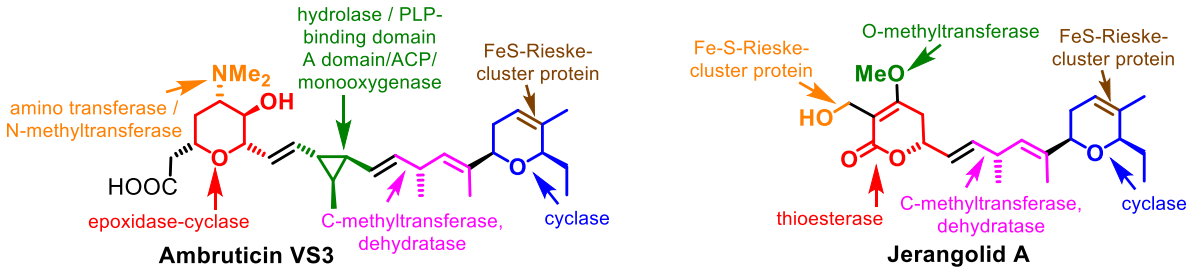

The aim of this project was the *in vitro* study of the biosynthetic pathways of the potent antifungal polyketides ambruticin and jerangolid on the enzymatic level. After biochemical characterisation of key enzymes in both pathways, it was planned to evaluate these enzymes regarding their biocatalytic potential and finally apply promising candidates in chemoenzymatic routes to both compounds.

Work on all five envisaged work packages was successfully carried out. The genes for all enzymes and domains of interest were cloned and protocols for their soluble expression in *E. coli* and their purification were developed. The synthesis of appropriate substrate surrogates for enzyme testing was also fully achieved.

Activity assays for several of the key enzymes were successfully carried out so that the biosynthesis of mayor structural elements, like the conserved hydropyran ring, the skipped dienes in both molecules as well as the 4-methoxy-5,6-dihydro-pyranone in jerangolid were elucidated. Novel enzymatic activities were uncovered in the course of these studies and a better understanding of unconventional biosynthesis mechanisms was gained.

The substrate tolerance as well as the applicability on the semipreparative and the preparative scale was investigated for some of these successfully characterised enzymes. They can now be applied in efficient chemoenzymatic routes, for example to dihydro-derivatives of the conserved eastern moiety of both natural products. Due to the observed substrate tolerance, the synthesis of further derivatives should be possible *via* these routes.

This work has expanded the current repertoire of biocatalysis by enabling the direct enzymatic synthesis of oxygen heterocycles, an abundant structural element of many pharmacologically relevant natural products. These and further results from the project are thus not only of interest for biosynthesis

research, but also for natural product synthesis and medicinal chemistry as well as drug research.

One project-related manuscript was published in *Angewandte Chemie*, which describes a novel type of cyclase domain, AmbDH3, with significant potential to be used as a biocatalytic tool. Three further manuscripts will be finalised and submitted at the end of the year 2015/beginning of 2016. The project results were furthermore presented to the public in form of 13 posters and 19 oral presentations. A documentary for “Beilstein TV” from the “Beilstein Institute” about the research group and part of the work carried out during the project was recorded and will be published under http://www.beilstein.tv/all/ by December 2015.

Support by the *Carreer Integration Grant* has significantly contributed to the professional development and reintegration of the fellow. The preliminary work funded by the CIG greatly helped in acquiring further funding like a prestigious Emmy Noether fellowship from the *Deutsche Forschungsgemeinschaft* (DFG) and a PhD fellowship. The independent junior research group at the *Centre for Biomolecular Drug Research* in Hannover currently consists of six PhD students and three master students.