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The elaboration of polyketide natural products with artificial building blocks: A combination of organic and microbial synthesis

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Polyketides are among the most important natural products used in modern medicine for the treatment of different conditions, from bacterial infections to cancer. Their structures bristle with complex redox patterns and stereochemical information and render them challenging and at the same time rewarding synthesis targets. More than 80% of all polyketide require derivatization to adjust them to the pharmaceutical application, which is highly demanding due to the structural complexity.

Established derivatization strategies comprise partial synthesis and in few cases the total synthesis of natural product analogs; both approaches are in many cases complicated and costly which limits their acceptance in modern pharmaceutical R&D.

Hence, we decided to develop alternative strategies that merge the flexibility of organic synthesis with the highly-efficient biosynthetic capability in generating molecular complexity. Small building blocks, analogous to polyketide biosynthetic pathways, are synthesized and supplied to the biosynthetic machinery of polyketide-producing bacteria. The result is the chemo-microbial synthesis of focused natural product libraries, yielding new compounds with interesting biological activities that are otherwise not efficiently accessible.

The involved enzymes require enzyme-engineering to alter the substrate profile. They show complete enantiospecificicity, enabling the racemic synthesis of small building blocks as the enzymatic machinyer performs an in situ racemate resolution. The overall process yields stereochemically pure polyketide derivatives with up to 17 stereogenic centres.

The talk will show the biosynthetic multi-step cascade towards polyletide natural products and show their potential as a toolbox for organic synthesis and medicinal chemistry.

Biography

Frank Schulz has completed his PhD in 2007 with a thesis at the Max-Planck-Institute of Coal Research under supervision of Manfred T. Reetz and pursued postdoctoral studies at Cambridge University in the laboratory of Peter F. Leadlay. From 2009 on he was Beilstein Professor of Organic Chemistry at the TU Dortmund. Since 2013, he is professor of organic chemistry at the Ruhr University Bochum, synthesizing natural product derivatives using a variety of techniques from organic synthesis and biochemistry.

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