PhD Thesis

Syntheses and stereochemistry of hydroxy-substituted alicyclic β-amino acid derivatives

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A. INTRODUCTION AND AIMS

β-Amino acids and their derivatives can be found in a large number of natural products. Representative examples include Cispentacin ((1*R*,2*S*)-2-aminocyclopentanecarboxylic acid) and its synthetic 4-methylene analogue Icofungipen, which exhibit antifungal activity. Cyclic β-amino acids can be widely used as building blocks for the preparation of modified analogues of peptides. They can be starting substances for the synthesis of different heterocycles, in drug research and also in combinatorial chemistry. Among the β-amino acids, the hydroxy-functionalized derivatives are of considerable importance because they also occur in many important natural products (Taxol and Oryzoxymycin) and are building blocks for pharmaceutically important substances.

In view of the growing importance of β-amino acid derivatives, my PhD work had the major aim of developing simple and efficient routes for the preparation of new hydroxy-functionalized alicyclic β-amino acids. The preparative work was focused on preparing new mono- and dihydroxy-substituted cyclopentane-, cyclohexane- and cyclooctane-β-amino acid derivatives, starting from β-lactam via amino acids and aminocarboxylates, exploiting the reactivity of the ring double bond. A further aim was to study the stereo- and regioselectivity of the different approaches followed, based on the formation of bromooxazoline or iodolactonization and diastereoselective OsO_4-catalysed dihydroxylation of esters.

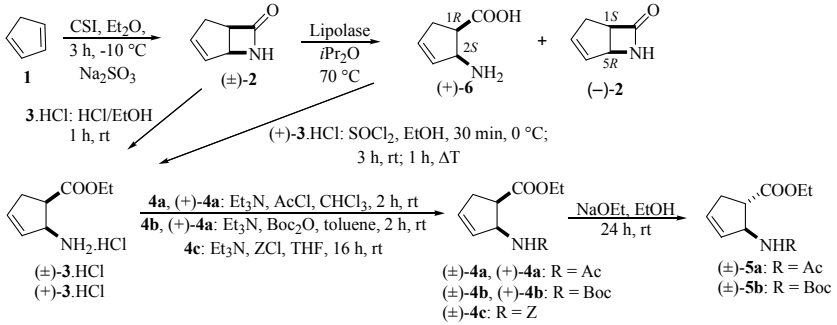
B. METHODS

The reactions were accomplished on the gram scale. The derivatives prepared were purified by crystallization and column chromatography. The new derivatives were characterized by their physical constants (melting point and optical rotation), spectroscopic data (NMR) and elemental analysis. The enantiopurities of the starting materials and final products were proved by GC and HPLC. The stereochemistry of the novel materials was determined by NMR spectroscopy and X-ray crystallography.

C. RESULTS AND DISCUSSION

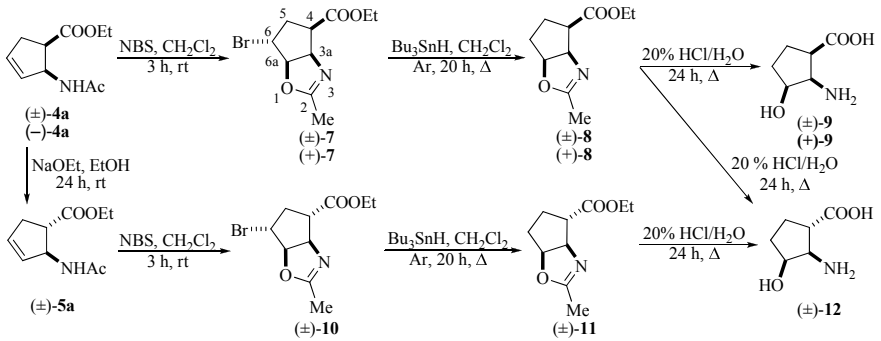
I. Syntheses of the mono- and dihydroxycyclopentane-β-amino acids

The racemic starting substances were prepared via the 1,2-cycloaddition of CSI and cyclopentadiene, which resulted in *cis*-6-azabicyclo[3.2.0]hept-3-en-7-one ((±)-**2**). This was reacted with ethanolic HCl to obtain ethyl *cis*-2-aminocyclopent-3-enecarboxylate hydrochloride ((±)-**3**.HCl). Protection of the amino group of ester hydrochloride (±)-**3**.HCl resulted in *N*-acetyl- ((±)-**4a**), *N*-Boc- ((±)-**4b**) or *N*-Z-protected esters ((±)-**4c**), which was followed by NaOEt isomerization of (±)-**4a** and (±)-**4b** to give the *trans N*-protected amino esters (±)-**5a** and (±)-**5b** in yields of 37-51% (Scheme 1).



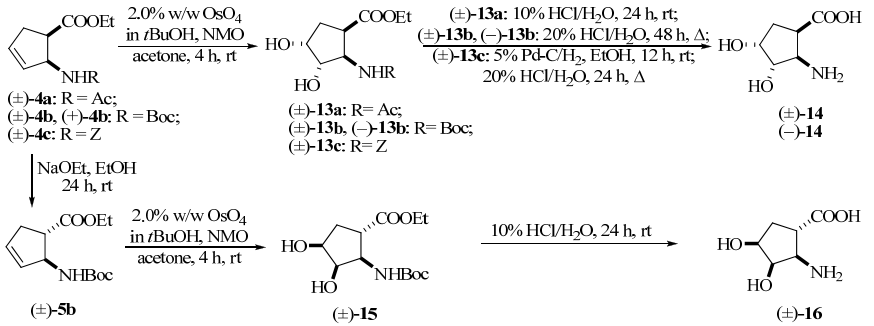
Scheme 1

The reactions of ethyl *cis*- and *trans*-2-acetylaminocyclopent-3-enecarboxylate ((±)-**4a**, (±)-**5a)** with NBS at room temperature afforded the bicyclic ethyl (3a*R**,4*R**,6*R**,6a*R**)- ((±)-**7**) and ethyl (3a*R**,4*S**,6*R**,6a*R**)-6-bromo-2-methyl-4,5,6,6a-tetrahydro-3aH-cyclopentaoxazole-4-carboxylate ((±)-**10**) in yields of 71-86%. On reduction of the bromo group with Bu_3SnH, followed by opening of the oxazoline ring by refluxing in 20% aqueous HCl, (1*S**,2*R**,3*S**)-2-amino-3-hydroxycyclopentane-carboxylic acid ((±)-**12**) was obtained. (1*R**,2*R**,3*S*)-2-Amino-3-hydroxycyclopentane-carboxylic acid ((±)-**9**) could be isolated from the mother liquor only by fractional crystallization (Scheme 2).



Scheme 2

Dihydroxylation of ethyl *cis*-2-acetylaminocyclopent-3-enecarboxylate ((±)-**4a**), ethyl *cis*- and *trans*-2-*tert*-butoxycarbonylaminocyclopent-3-enecarboxylate ((±)-**4b**, (±)-**5b**) and ethyl *cis*-2-benzyloxycarbonylaminocyclopent-3-enecarboxylate ((±)-**4c**) was carried out with a catalytic amount of OsO_4 and NMO as a stochiometric co-oxidant in acetone. The synthesized ethyl (1*R**,2*S**,3*S**,4*R**)-2-acetylamino-3,4-dihydroxy-cyclopentanecarboxylate ((±)-**13a**) and its *N*-Boc ((±)-**13b**) and *N*-*Z*-protected ((±)-**13c**) counterparts, just like the ethyl (1*R**,2*R**,3*S**,4*R**)-2-*tert*-butoxycarbonylamino-3,4-dihydroxycyclopentane-carboxylate ((±)-**15**), were deprotected under acidic conditions to result in (1*R**,2*R**,3*S**,4*R**)-2-amino-3,4-dihydroxycyclopentanecarboxylic acid ((±)-**14**) and (1*S**,2*R**,3*S**,4*R**)-2-amino-3,4- dihydroxycyclopentanecarboxylic acid ((±)-**16**) (Scheme 3).

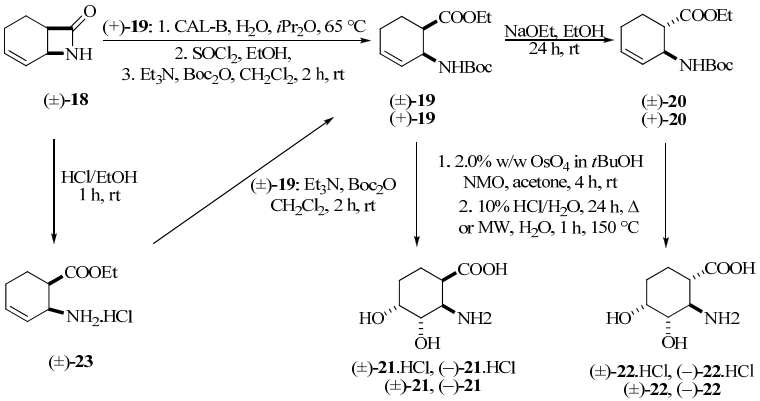


Scheme 3

The optically pure mono- and dihydroxycyclopentane-β-amino acids ((+)-**9** and (–)-**14**) were also prepared by the synthetic methods mentioned above, but with a slight modification. The starting amino acid (+)-**6** was synthesized from racemic β-lactam (±)-**2** by Lipolase-catalysed ring opening, followed by esterification with $SOCl_2$ in EtOH (Scheme 1).

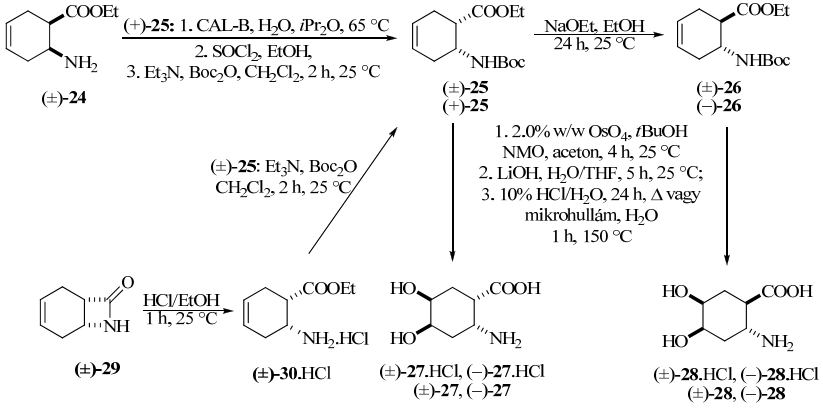
II. Syntheses of the dihydroxycyclohexane-β-amino acids

Osmylation was accomplished from ethyl (1*R*,2*S*)-2-*tert*-butoxycarbonylamino-cyclohex-3-enecarboxylate ((+)-**19**) and ethyl (1*S*,2*R*)-2-*tert*-butoxycarbonylamino-cyclohex-4-enecarboxylate ((+)-**25**), which were prepared by CAL-B-catalysed hydrolysis of racemic β-lactam (±)-**18** or amino ester (±)-2**4**. After esterification and *N*-protection, the compounds were isomerized to esters (+)-**20** and (–)-**26** with NaOEt. In the acidic hydrolysis of the protecting groups, a newly published deprotection reaction was also applied in order to improve the yields of the final products. MW irradiation in water at 150 °C for 1 h resulted in the expected (1*R*,2*R*,3*S*,4*R*)- and (1*S*,2*R*,3*S*,4*R*)-2-amino-3,4-dihydroxycyclohexane-carboxylic acids ((–)-**21**, and (–)-**22**), and (1*S*,2*R*,4*R*,5*S*)- and (1*R*,2*R*,4*R*,5*S*)-2-amino-4,5-dihydroxycyclohexanecarboxylic acids ((–)-**27**, and (–)-**28**), in yields of 70-77% (Scheme 4 and 5).



Scheme 4

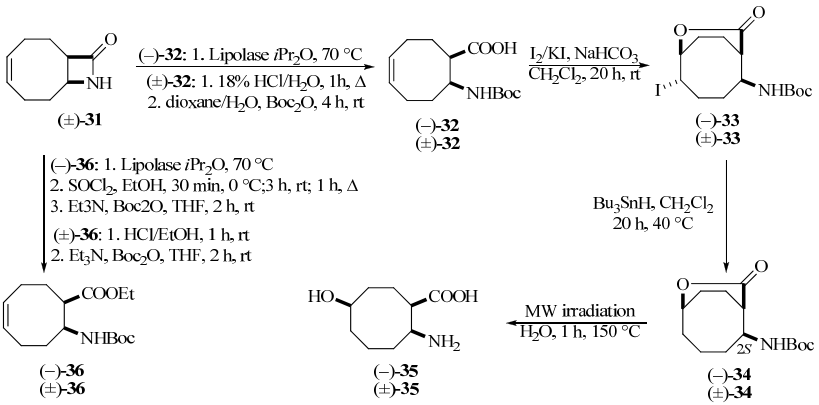
The racemic dihydroxy compounds were prepared via ring opening of β-lactams (±)-**18** and (±)-**29** with EtOH/HCl**,** followed by *N*-protection of the amino group (Schemes 4 and 5).



Scheme 5

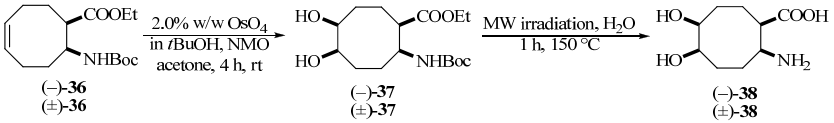
III. Synthesis of the mono- and dihydroxycyclooctane-β-amino acids

Iodolactonization was applied for the preparation of (1*R*,2*S*,6*R*)-2-amino-6-hydroxycyclooctanecarboxylic acid (–)-**35**. The starting (1*R*,2*S*)-2-*tert*-butoxycarbonylaminocyclooct-5-enecarboxylic acid ((–)-**32**) was prepared by the Lipolase-catalysed reaction of (1*R**,2*S**)-9-azabicyclo[6.2.0]dec-4-en-10-one ((±)-**31**), followed by *N*-protection of the amino group with Boc_2O. Reaction of the enantiopure *N*-Boc-amino acid (–)-**32** with I_2/KI in a two-phase solvent system resulted in iodolactone (–)-**33**. Reduction of the iodo group with Bu_3SnH and hydrolysis of the lactone ring by MW irradiation gave the (1*R*,2*S*,6*R*)-2-amino-6-hydroxycyclooctanecarboxylic acid ((–)-**35**) in *ee* > 99% (Scheme 6).



Scheme 6

The investigations of OsO_4 dihydroxylation were extended to the cyclooctane skeleton. (1*R*,2*S*,5*R*,6*S*)-2-Amino-5,6-dihydroxy-cyclooctanecarboxylic acid ((–)-**38**) was prepared from the amino-ester (–)-**36** by using a catalytic amount of OsO_4 and NMO. In the last step, deprotection was performed with MW irradiation (Scheme 6 and 7).



Scheme 7

The racemic mono- and dihydroxycyclooctane-β-amino acids (±)-**35** and (±)-**38** were also prepared via ring opening of β-lactams (±)-**31** with HCl or with EtOH/HCl**,** followed by *N*-protection of the amino group.

D. STEREOCHEMISTRY

The stereochemistry of the newly prepared compounds was proved by 1- and 2-dimensional NMR mesurements. In the case of the dihydroxycyclopentanecarboxylic acids (±)-**14** and (±)-**16**, the ring-closure reactions of 1,2-disubstituted 1,2- and 1,3-difunctionalized cycloalkanes also affirmed the structure. The Molecular Operating

Environment software (MOE 2008.10) was used to certify the stereochemistry of the compound (±)-**27** and (±)-**28**. The X-ray analyses unambiguously confirmed the structure of the mono- and dihydroxycyclooctanecarboxylic acids (±)-**35** and (±)-**38**.

E. PUBLICATIONS

I. **Gabriella Benedek**, Márta Palkó, Edit Wéber, Tamás A. Martinek, Enikő Forró, Ferenc Fülöp:
Efficient synthesis of hydroxy-substituted cispentacin derivatives
Eur. J. Org. Chem. **2008**, 3724–3730.
i.f.: 3.016

II. **Gabriella Benedek**, Márta Palkó, Edit Wéber, Tamás A. Martinek, Enikő Forró, Ferenc Fülöp:
Efficient synthesis of 3,4- and 4,5-dihydroxy-2-amino-cyclohexanecarboxylic acid enantiomers
Tetrahedron: Asymmetry **2009**, *20*, 2220-2225.
i.f.: 2.796

III. Róbert Berkecz, István Ilisz, **Gabriella Benedek**, Ferenc Fülöp, Daniel W. Armstrong, Antal Péter:
High-performance liquid chromatographic enantioseparation of 2-aminomono- and dihydroxycyclopentanecarboxylic and 2-aminodihydroxycyclohexane-carboxylic acids on macrocyclic glycopeptide-based phases
J. Chromatogr. A. **2009**, *1216*, 927-932.
i.f.: 3.756

IV. Márta Palkó, **Gabriella Benedek**, Enikő Forró, Edit Wéber, Mikko Hänninen, Reijo Sillanpää, Ferenc Fülöp:
Synthesis of mono- and dihydroxy-substituted 2-aminocyclooctanecarboxylic acid enantiomers
Tetrahedron: Asymmetry **2010**, *21*, 957-961.
i.f.: 2.796

Sum of impact factors of the published papers:12.364

F. CONFERENCE LECTURES

V. **Benedek Gabriella:**
Ciklopenténvázas β-aminosav-származékok diasztereo- és régioszelektív hidroxilálása
„A Szegedi Ifjú Szerves Kémikusok Támogatásáért" Alapítvány tudományos előadóülése,
Szeged, 2007. január 17.

VI. **Gabriella Benedek**, Márta Palkó, Loránd Kiss, Tamás A. Martinek, Ferenc Fülöp:
Efficient syntheses of hydroxy-substituated β-aminocyclopentanecarboxylic acids
Blue Danube Symposia on Heterocyclic Chemistry (BDSCH) 12,
June 10-13, 2007, Tihany, Hungary, Abstr.: PO-6.

VII. **Benedek Gabriella:**
Ciklopenténvázas β-aminosav-származékok diasztereo- és régioszelektív hidroxilálása
Magyar Tudomány ünnepe – PhD hallgatóink eredményei
Szeged, 2007. november 6.

VIII. **Benedek Gabriella**, Palkó Márta, Wéber Edit, Martinek A. Tamás, Forró Enikő, Fülöp Ferenc:
Hidroxilált ciszpentacin származékok előállítása
MKE Vegyészkonferencia
Hajdúszoboszló, 2008. június 19-21., Abstr.: P-2.

IX. **Gabriella Benedek**, Márta Palkó, Edit Wéber, Tamás A. Martinek, Enikő Forró, Ferenc Fülöp:
Efficient Syntheses of hydroxy-substituted cispentacin derivatives
XXIIIrd European Colloquium on Heterocyclic Chemistry
September 9-13, 2008, Antwerp, Belgium, Abstr.: P022.

X. **Gabriella Benedek**, Márta Palkó, Edit Wéber, Tamás A. Martinek, Enikő Forró, Ferenc Fülöp:
Efficient syntheses of hydroxy-substituted β-aminocyclohexanecarboxylic acids
COST Action CM0803, Foldamers: building blocks, structure and function
September 24-26, 2009, Szeged, Hungary, Abstr.: P05.