Switchable Chemoenzymatic Synthesis of Natural Product-like Pyrroloindolines or Serotonin analogues *via* an Interrupted Fischer Indole Synthesis

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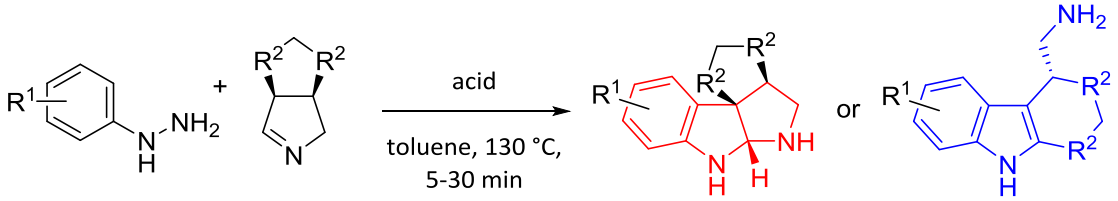
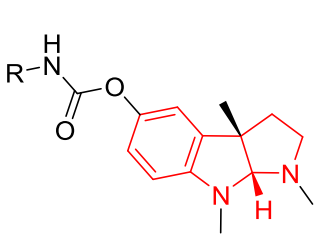
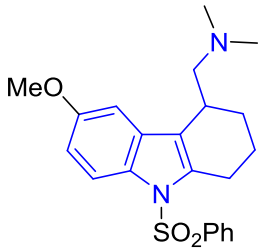
Pyrroloindoline alkaloids constitute a diverse class of natural products that exhibit interesting biological properties including anticholinesterase, analgesic and antitumour activity. Several representatives of the pyrroloindoline natural product class have been prepared by total synthesis, but these often multistep procedures do not allow straightforward systematic variation of the substituents and scaffold. Herein, we describe the synthesis of natural product-like pyrroloindolines by an asymmetric cascade reaction[1] based on interrupted Fischer indole synthesis.[2] This highly selective and tunable reaction between arylhydrazines and bicyclic imines, which are derived from *meso*-pyrrolidines by biocatalytic oxidation,[3] provides access to pharmaceutically interesting constrained analogues of bioactive molecules in high optical purity using a short and efficient synthesis.



A subtle change in the reaction conditions results in a completely selective switch of the reaction outcome towards constrained tryptamines by a rare Wagner-Meerwein-type rearrangement known as the Plancher rearrangement.[4] These constrained tryptamine and, in particular, serotonin analogues are of high interest for drug discovery due to their ability to modulate neurotransmitter receptors involved in neurodegenerative diseases such as Alzheimer's disease. A thorough investigation of the regioselectivity for both the interrupted Fischer indole synthesis and the Plancher rearrangement is presented, providing interesting insight in the reaction mechanism.



cholinesterase inhibitors



5-HT$_6$ serotonin (5-HT) receptor antagonist

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3. V. Kohler, K. R. Bailey, A. Znabet, J. Raftery, M. Helliwell and N. J. Turner, *Angew. Chem. Int. Ed.*, **2010**, *49*, 2182-2184.
4. C. C. J. Loh, G. Raabe, D. Enders, *Chemistry-a European Journal* **2012**, *18*, 13250-13254.