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Hamburg, 15th-19th May 2018, Book of Abstracts

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Programme

Tuesday 15 May 2018	
15:00-18:00	Arrival, Registration and Check in
18:30	Dinner
Wednesday 16 May 2018	
8:00	Breakfast
	Synthetic Methodology I Chair: Christian B. W. Stark, Hamburg
9:00-9:10	Welcome
9:10-9:40	**Jacek Mlynarski**, Cracow, Keynote Lecture: *Zinc Instead of Noble Metals: Enantioselective Reduction and Carbon-Carbon Bond Forming Reactions Promoted by Zinc Complexes*
9:40-10:00	**Krista Suta** et al., Riga: *Application of Liquid SO_2 as a Solvent for Organic Synthesis*
10:00-10:10	**Krzysztof Gutkowski** et al., Warsaw: *Synthesis and Photophysical Properties of N-Arylated Diketopyrralopyrroles*
10:10-10:30	**Lukasz Albrecht**, Łódź, Invited Lecture: *Vinylogous synthetic strategies in asymmetric organocatalysis*
10:30-10:50	Coffee break
	Glycoscience I Chair: Ernst Schaumann, Clausthal
10:50-11:20	**Slawomir Jarosz**, Warsaw, Keynote Lecture: *Stereoselective Synthesis of Sugar Mimetics from Simple Monosaccharides*
11:20-11:30	**Sven O. Jaeschke** et al., Kiel: *Maltose as a Scaffold Molecule for the Synthesis of Heteromultivalent Glycoclusters*
11:30-11:40	**Sophia Boden** et al., Düsseldorf: *Varying Hydrophobicity of Precision Glycomacromolecules and the Effect on Lectin Binding*
11:40-11:50	**Matylda Stefaniak** et al., Cracow: *Synthesis of Ulosonic Acids via Zinc- and Iron-promoted Asymmetric Hetero Diels-Alder Reaction*
11:50-12:10	**Ulrika Westerlind**, Dortmund, Invited Lecture: *Exploring Bacterial Lectin Recognition Events of Synthetic Mucin Glycopeptide Ligands*
12:10-14:00	Lunch break

	Natural Product Chemistry I Chair: Daniel T. Gryko, Warsaw
14:00-14:30	**Jeroen Dickschat**, Bonn, Keynote Lecture: *Tracing Terpenes with Isotopes*
14:30-14:45	**Christian B. W. Stark**, Hamburg: *Biomimetic Natural Product Synthesis*
14:45-15:00	**Nina Schützenmeister** et al., Hamburg: *Total Syntheses of Marine Natural Products*
15:00-15:20	**Malte Brasholz**, Rostock, Invited Lecture: *New Catalytic Photooxygenations of Indole Alkaloids*
15:20-15:30	**Gunnar Ehrlich** et al., Hamburg: *Synthesis of Cytospolides D, M, O, and Q and Late-Stage Diversification of Derivatives Thereof*
15:30-15:40	**Christian Bartens** et al., Hannover: *New seco-Progeldanamycin Derivatives: Tools to Study the Substrate Flexibility of the Amide Synthase GdmF*
15:40-15:50	**Fabian Schneider** et al., Konstanz: *Studies towards the Total Synthesis of Canataxpropellane*
15:50-16:30	Coffee break
16:30-16:45	**Johannes Panten**, Holzminden: *Aroma Molecules from Renewable Resources*
16:45-16:55	**Dominik Rekow** et al., Stuttgart: *A Chemoenzymatic Approach to Cembranoid Analogue*
16:55-17:05	**Caroline Poock** et al., Hannover: *Total Synthesis of Nannocystin Ax*
17:05-17:15	**Jevgenija Luginina** et al., Riga: *Synthesis of Novel Betulin Conjugates*
	Supramolecular Chemistry Chair: Paul Margaretha, Hamburg
17:20-17:40	**Riina Aav**, Tallinn, Invited Lecture: *Hemicucurbiturils and their Dynamic Chemistry*
17:40-18:00	**Marcin Stępień**, Wroclaw, Invited Lecture: *From Coronoid Macrocyles to Stable Biradicaloid Systems*
18:00-18:10	**Monika Chwastek** et al., Warsaw: *Towards New Macrocylic Scaffolds*
18:10-18:20	**Agnieszka Czapik** et al., Poznań: *Trityl Group as a Tool for Construction of Multicomponent Supramolecular Materials*
18:20-18:30	**Sandra Kaabel** et al., Tallinn: *Template-driven Assembly of Hemicucurbit[n]uril Macrocycles in the Solid State*
18:30-18:50	**Agnieska Szumna** et al., Warsaw, Invited Lecture: *Dynamic Peptidic Containers - a Road towards Bio-inspired Self-assembly*
19:30	Dinner

Thursday 17 May 2018	
7:30	Breakfast
	Synthetic Methodology II Chair: Maris Turks, Riga
8:30-9:00	**Daniel T. Gryko**, Warsaw, Keynote Lecture: *Pyrrolo[3,2-b]pyrroles - from Serendipitous Discovery to the Most Electron-rich Aromatic Heterocycles*
9:00-9:10	**Asta Žukauskaite** et al., Kaunas: *Synthesis and Anti-mitotic Activity of Variously Substituted 2H-Pyrazolo[4,3-c]pyridines*
9:10-9:20	**Szymon Buda** et al., Cracow: *Intramolecular Tandem Seleno-Michael/Aldol Reaction Promoted by in situ Generated Lithium n-Butylselenoates*
9:20-9:30	**Lukasz W. Ciszewski** et al., Warsaw: *Photoalkylation of Electron-rich Heteroarenes with α-Diazo Esters*
9:30-9:40	**Halina Zhylitskaya** et al., Wroclaw: *Donor-Acceptor Pyrrole Hybrids: Versatile Building Blocks for Electron-Deficient Chromophores with Multi-Redox Activity*
9:40-9:50	**Vilija Krišciuniene** et al., Kaunas: *Synthesis of New Heterocyclic Building Blocks Bearing the Azetidine Structural Unit*
9:50-10:00	**Maciej Stodulski** et al., Warsaw: *Visible Light Mediated Oxidation of N,N-Dimethylamines*
10:00-10:20	**Marcin Kwit**, Poznań, Invited Lecture: *Tuning of Molecular and Supramolecular Properties of Polyimine Macrocycles and Organic Cages*
10:20-10:50	Coffee break
	Catalysis I Chair: Jacek Mlynarski, Cracow
10:50-11:20	**Lutz Ackermann**, Göttingen, Keynote Lecture: *Selectivity Control in C–H Activation*
11:20-11:30	**Piotr Drelich** et al., Łódź: *Novel Organocatalytic Approach to Polysubstituted Tetrahydro-1,2-oxazines Employing a New Class of Aminooxylating Reagents*
11:30-11:40	**Beata Gatlik** et al., Warsaw: *Pd-catalyzed Perfluoroalkylative Carbonylation of Alkynes: A Facile Route to α,β-Unsaturated Esters*
11:40-11:50	**Sebastian Frankowski** et al., Łódź: *Asymmetric Organocatalysis in the Synthesis of Nitrogen-containing Heterocycles*
11:50-12:20	**Dorota Gryko**, Warsaw, Keynote Lecture: *Porphyrinoids as Catalysts for Light Induced C-C Bond Forming Reactions*
12:20-14:00	Lunch break

	Natural Product Chemistry II Chair: Slawomir Jarosz, Warsaw
14:00-14:30	**Roderich Süßmuth**, Berlin, Keynote Lecture: *Ribosomal and Non-ribosomal Peptides from Bacteria and Fungi – Structural and Biosynthetic Aspects*
14:30-14:40	**Daniel Lücke** et al., Hannover: *Total Synthesis of Pericoannosin A*
14:40-14:50	**Jan Rinkel** et al., Bonn: *Labelling Studies on CYP-catalysed Terpene Oxidations*
14:50-15:00	**Janina Meyer** et al., Hannover: *Syntheses of Carolactone Derivatives as Highly Potent Biofilm Inhibitors*
15:00-15:20	**Katarzyna Duda**, Borstel, Invited Lecture: *Lipids from Pollen: what are the Structures Behind Neglected Players in the Allergic Airway Inflammation*
15:20-15:30	**Grete Hoffmann** et al., Münster: *Short and Protecting Group free Approach to t(-)-Δ8-THC-Motif: Synthesis of THC-Analogues, (-)-Machaeriol B and D*
15:30-15:40	**Kinga Kuczynska** et al., Warsaw: *The Transformation of Betulin Core*
15:40-16:10	**Sabine Laschat**, Stuttgart, Invited Lecture: *Adventures and Detours in the Synthesis of Macrolides and Cembranoids*
16:10-16:40	Coffee break
	Various Topics in Organic Chemistry Chair: Thomas Hackl, Hamburg
16:40-17:10	**Maris Turks**, Riga, Keynote Lecture: *Fluorescent Triazolyl Purines and their Nucleoside Congeners*
17:10-17:20	**Axel T. Neffe** et al., Hamburg and Teltow: *Fe-Catalyzed Access to Oligodepsipeptides and their Application in Biomedicine*
17:20-17:30	**Lukasz G. Lukasiewicz** et al., Warsaw: *Symmetry Breaking in Pyrrolo[3,2-b]pyrroles: Synthesis, Solvatofluorochromism and Two-photon Absorption*
17:30-17:40	**Mykhaylo A. Potopnyk** et al., Warsaw: *N,O p-Conjugated (Benzo/Naphtho)Thiazole BF_2 Complexes*
17:40-17:50	**Anke Bollen** et al., Hamburg: *SMART Metabolite ID: A Novel Strategy for the Identification of Unknown Metabolites from Complex Extracts*
17:50-18:00	**René Bachmann** et al., Hamburg: *Metabolic Change of Hazelnuts by Harming Processes and Quality Control by ^{1}H-NMR-Spectroscopy*
18:00-18:10	**Tomasz Madry** et al., Poznań: *Diarylmethane based new chromophoric probes for stereochemical assignments*
18:10-18:40	**Gregorz Litwinienko**, Warsaw, Keynote Lecture: *Solvent Effects in Free Radical Chemistry - from Homogeneous Solutions to Dispersed, Biologically Relevant Systems*
19:00	Dinner

Friday 18 May 2018	
8:00	Breakfast
	Glycoscience II Chair: Thisbe K. Lindhorst, Kiel
9:00-9:30	**Laura Hartmann**, Düsseldorf, Keynote Lecture: *Synthesis and Applications of Sequence-controlled Glycomacromolecules*
9:30-9:40	**Sandra Behren** et al., Dortmund: *Chemistry Based Tools to Explore Tyrosine O-Glycosylation*
9:40-9:50	**Lukasz Szyszka** et al., Warsaw: *Chiral Cyclotriveratrylene-based Molecular Containers with Sucrose Unit*
9:50-10:20	**Guillaume Despras**, Kiel, Invited Lecture: *Design, Synthesis and Properties of Shape-switchable Glycomacrocycles*
10:20-10:50	Coffee break
	Catalysis II Chair: Dorota Gryko, Warsaw
10:50-11:20	**Armido Studer**, Münster, Keynote Lecture: *Electron Catalysis*
11:20-11:35	**Alexander Breder** et al., Göttingen: *Photocatalytic Aerobic Phosphatation of Alkene*
11:35-11:50	**Rafal Loska** et al., Warsaw: *Aza-BODIPY Analogues with Exceptionally Large Stokes Shift Values*
11:50-12:00	**Aleksandra J. Wierzba** et al., Warsaw: *Vitamin B_{12} as a Delivery Agent – a Chemical Point of View*
12:00-12:20	**Wojciech Chaladaj**, Warsaw, Invited Lecture: *Pd-catalyzed Additions to Alkynes with Subsequent Cross-coupling*
12:20-12:25	Closing
12:25-13:30	Lunch break
13:30	**Excursion** (Bus, Boat, Habour, Elbphilharmonie, Hafencity, City) concluding at:
19:00	**Symposium Dinner** at Restaurant “Parlament”
Saturday 19 May 2018	
8:00	Breakfast
	Departure

Abstracts

In Chronological Order

Zinc Instead of Noble Metals: Enantioselective Reduction and Carbon-Carbon Bond Forming Reactions Promoted by Zinc Complexes

Jacek Mlynarski

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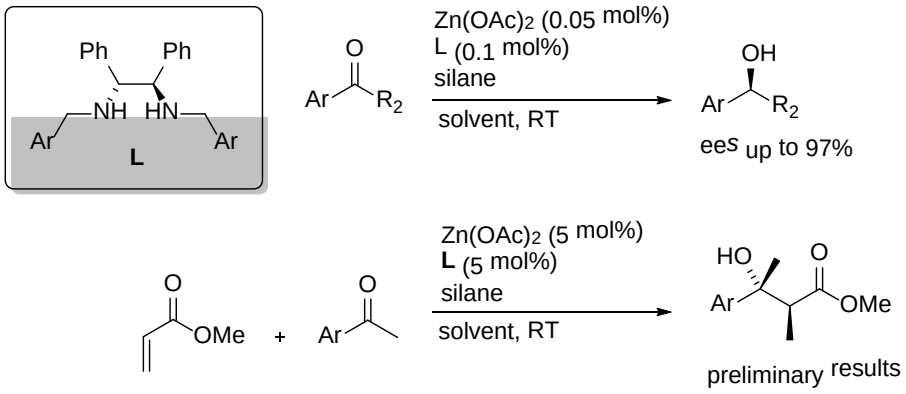
Keywords: zinc, aldol reaction, hydrosilylation

Asymmetric catalysis with the use of chiral metal complexes is still the most important method for the stereoselective formation of carbon-carbon and carbon-heteroatom bonds. After more than 40 years from the first use of transition metals for the catalytic asymmetric hydrogenation of alkenes and carbonyl compounds, the most efficient catalysts for these transformations are still compounds composed of rhodium, iridium, ruthenium or platinum. Recently, environmentally benign and less expensive catalysts have also been exhaustively explored leading to broad acceptance of earth-abundant metals such as zinc[1] and iron[2] in asymmetric synthesis. Previously our team showed that zinc[3] and iron[4] complexes can be efficient catalysts for many types of stereoselective additions to the carbonyl group including transformations in aqueous environment. Recently, we have also shown that the use of zinc complexes in the hydrosilylation reaction of prochiral ketones and imines can be much more efficient then application of platinum complexes.[5]



Acknowledgements

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Application of Liquid SO_2 as a Solvent for Organic Synthesis

Krista Suta, Jevgeņija Lugiņina, Daniels Posevins and Māris Turks

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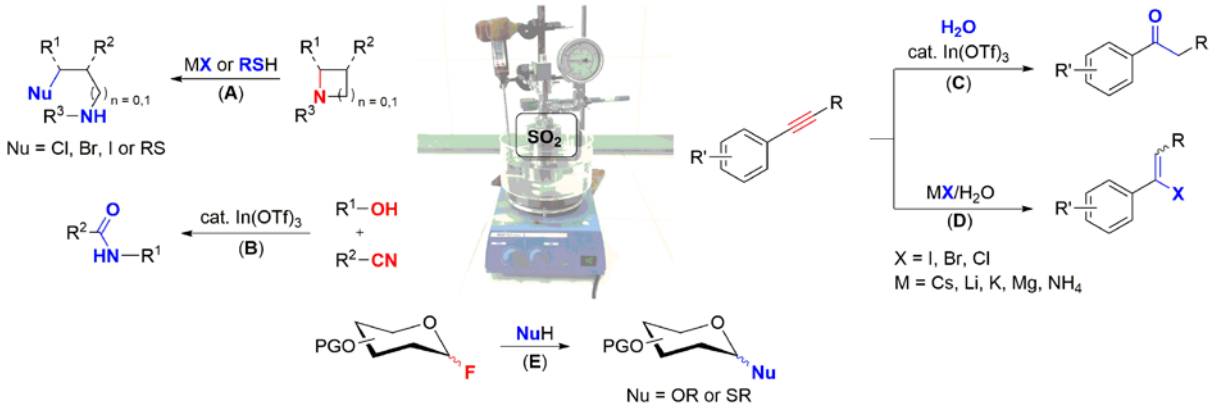
Keywords: sulfur dioxide, solvent, Lewis acid

Due to relatively high boiling point (-10 °C) and low vapor pressure (8 bar at 60 °C), sulfur dioxide (SO_2) can be easily liquefied and handled in its liquid state. Liquid SO_2 is one of the few polar solvents that possess Lewis acid properties. Besides, both organic and inorganic substances readily dissolve in liquid SO_2 due to its high dipole moment (1.6 D). All these facts make liquid SO_2 a unique solvent for organic synthesis, especially, for transformations involving charged intermediates.

Our group has: (**A**) discovered that unprotected and carbamate-protected aziridines and azetidines undergo efficient ring-opening reactions in liquid SO_2 with I and II group metal halides and thiols;[1,2] (**B**) found application of liquid SO_2 as an interesting solvent for the Ritter reaction in the presence of catalytic amount of In(III) triflate;[3] (**C**) developed In(III) or Hf(IV) triflate catalyzed conditions for hydration of aryl alkynes in liquid SO_2 without direct addition of Brønsted acid; (**D**) found that NH_4I and also various I and II group metal halides (I, Br, Cl) in the presence of water can act as halide sources for synthesis of α-aryl vinyl halides from alkynes in liquid SO_2.

Finally, our initial studies of glycosidic bond formation in liquid SO_2 have revealed promoting effect of this unconventional solvent for glycosylation of alcohols and thiols using glycosyl fluorides as glycosyl donors (**E**).



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Synthesis and Photophysical Properties of *N*-Arylated Diketopyrrolopyrroles

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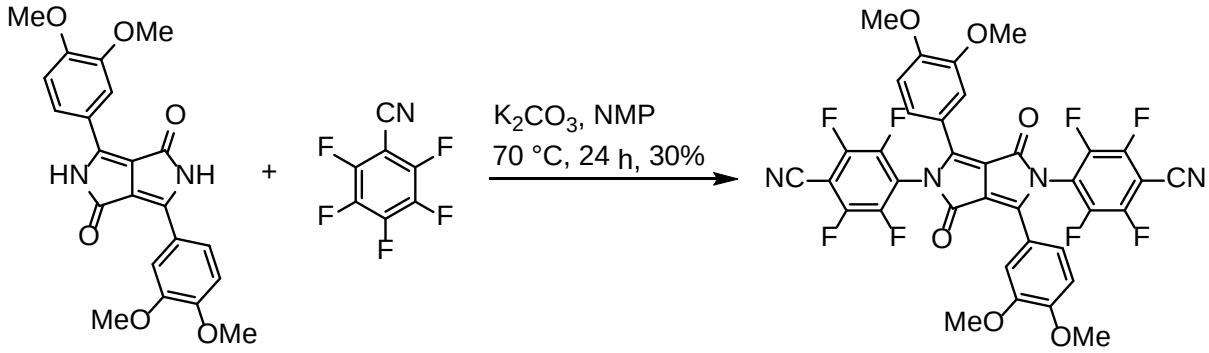
Keywords: dyes/pigments, heterocycles, fluorescence

Diketopyrrolopyrroles (DPPs) are a family of high-performance industrial pigments discovered by Farnum and progressed by Ciba-Geigy.[1] DPPs played a key role in developments in organic electronics,[2] have been employed as two-photon absorbing materials.[3] This popularity of DPPs results from the combination of very interesting optical properties with straightforward synthesis. One of the most common modifications of DPPs, namely *N*-alkylation, is usually carried out in polar aprotic media in the presence of a base, and the obtained species often show improved solubility and fluorescence properties.[4] The bis-*N*-arylated DPPs are scarcely present in the literature. One of the most common approaches is based on the reaction between corresponding aryl fluoride and DPP in the presence of a base, but unfortunately the scope of this method is strongly limited. Indeed, only the use of aryl fluorides containing at least one NO_2 group, have been successful with this approach.[5] In the present work, we investigated the *N*-arylation of DPPs with aryl fluorides lacking NO_2 substituents. The reaction between pentafluorobenzonitrile and corresponding DPP possessing 3,4-dimethoxyphenyl substituents led to desired product. The bis-*N*-arylated DPPs exhibit strong fluorescence both in solution and in the solid state.[6]



Scheme. 1 The *N*-arylation of diketopyrrolopyrrole using pentafluorobenzonitrile

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Vinylogous Synthetic Strategies in Asymmetric Organocatalysis

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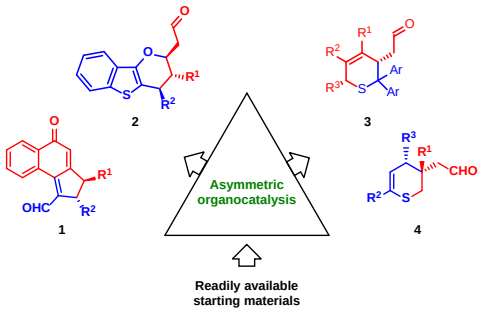
Keywords: asymmetric organocatalysis, vinylogy, biologically relevant compounds

The development of methods for the preparation of biologically relevant compounds in enantiomerically enriched form is of significance for contemporary organic chemistry. Enantioselective reactions where prochiral substrates are converted into enantiomerically enriched products in the presence of chiral catalyst are of great importance.[1] Recently, asymmetric organocatalysis has become a highly useful tool enabling for the efficient asymmetric induction based on diverse activation modes.[2] Within this research area, the application of vinylogy concept created new synthetic possibilities.[3]

Herein, we report our studies on organocatalytic, enantioselective vinylogous strategies for the synthesis of biologically relevant molecules such as: carboannulated naphthalen-1(4*H*)-one derivatives **1**, benzothiophenes **2** and dihydro-(2*H*)-thiopyrans **3** and **4**.[4] The devised approaches utilize readily available chiral organocatalysts to control stereochemical reaction outcomes.



Acknowledgements

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Stereoselective Synthesis of Sugar Mimetics from Simple Monosaccharides

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Keywords: iminosugars, carbasugars, stereoselective synthesis

The concise approach to bicyclic sugar mimetics: imino- and carbasugars from simple monosaccharides will be presented. First method is based on the fragmentation of sugar allyltin derivatives (*e.g.* **5**, prepared from D-glucose in *ca* 10 steps; route ***a*** in Fig. 1) into dienoaldehyde **1** (exclusively *E*-configuration across the internal double bond). This aldehyde was converted into bicyclic carbasugars (*e.g.* **3** or **4b**). Alternatively it was transformed into bicyclic iminosugars: **2** or **4a**.[1,2]. The configuration at the ring junction is fixed, which results from the mechanism of the cyclization of intermediates (*e.g.* **1a**).

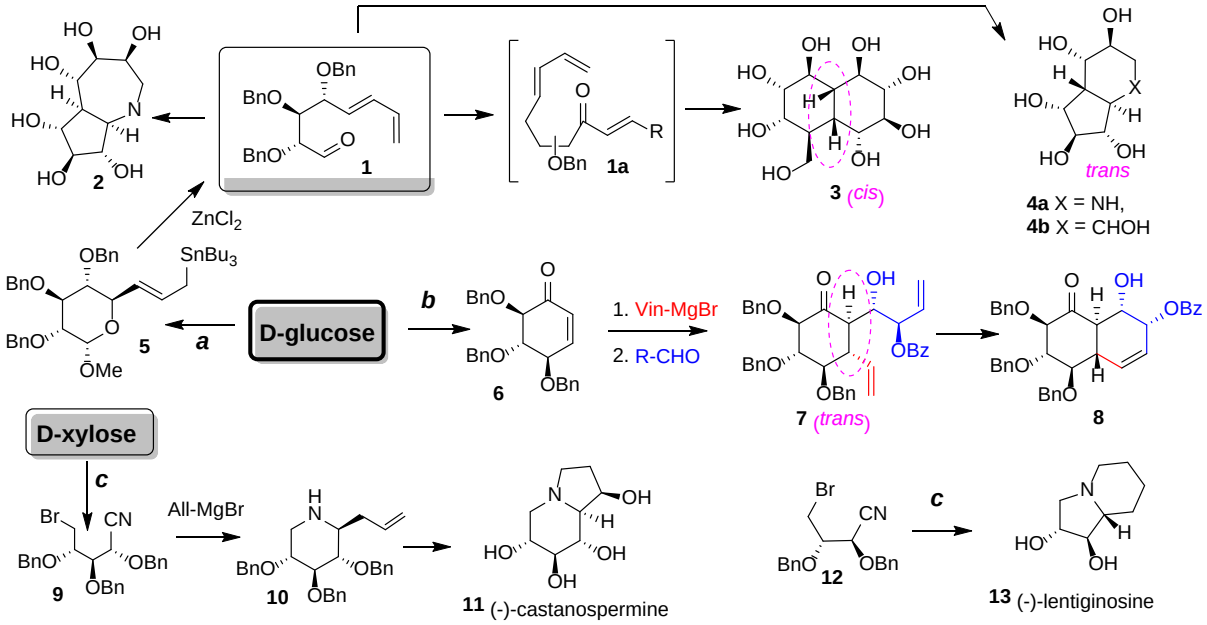

Fig. 1 Preparation of sugar mimetics (imino- and carbasugars) from simple monosaccharides

The problem of obtaining the alternative isomers of decalin was solved by an introduction of both substituents in the *trans*-relation before cyclization (route ***b***).

Besides the 'allyltin' approach to iminosugars (*e.g.* **2** and **4a**), we have elaborated another one starting from the corresponding sugar derived bromonitriles (*e.g.* **9** or **12**).[2,3].

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Maltose as a Scaffold Molecule for the Synthesis of Heteromultivalent Glycoclusters

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Keywords: glycoscience, heteromultivalency, synthesis

Cell surfaces are covered with complex glycoconjugates forming a thick sweet layer called the cell's glycocalyx. Glycocalyx constituents play a fundamental role in biology, i.e. in cell recognition and cell adhesion processes. The biological meaning of glycocalyx glycoconjugates is "decoded" by the interaction with specific proteins, called the lectins. The interaction between lectins and their carbohydrate ligands is fine-tuned by multivalency effects, which have been extensively reviewed.[1] Synthetic multivalent glycomimetics are valuable tools in multivalency studies.[1]

For the design of multivalent glycomimetics, the choice of a suitable scaffold molecule is important. We have shown earlier, that carbohydrate scaffolds are favorable structures for the construction of multivalent oligosaccharide mimetics.[2] Carbohydrates provide a defined and rigid conformation, possess a distinct stereochemistry, and in addition, their multifunctionality offers various possibilities for flexible derivatization. We have shown earlier, that mannose can be turned into multivalent scaffold glycosides of an AB_4-type, serving in the preparation of homomultivalent glycomimetics.[3],[4]

Here we show the synthesis of a new orthogonally functionalized ABC-type scaffold based on maltose, which can be diversely derivatized into heteroglycoclusters (Fig. 1). Maltose was modified at the anomeric position and at the 6- and 6'-position, respectively. The anomeric functionalization with an alkyne allows the attachment of a linker for immobilization on a surface (e. g. polystyrene, gold) or other further derivatization. The primary positions were derivatized as orthogonally protected amino groups allowing sequential modification by peptide coupling in order to achieve heteroglycoclusters (Fig. 1). Testing of the ligand properties of the synthesized maltose-based heteroglycoclusters and evaluation of "heterocluster effects"[5] is planned in bacterial adhesion studies.

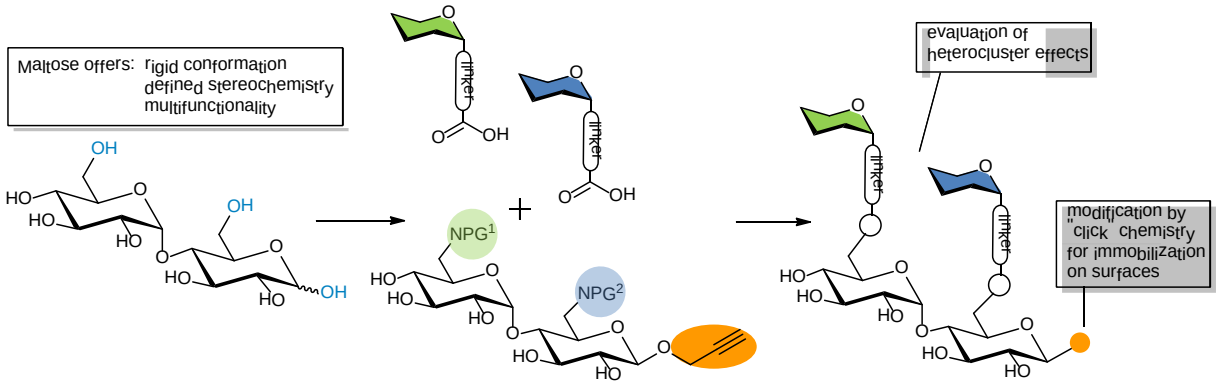

Fig. 1 Maltose-based multifunctional scaffold for functionalization with various carbohydrate ligands

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Varying Hydrophobicity of Precision Glycomacromolecules and the Effect on Lectin Binding

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Keywords: precision glycomacromolecules, carbohydrate lectin interactions, solid phase synthesis

Carbohydrate lectin interactions are involved in many biological processes such as cell-cell communication and pathogen recognition [1]. Studying the underlying ligand receptor binding mechanisms involved, it is especially interesting in terms of the generally multivalent nature of carbohydrate interactions. Since single carbohydrate ligand lectin interactions are usually weak, increased binding affinities are realized by simultaneous presentation of multiple ligands. This is not only true in Nature but can also be applied for the design of artificial or so-called glycomimetic ligands based on the multivalent presentation of carbohydrates on a synthetic scaffold. Today, it is well understood that not only the multivalent presentation but also the composition of such a scaffold can influence lectin binding. One opportunity to further increase ligand affinity is through the introduction of hydrophobic entities as many lectin receptors exhibit a hydrophobic region near their carbohydrate recognition domain [2].

In this study, we employ previously introduced solid phase polymer synthesis to obtain a series of monodisperse, sequence-defined glycooligo(amidoamines), so-called precision glycomacromolecules, with straightforward variation of the chemical backbone properties. The combination of a hydrophobic aliphatic, an aromatic and a hydrophilic spacer building block and their stepwise assembly on solid support leads to the gradual change in backbone characteristics from more hydrophilic to more hydrophobic properties. Carbohydrate ligands are introduced via copper catalyzed azide alkyne cycloaddition of α-D-mannopyranoside-azide derivatives onto alkyne side chains along the scaffold following well-established procedures [3].

Lectin binding behavior is evaluated by means of isothermal titration calorimetry (ITC) and surface plasmon resonance (SPR) with the model lectin Concanavalin A (Con A) as well as in a bacterial inhibition competition study against the *E. coli* FimH receptor. The results show that glycomacromolecule lectin interaction is affected by a change in ligand valency and backbone hydrophobicity. However, the impact of backbone hydrophobicity is rather small compared to previous studies with hydrophobic entities in linker position pointing towards a difference in the underlying mechanism of binding enhancement [4].

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Synthesis of Ulosonic Acids via Zinc- and Iron-Promoted Asymmetric Hetero Diels-Alder Reaction

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Keywords: ulosonic acids, zinc, iron

Ulosonic acids (3-deoxy-aldonic acids) are family of naturally occurring sugar derivatives, which are synthesized by stereoselective enzyme catalyzed addition of phosphoenolpyruvate (PEP) to the corresponding aldoses.[1] All these acids are involved in many biologically important processes and thus they attract attention of many researchers.

Recently, we have showed that, this type of compounds can be obtained in biomimetic, stereocontroled aldol reaction.[2-4 However, an alternative approach to this synthesis is the use of hetero Diels-Alder (HDA) reaction between diene and glyoxalates (Fig. 1). Based on the current state of the art in enantioselective HDA reaction in the synthesis of ulosonic acids, [5-8] we would like to propose an innovative use of chiral zinc and iron complexes, which have not yet been widely used in this type of reaction.

In this work, we present the application of an enantioselective cycloaddition reaction of glyoxalate to dienes in stereocontroled construction of the pyranose system (Fig. 1). This approach is the shortest synthetic route for ulosonic acids skeleton, therefore this reaction requires enantioselective control by application of suitable catalysts.

Here, we present our effort towards high stereoselectivity of model reaction. We tested zinc and iron complexes with commercially available BOX and PyBOX ligands. Application of selected condition resulted in formation of derived pyranose ring with good overall yield (39 - 81%) and high enantiomeric excess (58 up to 91% *ee)*.

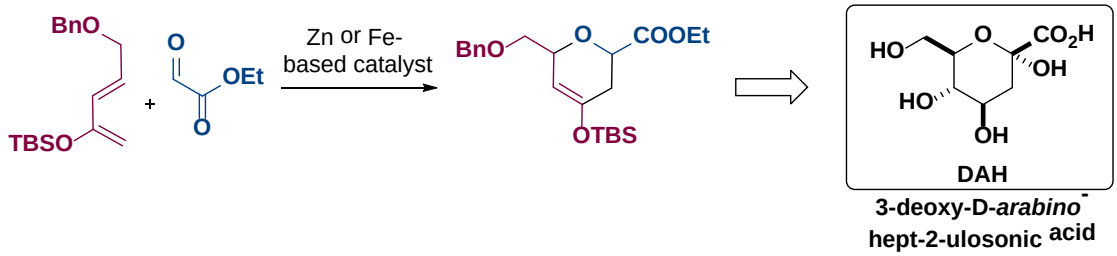

Fig. 1 The hetero-Diels-Alder reaction in the synthesis of ulosonic acids derivatives

Acknowledgements

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Exploring Bacterial Lectin Recognition Events of Synthetic Mucin Glycopeptide Ligands

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Keywords: *g*lcycopeptides, mucins, lectins

Mucins are densely glycosylated proteins that populate the cell-surface of epithelial tissues.[1] The extracellular tandem repeat peptide regions rich on proline, threonine and serine residues characterize the mucins. By display of *O*-glycans often organized in a multivalent fashion, the mucins and mucin like glycoproteins are involved in a plethora of cell-surface binding events.[2] Glycans on mucins often act as ligands for invading pathogens, studies of such interactions are useful for characterization of microbes and viruses as well as to develop new anti-adhesive drugs. Mucins also play a critical role in cancer progression and through aberrant glycosylation tumor-cell adhesion and anti-adhesion events can be modulated. By chemical synthesis of well-defined glycan and glycopeptide probes we aim to identify and map the functions of mucins and their interacting binding partners involved in cancer and infection processes.

In recent years we have developed efficient total synthesis strategies to construct over 300 different mucin *O*-glycopeptides modified with short tumor-associated glycan structures and more complex elongated mucin core structures.[3-5] Using enzymes, the elongated core structures were further diversified by fucosylation, sialylation and polyLacNAc. The synthetic glycopeptides have been immobilized on biocompatible hydrogel slides that display the glycopeptides in a multivalent mode. Microarray analysis to evaluate binding epitopes of antibodies directed against tumor-associated mucin glycopeptide antigens[5-7] and lectins (galectins) that are involved in tumor progression have been preformed. Analysis of virus and bacterial lectin recognition is currently in progress. Our recent findings will be described at the German-Polish-Baltic organic chemistry meeting in Hamburg.

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Tracing Terrestrial Terpenes with Isotopes

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Keywords: terpenes, biosynthesis, enzyme mechanisms

The recent advances in genome sequencing have revealed a large number of terpene cyclases in bacteria,[1] fungi,[2] and eukaryotic microorgansism such as social amoebae.[3] Several of the encoded enzymes have been characterised during the past two decades by genome mining approaches. The terpene cyclase catalysed reactions frequently yield only one specific product with a high degree of stereocontrol. The complex mechanisms of terpene cyclisations can be addressed by quantum chemical calculations,[4] or experimentally by the use of isotopically labelled probes.

Among the uncharacterised enzymes, di- and sesterterpene cyclases are most interesting, because these enzymes usually make previously unknown compounds and their cyclisation mechanisms are generally more complex than those for mono- or sesquiterpene cyclases, as was impressively shown by the recent labelling studies on the bacterial cyclooctat-9-en-7-ol synthase.[5] During the past few years my group has synthesised various isotopically labelled oligoprenyl diphosphates that can be used to efficiently unravel the cyclisation mechanisms of terpene cyclases for new compounds with unprecedented structures (Fig. 1).[6] The application of labelled precursors in mechanistic investigations on the most interesting newly discovered terpene cyclases will be discussed.

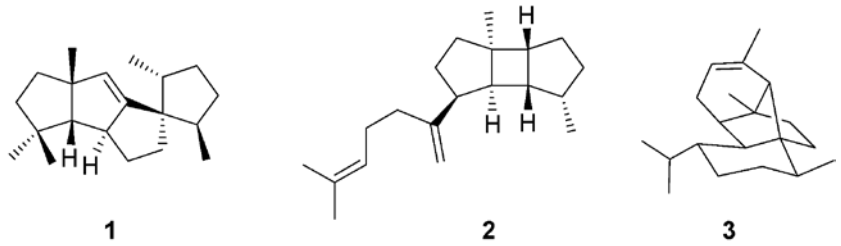

Fig. 1 Structures of recently identified terpenes

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Biomimetic Natural Product Synthesis

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Keywords: natural products, total synthesis, biomimetic chemistry

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.

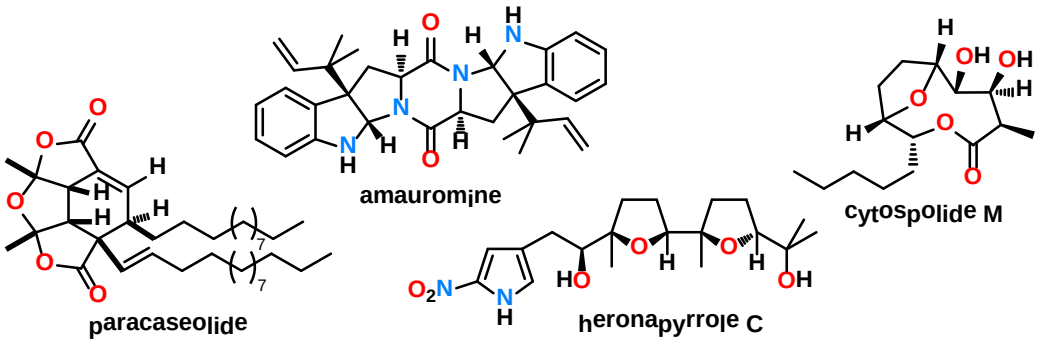

Fig. 1 Selected structures of natural products assembled in a biomimetic fashion

Expedient synthetic methodology[2] not merely imitates nature's 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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Total Syntheses of Marine Natural Products

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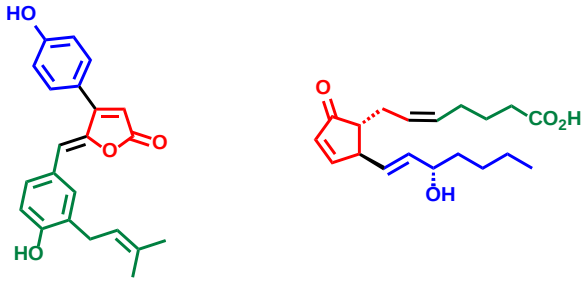
Keywords: natural products, total synthesis, antiinfectives

Marine organisms such as corals and invertebrates are important sources for potent (lead) structures for drug development.

In 2014, rubrolide R **1** and S were isolated from the marine-derived fungus *Aspergillus terreus (*OUCMDZ-1925).[1] Both structures reveal biological activity against influenza A and rubrolide S has also shown activity against the tobacco mosaic virus.[2] The protecting group free and short total syntheses of these two novel natural products is essential for further biological investigations, in particular for antiviral and antibiotic activity of rubrolide analogues.[3]



Rubrolide R **1** Prostaglandin A_2 **2**

Fig. 1 Rubrolide R **1** and Prostaglandin A_2 **2**

In 1986, Prostaglandin A_2 **2** (PG A_2) has been isolated from the coral *Plexaura homomalla*.[4] Prostaglandins are ubiquitous hormon-like messenger molecules, which have been originally isolated, including PG A_2 **2**, from human seminal plasma.[5] Due to its cytotoxic and anti-fouling properties this natural product is an interesting target for stereoselective total synthesis, which was conducted in short and divergent manner.[6]

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New Catalytic Photooxygenations and Rearrangements of Indole Alkaloids

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Keywords: alkaloids, photooxygenation, rearrangements

Spirocyclic 2-oxindoles constitute a fascinating class of oxygenated indole alkaloids, and many of these natural products possess valuable biological properties such as antihypertensive, analgesic, antitumor, and antiviral activity. The typical core structure encountered in monoterpene spiro-2-oxindoles is the spiro[pyrrolidine-3,3'-oxindole] motif **I** which can be accessed in a biomimetic fashion from a parent tetrahydro-*β*-carboline **II** *via* photooxygenation followed by 1,2-rearrangement (Fig. 1).

However, regioisomeric 2,2-disubstituted pseudoindoxyls are formed in a competing semipinacol rearrangement,[1] and therefore, steering product selectivity is often challenging. Phosphoric acids were indentified as ideal organocatalysts for the highly regioselective 1,2-rearrangement of 3-hydroxyindolenines to 2-oxindoles, with a predictable product selectivity arising from an efficient dual activation mode.[2]

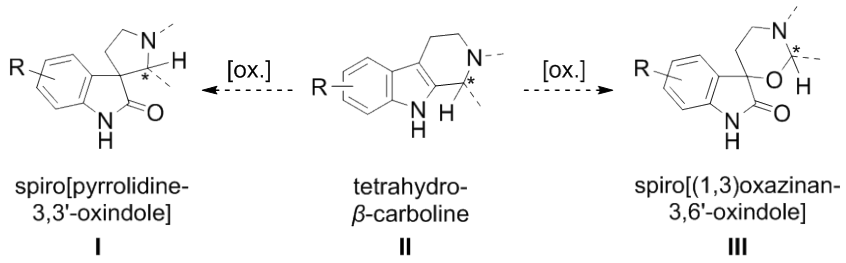

Fig. 1 Divergent oxidative rearrangements of indole alkaloids

A few natural spiro-2-oxindoles possess a peculiar spiro-[(1,3)oxazinan-3,6'-oxindole] ring system **III** whose biosynthesis is yet to be elucidated, but putatively proceeds *via* a divergent and unusual oxidative indole rearrangement, with concomitant incorporation of two oxygen atoms into the product structure. A new catalytic photooxygenation of indole alkaloids to spirooxindole-1,3-oxazines was developed, and a mechanistic investigation led to a refined mechanistic picture.

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Synthesis of Cytospolides D, M, O, and Q and Late-Stage Diversification of Derivatives Thereof

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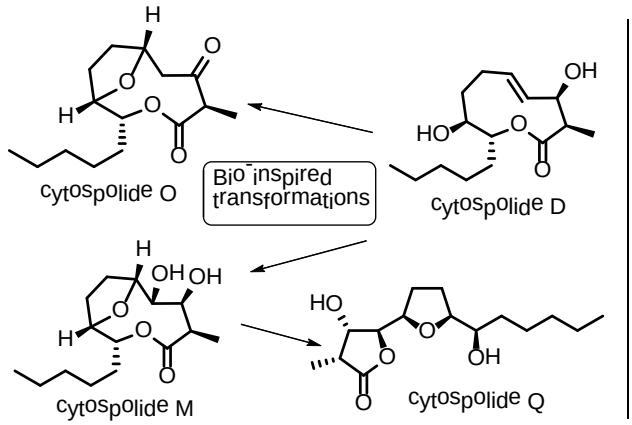
Keywords: macrolides, biomimetic conversion, natural products



Scheme 1 Biomimetic synthesis of cytospolides M, O and Q based on precursor D

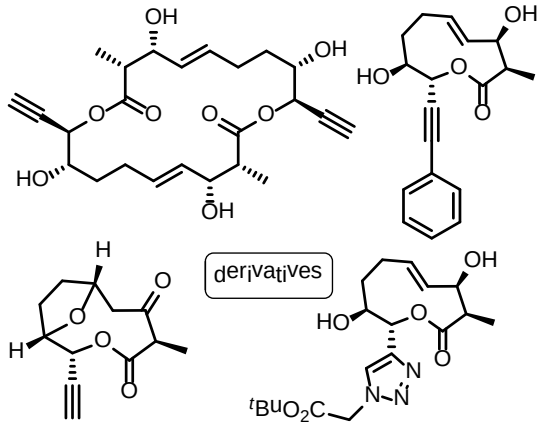


Fig 1 Further functionalized compounds

The large group of the cytospolides (A–Q), produced by the endophytic fungus *Cytospora sp*. from *Ilex canariensis*, was discovered in 2011.[1] Most of the isolated natural derivatives show a close relationship regarding their core structure and only differ in their acetylation pattern. The more complex and structurally divers cytospolides M, O and Q are assumed to be biosynthetically derived from cytospolide D as the common precursor. Since their first publication, especially the more bioactive members have attracted considerable research effort.[2] In our search for biologically active compounds we developed a total synthesis of cytospolide D and made use of bio-inspired transformations to enable access to cytospolides M, O, and Q. [3]

Furthermore, we set up an alternative synthesis with an alkyne-modified side chain, which allows us to functionalize the cytospolide core structures at a late stage of the synthesis. During extensive screening of lactonization conditions, we observed the formation of diolides and triolides depending on the protecting groups used. Thus, we have now access to a broad variety of structurally divers natural product derivatives to investigate the structure-activity relationship and identify the biological target structure.

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New *seco*-Progeldanamycin Derivatives: Tools to Study the Substrate Flexibility of the Amide Synthase GdmF

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Keywords: Amide synthase GdmF, Geldanamycin, Hsp90 inhibitors

Geldanamycin (**1**), a benzoquinoid ansamycin antibiotic produced by *Streptomyces hygroscopicus*, is a potent inhibitor of Hsp90. It binds to the *N*-terminal ATP-binding pocket of Hsp90 acting as an ADP/ATP mimic.[1] The Hsp90 chaperone machinery is crucial for the survival and growth of cancer cells, as it protects mutated and overexpressed oncoproteins from misfolding and degradation.[2] Since Hsp90 clients include kinases, transcription factors and other cancer-related proteins geldanamycin and its derivatives are potential anticancer chemotherapeutic agents.[3] Despite its high *in vitro* activity geldanamycin failed to exhibit clinical potential due to limited *in vivo* stability, severe hepatotoxicity and low solubility in aqueous solutions.[4]

The purpose of this project is to study the substrate flexibility of the amide synthase GdmF which catalyzes the macrolactamization in the biosynthesis of geldanamycin.[5],[6] *seco*-Progeldanamycin derivative **6** was synthesized and applied in an enzymatic study with heterologously expressed GdmF. [7],[8] Mass spectrometric analysis revealed that macrolactam **7** was formed in traces. Thus, it was proven that the GdmF accepts and biosynthetically transforms complex modified substrates.

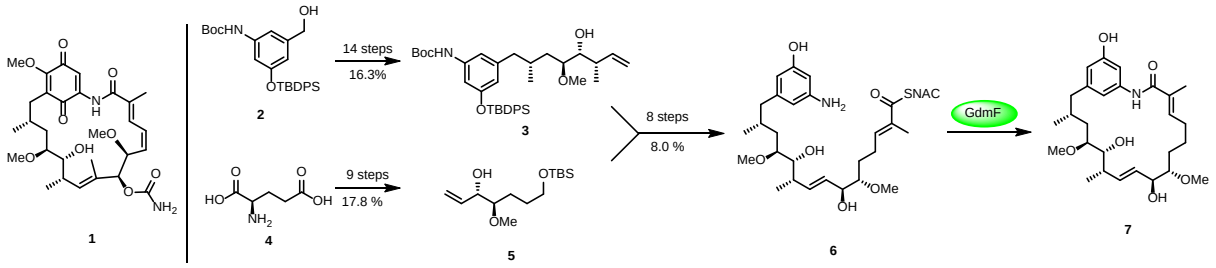

Fig. 1 Synthesis of *seco*-progeldanamycin derivative **6** and its application in an enzyme assay with GdmF.

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Studies towards the Total Synthesis of Canataxpropellane

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Keywords: total synthesis, taxane terpenoid, propellane

Canataxpropellane is a member of the taxane terpenoid family originally isolated from *Taxus canadensis*.[1] The structure belongs to the subgroup of complex taxanes possessing an unprecedented 5/5/5/4/6/6/6-membered heptacyclic ring system. Canataxpropellane comprises unique structural features as a [3.3.2]- and a [4.4.2]-propellane substructure along with a fully substituted cyclobutane moiety and a cage like backbone. To date it has not yet been subject to any studies towards its synthesis or biological activity.

We present an efficient convergent synthetic approach towards the key features of the structure utilizing a Diels-Alder reaction and [2+2] cycloaddition, eventually achieving the completion of the heptacyclic carbon skeleton and will discuss the remaining synthetic challenges towards a first total synthesis of canataxpropellane.

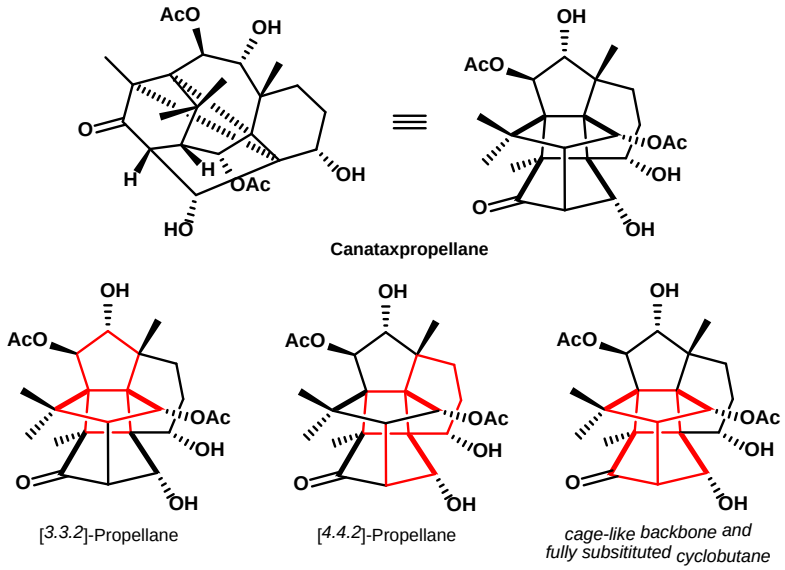

Fig. 1 Structural Features of Canataxpropellane

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Aroma Molecules from Renewable Resources

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Keywords: waste streams, crude sulfate turpentine, aroma molecules

The term „Green Chemistry“ has become an established synonym for all efforts to improve the sustainable development in chemistry. One of the mental fathers of this term, Paul Anastas, has defined in total 12 principles for „Green Chemistry“.[1] In this lecture I would like to focus on one of these principles and to demonstrate, how the fragrance industry could contribute to this object.

It is the principle of using “renewable resources as raw materials whereever it is possible”. This is not significantly new in the world of Fragrance Chemistry. The whole perfumery has its origin in the application of natural resources like essential oils, natural extracts etc. But after a matchless triumphant progress of substances from fossil resources, ingredients from natural or renewable resources today are used only in small areas, as for example the Fine Fragrance Perfumery. However, the natural raw materials contain some hydrocarbons which are not suitable as smelling substances. These hydrocarbons consist of outstanding carbon skeletons, which are difficult to produce synthetically and offers excellent possibilities for oxygen functionalization reactions leading to interesting new fragrance molecules [~195].

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A Chemoenzymatic Approach to Cembranoid Analogues

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Keywords: *natural product synthesis, chemoenzymatic, cembranoid analogues*

Cembranoids are 14-membered macrocyclic diterpenes of mostly marine origin which have been discovered in 1962 and include hundreds of representatives.[1] These class of natural products display a variety of interesting biological activities, such as cytotoxicity, antibacterial, anti-viral and anti-inflammatory activities.[2]

Macrocyclization by ring-closing metathesis (RCM) with Grubbs II catalyst is an attractive way to construct cembranoid analogues. The substitution pattern in acyclic tetraene **2** steers the metathesis pathway in the direction of macrocyclization, affording cembranoid analogue **1** in 61% yield (*E*/*Z* ration 99:1, Fig 1). Competing reactions such as cross metathesis and formation of six-membered rings were suppressed.[3]

Late-stage oxyfunctionalization of cembranoid scaffolds has been recognized as a powerful tool in the synthesis of these complex molecules. To achieve this goal, cytochrome P450 monooxygenases are often used as biocatalysts.[4]

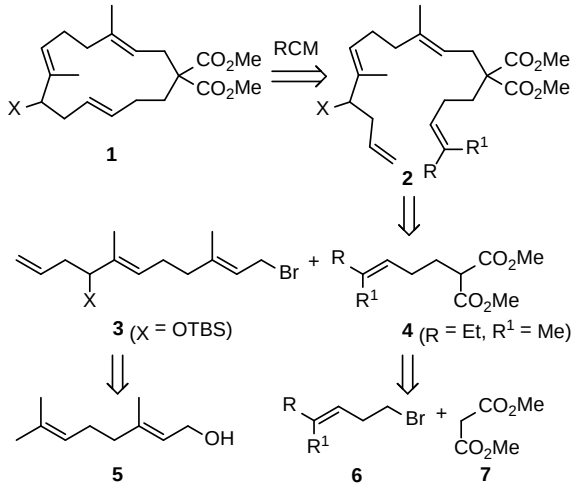

Fig. 1 Retrosynthetic pathway to cembranoid analogues **1**.

Acknowledgements

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Total Synthesis of Nannocystin Ax

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Keywords: natural product synthesis, depsipeptide, nannocystins

The cytotoxic 21-membered depsipeptide nannocystin Ax (**1**) was isolated from the myxobacterial genus *Nannocystis* sp by the group of Hoepfner (Novartis) [1]. Moreover, other members of the nannocystin family have been isolated which differ in the peptide part and may contain an α,β-epoxyamide [1,2]. In biological studies an antiproliferative activity against various cancer cell lines in the nanomolar range (IC_{50} = 5.4 nM for **1**, HCT-116) was observed for all family members. Based on these observations the nannocystin family could be a promising starting point for drug development. Therefore, our group aimed for the total synthesis of nannocystin Ax (**1**) [3]. Besides that two total syntheses of nannocystin Ax (**1**) [4,5] and four total syntheses of nannocystin A [6,7,8,9] have been achieved by other groups. Our retrosynthetic approach towards nannocystin Ax (**1**) was based on its division into a polyketide and a tripeptide segment. The macrocycle was closed by a macrolactamization. The linear precursor was obtained *via* successive amidation and esterification reactions from northern fragment **2** and peptide fragments **3**, **4** and **5**. For the synthesis of polyketide fragment **2** a vinylogous Horner-Wadsworth-Emmons (HWE) reaction and an asymmetric vinylogous Mukaiyama aldol reaction (VMAR) for installation of the C 11 stereocenter were utilized as key steps.

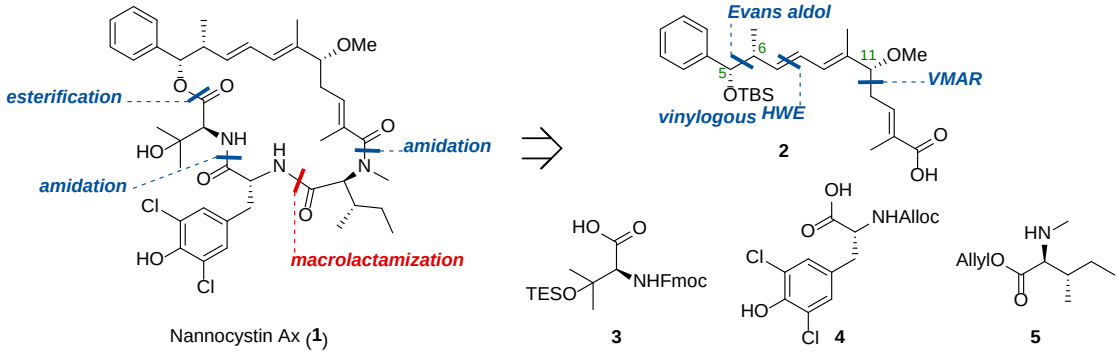

Fig. 1 Retrosynthetic analysis of nannocystin Ax (**1**)

Acknowledgements

We thank Dr. Phillip Krastel (Novartis Institutes for BioMedical Research) for providing the NMR spectrum of natural nannocystin Ax.

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Synthesis of Novel Betulin Conjugates

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Keywords: betulin, triazole, isoxazole

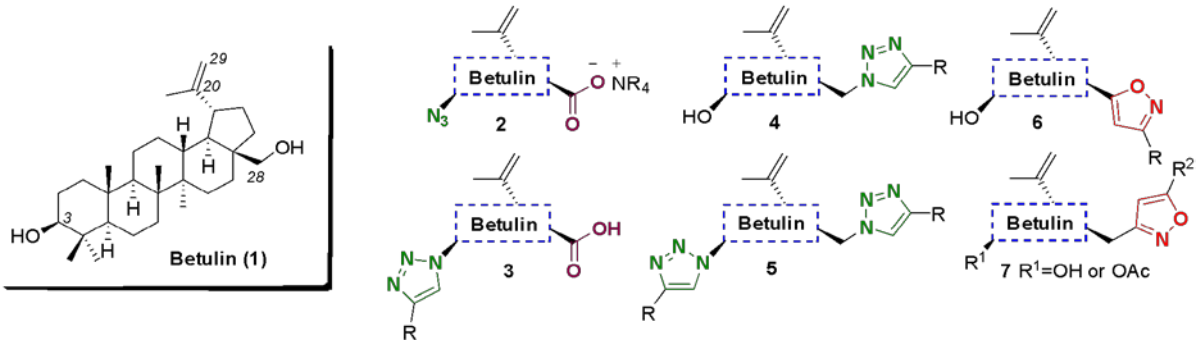
Betulin is an abundant naturally occurring triterpene, most commonly found in birch bark. Research shows that betulin and its derivatives possess wide spectrum of biological activities such as anti-HIV, anti-inflammatory, and anticancer properties.[1,2] Use of betulin is limited by its low solubility in water. Therefore, structural modifications of betulin with new functional groups to improve both the bioactivity and solubility in water are being made.[3]

In this work, various conjugates were obtained starting from betulin (**1**). 3-Azido betulinic acid was prepared by standard Jones oxidation, reductive amination at C(3) position and diazotransfer reaction sequence. Subsequently, it was converted into corresponding salts **2** with ammonia, choline, and some amino acids. Compound **2** was also employed in Cu(I) catalyzed azide-alkyne 1,3-dipolar cycloaddition reactions to obtain C(3)-triazolyl conjugate **3**.

To obtain C(28) betulin-triazole monoconjugates **4**, primary alcohol was chemoselectively oxidized. The obtained aldehyde was treated with hydroxylamine hydrochloride to obtain corresponding oxyme. Following catalytic hydrogenation gave amines with or without reduced C(20)-C(29) double bond. From the obtained amines corresponding azides and triazoles **4** were created *via* described two-step procedure. Betulin derivatives containing two triazole substituents **5** were synthesized in 5 steps, starting with Swern oxidation that gives ketoaldehyde. The treatment with hydroxylamine hydrochloride provided dioxyme that was used in reductive amination with $NaCNBH_3$ to obtain corresponding diamine, which again through azide intermediate provided target compounds **5**.

Finally, betulin-isoxazole derivatives **6** were prepared using alkynyl-betulin as a dipolarophile component in 1,3-dipolar cycloaddition reaction with different oxymes, while compound **7** was generated using nitroethyl-betulin as a dipole precursor.

Novel triterpene conjugates were tested on a rare cancer cell lines and observed cytotoxicity will be reported.



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Dynamic Hemicucurbit[*n*]urils

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Keywords: chiral macrocycles, cucurbiturils, templated synthesis, dynamic covalent chemistry, host-guest chemistry

Hemicucurbiturils (HCs) are macrocyclic container molecules, which are able to form host-guest complexes and therefore can serve as a key element in many supramolecular applications. HCs are single bridged sub-branch of the double bridged pumpkin shaped cucurbiturils[1] (CBs), where cyclic urea monomers are connected through methylene linkers.

This presentation will cover tunable synthesis of cyclohexanohemicucurbiturils (cycHCs) through dynamic covalent chemistry of acylaminal linkers and anionic templates.[2-5] Chiral (*S,S*)- or (*R,R*)- and *meso*-(*R,S*) (*N,N'*)-cyclohexa-1,2-diylurea monomers give rise to diastereomeric HCs with different cavity shapes. Monomers that are chiral, enatiopure and C_2-symmetric result in ball-shaped oligomeric macrocycles either (*S,S*)- or (*R,R*)- and cycHC[6] or cycHC[8] in high yield and as a single stereoisomer.[3,5] Condensation of achiral, (*R,S*)-monomer with formaldehyde leads to formation of diastereomeric linear oligomers and subsequently to two diastereomeric (*R,S*)- and *inverted*-(*R,S*)-cycHC[6] are formed. Driving factors of selectivity of formation of homologues and diastereomeric cycHCs will be discussed. Also complexation charactristics of cycHCs will be presented.[6,7]

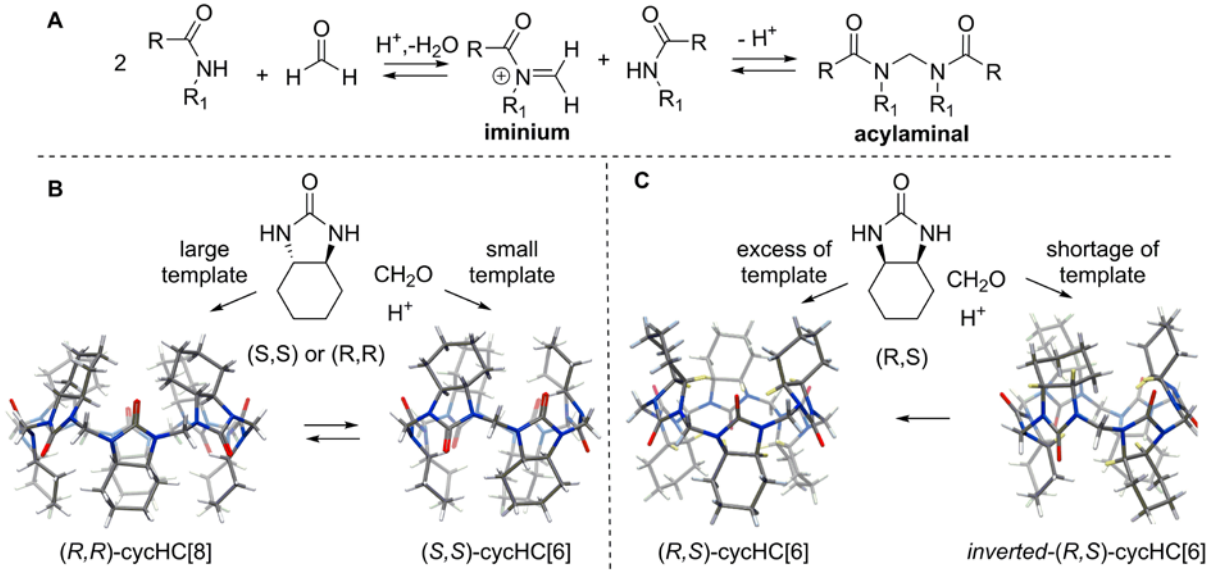

Fig. 1 Dynamic acylaminal linkers (A) and templated synthesis of chiral (B) and achiral (C) cycHC[*n*]s

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From Coronoid Macrocyles to Stable Biradicaloid Systems

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Keywords: aromaticity, biradicaloids, organic synthesis

The interest in open shell aromatic molecules is motivated by the fundamental aspects of their electronic structure, posing considerable challenges to synthetic, physical, and theoretical chemists, and by their unique properties, with emerging applications in materials science.[1–3] Modern strategies of creating biradicaloid molecules typically combine quinoidal, aromatic, and antiaromatic substructures in ways that stabilize open-shell configurations and high-spin states.

Our own research on coronoid aromatics containing hetero- and carbocyclic ring systems[4–6] (Fig. 1) provides access to novel pi-conjugated frameworks that can be tailored into structures with a distinct multiconfigurational character. In this contribution we will discuss our recent synthetic advances and describe the spectroscopic and supramolecular features of these systems.

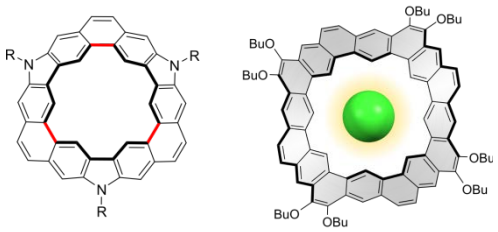

Fig. 1 Chrysaorole[4] and octulene[6]

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Towards New Macrocylic Scaffolds

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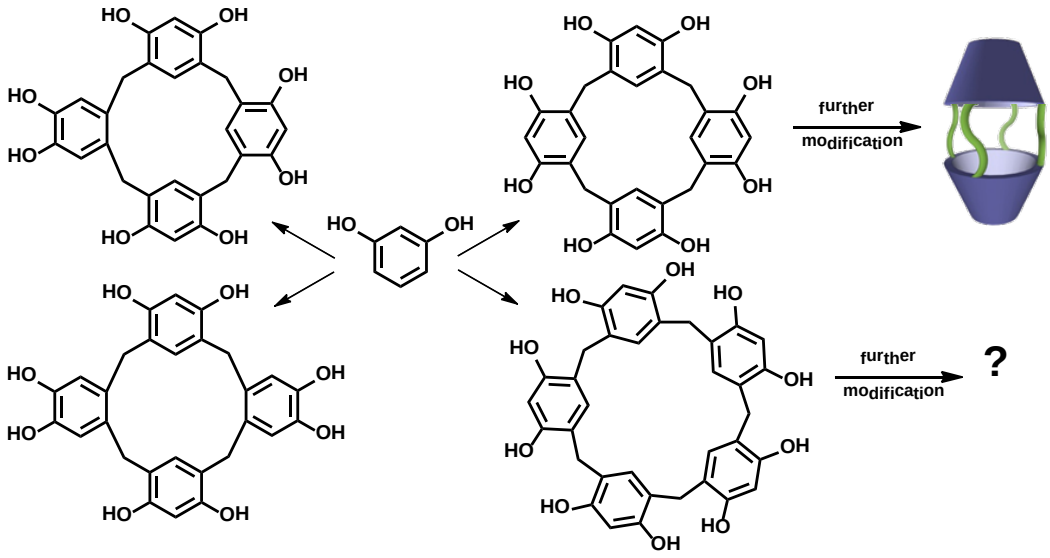
Keywords: macrocycles, supramolecular chemistry

For decades, chemists have been attempting to mimic the structures and exquisite reactivity of compounds commonly found in nature. Most of the reactions in biological systems proceed in confined, molecular-sized and well-defined spaces (e.g. binding sites of enzymes). To effectively realize these goals in artificial systems, chemists need high yielding synthetic strategies that would allow them to construct properly-shaped scaffolds. In this regards, macrocyclic compounds,[1] that provide concave shapes play a unique role. After further functionalization, macrocyclic scaffolds have already found applications in mimicking biological functions (e.g. catalytic) or in the development of new materials.

Special attention is being paid to polar macrocycles, that can offer compatibility with natural aqueous environment.[2] The number of such polar macrocycles, available by simple synthesis and easily modifiable, is still limited. The aim of my work is to expand the pool of such macrocycles. I concentrate on the synthesis of new hydrophilic homomacrocyles based on a resorcinol and on hybrid macrocycles. Then the new macrocycles are modified by formylation[3] and used as scaffolds for synthesis of new chiral molecular capsules by means of dynamic covalent chemistry and self-assembly.



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Trityl Group as a Tool for Construction of Multicomponent Supramolecular Materials

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Keywords: trityl group, molecular complexes,

Trityl group is a protection group widely used in organic synthesis.[1] The presence of this bulky substituent in given compounds may cause the formation of empty spaces in the crystal structure, potentially available for the guest molecules.[2]

The presented studies are aimed at tracing the ability of triphenylacetic amide to form multicomponent supramolecular systems. Host-guest systems are built based on relatively weak non-covalent interactions. The guest's molecules are selected organic bases (aromatic or aliphatic) with strictly defined geometry. The structural analysis of the crystalline products showed that the obtained supramolecular assemblies may constitute molecular complexes and salts, in which the amide molecules and bases are connected *via* O-H···N or N^{+}-H···O^{-} hydrogen bonds. The three-dimensional structure is stabilized by O-H···O and van der Waals interaction.

The stoichiometry of the obtained materials, the type of inclusion and flexibility of conformation of the host molecules depending on the composition of molecular crystals will be shortly discussed (Fig. 1).

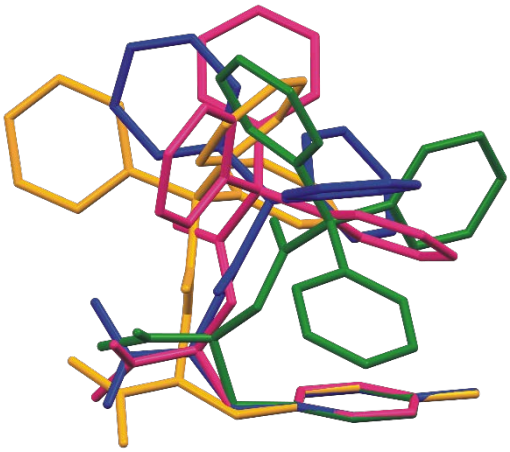

Fig. 1 Conformational flexibility of the *N*-triphenylacetyl-L-tyrosine molecule in the crystal structure.

Acknowledgements

This work was supported by research grant from National Science Center (NCN) Poland, DEC-2016/B/ST/00100.

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Template-Driven Assembly of Hemicucurbit[*n*]uril Macrocycles in the Solid State

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Keywords: anion binding, host-guest chemistry, templated solid-state synthesis

Chiral macrocyclic receptors cyclohexanohemicucurbiturils (cycHC[*n*])[1,2] are capable of binding anionic[3] (Figure 1, right) and electron-rich guests, and could potentially be employed in a range of target structures, such as sensors, in asymmetric catalysis or as components of pharmaceutical delivery systems. The synthesis of 6- and 8-membered cycHC[*n*] is carried out in strong acids and can be directed by the choice of an anionic template.[1,2,4] Recently, we have explored the formation of these macrocyclic host molecules in the solid state. Mechanochemistry is a rapidly advancing "CleanTech" synthetic technique, which utilizes mechanical agitation to achieve chemical transformations in the absence of bulk solvents.[5] Recent applications of solvent-free mechanosynthesis of covalently-bonded nanocapsules have revealed improved reaction yields, product selectivity and isolation.[6]

Herein, the template-directed solvent-free synthesis of cycHC[*n*] selectively and quantitatively from cyclohex-1,2-diylurea and paraformaldehyde will be presented. Liquid-assisted grinding (LAG) of reactants in the presence of catalytic amount of acid produces a set of polymerization products from which a desired macrocyclic product can be amplified in the presence of a suitable supramolecular template in a solvent-free process (Fig. 1, left). Besides providing a green route for the synthesis of these macrocycles by removing the bulk of the used acid and solvents, these solvent-free processes offer unique examples of supramolecular control over reversible covalent bond formation in the solid state.

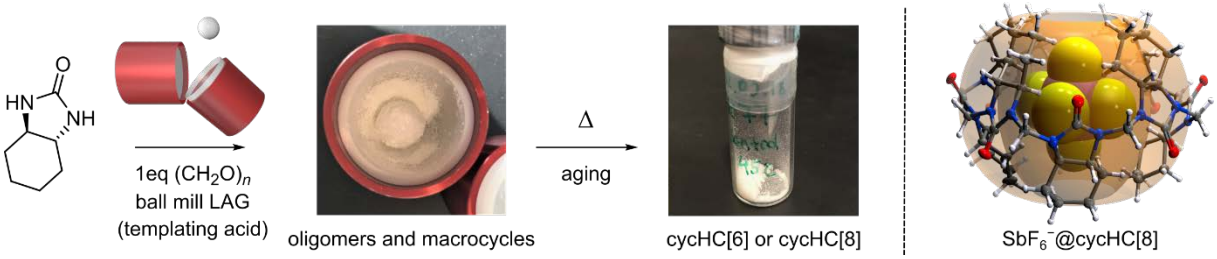

Fig. 1 General scheme for the solid-state synthesis of cycHC[*n*] (left) and an anion inclusion complex of cycHC[8] with SbF_6^- (right)

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Dynamic Peptidic Containers - a Road Towards Bio-Inspired Self-Assembly

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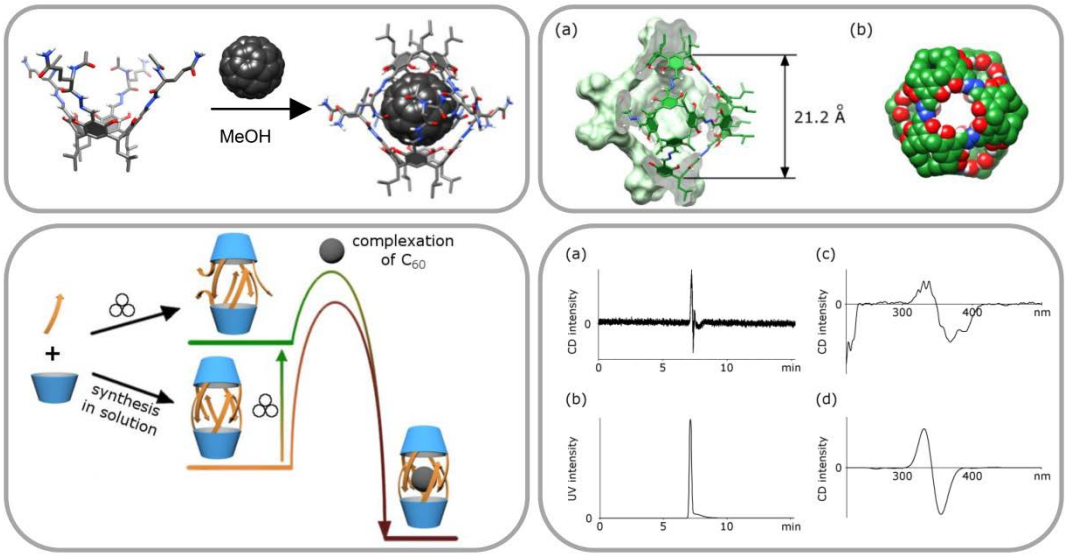
Keywords: peptides, supramolecular chemistry in water, templation

Self-assembled peptidic structures are gaining attention as biocompatible synthetic materials for regenerative medicine or for drug delivery. However, application of '*de novo*' designed peptides, especially for the formation of porous materials, is limited by conformational lability, tendency to non-specific aggregation and low availability of long synthetic peptides in the large scale. Here we present the spontaneous formation of peptidic capsules using easily available short peptides by dynamic covalent chemistry (DCC) and self-assembly. Dynamic approach, supported by formation of minimal β-barrel motifs, allows for errors' corrections and enables amplification of selected capsules from among a number of possible products. We show various ways of controlling non-covalent assembly/disassembly of peptidic structures by classical means (polarity and chirality) and non-classical approaches (templation or mechanochemical methods) and discuss ways towards self-assembly in aqueous media.



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This work was supported by National Science Center grants: SYMFONIA 2016/20/W/ST5/00478 and Diamentowy Grant 0206/DIA/2016/45.

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Pyrrolo[3,2-*b*]pyrroles – Electron-Rich Functional Heterocycles

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Keywords: dyes, pyrrole, fluorescence

Recently we have discovered and optimized the first practical synthesis of non-fused pyrrolo[3,2-*b*]pyrroles *via* domino reaction of aldehydes, primary amines, and butane-2,3-dione.[1] Six bonds are formed in heretofore unknown tandem process, which gives rise to substituted pyrrolo[3,2-*b*]pyrroles – the 'missing link' on the map of aromatic heterocycles. Unparalleled simplicity and versatility of this one-pot reaction, non-chromatographic purification and superb optical properties (including strong violet, blue or green fluorescence both in solution as well as in the solid state), brought these molecules from virtual non-existence to the intensively investigated area functional π-systems.

The parent 1,4-dihydro-pyrrolo[3,2-*b*]pyrroles served as building block to construct various π-expanded analogs including diindolo[2,3-*b*:2′,3′-*f*]pyrrolo[3,2-*b*]pyrroles.[2,3] These compounds constitute the most electron-rich ladder-type heteroacenes known to date - E_{HOMO} was located at (−4.6)-(−5.1) eV. Strongly fluorescent diindolo[2,3-*b*:2′,3′-*f*]pyrrolo[3,2-*b*]pyrroles represent the longest ladder-type heteroacenes and the only existing compounds bearing the 1,4,5,8-tetrahydropyrrolo[3,2-*b*]pyrrolo[2',3':4,5]pyrrolo[2,3-*d*]pyrrole core.

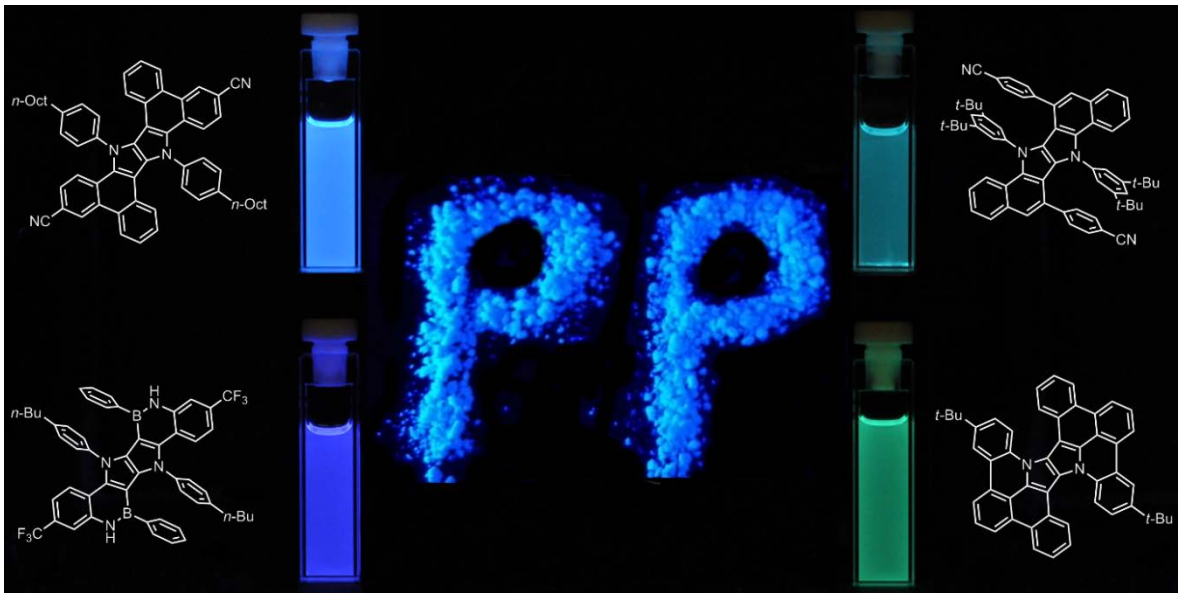

Fig. 1 Structural diversity originating from tetraryl-pyrrolo[3,2-*b*]pyrroles

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Synthesis and Anti-Mitotic Activity of Variously Substituted 2*H*-Pyrazolo[4,3-*c*]pyridines

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Keywords: apoptosis, G2/M cell cycle arrest, pyrazole

Due to its wide spectrum of biological activities, pyrazole is a common structural unit in many pharmaceuticals and a central axis of numerous ongoing studies devoted to the synthesis and biological evaluation of novel pyrazole moiety-bearing molecules. Among the vast variety of biologically active annelated pyrazole derivatives, synthetically demanding 2*H*-pyrazolo[4,3-*c*]pyridines are relatively understudied.

In this study, an efficient approach for the synthesis of variously substituted 2*H*-pyrazolo[4,3-*c*]pyridines, employing Sonogashira coupling and a subsequent substituent-tolerant annulation reaction in the presence of ammonia, was developed. As a result, a library of 2*H*-pyrazolo[4,3-*c*]pyridines, varying by the substituents at the 2-, 4-, and 6-positions was synthesized. These compounds were evaluated for their cytotoxicity against K562 and MCF-7 cancer cell lines. The most potent compounds displayed low micromolar GI_{50} values in both cell lines. The active compounds induced dose-dependent cell-cycle arrest in mitosis, as shown by flow cytometric analysis of DNA content and phosphorylation of histone H3 at serine-10. Moreover, biochemical assays revealed increased activities of caspases-3/7 in treated cells, specific fragmentation of PARP-1, and phosphorylation of Bcl-2, collectively confirming apoptosis as the mechanism of cell death. The mechanism of cellular action of these compounds, however, still remains unclear.

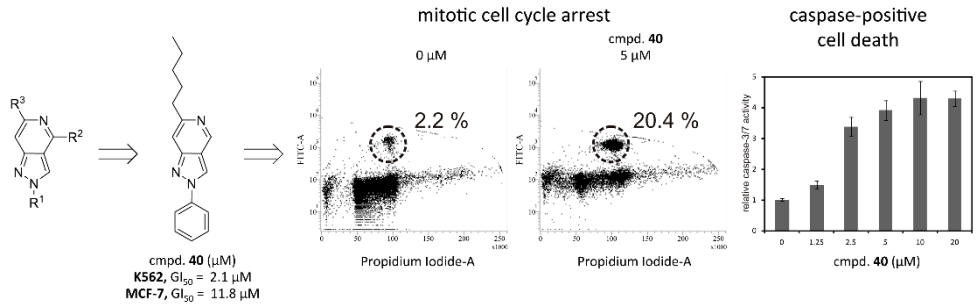

Fig. 1 Novel 2*H*-pyrazolo[4,3-*c*]pyridine derivative **40** and its antimitotic and proapototic activity

Acknowledgements

This work was supported by grants No. LO1204 (Sustainable development of research in the Centre of the Region Haná) from the National Program of Sustainability I, MEYS, IGA_PrF_2017_013 and IGA_PrF_2018_006.

Intramolecular Tandem Seleno-Michael/Aldol Reaction Promoted by *in situ* Generated Lithium *n*-Butylselenolates

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Keywords: intramolecular cyclization, seleno-Michael, β-valienamine

Morita-Baylis-Hillman (MBH) reaction is an important tool which constantly grew over last two decades. Application of thio-Michael or seleno-Michael reaction as a first step into the tandem process such as MBH reaction has developed rapidly over the last decade. Ortho-acidic aromatic thiols[1] and more simple thiolates[2,3] have been studied as efficient catalysts of intramolecular MBH reaction.

An efficient protocol for the direct construction of ethyl cyclohex-1-ene-1-carboxylate derivatives from oxo-α,β-unsaturated ester via an one-pot intramolecular seleno-Michael/aldol/oxidation-elimination process was developed.[4] Lithium *n*-butylselenolate generated in situ gave the intramolecular MBH product with up to 72% yield. Presented one-pot strategy helped to avoid a serious drawback such as very bad smelling of selenols. The key cyclohexenyl intermediate 7 was synthesized in 6 steps from D-xylose in 26% overall yield via intramolecular seleno-Michael/aldol reaction and transformed to β-(+)-valienamine with 8% yield total.

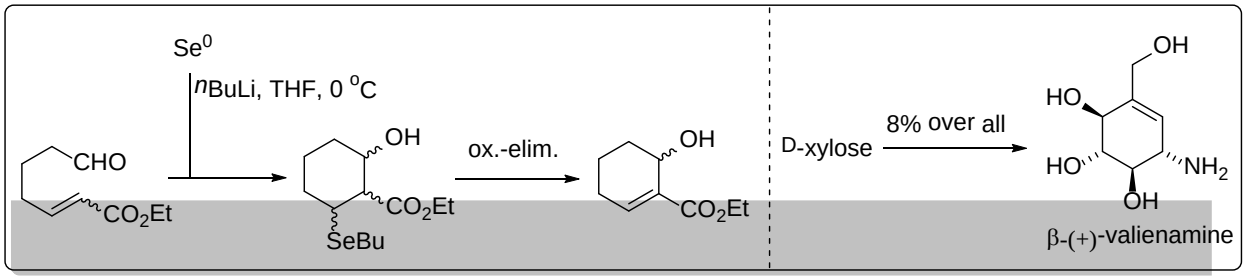

Fig.1 General scheme of one-pot intramolecular seleno-Michael/aldol reaction promoted by lithium *n*-butyl selenolates.

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Photoalkylation of Electron-Rich Heteroarenes with α-Diazo Esters

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Keywords: photoredox catalysis, aromatic heterocycles, α-diazo esters

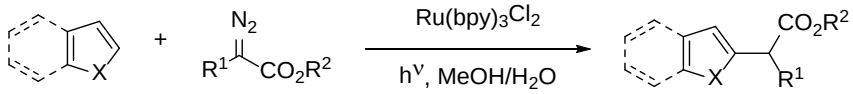
Five membered heteroaromatic rings are common skeletons of pharmaceuticals, agrochemicals, and functional dyes. Therefore, development of new methods for their functionalization, especially alkylation is an important branch of modern organic chemistry.

Classical methods for C-H alkylation of electron-rich heteroaromatic compounds are suitable only for functionalization of simple heterocyclic derivatives, as required conditions are destructive for many functional groups. Modern procedures, employing transition metal catalysis broadens the range of aromatic compounds. Yet due to the character of a catalyst they require anhydrous reagents and often elevated temperatures.

In recent years photoredox catalysis has emerged as a facile synthetic tool,[1] in particular for formation of C-C bond, also in alkylation of electron-rich heterocyclic rings.[2,3] These photoredox alkylations employ ruthenium or iridium photocatalyst to reduce electrodeficient alkyl halides giving radicals which easily reacts with electron-rich heteroaromatic rings. Utilization of Au(I) photocatalyst allows similar reaction for simple alkyl bromides, yet this process inherently suffers from low selectivity due to ambiguous character of the radical.[4]

Recently, we have reported photoredox-catalyzed α-alkylation of *in situ* formed enamines with diazoesters,[5,6] consequently Meggers *et al.* presented enantioselective alkylation of 2-acylimidazoles using rhodium complex and ruthenium photoredox catalyst.[7]

Therefore, we expected identical reactivity of ethyl diazoacetate towards 1-methylindole and to our delight the reaction worked to provide product of alkylation in position 2. Herein, we report new method for alkylation of electron-rich heteroaromatic compounds using photoredox-catalyzed reactions with diazoesters.



Acknowledgements

I would like to thank Polish Ministry of Science and Higher Education (grant no. 0205/DIA/2016/45) for financial support of this work.

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Donor-Acceptor Pyrrole Hybrids: Versatile Building Blocks for Electron-Deficient Chromophores with Multi-Redox Activity

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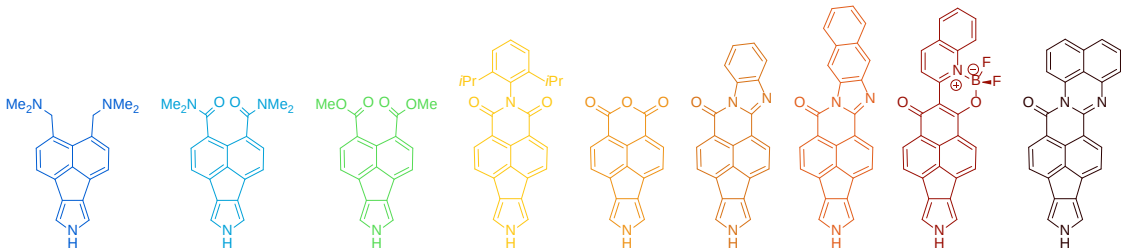
Keywords: pyrrole, naphthalenediimide, electron-deficient

The development of new two-dimensionally fused heteroaromatics with precisely controlled electronic properties requires efficient and versatile synthetic strategies capable of producing complex conjugated ring systems.[1] Looking for appropriate heterocyclic building blocks, we recently synthesized a new donor—acceptor hybrid, combining naphthalenediamide (NDA) and pyrrole motifs, which was prepared via six-step synthesis from acenaphthene.[2] Starting from the diamide functionality of this NDA-pyrrole, a family of derivatives were prepared (Fig. 1) using functional group interconversion and annulation reactions. These pyrroles show highly variable fluorescence properties and can be used as building blocks for the synthesis of electron-deficient oligopyrroles.[2-4] The latter application is demonstrated through the development of π-extended porphyrins containing NDA or naphthalenediimide units. These new macrocycles exhibit simultaneously tunable visible and near-IR absorptions, an ability to accept up to 8 electrons via electrochemical reduction, and high internal molecular free volumes. Such features make these systems of interest as functional chromophores, charge-storage materials, and tectons for crystal engineering.



pyrrole charge	0.07	0.09	0.12	0.15	0.17	0.14	0.14	0.15	0.13
HOMO, eV	–5.29	–5.46	–5.64	–5.79	–5.91	–5.59	–5.48	–5.74	–5.16
LUMO, eV	–1.48	–1.77	–2.08	–2.63	–2.78	–2.68	–2.70	–2.81	–2.61
HLG, eV	3.81	3.70	3.56	3.16	3.13	2.91	2.78	2.94	2.55
TD bandgap/*f*	3.58/0.37	3.45/0.39	3.31/0.35	3.01/0.56	2.98/0.46	2.52/0.18	2.52/0.63	2.46/0.07	2.27/0.59
Dipole, D	3.2	5.7	6.9	11.9	15.7	11.0	11.4	8.4	9.6

Fig. 1 Donor-acceptor pyrrole hybrids library

Acknowledgements

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Synthesis of New Heterocyclic Building Blocks Bearing the Azetidine Structural Unit

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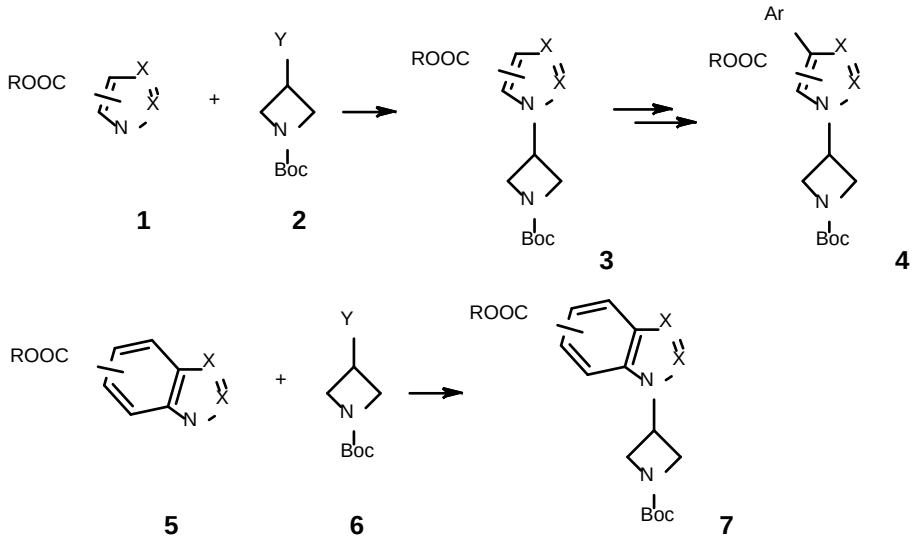
Keywords: azetidine, pyrazole, indole, building blocks

The aim of the present work is the synthesis of heterocyclic carboxylates bearing an azetidin-3-yl substituent at the nitrogen atom. The azetidine moiety has previously been identified as a privileged motif within medicinal chemistry.[1-3] The synthetic combination of two pharmacologically relevant nitrogen containing heterocycle (pyrazole, imidazole, pyrrole, indole, indazole, benzoimidazole) and azetidine motifs can provide interesting building blocks for development of lead molecules. The synthesis strategy included coupling of various carboxylates with 3-hydroxy-, 3-mesyloxy- and 3-iodoazetidines. For example, treatment of structurally *symmetrical* ethyl pyrazole-4-carboxylate **1** with *N*-Boc protected 4-iodoazetidine **2** (Y = I) in the presence of cesium carbonate afforded compound **3** as a sole product in a good yield, while analogous reaction of unsymmetrical ethyl pyrazole-5-carboxylate gave a mixture of isomeric compounds. The Mitsunobu reaction of pyrazoles with 4-hydroxyazetidine was carried out as well. The bromination of the obtained *N*-(azetidin-3-yl) substituted pyrazoles was performed and Pd-catalyzed cross-coupling reactions of the obtained bromo substrates were investigated.



Scheme 1 R = Me, Et; X = C, N; Y = OH, OMs, I

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Visible Light Mediated Oxidation of *N*,*N*-Dimethylamines

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Keywords: photocatalysis, indole, amines

Visible light photocatalysis became emerging strategy for the preparation of biologically active compounds and fine chemicals based on heterocycles. This methodology enables to conduct organic reactions in an environmentally conscious fashion and meets expectations for more sustainable chemical processes. Another advantage of visible light approaches is compatibility with broad functional groups and employment in numerous chemical transformations.[1-3]

The indole as widespread heterocyclic moiety constitutes a privilege structure in numerous of natural products and pharmaceutical compounds. Many of them indicate interesting biological activities, e.g. antimigraine (Sumatriptan), antimicrobial/antiparasitic (Flustramine), anti-HIV (Coscinamide), cytotoxic (Dragmacidin), antiserotonin (Gelliusine A), antiviral (Eudistomin), antiinflammatory (Chelonin), Ca-releasing (9-Methyl-7-bromoeudistomin D) and more.[4]

This presentation will describe visible light mediated oxidation of 3-*N*,*N*-(dimethylaminomethyl) indoles bearing various substituents which leads to a series of 3-carbaindole derivatives. A plausible mechanism and application of this transformation in the formal synthesis of (-)-Vincorine will be also showed.

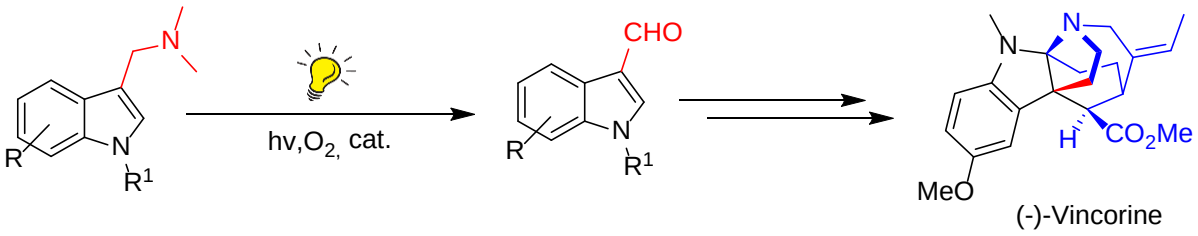

Fig. 1 Visible light oxidation of *N*,*N*-dimethylaminomethyl derivatives

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Tuning of Molecular and Supramolecular Properties of Polyimine Macrocycles and Organic Cages

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Keywords: shape-persistent macrocycle, preorganization, self-assembly

A unique combination of functionality, structural flexibility and shape persistency makes macrocycles and molecular cages as essential molecular entities that have displayed applications useful in various aspects of chemistry and biochemistry. Among macrocycles, the symmetrical (poly)cyclic polyimines have shown great utility in the design of molecules and supermolecules varied in shape and properties.[1]

The reversible and thermodynamically controlled cycloimination reaction is governed by configurational and conformational constraints imposed on the intermediate products, which ensures a sufficiently high level of pre-organization. The high geometrical control over the macrocycle structure has exhibited profound effect on their assembly mode.

It is interesting to show how the structure of small building blocks affects the structure of macrocyclic product and further, how influenced the association mode of the given macromolecule. The latter is of primarily importance in supramolecular and in material chemistry.

For instance, reduction of symmetry of di- or trialdehyde by replacing one of the aromatic hydrogen with hydroxyl group and additional functionalization of the aromatic ring provide a new class of compounds of structure determined by hydroxyl group and/or large substituent(s).[2] These compounds may act as efficient ligands/catalysts in asymmetric synthesis or small molecular weight supergelators.

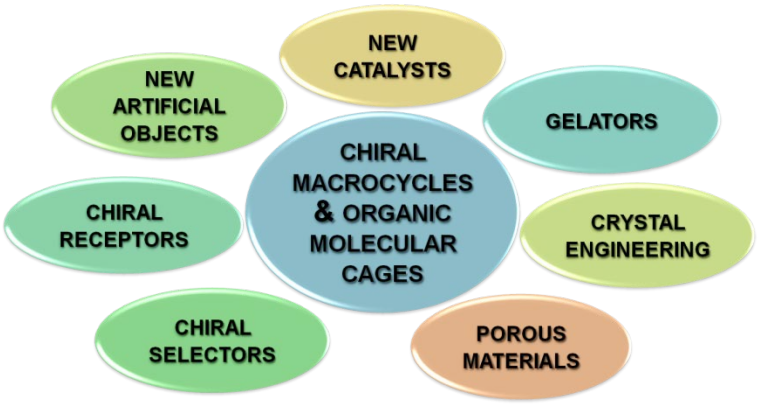

Fig. 1 Several aspects of macrocycle and cage compounds chemistry

Acknowledgements

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Selectivity Control in C–H Activation

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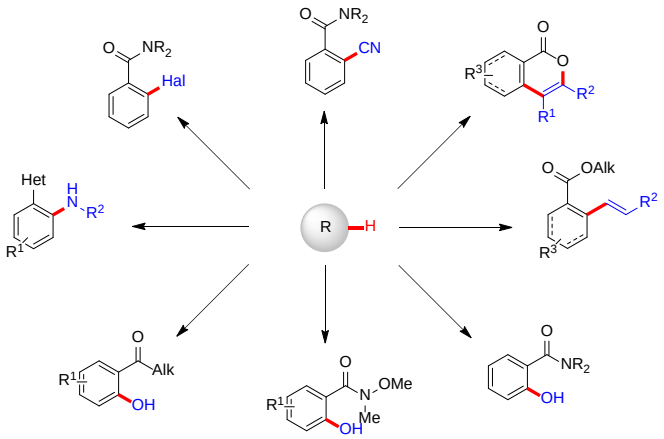
Keywords: C–H activation, peptides, elctrocatalysis

C–H activation has surfaced as a powerful platform in molecular synthesis, with transformative applications to material sciences and drug discovery, among others.[1] In this context, we have introduced bifunctional bases, such as phosphinous acids and carboxylates, as additives for positional selective C–H arylations and alkylations with versatile ruthenium(II) complexes,[2] displaying complementary selectivities as compared to palladium, nickel, cobalt, iron, copper or manganese catalysis.[3] Detailed mechanistic insights into the working mode of the key C–H ruthenation step set the stage for ruthenium(II)-catalyzed twofold C–H functionalizations as well as step-economical oxidative alkyne annulations.[4,5] The oxidative C–H functionalization strategy proved broadly applicable and enabled, among others, ruthenium(II)-catalyzed oxygenations, and nitrogenations, *meta*- and *para*-selective arene diversification.[6] Likewise, late-stage peptide diversification[7] and electrochemical C–H activations will be discussed.[8]



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Novel Organocatalytic Approach to Polysubstituted Tetrahydro-1,2-oxazines Employing a New Class of Aminooxylating Reagents

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Keywords: organocatalysis, tetrahydro-1,2-oxazine, 1,4-aminoalcohol

The development of innovative synthetic methods enabling a facile and straightforward access to biologically active molecules or privileged structural motifs, constitutes a highly relevant topic in contemporary organic chemistry.[1] One particularly visible trend within this research area is related to the use of chiral catalysts to control stereochemical reaction outcomes. Asymmetric organocatalytic cascade reactivities allowing for the selective formation of two or more new chemical bonds in a single chemical operation are of particular importance. Tetrahydro-1,2-oxazine constitutes a privileged structure as the cleavage of the N–O bond in such a ring system enables a direct access to 1,4-amino alcohol derivatives.

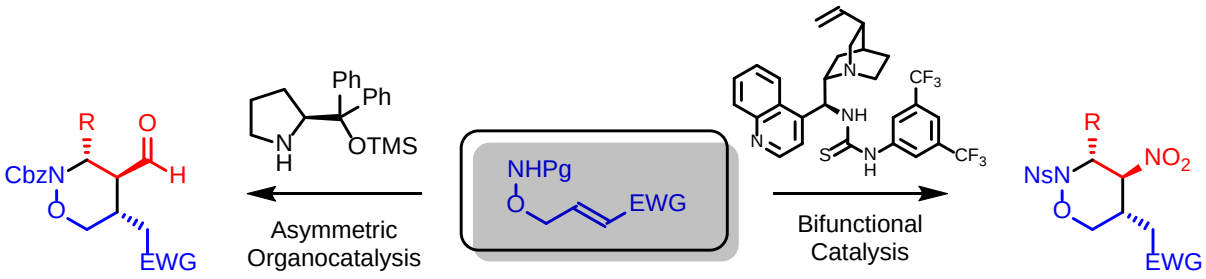

Fig. 1 Organocatalytic approach to polysubstituted tetrahydro-1,2-oxazines

Herein, we present our studies on the application of novel aminooxylating reagents in the stereocontrolled synthesis of polysubstituted tetrahydro-1,2-oxazine derivatives. Due to the presence of an electron poor double bond as well as a highly nucleophilic protected amine group directly neighboring to an oxygen atom (α-heteroatom effect) they can be considered as synthetic equivalents of a d^0a^3 synthon. The developed cascade reactivity proceeds efficiently with α,β-unsaturated aldehydes[2] or nitroolefins[3] as starting materials in a sequence aza-Michael–Michael reaction. The target products, bearing three contiguous stereocenters, have been obtained with high yields (up to 97%) and excellent stereocontrol (> 20:1 dr, up to 99.5:0.5 er).

Acknowledgements

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Pd-Catalyzed Perfluoroalkylative Carbonylation of Alkynes: A Facile Route to α,β-Unsaturated Esters.

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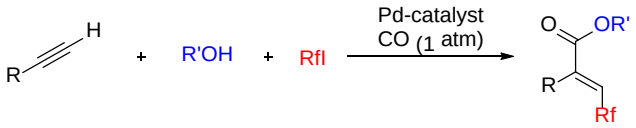
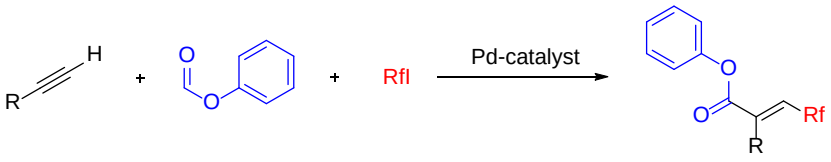
Keywords: palladium, perfluorocarbonylation, tandem reaction

Fluorine appears as the element of extremes. It is the most electronegative element in the periodic table and one of the most reactive. On the other hand, fluorine forms particularly strong, short and highly unreactive C-F bonds. Moreover, fluorinated organic compounds are almost isosteric to their C-H counterparts. Fluorinated compounds exerts a range of interesting physiological properties including, improvement of biostability, increase of lipophilicity, enzyme substrate mimicking and capability for oxygen transport, among others. They are widely used in many branches of chemistry, for instance medicinal, material and polymer chemistry.[1] However, the synthesis of organofluorine compounds is still challenging and further developed is highly desirable.

We have developed tandem, multicomponent, Pd-catalized esterification procedures for the synthesis of perfluoro-substituted compounds with CO,[2] as well as with phenyl formate as a CO surrogate. The carbonylation proceeds smoothly under mild conditions, low catalyst loading and atmospheric pressure of carbon monoxide (or without the use of external CO) to afford the corresponding α,β-unsaturated esters employing inexpensive and readily accessible starting materials – alkynes, iodoperfluoroalkanes.



Scheme 1. Palladium catalyzed carbonylation.



Scheme 2. Palladium catalyzed carbonylation without external CO

Acknowledgements

Financial support from the Polish National Science Centre (Grant decisions DEC-2016/21/B/ST5/03178) is gratefully acknowledged.

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Asymmetric Organocatalysis in the Synthesis of Nitrogen-Containing Heterocycles

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Keywords: aziridine, pyrrolidine, organocatalysis

Heterocyclic compounds containing nitrogen atom in their structure are relevant building blocks in the synthesis of drugs and other biologically active compounds.[1],[2] Here, we present organocatalytic approaches to both enantiomerically enriched *N*-protected aziridines **1**[3] and pyrrolidine-2-thiones **2**[4]. *Cis*-2,3-aziridine aldehydes **1** have been obtained from α,β-unsaturated aldehydes in high yields and good stereoselection employing chiral secondary amine as catalyst. The strategy utilizes unprecedented post-reaction isomerization as a key step. Pyrrolidine-2-thiones **2** were obtained in organocatalytic cascade reaction of isothiocyanates derived from phenyl glycine and alkylidene barbiturates. The synthesis of spirocyclic heterocycles bearing a quaternary α-amino acid moiety or α-aminophosphonate group have been efficiently realized using bifunctional catalyst.

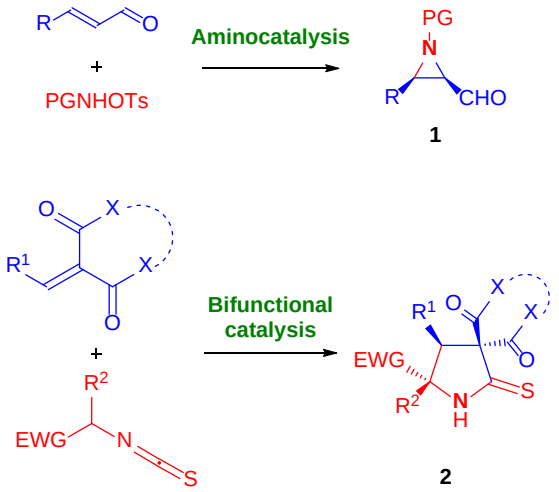

Fig. 1 Synthesis of nitrogen-containing heterocycles

Acknowledgements

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Porphyrinoids as catalysts for light induced C-C bond forming reactions

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Keywords: *photo*catalysis, porphyrins, radicals

„Do as nature, work as nature, and produce as nature" (Bao-Lian Su)

Our life depends on porphyrinoids - pigments of life. They are responsible for oxygen transport (heam), electron transport (cytochrome c), and photosynthesis (chlorophyll a). Chlorophylls are, in the first instance, responsible for transforming light energy into the chemical reactivity with the ultimate production of starch (**photosynthesis**). We should follow nature and exploit potential of pigments of life. Photoredox catalysis has recently emerged as powerful tool for the formation of C-C bonds mainly catalyzed by ruthenium and iridium complexes.[1] But, they are both very expensive and undesirable by pharmaceutical industry. On the other hand, organic dyes exhibit considerable advantages and in fact they have been shown to act as photoredox catalysts with eosin Y being the most widely studied.[2]

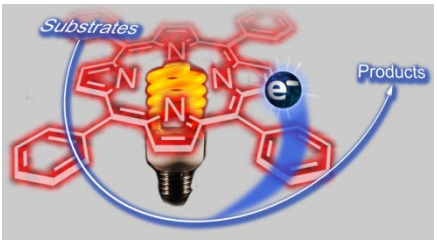

Fig. 1 Transfers of electrons in reactions catalyzed by porphyrinoids

This presentation will highlight a successful application of porphyrinoids as catalysts for visible-light induced selective functionalizations. In particular, these compounds are effective in catalyzing C-C bond forming reactions involving the reductive or oxidative quenching. Employing dual catalytic system – photocatalysis merged with enamine-iminium catalysis alkylation of carbonyl compounds at the α position was accomplished.[3] Porphyrins with tuned physicochemical properties, via tailoring various substituents at the periphery of the macrocycle, are also effective in catalyzing light-induced direct arylation of heteroarenes and cumarins with diazonium salts.[4] The reaction afforded arylated products in good yields and tolerates a wide range of functional groups. Along this line, we have proposed vitamin B_{12} *photochemical activation* in bond forming and cleavage reactions.[5] TiO_2 can be utilized in a catalytic system with vitamin B_{12}, allowing for the efficient photocatalytic reduction of Co(III) to Co(I). Under light irradiation vitamin B_{12} derivative unusually catalyzes new olefinic sp^2 C-H alkylation reaction and acylation of activated olefins.[6]

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Ribosomal and Non-Ribosomal Peptides from Bacteria and Fungi – Structural and Biosynthetic Aspects

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Keywords: ribosomal, non-ribosomal, peptides, natural products

Recently, peptides have gained great interest in the pharmaceutical industry, since they display properties which are unmet by small molecules or biologics. Wanted properties peptides comprise the inhibition of protein-protein-interactions, while bioavailability and permeability commonly are pharmacokinetic properties which require an optimization to be addressed by peptide synthesis.[1]

In Nature, ribosomal (RiPPs)[2] and non-ribosomal peptides (NRPs)[3] from bacteria and fungi provide an enormous structural diversity combined to remarkable bioactivities, e.g. antibacterial, antifungal, anticancer and others. While still being important in recent years, the discovery has partially shifted from classical screening approaches to genome mining.[4] In addition, the past years have seen an enormous progress in the understanding of biosynthetic assembly which also has an influence on the engineering and (re)design of structural diversity e.g. by combinatorial biosynthesis approaches [1,2]. The lecture will give insights into recent advances in the field.

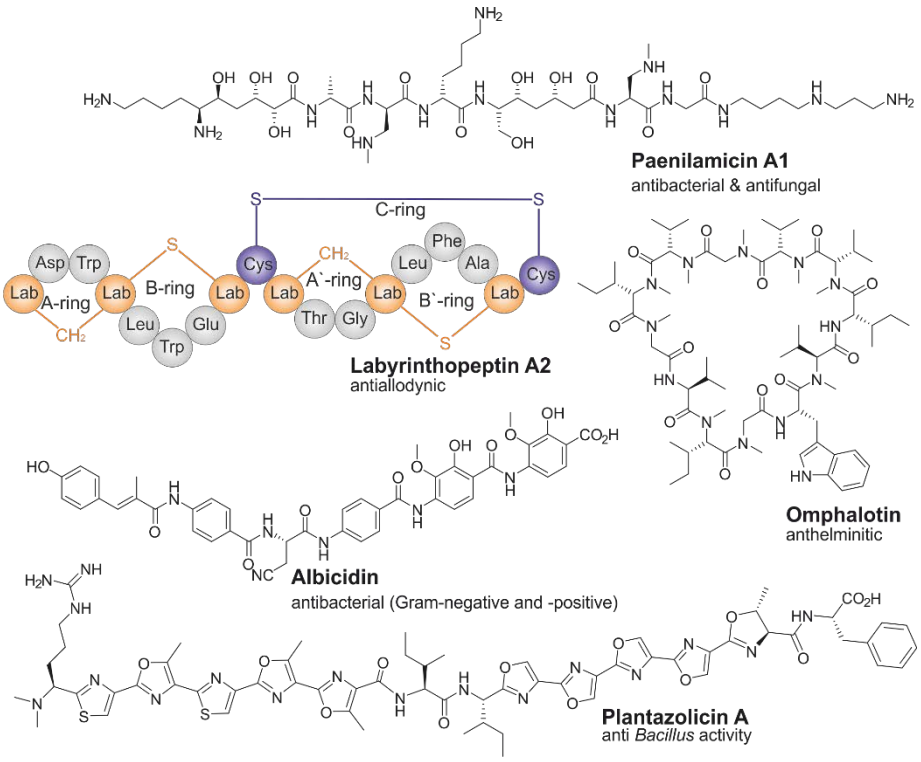

Fig. 1 Structures of Labyrinthopeptin A2 (RiPP), Omphalotin (RiPP), Plantazolicin (NRP), Albicidin (NRP), and Paenilamicin (NRP)

We will present previous findings on the structure elucidation and biosynthesis of peptide structures (Fig. 1), e.g. the labyrinthopeptins,[5,6] plantazolicin,[7] albicidin[8] and omphalotin,[9] together with the assignment of unusual biosynthetic pathways and remarkable bioactivities. While in some cases, e.g. albicidin[10] and plantazolicin,[11] the total synthesis was an enormous challenge, it facilitated structure-activity-relationship studies and contributed to a better understanding of the structural design.

Acknowledgements

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Total Synthesis of Pericoannosin A

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Keywords: natural product synthesis, pericoannosin A, hybrid peptide-polyketide

Pericoannosin A (**1**) was isolated from the endophytic fungus *Periconia* sp. F-31 by Dai and co-workers in 2015. The hybrid peptide-polyketide shows a modest anti-HIV activity (IC_{50} = 69.6 µM) along with a hexahydro-1H-isochromen-5-isobutylpyrrolidin-2-one skeleton that has not been found in any other natural products so far.[1] Because of its unique structure we were interested in a synthetic access to this natural product. For our retrosynthetic approach lactol formation was chosen as one of the last steps. The desired precursor was built up *via* an aldol reaction of aldehyde **2** and lactam **3**. Lactam **3** was synthesized utilizing a literature known procedure for the Boc-protected lactam.[2] The cyclohexene moiety of aldehyde **2** was built up using a stereoselective Diels-Alder reaction of isoprene (**4**) and dienophile **5**. A Horner-Wadsworth-Emmons (HWE) olefination and a stereoselective glycolate aldol reaction were the key steps en route to dienophile **5**, tracing the whole synthesis back to tiglic aldehyde (**6**).

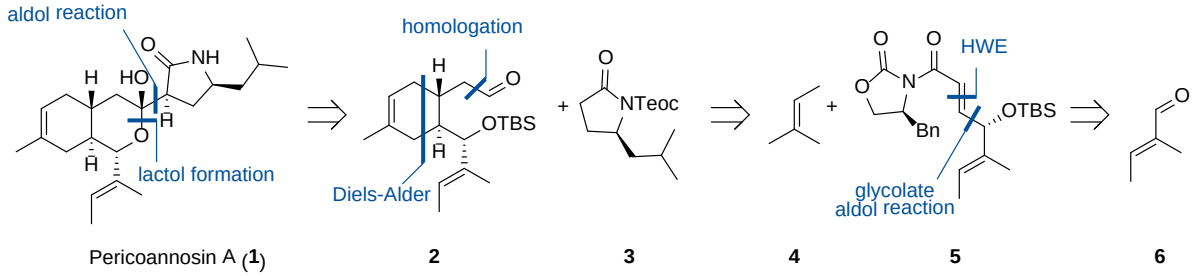

Fig. 1 Retrosynthetic analysis of pericoannosin A (**1**)

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Labelling Studies on CYP-Catalysed Terpene Oxidations

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Keywords: terpenoids, isotopes, cytochrome P450

Within the largest class of natural products, namely terpenoids, most of the bioactive compounds like the chemotherapy medication taxol possess an oxidised terpene skeleton.[1] Biosynthetically, these molecules are made by tailoring enzymes able to functionalise the terpene hydrocarbons, alcohols or ethers synthesised by terpene cyclases. One important class of these interesting enzymes are cytochrome P450 monooxygenases (CYPs), whose genes are often found in close proximity to a terpene cyclase.[2] Because of their astonishing reactivity, CYPs can also be used to oxidise terpenes without a genetic relationship to get access to modified natural products.[3]
Our main interest is to establish and explore labelling techniques for the structure elucidation of CYP products and mechanistic details of CYP reactions. Therefore, we combined a CYP from the myxobacterium *Sorangium cellulosum*[4] with known terpene cyclase products,[5] which gave access to *in vitro* studies of CYP reactions with labelled substrates from labelled terpene precursors.[6] In this talk, few examples will be discussed how ^{13}C-labelling is useful for identification of the oxidised position of (+)-t-muurolol (**1**) using microscale reactions and to answer stereochemical questions in the unusual oxidation sequence of (+)-isodauc-8-en-11-ol (**2**) to **3** and **4** (Fig. 1).

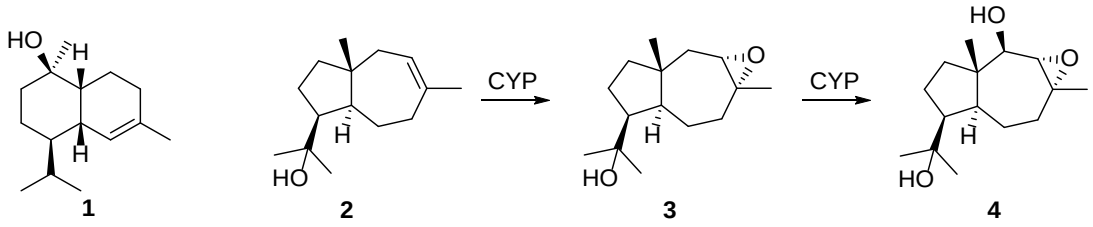

Fig. 1 Structures of investigated CYP substrates and their products

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Syntheses of Carolacton Derivatives as Highly Potent Biofilm Inhibitors

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Keywords: natural products, totalsynthesis, demethylated derivatives

Carolacton (**1a**) is a secondary metabolite of myxobacterium *Sorangium cellulosum* (*So ce960*).

In 1998, it was discovered and isolated because of its antibiotic activity against *Escherichia coli* strain *tolC* bacteria in the Helmholtz Centre for Infection Research in Braunschweig.[1],[2] In 2012, the first total synthesis of Carolacton (**1a**) was achieved in our laboratories which was based on key dissections depicted in Fig. 1.[3]

Carolacton (**1a**) distinguishes itself in its unique ability to inhibit biofilms of the caries- and endocarditis-associated bacterium *Streptococcus mutans* even at nanomolar concentrations. Biofilm-associated infections have become a major concern in clinical treatment since bacterial biofilms are inherently resistant to extreme pH- and temperature conditions as well as antimicrobial agents. The synthesis of natural products and derivatives with novel modes of actions is a promising way to inhibit biofilms. However, the exact mode of action of Carolacton (**1a**) is still not elucidated.[4]

Here we present our recent results towards the syntheses of highly active Carolacton derivatives including Carolactam (**1b**) and provide preliminary results on the relationship between structure and activity. In this regard, the syntheses of demethylated derivatives such as **2**-**4** are of particular interest to figure out the influence of the presence of methyl groups - widespread abundant in polyketides - on the global conformation of such macrolactons and link these data to biological activity (Fig. 1).

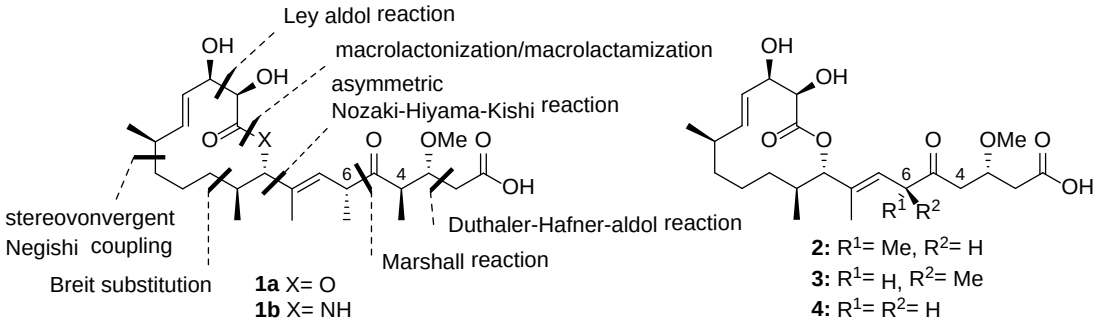

Fig. 1 Retrosynthetic key dissections of Carolacton (**1a**) and Carolactam (**1b**) and new demethylated derivatives (**2**-**4**)

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Lipids from Pollen: What are the Structures behind Neglected Players in the Allergic Airway Inflammation

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Keywords: pollen, timothy grass, phytoprostanes, glycolipids, allergic airway inflammation

Nearly 30% cases of bronchial allergic asthma are induced by grass pollen.[1] Apart from proteins (allergens) pollen coat comprises a large range of lipids (pollenkitt) essential for its reproduction.[2] These small molecular compounds are co-delivered with the allergens having the potential of modulating the immune system of subjects by interacting with innate immune cells.[3] Previous reports showed that pollen derived phospholipids activated Natural Killer T cells (NKT)[4] and pollen associated lipid mediators (phytoprostanes E_1, PPE_1, also named 9-E_1- and 16-E_1-phytoprostanes) - dendritic cells (DCs)[5] towards an allergic phenotype.

Nevertheless, the detailed structure-activity relationship between lipid classes and reactive immune cells in the context of allergic inflammation remains poorly understood. Therefore, we aimed to isolate and characterize the chemical structures of the lipid classes present in Timothy grass (*Phleum pratense*) pollen and to determine their role in allergic inflammation. We isolated different lipid species utilizing water extraction[5] or chloroform/methanol extraction, separation on silica column followed by HPLC fractionation. The chemical structures of isolated compounds were determined by GC-MS, ESI-MSn and NMR analyses. The biological activity of the total pollen extract and subsequent fractions was tested on different murine and human cells-based systems using flow cytometry.

In the aqueous pollen extract (APE [5]) we found PPF_1-I (16-F_{1t}-PhytoPs) and PPE_1-I (16- E_{1t}-PhytoPs), -II (9- E_{1t}-PhytoPs) [6] and Gro-PPE_1. APE induced murine mast cell (MCs) chemotaxis and IL-6 release; and enhanced IgE-dependent degranulation of human lung-derived and murine MCs, demonstrating a role in the immediate effector phase of allergic inflammation. On murine DCs, APE selectively induced the upregulation of CD1d, likely preparing lipid-antigen presentation to NKT cells. In two fractions of organic extract we have identified ceramides, phytoceramides and digalactosyl-di-acyl-glycerol. These fractions induced proliferation of murine NKT cells *ex vivo*, *in vivo* induced eosinophilic infiltration into the airways, a hallmark of allergic asthma. Finally, these fractions were recognized by human NKT and $\gamma\delta$T cells from peripheral blood, evidenced by the expression of the activation marker CD69.

Taken together, our results provide an insight into structure-activity relationship for lipid classes in the process of allergic inflammation.

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Short and Protecting Group Free Approach to the (–)-Δ^8-THC-Motif: Synthesis of THC-Analogues, (–)-Machaeriol B and D

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Keywords: tetrahydrocannabinol, one-step synthesis, late-stage diversification

Since the discovery of the biological and medical importance of (–)-Δ^9-tetrahydrocannabinol and its isomer (–)-Δ^8-THC, the cannabinoid family has gained a lot of research interest of scientists worldwide. They are interacting with cannabinoid receptors CB_1 and CB_2 which represent key drug targets for the treatment of a number of diseases.[1]
Machaeriols such as (+)-machaeriol B and (+)-machaeriol D are natural products with cannabinoid related structure. First investigations revealed that these compounds have potent *in vitro* antimalarial activity.[2]

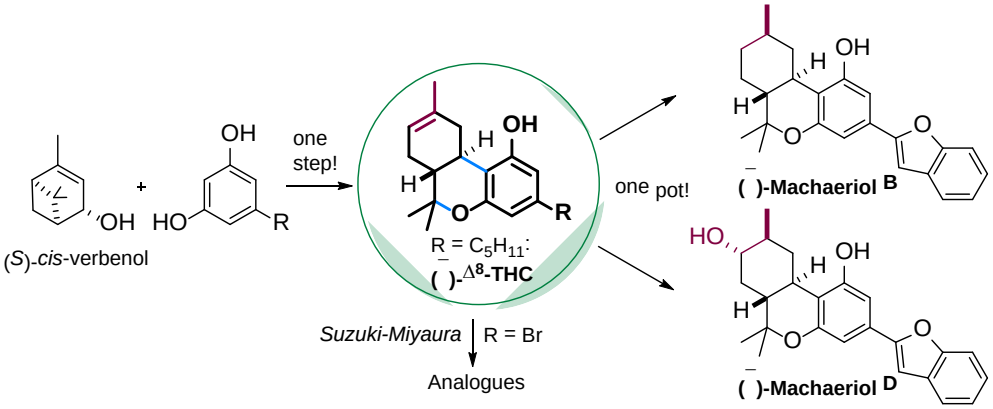

Fig. 1 *Friedel-Crafts* alkylation and cyclisation of (*S*)-*cis*-verbenol with resorcinol derivatives constructs in one step the tetrahydrodibenzopyran motif of (–)-Δ^8-THC also found in other natural products

Herein we present a short and protecting group free approach in which the *Friedel-Crafts* alkylation and cyclisation of (*S*)-*cis*-verbenol with resorcinol derivatives is used to construct in one step the tetrahydrodibenzopyran motif of (–)-Δ^8-THC also found in other natural products. Using a benzofuryl substituted resorcinol, followed by diastereoselective hydroboration and oxidative or reductive work-up directly provide (–)-machaeriol B and D in 42% and 43% overall yields. Bromoresorcinol as coupling partner delivers Br–THC that can be applied for late stage diversification by *Suzuki-Miyaura* cross coupling to readily access (–)-Δ^8-THC analogues.

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The Transformation of Betulin Core

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Keywords: triterpenoids, lupane saponins, betulin

Betulin, widely widespread in nature, belongs to the lupane triterpenes. The richest source of betulin is the outer layer of a birch bark. Betulin and its derivatives show high biological activity; *eg.* cytotoxicity, anti-inflammatory and antiviral effects. The broad spectrum of biological activity, low toxicity and high availability of betulin attract attention of the pharmaceutical and cosmetic industries.

In our laboratory we have developed synthesis of new modified lupane triterpenoids and lupane saponins. In vitro studies indicated that the presence of oxygen atom located on the C-17 side chain is necessary for the cytotoxicity of the studied compounds. Large number of tested derivatives enabled us to relate their cytotoxicity and structure. As a result, preliminary determination of active sites in the structure of the studied lupanes was possible. This encouraged us to undertake broader research into the influence of betulin E-ring modification on the biological activity. Modifications included replacing oxygen atom in the side chain with sulfur or selenium atoms as well as the opening of the E ring. As we expect, it could enhance anticancer effect. Details will be presented during the conference.

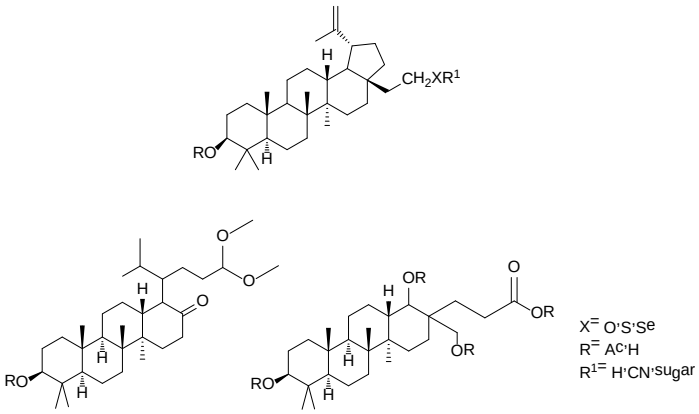

Fig. 1 Examples of structures containing degraded E-ring

Acknowledgement

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Adventures and Detours in the Synthesis of Macrolides and Cembranoids

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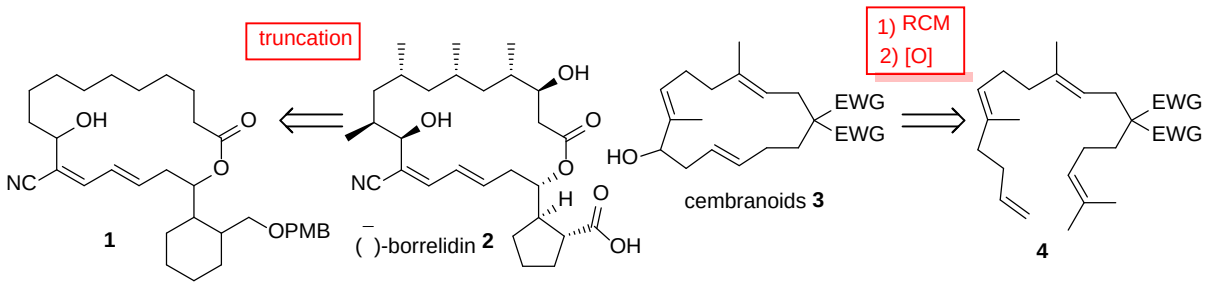
Keywords: natural product synthesis, macrolides, cembranoids, chemoenzymatic, metathesis

Secondary metabolites such as macrolides and cembranoids are of great interest due to their large structural diversity and broad range of biological properties. Both natural product classes present unique challenges to the synthetic chemist often resulting in tedious synthetic access, which hampers a detailed biological and pharmacological assessment of these compounds. Two strategies will be presented to overcome these limitations. One approach consists of truncation, i.e. minimization of molecular complexity, which will be showcased for the macrolide (-)-borrelidin **2** including biological studies.[1,2] An alternative approach employs a combination of catalytic ring closing metathesis (RCM) and late stage biocatalytic oxidation. This chemoenzymatic route will be discussed for cembranoids **3**.[3,4] In both cases complementary quantum-chemical calculations have provided additional insight into the mechanism.



Acknowledgements

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Fluorescent Triazolyl Purines and their Nucleoside Congeners

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Keywords: purines, azoles, S_NAr reactions

Azolylpurines and azolylpurine nucleosides have important medicinal and biological applications.[1] We have developed a novel approach for the synthesis of C(2) and C(6) modified purines and purine nucleoside analogues of type **3** containing 1,2,3-triazolyl substituents.[2,3] The method uses 2,6-diazidopurine derivatives **1** as the key starting materials. The latter can be transformed into novel structural entities – 2,6-bis(1,2,3-triazol-1-yl)purine derivatives **2** – including nucleoside analogs. It was found that 1,2,3-triazolyl substituent acts as excellent leaving group and permits nucleophilic aromatic substitution (**2**→**3**) (Fig. 1). Thus, regioselective S_NAr reactions with various nucleophiles like amines,[2,4] thiols,[3] amino acids and peptides,[5] hydrazines, anilines, alcohols and deprotonated C-H acids are possible for compounds **2** at C(6).

Further investigations lead to the use of diazide **1** as a substrate for S_NAr reactions. Depending on the nature of *N*(9) substituent (Q), the incoming nucleophile and the experimental conditions, selectivity towards differently substituted compounds **4** and **5** can be achieved. This is mainly determined by azide-tetrazole tautomerism **1-A** ↔ **1-T**. We have found that 2-(1,2,3-triazolyl)adenine/adenosine analogs **3** (Nu = NY_2) and their regioisomers **6** possess excellent fluorescent properties. Compounds **3** and **6** can be applied both for fluorescent oligonucleotide synthesis[4] and for OLED technologies. Moreover, the developed chemistry permits synthesis of novel purine conjugates containing 5-membered heterocycles at C(2) (compounds of type **7**).

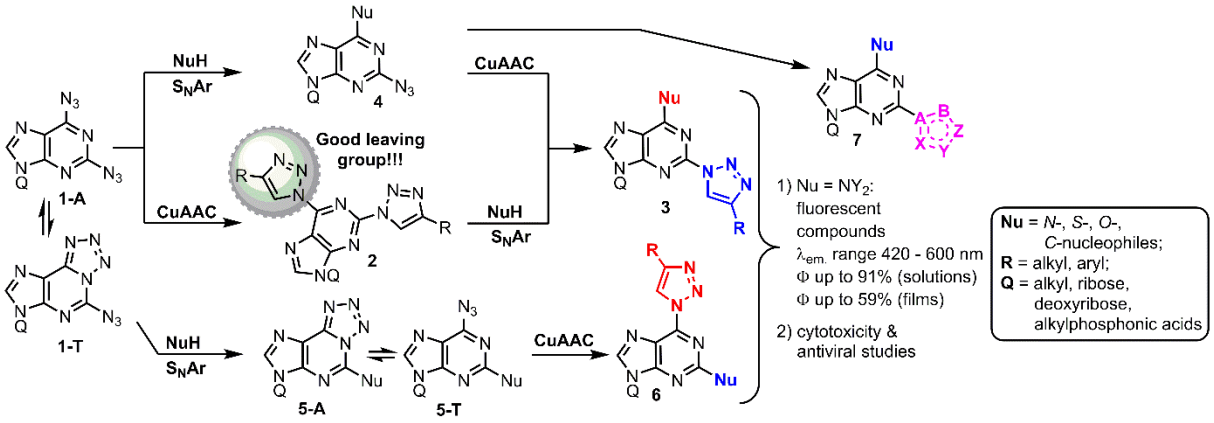

Fig. 1. Azidopurines and (1,2,3-triazol-1-yl)purines as substrates in S_NAr reactions.

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Fe-Catalyzed Access to Oligodepsipeptides and their Application in Biomedicine

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Keywords: ring-opening polymerization, catalysis, biomimetic material

Oligodepsipeptides (ODP) are oligomers with an alternating sequence structure of α-amino and α-hydroxy carboxylic acids, which have shown potential as degradable and versatile biomaterials. The synthetic access to substituted 2,5-morpholinediones used in the ring-opening polymerization (ROP) as well as the ROP itself are challenging due to modest yield, limited molar masses reached, as well as drop in activity when bulky substituents are present. Moreover, the typically used Sn-based catalysts in the ROP have raised concerns regarding environmental impact as well as toxicity.

We introduced iodide nucleophilic catalysis in the ring closure to raise the yields of several synthesized morpholinediones,[1] e.g. based on benzyl protected serine and tyrosine. Furthermore, in a systematic study comparing Lewis acidic main group and transition metal catalysts, it could be demonstrated that the relatively soft $Fe(OAc)_2$ is an effective catalyst in the ring-opening polymerization of morpholinediones and other lactones, outperforming harder catalysts with low steric demand such as $Mg(OEt)_2$, $In(OEt)_3$, $Al(OEt)_3$ and $Fe(OEt)_3$ and acting at least as good as the classic tin(II)octanoate, but being less sensitive and potentially less toxic. In typical syntheses, ODPs with M_ns of ~ 5 kDa and low polydispersities (1.1) were received, while no racemization occurred and MALDI-ToF analysis revealed that side reactions in ROP such as formation of cyclic structures were suppressed.

The oligodepsipeptides could be used in the formation of nanoparticulate structures either alone[2] or as middle block in triblockcopolymers with polyethyleneimine.[3] The latter could be successfully employed as transfection agents for primary human cells. The particle formation and stability are putatively supported by interchain interactions of the oligodepsipeptides. As depsipeptides are easily variable via their amino acid subunit, the improved syntheses may offer the opportunity to exploit further this material class and the specificity in interactions supported by sequence structure and stable conformations.

Acknowledgements

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Symmetry Breaking in Pyrrolo[3,2-*b*]pyrroles: Synthesis, Solvatofluorochromism and Two-photon Absorption

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Keywords: solvatofluorochromism, two-photon absorption, dyes

Five centrosymmetric and one dipolar pyrrolo[3,2-*b*]pyrroles, possessing, respectively, either two- or one strongly electron-withdrawing nitro groups have been synthesized in a straightforward manner from simple building blocks. In the centrosymmetric compounds, the nitroaryl groups induced spontaneous breaking of inversion symmetry in the excited-state, leading to large solvatofluorochromism. To study the origin of this effect, the series employed peripheral structural motifs that control the degree of conjugation via altering of dihedral angle between the 4-nitrophenyl moiety and the electron-rich core. We observed that for compounds with a larger dihedral angle, fluorescence quantum yield decreased quickly when exposed to even moderately polar solvents. Reducing the dihedral angle (i.e., placing the nitrobenzene moiety in the same plane as the rest of the molecule) moderated the dependence on solvent polarity so that the dye exhibited significant emission, even in THF. To investigate at what stage the symmetry breaking occurs, we measured two-photon absorption (2PA) spectrum and 2PA cross-sections (σ_2) for all six compounds. In summary, we have presented a concept for modulating the excited-state process by changing the dihedral angle between electron-withdrawing peripheral subunits and the electron-rich pyrrolo[3,2-*b*]pyrrole core. Regardless of the degree of conjugation between the nitrobenzene moieties and the pyrrolopyrrole core, the centrosymmetric dyes of this type displayed solvatofluorochromism when the dihedral angle is variable. Suppression of this phenomenon could be achieved via planarization of the molecule, which was synthetically achieved via oxidative aromatic coupling.[1]

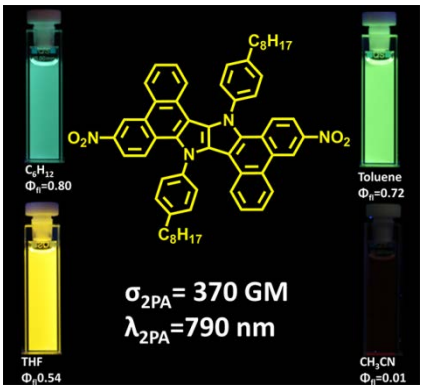

Fig. 1 The strong solvatofluorochromism for centrosymmetric pyrrolo[3,2-*b*]pyrroles possessing two nitro groups

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N,*O* π-Conjugated (Benzo/Naphtho)Thiazole BF_2 Complexes

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Keywords: organoron complex, 1,3-thiazole, luminescence

The evolution of new technologies entails an intensive research work in the area of photoactive organic materials. The development of luminescent compounds, which can serve as components of various optoelectronic devices such as organic light-emitting diodes (OLEDs)[1] or light-emitting electrochemical cells (OLECs) [2] optical sensing materials in biological[3] and supramolecular[4] systems, is one of the biggest scientific challenges.

In this context, organoboron complexes have many advantages as compared to other luminophores (porphyrins, metal complexes, etc.): strong absorption bands in the UV-visible light; high luminescent quantum yield, high extinction coefficient and photostability; relatively long excitation life-time; high solubility in common organic solvents; they are not sensitive to environment e.g. pH.[5]

In this communication, a design and synthesis of a new class of organoboron complexes will be presented. Our synthetic strategy is based in the incorporation of the electron-rich 1,3-thiazole ring into the complex structure. We investigated a library of thiazolo[3,2-c][1,3,5,2]oxadiazaborinine derivatives (**1**), as well as, their benzo[d]thiazole and naphtho[1,2-d]thiazole analogous (**2** and **3**) (Fig. 1). Electronic, photophysical and structural properties of the synthesized complexes will be discussed during the presentation.

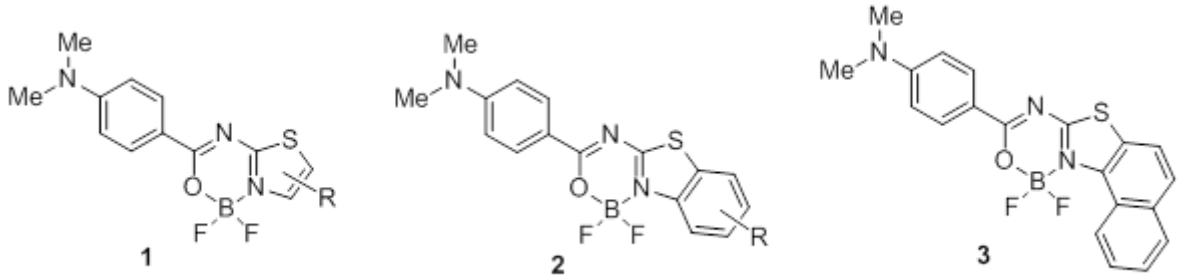

Fig. 1 Organoboron complexes with 1,3-thiazole, benzo[*d*]thiazole and naphtho[1,2-*d*]thiazole units

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SMART Metabolite ID: A Novel Strategy for the Identification of Unknown Metabolites from Complex Extracts

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Keywords: Metabolomics, NMR, identification

As an emerging field metabolomics enables new strategies for solving chemical or biological questions. The high number of metabolites in cell-systems or biological material is a very challenging part in the identification of single metabolites in terms of large concentration differences and chemical diversity.[1,2]
For targeted approaches as well as biological interpretation a reliable structural identification of metabolites is required. Particularly, the identification of unknown substances can become very difficult without isolating each metabolite. The isolation can become a very time-consuming step and new strategies in structure elucidation of metabolites are required.
This work shows the advantages of a crude HPLC-based pre-fractionation strategy followed by NMR-based analysis with selective radiation in terms of metabolite identification from a polar extract. Those two aspects -first the crude pre-fractionation, second the selective NMR experiments - are able to solve a large number of problems in mixture analysis from 1D ^{1}H NMR spectra, such as salt, dynamic range, signal overlapping and sensitivity problems.
With this strategy we were able to identify, in addition to several commonly known metabolites, two very unusual metabolites of a polar extract from white *Asparagus officinalis*, valine betaine and *S*-[2-carboxy-1-methylethyl]-L-cysteine, that are not enlisted in commonly used metabolomics databases.

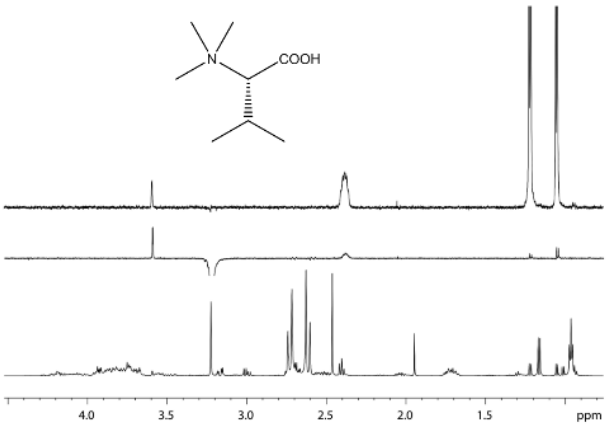

Fig. 1 Identification of valine betaine. From below: NMR Proton Spectrum of one fraction of the crude HPLC pre-fractionation; selective NOESY spectrum with a radiation on the methylene groups (3.22 ppm); selective TOCSY spectrum of the valine-like-spinsystem with a radiation on one methyl group (1.05 ppm).

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Metabolic Change of Hazelnuts by Harming Processes and Quality Control by ^{1}H-NMR-Spectroscopy

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Keywords: Metabolomics, ^{1}H-NMR-spectrocopy, Hazelnut

The study of metabolic changes (metabolomics) is a rapidly growing field of research. Starting with the detection of potential disease markers in the 1970s, applications reach from toxicological and/or pharmacological studies to the field of food analysis.[1–3] The metabolome is the last step in the so-called omics cascade where it reacts most sensitive to changes in genome, transcriptome, proteome or metabolome level of an organism. A major problem in food processing is the contamination or infestation with mold. Molds or their metabolites can lead to allergic reactions in the human organism. Furthermore, they can produce mycotoxins, which are toxic and carcinogenic. These mycotoxins are problematic because they are stable to heat and acids and they can remain stable even when processing the affected food. It is estimated that about 50% of all grains are contaminated with detectable mycotoxin concentrations.[4] Their detection in food usually applies LC/MS and is dependent on comparatively large amounts of samples. We used the metabolomics approach and the related advantages like small sample amount and a high sample throughput to detect significant changes due a mold infection. Therefore, hazelnuts were infected with different strains of mold, to observe the change in the metabolome over a period of two weeks. For visualizing these changes, we developed a *signal pattern plot* showing individual signal trends over the observation time. Signals that change specifically upon infection compared a to reference sample are easily identified and allow the assignment of chemical/biological markers.

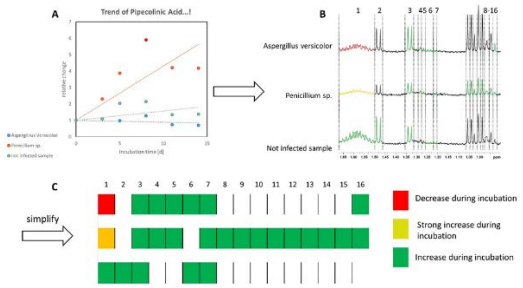

Fig. 1 Signal pattern plot for visualization of metabolic changes upon mold infection of hazelnut.

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Diarylmethane-Based New Chromophoric Probes for Stereochemical Assignments

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Keywords: chirality transfer, probe, ECD

The information about three-dimensional structure of chiral, optically active inductor molecule may be transmitted to achiral but conformationally flexible reporter molecule in process of chirality transfer. While inductor may contain various chirality elements, the reporter molecule should demonstrate an adequate level of sensitivity to even minimal changes in inductor structure. The mechanism of action of these probes is based on sterical interactions between inductor and reporter. As a result, the reporter molecule become dynamically chiral, therefore optically active. The process of chirality transfer can be conveniently monitored be the use of ECD measurements. Recently we have determined mechanism of action of benzhydryl chromophoric probes.[1,2]
However, the benzhydryl group has its weakness, like narrow measuring range and difficult to define electric transitions within aromatic rings. Thus, we decided to provide more versatile chromophoric probe with batochromically shifted measuring range and precisely defined electric transitions. All of the above properties may be assigned to chromophoric probe based on dinaphthylmethane, which is also much more sensitive to chiral surrounding.
Efficiency of our new chromophoric probe will be presented on number of different model molecules. Conclusions from experimental ECD spectra will be justified by theoretical studies using DFT methods.

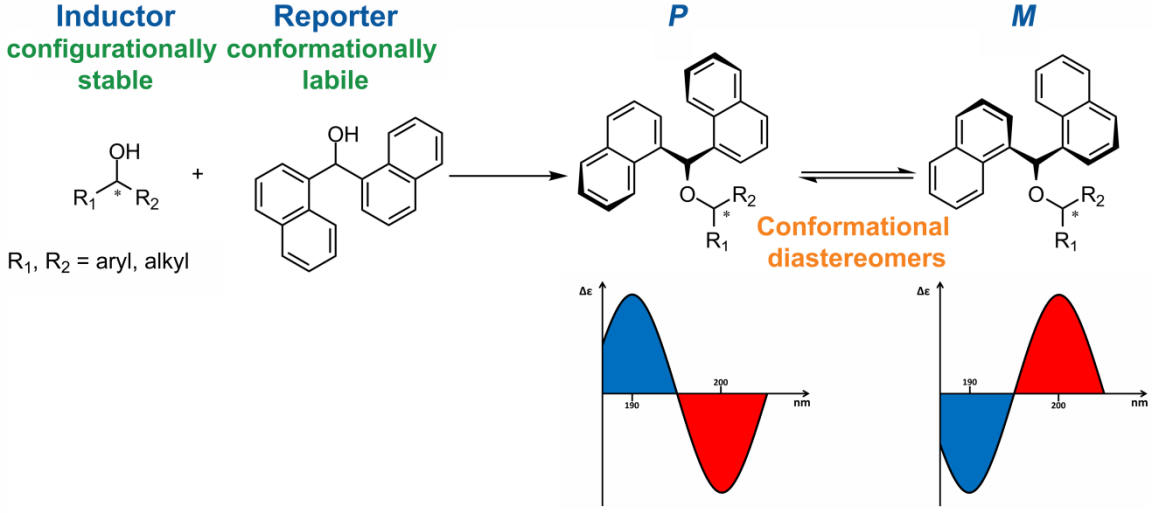

Fig. 1 Chirality transmission within inductor-reporter system

Acknowledgements

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Solvent Effects in Free Radical Chemistry – from Homogeneous Solutions to Dispersed, Biologically Relevant Systems

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Keywords: solvent effect, kinetics, radicals

First report on the role of a solvent on the rate of Hydrogen Atom Transfer from a phenol to a radical was published in 1964.[1] Forty years later the solvent/phenol interactions were explained and interpreted as the Kinetic Solvent Effect (KSE), later resulting in the quantitative description of the KSE in 2001.[2,3] The next years brought substantial increase of the knowledge on the role of non-covalent interactions in a reaction of radicals with phenolic antioxidants[4,5] to give a present description of the overall reactivity of phenols and mechanisms of their antioxidant action as depending on the structure of a phenol, its acidity, and on the surrounding medium (acid/base equilibrium, microenvironment, presence of ions).

The presentation will be focused on some examples of solvent effects in the chemistry of free radicals in homogeneous solutions with their possible impact on the biologically-relevant biphasic systems. Our recent studies of the antiradical activity of polyphenols,[4] catechols and catecholamines[5] indicate a crucial role of microenvironment in the reaction mechanism in biphasic systems and we evaluated the influence of pH, concentration of antioxidants, and the role of their partition coefficients. The kinetics of reactions of catecholamines with peroxyl radicals (as mediators of oxidative stress) might be connected with aetiology and therapy of neurodegenerative diseases, we studied the interactions of catecholamines with biomembranes and we proposed a model of such interactions, with electrostatic forces as dominating component.[6] Catecholamines are also good example of a dramatic role of pH on the synergy or antagonism between antioxidants in biphasic lipid / water systems.

Last part of this talk will be devoted to a reaction of analogue of α-tocopherol with superoxide radical anion – recently we described an unusual stoichiometry of this process carried out in homogeneous solutions and, basing on the studies of KSE, we proposed a possible mechanism.[7]

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Synthesis and Applications of Sequence-Controlled Glycomacromolecules

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Keywords: solid phase polymer synthesis, polymeric biomimetics, precision glycomacromolecules

Over the last years, polymer chemists have tackled the challenge of synthesizing increasingly defined polymeric materials with narrow dispersities, monomer sequences and controlled architecture.[1] Such well-defined structures are particularly relevant for the use of polymers as biomimetic materials, allowing for new insights into their structure-property relationships and thereby realizing new and improved applications in biotechnology and biomedicine.

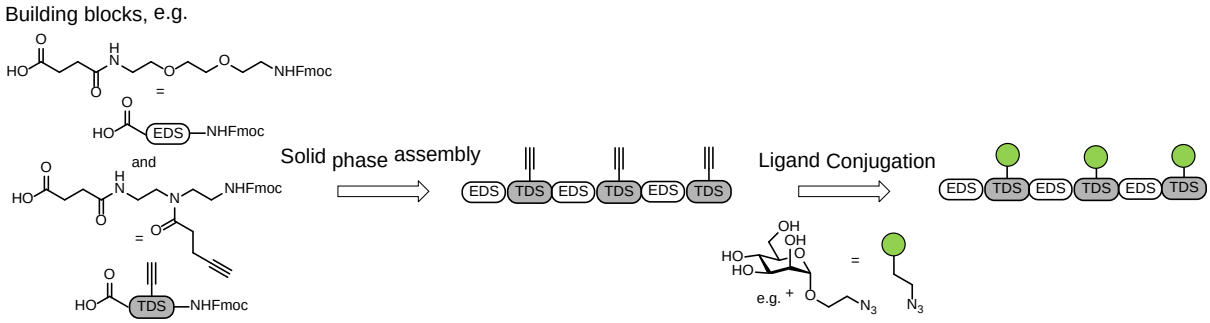

Fig 1 Schematic solid phase assembly of sequence-controlled glycomacromolecules[2]

In our group, we are specifically interested in the synthesis and characterization of glycomacromolecules, synthetic polymer scaffolds with pending sugar ligands. Glycomacromolecules are important tools to study complex binding mechanisms in multivalent sugar-lectin interactions, which are of high importance in various biological processes such as cell-cell interactions or pathogen recognition. Recently, we have introduced the so-called solid phase polymer synthesis that allows us to synthesize monodisperse, sequence-controlled glycomacromolecules.[2-4] The lecture will present the synthetic concept based on the stepwise assembly of tailor-made building blocks on solid support, the introduction of different sugar ligands at controlled positions along the scaffold and variations of different structural parameters such as linkers or the overall architecture of the glycomacromolecules. Furthermore, binding studies of selected glycomacromolecules addressing different lectin receptors will be discussed, also in the context of potential applications of sequence-controlled glycomacromolecules *e.g.* in drug delivery or as inhibitors of bacterial adhesion.

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Chemistry-Based Tools to Explore Tyrosine *O*-Glycosylation

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Keywords: tyrosine *O*-glycosylation, amino acids, glycopeptides

Protein *O*-glycosylation on Thr and Ser residues are of great impact in key biological functions. In 2011, it was described that mucin type *O*-glycosylation also modify Tyr residues, a modification long time overseen.[1,2] In a later glycoproteomic study, mitochondrial glycopeptides were additionally identified with Tyr glycosylation.[3] However, it could not be confirmed if the *O*-glycosylations were of mucin type or *O*-GlcNAcylation due to lack of proteomic tools that differentiate between GalNAc and GlcNAc residues. In 2015, the Hart group described that numerous mitochondrial proteins are densely modified by *O*-GlcNAcylation, including nearby sites of the previously identified HexNAc-Tyr modified glycoproteins.[4] Nevertheless, until now β-*O*-GlcNAcylation on Tyr is not described as a known modification since current methods were not able to prove its identity.

Here, we present the development of molecular tools to enable chemical biology studies of GalNAc- and GlcNAc-Tyr modifications. In studies of synthetic peptides modified with β-GlcNAc- (*O*-GlcNAcylation) and α-GalNAc- (mucin type) glycans attached on Thr or Ser residues, we could show that MS-fragmentation patterns differ.[5,6] In the same way we confirmed that these differences in oxonium-ion MS-fragmentation also apply for Tyr *O*-glycosylation. Our synthetic glycopeptide library consisting of α- and β-GlcNAc- and mucin type α-GalNAc-Ser, Thr and Tyr glycopeptides was further applied to evaluate binding preferences of lectins commonly used in lectin weak affinity chromatography (LWAC) and to perform OGA and OGT enzyme assays. Polyclonal rabbit antibodies directed against GlcNAc- and GalNAc-Tyr modifications were also generated, thereby creating additional tools for enrichment and identification of Tyr glycosylation.

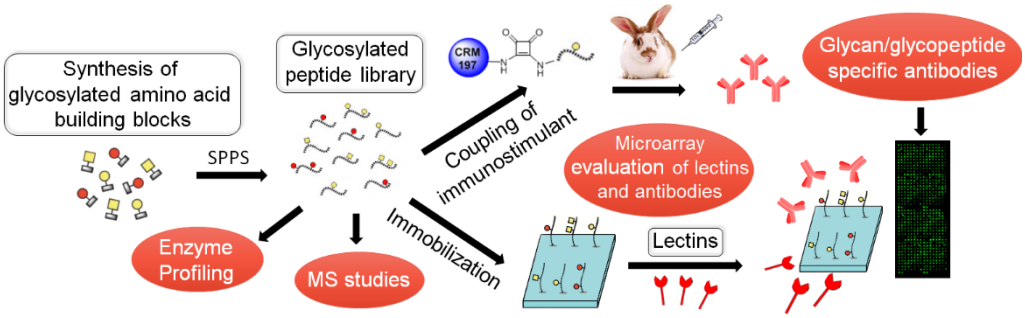

Fig. 1 Development of tools to explore tyrosine *O*-glycosylation.

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Chiral Cyclotriveratrylene-Based Molecular Containers with Sucrose Unit

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Keywords: sucrose, cyclotriveratrylene, chiral recognition

Chiral recognition of biologically important compounds by synthetic receptors, being the main trend in supramolecular chemistry, plays a significant role in pharmaceutical and biological research.[1,2]

Macrocyclic derivatives with sucrose scaffold can be applied as receptors for the complexation of chiral guests.[3] On the other hand, cyclotriveratrylene and its derivatives are well-known molecular receptors for metals, fullerens, ammonium salts, and small organic compounds.[4,5]

This communication will present the synthesis pathway to new chiral molecular containers composed of both building blocks. Sucrose, in a three-step synthesis, was converted into 2,3,3',4,4'-penta-*O*-benzyl derivative **1**, which was subsequently transformed into triiodide **2**. The combination of the cyclotriveratrylene unit **3** with triple alkylating agent **2** afforded two chiral molecular containers ***P*-4** and ***M*-4**.

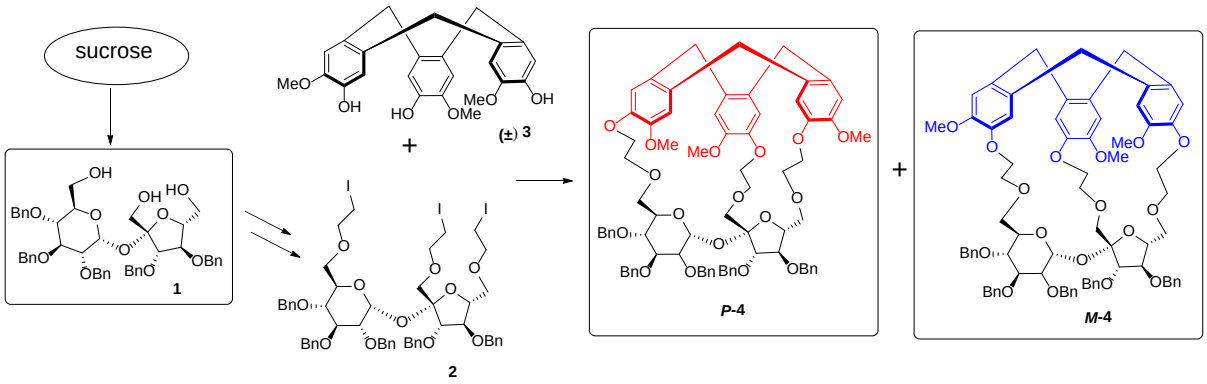

Fig. 1 Synthesis of chiral molecular containers based on sucrose

These receptors are the first molecular containers obtained from sucrose and cyclotriveratrylene moiety. Complexing properties of containers ***P*-4** and ***M*-4** will be discussed.

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Design, Synthesis and Properties of Shape-Switchable Glycomacrocycles

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Keywords: glycomacrocycle, photoswitch, chiroptical switch

Macrocycles are challenging synthetic targets that display unique properties stemming from their circular shape.[1] Carbohydrates are cheap and highly relevant building blocks for achieving macrocycles because they are chiral, polyfunctional, and their restricted conformational freedom imparts rigidity to the macrocyclic backbone, thereby resulting in a well-defined molecular shape.[2]

Enabling the conformational switching of glycomacrocycles upon the influence of external stimuli is an attractive means of selectively modulating their molecular and supramolecular features. This approach can be implemented by the incorporation of one or several photoresponsive azobenzene hinges into the macrocyclic backbone.[3] Indeed, light is a spatiotemporally resolved and non-invasive stimulus, and the azobenzene photoswitch offers excellent and widely tunable photochromic properties.

By using different synthetic strategies and molecular designs, we were able to build a set of different photoswitchable macrocyclic architectures displaying unique properties. On the one hand, the azobenzene *trans*/*cis* photoisomerization drives a large and reversible geometrical change in the overall structure. On the other hand, a transfer of chirality operates from the sugar units to the azobenzene, hence resulting in a spatially directed photoswitching.[3,4] Such a reciprocal transmission of information between the carbohydrates and the azobenzene(s) through the cyclic structure opens up a new way for the conception of smart molecular systems with applications in supramolecular chemistry, chiroptical devices or nanomachines.

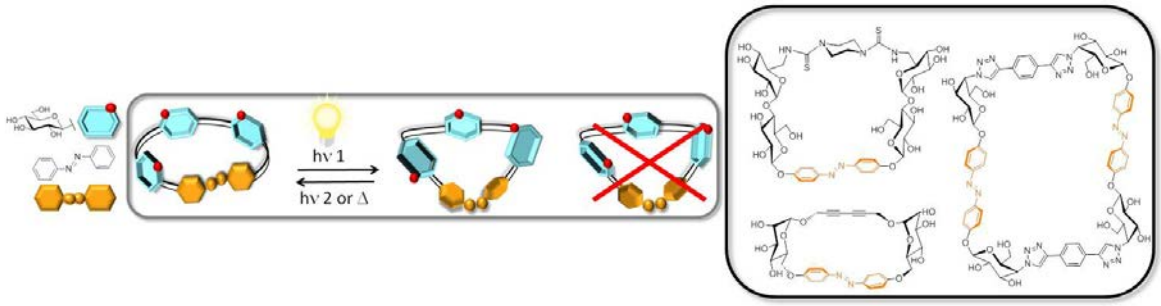

Fig. 1 Left: shape switching of glycomacrocycle and unidirectional photoisomerization of the azobenzene hinge. Right: examples of structures prepared by our group

Acknowledgements

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Electron Catalysis

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Keywords: radicals, radical anions, redox catalysis

Radical reactions are routinely considered in synthetic planning, and highly active research continues on new ways to make and use radicals. Because the products of radical-molecule reactions are again radicals, such processes are perfectly suited to be run as sequential reactions (cascades). Likewise, because radicals can be oxidized or reduced, radical-ionic crossover reactions can be implemented. Such cascade reactions serve well the goal of step economy in organic synthesis. As compared to non-radical processes, most radical reactions are very fast. Radical chain reactions require only a small amount of an initiator and addition of a catalyst is generally not necessary. Therefore, it is often difficult to catalyze radical transformations since background chain reactions are so fast.[1]

In the lecture the concept of using the electron as a catalyst will be discussed.[1,2] It will be shown that the electron is an efficient catalyst for conducting various types of radical cascade reactions that proceed via radical and radical ion intermediates. The “electron is a catalyst” paradigm unifies mechanistically an assortment of synthetic transformations that otherwise have little or no apparent relationship. Some recent examples on the use of the electron as a catalyst will be discussed.[3]

It will be emphasized how a negative charge can significantly weaken the neighbouring C–H bond and activate this bond towards H-atom transfer.[3e,j] Moreover, the activation of a C–H bond next to a C-radical towards deprotonation is a key point in the field of electron-catalysis. This issue will be addressed in the lecture. Extending that concept, the use of a negative charge to activate a C–C sigma-bond towards homolysis is also discussed.[3i,k] For example, electron catalyzed transition metal-free β-alkenylation-α-perfluoroalkylation of unactivated alkenes via radical 1,4 or 1,5-alkenyl migration will be presented. Electrochemistry can be applied to initiate electron-catalyzed processes.[3m]

It will be further shown, that readily generated vinyl boron ate complexes, generally used as substrates in the Suzuki-Miaura coupling, are efficient radical acceptors to conduct electron-catalyzed modular synthesis comprising a radical polar cross over step.[3h] This approach has recently been successfully applied to the development of a novel method for the preparation of highly enantioenriched α-chiral ketones.[3l]

Acknowledgements

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Photocatalytic Aerobic Phosphatation of Alkenes

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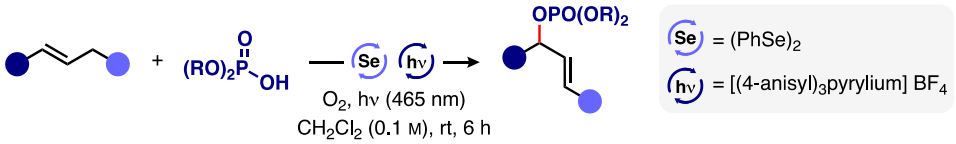
[2] *These authors contributed equally to this project.*
Keywords: chalcogen Lewis-acids, photoredox catalysis, alkene oxidations

Phosphoric esters and their derivatives play eminent roles in a variety of scientific disciplines such as chemistry, biology, pharmacology, and material sciences. Representative examples, highlighting the importance of organic phosphates, inter alia encompass the storage of genetic information or energy in the form of DNA and ATP, respectively, the regulation of protein interactions,[1] and the modulation of drug activities.[2] In addition, chiral hydrogen phosphates are frequently employed as organo-catalysts in numerous asymmetric transformations.[3] Phosphoric esters are furthermore often encountered in industrial materials such as plasticizers and flame retardants.[4] In the context of transition metal-catalyzed cross coupling reactions, organic phosphates are also commonly used as electrophilic reaction partners.[5] Against this background, the profound demand for strategically sound and economic protocols for the facile construction of organic phosphates derived from readily available and inexpensive starting materials becomes lucidly evident. Traditional methods for the synthesis of phosphoric esters often rely on the use of pre-activated and pre-functionalized substrates such as phosphoric acid halide derivatives in combination with alcohols and Brønsted-base additives. Unfortunately, the stoichiometric usage of phosphoric acid halides is to some degree hampered by their corrosiveness, toxicity, and sensitivity toward moisture. In order to adequately address these deficits, our group has recently developed a new catalytic regime that allows for the oxidative conversion of simple, non-activated alkenes with non-activated hydrogen phosphates using mere O_2 as the terminal oxidant (Scheme 1)[6] The title method is enabled by the dual-catalytic interplay of a diselenide and a pyrylium salt via a proton-coupled electron-transfer. Under optimal conditions, this procedure provides access to a broad panoply of diversely functionalized allylic phosphoric ester.



Scheme 1 Oxidative phosphatation of alkenes through dual photoredox/selenium catalysis

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Aza-BODIPY Analogues with Exceptionally Large Stokes Shift Values

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Keywords: boron dipyrromethene, Stokes shift, cycloaddition

Design and synthesis of new chromophores with desired optical and photophysical properties is a rapidly developing area of organic synthesis. One of the most recent and promising approaches to modification of the widely used fluorescent BODIPY dyes is replacement of their pyrrole units with other heterocyclic systems. An efficient cycloaddition-based synthetic strategy has been developed that allows for construction of structurally diverse bis(heteroaryl)methane ligands from two given azine or azole *N*-oxides and appropriate fluorinated synthons.[1] An analogous cycloaddition reaction involving heteroaryl isocyanates and aromatic *N*-oxides enabled straightforward preparation of bis(heteroaryl)amine ligands, complexation of which with boron fluoride led to azine-imidazole *aza*-BODIPY analogues.[2] As a new class of fluorescent dyes, these compounds exhibited very promising properties: high stability, large fluorescence quantum yield, fluorescence solvatochromism and very large Stokes shift values. The last feature is associated with their strong fluorescence in crystalline phase. Strong fluorescence of isoquinoline-derived complexes in polar environment may facilitate design of new dyes for imagining of living cells and tissues.

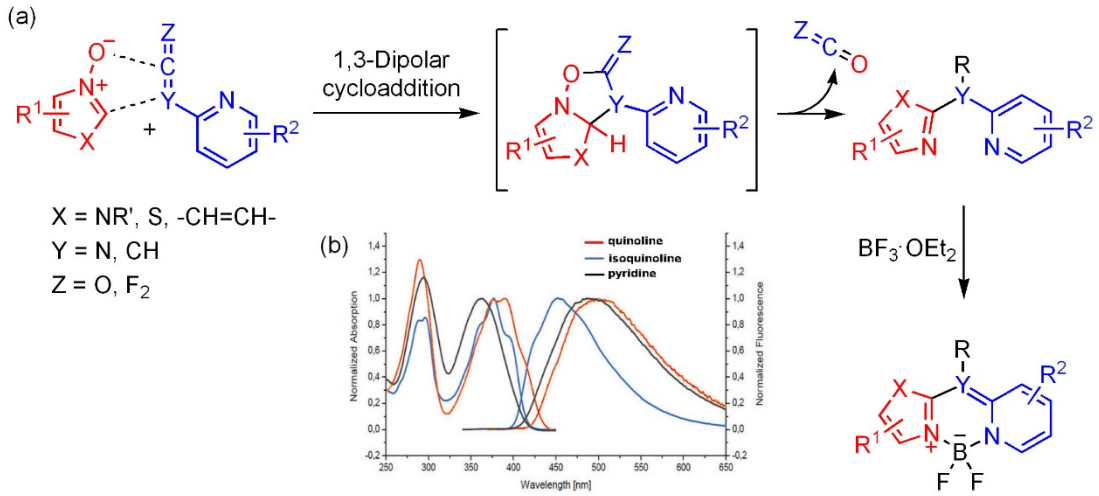

Fig. 1 (a) Synthesis of the azine-imidazole BODIPY analogues. (b) Absorption and emission spectra

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Vitamin B_{12} as a Delivery Agent – a Chemical Point of View

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Keywords: vitamin B_{12}, corrins, drug delivery

Delivery of an active compound to its site of action is one of the crucial issues in drug development. A promising strategy is to use naturally occurring compounds, such as vitamin B_{12} (cobalamin, Cbl) due to its unique ability to penetrate cells via a system of transport proteins.[1] In order for B_{12} to act as a carrier, its structure must be modified to allow selective coupling of biologically active compounds and at the same time high affinity to transport proteins must be retained. Selective and high-yielding functionalization of B_{12} are highly desirable, however remain challenging. Our group has introduced new methods allowing to achieve this goal (Fig. 1, A). Now, B_{12} can be selectively and directly attached to alkynes (via CuAAC)[2] acids (via amide bond formation)[3] or thiols (via disulfide bond formation).[4] Also reduction-free, direct alkynylation of vitamin B_{12} at the cobalt center and modifications at previously unexplored *meso* position have been developed.[5,6]

The idea of using cobalamin as a delivery vehicle is well documented in mammals, however such approach has not been applied to bacteria yet. Thus, in our work we focus on creating a connection of B_{12} and PNA (peptide nucleic acid) that will be targeted at bacterial DNA or RNA (Fig. 1, B)[7,8] The use of such short, modified oligonucleotides as inhibitors of bacterial translation seems a promising alternative for antibiotics, which are currently overused leading to fast development of bacterial resistance. We found that vitamin B_{12} transports antisense PNA into *Escherichia coli* cells more efficiently than the most widely used cell-penetrating peptide (KFF)3K. The results of our study provide the foundation for considering vitamin B_{12} as a delivery tool for PNA oligonucleotides into bacteria.

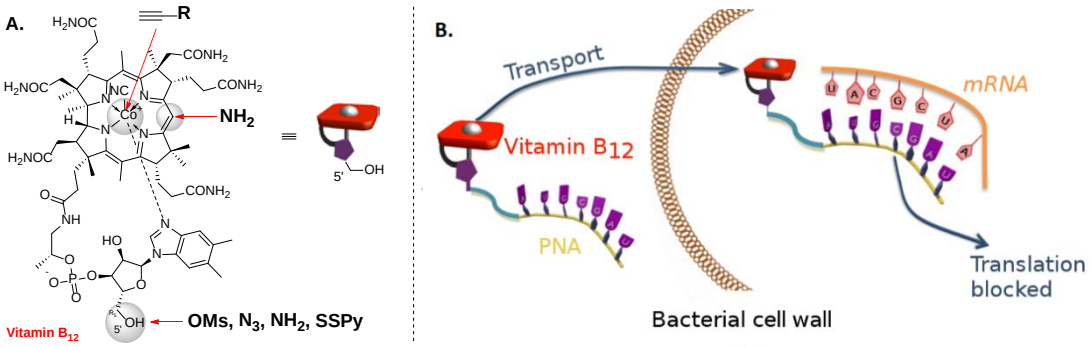

Fig. 1 Sites suitable for conjugation in B_{12} (**A**). Vitamin B_{12} as a PNA transporter (**B**)

Acknowledgements

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Pd-Catalyzed Additions to Alkynes with Subsequent Cross-Coupling

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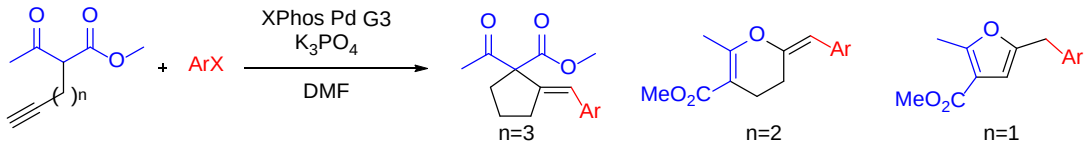
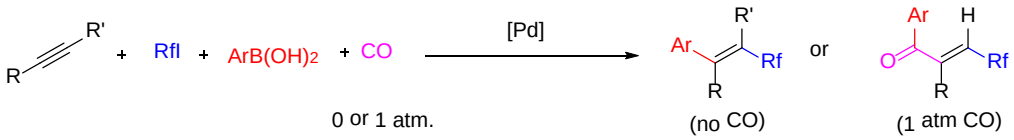
Keywords: palladium, alkynes, tandem reactions

Palladium is one of the most widely used metals in catalytic processes, both in academic and industrial laboratories. Due to its ability to adapt multiple oxidation states (usually between 0 and IV) and a wide span of possible mechanistic roles (carbophilic Lewis acidity, 1e- and especially 2e- redox activity), a great number of effective procedures for Pd-catalyzed transformations have been developed to date, of which cross-couplings are of most importance. In contrast to simple two-component transformations, Pd-mediated tandem reactions involving the efficient assembly of several components for rapid buildup of molecular complexity are still underdeveloped.

In this presentation, the elaboration of methodologies based on the application of Pd catalysis for the efficient and versatile double functionalization of alkynes will be discussed. These strategies are based on additions to C-C triple bonds followed by the functionalization of the nascent vinyl-Pd species via cross-coupling. Two classes of reactions will be presented, with focus on their scope as well as on the mechanistic aspects. The first one involves the tandem nucleophilic cyclization of acetylenic β-ketoesters followed by cross-coupling with aryl halides, leading to both carbo- and heterocyclic compounds with tolerance of a broad range of functionalities (Scheme 1).[1] The second class of transformations involves the multicomponent perfluoroalkylative functionalization of terminal and internal alkynes (Scheme 2).[2] The overall process engages a radical Pd-catalyzed addition of a fluoroalkyl iodide to the alkyne moiety, followed by cross coupling with an arylboronic acid. The carbonylative, four-component variant will also be discussed.



Scheme 1



Scheme 2

Acknowledgements

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