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A Novel Synthesis of (*R*)- and (*S*)-α-Alkylated Aspartic and Glutamic Acids: α-Alkylated Aspartic Succinimides as New Type of β-Turn Type II and II' Mimetics

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Abstract: A novel and efficient synthesis of optically pure (*R*)- and (*S*)-α-methyl glutamic acid (**1**), (*R*)- and (*S*)-α-methyl aspartic acid (**2a**) and (*R*)- and (*S*)-α-isobutyl aspartic acid (**2b**) using L-phenylalanine cyclohexylamide **4** as chiral auxiliary is described. Crystal structures show that the (*R*)- and (*S*)-α-methyl glutamic acid derivatives (*S,S*)-**5** and (*R,S*)-**6** adopt β-turn type I geometries, whereas the corresponding aspartimide derivatives (*R,S*)-**12a,b** form a β-turn type II and (*S,S*)-**11a** a β-turn type II'. These findings suggest, that the succinimide derivatives of (*R*)- and (*S*)-α-alkyl aspartic acids can serve as building blocks to stabilise β-turns of type II (or II') in peptides depending on their absolute configuration.

1. Introduction

Among the increasing number of non-proteinogenic amino acids the α,α-disubstituted glycines play an important role due to their ability to induce and stabilise different types of secondary structures when incorporated into small- to medium-size peptides.[1] It has been shown,[2] that the (*R*)- and (*S*)-enantiomers of certain α,α-disubstituted amino acids can stabilise different types of β-turns in short peptides and that in general peptides containing these building blocks show an increased stability towards biological and chemical degradation[3]. For these reasons, both enantiomers of α,α-disubstituted amino acids can serve as interesting tools to modulate conformations of small peptides.

In this paper we describe a novel synthesis of optically pure (*R*)- and (*S*)-α-methyl glutamic and aspartic acids **1** and **2a** (see Fig. 1), respectively, and for the first time, the preparation of (*R*)- and (*S*)-α-isobutyl aspartic acid **2b** (Fig. 1) based on our previously described general strategy for the synthesis of α,α-disubstituted amino acids.[4-6]

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a) Part of Ph. D. Thesis of *U. B.*, University of Zürich, 1995.

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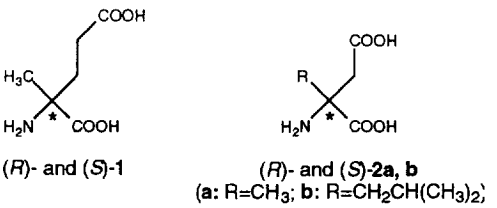
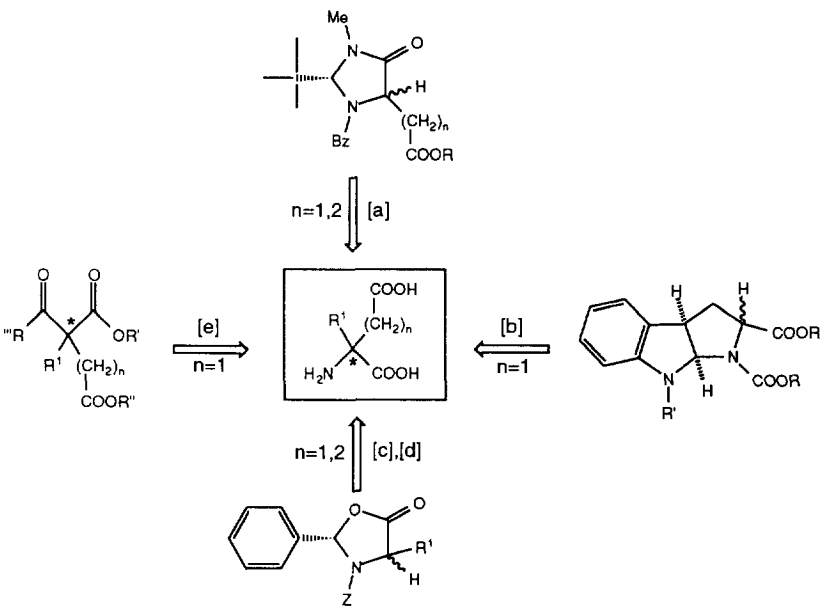


Figure 1.

The following approaches towards the synthesis of optically pure α-substituted aspartic and glutamic acids have been described as shown in Scheme 1. These methods include Seebach's method via stereoselective alkylation of the *trans*- or *cis*-imidazolidinones (route **a**),[7] Mutter's variation via alkylation of oxazolidinones (route **c**, **d**),[8,9] asymmetric synthesis via Schmidt rearrangement of α,α-dialkylated β-esters (route **e**)[10] and an enantioselective synthesis starting from (*S*)-tryptophan (route **b**).[11]

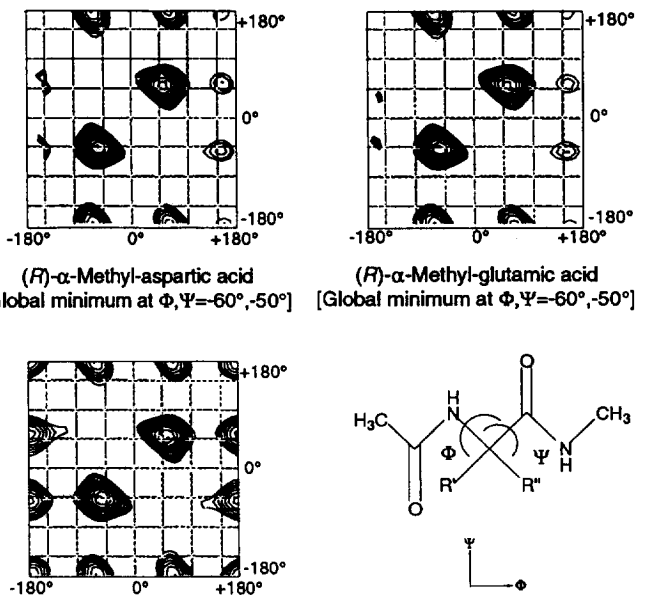


Scheme 1.

Whereas the synthesis of α-substituted aspartic and glutamic acids is quite well established, very little is known about the conformational behaviour of these compounds when incorporated into small peptides. Calculated Ramachandran plots[12] of (*R*)- and (*S*)-α-methyl-glutamic and aspartic acids show close similarities to α-amino-isobutyric acid (*Aib*, see Fig. 2). This suggests, that these amino acids should be strongly helix- and β-turn compatible.[13]

The helix-formation parameters as determined by Fersht[14,15] show a rather low propensity for L-aspartate and L-glutamate to occur in helical domains of proteins. We reasoned, that an α-methyl substituent should significantly increase the helix compatibility of these amino acids in peptides and proteins as can be seen from the corresponding Ramachandran plots (Fig. 2).

In an interesting study, Mutter et al.[16] incorporated (*R*)- and (*S*)-α-methyl aspartic acid into amphiphilic model peptides (Ac-YAA-*X*-AKEAAEKA-*X*-AAK-NH_2 / *X*=(*R*)- or (*S*)-α-Me-Asp) and observed a significant increase of helicity for the (*R*)-enantiomer at pH 2, which was not the case for the (*S*)-enantiomer.



The backbone torsional angles were systematically varied by 10 degrees followed by unconstrained relaxation of the structure in the *MOLOC* - forcefield. [17,18]

Figure 2. Ramachandran Map for amino acids of type **1** and **2a**.

Since in amphiphilic peptides intramolecular *i* to *i+4* side chain interactions of L-lysine and L-glutamate may contribute significantly to the stabilisation of α-helical conformations, the conformational properties of α-methyl aspartic acid were difficult to extract from these peptides. Therefore we were interested to study the conformational behaviour of amino acids of type **1** and **2** as well as their succinimide and pyroglutamate analogues **11, 12** and **14, 15** (see Scheme 3), respectively, in small hydrophobic peptides.

In this paper, we describe an efficient synthesis of optically pure α-alkylated aspartic acids **2a, b** and their succinimide analogues **11, 12** and α-methyl glutamic acid **1** and its pyroglutamate analogues **14, 15** using L-Phe-cyclohexylamide as resolving agent.[5] Their structures were confirmed by X-ray analyses, which show that the crystalline peptides (*R,S*)-**12a,b** adopt β-turn type II conformations and peptide (*S,S*)-**11a** forms a β-

turn type II'. These findings indicate that the succinimide analogues of α-alkylated aspartic acids can serve as building blocks to stabilise β-turns of type II (or II') in peptides depending on the configuration of the corresponding α-alkyl aspartic acid precursors. The α-substituent does not only facilitate succinimide ring formation due to a possible geminal dialkyl effect, it also increases the stability towards ring opening at the α- or β-carboxyl groups of the succinimide moiety in compounds of type **11** and **12** compared to their natural analogues. The intermediate succinimide ring formation and the corresponding α- and β-ring openings are well known side reactions of L-aspartic acid in peptides.[19]

2. Synthesis of optically pure (*R*)- and (*S*)-α-methyl glutamic acid

Optically pure α-alkylated glutamic acids can be obtained using several methods.[7-11] Recently we presented a general approach to the synthesis of 4,4-disubstituted-2-phenyl-1,3-oxazol-5(4*H*)-ones ("azlactones"),[20, 21] which are useful precursors for the synthesis of optically pure (*R*)- and (*S*)-α,α-disubstituted amino acids combining two side chains of proteinogenic or non-proteinogenic amino acids at the α-carbon ("α-chimeras"). Applying this methodology to the synthesis of α-methyl glutamic acid, we prepared the corresponding azlactone (*rac*)-**3** (see Scheme 2) which reacted with L-Phe-cyclohexylamide[5] **4** to yield the diastereomeric peptides (*S,S*)-**5** and (*R,S*)-**6** which were easily separated by flash chromatography (FC).[22]

The absolute configurations of peptides **5** and **6** were unambiguously determined from their corresponding crystal structures, based on the known (*S*)-configuration of L-Phe (Fig. 3 , Fig. 4). It is interesting to note, that the backbones of peptides **5** and **6** both adopt β-turn type I geometries (see also Table 1 in section 4).

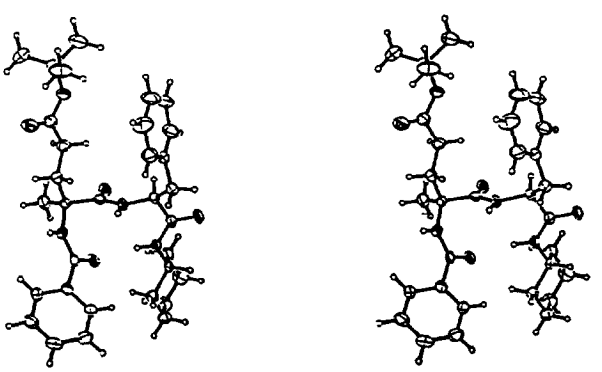
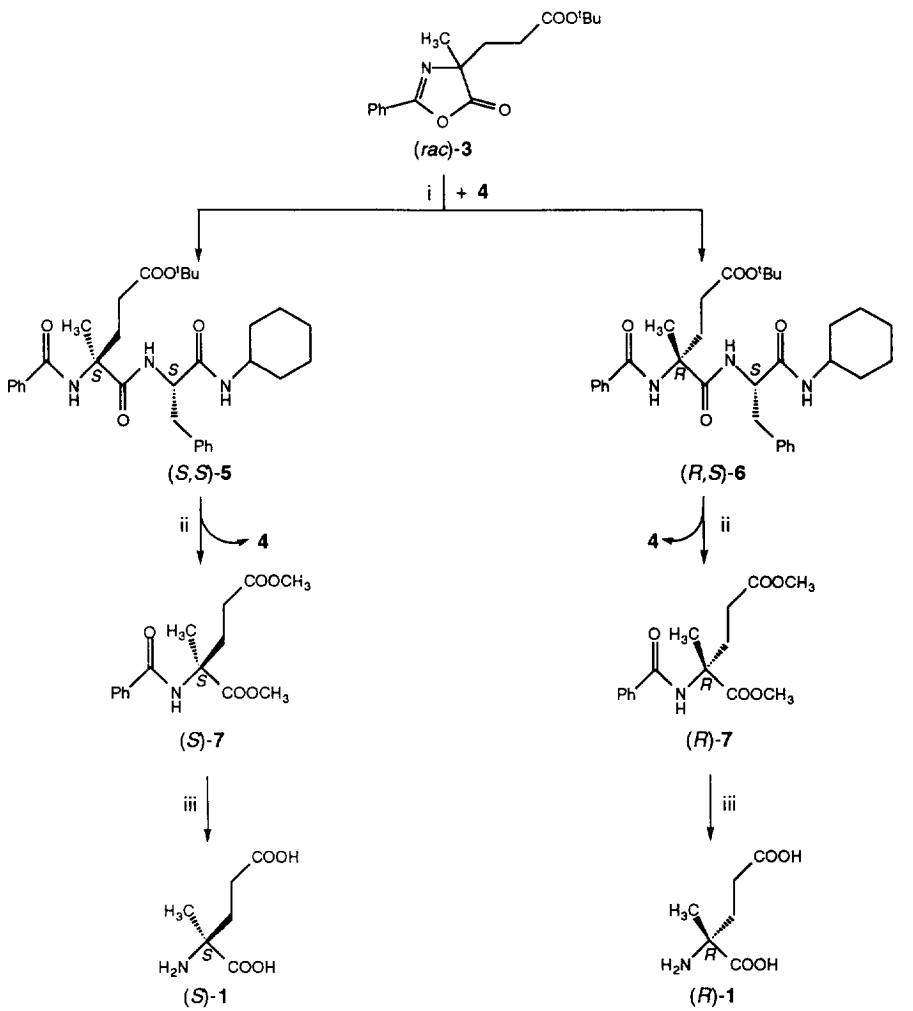


Figure 3. Stereoplot[b)] of crystal structure of (*S,S*)-**5**.

b) The thermal ellipsoids are drawn at 30% probability level; H-atoms are shown as small circles of arbitrary size.



i: L-Phe-cyclohexylamide **4**, 1-methyl-pyrrolidone (NMP), 70°, 8h;
ii: CF_3SO_3H, MeOH, reflux, 12h; iii: 25% aq. HCl, dioxane, 80°, 6h.

Scheme 2.

Selective amide cleavage in diastereomers **5** and **6** using trifluoromethane sulfonic acid (CF_3SO_3H) in MeOH at 80° gave the optically pure dimethylesters (*S*)-**7** and (*R*)-**7** and more than 90% recovery of the chiral auxiliary in optically pure form. As previously shown,[5] this selective amide cleavage is based on the preferred intramolecular formation of 2-phenyl-1,3-oxazol-5(4*H*)-one intermediates due to the geminal dialkyl effect.

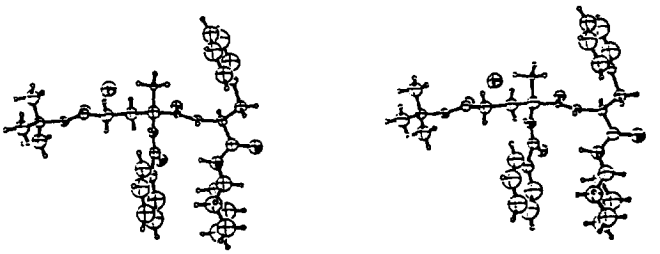
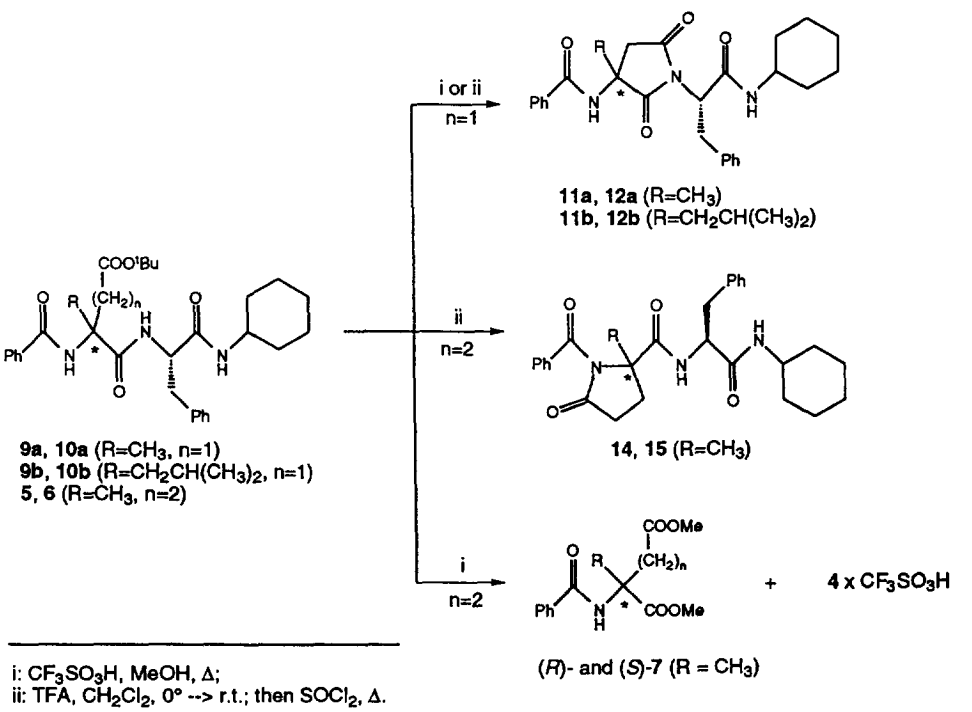


Figure 4. Stereoplot[b] of crystal structure of (*R,S*)-**6**.

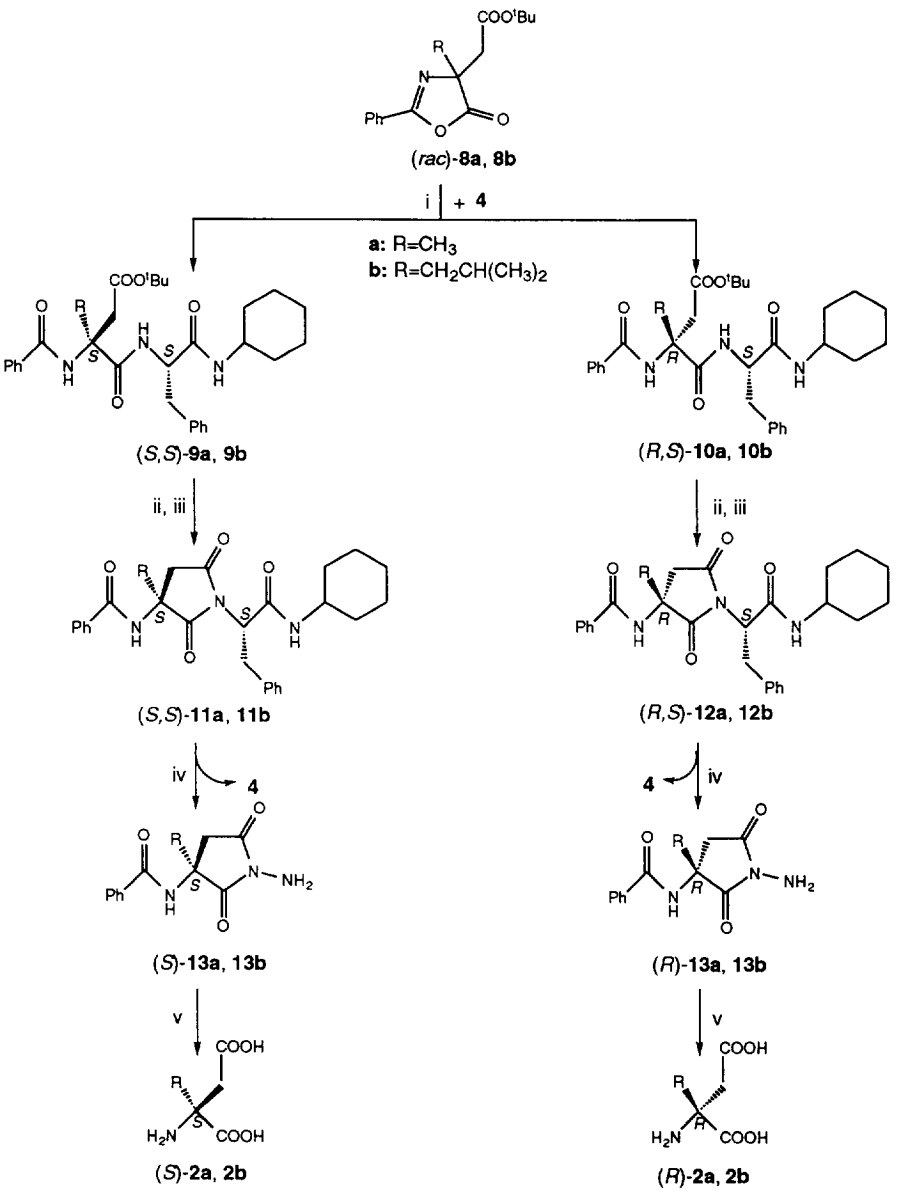
Under the reaction conditions these intermediates were converted into (*R*)- and (*S*)-**7** without other competing amide cleavages. The enantiomerically pure esters (*S*)-**7** and (*R*)-**7** were hydrolysed using 25% aq. HCl in dioxane to yield the free amino acids (*S*)-**1** and (*R*)-**1**. Treatment of the diastereomeric peptides with TFA in CH_2Cl_2 followed by addition of $SOCl_2$ gave the corresponding pyroglutamate derivatives **14** and **15** in high yields (Scheme 3).



Scheme 3.

3. Synthesis of optically pure (*R*)- and (*S*)-α-alkylated aspartic acids

Following the same strategy, the diastereomeric peptides (*S,S*)-**9a**, (*R,S*)-**10a** (R = methyl) and (*S,S*)-**9b**,



i: L-Phe-cyclohexylamide **4**, NMP, 50-80°, 5-12h; ii: TFA, CH_2Cl_2, 0°→ r.t.,1h; iii: $SOCl_2$, CH_2Cl_2, reflux, 8-12h; iv: $H_2NNH_2.H_2O$, EtOH, reflux, 12h; v: 25% aq. HCl, dioxane, 80°, 6h.

Scheme 4.

(*R,S*)-**10b** (R = *iso*-butyl) were obtained from (*rac*)-**8a,b**[20](see Scheme 4) by reaction with the chiral amine **4** and separation of the resulting diastereomers.

Surprisingly, treatment of the diastereomeric peptides **9a,b** and **10a,b** with CF_3SO_3H in MeOH at 80° gave the corresponding succinimide derivatives **11a,b** and **12a,b** and not the expected selective amide cleavage products as observed in the case of **5** and **6** (see Scheme 3), which emphasises the stability of these compounds under acidic conditions. The absolute configurations of **11a**, **12a** and **12b** (Fig. 5-7) could be determined by X-ray structure analyses, using the known absolute configuration of L-Phe in the chiral auxiliary. It is interesting to note, that crystalline (*R,S*)-**11a** and (*S,S*)-**12a** adopt β-turn conformations of type II and type II', respectively. This indicates a predominant conformation-inducing effect by the aspartyl succinimide building block (for a more detailed discussion see chapter 4). Using the much milder reaction conditions as shown in Scheme 4 (ii, iii) instead of the original cleaving conditions, peptides **11a,b** and **12a,b** could be obtained in quantitative yields (Scheme 4).

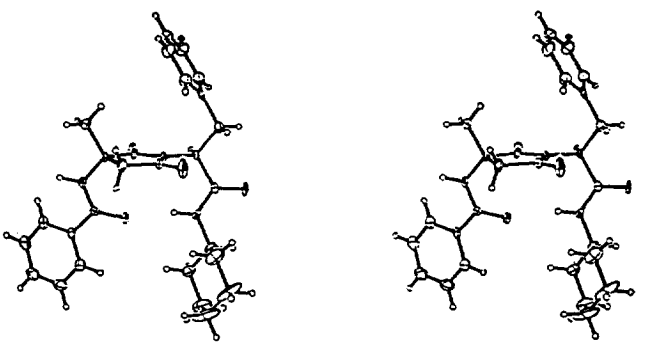


Figure 5. Stereoplot[b)] of crystal structure of (*S,S*)-**11a**.

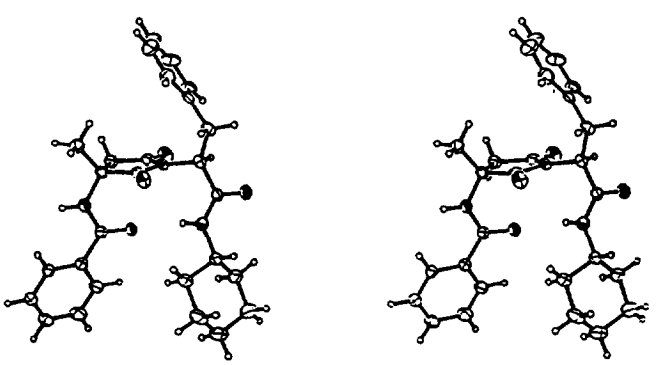


Figure 6. Stereoplot[b)] of crystal structure of (*R,S*)-**12a**.

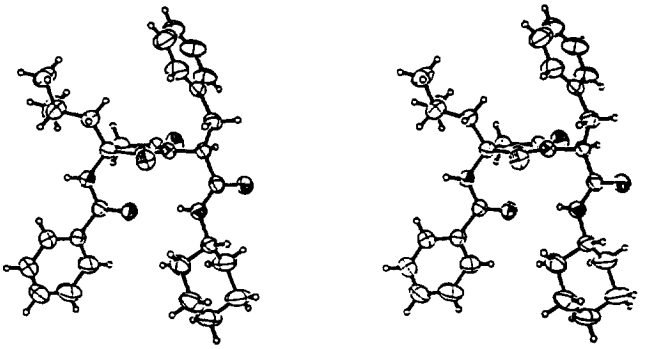


Figure 7. Stereoplot[b] of crystal structure of (*R,S*)-**12b**.

Cleavage of the peptides **11** and **12** with concomitant recovery of the chiral auxiliary was achieved by treatment with ethanolic hydrazine followed by chromatography on silicagel. The resulting optically pure 1-amino succinimide derivatives (*S*)-**13a,b** and (*R*)-**13a,b** could be hydrolysed with 25% aqueous HCl in dioxane to the free α-alkyl-aspartates (*S*)-**2a,b** and (*R*)-**2a,b**. The structure of the intermediate 1-amino succinimide derivative was confirmed by X-ray analysis for the crystalline (*S*)-**13a** (see Fig. 8). We note that the pKa-value of the protonated primary amine of (*S*)-**13a** is < 2, which is consistent with pKa-values of similar compounds in the literature.[23, 24]

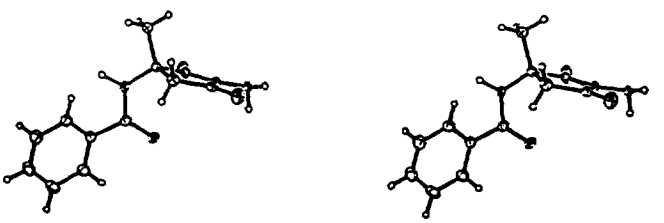
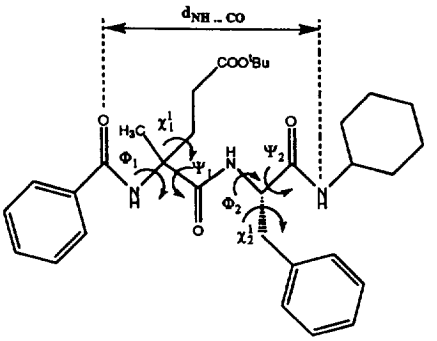


Figure 8. Stereoplot[b] of crystal structure of (*S*)-**13a**.

4. Conformational aspects of α-alkylated aspartic acids in the crystalline state.

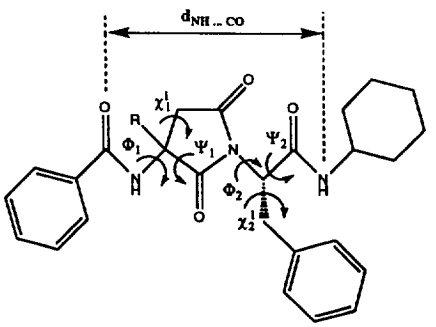
The absolute configurations of the α-methyl glutamic- and α-alkyl aspartic acid building blocks of type **1** and **2** (Fig. 1) were unambiguously determined by X-ray-structure analyses of the corresponding *N*-benzoyl protected L-Phe cyclohexylamide derivatives **5**, **6**, **11** and **12**. All technical data of these crystal structures are given in the Experimental Part (see Table 3). Relevant geometrical data of peptides **5** and **6** are listed in Table 1, those of peptides **11a**, **12a** and **12b** in Table 2.

Table 1. Geometrical data of peptides **5** and **6**.



Diastereomer	Φ_1	Ψ_1	Φ_2	Ψ_2	χ_1^1	χ_2^1	d [Å]	*Turn Type* [c]
(*S,S*)-**5**	-44°	-48°	-81°	+2°	+172°	-71°	2.89	Type I ($\alpha_R\alpha_R$)
(*R,S*)-**6**	-53°	-42°	-103°	+20°	+52°	-59°	3.10	Type I ($\alpha_R\alpha_R$)

Table 2. Geometrical data of peptides **11a**, **12a** and **12b**.



Diastereomer	R	Φ_1	Ψ_1	Φ_2	Ψ_2	χ_1^1	χ_2^1	d [Å]	*Turn Type* [c]
(*S,S*)-**11a**	CH_3	+53°	-128°	-118°	+35°	+124°	-53°	2.89	Type II'($\varepsilon\alpha_R$)
(*R,S*)-**12a**	CH_3	-58°	+120°	+56°	+29°	-114°	-46°	2.97	Type II($\beta_P\alpha_L$)
(*R,S*)-**12b**	*i*-Bu	-57°	+125°	+63°	+19°	-120°	-46°	3.01	Type II($\beta_P\alpha_L$)

[c] Turn nomenclature given in brackets according to lit. 25.

The diastereomeric peptides **12a** and **12b** exhibit some interesting aspects of peptide folding and packing. Peptide (*R,S*)-**12a** adopts a β-turn type II conformation (see Fig. 6) with the *N*-benzoyl protected α-methylated building block at position *i+1* and L-Phe at position *i+2* of the β-turn. The *N*-terminal benzoyl and *C*-terminal cyclohexylamide moieties are juxtaposed in the plane of the turn forming a transannular H-bond between the benzoyl carbonyl group and the cyclohexylamide NH group. The succinimide ring which derived from the aspartic acid side chain locks the central peptide unit into an orientation almost perpendicular to the plane of the turn.

The global minimum of the calculated Ramachandran plot for (*R*)-α-methyl-aspartic acid lies in the region which is compatible with β-turns of type I, III or II' (see Fig. 2). Cyclisation of the aspartyl side chain to its succinimide derivative freezes the Ψ_1-torsional angle of peptide **12a** to around +120°, which is the theoretical value of a β-turn type II. This is exactly what is observed in the crystal state of (*R,S*)-**12a**. Conformational studies in solution, which will be published independently, show that the open-chain α-alkylated aspartate derivatives of type **9** and **10** adopt β-turn type I conformations. This is consistent with the crystal structures of the open-chain glutamates of type **5** and **6**, which also adopt type I turn conformations in solution. These observations indicate that α-alkylated aspartic acids are interesting peptide building blocks, which not only induce β-turn type conformations, but also allow us to switch from one type of β-turn to another simply by cyclising the acidic side chain to the succinimide derivative.

While peptides **5**, **6** and **11a** crystallised in the space-group $P2_12_12_1$, peptide **12a** crystallised in space group R 3 . A survey in the Cambridge Crystal Structure Database[26] of 2404 crystal structures of peptides showed no other peptide crystallising in this space group.

5. Conclusions.

We describe a novel and efficient synthesis of optically pure (*R*)- and (*S*)-α-methyl glutamic acid (**1**), (*R*)- and (*S*)-α-methyl aspartic acid (**2a**) and (*R*)- and (*S*)-α-isobutyl aspartic acid (**2b**) using L-phenylalanine cyclohexylamide (**4**) as chiral auxiliary. Based on the X-ray structures of the intermediate peptides (*S,S*)-**5** and (*R,S*)-**6** (Scheme 2, Fig. 3 and 4) we demonstrate that (*R*)- and (*S*)-α-methyl glutamic acids are highly β-turn type I compatible taking the position *i+1* in the turn. Treatment of (*S,S*)-**5** and (*R,S*)-**6** with TFA and $SOCl_2$ resulted in an efficient cyclisation to the corresponding pyroglutamate derivatives **14** and **15** (Scheme 3). Based on the crystal structures of (*R,S*)-**12a**, **b** and (*S,S*)-**11a** (Scheme 4, Fig. 5-7) we show, that the succinimide derivatives of (*R*)- and (*S*)-α-alkyl aspartic acids adopt β-turn type II (and II') geometries, respectively, depending on their absolute configurations. These findings suggest, that (*R*)- and (*S*)-α-alkyl aspartic- and glutamic acids and their succinimide- and pyroglutamate derivatives are ideal tools to modulate different types of β-turn conformations in small peptides.

Experimental Part

All reactions with air or moisture sensitive reactants were carried out in oven- or flame-dried glassware under a positive pressure of Ar. Chemicals were purchased from Aldrich / Fluka or from local manufacturers. Reaction solvents and liquid reagents were purified by distillation shortly before use. CH_2Cl_2 was distilled under Ar from CaH_2. 1-Methyl-pyrrolidone (NMP) was kept over molecular sieves. Anal. TLC: 2.5 x 10 cm

precoated TLC-plates, SiO_2 60F-254, layer-thickness 0.25 mm (E. Merck & Co, Darmstadt, Germany). Flash chromatography (FC): E. Merck, SiO_2 60 (230-400 mesh ASTM) according to lit. 22. M.p.: Mel-Temp II apparatus, Laboratory devices, USA; incorrected. Ion-exchange chromatography: Analytical Grade Cation exchange resin Biorad AG 50W-X8 (100-200 mesh, hydrogen form), Richmond, USA. IR: Nicolet-7199 FT spectrophotometer; solids in KBr pellets, liquids as thin films; characteristic bands in cm^{-1}. ^1H-NMR: Bruker-AC-250 apparatus at 250 MHz; TMS as internal standard; chemical shifts (ranges and signal centers) in ppm; J in Hz. MS: EI (AEI / MS-9, UK), IS (API-III, Perkin Elmer, Canada). X-ray data were collected on a Siemens-Nicolet diffractometer fitted with an LT-cooling apparatus. All calculations were carried out with the SHELXTL PLUS (VAX II) package. Refinement method: full-matrix least-squares; quantity minimised: $\Sigma w(F_O-F_C)^2$; H-atoms: riding models, fixed anisotropic *U*; weighting scheme, $w^{-1} = \sigma^2(F)+0.001F^2$. Coordinates and thermal parameters will be deposited with the Crystallographic Data Centre.[d]

Table 3. Crystal data, solution and refinement

	(*S,S*)-5	(*R,S*)-6	(*S,S*)-11a	(*R,S*)-12a	(*R,S*)-12b	(*S*)-13a
Empirical Formula	$C_{32}H_{43}N_3O_5$	$C_{32}H_{43}N_3O_5$ x H_2O	$C_{27}H_{31}N_3O_4$	$C_{27}H_{31}N_3O_4$	$C_{30}H_{37}N_3O_4$ x *i*-PrOH	$C_{12}H_{13}N_3O_3$
Color	colourless	colourless	colourless	colourless	colourless	colourless
Habit	prismatic	prismatic	prismatic	prismatic	prismatic	prismatic
Crystal Size [mm]	0.15x0.35x0.4		0.2x0.2x0.9	0.25x0.35x0.4	0.37x0.6x0.8	0.1x0.4x0.5
Crystal System	Monoclinic	Orthorhombic	Orthorhombic	Rhombohedral	Rhombohedral	Orthorhombic
Space Group	$P2_12_12_1$	$P2_12_12_1$	$P2_12_12_1$	R3	R3	$P2_12_12_1$
Unit Cell Dimensions (Å;deg)	a = 5.774(2)	a = 11.014(3)	a = 9.343(2)	a = 23.617(5)	a = 24.195(5)	a = 8.510(2)
	b = 18.193(5)	b = 15.208(5)	b = 18.880(4)	b = 23.617(5)	b = 24.195(5)	b = 11.380(2)
	c = 14.810(5)	c = 22.480(9)	c = 28.895(6)	c = 13.130(5)	c = 15.088(5)	c = 12.580(3)
	β = 93.96(2)					
Volume [$Å^3$]	1552.0(8)	3766(2)	5091(2)	6342(3)	7649(3)	1218.3(5)
Z	2	4	8	9	3	4
Formula Weight	549.7	565.7	461.5	461.5	562.7	247.25
Density [mg/m^3]	1.176	0.998	1.204	1.088	1.117	1.348
Absorption Coefficient [mm^{-1}]	0.079	0.069	0.657	0.074	0.606	0.099
F(000)	592	1216	1968	2214	2736	520
Radiation	MoKα	MoKα	CuKα	MoKα	CuKα	MoKα
Wavelength [Å]	0.71073	0.71073	1.54178	0.71073	1.54178	0.71073
2θ Range [deg]	0 - 56	0 - 56	0 - 112	0 - 56	0 - 112	0 - 56
Reflections collected	4277	5081	3779	3698	2392	1911
Independent Reflections	3900	5081	3751	3573	2392	1692
Final R indices (I > 2σ(I))	R=5.64%	R=13.39%	R=5.38%	R=6.64%	R=5.37%	R=4.47%
R indices (all data)	-	-	-	-	R=5.53%	R=6.18%

Experimental

Procedure A: A mixture of 5.0 mmol of the azlactone of type **3** (or **8a, b**) and 7.5 mmol of L-Phe-cyclohexylamide[5] **4** in 1-methyl-pyrrolidone (NMP, 5 ml) was heated for 5-12h at 50-80° in a pyrolysis tube, cooled to r.t., poured onto ice and 1N HCl. The aqueous phase was extracted with EtOAc (2 x 10 ml). The combined organic layers were washed with H_2O (2 x 10 ml), sat. brine (10 ml), dried (Na_2SO_4) and the solvents were evaporated. The crude residue was purified on SiO_2 by flash chromatography[22] as indicated. The two diastereomeric peptides of type **5** and **6** (or **9a,b** and **10a,b**) were further purified as indicated.

Procedure B: The diastereomeric peptides of types **5** or **6** (10 mmol) were dissolved under argon in MeOH (25 ml) in a pyrolysis tube and cooled to 0°. Trifluoromethane sulfonic acid (30 mmol) was added, the reaction mixture was refluxed for 12h and poured onto ice and 1N HCl. The aqueous phase was extracted with EtOAc (2 x 50 ml). The combined organic layers were washed with H_2O (2 x 50 ml), sat. brine (25 ml), dried (Na_2SO_4) and the solvents were evaporated. The chiral auxiliary **4** was recovered as the trifluoromethane

[d] The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW.

sulfonate salt by precipitation from the crude oil using CH_2Cl_2 and subsequent filtering. The filtrate was evaporated and the resulting residue was chromatographed on SiO_2 to give the dimethylester of type **7** which was further purified as indicated.

Procedure C: The dimethylester of type **7** (10 mmol) was dissolved in a solution of 25% aq. HCl (10 ml) in dioxane (10 ml) and was refluxed in a pyrolysis tube for 6h. The reaction mixture was poured onto ice and the aqueous phase was washed with Et_2O (2 x 50 ml) and evaporated. The crude residue was chromatographed using an cation-exchange resin and further purified as indicated.

Procedure D: Modification of *Procedure C* with compounds of type **13** as starting materials.

Procedure E: The diastereomeric peptide (10 mmol) of type **9** (or **10**) was dissolved in CH_2Cl_2 (15 ml) in a pyrolysis tube and cooled to 0°. Trifluoroacetic acid (TFA, 10 ml) was added and the reaction mixture was allowed to come slowly to r.t. The mixture was cooled again to 0° and $SOCl_2$ (1 ml) was added, the reaction mixture was refluxed for 8-12h, the solvents were evaporated under reduced pressure, the residue was chromatographed on SiO_2 and further purified as indicated.

Procedure F: The diastereomeric peptide of type **11** or **12** (10 mmol) was dissolved in 20 ml of a 1M ethanolic hydrazine solution and refluxed for 18h in a pyrolysis tube. The solvents were removed under reduced pressure, the residue was chromatographed on SiO_2 and further purified as indicated.

Procedure G: Modification of *Procedure E* with compounds **5** or **6** as starting materials.

(*S*)-2-Amino-2-methyl-pentanedioic acid (*S*)-1. From (*S*)-**7** (2.6 g, 8.86 mmol) according to *Procedure C* gave after chromatography on an cation-exchange resin Biorad-AG-50W-X8 (100 g) and drying over P_2O_5 under reduced pressure 1.26 g (90%) of (*S*)-**1** as an amorphous solid. $[\alpha]_D^{20}$=-9° (H_2O, c=0.1); IR(KBr): 3428*s* (br.), 3099*s* (br.), 1593*s* (br.), 1399*s*, 1128*w*, 791*w*; ^{1}H-NMR (250 MHz, D_2O): 2.37-2.00 (*m*, 4 H, $(CH_2)_2$), 1.50 (*s*, 3 H, CH_3); MS(ISN): 160.2 ($(M-H)^-$, 100), 142.1 (25).

(*R*)-2-Amino-2-methyl-pentanedioic acid (*R*)-1. From (*R*)-**7** (1.5 g, 5.11 mmol) according to *Procedure C* gave after chromatography on a cation-exchange resin Biorad-AG-50W-X8 (50 g) and drying over P_2O_5 under reduced pressure 780 mg (98%) of (*R*)-**1** as a colourless oil. $[\alpha]_D^{20}$=+10° (H_2O, c=0.19); IR-, NMR- and MS-spectra are in close agreement to (*S*)-**1**.

(*S*)-2-Amino-2-methyl-butanedioic acid (*S*)-2a. From (*S*)-**13a** (750 mg, 3.03 mmol) according to *Procedure D* gave after chromatography on a cation-exchange resin (50 g) and lyophilization 400 mg (90%) of (*S*)-**2a** as a white solid. M.p. 131-134°; $[\alpha]_D^{20}$=+36° (H_2O, c=0.18); IR(Film): 2981*s* (br.), 1594*s* (br.), 1405*s*, 1275*m*, 1241*m*, 1123*m*, 957*w*, 882*w*; ^{1}H-NMR (250 MHz, D_2O): 2.84, 2.56 (2*d*, J_{AB} = 16 Hz, 2H, CH_2CO), 1.47 (*s*, 3H, CH_3); MS(EI): 147 ($M^{+\cdot}$, <1), 102 (50), 84 (30), 42 (100).

(*R*)-2-Amino-2-methyl-butanedioic acid (*R*)-2a. From (*R*)-**13a** (780 mg, 3.15 mmol) according to *Procedure D* gave after chromatography on a cation-exchange resin (50 g) and lyophilization 430 mg (93%) of (*R*)-**2a** as a white solid. M.p. 131-133°; $[\alpha]_D^{20}$=-40° (H_2O, c=0.2); IR-, NMR- and MS-spectra are in close agreement to (*S*)-**2a**.

(*S*)-2-Amino-2-isobutyl-butanedioic acid (*S*)-2b. From (*S*)-**13b** (720 mg, 2.49 mmol) according to *Procedure D* gave after chromatography on a cation-exchange resin (50 g) and lyophilization 360 mg (95%) of (*S*)-**2b** as a yellow oil. $[\alpha]_D^{20}$=+8.5° (H_2O, c=0.2); IR(Film): 3459*s* (br.), 2956*s* (br.), 2682*m*, 1606*s*, 1494*s*, 1410*s*, 1295*m*, 1125*w*, 974*w*, 799*w*, 623*w*; ^{1}H-NMR (250 MHz, D_2O): 2.82, 2.53 (2*d*, J_{AB} = 18 Hz, 2H, CH_2CO), 1.80-1.65 (*m*, 3H, CH_2CH), 0.96-0.91 (*m*, 6H, $(CH_3)_2$); MS(ISN): 188.2 ($(M-H)^-$, 100).

(*R*)-2-Amino-2-isobutyl-butanedioic acid (*R*)-2b. From (*R*)-**13b** (120 mg, 0.41 mmol) according to *Procedure D* gave after chromatography on a cation-exchange resin (12 g) and lyophilization 73 mg (94%) of (*R*)-**2b** as a yellow oil. $[\alpha]_D^{20}$=-9.5° (H_2O, c=0.2); IR-, NMR- and MS-spectra are in close agreement to (*S*)-**2b**.

(*S*)-4-Benzoylamino-4-[(*S*)-1-cyclohexylcarbamoyl-2-phenyl-ethylcarbamoyl]-pentanoic acid *tert.*-butyl ester (*S,S*)-5 and **(*R*)-4-benzoylamino-4-[(*S*)-1-cyclohexylcarbamoyl-2-phenyl-ethylcarbamoyl]-pentanoic acid *tert.*-butyl ester (*R,S*)-6.** From (*rac*)-3-(4-methyl-5-oxo-2-phenyl-4,5-dihydro-oxazol-4-yl)-propionic acid *tert.*-butyl ester[20] (*rac*-**3**, 4.14 g, 13.65 mmol) according to *Procedure A* gave after chromatography on SiO_2 (700 g) with hexane/EtOAc ((1:1) + 0.5% *i*-PrOH) first after drying under reduced pressure 2.85 g (38%) of (*S,S*)-**5** as a white solid. M.p. 122-125°. $[\alpha]_D^{20}$=-26° ($CHCl_3$, c=0.1); IR(KBr): 3422*m*, 2932*m*, 1730*m*, 1643*s*, 1535*s*, 1254*m*, 1154*m*, 697*w*; ^{1}H-NMR (250 MHz, $CDCl_3$): 8.49 (*s*, NH), 7.77-7.75 (*m*, 2 arom. H), 7.56-7.45 (*m*, 3 arom. H), 7.07-7.05 (*m*, 5 arom. H, 1 NH), 6.25 (*d*, *J* = 8 Hz, NH), 4.64 (*m*, CHCO), 3.75 (*m*, HNC**H**), 3.18, 3.14 (2*d*, J_{AB} = 4 Hz, 2 H, C**H$_2$**Ph), 2.45-2.05 (*m*, 2 H, CH_2CO), 1.97-1.68 (*m*, ~7 aliph. H), 1.62 (*s*, 3 H, CH_3), 1.51 (*s*, 9 H, $C(CH_3)_3$), 1.29-1.23 (*m*, ~5 aliph. H); MS(ISP): 572.4 (M^+·+ Na^+, 35), 550.5 (M^+·+ H^+, 100), 472.5 (55).

Further elution yielded 3.15 g (42%) of (*R,S*)-**6** as a white solid. M.p. 154-157°; $[\alpha]_D^{20}$=-15.5° ($CHCl_3$, c=0.2); IR(KBr): 3420*m*, 2930*m*, 1723*s*, 1634*s*, 1544*s*, 1215*w*, 1156*m*, 693*m*; ^{1}H-NMR (250 MHz, $CDCl_3$): 7.80-7.78 (*m*, 2 arom. H), 7.77 (*s*, NH), 7.52-7.40 (*m*, 3 arom. H), 7.23-7.18 (*m*, 5 arom. H), 6.55-6.52 (*m*, 2 NH), 4.65-4.57 (*m*, CHCO), 3.80-3.63 (*m*, HNC**H**), 3.19-3.14 (*m*, 2 H, C**H$_2$**Ph), 2.40-2.04 (*m*, 4 aliph. H), 1.80-1.62 (*m*, 6 aliph. H), 1.55 (*s*, 3 H, CH_3), 1.43 (*s*, 9 H, $C(CH_3)_3$), 1.29-1.09 (*m*, 5 aliph. H); MS(ISP): 572.4 (M^+·+ Na^+, 55), 550.4 (M^+·+ H^+, 100). Anal. calc. for $C_{32}H_{43}N_3O_5$ (549.71): C 69.92, H 7.88, N 7.64; found: C 69.99, H 7.89, N 7.57.

(*S*)-2-Benzoylamino-2-methyl-pentanedioic acid dimethyl ester (*S*)-7. From (*S,S*)-**5** (9.6 g, 15.65 mmol) according to *Procedure B* gave after chromatography on SiO_2 (800 g) with hexane/EtOAc (2:1) and after drying under reduced pressure 2.97 g (58%) of (*S*)-**7** as a colourless oil. $[\alpha]_D^{20}$=+9° ($CHCl_3$, c=0.2); IR(Film): 3349*w*, 2952*w*, 1740*s*, 1645*s*, 1530*s*, 1124*s*, 716*m*, 692*m*; ^{1}H-NMR (250 MHz, $CDCl_3$): 7.83-7.79 (*m*, 2 arom. H), 7.51-7.40 (*m*, 3 arom. H, 1 NH), 3.80 (*s*, 3 H, CH_3), 3.65 (*s*, 3 H, CH_3), 2.70-2.25 (*m*, 4 aliph. H), 1.74 (*s*, 3 H, CH_3); MS(EI): 293 (M^+·, <1), 234 (20), 112 (30), 105 (100), 77 (34).

(*R*)-2-Benzoylamino-2-methyl-pentanedioic acid dimethyl ester (*R*)-7. From (*R,S*)-**6** (4.7 g, 8.55 mmol) according to *Procedure B* gave after chromatography on SiO_2 (400 g) with hexane/EtOAc (2:1) and after drying under reduced pressure 1.62 g (64%) of (*R*)-**7** as a colourless oil. $[\alpha]_D^{20}$=-9° ($CHCl_3$, c=0.2); IR-, NMR- and MS-spectra are in close agreement to (*S*)-**7**.

(*S*)-3-Benzoylamino-*N*-[(*S*)-1-cyclohexylcarbamoyl-2-phenyl-ethyl]-3-methyl-succinamic acid *tert.*-butyl ester (*S, S*)-9a and (*R*)-3-benzoylamino-*N*-[(*S*)-1-cyclohexylcarbamoyl-2-phenyl-ethyl]-3-methyl-succinamic acid *tert.*-butyl ester (*R,S*)-10a. From (*rac*)-(4-methyl-5-oxo-2-phenyl-4,5-dihydro-oxazol-4-yl)-acetic acid *tert.*-butyl ester[20] (*rac*-**8a**, 8.5 g, 29.38 mmol) according to *Procedure A* gave after chromatography on SiO_2 (1000 g) with hexane/EtOAc (2:1) ---> (1:1) first after drying under reduced pressure 7.22 g (46%) of (*S,S*)-**9a** as a white solid. M.p. 77-79°; $[\alpha]_D^{20}$=-42° (DMSO, c=0.1); IR(KBr): 3344*m* (br.), 2933*m*, 1710*m*, 1645*s*, 1528*s*, 1482*m*, 1161*m*, 699*w*; ^{1}H-NMR (250 MHz, $CDCl_3$): 8.19 (*s*, NH), 7.74-7.71 (*m*, 2 arom. H), 7.57-7.47 (*m*, 3 arom. H), 7.13-7.11 (*m*, 5 arom. H), 6.79 (*d*, *J* = 8 Hz, NH), 6.35 (*d*, *J* = 8 Hz, NH), 4.71-4.58 (*m*, 1 H, NCHCO), 3.82-3.63 (*m*, 1 H, CONHC**H**), 3.17-3.13 (*m*, 2 H, C**H$_2$**Ph), 2.70, 2.42 (2*d*, J_{AB} = 16 Hz, 2 H, CH_2CO), 2.0-1.62 (*m*, 5 aliph. H), 1.60 (*s*, 3 H, CH_3), 1.46 (*s*, 9 H, $(CH_3)_3$), 1.42-1.02 (*m*, 5 aliph. H);

MS(ISP): 558.6 ($M^{+\cdot}$ + Na^+, 45), 536.6 ($M^{+\cdot}$ + H^+, 100), 480.6 (40), 462.5 (30). Anal. calc. for $C_{31}H_{41}N_3O_5$ (535.69): C 69.51, H 7.71, N 7.84; found: C 68.92, H 7.69, N 7.51.

Further elution yielded 5.44 g (35%) of (*R,S*)-**10a** as a white solid. M.p. 181-183°; $[\alpha]_D^{20}$=-6.5° (DMSO, c=0.2); IR(KBr): 3316*s*, 2932*m*, 1728*s*, 1669*s*, 1642*s*, 1537*s*, 1254*m*, 1160*m*, 696*m*; ^{1}H-NMR (250 MHz, $CDCl_3$): 7.75-7.72 (*m*, 2 arom. H), 7.55-7.45 (*m*, 3 arom. H), 7.40 (*s*, NH), 6.63 (*d*, *J* = 8 Hz, NH), 6.53 (*d*, *J* = 8 Hz, NH), 4.69-4.55 (*m*, 1 H, NCHCO), 3.83-3.60 (*m*, 5 aliph. H), 3.27-3.11 (*m*, 2 H, CH_2Ph), 3.05, 2.76 (2*d*, J_{AB} = 16 Hz, 2 H, CH_2CO), 1.88-1.55 (*m*, ~6 aliph. H), 1.51 (*s*, 3 H, CH_3), 1.40 (*s*, 9 H, $(CH_3)_3$), 1.35-1.02 (*m*, 5 aliph. H); MS(ISP): 558.6 ($M^{+\cdot}$ + Na^+, 35), 536.6 ($M^{+\cdot}$ + H^+, 100), 480.6 (25), 462.5 (15). Anal. calc. for $C_{31}H_{41}N_3O_5$ (535.69): C 69.51, H 7.71, N 7.84; found: C 69.17, H 7.83, N 7.70.

(*S*)-3-Benzoylamino-3-[(*S*)-1-cyclohexylcarbamoyl-2-phenyl-ethylcarbamoyl]-5-methyl-hexanoic acid *tert.*-butyl ester (*S, S*)-9b and (*R*)-3-benzoylamino-3-[(*S*)-1-cyclohexylcarbamoyl-2-phenyl-ethylcarbamoyl]-5-methyl-hexanoic acid *tert.*-butyl ester (*R,S*)-10b. From (*rac*)-(4-isobutyl-5-oxo-2-phenyl-4,5-dihydro-oxazol-4-yl)-acetic acid *tert.*-butyl ester[20] (*rac*-**8b**, 3.2 g, 9.66 mmol) according to *Procedure A* gave after chromatography on SiO_2 (600 g) with CH_2Cl_2/Et_2O (8:2) and drying under reduced pressure first 1.61 g (43%) of (*S,S*)-**9b** as a white solid. M.p. 88-91°; $[\alpha]_D^{20}$=-22° (DMSO, c=0.1); IR(KBr): 3347*m* (br.), 2932*s*, 1710*s*, 1641*s*, 1508*s*, 1481*s*, 1159*m*, 698*w*; ^{1}H-NMR (250 MHz, $CDCl_3$): 7.95 (*s*, NH), 7.79-7.76 (*m*, 2 arom. H), 7.52-7.44 (*m*, 3 arom. H), 7.26-7.21 (*m*, ~5 arom. H), 6.61 (*d*, *J* = 8 Hz, NH), 6.44 (*d*, *J* = 8 Hz, NH), 4.62-4.59 (*m*, 1 H, NCHCO), 3.84-3.64 (*m*, 1 H, CONHC**H**), 3.46, 2.60 (2*d*, J_{AB} = 16 Hz, 2 H, CH_2CO), 3.49-3.11 (*m*, 2 H, CH_2Ph), 1.75-1.00 (*m*, ~13 aliph. H), 1.32 (*s*, 9 H, $(CH_3)_3$), 0.85-0.81 (*m*, ~3 H, CH_3), 0.69-0.67 (*m*, ~3H, CH_3); MS(ISP): 595.5 ($M^{+\cdot}$ + Na^+, 30), 578.5 ($M^{+\cdot}$ + H^+, 100).

Further elution yielded 1.2 g (32%) of (*R,S*)-**10b** as a white solid. M.p. 99-102°; $[\alpha]_D^{20}$=-8° (DMSO, c=0.2); IR(KBr): 3354*m* (br.), 2931*m*, 1726*m*, 1643*s*, 1536*m*, 1483*m*, 1158*m*, 696*w*; ^{1}H-NMR (250 MHz, $CDCl_3$): 7.76-7.72 (*m*, 2 arom. H), 7.54-7.42 (*m*, 3 arom. H), 7.37 (*s*, NH), 7.26-7.20 (*m*, 5 arom. H), 6.83 (*d*, *J* = 8 Hz, NH), 6.19 (*d*, J_{AB} = 8 Hz, NH), 4.59-4.56 (*m*, 1 H, NCHCO), 3.69-3.60 (*m*, 1 H, CONHC**H**), 3.19-3.02 (*m*, ~2 H, CH_2Ph), 2.10-1.07 (*m*, ~22 H), 0.91-0.77 (*m*, ~6 H, $(CH_3)_2$); MS(ISP): 600.4 ($M^{+\cdot}$ + Na^+, 20), 595.4 ($M^{+\cdot}$+NH_4^+, 35), 578.4 ($M^{+\cdot}$ + H^+, 100); anal. calc. for $C_{34}H_{47}N_3O_5$ (577.77): C 70.68, H 8.20, N 7.27; found C 70.27, H 8.18, N 7.23.

***N*-[(*S*)-1-[(*S*)-1-Cyclohexylcarbamoyl-2-phenyl-ethyl]-3-methyl-2,5-dioxo-pyrrolidin-3-yl]-benzamide (*S,S*)-11a.** From (*S,S*)-**9a** (7.0 g, 13.07 mmol) according to *Procedure E* gave after chromatography on SiO_2(500 g) with EtOAc and drying under reduced pressure 5.6 g (93%) of (*S,S*)-**11a** as a white solid. M.p. 222-224°; $[\alpha]_D^{20}$=-94.5° (DMSO, c=0.2); IR(KBr): 3356*w*, 2932*w*, 2854*w*, 1713*m*, 1642*m*, 1543*m*, 1131*w*, 1093*w*, 702*w*; ^{1}H-NMR (250 MHz, DMSO-d_6): 9.20 (*s*, NH), 7.88-7.85 (*m*, 2 arom. H), 7.59-7.47 (*m*, 3 arom. H), 7.33-7.13 (*m*, 6 H, 5 arom. H, 1 NH), 4.73-4.70 (*m*, 1 H, NCHCO), 3.75-3.54 (*m*, 1 H, CONHC**H**), 3.44, 3.22 (2*d*, J_{AB} = 10 Hz, 2 H, CH_2Ph), 2.86, 2.68 (2*d*, J_{AB} = 14 Hz, 2 H, CH_2CO), 1.92-1.60 (*m*, 5 aliph. H), 1.44-1.06 (*m*, ~5 aliph. H), 1.03 (*s*, 3 H, CH_3); MS(ISP): 500.1 ($M^{+\cdot}$ + K^+, 55), 484.5 ($M^{+\cdot}$ + Na^+, 100), 462.5 (10), 326.5 (10).

***N*-[(*R*)-1-[(*S*)-1-Cyclohexylcarbamoyl-2-phenyl-ethyl]-3-methyl-2,5-dioxo-pyrrolidin-3-yl]-benzamide (*R,S*)-12a.** From (*R,S*)-**10a** (5.3 g, 9.89 mmol) according to *Procedure E* gave after chromatography on SiO_2 (500 g) with hexane/EtOAc (1:1) and drying under reduced pressure 4.57 g (100%) of (*R,S*)-**12a** as a white solid. M.p. 99-101°; $[\alpha]_D^{20}$=-110° (DMSO, c=0.2); IR(KBr): 3357*m*, 2933*w*, 1718*s*, 1642*s*, 1538*m*, 1228*w*, 699*w*; ^{1}H-NMR (250 MHz, DMSO-d_6): 9.25 (*s*, NH), 7.95-7.92 (*m*, 2 arom. H), 7.61-7.52 (*m*, 3 arom. H), 7.24

(*d*, *J* = 8 Hz, NH), 7.27-7.09 (*m*, 5 arom. H), 4.94, 4.87 (2*d*, J_{AB} = 4 Hz, 1 H, NCHCO), 3.75-3.44 (*m*, 2 H, CH_2Ph, CONHCH), 3.75 (*d*, J_{AB} = 8 Hz, 1 H, CH_2Ph), 2.98, 2.54 (2*d*, J_{AB} = 16 Hz, 2 H, CH_2CO), 1.86-1.50 (*m*, 5 aliph. H), 1.48-0.92 (*m*, ~5 aliph. H), 1.20 (*s*, 3 H, CH_3); MS(ISP): 500.3 ($M^{+\cdot}$ + K^+, 42), 484.4 ($M^{+\cdot}$ + Na^+, 100), 462.4 ($M^{+\cdot}$ + H^+, 38), 340.2 (5).

***N*-[(*S*)-1-[(*S*)-1-Cyclohexylcarbamoyl-2-phenyl-ethyl]-3-isobutyl-2,5-dioxo-pyrrolidin-3-yl]-benzamide (*S,S*)-11b.** From (*S,S*)-**9b** (700 mg, 1.21 mmol) according to *Procedure E* gave after chromatography on SiO_2 (70 g) with hexane/EtOAc (1:1) and drying under reduced pressure 605 mg (99%) of (*S,S*)- **11b** as a yellow solid. M.p. 186-189°; $[\alpha]_D^{20}$=-110° (DMSO, c=0.2); IR(KBr): 3359*m*, 2932*m*, 1714*s*, 1646*s*, 1535*m*, 1388*m*, 1175*w*, 698*w*; ^{1}H-NMR (250 MHz, DMSO-d_6): 8.91 (*s*, NH), 7.82-7.14 (*m*, 11 H, 10 arom. H, 1 NH), 4.85, 4.75 (2*d*, J_{AB} = 4 Hz, 1 H, NCHCO), 3.75-3.54 (*m*, 1 H, CONHCH), 3.52, 3.48 (2*d*, J_{AB} = 4 Hz, 1 H, CH_2Ph), 3.0-2.52 (*m*, 2 H, CH_2CO), 1.75-0.98 (*m*, ~13 aliph. H), 0.72-0.67 (*m*, ~6 H, $(CH_3)_2$); MS(ISP): 504.5 ($M^{+\cdot}$ + H^+, 100).

***N*-[(*R*)-1-[(*S*)-1-Cyclohexylcarbamoyl-2-phenyl-ethyl]-3-isobutyl-2,5-dioxo-pyrrolidin-3-yl]-benzamide (*R,S*)-12b.** From (*R,S*)-**10b** (440 mg, 0.76 mmol) according to *Procedure E* gave after chromatography on SiO_2 (50 g) with $CHCl_3$/ MeOH (9:1) and drying under reduced pressure 379 mg (99%) of (*R,S*)-**12b** as a white solid. M.p. 94-97°; $[\alpha]_D^{20}$=-89° (DMSO, c=0.1); IR(KBr): 3347*m*, 2932*m*, 1717*s*, 1642*s*, 1549*m*, 1175*w*, 697*w*; ^{1}H-NMR (250 MHz, DMSO-d_6): 8.90 (*s*, NH), 7.89-7.86 (*m*, 2 arom. H), 7.61-7.12 (*m*, 9 H, 8 arom. H, 1 NH), 5.06, 5.00 (2*d*, *J* = 4 Hz, 1 H, NCHCO), 3.59-3.53 (*m*, 1 H, CONHCH), 3.59-3.23 (*m*, 2 H, CH_2Ph), 3.0, 2.64 (2*d*, J_{AB} = 16 Hz, 2 H, CH_2CO), 1.75-1.0 (*m*, ~13 aliph. H), 0.87-0.78 (*m*, ~6 H, $(CH_3)_2$); MS(ISP): 504.5 ($M^{+\cdot}$ + H^+, 100).

***(S)*-*N*-(1-Amino-3-methyl-2,5-dioxo-pyrrolidin-3-yl)-benzamide (*S*)-13a.** From (*S,S*)-**11a** (500 mg, 1.08 mmol) according to *Procedure F* gave first after chromatography on SiO_2 (50 g) with $CHCl_3$/MeOH (9:1) and drying under reduced pressure 203 mg (77%) of **4** (= L-Phe-cyclohexylamide) as a white solid. All physical and spectral data are in close agreement with lit. 5.

Further elution with $CHCl_3$/ MeOH (4:1) yielded after drying under reduced pressure 179 mg (67%) of (*S*)-**13a** as a white solid. M.p. 234-236°; $[\alpha]_D^{20}$=-37° (DMSO, c=0.1); IR(KBr): 3286*m*, 1790*w*, 1710*s*, 1645*s*, 1556*m*, 1227*m*, 698*w*; ^{1}H-NMR (250 MHz, DMSO-d_6): 8.89 (*s*, NH), 7.87-7.85 (*m*, 2 arom. H), 7.57-7.45 (*m*, 3 arom. H), 4.99 (*s*, 2 H, NH_2), 2.92, 2.72 (2*d*, J_{AB} = 14 Hz, 2 H, CH_2CO), 1.49 (*s*, 3 H, CH_3); MS(ISP): 248.3 ($M^{+\cdot}$ + H^+, 100).

***(R)*-*N*-(1-Amino-3-methyl-2,5-dioxo-pyrrolidin-3-yl)-benzamide (*R*)-13a.** From (*R,S*)-**12a** (3.49 g, 7.56 mmol) according to *Procedure F* gave first after chromatography on SiO_2 (400 g) with $CHCl_3$/MeOH (9:1) and drying under reduced pressure 1.51 g (81%) of **4** (= L-Phe-cyclohexylamide) as a white solid. All physical and spectral data are in close agreement with lit. 5.

Further elution with $CHCl_3$/MeOH (4:1) yielded after drying under reduced pressure 1.3 g (70%) of (*R*)-**13a** as a white solid. M.p. 233-236°; $[\alpha]_D^{20}$=+34° (DMSO, c=0.1); IR-, NMR- and MS-spectra are in close agreement to (*S*)-**13a**.

***(S)*-*N*-(1-Amino-3-isobutyl-2,5-dioxo-pyrrolidin-3-yl)-benzamide (*S*)-13b.** From (*S,S*)-**11b** (1.9 g, 3.77 mmol) according to *Procedure F* gave first after chromatography on SiO_2 (100 g) with $CHCl_3$/MeOH (9:1) and drying under reduced pressure 762 mg (82%) of **4** (= L-Phe-cyclohexylamide) as a white solid. All physical and spectral data are in close agreement with lit. 5.

Further elution with $CHCl_3$/MeOH (4:1) yielded after drying under reduced pressure 731 mg (67%) of (*S*)-**13b** as a yellow solid. M.p. 138-143°; $[\alpha]_D^{20}$=-31.3° (DMSO, c=0.15); IR(KBr): 3336*w* (br.), 2960*w*, 1710*s*, 1654*m*, 1524*w*, 1213*w*, 698*w*; ^{1}H-NMR (250 MHz, DMSO-d_6): 8.62 (*s*, ~1 NH), 7.85-7.82 (*m*, 2 arom. H), 7.56-7.44 (*m*, 3 arom. H), 5.08 (*s*, ~2 H, NH_2), 2.94, 2.72 (2*d*, J_{AB} = 13 Hz, 2 H, CH_2CO), 2.0-1.6 (*m*, 3 H, **CHCH$_2$**), 0.96-0.85 (*m*, 6 H, $(CH_3)_2$); MS(EI): 289 ($M^{+\cdot}$, < 1), 230 (22), 122 (26), 105 (100), 77 (44).

(*R*)-*N*-(1-Amino-3-isobutyl-2,5-dioxo-pyrrolidin-3-yl)-benzamide (*R*)-13b. From (*R,S*)-**12b** (370 mg, 0.73 mmol) according to *Procedure F* gave first after chromatography on SiO_2 (30 g) with $CHCl_3$/MeOH (9:1) and drying under reduced pressure 170 mg (80%) of **4** (= L-Phe-cyclohexylamide) as a white solid. All physical and spectral data are in close agreement with lit. 5.

Further elution with $CHCl_3$/MeOH (4:1) yielded after drying under reduced pressure 142 mg (67%) of (*R*)-**13b** as a white solid. M.p. 140-145°; $[\alpha]_D^{20}$=+32.5° (DMSO, c=0.2); IR-, NMR- and MS-spectra are in close agreement to (*S*)-**13b**.

(*S*)-1-Benzoyl-2-methyl-5-oxo-pyrrolidine-2-carboxylic acid (*S*)-(1-cyclohexylcarbamoyl-2-phenyl-ethyl)-amide (*S,S*)-14. From (*S,S*)-**5** (100 mg, 0.18 mmol) according to *Procedure G* gave after chromatography on SiO_2 (10 g) with EtOAc and drying under reduced pressure 82 mg (95%) of (*S,S*)-**14** as a white solid. M.p. 80-82°; $[\alpha]_D^{20}$=+19° (DMSO, c=0.2); IR(KBr): 3383*m*, 2931*s*, 2854*w*, 1748*s*, 1664*s*, 1532*m*, 1450*m*, 1292*s*, 1144*w*, 735*w*, 702*m*; ^{1}H-NMR (250 MHz, DMSO-d_6): 7.95 (*d*, *J* = 9 Hz, NH), 7.59-7.25 (*m*, 10 arom. H, 1 NH), 4.51-4.42 (*m*, 1 H, CONHC**H**), 3.52-3.48 (*m*, **CH**C_6H_{10}), 3.15, 2.82 (2*d*, J_{AB} = 6 Hz, PhC**H**$_2$), 2.32-1.85 (*m*, 4 aliph. H), 1.75-1.02 (*m*, 10 aliph. H), 1.58 (*s*, CH_3); MS (ISP): 498 ($M^{+\cdot}$ + Na^+, 26), 493.6 ($M^{+\cdot}$ + NH_4^+, 28), 476.6 ($M^{+\cdot}$ + H^+, 100).

(*R*)-1-Benzoyl-2-methyl-5-oxo-pyrrolidine-2-carboxylic acid (*S*)-(1-cyclohexylcarbamoyl-2-phenyl-ethyl)-amide (*R,S*)-15. From (*R,S*)-**6** (100 mg, 0.18 mmol) according to *Procedure G* gave after chromatography on SiO_2 (10 g) with $CHCl_3$/MeOH (9:1) and drying under reduced pressure 79 mg (91%) of (*R,S*)-**15** as a yellow solid. M.p. 66-68°; $[\alpha]_D^{20}$=-25° (DMSO, c=0.08); IR(KBr): 3383*w*, 2932*w*, 1746*w*, 1644*s*, 1538*m*, 1450*w*, 1292*m*, 701*m*; ^{1}H-NMR (250 MHz, DMSO-d_6): 7.95 (*d*, *J* = 9 Hz, NH), 7.57-7.30(*m*, ~5 arom. H, 1 NH), 7.25-7.15 (*m*, 5 arom. H), 4.51-4.45 (*m*, 1 H, CONHC**H**), 3.6-3.34 (*m*, **CH**C_6H_{10}), 3.12, 2.85 (2*d*, J_{AB} = 6 Hz, PhC**H**$_2$), 2.5-2.0 (*m*, ~4 aliph. H), 1.75-1.02 (*m*, ~10 aliph. H), 1.64 (*s*, CH_3); MS (ISP): 498.5 ($M^{+\cdot}$ + Na^+, 22), 476.5 ($M^{+\cdot}$ + H^+, 100).

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