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Towards Control of χ-Space: Conformationally Constrained Analogues of Phe, Tyr, Trp and His

Susan E. Gibson (née Thomas),[a]* Nathalie Guillo[a] and Matthew J. Tozer[b]

[a] Department of Chemistry, Imperial College of Science, Technology and Medicine, South Kensington, London SW7 2AY, U.K.

[b] James Black Foundation, 68 Half Moon Lane, London SE24 9JE, U.K.

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1. Introduction

Peptide science began in 1902 when Fisher and Hofmeizer proposed independently that proteins were long chains of α-amino acids linked to each other through amide bonds between the carboxyl and amino groups.[1] The significance of peptides in all life processes became apparent in the 1950's. In particular, du Vigneaud's isolation, characterisation and synthesis of the peptide hormones oxytocin and vasopressin, and Sanger's elucidation of the sequence of bovine insulin, are understandably considered major milestones in peptide history, and these scientists were rewarded independently with the Nobel Prize (Figure 1).[1]

* E-Mail: s.gibson@ic.ac.uk Fax: +44 171 594 5804

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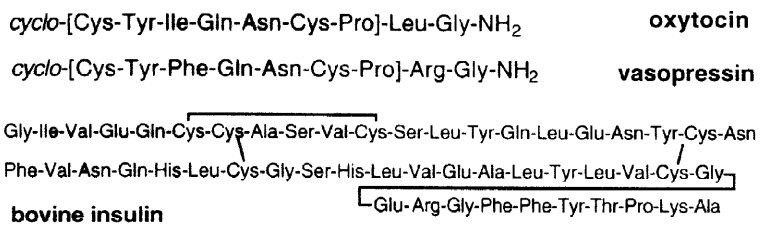


Figure 1. The primary structure of oxytocin, vasopressin, and bovine insulin

It rapidly emerged that the conformation (secondary and tertiary structures) of a peptide was as crucial as its sequence (primary structure) for biological activity. Now conformation is regarded as the critical issue in the design of more selective and/or more potent peptides as enzyme inhibitors, and agonists or antagonists at receptors.

Since the 1960s, advances in electronic theory and the understanding of chemical structure have allowed Ramachandran, Scheraga and others to establish the relationship between the torsional angles ϕ (phi), ψ (psi) and ω (omega) (Figure 2) of the individual amino acid residues and the secondary structures of peptides[2] i.e. helices, sheets, turns etc. An equally important area, though much less explored, is that of the three-dimensional structure of the side chain moieties which can be characterised by the torsional angles χ^1, χ^2, etc. (Figure 2), the so-called chi space.

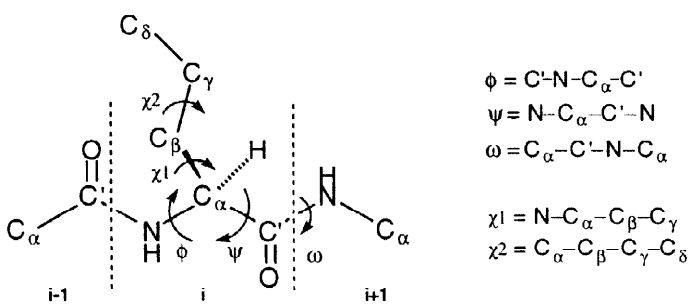


Figure 2. Definition of the dihedral angles ϕ, ψ, ω and χ of a peptide

The χ angles in conjunction with the backbone angles define the position of side-chain functional groups in space and thus must be regarded as of key importance in understanding the mode of action of peptides.[3] Although pioneering studies have provided some insight into how the control of χ space might be fruitful in the development of peptide ligands, a full understanding of χ space and how to manipulate it is still some way from being realised. It is expected that much effort will be directed towards understanding and exploiting this area in the next few years. Of the many tools that will be required to aid investigations of χ space, an array of non-proteinogenic α-amino acids with well-defined complementary χ-characteristics are clearly of considerable importance. Synthesis of non-proteinogenic α-amino acids has been a popular area of endeavour in recent years and there are many examples of conformationally restricted amino acids in the chemical literature. In most cases, however, scant attention has been paid to the conformational profile of such molecules, and in particular their role in χ-space has more often than not been overlooked.

In this review we delineate the current level of understanding of the conformational properties of unnatural amino acids, in order to stimulate more modeling studies, analysis and rational design of conformationally constrained analogues of α-amino acids. The current relationship between structure and conformational constraint will be depicted by presenting known χ-constrained, synthetic analogues of aromatic proteinogenic amino acids, and by discussing the nature of the constraint. A critical summary of the synthetic approaches to the analogues will also be included in order that the reader may identify the most practical route to each analogue. The potential provided by a fuller understanding of these amino acids and future rational design of related amino acids will be underlined in the second part of the review by the presentation of two examples of the use of conformationally constrained α-amino acids in a biological context.

(With respect to coverage, we have chosen to focus on analogues of the aromatic proteinogenic amino acids Phe, Tyr, Trp and His, because aromatic groups on a peptidic ligand often play a central role in the interaction with the receptor. In fact, the elimination of such groups often leads to an inversion of action (agonist/antagonist) or to reduced affinity.[4] Derivatives with unnatural substitution(s) on the aromatic ring have been excluded as have didehydro- and *N*-alkylated derivatives.)

2. Synthesis and Conformational Analysis of χ-Constrained Aromatic α-Amino Acids

2.1. Background

In the proteinogenic α-amino acids, the side chain torsional angle χ^1 can assume three low energy staggered conformations: *gauche*-(−), *trans*, and *gauche*-(+) as illustrated by the Newman projections of the (*S*)- and (*R*)-amino acids (Figures 3 and 4). [Note that the gauche-(-) conformations, for example, of the (*S*)- and (*R*)-enantiomers of the amino acids are quite different with respect to the orientation of the aryl group.] Although the staggered conformations are the preferred ones, the aromatic group readily rotates about the Cα–Cβ and Cβ–Cγ bonds so that χ^1 and χ^2 cover a 360° range.

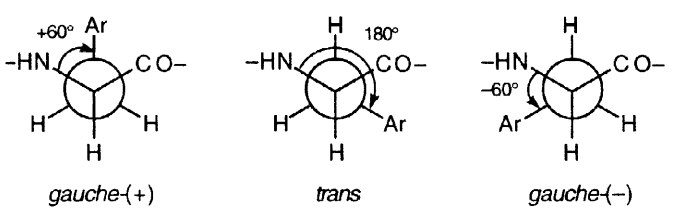


Figure 3. The staggered conformations of aromatic (*S*)-amino acids and the values of the χ^1 angles

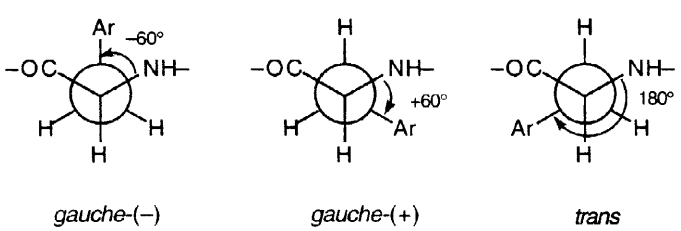


Figure 4. The staggered conformations of aromatic (*R*)-amino acids and the values of the χ^1 angles

In the analogues of Phe, Tyr, Trp and His described below, these rotations, and consequently the position of the aromatic group, are hindered or limited through structural modification. It is inevitable that, in some cases, the torsional angles ϕ, ψ, and possibly ω are also altered relative to the natural amino acid as a consequence of the structural change.

We have divided the constrained analogues into three classes. β-Substituted and α,β-substituted amino acids will be presented first. This will be followed by a discussion of cyclic amino acids and finally the "imino acids" in which the nitrogen is part of a ring will be reviewed (Figure 5).

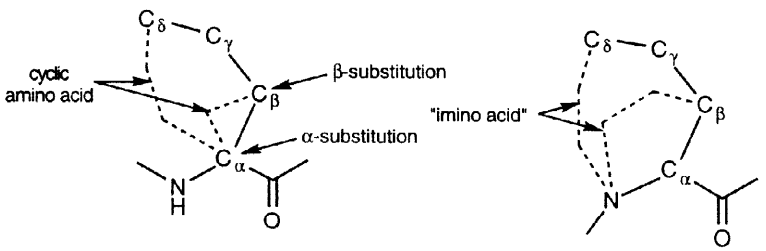


Figure 5. Classification of constrained α-amino acids

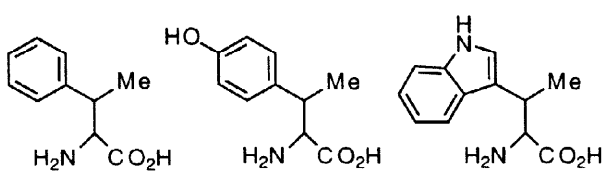
2.2. Constraint of Aromatic Amino Acids by Substitution

We will firstly consider analogues of the amino acids Phe, Tyr, Trp and His in which a β-hydrogen has been substituted by a methyl or phenyl group, followed by analogues in which both the α and β positions are substituted. The torsional angle χ^1 of the substituted amino acids is restricted in these analogues by van der Waals interactions.

2.2.1. β-Substitution

i) β-Methyl Amino Acids

In constrast to α-substitution, which has little effect on χ^1 (Figure 6i), the introduction of a methyl group at the β-position directly enhances the population of one χ^1 rotamer (Figure 6ii). As illustrated for (2*S*,3*R*)-β-MePhe (Figure 6ii), steric interactions between vicinal substituents suggest that a *trans* side chain conformation is preferred to the *gauche*-(−) and *gauche*-(+) conformations. The same analysis for each of the four stereoisomers of **1-3** has lead to the predictions summarised in Table 1. NMR studies of peptides containing **1** and **3** have confirmed the predicted preferences.[3]



β-MePhe **1** β-MeTyr **2** β-MeTrp **3**

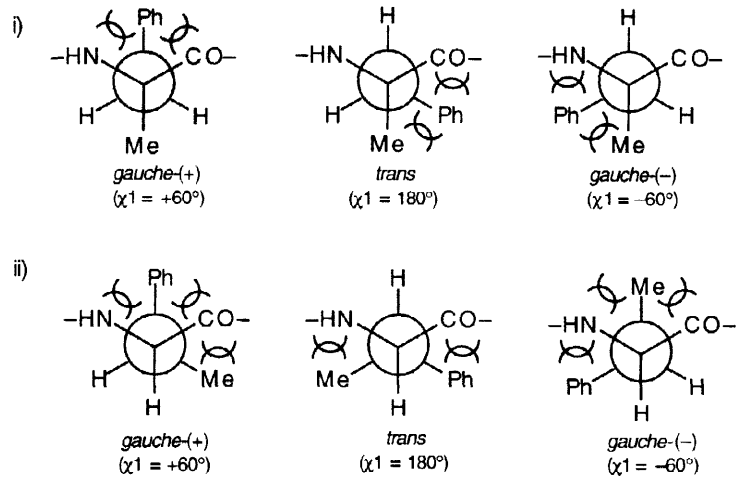
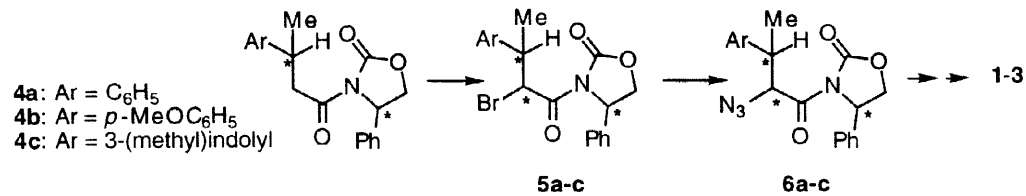


Figure 6. The effect of i) α-substitution and ii) β-substitution on the population of χ^1 rotamers of aromatic (*S*)-amino acids

stereoisomers of 1-3	preferred conformation
(2*S*,3*S*)	*gauche*-(–)
(2*S*,3*R*)	*trans*
(2*R*,3*R*)	*gauche*-(+)
(2*R*,3*S*)	*trans*

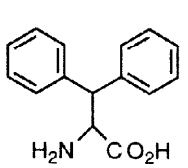
Table 1. Preferred conformations of **1-3** for each of their stereoisomers

Of the routes available to stereochemically pure samples of β-substituted amino acids **1-3**,[5] their asymmetric synthesis via Evans' methodology is the most general.[6] Thus, the four stereoisomers of **4a** have been isolated after separation by crystallisation of the diastereomeric pairs obtained from the coupling of 3-(±)-phenylbutyric acid with either (*S*)- or (*R*)-4-phenyl-2-oxazolidinone. Stereoselective bromination of **4a** occurred in >99% d.e. to give **5a** and was followed by an S_N2 azide displacement to give **6a**. Removal of the chiral auxiliary (which can be recycled), and reduction of the azido group afforded the four individual optically pure isomers of **1** in 24-25% overall yield from 3-(±)-phenylbutyric acid on a multigram scale (>2g).[7] Similar methodology has been applied to the stereoisomers **4b**,[8] and **4c**[9] to afford **2** and **3** in >95% d.e. and 27-53% overall yield (for more details and recent improvements of this methodology see reference 3).

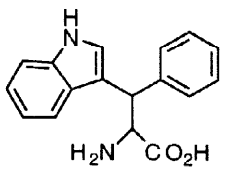


ii) β-Phenyl Amino Acids

The preferred conformations of β-diphenylalanine (Dip) **7** and β-phenyltryptophan **8** may be predicted using arguments similar to those used for the β-methylated amino acids **1-3** (see Table 1).

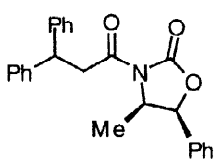


Dip **7**

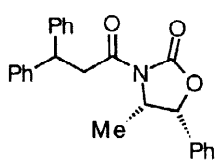


β-PhTrp **8**

Racemic Dip **7** may be prepared in various ways,[10] and two enantioselective syntheses of **7** have been developed.[11,12] The most attractive is based on Evans' methodology and commences with the coupling of 3,3-diphenylpropionic acid with (4*R*,5*S*)- and (4*S*,5*R*)-4-methyl-5-phenyl-2-oxazolidinones to give the acyloxazolidinones **9a** and **9b** respectively. After deprotonation, reaction with trisyl azide, removal of the chiral auxiliary and reduction of the azido group, (*R*)-(−)-Dip and (*S*)-(+)-Dip were produced in >99% e.e. and 60% overall yield from diphenylpropionic acid.[11]

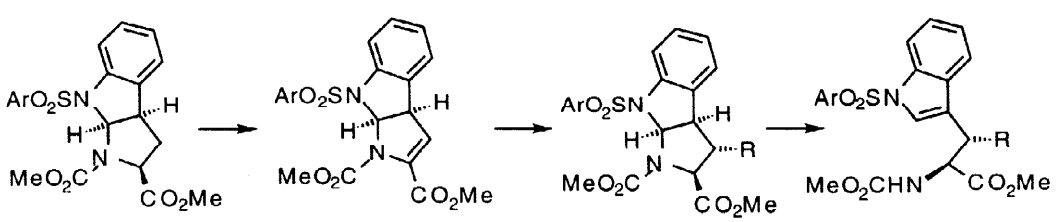


9a



9b

(2*S*,3*S*)-β-Phenyltryptophan **8** has been synthesised in 27% overall yield from the indole derivative **10**, which is commercially available or can be prepared from (*S*)-Trp.[13] Addition of a higher order cuprate to the dehydro-derivative **11** gave **12** in >95% d.e., which upon treatment with trifluoroacetic acid opened to the Trp system **13**. Subsequent desulfonylation and hydrolysis afforded (2*S*,3*S*)-**8**. [An analogous set of reactions has been used to generate (2*S*,3*S*)-β-methyltryptophan **3**.[13]]

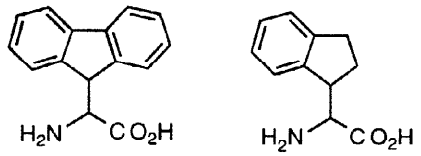


10 **11** **12** **13**

iii) Miscellaneous β-Substitutions

Further rigidification of β-substituted systems has been achieved by tying the β-substituent to the aromatic group. Thus in 9-fluorenylglycine (Flg) **14** and 1-indanylglycine (Ing) **15**, not only is χ^1 limited as it is for **1**

and **7** (Figure 7), but the orientation of the aromatic group (and thus χ^2) is also controlled by the additional cyclopentane ring.



Flg **14** Ing **15**

Molecular modelling of Ac-Flg-NH_2 and Ac-Ing-NH_2, with fixed angles $\phi = -60°$, $\psi = -30°$ to simulate a β-turn, indicated that the preferred conformations for stereoisomers of Flg and Ing differ from the other rotamers by 0.6-3.3 kcal/mol (Table 2).[14]

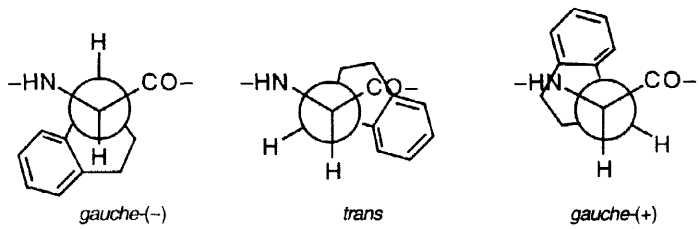
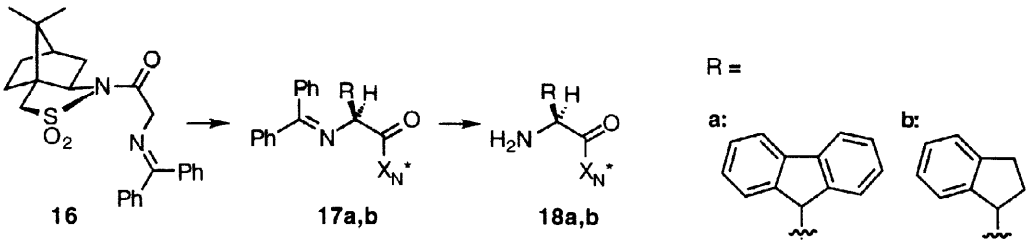


Figure 7. The staggered rotamers of (*S*)-Ing **15**

amino acid	rotamer	ΔE (kcal/mol)
(2*S*)-Ac-Flg-NH_2	*gauche*(−), *trans*	3.3
	gauche(+), *gauche*(−)	0.0
	trans, *gauche*(+)	2.2
(2*S*,3*S*)-Ac-Ing-NH_2	*gauche*(−)	0.0
	trans	2.2
	gauche(+)	0.6
(2*S*,3*R*)-Ac-Ing-NH_2	*gauche*(−)	2.2
	trans	1.0
	gauche(+)	0.0

Table 2. Difference in energies of the rotamers of stereoisomers of Flg **14** and Ing **15**

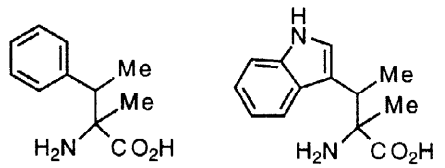
Diastereoselective alkylation of the sultam-derivative **16** leads to enantiomerically pure samples of **14** and **15**. (This route has also been used to synthesise Dip **7**.[12]) Alkylation of **16** with 9-bromofluorene and 1-bromoindane occurred in >95% d.e. to give **17a** and **b** respectively. Acidic hydrolysis of **17a,b** gave the *N*-(α-aminoacyl)-sultam **18a,b**. Removal of the sultam group of compound **18a** afforded (*S*)-Flg in 56% overall yield from **16**.[12] The diastereomers of **18b** were separated by column chromatography. After cleavage of the sultam group, enantiomerically pure (2*S*,3*S*)-Ing and (2*S*,3*R*)-Ing were obtained in 31-36% overall yield from **16**.[15]



16 17a,b 18a,b

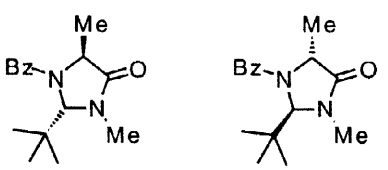
2.2.2. α,β-Disubstitution

Simultaneous α- and β-substitution of Phe and Trp is likely to restrict the range of the torsional angle χ^1 of the resulting amino acids. Unfortunately no conformational analysis of α,β-dimethylphenylalanine **19** and α,β-dimethyltryptophan **20** is available and since the interactions in the three possible staggered conformations of **19** and **20** are very similar, it is not possible *a priori* to draw conclusions about their preferred conformation.



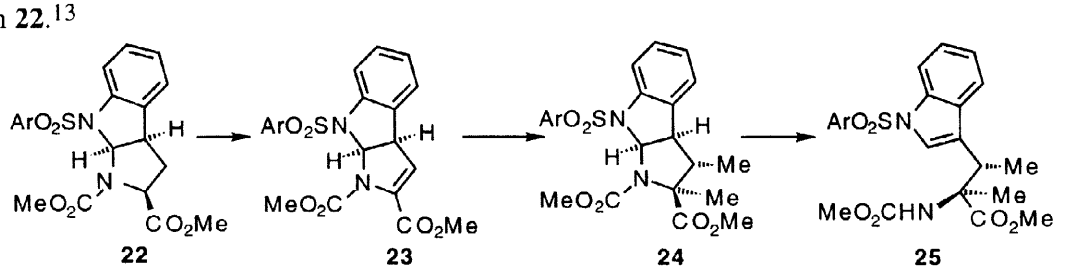
α,β-(Me)$_2$-Phe **19** α,β-(Me)$_2$-Trp **20**

The synthesis of the four stereoisomers of α,β-dimethylphenylalanine **19** has been achieved by diastereoselective alkylation of the imidazolidinones **21a** and **b**. Deprotonation of **21a** and **b** followed by reaction with 1-phenylethyl bromide afforded mixtures of diastereomers, which were separated by crystallisation. Hydrolysis of the individual stereoisomers provided the four possible stereoisomers of **19** in 16 to 60% overall yields from compounds **21a** and **b** on a large scale (up to 58 g of **21a**).[16]



21a **21b**

The (2*S*,3*S*)-isomer of α,β-dimethyltryptophan **20** has been prepared from the Trp derivative **22** by treatment of **23** with dilithium dimethylcyanocuprate and quenching with iodomethane, which gave a single diastereomer **24**. Opening of **24** with trifluoroacetic acid and subsequent hydrolysis of **25** gave (2*S*,3*S*)-**20** in 63% overall yield from **22**.[13]



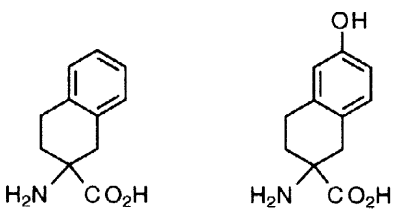
22 **23** **24** **25**

2.3 Cyclic Amino Acids

Cyclic derivatives of the proteinogenic aromatic amino acids fall into two categories: those in which the torsional angle χ^1 is restricted by tethering C_α to the aromatic ring (usually to an ortho carbon) - these will be discussed first, and those in which χ^1 is restricted by tethering C_α to C_β. In contrast to Section 2.2, in which χ^1 values were limited by van der Waals interactions, the χ^1 values of the amino acids discussed in this section are mainly limited by covalent constraint; indeed, many of the amino acids described towards the end of the section are essentially rigid.

2.3.1. Tetralin Derivatives

The torsion angles χ^1 and χ^2 are limited in the tetralin derivatives 2-aminotetralin-2-carboxylic acid (Atc) **26**[17] and 2-amino-6-hydroxytetralin-2-carboxylic acid (Hat) **27**.[18]



Atc **26** Hat **27**

Only one of the *gauche* rotamers is accessible to each enantiomer as illustrated for (*S*)-Atc (Figure 8). Molecular modeling of (*R*)- and (*S*)-Hat suggests that the energy difference between the accessible *gauche* and *trans* conformations is negligible (0.1 and 0.3 kcal/mol respectively).[18]

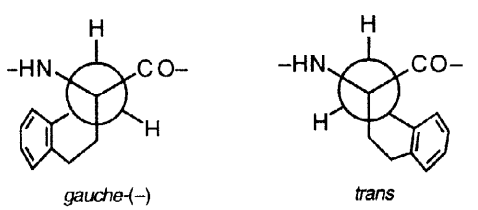
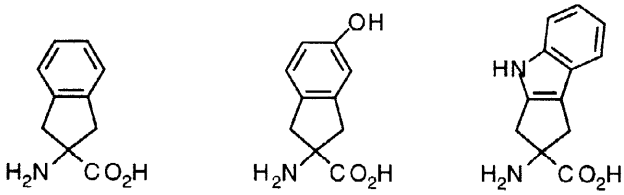


Figure 8. The staggered rotamers of (*S*)-Atc **26**

Racemic mixtures of Atc **26**[17] and Hat **27**[18] have been made via spirohydantoin derivatives prepared from commercially available 2-tetralone or 6-methoxy-2-tetralone. Hydrolysis afforded (±)-Atc **26** and (±)-Hat **27** in 60 and 64% overall yield respectively. Resolutions of the racemates has been accomplished by chromatographic separation of diastereomeric mixtures of tripeptides followed by hydrolysis. This procedure produced (*R*)- and (*S*)-Atc in 41 and 36% yield from (±)-Atc **26**, and (*R*)- and (*S*)-Hat in 32 and 34% yield from (±)-Hat **27**.[19]

2.3.2. Indan derivatives

As with the tetralin derivatives, only two conformations are accessible to the indan derivatives **28-30**: one *gauche* rotamer and the *trans* rotamer (Figure 9).



Aic **28** Hai **29** **30**

Molecular modelling for Hai **29** showed that the energy difference between the two rotamers was only 0.2 kcal/mol.[18]

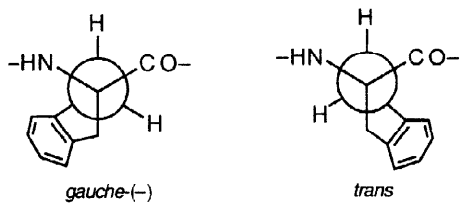
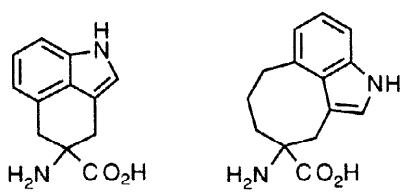


Figure 9. The staggered rotamers of (*S*)-Aic **28**

2-Aminoindan-2-carboxylic acid (Aic) **28**,[17] 2-amino-5-hydroxyindan-2-carboxylic acid (Hai) **29**[18] and 2-amino-2-carboxy-cyclopent[*b*]indole **30**[20] have been synthesised via spirohydantoin derivatives of 2-indanone, 5-hydroxy-2-indanone and 2-cyclopentanone[*b*]indole. Hydrolysis of these derivatives gave Aic, (±)-Hai and (±)-**30** in 60, 60 and 36% overall yield respectively.

2.3.3. Further Tryptophan Derivatives

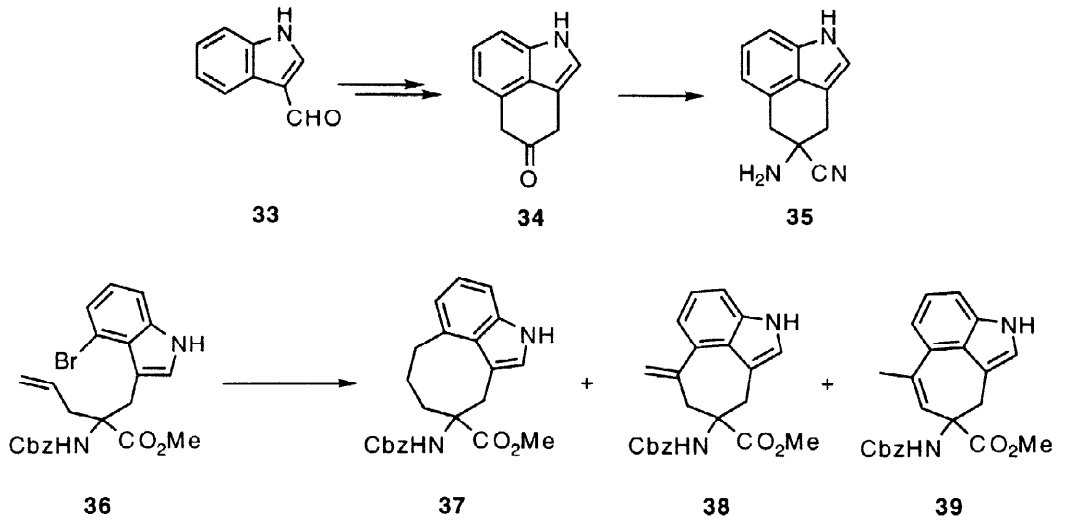
The tricyclic amino acids **31** and **32** differ from the amino acids described thus far in this section in that their α-carbon is tethered not to an ortho position of the aromatic ring, but to a more remote carbon. They are thus structurally unusual and are constrained in a manner quite different to other analogues reported to date. Unfortunately, conformational analysis of these has not been reported.



31 **32**

4-Amino-1,3,4,5-tetrahydrobenz[*cd*]indole-4-carboxylic acid **31** was prepared via a Strecker reaction from ketone **34**, which was obtained in 5 steps and 26% overall yield from indole-3-carboxaldehyde **33**. The α-aminonitrile product of the Strecker **35** reaction was converted to the α-amidoamine, which was hydrolysed to give the desired amino acid **31** in 84% yield.[21] The key intermediate **36** in the synthesis of the eight-membered ring Trp analogue **32** was prepared in 9 steps and 11% overall yield from 4-bromoindole. Cyclisation of **36** using the Heck reaction afforded a 2:1 mixture of the *endo*-cyclised product **37** and the *exo*-cyclised products **38**

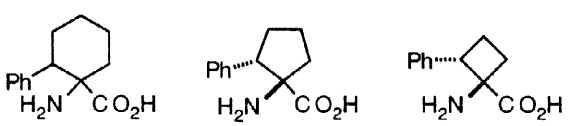
and **39**. The compound of interest, **37**, was isolated in 30% yield, and then hydrogenolysed to give the methyl ester derivative of **32** in 90% yield after crystallisation.[22]



33 **34** **35** **36** **37** **38** **39**

2.3.4. An Attractive Series of Cα-Cβ Tethered Amino Acids

Although amino acids **40-2** represent an attractive series of constrained analogues of Phe, their conformational properties have not been studied in detail.



40 **41** **42**

It is possible, however, to predict that the six-membered ring **40** is likely to adopt chair conformations. Thus, the amino acid *cis*-**40** will exclude the *trans* conformation ($\chi^1 = 180°$) (Figure 10) whereas *trans*-**40** will only access the *trans* and one *gauche* conformation. The five-membered ring amino acid **41** should differ significantly from **40** in conformational flexibility and it is difficult to predict its preferred conformation(s). In constrast cyclobutane derivative **42** is almost rigid and presumably constrained in an eclipsed conformation with χ^1 close to 120°.

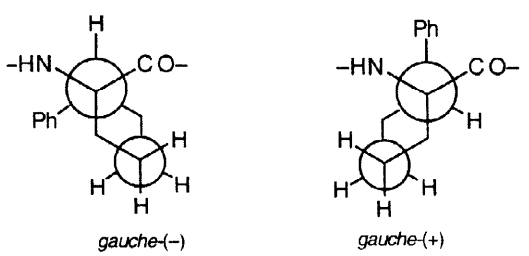
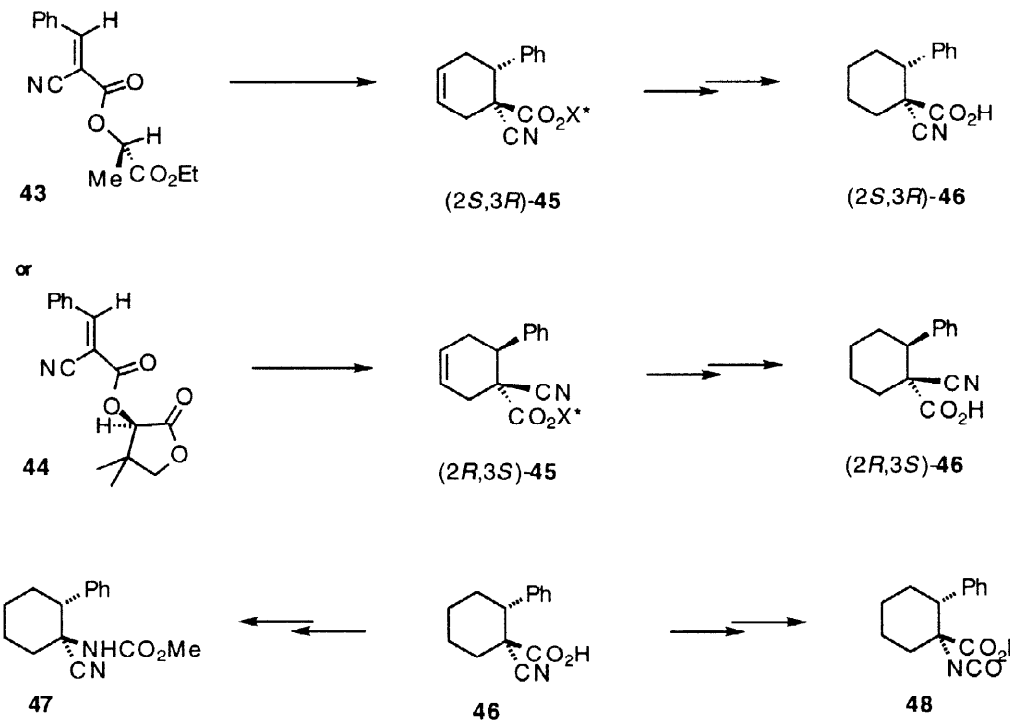


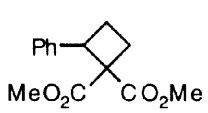
Figure 10. The staggered rotamers of (*S*)-*cis*-**40**

All four stereoisomers of **40** are available. The asymmetric Diels–Alder reaction of chiral (*E*)-2-cyanocinnamates **43** and **44** with 1,3-butadiene in the presence of TiCl4 provides cycloadducts (2*S*,3*R*)-**45** and

(2*R*,3*S*)-**45** in 94:6 and 3:97 ratios respectively. After hydrolysis of the ester and hydrogenation, the saturated cyanocarboxylic acids (2*S*,3*R*)-**46** and (2*R*,3*S*)-**46** were transformed into the acyl azides, which were converted to the carbamates (2*S*,3*R*)-**47** and (2*R*,3*S*)-**47** by means of the Curtius rearrangement; hydrolysis then gave enantiomerically pure *cis*-isomers (2*S*,3*R*)-**40** and (2*R*,3*S*)-**40** in 48 and 44% overall yield from **43** and **44** respectively. The *trans*-diastereomers have also been prepared from **46**. The cyano group was successively transformed into an amido group and then to an isocyanate using the Hofmann rearrangement to give (2*R*,3*R*)-**48** and (2*S*,3*S*)-**48**. Finally hydrolysis gave (2*R*,3*R*)-**40** and (2*S*,3*S*)-**40** in 43 and 39% overall yield from **43** and **44** respectively.[23]



Racemic *trans*-1-amino-2-phenylcyclopentane-1-carboxylic acid **41**[24] has been made in 21% overall yield from the appropriate ketone via the spirohydantoin. Racemic *trans*-1-amino-2-phenylcyclobutane-1-carboxylic acid **42** has been prepared by selective hydrolysis of the ester group *trans* to the phenyl moiety of **49**. A Curtius degradation of the carboxylic acid group thus formed followed by hydrolysis of the remaining methyl ester afforded amino acid **42** in 94% overall yield.[25]



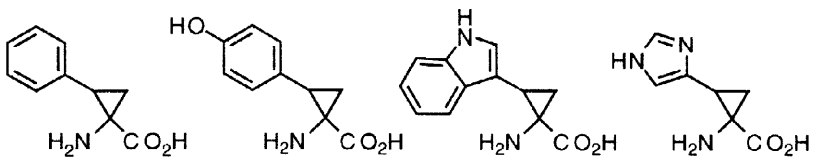
49

2.3.5. Conformationally Rigid Amino Acids

There are two categories of conformationally rigid amino acids: those in which χ^1 is fixed whilst χ^2 is unrestricted and those in which both χ^1 and χ^2 are fixed.

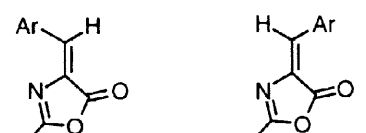
i) Amino Cyclopropanecarboxylic Acids (ACC)

The amino acids **50-53** are constrained in an eclipsed conformation. The torsional angle χ^1 is fixed and equal to 0, +120 and −120° depending on the stereoisomer, whilst χ^2 is unrestricted.



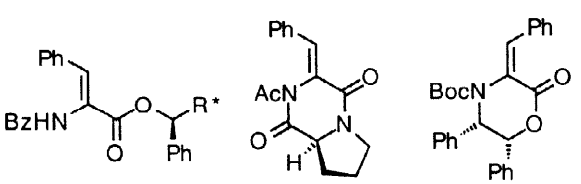
∇-Phe **50** ∇-Tyr **51** ∇-Trp **52** ∇-His **53**

The chemistry and incorporation into peptides of 1-amino-2-cyclopropanecarboxylic acids have been reviewed by Stammer in 1990[26] and by Daunis *et al.* in 1993.[27] The most general route to amino acids 2,3-methanophenylalanine (∇-Phe) **50**,[28] 2,3-methanotyrosine (∇-Tyr) **51**,[29] 2,3-methanotryptophan (∇-Trp) **52**[30] and 2,3-methanohistidine (∇-His) **53**[31] involves cyclopropanation of 2-aryl-4-benzylideneoxazolones **54**, which are formed by 1,3-dipolar cycloaddition of diazomethane, followed by thermolysis of the intermediate pyrazoline. The (*Z*)- or (*E*)-geometric isomer of each amino acid can be obtained by starting with easily accessible (*Z*)-**54** or (*E*)-**54**. The cyclopropanation works moderately well and subsequent chemical transformations provide the amino acids in low to moderate overall yield from **54** (8-38%).



(*Z*)-**54** (*E*)-**54**

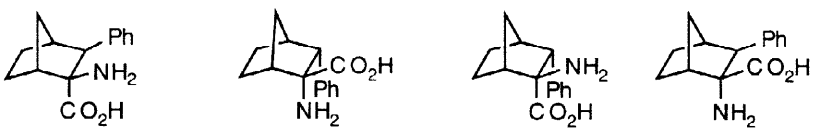
Several asymmetric syntheses of (*Z*)-**50** and (*E*)-**50** have been reported recently. An approach that has received considerable attention was based on selective cyclopropanation of a non-racemic chiral substrate e.g. α-benzamidocinnamates **55**, diketopiperazine **56** or α,β-unsaturated lactone **57**. Cyclopropanation of **55** gave a mixture of pyrazolines in a 60:40 diastereomeric ratio, which provided the enantiomers (*Z*)-(2*S*,3*S*)-(−)-**50** and (*Z*)-(2*R*,3*R*)-(+)-**50** respectively in 27 and 18% overall yield from **55** and 3 steps, after separation by column chromatography, photolysis and hydrolysis.[32] Cyclopropanation of **56** occurred with better diastereoselectivity (5:95); the minor diastereomer was removed after crystallisation to afford (+)-(*Z*)-**50** after hydrolysis (in 47% overall yield from **56** in 3 steps).[32] The most successful route was the cyclopropanation of **57** since it gave a single diastereomer; moreover this opened up the pathway to (*E*)-(2*S*,3*R*)-(+)-**50** (9 steps, 21% yield from **57**).[33]



55 **56** **57**

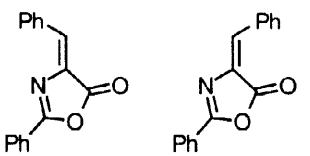
ii) Methanocyclohexane Derivatives

As with the previous amino acids **50-53**, the χ^1 angles of methanocyclohexane derivatives **58-61** are fixed and equal to 0, +120 or −120° depending upon the stereoisomer under consideration, whilst χ^2 is unrestricted.



58 **59** **60** **61**

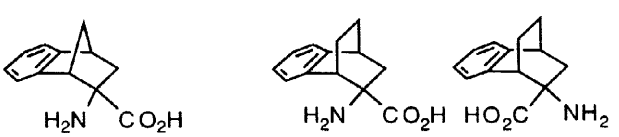
2-Amino-3-phenylnorbornane-2-carboxylic acids (or methanocyclohexanologues) **58-61** have been prepared using, as the key step, a Diels–Alder reaction between cyclopentadiene and one of the dienophiles ethyl α-nitrocinnamate[34] (*E*)-methyl α-cyanocinnamate[35] and (*Z*)- or (*E*)-2-phenyl-4-benzylidene-5(4H)-oxazolones **62**.[36] Focussing on the Diels-Alder reaction between cyclopentadiene and (*Z*)-**62** and (*E*)-**62**, the product mixtures of *endo*- and *exo*-spiroxazolones were hydrolysed and the amino acids were separated via an iodolactonisation procedure. Hydrogenolysis of the carbon-carbon double bond and subsequent hydrolysis of the benzamido group gave the amino acids **58** and **59** in 17 and 26% from (*Z*)-**62** and amino acids **60** and **61** in 39 and 5% overall yields from (*E*)-**62**.



(*Z*)-**62** (*E*)-**62**

iii) Methano- and Ethanotetralin Derivatives

The amino acids **63** and **64** are the most rigid analogues of Phe ever synthesised. The values of χ^1 are −60 or −180° and χ^2 is −60°.



63 **64a** **64b**

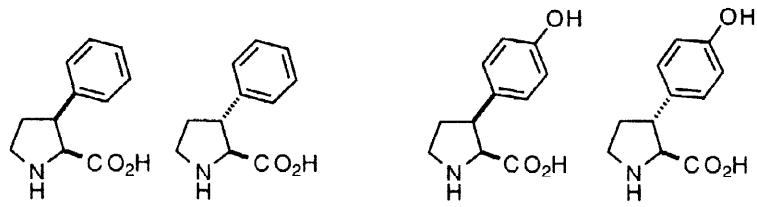
2-*endo*-Amino-1,2,3,4-tetrahydro-1,4-methanonaphthalene-2-*exo*-carboxylic acid **63** has been prepared in 21% overall yield via the Strecker method and in 61% overall yield via the Bucherer method from the corresponding ketone. Interestingly the two methods gave exclusively stereoisomer **63**.[37] The synthesis of 2-amino-1,2,3,4-tetrahydro-1,4-ethanonaphthalene-2-carboxylic acid **64** has been achieved similarly. Again the yields via the Bucherer route were superior but this time a nearly equal mixture of isomeric hydantoins was obtained from the appropriate ketone. Separation of the two hydantoins by fractional crystallisation or column chromatography followed by hydrolysis gave **64a** and **64b** in 54 and 27% overall yield respectively.[38]

2.4. Constrained "Imino Acids"

In the "imino acids", the nitrogen of the amino functional group is part of a ring. This may have serious consequences for the conformation of the peptide, peptidomimetic etc into which the amino acid is incorporated, since the nitrogen is consequently unable to act as a hydrogen bond donor unless it is located in a terminal position of the larger molecule. Nevertheless, as will be seen in Section 3, this type of amino acid has proven very useful in biological studies. In this section, amino acids which are tethered from the nitrogen to Cβ will be presented first, followed by amino acids which are tethered between the nitrogen and the aromatic ring.

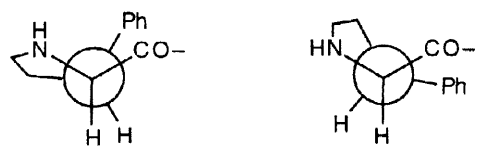
2.4.1. Aryl-Proline Derivatives

Rotational freedom in the Phe and Tyr analogues **65-68** is severely limited for χ^1 but unrestricted about χ^2.



65 **66** *cis*-Hpp **67** *trans*-Hpp **68**

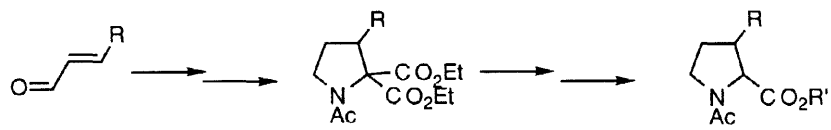
In both the *cis*- and *trans*-geometric isomers one of the *gauche* rotamers is physically not accessible (Figure 11). Furthermore, molecular modeling of (2*S*,3*R*)-**67** and (2*S*,3*R*)-**68** indicated that the *trans* conformation was preferred by up to 2 kcal/mol over the accessible *gauche* isomer.[18]



gauche-(+) *trans*

Figure 11. The staggered rotamers of (2*S*,3*R*)-**66**

Amino acids **65-8** are available via a route which began with condensation of diethyl acetamidomalonate with the α,β-unsaturated aldehydes **69.** Subsequent 5-deoxygenation gave the pyrrolidine derivatives **70**. As a result of slightly different reaction conditions, saponification and decarboxylation of **70a** and **70b** afforded the ethyl ester **71a** and the carboxylic acid **71b** respectively. The *cis*- and *trans*-isomers of **71a** were separated by selective saponification of the ester of the *trans*-isomer.[39] *N*-Deacetylation and *O*-demethylation of **71b** provided *cis*-Hpp **67** and *trans*-Hpp **68** which were *N*-Boc protected and separated by preparative reverse-phase HPLC.[18,40]

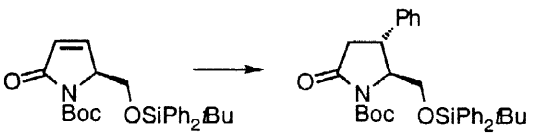


69a: R=Ph
69b: R=*p*-MeOC$_6$H$_4$

70a: R=Ph
70b: R=*p*-MeOC$_6$H$_4$

71a: R=Ph, R'=Et
71b: R=*p*-MeOC$_6$H$_4$, R'=H

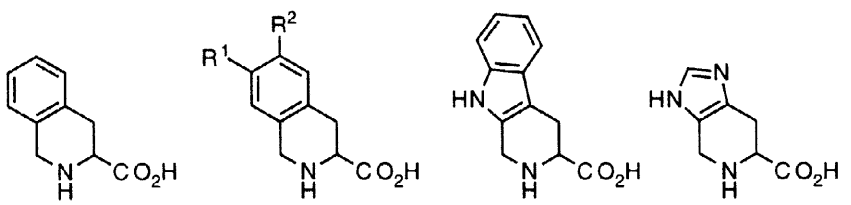
To separate enantiomers of **66**, its *N*-acetyl-derivative was coupled with (*S*)-(–)-α-methylbenzylamine.[39a] The resulting diastereomers were separated by column chromatography and then hydrolysed to give (2*R*,3*S*)-**66** and (2*S*,3*R*)-**66** in 30 to 40% yield. A diastereoselective synthesis of (2*S*,3*R*)-**66** has also been reported, the key step being a 1,4-conjugate addition of cuprate or Grignard reagent to the readily available (*S*)-pyroglutamic acid derivative **72**.[41] This addition proceeded in >98% d.e. and good yield. Compound (2*S*,3*R*)-**66** was subsequently obtained from **73** in three steps and 16% yield. This synthetic strategy should also be applicable to the synthesis of (2*R*,3*S*)-**66** starting with commercially available (*R*)-pyroglutamic acid.



72 **73**

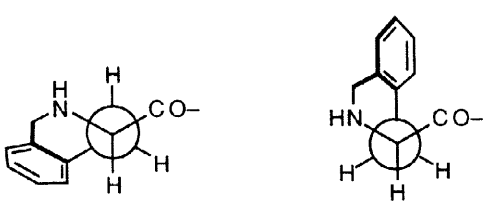
2.4.2. Pipecolic Acid Derivatives

The bicyclic nature of **74-78** means that both χ^1 and χ^2 are greatly limited.



Tic **74** Htc **75** : R^1=OH, R^2=H; *m*-Htc **76** : R^1=H, R^2=OH Tcc **77** Spi **78**

For the (*S*)-amino acids (Figure 12), the *gauche*-(–) and the *gauche*-(+) conformations are both available with the *trans* rotamer being eliminated.[18]



gauche-(–) *gauche*-(+)

Figure 12. The staggered rotamers of (*S*)-Tic **74**

1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid (Tic) **74**,[42] 1,2,3,4-tetrahydro-7-hydroxyisoquinoline-3-carboxylic acid (Htc) **75**,[43] 1,2,3,4-tetrahydro-6-hydroxyisoquinoline-3-carboxylic acid (*m*-Htc) **76**,[44] 3-carboxy-1,2,3,4-tetrahydro-2-carboline (Tcc) **77**[45] and spinacine (Spi) **78**[46] have all been synthesised using the Pictet–Spengler reaction[47] or modifications thereof, i.e. by cyclocondensation of the amino acids Phe, Tyr, *m*-Tyr, Trp and His respectively with formaldehyde in the presence of concentrated hydrochloric acid. In general

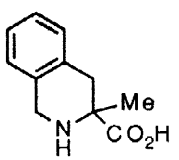
these reactions proceed in good yields (70-97% yield) except in the case of tyrosine, when polymerisation occurs. This can be avoided by performing the reaction under weakly acidic conditions,[44] or by starting from tyrosine derivatives in which the positions *ortho* to the phenolic OH are blocked by halogen atoms.[43]

(±)-Tic **74** may also be prepared efficiently in one pot via base catalysed cyclisation of 1,2-bis(halomethyl)benzenes with diethyl acetamidomalonate followed by hydrolysis and decarboxylation in 65-70% yield.[48] This method may be performed on a large scale and is safer than the Pictet–Spengler approach as it avoids the possible formation of extremely carcinogenic di-(chloromethyl) ether (by reaction of hydrochloric acid with formaldehyde).

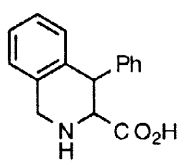
Enantiomerically pure amino acids **74-78** may be obtained using enantiomerically pure amino acids in the Pictet–Spengler reaction. Partial racemisation[43] occurs during the course of the reaction and fractional crystallisation is necessary to obtain the desired amino acids in good e.e. (90-99%).[49,50]

2.4.3. α-, β- and α,β-Substitutions on Tic

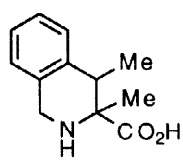
Of the Tic derivatives **79-81**, conformational studies have only been performed on **81**. Interestingly, the *gauche*-(+) conformation is preferred over the *gauche*-(-) conformation by 13.5 kcal/mol for (2*R*,3*S*)-**81** and by 5 kcal/mol for (2*R*,3*R*)-**81** in Ac-(Me)$_2$-Tic-NHMe.[16] Thus it appears that here the cyclisation and substitution constraints are additive, producing molecules which are essentially locked into one conformation.



α-MeTic **79**



β-PhTic **80**



α,β-(Me)$_2$-Tic **81**

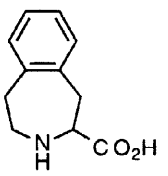
Racemic 2-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (α-MeTic) **79**[51] has been synthesised in 63% yield from (±)-α-methylphenylalanine by the Pictet–Spengler reaction. An asymmetric synthesis of **79** has been achieved and is based on the diastereoselective alkylation in 97% e.e. of a commercially available bislactim ether with a dibromoxylene followed by spontaneous cyclisation upon heating. Hydrolysis of the intermediate afforded (*R*)-**79** in good yield.[52]

The four stereoisomers of 1,2,3,4-tetrahydro-4-phenyl-isoquinoline-3-carboxylic acid (β-PhTic) **80**[53] have been prepared via the Pictet–Spengler reaction of the *N*-carbamates of (*R*)- and (*S*)-Dip **7** methyl esters. The diastereomers obtained were separated by column chromatography and hydrolysis gave the β-PhTic *trans*- and *cis*-isomers in 35-48 and 13-18% overall yield from their respective Dip parents.

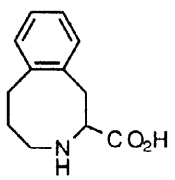
The stereoisomers of α,β-dimethyl-Tic **81** have been synthesised in 71-84% yield from the four stereoisomers of α,β-dimethylphenylalanine **19** using the Pictet–Spengler reaction.[16]

2.4.4. A Homologous Series Based on Tic

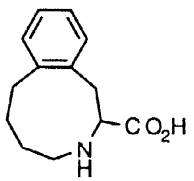
The 7-, 8- and 9-membered rings analogues of Tic, 2,3,4,5-tetrahydro-1*H*-3-benzazepine-2-carboxylic acid (Sic) **82**, 1,2,3,4,5,6-hexahydro-3-benzazocine-2-carboxylic acid (Hic) **83**, and 2,3,4,5,6,7-hexahydro-1*H*-3-benzazonine-2-carboxylic acid (Nic) **84**, have been prepared by two routes from substrates **85a-c**, which were obtained in 42, 32 and 27% yield from commercially available 2-iodobenzyl alcohol.



Sic **82**

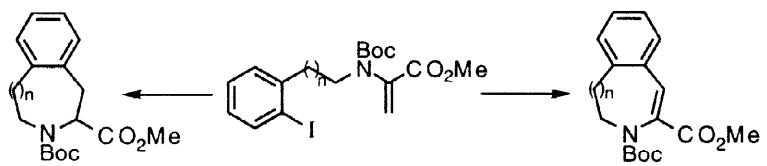


Hic **83**



Nic **84**

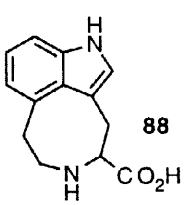
An intramolecular Heck reaction gave the 7-, 8- and 9-*endo*-cyclised products **86a-c** in 55, 73 and 86% yield respectively[54] whereas a radical cyclisation approach gave **87a-c** in 73, 71 and 52% yield.[55] Hydrogenation of the double bond of **86** and removal of the protecting groups in **87** afforded Sic, Hic and Nic. Thus the two routes are complementary and provide Sic, Hic and Nic in 9-12 steps and 14-30% overall yield.



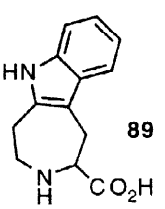
87a-c **85a-c** **86a-c**

2.4.5. Medium-sized Ring Derivatives of Trp

The tricyclic Trp derivatives **88** and **89** present two distinct modes of tethering the indole unit of Trp to the amino acid nitrogen. In both instances χ^1 will be limited by the cyclic structure, but the greatest difference will be in χ^2 values. Unfortunately their conformational analyses have not been reported to date.

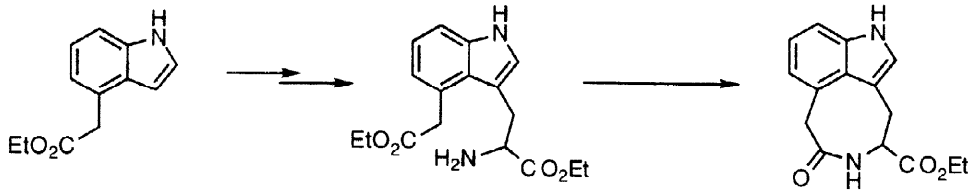


88



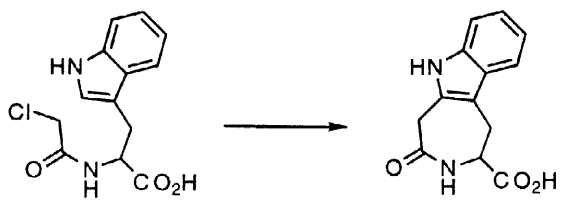
89

A synthetic route which could provide the eight-membered ring compound **88** on a larger scale than the initial photochemical cyclisation routes[56] has been reported.[57] It is based on the thermal lactamisation of intermediate **91**, which was obtained in two steps from 4-(carboethoxymethyl)indole **90**. A chemoselective reduction of the amide group in **92** afforded the ethyl ester of **88** in 15% overall yield from **90**. Saponification would provide **88**.



90 91 92

The seven-membered ring derivative **94** has been unexpectedly obtained by photocyclisation of *N*-chloroacetyl tryptophan **93** (no yield given).[56] Selective reduction of the amide group as for **92**, should provide access to **89**.



93 94

2.5. Summary of Molecular Mechanics Calculations of χ^1 and χ^2

The results of the molecular modeling available for the amino acids described in the previous sections are summarised in Table 3.

3. Applications in Medicinal Chemistry

3.1. General

Structure-activity investigations have shown that a relatively short sequence of four to eight amino acids is usually responsible for the biological activity of peptides. Moreover, the side chain groups of the constituent amino acids are generally responsible for the interactions with the receptor that lead to binding and/or activation.[4,61] Hence the aim in conformational design is often the construction of a suitable scaffold to carry the relevant functional groups in a suitable spatial arrangement. The concept of topographical design of peptide ligands was introduced nearly ten years ago by V. Hruby.[62] It involves creating a particular three dimensional arrangement of the side chains in a peptide by constraining, biasing or fixing the side chain conformers using the amino acids of the type described in the previous sections. It is important to realise that the orientation of a side chain *relative to the peptide backbone* varies dramatically from one conformation to another. For example, in the *gauche*-(+) conformation of the (*S*)-, proteinogenic aromatic amino acids, the aromatic group is located below/above the peptide backbone, in the *trans* conformation the aromatic ring points toward the *C*-terminus, and in the *gauche*-(−) conformation, it points toward the *N*-terminus of the peptide chain.

amino acid	label	rotamer	χ^1 (°)	χ^2 (°)	ΔE (kcal/mol)[a,b]	ref
Atc	(*S*)-**26**	*trans*	−180	+25	(−)	17
		gauche(+)	−60	−25	(−)	
	(*R*)-**26**	*trans*	+180	−25	(−)	17
		gauche(−)	+60	+25	(−)	
Hat	(*S*)-**27**	*trans*	−168	+20	0.3	18
		gauche(−)	−71	−20	0.0	
	(*R*)-**27**	*trans*	+168	−20	0.1	18
		gauche(+)	+71	+20	0.0	
Aic	**28**	*trans*	−160	+20	(−)	58
		gauche(−)	−80	−20	(−)	
Hai	**29**	*trans*	−134	+9	0.0	18
		gauche(−)	−97	−13	0.2	
cis-Hpp	(2*S*,3*R*)-**67**	*trans*	−151	+64	0.0	18
		gauche(−)	−91	+68	2.0	
trans-Hpp	(2*S*,3*S*)-**68**	*trans*	+165	+99	1.8	18
		gauche(+)	+88	−66	0.0	
Tic[c]	(*R*)-**74**	*gauche*(−)	-59	+34	(-)	59
Htc	(*S*)-**75**	*gauche*(−)	−36	+41	0.0	18
		gauche(+)	+30	−39	0.3	
Tcc	(*S*)-**77**	*gauche*(−)	−47	+18	(−)	60
		gauche(+)	+48	−20	(−)	
α,β-(Me)$_2$Tic[d]	(2*R*,3*S*)-**81**	*gauche*(+)	+55	(−)	0.0	16
		gauche(−)	−71	(−)	13.5	
	(2*R*,3*R*)-**81**	*gauche*(+)	+52	(−)	0.0	16
		gauche(−)	−64	(−)	5.0	

a) ΔE: calculated energy difference between the entry and the global minimum of the compound; b) (−): ΔE not calculated; c) data from an X-ray analysis of p-Bz-L-Pro-D-Tic-NHMe; d) study of Ac-(2,3-Me$_2$)Tic-NHMe.

Table 3. Experimental values of the torsional angles χ^1 and χ^2 in low energy conformations of constrained amino acids calculated by molecular modelling

Increasing attention is now being given to the incorporation of conformationally restricted amino acids Phe, Tyr and Trp (and more rarely His) into peptides and their analogues, not only in order to examine the conformational requirements of the side chain for bioactivity, but also in the hope of obtaining more selective and potent ligands. For example, the properties and use of the four stereoisomers of β-alkylated derivatives of Phe and Trp have been studied extensively.[3] For a given peptide, incorporation of each stereoisomer results in the same backbone conformation, but produces different topographies of the peptides thus leading to significant differences in potency and selectivity.

In this section, in order to provide the reader with an insight into the biological potential of the amino acids detailed in Section 2, we describe two areas where the use of constrained analogues of Phe and Tyr have had a significant impact, namely, the development of selective opioid ligands, and the identification of potent Ras farnesyl transferase inhibitors. [NB. In this section, the absolute configuration of the α-carbon is designated with the prefix D- for (*R*)-amino acids, and no prefix for the (*S*)-amino acids.]

3.2. Development of Selective Opioid Ligands

3.2.1. Opioid Receptors

Opioid receptors are distributed widely throughout the brain and the peripheral tissues of all animals.[63] Potent agonists for the opioid receptors have the potential to attenuate acute and chronic pain whereas potent antagonists could alleviate addiction to narcotic alkaloids and alcohol dependence, and serve as immunosuppressive agents. The existence of at least three major opioid receptor classes μ, δ and κ, is now well established. The endogeneous mammalian opioid ligands, enkephalins, endorphins and dynorphins, are not particularly selective towards the different receptor classes, but dermorphins and deltorphins, isolated from frog skin secretions, are μ- and δ-selective respectively. An important goal in this area of research has been to develop highly selective and potent ligands to help elucidate the functions of opioid receptors and their subtypes.

3.2.2. δ-Opioid Receptor Antagonists

An important feature of dermorphins and deltorphins is their common *N*-terminus tripeptide sequence "Tyr-D-Xaa-Phe". Interestingly, structure-activity studies of this common fragment suggested that it plays a pivotal role in opioid selectivity. For example, in 1992, Schiller and co-workers reported that the simple peptide **95**, which is a μ-selective agonist, becomes a δ-selective antagonist when D-Phe is replaced with Phe in position 2 (peptide **96**).[64] Furthermore, the activity profile and stability of peptide **96** was dramatically improved by successively using Tic in position 2 (peptides **97** and **98**),[64] having a free carboxylic acid group (peptides **99** and **100**),[64] and by introducing a reduced peptide bond [CH_2NH] between Tic and Phe (pseudopeptides **101** and **102**).[65]

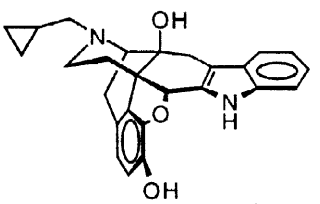
Tyr-D-Phe-Phe-Phe-NH_2	**95**	Tyr-Tic-Phe-Phe-OH (TIPP)	**99**
Tyr-Phe-Phe-Phe-NH_2	**96**	Tyr-Tic-Phe-OH (TIP)	**100**
Tyr-Tic-Phe-Phe-NH_2	**97**	Tyr-Ticψ[CH_2NH]Phe-Phe-OH (TIPP[ψ])	**101**
Tyr-Tic-Phe-NH_2	**98**	Tyr-Ticψ[CH_2NH]Phe-OH (TIP[ψ])	**102**

The di- and tripeptides antagonists **103-6**, reported in 1994 by Temussi and co-workers, proved to be even more δ-selective than TIP(P), (**99** and **100**), but were less potent.[66] This disadvantage was remedied by

replacing Tyr^1 with 2',6'-dimethyl-L-tyrosine (Dmt) (peptides **107-111**)[67,68] and *N,N*-$(Me)_2$-Dmt (peptides **112-115**) to give more hydrophobic and further restricted analogues of **103-6**.[69] These peptides surpassed the δ-selectivity of all opioid ligands known to date, in particular peptide **107** (K_i^{μ}/K_i^{δ} = 150,800). Peptides **112-4** are considerably more selective and of similar potency to the benchmark non-peptide δ-antagonist naltrindole **116**[70] in the mouse *vas deferens* assay. Interestingly, as seen in the original peptide **95**, a change of chirality from L- to D-Tic^2 in peptides **97, 98, 104, 105, 108** and **110** reversed the opioid activity from δ-antagonist to μ-agonist.

Tyr-Tic-OH	**103**	Dmt-Tic-Ala-NH_2	**110**
Tyr-Tic-NH_2	**104**	*cyclo*-(Dmt-Tic)	**111**
Tyr-Tic-Ala-OH	**105**	*N,N*-$(Me)_2$-Dmt-Tic-OH	**112**
Tyr-Tic-Ala-NH_2	**106**	*N,N*-$(Me)_2$-Dmt-Tic-NH_2	**113**
Dmt-Tic-OH	**107**	*N,N*-$(Me)_2$-Dmt-Tic-Ala-OH	**114**
Dmt-Tic-NH_2	**108**	*N,N*-$(Me)_2$-Dmt-Tic-Ala-NH_2	**115**
Dmt-Tic-Ala-OH	**109**		

Conformational analysis of **99-102, 104, 106, 108** and **111** (based on NMR studies, molecular modeling and X-ray data), revealed that their low energy conformations are consistent with the structure of the highly potent but non-selective opioid antagonist naltrindole **116**.[71-2] Hence their respective bioactive conformations are probably very similar. Unlike the aromatic ring of Tic, the aromatic side chains of residues 3 and/or 4 are not required for δ-selectivity; they only provide additional binding energy due to their lipophilic character.[73] This leaves Tyr^1-Tic^2 and Dmt^1-Tic^2 responsible for antagonism at the δ-opioid receptor: in other words they are the recognition site ("message domain") of the peptides. *In vivo* results obtained for **99, 100, 107** and **109** are very encouraging and these peptides may be used as templates for the construction of still more active δ-opioid antagonists.[74]



116

3.2.3. δ-Opioid Receptor Agonists

The cyclic enkephalin analogue DPDPE **117** is a highly selective lead for δ-opioid receptor agonists. Its further constrained analogue, JOM-13 **118**, has higher affinity for the δ-opioid receptor, but is slightly less δ-selective (K_i^{μ}/K_i^{δ} = 60 and 204 respectively). Thus although the conformational flexibility of the backbone of **117** is considerably reduced on moving to **118**, the mobility of the side-chains of the Tyr^1 and Phe^3 residues, is still high. To elucidate their conformational requirements for bioactivity, the exocyclic Tyr^1 residue was replaced with *cis*-Hpp, *trans*-Hpp, Htc, Hat, Hai and α-MeTyr (peptides **119**),[18,40] and the Phe^3 residue was replaced with the four stereoisomers of β-MePhe (peptides **120**).[75] The incorporation of *cis*-Hpp^1 in **119** and (2*R*,3*R*)-β-$MePhe^3$ in **120** resulted in agonists with significantly higher δ-selectivity (K_i^{μ}/K_i^{δ} = 300 and 2100 respectively) and δ-affinity than **117** and **118**. From these results and molecular mechanics calculations, Mosberg and co-workers proposed a model for the bioactive conformation of **118** in which the side-chain

conformation of residue 1 was described by $\chi^1 \approx 180°$ and $\chi^2 \approx 90°$, and the side-chain conformation of residue 3 by $\chi^1 \approx -60°$.[18]

Tyr-*cyclo*-[D-Pen-Gly-Phe-D-Pen]OH (DPDPE) **117**
Tyr-*cyclo*-[D-Cys-Phe-D-Pen]OH (JOM-13) **118**
Xaa-*cyclo*-[D-Cys-Phe-D-Pen]OH **119**
Tyr-*cyclo*-[D-Cys-Xaa-D-Pen]OH **120**

A similar study conducted with DPDPE **117** has led to more selective analogues. In this case, Hat and the stereoisomers of β-MePhe were used to substitute Tyr^1 and the stereoisomers of β-MePhe were incorporated in place of Phe^4.[76]

3.2.4. μ-Opioid Receptor Antagonists

Starting from a somatostatin-derived cyclic peptide CTP **121**, Hruby and co-workers have reached the most potent and selective μ-opioid receptor antagonists to date by replacing inter alia $D\text{-}Phe^1$ with D-Tic (peptides **122-4**).[77]

D-Phe-*cyclo*-[Cys-Tyr-D-Trp-Lys-Thr-Pen]-Thr-NH_2 (CTP) **121**
D-Tic-*cyclo*-[Cys-Tyr-D-Trp-Lys-Thr-Pen]-Thr-NH_2 (TCTP) **122**
D-Tic-*cyclo*-[Cys-Tyr-D-Orn-Thr-Pen]-Thr-NH_2 (TCTOP) **123**
D-Tic-*cyclo*-[Cys-Tyr-D-Trp-Arg-Thr-Pen]-Thr-NH_2 (TCTAP) **124**
Gly-D-Tic-*cyclo*-[Cys-Tyr-D-Trp-Orn-Thr-Pen]-Thr-NH_2 **125**
D-Phe-*cyclo*-[Cys-D-Tic-D-Trp-Orn-Thr-Pen]-Thr-NH_2 **126**

NMR studies on these peptides have shown that when D-Tic is terminal it adopts the common *gauche*-(+) conformation, which orientates the aromatic ring away from the rest of the molecule, but places it on the same face as the other important parts of the pharmacophore. When D-Tic is internal (peptides **125** and **126**),[77] a dramatic loss of affinity and selectivity is observed. NMR studies of these peptides demonstrated that the backbone conformation of the peptide remained unchanged but that the internal D-Tic residue now adopts the rare *gauche*-(−) conformation as 1,2-pseudoequatorial repulsion destabilises the *gauche*-(+) conformation (Figure 13).[78]

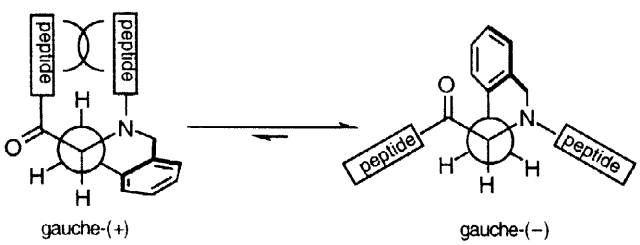


Figure 13. Two possible conformers of D-Tic in a peptide

3.3. Inhibition of Ras Farnesyl Transferase

3.3.1. A potential new class of anticancer drugs

Ras proteins are involved in regulating cellular growth in mammals.[79] Mutations in Ras proteins can lead to unregulated cell division and are found in a significant number of human cancers including pancreatic, colon and lung carcinomas.

Ras proteins undergo several post-translational modifications before reaching their site of action in the cell membrane. The first and most important modification is the *S*-farnesylation of a cysteine residue found in the

CA_1A_2X *C*-terminal sequence (where C is Cys^{186}, A_1 and A_2 are usually aliphatic amino acids and X is Met or Ser). This modification is catalysed by the enzyme farnesyl transferase (FTase) using farnesylpyrophosphate as a co-substrate. Genetic studies have shown that inhibition of Ras *S*-farnesylation blocks the Ras-induced cell transformation. As a result, inhibitors of farnesyl transferase might slow the growth of cancers in which oncogenic Ras proteins are involved; they thus represent a family of potential antitumour agents.

3.3.2. Development of Ras Farnesyl Transferase Inhibitors

Several types of FTase inhibitors have been reported, among them the Ras terminal tetrapeptides CA_1A_2X mentioned above, which are potent competitive inhibitors of FTase *in vitro*. In particular, Cys-Val-Phe-Met (CVFM) **127** has been used recently as a lead for the development of more potent and more biostable inhibitors.

	FTase inhibition IC_{50} (nM)	
Cys-Val-Phe-Met (CVFM)	37	**127**
Lys-Cys-Val-Phe-Met (KCVFM)	1000	**128**
Lys-Cys-Val-D-Tic-Met	20	**129**
Lys-Cys-(*N*-Me)Val-D-Tic-Met	5	**130**
Cys-Val-Aic-Met	2900	**131**
Cys-Val-(Δ-Phe)-Met	160	**132**
Cys-Val-Tic-Met	1	**133**

In 1995, the inhibitory activity of the peptide KCVFM **128** was dramatically increased by the replacement of Val-Phe with Val-D-Tic and by *N*-MeVal-D-Tic (peptides **129** and **130**).[79] An interesting study followed that demonstrated that when the aromatic ring of the Phe residue in **127** is held perpendicular to the backbone of the tetrapeptide with Aic (peptide **131**), the inhibitory potency decreases by 100 fold. In constrast, when the aromatic ring is held parallel to the backbone using didehydrophenylalanine (peptide **132**), the inhibitor is only slightly less potent than CVFM. A further breakthrough was made by substituting Phe with Tic to give the potent peptide **133**.[80] Subsequent amide bond modifications in **133** led to the more potent and selective inhibitors **134-6**, which also demonstrated enhanced activity in cell-based and isolated enzyme assays compared to the parent peptide **127**.[80]

	FTase inhibition IC_{50} (nM)	
Cys-ψ[CH_2NH]-Val-Tic-Met	0.60	**134**
Cys-Val-ψ[CH_2NH]-Tic-Met	0.37	**135**
Cys-ψ[CH_2NH]-Val-ψ[CH_2NH]-Tic-Met	0.75	**136**

Molecular modeling of KCVFM analogues **129** and **130** indicated that an extended conformation is prefered over a "turn-like" backbone structure.[143] NMR studies and molecular modeling would provide some interesting indications about the preferred conformation of Tic, *gauche*-(+) or *gauche*-(−), in peptides **133-6**.

3.4. Other Examples of Uses in Biological Studies

Constrained analogues of Phe, Tyr, Trp and His have been incorporated into various peptides. Their incorporation into lead peptides has led to more potent and more selective receptor antagonists of bradykinin (Tic)[81] and endothelin (D-Dip).[82] They have also proved to be useful in the development of angiotensin converting enzyme inhibitors (Tic)[83] and in the development of highly selective thrombin inhibitors (Dip, Flg, Tic).[10c,84] The control of χ^1 in residue 8 in [Sar^1-Xaa^8]-AII, offers either a potent angiotensin II agonist (Dip)

or a potent antagonist (Aic).[85] Analysis of position 3 of deltorphin I and/or II with Atc[86] and β-MePhe[87] led to the most active and δ-selective opioid receptor agonist deltorphin analogues reported to date.[86] Although the use of His analogues is quite rare, one example is its use in the analysis of position 4 of deltorphin A (Spi).[88] Constrained analogues of Phe (Tic, Dip, Flg, Ing) have been incorporated into positions 7 or 8 of substance P and used to probe the binding pocket S_7 and S_8 of tachykinin NK-1 receptor,[14,89] whilst Tic has been used in a search for new analogues of human growth hormone-releasing hormone.[90] Finally, the constrained Phe analogues, Tic, Sic, Hic and Hic have recently been incorporated into a CCK_B/gastrin receptor antagonist to probe the effect of constraining the aromatic group of Phe in a six-, seven-, eight- and nine-membered ring respectively. Interestingly, whilst the Tic, Sic and Hic containing compounds were relatively inactive, the Nic containing ligand displayed essentially identical biological characteristics as the parent Phe-containing ligand.[91]

4. Summary and Outlook

Topographical changes alone can greatly affect the potency and selectivity of peptidic ligands. Though this approach to ligand design is in its infancy, significant progress has been made and some very impressive peptide-based ligands have been discovered.

Conformationally constrained amino acids are important tools for the exploration of χ space. There is currently a variety of constrained analogues of Phe, Tyr, Trp and His available from routes based either on classical reactions combined with resolution procedures or on contemporary stereoselective methodology. These amino acids provide some degree of control over the orientation of the aromatic side-chains by restricting χ^1 and/or χ^2. There is, however, a need for a deeper understanding of the conformational properties of many of these amino acids, and for the design, synthesis and conformational analysis of novel amino acids with well-defined χ^1 and χ^2 angles.

Given the importance of peptides in biological systems, it is predicted that constrained analogues of the proteinogenic amino acids will become increasingly important tools in structure-activity studies, and in the rational design of pharmaceutical products.

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Biographical sketch

Susan E. Gibson

Nathalie Guillo

Matthew J. Tozer

Sue Gibson (née Thomas), born in 1960, studied Natural Sciences at Cambridge University before undertaking doctoral research work with Professor Stephen Davies at Oxford University. A Research Fellowship awarded by the Royal Society enabled her to study with Professor Albert Eschenmoser at the ETH Zürich, after which she returned to the UK to take up a Lectureship at the University of Warwick in 1985. In 1990 she moved to Imperial College, London and in late 1998 she will take up the Daniell Chair of Chemistry at King's College London. Sue Gibson's research interests include the synthesis and reactivity of transition metal complexes both in solution and polymer-bound, and applications of transition metal chemistry in organic synthesis, especially amino acid synthesis.

Nathalie Guillo, born in 1971, studied for her B.Sc. at Kingston University. She then moved to Imperial College, London to study for her Ph.D. under the guidance of Sue Gibson. Her research there included the synthesis of the novel amino acids Sic, Hic and Nic, and their incorporation into CCK_B/gastrin receptor antagonists. Nathalie Guillo is currently carrying out post-doctoral research with Professor Leo Paquette at the University of Ohio under the auspices of a Glaxo Fellowship.

Matt Tozer, born in 1965, studied undergraduate Chemistry at Imperial College. Postgraduate research at the same institution, under the guidance of Professor William Motherwell, introduced him to the areas of radical chemistry and fluorination methods, interests which he developed in his post-doctoral work with Professor Athel Beckwith at the ANU in Canberra and then Professor Jack Baldwin at Oxford University. In 1993 Matt Tozer joined the James Black Foundation in London, where he currently works as a medicinal chemist.