Plenary Speakers

Biomimetic Catalysis and Natural Product Synthesis

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Biomimetic natural product total synthesis can be a valuable strategy for the assembly of complex target molecules. It remains a powerful concept even 100 years after its first mention (and application) in literature.[1] Mimicry is often particularly effective when it comes to establishing sterically encumbered substructures or polycyclic frameworks. In addition, speculation on biosynthetic pathways can sometimes be used to postulate the most likely constitution or configuration and sometimes even allow to predict the structure of an as yet undiscovered metabolite. A putatively biomimetic synthesis can then be used to confirm (or correct) the structure of the respective natural product.

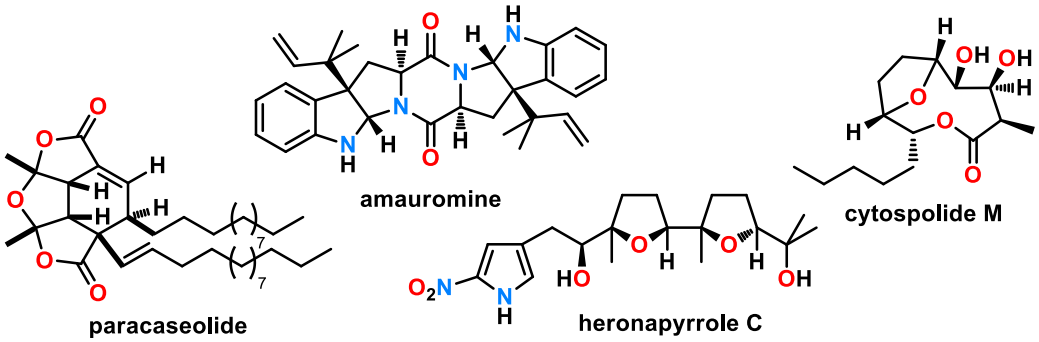

Figure 1: Selected structures of natural products assembled in a biomimetic fashion

Expedient synthetic methodology[2] not merely imitates natures pathways but enables access to other isomers and analogues. Selected examples from our program on biomimetic natural product synthesis including polyketides, meroterpenes, alkaloids and fatty acid type natural products will be presented.[3]

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Radical and Radical-Polar Crossover Transformations in the Synthesis of Complex Triterpenoids

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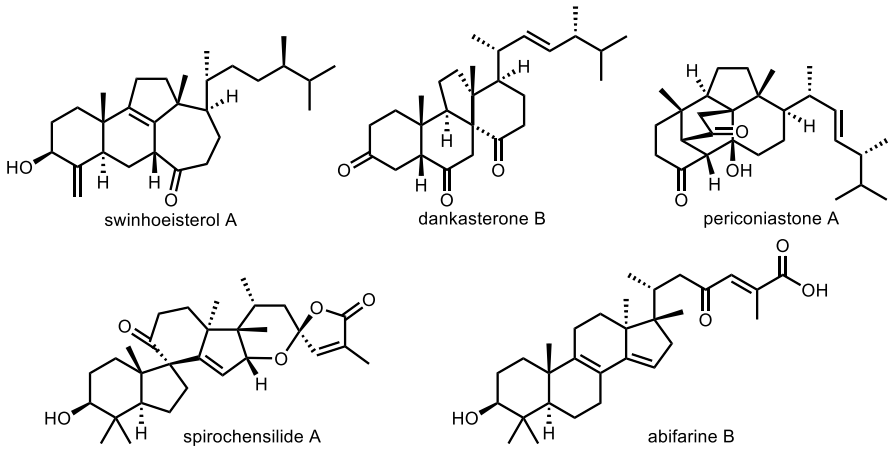
Facilitating and streamlining the access to rearranged and oxidized triterpenoids (see below) requires an understanding of nature's ways to biosynthesize these structures, i.e., of their biogenesis. Biomimetic synthesis can only then provide routes which typically outrival classical retrosynthetic planning.

In the absence of a plausible biogenesis proposal, this strategy is not accessible, though. Biogenesis proposals for rearranged triterpenoids have, in lieu of validated intermediates and enzymes, followed the paradigm of polar mechanisms and evoked ionic intermediates to account for skeletal rearrangements.

The aim of our research is to provide chemical evidence against this paradigm and cross this perceived limit of reactivity.

In this presentation, recent synthetic examples from our work will be discussed. As a result, polar transformations were not sufficient to access the target structures, but rather an intricate interplay of radical and polar reactivity led to success.



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Fatty acid synthases (FASs) enable access to new-to-nature compounds

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Multienzyme type I fatty acid (FASs) and polyketide synthases (PKSs) catalyze C-C bond forming reactions in compartmentalized space. Compartmentalization is largely achieved by the transacylation function of FASs and PKSs, i.e. the enzymatic reaction responsible for selecting substrates from the bulk cytoplasm, and further relies on the specific protein architecture as well as the shuttled distribution of substrates between the enzymatic domains. Controlling the transacylation function of FASs and PKSs is a powerful mean to modulate the product output of these proteins to access platform chemicals and bioactive compounds. [1,2]

Two examples for transacylation-based engineering will be presented in this talk: (i) We employed fungal FAS for the custom synthesis of platform chemicals, among them short-chain fatty acids, methylketones and lactones [3-5]. Here, some FAS constructs were modulated in their transferase function to work in sequence and to increase the complexity of the synthesized compounds. (ii) The mammalian FAS features high transacylation rates for a wide range of substrates [2]. We inserted the mammalian FAS transferase domain (MAT) into modular PKSs to enable the *in vitro* chemoenzymatic synthesis of new polyketides, including fluorinated 12- and 14-membered macrolactones with the same fluoro-methyl motif as in the next-generation antibiotic solithromycin [6].

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Assault, Siege or Trojan Horse Strategy: Use of Natural Products to Fight Bacterial Infections

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Multidrug resistant bacterial pathogens have become a major health concern. Especially infections by gram-negative bacteria are challenging, since their complex cell membrane architecture strongly impedes the uptake of drugs. Because microbial natural products continue to be the prime source to tackle these issues, we have investigated natural products as the basis for novel antibiotics.

The armeniaspirols represent a novel class of antibiotics with a unique spiro[4.4]non-8-ene chemical scaffold and potent activities against gram-positive pathogens.[1] I will report a concise total synthesis of (±) armeniaspirol A and disclose their mechanism of action, that might be also valid for other chloropyrrole-containing natural products.[1] A broad spectrum of gram-positive and gram-negative pathogens is addressed by cystobactamids, oligo-arylamids originally isolated from *Cystobacter sp.* Our efforts to optimize the antibiotic properties of the cystobactamids by medicinal chemistry will be presented.[2]

Beyond a classic 'assault' of bacteria with such antibiotics, the conjugation of natural products to targeting functions has been beneficial to improve their drug properties.[3] In the so-called Trojan Horse Strategy, antibiotics are conjugated to siderophores to hijack the bacterial siderophore transport system, and thereby enhance the intracellular accumulation of drugs.[4] We present novel artificial siderophores, characterize their transport and resistance mechanisms, and their efficacy when coupled to antibiotic natural products.[5] Finally, we present a novel approach for the selective bacterial targeting and infection-triggered release of antibiotic conjugates in the alternative siege concept, using the lipopeptide colistin as the antibiotic effector.[6]

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Identification and preclinical development of anti-infectives from myxobacterial natural products

Rolf Müller, Jennifer Herrmann, Daniel Krug, and Ronald Garcia

Amongst the well-established bacterial producers, myxobacteria have a great track record for the discovery of entirely new natural product scaffolds exhibiting promising bioactivities.[1] This is at least in part because they have been much less studied as compared to other traditional sources such as actinomycetes and bacilli. Comparisons of myxobacterial metabolite profiles with the number of underlying biosynthetic gene clusters encoded in their very large genomes show, that many compounds still remain unknown. Further, recent studies indicate that the order of myxobacteria likely comprises many more biodiverse representatives than previously assumed. According to metagenomics analyses, myxobacteria (including many underexplored representatives) are highly abundant in the soil microbiome, where they play a crucial role in soil nutrient and carbon cycling. Taken together with our recent genomic analyses, these findings suggest that the biosynthetic potential of myxobacteria is a long way from being exhausted.

Nevertheless, the issue of rediscovery is a major hurdle for myxobacterial extracts as well. In an attempt to tackle this issue, we recently demonstrated that chemical diversity correlates with taxonomic distance in myxobacteria.[2] Accordingly, we are more likely to isolate novel compound classes from strains which are phylogenetically distant from previously characterized strains as compared to closely related strains. This knowledge can be applied to prioritize strains for natural product discovery, thus increasing the chance of discovering compound classes with yet unknown chemical structures and biological activities. I will discuss recent results from our laboratory regarding the identification of novel bioactive natural products from myxobacteria based on different approaches, and will show our recent advances in their preclinical development.[3,4,5,6,7]

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PhD presentations

Insights into HDACi associated modes of action of SAHA-like pleiotropic anticancer compound Troxbam in 2D and 3D cell culture models

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Modulators of malignant tumours are as diverse as the disease itself. However, some common key features of cancer cells distinguish them from healthy cells, known as 'hallmarks of cancer'. Histone deacetylase inhibitors (HDACi), such as HDACi SAHA (suberoylanilide hydroxamic acid, a.k.a. vorinostat), target the hallmark of replicative immortality through disruption of DNA replication machinery. In drug discovery, the combination of different modes of action is becoming increasingly popular, as this allows several targets to be addressed by one substance. In cell-based assays for screening new investigational drugs, the use of 3D cell models instead of 2D monolayer cultures has been gaining importance. A key drawback of 2D tumour cell models is their lack of physiological relevance as they don´t consider essential factors of *in vivo* tumours. These factors may be observed by using 3D cell culture models, e.g. as multicellular tumour spheroids (MCTS). Using 2D monolayer cell cultures and 3D MCTS of HCT116 colon carcinoma cells we analysed the effects of the promising dual-mode anticancer agent Troxbam, as well as its structural congeners SAHA and combretastatin A-4. Troxbam showed distinct cytotoxic effects on human tumour cell lines and induced apoptosis by enhancing caspase-3 and -7 activities in 2D, as well as enhanced caspase-9 levels in 3D. Troxbam effectively reduced cellular motility and proliferative capacity of single cells. It also induced G2-M cell cycle arrest in HCT116 cells. Furthermore, it significantly reduced the growth of MCTS in 3D and induced cell death, associated with enhanced levels of reactive oxygen species. Troxbam also inhibited HDAC6 which is associated with over acetylation of tubulin and therefore disturbed dynamics of microtubules, observed in HCT116 cells. A distinct downstream association of HDAC inhibition in form of reduced survivin expression could further be proven. Survivin is a prominent member of the Inhibitor of Apoptosis Proteins (IAP), which is sharp differential expressed in cancer cells and usually not expressed in normal tissues, therefore it represents an interesting target for cancer therapy. Our study confirms Troxbam as an interesting alternative to established HDACi SAHA, approved by 2D and 3D tumour cell models.

Chemoenzymatic Synthesis of N-Glycans and Glycoconjugates

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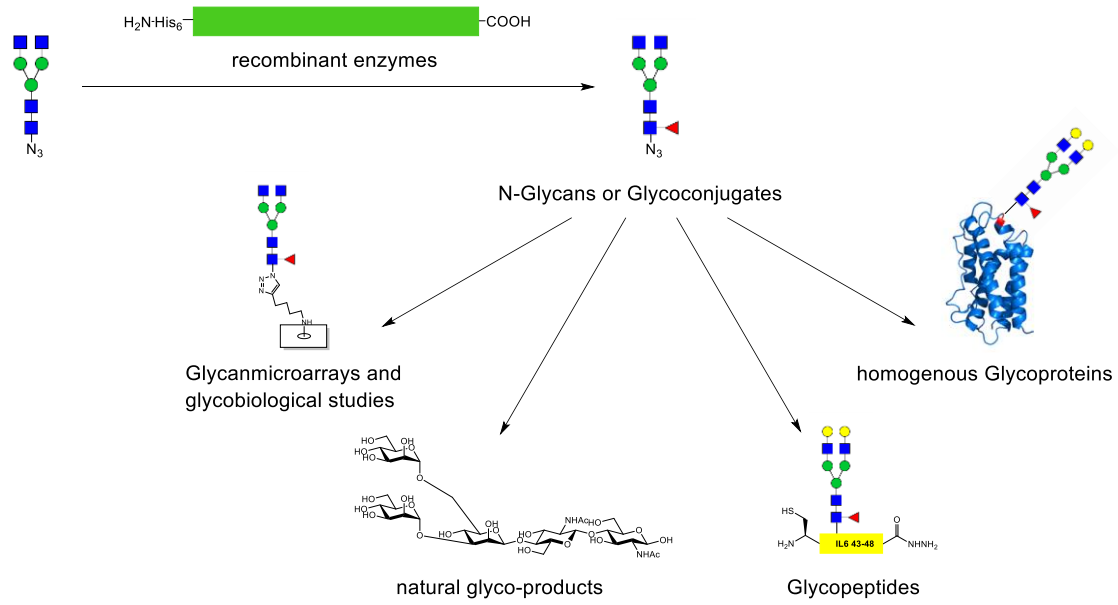
Glycosylated natural products are ubiquitous but frequently difficult to obtain in high purity. In our group we focus on the development of methods for the synthesis of N-glycans and complex glycoconjugates. Assaying synthetic glycoconjugates can reveal the glycan-related-response of biological systems (glycobiology).
The chemical synthesis of glycans and glycoconjugates typically involves many reaction steps, which can be time consuming and low yielding. In contrast chemoenzymatic approaches can provide a much easier access.[1] Glycans can be isolated from natural sources and serve as a starting material for enzymatic extension and digestion using the appropriate recombinant enzymes. The resulting N-glycans can be elaborated further to glycopeptides and homogenous glycoproteins.[2] Spacered glycoconjugates are used in glycan-microarrays, a unique tool for glycobiological studies in a wide range of applications.[3]



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First Diastereodivergent Route to Alkaloids of the Leontidine/Camoensine Family

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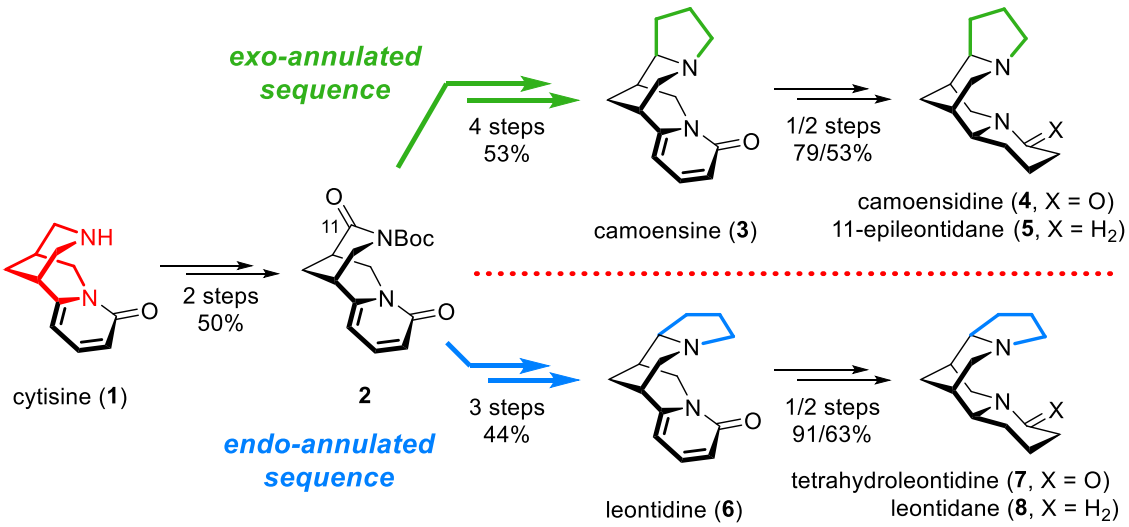
(–)-Sparteine, lupanine, and cytisine are the most prominent examples of the bisquinolizidine alkaloids, which are produced in plants of the family Fabaceae (Leguminosae).[1] Characteristic for this class of natural products is a central bispidine core (3,7-diazabicyclo[3.3.1]nonane), flanked by one or two piperidines or oxidized derivatives thereof. In addition to that exists a small number of quinolizidine-indolizidine alkaloids of the camoensine and leontidine subgroups, in which a pyrrolidine instead of a piperidine is annulated. Herein we present our diastereodivergent synthesis of all known natural derivatives **3**–**8** of both families.[2]



Our approach started from the easily accessible and commercially available alkaloid cytisine (**1**), which was oxidized by iodine and *N*-protected to give the key intermediate, *N*Boc-11-oxocytisine (**2**), in an overall yield of 50%. The orientation of the fused pyrrolidine was controlled by the order of the hydride/metal organyl addition: The members of the *exo*-pyrrolidine-fused camoensine family (**3**–**5**) were prepared by reduction of **2**, *exo*-selective Sakurai allylation, and final ring closure. The reversed sequence, Grignard addition followed by *exo*-selective reduction, furnished the *endo*-pyrrolidine-fused derivatives **6**–**8** of the leontidine subgroup.

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Advancing into new biocatalytic territories: Investigating a novel group of oxygen heterocycle-forming cyclases

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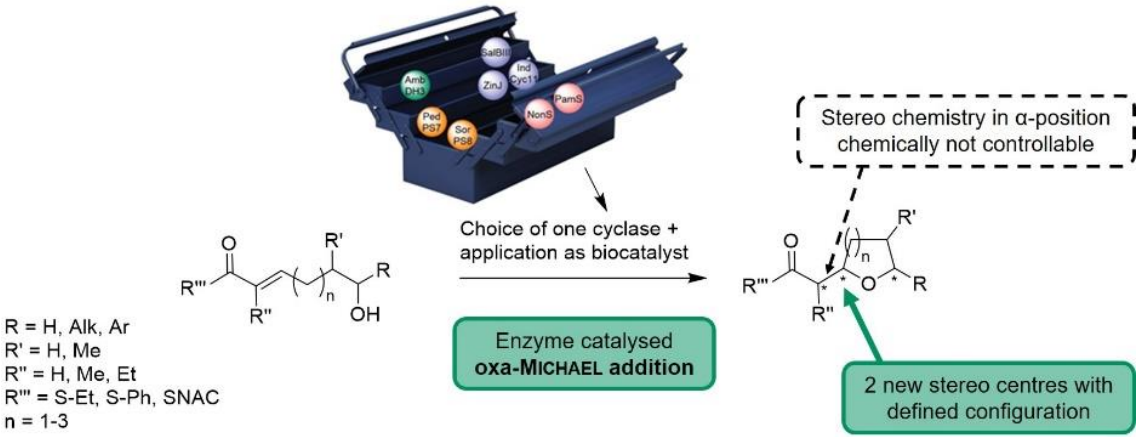
Oxygen-containing heterocycles are important structural motifs in organic compounds such as fine chemicals and natural products.[1] They are often characterized by a complex functionalization and a high density of stereocentres. Their synthesis therefore is mostly elaborate and requires highly specific synthetic methodology. The intramolecular oxa-Michael addition (IMOMA) is potentially one of the most powerful reactions for this task as it provides access to various ring sizes and could give control over multiple stereocentres. As the current methodology for chemical IMOMA often suffers from unreliable stereocontrol, a biocatalytic alternative that makes use of the high selectivity of enzymes could considerably improve the situation.

IMOMA cyclases, which form oxygen containing heterocycles *via* intramolecular oxa-MICHAEL addition, were only just recently characterized for the first time.[2,3] The domain AmbDH3 from the ambruticin polyketide synthase (PKS) shows a unique dual activity as a dehydratase and a pyran-forming cyclase and has extensively been studied by our group.[2,4,5] Initial studies have also been conducted by other groups for PedPS7 and SorPS8 from the pederin and sorangicin PKS, NonS from nonactin biosynthesis and SalBIII from the salinomycin pathway.



Using our work on AmbDH3 that uncovered attractive properties of this enzyme for an application in chemoenzymatic synthesis as a blueprint, we strive to expand our studies to other IMOMA cyclases. [5,6] For this purpose, we produce similar cyclases from various biosynthetic pathways and investigate them regarding relevant properties like substrate tolerance, stereoselectivity and preparative applicability. On the long term, we strive to generate a "*biocatalytic toolbox*" of oxygen heterocycle-forming cyclases that can be applied in the synthesis of chiral fine chemicals and heterocycle-containing drugs.

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