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Synthesis of Derivatives of ω-Isocyanato-α-methylamino, ω-Ureido-α-methylamino, and N^{α}-Methyl-α,ω-diamino Acids

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Summary. Homochiral N^{α}-methyl-2,3-diaminopropionic and N^{α}-methyl-2,4-diaminobutyric acid derivatives **8a,b** were obtained *via* a stereoconservative four-step synthesis starting from hexafluoroacetone protected *L*-aspartic and *L*-glutamic acid **2a**,**b**, respectively. Hexafluoroacetone protected ω-isocyanato-α-methylamino acids **4a**,**b** – the key intermediates of the synthesis – are versatile building blocks for amino acid and peptide modification and promising candidates for combinatorial chemistry. Upon reaction with alcohols, compounds **4** give activated N^{ω}-urethane protected ω-amino-α-methylamino acid derivatives **5–7**; upon reaction with amines, ω-ureido-α-methylamino acid derivatives **10–12** and 3-methylamino-pyrrolidin-2-ones **13** are available.

Keywords. Hexafluoroacetone; ω-Isocyanato-α-methylamino acid derivatives; N^{α}-Methyl-2,3-diaminopropionic acid derivatives and homologues; ω-Ureido-α-methylamino acids; 3-Methylamino-pyrrolidin-2-ones.

Introduction

The development of new routes to homochiral non-proteinogenic and non-natural amino acids is of current interest [1]. α-N-Methylamino acids, an interesting subclass of α-amino acids, are constituents of various peptides and depsipeptides isolated from plants, microorganisms, and marine species. Some of them exhibit highly interesting biological properties [2]. Incorporation of α-N-methylamino acids into key positions of peptides and depsipeptides should lead to enhanced proteolytic stability and to an increase in lipophilicity. Furthermore, certain α-N-methylamino acids themselves are biologically active compounds [3]. Consequently, a number of synthetic routes to homochiral α-N-methylamino acids already have been developed [4]. Especially multifunctional amino acids are interesting candidates for templates to construct apeptidic bioactive compounds.

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L-2,3-Diaminopropionic acid and its homologue *L*-2,4-diaminobutyric acid are non-proteinogenic amino acids found in a variety of natural products [5]. Interestingly, the family of anti-methicillin resistant *Staphylococcus aureus* peptide antibiotics TAN-1057 contains *L*-N^{α}-methyl-2,3-diaminopropionic acid [6]. ω-Isocyanato- and ω-ureido-α-methylamino acids and their derivatives are unknown to the best of our knowledge.

Results and Discussion

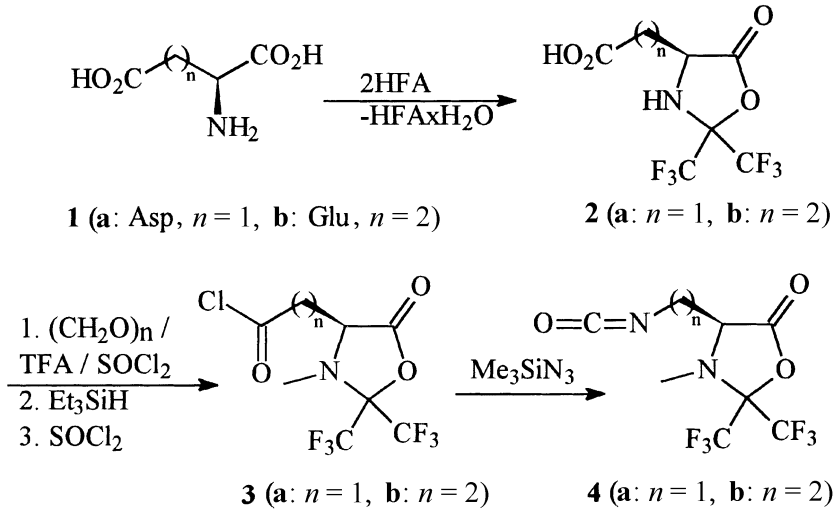
Recently we have described a new protection/activation strategy for α-amino, α-hydroxy, and α-mercapto acids using hexafluoroacetone. Hexafluoroacetone and α-amino acids react to give 2,2-*bis*(trifluoromethyl)-1,3-oxazolidin-5-ones (**1**$\rightarrow$**2**) in high yield [7]. This heterocyclization process results in a simultaneous protection of the α-amino group and the adjacent carboxylic group. Therefore, in the case of ω-carboxy-α-amino acids the α-carboxylic group is regioselectively activated towards nucleophiles [8]. Since the ω-carboxy group remains unaffected, the method can be applied for regioselective α-functionalization of ω-carboxy-α-amino acids. On the other hand, the ω-carboxy group can be selectively activated by transformation into its acid chloride [9].

Furthermore, hexafluoroacetone protected α-amino acids are perfectly suited for N-alkylation. They react in a three-component reaction with paraformaldehyde and thionyl chloride exothermally – without the need of a solvent – to give N-chloromethylamino acid derivatives which can be transformed into the corresponding N-methylamino acid derivatives by treatment with triethylsilane/trifluoroacetic acid in a one-pot procedure [10]. Recently, the N-methylation procedure was successfully applied to ω-carboxy-α-amino acids. Under the reaction conditions used the ω-carboxylic group is transformed into the acid chloride **3**. Compounds **3a**,**b** are distillable liquids and therefore easy to purify [11].

Heating of compounds **3** with trimethylsilyl azide results in the formation of isocyanates **4**. The latter are doubly activated derivatives of N^{α}-methyl-α,ω-diamino acids. Generally, the isocyanate function is more reactive towards nucleophiles than the lactone function. Consequently, compunds **4** can be regioselectively functionalized.

NMR investigations of **4a** show the non-equivalence of the two geminal CF_3 groups. In the ^{1}H NMR spectrum, the NCH_3 group furnishes a quartet ($J = 2$ Hz) caused by a five-bond coupling with one of the CF_3 groups. This coupling manifests itself in the ^{19}F NMR spectrum as a broad quartet at 4.28 ppm, whereas the quartet at -0.57 ppm consists of sharp lines. The ^{13}C NMR spectrum gives a broad singlet for the NCH_3 group at 32.85 ppm and two quartets (120.83 ppm ($^1J_{C,F} = 287$ Hz); 121.98 ppm ($^1J_{C,F} = 295$ Hz)) for the geminal pair of CF_3 groups. All four lines of the first quartet are additionally split into quartets with a very small coupling constant. Remarkably, the signal for the quarternary carbon atom connected to both CF_3 groups at 89.92 ppm is split into a septet. It represents an AB_3C_3 spin system with different coupling constants ($J_{AB} = 32.8$ Hz, $J_{A,C} = 30.1$ Hz) as could be verified by spin simulation.

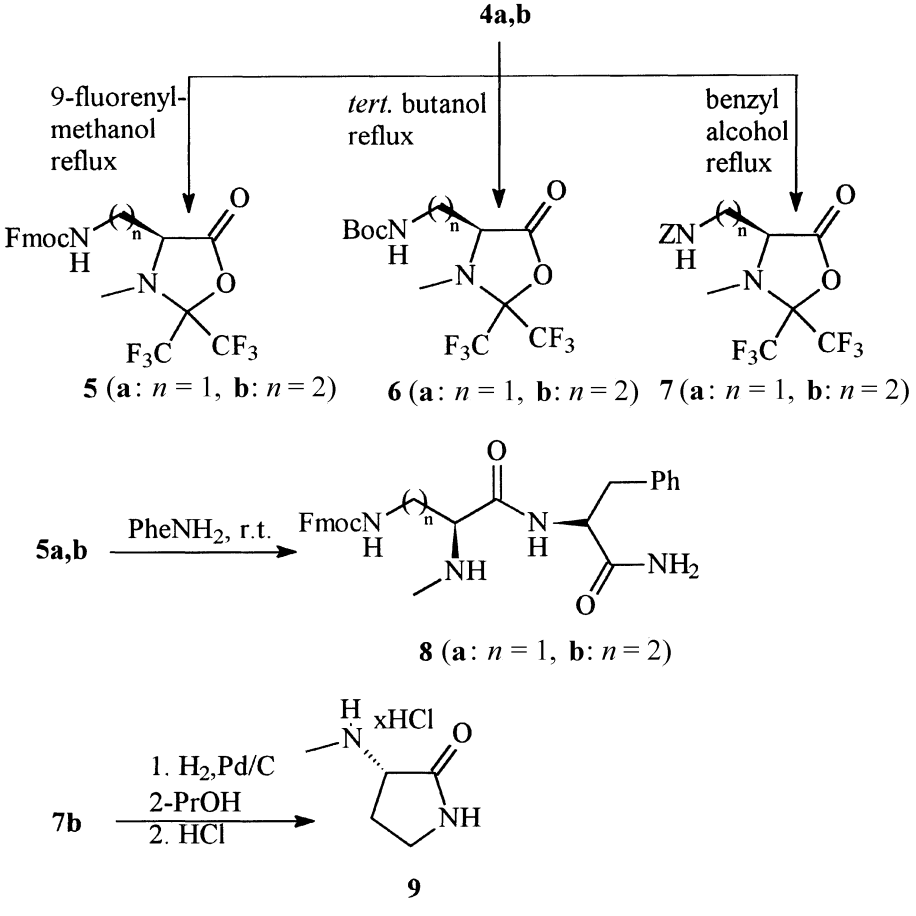
Heating compounds **4** with equimolar amounts of 9-fluorenyl methanol, *tert* butanol, or benzyl alcohol in chloroform gives the N^{ω}-*Fmoc*, N^{ω}-*Boc*, and N^{ω}-*Z* protected carboxy group activated derivatives **5–7** of ω-amino-α-methylamino



1 (**a**: Asp, $n = 1$, **b**: Glu, $n = 2$) **2** (**a**: $n = 1$, **b**: $n = 2$)

3 (**a**: $n = 1$, **b**: $n = 2$) **4** (**a**: $n = 1$, **b**: $n = 2$)

Scheme 1



5 (**a**: $n = 1$, **b**: $n = 2$) **6** (**a**: $n = 1$, **b**: $n = 2$) **7** (**a**: $n = 1$, **b**: $n = 2$)

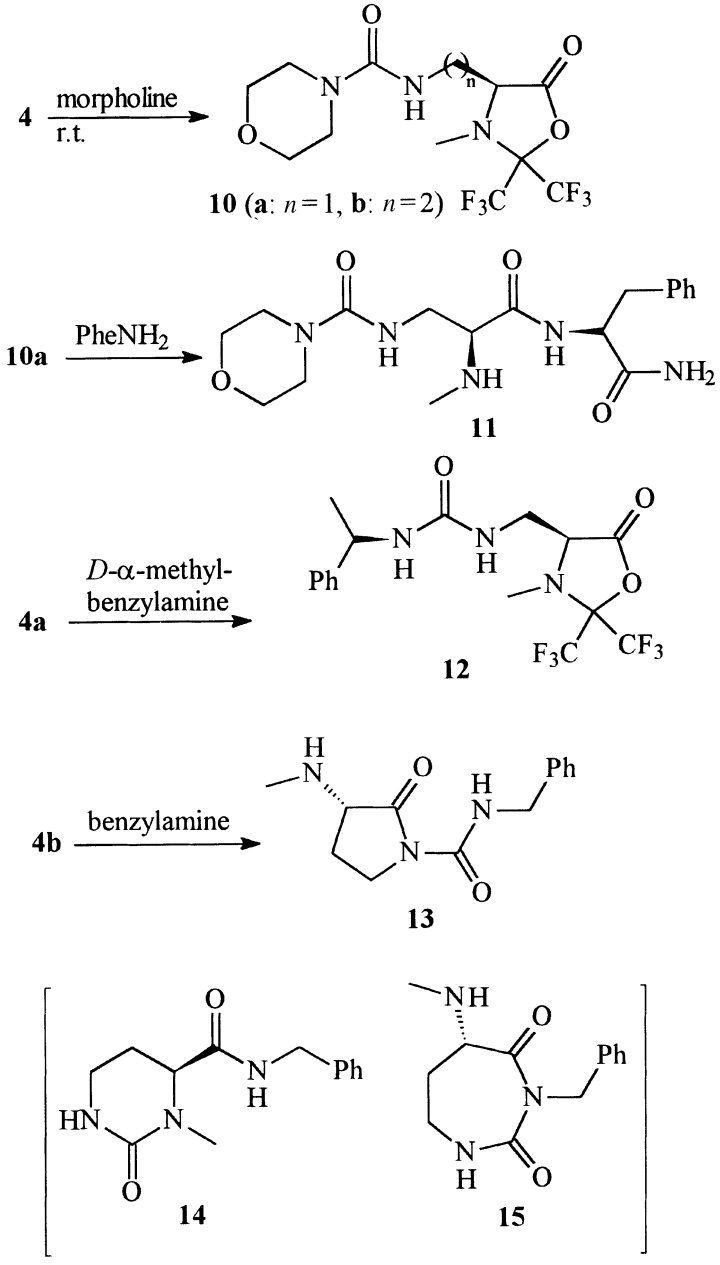
8 (**a**: $n = 1$, **b**: $n = 2$)

9

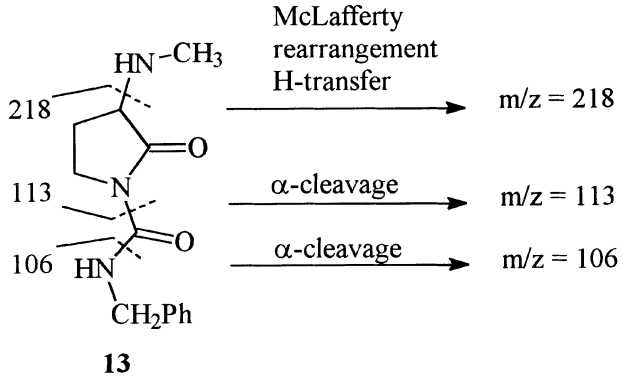
Scheme 2

acids, respectively. Subsequent lactone ring opening by nucleophiles like amino acid amides provides a simple preparative access to N-protected dipeptide derivatives of type **8**. The amide bond formation is connected with deprotection of the methylamino group which can be further functionalized.

When the ω-amino group of **7b** is deblocked hydrogenolytically, a spontaneous intramolecular aminolytic ring cleavage takes place to give 3(*S*)-3-methylamino-pyrrolidin-2-one. The compound is obtained analytically pure as its hydrochloride **9**.



Scheme 3



13

Scheme 4

The structural relationship of **9** with 3(*S*)-3-hydroxypyrrolidin-2-one, a biological active compound which seems to promote the process of human learning [12], is obvious. Compound **9** represents an α-methylamino *GABA* derivative.

Isocyanates **4** and *sec*. amines like morpholine react regioselectively to give ω-ureido-α-methylamino acid derivatives **10a**,**b** which are carboxyl group activated species. Therefore, they can be further functionalized by reaction with nucleophiles (**10a** → **11**).

Likewise, the primary amine *D*-α-methylbenzylamine adds to the isocyanate **4a** to give the ureido substituted α-methylamino acid derivative **12** with an unaffected lactone moiety. In contrast, the adduct first formed from benzylamine and **4b** spontaneously undergoes an intramolecular aminolytical lactone ring opening – similar to reaction **7b** → **9** – to give compound **13**.

The mass spectrum of compound **13** shows a fragmentation pattern similar to pyrrolidin-2-one **9**. The fragment ion $[M\text{-}29]^+$ is the result of a *McLafferty*-type elimination of $[H_2C=NH]$ from the exocyclic methylamino group and is inconsistent with structure **14**. The fragement ions $m/z = 106$ and 113 caused by α-cleavage from the molecular ion can only be explained convincingly with structure **13**. Thus, the alternative structures **14** and **15** can be ruled out.

Compound **13** is a new chiral member of the family of acylureas, some of which exhibit powerful insectizidal properties [13]. The reaction **4b** → **13** is an interesting alternative approach to this class of compounds. All synthetic steps described in this paper proceed stereoconservatively as shown by NMR experiments. Starting from *D*-aspartic and *D*-glutamic acid, the corresponding multifunctional N-methylamino acids of the *D*-series become available by the new strategy.

Experimental

Solvents were purified and dried prior to use. Reagents were used as purchased. Thin layer chromatography (TLC) was performed on alumina plates coated with Merck silica gel 60 F_{254}. Compounds were visualized by spraying with ceric ammonium nitrate in 9 *M* H_2SO_4 followed by heating to 100°C. Column chromatography was carried out on silica gel (32–63 µm, ICN Biomedicals). Melting points were determined with a Boetius heating table. Optical rotation indices $[\alpha]_D$ were measured with a Polartronic polarimeter (Schmidt & Haensch) in a 5 cm cell. For C, H, N

analyses a CHNO-Rapid-Elemental-Analyser (Hereaus) was used. The experimental values agreed satisfactorily with the calculated ones. Mass spectra were recorded on a VG 12-250 (Masslab) electron ionization spectrometer (EI = 70 eV) or by a VG ZAB-HSQ FAB spectrometer. IR spectra were obtained using an FTIR spectrometer (Genesis ATI Mattson). ^{1}H (200.041 or 300.075 MHz), ^{13}C (50.305 or 75.462 MHz), and ^{19}F NMR (188.205 or 282.380 MHz) spectra were recorded with a Varian Gemini 200 or a Varian Gemini 300 spectrometer. Internal *TMS* was used as reference for ^{1}H and ^{13}C NMR spectra, external trifluoroacetic acid for ^{19}F NMR spectra. Starting materials (**2**, **3**) were prepared according to Refs. [8, 11]. Abbreviations used: *DAP* = *L*-2,3-diaminopropionic acid, *DAB* = *L*-2,4-diaminobutyric acid.

3→**4** (*General procedure*)

To a solution of acid chloride **3** (20 mmol) in toluene (25 cm^3), a solution of trimethylsilyl azide (2.9 g, 25 mmol) in toluene (25 cm^3) was added dropwise and stirred at 80°C for several hours until the N_2 evolution ceased. After removal of the solvent the residue was distilled.

(4S)-4-Isocyanatomethyl-3-methyl-2,2-bis(trifluoromethyl)-1,3-oxazolidin-5-one (**4a**; $C_8H_6F_6N_2O_3$)

6.27 g (20 mmol) **3a** gave 4.79 g (82%) **4a**. M.p.: ∼r.t.; b.p.: ∼60°C (0.1 mm Hg, *Kugelrohr*); $[\alpha]_D^{25} = +8.7°$ ($c = 6.0$, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ = 2.76 (q, J = 2.0 Hz, 3H, CH_3), 3.57 (dd, ^3J = 2.3 Hz, ^2J = 13.9 Hz, 1H, CH_2), 3.68 (m, 1H, CH), 3.79 (dd, ^3J = 3.5 Hz, ^2J = 13.9 Hz, 1H, CH_2) ppm; ^{13}C NMR ($CDCl_3$): δ = 32.85 (br, (CH_3), 41.08 (CH_2), 61.25 (CH), 89.92 (m, $^2J_{C,F}$ = 32.8 Hz, $^2J_{C,F}$ = 30.1 Hz, $C(CF_3)_2$), 120.83 (qq, $^1J_{C,F}$ = 287 Hz, CF_3), 121.98 (q, $^1J_{C,F}$ = 295 Hz, CF_3), 125.05 (NCO), 167.76 (CO) ppm; ^{19}F NMR ($CDCl_3$): δ = −0.57 (q, J = 8.1 Hz, 3F, CF_3), 4.28 (br q, J = 8.1 Hz, 3F, CF_3), ppm; IR (film): ν = 2279 (NCO), 1842 ($CO_{lactone}$) cm^{-1}; MS (EI): *m/z* (%) = 292 [M]$^+$ (5), 236 (57), 195 (4).

(4S)-4-(2-Isocyanatoethyl)-3-methyl-2,2-bis(trifluoromethyl)-1,3-oxazolidin-5-one (**4b**; $C_9H_8F_6N_2O_3$)

6.55 g (20 mmol) **3b** gave 5.27 g (86%) **4b**. M.p.: 22–24°C; b.p.: ∼70°C (0.1 mm Hg, *Kugelrohr*); $[\alpha]_D^{25}$ = +52.0° (c = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ = 2.08 (m, 1H, CH_2CH), 2.16 (m, 1H, CH_2CH), 2.75 (q, J = 1.9 Hz, 3H, CH_3), 3.53 (m, 2H, NCH_2), 3.69 (m, 1H, CH) ppm; ^{13}C NMR ($CDCl_3$): δ = 29.8 (*C*H_2CH), 32.7 (br, CH_3), 37.5 (NCH_2), 57.8 (CH), 89.5 (m, $C(CF_3)_2$), 120.5 (q, J = 289 Hz, CF_3), 121.6 (q, J = 295 Hz, CF_3), 122.3 (NCO), 169.1 (CO) ppm; ^{19}F NMR ($CDCl_3$): δ = −0.99 (q, J = 8.3 Hz, 3F, CF_3), 4.40 (br q, J = 8.3 Hz, 3F, CF_3) ppm; IR (film): ν = 2277 (NCO), 1840 ($CO_{lactone}$) cm^{-1}; MS (EI): *m/z* (%) = 306 [M]$^+$ (4), 263 (8), 237 (11).

4→**5**, **6**, **7** (*General procedure*)

A mixture of **4** (9 mmol) and the corresponding alcohol (for **5**: 9-fluorenyl methanol (1.67 g, 8.5 mmol), for **6**: *tert*. butanol (0.63 g, 8.5 mmol), for **7**: benzyl alcohol (0.92 g, 8.5 mmol)) in $CHCl_3$ was stirred under reflux for 40 h. After removal of the solvent and the unreacted starting material *in vacuo* the residue was purified by flash chromatography.

(4S)-4-(9-Fluorenylmethoxycarbonylamino)methyl-3-methyl-2,2-bis(trifluoromethyl)-1,3-oxazolidin-5-one (**5a**; $C_{22}H_{18}F_6N_2O_4$)

2.65 g (9 mmol) **4a** gave 3.57 g (86%) **5a**. Oil; R_f = 0.3 (light petroleum/ethyl acetate = 2:1); $[\alpha]_D^{25}$ = +21.6° (c = 2.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ = 2.82 (br, 3H, CH_3), 3.62 (m, 3H, CHN,

CH_2N), 4.19 (m, 1H, C*H*CH_2O), 4.40 (m, 2H, CH_2O), 5.07 (br, 1H, NH), 7.26–7.81 (8H, fluorenyl) ppm; ^{13}C NMR ($CDCl_3$): δ = 33.4 (br, CH_3), 39.5 (CH_2N), 47.6 (*C*HCH_2O), 61.5 (CHN), 67.7 (CH_2O), 90.1 (m, *C*$(CF_3)_2$), 120.9 (q, J = 287 Hz, CF_3), 122.0 (q, J = 295 Hz, CF_3), 120.5, 125.5, 127.6, 128.2, 141.8, 144.1 (fluorenyl), 157.0 (CONH), 169.22 (CO) ppm; ^{19}F NMR ($CDCl_3$): δ = −0.94 (q, J = 8.2 Hz, 3F, CF_3), 4.14 (br q, J = 8.2 Hz, 3F, CF_3) ppm; IR (film): ν = 1838 ($CO_{lactone}$), 1710 ($CO_{urethane}$) cm^{-1}; MS (EI): *m*/*z* (%) = 488 [M]$^+$ (11), 178 (100).

(4S)-4-(2-(9-Fluorenylmethoxycarbonylamino)ethyl)-3-methyl-2,2-bis(trifluoromethyl)-1,3-oxazolidin-5-one (**5b**; $C_{23}H_{20}F_6N_2O_4$)

2.76 g (9 mmol) **4b** gave 4.14 g (97%) **5b**. M.p.: 86–88°C; R_f = 0.17 (ethyl acetate/light petroleum, = 1:3); $[\alpha]_D^{25}$ = +28.0° (c = 6.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ = 2.05 (br, 1H, CH_2CH), 2.15 (m, 1H, CH_2CH), 2.73 (m, 3H, CH_3), 3.23 (m, 1H, NCH_2), 3.41 (m, 1H, NCH_2), 3.66 (m, 1H, CHN), 4.14 (m, 1H, C*H*CH_2O), 4.42 (m, 2H, CHCH_2O), 4.92 (br, 1H, NH), 7.27–7.80 (8H, fluorenyl) ppm; ^{13}C NMR ($CDCl_3$): δ = 29.0 (CH_2CH), 33.3 (br, CH_3), 36.5 (NCH_2), 47.7 (*C*HCH_2O), 59.0 (CHN), 67.3, (CH*C*H_2O), 90.0 (m, *C*$(CF_3)_2$), 121.0 (q, J = 287 Hz, CF_3), 122.0 (q, J = 295 Hz, CF_3), 120.5, 125.5, 127.5, 128.2, 141.8, 144.3 (fluorenyl), 156.8 (CONH), 169.9 (CO) ppm; ^{19}F NMR ($CDCl_3$): δ = −0.83 (q, J = 8.1 Hz, 3F, CF_3), 4.45 (br q, J = 8.1 Hz, 3F, CF_3) ppm; IR (KBr): ν = 1835 ($CO_{lactone}$), 1695 ($CO_{urethane}$) cm^{-1}; MS (EI): *m*/*z* (%) = 502 [M]$^+$ (7).

(4S)-4-(tert. Butoxycarbonylamino)methyl-3-methyl-2,2-bis(trifluoromethyl)-1,3-oxazolidin-5-one (**6a**; $C_{12}H_{16}F_6N_2O_4$)

2.63 g (9 mmol) **4a** gave 1.59 g (51%) **6a**. M.p.: 97°C; R_f = 0.49 (light petroleum/ethyl acetate = 3:1); $[\alpha]_D^{25}$ = +8.3° (c = 3.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ = 1.42 (s, 9H, $C(CH_3)_3$), 2.81 (q, J = 2.0 Hz, 3H, NCH_3), 3.52 (m, 2H, CH_2), 3.61 (m, 1H, CH), 4.79 (br, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$): δ = 28.6 (C(*C*$H_3)_3$), 33.3 (br, NCH_3), 38.8 (CH_2), 61.8 (CH), 80.5 (*C*$(CH_3)_3$), 89.4 (m, *C*$(CF_3)_2$), 120.9 (q, J = 285 Hz, CF_3), 121.9 (q, J = 295 Hz, CF_3), 156.3 (CONH), 169.4 (CO) ppm; ^{19}F NMR ($CDCl_3$): δ = −0.86 (q, J = 8.1 Hz, 3F, CF_3), 4.15 (br q, J = 8.1 Hz, 3F, CF_3) ppm; IR (KBr): ν = 1842 ($CO_{lactone}$), 1709 ($CO_{urethane}$) cm^{-1}; MS (EI): *m*/*z* (%) = 366 [M]$^+$ (5), 293 (14), 237 (41), 168 (26), 57 (100).

(4S)-4-(2-(tert. Butoxycarbonylamino)ethyl)-3-methyl-2,2-bis(trifluoromethyl)-1,3-oxazolidin-5-one (**6b**; $C_{13}H_{18}F_6N_2O_4$)

2.76 g (9 mmol) **4b** gave 2.42 g (75%) **6b**. Oil; R_f = 0.37 (ethyl acetate/light petroleum = 1:3); $[\alpha]_D^{25}$ = +41° (c = 4.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ = 1.42 (s, 9H, $C(CH_3)_3$), 2.05 (m, 2H, CHCH_2), 2.72 (q, J = 2.2 Hz, 3H, NCH_3), 3.06 (m, 1H, NHCH_2), 3.32 (m, 1H, NHCH_2), 3.63 (m, 1H, CH), 4.67 (br, 1H, NH); ^{13}C NMR ($CDCl_3$): δ = 28.7 (C(*C*$H_3)_3$), 29.1 (CH*C*H_2), 33.2 (br, NCH_3), 36.0 (NH*C*H_2), 58.8 (CH), 80.1 (*C*$(CH_3)_3$), 89.5 (m, *C*$(CF_3)_2$), 121.0 (q, J = 290 Hz, CF_3), 122.2 (q, J = 296 Hz, CF_3), 156.4 (CONH), 170.0 (CO) ppm; ^{19}F NMR ($CDCl_3$): δ = −0.89 (q, J = 8.6 Hz, 3F, CF_3), 4.38 (br q, J = 8.6 Hz, 3F, CF_3) ppm; IR (film): ν = 1840 ($CO_{lactone}$), 1696 ($CO_{urethane}$) cm^{-1}; MS (EI): *m*/*z* (%) = 324 (14), 307 (10), 280 (64).

(4S)-4-(Benzoxycarbonylaminomethyl)-3-methyl-2,2-bis(trifluoromethyl)-1,3-oxazolidin-5-one (**7a**; $C_{15}H_{14}F_6N_2O_4$)

2.63 g (9 mmol) **4a** gave 2.93 g (86%) **7a**. Needles; m.p.: 90–91°C (*n*-hexane); R_f = 0.4 (light petroleum/ethyl acetate = 2:1); $[\alpha]_D^{25}$ = +18.4° (c = 2.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ = 2.80 (br, 3H, CH_3), 3.60 (m, 3H, CH, CHCH_2), 5.05 (m, 3H, NH, CH_2O), 7.34 (m, 5H, arom.) ppm; ^{13}C NMR

($CDCl_3$): δ = 33.3 (br, CH_3), 39.3 ($CHCH_2$), 61.6 (CH), 67.6 (CH_2O), 90.0 (m, $C(CF_3)_2$), 120.9 (q, J = 287 Hz, CF_3), 121.9 (q, J = 295 Hz, CF_3), 128.6, 128.8, 129.1, 136.6 (phenyl), 157.1 (CONH), 169.3 (CO) ppm; ^{19}F NMR ($CDCl_3$): δ = −0.98 (q, J = 8.1 Hz, 3F, CF_3), 4.14 (br q, J = 8.1 Hz, 3F, CF_3) ppm; IR (KBr): ν = 1838 ($CO_{lactone}$), 1699 ($CO_{urethane}$) cm^{-1}; MS (EI): m/z (%) = 400 $[M]^+$ (4), 309 (7), 236 (13), 91 (100).

(4S)-4-(2-(Benzoxycarbonylamino)ethyl)-3-methyl-2,2-bis(trifluoromethyl)-1,3-oxazolidin-5-one (**7b**; $C_{16}H_{16}F_6N_2O_4$)

2.76 g (9 mmol) **4b** gave 3.24 g (92%) **7b**. M.p.: 39–42°C; R_f = 0.27 ($CHCl_3$); $[\alpha]_D^{25}$ = +28.0° (c = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ = 2.05 (m, 1H, CHCH_2), 2.15 (m, 1H, CHCH_2), 2.73 (br, 3H, CH_3), 3.21 (m, 1H, CH_2NH), 3.41 (m, 1H, CH_2NH), 3.66 (m, 1H, CH), 4.89 (br, 1H, NH), 5.11 (m, 2H, CH_2O), 7.36 (m, 5H, phenyl) ppm; ^{13}C NMR ($CDCl_3$): δ = 28.7 ($CHCH_2$), 32.6 (br, CH_3), 36.0 (CH_2NH), 58.3 (CH), 66.7 (CH_2O), 89.5 (m, $C(CF_3)_2$), 120.6 (q, J = 287 Hz, CF_3), 121.7 (q, J = 295 Hz, CF_3), 127.9, 128.1, 128.4, 136.6 (phenyl), 156.6 (CONH), 169.5 (CO) ppm; ^{19}F NMR ($CDCl_3$): δ = −0.86 (q, J = 8.1 Hz, 3F, CF_3), 4.43 (br q, J = 8.1 Hz, 3F, CF_3) ppm; IR (KBr): ν = 1837 ($CO_{lactone}$), 1702 ($CO_{urethane}$) cm^{-1}; MS (EI): m/z (%) = 414 $[M]^+$ (7).

5→**8**, **10a**→**11** (*General procedure*)

A mixture of compound **5** or **10a** (0.5 mmol) and *L*-phenylalanine amide (0.16 g, 1.0 mmol) was dissolved in a mixture of 2-propanol (2 cm^3) and Et_2O (2 cm^3) and stirred for several days. After consumption of the oxazolidinone (TLC control), the white precipitate was filtered off and washed carefully with Et_2O to give a white powder.

N^{β}-(9-Fluorenylmethoxycarbonyl)-N^{α}-methyl-L-2,3-diaminopropionyl-L-phenylalanine amide (**8a**; $C_{28}H_{30}N_4O_4$)

0.98 g (2 mmol) **5a** gave 0.58 g (60%) **8a**. M.p.: 157–158°C; $[\alpha]_D^{25}$ = +8.0° (c = 1.0, *DMSO*); ^{1}H NMR (CD_3OD): δ = 2.06 (s, 3H, CH_3), 2.87 (m, 1H, CH_{2Phe}), 3.02 (m, 1H, CH_{2DAP}), 3.20 (m, 3H, CH_{DAP}, CH_{2DAP}, CH_{2Phe}), 4.19 (t, J = 6.7 Hz, 1H, CHCH$_2$), 4.35 (d J = 6.6 Hz, 2H, CHCH_2), 4.70 (m, 1H, CH_{Phe}), 7.16–7.40 (m, 9H, arom.), 7.63 (m, 2H, arom.), 7.78 (m, 2H, arom.) ppm; ^{13}C NMR (*DMSO*-d_6): δ = 34.3 (CH_3), 38.2 (CH_{2Phe}), 43.0 (CH_{2DAP}), 47.0 (CHCH$_2$O), 53.3 (CH_{Phe}), 64.4 (CH_{DAP}), 65.7 (CHCH$_2$O), 120.4, 125.5, 126.5, 127.3, 127.9, 128.2, 129.5, 137.9, 141.0, 144.1 (arom.), 156.6 ($CO_{urethane}$), 171.7, 173.1 (2 × CO) ppm; MS (FAB): m/z = 487.3 $[M+H]^+$, 509.2 $[M+Na]^+$.

N^{γ}-(9-Fluorenylmethoxycarbonyl)-N^{α}-methyl-L-2,4-diaminobutyryl-L-phenylalanine amide (**8b**; $C_{29}H_{32}N_4O_4$)

1.05 g (2 mmol) **5b** gave 0.55 g (55%) **8b**. M.p.: 141–143°C $[\alpha]_D^{25}$ = +16.3° (c = 1.0, *DMSO* + 5% *TFA*); ^{1}H NMR (*DMSO*-d_6 + 5% *TFA*): δ = (m, 2H, CHCH_{2DAB}), 2.02 (s, 3H, CH_3), 2.76 (m, 1H, CH_{2Phe}), 3.11 (m, 3H, CH_2N, CH_{2Phe}), 3.54 (m, 1H, CH_{DAB}), 4.17 (m, 1H, CHCH$_2$), 4.35 (m, 2H, CHCH_2), 4.72 (m, 1H, CH_{Phe}), 7.05–7.35 (m, 9H, arom.), 7.59 (m, 2H, arom.), 7.78 (m, 2H, arom) ppm; ^{13}C NMR (*DMSO*-d_6 + 5% *TFA*): δ = 30.2 ($CHCH_{2DAB}$), 30.6 (CH_2N), 35.6 (CH_3) 38.3 (CH_{2Phe}), 46.9 (CHCH$_2$O), 53.7 (CH_{Phe}), 58.6 (CH_{DAB}) 65.4 (CHCH$_2$O), 119.5, 124.6, 126.1, 126.6, 127.2, 127.7, 128.9, 137.1, 140.7, 143.6 (arom.), 158.4 ($CO_{urethane}$), 166.1, 172.6 (2 × CO) ppm; MS (FAB): m/z = 523 $[M+Na]^+$, 501 $[M+H]^+$.

N^{α}-Methyl-N^{β}-(N-morpholinylcarbonyl)-L-2,3-diaminopropionyl-L-phenylalanine amide (**11**, $C_{18}H_{27}N_5O_4$)

0.76 g (2 mmol) **10a** gave 0.52 g (71%) **11**. M.p.: 177–181°C; $[\alpha]_D^{25} = +6.0°$ ($c = 1.0$, *DMSO*); ^{1}H NMR (*DMSO*-d_6): $\delta = 1.99$ (s, 3H, CH_3), 2.86 (m, 1H, CH_{2Phe}), 3.04 (m, 3H, CH_{2DAP} CH_{2Phe}), 3.20 (t, $J = 5.0$ Hz, 4H, CH_2N), 3.34 (m, 1H, CH_{DAP}), 3.50 (t, $J = 5.0$ Hz, 4H, CH_2O), 4.41 (m, 1H, CH_{Phe}), 6.44 (br, 1H, NH), 7.17 (m, 5H, phenyl), 7.99 (br, 1H, NH) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta =$ 35.2 (CH_3), 38.6 (CH_{2Phe}), 43.6 (CH_{2DAP}), 44.6 (CH_2N), 53.9 (CH_{Phe}), 65.7 (CH_{DAP}), 66.8 (CH_2O), 127.2, 128.9, 130.2, 138.7 (phenyl), 158.7 (CO_{urea}), 172.9, 173.9 ($2 \times$ CO) ppm; MS (FAB): $m/z =$ 400.0 $[M+Na]^+$, 378.0 $[M+H]^+$.

(3S)-3-Methylaminopyrrolidin-2-one hydrochloride (**9**; $C_5H_{10}N_2O$ x HCl)

A mixture of 0.83 g (2 mmol) **7b** and 10% Pd/C (*ca.* 0.1 g) was stirred in 2-propanol under an atmosphere of H_2 overnight. The mixture was filtered to remove the catalyst, and the solvent was evaporated. The residue was dissolved in 3 *N* HCl (3 cm^3). After evaporation to dryness the residue was stirred carefully with Et_2O (5 cm^3)/EtOH (0.5 cm^3) for 12 h. Filtration and drying gave 0.21 g (69%) **9** as a white solid.

M.p.: 259–262°C (decomp.); $[\alpha]_D^{25} = -34.4°$ ($c = 0.9$, H_2O); ^{1}H NMR (D_2O): $\delta = 2.05$ (m, 1H, CH_2CH), 2.51 (m, 1H, CH_2CH), 2.65 (s, 3H, CH_3), 3.31 (m, 2H, CH_2N), 3.96 (m, 1H, CH) ppm; ^{13}C NMR (D_2O): $\delta = 24.2$ (*C*H_2CH), 31.3 (CH_3), 39.7 (CH_2N), 58.1 (CH), 172.8 (CO) ppm; IR (KBr): $\nu = 1731$ (CO) cm^{-1}; MS (EI): *m/z* (%): 114 $[M\text{-HCl}]^+$ (25), 85 $[M\text{-HCl-NH}=CH_2]^+$ (100), 70 $[C_4H_8N]^+$ (21).

4→**10**, **4a**→**12**, **4b**→**13** (*General procedure*)

To a solution of **4** (2 mmol) in Et_2O (2 cm^3), a solution of the amine (morpholine: 0.17 g, 2 mmol; benzyl amine: 0.21 g, 2 mmol; *D*-α-methyl benzylamine: 0.24 g, 2 mmol) in Et_2O (2 cm^3) was added dropwise. After complete consumption of the starting material (TLC control) the volatiles were evaporated *in vacuo* and the residue was purified by flash chromatography.

(4S)-3-Methyl-4-(N-morpholinylcarbonylaminomethyl)-2,2-bis(trifluoromethyl)-1,3-oxazolidin-5-one (**10a**; $C_{12}H_{15}F_6N_3O_4$)

0.58 g (2 mmol) **4a** gave 0.48 g (64%) **10a**. M.p.: 126°C; $[\alpha]_D^{25} = +44.5°$ ($c = 4.0$, $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 2.81$ (q, $J = 2.0$ Hz, 3H, CH_3), 3.32 (m, 4H, NCH_2), 3.58 (m, 1H, CHCH_2), 3.73 (m, 1H, CHCH_2), 3.67 (m, 5H, OCH_2, CH), 4.84 (br, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$): $\delta =$ 33.4 (br, CH_3), 39.1 (CH*C*H_2), 44.2 (NCH_2), 61.2 (OCH_2), 66.8 (CH), 90.0 (m, *C*$(CF_3)_2$), 120.9 (q, J = 287 Hz CF_3), 121.9 (q, $J = 295$ Hz, CF_3), 157.8 (CONH), 169.9 (CO) ppm; ^{19}F NMR ($CDCl_3$): δ = −0.99 (q, $J = 8.1$ Hz, 3F, CF_3), 4.22 (br q, $J = 8.1$ Hz, 3F, CF_3) ppm; IR (KBr): $\nu = 1837$ ($CO_{lactone}$), 1640s (CO_{urea}) cm^{-1}; MS (EI): *m/z* (%) = 379 [M]+ (18), 310 (5), 236 (7), 143 (56), 114 (100).

(4S)-3-Methyl-4-[2-(N-morpholinylcarbonylamino)ethyl]-2,2-bis(trifluoromethyl)-1,3-oxaxolidin-5-one (**10b**; $C_{13}H_{17}F_6N_3O_4$)

0.61 g (2 mmol) **4b** gave 0.76 g (97%) **10b**. Viscous oil; $R_f = 0.27$ (ethyl acetate); $[\alpha]_D^{25} = +38.0°$ ($c = 4.0$, $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 2.06$ (m, 1H, CHCH_2), 2.19 (m, 1H, CHCH_2), 2.73 (q, J = 2.0 Hz, 3H, CH_3), 3.27 (m, 1H, NHCH_2), 3.41 (m, 1H, NHCH_2), 3.30 (m, 4H, NCH_2), 3.66 (m, 5H, CH, OCH_2), 4.60 (br, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 28.6$ (CH*C*H_2), 33.3 (br, CH_3),

36.3 ($NHCH_2$), 44.3 (NCH_2), 59.2 (CH), 66.9 (OCH_2), 90.6 (m, $C(CF_3)_2$), 121.1 (q, $J = 287$ Hz, CF_3), 122.1 (q, $J = 298$ Hz, CF_3), 158.0 (CONH), 170.5 (CO) ppm; ^{19}F NMR ($CDCl_3$): $\delta = -0.69$ (q, $J = 8.1$ Hz, 3F, CF_3), 4.46 (br q, $J = 8.1$ Hz, 3F, CF_3) ppm; IR (film): $\nu = 1838$ ($CO_{lactone}$), 1632 (CO_{urea}) cm^{-1}; MS (EI): *m/z* (%) = 393 $[M]^+$ (48).

(4S)-3-Methyl-4-(N-(D-α-methylbenzylamino)carbonylamino)methyl-2,2-bis(trifluoromethyl)-1,3-oxazolidin-5-one (**12**; $C_{16}H_{17}F_6N_3O_3$)

0.58 g (2 mmol) **4a** gave 0.65 g (79%) **12**. Oil; $R_f = 0.43$ (ethyl acetate/light petroleum = 1:1); $[\alpha]_D^{25} = +49.2°$ ($c = 5.0$, $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 1.41$ (br, $J = 6.8$ Hz, 3H, CH_3), 2.71 (br, 3H, NCH_3), 3.52 (m, 3H, CH, CH_2) 4.76 (br, 1H, NH), 5.13 (m, 1H, C*H*CH_3), 5.25 (br, 1H, NH), 7.28 (m, 5H, phenyl) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 23.0$ (CH_3), 32.8 (br, NCH_3), 38.3 (CH_2), 50.2 (*C*HCH_3), 61.0 (CH), 89.5 (m, $C(CF_3)_2$), 120.5 (q, $J = 287$ Hz, CF_3), 121.5 (q, $J = 295$ Hz, CF_3), 125.8, 127.3, 128.7, 144.0 (phenyl), 157.5 (CONH), 169.5 (CO) ppm; ^{19}F NMR ($CDCl_3$): $\delta = -0.97$ (q, $J = 8.1$ Hz, 3F, CF_3), 4.22 (br q, $J = 8.1$ Hz, 3F, CF_3) ppm; IR (film): $\nu = 1838$ ($CO_{lactone}$), 1638 (CO_{urea}) cm^{-1}; MS (EI): *m/z* (%) = 413 $[M]^+$ (4).

(3S)-1-Benzylaminocarbonyl-3-methylaminopyrrolidin-2-one (**13**; $C_{13}H_{17}N_3O_2$)

0.61 g (2 mmol) **4b** gave 0.42 g (85%) **13**. Oil; $R_f = 0.67$ (ethyl acetate); $[\alpha]_D^{25} = -16.3°$ ($c = 2.4$, $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 1.78$ (m, 1H, $CHCH_2$), 2.11 (br, 1H, NH), 2.27 (m, 1H, $CHCH_2$), 2.44 (s, 3H, CH_3), 3.49 (m, 2H, CH_2N), 3.95 (m, 1H, CH), 4.47 (d = 5.8 Hz, 2H, CH_2Ph), 7.28 (m, 5H, phenyl), 8.66 (br, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 25.6$ ($CHCH_2$), 34.4 (CH_3), 42.6 (CH_2N), 44.2 (CH_2Ph), 62.3 (CH), 127.9, 128.1, 129.1, 138.7 (phenyl), 153.2 (CONH), 176.9 (CO) ppm; IR (film): $\nu = 1720$ (CO_{lactam}), 1542 (CO_{urea}) cm^{-1}; MS (EI): *m/z* (%) = 247 $[M]^+$ (18), 218 $[M\text{-}NH{=}CH_2]^+$ (25), 216 (28), 204 $[M\text{-}CONH]^+$ (3), 133 $[PhCH_2NCO]^+$ (5), 113 $[M\text{-}CONHCH_2Ph]^+$ (22), 106 $[C_6H_5CHNH_2]^+$ (16), 91 $[C_7H_7]^+$ (69), 85 $[C_4H_7NO]^+$ (25), 70 $[C_4H_8N]^+$ (85), 65 $[C_5H_5]^+$ (18), 56 $[C_3H_6N]^6$ (100).

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