

Cite this: *Chem. Sci.*, 2020, 11, 8132

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†

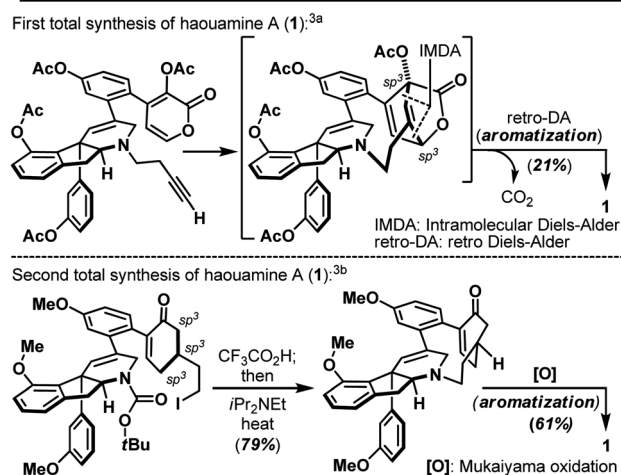
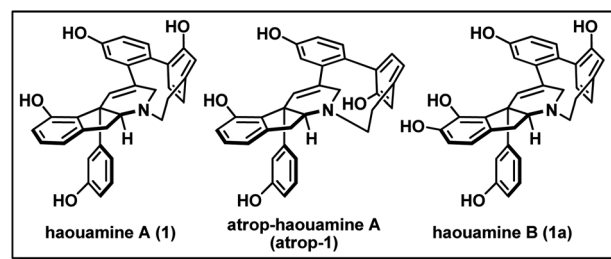
Kun Ho (Kenny) Park, Antonio Rizzo and David Y.-K. Chen *

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

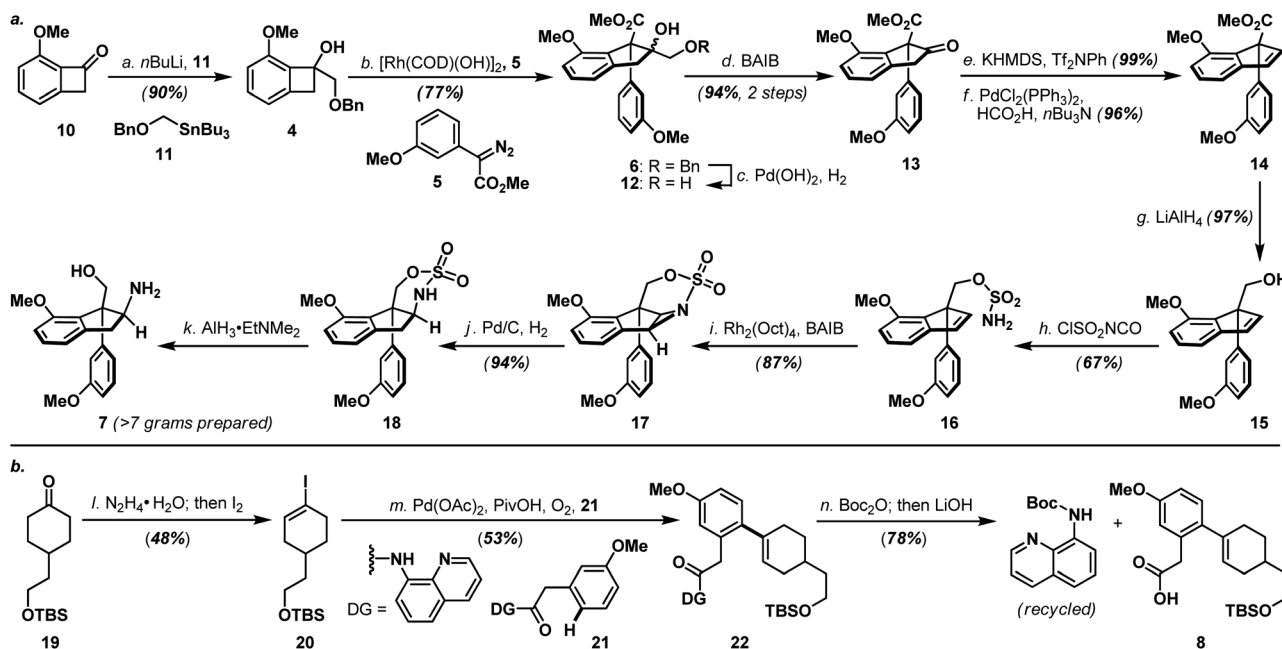


Scheme 1 Structures of haouamine A (1), atrop-haouamine A (atrop-1), haouamine B (1a) and reported syntheses of the strained cyclophane.

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 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, $-78\text{ }^{\circ}\text{C}$, 50 min, 90%; (b) **5** (1.05 equiv.), $[\text{Rh}(\text{COD})(\text{OH})]_2$ (0.008 equiv.), toluene, 0 to $25\text{ }^{\circ}\text{C}$, 3 h, 77%; (c) $\text{Pd}(\text{OH})_2$ (5 wt% on carbon, 18% wt/wt), H_2 (1 atm, balloon), MeOH, $25\text{ }^{\circ}\text{C}$, 15 h; (d) BAIB (1.0 equiv.), CH_2Cl_2 , $25\text{ }^{\circ}\text{C}$, 3.5 h, 94% over 2 steps; (e) KHMDS (0.7 M in toluene, 1.1 equiv.), Trf_2NPh (1.3 equiv.), THF, $-78\text{ }^{\circ}\text{C}$, 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, $60\text{ }^{\circ}\text{C}$, 1.5 h, 96%; (g) LiAlH_4 (1.1 equiv.), Et_2O , 0 to $25\text{ }^{\circ}\text{C}$, 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), $25\text{ }^{\circ}\text{C}$, 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 $40\text{ }^{\circ}\text{C}$, 4 h, 87%; (j) Pd/C (10 wt% on carbon, 45% wt/wt), H_2 (1 atm, balloon), EtOAc, $25\text{ }^{\circ}\text{C}$, 3 h, 94%; (k) $\text{AlH}_3\cdot\text{EtNMe}_2$ (0.5 M in toluene, 6.0 equiv.), toluene, 25 to $110\text{ }^{\circ}\text{C}$, 6 h; (l) $\text{N}_2\text{H}_4\cdot\text{H}_2\text{O}$ (4.0 equiv.), MeOH, $25\text{ }^{\circ}\text{C}$, 14 h; then I_2 (2.0 equiv.), Et_3N (10.0 equiv.), Et_2O , 0 to $25\text{ }^{\circ}\text{C}$, 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 , $100\text{ }^{\circ}\text{C}$, 14 h, 53% (2 cycles); (n) Boc_2O (3.0 equiv.), DMAP (0.5 equiv.), CH_3CN , $60\text{ }^{\circ}\text{C}$, 16 h; then $\text{LiOH}\cdot\text{H}_2\text{O}$ (8.5 equiv.), THF/ H_2O (3 : 1), 25 to $60\text{ }^{\circ}\text{C}$, 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).

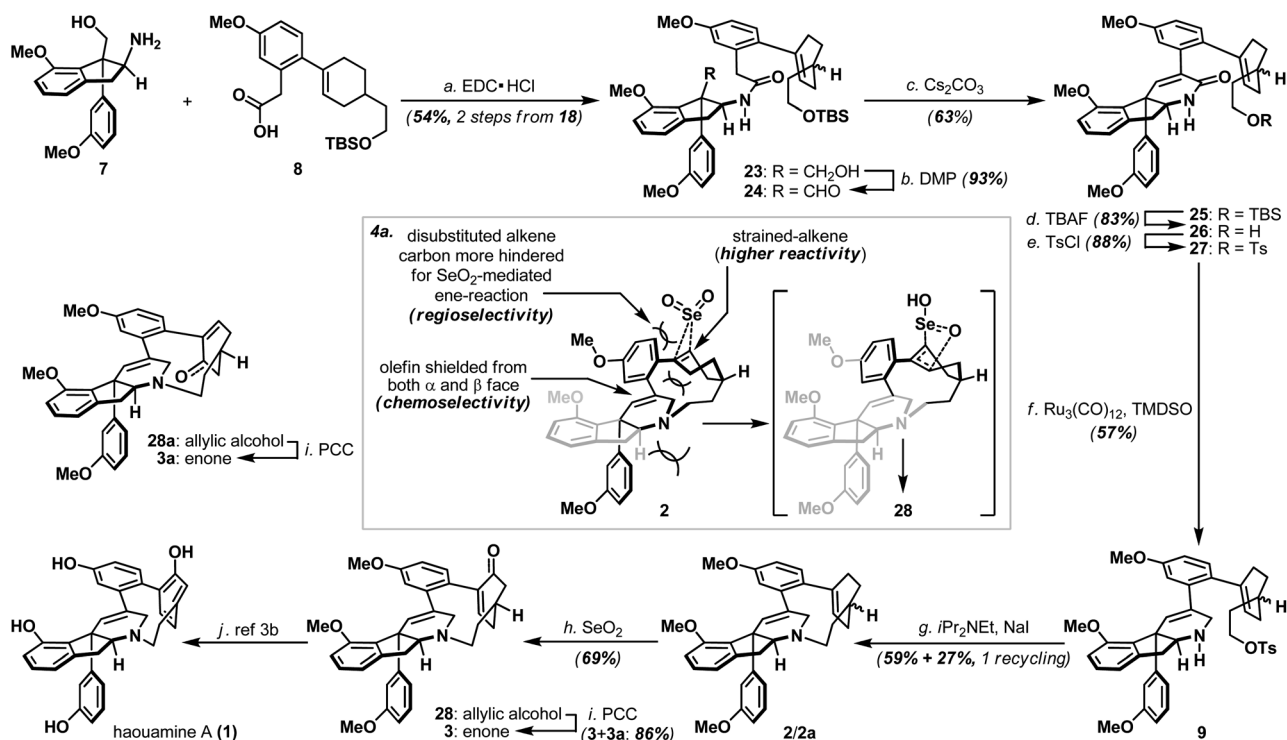
conducted an exhaustive study of conventional oxidation protocols (osmium-catalyzed dihydroxylation, peracid-mediated epoxidation, hydroboration-oxidation, metal-catalyzed and SeO_2 -mediated allylic oxidation. For details, see ESI^\dagger), and recognizing the possibility to directly access the previously 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 ($100\text{ }^{\circ}\text{C}$) 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 $45\text{ }^{\circ}\text{C}$ 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-

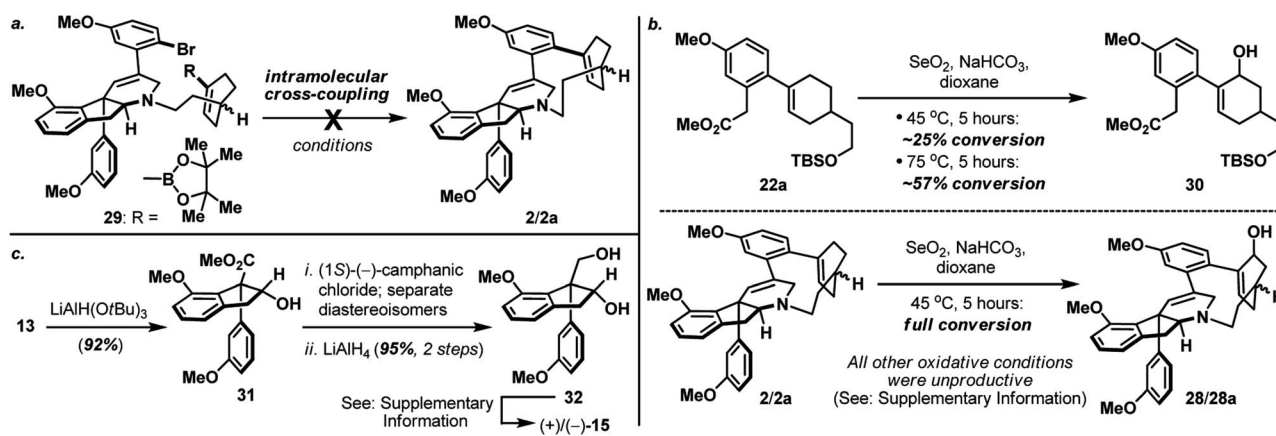




Scheme 4 Late-stage oxidation enabled synthesis of hauamine A (1); (a) 3-dimensional rendering and hypothetical transition-state structure to rationalize the highly effective late-stage oxidation/oxygenation of macrocycle 2. Reagents and conditions: (a) EDC·HCl (1.1 equiv.), *i*Pr₂NEt (2.2 equiv.), 8 (1.05 equiv.), CH₂Cl₂, 25 °C, 14 h, 54% for 2 steps from 18; (b) DMP (1.4 equiv.), CH₂Cl₂, 0 to 25 °C, 4 h, 93%; (c) Cs₂CO₃ (4.0 equiv.), CH₃CN/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.), Et₃N (5.0 equiv.), CH₂Cl₂, 25 °C, 4 h, 88%; (f) Ru₃(CO)₁₂ (0.1 equiv.), TMDSO (10.0 equiv.), toluene, 60 °C, 14 h, 57% (+27 10%); (g) NaI (10 equiv.), *i*Pr₂NEt (10 equiv.), CH₃CN, 90 °C, 16 h + 16 h, 59% + 27% with one recycling; (h) SeO₂ (1.8 equiv.), NaHCO₃ (5.0 equiv.), 1,4-dioxane, 45 °C, 5 h, 69%; (i) PCC (2.0 equiv.), Celite®, CH₂Cl₂, 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-tetramethylidisiloxane.

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 hauamine 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) SeO₂-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

- 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.
- 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.
- (a) P. S. Baran and N. Z. Burns, Total Synthesis of (\pm)-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.
- 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, Magnesiato-Utilized/Benzynes-Mediated Approach to Indenopyridones from 2-Pyridones: An Attempt to Synthesize the Indenopyridine Core of Haouamine, *Org. Lett.*, 2019, **21**, 9667–9671.
- M. C. White and J. Zhao, Aliphatic C–H Oxidations for Late-Stage Functionalization, *J. Am. Chem. Soc.*, 2018, **140**, 13988–14009.
- 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.
- 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.
- 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.
- 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.
- For preparation of quinolinamide **21**, see: Q. Zhao, T. Poisson, X. Pannecoucke, J.-P. Bouillon and T. Besset, Pd-Catalyzed Diastereoselective Trifluoromethylthiolation



- 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 Meigynin 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-Et₃N 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(sp²)-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 (K₂CO₃, 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 Herquiline 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 Herquelines B and C, *J. Am. Chem. Soc.*, 2019, **141**, 29–32; (c) X. Zhu, C. C. McAtee and C. S. Schindler, Total Syntheses of Herquelines 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 SeO₂-mediated allylic oxidation) in substrate **2** exhibited a notable “twist” in contrast with the alkene in substrate **22a**. For details, see ESI.†

