Ph.D. Thesis

Syntheses and applications of novel *β*-amino acids

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Introduction and aims

Interest in *β*-amino acids has increased during the past several years, due to their importance in multiple lines of research (combinatorial chemistry, medicinal chemistry, molecular design, proteomics, *etc.*). My research work covered three topics connected with *β*-amino acids: enantioselective syntheses of chiral auxiliaries and building blocks based on natural monoterpene sources; hydroxy group functionalization of alicyclic *β*-amino acids; and the application of combinatorial chemistry in aqueous medium to make *β*-lactam libraries.

My primary aim was to prepare *β*-amino acid derivatives which may be utilized as chiral auxiliaries and catalysts in enantioselective syntheses, or chiral building blocks in the asymmetric syntheses of potential pharmacons, *β*-amino acid oligomers and modified analogues of natural peptides. I set out to achieve the syntheses and transformations (*e.g.* cyclization) of *β*-amino acid derivatives prepared from (+)-3-carene, a commercially available monoterpene source.

My second aim was to study the iodocyclization of unsaturated *β*-amino acid derivatives in order to obtain saturated analogues of oryzoxymycin, the first alicyclic hydroxy-*β*-amino acid.

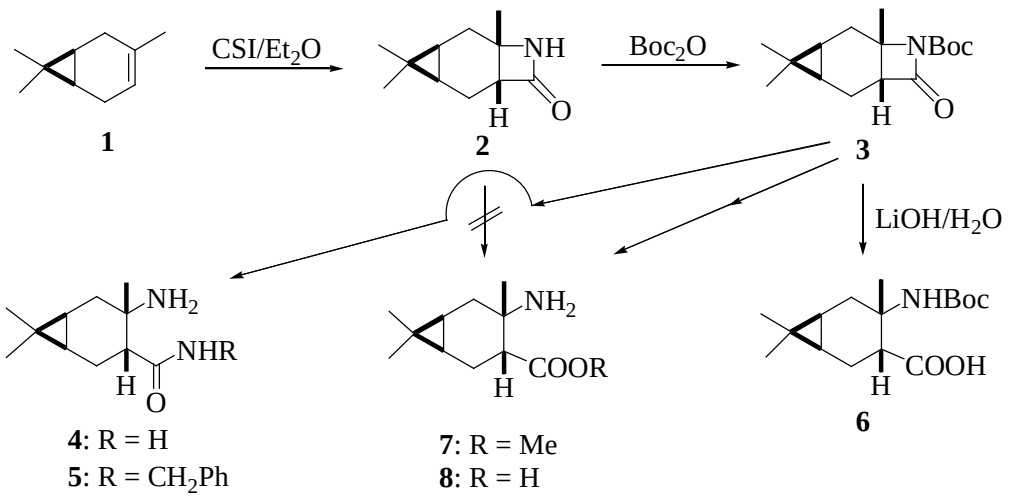
My third aim was to investigate the effect of water as solvent in the Ugi four-centre three-component reaction (U-4C-3CR) and compare with the use of organic solvents. With alicyclic *β*-amino acids as building blocks, bi- and tricyclic *β*-lactam libraries were generated in aqueous medium.

Results and Discussion

I. Syntheses and transformations of novel *β*-amino acid derivatives of enantiomeric monoterpenes

The regio- and stereoselective cycloaddition of chlorosulfonyl isocyanate (CSI) to (+)-3-carene **1** furnished the optically pure *β*-lactam **2**. Since the strongly constrained carene ring system was broken down during the conventional *β*-lactam ring-opening process, activation of the carboxamide bond seemed necessary. The nucleophilic ring opening of *N*-Boc-protected

azetidinone **3** was carried out with different amines (*e.g.* NH_3 or benzylamine) and deprotection of the intermediate *N*-Boc amides, which resulted in amides **4** and **5**. Further ring opening of **3** under mild conditions gave the corresponding *N*-Boc-protected derivative and, after deprotection, amino ester **7,** which was converted to the desired amino acid **8** (Scheme 1).

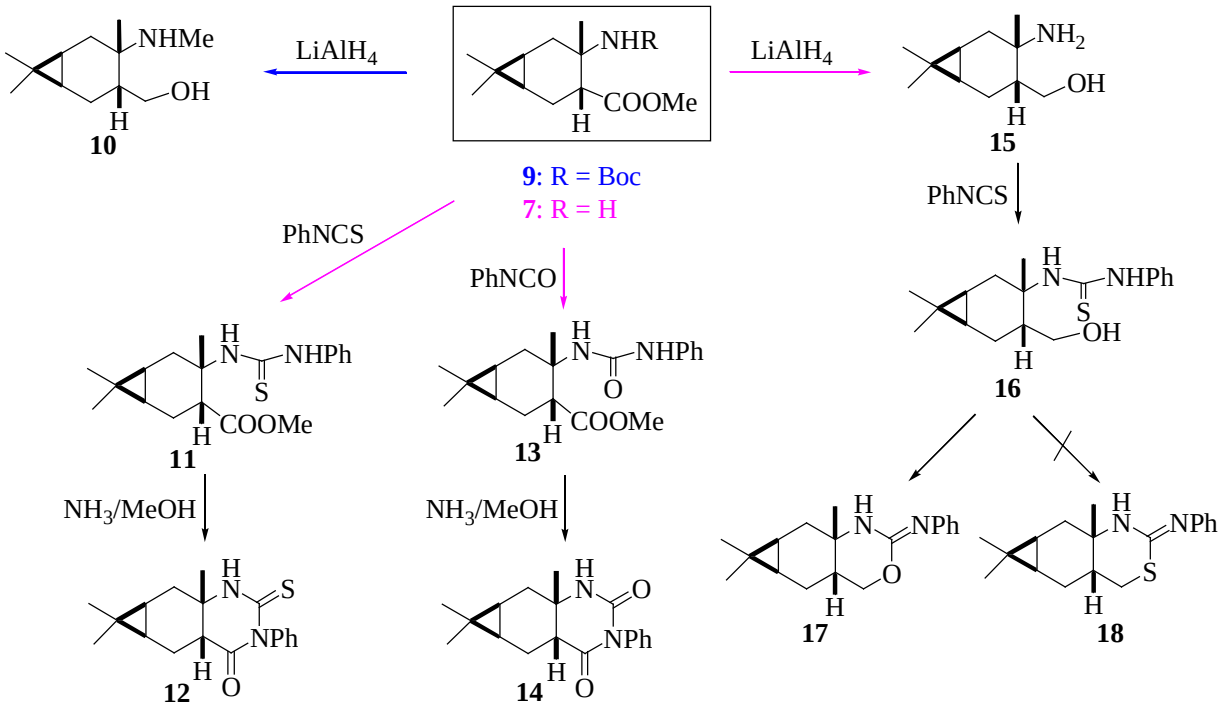


Scheme 1

N-Boc amino ester **9** was reduced to *N*-methyl amino alcohol **10** with $LiAlH_4$, and its deprotected analogue **7** to the corresponding amino alcohol **15**. When amino ester **7** was reacted with phenyl isothiocyanate or phenyl isocyanate, thiourea **11** and urea intermediate **13** were obtained, which were transformed to 2-thioxo-4-pyrimidinone **12** and 2,4-pyrimidinedione **14** by base-catalysed ring closure.

With phenyl isothiocyanate, amino alcohol **15** furnished thiourea adduct **16**, which was converted to 2-phenylimino-1,3-oxazine **17**. Preparation of the corresponding thiazine **18** failed: only the decomposition of **18** was observed (Scheme 2).

The synthetized *β*-amino acid derivatives may serve as chiral building blocks in the asymmetric syntheses of potential pharmacons, *β*-amino acid oligomers and modified analogues of natural peptides. They can also be used as chiral auxiliaries and catalysts in enantioselective syntheses.

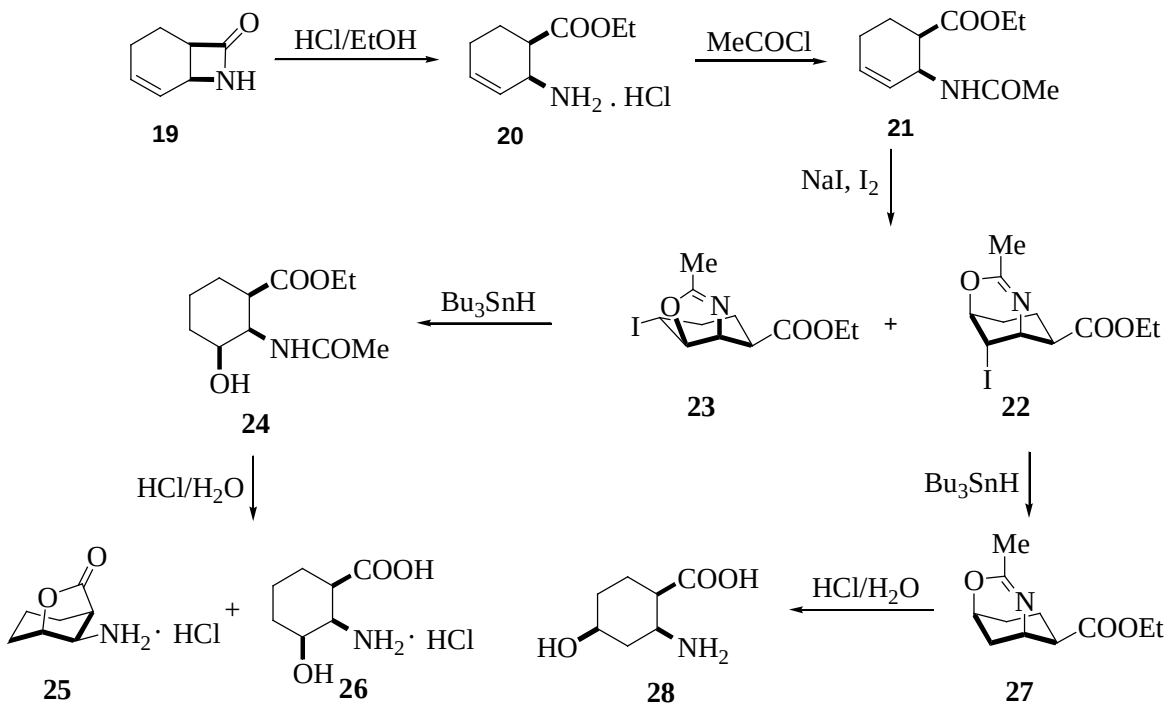


Scheme 2

II. Synthesis of 3- and 4-hydroxy-substituted amino acids

β-Lactam **19** was synthetized from 1,3-cyclohexadiene by CSI addition, a well-known literature method. Ring opening of **19**, followed by acylation of amino ester **20**, led to amide **21**, which was reacted with I_2 and NaI to afford a 30:70 mixture of iodooxazine **22** and iodooxazoline **23**. When compound **22** was dehalogenated, bicyclic oxazine **27** was obtained. The hydrolysis of **27** resulted in 2-amino-4-hydroxycyclohexanecarboxylic acid **28**.

When the deiodination of **23** was attempted, the oxazoline proved to be unstable and only the ring-opened *N*-acetylamino ester **24** could be isolated. Hydrolysis of **24** under acidic conditions furnished a mixture of 3-hydroxy-substituted amino acid **26** and amino lactone **25** (Scheme 3).

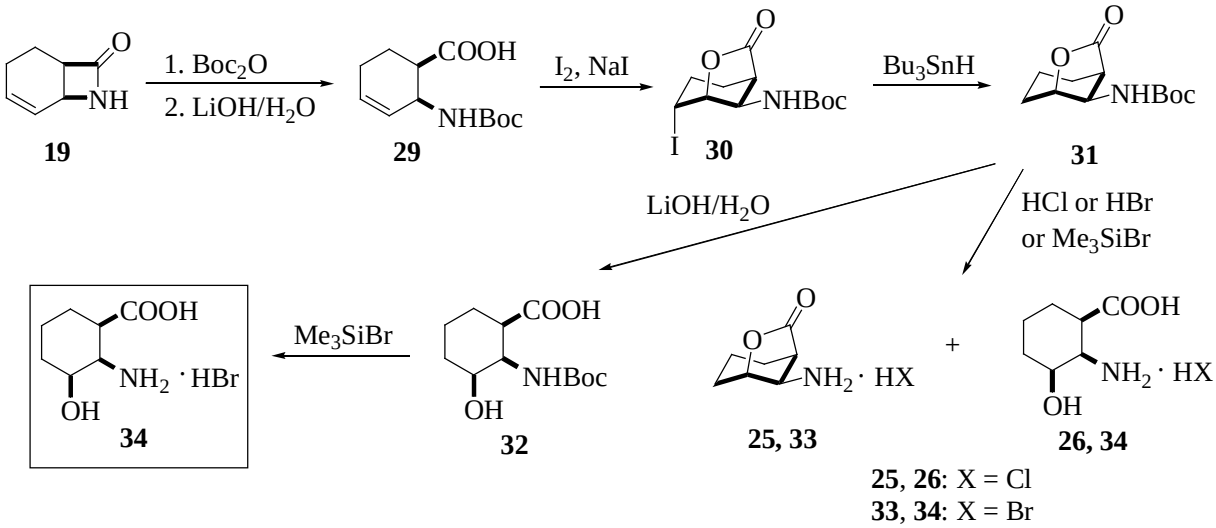


Scheme 3

The synthesis of the 3-hydroxy-substituted *β*-amino acid was also carried out from *N*-Boc-amino acid **29**, which was prepared by *N*-Boc protection of *β*-lactam **19**. Iodolactonization achieved under the same conditions as applied above afforded iodolactone **30**. After dehalogenation, lactone **31** was transformed to *N*-Boc-hydroxyamino acid **32**. Deprotection of **32** with Me_3SiBr resulted in 2-amino-3-hydroxycyclohexanecarboxylic acid **34**.

When ring opening of *N*-Boc-lactone **31** was performed with different acidic reagents, a variable mixture of hydroxyamino acid **26** or **34** and deprotected amino lactone **25** or **33** was observed. These results suggested that the first step should be the hydrolysis of the lactone ring, followed by deprotection; otherwise, a very stable amino lactone **25** or **33** was formed.

When this method was extended to chiral compounds, the chiral 3-hydroxy-substituted *β*-amino acids (+)- and (-)-**29** were obtained.

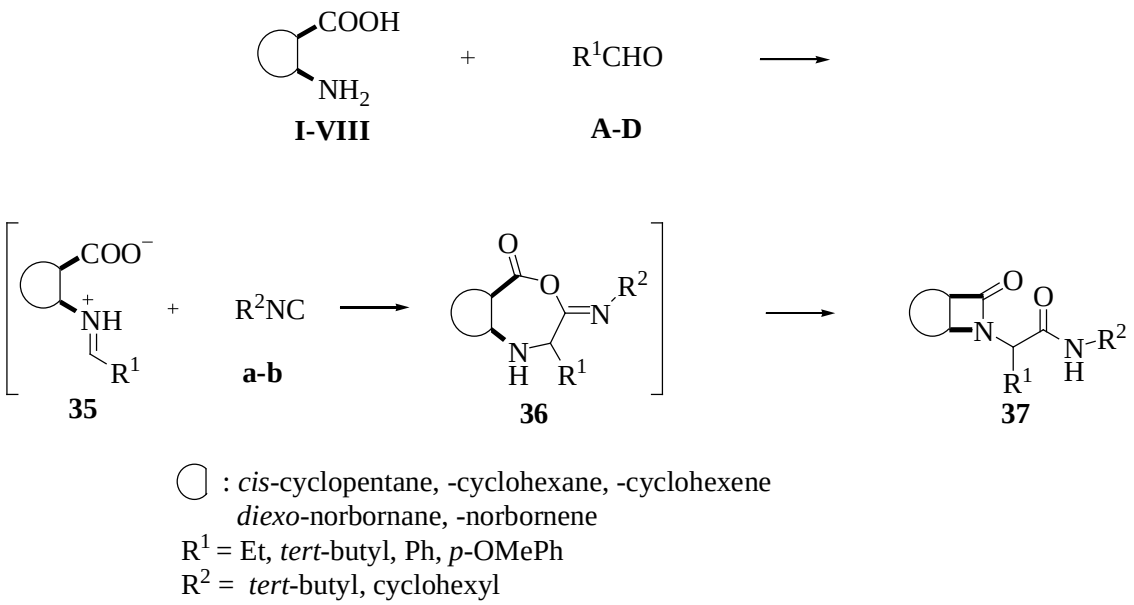


Scheme 4

III. Application of the aqueous U-4C-3CR to synthetize *β*-lactams

The traditional Ugi four-component condensation (U-4CC) incorporates a carboxylic acid, an amine, a carbonyl compound and an isocyanide in a one-pot condensation. In the modified U-4C-3CR, the cyclic *β*-amino acid supplies the carboxylic acid and the amino function. In our Institute, preliminary experiments have recently focused on the synthesis of an Ugi library generated by bifunctional *β*-amino acids, various aldehydes and isocyanide building blocks in MeOH; the conversion was complete in 3 days at room temperature. The aim was to compare the efficiency of an aqueous medium with that of MeOH as solvent during the preparation of the analogue library.

In the first step, the reaction of the *β*-amino acid (**I**-**VIII**) with the aldehyde (**A**-**D**) resulted in protonated Schiff's base **35**; this way followed by addition of the isocyanide (**a**, **b**) to afford *β*-lactam **37** via intramolecular cyclization (**36**) and rearrangement.



Scheme 5

We used 8 different alicyclic amino acids (**I-VIII**), aliphatic and aromatic aldehydes (**A**-**D**) and cyclohexyl or *tert*-butyl isocyanide (**a**, **b**) (Figure 1).

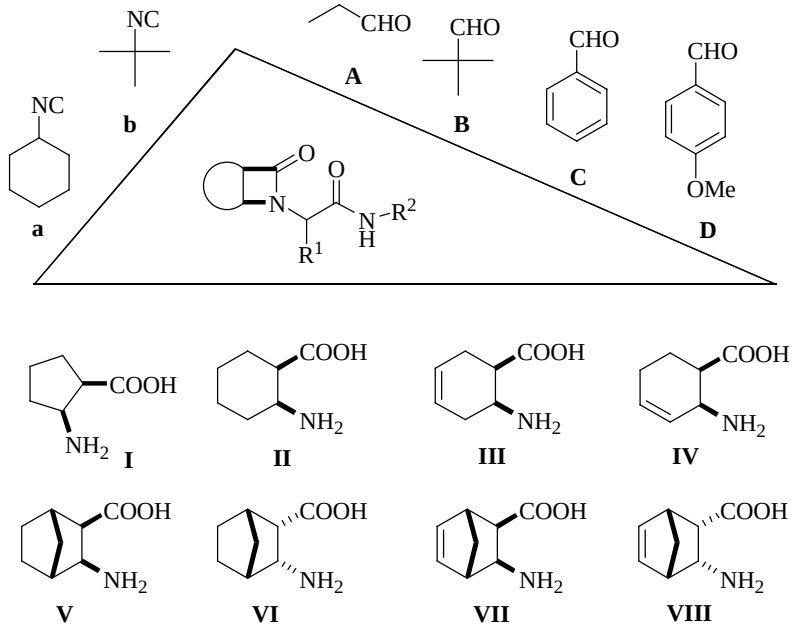


Figure 1

For this protocol, different quantities of water were used to find the critical concentration of the corresponding intermediate Schiff bases. During these experiments, the concentration was the factor determining whether the precipitation process occurred. Precipitation could be generated when less water-soluble *β*-amino acids and an appropriate amount of water were applied. In this way, the reactions were complete in higher yields in 1 day at room temperature instead of in 3 days in MeOH.

In all cases, a new stereogenic centre was formed at position C-2 of the acetamido group of the generated *β*-lactam **37** resulting in diastereoselective reactions. Most of the condensations were carried out with a good diastereomeric ratio, which in some cases, attained 100%. When we used sterically less hindered aliphatic aldehydes, the precipitated product obtained could be isolated easily with good purity and yield by simple filtration. Without precipitation, the products were separated by extraction in an organic solvent.

As exemplified in these experiments, the unique solvating properties of water have been shown to have beneficial effects on the Ugi reaction in terms of both rate and diastereoselectivity and a shorter reaction time.

Publications related to the Ph.D. thesis

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Synthesis and transformation of novel cyclic *β*-amino acid derivatives from (+)-3-carene
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III. Iván Kanizsai, **Szilvia Gyónfalvi**, Zsolt Szakonyi, Reijo Sillanpää, Ferenc Fülöp
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Green Chem. **2007**, *9***,** 357-360. if. 4.836

Total if. 10.384

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XXV. Kémiai Előadói Napok, 2003. okt. 28-30., Szeged

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Workshop, 19 September 2003, Ghent, Belgium

VIII. **Gyónfalvi Szilvia**, Szakonyi Zsolt, Fülöp Ferenc

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IX. **Gyónfalvi Szilvia**, Szakonyi Zsolt, Fülöp Ferenc

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XII. Ferenc Fülöp, Márta Palkó, **Szilvia Gyónfalvi**, Zsolt Szakonyi, Norbert De Kimpe

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Hidroxilezett ciklusos *β*-aminosavak szintézise jódlakton és jódoxazin intermediereken keresztül

MTA Alkaloidkémiai Munkabizottság előadóülése, 2005. május 9-10., Balatonfüred

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Heterociklusos Munkabizottsági Ülés, 2006. június 7-9., Balatonszemes

XVI. Iván Kanizsai, **Szilvia Gyónfalvi**, Zsolt Szakonyi, Ferenc Fülöp:
Synthesis of bi- and tricyclic *β*-lactams via Ugi-4C-3C reactions in water and organic media
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