Peptide Catalysis in Aqueous Emulsions

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1. General aspects and materials

Materials and reagents were of the highest commercially available grade and used without further purification. Reactions were monitored by thin layer chromatography using Merck silica gel 60 F254 plates. Compounds were visualized by UV, $KMnO_4$ and ninhydrin. Flash chromatography was performed using Fluka silica gel 60 (230-400 mesh). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX 400 or a VARIAN Mercury 300 MHz spectrometer. Chemical shifts are reported in ppm using TMS or the residual solvent peak as a reference. HPLC analyses were performed on an analytical HPLC with a diode array detector from Shimadzu or on an analytical Dionex UlitMate 3000 HPLC system. Electrospray ionisation (ESI) mass spectrometry was performed on a Bruker Esquire 3000 Plus or Bruker Amazon Speed. Electrospray ionization high-resolution mass spectra (ESI-HRMS) were performed on a Bruker maXis by the MS service at the Laboratory for Organic Chemistry, ETH Zurich.

2. Synthesis of the catalysts

2.1. Peptides 1 and 1e – 1g (solid phase peptide synthesis)

General protocols for solid phase peptide synthesis

Peptide **1** and **1e – 1g** were prepared on solid phase following the general protocol for Fmoc/tBu peptide synthesis according to the procedures described below.

Functionalization of Rink Amide resin: The first amino acid was coupled to a pre-swollen suspension of Rink Amid resin according to the "*General procedure for peptide couplings"* described below.

Functionalization of Wang resin: To a pre-swollen suspension of Wang OH resin in CH_2Cl_2, was added a solution of the Fmoc amino acid (3 equiv.), *N*-methylimidazole (2.5 eq) and MSNT (3 eq) in CH_2Cl_2. The reaction mixture was agitated at room temperature for 1 h, then washed with DMF (3x) and CH_2Cl_2 (5x). Quantitative Fmoc tests were performed as spot checks.

General procedure for peptide couplings: $^{i}Pr_2NEt$ (4.5 eq) was added to a solution of Fmoc-Xxx-OH (1.5 eq) and HCTU (1.5 eq) in DMF. The activated amino acid was added as a solution in DMF (≈500 mM concentration) to the amino-functionalized resin,

swollen in DMF and the mixture was agitated for 1.5 h before washing with DMF (3x) and CH_2Cl_2 (5x).

General procedure for Fmoc-deprotections: 40% piperidine in DMF was added to the resin (preswollen in DMF) and the reaction mixture was agitated for 10 min, drained and the piperidine treatment repeated for another 10 min. Finally the resin was washed with DMF (3x) and CH_2Cl_2 (5x).

General procedure for the cleavage of the peptide from Rink Amide or Wang Resin: The solid supported peptide was cleaved from the Rink Amide resin by treatment with a mixture of TFA:CH_2Cl_2 2:1 for 1 h and a second time for 20 min. Pooling of filtrates and removal of all volatiles under reduced pressure followed by precipitation with Et_2O afforded the peptide as its TFA salt.

General procedure for the cleavage of the peptide from PS-TEG-NH_2 resin: The solid supported peptide was cleaved from the PS-TEG-NH_2 resin including the tetraethylene glycol moiety by treatment with a mixture of TFA:triflic acid:TIS 8:1:1 for 1 h and a second time for 20 min. Pooling of filtrates and removal of all volatiles under reduced pressure followed by precipitation with Et_2O afforded the peptide as its TFA salt.

H-D-Pro-Pro-Glu-NH_2 (1): Peptide **1** was prepared on Rink Amide AM resin (0.62 mmol/g) on up to a 3.1 mmol scale using the general protocols for solid phase peptide synthesis. TFA·H-D-Pro-Pro-Glu-NH_2 was obtained as a white solid. Spectroscopic data are in agreement with published data.[1,2]

H-D-Pro-Pro-Glu-Ada-TEG (1e): The peptide was prepared on PS-TEG-NH_2 resin (0.95 mmol/g) on a 250 μmol scale using the general protocols for solid phase peptide synthesis. TFA·H-D-Pro-Pro-Glu-Ada-TEG was obtained as a white solid.
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.17 (d, *J* = 6.0 Hz, 1H), 7.01 (t, *J* = 5.5 Hz, 1H), 6.90 (t, *J* = 5.1 Hz, 1H), 4.54 (t, *J* = 7.6 Hz, 1H), 4.41 (t, *J* = 6.1 Hz, 1H), 4.34 – 4.21 (m, 1H), 4.04 – 3.88 (m, 1H), 3.81 – 3.67 (m, 5H), 3.67 – 3.56 (m, 8H), 3.56 – 3.48 (m, 3H), 3.48 – 3.32 (m, 3H), 3.32 – 3.13 (m, 2H), 2.55 – 1.86 (m, 14H), 1.66 – 1.55 (m, 2H), 1.55 – 1.43 (m, 2H), 1.43 – 1.10 (m, 14H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 181.5, 173.7, 170.8, 170.1, 169.3, 72.7, 70.7, 70.5, 70.4, 70.1, 62.0, 61.5, 59.2, 54.7, 47.5, 45.2, 39.7, 39.2,

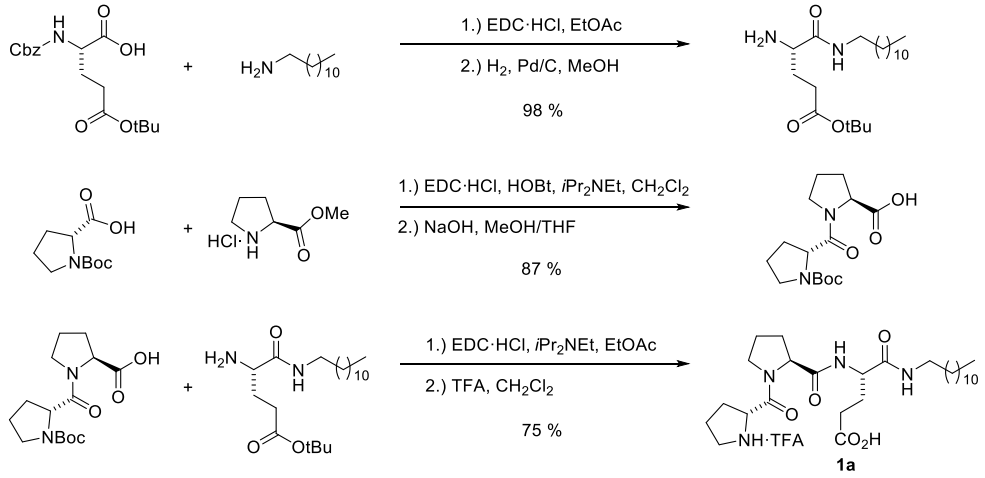
36.7, 32.6, 31.1, 29.7 - 29.3 (m), 27.9, 27.0, 25.9, 24.8, 24.6; MS (ESI, $[M+H]^+$) Calcd for $C_{35}H_{63}N_5NaO_{10:}$ 736.5. Found 736.7.

H-D-Pro-Pro-Glu-Ada$_2$-TEG (1f): The peptide was prepared on PS-TEG-NH_2 resin (0.95 mmol/g) on a 250 μmol scale using the general protocols for solid phase peptide synthesis. TFA·H-D-Pro-Pro-Glu-Ada$_2$-TEG was obtained as a white solid.
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (s, 1H), 6.99 (s, 1H), 6.86 (s, 2H), 5.81 – 5.60 (m, 1H), 4.56 (t, *J* = 8.0 Hz, 1H), 4.43 (t, *J* = 6.1 Hz, 1H), 4.35 – 4.22 (m, 1H), 4.07 – 3.91 (m, 1H), 3.71 (dd, *J* = 5.7, 3.0 Hz, 5H), 3.68 – 3.57 (m, 9H), 3.56 – 3.48 (m, 3H), 3.47 – 3.35 (m, 3H), 3.29 – 3.13 (m, 5H), 2.57 – 1.83 (m, 16H), 1.70 – 1.55 (m, 4H), 1.55 – 1.40 (m, 4H), 1.40 – 1.13 (m, 28H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 181.4, 173.5, 173.1, 170.4, 169.9 169.4, 72.6, 70.6, 70.4, 70.3, 70.0, 69.9, 61.8, 61.5, 59.4, 54.7, 47.3, 44.9, 39.5, 39. 5, 39.1, 36.8, 36.6, 32.2, 29.6, 29.4 - 29.3 (m), 29.2, 27.7, 26.9, 26.8, 25.8, 25. 8, 25.5, 24. 9, 24.5; HRMS (ESI): *m/z* calcd for $C_{47}H_{87}N_6O_{11}$: 911.6427 [M+H^+]; found: 911.6429.

H-D-Pro-Pro-Glu-Ada$_3$-TEG (1g): The peptide was prepared on PS-TEG-NH_2 resin (0.95 mmol/g) on a 250 μmol scale using the general protocols for solid phase peptide synthesis. TFA·H-D-Pro-Pro-Glu-Ada$_3$-TEG was obtained as a white solid.
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.11 (s, 1H), 7.00 (s, 1H), 6.85 (s, 1H), 5.68 (d, *J* = 17.0 Hz, 2H), 4.55 (t, *J* = 8.2 Hz, 1H), 4.48 – 4.37 (m, 1H), 4.34 – 4.20 (m, 1H), 4.08 – 3.93 (m, 1H), 3.78 – 3.69 (m, 5H), 3.69 – 3.56 (m, 10H), 3.57 – 3.48 (m, 3H), 3.48 – 3.34 (m, 3H), 3.35 – 3.08 (m, 8H), 2.52 – 1.84 (m, 18H), 1.74 – 1.54 (m, 6H), 1.54 – 1.39 (m, 6H), 1.38 – 0.95 (m, 42H); ^{13}C NMR (101 MHz, 5% $CDCl_3$ in CD_3OD) δ 182.4, 176.1, 175.9, 172.8, 172.4, 169.6, 73.5, 71.4, 71.4, 71.1, 71.0, 70.4, 62.7, 62.0, 60. 9, 55.9, 45.8, 40.3, 40.2, 40.1, 37.1, 37.0, 33.8, 30.5, 30.7 – 29.9 (m), 27.9, 27.8, 27.8, 26.9, 26.8, 26.5, 25.2, 24.6; HRMS (ESI): *m/z* calcd for $C_{59}H_{109}N_7NaO_{12}$: 1130.8026 [M+Na^+]; found: 1130.8013.

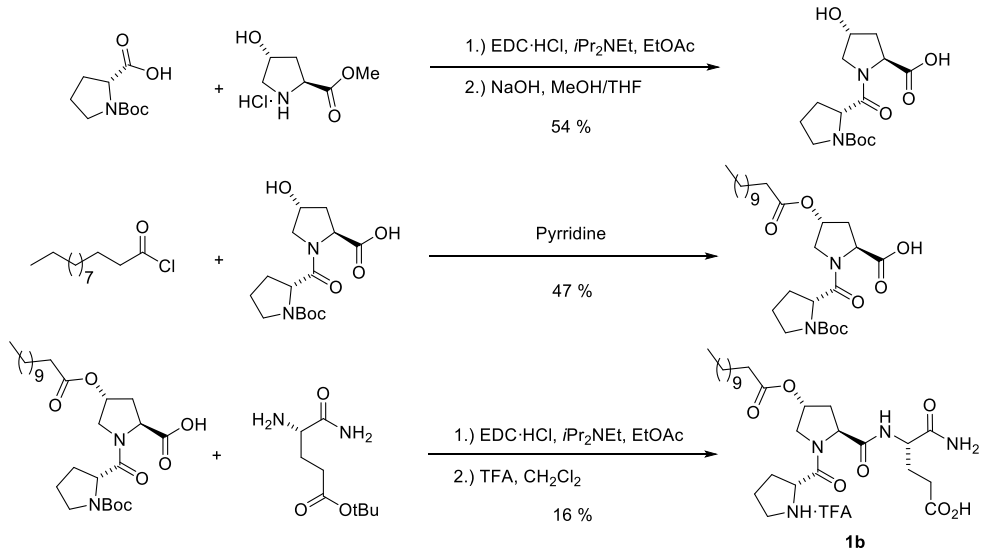
2.2. Peptides 1a-d (solution phase synthesis)

H-D-Pro-Pro-Glu-NH-$C_{12}H_{25}$ (1a): Catalyst **1a** was prepared by solution phase peptide synthesis as described previously[3] according to the strategy outlined below (Scheme S-1). Spectroscopic data are in agreement with published data.[3]



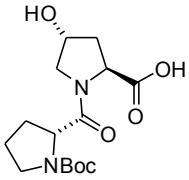
*Scheme S-1. Synthesis of Peptide Catalyst **1a***

H-D-Pro-Hyp($OCOC_{11}H_{23}$)-Glu-NH_2 (1b): Catalyst **1b** was prepared by solution phase peptide synthesis according to the strategy outlined below (Scheme S-2).



*Scheme S-2. Synthesis of Peptide Catalyst **1b***

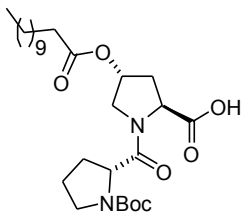
Boc-D-Pro-Hyp-OH



Boc-D-Pro-OH (1.77 g, 8.22 mmol, 1.0 eq), and EDC·HCl (1.89 g, 8.60 mmol, 1.05 eq) were suspended in EtOAc (10 mL). Then *i*Pr_2NEt (3.37 mL, 19.3 mmol, 2.3 eq) was added and the mixture was stirred for 10 min before H-Hyp-OMe·TFA (1.99 g, 8.22 mmol, 1.0 eq) was added. The mixture was stirred at room temperature for 6 h, diluted with 20 mL of EtOAc and washed with 1 m HCl (20 mL), water (20 mL), sat. $NaHCO_3$ (20 mL) and brine (20 mL). The combined aqueous layers were re-extracted with EtOAc (10 × 50 mL). The combined organic layers were dried over Na_2SO_4. The solvent was removed under reduced pressure and the resulting colourless solid was purified by column chromatography on silica gel eluting with 10% MeOH in CH_2Cl_2 yielding 1.51 g of a colourless solid. The solid was suspended in a 1:1 mixture of THF and MeOH and 360 mg (9.0 mmol, 2.0 eq) of sodium hydroxide in a minimal amount of water was added. The mixture was stirred for 1.5 h. The resulting solution was acidified with 10 mL of a 1 M HCl solution and extracted with CH_2Cl_2 (5x50 mL). The combined organic layers were dried over Na_2SO_4. Removal of the solvent under reduced pressure yielded 1.44 g of a colourless solid (54%).

^{1}H NMR (400 MHz, CD_3OD) δ 4.57 – 4.47 (m, 2H), 4.46 – 4.36 (m, 1H), 3.78 (dd, *J* = 10.9, 4.4 Hz, 1H), 3.68 – 3.47 (m, 2H), 3.47 – 3.35 (m, 1H), 2.43 – 2.17 (m, 2H), 2.17 – 2.03 (m, 2H), 2.03 – 1.70 (m, 2H), 1.44 (s, 9H); ^{13}C NMR (101 MHz, CD_3OD) δ 175.1, 174.0, 155.9, 81.6, 71.0, 59.6, 55.8, 47.8, 38.5, 31.3, 28.7, 28. 5, 24.3; MS (ESI, $[M+Na]^+$) Calcd for $C_{15}H_{24}N_2NaO_6$: 351.2. Found: 351.3.

Boc-D-Pro-Hyp($COC_{11}H_{23}$)-OH

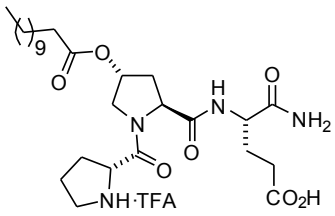


Lauric acid (1.22 g, 6.10 mmol, 2.0 eq) was added to thionyl chloride (3.12 mL, 42.6 mmol, 14 eq) and the resulting solution refluxed for 1.5 h. The reflux condenser was replaced by a distillation bridge and the excess thionyl chloride was removed under reduced pressure (100 mbar). To the resulting brown residue was added dropwise Boc-D-Pro-Hyp-OH (1.00 g, 3.05 mmol, 1.0 eq) in 1.5 mL pyridine at 0°C. The resulting mixture was diluted with 5 mL CH_2Cl_2 and stirred at room temperature for 40 h. The reaction mixture was added to a mixture of 50 mL 1M HCl and 10 g ice and extracted with CH_2Cl_2 (3x 50 mL). The combined organic layers were dried over $NaSO_4$ and evaporated to dryness. The resulting brown solid was purified by column chromatography on silica gel eluting with CH_2Cl_2/MeOH/HOAc (100:10:1) providing 726 mg of a light brown solid (726 mg, 47%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.47 – 5.26 (m, 1H), 4.88 – 4.65 (m, 1H), 4.49 – 4.17 (m,

1H), 4.17 – 3.76 (m, 1H), 3.76 – 3.31 (m, 3H), 2.67 – 1.73 (m, 8H), 1.71 – 1.53 (m, 2H), 1.44 and 1.40 (2 x s, 9H), 1.35 – 1.19 (m, 16H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.4, 174.5, 173.5, 153.7, 80.4, 72.3, 69.2, 58.9, 57.9, 53.6, 53.5, 46.9, 46.7, 35.3, 30.2, 29.7 – 29.5 (m), 28.4, 28.2, 28.2, 28.1, 24.8, 24.5, 23.6, 20.9, 14.1; (Mixture of two conformers in a ratio of approximately 2.5:1); MS (ESI, $[M+Na]^+$) Calcd for $C_{27}H_{46}N_2NaO_7$: 533.3. Found: 533.6.

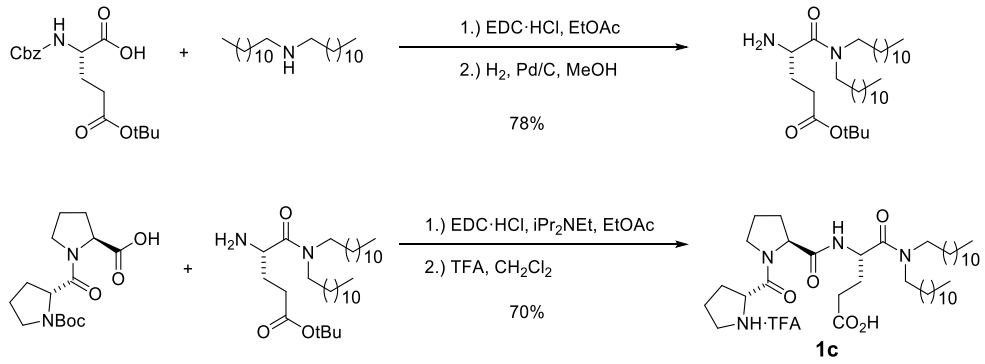
TFA·H-D-Pro-Hyp($COC_{11}H_{23}$)-Glu-NH_2 (1b)



Boc-D-Pro-Hyp($COC_{11}H_{23}$)-OH (727 mg,1.42 mmol, 1.0 eq), HCl·H-Glu(O*t*Bu)-NH_2 (340 mg, 1.42 mmol, 1.0 eq) and EDC·HCl (326 mg, 1.70 mol, 1.2 eq) were suspended in 3 mL EtOAc and *i*Pr_2NEt (583 µL, 3.41 mmol, 1.2 eq) was added. The resulting suspension was stirred at room temperature over night. The reaction mixture was diluted with 20 mL EtOAc and washed with 1m HCl (2x15 mL), 10% $NaHCO_3$ (2x 15 mL) and dried over Na_2SO_4. The residue was purified by column chromatography on silica gel eluting with 5 % MeOH in EtOAc. The resulting colourless oil was dissolved in a mixture of TFA and CH_2Cl_2 2:1 and stirred at room temperature for 30 min. Removal of all volatile components under reduced pressure provided the peptide as the TFA salt (145 mg, 16 %).

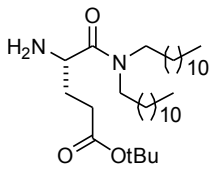
^{1}H NMR (400 MHz, CD_3OD) δ 5.44 – 5.35 (m, 1H), 4.56 (t, J = 8.1 Hz, 1H), 4.51 (dd, J = 8.7, 7.1 Hz, 1H), 4.40 (dd, J = 9.4, 4.6 Hz, 1H), 3.94 (dd, J = 11.7, 4.4 Hz, 1H), 3.72 (dt, J = 11.7, 1.7 Hz, 1H), 3.43 (dt, J = 11.3, 7.0 Hz, 1H), 3.40 – 3.30 (m, 1H), 2.59 – 2.38 (m, 3H), 2.34 (t, J = 7.4 Hz, 2H), 2.27 (ddd, J = 13.6, 7.9, 5.1 Hz, 1H), 2.22 – 2.02 (m, 3H), 2.02 – 1.84 (m, 2H), 1.60 (p, J = 7.4 Hz, 2H), 1.41 – 1.21 (m, 18H), 0.92 – 0.86 (m, 3H); ^{13}C NMR (101 MHz, CD_3OD) δ 176.7, 175.9, 174.5, 173.4, 168. 8, 73.9, 60.5, 60.4, 53. 9, 53.6, 47.7, 36.0, 34.9, 33.1, 31.2, 30.7, 30.6, 30.5, 30.4, 30.2, 29.8, 28.6, 25.9, 25.2, 23.7, 14.4; HRMS (ESI): *m/z* calcd for $C_{27}H_{47}N_4O_5$: 539.3439 [M+H^+]; found: 539.3439.

H-D-Pro-Pro-Glu-N($C_{12}H_{25}$)$_2$ (1c): Catalyst **1c** was prepared by solution phase peptide synthesis according to the strategy outlined below (Scheme S-3).



*Scheme S-3. Synthesis of Peptide Catalyst **1c***

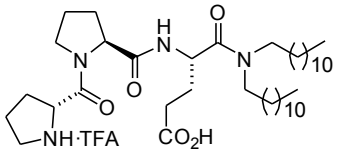
H-Glu(O*t*Bu)N($C_{12}H_{25}$)$_2$



Z-Glu(O*t*Bu)-OH (1.00 g, 2.96 mmol, 1.0 eq), didodecylamine (1.05 g, 2.96 mmol, 1.0 eq) and EDC·HCl (681 mg, 3.55 mmol, 1.2 eq) were suspended in EtOAc (15 mL) and stirred at room temperature over night. The reaction mixture was diluted with 80 mL EtOAc and washed with 0.1 M HCl (3 × 20 mL), 5 % Na_2CO_3 (2 × 20 mL) and brine (40 mL). The organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The resulting colourless solid was dissolved in 15 mL MeOH. Pd/C (10 % w/w, 150 mg) was added and the mixture was stirred under a hydrogen atmosphere at room temperature for 5 h. The reaction mixture was filtered over a pad of celite. The celite was washed with MeOH (3 × 5 mL). The solvent was removed under reduced pressure to give a colorless solid (1.23 g, 78 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 4.5 Hz, 1H), 3.59 (dd, *J* = 9.2, 4.1 Hz, 1H), 3.56 – 3.39 (m, 2H), 3.15 – 2.97 (m, 2H), 2.46 (ddd, *J* = 16.6, 8.5, 6.7 Hz, 1H), 2.39 – 2.25 (m, 1H), 1.92 – 1.80 (m, 1H), 1.67 – 1.45 (m, 5H), 1.43 (s, 9H), 1.37 – 1.14 (m, 36H), 0.86 (t, *J* = 6.7 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.1, 172.8, 80.2, 50.2, 47.2, 46.1, 31.9, 31.3, 30.7, 29.6 - 29.5 (m), 29.4, 29.3, 29.3, 28.1, 28.1, 27.7, 27.0, 26.8, 22.7, 14.1; MS (ESI, $[M+H]^+$) Calcd for $C_{33}H_{67}N_2O_3$: 539.5. Found: 539.8.

TFA·H-D-Pro-Pro-Glu-N($C_{12}H_{25}$)$_2$ (1c)

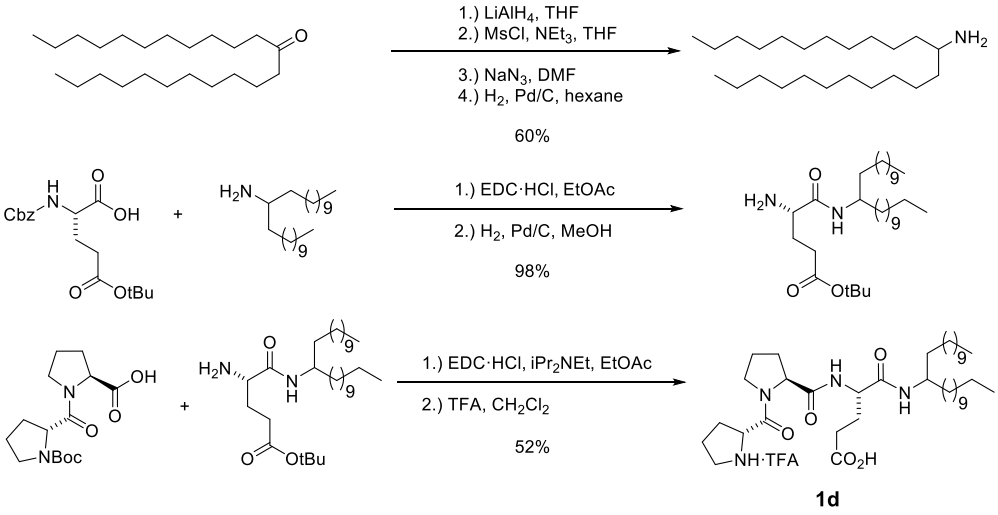


Boc-D-Pro-Pro-OH (380 mg, 1.22 mmol, 1.0 eq) and EDC·HCl (280 mg, 1.46 mmol, 1.2 eq) were suspended in 10 mL EtOAc and *i*Pr$_2$NEt (251 µL, 1.2 eq) followed by H-Glu(O*t*Bu)-N($C_{12}H_{25}$)$_2$ were added. The suspension was stirred at room temperature for 4h. The mixture was diluted with EtOAc (20 mL) and

washed with 1 M HCl (10 mL), H_2O (10 mL), sat. $NaHCO_3$ (10 mL) and brine (2 × 10 mL). The organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The resulting residue was purified by column chromatography on silica gel eluting with a mixture of EtOAc and pentanes (2:1). The colorless oil was dissolved in 3 mL TFA/CH_2Cl_2 2:1 and stirred at room temperature for 60 min. Removal of all volatile components under reduced pressure provided the peptide as the TFA salt (579 mg, 70 %).

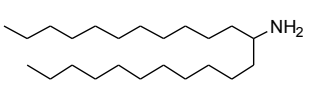
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 7.4 Hz, 1H), 4.86 – 4.69 (m, 2H), 4.59 – 4.49 (m, 1H), 3.84 – 3.72 (m, 1H), 3.62 – 3.33 (m, 5H), 3.33 – 3.24 (m, 1H), 3.09 (dt, J = 13.0, 7.5 Hz, 1H), 2.64 – 2.33 (m, 3H), 2.29 – 1.78 (m, 9H), 1.47 – 1.53 (m, 2H), 1.54 – 1.42 (m, 2H), 1.39 – 1.12 (m, 36H), 0.87 (t, J = 6.8 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.9, 171.0, 170.0, 168.3, 60.9, 59.0, 49.5, 48.1, 47.1, 47.0, 46.7, 31.9, 29.7 – 29.4 (m), 29.3, 29.1, 29.0, 28.8, 28.6, 27.4, 26.9, 26.8, 26.5, 24.8, 24.4, 22.7, 14.1; HRMS (ESI): *m/z* calcd for $C_{39}H_{73}N_4O_5$: 677.5575 [M+H^+]; found: 677.5573.

H-D-Pro-Pro-Glu-NH-CH($C_{11}H_{23}$)$_2$ (1d): Catalyst **1d** was prepared by solution phase peptide synthesis according to the strategy outlined below (Scheme S-4).



*Scheme S-4. Synthesis of Peptide Catalyst **1d***

12-Aminotricosane



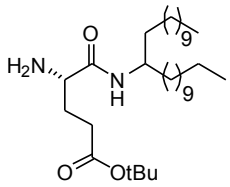
$LiAlH_4$ (682 mg, 18.0 mmol, 1.2 eq) was placed in 10 mL of THF. The mixture was cooled to 0°C and a suspension of 13-tricosanone (5.00 g, 14.8 mmol, 1.0 eq) in THF was added. The ice bath was removed and stirring was continued for 6 h. The reaction mixture was poured into 100 mL ice/water and extracted with CH_2Cl_2 (4x50 mL). The combined extracts were

dried over Na_2SO_4 and the solvent was removed under reduced pressure to give 12-tricosanol as a colourless solid. The alcohol (3.00 g, 8.81 mmol, 1.0 eq) was dissolved in 60 mL THF, NEt_3 (1.35 mL, 9.69 mmol, 1.1 eq) was added followed by the dropwise addition of MsCl (1.96 mL, 25.3 mmol, 2.9 eq). The resulting suspension was stirred at room temperature for 90 min, filtered, washed with 15 mL of H_2O and 5 mL of brine and dried over Na_2SO_4. Removal of all volatiles under reduced pressure resulted in a colourless oil which was dissolved in 50 mL DMF. Sodium azide (2.36 g, 36.3 mmol, 4.8 eq) was slowly added in portions. The resulting suspension was heated to 85°C over night. The reaction mixture was allowed to cool to room temperature followed by the addition of 100 mL hexanes and 20 mL H_2O. The organic layer was washed with 20 mL sat. $NaHCO_3$ solution and brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the resulting residue purified by column chromatography on silica gel eluting with pentanes. 12-azidotricosane was obtained as a colorless oil. The oil was dissolved in 20 mL hexane and Pd/C (10% w/w, 58 mg) was added. The resulting mixture was stirred under a H_2 atmosphere over night. Filtration through a plug of Celite and removal of the solvent under reduced pressure provided 12-aminotricosane as a colorless solid (2.23 g, 60 % overall yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.73 – 2.59 (m, 1H), 1.48 – 1.10 (m, 42H), 0.87 (t, *J* = 6.7 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 51.2, 38.2, 31.9, 29.8, 29.7 – 29.6 (m), 29.3, 26.2, 22. 7, 14.1.

Spectroscopic data is in agreement with published data.[4]

H-Glu(O*t*Bu)-NH-CH($C_{11}H_{23}$)$_2$

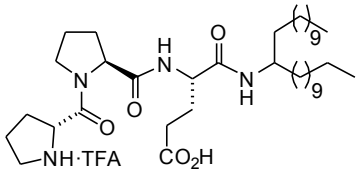


Z-Glu(OtBu)-OH (100 mg, 295 µmol, 1.0 eq), 12-aminotricosane (100 mg, 295 µmol, 1.0 eq) and EDC·HCl (68.6 mg,354 µmol, 1.2 eq) were suspended in EtOAc (5 mL) and stirred at room temperature for 3 h. The reaction mixture was diluted with 15 mL of EtOAc and washed with 1 m HCl (2x10 mL), sat. $NaHCO_3$ (10 mL) and brine (10 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the resulting colorless solid was dissolved in 6 mL of a 5:1 mixture of MeOH and hexane. Pd/C (10% w/w, 5 mg) was added and the resulting mixture was stirred under a H_2 atmosphere for 3 h. Filtration through a plug of silica and removal of the solvents under reduced pressure provided 151 mg of a colorless solid (98 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.88 (d, *J* = 9.3 Hz, 1H), 3.98 – 3.77 (m, 1H), 3.37 (dd, *J* = 7.5, 5.0 Hz, 1H), 2.41 – 2.31 (m, 2H), 2.12 – 2.02 (m, 1H), 1.87 – 1.75 (m, 1H), 1.59 – 1.04 (m, 40 H), 1.44 (s, 9H); 0.87 (t, *J* = 6.6 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.8, 172.9, 80.5, 54.8, 48.8, 35.2, 31. 9, 31.2, 30.5, 29.6, 29.6, 29.6 - 29.2 (m), 28.1,

26.4, 22. 7, 14.1; MS (ESI, $[M+H]^+$) Calcd for $C_{32}H_{65}N_2O_3$: 525.5. Found: 525.7.

H-D-Pro-Pro-Glu-NH-CH($C_{11}H_{23}$)$_2$ (1d)

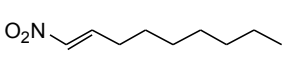


Boc-D-Pro-Pro-OH (59.5 mg, 191 µmol, 1.0 eq), H-Glu(O*t*Bu)-NH-CH($C_{11}H_{23}$)$_2$ (100 mg, 191 µmol, 1.0 eq) and EDC·HCl (43.9 mg, 229 µmol, 1.2 eq) were suspended in 3 mL EtOAc and *i*Pr_2NEt (39.2 µL, 229 µmol, 1.2 eq) was added. After stirring at room temperature over night the reaction mixture was diluted with 20 mL EtOAc and washed successively with 1M HCl (3x10 mL), sat. $NaHCO_3$ (2x10 mL) and brine (10 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with EtOAc. The resulting colorless oil was dissolved in a mixture of TFA and CH_2Cl_2 2:1 and stirred at room temperature for 90 min. Removal of all volatile components under reduced pressure gave the peptide as the TFA salt (77.2 mg, 52 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (d, *J* = 7.5 Hz, 1H), 6.37 (d, *J* = 9.0 Hz, 1H), 4.78 (t, *J* = 7.8 Hz, 1H), 4.53 (dd, *J* = 8.8, 2.4 Hz, 1H), 4.47 (td, *J* = 7.2, 2.2 Hz, 1H), 3.97 – 3.71 (m, 3H), 3.52 (td, *J* = 9.7, 6.9 Hz, 1H), 3.45 – 3.30 (m, 1H), 2.67 – 2.44 (m, 3H), 2.44 – 2.24 (m, 3H), 2.24 – 1.92 (m, 4H), 1.84 – 1.70 (m, 1H), 1.63 – 1.04 (m, 41H), 0.87 (t, *J* = 6.7 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.5, 169.4, 169.1, 168.9, 62.0, 59.2, 53.1, 49.2, 47.5, 46.9, 42.8, 35.1, 34.8, 31.9, 31.9, 30.1, 29.9 – 29.2 (m), 28.8, 26.0, 25.6, 25.6, 24.9, 24.3, 23.9, 22.7, 14.1; HRMS (ESI): *m/z* calcd for $C_{38}H_{71}N_4O_5$: 663.5419 [*M*+H^+]; found: 663.5417.

3. Synthesis of not commercially available nitroolefins

(*E*)-Nitronon-1-ene

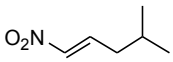


To a solution of octanal (2.44 mL, 20.0 mmol, 1.0 eq) and nitromethane (2.18 mL, 40.0 mmol, 2.0 eq) in toluene (10 mL) was added a functionalized mesoporous silica catalyst (500 mg, aminopropyl-MCM).[5] The resulting mixture was heated to 100°C over night. The catalyst was removed by filtration and the resulting solution concentrated *in vacuo* on a rotary evaporator. Column chromatography on silica gel eluting with a mixture of pentane and EtOAc (10:1) provided 2.16 g of a yellow oil (76 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (dt, *J* = 13.4, 7.3 Hz, 1H), 6.97 (d, *J* = 13.4 Hz, 1H), 2.26 (q, *J* = 7.3, 2H), 1.50 (p, *J* = 7.2 Hz, 2H), 1.39 – 1.18 (m, 8H), 0.87 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142. 8, 139.5, 31.6, 29.0, 28.9, 28.4, 27.7, 22.5, 14.0.

Spectroscopic data is in agreement with published data.[6]

(*E*)-4-Methyl-nitropent-1-ene



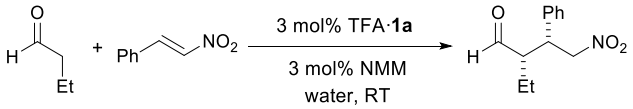
To a solution of *iso*-valeraldehyde (1.25 mL, 11.6 mmol, 1.0 eq) and nitroethane (1.27 mL, 23.2 mmol, 2.0 eq) in toluene (10 mL) was added a functionalized mesoporous silica catalyst (500 mg, aminopropyl-MCM).[5] The resulting mixture was heated to 100°C over night. The catalyst was removed by filtration and the resulting solution concentrated *in vacuo* on a rotary evaporator. Column chromatography on silica gel eluting with a mixture of pentane and EtOAc (10:1) provided 902 mg of a yellow oil (60 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 (td, *J* = 13.4, 9.0 Hz, 1H), 6.97 (td, *J* = 13.2 Hz, 1H), 2.21 – 2.13 (m, 2H), 1.77 - 1.89 (m, 1H), 0.96 (d, *J* = 6.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.5, 140.1, 37.2, 27.7, 22.2, 22.2.

Spectroscopic data is in agreement with published data.[6]

4. Catalytic reactionsAdditional reaction conditions examined within this study

Substrate concentration and equivalence

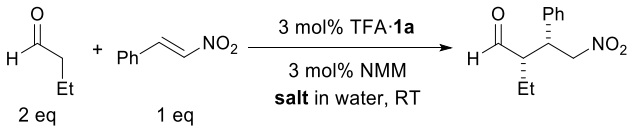


	Butanal conc. [M]	Nitrostyrene conc. [M]	Ratio	Time [h]	Conversion [%][a]	dr[a]	*ee* [%][b]
1	0.88	0.44	2:1	8	>95	98:2	91
2	0.44	0.44	1:1	18	80	96:4	89
3	0.44	0.88	1:2	8	>95	97:3	90
4	1.32	0.44	3:1	8	>95	97:3	91
5	2.20	0.44	5:1	8	>95	97:3	91
6	0.30	0.15	2:1	24	>95	95:5	88
7	0.44	0.22	2:1	24	>95	97:3	90
8[c]	1.76	0.88	2:1	2	80	91:9	91
9[c]	4.40	2.20	2:1	2	90	89:11	90

a Determined by ^{1}H-NMR analysis of the crude reaction mixture. b Determined by chiral-phase HPLC analysis.

c The reaction mixture consisted of large droplets in water rather than an emulsion.

Use of inorganic salt solutions as the reaction medium

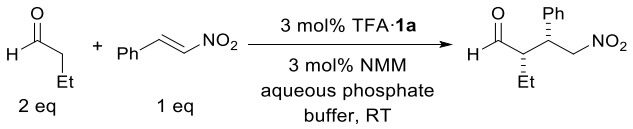


	salt	Time [h]	Conversion [%][a]	dr[a]	*ee* [%][b]
1	*none*	8	>95	98:2	91
2	NaCl	8	>95	97:3	91
3	NaCl (sat.)	8	>95	92:8	91
4	NH_4Cl	8	>95	96:4	90
5[c]	$NaHSO_4$	--	--	--	--
6	$NaHCO_3$	4	>95[d]	94:6	83
7	KOAc	2	>95	90:10	83
8	$NaNO_3$	2	>95	97:3	84

a Determined by ^{1}H-NMR analysis of the crude reaction mixture. b Determined by chiral-phase HPLC analysis.

c No reaction. d Large amounts of a precipitate formed in the course of the reaction.

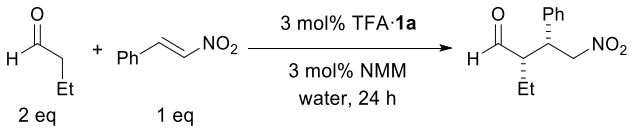
Effect of pH on the reaction



	pH	buffer conc. [mM]	Time[h]	Conversion [%][a]	dr[a]	*ee* [%][b]
1	4.8	10	<36	>95	97:3	90
2	5.0	10	<36	>95	96:4	91
3	5.0	1	8	73	95:5	90
4	5.5	10	8	>95	97:3	90
5	6.5	10	8	>95	96:4	91
6	8.0	10	8	>95	95:5	87
7	8.5	1000	8	>95	95:5	86

a Determined by ^{1}H-NMR analysis of the crude reaction mixture. b Determined by chiral-phase HPLC analysis.

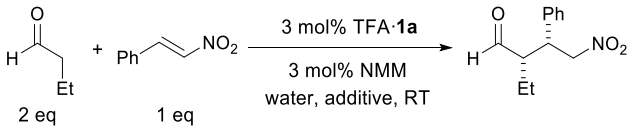
Effect of temperature



	temp [°C]	conversion [%]	dr[a]	*ee* [%][b]
1	RT	quant.	98:2	91
2	12	57	96:4	90
3	5	12	99:1	91
4	0	5	99:1	90
5	-10	no reaction	--	--

a Determined by ^{1}H-NMR analysis of the crude reaction mixture. b Determined by chiral-phase HPLC analysis.

Complete list of examined organic additives

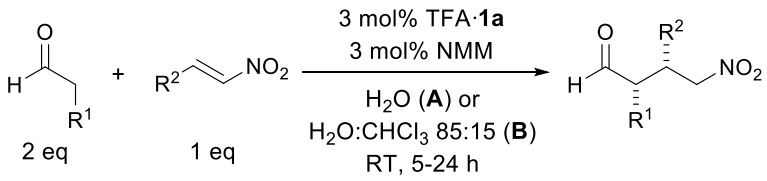


	additive	Time [h]	Conversion [%][a]	dr[a]	*ee* [%][b]
1	*none*	8	>95	98:2	91
2	lauric acid (10 mol%)	14	>95	93:7	91
3	lauric acid (50 mol%)	14	>95	95:5	90
4	EtOH (10% v/v)	8	>95	99:1	92
5	*i*PrOH (10% v/v)	8	79	99:1	92
6	*t*BuOH (10% v/v)	8	85	99:1	92
7	DMSO (10% v/v)	8	>95	97:3	91
8	acetone (10% v/v)	6	77	97:3	90
9	Et_2O (10% v/v)	<36	>95	95:5	91
10	dioxane (10% v/v)	<36	>95	95:5	91
11	DME (10% v/v)	6	>95	99:1	92
12	THF (10% v/v)	6	68	97:3	92
13	EtOAc (10% v/v)	<36	>95	96:4	91
14	MeCN (10% v/v)	<36	>95	96:4	90
15	$CHCl_3$ (10% v/v)	14	>95	96:4	93
16	toluene (10% v/v)	14	>95	97:3	93
17	PEG (700 g/mol, 100 mg)	5	32	91:9	91
18	PEG (6000 g/mol, 100 mg)	5	17	96:4	94
19	$CHCl_3$ (15% v/v)	5	>95	97:3	95
20	toluene (15% v/v)	14	53	97:3	94

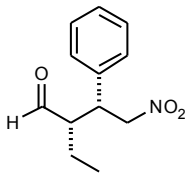
a Determined by ^{1}H-NMR analysis of the crude reaction mixture. b Determined by chiral-phase HPLC analysis.

4.2. General procedure for the conjugate addition reaction between aldehydes and nitroolefins in aqueous medium To a solution of the peptide (as the TFA salt, 13.2 μmol, 3 mol%) and *N*-methylmorpholine (13.6 μmol, 3 mol%) in water (1 mL, conditions **A**) or water and $CHCl_3$ (85:15, 1.2 mL, conditions **B**), was added aldehyde (880 μmol, 2.0 eq.) and the nitroolefin (440 μmol, 1.0 eq.). The reaction mixture was sonicated until no more solid nitroolefin was observed and a stable white emulsion was obtained (approximately 2 min). The resulting emulsion was agitated at room temperature. After consumption of the nitroolefin, sodium chloride (330 mg) was added. The aqueous layer was extracted with $CHCl_3$ (5 x 1 mL). The combined organic layers were concentrated and directly purified by flash column chromatography on silica gel eluting with a mixture of cyclohexane and EtOAc.

4.3. Analytical data of γ-nitroaldehydes



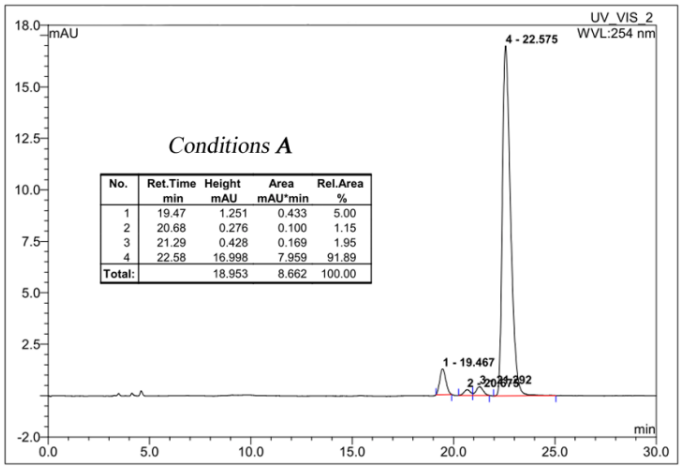
(2*S*,3*R*)-2-Ethyl-4-nitro-3-phenylbutanal



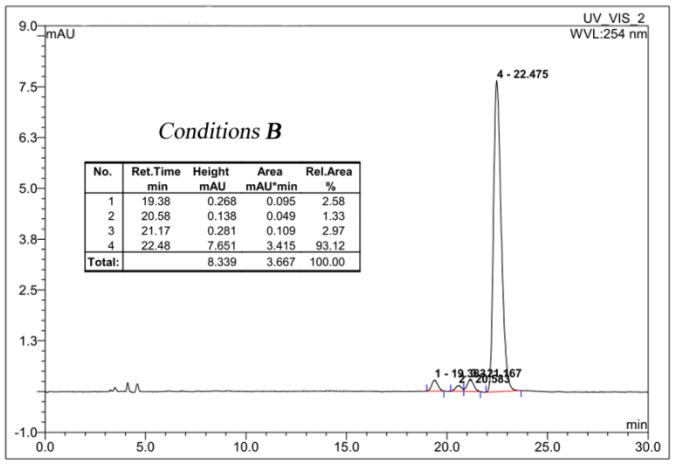
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.72 (d, *J* = 2.6 Hz, 1H), 7.32 (m, 3H), 7.18 (m, 2H), 4.72 (dd, *J* = 5.0 Hz, 12.7 Hz, 1H), 4.63 (dd, *J* = 9.7 Hz, 12.7 Hz, 1H), 3.79 (dt, *J* = 5.0 Hz, 9.8 Hz, 1H), 2.68 (dddd, *J* = 2.6 Hz, 5.0 Hz, 7.6 Hz, 10.1 Hz, 1H), 1.51 (m, 2H), 0.84 (t, *J* = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.1, 136.8, 129.1, 128.1, 128.0, 78.5, 55.0, 42.7, 20.4, 10.7.

Spectroscopic data is in agreement with published data.[1]

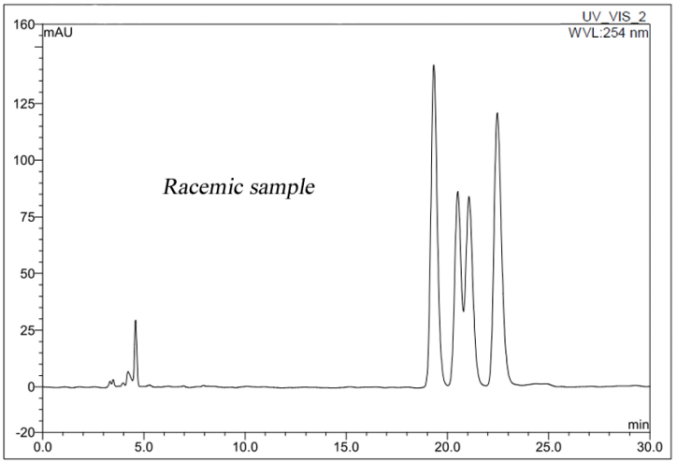
The enantiomeric excess was determined by HPLC using a Chiracel AD-H column (*n*-hexane/*i*-PrOH 98:2, 25°C) at 0.9 mL/min, UV detection at 254 nm: t_R : (*syn,* minor) = 19.5 min, (*syn*, major) = 22.6 min.



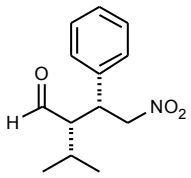
No.	Ret.Time min	Height mAU	Area mAU*min	Rel.Area %
1	19.47	1.251	0.433	5.00
2	20.68	0.276	0.100	1.15
3	21.29	0.428	0.169	1.95
4	22.58	16.998	7.959	91.89
Total:		18.953	8.662	100.00



No.	Ret.Time min	Height mAU	Area mAU*min	Rel.Area %
1	19.38	0.268	0.095	2.58
2	20.58	0.138	0.049	1.33
3	21.17	0.281	0.109	2.97
4	22.48	7.651	3.415	93.12
Total:		8.339	3.667	100.00



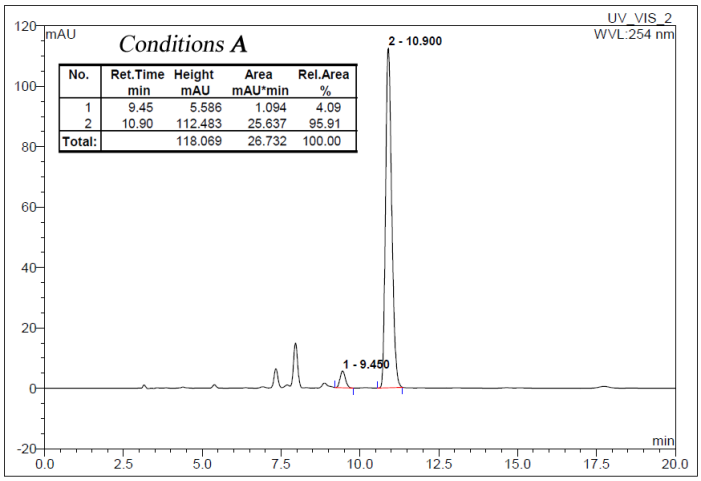
(2*S*,3*R*)-2-Isopropyl-4-nitro-3-phenylbutanal

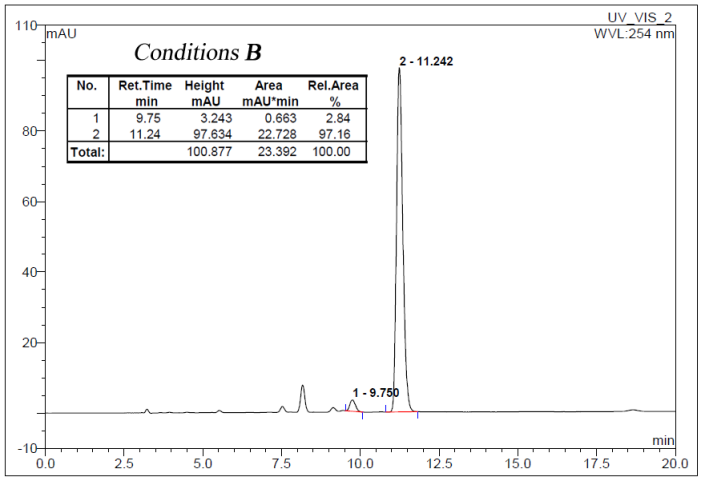


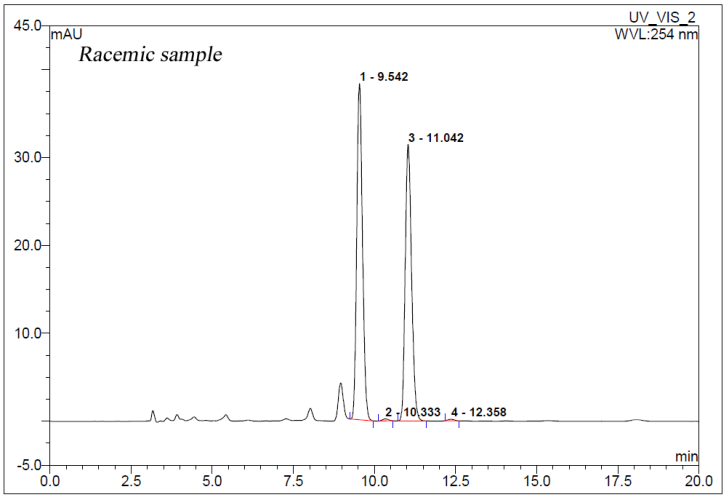
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.92 (d, *J* = 2.6 Hz, 1H), 7.38 – 7.25 (m, 3H), 7.21 – 7.16 (m, 2H), 4.67 (dd, *J* = 12.5, 4.4 Hz, 1H), 4.57 (dd, *J* = 12.5, 9.9 Hz, 1H), 3.90 (td, *J* = 10.3, 4.4 Hz, 1H), 2.77 (ddd, *J* = 10.7, 4.2, 2.6 Hz, 1H), 1.72 (heptd, *J* = 7.0, 4.2 Hz, 1H), 1.09 (d, *J* = 7.2 Hz, 4H), 0.88 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.3, 137.1, 129.1, 128.1, 127.9, 79.0, 58.7, 41.9, 27. 9, 21.6, 17.0.

Spectroscopic data is in agreement with published data.[1]

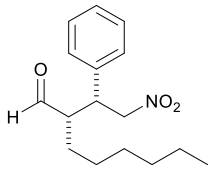
The enantiomeric excess was determined by HPLC using a Chiracel AD-H column (*n*-hexane/*i*-PrOH 95:5, 25°C) at 1.0 mL/min, UV detection at 254 nm: t_R : (*syn,* minor) = 9.5 min, (*syn*, major) = 11.0 min.







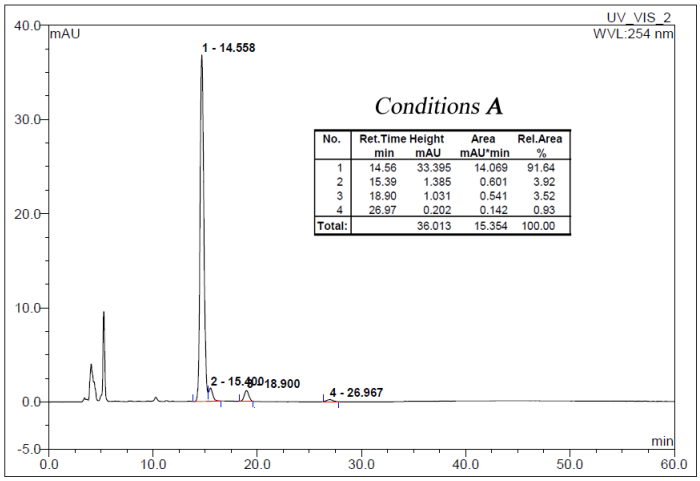
(*S*)-2-((*R*)-2-Nitro-1-phenylethyl)octanal

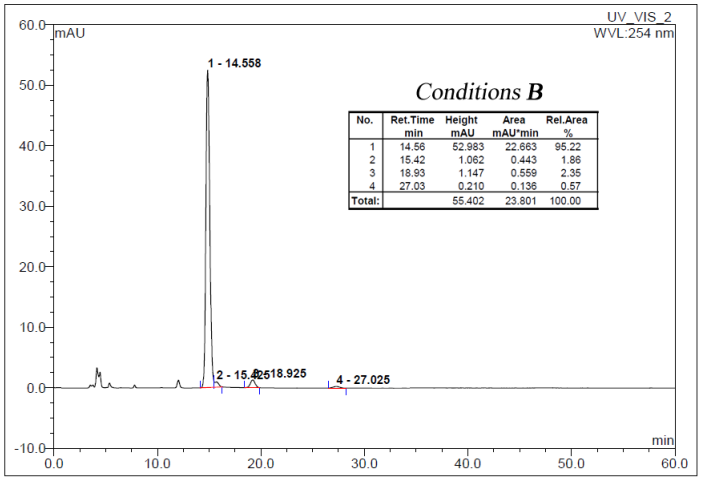


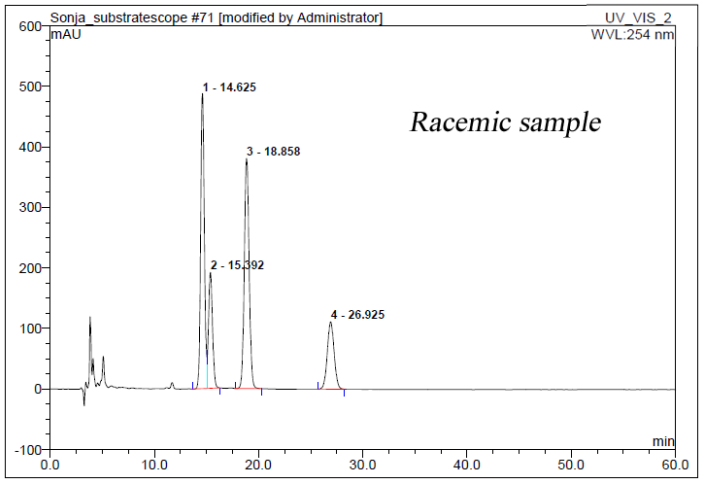
^{1}H NMR (300 MHz, $CDCl_3$) δ 9.71 (d, *J* = 2.7 Hz, 1H), 7.40 – 7.28 (m, 3H), 7.22 – 7.13 (m, 2H), 4.71 (dd, *J* = 12.7, 5.5 Hz, 1H), 4.64 (dd, *J* = 12.7, 9.3 Hz, 1H), 3.77 (td, *J* = 9.3, 5.5 Hz, 1H), 2.76 – 2.63 (m, 1H), 1.53 – 1.05 (m, 10H), 0.86 – 0.78 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.3, 136.8, 129.1, 128.1, 128.0, 78.4, 53.9, 31.3, 29.0, 27.3, 26.3, 22.4, 13.9.

Spectroscopic data is in agreement with published data.[7]

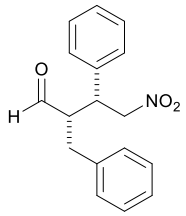
The enantiomeric excess was determined by HPLC using a Chiracel OD-H column (*n*-hexane/*i*-PrOH 90:10, 25°C) at 1.0 mL/min, UV detection at 254 nm: t_R : (*syn,* major) = 14.6 min, (*syn*, minor) = 18.9 min.







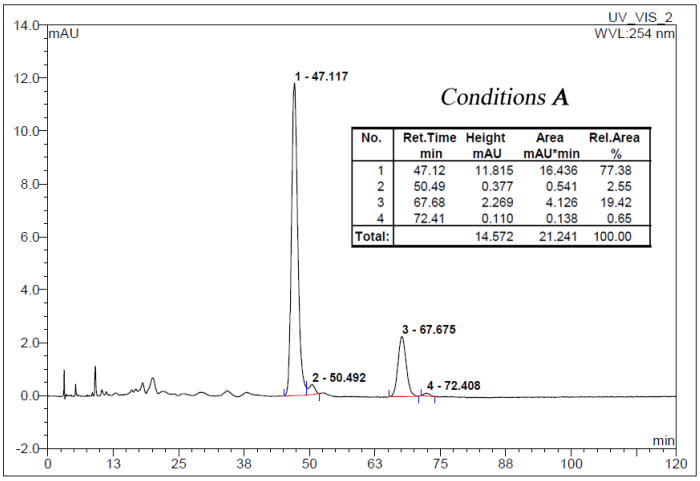
(2*S*,3*R*)-2-Benzyl-4-nitro-3-phenylbutanal



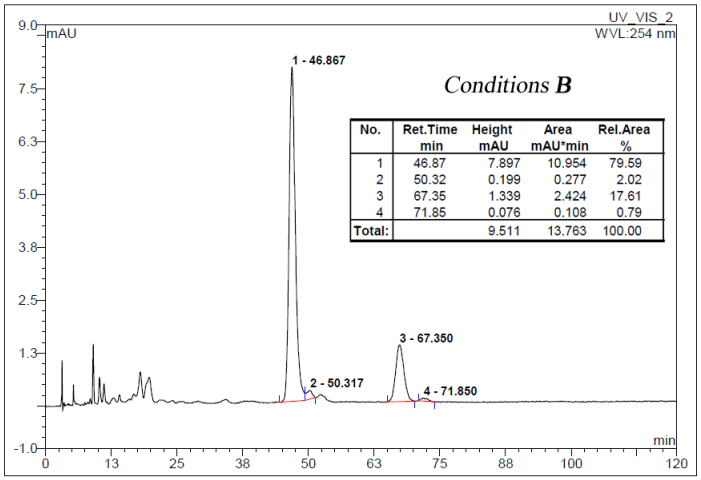
^{1}H NMR (300 MHz, $CDCl_3$) δ 9.72 (d, *J* = 2.3 Hz, 1H), 7.43 – 7.10 (m, 8H), 7.07 – 7.00 (m, 2H), 4.76 – 4.67 (m, 2H), 3.83 (td, *J* = 8.5, 6.3 Hz, 1H), 3.17 – 3.03 (m, 1H), 2.82 – 2.70 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.9, 137.1, 136.7, 129.2, 128.8, 128.7, 128.3, 128.0, 126.9, 78.0, 55.3, 43.4, 34.2.

Spectroscopic data is in agreement with published data.[1]

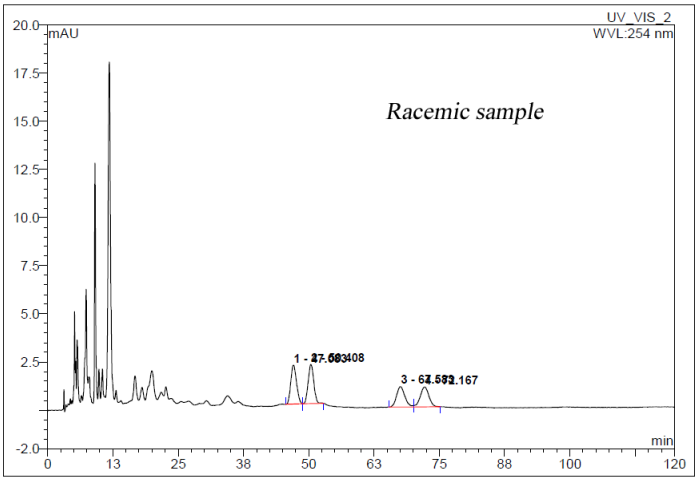
The enantiomeric excess was determined by HPLC using a Chiracel OD-H column (*n*-hexane/*i*-PrOH 95:5, 40°C) at 1.0 mL/min, UV detection at 254 nm: t_R : (*syn,* major) = 47.1 min, (*syn*, minor) = 50.4 min.



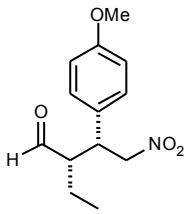
No.	Ret.Time min	Height mAU	Area mAU*min	Rel.Area %
1	47.12	11.815	16.436	77.38
2	50.49	0.377	0.541	2.55
3	67.68	2.269	4.126	19.42
4	72.41	0.110	0.138	0.65
Total:		14.572	21.241	100.00



No.	Ret.Time min	Height mAU	Area mAU*min	Rel.Area %
1	46.87	7.897	10.954	79.59
2	50.32	0.199	0.277	2.02
3	67.35	1.339	2.424	17.61
4	71.85	0.076	0.108	0.79
Total:		9.511	13.763	100.00



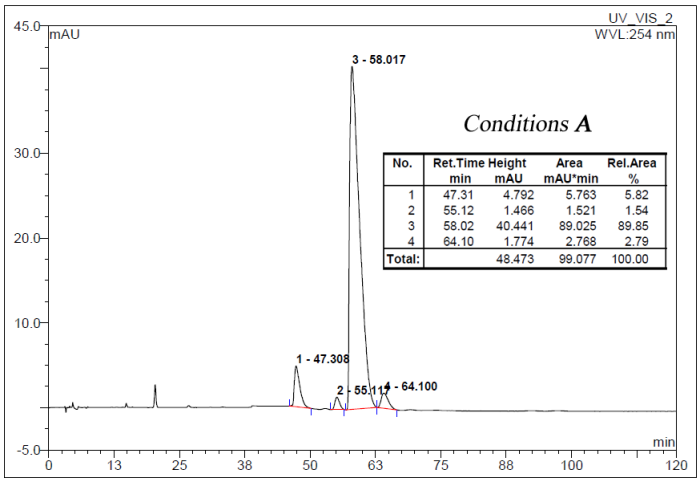
(2*S*,3*R*)-2-Ethyl-3-(4-methoxyphenyl)-4-nitrobutanal



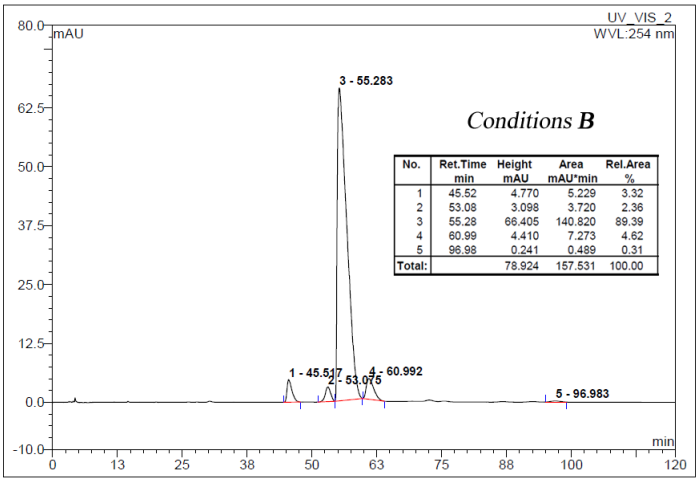
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (d, *J* = 2.6 Hz, 1H), 7.11 – 7.05 (m, 2H), 6.88 – 6.83 (m, 2H), 4.68 (dd, *J* = 12.5, 5.0 Hz, 1H), 4.57 (dd, *J* = 12.5, 9.9 Hz, 1H), 3.77 (s, 3H), 3.76 – 3.67 (m, 1H), 2.62 (dddd, *J* = 10.2, 7.5, 4.7, 2.6 Hz, 1H), 1.57 – 1.41 (m, 2H), 0.81 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.3, 159.2, 129.0, 128.5, 114.4, 78.7, 55.2, 55.1, 42.0, 20.3, 10.6.

Spectroscopic data is in agreement with published data.[8]

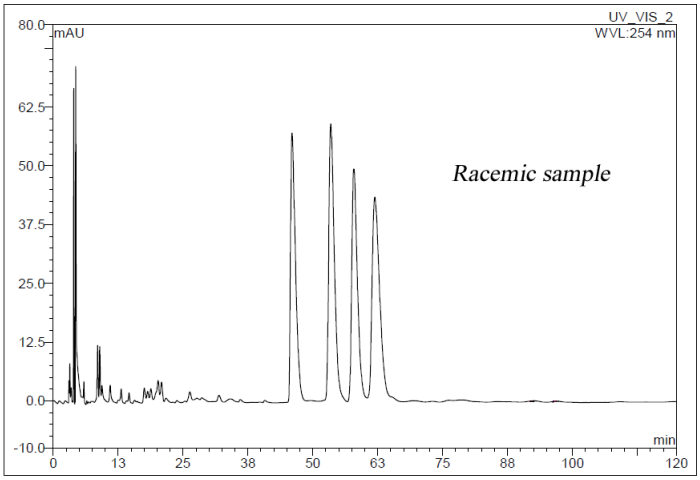
The enantiomeric excess was determined by HPLC using a Chiracel AD-H column (*n*-hexane/*i*-PrOH 99.5:0.5, 25°C) at 1.0 mL/min, UV detection at 254 nm: t_R : (*syn,* minor) = 47.3 min, (*syn*, major) = 58.0 min.



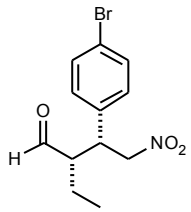
No.	Ret.Time min	Height mAU	Area mAU*min	Rel.Area %
1	47.31	4.792	5.763	5.82
2	55.12	1.466	1.521	1.54
3	58.02	40.441	89.025	89.85
4	64.10	1.774	2.768	2.79
Total:		48.473	99.077	100.00



No.	Ret.Time min	Height mAU	Area mAU*min	Rel.Area %
1	45.52	4.770	5.229	3.32
2	53.08	3.098	3.720	2.36
3	55.28	66.405	140.820	89.39
4	60.99	4.410	7.273	4.62
5	96.98	0.241	0.489	0.31
Total:		78.924	157.531	100.00



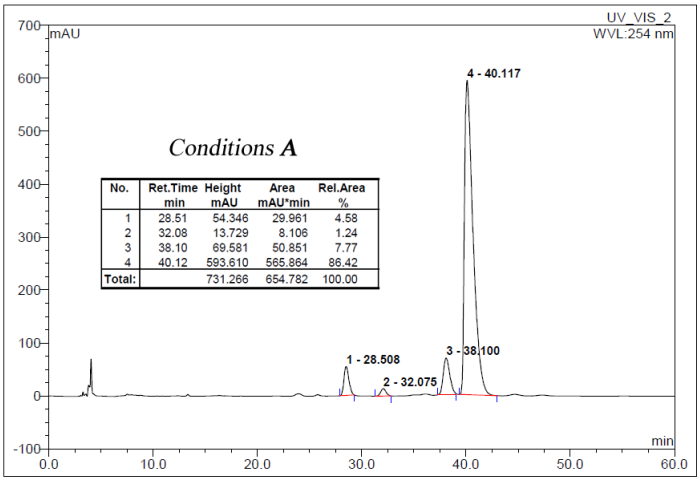
(2*S*,3*R*)-2-Ethyl-3-(4-bromophenyl)-4-nitrobutanal



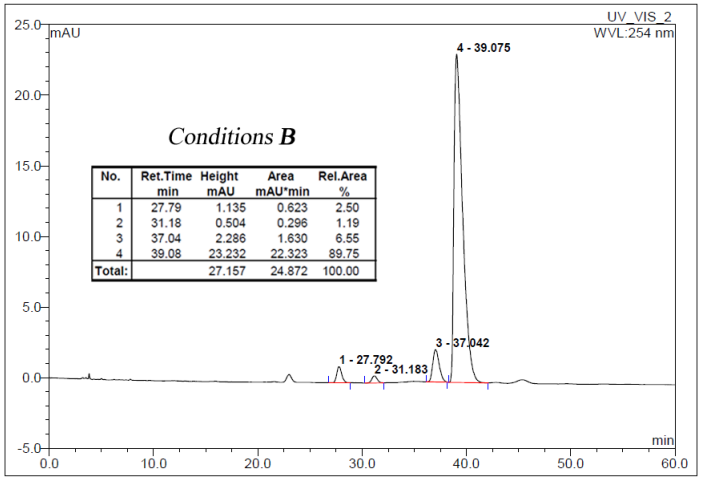
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (d, *J* = 2.3 Hz, 1H), 7.53 – 7.41 (m, 2H), 7.10 – 7.03 (m, 2H), 4.72 (dd, *J* = 12.8, 4.8 Hz, 1H), 4.59 (dd, *J* = 12.8, 9.9 Hz, 1H), 3.77 (td, *J* = 9.9, 4.8 Hz, 1H), 2.66 (dddd, *J* = 10.3, 8.2, 4.8, 2.3 Hz, 1H), 1.60 – 1.41 (m, 2H), 0.83 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.6, 135.9, 132.3, 129.7, 122.1, 78.2, 54.6, 42.1, 20.3, 10.5.

Spectroscopic data is in agreement with published data.[6]

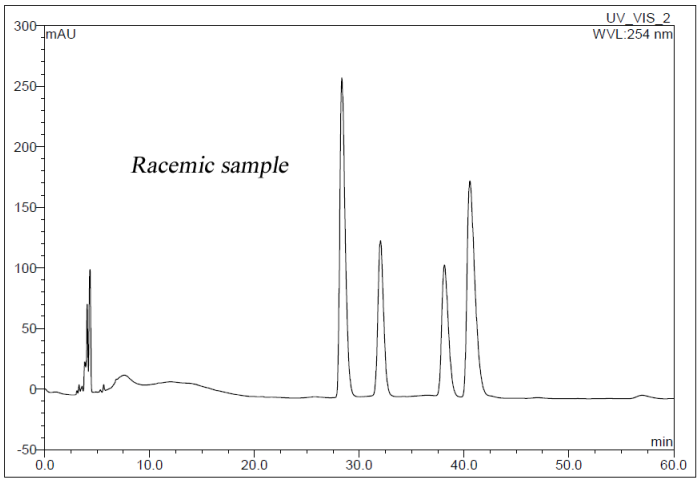
The enantiomeric excess was determined by HPLC using a Chiracel AD-H column (*n*-hexane/*i*-PrOH 98.5:1.5, 25°C) at 1.0 mL/min, UV detection at 254 nm: t_R : (*syn,* minor) = 28.5 min, (*syn*, major) = 40.1 min.



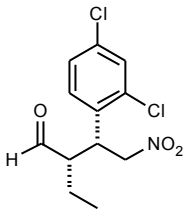
No.	Ret.Time min	Height mAU	Area mAU*min	Rel.Area %
1	28.51	54.346	29.961	4.58
2	32.08	13.729	8.106	1.24
3	38.10	69.581	50.851	7.77
4	40.12	593.610	565.864	86.42
Total:		731.266	654.782	100.00



No.	Ret.Time min	Height mAU	Area mAU*min	Rel.Area %
1	27.79	1.135	0.623	2.50
2	31.18	0.504	0.296	1.19
3	37.04	2.286	1.630	6.55
4	39.08	23.232	22.323	89.75
Total:		27.157	24.872	100.00



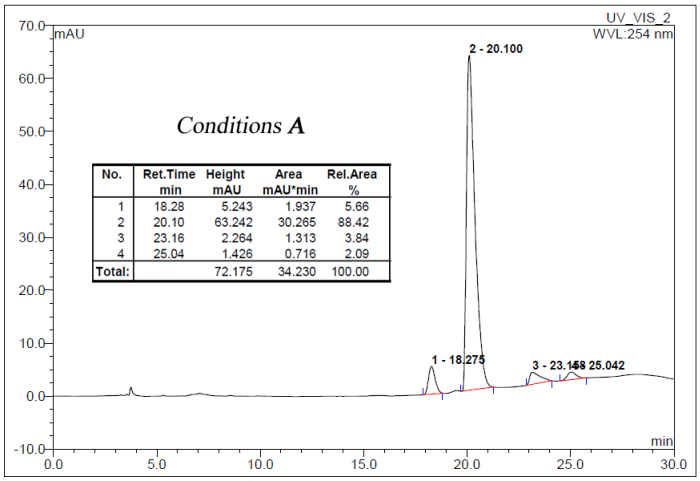
(2*S*,3*R*)-2-Ethyl-3-(2,4-dichlorophenyl)-4-nitrobutanal



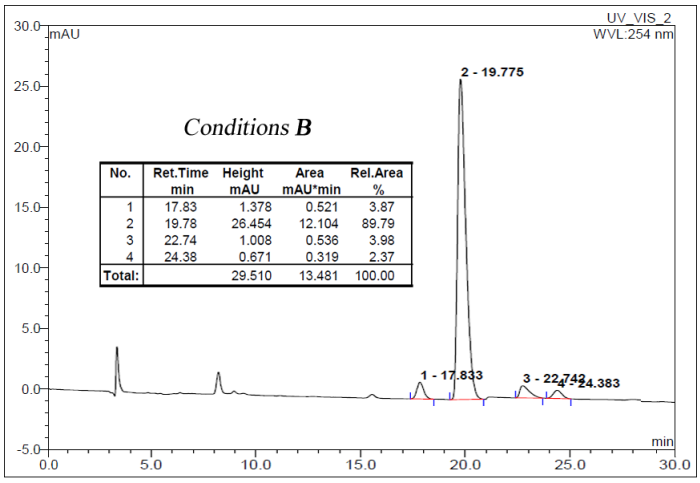
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.72 (d, *J* = 2.1 Hz, 1H), 7.43 (d, *J* = 2.2 Hz, 1H), 7.26 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.16 (d, *J* = 8.4 Hz, 1H), 4.84 (dd, *J* = 13.0, 9.2 Hz, 1H), 4.68 (dd, *J* = 13.0, 4.4 Hz, 1H), 4.30 (td, *J* = 9.2, 4.4 Hz, 1H), 2.93 (dddd, *J* = 9.2, 7.4, 5.2, 2.1 Hz, 1H), 1.67 – 1.44 (m, 2H), 0.87 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.4, 135.1, 134.5, 133.2, 130.3, 127.8, 76.5, 53.7, 38.7, 20.4, 10.6.

Spectroscopic data is in agreement with published data.[6]

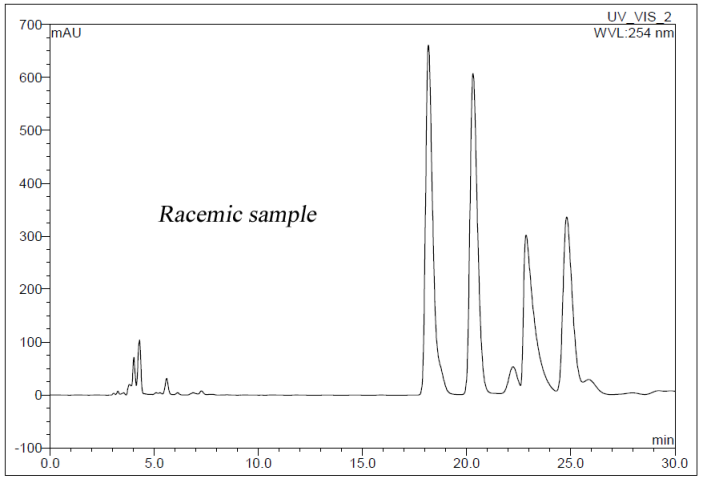
The enantiomeric excess was determined by HPLC using a Chiracel AD-H column (*n*-hexane/*i*-PrOH 98.5:1.5, 25°C) at 1.0 mL/min, UV detection at 254 nm: t_R : (*syn,* minor) = 18.3 min, (*syn*, major) = 20.1 min.



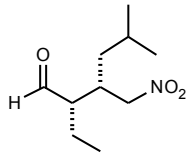
No.	Ret.Time min	Height mAU	Area mAU*min	Rel.Area %
1	18.28	5.243	1.937	5.66
2	20.10	63.242	30.265	88.42
3	23.16	2.264	1.313	3.84
4	25.04	1.426	0.716	2.09
Total:		72.175	34.230	100.00



No.	Ret.Time min	Height mAU	Area mAU*min	Rel.Area %
1	17.83	1.378	0.521	3.87
2	19.78	26.454	12.104	89.79
3	22.74	1.008	0.536	3.98
4	24.38	0.671	0.319	2.37
Total:		29.510	13.481	100.00



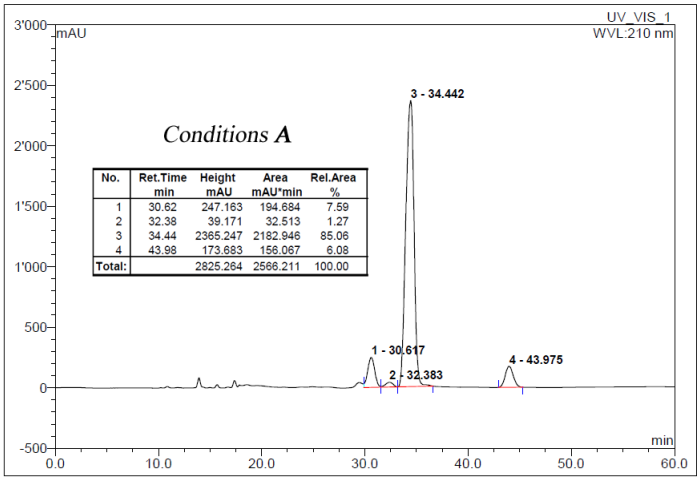
(2*S*,3*S*)-2-Ethyl-5-methyl-3-(nitromethyl)hexanal



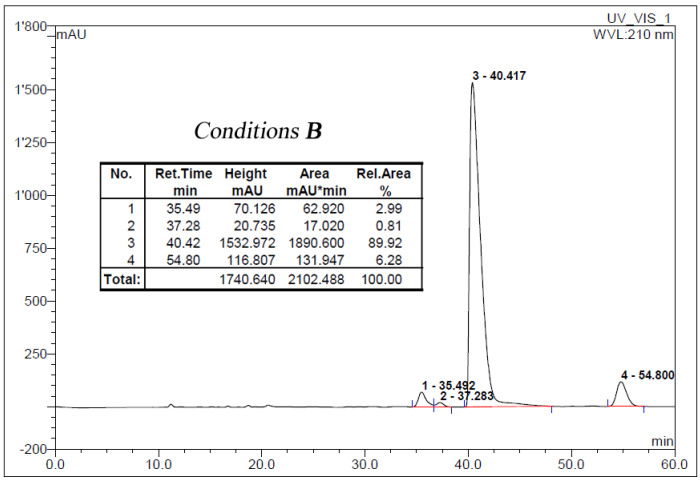
NMR (400 MHz, $CDCl_3$) δ 9.72 (d, *J* = 1.3 Hz, 1H), 4.47 (dd, *J* = 6.4, 12.5 Hz, 1H), 4.42 (dd, *J* = 6.6, 12.5 Hz, 1H), 2.73 (m, 1H), 2.43 (dtd, *J* = 1.3, 4.7, 6.0 Hz, 1H), 1.80 (m, 1H), 1.61 (m, 1H), 1.50 (dqd, *J* = 4.9, 7.4, 14.8 Hz, 1H), 1.24 (m, 2H), 1.01 (t, *J* = 7.4 Hz, 3H), 0.92 (d, *J* = 4.9 Hz, 3H), 0.90 (d, *J* = 4.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.0, 77.1, 54.0, 38.3, 34.7, 25.2, 22.7, 22.0, 18.5, 12.2.

Spectroscopic data is in agreement with published data.[6]

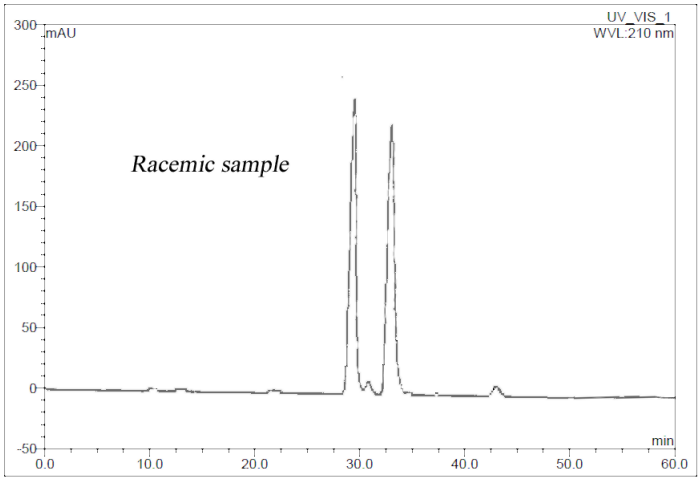
The enantiomeric excess was determined by HPLC using a Chiracel AD-H column (*n*-hexane/*i*-PrOH 99.25:0.75, 25°C) at 0.3 mL/min, UV detection at 210 nm: t_R : (*syn,* minor) = 35.5 min, (*syn*, major) = 40.1 min.



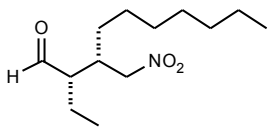
No.	Ret.Time min	Height mAU	Area mAU*min	Rel.Area %
1	30.62	247.163	194.684	7.59
2	32.38	39.171	32.513	1.27
3	34.44	2365.247	2182.946	85.06
4	43.98	173.683	156.067	6.08
Total:		2825.264	2566.211	100.00



No.	Ret.Time min	Height mAU	Area mAU*min	Rel.Area %
1	35.49	70.126	62.920	2.99
2	37.28	20.735	17.020	0.81
3	40.42	1532.972	1890.600	89.92
4	54.80	116.807	131.947	6.28
Total:		1740.640	2102.488	100.00



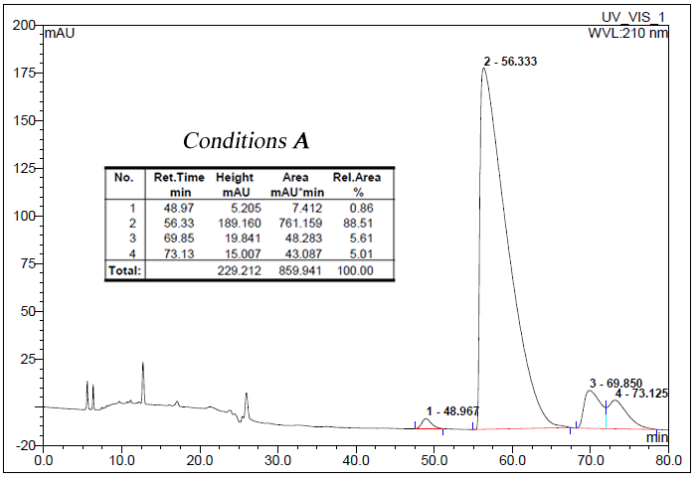
(2*S*,3*S*)-2-Ethyl-3-(nitromethyl)decanal



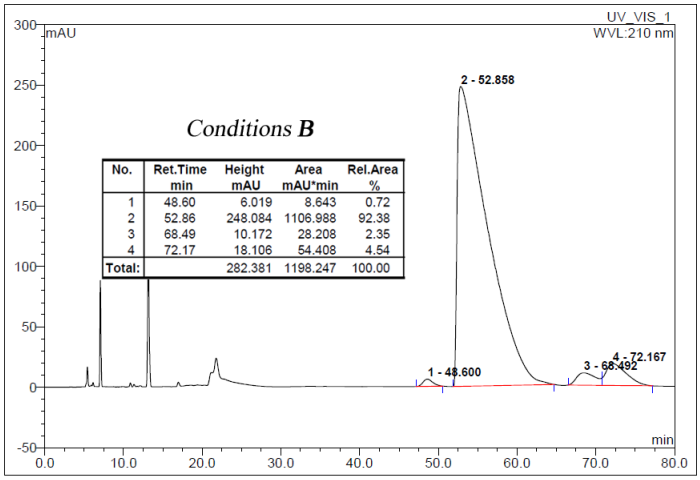
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (d, *J* = 1.5 Hz, 1H), 4.46 (dd, *J* = 12.6, 6.8 Hz, 1H), 4.41 (dd, *J* = 12.4, 6.4 Hz, 1H), 2.63 (qd, *J* = 6.4, 4.8 Hz, 1H), 2.40 (ddt, *J* = 8.4, 4.9, 2.4 Hz, 1H), 1.78 (ddq, *J* = 14.5, 8.7, 7.4 Hz, 1H), 1.52 (dqd, *J* = 14.8, 7.5, 4.7 Hz, 1H), 1.45 – 1.16 (m, 12H), 0.99 (t, *J* = 7.4 Hz, 3H), 0.90 – 0.81 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.1, 77.0, 53.9, 36.8, 31.7, 29.4, 29.1, 29.0, 26.7, 22.6, 18.6, 14.0, 12.1.

Spectroscopic data is in agreement with published data.[6]

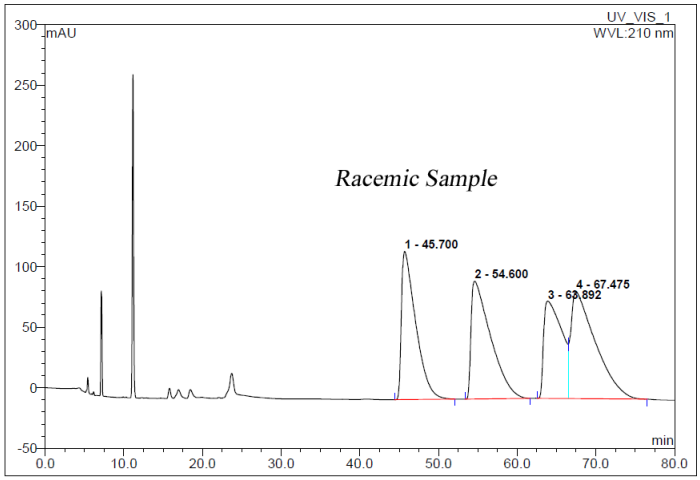
The enantiomeric excess was determined by HPLC using a Chiracel AD-H column (*n*-hexane/*i*-PrOH 99.8:0.2, 25°C) at 0.6 mL/min, UV detection at 210 nm: t_R : (*syn,* major) = 56.3 min, (*syn*, minor) = 73.1 min.



No.	Ret.Time min	Height mAU	Area mAU*min	Rel.Area %
1	48.97	5.205	7.412	0.86
2	56.33	189.160	761.159	88.51
3	69.85	19.841	48.283	5.61
4	73.13	15.007	43.087	5.01
Total:		229.212	859.941	100.00



No.	Ret.Time min	Height mAU	Area mAU*min	Rel.Area %
1	48.60	6.019	8.643	0.72
2	52.86	248.084	1106.988	92.38
3	68.49	10.172	28.208	2.35
4	72.17	18.106	54.408	4.54
Total:		282.381	1198.247	100.00



5. References

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