112. Synthesis, Conformational Properties, and Synthetic Applications of Novel Optically Pure α,α-Disubstituted (*R*)- and (*S*)-Glycines ('α-Chimeras') Combining Side Chains of Asp, Glu, Leu, Phe, Ser, and Val

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Dedicated to Prof. *Vladimir Prelog* on the occasion of his 90th birthday

(15.V.96)

A series of novel open-chain and cyclic conformationally constrained α,α-disubstituted (*R*)- and (*S*)-glycine derivatives ('α-chimeras') combining side chains of Asp, Glu, Leu, Phe, Ser, and Val have been efficiently synthesized by using α-alkylation of racemic 4-monosubstituted 2-phenyl-1,3-oxazol-5(4*H*)-ones of type **5**, resolution after reaction with (*S*)-phenylalanine cyclohexylamide (**8**) as chiral auxiliary, a novel azlactone/dihydrooxazole interconversion reaction to synthesize optically pure α-substituted (*R*)- and (*S*)-serine derivatives coupled with succinimide-ring formation of aspartic-acid derivatives. Based on X-ray structures of (*R,S*)-**9b**, (*R,S*)-**11c**, (*R,S*)-**18**, and (*S,S*)-**30**, the absolute configuration of these novel amino-acid building blocks could be unambiguously determined and their preferred conformations in the crystalline state be assessed. The high preference of the open-chain derivatives (*R,S*)-**1**, (*S,S*)-**3**, and (*R,S*)-**11c** for β-turn type-I conformations, as well as of the succinimide derivatives (*R,S*)-**2**, (*S,S*)-**19**, (*S,S*)-**24**, (*S,S,S*)-**26**, and (*R,S*)-**29** for β-turn type-II conformations and of (*S,S*)-**4**, (*R,S*)-**18**, (*R,S*)-**23**, and (*S,S*)-**30** for β-turn type-II′ conformations could be confirmed in solution by using CD and NMR spectroscopy. Finally, the spiro derivatives (*R,S*)-**29** and (*S,S*)-**30** incorporating the 'α-chimera' of Asp/Glu constitute doubly constrained peptide building blocks combining the properties of α-substituted prolines and aspartimides.

1. Introduction. – Unnatural amino acids bearing side chains other than those present in the 20 coding α-amino acids are of interest in many important areas of research. These amino acids can change the pharmacological and physicochemical properties and enzymatic stability of small peptides of interest [1] [2]. Especially heteroaryl analogues of (*S*)-phenylalanine (Phe) have been studied and synthesized by the powerful techniques of catalytic asymmetric hydrogenation [3].

Among the vast family of non-standard amino acids, the α,α-disubstituted glycines play an important role [4] [5]. In addition of having the potential of altering the chemical properties by variation of the nature of the side chains R^1 and R^2 (*Fig. 1*), these amino acids can stabilize small peptides in rather well defined conformations by reducing the conformational flexibility of the backbone [6] [7].

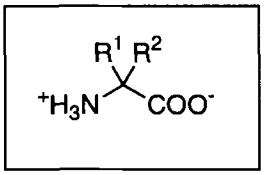


Fig. 1. *α,α-Disubstituted glycines*

[1]) Part of the Ph. D. thesis of *M. A.*, University of Zürich, 1996.
[2]) Part of the Ph. D. thesis of *U. B.*, University of Zürich, 1996.

It has been well documented by NMR measurements, CD spectroscopy, and X-ray diffraction that (*R*)- and (*S*)-α-amino-α-methyl acids can stabilize different types of β-turn conformations in small peptides depending on their absolute configurations [6–10]. While the conformational properties of cyclic and open-chain α,α-disubstituted (*R*)- and (*S*)-glycines bearing two non-functionalized side chains R^1 and R^2 (*Fig. 1*) are quite well understood and range from stabilizing β-turn type-I [6] [8], type-II [7], and type-II′ [7] [11], 3_{10}- and α-helical [11–15], and extended [16–20] conformations, the conformational properties of the parent disubstituted (*R*)- and (*S*)-glycines bearing functionalized and polar side chains have been much less investigated.

As part of a program of synthesizing and analyzing the conformational properties of disubstituted (*R*)- and (*S*)-glycines as conformationally restricted analogues of standard amino acids, we developed a general and high-yielding strategy towards the synthesis of a whole range of optically pure cyclic and open-chain α,α-disubstituted glycines [7–11]. This synthetic route provides a rapid and easy access to α-chimeras combining the side chains of functionalized amino acids like aspartic acid (Asp) [7], glutamic acid (Glu) [7], serine (Ser) [21], lysine (Lys) [15], and tyrosine (Tyr) [8]. Likewise, (*R*)- and (*S*)-(aminomethyl)alanine (Ama) and (*R*)- and (*S*)-aminomethyl-leucine (Aml) [9] could be readily obtained. They were designed and shown to have excellent properties as building blocks to stabilize amphiphilic α-helical peptides. In addition, we were able to show that (*R*)- and (*S*)-α-methyl(alkyl)-aspartic-acid derivatives **1** and **3** and their corresponding succinimide derivatives **2** and **4** can stabilize β-turn type-I, -II, and -II′ conformations depending on the absolute configuration of the incorporated non-standard amino acid (*Fig. 2*) [7].

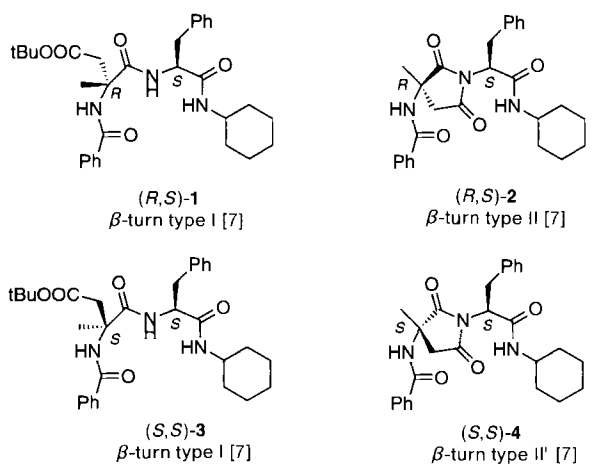


Fig. 2. *α-Methylaspartic acid derivatives* **1** *and* **3** *and their succinimid derivatives* **2** *and* **4**, *resp.*

Finally, using a novel dihydrooxazole/azlactone interconversion reaction (**A** ⇄ **B**, *Fig. 3*), we were able to synthesize the optically pure (*R*)- and (*S*)-α-methyl(alkyl)-serine derivatives of type **B** and to incorporate them into small peptides without further protective-group manipulations [21].

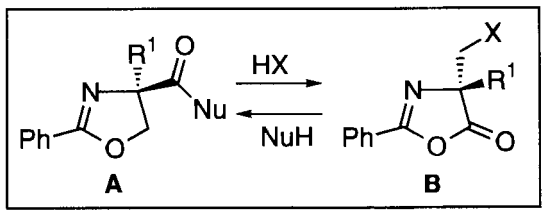
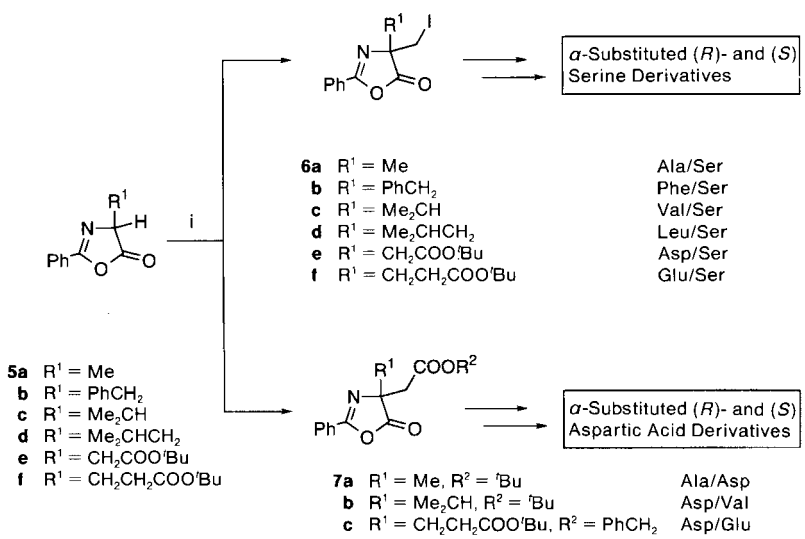


Fig. 3. *4,5-Dihydrooxazole/azlactone interconversion*

In the present paper, we like to present the synthesis and the conformational properties of some novel, optically pure α,α-disubstituted (*R*)- and (*S*)-glycine derivatives corresponding to the 'α-chimeras' of Phe/Ser, Val/Ser, Asp/Ser, Glu/Ser, and Asp/Glu and their cyclic dihydrooxazole and succinimide analogues starting from the racemic 4,4-disubstituted 2-phenyl-1,3-oxazol-5(4*H*)-ones **6a–f** and **7c** (*Scheme 1*). These azlactones were synthesized by an alkylation procedure [22] from 4-monosubstituted 2-phenyl-1,3-oxazol-5(4*H*)-ones **5a–f**. The optically pure α,α-disubstituted glycine derivatives can be obtained by resolution of dipeptide intermediates with the chiral auxiliary (*S*)-phenylalanine cyclohexylamide [8–10]. Using Asp side-chain cyclization to the corresponding succinimide analogues [7] in combination with the novel azlactone/dihydrooxazole interconversion reaction [21] allowed us to synthesize the conformationally constrained spirocyclic Asp/Ser analogues (*R,S*)-**18** and (*S,S*)-**19** (*Scheme 5*) and Asp/Glu analogues (*R,S*)-**29** and (*S,S*)-**30** (*Scheme 7*).

Based on the X-ray crystal structures of compounds (*R,S*)-**9b**, (*R,S*)-**11c**, (*R,S*)-**18**, and (*S,S*)-**30** (*Figs. 4–7*), we could unambiguously determine the absolute configurations

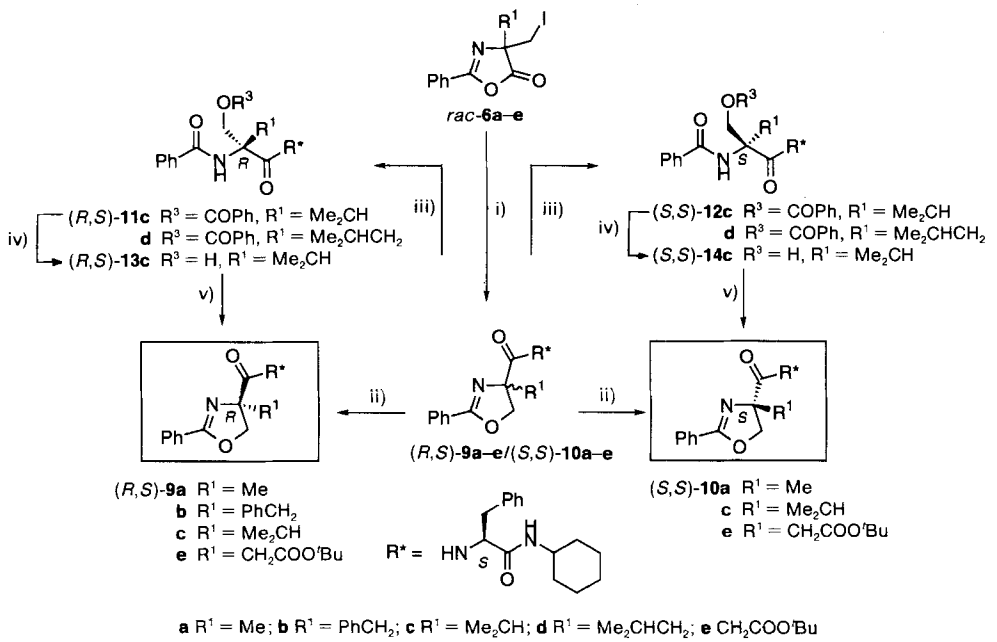
Scheme 1



of the described novel amino-acid derivatives as well as their preferred conformations in the crystalline state[3]).

2. α-Substituted Serine Derivatives. – Starting from the racemic 4-monosubstituted 2-phenyl-1,3-oxazol-5(4*H*)-ones **5a–f**, which were obtained from the corresponding commercially available *N*-benzoylated amino acids, alkylation using NaH and diiodomethane in DMF afforded the racemic 4-alkyl-2-phenyl-1,3-oxazol-5(4*H*)-ones *rac*-**6a–f** in 35–85% overall yield [22]. The azlactones **6a–e** were subsequently treated with (*S*)-phenylalanine cyclohexylamide (**8**) and ethyldiisopropylamine (Et(i-Pr)$_2$N) in *N*-methylpyrrolidin-2-one (NMP) at temperatures ranging from 50 to 100° to yield a 1:1 mixture of the diastereoisomeric dihydrooxazoles (*R,S*)-**9a–e** and (*S,S*)-**10a–e** in high yield (*Scheme 2*). In the case of the dihydrooxazoles (*R,S*)-**9a,e** and (*S,S*)-**10a,e** [21] [23], the diastereoisomers could be easily separated by flash chromatography (FC) [24], whereas (*R,S*)-**9b** was obtained by crystallization in optically pure form. X-Ray structures of (*S,S*)-**10a** [21] and (*R,S*)-**9b** (see discussion in *Sect. 5*) unambiguously determined the absolute configurations of these amino-acid derivatives.

Scheme 2



a R^1 = Me; **b** R^1 = PhCH$_2$; **c** R^1 = Me$_2$CH; **d** R^1 = Me$_2$CHCH$_2$; **e** CH$_2$COO'Bu

i) (*S*)-Phe-cyclohexylamide (**8**), NMP, Et(i-Pr)$_2$N, 50–80°. ii) Flash chromatography or crystallization. iii) 2N aq. HCl, dioxane; then aq. NaHCO$_3$; then Et(i-Pr)$_2$N, benzoyl chloride, DMA. iv) LiOH, THF/MeOH/H$_2$O 3:1:1. v) SOCl$_2$, CH$_2$Cl$_2$.

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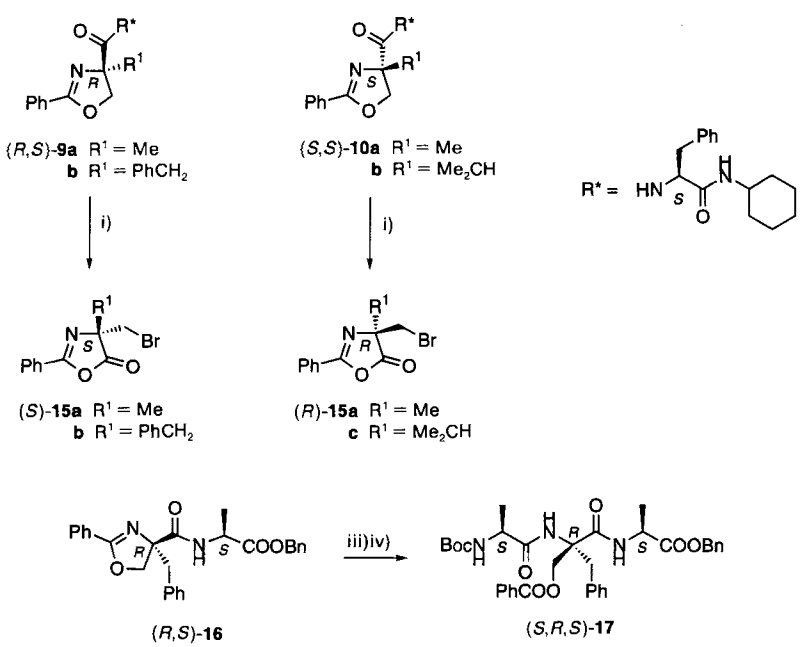
[3]) Compounds (*R,S*)-**1**, (*R,S*)-**2**, (*S,S*)-**3**, (*S,S*)-**4**, (*R,S*)-**23**, and (*S,S*)-**24** were examined by CD spectroscopy in CF$_3$COOH/H$_2$O 1:1 and exhibit the expected β-turn type-I, -II, and -II′ conformations in solution, thus reconfirming the X-ray results [7].

A more general way to generate the optically pure dihydrooxazoles (*R,S*)-**9** and (*S,S*)-**10** consists in a small detour *via* separation of the corresponding *N,O*-dibenzoylated dipeptides (*R,S*)-**11** and (*S,S*)-**12** (*Scheme 2*) obtained by hydrolysis of the dihydrooxazoles using aqueous 2N HCl in dioxane and subsequent *N*-benzoylation of the intermediate amine with benzoyl chloride and $Et(i\text{-}Pr)_2N$ in *N,N*-dimethylacetamide (DMA) in high yield, as shown for (*R,S*)-**11c,d** and (*S,S*)-**12c,d**. The X-ray structure of (*R,S*)-**11c** unambiguously confirmed the absolute configuration. The absolute configuration of (*R,S*)-**11d** was tentatively deduced from the corresponding (*R,S*)-α-(aminomethyl)-leucine analogue [9], which was assigned by X-ray structure analysis. As previously shown for similar cases [8–11], the separation of diastereoisomeric dipeptides of type **11** and **12** was very general and based on significant differences in the preferred conformations of the two diastereo-isomers [9] [10]. Saponification of dipeptides (*R,S*)-**11** and (*S,S*)-**12** with LiOH in THF/MeOH/H_2O 3:1:1 afforded the free alcohols (*R,S*)-**13** and (*S,S*)-**14** quantitatively (exemplified for (*R,S*)-**13c** and (*S,S*)-**14c**, *Scheme 2*), which gave, after treatment with $SOCl_2$, the dihydrooxazoles (*R,S*)-**9c** and (*S,S*)-**10c**.

Both described strategies allowed us to synthesize the key dihydrooxazoles (*R,S*)-**9a, b, c, e** and (*S,S*)-**10a, c, e** (for (*R,S*)-**9a** and (*S,S*)-**10a**, see [21] [23]) in optically pure form in good overall yields and should be transferable to other α-substituted serine derivatives.

Another important aspect of the azlactone/dihydrooxazole interconversion reaction is the facile incorporation of optically pure α-substituted serine derivatives into peptides

Scheme 3



i) 33% HBr/AcOH, Ac_2O. ii) (*S*)-Ala-OBn·HCl, $Et(i\text{-}Pr)_2N$, NMP. iii) 2N aq. HCl, dioxane, then aq. $NaHCO_3$. iv) TATU, HOAT, DMF, $Et(i\text{-}Pr)_2N$, Boc-(*S*)-Ala-OH.

without using additional protective groups by converting (*R,S*)-**9** and (*S,S*)-**10** to the intermediate optically pure 4-substituted (*R*)- and (*S*)-4-(bromomethyl)-2-phenyl-1,3-oxazol-5(4*H*)-ones **15** (*Scheme 3*). Thus, (*R,S*)-**9a**, (*S,S*)-**10a**, (*R,S*)-**9b**, and (*S,S*)-**10c** were treated with 33% HBr/AcOH and Ac_2O at 80–100° to yield the optically pure 4-(bromomethyl)azlactones (*R*)- and (*S*)-**15a**, (*R*)-**15b**, and (*S*)-**15c**[4]), respectively [21] [23]. As already shown for (*R*)- and (*S*)-**15a**, we were able to incorporate azlactone (*S*)-**15b** into a tripeptide sequence without using additional activation and protective groups. Coupling of (*S*)-**15b** and (*S*)-Ala-OBn with Et(i-Pr)$_2$N in NMP at 80° afforded dihydrooxazole (*R,S*)-**16** in high yield. Hydrolysis, using aqueous 2N HCl in dioxane, yielded the intermediate *O*-benzoylated amine which was directly coupled to Boc-(*S*)-Ala-OH using the highly efficient coupling reagent TATU (= *O*-(1*H*-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate) and HOAt (= 1-hydroxy-1*H*-7-azabenzotriazole = 1-hydroxy-1*H*-1,2,3-triazolo[4,5-*b*]pyridine) described by *Carpino* [25] to yield tripeptide (*S,R,S*)-**17**. It is interesting to note that we did not observe an *O* → *N*-benzoyl shift during the hydrolysis, extraction, and coupling procedures. This example nicely demonstrates the synthetic potential of the azlactone/dihydrooxazole interconversion in combination with the use of Phe-cyclohexylamide **8** as chiral auxiliary.

3. Asp/Ser Derivatives. – α-Methyl(alkyl)aspartic-acid derivatives and their corresponding succinimide analogues show a high preference for β-turn type-I, -II, and -II′ conformations [7]. Especially interesting was the observation of a shift from β-turn type I to type II or II′ in going from the open-chain Asp derivatives to the cyclic succinimide derivatives depending on the absolute configuration, as shown by several X-ray structures [7] and NMR solution structures [26]. Since serine shows a high prevalence of β-turns at the exposed positions ($i + 1$) and ($i + 2$) [27] [28], we were interested to investigate whether or not the (*R*)- and (*S*)-'α-chimeras' of Asp/Ser would be interesting β-turn mimetics at the ($i + 1$) position of β-turns placing a CH_2OH group in the correct exposed position. Furthermore, we were interested to see whether or not the corresponding succinimide derivatives of Asp/Ser would also show this β-turn switch from type I to type II or II′ depending on their absolute configurations. The experimental realization of this concept is shown in *Scheme 4*.

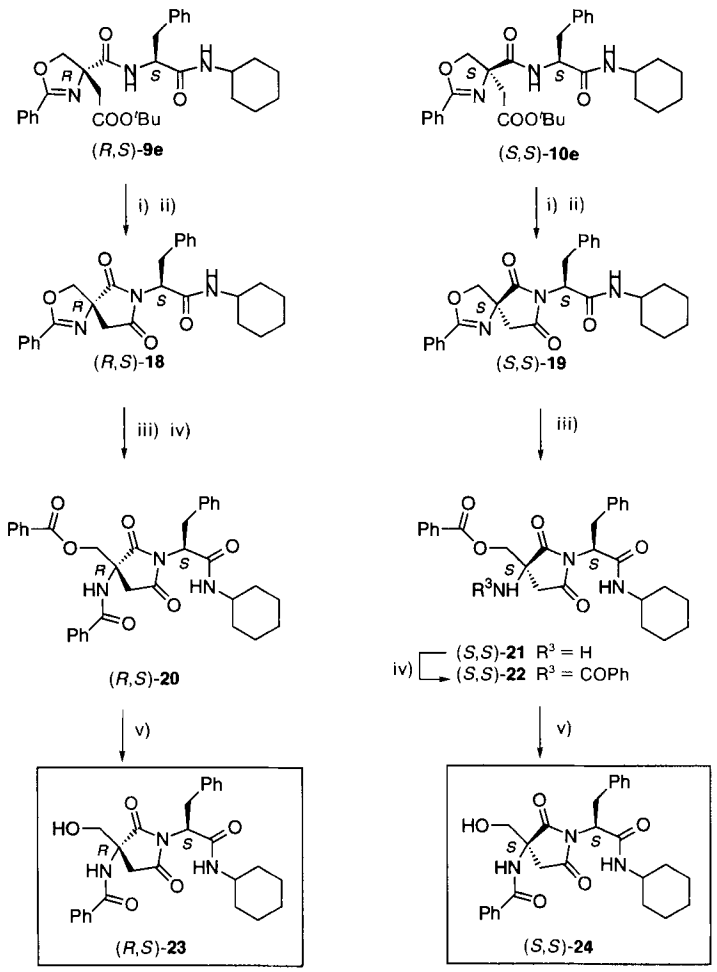
The dihydrooxazoles (*R,S*)-**9e** and (*S,S*)-**10e** were individually treated with CF_3COOH in CH_2Cl_2 at 0° and the intermediate acids cyclized in high yields to the spiro derivatives (*R,S*)-**18** and (*S,S*)-**19**, respectively, using $SOCl_2$ [7]. Based on the X-ray crystal structure of (*R,S*)-**18** (see below, *Fig. 6*), we could unambiguously determine the absolute configuration at the crucial quaternary centre based on the known (*S*)-chirality of Phe. Although the dihydrooxazole moiety cannot form a complete β-turn, the φ and ψ angles around the succinimide ring and the (*S*)-Phe moieties correspond well to a β-turn of type II′ (see below, *Table 2*). These values compare very nicely with those described for (*R,S*)-**2** [7] [26]. Hydrolysis of spiro compounds (*R,S*)-**18** and (*S,S*)-**19** with aqueous 2N HCl in dioxane and subsequent benzoylation, using benzoyl chloride and Et(i-Pr)$_2$N in DMA, resulted in the formation of (*R,S*)-**20** and (*S,S*)-**22** in high yields. Transesterification using NaCN in MeOH cleanly removed the *O*-benzoyl group to form the final

[4]) Reaction mechanisms for the azlactone/dihydrooxazole interconversion have already been discussed in [21] [23].

products (*R*,*S*)-**23** and (*S*,*S*)-**24**. These compounds show CD spectra[5]) similar to those of the parent α-methyl-Asp succinimide derivatives (*R*,*S*)-**2** and (*S*,*S*)-**4**, respectively (*Fig. 2*), indicating again the strong conformational bias for β-turn type-II and -II′ conformations of the succinimide ring moiety.

As indicated in *Scheme 5*, (*S*,*S*)-**21** was incorporated into the tripeptide derivative (*S*,*S*,*S*)-**26** *via* (*S*,*S*,*S*)-**25** by peptide coupling reaction using TATU, HOAT [25], Et(i-Pr)$_2$N, and Boc-Ala-OH in DMF and cleavage of the *O*-benzoyl group using NaCN

Scheme 4



i) CF_3COOH, CH_2Cl_2. ii) $SOCl_2$. iii) 2N aq. HCl, dioxane; then aq. $NaHCO_3$ and extraction. iv) Et(i-Pr)$_2$N, CH_2Cl_2, benzoyl chloride. v) NaCN, MeOH, Δ.

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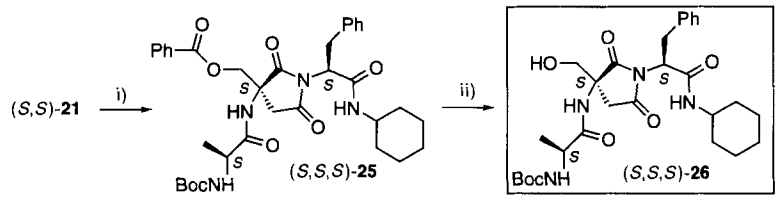
[5]) For detailed discussion of the CD spectra, see *Chapt. 5.2* and *Figs. 9–11*.

Scheme 5

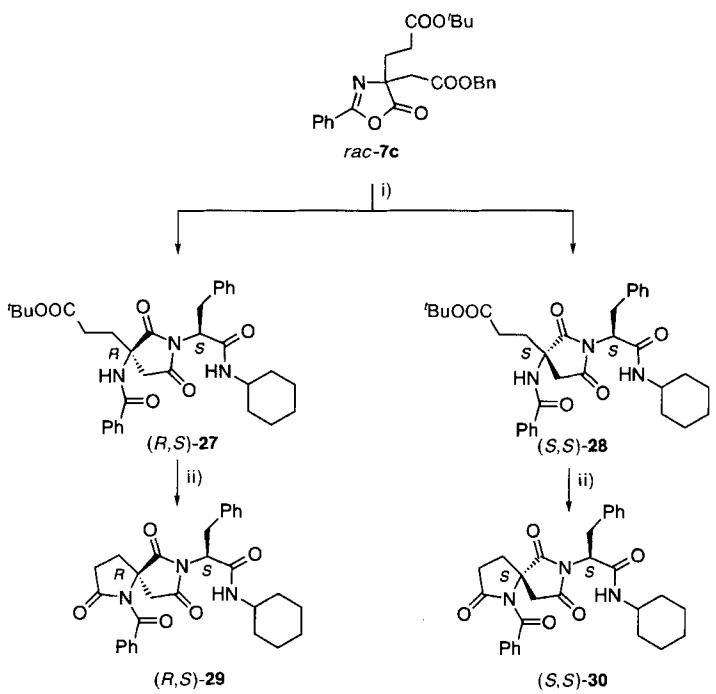


i) TATU, HOAT, $Et(i\text{-}Pr)_2N$, Boc-(*S*)-Ala-OH. ii) NaCN, MeOH, *Δ*.

in MeOH. This reaction sequence shows that the succinimide ring is fully compatible with the mild reaction conditions applied for the incorporation of this Asp/Ser 'α-chimera' into a peptide sequence.

4. Asp/Glu Derivatives. – Treatment of racemic azlactone *rac*-**7** with the chiral auxiliary **8** under the standard reaction conditions gave the separable diastereoisomeric succinimide derivatives (*R,S*)-**27** and (*S,S*)-**28** in high yield (*Scheme 6*). It is worth noting that under the coupling conditions, spontaneous cyclization to the imide derivatives occurred with concomitant liberation of benzyl alcohol. Cleavage of the *t*-Bu esters using

Scheme 6



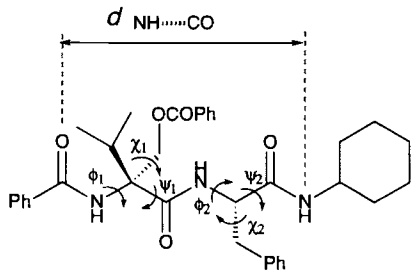
i) (*S*)-Phe-cyclohexylamide (**8**), NMP, *Δ*. ii) CF_3COOH, CH_2Cl_2, 0°, then $SOCl_2$.

CF_3COOH in CH_2Cl_2 at 0° and addition of $SOCl_2$ led to cyclization to the spirocyclic pyroglutamate succinimide derivatives (*R,S*)-**29** and (*S,S*)-**30** in high yields. Similar cyclizations to pyroglutamate derivatives of α-methylaspartate had been investigated in our group [7]. It was shown that pyroglutamates exhibit β-turn type-II and -II′ conformations [26] depending on their absolute configurations, similarly to the corresponding α-methylproline derivatives. These spiro-pyroglutamate/succinimide derivatives (*R,S*)-**29** and (*S,S*)-**30** incorporating the 'α-chimeras' of (*R*)- and (*S*)-Asp/Glu can be regarded as doubly constrained peptide mimetics combining the properties of α-substituted prolines and α-substituted aspartates. The absolute configurations of (*R,S*)-**29** and (*S,S*)-**30** could unambiguously be determined by an X-ray structure of (*S,S*)-**30** (see below, *Fig. 7*). It is interesting to note that these spiro compounds can be nicely superimposed with the corresponding X-ray structures of (*S,S*)-**4**[6]) (see below, *Fig. 8*) [26].

5. Conformational Aspects. – 5.1. *X-Ray Structures of* (R,S)-**9b**, (R,S)-**11c**, (R,S)-**18**, *and* (S,S)-**30**. The following figures show the ORTEP stereoplots of components (*R,S*)-**9b** (*Fig. 4*), (*R,S*)-**11c** (*Fig. 5*), (*R,S*)-**18** (*Fig. 6*), and (*S,S*)-**30** (*Fig. 7*). The characteristic torsional angles ϕ_1, ψ_1, ϕ_2, ψ_2, χ_1, and χ_2 are shown in *Tables 1–3*, and the crystal data are summarized in *Table 4*.

Whereas dihydrooxazole (*R,S*)-**9b** (*Fig. 4*) shows a rather extended backbone structure, similar to the parent α-methylserine derivative [21], the open-chain α-isopropylserine derivative (*R,S*)-**11c** (*Fig. 5*) exhibits a clear β-turn type-I [29] backbone structure (*Table 1*), which parallels previous findings in the α-methylaspartate and -glutamate series [7] [26]. In contrast to the dihydrooxazole (*R,S*)-**9b**, the Asp/Ser derivative (*R,S*)-**18** (*Fig. 6*) shows a tendency to form a β-turn of type II′ [30–33]. This indicates again the high propensity of the α-substituted Asp-imide moiety to stabilize β-turn type-II or -II′ geometries [7] [26] [30–33], depending on the configuration at the C(α)-atom. The structure of (*R,S*)-**18** almost perfectly matches the X-ray structure of (*S,S*)-**4** [7] around

Table 1. *Geometrical Data of Peptide* (R,S)-**11c**



	Φ_1	Ψ_1	Φ_2	Ψ_2	X_1	X_2	d [Å]	Turn type
(*R,S*)-**11c**	−55°	−33°	−81°	−8°	+64°	−56°	2.94	type I

[6]) Confirming again the strong preference of α-substituted (*R*)- and (*S*)-aspartimide-containing peptides for β-turns of type II′ and II, respectively.

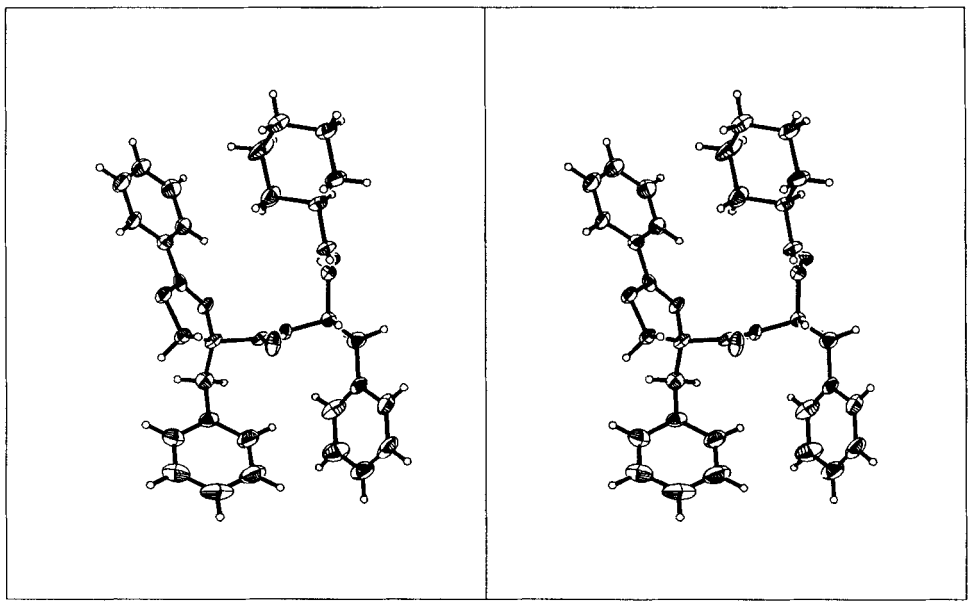


Fig. 4. *ORTEP Stereoplot of the X-ray crystal structure of dihydrooxazole* (R,S)-**9b**

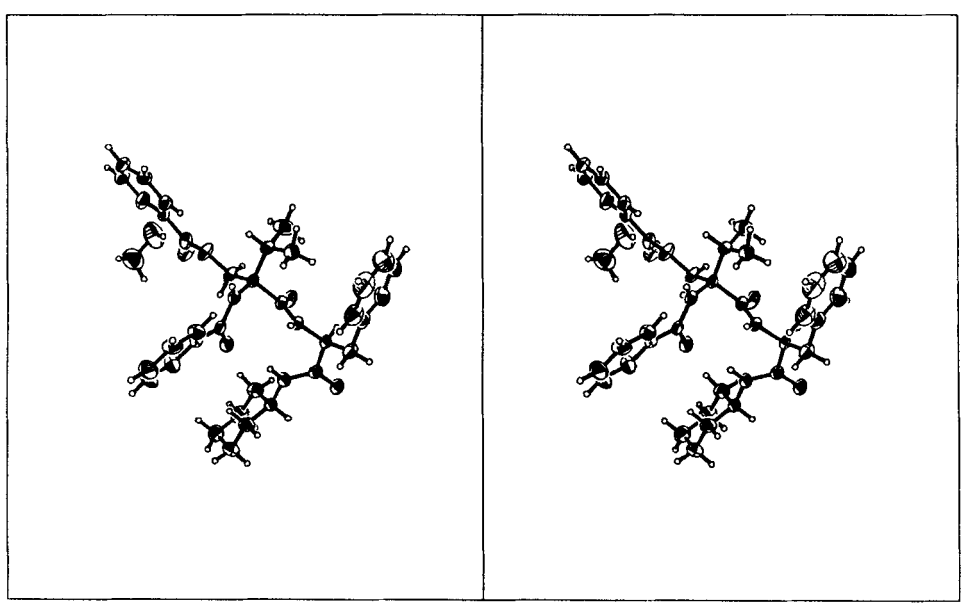


Fig. 5. *ORTEP Stereoplot of the X-ray crystal structure of dipeptide* (R,S)-**11c**

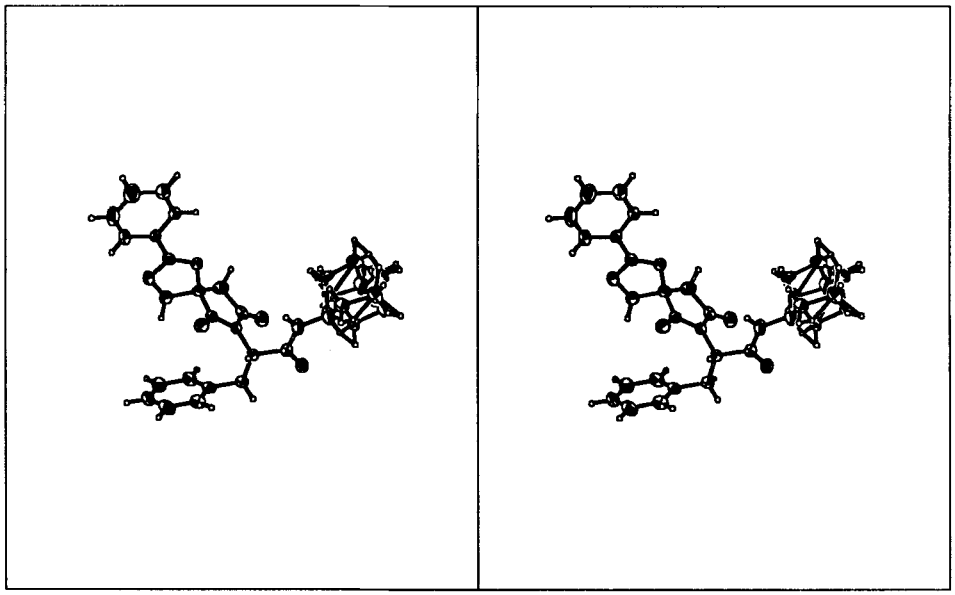


Fig. 6. *ORTEP Stereoplot of the X-ray crystal structure of the Asp/Ser derivative (*R,S*)-***18***.* Superposition of two conformers that differ only in the cyclohexyl moiety.

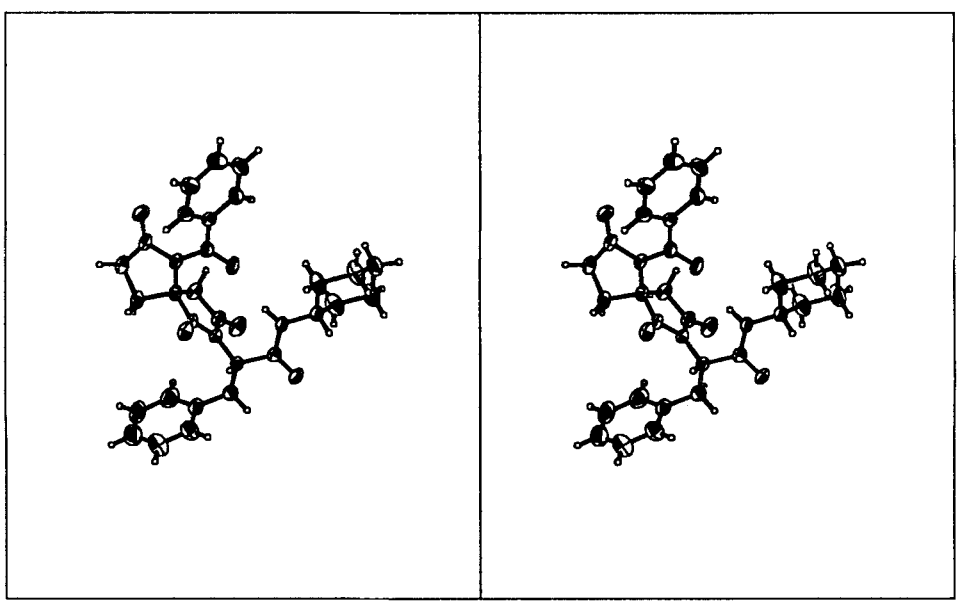
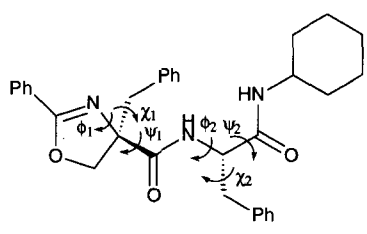
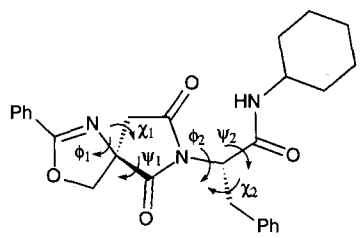


Fig. 7. *ORTEP Stereoplot of the X-ray crystal structure of the Asp/Glu derivative (*S,S*)-***30***

Table 2. *Geometrical Data of Ser Derivatives (*R,S*)-***9b*** and (*R,S*)-***18***



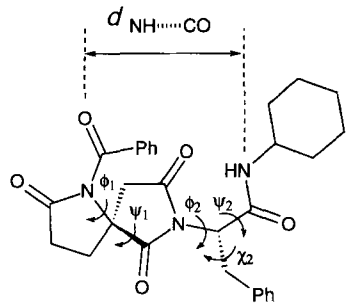
(*R,S*)-**9b**



(*R,S*)-**18**

	Φ_1	Ψ_1	Φ_2	Ψ_2	X_1	X_2	Turn type
(*R,S*)-**9b**	−113°	−48°	−101°	+96°	−175°	−64°	extended
(*R,S*)-**18**	−109°	−127°	−137°	+58°	+124°	−59°	type II′ ($\varepsilon\alpha_R$)

Table 3. *Geometrical Data of (*S,S*)-***30***



	Φ_1	Ψ_1	Φ_2	Ψ_2	X_2	*d* [Å]	Turn type
(*S,S*)-**30**	+52°	−129°	−112°	+29°	−30°	3.01	type II′ ($\varepsilon\alpha_R$)

the succinimide and Phe-cyclohexylamide portions. The X-ray crystal structure of (*S,S*)-**30** (*Fig. 7*) matches almost ideally a β-turn type-II′ backbone structure, very similarly to (*S,S*)-**4** [7] (see *Fig. 8*).

5.2. *CD Spectra of (*R,S*)-***1*** and (*S,S*)-***3*** and of the Succinimide Derivatives (*R,S*)-***2***, (*S,S*)-***4***, (*R,S*)-***23***, (*S,S*)-***24***, (*R,S*)-***29***, and (*S,S*)-***30***.* Whereas most of the conformational studies on α,α-disubstituted-glycine-containing small peptides were performed using X-ray crystal data [4] [7–11] [16–21] [34], very little has been published about their preferred conformation in solution using CD and NMR spectroscopy [35]. An interesting study using temperature-dependent shifts of amide protons on a series of tripeptides incorporating optically pure α,α-disubstituted glycines such as (*R*)- and (*S*)-methylvaline was performed by *Wipf* and *Heimgartner* [6] [35] [36]. Here, we report some preliminary results using CD spectroscopy to analyze the derivatives (*R,S*)-**1** and (*S,S*)-**3**, and their

Table 4. *X-Ray Structure Data for (R,S)-***9b**, *(R,S)-***11c**, *(R,S)-***18**, *and (S,S)-***30**

	(*R*,*S*)-**9b**	(*R*,*S*)-**11c**	(*R*,*S*)-**18**	(*S*,*S*)-**30**
Crystal data				
Empirical formula	$C_{32}H_{35}N_3O_3$	$C_{35}H_{41}N_3O_5$	$C_{27}H_{29}N_3O_4$	$C_{29}H_{31}N_3O_5$
Crystallization solvent	MeOH	MeOH	AcOEt	propanol
Color and habit	colorless, needles	colorless, prismatic	colorless, prismatic	colorless, prismatic
Crystal system	monoclinic	monoclinic	monoclinic	orthorhombic
Space group	$C2$	$P2_1$	$P2_1$	$P2_12_12_1$
Unit cell dimensions				
a [Å]	19.903	10.023	14.645	6.126
b [Å]	5.244	17.075	5.518	17.784
c [Å]	27.374	11.152	15.609	24.227
β [°]	109.64	115.79	112.10	–
Volume [Å^3]	2689.9	1718.5	1168.6	2652.8
Z	4	2	2	4
Formula weight	509.6	615.84	459.53	501.57
Density (calc.) [mg/m^3]	1.258	1.190	1.306	1.256
Absorption coeff. [mm^{-1}]	0.644	0.653	0.089	n.a.
F(000)	1088	660	488	1064
Data collection				
Radiation	CuK_α	CuK_α	MoK_α	CuK_α
Temperature (K)	183	173	293	163
2θ Range (deg)	3–110	4.4–56.75	0–56	0–112
Scan type	2θ-θ	2θ-θ	ω	2θ-θ
Reflections collected	1973	3076	3216	2083
Independent reflections	1928	2576	3101	2083
Reflections ($F > 4\sigma$)	1794	n.a.	n.a.	n.a.
R(int)	2.92%	1.15%	2.94%	4.75%
Absorption correction	none	none	none	none
Solution and refinement				
Solution method	direct	direct	direct	direct
Final R index (all data)	6.10%	4.98%	10.38%	5.32%

succinimide derivatives (*R*,*S*)-**2** and (*S*,*S*)-**4** (*Fig. 9*), the Asp/Ser 'α-chimeras' (*R*,*S*)-**23** and (*S*,*S*)-**24** (*Fig. 10*), and the Asp/Glu 'α-chimeras' (*R*,*S*)-**29** and (*S*,*S*)-**30** (*Fig. 11*). The CD spectra of these compounds were recorded routinely in CF_3CH_2OH and CF_3CH_2OH/H_2O 1:1 at different pH values. The spectra show only small differences under the different conditions. Thus, for convenience, only the spectra in CF_3CH_2OH/H_2O 1:1 are shown in *Figs. 9–11*.

The CD spectra of the open-chain Asp derivatives (*R*,*S*)-**1** and (*S*,*S*)-**3** (*Fig. 9*) show the characteristics of a β-turn type-**I** conformation [26] [29] [37]. Both the (*R*)- and (*S*)-configurations at the quaternary centre are tolerated and compatible with a β-turn type-I conformation. The parent succinimide derivatives (*R*,*S*)-**2** and (*S*,*S*)-**4**, however, show the typical CD curves for a β-turn of type II and a β-turn of type II′, respectively, according to *Fasman et al.* [26] [38]. The CD spectra indicate a good correlation between the preferred conformations in solution with those observed by X-ray in the solid state [7]. As noted before [7], we observed a conformational switch from the β-turn of type **I** to the β-turn of type II/II′ in solution as well as in the solid state upon succinimide ring

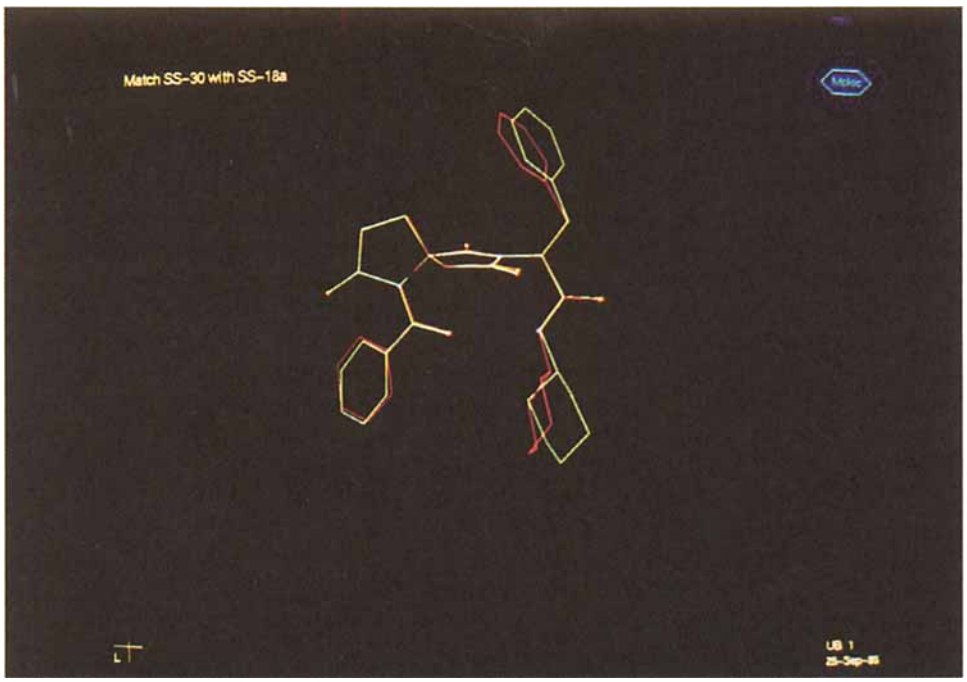


Fig. 8. *C(α) Match of the X-ray crystal structures of* (S,S)-**30** *and* (S,S)-**4**

formation. This fact is strongly underlined by the CD spectra of the Asp/Ser derivatives (*R*,*S*)-**23**[7]) and (*S*,*S*)-**24** (*Fig. 10*), which again show a β-turn of type II′ and a β-turn of type II, respectively. Similarly, the Asp/Glu derivatives (*R*,*S*)-**29** and (*S*,*S*)-**30** behave exactly like (*R*,*S*)-**2** and (*S*,*S*)-**4**, showing almost perfect mirror images of β-turn type-II and type-II′ curves (*Fig. 22*, see also *Fig. 8* for X-ray structure). In summary, all the corresponding succinimide-containing structures (*R*,*S*)-**2**, (*S*,*S*)-**24**[7]), and (*R*,*S*)-**29** show β-turn type-II and (*S*,*S*)-**4**, (*R*,*S*)-**23**[7]), and (*S*,*S*)-**30** β-turn type-II′ conformations, in solution and in the crystalline state, indicating that the two succinimide carbonyl groups enforce a strong conformational constraint on ϕ_2, ψ_2, and χ_2.

In addition to the CD study, we investigated the solution structures of (*R*,*S*)-**2** and (*S*,*S*)-**4** in detail by 2D-NMR [26]. *Fig. 12* shows a C(α) match of the X-ray structure of (*S*,*S*)-**4** (in white) with the corresponding lowest-energy solution conformation (in green), compatible with the most important observed NOE constraints (intensities and distances) [26]. The close match of the two structures underscores again the strong preference for this β-turn type-II′ conformations observed also in the CD spectra (*Fig. 9*).

6. Conclusions and Outlook. – We described the successful synthesis of optically pure α,α-disubstituted (*R*)- and (*S*)-glycines ('α-chimeras'), combining the side chains of Asp,

[7]) In the Asp/Ser derivatives (*S*,*S*)-**24** and (*R*,*S*)-**23**, the first configurational prefix is reversed due to the higher priority of the Ser side chain over the Asp side chain.

Glu, Leu, Ser, and Val. These syntheses are based on the α-alkylation of 4-monosubstituted 2-phenyl-1,3-oxazol-5(4*H*)-ones [22], using (*S*)-phenylalanine cyclohexylamide (**8**) [7–11] in combination with the clean azlactone/dihydrooxazole interconversion reaction [21] [23] and the efficient formation of Asp-imide derivatives [7]. Whereas the open-chain derivatives (*R,S*)-**1** (Ala/Asp), (*S,S*)-**3** (Ala/Asp), and (*R,S*)-**11c** (Ser/Val) adopt β-turn type-I conformations as shown by X-ray diffraction and CD spectroscopy, the corresponding cyclic succinimide derivatives (*R,S*)-**2**, (*S,S*)-**19**, (*S,S*)-**24**, (*S,S,S*)-**26**, and (*R,S*)-**29** show β-turn type-II and (*S,S*)-**4**, (*R,S*)-**18**, (*R,S*)-**23**, and (*S,S*)-**30** β-turn type-II′ conformations, respectively. Using the azlactone/dihydrooxazole interconversion strategy [21] [23], it was possible to incorporate the 'α-chimera' corresponding to the (*R*)-enantiomer of Phe/Ser into a tripeptide sequence without further protective-group manipulations, starting from the optically pure (bromomethyl)azlactone (*S*)-**15b** (*Scheme 3*). Derivatives of the 'α-chimera' of Asp/Ser, such as (*R,S*)-**23** and (*S,S*)-**24**

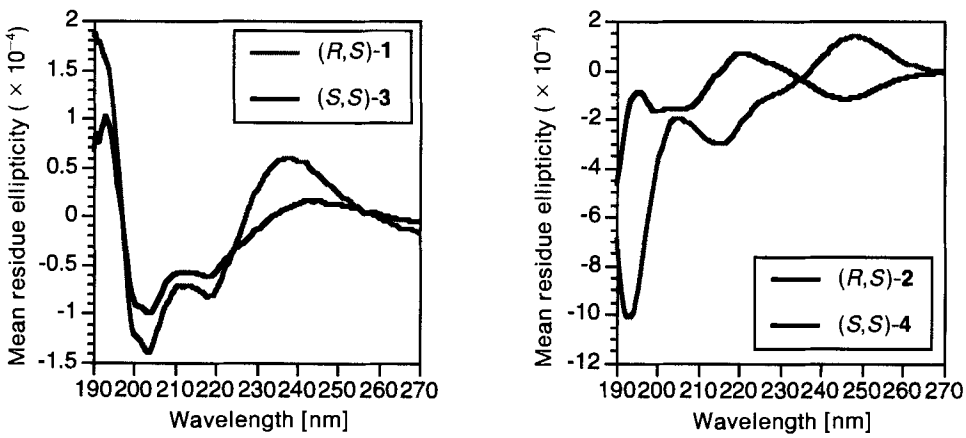


Fig. 9. *CD Spectra of the α-Me-Asp derivatives* (R,S)-**1** *and* (S,S)-**3**, *and of their corresponding succinimide derivatives* (R,S)-**2** *and* (S,S)-**4**

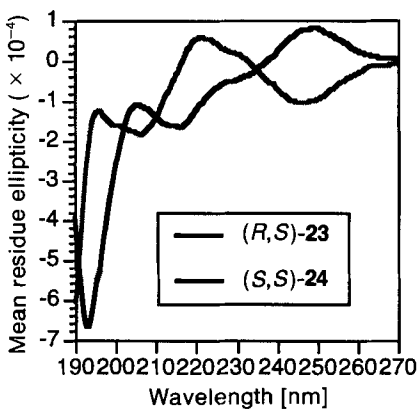


Fig. 10. *CD Spectra of the Asp/Ser derivatives* (R,S)-**23** *and* (S,S)-**24**

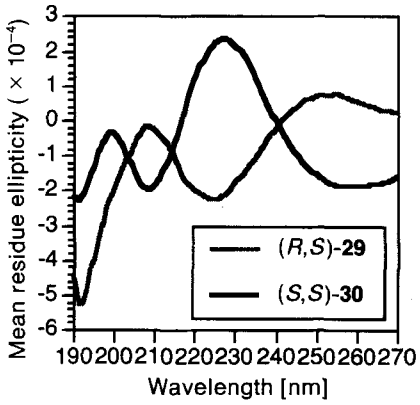


Fig. 11. *CD Spectra of Asp/Glu derivatives* (R,S)-**29** *and* (S,S)-**30**

(*Scheme 4*), are particularly valuable peptide building blocks, since they represent simple β-turn type-II and type-II′ mimetics, placing a conformationally constrained serine at the crucial ($i + 1$) position of the turn. Finally, the spiro derivatives (*R*,*S*)-**29** and (*S*,*S*)-**30** (*Scheme 6*), derived from the 'α-chimera' of Asp/Glu, constitute doubly constrained peptide building blocks, combining both the characteristic constraints of α-substituted prolines and aspartimides. It is noteworthy that the conformations of (*R*,*S*)-**1**, (*R*,*S*)-**2**,

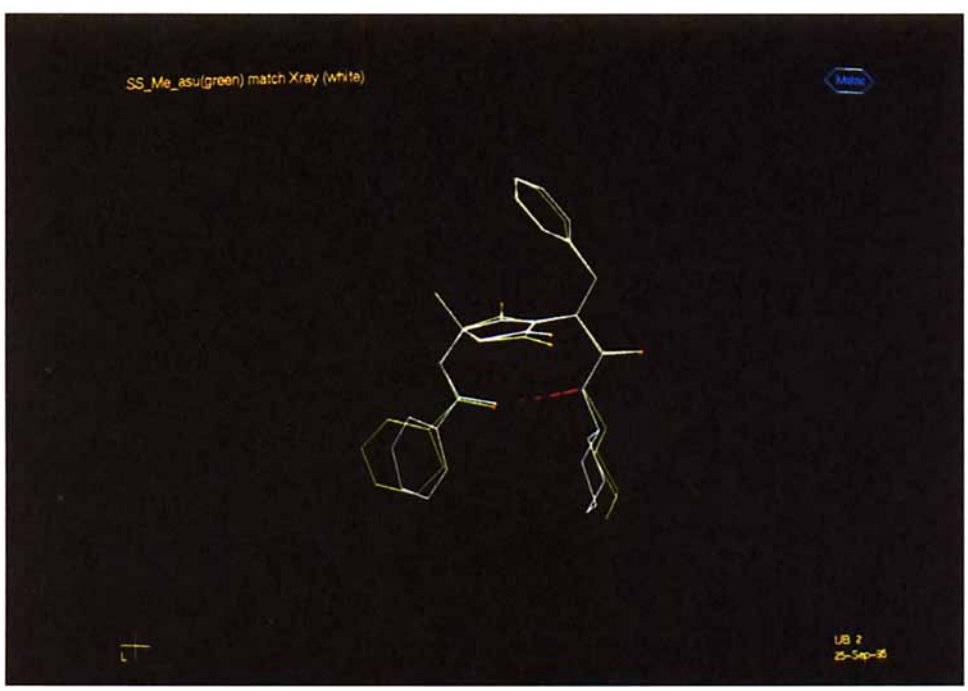


Fig. 12. *C(α) Match of the X-ray crystal structure of* (S,S)-**4** (white) *with the corresponding lowest-energy conformation from NOE screening* (green)

(*S,S*)-**3**, (*S,S*)-**4**, (*R,S*)-**18**, and (*S,S*)-**30** observed in the crystalline state could be confirmed in solution using CD and NMR spectroscopy. Using the described synthetic strategies, other novel optically pure 'α-chimeras', such as of Asp/His, Asp/Lys, Asp/Trp, and Asp/Tyr, with appropriate conformational control and interesting biological potential, should be available.

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Experimental Part

General. See [10]. CD Spectra: *Dichrograph-CD6* (*Jobin-Yvon*, Paris) spectrometer; calibration with epiandrosterone ($\Delta\varepsilon = 3.3$ at 303 nm) and camphorsulfonic acid ($\Delta\varepsilon = -4.72$ at 188 nm and 2.37 at 289 nm); data collection every 0.5 nm; samples typically in a 0.05-cm pathlength cell, at 20°, unless otherwise stated. The observed $\Delta\varepsilon$ values were recalculated as molecular-residue ellipticities [θ] [deg cm^2 dmol^{-1}] and the baseline, taken with a solvent-filled cell, was subtracted from the spectra. The final spectra were the average of two scans and smoothed to improve appearance.

*(4R)-4-Benzyl-*N*-[(1S)-1-(cyclohexylcarbamoyl)-2-phenylethyl]-4,5-dihydro-2-phenyloxazole-4-carboxamide* ((*R,S*)-**9b**) *and (4S,1'S)-Diastereoisomer* (S,S)-**10b**/(R,S)-**9b**. To a stirred soln. of *rac*-**6b** (4.4 g, 11.2 mmol) and **8** (4.1 g, 16.8 mmol) in NMP (40 ml) under Ar was added Et(i-Pr)$_2$N (3.9 ml, 22.4 mmol). The mixture was stirred at 70° for 24 h and poured onto ice, H_2O (100 ml), and AcOEt (100 ml). The org. layer was extracted with H_2O (150 ml) and sat. brine (150 ml), dried (Na_2SO_4), and evaporated. The residue was chromatographed (SiO_2 (250 g), hexane/AcOEt 3:2): 4.3 g (75%) of (*R,S*)-**9b**/(*S,S*)-**10b** as a white powder. (*R,S*)-**9b** was crystallized from hexane/AcOEt 2:1. Crystallization from MeOH gave crystals suitable for X-ray analysis. M.p. 174–176°. $[\alpha]_D = +32$ ($CHCl_3$, $c = 0.1$). IR (KBr): 3427*w* (br.), 3314*m* (br.), 2931*m*, 2854*w*, 1647*s* (br.), 1527*s* (br.), 1496*m*, 1450*m*, 1362*w*, 1067*w*, 744*w*, 697*s*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 7.95–7.85 (*m*, 2 arom. H); 7.55–7.2 (*m*, 11 arom. H, NH); 7.15–7.05 (*m*, 2 arom. H); 5.25 (*d*, $J = 10$, NH); 4.58, 4.37 (2*d*, *AB*, $J_{AB} = 9$, 2 aliph. H); 4.45–4.3 (*m*, 1 aliph. H); 3.65–3.5 (*m*, 1 aliph. H); 3.20, 2.98 (2*d*, *AB*, $J_{AB} = 13$, 2 aliph. H); 2.87 (*dd*, *ABX*, $J_{AB} = 14$, $J_{AX} = 5$, 1 aliph. H); 2.64 (*dd*, *ABX*, $J_{AB} = 14$, $J_{BX} = 8$, 1 aliph. H); 1.7–1.4 (*m*, 5 aliph. H); 1.3–1.25 (*m*, 2 aliph. H); 1.1–0.7 (*m*, 3 aliph. H). EI-MS: 532 (14), 510 (100, $[M + H]^+$), 411 (9).

*(4S)-*N*-[(1S)-1-(Cyclohexylcarbamoyl)-2-phenylethyl]-4,5-dihydro-4-isopropyl-2-phenyloxazol-4-carboxamide* ((*S,S*)-**10c**) *and (4R,1'S)-Diastereoisomer* (R,S)-**9c**/(S,S)-**10c**. To a stirred soln. of *rac*-**6c** (13.6 g, 39.3 mmol) and **8** (19.38 g, 78.7 mmol) in DMA under Ar was added Et(i-Pr)$_2$N (16.8 ml, 98.4 mmol). The mixture was stirred at 100° for 30 h and poured onto ice, H_2O (200 ml), and AcOEt (250 ml). The org. layer was extracted with H_2O (200 ml) and sat. brine (150 ml), dried (Na_2SO_4), and evaporated. The residue was chromatographed (SiO_2 (500 g), hexane/AcOEt 6:1 → 4:1): 15.1 g (83%) of (*R,S*)-**9c**/(*S,S*)-**10c**. Pale yellow foam. M.p. 64–66°. IR (KBr): 3377*m* (br.), 3314*m* (br.), 2931*s* (br.), 2854*m*, 1648*s* (br.), 1513*s* (br.), 1498*s*, 1450*m*, 1355*m*, 1294*m*, 1084*w* (br.), 1027*w*, 972*w* (br.), 743*w*, 697*s*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 8.0–7.9 (*m*, 2 arom. H); 7.6–7.0 (*m*, 8 arom. H, NH); 5.85, 5.56 (2*d*, NH); 4.6–4.25 (*m*, 3 aliph. H); 3.8–3.55 (*m*, 1 aliph. H); 3.25–2.95 (*m*, PhCH_2); 2.25–2.05 (*m*, 1 aliph. H); 1.95–1.0 (*m*, 10 aliph. H); 1.0–0.75 (*m*, 6 aliph. H). EI-MS: 464 (11), 463 (38), 462 (100, $[M + H]^+$).

To a stirred soln. of (*S,S*)-**14c** (0.3 g, 0.63 mmol) in CH_2Cl_2 (3.0 ml) at 0° under Ar was slowly added $SOCl_2$ (0.04 ml in 1 ml CH_2Cl_2, 0.7 mmol). The mixture was stirred at r.t. for 4 h and poured onto ice, 0.1N aq. NaOH (10 ml), and AcOEt (10 ml). The org. layer was extracted with sat. aq. $NaHCO_3$ soln. (20 ml), dried (Na_2SO_4), and evaporated. The residue was chromatographed (SiO_2 (30 g), hexane/AcOEt 6:1 → 3:1): 0.23 g (78%) of (*S,S*)-**10c**. White powder. M.p. 52–54°. $[\alpha]_D = -62$ ($CHCl_3$, $c = 0.05$). IR (KBr): 3428*m* (br.), 2931*w* (br.), 2854*w*, 1648*s* (br.), 1497*m*, 697*w*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 8.0–7.95 (*m*, 2 arom. H); 7.55–7.45 (*m*, 3 arom. H); 7.25–7.0 (*m*, 5 arom. H); 5.85 (*d*, $J = 8$, NH); 4.55 (*q*, $J = 8$, 1 aliph. H); 4.31, 4.26 (2*d*, *AB*, $J_{AB} = 9$, 2 aliph. H); 3.85–3.65 (*m*, 1 aliph. H); 3.1–2.95 (*m*, PhCH_2); 2.2–2.1 (*m*, 1 aliph. H); 1.95–1.75 (*m*, 2 aliph. H); 1.45–1.0 (*m*, 8 aliph. H); 0.96, 0.87 (2*d*, $J_{AX} = 8$, 6 aliph. H). EI-MS: 463 (34), 462 (100, $[M + H]^+$).

*(4R)-4,5-Dihydro-4-isobutyl-2-phenyl-*N*-[(1S)-1-(cyclohexylcarbamoyl)-2-phenylethyl]oxazole-4-carboxamide* ((*R,S*)-**9d**)/*(4S,1'S)-Diastereoisomer* (S,S)-**10d**. A mixture of *rac*-**6d** (2.0 g, 5.6 mmol), **8** (2.07 g, 8.4 mmol),

and Et(i-Pr)$_2$N (2.09 ml, 16.8 mmol) in NMP (18 ml) was stirred in a pyrolysis tube for 48 h at 80°, cooled to r.t. and poured onto ice, H_2O (50 ml), and AcOEt (80 ml). The org. layer was extracted with H_2O (2 × 30 ml) and sat. brine (50 ml), dried ($MgSO_4$), and evaporated. The residue was suspended in Et_2O/hexane 1:1, filtered and dried: 2.45 g (92%) of (*R,S*)-**9d**/(*S,S*)-**10d** 1:1. IR (KBr): 3322*m* (br.), 3070*w*, 2930*s*, 2854*w*, 1647*s*, 1533*m*, 1450*m*, 1360*w*, 1320*w*, 1085*w*, 698*s*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 8.05–7.9 (*m*, 2 arom. H); 7.6–6.95 (*m*, 8 arom. H, NH); 5.77, 5.57 (2 br. *d*, *J* = 8, 6.5, NH, 1:1 mixture of diastereoisomers); 4.75–4.45 (*m*, 1 aliph. H); 4.35–4.15 (*m*, 2 *AB*, OCH_2, 1:1 mixture of diastereoisomers); 3.85–3.55 (*m*, 1 aliph. H); 3.25–2.95 (*m*, 2 aliph. H); 2.0–0.75 (*m*, 19 aliph. H). ISP-MS: 498.3 (15, $[M + Na]^+$), 476.5 (100, $[M + H]^+$).

tert-*Butyl (4*R*)-4-[(1*S*)-1-(Cyclohexylcarbamoyl)-2-phenylethylcarbamoyl]-4,5-dihydro-2-phenyloxazole-4-acetate* ((*R,S*)-**9e**) *and (4*S,*1'*S*)-Diastereoisomer (*S,S*)-***10e***. A mixture of *rac*-**6e** (2.0 g, 4.8 mmol), **8** (1.80 g, 7.3 mmol), and Et(i-Pr)$_2$N (1.64 ml, 16.8 mmol) in NMP (40 ml) was stirred in a pyrolysis tube for 32 h at 80°, cooled to r.t., and poured onto H_2O (100 ml) and AcOEt (200 ml). The org. layer was washed with H_2O (2 × 50 ml), the combined aq. phase extracted with AcOEt (50 ml), and the combined org. phase washed with brine (100 ml), dried ($MgSO_4$), and evaporated. The residue was chromatographed (SiO_2 (400 g), AcOEt/hexane 1:3 → 1:2) to yield first (*R,S*)-**9e** (1.15 g, 45%). Amorphous solid. $[\alpha]_D$ = +40 ($CHCl_3$, *c* = 0.1). IR (KBr): 3314*m*, 3075*w*, 2974*w*, 2931*s*, 1731*s*, 1647*s*, 1514*s*, 1451*m*, 1366*m*, 1296*w*, 1159*s*, 698*s*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 8.0–7.9 (*m*, 2 arom. H); 7.55–7.15 (*m*, 8 arom. H, NH); 6.45 (br. *d*, *J* = 8, NH); 4.66, 4.52 (2*d*, *AB*, J_{AB} = 8, 2 aliph. H); 4.45–4.35 (*m*, 1 aliph. H); 3.75–3.55 (*m*, 1 aliph. H); 3.3–3.15, 3.1–3.0 (2*m*, *ABX*, 2 aliph. H); 2.80, 2.70 (2*d*, *AB*, J_{AB} = 14, 2 aliph. H); 1.8–1.4 (*m*, 4 aliph. H); 1.37 (*s*, *t*-Bu); 1.35–0.75 (*m*, 6 aliph. H). ISP-MS: 534.4 (100, $[M + H]^+$), 478.4 (75).

Further elution yielded, after drying under reduced pressure, 1.10 g (43%) of (*S,S*)-**10e**. Amorphous solid. $[\alpha]_D$ = −83 ($CHCl_3$, *c* = 0.1). IR (KBr): 3369*m*, 3080*w*, 3040*w*, 2977*w*, 2932*m*, 2855*w*, 1723*s*, 1690*s*, 1672*s*, 1646*s*, 1510*s*, 1452*w*, 1366*m*, 1296*w*, 1216*w*, 1159*m*, 698*m*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 8.0–7.9 (*m*, 2 arom. H); 7.65–7.55 (*m*, 1 arom. H); 7.55–7.45 (*m*, 2 arom. H); 7.20 (br. *d*, *J* = 8, NH); 7.15–6.9 (*m*, 5 arom. H); 6.86 (br. *d*, *J* = 8, NH); 4.75–4.6 (*m*, 1 aliph. H); 4.23, 4.14 (2*d*, *AB*, J_{AB} = 9, 2 aliph. H); 3.9–3.7 (*m*, 1 aliph. H); 3.3–3.0 (*m*, *ABX*, 2 aliph. H); 3.08, 2.50 (2*d*, *AB*, J_{AB} = 15, 2 aliph. H); 2.0–1.55 (*m*, 4 aliph. H); 1.42 (*s*, *t*-Bu); 1.5–1.0 (*m*, 6 aliph. H). ISP-MS: 534.4 (100, $[M + H]^+$), 478.4 (50).

*(2*R*)-2-(Benzoylamino)-2-[(1*S*)-1-(cyclohexylcarbamoyl)-2-phenylethylcarbamoyl]-3-methylbutyl Benzoate* ((*R,S*)-**11c**) *and (2*S,*1'*S*)-Diastereoisomer (*S,S*)-***12c***. To (*R,S*)-**9c**/(*S,S*)-**10c** (15.1 g, 32.8 mmol) in dioxane (80 ml) at 0° was added 2N aq. HCl (50 ml, 100 mmol). The mixture was stirred at r.t. for 3 h and poured onto ice, sat. aq. $NaHCO_3$ soln. (100 ml) and $CHCl_3$ (100 ml). The org. layer was dried (Na_2SO_4) and evaporated. The residue was dried under h.v. for 15 min and dissolved in NMP (50 ml), cooled to 0°, and treated with Et(i-Pr)$_2$N (11.2 ml, 65.6 mmol) and benzoyl chloride (5.7 ml, 49.1 mmol). The mixture was stirred at r.t. for 2.5 h and poured onto ice, 0.1N aq. HCl (50 ml), and AcOEt (100 ml). The org. layer was washed with H_2O (50 ml), dried (Na_2SO_4), and evaporated. The residue was chromatographed (SiO_2 (500 g), hexane/AcOEt 2:1 → 3:2 → 1:1): 6.4 g (33%) of (*R,S*)-**11c** after crystallization from MeOH. Crystallization from MeOH also gave crystals suitable for X-ray analysis. M.p. 200–202°. $[\alpha]_D$ = +29 ($CHCl_3$, *c* = 0.1). IR (KBr): 3420*m*, 3257*m*, 2934*m*, 1721*s*, 1668*s*, 1637*s*, 1530*m* (br.), 1488*s*, 1276*s*, 1117*m* (br.), 1071*w*, 716*m*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 7.95–7.05 (*m*, 15 arom. H); 6.65 (*s*, NH); 6.61 (*d*, *J* = 8, NH); 6.53 (*d*, *J* = 8, NH); 5.10, 5.01 (2*d*, *AB*, J_{AB} = 14, 2 aliph. H); 4.75–4.65 (*m*, 1 aliph. H); 3.8–3.65 (*m*, 1 aliph. H); 3.13 (*d*, *J* = 8, PhCH_2); 2.5–2.3 (*m*, 1 aliph. H); 1.9–1.1 (*m*, 10 aliph. H); 1.04, 0.85 (2*d*, *J* = 8, 6 aliph. H). EI-MS: 623 (29), 622 (76), 607 (6), 606 (91), 585 (44), 584 (100, $[M + H]^+$).

Further elution of the column yielded 8.3 g (43%) of (*S,S*)-**12c** after crystallization from MeOH. M.p. 156–157°. $[\alpha]_D$ = −32 ($CHCl_3$, *c* = 0.05). IR (KBR): 3426*s* (br.), 2932*m*, 2855*w*, 1724*m*, 1650*s* (br.), 1513*m* (br.), 1483*m*, 1274*m* (br.), 1118*w* (br.), 713*w* (br.). ^{1}H-NMR ($CDCl_3$, 250 MHz): 8.0–7.0 (*m*, 15 arom. H, 2 NH); 6.13 (*d*, *MX*, J_{MX} = 8, NH); 5.07, 4.86 (2*d*, *AB*, J_{AB} = 12, 2 aliph. H); 4.38 (*ddd*, *ABMX*, $J_{AX} = J_{BX} = J_{MX}$ = 8, 1 aliph. H); 3.75–3.6 (*m*, 1 aliph. H); 3.17 (*dd*, *ABX*, J_{AX} = 8, J_{AB} = 12, 1 H, PhCH_2); 3.01 (*dd*, *ABX*, J_{BX} = 8, J_{AB} = 12, 1 H, PhCH_2); 2.85–2.7 (*m*, 1 aliph. H); 1.85–1.2 (*m*, 10 aliph. H); 1.15–0.95 (*m*, 6 aliph. H). ISP-MS: 606 (8), 586 (38), 584 (100, $[M + H]^+$).

*(2*R*)-2-(Benzoylamino)-2-[(1*S*)-1-(cyclohexylcarbamoyl)-2-phenylethylcarbamoyl]-4-methylpentyl Benzoate* ((*R,S*)-**11d**) *and (2*S,*1'*S*)-Diastereoisomer (*S,S*)-***12d***. To a stirred soln. of (*R,S*)-**9d**/(*S,S*)-**10d** 1:1 (2.40 g, 5.05 mmol) in dioxane (20 ml) at 5°, was added 2N aq. HCl (20 ml). The mixture was stirred for 2 h at r.t. and poured onto ice, sat. aq. $NaHCO_3$ (30 ml), and $CHCl_3$ (60 ml). The aq. layer was extracted with $CHCl_3$ (2 × 40 ml) and AcOEt (50 ml), the combined org. fraction dried ($MgSO_4$) and evaporated, and the residue dried under reduced pressure. The residue was dissolved in DMA (15 ml), cooled to 0°, and treated with Et(i-Pr)$_2$N (1.30 ml, 7.55 mmol) and benzoyl chloride (0.71 ml, 6.1 mmol). The mixture was stirred for 30 min at 0° and for 1 h at r.t. and then poured onto ice, H_2O (50 ml), and AcOEt (100 ml). The org. layer was extracted with H_2O (2 × 30 ml), dried ($MgSO_4$), and evaporated. The residue was chromatographed (SiO_2 (250 g), hexane/Et_2O 7:1 → 5:1): (*R,S*)-**11d**

(1.24 g, 42%). Amorphous solid. $[\alpha]_D = +5$ ($CHCl_3$, $c = 0.1$). IR (KBr): 3366*m* (br.), 3065*w*, 2932*m*, 2855*w*, 1726*s*, 1643*s*, 1602*w*, 1508*s*, 1482*s*, 1450*m*, 1273*s*, 1115*w*, 713*m*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 8.0–7.9 (*m*, 2 arom. H); 7.8–7.7 (*m*, 2 arom. H); 7.6–7.35 (*m*, 7 arom. H, NH); 7.25–7.05 (*m*, 4 arom. H); 6.79 (br. *d*, $J = 8$, NH); 5.72 (br. *d*, $J = 9$, NH); 5.00, 4.79 (2*d*, *AB*, $J_{AB} = 12$, 2 aliph. H); 4.65–4.5 (*m*, 1 aliph. H); 3.8–3.6 (*m*, 1 aliph. H); 3.15–3.05, 3.0–2.85 (2*m*, *ABX*, 2 aliph. H); 2.55–2.35 (*m*, 1 aliph. H); 1.85–1.5 (*m*, 7 aliph. H); 1.4–0.9 (*m*, 5 aliph. H); 0.89, 0.84 (2*d*, $J = 7$, 2 Me). ISP-MS: 620.5 (50, $[M + Na]^+$), 598.5 (100, $[M + H]^+$).

Further elution gave 1.21 g (40%) of (*S,S*)-**12d**. Amorphous solid. $[\alpha]_D = +10$ ($CHCl_3$, $c = 0.1$). IR (KBr): 3366*m* (br.), 3065*w*, 2932*m*, 1726*s*, 1643*s*, 1482*s*, 1450*m*, 1273*s*, 1115*w*, 713*m*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 8.1–8.0 (*m*, 2 arom. H); 7.85 (br. *s*, NH); 7.75–7.65 (*m*, 2 arom. H); 7.65–7.3 (*m*, 6 arom. H); 7.05–6.8 (*m*, 4 arom. H); 6.54 (br. *d*, $J = 8$, NH); 6.06 (br. *d*, $J = 9$, NH); 5.13, 4.58 (2*d*, *AB*, $J_{AB} = 12$, 2 aliph. H); 4.6–4.5 (*m*, 1 aliph. H); 3.75–3.55 (*m*, 1 aliph. H); 3.35–3.25, 2.8–2.65 (2*m*, *ABX*, 2 aliph. H); 2.5–2.35, 2.05–1.9 (2*m*, *ABX*, 2 aliph. H); 1.8–1.0 (*m*, 6 aliph. H); 1.4–0.85 (*m*, 5 aliph. H); 0.94, 0.83 (2*d*, $J = 7$, 2 Me). ISP-MS: 620.4 (50, $[M + Na]^+$), 598.5 (100, $[M + H]^+$).

N-{*(1R)-1-[(1S)-1-(Cyclohexylcarbamoyl)-2-phenylethylcarbamoyl]-1-(hydroxymethyl)-2-methylpropyl*}-*benzamide* ((*R,S*)-**13c**). To a stirred soln. of (*R,S*)-**11c** (0.5 g, 0.86 mmol) in THF/MeOH/H_2O 3:1:1 (10 ml) at 0° was added LiOH·H_2O (72 mg, 1.72 mmol). The mixture was stirred at r.t. overnight and poured onto ice, sat. aq. $NaHCO_3$ soln. (50 ml) and AcOEt (50 ml). The org. layer was dried (Na_2SO_4) and evaporated. The crude product was chromatographed (SiO_2 (50 g), Et_2O/i-PrOH 99:1 → 49:1): 0.37 g (90%) of (*R,S*)-**13c**. White powder. M.p. 75–77°. $[\alpha]_D = 0$ ($CHCl_3$, $c = 0.1$). IR (KBr): 3422*m* (br.), 3319*m* (br.), 2932*m*, 2855*w*, 1646*s* (br.), 1517*s* (br.), 1288*w* (br.), 1054*w* (br.), 700*w* (br.). ^{1}H-NMR ($CDCl_3$, 250 MHz): 7.75–7.45 (*m*, 5 arom. H); 7.25–7.15 (*m*, 5 arom. H, NH); 6.75 (*s*, NH); 6.33 (*d*, $J = 10$, NH); 4.7–4.6 (*m*, 1 aliph. H); 4.05–3.95 (*m*, 2 aliph. H); 3.8–3.6 (*m*, 1 aliph. H, OH); 3.21 (*dd*, *ABX*, $J_{AX} = 6$, $J_{AB} = 16$, 1 H, PhCH_2); 3.11 (*dd*, *ABX*, $J_{BX} = 8$, $J_{AB} = 16$, 1 H, PhCH_2); 2.85–2.65 (*m*, 1 aliph. H); 1.85–0.95 (*m*, 10 aliph. H); 0.87, 0.78 (2*d*, $J = 8$, 6 aliph. H). EI-MS: 502 (23), 481 (43), 480 (100, $[M + H]^+$), 462 (16).

N-{*(1S)-1-[(1S)-1-(Cyclohexylcarbamoyl)-2-phenylethylcarbamoyl]-1-(hydroxymethyl)-2-methylpropyl*}-*benzamide* ((*S,S*)-**14c**). As described for (*R,S*)-**13c**, with (*S,S*)-**12c** (3.0 g, 5.1 mmol), THF/MeOH/H_2O 3:1:1 (50 ml), and LiOH·H_2O (0.42 g, 10 mmol). Chromatography (SiO_2 (200 g), Et_2O/i-PrOH 99:1 → 49:1) gave 2.2 g (90%) of (*S,S*)-**14c**. White powder. M.p. 77–79°. $[\alpha]_D = -66$ ($CHCl_3$, $c = 0.1$). IR (KBr): 3372*m* (br.), 3308*m* (br.), 2932*m*, 2855*w*, 1661*s* (br.), 1642*s* (br.), 1516*s* (br.), 1486*m*, 1451*w*, 1304*w*, 1256*w*, 701*w*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 7.75–7.45 (*m*, 5 arom. H, NH); 7.25–7.15 (*m*, 5 arom. H); 6.91 (*s*, NH); 6.19 (*d*, $J = 10$, NH); 4.75–4.6 (*m*, 1 aliph. H); 4.2–3.9 (*m*, 2 aliph. H, OH); 3.8–3.65 (*m*, 1 aliph. H); 3.28 (*dd*, *ABX*, $J_{AX} = 6$, $J_{AB} = 16$, 1 H, PhCH_2); 3.16 (*dd*, *ABX*, $J_{BX} = 8$, $J_{AB} = 16$, 1 H, PhCH_2); 2.8–2.6 (*sept.*, 1 aliph. H); 1.95–0.95 (*m*, 10 aliph. H); 0.89, 0.85 (2*d*, $J_{AX} = 8$, 6 aliph. H). EI-MS: 502 (33), 481 (47), 480 (100, $[M + H]^+$), 463 (21), 462 (57).

(S)-4-Benzyl-4-(bromomethyl)-2-phenyloxazol-5(4H)-one ((*S*)-**15b**). A soln. of (*R,S*)-**9b** (100 mg, 0.2 mmol) in 33% HBr/AcOH (0.5 ml) and Ac_2O (0.2 ml) was stirred in a sealed tube at 90° for 8 h. The solvents were removed under h.v., and the residue was chromatographed (SiO_2 (20 g), hexane/AcOEt 4:1): 1.08 g (53%) of (*S*)-**15b**. White powder. M.p. 77–79°. $[\alpha]_D = +64$ ($CHCl_3$, $c = 0.1$). IR (KBr): 3420*w* (br.), 1813*s* (br.), 1650*s* (br.), 1494*m*, 1452*m*, 1289*m*, 1099*m*, 1056*m*, 980*s* (br.), 890*w* (br.), 779*w*, 698*s* (br.). ^{1}H-NMR ($CDCl_3$, 250 MHz): 7.95–7.85 (*m*, 2 arom. H); 7.6–7.5 (*m*, 1 arom. H); 7.5–7.4 (*m*, 2 arom. H); 7.2–7.15 (*m*, 5 arom. H); 3.83, 3.74 (2*d*, *AB*, $J_{AB} = 10$, 2 aliph. H); 3.28, 3.20 (2*d*, *AB*, $J_{AB} = 12$, 2 aliph. H). EI-MS: 343 (2, M^+), 265 (2), 264 (8), 174 (6), 173 (40), 106 (4), 105 (44), 91 (100), 77 (22).

(R)-4-(Bromomethyl)-4-isopropyl-2-phenyloxazol-5(4H)-one ((*R*)-**15c**). A soln. of (*S,S*)-**10c** (0.16 g, 0.34 mmol) in 33% HBr/AcOH (1 ml) and Ac_2O (0.4 ml) was stirred in a sealed tube at 90° for 10 h and at 110° for 4 h. The solvents were removed under h.v., and the residue was chromatographed (SiO_2 (20 g), hexane/AcOEt 6:1): 42 mg (42%) of (*R*)-**15c**. Pale yellow powder. M.p. 50–52°. $[\alpha]_D = +22$ ($CHCl_3$, $c = 0.09$). IR (KBr): 3434*w* (br.), 2931*w*, 1811*s*, 1653*s*, 1450*w*, 1330*w*, 1290*m*, 1047*m*, 1018*m*, 972*m*, 890*w*, 695*s*, 667*w*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 8.1–8.0 (*m*, 2 arom. H); 7.65–7.45 (*m*, 3 arom. H); 3.80, 3.75 (2*d*, *AB*, $J_{AB} = 8$, CH_2Br); 2.4–2.2 (*m*, 1 aliph. H); 1.11, 1.00 (2*d*, $J_{AX} = 8$, 6 aliph. H). EI-MS: 296 (1, $[M + H]^+$), 295 (2, M^+), 255 (12), 174 (100), 105 (96), 77 (32).

Benzyl (2S)-2-[(4R)-4-Benzyl-4,5-dihydro-2-phenyloxazol-4-ylcarbonylamino]propianoate ((*R,S*)-**16**). To a stirred soln. of (*S*)-**15b** (1.22 g, 3.54 mmol) and (*S*)-Ala-OBn·HCl (1.52 g, 7.09 mmol) in DMA (10 ml) at 0° under Ar Et(i-Pr)$_2$N was added (3 ml, 17.6 mmol). The mixture was stirred at 50° for 18 h, cooled to r.t., and poured onto ice, H_2O (100 ml), and AcOEt (100 ml). The org. layer was extracted with sat. brine (100 ml), dried ($MgSO_4$), and evaporated. The residue was chromatographed (SiO_2 (160 g), hexane/AcOEt 6:1 → 4:1): 1.33 g (85%) of (*R,S*)-**16**. Pale yellow oil. IR (film): 3421*w*, 3000*w*, 1742*m* (br.), 1676*s* (br.), 1643*m*, 1512*m* (br.), 1502*m*, 1451*w*, 1260*w* (br.), 1159*w* (br.), 1061*w* (br.), 698*s*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 8.0–7.9 (*m*, 2 arom. H); 7.65–7.2 (*m*, 13 arom. H); 7.12 (*d*, $J = 8$, NH); 5.12, 5.05 (2*d*, *AB*, $J_{AB} = 12$, PhCH_2); 4.58, 4.38 (2*d*, *AB*, $J_{AB} = 8$, PhCH_2);

4.65–4.5 (*m*, 1 aliph. H); 3.27, 3.03 (2*d*, *AB*, J_{AB} = 12, 2 aliph. H); 1.25–1.15 (*m*, 3 aliph. H). EI-MS: 465 (31, $[M + Na]^+$), 444 (39), 443 (100, $[M + H]^+$).

(2R)-2-[(1S)-(Benzyloxycarbonyl)ethylcarbamoyl]-2-{(2S)-2-[(tert-butoxy)carbonylamino]propanoylamino}-3-phenylpropyl Benzoate ((*S,R,S*)-**17**). To a stirred soln. of (*R,S*)-**16** (1.3 g, 2.94 mmol) in dioxane (18 ml) at 5° was added 0.5N aq. HCl (12 ml). The mixture was stirred at r.t. overnight and poured onto ice, sat. aq. $NaHCO_3$ soln. (50 ml) and AcOEt (50 ml). The org. layer was dried ($MgSO_4$) and evaporated. The residue was dissolved in DMF (5 ml) at 0° and added to a prestirred soln. of Boc-(*S*)-Ala-OH (1.02 g, 5.34 mmol), HOAT (0.9 g, 6.68 mmol), and HATU (1.3 g, 4.00 mmol) in DMF (20 ml). Et(i-Pr)$_2$N (1.15 ml, 6.68 mmol) was added and the mixture stirred at r.t. for 22 h and poured onto ice, 0.1N aq. HCl (50 ml), and AcOEt (50 ml). The org. layer was extracted with sat. aq. $NaHCO_3$ soln. (100 ml), dried (Na_2SO_4), and evaporated. The residue was chromatographed (SiO_2 (200 g), hexane/AcOEt 4:1 → 3:1 → 2:1): 1.08 g (64%) of (*S,R,S*)-**17**. White powder. M.p. 130–132°. $[\alpha]_D = -30$ ($CHCl_3$, $c = 0.1$). IR (KBr): 3373*m* (br.), 3284*m* (br.), 2980*w*, 1729*s* (br.), 1682*s* (br.), 1654*s* (br.), 1530*m* (br.), 1500*m*, 1452*m*, 1275*s* (br.), 1171*m* (br.), 707*m* (br.). ^{1}H-NMR ($CDCl_3$, 250 MHz): 8.05–8.0 (*m*, 2 arom. H); 7.6–7.55 (*m*, 1 arom. H); 7.45–7.3 (*m*, 6 arom. H); 7.3–7.2 (*m*, 4 arom. H); 7.15–7.05 (*m*, 2 arom. H, 2 NH); 5.21, 5.13 (2*d*, *AB*, J_{AB} = 12, PhCH_2); 4.95–4.8 (*m*, 2 aliph. H, 1 NH); 4.65–4.55 (*m*, 1 aliph. H); 4.1–3.95 (*m*, 1 aliph. H); 3.57, 3.91 (2*d*, *AB*, J_{AB} = 14, PhCH_2); 1.4–1.3 (*m*, 6 aliph. H); 1.36 (*s*, 9 aliph. H). ISP-MS: 670 (6), 654 (100, $[M + Na]^+$), 585 (12), 553 (11).

(αS,5R)-α-Benzyl-N-cyclohexyl-6,8-dioxo-2-phenyl-3-oxa-1,7-diazaspiro[4.4]non-1-ene-7-propanamide ((*R,S*)-**18**). To a stirred soln. of (*R,S*)-**9e** (500 mg, 1.01 mmol) in CH_2Cl_2 (1.5 ml) at 0° under Ar was added CF_3COOH (1.5 ml). The mixture was stirred at 0° for 30 min and for 5 h at r.t. Then $SOCl_2$ (0.22 ml) was added at 0°. The mixture was stirred at r.t. for 18 h and then poured onto ice, 0.5N aq. NaH_2PO_4 (10 ml), and AcOEt (15 ml). The org. layer was washed with sat. brine (10 ml), dried ($MgSO_4$), and evaporated. The residue was chromatographed (SiO_2 (50 g), AcOEt/hexane 1:3 → 1:2) to yield, after crystallization from Et_2O and drying under reduced pressure, 3.75 mg (81%) of (*R,S*)-**18**. White solid. Crystallization from AcOEt gave crystals suitable for X-ray analysis. M.p. 181–182°. $[\alpha]_D = -172$ ($CHCl_3$, $c = 0.4$). IR (KBr): 3430*m* (br.), 3391*m*, 3075*w*, 2931*m*, 2855*w*, 1791*w*, 1712*s*, 1640*s*, 1529*w*, 1450*w*, 1382*m*, 1174*w*, 702*m*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 7.95–7.8 (*m*, 2 arom. H); 7.6–7.15 (*m*, 8 arom. H); 5.92 (br. *d*, NH); 5.05–4.9 (*m*, *ABX*, 1 aliph. H); 4.29, 4.04 (2*d*, *AB*, J_{AB} = 11, 2 aliph. H); 3.9–3.7 (*m*, 1 aliph. H); 3.6–3.35 (*m*, 2 aliph. H); 3.04, 2.64 (2*d*, *AB*, J_{AB} = 18, 2 aliph. H); 2.95–2.8 (*m*, 2 aliph. H); 2.8–2.5 (*m*, 3 aliph. H); 1.45–1.05 (*m*, 5 aliph. H). ISP-MS: 482.2 (100, $[M + Na]^+$), 460.4 (50, $[M + H]^+$).

(αS,5S)-α-Benzyl-N-cyclohexyl-6,8-dioxo-2-phenyl-3-oxa-1,7-diazaspiro[4.4]non-1-ene-7-propanamide ((*S,S*)-**19**). As described for (*R,S*)-**18**, with (*S,S*)-**10e** (5.34 g, 10.0 mmol), CH_2Cl_2 (20 ml), CF_3COOH (20 ml), and $SOCl_2$ (3.57 g, 30.0 mmol; 15 h at r.t.). Workup with 10% aq. NaH_2PO_4 soln. (100 ml), AcOEt (150 ml), and sat. brine (50 ml), and chromatography (SiO_2 (250 ml), AcOEt/CH_2Cl_2 5:95) yielded 3.83 g (83%) of (*S,S*)-**19**. Amorphous solid. $[\alpha]_D = -100$ ($CHCl_3$, $c = 0.05$). IR (KBr): 3437*m*, 3305*m*, 2934*m*, 2855*w*, 1783*w*, 1711*s*, 1655*s*, 1640*s*, 1542*w*, 1451*w*, 1382*m*, 1325*w*, 1195*w*, 703*m*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 7.95–7.85 (*m*, 2 arom. H); 7.5–7.45 (*m*, 1 arom. H); 7.45–7.35 (*m*, 2 arom. H); 7.35–7.1 (*m*, 5 arom. H); 6.71 (br. *d*, J = 8, NH); 5.1–4.95 (*m*, 1 aliph. H); 4.75, 4.19 (2*d*, *AB*, J_{AB} = 9, 2 aliph. H); 3.85–3.65 (*m*, 1 aliph. H); 3.65–3.55, 3.5–3.35 (2*m*, *ABX*, 2 aliph. H); 2.98, 2.51 (2*d*, *AB*, J_{AB} = 18, 2 aliph. H); 1.95–1.75 (*m*, 2 aliph. H); 1.75–1.45 (*m*, 3 aliph. H); 1.45–1.0 (*m*, 5 aliph. H). EI-MS: 459 (5, M^+), 334 (23), 333 (100), 120 (4), 105 (7), 104 (6).

(3R)-3-(Benzoylamino)-1-[(1S)-(cyclohexylcarbamoyl)-2-phenylethyl]-2,5-dioxopyrrolidin-3-ylmethyl Benzoate ((*R,S*)-**20**). To a stirred soln. of (*R,S*)-**18** (200 mg, 0.44 mmol) in dioxane (2 ml) at 0° was added 2N aq. HCl (1 ml). The mixture was stirred for 3 h at 0° and poured onto ice, sat. aq. $NaHCO_3$ soln. (5 ml), and AcOEt (10 ml). The org. layer was washed with sat. brine (5 ml), dried ($MgSO_4$), and evaporated. The residue was dried under reduced pressure and dissolved in CH_2Cl_2 (2 ml) and cooled to 0°. Et(i-Pr)$_2$N (0.11 ml, 0.66 mmol) and benzoyl chloride (77 µl, 0.66 mmol) were added. The mixture was stirred for 30 min at 0° and poured onto H_2O (5 ml) and AcOEt (10 ml). The org. layer was washed with sat. brine (5 ml), dried ($MgSO_4$), and evaporated. The residue was chromatographed (SiO_2 (20 g), hexane/AcOEt 2:1) to yield, after drying under reduced pressure, 250 mg (98%) of (*R,S*)-**20**. Amorphous solid. $[\alpha]_D = -81$ ($CHCl_3$, $c = 0.5$). IR (KBr): 3435*m* (br.), 3360*m*, 3045*w*, 2932*w*, 2854*w*, 1790*w*, 1721*s*, 1646*s*, 1602*w*, 1537*m*, 1452*w*, 1390*w*, 1270*m*, 1176*w*, 713*w*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 8.13 (br. *s*, NH); 8.1–8.0 (*m*, 2 arom. H); 7.8–7.6 (*m*, 3 arom. H); 7.6–7.4 (*m*, 5 arom. H); 7.35–7.15 (*m*, 5 arom. H); 7.02 (br. *d*, J = 8, NH); 5.05–4.9 (*m*, *ABX*, 1 aliph. H); 4.42, 3.31 (2*d*, *AB*, J_{AB} = 12, 2 aliph. H); 3.95–3.75 (*m*, 1 aliph. H); 3.7–3.6, 3.55–3.4 (2*m*, *ABX*, 2 aliph. H); 2.86 (*s*, 2 aliph. H); 2.05–1.9 (*m*, 2 aliph. H); 1.9–1.65 (*m*, 3 aliph. H); 1.5–1.1 (*m*, 5 aliph. H). ISP-MS: 599.4 (20, $[M + NH_4]^+$), 582.3 (50, $[M + H]^+$).

{(3S)-3-Amino-1-[(1S)-1-(cyclohexylcarbamoyl)-2-phenylethyl]-2,5-dioxopyrrolidin-3-yl}methyl Benzoate ((*S,S*)-**21**). To a stirred soln. of (*S,S*)-**19** (1.62 g, 3.53 mmol) in dioxane (8 ml) at 5° was added 2N aq. HCl (8 ml).

The mixture was stirred for 30 min at 0° and 3 h at r.t. Then it was poured onto ice, sat. aq. $NaHCO_3$ soln. (50 ml), and $CHCl_3$ (100 ml). The aq. layer was extracted with $CHCl_3$ (2 × 50 ml), the combined org. phase dried ($MgSO_4$), and evaporated, and the residue chromatographed (SiO_2 (70 g), $CHCl_3$/MeOH 1:9) to yield, after drying under reduced pressure, 1.46 g (87%) of (*S,S*)-**21**. Amorphous solid. $[\alpha]_D = -32$ ($CHCl_3$, $c = 0.1$). IR (KBr): 3373*m*, 2933*m*, 2855*m*, 1783*w*, 1734*s*, 1719*s*, 1660*s*, 1538*m*, 1462*m*, 1390*m*, 1314*m*, 1272*s*, 1177*m*, 1114*m*, 1070*m*, 765*w*, 713*s*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 8.0–7.9 (*m*, 2 arom. H); 7.65–7.5 (*m*, 1 arom. H); 7.5–7.35 (*m*, 2 arom. H); 7.3–7.1 (*m*, 5 arom. H); 6.20 (br. *d*, $J = 8$, NH); 5.05–4.85 (*m*, 1 aliph. H); 4.35–4.2 (*m*, 2 aliph. H); 3.85–3.65 (*m*, 1 aliph. H); 3.55–3.2 (*m*, 2 aliph. H); 2.84, 2.44 (2*d*, *AB*, $J_{AB} = 18$, 2 aliph. H); 1.82 (br. *s*, NH_2); 1.75–0.95 (*m*, 10 aliph. H). ISP-MS: 500 (12, $[M + Na]^+$), 478 (100, $[M + H]^+$).

{(3S)-3-(Benzoylamino)-1-[(1S)-1-(cyclohexylcarbamoyl)-2-phenylethyl]-2,5-dioxopyrrolidin-3-yl}methyl Benzoate ((*S,S*)-**22**). To a stirred soln. of (*S,S*)-**21** (200 mg, 0.42 mmol) in CH_2Cl_2 (1.3 ml) at 0° was added Et(i-Pr)$_2$N (80 µl, 0.46 mmol) and benzoyl chloride (73 µl, 0.63 mmol). The mixture was stirred for 30 min at 0° and 2 h at r.t. and then treated in analogy to (*R,S*)-**20**. Chromatography (SiO_2 (10 g), CH_2Cl_2/AcOEt 9:1) gave 231 mg (95%) of (*S,S*)-**22**. Amorphous solid. $[\alpha]_D = -110$ (CH_2Cl_2, $c = 0.1$). IR (KBr): 3364*m*, 2932*m*, 2855*m*, 1788*w*, 1723*s*, 1642*s*, 1541*m*, 1390*m*, 1320*w*, 1271*s*, 1223*w*, 1175*m*, 1111*m*, 764*w*, 712*s*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 8.15 (br. *s*, NH); 8.1–8.0 (*m*, 2 arom. H); 7.85–7.75 (*m*, 2 arom. H); 7.6–7.4 (*m*, 5 arom. H); 7.35–7.15 (*m*, 5 arom. H); 7.13 (br. *d*, $J = 8$, NH); 5.3–5.15 (*m*, 1 aliph. H); 4.36, 3.71 (2*d*, *AB*, $J_{AB} = 12$, 2 aliph. H); 3.9–3.75 (*m*, 1 aliph. H); 3.85–3.7, 3.55–3.4 (2*m*, *ABX*, 2 aliph. H); 3.03, 2.71 (2*d*, *AB*, $J_{AB} = 18$, 2 aliph. H); 2.05–1.55 (*m*, 5 aliph. H); 1.5–1.0 (*m*, 5 aliph. H). ISP-MS: 604 (28, $[M + Na]^+$), 599 (16, $[M + NH_4]^+$), 582 (100, $[M + H]^+$).

N-*{(3R)-1-[(1S)-1-(Cyclohexylcarbamoyl)-2-phenylethyl]-3-(hydroxymethyl)-2,5-dioxopyrrolidin-3-yl}benzamide* ((*R,S*)-**23**). A mixture of (*R,S*)-**20** (190 mg, 0.33 mmol) and KCN (50 mg) in MeOH (2 ml) was stirred for 1 h at 65°. The solvents were removed, and the residue was chromatographed (SiO_2 (20 g), AcOEt/hexane 1:1) to yield, after drying under reduced pressure, 145 mg (92%) of (*R,S*)-**23**. Amorphous solid. $[\alpha]_D = -106$ ($CHCl_3$, $c = 0.2$). IR (KBr): 3444*m* (br.), 3075*w*, 2933*m*, 2855*w*, 1789*w*, 1715*s*, 1645*s*, 1540*s*, 1488*w*, 1452*w*, 1390*m*, 1318*w*, 1254*w*, 1141*w*, 702*m*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 7.8–7.7 (*m*, 2 arom. H); 7.65–7.4 (*m*, 3 arom. H); 7.35–7.05 (*m*, 5 arom. H, NH); 7.04 (br. *d*, $J = 9$, NH); 5.0–4.85 (*m*, 1 aliph. H); 3.9–3.75 (*m*, 1 aliph. H); 3.7–3.55, 3.2–3.1 (2*m*, *ABX*, 2 aliph. H); 3.55–3.45, 3.45–3.25 (2*m*, *ABX*, 2 aliph. H); 2.89, 2.50 (2*d*, *AB*, $J_{AB} = 18$, 2 aliph. H); 2.4–2.3 (*m*, OH); 2.05–1.85 (*m*, 2 aliph. H); 1.85–1.55 (*m*, 3 aliph. H); 1.45–1.1 (*m*, 5 aliph. H). ISP-MS: 500.1 (15, $[M + Na]^+$), 478.2 (100, $[M + H]^+$).

N-*{(3S)-1-[(1S)-(Cyclohexylcarbamoyl)-2-phenylethyl]-3-(hydroxymethyl)-2,5-dioxopyrrolidin-3-yl}benzamide* ((*S,S*)-**24**). A mixture of (*S,S*)-**22** (87.3 mg, 0.15 mmol) and NaCN (22.7 mg, 0.463 mmol) in MeOH (0.9 ml) was stirred at 60° for 1.5 h, cooled to r.t., and poured onto ice, H_2O (3 ml), and AcOEt (10 ml). The org. layer was extracted with sat. brine (5 ml), dried ($MgSO_4$), and evaporated. The residue was chromatographed (SiO_2 (5 g), AcOEt/hexane 1:1) to yield, after drying under high vacuum, 71 mg (99%) of (*S,S*)-**24**. Amorphous solid. $[\alpha]_D = -67$ (CH_2Cl_2, $c = 0.1$). IR (KBr): 3427*w*, 2933*m*, 2860*w*, 1785*w*, 1715*s*, 1644*s*, 1542*m*, 1158*w*, 755*w*, 705*w*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 7.8–7.7 (*m*, 2 arom. H); 7.65–7.4 (*m*, 3 arom. H); 7.35–7.1 (*m*, 5 arom. H); 7.07 (br. *d*, $J = 9$, NH); 6.86 (br. *s*, NH); 5.25–5.15 (*m*, 1 aliph. H); 3.9–3.75 (*m*, 1 aliph. H); 3.8–3.7, 3.5–3.35 (2*m*, *ABX*, 2 aliph. H); 3.71 (br. *s*, OH); 3.61, 2.74 (2*d*, *AB*, $J_{AB} = 12$, 2 aliph. H); 2.97, 2.73 (2*d*, *AB*, $J_{AB} = 19$, 2 aliph. H); 2.05–1.5 (*m*, 5 aliph. H); 1.5–1.0 (*m*, 5 aliph. H). ISP-MS: 500 (22, $[M + Na]^+$), 478 (100, $[M + H]^+$).

{(3S)-3-{(2S)-2-[(tert-Butoxy)carbonylamino]propanoylamino}-1-[(1S)-1-(cyclopropylcarbamoyl)-2-phenylethyl]-2,5-dioxopyrrolidin-3-yl}methyl Benzoate ((*S,S,S*)-**25**). To a stirred soln. of (*S,S*)-**21** (200 mg, 0.415 mmol) and Boc-(*S*)-Ala-OH (154 mg, 0.838 mmol) in DMF (1.3 ml) at 0° was added HATU (270 mg, 0.838 mmol), HOAT (114 mg, 0.838 mmol), and Et(i-Pr)$_2$N (162 mg, 1.26 mmol). The mixture was stirred for 2 h at r.t. and poured onto ice, 0.1N aq. HCl (5 ml), and AcOEt (10 ml). The org. layer was washed with sat. brine (5 ml), dried ($MgSO_4$), and evaporated. The residue was chromatographed (SiO_2 (25 g), CH_2Cl_2/AcOEt 9:1) to yield, after drying under high vacuum, 234 mg (86%) of (*S,S,S*)-**25**. Amorphous solid. $[\alpha]_D = -86$ (CH_2Cl_2, $c = 0.1$). IR (KBr): 3261*m*, 2978*m*, 2934*m*, 1802*w*, 1730*s*, 1723*s*, 1654*m*, 1539*m*, 1452*w*, 1390*m*, 1365*m*, 1319*w*, 1269*s*, 1171*m*, 1107*m*, 1070*m*, 765*w*, 712*w*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 8.1–8.0 (*m*, 2 arom. H); 7.73 (br. *s*, NH); 7.7–7.6 (*m*, 1 arom. H); 7.55–7.4 (*m*, 2 arom. H); 7.3–7.1 (*m*, 5 arom. H); 6.98 (br. *d*, $J = 8$, NH); 5.2–5.1 (*m*, 1 aliph. H); 4.75 (br. *d*, $J = 6$, NH); 4.25–4.1 (*m*, 1 aliph. H); 4.15, 3.68 (2*d*, *AB*, $J_{AB} = 12$, 2 aliph. H); 3.85–3.7 (*m*, 1 aliph. H); 3.75–3.7, 3.5–3.35 (2*m*, *ABX*, 2 aliph. H); 2.80, 2.63 (2*d*, *AB*, $J_{AB} = 18$, 2 aliph. H); 1.95–1.55 (*m*, 5 aliph. H); 1.45–1.0 (*m*, 5 aliph. H); 1.36 (*s*, *t*-Bu); 1.33 (*d*, $J = 7$, 3 aliph. H). ISP-MS: 671 (45, $[M + Na]^+$), 666 (79, $[M + NH_4]^+$), 649 (100, $[M + H]^+$), 593 (27).

(2S)-2-[(tert-Butoxy)carbonylamino]-N-{(3S)-1-[(1S)-1-(cyclohexylcarbamoyl)-2-phenylethyl]-3-(hydroxymethyl)-2,5-dioxopyrrolidin-3-yl}propanamide ((*S,S,S*)-**26**). A mixture of (*S,S,S*)-**25** (97.3 mg, 0.15 mmol) and NaCN (22.7 mg, 0.463 mmol) in MeOH (0.9 ml) was stirred for 1.5 h at 60° in a sealed tube, then cooled to r.t., and

poured onto ice, H_2O (3 ml), and AcOEt (6 ml). The org. layer was dried ($MgSO_4$) and evaporated. The residue was chromatographed (SiO_2 (5 g), AcOEt/hexane 1:1) to yield, after drying under high vacuum, 72 mg (88%) of (*S,S,S*)-**26**. Amorphous solid. $[\alpha]_D = -72$ ($CHCl_3$, $c = 0.1$). IR (KBr): 3344*m*, 2977*w*, 2934*m*, 2856*w*, 1736*w*, 1717*s*, 1695*s*, 1651*m*, 1543*m*, 1453*m*, 1254*m*, 1169*m*, 1073*m*, 1024*w*, 750*w*, 702*w*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 7.35–7.2 (*m*, 3 arom. H); 7.2–7.05 (*m*, 2 arom. H); 6.93 (br. *d*, $J = 9$, NH); 5.2–5.1 (*m*, 1 aliph. H); 4.77 (br. *d*, $J = 7$, NH); 4.25–4.15 (*m*, 1 aliph. H); 3.85–3.7 (*m*, 1 aliph. H); 3.8–3.65, 3.5–3.35 (2*m*, *ABX*, 2 aliph. H); 3.75 (br. *s*, OH); 3.28, 3.15 (2*d*, *AB*, $J_{AB} = 12$, 2 aliph. H); 2.76, 2.39 (2*d*, *AB*, $J_{AB} = 18$, 2 aliph. H); 1.95–1.55 (*m*, 5 aliph. H); 1.5–1.0 (*m*, 5 aliph. H); 1.44 (*s*, *t*-Bu); 1.33 (*d*, $J = 7$, 3 aliph. H). ISP-MS: 567 (38, $[M + Na]^+$), 562 (51, $[M + NH_4]^+$), 545 (100, $[M + H]^+$).

tert-*Butyl (3*R*)-3-(Benzoylamino)-1-[(1*S*)-1-(cyclohexylcarbamoyl)-2-phenylethyl]-2,5-dioxopyrrolidine-3-propanoate* ((*R,S*)-**27**) *and (3*S*,1′*S*)-Diastereoisomer* (*S,S*)-**28**. To a stirred soln. of *rac*-**7c** (1.3 g, 2.97 mmol) and **8** (1.05 g, 4.2 mmol) in NMP (5 ml) under Ar was added Et(i-Pr)$_2$N (0.77 ml, 4.5 mmol). The mixture was stirred at 70° for 12 h and poured onto ice, 1N aq. HCl (10 ml), and AcOEt (10 ml). The org. layer was extracted with H_2O (10 ml) and sat. brine (10 ml), dried (Na_2SO_4), and evaporated. The residue was purified by semi-prep. HPLC *Sperisorb 55W 500* (3 mm) with CH_2Cl_2/*t*-BuOMe/hexane 45:5:50 to give 390 mg (31%) of (*S,S*)-**28**. White foam. $[\alpha]_D = -94$ ($CHCl_3$, $c = 0.2$). IR (film): 3356*m*, 2932*m*, 1717*s*, 1645*m*, 1538*m*, 1155*m*, 699*w*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 8.92 (*s*, NH); 7.8–7.7 (*m*, 2 arom. H); 7.5–7.35 (*m*, 3 arom. H); 7.25–7.0 (*m*, 5 arom. H); 5.0–4.85 (*m*, 1 aliph. H); 3.95–3.75 (*m*, 1 aliph. H); 3.55–3.45 (*m*, PhCH_2); 2.95, 2.45 (2*d*, $J_{AB} = 17$, 2 aliph. H); 2.2–2.0 (*m*, 4 aliph. H); 1.8–1.05 (*m*, 10 aliph. H); 1.46 (*s*, *t*-Bu). ISP-MS: 576.7 (100, $[M + H]^+$).

Further elution yielded 450 mg (35%) of (*R,S*)-**27**. White foam. $[\alpha]_D = -91$ ($CHCl_3$, $c = 0.2$). IR (film): 3356*m*, 2933*m*, 1718*s*, 1644*s*, 1539*s*, 1388*m*, 1324*m*, 1236*m*, 1155*s*, 698*w*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 9.09 (*s*, NH); 7.85–7.75 (*m*, 2 arom. H); 7.55–7.45 (*m*, 3 arom. H); 7.25–7.05 (*m*, 5 arom. H); 5.21 (*dd*, $J = 11$, 1 aliph. H); 3.95–3.75 (*m*, 1 aliph. H); 3.15, 2.25 (2*d*, $J_{AB} = 18$, 2 aliph. H); 2.5–2.0 (*m*, 4 aliph. H); 2.0–1.05 (*m*, 11 aliph. H); 1.49 (*s*, *t*-Bu). ISP-MS: 576.6 (100, $[M + H]^+$).

*(α*S*,5*R*)-1-Benzoyl-α-benzyl-*N*-cyclohexyl-2,6,8-trioxo-1,7-diazaspiro[4.4]nonane-7-acetamide* ((*R,S*)-**29**). To a stirred soln. of (*R,S*)-**27** (130 mg, 0.23 mmol) in CH_2Cl_2 (10 ml) in a pyrolysis tube at 0° was added CF_3COOH (4 ml). The mixture was stirred for 2 h at r.t. and cooled to 0°. $SOCl_2$ (0.4 ml) was added, the mixture refluxed overnight and then evaporated, and the residue chromatographed (SiO_2 (15 g), $CHCl_3$/MeOH 9:1): 112 mg (99%) of (*R,S*)-**29**. Light yellow powder. M.p. 193–196°. $[\alpha]_D = -45$ (DMSO, $c = 0.2$). IR (KBr): 3391*m*, 2932*m*, 1773*s*, 1720*s*, 1666*s*, 1531*m*, 1391*m*, 1317*m*, 1164*m*, 725*w*, 695*w*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 7.65–7.6 (*m*, 3 arom. H); 7.5–7.45 (*m*, 2 arom. H); 7.3–7.15 (*m*, 5 arom. H); 7.03 (*d*, $J = 9$, NH); 4.89 (*dd*, $J = 6$, 1 aliph. H); 3.65–3.5 (*m*, 1 aliph. H); 3.46, 3.25 (2*d*, $J_{AB} = 8$, PhCH_2); 3.21, 2.89 (2*d*, $J_{AB} = 16$, 2 aliph. H); 2.75–2.6 (*m*, 4 aliph. H); 2.25–0.95 (*m*, *ca.* 12 aliph. H). ISP-MS: 524.4 (42, $[M + Na]^+$), 519.5 (48, $[M + NH_4]^+$), 502.4 (100, $[M + H]^+$).

*(α*S*,5*S*)-1-Benzoyl-α-benzyl-*N*-cyclohexyl-2,6,8-trioxo-1,7-diazaspiro[4.4]nonane-7-acetamide* ((*S,S*)-**30**). As described for (*R,S*)-**29**, with (*S,S*)-**28** (140 mg, 0.24 mmol), CH_2Cl_2 (10 ml), CF_3COOH (4 ml), and $SOCl_2$ (0.4 ml): 122 mg (100%) of (*S,S*)-**30**. Yellow powder. Crystallization from PrOH gave crystals suitable for X-ray analysis. M.p. 231–233°. $[\alpha]_D = -123.5$ (DMSO, $c = 0.2$). IR (KBr): 3303*m*, 2933*w*, 1772*w*, 1716*s*, 1674*m*, 1648*m*, 1321*w*, 1239*w*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 7.65–7.6 (*m*, 2 arom. H); 7.5–7.45 (*m*, 3 arom. H); 7.3–7.2 (*m*, 6 H, 5 arom., NH); 4.73 (*dd*, $J = 9$, 1 aliph. H); 3.75–3.50 (*m*, 1 aliph. H); 3.45, 3.15 (2*d*, $J_{AB} = 9$, PhCH_2); 3.21, 3.01 (2*d*, 2 aliph. H); 2.75–2.55 (*m*, 4 aliph. H); 2.25–1.0 (*m*, *ca.* 11 aliph. H). ISP-MS: 519.4 (48, $[M + NH_4]^+$), 502.4 (100, $[M + H]^+$).

REFERENCES

[1] G. L. Olson, M. E. Voss, D. E. Hill, M. Kahn, V. S. Madison, C. M. Cook, *J. Am. Chem. Soc.* **1990,** *112,* 323.
[2] V. J. Hrubi, F. A. Obeidi, W. Kazmiersky, *Biochem. J.* **1990,** *268,* 249.
[3] T. Masquelin, E. Broger, K. Müller, R. Schmid, D. Obrecht, *Helv. Chim. Acta* **1994,** *77,* 1395.
[4] B. Di Blasio, V. Pavone, A. Lombardi, C. Pedone, E. Benedetti, *Biopolymers* **1993,** *33,* 1037.
[5] I. L. Karle, P. Balaram, *Biochemistry* **1990,** *29,* 6747.
[6] P. Wipf, H. Heimgartner, *Helv. Chim. Acta* **1988,** *71,* 258.
[7] D. Obrecht, O. Bohdal, C. Lehmann, P. Schönholzer, K. Müller, *Tetrahedron* **1995,** *51,* 10883.
[8] D. Obrecht, C. Lehmann, R. Ruffieux, P. Schönholzer, K. Müller, *Helv. Chim. Acta* **1995,** *78,* 1567.
[9] D. Obrecht, H. Karajiannis, C. Lehmann, P. Schönholzer, C. Spiegler, K. Müller, *Helv. Chim. Acta* **1995,** *78,* 703.

[10] D. Obrecht, U. Bohdal, C. Broger, D. Bur, C. Lehmann, R. Ruffieux, P. Schönholzer, C. Spiegler, K. Müller, *Helv. Chim. Acta* **1995,** *78,* 563.
[11] D. Obrecht, C. Spiegler, P. Schönholzer, K. Müller, H. Heimgartner, F Stierli, *Helv. Chim. Acta* **1992,** *75,* 1666.
[12] M. Mutter, *Angew. Chem.* **1985,** *97,* 639.
[13] C. Toniolo, *CRC Critical Rev. Biochem.* **1980,** *9,* 1.
[14] B. V. V. Prasad, P. Balaram, *CRC Critical Rev. Biochem.* **1984,** *16,* 307.
[15] C. E. Spiegler, 'Synthesis and Conformation Studies of Peptides Containing Novel α,α-Disubstituted Amino Acids', Ph.D. Thesis, 1993, University of Zürich.
[16] E. Benedetti, C. Toniolo, P. Hardy, V. Barone, B. Bavoso, B. Di Blasio, P. Grimaldi, F. Lelj, V. Pavone, C. Pedone, G. M. Bonora, I. Lingham, *J. Am. Chem. Soc.* **1984,** *106,* 8146.
[17] G. M. Bonora, C. Toniolo, B. Di Blasio, V. Pavone, C. Pedone, E. Benedetti, I. Lingham, P. G. M. Hardy, *J. Am. Chem. Soc.* **1984,** *106,* 8152.
[18] V. Barone, F. Lelj, A. Bavoso, B. Di Blasio, P. Grimaldi, V. Pavone, C. Pedone, *Biopolymers* **1985,** *24,* 1759.
[19] M. Crisma, G. Valle, G. M. Bonora, C. Toniolo, F. Lelj, V. Barone, F. Fraternali, P. M. Hardy, H. L. S. M. Maia, *Biopolymers* **1991,** *31,* 637.
[20] C. Toniolo, E. Benedetti, *ISI Atlas Sci.: Biochem.* **1988,** 255.
[21] D. Obrecht, M. Altorfer, C. Lehmann, P. Schönholzer, K. Müller, *J. Org. Chem.* **1996,** to be published.
[22] D. Obrecht, U. Bohdal, R. Ruffieux, K. Müller, *Helv. Chim. Acta* **1994,** *77,* 1423.
[23] M. Altorfer, 'Templates for the Position-Independent Nucleation of α-Helices in Peptides', Ph.D. Thesis, 1996, University of Zürich.
[24] W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **1978,** *43,* 2923.
[25] L. A. Carpino, *J. Am. Chem. Soc.* **1993,** *115,* 4397.
[26] U. W. Bohdal, 'Synthesis and Conformational Studies of Peptides Containing α-Alkylated Aspartic and Glutamic Acids and Their Succinimide and Pyroglutamate Derivatives', Ph.D. Thesis, 1996, University of Zürich.
[27] C. M. Wilmot, J. M. Thornton, *J. Mol. Biol.* **1988,** *203,* 221.
[28] C. M. Wilmot, J. M. Thornton, *Protein Eng.* **1990,** *3,* 479.
[29] S. Brahms, J. Brahms, *J. Mol. Biol.* **1980,** *138,* 149.
[30] S. Capasso, L. Mazzarella, F. Sica, A. Zagari, *Int. J. Pept. Protein Res.* **1984,** *24,* 588.
[31] S. Capasso, L. Mazzarella, F. Sica, A. Zagari, *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1987,** *43,* 1607.
[32] S. Capasso, C. R. Mattia, L. Mazzarella, A. Zagari, G. Cascarano, C. Giacovazzo, *Acta Crystallogr., Sect. B: Struct. Sci.* **1992,** *48,* 285.
[33] L. Mazzarella, I. Schow, F. Sica, A. Zagari, *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1988,** *44,* 880.
[34] M. Crisma, G. Valle, C. Toniolo, S. Prasad, R. B. Rao, P. Balaram, *Biopolymers* **1995,** *35,* 1.
[35] S. Prasad, R. B. Rao, P. Balaram, *Biopolymers* **1995,** *35,* 11.
[36] P. Wipf, R. W. Kunz, R. Prewo, H. Heimgartner, *Helv. Chim. Acta* **1988,** *71,* 268.
[37] J. H. Dyson, P. E. Wright, *Annu. Rev. Biophys. Chem.* **1991,** *20,* 519.
[38] M. Hollósi, Z. S. Majer, A. Z. Ronai, A. Mahyar, K. Medzihradsky, S. Holly, A. Perczel, G. D. Fasman, *Biopolymers* **1994,** *34,* 177.