Enoate-Reductases for the Synthesis of 1,3-Amino Alcohols and β-Amino Acids

Supervisors / institute:

Main supervisor: Thomas J. J. Müller, Institute of Organic Chemistry and Macromolecular Chemistry

Co-supervisor: Jörg Pietruszka, Institute of Bioorganic Chemistry

Project background and description:

1,3-Amino alcohols appear as structural motifs in various natural products and have become highly important synthetic building blocks in organic synthesis. Likewise β-amino acids have received considerable importance in biological and medicinal chemistry. Based upon the easy synthetic access to enaminones and β-aminoenoates with a broad substitution pattern by multicomponent synthesis the enzymatic reduction of the enamino functionality to an amine provides a concise, efficient chemoenzymatic approach to the title compounds.

Enoate reductases are redox enzymes, which can be fuelled with glucose as sacrificing reductants and render a very mild enantioselective method for Michael-type hydride transfer at ambient temperature and pressure conditions.

The conceptual approach starts with the systematic screening of available enoate reductases from IBOC, their evaluation with respect to substrate specificity and selectivity, stereoselectivity (in particular diastereoselectivity in combination with alcohol dehydrogenase mediated reductions of enaminones directly to 1,3-amino alcohols), and leads to developing models and tailor-made optimized enzymes for the enantioselective reduction. Finally, the concatenation of chemical substrate formation followed by the enzymatic reduction in a one-pot fashion is the ultimate goal for this novel environmentally benign tool. The application in a concise enantioselective synthesis of nicotine receptor stimulating piperidine alkaloid (-)-lobelin is proposed.

A close co-operation with the bioorganic team of Prof. Pietruszka, the computational team Prof. Gohlke as well as protein crystallography of Prof. Groth is very important for the success of the project.

Aims of the project:

- Stereoselective reductions of enaminones/β-aminoenoates with known and new enoate reductases and combinations with alcohol dehyrogenases
- Application of enzymes in organic synthesis
- Co-operation with the groups of Jörg Pietruszka (IBOC), Holger Gohlke (computational pharmaceutical chemistry) and Georg Groth (protein crystallography)

Requirements:

- Master degree in chemistry or biochemistry
- experience in organic synthesis

Additional information:

http://www.tjjmueller.de

Comprehensive reading on multicomponent synthesis of heterocycles via ynones:

T. J. J. Müller, Top. Heterocycl. Chem. ***2010****, 25, 25-94.*