A New Approach to *N*-Methylaspartic, *N*-Methylglutamic, and *N*-Methyl-α-aminoadipic Acid Derivatives

Klaus Burger,*[a] and Jan Spengler[a]

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N-Methylaspartic acid derivatives and its homologues are obtained by a stereoconservative one-pot procedure from hexafluoroacetone-protected aspartic and glutamic acid, **2a** and **2b**, respectively. α-Aminoadipic acid (**5c**) and its derivative **6c** are accessible from the corresponding glutamic acid derivative **9b** by a Wolff rearrangement. A variety of homochiral *N*-methylamino acids, **5** and **12**, and their derivatives, **6** and **8**−**11**, become readily available by the new synthetic concept.

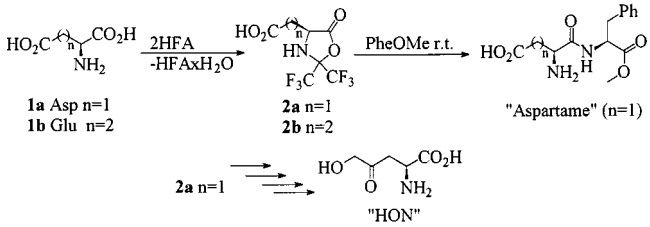
Introduction

The development of new strategies for the synthesis of homochiral non-proteinogenic and non-natural amino acids is of current interest.[1] Some represent new building blocks for the construction of peptide mimetics, glycopeptide mimetics, synthetic enzymes, new drugs, and agrochemicals.[2] Furthermore, they are valuable starting materials for combinatorial chemistry.[3]

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 activities.[4] Incorporation of α-*N*-methylamino acids into key positions of peptides and depsipeptides leads to an enhanced proteolytic stability, to an increase in lipophilicity, and to a stabilization of secondary structure domains. Certain α-*N*-methylamino acids are themselves biologically active compounds.[5] Consequently, a number of synthetic routes to homochiral α-*N*-methylamino acids have been developed.[6]

Results and Discussion

Recently, we decribed a new protection/activation strategy for α-amino acids using hexafluoroacetone. Hexafluoroacetone and α-amino acids react to give bis(trifluoromethyl)-substituted oxazolidin-5-ones in high yields. This heterocyclization process results in a simultaneous protection of the α-amino group and the α-carboxylic group. Furthermore, the α-carboxylic group is activated towards nucleophiles. Functional groups present in the side chain − like the carboxyl moiety − remain unaffected.[7] Consequently, the method can be applied to regioselective group manipulation of ω-carboxy α-amino acids. The efficiency of this concept was demonstrated by a two-step synthesis of the sweetener "aspartame".[8] Selective activation of the ω-carboxylic group can be achieved by transformation into the acid chloride, as demonstrated by a five-step synthesis of HON (5-hydroxy-4-oxo-norvaline) starting from aspartic acid.[9]



Scheme 1. Regioselective functionalization of α-amino acids

Furthermore, hexafluoroacetone-protected α-amino acids are also perfectly suited for *N*-alkylation. In a three-component reaction, hexafluoroacetone-protected α-amino acids, paraformaldehyde, and thionyl chloride react to give *N*-chloromethylamino acid derivatives, which can be transformed into *N*-methylamino acid derivatives on treatment with triethylsilane/trifluoroacetic acid.[10]

We now want to disclose that the new *N*-methylation procedure can also be applied to ω-carboxy α-amino acids. Hexafluoroacetone-protected aspartic and glutamic acid[8] react in trifluoroacetic acid (as solvent) with paraformaldehyde and thionyl chloride, giving *N*-chloromethylation. In a parallel reaction, the ω-carboxylic group is transformed into the acid chloride. The presence of trifluoroacetic acid as a solvent avoids the formation of the pyroglutamic acid derivative in the case of glutamic acid. The reaction mixture was treated with triethylsilane to transform the chloromethyl group into the methyl group. After evaporation of the volatiles in vacuo, the residue was heated under reflux with an excess of thionyl chloride to ensure that the ω-carboxylic group is completely transformed into the acid chloride **3** which can be easily purified by distillation.

The free acids **4** were obtained from acid chlorides **3** upon stirring in wet THF at room temperature. Complete deblocking of the amino acids was obtained by stirring with

[a] Department of Organic Chemistry, University of Leipzig, Johannisallee 29, D-04103 Leipzig, Germany
Fax: (internat.) + 49-(0)341/973-6599
E-mail: burger@organik.chemie.uni-leipzig.de

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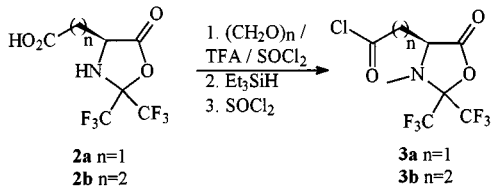
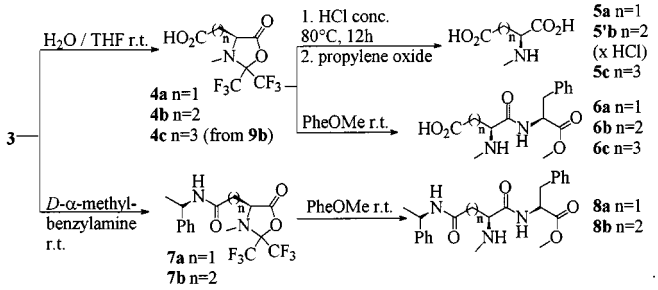


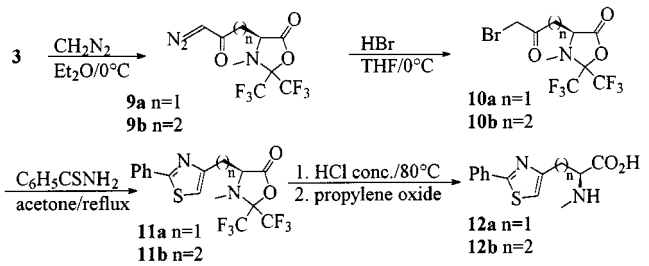
Scheme 2. *N*-Methylation of α-amino acids

concd. HCl at 80°C for 12 h (**4** → **5**). Since the *N*-methylated amino acid derivatives **4** are α-carboxylic group activated species, they readily can be transformed into dipeptide derivatives (**4** → **6**). Compounds **3** can be regioselectively functionalized in a two-step procedure (**3** → **7** → **8**).



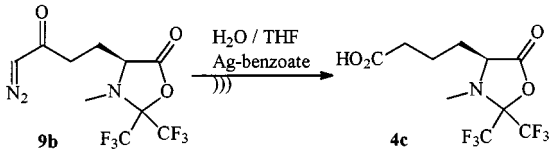
Scheme 3. Regioselective functionalization of α-methylamino acids

Acid chlorides **3**, on reaction with an excess of diazomethane gave the corresponding diazo ketones **9**, which by themselves are interesting synthetic intermediates. They represent *N*-methyl derivatives of DONV[11] (5-diazo-4-oxonorvaline, **9a**) and DON[12] (5-diazo-4-oxo-norleucine, **9b**), respectively. Bromo ketones **10** are obtained from **9** on stirring with concd. HBr in THF at 0°C. Compounds **10** are versatile starting materials for the Hantzsch reaction.[13] On treatment with thioamides, compounds **10** readily react to give a variety of α-(methylamino) ω-(thiazol-4-yl) carboxylic acids, e.g. **12**, via compounds **11**.[14]



Scheme 4. Synthesis of heterocyclic α-methylamino acids

Diazo ketones are suitable starting materials for homologation reactions of the Wolff type. The Ag^+/base-catalyzed reaction of diazo ketones is reported to be promoted substantially by sonication at room temperature.[15] It was found that base-free Ag^+-catalyzed Wolff rearrangement of **9b** to **4c** proceeds smoothly at room temperature on sonication using an ultrasound cleaning bath.[16] To our best knowledge, homochiral α-(methylamino)adipic acid and their derivatives are not described so far.



Scheme 5. Synthesis of α-(methylamino)adipic acid derivatives

In all experiments described in the paper, no substantial racemization could be detected. Starting from D-aspartic and D-glutamic acid, the corresponding *N*-methylamino acids of the D-series became available.

Experimental Section

General Remarks: Solvents were purified and dried prior to use. Reagents were used as purchased. − Thin layer chromatography (TLC) was performed on aluminia plates coated with Merck silica gel $60F_{254}$. Compounds were visualized by spraying with ceric ammonium nitrate in 9 M H_2SO_4 followed by heating up to 100°C. − Column chromatography was carried out on silica gel (32−63 μm, ICN Biomedicals). − Melting points were determined with a Boëtius 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 (Heraeus) was used. − Mass spectra were recorded with a VG 12−250 (Masslab) electron-ionization spectrometer (EI = 70 eV) or a VG ZAB-HSQ FAB spectrometer. − IR spectra were obtained by 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. Tetramethylsilane was used as reference standard for ^{1}H- and ^{13}C-NMR spectra (internal) and trifluoroacetic acid for ^{19}F-NMR spectra (external).

General Procedure (2 → 3): Oxazolidinone **2**[8] (50 mmol) and paraformaldehyde (3.0 g, 100 mmol) were dissolved in trifluoroacetic acid (50 mL), and thionyl chloride (10 mL) was then added. The flask was equipped with a reflux condenser which was connected to a bubbler. The mixture was stirred overnight at room temperature. On addition of triethylsilane (11.6 g, 16 mL, 100 mmol), a strong exothermic reaction with gas evolution started, after a short induction period. The mixture was stirred until gas evolution ceased (ca. 0.5 h). When the reaction was complete (^{19}F-NMR analysis) the volatile compounds were evaporated in vacuo and the residue was treated with thionyl chloride at reflux for 3 h. The excess thionyl chloride was distilled off. Distillation of the residue in vacuo gave the pure products **3**.

[(4*S*)-3-Methyl-5-oxo-2,2-bis(trifluoromethyl)-1,3-oxazolidin-4-yl]acetyl Chloride (3a): Reaction of **2a** (14.1 g, 50 mmol) gave 10.2 g (65%) of **3a**. − M.p. 28−29°C. − B.p. 48−50°C (0.3 Torr). − $[\alpha]_D^{25}$ = +17.6 (*c* = 2.5, $CHCl_3$). − ^{1}H NMR ($CDCl_3$): δ = 2.76 (q, 3 H, *J* = 2.0 Hz, CH_3), 3.33 (dd, 1 H, *J* = 18.0 Hz, 5.2 Hz, CH_2), 3.49 (dd, 1 H, *J* = 18.0 Hz, 4.2 Hz, CH_2), 3.97 (m, 1 H, CH). − ^{13}C NMR ($CDCl_3$): δ = 33.6 (br., CH_3), 47.1 (CH_2), 57.7 (CH), 90.0 [m, $C(CF_3)_2$], 120.7 (q, *J* = 287 Hz, CF_3), 121.9 (q, *J* = 295 Hz, CF_3), 168.2 (CO), 170.5 (COCl). − ^{19}F NMR (CDCl3): δ = −0.66 (m, 3 F, CF_3), 4.42 (m, 3 F, CF_3).

− IR (KBr): $\tilde{\nu}$ = 1842 cm^{-1} (CO), 1799 (COCl). − MS (EI), *m/z* (%): 313 $[M]^+$ (13), 249 (28), 236 (35). − $C_8H_6ClF_6NO_3$ (313.5): calcd. C 30.65, H 1.93, N 4.47; found C 30.65, H 1.99, N 4.49.

3-[(4*S*)-3-Methyl-5-oxo-2,2-bis(trifluoromethyl)-1,3-oxazolidin-4-yl]propionyl Chloride (3b): Reaction of **2b** (14.8 g, 50 mmol) gave 13.4 g (82%) of **3b** as a yellowish oil. − B.p. 58−60°C (0.1 Torr). − $[\alpha]_D^{25}$ = +33.0 (*c* = 2.0, $CHCl_3$). − ^{1}H NMR ($CDCl_3$): δ = 2.24 (m, 2 H, CH_2CH), 2.73 (q, 3 H, *J* = 1.9 Hz, CH_3), 3.01 (m, 2 H, CH_2CO), 3.71 (m, 1 H, CH). − ^{13}C NMR ($CDCl_3$): δ = 23.7 (*C*H_2CH), 32.9 (br., CH_3), 40.8 (*C*H_2CO), 59.1 (CH), 89.5 [m, *C*(CF_3)$_2$], 120.5 (q, *J* = 288 Hz, CF_3), 121.5 (q, *J* = 295 Hz, CF_3), 168.7 (CO), 173.1 (COCl). − ^{19}F NMR ($CDCl_3$): δ = −0.90 (m, 3 F, CF_3), 4.37 (m, 3 F, CF_3). − IR (film): $\tilde{\nu}$ = 1838 cm^{-1} (CO), 1801 (COCl). − MS (EI), *m/z* (%): 327 $[M]^+$ (2), 292 (41), 249 (43). − $C_9H_8ClF_6NO_3$ (327.6): calcd. C 33.00, H 2.46, N 4.28; found C 32.86, H 2.35, N 4.07.

General Procedure (3 → 4): Oxazolidinone **3** (10 mmol) was dissolved in wet THF and stirred until the smell of the acid chloride vanished (ca. 1.5 h). After evaporating in vacuo, the residue was recrystallized from *n*-hexane.

[(4*S*)-3-Methyl-5-oxo-2,2-bis(trifluoromethyl)-1,3-oxazolidin-4-yl]-acetic Acid (4a): Reaction of **3a** (3.13 g, 10 mmol) gave 2.6 g (74%) of **4a**. − M.p. 75−78°C. − $[\alpha]_D^{25}$ = +9.3 (*c* = 2.0, $CHCl_3$). − ^{1}H NMR ($CDCl_3$): δ = 2.75 (q, 3 H, *J* = 2.0 Hz, CH_3), 2.91 (m, 2 H, CH_2), 3.92 (m, 1 H, CH). − ^{13}C NMR ($CDCl_3$): δ = 33.5 (br., CH_3), 35.1 (CH_2), 57.8 (CH), 89.9 [m, *C*(CF_3)$_2$], 120.9 (q, *J* = 287 Hz, CF_3), 122.1 (q, *J* = 296 Hz, CF_3), 169.0 (CO), 175.6 (CO_2H). − ^{19}F NMR ($CDCl_3$): δ = −0.59 (m, 3 F, CF_3), 4.42 (m, 3 F, CF_3). − IR (KBr): $\tilde{\nu}$ = 1839 cm^{-1} (CO), 1710 (CO_2H). − MS (EI), *m/z* (%): 295 $[M]^+$ (41), 249 (100), 198 (50), 180 (100). − $C_8H_7F_6NO_4$ (295.1): calcd. C 32.56, H 2.39, N 4.74; found C 32.79, H 2.64, N 5.21.

3-[(4*S*)-3-Methyl-5-oxo-2,2-bis(trifluoromethyl)-1,3-oxazolidin-4-yl]-propionic Acid (4b): Reaction of **3b** (3.28 g, 10 mmol) gave 2.63 g (85%) of **4b**. − M.p. 86−88°C. − $[\alpha]_D^{25}$ = +23.8 (*c* = 1.0, $CHCl_3$). − ^{1}H NMR ($CDCl_3$): δ = 2.20 (m, 2 H, CH_2CH), 2.49 (m, 2 H, CH_2CO_2H), 2.73 (q, 3 H, *J* = 1.9 Hz, CH_3), 3.71 (m, 1 H, CH). − ^{13}C NMR ($CDCl_3$): δ = 23.6 (*C*H_2CH), 28.1 (*C*H_2CO_2H), 33.2 (br., CH_3), 59.8 (CH), 89.9 [m, *C*(CF_3)$_2$], 121.0 (q, *J* = 287 Hz, CF_3), 122.1 (q, *J* = 296 Hz, CF_3), 169.7 (CO), 179.2 (CO_2H). − ^{19}F NMR ($CDCl_3$): δ = −0.83 (m, 3 F, CF_3), 4.42 (m, 3 F, CF_3). − IR (KBr): $\tilde{\nu}$ = 1840 cm^{-1} (CO), 1716 (CO_2H). − MS (EI), *m/z* (%): 309 $[M]^+$ (20), 291 (34), 263 (26), 249 (100). − $C_9H_9F_6NO_4$ (309.2): calcd. C 34.96, H 2.93, N 4.53; found C 35.15, H 3.10, N 4.84.

General Procedure (4 → 5, 11 → 12): Oxazolidinone **4** or **11** (2 mmol) was dissolved in dioxane (3 mL)/concd. HCl (3 mL) and stirred at 80°C for 12 h. The solution was evaporated to dryness and the residue dissolved in EtOH (1 mL). Stirring with propylene oxide (3 mL) gave the free amino acids **5** and **12** as white precipitates which were dried in vacuo.

L-*N*-Methylaspartic Acid (5a): Reaction of **4a** (0.59 g, 2 mmol) gave 0.25 g (85%) of **5a**. − M.p. 183−186°C; ref.[6a] 187−190°C. − $[\alpha]_D^{25}$ = +14.0 (*c* = 2.0, H_2O); ref.[17] +14.2 (*c* = 2.0, H_2O). − ^{1}H-NMR-identical to literature data.[6a]

L-*N*-Methylglutamic Acid Hydrochloride (5′b): Oxazolidinone **4b** 0.62 g (2 mmol) was dissolved in dioxane (3 mL)/concd. HCl (3 mL) and stirred at 80°C for 12 h. The solution was concentrated to dryness. The residue was stirred in dry ether (20 mL), filtered and dried in vacuo to give 0.23 g (59%) of **5′b** as a hygroscopic solid. − M.p. 139−142°C; ref.[18] 156−161°C. − $[\alpha]_D^{25}$ = +21.7 (*c* = 7.0, H_2O); ref.[19] +21.0 (*c* = 7.0, H_2O). − ^{1}H NMR (D_2O): δ = 2.28 (m, 2 H, CH_2CH), 2.66 (td, 2 H, *J* = 7.5 Hz, 1.9 Hz, CH_2CO_2H), 2.82 (s, 3 H, CH_3), 4.00 (m, 1 H, CH). − ^{13}C NMR (D_2O): δ = 26.6 (*C*H_2CH), 32.1 (*C*H_2CO_2H), 34.5 (CH_3), 63.4 (CH), 174.0, 179.1 (2 × CO_2H). − MS (EI), *m/z* (%):161 [M − HCl]$^+$ (20), 116 [M − CO_2H − HCl]$^+$ (60), 98 (100). − $C_5H_{11}NO_4$ × HCl (197.6): calcd. with $^1/_8$ H_2O C 36.06, H 6.18, N 7.01; found C 35.96, H 5.74, N 6.74.

L-α-Methylaminoadipic Acid (5c): Reaction of **4c** (0.65 g, 2 mmol) gave 0.22 g (63%) of **5c**. − M.p. 157−159°C. − $[\alpha]_D^{25}$ = +18.7 (*c* = 1.5, H_2O). − ^{1}H NMR (D_2O): δ = 1.51 (m, 2 H, CH_2), 1.75 (m, 2 H, CH_2CH), 2.29 (t, 2 H, *J* = 7.0 Hz, CH_2CO_2H), 2.55 (s, 3 H, CH_3), 3.46 (t, 1 H, *J* = 6.0 Hz, CH). − ^{13}C NMR (D_2O): δ = 22.6 (CH_2), 31.4 (*C*H_2CH), 34.6 (CH_3), 36.2 (*C*H_2CO_2H), 66.0 (CH), 176.2, 180.9 (2 × CO_2H). − MS (EI), *m/z* (%): 175 $[M]^+$ (8), 158 (48), 113 (100). − $C_7H_{13}NO_4$ (175.2): calcd. C 47.99, H 7.48, N 8.00; found C 48.21, H 7.50, N 7.84.

(2*S*)-*N*-Methyl-3-(2-phenyl-1,3-thiazol-4-yl)alanine (12a): Reaction of **11a** (0.82 g, 2 mmol) gave 0.38 g (73%) of **12a**. − M.p. 218−232°C (dec.). − $[\alpha]_D^{25}$ = + 23.3 (*c* = 2.0, DMSO+ 5% TFA). − ^{1}H NMR ([D$_6$]DMSO + 5% TFA): δ = 2.66 (s, 3 H, CH_3), 3.39 (m, 2 H, CH_2), 4.36 (m, 1 H, CH), 7.49 (m, 4 H, arom.), 7.93 (m, 2 H, arom.). − ^{13}C NMR ([D$_6$]DMSO + 5% TFA): δ = 30.7 (CH_2), 32.5 (CH_3), 60.2 (CH), 118.8 (S−*C*H=C), 127.2, 130.1, 131.3, 133.9 (phenyl), 151.4 (S−CH=*C*), 168.4 [*C*(Ph)], 170.6 (CO_2H). − MS (EI), *m/z* (%): 262 $[M]^+$ (4), 217 [M − CO_2H]$^+$ (11), 175 (100). − $C_{13}H_{14}N_2O_2S$ (262.3): calcd. C 59.52, H 5.38, N 10.68; found C 59.26, H 5.37, N 10.51.

(2*S*)-2-(Methylamino)-4-(2-phenyl-1,3-thiazol-4-yl)butyric Acid (12b): Reaction of **11b** (0.85 g, 2 mmol) gave **12b** (0.45 g, 81%). − M.p. 216−219°C (dec.). − $[\alpha]_D^{25}$ = +34.3 (*c* = 2.0, DMSO + 5% TFA). − ^{1}H NMR ([D$_6$]DMSO + 5% TFA): δ = 2.31 (m, 2 H, CH_2CH), 2.67 (s, 3 H, CH_3), 2.92 (m, 2 H, CH_2CH_2CH), 4.06 (m, 1 H, CH), 7.48 (m, 4 H, arom.), 7.93 (m, 2 H, arom.). − ^{13}C NMR ([D$_6$]DMSO + 5% TFA): δ = 26.6 (*C*H_2CH), 28.3 (*C*H_2CH_2CH), 31.5 (CH_3), 59.7 (CH), 115.3 (S−*C*H=C), 126.3, 129.4, 130.4, 133.3 (phenyl), 155.9 (S−CH=*C*), 167.1 [*C*(Ph)], 170.3 (CO_2H). − MS (EI), *m/z* (%): 276 $[M]^+$ (4), 231 [M − CO_2H]$^+$ (21), 188 (35), 175 (100). − $C_{14}H_{16}N_2O_2S$ (276.4): calcd. C 60.85, H 5.84, N 10.14; found C 60.51, H 5.70, N 10.12.

General Procedure (4 → 6, 7 → 8): Oxazolidinone **4** or **7** (2 mmol) and L-methyl phenylalaninate (0.72 g, 4 mmol) were dissolved in dry ether (2 mL) and stirred for several days. The progress of the reaction was monitored by TLC. The white precipitate was filtered off, dissolved in H_2O (50 mL) and lyophilized. Hexafluoroacetone hydrate was removed from the product by repeated lyophilization.

Methyl (*N*-Methyl-L-asparagyl)-L-phenylalaninate (6a): Using the above procedure, **4a** (0.59 g, 2 mmol) gave 0.47 g (76%) of **6a**, which had a sweet taste. − M.p. 141−143°C. − $[\alpha]_D^{25}$ = −30.5 (*c* = 2.0, H_2O); − ^{1}H NMR (D_2O): δ = 2.26 (s, 3 H, CH_3), 2.55 (m, 2 H, CH_2CH), 2.84 (dd, 1 H, *J* = 14.0, 10.2 Hz, CH_2Ph), 3.20 (dd, 1 H, *J* = 13.8, 5.0 Hz, CH_2Ph), 3.63 (s, 3 H, OCH_3), 3.82 (m, 1 H, CH_{Asp}), 4.65 (m, 1 H, CH_{Phe}), 7.18 (m, 5 H, phenyl). − ^{13}C NMR (D_2O): δ = 31.9 (CH_3), 36.7, 36.9 (2 × CH_2), 53.4, 54.5 (CH_{Phe}, OCH_3), 59.4 (CH_{Asp}), 127.7, 129.3, 129.7, 136.9 (phenyl), 168.5, 173.3, 176.0 (3 × CO). − MS (FAB), *m/z* (%): 331.0 [M + Na]$^+$, 309.0 [M + H]$^+$. − $C_{15}H_{20}N_2O_5$ (308.3): calcd. with $^1/_4$ H_2O C 54.46, H 6.86, N 8.46; found C 54.48, H 6.28, N 8.26.

Methyl (*N*-Methyl-L-glutamyl)-L-phenylalaninate (6b): Reaction of **4b** (0.62 g, 2 mmol) gave 0.46 g (71%) of **6b**. − M.p. 124−127°C. − $[\alpha]_D^{25}$ = −9.0 (*c* = 2.0, H_2O). − ^{1}H NMR (D_2O): δ = 1.86 (m,

2 H, CH_2CH), 2.14 (m, 5 H, CH_2CO$_2$H, CH$_3$), 2.82 (dd, 1 H, J = 13.8 Hz, 10.4 Hz, CH$_2$Ph), 3.22 (dd, 1 H, J = 14.2 Hz, 5.4 Hz, CH$_2$Ph), 3.63 (s, 3 H, OCH$_3$), 3.85 (m, 1 H, CH$_{Glu}$), 4.73 (dd, 1 H, J = 10.6 Hz, 5.2 Hz, CH$_{Phe}$), 7.13−7.22 (m, 5 H, phenyl). − ^{13}C NMR (D$_2$O): δ = 27.1 (*C*H$_2$CH), 31.7 (*C*H$_2$CO$_2$H), 33.0 (CH$_3$), 36.8 (CH$_2$Ph), 53.4 (OCH$_3$), 54.4 (CH$_{Phe}$), 61.8 (CH$_{Glu}$), 127.7, 129.3, 129.6, 136.9 (phenyl), 168.7, 173.2, 180.7 (3 × CO). − MS (FAB), *m*/*z* (%): 344.9 [M + Na]$^+$, 323.0 [M + H]$^+$. − C$_{16}$H$_{22}$N$_2$O$_5$ (322.4): calcd. with $^3/_4$ H$_2$O C 57.21, H 7.13, N 8.34; found C 57.08, H 6.88, N 8.23.

Methyl (L-α-Methylaminoadipyl)-L-phenylalaninate (6c): Compound **4c** (0.63 g, 2 mmol) gave 0.45 g (68%) of **6c**. − M.p. 150−152°C. − [α]$_D^{25}$ = −7.5 (*c* = 2.0, H$_2$O). − ^{1}H NMR (D$_2$O): δ = 1.52 (m, 2 H, CH$_2$), 1.75 (m, 2 H, C*H*$_2$CH), 2.04 (t, 2 H, J = 6.6 Hz, C*H*$_2$CO$_2$H), 2.21 (s, 3 H, CH$_3$), 2.95 (dd, 1 H, J = 14.0, 11.0 Hz, CH$_2$Ph), 3.30 (dd, 1H, J = 13.6, 5.0 Hz, CH$_2$Ph), 3.67 (m, 1 H, CH), 3.73 (s, 3 H, OCH$_3$), 4.85 (m, 1 H, CH$_{Phe}$), 7.21−7.40 (m, 5 H, phenyl). − ^{13}C NMR (D$_2$O): δ = 23.7 (CH$_2$), 32.9 (*C*H$_2$CH), 34.1 (CH$_3$), 39.2 (*C*H$_2$CO$_2$H), 39.4 (CH$_2$Ph), 56.0 (OCH$_3$), 56.9 (CH$_{Phe}$), 64.3 (CH), 130.1, 131.7, 132.1, 139.4 (phenyl), 171.0, 175.6, 184.7 (3 × CO). − MS (FAB), *m*/*z* (%): 359.0 [M + Na]$^+$, 337.0 [M + H]$^+$. − C$_{17}$H$_{24}$N$_2$O$_5$ (336.4): calcd. with $^1/_3$ H$_2$O C 59.63, H 7.26, N 8.18; found C 59.57, H 7.09, N 8.05.

Methyl [L-*N*-Methyl-β-(D-α-methylbenzylamido)asparagyl]-L-phenylalaninate (8a): The reaction of **7a** (0.8 g, 2 mmol) gave 0.63 g (76%) of **8a**. Purification was performed by column chromatography; R_f = 0.35 (CHCl$_3$/light petroleum ether/MeOH, 6:3:1). − M.p. 80−82°C. − ^{1}H NMR (CDCl$_3$): δ = 1.40 (d, 3 H, J = 6.9 Hz, CHC*H*$_3$), 2.21 (br., 1 H, NH), 2.25 (s, 3 H, CH$_3$), 2.23 (m, 1 H, C*H*$_2$CH), 2.41 (m, 1 H, C*H*$_2$CH), 2.94 (dd, 1 H, J = 13.9, 7.2 Hz, C*H*$_2$Ph), 3.01 (dd, 1 H, J = 13.8, 5.7 Hz, C*H*$_2$Ph), 3.22 (m, 1 H, CH$_{Asp}$), 3.66 (s, 3 H, OCH$_3$), 4.74 (m, 1 H, CH$_{Phe}$), 5.00 (m, 1 H, C*H*CH$_3$), 6.69 (br., 1 H, NH), 7.03−7.65 (m, 10 H, 2 × phenyl), 7.65 (br., 1 H, NH). − ^{13}C NMR (CDCl$_3$): δ = 22.6 (CH*C*H$_3$), 35.1 (CH$_3$), 38.4 (CH$_{2Asp}$ and CH$_{2Phe}$), 49.3 (*C*HCH$_3$), 52.7 (OCH$_3$), 53.4 (CH$_{Phe}$), 62.3 (CH$_{Asp}$), 126.6, 127.5, 127.7, 129.0, 129.1, 129.7, 135.5, 144.0 (2 × phenyl), 170.6, 172.2, 173.7 (3 × CO). − C$_{23}$H$_{29}$N$_3$O$_4$ (411.5): calcd. with $^1/_2$ H$_2$O C 65.69, H 7.19, N 9.99; found C 65.59, H 7.21, N 9.60.

Methyl [L-*N*-Methyl-γ-(D-α-methylbenzylamido)glutamyl]-L-phenylalaninate (8b): Similarly, 0.82 g (2 mmol) of **7b** gave 0.41 g (48%) of **8b**. − M.p. 160−163°C. − [α]$_D^{25}$ = + 68.7 (*c* = 1.0, CHCl$_3$). − ^{1}H NMR (CDCl$_3$): δ = 1.45 (d, 3 H, J = 6.8 Hz, CHC*H*$_3$), 1.65−1.92 (m, 4 H, C*H*$_2$CH, C*H*$_2$CO), 2.28 (s, 3 H, CH$_3$), 2.95 (m, 2 H, CH$_{Glu}$, CH$_2$Ph), 3.23 (m, 1 H, CH$_2$Ph), 3.75 (s, 3 H, OCH$_3$), 4.90 (m, 1 H, CH$_{Phe}$), 5.51 (m, 1 H, C*H*CH$_3$), 6.30 (br., 1 H, NH), 7.10−7.35 (m, 10 H, 2 × phenyl), 7.61 (br., 1 H, NH). − ^{13}C NMR (CDCl$_3$): δ = 22.2 (CH*C*H$_3$), 30.0 (*C*H$_2$CH), 33.0 (*C*H$_2$CO), 35.6 (CH$_3$), 38.5 (CH$_2$Ph), 49.1 (*C*HCH$_3$), 52.7 (OCH$_3$), 52.9 (CH$_{Phe}$), 64.4 (CH$_{Glu}$), 126.7, 127.5, 127.8, 129.0, 129.1, 129.6, 136.8, 143.8 (2 × phenyl), 172.0, 172.6, 174.0 (3 × CO). − MS (FAB), *m*/*z* (%):448.3 [M + Na]$^+$, 426.3 [M + H]$^+$. − C$_{24}$H$_{31}$N$_3$O$_4$ (425.5): calcd. with $^1/_4$ H$_2$O C 67.03, H 7.38, N 9.77; found C 67.22, H 7.21, N 9.72.

General Procedure (3 → 7): To a solution of **3** (3 mmol) in dichloromethane (25 mL) D-α-methylbenzylamine (0.36 g, 3 mmol) was added slowly at 0°C with stirring. The mixture was allowed to warm up to room temperature. The organic phase was washed with water (3 × 5 mL), dried (MgSO$_4$), filtered, and concentrated. Recrystallization or flash chromatography gave pure compounds **7**.

[(4*S*)-3-Methyl-5-oxo-2,2-bis(trifluoromethyl)-1,3-oxazolidin-4-yl]-*N*-(D-α-methylbenzyl)acetamide (7a): Reaction of 0.94 g (3 mmol) of **3a** gave 0.78 g (65%) of **7a**. − M.p. 149−150°C. − [α]$_D^{25}$ = + 66.0 (*c* = 1.0, CHCl$_3$). − ^{1}H NMR (CDCl$_3$): δ = 1.51 (d, 3 H, J = 8.8 Hz, CHC*H*$_3$), 2.60 (q, 3 H, J = 2.2 Hz, CH$_3$), 2.47 (dd, 1 H, J = 15.2 Hz, 6.4 Hz, C*H*$_2$CH), 2.73 (dd, 1 H, J = 15.4 Hz, 4.8 Hz, C*H*$_2$CH), 4.15 (t, 1 H, J = 5.6 Hz, CH), 5.12 (m, 1 H, C*H*CH$_3$), 6.00 (br., 1 H, NH), 7.32 (m, 5 H, phenyl). − ^{13}C NMR (CDCl$_3$): δ = 21.9 (CH*C*H$_3$), 33.6 (br., CH$_3$), 38.8 (*C*H$_2$CH), 49.8 (*C*HCH$_3$), 58.0 (CH), 90.1 [m, *C*(CF$_3$)$_2$], 120.9 (q, J = 287 Hz, CF$_3$), 121.9 (q, J = 295 Hz, CF$_3$), 126.6, 128.1, 129.3 and 143.1 (phenyl), 167.4 (CO), 170.2 (CONH). − ^{19}F NMR (CDCl$_3$): δ = −1.13 (m, 3 F, CF$_3$), 4.39 (m, 3 F, CF$_3$). − IR (KBr): $\tilde{\nu}$ = 1848 cm^{-1} (CO$_{lactone}$), 1649 (CO$_{amide}$). − MS (EI), *m*/*z* (%): 398 [M]$^+$ (5), 294 (11), 250 (13), 105 (100). − C$_{16}$H$_{16}$F$_6$N$_2$O$_3$ (398.3): calcd. C 48.25, H 4.05, N 7.03; found C 47.96, H 4.04, N 6.82.

***N*-(D-α-Methylbenzyl)-3-[(4*S*)-3-methyl-5-oxo-2,2-bis(trifluoromethyl)-1,3-oxazolidin-4-yl]propionyl Amide (7b):** Reaction of **3b** (0.98 g, 3 mmol) gave 0.8 g (65%) of **7b**. − M.p. 52−54°C (*n*-hexane). − [α]$_D^{25}$ = + 80.0 (*c* = 1.0, CHCl$_3$). − ^{1}H NMR (CDCl$_3$): δ = 1.49 (d, 3 H, J = 7.0 Hz, CHC*H*$_3$), 2.08−2.06 (m, 4 H, C*H*$_2$CH, C*H*$_2$CO), 2.68 (q, 3 H, J = 2.2 Hz, CH$_3$), 3.68 (m, 1 H, CH), 5.09 (m, 1 H, C*H*CH$_3$), 5.68 (br., 1 H, NH), 7.21−7.30 (m, 5 H, phenyl). − ^{13}C NMR (CDCl$_3$): δ = 22.1 (CH*C*H$_3$), 24.5 (*C*H$_2$CH), 29.8 (*C*H$_2$CO), 32.1 (br., CH$_3$), 49.4 (*C*HCH$_3$), 59.8 (CH), 89.3 [m, *C*(CF$_3$)$_2$], 121.0 (q, J = 287 Hz, CF$_3$), 122.1 (q, J = 295 Hz, CF$_3$), 126.6, 127.8, 129.1, 143.8 (phenyl), 170.3, 171.0 (2 × CO). − ^{19}F NMR (CDCl$_3$): δ = −0.83 (m, 3 F, CF$_3$), 4.40 (m, 3 F, CF$_3$). − IR (KBr): $\tilde{\nu}$ = 1838 cm^{-1} (CO$_{lactone}$), 1641 (CO$_{amide}$). − MS (EI), *m*/*z* (%): 412 [M]$^+$ (19), 342 (2), 306 (24). − C$_{17}$H$_{18}$F$_6$N$_2$O$_3$ (412.3): calcd. C 49.53, H 4.40, N 6.80; found C 49.13, H 4.47, N 6.56.

General Procedure (3 → 9): To a solution of diazomethane (8−10 equiv.) in ether (150 mL), oxazolidinone **3** (30 mmol in 50 mL of Et$_2$O) was added dropwise at 0°C with stirring. Stirring was continued until gas evolution ceased (ca. 1.5 h). The reaction mixture was allowed to warm to room temperature and the volatiles were removed in vacuo (caution must be taken for the diazomethane). The residue was purified by kugelrohr distillation.

(4*S*)-4-(3-Diazo-2-oxopropyl)-3-methyl-2,2-bis(trifluoromethyl)-1,3-oxazolidin-5-one (9a): Using the above procedure, 9.4 g (30 mmol) of **3a** gave 7.18 g (75%) of **9a**. − M.p. 45−47°C. − B.p. 94−97°C (0.7 Torr). − [α]$_D^{25}$ = +1.7 (*c* = 3.0, CHCl$_3$). − ^{1}H NMR (CDCl$_3$): δ = 2.70 (q, 3 H, J = 1.6 Hz, CH$_3$), 2.78 (m, 2 H, C*H*$_2$CH), 4.16 (m, 1 H, CH), 5.35 (s, 1 H, CH=N$_2$). − ^{13}C NMR (CDCl$_3$): δ = 33.8 (br., CH$_3$), 42.0 (*C*H$_2$CH), 56.2 (CH=N$_2$), 57.3 (CH$_3$), 90.1 [m, *C*(CF$_3$)$_2$], 120.9 (q, J = 288 Hz, CF$_3$), 121.9 (q, J = 295 Hz, CF$_3$), 170.0 (CO), 189.3 (*C*OCH$_2$). − ^{19}F NMR (CDCl$_3$): δ = −1.07 (m, 3 F, CF$_3$), 4.30 (m, 3 F, CF$_3$). − IR (KBr): $\tilde{\nu}$ = 2112 cm^{-1} (CN$_2$), 1842 (CO$_{lactone}$), 1648 (CO$_{ketone}$). − MS (EI), *m*/*z* (%):249 [M − COCHN$_2$]$^+$ (64), 236 [M − CH$_2$COCHN$_2$]$^+$ (16), 180 (53). − C$_9$H$_7$F$_6$N$_3$O$_3$ (319.2): calcd. C 33.87, H 2.21; found C 33.79, H 2.27.

(4*S*)-4-(4-Diazo-3-oxobutyl)-3-methyl-2,2-bis(trifluoromethyl)-1,3-oxazolidin-5-one (9b): Similarly, **3b** (9.83 g, 30 mmol) gave 9.0 g (85%) of **9b**. − B.p. 75−80°C (0.1 Torr); R_f = 0.3 (light petroleum/ethyl acetate, 3:1). − [α]$_D^{25}$ = +22.7 (*c* = 1.5, CHCl$_3$). − ^{1}H NMR (CDCl$_3$): δ = 2.18 (m, 2 H, C*H*$_2$CH), 2.40 (m, 2 H, COC*H*$_2$), 2.70 (q, 3 H, J = 2.0 Hz, CH$_3$), 3.67 (m, 1 H, CH), 5.25 (br., 1 H, CH=N$_2$). − ^{13}C NMR (CDCl$_3$): δ = 23.7 (*C*H$_2$CH), 33.2 (br., CH$_3$), 34.5 (CO*C*H$_2$), 55.2 (CH=N$_2$), 59.8 (CH), 90.0 [m, *C*(CF$_3$)$_2$], 121.0 (q, J = 288 Hz, CF$_3$), 122.0 (q, J = 295 Hz, CF$_3$), 169.9 (CO), 193 (*C*OCH$_2$). − ^{19}F NMR (CDCl$_3$): δ = −0.95 (m, 3 F, CF$_3$), 4.30 (m, 3 F, CF$_3$). − IR (film): $\tilde{\nu}$ = 2109 cm^{-1} (CN$_2$), 1837 (CO$_{lactone}$),

1645 (CO_{ketone}). – MS (EI), *m/z* (%): 333 $[M]^+$ (5). – $C_{10}H_9F_6N_3O_3$ (333.2): calcd. C 36.05, H 2.72; found C 35.77, H 2.69.

General Procedure (9 → 10): To a solution of diazo ketone **9** (15 mmol) in THF (40 mL) concd. HBr (10 mL) was added at 0°C, stirring was continued until gas evolution ceased. The mixture was concentrated and the residue dissolved in dichloromethane (50 mL), washed with ice-cold $NaHCO_3$ solution (3 × 5 mL) and water (3 × 5 mL), dried ($MgSO_4$), filtered, and concentrated. Recrystallization or flash chromatography gave pure compounds **10**.

(4*S*)-4-(3-Bromo-2-oxopropyl)-3-methyl-2,2-bis(trifluoromethyl)-1,3-oxazolidin-5-one (10a): Reaction of **9a** (4.79 g, 15 mmol) gave 4.24 g (76%) of **10a**. – M.p. 62–63°C (*n*-hexane/chloroform). – $[\alpha]_D^{25}$ = +25.7 (*c* = 3.0, $CHCl_3$). – ^{1}H NMR ($CDCl_3$): δ = 2.69 (q, 3 H, *J* = 2.0 Hz, CH_3), 3.06 (dd, 1 H, *J* = 18.4 Hz, 5.4 Hz, C*H*$_2$CH), 3.31 (dd, 1 H, *J* = 18.4 Hz, 4.4 Hz, C*H*$_2$CH), 3.91 (s, 2 H, CH_2Br), 4.07 (t, 1 H, *J* = 4.6 Hz, CH). – ^{13}C NMR ($CDCl_3$): δ = 33.8 (br., CH_3), 34.1 (CH_2Br), 40.8 (*C*H$_2$CH), 56.9 (CH), 89.9 [m, *C*(CF_3)$_2$], 120.8 (q, *J* = 288 Hz, CF_3), 121.8 (q, *J* = 296 Hz, CF_3), 169.8 (CO), 197.8 (*C*OCH_2). – ^{19}F NMR ($CDCl_3$): δ = −0.85 (m, 3 F, CF_3), 4.38 (m, 3 F, CF_3). – IR (KBr): $\tilde{\nu}$ = 1834 cm^{-1} ($CO_{lactone}$), 1747 (CO_{ketone}). – MS (EI), *m/z* (%):373 and 371 $[M]^+$ (3), 292 (100), 236 (10). – $C_9H_8BrF_6NO_3$ (372.1): calcd. C 29.05, H 2.17, N 3.76; found C 29.40, H 2.22, N 3.69.

(4*S*)-4-(4-Bromo-3-oxobutyl)-3-methyl-2,2-bis(trifluoromethyl)-1,3-oxazolidin-5-one (10b): Reaction of **9b** (5.0 g, 15 mmol) gave 4.69 g (81%) of **10b** as an oil. – R_f = 0.4 (light petroleum/ethyl acetate, 4:1). – $[\alpha]_D^{25}$ = +17.6 (*c* = 4.5, $CHCl_3$). – ^{1}H NMR ($CDCl_3$): δ = 2.19 (m, 2 H, C*H*$_2$CH), 2.67–2.82 (m, 5 H, CH_3, CH_2CH_2CO), 3.68 (m, 1 H, CH), 3.90 (s, 2 H, CH_2Br). – ^{13}C NMR ($CDCl_3$): δ = 22.9 (*C*H$_2$CH), 33.3 (br., CH_3), 33.8 (CH_2Br), 34.3 (CH_2CH_2CO), 59.7 (CH), 89.9 [m, *C*(CF_3)$_2$], 120.9 (q, *J* = 286 Hz, CF_3), 122.0 (q, *J* = 295 Hz, CF_3), 169.7 (CO), 200.9 (CH_2CO). – ^{19}F NMR ($CDCl_3$): δ = −0.84 (m, 3 F, CF_3), 4.43 (m, 3 F, CF_3). – IR (film): $\tilde{\nu}$ = 1837 cm^{-1} ($CO_{lactone}$), 1722 (CO_{ketone}). – MS (EI), *m/z* (%): 387 and 385 $[M]^+$ (7), 306 (86), 128 (100). – $C_{10}H_{10}BrF_6NO_3$ (386.1): calcd. C 31.11, H 2.61, N 3.63; found C 31.30, H 2.52, N 3.88.

General Procedure (10 → 11): A solution of bromo ketone **10** (3 mmol) and thiobenzamide (0.49 g, 3.6 mmol) in acetone (10 mL) was heated under reflux for 3 h. The clear solution was stirred for 12 h at room temperature. After concentration, the residue was suspended in an ice-cold concd. aqueous solution of $NaHCO_3$ (3 mL) and extracted with ether (20 mL). The organic layer was washed (2 × 5 mL of $NaHCO_3$ half-concd., 2 × 5 mL of H_2O), dried ($MgSO_4$), and concentrated. Recrystallization or flash chromatography gave pure compounds **11**.

(4*S*)-3-Methyl-4-[(2-phenyl-1,3-thiazol-4-yl)methyl]-2,2-bis-(trifluoromethyl)-1,3-oxazolidin-5-one (11a): Reaction of **10a** (1.12 g, 3 mmol) gave 0.88 g (71%) of **11a** as a yellowish oil. – R_f = 0.42 (light petroleum/ethyl acetate, 4:1). – $[\alpha]_D^{25}$ = +2.8 (*c* = 2.5, $CHCl_3$). – ^{1}H NMR ($CDCl_3$): δ = 2.81 (q, 3 H, *J* = 2.0 Hz, CH_3), 3.23 (dd, 1 H, *J* = 14.8 Hz, 4.6 Hz, C*H*$_2$CH), 3.35 (dd, 1 H, *J* = 14.8 Hz, 5.2 Hz, C*H*$_2$CH), 4.09 (t, 1 H, *J* = 5.0 Hz, CH), 7.01 (s, 1 H, S–CH=C), 7.43 (m, 3 H, phenyl), 7.89 (m, 2 H, phenyl). – ^{13}C NMR ($CDCl_3$): δ = 32.8 (*C*H$_2$CH), 33.5 (br., CH_3), 60.6 (CH), 89.9 [m, *C*(CF_3)$_2$], 116.6 (S–*C*H=C), 120.8 (q, *J* = 286 Hz, CF_3), 122.2 (q, *J* = 296 Hz, CF_3), 127.0, 129.5, 130.6, 134.0 (phenyl), 151.6 (S–CH=*C*), 168.7, 169.9 [*C*(Ph), CO]. – ^{19}F NMR ($CDCl_3$): δ = −1.13 (m, 3 F, CF_3), 4.22 (m, 3 F, CF_3). – IR (KBr): $\tilde{\nu}$ = 1840 cm^{-1} (CO). – MS (EI), *m/z* (%): 410 $[M]^+$ (57), 395 (11), 174 (100). – $C_{16}H_{12}F_6N_2O_2S$ (410.3): calcd. C 46.83, H 2.94, N 6.83; found C 46.83, H 2.65, N 6.77.

(4*S*)-3-Methyl-4-[2-(2-phenyl-1,3-thiazol-4-yl)ethyl]-2,2-bis-(trifluoromethyl)-1,3-oxazolidine-5-one (11b): Reaction of **10b** (1.16 g, 3 mmol) gave 0.94 g (74%) of **11b**. – M.p. 90°C; R_f = 0.45 (light petroleum/ethyl acetate, 4:1). – $[\alpha]_D^{25}$ = +41.0 (*c* = 3.0, $CHCl_3$). – ^{1}H NMR ($CDCl_3$): δ = 2.32 (m, 2 H, C*H*$_2$CH), 2.74 (q, 3 H, *J* = 2.2 Hz, CH_3), 2.78 (m, 1 H, C*H*$_2$CH$_2$CH), 3.02 (m, 1 H, C*H*$_2$CH$_2$CH), 3.73 (m, 1 H, CH), 6.94 (s, 1 H, S–CH=C), 7.44 (m, 3 H, phenyl), 7.93 (m, 2 H, phenyl). – ^{13}C NMR ($CDCl_3$): δ = 25.9 (*C*H$_2$CH), 29.0 (*C*H$_2$CH$_2$CH), 33.3 (br., CH_3), 60.1 (CH), 90.0 [m, *C*(CF_3)$_2$], 114.3 (S–*C*H=C), 121.1 (q, *J* = 285 Hz, CF_3), 122.2 (q, *J* = 294 Hz, CF_3), 126.9, 129.4, 130.4, 134.2 (phenyl), 156.7 (S–CH=*C*), 168.5, 170.0 [*C*(Ph), CO]. – ^{19}F NMR ($CDCl_3$): δ = −0.73 (m, 3 F, CF_3), 4.40 (m, 3 F, CF_3). – IR (KBr): $\tilde{\nu}$ = 1837 cm^{-1} (CO). – MS (EI), *m/z* (%): 424 $[M]^+$ (12), 175 (100). – $C_{17}H_{14}F_6N_2O_2S$ (424.4): calcd. C 48.12, H 3.33, N 6.60; found C 48.01, H 3.33, N 6.27.

4-[(4*S*)-3-Methyl-5-oxo-2,2-bis(trifluoromethyl)-1,3-oxazolidin-4-yl]-butyric Acid (4c): Diazo ketone **9b** (3.33 g, 10 mmol) was dissolved in THF/H_2O (15 mL/5 mL). On addition of silver benzoate (0.23 g, 1 mmol) the mixture became muddy brown. On sonication using an ultrasound cleaning bath, gas evolution increased. The progress of the reaction was monitored by TLC. In case the reaction ceased before complete consumption of the starting material, further silver benzoate was added. After complete consumption of the starting material, the mixture was concentrated, dissolved in dichloromethane (50 mL), filtered, washed (3 × 10 mL of H_2O), dried ($MgSO_4$), and purified by flash chromatography. Compound **4c** (1.78 g, 55%) was obtained as a colourless oil. – R_f = 0.1–0.4 (ethyl acetate/light petroleum ether/1% HOAc, 2:3). – $[\alpha]_D^{25}$ = +29.3 (*c* = 2.5, $CHCl_3$). – ^{1}H NMR ($CDCl_3$): δ = 1.49 (m, 1 H, C*H*$_2$CH$_2$CH), 1.80–1.94 (m, 3 H, C*H*$_2$CH$_2$CH, C*H*$_2$CH), 2.39 (m, 2 H, C*H*$_2$CO$_2$H), 2.71 (q, *J* = 2.0 Hz, CH_3), 3.64 (m, 1 H, CH). – ^{13}C NMR ($CDCl_3$): δ = 18.6 (*C*H$_2$CH$_2$CH), 28.1 (*C*H$_2$CH), 33.1 (br., CH_3), 33.6 (*C*H$_2$CO$_2$H), 60.4 (CH), 89.9 [m, *C*(CF_3)$_2$], 121.1 (q, *J* = 287 Hz, CF_3), 122.2 (q, *J* = 295 Hz, CF_3), 169.9 (CO), 179.8 (CO_2H). – ^{19}F NMR ($CDCl_3$): δ = −0.73 (m, 3 F, CF_3), 4.36 (m, 3 F, CF_3). – IR (KBr): $\tilde{\nu}$ = 1839 cm^{-1} ($CO_{lactone}$), 1714 (CO_2H). – MS (EI), *m/z* (%): 323 $[M]^+$ (7), 305 (29), 249 (100). – $C_{10}H_{11}F_6NO_4$ (323.2): calcd. C 37.16, H 3.43, N 4.33; found C 37.17, H 3.71, N 4.47.

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