TUNEABLE ACCESS TO MEDICINALLY RELEVANT SCAFFOLDS VIA AN ENANTIOSELECTIVE DEAROMATIVE CYCLISATION CASCADE

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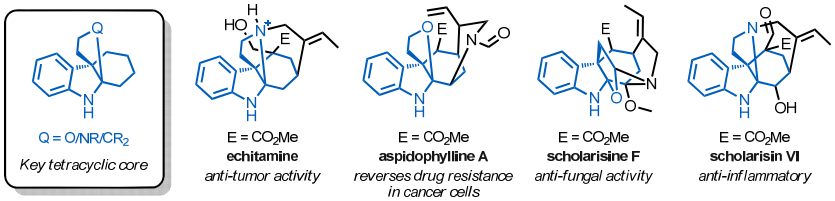
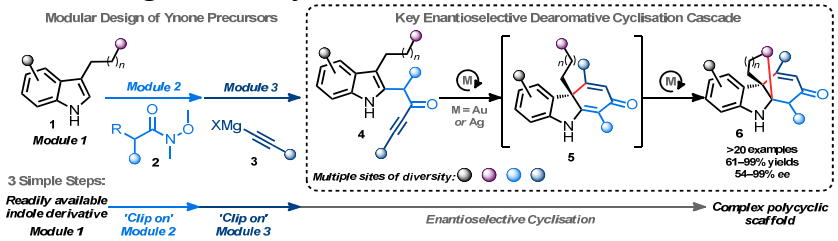
The akuammiline alkaloids are a family of natural products which have recently emerged as high-profile targets due to their outstanding medicinal properties (Scheme 1). Their complex polycyclic core continues to captivate synthetic chemists, inspiring the development of novel methodologies to access these privileged frameworks.[1]



Scheme 1. Select examples of akuammiline alkaloids and their biological properties

The ability to systematically change functionality at precise positions on a drug molecule is vital to understand how to improve its efficacy and biocompatibility. Current routes to the above scaffolds are usually streamlined towards a single specific product, requiring late-stage site-selective functionalisation of such scaffolds which remains a difficult challenge and severely hinders the development of drug molecules containing such complex polycyclic cores. Therefore, the development of more general and tuneable processes, able to furnish iterations of the above medicinally relevant core is highly desirable.

Herein we describe the rapid construction of the key akuammiline alkaloid core *via* an unprecedented enantioselective dearomatisation cyclisation cascade (4 → 6), furnishing polycyclic scaffolds (6) in excellent yields and enantioselectivities (Scheme 2, inside box). To further increase the utility of this methodology, a novel modular synthesis approach was employed whereby simple readily available compounds (1-3) were 'clipped' together to generate a range of functionalised ynone precursors (4). These precursors then undergo the aforementioned key complexity-generating step furnishing the desired scaffolds (6). By using this modular approach, a vast set of compounds could be rapidly assembled with precise introduction of functionality, therefore reducing the need for late-stage site-selective modifications. The excellent functional group tolerance and operational simplicity of our method, coupled with the remarkable yields and selectivities obtained makes this an extremely powerful strategy, accessing a collection of complex polycyclic scaffolds possessing the fundamental akuammiline core required for biological activity.



Scheme 2. Modular approach to ynone precursors and dearomative cyclisation cascade

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[1] B. D. Horning and D. W. C. MacMillan, *J. Am. Chem. Soc.* **2013**, 135, 6442; J. M. Smith, J. Moreno, B. W. Boal and N. K. Garg, *Angew. Chem. Int. Ed.* **2015**, 54, 100; Z.-X. Zhang, S.-C. Chen and L. Jiao, *Angew. Chem. Int. Ed.* **2016**, 55, 8090.