2.2 equiv.), **8** (1.05 equiv.), CH_2Cl_2, 25 °C, 14 h, 54% for 2 steps from **18**; (b) DMP (1.4 equiv.), CH_2Cl_2, 0 to 25 °C, 4 h, 93%; (c) Cs_2CO_3 (4.0 equiv.), CH_3CN/MeOH (10 : 1), 60 °C, 8 h, 63%; (d) TBAF (1.0 M in THF, 2.0 equiv.), THF, 0 to 25 °C, 14 h, 83%; (e) TsCl (2.0 equiv.), DMAP (0.2 equiv.), Et_3N (5.0 equiv.), CH_2Cl_2, 25 °C, 4 h, 88%; (f) $Ru_3(CO)_{12}$ (0.1 equiv.), TMDSO (10.0 equiv.), toluene, 60 °C, 14 h, 57% (+**27** 10%); (g) NaI (10 equiv.), iPr_2NEt (10 equiv.), CH_3CN, 90 °C, 16 h + 16 h, 59% + 27% with one recycling; (h) SeO_2 (1.8 equiv.), $NaHCO_3$ (5.0 equiv.), 1,4-dioxane, 45 °C, 5 h, 69%; (i) PCC (2.0 equiv.), Celite®, CH_2Cl_2, 25 °C, 4 h, **3**: 58%, **3a**: 28%. DMP = Dess–Martin Periodinane; EDC = *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide; EtOAc = ethyl acetate; PCC = pyridinium chlorochromate; TBAF = tetra-*n*-butylammonium fluoride; TMDSO = 1,1,3,3-tetramethyldisiloxane.

catalyzed carbon–carbon and carbon–nitrogen bond forming processes, namely a diazo-ester (**5**) insertion to benzocyclobutanol **4** and an intramolecular aziridination of sulfamate **16**, respectively. Collectively, the modular synthetic approach developed herein and ample supply of amino-alcohol **7** should enable a ready access to other members of the haouamine family and designed analogues, which is currently under investigation in our laboratory.



Scheme 5 (a) Attempted formation of macrocycle **2**/**2a** *via* intramolecular Suzuki cross-coupling of boronic ester-aryl bromide **29**; (b) SeO_2-mediated allylic oxidation of bicyclic substrate **22a** *versus* macrocycle **2**/**2a**; (c) Synthesis of optically active alkenyl alcohol **15**. For details, see ESI.†

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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13 In comparison, Suzuki cross-coupling based synthesis of bicyclic carboxylic acid **8** involved more costly reagents and stringent experimental conditions, particularly in the triflation of ketone **19** and subsequent boronic ester formation. The simplicity of building block **20** and the implementation of aerobic CH-activation based cross-coupling both represented significant improvements compared to the reported total syntheses of haouamines (ref. 3 and 4a–c).

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19 In addition to experimental evidences (Scheme 5a and b), preliminary computation studies suggested the alkene (which participated in SeO_2-mediated allylic oxidation) in substrate **2** exhibited a notable "twist" in contrast with the alkene in substrate **22a**. For details, see ESI.†