Russian Chemical Reviews **73** (8) 785 – 810 (2004) © 2004 Russian Academy of Sciences and Turpion Ltd

DOI 10.1070/RC2004v073n08ABEH000912

Conformationally rigid cyclic α-amino acids in the design of peptidomimetics, peptide models and biologically active compounds

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Abstract. A class of conformationally rigid cyclic α-amino acids that can be used in the synthesis of peptidomimetics, peptide models and biologically active compounds is surveyed. The rigid frameworks of such amino acids enable 'fixation' of strictly defined torsion angles and hence prediction and deliberate tuning of the conformation of a polypeptide chain. Recent data on the structures and methods of the synthesis of such amino acids are presented. The bibliography includes 259 references.

I. Introduction

Synthesis of compounds with constrained conformational flexibility increasingly attracts the attention of chemists. It is commonly assumed that restriction of the conformational flexibility of molecules by structural modifications may serve as an efficient tool in the studies of, and control over, properties of various compounds. In particular, by 'fixing' a ligand molecule in the so-called biologically active conformation, one can achieve high efficiency and selectivity of its interaction with the corresponding receptor. Restriction of the conformational flexibility of chiral ligands in metal complex catalysts allows enhancement of the enantioselectivity of catalytic asymmetric reactions.[1]

The vast majority of studies which make use of this approach relate probably to the synthesis of peptidomimetics and peptide models. Synthesis of peptidomimetics is aimed at improvement of the properties of natural peptides, first of all, of their biological activities,[2] whereas that of peptide models, at studies of the properties of peptides and proteins. For instance, peptidomimetics with improved pharmacological characteristics (solubility, bioselectivity, resistance to *in vivo* degradation, *etc*.) can be prepared by modifying structures of amino acid constituents of a bilogically active natural peptide. Compounds utilised in studies of the mechanism of the enzyme catalysis may be mentioned as examples of peptide models.[3]

Both peptidomimetics and peptide models may have either peptide or non-peptide nature. A key principle of their design consists of the incorporation of conformationally constrained or rigid analogues of natural amino acids into the peptide chain.

Up to now, numerous conformationally constrained and rigid amino acids, as well as peptidomimetics and artificial peptides on their base, have been synthesised. Methods for the preparation of these compounds and their biochemical properties have been surveyed in a number of reviews.[4 – 15] Nevertheless, issues related to the structural features and conformational properties of these compounds as well as to the design of peptidomimetics and peptide models with conformationally constrained amino acids have not been adequately addressed so far. The goal of the present review is to span this gap.

Among the whole range of the known amino acids that are characterised by restricted conformational flexibility, conformationally rigid α-amino acids deserve particular mention. Hereinafter, substances the molecules of which exist in a unique conformation, are referred to as conformationally rigid α-amino acids (CRA).† These also encompass amino acids where only a specific fragment is rigid. Conformationally rigid amino acids have several advantages in the design of peptidomimetics and peptide models over amino acids that are conformationally constrained but not rigid. Rigid molecules or molecular fragments are characterised by 'fixed' bond and torsion angles, which are either known or can be calculated with sufficient accuracy by molecular mechanics. The values of these angles are virtually independent of the structure and conformation of the remaining part of the polypeptide chain. Furthermore, rigid fragments formed by CRA can impose a specific chain conformation on their immediate proximity. This simplifies the design of peptidomimetics or artificial peptides with desired characteristics.

This approach limits the number of amino acids applicable in the design, however the structural diversity of CRA is fairly broad as will be shown below. Many of the theoretically possible CRA have not been synthesised so far and one goal of the present review is to draw the attention of chemists to their synthesis.

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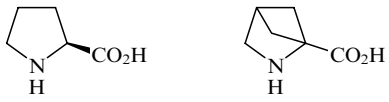
Received 18 March 2004
Uspekhi Khimii **73** (8) 849 – 876 (2004); translated by Ya V Zubavichus

† In the present review, the generalised meaning of the term conformation is adopted, *viz*., a conformation is understood as any spatial mutual arrangement of nuclei comprising a molecule, which can be realised without disturbing integrity of the molecule.[16 – 19]

Since the term 'conformational rigidity' is central in this review, it deserves a dedicated consideration.

II. Conformationally constrained and conformationally rigid molecules

Two terms 'conformationally constrained (restricted)' and 'conformationally rigid' frequently occur in the scientific literature and are commonly considered as being intuitively obvious. L-Proline (**1**) and its bicyclic analogue 2,4-methanoproline (**2**) may be taken as examples of a conformationally constrained and a conformationally rigid molecule, respectively.



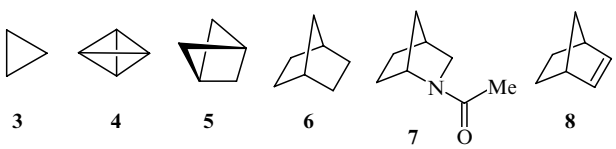
1 **2**

The presence of a five-membered ring in **1** substantially restricts the conformational flexibility of both the L-proline molecule and peptides containing its residue. Nevertheless, there exists a set of proline conformations such that transitions between them do not require significant energy expenditure.[20] The molecule of **2**, a proline analogue, is regarded as rigid, because its conformational mobility is severely restricted by the methylene bridge. Nevertheless, it does not comply with the strict definition of CRA given in the preceeding section, as it can still adopt more than one conformation.

The Chemical Encyclopaedic Dictionary [21] gives the following definition of the term 'rigid molecule': 'A characteristic feature of rigid molecules is that a transition from one of their equilibrium conformations to another requires a considerable energy (>100 kJ mol^{-1})... Only transpositions of nuclei which are realised by rigid rotations or mirror reflections of the molecule as a whole without cleavage of chemical bonds are allowed in rigid molecules'. The major drawback of this definition, in our opinion, is that it poses a specific value of the maximum energy of a configurational (conformational) transition, *i.e.*, 100 kJ mole^{-1}. Even neglecting the arbitrariness in the selection of this value, this definition can hardly be applied to a particular molecule since the exact energy profile of its conformational transitions is typically unknown.

It would be appropriate here to refer to aromatic and heteroaromatic compounds. For a long time (see, for instance, Refs 21–23), it has been believed that they represent rigid structures. However, recent theoretical and experimental studies have revealed substantial flexibility of benzene [24] and pyridine [25] rings: a change in the torsion angle by 20° in these aromatic systems results in an energy increase of not more than 13 kJ mol^{-1}. Alkenes and fragments with a triple bond cannot also be classified as conformationally rigid. According to a recent theoretical and experimental studies,[26] bond and torsion angles in unsaturated compounds can experience noticeable distortions at energy not exceeding 20 kJ mol^{-1}.

Alternatively, the conformational rigidity may be defined in a more strict and versatile way using a topological approach based on the graph theory. Within this approach, rigid molecules were described as rigid graphs with edges of fixed lengths.[27] Note that various conformationally rigid molecules can be constructed theoretically using the graph theory; these molecules, however, can prove to be unstable or non-existent in reality. The three-membered ring **3** is evidently classified as conformationally rigid. The graph **4** is also rigid but unsubstituted tetrahedrane with this skeleton is so unstable that all attempts at its synthesis undertaken so far have failed.[26]



3 **4** **5** **6** **7** **8**

At resent, there is no uniform criterion of conformational rigidity, therefore, the attribution of a particular amino acid to conformationally rigid ones is based in the following discussion primarily on literature data concerning their structures and conformational mobilities. Analysis of the published data allowed us to conclude that cyclic and polycyclic cages with fixed torsion and bond angles in their CR_4 fragments and those involving sp^2- and sp-hybridised atoms are regarded as rigid most frequently. For the former class, this is due to large force constants of both bonds and angles, while the latter class lies beyond the scope of the present review. In particular, polycyclic molecules with bridges involving 0 or 1 atom (*e.g.*, the molecule **5**) are referred to as rigid. Polycyclic molecules with two-atomic bridges are also often considered as rigid in the literature (*e.g.*, compound **6**), especially in those cases where the structure is additionally 'reinforced' by an amide group or by multiple bonds (*e.g.*, the structures **7** and **8**).

The following structural types of CRA will be considered as rigid in the following discussion:

(1) mono- and spirocyclic compounds with three- and four-membered rings;

(2) bicyclic compounds with short bridges comprising from 0 to 2 atoms;

(3) tri- and polycyclic compounds with sufficiently short bridges.

In the next sections, the major attention will be paid to conformationally rigid analogues of natural α-amino acids. This is primarily due to the fact that the design of conformationally constrained peptidomimetics or peptide models typically implies replacement of natural amino acids in the native peptide by structurally most similar analogues; the so-called 'topomers' or 'topologically equivalent' amino acids. The principles of such a 'topographic' design of peptides have been formulated quite recently.[28, 29] Evidently, in this case, the results of conformational and biological studies can be more easily interpreted since earlier experimental data on related natural amino acids can be used for comparison.

The synthesis of CRA that are not close analogues of natural α-amino acids is also of substantial practical and theoretical interest. The molecules of CRA can contain two or more fragments of natural amino acids (such amino acids are referred to as 'chimeric').

The literature data search has been accomplished using electronic databases, *viz.*, Beilstein Crossfire, SciFinder and the Cambridge Structural Database (CSD).[30]

III. Principles of the design of peptidomimetics and peptide models comprising conformationally rigid amino acids

The design of peptidomimetics and peptide models comprising CRA is based on the knowledge of the features of the secondary structure elements of peptides. The three major types of secondary structures of peptides adopted currently include helices (*I*), β-folded structures (*II*) and bends (*III*) (Fig. 1).[28, 31–33]

Conformations of polypeptide chains corresponding to each of the secondary structure elements can be described in terms of the torsion angles φ, ψ and ω whereas the conformation of side chains of amino acids can be described in terms of the torsion angles χ_1, χ_2, χ_3, and so forth (Fig. 2).

The most typical (*i.e.*, mean or standard) values of the torsion angles φ, ψ and ω for the secondary structure elements of peptides and proteins determined as a result of analysis of numerous experimental structural data and computer simulations are summarised in Table 1.[28, 32] Based on the values of the torsion angles φ, ψ and ω given in Table 1, it is possible to predict in the first approximation the effects of a replacement of a natural amino acid by its conformationally rigid analogue with fixed torsion

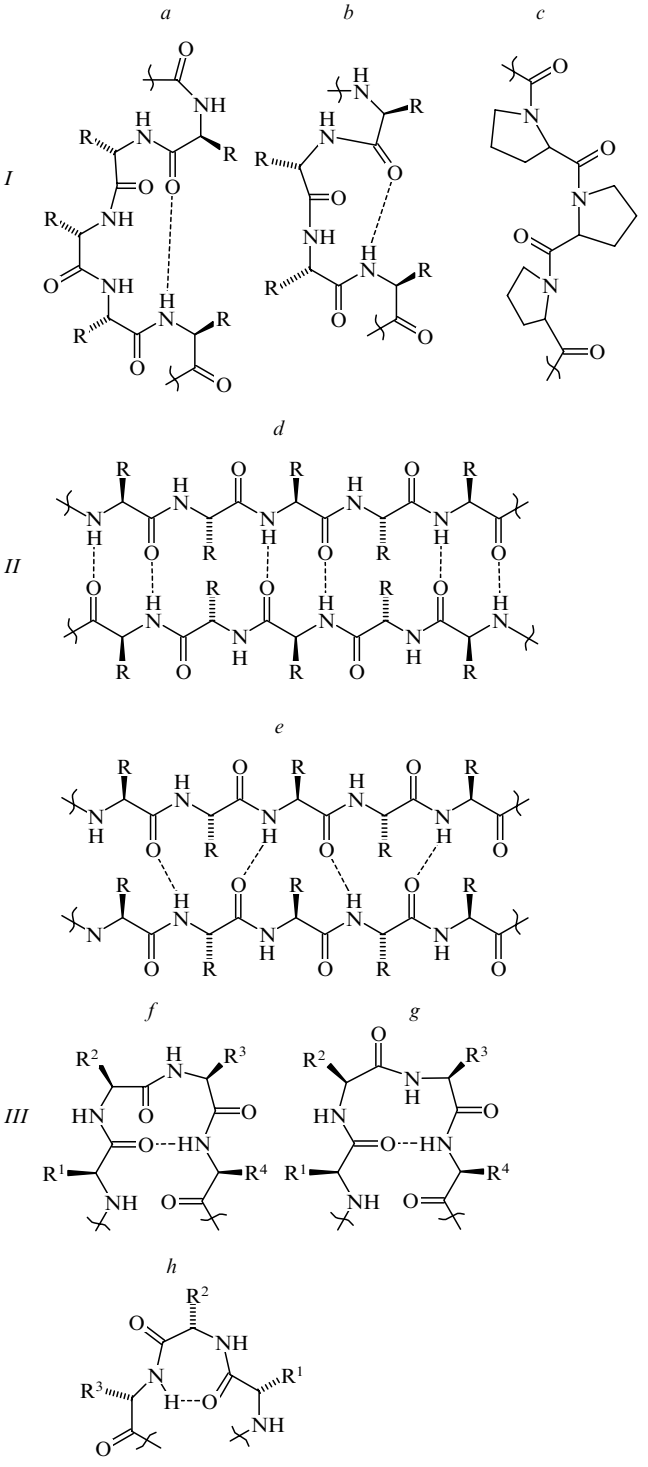
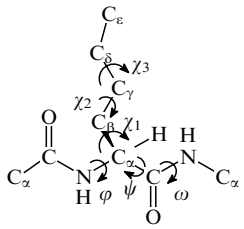


Figure 1. Elements of the secondary structure of peptides and proteins: (*I*) helices: α-helix (right-handed) (*a*), 3_{10}-helix (right-handed) (*b*), polyproline II helix (left-handed) (*c*); (*II*) β-folded structures: antiparallel (*d*), parallel (*e*); (*III*) bends: type I β-bend (*f*), type II β-bend (*g*), γ-bend (*h*).

angles (most frequently, it is the torsion angle φ that is fixed) on the conformation of the peptide fragment. It is noteworthy that the torsion angles exert a decisive influence on the conformation of the whole fragment involving CRA. If torsion angles at the peptide bond formed by a CRA are close to the respective torsion angles of a secondary structure element of the native peptide, stabilisation of this structure element is expected. Otherwise, this will be destabilised and a change of its conformation can be predicted with a sufficient degree of accuracy.



Torsion angle	Notation
$C-N-C_\alpha-C$	φ
$N-C_\alpha-C-N$	ψ
$C_\alpha-C-N-C_\alpha$	ω
$N-C_\alpha-C_\beta-C_\gamma$	χ_1
$C_\alpha-C_\beta-C_\gamma-C_\delta$	χ_2
$C_\beta-C_\gamma-C_\delta-C_\varepsilon$	χ_3

Figure 2. The torsion angles φ, ψ, ω and χ in peptides.

Table 1. Mean values of the torsion angles φ, ψ and ω (deg.) typical of different elements of the secondary structure of peptides and proteins.

Secondary structure element	φ	ψ	ω
Helices			
α-helix	−57	−47	180
3_{10}-helix	−60	−30	180
polyproline I helix	−83	158	0
polyproline II helix	−76	146	180
β-Folded structures			
parallel	−119	113	–
antiparallel	−139	135	–
extended chain	180	180	–
β-Bends [a]			
type I	−60 (φ_{i+1}); −90 (φ_{i+2})	−30 (ψ_{i+1}); 0 (ψ_{i+2})	
type I′	60 (φ_{i+1}); 90 (φ_{i+2})	30 (ψ_{i+1}); 0 (ψ_{i+2})	
type II	−60 (φ_{i+1}); 80 (φ_{i+2})	120 (ψ_{i+1}); 0 (ψ_{i+2})	
type II′	60 (φ_{i+1}); −80 (φ_{i+2})	−120 (ψ_{i+1}); 0 (ψ_{i+2})	
type III	−60 (φ_{i+1}); −60 (φ_{i+2})	−30 (ψ_{i+1}); −30 (ψ_{i+2})	
type III′	60 (φ_{i+1}); 60 (φ_{i+2})	30 (ψ_{i+1}); 30 (ψ_{i+2})	
γ-Bend	−65 (φ_{i+1})	120 (ψ_i); 80 (ψ_{i+1}); −120 (ψ_{i+2})	

[a] By definition, a β-bend involves four amino acid residues. They are enumerated as *i*th to $i+3$th residue starting from the N-end. The indices of the torsion angles correspond to this enumeration.

This also holds for the torsion angles χ that characterise spatial arrangement of the peptide side chains. Knowledge of these torsion angles is exceptionally important for the understanding of the functions of the peptides. Unfortunately, studies devoted to the torsion angles χ in natural peptides are rather scarce.

In some cases, 'stereolibraries' of CRA have been compiled, which represent diastereomeric series of amino acids that are close structural analogues of the corresponding natural amino acids. In these series, strictly fixed torsion angles vary from one compound to another. Synthesis of a series of peptidomimetics or peptide models on the basis of such a library enables elucidation of the relationships between the properties of peptides and their conformations and thus increases the efficacy of the search for biologically active compounds and drugs.

However, the conformation of a peptide fragment does not depend only on the torsion angles in the CRA residue. Any structural modification (even a minor one) of a natural amino acid affects to a certain extent all the angles describing the conformation of a peptide fragment close to modification. As an

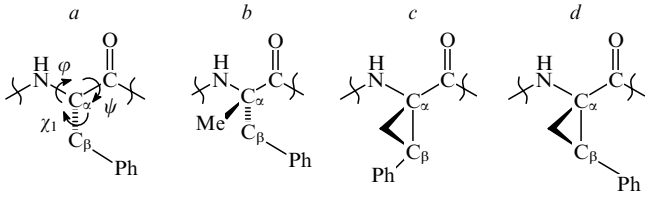
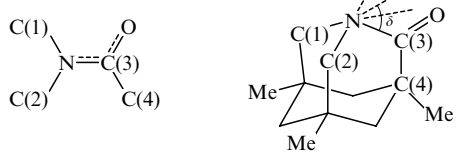


Figure 3. Structural modifications of the L-phenylalanine residue.

example, let us consider a diasteriomeric series of amino acid analogues of L-phenylalanine (Fig. 3).

Replacement of an L-phenylalanine residue (Fig. 3 *a*) in a peptide chain by its α-methyl derivative (Fig. 3 *b*) sterically hinders the free rotation around the bonds $C_\alpha-N$, $C_\alpha-C$ and $C_\alpha-C_\beta$. This modification influences the torsion angles φ, ψ and χ to nearly the same extent. Introduction of rigid analogues of L-phenylalanine containing a cyclopropane moiety (Figs 3 *c* and 3 *d*) results in the fixation of the angle χ_1. This also affects the angles φ and ψ: the L-phenylalanine analogue shown in Fig. 3 *c* is characterised by hindered rotation around the $C_\alpha-N$ bond while that shown in Fig. 3 *d* is characterised by hindered rotation around the $C_\alpha-C$ bond. Additionally, the well-known 'unsaturated' character of the cyclopropane ring results in a decrease in the torsion angle ψ due to the conjugation between the ring and the carbonyl group π-system. Unfortunately, no detailed conformational analysis of this kind for peptide fragments has been performed for almost all known CRA.

Let us now discuss the effects of changes in the torsion angle ω on the conformation of the peptide fragment in the proximity of modification. What is important is that the angle ω does not adequately reflect structural features of the peptide bond NH–CO in all cases. In an ideal case (the $C_\alpha-C-N-C_\alpha$ fragment is planar), this angle is 0° for the *cis*-configuration of the peptide bond and 180° for the *trans*-configuration. In the majority of amino acid residues constituting natural proteins, the peptide bonds have the *trans*-configuration although bonds with the *cis*-configuration are also encountered sometimes. Furthermore, the NH–CO fragment can be non-planar. The *cis*–*trans*-isomerisation of peptide bonds is closely related to many biologically important processes, primarily, to folding and unfolding.[34, 35] It has been shown that amides of cyclic amino acids with a nitrogen atom in the ring (these amino acids form tertiary amides in peptides) are characterised by noticeable pyramidalisation of the nitrogen and carbon atoms of the bond NH–CO and by 'twisting' around this bond. The following parameters have been suggested for quantitative description of the conformation of such a non-planar amide fragment: the twist angle τ [τ is the angle between the planes defined by the atoms C(1)NC(2) and OC(3)C(4)];[36–39] parameters ω_0(N) and ω_0(C), which reflect pyramidalisation of bonds at the nitrogen and carbon atoms, respectively; and the tilt angle (δ) between the N–C(3) bond and the plane defined by the C(1)C(2)N atoms. The substantial pyramidalisation of bonds at the nitrogen atom and 'twisting' of the amide bond can be achieved in rigid systems, such as



[$\tau = \delta = 0°$, ω_0 (N) = 360°]

9 [$\tau = 90°$, $\delta = 57°$, ω_0 (N) = 326°]

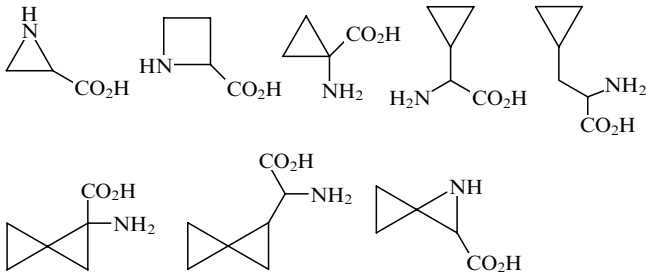
$\tau = [\angle C(4)C(3)NC(2) + \angle OC(3)NC(1)]/2$;
ω_0 (N) = ∠C(1)NC(2) + ∠C(2)NC(3) + ∠C(1)NC(3).

derivatives of 1-azaadamantan-2-one **9**. Thus, angles τ, pyramidalisation parameters ω_0(N) (hereinafter ω_0) and tilt angles δ will be discussed for peptide fragments bearing CRA (provided that the respective information is given in the original papers).

Finally, in the design of peptidomimetics and peptide models based on CRA, one should take into account changes in the chemical properties of the respective peptide fragments induced by the substitution of CRA for natural amino acids.

IV. Conformationally rigid cyclic and spirocyclic amino acids with three- and four-membered rings

The major types of known fragments of CRA, the conformational rigidity of which is due to the presence of small (three- and four-membered) rings are as follows:

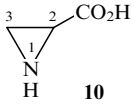


It is of note that the four-membered ring in azetidine-2-carboxylic acid is conformationally flexible but it acquires rigidity in peptides due to involvement of the nitrogen atom of the azetidine ring in the amide bond. Therefore, azetidine-2-carboxylic acid is also classified as a CRA.

A common feature of the CRA described in this section is a significant angle strain within the small rings, which strongly affects not only the structure but chemical properties of both the acids and their derivatives.

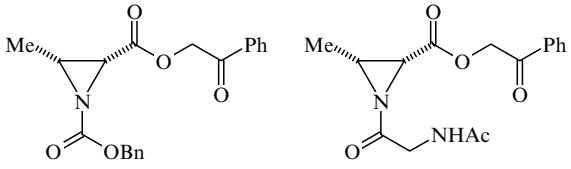
1. Aziridine-2-carboxylic acid and its derivatives

Aziridine-2-carboxylic acid (**10**)‡ may be regarded both as α- and β-amino acid with the angles φ and χ strictly fixed.



10

Unfortunately, there have been only a few structural studies of derivatives of the acid **10**, and no single-crystal X-ray diffraction data on peptides containing this residue have been published so far. Nevertheless, conformational properties of such peptides may be judged from the single-crystal X-ray diffraction studies of compounds **11** and **12**.[34]



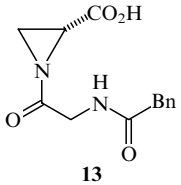
11 **12**

The experimental results suggest significant pyramidalisation of the nitrogen atom, which is evidently a consequence of the angle strain in the three-membered ring. The angle δ in **11** and **12** amounts to 37–38°, *i.e.*, the nitrogen atom is virtually tetrahedral as in the case of sp^3-hybridisation.

‡ The residue of aziridine-2-carboxylic acid in peptides is denoted as Azy.

Single-crystal X-ray diffraction studies of **11**, **12** and aziridine amides demonstrate that the steric strain within the three-membered ring results not only in pyramidalisation of bonds at the nitrogen atom but in the twisting of the amide bond as well. These compounds can serve as models in studies of the transition state of the *cis*–*trans*-isomerisation of amides, *i.e.*, the process that plays a key role in the folding of protein molecules.

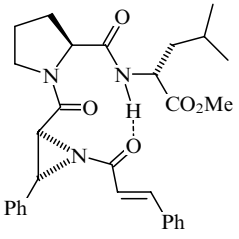
Twisting of the amide bond can lead to substantial changes in the properties of this amide fragment as has been demonstrated in a case study of a derivative of 1-azaadamantan-2-one (**9**).[39] In particular, it was found that twisting results in increased reactivity of the amide bond with respect to nucleophiles and in substantial basicity of the nitrogen atom (pK_a of **9** in water is 5.2). According to calculations,[40] aziridine amides undergo protonation at the nitrogen atom under physiological conditions in contrast to unstrained amides that are very weak bases. This fact is of great importance in the design of peptidomimetics and peptide models comprising Azy.



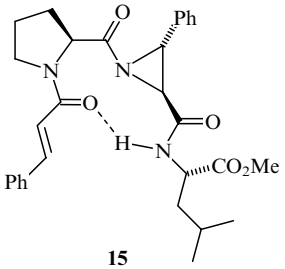
13

In a study on *N*-(phenylacetyl)glycyl-D-aziridine-2-carboxylic acid (**13**),[41] it was found that this compound with a non-planar amide group was a substrate for β-lactamases, which confirmed a hypothesis on the evolution of DD-peptidases into β-lactamases. As a result of this evolution, the enzyme active site is modified so as to provide more efficient binding of non-planar β-lactams (which are natural substrates for β-lactamases) with respect to unstrained planar amides.

The structure of several peptides containing aziridine-2-carboxylic acid residues can be inferred from spectroscopic data. For instance, NMR studies of solutions of the tripeptides **14** and **15**, which contain 3-Ph-Azy residues (a conformationally rigid analogue of phenylalanine) and L-proline, have shown that the terminal amino acid residues form a 10-membered ring involving the hydrogen bonds NH···OC typical of β-bends.[42]



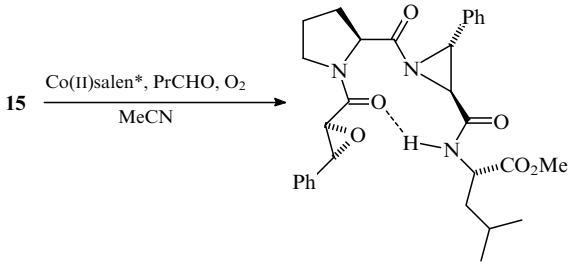
14



15

The tripeptide **15** has been utilised as a model compound to rationalise high diastereoselectivity of epoxidation of double bonds in peptides based on *N*-cinnamoyl-L-proline derivatives catalysed by cobalt(II).[43] It was suggested that the major reason for the stereoselectivity of the epoxidation is the presence of γ- and β-bends in these peptides, which directs the attack of the reagent strictly from one side of the double bond plane. High diastereoselectivity of the epoxidation reaction of the tripeptide **15**, the conformation of which in the region of β-bends is similar to that in the above peptides, has justified this hypothesis.

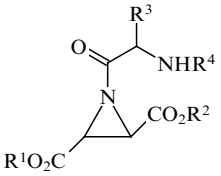
The model studies described above are scarce and by no means systematic. Quite another property of derivatives of aziridine-2-carboxylic acid, *viz*., the ease of opening of the strained three-membered ring under the action of nucleophiles, is exploited more frequently.§ This property makes it possible to use aziridine-2-carboxylic acid and its derivatives as irreversible inhibitors of enzymes. For instance, the acid **10** itself was used as an inhibitor of cysteine proteases. It selectively deactivates the thiol group and does not react with other nucleophilic groups present in the active sites of the proteases.[44]



Co(II)salen* is a polyaniline-supported Co(II)-salen complex.

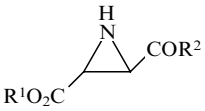
Unfortunately, Azy-containing peptides are toxic due to its high reactivity, which prevents their use as drugs.

Later, a number of inhibitors of cysteine proteases based on aziridine-2,3-dicarboxylic acid (Azi, **16**–**18**) derivatives were discovered. A common structural feature of these inhibitors is the presence of a peptide fragment and a reactive aziridine ring. The peptide fragment binds to the active site of the enzyme and the aziridine ring irreversibly reacts with the thiol group.[45,46] Unfortunately, the influence of the rigid residue of aziridine-2,3-dicarboxylic acid on the conformation of the molecules under study has not been analysed, although it is the conformation of the inhibitor that can define the efficiency of its binding to the active site of the enzymes.



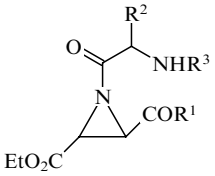
16

R^1 = Et, H; R^2 = Et, Bn; R^3 is an amino acid residue; R^4 is a protecting group, an amino acid or a peptide residue.



17

R^1 = Et, H; R^2 is an amino acid or a peptide residue.

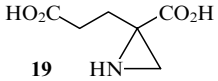


18

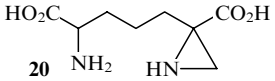
R^1 is an amino acid or a peptide residue; R^2 is a side chain of an amino acid; R^3 is a protecting group.

Recently, the influence of free carboxylic groups in molecules of similar inhibitors on the inhibition efficiency has been investigated.[47]

Among other inhibitors studied, 2-(2-carboxyethyl)- (**19**)[48] and 2-(4-amino-4-carboxybutyl)aziridine-2-carboxylic acids (**20**)[49] are worth noting. They act as irreversible inhibitors of glutamate racemase and diaminopimelic acid epimerase, respectively.



19



20

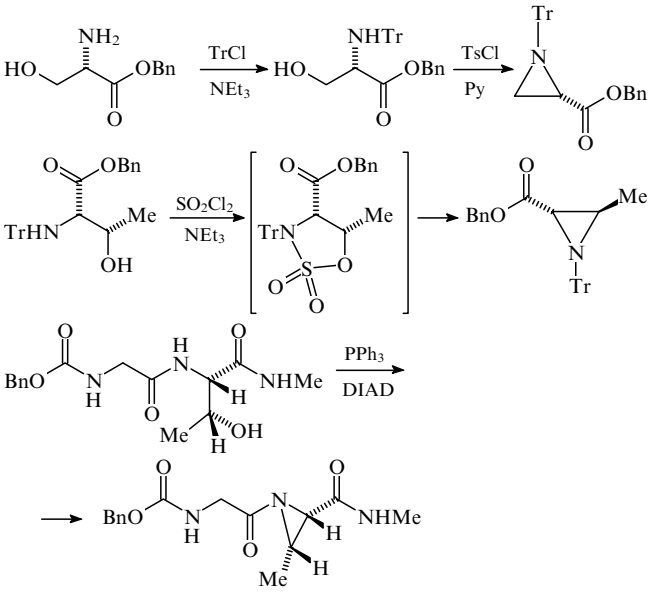
A number of methods for the preparation of aziridinecarboxylic acid and its derivatives have been developed and the major

§ It is of note that the residues of aziridine-2-carboxylic acid or its derivatives in peptides are additionally activated due to the presence of an electron-withdrawing carboxyl group linked to the nitrogen atom.

attention has been paid to the stereoselective syntheses. The development of new methods for the synthesis of these compounds was encouraged by their potential use as convenient precursors of alkaloids, β-lactam antibiotics and other biologically active compounds rather than as conformationally rigid analogues of natural amino acids in the synthesis of peptidomimetics and peptide models.[7] These methods are primarily based on the ease and selectivity of the nucleophilic opening of the aziridine ring.

The basic method for the synthesis of aziridinecarboxylic acid and its derivatives consists of cyclisation of α-amino β-hydroxy acids (Scheme 1), in particular, of serine and threonine.[50–52] (The starting chiral α-amino β-hydroxy acids can be produced from tartaric acid.[53])

Scheme 1

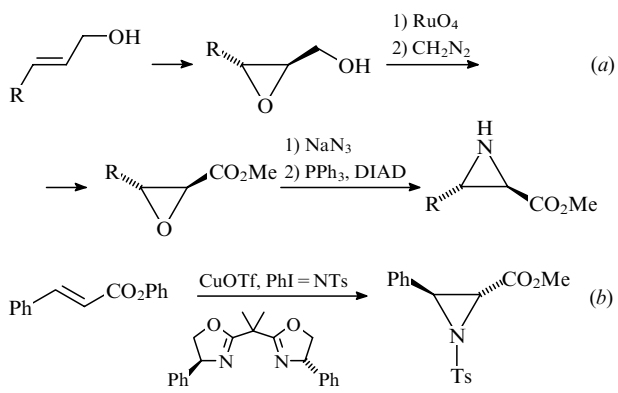


Tr = Ph_3C, Ts = $SO_2C_6H_4Me$-4,
DIAD is diisopropyl azodicarboxylate.

Cyclisation is most frequently performed under conditions of the Mitsunobu reaction (see Scheme 1). For the synthesis of substituted aziridinecarboxylic acids, reactions of sulfinylimides with lithium α-bromoenolates (the aza-Darzen reaction) are typically exploited.[54]

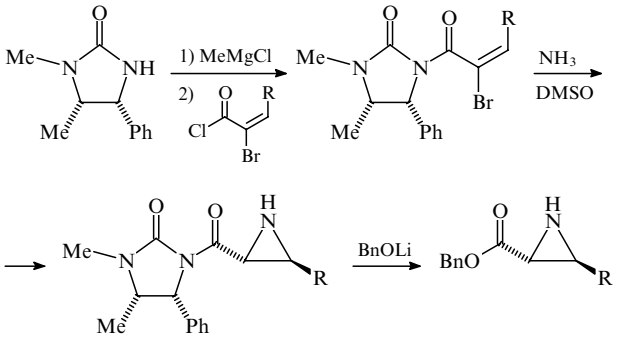
Chiral aziridinecarboxylic acids are prepared through asymmetric synthesis. The current approaches are represented in Scheme 2. The key stage in these transformations is the Sharpless catalytic asymmetric epoxidation (pathway *a*)[55,56] or asymmetric aziridination of a C=C double bond (pathway *b*).[57]

Scheme 2



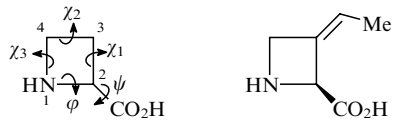
Tf = CF_3SO_2.

Syntheses using chiral auxiliary groups, *e.g.*, (4*S*,5*R*)-1,5-dimethyl-4-phenylimidazolidin-2-one, for the stereoselectivity control are worth mentioning. A scheme of the synthesis of aziridine-2-carboxylic acid derivatives by the Gabriel–Cromwell reaction used to build up the aziridine ring is shown below.[58,59]



2. Azetidine-2-carboxylic acid and its derivatives

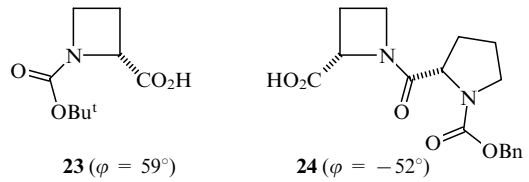
The residue of azetidine-2-carboxylic acid (**21**), when incorporated into a peptide chain, loses its mobility and becomes (φ,χ)-rigid because the nitrogen atom becomes involved in the amide bond.¶ (The Aze residue is the closest homologue of Pro.)



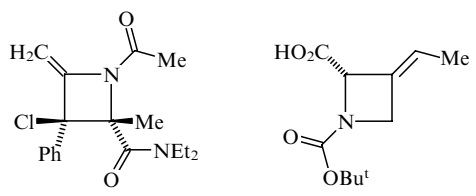
21 **22**

The amino acid **21** has been found in nature.[60] The unique amino acid **22** (polyoximic acid) was isolated from fungicide antibiotic polyoxines (peptide nucleosides).[61] It is noteworthy that the configuration of the exocyclic double bond in **22** was first erroneously assigned as *E*, but later its *Z* configuration was reliably established by structural studies and synthesis.[62]

Following structural elucidation of **21**, it was suggested that the biological activity of peptides containing the Aze residue is determined by the peculiarities of their secondary structures, and the conformational properties of azetidine-2-carboxylic acid differ from those of proline and other natural amino acids. Further structural studies have confirmed this suggestion. Compounds **23**–**26**, which are derivatives of azetidine-2-carboxylic acid[63–65] and *trans*-polyoximic acid,[66] have been used as model substances in the evaluation of conformational features of Aze in peptides.



23 (φ = 59°) **24** (φ = −52°)



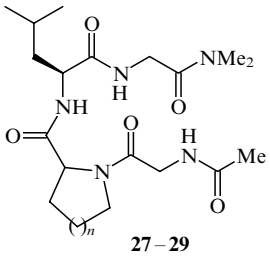
25 (φ = 56°) **26** (φ = −67°)

The azetidine rings in compounds **23**–**26** are virtually planar, which justifies the assignment of the Aze residue to conformationally rigid fragments.

¶ The residue of azetidine-2-carboxylic acid in peptides is denoted as Aze or, less frequently, Azt.

The absolute values of the torsion angle φ in **23**–**26** ($\sim 55^\circ$) are smaller by approximately 20° than in proline ($\sim 75^\circ$), which may be responsible for the differences in conformations of Aze- and Pro-containing peptides. Pyramidalisation of the nitrogen atom in Aze is substantially less pronounced than in a more strained Azy residue; the same is true for the angle δ, which is $\sim 5^\circ$ in **23**–**26** according to X-ray diffraction data. On the other hand, the Aze residue is more strained than Pro, which is reflected in a decrease in the energy barrier to the *cis*–*trans* isomerisation of the peptide bond. According to the results of dynamic NMR studies, the energy barrier to the *cis*–*trans* isomerisation in two model peptides, Ala-Aze-$NHC_6H_4NO_2$-4 and Ala-Gly-Aze-$NHC_6H_4NO_2$-4, is lower than in related peptides Ala-Pro-$NHC_6H_4NO_2$-4 and Ala-Gly-Pro-$NHC_6H_4NO_2$-4 by 10 kJ mol^{-1}.[67]

Taking into account the rigidity of the Aze unit, one should expect that substitution of Aze for Pro in peptides will inevitably affect conformation of the secondary structure elements in those fragments that previously contained proline.[68] Proline residues are often encountered in the $(i+1)$th positions of β-bends.[68] NMR studies of model tetrapeptides **27**–**29** using the NOESY technique showed that all these peptides reveal β-bends, although the distance between terminal amino acid residues in the azetidine-containing peptide ($n = 0$) is longer than in its proline-containing analogue ($n = 1$).[69]



27–**29**

$n = 0$ (**27**), 1 (**28**), 2 (**29**).

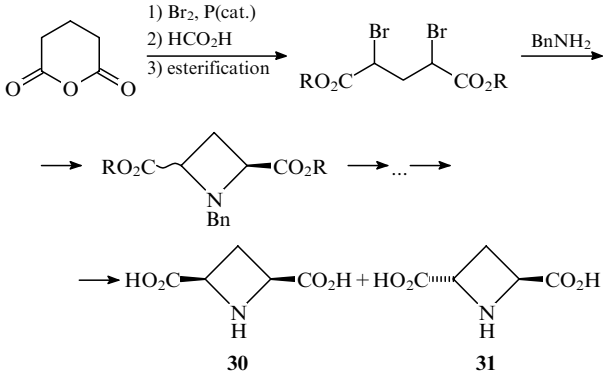
Introduction of 3- or 4-substituted Aze residues into peptides offers extended possibilities of control over the conformation of their side chains owing to the strictly fixed torsion angles χ in Aze. The values of these angles in several peptides containing the Aze residue have been reported.[64, 70]

Although a method for the preparation of racemic azetidine-2-carboxylic acid starting from γ-butyrolactone was developed rather long ago,[71–73] the synthesis of enantiomerically pure azetidine-2-carboxylic acid was accomplished only in 2003.[74] There are only a few efficient stereoselective methods for the preparation of its derivatives substituted at positions 3 or 4.

The isomers of azetidine-2-carboxylic acid **30** and **31** (which may be considered as glutamic acid analogues) were synthesised using a method similar to that applied for unsubstituted acid **21** (Scheme 3).[75]

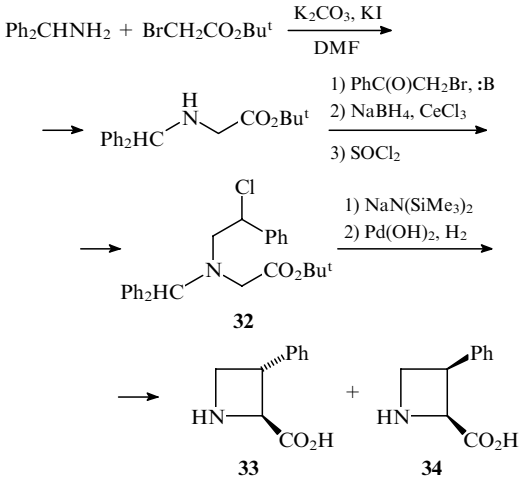
Intramolecular nucleophilic cyclisation has also been used to construct the azetidine ring.[76] In particular, intramolecular nucleophilic substitution of the Cl atom in **32** yielded two diastereomers of 3-phenylazetidine-2-carboxylic acid † **33** and **34** (Scheme 4).

Scheme 3



30 **31**

Scheme 4

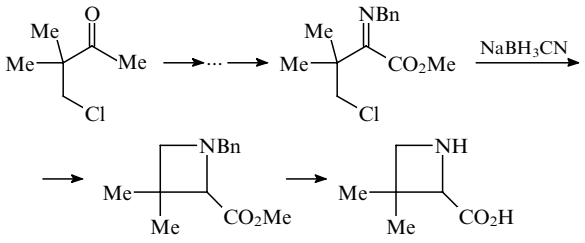


32

33 **34**

In both cases, racemic diastereomeric products were separated using liquid chromatography on silica gel.

Intramolecular nucleophilic cyclisation has also been utilised in the synthesis of 3,3-dimethylazetidine-2-carboxylic acid (an analogue of Leu).[77]



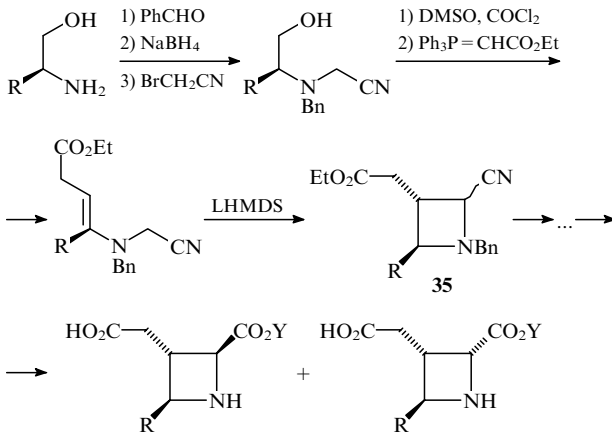
Recently, asymmetric synthesis of 2-cyanoazetidines **35**, precursors of substituted azetidine-2-carboxylic acids, has been accomplished. In this case, the cyclisation was realised through the stereoselective intramolecular Michael addition.[78] The use of optically pure β-amino alcohols as the starting compounds provided enantiomerically pure target amino acids (Scheme 5).

Taking into account that a four-membered ring is substantially less strained than a three-membered ring, one could expect that azetidine-2-carboxylic acid derivatives would appear more suitable for the design of peptidomimetics and peptide models than highly reactive aziridine-2-carboxylic acid derivatives. However, the lack of general stereoselective methods for synthesis of azetidine-2-carboxylic acid derivatives prevented their wide use. The unsubstituted amino acid **21** is the only exception which is available in multigram quantities either synthetically or from natural sources.

The acid **21** was frequently introduced into peptidomimetics in the course of systematic search for new drugs. An investigation into the structure–activity relationship for tripeptide inhibitors of thrombin (*i.e.*, the enzyme that plays an important bioregulative role in blood coagulation) [79] may be mentioned as an example. In particular, it was shown that the inhibition activity of tripeptides is strongly affected by the conformation of the central amino acid residue. Taking this into account, modification of a known thrombin inhibitor, *viz.*, Boc-D-Phe-Pro-Arg-H, by replacing the constituent amino acid residues by their conformationally constrained analogues was carried out.[79] Substitution of conformationally rigid Aze for Pro in this tripeptide resulted in a twofold increase in the inhibitory activity. Conversely, substitution of conformationally flexible residue of pipecoline-2-carboxylic acid

† 3-Phenylazetidine-2-carboxylic acid is a phenylalanine (Phe) analogue.

Scheme 5

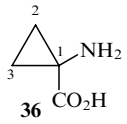


LHDMS is lithium hexamethyldisilazanide.

for Pro decreased the inhibitory activity by about two orders of magnitude.

3. 1-Aminocyclopropanecarboxylic acid and its derivatives

In contrast to aziridine-2-carboxylic acid and its derivatives described above, 1-aminocyclopropanecarboxylic acid (**36**, ACC) and its derivatives are very often used as CRA in the synthesis of peptidomimetics and peptide models.

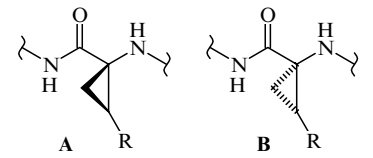


36

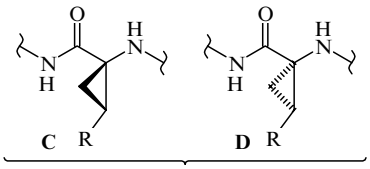
To date, cyclopropane analogues (also referred to as 2,3-methanologues or cyclopropanologues of α-amino acids) of all natural amino acids have been synthesised together with numerous artificial α-amino acids with a cyclopropane ring. Furthermore, starting from these amino acids, an array of peptides have been prepared and their structures, conformations and biological activities have been investigated. There are several reasons for such popularity of ACC and its derivatives. Primarily, it is due to the fact that the conformational rigidity of ACC derivatives (for ACC derivatives, the torsion angle χ_1 is fixed) is achieved by a minor structural modification of the respective conformationally flexible analogues, *viz*., through introduction of a methylene bridge between the α- and β-carbon atoms. This simplifies interpretation of results of conformational and biochemical studies.

Introduction of substituents into the cyclopropane ring provides the structural diversity of this type of CRA, which makes it possible to produce arrays of stereoisomeric amino acids (*i.e*., 'stereolibraries' of CRA).

For instance, 3-substituted ACC exists as four stereoisomers **A**–**D**. The residue of each of the stereoisomers introduced into a peptide is characterised by a specific torsion angle χ_1, which can easily be estimated using molecular mechanics calculations.



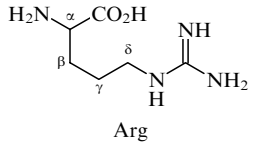
cis-Methanologues ($\chi_1 \approx 0°$)



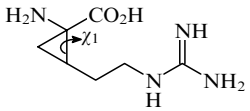
trans-Methanologues ($\chi_1 \approx -145°$ and $145°$, respectively)

For amino acids with a long side chain (*e.g*., for arginine, Arg), two types of methanologues **37** and **38** can be obtained, which differ from each other in the length of the side chain. This increases the number of available topomers of the natural amino acids.

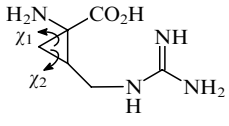
The cyclopropane fragments in the compounds **37** (2,3-methanoarginine, cyclo-Arg) and **38** (cyclo-Arg′) were introduced by insertion of a methylene bridge across the $C_\alpha - C_\beta$ bond and by formation of a $C_\alpha - C_\gamma$ bond, respectively. As a result, cyclo-Arg is characterised by a fixed angle χ_1 whereas in cyclo-Arg′, it is the angles χ_1 and χ_2 that are fixed. Therefore, the conformational mobility of the amino acid **38** is less than that of **37**.



Arg



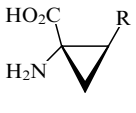
37 (cyclo-Arg)



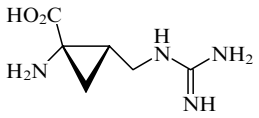
38 (cyclo-Arg′)

Yet another reason for the wide application of ACC and its derivatives in the design of peptidomimetics and peptide models is their accessibility. A number of efficient ways of their synthesis have been developed (including syntheses in gram quantities).

Finally, it is worth noting that 1-aminocyclopropanecarboxylic acid (**36**) itself and some of its derivatives occur in nature. The acid **36** is a precursor of ethylene, a plant hormone, furthermore, it is an important metabolite of methionine in plants.[80] Alkyl-substituted ACC, *i.e*., coronamic acid (**39a**, R = Et) and norcoronamic acid (**39b**, R = Me) have been isolated from hydrolysates of bacterial toxins coronatine and norcoronatine (in *Pseudomonas coronafaciens* and *Pseudomonas syringae*).[81,82] Carnosadine (**40**), which is an arginine analogue, has been isolated from the red alga *Grateloupia carmasa*.[83,84]



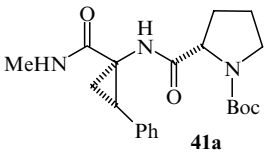
39a,**b**



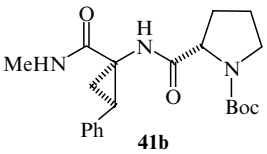
40

Although the number of the known methanologues of natural amino acids is presently quite large, there have been only a few detailed structural and conformational studies of peptides that include these acids. The most studied peptides are those containing methanologues of methionine,[85–87] phenylalanine[88,89] and diphenyl-substituted ACC.[90–92] A number of conformational features have been revealed for the peptides based on ACC derivatives due to the presence of strained conformationally rigid three-membered rings. X-ray diffraction study of model dipeptides R^1CO-L-Pro-c_3Phe-NHR^2 (c_3Phe stands for phenyl-substituted 1-aminocyclopropanecarboxylic acids) **41a**,**b** (see Refs 88, 89) and **42** (see Ref. 92) has shown that the torsion angle χ_1 is virtually constant over this series of compounds and equal, on average, to $7\pm3°$ and $136\pm1°$ for the two diastereomers. The deviations of the angles φ and ψ from the respective mean values are due to steric repulsion of substituents in the cyclopropane rings of dipeptides **41a**,**b** and **42a**,**b** from the atoms that

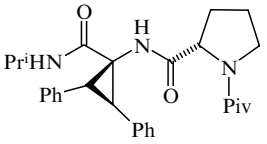
form the polypeptide chain. The absolute value of φ in **41a**,**b**, **42a**,**b**, **43**–**45** is, on average, 83°; and the scatter of this value is quite small, *i.e.*, ~7° (see Refs. 89, 90, 92–95). In the majority of cases, the angle ψ is close to 0°. This suggests that the ACC residue in peptides is not only χ-rigid but φ-rigid as well. X-Ray diffraction study of **45** (which is a 2,3-methanologue of proline) has shown[95] that the angle φ (−76°) virtually does not differ from that in L-Pro. Thus, cyclo-L-Pro can be used as a conformationally rigid proline analogue in the design of peptidomimetics and peptide models.

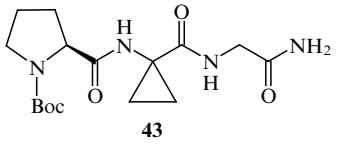


41a



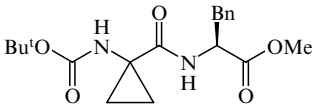
41b



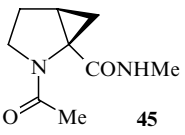


43

42a (2*R*,3*R*), **42b** (2*S*,3*S*)



44

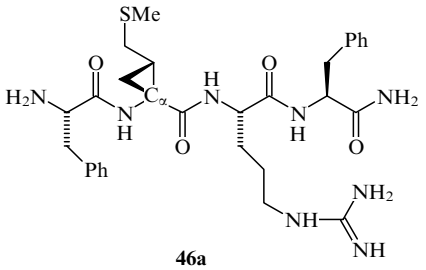


45

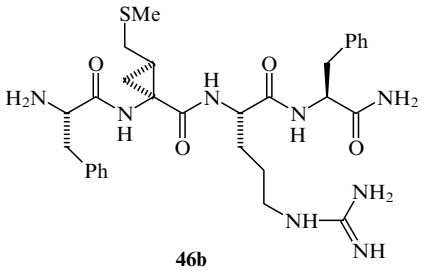
Compound	Torsion angles /deg			Ref.
	φ	ψ	χ_1	
41a	89	−4.5	135	88
41b	77	−11	−4	89
42	86	−20	7 (138)	92
43	84	−8.5	–	93
44	−84.5	0	–	94
45	−76	−7	–	95

From the aforementioned mean values of the torsion angles φ and ψ it was possible to conclude that peptides bearing ACC residues tend to form β-bends with the ACC residues in the (i + 2)th position.[93,94] Undoubtedly, the conformation of peptides in solutions can be different; therefore, the peptides were studied using not only X-ray diffraction, but NMR and IR spectroscopy and computer simulations as well.[88,89] It was concluded that 2,3-methanophenylalanine (a phenylalanine analogue) induces formation of β-bends in peptides, the type of the bend (β-I or β-II) being governed by the orientation of the substituent (Ph) at the C(3) atom of the cyclopropane ring, which is dictated by the strictly fixed torsion angle χ_1. For the model dipeptides **41a**,**b**, it has been shown experimentally for the first time that the orientation of the side chain can induce a specific conformation of the polypeptide chain.

The influence of methionine *cis*- and *trans*-methanologues on the conformation of peptides has been elucidated for the peptidomimetics **46a**,**b** as examples.[85–87] The conformation of **46a**,**b** in solutions has been studied using NMR and circular dichroism spectroscopy supplemented with computer simulations.[86,87] It was found that introduction of methionine methanologues into peptides gives rise to γ-bends irrespective of the isomer. Presumably, the tendency to form γ-bends relates not only to fixed values of the torsion angles φ and ψ, but to a larger value of the N−C_α−C(O) bond angle (117°) as well, which, in these compounds, substantially exceeds the corresponding values typical of residues of unstrained amino acids (~ 112° according to the CSD data).



46a

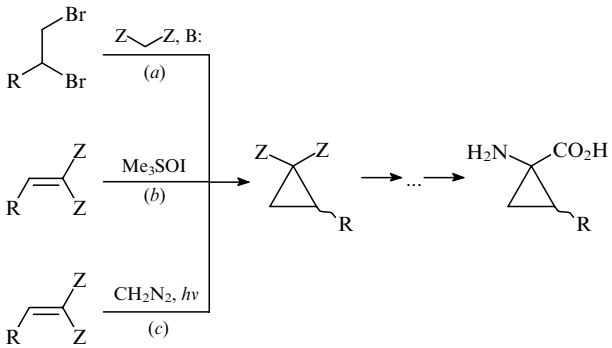


46b

The synthesis of methanologues of natural and other amino acids with a cyclopropane ring has been recently surveyed.[4,6] Therefore, in the present review we shall just outline the known methods for the preparation of ACC and discuss in more detail only methods developed in recent years.

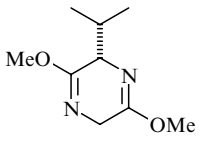
Among the most frequently applied methods of synthesis of ACC, the following are the most popular: bisalkylation (*a*), addition of oxosulfonium ylides (*b*) and 1,3-dipolar cycloaddition of diazomethane (*c*) (Scheme 6).[6]

Scheme 6

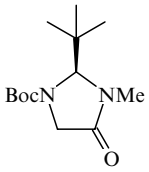


Z is an electron-withdrawing group.

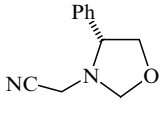
For the preparation of optically active amino acids, diastereo- and enantioselective syntheses have been developed, which make use of chiral auxiliary groups. Essentially, these syntheses exploit asymmetrical versions of the reactions *a*–*c* (Scheme 6). For instance, the bisalkylation (*a*) was conducted with a chiral glycine equivalent, *i.e.*, the Schollkopf bislactim esters (**47**),[96] the Seebach imidazolidinones (**48**)[6] or 1,3-oxazolidine chiral derivatives (**49**).[6] The diastereoselective addition of oxosulfonium ylides to derivatives of tetrahydrooxazinone **50** (*b*) has led to methanologues of amino acids. The 1,3-dipolar cycloaddition of diazomethane (*c*) was realised for a terpenoid derivative **51**.[6]



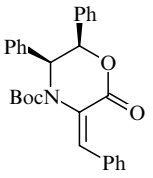
47



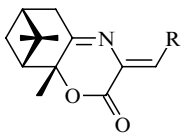
48



49

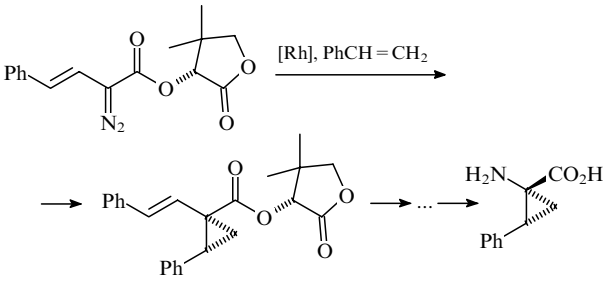


50



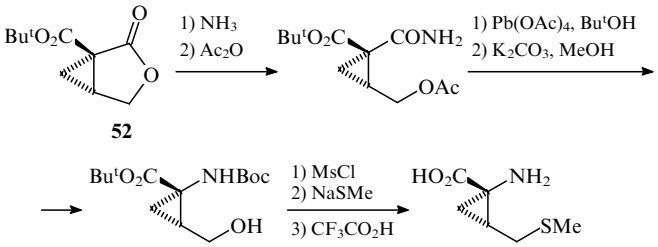
51

Elaboration of the synthetic routes that allowed preparation of ACC and its derivatives in multigram quantities is a significant achievement in this field. Among such routes, preparation of (2*R*,3*R*)-cyclo-Phe catalysed by rhodium complexes is worth a special note.[6]



Syntheses of ACC derivatives including cyclo-Met, cyclo-Arg, cyclo-Arg′, cyclo-Glu, cyclo-Gln and cyclo-Lys starting from a chiral lactone **52** proved to be extremely efficient. This lactone can be synthesised from D-mannitol, which is an accessible natural chiral compound.[6] The strategy of the synthesis of ACC derivatives starting from the lactone **52** is illustrated in Scheme 7 with (*Z*)-cyclo-Met as an example.

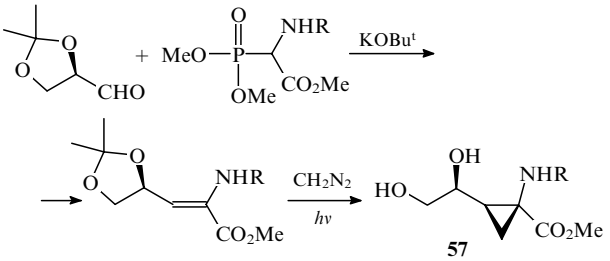
Scheme 7



52

In a series of recent studies, available chiral compounds have been used as the starting materials in the stereoselective synthesis of ACC derivatives. In particular, starting from the optically active alcohols **53** and **54**, *allo*-norcoronamic acid (**55**) and (2*S*,3*R*)-methanoproline (**56**), respectively, were synthesised (Scheme 8). The key step in these syntheses was the condensation of the corresponding cyclic sulfates with methyl benzylideneglycinate.[97, 98]

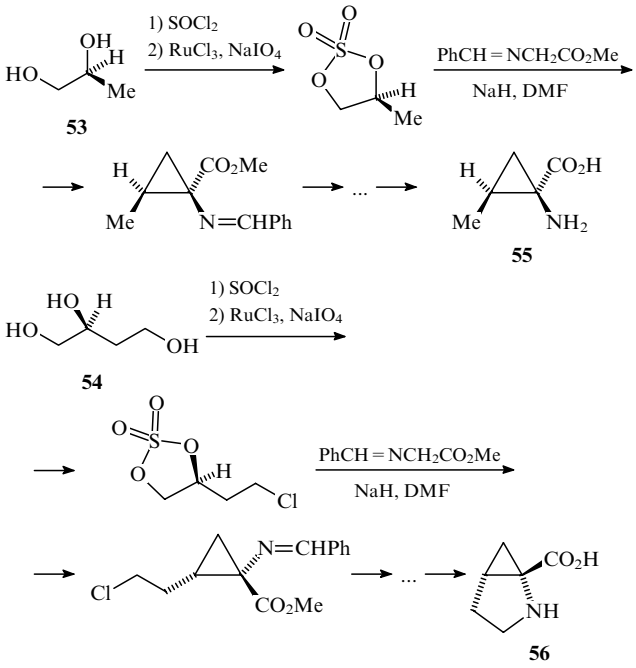
Several methanologues of natural amino acids have been prepared by functionalisation of a dihydroxy-derivative **57** synthesised starting from D-glyceraldehyde.[99]



57

Transition metal complexes are often used in the stereoselective syntheses of ACC derivatives both as catalysts and reagents. The use of palladium complexes in the synthesis of functionalised cyclopropane derivatives [100, 101] and the stereoselective cyclopropanation of alkenes by Fischer dialkylaminocarbene complexes [102] have been reported.

Scheme 8



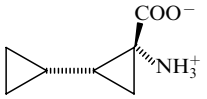
53

55

54

56

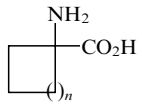
ACC, its derivatives and peptidomimetics or peptide models based on them have been the subject of numerous biochemical studies. The most prominent examples will be given here. As has been mentioned above, ACC is a precursor in the biosynthesis of ethylene. This reaction is catalysed by the iron-containing enzyme ACC oxidase. Two mechanisms of functioning of this enzyme have been suggested,[103] *viz*., nitrene- and radical-mediated ones. Recently, convincing arguments in favour of the free radical-mediated biochemical conversion of ACC into ethylene have been obtained. The formation of penta-1,4-diene upon oxidation of 2-cyclopropyl-substituted ACC (**58**) in the presence of this enzyme may be considered as an indirect proof of this suggestion.[104]



58

Russian scientists have observed [105] formation of tetrachlorophenoxy radicals upon enzymatic oxidation of ACC *in vitro* in the presence of an inhibitor, *viz*., tetrachlorohydroquinone, which also supports the radical mechanism of ACC oxidase action. ACC itself,[106] its various alkyl derivatives,[107–109] cyclo-Pro [95] and the respective hydroxamic acid [110] have been used to study the topology of the active site of ACC oxidase and the mechanism of its action.

An interesting example of studies aimed at the elucidation of factors responsible for the sweet taste of asparagine-containing dipeptides is the use of peptides containing ACC or its alkyl-substituted derivatives. Substitution of an ACC residue or its homologues, *i.e*., 1-aminocycloalkanecarboxylic acids **59**–**63**, for an L-Phe residue in Aspartame® (L-Asp-L-Phe-OMe) made it possible to reveal the dependence of the taste properties of the respective dipeptides on the steric volume of the C terminal residue. In particular, substitution of the ACC residue (**36**) and its homologues **59** and **60** for L-Phe retains the sweet taste of the dipeptide. At the same time, substitution of the residues **61** and **62** for L-Phe yields bitter dipeptides whereas the peptide containing a residue of **63** is tasteless.[111]



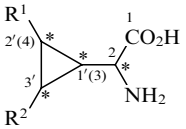
59 – 63

n = 1 (**59**), 2 (**60**), 3 (**61**), 4 (**62**), 5 (**63**).

Later, conformations of similar dipeptides containing residues of methyl-, dimethyl- and trimethyl-derivatives of ACC were analysed.[112] It was concluded that the observed changes in taste of the dipeptides are defined by their conformation, which depends upon the configuration of the cyclopropane-containing CRA in the dipeptide.

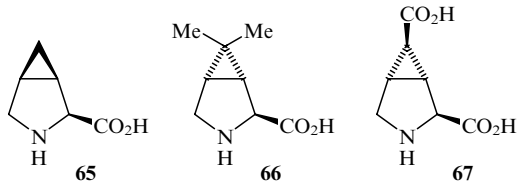
4. 3,4-Methanologues of α-amino acids

3,4-Methano-α-amino acids **64** are structural isomers of the 2,3-methano-α-amino acids discussed above.



64

Molecules of 2,3-methanoamino acids are characterised by the fixed torsion angles $\chi_{1(2)}$ whereas their 3,4-cyclopropyl analogues reveal strictly fixed torsion angles $\chi_{2(3)}$. The presence of a cyclopropane fragment in such amino acids imposes only small restrictions on the angle χ_1 and does not influence significantly the angles of the peptide chain in the corresponding peptides. An exception to this tendency is the respective proline analogue, one isomer of which, *viz*., *cis*-3,4-methylene-L-proline (**65**), has been found in nature. Its structure has been confirmed by X-ray diffraction study and synthesis.[113]

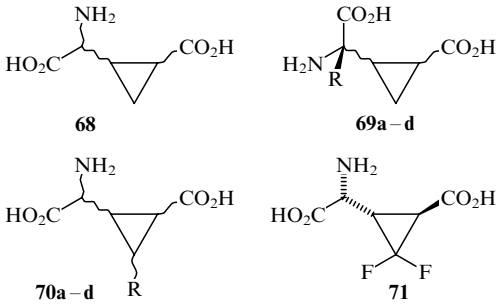


65 **66** **67**

In the 3,4-methanologue of proline, the torsion angles φ and χ are also fixed. This property was successfully employed in the design of mimetics of the polyproline II helix, which plays an important role in the processes of intracellular signal transmission.[114] The chimeric amino acids **66** and **67** have been investigated. They may be considered as analogues of both proline and leucine (the former) and proline and glutamic acid (the latter). A detailed conformational analysis of di- and tripeptides containing residues of **66** and **67** has shown that the torsion angles φ, ψ, χ_1 and χ_2 therein are $-70°$, $131°$, $-57°$ and $-158°$, respectively. These values agree with angles typical of the left-handed helix conformation of polyproline II (see Table 1).[115, 116] This conformational analysis was performed on the basis of the NMR data (for **66**) and results of computer simulations (for **66**, **67**). It is noteworthy that the calculations using molecular mechanics (MM) and *ab initio* (HF/6-31G* basis set) approaches yielded virtually identical geometric parameters of these two molecules. This illustrates an important advantage of the use of CRA in the design of peptidomimetics: the structure of their peptide fragments can be predicted on the basis of simple computational methods.

Compilation of 'stereolibraries', *i.e*., diastereomeric series of amino acids differing from each other in the configuration of chiral centres, is also possible for 3,4-methanologues. For instance, 2′-substituted derivatives have eight stereoisomers while 2′,3′-disubstituted amino acid analogues have sixteen isomers.

The large number of stereoisomers of 3,4-methanologues has been used in a study of neuroreceptors activated by L-glutamic acid. At present, several types of receptors that interact with L-glutamic acid are known. It has been suggested that L-glutamic acid interacts with different receptors adopting different conformations. This hypothesis was strongly supported by the synthesis and investigation of all diastereomers of 2-(carboxycyclopropyl)-glycine (CCG) **68**.[117, 118]

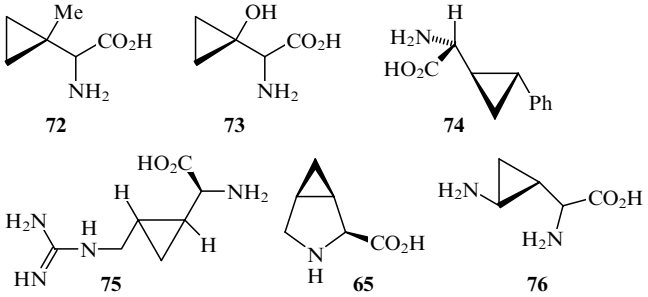


68 **69a – d** **70a – d** **71**

R = Alk (**a**), Ph (**b**), CH_2OMe (**c**), CO_2H (**d**).

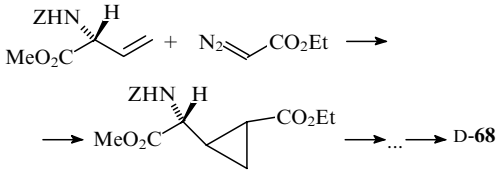
It was established that in many cases the diastereomers CCG interact with different neuroreceptors selectively. Synthesis and biological studies of α-substituted derivatives of CCG, compounds **69a – d** [119, 120] as well as the compilation of 'stereolibraries' for 2′,3′-disubstituted derivatives **70a – d** [121 – 125] and the synthesis of difluoro-substituted derivative **71** [126] provided further confirmation of this hypothesis and a significant contribution to the understanding of mechanisms of neurophysiological processes. All 16 stereoisomers of 2′-carboxy-3′-phenylcyclopropylglycine (**70b**) have been synthesised.

Analogues of other natural amino acids, such as valine, serine,[127] homophenylalanine,[128] arginine,[129] proline [130] and ornithine [131] (**72 – 75**, **65** and **76**) have also been synthesised.



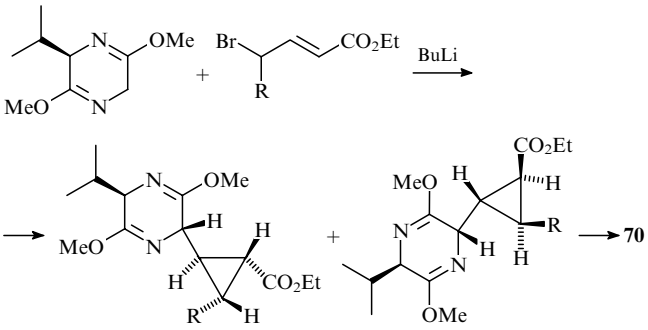
72 **73** **74** **75** **65** **76**

Methods for the synthesis of 3,4-methanologues of amino acids are analogous to those of 2,3-methanologues. Similarly, the key step of these syntheses usually consists of the build up of a cyclopropane ring. In this respect, major efforts were aimed at the optimisation of the respective tranformations to the suitable level of diastereoselectivity. The most frequently applied method is cyclopropanation of a C=C double bond, *i.e*., addition of carbenes or carbenoids. The synthesis of D-2-(carboxycyclopropyl)glycine can be mentioned as an example of this approach.[118]

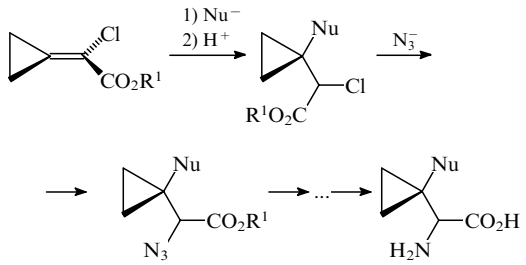


For the preparation of glycine derivatives (*e.g.*, of **70**), the Michael addition followed by elimination of hydrogen bromide was also applied to form a cyclopropane ring (Scheme 9).[121]

Scheme 9



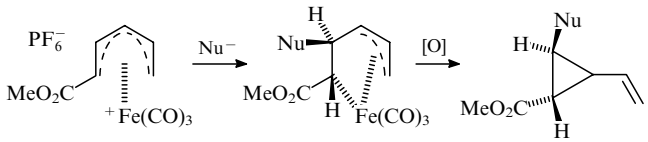
An original route to the synthesis of substances from this class of CRA has been suggested by de Meijere *et al.*[127] This involves 1,4-addition of nucleophiles to 2-chloro-2-cyclopropylideneacetates with subsequent substitution of azide for chloride, reduction and deprotection.



Nu = H, Me, NH_2, CH_2CO_2H, SMe.

The key step of the synthesis of proline 3,4-methanologues [130] is the formation of the pyrrolidone ring as a result of the intramolecular insertion of a carbene (*viz.*, cyclopropylidene) at the C–H bond.

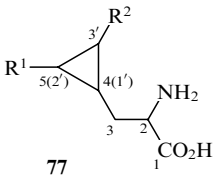
Yet another new original approach to the synthesis of carboxycyclopropylglycine derivatives consists of the addition of stabilised C-nucleophiles to tricarbonyl(1-methoxycarbonylpentadienyl)iron cation.[132]



Nu is a glycine synthon.

5. 4,5-Methanologues of α-amino acids

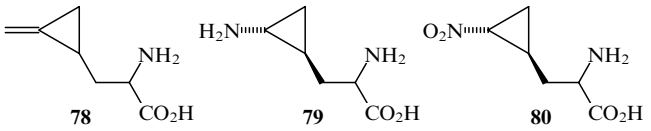
4,5-Methano-α-amino acids (**77**) are used in the synthesis of peptidomimetics and biologically active substances substantially less frequently. It is no surprise since only the torsion angle χ_3, which is situated quite far from the peptide chain, is strictly fixed in these molecules.



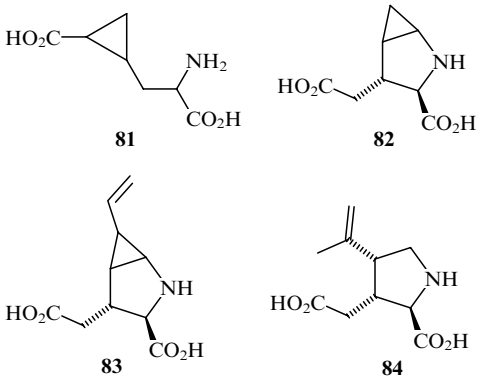
77

4,5-Methanologues of amino acids can be classified as CRA only formally. The presence of a cyclopropane moiety in 4,5-methano-α-amino acids imposes only small constrains on the torsion angle χ_2 and virtually does not affect the torsion angles φ and ψ within the polypeptide chain as well as the angle χ_1 in the respective peptides.

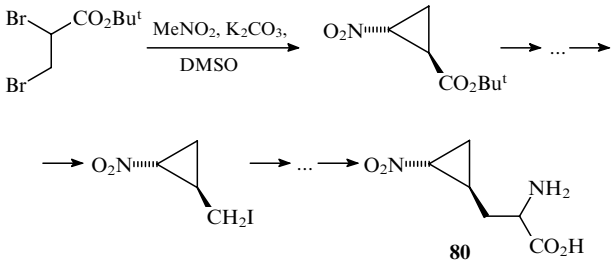
Although 4,5-methanologues of amino acids have attracted insignificant attention from researchers, they are quite abundant in nature. In particular, the compound **78**, the so-called hypoglycine A, occurs in some unripe fruits.[133] Another derivative, *trans*-(2-aminocyclopropyl)alanine (**79**), is the key component of a novel antitumour antibiotic Belastosin A.[134] Yet another derivative, *trans*-(2-nitrocyclopropyl)alanine (**80**), represents a rare example of a naturally occurring substance bearing a nitro group;[135] it is a component of a macrolide antibiotic Hormaomycine.



This class of compounds also includes the recently synthesised 2-aminoadipic acid analogue **81** [136] as well as chimeric amino acids **82** and **83**, which may be regarded as analogues of glutamic acid and proline simultaneously (the acid **83** also contains a fragment of α-cainic acid **84**, which is a naturally occurring non-proteinogenic amino acid).[137]

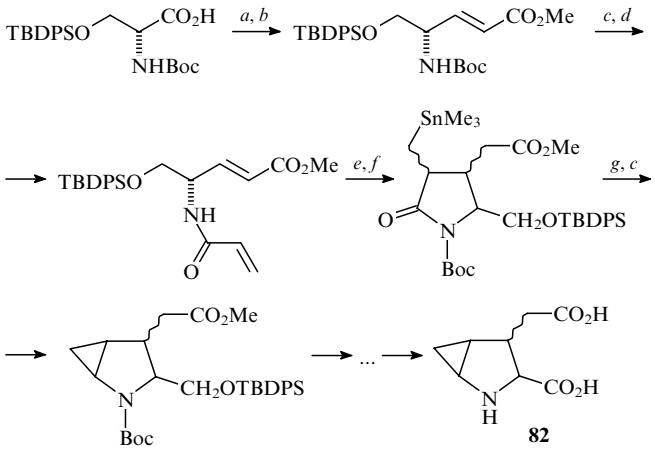


As in the case of 3,4-methanologues, the key step in the synthesis of compounds **78**–**83** is the construction of a cyclopropane ring or of a bicyclic core in the case of **82** and **83**. For the synthesis of **80**, the three-membered ring was formed using alkylation of nitromethane (the Henry reaction).



In the synthesis of compounds **82** and **83**, the five-membered and three-membered rings are built up consecutively. For instance, the acid **82** was synthesised according to Scheme 10.

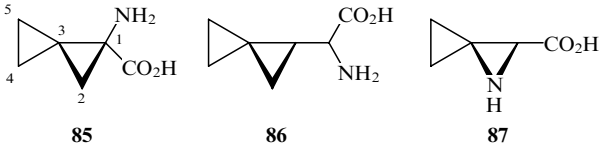
Scheme 10



TBDPS is *tert*-butyldiphenylsilyl;
(*a*) Bu^i_2AlH; (*b*) $Ph_3P=CHCO_2Me$; (*c*) CF_3CO_2H; (*d*) $CH_2=CHCOCl$; (*e*) Me_3SnCl, $NaBH_3CN$, azobisisobutyronitrile; (*f*) Boc_2O, 4-dimethylaminopyridine, Et_3N; (*g*) $LiBHEt_3$.

6. Spiro[2.2]pentane derivatives

Three types of spirocyclic CRA (compounds **85**–**87**) have been synthesised.



85 **86** **87**

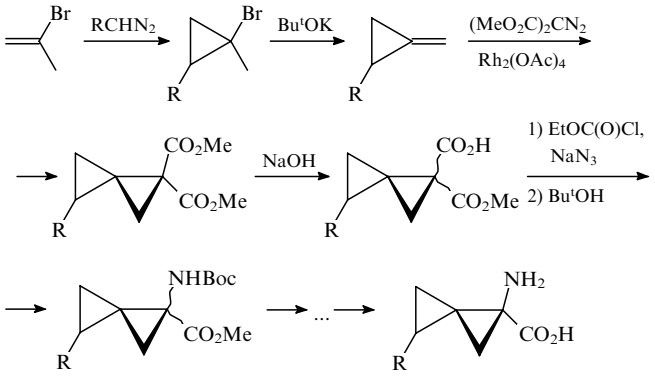
The molecule **85** with a spiro[2.2]pentane skeleton is characterised by the bond lengths and angles strongly distorted with respect to standard mean values.[26, 138] In particular, the C–C bonds involving the spiroatoms C(3) are shortened on average by 0.07 Å, while the bond angles are distorted even more strongly (the values lie in the range from 59° to 135°).

No structural data on the compound **87** with a 1-azaspiro-[2.2]pentane framework have been published. The torsion angles in the molecule **85** have been reported by Pelliciari *et al.*,[138] the corresponding values for **87** can be estimated only approximately.

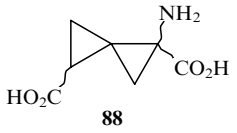
Compounds with spiro[2.2]pentane and 1-azaspiro[2.2]pentane frameworks are synthesised by different routes.

In particular, two consecutive [2 + 1]cycloaddition reactions involving carbene or carbenoid intermediates have been used for the preparation of 2-aminospiro[2.2]pentane-2-carboxylic acid (Scheme 11).[139]

Scheme 11

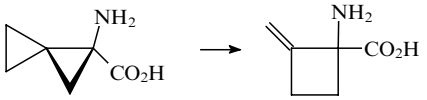


This route was also applied to the synthesis of compounds **85**, **86** and 4-carboxy-substituted derivative **88**, an analogue of glutamic acid. The latter compound was obtained in the form of four diastereomeric pairs.



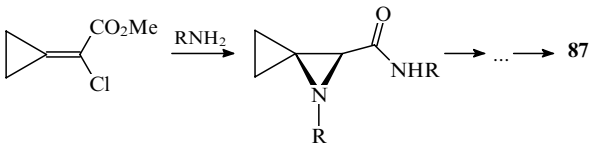
88

It is of note that compound **85** is unstable and spontaneously rearranges into a cyclobutane derivative **89** in aqueous solution in 2 weeks.[139]



85 **89**

1-Azaspiro[2.2]pentane-2-carboxylic acid (**87**) is formed by the reaction of methyl(chloro)cyclopropylideneacetate with primary amines or ammonia.



The amino acid **87** has proven to be relatively stable, it has been used to prepare a glycine-containing dipeptide.[140]

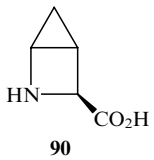
Diastereomers of compound **88** have been extensively studied as regards their binding to typical ionotropic and metabotropic glutamic acid receptors. Since the results of the biological assays were negative in all cases, one may assume that all these compounds are characterised by a spatial configuration of functional groups energetically unfavourable for glutamic acid. Weak binding was observed only with ionotropic *N*-methyl-D-aspartate (NMDA) receptor.[138]

V. Bi- and polycyclic conformationally rigid amino acids with an endocyclic nitrogen atom

Amino acids discussed in this and following sections represent bi- or polycyclic structures, which enable fixation of a larger number of torsion angles as compared to the monocyclic CRA discussed above.

This Section is devoted to amino acids possessing an amine nitrogen atom incorporated into a polycycle. Consequently, the torsion angle φ is strictly fixed in all corresponding peptides. Furthermore, the torsion angle χ_1 (and very often other angles χ as well) is fixed.

It is convenient to classify these amino acids according to the ring containing the nitrogen atom. There are only a few published examples of compounds possessing three- and four-membered C_nN rings (n = 2, 3). In addition to the spirocyclic compounds considered above, 2-azabicyclo[2.1.0]pentane-3-carboxylic acid (also referred to as 3,4-methanoazetidine-2-carboxylic acid **90**) has been reported.[141]



90

On the other hand, amino acids with larger C_nN rings ($n \geqslant 6$) are not rigid (furthermore, such amino acids are rare). Therefore, only amino acids with five- and six- membered C_nN rings ($n = 4$, 5), which are proline and pipecolic acid analogues, respectively, will be discussed below.

1. Proline analogues

Proline occupies a special place among proteinogenic amino acids due to its unique structure. In this amino acid, the amine nitrogen atom is involved in the five-membered ring, which gives rise to the following changes in the conformation of a proline-containing polypeptide chain:

— due to the absence of a hydrogen atom at the nitrogen atom, the latter cannot form hydrogen bonds;

— the *trans*-configuration of a polypeptide chain becomes only slightly more favourable than the *cis*-configuration;[142–144]

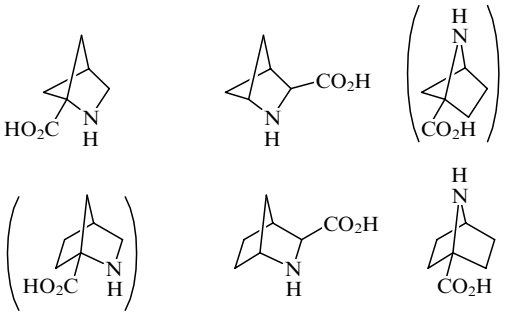
— due to steric hindrance, the values of the torsion angle φ within the five-membered ring vary in the range of $-75^\circ \pm 30^\circ$ (see Ref. 20) (the range of possible values of the torsion angle ψ is also limited due to steric requirements);

— due to significant steric strains, the nitrogen atom is substantionally pyramidalised and the amide bond is twisted;[142, 145]

— the polypeptide loses its capability to form α-helices and thus the tendency towards formation of β-bends is strengthened (especially in the case of the *cis*-configuration of the peptide bond), which explains the higher content of proline in active and peptide-binding sites of enzymes.[144]

It is of note that the above features are typical to a certain extent of all amino acids having an endocyclic nitrogen atom involved in the polypeptide chains. These are more pronounced for amino acids with strained rings.

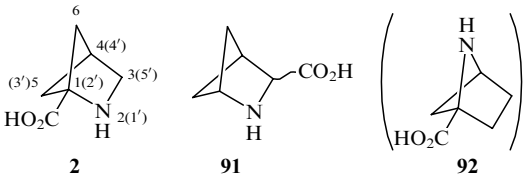
In order to confer conformational rigidity on the proline ring, it is necessary to introduce bridges with a length of 1 or 2 atoms into the molecule. When such a bridge links two adjacent positions in the ring, proline methanologues are formed, which were considered above. Other examples of theoretically possible bicyclic amino acids representing proline analogues are shown below (hereinafter, the structural types that have not been reported in the literature to date are given in parentheses):



Polycyclic proline analogues with more than two rings will be discussed separately.

a. 2-Azabicyclo[2.1.1]hexane derivatives

2-Azabicyclo[2.1.1]hexane-1-carboxylic acid (**2**) or 2,4-methanoproline (atom enumeration in parentheses corresponds to that for proline) was isolated in 1980 from the seeds of legume *Ateleia herbert smithii* among other new amino acids.[146] Recently, this acid has also been isolated from the plant *Bocoa alterna*.[147]



2 **91** **92**

2,4-Methanoproline (**2**) is one of a few naturally occurring proline analogues; the residue of this amino acid in peptides is denoted as 2,4-MePro. In addition to 2,4-methanoproline, two other proline analogues having an azabicyclo[2.1.1]hexane skeleton are possible, *viz*., 3,5-methanoproline (*exo*-**91**) and 2,5-methanoproline (**92**).

exo-3,5-Methanoproline and 2,4-methanoproline **2** have been synthesised quite recently,[148] whereas no synthesis of their 5-aza-analogue **92** has been reported so far.

The bond lengths in the molecule of 2-azabicyclo[2.1.1]hexane-1-carboxylic acid (**2**) are very similar to those in proline but the bond angles in the two molecules are somewhat different (Table 2).[145, 149] The largest difference is observed for the C(2′)–C(3′)–C(4′) and C(2′)–C(6)–C(4′) angles due to the strain in the cyclobutane moiety. The differences in the C(3′)–C(4′)–C(5′) and C(3′)–C(4′)–C(6) angles are probably caused by a specific distortion of the framework, which will be discussed below.

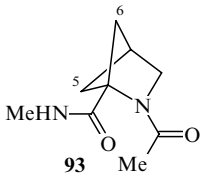
Table 2. The values of the bond angles in 2,4-methanoproline and proline (atom enumeration corresponds to that in proline).

Angle	Value (deg)	
	2,4-MePro	Pro
N–C(5′)–C(4′)	97.0	103
C(3′)–C(4′)–C(5′)	103.1	103
C(3′)–C(4′)–C(6)	100.5	103
C(2′)–C(3′)–C(4′)	82.4	103
C(2′)–C(6)–C(4′)	81.9	

Polypeptides containing a 2,4-MePro residue are characterised by fixed torsion angles φ and χ (the values of these angles may be found elsewhere [149, 150]).

No structural data on 3,5-methanoproline have been published. However, owing to the rigidity of its bicyclic framework, its structural parameters can be predicted on the basis of respective data for the 2,4-isomer.

One may conclude that the angle φ in the 2,4-MePro residue should be 0° assuming the symmetry of the 2-azabicyclo[2.1.1]-hexane framework and planarity of the amide moiety. However, the experimental value of this angle determined for *N*-acetyl-2,4-methanoproline-*N*′-methylamide (**93**)‡ is 29° (see Ref. 150).



93

The observed deviation from the ideal value of 0° is due to distortion of the 2-azabicyclo[2.1.1]hexane framework of **93**, which results in the non-equivalency of the C(5) and C(6) atoms.

The sum of the bond angles at the nitrogen atom in **93** is 356°, *i.e*., virtually no pyramidalisation of the nitrogen atom occurs. This supports the above suggestion that the distortion of the angle φ originates in the deformation of the framework. Numerous structural data on the unsubstituted acid **2** in solutions suggest that the molecules of **2** exist in the form of two interconverting enantiomers, which means, strictly speaking, that they are not rigid.

‡ This type of compounds are quite often applied to prepare peptide models in order to estimate the torsion angles in the respective polypeptide chain.

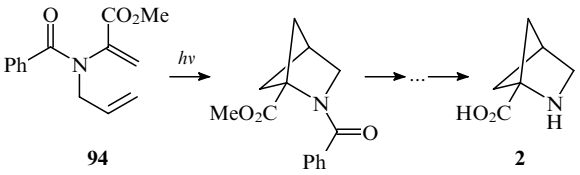
The value of the angle φ in peptides containing an *exo*-3,5-methanoproline (**91**) residue should be -60° taking into account the fact that the bicyclic framework is symmetrical and the amide bond is planar. However, the bicyclic framework is expected to be distorted in this case as well.

The tilt angle (δ) of the amide bond (at the tertiary nitrogen atom) in compound **93** is 16° and the twist angle $\tau = 10^\circ$.

The torsion angle ω in compound **93** is equal to -178° (this molecule adopts the *trans*-conformation in crystals). As has been shown, the *trans*-isomer of **93** is more stable than the *cis*-isomer both in the solid state and in solutions.[149, 150]

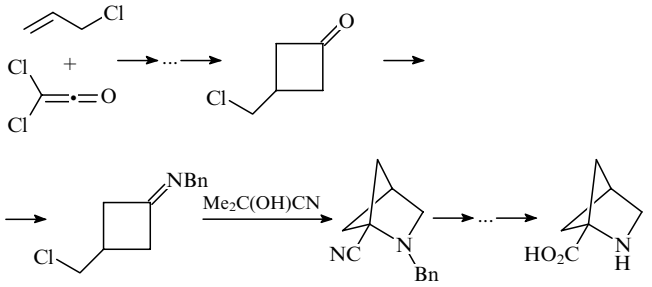
There are several approaches to the synthesis of 2,4-methanoproline. All of them are based on the [2+2]-cycloaddition reaction.

Earlier,[151–153] the photochemical cyclisation of the diene **94** was employed (the only difference between several suggested procedures consisted of the routes for the preparation of the diene **94**).



94 **2**

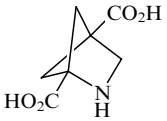
Alternatively, a recently suggested method for the synthesis of 2,4-methanoproline includes [2+2]-cycloaddition with dichloroketene followed by cyclisation.[154]



Rearrangement of 2-azabicyclo[2.2.0]hex-5-enes following addition of bromine[155] is rarely used for the preparation of 2,4-methanoproline due to difficulties associated with the introduction of a 1-carboxy group. Nevertheless, this reaction is a very promising method for the formation of the 2-azabicyclo[2.1.1]-hexane framework.

Although 2-azabicyclo[2.1.1]hexane has been known for a long time, it has rarely been used for the synthesis of amino acids. For instance, carboxylation of unsubstituted 2-azabicyclo[2.1.1]-hexane cannot be regarded as a method for the preparation of 2,4-methanoproline since it yields an equimolar mixture of 2,4- and 3,5-methanoprolines (it is of note, however, that it is exactly by this route that the 3,5-isomer **91** has been produced).[148]

Only one functionalised 2,4-methanoproline derivative, *viz*., glutamic acid analogue **95**, has been synthesised to date. It is formed in the photochemical [2+2]-cyclisation of the respective diene precursor[156] (similar to the synthesis of the acid **2** from the diene **94**).



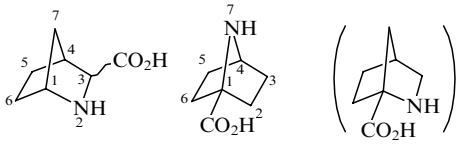
95

Like other functionalised proline analogues, the amino acid **95** is chimeric since it simultaneously mimics glutamic acid and proline.

The biological activity of 2,4-methanoproline and its derivatives is quite well explored. In particular, 2,4-methanoproline has been introduced in place of proline into oligopeptides bradykinin and angiotensin II[157] that are neurotransmitters playing a crucial role in the regulation of blood pressure and heart functioning. Unfortunately, the synthetic analogues proved less active than the original oligopeptides. Compound **95** has been tested as an inhibitor of a sodium-dependent glutamate transport protein.[156]

b. Derivatives of 2-azabicyclo[2.2.1]heptane-3-carboxylic and 7-azabicyclo[2.2.1]heptane-1-carboxylic acids

Compounds with the norbornane framework are widely employed in the synthesis of diverse conformationally rigid substances. In particular, aza-derivatives of norbornane have been used in the design of CRA analogous to proline. In principle, there are three possible variants of incorporation of proline into the norbornane framework (compounds **96**–**98**).

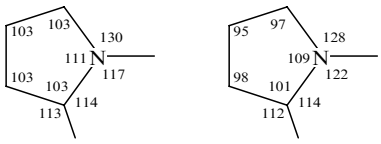


96 **97** **98**

To date, only 2-azabicyclo[2.2.1]heptane-3-carboxylic (**96**) and 7-azabicyclo[2.2.1]heptane-1-carboxylic (**97**) acids along with some of their derivatives have been synthesised.

2-Azabicyclo[2.2.1]heptane-3-carboxylic acid (**96**) (its residue in peptides is denoted as Abh) has been known for a relatively long time.[158] It was one of the first artificial conformationally rigid analogues of proline.

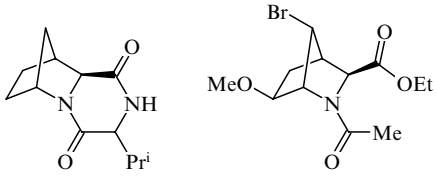
An analysis of X-ray diffraction data on proline[145] and the acid **96**[159] has revealed important differences in the bond angles within the pyrrolidine rings of the two substances despite similarity of the respective bond lengths. The values of the bond angles (in deg.) in model peptides containing Pro and Abh residues are given below.



Pro Abh

Owing to the rigid framework of 2-azabicyclo[2.2.1]heptane-3-carboxylic acid, peptides with an Abh residue are characterised by the fixed torsion angle φ. The same is valid for the torsion angles χ (the values of these torsion angles for the *exo*-isomer **96** are given elsewhere,[159, 160] similar values are expected for the *endo*-isomer).

Assuming that the bicyclic framework of **96** is symmetrical and the amide bond is planar, the torsion angle φ should be equal to -60°. Although there have been no dedicated investigations on this topic, the available data for **99** ($\varphi = -39^\circ$)[160] and **100** ($\varphi = -73^\circ$)[159] allow one to suggest that the real value of this torsion angle in **96** will deviate from the ideal value (-60°). The large deviation of the torsion angle φ from -60° observed for **99** can be partly attributed to the presence of a six-membered ring.



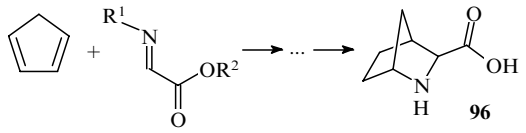
99 **100**

The nitrogen atoms in **99** and **100** are characterised by insignificant pyramidalisation ($\omega_0 \approx 358^\circ$), however, the respec-

tive peptide bonds are non-planar. The non-planarity of the amide bonds is evidenced by the values of the angles δ and τ: $\delta = 14°$, $\tau = 8°$ and $\delta = 14°$, $\tau = 6°$ for **99** and **100**, respectively.

The compound **100** in crystals adopts the *trans*-conformation ($\omega = -177°$). No data on the amide bond configuration in solutions of **100** are available.

The principal method for the synthesis of 2-azabicyclo[2.2.1]-heptane-3-carboxylic acid is the Diels–Alder reaction of cyclopentadiene (as a diene) and imine (as a dienophile) that is normally generated *in situ*.[158, 161, 162]



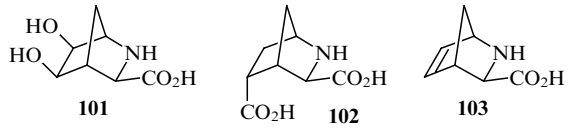
96

Using this reaction, optically active 2-azabicyclo[2.2.1]heptane-3-carboxylic acid (*exo*-**96**) can be produced in gram quantities.[161]

Substituted amino acids are usually prepared by a modification of the double bond formed at the cycloaddition stage.

Other routes to the synthesis of the amino acid **96** are based on different intramolecular cyclisations but they found only limited applications.[163]

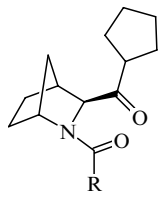
Despite the apparent simplicity of the preparation of 2-azabicyclo[2.2.1]heptane-3-carboxylic acid derivatives, there are only a few known representatives of this class. In addition to the unsubstituted compound **96**, only analogues of homoserine and glutamic acid have been reported, *i.e.*, **101** (along with its protected derivatives) [164] and **102,**[163] respectively.



101 **102** **103**

Compound **103** has also been synthesised. Since it tends to rearrange in acidic media, it was isolated only in the protected form.[165]

2-Azabicyclo[2.2.1]heptane-3-carboxylic acid (**96**) is widely employed in asymmetric synthesis.[166] It has also been used for the preparation of analogues of fragments of the tumour growth factor TGFα (see Ref. 167) and inhibitors of prolylendopeptidase § **104**–**107** (see Ref. 168).



104–**107**

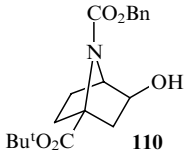
R = $Ph(CH_2)_3$ (**104**), PhCHCH$_2$CHCH$_2$ (**105**), (cyclo-C_3H_5)$_2$CH$(CH_2)_3$ (**106**), Bu^{t}O (**107**).

In contrast to 2-azabicyclo[2.2.1]heptane-3-carboxylic acid (**96**), 7-azabicyclo[2.2.1]heptane-1-carboxylic acid (**97**) has been prepared only quite recently.[169, 170]

An analysis of structural data indicates that the bond lengths and bond angles in 7-azabicyclo[2.2.1]heptane are virtually identical to those in proline (except for the angles at the nitrogen atom).[145] Certain differences in the latter (by up to 7° as compared to proline) are due to the pyramidalisation of the nitrogen atom.

An analysis of the dihedral angles shows that the angle φ as well as all angles χ in the 7-azabicyclo[2.2.1]heptane molecule are fixed (the values of these angles can be found elsewhere [171, 172]).

The theoretical value of the angle φ calculated under the assumption that the framework is symmetrical and the amide bond is planar is equal to 0°. For the sake of structural elucidation of peptides, a series of model oligopeptides with a residue of **97** (for this residue, a notation Ahc is adopted) has been synthesised. According to X-ray diffraction data, the angle φ in the protected dipeptides Piv-Ahc-L-Ser-NHMe (**108**) and Piv-L-Ser-Ahc-NHMe (**109**) strongly deviates from the theoretical value of 0°, similarly to the aforementioned case of dipeptides with a 2,4-methanoproline residue: $\varphi = -36°$ (for **108**), 40° and 44° (for two crystalline modifications of **109**). Compound **110** is characterised by an even larger deviation ($\varphi = \pm 51°$).[172]



110

The norbornane framework in **108**–**110** is undistorted and the deviation of the angle φ from the idealised value of 0° occurs due to the pyramidalisation at the nitrogen atom. Strictly speaking, the molecules again lose rigidity as regards the angle φ.

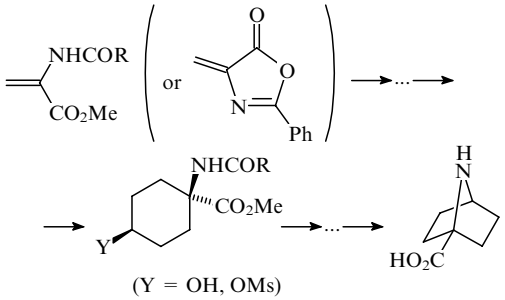
The torsion angle ω_0 is 346° in the case of Piv-Ahc-L-Ser-NHMe. Such a low value of ω_0 is observed only in a few amides (*e.g.*, in aziridine derivatives). The amide bond in **108** is characterised by the following values: $\delta = 34°$, $\tau = 5°$. For **110**, the respective parameters are 335° (ω_0), 43° (δ) and 17° (τ).

In the crystals of **110**, the angle ω is 133°, which corresponds to the *trans*-configuration. Meanwhile, the angle ω is close to ±180° in all the dipeptides studied.

Introduction of an Ahc residue into a peptide chain in place of proline stabilises the β-bend (type I).[171]

There are several approaches to the synthesis of the 7-azabicyclo[2.2.1]heptane framework. The amino acid **97** has been prepared for the first time using a radical cyclisation of 1-(*o*-bromobenzoyl)-2-(prop-2-enyl)pyrrolidines,[169, 170] which yields a series of by-products, including 8-azabicyclo[3.2.1]octane derivatives. This method is inefficient for the synthesis of the amino acid **97**; it is used solely for the preparation of 7-azabicyclo[2.2.1]heptane unsubstituted at position 1.

Another method utilises a nucleophilic substitution reaction that is accompanied by formation of a bond between the nitrogen and carbon C(4) atoms. To form the 6-membered ring, the Diels–Alder reaction is applied, in which the Danishefsky diene [CH_2=C(OSiMe_3)CH=CH-OMe] or 3-methoxy-1,3-butadiene are used as the dienes and 2-acylamidoacrylates as the dienophiles. The general scheme of the synthesis is depicted below.[173–177]



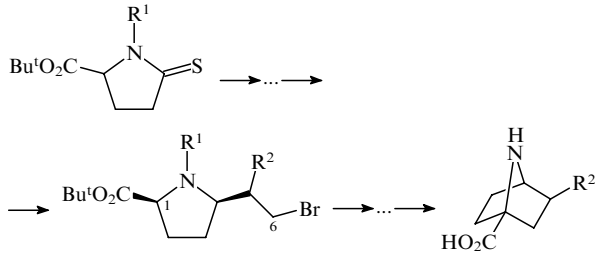
(Y = OH, OMs)

This method is especially convenient for the synthesis of 2-substituted derivatives.

Yet another approach to the synthesis of 7-azabicyclo[2.2.1]-heptane-1-carboxylic acid has been suggested,[172] which implies

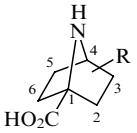
§ Prolylendopeptidase is the only enzyme capable of splitting the C-terminal peptide bond formed by the proline residue. This enzyme splits neuropeptides involved into the learning and remembering processes; thus it is one of the targets within the scope of curing of the Alzheimer decease and amnesia.

formation of a bond between the C(1) and C(6) atoms as a result of alkylation of the respective enolate anion.



This method has been used to produce a number of chimeric 3-substituted amino acids.

It should be noted that all amino acids having a 7-azabicyclo[2.2.1]heptane framework, except for the unsubstituted amino acid **97**, are chimeric since they always mimic proline in addition to the natural amino acid representing their most direct analogue. In particular, 2- and 3-substituted chimeric acids **111**–**121** have been synthesised, which are analogues of phenylalanine, 4-hydroxyproline, glutamic acid, homophenylalanine, ornithine, arginine, lysine and serine.[172–174, 177, 178]

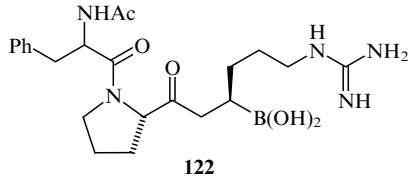


111–**121**

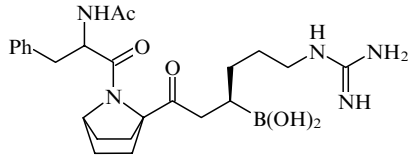
R = 2-Ph (**111**),[174] 2-CH_2CO_2H (**112**),[177] 3-OH (**113**),[177] 3-Ph (**114**),[172] 2-CO_2H (**115**),[173] 2-Pr^n (**116**),[173] 3-CO_2H (*exo*- and *endo*-**117**),[172] 2-OH (*exo*- and *endo*-**118**),[178] 3-CH_2NH_2 (*exo*- and *endo*-**119**),[172] 3-$CH_2NHC(=NH)NH_2$ (*exo*- and *endo*-**120**),[172] 3-$CH_2CH_2NH_2$ (**121**).[172]

Only protected derivatives of the amino acids **117**, **119**–**121** have been prepared.[172]

The unsubstituted amino acid **97** has been utilised in the synthesis of peptidomimetics. In particular, substitution of Ahc for Pro in the peptide Ac-D-Phe-Pro-boroArg-OH (**122**, DuP714), a thrombin inhibitor, yielded the peptidomimetic **123**. This peptidomimetic manifested the 30-fold lower thrombin affinity than the original peptide **122**, which allowed the authors to conclude[179] that the conformation of the model compound in the bound state does not correspond to that of the object being modeled.



122

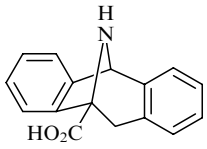


123

A benzyl derivative of the amino acid **113** has been introduced into a proline-containing inhibitor of HIV-I protease. The mimetic obtained manifested quite a high degree of binding to the enzyme.[180]

c. Other proline analogues

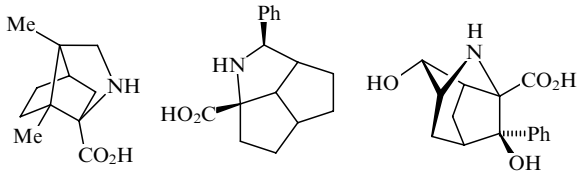
As has been mentioned above, the bridges in bicyclic CRA should include 0, 1 or 2 atoms, the presence of sp^2-hybridised atoms in the bridge enhances the conformational rigidity of the CRA molecule. For bridges containing a π-bond, lengths of up to three atoms are possible. For instance, compound **124**[181, 182] with a 2,5-bridge is classified as a CRA.



124

Compound **124** has been prepared as a potential ligand for the NMDA receptor but it can be formally regarded as a proline analogue.

The tricyclic amino acids **125**–**127** can also be considered as proline analogues.



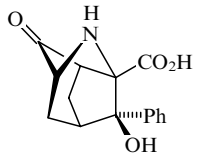
125 **126** **127**

Compound **125** has been prepared in several steps starting from camphor.[183] The molecule **125** is extremely rigid. This fact makes **125** very promising for the synthesis of peptidomimetics.

The tricyclic compound **126** is produced by intramolecular [3 + 2]-cycloaddition. This is a key intermediate in the synthesis of guanidine alkaloids.[184] It was isolated only in the protected form.

Compound **127** is of particular interest. It has the full right to be named a 'hyperchimeric' amino acid since it is an analogue of eight natural amino acids: proline, serine, homoserine, phenylalanine, threonine, isoleucine, valine and 4-hydroxyproline.[185]

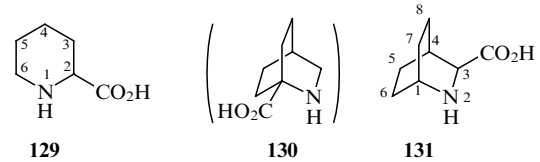
No structural data on **124**–**127** are available, although the results of an X-ray diffraction study of the amino acid **128** (which is a precursor of **127**) have been published.[185]



128

2. Pipecolic acid analogues

Pipecolic acid **129** is a non-natural cyclic α-amino acid that represents a proline homologue.

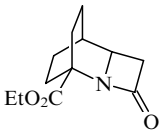


129 **130** **131**

To confer rigidity on the pipecolic acid framework, it has to be included into a bicycle with the bridge linking positions 2 and 5 (or 3 and 6). The case of a bridge containing only one atom has been discussed above since it is the 2-azanorbornane framework. In the case of a bridge containing two atoms, two structural types **130** and **131** are possible.

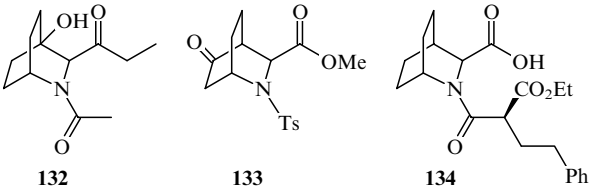
To date, only compound **131** with a carboxy group at the position 3 has been synthesised. Compound **130** has not been

reported although its β-lactam derivative has been characterised.[186]



2-Azabicyclo[2.2.2]octane-3-carboxylic acid (**131**) is quite often used as a substitute for the proline residue although it is actually an analogue of pipecolic acid (for the residue of this acid, a notation Abo is adopted). This acid can be rather easily prepared in the enantiomerically pure form.

No dedicated structural studies on the 2-azabicyclo[2.2.2]octane framework of **131** have been conducted so far, although its amide **132** (see Ref. 187), tosyl derivative **133** (see Ref. 188) and the drug Zabicipril (S 9650-3) **134** (see Ref. 189) have been studied using X-ray diffraction.



132 **133** **134**

An analysis of these structural data indicates that the C–C bonds of the piperidine rings within the 2-azabicyclo[2.2.2]octane framework are slightly (approximately by 0.03 Å) longer than in pipecolic acid;[190] no substantial difference in the bond angles is observed.

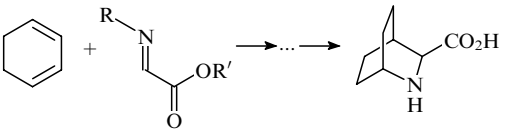
Formally, the two piperidine rings in **131**, *i.e.*, C(1)NC(3)C(4)C(5)C(6) and C(1)NC(3)-C(4)C(8)C(7), can be distinguished. According to experimental results,[190] the absolute values of the torsion angles in these rings are not identical, which indicates that the framework is somewhat distorted (as in the case of 2,4-methanoproline).

Theoretically, the value of the angle φ in derivatives of 2-azabicyclo[2.2.2]octane-3-carboxylic acid assuming the symmetrical framework and the undistorted amide bond is -60°. According to X-ray diffraction data, this value is -65° in **133** (*i.e.*, the deviation from the idealised value is small). In Zabicipril **134**, the respective torsion angle is -63°.

The pyramidalisation parameter (ω_0) of the nitrogen atom in **132** is 359.7°. Distortion of the amide bond is also insignificant ($\tau = 4^\circ$ and $\delta = 9^\circ$), *i.e.*, the amide bond in derivatives of 2-azabicyclo[2.2.2]octane is virtually planar.

According to X-ray diffraction data, the amide bond is characterised by the *trans*-configuration in **132** and **134** ($\omega = -172^\circ$ and 174° for **132** and **134**, respectively).

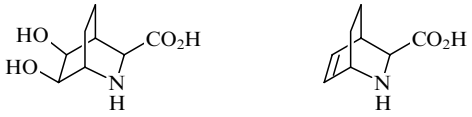
The amino acid **131** and its derivatives can be prepared using several methods. As in the case of azanorbornane, the basic method for the construction of this framework is the Diels–Alder reaction.[189, 191]



Functionalised derivatives can be produced by modification of the double bond that is formed in the cycloaddition reaction.[191]

Among other synthetic routes, the following are worth a special note: the reaction of 1,2-dihydropyridines with dienophiles,[192] the intramolecular Dieckmann and Michael reactions,[193] intramolecular S_N2 epoxide opening.[194]

Despite the apparent simplicity of these syntheses, only a few chimeric amino acids with the 2-azabicyclo[2.2.2]octane framework have been prepared, including dihydroxy-substituted acid **135**, its protected derivatives and unsaturated acid **136**.[191]

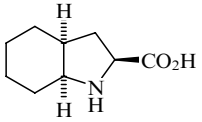


135 **136**

Derivatives of 2-azabicyclo[2.2.2]octane-3-carboxylic acid are widely applied in asymmetric synthesis.[191, 195]

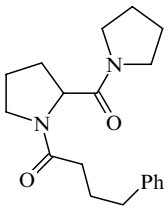
Numerous peptidomimetics have been synthesised based on Abo, in particular, the aforementioned Zabicipril **134**, which represents an efficient inhibitor of angiotensin converting enzyme (ACE), which plays a crucial role in blood pressure regulation.[196] The angiotensin II mimetic **134** is a promising antihypertensive drug.[189] This represents an example of a successful drug design: the peptidomimetic obtained retains activity of the native peptide and it is more stable against biodegradation, which gives rise to a strong prolongation effect.

The amino acid **131** along with the aforementioned acid **96** (Abh) and conformationally constrained but not rigid perhydroindole-2-carboxylic acid **137** (Phi) are often used in complex investigations of peptidomimetics as regards their biological activity.



137

For instance, these amino acids have been utilised to mimic the prolylendopeptidase inhibitor SUAM 1221 (**138**), which is a proline derivative.[168]



138

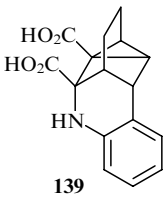
In addition to modifications involving the side chain of the acid residue,¶ different substitutes for the central proline residue were tested. The best results were achieved when the proline resudue was replaced by the Phi residue, although Abo and Abh also gave promising results.

The same amino acids have been probed as substitutes for proline in the tripeptides Val-Pro-Val and Val-Pro-Lys in the search for efficient selective inhibitors of the human leucocyte elastase (HLE).[197] The synthetic peptidomimetics manifested high potential as long-lasting inhibitors of pulmonary tissue degradation related to HLE.

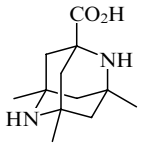
Furthermore, the amino acid **131** has been used for the preparation of antagonists for the tetrapeptide tachykinin. Introduction of an Abo residue into the peptidomimetic resulted in prolongation of the activity of the synthetic antagonist.[198]

Among other analogues of pipecolic acid, the polycyclic compounds **139** and **140** are of special interest. The polycyclic compound **139** is an analogue of pipecolic and glutamic acids. It has been produced as a protected derivative in a small yield by the reaction of substituted bicyclo[2.2.2]hexadiene with *o*-iodoaniline catalysed by palladium(II).[199]

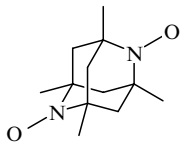
¶ These modifications were conducted within the principles of the strict conformational fixation (by introduction of cyclopropane fragments), which yielded positive results in some cases.



139



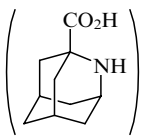
140



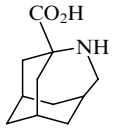
141

Compound **140** is formed as an intermediate in the synthesis of a biradical **141**, an organic ferromagnetic species.[200] It may be assumed that the presence of an additional nitrogen atom would impart particular properties to the biologically active substances produced on its base.

It is of note that the non-functionalised 2-azaadamantane derivative **142** has not been prepared so far despite the fact that adamantane is frequently used in the synthesis of CRA. Only a homologue of 2-azaadamantane **143** has been reported,[201] which is not conformationally rigid, however.



142

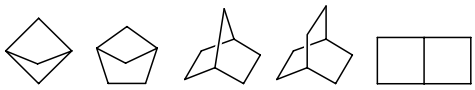


143

VI. Bi- and polycyclic conformationally rigid amino acids with an exocyclic nitrogen atom

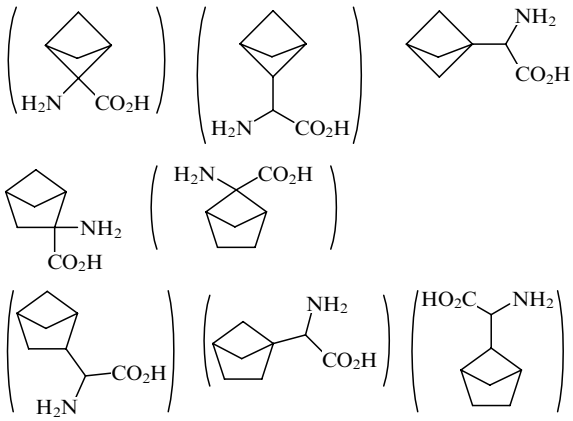
In the case of bi- and polycyclic amino acids discussed above, the conformational rigidity is achieved by inclusion of the nitrogen-containing ring into a polypeptide chain. In contrast, the torsion angles of the polypeptide chain are not fixed for cyclic amino acids with an exocyclic nitrogen atom, although the respective amino acids are χ-rigid.

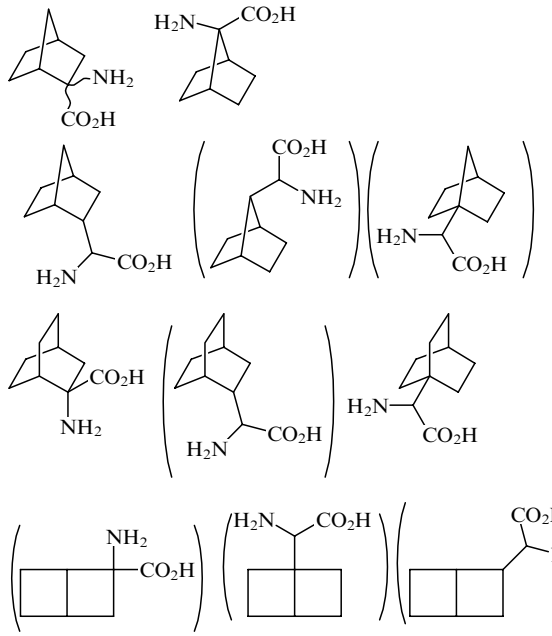
There are several rigid bicyclic cages, in particular, bicyclo[1.1.1]pentane (**A**), bicyclo[2.1.1]hexane (**B**), norbornane (**C**), bicyclo[2.2.2]octane (**D**) and bicyclo[2.2.0]hexane (**E**) with bridge lengths not more than two atoms (cyclopropane derivatives have been thoroughly discussed above and thus are not mentioned here):



A **B** **C** **D** **E**

The respective amino acids are known for all these bicyclic systems (except for bicyclo[2.2.0]hexane):



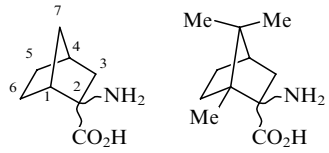


It can be noted that these bicyclic cages fix either all torsion angles χ or only some of them. Therefore, for further discussion, it is convenient to differentiate between the χ_1-rigid amino acids and other χ_n-rigid amino acids ($n \geqslant 2$).

In addition to the bicyclic amino acids, polycyclic amino acids are also known. However, examples of these are scarce (these include derivatives of adamantane, cubane and fullerene C_{60}).

1. Norbornane derivatives

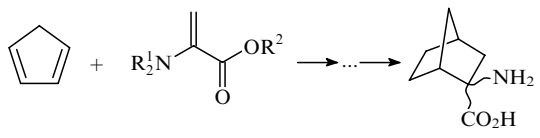
2-Aminonorbornane-2-carboxylic acid (**144**) (its residue in peptides is denoted as Bch) has been known from the mid-1950's,[202, 203] whereas synthesis of its trimethyl derivative, the camphor analogue **145**, was reported even earlier.[204] Potential biological activity of **144** was discussed following its preparation.[205]



144a,**b** **145a**,**b**

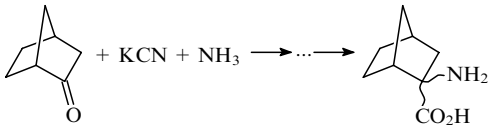
The values of the torsion angles in the bicyclo[2.2.1]hexane cage are given elsewhere.[206, 207] Introduction of functional groups into the norbornane framework gives rise to only minor changes in the torsion angles (by not more than 15°). Only the angles involving the substituents are mostly affected. No distinct effect of the norbornane fragment on the torsion angles within the polypeptide chain has been revealed.

Methods for the synthesis of norbornane-based amino acids have been recently surveyed,[11, 12] therefore, we shall just mention them. The most popular method is based on the Diels–Alder cycloaddition reaction of cyclopentadiene to derivatives of α,β-unsaturated α-amino acids.[202, 203, 208–216]

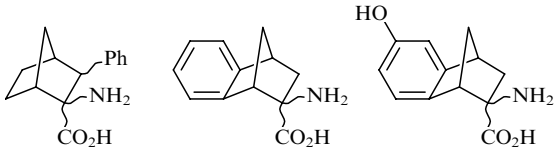


Dienophiles substituted at the β-position can also be employed in this reaction. Diastereo- and enantioselective modifications of this method have been elaborated.

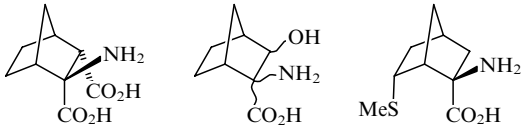
Another approach utilises the classical Strecker and Bucherer–Lieb reactions [204, 205, 217, 218] starting from 2-norbornanone, which in turn is produced by the Diels–Alder reaction.



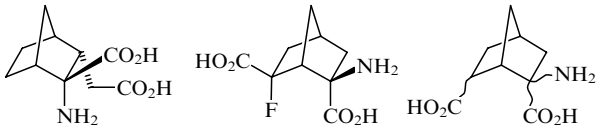
Numerous CRA with the norbornane cage have been prepared. In addition to the unsubstituted acid **144**, various functionalised derivatives **146**–**155** (which represent analogues of phenylalanine,[208, 209, 217] tyrosine,[217] aspartic acid,[211, 212] serine,[213] methionine,[219] glutamic acid [211, 219–221]), including polyhydroxy-compounds **156a**–**d** [216] have been prepared. All of these compounds are fully χ-rigid (except for **152**, which is χ_1-rigid).



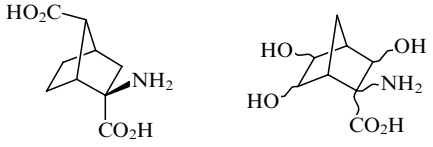
146a–d **147a,b** **148a,b**



149 **150a,b** **151**



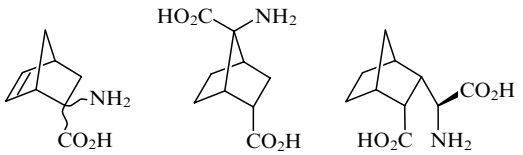
152 **153** **154a–d**



155 **156a–d**

For the synthesis of 3-substituted derivatives, the respective substituted cyclopentadienes are used, 6- and 7-substituted derivatives are produced by functionalisation of the double bond.

The unsaturated derivative **157** has been prepared only in the protected form.



157 **158** **159**

7-Aminonorbornane-2,7-dicarboxylic acid **158** has been synthesised, which is also an analogue of glutamic acid.[221]

Among norbornylglycine derivatives, only the acid **159** is known,[211] which is also a glutamic acid analogue †. This type of amino acids are not χ_1-rigid, that is why probably they attract only limited interest.

The biological activity of the unsubstituted 2-aminonorbornane-2-carboxylic acid (**144**) has been studied. For instance, it has been shown that this acid is selectively transported into nearly all cells by sodium-independent systems responsible for the transport of hydrophobic amino acids.[223] The acid is almost excluded from the metabolism and thus it can be accumulated in tissues. The Bch residue mimics most closely the properties of leucine (and, to a lesser extent, of isoleucine and valine), which makes it possible to monitor pathways of leucine transport in tissues through the use of ^{14}C-labeled Bch or to inhibit this transport. In particular, with the help of the acid **144**, the sodium-independent transport systems of phenylalanine and leucine have been shown to be identical. Furthermore, it was demonstrated that the transport system is selective to one of the diastereomers **144a** or **144b**.

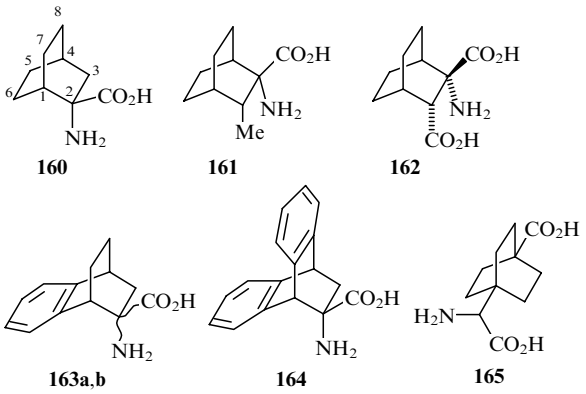
The diastereomers **144a** and **144b**, as was established in the course of the study of their transport, manifest hypoglycaemic activity (that is also typical of leucine [224]), and the effect of a decrease in the glucose concentration in blood was long-lasting. As a side effect, concentrations of at least five amino acids in blood plasma were observed to decrease. Physiological tests on rats showed that the acid **144** is non-toxic; it was almost completely excreted with urine.

Another activity was observed for the acid **144** introduced into rat mitochondria: Bch stimulates the glutamine catabolism by activating mitochondrial glutaminase (this activity was not observed for leucine).[225] The processes of insulin release and glutaminase activation under action of Bch are coupled.[226]

The biological activity of the acid **154**, which is a glutamic acid analogue, has also been studied. The activity of this acid towards metabotropic glutamic acid receptors mGluR1 and mGluR2 has been revealed.[220]

2. Bicyclo[2.2.2]octane derivatives

Amino acids with the bicyclo[2.2.2]octane framework are best studied as regards the number of derivatives synthesised. The unsubstituted acid **160** [227] as well as its derivatives **161**–**164** [203, 228–231] have been prepared and characterised.



160 **161** **162**

163a,b **164** **165**

The values of the torsion angles in the bicyclo[2.2.2]octane cage are given elsewhere.[228, 232] An analysis of the structural data indicates that amino acids with a bicyclo[2.2.2]octane framework are characterised by distorted torsion angles (especially, in the case of bulky substituents).

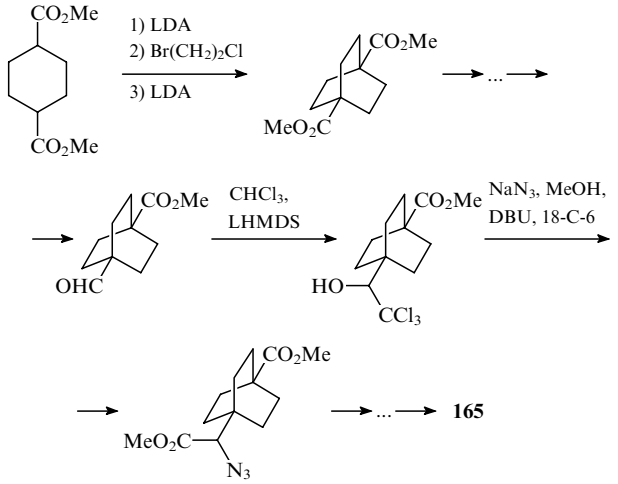
Another amino acid **165**, in which the C_α atom is exocyclic with respect to the bicyclo[2.2.2]octane framework, has been reported.[233]

Methods for the synthesis of amino acids with a bicyclo[2.2.2]octane cage are generally similar to those of norbornane derivatives, which have been discussed above. They include the Diels–Alder reaction of 1,3-cyclohexadiene with α,β-dehydroalanines, the Strecker and Bucherer reactions.[228–230] The acid **165** is formed by alkylation of enolates (Scheme 12).

The unsubstituted amino acid **160** manifests biological activity analogous to 2-aminonorbornane-2-carboxylic acid **144** .[234] Compounds **163a,b** have been investigated as analogues of phenylalanine in the inhibition of phenylalanylhydroxylase and phenylalanyldecarboxylase.

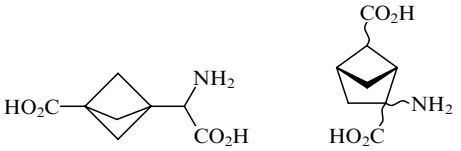
† Synthetic glutamic acid analogues attracts significant interest and thus they are especially numerous.[222]

Scheme 12



3. Derivatives of bicyclo[1.1.1]pentane and bicyclo[2.1.1]hexane

To date, only one CRA **166** with a bicyclo[1.1.1]pentane framework [235] and one acid **167** (four diastereomers) with the bicyclo[2.1.1]hexane framework [236, 237] are known. They both may be considered as analogues of glutamic acid.

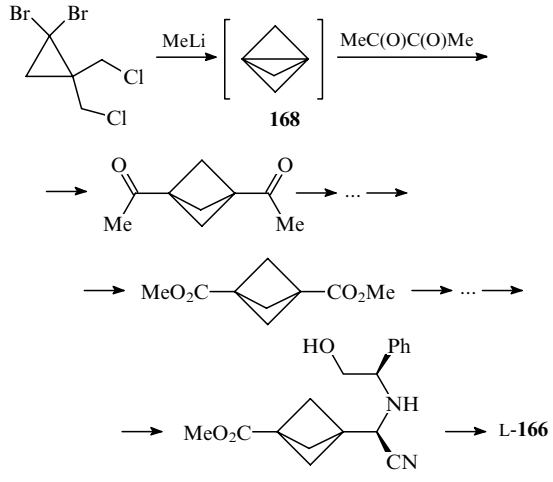


166 **167a–d**

Values of the torsion angles in bicyclo[1.1.1]pentane [238, 239] and bicyclo[2.1.1]hexane [240, 241] have been reported. These two frameworks deserve special consideration since they are extremely rigid and characterised by relatively small steric volume. Therefore, one may hope that other amino acids with these cages will be synthesised in the future, although the synthesis of such compounds is challenging. The diastereomers **167a–d** were prepared by an intramolecular photochemical [2 + 2]-cycloaddition from the appropriately substituted 1,5-diene [236] or by a contraction of the norbornane system through photochemical decomposition of α-diazoketones.[237] The amino acid **166** has been synthesised *via* [1.1.1]propellane **168** (Scheme 13).[235]

Binding of the amino acids **166** and **167** to the corresponding receptor has been elucidated. Compound **166** proved to be a fairly efficient selective antagonist of the glutamate metabotropic

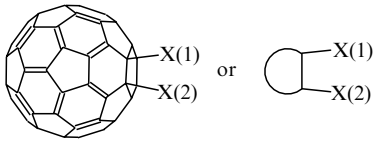
Scheme 13



receptors mGluR1 and one of the diastereomers **167a–d** was active as a common antagonist of all the mGluR receptors tested.

4. Fullerene derivatives

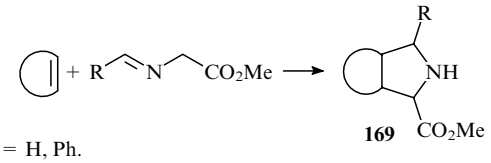
Over the last decade, numerous studies related to a greater or lesser extent to fullerene C_{60} have appeared. Taking into account the rigidity of the buckminsterfullerene cage, its introduction into side chains of amino acids is expected to lead to strict fixation of the torsion angles χ. However, due to specific restrictions related to the structure of the C_{60} molecule as well as to available methods of fullerene functionalisation, only χ_2-rigid CRA are known to date, which have been prepared by introduction of functional groups at adjacent positions of the fullerene cage.



In these compounds, the fullerene cage strictly fixes only one dihedral angle, *viz*., X(1)–C(1)–C(2)–X(2). Ideally, this angle should be close to 0° but no structural data on this class of CRA are available.

There are two ways to introduce an α-amino acid fragment into the fullerene cage.

The first one is based on the [3 + 2]-cycloaddition reaction, which gives rise to proline analogues.[242, 243] Protected proline analogues **169** with R = H (see Ref. 242) or Ph (see Ref. 243) have been produced.

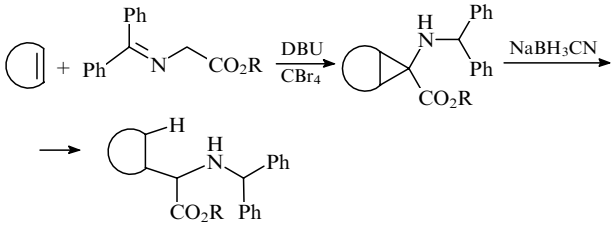


169

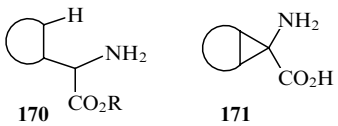
R = H, Ph.

Alternatively, proline analogues can be prepared by the direct photochemical reaction of fullerene with amino acid esters.[244] The products formed in this reaction are similar to those considered above but the mechanisms of the two reactions are distinctly different. The photochemical reaction proceeds through formation of radical intermediates. It has been applied to prepare protected proline analogue **169** with R = CO_2Me.[244]

The second way is based on a reaction that looks similar to [2 + 1]-cycloaddition but follows a different mechanism.[245]



This method has been applied to prepare 1,2-dihydro[60]fullerenylglycine (**170**) and aminomethano[60]fullerenecarboxylic acid (**171**).



170 **171**

Furthermore, this method has been successfully exploited in the synthesis of bismethano[60]fullerenylglycines, which yield monosubstituted 1,2-dihydrofullerene upon reduction.

The amino acids mentioned in this Section are characterised by a wide range of interesting biological properties, and are especially promising in such fields as photodynamic therapy,

developments of HIV protease inhibitors[246] and antibacterial drugs.[247]

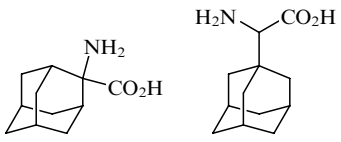
5. Miscellaneous conformationally rigid polycyclic amino acids

In the previous sections, CRA with side chains representing quite bulky carbon cages devoid of any functional groups have been considered. Biological properties of these compounds have been described in detail with 2-aminonorbornane-2-carboxylic acid as an example. It has been shown that such CRA may be regarded as analogues of hydrophobic proteinogenic amino acids, in particular, of isoleucine, and they are superior in some respects to the latter. First, they do not metabolise. Second, owing to the conformational rigidity, they are quite compact despite their relatively high molecular mass. Third, they are characterised by higher lipophilicity, which allows them to penetrate through various intra- and intercellular barriers. Thus, it is not surprising that the search for new cage amino acids continues. New structures can provide new capabilities for the design of *ad hoc* amino acids with specific conformations of their side chains.

Adamantane and cubane, which are characterised by highly symmetrical frameworks, take a special place among polycyclic hydrocarbons. While an appreciable number of studies have been devoted to the synthesis of adamantane-based CRA, cubane has been slipping the attention of researchers so far.

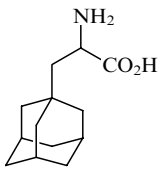
The values of the torsion angles within the adamantane cage of the corresponding amino acids and their derivatives are given elsewhere;[248,249] the respective data on the cubane cage are reported in Refs 250, 251. The experimental data indicate that the adamantane and cubane cages are essentially undistorted.

Three unsubstituted amino acids with the adamantane cage are known to date, *viz*., 2-aminoadamantane-2-carboxylic acid (**172**),[252,253] (1-adamantyl)glycine (**173**)[254] and 3-(1-adamantyl)-alanine (**174**)[255] (the latter can be classified as CRA only formally; such a remote χ_3-rigidity plays only a minor role) and 1,3-adamantylidenediglycine (**175**).[256] Derivatives of the acids **172**–**174** methylated at bridgehead carbon atoms have also been prepared.

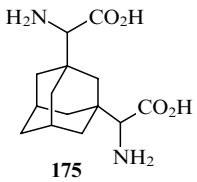


172

173



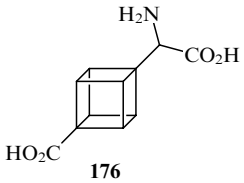
174



175

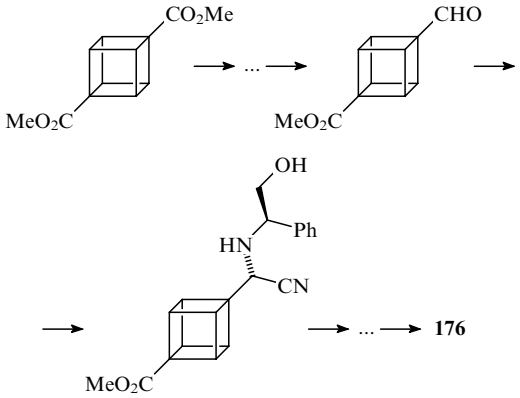
Compounds containing the adamantane cage have been used as the starting materials in the syntheses of the amino acids **172**–**174**. In particular, the amino acid **172** was synthesised from 2-adamantanone by the classical Strecker and Bucherer–Lieb reactions.[252,253] Compounds **173** and **174** have been prepared starting from adamantylacetic and adamantylpropionic acids, respectively, by α-halogenation (*e.g*., according to the Hell–Volhard–Zelinsky reaction) followed by substitution of the amino group for the halogen atom.[255] Compound **175** has been prepared similarly.[256]

In the case of cubane, only one CRA **176** is known, which is a glutamic acid analogue.[257]



176

Its synthesis has been performed starting from dimethylcubanedicarboxylate using a method similar to that used for the preparation of bicyclo[1.1.1]pentane (**166**) considered above.

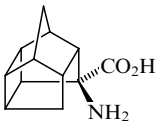


(1-Adamantyl)glycine (**173**) is an active inhibitor of leucine and methionine transport (like 2-aminonorbornane-2-carboxylic acid), however, its introduction into neoplasmatic cells did not produce the anticipated antitumour effect.[254]

Introduction of the amino acid **173** into small peptides yields model compounds which at room temperature predominantly adopt a conformation typical of the γ-bend.[258] This is very unusual since CRA typically stabilise various β-bends.

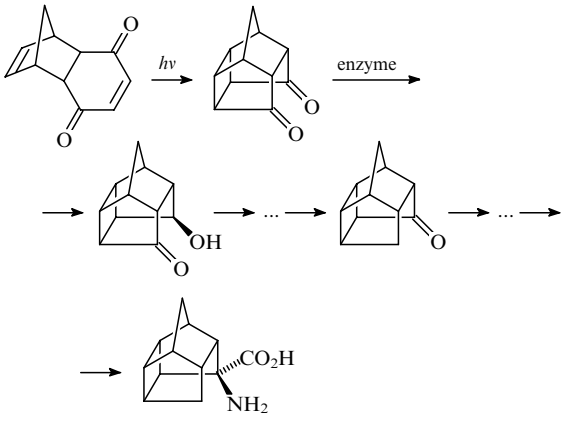
Compounds **173**–**175** manifest antiviral activity, which is, however, solely due to the presence of the adamantyl substituent.[255] A study of binding of compound **176** to metabotropic glutamate receptors has revealed that it represents a selective antagonist of mGluR1.[257]

The consideration of polycyclic amino acids with an exocyclic nitrogen atom will be incomplete, if we omit another unique substance, *viz*., pentacyclic CRA **177**, which is a pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane derivative.[259]



177

Compound **177** has been prepared by a multistep synthesis starting from the adduct of cyclopentadiene and *p*-benzoquinone.



VII. Conclusion

Nowadays, the assortment of conformationally rigid cyclic amino acids which can be utilised in the design of peptidomimetics, peptide models and biologically active compounds, is quite wide. Some of the theoretically possible structures have not been realised so far, therefore, we expect that this list will soon be extended with new CRA suitable for the design. Furthermore, new stereoselective routes to the synthesis of the known amino acids will be elaborated since much research effort is put into this field. The primary reason for these efforts is that CRA enable preparation of peptides with high selectivity of their biological activities and degradation stability and thus are of significance as potential drugs. Introduction of CRA residues into the polypeptide chain has advantages within the context of the design of peptidomimetics and peptide models due to the particular conformational rigidity of these residues. CRA residues are able to stabilise or conversely destabilise specific elements of the secondary structure of peptides. This allows prediction of conformations of the peptides within a certain confidence level and thus gives a partial control over their biological function.

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