56. An Efficient Synthesis of Optically Pure (*R*)- and (*S*)-2-(Aminomethyl)alanine ((*R*)- and (*S*)-Ama) and (*R*)- and (*S*)-2-(Aminomethyl)leucine ((*R*)- and (*S*)-Aml)

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Dedicated to Prof. *M. Hesse* on the occasion of his 60th birthday

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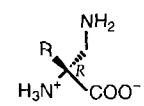
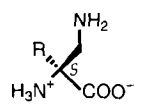
An efficient synthesis of enantiomerically pure (*R*)- and (*S*)-2-(aminomethyl)alanine ((*R*)- and (*S*)-Ama) **1a** and (*R*)- and (*S*)-2-(aminomethyl)leucine ((*R*)- and (*S*)-Aml) **1b** is described (*Schemes 1* and *2*). Resolution of the racemic amino acids was achieved using L-phenylalanine cyclohexylamide (**2**) as chiral auxiliary. The free amino acids **1a, b** were converted to the N^{α}-Boc,N^{γ}-Z-protected derivatives **11a, b** (*Scheme 3*) ready for incorporation into peptides. Based on the three crystal structures of the diastereoisomeric peptides **8a**, **8b**, and **9b**, the absolute configurations in both series were determined. β-Turn type-I geometries were observed for structures **8b** and **9b**, whereas **8a** crystallized in an extended backbone conformation.

1. Introduction. – As part of our program to study the conformational properties of novel and interesting α,α-disubstituted amino acids in small peptides, we were faced with the problem to develop an efficient and quick synthesis of optically pure (*R*)- and (*S*)-2-(aminomethyl)alanine ((*R*)- and (*S*)-Ama = L and D-Ala(2-NH_2CH_2), resp.) **1a** and (*R*)- and (*S*)-(aminomethyl)leucine ((*R*)- and (*S*)-Aml = L and D-Leu(2-NH_2CH_2), resp.) **1b**.



(*R*)-**1a** R = Me
(*R*)-**1b** R = Me_2CHCH_2



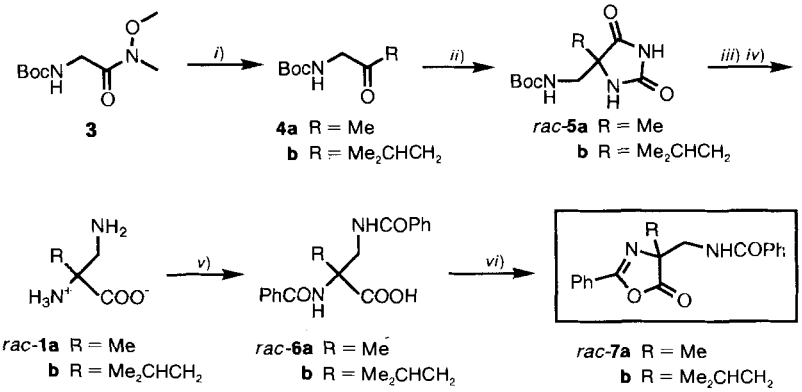
(*S*)-**1a** R = Me
(*S*)-**1b** R = Me_2CHCH_2

We were especially interested to investigate whether building blocks of type **1** can stabilize α-helical conformations in peptides, due to their amphiphilic character combined with the known inherent propensities of certain α,α-disubstituted amino acids to stabilize β-turn and α-helical conformations [1] [2].

2. Synthesis of (*R*)- and (*S*)-Ama and (*R*)- and (*S*)-Aml. – Recently, we reported a general synthesis of optically pure (*R*)- and (*S*)-α,α-disubstituted amino acids [2–4], using L-phenylalanine cyclohexylamide (**2**) as chiral auxiliary. The synthesis of (*R*)- and (*S*)-Ama and (*R*)- and (*S*)-Aml following this approach is outlined in *Schemes 1* and *2*.

[1] Part of Ph. D. thesis of *H. K.*, University of Bern, 1994.
[2] Part of Ph. D. thesis of *C. S.*, University of Zürich, 1993.

Scheme 1



i) RMgCl, THF/Et_2O. *ii*) $(NH_4)_2CO_3$, KCN, EtOH/H_2O. *iii*) CF_3COOH, CH_2Cl_2. *iv*) $Ba(OH)_2 \cdot 8\ H_2O$, Δ. *v*) Me_3SiCl, $(i\text{-}Pr)_2NEt$, CH_2Cl_2, PhCOCl. *vi*) DCC or Ac_2O, CH_2Cl_2.

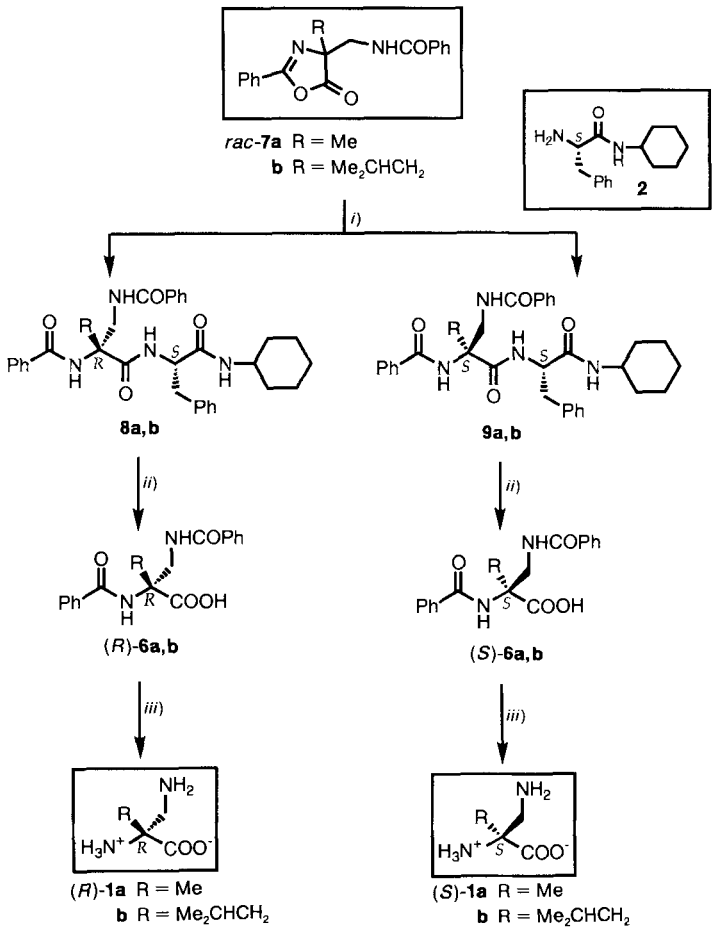
Treatment of the *N*-methoxy-*N*-methylamide **3**[3]) of Boc-glycine with 2.2–2.5 equiv. of either MeMgCl or Me_2CHCH_2MgCl in Et_2O/THF yielded the ketones **4a** and **4b** [5], respectively, which were subjected to *Bucherer-Bergs* reaction conditions [6] to give the corresponding hydantoins *rac*-**5a** and -**5b** in good yields (*Scheme 1*). Cleavage of the Boc groups with CF_3COOH in CH_2Cl_2, saponification using $Ba(OH)_2$ at 120–130°, and chromatography on *Bio-Rad-50W-X8* ion-exchange resin gave the racemic amino acids *rac*-**1a** and -**1b** in high yields. These were dibenzoylated *via* transient silylation according to *Kricheldorf* [7] yielding *rac*-**6a** and -**6b**, respectively, which were subsequently cyclized using *N*,*N*-dicyclohexylcarbodiimide (DCC) in CH_2Cl_2 or Ac_2O to give the key intermediates, the 4,4-disubstituted 2-phenyl-1,3-oxazol-5(4*H*)-ones *rac*-**7a** and -**7b**.

Treatment of *rac*-**7a** and -**7b** with L-phenylalanine cyclohexylamide (**2**) in *N*-methylpyrrolidin-2-one (NMP) at 50–80° gave, after flash chromatography (FC) [8], the diastereoisomeric peptides **8a** and **9a** as well as **8b** and **9b**, respectively, in excellent yields (*Scheme 2*). The absolute configurations of these peptides could be determined by X-ray crystallography of **8a** (*R*,*S*), **8b** (*R*,S), and **9b** (*S*,*S*) (*cf.* below, *Figs. 2–5*). Selective amide cleavage using CF_3SO_3H (3 equiv.) in toluene at 50° gave the intermediate azlactones (*R*)- and (*S*)-**7a** and (*R*)- and (*S*)-**7b**, which were directly converted to the corresponding methyl esters by addition of MeOH. Removal of the solvents and addition of CH_2Cl_2 to the residue resulted in the precipitation of the CF_3SO_3H salt of **2**. Using this procedure, up to 85–95% of the chiral auxiliary **2** could be recovered in optically pure form. The residue of the CH_2Cl_2 solution was saponified using 3N aqueous NaOH in dioxane. After acidification and crystallization, the optically pure acids (*R*)- and (*S*)-**6a** and (*R*)- and (*S*)-**6b** were obtained in high yields. They were hydrolyzed in a mixture of 25% aqueous HCl/dioxane 1:1 at 100° and purified by chromatography on *Bio-Rad-50W-X8* ion-exchange resin to provide the optically pure (*R*)- and (*S*)-Ama **1a** and (*R*)- and (*S*)-Aml **1b**[4]).

[3]) Prepared in 81% yield according to *Nahm* and *Weinreb* [5].

[4]) For a recently patented alternative synthesis, see [9].

Scheme 2

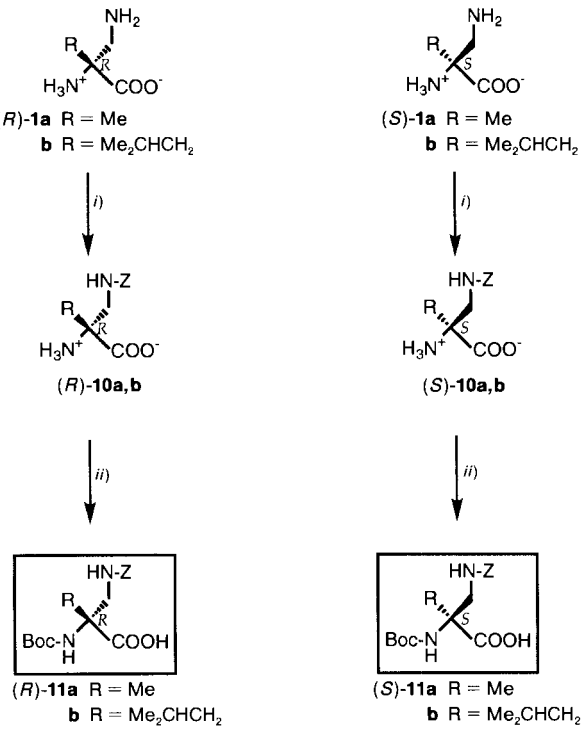


i) **2**, NMP, 50–80°. *ii*) CF_3SO_3H, toluene, 50°; then MeOH, r.t.; then 3N aq. NaOH, dioxane/H_2O or $LiOH \cdot 1H_2O$, THF/MeOH/H_2O. *iii*) 25% aq. HCl, dioxane, 100°.

3. Selective Protection of the Two Amino Groups of (*R*)- and (*S*)-Ama and (*R*)- and (*S*)-Aml. – For the use of the amino acids (*R*)- and (*S*)-Ama **1a** and (*R*)- and (*S*)-Aml **1b** in peptide synthesis, an efficient protocol for the selective protection of the two amino groups had to be devised. Our strategy is shown in *Scheme 3*.

Selective Z protection of the 2-aminomethyl groups in (*R*)- and (*S*)-Ama **1a** and (*R*)- and (*S*)-Aml **1b** was achieved by slow addition of 1.2 equiv. of *N*-[(benzyloxy)carbonyloxy]succinimid (Z-OSu) in dioxane to a solution of **1a** or **1b** in aqueous Na_2CO_3 solution at temperatures below 0° to yield the monoprotected amino acids (*R*)- and (*S*)-**10a** and (*R*)- and (*S*)-**10b** (*Scheme 3*). Subsequent Boc protection of the 2-amino groups could be effected once again by using the *Kricheldorf* method [7] which gave the fully protected amino-acid building blocks (*R*)- and (*S*)-**11a** and (*R*)- and (*S*)-**11b** in optically pure form and ready for incorporation into peptides.

Scheme 3



i) Na_2CO_3, H_2O, dioxane, Z–OSu, $-20\rightarrow0°$. *ii*) Me_3SiCl, CH_2Cl_2; then $(i\text{-}Pr)_2NEt$, Boc_2O, Δ.

4. Absolute Configurations of (*R*)- and (*S*)-Ama 1a and (*R*)- and (*S*)-Aml 1b and Discussion of the Conformational Characteristics of 8a and 9b in the Crystalline State. – In the case of the alanine series, crystallization and X-ray structure determination for one diastereoisomer, the (*R*,*S*)-Ama derivative **8a**, allowed us to determine the absolute configuration by means of the internal chiral reference of L-phenylalanine (*cf. Fig. 1*). For the leucine series, both diastereoisomers, the (*R*,*S*)- and (*S*,*S*)-Aml derivatives **8b** and **9b**, could be crystallized and analyzed (*cf. Figs. 2* and *3*, resp.).

It is of interest to note that both epimeric leucine derivatives **8b** and **9b** adopt β-turn type-I geometries with a main chain C=O···H–N H-bond, despite the inversion of

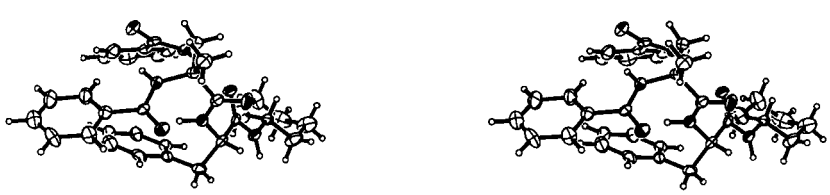


Fig. 1. *Stereoscopic projection of the X-ray structure of* (R)*-2-(aminomethyl)alanine* ((*R*)-Ama) *derivative* **8a**

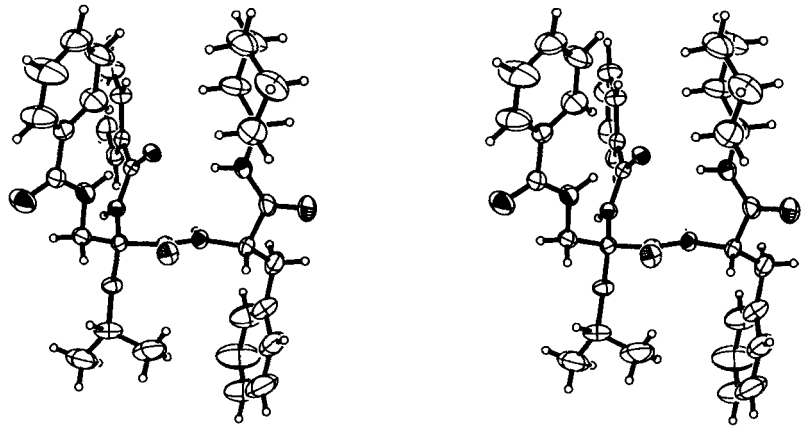


Fig. 2. *Stereoscopic projection of the X-ray structure of* (R)*-2-(aminomethyl)leucine* ((*R*)-Aml) *derivative* **8b**

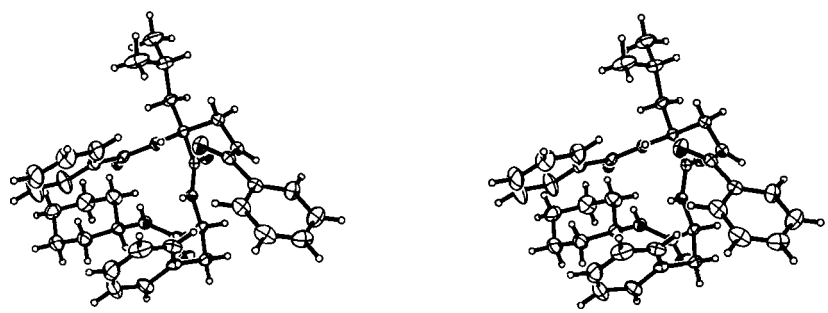


Fig. 3. *Stereoscopic projection of the X-ray structure of* (S)*-2-(aminomethyl)leucine* ((*S*)-Aml) *derivative* **9b**

configuration at the C(α) atom of the first amino acid (*Fig. 4*). The (*N*-benzoylamino)-methyl side chains, however, fold back onto the main chain in two different ways: In the (*R*)-epimer **8b**, a short turn involving the side chain amide H-atom and the C=O group of the N-terminal benzoyl unit is formed, whereas in the (*S*)-epimer **9b**, the side chain benzoyl C=O group accepts a H-bond from the main-chain amide unit. Both H-bonded turns between main-chain and side-chain amide units can be classified as 2_7-turns [12]. This structural element does, however, not conform to either a classical or an inverse γ-turn [13]. An analogous folding of side chains onto their own N^a is observed for 3% of Glx (Gln and Glu) residues in a representative set of well resolved protein X-ray structures [14]. By contrast, the (*R*,*S*)-Ama diastereoisomer **8a** adopts an extended main chain with a H-bonded turn-like fold involving the aminomethyl side chain. This main-chain conformation seems to be found only in conjunction with unusual amino-acid residues, since it could not be identified in proteins [10] [15–17]. Interestingly, this conformation does not correspond to a minimum on the energy surface determined by recent *ab initio* calculations [18]; however, the related conformation termed $\alpha_D\varepsilon_L$ by those authors is a stable minimum in the force field ECEPP/2 ([18] and ref. cit. therein) as well as in our in-house force field MAB [19].

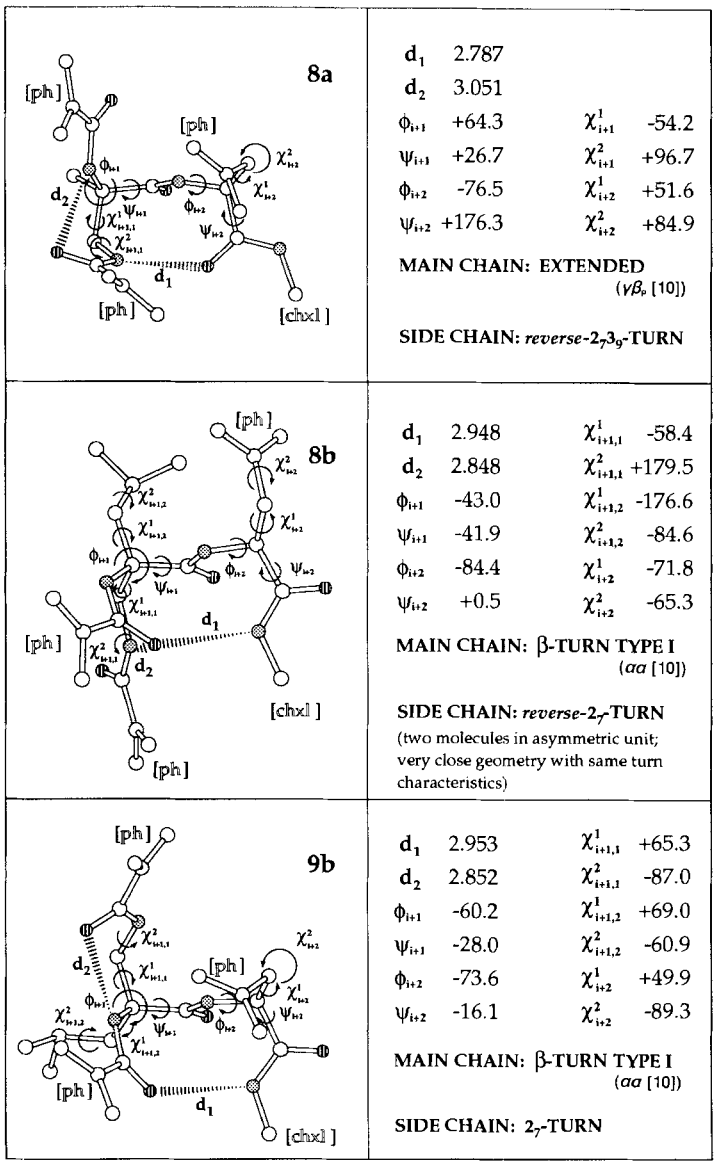


Fig. 4. *Conformational characteristics of the crystalline branched tetraamides* **8a**, **8b**, *and* **9b**. Designation of torsional angles according to IUPAC-IUB recommendations [11].

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Experimental Part

General. All reactions with air- or moisture-sensitive reactants and solvents were carried out in oven- or flame-dried glassware under a positive pressure of dry Ar. Reaction solvents and liquid reagents were purified by distillation shortly before use. THF was distilled under Ar from Na with benzophenone ketyl as indicator, CH_2Cl_2 from powdered CaH_2, and DMF over ninhydrin and kept over 4 Å molecular sieves. All other reactants were 'reagent-grade' unless described otherwise. Anal. TLC: 2.5 × 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 [7]. M.p.: *Büchi-SMP-20* apparatus; uncorrected. IR Spectra: *Nicolet-7199-FT* spectrophotometer; solids in KBr pellets, liquides as thin films; characteristic bands in cm^{-1}. ^{1}H-NMR Spectra: *Bruker-AC-250* apparatus, at 250 MHz; in $CDCl_3$; $SiMe_4$ as internal standard; chemical shifts of signal centres and ranges in ppm (δ), J in Hz. MS: FAB = fast-atom-bombardment ionization, ISP = ion-spray ionization, positive mode, ISN = ion-spray ionization, negative mode.

rac-*2,3-Diamino-2-methylpropanoic Acid* (*rac*-**1a**). To a stirred suspension of *rac*-**5a** (11.5 g, 47.5 mmol) in CH_2Cl_2 (75 ml) was added CF_3COOH (50 ml) at 0°, and the mixture was stirred for 3 h at 0°. After evaporation, the solid residue was dried under reduced pressure, suspended in Et_2O (100 ml), filtered, and dried under reduced pressure: 11.5 g (100%) of rac-*5-(aminomethyl)-5-methylimidazolidin-2,4-dione trifluoroacetate*. White solid. M.p. (dec.) > 238°. IR (KBr): 3375*w* (br.), 3164*m* (br.), 3081*m* (br.), 1823*m*, 1728*s*, 1672*s*, 1626*m*, 1554*m*, 1418*m*, 1390*w*, 1341*w*, 1282*w*, 1205*m*, 1154*m*, 1150*w*, 1170*w*, 723*w*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 5.98 (br. *s*, NH); 7.93 (*s*, NH); 3.11, 2.92 (2*d*, *AB*, J_{AB} = 13.5, CH_2); 1.33 (*s*, Me): MS: 143 (< 1, M^+ (free amine)), 114 (20), 69 (16), 45 (23), 30 (100).

A mixture of this trifluoroacetate (11.5 g, 47.5 mmol) and $Ba(OH)_2 \cdot 8\ H_2O$ (59.95 g, 190 mmol) in H_2O (140 ml) was stirred for 48 h at 140° in a steel autoclave, cooled to r.t., and acidified by addition of 4N aq. H_2SO_4 (50 ml). The suspension was vigourously stirred and heated for 1 h on a steam bath, the precipitate ($BaSO_4$) filtered, and the residue washed with H_2O. The filtrate was evaporated to *ca.* 50 ml and chromatographed on *Bio-A6-50W-X8* ion-exchange resin (100 g). After the column was washed with H_2O to pH 7, the product was eluated with 0.5N aq. NH_3 to give, after lyophilization and drying over P_2O_5 under reduced pressure, 4.7 g (84%) of *rac*-**1a**. White powder. M.p. 229–230°. IR (KBr): 3420*w* (br.), 3343*s*, 3091*m*, 3000*m*, 2971*m*, 2941*s*, 2877*m*, 2681*m*, 1658*s*, 1589*s*, 1467*s*, 1413*s*, 1368*s*, 1285*m*, 1183*w*, 1066*w*, 992*w*, 871*m*. ^{1}H-NMR (D_2O, 250 MHz): 3.09, 2.94 (2*d*, *AB*, J_{AB} = 13.5, CH_2); 1.39 (*s*, Me). MS: 118 (< 1, M^+), 89 (44), 73 (12), 42 (42).

(R)-2,3-Diamino-2-methylpropanoic Acid ((*R*)-**1a**). A mixture of (*R*)-**6a** (2.78 g, 8.52 mmol) in dioxane (10 ml) an 25% aq. HCl soln. (20 ml) was heated for 18 h at 100°, cooled to r.t., and evaporated. The residue was purified by ion-exchange chromatography (60 g of *Bio-Rad-50W-X8* resin) to yield, after drying over P_2O_5 under reduced pressure, 680 mg (67.6%) of (*R*)-**1a**. White solid. M.p. (dec.) 202–204°. $[\alpha]_D$ = −4.5 (MeOH, *c* = 0.2). IR (KBr): 3347*m*, 3279*w* (br.), 3106*m* (br.), 2972*m*, 2934*m*, 2555*w* (br.), 1640*m* (br.), 1598*s*, 1570*s* (br.), 1446*w*, 1404*m*, 1369*m*, 1337*m*, 1266*w*, 1215*w*, 1116*w*, 983*m*. ^{1}H-NMR (D_2O, 250 MHz): 3.47 3.37 (2*d*, *AB*, J_{AB} = 13.9, CH_2); 1.60 (*s*, Me). FAB-MS: 119.1 (20, $[M + H]^+$), 109.1 (70), 91.2 (100).

Enantiomer (S)-**1a**. From (*S*)-**6a** (2.38 g, 7.29 mmol) as described for (*R*)-**1a**: 730 mg (84.4%) of (*S*)-**1a**. M.p. (dec.) 203–205°. $[\alpha]_D$ = +5.0 (MeOH, *c* = 0.2). Spectral data: in agreement with those for (*R*)-**1a**.

rac-*2-Amino-2-(aminomethyl)-4-methylpentanoic Acid* (rac-**1b**). A soln. of *rac*-**5b** (13.3 g, 46.6 mmol) in CF_3COOH (30 ml) was stirred for 1 h at 0° and at r.t. for 1 h. The solvent was evaporated, giving a white solid, which was stirred for 15 min in Et_2O (50 ml), filtered, and dried under high vacuum: 13.83 g (99.2%) of rac-*5-(aminomethyl)-5-(2-methylpropyl)imidazolidine-2,4-dione trifluoroacetate*. M.p. > 231° (dec.). IR (KBr): 3367*m*, 3170*m*, 3075*m*, 2963*m*, 1786*m*, 1710*s*, 1665*s*, 1626*s*, 1531*w*, 1414*m*, 1208*s*, 1177*s*, 1128*s*, 842*m*, 794*m*, 770*m*, 724*m*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 11.05 (*s*, 1 NH); 8.07 (br. *s*, NH_3^+); 7.98 (*s*, 1 H); 3.10, 2.90 (*AB*, J_{AB} = 12.5, CH_2N); 1.7–1.45 (*m*, 3 aliph. H); 0.90, 0.82 (2*d*, *J* = 6.0, Me_2CH). MS: 185 (< 1, M^+), 156 (24), 113 (50), 69 (25), 45 (24), 30 (100). Anal. calc. for $C_{10}H_{16}F_3N_3O_4$ (299.25): C 40.14, H 5.39, N 14.04; found: C 39.87, H 5.38, N 13.83.

To a mixture of this trifluoroacetate (13.5 g, 45.1 mmol) and $Ba(OH)_2 \cdot 8\ H_2O$ (56.93 g, 180 mmol) in a steel autoclave was added H_2O (130 ml). The mixture was stirred for 48 h at 140°, cooled to r.t., and slowly acidified under vigourous stirring with 4N aq. H_2SO_4 to pH 1–2. The suspension was stirred on a steam bath for 1 h, cooled to r.t., and filtered and the precipitate ($BaSO_4$) washed with H_2O (100 ml). The amino acid in the filtrate was purified by ion-exchange chromatography (100 g of cation-exchange resin (*Bio-Rad, AG 50 W-X8*): 6.85 g (94.7%) of *rac*-**1b**. White powder. M.p. 224.5–226.5°. IR (KBr): 3355*m*, 3302*m*, 3039*m*, 2957*s*, 2872*m*, 2620*m* (br.), 1657*m*, 1605*s*, 1579*s*, 1430*m*, 1400*s*, 1340*m*, 1277*m*, 1190*w*, 957*s*, 860*m*, 756*w*, 529*m*. ^{1}H-NMR (D_2O, 250 MHz): 3.12, 2.85

(AB, J_{AB} = 13.5, CH_2N); 1.8–1.5 (*m*, 3 aliph. H); 0.95, 0.90 (2*d*, *J* = 6.5, $Me_2CH)_2$. FAB-MS: 161 (100, $[M + H]^+$), 144 (17) 115 (16). Anal. calc. for $C_7H_{16}N_2O_2$ (160.22): C 52.48, H 10.07, N 17.49; found: C 52.19, H 9.80, N 17.38.

Enantiomer (R)-**1b**. A mixture of (*R*)-**6b** (1.0 g, 2.71 mmol), 25% aq. HCl soln. (4 ml), and dioxane (4 ml) was heated at 100° for 80 h, cooled to r.t., and poured onto ice (50 g), H_2O (75 ml), and Et_2O (50 ml). The aq. layer was extracted twice with Et_2O (50 ml), and then the H_2O was evaporated. The crude amino acid was purified by ion-exchange chromatography (20 g of *Bio-Rad, AG 50 W-X8* resin): 434 mg (93.5%) of (*R*)-**1b**. White powder. M.p. > 220° (dec.). $[\alpha]_D$ = +32.0 (H_2O, *c* = 0.2). Spectra: in close agreement with those of *rac*-**1b**.

Enantiomer (S)-**1b**. As described for (*R*)-**1b**, with (*S*)-**6b** (2.3 g, 6.24 mmol), 25% aq. HCl (9 ml), and dioxane (9 ml; 30 g of *Bio-Rad, AG 50 W-X8*): 932 mg (93.2%) of (*S*)-**1b**. White powder. M.p. > 226° (dec.). $[\alpha]_D$ = −25.2 (H_2O, *c* = 0.2). Spectra: in agreement with those of *rac*-**1b**.

tert-*Butyl (2-Oxopropyl)carbamate* (**4a**). To a stirred soln. of 2-[(*tert*-butoxy)carbonylamino]-*N*-methoxy-*N*-methylacetamide (**3**; 15.5 g, 71.0 mmol) in THF (20 ml) and Et_2O (150 ml) was added under Ar a soln. of MeMgCl (47.0 ml, 3M in Et_2O) at −40°. The suspension was allowed to come to 0°, stirred 1 h at 0° and overnight at r.t., and poured onto 2N aq. HCl (50 ml) and ice. The aq. phase was extracted with Et_2O, the combined org. fraction washed with sat. brine, dried ($MgSO_4$), and evaporated, and the residue chromatographed (SiO_2 (1 kg), toluene/AcOEt 1:1) to yield first, 2.40 g (15.5%) of **3** and, after bulb-to-bulb distillation under reduced pressure, 8.78 g (56.6% or 87.7% based on recovered **3**) **4a**. Colourless liquid. B.p. 65°/0.02 mbar. IR (film): 3364*m*, 2979*m*, 2931*w*, 1725*s*, 1711*s*, 1515*s*, 1456*w*, 1367*s*, 1285*m*, 1251*m*, 1165*s*, 1077*w*, 884*w*. ^{1}H-NMR (250 MHz, $CDCl_3$): 5.23 (br. *s*, NH); 4.03 (*d*, *J* = 4.7, CH_2); 2.18 (*s*, Me); 1.45 (*s*, *t*-Bu). MS: 173 (< 1, M^+), 130 (8), 117 (8), 100 (8), 59 (30), 57 (100), 43 (21), 41 (36). Anal. calc. for $C_8H_{15}NO_3$ (173.21): C 55.47, H 8.73, N 8.09; found: C 55.43, H 8.73, N 8.35.

tert-*Butyl (4-Methyl-2-oxopentyl)carbamate* (**4b**). As described for **4a**, with **3** (15.5 g, 71 mmol) and 2M Me_2CHCH_2MgCl in Et_2O (88.75 ml, 177.5 mmol; 1 h at −40° 0.5 h at 0°, 5 h at r.t.). Workup with ice (100 g)/0.05N aq. HCl (200 ml)/Et_2O (200 ml), then brine (150 ml). Chromatography (SiO_2 (800 g), hexane/AcOEt 4:1) gave 11.93 g (78.1%) of **4b**. Colourless oil. A sample distilled at 65°/0.001 mbar for analysis. IR (KBr): 3373*m*, 2960*s*, 2932*m*, 2873*m*, 1711*s*, 1504*s*, 1367*s*, 1279*s*, 1250*s*, 1168*s*, 1014*m*, 869*w*, 781*w*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 5.26 (br *s*, 1 NH); 3.99 (*d*, *J* = 4.7, 2 H–C(1)); 2.30 (*d*, *J* = 6.7, 2 H–C(3)); 2.25–2.05 (*m*, H–C(4)); 1.45 (*s*, *t*-Bu); 0.94 (*d*, *J* = 6.5, Me_2CH). MS: 159 (6), 142 (4), 130 (2), 117 (1), 85 (28), 57 (100), 41 (32).

rac-tert-*Butyl [(4-Methyl-2,5-dioxoimidazolidin-4-yl)methyl]carbamate* (*rac*-**5a**). A mixture of **4a** (8.78 g, 40.4 mmol), $(NH_4)_2CO_3$ (16.1 g, 141.6 mmol), and KCN (3.94 g, 60.6 mmol) in 70% aq. EtOH (200 ml) was stirred under Ar for 20 h at 50°, then cooled to 0°. A steady steam of Ar was passed through the soln. for 1 h. The mixture was poured onto ice and 1N aq. HCl (150 ml) and extracted (AcOEt), the org. phase washed (sat. brine), dried ($MgSO_4$), and evaporated, and the residue suspended in hexane, filtered, and dried under reduced pressure: 9.8 g (*ca.* 100%) of *rac*-**5a**. White powder which was not further purified. M.p. 197–198°. IR (KBr): 3384*m*, 3331*m*, 3203 (br.), 3069*w*, 2979*w*, 2935*w*, 1727*s*, 1705*s*, 1529*w*, 1454*w*, 1393*m*, 1369*m*, 1346*w*, 1307*w*, 1276*w*, 1248*m*, 1171*m*, 777*w*. ^{1}H-NMR ((D_6)DMSO, 250 MHz): 10.58 (br. *s*, NH); 7.65 (br. *s*, NH); 6.84 ('*t*', *J* = 6.3, CH_2NH); 3.13 (*d*, *J* = 6.3, CH_2NH); 1.37 (*s*, *t*-Bu); 1.18 (*s*, Me). MS: 243 (< 1, M^-), 187 (3), 170 (10), 114 (66), 99 (8), 57 (100), 41 (27).

rac-tert-*Butyl {[4-(2-Methylpropyl)-2,5-dioxoimidazolidin-4-yl]methyl}carbamate* (*rac*-**5b**). A mixture of $(NH_4)_2CO_3$ (21.52 g, 189 mmol), KCN (5.26 g, 80.9 mmol), and **4b** (11.60 g, 53.9 mmol) in 70% aq. EtOH was stirred at 50° overnight. The mixture was cooled to r.t. and poured onto ice (150 g), 1N aq. HCl (150 ml), and AcOEt (400 ml; HCN gas produced passed through bleach). The org. layer was extracted with sat. brine and dried ($MgSO_4$), the volume reduced to 200 ml, and the soln. left overnight at 0°. The white precipitate was filtered off and dried under high vacuum: 6.37 g (41%) of *rac*-**5b**. The filtrate was evaporated and chromatographed (SiO_2 (500 g), 5% MeOH/$CHCl_3$): further 7.21 g (46.9%) of *rac*-**5b**. M.p. 195–197°. IR (KBr): 3362*m*, 3234*m*, 2959*m*, 2932*m*, 2872*w*, 1781*m*, 1723*s*, 1705*s*, 1540*w*, 1367*m*, 1281*m*, 1252*w*, 1176*m*, 992*w*, 651*w*. ^{1}H-NMR ((D_6)DMSO, 250 MHz): 10.59 (*s*, 1 NH); 7.60 (*s*, 1 NH); 6.80 ('*t*', $NHCH_2$); 3.11 (*d*, *J* = 6.3, $NHCH_2$); 1.65–1.4 (*m*, 3 aliph. H); 1.37 (*s*, *t*-Bu); 0.87, 0.78 (2*d*, *J* = 6.4, Me_2CH). MS: 229 (4), 217 (7), 156 (68), 113 (60), 57 (100), 41 (29), 30 (82). Anal. calc. for $C_{13}H_{23}N_3O_4$ (285.34): C 54.72, H 8.12, N 14.73; found: C 54.73, H 8.12, N 14.78.

rac-*2,3-Bis(benzamido)-2-methylpropanoic Acid* (*rac*-**6a**). To a mechanically stirred suspension of *rac*-**1a** (1.2 g, 10.0 mmol) in CH_2Cl_2 (25 ml) was added chlorotrimethylsilane (6.3 ml, 50.0 mmol) at r.t. The mixture was refluxed for 1 h and then cooled to r.t. $(i\text{-}Pr)_2NEt$ (10.3 ml, 60.0 mmol) was added, the mixture refluxed for 1.5 h and then cooled to 0°. Benzoyl chloride (2.5 ml, 22 mmol) was added and the mixture stirred for 2 h at r.t. and poured onto ice, H_2O, and AcOEt. The aq. phase was extracted with AcOEt, the combined org. layer washed with sat. brine, dried ($MgSO_4$), and evaporated, and the residue crystallized from hexane/AcOEt to give, after drying under reduced pressure, 2.71 g (84%) of *rac*-**6a**. White powder. M.p. 198–199°. IR (KBr): 3320*m*, 3063*w*, 2943*w*, 1739*s*, 1653*s*, 1620*m*, 1600*m*, 1575*m*, 1544*s*, 1489*m*, 1448*w*, 1320*m*, 1213*w*, 1120*w*, 714*m*. ^{1}H-NMR ((D_6)DMSO,

250 MHz): 12.48 (br. *s*, COOH); 8.67 (br. *s*, 2 NH); 7.9–7.75 (*m*, 4 arom. H); 7.6–7.4 (*m*, 6 arom. H); 3.9–3.7 (*m*, CH_2); 1.46 (*s*, Me). MS: 326 (< 1, M^+), 281 (25), 105 (100), 77 (42).

(R)-2,3-Bis(benzamido)-2-methylpropanoic Acid ((*R*)-**6a**). To a stirred soln. of **8a** (4.77 g, 8.60 mmol) in toluene (50 ml) was added at 0° CF_3SO_3H (2.27 ml, 25.8 mmol) under Ar. The mixture was stirred for 4 h at 80° and then cooled to r.t. MeOH (50 ml) was added and the mixture stirred overnight at r.t. and evaproated. CH_2Cl_2 (100 ml) was added, the suspension stirred for 1 h and filtered, and the solid residue dried: 3.27 g (96%) of L-phenylalanaine cyclohexylamide-trifluoromethanesulfonate as a white solid. The filtrate was evaporated, the residue dissolved in dioxane (40 ml), 3N aq. NaOH (30 ml) added at 0°, and the mixture stirred for 6 h at r.t. The mixture was acidified with 2N aq. HCl and extracted with AcOEt (3 × 75 ml), the combined org. fraction dried ($MgSO_4$) and evaporated, and the residue dried under reduced pressure. The white solid was suspended in Et_2O/hexane 1:1, the suspension stirred for 1 h and filtered, and the solid dried under reduced pressure: 2.71 g (96.4%) of (*R*)-**6a**. M.p. 193–195°. $[\alpha]_D = +50.5$ (MeOH, *c* = 0.2). IR (KBr): 3338*m* (br.), 3062*w*, 2994*w*, 2941*w*, 1725*m*, 1648*s*, 1621*s*, 1542*s*, 1457*w*, 1311*m*, 1254*m*, 1201*w*, 1151*w*, 714*m*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 12.47 (br. *s*, COOH); 8.8–8.6 (br. *m*, 2 NH); 7.9–7.75 (*m*, 4 arom. H); 7.6–7.4 (*m*, 6 arom. H); 3.9–3.65 (*m*, CH_2NH); 1.47 (*s*, Me). ISP-MS: 327.2 (100, $[M + H]^+$).

*Enantiomer (S)-***6a**. From **9a** (4.26 g, 7.658 mmol) as described for (*R*)-**6a**: 2.45 g (97.7%) of (*S*)-**6a**. M.p. 193.5–195.0°. $[\alpha]_D = -49.0$ (MeOH, *c* = 0.2). Spectral data: in agreement with those of (*R*)-**6a**.

rac-*2-Benzamido-2-(benzamidomethyl)-4-methylpentanoic Acid* (*rac*-**6b**). As described for *rac*-**6a**, with *rac*-**1b** (1.60 g, 10.0 mmol; reaction with benzoyl chloride for 3 h). The residue was suspended in Et_2O, filtered, and dried under reduced pressure: 3.10 g (86%) of *rac*-**6b**. White powder. M.p. 191–192°. IR (KBr): 3386*w*, 3063*w*, 3030*w*, 2958*w*, 2871*w*, 2600*w* (br.), 1723*m*, 1651*s*, 1530*s*, 1480*m*, 1366*w*, 1232*w*, 1154*w*, 713*m*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 12.8 (br. *s*, COOH); 8.39 (*t*' (br.), NH); 8.17 (br. *s*, NH); 7.9–7.75 (*m*, 4 arom. H); 7.6–7.4 (*m*, 6 arom. H); 4.1–3.95, 3.9–3.75 (2*dd*, *ABX*, CH_2NHCOPh); 2.1–1.85 (*m*, 2 aliph. H); 1.85–1.65 (*sept.*, *J* = 6.5, 1 alph. H); 0.91–0.85 (2*d*, *J* = 6.5, 6 aliph. H). MS: 368 (< 1, M^+), 235 (10), 203 (18), 161 (16), 105 (100), 77 (42). Anal. calc. for $C_{21}H_{24}N_2O_4$: C 68.46, H 6.57, N 7.60; found: C 68.19, H 6.55, N 7.56.

(R)-2-Benzamido-2-(benzamidomethyl)-4-methylpentanoic Acid ((*R*)-**6b**). To a stirred soln. of **8b** (1 g, 1.76 mmol) in dry toluene (10 ml) under Ar was added CF_3SO_3O (0.46 ml, 5.23 mmol). The mixture was heated at 80° for 1.5 h and then cooled to r.t. MeOH (5 ml) was added, the mixture stirred for a further 1.5 h at r.t. and evaporated, the residue dissolved in AcOEt (150 ml), and the org. soln. washed with ice-cold 0.5N aq. HCl (2 × 75 ml) and sat. brine (75 ml). The org. layer was dried ($MgSO_4$) and evaporated. The residue was dissolved in THF/MeOH/H_2O 3:1:1 (10 ml) and LiOH·1 H_2O (221 mg, 5.28 mmol) added (further LiOH·H_2O (74 mg) was added after 1 h as the pH was *ca.* 7). The mixture was stirred for 12 h at r.t., the pH adjusted to 7 with 2N aq. HCl, and the org. solvents were evaporated. The residue was poured onto ice (50 g) and AcOEt (100 ml) and washed with 1N aq. HCl (2 × 75 ml). The org. layer was dried ($MgSO_4$) and evaporated and the residue washed with Et_2O (2 × 5 ml) and dried under high vacuum: 624 mg (96.3%) of (*R*)-**6b** as a white solid. As small sample was recrystallized from AcOEt/hexane for analysis. M.p. 217–218°. $[\alpha]_D = -27.0$ (MeOH, *c* = 0.28). IR (KBr): 3400*s*, 3064*m*, 3032*m*, 2956*s*, 2872*w*, 2600*w* (br.), 1726*s*, 1656*s*, 1544*s*, 1488*s*, 1449*m*, 1311*m*, 1220*m*, 711*m*, 600*m*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 12.79 (*s*, 1 COOH); 8.38 (*t*, *J* = 6.3, N*H*CH_2); 8.17 (*s*, 1 NH); 7.9–7.75 (*m*, 4 arom. H); 7.6–7.4 (*m*, 6 aliph. H); 4.02, 3.82 (2*dd*, $J_{AB} = 13.7$, $J_{AX} = J_{BX} = 6.3$, NHC*H*$_2$); 2.05–1.9 (*m*, CH_2CH); 1.75 (*sept.*, *J* = 6.2, Me_2C*H*); 0.91, 0.85 (2*d*, *J* = 7.5, *Me*$_2$CH). ISP-MS: 391 (27, $[M + Na]^+$), 386 (53, $[M + NH_4]^+$), 369 (100, $[M + H]^+$). Anal. calc. for $C_{21}H_{24}N_2O_4$ (368.43): C 68.43, H 6.57, N 7.60; found: C 68.51, H 6.45, N 7.42.

*Enantiomer (S)-***6b**. From **9b** (3.75 g, 6.59 mmol) as described for (*R*)-**6b**. Washing with Et_2O (2 × 7 ml) and drying under high vacuum yielded 2.3 g (94.7%) of (*S*)-**6b**. White solid. M.p. > 201° (dec.). $[\alpha]_D = +31.5$ (MeOH, *c* = 0.2). ^{1}H-NMR, IR, and MS: in close agreement with those of (*R*)-**6b**.

rac-*4-(Benzamidomethyl)-4-methyl-2-phenyl-1,3-oxazol-5(4*H*)-one* (*rac*-**7a**). A stirred soln. of *rac*-**6a** (2.7 g, 8.80 mmol) in Ac_2O (20 ml) was heated for 1 h at 90° and then evaporated. The residue was dissolved in toluene and evaporated (2–3 times). Drying under reduced pressure gave 2.44 g (100%) of *rac*-**7a**. White pwoder. M.p. 139–140°. IR (KBr): 3425*w* (br.), 3300*m*, 3066*w*, 2981*w*, 2934*w*, 2872*m*, 1814*s*, 1650*s*, 1602*w*, 1538*s*, 1451*m*, 1179*m*, 1006*s*, 911*w*, 696*s*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 8.66 (*t*', NH); 7.95–7.85 (*m*, 2 arom. H); 7.75–7.35 (*m*, 8 arom. H); 3.67 (*d*, *J* = 6.3, CH_2NHCOPh); 1.51 (*s*, Me). MS: 308 (< 1, M^+), 175 (24), 134 (16), 105 (100), 77 (34). Anal. calc. for $C_{18}H_{16}N_2O_3$ (308.34): C 70.12, H 5.23, N 9.09; found: C 70.00, H 5.12, N 8.29.

rac-*4-(Benzamidomethyl)-4-(2-methylpropyl)-2-phenyl-1,3-oxazol-5(4*H*)-one* (*rac*-**7b**). As described for *rac*-**7a**, with *rac*-**6b** (3.10 g, 8.40 mmol) in Ac_2O (20 ml): 2.94 g (100%) of *rac*-**7b**. White powder. M.p. 114.5–115.0°. IR (KBr): 3432*m*, 3304*m*, 3065*w*, 3033*w*, 2931*m*, 2872*w*, 1813*s*, 1538*m*, 1490*m*, 1453*m*, 1318*m*, 1290*m*, 1169*w*, 990*m*, 883*w*, 699*m*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 8.1–8.0 (*m*, 2 arom. H); 7.75–7.35 (*m*, 8 arom. H); 6.4–6.25 (*m*,

NHCH$_2$); 4.08, 3.72 (*2dd*, J_{AB} = 7.0, J_{AX} = 13.0, J_{BX} = 14.0, NHCH_2); 2.06, 1.92 (*2dd*, J_{AB} = 6.0, J_{AX} = J_{BX} = 14.0, CH_2CH); 0.92, 0.88 (*2d*, *J* = 7.0, Me_2CH). ISP-MS: 373 (38, $[M + Na]^+$), 351 (85, $[M + H]^+$), 23 (28), 201 (100). Anal. calc. for $C_{21}H_{22}N_2O_3$ (350.42): C 71.98, H 6.33, N 7.99; found: C 71.79, H 6.54, N 7.80.

(S)-N^2-[(R)-2,3-Bis(benzamido)-2-methylpropanoylphenylalanine Cyclohexylamide (**8a**) *and (S,S)-Isomer* **9a**. A stirred soln. of *rac*-**7a** (2.44 g, 7.90 mmol) and (*S*)-phenylalanine cyclohexylamide (**2**; 2.9 g, 11.90 mmol) in *N*-methylpyrrolidin-2-one (14 ml) was heated for 20 h at 80°. After evaporation, the residue was chromatographed (SiO_2 (300 g), hexane/AcOEt 1:2) to yield first, after drying under reduced pressure, 1.87 g (42.7%) of **8a**. White solid. M.p. 180–180°. $[\alpha]_D$ = +25.4 ($CHCl_3$, *c* = 1.0). IR (KBr): 3410*m*, 3358*m*, 3060*w*, 2935*m*, 2852*w*, 1690*s*, 1673*s*, 1653*s*, 1536*s*, 1490*m*, 1455*w*, 712*m*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 8.63 (br. *s*, NH); 8.45–8.35 (*m*, NH); 8.0–7.8 (*m*, 3 arom. H); 7.8–7.75 (*m*, 2 arom. H); 7.6–7.4 (*m*, 5 arom. H, 1 NH); 7.25–7.1 (*m*, 5 arom. H); 4.5–4.4 (*m*, NHC*H*); 3.85–3.7 (*m*, NHC*H*); 3.65–3.4 (*m*, CH_2NHCOPh, 1 aliph. H); 3.25–3.15, 2.95–2.75 (*2m*, *ABX*, PhCH_2); 1.8–1.5 (*m*, 5 aliph. H); 1.4–1.0 (*m*, 5 aliph. H); 1.17 (*s*, Me). ISP-MS: 555.4 (100, $[M + H]^+$), 456 (19).

Crystals suitable for X-ray analysis (*cf. Table*) were grown from MeCN.

Table. *X-Ray Analysis of* **8a**, **8b**, *and* **9b**

	8a	**8b**	**9b**
Crystal data			
Empirical formula	$C_{33}H_{38}N_4O_4$	$C_{36}H_{44}N_4O_4 \cdot C_3H_8O_2$	$C_{36}H_{44}N_4O_4$
Colour; habit	colourless, prismatic	colourless, prismatic	colourless, prismatic
Crystal size [mm]	0.45 × 0.45 × 0.75	0.45 × 0.50 × 0.5	0.15 × 0.50 × 0.65
Crystal system	hexagonal	monoclinic	orthorhombic
Space group	$P6_1$	$P2_1$	$P2_12_12_1$
Unit cell dimensions			
a [Å]	9.340(3)	8.991(5)	10.429(4)
b [Å]		17.063(5)	11.330(4)
c [Å]	58.58(5)	25.266(5)	28.449(10)
β [deg.]		94.060(5)	
Volume [Å^3]	4426(4)	3867(2)	3361(2)
Z	6	4	4
Formula weight	554.7	596.8	596.8
Density (calc.)	1.25	1.26	1.18
Absorption coefficient [mm^{-1}]	0.083	0.0268	0.616
F(000)	1776	640	1280
Data collection			
Radiation	MoK_α	CuK_α	CuK_α
Temperatur [K]	223	300	183
2*θ* Range [deg.]	0–56	0–112	0–112
Scan type	*ω*	2*θ*–*θ*	2*θ*–*θ*
Scan speed [deg./min]	1.1–14.65	1.0–20.0	2.4–15.0
Scan range [*ω*]	0.4	0.72	1.4
Independent reflexions	3681	5326	2534
Observed reflexions	2267	6200	2231
Absorption correction	none	none	none
Solution and refinement			
Solution	direct methods	direct methods	direct methods
Data-to-parameter ratio	6:1:1	5.7:1	5.6:1
Finel *R* index (obs. data)	6.17	8.24	4.40

Further elution of the column gave, after drying under reduced pressure, 1.60 g (36.5%) of **9a**. White solid. M.p. 179–180°. $[\alpha]_D$ = +21.3 ($CHCl_3$, *c* = 1.0). IR (KBr): 3412*m*, 3308*m*, 3063*w*, 3029*w*, 2933*m*, 2855*w*, 1649*s*, 1600*w*, 1580*w*, 1538*s*, 1450*m*, 1312*w*, 896*m*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 9.06 (br. *s*, NH); 8.79 ('*t*', NH); 8.07 (*d*, *J* = 8.5, 1 arom. H); 7.95–7.85 (*m*, 4 arom. H); 7.65–7.45 (*m*, 5 arom. H, 1 NH); 7.41 (*d*, *J* = 8.0, NH); 7.2–7.0 (*m*, 5 arom. H); 4.5–4.4 (*m*, NHC*H*); 3.6–3.4 (*m*, NHC*H*, 1 aliph. H); 3.25–3.1, 2.95–2.8 (*2m*, *ABX*, PhCH_2); 1.8–1.5 (*m*, 5 aliph. H); 1.36 (*s*, Me); 1.3–1.05 (*m*, 5 aliph. H). MS: 555.5 (100, $[M + H]^+$).

(S)-N²-[(R)-Benzamido-2-(benzamidomethyl)-4-methylpentanoyl]phenylalanine Cyclohexylamide (**8b**) *and (S,S)-Isomer* **9b**. As described for **8a** and **9a**, with *rac*-**7b** (2.93 g, 8.30 mmol), **2** (3.08 g, 12.5 mmol), and *N*-methylpyrrolidin-2-one (16 ml). Chromatography (SiO_2 (300 g), hexane/AcOEt 1:1→1:2) yielded first, after precipitation from hexane/AcOEt, 2.28 g (46.0%) of **8b**. Amorphous solid. M.p. > 86° (sint.). R_f (3% i-PrOH/Et_2O) 0.53. $[\alpha]_D = +2.5$ (MeOH, $c = 0.2$). IR (KBr): 3420*m*, 3322*m*, 3063*w*, 3029*w*, 2931*m*, 2854*w*, 1645*s*, 1532*s*, 1485*s*, 1450*m*, 1308*m*, 699*m*. ^{1}H-NMR ((D_6)DMSO, 400 MHz): 8.22 (*s*, 1 NH); 8.15–8.05 (*m*, N*H*CH_2); 7.95 (*d*, $J = 7.0$, 1 NH); 7.87 (*d*, $J = 7.0$, 2 arom. H); 7.85–7.75 (*m*, 1 NH, 2 arom. H); 7.6–7.4 (*m*, 6 arom. H); 7.25–7.05 (*m*, 5 arom. H); 4.4–4.35 (*m*, PhCH_2C*H*); 3.94, 3.82 (2*dd*, $J_{AB} = 14.0$, $J_{AX} = J_{BX} = 5.3$, NHCH_2); 3.55–3.45 (*m*, 1 aliph. H); 3.1–3.0, 2.95–2.85 (2*m*, PhCH_2); 2.0–1.9 (*m*, 1 aliph. H); 1.75–1.6 (*m*, *ca.* 4 aliph. H); 1.6–1.5 (*m*, 1 aliph. H); 1.47 (*m*, Me_2C*H*); 1.3–1.05 (*m*, 6 aliph. H); 0.69, 0.60 (2*d*, $J = 7.0$, *Me*$_2$CH). ISP-MS: 619 (100, $[M + Na]^+$), 597 (62, $[M + H]^+$), 498 (15), 351 (71). Anal. calc. for $C_{36}H_{44}N_4O_4$ (596.77): C 72.46, H 7.43, N 9.39; found: C 72.65, H 7.62, N 9.30.

Crystals for X-ray determination (*cf. Table*) were grown from propane-1,2-diol.

Further elution of the column yielded 1.99 g (40.2%) of **9b**. Amorphous solid. M.p. 232–233°. R_f (3% i-PrOH/Et_2O) 0.12. $[\alpha]_D = +57.0$ (MeOH, $c = 0.1$). IR (KBr): 3414*m*, 3306*m*, 3062*w*, 3029*w*, 2933*m*, 2856*w*, 1646*s*, 1536*s*, 1487*m*, 1450*w*, 1311*w*, 696*m*. ^{1}H-NMR ((D_6)DMSO, 400 MHz): 8.3–8.2 (*m*, 2 NH); 8.2–8.1 (*m*, N*H*CH_2); 7.90 (*s*, 1 NH); 7.77, 7.65 (2*d*, $J = 7.0$, 4 arom. H); 7.55–7.45 (*m*, 2 arom. H); 7.45–7.4 (*m*, 4 arom. H); 7.35 (*d*, $J = 8.8$, 2 arom. H); 7.23 (*t*, $J = 7.5$, 2 arom. H); 7.2–7.1 (*m*, 1 arom. H); 4.7–4.6, 4.6–4.5 (2*m*, CONHC*H*); 3.65–3.5 (*m*, NHCH_2); 3.15–3.05, 3.0–2.9 (2*m*, PhCH_2); 2.4–2.3 (*m*, 1 aliph. H); 1.8–1.65 (*m*, 6 aliph. H); 1.65–1.55 (*m*, 1 aliph. H); 1.35–1.1 (*m*, *ca.* 5 aliph. H);0.68, 0.30 (2*d*, $J = 7.0$, *Me*$_2$CH). ISP-MS: 635 (11, $[M + K]^+$), 619 (100, $[M + Na]^+$), 597 (64, $[M + H]^+$), 351 (73). Anal. calc. for $C_{36}H_{44}N_4O_4$ (596.77): C 72.46, H 7.43, N 9.39; found: C 72.34, H 7.71, N 9.29.

Crystals for X-ray determination (*cf. Table*) were grown from i-PrOH.

(R)-2-Amino-3-[(benzyloxy)carbonylamino]-2-methylpropanoic Acid ((*R*)-**10a**). To a stirred soln. of (*R*)-**1a** (560 mg, 4.74 mmol) in H_2O (4 ml) and 10% aq. Na_2CO_3 soln. (5.0 ml) was slowly added a soln. of *N*-[(benzyloxy)carbonyloxy]succinimide (1.30 g, 5.22 mmol) in dioxane (10 ml) at −20° and stirred for 1 h at −20°. The suspension was brought to 0°, stirred for 4 h (clear soln.), acidified with 0.5N aq. HCl, and stirred for 30 min at 0°. The mixture was filtered, the residue dried under reduced pressure, and the crude solid (1.30 g) purified by prep. HPLC (*Lichrosorb RP 18*, 5 × 25 cm, 100% H_2O (+0.1% CF_3COOH→100% EtOH (+0.1% CF_3COOH in 340 min): 900 mg (75.2%) of (*R*)-**10a**. White amorphous solid. $[\alpha]_D = +12.5$ (MeOH, $c = 0.2$). IR (KBr): 3311*m* (br.), 3068*m* (br.), 3036*m*, 2951*m*, 2572*w* (br.), 1695*s*, 1673*s*, 1530*m* (br.), 1431*w*, 1370*w*, 1262*m*, 1199*m*, 1163*m*, 1024*w*, 697*w*. ^{1}H-NMR ((D_6)DMSO, 250 MHz): 8.30 (br. *s*, *ca.* 3 NH); 7.7–7.6 (*m*, CH_2N*H*Z); 7.45–7.25 (*m*, 5 arom. H); 5.1–4.95 (*m*, *AB*, PhCH_2O); 3.55–3.35 (*m*, CH_2NHZ); 1.39 (*s*, Me). ISP-MS: 253.3 (100, $[M + H]^+$).

Also isolated were 130 mg (7.8%) of *(R)-2,3-bis[(benzyloxy)amino]-2-methylpropanoic acid*. Hygroscopic amorphous solid. $[\alpha]_D = +36.0$ (MeOH, $c = 0.2$). IR (film): 3336*m* (br.), 3065*w*, 3033*w*, 2949*w*, 1708*s* (br.), 1554*m* (br.), 1454*w*, 1256*m* (br.), 1148*w*, 1073*w*, 697*w*. ^{1}H-NMR ((D_6)DMSO, 250 MHz): 12.59 (br. *s*, COOH); 7.5–7.2 (*m*, 10 arom. H, 2 N*H*Z); 5.1–4.9 (*m*, 2 PhCH_2); 3.6–3.5, 3.45–3.25 (2*m*, CH_2NHZ); 1.26 (*s*, Me). ISP-MS: 409.3 (40, $[M + Na]^+$), 404.4 (80, $[M + NH_4]^+$), 387.3 (100, $[M + H]^+$), 343.3 (60).

Enantiomer (S)-**10a**. From (*S*)-**1a** (400 mg, 3.39 mmol) as described for (*R*)-**10a**: 641 mg (75%) of (*S*)-**10a**. $[\alpha]_D = -12.0$ (MeOH, $c = 0.2$). Spectral data: in agreement with those of (*R*)-**10a**.

(R)-2-Amino-2-[(benzyloxy)carbonylaminomethyl]-4-methylpentanoic Acid ((*R*)-**10b**). A soln. of (*R*)-**1b** (200 mg, 1.25 mmol) in H_2O (0.8 ml) and 10%aq. Na_2CO_3 soln. (1.3 ml, 30.3 mmol) were stirred vigourously at 0°. To the mixture was added dropwise a soln. of *N*-[(benzyloxy)carbonyloxy]succinimide (343 mg, 1.38 mmol) in dioxane (2 ml). The resulting white suspension was stirred at 0° for 3 h and filtered and the white solid washed with dioxane/H_2O 1:1 (2 × 3 ml) and dried under high vacuum: 339 mg (92.1%) of (*R*)-**10b**. M.p. > 214° (dec). $[\alpha]_D = +40.0$ (MeOH, $c = 0.1$). ^{1}H-NMR , IR, and MS: in close agreement with those of *rac*-**10b**.

Enantiomer (S)-**10b**. As described for (*R*)-**10b**, with (*S*)-**1b** (400 mg, 2.50 mmol), H_2O (1.6 ml), 10% aq. Na_2CO_3 soln. (2.66 ml, 30.3 mmol), *N*-[(benzyloxy)carbonyloxy]succinimide (686 mg, 2.75 mmol), and dioxane (4 ml). Washing with dioxane/H_2O 1:1 (2 × 5 ml): 505 mg (68.6%) of (*S*)-**10b**. The volume of the filtrate was reduced by half and kept at 0° overnight and the white precipitate filtered off and dried under high vacuum: further 201 mg (27.3%) of (*S*)-**10b**. M.p. > 214° (dec.). $[\alpha]_D = -39.1$ (MeOH, $c = 0.1$). ^{1}H-NMR, IR, and MS: in close agreement with those of *rac*-**10b**.

*(R)-3-[(Benzyloxy)carbonylamino]-2-[(*tert*-butoxy)carbonylamino]-2-methylpropanoic Acid* ((*R*)-**11a**). To a stirred mixture of (*R*)-**10a** (450 mg, 1.78 mmol) and CH_2Cl_2 (5 ml) was added chlorotrimethylsilane (0.57 ml, 4.46 mmol). After 1.5 h stirring at 60° and cooling to 0°, (i-Pr)$_2$NEt (0.83 ml, 4.85 mmol) and di(*tert*-butyl)dicarbonate (0.78 g, 4.85 mmol) were added. The mixture was stirred for 24 h at 60°, cooled to r.t., and evaporated. The residue

was extracted with Et_2O (25 ml) and ice-cold 0.1N aq. NaOH, the aq. layer acidified to pH 2 with 1N aq. HCl and reextracted with AcOEt (2 × 40 ml), and the combined org. phase dried ($MgSO_4$) and evaporated. The white solid was suspended in hexane, stirred for 30 min, filtered, and dried under reduced pressure: 440 mg (70.1%) of (*R*)-**11a**. $[\alpha]_D = +37.7$ ($CHCl_3$, $c = 0.15$). IR (KBr): 3371*m* (br.), 3068*w*, 2982*w*, 2942*w*, 2640*w* (br.), 1716*s*, 1523*w*, 1455*w*, 1399*w*, 1369*w*, 1254*m*, 1162*m*, 1074*w*. ^{1}H-NMR ($CDCl_3$, 250 MHz): 7.45–7.25 (*m*, 5 arom. H); 6.19 (br. *s*, NH); 5.50 (br. *s*, NH); 5.12 (*s*, PhCH_2O); 3.7–3.45 (*m*, CH_2NHZ); 1.53 (*s*, Me); 1.46 (*s*, *t*-Bu). ISN-MS: 351.3 (100, $[M - H]^-$), 277.3 (20).

Enantiomer (S)-**11a**. From (*S*)-**10a** (400 mg, 1.59 mmol) as described for (*R*)-**11a**: 459 mg (82%) of (*S*)-**11a**. $[\alpha]_D = -37.0$ ($CHCl_3$, $c = 0.2$). Spectral data: in agreement with those of (*R*)-**11a**.

*(R)-2-[(Benzyloxy)carbonylaminomethyl]-2-[(*tert*-butoxy)carbonylamino]-4-methylpentanoic Acid* ((*R*)-**11b**). As described for (*R*)-**11a**, with (*R*)-**10b** (350 mg, 1.19 mmol), CH_2Cl_2 (6.5 ml), chlorotrimethylsilane (0.38 ml, 2.97 mmol; 1 h at 60°), (i-Pr)$_2$NEt (0.55 ml, 3.21 mmol), and di(*tert*-butyl)dicarbonate (519 mg, 2.38 mmol) in CH_2Cl_2 (1.5 ml; 20 h at 60°). Extraction with Et_2O (50 ml) and reextraction with AcOEt (2 × 50 ml). The white solid was dried under high vacuum: 397 mg (84.6%) of (*R*)-**11b**. M.p. 154.5°. $[\alpha]_D = -14.0$ (MeOH, $c = 0.1$). IR (KBr): 3421*m*, 3326*m*, 2966*m*, 2623*w* (br.), 1740*s*, 1699*s*, 1559*m*, 1497*s*, 1446*m*, 1403*m*, 1320*m*, 1272*s*, 1156*s*, 1067*m*, 740*w*, 697*w*, 546*w*. ^{1}H-NMR ((D$_6$)DMSO, 250 MHz): 12.80 (*s*, 1 COOH); 7.45–7.25 (*m*, 5 arom. H); 7.2–7.05 (*m*, N*H*CH$_2$); 6.31 (*s*, 1 NH); 5.1–4.9 (*m*, PhCH_2O); 3.55–3.4 (*d*, NHCH_2); 1.85–1.7 (*m*, 1 aliph. H); 1.7–1.5 (*m*, 2 aliph. H); 1.36 (*s*, *t*-Bu); 0.9–0.75 (*m*, *M*e$_2$CH). ISN-MS: 393 (100, $[M-H]^-$).

Enantiomer (S)-**11b**. From (*S*)-**10b** (350 mg, 1.19 mmol) as described for (*R*)-**11b**: 386 mg (82.3%) of (*S*)-**11b**. White solid. A small sample was recrystallized from MeCN for analysis. M.p. 159.8–160°. $[\alpha]_D = +15.0$ (MeOH, $c = 0.1$). ^{1}H-NMR, IR, and MS: in close agreement with those of (*R*)-**11b**.

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