

RESEARCH ARTICLE

View Article Online
View Journal | View IssueCite this: *Org. Chem. Front.*, 2016, 3, 62

Asymmetric total synthesis of *Lycopodium* alkaloids α -obscurine, *N*-desmethyl- α -obscurine, β -obscurine and *N*-desmethyl- β -obscurine†

Jian-Guo Fu, Guang-Qiang Xu, Rui Ding, Guo-Qiang Lin and Bing-Feng Sun*

Received 6th November 2015,
Accepted 17th November 2015

DOI: 10.1039/c5qo00355e

rsc.li/frontiers-organic

The asymmetric total synthesis of α -obscurine (**1**), β -obscurine (**2**), *N*-desmethyl- α -obscurine (**3**), and *N*-desmethyl- β -obscurine (**4**) was accomplished. Key reactions in the construction of the A/B/C-ring system include the Buchwald–Hartwig coupling reaction, the Heck cyclization, and the diastereoselective hydrogenation.

Among the *Lycopodium* alkaloids, lycodine-type alkaloids constitute a unique family to which the well-known memory-enhancing natural product huperzine A belongs.¹ α -Obscurine (**1**), β -obscurine (**2**), *N*-desmethyl- α -obscurine (**3**), and *N*-desmethyl- β -obscurine (**4**) are lycodine-type alkaloids. Some of these historic molecules were identified as early as seven decades ago. Interestingly, these natural products may be biogenetically relevant to huperzine A. As proposed previously, compound **5**, which in principle could be a general intermediate to all *Lycopodium* alkaloids, may engender deacetylflabellidine, a natural product, *via* a Mannich-type cyclization.^{2,7c,9b} Deacetylflabellidine might undergo oxidation, dehydrogenation and methylation to produce **1–4**, prior to further oxidative modifications leading to huperzine A (Scheme 1).

Obscurine was first isolated in 1942 by Manske and Marion³ from *Lycopodium obscurum* and was shown by Moore and Marion⁴ in 1953 to be actually a mixture of α -obscurine (**1**) and β -obscurine (**2**). In 1962, Ayer and co-workers successfully established the structure of **1** and **2** with the relative as well as the absolute stereochemistry by using a chemical correlation strategy.⁵ Moreover, they isolated *N*-desmethyl- α -obscurine (**3**) as a natural product and demonstrated that it could be obtained by demethylation of **1**.⁵ In the same paper, Ayer reported the preparation of *N*-desmethyl- β -obscurine (**4**) from β -obscurine (**2**).⁵ And in 1989 *N*-desmethyl- β -obscurine (**4**) was verified to be a natural product.⁶



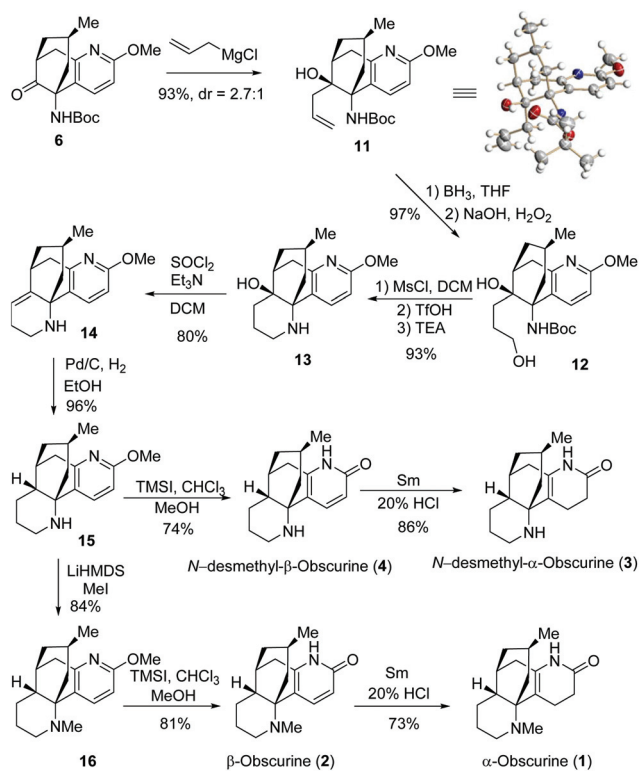
Scheme 1 Obscurines **1–4** in the proposed biosynthetic pathway leading to huperzine A.

CAS Key Laboratory of Synthetic Chemistry of Natural Substances, Shanghai Institute of Organic Chemistry, 345 Lingling Road, Shanghai 200032, China.

E-mail: bjsun@sioc.ac.cn

† Electronic supplementary information (ESI) available: Experimental procedures, spectroscopic data, and copies of ¹H, ¹³C and 2D NMR spectra. CCDC 1412716 and 1412717. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5qo00355e

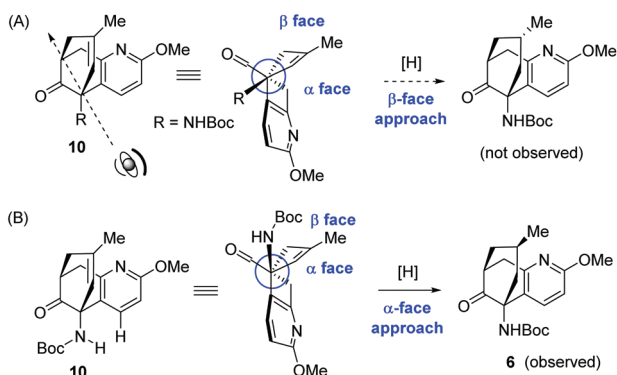
After Ayer's chemical transformations of α -obscurine (**1**) and β -obscurine (**2**) to *N*-desmethyl- α -obscurine (**3**) and *N*-desmethyl- β -obscurine (**4**), respectively, Schumann accomplished the first total synthesis of α -obscurine (**1**) and *N*-desmethyl- α -obscurine (**3**) as racemic forms in 1983.⁷ Schumann's elegant synthesis featured a highly convergent construction of the tetracyclic skeleton, which assembled A/D- and C-ring segments by an endgame biomimetic Mannich cyclization forming a B-ring. In 2010, by harnessing Schumann's strategy, Sarpong and co-workers rendered an asymmetric synthesis of *N*-desmethyl- α -obscurine (**3**) *en route* to the total synthesis



Scheme 4 Total synthesis of obscurines 1–4.

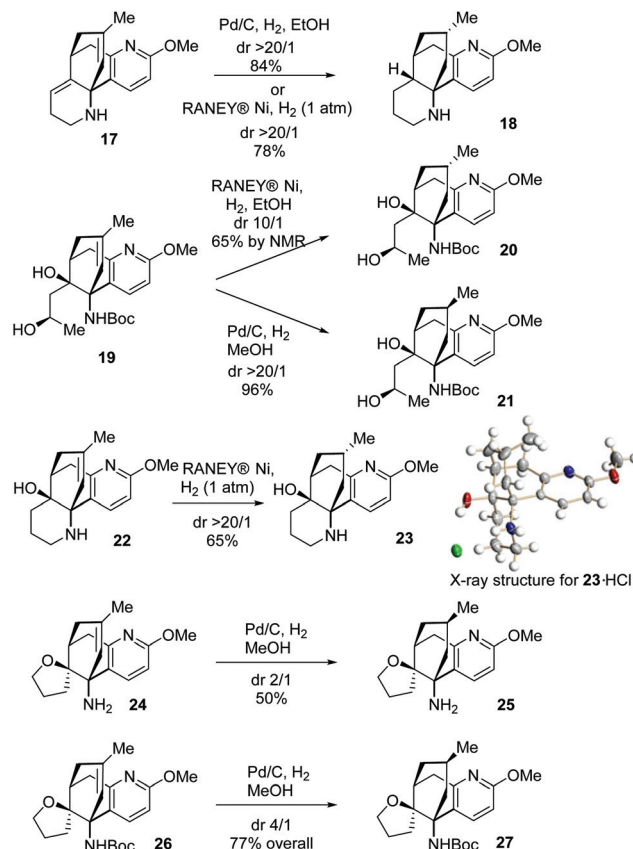
to afford **1** in good yields. The spectroscopic data of the synthetic samples of **1–4** matched those in the literature.

The facial selectivity in the hydrogenation of **10** is intriguing and deserves more comments. At a first glance, it seems that the undesired product stemming from the β -face approach would be more favoured. As depicted in Scheme 5A, the β face of the olefinic double bond corresponds to the convex side of the bicyclic framework. Therefore, the β face should have been more accessible for the hydrogenation, leading to the undesirable facial selectivity. However, the observed predominant product **6** resulted from the α face hydrogenation. This discrepancy possibly originated from the haptophilicity of the heteroatoms in the

Scheme 5 Conformational analysis for the hydrogenation of **10**.

substrate.¹³ Moreover, the *N*-Boc group could also play a critical role by shielding the β face of the olefin, presumably as a result of minimizing its interaction with the pyridine moiety (Scheme 5B). However, the free ketoamine derived from **10** was not available for the hydrogenation reaction due to its lability.

To further gain an insight into the facial selectivity of the hydrogenation in this unique molecular framework, the catalytic hydrogenation reactions of more substrates containing the A/B/C ring system were investigated (Scheme 6). The hydrogenation of **17**, catalysed either by Pd/C or RANEY® Ni, gave **18** essentially as a sole stereoisomer resulting from the β -face approach. In contrast, **19** underwent divergent hydrogenation reactions, furnishing predominantly **20** or **21** contingent on the catalytic conditions. The hydrogenation of **22** catalysed by RANEY® Ni furnished **23**.¹⁰ Further, the parallel hydrogenation reactions of **24** and **26** provided preferably **25** and **27**, respectively. These results clearly demonstrated that the Boc group benefited the hydrogenation reactions catalysed by Pd/C to deliver products with the desired facial selectivity while the OH group exerted a strong haptophilic effect in the RANEY® Ni-catalysed hydrogenation leading to the opposite facial selectivity. Importantly, these results can be of particular synthetic interest in view of the fact that both configurations at this stereocenter are present in natural products, such as acrifoline and annofoline.¹⁴

Scheme 6 Catalytic hydrogenation of **17**, **19**, **22**, **24** and **26**.

Conclusions

In summary, we have accomplished the asymmetric total synthesis of α -obscurine (**1**), β -obscurine (**2**), *N*-desmethyl- α -obscurine (**3**), and *N*-desmethyl- β -obscurine (**4**) with a new strategy, which features the approach to the A/B/C-ring system prior to the construction of the D-ring. Key reactions include the previously realized Buchwald–Hartwig coupling and the Heck cyclization reactions, and the newly developed diastereoselective hydrogenation, in a combined fashion to attain the A/B/C-ring system. In particular, the enabling hydrogenation reaction of **10** that fostered the critical C15 stereocenter, together with the hydrogenation reactions of **17**, **19**, **22**, **24** and **26**, constitute a collection of intriguing examples that can readily lend themselves to the total synthesis of relevant natural products. Endeavours along this line are currently underway and will be reported in due course.

Acknowledgements

We gratefully acknowledge the financial support from the National Natural Science Foundation of China (grant No. 21172246, 21290180, 21472210), and Youth Innovation Promotion Association CAS.

Notes and references

- (a) Y. Hirasawa, J. Kobayashi and H. Morita, *Heterocycles*, 2009, **77**, 679; (b) G. T. Ha, R. K. Wong and Y. Zhang, *Chem. Biodiversity*, 2011, **8**, 1189; (c) A. R. Desilets, J. J. Gickas and K. C. Dunican, *Ann. Pharmacother.*, 2009, **43**, 514; (d) A. P. Kozikowski and W. Tuckmantel, *Acc. Chem. Res.*, 1999, **32**, 641.
- (a) X. Q. Ma and D. R. Gang, *Nat. Prod. Rep.*, 2004, **21**, 752; (b) T. Hemscheidt, *Top. Curr. Chem.*, 2000, **209**, 175; (c) T. Hemscheidt and I. D. Spenser, *J. Am. Chem. Soc.*, 1996, **118**, 1799.
- R. H. F. Manske and L. Marion, *Can. J. Res.*, 1942, **20**, 87.
- B. P. Moore and L. Marion, *Can. J. Chem.*, 1953, **31**, 952.
- W. A. Ayer, J. A. Berezowsky and G. C. Iverach, *Tetrahedron*, 1962, **18**, 567.
- W. A. Ayer and G. C. Kasitu, *Can. J. Chem.*, 1989, **67**, 1077.
- (a) D. Schumann, H. J. Müller and A. Naumann, *Liebigs Ann. Chem.*, 1982, 1700; (b) D. Schumann, H. J. Müller and A. Naumann, *Liebigs Ann. Chem.*, 1982, 2057; (c) D. Schumann and A. Naumann, *Liebigs Ann. Chem.*, 1983, 220.
- D. F. Fischer and R. Sarpong, *J. Am. Chem. Soc.*, 2010, **132**, 5926.
- (a) R. Ding, B. F. Sun and G. Q. Lin, *Org. Lett.*, 2012, **14**, 4446; (b) R. Ding, J. G. Fu, G. Q. Xu, B. F. Sun and G. Q. Lin, *J. Org. Chem.*, 2014, **79**, 240; (c) J. Wang, B.-F. Sun, K. Cui and G.-Q. Lin, *Org. Lett.*, 2012, **14**, 6354; (d) J. Wang, S.-G. Chen, B.-F. Sun, G.-Q. Lin and Y.-J. Shang, *Eur. J. Chem.*, 2013, **19**, 2539; (e) X.-L. Wang, Y.-Y. Lu, J. Wang, X. Wang, H.-Q. Yao, G.-Q. Lin and B.-F. Sun, *Org. Biomol. Chem.*, 2014, **12**, 3562; (f) J. Wang, W.-B. Sun, Y.-Z. Li, X. Wang, B.-F. Sun, G.-Q. Lin and J.-P. Zou, *Org. Chem. Front.*, 2015, **2**, 674.
- CCDC 1412716 (**11**) and CCDC 1412717 (**23**) contain the supplementary crystallographic data for this paper.
- (a) L. Qian and R. Ji, *Tetrahedron Lett.*, 1989, **30**, 2089; (b) Y. Xia and A. P. Kozikowski, *J. Am. Chem. Soc.*, 1989, **111**, 4116.
- Y. Kamochi and T. Kudo, *Chem. Pharm. Bull.*, 1995, **43**, 1442.
- For selected examples of haptophilic hydrogenation, see: (a) H. W. Thompson and R. E. Naipawer, *J. Am. Chem. Soc.*, 1973, **95**, 6379; (b) H. W. Thompson and J. K. Wong, *J. Org. Chem.*, 1985, **50**, 4270; (c) L. E. Overman and A. L. Tomasi, *J. Am. Chem. Soc.*, 1998, **120**, 4039; (d) J. Tamiya and E. J. Sorensen, *J. Am. Chem. Soc.*, 2000, **122**, 9556; (e) J. Tamiya and E. J. Sorensen, *Tetrahedron*, 2003, **59**, 6921; (f) Q. Zhou, X. Chen and D. Ma, *Angew. Chem., Int. Ed.*, 2010, **49**, 3513; (g) K. Molawi, N. Delpont and A. M. Echavarren, *Angew. Chem., Int. Ed.*, 2010, **49**, 3517; (h) J. Wang, S.-G. Chen, B.-F. Sun, G.-Q. Lin and Y.-J. Shang, *Chem. – Eur. J.*, 2013, **19**, 2539.
- (a) W. N. French and D. B. MacLean, *Can. J. Chem.*, 1961, **39**, 2100; (b) R. H. Burnell and D. R. Taylor, *Tetrahedron*, 1961, **15**, 173; (c) W. A. Ayer, L. M. Browne, A. W. Elgersma and P. P. Singer, *Can. J. Chem.*, 1990, **68**, 1300.