Amino Acids (2008) 34: 1–24
DOI 10.1007/s00726-007-0588-y
Printed in The Netherlands

Amino Acids

Structural diversity of bicyclic amino acids

Review Article

A. Trabocchi, D. Scarpi, and **A. Guarna**

Dipartimento di Chimica Organica "Ugo Schiff" and Laboratorio di Progettazione, Sintesi e Studio di Eterocicli Bioattivi (HeteroBioLab), Università degli Studi di Firenze, Polo Scientifico e Tecnologico, Sesto Fiorentino, Firenze, Italy

Received June 22, 2007
Accepted July 12, 2007
Published online August 15, 2007;

Summary. Over the years biomedical research has been constantly oriented towards the development of new therapeutics based on bioactive peptides and their analogues. In particular, the generation of compounds having structures and functions similar to bioactive peptides, named "peptidomimetics", raised much interest among organic and medicinal chemists due to the possibility by using such compounds to improve both potency and stability of peptidic lead compounds. In the context of this research area, unnatural amino acids are of great interest in drug discovery, and their use as new building blocks for the development of peptidomimetics with high diversity level and possessing high-ordered structures is of special interest. In particular, medicinal chemistry has taken advantage of the use of amino acid homologues and of cyclic and polycyclic templates to introduce elements of diversity for the generation of new molecules as drug candidates. Bicyclic amino acids have been developed as reverse turn mimetics and dipeptide isosteres, and the constraint imposed by their structures has been reported as a tool for controlling the conformational preferences of modified peptides. Moreover, synthetic efforts have been driven to the generation of diverse structures based on the modulation of ring size and scaffold decoration by suitable functional groups. Herein is reported an overview of different classes of bicyclic amino acids, taking into account the strategies to achieve structurally diverse templates, and some implications in medicinal chemistry are also disclosed.

Keywords: Scaffold – Peptide – Peptidomimetic – Drug design

Introduction

The development of new drugs based on peptides and proteins is of fundamental importance in biomedical research. An area of significant importance which provides new dimensions to the field of molecular diversity and drug discovery is the area of peptidomimetics, which is characterized by introducing both structural and functional specific modifications to lead peptides, and maintaining the features responsible for biological activity (Giannis and Kolter, 1993; Gante, 1994). As a part of this research area, unnatural amino acids are of valuable interest in drug discovery, and their use as new building blocks for the development of peptidomimetics carrying high diversity level and the capability to generate high-ordered structures is a key tool in medicinal chemistry. β-Amino acids gathered interest in the so-called "peptidomimetic approach", where a peptide lead is processed into a new non-peptidic molecule in a hierarchical approach, and in general amino acid homologues have been used for the generation of new molecules as drug candidates taking into account the additional elements of diversity. Specifically, the extra methylenic unit between the amino and carboxyl terminus in β-amino acids results in an increase of the molecular diversity in terms of number of stereoisomers, and of functional group variety. Synthetic chemists have come up to many synthetic approaches to the creation of β-amino acids, giving a great variety of compounds as a tool for medicinal chemistry (Cole, 1994; Sewald, 1996; Abdel-Magid et al., 1999; Juaristi and Lopez-Ruiz, 1999), and selected β-amino acids proved to be of great interest in the field of foldamers, as the corresponding β-peptides showed excellent capabilities to generate stable secondary structures such as β-turns, β-sheets and α-helices (Iverson, 1997; Seebach and Matthews, 1997; Gellman, 1998). Also, γ- and δ-amino acids gathered the same interest, as the investigation of the folding properties of γ- (Hanessian et al., 1998; Hintermann et al., 1998) and δ-peptides (Szabo et al., 1998) proved their

capability to generate stable secondary structures. As well as homologation, the panel of new molecular systems for peptidomimetic chemistry includes α-amino acids carrying modified side-chains, and rigid cyclic compounds as amino acid and dipeptide isosteres with added conformational restriction, which are of primary interest as they influence the conformational preferences of peptide leads. Specifically, a high number of papers reported the synthesis of cyclic compounds from α- to ε-amino acids, and some reviews also reported on recent achievements of polycyclic templates. This review will focus on recent synthetic approaches covering the years from 2000 to present, and relevant applications in medicinal chemistry of bicyclic amino acids, taking into account the structural diversity imposed by the bicyclic scaffolds.

Bicyclic α-amino acids

The synthesis and application of fused bicyclic α-amino acids have received much attention in recent years. Many of these amino acids are carriers of pharmacological activities, and they have been used as building blocks for the synthesis of conformationally constrained peptides. Starting from proline, the unique secondary naturally proteinogenic amino acid, many synthetic efforts have been concentrated upon the creation of heterocyclic species carrier of chemical diversity. Also, different ring-sizes have been taken into account, as well as the exploration of more complex structural variants among the class of α-amino acids. The most relevant examples of bicyclic α-amino acids can be divided into three groups according to their structural features, as synthetic methods have been developed for the preparation of bicyclic proline analogues, α,α-disubstituted bicyclic α-amino acids, and bicyclic homoproline or pipecolic-based α-amino acids.

Bicyclic proline analogues

Proline confers conformational restrictions to peptides, which can induce the formation of β- and γ-turns, thus its replacement with analogues can provide additional insight about receptor recognition and affinity. Thus, much effort has been devoted towards the exploration of structural variants carriers of higher conformational constraint and chemical diversity. The sub-group concerning bicyclic proline analogues is very rich in chemical diversity, and several papers reported the synthesis of bicyclic compounds varying the structural asset around the five-membered ring of proline. In particular, synthetic approaches have been reported for the construction of bicycles having

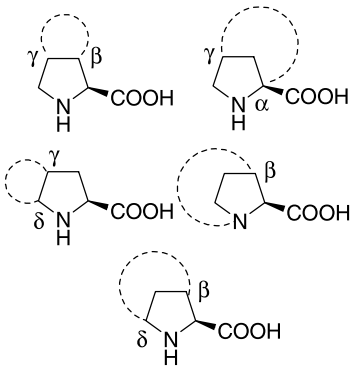

Fig. 1

ring junctions at different positions of the proline ring, as shown in Fig. 1.

Numerous examples account for the β/γ-ring junction at the proline nucleus, and bicycles varying in the ring-size and the nature of the second cycle have been reported. 3,4-Methanoproline (3-aza-bicyclo[3.1.0]hexane-2-carboxylic acid), has been found to be a potent inhibitor of the proline metabolism, and several syntheses of racemic and enantiomerically pure 3,4-methanoproline have been developed. Also, numerous synthetic analogs of 3,4-methanoproline have attracted considerable attention as pharmaceutically relevant compounds and conformationally constrained scaffolds for peptide chemistry (Fig. 2).

Brackmann et al. (2006) recently reported on a synthetic strategy towards the development of orthogonally Fmoc/Boc-protected enantiopure 3,4-(aminomethano)-proline with the aim of providing a new interesting scaffold for peptide chemistry, able to work both as an α-, or γ-amino acid, depending on the protecting group strategy. The synthetic path (Fig. 3) started from Gardner's alde-

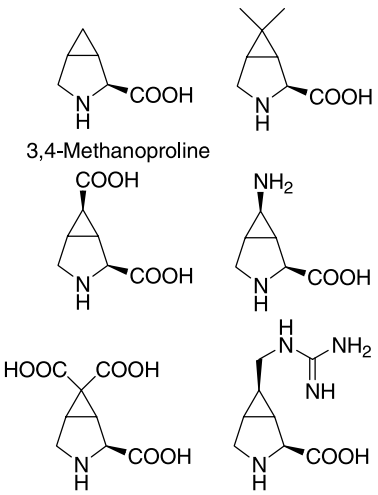

Fig. 2

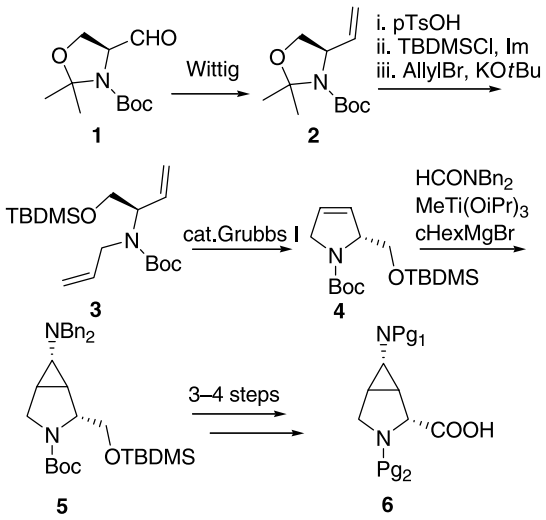

Fig. 3

hyde **1**, readily obtainable from serine in 4 to 5 steps, which was converted into protected *N*-allylvinylglycinol **3**, and successively allowed to cyclize by means of ring closing metathesis using Grubbs'catalyst. Finally, titanium-mediated aminocyclopropanation of the resulting protected 3,4-dehydro-prolinol **4** provided the corresponding protected 3,4-(aminomethano)prolinol **5** as a substrate for further manipulations to achieve the bicyclic α-/γ-diamino acids of general formula **6**, orthogonally protected with Fmoc- and Boc-groups in the two possible ways.

The catalytic Pauson-Khand reaction was applied for the stereoselective synthesis of a racemic cyclopenta[c]-proline derivative **10** (Jiang and Xu, 2002). The strategy consisted in the synthesis of 1,6-enyne amino ester **9** by the reaction of alkenylboronic acid **7** with propargylamine **8** and glyoxylic acid, followed by $Co_2(CO)_8$-catalyzed Pauson-Khand reaction to access the corresponding bicyclic system **10** (Fig. 4).

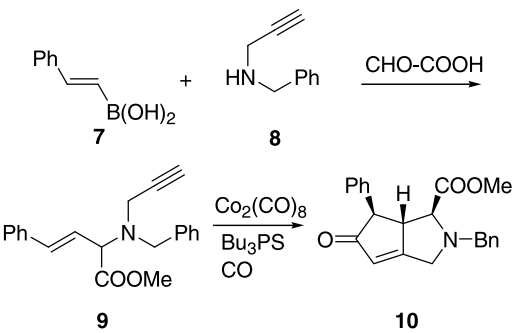

Fig. 4

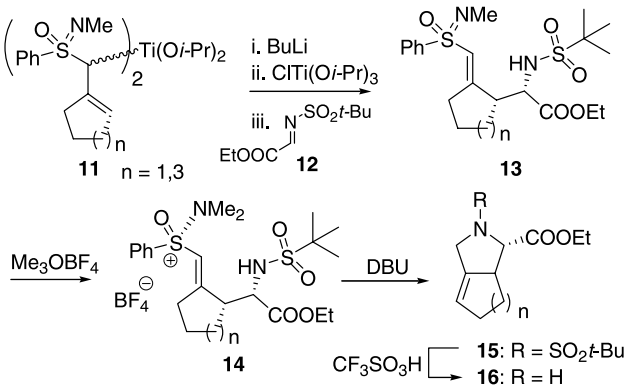

Fig. 5

A similar cyclopentaproline-based bicyclic system **15** has been reported by Koep et al. (2003) which was prepared by an asymmetric synthesis starting from cyclic bis(allylsulfoximine)titanium complexes of general formula **11** and *N*-*t*-butylsulfonyl imino ethyl ester **12**. Regio- and diastereoselective amino alkylation of **11** with **12** gave the intermediate adduct **13** that was *N*-methylated with Me_3OBF_4, followed by migratory cyclization of the resulting salt **14**, to give access to both protected bicyclo[3.3.0]- and bicyclo[5.3.0]amino acid structures of general formula **15** (Fig. 5).

Jeannotte and Lubell (2004) reported a method for the synthesis of fused pyrroloprolines **19** through the aldol condensation of a 4-oxoproline derivative **17** with several Boc-α-amino aldehydes followed by acid catalyzed cyclization (Fig. 6). An additional, but less successful method required allylation of the oxoproline, followed by Wacker oxidation to give the corresponding 1,4-dione, which was converted to mixture of pyrrolopyrrole and pyrroloproline in varying amounts (figure not shown). Also, selective deprotection of pyrrole nitrogen and subsequent alkyl-

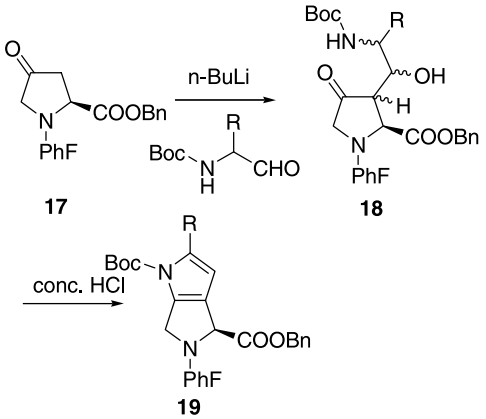

Fig. 6

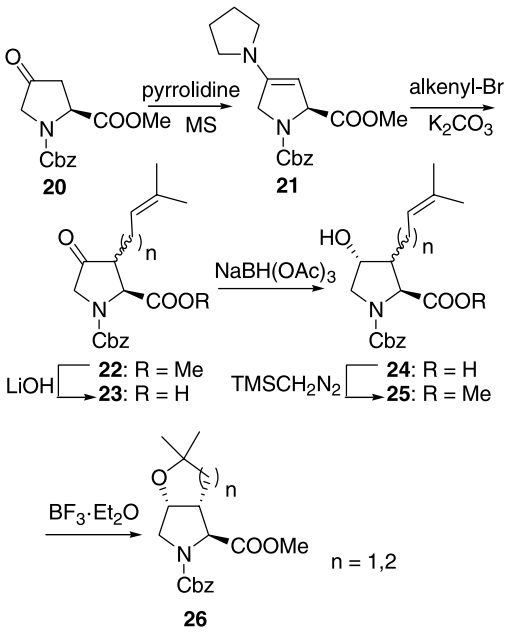

Fig. 7

ation was explored so as to expand the chemical diversity of the new amino acid structure.

The preparation of 3,4-fused tetrahydropyran and tetrahydrofuran prolines has been achieved from ketone **20** through alkylation with prenyl or methallyl bromide of the preformed enamine **21** with pyrrolidine, followed by stereoselective reduction of the keto group of **23** and final Lewis acid mediated cyclization of **25** to give the title bicyclic structure **26** (Fig. 7) (Liu et al., 2004). Interestingly, the authors reported a marked stereoselectivity of the reduction with $NaBH(OAc)_3$ when it was carried out on the molecule having the free COOH, due to the coordination of the borohydride species, thus leading to an asymmetric attack to the keto group.

The well-known 2,4-methanoproline (or 2-aza-bicyclo[2.1.1]hexane-1-carboxylic acid) can be accounted as an example of ring junction at α- and γ-carbon of proline, and several syntheses to achieve this interesting natural product have been reported over the years. Recently, analogues of 2,4-methanoproline have been achieved from an intramolecular ring closure of the four-membered-ring amino acid **31** (Fig. 8). Specifically, 3-(benzyloxymethyl)-cyclobutanone **29** was converted in the corresponding diastereomeric mixture of hydantoins by reaction with KCN and ammonium carbonate, which were separated by fractional crystallization to give **30**, and successively hydrolyzed to the 3-(bromomethyl)cyclobutanyl amino acid **31** as the precursor for the bicyclic 2,4-methanoproline **32** (Rammeloo and Stevens, 2002).

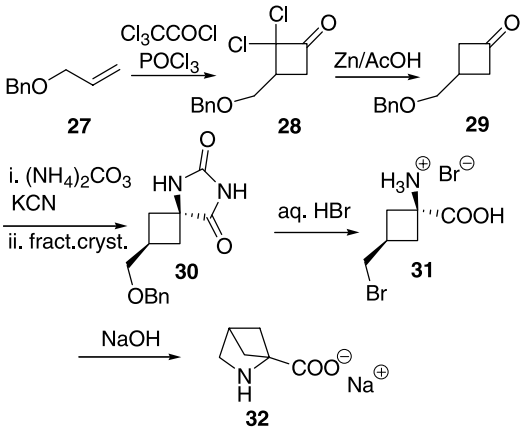

Fig. 8

The same authors also reported an improved synthesis of 3-(chloromethyl)cyclobutanone **33**, and an additional method to give *N*-alkylated analogues **35** from imine **34** through HCN addition, followed by conversion of the nitrile group to COOH by HBr, and final cyclization in aqueous NaOH to give racemic bicyclic **37** (Fig. 9) (Rammeloo et al., 2002).

A similar strategy was applied for the synthesis of 2,4-methanoproline homologues (Grygorenko et al., 2006). Specifically, 3-(chloromethyl)cycloalkanones **38**, **40** and **42** were converted to the corresponding imines and subjected to tandem cyanide addition – intramolecular cyclization to achieve the resultant homologues **39**, **41** and **43** after Pd-catalyzed hydrogenolysis, as shown in Fig. 10.

As an effort to synthesize the putative aeruginosin EI461 peptide, which is of interest as a naturally occurring protease inhibitor, Valls et al. (2001) reported a new bicyclic prolines **46**–**49** with a cyclohexanone ring fused at the γ- and δ-carbons, which was prepared starting from tyrosine. Specifically, the dihydroanisole **45** resulting from Birch reduction of *O*-methyl-tyrosine **44** with lithium in ammonia and ethanol, was treated with 3N HCl to give

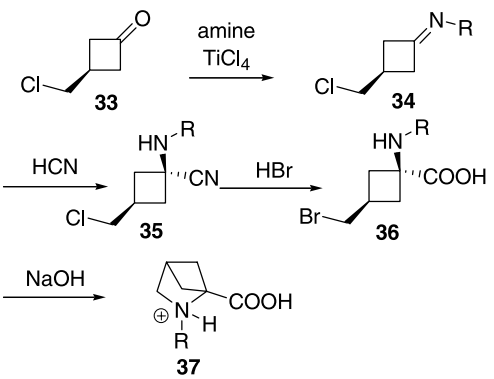

Fig. 9

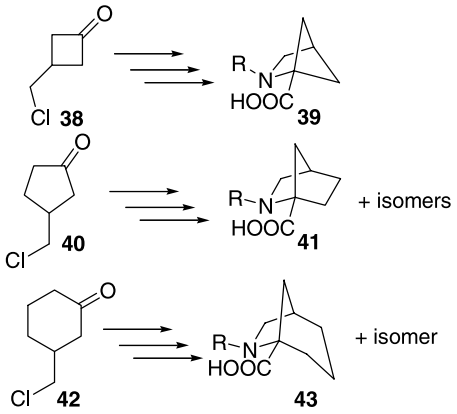

Fig. 10

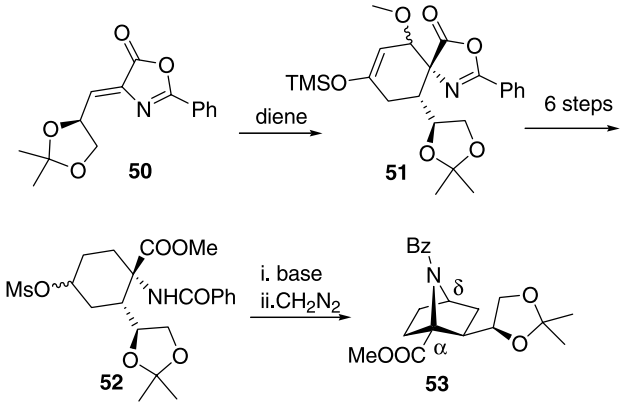

Fig. 12

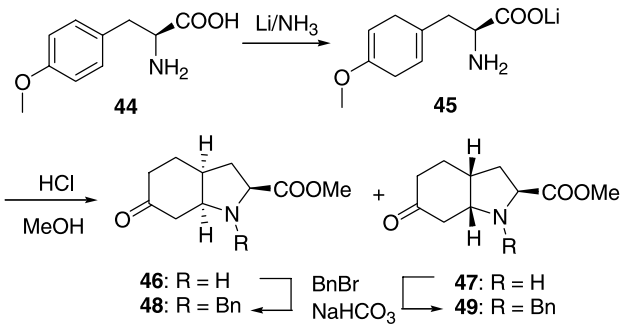

Fig. 11

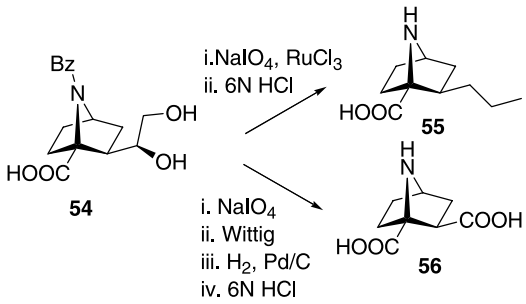

Fig. 13

the corresponding bicyclic *cis*-fused compounds **46** and **47**, which were successively benzylated to the 1:1 mixture of **48** and **49** (Fig. 11).

The structural diversity of bicyclic prolines by ring junction at α- and δ-carbons gives access to molecular structures with the bridgehead nitrogen atom (7-aza-bicyclo[2.2.1]heptane-1-carboxylic acid). Buñuel et al. (2001) described the application of asymmetric Diels-Alder cycloaddition of Danishefsky's diene with a chiral oxazolone **50** derived from protected (*R*)-glyceraldehyde to give the cyclohexane intermediate **51**, which upon cyclization gave the corresponding 7-aza-bicyclo[2.2.1]-heptane-based proline analogue **53** (Fig. 12). The intermediate oxazolone **50** could be obtained easily from reaction of benzoyl-glycine with protected glyceraldehyde, which was successively reacted with the diene to provide the spiranic system **51**. Subsequent elaboration of the keto group afforded the corresponding mesylate **52**, which upon treatment with either NaH or *t*-BuOK gave the title bicyclic α-amino acid **53**.

Also, the authors reported interesting manipulations of the dioxolane ring of **54**, i.e., diol oxidation to either aldehyde or carboxylic acid moiety, to provide after subsequent elaborations the β-alkyl or α/β-dicarboxylic acid species **55** and **56** as norleucine and aspartic acid isosteres, respectively (Fig. 13).

The same research group recently reported the functionalization of the γ-carbon of the 7-aza-bicyclo[2.2.1]heptane system so as to provide chemical diversity at the β-substituent of the amino acid, which has been reported to induce stable type-I β-turn conformations in minimal model peptides (Gil et al., 2005). Specifically, the achievement of the aldehyde coming from the diol moiety oxidation gave access to the insertion of a hydroxymethyl group, which after transformation to a better leaving group was treated with a variety of nucleophiles. Particularly interesting is the introduction of the azido group in **57**, which was successively converted in a pool of additional functional groups, namely amino-, nitro-, carbamate-, and triazolyl-substituted compounds **58**, **59**, **60**, and **61**, respectively, useful for expanding the chemical diversity (Fig. 14).

As regarding to fused β/δ-bicyclic proline analogues, a recent paper reported a multigram synthesis of enantiopure 2-aza-bicyclo[2.2.1]heptane-3-carboxylic acid **66**, which is of interest in peptide chemistry and in the design of chiral ligands used in asymmetric catalysis (Tararov

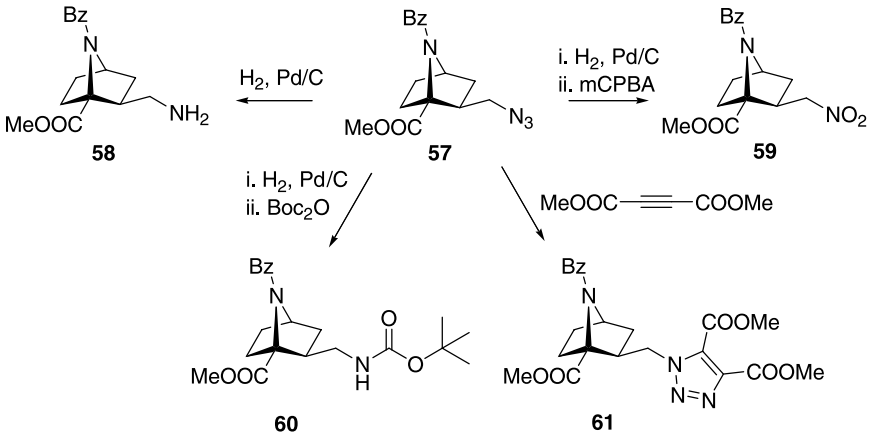

Fig. 14

et al., 2002). The asymmetric synthesis was achieved via stereoselective hetero Diels-Alder cycloaddition of cyclopentadiene with imine **62** deriving from ethyl glyoxylate and (*R*)-phenylethylamine, followed by hydrogenolysis of the double bond of **63** and of the phenylethyl group of **64**, to give **65** without using any chromatographic purification and in an overall yield of about 40% (Fig. 15).

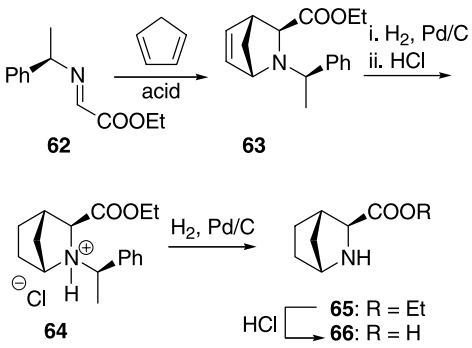

Fig. 15

Finally, bicyclic tertiary α-amino acids (or 1-aza-bicyclo[2.2.1]heptane-2-carboxylic acid and 1-aza-bicyclo[2.2.1]heptane-7-carboxylic acid) have been conceived by tethering the nitrogen atom with the β-carbon, thus resulting in constrained structures with interesting properties as neuronal nicotinic receptor ligands (Strachan et al., 2006). The synthetic procedure for **73** and **77** consisted in alkylation of glycine-derived imine **70** or nitroacetate **67** with pyran electrophiles, followed by acid-mediated opening and subsequent cyclization in ammonium hydroxyde to give the desired bicyclic compounds **73** and **77** as

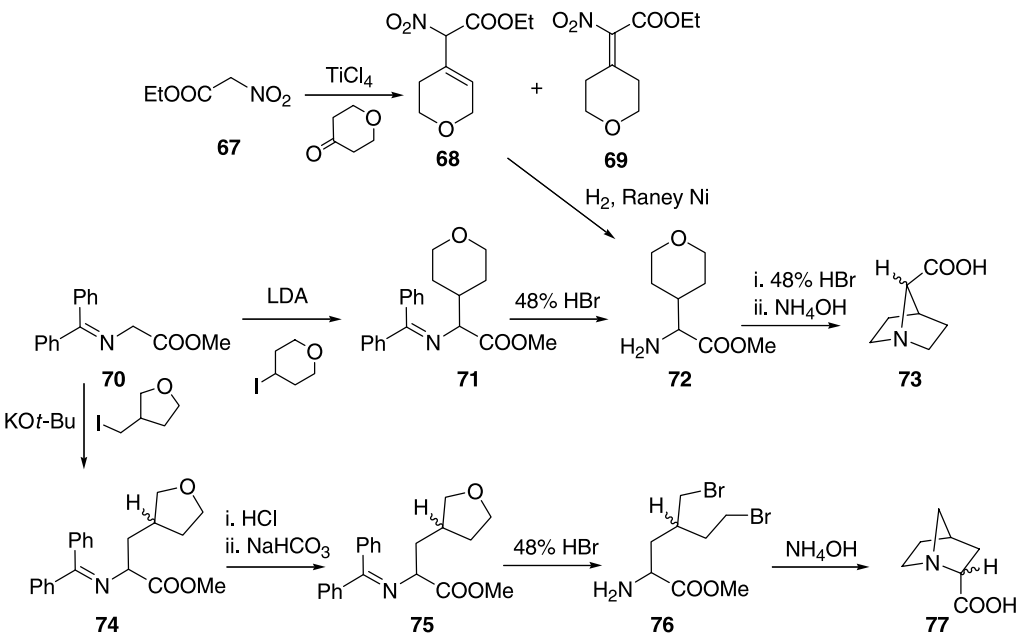

Fig. 16

racemates (Fig. 16). In the case of nitroacetate as precursor, the corresponding adduct **68** was converted to **72** by reduction with hydrogen and Raney Ni.

Pipecolic-based bicyclic α-amino acids

The pipecolic nucleus has attracted the attention of organic and peptide chemists in analogy with proline, as it proved to act as a valuable structural member of important bioactive compounds, and also it has been demonstrated to play a key role in the conformational preferences of peptides containing such structure. Thus, the synthesis of functionalized analogues of pipecolic acid is ever active, and also structures bearing the six-membered ring nucleus have been also reported. Czombos et al. (2000) reported a complete strategic approach toward the synthesis of tricyclic α-amino acids having both the cyclopropane and pipecolic acid structures embedded in the proposed molecules (Fig. 17). These compounds were reported as constrained phenylalanine analogues, expecially relating to tetrahydroisoquinoline-based amino acids. The synthesis of **81** consisted in the cyclopropanation via dimethylsulfoxonium methylide of *N*- and *O*-protected 1,2-dihydroisoquinoline derivative **80**, which in turn was achieved via the Wittig reaction of the phosphorus ylide **78** with *N*-alkoxycarbonyloxamates **79**, and subsequent ring closure to achieve **81** (Fig. 17).

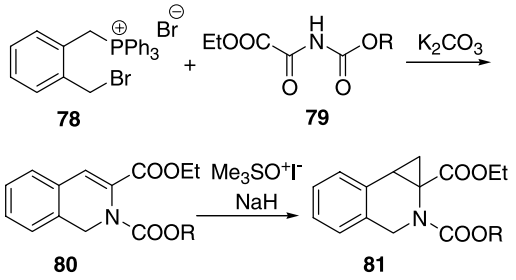

Fig. 17

Pipecolic-based bicyclic α-amino acids having a hexahydro-cyclopenta[c]pyridine structure **86** were reported as a result of selective allylation of protected imino ester with bis(allylsulfoximine)titanium complexes, followed by propargylation of the nitrogen atom of **82** to give the corresponding enynes **83**. Successively, the resulting γ,δ-unsaturated-α-amino esters were converted to the corresponding cobalt complexes **84**, and subjected to diastereoselective Pauson-Khand cycloaddition to give the sulfonimidoyl-free bicyclic amino acids **85** (Fig. 18) (Günter and Gais, 2003).

Also, a similar bicyclic system **90** was developed recently in a combinatorial approach, using fluorus mixture synthesis towards the preparation of 4-(alkylidene)cyclopentenones having the pipecolic nucleus within the heterobicyclic structure (Manku and Curran, 2005). Specifically, Curran and Manku described the development of a library of 4-alkylidene cyclopentenones by conversion of a mixture of different α-amino acids differently tagged with fluorus benzyl carbamates to the corresponding propargyl esters **87**, which were successively subjected to an ester-enolate Claisen rearrangement to give a mixture of allenic amino esters **88** (Fig. 19). The subsequent alkynyl allenes **89** were obtained by reaction with propargyl bromide, and reacted under formal Pauson Khand [2 + 2 + 1] cycloaddition with CO and catalytic $[Rh(CO)_2Cl]_2$ to give the final 4-alkylidene cyclopentenones **90**, which were finally separated by fluorus HPLC and amine deprotected.

Saturated *cis*- and *trans*-fused bicyclic α-amino acids as conformationally restricted analogues of pipecolic acids were described by Hattori and Grossman (2003) as a result of double Michael reaction of a tethered diacid and *p*-anisyl ethynyl ketone, followed by cyclization via manipulation of the cyano group and oxidation of the *p*-anisyl group. Also, the substitution level was modulated by decyanation or decarboethoxylation of the intermediates. As an example, double Michael reaction of tethered di-

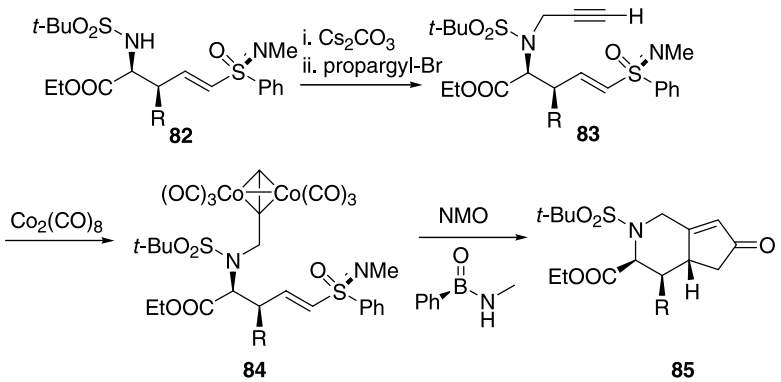

Fig. 18

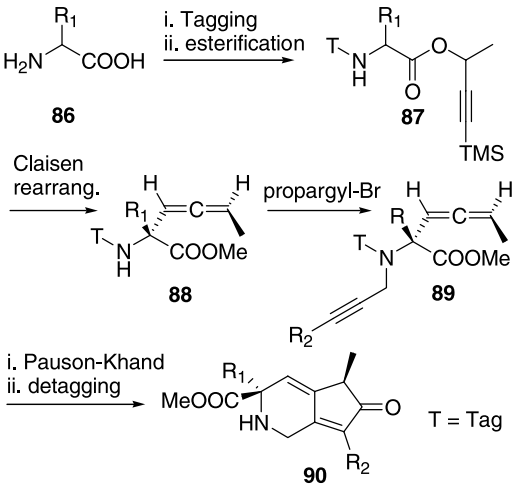

Fig. 19

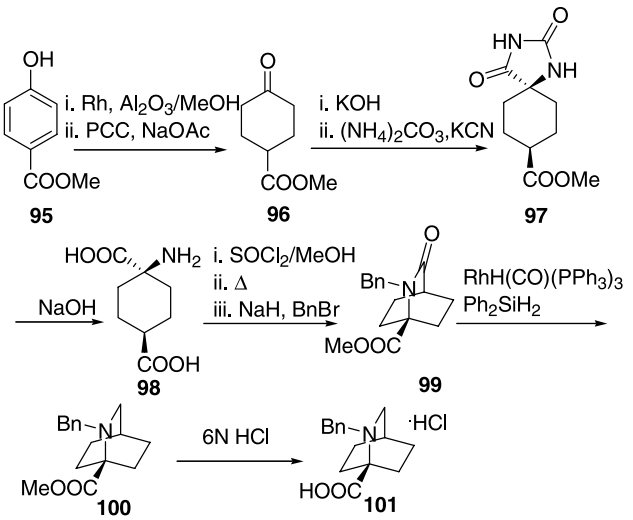

Fig. 21

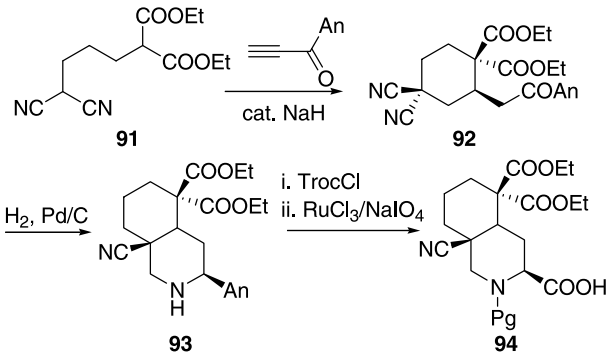

Fig. 20

acid **91** gave the substituted cyclohexane **92**, followed by hydrogenation over Pd/C to achieve the perhydroisoquinolinic system **93**. The corresponding bicyclic α-amino acid **94** was successively obtained by amine protection with Troc group and subsequent oxidation of the anisyl moiety to the COOH group (Fig. 20).

Casabona and Cativiela (2006) reported the synthesis of a constrained bicyclic pipecolic analogue **101** starting from cheap and readily available compounds. Reduction of the aromatic ring of methyl 4-hydroxybenzoate **95** provided the corresponding cyclohexanone **96**, which was subjected to the Bucherer-Bergs reaction with ammonium carbonate and KCN to give the spiranic hydantoin **97**, successively converted to the α-amino acid **98** by hydrolysis with NaOH (Fig. 21). Notably, hydantoin formation under the reported conditions gave predominantly the *cis* stereoisomer **98** as a consequence of steric hyndrance of the carbomethoxy group at position 4 of the cyclohexane ring. In order to access the bicyclic system, the carboxylic groups were esterified, to allow the intramolecular amide bond formation by heating at high temperatures for few minutes to give **99**. Finally, the best method for the chemoselective reduction of the amidic carbonyl group in the presence of the methyl ester was achieved by *N*-benzylation followed by treatment with diphenylsilane as reducing agent and $RhH(CO)(PPh_3)_3$ as catalyst. Final acidic hydrolysis provided the title bicyclic amino acid **101**.

Among interesting applications of pipecolic-based bicyclic amino acids, Dyatkin et al. (2004) reported on aza-bicyclic amino acid sulfonamides **102** as $\alpha_4\beta_1/\alpha_4\beta_7$ integrin antagonists (Fig. 22). The authors demonstrated the suitability of the aza-bicyclo[2.2.2]octane scaffold by conformational analysis of the targets containing a selected ligand of this class of bicyclic structures.

Also, the same authors successively reported further data on the same topic investigating the effect of the functional group at the nitrogen atom of the bicyclic structure over biological activity, thus resulting in low nanomolar inhibitors having such atom functionalized as an amido group (Dyatkin et al., 2005).

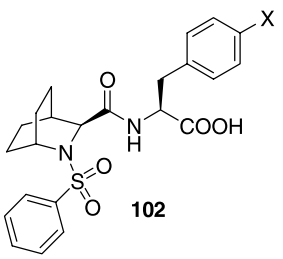

Fig. 22

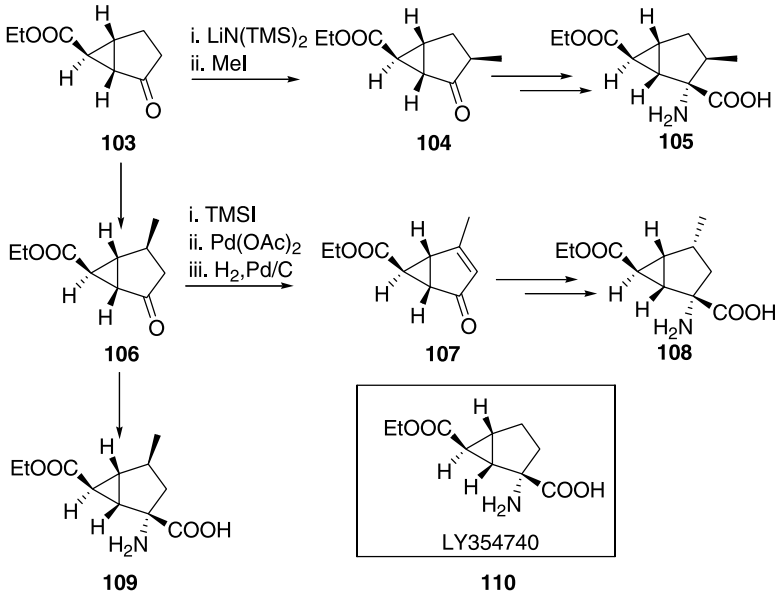

Fig. 23

α,α-Disubstituted bicyclic α-amino acids

Amino acids in this class are based on the structure of compound LY354740 **110** (Fig. 23), a highly potent and selective agonist of metabotropic glutamate (mGlu) receptors 2 and 3. Due to the pharmacological interest of this compound, further modifications of the original structure have been carried out by researchers of Eli Lilly & C. (Dominguez et al., 2005). The synthesis started from methylation of the enolate of **103**, followed by conversion of the keto group to the α-carbon bearing the amino and carboxylic groups of **105** via hydantoin formation. The C_4-methyl-substitued variants **109** could also be obtained via **106**, which by formation of unsaturated **107** gave rise to **108** having the C_4 stereocenter with inverted configuration relatively to **109**.

Compounds **113** and **114**, envisioned as conformationally constrained homologues of glutamic acid, were obtained by Conti et al. (2003) via 1,3-dipolar cycloaddition of ethoxycarbonylformonitrile oxide **112** to the mixture of stereoisomeric protected 1-amino-cyclopent-3-enecarboxylic acid **111** (Fig. 24). The fully deprotected derivatives of **113** and **114** were tested towards glutamate receptor subtypes, indicating compound **114** as a potent antagonist at the NMDA receptor, whereas compound **113** did not show any biological activity towards any ionotropic glutamate receptors.

Finally, conformationally constrained α,α-disubstituted α-amino acids **117** and **118**, having two aryl moieties embedded in the scaffold were obtained from regioselective Diels-Alder reactions of 2-acetamidoacrylates **115** and 9-substituted anthracenes **116** (Yang and Doweyko, 2005). The use of nitrobenzene under termal and of DMF under microwave conditions resulted in improved yields and enhanced *meta*-regioselectivity (Fig. 25).

Our contribution to the sub-class of bicyclic α-amino acids has been focused on the synthesis of 6,8-dioxa-3-

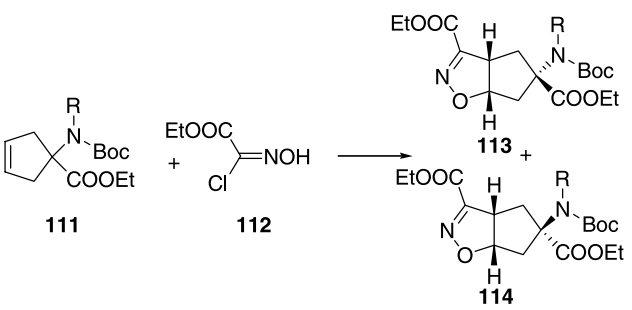

Fig. 24

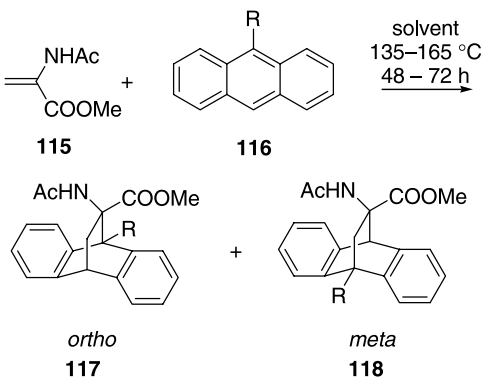

Fig. 25

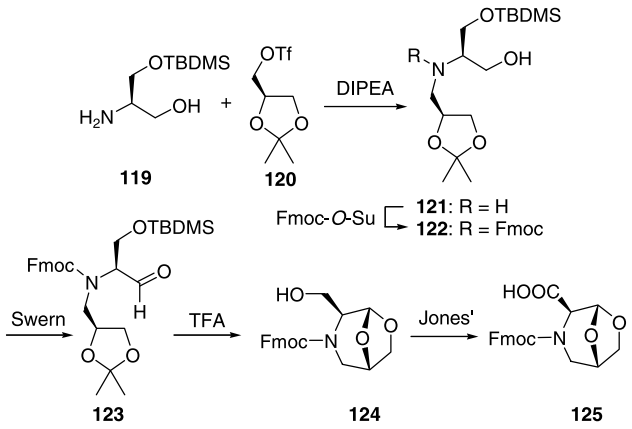

Fig. 26

azabicyclo[3.2.1]octane-based α-amino acids. Depending on the choice of building blocks from the chiral pool, it was achieved the preparation of bicyclic proline analogues having the carboxylic function at position 4 or 2 of the scaffold. Specifically, by reacting serine and glyceraldehyde derivatives **119** and **120**, respectively, it was obtained the 4-carboxy-6,8-dioxa-3-azabicyclo[3.2.1]octane acid **125** in five steps, as shown in Fig. 26 (Trabocchi et al., 2003). Coupling of isopropylidene-glycerol triflate **120** with *O*-TBDMS-serinol **119** afforded the adduct **121**, which, after Fmoc protection and oxidation to the intermediate aldehyde **123**, was treated with neat TFA to afford the title scaffold **124** having the free hydroxymethyl group. Final Jones' oxidation gave the bicyclic α-amino acid **125**.

We prepared also the parent isomer **131**, having the carboxylic function at position 2 by reaction of glycinal **128** protected as dimethylacetal and the ascorbic acid derivative **126**, according to Fig. 27 (Lalli et al., 2006). Subsequent *N*-Fmoc protection and acid cyclization in neat TFA gave directly the bicyclic compound **131** as free acid, as a consequence of assisted conversion of the intermediate carboxylate to the corresponding carboxylic acid. The two amino acids, as well as showing differences in the substitution pattern, allowed to have in hands the carboxylic function both in *exo* and *endo* configuration with respect to the bicyclic scaffold, thus enabling further applications as constrained isosteres of secondary amino acids in peptidomimetic chemistry.

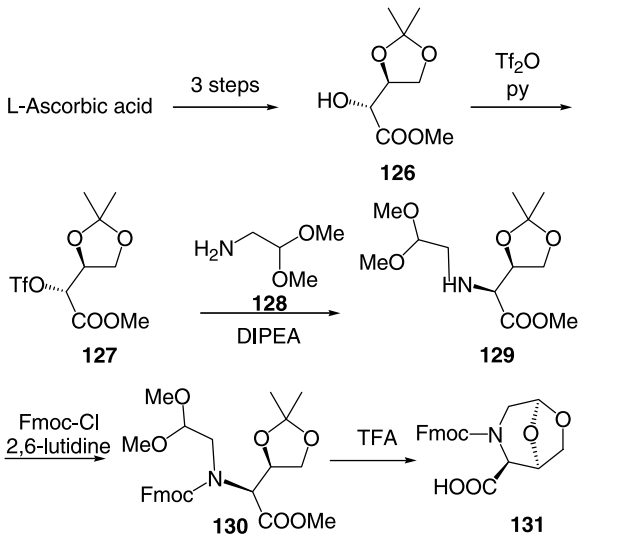

Fig. 27

Bicyclic β-amino acids

As regarding to β-amino acids possessing a bicyclic scaffold, relevant examples can be grouped mainly into [x.y.0] and [x.y.1] sub-classes.

Bicyclo[x.y.0]scaffolds

Recently, the ring-rearrangement methatesis (RRM) has been proposed to obtain bicyclic α- and β-amino acids starting from norbornene and oxabornene systems (Maechling et al., 2006). According to Fig. 28, the synthetic procedure consisted in amine protection of **132** and **135** via tosylation, followed by alkylation with either propargyl or allyl bromide, followed by RRM of the intermediates **133** and **136**. The reactions to give [4.3.0]-bicyclic α- and β-amino acids proceeded in fair yield, with the exception of **137**, which required higher catalyst load and ethylene pressure. Also, the authors reported the achievement of cyclic peptide sulfonamides by changing the type of catalyst, thus allowing an entry to this class of molecules.

A cispentacin-derived bicyclic β-amino acid was incorporated into the GnRH (gonadotropin releasing hormone) sequence as a turn inducer (Fig. 29) (Langer et al., 2002). The authors reported the synthesis of the amino acid and the conformational analysis by NMR and computational

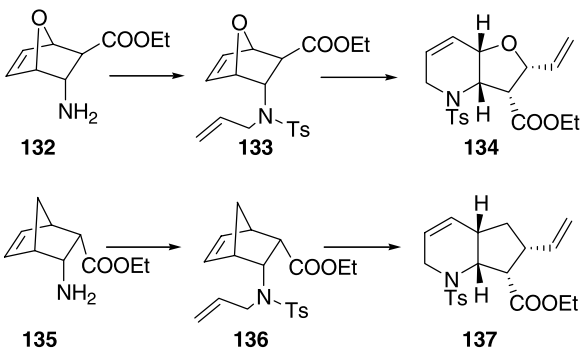

Fig. 28

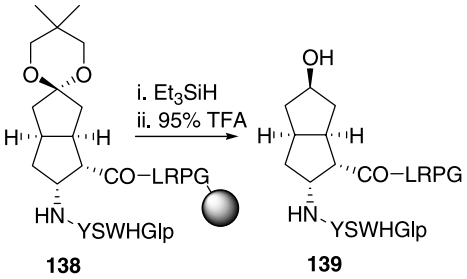

Fig. 29

methods of the GnRH analogue **139** containing such bicyclic scaffold, suggesting the presence of a β-turn conformation similar to the native bioactive peptide hormone. Moreover, the modified peptide **139** showed a biological activity as an agonist with respect to the human GnRH receptor, with comparable potency as the natural peptidic hormone. Of particular interest is the reduction of the carbonyl group of resin-bound **138** to hydroxylic function on solid-phase with complete stereoselectivity, followed by cleavage from the resin to achieve the final GnRH analogue **139** (Fig. 29).

Bicyclo[x.y.1]scaffolds

Huet et al. reported a new synthetic method for the preparation of scaffolds having a 2-aza-bicyclo[2.1.1]hexane structure (Lescop et al., 2001), which consisted in the cyclization with NaH of 2-bromo-1-phenylselenylcyclobutane derivative **140**. Further manipulations of the bicyclic diamine **141**, whose key step consisted in the conversion of the primary amino group to a hydroxy function, allowed to achieve the β-isomer of 2,4-methanoproline **145** (Fig. 30).

More recently, Basso et al. (2005) described the synthesis of 7-oxabicyclo[2.2.1]-based β-amino acids, which

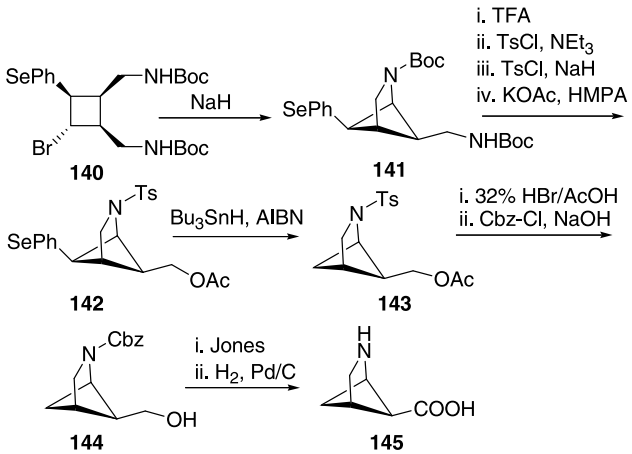

Fig. 30

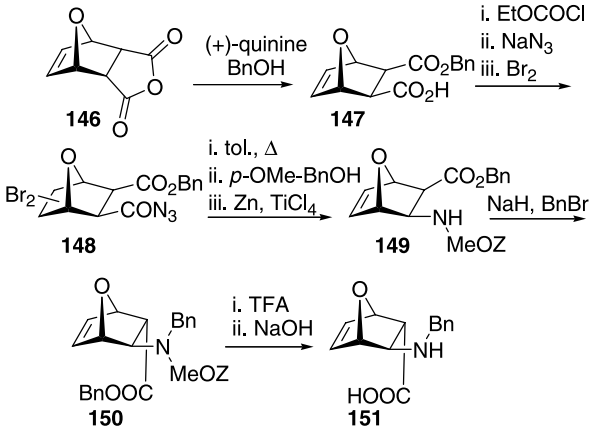

Fig. 31

were used as turn mimetics and as chiral auxiliary for an intramolecular Ugi four-component synthesis of α-amino acids. The preparation of the bicyclic amino acid **151** started from the amine-mediated asymmetrization of *meso* anhydride **146**, followed by Curtius rearrangement of the corresponding acyl azide **148**, epimerization of the vicinal C–H stereocenter, and subsequent *N*-benzylation and deprotection of **149** (Fig. 31).

Carbocyclic structure **155**, having the amino and carboxylic group oriented in *endo* and *exo* positions, respectively, was applied for the synthesis of VLA-4 integrin antagonists by coupling the amino group to *N*-arylsulfonyl proline residues (Chang et al., 2007). The synthesis of the bicyclic template **155** was achieved by Diels-Alder cycloaddition of methyl (*E*)-3-nitroacrylate **152** with cyclopentadiene to provide the corresponding adducts **153** and **154** in 6:1 ratio. Subsequent double bond hydrogenation afforded the bicyclic amino acid **155**, which was further elaborated to give the selective VLA-4 receptor antagonist **156** with an $IC_{50} = 54$ nM (Fig. 32).

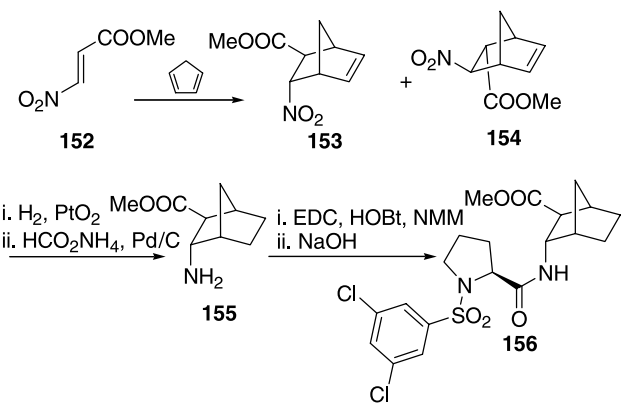

Fig. 32

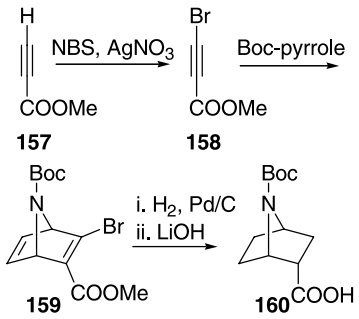

Fig. 33

The 7-azabicyclo[2.2.1]heptane-3-carboxylic acid skeleton has been reported for the construction of β-amino acids oligomers taking into advantage of the *cis*/*trans* isomerism of the non-planar amide bonds (Otani et al., 2006). Synthesis of the *endo*-bicyclic β-amino acid **160** consisted in bromination of methyl propargylate **157**, followed by cycloaddition with Boc-pyrrole and subsequent hydrogenation of **159** to obtain the title scaffold (Fig. 33). The racemic resolution was achieved by repeated recrystallizations of the derivatives resulting by reaction of the COOH group of **160** with Oppolzer's camphorsultam as chiral auxiliary.

Alcaide and Sáez (2005) reported a convenient regio- and stereoselective route to fused tricyclic β-lactams, which were obtained by intramolecular nitrone-alkene cycloaddition reactions of 2-azetidinones carrying both the formyl and alkenyl groups. The polycyclic scaffolds were further elaborated to achieve polyfunctional compounds such as carbacepham derivatives and different types of bicyclic β-amino acids (Fig. 34).

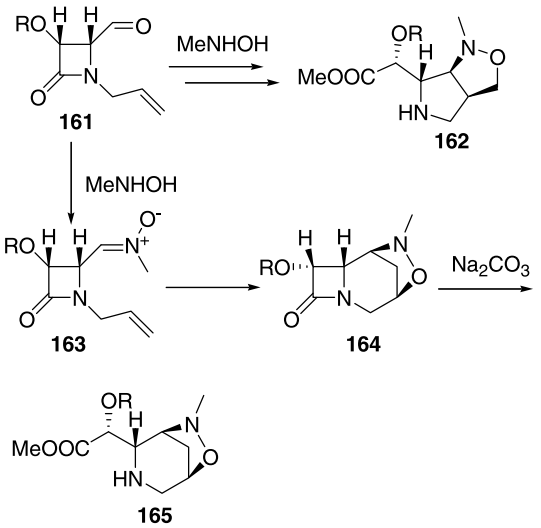

Fig. 34

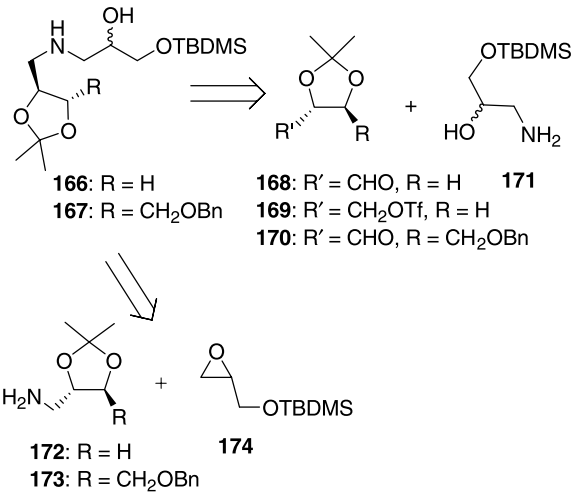

Fig. 35

According to the general class of 6,8-dioxa-3-aza-bicyclo[3.2.1]octanes, entries to the class of β-amino acids consisted in the synthesis of bicyclic scaffolds as depicted in Fig. 36 (Danieli et al., 2005), which where obtained from coupling of sugar derivatives and β-amino alcohols deriving from ring-opening of glycidyl derivatives (Fig. 35). Two synthetic approaches for the preparation of the useful intermediates **166**, **167** where followed, consisting in the reaction of β-amino alcohol **171**, obtained from ring opening of glycydyl derivatives, with protected glyceraldehyde derivatives **168**–**170**, or in the ring opening of TBDMS-protected glycidol **174** with dioxolane-methanamine **172**, **173**, obtained from glyceraldehyde derivatives.

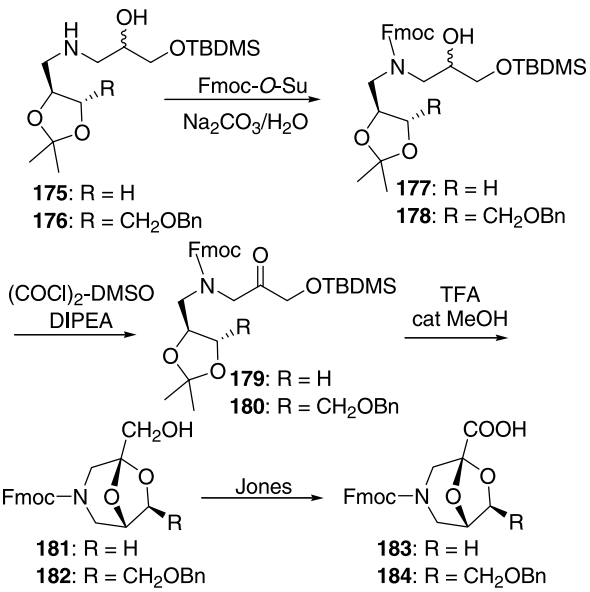

Fig. 36

Subsequent amine protection, oxidation to ketone **179**, and cyclization in TFA afforded the bicyclic template **181**, which upon Jones oxidation resulted in the corresponding bicyclic β-amino acid **183**. Also, using tetroses as a source for the sugar-based component, additional chemical diversity was introduced at position 7 to access compound **184**.

Bicyclic γ-amino acids

Bicyclo[x.y.0]scaffolds

The bicyclic pyrrolizidinone skeleton of **185** and **186** (Fig. 37) was obtained by 1,3-dipolar cycloaddition of the cyclic nitrone **188** and acrylamide **189** (Cordero et al., 2005). Two main products were obtained as racemic mixtures (**190** and **191**) and, after separation, they underwent the same synthetic route, here depicted for (±)-**190** only. The reductive cleavage/cyclization step was then followed by alcohol group transformation into the target γ-amino acid **185**.

The synthesis of enantiopure compound **185** was achieved by separation of diastereoisomeric intermediates obtained from (±)-**187** and containing (1*R*)-1-phenylethylamine as chiral auxiliary (Fig. 38).

These compounds were then coupled with natural α-amino acids to synthesize a model sequence that was used for conformational studies: NMR experiments revealed that **185a**, **185b** and (±)-**186** were effective VI β-turn mimetics. Different nitrones and acrylamides can be used, such as compounds **192**–**194** (Salvati et al., 2005) as starting materials, affording orthogonally protected and further substituted amino acids **195** and **196** (Fig. 39).

Bicyclic γ-amino acids already conjugated to sugar moiety were synthesized starting from the natural iridoid aucubin (Mouriès et al., 2003). The two glycosylated hydroxyl-compounds **198** and **199** were prepared by chiral pool synthesis in eight steps (Fig. 40).

Compound **197**, that already contains the amino group, was the key intermediate for the obtainment of both cyclopenta[*c*]pyran and cyclopenta[*c*]furan derivatives **198** and **199**, respectively. The introduction of the carboxylic group to give the former was achieved by formyl insertion on the double bond by means of Vilsmeier reaction followed by carbonyl oxidation, whereas **199** was obtained by oxidation of the dihydropyran double bond to a iodolactol, followed by first a rearrangement in alkaline medium and then the carbonyl oxidation. Finally, the two deprotection steps afforded the title compounds. The asymmetric synthesis of γ-amino acids from allyltitanium sulfoximines has been reported more recently (Köhler et al., 2007). This strategy was developed mainly to afford acyclic compounds, but an example of a bicyclic structure was also described (Fig. 41).

The titanation of the lithiated allylic sulfoximine, derived from **200** treated with *n*-BuLi, furnished the corresponding allyltitanium complex that reacted with furan-2-carbaldehyde, affording the homoallylic alcohol intermediate **201** (Fig. 41). The conversion of the latter into γ-amino acid **203** required a stereoselective insertion of the amino group on the double bond that was obtained by an intramolecular carbamate amination (**202**). Transformation of the intermediate **202** into the title bicyclic γ-amino acid **203** involved the oxidation of the furan ring and the substitution of the sulfoximine group by a carboxy group.

Bicyclo[x.y.1]scaffolds

This class is mainly represented by 6,8-dioxa-3-aza-bicyclo[3.2.1]octane-7-carboxylic acids **204** named Bicycles

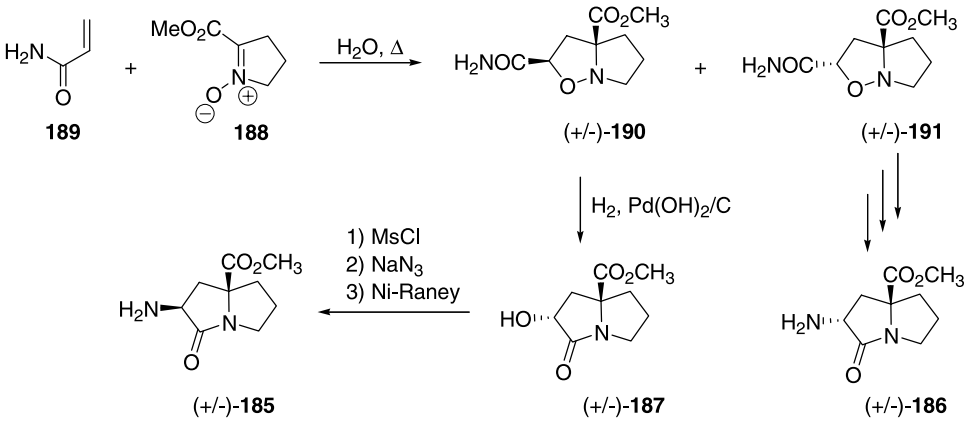

Fig. 37

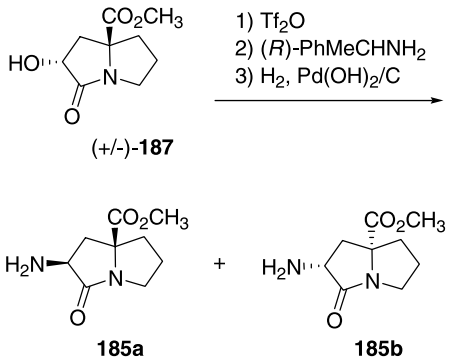

Fig. 38

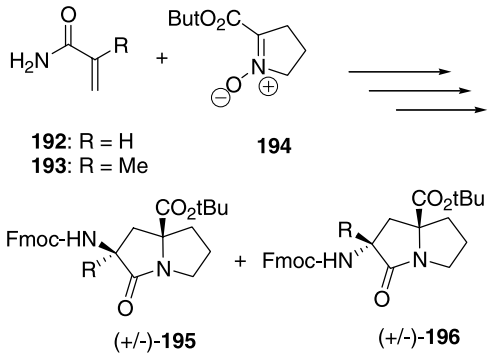

Fig. 39

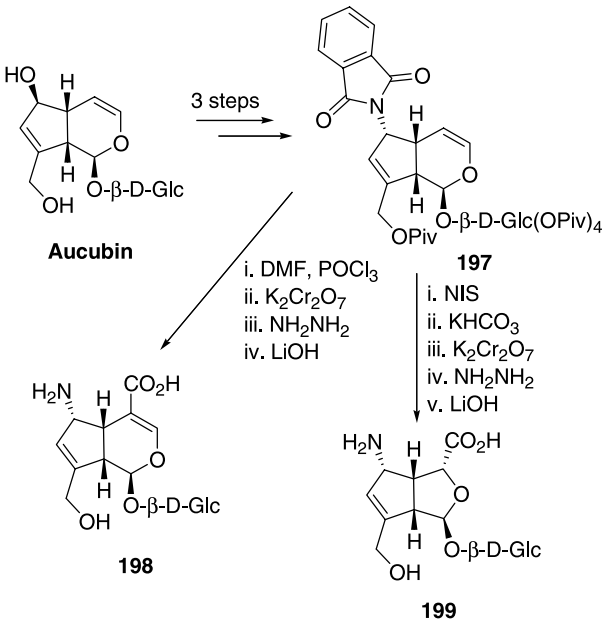

Fig. 40

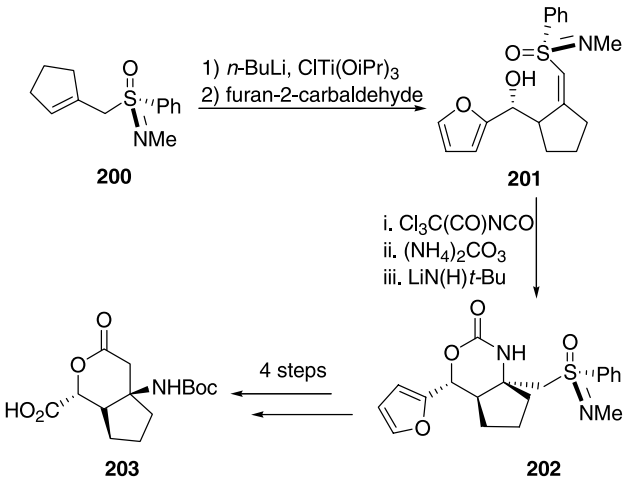

Fig. 41

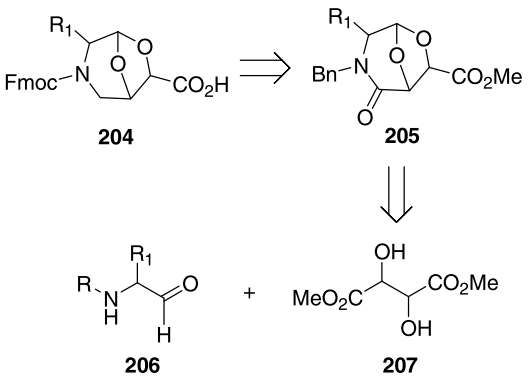

Fig. 42

from Tartaric acid and Amino acid (BTAa, Fig. 42) (Trabocchi et al., 2006), easily synthetizable from the condensation of α-amino aldehyde derivatives **206** with tartaric acid **207** or sugar derivatives in a stereoselective fashion (Trabocchi et al., 2003).

As an example, the synthesis of the L-phenylalanine derivative **213** is reported (Fig. 43).

Phenylalanine-derived alcohol **208** is coupled with L-tartaric acid monoester derivative **209** to give the corresponding amide **210**, that was oxidized at the primary alcohol group and cyclized in refluxing toluene to give **212**. Further manipulations of **212** afforded the Fmoc-amino acid **213**. The so obtained γ-amino acids proved to be compatible with solid phase synthesis techniques (Danieli et al., 2005) and could be incorporated in different peptide sequences, also as oligomers (Machetti et al., 2000). In particular, when the carbon atom bearing the carboxy group has an *endo* configuration, the compound can act as a dipeptide isostere reverse turn mimetic, mimicking the $i+1-i+2$ portion of a common β-turn (Fig. 44).

This was demonstrated by the introduction of a 7-*endo* BTAa in a cyclic Bowman Birk inhibitor (BBI) peptide (Scarpi et al., 2001), where the scaffold was able to main-

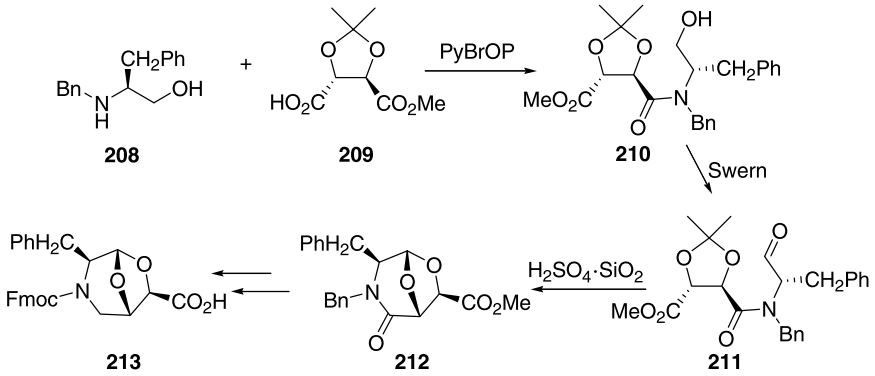

Fig. 43

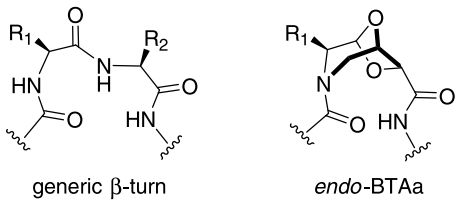

Fig. 44

tain the existing turn as Ile-Pro mimetic. Further conformational studies, performed on linear peptides containing leucine-derived BTAa (Trabocchi et al., 2002), confirmed the reverse turn inducing properties of these bicyclic γ-amino acids.

Bicyclic δ-amino acids

Many of the bicyclic δ-amino acids have been designed as dipeptide mimetic replacements of the $i+1$ and $i+2$ residues in β-turn systems. For this reason, attempts to correctly positioning the amino- and carboxyl-termini of the dipeptidomimetic unit resulted in an obligatory δ-amino acid, often incorporating an amide bond in the bicyclic backbone (Fig. 45).

Since the ring size can be varied by simple carbon atoms chain elongation by using the same synthetic strategy, herein the systematic classification of this class of compounds was based on their heterocyclic scaffolds.

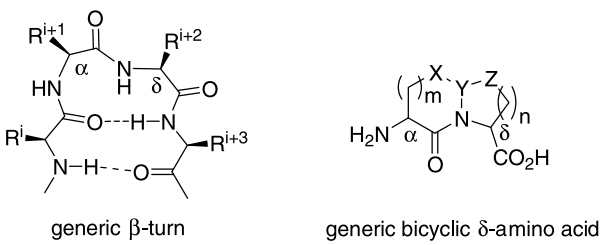

Fig. 45

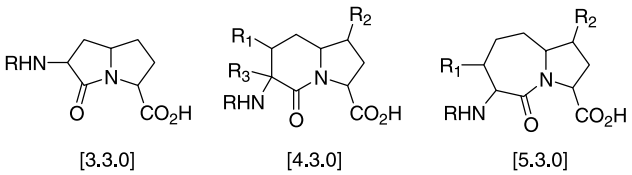

Fig. 46

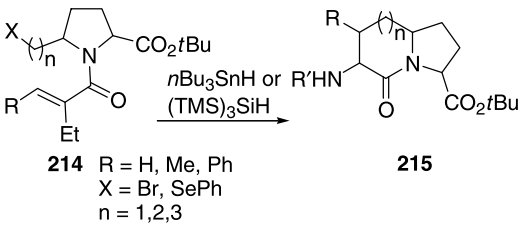

Fig. 47

Azabicycloalkanes

Most syntheses focused on proline-based bicyclic δ-aminoacids, that can be divided into numerous azabicyclo[x.3.0]alkane subclasses (see Fig. 46 for few examples).

In most cases the key step of the synthesis is the lactam ring formation that can be obtained by different approaches: the radical addition to an olefinic double bond (Fig. 47; Belvisi et al., 2004); alkylation of malonate enolate (Fig. 48A; Wang et al., 2002; Belvisi et al., 2004); ring closing metathesis (Fig. 48B; Belvisi et al., 2004); intramolecular alkylation followed by amidation and Hoffman rearrangement (Fig. 48C; Belvisi et al., 2004); aldol condensation (Bravin et al., 2004). Further functional groups at the α-position could be inserted on the final scaffold by alkylation under basic conditions (Manzoni et al., 2006).

Due to the chosen synthetic route, unsaturated bicyclic δ-amino acids are often obtained and then transformed into the saturated ones by stereoselective hydrogenation (Zhang et al., 2002). However, the unsaturated scaffold

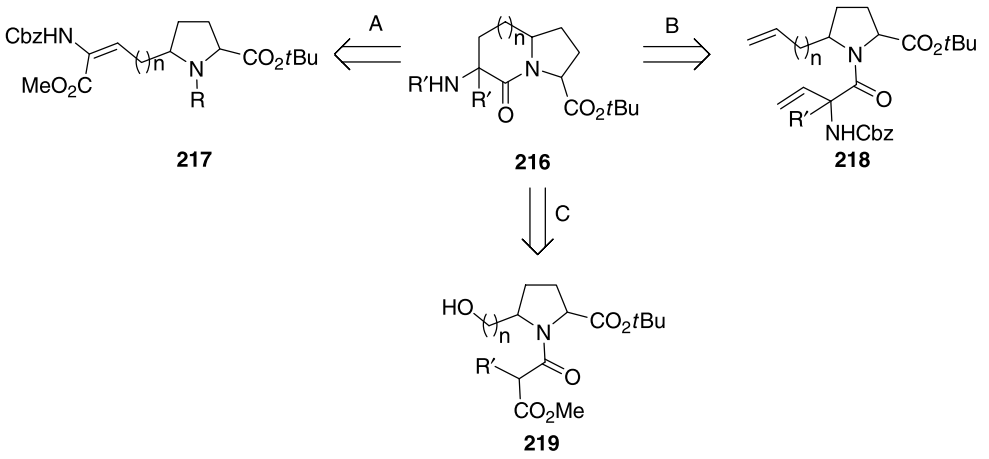

Fig. 48

can also act as a peptidomimetic (Millet et al., 2002) because of the presence of a double bond that increases the rigidity of the bicyclic structure.

Additional rigidity and diverse physical properties were obtained with the synthesis of bicyclic 2-pyridone structure **221** (Dragovich et al., 2002) that was obtained starting from 2-hydroxy-6-methylnicotinonitrile (**220**, Fig. 49). Key steps of the synthesis involved the osmium-catalyzed asymmetric dihydroxylation of an olefinic intermediate and its intramolecular cyclization.

Alternative routes for saturated azabicycloalkanes are represented by Eschenmoser condensation of *N*-benzyl thiolactam **222** (Fig. 50) and bromoester **223**, followed by hydrogenation and intramolecular cyclization. Final alkaline hydrolysis afforded the free amino acid **224** (Davies et al., 2003).

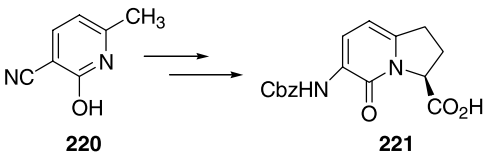

Fig. 49

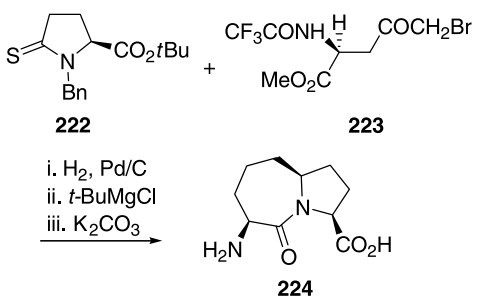

Fig. 50

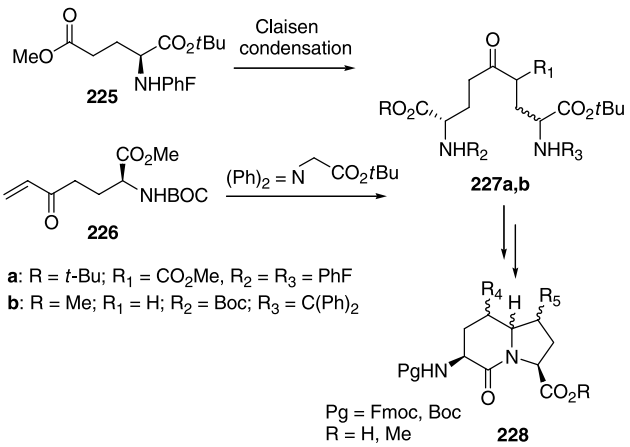

Fig. 51

The fused ring system can also be obtained starting from intermediate **227** that can be synthesized either via the Claisen self-condensation of γ-methyl α-*t*-butyl *N*-PhF-L-glutamate (**225**, Fig. 51; Polyak and Lubell, 2001; Ramana Rao et al., 2007) or via Michael addition of *N*-diphenylmethyleneglycine *t*-butyl ester on an acyclic γ-vinyl ketone (**226**; Mandal et al., 2005). The β-keto ester **227a** and the 5-oxo diaminoazelate **227b** underwent few reaction steps to afford the desired *N*-Boc-protected 2-amino ester **228**.

Ring closing metathesis, that was already successfully used for azabicyclo[5.3.0]alkanes (Belvisi et al., 2004), was further employed as key step for the synthesis of [4.3.0] (Hanessian et al., 2003), [6.3.0] (Duggan et al., 2005) and [7.3.0] analogous systems (Harris et al., 2003). Detailed conformational analysis by NMR, IR and molecular modelling techniques (Belvisi et al., 2000a), as well as applications in RGD-based cyclopeptides as $\alpha_v\beta_3$-

integrin ligands (Belvisi et al., 2000b; Belvisi et al., 2006) proved these compounds to act as reverse turn mimetics. A methodology based on click chemistry has also been developed to conjugate this class of scaffolds with fluorescent groups or biotin (Arosio et al., 2006). Furthermore, the introduction of azabicyclo[X.Y.0]alkanes into peptide sequences by solid phase synthesis on HMBA resin resulted in the achievement of two new agonists to the opioid receptor-like (ORP1) receptor (Halab et al., 2002).

Diazabicycloalkanes

Reported examples of amino acids belonging to this class possess a bridgehead nitrogen atom in the bicyclic backbone that can be assembled either by building one ring at a time or by forming both rings in the same synthetic step. In the first case, for example, α,α-dialkylated amino acid **229** (Fig. 52) was oxidized by ozonolysis to the corresponding aldehyde, whose cyclic hydrazone derivative was then reduced to the tetrahydropyridazinone **230**. Subsequent treatment of **230** with formaldehyde and an excess of ethyl acrylate afforded amino ester **231** by means of a 1,3-dipolar cycloaddition (Gardiner and Abell, 2003).

A different approach involved the synthesis of a dipeptide moiety and its cyclization. The proline derivative **232** (Fig. 53) was coupled with L-phenylalanine to obtain the

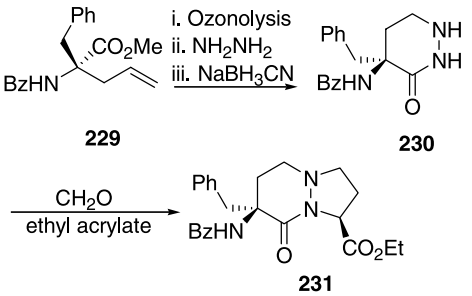

Fig. 52

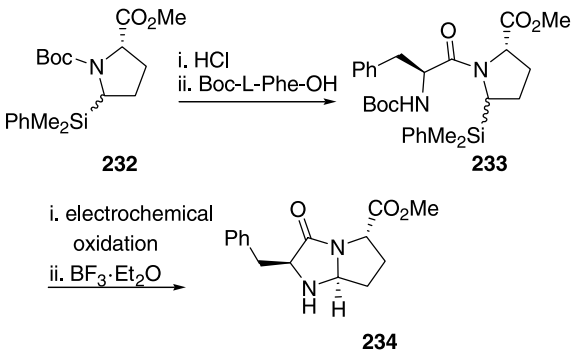

Fig. 53

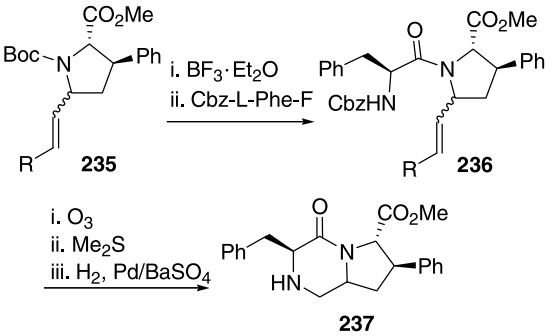

Fig. 54

dipeptide **233**, which underwent a constant-current electrochemical oxidation, followed by cyclization to diazabicycle **234** through nucleophilic attack on the *N*-acyliminium ion intermediate generated by Lewis acid action (Sun et al., 2006).

Analogously, the vinyl substituted proline **235** (Fig. 54) was coupled with L-phenylalanine and the vinyl substituent of **236** was transformed into a formyl group by ozonolysis reaction and treatment with dimethyl sulfide, then the intramolecular imino cyclization lead to a 6-membered ring hemiaminal that was converted into the amino ester **237** by reduction with hydrogen and Pd on barium sulfate (Tong et al., 2000).

Dipeptides containing bicyclic α-amino acids were also used as starting material for the synthesis of diazabicyclic δ-amino acids (Maison et al., 2004). The synthesis starts from azabicycloalkenes **238** (Fig. 55), that are bis(hydroxylated) and *N*-coupled with suitable natural α-amino acids. The key step is the oxidative cleavage of the resulting dipeptide **239** to give the diazabicyclic δ-amino acid **240** that can be further functionalized with few additional steps.

The alternative synthetic route, i.e., both rings formation in the same synthetic step, was carried out starting from linear dipeptides. By heating **241** (Fig. 56) in acidic medium and in the presence of sodium acetate

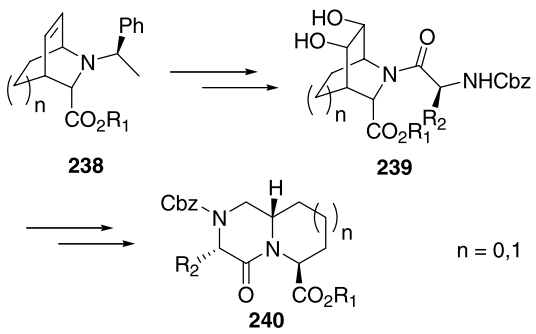

Fig. 55

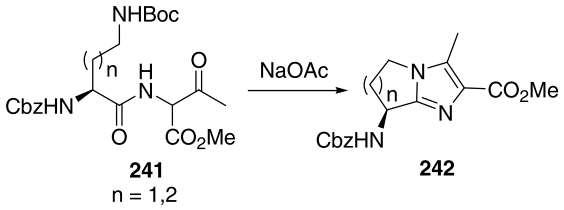

Fig. 56

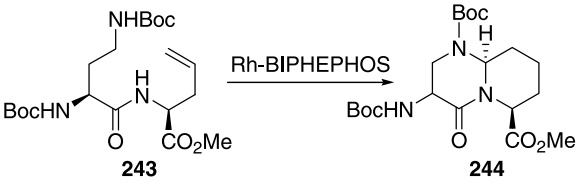

Fig. 57

(Haberhauer and Rominger, 2003), amino acid **242** was obtained, whose structure is formed by an imidazole ring condensed to either a 5- or a 6-membered cycloalkane.

Rhodium-catalyzed cyclohydrocarbonylation on **243** (Fig. 57) afforded the amino acid **244** in one stereoselective step (Chiou et al., 2007). The reaction mechanism involved the regioselective hydroformylation of the double bond followed by the first cyclization to yield a cyclic hemiamidal. After conversion of the latter into the corresponding *N*-acyliminium ion, the second cyclization through an intramolecular nucleophile addition took place to give the bicyclic compound.

Oxazabicycloalkanes

Oxazolopiperidin-2-ones were synthesized as rigidified mimetics of the Ala-Pro dipeptide (Estiarte et al., 2000). The synthesis started from Cbz-(*S*)-glutamic acid (Fig. 58), and afforded aldehyde **245** in three steps, which successively was condensed with Ser-OMe hydrochloride in a ''one pot'' process to give a mixture of diastereoisomers **246a** and **246b**. Complete stereocontrol of the reaction outcome was obtained by operating at room temperature (**246a** unique product).

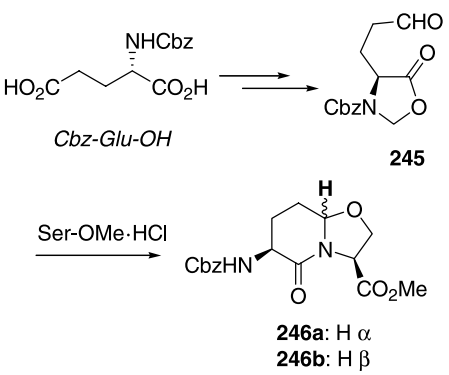

Fig. 58

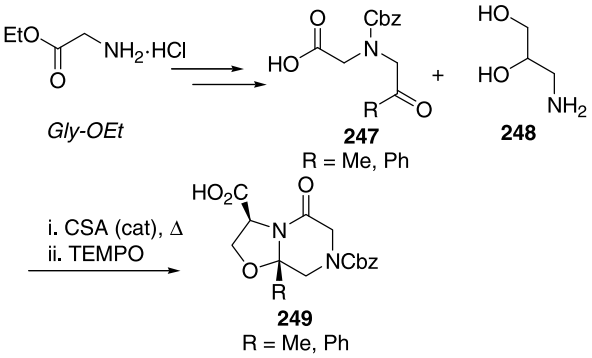

Fig. 59

Deprotection and hydrolysis steps afforded the final δ-amino acid that was inserted in a model peptide, proving that the new peptidomimetic adopted a stable type-II′ β-turn conformation in water. Oxazolo moiety is also present in bicyclic lactam scaffolds derived from the condensation of 3-aza-1,5-ketoacids and amino alcohols (Bencsik et al., 2003). The ketoacid **247** (Fig. 59) was obtained starting from glycine ethyl ester hydrochloride and a suitable α-bromoketone, followed by Cbz-protection and ester hydrolysis. By heating **247** and racemic serinol **248** in the presence of catalytic camphor sulfonic acid in refluxing toluene under Dean-Stark conditions, bicyclic condensation took place affording the corresponding serinol derivative as a racemic single diastereoisomer. Subsequent TEMPO-catalyzed oxidation produced the target *N*-Cbz amino acid **249** containing the oxazolo[3,2-*a*]pyrazin-5-one core structure.

Two more examples of oxazabicycloalkanes were synthesized in analogy with synthetic routes reported for diazabicycloalkane scaffolds, i.e., by rhodium-catalyzed cyclohydrocarbonylation (Fig. 60; Chiou et al., 2007) and by electrochemical oxidation (Fig. 61; Sun et al., 2006), using suitably functionalized starting materials.

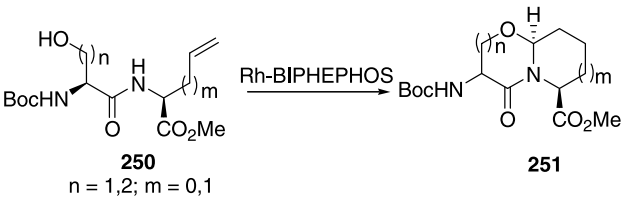

Fig. 60

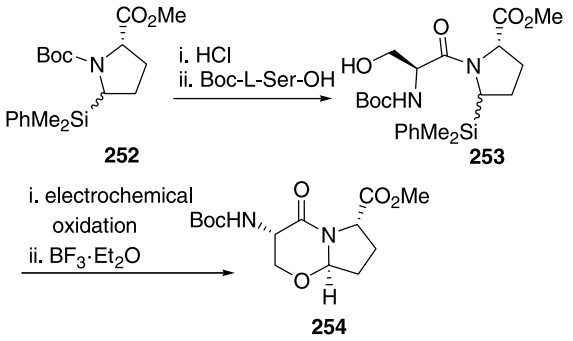

Fig. 61

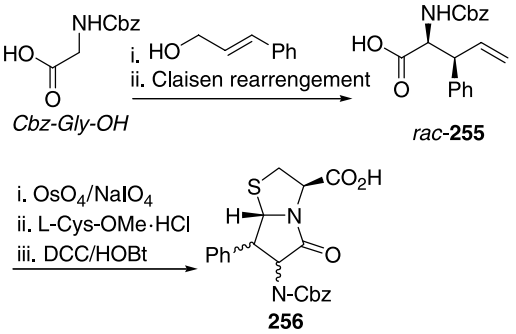

Fig. 62

Thiazabicycloalkanes

Most structures belonging to this class contain the thiazolo moiety usually built from cysteine as oxazolo rings derived from serine. For example, esterification of *N*-CBz-glycine (Fig. 62) with phenylpropenol followed by a highly diastereoselective Claisen rearrangement generated a racemic mixture of β-vinyl phenylalanines **255**. Oxidative cleavage of the double bond and coupling with L-cysteine methyl ester gave a cyclic mono acid, which cyclized with DCC/HOBt to bicyclic **256** (Qiu et al., 2001), having the *trans* relative stereochemistry of *N*-Cbz and phenyl groups.

Enantiopure amino acids homologous to **255** were obtained from a glycine equivalent in a Ni(II) complex with (*S*)-BPB [(*S*)-1-benzyl-pyrrolidine-2-carboxylic acid (2-benzoyl-phenyl)-amide] (Gu et al., 2002). Compound **257** underwent the oxidative cleavage and the coupling with L-cysteine but in this case the bicyclic scaffold **258** was directly formed under the reaction conditions in a stereoselective way (Fig. 63). Analogous chemical strategy afforded substituted thiazolopiperidones (Gu et al., 2003) and, with slight modifications, could be applied to solid phase synthesis (Gu et al., 2004).

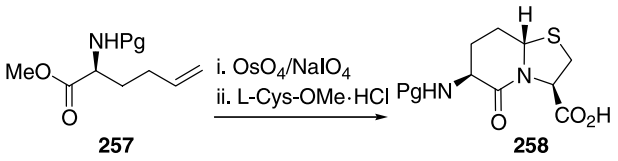

Fig. 63

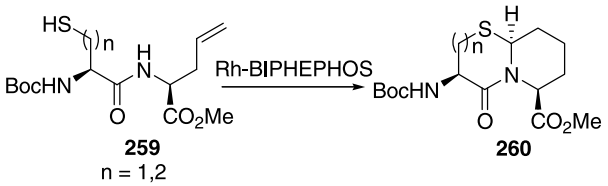

Fig. 64

Finally, the general methodology developed by Chiou et al. (2007), afforded [1,3]thiazinan-4-one- and [1,3]thiazepan-4-one-based bicyclic amino acids **260** by rhodium-catalyzed cyclohydrocarbonylation of **259** (Fig. 64).

Miscellaneous

Spirocyclic amino acids

Extensive molecular modelling calculations with high-level ab initio methods were carried out on spiro-β-lactam systems, suggesting that these compounds combine the structural features required for inducing a β-turn motif (Alonso et al., 2001). The key step of the synthesis (Fig. 65) was a Staudinger reaction of a cyclic ketene (**262**), obtained from Cbz-proline, with a glycine-derived imine. Compound **263** was obtained as a consequence of *cis* stereoselectivity of the process.

Conformational analysis via NMR experiments demonstrated the scaffold to stabilize a β-turn conformation with a geometry close to ideal type-II β-turn. A more recent synthesis allows to obtain spirocyclic-β-lactams

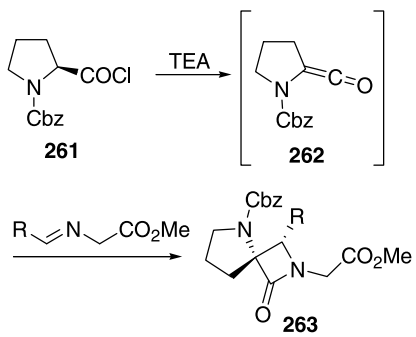

Fig. 65

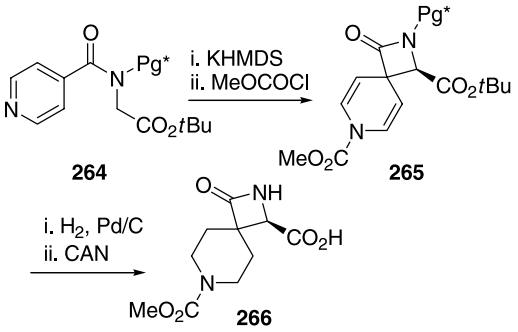

Fig. 66

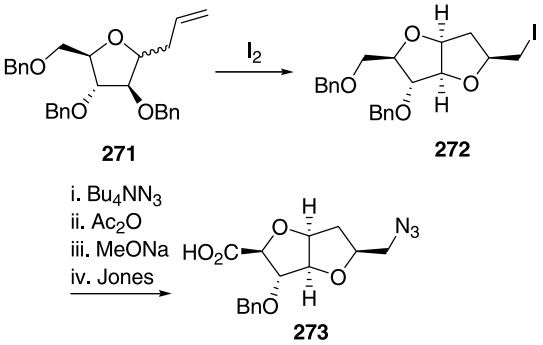

Fig. 68

by stereoselective dearomatizing cyclization of the enolates of *N*-nicotinoyl glycine derivatives (Arnott et al., 2006). Precursor **264** (Fig. 66) was obtained by acylating *N*-protected glycine *t*-butyl ester with nicotinoyl chloride. The ester was treated with KHMDS to form the enolate that cyclized onto the pyridine ring, resulting in the corresponding dihydropyridine that was in situ protected as carbomethoxy carbamate **265**. Hydrogenation and CAN-mediated deprotection afforded spiro-β-lactam **266**. Interestingly, enantiopure α-methyl-*p*-methoxybenzyl used as *N*-protecting group for glycine precursor was able to induce a stereoselective dearomatizing cyclization, and the final product **266** could be obtained with up to 88% ee.

Spiro-γ-lactams found a recent application in medicinal chemistry (Bittermann et al., 2004). The neurotensin C-terminal hexapeptide, NT(8-13), was found to adopt a β-strand-like conformation while bound to the NT1 receptor. Therefore, the original peptide sequence Arg-Arg-Pro-Tyr-Ile-Leu was modified by the substitution of Pro-Tyr with of a spirocyclic dipeptide mimetic. Natural proline was transformed into the α-allylproline methyl ester and, subsequently, Boc-protected and saponified to afford building block **267** (Fig. 67). Treatment of the terminal alkene with ozone, followed by reductive work-up procedure, gave intermediate **268** that was reductively coupled

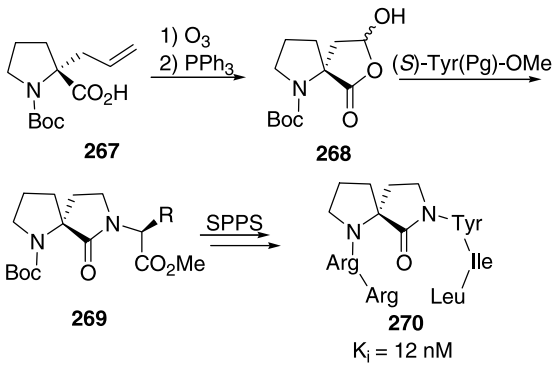

Fig. 67

with suitably protected L-tyrosine to give the spiro-compound **269**. Peptide **270** was finally synthesized by Boc chemistry on a PAM resin, following standard HATU coupling and TFA deprotection protocols.

The lactam-bridged neurotensin analog **270** was in vitro evaluated for its ability to compete with [^{3}H]neurotensin ($K_D = 1.3$ nM) in binding NT1 receptor and a very high binding affinity was found ($K_i = 12$ nM).

Carbohydrate-derived amino acids

The conformational rigidity of the pyran and furan rings makes carbohydrate-derived amino acids interesting building blocks in the introduction of specific secondary structures in peptides. For example, compound **273** (Fig. 68) was incorporated into the cyclic peptide containing the RGD loop sequence by SPPS using Fmoc chemistry (Peri et al., 2000). Reduction of the azide to amine group and the coupling with the desired amino acid was realized in one pot in the presence of Bu_3P and carboxylic acid activating agents.

Allyl compound **271**, deriving from allylation of 2,3,5-tri-*O*-benzyl-D-arabinofuranose, underwent iodocyclization to **272** as diastereomeric mixture, easily separated by chromatography. This step, crucial for the formation of bicyclic scaffolds, consisted in the intermediate iodonium ion opening by attack of the γ-benzyloxy group and formation of cyclic iodoether with simultaneous debenzylation. The final azido acid **273** was obtained by reaction with Bu_4NN_3, followed by selective deprotection steps and primary alcohol Jones oxidation. Analogous synthetic strategy was used to obtain the spirocyclic azido acid **276** (Fig. 69).

Recently, a set of bicyclic furano-oxetane scaffolds was proposed as constrained δ- or ε-amino acids (van Well et al., 2003). The synthetic strategy is based upon CO-insertion of fully protected β-D-ribofuranoside **277**, fol-

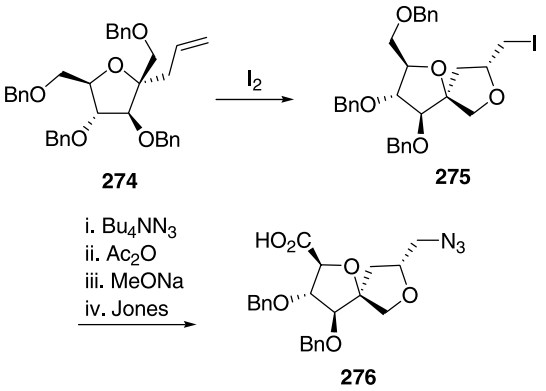

Fig. 69

lowed by conversion of primary alcohol function at C-1 to azide to generate the δ-amino acid precursor **279** (Fig. 70). After a few protection/deprotection steps and aldol condensation with formaldehyde, the oxetane forming cyclization step produced **283**, that was finally converted into the corresponding *N*-Boc protected δ- (**285**) and ε-amino acid (**286**) by few more manipulations. Inversion of functional groups to obtain the isomeric δ-amino acid **287** was accomplished by protection of alcohol function at C-1 of **278** as TBDPS ether (**280**), followed by the synthetic steps for the formation of bicyclic intermediate **284** similarly for the preparation of **283**. Conversion of the hydroxyl function at C-5 to Boc protected amino group proceeded via azide formation.

More bicyclic amino acids

The methodology proposed by Clayden and co-workers (Arnott et al., 2006) for the synthesis of spirocyclic amino acid **266** could also afford bicyclic δ/ε-amino acids (**290**, Fig. 71). Precursor **288** was obtained by acylating *N*-protected glycine *t*-butyl ester with isonicotinoyl chloride. The subsequent steps proceeded similarly as discussed above.

Only few papers reported ε-amino acids based on bicyclic[3.3.0]octane skeleton, though their bicyclic structure has interesting features because of the rigid ring junction as well as the conformationally flexible end terminations (Yeo et al., 2006). The most interesting application of this bicyclic system in peptide chemistry was bis-guanidinium-bicyclo[3.3.0]octane that was used to induce α-helix secondary structure in oligopeptides (Hackling et al., 2003). Synthesis starting from enyne **291** (Fig. 72) could be very practical since the catalytic Pauson-Khand reaction is well optimized to afford the bicyclic intermediate **292** in more than 100 g at a batch (Yeo et al., 2006). Chemical manipulations of **292** gave all the four stereoisomers of the target bicyclic ε-amino acid (only **293** was herein reported), and included hydrogenation of double bond over Pd/C, protection of the carbonyl group and monodecarboxylation. Introduction of the α-methyl group by quenching the carbanion generated by LDA base with MeI followed by carbonyl deprotection and reduction, afforded

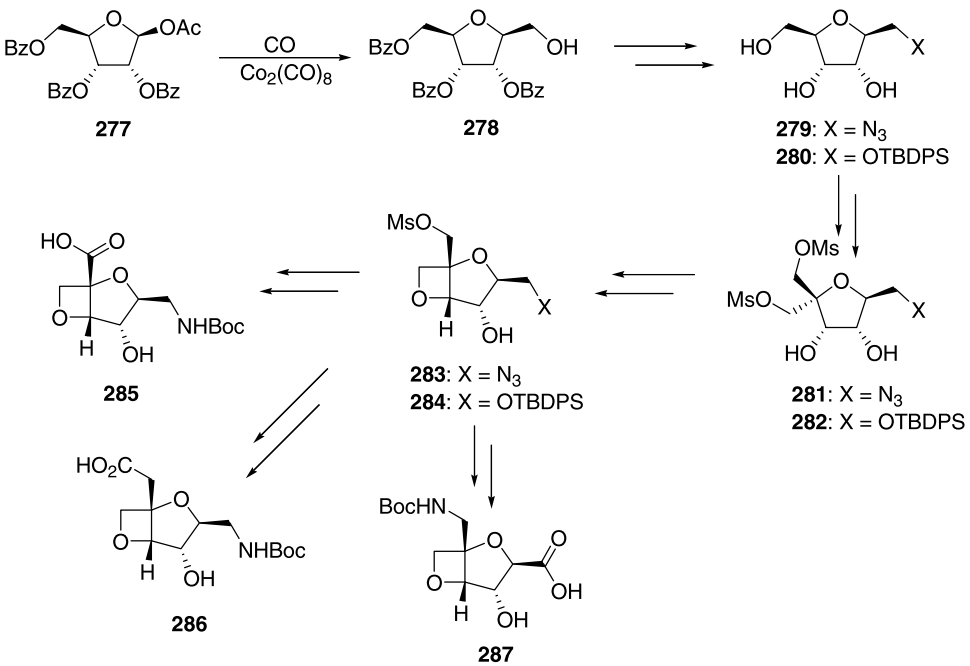

Fig. 70

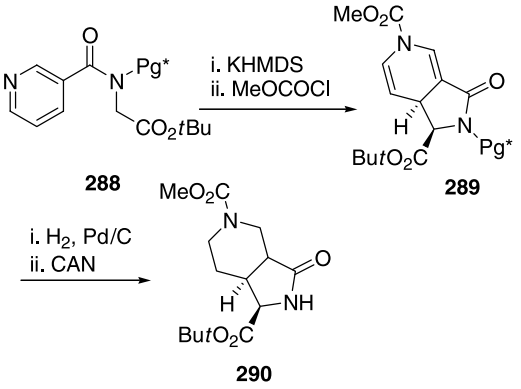

Fig. 71

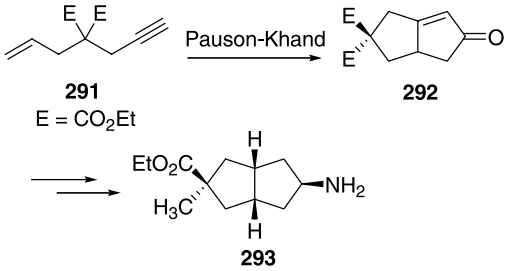

Fig. 72

the alcohol intermediate that was then transformed into final compound **293** by Mitsunobu reaction carried out in the presence of phthalimide, followed by NH_2NH_2 treatment. Chromatographic separation of the four diastereoisomers was carried out before the Mitsunobu reaction step.

The so obtained bicyclic ε-amino acid was also inserted into a linear peptide proving its compatibility with SPPS techniques.

Conclusions

Research oriented in the design, synthesis and applications of bicyclic amino acids from 2000 to present demonstrated a constant interest towards constrained structures capable to function as peptidomimetics with high rigidity and chemical diversity. The variety of bicyclic compounds proved a vivid interest towards the application of modern synthetic methodologies to build complex and unusual templates, and also detailed conformational analysis of selected scaffolds in model or bioactive peptides indicated the role of this bicyclic structures in limiting the conformational access of peptidic fragments. In particular, relevant applications as reverse turn nucleators were reported, expecially regarding the class of α- and δ-amino acids as proline mimetics and dipeptide isosteres, respectively. Finally, some examples of the application of selected bicyclic amino acids in medicinal chemistry confirmed the interest towards complex and polyfunctional templates in the peptidomimetic approach, which further indicates this area of synthetic chemistry as an important tool for the generation of drug candidates from bioactive peptides.

References

Abdel-Magid AF, Cohen JH, Maryanoff CA (1999) Chemical process synthesis of β-amino acids and esters. Curr Med Chem 6: 955–970

Alcaide B, Sáez E (2005) Diastereoselective route to novel fused or bridged tricyclic β-lactams through intramolecular nitrone-alkene cycloaddition of 2-azetidinone-tethered alkenylaldehydes – synthetic applications to carbacephams and cyclic β-amino acid derivatives. Eur J Org Chem: 1680–1693

Alonso E, López-Ortuz F, del Pozo C, Peralta E, Macías A, González J (2001) Spiro β-lactams as β-turn mimetics. Design, synthesis, and NMR conformational analysis. J Org Chem 66: 6333–6338

Arnott G, Clayden J, Hamilton SD (2006) Aza-bicyclic amino acids by stereoselective dearomatizing cyclisation of the enolates of *N*-nicotinoyl glycine derivatives. Org Lett 8: 5325–5328

Arosio D, Bertoli M, Manzoni L, Scolastico C (2006) Click chemistry to functionalise peptidomimetics. Tetrahedron Lett 47: 3697–3700

Basso A, Banfi L, Riva R, Guanti G (2005) A novel highly selective chiral auxiliary for the asymmetric synthesis of L- and D-α-amino acid derivatives via a multicomponent Ugi reaction. J Org Chem 70: 575–579

Belvisi L, Bernardi A, Manzoni L, Potenza D, Scolastico C (2000a) Conformational analysis of azabicycloalkane amino acid scaffolds as reverse-turn inducer dipeptide mimics. Eur J Org Chem: 2563–2569

Belvisi L, Gennari C, Madder A, Mielgo A, Potenza D, Scolastico C (2000b) Rationally designed bicyclic lactams control different turn motifs and folding patterns in hexapeptide mimics. Eur J Org Chem: 695–699

Belvisi L, Colombo L, Manzoni L, Potenza D, Scolastico C (2004) Design, synthesis, conformational analysis and application of azabicycloalkane amino acids as constrained dipeptide mimics. Synlett: 1449–1471

Belvisi L, Bernardi A, Colombo M, Manzoni L, Potenza D, Scolastico C, Giannini G, Marcellini M, Riccioni T, Castorina M, Lo Giudice P, Pisano C (2006) Targeting integrins: insights into structure and activity of cyclic RGD pentapeptide mimics containing azabicycloalkane amino acids. Bioorg Med Chem 14: 169–180

Bencsik JR, Kercher T, O'Sullivan M, Josey JA (2003) Efficient, Stereoselective synthesis of oxazolo[3,2-a]pyrazin-5-ones: novel bicyclic lactam scaffolds from the bicyclocondensation of 3-aza-1,5-ketoacids and amino alcohols. Org Lett 5: 2727–2730

Bittermann H, Einsiedel J, Hübner H, Gmeiner P (2004) Evaluation of lactam-bridged neurotensin analogues adjusting $\psi(Pro^{10})$ close to the experimentally derived bioactive conformation of NT(8-13). J Med Chem 47: 5587–5590

Brackmann F, Colombo N, Cabrele C, de Meijere A (2006) An improved synthesis of 3,4-(aminomethano)proline and its incorporation into small oligopeptides. Eur J Org Chem: 4440–4450

Bravin FM, Busnelli G, Colombo M, Gatti F, Manzoni L, Scolastico C (2004) Synthesis of conformationally restricted and optically pure analogues of serine-proline dipeptide via aldol condensation. Synthesis: 353–358

Buñuel E, Gil AM, Díaz-De-Villegas MD, Cativiela C (2001) Synthesis of constrained prolines by Diels-Alder reaction using a chiral unsaturated oxazolone from (*R*)-glyceraldehyde as starting material. Tetrahedron 57: 6417–6427

Casabona D, Cativiela C (2006) Efficient synthesis of a new pipecolic acid analogue with a bicyclic structure. Tetrahedron 62: 10000–10004

Chang LL, Truong Q, Doss GA, MacCoss M, Lyons K, McCauley E, Mumford R, Forrest G, Vincent S, Schmidt JA, Hagmann WK (2007) Highly constrained bicyclic VLA-4 antagonists. Bioorg Med Chem Lett 17: 597–601

Chiou WH, Mizutani N, Ojima I (2007) Highly efficient synthesis of azabicyclo[x.y.0]alkane amino acids and congeners by means of Rh-catalyzed cyclohydrocarbonylation. J Org Chem 72: 1871–1882

Cole DC (1994) Recent stereoselective synthetic approaches to β-amino acids. Tetrahedron 50: 9517–9582

Conti P, De Amici M, Joppolo di Ventimiglia S, Stensbøl TB, Madsen U, Bräuner-Osborne H, Russo E, De Sarro G, Bruno G, De Micheli C (2003) Synthesis and anticonvulsant activity of novel bicyclic acidic amino acids. J Med Chem 46: 3102–3108

Cordero FM, Pisaneschi F, Meschini Batista K, Valenza S, Machetti F, Brandi A (2005) A new bicyclic dipeptide isostere with pyrrolizidinone skeleton. J Org Chem 70: 856–867

Czombos J, Aelterman W, Tkachev A, Martins JC, Tourwé D, Péter A, Tóth G, Fülöp F, De Kimpe N (2000) Convenient synthesis of 3,4-methano-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid and its derivatives as doubly constrained nonproteinogenic amino acid derivatives. J Org Chem 65: 5469–5475

Danieli E, Trabocchi A, Menchi G, Guarna A (2005) Synthesis of glycidol- and sugar-derived bicyclic β- and γ/δ-amino acids for peptidomimetic design. Eur J Org Chem: 4372–4381

Davies DE, Doyle PM, Farrant RD, Hill RD, Hitchcock PB, Sanderson PN, Young DW (2003) Synthesis of an external β-turn based on the GLDV motif of cell adhesion proteins. Tetrahedron Lett 44: 8887–8891

Dominguez C, Prieto L, Valli MJ, Massey SM, Bures M, Wright RA, Johnson BG, Andis SL, Kingston A, Schoepp DD, Monn JA (2005) Methyl substitution of 2-aminobicyclo[3.1.0]hexane 2,6-dicarboxylate (LY354740) determines functional activity at metabotropic glutamate receptors: identification of a subtype selective mGlu2 receptor agonist. J Med Chem 48: 3605–3612

Dragovich PS, Zhou R, Prins TJ (2002) Synthesis of an optically active, bicyclic 2-pyridone dipeptide mimetic. J Org Chem 67: 741–746

Duggan HME, Hitchcock PB, Young DW (2005) Synthesis of 5/7-, 5/8- and 5/9-bicyclic lactam templates as constraints for external β-turns. Org Biomol Chem 3: 2287–2295

Dyatkin AB, Hoekstra WJ, Kinney WA, Kontoyianni M, Santulli RJ, Kimball ES, Fisher MC, Prouty SM, Abraham WM, Andrade-Gordon P, Hlasta DJ, He W, Hornby PJ, Damiano BP, Maryanoff BE (2004) Aza-bicyclic amino acid sulfonamides as $\alpha_4\beta_1/\alpha_4\beta_7$ integrin antagonists. Bioorg Med Chem Lett 14: 591–596

Dyatkin AB, Gong Y, Miskoswski TA, Kimball ES, Prouty SM, Fisher MC, Santulli RJ, Schneider CR, Wallace NH, Hornby PJ, Diamond C, Kinney WA, Maryanoff BE, Damiano BP, He W (2005) Aza-bicyclic amino acid carboxamides as $\alpha_4\beta_1/\alpha_4\beta_7$ integrin receptor antagonists. Bioorg Med Chem 13: 6693–6702

Estiarte MA, Rubiralta M, Diez A (2000) Oxazolopiperidin-2-ones as Type II′ β-turn mimetics: synthesis and conformational analysis. J Org Chem 65: 6992–6999

Gante J (1994) Peptidomimetics-tailored enzyme inhibitors. Angew Chem Int Ed Engl 33: 1699–1720

Gardiner J, Abell AD (2003) A diastereoselective synthesis of the tetrahydropyridazinone core of 2-oxo-1,6-diazobicyclo[4.3.0]nonane-9-carboxylate-based peptidimimetics starting from (*S*)-phenylalanine. Tetrahedron Lett 44: 4227–4230

Gellman SH (1998) Foldamers: a manifesto. Acc Chem Res 31: 173–180

Giannis A, Kolter T (1993) Peptidomimetics for receptor ligands-discovery, development, and medical perspectives. Angew Chem Int Ed Engl 32: 1244–1267

Gil AM, Orús E, López-Carrillo V, Buñuel E, Cativiela C (2005) New enantiopure 7-azabornane β-substituted prolines by S_N2 displacements at the C_γ of the side chain. Tetrahedron Asymmetr 16: 3115–3123

Grygorenko OO, Artamonov OS, Palamarchuk GV, Zubatyuk RI, Shishkin OV, Komarov IG (2006) Stereoselective synthesis of 2,4-methanoproline homologues. Tetrahedron Asymmetr 17: 252–258

Gu X, Tang X, Cowell S, Ying J, Hruby VJ (2002) A novel strategy toward [6,5]-bicyclic β-turn dipeptide. Tetrahedron Lett 43: 6669–6672

Gu X, Cowell S, Ying J, Tang X, Hruby VJ (2003) Synthesis of β-phenyl-δ,ε-unsaturated amino acids and stereoselective introduction of side chain groups into [4,3,0]-bicyclic β-turn dipeptides. Tetrahedron Lett 44: 5863–5866

Gu X, Ying J, Agnes RS, Navratilova E, Davis P, Stahl G, Porreca F, Yamamura HI, Hruby VJ (2004) Novel design of bicyclic β-turn dipeptides on solid-phase supports and synthesis of [3.3.0]-bicyclo$^{[2,3]}$-Leu-enkephalin analogues. Org Lett 6: 3285–3288

Günter M, Gais HJ (2003) Asymmetric synthesis of fused bicyclic α-amino acids having a hexahydro-cyclopenta[*c*]pyridine skeleton via intramolecular Pauson-Khand reaction of 1-sulfonimidoyl-substituted 5-azaoct-1-en-7-ynes. J Org Chem 68: 8037–8041

Haberhauer G, Rominger F (2003) Straightforward synthesis of a novel class of rigid bicyclic dipeptidomimetics from simple dipeptides: fused imidazole amino acids. Synlett: 780–784

Hackling A, Ghosh R, Perachon S, Mann A, Höltje HD, Wermuth CG, Schwartz JC, Sippl W, Sokoloff P, Stark H (2003) *N*-(ω-(4-(2-Methoxyphenyl)piperazin-1-yl)alkyl)carboxamides as dopamine D_2 and D_3 receptor ligands. J Med Chem 46: 3883–3899

Halab L, Becker JAJ, Darula Z, Tourwé D, Kieffer BL, Simoni F, Lubell WD (2002) Probing opioid receptor interactions with azacycloalkane amino acids. Synthesis of a potent and selective ORL1 anatagonist. J Med Chem 45: 5353–5357

Hanessian S, Luo X, Schaum R, Michnick S (1998) Design of secondary structures in unnatural peptides: stable helical γ-tetra-, hexa-, and octapeptides and consequences of α-substitution. J Am Chem Soc 120: 8569–8570

Hanessian S, Sailes H, Munro A, Therrien E (2003) Synthesis of diversely functionalized indolizidinones and related bicyclic lactams using intramolecular Grubbs olefin metathesis and Dieckmann condensation. J Org Chem 68: 7219–7233

Harris PW, Brimble MA, Gluckman PD (2003) Synthesis of cyclic proline-containing peptides via ring-closing metathesis. Org Lett 5: 1847–1850

Hattori K, Grossman RB (2003) Functionalized cis- and trans-fused bicyclic α-amino acids via stereoselective double annulation and dequaternization reactions. J Org Chem 68: 1409–1417

Hintermann T, Gademann K, Jaun B, Seebach D (1998) Gamma-peptides forming more stable secondary structures than alpha-peptides: synthesis and helical NMR-solution structure of the gamma-hexapeptide analog of H-(Val-Ala-Leu)(2)-OH. Helv Chim Acta 81: 983–1002

Iverson BL (1997) Betas are brought into the fold. Nature 385: 113–115

Jeannotte G, Lubell WD (2004) Synthesis of fused heteroarylprolines and pyrrolopyrroles. J Org Chem 69: 4656–4662

Jiang B, Xu M (2002) Catalytic diastereoselective Pauson-Khand reaction: an efficient route to enantiopure cyclopenta[*c*]proline derivatives. Org Lett 4: 4077–4080

Juaristi E, Lopez-Ruiz H (1999) Recent advances in the enantioselective synthesis of β-amino acids. Curr Med Chem 6: 983–1004

Koep S, Gais HJ, Raabe G (2003) Asymmetric synthesis of unsaturated fused bicyclic proline analogues through amino alkylation of cyclic bis(allylsulfoximine)titanium complexes and migratory cyclization of δ-amino alkenyl aminosulfoxonium salts. J Am Chem Soc 125: 13243–13251

Köhler F, Gais HJ, Raabe G (2007) Asymmetric synthesis of highly substituted γ-amino acids from allyltitanium sulfoximines. Org Lett 9: 1231–1234

Lalli C, Trabocchi A, Guarna F, Mannino C, Guarna A (2006) Synthesis of a bicyclic proline analogue from L-ascorbic acid. Synthesis: 3122–3126

Langer P, Kählig H, Zierler-Gould K, Bats JW, Mulzer J (2002) A bicyclic cispentacin derivative as a novel reverse turn inducer in a GnRH mimetic. J Org Chem 67: 6878–6883

Lescop C, Mévellec L, Huet F (2001) A new synthesis of 2-azabicyclo[2.1.1]hexanes. J Org Chem 66: 4187–4193

Liu YT, Wong JK, Tao M, Osterman R, Sannigrahi M, Girijavallabhan VM, Saksena A (2004) Carboxy mediated stereoselective reduction of ketones with sodium triacetoxyborohydride: synthesis of novel 3,4-fused tetrahydropyran and tetrahydrofuran prolines. Tetrahedron Lett 45: 6097–6100

Machetti F, Ferrali A, Menchi G, Occhiato EG, Guarna A (2000) Oligomers of enantiopure bicyclic γ/δ-amino acids (BTAa). 1. Synthesis and conformational analysis of 3-aza-6,8-dioxabicyclo[3.2.1]octane-7-carboxylic acid oligomers (PolyBTG). Org Lett 2: 3987–3990

Maechling S, Norman SE, McKendrick JE, Basra S, Köppner K, Blechert S (2006) Ring-rearrangement metathesis of bicyclic amino acid derivatives. Tetrahedron Lett 47: 189–192

Maison W, Grohs DC, Prenzel AHGP (2004) Efficient synthesis of structurally diverse diazabicycloalkanes: scaffolds for modular dipeptide mimetics with tunable backbone conformations. Eur J Org Chem: 1527–1543

Mandal PK, Kaluarachchi KK, Ogrin D, Bott SG, McMurray JS (2005) An efficient synthesis of the constrained peptidomimetic 2-oxo-3-(*N*-9-fluorenyloxycarbonylamino)-1-azabicyclo[4.3.0]nonane-9-carboxylic acid from pyroglutamic acid. J Org Chem 70: 10128–10131

Manku S, Curran DP (2005) Fluorus mixture synthesis of 4-alkylidene cyclopentenones via a rhodium-catalyzed $[2+2+1]$ cycloaddition of alkynyl allenes. J Comb Chem 7: 63–68

Manzoni L, Belvisi L, Di Carlo E, Forni A, Invernizzi D, Scolastico C (2006) Synthesis of functionalized azabicycloalkane amino acids as dipeptide mimics. Synthesis: 1133–1140

Millet R, Domarkas J, Rombaux P, Rigo B, Houssin R, Hénichart JP (2002) Synthesis of an azabicycloalkane amino acid scaffold as potential rigid dipeptide mimetic. Tetrahedron Lett 43: 5087–5088

Mouriès C, Deguin B, Lamari F, Foglietti MJ, Tillequin F, Koch M (2003) Homochiral rigid γ-amino acid glycosides from aucubin. Tetrahedron Asymm 14: 1083–1086

Otani Y, Futaki S, Kiwada T, Sugiura Y, Muranaka A, Kobayashi N, Uchiyama M, Yamaguchi K, Ohwada T (2006) Oligomers of β-amino acid bearing non-planar amides form ordered structures. Tetrahedron 62: 11635–11644

Peri F, Cipolla L, La Ferla B, Nicotra F (2000) Synthesis of bicyclic sugar azido acids and their incorporation in cyclic peptides. Chem Commun: 2303–2304

Polyak F, Lubell WD (2001) Mimicry of peptide backbone geometry and heteroatomic side-chain functionality: synthesis of enantiopure indolizidin-2-one amino acids possessing alcohol, acid, and azide functional groups. J Org Chem 66: 1171–1180

Qiu W, Gu X, Soloshonok VA, Carducci MD, Hruby VJ (2001) Stereoselective synthesis of conformationally constrained reverse turn dipeptide mimetics. Tetrahedron Lett 42: 145–148

Ramana Rao MHV, Pinyol E, Lubell WD (2007) rigid dipeptide mimics: synthesis of enantiopure C6-functionalized pyrrolizidinone amino acids. J Org Chem 72: 736–743

Rammeloo T, Stevens CV (2002) A new and short method for the synthesis of 2,4-methanoproline. Chem Commun: 250–254

Rammeloo T, Stevens CV, De Kimpe N (2002) Synthesis of 2,4-methanoproline analogues via an addition-intramolecular substitution sequence. J Org Chem 67: 6509-6513

Salvati M, Cordero FM, Pisaneschi F, Bucelli F, Brandi A (2005) New developments in the synthesis of pyrrolizidinone-based dipeptide isosteres. Tetrahedron 61: 8836–8847

Scarpi D, Occhiato EG, Trabocchi A, Leatherbarrow RJ, Brauer ABE, Nievo M, Guarna A (2001) Introduction of the new dipeptide isostere 7-*endo*-BtA as reverse turn inducer in a Bowman-Birk proteinase inhibitor: synthesis and conformational analysis. Bioorg Med Chem 9: 1625–1632

Seebach D, Matthews JL (1997) β-Peptides: a surprise at every turn. Chem Commun: 2015–2022

Sewald N (1996) Stereoselective synthesis of β-amino acids via conjugate addition of nitrogen nucleophiles to α,β-unsaturated esters. Recent advances. Amino Acids 11: 397–408

Strachan JP, Whitaker RC, Miller CH, Bhatti BS (2006) Synthesis of bicyclic tertiary α-amino acids. J Org Chem 71: 9909–9911

Sun H, Martin C, Kesselring D, Keller R, Moeller KD (2006) Building functionalized peptidomimetics: use of electroauxiliaries for introducing *N*-acyliminium ions into peptides. J Am Chem Soc 128: 13761–13771

Szabo L, Smith BL, McReynolds KD, Parrill AL, Morris ER, Gervay J (1998) Solid phase synthesis and secondary structural studies of $(1->5)$-amide linked sialooligomers. J Org Chem 63: 1074–1078

Tararov VI, Kadyrov R, Kadyrova Z, Dubrovina N, Börner A (2002) An improved synthesis of enantiopure 2-azabicyclo[2.2.1]heptane-3-carboxylic acid. Tetrahedron Asymm 13: 25–28

Tong Y, Fobian YM, Wu M, Boyd ND, Moeller KD (2000) Conformationally constrained substance P analogues: the total synthesis of a constrained peptidomimetic for the Phe^7-Phe^8 region. J Org Chem 65: 2484–2493

Trabocchi A, Cini N, Menchi G, Guarna A (2003) A new bicyclic proline-mimetic amino acid. Tetrahedron Lett 44: 3489–3492

Trabocchi A, Menchi G, Guarna F, Machetti F, Scarpi D, Guarna A (2006) Design, synthesis, and applications of 3-aza-6,8-dioxabicyclo[3.2.1]octane-based scaffolds for peptidomimetic chemistry. Synlett: 331–353

Trabocchi A, Occhiato EG, Potenza D, Guarna A (2002) Synthesis and conformational analysis of small peptides containing 6-*endo*-BT(t)L scaffolds as reverse turn mimetics. J Org Chem 67: 7483–7492

Valls N, López-Canet M, Vallribera M, Bonjoch J (2001) First total syntheses of aeruginosin 298-A and aeruginosin 298-B, based on a stereocontrolled route to the new amino acid 6-hydroxyoctahydroindole-2-carboxylic acid. Chem Eur J 7: 3446–3460

van Well RM, Meijer MEA, Overkleeft HS, van Boom JH, van der Marel GA, Overhand M (2003) Synthesis of bridged sugar amino acids: a new entry into conformationally locked δ- and ε-amino acids. Tetrahedron 59: 2423–2434

Wang W, Yang J, Ying J, Xiong C, Zhang J, Cai C, Hruby VJ (2002) Stereoselective synthesis of dipeptide β-turn mimetics: 7-benzyl and 8-phenyl substituted azabicyclo[4.3.0]nonane amino acid esters. J Org Chem 67: 6353–6360

Yang BV, Doweyko LM (2005) Highly regioselective Diels-Alder reactions of 9-substituted anthracenes and 2-acetamidoacrylate: synthesis of conformationally constrained α-amino acids. Tetrahedron Lett 46: 2857–2860

Yeo SJ, Jeong KS, Han H, Kim J, Jeong N (2006) ε-Amino acids based on bicyclic skeleton: bicyclo[3.3.0]octane-5-amino-1-carboxylic acids. Tetrahedron Lett 47: 7389–7393

Zhang J, Xiong C, Wang W, Ying J, Hruby VJ (2002) Stereoselective bromination-Suzuki cross-coupling of dehydroamino acids to form novel reverse-turn peptidomimetics: substituted unsaturated and saturated indolizidinone amino acids. Org Lett 4: 4029–4032

Authors' address: Antonio Guarna, Dipartimento di Chimica Organica "Ugo Schiff" and Laboratorio di Progettazione, Sintesi e Studio di Eterocicli Bioattivi (HeteroBioLab), Università degli Studi di Firenze, Polo Scientifico e Tecnologico, Via della Lastruccia 13, I-50019 Sesto Fiorentino, Firenze, Italy,
Fax: +39-0-554-573 569, E-mail: antonio.guarna@unifi.it