

EDGE ARTICLE

[View Article Online](#)
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All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 23rd April 2020

Accepted 15th June 2020

DOI: 10.1039/d0sc02299c

rsc.li/chemical-science

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

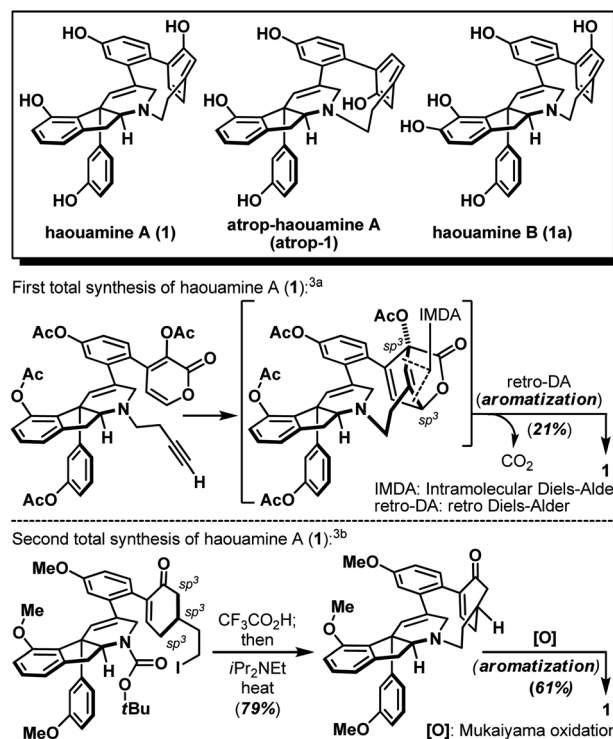
Kun Ho (Kenny) Park, Antonio Rizzo and David Y.-K. Chen *

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 indeno-tetrahydropyridine 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” oxidation⁵ 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

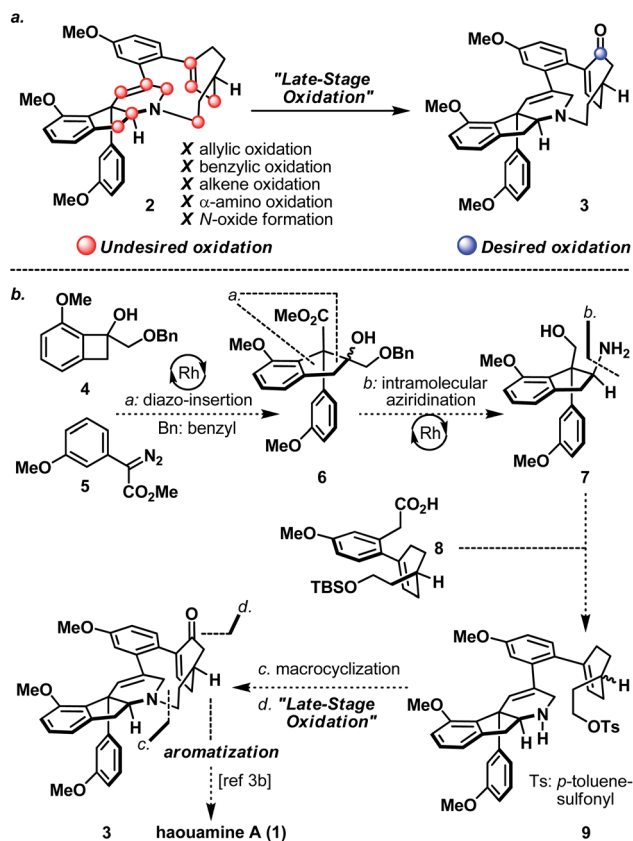
their preparation, site-selectivity of this unprecedented late-stage oxidation/oxygenation is expected to pose a serious challenge. Furthermore, we also envisaged the application of two rhodium-catalyzed processes ((a) diazo-insertion⁶ and (b) intramolecular aziridination;⁷ Scheme 2b) starting from two 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.

Department of Chemistry, Seoul National University, Gwanak-1 Gwanak-ro, Gwanak-gu, Seoul 08826, South Korea. E-mail: davidchen@snu.ac.kr

† Electronic supplementary information (ESI) available. See DOI: 10.1039/d0sc02299c



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

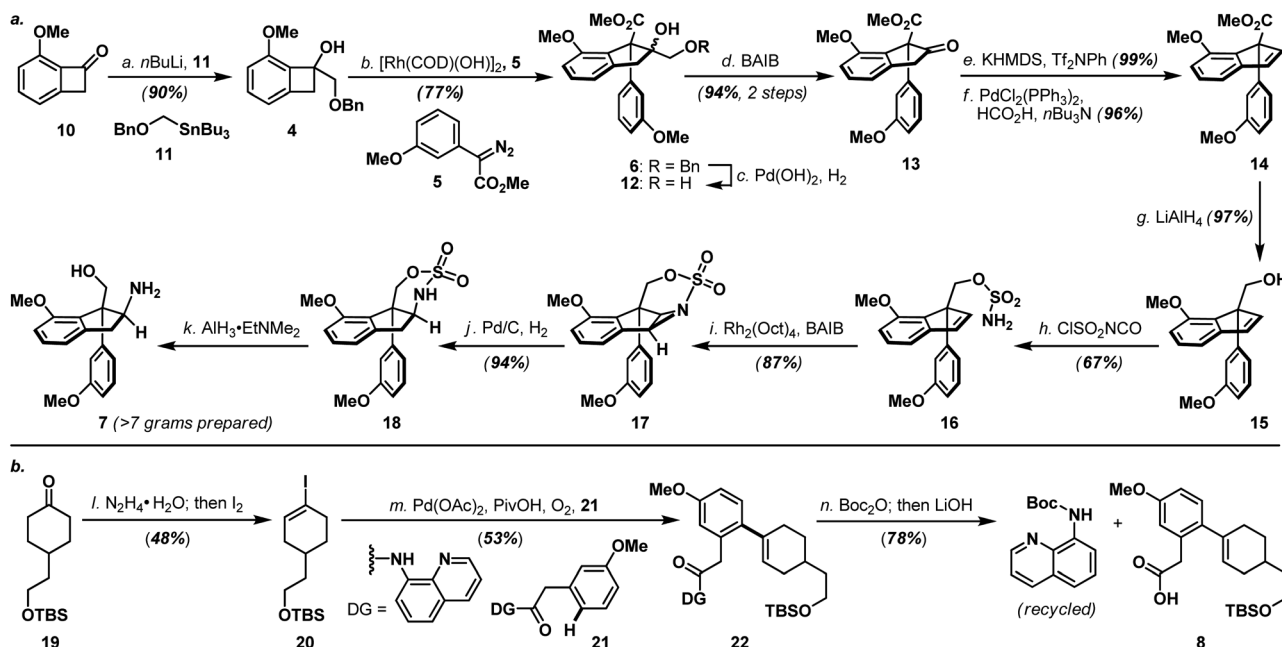
aziridine 17 in high yield as the sole product (*e.g.* nitrene CH-insertion product(s) was not observed). Sequential reductive transformations on 17 that involved rupture of its aziridine (Pd/C, H₂) and cleavage of the sulfamate (AlH₃·EtNMe₂) yielded amino-alcohol 7 with spectroscopic data in full accordance 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-workers¹² 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 reduction¹⁵ 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-coupling¹⁶ featured in the herquiline 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 sp³ 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.), $[\text{Rh}(\text{COD})(\text{OH})]_2$ (0.008 equiv.), toluene, 0 to 25°C , 3 h, 77%; (c) $\text{Pd}(\text{OH})_2$ (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.), Trf_2NPh (1.3 equiv.), THF, -78°C , 2 h, 99%; (f) $\text{PdCl}_2(\text{PPh}_3)_2$ (0.05 equiv.), $n\text{Bu}_3\text{N}$ (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.), $\text{CH}_3\text{CN}/\text{DMA}$ (7 : 9), 25°C , 7.5 h, 67%; (i) $\text{Rh}_2(\text{Oct})_4$ (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) $\text{AlH}_3\cdot\text{EtNMe}_2$ (0.5 M in toluene, 6.0 equiv.), toluene, 25 to 110°C , 6 h; (l) $\text{N}_2\text{H}_4\cdot\text{H}_2\text{O}$ (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.), $\text{Pd}(\text{OAc})_2$ (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 $\text{LiOH}\cdot\text{H}_2\text{O}$ (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; $\text{Rh}_2(\text{Oct})_4$ = rhodium(III) octanoate, dimer; Trf_2NPh = *N*-phenyl-bis(trifluoromethanesulfonyl)imide).

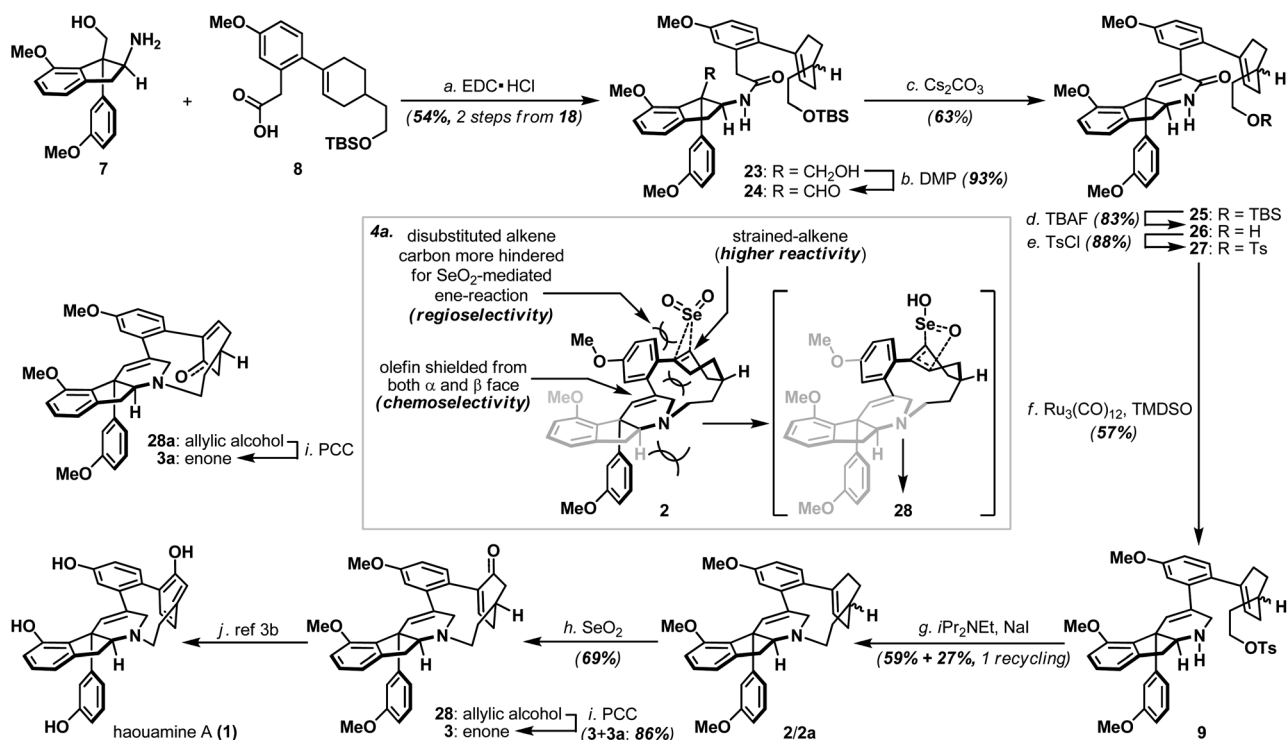
conducted an exhaustive study of conventional oxidation protocols (osmium-catalyzed dihydroxylation, peracid-mediated epoxidation, hydroboration-oxidation, metal-catalyzed and SeO_2 -mediated allylic oxidation. For details, see ESI†), and recognizing the possibility to directly access the previously 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 $\sim 25\%$ 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-

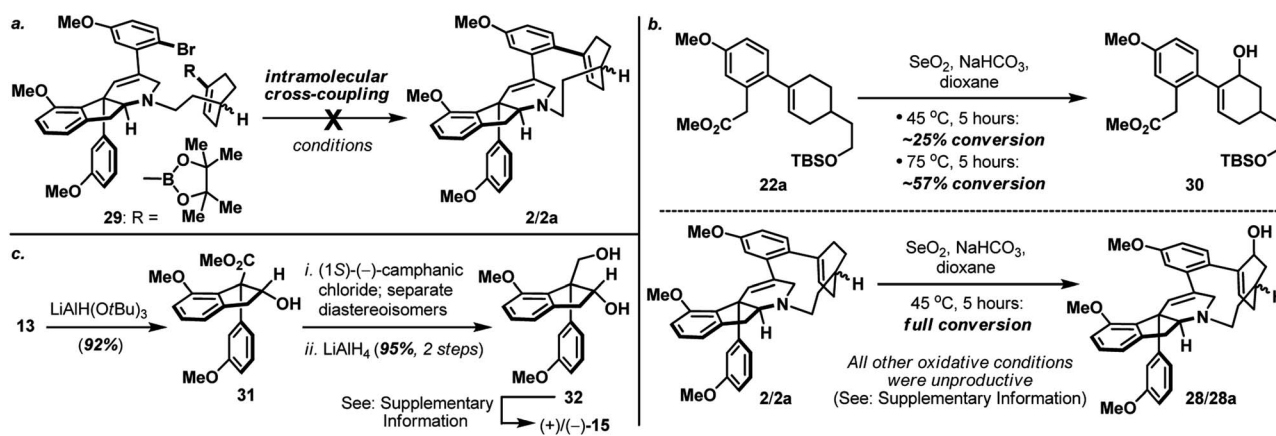




Scheme 4 Late-stage oxidation enabled synthesis of haouamine A (1); (a) 3-dimensional rendering and hypothetical transition-state structure to rationalize the highly effective late-stage oxidation/oxygenation of macrocycle 2. Reagents and conditions: (a) EDC·HCl (1.1 equiv.), iPr_2NEt (2.2 equiv.), **8** (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

This work was supported by National Research Foundation of Korea (NRF) grant funded by the Korean government (MSIP) (No. 2013R1A1A2057837; and 2014R1A5A1011165, Center for New Directions in Organic Synthesis), and Novartis. Antonio Rizzo was supported by the BK21Plus Program, Ministry of Education. We thank Geun Seok Lee and Suyong Goh for preliminary synthetic studies toward the synthesis of amino-alcohol **7**.

Notes and references

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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 SeO₂-mediated allylic oxidation) in substrate **2** exhibited a notable “twist” in contrast with the alkene in substrate **22a**. For details, see ESI.†

