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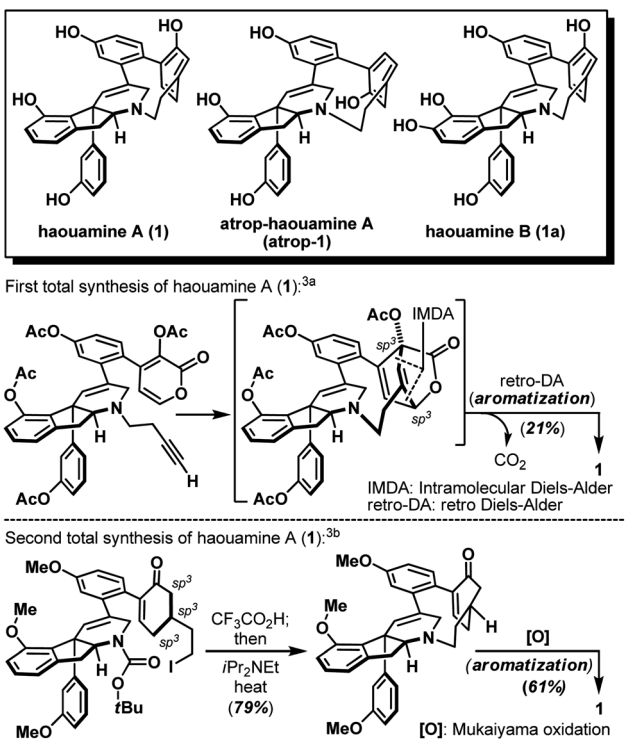
# Late-stage and strain-accelerated oxidation enabled synthesis of haouamine A†

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" 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.

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

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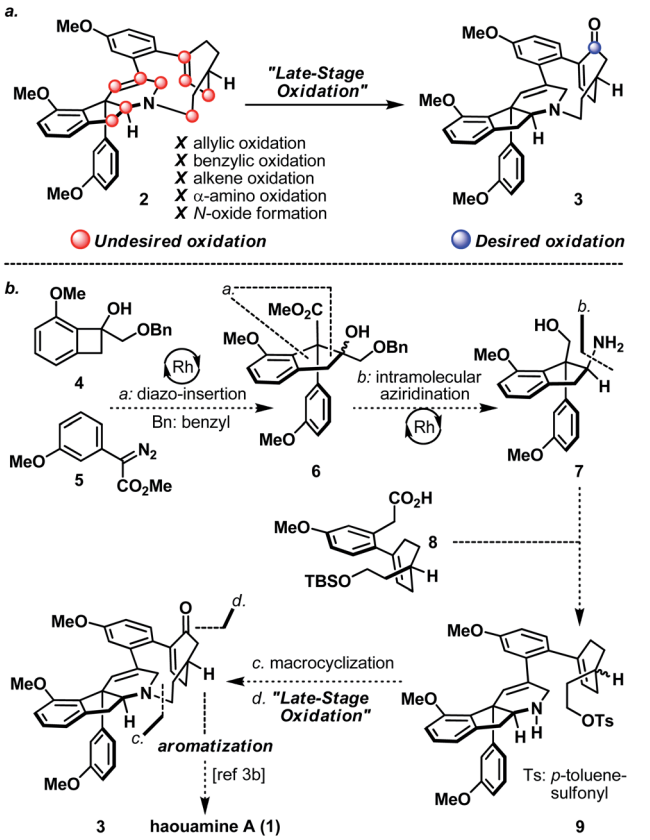


Scheme 2 (a) Desired and undesired oxidation of "Deoxygenated" macrocycle 2; (b) proposed synthesis of haouamine A (1) in this work from building blocks 4, 5, and 8.

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

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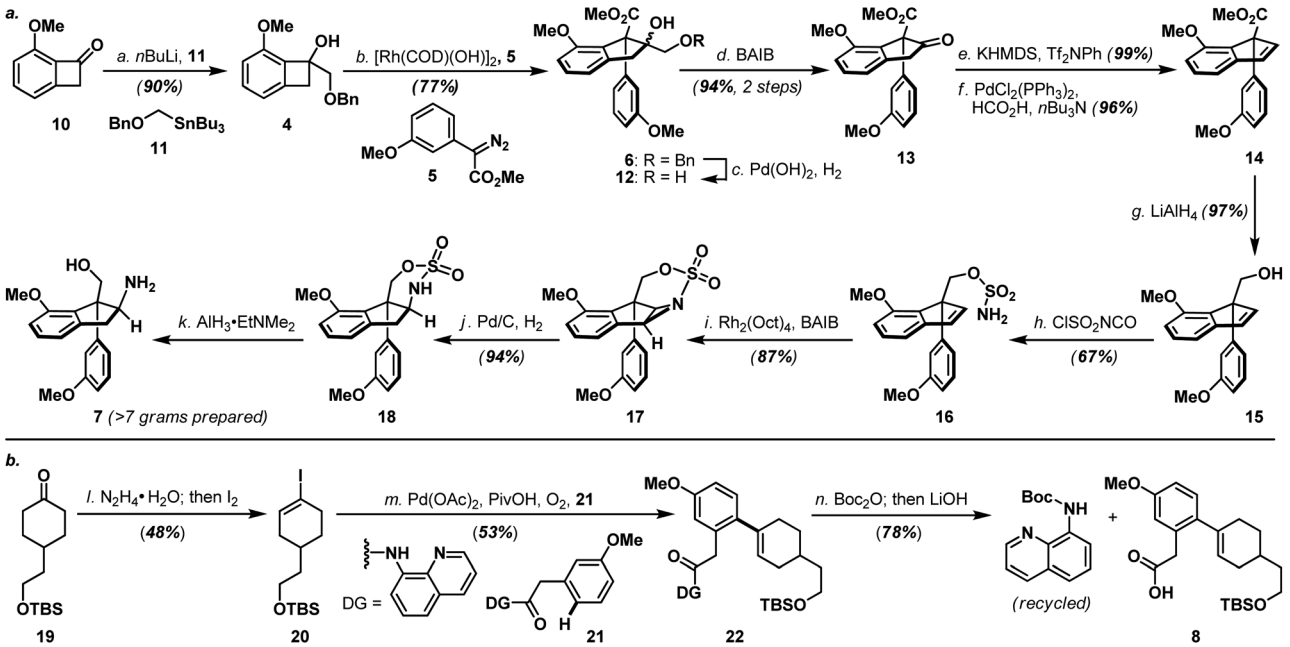


Scheme 3 (a) Preparation of amino-alcohol **7**; (b) preparation of bicyclic carboxylic acid **8**. Reagents and conditions: (a) **11** (1.05 equiv.), *n*BuLi (2.5 M in hexanes, 1.05 equiv.), THF, −78 °C, 50 min, 90%; (b) **5** (1.05 equiv.), $[Rh(COD)(OH)]_2$ (0.008 equiv.), toluene, 0 to 25 °C, 3 h, 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-

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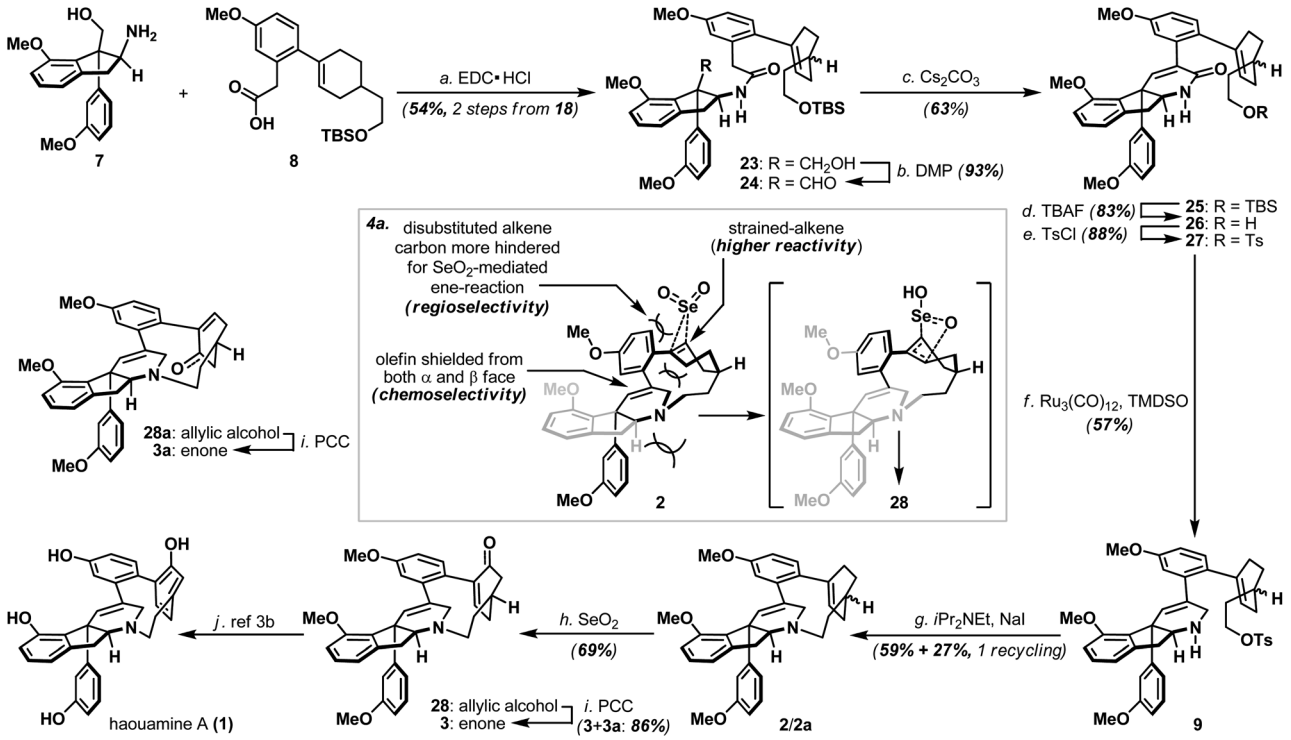
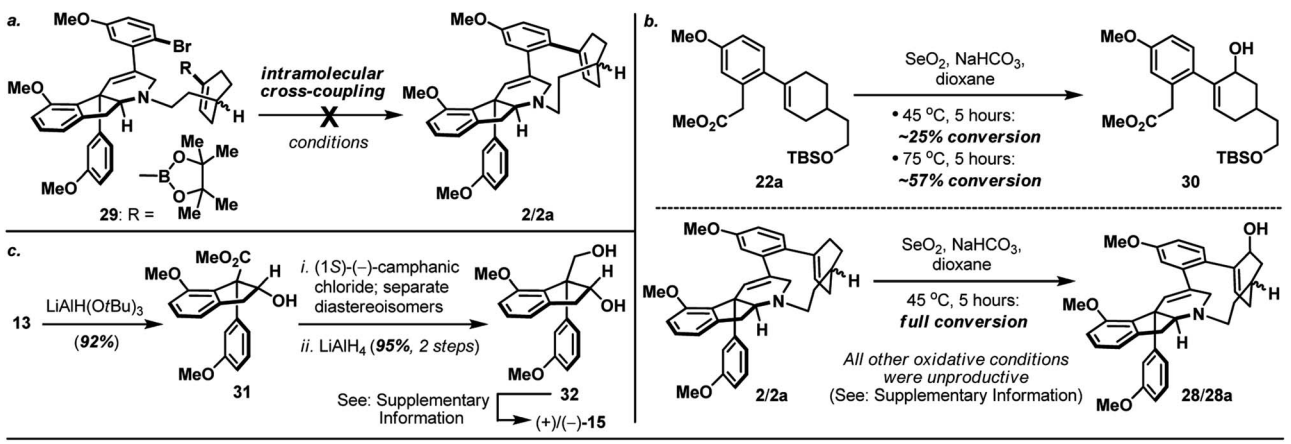



Scheme 4 Late-stage oxidation enabled synthesis of haouamine A (**1**); (a) 3-dimensional rendering and hypothetical transition-state structure to rationalize the highly effective late-stage oxidation/oxygenation of macrocycle **2**. Reagents and conditions: (a) EDC·HCl (1.1 equiv.), $iPr_2NEt$ (2.2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

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## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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## Notes and references

1 For reviews, see: (*a*) T. Gulder and P. S. Baran, Strained Cyclophane Natural Products: Macrocyclization at Its Limits, *Nat. Prod. Rep.*, 2012, **29**, 899–934; (*b*) T. Tsuji, Highly Strained Cyclophanes, in *Mod. Cyclophane Chem.*, ed. R. Gleiter and H. Hopf, Wiley-VCH, Weinheim, 2004, pp. 81–104; (*c*) T. Tsuji, Extremely Strained Paracyclophanes: Preparation, Structures, and Properties, *Adv. Strained Interesting Org. Mol.*, 1999, **7**, 103–152; (*d*) F. Bickelhaupt and W. H. de Wolf, Unusual Reactivity of Highly Strained Cyclophanes, *J. Phys. Org. Chem.*, 1998, **11**, 362–376; (*e*) F. Bickelhaupt and W. H. de Wolf, Small and Strained Cyclophanes, *Adv. Strain Org. Chem.*, 1993, **3**, 185–227; (*f*) D. J. Cram and J. M. Cram, Cyclophane Chemistry: Bent and Battered Benzene Rings, *Acc. Chem. Res.*, 1971, **4**, 204–213.

2 L. Garrido, E. Zubia, M. J. Ortega and J. Salva, Haouamines A and B: A New Class of Alkaloids from the Ascidian Aplidium haouarianum, *J. Org. Chem.*, 2003, **68**, 293–299.

3 (*a*) P. S. Baran and N. Z. Burns, Total Synthesis of (±)-Haouamine A, *J. Am. Chem. Soc.*, 2006, **128**, 3908–3909; (*b*) N. Z. Burns, I. N. Krylova, R. N. Hannoush and P. S. Baran, Scalable Total Synthesis and Biological Evaluation of Haouamine A and Its Atropisomer, *J. Am. Chem. Soc.*, 2009, **131**, 9172–9173.

4 For total syntheses, see: (*a*) M. Matveenko, G. Liang, E. M. W. Lauterwasser, E. Zubia and D. Trauner, A Total Synthesis Prompts the Structure Revision of Haouamine B, *J. Am. Chem. Soc.*, 2012, **134**, 9291–9295; (*b*) Y. Momoi, K.-i. Okuyama, H. Toya, K. Sugimoto, K. Okano and H. Tokuyama, Total Synthesis of (−)-Haouamine B Pentaacetate and Structural Revision of Haouamine B, *Angew. Chem., Int. Ed.*, 2014, **53**, 13215–13219; (*c*) H. Tsukamoto, S. Nakamura, A. Tomida and T. Doi, Scalable Total Syntheses and Structure-Activity Relationships of Haouamine A, B, and their Derivatives as Stable Formate Salts, *Chem.–Eur. J.*, DOI: 10.1002/chem.202001756. For formal synthesis and synthetic studies, see: (*d*) J. H. Jeong and S. M. Weinreb, Formal Total Synthesis of the Cytotoxic Marine Ascidian Alkaloid Haouamine A, *Org. Lett.*, 2006, **8**, 2309–2312; (*e*) A. Furstner and J. Ackerstaff, Formal Total Synthesis of (−)-Haouamine A, *Chem. Commun.*, 2008, 2870–2872; (*f*) T. Taniguchi, H. Zaimoku and H. Ishibashi, Formal Total Synthesis of Haouamine A, *J. Org. Chem.*, 2009, **74**, 2624–2626; (*g*) N. D. Smith, J. Hayashida and V. H. Rawal, Facile Synthesis of the Indeno-Tetrahydropyridine Core of Haouamine A, *Org. Lett.*, 2005, **7**, 4309–4312; (*h*) P. Wipf and M. Furegati, Synthesis of the 3-Aza-[7]-paracyclophane Core of Haouamine A and B, *Org. Lett.*, 2006, **8**, 1901–1904; (*i*) T. Tanaka, H. Inui, H. Kida, T. Kodama, T. Okamoto, A. Takeshima, Y. Tachi and Y. Morimoto, Diastereoselective Synthesis of the Indeno-tetrahydropyridine Core Bearing a Diaryl-substituted Stereogenic Quaternary Carbon Center of Haouamine B, *Chem. Commun.*, 2011, **47**, 2949–2951; (*j*) E. Fenster, C. Fehl and J. Aubé, Use of a Tandem Prins/Friedel–Crafts Reaction in the Construction of the Indeno-Tetrahydropyridine Core of the Haouamine Alkaloids: Formal Synthesis of (−)-Haouamine A, *Org. Lett.*, 2011, **13**, 2614–2617; (*k*) L. Cao, C. Wang and P. Wipf, Grob-Type Fragmentation Releases Paracyclophane Ring Strain in a Late-Stage Precursor of Haouamine A, *Org. Lett.*, 2019, **21**, 1538–1541; (*l*) T. J. Idzik, A. Borzyszkowska-Ledwig, L. Struk and J. G. Sosnicki, Magnesiate-Utilized/Benzyne-Mediated Approach to Indenopyridones from 2-Pyridones: An Attempt to Synthesize the Indenopyridine Core of Haouamine, *Org. Lett.*, 2019, **21**, 9667–9671.

5 M. C. White and J. Zhao, Aliphatic C–H Oxidations for Late-Stage Functionalization, *J. Am. Chem. Soc.*, 2018, **140**, 13988–14009.

6 Y. Xia, Z. Liu, Z. Liu, R. Ge, F. Ye, M. Hossain, Y. Zhang and J. Wang, Formal Carbene Insertion into C–C Bond: Rh(I)-Catalyzed Reaction of Benzocyclobutenols with Diazoesters, *J. Am. Chem. Soc.*, 2014, **136**, 3013–3015.

7 For intramolecular aziridination leading to an analogous ring system, see: P. M. Wehn and J. Du Bois, A Stereoselective Synthesis of the Bromopyrrole Natural Product (−)-Agelastatin A, *Angew. Chem., Int. Ed.*, 2009, **48**, 3802–3805.

8 For preparation of ketone **10**, see: P. H. Chen, N. A. Savage and G. Dong, Concise Synthesis of Functionalized Benzocyclobutenones, *Tetrahedron*, 2014, **70**, 4135–4146. For preparation of (benzyloxymethyl)tri-*n*-butylstannane (**11**), see: V. Di Bussolo, A. Fiasella, M. R. Romano, L. Favero, M. Pineschi and P. Crotti, Stereoselective Synthesis of 2,3-Unsaturated-aza-O-glycosides *via* New Diastereoisomeric *N*-Cbz-imino Glycal-Derived Allyl Epoxides, *Org. Lett.*, 2007, **9**, 4479–4482.

9 For preparation of diazo ester **5**, see: W. Chan, S. Yeung, Z. Zhou, A. S. C. Chan and W. Yu, Ruthenium Catalyzed Directing Group-Free C2-Selective Carbenoid Functionalization of Indoles by α-Aryldiazoesters, *Org. Lett.*, 2010, **12**, 604–607.

10 For preparation of quinolinamide **21**, see: Q. Zhao, T. Poisson, X. Pannecoucke, J.-P. Bouillon and T. Besset, Pd-Catalyzed Diastereoselective Trifluoromethylthiolation

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of Functionalized Acrylamides, *Org. Lett.*, 2017, **19**, 5106–5109.

11 For preparation of cyclohexanone **19**, see: (*a*) S. Desrat, C. Remeur and F. Roussi, Development of an Efficient Route Toward Meiogynin A-Inspired Dual Inhibitors of Bcl-xL and Mcl-1 Anti-Apoptotic Proteins, *Org. Biomol. Chem.*, 2015, **13**, 5520–5531; (*b*) M. Ihara, T. Taniguchi, K. Makita, M. Takano, M. Ohnishi, N. Taniguchi, K. Fukumoto and C. Kabuto, Synthesis of Polycyclic Cyclobutane Derivatives by Tandem Intramolecular Michael-Aldol Reaction Under Two Complementary Conditions: TBDMSOTf-$Et_3N$ and TMSI-$(TMS)_2NH$, *J. Am. Chem. Soc.*, 1993, **115**, 8107–8115.

12 Y. Zhao, G. He, W. A. Nack and G. Chen, Palladium-Catalyzed Alkenylation and Alkynylation of *ortho*-C($sp^2$)–H Bonds of Benzylamine Picolinamides, *Org. Lett.*, 2012, **14**, 2948–2951.

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).

14 Notably, intramolecular aldol condensation of aldehyde **24** under the conditions described by Weinreb and Wipf groups ($K_2CO_3$, MeOH, 60 °C, ref. 4d and k) afforded lactam **25** in significantly lower yield.

15 H. Nagashima, Efficient Transition Metal-Catalyzed Reactions of Carboxylic Acid Derivatives with Hydrosilanes and Hydrosiloxanes, Afforded by Catalyst Design and the Proximity Effect of Two Si–H Groups, *Synlett*, 2015, **26**, 866–890.

16 T. O. Ronson, R. J. K. Taylor and I. J. S. Fairlamb, Palladium Catalysed Macrocyclisations in the Total Synthesis of Natural Products, *Tetrahedron*, 2015, **71**, 989–1009.

17 (*a*) J. B. Cox, A. Kimishima and J. L. Wood, Total Synthesis of Herquline B and C, *J. Am. Chem. Soc.*, 2019, **141**, 25–28; (*b*) C. He, T. P. Stratton and P. S. Baran, Concise Total Synthesis of Herqulines B and C, *J. Am. Chem. Soc.*, 2019, **141**, 29–32; (*c*) X. Zhu, C. C. McAtee and C. S. Schindler, Total Syntheses of Herqulines B and C, *J. Am. Chem. Soc.*, 2019, **141**, 3409–3413.

18 M. R. Wilson and R. E. Taylor, Strained Alkenes in Natural Product Synthesis, *Angew. Chem., Int. Ed.*, 2013, **52**, 4078–4087.

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.†