Jürgen Liebscher

Stereoselective Synthesis

The research interest of the group is directed to the development of new synthetic methods and new products, in particular biologically important compounds. Stereoselective synthesis using amino acids, terpenes or sugar derivatives as chiral agents plays a key function in the synthetic activities. Synthetic targets are analogues of natural products, natural products and activity directed heterocyclic products. Several pharmacological activities, specific enzyme inhibition, molecular recognition and formation of supramolecular assemblies are targeted. At present the group is active in the following projects.

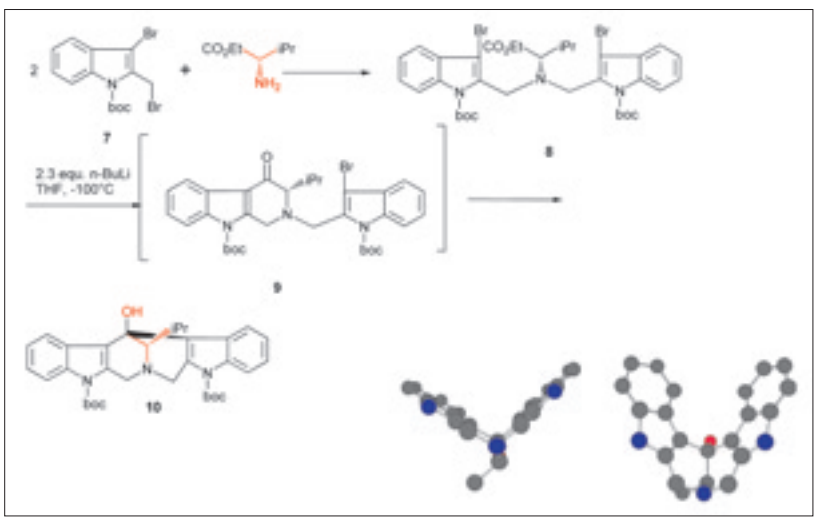
Synthesis of Alkaloid-Analogues and Azasugars from Proteinogenic α-Amino Acids

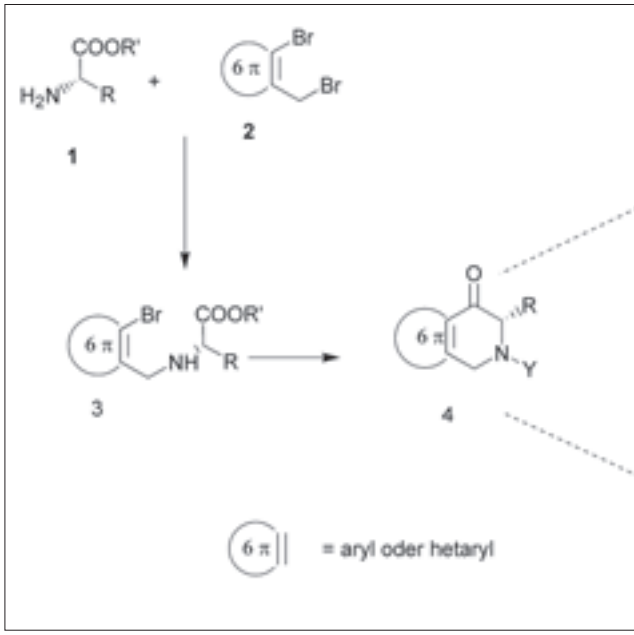
Ester 1 of proteinogenic α-amino acids are used to establish optically active condensed tetrahydropyrid-3-ones 4 by first alkylation with o-bromobenzyl bromides 2 or heterocyclic analogues followed by bromo-lithium exchange and cyclisation. (Scheme 1) [1] Both, the functional groups and the chirality of 4, allow wide synthetic application. Thus bridged heterocyclic systems 5 related to amarillidaceae alkaloids can be formed or the starting heterocyclic ring is opened to give access to new unnatural deoxyazasugars 6.

An example of the synthesis of annelated heterocycles is shown in Scheme 2, where the dialkylation product 8 was double cyclised by twofold bromo-lithium exchange to afford polycyclic products 10. [2] These butterfly-shaped molecules exhibit interesting HIV RNAse-H inhibiting properties.

Condensed oxazolopyridones, such as 12, obtained by reaction of the bromomethyloxazole 11 and α-amino esters, such as N-benzenesulfonyl alanine ester, could be stereoselectively reduced and ring opened to afford novel deoxyazasugars 16 in the talose series. [3,4] This strategy can be extended to other heterocycles

Scheme 2
Biologically Active Polycyclic Tetrahydropyridines





Scheme 1
Synthesis of Alkaloide-Analogoues and Azasugars from α-Amino Acids

and amino acids as well as to other configurations of the products. Azasugars are candidates for inhibitors of glycosidase, a pharmacologically interesting enzyme. (Scheme 3)

Stereoselective Synthesis of Amino Acid Derivatives and Fungal Metabolites by the Help of Ylidenepiperazinondiones

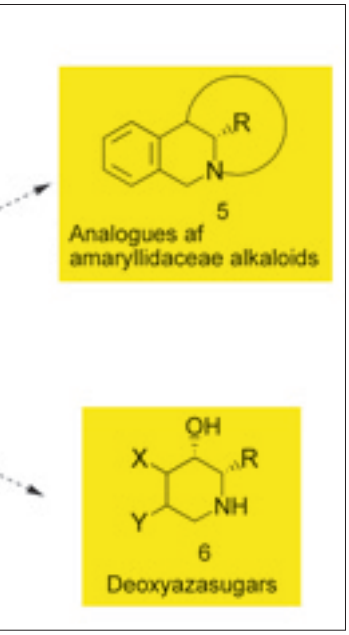
3-Ylidene-piperazin-2,5-diones 17 are cyclic dipeptides. They occur in nature and are easily available by synthesis. The potential of such products as reactants in stereoselective synthesis by addition reactions to the C-C-double bond is exploited. [5, 6, 7] The resulting adducts 19 can be hydrolysed to afford optically active unnatural amino acids, as for example compounds 21 and 22. On the other side, cycloaddition reactions are possible with intermediates 18 giving access to interesting polycyclic products, such as indole derivatives 23, which are important in the biosynthesis of fungal metabolites, such as *brevianamides*. [8,9] (Scheme 4, 5)

Optically Active Reissert Compounds

New steroselective 1,2-addition of cyanide and an acylchloride to isoquinolines gives access to optically ac-

Stereoselektive Synthese

Der Arbeitskreis befasst sich mit der Entwicklung von neuen Synthesemethoden für neue Produkte, insbesondere von biologisch wichtigen Verbindungen. Dabei spielen asymmetrische Synthesen auf der Basis von Naturprodukten, wie beispielsweise Aminosäuren, Terpenen oder Zuckerderivaten eine wesentliche Rolle. Mit den entwickelten Produkten werden verschiedene pharmakologische Wirkungen, spezifische Enzyminhibierungen sowie Möglichkeiten der molekularen Erkennung und der Ausbildung supramolekularer Strukturen verfolgt.



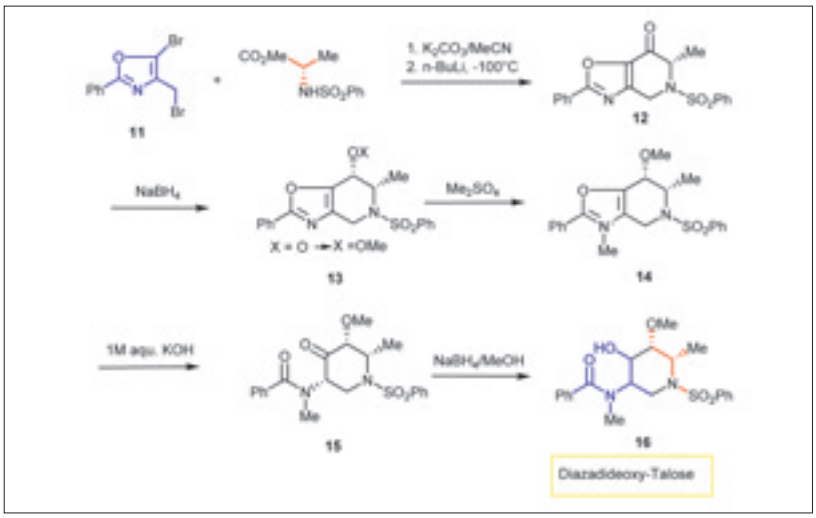
tive Reissert Compounds 24, making use of chiral catalysts or chiral auxiliaries. These products exhibit a wide potential for the synthesis of unnatural amino acids such as 25. These are interesting building blocks for peptidomimetics or for annelated systems 26 and 27, which are related to pharmaceutically active alkaloids. [10, 11] (Scheme 6)

Novel Peroxides via Hydroperoxid-Rearrangement

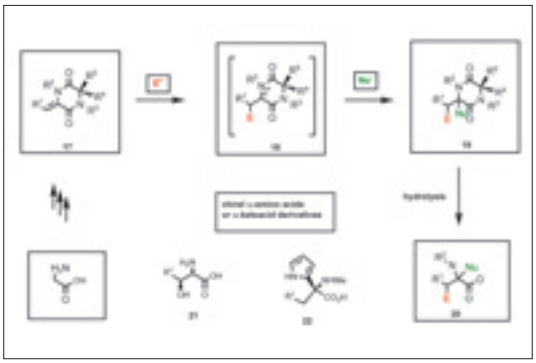
Rearrangement of cyclic hydroperoxides such as 28 gives rise to new hydroperoxide and peroxide structures 29, 30 and 31. Product formation depends on substituents, ring size and annelated ring. [12, 13] Naturally occurring cyclic alcohols are incorporated in the investigations in order to check, if similar hydroperoxide rearrangements can occur in nature. Products 29, 30, 31 show pharmacological activity against *plasmodium falciparum* and thus are interesting in the development of new antimalaria compounds, which are structural related to the highly active natural occurring *artemisinine*. Further transformation of products 29, 30 and 31 with specific substituents R allow to synthesise novel peroxides such as 32 and 33. (Scheme 7)

Amphiphilic Nucleic Acid Building Blocks – Development and Application in Biochemistry and Biology

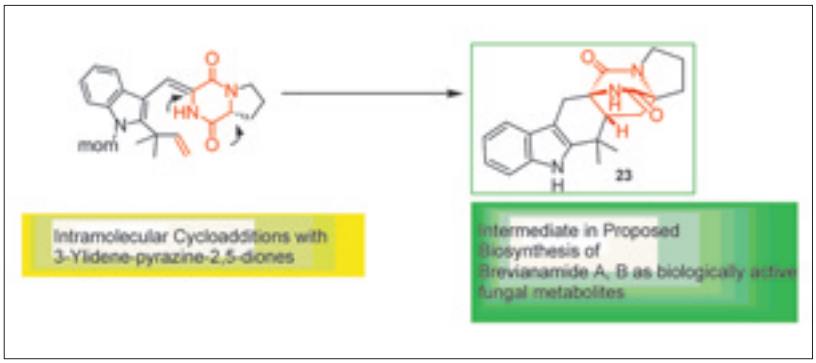
Combined structures consisting of the normal nucleic acid building blocks, i.e. nucleobases and ribose or desoxyribose, and lipophilic substituents such as long chained alkyl or alkenyl substituents, fatty acids or diglycerides are developed. Such amphiphilic building blocks will arrange in supramolecular structures, such as micelles, vesicles and bilayers and exhibit the



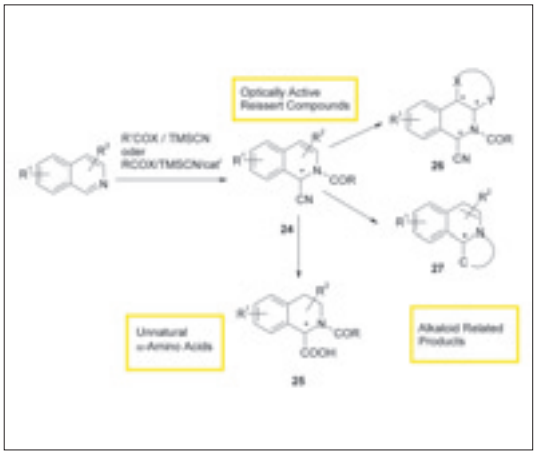
Scheme 3
Synthesis of Azasugars from α-Amino Acids



Scheme 4 (top left)
Quaternary α-Amino Acid Derivatives via Addition to 3-Ylidene-piperazin-2,5-diones



Scheme 5 (top right)
Synthesis of Precursors of Fungal Metabolites



Scheme 6
Optical Active Reissert Compounds

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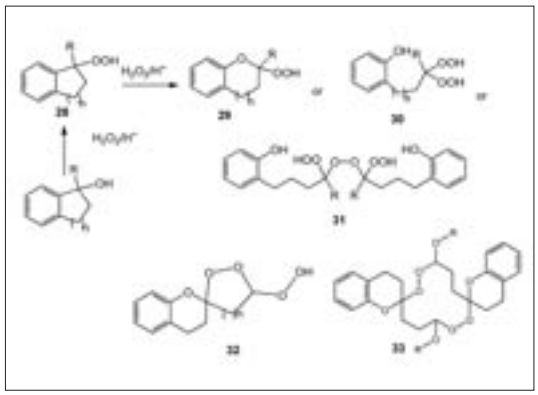


Scheme 7
Potential Antimalaria Compounds

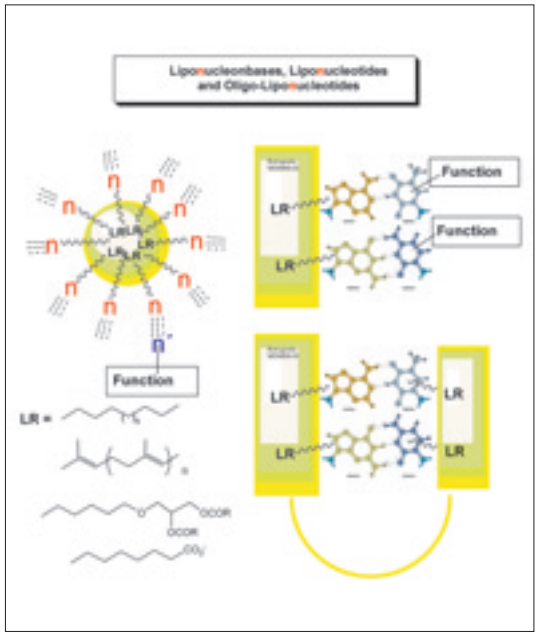
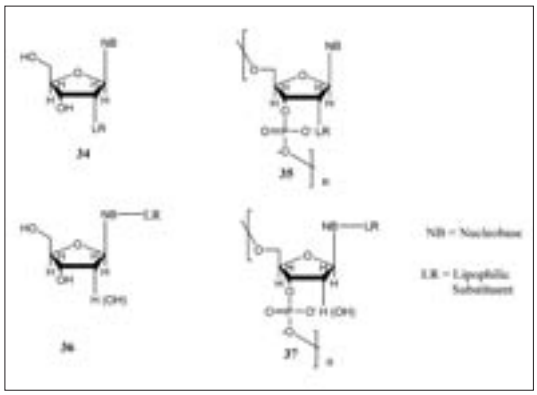


Fig. 1
Liponucleonbases, Liponucleotides, and Oligo-Liponucleotides

potential of molecular recognition by base-base pairing similar to nucleic acids. (Scheme 8; Fig. 1)

This ability shall be used to fix functions to the supramolecular structures. Combining amphiphilic nucleic acid building blocks with biological or biocompatible membranes directs the polar nucleobases to the polar side of the membrane. The amphiphilic components float in the membrane and shall be organised in defined assemblies by bringing them into contact with monostranded DNA or PNA. This principle will be used to structure and functionalise such membranes. (Fig. 1)



Scheme 8
Amphiphilic Nucleic Acid Building Blocks

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