Generation of Key Intermediates for the Synthesis of (+)-Crinamine and Derivatives by Chiron Approach

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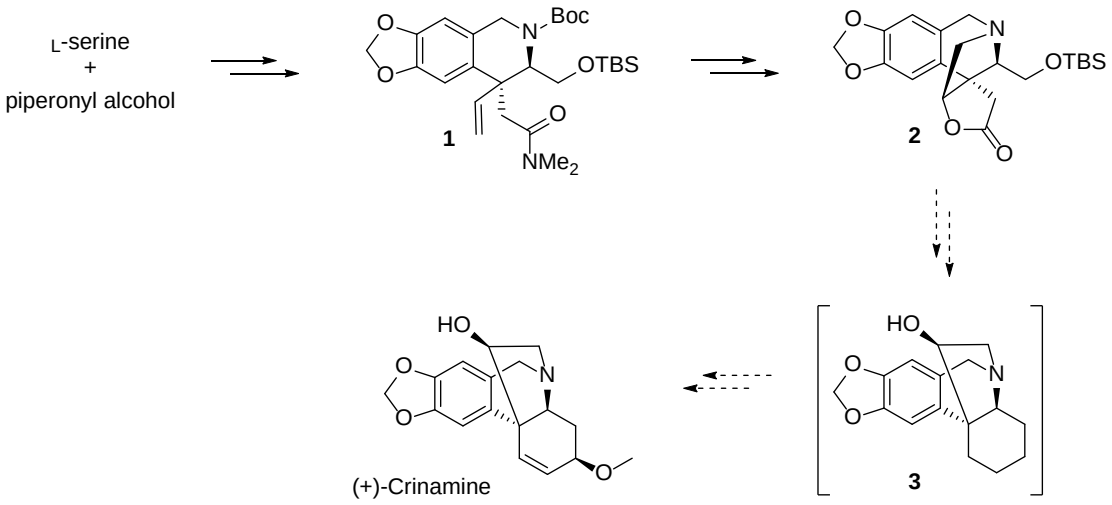
Amaryllidaceae alkaloids represent a class of highly physiologically active compounds characterized by antitumor, antiviral, acetylcholinesterase inhibition, analgesic and antimalarial activities.[1] Total syntheses of these challenging molecules should enable access to the natural products and to potential useful analogues and derivatives.

Due to its complex structure based on pentacyclic bridged ring phenanthroline system featuring four defined stereogenic centers (+)-Crinamine was chosen as an ambitious target for asymmetric total synthesis.



Starting from L-serine and piperonyl alcohol, an “ex-chiral-pool” sequence[2] affords amide **1** including the defined configured quaternary C centre because of an efficient asymmetric induction applying Eschenmoser Claisen rearrangement.[3]

Spirocycle **2** displays three of four stereogenic centres of (+)-Crinamine with correct configuration, which could be determined by X-ray crystal structure analysis. Current investigations focus on using spirocycle **2** as key intermediate for introduction of a C_1-segment required for D-ring completion. Finally, a structure representing the entire

framework of Crinine-type alkaloids (cf. **3**) should serve as precursor for total syntheses of enantiopure (+)-Crinamine and analogues.

Literature*:*

[1] Jin, Z. *Nat Prod Rep* **2009**, *26*, 363.

[2] Bernhard, S. *Synthese von Crinan-Alkaloid-Vorstufen*, Dissertation, Johannes Gutenberg University Mainz, Mainz, **2015**.

[3] Kümmerer, N. *Aufbau von optisch aktiven Vorstufen zur Totalsynthese von (+)-Crinamin*, Master-Arbeit, Johannes Gutenberg University Mainz, Mainz, **2016**.