Synthesis of azabicyclic natural product analogues aiming at biological activity

Christian Stevens, Thomas Heugebaert, Melissa Vanovertveldt, Iris Wauters

Ghent University, Gent, Belgium

Many natural products with interesting biological activity contain azabicyclic or bridged nitrogen containing scaffolds. These conformationally restricted compounds are characterised by a considerable ring strain which may complicate ringclosing reactions.

The lecture will discuss ringclosing methodology for the synthesis of several classes of azabicyclic and azamulticyclic derivatives designed towards agrochemical or medicinal applications.

A dynamic ring closure has been deloped for the synthesis of 7-azabicyclo[2.2.1]heptanes. This skeleton is present in epibatidine, a very active analgesic compound isolated from the skin of the Ecuadorian frog *Epipedobates tricolor.* Its potency was proven to be 200-fold higher than morphine, however epibatidine cannot be used clinically because of its high toxicity. Different classes of epibatidine analogues have been prepared trying to minimize toxicity while maintaining the analgesic properties.

Gold catalysed ringclosing reactions have been developed for the synthesis of functionalised isoindoles, dehydrothiazoles and pyrroles.The ring closing involves a 5-exodig cyclization, followed by a [1,3]-alkyl shift and a [1,5]-H shift.

Diketopiperazines are well recognized as an important moiety in medicinal active secondary metabolites of plants. We developed a new cyclization for the straightforward synthesis of constrained diketopiperazine analogues of the brevianamide family. This new class of analogues with a 3,5-bridged structure and bearing an alfa-chloro amine function allows the synthesis of a library of compounds using a variety of nucleophiles. We also performed ab initio calculations to get insight on the mechanism of the DKP-tryptophane ring closure.