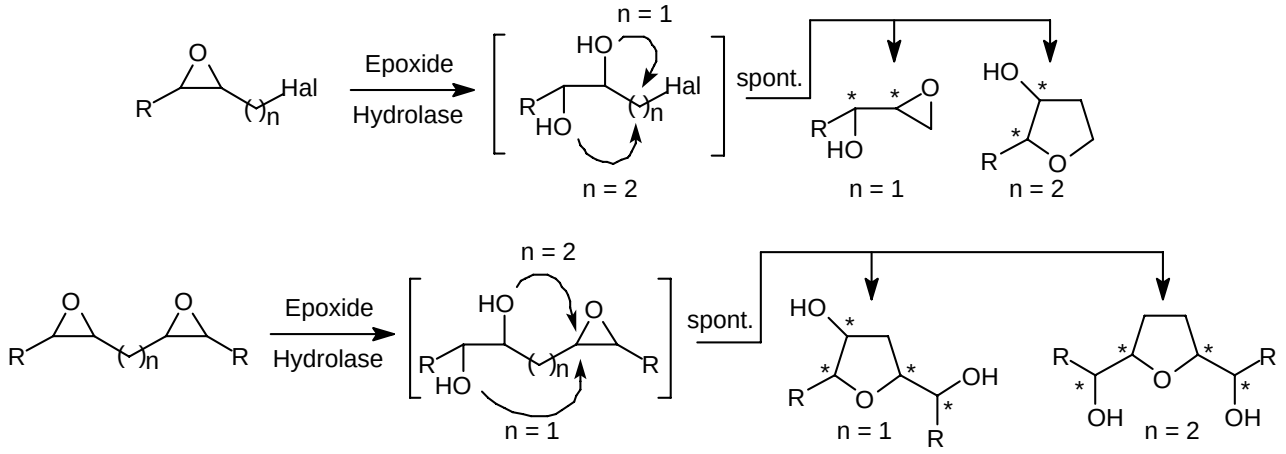
Simultaneous Creation of Multiple Stereocenters via Enzyme-Triggered Cascade-Reactions.

K. Faber, S. M. Glueck, S. F. Mayer, B. T. Ueberbacher
Department of Chemistry, Organic & Bioorganic Chemistry, University of Graz,
Heinrichstrasse 28, A-8010 Graz, Austria. <Kurt.Faber@Uni-Graz.at>.

Cascade-reactions provide rapid and efficient access to complex organic molecules. In case the cascade is triggered by an enzyme, its stereochemical course can be directed in an asymmetric fashion to furnish nonracemic products [1]. This protocol is widely used in Nature for the biosynthesis of complex natural products but is largely underexploited as a synthetic tool. We have recently shown that the biotransformation of haloalkyl-oxiranes by bacterial epoxide hydrolases initiates a hydrolysis-cyclisation cascade to furnish hydroxy-epoxides (n = 1) or -tetrahydrofurans (n = 2) with the simultaneous 'creation' of two asymmetric centers [2]. The latter compounds were used as chiral building blocks for the asymmetric total synthesis of various natural products, such as Pestalotin, a Jamaican rum constituent [3] and Panaxytriol [4].



This methodology was successfully extended to solve to an even more challenging task - the sequential biohydrolysis-cyclisation of methylene- or ethylene-interrupted bis-epoxides. Enzyme-initiated hydrolysis-cyclisation of the latter compounds gave rise to THF-products possessing four stereogenic centers in high d.e. and e.e. [5]. The latter reaction sequence strongly resembles a biomimetic strategy for the synthesis of the THF-core of *Annonaceous acetogenins*, a large and important group of bioactive secondary metabolites from tropical plants showing a diverse spectrum of bioactivity.

This study was performed within the Spezialforschungsbereich Biokatalyse and financial support by the Fonds zur Förderung der wissenschaftlichen Forschung is gratefully acknowledged.

[1] S. F. Mayer, W. Kroutil, K. Faber, *Chem. Soc. Rev.* **2001**, *30*, 332.
[2] S. F. Mayer, A. Steinreiber, R. V. A. Orru, K. Faber, *Eur. J. Org. Chem.* **2001**, 4537.
[3] S. F. Mayer, A. Steinreiber, M. Goriup, R. Saf, K. Faber, *Tetrahedron: Asymmetry* **2002**, *13*, 523.
[4] S. F. Mayer, A. Steinreiber, R. V. A. Orru, K. Faber, *J. Org. Chem.*, **2002**, *67*, 9115.
[5] S. Glueck, S. F. Mayer, W. M. F. Fabian, K. Faber, *Chem. Eur. J.* **2004**, *10*, 3467.