Synthesis and Properties of New Chiral Heterocyclic Peptide Mimetics

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To my Parents

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Table of Contents

1.1 Introduction*

The *de novo* design of peptides and peptidomimetics with a defined conformation is an important question in biology and chemistry.[1,2] To provide answers, general principles that guide the design must be developed. In case of proteins and peptides their biological response relays on the interaction of a part of the accessible three-dimensional surface with a complimentary surface of the binding partner.[3,4,5] The peptide backbone serves as a scaffold for the presentation of the amino acid side chain functional groups involved in the interaction, but the oligoamide backbone can also participate. The various functional groups, if properly arranged in space, can perform an enormous number of chemical functions which are the basis of all biological processes and life. In the case of *de novo* design of peptide and protein backbone conformations, structural constraints are used to limit their flexibility. One very successful approach, among others,[6] is the introduction of two substitutents at the α position of an α-amino acid.

C^{α}-Tetrasubstituted α-amino acids are non-proteinogenic modified amino acids, in which the hydrogen atom at the α-position of α-amino acids is replaced by an alkyl or aryl substituent. C^{α}-Tetrasubstituted α-amino acids play an important role in the *de novo* design of peptides and peptidomimetics with enhanced properties, because they possess a stereochemically stable quaternary carbon center which results, after incorporation into peptides, in a significant conformational bias. The orientation of the aromatic ring of an amino acid residue can also be restricted by these modifications. Another advantage of C^{α}-tetrasubstitution is the enhanced lipophilicity of the peptide molecule, which may be of importance to cross the blood-brain barrier or other membranes.

A larger peptide can show several different equilibrium conformations in solution, which differ in their biological activity. To lock the peptide in one specific conformation, it is necessary to bias or constrain the peptide to prefer a particular backbone conformation. Sterically constrained C^{α}-tetrasubstituted α-amino acid can achieve this task.

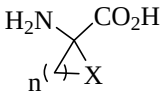
A number of notable successes have been reported, where small peptide fragments were used as antigens for eliciting immune responses to protein epitopes. However, the overall approach suffers from the fact that the peptide antigens are conformationally

* This introduction is part of a published review, see: Maity, P.; König, B. *Pept. Sci.* **2008**, *90*, 8-27.

flexible and cause a wider range of antibodies to be raised against the peptide. This leads to an inefficient immune response. Again, conformationally constrained peptide fragments can help to overcome these drawbacks. Another use of chiral C^{α} -tetrasubstituted α-amino acids is their application as valuable building blocks in organic synthesis and as core structure of catalysts for asymmetric bond formation reactions.

Therefore, numerous attempts to the synthesis of C^{α}-tetrasubstituted amino acids have been performed, many of which involve an optical resolution of the racemic form.[7] Recent efforts mainly focus on asymmetric transformations based on the alkylation of enolates from bislactones,[8] oxazinones,[9] imidazolidinones[10] and other procedures.[11] These methods have been documented by Seebach[12] and Cativiela[13] in their excellent reviews.

In cyclic C^{α} -tetrasubstituted α-amino acids (Figure 1), to which the focus of this introduction is limited, both α-substituents are covalently connected. The ring introduces steric constraints into the amino acid residue and changes in the chemical reactivity of the pendant functional groups, e.g., a reduced rate of hydrolysis of a peptide or an ester group.



n = 1- 5

X = CH_2, NH, O, S

Figure 1. General representation of cyclic C^{α}-tetrasubstituted α-amino acids.

In this introduction we focus exclusively on the synthesis and use of C^{α}-tetrasubstituted cyclic α-amino acids as structure determining and inducing elements. The survey will cover the recent synthetic approaches to prepare such amino acids. Cativiela´s[13] earlier review covers acyclic and cyclic C^{α}-tetrasubstituted α-amino acids, but in the past seven years several new synthetic routes have been reported. Toniolo et al.[14] discussed the effect of C^{α}-tetrasubstituted cyclic α-amino acids within their paper on conformation control by the Thorpe-Ingold effect. We cover in this introduction recent examples of conformationally stable turn structures of short peptides induced by C^{α}-tetrasubstituted cyclic α-amino acids and discuss typical examples of the ring size of the C^{α}-

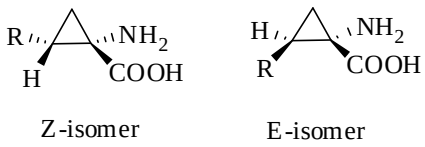
tetrasubstituted cyclic α-amino acids beginning with three-membered rings, continuing with four, five, six membered rings and finally ring structures larger than six-membered.

1.2. Cyclopropane amino acids[15]

1.2.1. Synthesis

The cyclopropane motif is a valuable structure in enantioselective synthesis[16] with representation in more than 4000 natural products and 100 therapeutic agents. Cyclopropane amino acids are found to inhibit amino acid processing enzymes of medical interest, by various mechanisms. They also have potential as conformation restriction moieties in bioactive peptides causing the stabilization of a peptide towards enzyme cleavage. The presence of a strained electrophilic cyclopropane ring may lead to covalent attachment of the peptide to an enzyme active site leading to enzyme inhibition. If conformational effects of the cyclopropane amino acid on a peptide are understood, active site mapping becomes possible.

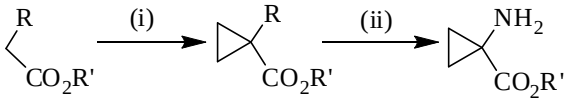
Each ring mono-substituted cyclopropane α-amino acids analog exists in diastereomeric *E* and *Z*-forms (Figure 2) in which the characteristic functionality at the β-carbon atom of the specific amino acid is *cis* to the carboxyl or to the amino function, respectively.



Z-isomer E-isomer

Figure 2. Isomers of monosubstituted cyclopropane α-amino acids.

Cyclopropane amino acids were first isolated from cider apples and perry pears by Burroughs[17] and identified as an intermediate in the biosynthesis of ethylene.[18] During the past two decades several new synthetic approaches for the synthesis of cyclopropane amino acids have been reported.[13,14] One of the earliest and most straightforward synthetic methods used the alkylation of a glycine derivative or its congener with ethylene dibromide or its equivalent.[19] Scheme 1 depicts the first preparation of a cyclopropane amino acid.



R = NC, $N=CR_2$
R' = Me, Et

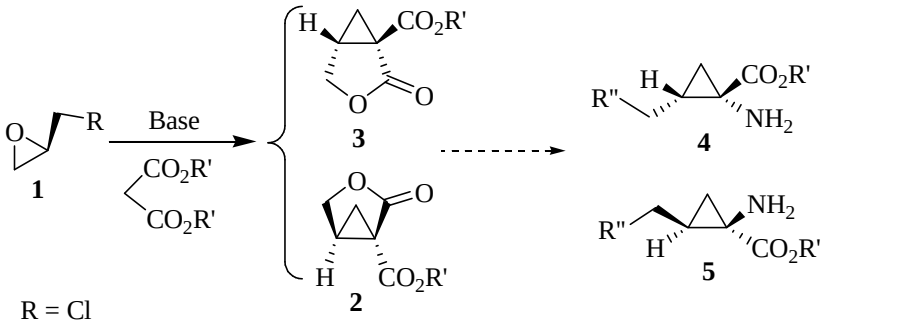
(i) $BrCH_2CH_2Br$/Base

(ii) HCl/H_2O

Scheme 1. An early preparation of cyclopropane amino acids.

The first approach for an asymmetric synthesis of cyclopropane amino acids was described by Pirrung[20] in 1986 that involves the synthesis of both enantiomers of *allo*-norcoronamic acid (*cis*-methyl-Acc). In the following review we focus on cyclopropane amino acids, which were used to induce turn structures when introduced in short peptides and refer the interested reader for the recent asymmetric synthesis of other cyclopropane amino acids to the review of Cativiela.[13]

Pirrung[21] and Burgess [22] described the diastereoselective synthesis of homo analogues of serine, methionine, leucine and others (Scheme 2) starting from enantiomerically pure (*R/S*)-epichlorohydrine or (*R/S*)-glycidyl triflate as the 1,2-dielectrophile and different malonate esters in the presence of sodium hydride.



R = Cl
OTf

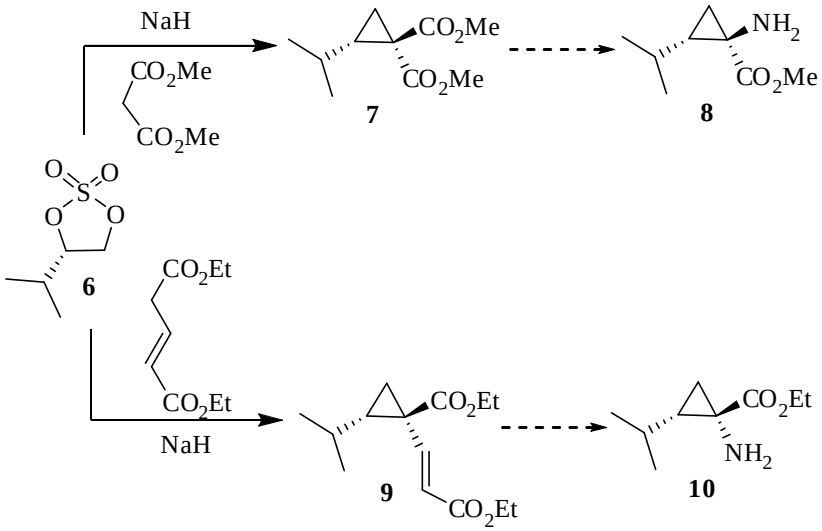
R' = Me, *t*-Bu

R" = OH, CN, OBn, SMe, NH_2, N_3, $CONH_2$

Scheme 2. Synthesis of cyclopropane amino esters **4** and **5**.

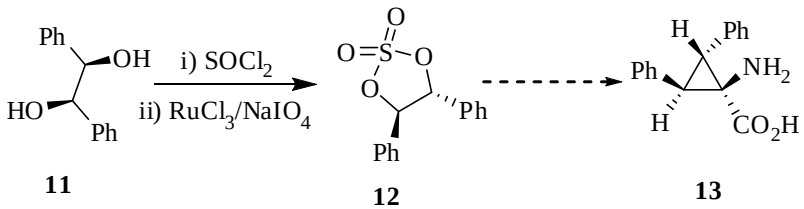
The resulting lactones (**2**, **3**) were treated with methanolic ammonia to yield amides, which were converted by subsequent reactions into the desired cyclopropane amino esters **4** and **5**.

Enantiomerically pure D- and L-valine[23] are useful starting materials for the synthesis of all four stereoisomers of 1-amino-2-isopropylcyclopropanecarboxylic acid. A cyclic sulphate (**6**), prepared from L-valine in a four-step procedure, reacts with dimethyl malonate or diethyl gluconate, to afford the key intermediates for the synthesis of (*R*, *S*) - and (*S*, *S*)- leucine surrogates followed by standard transformations (Scheme 3). Enantiomers of the target structures can be obtained starting from D-valine.



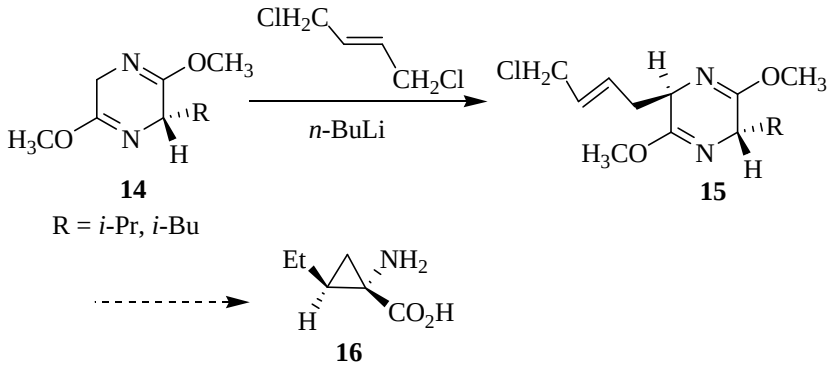
Scheme 3 Synthesis of stereoisomers of 1-amino -2-isopropylcyclopropanecarboxylic acid esters **8** and **10**.

The cyclic sulphate (**12**) obtained from (1*R*, 2*R*)-1,2-diphenyl-1,2-ethanediol (**11**) reacts with diethylglutaconate, which can be conveniently elaborated to afford (1*S*, 2*S*)-1-amino-2, 3-diphenylcyclopropanecarboxylic acid **13** (Scheme 4).[24]



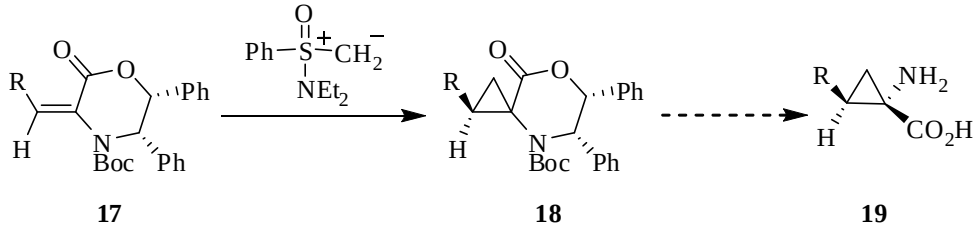
Scheme 4. Synthesis of 1-amino-2, 3-diphenylcyclopropanecarboxylic acid **13**.

Cyclic chiral glycine equivalents usually give rise to better selectivities in asymmetric reactions. Bis-lactim ethers described by Schöllkopf are well known chiral intermediates for the asymmetric synthesis of amino acids. Bis–lactim ethers derived from L-valine and glycine or L-*tert*-leucine and glycine have been used as starting materials in the synthesis of (1*R*, 2*R*)-*allo*-coronamic acid (**16**) (Scheme 5).



Scheme 5. Synthesis of (1*R*, 2*R*)-*allo*-coronamic acid **16**.

Williams et al.[25] described the first asymmetric synthesis of 2-substituted 1-amino cyclopropane carboxylic acids using double bond cyclopropanation of a chiral didehydroamino acid derivative (**17**). The intermediates (**18**) were then transformed into the desired 2-substituted 1-amino cyclopropane carboxylic acids **19** (Scheme 6).

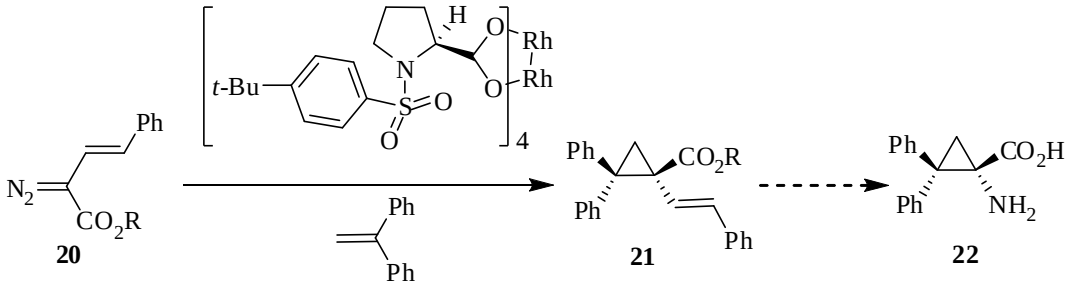


R = CH_3 (de, 100%), Et (de, 100%),
n-Pr (de, 100%), Ph (de, 100%)

Scheme 6. Synthesis of 2-substituted 1-amino cyclopropanecarboxylic acids **19**.

A detailed study using rhodium (II) N-(p-*tert*-butylbenzenesulfonyl) prolinate as a catalyst determined the key factors that control the enantioselectivity. The study concluded that the level of asymmetric induction is strongly enhanced by the use of non-polar solvents, while increasing the size of the ester on the carbenoid results in a significant drop in enantioselectivity. Even better selectivity is observed when rhodium

(II) *N*-(p-dodecylbenzene sulfonyl) prolinate is used as a catalyst at -78ºC. The product **21** was converted into the desired amino acid **22** in subsequent steps (Scheme 7).



Scheme 7. Synthesis of 2-phenyl 1-amino cyclopropanecarboxylic acid **22**

1.2.2. Induction of turn/helical structures in short peptides.

Unlike α- or β-methyl amino acids,[26] 2, 3-methano amino acids have rigidly defined χ^1 orientation. Consequently, 2, 3-methano amino acids should have marked effects on secondary structures. The solid state structures of some of the derivatives have been deduced via crystallography.[27]

Burgess et al.[28,29] reported methionine analogs of cyclopropane amino acids (methano-methionine) which induce a γ-turn structure in solution when incorporated into a short peptide. Tetrapeptide H-Phe-(2*S*, 3*S*)-cyclo-Met-Arg-Phe-NH_2 was prepared by using a solid phase approach. Different NMR studies confirmed that the tetrapeptide showed γ-turn possessing *i*←*i+2* (C=O···H-N) intramolecular hydrogen bond (Figure 3).

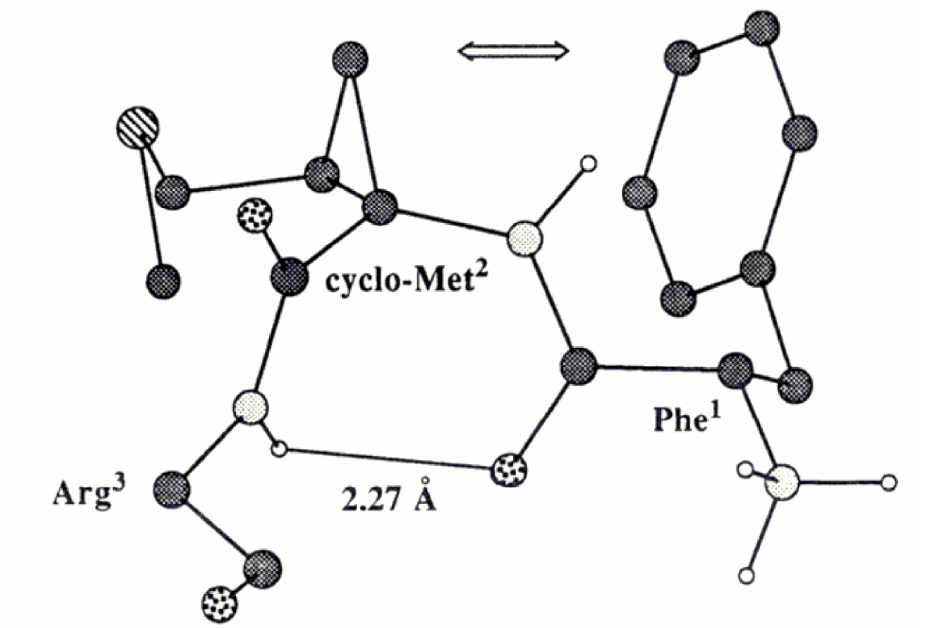
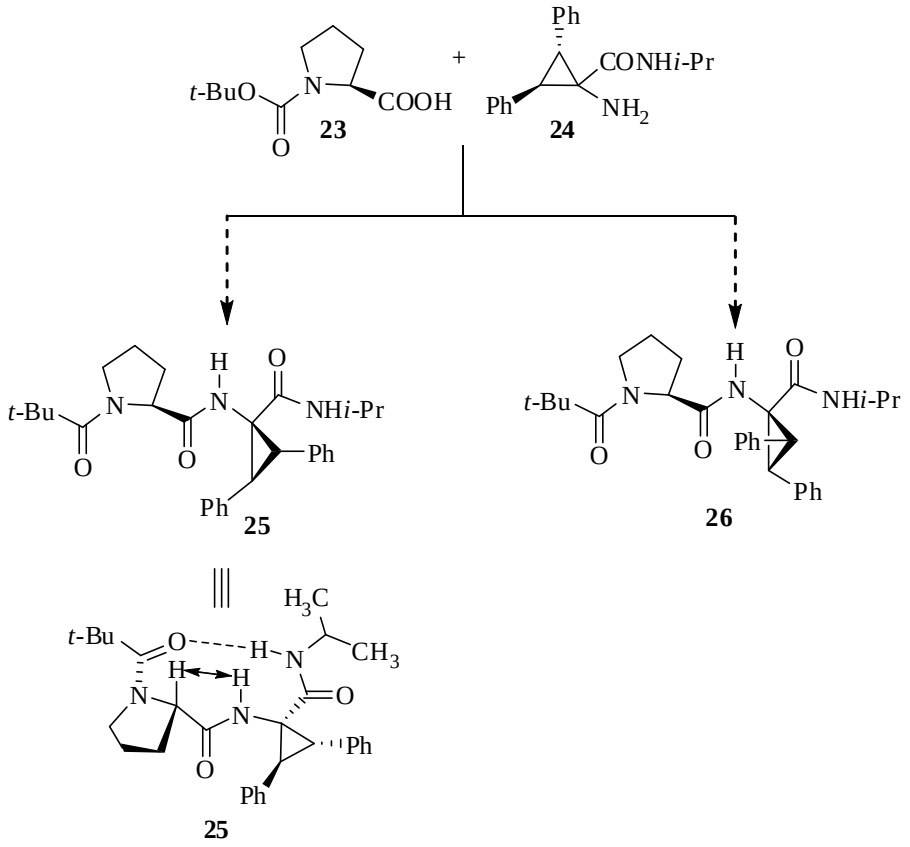


Figure 3. Truncated representation of the γ-turn region centered at cyclo-Met and the close proximity of the cyclopropane ring and the aromatic ring. The contact at 2.27 Å corresponds to an H-bond between the Arg N*H* and the Phe C*O*.

Jiménez et al.[30] have investigated the properties of Pro-cyclopropyl-2, 3-diphenyl α-amino acid ($c_3$diPhe) dipeptides. Coupling of N-terminally protected L-proline (**23**) with the racemic $c_3$diPhe (**24**) yields two diastereomers **25** and **26** (Scheme 8). One of the diastereomers forms a β-turn (type II), which was confirmed by X-ray diffraction structure analysis (Figure 4).



Scheme 8. Coupling of **24** with N-substituted L-proline.

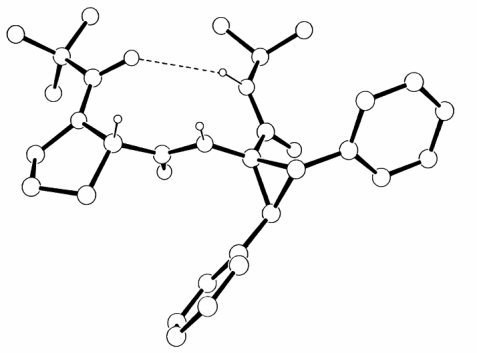


Figure 4. X-ray diffraction structure of compound **25** (β-II-turn). Most of the hydrogen atoms are omitted for clarity. The intramolecular hydrogen bond is represented as dashed line.

In 2005 Jiménez et al. reported[31] that different substituents in cyclopropane α-amino acids give different turn structures if incorporated into a short peptide. Racemic N'-methyl-2, 2-diphenyl-1-aminocyclopropane-carboxamide (H-c_3Dip-NHMe) was

coupled to N-*tert*-butoxycarbonyl-L-proline by the mixed anhydride method. The two column separable diastereomers showed a β-turn type II structure and two consecutive γ-turns, respectively, in the solid state. The report described the first observation of two consecutive γ-turns (Figure 5).

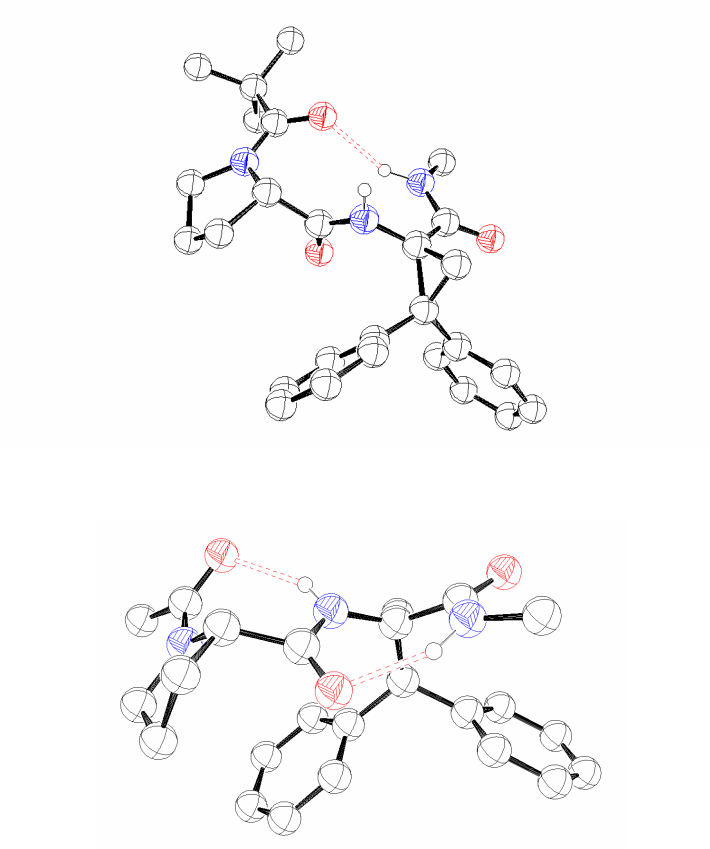
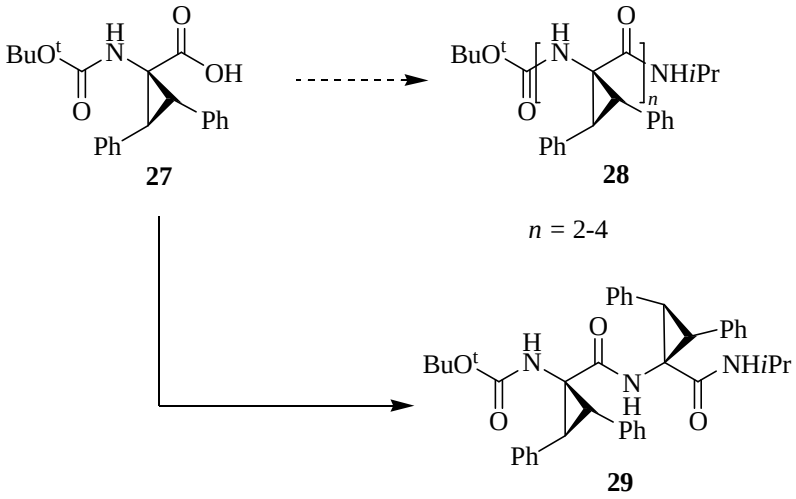


Figure 5. a) Top: X-ray diffraction structure of Piv-L-Pro-L-c_3Dip-NHMe accommodating a β-II turn. The intramolecular *i*←*i+3* hydrogen bond is indicated by a dashed line. Only the proline Cα and amide hydrogen atoms are shown, b) Bottom: X-ray diffraction structure of Ac-L-Pro-D-c_3Dip-NHMe exhibiting two consecutive γ turns, each stabilized by an intramolecular *i*←*1+2* hydrogen bond (dashed lines). Only the proline Cα and amide hydrogen atoms are shown.

Toniolo et al.[32] used $c_3$diPhe to investigate the relationship between the α-amino acid side- chain chirality and the screw sense of its turn or helical conformations in the absence of any potentially overlapping influence that arises from the asymmetric α-carbon. Starting from Boc-(2*R*, 3*R*) $c_3$diPhe-OH[33] (**27**) they synthesized a series of terminally protected (2*R*, 3*R*) $c_3$diPhe homochiral homopeptides up to the tetramer (**28)**

level in 61-80% yield by activating the amino acid carboxyl function with HOAt /HATU[34] in dry DCM in the presence of DIPEA (Scheme 9). The compounds are long enough to fold into multiple β-turn conformations and even into short 3_{10}-helices.



Scheme 9. Synthesis of helical peptides **28** and **29**.

The heterochiral dipeptide **29** was reported from the same groups,[35] with excellent yield after 4 days of reaction between Boc-(2*S*, 3*S*) $c_3$diPhe-OH and H-(2*R*, 3*R*) $c_3$diPhe-NH*i*Pr using the same coupling reagents. The single crystal structure shows the molecule folded in a type-I' β-turn conformation, stabilized by a weak intramolecular (Boc)C=O···H-N(NH*i*Pr) hydrogen bond, which closes a 10-membered atom ring (Figure 6). But in the crystal state the self-assembly of compound **29** through intermolecular hydrogen bonds leads to the formation of a supramolecular helix of large diameter (18 Å), internally decorated with phenyl rings. As a result, a hollow helical channel large enough to accommodate guest molecules was observed. This implies that compound **29** incorporates a highly restricted cyclopropane phenyalanine analogue ($c_3$diPhe) with remarkable conformational properties.

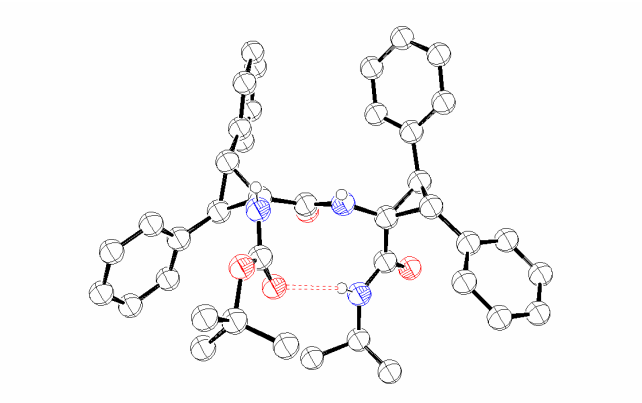


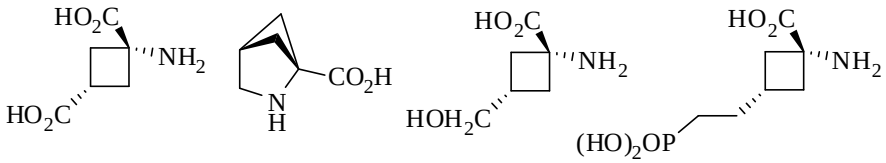
Figure 6. X-ray diffraction structure of Boc-[(2*R*, 3*R*) $c_3$diPhe] $_2$-NH*i*Pr (**29**). The intramolecular hydrogen bond is represented by a dashed line.

Earlier work investigated the structures of homo-oligomers of Ac_3c. For a detailed account we refer to ref. 14. The results indicated the propensity of tri- and tetrapeptides of this kind to fold into type I β-bends and distorted 3_{10} helices, respectively.[36,37,38] This is in contrast to homopeptides of 1-aminoisobutyric acid (Aib), 1-aminocyclopentane-carboxylic acid (Ac_5c) or 1-aminocyclohexanecarboxylic acid (Ac_6c) of similar length, for which regular type III β-bends and 3_{10} helices are found.

1.3. 1-Aminocyclobutanecarboxylic acids

1.3.1. Synthesis

Although the chemistry of small ring systems is well studied,[39] α-amino acids from the cyclobutane series have received only little attention. Recent use of 1-aminocyclobutane carboxylic acids in the field of medicinal chemistry is an exception (Figure 7).



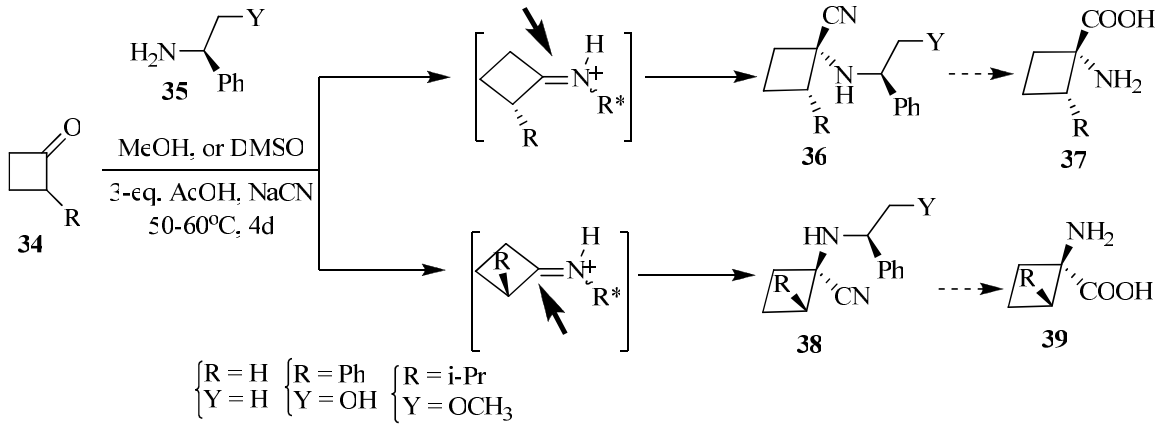
30 **31** **32** **33**

Figure 7. Structures of typical 2, 4-methano α-amino acids (**30**-**33**).

In 1980 Bell et al.[40] reported the first isolation of 2, 4-methano amino acids (2, 4-MAAs), namely *cis* -2, 4-methanoglutamic acid (2, 4-MGlu, **30**) and 2, 4-

methanoproline (2, 4-MPro, **31**) from the seeds of *Ateleia Herbert smithii*. Later, *cis*-1-amino-3-hydroxymethanocyclobutane carboxylic acid (**32**) was isolated by Austin et al. from the same source.[41] In 1990 *trans*-2, 4-methanoglutamic acid was described as a highly potent NMDA agonist,[42] whereas other 1, 3-disubstituted cyclobutane derived α-amino acids, such as **33**, act as NMDA antagonists and anticonvulsive drugs,[43] respectively. Furthermore, incorporation of various 2, 4-MAAs into bioactive peptides increases their stability towards enzyme degradation and altered their biological properties remarkably.[44] The first synthetic approach was reported by Gaoni et al.,[45] providing a wide range of achiral or racemic 1-aminocyclobutane carboxylic acids and their corresponding 1, 3-dicarboxylic acids.

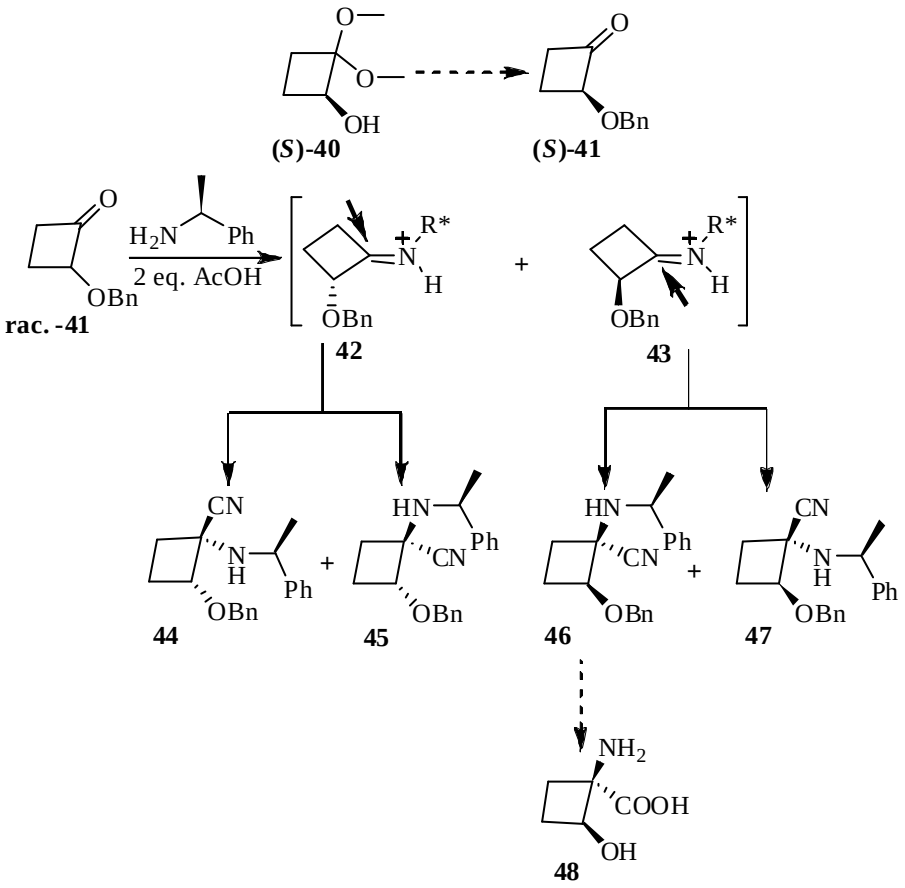
In 2003, Frahm et al.[46] and Fadel et al.[47] reported the synthesis of β-alkylated cyclobutane amino acids using 2-substituted cyclobutanones as starting material (**34**). The racemic 2-substituted cyclobutanones **34** were prepared from cyclopropyl aldehyde by a modified enlargement method[48] or from 1, 3-dibromobutane and tosylmethylisocyanide (TosMiC)[49]. Under acidic conditions, the ketones **34** were condensed with the chiral auxiliary (*S*) - 1-phenylethylamine or derivatives **35** to give corresponding iminium mixtures, which by *in situ* addition of sodium cyanide to the C=N bond would predominantly afford one diastereomer of the four possible α-aminonitrile isomers. In subsequent steps (hydrolysis and hydrogenolysis) the α-aminonitrile isomers were converted into the desired amino acids (Scheme 10).



Scheme 10. Synthesis of cyclobutane α-amino acids **37** and **39**.

In 2006 Hazelard et al.[50] reported the preparation of an enantiopure 1-amino-2-hydroxy-cyclobutane carboxylic acid (serine analogue, c_4Ser)-in four steps, starting from racemic cyclobutanones and a chiral benzylic amine as chiral auxiliary.

An easy and efficient one-pot reaction from readily available 2-benzyloxycyclobutanone (**41**) gave a kinetic or thermodynamic nitrile with good selectivity by means of an asymmetric Strecker synthesis. After separation, the major *trans*-amino nitrile underwent basic hydrolysis and hydrogenolysis, followed by acidic hydrolysis, to give optically active (1*R*, 2*R*)-1-amino-2-hydroxycyclobutanecarboxylic acid (**48**), serine derivatives (Scheme 11).



Scheme 11. Stereoselective synthesis of 1-amino-2-hydroxycyclobutane carboxylic acid, an analogue of serine (**48**).

The absolute configuration was established by X-ray diffraction structure analysis of the corresponding *cis*-amino nitrile, **44** (Figure 8)

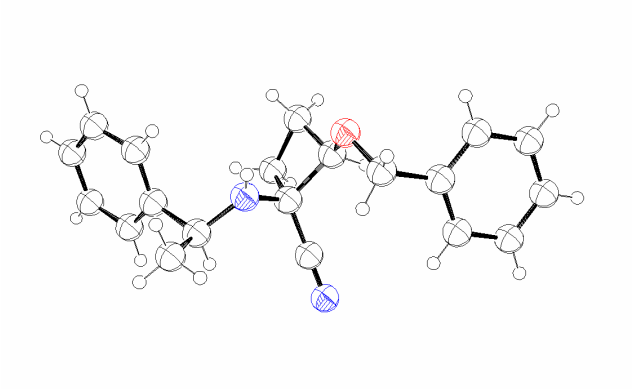
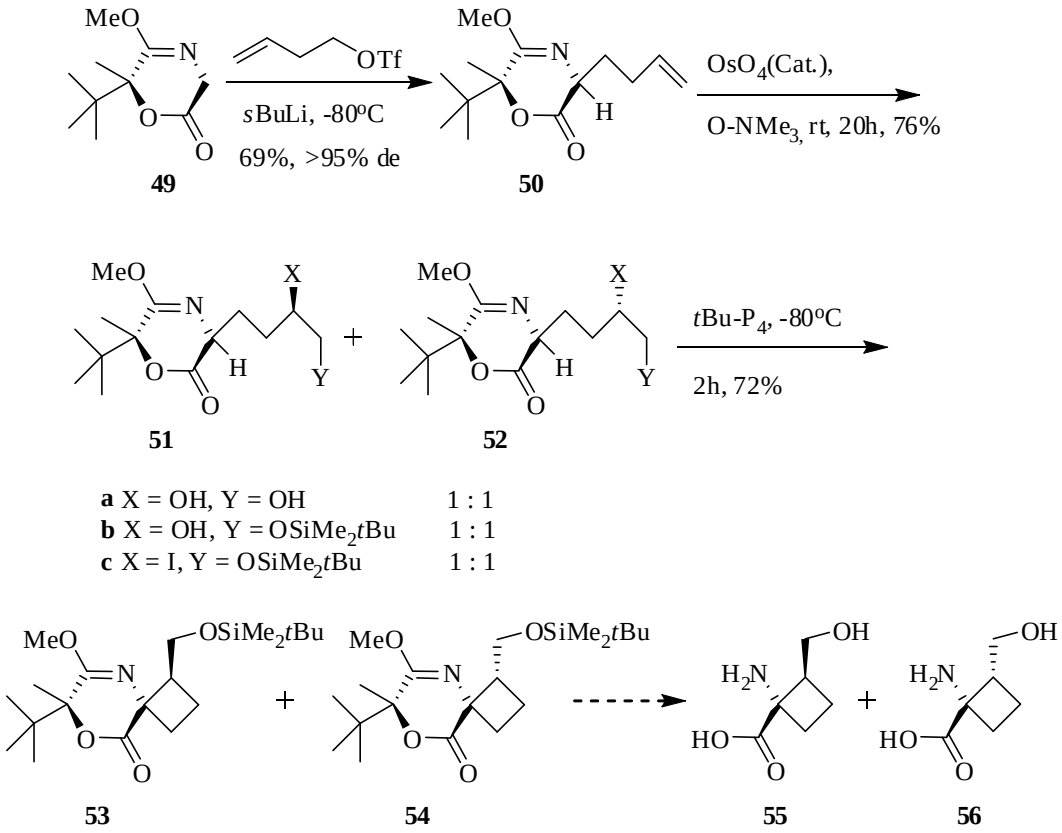


Figure 8. X-ray diffraction structure of compound **44**.

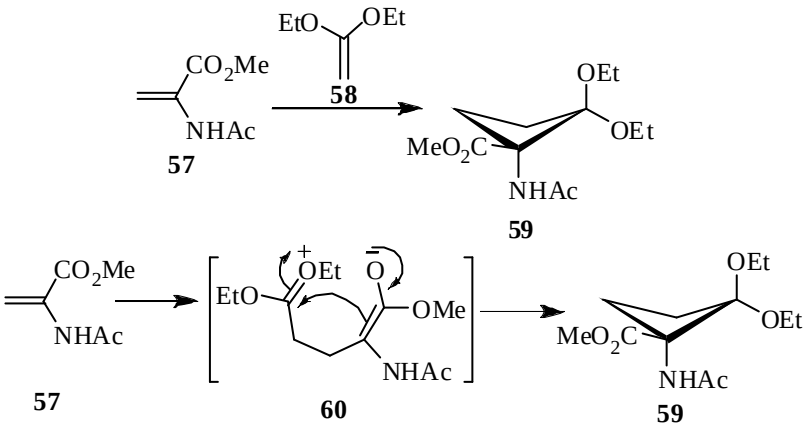
Wanner and co workers [51] reported the synthesis of all four stereoisomers of [(1*S*, 2*S*)-, (1*R*, 2*R*)-, (1*S*, 2*R*)-, (1*R*, 2*S*)-] of 1-amino-2 hydroxymethyl-cyclobutanecarboxylic acid. The synthesis was based on the chiral glycine equivalent **49**, which is available in both enantiomeric forms (Scheme 12).



Scheme 12. Synthesis of 1-amino-2-(hydroxymethyl)-cyclobutanecarboxylic acids **55** and **56**.

The key step involves the cyclization of silyl-protected iodohydrines **51c** and **52c** to the corresponding *spiro* derivatives **53** and **54** with the aid of the phosphazenic base *t*Bu-P_4. The final compounds (**55** and **56**) were prepared in subsequent steps and displayed a moderate potency as ligands for the glycine binding site of the NMDA receptor.

In 2003 Avenoza et al.[52] described a thermal [2+2] cycloaddition involving 2-acylaminoacrylates and ketene diethylacetal (Scheme 13). The reaction gave a new substituted cyclobutane skeleton that can be transformed into protected β-hydroxycyclobutane-α-amino acids. An asymmetric version of this cycloaddition was reported using sterically hindered aluminium aryloxides or methylaluminoxane as Lewis acids.



Scheme 13. Synthesis of protected β-hydroxycyclobutane-α-amino acids.

The 3D-structure of compound **59** was unambiguously determined by X-ray diffraction (Figure 9).

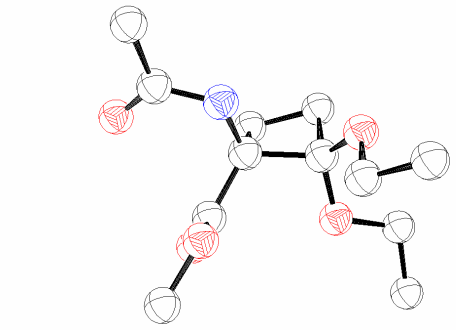


Figure 9. X-ray diffraction structure of compound **59**.

1.3.2. Induction of turn/helical structures in short peptides

Toniolo et al.[14,53] reported a series of homo peptides Z-(Ac_4c)$_n$-O*t*Bu, with n = 3 and 4. Spectroscopic and X-ray diffraction analyses revealed that Ac_4c, similar as Ac_7c, Ac_9c and $Ac_{12}c$ residues pass a remarkable conformational restriction to the peptide backbone. Figure 10 shows the structure of a tetramer Z-(Ac_4c)$_4$-O*t*Bu in the solid state adopting a helical conformation. Interestingly, the largely preferred conformations of regular type III/III´ β-bends and 3_{10}/α-helices for 1-amino-1-cycloalkanecarboxylic acids (Ac_nc; n = 4 – 12) with cycles larger than cyclopropyl, closely resemble those of 1-amino-isobutyric acid (Aib). For a more detailed discussion we refer to ref. 14.

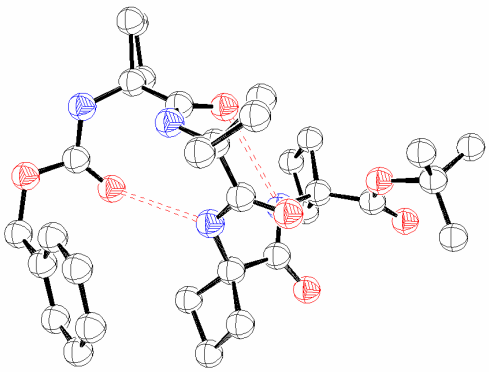


Figure 10 X-ray diffraction structure of Z-(Ac_4c)$_4$-O*t*Bu. The two intramolecular H bonds are represented by dashed lines.

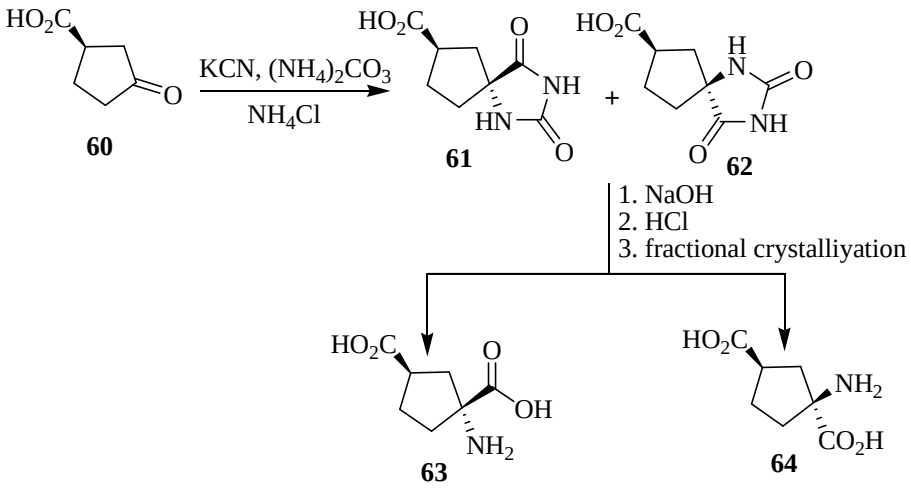
1.4. 1-Aminocyclopentanecarboxylic acids

1.4.1. Synthesis

The unnatural α-amino acid 1-amino-cyclopentane carboxylic acid (ACPC) has been reported to inhibit the growth of Novikoff rat hepatoma,[54] Walker rat carcinoma 256,[55] sarcoma 180 and carcinoma 755.[56] Berlinguet et al.[57] reported that this amino acid does not undergo any metabolic change and Sarkar and co workers[58] established the mechanism of its action.

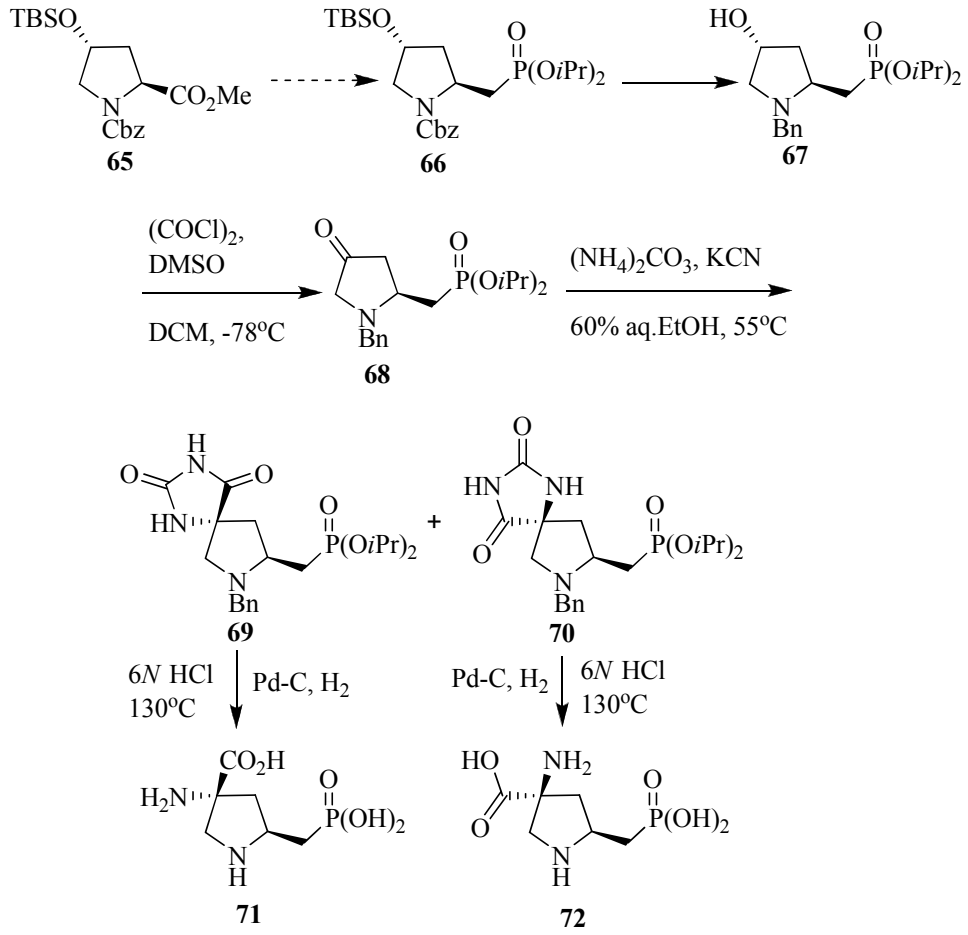
Strecker or Bucherer-Bergs synthesis is the most frequently used method to prepare 1-aminocyclopentane carboxylic acids starting from the cyclopropane ring. The four stereoisomers of 1-aminocyclopentane-1,3-dicarboxylic acid (ACPD), which are conformationally constrained analogues of glutamate, have been found to act as excitatory amino acids and were obtained from 3-oxocyclopentane carboxylic acid.[59] A

mixture of the (1*S*, 2*S*) and (1*R*, 2*R*) stereoisomers of ACPD was obtained from the (*R*)-enantiomer after Strecker-type formation of a hydantoin followed by hydrolysis. Fractional crystallization of the mixture allows the isolation of both compounds in diastereomerically pure form. (Scheme 14).



Scheme 14. Synthesis of two stereoisomers of 1-aminocyclopentane-1, 3-dicarboxylic acid (ACPD) (**63** and **64**).

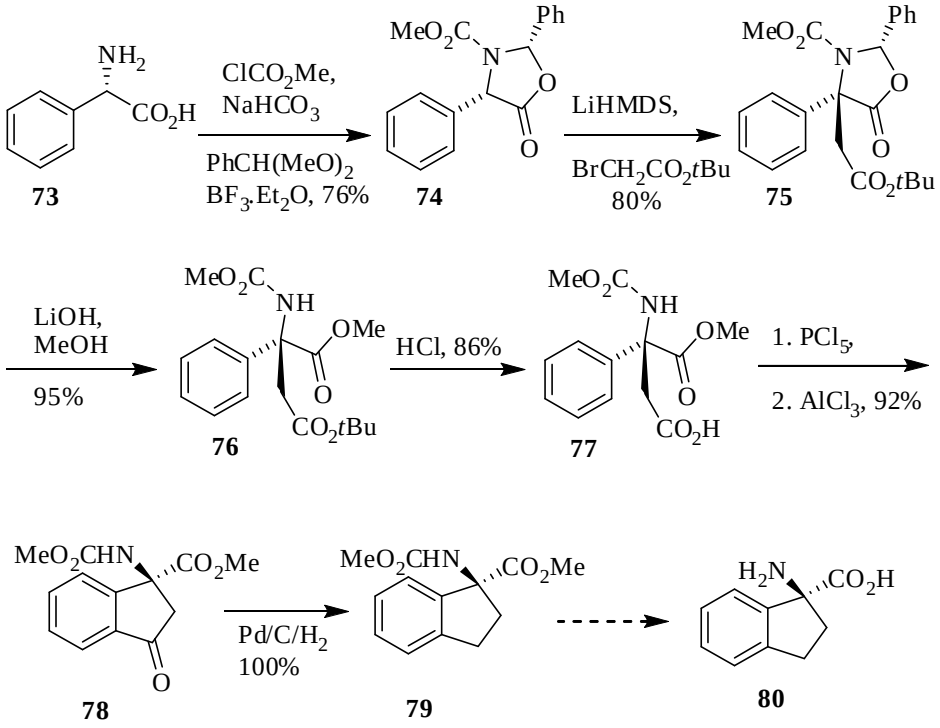
Asymmetric synthesis of 4-amino-4-carboxy-2-phosphonomethylpyrrolidines **71** and **72**, which can be viewed as novel conformationally restricted analogues of 2-amino-5-phosphonopentanoic acid (AP 5) incorporated into the pyrrolidine ring, was achieved from *trans*-4-hydroxy-L-proline as a homochiral starting material. The hydroxy group was converted to the corresponding ketone by Swern oxidation[60] to afford compound **68**. The Bucherer-Bergs reaction of **68** with ammonium carbonate and potassium cyanide in 60% aqueous ethanol gave the spirohydantoin (2*S*, 4*R*)-**69** and (2*S*, 4*S*)-**70** as pure diastereomers in the ratio of 84:16, respectively, in 75% yield. Finally, hydrolysis of **69** and **70** with 6 N HCl followed by hydrogenolysis gave the desired products **71** and **72** after purification on ion exchange column (Scheme 15).



Scheme 15. Synthesis of 4-amino-4-carboxy-2-phosphonomethylpyrrolidines **71** & **72.**

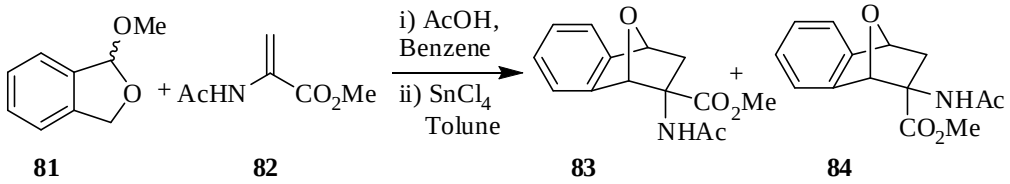
1-Aminoindan-1, 5-dicarboxylic acid (AIDA)[61] and 1-amino -5-phosphenoindan-1-carboxylic acid (APICA)[62]are two subtype-selective antagonists for metabolic glutamate receptors (mGluRs)[63]. Recently, both racemic AIDA and APICA have become useful pharmaceutical tools in seeking the roles of mGluRs in physiological processes. Ma et al.[64] reported a new strategy to synthesize these compounds (Scheme 16). (*R*)-Phenylglycine (**73**) was protected by methyl chloroformate to afford the carbamate, which was reacted with benzaldehyde dimethyl acetal in methylene chloride in the presence of boron trifluoride etherate to produce *cis*-oxazolidinone (**74**)[65]. Alkylation of **74** with *tert*-butyl bromoacetate provides compound **75** in 80% yields with more than 97% diastereoselectivity. The oxazolidinone ring of **75** was opened by treatment with LiOH in methanol to give diester **76** in 95% yields. Selective deprotection of the *tert*-butyl group with HCl in DCM yielded **77**. Compound **77** was then cyclized by using

Friedel-Craft acylation in 92%. The subsequent reduction of the ketone **78** gave compound **79**, which was further transformed to amino acid **80**.



Scheme 16. Synthesis of 1-aminoindan-1-carboxylic acid **80**.

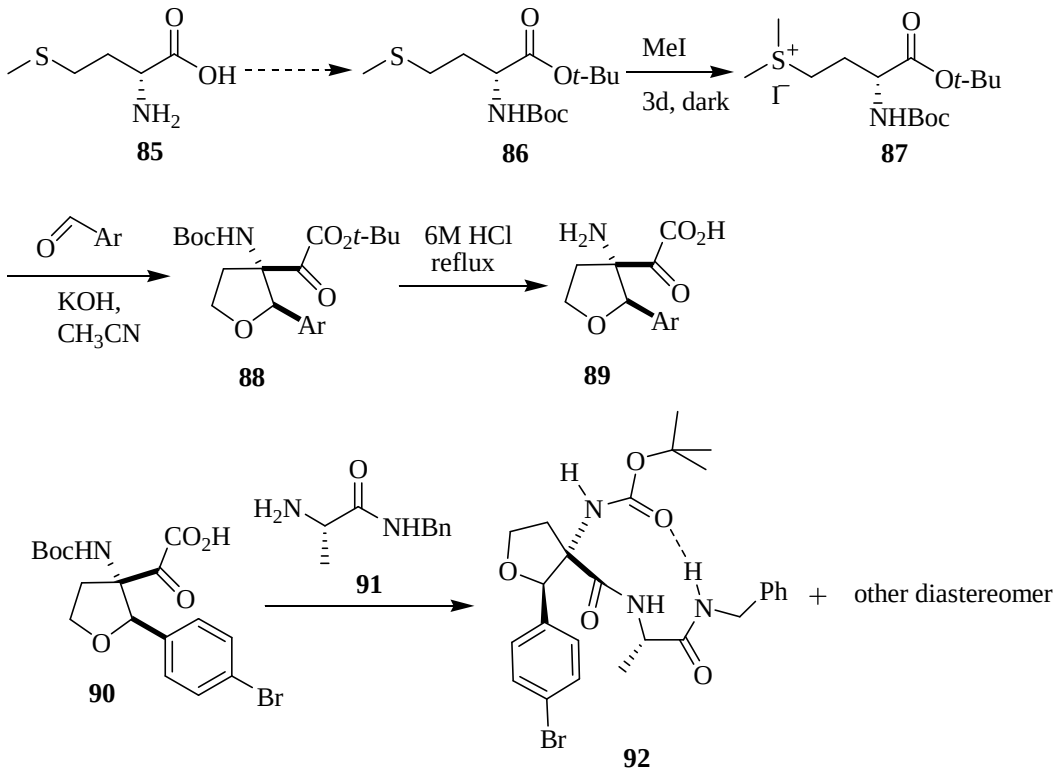
In situ generated isobenzofuran has been frequently used as reactive intermediate for the synthesis of 9-oxabenzonorbornenes.[66] To synthesize the reactive intermediates, Tamaki and co workers[67] examined the reaction of 1-methoxyphthalane (**81**) with methyl N-acetyl-α, β-dehydroalaninate (**82**), which occurred smoothly in refluxing benzene in the presence of a catalytic amount of AcOH to afford the adducts **83** and **84** in good yield and in ratio of 7:1 (Scheme 17).



Scheme 17. Synthesis of compounds **83** and **84**.

1.4.2. Induction of turn/helical structures in short peptides

We have recently synthesized tetrahydrofuran C^{α}-tetrasubstituted α-amino acids (TAA),[68] starting from L-methionine (**85**) (Scheme 18). Compound **87** reacted with aromatic aldehydes in the presence of KOH to afford compound **88**. The reaction is highly diastereoselective (>97:3; *trans : cis*), but yields racemic products. Compounds **89** were obtained upon hydrolysis of compounds **88** by 6M HCl. The racemic amino acid **90** was coupled with compound **91** under standard peptide coupling conditions to afford dipeptide **92** and its other diastereomer. The X-ray diffraction analysis of the compound **92** showed a type I β-turn structure with a strong intramolecular hydrogen bond (Figure 11)



Scheme 18. Synthesis of tetrahydrofuran C^{α}-tetrasubstituted amino acids (TAA).

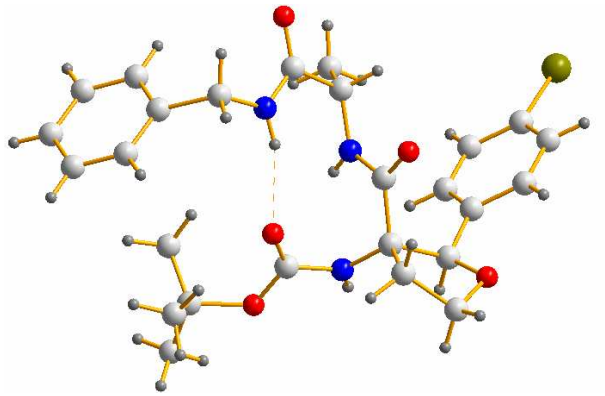
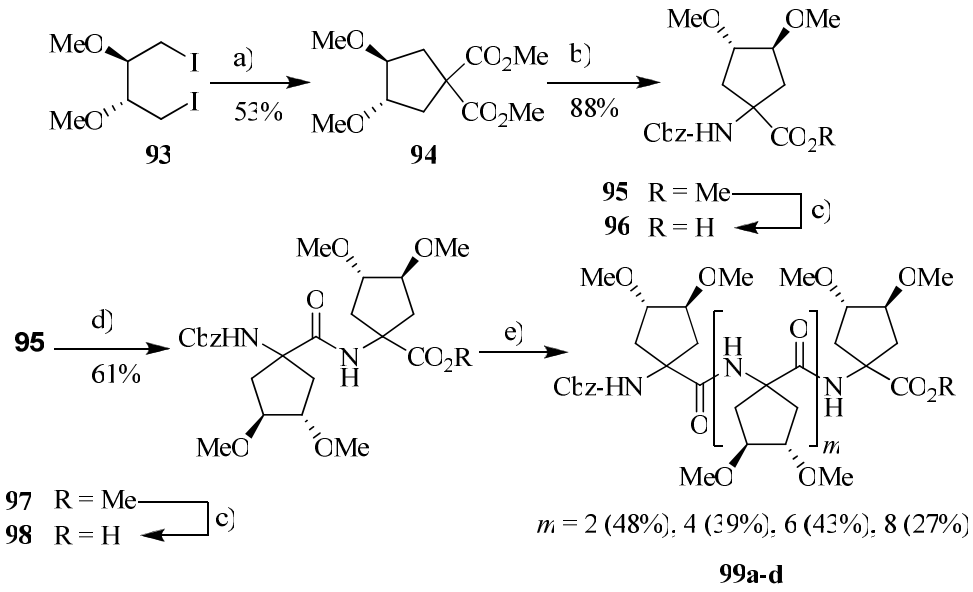


Figure 11. X-ray diffraction structure of **92** shows a type I β-turn form with a 10-atom intramolecular hydrogen bond (showed by dashed line).

Among proteinogenic L-α-amino acids, only isoleucine and threonine possess an additional chiral center in their side chain. However, it was not clear how the chirality of the side chain influences the secondary structure of peptides.[69] Addressing this issue, Tanaka et al.[70] reported in 2004 how the asymmetric center of the α-amino acid side chain alone controls the screw sense of oligopeptide helices consisting only of amino acids without a chiral center at the α-carbon. They synthesized a chiral, cyclic, C^{α}-tetrasubstituted [(*S*, *S*)-Ac_5c^{dOM}] α-amino acid (**96**), in which the α-carbon has no asymmetric center, but the side chain β-carbons do. (*S*, *S*) - Ac_5c^{dOM} homopeptides therefore do not possess asymmetric centers along the backbone of the peptide, but they have asymmetric centers in the side-chain cyclopentane rings. Thus, the screw sence of the secondary structure is affected only by the side-chain chiral centers.[71] The synthesis starts from optically active compound **93** (Scheme 19). The preferred secondary structure of the homopeptides in $CDCl_3$ solution was first studied by FT-IR absorption and ^1H NMR spectroscopy. The 3D-structures of the terminally protected octapeptide **99c** (Figure 12) and hexapeptide **99b** were determined by X-ray diffraction. In the asymmetric unit of **99b** one left-handed helical structure (mean value φ = 60.9º, ψ = 46.8º), (which is not a 3_{10}-helix, but an α-helix) exists along with three water molecules. Five intramolecular hydrogen bonds stabilize the α-helical structure.



Scheme 19. Synthesis of (*S*,*S*)-Ac_5c^{dOM} and its homopeptides. Reagents and conditions: a) dimethyl malonate, KO*t*Bu; b) 1. NaOH, 2. DPPA, 3. BnOH; c) NaOH; d) 1. Pd/C, H_2, 2. EDC, HOBt, **96**, MeCN, rt; e) 1. Pd/C, H_2, 2. EDC, HOBt, **98**, MeCN, rt.

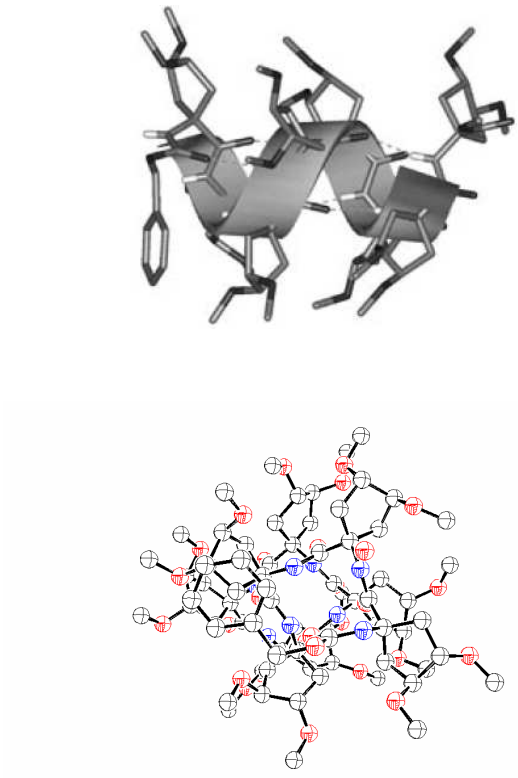
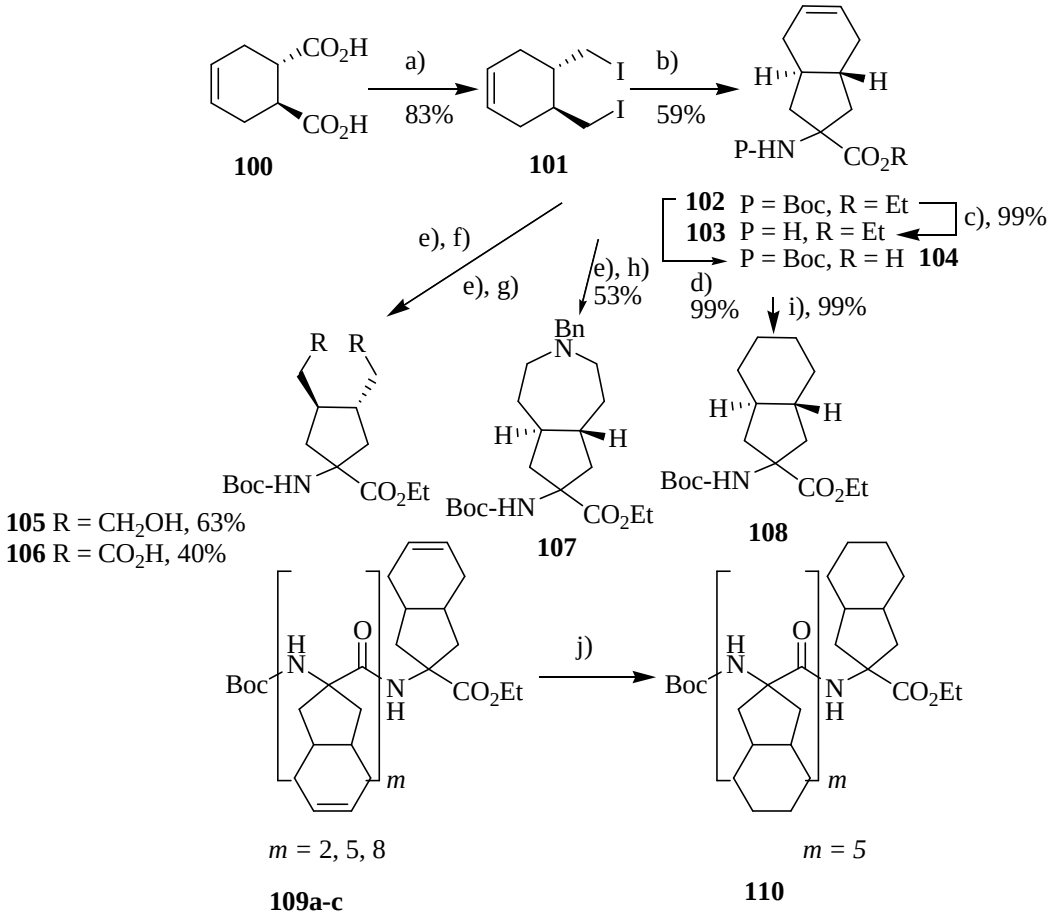


Figure 12. X-ray diffraction structure of compound **99b** viewed perpendicular to the helical axis (top); ORTEP drawing viewed along the α-helical axis (α-helical wheel) (bottom).

Extending the work, the same group reported[72] C^{α}-tetrasubstituted [(*S*, *S*)-Ac_5c^{dOM}] α-amino acids having chirality only in the cyclic side chain. The synthesis started from (*S*, *S*)-cyclohex-4-ene-1,2-dicarboxylic acid (**100**) and is summarized in Scheme 20.[73]

In the crystal state the asymmetric unit of **109b** contains four independent molecules along with two ethanol molecules (Figure 13). Two molecules form a right-handed 3_{10}-helix and the other two a left-handed 3_{10}-helix.



Scheme 20. Synthesis of C^{α}-tetrasubstituted α-amino acids having chirality only in the cyclic side chain. Reagents: (a) 1. $LiAlH_4$; 2. I_2, PPh_3; (b) 1. NaH, $CNCH_2CO_2Et$; 2. HCl; 3. Boc_2O; (c) H^+; (d) NaOH; (e) O_3; (f) $NaBH_4$; (g) Oxone; (h) $BnNH_2$, $NaBH_3CN$; (i) H_2, Pd-C; (j) H_2, $Pd(OH)_2$-C

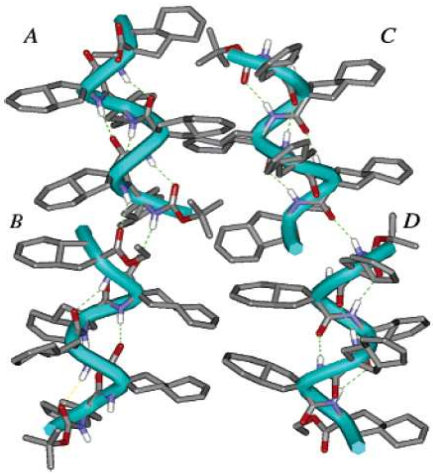


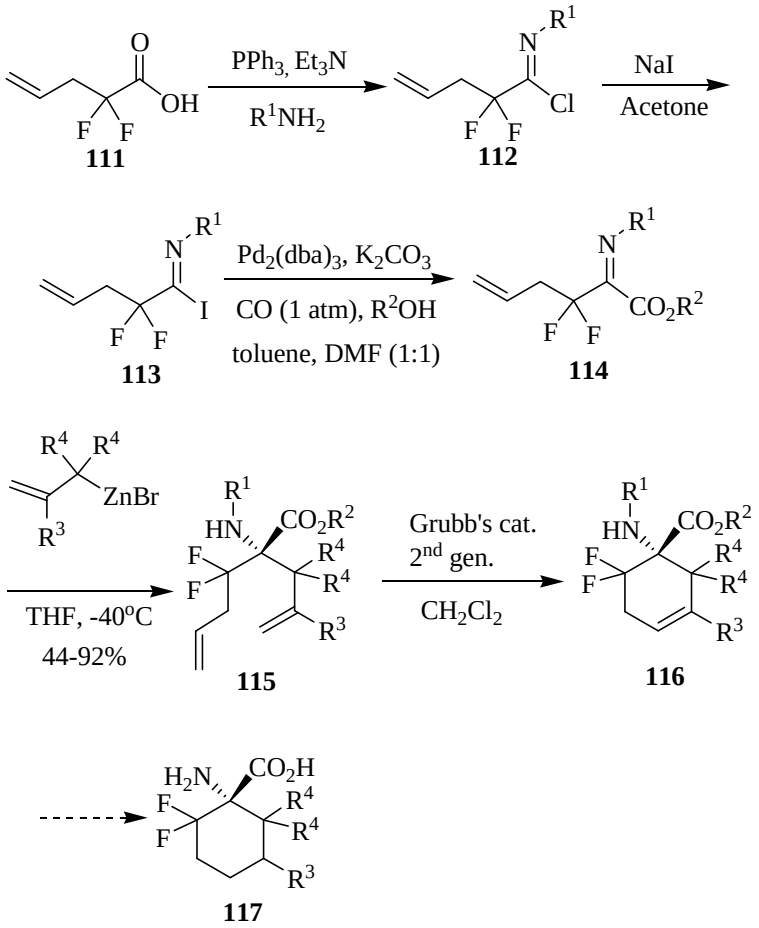
Figure 13. Four crystallographically independent molecules (*A*-*D*) of **109b**, determined by X-ray diffraction analysis.

1.5. 1-Aminocyclohexanecarboxylic acid

1.5.1. Synthesis

The 1-aminocyclohexane carboxylic acid framework has been used in the design of potent cathepsin K inhibitors[74] and V2 agonists of arginine vasopressin.[75] The detailed synthetic strategy has been described by Cativiela[13].

In 2006 Fustero et al.[76] reported β, β-difluorinated derivatives of these amino acids, because the presence of fluorine atoms often induces significant changes in the physical properties, biological activities and metabolic profiles of the resulting peptides.[77] 2, 2-Difluoro-4-pentenoic acid (**111**) was transformed into the corresponding imidoyl chlorides (**112**), which were converted into imidoly iodides (**113**) with NaI in dry acetone. These intermediates were treated with CO and several alcohols in the presence of a catalytic amount of $Pd_2(dba)_3$ to afford imino esters (**114**) in moderate yields, which were subsequently chemoselective allylated. Among several organometallic reagents, allyl zinc compounds delivered the desired racemic product almost in quantitative yields, which was then cyclized to **116** using the Grubb's 2nd generation catalyst. Subsequent steps gave the target di-fluorinated 1- aminocyclohexanecarboxylic acid (**117**) (Scheme 21).



Scheme 21. Synthesis of β, β-difluorinated 1-aminocyclohexane carboxylic acid **117**.

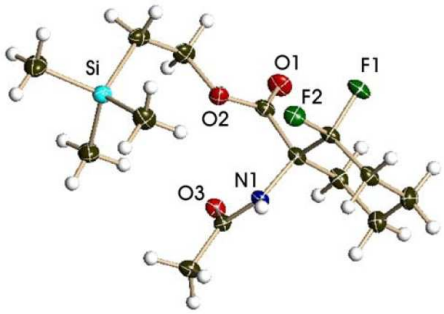
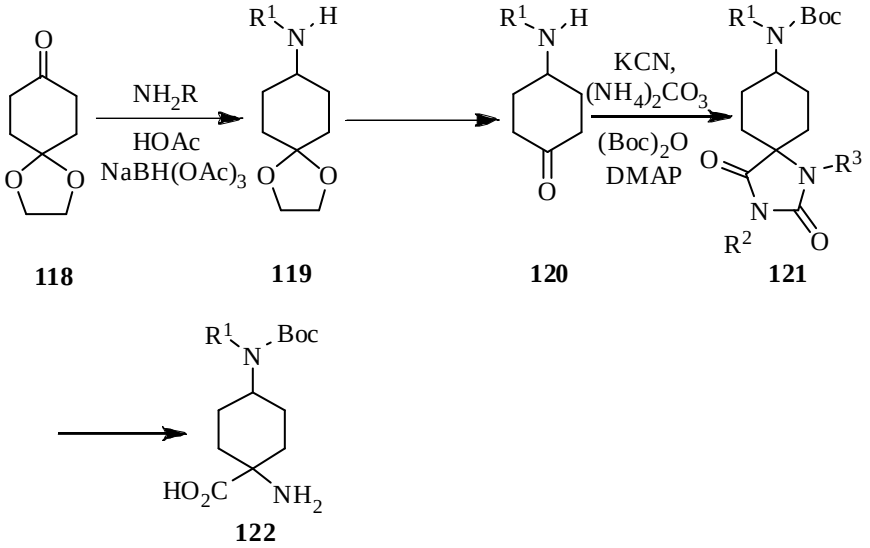


Figure 14. X-ray diffraction structure of compound **116**, with R_1 = Ac, R_2 = $(CH_2)_2$TMS, R_3 and R_4 = H.

The synthesis of orthogonally protected 1-aminocyclohexane carboxylic acids begins with a reductive amination on the commercially available 1, 4-dicyclohexanone monoethylene ketal **118** with the amine of choice, acetic acid and sodium

triacetoxyborohydride in dichloromethane to afford **119.** In the next two steps the acetal was deprotected to **120** and the secondary amine was Boc-protected to **121**. Ketone **120** was converted to hydantoin **121** using the Bucherer-Bergs procedure.[78] Selective hydrolysis of **121** gave **122**. (Scheme 22)[79]

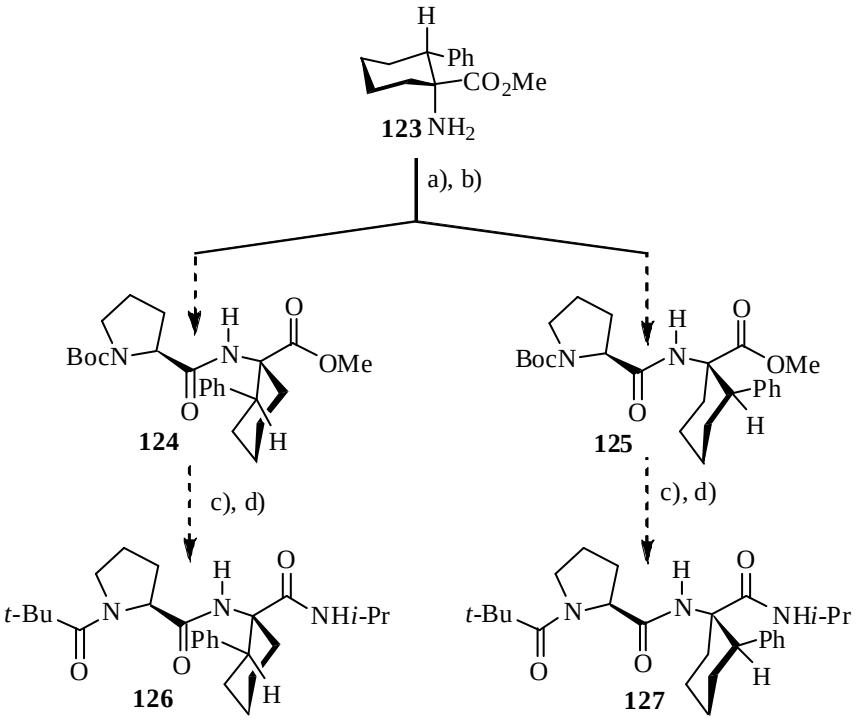


Scheme 22. Synthesis of orthogonally protected 1-aminocyclohexane carboxylic acid **122**.

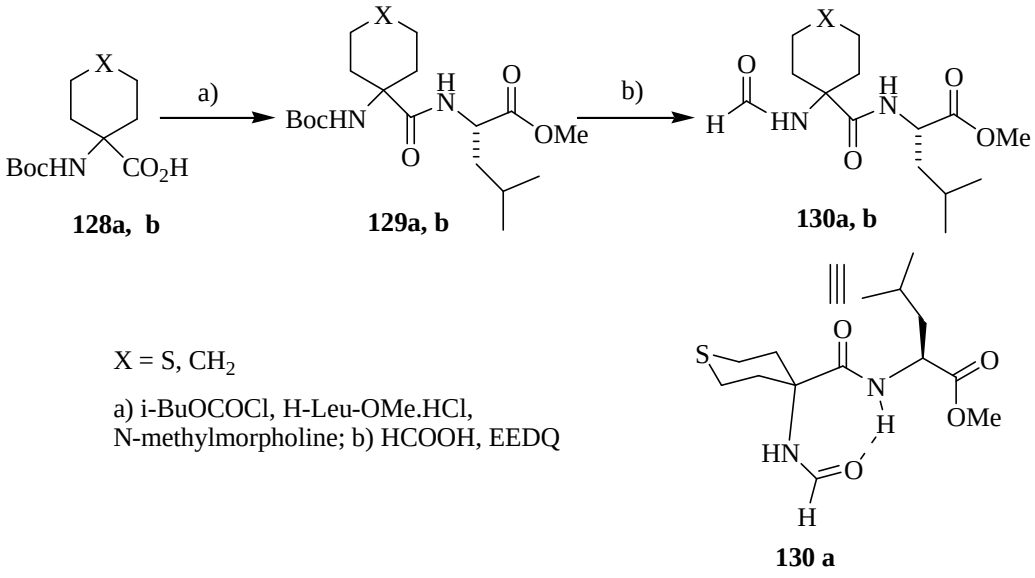
1.5.2. Induction of turn/helical structures in short peptides

The cyclic amino acids, which are constructed from a 6-membered ring backbone, have high helix promoting effects. Yokum et al.[80] showed that even very short peptides, enriched with amino acids having the general structure **122**, retain a 3_{10}-/α-helix equilibrium in organic and aqueous phase solvent mixtures.

Jiménez et al.[81] synthesized peptides Piv-L-Pro-(*S*,*S*)c_6Phe-NH^{i}Pr (**126**) and Piv-L-Pro-(*R*,*R*)c_6Phe-NH^{i}Pr (1**27**) (Scheme 23). Their conformational properties were studied in the crystal state by X-ray diffraction and in solution by ^{1}H-NMR and FT-IR absorption spectroscopy, and the results were compared to those of the analogous dipeptides containing L- and D-Phe. They also showed by theoretical calculations that discrimination between the type-I and type-II β-turns occurs due to the existence of an NH to π-phenyl ring interaction.



Scheme 23. Synthesis of the two Piv-Pro-c_6Phe-NH^{i}Pr dipeptides **126** and 1**27** from racemic H-c_6Phe-OMe (**123)**. Conditions: (a) Boc-L-Pro-OH/^{i}BuOCOCl/NMM/CH_2Cl_2, -15º C 24 h; yield: 85%. (b) Eluant AcOEt/hexanes 1/1; R_f 0.67 (*S*,*S*), 0.50 (*R*,*R*). (c) ^{i}PrNH$_2$/AlMe$_3$/toluene, 0º C 1 h, 50º C 36 h; yield 48-50%. (d) 1: TFA/CH_2Cl_2 2/3, rt, 2 h. 2: Piv$_2$O/Et$_3$N/DMAP/CH_2Cl_2, 0 º C 1 h, rt overnight; yield 83-85%.

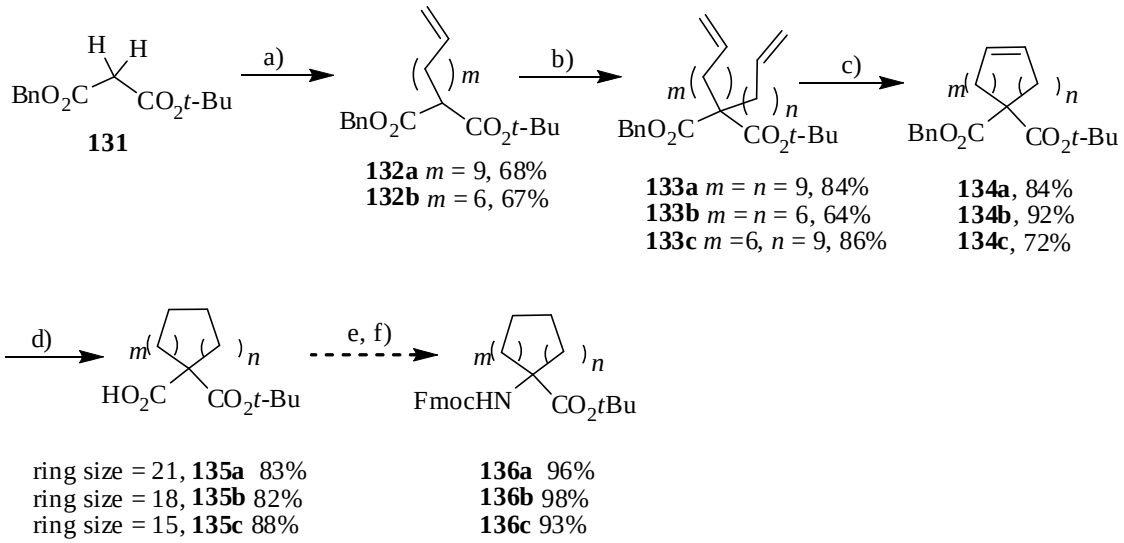


Scheme 24. Synthesis of compound **130a,b** and their γ-turn conformation in $CDCl_3$.

Amino acid derivatives **128a-b** were prepared and coupled with (*S*)-H-Leu-OMe (Scheme 24)[82]. The di-peptides were unable to form a *1←4* H-bond, but adopted a γ-turn structure in $CDCl_3$ solution. The conformation was not retained in DMSO.

1.6. Miscellaneous

Hydrophobic amino acids play an essential role in the molecular architectures of proteins and peptides. Such amino acids are commonly found in the transmembrane regions of membrane proteins and ion channels, embedded in the lipid bilayers.[83] Farnesylation (transfer of 15 carbon atoms) and geranylgeranylation (transfer of 20 carbon atoms) of cysteine side chains are known to have dramatic effects on the hydrophobicity of proteins and have been proposed to be important for signal transduction.[84] Various unnatural amino acids with hydrophobic side chains have been explored as building blocks for peptides that provide novel hydrophobic cores.[85] Amino acids with C^{α}-tetrasubstituted cycloaliphatic groups are intriguing, because α, α-disubstitution constrains the conformation of a peptide chain and also causes changes in hydrophobicity.[86] Ohwada et al.[87] have described a general approach to synthesize the amino acids with large saturated hydrocarbon ring in the, α, α-position (Scheme 25).



Scheme 25. Synthesis of protected macrocyclic C^{α}-tetrasubstituted α-amino acids. a) CH_2=CH$(CH_2)_m$Br, NaH, DMSO, rt; b) CH_2=CH$(CH_2)_n$Br, NaH, DMSO, rt; c) [$(PCy_3)_2Cl_2Ru$=CHPh], CH_2Cl_2, reflux.; d) H_2, Pd/C, AcOEt; e) DPPA, Et_3N, benzene, reflux; f) 9-fluorenylmethanol, toluene, reflux; rt.

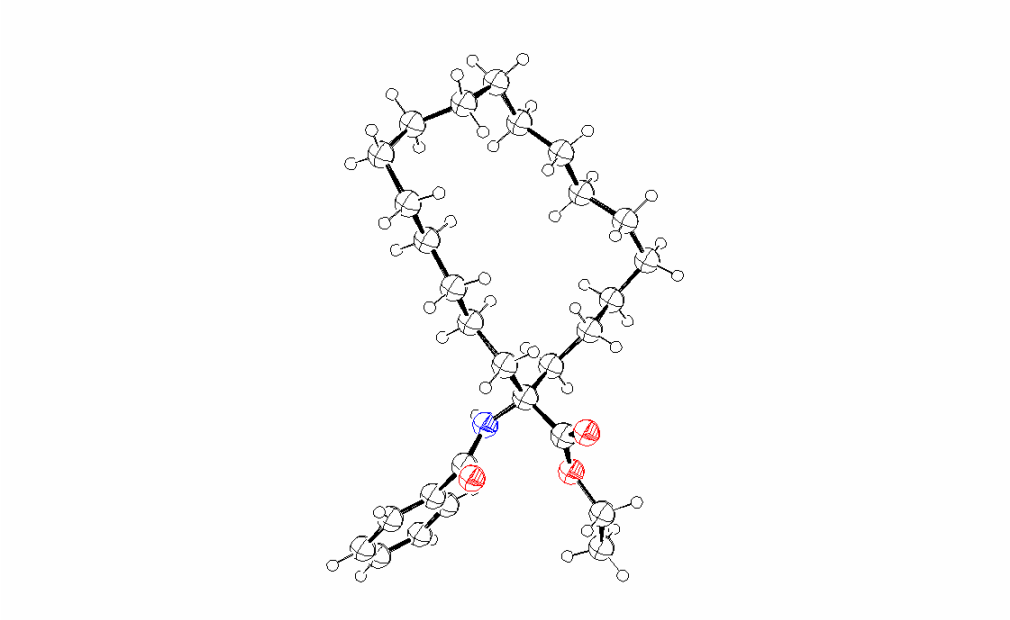


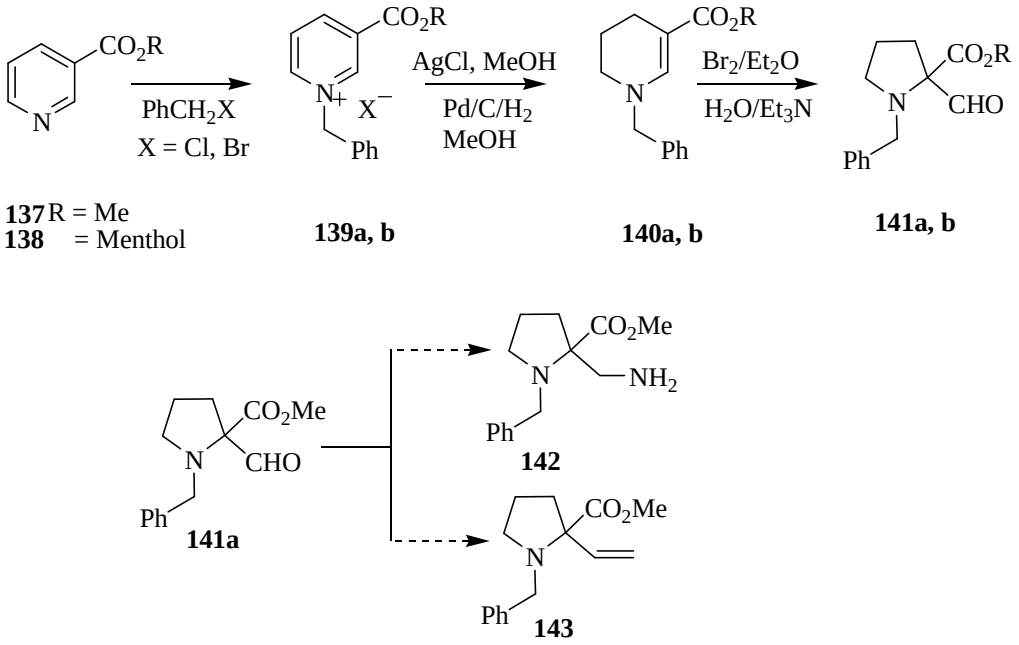
Figure 15. X-ray diffraction structure of the N-benzoyl ethyl ester derivative of the macrocyclic α-amino acid containing an 18-membered ring.

C^{α}-Tetrasubstituted α-amino acid derivatives bearing 21-membered (**136a**), 18-membered (**136b**) and 15-membered (**136c**) rings, respectively, were synthesized efficiently through ring-closing metathesis reactions of the appropriate dialkenyl malonate precursors (**133a-c**), which were derived from malonates **131** (Scheme 25).[88] Stepwise alkylation of malonate derivative **131** in the presence of NaH/DMSO gave the monoalkylated products (**132 a, b**) in moderate to high yields, while the second alkylation step yield was generally high and insensitive to the chain length of the second alkyl bromide. The ring-closing metathesis reactions of the dialkenylated precursors (**133a-c**) leading to **134 a-c** were carried out by treatment with Grubbs' ruthenium catalyst in dichloromethane.

The C^{α}-tetrasubstituted cycloaliphatic amino acids bearing large rings were incorporated into short peptide chains using the Fmoc solid-phase method. The design of these peptides was based on the sequence of helical peptides, composed of alanine, lysine and glutamic acid. In such helical peptide sequence two alanines at the 3 and 10 positions were replaced by C-18 rings on the same side of the helix. The energy minimized structure predicts stable conformers for the modified peptide.

In 2000 Trancard et al.[89] reported a new stereoselective approach to access so called 'proline chimeras', in which the heterocyclic part of the amino acid is substituted in

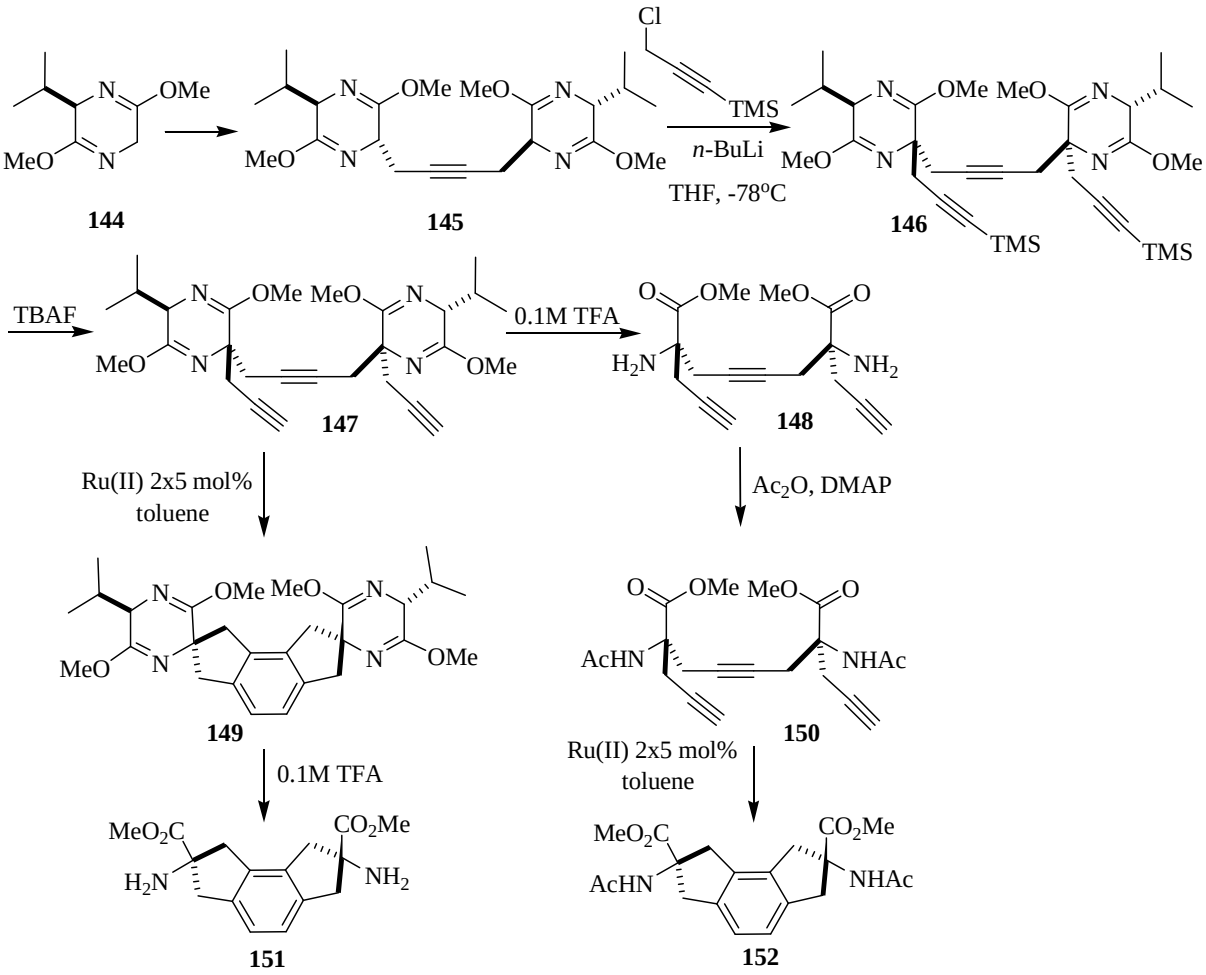
such a way that the chimera combines the conformational constituent of proline with the side chain of another amino acid. Benzylation of the starting nicotinates (**137** and **138**) by benzyl halide gave the corresponding pyridinium salts (**139 a**, **b**) in excellent yield. The Wekert procedure[90] was used for partial hydrogenation to **140 a**, **b**. As bromide is a potential catalyst poison, it was exchanged with chloride using AgCl. Finally, the ring size reduction[91] gave the desired products **141 a, b.** The aldehyde group was converted to different functionalities (Scheme 26).



Scheme 26. Synthesis of new proline chimeras.

Cystine is an important four atom bridged bis-α-amino acid. The group of Undheim used C4-bridged analogues where the disulphide moiety was replaced by a C2-unit. In 2001[92] they reported a methodology which leads to rigid bis-α-amino acid structures in the form of tricyclic bridges. The distance between the amino acid centers can be varied by the ring size in the tricyclic bridge.[93] A C4-alkyne bridge was initially constructed by alkylation of lithiated (2*R*)-2, 5-dihydro-2-isopropyl-3, 6-dimethoxy-pyrroline (**144**) as chiral auxiliary with 1, 4-dibromo-2-butyne (Scheme 27). The reaction is stereoselective in that the electrophile becomes attached *trans* to the isopropyl group (**145**).[94] The second alkylation with TMS protected propargyl chloride gave the dialkylated product **146** in 60% yield. Removal of the TMS-protecting group in compound **146** proceeded

readily with tetrabutylammonium fluoride (TBAF) to give **147**. The deprotected material was hydrolyzed with TFA in aqueous acetonitrile at room temperature to afford compound **148,** which was acetylated using Ac_2O and DMAP. This compound (**150**) undergoes RCM in the presence of a Ru (II) catalyst to yield compound **152** in 58%.



Scheme 27. Synthesis of indacene-bridged bis-(α-amino acid) derivatives.

Toniolo and co workers[53] investigated C^{α}-tetrasubstituted alicyclic α-amino acids containing larger rings (Ac_nc, n = 7, 8,[95] 9, and 12). In the peptides examined, all the Ac_nc residues are found in the helical region of the conformational space. Although their effective volume and hydrophobicity is quite different, a comparable conformational preference is observed.

1.7. Glossary

Different types of bends are defined according to the number and spatial arrangement of the residues involved. β-Turns (or β-bend) (Figure 16) are the most abundant and best characterized group of secondary folding structures.[2a,2b,96,97,98] They comprise four amino acid residues connected by three amide groups. About three-quarter of tight turns feature a 1←4 (C_{10}) H-bond between the backbone CO (*i*) and NH (*i+3*) groups and the distance between the C^{α} (*i*) and the C^{α} (*i+3*) is < 7Å.

A γ-turn is defined by the existence of a hydrogen bond between the CO group of one of the residue (*i*) and the NH of the (*i*+2) th residue.[99,100]

A 3_{10}-helix[101] is defined by the existence of a hydrogen bond between the CO group of one of the residue (*i*) and the NH of the (*i*+3) th residue (subtype III or helical β-turn[96,97,98]).

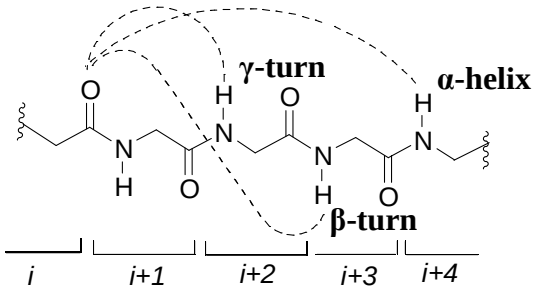


Figure 16. Schematic representation of the intramolecular hydrogen bond that stabilizes the β-turn (*i*←*i*+3), the γ-turn (*i*←*i*+2) and the α-turn (*i*←*i*+4) in a peptide chain.

1.8. Conclusion

Recent trends in the synthesis of cyclic C^{α}-tetrasubstituted amino acids with ring sizes varying from three to six and their incorporation in short peptide to give definite turn structure were summarized in this review. Most of those synthetic routes are based on stereoselective syntheses using chiral auxiliaries. The overall shape and intrinsic stereoelectronic properties of the amino acids important for molecular recognition, signal transduction, enzymatic specificity, immunomodulation, and other biological effects depends on the arrangement of the side chain groups in three-dimensional chi space (χ^1, χ^2 etc. torsional angles). Cyclic C^{α}-tetrasubstituted amino acids are valuable tools for the preparation of structurally defined peptides. In particular, their rigid and predictable structures and their good accessibility make them attractive as building blocks in the synthesis of artificial peptides.

1.9. References and notes

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Tetrahydrofuran C^{α}-Tetrasubstituted Amino Acids: Two Consecutive *β*-Turns in a Crystalline Linear Tripeptide*

2.1. Introduction

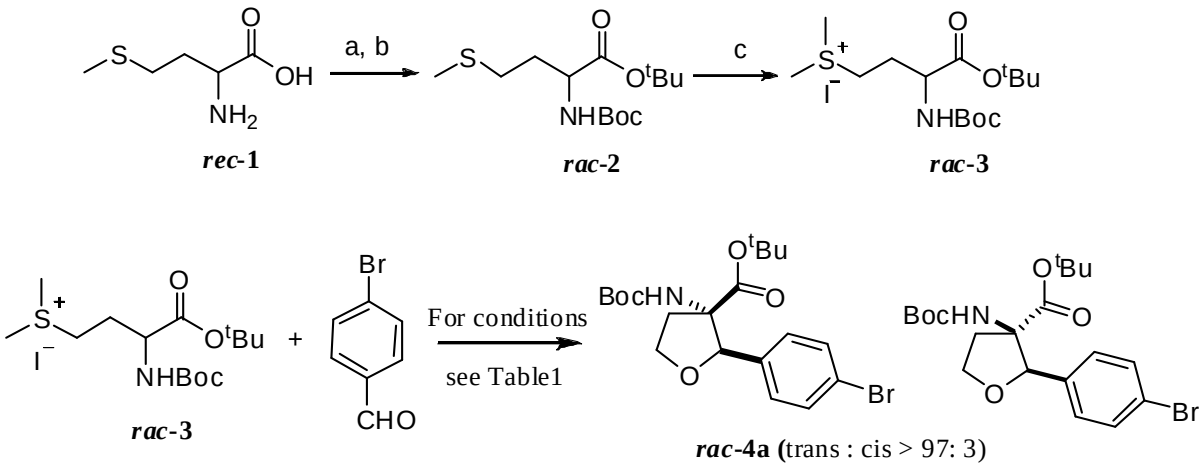
The conformation of a peptide is crucial for its biological activity.[1] Most small natural peptides are conformational flexible, show structural dependence on the environment and are therefore not suitable to study or control secondary peptide structures. One of the successful approaches to restrict peptide conformation is the introduction of side chain restricted amino acids.[2,3] Disubstitution by alkyl or aryl groups in the α position of an α amino acid leads to conformational constraint (Thorpe-Ingold effect) and a stereochemically stable quaternary carbon center.[4] Different methods to incorporate functionality in the α position of an amino acid or using α, β-unsaturated amino acids as precursors have been reported[5]. Toniolo[6] recently reviewed the effect of C^{α} tetrasubstitution on the structure of homo oligoamides mostly resulting in stable 3_{10} or α-helices.[7] In short peptides C^{α}-alkylated α-amino acids stabilize turn structures,[8] which in general have received particular attention, because they play an important role in globular proteins from both structural and functional points of view.[9]

A polypeptide chain cannot fold into a compact structure without turns, which usually occur on the solvent exposed surface of proteins and hence probably represent antigenic sites involved in molecular recognition.[10] Many naturally occurring oligopeptides have been proposed to adopt turns in their bioactive conformation.[11] Different types of bends are defined according to the number and spatial arrangement of the residues involved, and β-turns (β-bends reverse turn) are the most abundant and best characterized group of folded secondary structures.[12] Subclasses of β-turns are further distinguished on the basis of the backbone dihedral angles (φ, ψ) associated with central i+1 and i+2 positions. In the last years several artificial turn inducing structures were reported by Nowick,[13] Schmuck,[14] Frigel,[15] Kelly,[16] Gellman,[17] Balaram[18] and others. We report here the preparation and structural characterization of C^{α}-tetrasubstituted tetrahydrofuran amino acids (TAAs) from methionine, which induce two consecutive *β*-turns as part of a tripeptide of aliphatic alpha amino acids.

* The investigations described in this chapter have already published (Maity, P.; Zabel, M.; König, B. *J. Org. Chem.* **2007**, *72*, 8046-8053). All the X-ray crystallography was determined by Zabel, M.

2.2. Results and discussion

The key step of the TAA (Tetrahydrofuran Amino Acid) synthesis is the aldol-type reaction of a methionine derived sulfonium salt[19] with an aldehyde followed by a cyclization. Scheme 1 shows the preparation of the sulfonium salt ***rac*-3** starting from the racemic amino acid methionine (***rac*-1**). The methionine sulfonium iodide ***rac*-3** was treated with KOH. Acidic protons are found at the sulfonium moiety and at the α-carbon of the amino acids. Under the reaction conditions the α-proton of the amino acid is removed and its stereoinformation is lost. The ester enolate reacts with the carbonyl group of the aromatic aldehyde and the intermediate alkoxide substitutes intramolecularly dimethylsulfide giving tetrahydrofuran amino acids ***rac*-4** with high diastereoselectivity of the α- and β-stereocenters. A proposed mechanism of the reaction is outlined in Figure 1.



Scheme 1. Synthesis of the protected methionine sulfonium salt ***rac*-3** and its conversion to TAA ***rac*-4a**: a) $(Boc)_2O$, 1.25 (M) NaOH, 1,4-dioxan, 3.5h, rt, 90%; b) DCC, DMAP, ^{t}BuOH, DCM, 14h, rt, 82%; c) MeI, $(CH_3)_2CO$, 3d, rt in the dark, 78%.

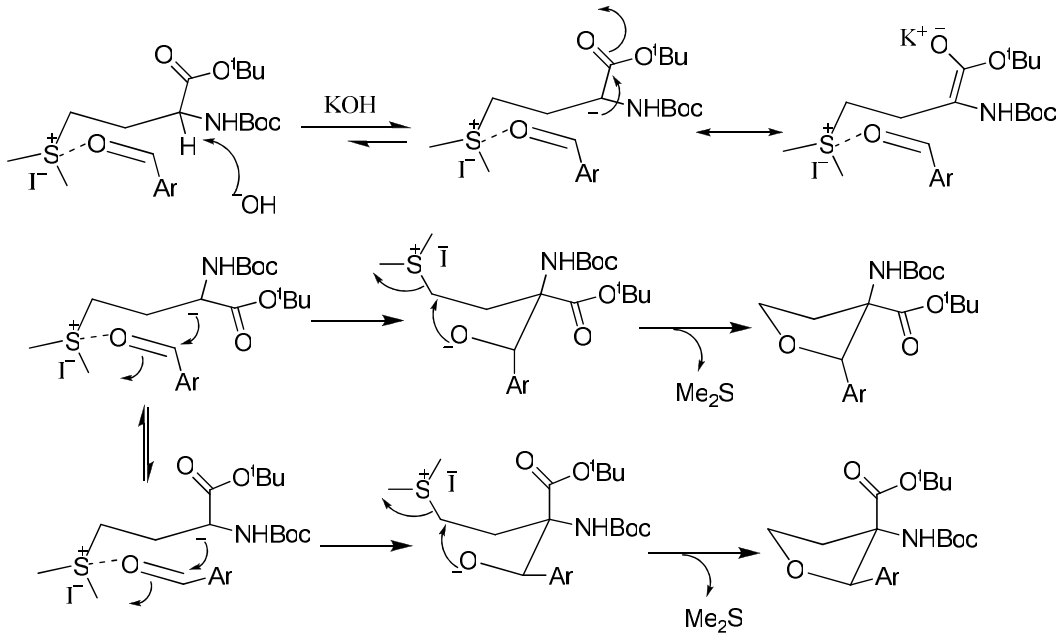


Figure 1 Proposed reaction mechanism of tetrahydrofuran C^{α} tetrasubstituted amino acid formation.

A series of optimizations revealed that aromatic aldehydes with an electron withdrawing substituent and a sterically demanding protecting group for the carboxyl function, such as ^{t}Bu, give the best reaction conversions and stereoselectivities. Decrease of the reaction temperature from room temperature to -5^{o}C increases product yields and selectivity. Several solvents and bases were tested. The reaction occurred smoothly in polar solvents. As KOH is not soluble in less polar solvents, such as dichloromethane and toluene, tetrabutlyammonium bromide was added as phase transfer catalyst. However, yields are moderate in these solvents. Among all solvents CH_3CN gave the best yield of the desired product in 2 to 3 h (Table 1). Additionally, the scope of the reaction and its dependence on steric and electronic properties of the aryl aldehyde was investigated (Table 2). Electronic effects on the reaction yield are small, while diastereoselectivity depends on the aldehyde. The relative stereochemistry of the major diastereoisomer was confirmed by X-ray diffraction analysis of compound ***rac*-4e** (Figure 2) and compound ***rac*-4n** (benzyl ester of ***rac*-4a**, see appendix for X-ray structure). With benzene, naphthalene and cinnamic aldehydes high selectivity (*trans/cis* ≥ 97/3) with moderate to good yields (45-78%; 50 – 95% according to aldehyde conversion) were obtained, whereas the diastereoselectivity was poor with furfural and *p*-cyanobenzaldehyde.

Table 1. Optimization of the reaction conditions converting compound ***rac*-3** to TAA ***rac*-4a**

Solvent	**Base**	**Reaction temp. [^{0}C]**	**Reaction time [h]**	**Yield [%]**	***Anti*/*Syn*[b] ratio**
[a]DCM	KOH KO^{t}Bu	20	5 4.5	40 47	97/3
^{t}BuOH	KOH	-5	3.5	40	97/3
DMF	KOH CsOH	-5	2 1.5	55 54	96/4
[a]Toluene	KOH KO^{t}Bu	20	4 3	52 60	96/4
CH_3CN	KOH KO^{t}Bu CsOH	-5	3 2 2	78 60 65	>97/3

[a] Tetrabutyl ammonium bromide (10 mol%) was added as phase transfer catalyst, [b] The *trans/cis* ratio was determined by HPLC.

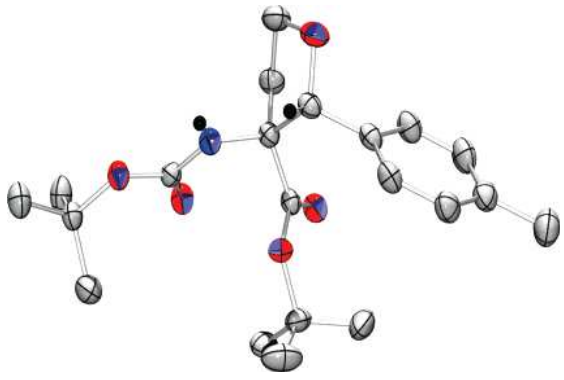
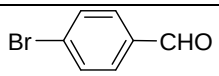
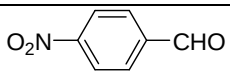
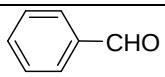
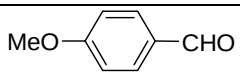
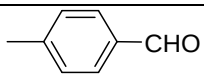
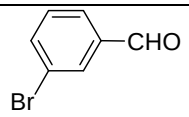
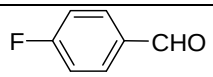
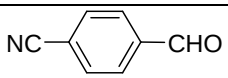
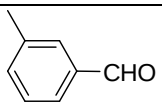
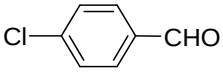
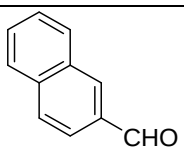
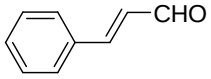
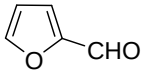


Figure 2. X-Ray diffraction analysis of the major diastereomere of compound ***rac*-4e** confirming the *trans*-configuration. For clarity only the amide hydrogen atoms are shown.

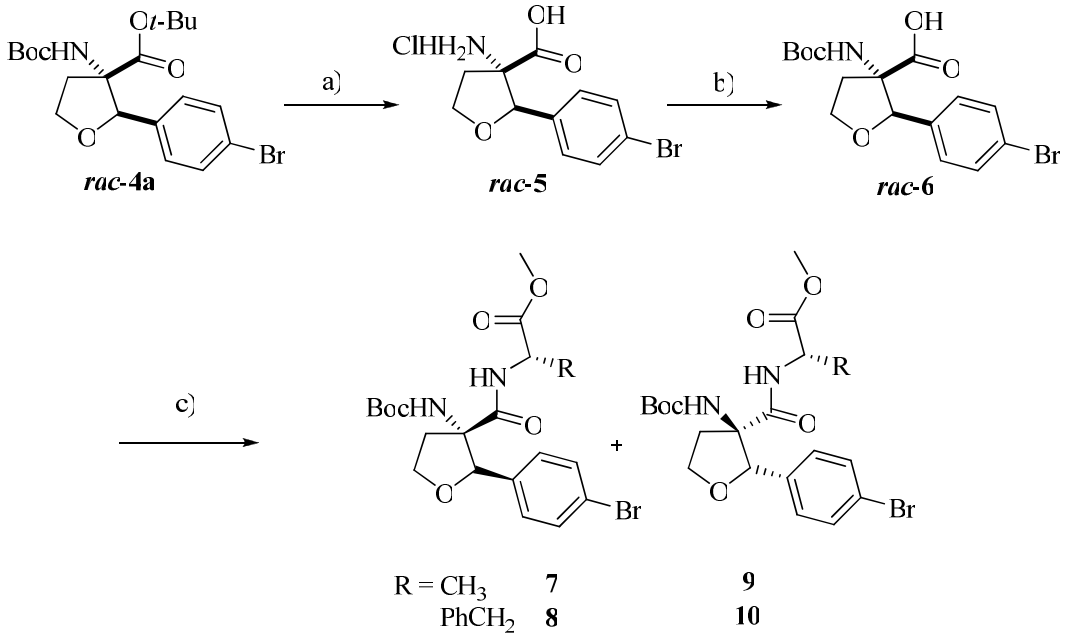
Table 2: Scope of the reaction of sulfonium salt ***rac*-3** with aromatic aldehydes

Entry	Base	Temp. (°C)	Time (h)	Product	Yield[a] (%)	*Trans/Cis* ratio
	KOH	-5 to rt	3	***rac*-4a**	78 [95]	97/3[b]
	KOH	-5	0.5	***rac*-4b**	35 [50]	96/4[b]
	KOH	-5 to rt	2	***rac*-4c**	70 [85]	97/3[b]
	KOH	-5	2	***rac*-4d**	50 [80]	96/4[b]
	KOH	-5 to rt	2	***rac*-4e**	55 [90]	96/4[b]
	KOH	-5	3	***rac*-4f**	47 [70]	20/1[c]
	KOH	-5 to rt	2	***rac*-4g**	63 [74]	20/1[c]
	CsOH	-5 to rt	2.5	***rac*-4h**	55 [87]	9/1[c]
	CsOH	-5	3	***rac*-4i**	55 [60]	20/1[c]
	CsOH	-5 to rt	2.5	***rac*-4j**	55 [70]	20/1[c]
	KOH	-5 to rt	3	***rac*-4k**	55 [67]	20/1[c]

	KOH	-5 to rt	2.5	***rac*-4l**	58 [80]	20/1[c]
	KO-^{t}Bu	-5	4	***rac*-4m**	56 [75]	3/1[d]

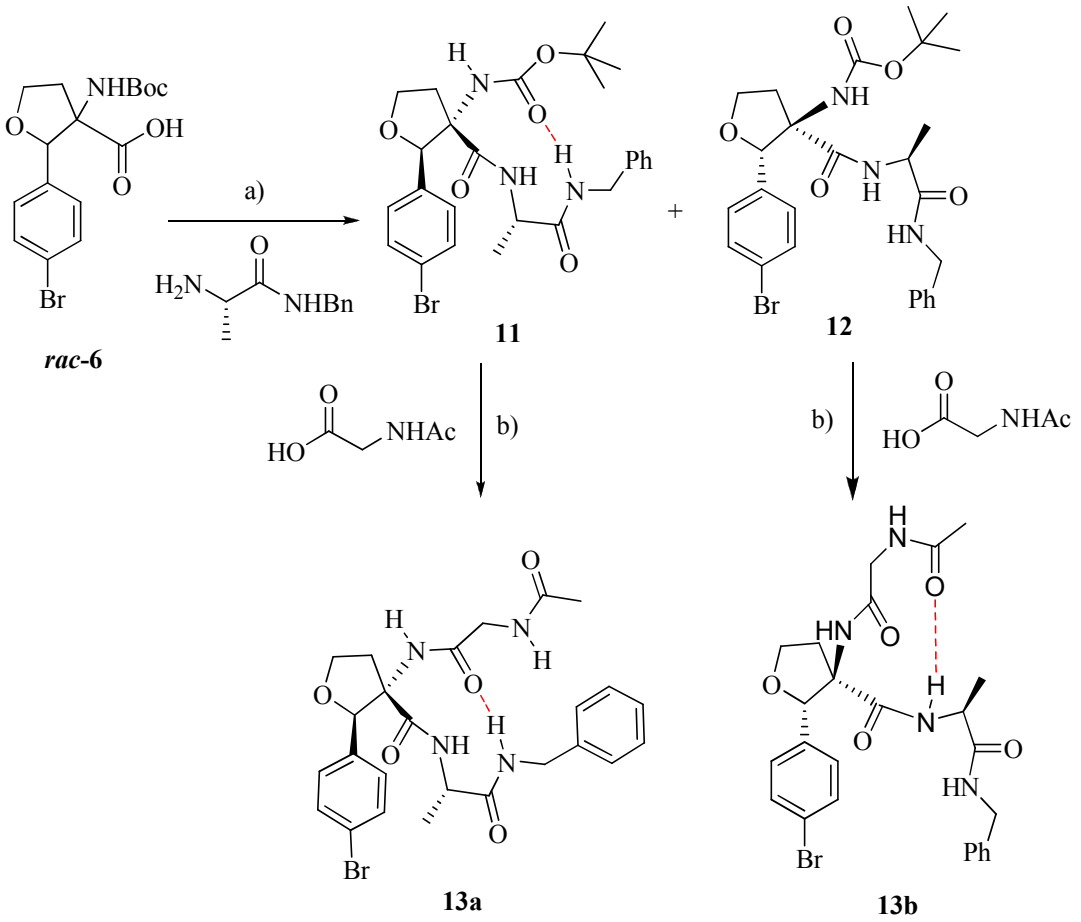
[a] The isolated yield was determined with respect to the aryl aldehyde used. The isolated yield with respect to the converted aryl aldehyde is given in brackets. [b] Selectivity was determined by HPLC on achiral column. [c] Selectivity was determined by column chromatographic separation. [d] Determined by NMR.

Compound ***rac*-4a** was converted into the carboxylic acid ***rac*-5** (Scheme 2) by treatment with 6M HCl in methanol affording the hydrochloride salt of the free amino acid quantitatively. N-Reprotection with Boc-anhydrid gave compound ***rac*-6**.[20] Using standard peptide coupling conditions, the racemic carboxylic acid ***rac*-6** was coupled with L-alanine methyl ester hydrochloride and L-phenylalanine methyl ester hydrochloride giving dipeptides **7-10** in moderate yields. The diastereomers were separated by column chromatography and X-ray diffraction structure were obtained for the *R,S,S*-isomer **7** and *S,R,S*-isomer **9**.



Scheme 2. Deprotection of TAA and coupling with chiral amino acids: a) 6M HCl, MeOH, reflux, 6h, quantitative; b) $(Boc)_2O$, 1.25 (M) NaOH, 4h, rt, 60%; c) DIPEA, EDC, HOBt, L-alanine methyl ester hydrochloride or L-phenylalanine methyl ester hydrochloride, DCM, 24h, rt, 60% and 55%, respectively.

TAAs were incorporated into a short peptide chain to demonstrate their ability to induce a turn structure (Scheme 3).[21] Compound ***rac*-6** was coupled with the benzyl amide of L-alanine and the diastereomers **11** and **12** were separated by column chromatography. The crystalline structure of dipeptide **11** confirmed the *R,S,S* configuration. The molecule adopts a *β*-turn type I conformation with terminal Boc-CO and benzylamide NH groups intramolecularly hydrogen bonded [N···O: 2.92 Å; N−H…O: 163º]. The torsion angles (φ, ψ) of the TAA *i+1* (-61.7, -25.2) and L-Ala *i+2* (-82.9, -2.0) residues correspond to a *β*-turn type I (Figure 3).[22] The X-ray diffraction analysis of the *S,R,S* diastereomer **12** (see appendix for X-ray structure) shows no intramolecular hydrogen bonds or turn structure formation.



Scheme 3 . Incorporation of TAA ***rac*-6** into a short peptide chain: a) Et_2O-HCl DIPEA, EDC, HOBt, DCM, 24h, rt, 50%; b) (i) Et_2O-HCl, (ii) DIPEA, EDC, HOBt, DMF, 3d, rt, 41%.

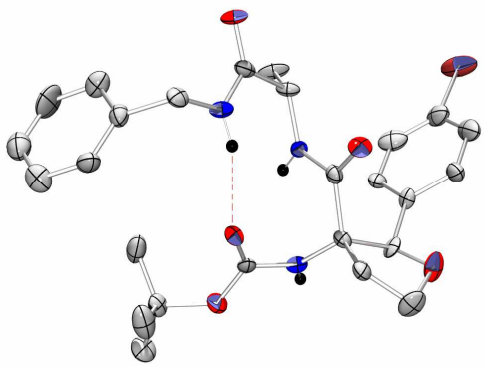


Figure 3. X-Ray diffraction structure of the compound **11** accommodating a β I turn in the crystal state. The intramolecular $i+3 \rightarrow i$ hydrogen bond is indicated by a dashed line. Only the amide hydrogen atoms are shown.

After Boc-deprotection isomer **11** was coupled with acetylated glycine yielding tripeptide **13a**. Instead of a simple elongated *β*-turn structure, a conformation consisting of two consecutive *β* turns type III, slightly deviating from an ideal 3_{10} helix structure, was observed in the solid state (Figure 4). The torsion angles (φ, ψ) for the left side turn Gly *i+1* (-62.4°, -21.0°), TAA *i+2* (-55.1°, -26.0°) and for the right side turn TAA *i+2* (-55.1°, -26.0°), L-Ala (-71.6°, -31.5°) resemble the typical values (-60º, -30º and -60º, -30º). The structure is stabilized by two intramolecular hydrogen bonds (N…O: 2.92 Å, N−H…O: 163º) and (N…O: 3.26 Å, N−H…O: 149º). A 2D ROESY spectrum (Figure 6) provides evidence for the existence of the proposed conformation in solution. Additional support comes from a variable-temperature NMR study in DMSO-*d*6: Temperature coefficients of the amide protons H_d (-0.58 ppb/K) and H_c (-3.17 ppb/K) possibly indicate strong intramolecular hydrogen bonds, and temperature coefficients of H_a and H_b are significantly higher (-5.35 ppb/K and -7.20 ppb/K, respectively; see Figure 5 for data). However, temperature coefficients are only assessed as an indication because a more detailed analysis is required to unambiguously correlate their values to hydrogen bonding as shown by Andersen et al.[23] Compound **12** was also coupled in same condition with acylated glycine to afford compound **13b**. The X-ray crystal structure shows an intramolecular H-bond with 10-member ring has formed to give β-turn type-II structure (see appendix for x-ray structure).

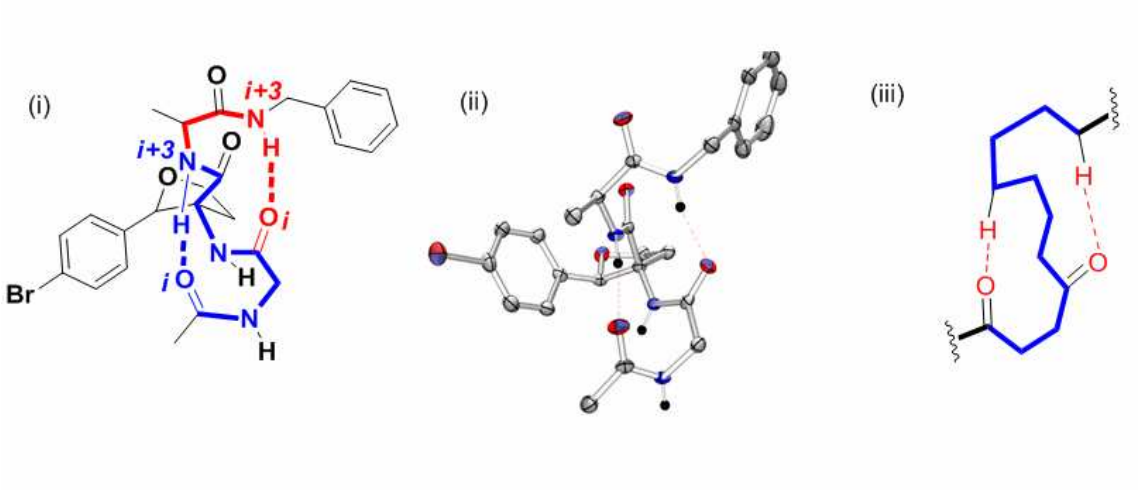
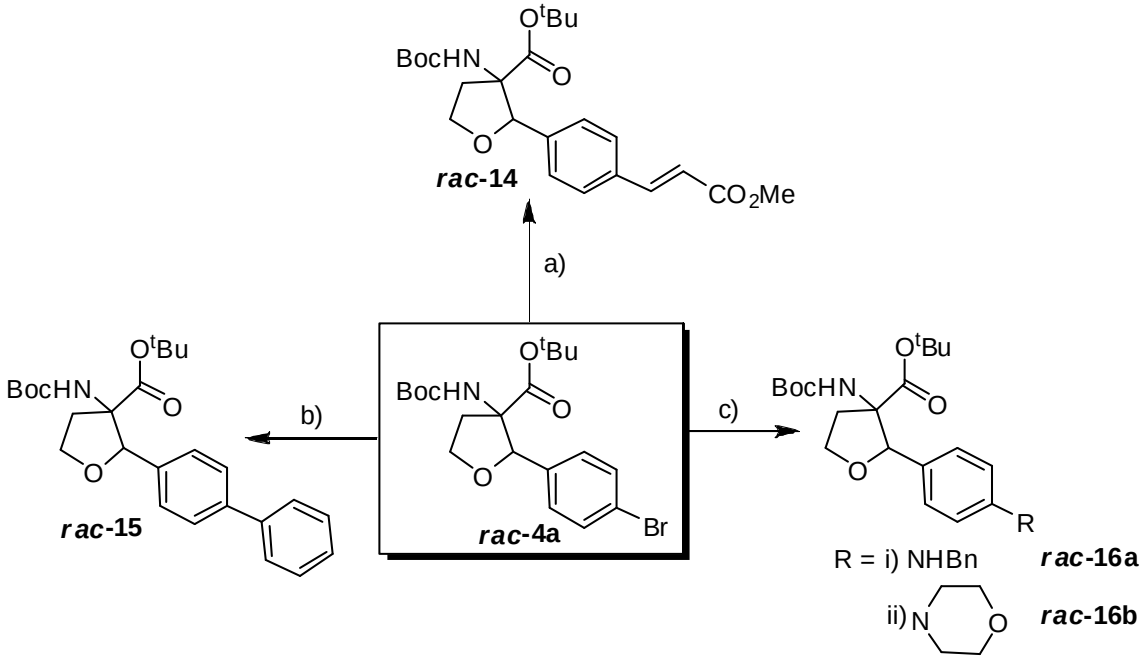


Figure 4. Structure (i) and X-ray diffraction analysis (ii) of compound **13a** exhibiting two consecutive β turns, each stabilized by an intramolecular *i+3→i* hydrogen bond (dashed lines). Only amide hydrogen atoms are shown. (iii) back bone structure of the tripeptide.

The bromine substituent in compound ***rac*-4a** allows a subsequent functionalization of the TAA, which may be of use for specific labelling or modification of properties of the turn motif. Conventional Suzuki,[24] Heck,[25] and Buchwald[26] coupling (Scheme 4) gave derivatives ***rac*-14** to ***rac*-16a,b**.



Scheme 4. Cross coupling reactions: a) Methylacrylate, Et_3N, $Pd(OAc)_2$, $P(o\text{-}tolyl)_3$, in DMF, 14h, 80°C, 71%; b) phenylboronic acid, Na_2CO_3, $Pd(OAc)_2$, TBAB, in water : DMF (1:1), 100°C, 71%; c) benzylamine or morpholine, K_3PO_4, 2-isobutyryl-cyclohexanone in DMF, 100°C, 75% or 35%.

2.3. Temperature dependence of NMR chemical shifts

Temperature dependence of chemical shifts was measured to identify possible strong intramolecular hydrogen bonds in solution. The ^{1}H-NMR spectra were recorded at various temperatures on a 600 MHz spectrometer. Table 3 shows the determined chemical shift values (ppm) for each NH group of the examined compounds in the range of 293-373 K.

Table 3. Determined ^{1}H resonance chemical shift in ppm for NH protons at various temperature in [d6]-DMSO

A) Compound **13a**

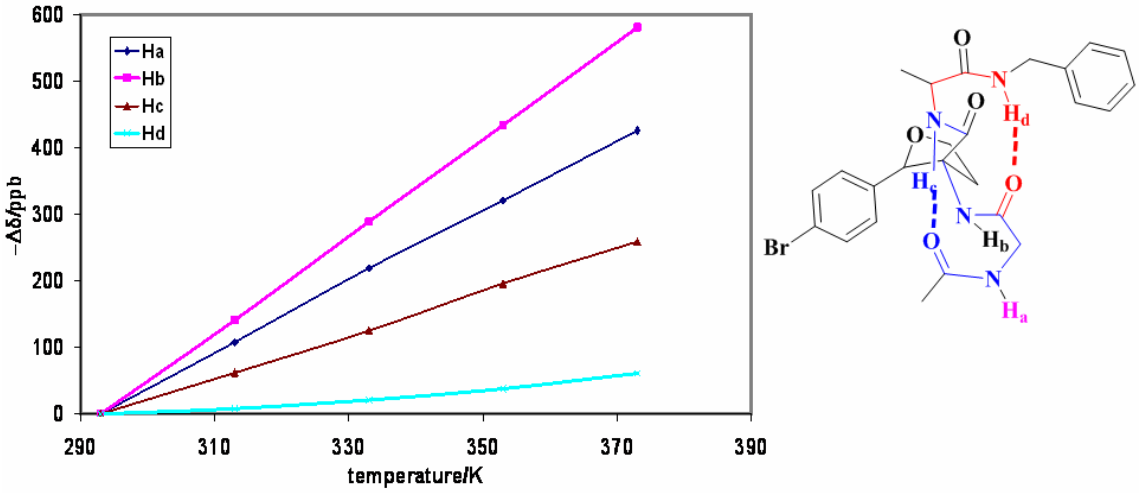
T[K]/ NH[ppm]	**NH_a**	**NH_b**	**NH_c**	**NH_d**
293K	8.245	9.027	7.356	7.558
313K	8.137	8.886	7.288	7.550
333K	8.026	8.738	7.225	7.537
353K	7.924	8.593	7.160	7.520
373K	7.819	8.446	7.097	7.497

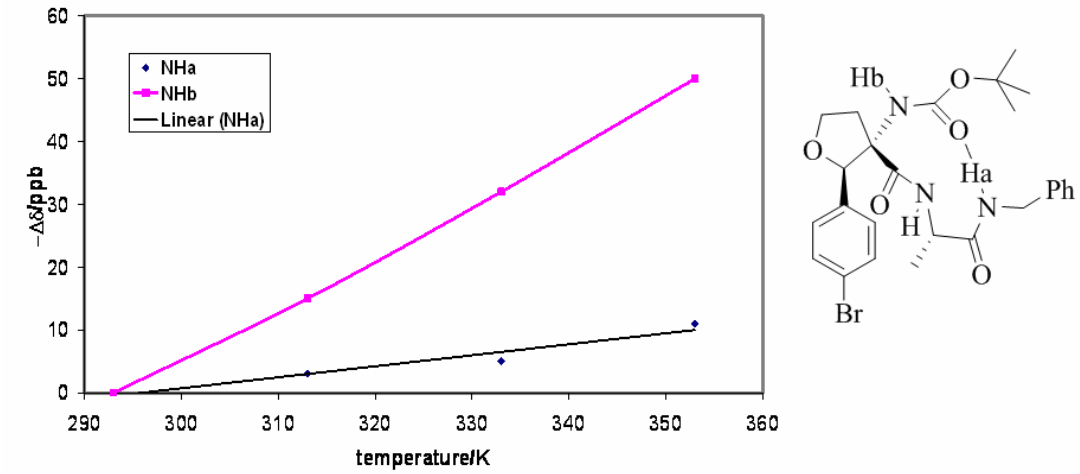
B) Compound **11**

T[K]/ NH[ppm]	**NH_a**	**NH_b**
293K	7.975	7.873
313K	7.972	7.858
333K	7.970	7.841
353K	7.964	7.823

The resonance values from Table 3 were used to calculate the temperature dependence of the chemical shift. The measured values were plotted and fitted to a linear correlation function. From the plotted graph we calculated the corresponding temperature coefficient in ppb/K. These values were used to estimate the possibility of hydrogen bonds, using the following boundaries: Hydrogen bonds very likely for values smaller than -2 ppb/K; intermediate range from -2 to -3 ppb/K and no hydrogen bonding for values larger than -4 ppb/K.

Figure 5. Temperature dependence of amide proton resonances in tripeptide **13a** and dipeptide **11**





2.4. ROESY experiments

1D-ROESY measurements in [d6]-DMSO was performed at 300K on a Bruker DRX-600 spectrometer with a working frequency of 600.13 MHz. The difference ROESY experiment with selective excitation using the modified DPFGSE pulse sequence (q3 Gaussian cascade Double Pulse Field Gradient Spin Echo) was used. For every irradiated proton a series of 5 experiments with different mixing times (from 10 ms to 1

s) and with a relaxation delay of 2 s were acquired. An exponential window function with 4 Hz line broadening was applied before the Fourier transformation (FT) and a baseline correction was conducted after the FT.

2D-ROESY experiments with a mixing time of 500 ms were performed for structural calculations. Signal overlap restricts the number of observable intrastrand contacts. At least four ROESY interactions were detected for NH (13) and two for NH (16), as illustrated in Figure 6.

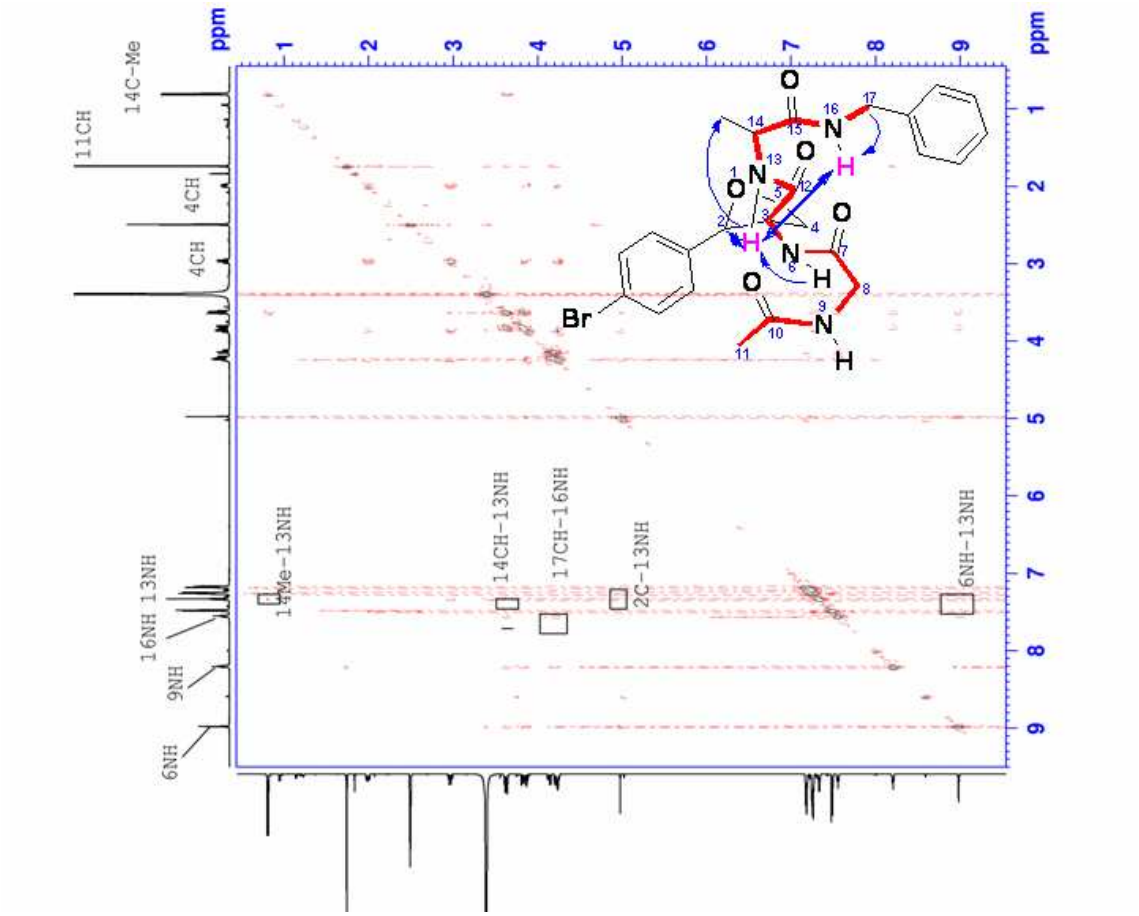
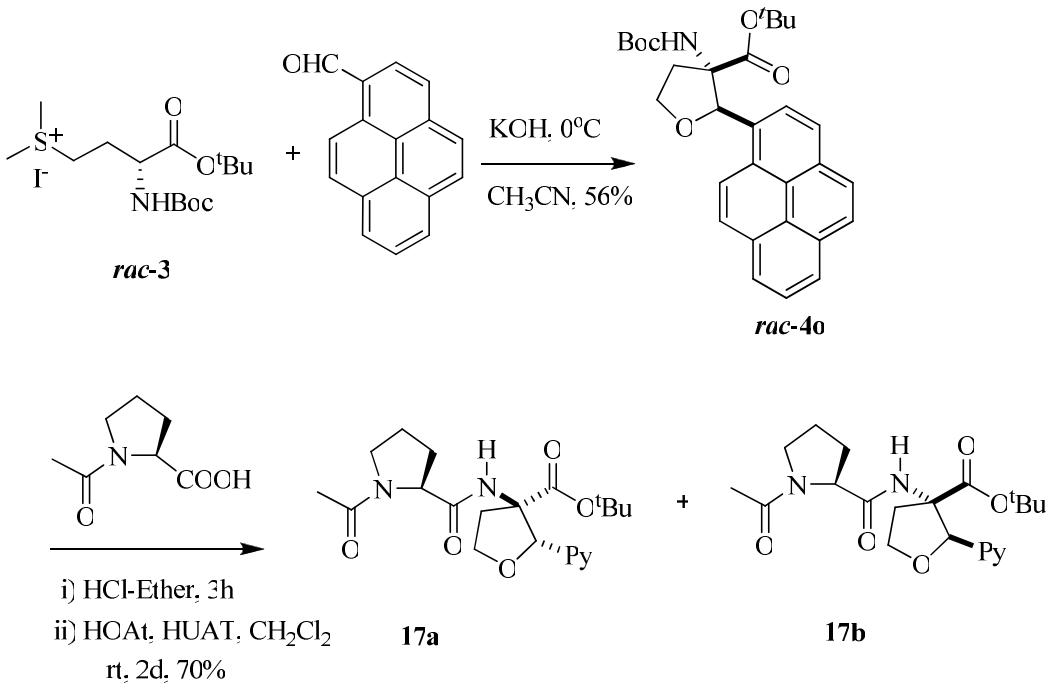


Figure 6. ROESY spectrum for compound **13a** and illustration of observed contacts in solution.

2.5. Fluorescent amino acid and it's incorporation into peptide chain†

Fluorescence spectroscopy has become one of the most useful tools in conformational studies of biopolymers[27] and for visualizing intracellular processes or molecular interactions.[28] Introduction of fluorescence moiety into the peptide chain can be achieved either by reaction with fluorescence prove with functional groups present in peptide chains (carboxylate, amino group, hydroxyl, sulphahydryl) or by direct use of an amino acid bearing fluorescent function at their side chain. Among the proteinogenic amino acids only two possess fluorescent properties (Trp, and Tyr), but sometimes native peptides do not contain these amino acids or their photophysical behavior in complex[29]. Incorporation of amino acid with photophysical behavior different from the native fluorescent amino acids into peptide chain seems to be beneficial. In this consequence *synthetic* fluorescent amino acids may exhibit significant advantages over the related *protein* (Trp, Tyr) residue in terms of potentially different and improved properties.[30] So we prepared the pyrene substituted tetrahydrofuran C^{α}-tetrasubstituted amino acid, and incorporated in short peptide chain which shows turn structure in solid sate. Toniolo et al. [31] took advantage of the fluorescence, the rigidity and the axial chirality of 2', 1' : 1, 2; 1", 2" : 3:4-dinaphthcyclo-hepta-1, 3-diene-6-amino-6-carboxylic acid (Bin)[32], a C^{α}-tetrasubstituted glycine derivative from 1, 1'-binapthyl, to carry out photophysical studies involving intramolecular energy transfer (fluorescence quenching) and intramolecular spin polarization (CIDEP) effects in conformationally constrained peptide based system. C^{α}-tetrasubstituted amino acids are effective for β-turn and helix inducer in peptides.[33] The compound ***rac*-3** and pyrene aldehyde were reacted in presence of KOH as a base in CH_3CN to give compound ***rac*-4o** diastereoselectily (trans/cis is 20:1) with moderate yield of 56% (Scheme 1). Then compound ***rac*-4o** was coupled with N-acetyl-$_L$-proline in presence of HOAt[34] and HUAT as coupling reagents in DCM. Column chromatography allowed the separation of the resulting diastereomeric dipeptides (**17a, 17b**), which were isolated in optically pure form (Scheme 4).

† Manuscript in preparation.



Scheme 5. Synthesis of fluorescent amino acid and it's incorporation in peptide chain.

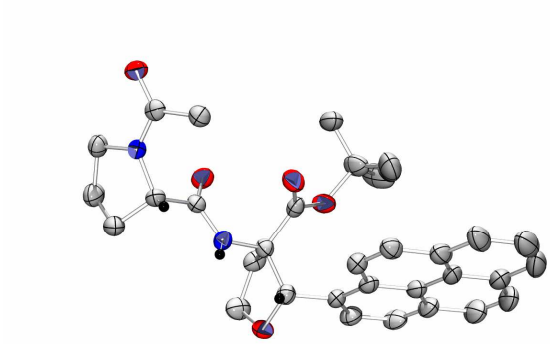


Figure 7. X-ray diffraction structure of compound **17a**

The absorption spectrum of compound **17b** in MeOH shows two peaks at 377 nm and 396 nm (Figure 8).

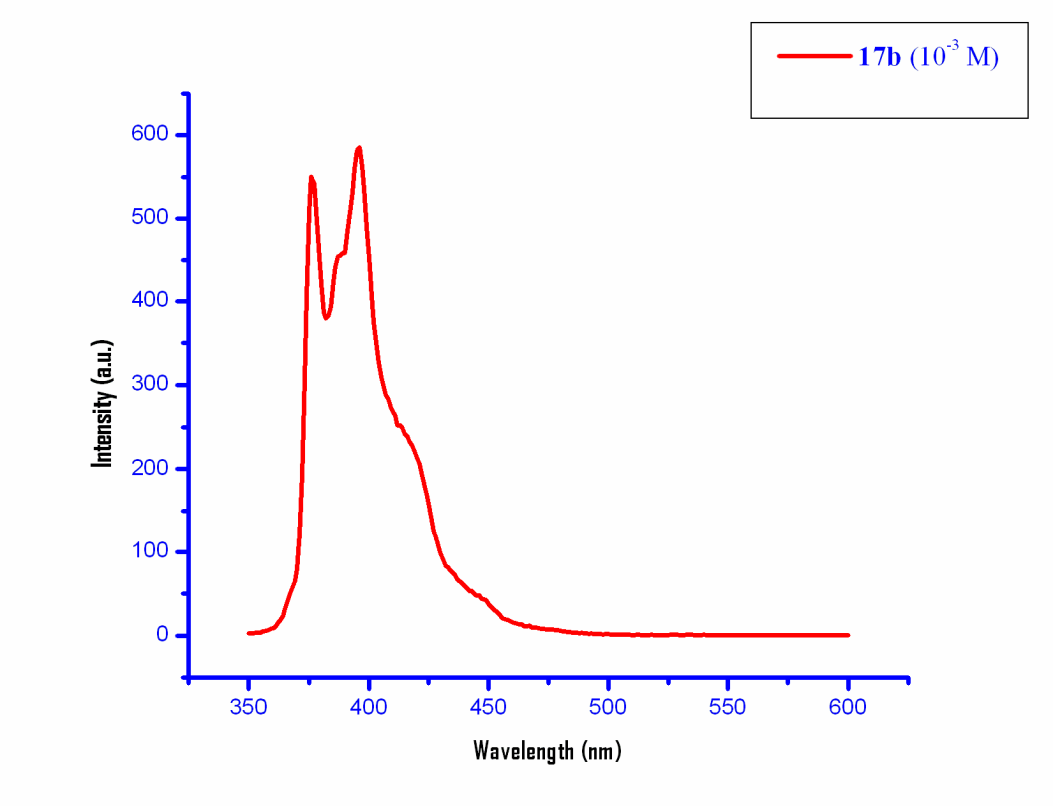


Figure 8. Absorption spectrum of compound **17b** in MeOH

2.6. Conclusion

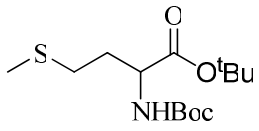
In summary, we have reported the racemic diastereoselective synthesis of C^{α} tetrasubstituted tetrahydrofuran amino acids (TAA) from readily available methionine. Dipeptides of TAA and chiral amino acids yield diastereomers, which are readily separated by column chromatography. Short peptide sequences containing the *R,S*-isomer of TAA show a stable turn structure in the crystal state and in solution. Two consecutive β-turn type III turns, resembling a distorted 3_{10} helix structure, are found for a tripeptide amide consisting of Gly-TAA-Ala. Good accessibility and variable modification by transition metal-catalyzed coupling reactions make TAAs a useful addition to the family of C^{α}-tetrasubstituted α-amino acids and artificial turn structures in peptide research.

2.7. Experimental Section:

General: Melting points were determined on a melting point apparatus and are uncorrected. Specific rotations were measured on a polarimeter using a 10 cm cell. NMR spectra were recorded in $CDCl_3$ at 300 MHz (^1H) or 75 MHz (^{13}C) unless stated otherwise. Structural assignments are based on DEPT and COSY experiments where applicable. The multiplicity of the carbon atoms is given as (+) = CH_3 or CH, (-) = CH_2 and (C_{quat}) for quaternary carbon atoms. Analytical TLC plates (silica gel 60 F_{254}) and silica gel 60 (70-230 or 230-400 mesh) for column chromatography (CC) were purchased from Merck. Visualization of spots by UV light and/or staining with phosphomolybdate or ninhydrin, both in ethanol. CH_3CN, CH_2Cl_2, and Et_2O were dried by standard procedures and stored over molecular sieves or Na. PE means petrol ether with a boiling range of 70-90 ^oC. All other solvents and chemicals were of reagent grade and used with out further purification.

***tert*-Butyl methionine** : Racemic methionine (10 g, 67 mmol), 1,4-dioxane (40 mL) and 1.25 M aqueous NaOH (53 mL) were stirred and cooled to 6°C. Then a solution of di-*tert*-butyl-dicarbonate (15.4 g, 70.4 mmol) in 1,4-dioxane (12 mL) was added over 15 min. The cooling bath was removed and the reaction stirred for 3.5 h. The dioxane was removed in *vacuo*, the remaining mixture was diluted with 1M aqueous $KHSO_4$ (68 mL) and extracted with EtOAc (1x40, 1x25 mL). The combined organic layers were washed with water (24 mL), brine (4 mL) and dried over $MgSO_4$.The solvent was removed to give pure *tert*-butyl methionine as colourless liquid (15 g, 90%).

***tert*-Butyl)-4-(2-(*tert*-butoxycarbonylamino methylthio)butanoate (*rac*-2a)**

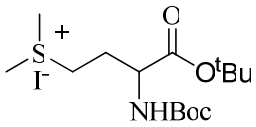


To a cooled (0°C) solution of *tert*-butyl methionine (2 g, 8 mmol), DMAP (0.08 g, 0.67 mmol) and *tert*-butanol (0.71 g, 9.6 mmol) in dry CH_2Cl_2 (20 mL) N,N´-dicyclohexylcarbodiimide (2.15 g, 10.4 mmol) was added with stirring and the reaction mixture was stirred at 0°C for 2 h. After stirring for 12h at room temperature, the

precipitated dicyclohexylurea was filtered off and washed with DCM (2x10 mL). The organic layer was washed with 1M HCl (2x5 mL), a saturated aqueous solution of $NaHCO_3$ (2x10mL) and water (2x5mL) and dried over $MgSO_4$. Then the solvent was evaporated in *vacuo*, and the crude product was purified by column chromatography (SiO_2, PE : diethyl ether 4:1) to give 2 g of compound **2** (82% yield). R_f = 0.20 (diethyl ether : PE = 1:4)

^{1}H NMR (300 MHz, $CDCl_3$) δ =1.45 (s, 18H), 1.99 (m, 1H, -C*H*H-), 2.11 (s, 3H), 2.15 (m, 1H, -CH*H*-), 2.58 (m, 2H), 4.45 (bs, 1H), 5.25 (bs, 1H). - ^{13}C NMR (75.5 MHz, $CDCl_3$), δ = 27.64 (+, 3C), 27.99 (+, 3C), 28.30 (-), 30.40 (-), 53.38 (+), 65.83 (+), 72.08 (C_{quat}), 77.28 (C_{quat}), 155.33 (C_{quat}), 171.36 (C_{quat}). MS [ESI H_2O/AcN]: m/z (%) = 305.5 [MH^+] (100).

(4-*tert*-Butoxy 3-(*tert*-butoxycarbonylamino)-4-oxobutyl)dimethylsulfonium iodide (*rac*-3a)



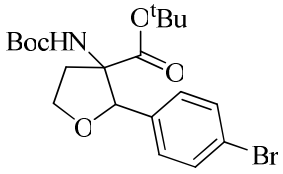
Compound **2** (10 g, 32.7 mmol), methyl iodide (46.86 g, 0.33 mol) and acetone (10 mL) were stirred at room temperature for 3 d in the dark. During this time a white precipitate was formed. After cooling in an ice bath for 4 h, the precipitate was filtered off and washed with chilled solvent (0°C temp. diethyl ether : acetone 9:1, 2x10 mL). This solid was dried in *vacuo* yielding compound **3** (11.4 g, 78%) in analytical pure form.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.45 (s, 9H), 1.47 (s, 9H), 2.29 (m, 1H,-C*H*H-), 2.32 (m, 1H, -CH*H*), 3.30 (d, 6H), 3.70 (m, 1H, -SC*H*H-), 3.75 (m, 1H, -SCH*H*-), 4.15 (bs, 1H), 5.70 (bs, 1H). - ^{13}C NMR (75.5MHz, $CDCl_3$) δ = 15.48 (+), 28.00 (+), 28.05 (+), 29.92 (-), 32.56 (-), 53.39 (+), 80.63 (C_{quat}), 82.12 (C_{quat}), 169.65 (C_{quat}), 171.00 (C_{quat}). MS [ESI, H_2O/AcN]: m/z (%) = 320.1 [M^+-I] (100).

Sulfonium salt cyclization, typical procedure: An oven or flame dried flask was cooled under a stream of nitrogen and charged with sulfonium iodide **3** (1 mmol) in acetonitrile (4 mL/mmol). The colourless solution was cooled to 0°C and powdered KOH or KO^{t}Bu or CsOH (1 mmol) was added and the reaction mixture was stirred for

15 min. Then the aryl aldehyde (0.9 mmol) was added and the mixture was stirred for another 2-4 h. After consumption of all of the starting material, the reaction mixture was quenched by adding water (3 mL/mmol). The reaction mixture was dilute with diethyl ether (4 mL/mmol) and transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with diethyl ether (2x5 mL/mmol). Then combined ether layers were washed with brine, dried over $MgSO_4$ and the solvent was removed in *vacuo*. The crude product was purified by flash column chromatography on silica gel using 10-15% diethyl ether / PE as the eluant.

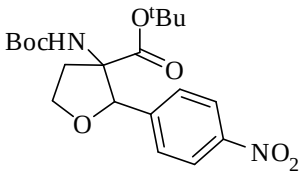
2-(4-Bromo-phenyl)-3-*tert*-butoxycarbonylamino-tetrahydro-furan-3-carboxylic acid tert butylester (*rac*-4a)



Yield = 60%, using KOtBu as a base**,** 82%, using KOH as a base and 65%, using CsOH as a base; *R*f = 0.23 (diethyl ether : PE = 1:4), m.p = 131-133°C.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.09 (s, 9H), 1.45 (s, 9H), 2.61-2.68 (m, 2H), 4.16-4.33(m, 2H), 5.00 (bs, 1H), 5.71 (bs, 1H), 7.20 (d, *J* = 8.23 Hz, 2H), 7.42 (d, J = 8.23 Hz, 2H). - ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 27.42 (+), 28.40 (+), 35.80 (-), 67.91 (-), 69.63 (+), 80.13 (C_{quat}), 82.62 (C_{quat}), 84.42 (C_{quat}), 121.75 (C_{quat}), 127.91 (+), 131.02 (+), 136.7 (C_{quat}), 154.3 (C_{quat}), 170.03 (C_{quat}), MS [ESI; CH_2Cl_2/MeOH+10mmol NH_4OAc] = 442.2, 444.2 [MH^+] (80), 459.3, 461.3 [$M\text{-}NH_4^+$] (75) .- IR (KBr): $\tilde{\nu}$ cm^{-1} = 3362, 2975, 2932, 2873, 2199, 1509, 1454, 1392. Anal. calcd. For $C_{20}H_{28}BrNO_5$ (442.34): C 54.30, H 6.38, N 3.17, found C 54.27, H 6.67, N 3.16.

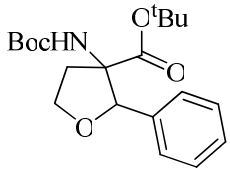
***tert*-Butly 3-(*tert*-butoxycarbonylamino)-2-(4-nitrophenyl)tetrahydrofuran-3-carboxylate (*rac*-4b)**



Yield = 35%, using KOH as base; R_f = 0.18 (diethyl ether : PE = 3:17), m.p.= 146-148°C.

^{1}H NMR (300MHz, $CDCl_3$) δ = 1.30 (s, 9H), 1.50 (s, 9H), 2.55 (m, 1H, -C*H*H-), 2.80 (m, 1H, -CH*H*-), 4.05 (m, 1H, -OC*H*H-), 4.25 (m, 1H, -OCH*H*-), 4.45 (bs, 1H), 5.25 (bs, 1H), 7.55 (d, *J* = 9.26 Hz, 2H), 8.23 (d, *J* = 9.26 Hz, 2H). - ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 27.92 (+), 28.12 (+), 35.80 (-), 67.04 (-), 68.09 (+), 82.65 (C_{quat}), 84.87 (C_{quat}), 123.44 (+), 128.08 (C_{quat}), 147.88 (+), 154.45 (C_{quat}), 170.47 (C_{quat}), 171.5 (C_{quat}). - MS [ESI; CH_2Cl_2/MeOH+10mmol/1 NH_4OAc] = 409.2 [MH^+] (100), 426.2 [M-NH_4^+] (55) - IR (KBr): $\tilde{\nu}$ cm^{-1} = 3375, 2981, 2934, 2877, 1730, 1603, 1504, 1452. Anal. calcd. For $C_{20}H_{28}N_2O_7$ (408.45): C 58.81, H 6.91, N 6.86, found C 58.45, H 7.07, N 6.85.

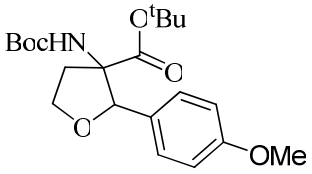
3-*tert*-Butoxycarbonylamino-2-phenyl-tetrahydro-furan-3-carboxylic acid tert butyl ester (*rac*-4c)



Yield = 70%, using KOH as a base; R_f = 0.21 (diethyl ether / PE = 3:17), m.p.= 61-63°C.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.09 (s, 9H), 1.45 (s, 9H), 2.50-2.80 (m, 2H), 4.23 (m, 1H, -OC*H*H-), 4.33 (m, 1H, -OCH*H*-), 5.02 (bs,1H), 5.60 (bs, 1H), 7.25-7.30(m, 5H). - ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 27.92 (+), 28.12 (+), 35.83 (-), 67.04 (-), 82.65 (C_{quat}), 84.87 (C_{quat}), 123.44 (+), 128.08 (C_{quat}), 133.53 (+), 137.52 (+), 150.61 (+), 154.54 (+), 155.36 (C_{quat}), 170.09 (C_{quat}). - MS [ESI; CH_2Cl_2/MeOH+10mmol/1 NH_4OAc] = 364.3 [MH^+] (100), 381 [M-NH_4^+] (50). - IR (KBr): $\tilde{\nu}$ cm^{-1} = 3358, 2978, 2932, 2872, 1720, 1494, 1454, 1365. Anal. calcd. For $C_{20}H_{29}NO_5$ (363.45): C 66.09, H 8.04, N 3.85, found C 65.89, H 8.32, N 3.32.

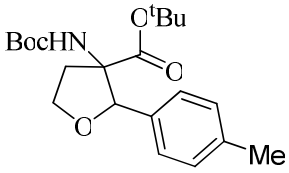
3-*tert*-Butoxycarbonylamino-2-(4-methoxy-phenyl)-tetrahydro-furan-3-carboxylic acid tert butyl ester (*rac*-4d)



Yield = 50%, using KOH as a base, 45%, using KO^{t}Bu as a base; R_f = 0.25 (diethyl ether / PE .= 1:4) m.p.= 97-99°C.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.13 (s, 9H), 1.49 (s, 9H), 2.52-2.65 (m, 1H, -C*H*H-), 2.68-2.82 (m, 1H, -CH*H*-), 3.78 (s, 3H), 4.11-4.23 (m, 1H, -OC*H*H-), 4.27-4.35 (m, 1H, -OCH*H*-), 4.93 (bs, 1H), 5.48 (bs, 1H), 6.80 (d, *J* = 7.96 Hz, 2H), 7.25 (d, *J* = 7.96 Hz, 2H). - ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 27.49 (+), 28.41 (+), 55.00, 67.74 (-), 69.14, 82.08 (C_{quat}), 113.00 (+), 127.57 (C_{quat}), 129.50 (+), 154.54 (C_{quat}), 159.46 (C_{quat}), 170.08 (C_{quat}). - MS [ESI; CH_2Cl_2/MeOH+10mmol/1 NH_4OAc]. 394.2 [MH^+] (60), 411.2 [M-NH_4^+] (20). - IR (KBr): $\tilde{\nu}$ cm^{-1} = 3359, 2975, 2931, 2881, 1707, 1613, 1583, 1510. Anal. calcd. For $C_{21}H_{31}NO_6$ (393.47): C 64.10, H 7.94, N 3.56, found C 64.33, H 7.64, N 3.37.

3-*tert*-Butoxycarbonylamino-2-(4-methyl-phenyl)-tetrahydro-furan-3-carboxylic acid tert butyl ester (*rac*-4e)

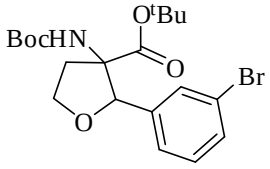


Yield = 55%, using KOH as a base; R_f = 0.22 (diethyl ether : PE = 3:17), m.p.= 135-138°C.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.09 (s, 9H), 1.47 (s, 9H), 2.30 (s, 3H), 2.65 (m,1H,-C*H*H-), 2.72 (m,1H,-CH*H*-), 4.11 (m, 1H, -OC*H*H-),4.32 (m, 1H, -OCH*H*) 5.02 (bs,1H,CH-), 5.65 (bs,1H), 6.92 (d, *J* = 7.95 Hz, 2H), 7.45 (m, J = 7.95 Hz, 2H). - ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 21.12 (+), 27.41 (+), 29.94 (+), 35.73 (-), 67.78 (-), 69.74 (+), 82.05 (C_{quat}), 82.07 (C_{quat}), 85.74 (C_{quat}), 126.21 (+), 128.61 (+), 134.38 (C_{quat}), 137.63 (C_{quat}), 154.57 (C_{quat}), 170.07 (C_{quat}). - MS [ESI; CH_2Cl_2/MeOH+10mmol/1

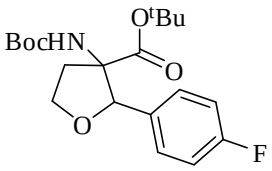
NH_4OAc] = 378.2 [MH^+] (100), 395.2 [M-NH_4^+] (20), IR (KBr): $\tilde{\nu}$ cm^{-1} = 3357, 2978, 2930, 2870, 2783, 2199, 1703, 1610, 1514, 1450. Anal. calcd. for $C_{21}H_{31}NO_5$ (377.47): C 66.82, H 8.28, N 3.71, found C 66.91, H 8.62, N 3.58.

***tert*-Butyl 2-(3-bromophenyl)-3-(*tert*-butoxycarbonylamino)tetrahydrofuran-3-carboxylate (*rac*-4f)**



Yield = 50%, using KOH as a base; R_f = 0.14 (diethyl ether: PE = 3:17).
^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.15 (s, 9H), 1.48 (s, 9H), 2.59-2.71 (m, 2H), 4.18-4.36 (m, 2H), 5.07 (bs, 1H), 5.65 (bs, 1H), 7.13-7.23 (m, 2H), 7.36-7.41 (m, 1H), 7.53-7.55 (m, 1H). - ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 27.43 (+), 28.41 (+), 35.76 (-), 67.97 (-), 69.59 (+), 80.14 (C_{quat}), 82.70 (C_{quat}), 84.02 (C_{quat}), 122.27 (+), 124.67 (+), 129.35 (C_{quat}), 129.54 (+), 130.88 (C_{quat}), 140.05 (+), 154.34 (C_{quat}), 170.03(C_{quat}). - MS[ESI; CH_2Cl_2/MeOH+10 mmol/1 NH_4OAc]. 442.2 [MH^+] (30), 459.0. [MNH_4^+] (30), 403.0 [M-NH_4^+-C_4H_8] (100) - IR (KBr): $\tilde{\nu}$ cm^{-1} = 3361, 3070. 2978, 2621, 2534, 2199, 1698, 1570, 1479, 1393.

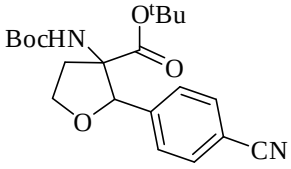
***tert*-Butyl 3-(*tert*-butoxycarbonylamino)-2-(4-fluro-phenyl)tetrahydrofuran-3-carboxylate (*rac*-4g)**



Yield = 63%, using KOH as a base. R_f = 0.12 (diethyl ether : PE= 1: 4), m.p = 89-92°C.
^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.09 (s, 9H), 1.49 (s, 9H), 2.67-2.78 (m, 2H), 4.16-4.33(m, 2H), 5.00 (bs, 1H), 5.71 (bs, 1H), 7.00 (m, 2H), 7.42 (m, 2H). - ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 27.44(+), 28.40 (+), 35.80 (-), 67.91 (-), 69.63 (+), 80.13 (C_{quat}), 82.62 (C_{quat}), 84.42 (C_{quat}), 114.99 (+), 127.98 (+), 131.01 (C_{quat}), 154.38(C_{quat}), 160 (C_{quat}), 170.03 (C_{quat}). - MS [ESI; CH_2Cl_2/MeOH+10mmol NH_4OAc]. =.382.1[MH^+]

(40); 343.1[MNH_4^+-C_4H_8], (100); 326.1[MH^+-C_4H_8],(60). - IR (KBr): $\tilde{\nu}$ cm^{-1} = 3377, 2980, 2863, 2199, 1710, 1606, 1495, 1447.

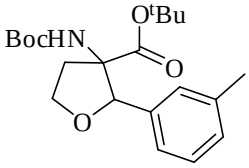
tert-Butyl 3-(_tert_-butoxycarbonylamino)-2-(4-cyano-phenyl)tetrahydrofuran-3-carboxylate (_rac_-4h)



Syn/anti = 9:1. Yield = 55%, using KOH as a base; R_f = 0.14 (diethyl ether : PE. = 3:17), m.p.= 128-130°C.

Resonance signals of the *anti* isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.06 (s, 9H), 1.46 (s, 9H), 2.71-2.49 (m, 2H), 4.31-4.20 (m, 2H), 5.02 (bs, 1H), 5.65 (bs, 1H), 7.45 (d, *J* = 8.78 Hz, 2H), 7.58 (d, *J* = 8.78 Hz, 2H). Resonance signals of the *syn* isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.28 (s, 9H), 1.47 (s, 9H), 2.56 (m, 1H, -C*H*H-), 2.77 (m, 1H, -CH*H*-), 4.03 (m, 1H,-OC*H*H-), 4.23 (m, 1H, -OCH*H*-), 4.38 (bs, 1H), 5.15 (bs, 1H), 7.45 (d, *J* = 8.78 Hz, 2H), 7.64 (d, *J* = 8.78 Hz, 2H).- ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 27.40 (+), 28.40 (+), 36.08 (-), 68.07 (-), 69.51, 80.31 (C_{quat}), 82.95 (C_{quat}), 83.52 (+), 111.47 (C_{quat}), 118.78 (C_{quat}), 126.13 (+), 131.71(+), 143.47 (C_{quat}), 154.20 (C_{quat}), 170.00 (C_{quat}). - MS [ESI; CH_2Cl_2/MeOH+10mmol/1 NH_4OAc] = 389.3 [MH^+] (30), 406.3 [M-NH_4^+] (45), 350.3 [M-NH_4^+-C_4H_8] (56). - IR (KBr): $\tilde{\nu}$ cm^{-1} = 3357, 2982, 2910, 2877, 1698, 1613, 1524, 1425. Anal. calcd. For $C_{21}H_{28}N_2O_5$ (388.14): .C 64.93, H 7.27, N 7.21, found C 64.87, H 7.54, N 7.07.

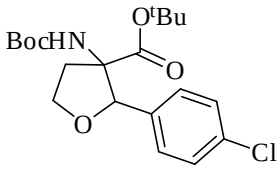
tert-Butyl 3-(_tert_-butoxyxycarbonylamino)-2-_m_-tolyltetrahydro-furan-3-carboxylate (_rac_-4i)



Yield = 55%, using KOH as a base; R_f = 0.14 (diethyl ether : PE = 3:17).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.00 (s, 9H), 1.40 (s, 9H), 2.22 (s, 3H), 2.64-2.78 (m, 1H, -C*H*H-), 2.72 (m, 1H, -CH*H*-), 4.13 (m, 1H, -OC*H*H-),4.24 (m, 1H, -OCH*H*) 4.89 (bs, 1H, CH-), 5.60 (bs, 1H, NH-), 6.90-7,14 (m, 5H). - ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 21.12 (+), 27.41 (+), 29.94 (+), 35.73 (-), 67.78 (-), 69.74 (+), 82.05 (C_{quat}), 82.07 (C_{quat}), 85.74 (C_{quat}), 126.21 (+), 128.61 (+), 134.38 (C_{quat}), 137.63 (C_{quat}), 154.57 (C_{quat}), 170.07 (C_{quat}). - MS [ESI; CH_2Cl_2/MeOH+10mmol/1 NH_4OAc]. 378.2 [MH^+] (100), 395.2 [M-NH_4^+] (20) - IR (KBr): $\tilde{\nu}$ cm^{-1} = 3357, 2978, 2930, 2870, 2783, 2199, 1703, 1610, 1514, 1450.

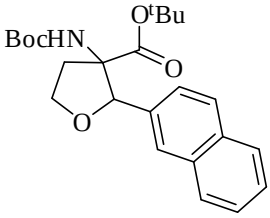
tert-Butyl 3-(_tert_-butoxycarbonylamino)-2-(4-chloro-phenyl)tetrahydrofuran-3-carboxylate (_rac_-4j)



Yield = 55%, using KOH as a base; R_f = 0.13 (diethyl ether : PE= 3:17) m.p = 107-110°C.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.12 (s, 9H), 1.47 (s, 9H), 2.60-2.65 (m, 2H), 4.15-4.38 (m, 2H), 5.00 (bs, 1H), 5.60 (bs, 1H), 7.27 (m, 4H). - ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 27.41 (+), 29.94 (+), 35.62 (-), 67.90 (-), 69.63 (C_{quat}), 82.52 (C_{quat}), 127.58 (+), 128.08 (+), 133.65 (C_{quat}), 137.63 (C_{quat}), 154.57 (C_{quat}), 170.07 (C_{quat}). - MS [ESI; CH_2Cl_2/MeOH + 10mmol/1 NH_4OAc] = 378.2 [MH^+] (100), 395.2 [M-NH_4^+] (20) - IR (KBr): $\tilde{\nu}$ cm^{-1} = 3375 , 2981, 2934, 2877, 1730, 1603, 1504, 1452. Anal. calcd. For $C_{20}H_{28}ClNO_5$ (397): C 60.37, H 7.09, N 3.51, found C 60.45, H 7.07, N 3.53.

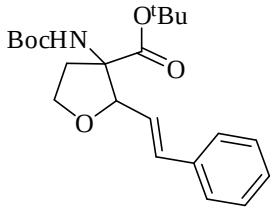
tert-Butyl 3-(_tert_-butoxycarbonylamino)-2-(naphthalene-2-ly)tetrahydrofuran-3-carboxylate (_rac_-4k)



Yield = 55%, using KOH as a base; R_f = 0.22 (diethyl ether : PE = 1:4), m.p = 140-143°C.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.00 (s, 9H), 1.45 (s, 9H), 2.50-2.80 (m, 2H), 4.23 (m, 1H, -OC*H*H-), 4.33 (m, 1H, -OCH*H*-), 5.02 (bs, 1H), 5.60 (bs, 1H), 7.45 (m, 3H), 7.80(m, 4H). - ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 27.92 (+), 28.12 (+), 35.83 (-), 67.04 (-), 82.65 (C_{quat}), 84.87 (C_{quat}), 123.44 (+), 128.08 (C_{quat}), 133.53 (+), 137.52 (+), 150.61 (+), 154.54 (+), 155.36 (C_{quat}), 170.09 (C_{quat}) - IR (KBr): $\tilde{\nu}$ cm^{-1} = 3360 , 2978, 2931, 2878, 2199, 1703, 1504, 1454. - HRMS cald. for $C_{24}H_{31}NO_5$ (413.2206) found 413.2205 ± .2. Anal. calcd. For $C_{24}H_{31}NO_5$ (413): C 69.71, H 7.56, N 3.39, found C 69.51, H 7.74, N 3.30.

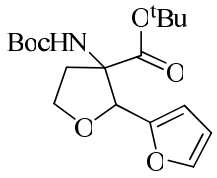
***(E)*-*tert*-Butyl 3-(*tert*-butoxycarbonylamino)-2-styryltetrahydrofuran-3-carboxylate (*rac*-4l)**



Yield = 53%, using KOH as a base; R_f = 0.14 (diethyl ether : PE = 3:17), m.p = 134-136°C.

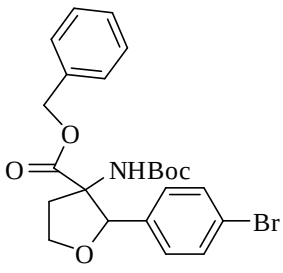
^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.39 (s, 9H), 1.46 (s, 9H), 2.46 (m, 1H, -CH*H*-), 2.73-2.82 (m, 1H, -C*H*H-), 4.07 (m, 1H, -OCH*H*-), 4.21 (m, 1H, -OC*H*H-), 4.44 (d, *J* = 6.31 Hz, 1H), 5.30 (bs, 1H), 6.02-6.12 (dd, *J* = 15.92 Hz, 7.14 Hz, 1H), 6.60-6.65 (d, *J* = 15.92 Hz, 1H), 7.22-7.35 (m, 5H). - ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 27.93 (+), 28.35 (+), 35.17 (-), 67.61 (-), 69.5 (C_{quat}), 80.02 (C_{quat}), 82.17 (C_{quat}), 85.50 (+), 124.27 (+), 126.66 (+), 128.00 (+), 133.36 (+), 136.13 (+), 154.78 (C_{quat}), 169.92 (C_{quat}). - MS [ESI; CH_2Cl_2/MeOH+10mmol/1 NH_4OAc]. = 390.2 [MH^+] (100), 278 [M-2xC_4H_8] (35), 407.2 [M-NH_4^+] (15) - IR (KBr): $\tilde{\nu}$ cm^{-1} = 3375, 2981, 2934, 2877, 1730, 1603, 1504, 1452. Anal. calcd. For $C_{22}H_{31}NO_5$ (389.49): C 67.84, H 8.02, N 3.60, found C 67.73, H 8.21, N 3.55.

***tert*-Butyl 3-(*tert*-butoxycabonylamino)octahydro-2, 2'-bifuran-3-carboxylate (*rac*-4m)**



trans/cis. = 3:1. Yield = 56%, using KO^{t}Bu as a base; R_f= 0.26 (diethyl ether : PE = 1:4), m.p.= 77-80°C. Resonance signals of *trans* isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.29 (s, 9H), 1.45 (s, 9H), 2.50 (m, 1H, -C*H*H), 2.87-2.99 (m, 1H, -CH*H*-), 4.13 (m, 1H, -OCH*H*-), 4.30 (m, 1H, -OC*H*H-), 4.89 (bs, 1H), 5.35 (bs, 1H), 6.32 (m, 2H), 7.36 (m, 1H). - ^{1}H NMR (300 MHz, C_6D_6) δ = 1.25 (s, 9H), 1.43 (s, 9H), 2.39-2.52 (m, 1H, -C*H*H), 2.96-3.08 (m, 1H, -CH*H*-), 3.81-3.91 (m, 1H, -OCH*H*-), 4.09-4.17 (m, 1H, -OC*H*H-), 4.76 (bs, 1H), 5.34 (bs, 1H), 5.94-5.98 (m, 1H), 6.23-6.26 (m, 1H), 6.92-6.95 (m, 1H). - Resonance signals of the *cis* isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.39 (s, 9H), 1.49 (s, 9H), 2.56 (m, 1H, -C*H*H), 2.78-2.85 (m,1H,-CH*H*-), 4.13 (m, 1H, -OCH*H*-), 4.30 (m, 1H, -OC*H*H-), 4.87 (bs, 1H), 5.30 (bs, 1H), 5.97 (m, 2H), 6,98 (m, 1H) - ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 27.58 (+), 28.33 (+), 35.17 (-), 68.12 (-), 69.05 (C_{quat}), 80.15 (C_{quat}), 81.05 (+), 81.93 (C_{quat}), 108.19 (+), 110.32 (+), 142.38 (+), 150.63 (C_{quat}), 154.93 (C_{quat}), 169.19 (C_{quat}). - MS[ESI;CH_2Cl_2/MeOH+10mmol/1 NH_4OAc] = 354.1 [MH^+] (100), 371.2 [M-NH_4^+] (30). - IR (KBr): $\tilde{\nu}$ cm^{-1} = 3357, 3119, 2978, 2933, 2868, 2199, 1737, 1703, 1514, 1448. Anal. calcd. For $C_{18}H_{27}NO_6$ (353.42): C 61.17, H 7.70, N 3.96, found C 60.94, H 7.69, N 3.90.

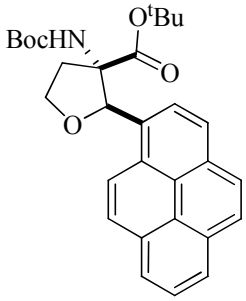
Benzyl 2-(4-bromophenyl)-3-(*tert*-butoxycarbonylamino)tetrahydrofuran-3-carboxylate (*rac*-4n)



Yield = 20%, using KOH as a base; 25%, using CsOH as a base; R_f = 0.14 (diethyl ether : PE = 3 : 17), m.p. = 137-138°C.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.43 (s, 9H), 2.62 (m, 1H, -CH*H*-), 2.82 (m, 1H, -C*H*H-), 4.20 (m, 1H, -OCH*H*-), 4.37(m, 1H, -OC*H*H-), 4.72 (s, 2H), 4.96 (bs, 1H), 5.54 (bs, 1H,), 7.13 (m, 4H), 7.33 (m, 5H). - ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 28.32 (+), 35.20 (-), 67.58(-), 67.97 (-), 70.04 (+), 80.50 (C_{quat}), 85.17 (Cquat), 122.29 (C_{quat}), 127.69 (+), 128.46 (+), 128.50 (+), 128.54 (+), 131.23 (+), 134.72 (C_{quat}), 135.99 (C_{quat}), 154.51 (C_{quat}), 170.79 (C_{quat}). - MS [ESI;CH_2Cl_2/MeOH+10mmol NH_4OAc].=.476.1, 478.1 [MH^+] (50), 493.2, 495.2 ($M+NH_4^+$) - IR (KBr): $\tilde{\nu}$ cm^{-1} = 3348, 3303, 3061, 3029, 2978, 2941, 2887, 2867, 2800, 2199, 1668, 1591, 1517, 1452. Anal. calcd. For $C_{23}H_{26}BrNO_5$ (476.19): C 57.99, H 5.50, N 2.94, found C 57.95, H 5.72, N 2.93.

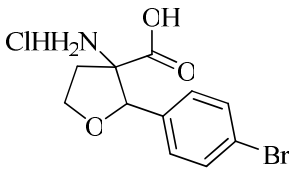
tert-Butyl-3-(_tert_-butoxycarbonylamino)-2-(pyrene-1-yl)tetrahydrofuran-3-carboxylate (_rac_-4o)



Yield = 65%, using KOH as base; R_f = 0.18 (diethyl ether: PE = 3:17), m.p.= 159-161°C.

^{1}H NMR (300MHz, $CDCl_3$) δ = 0.80 (s, 9H), 1.58 (s, 9H), 2.80-2.99 (m, 2H), 4.39-4.59(m, 2H), 5.72 (bs, 1H), 6.23 (bs, 1H), 7.97-8.31 (m, 9H). - ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 27.92 (+), 28.12 (+), 35.80 (-), 67.04 (-), 68.09 (+), 82.65 (C_{quat}), 84.87 (C_{quat}), 123.44 (+), 128.08 (C_{quat}), 147.88 (+), 154.45 (C_{quat}), 170.47 (C_{quat}), 171.5 (C_{quat}). - MS [ESI; CH_2Cl_2/MeOH+10mmol/1 NH_4OAc] = 488.3 [MH^+] (90), 505 [M-NH_4^+] (100), 992.7 [2M-NH_4^+] (100), - IR (KBr): $\tilde{\nu}$ cm^{-1} = 3359, 2974, 2830, 2867, 1750, 1703, 1506, 1454. Anal. calcd. For $C_{30}H_{33}NO_5$ (487.36): C 73.90, H 6.82, N 2.87, found C 73.80, H 7.17, N 2.58.

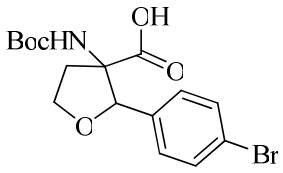
3-Amino-2-(4-bromo-phenyl)-tetrahydro-furan-3-carboxylic acid hydrochloride (*rac*-5)



To a solution of compound ***rac*-4a** (2 g, 4.5 mmol), in 20 mL of methanol 10 mL of 6 (M) HCl was added. The reaction mixture was heated to reflux temperature for 6 h, then cooled to room temperature and stirred for another 2 h. The reaction mixture was concentrated by removal of methanol; remaining parts of the reaction mixture were lyophilized yielding quantitatively a white solid of the corresponding hydrochloride salt (1.4 g). The compound was used in the next step without further purification.

^{1}H NMR (300 MHz, MeOD) δ = 2.32 (m, 1H, -CH*H*-), 2.92 (m, 1H, -C*H*H-), 4.17 (m, 1H, -OCH*H*-), 4.56(m, 1H, -OC*H*H-), 5.00 (bs, 1H), 7.34 (d, *J* = 8.23 Hz, 2H), 7.53 (d, *J* = 8.23 Hz, 2H). - ^{13}C NMR (75.5 MHz, MeOD) δ = 36.23 (-), 68.59 (-), 69.91 (+), 87.77 (C_{quat}), 123.89 (+), 129.76 (C_{quat}), 132.45 (C_{quat}), 136.24 (+), 170.39 (+). - MS [ESI;CH_2Cl_2/MeOH+10mmol NH_4OAc].=.286.1, 288.1 [MH^+-Cl] (30), 303.2, 305.2 [$M+NH_4^+$] (100).

2-(4-Bromo-phenyl)-3-*tert*-butoxycarbonylamino-tetrahydro-furan-3-carboxylic acid (*rac*-6)



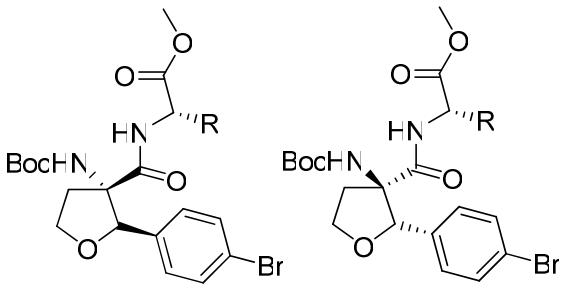
Procedure A (Starting from Compound ***rac*-5)** : Compound ***rac*-5** (1 g, 3.13 mmol), 1,4-dioxan (5 mL) and 1.25 M aqueous NaOH (7 mL) were stirred and cooled to 6°C for 10 min. Then a solution of di-*tert*-butyl-dicarbonate (0.75 g, 3.45 mmol) in 1,4-dioxan (2 mL) was added over 5 min. The cooling bath was removed and the reaction stirred for 3.5 h. The dioxane was removed in *vacuo*, the residue diluted with 1M aqueous $KHSO_4$ (2 mL) and extracted with EtOAc (1x4, 1x3mL). The combined organic layers were

washed with water (2 mL), brine (2 mL) and dried over $MgSO_4$. The solvent was removed to give pure ***rac*-6** as a white solid (0.72 g, 60%).

Procedure B (Starting from compound ***rac*-4n**): Compound ***rac*-4n** (500 mg, 1.05 mmol) was dissolved in ethanol (5 mL), then 150 mg of KOH was added to the solution and the mixture was refluxed for 24 h. The reaction mixture was cooled and ethanol was evaporated. The obtained yellow solid was dissolved in water (3 mL) and extracted with diethyl ether (2x2 mL) to remove all organic impurities. The aqueous solution was acidified with citric acid (10%, 2mL) and extracted with ethyl acetate (2 x 3 mL). The combined organic layers were washed with brine (1 mL) and dried over $MgSO_4$. The solvent was removed to give pure compound ***rac*-6** (97 mg) as a white solid in 24% yield. This compound was used for next step with out further purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.44 (s, 9H), 2.68-2.78 (m, 1H, CHH), 3.30 (m, 1H, CHH), 4.15-4.25(m, 1H, -OCHH), 4.32 (m, 1H, OCHH-), 5.10 (bs, 1H), 5.61 (bs, 1H), 7.10-7.22 (m, 2H), 7.40-7.50 (m, 2H). - ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 28.40 (+), 35.80 (-), 67.91 (-), 69.63 (+), 82.62 (C_{quat}), 84.42 (C_{quat}), 121.75 (C_{quat}), 127.91 (+), 131.02 (+), 136.72 (C_{quat}), 154.3 (C_{quat}), 170.03 (C_{quat}). - MS [ESI;CH_2Cl_2/MeOH+10mmol NH_4OAc].=.442.2 [M^+H] (80), 459.3 [M-NH_4^+] - IR (KBr): $\tilde{\nu}$ cm^{-1} = 3362, 2975, 2932, 2873, 2199, 1509, 1454, 1392.

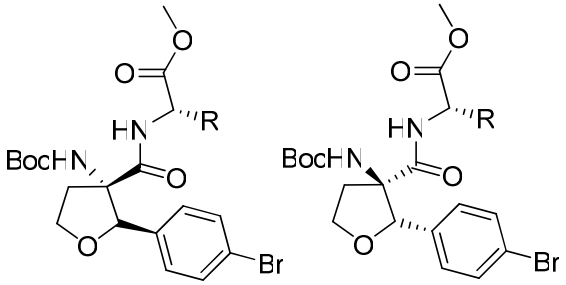
Dipeptide esters 7 and 9



Compound rac-**6** (100 mg, .26 mmol) was dissolved in CH_2Cl_2 (1.5 mL) and the hydrochloride salt of alanine methylester (36 mg, 0.26 mmol), EDC (40 mg, 0.26 mmol), HOBT (35 mg, 0.26 mmol) and DIPEA (84 mg, 0.65 mmol) were added. The reaction mixture was stirred at room temperature for 24 h, quenched with water (2 mL)

and 1M $KHSO_4$ (3 mL), diluted by adding 3 mL of diethyl ether and transferred to a separating funnel. The aqueous layer was extracted with diethyl ether (2x3 mL). Then combined ether layers were washed with brine solution (2 mL), dried over $MgSO_4$ and the solvent was removed in *vacuo*. The crude product was purified by flash column chromatography on silica gel using 30-40% diethyl ether / petrol ether as the eluant to give 73.2 mg (60%) of compounds **7** and **9** as white solids. Compound **7**: mp = 117-118°C, $[\alpha]_D^{25^\circ}$ = +34.3 (c = 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 0.90 (bs, 3H), 1.49 (s, 9H), 2.50 (m, 1H, -CH*H*-), 2.85 (m, 1H, -C*H*H-), 3.65 (s, 3H), 4.10 (qn, J = 6.79 Hz, 1H), 4.27-4.38 (m, 2H), 5.43(bs, 1H), 6.25 (bs, 1H), 6.45 (bs, 1H), 7.20 (d, *J* = 8.25 Hz, 2H), 7.40 (d, *J* = 8.25 Hz, 2H). - ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 17.55 (+), 28.43 (+), 36.08 (-), 48.01(+), 52.47 (+), 66.62 (-), 67.11 (+), 80.07 (Cquat), 121.44 (C_{quat}), 126.82 (+), 131.13 (+), 136.12 (C_{quat}), 154.51 (C_{quat}), 170.79 (C_{quat}), 172.98 (C_{quat}). - MS [PI-LSIMS; MeOH/Glycerine].=.471.3, 473.3 [MH^+] (60), 415.3, 417.3 [M^+-C_4H_8] (50) - IR (KBr): $\tilde{\nu}$ cm^{-1} = 3356, 3348, 3303, 3061, 3029, 2978, 2941, 2887, 2867, 2800, 2199, 1668. Anal. calcd. For $C_{20}H_{27}BrN_2O_6$ (476.19): C 50.96, H 5.77, N 5.94, found C 50.92, H 6.05, N 5.87. Compound **9**: mp = 127-130°C, $[\alpha]_D^{25^\circ}$ = -34.3 (c = 1.0, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 0.92 (d, *J* = 6.24 Hz, 3H), 1.49 (s, 9H), 2.53 (m, 1H, -CH*H*-), 2.88 (m, 1H, -C*H*H-), 3.72 (s, 3H), 4.24 (qn, J = 7.34 Hz, 1H), 4.34 (m, 2H), 5.44 (bs, 1H), 6.28 (bs, 1H), 6.47 (d, *J* = 5.87 Hz, 1H), 7.22 (d, J = 8.44 Hz, 2H), 7.41 (d, J = 8.44 Hz, 2H). - ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 18.26 (+), 28.38 (+), 35.91 (-), 48.18 (+), 52.46 (+), 66.69 (-), 67.78 (+), 80.27 (C_{quat}), 121.65 (C_{quat}), 127.30 (+), 131.01 (+), 135.71 (C_{quat}), 154.32 (C_{quat}), 170.61 (C_{quat}), 172.66 (C_{quat}). - MS [PI-LSIMS; MeOH/Glycerine].=.471.3, 473.3 [M^+H] (60), 415.3, 417.3 [M^+-C_4H_8] (50) - IR (KBr): $\tilde{\nu}$ cm^{-1} = 3348, 3303, 3061, 3029, 2978, 2941, 2887, 2867, 2800, 2199, 1668, 1591, 1517, 1452. Anal. calcd. For $C_{20}H_{27}BrN_2O_6$ (476.19): C 50.96, H 5.77, N 5.94, found C 51.02, H 6.12, N 5.86.

Dipeptide esters 8 and 10:

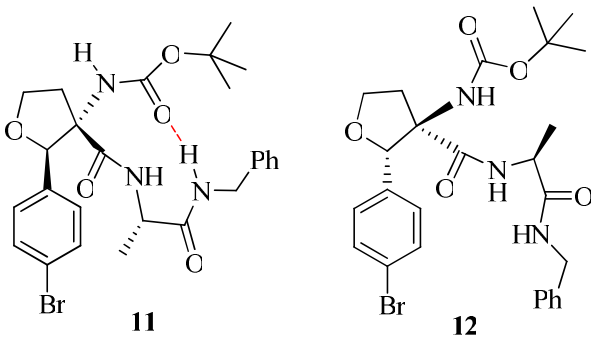


R = CH_2Ph **8** **10**

The compounds were prepared following the same procedure as given for the preparation of **7** and **9**, using phenylalanine hydrochloride salt instead of alanine hydrochloride salt. The reaction gave 55% isolated product yield. Compound **8**: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.47 (s, 9H), 2.79 (m, 1H, -CH*H*-), 2.97-3.10 (m, 1H, -C*H*H-), 3.60 (s, 3H), 4.02 (m, 1H), 4.15-4.31 (m, 3H), 4.41 (m, 1H), 5.38 (bs, 1H), 6.19 (bs, 1H), 6.57 (bs, 1H), 7.02-7.14 (m, 4H), 7.26-7.37 (m, 5H). - ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 28.43 (+), 35.45 (-), 37.61 (-), 52.38 (+), 53.19 (+), 53.82 (+), 66.21 (-), 80.08 (Cquat), 121.46 (C_{quat}), 126.82 (+), 127.28 (+), 127.40 (+), 128.62 (+), 128.94 (C_{quat}), 129.13 (+), 131.19 (+), 135.77 (C_{quat}), 154.06 (C_{quat}), 171.05 (C_{quat}), 171.67 (C_{quat}). - MS [PI-LSIMS; MeOH/Glycerine] = 546.14, 547.4 [MH^+] (60),- IR (KBr): $\tilde{\nu}$ cm^{-1} = 3356, 3348, 3303, 3061, 3029, 2978, 2941, 2887, 2867, 2800, 2199, 1668.

Compound **10**: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.49 (s, 9H), 2.81 (m, 1H, -CH*H*-), 2.95 (m, 1H, -C*H*H-), 3.65 (s, 3H), 4.04 (m, 1H), 4.20-4.34 (m, 3H), 4.43 (m, 1H), 5.40 (bs, 1H), 6.23 (bs, 1H), 6.60 (bs, 1H), 7.00-7.12 (m, 4H), 7.22-7.35 (m, 5H). - ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 29.43 (+), 36.45 (-), 37.61 (-), 52.38 (+), 53.19 (+), 53.82 (+), 66.21 (-), 80.08 (Cquat), 121.46 (C_{quat}), 123.82 (+), 127.38 (+), 127.45 (+), 128.69 (+), 128.94 (C_{quat}), 129.13 (+), 131.19 (+), 135.77 (C_{quat}), 155.06 (C_{quat}), 171.06 (C_{quat}), 171.77 (C_{quat}).

Dipeptide amides 11 and 12.



The compounds were prepared as described above. The reaction gave an isolated yield of 50% of the two diastereomers. Compound **11**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.15 (d, *J* = 7.12 Hz, 3H), 1.43 (s, 9H), 2.55-2.64 (m, 1H, -CH*H*-), 2.69-2.81 (m, 1H, -C*H*H-), 4.00 (m, 1H), 4.20-4.28 (m, 2H), 4.34-4.44 (m, 3H), 5.12(bs, 1H), 5.88 (bs, 1H), 6.24 (bd, 1H), 6.34 (t, 1H), 7.17-7.39 (m, 9H). - ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 17.98 (+), 28.29 (+), 36.08 (-), 43.34 (-), 49.20 (+), 67.16 (-), 68.42 (+), 80.91 (C_{quat}), 83.01 (C_{quat}), 122.05 (C_{quat}), 127.35 (+), 127.50 (+), 128.58 (+), 131.32 (+), 135.74 (C_{quat}), 137.99 (C_{quat}), 154.78 (C_{quat}), 170.54 (C_{quat}), 171.22 (C_{quat}). - MS [ESI; CH_2Cl_2/MeOH + 10 mmol NH_4OAc].=.546.2, 548.2 [MH^+] (100), 490.1, 492.1 [M^+-C_4H_8] (26).

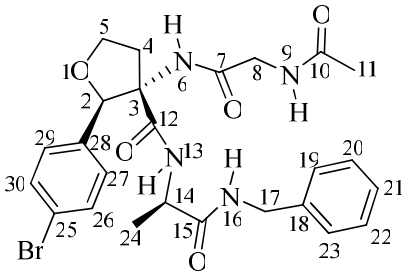
Compound **12**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (d, *J* = 6.82 Hz, 3H), 1.48 (s, 9H), 2.38-2.53 (m, 1H, -CH*H*-), 2.69-2.81 (m, 1H, -C*H*H-), 4.00-4.10 (m, 1H), 4.25-4.48 (m, 4H), 5.32 (bs, 1H), 6.12 (bs, 1H), 6.25 (bt, 1H), 6.60 (d, *J* = 6.60 Hz, 1H), 7.16-7.40 (m, 9H). - ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 17.76 (+), 28.42 (+), 35.82 (-), 43.53 (-), 49.02(+), 66.75 (-), 67.70 (+), 80.35 (C_{quat}), 81.24 (C_{quat}), 121.60 (C_{quat}), 127.08 (+), 127.59 (+), 128.77 (+), 131.14 (+), 136.16 (C_{quat}), 137.81 (+), 154.20 (C_{quat}), 170.92 (C_{quat}), 171.38 (C_{quat}).

Tripeptide amide 13a and 13b.

Compound **11** (100 mg, .26 mmol) was dissolved in 5 mL of DCM. To this solution 2 mL of HCl saturated diethyl ether solution was added and the mixture was stirred for 20 min at room temperature. The solvent was evaporated and the resulting white solid was dissolve in DMF (1.5 mL). DIPEA (89 mg, 0.67 mmol), Ac-Gly-OH (36 mg, 0.32 mmol), EDC (65 mg, 0.41 mmol), and HOBT (66 mg, 0.41 mmol) were added. The

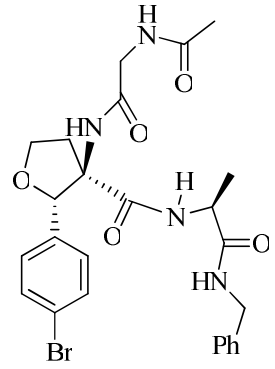
reaction mixture was stirred at room temperature for 3 days, quenched with water (2 mL) and 1M $KHSO_4$ (3 mL), diluted by adding 3 mL of diethyl ether and transferred into a separatory funnel. The aqueous layer was extracted with diethyl ether (2x3 mL), the combined ether layers were washed with brine solution (2 mL), dried over $MgSO_4$ and the solvent was removed in *vacuo*. The crude product was purified by HPLC to give 41 mg of compound **13a** (40% yield).

Compound 13a:



^{1}H NMR (600 MHz, d6-DMSO): δ = 0.80 (d, *J* = 7.47 Hz, 3H, COSY, HSQC: H-24), 1.74 (s, 3H, COSY, HSQC: H-11), 1.99 (m, 1H, COSY, HSQC: H-$4_{a/b}$), 2.97 (m, 1H, COSY, HSQC: H-$4_{b/a}$), 3.50-3.7 (m, 2H, COSY, HMBC: H-14 and H-$8_{a/b}$), 3.82 (dd, 1H, *J* = 15.94 Hz, 5.14 Hz, COSY, HMBC: H-$8_{b/a}$), 3.87 (m, 1H, COSY, HMBC: H-$5_{a/b}$), 4.15 (m, 1H, COSY, HMBC: H-$17_{a/b}$), 4.25(m, 2H, COSY, HMBC: H-$17_{b/c}$ and H-$5_{b/a}$), 4.98 (s, 1H, COSY, HMBC: H-2), 7.16 (m, 3H, aromatic), 7.27 (m, 4H, aromatic), 7.35 (d, *J* = 7.47 Hz, 1H, COSY, HMBC: H-13), 7.49 (m, 2H, aromatic), 7.58 (t, *J* = 6.36 Hz, 1H, COSY, HMBC: H-16), 8.20 (t, *J* = 5.25 Hz, COSY, HMBC: H-9), 9.00 (s, 1H, COSY, HMBC: H-6). - ^{13}C NMR (151 MHz, d6-DMSO) δ = 16.40 (+, HSQC: C-24), 22.10 (+, HSQC: C-11), 35.67 (-, HSQC: C-4), 41.82 (-, HSQC: C-8 or C-17), 43.10 (-, HSQC, C-8 or C-17), 48.61(+, HSQC: C-14), 67.31 (-, HSQC: C-5), 69.65 (+, HSQC: C-2), 84.83 (C_{quat}, HSQC, C-3), 121.00 (C_{quat}), 126.51 (+), 126.77 (+), 127.04 (+), 128.09 (+), 128.23 (+), 128.67 (+), 130.40 (+), 137.30 (C_{quat}), 139.19 (+), 168.50 ($C_{quat,}$ HMBC: C-12), 170.45 (C_{quat}, HMBC: C-10), 171.46 (C_{quat}, HMBC: C-7), 171.70 (C_{quat}, HMBC: C-15). - MS [PI-LSIMS; MeOH/glycerine].=.545.3, 547.3 [MH^+] (100).

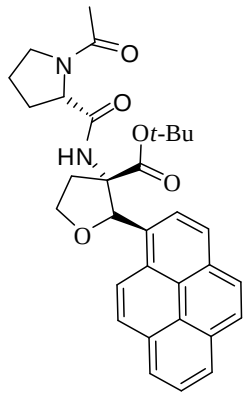
Compound 13b:



^{1}H NMR (600 MHz, d6-DMSO): δ = 0.95 (d, *J* = 7.06 Hz, 3H), 1.84 (s, 3H), 2.21-2.26 (m, 1H), 2.49 (s, 3H), 2.26-2.72 (m, 1H), 3.30 (s, 2H), 3.37-3.79 (m, 2H), 3.82-3.92 (m, 2H), 4.21-4.26 (m, 3H), 5.02 (s, 1H), 7.17-7.23 (m, 5H), 7.30-7.35 (m, 4H), 7.41-7.43 (d, *J* = 8.07 Hz, 1H), 8.00 (t, *J* = 6.36 Hz, 1H), 8.18 (t, *J* = 6.36 Hz, 1H).
^{13}C NMR (151 MHz, d6-DMSO): δ = 17.67 (+), 22.26 (+), 33.73 (-), 42.00 (-), 42.64 (-), 48.32 (+), 66.99 (-), 69.69 (+), 84.36 (C_{quat}), 120.66 (C_{quat}), 126.66 (+), 127.01 (+), 128.19 (+), 128.57 (+), 130.70 (+), 137.70 (C_{quat}), 139.14 (+), 167.92 (C_{quat}), 169.83 (C_{quat}), 169.89 (C_{quat}), 171.37 (C_{quat}), 201.75 (C_{quat}). –MS [PI-LSIMS; MeOH/glycerine] = 545.2, 547.2 [MH^{+}] (100). Anal. Calcd. For $C_{25}H_{29}N_4O_5Br$ (544.34) C 55.05, H 5.36, N 10.27 found C 54.49, H 5.39, N 10.38.

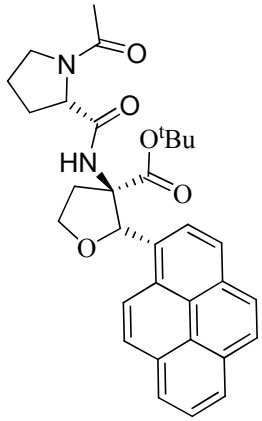
Peptide coupling reaction: Compound ***rac*-4o** (100 mg, .21 mmol) was dissolved in 3 mL of CH_2Cl_2. To this solution 2 mL of HCl saturated ether solution was added and stirred for 20 min at room temperature. The solvent was evaporated by *vacuo* and the resulting light yellow solid was dissolve in dry 3 mL CH_2Cl_2 followed by N-acetylated L-proline (39 mg, .25 mmol) , HOAt (16.7 mg, .12 mmol), HBTU (95 mg, .25 mmol) and DIPEA (133 mg, 1.25 mmol). The reaction mixture was stirred at room temperature for 2 days, quenched with 1M $KHSO_4$ (2 mL), diluted with 4 mL EtOAc and transferred to a separating funnel. The aqueous layer was extracted with EtOAc (2x3 mL). The combined EtOAc layers were washed with 3 mL of brine solution, dried over $MgSO_4$ and the solvent was removed in *vacuo*. The crude product was purified by flash column chromatography on silica gel using 40-45% EtOAc in CH_2Cl_2 as eluent to afford 40 mg (75% of yield, total 80 mg of product) of each compound **17a** and **17b** as light yellow solid.

(2*S*, 3*R*)-*tert*-Butyl 3-((*S*)-1-acetylpyrrolidine-2-carboxamido)-2-(pyren-1-yl)tetrahydrofuran-3-carboxylate (17a)



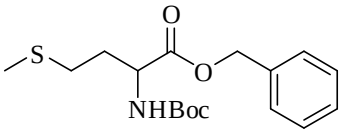
R_f = 0.28 (EtOAc : CH_2Cl_2 = 1:1), m.p.= 159-161°C, $[\alpha]^D$ = +53.9º (c = 0.2, $CHCl_3$). ^{1}H NMR (600MHz, $CDCl_3$) δ = 0.45 (s, 9H), 1.87-1.93 (m, 1H), 2.00-2.05(m, 1H), 2.07-2.14 (m, 1H), 2.29 (s, 3H), 2.53-2.61 (m, 2H), 3.07-3.13 (m, 1H), 3.46-3.55 (m, 2H), 4.25-4.29 (m, 1H), 4.52-4.55(m, 1H), 4.71-4.80 (m, 1H), 6.11 (s, 1H), 7.98-8.36 (m, 9H), 8.67 (s, 1H). - ^{13}C NMR (150.9MHz, $CDCl_3$) δ = 22.73 (+), 25.28 (-), 36.80 (-), 38.65 (+), 48.47 (-), 59.57 (+), 68.34 (-), 71.48 (+), 81.09 (C_{quat}), 84.35 (C_{quat}), 123.72 (+), 124.40 (+), 124.64 (+), 124.85 (+), 125.53 (C_{quat}), 125.53 (C_{quat}), 125.75 (C_{quat}), 127.29 (C_{quat}), 127.34 (C_{quat}), 127.50 (C_{quat}), 128.77 (+), 130.52 (+), 130.99 (C_{quat}), 131.32 (C_{quat}), 131.69 (+), 168.68 (C_{quat}), 170.26 (C_{quat}), 171.33 (C_{quat}). - MS [ESI; CH_2Cl_2/MeOH+10mmol/1 NH_4OAc] = 544.4 [MH^+] (60), 505 [$M\text{-}NH_4^+$] (100), - IR (KBr): $\tilde{\nu}$ cm^{-1} = 3258, 3223, 3049, 2976, 2889, 1923, 1730, 1685, 1618, 1550, 1452, 1430. Anal. calcd. For $C_{32}H_{34}N_2O_5$ (526.25): C 72.98, H 6.51, N 5.32, found C 72.70, H 6.77, N 5.30.

(2*R*, 3*S*)-*tert*-Butyl 3-((*S*)-1-acetylpyrrolidine-2-carboxamido)-2-(pyren-1-yl)tetrahydrofuran-3-carboxylate (17b)



R_f = 0.20 (EtOAc: CH_2Cl_2 = 1:1), m.p.= 159-161°C, $[\alpha]^D$ = -53.9º (c = 0.2, $CHCl_3$). ^{1}H NMR (600MHz, $CDCl_3$) δ = 0.45 (s, 9H), 1.87-1.93 (m, 1H), 2.00-2.05(m, 1H), 2.07-2.14 (m, 1H), 2.29 (s, 3H), 2.53-2.61 (m, 2H), 3.07-3.13 (m, 1H), 3.46-3.55 (m, 2H), 4.25-4.29 (m, 1H), 4.52-4.55(m, 1H), 4.71-4.80 (m, 1H), 6.11 (s, 1H), 7.98-8.36 (m, 9H), 8.67 (s, 1H). - ^{13}C NMR (150.9MHz, $CDCl_3$) δ = 22.73 (+), 25.28 (-), 36.80 (-), 38.65 (+), 48.47 (-), 59.57 (+), 68.34 (-), 71.48 (+), 81.09 (C_{quat}), 84.35 (C_{quat}), 123.72 (+), 124.40 (+), 124.64 (+), 124.85 (+), 125.53 (C_{quat}), 125.53 (C_{quat}), 125.75 (C_{quat}), 127.29 (C_{quat}), 127.34 (C_{quat}), 127.50 (C_{quat}), 128.77 (+), 130.52 (+), 130.99 (C_{quat}), 131.32 (C_{quat}), 131.69 (+), 168.68 (C_{quat}), 170.26 (C_{quat}), 171.33 (C_{quat}). - MS [ESI; CH_2Cl_2/MeOH+10mmol/1 NH_4OAc] = 544.4 [MH^+] (60), 505 [$M\text{-}NH_4^+$] (100), - IR (KBr): $\tilde{\nu}$ cm^{-1} = 3349, 3041, 2976, 2880, 2208, 1924, 1624, 1531, 1447. Anal. calcd. For $C_{32}H_{34}N_2O_5$ (526.25): C 72.98, H 6.51, N 5.32, found C 72.70, H 6.77, N 5.30.

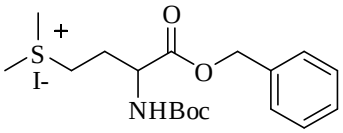
Benzyl 2-(*tert*-butoxycarbonylamino)-4-(methylthio) butanoate (*rac*-2b)



^{1}H NMR (300MHz, $CDCl_3$) δ =1.45 (s, 18H), 1.99 (m, 1H, C*H*H-), 2.11 (s, 3H), 2.15 (m, 1H, CH*H*), 2.58 (m, 2H), 4.45 (bs, 1H), 5.25 (bs, 1H).^{13}C NMR (75.5 MHz, $CDCl_3$),

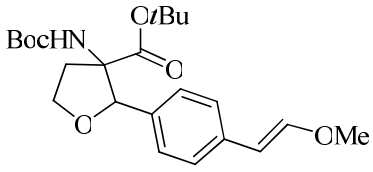
δ =27.64 (+), 27.99 (+), 28.30 (-), 30.40 (-), 53.38 (+), 65.83 (+), 72.08 (C_{quat}), 77.28 (C_{quat}), 155.33 (C_{quat}), 171.36 (C_{quat}). MS [ESI H_2O/AcN]: m/z (%) = 305.5 [MH^+] (100)

(4-(Benzyloxy)-3-(*tert*-butoxycarbonylamino)-4-oxobutyl)dimethylsulfonium iodide (*rac*-3b)



^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.45 (s, 9H), 1.47 (s, 9H), 2.29 (m, 1H,-C*H*H-), 2.32 (m, 1H, -CH*H*), 3.30 (d, 6H), 3.70 (m, 1H, -SC*H*H-), 3.75 (m, -SCH*H*-), 4.15 (bs, 1H), 5.70 (bs, 1H). ^{13}C NMR (75.5MHz, $CDCl_3$) δ = 15.48 (+), 28.00 (+,), 28.05 (+), 29.92 (-), 32.56 (-), 53.39 (+), 80.63 (C_{quat}), 82.12 (C_{quat}), 169.65 (C_{quat}), 171.00 (C_{quat}). MS [ESI, H_2O/AcN]: m/z (%) = 320.1 [M+] (100)

***tert*-Butyl 3-(*tert*-butoxycarbonyl)-2-(4-((E)-2-(methoxycarbonyl)vinyl)phenyl)-tetrahydrofuran-3-yl carbamate (*rac*-14)**

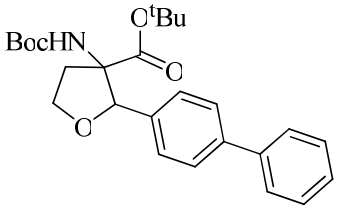


A mixture of 0.57 mmol of compound rac-**4a** (250 mg), 0.68 mmol methylacrylate (58 mg), 0.68 mmol triethyl amine, 1 mol% palladium acetate and 0.03 mmol tris(o-tolyl)phosphine in 2 mL of DMF was heated to 100°C under argon for 14h. After the consumption of all of the starting material the mixture was cooled to room temperature, 2 mL of 1M $KHSO_4$ were added and the mixture was extracted (3x1 mL) with diethyl ether. The combined organic fraction was dried over $MgSO_4$ and the solvent was evaporated to give a solid crude product, which was purified by column chromatography (silica gel, 1:1 diethyl ether : petrol ether) affording 180 mg (71%) of the white solid product rac-**14,** m.p = 146-149°C.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.09 (s, 9H), 1.46 (s, 9H), 2.61-2.68 (m, 2H), 3.80 (s, 3H) 4.16-4.33(m, 2H), 5.09 (bs, 1H), 5.65 (bs, 1H), 6.41 (d, *J* = 15.92 Hz,, 1H), 7.35 (d,

J = 8.23 Hz, 2H), 7.50 (d, *J* = 8.23 Hz, 2H), 7.65 (d, *J* = 15.92 Hz, 1H). - ^{13}C NMR (75.5 MHz, CDCl3) δ = 27.38 (+), 28.41 (+), 35.94 (-), 51.72 (+), 67.97 (-), 69.71 (+), 80.10 (C_{quat}), 82.50 (C_{quat}), 84.72 (C_{quat}), 117.73 (+), 126.72 (C_{quat}), 127.66 (+), 131.95 (+), 140.16 (C_{quat}), 144.47 (+), 154.3 (C_{quat}), 167.45 (C_{quat}), 170.05 (C_{quat}). - MS [ESI;CH_2Cl_2/MeOH+10mmol NH_4OAc].=.448.2 [MH^+] (40), 465.3 [M-NH_4^+] (35), 409.2 [M-NH_4^+-C_4H_8] (100). - IR (KBr): cm-1 = 3362, 2975, 2932, 2873, 2199, 1509, 1454, 1392. Anal. calcd. For $C_{24}H_{33}NO_7$ (447.34): C 64.41, H 7.43, N 3.13, found C 64.27, H 7.67, N 3.16.

Compound *rac*-15.

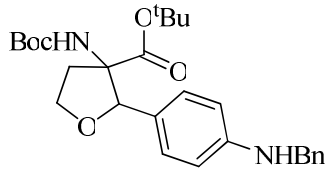


In a 25 mL Schlenk flask were placed compound ***rac*-4a** (250 mg, 0.567 mmol), phenylboronic acid (83 mg, 0.68 mmol), Na_2CO_3 (240 mg, 2.27 mmol), $Pd(OAc)_2$ (2 mg, 6 μmol), tetrabutyl ammonium bromide (183 mg, 0.567 mmol) and 2 mL of a water / DMF (1:1) mixture. The flask was sealed with a septum and placed into an oil bath preheated to 100ºC. The reaction mixture was held at this temperature for 20h, cooled to room temperature, water and diethyl ether (10 mL of each) were added and organic material was removed by extraction. After further extraction of the aqueous layer with diethyl ether the organic phases were combined, dried over $MgSO_4$ and the diethyl ether was removed in vacuo, leaving the crude product, which was purified by column chromatography (silica gel, 1:4 diethyl ether: PE) affording 250 mg (71%) of the white solid product **15**, m.p = 80-83°C.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.12 (s, 9H), 1.50 (s, 9H), 2.57-2.85 (m, 2H), 4.18-4.41(m, 2H), 5.09 (bs, 1H), 5.56 (bs, 1H), 7.31-7.59 (m, 9H). - ^{13}C NMR (75.5 MHz, CDCl3) δ = 27.40 (+), 28.44 (+), 35.95 (-), 67.49 (-), 69.89 (+), 80.07 (C_{quat}), 82.26 (C_{quat}), 85.47 (C_{quat}), 126.73 (C_{quat}), 127.08 (+), 127.32 (+), 127.41 (+), 127.59 (+), 127.97 (+), 128.89 (+), 131.04 (+), 136.65 (C_{quat}), 140.94 (C_{quat}), 154.3 (C_{quat}), 170.10 (C_{quat}). - MS [ESI;CH_2Cl_2/MeOH+10mmol NH_4OAc].=440.3 [MH^+] (65), 457.3 [M-NH_4^+] (60), 401.2 [M-NH_4^+-C_4H_8] (100). - IR (KBr): cm-1 = 3362, 2975, 2932, 2873,

2199, 1509, 1454, 1392. Anal. calcd. For $C_{26}H_{33}NO_5$ (439.54): C 71.05, H 7.57, N 3.19, found C 70.82, H 7.66, N 3.15.

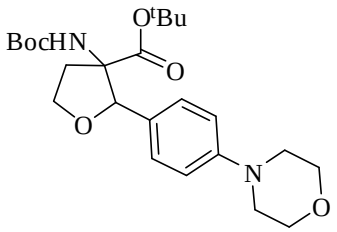
***tert*-Butyl 3-(*tert*-butoxycarbonyl)-2-(4-(benzylamino)phenyl)-tetrahydrofuran-3-yl carbamate (*rac*-16a)**



An oven-dried Schlenk flask equipped with a Teflon septum was charged with a magnetic stir bar, 3 mL of DMF, compound ***rac*-4a** (250 mg, 0.567 mmol), CuI (5.5 mg, 0.028 mmol, 5 mol%), and K_3PO_4 (240 mg, 1.134 mmol). The flask was evacuated and filled with argon (this procedure was repeated three times). Under a flow of argon, the appropriate amine (91 mg, 0.851 mmol) was added by syringe. Finally, 2-isobutyryl-cyclo hexanone (20 mg, 0.113 mmol, 20 mol%) was added *via* syringe. The mixture was heated to 100ºC for 10h. Upon completion of the reaction, the mixture was allowed to cool to room temperature, diluted with 5 mL of water, the aqueous layer was extracted with diethyl ether (3x3 mL), the total organic fraction was dried over $MgSO_4$ and the solvent was removed in vacuo. The crude product was purified by column chromatography (silica gel, diethyl ether: PE 2:3) affording 200 mg (yield, 75%) of pure compound ***rac*-16a** as white solid. m.p.122-125ºC.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.15 (s, 9H), 1.47 (s, 9H), 2.47-2.60 (m, 1H), 2.72-2.84 (s, 1H), 4.10 (q, *J* = 8.05 Hz, 1H), 4.25-4.30 (m, 1H), 4.32 (s, 2H), 4.80 (bs, 1H), 5.40 (bs, 1H), 6.55 (d, *J* = 8.50 Hz, 2H), 7.15 (d, *J* = 8.50 Hz, 2H), 7.27-7.35 (m, 5H). - ^{13}C NMR (75.5 MHz, CDCl3) δ = 27.53 (+), 28.40 (+), 35.59 (-), 48.09 (-), 67.62 (-), 69.85 (+), 79.90 (C_{quat}), 81.81 (C_{quat}), 86,56 (C_{quat}), 112.40 (+), 126.00 (C_{quat}), 127.16 (+), 127.31 (+), 127.56 (+), 128.59 (+), 139.36 (C_{quat}), 147.97 (C_{quat}), 154.74 (C_{quat}), 170.05 (C_{quat}). - MS [ESI;CH_2Cl_2/MeOH+10mmol NH_4OAc].=.469.3 [MH^+] (100), 486.3 [M-NH_4^+] (65). - IR (KBr): cm^{-1} = 3362, 2975, 2932, 2873, 2199, 1509, 1454, 1392. Anal. calcd. For $C_{27}H_{36}N_2O_5$ (468.58): .C 69.21, H 7.74, N 5.98, found C 69.17, H 7.67, N 6.00.

tert*-Butyl 3-(*tert*-butoxycarbonylamino)-2-(4-morpholinophenyl)tetrahydrofuran-3 carboxylate** (rac*-16b**)



The compound was prepared by using the same procedure as described for ***rac*-16a**. The isolated yield was 35%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.14 (s, 9H), 1.50(s, 9H), 2.52--2.60 (m, -CH*H*-, 1H), 2.70-2.80 (m, -C*H*H-, 1H), 3.10 (m, 4H) 3.80-3.90 (m, 4H), 4.09-4.18 (m, -OCH*H*-, 1H), 4.27-4.38 (m, -OC*H*H-, 1H), 4.90 (bs, 1H), 5.50 (bs, 1H), 6.80 (d, *J* = 8.42 Hz, 2H), 7.20 (d, *J* = 8.42 Hz, 2H). - ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 27.51 (+), 28.40 (+), 35.94 (-), 49.59 (-), 66.79 (-), 67.74 (-), 67.79 (+), 69.80 (+), 81.95 (C_{quat}), 82.50 (C_{quat}), 84.72 (C_{quat}), 117.73 (+), 126.72 (C_{quat}), 127.66 (+), 131.95 (+), 140.16 (C_{quat}), 144.47 (+), 154.3 (C_{quat}), 167.45 (C_{quat}), 170.05 (C_{quat}). - MS [ESI;CH_2Cl_2/MeOH+10mmol NH_4OAc].=.449.2 [MH^+] (100).

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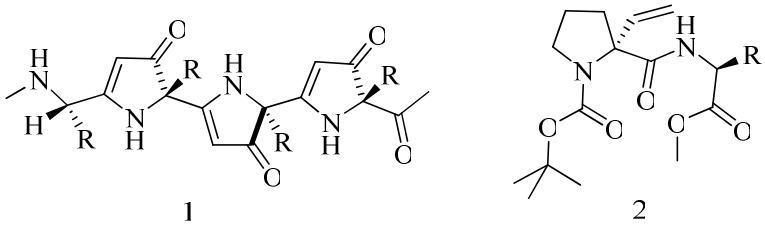
Synthesis of 3-Oxo-2,3-dihydro-pyrrole Amino Acids as Chiral Dipeptidomimics*

3.1. Introduction

A peptidomimic imitates peptide structures by controlled spatial disposition of functional groups and a general analogous structure. Previously reported peptidemimics based on oligo-3-oxo-2,3-dihydro-pyrroles have been used as protease inhibitor and ligand for hormone and protein receptors.[1] Their chiral sequence can adopt the bioactive conformation of peptide ligands while exhibiting good pharmacokinetic properties.[2] Smith and Hirschmann[3] first prepared 2,5-linked 3-oxo-2,3-dihydro-pyrroles **1** starting from chiral natural amino acids (Figure 1). Seebach et al.[4] have prepared α-substituted proline derivatives with retaining the chirality, which was further developed into β-turn peptide mimics **2** by Gmeiner et al.[5] Recently Chakarborty et al. introduced 5-(aminomethyl)pyrrole-2-carboxylic acid as a constrained surrogate of Gly-Δ-Ala[6]. Our group elaborated the pyrrole amino acid building block and reported the synthesis of methoxypyrrole amino acids (MOPAS), their facile introduction into peptide structures and intra- and intermolecular peptide binding properties[7]. We have also reported chiral dipeptide mimic H_2N-Val-Δ-Ala-OEt, which has been prepared using chiral auxiliary approach[8].

Extending this, we are reporting here the synthesis of 2-allyl-2,3-dihydro-3-oxo pyrrole amino acids by stereoselective chiral allylation using the Trost ligand[9] as chiral control element.



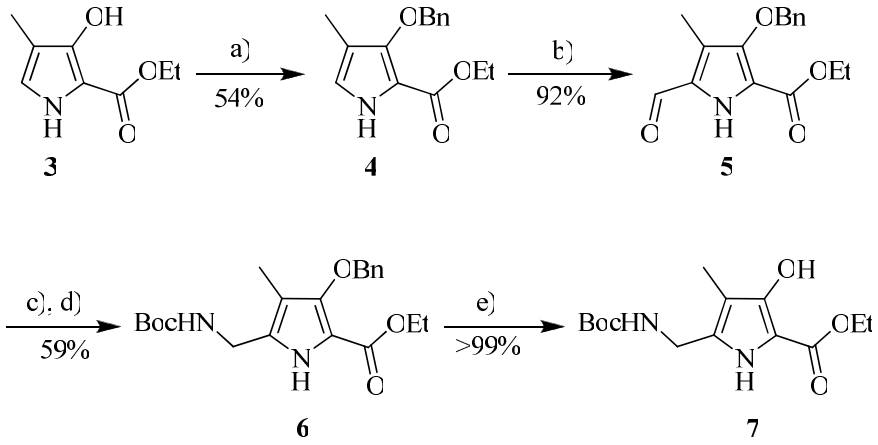
1 2

Figure 1 Structures of 2,5-linked 3-oxo-2,3-dihydro-pyrroles **1** and β-turn peptide mimics **2**.

* The results of this chapter have been published: Maity, P.; König, B. *Synthesis*, **2006**, 2719-2724.

3.2. Results and discussion

First, we prepared 3-hydroxy pyrrole amino acids (HOPAS) **7** as starting material for the asymmetric synthesis of a chiral 3-oxo-2,3-dihydro pyrrole amino acid, such as **8**. Scheme 1 summarizes the synthetic steps. The hydroxyl group of pyrrol **3**,[10] was benzyl protected, formylated in **5**-position, converted into Boc-protected amino ester **6** and debenzylated to give **7**



Scheme 1. Synthesis of HOPAS **7**. a) BnCl, K_2CO_3, in DMF, 85^o C, 16h. b) $POCl_3$, DMF, in DCE, reflux, 2.5h c) NH_2Boc, HCOOH, p-TsONa, in THF/H_2O, rt, 72h, d) $NaBH_4$, THF, rt., 2h e) Pd-C/H_2, MeOH, rt, 24h.

The basic hydrolysis of 2-ethyl-3-hydroxy-pyrrole carboxylates is known to be difficult. In basic media the compound exists in its two tautomeric forms (Figure 2).[11] Using this property we intended to introduce an allyl group at carbon C-2 *via* Pd-catalyzed allylation in a stereoselective manner using the chiral Trost ligand.[12,13] The allylated 3-oxo-2,3-dihydro pyrrole amino acids **8** was obtained (Scheme 2), but the yield (35%) and the enantiomeric excess (28 % ee) of the reaction are unsatisfactory.

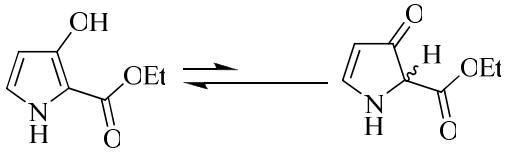
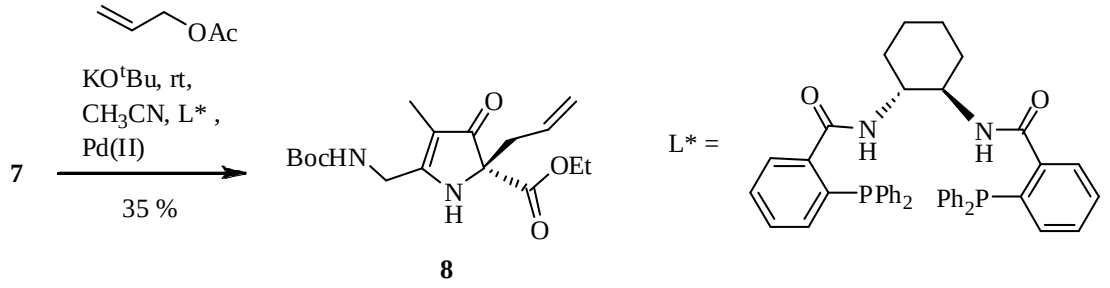


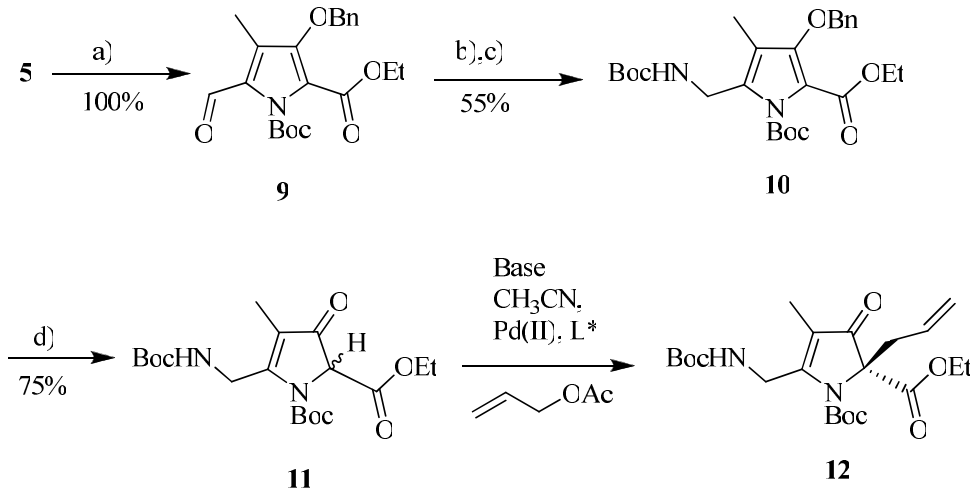
Figure 2. Tautomers of 2-ethyl-3-hydroxy-pyrrolcarboxylate

During the alkylation reaction the thermodynamically unfavourable loss of aromaticity occurs, which may explain the difficulties. Introduction of an electron withdrawing group on the pyrrole nitrogen, which reduces the availability of the lone pair,[14] may improve the situation. Therefore, *N*-Boc protected pyrrole **10** was prepared starting from **5** (Scheme 3). The NMR spectrum of 3-hydroxyl pyrrole **11** in $CDCl_3$ reveals the presence of the keto tautomer as the only isomer, which indicates the reduced heteroaromatic character of the pyrrole ring.



Scheme 2. Synthesis of allylated 3-oxo-2,3-dihydro-pyrrole amino acid **8**.

The reaction of 3-oxo-2,3-dihydro pyrrole **11** with allylacetate in the presence allylpalladium(II)chloride as catalyst and the chiral Trost ligand gave the desired compound in good yield. Table 1 summarizes the results for different conditions. An ee of 68% was observed at 0^{o}C with KO^{t}Bu as base in CH_3CN. Decrease of the reaction temperature to -35^{o}C increased the optical purity of the isolated product to 71% ee with a chemical yield of 87%. Compound **12** was fully characterized by spectroscopic methods. The transition state model for the formation of the quaternary centre predicts an "*R*" configuration if the [*R,R*] stereoisomer of the Trost ligand is used.[12] This is supported by the optical rotation of **12** $[\alpha]^D$ = +143.8º, which corresponds to $[\alpha]^D$ = +22.0º reported for the structurally related compound *R*-2,4-dibenzyl-2-(3-methyl-but-2-enly)-1,2-dihydro-pyrrole-3-one.[1]



Scheme 3. Synthesis of Boc-protected pyrrol **10** and its asymmetric allylic alkylation to 3-oxo-2,3-dihydro-pyrrole amino acid **12**. a) Boc_2O, DMAP in DCM, 2h, room temp. b) NH_2Boc, HCOOH, p-TsONa, THF/H_2O, room temp., 2d c) $NaBH_4$, THF, room temp., 2h d) Pd/C, H_2, $MeOH:CHCl_3$ (8:1).

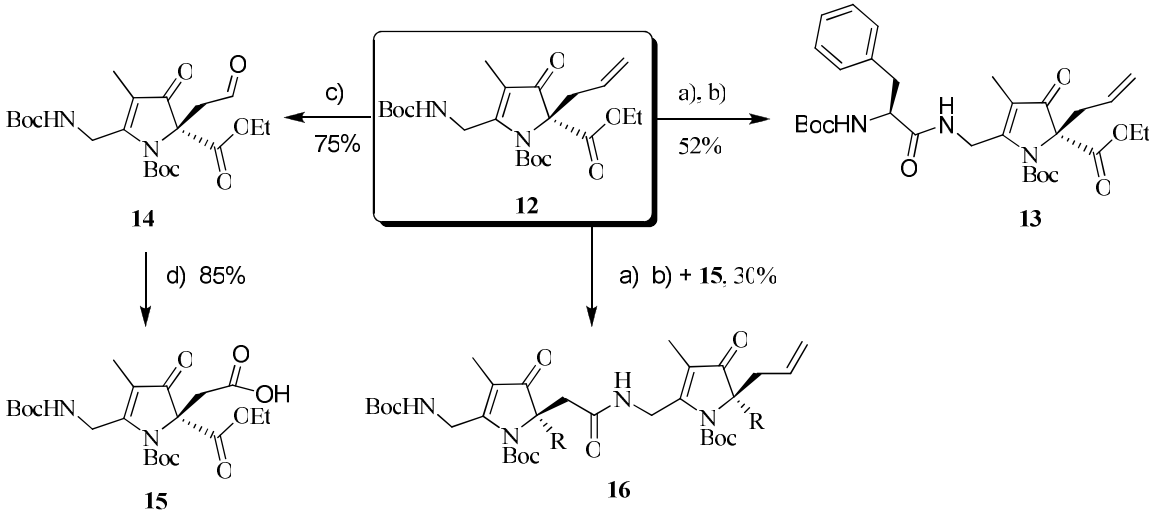
Base	Solvent	Reaction time [h]	Temper-ature [°C]	Yield [%]	ee[a] [%]
KO^tBu	CH_3CN	2.0	0	83	68
KO^tBu	CH_3CN	2.5	-22	87	71
NaH	THF	0.2	rt	90	17
NaH	THF	6.0	-15 to 0	95	31
^nBuLi	THF	1.5	-78	80	9

[a]Optical purity was determined by chiral HPLC analysis.

Table 1. Yield and optical purity of compound 12 at different reaction conditions.

To demonstrate the ability of compound **12** to be incorporated into peptide chains, the Boc protecting group of the primary amine was removed selectively using HCl in ether. The amine was coupled using standard peptide coupling conditions with Boc-Phe-OH giving tripeptide **13** in 52% yield. The allyl group of **12** allows the introduction of additional functional groups if desired. The conversion into aldehyde **14** succeeds using K_2OsO_4 and $NaIO_4$ in THF and H_2O.[15] The aldehyde was converted into the

corresponding acid **15** by using $NaClO_2$, NaH_2PO_4 and H_2O_2 (30 vol.% in water) in CH_3CN and H_2O.[16] Compound **15** resembles the structure of a partially constrained dipeptide of glycine and a β-amino acid. Acid **15** was coupled using standard peptide coupling conditions with Boc-deprotected compound **12** to give the tetrapeptide structure **16**[17] in 30 % yield.



Scheme 4. Synthesis of peptides **13** and **16**. a) HCl, ether b) EDC, HOBT, DIPEA, CH_2Cl_2, rt.; c) K_2OsO_4, $NaIO_4$, THF/H_2O; d) $NaClO_2$, NaH_2PO_4, H_2O_2 in CH_3CN & H_2O (4:1), rt.

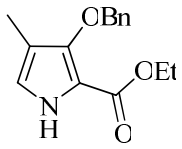
3.3. Conclusion

We have used the enantioselective Pd-catalyzed allylic alkylation with the Trost ligand to convert *N*-Boc protected 3-hydroxy pyrrole **11** into 3-oxo-2,3-dihydro-pyrrole amino acid **12** breaking the heteroaromatic π-system. With KO^tBu as a base at low reaction temperatures an ee of 71% with a chemical yield of 87% was obtained. 3-Oxo-2,3-dihydro-pyrrole amino acid **12** resembles the structure of a partially constrained dipeptide, which may find use in the synthesis of more extended peptide mimics.

3.4. Experimental section

Melting points were determined on a melting point apparatus and are uncorrected. Specific rotations were measured on a polarimeter using a 10 cm cell. NMR spectra were recorded in $CDCl_3$ at 300 MHz (^1H) or 75 MHz (^{13}C) unless stated otherwise. Structural assignments are based on DEPT and COSY experiments where applicable. The multiplicity of the carbon atoms is given as (+) = CH_3 or CH, (-) = CH_2 and (C_{quat}) for quaternary carbon atoms. Analytical TLC plates (silica gel 60 F_{254}) and silica gel 60 (70-230 or 230-400 mesh) for column chromatography (CC) were purchased from Merck. Visualization of spots by UV light and/or staining with phosphomolybdate or ninhydrine, both in ethanol. DMF, CH_3CN, THF, and Et_2O were dried by standard procedures and stored over molecular sieves or Na. PE means petrol ether with a boiling range of 70-90 ^oC. All other solvents and chemicals were of reagent grade and used with out further purification. The Trost ligand was prepared as described in the literature.[9,18]

Ethyl 3-benzyloxy-4-methyl-1H-pyrrole-2-carboxylate (4):

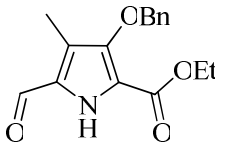


To a stirred solution of hydroxypyrrole **3** (12 g, 70.9 mmol) in dry DMF, K_2CO_3 (9.8 g, 71 mmol) was added followed by benzylchloride (8.98 g, 70.9 mmol). The suspension was stirred for 14 h at 70ºC and 4 h at 110ºC. Then 820 mg (6.47 mmol) of benzylchloride was added and the solution was heated for another 1 h at the same temp. The reaction mixture was allowed to cool down to rt, and poured into 1L of water. The aqueous layer was extracted with ethyl acetate (3 x 150 mL). Then the combined organic layers were washed with 10% of aqueous Na_2CO_3 (100 mL), water (2 x 100 mL) and dried over $MgSO_4$. The solvent was removed in vacuum to get the oily product which was solidified by addition of PE. The solid was recrystallized from MeOH to afford 9.93 g (54%) of compound **4**. m.p. 78-83ºC.

^1H NMR : δ = 1.35 (t, *J* = 7.14 Hz, 3 H), 1.91 (s, 3 H), 4.35 (q, *J* = 7.14 Hz, 2 H), 5.07 (s, 2 H), 6.57 (m, 1 H), 7.27-7.50 (m, 5 H), 8.45 (bs, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 8.3 (+), 14.3 (+), 59.0 (-), 75.4 (-), 110.5 (C_{quat}), 111.4 (C_{quat}), 120.3 (+), 127.7 (+), 128.0 (+), 128.0 (+), 137.7 (C_{quat}), 149.1 (C_{quat}), 159.6 (C_{quat}). MS (70 eV): *m/z* (%)=

259 (48) [M^+], 186 (14) [M^+-$C_3H_5O_2$], 91 (100) [$C_7H_7^+$]. IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3298, 2974, 2862, 1660, 1466, 1411, 1288. Anal. calcd. For $C_{15}H_{17}NO_3$ (259.31): C 69.48, H 6.61, N 5.40, found C 69.26, H 6.27, N 5.34.

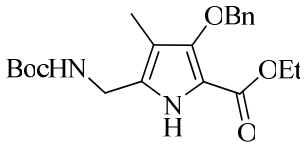
3-Benzyloxy-5-formyl-4-methyl-1H-pyrrole-2-carboxylic acid (**5**):



A solution of compound **4** (7.43 g, 28.7 mmol) in 75 mL of 1,2-dichloroethane was added drop wise to an ice cold solution of DMF (2.3 g, 31.5 mmol) in 75 mL of 1,2-dichloroethane containing $POCl_3$ (4.83 g, 31.5 mmol). After stirring at room temp. for 1 h the mixture was heated to reflux for 2 h, then cooled to room temp., 50 mL of EtOAc and 100 mL of H_2O were added and the organic layer was separated. The aqueous layer was washed with EtOAc (2 x 100 mL) and the combined organic layer were washed with 10% aqueous Na_2CO_3 (5 x 150 mL) and dried over $MgSO_4$. Evaporation of the solvent gave 7.85 g crude product which was purified by CC on silica gel (PE : EtOAc, 70 : 30; R_f = 0.43) Yield: 7.60 g (92%) of **3**, m.p.= 81-83ºC.

^{1}H NMR: δ = 1.38 (t, *J* = 7.14 Hz, 3 H), 2.12 (s, 3 H), 4.38 (q, *J* = 7.14 Hz, 2 H), 5.06 (s, 2 H), 7.30-7.47 (m, 5 H), 9.25 (bs, 1 H), 9.71 (bs, 1 H). ^{13}C NMR: δ = 6.8 (+), 14.4 (+), 61.2 (-), 77.1 (-), 117.8 (C_{quat}), 123.1 (C_{quat}), 127.7 (C_{quat}), 128.3 (+), 128.5 (+), 128.5 (+), 137.0 (C_{quat}), 148.7 (C_{quat}), 159.6 (C_{quat}), 179.1 (+). MS (70 eV): *m/z* (%)= 287 (22) [M^+], 91 (100) [$C_7H_7^+$]. IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3258, 2938, 2817, 169, 1672, 1555, 1507, 1487, 1377, 1280. Anal. calcd. For $C_{16}H_{17}NO_4$ (287.32): C 66.89, H 5.96, N 4.88, found C 66.79, H 5.95, N 4.87.

Ethyl 3-benzyloxy-5-(*tert*-butoxycarbonyl amino-methyl)-4-methyl-1H-pyrrole-2-carboxylate (**6**):

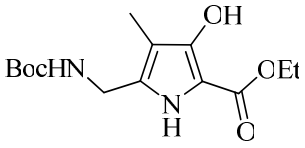


A mixture of *tert*-butylcarbamate (554 mg, 4.73 mmol), 1.9 mL of THF, 2 mL of H_2O, sodium *p*-toluene sulfinate (843 mg, 4.73 mmol), aldehyde **5** (1 g, 4.73 mmol) and 1.18

mL of formic acid were stirred until it became homogeneous and stirred for 6 days at room temp. The solid product was filtered off with suction, washed successively with water, PE and dried over P_2O_5 to give 2.02 g of a tosylated intermediate**,** which was used for the next step without further purification. The compound (522 mg) was added portion wise to a suspension of $NaBH_4$ (72 mg, 1.92 mmol) in 5 mL of THF while the mixture was ice cooled. Stirring was continued for 15 min with ice cooling and 2 h at room temp. The mixture was ice cooled again, quenched with 1 mL of sat. aqueous NH_4Cl, stirring was continued for 30 min, the organic layer was separated and the aqueous layer was extracted with 15 mL of CH_2Cl_2. The combined layers was dried over $MgSO_4$ and evaporated. The crude product was purified by CC on silica gel ($CHCl_3$: acetone 95:5 to 90:10; R_f (90:10) = 0.68) to give 232 mg (59%) of compound **6** m.p. compound **6**: 112.5-113ºC;

^{1}H NMR: δ = 1.34 (t, J = 7.14 Hz), 1.46 (s, 9 H), 1.86 (s, 3 H), 4.16 (m, 2 H), 4.32 (q, J = 7.14 Hz, 2H), 4.98 (bs, 1 H), 5.04 (s, 2 H), 7.27-7.49 (m, 5 H), 9.08 (bs, 1 H). ^{13}C NMR: δ = 7.2 (+), 14.5 (+), 28.4 (+), 35.9 (-), 60.1 (-), 76.7 (-), 80.1 (C_{quat}), 110.4 (C_{quat}), 110.7 (C_{quat}), 127.9 (+), 128.2 (+), 128.3 (+), 129.5 (C_{quat}), 137.8 (C_{quat}), 149.7 (C_{quat}), 156.6 (C_{quat}), 160.4 (C_{quat}). IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3357, 3282, 2980, 2934, 1687, 1665, 1531, 1461, 1294, 1171, 1027. Anal. calcd. For $C_{21}H_{28}N_2O_5$ (388.47) : C 64.93, H7.27, N 7.21, found C 64.74, H 7.64, N 7.00.

Ethyl 5-(tert-butoxycarbonylamino-methyl)-3-hydroxy-4-methyl-1H-pyrrole-2-carboxylate (**7**)**:**

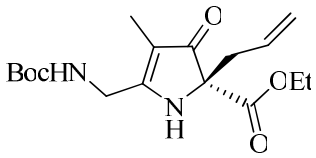


To a solution of compound **6** (100 mg, 257µmol) in EtOAc (3 mL), 10 mg of Pd-C (10% Pd) was added and the mixture was transferred to an autoclave. The mixture was stirred for 48 h under H_2 (10 bar) at room temp. The solution was filtered through celite. The solvent was evaporated in vacuum to give compound **7** (76.7 mg, 257µmol, quant.), m.p. 102-103ºC.

^{1}H NMR: δ = 1.34 (t, ^3J =7.14 Hz, 3 H), 1.46 (s, 9 H), 1.94 (s, 3 H), 4.15 (m, 2 H), 4.31 (q, ^3J = 7.14 Hz, 2 H), 4.89 (bs, 1 H), 7.69 (bs, 1 H), 8.47 (bs, 1 H). ^{13}C NMR: δ = 6.5

(+), 14.6 (+), 28.3 (+), 59.9 (-), 77.2 (C_{quat}), 80.3 (C_{quat}), 104.2 (C_{quat}), 104.6 (C_{quat}), 131.2 (C_{quat}), 152.7 (C_{quat}), 156.7 (C_{quat}). IR (KBr) : $\tilde{\nu}$ (cm^{-1}) = 3354, 3281, 2972, 2929, 1675, 1536, 1482, 1293, 1247. MS (ESI, CH_2Cl_2/MeOH + 10 mmol/1 NH_4OAc): m/z (%) = 299 (100) [$M+H^+$], 243 (13) [$M+H^+-C_4H_8$]. Anal. calcd. For $C_{14}H_{22}N_2O_5$ (298.34): C 56.36, H 7.43, N 9.39, found C 56.17, H 7.78, N 9.06.

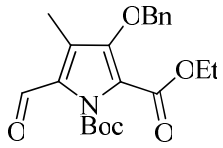
Ethyl 2-allyl-5-(tert-butoxycarbonylamino-methyl)-4-methyl-3-oxo-2,3-dihydro-1H-pyrrole-2-carboxylate (**8**):



To a flask containing a solution of compound **7** (2 g, 6.5 mmol) in 25 ml of dry CH_3CN, KO^tBu (0.73 g, 6.5 mmol) was added under dinitrogen. The mixture was stirred for 15 min at 0ºC. Meanwhile, the palladium complex (η^3-$C_3H_5PdCl)_2$ (36.5 mg, 100 µmol) and (*R, R*)-Trost ligand (69.2 mg, 100 µmol) were dissolved in dry CH_3CN and stirred for 15 min at rt before ally acetate (2.10 mL, 19.54 mmol) was added and stirring was continued at room temp. for additional 5 min. The catalyst solution was cooled to 0ºC before syringed into the enolate solution at 0ºC. The mixture was stirred for 1 d. The reaction was quenched with sat. aqueous NH_4Cl (10 mL) and the mixture was stirred vigorously for 10 min. Water (20 mL) was added to dissolve the precipitates. Extraction with ether (3 x 30 mL), drying of the organic phase ($MgSO_4$) and removal of the solvent in vacuum gave the crude product which was purified by CC on silica gel (PE : EtOAc; 1 : 1; R_f = 0.32) to give 768 mg of **8** as a colorless oil in 35% yield.

^{1}H NMR: δ = 1.27 (m, 3 H), 1.46 (s, 9 H), 1.66 (s, 3 H), 2.43 (m, 1 H), 2.93 (m, 1H), 4.16 (m, 1 H), 4.19 (m, 2 H), 4.24 (m, 1 H), 4.98 (m, 1 H), 5.10 (m, 1 H), 5.15 (m, 1 H), 5.67 (m, 1 H), 5.81 (m, 1 H). ^{13}C NMR: δ = 6.0 (+), 14.2 (+), 28.3 (+), 38.0 (-), 39.9 (-), 62.4 (-), 72.6 (C_{quat}), 105.5 (C_{quat}), 119.8 (-), 131.6 (+), 156.4 (C_{quat}), 167.4 (C_{quat}), 173.7 (C_{quat}), 196.1 (C_{quat}). IR (NaCl): $\tilde{\nu}$ (cm^{-1}) = 3327, 2983, 2933, 1772, 1729. MS (ESI, CH_2Cl_2/MeOH + 10 mmol/1 NH_4OAc): m/z (%) = 339.1 (100) [$M+H^+$], 283.0 (15) [$M+H^+-C_4H_8$].

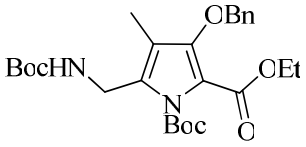
1-*tert*-Butyl-2-ethyl 3-benzyloxy-5-formyl-4-methyl-pyrrole-1,2-dicarboxylate (9) :



To a solution of compound **5** (5 g, 17.42 mmol) in dry CH_2Cl_2 (100 mL) at room temp. DMAP (2.2 g, 18.0 mmol) was added and the mixture was stirred for 10 min under nitrogen. $(Boc)_2O$ (3.93 g, 18.0 mmol) was added and the mixture was stirred for another 30 min. The solution was washed with water (4 x 100 mL) and dried over $MgSO_4$. The solvent was evaporated in vacuum and the crude product was purified by CC on silica gel (PE: EtOAc; 2:1; R_f = 0.60; 1:4, EtOAc : PE) to give 6.7 g of **9** (quantitative yield) as a colorless oil.

^{1}H NMR: δ = 1.35 (3 H, t, *J* = 7.14 Hz), 1.69 (s, 9 H), 2.20 (s, 3 H,), 4.35 (q, *J* = 7.14 Hz, 2 H), 5.00 (s, 2 H), 7.27-7.50 (m, 5 H), 10.05 (s, 1 H). ^{13}C NMR: δ = 8.3 (+), 14.2 (+),27.5 (+), 61.6 (-), 77.4 (-) , 86.4 (C_{quat}), 118.9 (C_{quat}), 125.1 (C_{quat}), 128.3 (+), 128.4 (+), 128.6 (+), 136.60 (+), 148.23 (C_{quat}), 148.81 (C_{quat}), 160.05 (C_{quat}), 181.55 (C_{quat}). IR (NaCl): $\tilde{\nu}$ (cm^{-1}) = 3444, 3145, 3005, 2977, 2933, 2875, 2200, 1729, 1754, 1603, 1500, 1462, 1432, 1389, MS (ESI, CH_2Cl_2/MeOH + 10 mmol/1 NH_4OAc) : m/z (%) = 388.2 (95) [M+H$^+$], 288.1 (100) [M+H$^+$-C_4H_8].– Anal. calcd. For $C_{21}H_{25}NO_6$ (387.44) : C 65.10, H 6.50, N 3.62, found C 64.92, H 6.57, N 3.52

1-*tert*-Butyl-2-ethyl-3-benzyloxy-5-(tert-butoxycarbonylamino-methyl)-4-methyl-pyrrole-1,2-dicarboxylate (**10**):



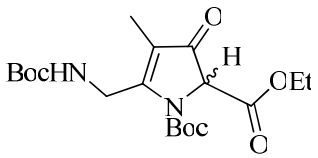
A mixture of *tert*-butylcarbamate (302 mg, 2.58 mmol), 1.9 mL of THF, 2 mL of H_2O, sodium *p*-toluene sulfinate (459.8 mg, 2.58 mmol), aldehyde **9** (1 g, 2.58 mmol) and 1.18 mL of formic acid were stirred until a homogeneous mixture was obtained, which was stirred for 2 days at room temp. The solid product was filtered off with suction, washed successively with water, PE and dried over P_2O_5 to give 2.02 g of 1-*tert*-butyl-2-ethyl-3-benzyloxy-5-[*tert*-butoxycarbonylamino-(toluene-4-sulfinyloxy)-methyl]-4-

methyl pyrrole-1,2-dicarboxylate, which was used for the next step without further purification.

To a suspension of $NaBH_4$ (72 mg, 1.92 mmol) in 5 mL THF 1-*tert*-butyl-2-ethyl-3-benzyloxy-5-[*tert*-butoxycarbonylamino-(toluene-4-sulfinyloxy)-methyl]-4-methyl-pyrrole-1,2-dicarboxylate (522 mg) was added portion wise while the mixture was ice cooled. Stirring was continued for 15 min with ice cooling and 2 h at room temp. The mixture was ice cooled again, quenched with 1 mL of sat. aqueous NH_4Cl, stirring was continued for 30 min, the organic layer was separated and the aqueous layer was extracted with 15 mL of CH_2Cl_2. The combined layers was dried over $MgSO_4$ and evaporated. The crude product was purified by CC on silica gel (EtOAc: PE; 1:4, R_f = 0.59) to give 232 mg (55%) of compound **10**, which was recrystallyzed from ether, m.p. = 103-105ºC.

^{1}H NMR: δ = 1.34 (t, J = 7.14 Hz, 3H), 1.47 (s, 9 H), 1.63 (s, 9H), 2.06 (s, 3 H), 4.25 (m, 4H), 5.05 (s, 2 H), 5.51 (bs, 1 H), 7.27-7.49 (m, 5 H). ^{13}C NMR: δ = 7.6 (+), 14.6 (+), 15.3 (+), 27.6 (+),28.4 (+), 35.1 (-), 60.8 (-), 60.8 (+), 77.1 (-), 85.3 (C_{quat}), 114.1 (C_{quat}), 115.3 (C_{quat}), 128.1 (+), 128.1 (+), 128.4 (+), 132.1 (+), 137.6 (+), 149.6 (C_{quat}), 151.6 (C_{qart}), 155.6 (C_{quat}), 160.7 (C_{quat}). MS (ESI, CH_2Cl_2/MeOH + 10 mmol/1 NH_4OAc): m/z (%) = 489.3 (100) [$M+H^+$], 433.1 (10) [$M+H^+-C_4H_8$] , 389.2 (20) [$M+H^+-2C_4H_8$]. IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3448, 3245, 3035, 2977, 2933, 2875, 2200, 1739, 1714, 1603, 1500, 1462, 1432, 1389, 1336, 1302, 1238. Anal. calcd. For $C_{26}H_{36}N_2O_7$ (488.59) : C 63.92, H 7.43, N 5.73, found C 63.83, H 7.71, N 5.64.

1-*tert*-Butyl-2-ethyl-5-(tert-butoxycarbonylaminomethy)-4-methyl-3-oxo-2,3-dihydro-pyrrole-1,2-dicarboxylate (**11**)**:**



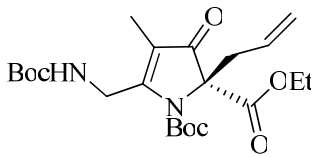
Compound **10** (2 g, 4.1 mmol) was dissolved in 2 mL of $CHCl_3$ and 10 mL of MeOH. Pd/C (200 mg, 10 % Pd) was added and the mixture was transferred into an autoclave. The mixture was stirred for 2 h under H_2 (8 bar) at room temp. The solution was filtered through celite and the solvent was evaporated in vacuum to give the crude product,

which was purified by CC on silica gel (PE : EtOAc, 4 : 1; R_f = 0.32 (1:4 , EtOAc: PE) to give 1.2 g (75 %) of compound **11** as a colorless oil. At room temperature the compound shows slow decomposition; refrigerate.

^{1}H NMR: δ = 1.34 (t, ^3J =7.14 Hz, 3 H), 1.43 (s, 9 H), 1.53 (s, 9 H), 1.86 (s, 3 H), 4.31 (q, ^3J = 7.14 Hz, 2 H), 4.54 (m, 2 H), 4.79 (s, 1 H), 5.56(bs, 1 H). ^{13}C NMR: δ = 6.6 (+), 14.2 (+), 28.0 (+), 28.4 (+), 36.5 (-), 62.0 (-), 67.0 (+), 79.3 (C_{quat}), 83.7 (C_{quat}), 117.7 (C_{quat}), 149.2 (C_{quat}), 155.5 (C_{quat}), 164.1 (C_{quat}), 165.5 (C_{quat}), 192.3 (C_{quat}). IR (NaCl): $\tilde{\nu}$ (cm^{-1}) = 3453, 3412, 3101, 2973, 2943, 1763, 1724, 1698, 1623, 1489, 1367.

MS (ESI, CH_2Cl_2/MeOH + 10 mmol/1 NH_4OAc): *m/z* (%) = 399 (100) [M+H$^+$], 343.1 (17) [M+H$^+$-C_4H_8]. Anal. calcd. For $C_{19}H_{30}N_2O_7$ (398.46) : C 57.27, H 7.59, N 7.03, found C 55.28, H 7.31, N 6.65.

1-*tert*-Butyl-2-ethyl-2-allyl-5-(*tert*-butoxycarbonylamino-methy)-4-methyl-3-oxo-2,3-dihydro-pyrrole-1,2-dicarboxylate (**12**):

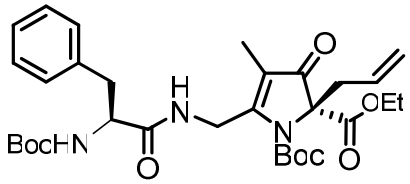


To a flask containing a solution of compound **11** (0.3 g, 0.8 mmol) in 15 mL of dry CH_3CN, KO^{t}Bu (0.09 g, 0.8 mmol) was added under nitrogen. The mixture was stirred for 15 min at -22ºC. Meanwhile the palladium catalyst (η^3-$C_3H_5PdCl)_2$ (27.6 mg, 75 μmol) and (*R*,*R*)-Trost ligand (52.2 mg, 75 μmol) were dissolved in 5 mL dry CH_3CN and stirred for 15 min at rt before allyl acetate (0.4 mL, 3.8 mmol) was added. Stirring was continued at rt for additional 5 min. The catalyst solution was cooled to -22ºC before syringed into the enolate solution at -22ºC. The resulting mixture was stirred for 2.5 h at -22ºC. The reaction was quenched with sat. aq NH_4Cl (5 mL) and the mixture was stirred vigorously for 10 min. Water (10 mL) was then added to dissolve the formed precipitates. Extraction with ether (3 x 15 mL), drying of the organic phase ($MgSO_4$) and removal of the solvent in vacuum gave the crude product, which was purified by CC on silica gel (PE: EtOAc; 1:4; R_f = 0.37) to give 275 mg (87%) of **12** as colorless oil. $[\alpha]^D$ = +143.8º (c = 0.2, $CHCl_3$).

^{1}H NMR: δ = 1.27 (m, ^{3}J= 7.14 Hz, 3 H), 1.43 (s, 9 H), 1.49 (s, 9H), 1.66 (s, 3 H), 3.05 (d, 2 H), 4.16 (q, ^{3}J=7.14 Hz, 2 H), 4.36-4.54 (m, 2 H), 4.96-5.10 (m, 2 H), 5.23-5.37

(m, 1 H), 5.50-5.60 (bs, 1 H). ^{13}C NMR: δ = 6.0 (+), 14.2 (+), 28.3 (+), 38.0 (-), 39.9 (-), 62.4 (-), 72.6 (C_{quat}), 105.5 (C_{quat}), 119.8 (-), 131.6 (+), 156.4 (C_{quat}), 167.4 (C_{quat}), 173.7 (C_{quat}), 196.1 (C_{quat}). IR (NaCl): $\tilde{\nu}$ (cm^{-1}) = 3454, 3402, 3081, 2980, 2933, 1753, 1716, 1698, 1622, 1489, 1367, 1285, 1246, 1166, 1115, 1068. MS (ESI, CH_2Cl_2/MeOH + 10 mmol/1 NH_4OAc) : *m/z* (%) = 339.1 (100) [$M+H^+$], 283.0 (15) [$M+H^+-C_4H_8$]. Anal. calcd. For $C_{22}H_{34}N_2O_7$ (438.53) : C 60.26, H 7.82, N 6.39, found C 59.71, H 7.64, N 6.09.

2-Allyl-5-[(2-*tert*-butoxycarbonylamino-3-phenyl-propinoylamino)-methyl]-4-methyl-3-oxo-2,3-dihydro-pyrrole-1,2-dicarboxylicacid-1-*tert*-butyl ester-2-ethyl ester (13):



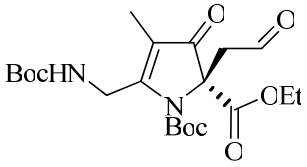
Compound **12** (100 mg, 0.25 mmol) was dissolved in CH_2Cl_2 (4 mL) in which HCl-saturated ether (4 mL) was added and the mixture was stirred at rt overnight. The resulting ammonium salt (90 mg, 0.24 mmol) was dissolved in a solution of *N*-Boc phenylalanine (82.7 mg, 0.312 mmol), EDC (60 μL, 0.312 mmol), HOBT (42.1 mg, 0.312 mg), and DIPA (o.09 mL, 0.528 mmol) in 5 mL of CH_2Cl_2 and stirred for 4 h at room temp. Then the reaction mixture was washed with water (2 x 5 mL), 5% aqueous $KHSO_4$ (5mL), and 2 mL of saturated aqueous $NaHCO_3$. The resulting solution was dried over $MgSO_4$, and the solvent was evaporated to give compound **13** as a white solid in 52% yield. $[\alpha]^D$ = -110.3º (c = 0.007, $CHCl_3$), m.p. = 58-60ºC.

^{1}H NMR: δ = 1.25 (t, ^3J =7.14 Hz, 3 H), 1.43 (s, 9 H), 1.53 (s, 9 H), 1.86 (s, 3 H), 2.85-3.14 (m, 4H), 4.19 (q, ^3J = 7.14 Hz, 2 H), 4.29-4.51 (m, 2H), 4.61-4.72 (m, 1H), 4.75-5.10 (m, 3H), 5.16-5.27 (m, 1H), 6.90 (bs, 1H), 7.13-7.37 (m, 5H). ^{13}C NMR: δ = 6.6 (+), 14.1 (+), 28.1 (+), 28.2 (+),35.3 (-), 38.3(-), 38.8 (-),55.5 (+), 62.4 (-), 73.7 (C_{quat}), 84.0 (C_{quat}), 83.7 (C_{quat}), 117.7 (C_{quat}), 119.9 (-), 120.0 (+), 128.6 (+), 129.4 (+), 129.8 (+), 136.4 (C_{quat}),.149.2 (C_{quat}), 164.7 (C_{quat}), 165.5 (C_{quat}), 170.7(C_{quat}), 195.6 (C_{quat}).

IR (KBr): $\tilde{\nu}$ (cm^{-1}) = 3424, 3365, 2978, 2933, 2872, 2362, 2199, 1944, 1753, 1702, 1620, 1498, 1454, 1367, 1280. MS (ESI, CH_2Cl_2/MeOH + 10 mmol/1 NH_4OAc): *m/z* (%) = 586.5 (100) [$M+H^+$], 530.5 (21) [$M+H^+-C_4H_8$], 630.6 (25) [$M+NH_4^+$]. Anal.

calcd. For $C_{31}H_{43}N_3O_8$ (585.70): C 63.57, H 7.40, N 7.17, found C 63.80, H 7.21, N 7.54

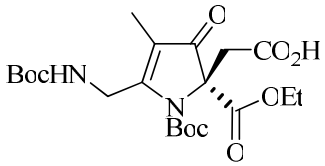
1-*tert*-butyl-2-ethyl-5-(*tert*-butoxycarbonylaminomethyl)-4-methyl-3-oxo-2-(-2-oxo-ethyl)-2,3-dihydro-pyrrole-1,2-dicarboxylate (**14**):



Compound **12** (200 mg, 0.46 mmol) was dissolved in THF: H_2O (4: 1, 12 mL). This solution was stirred under N_2 and potassium osmate (VI)-dihydrate (20 mg) was added. The reaction turned dark brown. After 5 min $NaIO_4$ (312 mg) was added in three batches over a 10 min period. The reaction turned light green, and stirring was continued for 5 h. The reaction was diluted with Et_2O (10 mL) and water (5 mL). The aqueous layer was extracted with Et_2O (2 x 12 mL). The combined ether layers were washed with brine (5mL), and dried over $MgSO_4$. Removal of solvent in vacuum gave a colourless oil, which was chromatographed on silica gel (EtOAc: PE 1 : 3; R_f = 0.4) to give 150 mg (75%) of compound **14**, as a colourless oil. . $[\alpha]^D$ = +17.7º (c = 0.007, $CHCl_3$).

^{1}H NMR: δ = 1.27 (t, ^3J = 7.14 Hz, 3 H), 1.43 (s, 9 H), 1.47 (s, 9 H), 1.90 (s, 3 H), 3.20-3.42 (m, 2 H), 4.15-4.23 (q, ^3J = 7.14 Hz, 2 H), 4.45-4.51(d, 2 H), 5.40-5.55 (bs, I H), 9.55(s, 1 H). ^{13}C NMR: δ = 6.0 (+), 14.2 (+), 28.3 (+), 38.0 (-), 39.9 (-), 62.4 (-), 72.6 (C_{quat}), 105.5 (C_{quat}), 119.8 (-), 131.6 (+), 156.4 (C_{quat}), 167.4 (C_{quat}), 173.7 (C_{quat}), 196.1 (C_{quat}). IR (NaCl): $\tilde{\nu}$ (cm^{-1}) = 3453, 2980, 2930, 2728, 2199, 2097, 1789, 1698, 1622, 1492, 1365, 1284, 1247, 1167. MS (ESI, CH_2Cl_2/MeOH + 10 mmol/1 NH_4OAc): *m/z* (%) = 441.2 (100) [$M+H^+$], 385.1 (30) [$M+H^+-C_4H_8$], 285.0 (30) [$M+H^+-2C_4H_8-CO_2$]. Anal. calcd. For $C_{21}H_{32}N_2O_8$ (440.50): C 57.26, H 7.32, N 6.36, found C 57.28, H 7.51, N 6.65

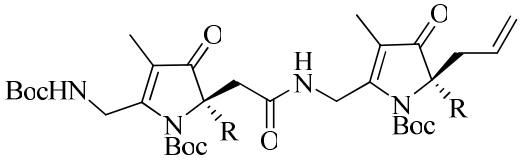
5-(*tert*-Butoxycarbonylaminomethyl)-2-carboxy methyl-4-methyl-3-oxo-2,3-dihydro-pyrrole-1,2-di carboxylic acid-1-tert-butyl ester-2-ethyl ester (15):



The aldehyde **14** (40 mg, 0.09 mmol) and sodium dihydrogenphosphate monohydrate (21 mg, 0.17 mmol) were dissolved in a 4:1 CH_3CN - H_2O solution (2.5 mL). H_2O_2 (1.5 mL) and sodium chlorite (32 mg, 0.35 mmol) were added and the resulting mixture was stirred for another 30 mins. Water (1 mL) was added and the aqueous layer was extracted with EtOAc (3 x 1 mL). The combined organic layers were washed with brine (1 mL), dried over $MgSO_4$ and concentrated to give compound **15** (35 mg, 85 % yield). R_f = 0.12 (1:1, EtOAc: P.E). $[\alpha]^D$ = +15.4º (c = 0.015, $CHCl_3$).

^{1}H NMR: δ = 1.27 (t, ^3J = 7.14 Hz, 3 H), 1.43 (s, 9 H), 1.47 (s, 9 H), 1.90 (s, 3 H), 3.20-3.42 (m, 2 H), 4.15-4.23 (q, ^3J = 7.14 Hz, 2 H), 4.45-4.51(d, 2 H), 5.40-5.55 (bs, I H), 9.55(s, 1 H). ^{13}C NMR: δ = 6.0 (+), 14.2 (+), 28.3 (+), 38.0 (-), 39.9 (-), 62.4 (-), 72.6 (C_{quat}), 105.5 (C_{quat}), 119.8 (-), 131.6 (+), 156.4 (C_{quat}), 167.4 (C_{quat}), 173.7 (C_{quat}), 196.1 (C_{quat}). IR (NaCl): $\tilde{\nu}$ (cm^{-1}) = 3435, 2982, 2913, 2728, 2200, 2097, 1698, 1650, 1622, 1492, 1365, 1284, 1247, 1167. MS (ESI, CH_2Cl_2/MeOH + 10 mmol/1 NH_4Ac): *m/z* (%) = 457.3 (100) [M+H$^+$], 474.3 (75) [M+NH_4^+]. HRMS ($C_{21}H_{32}N_2O_9$): calcd For $C_{21}H_{33}N_2O_9$ [MH$^+$] 457.2186, found 457.2188 ± .42

Compound 16:



Compound **12** (28 mg, 0.06 mmol) was dissolved in CH_2Cl_2 (2 mL), HCl-saturated ether (2 mL) was added and the reaction mixture was stirred at rt overnight. The resulting ammonium salt (24 mg, 0.06 mmol) was dissolved in a solution of compound **15** (30 mg, 0.065 mmol), EDC (0.01 mL, 0.065 mmol), HOBT (10.0 mg, 0.065 mmol), and DIPA (0.03 mL, 0.15 mmol) in 2 mL of CH_2Cl_2 and stirred for 4 h at room temp. The reaction mixture was washed with water (2x1 mL), 5% aqueous $KHSO_4$ (1 mL), and 1 mL of saturated aqueous $NaHCO_3$. The resulting solution was dried over $MgSO_4$ and the

solvent was evaporated to give a colourless oil which was chromatographed on silica gel (EtOAc: PE 1 : 3; R_f = 0.15) to give 12 mg (30%) of compound **16**, as a colorless oil.

^{1}H NMR: δ = 1.26 (m, 6 H), 1.45 (s, 9 H), 1.51 (s, 9H),1.54 (s, 9H), 1.80 (s, 3 H), 1.90 (s, 3 H), 3.05 (m, 2 H), 3.20 (m, 2 H), 4.18 (m, 4 H), 4.30 (dd, ^3J = 5.88 Hz, ^2J = 14.75 Hz., -C*H*H), 4.48 (m, 2H), 4.58 (dd, ^3J = 5.88 Hz, ^2J = 14.75 Hz., -CH*H*), 5.05-5.07 (m, 2 H), 5.23-5.26 (m, 1 H), 5.58 (bs, 1 H), 6.60 (bs, 1 H). ^{13}C NMR: δ = 6.5 (+), 6.7 (+), 14.3 (+), 14.2 (+), 28.3 (+), 28.4 (+), 29.0 (+), 34.9 (-), 36.7 (-), 38.2 (-), 40.6 (-), 62.2 (-), 62.6 (-), 71.8 (C_{quat}), 73.8 (C_{quat}), 79.5 (C_{quat}), 84.0 (C_{quat}), 117.5 (C_{quat}), 119.9 (-), 120.2 (C_{quat}), 129.5 (+), 129.7 (+), 148.9 (C_{quat}), 149.3 (C_{quat}), 155.5 (C_{quat}), 164.7 (C_{quat}), 165.3 (C_{quat}), 165.4 (C_{quat}), 166.0 (C_{quat}), 166.4 (C_{quat}), 195.0 (C_{quat}), 195.5 (C_{quat}). MS (ESI, CH_2Cl_2/MeOH + 10 mmol/1 NH_4OAc): *m/z* (%) = 777.6 (100) [$M+H^+$], 794 (20) [$M+NH_4$].

3.5. References and Notes

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Synthesis of 1, 4-Dipiperazino-Benzene Scaffolds as α-Helix Mimetics*

4.1. Introduction

The α-helix is one of the most common structural motifs in protein secondary structures. Over 40% of all residues in proteins exist in an α-helical geometry.[1] α-Helices are of particular importance for protein-protein, protein-DNA, and protein-RNA interactions.[2] However, to study such interactions with peptides is difficult, because they are flexible and proteolytically unstable. Therefore mimicking scaffolds[3] have been developed that project side-chain functionality with similar distance and angular relationships to those found in α-helices. The critical interactions are found along a 'face' of the helix involving side chains from the *i, i+3* or *i+4*, *i+7,* and *i+11* residues. These side chains take defined distances and angular relationships in α-helices.[4] Molecules that can predictably and selectively reproduce these projections are valuable tools in molecular biology and potential leads in drug discovery.[5] Advantages, if compared to peptides, are an improved stability, lower molecular weight, and in some case a better bioavailability. Kahne et al.[6] reported a pentasaccharide scaffold as an α-helix mimic presenting multiple charged groups that selectively bind the minor grove of DNA and not RNA. β-Peptides have been used by Gellman et al.[7] and Schepartz et al.[8] to mimic an α-helix. Recently, Hamilton and co-workers[9] have developed mimetics of the hydrophobic face of an α-helix using a terphenyl scaffold. The tris-*ortho*-substituted terphenyl can mimic the *i*, *i+4*, and *i+7* residues of the α-helix by adopting a staggered conformation that closely reproduces the angular orientation of the peripheral functionalities on the helical surface. Synthetic foldamers mimicking extended α-helices are accessible using benzoylurea oligomers.[10] Rebek et al. reported the synthesis of small libraries of low molecular weight α-helix mimetics having a pyridazine ring in the central position.[11]

We now describe the synthesis of a new class of inherently chiral α-helix mimetics consisting of a 1,4-disubstituted central benzene ring and two substituted piperazines[12] bearing hydrophobic side chains, with defined configuration. Inspired by Hamilton's terphenyl scaffolds, we sought for an improved synthetic accessibility, good water solubility and inherent chirality, while keeping dynamic and relative orientation of the key side chain functionalities. Figure 1 shows the structure of the calculated[13] most stable conformer of a 1,4-di-piperazino benzene and its relation to the α-helix structure.

* Manuscript in preparation

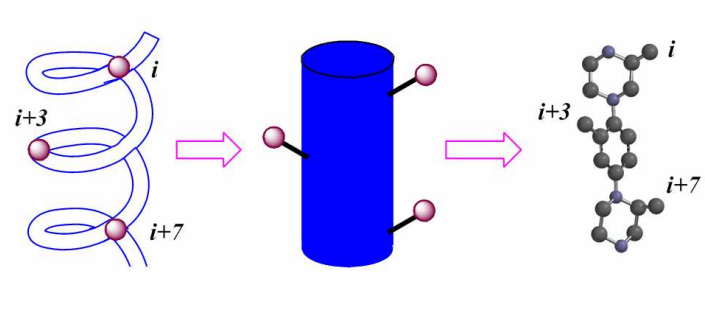
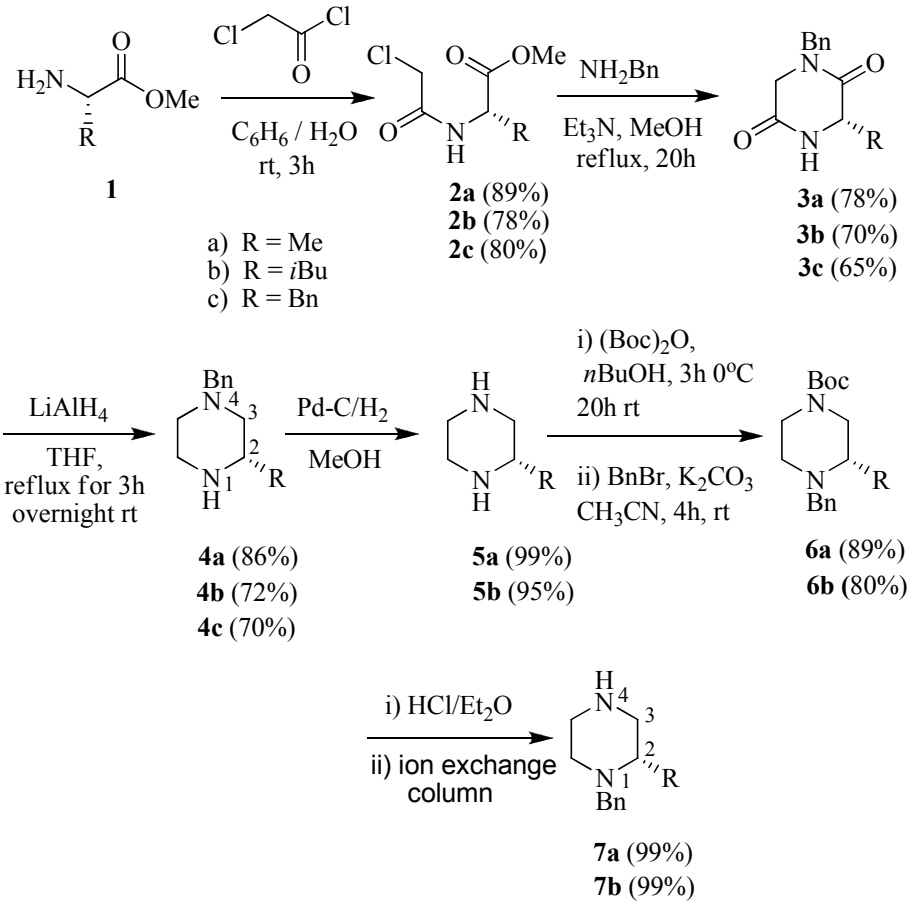


Figure 1. Residues in an α-helix and 1,4-di-piperazino benzene

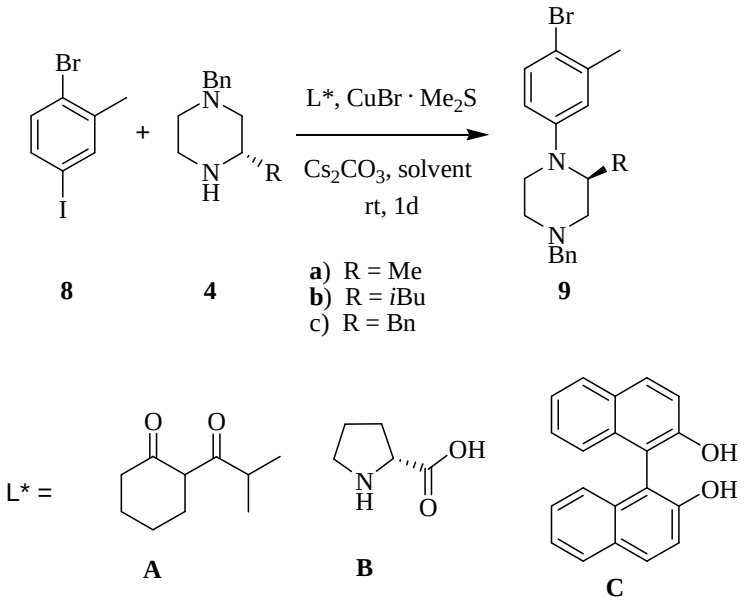
4.2. Results and discussion

We follow a previously reported route[14] to synthesize enantiomerically pure mono substituted piperazines (Scheme 1) starting from chiral amino acids. The amino esters **1** were treated with $ClCH_2COCl$ and $NaHCO_3$ in a mixture of water and benzene, which gave the products **2** in high purity and good yields. The crude products were reacted with benzylamine in methanol giving the key intermediate diketopiperazines **3** in good yield through a 1,5-cyclo condensation reaction.[15] The diketopiperazines **3** were reduced by $LiAlH_4$ to give mono-substituted piperazines **4** bearing a Bn protecting group on nitrogen atom 4. A series of deprotection and reprotection steps leads to piperazines **7**, which are Bn protected at nitrogen atom 1.



Scheme 1 Synthesis of protected chiral piperazines **4a-c** and **7a-b**

The synthesis of 1,4-dipiperazino benzene starts from 2-bromo-5-iodotoluene (**8**) and **(*S*)-**1-benzyl-3-alkylpiperazine (**4a-c**). The preferred substitution of the iodo-substituent is expected in transition metal catalyzed N-arylation reactions. Several ligands have been introduced to promote copper-catalyzed *N*-arylation of aliphatic secondary amines, most notably N,N-diethylsalicylamide,[16] amino acids,[17] and amino alcohols.[18] Wan and co-workers reported copper powder/*rac*-BINOL or (copper+CuI)/*rac*-BINOL as a catalytic system; but the N-arylation requires elevated temperatures of 90-125ºC.[19] Recently Buchwald and co-workers developed a highly selective room temperature copper-catalyzed N-aryl coupling reaction using CuI and a cyclic *β*-diketone as the catalytic system and Cs_2CO_3 as base.[20] Jiang and co-workers reported room temperature copper catalyzed C_{aryl}-N coupling using CuBr/ *rac*-BINOL as catalyst.[21] The number of reported examples of room temperature coupling reactions of aryl-iodides and ortho-substituted cyclic secondary amines is small. [22]



Ligand	Base	Solvent	R	Yield (%)
A	K_3PO_4	DMF	CH_3	10
A	K_3PO_4	DMSO	CH_3	7
A	Cs_2CO_3	DMF	CH_3	16
B	Cs_2CO_3	DMSO	CH_3	0
C (20%)	K_3PO_4	DMF	CH_3	30
C (20%)	Cs_2CO_3	DMF	CH_3	40
C (30%)	Cs_2CO_3	DMF	CH_3	60
C (30%)	Cs_2CO_3	DMF	*i*Bu	48
C (30%)	Cs_2CO_3	DMF	Bn	54

Table 1. Optimization of the catalytic condition for the copper-catalyzed C_{aryl}-N bond formation of 2-bromo-5-iodotoluene (**8**) and (*S*)-1-benzyl-3-alkylpiperazine (**4a-c**) to give 1,4-dipiperazino benzenes **9**

We used the inexpensive and readily available catalytic system consisting of CuBr, racemic BINOL (1,1´-binapthyl-2,2`-diol) and Cs_2CO_3 to achieve the formation of C_{aryl}-N (*ortho*-substituted piperazine) bonds at room temperature. The reaction conditions were optimized (Table 1) with (*S*)-1-benzyl-3-methylpiperazine (**4a**) and 2-bromo-5-iodotoluene (**8**). 2-Isobutyrylcyclohexanone, *L*-proline, and racemic BINOL as ligands were reacted in DMF or DMSO with 20 mol% CuBr and Cs_2CO_3 as the base. Racemic

BINOL (30 mol%) gave the highest yields and 90% of the racemic BINOL was recovered after the reaction; yields decease with increasing steric bulk of the alkyl side chain in the piperazine ring. The X-ray diffraction analysis of compound **9b** (Figure 2) reveals a chair conformation of the piperazine ring in the solid state which the *i*-Bu substituent in an axial position.

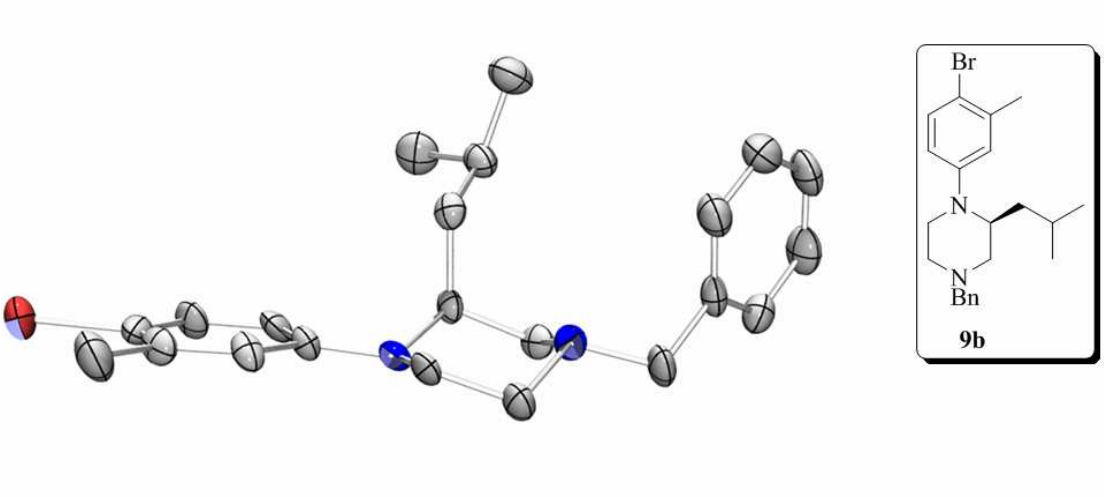
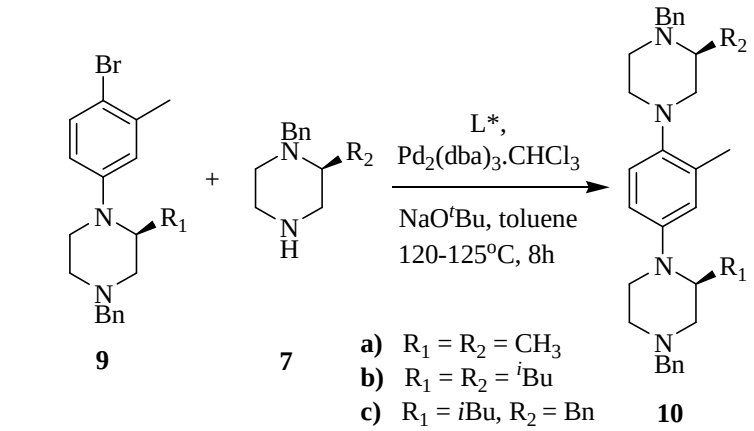
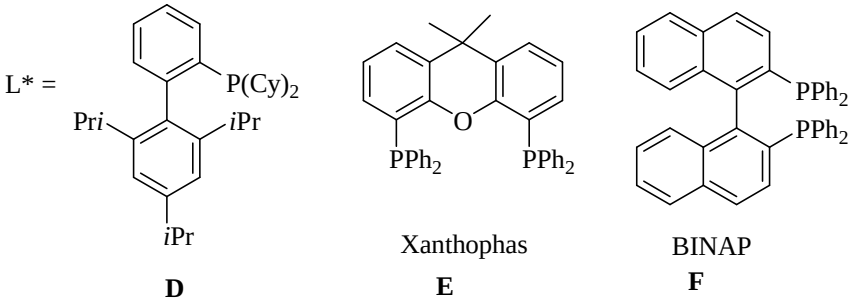


Figure 2. Structure of compound **9b** in the solid state determined by Röntgen analysis

The second C_{aryl}-N bond formation was accomplished by a palladium-catalyzed reaction (Table 2). Palladium-catalyzed amination of aryl halides has been shown to be a general method for the formation of aromatic carbon-nitrogen bonds.[23] More recently, Buchwald and co-workers[24] reported substituted and unsubstituted biaryl mono-phosphine ligands (**D**), which are very effective in C_{aryl}-N bond formation processes. We have tested the three ligands **D**, **E** and **F** for the formation of the second C_{aryl}-N bond in compounds **9**. In all cases, $Pd_2(dba)_3.CHCl_3$ / L* (**D/E/F**) was used as the catalyst, NaO^tBu as the base, and toluene as the solvent. Again, racemic-BINAP (**F**) gave the highest yield (up to 75%) at 125-128ºC for this reaction in our hands (Table 2).

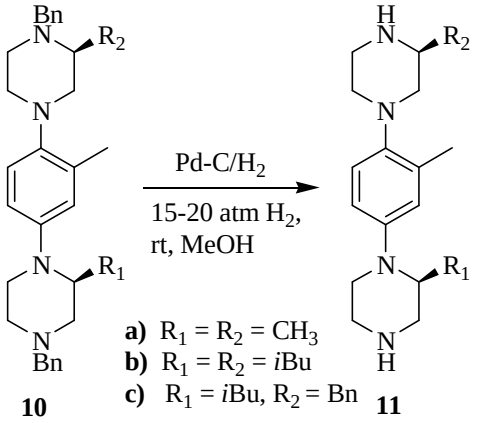




Ligand	R_1	R_2	Yield (%)
D	CH_3	CH_3	0
E	CH_3	CH_3	5
F	CH_3	CH_3	75
F	*i*Bu	*i*Bu	70
F	*i*Bu	Bn	72

Table 2. Optimization of the catalytic conditions for the palladium-catalyzed C_{aryl}-N bond formation of compounds **9a-c** and **(S)**-1-benzyl-2-alkylpiperazine (**7a-b**) giving compounds **10**

The dibenzyl protected compounds **10a-c** were deprotected by Pd-C/H_2 (Scheme 2) to afford compounds **11a-c** which show good water solubility.



Scheme 2. 1,4-Dipiperazino-benzenes **11**

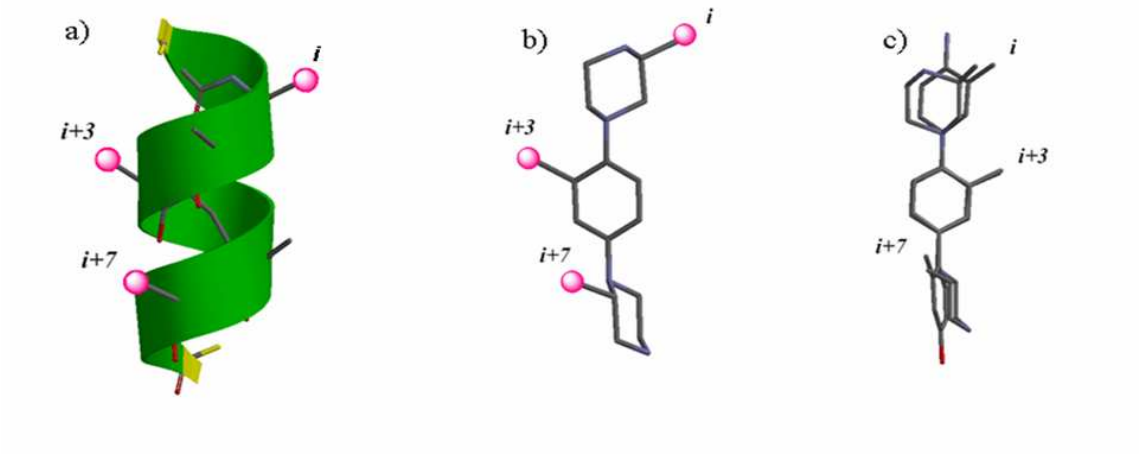


Figure 3. a) Schematic representation of an idealized ala α-helix with *i*, *i* + 3, and *i* + 7 substituents; b) structure of compound **11a** as HBr-salt in the solid state, determined by X-ray analysis; for clarity all H-atoms and Br-atoms were omitted; c) Superposition of the structure of compound **11a** with the structure of Hamilton´s methyl substituted terphenyl compound;[9a] both structures were determined by Röntgen structure analysis

The distance between the substituents [*i* to *i+3* = 5.55 Å, *i+3* to *i+7* = 6.22 Å, *i* to *i+7*= 8.89 Å] in key position were calculated from the X-ray diffraction structure (Figure 3b). The values are comparable with these found in an idealized alanine α-helix [*i* to *i+3* = 5.6 Å, *i+3* to *i+7* = 6.3 Å, *i* to *i+7*= 10.6 Å]. A comparison of the structure of compound **11a** with the reported structure of Hamilton´s methyl-substitued terphenyl compound,[9a] shows a striking similarity of arrangement of the methyl substituents.

4.3. Concentration dependence of the circular dichroism signal and NMR resonances

A circular dichroism (CD) spectra of compound **11b** was measured at 21° C between 200 and 300 nm in water (see supporting info for experimental details). The CD spectrum (Figure 4) shows a signal in the range of 245-255 nm arising from the aromatic chromophore in its chiral environment. The intensity of the CD signal depends on the concentration of **11b**: With increasing concentration the signal intensity decreases, which is interpreted as an increasing aggregation of the hydrophobic helix parts in the polar solvent.

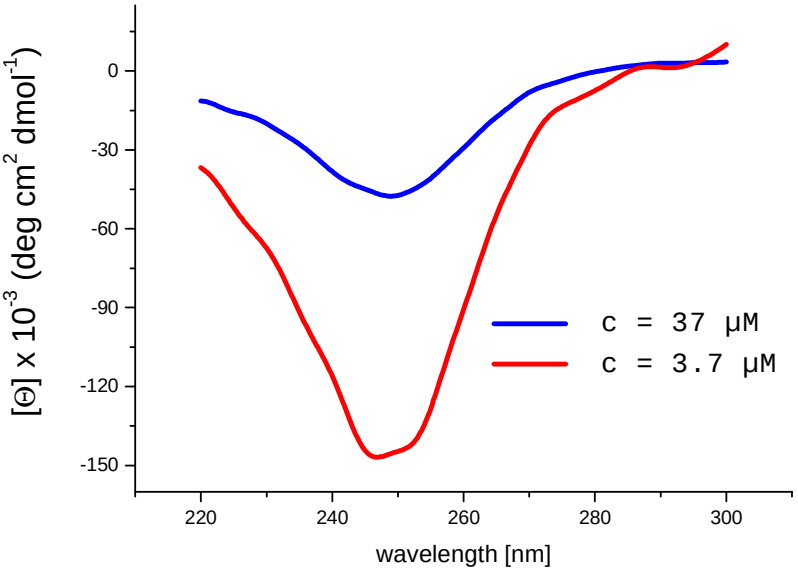


Figure 4. Concentration dependent CD spectrum of compound **11b**

Resonances of the ^{1}H-NMR spectrum of compound **11b** show also a dependence on the sample concentration. Figure 5 gives the resonance signals of the methyl protons of the isobutyl groups. The splitting pattern clearly changes with concentration of **11b**. This observation confirms the suggested aggregation of 1,4-dipiperazino benzene in aqueous solution at concentrations higher than approx. 10 µmol/L.

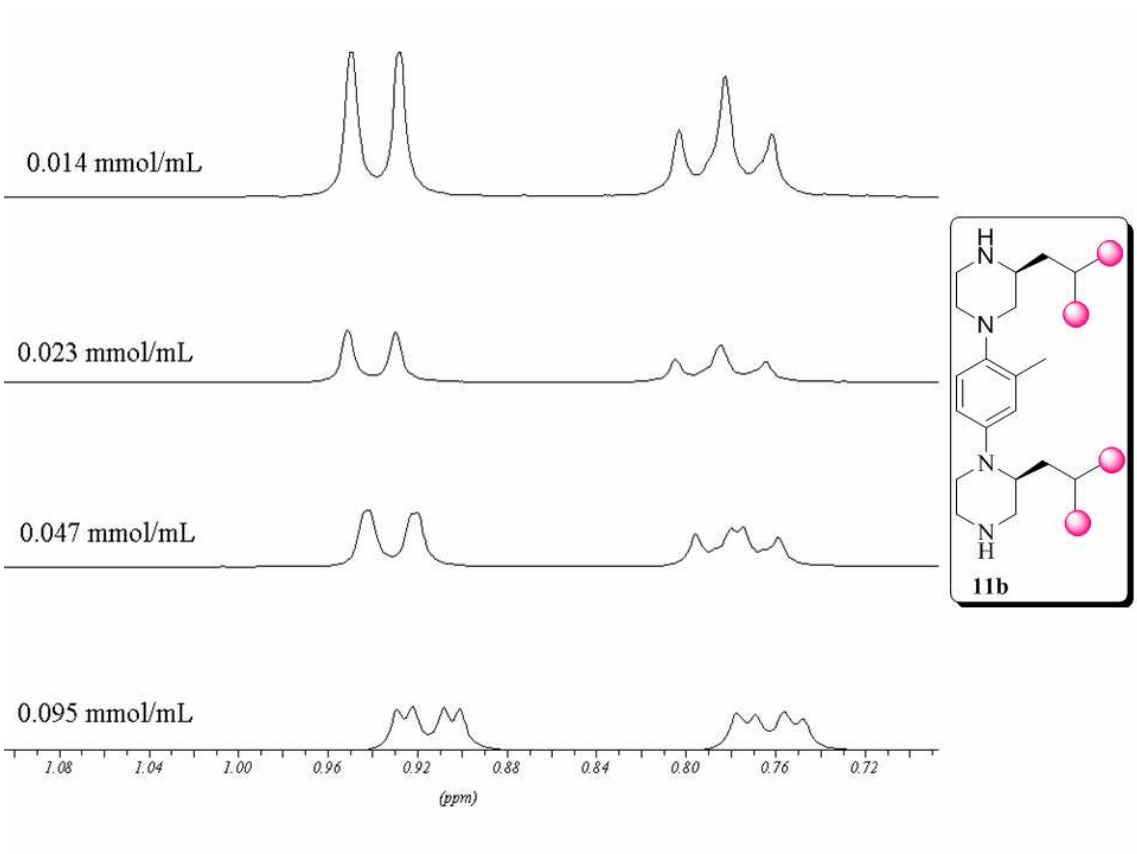


Figure 5. Concentration dependence of the NMR-resonance signals of the isobutyl methyl groups of compound **10b**.

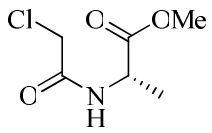
4.4. Conclusion

1,4-Dipiperazino benzenes have been prepared as a new class of inherently chiral α-helix structural mimetics. Protected piperazines as the key synthetic intermediates were synthezised from chiral amino acids. Subsequent copper- and palladium-catalyzed C_{arly}-N coupling reactions lead to the target products in good yields. Racemic BINAP proved to be the best ligand for both reactions. The X-ray structure analysis of the 1,4-dipiperazino benzenes reveals a suitable spatial arrangement of the key substituents to act as a structural mimetic for α-helical structures. The compounds start to aggregate in aqueous solution at concentrations exceeding approx. 10 μmol/L, as indicated by CD and NMR measurements. If compared to previously reported α-helix mimetics, 1,4-dipiperazino benzenes possess chiral centers, which determine the overall chirality of the compound. The CD signal of the central benzene chromophor shows this induction. 1,4-Dipiperazino benzenes allow now the investigation of the effect of the helix mimetic chirality on its protein binding ability. Studies in this direction are in progress.

4.5. Experimental section

General: Melting points were determined on a melting point apparatus and are uncorrected. Specific rotations were measured on a polarimeter using a 10 cm cell. NMR spectra were recorded in $CDCl_3$ at 300 MHz (^1H) or 75 MHz (^{13}C) unless stated otherwise. Structural assignments are based on DEPT and COSY experiments where applicable. The multiplicity of the carbon atoms are given as (+) = CH, CH_3 or (-) = CH_2 and (C_{quat}) for quaternary carbon atoms. Analytical TLC plates (silica gel 60 F_{254}) and silica gel 60 (70-230 or 230-400 mesh) for column chromatography (CC) were purchased from ACROS. Spots were visualized by UV light and/or staining with phosphomolybdate or ninhydrin, both in ethanol. DMF, toluene, and MeOH were dried by standard procedures and stored over molecular sieves or Na. PE means petrol ether with a boiling range of 70-90ºC. All other solvents and chemicals were of reagent grade and used without further purification.

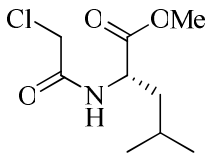
(*S*)-Methyl 2-(2-chloroacetamido)propanoate (2a):



To a suspension of L-alanine (26.7 g, 0.30 mol) in CH_3OH (200 mL) cooled in an ice-salt bath, $SOCl_2$ (87.5 mL, 1.2 mol) was added drop-wise while stirring. After the addition the resulting mixture was stirred for an additional 6h at rt. The clear solution was concentrated to dryness, and without any further purification, the solid was dissolved in water (120 mL) and cooled in ice-salt bath. To the solution, $NaHCO_3$ (60 g, 0.71 mol) was added in one portion, and then the solution of chloroacetyl chloride (23.8 mL, 0.3 mol) in benzene (100 mL) was added dropwise. After the addition, the reaction mixture was stirred for an additional 3h at rt. The aqueous layer was extracted twice with benzene (100 mL), and the combined organic phases were dried over anhydrous $MgSO_4$. Subsequent filtration and removal of organic solvent *in vacuo* gave a crude product (47.95 g, 89%), which was purified by column chromatography on silica gel (3:1, PE: EtOAc) to give 43.0g (81%) of product as a colorless oil.

^{1}HNMR ($CDCl_3$): δ = 1.45 (d, J = 7.13 Hz, 3H), 3.77 (s, 3H), 4.06 (s, 2H), 4.60 (m, 1H), 7.12 (b s, 1H).

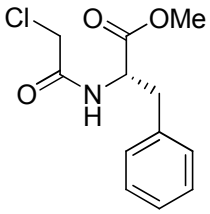
(*S*)-Methyl 2-(2-chloroacetamido)-4-methylpentanoate (2b):



The compound was prepared by the same procedure described above. Yield: 78%, colorless oil.

^{1}HNMR ($CDCl_3$): δ = 0.95 (d, J = 7.13 Hz, 6H), 1.57-1.78 (m, 3H), 3.77 (s, 3H), 4.06 (s, 2H), 4.60 (m, 1H), 7.01 (bs, 1H).

(*S*)-Methyl 2-(2-chloroacetamido)-3-phenylpropanoate (2c):

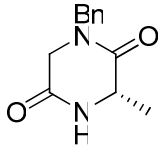


The compound was prepared by the same procedure described above. Yield: 80%, colorless oil.

^{1}HNMR ($CDCl_3$): δ = 3.13-3.18 (dd, J = 3.89 Hz, J = 3.89Hz, 2H), 3.77 (s, 3H), 4.01 (s, 2H), 4.83-4.91 (m, 1H), 6.94-7.02 (bs, 1H), 7.09-7.34 (m, 5H).

^{13}CNMR ($CDCl_3$): δ = 37.8 (-), 42.4 (-), 52.5 (+), 53.4 (+), 127.4 (+), 128.7 (+), 129.24 (+), 135.0 (+), 135.4 (+), 165.6 (C_{quat}), 171.3 (C_{quat}).

(*S*)-1-Benzyl-3-methylpiperazine-2, 5-dione (3a):

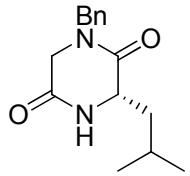


A solution of benzylamine (24.1 mL, 0.22 mol) in CH_3OH (180 mL) was added dropwise over 1.5 h to a solution of compound **2a** (32.8 g, 0.183 mol) and TEA (73.2

mL, 0.55 mol) in CH_3OH (180 mL) and refluxed for 20h, the pale yellow solution was cooled to rt and concentrated, and the residue was dissolved in 150 mL CH_2Cl_2. The organic phase was washed with 100 mL of 5% aqueous citric acid, 100 mL of saturated aqueous $NaHCO_3$, and 100 mL of brine, and dried over $MgSO_4$. Subsequent filtration and removal of organic solvent *in vacuo* gave a pale yellow solid, which was recrystallized from toluene to give 31.1 g (78%) of compound **3a** as a white solid. Mp 138-140ºC; $[\alpha]_D$ = -8.85º (c = 2, $CHCl_3$);

^{1}HNMR ($CDCl_3$): δ = 1.53 (d, J = 7.04 Hz, 3H), 3.83 (s, 2H), 4.16 (m, 1H), 4.60 (s, 2H), 7.23-7.39 (m, 5H).

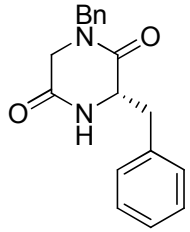
(*S*)-1-Benzyl-3-isobutylpiperazine-2, 5-dione (3b):



The compound was prepared by the same procedure described above. Yield: 70%, white crystalline solid.

^{1}HNMR ($CDCl_3$): δ = 0.96 (d, J = 6.31 Hz, 3H), 0.98 (d, J = 6.31 Hz, 3H), 1.57-1.86 (m, 3H), 3.83 (m, 2H), 4.16 (m, 1H), 4.63 (d, J = 14.82 Hz, 1H), 4.64 (d, J = 14.82Hz, 1H), 7.20-7.39 (m, 5H).

(*S*)-1, 3-Dibenzylpiperazine-2, 5-dione (3c):

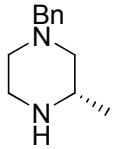


The compound was prepared by the same procedure described above. Yield: 65%, white crystalline solid.

^{1}HNMR ($CDCl_3$): δ = 2.89 (d, J = 17.59 Hz, 1H), 3.12 (d, J = 4.52 Hz, 1H), 3.15 (d, J = 4.52 Hz, 1H), 3.23 (d, J = 6.18 Hz, 1H), 3.25 (d, J = 6.18 Hz, 1H), 3.48 (d, J = 17.59 Hz, 1H), 4.40 (m, 1H), 4.60 (s, 2H), 7.13-7.39 (m, 10H).

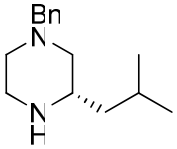
^{13}CNMR ($CDCl_3$): δ = 40.9 (-), 48.4 (-), 49.7 (-), 56.5 (+), 127.5 (+), 128.1 (+), 128.7 (+), 128.9 (+), 130.1 (+), 134.8 (C_{quat}), 134.9 (C_{quat}), 165.3 (C_{quat}), 166.3 (C_{quat}).
MS [CI-MS; NH_3] = 312.2 [M-NH_4^+] (100), 295.1 [M-H^+] (20).

(*S*)-1-Benzyl-3-methylpiperazine (4a):



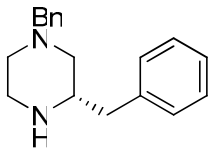
A solution of diketopiperazine, **3a** (11.5 mmol) in THF (25 mL) was added dropwise to the refluxing mixture of $LiAlH_4$ (52 mmol) in THF (50 mL). The mixture was refluxed for 3h, and then stirred overnight at rt. The mixture was quenched with saturated $MgSO_4$ solution, and the aluminate salts were filtered. The salts were extracted several times with ether. The combined organic layers were concentrated to afford the crude piperazine as oil. Yield: 86%.
^{1}HNMR ($CDCl_3$): δ = 1.00 (d, J = 6.20 Hz, 3H), 1.66 (m, 1H), 1.95-2.05 (m, 1H), 2.74-2.94 (m, 5H), 3.48 (s, 2H), 7.24-7.33 (m, 5H).

(*S*)-1-Benzyl-3-isobutylpiperazine (4b):



The compound was prepared by the same procedure described above. Yield: 72%, colorless oil, becomes solid on standing.
^{1}HNMR ($CDCl_3$): δ = 0.86 (d, J = 4.94 Hz, 3H), 0.88 (d, J = 4.94 Hz, 3H), 1.05-1.28 (m, 2H), 1.57-1.73 (m, 2H), 1.95-1.97 (dt, J = 4.12 Hz, J = 10.70 Hz, 1H), 2.70-2.98 (m, 5H), 3.50 (q, J = 7.96 Hz, 2H), 7.21-7.33 (m, 5H).
^{13}CNMR ($CDCl_3$): δ = 22.4 (+), 23.3 (+), 24.3 (+), 43.8 (-), 45.9 (-), 52.8 (+), 54.0 (-), 60.6 (-), 63.4 (-), 127.0 (+), 128.2 (+), 129.0 (+), 129.3 (+), 138.1 (C_{quat}). MS [CI-MS; NH_3] = 233.2 [M-H^+] (100).

(*S*)-1, 3-Dibenzylpiperazine (4c):



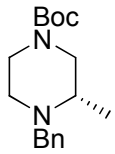
The compound was prepared by the same procedure described above. Yield: 70%, colorless oil, become solid upon standing.

^{1}HNMR ($CDCl_3$): δ = 2.89 (d, J = 17.59 Hz, 1H), 3.12 (d, J = 4.52 Hz, 1H), 3.15 (d, J = 4.52 Hz, 1H), 3.23 (d, J = 6.18 Hz, 1H), 3.25 (d, J = 6.18 Hz, 1H), 3.48 (d, J = 17.59 Hz, 1H), 4.40 (m, 1H), 4.60 (s, 2H), 7.13-7.39 (m, 10H).

^{13}CNMR ($CDCl_3$): δ = 40.9 (-), 48.4 (-), 49.7 (-), 56.5 (+), 127.5 (+), 128.1 (+), 128.7 (+), 128.9 (+), 130.1 (+), 134.8 (C_{quat}), 134.9 (C_{quat}), 165.3 (C_{quat}), 166.3 (C_{quat}).

MS [CI-MS; NH_3] = 312.2 [M-NH_4^+] (100), 295.1 [M-H^+] (20).

(*S*)-*tert*-Butyl 4-benzyl-3-methylpiperazine-1-caboxylate (6a):



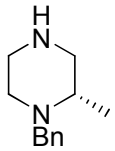
A mixture of compound **4a** (9.51 g, 0.05 mol), 10% palladium on carbon (1.2 g) and CH_3COOH (0.5 mL) in CH_3OH (100 mL) was stirred under 5 atm of H_2 at rt for 24h. The catalyst was removed by filtration and washed with CH_3OH. The combined filtrate was concentrated to afford **5a** as colorless solid, with 99% of yield.

Without any further purification the solid **5a** (49.9 mmol) was dissolved in 44 g 1-butanol (0.05 wt. % H_2O content), cooled to 0ºC. To this solution $(Boc)_2O$ (50 mmol) in 10 mL of 1-butanol was added dropwise. The reaction mixture was stirred for 2h at 0-5ºC and 12h at rt. 1-Butanol was removed by *vacuo* to afford crude oil which was dried in high vacuum overnight. The crude product was dissolved in 15 mL dry CH_3CN. Benzyl bromide (45 mmol) and K_2CO_3 (10g) were added, and the reaction mixture was stirred at room temperature for 4h. After consumption of all starting material, the reaction mixture was quenched by 50 mL of water, and the product was extracted with ethyl acetate (3x 30 mL). The organic phase was dried over $NaSO_4$ and the solvent was removed in *vacuo*. The product was purified by column chromatography, eluting with

petrol ether and ethyl acetate (4:1) to afford **6a** as colorless oil. Overall two steps yield was 89%.

^{1}HNMR ($CDCl_3$): δ = 1.13 (d, J = 6.31 Hz, 3H), 1.45 (s, 9H), 2.07 (m, 1H), 2.44(m, 1H), 2.61-2.67 (m, 1H), 2.78-2.95 (m, 1H), 3.02-3.21 (m, 2H), 3.16-3.80 (m, 2H), 7.23-7.36 (m, 5H).

(S)-1-Benzyl-2methylpiperazine (7a)

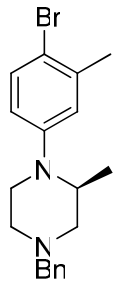


The compound **6a** (1g) was dissolved in 20 mL of CH_2Cl_2 and HCl saturated ether (10 mL) and reaction mixture was stirred until all the starting material consumed (checked by TLC). After completion of the reaction, solvent was removed in *vacuo* to afford the product as HCl-salt. Then the product was passed through strongly basic ion-exchange column to give pure product as light yellow oil quantitatively.

General Procedure for Cu (I) mediated C-N Coupling:

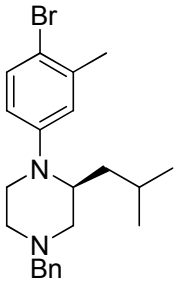
An oven dried schlenk flask was charged with CuBr.Me_2S (41 mg, 0.2 mmol) and then it was preheated at 50-60ºC under high vacuum for the removal of complexed Me_2S. It was backfilled with nitrogen, then 1,1'-binaphthyl-2,2'-diol (57 mg, 0.2 mmol), Cs_2CO_3 (424 mg, 2 mmol), and amine (1.5 mmol) were added to the flask. Aryl halide (1 mmol) liquid and DMF (1 mL) were added to the flask under nitrogen atmosphere. The mixture was allowed to stir under nitrogen atmosphere at the rt for 24h. After completion of the reaction, the mixture was diluted with diethyl ether and the solution filtered to remove insoluable inorganic salts. Removal of the solvent at rotary evaporator, followed by column chromatography on silica gel, using petroleum ether/diethylether (60:1 to 4:1) as eluent was afforded the desired product.

(*S*)-4-Benzyl-1-(4-bromo-3-methylphenyl)-2-methylpiperazine (9a):



^{1}HNMR ($CDCl_3$) δ: 1.08 (d, J = 6.60 Hz, 3H), 2.33 (s, 3H), 2.31-2.37 (dd, J = 3.81, J = 3.96 Hz, 1H), 2.45-2.48 (dd, J = 3.81, J = 3.96 Hz, 1H), 2.60-2.63 (dd, J = 1.75, J = 1.75 Hz, 1H), 2.81-2.83 (m, 1H), 3.10-3.21 (m, 2H), 3.48 (d, J = 13.20 Hz, 1H), 3.59 (d, J = 13.20 Hz, 1H), 3.75-3.86 (m, 1H), 6.60-6.62 (dd, J = 3.23, J = 3.23 Hz, 1H), 6.77 (d, J = 3.23 Hz, 1H), 7.24-7.42 (m, 6H).
^{13}CNMR ($CDCl_3$) δ: 13.2 (+), 23.3 (+), 44.6 (-), 51.2 (+), 53.4 (-), 58.6 (-), 62.8 (-), 114.1 (+), 116.0 (+), 119.3 (+), 127.0 (+), 128.2 (+), 128.8 (+), 132.5 (+), 138.1 (+), 138.5 (+), 149.6 (C_{quat}). - MS [CI-MS; (NH_3)] = 359.1, 361.1 [M-H^+] (100), 281.3 [M-Br^+] (15).

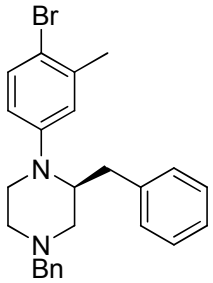
(*S*)-4-Benzyl-1-(4-bromo-3-methylphenyl)-2-isobutylpiperazine (9b):



^{1}HNMR ($CDCl_3$) δ: 0.81 (d, J = 6.58 Hz, 3H), 0.83 (d, J = 6.58 Hz, 3H), 1.04-1.08 (m, 1H), 1.31-1.37 (m, 1H), 1.90-1.94 (m, 1H), 2.24-2.32 (m, 2H), 2.33 (s, 3H), 2.75-2.78 (dt, J = 11.18, J = 2.19 Hz, 1H), 2.87-2.88 (dq, J = 11.18, J = 2.19 Hz, 1H), 3.12-3.14 (dt, J = 11.61, J = 3.28 Hz, 1H), 3.22-3.24 (td, J = 3.28, J = 11.61 Hz, 1H), 3.41 (d, J = 13.37 Hz, 1H), 3.63 (d, J = 13.37 Hz, 1H), 3.70-3.74 (m, 1H), 6.56 (dd, J = 2.85, J = 2.63 Hz, 1H), 6.70 (d, J = 2.65 Hz, 1H), 7.24-7.37 (m, 6H).

^{13}CNMR ($CDCl_3$) δ: 21.5 (+), 23.6 (+), 23.8 (+), 25.1 (+), 35.2 (-), 43.4 (-), 53.3 (+), 53.8 (-), 54.8 (-), 62.8 (-), 112.9 (+), 114.8 (+), 117.9 (+), 127.0 (+), 128.2 (+), 128.8 (+), 132.5 (+), 138.0 (+), 138.6 (+), 149.2 (C_{quat}). - MS [CI-MS; (NH_3)] = 401.1, 403.1 [M-H^+] (100), 323.2 [M-Br^+] (15).

(*S*)-2, 4-Dibenzyl-1-(4-bromo-3-methylphenyl) piperazine (9c):

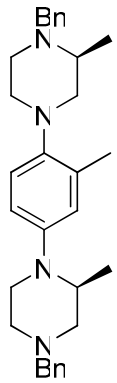


^{1}HNMR ($CDCl_3$) δ: 2.13 (dd, J = 11.26, J = 3.07 Hz, 1H), 2.30 (dt, J = 11.26, J = 3.58 Hz, 1H), 2.39 (s, 3H), 2.50 (dd, J = 12.80, J = 2.30 Hz, 1H), 2.87-2.88 (dq, J = 11.18, J = 2.19 Hz, 1H), 3.12-3.14 (dt, J = 11.61, J = 3.28 Hz, 1H), 3.22-3.24 (td, J = 3.28, J = 11.61 Hz, 1H), 3.41 (d, J = 13.37 Hz, 1H), 3.63 (d, J = 13.37 Hz, 1H), 3.70-3.74 (m, 1H), 6.56 (dd, J = 2.85, J = 2.63 Hz, 1H), 6.70 (d, J = 2.65 Hz, 1H), 7.24-7.37 (m, 6H).
^{13}CNMR ($CDCl_3$) δ: 21.5 (+), 23.6 (+), 23.8 (+), 25.1 (+), 35.2 (-), 43.4 (-), 53.3 (+), 53.8 (-), 54.8 (-), 62.8 (-), 112.9 (+), 114.8 (+), 117.9 (+), 127.0 (+), 128.2 (+), 128.8 (+), 132.5 (+), 138.0 (+), 138.6 (+), 149.2 (C_{quat}). - MS [CI-MS; (NH_3)] = 401.1, 403.1 [M-H^+] (100), 323.2 [M-Br^+] (15).

General Procedure for Pd (0) mediated C-N Coupling:

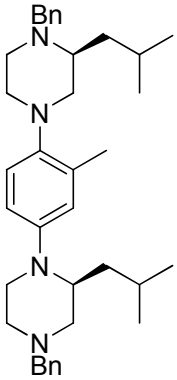
An ovendried Schlenk flask was charged with the aryl iodide (0.5 mmol), amine (0.6 mmol), NaO-^{t}Bu (67 mg, 0.7 mmol), $Pd_2(dba)_3.CHCl_3$ (2.3 mg, 0.0025 mmol, 1 mol % of Pd), BINAP (4.7 mg, 0.0075 mmol) and purged with argon. Toluene (1 mL) was added, and the reaction mixture was heated at 120-125ºC under argon for 8h until the reaction had proceeded to completion as judged by GC or TLC analysis. The reaction mixture was taken up in ethyl acetate (20 mL), filtered, and concentrated in *vacuo*. The crude product was then purified by flash chromatography on silica gel.

(S)-1-Benzyl-4-(4-((S)-4-benzyl-2-methylpiperazine-1-yl)-2-methylphenyl)-2-methylpiperazine (10a)



^{1}HNMR ($CDCl_3$) δ: 1.05 (d, J = 6.46 Hz, 3H), 1.24 (d, J = 5.72 Hz, 3H), 2.30 (s, 3H), 2.34-2.40 (m, 1H), 2.45-2.51 (m, 2H), 2.57-2.61 (m, 1H), 2.63-2.76 (m, 3H), 2.78-2.84 (m, 2H), 2.87-2.91 (m, 1H), 2.95-2.98 (m, 1H), 3.11-3.14 (m, 2H), 3.29 (d, J = 13.05 Hz, 1H), 3.51 (d, J = 13.05 Hz, 1H), 3.61 (d, J = 13.05 Hz, 1H), 3.63-3.67 (m, 1H), 4.11 (d, J = 13.05 Hz, 1H), 6.77-6.79 (dd, J = 8.51 Hz, J = 2.64 Hz, 1H), 6.83 (d, J = 2.64 Hz, 1H), 6.97 (d, J = 8.51 Hz, 1H), 7.26-7.41 (m, 10H).
^{13}CNMR ($CDCl_3$) δ: 14.1 (+), 18.0 (+), 47.2 (-), 51.5 (-), 52.0 (+), 52.4 (-), 53.7 (-), 55.7 (+), 58.2 (-), 59.3 (-), 59.6 (-), 62.9 (-), 116.6 (+), 119.6 (+), 121.5 (+), 126.8 (+), 126.9 (+), 128.2 (+), 128.9 (+), 129.1 (+), 133.4 (+), 138.5 (C_{quat}), 139.0 (C_{quat}), 145.0 (C_{quat}), 146.2 (C_{quat}). - MS [CI-MS; (NH_3)] = 469.2 [$M\text{-}H^+$] (100).

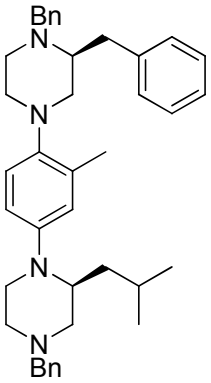
(S)-1-Benzyl-4-(4-((S)-4-benzyl-2-isobutylpiperazine-1-yl)-2-methylphenyl)-2-isobutylpiperazine (10b)



^{1}HNMR ($CDCl_3$) δ: 0.80-0.84 (dd, J = 6.74, J = 13.59 Hz, 6H), 0.89-0.96 (dd, J = 6.724, J = 21.04 Hz, 6H), 1.07-1.13 (m, 1H), 1.33-1.40 (m, 1H), 1.57-1.67 (m, 2H), 1.81-1.87 (m, 1H), 2.26 (s, 3H), 2.32-2.41 (m, 3H), 2.58-2.65 (m, 2H), 2.67-2.74 (m, 1H), 2.75-2.86 (m, 4H), 3.03 (d, J = 9.10 Hz, 1H), 3.10-3.17 (m, 1H), 3.18-3.22 (m, 1H), 3.28 (d, J = 12.55 Hz, 1H), 3.42 (d, J = 12.55 Hz, 1H), 3.61-3.67 (m, 3H), 4.07 (d, J = 13.01 Hz, 1H), 6.65-6.69 (dd, J = 8.60 Hz, J = 2.68 Hz, 1H), 6.72 (d, J = 2.68 Hz, 1H), 6.94 (d, J = 8.60 Hz, 1H), 7.23-7.40 (m, 10H).

^{13}CNMR ($CDCl_3$) δ: 18.1 (+), 21.5 (+), 22.2 (+), 23.8 (+), 23.9 (+), 25.1 (+), 25.9 (+), 35.3 (-), 38.3 (-), 44.8 (-), 51.0 (-), 51.9 (-), 53.6 (+), 54.1 (-), 55.4 (-), 57.2 (+), 58.0 (-), 58.9 (-), 114.4 (+), 119.2 (+), 119.8 (+), 126.7 (+), 126.9 (+), 128.1 (+), 128.2 (+), 128.8 (+), 129.0 (+), 133.4 (+), 133.5 (C_{quat}), 138.6 (+), 139.4 (C_{quat}), 143.9 (C_{quat}), 145.9 (C_{quat}). – HRMS (EI-MS) calculated for $C_{37}H_{52}N_4$ [$M^{\cdot+}$]: 552.4192; found 552.4182.

(S)-1, 2-Dibenzyl-4-(4-((S)-4-benzyl-2-isobutylpiperazine-1-yl)-2-methylphenyl) piperazine (10c)



^{1}HNMR ($CDCl_3$) δ: 0.92-0.96 (dd, J = 22.14, J = 6.14 Hz, 6H), 1.12-1.19 (m, 1H), 1.52-1.73 (m, 3H), 2.17-2.19 (dd, J = 11.18, J = 2.85 Hz, 1H), 2.31 (m, 4H), 2.38-2.43 (m, 1H), 2.63-2.67 (m, 2H), 2.71-2.73 (dt, J = 11.18, J = 1.32 Hz, 1H), 2.81-2.89 (d, J = 11.18 Hz, 1H), 2.96 (d, J = 8.55 Hz, 1H), 3.19 (t, J = 11.83 Hz, 1H), 3.19-3.32 (m, 3H), 3.40 (d, J = 14.03 Hz, 1H), 3.59 (d, J = 14.03 Hz, 1H), 3.78-3.81 (dd, J = 10.74, J = 2.41 Hz, 1H), 4.09 (d, J = 11.83 Hz, 1H), 6.77-6.80 (dd, J = 2.63, J = 8.55 Hz, 1H), 6.82 (d, J = 2.41 Hz, 1H), 6.95-6.97 (m, 2H), 7.03 (d, J = 8.55 Hz, 1H), 7.10-7.25 (m, 3H), 7.25-7.42 (m, 10H).

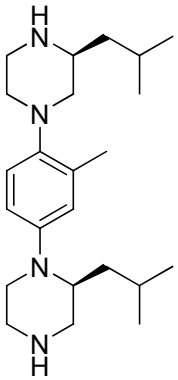
^{13}CNMR ($CDCl_3$) δ: 18.2 (+), 22.2 (+), 23.9 (+), 25.8 (+), 32.3 (-), 38.5 (-), 43.9 (-), 51.2 (-), 51.9 (+), 53.5 (-), 53.8 (-), 57.26 (+), 58.0 (-), 58.8 (-), 63.0 (-), 113.3 (+), 114.1

(+), 117.1 (+), 118.8 (+), 120.1 (+), 125.7 (+), 126.8 (+), 127.1 (+), 128.2 (+), 129.0 (+), 129.3 (+), 129.4 (+), 133.8 (+), 138.5 (C_{quat}), 139.5 (C_{quat}), 140.3 (C_{quat}), 144.0 (C_{quat}), 145.6 (C_{quat}). - MS [CI-MS; (NH_3)] = 587.2 [M-H^+] (100).

General procedure for benzyl deprotection reaction:

A mixture of dibenzyl protected compound (0.05 mmol), 10% palladium on carbon (20 mol%) and CH_3COOH (2 drops) in CH_3OH (3 mL) was stirred under 15 atm of H_2 at rt for 24 h. After completion of the reaction the solution was passed over celite to remove the catalyst and washed several times with CH_3OH. The combined filtrate was concentrated to give a hygroscopic solid in quantitative yield

(S)-2-isobutyl-1-(4-((S)-3-isobutylpiperazine-1-yl)-3-methylphenyl) piperazine (**11b**)



^{1}HNMR (D_2O) δ: 0.66-0.68 (dd, J = 2.74, J = 6.31 Hz, 6H), 0.81-0.84 (dd, J = 2.19, J = 6.31 Hz, 6H), 1.02-1.14 (m, 1H), 1.27-1.62 (m, 5H), 2.19 (s, 3H), 2.23-2.71 (m, 1H), 2.28-2.94 (m, 1H), 3.10-3.49 (m, 10H), 3.68 (m, 1H), 6.85-7.00 (m, 3H).

Circular dichroism measurements.

Measurements were performed on a Jasco J-710 spectrometer. The length of the cylindrical cuvettes was 1 cm. The resolution was 0.2 nm, the band width 1.0 nm, the sensitivity 20 mdeg, the response 0.25 s, and the speed 20 nm/min. The background was subtracted to each spectrum. The absorption values were measured as molar ellipticity per residue (deg cm^2 $dmol^{-1}$).

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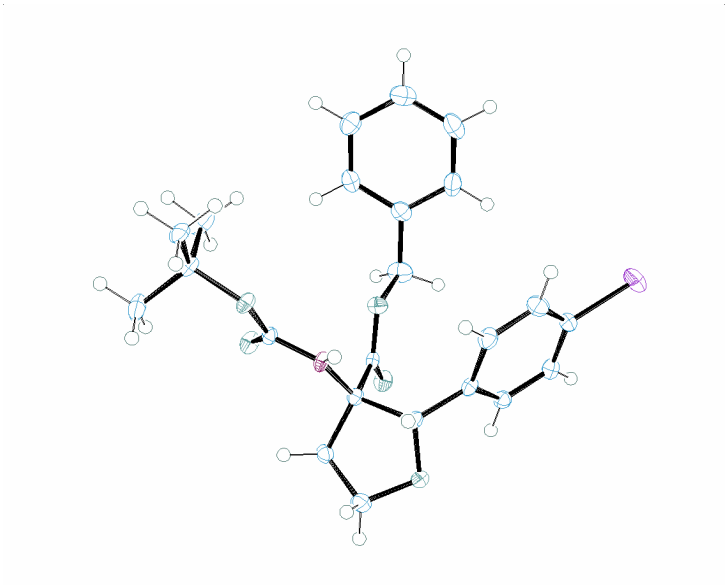
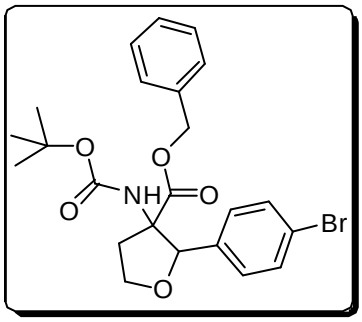
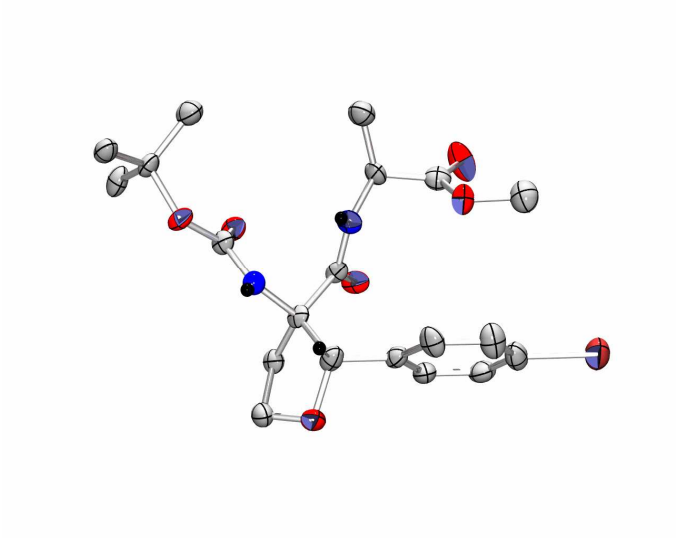
5.1. X-ray diffraction structure

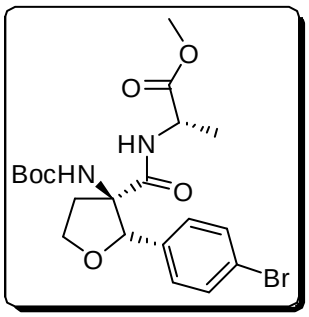




Crystal Data:

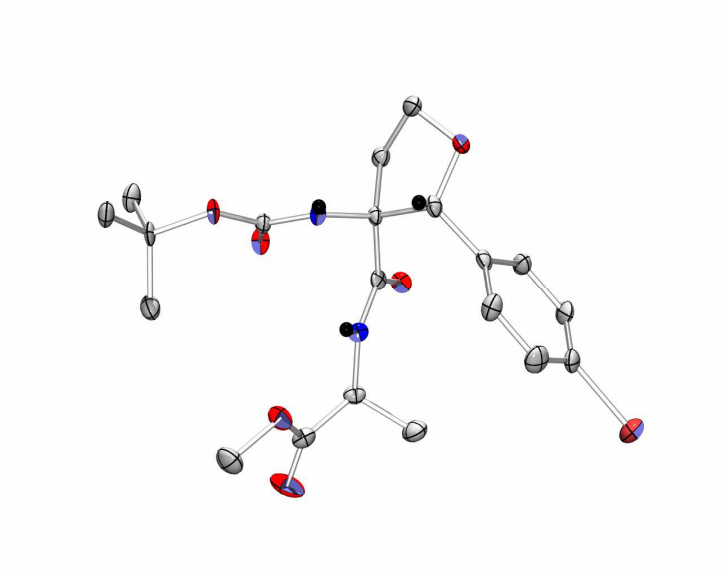
Empirical formula;	$C_{23}H_{26}BrNO_5$	
Formula weight;	476.35	
Crystal size;	0.48 x 0.19 x 0.11 mm	
Crystal description;	prism	
Crystal colour;	colourless	
Crystal system;	Monoclinic	
Space group;	C c	
Unit cell dimensions	a = 15.5362(9) Å	α = 90º
	b = 13.2881(12) Å	β = 102.158 (7)º
	c = 22.1144(13) Å	γ = 90º.
Volume	4463.0(6) $Å^3$	
Z, Calculated density	8, 1.418 Mg/m^3	
Absorption coefficient	1.875 mm^{-1}	
F(000)	1968	

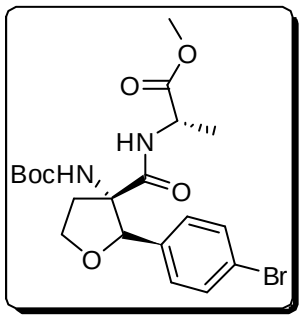




Crystal Data

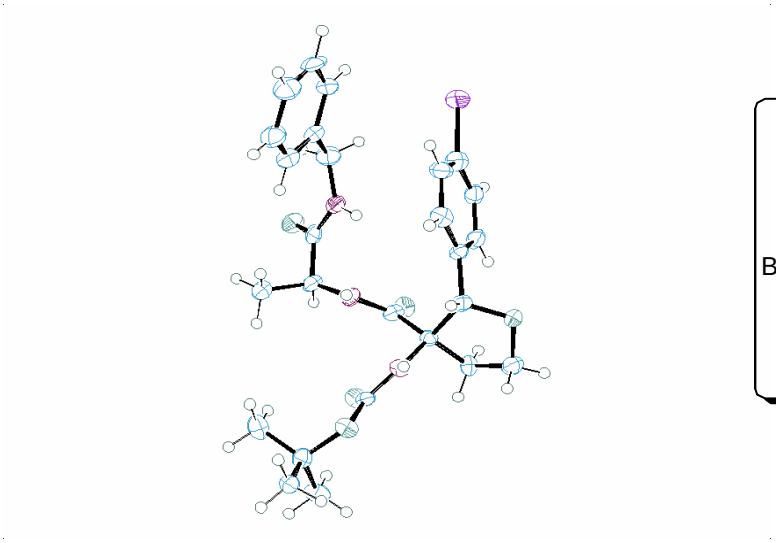
Empirical formula	$C_{20}H_{27}BrN_2O_6$	
Formula weight	471.34	
Crystal size	0.270 x 0.140 x 0.140 mm	
Crystal description	needle	
Crystal colour	colourless	
Crystal system	Monoclinic	
Space group	P 21	
Unit cell dimensions	a = 10.7776(14) Å	α = 90°
	b = 6.1129(13) Å	β = 91.201(13)°
	c = 16.069(3) Å	γ = 90°
Volume	1058.4(3) $Å^3$	
Z, Calculated density	2, 1.456 Mg/m^3	
Absorption coefficient	2.937 mm^{-1}	
F (000)	488	

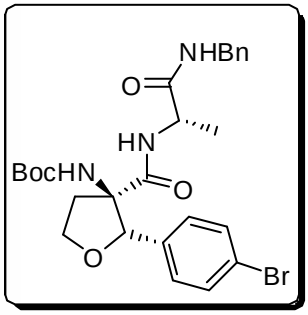




Crystal Data

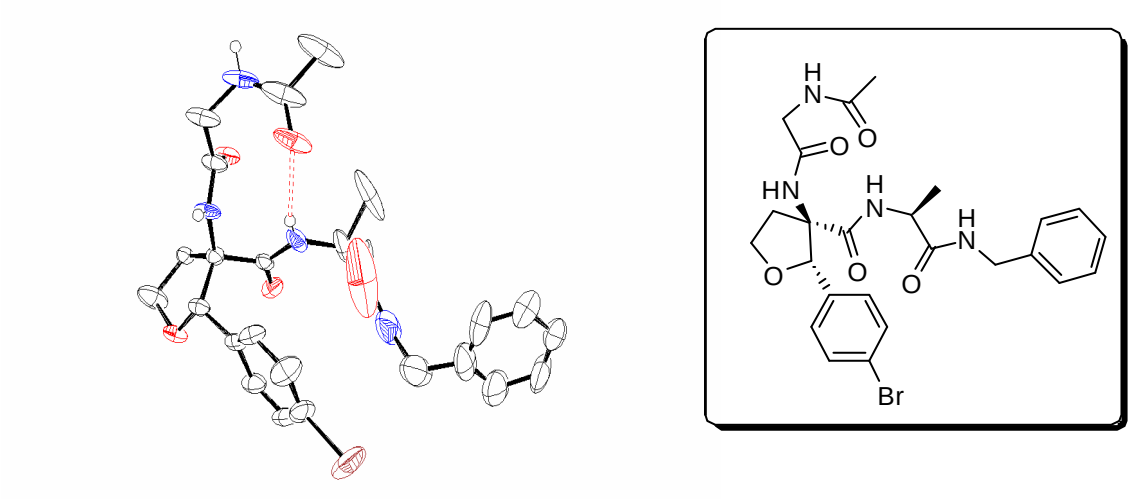
Empirical formula	$C_{20}H_{27}BrN_2O_6$	
Formula weight	471.34	
Crystal size	0.340 x 0.085 x 0.024 mm	
Crystal description	thin plate	
Crystal colour	colourless	
Crystal system	Monoclinic	
Space group	P 21	
Unit cell dimensions	a = 10.7567(4) Å	α = 90°
	b = 6.1367(3) Å	β = 102.512(3)°
	c = 16.4151(6) Å	γ = 90°
Volume	1057.84(8) $Å^3$	
Z, Calculated density	2, 1.477 Mg/m^3	
Absorption coefficient	1.981 mm^{-1}	
F(000)	486	





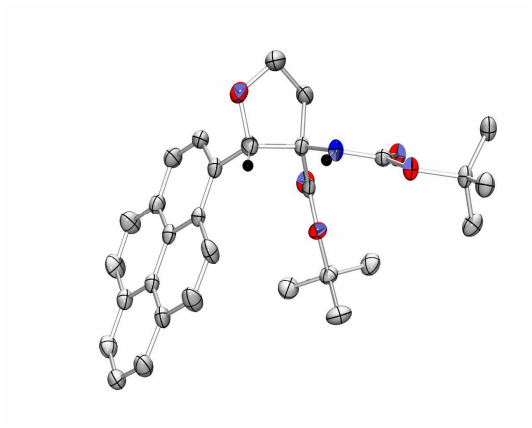
Crystal Data

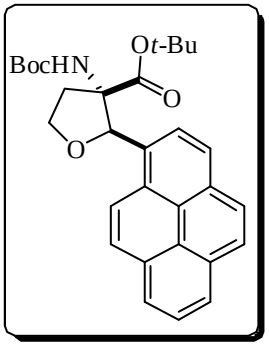
Empirical formula	$C_{26}H_{32}BrN_3O_5$	
Formula weight	546.45	
Crystal size	0.420 x 0.250 x 0.010 mm	
Crystal description	flat needle	
Crystal colour	colourless	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 5.97218(14) Å	α = 90º
	b = 10.8774(3) Å	β = 90º
	c = 38.7354(11) Å	γ = 90º
Volume	2516.32(12) $Å^3$	
Z, Calculated density	4, 1.442 Mg/m^3	
Absorption coefficient	2.575 mm^{-1}	
F(000)	1136	



Crystal Data

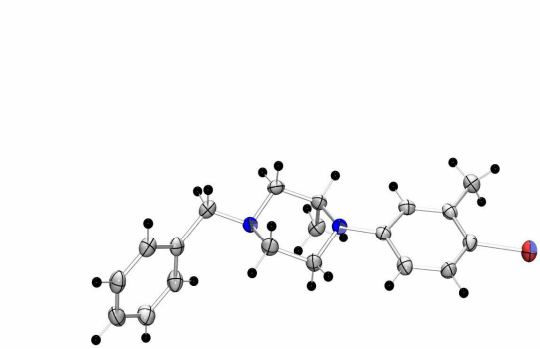
Empirical formula	$C_{25}H_{29}BrN_4O_5$	
Formula weight	545.42	
Crystal size	0.480 x 0.040 x 0.010 mm	
Crystal description	needle	
Crystal colour	colourless	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 5.71880(10) Å	α = 90º
	b = 15.9547(2) Å	β = 90º
	c = 27.6460(4) Å	γ = 90º
Volume	2522.47(7)Å^3	
Z, Calculated density	4, 1.436 Mg/m^3	
Absorption coefficient	2.581 mm^{-1}	
F(000)	1128	

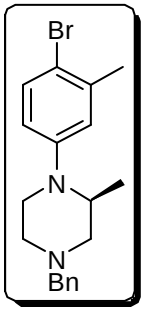




Crystal Data

Empirical formula	$C_{30}H_{33}NO_5$	
Formula weight	487.57	
Crystal size	0.410 x 0.060 x 0.020 mm	
Crystal description	flat needle	
Crystal colour	colourless	
Crystal system	Monoclinic	
Space group	P 21/c	
Unit cell dimensions	a = 5.88530(10) Å	α = 90º
	b = 20.9715(3) Å	β = 91.4300(10)º
	c = 20.6745(3) Å	γ = 90º
Volume	2550.93(7) Å3	
Z, Calculated density	4, 1.270 Mg/m^3	
Absorption coefficient	0.692 mm^{-1}	
F(000)	1040	





Crystal Data

Empirical formula	$C_{22}H_{29}BrN_2$	
Formula weight	401.37	
Crystal size	0.310 x 0.160 x 0.080 mm	
Crystal description	flat rod	
Crystal colour	colourless	
Crystal system	Monoclinic	
Space group	P 21	
Unit cell dimensions	a = 9.3190(3) Å	α = 90º
	b = 5.5464(2) Å	β = 96.756(2)º
	c = 19.6979(4) Å	γ = 90º
Volume	1011.05(5) Å^3	
Z, Calculated density	2, 1.318 Mg/m^3	
Absorption coefficient	2.798 mm^{-1}	
F(000)	420	

5.2. Abbreviations

abs.	Absolute
AcOH	Acetic acid
Ac_2O	Acetic anhydride
Ac_nc	1-aminocycloalkanecarboxylic acid
Ac_3c	1-aminocyclopropanecarboxylic acid
Ac_4c	1-aminocyclobutanecarboxylic acid
Ac_5c	1-aminocyclopentanecarboxylic acid
Ac_6c	1-aminocyclohexanecarboxylic acid
Ac_7c	1-aminocycloheptanecarboxylic acid
Ac_8c	1-aminocyclooctanecarboxylic acid
Ac_9c	1-aminocyclononanecarboxylic acid
Ar	Aromatic
atm	Atmosphere
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
Bz	Benzyl
*i*Bu	Isobutyle
BuLi	Butyl lithium
c	Concentration
cat.	Catalyst
Cbz	Carbobenzyloxy
CD	Circulardichroismus
d	Day
c_3Arg	1-amino-2-(2-guanidinoethyl)cyclopropane-1,2-dicarboxylic acid
c_3Asp	1-aminocyclopropane-1,2-dicarboxylic acid
c_3Leu	1-amino-2-isopropylcyclopropanecarboxylic acid
c_3Met	1-amino-2-methylthiomethylcyclopropanecarboxylic acid
c_3Phe	1-amino-2-phenylcyclopropanecarboxylic acid
c_6Phe	1-amino-2-phenylcyclohexanecarboxylic acid
DCC	Dicyclohexylcarbodiimide
DCM	Dichloromethane
DIPEA	(*N*,*N*)-Diisopropyleethylamine
DMAP	Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethylsulfoxide
dr	Diatereomeric ratio
ee	Enantomeric excess
EDC	N-(3-Dimethylaminopropyl)-N'-ethyl carbodiimide
EI	Electron impact (MS)
eq	Equivalent
ESI	Electrosprayionisation
EtOH	Ethanol
EtOAc	Ethylacetate
FAB	Fast Atom Bombardement
Gly	Glycine
h	Hour(s)

HATU	2-(7-Aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluro phosphate
HOAt	1-Hydroxy-7-azabenzotriazole
HOBt	1-Hydroxybenzotriazole
HOPAS	Hydroxypyrrole amino acid (5-Aminomethyl-3-methoxy-4-methyl-1H-pyrrole-2-carboxylic acid)
HPLC	High pressure liquid chromatography
HRMS	High resolution mass spectrum
Ile	Isoleucine (L-Isileucine)
IR	Infrared (spectrum)
J	Coupling constant
Leu	Leucine (L-Leucine)
LAH	Lithium aluminium hydride
LDA	Lithium diisopropyle amine
M	Moleculeion
Me	Methyl
min.	Minute(s)
MS	Mass spectrum
MeOH	Methanol
NMR	Nuclear magnetic resonance
NOE	Nuclear overhauser effect
PE	Petrole ethers 40/60
PG	Protecting group
Ph	Phenyl
Phe	Phenylalanine (L-Phenylalanine)
Pro	Proline (L-Proline)
quant.	Quantitative
ROESY	Rotating frame nuclear overhauser enhanced spectroscopy
rt	Room temperature
TBAF	Tetrabutyl ammonium fluoride
TFA	Trifluroacetic acid
UV	Ultraviolate

5.3. Curriculum Vitae

Prantik Maity

1st January 1981

Education and Qualification

2004-2007	Ph.D. work in Organic Chemistry in the research group of Prof. Dr. B. König, University of Regensburg, Germany.
2002-2004	M.Sc. in Chemistry Department of Chemistry, Indian Institute of Technology Madras, India
1999-2002	B.Sc. in Chemistry (Honors, 1st class) University of Calcutta, India

Publications

1. Synthesis of 3-Oxo-2,3-dihydropyrrole Amino acids as Chiral Dipeptidomimics. Maity, P.; König, B. *Synthesis* **2006**, *16*, 2719-2724.

2. Tetrahydrofuran Cα-Tetrasubstituted Amino acids: Two Consecutive β-Turns in a Crystalline Linear Tripeptide. Maity, P.; Zabel, M. König, B. *J. Org. Chem*. **2007**, *72*, 8046-8053.

3. Enantio- and Diastereoselective Synthesis of Cyclic C^{α}-Tetrasubstituted α-Amino acids and Their Use to Induce Stable Conformations in Short Peptides. Maity, P.; König, B. *Pept. Sci*. **2008**, *90*, 8-27.

Poster Presentations

1. Diastereoselective Synthesis of Conformationally Restricted α, β-Disubstituted Amino acids. Maity, P.; König, B. 111th International Summer Course at BASF, Ludwigshafen, Germany.