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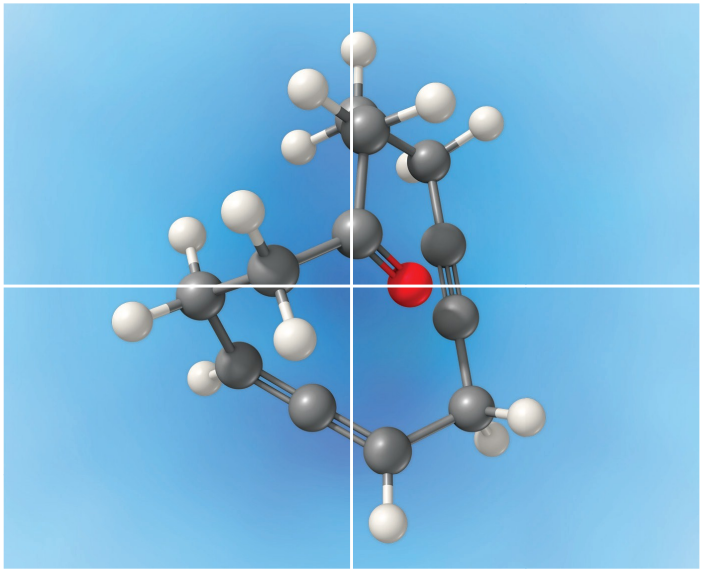

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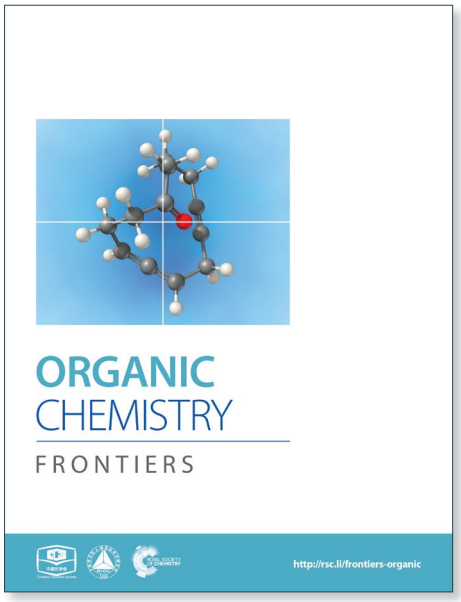

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Asymmetric total synthesis of *Lycopodium* alkaloids α-obscurine, *N*-desmethyl-α-obscurine, β-obscurine and *N*-desmethyl-β-obscurine†

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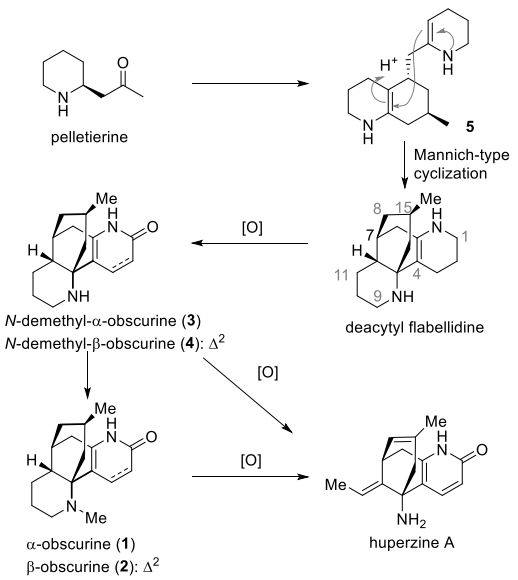
The asymmetric total synthesis of α-obscurine (1), β-obscurine (2), *N*-desmethyl-α-obscurine (3), and *N*-desmethyl-β-obscurine (4) was accomplished. Key reactions in the construction of the A/B/C-ring system include the Buchwald-Hartwig coupling reaction, the Heck cyclization, and the diastereoselective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

Among *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 Marion[3] from *Lycopodium obscurum* and was shown by Moore and Marion[4] 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]

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 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 of (+)-complanadine A.[8] To the best of our knowledge, these constitute the only synthetic endeavours toward these molecules.



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

In the past several years, we have been involved in the total syntheses of biologically significant natural products.[9] Among these, a collective total synthesis of huperzine A, huperzine B and huperzine U has been accomplished efficiently by employing a unified synthetic strategy.[9a,b] In this paper, we report the asymmetric total synthesis of **1**~**4** by harnessing the same synthetic strategy. As depicted in Scheme 2, the tricyclic

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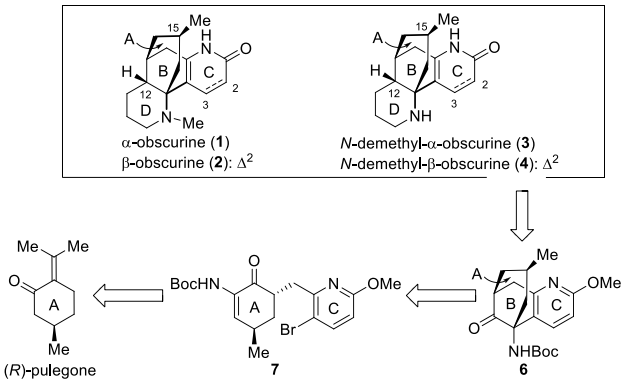
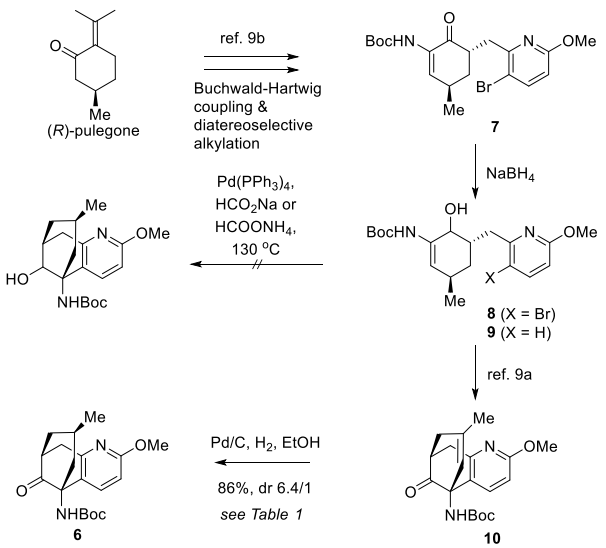
compound **6** containing the A/B/C-ring system was chosen as the key precursor to obscurines **1**~**4**. The C12 chiral centre in the target molecules was anticipated to be established via a diastereoselective hydrogenation of the olefinic double bond after the D-ring was constructed. Compound **6** with its [3.3.1] bicyclic core would stem from **7** and may be further traced back to (*R*)-pulegone.[9a] The establishment of C15 stereogenic centre was envisaged to be a critical undertaking.



Scheme 2 Retrosynthetic analysis for **1**~**4**.

Initially, a reductive Heck cyclization was envisioned to transform **7** to **6** with the stereocenter conserved. Thus, the synthetic journey commenced with the preparation of **7** and **8** from (*R*)-pulegone on a deca-gram scale.[9a,b] The reductive Heck cyclization of **8** was attempted. Unfortunately, under various tested conditions, the anticipated cyclization was not observed while compound **9** was isolated as a by-product. We reasoned that the reductive debromination might be significantly faster as compared to the desired Heck cyclization, leading to the formation of **9**.



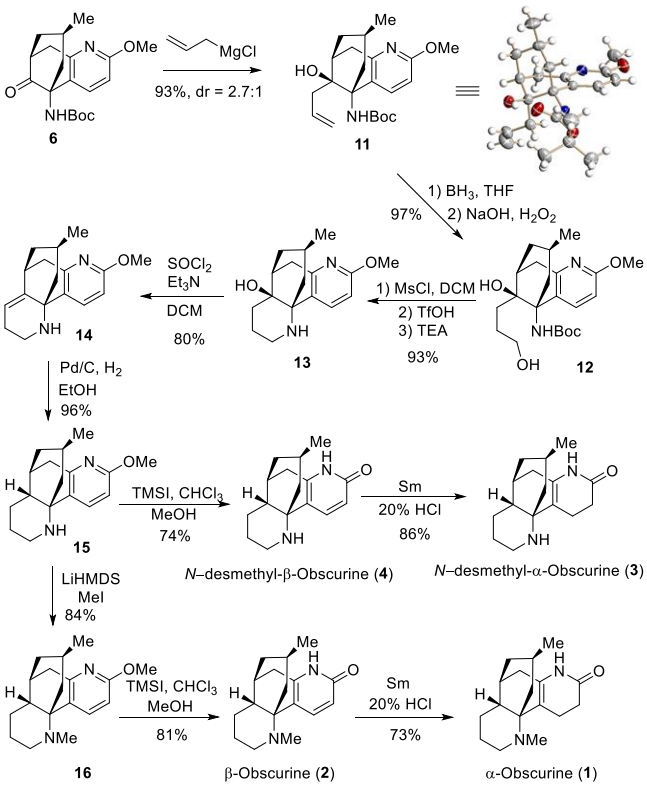
Scheme 3 Synthesis of **6**.

We sought to attack this problem by resorting to a stepwise strategy involving Heck cyclization and the subsequent diastereoselective hydrogenation. The Heck cyclization had favourably been achieved before[9a,b] which, however, would eliminate the original chirality at the carbon to be C15 in the target molecules. As a consequence, it would become necessary to effect a diastereoselective hydrogenation to restore the chiral center after the Heck reaction.

In light of this strategy, **8** was first transformed to **10** according to our previous conditions.[9a] With **10** in hand, we investigated the crucial diastereoselective hydrogenation. Under a hydrogen atmosphere of normal pressure, several conventional catalysts were tested for the reaction and the results were summarized in Table 1. Crabtree's catalyst did not show any catalytic activity for this reaction (entry 1). The Raney nickel catalysed hydrogenation resulted in a 1/1 mixture of diastereoisomers (entry 2). Delightfully, hydrogenation catalysed by palladium on carbon furnished a favourable 6.4/1 diastereoselectivity (entry 3). The stereochemistry of the major product would be confirmed at a later stage.

Table 1 Catalytic hydrogenation of **10**.

Entry	Conditions	Yield%	dr
1	Crabtree's cat.	-	-
2	Raney Ni	-	1/1
3	Pd/C, EtOH	86	6.4/1



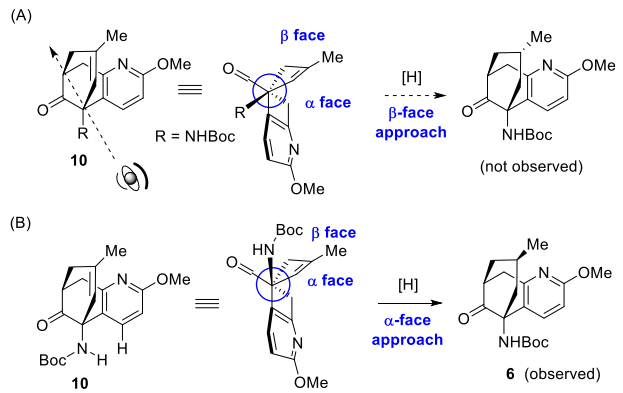
Scheme 4 Total synthesis of obscurines **1**~**4**.

With the key intermediate **6** in hand, we focused ourselves on the construction of the last piperidine D-ring (Scheme 4). Allylation of **6** generated **11** and 12-*epi*-**11** as a separable 2.7/1 mixture. The structure of the major isomer **11** was established by

X-ray crystallographic analysis,[10] thereby confirming the structure of **6**. Hydroboration of **11** followed by oxidative workup produced diol **12**, which was subjected to a one-pot protocol involving mesylation, deprotection, and basification, to furnish **13**. Dehydration of **13** resulted in **14**, which underwent diastereoselective hydrogenation on Pd/C to deliver **15** with all the stereochemistry properly loaded.

Eventually, compound **15** was converted to the target molecules (Scheme 4). Treatment of **15** with TMSI provided *N*-desmethyl-β-obscurine (**4**) in 74% yield.[11] Reduction of **4** with Sm/HCl delivered *N*-desmethyl-α-obscurine (**3**) in 86% yield.[12] On the other hand, **15** underwent *N*-methylation with LiHMDS/MeI to give **16**. Under similar conditions, **16** was subjected to *O*-demethylation to furnish β-obscurine (**2**), which was reduced to afford **1** in good yields. The spectroscopic data of the synthetic samples of **1**~**4** matched those in literature.

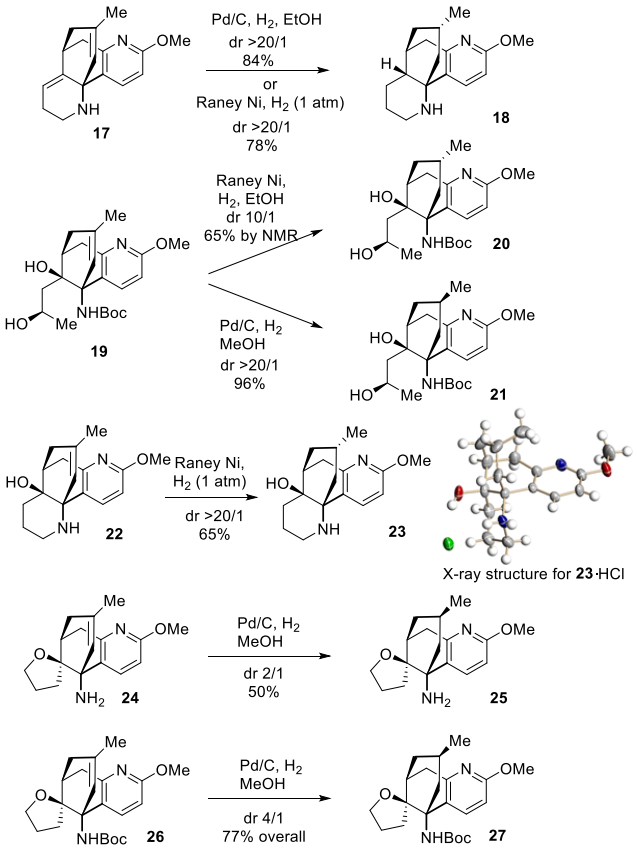
The facial selectivity in the hydrogenation of **10** is intriguing and deserves more comments. At a first glance, it seems that the undesired product stemming from the β-face approach would be more favoured. As depicted in Scheme 5 A, the β face of the olefinic double bond corresponds to the *convex* 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** was resulted from the α face hydrogenation. This discrepancy was possibly originated from the haptophilicity of the heteroatoms in the 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 5 B). However, the free ketoamine derived from **10** was not available for the hydrogenation reaction due to its lability.



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

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. 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 strong haptophilic effect in the Raney Ni-catalysed hydrogenation leading to the opposite facial selectivity. Importantly, these results can be of particular synthetic interests 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 A/B/C-ring system prior to the construction of 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

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