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Resolution of (1*R*,2*R*)- and (1*S*,2*S*)-Cyclic Constrained Phenylalanine Analogues (c_6Phe). Conformations of (1*R*,2*R*)- and (1*S*,2*S*)-c_6Phe containing Peptides

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Abstract: The enantiomerically pure (1*R*,2*R*)- and (1*S*,2*S*)-1-amino-2-phenylcyclohexane-1-carboxylic acids (c_6Phe) **3a** and **3b** were synthesized in good yields by a resolution method described by Obrecht. This method involves the formation of the diastereoisomeric peptides **7a** and **7b** followed by chromatographic separation. The free (1*R*,2*R*)- and (1*S*,2*S*)-c_6Phe amino acids (**3a** and **3b**) were converted into appropriately protected phenylalanine analogues **10a** and **10b** for possible use in peptide synthesis. The conformational analysis, in solution, of these peptides revealed that dipeptide **3a** shows an extended-type conformation, while dipeptide **3b** shows a type I β-turn geometry. In addition, we have prepared the unsaturated peptides **11a** and **11b** and the structure of **11b**, determined by X-ray analysis, also shows a type I β-turn conformation in the solid state. The NMR data of this dipeptide (**11b**) allowed the characterisation of the type I β-turn conformation in solution and established it to be similar to the solid state structure. These results suggest that c_6Phe can be used as building blocks to stabilise type I β-turns or extended chains in peptides, depending on their absolute configurations.

Keywords: Diels-Alder reactions. Amino acids and derivatives. Peptide analogues/mimetics. Resolution.

Introduction

The conformational flexibility of peptides is one of the limitations of their use as drug leads. Because of this, in recent years, several conformationally restricted analogues of bioactive peptides (peptidomimetics) have been developed in order to establish a three-dimensional structure-bioactivity relationship and to design new pharmacological agents with more selective properties than the original peptides [1]. There are a number of different approaches to the synthesis of conformationally restricted peptidomimetics at the amino acid level and, in this context, the systematic exchange of individual amino acids by the corresponding modified amino acid is well established [2]. For example, conformational restriction through $C_i^{\alpha} \leftrightarrow C_i^{\alpha}$ cyclization generates the family of 1-aminocycloalkane-1-carboxylic acid (Ac_nc) residues and different studies of the preferred conformations of peptides characterised by the Ac_nc (n = 3–9) residues have been the subject of recent reviews [3]. Moreover, it is known that certain cyclic α,α-disubstituted amino acids, notably those with n = 3, 5 and 6, tend to induce α-helical or β-turn conformations when they are incorporated into peptides.

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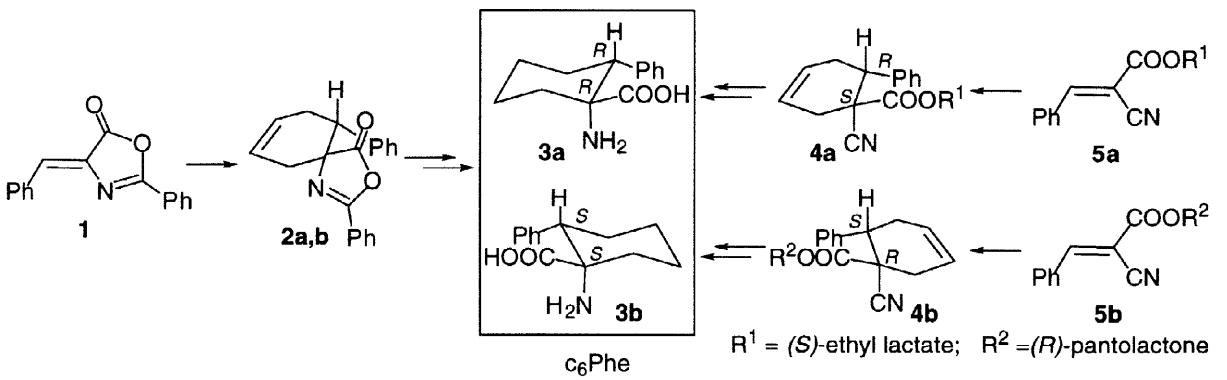
Synthesis of cyclic amino acid analogues of Phe: c_6Phe

As a part of our research project on the synthesis of new α-amino acids with conformational rigidity and with the aim of contributing to the development of cyclic conformationally restricted amino acids, in particular analogues of phenylalanine (Phe), we have reported the synthesis of 1-amino-*t*-2-phenylcyclohexane-*r*-1-carboxylic acid (**3a,b**) (c_6Phe) in its racemic form [4] by the Diels–Alder reaction of (*Z*)-2-phenyl-4-benzyliden-5(4H)-oxazolone (**1**) and 1,3-butadiene. In order to incorporate this c_6Phe amino acid into peptides, we are interested in both enantiomers of this novel non-proteinogenic amino acid. In this context, we have recently published the asymmetric synthesis of (1*R*,2*R*)- and (1*S*,2*S*)-1-amino-2-phenylcyclohexane-1-carboxylic acids (**3a** and **3b**) [(1*R*,2*R*)- and (1*S*,2*S*)-c_6Phe] starting from the corresponding cycloadducts of the Diels–Alder reaction between 1,3-butadiene and the chiral (*E*)-2-cyanocinnamates **5a** and **5b** as dienophiles, using (*S*)-ethyl lactate and (*R*)-pantolactone as chiral auxiliaries [5]. (Scheme 1).

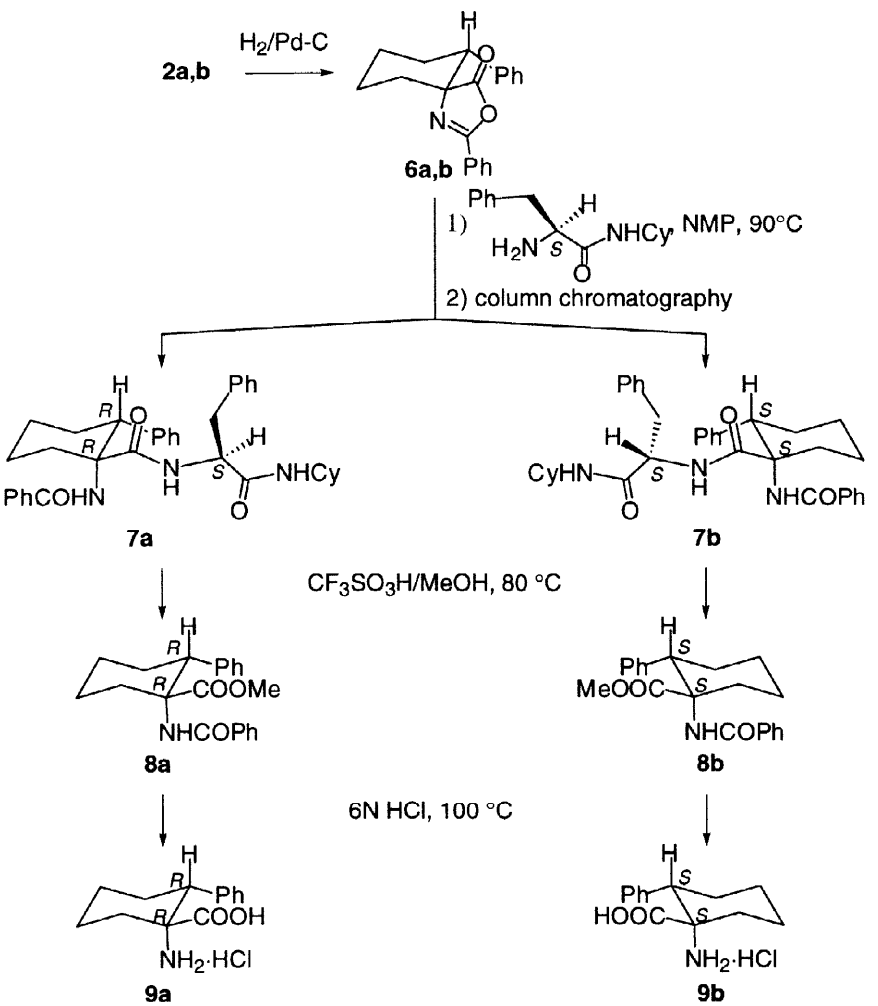


Scheme 1

Further transformations of the cyano and carboxylate groups of cycloadducts **4a** and **4b** into the corresponding amino and carboxylic acid groups allowed the synthesis of both enantiomerically pure amino acids, but only in 22% yield, from dienophiles. Nevertheless, these apparently simple transformations suffered from significant synthetic difficulties that produced a decrease in the yield of the amino acids and, consequently, the amino acids could not be obtained in an easy and quick way. Due to this fact, and encouraged by the excellent yield obtained in the synthesis of this racemic amino acid from the unsaturated 5(4H)-oxazolone, we decided to explore the scope of the asymmetric Diels–Alder reaction between the 5(4H)-oxazolone and 1,3-butadiene using different chiral catalysts. Such a method has not previously allowed the successful synthesis of both stereoisomers. For this reason we have considered that, in this particular case, an efficient method for the resolution of the racemic c_6Phe **3a,b** is more practical than an enantioselective synthesis.

In this paper we present a very efficient strategy for resolution of racemic c_6Phe **3a,b**. This strategy was previously developed and reported by Obrecht to prepare and resolve both cyclic and acyclic *N*-acylated α,α-disubstituted amino acids [6]. The method is based on the formation of diastereoisomeric dipeptides, which are easily separated by column chromatography. Once separated, these diastereoisomers are selectively cleaved to give, in

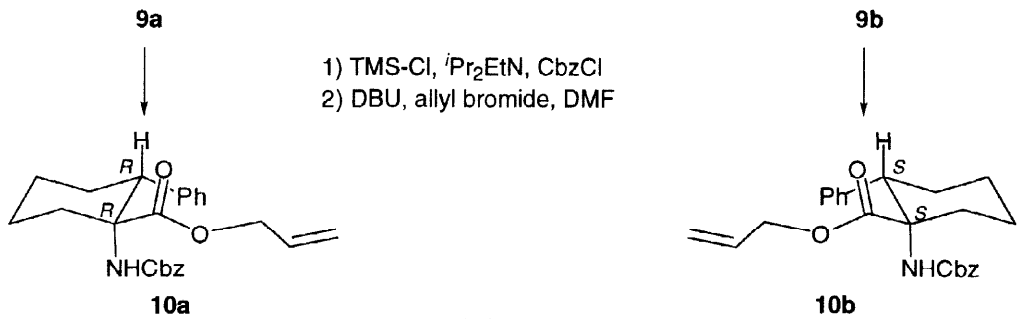
high yield, the corresponding *N*-acylated amino esters. In our case, the synthesis of the two enantiomerically pure amino acid analogues of Phe started from the racemic Diels–Alder cycloadduct **2a,b**. The double bond of this system was hydrogenated in the presence of palladium/carbon as a catalyst to obtain the racemic 2'-phenylcyclohexane-1-spiro-2-phenyl-5(4H)-oxazolone **6a,b**, which was smoothly reacted with L-phenylalanine cyclohexylamide in *N*-methylpyrrolidin-2-one (NMP) as a solvent, at 90 °C. The corresponding diastereoisomeric peptides **7a** and **7b** were obtained in good yields after silica gel column chromatography using hexane/ethyl acetate (7:3) as eluent. Each diastereoisomeric peptide **7a** and **7b** was separately treated with trifluoromethanesulphonic acid in MeOH at 80 °C to give the optically pure methyl esters **8a** and **8b**. Finally, hydrolysis of the benzamido and methyl ester groups with aqueous 6N HCl at 100 °C gave the optically pure c_6Phe as chlorhydrate derivatives **9a** and **9b**. In order to assess the enantiomeric purity and determine the absolute configuration of each amino acid, these chlorhydrate derivatives were each dissolved in EtOH and propylene oxide was then added. After 2 hours at reflux, the free amino acids **3a** and **3b** were obtained and the observed optical rotations were in agreement with those described in the literature [5]. (Scheme 2).



Scheme 2

Protection of amino acids c_6Phe

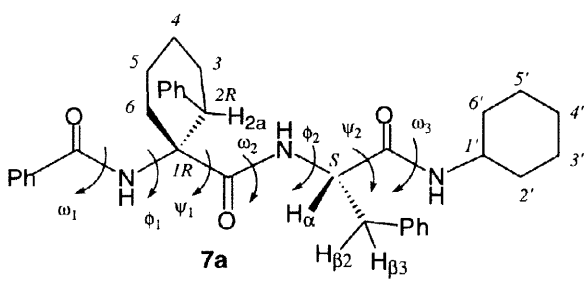
The optically pure c_6Phe **3a** and **3b** are potentially interesting amino acids for incorporation into short peptides and, consequently, the corresponding amino acids with suitable protecting groups were required [7]. Indeed, it is advisable in peptide synthesis to dispose of the orthogonally doubly protected amino acids, so we chose the combination of the *N*-benzyloxycarbonyl group (*N*-Cbz) with the allylic ester group. Firstly, the Cbz-protected amino acids were obtained using the Kricheldorf method [8], which is based on the addition of Me_3SiCl (TMS–Cl) to the corresponding amino acid chlorhydrate derivatives **9a** and **9b**. We then carried out the reaction with $^iPr_2EtN$ and benzyl chloroformate (Cbz–Cl). The Cbz-protected c_6Phe were not be purified, but were conveniently converted into the corresponding allyl esters by the action of DBU and allyl bromide in DMF to give, in high yield, the desired orthogonally doubly protected Phe analogues **10a** and **10b**. (Scheme 3).



Scheme 3

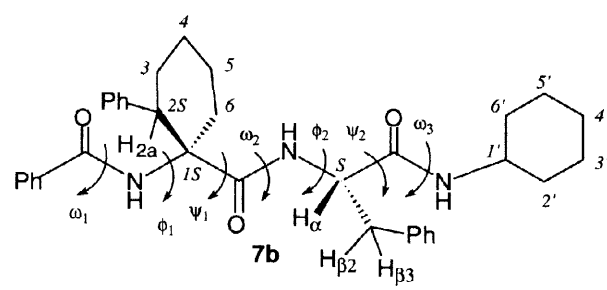
Conformational Analysis of dipeptides containing c_6Phe

In order to determine the interesting conformational aspects of dipeptides **7a** and **7b**, we first studied their conformational analysis in solution [9] and later in the solid state. The most representative proton resonance assignment in the ^{1}H-NMR spectra of peptides **7a** and **7b** was made on the basis of coupling constants, selective proton-proton homonuclear decoupling experiments, proton-proton COSY experiments and proton-carbon COSY experiments. The results of these studies are summarised in Table 1. Starting from the scalar couplings $^3J_{NHPhe\text{-}\alpha}$ and applying the Karplus equation [10], using the parametrization of Pardi and coworkers [11], we obtained two possible values for the dihedral angles ϕ_2 for every peptide. (Figure 1).



BzN-(1*R*,2*R*)-c_6Phe-(*S*)-Phe-CONHCy

ϕ_2 = –148.2 or –91.7



BzN-(1*S*,2*S*)-c_6Phe-(*S*)-Phe-CONHCy

ϕ_2 = –145.2 or –94.7

Figure 1

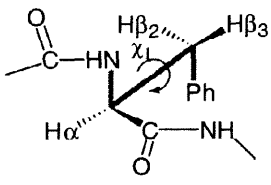
Table 1. ^{1}H-NMR data[a] of the most characteristic resonances of dipeptides **7a** (left) and **7b** (right).

$H_{\beta 2}$	2.86(dd, 1H, $J_{\beta 2-\beta 3}$=13.5, $J_{\beta 2-\alpha}$=8.1)	$H_{\beta 2}$	2.02(dd, 1H, $J_{\beta 2-\beta 3}$=13.2, $J_{\beta 2-\alpha}$=6.0)
$H_{\beta 3}$	3.05(dd, 1H, $J_{\beta 3-\beta 2}$=13.5, $J_{\beta 3-\alpha}$=6.0)	H_{6a}	2.23('t'd, 1H, J_{6a-6e}~J_{6a-5a}=14.4, J_{6a-5e}=6.0)
$H_{1'}$, H_{2a}	3.37-3.52(m, 2H)	H_{6e}	2.84(m, 1H)
H_α	4.34('t'd, 1H, $J_{\alpha\text{-NHPhe}}$~$J_{\alpha-\beta 2}$=8.1, $J_{\alpha-\beta 3}$=6.0)	$H_{\beta 3}$, H_{2a}	3.29-3.41(m, 2H)
		$H_{1'}$	3.61-3.72(m, 1H)
NHCy	5.27(d, 1H, $J_{\text{NHCy-1'}}$=6.0)	H_α	4.51(ddd, 1H, $J_{\alpha\text{-NHPhe}}$=8.4, $J_{\alpha-\beta 2}$=6.0, $J_{\alpha-\beta 3}$=2.7)
NHCOPh	6.29(brs, 1H)		
NHPhe	6.66(d, 1H, $J_{\text{NHPhe-}\alpha}$=6.0)	NHPhe	5.41(d, 1H, $J_{\text{NHPhe-}\alpha}$=8.4)
		NHCOPh	6.35(brs, 1H)
		NHCy	6.76(d, 1H, $J_{\text{NHCy-1'}}$=6.0)

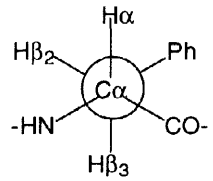
[a] The spectra were recorded in $CDCl_3$ and TMS was used as the internal standard. The chemical shifts are reported in ppm on the δ scale and coupling constants in Hz.

On the other hand, the analysis of $^3J_{\alpha\text{-}\beta}$ in the Phe residue of both peptides provides information about the dihedral angle χ_1. In particular, it is observed that in the peptide **7a** there is more than one rotamer conformation (t2g3, g2t3 and g2g3) due to the conformational flexibility of the $-CH_2Ph$ side chain [12]. When the fractional populations t2g3, g2t3, g2g3 for three staggered rotamers about the C_α–C_β bond of Phe were calculated using the *J*-coupling for Pachler's equation [13], the average P_X-values obtained were 0.53, 0.29, 0.18, respectively (the values of t2g3, and g2t3 are interchangable). These values indicate that 53% of the rotamer population shows a dihedral angle χ_1 of 60° or 180°. Up to now it has been impossible to discriminate between these values, although Hruby [16a] reported that in short peptides the aromatic ring of the Phe residue adopts a position far removed from the main chain of the peptide. In the case reported here this corresponds to a χ_1 value of 180°. (Figure 2).

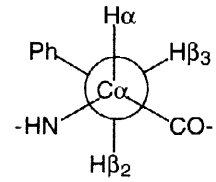
In contrast, in peptide **7b** the analysis of $^3J_{\alpha\text{-}\beta}$ reveals that the 69% of the rotamer population shows a dihedral angle χ_1 of –60°, corresponding to the gauche-gauche (g2g3) conformation. (Figure 2).



Peptide **7a**

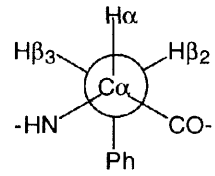


g2t3 (χ_1= 180°)



t2g3 (χ_1= 60°)

Peptide **7b**



g2g3 (χ_1= -60°)

Figure 2

By means of ^{1}H-NMR spectroscopy we have studied the possible formation of hydrogen bonds in these systems. The presence of hydrogen-bonded NH resonances has usually been confirmed by measuring the degree of solvent exposure of each NH group in a given peptide [14]. In the present study, we have used the criterion of the solvent dependence of the NH chemical shifts in $CDCl_3$/DMSO-d_6 mixtures. The NH resonances in peptides **7a** and **7b** could be assigned in a straightforward manner. The signals for NHCOPh appear as broad singlets at 6.29 and 6.35 ppm, respectively. On the other hand, NHCy appeared as doublets coupled with the $H_{1'}$ protons of the cyclohexane ring, at relatively high field (5.27 ppm) in peptide **7a** and at lower field (6.76 ppm) in peptide **7b**. In the latter case this indicates the possible involvement of hydrogen bonding [15]. The remaining doublet NH resonances show coupling with H_α of the Phe residue and this appeared in the peptides **7a** and **7b** at 6.66 ppm and 5.41 ppm, respectively.

As shown in Figure 3, the NHCy resonance in $CDCl_3$ for peptide **7a** was markedly shifted to a lower field upon adding the strong hydrogen-bond accepting DMSO-d_6 solvent. Nevertheless, the NHCOPh and NHPhe resonances were less affected by the addition of DMSO-d_6. This fact indicates that NHPhe and NHCOPh have a solvent-shielded nature due to the presence of intramolecular hydrogen bonds. All the NH chemical shifts changed in a similar way up to DMSO-d_6 concentrations of 40% (v/v), suggesting that no major conformational change occurred in this experiment. The same experiment for peptide **7b** shows that NHCy and NHPhe are involved in intramolecular hydrogen-bonds. (Figure 3).

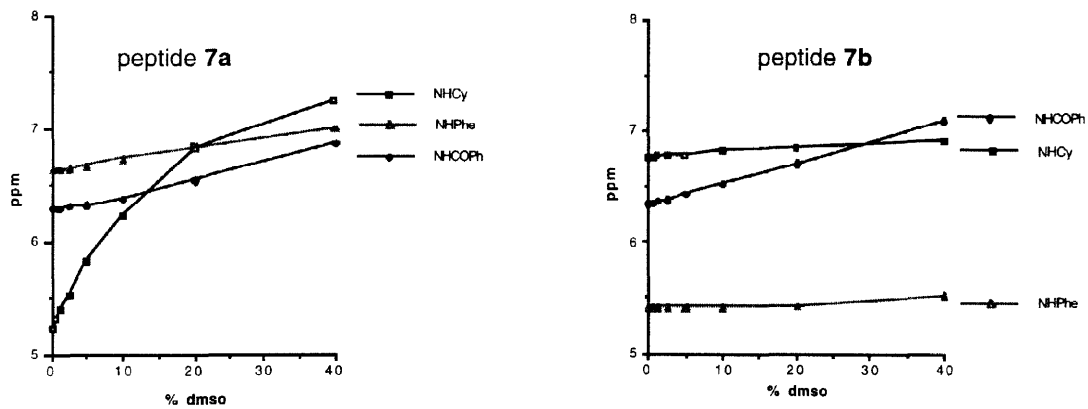
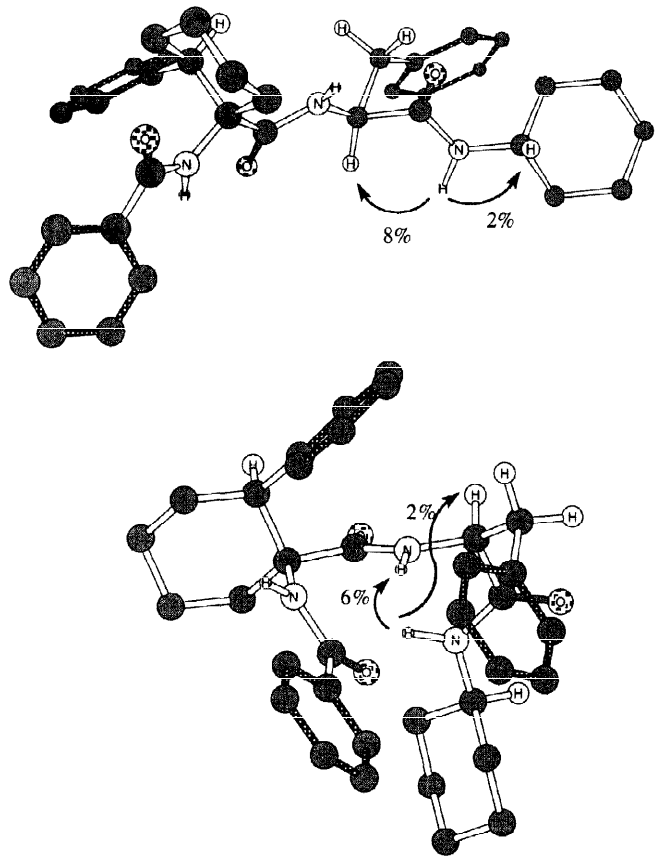


Figure 3

In order to obtain further information concerning the main chain conformations, difference NOE experiments were carried out [16]. When the NHCy proton was irradiated in peptide **7a**, enhancements of 8% and 2% were observed in the H_α and $H_{1'}$ protons, respectively. However, such an NOE enhancement was not observed in NHPhe. An NOE enhancement was also not observed in NHCy when NHPhe was presaturated. The most relevant NOE data observed in peptide **7b** were those corresponding to the NHPhe (6%) and H_α (2%) protons when the proton NHCy was irradiated. These observed NOE enhancements suggest that the most probable values for the dihedral angles ϕ_2 will be near to –148.2° in peptide **7a** and to –94.7° in peptide **7b**. (Figure 4).



peptide **7a**

peptide **7b**

Figure 4

Taking into account the fact that the above empirical information on dihedral angles of peptides, obtained from 1D-NMR experiments, is not sufficient to define a specific conformation, we have built the simple models using the INSIGHT II program based on NMR parameters. We have subsequently optimized these starting structures with the molecular mechanics force fields CVFF and CFF91 implemented in the above program [17].

The lowest energy conformations for peptides **7a** and **7b** correspond to the structures shown in Figure 4 and the distances and the dihedral angles are represented in Table 2. Peptide **7a**, containing the (1*R*,2*R*)-c$_6$Phe residue, shows an extended-type conformation, while peptide **7b**, (1*S*,2*S*)-c$_6$Phe, shows a type I β-turn. Both structures contain two hydrogen bonds [18].

In order to establish a comparison between the conformations that these peptides exhibit in solution and in the solid state, we attempted to crystallize them; however, we could not obtain monocrystals of dipeptides. In contrast, we could obtain the X-ray structure [19] of unsaturated peptide **11b**, which also shows a type I β-turn structure (Figure 5). Peptide **11b** was obtained from racemic unsaturated 5(4H)-oxazolone cycloadduct **2a** by reaction with L-phenylalanine cyclohexylamide in NMP at 90 °C. The resulting unsaturated diastereoisomeric peptides **11a** and **11b** were separated by silica gel column chromatography eluting with hexane/ethyl acetate (7:3). (Scheme 4).

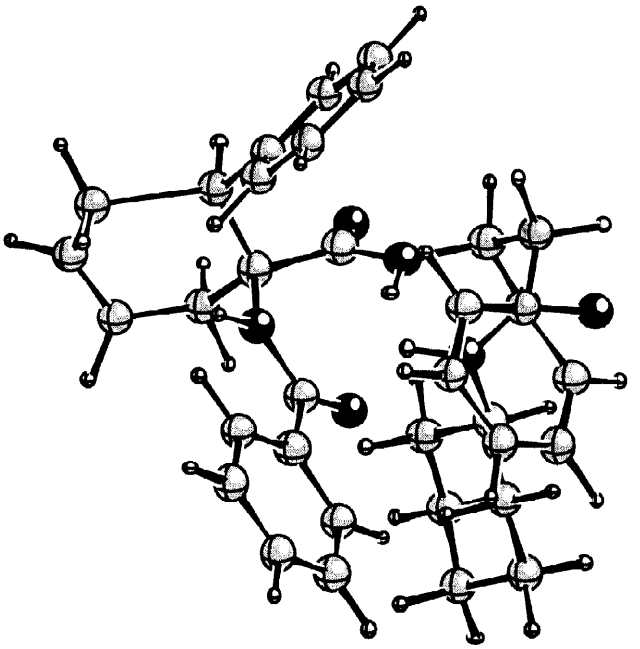
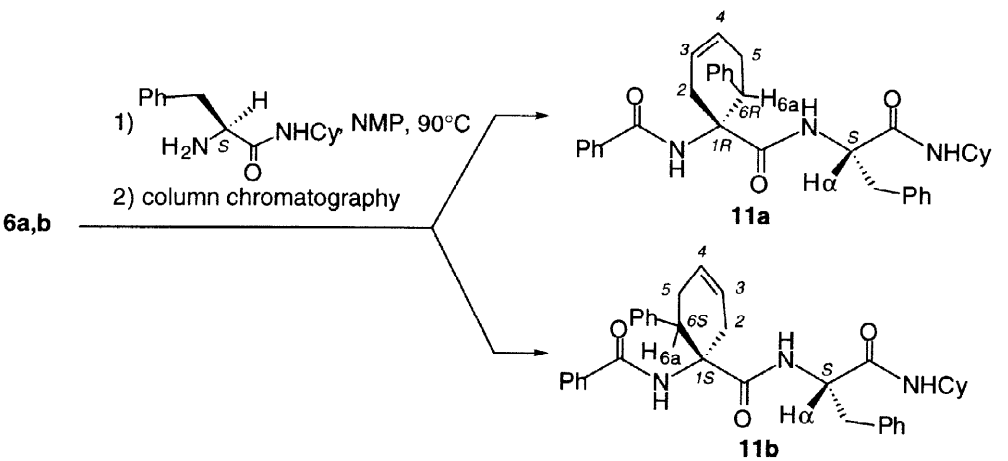


Figure 5



Scheme 4

The NMR spectra of the unsaturated peptide **11b**, the NOE difference experiments and solvent accesibility ($CDCl_3$/DMSO-d_6) are similar to those obtained in the saturated peptide **7b** with the same configuration (Figure 6). This starting structure was also optimized with the molecular mechanics force fields CVFF and CFF91 implemented in the INSIGHT II program. These results make it possible to compare both peptides of configuration (*S*,*S*,*S*) and we could establish that both peptides have the same conformation in the solid state as in solution and are folded according to a type I β-turn with stabilizing intramolecular i+3→i hydrogen bonds. Table 2 show the values of the dihedral angles for the residues i+1 and i+2 in peptides **7b** and **11b**. These values were obtained from the conformational analysis in solution and in the solid state, and the values of these angles are as one would expect for the ideal type I β-turn.

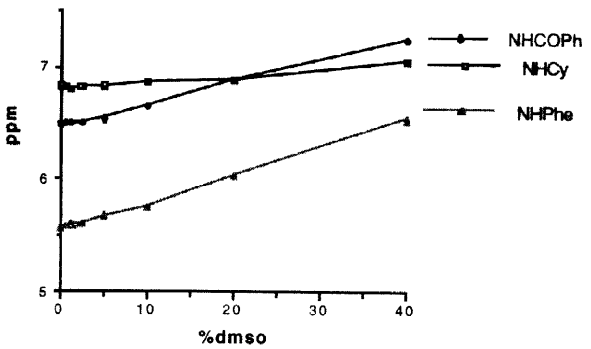


Figure 6

Table 2 Distances, ϕ and ψ in peptides **7b** and **11b**.

	7b solution[a]	**7b** solution[b]	**11b** solution[a]	**11b** solution[b]	**11b** solid state	ideal β-turn I
ϕ (i+1)	–50°	–58°	–46°	–58°	–50°	–60°
ψ (i+1)	–20°	–19°	–31°	–20°	–27°	–30°
ϕ (i+2)	–73°	–82°	–68°	–80°	–76°	–90°
ψ (i+2)	15°	–1°	–21°	–2°	0°	0°
d[PhCO···HNCy]	2.07 Å	2.03 Å	2.00 Å	2.02 Å	1.98 Å	--
d[PhCO···HNPhe]	2.26 Å	2.90 Å	2.89 Å	2.90 Å	3.04 Å	--

[a] Optimization using the cvff force field implemented in the Insight II program
[b] Optimization using the cff91 force field implemented in the Insight II program

In summary, we have prepared, in good yield, the enantiomerically pure c_6Phe amino acids **3a** and **3b** by resolution of the corresponding diastereoisomeric dipeptides **7a** and **7b**, and also the unsaturated dipeptides **11a** and **11b**. The peptides **7b** and **11b** show type I β-turn structures both in the solid state and in solution, suggesting that these compounds could constitute interesting building blocks for probing the relevance of β-turn secondary structures in peptides of biological significance and could be used for protein engineering. Moreover, the presence of the phenyl ring in the i+2 residue represents an additional advantage in the β-turn by virtue of having aromatic or hydrophobic amino acids in the third residue.

The results obtained in this paper complement the study reported by Toniolo *et al.* [3] concerning the stereochemically constrained peptides containing the Ac_6c residue. These studies suggest that this residue should be an important component in the design of stereochemically rigid analogues of biologically active peptides, since this class of amino acid can be used to stabilise folded, helical structures or fully extended chains. In our case the cyclic analogues of Phe (c_6Phe) could be used to stabilise folded (β-turn) or extended chains, depending on whether (1*S*,2*S*)- or (1*R*,2*R*)- configurations are employed.

Further studies to incorporate the c_6Phe amino acids in other peptides are in progress.

Acknowledgements: We are indebted to the *Dirección General de Investigación Científica y Técnica* (PB94-0578-C02-02) and to the *Universidad de La Rioja* for their generous support. J. H. B. thanks the *Ministerio de Educación y Ciencia* for a doctoral fellowship.

Experimental section

Solvents were purified according to standard procedures. Analytical TLC was performed using Polychrom SI F_{254} plates. Column chromatography was performed using Silica gel 60 (230–400 mesh). ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker ARX-300 spectrometer. ^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ with TMS as the internal standard and in D_2O-TFA with TMS as the external standard using a coaxial microtube (chemical shifts are reported in ppm on the δ scale, coupling constants in Hz). Melting points were determined on a Büchi SMP-20 melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 341 polarimeter in 1 and 0.5 dm cells of 1 and 3.4 mL capacity, respectively. Microanalyses were carried out on a Perkin-Elmer 240-C analyser and are in good agreement with the Calculated values.

(±)-cis-2-Phenylcyclohexane-1-spiro-{4'[2'-phenyl-5'(4'H)-oxazolone]} (**6a,b**)

A solution of 1 M $AlCl_2Et$ in hexane (3.75 mL) was added to a solution of oxazolone **1** (1.24 g, 5 mmol) in dry CH_2Cl_2 (10 mL) under an inert atmosphere. After stirring the reaction mixture for 1 h at 0 °C, a solution of 1,3-butadiene (2.97 g, 55 mmol) in dry CH_2Cl_2 (5 mL), at the same temperature, was added dropwise and the mixture was stirred for a further 72 h at 0 °C. The reaction was quenched by the addition of solid $Na_2CO_3 \cdot 10H_2O$, the precipitate was removed by filtration and the solvent was evaporated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/ethyl acetate 9:1) to afford 994 mg (64%) of cycloadduct **2a,b** as an oil. A solution of compound **2a,b** (994 mg, 3.5 mmol) in CH_2Cl_2 (15 mL) was hydrogenated, using 10% palladium/carbon as a catalyst, at room temperature for 21 h. The catalyst and the solvent were removed to quantitatively give compound **6a,b** as an oil.

Anal. Calcd. for $C_{20}H_{19}NO_2$ C: 78.66, H: 6.27, N: 4.59; found C: 78.54, H: 6.41, N: 4.47.

^{1}H-NMR($CDCl_3$): δ = 1.60–2.18 (m, 7 H); 2.26–2.40 (m, 1 H); 3.17 (dd, 1 H, $J_{2a\text{-}3a}$ = 13.2, $J_{2a\text{-}3e}$ = 3.6, H_{2a}); 7.12–7.20 (m, 5 H, Arom.); 7.41–7.58 (m, 3 H, Arom.); 7.86–7.92 (m, 2 H, Arom.).

^{13}C-NMR($CDCl_3$): δ = 21.3, 26.1, 28.1, 35.2, 50.1, 73.7 (C_1, C_2, C_3, C_4, C_5, C_6); 126.1, 127.2, 127.8, 127.9, 128.5, 128.7 132.2, 139.5 (Arom); 160.6 (C=N); 179.9 (COO).

(1R,2R)-[1-Benzamide-2-phenylcyclohexane-1-carboxamide]-(S)-phenylalanine cyclohexylamide (**7a**) *and (1S,2S)-[1-Benzamide-2-phenylcyclohexane-1-carboxamide]-(S)-phenylalanine cyclohexylamide* (**7b**)

A solution of (*S*)-phenylalanine cyclohexylamide (1.60 g, 6.66 mmol) in *N*-methylpyrrolidin-2-one (NMP) (3 mL) was added to a solution of compound **6a,b** (994 mg, 3.26 mmol) in NMP (4 mL) under an inert atmosphere. The reaction mixture was stirred for 48 h at 90 °C and was allowed to cool to room temperature, and then poured onto a mixture of ice (25 g), 1N HCl (25 mL) and ethyl acetate (48 mL). After stirring for 30 min the

mixture was allowed to separate into two phases, the organic layer was washed with H_2O (2 x 20 mL) and the aqueous phase was extracted with ethyl acetate (2 x 20 mL). The combined organic phases were washed with brine (2 x 20 mL), dried over anhydrous Na_2SO_4, filtered and the solvent was removed to give the mixture of diastereoisomeric peptides, which were separated by silica gel column chromatography using hexane/ethyl acetate (1:1) as eluent. In this way 680 mg of peptide **7a** (31%) and 690 mg of peptide **7b** (32%) were obtained as colourless solids.

Peptide **7a**: Anal. Calcd. for $C_{35}H_{41}N_3O_3$ C: 76.19, H: 7.49, N: 7.62; found C: 76.24, H: 7.34, N: 7.53.

$[\alpha]^{25}_D$(c = 3.29, $CHCl_3$) = –27.5. Mp: 118–9 °C.

^{1}H-NMR($CDCl_3$): δ = 0.68–2.06 (m, 17 H); 2.86 (dd, 1 H, $J_{\beta2\text{-}\beta3}$ = 13.5, $J_{\beta2\text{-}\alpha}$ = 8.1, Hβ2); 3.05 (dd, 1 H, $J_{\beta3\text{-}\beta2}$ = 13.5, $J_{\beta3\text{-}\alpha}$ = 6.0, Hβ3); 3.09–3.13 (m, 1 H); 3.37–3.52 (m, 2 H, $H_{1'}$, H_{2a}); 4.34 ('t'd, 1 H, $J_{\alpha\text{-NHPhe}}$~ $J_{\alpha\text{-}\beta2}$=8.1, $J_{\alpha\text{-}\beta3}$=6.0, Hα); 5.27 (d, 1 H, $J_{\text{NHCy-}1'}$ = 6.0, NHCy); 6.29 (brs, 1 H, NHCOPh); 6.66 (d, 1 H, $J_{\text{NHPhe-}\alpha}$ = 6.0, NHPhe); 7.10–7.27 (m, 10 H, Arom.); 7.42–7.56 (m, 3 H, Arom.); 7.65–7.73 (m, 2 H, Arom.).

^{13}C-NMR($CDCl_3$): δ = 21.1, 24.6, 24.7, 25.4, 25.5, 27.1, 30.4, 32.5, 32.7 (C_3, C_4, C_5, C_6, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$, $C_{6'}$); 38.7 (Cβ); 48.0, 48.1 ($C_{1'}$, C_2); 51.9 (Cα); 65.0 (C_1); 126.7, 126.8, 127.6, 127.9, 128.5, 128.8, 128.9 129.4, 131.9, 134.7, 137.1, 140.1 (Arom.); 167.4, 168.7, 172.2 (3 x CONH).

Peptide **7b**: Anal. Calcd. for $C_{35}H_{41}N_3O_3$ C: 76.19, H: 7.49, N: 7.62; found C: 76.31, H: 7.56, N: 7.50.

$[\alpha]^{25}_D$(c = 3.74, $CHCl_3$) = +115.6. Mp: 210 °C (d).

^{1}H-NMR($CDCl_3$): δ = 0.85–2.00 (m, 16 H); 2.02 (dd, 1 H, $J_{\beta2\text{-}\beta3}$ = 13.2, $J_{\beta2\text{-}\alpha}$ = 6.0, Hβ2); 2.23 ('t'd, 1 H, $J_{6a\text{-}6e}$~$J_{6a\text{-}5a}$ = 14.4, $J_{6a\text{-}5e}$ = 6.0, H_{6a}); 2.84 (m, 1 H, H_{6e}); 3.29–3.41 (m, 2 H, Hβ3, H_{2a}); 3.61–3.72 (m, 1 H, $H_{1'}$) 4.51(ddd, 1 H, $J_{\alpha\text{-NHPhe}}$ = 8.4, $J_{\alpha\text{-}\beta2}$ = 6.0, $J_{\alpha\text{-}\beta3}$ = 2.7, Hα); 5.41 (d, 1 H, $J_{\text{NHPhe-}\alpha}$ = 8.4, NHPhe); 6.11–6.20 (m, 2 H, Arom.) 6.35 (brs, 1 H, NHCOPh); 6.55–6.68 (m, 3 H, Arom.); 6.76 (d, 1 H, $J_{\text{NHCy-}1'}$ = 6.0, NHCy); 7.20–7.60 (m, 10 H, Arom.).

^{13}C-NMR($CDCl_3$): δ = 20.8, 25.1, 25.2, 25.5, 25.6, 26.7, 29.2, 32.5, 32.8 (C_3, C_4, C_5, C_6, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$, $C_{6'}$); 36.0 (Cβ); 48.4, 48.5 ($C_{1'}$, C_2); 51.9 (Cα); 65.0 (C_1); 126.6, 126.8, 128.0, 128.1, 128.2, 128.8 128.9, 129.0, 132.3, 133.3, 134.8, 140.0 (Arom.); 167.2, 169.2, 170.4 (3 x CONH).

Methyl (1R,2R)-1-benzamide-2-phenylcyclohexane-1-carboxylate (**8a**)

Compound **7a** (540 mg, 0.98 mmol) was dissolved in MeOH (12 mL) and trifluoromethanesulphonic acid (0.26 mL, 2.94 mmol) was added at 0 °C under an inert atmosphere. The reaction was stirred for 48 h at reflux, cooled to room temperature and the solvent was removed *in vacuo* . The residue was suspended in CH_2Cl_2, filtered and the solvent evaporated. Compound **8a** was purified by silica gel column chromatography using hexane/ethyl acetate (7:3) as eluent, giving 227 mg (81%) of **8a** as an oil.

Anal. Calcd. for $C_{21}H_{23}NO_3$ C: 74.75, H: 6.87, N: 4.15; found C: 74.86, H: 6.80, N: 4.21.

$[\alpha]^{25}_D$(c = 2.95, $CHCl_3$) = –116.3.
^{1}H-NMR($CDCl_3$): δ = 1.48–1.64 (m, 2 H); 1.66–1.76 (m, 1 H); 1.82–1.96 (m, 2 H); 2.05–2.21 (m, 2 H); 3.22–3.29 (m, 2 H, H_{2a}, H_{6e}); 3.51 (s, 3 H, CO_2CH_3); 6.22 (brs, 1 H, NH); 7.14–7.20 (m, 2 H, Arom.); 7.22–7.50 (m, 6 H, Arom.); 7.62–7.70 (m, 2 H, Arom.).
^{13}C-NMR($CDCl_3$): δ = 20.7, 25.7, 26.7, 37.0, 49.6, 51.8 (C_2, C_3, C_4, C_5, C_6, $CO_2\underline{C}H_3$); 64.2 (C_1); 126.7, 127.4, 127.8, 128.5, 128.8, 131.4, 135.1, 140.0 (Arom); 167.7 (CONH); 173.3 ($\underline{C}O_2CH_3$).

Methyl (1S,2S)-1-benzamide-2-phenylcyclohexane-1-carboxylate (**8b**)

In the same way as described above for compound **8a**, enantiomer **8b** was obtained as an oil, in 88% yield starting from peptide **7b** (237 mg, 0.43 mmol).
Anal. Calcd. for $C_{21}H_{23}NO_3$ C: 74.75, H: 6.87, N: 4.15; found C: 74.64, H: 6.73, N: 4.26.
$[\alpha]^{25}_D$(c = 2.75, $CHCl_3$) = +115.1.

(1R,2R)-1-Amino-2-phenylcyclohexane-1-carboxylic acid (**3a**).

Compound **8a** (100 mg, 0.30 mmol) was dissolved in 10 N HCl (30 mL) and the mixture was heated under reflux for 48 h. The solvent was evaporated to leave a solid residue (the amino acid hydrochloride **9a**), which was dissolved in EtOH (6 mL) and then propylene oxide (2 mL) was added. The mixture was heated under reflux for 1 h and partially precipitated. After removal of the EtOH, the residue was dissolved in distilled water (2 mL) and eluted through a C_{18} reversed-phase Sep-pak cartridge which, after removal of water, gave 60 mg (91%) of α-amino acid **3a** as a colourless solid [20].
Anal. Calcd. for $C_{13}H_{17}NO_2$ C: 71.19, H: 7.82, N: 6.39; found C: 71.28, H: 7.75, N: 6.48.
$[\alpha]^{25}_D$(c = 6.00, 0.1M TFA in H_2O) = –21.1.

(1S,2S)-1-Amino-2-phenylcyclohexane-1-carboxylic Acid (**3b**)

In a similar way to that described above for compound **3a**, the free amino acid **3b** was obtained as a colourless solid in 91% yield starting from compound **8b** (100 mg, 0.30 mmol) [20].
Anal. Calcd. for $C_{13}H_{17}NO_2$ C: 71.19, H: 7.82, N: 6.39; found C: 71.03, H: 7.74, N: 6.25.
$[\alpha]^{25}_D$(c = 5.40, 0.1M TFA in H_2O) = +22.3.

Allyl (1R,2R)-1-(benzyloxy)carbonylamino-2-phenylcyclohexane-1-carboxylate (**10a**)

To a stirred solution of amino acid hydrochloride **9a** (166 mg, 0.65 mmol) in CH_2Cl_2, under an inert atmosphere at 0 °C, was added TMS–Cl (0.21 mL 1.62 mmol). After heating for 1 h at reflux, the mixture was then cooled to 0 °C and ^{i}Pr$_2$EtN (0.31 mL 1.62 mmol) was added. The mixture was stirred for 1 h at reflux, recooled to 0 °C and Cbz–Cl (0.12 mL 0.84 mmol) was added. The mixture was allowed to warm up to room temperature and stirred for 24 h, and was then poured onto a mixture of ice (5 g), 0.5N HCl (10 mL) and ethyl acetate (10 mL). The organic layer was washed with H_2O (2 x 20 mL) and brine (2 x 20 mL), dried over anhydrous Na_2SO_4, filtered and the solvent evaporated to give a residue corresponding

to Cbz protected (1*R*,2*R*)-c$_6$Phe, which was used in the next step without purification. To a solution of the above residue in dry DMF (3 mL), under an inert atmosphere at 0 °C, was addded DBU (0.17 mL, 0.78 mmol) and allyl bromide (0.12 mL, 1.3 mmol). The solution was stirred for 72 h at the same temperature and the solvent was removed to give an oily mixture, which was dissolved in CH_2Cl_2 (10 mL) and a mixture of ice (5 g) and ethyl acetate (5 mL) was added. After stirring for 5 min, the organic phase was washed with H_2O (2 x 20 mL) and brine (2 x 20 mL), dried over anhydrous Na_2SO_4, filtered and the solvent evaporated to afford the doubly protected amino acid, which was purified by silica gel column chromatography, eluting with hexane/ethyl acetate (1:1), to give 156 mg (61%) of compound **10a**.

Anal. Calcd. for $C_{24}H_{27}NO_4$ C: 73.26, H: 6.92, N: 3.56 ; found C: 73.19, H: 6.84, N: 3.43.

$[\alpha]^{25}_D$(c = 2.60, $CHCl_3$) = +20.2.

^{1}H-NMR($CDCl_3$): δ = 1.51–2.19 (m, 7 H); 2.90–3.10 (m, 1 H, H_{6e}); 3.20 (dd, 1 H, $J_{2a\text{-}3a}$ = 13.2, $J_{2a\text{-}3e}$ = 3.3, H_{2a}); 4.38–4.52 (m, 2 H, –CH=C$\underline{H}_2$); 4.88 (brs, 1 H, NH); 4.97–5.16 (m, 4 H, O–C$\underline{H}_2$–Ph, O–C$\underline{H}_2$–CH=CH$_2$); 5.58–5.73 (m, 1 H, –C$\underline{H}$=CH$_2$); 7.06–7.13 (m, 2H, Arom.); 7.23–7.38 (m, 8H, Arom.).

^{13}C-NMR($CDCl_3$): δ = 20.6, 25.9, 26.6, 31.4 (C_3, C_4, C_5, C_6); 49.6, 64.1, 65.6, 66.5 (C_1, C_2, O–$\underline{C}$H$_2$–CH=CH$_2$, O–$\underline{C}$H$_2$–Ph); 118.0, 127.7, 127.8, 128.0, 128.1, 128.5, 128.9, 131.6, 136.5, 139.8 (Arom., –$\underline{C}$H=$\underline{C}$H$_2$); 152.2 (OCONH); 173.0 (COO).

Allyl (1S,2S)-1-(benzyloxy)carbonylamino-2-phenylcyclohexane-1-carboxylate (**10b**)

In a similar way to that described above for compound **10a**, the protected amino acid **10b** was obtained as an oil, in 61% yield, starting from compound **9b** (0.65 mmol).

Anal. Calcd. for $C_{24}H_{27}NO_4$ C: 73.26, H: 6.92, N: 3.56; found C: 73.31, H: 6.87, N: 3.41.

$[\alpha]^{25}_D$(c = 2.60, $CHCl_3$) = –19.3.

(1R,6R)-[1-Benzamide-6-phenyl-3-cyclohexene-1-carboxamide]-(S)-phenylalanine cyclohexylamide (**11a**) *and (1S,6S)-[1-Benzamide-6-phenyl-3-cyclohexene-1-carboxamide]-(S)-phenylalanine cyclohexylamide* (**11b**)

In a similar way to that described above for compounds **8a** and **8b**, the unsaturated peptides **11a** and **11b** were obtained as colourless solids, in 72% (463 mg and 464 mg, respectively), starting from racemic unsaturated cycloadduct **2a,b** (2.35 mmol).

Peptide **11a**: Anal. Calcd. for $C_{35}H_{39}N_3O_3$ C: 76.47, H: 7.15, N: 7.64; found C: 76.31, H: 7.13, N: 7.63.

$[\alpha]^{25}_D$(c = 2.82, $CHCl_3$) = –7.9. Mp: 108–9 °C.

^{1}H-NMR($CDCl_3$): δ = 0.81–2.22 (m, 13 H); 3.04–3.19 (m, 2 H, $H_{\beta 3}$, H_{2e}); 3.37 (dd, 1 H, $J_{\beta 2\text{-}\beta 3}$ = 15.0, $J_{\beta 2\text{-}\alpha}$ = 6.0, $H_{\beta 2}$); 3.42–3.50 (m, 1 H, H_{6a}); 3.71–3.82 (m, 1 H, $H_{1'}$); 4.79 ('t'd, 1 H, $J_{\alpha\text{-NHPhe}} \sim J_{\alpha\text{-}\beta 2}$ = 9.0, $J_{\alpha\text{-}\beta 3}$ = 3.0, H_α); 5.61–5.80 (m, 2 H, H_3, H_4); 6.36 (d, 1 H, $J_{\text{NHPhe-}\alpha}$ = 6.0, NHPhe); 6.48 (brs, 1 H, NHCOPh); 7.12–7.56 (m, 16 H, NHCy, Arom.).

^{13}C-NMR($CDCl_3$): δ = 25.2, 25.4, 25.7, 29.1, 29.2, 32.6, 32.7 (C_2, C_5, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$, $C_{6'}$); 37.4 (C_β); 43.6 (C_6); 48.7 ($C_{1'}$); 55.0 (C_α); 59.8 (C_1); 123.0, 126.8, 126.9, 128.1,

128.4, 128.5, 128.6, 129.2, 129.3 129.4, 131.9, 133.3, 137.1, 140.9 (C_3, C_4, Arom.); 166.3, 169.5, 172.3 (3 x CONH).

Peptide **11b**: Anal. Calcd. for $C_{35}H_{39}N_3O_3$ C: 76.47, H: 7.15, N: 7.64; found C: 76.54, H: 7.16, N: 7.65.

$[\alpha]^{25}_D$(c = 3.01, $CHCl_3$) = +166.4. Mp: 180 °C (d).

^{1}H-NMR($CDCl_3$): δ = 0.82–1.81 (m, 10 H); 1.89 (dd, 1 H, $J_{\beta2\text{-}\beta3}$ = 13.2, $J_{\beta2\text{-}\alpha}$ = 6.0, $H_{\beta2}$); 2.43–2.45 (m, 1 H, H_{2e}); 2.60–2.75 (m, 1 H, H_{2a}); 2.92–3.16 (m, 2 H, H_{5e}, H_{5a}); 3.23 (dd, 1 H, $J_{\beta3\text{-}\beta2}$ = 13.2, $J_{\beta3\text{-}\alpha}$ = 3.3, $H_{\beta3}$); 3.46 (dd, 1 H, $J_{6a\text{-}5a}$ = 11.4, $J_{6a\text{-}5e}$ = 6.0, H_{6a}); 3.58–3.74 (m, 1 H, $H_{1'}$) 4.30 (ddd, 1 H, $J_{\alpha\text{-NHPhe}}$ = 7.8, $J_{\alpha\text{-}\beta2}$ = 6.0, $J_{\alpha\text{-}\beta3}$ = 3.3, H_α); 5.58 (d, 1 H, $J_{\text{NHPhe-}\alpha}$ = 7.8, NHPhe); 5.68–5.87 (m, 2 H, H_3, H_4); 6.42–6.55 (m, 2 H, Arom.); 6.70–6.88 (m, 4 H, NHCOPh, NHCy, Arom.); 7.24–7.70 (m, 11 H, Arom.).

^{13}C-NMR($CDCl_3$): δ = 25.0, 25.1, 25.5, 26.9, 30.4, 32.5, 32.7 (C_2, C_5, $C_{2'}$, $C_{3'}$, $C_{4'}$, $C_{5'}$, $C_{6'}$); 36.1 (C_β); 45.1 (C_6); 48.3 ($C_{1'}$); 52.6 (C_α); 62.6 (C_1); 123.6, 125.5, 126.6, 126.7,126.8, 128.1, 128.2, 128.8, 129.0, 129.1, 132.3, 133.5, 135.3, 139.4 (C_3, C_4, Arom.); 167.8, 169.2, 170.0 (3 x CONH).

References and notes

[1] (a) Liskamp, R. M. J. *Recl. Trav. Chim. Pays-Bas* **1994**, 1, 113. (b) Giannis, A.; Kolter, T. *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1244. (c) Wirth, T. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 225.

[2] Gante, J. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1699.

[3] (a) Benedetti, E.; Di Blassio, B.; Iacovino, R.; Menchise, V.; Saviano, M.; Pedone, C.; Bonora, G. M.; Ettorre, A.; Graci, L.; Formaggio, F.; Crisma, M.; Valle, G.; Toniolo, C. *J. Chem. Soc., Perkin Trans.* 2 **1997**, 2023. (b) Toniolo, C.; Benedetti, E. *Macromolecules* **1991**, *24*, 4004. (c) Toniolo, C. *Janssen Chim. Acta* **1993**, 11, 10. (d) Benedetti, E.; Toniolo, C.; Moretto, V.; Formaggio, F.; Crisma, M.; Bonora, G. M.; Santini, A.; Saviano, M.; Di Blassio, B.; Pedone, C. *J. Pept. Sci.* **1996**, 2, 14. (e) Toniolo, C. *Int. J. Pept. Protein Res.* **1990**, *35*, 287. (f) Benedetti, E. *Biopolymers (Peptide Science)* **1996**, *40*, 3.

[4] Avenoza, A.; Cativiela, C.; Díaz-de-Villegas, M. D.; Peregrina, J. M. *Tetrahedron* **1993**, *49*, 10987.

[5] Avenoza, A.; Cativiela, C.; París, M.; Peregrina, J. M. *J. Org. Chem.* **1994**, *59*, 7774.

[6] (a) Obrecht, D.; Spiegler, C.; Schönholzer, P.; Müller, K.; Heimgartner, H.; Stierli, F. *Helv. Chim. Acta* **1992**, *75*, 1666. (b) Obrecht, D.; Bohdal, U.; Broger, C.; Bur, D.; Lehmann, C.; Ruffieux, R.; Schönholzer, P.; Spiegler, C.; Müller, K. *Helv. Chim. Acta* **1995**, *78*, 563.(c) Obrecht, D.; Spiegler, C.; Schönholzer, P.; Müller, K.; Lehmann, C.; Ruffieux, R.; *Helv. Chim. Acta* **1995**, *78*, 1567. (d) Obrecht, D.; Bohdal, U.; Lehmann, C.; Schönholzer, P.; Müller, K. *Tetrahedron* **1995**, *51*, 10883. (e) Obrecht, D.; Altorfer, M.; Lehmann, C.; Schönholzer, P.; Müller, K. *J. Org. Chem.* **1996**, *61*, 4080.

[7] (a) Kocienski, P. J. *Protecting Groups*, George Thieme Verlag, Stuttgart, 1994.

(b) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, Wiley, New York, 1991.

[8] Kricheldorf, H. R. *Synthesis* **1970**, 592.

[9] Havel, H. A. *Spectroscopic Methods for Determining Protein Structure in Solution*, VCH Publishers, New York, 1996.

[10] Karplus, M. *J. Phys. Chem.* **1959**, *30*, 11.

[11] Pardi, A.; Billeter, M.; Wüthrich, K. *J. Mol. Biol.* **1984**, *180*, 741.

[12] Dyson, H. J.; Wright, P. E. in *Two Dimensional NMR Spectroscopy. Applications for Chemists and Biochemists*, Croasmun, W. R. and Carlson, R. M. K. Eds.; VCH Publishers, New York, 1994, Chapter 6, p 676.

[13] Pachler, K. G. P. *Spectrochim. Acta* **1964**, *20*, 581.

[14] (a) Hruby, V. J. in *Chemistry and Biochemistry of Amino Acids, Peptides and Proteins*, Weinstein, B. Ed.; Dekker, New York, 1974, vol. 3, pp 1–188. (b) Aubry, A.; Cung, M. T.; Marraud, M. *J. Am. Chem. Soc.* **1985**, *107*, 7640. (c) Pitner, T. P.; Urry, D. W. *J. Am. Chem. Soc.* **1972**, *94*, 1399.

[15] Günther, H. *NMR Spectroscopy*, Wiley, New York, 1995.

[16] (a) Bothner-By, A. A. in *Magnetic Resonance in Biology*. Shulman, R. G., Ed.; Academic Press, New York, 1979, pp 177–219. (b) Rao, B. N. N.; Kumar, A.; Balaram, H.; Ravi, A.; Balaram, P. *J. Am. Chem. Soc.* **1983**, *105*, 7623.

[17] Structures of **7a** and **7b** were built using the INSIGHT II molecular modelling program (version 2.1.0, San Diego: Biosym Technologies 1995 on an IRIS Silicon Graphics workstation). The ring conformations were initially fixed as those provided by another molecular mechanics calculations and NMR studies on related 2-phenylcyclohexanamino acids. The peptide bonds were orientated in a *trans* disposition. The CVFF and CFF91 force fields were used to optimize the molecular geometry.
CVFF: (a) Dauber-Osguthorpe, P.; Roberts, V. A.; Osguthorpe, D. J.; Wolff, J.; Genest, M.; Hagler, A. T. *Proteins: Structure, Function and Genetics* **1988**, *4*, 31. (b) Hagler, A. T.; Dauber, P. ; Lifson, S. *J. Am. Chem. Soc.* **1979**, *101*, 5122. (c) Hagler, A. T.; Dauber, P. ; Lifson, S. *J. Am. Chem. Soc.* **1979**, *101*, 5131.
CFF91: (a) Wilson, E. B.; Decius, J. C.; Cross, P. C. *Molecular Vibrations*, Dover, New York, 1980. (b) Maple, J. R.; Thacher, T. S.; Dinur, U.; Hagler, A. T. *Chemical Design Automation News* **1990**, *5*, 5. (c) Maple, J. R.; Dinur, U.; Hagler, A. T. *Proc. Nat. Acad. Sci. USA* **1988**, *85*, 5350. (d) Dinur, U.; Hagler, A. T. "Approach to empirical force fields", in *Review of Computational Chemistry*, vol. 2., Lipkwowitz, K. B.; Boyd, D. B. Eds.; VCH, New York, 1991, Chapter 4. (e) Waldman, M.; Hagler, A. T. *J. Comput. Chem.* **1993**, *14*, 1077. (f) Hill, J. R.; Sauer, J. *J. Phys. Chem.* **1994**, *98*, 1238. (g) Sun, H.; Mumby, S. J.; Maple, J. R.; Hagler, A. T. *J. Am. Chem. Soc.* **1994**, *116*, 2978.

[18] (a) Ramachandran, G. N.; Sasisekharan, V. *Advanced Protein Research* **1968**, *23*, 283. (b) Ball, J. B.; Hughes, R. A.; Alewood, P. F.; Andrews, P. R. *Tetrahedron* **1993**, *49*, 3467.

[19] Crystal data of dipeptide **11b**: $C_{35}H_{39}N_3O_3$, monoclinic, space group *C* 2/*c*, *a* = 9.113 (2), *b* = 10.594 (2), *c* = 32.541 (7) Å, V = 3141.5 (13) $Å^3$, Z = 4. Mo-$K\alpha$ radiation, λ = 0.71069 Å, graphite monochromator, $\omega/2\theta$ scan technique. A total of 6838 reflections were measured, and merged to 5533 unique reflections (R_{merg} = 0.0322). The structure was solved by direct methods (SHELXL 93). Least-squares (full matrix) refinement yielded R and R_W-values of 0.1599 and 0.1969 respectively. Complete data have been deposited at the Cambridge Crystallographic Data Centre.

[20] The ^1H- and ^{13}C-NMR data for enantiomerically pure c_6Phe amino acids are in accordance with those described by us in the literature: ref. 7