Poster Abstracts

Sesbanimide R, a Novel Cytotoxic Polyketide Produced by Magnetotactic Bacteria

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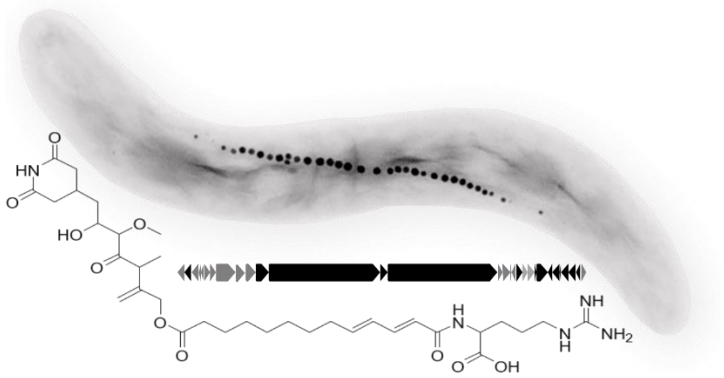
Genomic information from various magnetotactic bacteria suggested that besides their common ability to form magnetosomes, they potentially also represent a source of bioactive natural products. By using targeted deletion and transcriptional activation, we connected a large biosynthetic gene cluster (BGC) of the *trans*-acyltransferase polyketide synthase (*trans*-AT PKS) type to the biosynthesis of a novel polyketide in the alphaproteobacterium *Magnetospirillum gryphiswaldense*. Structure elucidation by mass spectrometry and nuclear magnetic resonance spectroscopy (NMR) revealed a secondary metabolite, sesbanimide R, resembling sesbanimides reported in other taxa with an additional arginine moiety. Sesbanimide R displayed strong cytotoxic activity against several carcinoma cell lines.



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The Disorazole Z Family of Highly Potent Anticancer Natural Products from Sorangium cellulosum

Structure, Bioactivity, Biosynthesis and Heterologous Expression

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Myxobacteria serve as a treasure trove for secondary metabolites. In the course of our ongoing search for bioactive natural products, a novel subclass of disorazoles termed disorazole Z was discovered. Ten disorazole Z family members were purified from a large-scale fermentation of the myxobacterium *Sorangium cellulosum* So ce1875, and characterised by ESI-*hr*MS, X-ray, NMR, and Mosher ester analysis. The main component disorazole Z1 shows comparable antitumor activity to disorazole A1[1] via binding to tubulin. Morever, the disorazole Z biosynthetic gene cluster (BGC) was identified and characterised from the alternative producer *S. cellulosum* So ce427 and compared to the known disorazole A BGC[2], followed by heterologous expression in the host *Myxococcus xanthus* DK1622. Pathway engineering paves the way for further biosynthesis studies and efficient heterologous production of disorazole Z congeners.

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Chemoenzymatic synthesis of *N,O*-glycosylated bikunin as a model proteoglycan

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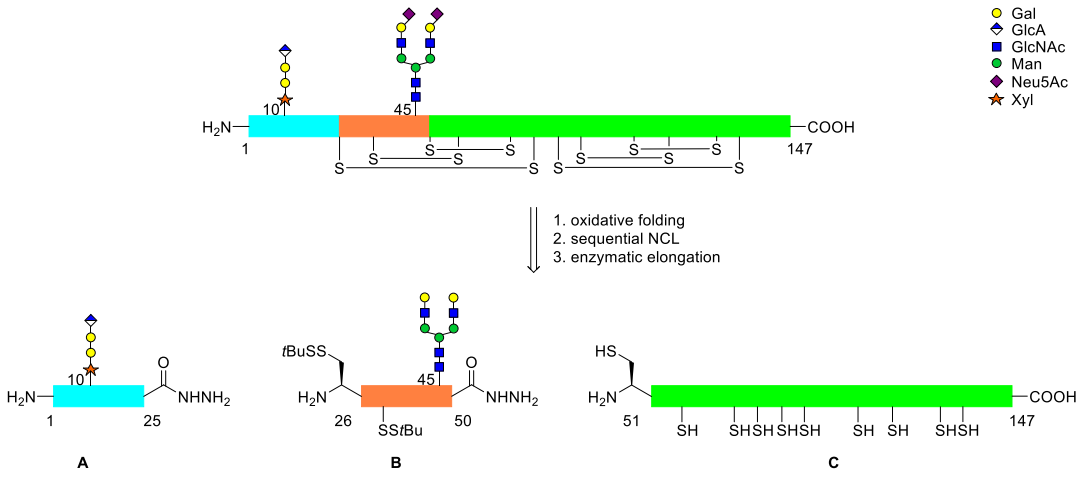
The chemoenzymatic synthesis of *N*-glycoproteins has evolved to a high level[1], however the synthesis of proteoglycans[2,3], is still in its infancy. Bikunin (Bik), also known as urinary trypsin inhibitor is a small proteoglycan, bearing a chondroitin sulphate (CS) chain at Ser-10 and a complex biantennary *N*-glycan at Asn-45.[4] As a serine protease inhibitor, bikunin inhibits various enzymes and displays a multitude of biological functions. Because of its anti-inflammatory properties, bikunin is used as a therapeutic agent and a marker. Depending on the severity of the inflammatory response the CS chain of bikunin can be extended.[5] Hence, we developed a chemoenzymatic strategy to access homogenous glycoforms of bikunin by sequential native chemical ligation (NCL). Bikunin was divided into three fragments (**A**-**C**), Bik 1-25 and Bik 26-50 were synthesized by Fmoc-SPPS, while the Cys-rich fragment Bik 51-147 **C** was obtained by recombinant expression in *E. coli* using a His_6-SUMO *tag.* By enzymatic modification of Bik 1-25, using the recombinant glycosyltransferases, XylT1, B4GalT7, B3GalT6 and B3GlcAT1, the tetrasaccharide linkage region of the glycosaminoglycan was assembled (**A**). The Bik 26-50 glycopeptide **B** was obtained by pseudoproline-assisted Lansbury aspartylation. The oxidative folding of bikunin was difficult, however gave biologically active glycoforms (~10 % yield). The activity of the bikunin glycoforms was measured by a trypsin inhibition assay.



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Total synthesis of stilbene dimers

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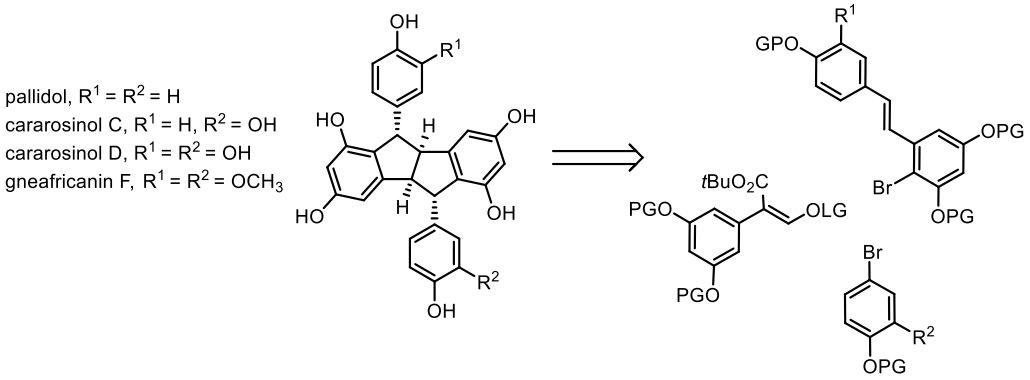
Stilbene dimers containing the indane skeleton are a growing class of polyphenolic natural products. Although the members of this class of polyketides exhibit a wide range of biological activities such as selective quenching of oxygen radicals,[1] inhibition of human colon tumorigenic cells,[2] inhibition of pancreatic α-amylase,[3] antioxidant activity,[4] and activity against HIV-1,[5] the studies of biological activities are limited by their scarce amounts available by extraction from Nature. Therefore, practical methods that allow rapid access to larger quantities of these natural products and their analogues are demanded.

We report a novel approach to stilbene dimers with indane skeleton exploiting two consecutive 1,4-additions and subsequent oxidation reactions in one pot to furnish the [5+5] core of indane stilbene dimers.



Scheme 1: Retrosynthetic analysis of naturally occurring stilbene dimers.

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Chemoenzymatic Approaches to Asymmetric *N*-Glycans

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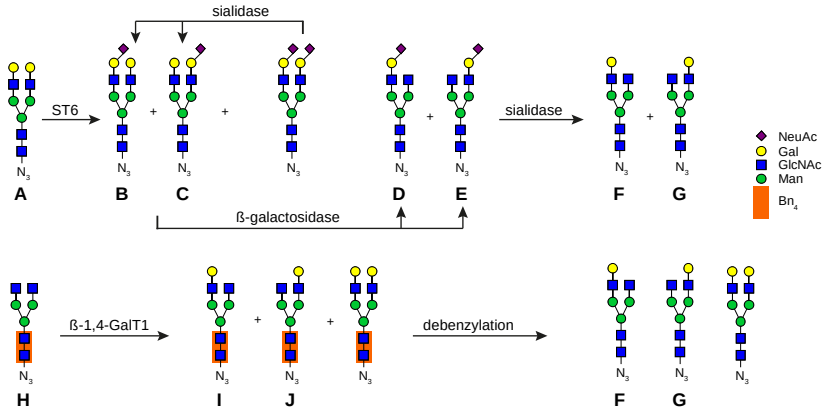
The presence of *N*-glycans can greatly influence the biological properties of *N*-glycoproteins. (1) To evaluate the biological recognition of *N*-glycans via glycan-microarrays, *N*-glycans with symmetrically and asymmetrically substituted branches (antennae) are needed. (2,3,4,5) Asymmetric *N*-glycans can be obtained by statistic conversions of the antennae of symmetric nonasaccharide azide **A**. Incomplete sialylation of **A** with a bacterial 2,6-sialyltransferase provided the asymmetric *N*-glycans **B** and **C**. Digestion of the mixture of **B** and **C** with ß-galactosidase yielded the corresponding monosialylated compounds **D** and **E**. Final desialylation of each asymmetric *N*-glycan gave the asymmetric octasaccharide azides **F** and **G**. The easiest route for the synthesis of **F** and **G** should be the partial galactosylation of the symmetric heptasaccharide azide. However, the separation of the regioisomers over a porous graphitic HPLC-column (PGC) is difficult and the ratio of both isomers is unfavourable (**F**:**G**, 10:1). Digestion of **A** with ß-galactosidase improves the ratio of **F** and **G** to 4:1. In contrast the partial galactosylation of benzyl-protected *N*-glycan **H** yields the monogalactosylated compounds **I** and **J** in nearly equal ratio. Additionally, the HPLC-separation of the isomers is markedly improved. The four benzyl groups were efficiently removed by a photochemical debenzylation method using riboflavintetraacetate (RFT) as a catalyst. (8,9)



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Natural products of early diverging fungi

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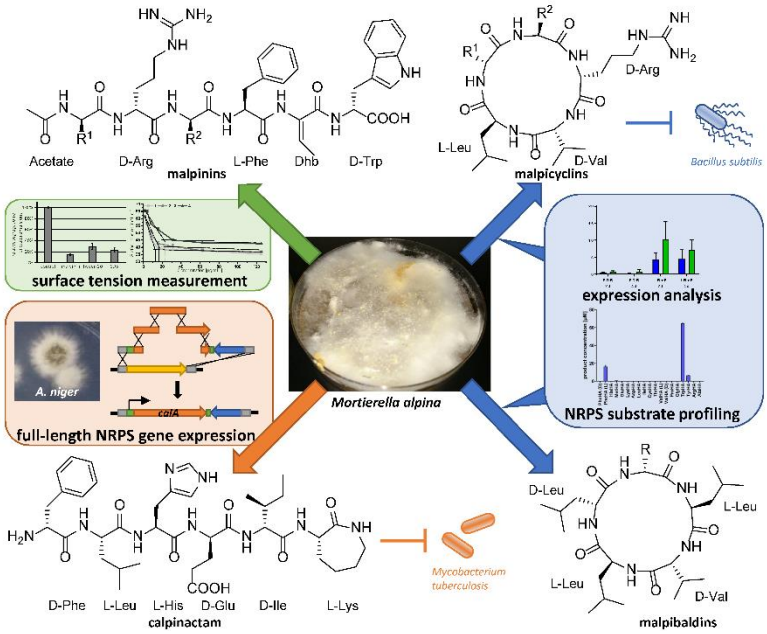

Fungi represent a prolific resource of bioactive natural products such as antibiotics, cholesterol-lowering drugs and immunomodulating agents. In the past 100 years, natural product research primarily focused on higher fungi (Dikarya) which include prominent toxin producers such as *Aspergillus* or *Amanita* species. In contrast, the secondary metabolism of early diverging fungi (EDF) is scarcely investigated. EDF have long time been considered not to produce natural products and secondary metabolism was solely assigned to symbiotic endobacteria.[1] Here, we disclose the pharmaceutical potential biosynthetic origin of metabolites of EDF of the subdivision *Mortierellomycotina*.

We present *Mortierella alpina* as a model organism to study the biosynthetic routes of EDF. *M. alpina* produces at least four different (iso)leucine-containing peptide families: (i) The biosurfactants malpinins are hexapeptides that are biosynthesized by an unusual heptamodular nonribosomal peptide synthetase (NRPS) MalA whose terminal module remains inactive.[1,2] Three of its adenylation domains are substrate-tolerant and incorporate artificial amino acids facilitating subsequent click chemistry.[3] The (ii) malpibaldins and the (iii) malpicyclins are cyclic pentapeptides with moderate antibiotic activity and are produced by two related, canonical NRPSs.[4] Interestingly, NRPS genes of EDF are not related to counterparts from higher fungi, but may have originated from bacterial NRPS genes via horizontal gene transfer. (iv) By heterologous expression of the 20 kb sized NRPS gene *calA* in *Aspergillus niger*, we give evidence that *calA* is required for the biosynthesis of the ε-caprolactam-containing compound calpinactam, a selective anti-mycobacterial agent.

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Investigations on RIESKE-Oxygenases JerP and JerL for Application in Chemoenzymatic Total Synthesis

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Tailoring processes in polyketide biosynthesis often contain chemically difficult or even impossible transformations. RIESKE-oxygenase catalysed tailoring processes gained growing attention during recent years as versatile catalysts that accomplish a broad range of different transformations. During the tailoring steps of jerangolid biosynthesis the RIESKE-oxygenases **JerP** and **JerL** catalyse the desaturation of a tetrahydropyran and a regioselective hydroxylation (*Fig. 1, A*). The oxygenases are closely linked to the reductases **JerO**, which regenerates them by oxidation of NAD(P)H, optionally being supported by a ferredoxin.[1,2]

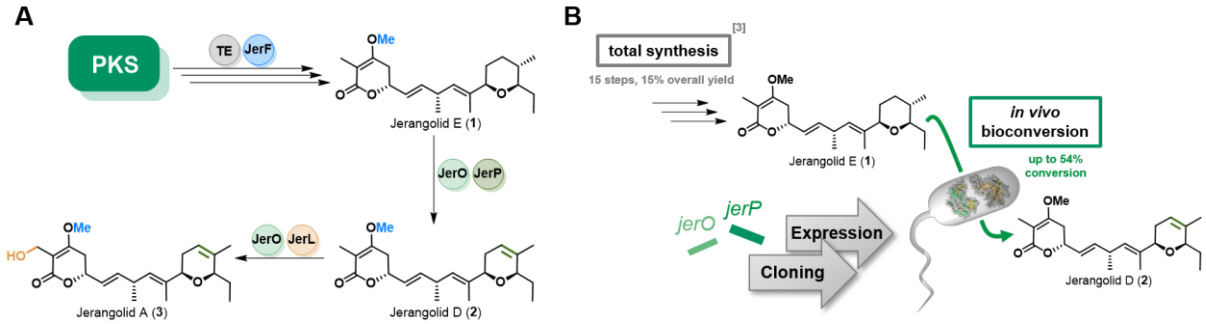

Fig. 1. (**A**) Tailoring process of jerangolid biosynthesis; (**B**) Conceptual scheme of chemoenzymatic strategy with usage of RIESKE-oxygenases to obtain natural products and derivatives.

We aim to better understand these tailoring processes and approach the responsible enzymes for an application in chemoenzymatic natural product synthesis as well as general biocatalysis. We are currently working on the development of a whole-cell bioconversion system. For this, we turned to co-expressing the genes of the individual RIESKE-oxygenases **JerP** and **JerL** with the monooxygenase **JerO**. The necessary natural substrates and their derivatives were obtained by total synthesis and used in whole-cell biotransformations with *Escherichia coli* co-expressing the **JerP**-**JerO** or the **JerL**-**JerO** gene couples, respectively. Desaturation and hydroxylation activity on Jerangolid E (**1**) could be verified under these settings.

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8,8'-Biflavone analogues: Scalable Synthesis of a Library of *Toxoplasma Gondii* Inhibitors

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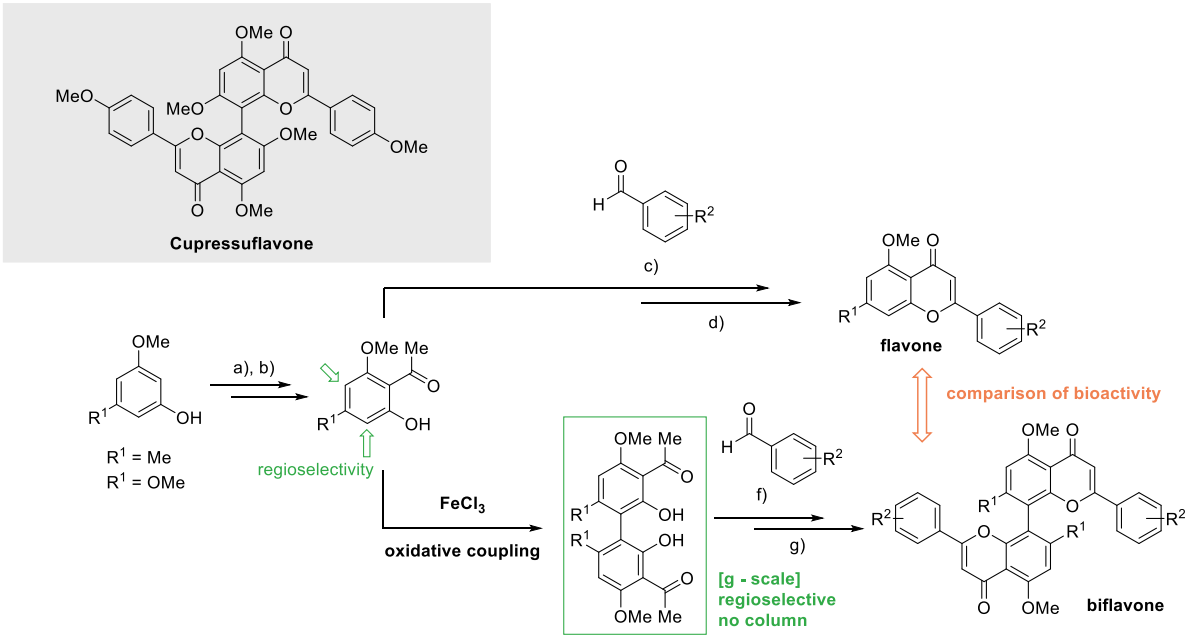
8,8'-biflavones are an elusive class of flavonoid natural products first isolated in 1966.[1] As of today, there have been several procedures for the synthesis of the naturally occurring Cupressuflavone (CUF). To the best of our knowledge only one attempt has been made to synthesize a non-natural derivative.[2] Activities against *Toxoplasma gondii* proliferation were investigated and the selectivity indices of the flavone dimers compared with their monomer counterparts. A key step is the regioselective oxidative coupling of the acetophenones to form the acetophenone dimers.[3] These key-intermediates are a reoccurring motif in different polyketide-based natural products.[4] DFT-calculations have been conducted to rationalize the regioselectivity of this coupling.[5] We present the robust, scalable synthesis of a diverse library of bioactive biflavones. We hope to show that the easy scale up, diversification and untapped potential of this compound class may result in further investigations of their bioactivities.



Scheme 1: Total synthesis of flavones and biflavones as natural product analogues. a) methylation b) Fries acetylation c)+f) chalcone syntheses d)+g) flavone syntheses

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Enantioselective Synthesis of C_2-Symmetric Polycyclic Organocatalysts

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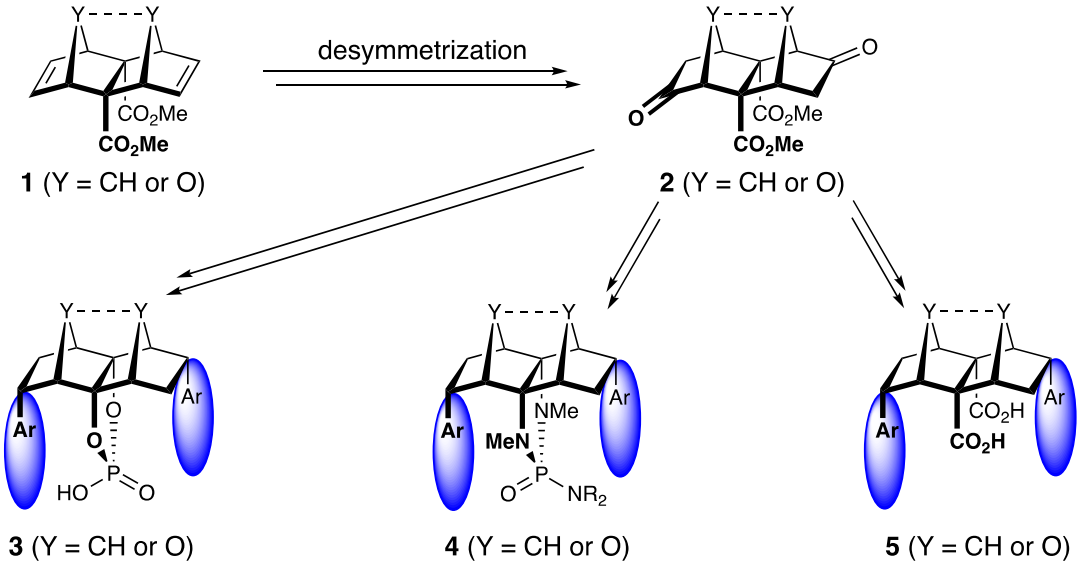
The C_2-symmetric 1,1'-binaphthyl framework (as in, e.g., BINOL and BINAM) belongs to the privileged chiral ligand backbones in asymmetric synthesis and it found application in many highly successful catalysts. In the field of enantioselective organocatalysis, it is the dominating backbone of chiral phosphoric acids, as, for example, in the well-known TRIP catalyst.[1] A chiral binaphthyl skeleton is also found in some phosphoramides,[2] which act as Lewis bases, and carboxylic acids.[3]

Our goal is to develop novel C_2-symmetric (1,1'-binaphthyl-free) backbones for organocatalysts that permit excellent levels of enantiocontrol. We think that a polycylic framework, as in the phosphoric acid **3**, the phosphoramide **4**, and the diacid **5**, will be well suited, because its rigidity in combination with the flanking aryl groups should provide a well-defined and highly enantiodifferentiating environment. Our synthesis of these organocatalysts started with the easily accessible, achiral diene **1**, which was desymmetrized to give the diketone **2**. The carbonyl groups will serve as attachment points for the flanking aryl groups and the ester groups will be further modified to provide the target molecules **3**–**5**.



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Enantioselective Lewis Base Catalyzed Allylation of Silyl Enols Ethers

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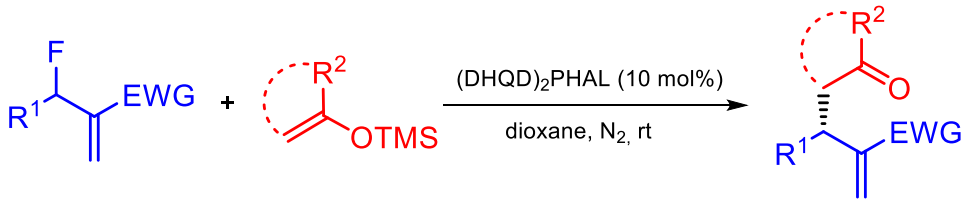
The scope of Lewis base catalyzed reactions is often limited, particularly with respect to the identity of the nucleophilic coupling partner.[1] For example, in Lewis base promoted allylations of C-nucleophiles using MBH carbonates, the reactions require stoichiometric amounts of chiral Lewis base promoter,[2] and the substrate scope is limited to sufficiently acidic C-H pronucleophiles.[3][4] We recently introduced the concept of latent nucleophiles in Lewis base catalyzed allylations of silylated N-centered latent nucleophiles. Here we report the application of the concept of latent nucleophiles to C-C bond formation and the development of enantioselective Lewis base catalyzed allylation of silyl enol ethers with allylic fluorides.



This poster describes the development and optimization of reactions conditions, evaluation of the reactions scope and mechanistic studies with a detailed discussion of factors influencing regioselectivity and stereoselectivity of substitution. The optimized reactions proceed as kinetic resolutions of the allylic fluorides and provide the products in high yields and with high enantioselectivity. The reaction products are amenable to rapid conversion to common structural motifs present in natural products and biologically active compounds

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Enantioselective Lewis–Base–Catalyzed Allylation of Latent Nucleophiles with Allylic Fluorides

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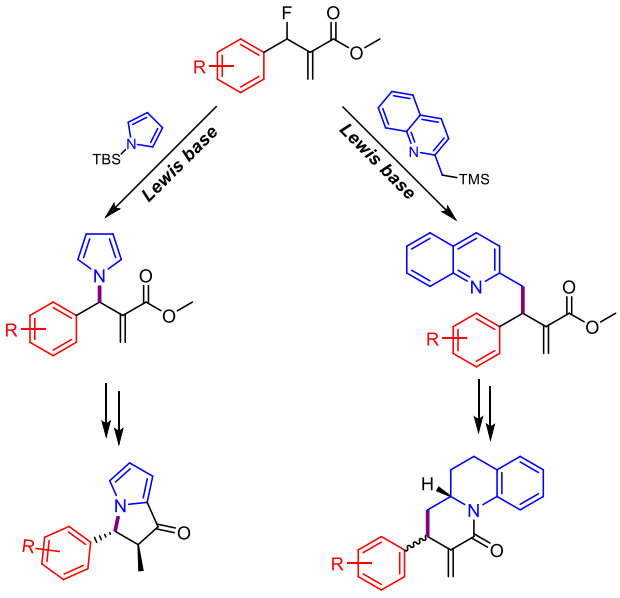
The most common problem in enantioselective Lewis base catalyzed reactions is the typically narrow scope for the nucleophilic reaction partner.[1] We developed the concept of latent nucleophiles to tackle this limitation and consequently expand the reaction repertoire to more challenging nucleophiles. Latent nucleophiles are species that are not markedly nucleophilic but can be activated by a certain stimulus. If the occurrence of this stimulus is a consequence of a prior activation of the electrophile by a Lewis base, both activated species will react selectively. Furthermore, if chiral Lewis bases are used the product can be generated in enantiomerically enriched form.

We demonstrated that silylated pyrroles and related heterocycles can be utilized as latent nucleophiles to provide enantiomerically enriched allylation products.[2] Encouraged by these findings, we developed a short synthetic sequence to pyrrolizin-1-ones[3] that show anti-amyloid properties making them a potential lead structure for development of medications for Alzheimer disease.[4] We put the concept of latent nucleophiles into further use in the unprecedented asymmetric *C*-allylation of quinaldines and picolines. The developed method renders access to manifold products and by using chiral Lewis bases, products with enantiomeric ratios of up to 94:6 are generated. These compounds can easily be transformed into molecular complex quinolizin-4-ones.[5]



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Asymmetric total synthesis of stilbenolignans based on an oxidative SET cascade

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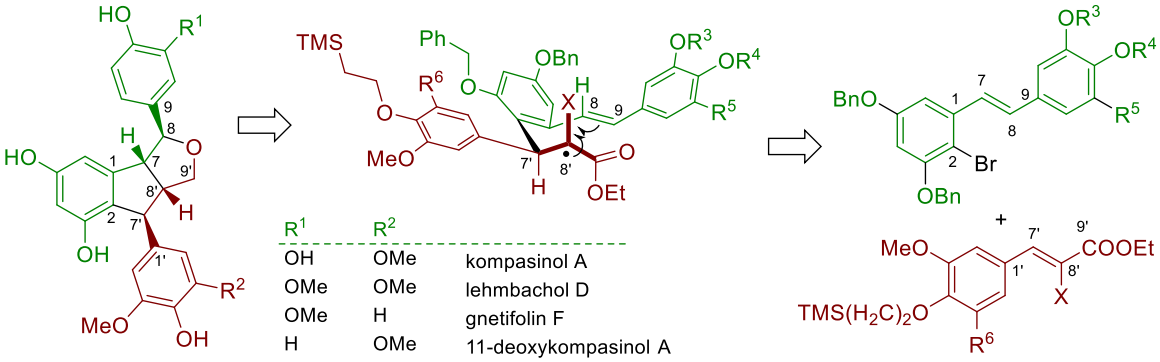
Furoindane stilbenolignans (FISs) are a structurally unique family of hybrid plant metabolites partly derived from a stilbene with the other part coming from a monolignol. Despite being scarcely known to the chemical community, they are widespread among the seed-bearing plants (spermatophytes) and have so far been found in at least nine unrelated genera in seven different plant families.[1] Their skeleton, characterized by three fused rings flanked by two aryl groups, is similar in constitution and configuration to the more well-known pallidol-type stilbene dimers, with which FISs may share similar biosynthesis. Although not yet verified, it presumably involves phenol oxidation followed by diastereoselective coupling of free radicals followed by polar cyclization steps.

Inspired by the biosynthesis, we present the first total synthesis of FISs featuring conjugate addition/oxidative SET cascade that is based on novel asymmetric direct addition of arylithiums to unsaturated esters. The short modular approach is suitable for most FISs and is fully stereoselective.

In addition to providing material for biological evaluation, the total synthesis aims to resolve the existing ambiguity regarding relative configuration of FISs. Importantly, comparing the physicochemical properties of optically and chemically pure synthetic FISs with the existing data should have strong implications for the biosynthetic origin of FIS and the potential role of a yet unknown dirigent protein.[2]



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Studies towards the Total Synthesis of Lycorine-type Amaryllidaceae Alkaloids

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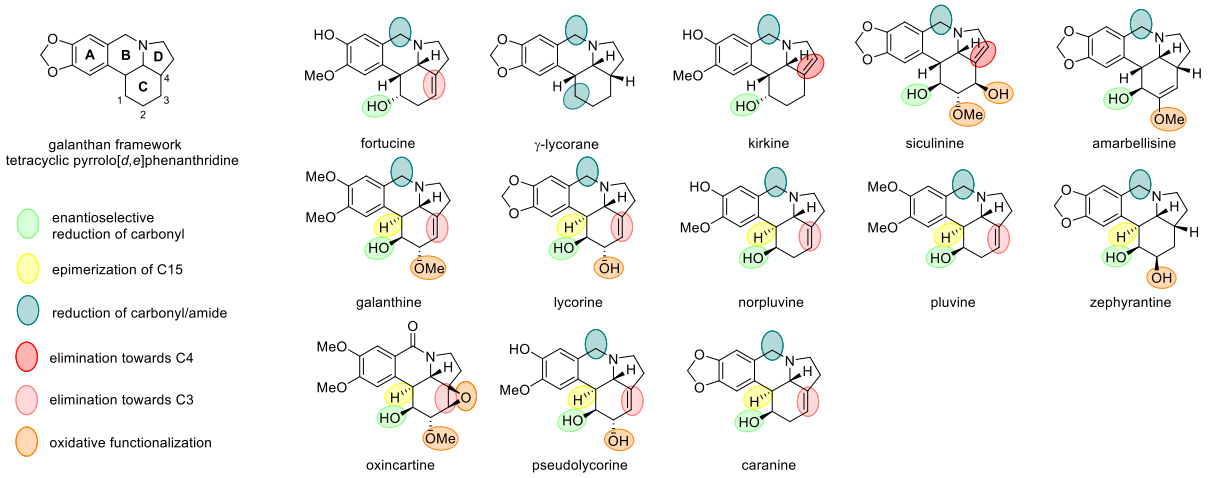
Lycorine-type alkaloids belong to the Amaryllidaceae alkaloid family, which have been studied for their pharmacological and biological properties in the past decades.[1] Their characteristic framework consists of a tetracyclic pyrrolo[*d,e*]phenanthridine (galanthan) core, with the majority of these alkaloids exhibiting a *trans*-junction between the B and C ring. However, only a few, like *γ*-lycorane, fortucine, siculinine and kirkine have a *cis*-junction between B/C.[2] Besides *γ*-lycorane, which has been extensively used for demonstrating the versatility of new synthetic methods,[3] only fortucine has been synthesized in both, racemic form and enantioselectively.[4]

In our retrosynthetic strategy, we envisioned accessing the *cis*-fused class of natural products by implementing a synthetic sequence consisting of a [2+2]-photocycloaddition, a Ramberg–Bäcklund ring contraction followed by a formal electrocyclic ring opening and a Kornblum–DeLaMare oxidation, which has already been successfully employed in the total synthesis of aspidodispermine from our group.[5] The resulting intermediate serves as a platform for accessing several natural products of the lycorine-type alkaloid family.
Remarkably, by epimerization of C15 also the *trans*-fused lycorine-type alkaloids become available by this divergent synthetic approach, emphasizing the versatility this strategy.
Routes to access this favored intermediate towards the synthesis of several natural products of the lycorine-type alkaloid family (Scheme 1) will be presented.



Scheme 2. Lycorine-type alkaloids accessible by our retrosynthetic strategy.

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First Diastereodivergent Route to Alkaloids of the Leontidine/Camoensine Family

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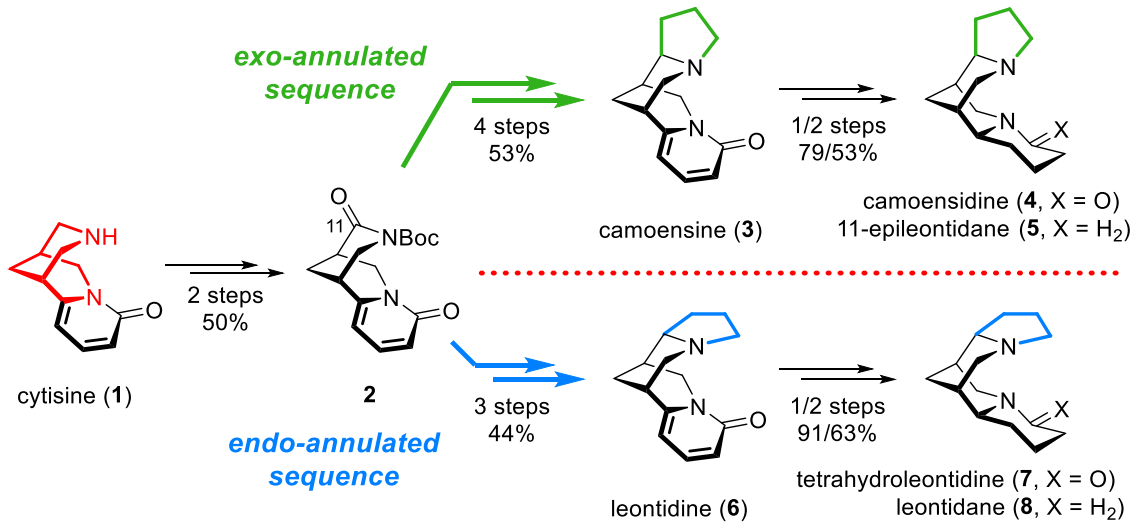
(–)-Sparteine, lupanine, and cytisine are the most prominent examples of the bisquinolizidine alkaloids, which are produced in plants of the family Fabaceae (Leguminosae).[1] Characteristic for this class of natural products is a central bispidine core (3,7-diazabicyclo[3.3.1]nonane), flanked by one 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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Towards the synthesis of massadine

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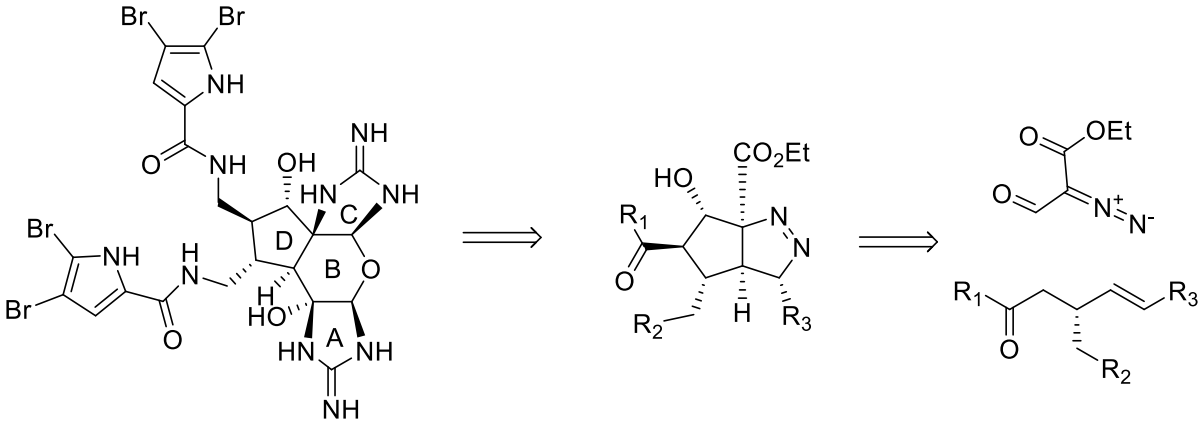
The pyrrole-imidazole family of alkaloids is a diverse class of over 200 marine natural products with a wide spectrum of biological activities.[1] The structural complexity of these nitrogen- and halogen-rich alkaloids is forged from a single biogenetic precursor, oroidin, by various cyclization, dimerization and tetramerization modes. Massadine, a hexacyclic member of the [3+2] dimeric subgroup of pyrrole-imidazole alkaloids with a dense array of functionalites and stereocenters, displays potent antifungal and neurotoxic activity.[2,3] Thus, practical methods that allow rapid access to massadine and its analogues are required.

We report the shortest synthesis of the carbocyclic core of massadine to date, which exploits an unprecedented tandem aldolization/[3+2] cycloaddition yielding bicyclic pyrazolines. Moreover, the conversion of a model bicyclic pyrazoline to the C,D-ring spirocyclic subunit of massadine is presented.



Scheme 1. **Retrosynthetic analysis of massadine.**

We thank the Institute of Organic Chemistry and Biochemistry, Czech Academy of Sciences for funding.

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Investigation of the synthetic potential of a novel cyclase: development of a multi-enzyme cascade for the production of chiral oxygen heterocycles

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Using biocatalysts in synthetic chemistry has several advantages such as mild reaction conditions and high selectivity. AmbDH3 is a bifunctional enzyme that catalyzes dehydration and intramolecular oxa-Michael additions (IMOMAs) of the 3,7-dihydroxythioester **1** leading to THP **3** in ambruticin biosynthesis.[1,2] The enzyme controls the formation of the two adjacent stereocenters at C-2 and C-3 and exhibits strong stereoisomer discrimination at C-6 and C-7 in favor of a 6*S*,7*R* configuration.[3]

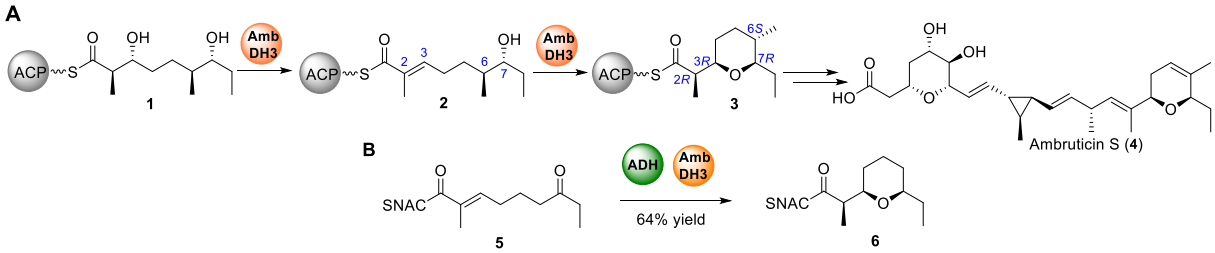

Figure 1: A: Dehydration-cyclization by AmbDH3; B: Conversion of 5 to the THP 6 by a ADH-AmbDH3 cascade.[1][2]

The available methodology for the chemical IMOMA reaction still suffers from a lack of stereoselectivity and substrate tolerance. Our previous investigations demonstrated relaxed substrate specificity and conserved stereoselectivity of AmbDH3 in the synthesis of chiral THPs, THFs and 1,4-dioxanes, thus underlining its potential as a novel biocatalyst. To improve its synthetic value, we explore various types of multi-enzyme cascades that provide highly efficient access to chiral oxygen heterocycles rings starting from readily accessible hydroxythioesters or ketothioesters.

The presented work deals with combining commercially available alcohol dehydrogenases (ADHs) with the IMOMA cyclase AmbDH3 to two-enzyme cascades. A library of substrate surrogates was synthesized and used to investigate the uncertain compatibility of the ADHs with this precursor type. ADH-catalyzed ketone reduction and AmbDH3-catalyzed IMOMA were successfully coupled to a one-pot reaction that transformed substrate **5** into the chiral THP **6** with 64% yield. Investigations on the substrate tolerance of this system, reaction scalability and its broader application in chemoenzymatic synthesis are ongoing.

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Development of Molecular Probes Based on the Flavonoids Fisetin and Sterubin for Correlative Light and Electron Microscopy

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Alzheimer's disease as a multifactorial disease is the most common form of dementia. Up to date, there are no treatments available that prevent, cure or slow down the disease's progression. Flavonoids such as fisetin and sterubin - and their chemical derivatives - hold considerable interest for the development of novel treatments due to their neuroprotective effects *in vitro* and even *in vivo*, combined with negligible toxicity.[(1,2)] For investigation into their exact mode of action and their respective targets, molecular probes have been developed as previously described[(3)] for both fisetin and sterubin by modifying the 7-*O* group of both flavonoids with a terminal alkyne moiety enabling tagging *via* a copper-catalysed click reaction (Fig. 1).

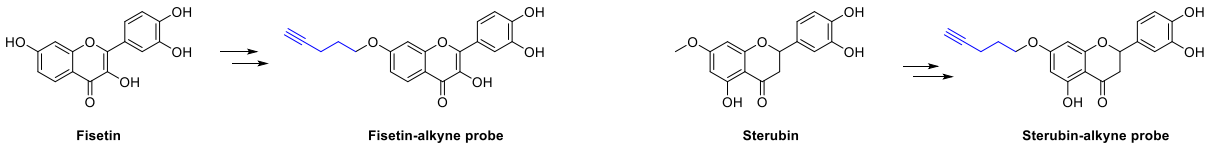

Figure 1. Design of fisetin- and sterubin-alkyne derivatives as molecular probes.

To compare the mode of action of the probes obtained to the parent molecules, various phenotypic screening assays, *i.e.* oxytosis, ferroptosis, and ATP-depletion assays, have been performed and proved comparable effects *in vitro*. Furthermore, Western blot analysis of intracellular proteins provided additional evidence for a similar mode of action. For visualization of the intracellular location of the flavonoids, we performed a CuAAC of the incubated compounds with the Cy3-azide on a murine hippocampal neuronal cell line (HT22 cells) with GFP-labelled mitochondria. High-resolution fluorescence imaging of the stained cells showed broad distribution of the compounds in the cells with a distinct enrichment in specific cellular components (Fig. 2).

For further investigation into the exact intracellular location of the compounds, we plan to perform click-correlative light and electron microscopy. This technique allows localization of fluorophore-tagged compounds by overlaying fluorescence images with SEM images of 100 nm thin cell-slices.[(4)]

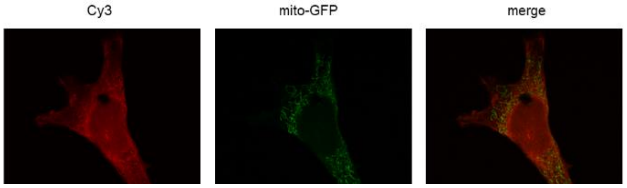

Figure 2. High-resolution imaging of mito-GFP HT22 cells incubated with 2 µM fisetin-alkyne probe. Left: Cy3-tagged probe; middle: mito-GFP; right: merge of both channels.

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Anti-tumoral NHC Au(I) thiolato complexes derived from HIF-1α inhibitor AC1-004 targeting thioredoxin reductase, and causing antiangiogenic effects in vivo

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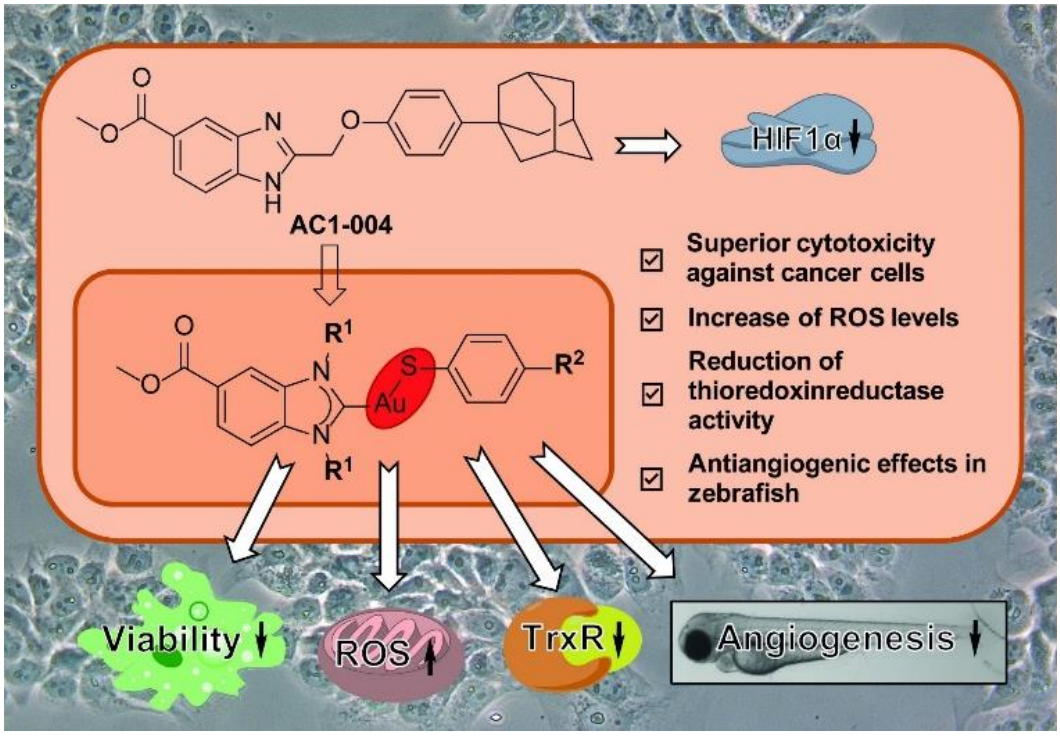
AC1-004 is a potent inhibitor of the hypoxia-inducible factor alpha (HIF-1a) pathway which is essential for the growth, angiogenesis and metastasis of tumors. We now modelled a series of gold(I) complexes on AC1-004 by retaining its 5-carboalkoxybenzimidazole as an NHC ligand while replacing its 2-aryloxymethyl residue with diversely modified thiolato gold(I) fragments. The intention was to augment the HIF-1a inhibition by further conducive effects typical of NHC gold complexes, such as an inhibition of the tumoral thioredoxin reductase (TrxR), an increase in reactive oxygen species (ROS), as well as cytotoxic and antiangiogenic effects. We report the synthesis and biological effects of nine such new N,N'-dialkylbenzimidazol-2-ylidene gold(I) complexes. They were obtained in average yields of 65% for the thiophenolato and 45% for the novel *p*-(2-adamantyl)thiophenolato complexes. The structure of one complex was validated via single-crystal X-ray diffraction. Structure activity relationships (SAR) were derived by variation of the N-substituents (Me, Et, *i*Pr, Pen, Bn) and of the thiolato ligand. Their cytotoxicity against various human cancer cell lines of different entities reached IC_{50} values in the single digit micromolar range. The complexes were assayed also for the induction of tumor cell apoptosis (activation of caspase-3/7), TrxR inhibition, antiangiogenic effects in Zebra fish and HIF-1α inhibition. Some promising candidates for further tests were identified.

Keywords: Anti-Angiogenesis, NHC, *gold (I) complexes*, *HIF-1α,* zebrafish, DNA, AC1-004, antitumoral.



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Developing a polyketide synthase module-centered multi-enzyme cascade for chemoenzymatic synthesis of antifungal polyketides

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Keywords: biocatalysis, chemoenzymatic synthesis, polyketide synthases.

Increasing efforts are put into the development of new antimycotics due to the spread of drug-resistant fungal pathogens. [1] Despite this, only a few groups of antifungal agents are currently available for human treatment. Myxobacterial secondary metabolites are known to exhibit remarkable biological activity and are therefore of high pharmacological interest. These include the related polyketide families of the ambruticins and jerangolids isolated from *Sorangium cellulosum* strains So ce10 and So ce307, respectively. [2,3] They display antimycotic activity against a broad range of pathogenic fungi with low toxicity in humans. Nonetheless, availability of ambruticins and jerangolids is impeded by their structural complexity.

A combinatorial approach of enzymatic transformations and organic synthesis has proven to be an effective strategy for the preparation of bioactive small molecules. We have previously investigated the role of two multifunctional dehydratase domains AmbDH3 and AmbDH4 as well as the *C*-methyltransferase (CMT) AmbM in the biosynthesis of the conserved pharmacophoric eastern fragment of the ambruticins and revealed their biocatalytic potential. [4,5,6] We now strive to exploit these enzymes for efficient chemoenzymatic syntheses of the ambruticins and jerangolids.

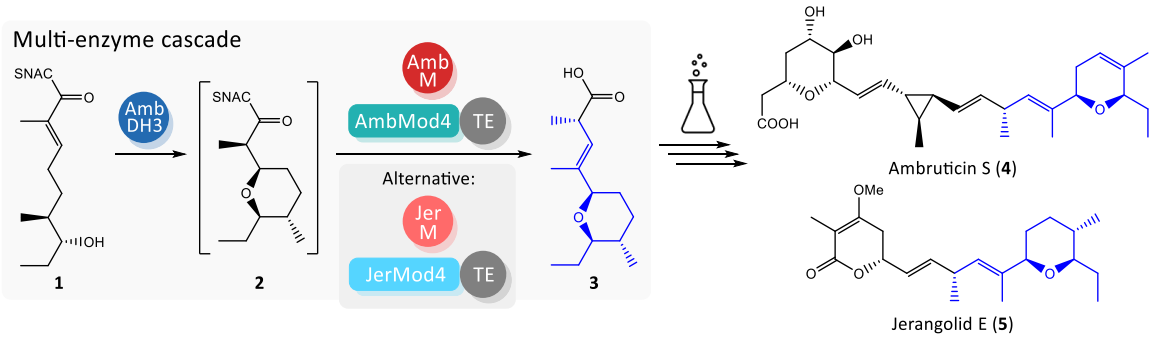

Figure 3. Multi-enzyme cascade for the synthesis of the ambruticin and jerangolid eastern fragment.

For this purpose, we intend to establish an *in vitro* multi-enzyme cascade that centers around the polyketide synthase modules 4 and which provides straight-forward access to the advanced intermediate **3** starting from the biomimetic tetraketide surrogate **1** (Figure 1). Synthetic gain and convenience of product isolation will be maximised by also integrating a tetrahydropyran-forming cyclase, a CMT as well as a suitable thioesterase into this cascade.

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Total synthesis of kibdelomycin, a broad-spectrum, gram-positive focused antibiotic

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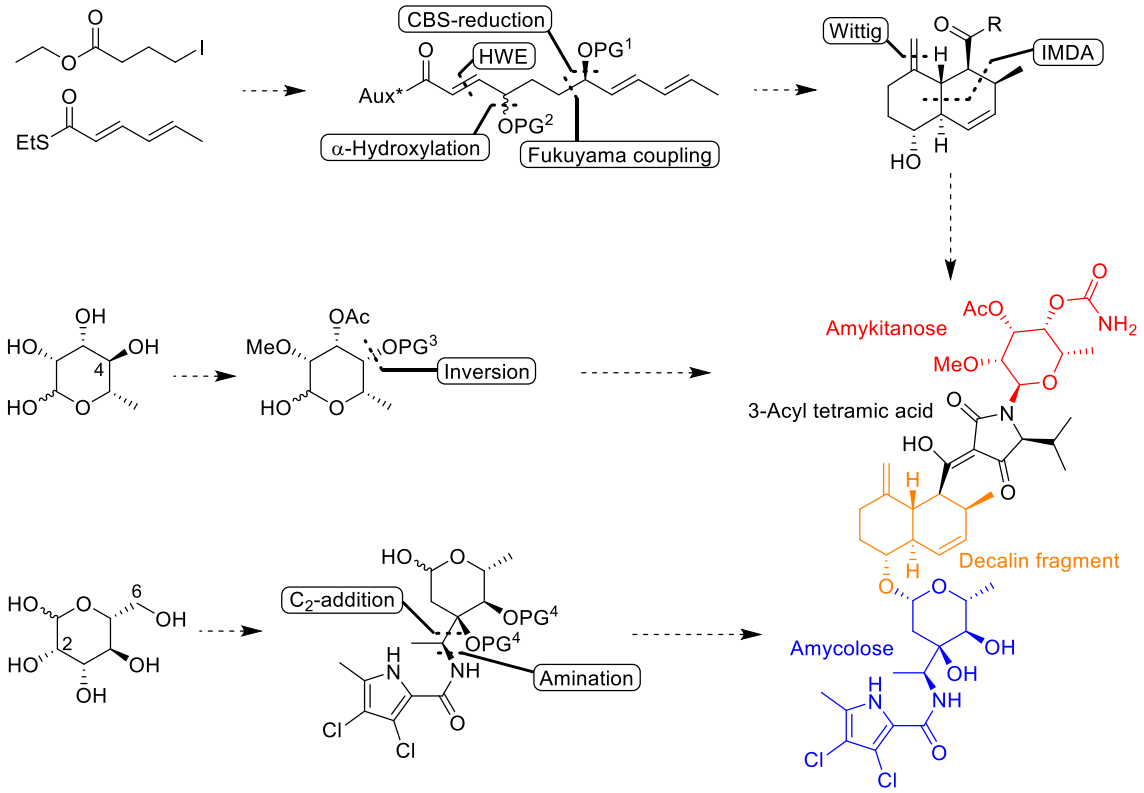
Due to the increasing problem of antibiotic resistance, new antibiotic compounds with novel modes of action, including such from natural sources, are desperately needed. The promising kibdelomycin was isolated in 2011 from *kibdelosporangium sp*. and later turned out to be structurally identical to amycolamicin, isolated from *Amycolatopsis* sp. MK575-fF5. (1,2) Its unique horseshoe-like mode of binding and so inhibiting the bacterial topoisomerase IV and gyrase B rules out any cross-resistance with other known classes of antibiotics. (3) Its structure features the highly functionalized sugar amykitanose linked via an *N*-glycosidic bond to a 3-acyltetramic acid. The latter is itself linked via a nonpolar decalin spacer to the 2-deoxy-sugar amycolose, which carries a pyrrole fragment. Our synthetic approach builts up the amykitanose fragment from l-rhamnose by inversion of the stereocenter at position 4, followed by selective acetylation and methylation. The amycolose moiety is synthesized starting from d-mannose which gets desoxygenated at positions 2 and 6, with subsequent diastereoselective introduction of a C_2-synthon, which itself is converted to an amide. The synthesis of the decalin fragment starts with the Pd-catalyzed cross coupling of iodinated butyric acid ethyl ester and sorbic acid thioester, followed by CBS reduction of the internal ketone. After α-hydroxylation of the ester and its reduction to the aldehyde, the Evans auxiliary is added via HWE-olefination. The following intramolecular Diels-Alder (IMDA) reaction affords the bicyclic structure which is subsequently methylenated and linked β-selectively to the amycolose. The convergent total synthesis is finished by the introduction of the tetramic acid and *N*-glycosylation with amykitanose.



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Revisiting Angiolams, a Class of Neglected Antibiotics From Myxobacteria

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For the last decades, antimicrobial resistance (AMR) has been on the rise, leading to an alarming number of almost five million deaths associated with bacterial AMR in 2019(1). Especially for the treatment of Gram negative bacteria, new antibiotics are needed, as the last new scaffold with activity against those bacteria was introduced more than 35 years ago. One promising source to find new antibiotic scaffolds targeting Gram negative bacteria, are myxobacteria, as they possess a great capability to produce new and diverse bioactive natural products(2).

The antibiotic angiolam A, which displays activity against *E. coli* TolC and few Gram positive bacteria, was first described from a Brazilian soil myxobacterium *Angiococcus disciformis* An d30 in 1985(3). However, no follow-up investigations were performed on the proposed mode of action (MoA) and biosynthesis.

Recently, angiolam A was observed in the crude extract of two myxobacteria isolated from the citizen science regional sampling project “Sample das Saarland” and could be linked to the activity against *E. coli* JW0451-2. Molecular networking revealed the presence of three new angiolam derivatives (B-D) that were successfully purified. Angiolam A-resistant mutants of *E. coli* TolC were generated and used to determine its cellular target, frequency of resistance and cross-resistance with other antibiotics.

Furthermore, a putative biosynthetic gene cluster (BGC) for biosynthesis of angiolams was observed in both new producers. It was confirmed in a genetically amenable alternative producer as gene disruptions in the putative BGC completely abolished production of angiolams.

In this work, we present structures, bioactivities, information about the MoA, and proposed *in silico* biosynthesis of this class of myxobacterial natural products.

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A Synthetic Approach to the Natural *N*-nitrosohydroxylamino Tetramic Acid JBIR-141

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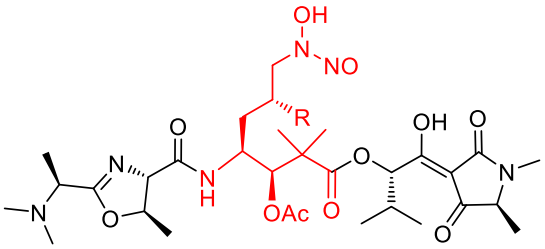
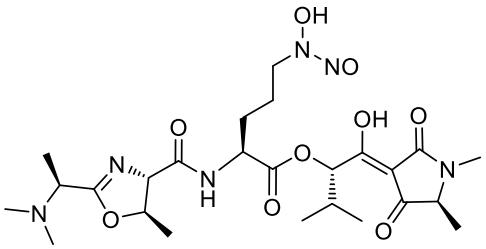
An analogue **3** of the *Streptomyces* metabolite JBIR-141[1], both featuring an unusual and delicate *N*-nitrosohydroxylamine, a 3-acyltetramic acid and an oxazoline, was synthesised from these three building blocks by a convergent strategy starting from L-alanine, L-threonine and (*S*)-glutamic acid.

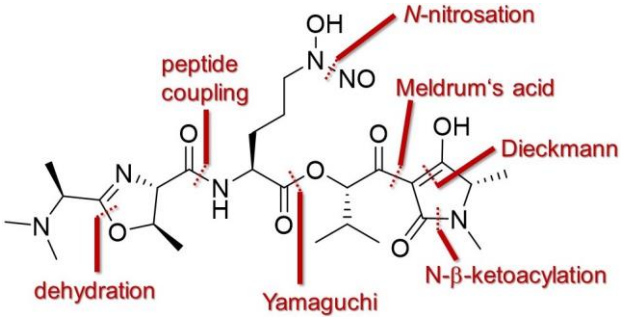


JBIR-141 (**1**): R = H
JBIR-142 (**2**): R = OH



analogue **3**

Key steps were the ring closure of an L-Ala – L-Thr derivative to give the oxazoline with retention of the configuration, a Dieckmann condensation to afford the 3-acyltetramic acid and the *N*-nitrosation of a protected hydroxylamino derivative of glutamic acid to build up the *N*-nitrosohydroxylamine. An adequate protecting group strategy was established along with optimised reaction conditions for the coupling of the three building blocks.[2]



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Cooperative Microbial Natural Product Formation

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The search for new bioactive natural products has prompted scientists to exploit both environmental and organismal diversity. We describe our efforts regarding this endeavor and we provide examples of cooperative natural product production. In particular, we show that soil bacteria can team up to counteract their common amoebal predator [1]. The bacteria cooperate *via* the exchange and modification of natural products. Here, a *Pseudomonas* strain produces the lipopeptide syringafactin, which is not toxic to amoebae but induces peptidases in a *Paenibacillus* strain. These enzymes convert syringafactin into molecules, which are highly amoebicidal (Fig. 1).

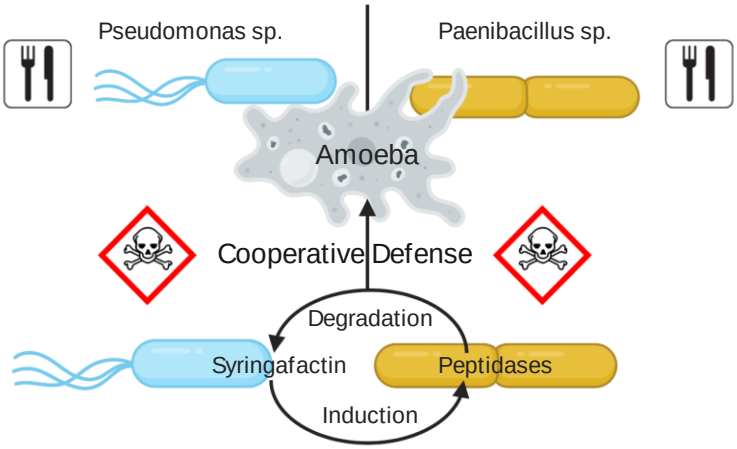

Figure 1. Cooperative bacterial anti-predator defense.

In addition, we show that the ubiquitous plant pathogen *Pseudomonas syringae* can detect and kill its amoebal predator [2]. The underlying mechanism relies on a chemical radar in which the bacterium secretes a signal lipopeptide, which is deacylated by the amoeba. The resulting peptides are sensed *via* a bacterial sensor protein that activates genes leading to the transformation of the predator-derived signal into an amoebicide.

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