

# Enantioselective Synthesis of $\beta$ -Aminoacids Symposium

Dieter Seebach, Honorary Chairman

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ICOS-AAS-1

**Ferenc Fülöp**

*Institute of Pharmaceutical Chemistry, Hungary*

Synthesis of Cyclic  $\beta$ -Amino Acids: Toolkits to Construct Foldamers

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ICOS-AAS-2

**Norbert De Kimpe**

*Ghent University, Belgium*

Synthesis and Rearrangements of  $\beta$ -Amino-cyclopropanecarboxylic Acid Derivatives

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ICOS-AAS-3

**Rosa M. Ortuño**

*Universitat Autònoma de Barcelona, Spain*

Cyclobutane Containing  $\beta$ -Amino Acids: Stereoselective Synthesis and Incorporation into Highly Rigid  $\beta$ -Peptides

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ICOS-AAS-4

**Peter Spiteller**

*Technische Universität München, Garching, Germany*

$\beta$ -Amino Acids In Nature

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ICOS-AAS-5

**David J. Aitken**

*Université Blaise Pascal, France*

Total Synthesis of Cyclotheonamide C: Focus on the  $\alpha$ -Oxo- $\beta$ -Aminoacid Moiety

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ICOS-AAS-6

**Claudio Palomo**

*Universidad del País Vasco, San Sebastián, Spain*

Catalytic Enantioselective Synthesis of  $\beta$ -Amino Acids

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ICOS-AAS-7

**Giuliana Cardillo**

*University of Bologna, Bologna, Italy*

Unusual  $\beta$ -Amino Acids: Synthesis and Application

## Synthesis of cyclic $\beta$ -amino acids: toolkits to construct foldamers

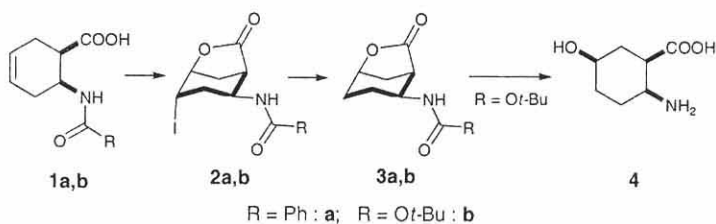
ICOS-AAS-1

Ferenc Fülöp

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The self-organizing  $\beta$ -peptides have attracted considerable interest in the fields of foldamer chemistry and biochemistry. These compounds exhibit various stable secondary structure motifs that can be exploited to construct biologically active substances and nanostructured tertiary structures. The secondary structures can be controlled via the  $\beta$ -amino acid sequence, and cyclic  $\beta$ -amino acid residues play a crucial role in the design. Present lecture will focus some new and important procedures for the preparation of hydroxylated cyclic  $\beta$ -amino acid monomers.

The  $\beta$ -amino acids containing a cycloalkene skeleton, are excellent starting substances for the introduction of polar substituents, *e.g.* hydroxy or amino groups, to the cycloalkane ring. Stereoselective iodolactonization was likewise the key step in the synthesis of *cis*-2-amino-5-hydroxycyclohexanecarboxylic acid (**4**). The reaction of *cis* *N*-acyl amino acids **1a,b** with  $I_2$  / KI in slightly alkaline medium produced iodolactones **2a,b**. Removal of the iodine was effected by reduction with tributyltin hydride, giving lactones **3a,b**. The *N*-Boc lactone was finally converted to the *all-cis* isomer of hydroxylated amino acid **4** by acid hydrolysis and ion-exchange chromatography.



Number of further selective strategies will be presented in the lecture.

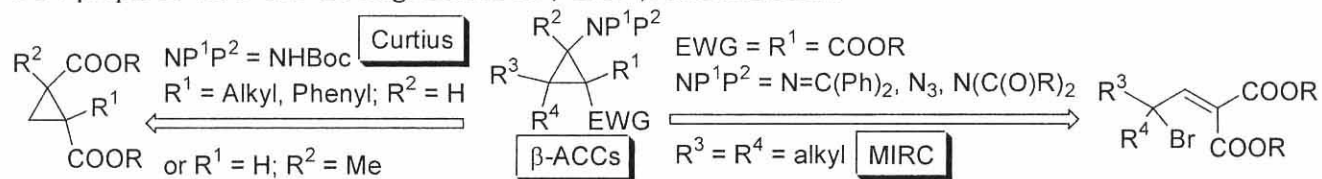
## Synthesis and rearrangements of $\beta$ -aminocyclopropanecarboxylic acid derivatives

ICOS-AAS-2

Sven Mangelinckx and Norbert De Kimpe.\* *Department of Organic Chemistry, Faculty of Bioscience Engineering, Ghent University, Coupure links 653, B-9000 Ghent, Belgium. email: norbert.dekimpe@UGent.be*

$\beta$ -Aminocyclopropanecarboxylic acids ( $\beta$ -ACCs) are the conformationally most severely restricted cycloalkyl bridged  $\beta$ -alanine or  $\gamma$ -aminobutyric acid (GABA) derivatives that can be envisioned, and are of special interest as constituents of  $\beta$ -peptides. However, since  $\beta$ -ACCs belong to the class of vicinally donor-acceptor substituted cyclopropanes which easily undergo ring opening reactions, an appropriate N-protecting group has to be introduced during the synthesis of  $\beta$ -ACCs.

In this presentation results on the synthesis of new N-protected  $\beta$ -ACCs are disclosed. Stereoselective synthesis of 1-alkyl-, 1-phenyl- and 2-methyl-substituted  $\beta$ -ACCs was accomplished via a strategy based on the Curtius reaction. Michael-induced ring closure (MIRC) reactions with selected N-nucleophiles afforded 3,3-dialkyl-1-alkoxycarbonyl-substituted  $\beta$ -ACCs while new  $\beta$ -aminocyclopropanecarbonitriles were prepared via 3-exo-tet ring closure of  $\gamma$ -halo- $\beta$ -aminonitriles.



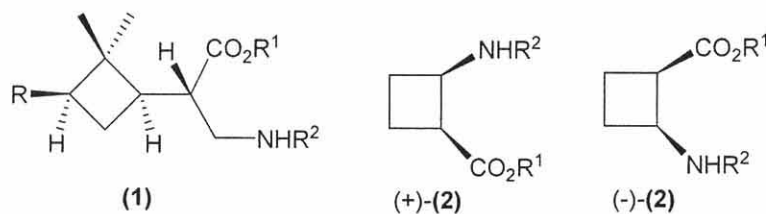
The reactivity of the new  $\beta$ -ACCs was also investigated, leading to interesting ring opening and ring transformation compounds, such as  $\gamma$ -oxocarboxylates, substituted alkenes,  $\gamma$ -amino acid derivatives, 1-pyrrolines and pyrrolidinones. Mechanistic as well as stereochemical details are also discussed.

## Cyclobutane Containing $\beta$ -Amino Acids: Stereoselective Synthesis and Incorporation Into Highly Rigid $\beta$ -Peptides

ICOS-AAS-3

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$\beta$ -Amino acids of types **(1)** and **(2)** have been stereoselective and efficiently synthesized by using suitable methodologies. Compounds **(1)** have been prepared through the diastereoselective addition of *N*-benzyl hydroxylamine to cyclobutyl enoates synthesized, in turn, from (-)-verbenone as a chiral precursor. Alternatively, a chemoenzymatic hydrolysis of a meso diester has been used to induce asymmetry and to provide a common intermediate in the enantiodivergent synthesis of both (+)- and (-)-**(2)** ( $R = R' = H$ ) and some derivatives. Structural studies on these compounds show the presence of *intramolecular* hydrogen bonds in solution. The  $\beta$ -peptides including these cyclobutane residues adopt helix-type foldings or  $\beta$ -turn conformations. In contrast, X-ray structural analysis of both the monomers and the oligomers shows the presence of *intermolecular* hydrogen bonds in the solid state determining a  $\beta$ -hairpin conformation for the individual molecules.



**$\beta$ -Amino Acids in Nature****ICOS-AAS-4****Peter Spiteller***Institut für Organische Chemie und Biochemie II, Technische Universität München,  
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In general,  $\beta$ -amino acids occur in all five kingdoms of living organisms. Especially bacteria and cyanobacteria, but also fungi and plants incorporate  $\beta$ -amino acids into secondary metabolites that serve as tools to secure their survival in competition with other organisms. Therefore, these compounds are often characterised by potent biological and physiological activities that are in many cases crucially based on their  $\beta$ -amino acid substructures.

For instance, the 3-phenylisoserine moiety is very important for the cytotoxic activity of taxol.  $\alpha$ -Hydroxy- $\beta$ -amino acid residues in natural products, such as microginin, bestatin or the microcystins are peptidase inhibitors since they mimic the transition state of these enzymes.  $\beta$ -Amino acids from natural sources often preserve “privileged structures” that fit to protein binding sites. Therefore, it is probably no accident that many  $\beta$ -amino acids occurring in ancient organisms possess an  $\alpha$ -hydroxy,  $\alpha$ -keto or an additional  $\alpha$ -amino group, since these compounds might have evolved together with enzymes, for instance, as ancient enzyme regulators. Consequently, the most promising sources for new lead structures are organisms obtained from previously poorly investigated habitats, such as protista, marine fungi or fruit-bodies of higher fungi.

However, there are no direct and specific methods for their detection in natural sources. In contrast,  $\beta$ -amino acid containing compounds are often found in nature by chance, exemplified by the detection of (*R*)- $\beta$ -Dopa, which we isolated in form of its blue iron-catechol-complex from the basidiomycete *Cortinarius violaceus* some years ago.

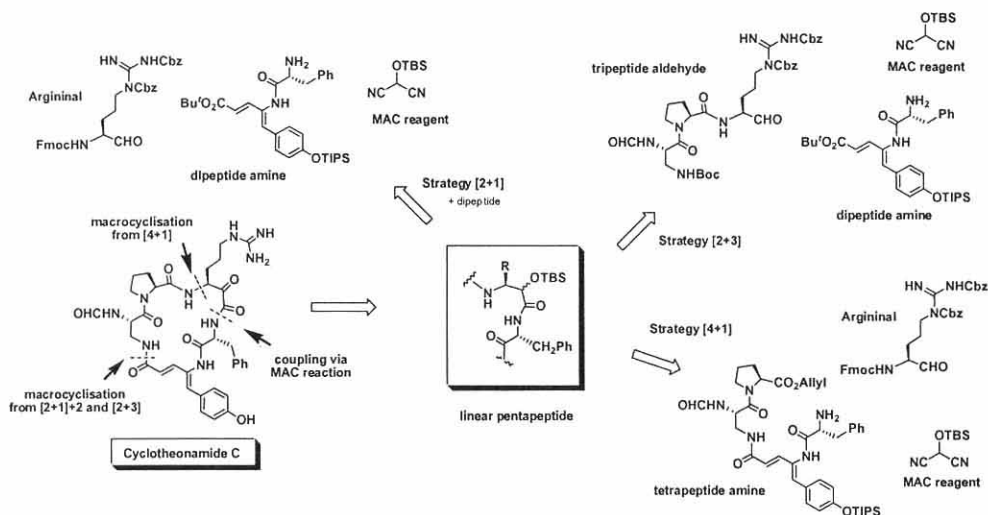
## Total Synthesis of Cyclotheonamide C: Focus on the $\alpha$ -Oxo- $\beta$ -Aminoacid Moiety

ICOS-AAS-5

David J. Aitken

Laboratoire SEESIB-CNRS, Département de Chimie, Université Blaise Pascal – Clermont-Ferrand II, 24 Avenue des Landais, 63177 Aubière cedex, France

Marine organisms are the source of an abundance of complex molecular structures, many of which have interesting and useful biological activities. Among these diverse molecular structures, a variety of substituted  $\beta$ -aminoacids can be found. One such case is the family of cyclic pentapeptides called cyclotheonamides (isolated from certain *Theonella* and *Ircinia* sponges) all of which incorporate an  $\alpha$ -oxo- $\beta$ -aminoacid related to arginine. In this lecture, I will present our recent developments of Nemoto's MAC (Masked Acyl Cyanide) methodology, a useful synthetic tool for the three-component construction of  $\alpha$ -hydroxy- $\beta$ -amino carboxamides. In an unprecedented application of this technique, we have coupled silyloxymalononitrile (the MAC reagent), highly conjugated peptide amines, and arginine derived aldehydes to give a key linear pentapeptide; macrocyclization, deprotection and oxidation of this advanced intermediate are the final steps in the total synthesis of Cyclotheonamide C.



## Catalytic Enantioselective Synthesis of $\beta$ -Amino Acids

ICOS-AAS-6

**Claudio Palomo**

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Two alternative, asymmetric routes to  $\beta$ -amino acids will be presented: Mannich type reaction of acetate equivalents with *N*-Boc imines, and hetero-Michael addition of carbamates to  $\alpha,\beta$ -unsaturated carboxylic acid surrogates. Initial studies led to the design of  $\alpha'$ -hydroxy ketone **1**, which upon enolization affords a highly ordered chelate capable of affording an efficient chiral-ity transfer event. We succeeded in the application of this design reagent to aldol and Mannich reactions. Significantly, the reagent is readily available from acetylene and (1R)-(+)-camphor, two commodity chemicals available in bulk, and detachment of the camphor unit from adducts is straightforward. Concurrent with these investigations it was also found that achiral  $\alpha'$ -hydroxy enones upon combination with chiral Lewis acids provide a new platform for carrying out highly enantioselective catalytic reactions. For example,  $\alpha'$ -hydroxy enones **2** react with carbamates in the presence of (S,S)-[Cu(<sup>t</sup>Bu-box)](OTf)<sub>2</sub> (10 mol %) to afford the corresponding adducts in high yield and selectivity. Final oxidative cleavage of the ketol moiety in the adducts gave the corresponding enantiopure carboxylic acids. Besides these examples, the cycloaddition of nitrones to enones **2** will also be briefly discussed as a further catalytic asymmetric route to  $\beta$ -amino acids.

## Unusual $\beta$ -amino acids: Synthesis and Application

**ICOS-AAS-7**

**Giuliana Cardillo**

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Recently, several methods for the stereoselective synthesis of polyfunctionalized  $\beta$ -amino acids have been developed. In particular,  $\alpha$ -alkyl,  $\alpha$ -hydroxy and  $\alpha$ -alkyl- $\alpha$ -hydroxy-amino acids have been prepared.

Small libraries of endomorphin-1-analogues containing  $\beta^3$ -amino acid and  $\beta^2$ -amino acid have been synthesized and their affinity toward the receptor and their resistance towards hydrolysis have been tested.

