

# ASYMMETRIC BIOCATALYTIC PICTET-SPENGLER REACTION TO SHORTCUT ORGANIC SYNTHESIS

Elisabeth Eger<sup>a</sup>, Willem Breukelaar<sup>a</sup>, Jörg H. Schrittwieser<sup>a</sup>, Adam Simon<sup>b</sup>,  
Gideon Grogan<sup>c</sup>, Ken Houk<sup>b</sup>, Wolfgang Kroutil<sup>a</sup>

<sup>a</sup>University of Graz, Institute of Chemistry, 8010 Graz, Austria

<sup>b</sup>UCLA, Molecular Biology Institute, Los Angeles, USA

<sup>c</sup>University of York, Department of Chemistry, York YO10 5DD, UK

The Pictet-Spengler reaction gives access to a large variety of N-heterocyclic compounds whereby various chemical protocols have been established including many stereoselective approaches [1-2]. However, only few protocols using chiral catalysts and allowing to take directly the aldehyde and amine as substrate have been described [3].

In nature a handful of substrate specific enzymes are known, like the norcoclaurine synthase or the strictosidine synthase. The strictosidine synthase has been described to transform tryptamine and the highly functionalized polar aldehyde secologanin to the corresponding (*S*)-configured strictosidine [1,4]. We have investigated this enzyme and could show that it also accepts non natural aldehydes. To our surprise, small aldehydes such as isovaleraldehyde are transformed to the corresponding (*R*)-product in essentially optically pure form [5]. This enabled to short-cut otherwise long synthetic routes. Solving the crystal structure of the enzyme did not lead to a clear explanation why the enzyme gives the (*R*)- instead of the expected (*S*)-product. Combining forces with MD-simulations led to an explanation. Modifying the catalyst allowed to extend the substrate scope and stereoselectivity of the catalyst.

---

[1] J. Stöckigt, A. P. Antonchick, F. Wu, H. Waldmann, *Angew. Chem. Int. Ed.* **2011**, *50*, 8538.

[2] M. Chrzanowska, A. Grajewska, M. D. Rozwadowska, *Chem. Rev.* **2016**, *116*, 12369.

[3] Selected example: R. S. Klausen, C. R. Kennedy, A. M. Hyde, E. N. Jacobsen, *J. Am. Chem. Soc.* **2017**, *139*, 12299.

[4] E.-M. Fischereeder, D. Pressnitz, W. Kroutil, *ACS Catal.* **2016**, *6*, 23.

[5] D. Pressnitz, E.-M. Fischereeder, J. Pletz, C. Kofler, L. Hammerer, K. Hiebler, H. Lechner, N. Richter, E. Eger, W. Kroutil, *Angew. Chem. Int. Ed.* **2018**, *57*, 10683.