78. Versatile Stereoselective Synthesis of Completely Protected Trifunctional α-Methylated α-Amino Acids Starting from Alanine

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A new route to completely protected α-methylated α-amino acids starting from alanine is described (see *Scheme*). These derivatives, which are obtained *via* base-catalyzed opening of the oxazolidinones (2*S*,4*R*)- and (2*R*,4*S*)-**2**, can be directly employed in peptide synthesis. The synthesis of both enantiomers of Z-protected α-methylaspartic acid β-(*tert*-butyl)ester (O^4-(*tert*-butyl) hydrogen 2-methylaspartates (*R*) or (*S*)-**4a**), α-methylglutamic acid γ-(*tert*-butyl) ester (O^5-(*tert*-butyl) hydrogen 2-methylglutamate (*R*)- or (*S*)-**4b**), and of N^6-bis-Boc-protected α-methyllysine (N^6,N^6-bis[(*tert*-butyloxy)carbonyl]-2-methyllysine (*R*)- or (*S*)-**4c**) is described in full detail.

Introduction. – In recent years, the *de novo* design of peptides and proteins with predetermined secondary and tertiary structures has rapidly become a subject of major interest and importance in the area of bioorganic chemistry [1]. One of the chemical tools that are potentially available for structure stabilization in peptides is the incorporation of α-methylated α-amino acids [2]; due to severe restrictions of the rotational freedom around their N–C(α) and C(α)–C=O bond [3], α-methylated α-amino acids may be generally expected to display helix-inducing properties, as has been explicitly demonstrated for 2-aminoisobutyric acid (Aib) [4] and (*S*)-2-amino-2-methylbutyric acid = (*S*)-isovaline; (*S*)-Iva [2a, b]. However, although several routes for the stereoselective synthesis of these conformationally restricted amino acids have been reported over the last few years [5], we found that a convenient method for the direct synthesis of enantiomerically pure protected derivatives, which are crucial for the incorporation of these unusual building blocks into peptides, is still missing[2]). We have, therefore, now developed a simple but versatile synthetic procedure for the preparation of chiral α-methylated amino acids that are suitably protected for use in peptide synthesis.

Results and Discussion. – The *Scheme* shows our general strategy for the synthesis of the above compounds, which takes advantage of the 'principle of self reproduction of chirality centers' introduced by *Seebach* and coworkers [5b], a method displaying several advantageous features. The starting material in all our syntheses was either D- or L-alanine, depending on which enantiomer of the α-methylated amino acid was desired[3]).

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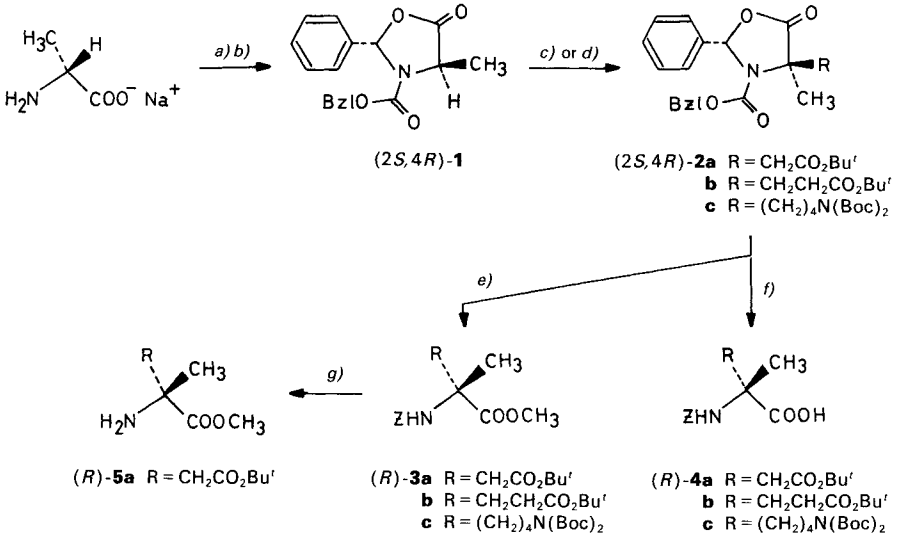
[2]) We have reported previously the synthesis of H-(*S*)-Ser(2-Me-*O*-Bu^t)-OH starting from the α-methylated α-amino acid [6].

[3]) Only the synthesis starting from D-alanine is described in the *General Part*; for the analogous enantiomeric series starting from L-alanine, see *Exper. Part*.

Scheme[3])



Boc = (*tert*-butyloxy)carbonyl; Z = (benzyloxy)carbonyl

a) Benzaldehyde, CH_2Cl_2, reflux.

b) Benzyl chloroformate, 0° to r.t.

c) LHMDS or LDA, alkyl halide, –78° for 3 h, then to r.t. over night.

d) LDA; $CH_2 = CHCO_2Bu^t$ –78° for 3 h, then to r.t. over night.

e) 2 Equiv. of NaOH or LiOH, MeOH/H_2O 10:1, r.t., 30 min.

f) 2 Equiv. of NaOH or LiOH, MeOH/H_2O 1:1, 45°, 1 h.

g) H_2, Pd/C, MeOH, 1 h, r.t.

D-Alanine was first converted to the *Schiff* base with benzaldehyde followed by cyclization to the oxazolidinone (2*S*,4*R*)-**1** by addition of benzyl chloroformate. Alkylations of (2*S*,4*R*)-**1** were performed with lithium bis(trimethylsilyl)amide (LHMDS) or lithium diisopropylamide (LDA) as base and *tert*-butyl bromoacetate [7] and $I(CH_2)_4N(Boc)_2$ as electrophiles; they proceeded with excellent stereoselectivity[4]) with attack of the electrophile from the face opposite to the phenyl group (→(2*S*,4*R*)-**2a** and (2*S*,4*R*)-**2c**, resp.). Oxazolidinone (2*S*,4*R*)-**2b**, the precursor for the α-methylglutamic acid γ-(*tert*-butyl) ester, was synthesized *via Michael* addition of *tert*-butyl acrylate to (2*S*,4*R*)-**1**. Product (2*S*,4*R*)-**2b** was formed in low yield (26%) but with high diastereoselectivity[5]). Addition of DMPU (*N*,*N*′-dimethylpropyleneurea) [8] suppressed the 1,4-addition almost quantitatively, an effect that had also been observed previously by *Seebach* and coworkers [9].

Oxazolidinone (2*S*,4*R*)-**2b** could be crystallized, and a computer-generated drawing of the X-ray structure is given in the *Figure*. Crystals of (2*S*,4*R*)-**2b** grown from Et_2O/pen-

[4]) Only one diastereoisomer could be detected by NMR spectroscopy of the purified oxazolidinones (2*S*,4*R*)-**2a** and (2*S*,4*R*)-**2c** and of their enantiomers. At a later stage, the diastereoisomeric purity of dipeptides Fmoc-Ala-X-OH (X = (*S*)-Asp(2-Me), (*R*)-Asp(2-Me), (*S*)-Lys(2-Me), (*R*)-Lys(2-Me)) was shown to be > 99% by HPLC. The synthesis of the peptides incorporating these α-methylated amino acids will be published elsewhere.

[5]) Only one diastereoisomer could be detected by NMR spectroscopy of the purified oxazolidinone (2*S*,4*R*)-**2b** and of its enantiomer. At a later stage, the diastereoisomeric purity of dipeptides Fmoc-Ala-X-OH (X = (*S*)-Glu(2-Me), (*R*)-Glu(2-Me)) was shown to be 98% by HPLC.

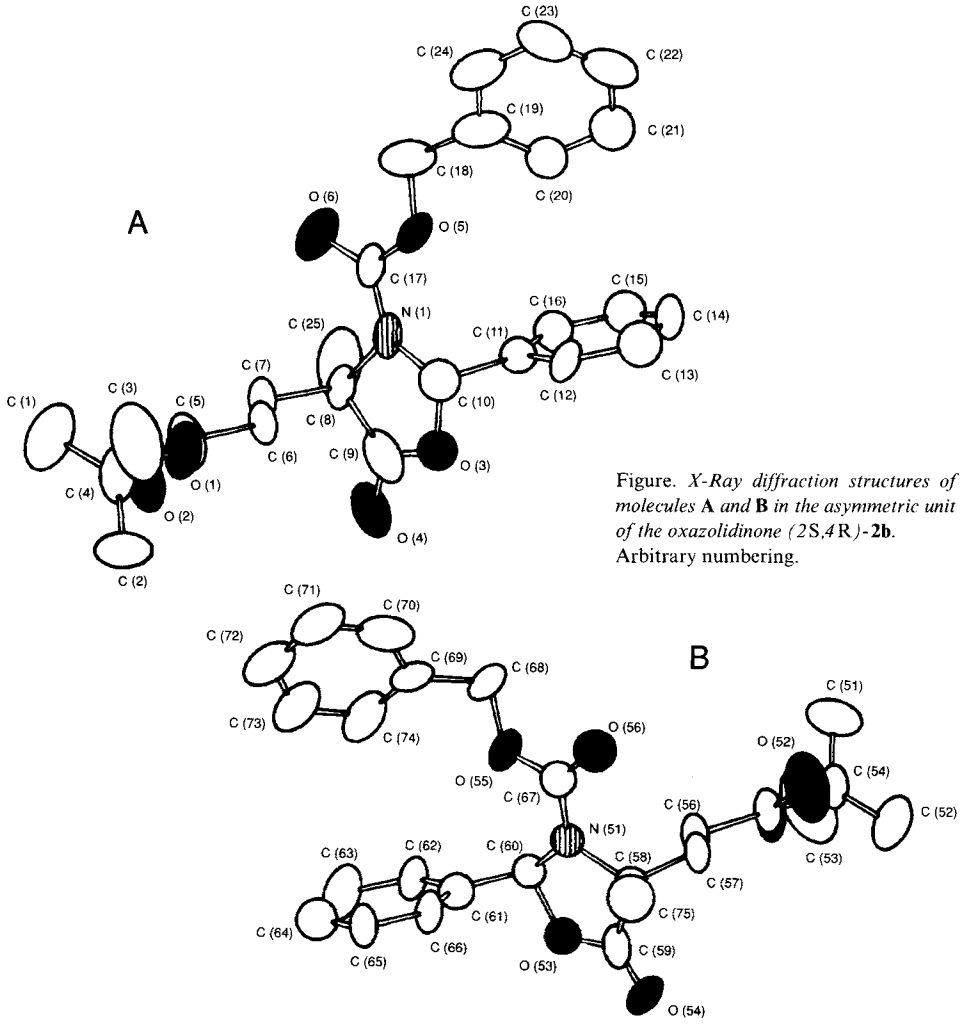


Figure. *X-Ray diffraction structures of molecules* **A** *and* **B** *in the asymmetric unit of the oxazolidinone (2S,4R)-***2b**. Arbitrary numbering.

tane are triclinic, space group $P1$, containing two molecules (**A** and **B**) per asymmetric unit. The structure was solved routinely using direct methods[6]). The results of the X-ray structural analysis confirm our stereochemical assignments of oxazolidinones (2*S*,4*R*)-**2a**–**c**, which were originally inferred from the crystal structure of a related oxazolidinone

[6]) Crystal data for oxazolidinone (2*S*,4*R*)-**2b**: $C_{25}H_{29}NO_6$, triclinic, space group $P1$ with $a = 13.743(2)$, $b = 9.817(1)$, $c = 9.906(1)$ Å, $\alpha = 112.0(1)°$, $\beta = 98.4(1)$, $\gamma = 99.8(1)°$; $Z = 2$, $D_c = 1.24$ gr·cm^{-3}. On a *Philips PW 1100* diffractometer, 5684 reflections were collected in the Θ–2Θ scan mode to $2\Theta = 56°$, using graphite-monochromatized Mo$K\alpha$ radiation ($\lambda = 0.7107$ Å). The structure was solved by direct methods using the SHELXS 86 program and refined by blocked least squares. The thermal parameters of all non-H-atoms were anisotropic. H-Atoms, partially found on a ΔF map and partially calculated were not refined. The final conventional R factor was 0.066 for the 1988 reflections considered observed [$F > 7\sigma(F)$]; R_w was 0.07 with $w = 1/(\sigma^2 F + 0.0018F^2)$. Refined atomic coordinates, anisotropic displacement parameters, bond lengths and angles have been deposited with the *Cambridge Crystallographic Data Centre*.

[5c] prepared by the same method. Further conformation came from the comparison of the optical rotation of (*S*)-2-methylaspartic acid (obtained from (*S*)-**4a** by hydrogenation and subsequent treatment with CF_3COOH) with literature data [10].

Key step in our synthesis is the base-promoted ring opening of the oxazolidinones (2*S*,4*R*)-**2** leading to protected amino-acid derivatives (*R*)-**3** and (*R*)-**4**[3]) which was carried out with NaOH [11] or LiOH in MeOH/H_2O mixtures. Depending on the reaction conditions, the Z-protected amino-acid esters (*R*)-**3a–c** or the Z-protected amino acids (*R*)-**4a–c** could be obtained selectively. Catalytic hydrogenation of (*R*)-**3a** gave access to the amino-acid ester (*R*)-**5a** in quantiative yield.

We are currently extending this new approach to protected derivatives of other trifunctional α-methylated α-amino acids. At the same time, we are synthesizing peptides containing different α-methylated α-amino acids in order to evaluate the putative β-turn and helix-stabilizing properties of these unusual building blocks.

Experimental Part

1. *General.* Reagents and solvents were purified by standard procedures [12]. All reactions involving Li derivatives were carried out under Ar. All chemicals (unless otherwise noted) were purchased from *Fluka AG*, Buchs, Switzerland. TLC: *Merck* precoated silica gel *60 F-254* plates; detection with UV light (254 nm) if possible, and/or by development with 20% phosphomolybdic acid in EtOH and/or Cl_2/starch/KI. Flash chromatography (FC): silica gel *60* (230–400 mesh; 0.04–0.063 mm, *Merck*); according to [13]. HPLC analysis: *Waters* HPLC system; *Vydac* C_{18} column (25 × 0.4 cm) using H_2O (0.09% of CF_3COOH)/90% aq. MeCN (0.09% of CF_3COOH) as eluants. M.p.: uncorrected. $[\alpha]_D$: *Perkin-Elmer-241* polarimeter. ^{1}H-NMR and ^{13}C-NMR spectra: *Bruker-250-FT* (250 MHz) and *Bruker-WH-360-FT* (360 MHz) spectrometer; δ in ppm rel. to TMS, *J* in Hz. MS: *Nermag R 10-10C* (chemical ionisation (CI)) and *Finnigan-1020* (fast-atom bombardement (FAB)) mass spectrometer.

2. *(2S,4R)-3-[(Benzyloxy)carbonyl]-4-methyl-2-phenyl-1,3-oxazolidin-5-one* ((2*S*,4*R*)-**1**). To a suspension of 12.5 g (0.112 mol) of sodium D-alaninate in 500 ml of dry CH_2Cl_2, 11.31 ml (0.112 mol) of benzaldehyde were added, and the mixture was refluxed using a *Dean-Stark* apparatus for 21 h. It was then cooled to 0°, 14 ml (0.110 mol) of benzyl chloroformate were added, and stirring was continued at 0° for 5 h and then overnight at 25°. The solvent was evaporated, the resulting residue dissolved in 500 ml of AcOEt and successively washed with 5% $NaHCO_3$ soln., 5% $KHSO_4$ soln., and H_2O. The org. layer was dried (Na_2SO_4) and evaporated. The crude product (a yellow oil) was dried under high vacuum and analyzed by ^{1}H-NMR and HPLC: *cis*/*trans*-isomers 1:2.5. Although the *cis*- and *trans*-isomers were not separable by TLC, other impurities were efficiently removed by FC with CH_2Cl_2/pentane 1:1. Separation of the two isomers was subsequently achieved by crystallization from $(i\text{-}Pr)_2O$ at −18° yielding 9.8 g (30.5%) of pure *trans*-oxazolidinone (2*S*,4*R*)-**1**. M.p. 77.3–78.4° $[\alpha]_D^{25} = -85.77$ (*c* = 0.56, CH_2Cl_2). ^{1}H-NMR ($C_2D_2Cl_4$, 60°): 7.45–6.90 (*m*, 10 arom. H); 6.47 (*s*, H–C(2)); 5.10–4.92 (*m*, $PhCH_2$); 4.51 (*q*, *J* = 6.8, H–C(4)); 1.67 (*d*, *J* = 6.8, Me–C(4)). ^{13}C-NMR ($C_2D_2Cl_4$, 60°): 172.07; 151.80; 136.47; 135.20; 129.96; 128.76; 128.35; 128.14; 127.74; 126.36; 89.29; 67.46; 51.95; 16.90. FAB-MS ($C_{18}H_{17}NO_4$ (311.34)): 312 ($[M + 1]^+$).

3. *Alkylations of Oxazolidinone Enolates with Alkyl Halides. General Procedure A.* A soln. of 10 mmol of 1,1,1,3,3,3-hexamethyldisilazane (HMDS) in 40 ml of THF was cooled to −78°, and 6.25 ml of 1.6M BuLi were added dropwise. The resulting soln. was stirred for 10 min at −78° and then transferred (*via* cannula) to a precooled (−78°) soln. of 7.5 mmol of oxazolidinone (2*S*,4*R*)-**1** in 40 ml of THF. The slightly yellow enolate soln. was stirred for 5–10 min at −78°, and then 9 mmol of alkyl halide were added. The mixture was stirred for 3 h at −78° and then allowed to warm to r.t. over night. THF was evaporated, the residue partioned between sat. aq. NH_4Cl soln. and Et_2O, the aq. layer separated and extracted twice with Et_2O, and the combined ether extract dried (Na_2SO_4) and evaporated to give the crude product. *General Procedure B.* As described in *General Procedure A*, but with $(i\text{-}Pr)_2NH$ instead of HMDS. The addition of DMPU [10] (10–12 ml) to the mixture in *Procedure A* or *B* had no effect on yields.

(2S,4R)-3-[(Benzyloxy)carbonyl]-4-{[(tert-butyloxy)carbonyl]methyl}-4-methyl-2-phenyl-1,3-oxazolidin-5-one ((2*S*,4*R*)-**2a**). From (2*S*,4*R*)-**1** and *tert*-butyl bromoacetate according to *Procedure A*. FC (toluene/AcOEt

10:1→10:0.5) of the crude product yielded 76% of (2*S*,4*R*)-**2a**. Colourless oil. ^{1}H-NMR ($C_2D_2Cl_4$, 60°): 7.58–6.77 (*m*, 10 arom. H); 6.49 (*s*, H–C(2)); 5.21–4.89 (*m*, PhCH_2); 3.68 (*d*, *J* = 7, 1 H, CH_2–C(4)); 2.92 (*d*, *J* = 7, 1 H, CH_2–C(4)); 1.75 (*s*, Me–C(4)); 1.42 (*s*, *t*-Bu). ^{13}C-NMR ($C_2D_2Cl_4$, 60°): 173.80; 168.93; 151.97; 136.96; 135.50; 129.72; 128.64; 128.47; 128.21; 127.83; 127.00; 89.81; 81.97; 67.48; 59.75; 41.65; 28.19; 28.06. FAB-MS ($C_{24}H_{27}NO_6$ (425.48)): 426 ([*M* + 1]$^+$).

*(2S,4R)-3-[(Benzyloxy)carbonyl]-4-{4-{bis[(*tert*-butyloxy)carbonyl]amino}butyl}-4-methyl-2-phenyl-1,3-oxazolidin-5-one* ((2*S*,4*R*)-**2c**). From (2*S*,4*R*)-**1** and *N*,*N*-bis[(*tert*-butyloxy)carbonyl]-4-iodobutanamine ($I(CH_2)_4N(Boc)_2$) according to *Procedure B*. FC (100% toluene→toluene/AcOEt 10:0.3) of the crude product yielded 76% of (2*S*,4*R*)-**2c**. Colourless oil. ^{1}H-NMR ($C_2D_2Cl_4$, 60°): 7.56–6.75 (*m*, 10 arom. H); 6.50 (*s*, H–C(2)); 5.30–4.82 (*m*, PhCH_2); 3.50 (*t*, CH_2N); 1.98–1.70 (*m*, CH_2); 1.76 (*s*, Me–C(4)); 1.65–1.40 (*m*, 2 CH_2); 1.52 (*s*, *t*-Bu); 1.30–1.20 (*m*, CH_2). FAB-MS ($C_{32}H_{43}N_2O_8$ (582.74)): 583 ([*M* + 1]$^+$).

4. *(2S,4R)-3-[(Benzyloxy)carbonyl]-4-{[(*tert*-butyloxy)carbonyl]ethyl}-4-methyl-2-phenyl-1,3-oxazolidin-5-one* ((2*S*,4*R*)-**2b**). A soln. of 1.12 ml (8 mmol) of (i-Pr)$_2$NH in 40 ml of THF was cooled to −78°, and 5 ml of 1.6M BuLi in hexane were added dropwise. The resulting soln. was stirred for 10 min at −78° and then transferred *via* cannula to a precooled soln. of 2.35 g (7.5 mmol) of (2*S*,4*R*)-**1**. The dark yellow enolate soln. was stirred for 10 min at 78°, and then 1.2 ml (8 mmol) of *tert*-butyl acrylate were added, resulting in an immediate decolourisation of the enolate soln. The mixture was stirred for 3 h at −78° and then allowed to warm to r.t. overnight. THF was evaporated, the residue partitioned between sat. aq. NH_4Cl soln. and Et_2O, the aq. layer separated and twice extracted with Et_2O, and the combined org. extract dried (Na_2SO_4) and evaporated. FC (100% toluene→toluene/AcOEt 10:0.3) of the crude product yielded 0.880 g (26.5%) of (2*S*,4*R*)-**2b** as a colourless oil which was crystallized from Et_2O/pentane. M.p. 97.3–98.0°. $[\alpha]_D^{25} = -52.49$ (*c* = 0.65, CH_2Cl_2). ^{1}H-NMR ($C_2D_2Cl_4$, 60°): 7.56–6.76 (*m*, 10 arom. H); 6.51 (*s*, H–C(2)); 5.08 (*m*, PhCH_2); 2.62 (br. *s*, CH_2–C(4)); 2.20 (br. *s*, CH_2); 1.75 (*s*, Me–C(4)); 1.50 (*s*, *t*-Bu). ^{13}C-NMR ($C_2D_2Cl_4$, 60°): 174.8; 172.5; 129.1; 128.2; 128.1; 81.2; 66.9; 59.9; 53.2; 32.2; 30.8; 28.5; 23.7. CI-MS ($C_{25}H_{29}NO_6$ (439.38)): 440 ([*M* + 1]$^+$).

5. *General Procedure C for the Preparation of* N$^\alpha$*-(Benzyloxycarbonyl)-α-methyl-Substituted α-Amino Acid Methyl Esters* (R)-**3**. To a soln. of oxazolidinone (2*S*,4*R*)-**2** in 8–10 ml of MeOH were added 2 equiv. of 4N aq. NaOH (or LiOH), and the mixture was stirred at r.t. for 30 min. It was then diluted with 50 ml of H_2O, and the aq. layer was extracted 3 times with AcOEt. The combined org. extracts were dried (Na_2SO_4) and evaporated to give the crude product.

O^4-(tert-*Butyl*) O^1-*Methyl* (R)-N^2-*[(Benzyloxy)carbonyl]-2-methylaspartate* (Z-(*R*)-Asp(2-Me,*O*-Bu^t)-OMe; (*R*)-**3a**) was obtained according to the *General Procedure C* from 3 g (7 mmol) of (2*S*,4*R*)-**2a** using LiOH. The crude product was purified by FC (toluene/AcOEt/AcOH 100:10:1): 2.45 g (81%) of (*R*)-**3a**, which was crystallized from pentane. M.p. 42.1–43.2°. $[\alpha]_D^{25} = +12.04$ (*c* = 0.30, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$): 7.31 (*s*, 5 arom. H); 6.10 (br. *s*, NH); 5.08 (*s*, PhCH_2); 3.70 (*s*, CO_2CH_3); 3.21 (*d*, *J* = 7.0, 1 H, CH_2(3)); 2.92 (*d*, *J* = 7, 1 H, CH_2(3)); 1.60 (*s*, *t*-Bu). ^{13}C-NMR ($CDCl_3$): 177.9; 169.6; 154.0; 136.1; 129.8; 128.3; 81.8; 61.4; 57.4; 42.1; 28.0; 23.1. CI-MS ($C_{18}H_{25}NO_6$ (337.18)): 338 ([*M* + 1]$^+$).

O^5-(tert-*Butyl*) O^1-*Methyl* (R)-N^2-*[(Benzyloxy)carbonyl]-2-methylglutamate* (Z-(*R*)-Glu(2-Me,*O*-Bu^t)-OMe; (*R*)-**3b**) was obtained according to the *General Procedure C* from 4.39 g (10 mmol) of (2*S*,4*R*)-**2b** using LiOH. The crude product was purified by FC (toluene/AcOEt/AcOH 100:10:1): 2.84 g (78%) of (*R*)-**3b**. Colourless oil. $[\alpha]_D^{25} = +3.75$ (*c* = 0.80, MeOH). ^{1}H-NMR ($CDCl_3$): 7.36 (*s*, 5 arom. H); 5.78 (br. *s*, NH); 5.10 (*s*, PhCH_2); 3.75 (*s*, CO_2CH_3); 2.48–2.05 (*m*, 2 CH_2); 1.59 (*s*, Me–C(2)); 1.45 (*s*, *t*-Bu). ^{13}C-NMR ($CDCl_3$): 174.5; 172.3; 128.9; 128.2; 81.1; 71.9; 60.0; 53.2; 32.1; 28.8; 23.7. CI-MS ($C_{19}H_{25}NO_6$ (365.42)): 366 ([*M* + 1]$^+$).

Methyl (R)-N^2-*[(Benzyloxy)carbonyl]*-N^6,N^6-*bis[(*tert*-butyloxy)carbonyl]-2-methyllysine* (Z-(*R*)-Lys(2-Me,*N*,*N*-Boc_2)-OMe; (*R*)-**3c**) was obtained according to the *General Procedure C* from 2.32 g (4 mmol) of (2*S*,4*R*)-**2c** using LiOH. The crude product was purified by FC (toluene/AcOEt/AcOH 100:10:1): 1.58 g (78%) of (*R*)-**3c**. Colourless oil. $[\alpha]_D^{25} = +3.84$ (*c* = 0.26, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$): 7.29 (*s*, 5 arom. H); 5.65 (br. *s*, NH); 5.08 (*s*, PhCH_2); 3.70 (*s*, CO_2CH_3); 3.50 (*t*, CH_2N); 1.78 (*m*, 1 H, CH_2); 1.75 (*m*, 1 H, CH_2); 1.53 (*s*, Me–C(2)); 1.49 (*s*, 2 *t*-Bu); 1.52–1.45 (*m*, CH_2); 1.07–1.02 (*m*, CH_2). CI-MS ($C_{26}H_{40}NO_8$ (508.57)): 509 ([*M* + 1]$^+$).

6. *General Procedure D for the Preparation of* N$^\alpha$*-(Benzyloxycarbonyl)-α-methyl-Substituted α-Amino Acids* (R)-**4**. To a soln. of 5 mmol of oxazolidinone (2*S*,4*R*)-**2** in 4 ml of MeOH were added 2 equiv. of 2N aq. NaOH (or LiOH); and the mixture was stirred for 1 h at 45°. It was then diluted with 50 ml of H_2O, and the aq. layer was extracted 3 times with Et_2O. The aq. layer was cooled to 0° and the pH adjusted to 3 with 2N HCl. The acidic aq. soln. was extracted 5 times with AcOEt, the org. layers were combined, dried (Na_2SO_4), and evaporated.

O^4-*(*tert-*Butyl) Hydrogen (*R*)-N^2-[(Benzyloxy)carbonyl]-2-methylaspartate* (Z-(*R*)-Asp(2-Me,*O*-Bu^t); (*R*)-**4a**) was obtained according to the *General Procedure D* from 3 g (7 mmol) of (2*S*,4*R*)-**2a** using LiOH. The crude product was purified by FC (toluene/AcOEt/AcOH 100:20:3): 1.80 g (76%) of (*R*)-**4a**, which was crystallized from $CHCl_3$/pentane. M.p. 88.2–89°. $[\alpha]_D = -3.84$ (*c* = 0.26, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$): 7.31 (*s*, 5 arom. H); 6.10 (br. *s*, NH); 5.09 (*d*, PhCH_2); 3.12 (*d*, *J* = 7.0, 1 H, CH_2(3)); 2.92 (*d*, *J* = 7, 1 H, CH_2(3)); 1.69 (*s*, Me–C(2)); 1.40 (*s*, *t*-Bu). ^{13}C-NMR ($CDCl_3$): 177.9; 169.6; 154.0; 136.1; 129.9; 128.1; 128.0; 81.8; 61.9; 57.5; 42.1; 27.9; 23.2. CI-MS ($C_{17}H_{23}NO_6$ (337.35)): 338 ([*M* + 1]$^+$).

O^5-*(*tert-*Butyl) Hydrogen (*R*)-N^2-[(Benzyloxy)carbonyl]-2-methylglutamate* (Z-(*R*)-Glu(2-Me,*O*-Bu^t); (*R*)-**4b**) was obtained according to the *General Procedure D* from 3.10 g (7 mmol) of (2*S*,4*R*)-**2b** using NaOH. The crude product was purified by FC (toluene/AcOEt/AcOH 100:20:3): 1.9 g (77%) of (*R*)-**4b**. Colourless oil. $[\alpha]_D^{25} = -1.15$ (*c* = 0.70, CH_2Cl_2). ^{1}H-NMR ($CDCl_3$): 7.35 (*s*, 5 arom. H); 5.98 (br. *s*, NH); 5.08 (*s*, PhCH_2); 2.42–2.07 (*m*, CH_2(3), CH_2(4)); 1.60 (*s*, Me–C(2)); 1.42 (*s*, *t*-Bu). CI-MS ($C_{18}H_{25}NO_6$(351.22)): 352 ([*M* + 1]$^+$).

*(*R*)-N^2-[(Benzyloxy)carbonyl]-N^6,N^6-bis[(*tert-*butyloxy)carbonyl]-2-methyllysine* (Z-(*R*)-Lys(2-Me,*N*,*N*, Boc_2); (*R*)-**4c**) was obtained according to the *General Procedure D* from 5.83 g (10 mmol) of (2*S*,4*R*)-**2c** using NaOH. The crude product was purified by FC (toluene/AcOEt/AcOH 100:20:3): 3.13 g (63.5%) of (*R*)-**4c**, which was crystallized from $CHCl_3$/pentane. M.p. 215–219° (dec.). $[\alpha]_D^{25} = +7.12$ (*c* = 0.66, MeCN). ^{1}H-NMR ($CDCl_3$): 7.32 (*s*, 5 arom. H); 5.72 (br. *s*, NH); 5.10 (*s*, PhCH_2); 3.51 (*t*, CH_2N); 2.38–1.10 (*m*, 3 CH_2); 1.50 (*s*, 2 *t*-Bu). CI-MS ($C_{25}H_{38}N_2O_8$ (494.63)): 495 ([*M* + 1]$^+$).

7. O^4-*(*tert-*Butyl) O^1-Methyl (*R*)-2-Methylaspartate* ((*R*)-Asp(2-Me,*O*-Bu^t)-OMe; (*R*)-**5a**). To a soln. of 125 mg (0.37 mmol) of (*R*)-**3a** in 3 ml of MeOH, 22.5 mg of 10% Pd/C was added. The mixture was hydrogenated for 1 h, then the catalyst was filtered and the solvent evaporated. The product was briefly dried under high vacuum (caution, (*R*)-**5a** is extremely volatile): 76.5 mg (95%) of (*R*)-**5a**. ^{1}H-NMR ($CDCl_3$): 3.72 (*s*, CO_2CH_3); 2.90 (*d*, *J* = 6.0, 1 H, CH_2(3)); 2.50 (*d*, *J* = 6.0, 1 H, CH_2(3)); 2.02 (br. *s*, NH_2); 1.43 (*s*, *t*-Bu); 1.32 (*s*, Me–C(2)). CI-MS ($C_{10}H_{19}NO_4$ (217.12)): 218 ([*M* + 1]$^+$).

8. N,N-*Bis[(*tert-*butyloxy)carbonyl]-4-iodobutanamine* (= *Di(*tert-*butyl) [(4-Iodobutyl)imino]dicarboxylate;* $I(CH_2)_4N(Boc)_2$). To 5 g of di(*tert*-butyl) iminodicarboxylate in 10 ml of EtOH were added 1.3 g (23 mmol) of KOH in 10 ml of EtOH. The mixture was stirred for 40 min at r.t., and the product was precipitated with dry Et_2O, collected by filtration, and dried under high vacuum. 5.75 g (98%) of di(*tert*-butyl) (potassioimino)dicarboxylate which was directly used for the next step without further purification. To a soln. of 5.75 g (22.5 mmol) of the K salt in 12 ml of DMF and 50 ml of dry CH_2Cl_2, 2.95 ml (25 mmol) of 1,4-dibromobutane were added, and the mixture was stirred for 3.5 h at 50°. After cooling to r.t., the mixture was filtered and the CH_2Cl_2 evaporated. The residue was taken up in 350 ml of AcOEt and washed with brine. The org. layer was dried ($MgSO_4$) and evaporated. Purification by FC (pentane/Et_2O 1:1) yielded 6.2 g (78.2%) of the bromide as a colourless oil. Conversion of the bromide to the iodide was carried out in 15 ml of dry acetone with 3.75 g (25 mmol) of NaI. The mixture was stirred for 24 h at r.t. in the dark, then the acetone was evaporated and the residue dissolved in 350 ml of Et_2O. The soln. was washed with H_2O, dried ($MgSO_4$), and evaporated. The residual oil was purified by short-column chromatography (Et_2O/penante 1:1): 6.2 g (88%) of the title compound, colourless oil.

Data of N,N-*Bis[(*tert-*butyloxy)carbonyl]-4-bromobutanamine:* ^{1}H-NMR ($CDCl_3$): 3.60 (*t*, CH_2N); 3.40 (*t*, CH_2Br); 1.88 (*m*, CH_2); 1.72 (*m*, CH_2); 1.50 (*s*, 2 *t*-Bu). CI-MS ($C_{14}H_{26}NO_4Br$ (352.207)): 352 (M^+), 354 ([*M* + 2]$^+$).

Data of N,N-*Bis[(*tert-*butyloxy)carbonyl]-4-iodobutanamine.* ^{1}H-NMR ($CDCl_3$): 3.60 (*t*, CH_2); 3.18 (*t*, CH_2I); 1.80 (*m*, CH_2); 1.72 (*m*, CH_2); 1.50 (*s*, 2 *t*-Bu). CI-MS ($C_{14}H_{26}NO_4I$ (399.203)): 400 ([*M* + 1]$^+$).

9. *Enantiomeric Series.* Experimental procedures and NMR data for (2*R*,4*S*)-**1**, (2*R*,4*S*)-**2a**–**c**, (*S*)-**3a**–**c**, (*S*)-**4a**–**c**, and (*S*)-**5a** are identical with those provided fro the corresponding enantiomeric compounds (see above).

(2*R*,4*S*)-**1**: M.p. 77.2–78.3°. $[\alpha]_D^{25} = +105.3$ (*c* = 0.45, CH_2Cl_2). (2*R*,4*S*)-**2b**: M.p. 97.4–98.0°. $[\alpha]_D^{25} = +52.96$ (*c* = 0.48, CH_2Cl_2). (*S*)-**3a**: M.p. 42.1–43.2°. $[\alpha]_D^{25} = -13.36$ (*c* = 0.37, CH_2Cl_2). (*S*)-**3b**: $[\alpha]_D^{25} = -8.36$ (*c* = 0.66, MeOH). (*S*)-**3c**: $[\alpha]_D^{25} = -4.63$ (*c* = 0.45, CH_2Cl_2). (*S*)-**4a**: M.p. 88.2–89.0°. $[\alpha]_D^{25} = +4.72$ (*c* = 0.46, CH_2Cl_2). (*S*)-**4b**: $[\alpha]_D^{25} = +1.14$ (*c* = 0.71, CH_2Cl_2). (*S*)-**4c**: M.p. 215–210° (dec.). $[\alpha]_D^{25} = -4.51$ (*c* = 0.27, CH_2Cl_2).

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