Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Supporting Information

N-Acyl glycinates as acyl donors in serine protease-catalyzed kinetic resolution of amines. Improvement of selectivity and reaction rate.

Malek Nechab,[a,b] Lahssen El Blidi,[a] Nicolas Vanthuyne,[b] Stéphane Gastaldi,*[a] Michèle P. Bertrand,*[a] and Gérard Gil*[b]

[a]Laboratoire de Chimie Moléculaire Organique, LCP UMR 6264,Boite 562, Université Paul Cézanne, Aix-Marseille III, Faculté des Sciences St Jérôme, Avenue Escadrille Normandie-Niemen, 13397 Marseille Cedex 20 (France). michele.bertrand@univ-cezanne.fr
[b]Laboratoire de Stéréochimie Dynamique et Chiralité, ISM2, UMR 6263, Université Paul Cézanne, Aix-Marseille III, Faculté des Sciences St Jérôme, Avenue Escadrille Normandie-Niemen, 13397 Marseille Cedex 20 (France). gerard.gil@univ-cezanne.fr

Experimental Section

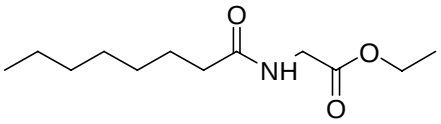
General : The ^{1}H and ^{13}C NMR spectra were recorded at 200, 300 or 400 MHz and 50, 75 or 100 MHz, respectively. Chemical shifts (δ) are reported in ppm and coupling constants (*J*) given in Hz. Enantiomeric excesses (*ee*) of amides were determined by analytical chiral HPLC. The solvents for chiral chromatography (*n*-hexane, 2-PrOH, EtOH) were HPLC grade. They were degassed and filtered on a 0.45 µm membrane before use. The chiral HPLC analyses were performed on Chiralcel OD-H (250*4.6mm, cellulose tris-(3,5-dimethylphenylcarbamate)) with UV detection. The retention times t_R are given in minutes for each enantiomer, the retention factors $k = (t_R - t_0)/t_0$ (t_0 is the retention time for an unretained peak determined by injection of tri-tertiobutyl-benzene), the enantioselectivity factor $\alpha = k_2/k_1$ and the resolution Rs are given to characterize the chiral separations. The enantiomeric excesses of the primary amine were determined, after derivatization in trifluoroacetamide with 1.5 equiv of *N*-methyl-bis-trifluoroacetamide, by gas chromatography (GC) analysis on a chromatograph fitted with a Lipodex D column with flame ionization detector (FID), using the derivatized racemic compounds as reference. Ethyl methoxyacetate, *N*-Acetyl glycine ethyl ester, *N*-benzoyl glycine ethyl ester, 2,2,2-trifluoroethyl butyrate,[1] amines (**1a**, **1b**, **1c**, **1d**, **1e**, **1g**, **1h**, **1j**, **1k**, **1l** and **1m**) are commercially available and used without further purification. *N*-butyryl-glycine ethyl ester,[2], *N*-lauroyl-glycine ethyl ester[3], compounds **1f**[4] and **1i**[5] were prepared according to literature procedures.

Immobilization of Alkaline Protease

Alkaline protease (120 mg) from Valley Research was dissolved in a solution of octyl α,β-D-glycopyranoside (15 mg) and Brij 56 (polyethylene glycol hexadecyl ether, 15 mg) in a phosphate buffer (pH 7.2 (unless otherwise stated), 6 mL) and the mixture was rapidly frozen in liquid N_2 and lyophilized for 12 hours.

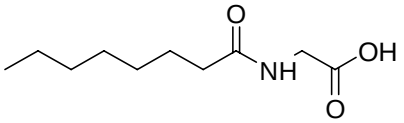
Acyl donor synthesis

N-Octanoylglycine ethylester.



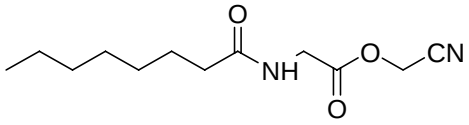
To a 0°C solution of glycine ethyl ester hydrochloride (10 mmol) in $CHCl_3$ (50 mL), triethylamine (1.2g, 12 mmol) was added. A solution of octanoyl chloride (12 mmol) in $CHCl_3$ (2 mL) was added dropwise and stirred overnight. The reaction mixture was shaken with 1 M HCl, water and brine, and finally dried over anhydrous Na_2SO_4. The solvent was removed and the residue purified by column chromatography on silica gel using a mixture of ether/pentane (62%). ^{1}H NMR (300 MHz, $CDCl_3$): 0.86 (t, 3 H, J = 6.8), 1.24-1.31 (m, 11 H), 1.59-1.69 (m, 2 H), 2.22 (t, 2 H, J = 7.4), 4.01 (d, 2 H, J = 5.1), 4.20 (q, 2H, J = 7.2), 6.02 (br s, 1 H).^{13}C NMR (CDCl3): 14.1 (CH_3), 14.2 (CH_3), 22.7 (CH_2), 25.7 (CH_2), 29.1 (CH_2), 29.3 (CH_2), 31.8(CH_2), 36.5 (CH_2), 41.4 (CH_2), 61.6 (CH_2), 170.3 (C), 173.4 (C).

N-Octanoylglycine.



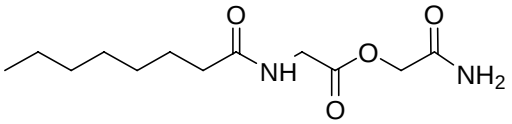
To 7.5g (100 mmol) of glycine in 16.2g of triethylamine (160 mmol) in a mixture of water (10 mL) and acetone (50 mL) was added dropwise (100 mmol) of octanoyl chloride at 0°C. After 24 hours at room temperature, acetone was evaporated under vacuum and the reaction mixture was extracted with methylene chloride (4x50 mL) after acidification to pH 2. The organic phase was dried ($MgSO_4$), concentrated and the crude product was purified by crystallization in hexane (13g, 65%). m.p. 92-93°C. ^{1}H NMR (200 MHz, $CDCl_3$+DMSO-d_6): 0.77 (t, 3H, J = 6.8), 1.21-1.35 (m, 8H), 1.50 (m, 2H), 2.24 (t, 2H, J = 8.0), 4.16 (d, 2H, J = 5.2), 4.62 (br s, OH), 6.49 (br s, NH). ^{13}C NMR (50 MHz, $CDCl_3$): 174.4 (CO) ; 172 (CO) ; 41.2 (CH_2) ; 36.2 (CH_2) ; 31.6 (CH_2) ; 29.1 (CH_2) ; 28.9 (CH_2); 25.6 (CH_2); 22.5 (CH_2); 13.9 (CH_3).

Cyanomethyl 2-(octanamido)acetate.



To a solution of octanoylglycine (402 mg, 2 mmol) in MeOH (4 mL) was added a solution of Cs_2CO_3 (326 mg, 1 mmol) in water (1.5 mL), and the mixture was evaporated under reduced pressure. After repeated evaporation to dryness with toluene, the cesium salt of octanoylglycine was mixed with 2-chloroacetonitrile (151 mg, 2 mmol) in DMF (8 mL) and the mixture was stirred at 60°C overnight. The mixture was partitioned between EtOAc (40 mL) and water (10 mL), and the aqueous phase was extracted further with EtOAc (2×10 mL). The combined organic extracts were washed successively with 1M aq. $NaHCO_3$ and water, and dried over Na_2SO_4. Evaporation of the solvent afforded white crystals, which were recrystallised from EtOAc–petroleum spirit (384 mg, 80%). m.p. 85-86°C.^{1}H NMR ($CDCl_3$, 200MHz): 0.87 (t, 3H, J = 6.8), 1.27-1.32 (m, 8 H), 1.63 (quint, 2H, J = 7.2), 2.25 (t, 2 H, J = 7.4), 4.12 (d, 2 H, J = 5.1), 4.78 (s, 2H), 6.02 (br s, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): 14.2 (CH_3), 22.7 (CH_2), 25.6 (CH_2), 29.1 (CH_2), 29.3 (CH_2), 31.7 (CH_2), 36.4 (CH_2), 40.9 (CH_2), 49.0 (CH_2), 113.9 (C), 168.9 (C), 173.7 (C).

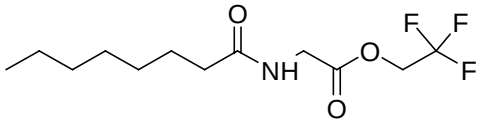
Carbamoylmethyl 2-(octanamido)acetate.



To a solution of octanoylglycine (402 mg, 2 mmol) in MeOH (4 mL) was added a solution of Cs_2CO_3 (326 mg, 1 mmol) in water (1.5 mL), and the mixture was evaporated under reduced pressure. After repeated evaporation to dryness with toluene, the cesium salt of octanoylglycine was mixed with 2-chloroacetamide (187 mg, 2 mmol) in DMF (8 mL) and the mixture was stirred at 60°C overnight. The mixture was partitioned between EtOAc (40 mL) and water (10 mL), and the aqueous phase was further extracted with EtOAc (2×10 mL), and the combined organic extracts were washed successively with 1 M aq. $NaHCO_3$ and water, and dried over Na_2SO_4. Evaporation of the solvent afforded white crystals, which were recrystallised from EtOAc–petroleum spirit; yield 408 mg (79%). m.p. 135-136°C. ^{1}H NMR ($CDCl_3$ + 2 drops of CD_3OD, 200MHz): 0.80 (t, 3 H, J = 6), 1.15-1.35 (m, 8 H), 1.51-1.59 (m, 2 H), 2.18 (t, 2 H, J = 7.4), 3.80 (s, 2 H), 4.40 (s, 2H), 6.00 (s, NH), 6.40-6.80 (m, NH_2). ^{13}C NMR ($CDCl_3$ + 2 drops DMSO-d_6, 75 MHz): 13.8 (CH_3), 22.2 (CH_2), 25.2 (CH_2), 28.6

(CH_2), 28.8 (CH_2), 31.3 (CH_2), 35.6 (CH_2), 41.4 (CH_2), 62.3 (CH_2), 168.9 (C), 169.4 (C), 174.4 (C).

2,2,2-Trifluoroethyl 2-(octanamido)acetate.



To octanoylglycine (2g, 10 mmol) and trifluoro ethanol (10 mmol, 1g) in 10 mL chloroform were added 10 mmol of dicyclohexyl carbodiimide (2.06g). The reaction mixture was heated at 65°C for 15 hours. The solvent was evaporated, the crude product was washed with diethyl ether. The crude product was purified by crystallization in hexane (1.98g, 70%). ^{1}H NMR (300 MHz, $CDCl_3$): 0.88 (t, 3H, J = 6.9), 1.21-1.35 (m, 8H), 1.65 (quint, 2H, J = 7.5), 2.24 (t, 2H, J = 7.5), 4.16 (d, 2H, J = 5.5), 4.53 (q, 2H, $^3J_{HF}$= 9.0), 6.00 (br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): 14.2 (CH_3), 22.7 (CH_2), 25.6 (CH_2), 29.1 (CH_2), 29.3 (CH_2), 31.8 (CH_2), 36.4 (CH_2), 41.0 (CH_2), 61.0 (q, CH_2, $^2J_{CF}$= 36.5), 122.0 (q, CF_3, $^1J_{CF}$= 275), 168.9 (C), 173.7 (C). White solid m.p. 76-77°C. HRMS ($[M+H]^+$, ESI): *m/z* calcd for: $C_{12}H_{21}NO_3F_3$: 284.1468. Found: 284.1469.

General Procedure for the kinetic resolution of amines

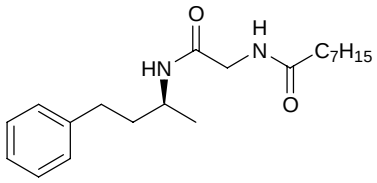
To a solution of 570 mg (2 mmol) *N*-octanoylglycine trifluoroethyl ester in 2 mL of 3-methyl-3-pentanol was added 50 mg of coated alkaline protease[6] and 298 mg (2 mmol) of phenylbutyl amine (**1a**). The resulting mixture was stirred at room temperature for 40 minutes. The amine ee was determined by GC after derivatization of an aliquot of the crude mixture in trifluoroacetamide with 1.5 equiv of *N*-methyl-bis-trifluoroacetamide. The enzyme was filtered off from the solution and washed with 10 mL of dichloromethane. Then 240 mg (1.1 mmol) of Boc_2O was added to the filtrate, and the mixture was stirred until complete consumption of amine monitored by TLC. The solvent was then evaporated and the crude mixture was purified on gel-silica (pentane/diethyl ether gradient 0 to 10% to afford the Boc-amine, then DCM/MeOH 98/2 to afford the amide).

General Procedure for the synthesis of racemic amides (2a-2m) for chiral HPLC analysis

To *N*-Octanoylglycine (1 mmol) and racemic amine (**1a-1m**) (1 mmol) in chloroform (5 mL) was added dicyclohexyl carbodiimide (1 mmol). The reaction mixture was heated at 65°C for 15 hours. The solvent was evaporated, the crude product was washed with diethyl ether. After

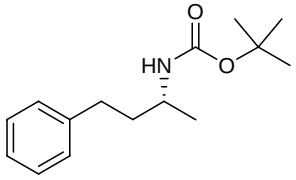
concentration, the product was purified by crystallization from hexane or chromatography on gel-silica (yield 60-90%).

_N_-(((_S_)-4-phenylbutan-2-ylcarbamoyl)methyl)octanamide (2a)



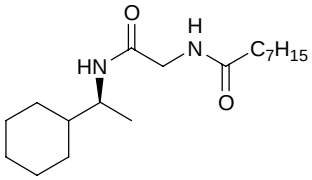
^{1}H NMR (300 MHz, $CDCl_3$): 0.88 (t, 3H, J = 6.5), 1.18 (d, 3H, J = 6.6), 1.21-1.33 (br m, 8H), 1.58-1.68 (m, 2H), 1.73-1.82 (m, 2H), 2.24 (t, 2H, J = 7.6), 2.63 (t, 2H, J = 8.0), 3.95 (d, 2H, J = 5.0), 3.98-4.08 (m, 1H), 6.50-6.55 (br m, 2NH), 7.16-7.30 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): 14.1 (CH_3), 20.9 (CH_3), 22.6 (CH_2), 25.7 (CH_2), 29.0 (CH_2), 29.3 (CH_2), 31.7 (CH_2), 32.5 (CH_2), 36.3 (CH_2), 38.4 (CH_2), 43.6 (CH_2), 45.3 (CH), 125.9 (CH), 128.3 (2xCH), 128.4 (2xCH), 141.7 (C), 168.5 (C), 174.0 (C). Yield 47%. White solid m.p. 85-86 °C; HPLC conditions: Chiralcel OD-H, *n*-hexane/ethanol 95:5, flow rate = 1 mL/min, UV 254 nm, t_R (*S*) = 9 min, t_R (*R*) = 13.2 min, k (*S*) = 1.90, k (*R*) = 3.26, α = 1.71, Rs = 3.22. ee 90%. $[\alpha]_D^{25}$ = -9 (*c* = 1.1 in $CHCl_3$). Anal. Calcd for $C_{20}H_{32}N_2O_2$: C, 72.25; H, 9.7; N, 8.43. Found: C, 72.07; H, 9.8; N, 7.75

***tert*-Butyl (*R*)-4-phenylbutan-2-ylcarbamate (Boc-(*R*)-1a)**



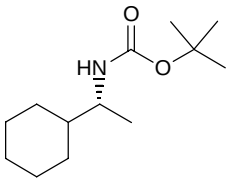
^{1}H NMR (300 MHz, $CDCl_3$): 1.18 (d, 3H, J = 6.6 Hz), 1.47 (s, 9H), 1.69-1.78 (m, 2H), 2.64-2.70 (m, 2H), 3.73 (m, 1H), 4.38 (br s, 1H), 7.19-7.32 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): 21.5 (CH_3), 28.5 (*t*-Bu), 32.6 (CH_2), 39.3 (CH_2), 46.5 (CH), 79.1 (C), 125.9 (CH), 128.4 (2 x CH), 128.5 (2 x CH), 142.0 (C), 155.5 (C). Yield 48%. White solid m.p. 84-85 °C. For determination of amine ee, GC conditions: Lipodex D, 170 °C, 15 min, 170-190 °C, 3 °C/min, t_R (*R*)-**1** = 11.22 min, t_R (*S*)-**1** = 12.45 min, k (*R*) = 3.07, k (*S*) = 3.21, α = 1.04, Rs = 1.94. $[\alpha]_D^{25}$ = +13.9 (*c* = 0.9 in $CHCl_3$). ee 96%. HRMS ($[M+H]^+$, ESI): *m/z* calcd for: $C_{15}H_{24}NO_2$: 250.1801. Found: 250.1800.

_N_-(((_S_)-1-cyclohexylethylcarbamoyl)methyl)octanamide (2b).



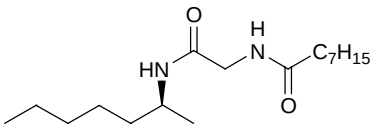
^{1}H NMR (300 MHz, $CDCl_3$): 0.87-1.30 (br m, 15H), 0.88 (superimposed t, 3H, J = 6.5), 1.09 (superimposed d, 3H, J = 6.9), 1.63-1.75 (m, 6H), 2.24 (t, 2H, J = 7.6), 3.79-3.84 (m, 1H). 3.93 (d, 2H, J = 5 Hz), 6.67 (d, NH, J = 8.7 Hz), 6.77 (br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): 14.1 (CH_3), 17.9 (CH_3), 22.7 (CH_2), 25.8 (CH_2), 26.3 (CH_2), 26.5 (CH_2), 29.0 (CH_2), 29.1 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 31.8 (CH_2), 36.4 (CH_2), 43.1 (CH), 43.8 (CH_2), 49.8 (CH), 168.4 (C), 174.0 (C). Yield 55%. White solid m.p. 106-107 °C (from AcOEt); $[\alpha]_D^{25}$ = +2.5 (c = 1.05 in $CHCl_3$). ee = 73%. HPLC conditions: Chiralcel OD-H, _n_-hexane/iPrOH 98:2, flow rate = 1 mL/min, UV 220 nm, t_R (_S_) = 10.8 min, t_R (_R_) = 13.1 min, k (_S_) = 2.48, k (_R_) = 3.22, α = 1.30. HRMS ($[M+H]^+$, ESI): *m/z* calcd for $C_{18}H_{35}N_2O_2$: 311.2693. Found: 311.2687.

***tert*-Butyl (_R_)-1-cyclohexylethylcarbamate (Boc-(_R_)-1b).**



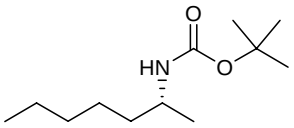
^{1}H NMR (300 MHz, $CDCl_3$): 0.94-1.77 (m, 11H), 1.04 (superimposed d, 3H, J = 6.8), 1.42 (superimposed s, 9H), 3.46-3.53 (m, 1H), 4.36 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 18.35 (CH_3), 26.4 (CH_2), 26.6 (CH_2), 28.6 (_t_-Bu), 29.0 (CH_2), 29.1 (CH_2), 43.6 (CH), 50.9 (CH), 78.9 (C), 155.7 (C). Yield 44%. White solid m.p. 58-59 °C. For determination of amine ee, GC conditions: Lipodex D column, injector 250°C, program: 15 min./130°C then 3°C/min from 130 to 180°C and 20 min./180°C. Detector: FID. t_R (_R_) = 14.86, t_R (_S_) = 15.41, k (_R_) = 4.21, k (_S_) = 4.40, α = 1.04, Rs = 1.83. $[\alpha]_D^{25}$ = +1.3 (c = 0.7 in $CHCl_3$) ee = 90%. HRMS ($[M+H]^+$, ESI): *m/z* calcd for $C_{13}H_{26}NO_2$: 228.1958. Found: 228.1955.

_N_-(((_S_)-heptan-2-ylcarbamoyl)methyl)octanamide (2c).



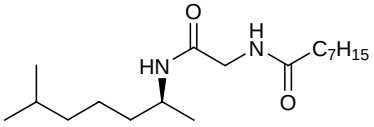
^{1}H NMR (300 MHz, $CDCl_3$): 0.85 (t, 6H, *J* = 6.6), 1.10 (d, 3H, *J* = 6.6), 1.18-1.24 (br m, 16H), 1.55-1.65 (m, 2H), 2.21 (t, 2H, *J* = 7.5), 3.82-3.97 (m, 1H), 3.90 (d, 2H, *J* = 5.0), 6.73 (d, NH, *J* = 8.3), 6.82 (t, NH, *J* = 5.0). ^{13}C NMR (75 MHz, $CDCl_3$): 14.1 (CH_3), 14.15 (CH_3), 20.8 (CH_3), 22.6 (CH_2), 22.7 (CH_2), 25.7 (CH_2), 25.8 (CH_2), 29.1 (CH_2), 29.3 (CH_2), 31.8 (2 x CH_2), 36.4 (CH_2), 36.8 (CH_2), 43.6 (CH_2), 45.6 (CH), 168.4 (C), 173.9 (C). Yield 50%. White solid m.p. 80-81 °C. HPLC conditions: Chiralcel OD-H, *n*-hexane/iPrOH 98:2, flow rate = 1 mL/min, UV 220 nm, t_R (*S*) = 9.5 min, t_R (*R*) = 11.4 min, k (*S*) = 2.06, k (*R*) = 2.68, α = 1.30. $[\alpha]_D^{25}$ = +5.2 (*c* = 1.1 in $CHCl_3$). ee = 92%. HRMS ($[M+H]^+$, ESI): *m/z* calcd for $C_{17}H_{35}N_2O_2$: 299.2693. Found: 299.2684.

tert-Butyl (*R*)-heptan-2-ylcarbamate (Boc-(*R*)-1c).



^{1}H NMR (300 MHz, $CDCl_3$): 0.86 (t, 3H, *J* = 6.7), 1.08 (d, 3H, *J* = 6.6), 1.27-1.36 (m, 8H), 1.42 (s, 9H), 3.6 (m, 1H), 4.3 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 14.1 (CH_3), 21.4 (CH_3), 22.7 (CH_2), 25.8 (CH_2), 28.5 (*t*-Bu), 31.8 (CH_2), 37.4 (CH_2), 46.6 (CH), 79.0 (C), 155.5 (C). Yield 44%. Colorless liquid For determination of amine ee, GC conditions: Lipodex D, 130 °C, 10 min, 130-180 °C, 3 °C/min, t_R (*R*) = 7.00 min, t_R (*S*) = 7.32 min, k (*R*) = 4.31, k (*S*) = 4.64, α = 1.08, Rs = 0.56. $[\alpha]_D^{25}$ = -4 (*c* = 1 in $CHCl_3$). ee = 96%. HRMS ($[M+H]^+$, ESI): *m/z* calcd for $C_{12}H_{26}NO_2$: 216.1958. Found: 216.1956.

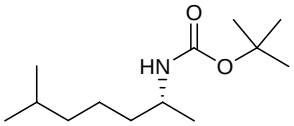
***N*-(((*S*)-6-methylheptan-2-ylcarbamoyl)methyl)octanamide (2d).**



^{1}H NMR (300 MHz, $CDCl_3$): 0.82-8.87 (m, 9H), 1.09-1.62 (m, 17H), 1.10 (superimposed d, 3H, *J* = 7.2), 2.21 (t, 2H, *J* = 7.6), 3.82-3.99 (m, 3H), 6.75 (d, NH, *J* = 8), 6.82 (br t, NH, *J* = 4.5). ^{13}C NMR (75 MHz, $CDCl_3$): 14.1 (CH_3), 20.8 (CH_3), 22.6 (2 x CH_3), 22.7 (CH_2), 23.9 (CH_2), 25.7 (CH_2), 27.9 (CH), 29.1 (CH_2), 29.3 (CH_2), 31.8 (CH_2), 36.4 (CH_2), 37.0 (CH_2), 38.8 (CH_2), 43.6 (CH_2), 45.6 (CH), 168.3 (C), 173.9 (C). Yield 52%. White solid m.p. 72-73 °C. HPLC conditions: Chiralcel OD-H, *n*-hexane/iPrOH 98:2, flow rate = 1 mL/min, UV 220 nm, t_R (*S*) = 11.0 min, t_R (*R*) = 13.6 min, k (*S*) = 2.55, k (*R*) = 3.39, α = 1.33. $[\alpha]_D^{25}$ = +4.9 (*c*

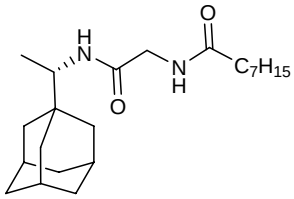
= 1 in $CHCl_3$). ee = 88%. HRMS ($[M+H]^+$, ESI): *m/z* calcd for $C_{18}H_{37}N_2O_2$: 313.2849. Found: 313.2843.

tert-Butyl (_R_)-6-methylheptan-2-ylcarbamate (Boc-(_R_)-1d).



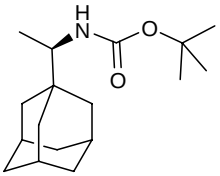
^1H NMR (300 MHz, $CDCl_3$): 0.85 (d, 6H, *J* = 6.6), 1.09 (d, 3H, *J* = 6.5), 1.16-1.36 (m, 7H), 1.43 (s, 9H), 3.61 (m, 1H), 4.30 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.4 (CH_3), 22.6 (CH_3), 22.7 (CH_3), 23.9 (CH_2), 28.0 (CH), 28.5 (*t*-Bu), 37.7 (CH_2), 38.9 (CH_2), 46.6 (CH), 79.0 (C), 155.5 (C). Yield 44%. Colorless liquid. $[\alpha]_D^{25}$ = -1.5 (*c* = 2.4 in $CHCl_3$). For determination of amine ee, GC conditions: Lipodex D, 140 °C, 25 min, 140-180 °C, 3 °C/min, t_R (*R*) = 6.48 min, t_R (*S*) = 6.73 min, k (*R*) = 1.76, k (*S*) = 1.85, α = 1.05, Rs = 1.85. ee > 99.5%. HRMS ($[M+Na]^+$, ESI): *m/z* calcd for $C_{13}H_{27}NO_2Na$: 252.1933. Found: 252.1928.

***N*-(((*S*)-2-adamantylethan-2-ylcarbamoyl)methyl)octanamide (2e).**



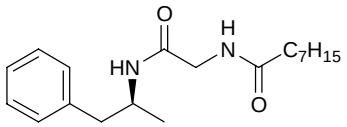
^1H NMR (200 MHz, $CDCl_3$): 6.80 (m, 1H), 6.60 (m, 1H), 3.92 (m, 2H), 3.67 (m, 1H), 2.25 (t, 2H, *J* = 7), 1.96 (m, 2H), 1.66 (m, 9H), 1.49 (m, 5H), 1.26 (m, 10H), 1.02 (d, 3H, *J* = 6.9), 0.86 (t, 3H, *J* =7). ^{13}C NMR (50 MHz, $CDCl_3$): 174.0 (C), 168.6 (C), 53.1 (CH), 43.6 (CH_2), 38.0 (CH_2), 36.8 (C), 36.0 (CH_2), 35.6 (CH_2), 31.4 (CH_2), 29.0 (CH_2), 28.8 (CH_2), 28.1 (CH), 25.6 (CH_2), 22.4 (CH_2), 14.0 (CH_3), 13.8 (CH_3). Yield 47%. White solid m.p. 132°C. $[\alpha]_D^{25}$ = +5 (c = 0.7, $CHCl_3$). HPLC conditions: Chiralcel OD-H, n-hexane/ethanol 98:2, flow rate = 1 mL/min, UV 220 nm, t_R (*S*) = 7.7 min, t_R (*R*) = 9.2 min, k (*S*) = 1.48, k (*R*) = 1.97, α = 1.33, Rs = 1.92. ee= 99%. HRMS ($[M+H]^+$, ESI): *m/z* calcd for: $C_{22}H_{39}N_2O_2$: 363.3006. Found: 363.3008. The assignment of the absolute configuration is based on the selectivity of the protease.

tert-Butyl (_R_)- 2-adamantylethan-2-ylcarbamate (Boc-(_R_)-1e).



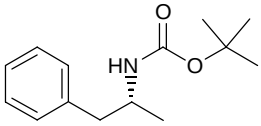
^{1}H NMR (200 MHz, $CDCl_3$): 4.37 (d, 1H, *J* = 2), 3.26 (m, 1H), 2.0 (m, 3H), 1.73-1.39 (m, 21H), 0.94 (d, 3H, *J* = 7). ^{13}C NMR (50 MHz, $CDCl_3$):155.6 (C) 54.5 (CH) 38.3 (CH_2) 37.1 (CH_2) 35.8 (C) 28.3 (CH) 28.2 (CH_3) 27.3 (CH) 14.9 (CH_3). Yield 52%. White solid m.p. 94-95°C. $[\alpha]_D^{25}$ = +3.75 (c = 6, $CHCl_3$). For determination of amine ee, GC conditions: Hydrodex βOAc (Macherey Nagel) 170°C, t_R (*S*) = 15.0 min, t_R (*R*) = 16.9 min, k (*S*) = 1.07, k (*R*) = 1.13, α = 1.06. ee= 90%. HRMS ($[M+H]^+$, ESI): *m/z* calcd for: $C_{17}H_{30}NO_2$: 280.2271. Found: 280.2269. The assignment of the absolute configuration is based on the selectivity of the protease.

_N_-(((_S_)-1-phenylpropan-2-ylcarbamoyl)methyl)octanamide (2f).



^{1}H NMR (300 MHz, $CDCl_3$): 0.87 (t, 3H, *J* = 6.6), 1.13 (d, 3H, *J* = 6.6), 1.25-1.33 (br m, 8H), 1.62 (m, 2H), 2.22 (t, 2H, *J* = 7.4), 2.68 (dd, 1H, *J* = 13.6, 7.1), 2.85 (dd, 1H, *J* = 13.6, 6.3), 3.85 (m, 2H), 4.21 (sept, 1H), 6.83 (br s, 1H), 6.95 (br s, 1H) 7.15-7.30 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): 14.1 (CH_3), 20.0 (CH_3), 22.7 (CH_2), 25.7 (CH_2), 29.1 (CH_2), 29.3 (CH_2), 31.8 (CH_2), 36.3 (CH_2), 42.7 (CH_2), 43.5 (CH_2), 46.7 (CH), 126.5 (CH), 128.4 (2xCH), 129.4 (2xCH), 138.2 (C), 168.4 (C), 173.9 (C). Yield 52%. White solid m.p. 97-98 °C. $[\alpha]_D^{25}$ = + 4.0 (*c* = 1 in $CHCl_3$). HPLC conditions: Chiralcel OD-H, *n*-hexane/iPrOH 95:5, flow rate = 1 mL/min, UV 254 nm, t_R (*S*) = 8.3 min, t_R (*R*) = 11.5 min, k (*S*) = 1.68, k (*R*) = 2.71, α = 1.61. ee = 60%. HRMS ($[M+H]^+$, ESI): *m/z* calcd for $C_{19}H_{31}N_2O_2$: 319.2380. Found: 319.2377.

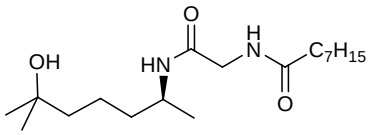
***tert*-Butyl (*R*)-1-phenylpropan-2-ylcarbamate (Boc-(*R*)-1f).**



^{1}H NMR (300 MHz, $CDCl_3$): 1.10 (d, 3H, *J* = 6.6), 1.44 (s, 9H), 2.67 (dd, 1H, *J* = 13.2, 7.4), 2.87 (dd, 1H, *J* = 13.2, 5.5), 3.92 (m, 1H), 4.41 (br s, 1H), 7.18-7.33 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): 20.3 (CH_3), 28.5 (3xCH_3), 43.1 (CH_2), 47.5 (CH), 79.2 (C), 126.4 (CH), 128.4 (2xCH), 129.6 (2xCH), 138.4 (C), 155.3 (C). Yield 37%. White solid m.p. 55-56°C. $[\alpha]_D^{25}$ =

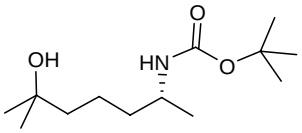
+0.82 (*c* = 0.5 in $CHCl_3$). For determination of amine ee, GC conditions: Lipodex D column, injector 250°C, program: 15 min/140°C, then 3°C/min from 140 to 180°C, and 20 min/180°C. Detector: FID. t_R (*R*) = 19.08 min, t_R (*S*) = 19.54 min, k (*R*) = 5.69, k (*S*) = 5.82, α = 1.02, Rs = 2.07. ee 91.5%. HRMS ($[M+H]^+$, ESI): *m/z* calcd for $C_{14}H_{22}NO_2$: 236.1645. Found: 236.1641.

N-(((*S*)-6-hydroxy-6-methylheptan-2-ylcarbamoyl)methyl)octanamide (2g).



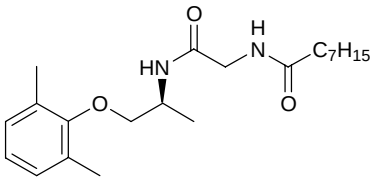
^{1}H NMR (300 MHz, $CDCl_3$): 0.82 (t, 3H, *J* = 6.8), 1.08 (d, *J* = 6.6, 3H), 1.14 (s, 6H), 1.21-1.23 (m, 8H), 1.38 (m, 6H), 1.56 (pseudo quint, *J* = 7.0, 2H), 2.19 (t, *J* = 7.9, 2H), 2.50 (s, OH), 3.85-3.93 (m, 3H), 7.00- 7.07 (m, 2NH). ^{13}C NMR (75 MHz, $CDCl_3$): 14.4 (CH_3), 20.9 (CH_2), 21.3 (CH_3), 22.9 (CH_2), 26.0 (CH_2), 29.41 (CH_2), 29.43 (CH_3), 29.6 (CH_2), 29.9 (CH_3), 32.1 (CH_2), 36.7 (CH_2), 37.5 (CH_2), 43.7 (CH_2), 43.9 (CH_2), 45.6(CH), 71.0 (C), 169.0 (CO), 174.5 (CO). Yield 51%. White solid m.p. 58-59°C. HPLC conditions: Chiralcel OD-H, *n*-hexane/EtOH 98:2, flow rate = 1 mL/min, UV 220 nm, t_R (*R*) = 21.14 min, t_R (*S*) = 24.73 min, k (*R*) = 5.82, k (*S*) = 6.98, α = 1.20. $[\alpha]_D^{25}$ = +8 (c = 0.75, $CHCl_3$). ee = 90%. HRMS ($[M+H]^+$, ESI): *m/z* calcd for $C_{18}H_{36}N_2O_3$: 329.2798. Found: 329.2798.

***tert*-Butyl (*R*)-6-hydroxy-6-methylheptan-2-ylcarbamate (Boc-(*R*)-1g).**



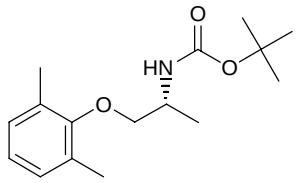
^{1}H NMR (300 MHz, $CDCl_3$): 1.11 (d, *J* = 6.6, 3H), 1.20 (s, 3H), 1.21 (s, 3H), 1.36-1.60 (m, 6H), 1.41 (superimposed s, 9H), 1.87 (br s, 1H), 3.63 (m, 1H), 4.36 (br d, *J* = 5.4, NH). ^{13}C NMR (75 MHz, $CDCl_3$): 21.0 (CH_2), 21.8 (CH_3), 28.8 (3xCH_3), 29.4 (CH_3), 29.8 (CH_3), 38.2 (CH_2), 43.8 (CH_2), 46.5 (CH), 71.2 (C), 79.4(C), 156.0 (CO). Yield 42%. White solid m.p. 56-57°C. $[\alpha]_D^{25}$ = - 3.2 (c = 0.5, $CHCl_3$). For determination of amine ee, GC conditions: Lipodex D column, injector 250°C, program: 15 min/160°C, then 3°C/min from 160 to 190°C. Detector: FID. t_R (*S*) = 7.80 min, t_R (*R*) = 8.05 min, k (*S*) = 1.89, k (*R*) = 2.60. ee = 96%. HRMS ($[M+H]^+$, ESI): *m/z* calcd for $C_{13}H_{28}NO_3$: 246.2064. Found: 246.2067.

***N*-(((*S*)-1-(2,6-dimethylphenoxy)propan-2-ylcarbamoyl)methyl)octanamide (2h).**



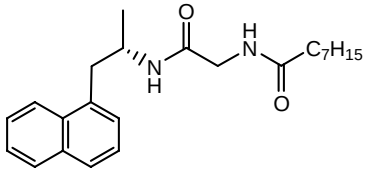
^{1}H NMR (400 MHz, $CDCl_3$): 0.85 (t, 3H, *J* = 6.7), 1.20-1.35 (m, 9H), 1.40 (d, 3H, *J* = 6.0), 1.55-1.70 (m, 2H), 2.20-2.36 (m, 8H), 3.69-3.75 (m, 2H), 3.91-4.04 (AB pattern of ABX, 2H, J_{AB} = 16.8), 4.40 (br s, NH), 6.59 (br s, NH), 6.88-6.98 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.1 (CH_3), 16.2 (2xCH_3), 17.6 (CH_3), 22.7 (CH_2), 25.7 (CH_2), 29.1 (CH_2), 29.3 (CH_2), 31.8 (CH_2), 36.4 (CH_2), 43.7 (CH_2), 45.7 (CH), 73.8 (CH_2), 124.2 (CH), 129.0 (2xCH), 130.8 (2xC), 155.0 (C), 168.6 (C), 173.9 (C). Yield 49%. White solid m.p. 94-95 °C. $[\alpha]_D^{25}$ = -7.8 (*c* = 1 in $CHCl_3$). HPLC conditions: Chiralcel OD-H, *n*-hexane/iPrOH 90:10, flow rate = 1 mL/min, UV 254 nm, t_R (*S*) = 9.6 min, t_R (*R*) = 15.5 min, k (*S*) = 2.10, k (*R*) = 4.00, α = 1.90. ee = 96.2%. HRMS ($[M+H]^+$, ESI): *m/z* calcd for $C_{21}H_{35}N_2O_3$: 363.2642. Found: 363.2639.

tert-Butyl (*R*)-1-(2,6-dimethylphenoxy)propan-2-ylcarbamate (Boc-(*R*)-1h).



^{1}H NMR (400 MHz, $CDCl_3$): 1.10 (d, 3H, *J* = 6.9), 1.37-1.46 (s, 9H), 2.27 (s, 6H), 3.68-3.78 (m, 2H), 4.00 (m, 1H), 4.90 (br s, 1H), 6.90-7.01 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 16.3 (2xCH_3), 18.0 (CH_3), 28.5 (CH_3), 46.8 (CH), 74.2 (CH_2), 79.4 (C), 124.1 (CH), 129.0 (2xCH), 130.9 (2xC), 155.2 (C), 155.5 (C). Yield 48%. White solid m.p. 69-70°C. $[\alpha]_D^{25}$ = +22.2 (*c* = 1 in $CHCl_3$). For determination of amine ee, GC conditions: Chrompack, 120 °C, isotherm, t_R (*R*) = 33.49 min, t_R (*S*) = 34.45 min, k (*R*) = 23.81, k (*S*) = 24.51, α = 1.03, Rs = 1.39. ee 96%. HRMS ($[M+H]^+$, ESI): *m/z* calcd for $C_{16}H_{26}NO_3$: 280.1907. Found: 280.1904.

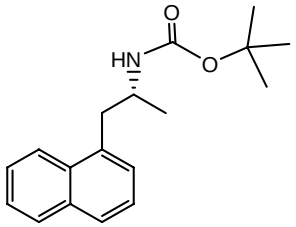
***N*-(((*S*)-1-(naphthalen-4-yl)propan-2-ylcarbamoyl)methyl)octanamide (2i).**



^{1}H NMR (200 MHz, $CDCl_3$): 8.27 (d, 1H, *J* = 8.2), 7.83 (d, 1H, *J* = 7.4), 7.74 (d, 1H, *J* = 7.8), 7.58-7.25 (m, 4H), 6.70-6.40 (m, 2H), 4.39 (sept, 1H, *J* = 6.2), 3.86 (d, 2H, *J* = 5.0), 3.52-

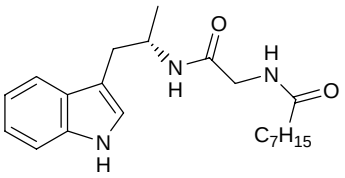
2.93 (AB pattern of ABX, 2H, J_{AB} = 13.6), 2.2 (t, 2H, J = 7), 1.65 (m, 2H), 1.45-1.30 (m, 8H), 1.14 (d, 3H, J = 6.7), 0.87 (t, 3H, J = 6.9). ^{13}C NMR (50 MHz, $CDCl_3$): 173.8 (C), 168.4 (C), 134.4 (C), 133.8 (C), 132.2 (C), 128.6 (CH), 127.5 (CH), 127.3 (CH), 126.0 (CH), 125.6 (CH), 125.2 (CH), 124.0 (CH), 46.2 (CH), 43.4 (CH_2), 40.0 (CH_2), 36.2 (CH_2), 31.6 (CH_2), 29.2 (CH_2), 29.0 (CH_2), 25.5 (CH_2), 22.5 (CH_2), 19.9 (CH_3), 14.0 (CH_3). Yield 52%. White solid m.p. 75 °C. $[\alpha]_D^{25}$ = +6.25 (c=1.4, $CHCl_3$). HPLC conditions: Chiralcel OD-H, *n*-hexane/iPrOH 90:10, flow rate = 1 mL/min, UV 254 nm, t_R (*S*) = 23.7 min, t_R (*R*) = 30.9 min, k (*S*) = 6.65, k (*R*) = 8.97, α = 1.35, Rs = 2.42. ee = 96%. HRMS ($[M+H]^+$, ESI): *m/z* calcd for: $C_{23}H_{33}N_2O_2$: 369.2536. Found: 369.2539. The assignment of the absolute configuration is based on the selectivity of the protease.

tert-Butyl (*R*)-1-(naphthalen-5-yl)propan-2-ylcarbamate (Boc-(*R*)-1i).



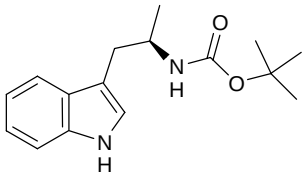
^{1}H NMR (200 MHz, $CDCl_3$): 8.22 (d, 1H, J = 8.8), 7.87-7.72 (m, 2H), 7.60-7.28 (m, 4H), 4.50 (br s, 1H), 4.09 (sept, 1H, J = 6.2), 3.56-3.47 (m, 1H), 3.01-2.90 (dd, 1H, J = 13.5, 8.1), 1.53 (s, 9H), 1.1 (d, 3H, J = 6.5). ^{13}C NMR (50 MHz, $CDCl_3$): 155.4 (C), 134.8 (C), 133.9 (C), 132.4 (C), 128.7 (CH), 127.7 (CH), 127.2 (CH), 126.1 (CH), 125.6 (CH), 125.4 (CH), 124.3 (CH), 79.1 (C), 47.2 (CH), 40.5 (CH_2), 28.5 (3xCH_3), 20.4 (CH_3). Yield 43%. White solid m.p. 107-108 °C. $[\alpha]_D^{25}$= -37.1 (c = 0.7, $CHCl_3$). For determination of amine ee by analysis of the trifluoroacetamide derivative, HPLC conditions: Chiralcel OD-H, *n*-hexane/EtOH 98:2, flow rate = 1 mL/min, UV 254 nm, t_R (*R*) = 16.4 min, t_R (*S*) = 21.7 min, k (*S*) = 4.29, k (*R*) = 6.00, α = 1.40, Rs = 1.92. Rs = 4.83. ee = 98%. HRMS ($[M+H]^+$, ESI): *m/z* calcd for: $C_{18}H_{24}NO_2$: 286.1801. Found: 286.1799. The assignment of the absolute configuration is based on the selectivity of the protease.

_N_-(((*S*)-1-(1H-indol-3-yl)propan-2-ylcarbamoyl)methyl)octanamide (2j).



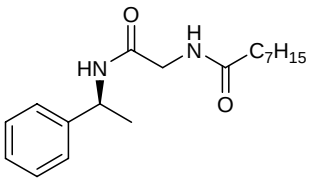
^{1}H NMR (400 MHz, $CDCl_3$): 0.89 (t, 3H, J = 6.8), 1.16 (d, 3H, J = 6.6), 1.27 (br s, 8H), 1.58 (m, 2H), 2.15 (t, 2H, J = 7.6), 2.88 (AB part of ABX, 2H, J_{AB} = 14.7), 3.76-3.86 (2 d, 2H, J = 5.0), 4.33 (hept, 1H, J = 6.6), 6.63 (m, 2H), 6.96 (d, 1H, J = 2.0), 7.10 (t, 1H, J = 7.1), 7.17 (t, 1H, J = 7.0), 7.33 (d, 1H, J = 7.0), 7.61 (d, 1H, J = 7.0), 8.57 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 13.1 (CH_3), 19.3 (CH_3), 21.6 (CH_2), 24.7 (CH_2), 28.1 (CH_2), 28.3.3 (CH_2), 30.7 (CH_2), 30.8 (CH_2), 35.3 (CH_2), 42.3 (CH_2), 45.1 (CH), 110.3 (CH), 110.8 (C),117.8 (CH), 118.4 (CH), 120.9 (CH), 122.0 (CH) 126.9 (C), 135.3 (C) 167.4 (C), 173.0 (C). Yield 51%. Amorphous solid; $[\alpha]_D^{25}$ = +2.2 (c = 1.3 in $CHCl_3$). HPLC conditions: Chiralcel OD-H, *n*-hexane/iPrOH 90:10, flow rate = 1 L/min, UV 254 nm, t_R (*S*) = 20.3 min, t_R (*R*) = 31.9 min, k (*S*) = 5.55, k (*R*) = 9.29, α = 1.67. ee = 79%. HRMS ($[M+H]^+$, ESI): *m/z* calcd for: $C_{21}H_{32}N_3O_2$: 358.2489. Found: 358.2492.

tert-Butyl (*R*)-1-(1H-indol-3-yl)propan-2-ylcarbamate (Boc-(*R*)-1j).



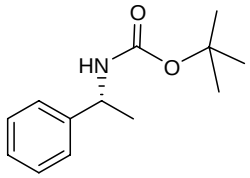
^{1}H NMR (300 MHz, $CDCl_3$): 1.13 (d, 3H, J = 6.6), 1.45 (s, 9H), 2.86 (dd, 1H, J = 6.6,14.3), 2.98 (dd, 1H, J = 5.2, 14.3), 4.00-4.05 (m, 1H), 4.48-4.54 (m, 1H), 6.99 (s, 1H), 7.15 (m, 2H), 7.37 (d, 1H, J = 7.8), 7.65 (d, 1H, J = 7.8), 8.35 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 20.7 (CH_3), 28.5 (3xCH_3), 32.4 (br CH_2), 47.0 (br CH), 79.2 (br C_q), 111.2 (CH) , 112.2 (C), 119.2 (CH), 119.4 (CH), 121.9 (CH), 122.4 (CH), 128.1 (C), 136.37 (C), 155.6 (C). Yield 44%. White solid m.p. 80-81 °C; $[\alpha]_D^{25}$ = +13.3 (c = 1.05 in $CHCl_3$). For determination of amine ee by analysis of the trifluoroacetamide derivative, HPLC conditions: Chiralcel OD-H, *n*-hexane/iPrOH 90:10, flow rate = 1 mL/min, UV 254 nm, t_R (*R*) = 18.4 min, t_R (*S*) = 24.0 min, k (*R*) = 4.94, k (*S*) = 6.74, α = 1.36. ee = 90%. HRMS ($[M+H]^+$, ESI): *m/z* calcd for: $C_{16}H_{23}N_2O_2$: 275.1754. Found: 275.1756.

***N*-(((*S*)-1-phenylethylcarbamoyl)methyl)octanamide (2k).**



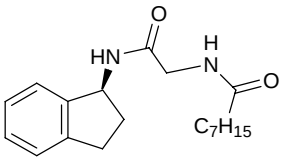
^{1}H NMR (300 MHz, $CDCl_3$): 0.83 (t, 3H, *J* = 6.8), 1.08-1.38 (m, 8H), 1.46 (d, 3H, *J* = 6.9), 1.55 (m, 2H), 2.19 (t, 2H, *J* = 7.9), 3.93 (d, 2H, *J* = 5.0), 5.05 (quint, 1H, *J* = 7.4), 6.71 (m, NH), 7.21- 7.34 (m, 5H+NH). ^{13}C NMR (75 MHz, $CDCl_3$): 14.1 (CH_3); 22.3 (CH_3); 22.7 (CH_2); 25.7 (CH_2); 29.1 (CH_2); 29.3 (CH_2); 31.7 (CH_2); 36.4 (CH_2); 43.6 (CH_2); 49.1 (CH); 126.1(CH), 127.3 (CH), 128.6 (CH), 143.3 (C); 168.2 (C); 174.0 (C). Yield 50%. White solid m.p. 66-67°C. $[\alpha]_D^{25}$ = -16.4 (c = 0.75, $CHCl_3$). HPLC conditions: Chiralcel OD-H, *n*-hexane/EtOH 95:15, flow rate = 1 mL/min, UV 254 nm, t_R (*R*) = 9.90 min, t_R (*S*) = 12.00 min, k (*R*) = 2.19, k (*S*) = 2.87, α = 1.31. ee = 66%. HRMS ($[M+H]^+$, ESI): *m/z* calcd for: $C_{18}H_{29}N_2O_2$: 305.2224. Found: 305.2225.

tert-Butyl (*R*)-1-phenylethylcarbamate (Boc-(*R*)-1k).[7]



^{1}H NMR (300 MHz, $CDCl_3$): 1.44 (m, 12H), 4.80 (m, 2H), 7.25- 7.35 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): 23.1 (CH_3); 28.8 (3xCH_3); 50.6 (CH); 126.3(CH), 127.5 (2xCH), 129.0 (2xCH), 144.4 (C); 155.5 (C). Yield 45%. White solid m.p. 78-79°C. $[\alpha]_D^{25}$ = +37.3 (c = 0.75, $CHCl_3$). For determination of amine ee, GC conditions: Lipodex D column, injector 250°C, program: 15 min/140°C, then 3°C/min from 140 to 180°C, and 20 min/180°C. Detector: FID, t_R (*S*) = 13.82 min, t_R (*R*)-**11** = 14.31 min, k (*R*) = 3.84, k (*S*) = 4.02, α = 1.04, Rs = 1.8. ee 68%.

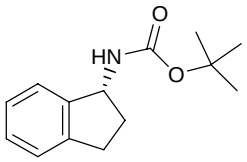
***N*-(((*S*)-2,3-dihydro-1H-inden-1-ylcarbamoyl)methyl)octanamide (2l).**



^{1}H NMR (300 MHz, $CDCl_3$): 0.89 (t, 3H, *J* = 6.6), 1.18-1.30 (br m, 8H), 1.46-1.58 (m, 2H), 1.76-1.88 (m, 1H), 2.16 (t, 2H, *J* = 7.6), 2.46-2.57 (m, 1H), 2.78-3.02 (m, 2H), 3.97 (d, 2H, *J* = 5), 5.38 (q, 1H, *J* = 7.8), 6.82 (br t, 1H), 7.13-7.24 (m, 5H, 1NH + 4HAr). ^{13}C NMR (75 MHz, $CDCl_3$): 14.1 (CH_3), 22.7 (CH_2), 25.6 (CH_2), 29.0 (CH_2), 29.3 (CH_2), 30.3 (CH_2), 31.7 (CH_2), 33.8 (CH_2), 36.3 (CH_2), 43.4 (CH_2), 54.8 (CH), 124.1 (CH), 124.8 (CH), 126.7 (CH), 128.0 (CH), 142.9 (C), 143.3 (C) 169.0 (C), 174.0 (C). Yield 48%. White solid m.p. 116-117 °C.; $[\alpha]_D^{25}$ = -21.2 (*c* = 1.05 in $CHCl_3$). HPLC conditions: Chiralcel OD-H, *n*-hexane/iPrOH

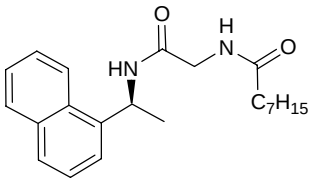
90:10, flow rate = 1 mL/min, UV 254 nm, t_R (*S*) = 5.9 min, t_R (*R*) = 9.3 min, k (*S*) = 0.90, k (*R*) = 2.00, α = 2.22. ee = 68%. HRMS ($[M+H]^+$, ESI): *m/z* calcd for $C_{19}H_{29}N_2O_2$: 317.2223. Found: 317.2220.

tert-Butyl (*R*)-2,3-dihydro-1H-inden-1-ylcarbamate (Boc-(*R*)-1l).



^{1}H NMR (300 MHz, $CDCl_3$): 1.51 (s, 9H), 1.72-1.87 (m, 1H), 2.53-2.67 (m, 1H), 2.79-3.02 (m, 2H), 4.76-5.80 (br m, 1H), 5.20 (q, 1H, *J* = 7.2), 7.20-7.35 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): 28.5 (3xCH_3), 30.1 (CH_2), 34.4 (CH_2), 56.0 (CH), 79.5 (C) 124.1 (CH), 124.8 (CH), 126.8 (CH), 127.9 (CH), 143.3 (C), 143.7 (C), 155.8 (C). Yield 41%. White solid m.p. 82-83°C. $[\alpha]_D^{25}$ = +38.7 (*c* = 1 in $CHCl_3$). For determination of amine ee, GC conditions: Lipodex D column, injector 250°C, program: 15 min/145°C, then 3°C/min from 145 to 180°C, and 20 min/180°C. Detector: FID t_R (*S*) = 25.16 min, , t_R (*R*) = 25.67 min, k (*S*) = 7.82, k (*R*) = 8.00, α = 1.02, Rs = 1.31. ee > 99.5%. HRMS ($[M+NH_4]^+$, ESI): *m/z* calcd for $C_{14}H_{23}N_2O_2$: 251.1754. Found: 251.1751.

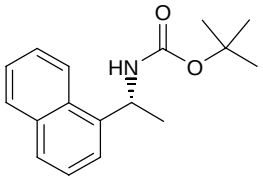
***N*-(((*S*)-1-(naphthalen-1-yl)ethylcarbamoyl)methyl)octanamide (2m).**



^{1}H NMR (300 MHz, $CDCl_3$): 0.89 (t, 3H, *J* = 6.7), 1.20-1.33 (m, 8H), 1.53 (m, 2H), 1.62 (d, 3H, *J* = 6.6), 2.17 (t, 2H, *J* = 7.8), 3.84-3.99 (AB pattern of ABX, 2H, J_{AB} = 16.2), 5.90 (quint, 1H, *J* = 6.9), 6.38 (m, 1H), 6.82 (d, 1H, *J* = 8.0), 7.44-7.51 (m, 4H), 7.75 (d, 1H, *J* = 7.8), 7.84 (d, 1H, *J* = 7.8) , 8.07 (d, 1H, *J* = 7.9). ^{13}C NMR (75 MHz, $CDCl_3$): 14.2 (CH_3), 21.3 (CH_3), 22.7 (CH_2), 25.7 (CH_2), 29.1 (CH_2), 29.3 (CH_2), 31.8 (CH_2), 36.5 (CH_2), 43.6 (CH_2), 45.1 (CH), 122.6 (CH), 123.2 (CH), 125.4 (CH), 125.9 (CH), 126.6 (CH), 128.4 (CH), 129.0 (CH), 131.0 (C), 134.0 (C), 138.4 (C), 168.0 (C), 173.9 (C). Yield 43%. White solid m.p. 132-133 °C. $[\alpha]_D^{25}$ = +1.8 (*c* = 1 in $CHCl_3$). ee = 96%. HPLC conditions: Chiralcel OD-H, *n*-hexane/iPrOH90:10, flow rate = 1 mL/min, UV 254 nm, t_R (*R*) = 9.6 min, t_R (*S*) = 15.4 min, k

(*R*) = 2.10, k (*S*) = 3.97, α = 1.89. HRMS ($[M+H]^+$, ESI): *m/z* calcd for $C_{22}H_{31}N_2O$: 355.2380. Found: 355.2377.

tert-Butyl (*R*)-1-(naphthalen-1-yl)ethylcarbamate (Boc-(*R*)-1m).



^{1}H NMR (300 MHz, $CDCl_3$): 1.45 (br s, 9H), 1.64 (d, 3H, *J* = 6.9), 4.89 (br s, 1H), 5.62 (m, 1H), 7.44-7.59 (m, 4H), 7.78 (d, 1H, *J* = 7.8), 7.88 (d, 1H, *J* = 7.8), 8.16 (d, 1H, *J* = 8.2). ^{13}C NMR (75 MHz, $CDCl_3$): 22.0 (CH_3), 28.5 (3xCH_3), 46.3 (CH), 79.6 (C), 122.2 (CH), 123.4 (CH), 125.4 (CH), 125.8 (CH), 126.4 (CH), 128.1 (CH), 128.9 (CH), 131.0 (C), 134.1 (2xC), 155.1 (C). Yield 45%. White solid m.p. 108-109 °C. $[\alpha]_D^{25}$ = +10.7 (*c* = 1 in $CHCl_3$). For determination of amine ee by analysis of the trifluoroacetamide derivative, HPLC conditions: Chiralcel OD-H, *n*-hexane/iPrOH 90:10, flow rate = 1 mL/min, UV 254 nm, t_R (*R*) = 6.8 min, t_R (*S*) = 10.5 min, k (*R*) = 1.20, k (*S*) = 2.39, α = 1.99. ee = 95%. HRMS ($[M+H]^+$, ESI): *m/z* calcd for $C_{17}H_{22}NO_2$: 272.1645. Found: 272.1644.

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