7.2 Ugi four-component reaction

General procedure for Ugi 5-center 4-component reaction

U5-4CR

Dry methanol was placed into a flame-dried flask under an argon atmosphere, and was cooled to –30°C. The reactants were added slowly via syringes at –30°C. Upon addition of all components reaction mixture temperature was allowed to rise to room temperature and was stirred for 24-240 hours at room temperature. The reaction mixture was filtered and the solvent was evaporated under reduced pressure leaving crude product or mixture of products.

7.2.1 Synthesis of α-acylaminoamides and fuctionalized pyrrolidinones

Synthesis of Methyl N^1-Benzyl-N^2-[(1*S*)-1-benzyl-2-methoxy-2-oxoethyl]glutaminate (84a)

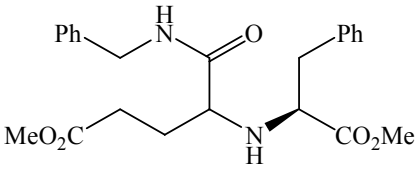
E 2 (IV 9)

Starting amounts:

0.376 g	(2.00 mmol) Siloxycyclopropanecarboxylate **53**
0.330 g	(2.00 mmol) L-Phenylalanine
0.235 g	(2.00 mmol) Benzylisocyanide
20 ml	MeOH, dry

Procedure according to **U5-4CR**
Reaction time: 96 hours

Purification: Column chromatography on activated alox with hexane/ethyl acetate 1:1
Yield: 266 mg (32 %) of **84a** as colourless oil; ratio of diastereoisomers: 82:18



84a

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 1.68–2.08 (m, 4 H, CH_2), 2.20 (t, *J* = 7.4 Hz, ≈ 0.8 H, CH), 2.45 (t, *J* = 7.4 Hz, ≈ 0.2 H, CH), 2.52–2.62 (m, ≈ 0.2 H, CH), 2.78–2.87 (m, ≈ 0.8 H, CH), 2.98–3.33 (m, ≈ 2.2 H, C*H*$_2$Ph, NH), 3.46–3.52 (m, ≈ 0.8 H, NH), 3.54, 3.63, 3.66*, 3.73* (4 s, 6 H, OMe), 4.21–4.31 (m, ≈ 0.4 H, NC*H*$_2$Ph), 4.37 (dd, *J* = 5.9, 2.2 Hz, ≈ 1.6 H, NC*H*$_2$Ph), 6.77 (bs, ≈ 0.2 H, NH), 7.09–7.36 (m, 10 H, Ph), 7.50 (t, *J* = 5.9 Hz, ≈ 0.8 H, NH).
^{13}C-NMR (62.9 MHz, $CDCl_3$): δ = 26.8, 28.0*, 29.8, 30.3*, 38.7, 39.6*, 42.2*, 42.8 (8 t, CH_2), 51.2, 51.3*, 51.5, 51.7* (4 q, OMe), 60.0, 60.6*, 61.5, 62.0* (4 d, CHN), 126.0, 126.5, 126.6, 126.8, 126.9, 127.0, 127.3, 127.6, 128.1, 128.2, 128.3, 128.8, 129.0 (13 d, Ph), 136.6, 137.3*, 138.1, 138.2* (4 s, Ph), 172.6*, 172.7, 173.2, 173.3*, 173.6, 174.4* (6 s, C=O); **minor isomer.*

IR (KBr): ν = 3330 cm^{-1} (N-H), 3085–2950 (C-H), 1735 (C=O), 1655 (C=O), 1200 (C-O).

MS (EI, 80 eV, 90 °C): *m/z* (%) = 412 (1, $[M]^+$), 321 (13), 279 (19), 278 (100), 218 (21), 186 (26), 91 (33 $[Bn]^+$).
HRMS (EI) *m/z* calculated for $[M^+]$: 412.19982, found: 412.19757.

$C_{23}H_{28}N_2O_5$ (412.5)	calc.	C 66.97	H 6.84	N 6.79
	found	C 66.97	H 5.82	N 6.35

Synthesis of Methyl N^2-[(1*S*)-1-Benzyl-2-methoxy-2-oxoethyl]-N^1-butylglutaminate (84b[a,b]) and Methyl 2-(2-(Butylcarbamoyl)-5-oxopyrrolidin-1-yl)-3-phenylpropanoate (85b)

E 3 (IV 15)

Starting amounts:

0.376 g	(2.00 mmol) Siloxycyclopropanecarboxylate **53**
0.330 g	(2.00 mmol) L-Phenylalanine
0.166 g	(2.00 mmol) *n*-Butylisocyanide
20 ml	MeOH, dry

Procedure according to **U5-4CR**

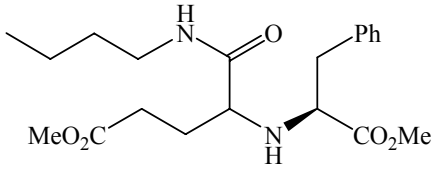
Reaction time: 54 hours

Purification: Column chromatography on activated alox with hexane/ethyl acetate 1:1, then HPLC (10 % *i*-propanol/hexane, 64 ml/min, 80 bar)

Yield: 135 mg (18 %) of **84b**[a] as colourless oil

33 mg (4 %) of **84b**[b] as colourless oil; ratio of diastereoisomers: 83:17

28 mg (4 %) of **85b** as colourless oil; ratio of diastereoisomers: > 95:5



84b[a,b]

84b[a]

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.91 (t, *J* = 7.2 Hz, 3 H, Me), 1.17–1.50 (m, 4 H, CH_2), 1.66–1.98 (m, 4 H, CH_2), 2.20 (t, *J* = 7.6 Hz, 2 H, CH_2), 2.81–3.22 (m, 3 H, CH, C*H*$_2$Ph), 3.49 (dd, *J* = 7.8, 5.9 Hz, 1 H, CH), 3.64, 3.67 (2 s, 6 H, OMe), 7.12-7.34 (m, 7 H, Ph, NH).

^{13}C-NMR (62.9 MHz, $CDCl_3$): δ = 13.5 (q, Me), 19.8, 28.0, 29.8, 31.4, 38.6, 38.7 (6 t, CH_2), 51.4, 51.7 (2 q, OMe), 60.6, 61.5 (2 d, CHN), 126.8, 128.4, 128.9 (3 d, Ph), 136.5 (s, Ph), 172.7, 173.4, 173.9 (3 s, C=O).

IR (KBr): ν = 3330 cm^{-1} (N-H), 3090–2855 (C-H), 1735 (C=O), 1675 (C=O), 1200 (C-O).

MS (EI, 80 eV, 90 °C): *m/z* (%) = 378 (1, $[M]^+$), 287 (11), 279 (18), 278 (100).
HRMS (EI) *m/z* calculated for $[M]^+$: 378.21547, found: 378.21731.

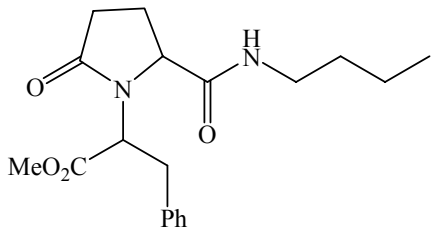
$C_{20}H_{30}N_2O_5$ (378.5)	calc.	C 63.47	H 7.99	N 7.40
	found	C 63.96	H 7.65	N 7.32

84b[b]

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.81–1.14 (m, 7 H, Me, CH_2), 1.80–2.13 (m, 2 H, CH_2), 2.42–2.64 (m, 4 H, CH_2), 2.91–3.08 (m, 3 H, CH, C*H*$_2$Ph), 3.21–3.26 (m, 1 H, CH), 3.68, 3.74 (2 s, 6 H, OMe), 6.36 (bs, 1 H, NH), 7.23–7.37 (m, 6 H, Ph, NH).
^{13}C-NMR (62.9 MHz, $CDCl_3$): δ = 13.6 (q, Me), 19.9, 28.7, 30.6, 31.4, 38.4, 40.0 (6 t, CH_2), 51.6, 52.0 (2 q, OMe), 61.4 (d, CHN), 62.2 (d, C-2), 126.8, 128.5, 129.5 (3 d, Ph), 137.9 (s, Ph), 172.5, 173.8, 174.8 (3 s, C=O).

IR (KBr): ν = 3330 cm^{-1} (N-H), 3090–2855 (C-H), 1735 (C=O), 1675 (C=O), 1200 (C-O).

MS (EI, 80 eV, 90 °C): *m/z* (%) = 378 (1, $[M]^+$) 287 (13), 279 (18), 278 (100).
HRMS (EI) *m/z* calculated for [M^+, $C_{20}H_{30}N_2O_5$]: 378. 21547, found: 378.21835.



85b

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.91 (t, *J* = 7.2 Hz, 3 H, Me), 1.15–1.60 (m, 4 H, CH_2), 1.41–2.18 (m, 2 H, CH_2), 2.15–2.46 (m, 2 H, CH_2), 2.91–3.36 (m, 6 H, CH, CH_2, C*H*$_2$Ph), 3.90 (s, 3 H, OMe), 7.11–7.37 (m, 5 H, Ph), 8.06 (bs, 1 H, NH).
^{13}C-NMR (62.9 MHz, $CDCl_3$): δ = 13.7 (q, Me), 20.1, 25.2, 29.2, 31.2, 34.2, 39.3 (6 t, CH_2), 53.3 (q, OMe), 59.7, 64.0 (2 d, NCH, C-2), 127.3, 128.9, 129.0 (3 d, Ph), 136.9 (s, Ph), 171.4, 175.8 (2 s, C=O).

IR (KBr): ν = 3310 cm^{-1} (N-H), 3085–2875 (C-H), 1740 (C=O), 1675 (C=O), 1230 (C-O).

MS (EI, 80 eV, 90 °C): *m/z* (%) = 346 (21, $[M]^+$), 247 (17), 246 (100), 218 (10), 186 (33), 121 (12), 91 (14 $[Bn]^+$), 84 (13), 41 (11).
HRMS (EI) *m/z* calculated for [M^+, $C_{19}H_{26}N_2O_4$]: 346.18925, found: 346.18683.

Synthesis of Methyl 4-[(Methoxycarbonyl)methylcarbamoyl]-4-[(S)-1-(methoxycarbonyl)-2-phenylethylamino]butanoate (84c)

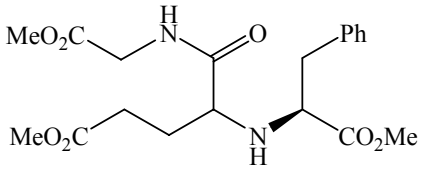
E 4 (IV 95)

Starting amounts:

0.376 g	(2.00 mmol) Siloxycyclopropanecarboxylate **53**
0.330 g	(2.00 mmol) L-Phenylalanine
0.198 g	(2.00 mmol) Methyl isocyanoacetate
20 ml	MeOH, dry

Procedure according to **U5-4CR**
Reaction time: 185 hours

Purification: Column chromatography on activated alox with hexane/ethyl acetate 1:1
Yield: 91 mg (12 %) of **84c** as colourless oil; ratio of diastereoisomers: 56:44



84c

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.83–4.57 (m, 11 H, CH, CH_2, NH), 3.63*, 3.64*, 3.67, 3.69, 3.70*, 3.74 (6 s, 9 H, OMe), 6.69 (bs, ≈ 0.6 H, NH), 7.07–7.43 (m, 5 H), 7.55 (bs, ≈ 0.4 H, NH).
^{13}C-NMR (62.9 MHz, $CDCl_3$): δ = 29.8, 30.2*, 36.7*, 38.8, 39.9*, 40.1, 40.3, 40.7* (8 t, CH_2), 51.5, 52.0*, 52.3, 54.4*, 55.8, 56.4* (6 q, OMe), 60.5, 61.2*, 61.3, 61.9* (4 d, CHN), 126.7, 126.9*, 127.0, 128.3*, 128.6*, 128.7, 129.0*, 129.1, 129.3*, 129.6 (10 d, Ph), 136.6*, 137.7 (2 s, Ph), 168.0, 169.6*, 171.8*, 171.9, 173.4, 173.6*, 174.0*, 174.6 (8 s, C=O); **minor isomer.*

IR (KBr): ν = 3330 cm^{-1} (N-H), 3060–2850 (C-H), 1740 (C=O), 1680 (C=O), 1210 (C-O).

MS (EI, 80 eV, 110 °C): *m/z* (%) = 394 (1, $[M]^+$), 303 (22), 279 (17), 278 (100), 186 (15).
HRMS (EI) *m/z* calculated for [M^+, $C_{19}H_{26}N_2O_5$]: 394.17400, found: 394.17843.

Synthesis of Methyl N^1-Benzyl-N^2-[(1*S*)-1-benzyl-2-methoxy-2-oxoethyl]-3-methylglutaminate (84d) and Methyl 2-(2-(Benzylcarbamoyl)-3-methyl-5-oxopyrrolidin-1-yl)-3-phenylpropanoate (85d)

E 5 (IV 4)

Starting amounts:

0.404 g	(2.00 mmol) Siloxycyclopropanecarboxylate **60**
0.330 g	(2.00 mmol) L-Phenylalanine
0.235 g	(2.00 mmol) Benzylisocyanide
20 ml	MeOH, dry

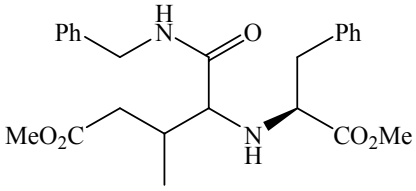
Procedure according to **U5-4CR**

Reaction time: 24 hours

Purification: Column chromatography on activated alox with hexane/ethyl acetate 1:1

Yield: 84 mg (10 %) of **84d** as colourless oil; ratio of diastereoisomers: 84:16

103 mg (13 %) of **85d** as colourless oil; ratio of diastereoisomers: 53:47



84d

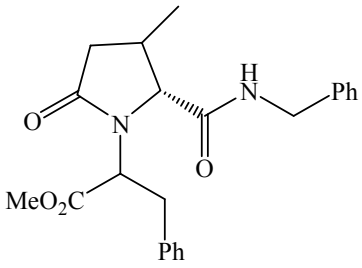
^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.75 (d, *J* = 6.9 Hz, 3 H, Me), 1.74–3.74 (m, 7 H, CH, CH_2, C*H*$_2$Ph), 3.54, 3.63 (2 s, 6 H, OMe), 4.39–4.42 (m, 2 H, NC*H*$_2$Ph), 6.67, 7.02 (2 bs, ≈ 0.32 H, NH), 7.07.16–7.34 (m, 10 H, Ph), 7.46, 7.54 (2 bs, ≈ 1.68 H, NH).

^{13}C-NMR (62.9 MHz, $CDCl_3$): δ = 15.1*, 15.6 (2 q, 3-Me), 33.5, 33.6* (2 d, CH), 37.5*, 38.3, 42.5*, 43.2, 43.3, 44.0* (6 t, CH_2), 51.4, 51.8, 52.0* (3 q, OMe), 62.4, 62.8*, 64.9*, 65.1 (4 d, CHN), 126.8, 126.9, 127.0, 127.1, 127.2, 127.3, 127.5, 127.8, 127.9, 128.3, 128.4, 128.5, 128.6, 128.7, 128.9, 129.0, 129.1, 129.2, 129.5, 129.9 (20 d, Ar), 136.7, 136.8*, 138.3, 138.4* (4 s, Ar), 172.2, 172.5*, 172.8, 173.1*, 173.8, 174.1* (6 s, C=O); **minor isomer.*

IR (KBr): ν = 3320 cm^{-1} (N-H), 3085–2850 (C-H), 1735 (C=O), 1675 (C=O), 1200 (C-O).

MS (EI, 80 eV, 90 °C): *m/z* (%) = 426 (1, $[M]^+$) 293 (18), 292 (100), 91 (39 $[Bn]^+$).
HRMS (EI) *m/z* calculated for $[M]^+$: 426.21547, found: 426.21722.

$C_{24}H_{30}N_2O_5$ (426.5)	calc.	C 67.59	H 7.09	N 6.57
	found	C 67.42	H 6.57	N 6.36



85d

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.76 (d, *J* = 6.9 Hz, 1.59 H, Me), 0.92* (d, *J* = 6.9 Hz, 1.41 H, Me), 1.82–2.62 (m, 3 H, CH, CH_2), 2.89–3.15 (m, 1 H, 2-H), 3.24–3.68 (m, 2 H, C*H*$_2$Ph), 3.64 (s, 3 H, OMe), 3.86–3.99 (m, 1 H, CHN), 4.22–4.50 (m, 2 H, NC*H*$_2$Ph), 7.10–7.35 (m, 10 H, Ph), 8.02 (bs, ≈ 0.53 H, NH), 8.12 (bs, ≈ 0.47 H, NH).
^{13}C-NMR (62.9 MHz, $CDCl_3$): δ = 15.7, 20.8* (2 q, Me), 31.0*, 33.0 (2 d, C-3), 34.2*, 34.4, 37.5*, 37.7, 43.3*, 43.4 (6 t, CH_2), 52.8, 52.9* (2 q, OMe), 58.8, 59.4*, 68.0*, 71.3 (4 d, NCH, C-2), 127.2, 127.4, 127.7, 127.8, 128.0, 128.6, 128.8, 128.9, 129.1, 129.2 (10 d, Ph), 136.6, 136.9*, 137.9, 138.0 (4 s, Ph), 168.7, 170.7*, 171.0*, 171.1, 175.0*, 181.7 (6 s, C=O); * *minor isomer.*

IR (KBr): ν = 3310 cm^{-1} (N-H), 3085–2875 (C-H), 1740 (C=O), 1675 (C=O), 1230 (C-O).

MS (EI, 80 eV, 90 °C): *m/z* (%) = 394 (19 $[M]^+$), 261 (18), 260 (100), 200 (22), 91 (40 $[Bn]^+$), 28 (11).

HRMS (EI) *m/z* calculated for $[M]^+$: 394.18925, found: 394.18832.

$C_{23}H_{26}N_2O_4$ (394.5)	calc.	C 70.03	H 6.64	N 7.10
	found	C 69.39	H 6.53	N 6.97

Synthesis of Methyl N^1-Benzyl-N^2-[(1*S*)-1-benzyl-2-methoxy-2-oxoethyl]-3,3-dimethylglutaminate (84e) and Methyl 2-(2-(Benzylcarbamoyl)-3,3-dimethyl-5-oxopyrrolidin-1-yl)-3-phenylpropanoate (85e)

Method A

E 6 (IV 13)

Starting amounts:

0.432 g	(2.00 mmol) Siloxycyclopropanecarboxylate **54**
0.330 g	(2.00 mmol) L-Phenylalanine
0.235 g	(2.00 mmol) Benzylisocyanide
20 ml	MeOH, dry

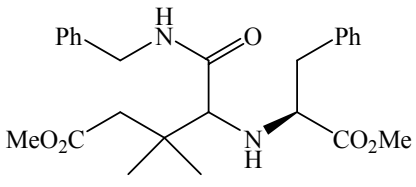
Procedure according to **U5-4CR**

Reaction time: 88 hours

Purification: Column chromatography on activated alox with hexane/ethyl acetate 1:1

Yield: 279 mg (32 %) of **84e** as colourless oil; ratio of diastereoisomers: 80:20

322 mg (39 %) of **85e** as colourless oil; ratio of diastereoisomers: 86:14



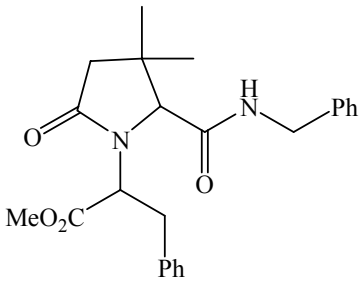
84e

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.86, 0.88, 0.99*, 1.06* (4 s, 6 H, Me), 2.01–2.43 (m, 5 H, CH, CH_2, C*H*$_2$Ph), 2.58–3.08 (m, 1 H, CH), 3.33–3.38 (m, 1 H, NH), 3.45, 3.51, 3.54*, 3.62* (4 s, 6 H, OMe), 4.35 (d, *J* = 5.2 Hz, 2 H, NC*H*$_2$Ph), 4.51* (bs, 2 H, NC*H*$_2$Ph), 6.97–7.29 (m, 11 H, Ph, NH).

^{13}C-NMR (62.9 MHz, $CDCl_3$): δ = 23.5, 23.6, 24.0*, 24.1* (4 q, Me), 35.5*, 37.0 (2 s, *C*Me$_2$), 38.9, 39.4*, 40.1, 42.1*, 42.7, 44.8* (6 t, CH_2), 50.6, 51.0, 51.3* (3 q, OMe), 61.3*, 63.2, 66.7, 68.1* (4 d, CHN), 125.6, 126.3, 126.7, 127.4, 127.0, 127.6, 127.8, 127.9, 128.1, 128.4, 128.5, 128.8 (12 d, Ph), 137.0*, 137.2, 138.0, 138.1* (4 s, Ph), 170.7*, 171.8, 172.6, 173.8 (4 s, C=O); * *minor isomer.*

IR (KBr): ν = 3320 cm^{-1} (N-H), 3085–2875 (C-H), 1735 (C=O), 1675 (C=O), 1230 (C-O).

MS (EI, 80 eV, 150 °C): *m/z* (%) = 440 (0.5, $[M]^+$), 325 (11), 307 (20), 306 (100), 290 (20), 274 (24), 169 (47), 148 (55), 147 (14), 121 (51), 91 (48 $[Bn]^+$), 78 (12), 63 (11), 28 (12).
HRMS (EI) *m/z* calculated for [M^+, $C_{25}H_{32}N_2O_5$]: 440.23112, found: 440.23355.



85e

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.64*, 0.72, 0.80*, 0.93 (4 s, 6 H, Me), 1.97* (d, *J* = 16.9 Hz, 1 H, 4-H), 2.00 (d, *J* = 16.7 Hz, 1 H, 4-H), 2.26 (d, *J* = 16.7 Hz, 1 H, 4-H), 2.28* (d, *J* = 16.9 Hz, 1 H, 4-H), 3.02*, 3.08 (2 s, 1 H, 2-H), 3.27–3.57 (m, 2 H, C*H*$_2$Ph), 3.58*, 3.60 (2 s, 3

H, OMe), 4.02 (dd, *J* = 10.1, 6.0 Hz, 1 H, CHN), 4.27–4.48 (m, 2 H, NC*H*$_2$Ph), 7.13–7.34 (m, ≈ 10.14 H, Ph, NH), 7.80 (bs, ≈ 0.86 H, NH).

^{13}C-NMR (62.9 MHz, $CDCl_3$): δ = 23.8, 24.4*, 29.4 (3 q, 3-Me), 34.5 (t, CH_2), 36.4, 36.5* (2 s, C-3), 43.3, 43.5*, 44.8 (3 t, CH_2), 52.6 (q, OMe), 58.4, 73.8 (2 d, NCH, C-2), 126.4, 126.7, 127.0, 127.4, 127.9, 128.0, 128.1, 128.5, 128.7, 129.0 (10 d, Ph), 136.1, 136.5*, 137.6, 138.0* (4 s, Ph), 169.1, 170.8, 174.5 (3 s, C=O); * *minor isomer.*

IR (KBr): ν = 3310 cm^{-1} (N-H), 3085–2870 (C-H), 1740 (C=O), 1675 (C=O), 1230 (C-O).

MS (EI, 80 eV, 150 °C): *m/z* (%) = 408 (10, $[M]^+$), 275 (18), 274 (100), 91 (25 $[Bn]^+$), 69 (10).

HRMS (EI) *m/z* calculated for $[M]^+$: 408.20490, found: 408.20266.

$C_{24}H_{28}N_2O_4$ (408.5)	calc.	C 70.57	H 6.91	N 6.86
	found	C 70.24	H 6.98	N 6.70

Method B

E 7 (IV 254)

Starting amounts:

0.432 g	(2.00 mmol) Siloxycyclopropanecarboxylate **54**
0.330 g	(2.00 mmol) L-Phenylalanine
0.235 g	(2.00 mmol) Benzylisocyanide
20 ml	MeOH, dry

Procedure according to **U5-4CR**

Reaction time: 120 hours

The crude product obtained after 120 h was dissolved in *p*-xylene and refluxed for 3 hours. The solvent was evaporated under reduced pressure leaving crude mixture.

Purification: Column chromatography on activated alox with hexane/ethyl acetate 1:1

Yield: 53 mg (6 %) of **84e** as colourless oil; ratio of diastereoisomers: 85:15

556 mg (68 %) of **85e** as colourless oil; ratio of diastereoisomers: 86:14

For analytical data see E5 (IV 13)

Synthesis of Methyl N^2-[(1*S*)-1-Benzyl-2-methoxy-2-oxoethyl]-N^1-butyl-3,3-dimethylglutaminate (84f) and Methyl 2-(2-(Butylcarbamoyl)-3,3-dimethyl-5-oxopyrrolidin-1-yl)-3-phenylpropanoate (85f)

E 8 (IV 22)

Starting amounts:

0.432 g	(2.00 mmol) Siloxycyclopropanecarboxylate **54**
0.330 g	(2.00 mmol) L-Phenylalanine
0.166 g	(2.00 mmol) *n*-Butylisocyanide
20 ml	MeOH, dry

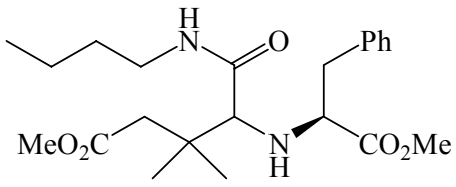
Procedure according to **U5-4CR**

Reaction time: 89 hours

Purification: Column chromatography on activated alox with hexane/ethyl acetate 1:1

Yield: 141 mg (17 %) of **84f** as colourless oil; ratio of diastereoisomers: 82:18

252 mg (34 %) of **85f** as colourless oil; ratio of diastereoisomers: > 95:5



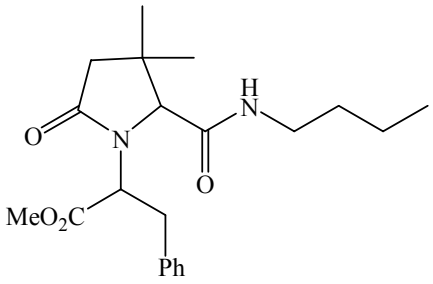
84f

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.64–1.54 (m, 13 H, CH_2, CH_3), 2.12–3.31 (m, 8 H, CH, CH_2), 3.62, 3.64, 3.66*, 3.72* (4 s, 6 H, OMe), 6.23 (bs, ≈ 0.34 H, NH), 6.71 (bs, ≈ 0.66 H, NH), 7.14–7.37 (m, 6 H, Ph, NH).
^{13}C-NMR (62.9 MHz, $CDCl_3$): δ = 13.6, 13.7* (2 q, Me), 20.1*, 20.2 (2 t, CH_2) 23.9, 24.4*, 24.5, 24.7* (4 q, Me), 31.4*, 31.5 (2 t, CH_2), 35.7*, 37.1 (2 s, *C*Me_2), 38.5*, 38.9, 39.4, 40.2*, 43.5*, 43.6 (6 t, CH_2), 51.3, 51.6, 51.9* (3 q, OMe), 61.8*, 63.6, 67.4, 68.9* (4 d, CHN), 126.6, 126.8*, 128.3, 128.4*, 129.3, 129.4* (6 d, Ph), 137.5, 137.6* (s, Ph), 168.2*, 170.7*, 171.8, 173.2, 174.2 (5 s, C=O); * *minor isomer.*

IR (KBr): ν = 3320 cm^{-1} (N-H), 3085–2870 (C-H), 1735 (C=O), 1675 (C=O), 1230 (C-O).

MS (EI, 80 eV, 90 °C): *m/z* (%) = 408 (15 [M^+ + H]), 407 (54 [$M]^+$), 389 (16), 347 (19), 315 (36), 307 (20), 306 (100), 246 (20), 234 (14), 214 (38), 176 (16), 174 (14), 156 (18), 144 (23), 132 (14), 131 (15), 130 (26), 129 (16), 121 (29), 120 (18), 112 (13), 105 (19), 104 (14), 103 (16), 91 (46 [Bn]$^+$), 85 (11), 83 (24), 82 (14), 69 (37), 59 (15), 57 (26), 55 (22).
HRMS (EI) *m/z* calculated for [M^+ + H] 407.25459, found: 407.24768.

$C_{22}H_{34}N_2O_5$ (406.5)	calc.	C 65.00	H 8.43	N 6.89
	found	C 66.46	H 7.83	N 7.20



85f

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.76 (s, 3 H, Me), 0.92 (t, *J* = 7.2 Hz, 3 H, Me), 0.99 (s, 3 H, Me), 1.21–1.48 (m, 4 H, CH_2), 2.06 (d, *J* = 16.8 Hz, 1 H, 4-H), 2.32 (d, *J* = 16.8 Hz, 1 H, 4-H), 3.12 (s, 1 H, 2-H), 3.16–3.53 (m, 4 H, NH*CH_2*, C*H_2*Ph), 3.82 (s, 3 H, OMe), 4.07–4.19 (m, 1 H, CH), 7.17–7.34 (m, 5 H, Ph), 7.59 (bs, 1 H, NH).
^{13}C-NMR (62.9 MHz, $CDCl_3$): δ = 13.5 (q, Me), 19.9 (t, CH_2), 24.4, 29.3 (2 q, Me), 31.1, 34.4 (2 t, CH_2), 36.2 (s, C-3), 38.9, 44.8 (2 t, CH_2), 52.8 (q, OMe), 58.4, 73.8 (2 d, NCH, C-2), 126.9, 128.7, 129.0 (3 d, Ph), 136.5 (s, Ph), 169.0, 171.1, 174.5 (3 s, C=O).

IR (KBr): ν = 3310 cm^{-1} (N-H), 3085–2875 (C-H), 1745 (C=O), 1675 (C=O), 1235 (C-O).

MS (EI, 80 eV, 90 °C): *m/z* (%) = 375 (14, [M^+ + H]), 315 (30), 307 (15), 274 (10), 236 (16), 214 (14), 91 (14 [Bn]$^+$), 84 (13), 41 (11).
HRMS (EI) *m/z* calculated for [M^+ + H]: 375.22838, found: 375.22000.

$C_{21}H_{30}N_2O_4$ (374.5)	calc.	C 67.36	H 8.07	N 7.48
	found	C 68.51	H 7.52	N 7.95

Synthesis of Methyl 4-((Methoxycarbonyl)methylcarbamoyl)-4-((S)-1-(methoxycarbonyl)-2-phenylethylamino)-3,3-dimethylbutanoate (84g) and Methyl 1-(1-Benzyl-2-methoxy-2-oxoethyl)-3,3-dimethyl-5-oxoprolylglycinate (85g)

Methode A

Starting amounts:

0.432 g	(2.00 mmol) Siloxycyclopropanecarboxylate **54**
0.330 g	(2.00 mmol) L-Phenylalanine
0.198 g	(2.00 mmol) Methyl isocyanoacetate
20 ml	MeOH, dry

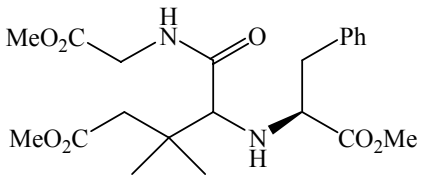
Procedure according to **U5-4CR**

Reaction time: 118 hours

Purification: Column chromatography on activated alox with hexane/ethyl acetate 1:1

Yield: 34 mg (4 %) of **84g** as colourless oil; ratio of diastereoisomers: 81:19

47 mg (6 %) of **85g** as colourless oil; ratio of diastereoisomers: > 95:5



84g

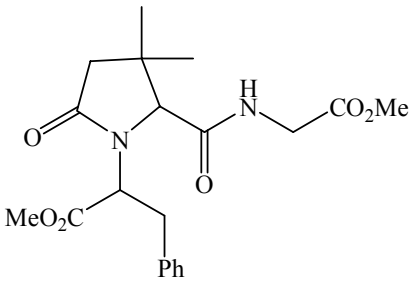
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 0.89, 0.94, 1.11*, 1.17* (4 s, 6 H, Me), 2.19–3.12 (m, 4 H, CH, CH_2), 3.65, 3.68*, 3.69, 3.73*, 3.76, 3.77* (6 s, 9 H, OMe), 3.84–4.30 (m, 4 H, CH_2), 6.60* (bs, ≈ 0.05 H, NH), 7.00–7.38 (m, 6 H, Ph, NH), 7.39 (bs, ≈ 0.95 H, NH).

^{13}C-NMR (125.8 MHz, $CDCl_3$): δ = 23.8, 24.4*, 24.8 (3 q, Me), 36.0*, 37.8 (2 s, *C*Me_2), 39.4, 40.2*, 40.5*, 40.9, 43.3*, 43.5 (6 t, CH_2), 51.5, 51.8, 52.2 (3 q, OMe), 61.7*, 63.5, 66.7 68.9* (4 d, CHN), 126.8, 128.4, 129.7 (3 d, Ph), 137.6 (s, Ph), 169.9, 171.9, 172.6, 174.7 (4 s, C=O); * *minor isomer.*

IR (KBr): ν = 3350 cm^{-1} (N-H), 3060–2850 (C-H), 1740 (C=O), 1680 (C=O), 1210 (C-O).

MS (EI, 80 eV, 90 °C): *m/z* (%) = 422 (1, $[M]^+$), 331 (22 $[M^+ - Bn]$), 313 (14), 309 (16), 307 (33), 306 (100), 299 (24), 275 (14), 250 (12), 214 (10), 192 (15), 177 (24), 150 (17), 118 (45), 105 (18), 91 (51 $[Bn]^+$), 83 (10), 69 (11), 28 (13).

HRMS (EI) *m/z* calculated for [M^+, $C_{21}H_{30}N_2O_7$]: 422.20530, found: 422.20721.



85g

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.80, 1.02 (2 s, 3 H, 3 H, Me), 2.06 (d, *J* = 16.7 Hz, 1 H, 4-H), 2.37 (d, *J* = 16.7 Hz, 1 H, 4-H), 3.22 (s, 1 H, 2-H), 3.30–3.48 (m, 2 H, C*H*$_2$Ph), 3.71, 3.79 (2 s, 3 H, 3 H, OMe), 3.88–4.15 (m, 3 H, NCH, C*H*$_2$CO$_2$Me), 7.20–7.37 (m, 5 H, Ph), 8.08 (br s, 1 H, NH).

^{13}C-NMR (62.9 MHz, $CDCl_3$): δ = 24.0, 29.2 (2 q, 3-Me), 34.3 (t, CH_2), 36.2 (s, C-3), 40.3, 44.5 (2 t, CH_2), 51.8, 52.6 (2 q, 2 OMe), 58.1, 73.2 (2 d, NCH, C-2), 126.7, 128.5, 128.8, (3 d, Ph), 136.4 (s, Ph), 169.6, 170.1, 171.2, 174.4 (4 s, C=O).

IR (KBr): ν = 3310 cm^{-1} (N-H), 3065–2875 (C-H), 1745 (C=O), 1700 (C=O), 1210 (C-O).

MS (EI, 80 eV, 160 °C): *m/z* (%) = 390 (18, $[M]^+$), 358 (14), 275 (38), 274 (100), 267 (28) 214 (22), 162 (16), 121 (18), 112 (22), 91 (24 $[Bn]^+$), 83 (39), 69 (23), 55 (12), 43 (30), 41 (11), 31 (13), 29 (11).

HRMS (EI, 80 eV) *m/z* calculated for $[M]^+$: 390.17909, found: 390.17855.

$C_{20}H_{26}N_2O_6$ (390.4)	calc.	C 61.53	H 6.71	N 7.17
	found	C 61.96	H 6.94	N 6.96

Method B

E 10 (IV 253)

Starting amounts:

0.432 g	(2.00 mmol) Siloxycyclopropanecarboxylate **54**
0.330 g	(2.00 mmol) L-Phenylalanine
0.198 g	(2.00 mmol) Methyl Isocyanoacetate
20 ml	MeOH, dry

Procedure according to **U5-4CR**

Reaction time: 240 hours.

The crude product obtained after 240h was dissolved in *p*-xylene and refluxed for 3 hours. The solvent was evaporated under reduced pressure leaving crude mixture.

Purification: Column chromatography on activated alox with hexane/ethyl acetate 1:1, then methanol/dichloromethane 4:1

Yield: 605 mg (78 %) of **85g** as colourless oil; ratio of diastereoisomers: > 95:5

For analytical data see E7 (IV 88)

Synthesis of Methyl N^2-[(1*S*)-1-Benzyl-2-methoxy-2-oxoethyl]-N^1-(4-methoxyphenyl)-3,3-dimethylglutaminate (84h[a,b]) and Methyl 2-(2-(4-Methoxyphenylcarbamoyl)-3,3-dimethyl-5-oxopyrrolidin-1-yl)-3-phenylpropanoate (85h)

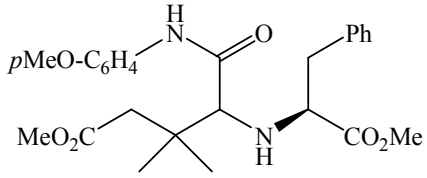
E 11 (IV 125)

Starting amounts:

0.432 g	(2.00 mmol) Siloxycyclopropanecarboxylate **54**
0.330 g	(2.00 mmol) L-Phenylalanine
0.266 g	(2.00 mmol) *p*-Methoxyphenylisocyanide
20 ml	MeOH, dry

Procedure according to **U5-4CR**
Reaction time: 111 hours

Purification: Column chromatography on activated alox with hexane/ethyl acetate 1:1, then HPLC (5 % *i*-propanol/hexane, 64 ml/min, 80 bar)
Yield: 320 mg (35 %) of **84h**[a] as of colourless oil
29 mg (3 %) of **84h**[b] as colourless oil; ratio of diastereoisomers: 92:8
267 mg (32 %) of **85h** as colourless oil; ratio of diastereoisomers: > 95:5



84h[a,b]

84h[a]

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.86, 0.91 (2 s, 3 H, 3 H, Me), 2.21 (d, *J* = 14.3 Hz, 1 H, CH_2), 2.30 (d, *J* = 14.3 Hz, 1 H, CH_2), 2.83–3.06 (m, 2 H, C*H*$_2$Ph), 3.17 (s, 1 H, CH), 3.41 (t, *J* = 6.9 Hz, 1 H, CH), 3.51, 3.63, 3.73 (3 s, 9 H, OMe), 6.77–6.85 (m, 2 H, Ar), 7.14–7.29 (m, 6 H, Ar, Ph, NH), 7.41–7.50 (m, 2 H, Ph), 8.86 (s, 1 H, NH).
^{13}C-NMR (62.9 MHz, $CDCl_3$): δ = 23.9, 24.8 (2 q, Me), 37.7, (s, *C*Me_2), 38.9, 39.4 (2 t, CH_2), 51.5, 51.8, 55.4 (3 q, OMe), 63.7, 68.3 (2 d, CHN), 114.1, 121.2, 126.7, 128.4, 129.3 (5 d, Ar), 131.1, 137.4, 156.2 (3 s, Ar), 170.4, 173.5, 174.3 (3 s, C=O).

IR (KBr): ν = 3315 cm^{-1} (N-H), 3060–2835 (C-H), 1740 (C=O), 1680 (C=O), 1245 (C-O).

MS (EI, 80 eV, 160 °C): *m/z* (%) = 456 (1, $[M]^+$), 307 (19), 306 (100), 274 (16), 214 (16), 162 (11).
HRMS (EI) *m/z* calculated for $[M]^+$: 456.22603, found: 456.22464.

$C_{25}H_{32}N_2O_6$ (456.5)	calc.	C 65.77	H 7.07	N 6.14
	found	C 65.76	H 6.95	N 6.16

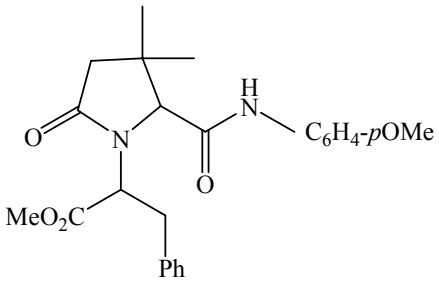
84h[b]

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 1.10, 1.15 (2 s, 3 H, 3 H, Me), 2.36 (d, *J* = 14.8 Hz, 1 H, CH_2), 2.44 (d, *J* = 14.8 Hz, 1 H, CH_2), 2.66–2.75 (m, 2 H, C*H*$_2$Ph), 3.08 (s, 1 H, CH), 3.36–3.41 (m, 1 H, CH), 3.64, 3.71, 3.75 (3 s, 9 H, OMe), 6.70–6.74 (m, 2 H, Ar), 6.90–6.94 (m, 2 H, Ar), 7.10–7.41 (m, 6 H, Ph, NH), 8.17 (s, 1 H, NH).
^{13}C-NMR (125.8 MHz, $CDCl_3$): δ = 24.7, 24.9 (2 q, Me), 36.4, (s, *C*Me_2), 40.1, 43.6 (2 t, CH_2), 51.4, 52.0, 55.4 (3 q, OMe), 61.8, 69.5 (2 d, CHN), 113.7, 121.2, 126.9, 128.7, 129.4 (5 d, Ar), 130.3, 137.5, 156.2 (3 s, Ar), 169.1, 172.6, 174.6 (3 s, C=O).

IR (KBr): ν = 3320 cm^{-1} (N-H), 3060–2835 (C-H), 1740 (C=O), 1675 (C=O), 1245 (C-O).

MS (**EI, 80 eV, 150 °C**): *m/z* (%) = 456 (2, $[M]^+$), 365 (11 [M^+ - Bn]), 341 (13), 307 (19), 306 (100), 274 (19), 214 (18), 162 (15).
HRMS (EI) *m/z* calculated for $[M]^+$: 456.22603, found: 456.22836.

$C_{25}H_{32}N_2O_6$ (456.5)	calc.	C 65.77	H 7.07	N 6.14
	found	C 66.52	H 6.93	N 6.04



85h

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.76, 1.05 (2 s, 3 H, 3 H, Me), 2.10 (d, *J* = 16.8 Hz, 2 H, 4-H), 2.37 (d, *J* = 16.8 Hz, 2 H, 4-H), 3.12 (s, 1 H, 2-H), 3.37–3.67 (m, 2 H, CH_2Ph), 3.78, 3.90 (2 s, 6 H, OMe), 4.18 (dd, *J* = 10.8, 5.5 Hz, 1 H, N-CH), 6.80–6.95 (m, 2 H, Ph), 7.18–7.36 (m, 5 H, Ph), 7.49–7.68 (m, 2 H, Ph), 9.47 (s, 1 H, NH).
^{13}C-NMR (62.9 MHz, $CDCl_3$): δ = 24.7, 29.7 (2 q, 3-Me), 34.6 (t, CH_2), 36.7 (s, C-3), 45.0 (t, CH_2), 53.3, 55.4 (2 q, OMe), 59.1, 74.9 (2 d, NCH, C-2), 114.0, 121.2, 127.2, 128.9, 129.2 (5 d, Ph), 130.8, 136.5, 156.4 (3 s, Ph), 167.4, 171.8, 174.7 (3 s, C=O).

IR (KBr): ν = 3300, 3275 cm^{-1} (N-H), 2965, 2930 (C-H), 1745 (C=O), 1665 (C=O), 1250 (C-O).

MS (EI, 80 eV, 160 °C): *m/z* (%) = 424 (46, $[M]^+$), 275 (17), 274 (100), 262 (13), 214 (18), 194 (12), 121 (13), 112 (11).
HRMS (EI, 80 eV) *m/z* calculated for $[M]^+$: 424.19982, found: 424.19915.

$C_{24}H_{28}N_2O_5$ (424.5)	calc.	C 67.91	H 6.65	N 6.60
	found	C 67.20	H 6.47	N 6.17

Synthesis of Methyl 2-(2-(Cyclohexenylcarbamoyl)-3,3-dimethyl-5-oxopyrrolidin-1-yl)-3-phenylpropanoate (85i)

E 12 (IV 96)

Starting amounts:

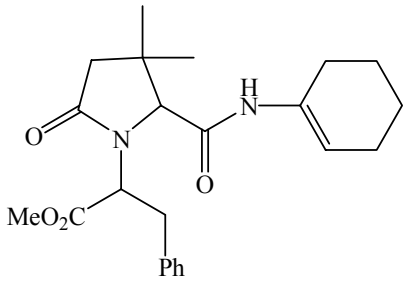
0.207 g	(0.96 mmol) Siloxycyclopropanecarboxylate **54**
0.159 g	(0.96 mmol) L-Phenylalanine
0.094 g	(0.89 mmol) Isocyanocyclohexene
9.60 ml	MeOH, dry

Procedure according to **U5-4CR**

Reaction time: 208 hours

Purification: Column chromatography on activated alox with hexane/ethyl acetate 1:1

Yield: 96 mg (27 %) of **85i** as colourless oil; ratio of diastereoisomers: > 95:5



85i

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.76, 1.01 (2s, 3 H, 3 H, Me), 1.51–1.72 (m, 4 H, CH_2), 2.02–2.20 (m, 4 H, CH_2), 2.05 (d, *J* = 16.9 Hz, 1 H, 4-H), 2.32 (d, *J* = 16.9 Hz, 1 H, 4-H), 3.01 (s, 1 H, 2-H), 3.32–3.74 (m, 2 H, C*H*$_2$Ph), 3.85 (s, 3 H, OMe), 4.11 (dd, *J* = 10.2, 5.9 Hz, 1 H, NCH), 6.14 (t, *J* = 3.8 Hz, 1 H, =CH), 7.17–7.34 (m, 5 H, Ph), 8.30 (br s, 1 H, NH).

^{13}C-NMR (62.9 MHz, $CDCl_3$): δ = 21.8, 22.4, 23.9 (3 t, CH_2), 24.6 (q, 3-Me), 27.5 (t, CH_2), 29.5 (q, 3-Me), 34.4 (t, CH_2), 36.6 (s, C-3), 45.0 (t, CH_2), 53.0 (q, OMe), 58.8, 74.6 (2 d, NCH, C-2), 113.8 (d, =*C*H), 127.1, 128.8, 129.1 (3 d, Ph), 132.3 (s, NC=), 136.6 (s, Ph), 167.4, 171.2, 174.6 (3 s, C=O).

IR (KBr): ν = 3310 cm^{-1} (N-H), 3060–2840 (C-H), 1745 (C=O), 1700 (C=O), 1225 (C-O).

MS (EI, 80 eV, 135 °C): *m/z* (%) = 398 (33, $[M]^+$), 306 (12), 275 (20), 274 (100), 261 (11), 260 (53), 214 (12), 181 (47), 177 (19), 121 (14), 113 (16), 112 (10), 91 (23 $[Bn]^+$), 84 (15), 73 (16), 69 (20), 59 (13), 56 (10), 55 (17), 43 (33), 41 (20), 29 (12), 28 (33).
HRMS (EI) *m/z* calculated for [M^+, $C_{23}H_{30}N_2O_4$]: 398.22055, found: 398.22332.

Synthesis of Methyl 2-[2-(2,4,4-Trimethylpentan-2-ylcarbamoyl)-3,3-dimethyl-5-oxopyrrolidin-1-yl]-3-phenylpropanoate (85j)

E 13 (IV 260)

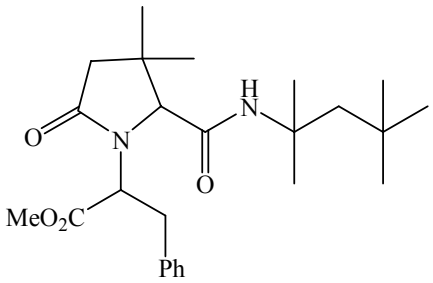
Starting amounts:

0.432 g	(2.00 mmol) Siloxycyclopropanecarboxylate **54**
0.330 g	(2.00 mmol) L-Phenylalanine
0.278 g	(2.00 mmol) 1,1,3,3-Tetramethylbutylisocyanide
20 ml	MeOH, dry

Procedure according to **U5-4CR**

Reaction time: 240 hours.
The crude product obtained after 240 h was dissolved in *p*-xylene and refluxed for 3 hours. The solvent was evaporated under reduced pressure leaving the crude mixture.

Purification: Column chromatography on silica gel with pentane/ethyl acetate 1:1, then HPLC (20 % *i*-propanol/hexane, 64 ml/min, 80 bar)
Ration of diastereoisomers in crude product: 73:27
Yield: 144 mg (17 %) of **85j**[a] as colourless crystals; ratio of diastereoisomers: > 95:5
408 mg (47 %) of **85j**[b] as colourless crystals; ratio of diastereoisomers: > 95:5



85j[a,b]

85j[a]

Melting point: 140-142 °C

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 0.66 (s, 3 H, Me), 0.96 (s, 12 H, Me), 1.32, 1.39 (2 s, 3 H, 3 H, Me), 1.44 (d, *J* = 14.6 Hz, 1 H, CH_2), 1.95 (d, *J* = 14.6 Hz, 1 H, CH_2), 1.96 (d, *J* = 16.7 Hz, 1 H, 4-H), 2.28 (d, *J* = 16.7 Hz, 1 H, 4-H), 2.94 (s, 1 H, 2-H), 3.26–3.44 (m, 2 H, C*H*$_2$Ph), 3.78 (s, 3 H, OMe), 4.04–4.11 (m, 1 H, CH), 7.03 (bs, 1 H, NH), 7.12–7.34 (m, 5 H, Ph).
^{13}C-NMR (125.8 MHz, $CDCl_3$): δ = 27.6, 29.3, 29.8, 31.4, 31.5 (5 q, Me), 34.7 (t, *C*H_2Ph), 36.1, 36.2 (2 s, *C*Me_3, C-3), 45.0, 52.0 (2 t, C-4, *C*H_2), 55.8 (q, OMe), 55.9 (s, N*C*Me_2), 58.7, 76.7 (2 d, NCH, C-2), 127.0, 128.8, 129.1 (3 d, Ph), 136.7 (s, Ph), 168.2, 170.9, 174.6 (3 s, C=O).

IR (KBr): ν = 3320 cm^{-1} (N-H), 3065–2780 (C-H), 1745 (C=O), 1665 (C=O), 1225 (C-O).

MS (EI, 80 eV, 110 °C): *m/z* (%) = 430 (7, $[M]^+$), 302 (13), 275 (21), 274 (100), 214 (21), 147 (10), 74 (24), 69 (16), 57 (12), 41 (10).
HRMS (EI) *m/z* calculated for $[M]^+$: 430.28317, found: 430.28527.

$C_{25}H_{38}N_2O_4$ (430.5)	calc.	C 69.74	H 8.90	N 6.51
	found	C 68.97	H 8.58	N 6.38

85j[b]

Melting point: 156-158 °C

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 0.73 (s, 3 H, Me), 1.00 (s, 9 H, Me), 1.05, 1.36, 1.45 (3 s, 3 H, 3 H, 3 H, Me), 1.58 (d, *J* = 14.9 Hz, 1 H, CH_2), 1.76 (d, *J* = 14.9 Hz, 1 H, CH_2), 1.91 (d, *J* = 16.3 Hz, 1 H, 4-H), 2.41 (d, *J* = 16.3 Hz, 1 H, 4-H), 2.87–2.97 (m, 1 H, C*H*$_2$Ph), 3.22–3.31 (m, 1 H, C*H*$_2$Ph), 3.43 (s, 1 H, 2-H), 3.63 (s, 3 H, OMe), 4.93–4.99 (m, 1 H, CH), 6.61 (bs, 1 H, NH), 7.15–7.31 (m, 5 H, Ph).
^{13}C-NMR (125.8 MHz, $CDCl_3$): δ = 23.8, 27.1, 28.5, 29.4, 31.5 (5 q, Me), 34.3 (t, *C*H_2Ph), 37.2, 37.4 (2 s, *C*Me_3, C-3), 44.2 (t, C-4), 52.3 (q, OMe), 53.3 (t, *C*H_2), 55.0 (d, NCH), 55.9 (s, N*C*Me_2), 70.4 (d, C-2), 126.9, 128.4, 128.6 (3 d, Ph), 135.8 (s, Ph), 168.0, 171.4, 175.4 (3 s, C=O).

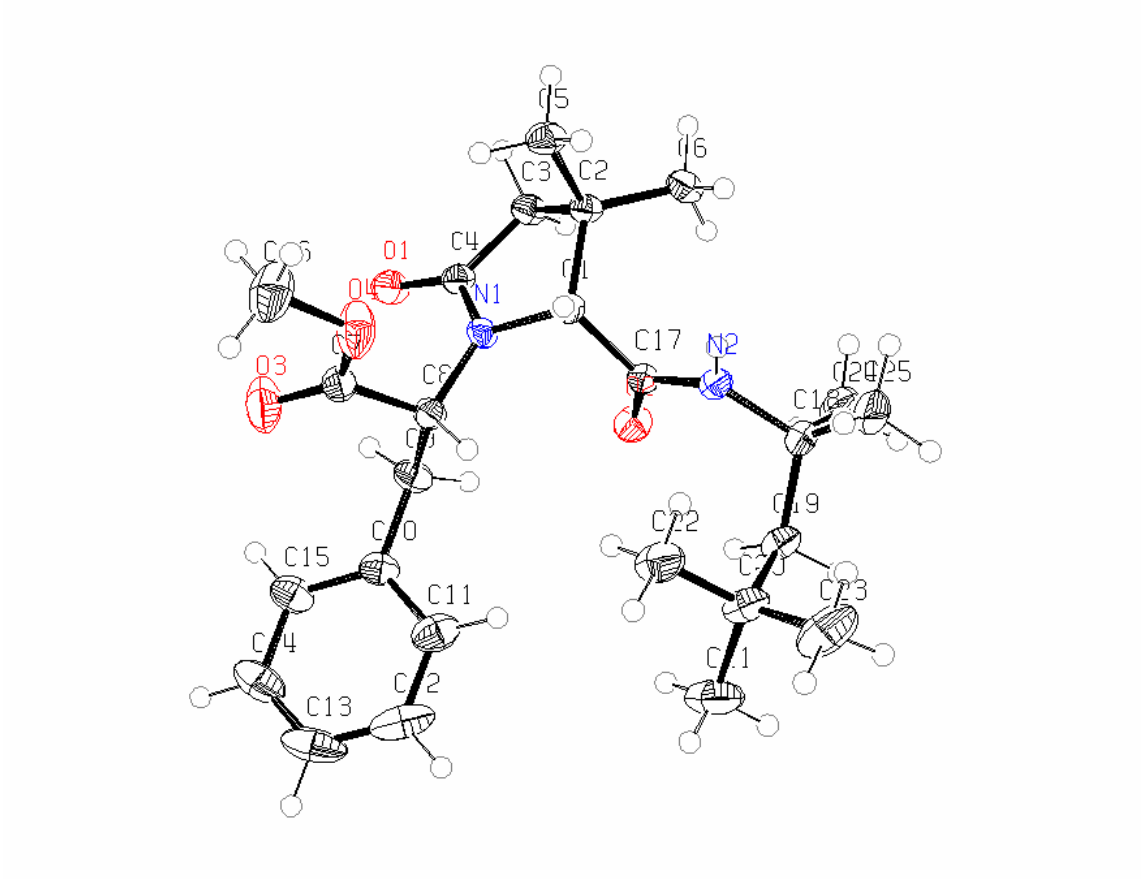
IR (KBr): ν = 3325 cm^{-1} (N-H), 3065–2875 (C-H), 1745 (C=O), 1670 (C=O), 1225 (C-O).

MS (EI, 80 eV, 90 °C): *m/z* (%) = 430 (7, $[M]^+$), 275 (21), 274 (100), 214 (22), 121 (10), 112 (11), 91 (10 $[Bn]^+$), 69 (18), 57 (15), 41 (12), 28 (30).
HRMS (EI) *m/z* calculated for $[M]^+$: 430.28317, found: 430.28477.

$C_{25}H_{38}N_2O_4$ (430.5)	calc.	C 69.74	H 8.90	N 6.51
	found	C 69.58	H 8.53	N 6.53

Crystal data and structure refinement for **85j**:

Crystals of **85j** for X-ray analysis have been obtained by recrystallization in ethyl acetate/hexane mixture.



Empirical formula	C25 H38 N2 O4	
Formula weight	430.57	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 8.482(2) Å	α= 90°.
	b = 13.644(3) Å	β= 110.606(4)°.
	c = 11.361(3) Å	γ = 90°.
Volume	1230.8(5) $Å^3$	
Z	2	
Density (calculated)	1.162 Mg/m^3	
Absorption coefficient	0.078 mm^{-1}	
F(000)	468	
Crystal size	.65 x .23x .2 mm^3	
Theta range for data collection	1.91 to 30.56°.	
Index ranges	-11<=h<=12, -17<=k<=19, -16<=l<=16	
Reflections collected	15263	
Independent reflections	7198 [R(int) = 0.0812]	

Completeness to theta = 30.56°	99.6 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	7198 / 1 / 292
Goodness-of-fit on F^2	1.023
Final R indices [I>2sigma(I)]	R1 = 0.0470, wR2 = 0.1147
R indices (all data)	R1 = 0.0535, wR2 = 0.1201
Absolute structure parameter	0.1(7)
Largest diff. peak and hole	0.354 and -0.184 e.Å^{-3}

Table 15. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for **85j**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
N(1)	780(1)	5852(1)	9597(1)	22(1)
N(2)	-921(1)	7979(1)	7661(1)	26(1)
O(1)	394(1)	4317(1)	10252(1)	34(1)
O(2)	-1106(1)	6349(1)	7166(1)	30(1)
O(3)	4647(2)	4785(1)	10906(1)	55(1)
O(4)	3946(2)	6274(1)	11351(1)	47(1)
C(1)	-27(2)	6813(1)	9360(1)	21(1)
C(2)	-1362(2)	6742(1)	10028(1)	22(1)
C(3)	-1656(2)	5633(1)	10051(1)	26(1)
C(4)	-76(2)	5170(1)	9991(1)	24(1)
C(5)	-515(2)	7122(1)	11377(1)	30(1)
C(6)	-3008(2)	7287(1)	9362(1)	28(1)
C(7)	3780(2)	5492(1)	10617(1)	27(1)
C(8)	2335(2)	5647(1)	9359(1)	23(1)
C(9)	2148(2)	4784(1)	8445(1)	29(1)
C(10)	3576(2)	4706(1)	7945(1)	28(1)
C(11)	3771(2)	5393(1)	7104(1)	38(1)
C(12)	5119(3)	5307(1)	6660(2)	51(1)
C(13)	6229(2)	4543(2)	7029(2)	52(1)
C(14)	6028(2)	3839(1)	7840(2)	46(1)
C(15)	4710(2)	3927(1)	8300(2)	35(1)
C(16)	5254(3)	6221(2)	12580(2)	53(1)
C(17)	-756(2)	7019(1)	7935(1)	23(1)
C(18)	-1719(2)	8415(1)	6393(1)	31(1)
C(19)	-774(2)	8137(1)	5503(1)	29(1)
C(20)	1045(2)	8479(1)	5706(1)	35(1)
C(21)	1618(2)	7860(2)	4795(2)	55(1)
C(22)	2274(2)	8295(2)	7043(1)	42(1)
C(23)	1132(3)	9558(2)	5361(2)	58(1)
C(24)	-3524(2)	8015(2)	5801(2)	51(1)
C(25)	-1783(3)	9518(1)	6603(2)	51(1)

7.2.2 Microwave assisted cyclization

Synthesis of (4*S*, 8a*R*)-2,4-Dibenzyl-8,8-dimethyldihydropyrrolo[1,2-*a*]pyrazine-1,3,6(2*H*,4*H*,7*H*)-trione (86)

E 14 (IV 128)

Starting amounts:

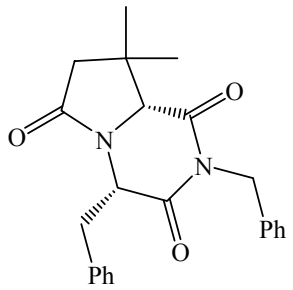
0.076 g	(0.186 mmol) Methyl 2-(2-(benzylcarbamoyl)-3,3-dimethyl-5-oxopyrrolidin-1-yl)-3-phenylpropanoate (**85e**) (dr 86:14)
10 ml	Ethyleneglycol

Procedure: Methyl 2-(2-(benzylcarbamoyl)-3,3-dimethyl-5-oxopyrrolidin-1-yl)-3-phenylpropanoate (**85e**) was dissolved in ethyleneglycol and irradiated in a microwave reactor in 10 cycles. Then water and diethyl ether were added, the layers were separated and the aqueous layer was extracted with diethyl ether. The combined organic phases were dried with Na_2SO_4 and the solvent was evaporated.

Microwave irradiation conditions:

Duration: 25 min
Power: 1000 W
Min T: 85 °C
Max T: 192 °C

Purification: Column chromatography on activated alox with hexane/ethyl acetate 1:1
Yield: 26 mg (37 %) of **57** as colourless crystals; ratio of diastereoisomers: >95:5



86

Melting point: 192-195 °C

^{1}H-NMR (250 MHz, $CDCl_3$): δ = 0.83, 1.28 (2 s, 3 H, 3 H, Me), 2.10 (d, *J* = 16.1 Hz, 1 H, 7-H), 2.25 (d, *J* = 16.1 Hz, 1 H, 7-H), 3.19–3.23 (m, 2 H, C*H*$_2$Ph), 3.23 (s, 1 H, 8a-H), 4.90 (d, *J* = 13.7 Hz, 1 H, NC*H*$_2$Ph), 4.99 (d, *J* = 13.7 Hz, 1 H, NC*H*$_2$Ph), 5.14 (t, *J* = 5.5 Hz, 1 H, NCH), 6.89–7.39 (m, 10 H, Ph).
^{13}C-NMR (62.9 MHz, $CDCl_3$): δ = 22.2, 26.4 (2 q, 8-Me), 37.9 (t, CH_2), 40.3 (s, C-8), 43.1, 46.4 (2 t, CH_2), 54.4, 64.1 (2 d, NCH, C-8a), 127.7, 127.9, 128.4, 128.9, 129.3, 129.4 (6 d, Ph), 135.2, 136.1 (2 s, Ph), 169.0, 169.5, 172.2 (3 s, C=O).

IR (KBr): ν = 3030–2920 cm^{-1} (C-H), 1690 (C=O).

MS (EI, 80 eV, 90 °C): *m/z* (%) = 377 (15, $[M^+ + H]$), 376 (58, $[M]^+$), 286 (19), 285 (99 $[M^+ - Bn]$), 257 (11), 203 (21), 91 (72 $[Bn]^+$), 83 (100), 55 (14).
HRMS (EI) *m/z* calculated for [M^+, $C_{23}H_{24}N_2O_3$]: 376.17869, found: 376.17633.

7.2.3 Ester hydrolysis

Synthesis of 1-(1-Benzyl-2-methoxy-2-oxoethyl)-3,3-dimethyl-5-oxoprolylglycine (87)

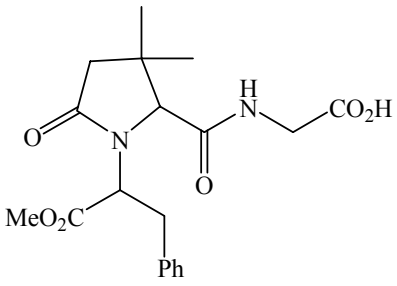
E 15 (IV 268)

Starting amounts:

0.492 g	(1.26 mmol) Methyl 1-(1-benzyl-2-methoxy-2-oxoethyl)-3,3-dimethyl-5-oxoprolylglycinate (**85g**)
0.159 g	(3.78 mmol) $LiOH \cdot H_2O$
5 ml	H_2O
5 ml	MeOH
15 ml	THF

Procedure: Diester **85g** was dissolved in a mixture of methanol and tetrahydrofuran, a solution of LiOH in water was added, and the resulting mixture was stirred over night at room temperature. 2 M HCl was added to adjust pH 7. Diethyl ether was added and the layers were separated. The aqueous layer was extracted with diethyl ether, the combined organic phases were dried with $MgSO_4$ and the solvent was evaporated.

Purification: Column chromatography on silica gel with pentane/ethyl acetate, then methanol/dichloromethane 4:1, then HPLC (25 % methanol/dichloromethane, 64 ml/min, 85 bar)
Yield: 280 mg (59 %) of **87** as colourless crystals; ratio of diastereoisomers: 71:29



87

Melting range: 266–269 °C

^{1}H-NMR (500 MHz, CD_3OD): δ = 0.41, 0.93*, 0.99, 1.08* (4 s, 6 H, Me), 1.86 (d, *J* = 16.2 Hz, ≈ 0.7 H, 4-H), 2.06 (d, *J* = 16.5 Hz, ≈ 0.3 H, 4-H), 2.46 (d, *J* = 16.5 Hz, ≈ 0.3 H, 4-H), 2.77 (d, *J* = 16.2 Hz, ≈ 0.7 H, 4-H), 3.40 (s, ≈ 0.7 H, 2-H), 3.45–3.47 (m, ≈ 0.6 H, C*H*$_2$Ph), 3.53 (s, ≈ 0.3 H, 2-H), 3.58 (s, ≈ 2.1 H, OMe), 3.66 (bs, ≈ 0.3 H, NCH), 3.74 (s, ≈ 0.9 H, OMe), 3.79 (d, *J* = 13.6 Hz, ≈ 1.4 H, C*H*$_2$Ph), 4.03 (s, ≈ 0.7 H, NCH), 4.07–4.09 (m, ≈ 0.6 H, C*H*$_2$CO$_2$H), 4.33 (d, *J* = 18.3 Hz, ≈ 0.7 H, C*H*$_2$CO$_2$H), 4.45 (d, *J* = 18.0 Hz, ≈ 0.7 H, C*H*$_2$CO$_2$H), 7.23–7.44 (m, 5 H, Ph); * *minor isomer.*
^{13}C-NMR (125.8 MHz, CD_3OD): δ = 20.8, 21.6*, 25.2, 25.9* (4 q, 3-Me), 32.5 (s, C-3), 34.2*, 34.5, 44.9*, 45.0, 45.2*, 45.4 (6 t, CH_2), 59.0 (q, OMe), 61.1, 63.8*, 70.2*, 72.9 (4 d, NCH, C-2), 126.3, 126.6, 126.7, (3 d, Ph), 135.5*, 136.4 (2 s, Ph), 167.6*, 167.7, 169.7, 174.9, 175.8 (5 s, C=O); * *minor isomer.*

IR (KBr): ν = 3385–3290 cm^{-1} (N-H, O-H), 3090–2875 (C-H), 1755 (C=O), 1685 (C=O), 1210 (C-O).

MS (EI, 80 eV, 170 °C): *m/z* (%) = 376 (3, $[M]^+$), 274 (13), 267 (18), 261 (31), 260 (79) 216 (28), 215 (14), 214 (58), 131 (12), 120 (10), 113 (21), 112 (60), 105 (44), 104 (21), 103 (17), 97 (12), 96 (11), 91 (63 $[Bn]^+$), 85 (12), 84 (12), 83 (100), 82 (16), 79 (13), 77 (24), 73 (12), 71 (30), 70 (13), 69 (82), 67 (12), 57 (20), 56 (27), 55 (44), 51 (13), 45 (32), 44 (75), 43 (39), 42 (16), 41 (50), 39 (14), 36 (20), 32 (25), 31 (15), 30 (21), 29 (33), 28 (96), 27 (15).
HRMS (EI, 80 eV) *m/z* calculated for [M^+, $C_{19}H_{24}N_2O_6$]: 376.16342, found: 376.16532.

Synthesis of 1-(1-Carboxy-2-phenylethyl)-3,3-dimethyl-5-oxoprolylglycine (88)

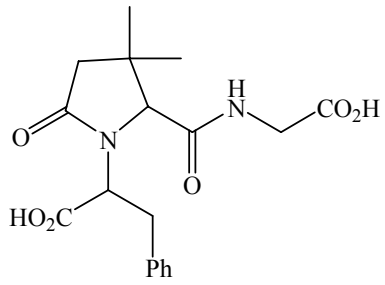
E 16 (IV 287)

Starting amounts:

0.035 g	(0.09 mmol) 1-(1-Benzyl-2-methoxy-2-oxoethyl)-3,3-dimethyl-5-oxoprolylglycine (**87**)
0.011 g	(0.27 mmol) $LiOH \cdot H_2O$
1 ml	H_2O
1 ml	MeOH
5 ml	THF

Procedure: Ester **87** was dissolved in a mixture of methanol and tetrahydrofuran, a solution of LiOH in water was added, and the resulting mixture was stirred over night at room temperature. 2 M HCl was added to adjust pH 7. Diethyl ether was added and the layers were separated. The aqueous layer was extracted with diethyl ether, the combined organic phases were dried with $MgSO_4$ and the solvent was evaporated.

Purification: Column chromatography on silica gel with pentane/ethyl acetate, then methanol/dichloromethane 4:1
Ratio of diastereoisomers in crude product: 84:16
Yield: 25 mg (77 %) of **88**[a] as colourless crystals; ratio of diastereoisomers: > 95:5
5 mg (15 %) of **88**[b] as colourless crystals; ratio of diastereoisomers: > 95:5



88

88[a]

Melting point: >300 °C

^{1}H-NMR (500 MHz, D_2O): δ = 0.81, 0.93 (2 s, 3 H, 3 H, Me), 2.04 (d, *J* = 17.0 Hz, 1 H, 4-H), 2.41 (d, *J* = 17.0 Hz, 1 H, 4-H), 3.01–3.22 (m, 2 H, C*H*$_2$Ph), 3.37 (bs, 1 H, 2-H), 3.59–3.68 (m, 2 H, C*H*$_2$CO$_2$H), 4.37–4.43 (m, 1 H, NCH), 7.21–7.34 (m, 5 H, Ph).
^{13}C-NMR (125.8 MHz, D_2O): δ = 23.7, 29.1 (2 q, 3-Me), 34.4 (t, *C*H$_2$Ph), 37.0 (s, C-3), 43.8, 45.4 (2 t, *C*H$_2$CO$_2$Me, C-4), 61.1, 73.8 (2 d, NCH, C-2), 127.2, 129.3, 129.6 (3 d, Ph), 138.8 (s, Ph), 172.5, 176.5, 176.6, 178.3 (4 s, C=O).

IR (KBr): ν = 3405–3345 cm^{-1} (O-H, N-H), 3085–2850 (C-H), 1665 (C=O), 1590 (C=O), 1255 (C-O).

MS (FAB (+)): *m/z* (%) = 155 (13), 154 (64), 153 (11), 152 (11) 149 (31), 138 (17), 137 (32), 136 (79), 119 (11), 107 (14), 106 (46), 105 (21), 104 (22), 91 (28), 90 (21), 89 (63), 79 (22), 78 (36), 77 (100), 76 (15), 75 (13), 74 (11), 71 (18), 69 (16), 66 (13), 62 (23), 61 (42), 60 (22), 57 (16), 55 (27), 51 (30).

88[b]

Melting point: >300 °C

^{1}H-NMR (500 MHz, D_2O): δ = 0.82, 0.94 (2 s, 3 H, 3 H, Me), 2.04 (d, *J* = 16.7 Hz, 1 H, 4-H), 2.41 (d, *J* = 16.7 Hz, 1 H, 4-H), 3.01–3.23 (m, 2 H, C*H*$_2$Ph), 3.42 (bs, 1 H, 2-H), 3.59–3.67 (m, 2 H, C*H*$_2$CO$_2$H), 4.34–4.47 (m, 1 H, NCH), 7.21–7.31 (m, 5 H, Ph).
^{13}C-NMR (125.8 MHz, D_2O): δ = 23.8, 25.2 (2 q, 3-Me), 35.6, (t, *C*H$_2$Ph), 38.4 (s, C-3), 40.1 (t, *C*H$_2$CO$_2$H), 45.4 (t, C-4), 61.1, 74.9 (2 d, NCH, C-2), 126.2, 129.2, 129.3 (3 d, Ph), 138.8 (s, Ph), 163.2, 170.6, 172.9, 176.3 (4 s, C=O).

IR (KBr): ν = 3530–3345 cm^{-1} (O-H, N-H), 3085–2875 (C-H), 1665 (C=O), 1590 (C=O), 1255 (C-O).

Synthesis of 1-(1-Benzyl-2-methoxy-2-oxoethyl)-3,3-dimethyl-5-oxoprolylglycine (87)

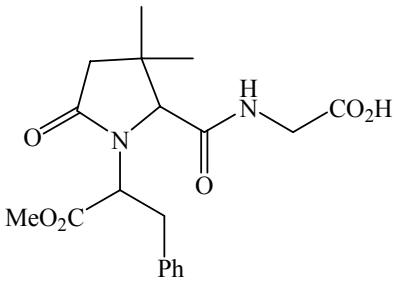
E 17 (IV 313)

Starting amounts:

0.115 g	(0.295 mmol) Methyl 1-(1-benzyl-2-methoxy-2-oxoethyl)-3,3-dimethyl-5-oxoprolylglycinate (**85g**)
1 ml	3 M HCl
1 ml	Diethyl ether

Procedure: Ester **85g** was dissolved in diethyl ether, 3 M HCl was added and the resulting mixture was stirred 12 hours at room temperature. Then diethyl ether was added and the layers were separated. The aqueous layer was extracted with diethyl ether, the combined organic phases were dried with $MgSO_4$ and the solvent was evaporated.

Purification: Column chromatography on silica gel with hexane/ethyl acetate 4:1, then methanol/dichloromethane 4:1
Yield: 33 mg (30 %) of **87** as colourless crystals; one diastereoisomer



87

Melting point: 177–179 °C

^{1}H-NMR (500 MHz, CD_3OD): δ = 0.99, 1.09 (2 s, 3 H, 3 H, Me), 2.03 (d, *J* = 16.4 Hz, 1 H, 4-H), 2.56 (d, *J* = 16.4 Hz, 1 H, 4-H), 3.21–3.25 (m, 2 H, C*H*$_2$Ph), 3.66 (s, 1 H, 2-H), 3.71 (s, 3 H, OMe), 3.81 (s, 2 H, C*H*$_2$CO$_2$H), 4.83 (t, *J* = 8.2 Hz, 1 H, NCH), 7.22–7.38 (m, 5 H, Ph).
^{13}C-NMR (125.8 MHz, CD_3OD): δ = 24.4, 29.8 (2 q, 3-Me), 36.4 (t, *C*H$_2$Ph), 38.6 (s, C-3), 44.8, 46.0 (2 t, *C*H$_2$CO$_2$H, C-4), 53.1 (q, OMe), 59.1, 73.4 (2 d, NCH, C-2), 128.2, 129.9, 130.6, (3 d, Ph), 138.7 (s, Ph), 172.0, 172.5, 176.3, 177.9 (4 s, C=O).

IR (KBr): ν = 3470–3305 cm^{-1} (N-H, O-H), 3085–2875 (C-H), 1740 (C=O), 1680 (C=O), 1245 (C-O).

MS (EI, 80 eV, 250 °C): *m/z* (%) = 361 (14, [M$^+$ - Me]), 358 (7, [M$^+$ - H$_2$O]), 271 (12), 270 (32), 267 (21), 91 (30 [Bn]$^+$), 83 (91), 56 (12), 55 (26), 45 (32), 44 (48), 43 (33), 42 (12), 41 (20), 30 (11), 29 (29), 28 (26), 27 (15), 18 (100), 17 (28).
HRMS (EI, 80 eV) *m/z* calculated for [M$^+$ - Me, $C_{18}H_{21}N_2O_6$]: 361.13995, found: 361.13866.
m/z calculated for [M$^+$ - H$_2$O, $C_{19}H_{21}N_2O_5$]: 358.15286, found: 358.15373.

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