Mono Thiomalonate as Thioester Enolate Equivalent – Enantioselective 1,4-Addition Reactions to Nitroolefins Under Mild Conditions

Paolo Clerici and Helma Wennemers*

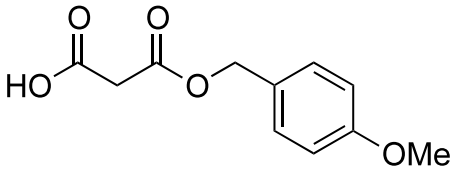
Department of Chemistry, University of Basel
St. Johanns-Ring 19, CH-4056 Basel (Switzerland)
Fax: +41-61-267-0976
e-mail: Helma.Wennemers@unibas.ch

Supporting Information

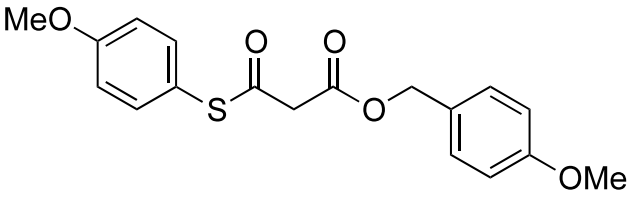
1. General aspects and materials

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 and $KMnO_4$. Flash chromatography was performed using Merck silica gel 60, particle size 40 – 63 μm. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX 400 spectrometer. Chemical shifts are reported in ppm using TMS or the residual solvent peak as a reference. Bruker Esquire 3000 Plus was used for electro spray ionization (ESI) mass spectrometry. HPLC analyses were carried out on an analytical HPLC with a diode array detector from Shimadzu. Cinchona alkaloid derivatives were prepared following known procedures.[1,2] The aliphatic nitro derivatives were prepared as described by Denmark *et al*. and Mioskowski *et al.*[3,4]

2. Synthesis of MTM 1



Malonic acid (100 mmol, 10.4 g, 2.0 eq) was dissolved under an inert argon atmosphere in dry acetonitrile (75 ml) and DMAP (10 mmol, 1.2 g, 0.2 eq) and 4-methoxybenzyl alcohol (50 mmol, 6.9 g, 1.0 eq) were added. The solution was cooled to 0°C and a solution of DCC (75 mmol, 15.5 g, 1.5 eq) in dry acetonitrile (25 ml) was added dropwise over 30 minutes. The reaction was kept at 0°C for 30 minutes and was then allowed to warm to room temperature. The reaction mixture was stirred at room temperature for other 2 hours followed by filtration of DCU and removal of all volatiles at reduced pressure. The crude mixture was re-dissolved in a mixture of CH_2Cl_2 (100 ml) and saturated aqueous $NaHCO_3$ (100 ml). The two phases were separated and the aqueous phase was washed twice with CH_2Cl_2. The pH of the aqueous phase was then decreased to pH 3 by addition of an aqueous solution of HCl (10%). The aqueous phase was reextracted with CH_2Cl_2 (3 times 80 ml each), and the combined organic phases were dried over $MgSO_4$. After filtration, all volatiles were removed at reduced pressure to yield a red solid that was used without further purification.



The solid was dissolved in dry CH_2Cl_2 (75 ml) and 4-methoxythiophenol (60 mmol, 8.4 g 1.2 eq) was added. The solution was cooled to 0°C and a solution of

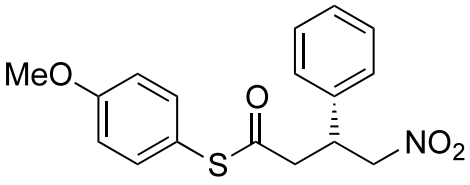
DCC (75 mmol, 15.5 g, 1.5 eq) in CH_2Cl_2 (25 ml) was added dropwise within 30 minutes. The reaction mixture was stirred for 30 minutes at 0°C and then at r.t. for two hours. DCU was removed by filtration and all volatiles were removed at reduced pressure. The crude compound was then purified by column chromatography using a gradient of CH_2Cl_2/pentane (7:3) to CH_2Cl_2. After removal of all the volatiles at reduced pressure, 13.8g (80%) of MTM **1** was isolated as white solid.
^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ = 7.32-7.29 (m, 4H), 6.95 (d, J = 8.7 Hz, 2H), 6.92 (d, J = 8.6 Hz, 2H), 5.13 (s, 2H), 3.82 (s, 3H), 3.81 (s, 3H), 3.66 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.0, 166.2, 161.4, 160.2, 136.6, 130.7, 127.7, 117.9, 115.4, 114.4, 67.7, 55.8, 55.7, 49.3; IR (KBr) ν 2937, 2840, 1733, 1695, 1250 cm^{-1}; MS (ESI): 369 (M+Na); Elemental analysis calcd (%) for $C_{18}H_{18}O_5S$: C 62.41, H 5.24; found: C 62.56, H 5.20.

3. General procedure for the 1,4-addition reactions in toluene:

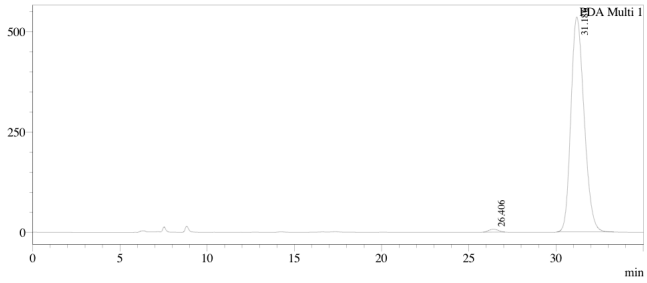
The nitroolefin (0.11 mmol, 1.10 equiv), MTM **1** (35 mg, 0.10 mmol), and the catalyst (0.001 mmol, 1 mol%) were dissolved in toluene (1 mL) in a capped vial at -50°C. After stirring the resulting solutions for 24 h, all volatiles were removed at reduced pressure. The oily residue was then dissolved in a solution of CH_2Cl_2 and TFA (2:1, 1 ml) and the mixture was stirred for 2 hours. After removal of all the volatiles at reduced pressure, the residue was dissolved in CH_2Cl_2 (0.5 ml) and DABCO (0.1 mol, 1.0 eq) was added. The mixture was stirred for 1 hour and then purified by column chromatography on silica gel (gradient of pentane/ethyl acetate 4:1 to 3:1; in the case of the aliphatic compounds the gradient was pentane/ethyl acetate 10:1 to 5:1).

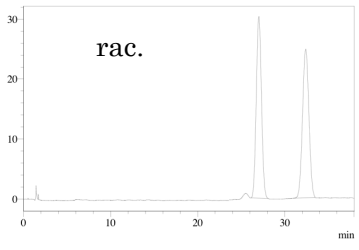
4. Analytical data of the 1,4-addition reaction products 8 a-o

(3R)-4-methoxyphenyl-4-nitro-3-phenylbutanethioate, ***8a***

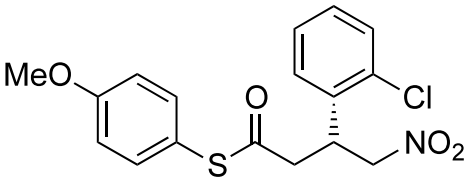


^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ = 7.33 (m, 3H), 7.22 (m, 4H), 6.91 (d, J = 8.9 Hz, 2H), 4.75 (dd, J = 6.7 Hz, 12.7 Hz, 1H), 4.66 (dd, J = 8.2 Hz, 12.7 Hz, 1H), 4.05 (m, J = 7.5 Hz, 1H), 3.81 (s, 3H), 3.07 (d, J = 7.4 Hz, 2H); ^{13}C NMR (100 MHz, CDCl3, 25 °C): δ = 195.9, 160.7, 137.7, 135.9, 129.2, 128.0, 127.4, 117.4, 114.8, 78.9, 55.3, 45.8, 40.2; MS (ESI): 332 (M+H); HPLC: Chiracel OD-H column with n-hexane/i-PrOH (1:1, 40°C) at 0.5 ml/min, UV detection λ = 254 nm: t_R: (*S*) = 26.5 min, (*R*) = 31.1 min (98% ee). The data is in agreement with that reported.[5]

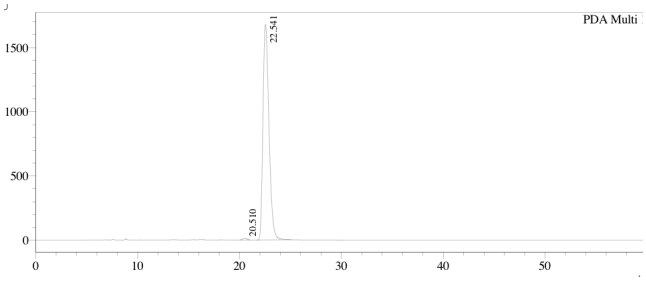


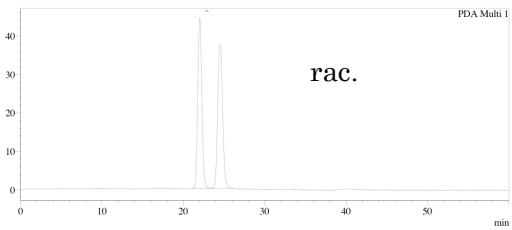


(3R)-4-methoxyphenyl-3-(2-chlorophenyl)4-nitrobutanethioate, ***8b*** *(Table 2 entry 3)*

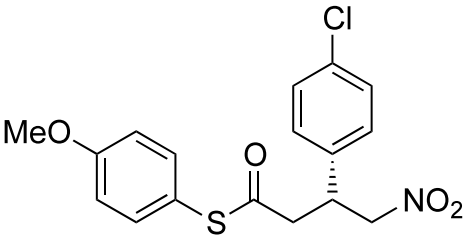


^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.47 – 7.42 (m, 1H), 7.31 – 7.21 (m, 5H), 6.98 – 6.91 (m, 2H), 4.86 (dd, J = 10.8, 5.1 Hz, 1H), 4.82 (dd, J = 10.8, 4.4 Hz, 1H), 4.55 (m, J = 7.0 Hz, 1H), 3.84 (s, 3H), 3.24 – 3.20 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 196.4, 161.3, 136.4, 135.4, 134.2, 130.9, 129.7, 128.8, 127.8, 117.8, 115.4, 77.5, 55.8, 44.5, 37.6; MS (ESI) (%): 366 (M (^{35}Cl)+H) (100), 368 (M (^{37}Cl)+H) (33); Elemental analysis calcd (%) for $C_{17}H_{16}ClNO_4S$: C 55.81, H 4.41, N 3.83; found: C 55.79, H 4.34, N 3.83. HPLC: Chiracel OD-H column with n-hexane/i-PrOH (1:1, 40°C) at 0.5 ml/min, UV detection λ = 254 nm: t_R: (*S*) = 20.5 min, (*R*) = 22.5 min (99% ee).

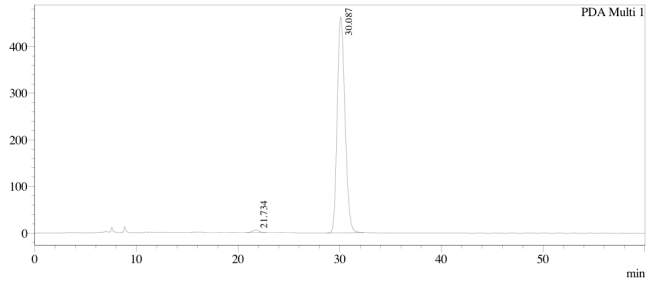


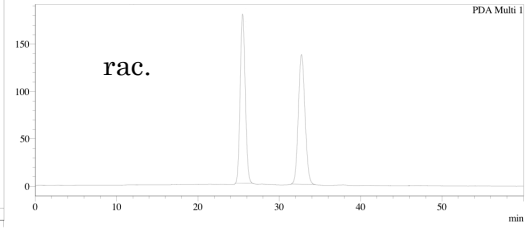


(3R)-4-methoxyphenyl-3-(4-chlorophenyl)4-nitrobutanethioate, ***8c***

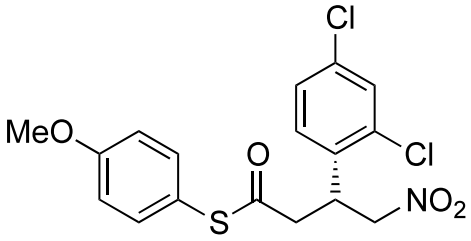


^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.32 (d, J = 8.5 Hz, 2H), 7.22 (d, J = 8.9 Hz, 2H), 7.16 (d, J = 8.4 Hz, 2H), 6.92 (d, J = 8.9 Hz, 2H), 4.72 (dd, J = 6.5 Hz, 12.8 Hz, 1H), 4.61 (dd, J = 8.4 Hz, 12.8 Hz, 1H), 4.01 (m, J = 7.1 Hz, 1H), 3.81 (s, 3H), 3.04 (d, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 195.7, 160.8, 136.3, 135.9, 133.9, 129.2, 128.8, 117.2, 114.9, 78.7, 55.3, 45.6, 39.8; MS (ESI) (%): 366 (M (^{35}Cl)+H) (100), 368 (M (^{37}Cl)+H) (34); HPLC: Chiracel OD-H column with n-hexane/i-PrOH (1:1, 40°C) at 0.5 ml/min, UV detection λ = 254 nm: t_R: (*S*) = 21.7 min, (*R*) = 30.0 min (98% ee). The data is in agreement with that reported.[5]

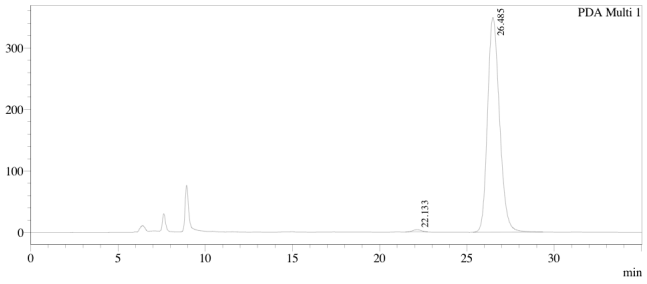


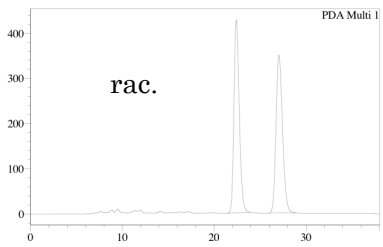


(3R)-4-methoxyphenyl-3-(2,4-dichlorophenyl)4-nitrobutanethioate, ***8d***

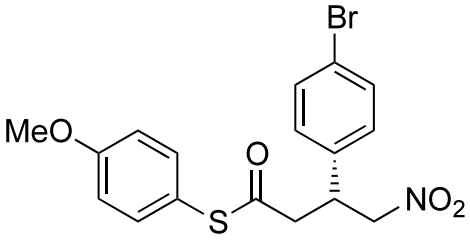


^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.4 (d, J = 2.13 Hz, 1H), 7.26 (m, 1H), 7.23 (m, 2H), 7.17 (d, J = 8.4 Hz, 1H), 6.93 (d, J = 8.9 Hz, 2H), 4.81 (dd, J = 4.9 Hz, 10.8 Hz, 1H), 4.77 (dd, J = 4.2 Hz, 10.8 Hz, 1H), 4.47 (m, 1H), 3.84 (s, 3H), 3.17 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 196.4, 160.7, 135.7, 134.4, 134.0, 133.9, 129.6, 129.0, 127.4, 117.1, 114.6, 76.9, 54.7, 43.9, 36.3; MS (ESI) (%): 400 (M (^{35}Cl, ^{35}Cl)+H) (100), 402 (M (^{35}Cl, ^{37}Cl)+H) (67), 404 (M (^{37}Cl, ^{37}Cl)+H) (10); HPLC: Chiracel OD-H column with n-hexane/i-PrOH (1:1, 40°C) at 0.5 ml/min, UV detection λ = 254 nm: t_R: (*S*) = 22.1 min, (*R*) = 26.5 min (99% ee). The data is in agreement with that reported.[5]

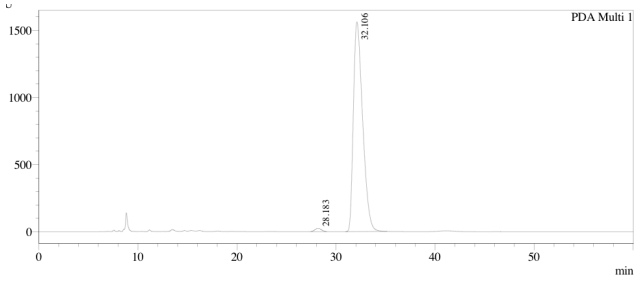


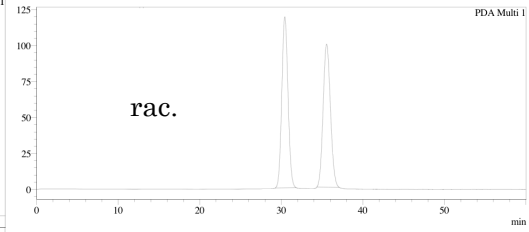


(3R)-4-methoxyphenyl-3-(4-bromophenyl)4-nitrobutanethioate, ***8e***

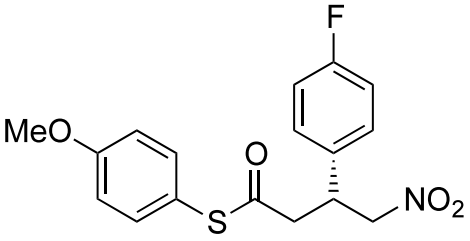


^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.48 (d, J = 8.4 Hz, 2H), 7.22 (d, J = 8.8 Hz, 2H), 7.11 (d, J = 8.4 Hz, 2H), 6.92 (d, J = 8.8 Hz, 2H), 4.73 (dd, J = 12.8, 6.5 Hz, 1H), 4.62 (dd, J = 12.8, 8.4 Hz, 1H), 4.07 – 3.96 (m, 1H), 3.82 (s, 3H), 3.05 (d, J = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 196.2, 161.3, 137.2, 136.4, 132.7, 129.6, 122.6, 117.7, 115.4, 79.1, 55.8, 46.0, 40.4; MS (ESI) (%): 410 (M (^{79}Br)+H) (100), 412 (M (^{81}Br)+H) (99); Elemental analysis calcd (%) for $C_{17}H_{16}BrNO_4S$: C 55.49.77, H 3.93, N 3.41; found: C 49.79, H 3.96, N 3.48; HPLC: Chiracel OD-H column with n-hexane/i-PrOH (1:1, 40°C) at 0.5 ml/min, UV detection λ = 254 nm: t_R: (*S*) = 28.1 min, (*R*) = 32.1 min (98% ee).

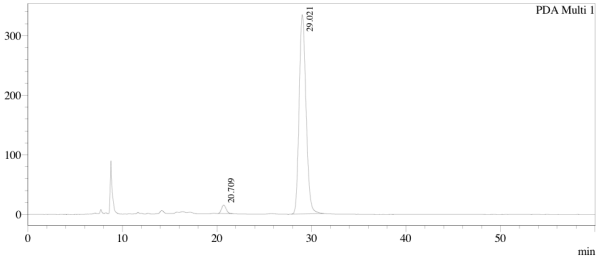


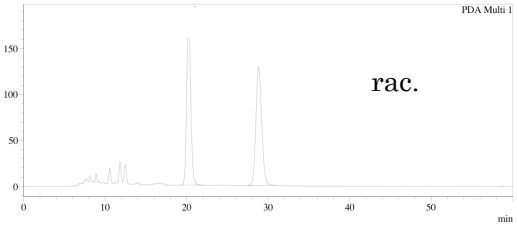


(3R)-4-methoxyphenyl-3-(4-fluorophenyl)4-nitrobuthanethioate, ***8f***

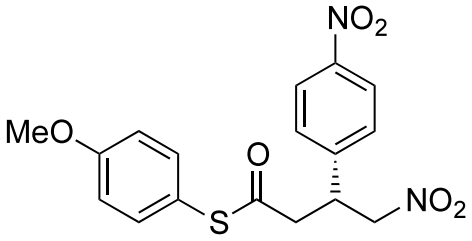


^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.23 - 7.18 (m, 4H), 7.08 - 7.02 (m, 2H), 6.95 - 6.90 (m, 2H), 4.74 (dd, J = 12.7, 6.6 Hz, 1H), 4.63 (dd, J = 12.7, 8.4 Hz, 1H), 4.11 - 3.98 (m, 1H), 3.82 (s, 3H), 3.05 (d, J = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 196.3, 164.5, 161.3, 136.4, 129.6, 129.5, 116.6, 116.4, 115.4, 79.5, 55.8, 46.3, 40.2; MS (ESI): 350 (M+H); Elemental analysis calcd (%) for $C_{17}H_{16}FNO_4S$: C 58.44; H, 4.62; N, 4.01; found: C, 58.60; H, 4.74; N, 3.91; HPLC: Chiracel OD-H column with n-hexane/i-PrOH (1:1, 40°C) at 0.5 ml/min, UV detection λ=254 nm: t_R: (*S*)= 20.7 min, (*R*)= 29.0 min (94%ee)

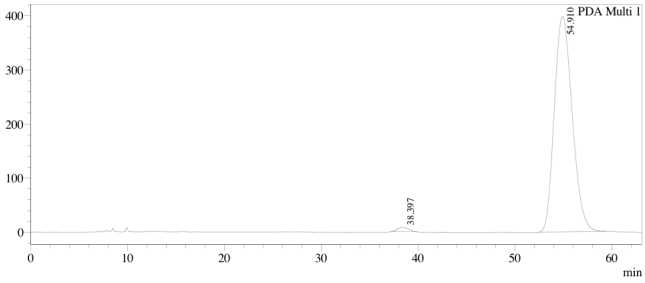


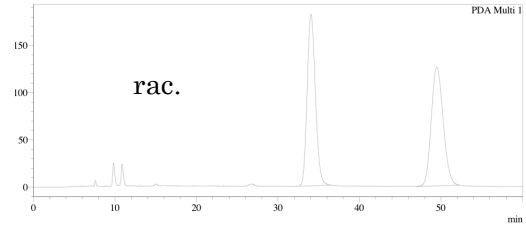


3R)-4-methoxyphenyl-3-(4-nitrophenyl)4-nitrobutanethioate, ***8g***

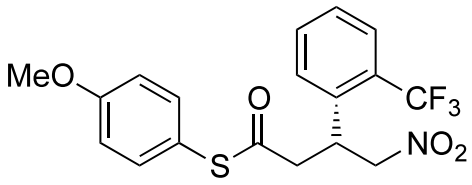


^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ = 8.22 (d, J = 8.8 Hz, 2H), 7.43 (d, J = 8.6 Hz, 2H), 7.20 (d, J = 8.9 Hz, 2H), 6.92 (d, J = 8.9 Hz, 2H), 4.80 (dd, J = 6.3Hz, 13.1 Hz, 1H), 4.70 (dd J = 8.6 Hz, 13.1 Hz, 1H), 4.18 (m, J = 7.1 Hz, 1H), 3.81 (s, 3H), 3.11 (d, J = 7.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 195.4, 161.0, 147.6, 145.1, 135.9, 128.6, 124.3, 116.9, 115.1, 78.2, 55.4, 45.3, 40.1; MS (ESI): 377 (M+H); HPLC: Chiracel OD-H column with n-hexane/i-PrOH (1:1, 40°C) at 0.5 ml/min, UV detection λ = 254 nm: t_R: (*S*) = 38.4 min, (*R*) = 54.9 min (97% ee). The data is in agreement with that reported.[5]

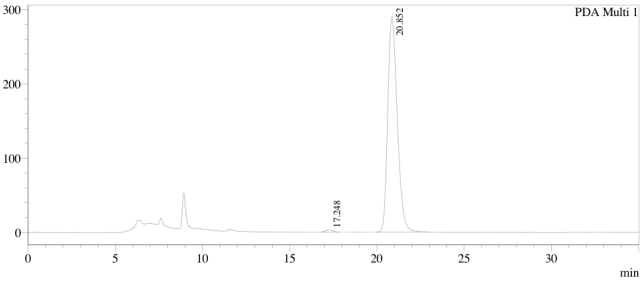


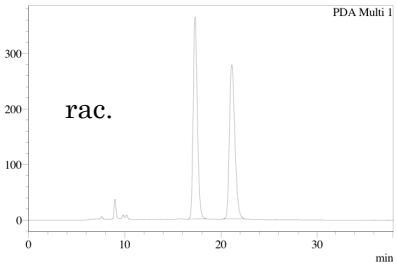


(3R)-4-methoxyphenyl 3-(2-(trifluoromethyl)phenyl)4-nitrobuthanethioate, ***8h***

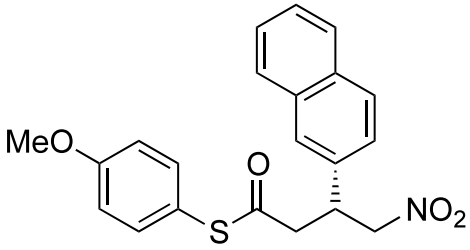


^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.55 (d, J = 7.8 Hz, 1H), 7.43 (t, J = 7.6 Hz, 1H), 7.29 (m, 2H), 7.08 (d, J = 8.7 Hz, 2H), 6.77 (d, J = 8.7 Hz, 2H), 4.66 (dd, J = 7.2 Hz, 13.9 Hz, 1H), 4.64 (dd, J = 7.4 Hz, 13.5 Hz, 1H), 4.32 (m, 1H), 3.66 (s, 3H), 3.98 (d, J = 7.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 195.9, 160.6, 136.4, 135.7, 131.6, 128.3, 127.8, 127.4, 126.4, 123.8, 117.0, 114.6, 77.7, 54.9, 45.4, 39.5; MS (ESI): 400 (M+H); HPLC: Chiracel OD-H column with n-hexane/i-PrOH (1:1, 40°C) at 0.5 ml/min, UV detection λ = 254 nm: t_R: (*S*) = 17.2 min, (*R*) = 20.8 min (99% ee). The data is in agreement with that reported.[5]

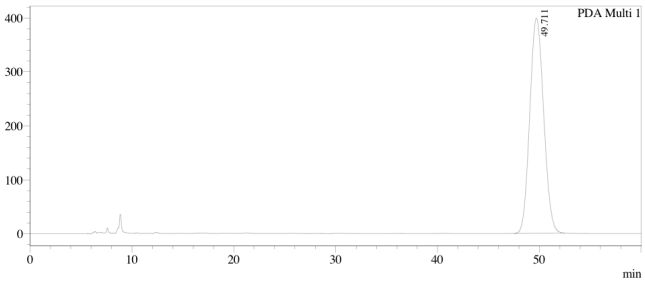


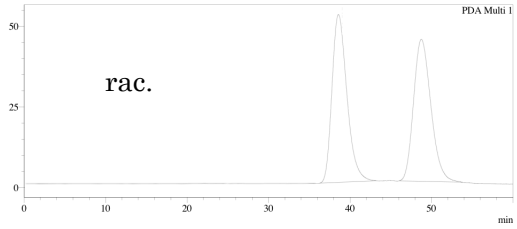


(3R)-4-methoxyphenyl-3-(2-naphtyl)4-nitrobutanethioate, ***8i***

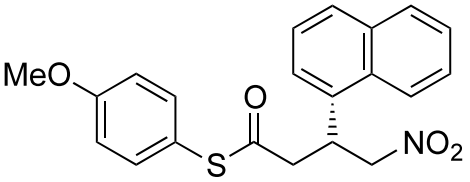


^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.91 – 7.77 (m, 3H), 7.69 (s, 1H), 7.56 – 7.47 (m, 2H), 7.34 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.18 (dd, *J* = 9.3, 2.6 Hz, 2H), 6.98 – 6.84 (m, 2H), 4.85 (dd, *J* = 12.7, 6.8 Hz, 1H), 4.77 (dd, *J* = 12.8, 8.1 Hz, 1H), 4.29 – 4.18 (m, 1H), 3.81 (s, 3H), 3.26 – 3.11 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 196.4, 161.3, 136.4, 135.6, 133.8, 133.3, 129.5, 128.3, 128.1, 127.1, 127.0, 126.8, 125.2, 117.8, 115.4, 79.4, 55.8, 46.4, 41.0; MS (ESI): 382 (M+H); Elemental analysis calcd (%) for $C_{21}H_{19}NO_4S$: : C, 66.13; H, 5.02; N, 3.67; found: 66.27; H, 5.06; N, 3.65; HPLC: Chiracel OD-H column with n-hexane/i-PrOH (1:1, 40°C) at 0.5 ml/min, UV detection λ = 254 nm: t_R: (*S*) = 38.6 min, (*R*) = 49.7 min (>99% ee).

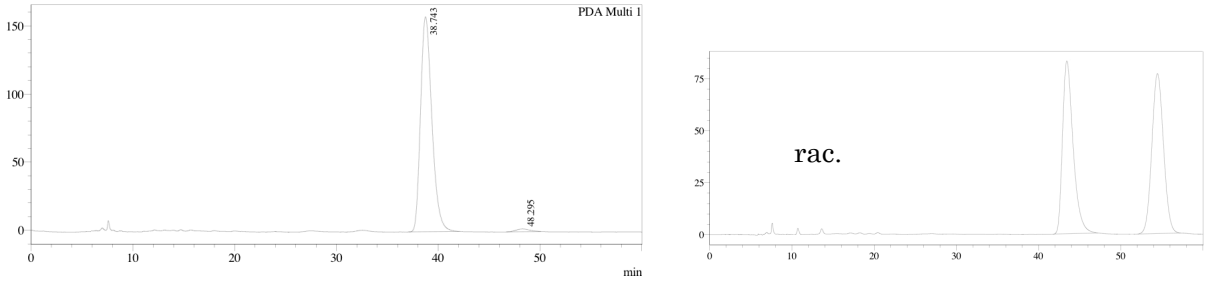




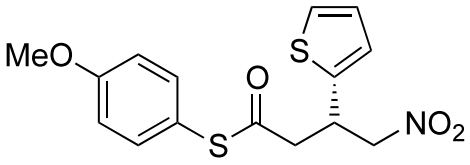
(3R)-4-methoxyphenyl-3-(1-naphtyl)4-nitrobutanethioate, ***8j***



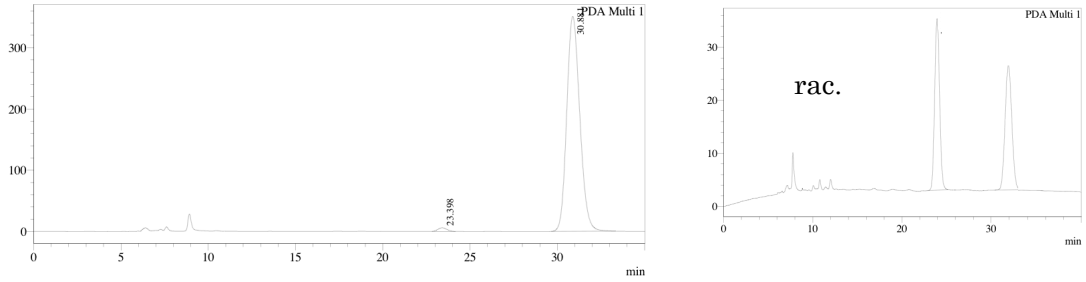
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.17 (d, *J* = 8.5 Hz, 1H), 7.90 (d, *J* = 8.1 Hz, 1H), 7.82 (d, *J* = 8.2 Hz, 1H), 7.61 (ddd, *J* = 8.5, 6.8, 1.4 Hz, 1H), 7.54 (ddd, *J* = 8.0, 6.9, 1.1 Hz, 1H), 7.47 (t, *J* = 7.7 Hz, 1H), 7.38 (d, *J* = 7.2 Hz, 1H), 7.21 – 7.16 (m, 2H), 6.93 – 6.88 (m, 2H), 5.06 – 4.96 (m, 1H), 4.87 (d, *J* = 7.1 Hz, 2H), 3.80 (s, 3H), 3.25 (m, *J* = 6.8, 5.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 196.6, 161.2, 136.4, 134.6, 134.2, 133.1, 131.3, 129.7, 129.1, 127.4, 126.5, 125.7, 122.6, 117.9, 115.3, 115.0, 78.8, 55.8, 46.1; MS (ESI): 382 (M+H); Elemental analysis calcd (%) for $C_{21}H_{19}NO_4S$: C, 66.13; H, 5.02; N, 3.67; found: C, 66.01; H, 5.18; N, 3.64; HPLC: Chiracel OD-H column with n-hexane/i-PrOH (1:1, 40°C) at 0.5 ml/min, UV detection λ = 254 nm: t_R: (*R*) = 38.7 min, (*S*) = 48.3 min (97% ee).



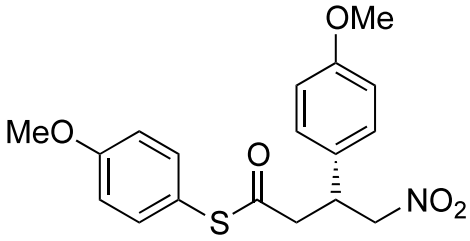
(3S)-4-methoxyphenyl-3-(thiophen-2-yl)4-nitrobutanethioate, ***8k***



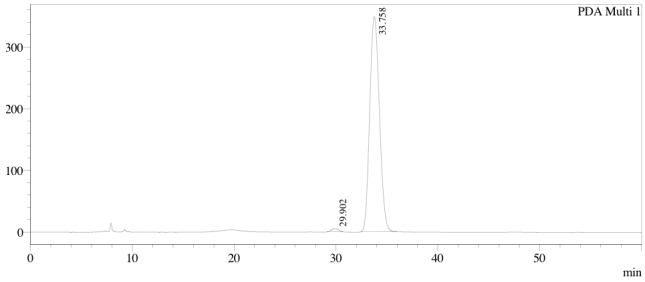
^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.25-7.19 (m, 3H), 6.94-6.88 (m, 4H), 4.76 (dd, J = 6.5 Hz, 12.8 Hz, 1H), 4.66 (dd, J = 7.8 Hz, 12.8 Hz, 1H), 4.37 (m, J = 7.1 Hz, 1H), 3.82 (s, 3H), 3.14 (dd, J = 6.9 Hz, 16.1 Hz, 1H), 3.12 (dd, J = 7.5 Hz, 16.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ = 195.7, 160.9, 140.4, 136.0, 127.1, 125.8, 124.9, 117.3, 114.9, 79.3, 55.3, 46.5, 35.9; MS (ESI): 338 (M+H); HPLC: Chiracel OD-H column with n-hexane/i-PrOH (1:1, 40°C) at 0.5 ml/min, UV detection λ = 254 nm: t_R: (*R*) = 23.4 min, (*S*) = 30.9 min (98% ee). The data is in agreement with that reported.[5]

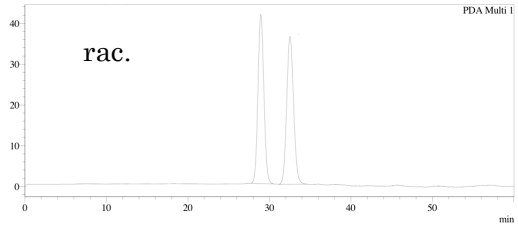


(3R)-4-methoxyphenyl-3-(4-methoxyphenyl)4-nitrobutanethioate, ***8l***

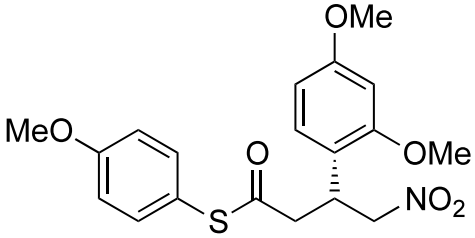


^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.23 (d, J = 8.9 Hz, 2H), 7.14 (d, J = 8.6 Hz, 2H), 6.92 (d, J = 8.9 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 4.71 (dd, J = 6.7 Hz, 12.6 Hz, 1H), 4.61 (dd, J = 8.3 Hz, 12.6 Hz, 1H), 4.00 (m, J = 6.8 Hz, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.04 (d, J = 7.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 196.0, 161.0, 159.2, 136.0, 129.6, 128.4, 117.5, 114.9, 114.3, 79.2, 55.3, 55.2, 46.0, 39.8; MS (ESI): 362 (M+H); HPLC: Chiracel OD-H column with n-hexane/i-PrOH (1:1, 40°C) at 0.5 ml/min, UV detection λ = 254 nm: t_R: (*S*) = 29.9 min, (*R*) = 33.8 min (98% ee). The data is in agreement with that reported.[5]

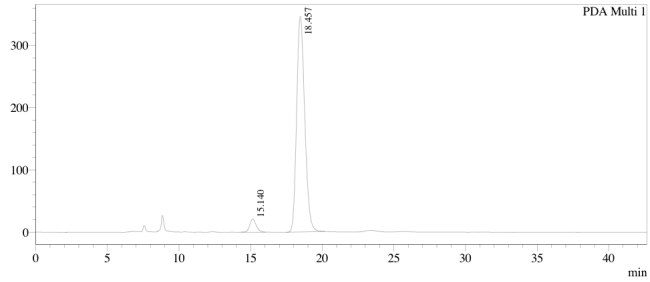


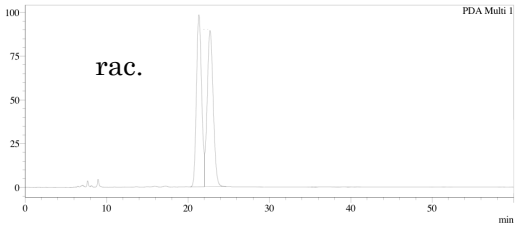


(3R)-4-methoxyphenyl-3-(2,4-dimethoxyphenyl)4-nitrobutanethioate, ***8m***

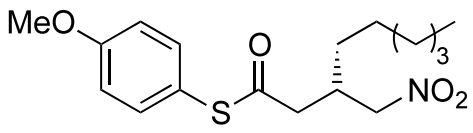


^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.21 – 7.16 (m, 2H), 6.94 – 6.87 (m, 3H), 6.80 (s, 1H), 6.44 (d, *J* = 5.5 Hz, 1H), 4.74 – 4.69 (m, 2H), 4.17 – 4.07 (m, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H), 3.20 – 3.01 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$). δ = 197.0, 161.0, 158.4, 156.9, 136.4, 131.4, 121.4, 118.5, 116.9, 115.2, 95.7, 78.2, 56.0, 55.9, 55.8, 44.8, 37.1; MS (ESI): 392 (M+H); Elemental analysis calcd (%) for $C_{19}H_{21}NO_6S$: C, 58.30; H, 5.41; N, 3.58; found: C, 58.51; H, 5.38; N, 3.74; HPLC: Chiracel OD-H column with n-hexane/i-PrOH (1:1, 40°C) at 0.5 ml/min, UV detection λ = 254 nm: t_R : (*S*) = 15.1 min, (*R*) = 18.4 min (91% ee).



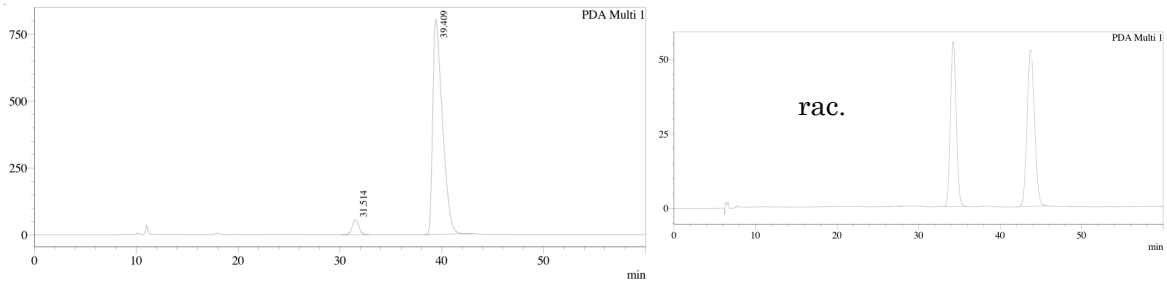


(3S)-4-methoxyphenyl 3-(nitromethyl) nonanethioate, ***8n***

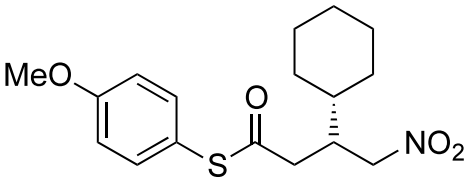


^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.31 (d, *J* = 8.9 Hz, 2H), 6.95 (d, *J* = 8.9 Hz, 2H), 4.51 (dd, *J* = 6.3 Hz, 12.4 Hz, 1H), 4.43 (dd, *J* = 6.0 Hz, 12.4 Hz, 1H), 3.82 (s, 3H), 2.80 (dd, *J* = 7.2 Hz, 16.2 Hz, 1H), 2.77 (dd, *J* = 5.6 Hz, 16.2 Hz, 1H), 2.70 (m, 1H), 1.36 (m, 10H), 0.89 (t, *J* = 6.94 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 197.0, 160.8, 136.1, 117.8, 114.9, 78.3, 55.4, 44.2, 34.7, 31.5, 31.2, 29.3, 26.1, 22.4, 13.9; MS (ESI): 340 (M+H); Elemental analysis calcd (%) for $C_{17}H_{25}NO_4S$: C, 60.15; H, 7.42; N, 4.13 found: C, 60.50; H, 7.45; N, 4.34; HPLC: Chiracel OD-H column with n-hexane/i-PrOH

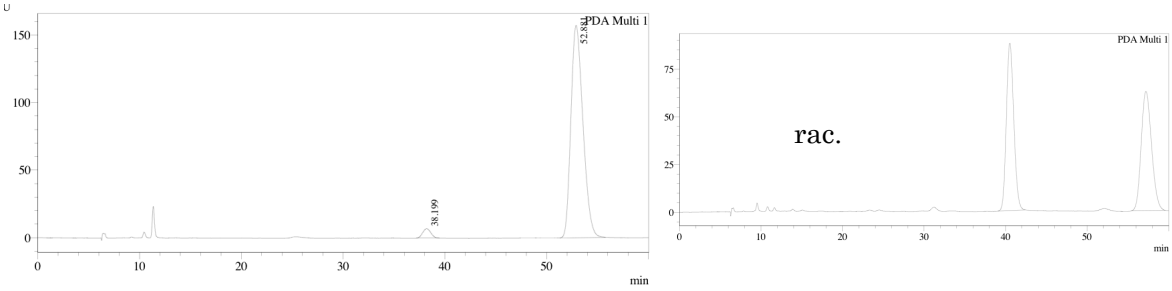
(95:5, 40°C) at 0.5 ml/min, UV detection λ = 254 nm: t_R: (*R*) = 31.5 min, (*S*) = 39.4 min (91% ee).



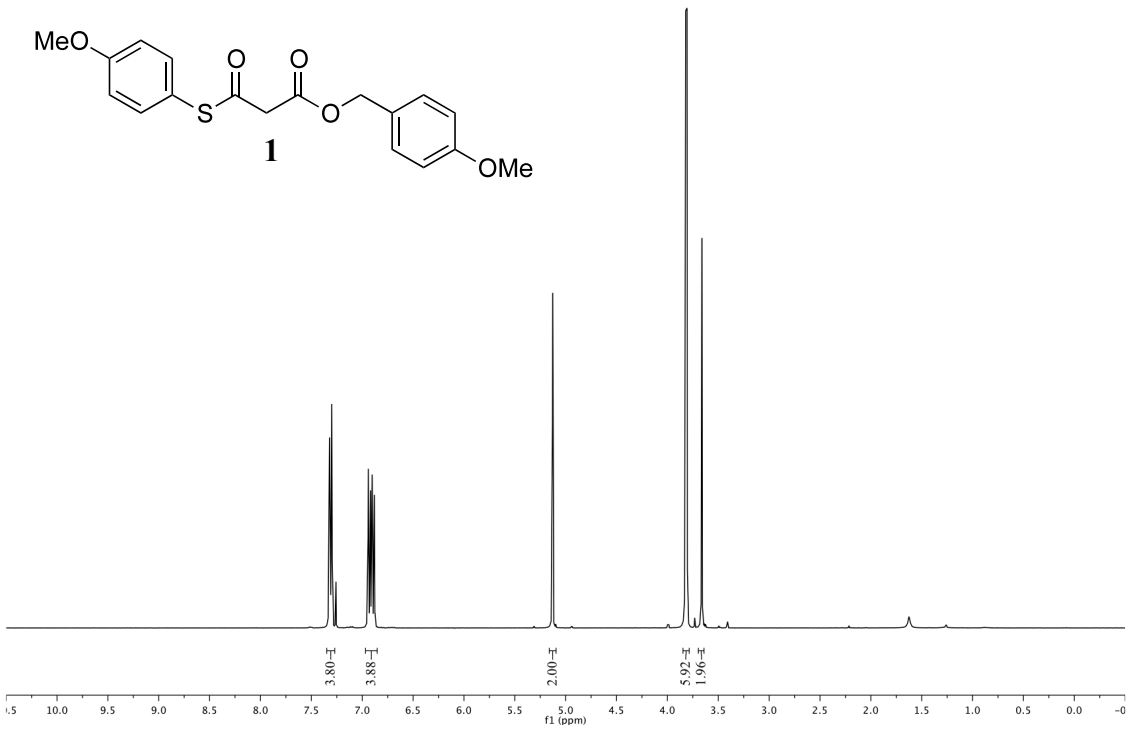
(3R)-4-methoxyphenyl 3-cyclohexyl 4-nitrobutanethioate, ***8o***



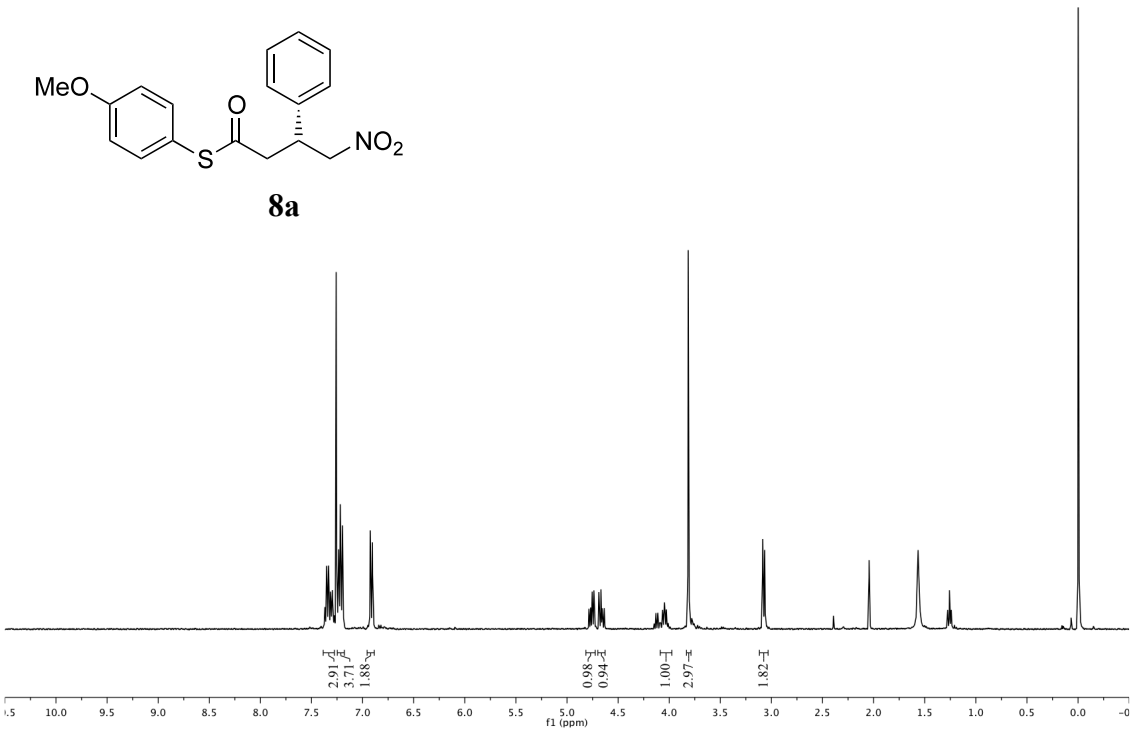
^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ = 7.31 (d, *J* = 8.9 Hz, 2H), 6.95 (d, *J* = 8.9 Hz, 2H), 4.49 (dd, *J* = 6.5 Hz, 12.8 Hz, 1H), 4.46 (dd, *J* = 6.3 Hz, 13.1 Hz, 1H), 3.82 (s, 3H), 2.84 (dd, *J* = 4.9 Hz, 15.7 Hz, 1H), 2.75 (m, 2H), 1.72 (m, 5H), 1.47 (m, 1H), 1.25-0.97 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C): δ = 197.2, 160.8, 136.0, 117.8, 114.9, 76.7, 55.3, 41.9, 39.8, 38.8, 29.9, 26.2, 26.1; MS (ESI): 338 (M+H); HPLC: Chiracel OD-H column with n-hexane/i-PrOH (95:5, 40°C) at 0.5 ml/min, UV detection λ = 254 nm: t_R: (*S*) = 38.2 min, (*R*) = 52.8 min (94% ee). The data is in agreement with that reported.[5]



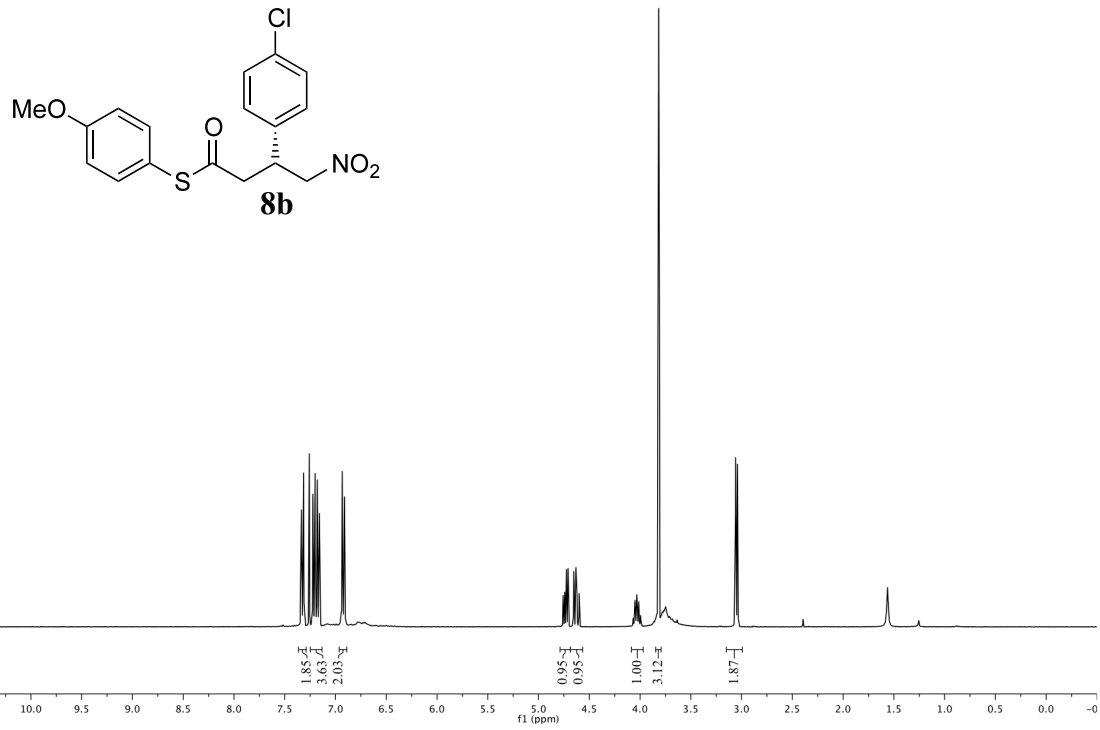
5. ^{1}H NMR spectra



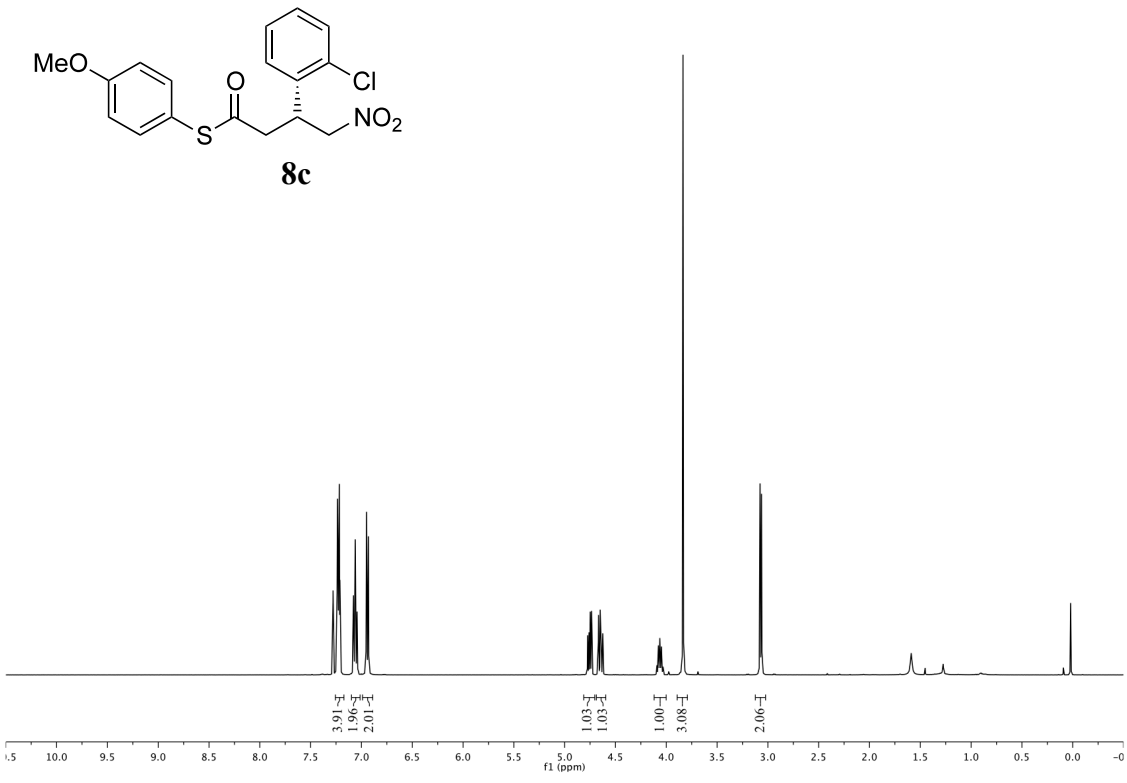
1



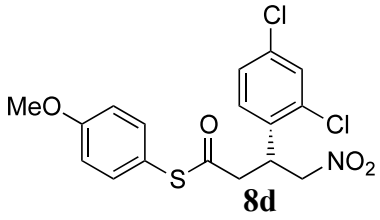
8a



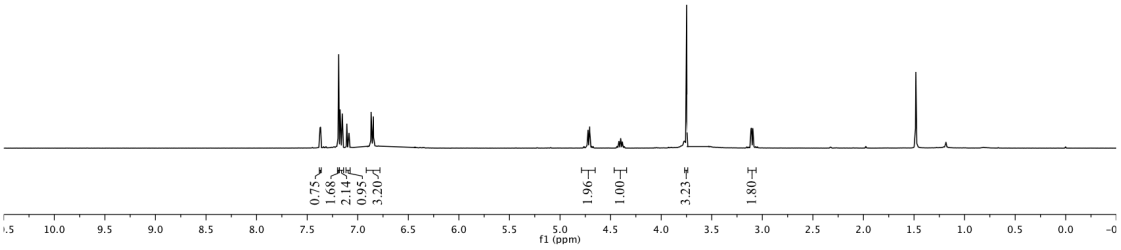
8b

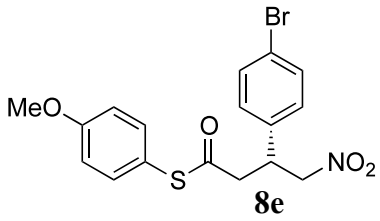


8c

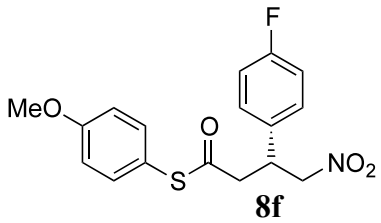


8d

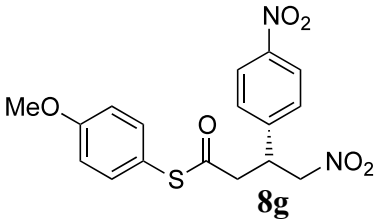




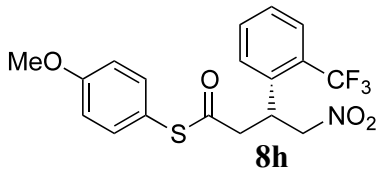
8e



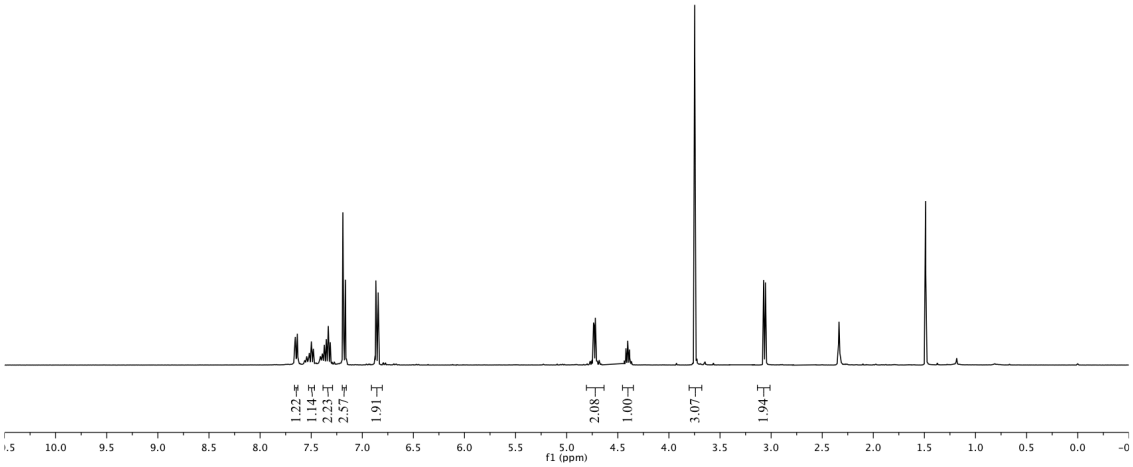
8f

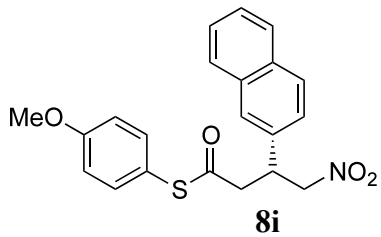


8g

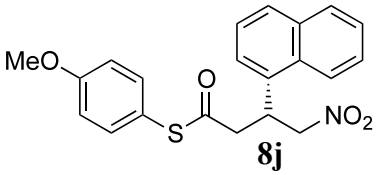


8h



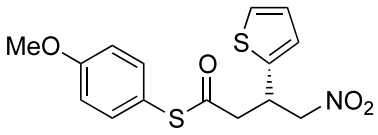


8i

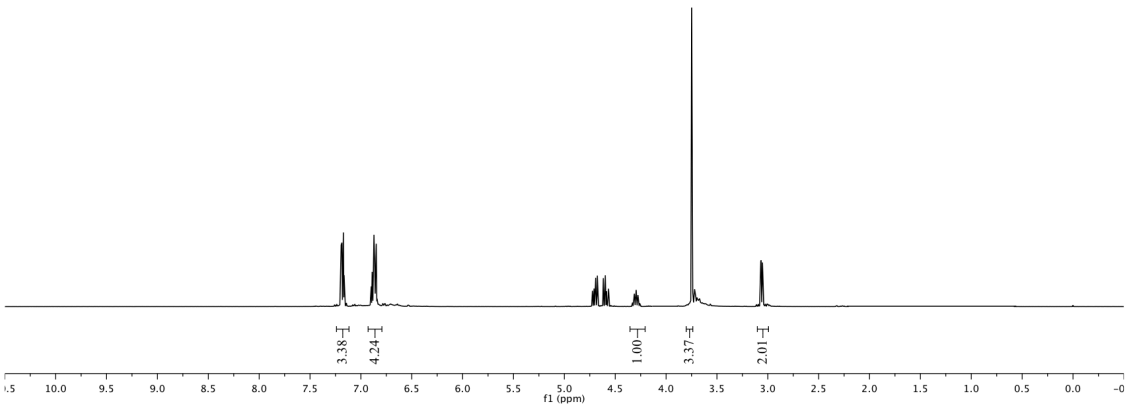

MeO
O
S
NO2

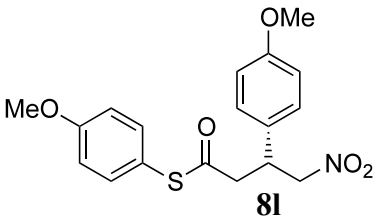
8j

0.98
0.97
0.97
0.99
1.00
1.00
0.99
1.89
1.93
1.00
1.98
3.04
2.00
f1 (ppm)

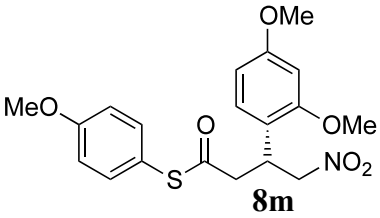

MeO
S
O
S
NO2

8k

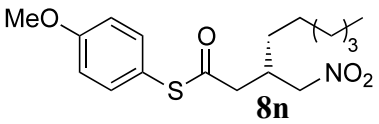

3.38
4.24
1.00
3.37
2.01
f1 (ppm)



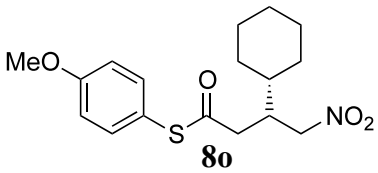
8l



8m

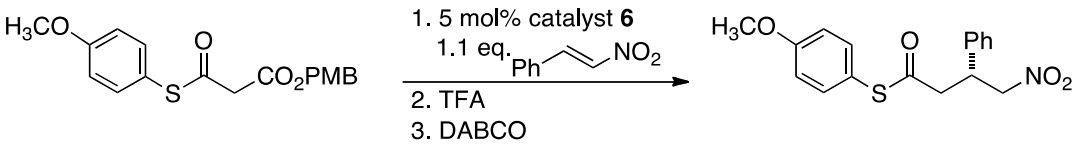


8n



8o

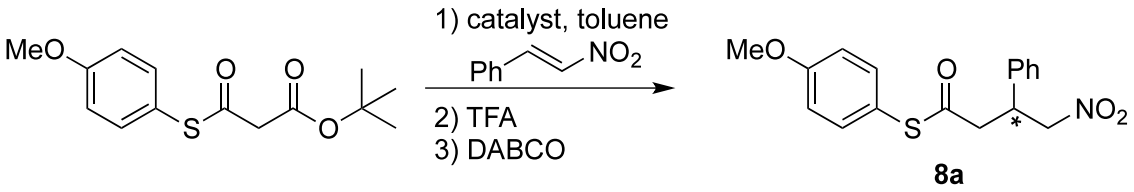
6. Solvent screening



entry	cat.	t (h)	solvent	T (°C)	Conv.[a] (%)	*ee*[b] (%)
1	**6**	24	Toluene	RT	quant.	90
2	**6**	24	DCM	RT	quant.	84
3	**6**	24	Et_2O	RT	quant.	83
4	**6**	24	THF	RT	80	79
5	**6**	24	Acetone	RT	70	77
6	**6**	24	Benzene	RT	quant.	87
7	**6**	24	Heptane	RT	quant.	75
8	**6**	24	EtOAc	RT	80	83
9	**6**	24	EtOH	RT	quant.	59

(a) estimated by TLC analysis, (b) determined by HPLC with OD-H chiral column

7. MTM bearing a *t*-Bu group as an acid labile protecting group



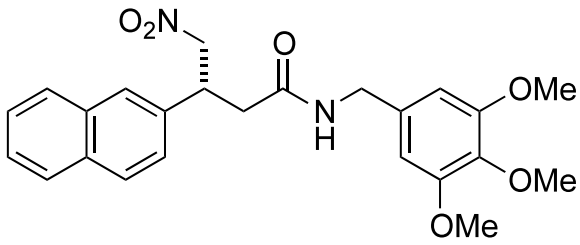
8a

entry	cat.	mol%	t (h)	T (°C)	Conv.[a] (%)	*ee*[b] (%)
1	**2**	5	24	RT	quant.	77 (*R*)
2	**3**	5	6	RT	quant.	78 (*R*)
3	**4**	5	6	RT	quant.	79 (*R*)
4	**5**	5	24	RT	50	75 (*R*)
5	**6**	5	6	RT	quant.	79 (*S*)
6	**7**	5	6	RT	quant.	79 (*S*)

(a) estimated by TLC analysis, (b) determined by HPLC with OD-H chiral column

10. Synthesis of 9, 10, 11, 12 and 13

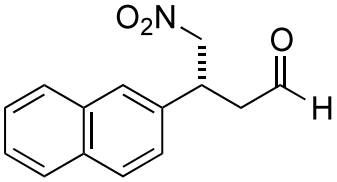
Preparation of 3,4,5-(trimethoxybenzyl) 3-(2-naphthyl) 4-nitrobutanamide (**9**)



The title compound **8i** (0.1 mmol, 38 mg, 1 eq) was dissolved in CH_2Cl_2, 3,4,5-trimethoxybenzylamide was added and the reaction was stirred for 48 h at rt. The volatiles were evaporated at reduced pressure and the crude mixture was purified with column chromatography using as eluent EtOAc/Pentane (1:3). The product **9** was isolated in 90% yield (0.090 mmol, 38.4 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.88 – 7.75 (m, 4H), 7.69 (s, 1H), 7.58 – 7.45 (m, 3H), 7.38 – 7.30 (m, 1H), 6.30 (s, 2H), 6.03 (s, 1H), 4.89 (dd, J = 12.6, 6.6 Hz, 1H), 4.79 (dd, J = 12.6, 7.9 Hz, 1H), 4.31 – 4.19 (m, 2H), 3.78 (s, 3H), 3.66 (s, 6H), 2.83 – 2.67 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 169.9, 153.7, 137.5, 136.4, 133.9, 133.8, 133.2, 129.3, 128.2, 128.0, 126.94, 126.9, 126.7, 125.3, 105.1, 79.8, 61.2, 56.3, 44.4, 41.2, 40.1; MS (ESI): 439 (M+H).

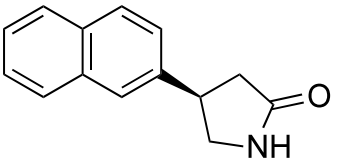
Preparation of 3-(2-naphthyl) 4-nitrobutanal (**10**)



A solution made dissolving **8a** (0.1 mmol, 38 mg, 1 eq) in dry acetone was transferred under argon in a two-necked flask. To the solution, Pd/C (10% Pd, 20 mg, 20 mol %) was added. Triethylsilane (0.3 mmol, 34 mg, 3 eq) was added dropwise over 5 minutes. The reaction was checked after 1.5 hours by TLC analysis. If the starting material was still present 1.5 more equivalents of triethylsilane should be added. The reaction was stirred at r.t. for 2 more hours. The catalyst was filtered through a pad of celite and the solvent was removed at reduced pressure. The chromatographic purification was performed with a gradient of EtOAc/Pentane from 1:10 to 1:3. The product **10** was isolated in 76% yield (18.5 mg 0.076 mmol)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.76 (s, 1H), 7.90 – 7.80 (m, 3H), 7.72 (d, J = 1.7 Hz, 1H), 7.56 – 7.48 (m, 2H), 7.37 (dd, J = 8.5, 1.9 Hz, 1H), 4.83 – 4.70 (m, 2H), 4.28 (m, J = 7.3 Hz, 1H), 3.15 – 2.99 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 199.1, 135.8, 133.8, 133.3, 129.6, 128.2, 128.1, 127.0, 126.8, 125.2, 79.7, 46.8, 38.5; MS (ESI): 382 (M+H).

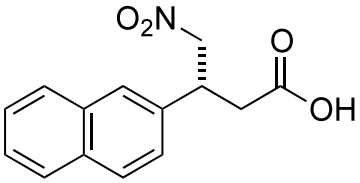
Preparation of 3-(2-naphthyl) cyclopentanelactam (**11**)



A solution of **8** (355 mg, 0.76 mmol) in THF (10 ml) was placed in a hydrogenation vessel, together with H_3PO_4 (85%, 10 mol%) and Raney-Nickel (1.5 g). The hydrogenation vessel was purged three times with hydrogen and the reaction pressure was kept at a pressure of 3 bar. After 72 h the mixture was filtered under nitrogen and the residue washed with THF and acetone (50 ml each). After removal of all volatiles at reduced pressure, the residue was purified by column chromatography on silica gel (10% MeOH in $CHCl_3$) to yield lactam **11** (105 mg, 67%) as slightly yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.83 (m, 3H), 7.70 (s, 1H), 7.50 (m, 2H), 7.41 (m, 1H), 4.14 (ψt, J = 8.4 Hz, 1H), 3.83 (ddd, J = 17.1, 14.4, 8.3 Hz, 2H), 2.97 (dd, J = 16.9, 9.1 Hz, 1H), 2.68 (dd, J = 17.0, 7.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.1, 139.3, 133.8, 133.0, 129.4, 128.1, 126.9, 126.4, 125.8, 125.0, 115.0, 56.0, 37.0, 35.2; MS (ESI): 212 (M+H).

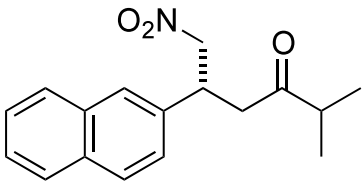
Preparation of 3-(2-naphthyl) 4-nitrobutanoic acid (**12**)



The compound **8a** (0.1 mmol, 38 mg, 1 eq) was dissolved in 2 ml of 2N NaOH. 10% v/v of methanol was added to ensure a clear solution. The reaction was stirred overnight. CH_2Cl_2 was added and the water phase was washed three times. The pH of the organic phase was decreased to pH 1 using concd HCl. The water phases were washed three times with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$. The solution was filtered and the volatiles were removed under reduced pressure. The title compound was isolated in >99% yield (26 mg, 0.1 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.90 – 7.78 (m, 3H), 7.70 (s, 1H), 7.56 – 7.46 (m, 2H), 7.34 (dd, J = 8.5, 1.8 Hz, 1H), 4.80 (dd, J = 12.7, 7.1 Hz, 1H), 4.72 (dd, J = 12.7, 7.8 Hz, 1H), 4.22 – 4.09 (m, 1H), 2.92 (d, J = 7.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 176.4, 135.7, 133.8, 133.3, 129.5, 128.3, 128.1, 127.0, 126.8, 125.2, 115.0, 79.7, 40.4, 37.7; MS (ESI): 244 (M+H).

Preparation of 2-methyl 5-(2-naphthyl) 6-nitrohexan-3-one (**13**)



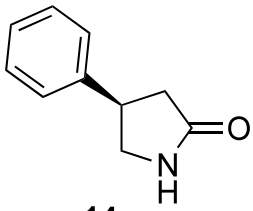
The synthesis was made according to the literature [6]

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.88 – 7.78 (m, 3H), 7.78 – 7.64 (m, 1H), 7.56 – 7.44 (m, 2H), 7.44 – 7.33 (m, 1H), 4.82 (dd, J = 12.4, 6.8 Hz, 1H), 4.74 (dd, J = 12.4, 7.8 Hz, 1H), 4.23 (m, J = 7.0 Hz, 1H), 3.12 – 2.96 (m, 2H), 2.56 (m, J = 6.9 Hz, 1H), 1.09 (d, J = 6.9 Hz, 3H), 1.03 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 211.8, 136.8, 133.8, 133.2, 129.3, 128.2, 128.1, 126.9, 126.9, 126.6, 125.4, 79.8, 43.5, 41.6, 39.6, 18.4, 18.3; MS (ESI): 286 (M+H)

10. Determination of the absolute configuration

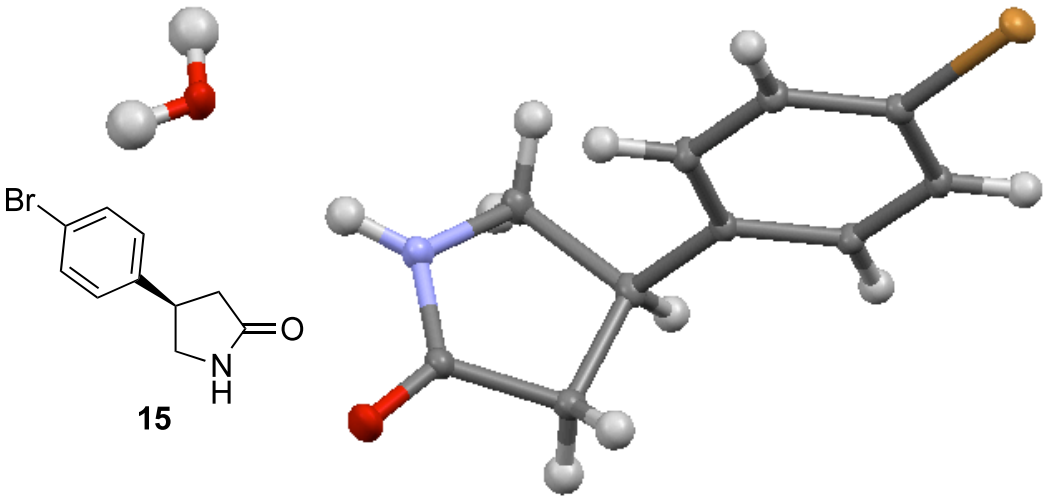
The absolute configuration was assigned based on:

a) *Polarimetry*: The optical rotation of lactam **14** was determined and assigned based by comparison with a previous report.[7]
Compound **14:** α^D = -35.5° (25°C, c = 0.95, MeOH), ref. 7: α^D = -37.8° (25°C, c = 0.95, MeOH).



14

b) *X-Ray Crystallography*: The absolute configuration of crystals obtained from lactam **15** (prepared by reduction of γ-nitrothioester **8e**) is *R*.



15

Crystal data of lactam **15**: formula C10H12Br1N1O2, M = 258.11, F(000) = 520, colourless plate, size 0.030 · 0.130 · 0.170 mm3, orthorhombic, spacegroup P 212121, Z = 4, a = 5.8120(5) Å, b = 6.7788(6) Å, c = 25.807(2) Å, α = 90°, β = 90°, γ = 90°, V = 1016.75(15) Å3, D calc. = 1.686 Mg · m-3. The crystal was measured on a Bruker Kappa Apex2 diffractometer at 123K using graphite-monochromated MoKα-radiation with λ = 0.71073 Å, Θmax = 44.202°. Minimal/maximal transmission 0.59/0.89, μ =

4.016 mm-1. The Apex2 suite has been used for data collection and integration. From a total of 59191 reflections, 8055 were independent (merging r = 0.046). From these, 5286 were considered as observed (I>2.0σ(I)) and were used to refine 128 parameters. The structure was solved by direct methods using the program SIR92. Least-squares refinement against F was carried out on all non-hydrogen atoms using the program CRYSTALS. R = 0.0221 (observed data), wR = 0.0381 (all data), GOF = 1.0800. Minimal/maximal residual electron density = -0.64/0.70 e Å-3. Chebychev polynomial weights were used to complete the refinement. Plots were produced using CAMERON. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Center, the deposition number is (CCDC 820405). Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

10. Bibliographic references:

[1] B. Vakulya, S. Varga, A. Csampai, T. Soós, *Org. Lett.* 2005, *7*, 1967-1969.
[2] S. H. McCooey, S. J. Connon, *Angew. Chem. Int. Ed.* **2005**, *44*, 6367-6370.
[3] D. Lucet, S. Sabelle, O. Kostelitz, T. Le Gall, C. Mioskowski, *Eur. J. Org. Chem.* **1999**, 2583-2591.
[4] S. E. Denmark, L. R. Marcin, *J. Org Chem.* **1993**, *58*, 3850-3856.
[5] J. Lubkoll, H. Wennemers, *Angew. Chem. Int. Ed. Engl.* 2007, **46**, 6841-6844.
[6] T. Miyazaki, X. Hanja, H. Tokuyama, T. Fukuyama, *Synlett* **2004**, 477-480.
[7] R. E. Zelle, *Synthesis* **1991**, 1023-1026.