Expanded substrate scope and catalyst optimization for the catalytic kinetic resolution of N-heterocycles

Supporting Information

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1. General Information

All reactions were carried out in oven dried glassware under N_2 using standard manifold techniques.[1] Chemicals were purchased from *Acros*, *Sigma-Aldrich* or *BioBlocks Inc.* and used without further purification unless otherwise stated. Compounds that are not described in the experimental part were synthesized according to literature procedures.

*i*PrOAc was degassed and stored over molecular sieves 4 Å. The achiral carbene catalyst 2-(2,4,6-trimethylphenyl)-2,5,6,7-tetrahydro-pyrrolo[2,1-c][1,2,4]triazol-4-ylium perchlorate was purchased from *BioBlocks Inc.* (BioBlocks Catalogue Number: BC003-13).

Flash column chromatography was performed on silica gel (*Silicycle* SiliaFlash F60, 230–400 mesh). Thin layer chromatography was performed on aluminium or glass backed plates pre-coated with silica gel (*Merck*, Silica Gel 60 F254).

NMR spectra were recorded on *Bruker* Avance 400 MHz, and Varian Mercury 300 MHz spectrometers using $CDCl_3$ as the solvent unless indicated otherwise. The residual signal of the undeuturated solvent was used as the internal standard. Infrared (IR) data was obtained on a *JASCO* FT-IR-4100 spectrometer with only major peaks being reported. Optical rotations were measured on a *JASCO* P-1010 operating at the sodium D line with a 100 mm path length cell.

Chiral HPLC (High-Performance Liquid Chromatography) and SFC (Supercritical Fluid Chromatography) was performed on *Jasco* liquid chromatography units. *Daicel* Chiralcel or Chiralpak columns (0.46 × 25 cm) were used. Details of chromatographic conditions are indicated under each compound.

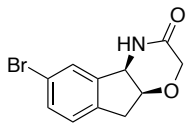
Melting points were measured on an *Electrothermal Mel-Temp* melting point apparatus and are uncorrected.

Mass spectra were recorded by the Mass Spectrometry Service Facility LOC at ETH Zürich. EI-MS (*m/z*): ESI-HIRES Micromass Autospel-ULTIMA spectrometer at 70 eV.

[1] J. Leonard, B. Lygo and G. Procter, *Advanced Practical Organic Chemistry*, Taylor & Francis, 1998.

2. Preparation of Hydroxamic Acid co-Catalyst ***2***

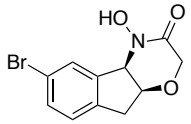
(4a*R*,9a*S*)-6-Bromo-4,4a,9,9a-tetrahydroindeno[2,1-*b*][1,4]oxazin-3(2*H*)-one[2]



A mixture of CF_3COOH (15 mL) and concentrated H_2SO_4 (4.5 mL) was cooled to 0 °C and (4a*R*,9a*S*)-4,4a,9,9a-tetrahydroindeno[2,1-*b*][1,4]oxazin-3(2*H*)-one[3] (3.00 g, 1.60 mmol) was added in one portion. *N*-Bromosuccinimide (2.90 g, 1.62 mmol) was added portion-wise via powder funnel, while keeping the temperature below 5 °C. After 1.5 h the yellow reaction mixture was slowly poured into ice-cold water (50 mL). CH_2Cl_2 (30 mL) was added and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 30 ml) and combined organic layers were washed with saturated aqueous sodium bicarbonate (20 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure to give the bromolactam as a yellow solid (3.30 g, 80 %).

$[\alpha]^{27}_D$ (c = 1.4, $CHCl_3$): +21.3; **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 169.4, 143.0, 138.2, 131.4, 127.3, 126.7, 121.0, 76.2, 66.4, 58.4, 37.2; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 8.30 (broad s, 1H), 7.48 (apparent s, 1 H), 7.45 (dd, *J* = 8.0, 1.2 Hz, 1 H), 7.15 (d, *J* = 8.0 Hz, 1 H), 4.75 (apparent t, *J* = 4.0 Hz, 1 H), 4.55 (apparent t, *J* = 4.0 Hz, 1 H), 4.15 (2d, *J* = 16.7 Hz, 2 H), 3.15 (dd, *J* = 16.8, 5.0 Hz, 1 H), 3.04 (d, *J* = 16.8 Hz, 1 H); **HRMS** (ESI): calculated for $[C_{11}H_{11}BrNO_2]^+$: m/z = 267.9968, found: m/z = 267.9971; **IR** ($\tilde{\nu}$ /cm^{-1}, neat): 3217, 1742, 1686, 1479, 1552, 1405, 1068, 769; **mp**: decomposes at 165 °C.

(4a*R*,9a*S*)-6-Bromo-4-hydroxy-4,4a,9,9a-tetrahydroindeno[2,1-*b*][1,4]oxazin-3(2*H*)-one (2)



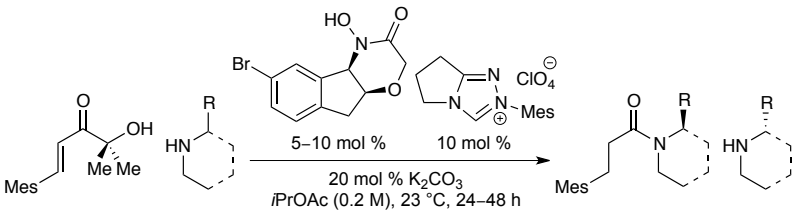
2

Bromolactam (2.70 g, 10.00 mmol) was dissolved in CH_3CN and bis(trimethylsilyl)acetamide (2.25 g, 11.00 mmol) was added dropwise. The resulting solution was heated at 80 °C for 1 h, followed by cooling to 23 °C and removal of the solvent *in vacuo* under Schlenk conditions. The resulting colorless oil was re-dissolved in CH_2Cl_2 (10 mL) and a solution of MoOPH[4] (4.86 g, 12.0 mmol) in CH_2Cl_2 (10 mL) was added dropwise over 5 min. The reaction was protected from light and left stirring for 3 days at 23 °C. The solvent was removed under reduced pressure and the resulting yellow solid was suspended in saturated aqueous tetrasodium ethylenediaminetetraacetate (Na_4EDTA) solution (200 mL) and stirred for 1 h after which pH of the solution was adjusted to 4–5 with 1 M HCl. The aqueous phase was extracted with EtOAc (6 × 70 mL) and the combined organic layers were washed with brine (50 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by flash chromatography (100 % EtOAc) afforded hydroxamic acid **2** (2.10 g, 73 %) as colorless solid.

$[\alpha]^{26}_D$ (c = 1.3, DMF): –5.8; **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 162.5, 140.8, 138.4, 131.9, 128.9, 126.5, 121.1, 78.1, 66.3, 65.5, 37.2; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.98 (s, 1 H), 7.45 (dd, *J* = 8.0, 1.5 Hz, 1 H), 7.15 (d, *J* = 8.0, 1 H), 5.10 (d, *J* = 4.3 Hz, 1 H), 4.70 (t, *J* = 4.3 Hz, 1 H), 4.95 (m, 2 H), 3.19 (dd, *J* = 16.8, 4.7 Hz, 1 H), 3.07 (d, *J* = 16.8 Hz, 1 H); **HRMS** (ESI): calculated for $[C_{11}H_{11}BrNO_3]^+$: m/z = 283.9912, found m/z = 283.9912; **IR** ($\tilde{\nu}$ /cm^{-1}, neat): 2749, 1742, 1650, 1478, 1433, 1327, 1123, 1048, 948; **mp:** decomposes at 175 °C.

[2] J. Duan, L. H. Zhang and W. R. Dolbier Jr, *Synlett*, 1999, 1245–1246.
[3] H. U. Vora, S. P. Lathrop, N. T. Reynolds, M. S. Kerr, J. Read de Alaniz and T. Rovis, *Org. Synth.*, 2010, **87**, 350–361.
[4] E. Vedejs and S. Larsen, *Org. Synth.*, 1986, **64**, 127–132.

3. General Procedure For the Kinetic Resolution of Amines



Hydroxamic acid co-catalyst **2** (7.1 mg, 25 µmol, 0.05 equiv), triazolium salt (16.4 mg, 50 µmol, 0.10 equiv), *α´*-hydroxyenone (81.4 mg, 0.35 mmol, 0.70 equiv), K_2CO_3 (13.8 mg, 0.1 mmol, 0.20 equiv) and the respective amine (0.50 mmol, 1.00 equiv) were dissolved in *i*PrOAc (2.5 mL, 0.20 M) and the reaction mixture was stirred at 23 °C for 24 hours.[5]

EtOAc (25 mL) was added, the mixture was filtered through Celite and concentrated *in vacuo*. The crude products were purified by column chromatography.

The s-factor (selectivity) was calculated using these equations:[6]

$$s = \frac{\ln[(1-C)(1-ee^{SM})]}{\ln[(1-C)(1+ee^{SM})]}$$

where ee^{SM} is the enantiomeric excess of the (acylated) recovered starting material amine or

$$s = \frac{\ln[1-C(1+ee^{PRODUCT})]}{\ln[(1-C(1-ee^{PRODUCT})]}$$

where $ee^{PRODUCT}$ is the enantiomeric excess of the amide product.

The conversion *C* was calculated using this equation:

$$C = \frac{100 \cdot ee^{SM}}{ee^{SM} + ee^{PRODUCT}}$$

The enantiomeric ratios (*er*s) were determined by HPLC- or SFC-separations. Details of chromatographic conditions are indicated under each compound. The absolute stereochemistry of the products was assigned by comparison with compounds reported in the literature or by analogy as indicated. All amides obtained showed hindered rotation on the NMR timescale or were conformational isomers at room temperature. This has been studied extensively.[7]

Racemic amides and racemic carbamates were synthesized by the previously published route.[8]

[5] Refer to Table 2 and 3 in the main article for the conditions.
[6] (*a*) H. B. Kagan and J. C. Fiaud, Kinetic Resolution. In *Topics in Stereochemistry*; Eliel, E. L.; Wilen, S. H., Eds.; Wiley, New York, 1988, **18**, 249–330; (*b*) J. M. Goodman, A.-K. Köhler and S. C. M. Alderton, *Tetrahedron Lett.*, 1999, **40**, 8715–8718. (c) http://www-jmg.ch.cam.ac.uk/tools/magnus/KinRes.html
[7] (*a*) Y. L. Chow, C. J. Colón and J. N. S. Tam, *Can. J. Chem.*, 1968, **46**, 2821–2825; (*b*) A. Rauk, D. F. Tavares, M. A. Khan, A. J. Borkent and J. F. Olson, *Can. J. Chem.*, 1983, **61**, 2572–2580.
[8] M. Binanzer, S.-Y. Hsieh and J. W. Bode, *J. Am. Chem. Soc*., 2011, **133**, 19698–19701.

4. Determination of Association Constant by NMR Titrations

A 0.2 M stock solution of hydroxamic acid **1** in $CDCl_3$ was prepared; 50 μL of this solution (0.01 mmol) was added to 13 NMR tubes individually. Different amounts of a 0.1 M stock solution of δ-valerolactam were added to each NMR tubes to obtain mixtures with 0.0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.5, and 2.0 equivalents of δ-valerolactam **9**. All NMR samples were diluted by additional $CDCl_3$ to a total volume of 500 μL. Individual chemical shift (δ) of the deshielded proton (O–H) was collected by ^{1}H NMR at 25 °C.

The association constant (K_a) and the maximal difference of chemical shifts ($\Delta\delta_{max}$, at the saturation of binding sites) were calculated by the following equation:[9a]

$$\Delta\delta = \delta - \delta_0 = \frac{\Delta\delta_{max}}{2}\left\{\frac{[LA]_t}{[HA]_t} + 1 + \frac{1}{K_a[HA]_t} \pm \sqrt{\left(\frac{[LA]_t}{[HA]_t} + 1 + \frac{1}{K_a[HA]_t}\right)^2 - 4\frac{[LA]_t}{[HA]_t}}\right\}$$

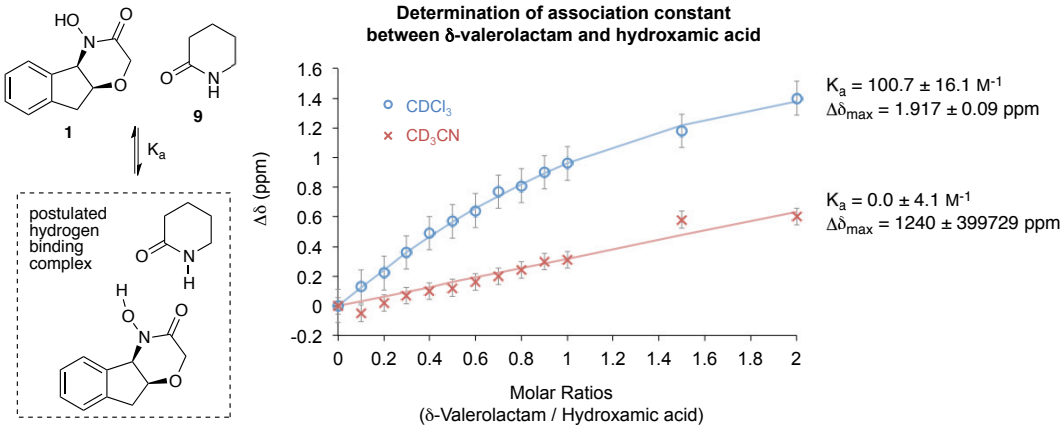
where δ is the observed chemical shift, δ_0 is the initial chemical shift of O–H in $CDCl_3$, $[LA]_t$ is the total concentration of δ-valerolactam, and $[HA]_t$ is the total concentration of hydroxamic acid.

Given the known concentration of $[HA]_t$ the above equation can be derived as the following:

$$y = \frac{\Delta\delta_{max}}{2}\left\{x + 1 + \frac{50}{K_a} \pm \sqrt{\left(x + 1 + \frac{50}{K_a}\right)^2 - 4x}\right\}$$

where x is the molar ratio of δ-valerolactam to hydroxamic acid and y is the difference of the chemical shifts.

The plots of x versus y are shown below. K_a and $\Delta\delta_{max}$ can be determined with a nonlinear least squares curve fitting method using Graphpad Prism software.[9b] The value of K_a in $CDCl_3$ is 100.7 ± 16.1 M^{-1} and $\Delta\delta_{max}$ is 1.917 ± 0.09 ppm.

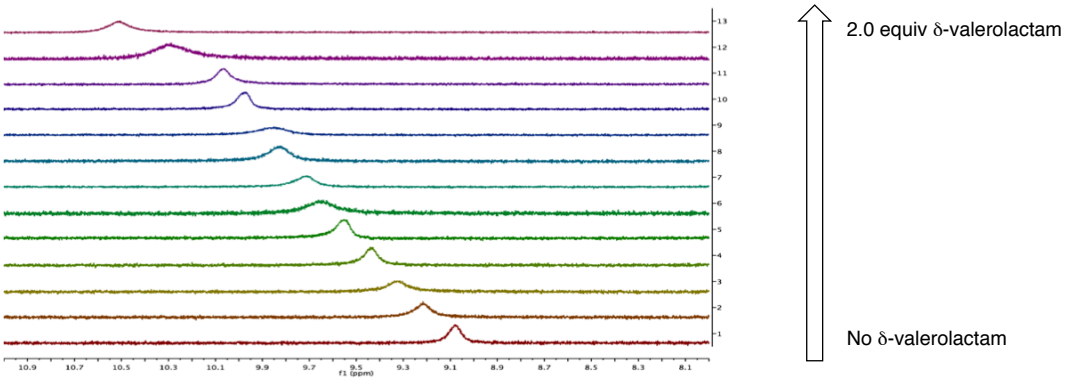


Scheme S1 NMR titration binding isotherm of hydroxamic acid with δ-valerolactam at 25 °C in $CDCl_3$ vs. CD_3CN.

[9] (*a*) Y. Cao, X. Xiao, R. Lu and Q. Guo, *J. Mol. Struct.*, 2003, **660**, 73–80; (*b*) See the software website: http://www.graphpad.com/prism/prism.htm.

The determination of association constant in CD_3CN was also followed by the same procedure. The value of K_a in CD_3CN is 0.0 ± 4.1 M^{-1} and $\Delta\delta_{max}$ is 1240 ± 399729 ppm. These ambiguous values were interpreted as almost no interaction of δ-valerolactam and hydroxamic acid.

(1) In $CDCl_3$



(2) In CD_3CN

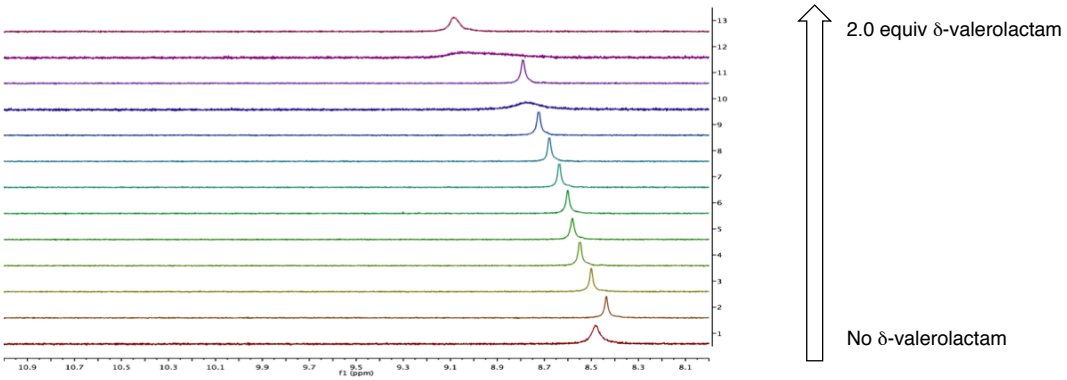
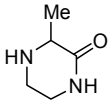


Figure S1 NMR titrations of hydroxamic acid with δ-valerolactam at 25 °C in $CDCl_3$ vs. CD_3CN.

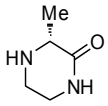
5. Resolved Amines

3-Methylpiperazin-2-one (Table 2, entry 1)

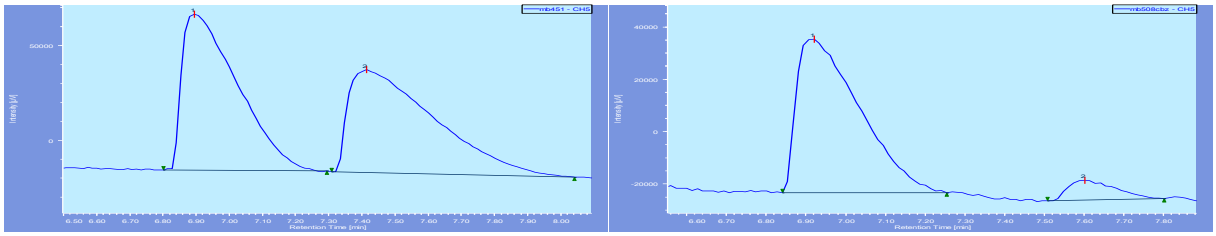


Racemic 3-methylpiperazin-2-one[10] (57.1 mg, 0.50 mmol) was resolved according to the general procedure. Recovered amine: 24 mg (42 %, *er* = 90:10); acylated product: 80 mg (56 %, *er* = 79:21); calculated conversion: 58 %; **s = 9**;

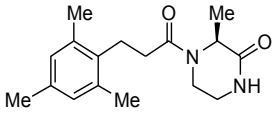
Recovered amine: **(3*R*)-3-methylpiperazin-2-one**



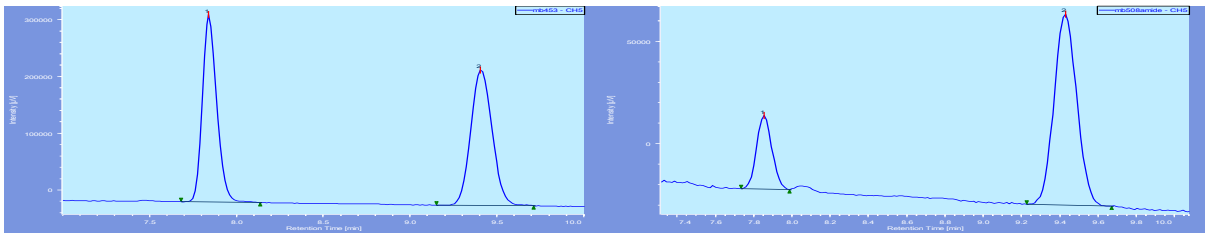
The amine was protected with benzyl chloroformate to determine the *er*:[11] $[\alpha]^{28}_{D}$ (c = 0.2, $CHCl_3$): +/– 0.0; **SFC**: column: Daicel Chiralpak ASH (4.6 × 250 mm); gradient: 5 % *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: t_R = 6.8 min (major) and 7.3 min (minor).



Amide product: **(3*S*)-4-(3-Mesitylpropanoyl)-3-methylpiperazin-2-one**

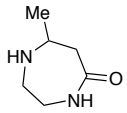


$[\alpha]^{24}_{D}$ (c = 4.0, $CHCl_3$): +59.6; at room temperature the ratio of rotamers was 50:50 as determined by ^{1}H NMR; **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 171.9, 170.8, 170.5, 170.3, 136.0, 135.9, 135.7, 134.2, 134.1, 129.0, 53.9, 51.2, 41.3, 41.2, 38.9, 34.4, 32.4, 31.8, 24.7, 24.6, 20.7, 19.7, 17.8, 16.4; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 6.83 (s, 2 H), 5.05 (q, *J* = 7.1 Hz, 0.5 H), 4.70 (dd, *J* = 13.6, 2.4 Hz, 0.5 H), 4.28 (q, *J* = 7.1 Hz, 0.5 H), 3.69 (br d, *J* = 12.6 Hz, 0.5 H), 3.46–3.21 (m, 2.5 H), 3.05–2.90 (m, 2.5 H), 2.58–2.32 (m, 2 H), 2.28 (s, 6 H), 2.23 (s, 3 H); 1.44 (t, *J* = 6.5 Hz, 3 H); **HRMS** (ESI): calculated for $[C_{17}H_{25}N_2O_2]^+$: m/z = 289.1911, found: m/z = 289.1914; **IR** ($\tilde{\nu}$ /cm^{-1}, neat): 3244, 2998, 2944, 2921, 1668, 1648, 1457, 1427, 1332, 1208, 1091, 1062; **SFC**: column: Daicel Chiralpak ODH (4.6 × 250 mm); gradient: 5 % *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: t_R = 7.8 min (minor) and 9.4 min (major).



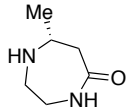
[10] K. M. Beck, K. E. Hamlin and A. W. Westo, *J. Am. Chem. Soc.*, 1951, **74**, 605–608.
[11] Substituted oxoazaheterocyclyl compounds, *Patent US* 2004/0102450 (compound 1735).

7-Methyl-1,4-diazepan-5-one (Table 2, entry 2)

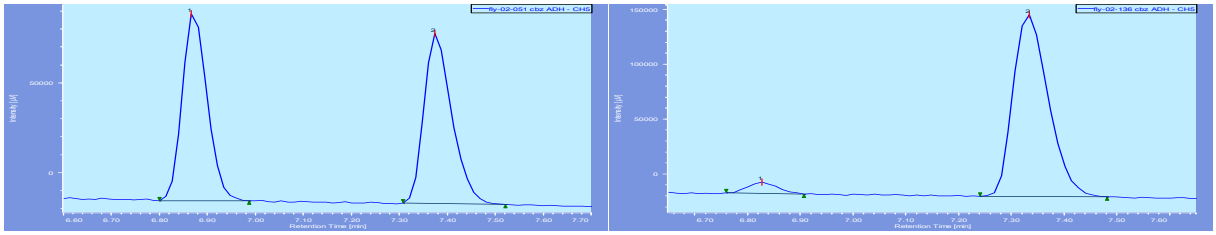


Racemic 7-methyl-1,4-diazepan-5-one[12] (64.1 mg, 0.50 mmol) was resolved according to the general procedure. Recovered amine: 27 mg (43 %, *er* = 95:5); acylated product: 81 mg (54 %, *er* = 88:12); calculated conversion: 54 %; **s = 22**;

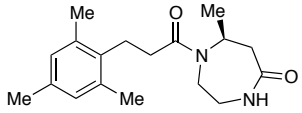
Recovered amine: **(7*R*)-7-methyl-1,4-diazepan-5-one**



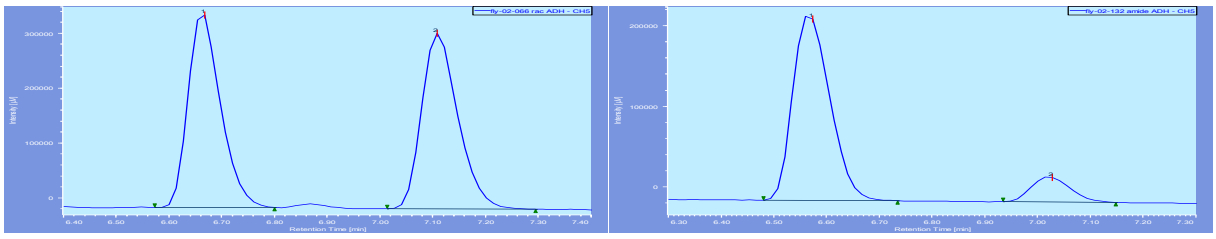
^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.25 (br, 1H), 3.28 (ddd, *J* = 14.1, 9.8, 4.1 Hz, 1 H), 3.15–2.98 (m, 2 H), 2.94 (dq, *J* = 13.1, 6.4 Hz, 1 H), 2.77 (dd, *J* = 13.1, 9.7 Hz, 1 H), 2.50 (dd, *J* = 14.2, 9.7 Hz, 1H), 2.35 (apparent d, *J* = 14.2 Hz, 1 H), 2.07 (br, 1 H), 1.09 (d, *J* = 6.4 Hz, 3H). The amine was protected with benzyl chloroformate to determine the *er*: **$[\alpha]^{26}_D$** (c = 1.0, $CHCl_3$): –20.8; **SFC**: column: Daicel Chiralpak ADH (4.6 × 250 mm); gradient: 5 % *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: t_R = 6.9 min (minor) and 7.4 min (major).



Amide product: **(7*S*)-1-(3-Mesitylpropanoyl)-7-methyl-1,4-diazepan-5-one**

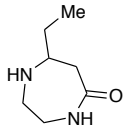


$[\alpha]^{26}_D$ (c = 1.0, $CHCl_3$): +20.1; at room temperature the ratio of rotamers was 55:45 as determined by ^{1}H NMR; **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 175.9, 174.7, 171.4, 171.2, 136.1, 136.0, 135.7, 134.5, 134.4, 129.1, 47.0, 43.8, 43.5, 42.8, 41.9, 39.1, 33.2, 32.6, 25.0, 25.0, 21.1, 20.8, 19.8, 16.6, 15.5; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.42 (br, 0.45 H), 7.16 (br, 0.55 H), 6.84 (s, 2 H), 5.26 (apparent dd, *J* = 6.0 Hz, 4.5 Hz, 0.45 H), 4.77 (apparent d, *J* = 15.3 Hz, 0.55 H), 4.18 (apparent dd, *J* = 6.3 Hz, 4.1 Hz, 0.55 H), 3.69 (apparent d, *J* = 15.4 Hz, 0.45 H), 3.36–3.30 (m, 0.55 H), 3.30–3.21 (m, 1 H), 3.18–3.08 (m, 1 H), 3.04–2.87 (m, 2.55 H), 2.75 (apparent dd, *J* = 14.7 Hz, 2.2 Hz, 0.45 H), 2.64 (apparent dd, *J* = 14.3 Hz, 2.2 Hz, 0.45 H), 2.58–2.37 (m, 3 H), 2.29 (s, 6 H), 2.24 (s, 3 H), 1.23 (overlaping d, *J* = 7.0 Hz, 3 H); **HRMS** (ESI): calculated for $[C_{18}H_{27}N_2O_2]^+$: m/z = 303.2067, found: m/z = 303.2070; **IR** (ν/cm^{-1}, neat): 3272, 2970, 2919, 1670, 1638, 1427, 1212, 1126, 754; **SFC**: column: Daicel Chiralpak ADH (4.6 × 250 mm); gradient: 5 % *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: t_R = 6.7 min (major) and 7.1 min (minor).



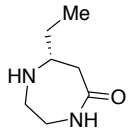
[12] Quinazolinone and isoquinolinone acetamide derivatives as V3 modulators and their preparation, pharmaceutical compositions and use in the treatment of diseases, *European Patent* EP2069315.

7-Ethyl-1,4-diazepan-5-one (Table 2, entry 3)

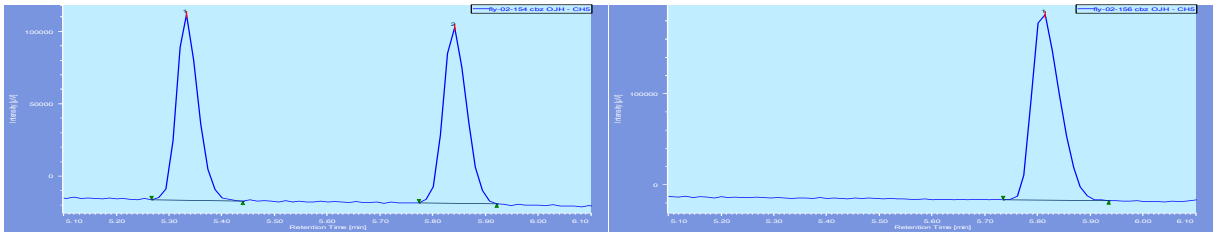


Racemic 7-ethyl-1,4-diazepan-5-one (71.1 mg, 0.50 mmol) was resolved according to the general procedure. Recovered amine: 25 mg (34 %, *er* > 99:1); acylated product: 76 mg (48 %, *er* = 78:22); calculated conversion: 64 %; **s > 20**;

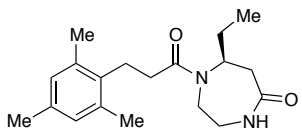
Recovered amine: **(7*R*)-7-Ethyl-1,4-diazepan-5-one**



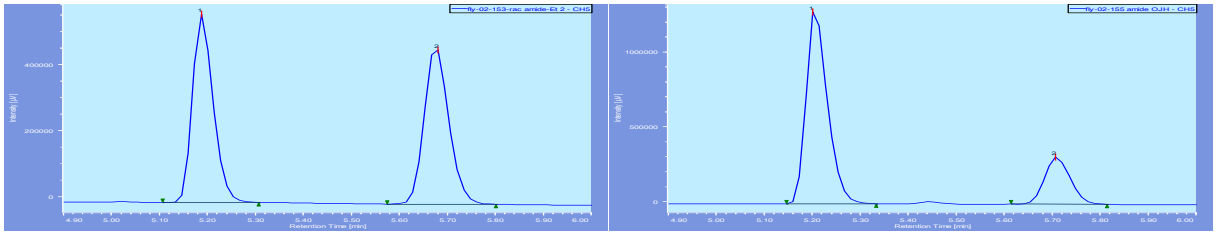
[α]$^{26}_{D}$ (c = 1.0, $CHCl_3$): +1.11; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = δ 7.25 (br, 1 H), 3.34–3.22 (m, 1 H), 3.09 (ddd, *J* = 20.3, 13.0, 5.5 Hz, 2 H), 2.76 (t, *J* = 11.4 Hz, 1 H), 2.66 (dd, *J* = 13.9, 7.2 Hz, 1 H), 2.55–2.35 (m, 2 H), 2.05 (br, 1 H), 1.49–1.34 (m, 2 H), 0.88 (t, *J* = 7.4 Hz, 3 H). The amine was protected with benzyl chloroformate to determine the *er*: **SFC**: column: Daicel Chiralpak OJH (4.6 × 250 mm); gradient: 5 % *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: t_R = 5.3 min (minor) and 5.8 min (major).



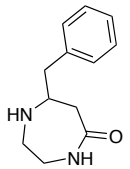
Amide product: **(7*S*)-7-Ethyl-1-(3-mesitylpropanoyl)-1,4-diazepan-5-one**



[α]$^{26}_{D}$ (c = 1.0, $CHCl_3$): +7.9; at room temperature the ratio of rotamers was 60:40 as determined by ^{1}H NMR; **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 176.1, 174.9, 172.0, 171.7, 136.1, 136.1, 135.7, 134.5, 134.5, 129.2, 129.1, 52.8, 47.6, 43.7, 43.5, 43.0, 42.6, 42.1, 39.2, 33.2, 32.8, 25.1, 25.0, 23.3, 22.5, 20.8, 19.8, 19.8, 10.5; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.40 (br, 0.4 H), 7.14 (br, 0.6 H), 6.85 (s, 2 H), 5.09–4.92 (m, 0.4 H), 4.81 (dd, *J* = 13.3 Hz, 1.7 Hz, 0.6 H), 4.00–3.81 (m, 0.6 H), 3.72 (apparent d, *J* = 15.0 Hz, 0.4 H), 3.39–3.18 (m, 1.6 H), 3.18–3.08 (m, 0.8 H), 3.08–2.87 (m, 2H), 2.80 (dd, *J* = 13.2 Hz, 10.5 Hz, 0.6 H), 2.73 (dd, *J* = 14.8 Hz, 2.7 Hz, 0.4 H), 2.65–2.55 (m, 1H), 2.55–2.35 (m, 2.6 H), 2.29 (s, 6H), 2.24 (s, 3H), 1.86–1.45 (m, 2H), 1.04–0.73 (m, 3H); **HRMS** (ESI): calculated for $[C_{19}H_{29}N_2O_2]^+$: m/z = 317.2224, found: m/z = 317.2217; **IR** (ν/cm^{-1}, neat): 3272, 2965, 2921, 1671, 1640, 1429, 1211, 1127, 961, 754; **SFC**: column: Daicel Chiralpak OJH (4.6 × 250 mm); gradient: 5 % *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: t_R = 5.2 min (major) and 5.7 min (minor).

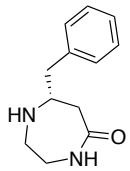


7-Benzyl-1,4-diazepan-5-one (Table 2, entry 4)

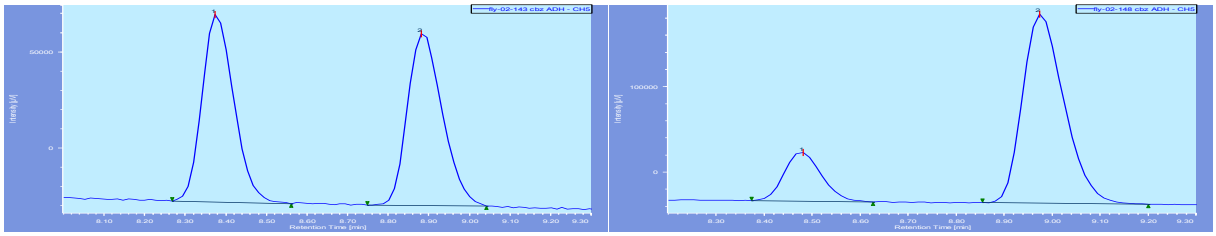


Racemic 7-benzyl-1,4-diazepan-5-one (102.1 mg, 0.50 mmol) was resolved according to the general procedure. Recovered amine: 40 mg (39 %, *er* = 81:19); acylated product: 75 mg (40 %, *er* = 94:6); calculated conversion: 41 %; **s = 30**;

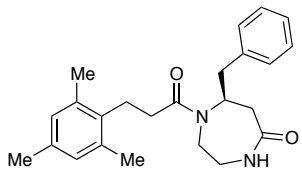
Recovered amine: **(7*R*)-7-benzyl-1,4-diazepan-5-one**



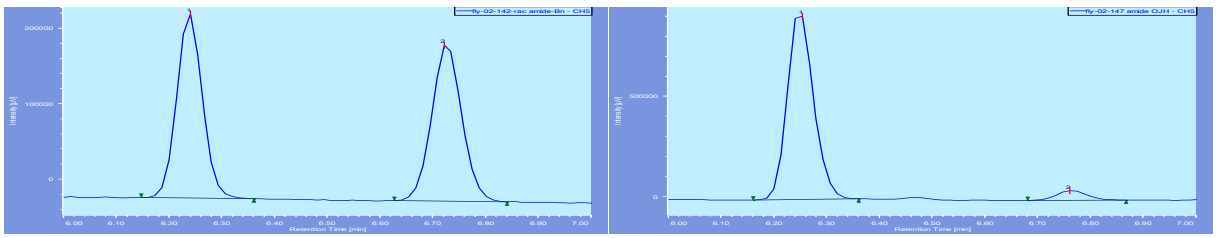
$[\alpha]^{26}_D$ (c = 1.0, $CHCl_3$): –12.0; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.44–7.10 (m, 6 H), 3.43–3.32 (m, 1 H), 3.16 (dt, *J* = 13.9, 6.4 Hz, 1 H), 3.12–3.01 (m, 2H), 2.85 (dd, *J* = 13.5, 4.5 Hz, 1 H), 2.75 – 2.54 (m, 4 H), 2.09 (br, 1 H); The amine was protected with benzyl chloroformate to determine the *er*: **SFC**: column: Daicel Chiralpak ADH (4.6 × 250 mm); gradient: 5 % *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: t_R = 8.4 min (minor) and 8.9 min (major).



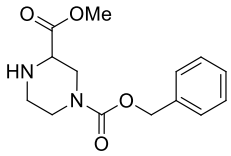
Amide product: **(7*S*)-7-benzyl-1-(3-mesitylpropanoyl)-1,4-diazepan-5-one**



$[\alpha]^{26}_D$ (c = 1.0, $CHCl_3$): +7.9; at room temperature the ratio of rotamers was 65:35 as determined by ^{1}H NMR; **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 175.5, 174.4, 172.2, 171.6, 137.4, 137.2, 136.2, 136.2, 135.8, 135.7, 134.6, 134.5, 129.2, 129.1, 129.0, 129.0, 128.6, 127.2, 126.8, 53.6, 47.5, 44.3, 43.6, 42.9, 42.9, 41.6, 39.7, 36.5, 33.1, 32.4, 24.9, 24.9, 20.9, 19.8, 19.7; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.37–7.20 (m, 4 H), 7.17–7.07 (m, 1.35 H), 6.85 (overlaping s, *J* = 9.5 Hz, 2 H), 6.72 – 6.61 (m, 0.65 H), 5.48 (td, *J* = 8.5 Hz, 3.0 Hz, 0.35 H), 5.03–4.88 (m, 0.65 H), 4.19 (td, *J* = 9.3 Hz, 5.4 Hz, 0.65 H), 3.72 (apparent d, *J* = 15.7 Hz, 0.35 H), 3.48–3.30 (m, 1.65 H), 3.26–3.20 (m, 0.7 H), 3.12 (ddd, *J* = 14.5 Hz, 9.4 Hz, 2.6 Hz, 0.65 H), 3.03 (ddd, *J* = 15.8 Hz, 9.7 Hz, 6.1 Hz, 1H), 2.95–2.83 (m, 2 H), 2.83–2.75 (m, 0.65 H), 2.74–2.59 (m, 2.35 H), 2.42–2.29 (m, 0.65 H), 2.27–2.25 (m, 6 H), 2.21 (dd, *J* = 11.4 Hz, 5.2 Hz, 0.65 H), 2.15 (s, 3 H), 1.97 (ddd, *J* = 16.2 Hz, 11.6 Hz, 4.9 Hz, 0.7 H); **HRMS** (ESI): calculated for $[C_{24}H_{31}N_2O_2]^+$: m/z = 379.2380, found: m/z = 379.2372; **IR** (ν/cm^{-1}, neat): 3264, 3004, 2920, 1671, 1643, 1203, 1123, 753, 701; **SFC**: column: Daicel Chiralpak OJH (4.6 × 250 mm); gradient: 5 % *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: t_R = 6.2 min (major) and 6.7 min (minor).

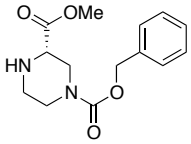


1-Benzyl 3-methyl piperazine-1,3-dicarboxylate (Table 2, entry 5)

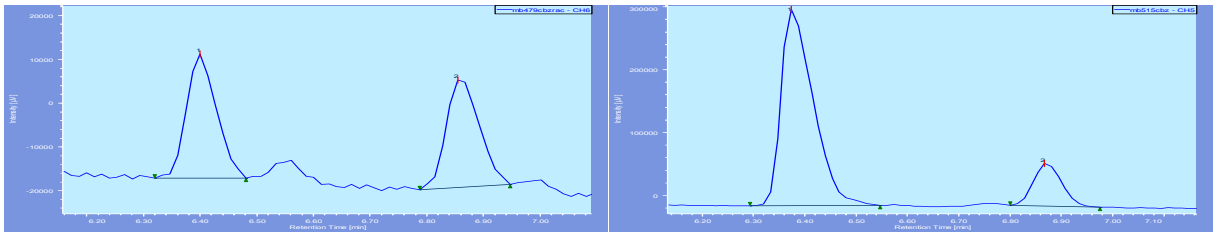


Racemic 1-benzyl 3-methyl piperazine-1,3-dicarboxylate[13] (139.2 mg, 0.5 mmol) was resolved according to the general procedure. Recovered amine: 77 mg (55 %, *er* = 84:16); acylated product: 99 mg (44 %, *er* = 92:8); calculated conversion: 45 %; **s = 23**;

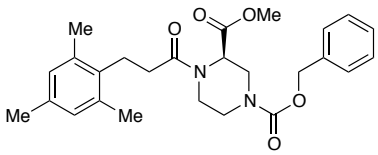
Recovered amine: **1-Benzyl 3-methyl (2*S*)-piperazine-1,3-dicarboxylate**



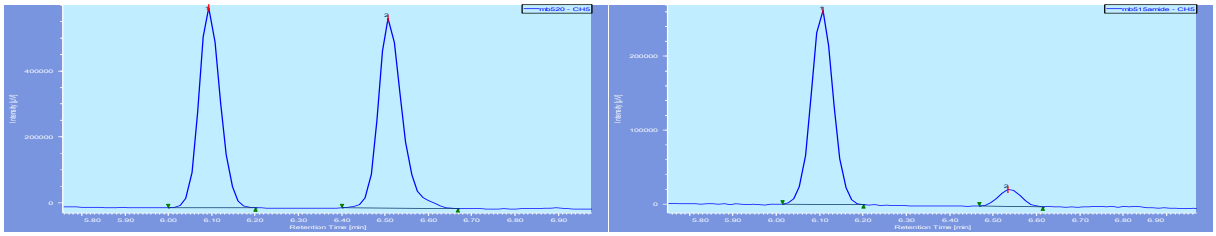
The amine was protected with benzyl chloroformate to determine the *er*: $[\alpha]^{25}_{D}$ (c = 1.3, $CHCl_3$): –7.1; **SFC**: column: Daicel Chiralpak OJH (4.6 × 250 mm); gradient: 5 % *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: t_R = 6.4 min (major) and 6.9 min (minor).



Acylated product: **1-Benzyl 3-methyl (3*R*)-4-(3-mesitylpropanoyl)piperazine-1,3-dicarboxylate**

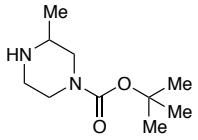


$[\alpha]^{25}_{D}$ (c = 3.8, $CHCl_3$): +2.9; **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 172.9, 172.6, 154.8, 136.2, 136.1, 136.0, 135.7, 135.6, 134.33, 134.27, 129.0, 128.5, 128.2, 127.94, 127.91, 67.5, 55.7, 52.7, 52.5, 51.9, 44.6, 44.4, 42.9, 42.4, 32.5, 32.1, 24.6, 24.5, 20.8, 19.7, 19.64, 19.57; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.40–7.28 (m, 5 H), 6.84 (br s, 2 H), 5.25 (dd, *J* = 4.5, 1.7 Hz, 1 H), 5.21–5.12 (m, 1 H), 5.11–5.04 (m, 1 H), 4.66 (dt, *J* = 13.6 Hz, 1.8 Hz, 0.5 H), 4.59 (d, *J* = 13.6 Hz, 0.5 H), 4.50–4.20 (m, 0.5 H), 4.18-3.90 (m, 1 H), 3.80–3.40 (m, 4.5 H), 3.11 (dd, J = 13.7, 4.2 Hz, 1 H), 3.02–2.70 (m, 4 H), 2.57–2.37 (m, 2 H), 2.30–2.23 (m, 9 H); **HRMS** (ESI): calculated for $[C_{26}H_{33}N_2O_5]^+$: m/z = 453.2384, found: m/z = 453.2371; **IR** ($\tilde{\nu}$ /cm^{-1}, neat): 3002, 2948, 2918, 1743, 1704, 1657, 1427, 1226, 1119; **SFC**: column: Daicel Chiralpak OJH (4.6 × 250 mm); gradient: 5 % *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: t_R = 6.1 min (major) and 6.5 min (minor).



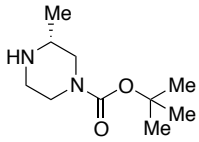
[13] Supplier: Fluorochem (CAS-number: 129799-11-7).

tert-Butyl 3-methylpiperazine-1-carboxylate (Table 2, entry 6)

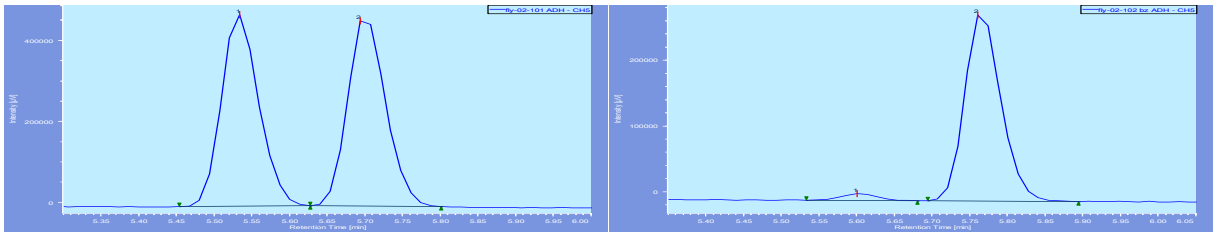


Racemic *tert*-butyl 3-methylpiperazine-1-carboxylate[14] (100.1 mg, 0.50 mmol) was resolved according to the general procedure. Recovered (Bz-protected) amine: 60 mg (35 %, *er* = 97:3); acylated product: 40 mg (21 %, *er* = 86:14); calculated conversion: 57 %; **s = 21**;

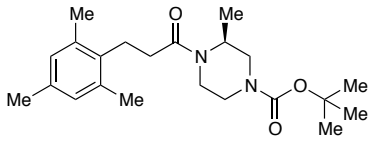
Recovered amine: **(3*R*)-*tert*-Butyl 3-methylpiperazine-1-carboxylate**



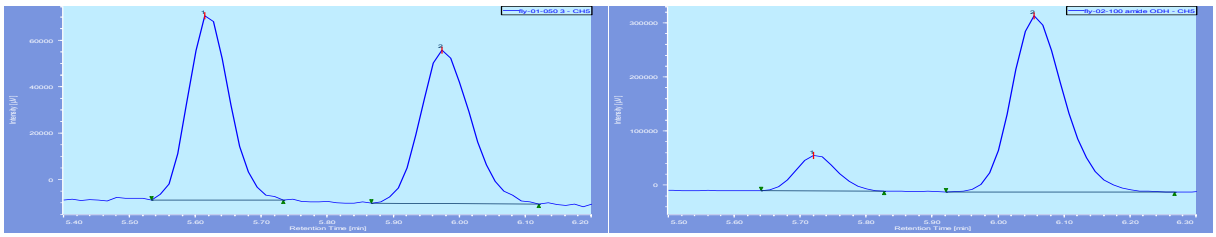
The amine was protected with benzoyl chloride to determine the *er*: $[\alpha]^{26}_{D}$ (c = 1.0, $CHCl_3$): –21.3; **SFC**: column: Daicel Chiralpak ADH (4.6 × 250 mm); gradient: 5 % *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: t_R = 5.5 min (minor) and 5.7 min (major).



Amide product: ***tert*-Butyl (3*S*)-4-(3-mesitylpropanoyl)-3-methylpiperazine-1-carboxylate**

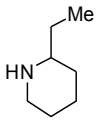


$[\alpha]^{26}_{D}$ (c = 1.0, $CHCl_3$): +14.5; at room temperature the ratio of rotamers was 50:50 as determined by ^{1}H NMR; **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 171.2, 155.1, 136.2, 135.7, 134.7, 129.2, 80.2, 48.9, 48.5, 47.1, 44.7, 44.1, 43.0, 40.4, 36.2, 32.9, 32.3, 28.5, 25.0, 20.9, 19.9, 16.1, 15.1; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 6.84 (s, 2 H), 4.81 (br, 0.5 H), 4.42 (apparent d, *J* = 11.7 Hz, 0.5 H), 4.01 (br, 0.5 H), 3.86 (br, 2 H), 3.42 (apparent d, *J* = 12.4 Hz, 0.5 H), 3.22 (apparent t, *J* = 11.4 Hz, 0.5 H), 3.04–2.61 (m, 4.5 H), 2.60–2.34 (m, 2 H), 2.29 (s, 6 H), 2.25 (s, 3 H), 1.46 (s, 9H), 1.16 (br, 3H); **HRMS** (ESI): calculated for $[C_{22}H_{35}N_2O_3]^+$: m/z = 375.2642, found: m/z = 375.2634; **IR** (ν/cm^{-1}, neat): 2973, 2921, 1698, 1646, 1421, 1365, 1267, 1172, 1134, 1038, 852; **SFC**: column: Daicel Chiralpak ODH (4.6 × 250 mm); gradient: 5 % *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: t_R = 5.7 min (minor) and 6.1 min (major).



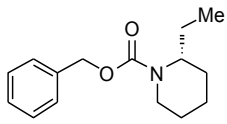
[14] Daiichi Pharmaceutical Co., LTD. *European Patent*, EP1591443 A1, 2005 (Page 61).

2-Ethyl piperidine (Table 3, entry 1)[8]

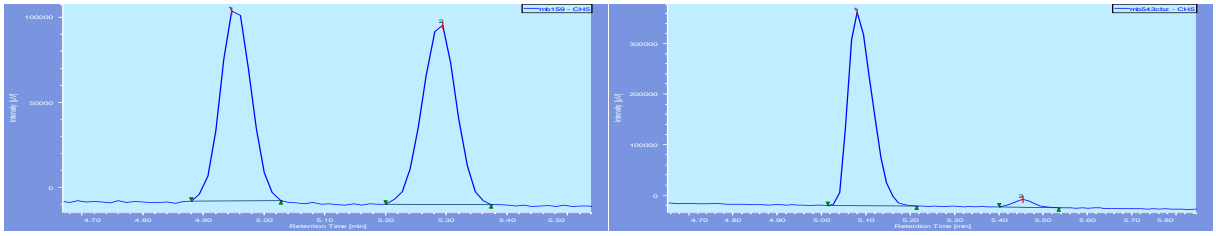


Racemic 2-ethyl piperidine (56.6 mg, 0.5 mmol) was resolved according to the general procedure. Recovered (Cbz-protected) amine: 49 mg (40 %, *er* = 97:3); acylated product: 79 mg (55 %, *er* = 86:14); calculated conversion: 57 %; **s = 21**;

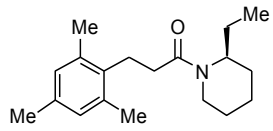
The recovered amine was characterized as its Cbz-derivative: **(*R*)-Benzyl 2-ethylpiperidine-1-carboxylate**[15]



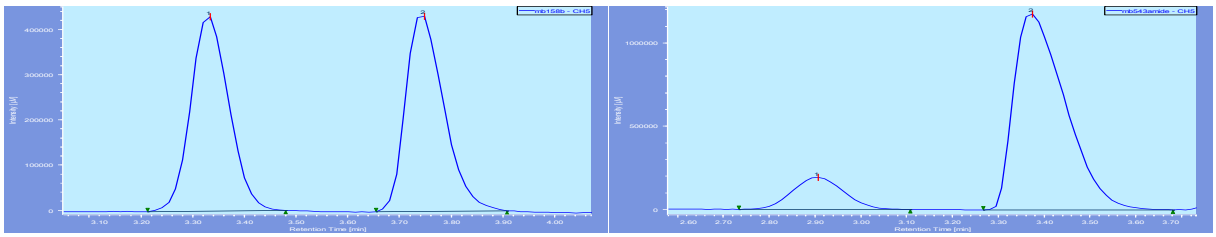
$[\alpha]^{23}_{D}$ (c = 2.0, $CHCl_3$): –16.8; **SFC**: column: Daicel Chiralpak ADH (4.6 × 250 mm); gradient: 5 % *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: t_R = 5.0 min (major) and 5.4 min (minor).



Acylated product: **(*S*)-1-(3-Mesitylpropanoyl)-2-ethylpiperidine**

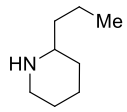


$[\alpha]^{23}_{D}$ (c = 3.5, $CHCl_3$): +8.5; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 6.82 (s, 2 H), 4.78–4.69 (m, 0.5 H), 4.59 (dd, *J* = 13.6, 3.1 Hz, 0.5 H), 3.74 (q, *J* = 6.7 Hz, 0.5 H), 3.57 (dd, *J* = 13.3, 2.8 Hz, 0.5 H), 3.06–2.89 (m, 2.5 H), 2.58 (dt, *J* = 13.3, 2.1 Hz, 0.5 Hz), 2.52–2.35 (m, 2 H), 2.30 (s, 6 H), 2.24 (s, 3 H), 1.79–1.24 (m, 8 H), 0.86 (t, *J* = 7.5 Hz, 1.5 H), 0.84 (t, *J* = 7.5 Hz, 1.5 H); **SFC**: column: Daicel Chiralpak ASH (4.6 × 250 mm); gradient: 5 % *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: t_R = 3.3 min (minor) and 3.7 min (major).



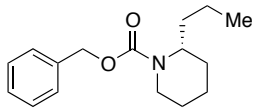
[15] S. J. Aitken, G. Grogan, C. S.-Y. Chow, N. J. Turner and S. L. Flitsch, *J. Chem. Soc., Perkin Trans. 1*, 1998, 3365–3370.

2-Propyl piperidine (Table 3, entry 2)[8]

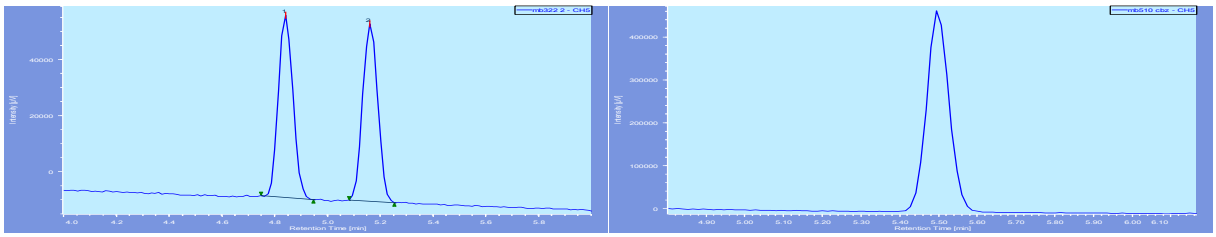


Racemic 2-propyl piperidine (63.6 mg, 0.5 mmol) was resolved according to the general procedure. Recovered (Cbz-protected) amine: 51 mg (39 %, *er* > 99:1); acylated product: 75 mg (50 %, *er* = 82:18); calculated conversion: 61 %; **s > 22**;

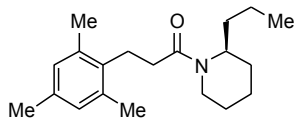
The recovered amine was characterized as its Cbz-derivative: **Benzyl (2*R*)-2-propylpiperidine-1-carboxylate**[16]



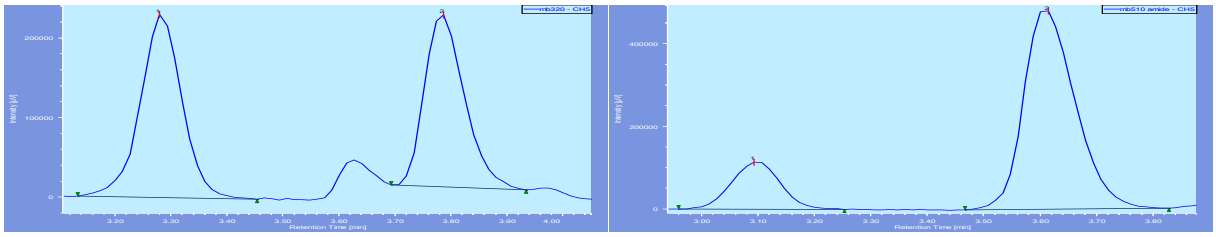
$[\alpha]^{23}_D$ (c = 0.9, $CHCl_3$): –22.8; **SFC**: column: Daicel Chiralpak ADH (4.6 × 250 mm); gradient: 5 % *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: t_R = 4.9 min (major) and 5.2 min (minor).



Acylated product: **(*S*)-1-(3-Mesitylpropanoyl)-2-propylpiperidine**

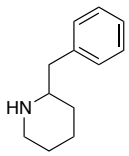


$[\alpha]^{23}_D$ (c = 3.6, $CHCl_3$): +16.7; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 6.84 (s, 2 H), 4.88–4.78 (m, 0.5 H), 4.58 (dd, *J* = 13.4, 3.4 Hz, 0.5 H), 3.81 (q, *J* = 7.3 Hz, 0.5 H), 3.56 (dd, *J* = 13.4, 2.8 Hz, 0.5 H), 3.08–2.88 (m, 2.5 H), 2.61 (dt, *J* = 13.6, 2.5 Hz, 0.5 Hz), 2.52–2.35 (m, 2 H), 2.29 (s, 6 H), 2.24 (s, 3 H), 1.70–1.15 (m, 10 H), 0.93 (t, *J* = 7.3 Hz, 1.5 H), 0.90 (t, *J* = 7.3 Hz, 1.5 H); **SFC**: column: Daicel Chiralpak ASH (4.6 × 250 mm); gradient: 5 % *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: t_R = 3.2 min (minor) and 3.8 min (major).



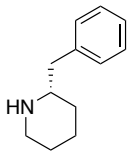
[16] K. Nagata, K. Nishimura, M. Yokoya and T. Itoh, *Heterocycles*, 2006, **70**, 335–344.

2-Benzyl piperidine (Table 3, entry 3)[8]

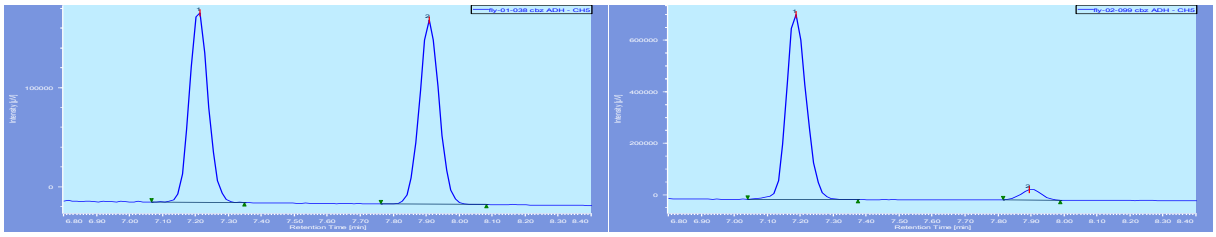


Racemic 2-benzyl piperidine (87.6 mg, 0.5 mmol) was resolved according to the general procedure. Recovered (Cbz-protected) amine: 41 mg (27 %, *er* = 94:6); acylated product: 76 mg (44 %, *er* = 91:9); calculated conversion: 52 %; **s = 29**;

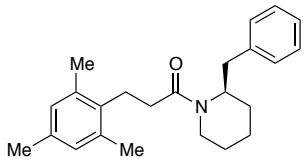
Recovered amine: **(2*S*)-2-Benzyl piperidine**



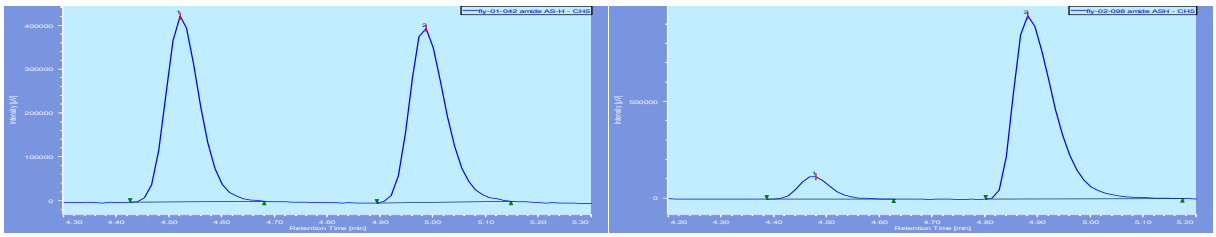
The amine was protected with benzyl chloroformate to determine the *er*: $[\alpha]^{24}_{D}$ (c = 1.0, $CHCl_3$): +32.0; **SFC**: column: Daicel Chiralpak ASH (4.6 × 250 mm); gradient: 5 % *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: t_R = 7.2 min (major) and 7.9 min (minor).



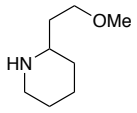
Acylated product: **(2*R*)-2-Benzyl-1-(3-mesitylpropanoyl)piperidine**



$[\alpha]^{23}_{D}$ (c = 1.0, $CHCl_3$): –32.2; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.33–7.24 (m, 3 H), 7.23–7.18 (m, 1 H), 7.07 (d, *J* = 7.0 Hz, 1 H), 6.82 (d, *J* = 15.7 Hz, 2 H), 5.08 (dd, *J* = 13.1, 6.6 Hz, 0.5 H), 4.76–4.68 (m, 0.5 H), 4.11–3.89 (m, 0.5 H), 3.62 (d, *J* = 13.1 Hz, 0.5 H), 3.19–3.06 (m, 1 H), 2.95–2.78 (m, 3 H), 2.78–2.58 (m, 1 H), 2.45–2.35 (m, 1 H), 2.28 (s, 2.7 H), 2.25 (s, 1.3 H), 2.24 (s, 1.7 H), 2.20–2.11 (m, 1 H), 2.15 (s, 3.3 H), 1.95–1.29 (m, 6 H); **SFC**: column: Daicel Chiralpak ADH (4.6 × 250 mm); gradient: 5 % *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: t_R = 4.5 min (minor) and 4.9 min (major).

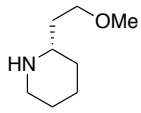


2-(2-Methoxyethyl)piperidine (Table 3, entry 4)

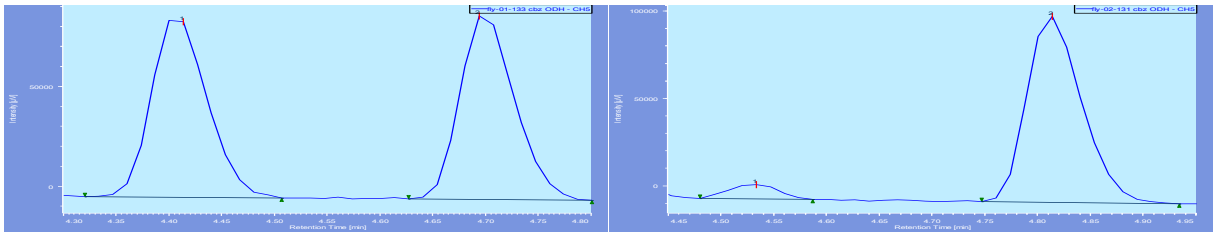


Racemic 2-(2-methoxyethyl)piperidine[17] (71.6 mg, 0.50 mmol) was resolved according to the general procedure. Recovered amine: 33 mg (46 %, *er* = 94:6); acylated product: 80 mg (51 %, *er* = 90:10); calculated conversion: 52 %; **s = 26**;

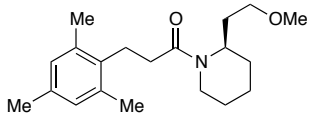
Recovered amine: **(2*S*)-2-(2-Methoxyethyl)piperidine**



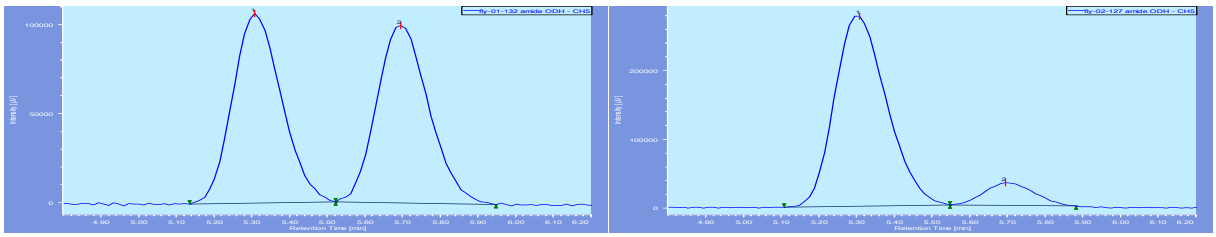
The amine was protected with benzyl chloroformate to determine the *er*:[18] **$[\alpha]^{25}_D$** (c = 1.0, $CHCl_3$): –22.1; **SFC**: column: Daicel Chiralpak ODH (4.6 × 250 mm); gradient: 5 % *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: t_R = 4.4 min (minor) and 4.7 min (major).



Amide product: **(2*R*)-1-(3-Mesitylpropanoyl)-2-(2-methoxyethyl)piperidine**

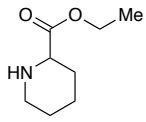


$[\alpha]^{25}_D$ (c = 1.0, $CHCl_3$): +3.2; at room temperature the ratio of rotamers was 60:40 as determined by ^{1}H NMR; **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 171.7, 171.1, 136.3, 136.2, 135.5, 135.4, 135.2, 135.1, 129.1, 129.0, 70.7, 68.9, 58.8, 58.7, 49.5, 45.9, 41.1, 36.5, 33.0, 32.3, 30.1, 30.0, 29.3, 28.8, 26.3, 25.6, 25.4, 25.2, 20.9, 19.8, 19.8, 19.3, 19.2; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 6.84 (s, 2 H), 4.93 (apparent t, *J* = 6.9 Hz, 0.4 H), 4.60 (apparent dd, *J* = 13.7 Hz, 3.1 Hz, 0.6 H), 4.13–4.03 (m, 0.6 H), 3.58 (apparent dd, *J* = 13.7 Hz, 2.6 Hz, 0.4 H), 3.46–3.22 (m, 2 H), 3.33 (s, 1.2 H), 3.26 (s, 1.8 H), 3.09 (td, *J* = 13.6 Hz, 2.1 Hz, 0.4 H), 3.04–2.85 (m, 2 H), 2.62–2.37 (m, 2.6 H), 2.31 (s, 6H), 2.25 (s, 3 H), 2.05–1.92 (m, 1 H), 1.80–1.68 (m, 1 H), 1.68–1.55 (m, 4 H), 1.55–1.45 (m, 1 H), 1.45–1.28 (m, 1 H); **HRMS** (ESI): calculated for $[C_{20}H_{32}NO_2]^+$: m/z = 318.2428, found: m/z = 318.2430; **IR** (ν/cm^{-1}, neat): 2931, 2864, 1638, 1446, 1423, 1269, 1113, 1013, 852; **SFC**: column: Daicel Chiralpak ODH (4.6 × 250 mm); isocratic 10 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: t_R = 5.3 min (major) and 5.7 min (minor).



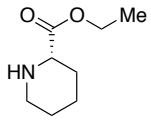
[17] Supplier: Sigma-Aldrich (MDL number: MFCD07368304).
[18] Pfizer Inc., K. O. K. Cameron and D. A. Perry, Patent WO2010/67233 A1, 2010 (Page 60).

Ethyl piperidine-2-carboxylate (Table 3, entry 5)[8]

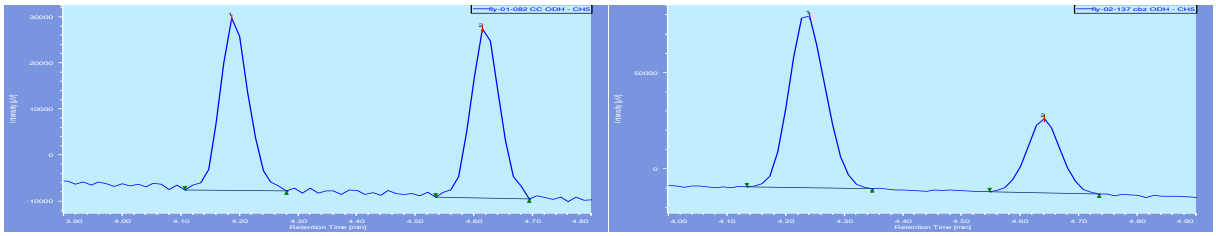


Racemic ethyl piperidine-2-carboxylate (78.6 mg, 0.5 mmol) was resolved according to the general procedure. Recovered amine: 48 mg (61 %, *er* = 71:29); acylated product: 51 mg (31 %, *er* = 93:7); calculated conversion: 33 %; **s = 20**;

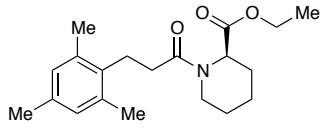
Recovered amine: **(2*S*)-Ethyl piperidine-2-carboxylate**



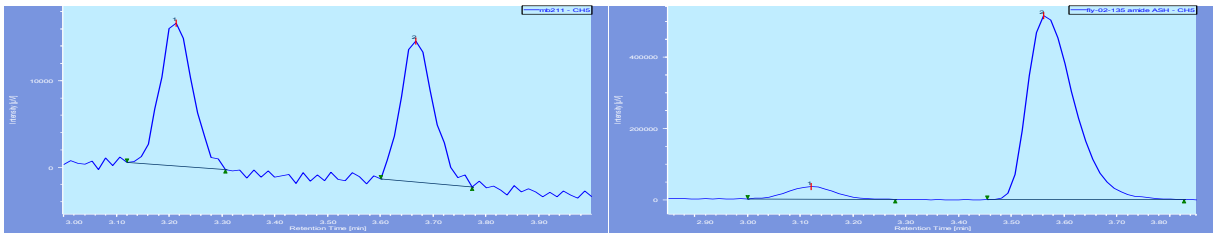
The amine was protected with benzyl chloroformate to determine the *er*: **$[\alpha]^{25}_D$** (c = 1.0, $CHCl_3$): –15.7; **SFC**: column: Daicel Chiralpak ASH (4.6 × 250 mm); gradient: 5 % *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: t_R = 4.2 min (major) and 4.6 min (minor).



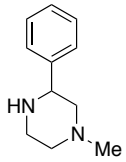
Acylated product: **Ethyl (2*R*)-1-(3-mesitylpropanoyl)piperidine-2-carboxylate**



$[\alpha]^{24}_D$ (c = 1.0, $CHCl_3$): +35.5; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 6.86–6.81 (m, 2 H), 5.40 (d, *J* = 5.1, 0.8 H), 4.60 (d, *J* = 13.7, 0.2 H), 4.43 (d, *J* = 4.9, 0.2 H), 4.25–4.12 (m, 2 H), 3.68 (d, *J* = 13.2, 0.8 H), 3.23 (apparent dt, *J* = 12.8, 2.9 Hz, 0.8 H), 3.00–2.88 (m, 1.8 H), 2.64 (apparent dt, *J* = 12.8, 2.0 Hz, 0.2 H), 2.52–2.08 (m, 12.2 H), 1.75–1.50 (m, 3 H), 1.45–1.31 (m, 2 H), 1.27 (t, *J* = 7.2 Hz, 2.4 H), 1.25 (t, *J* = 7.2 Hz, 0.6 H); **SFC**: column: Daicel Chiralpak ODH (4.6 × 250 mm); gradient: 5 % *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: t_R = 3.2 min (minor) and 3.7 min (major).

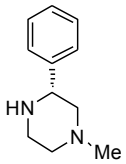


1-Methyl-3-phenylpiperazine (Table 3, entry 6)[8]

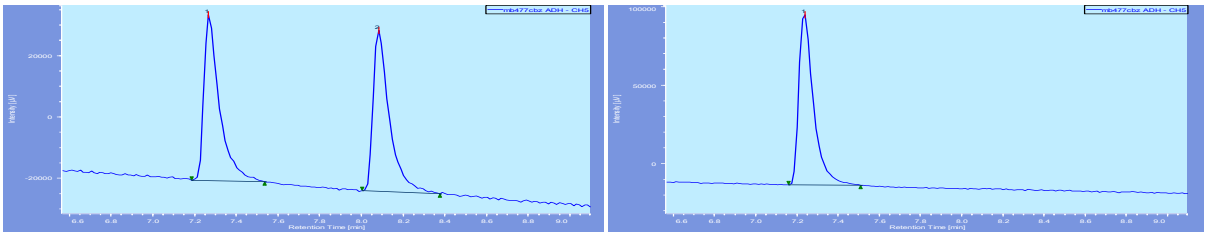


Racemic 1-methyl-3-phenylpiperazine (88.1 mg, 0.5 mmol) was resolved according to the general procedure. Recovered amine: 24 mg (27 %, *er* > 99:1); acylated product: 90 mg (51 %, *er* = 90:10); calculated conversion: 55 %; **s = 46**;

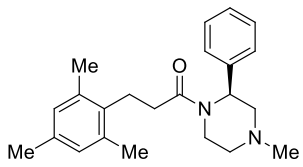
Recovered amine: **(3*R*)-1-Methyl-3-phenylpiperazine**



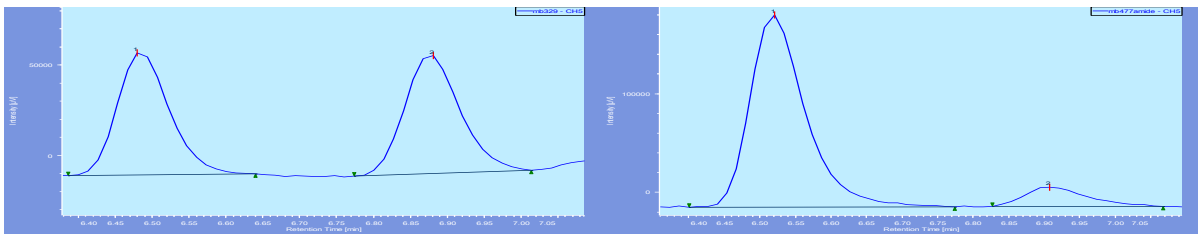
The amine was protected with benzyl chloroformate to determine the *er*:[19] $[\alpha]^{24}_{D}$ (c = 1.2, $CHCl_3$): –3.4; **SFC**: column: Daicel Chiralpak ADH (4.6 × 250 mm); gradient: 5 % *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: t_R = 7.3 min (major) and 8.1 min (minor).



Acylated product: **(2*S*)-1-(3-Mesitylpropanoyl)-4-methyl-2-phenylpiperazine**

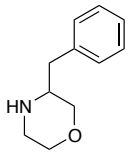


^{1}H NMR (400 MHz, $CDCl_3$): δ [ppm] = 7.60–7.10 (m, 5 H), 6.82 (s, 2 H), 4.90 (br s, 0.5 H), 4.87 (br s, 0.5 H), 4.58 (br s, 0.5 H), 3.52 (br s, 0.5 H), 3.33 (d, *J* = 11.8 Hz, 1 H), 3.25–2.85 (m, 3 H), 2.75 (d, *J* = 9.8 Hz, 1 H), 2.50 (br s, 1 H), 2.37–2.14 (m, 14 H), 1.98 (br s, 1 H); **SFC**: column: Daicel Chiralpak ODH (4.6 × 250 mm); gradient: 5 % *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: t_R = 6.5 min (major) and 6.9 min (minor). (The amide was purified by flash column chromatography with 5 % MeOH in CH_2Cl_2 with the addition of 1 % Et_3N.)



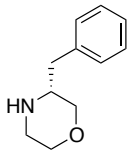
[19] M. van der Linden, J. Borsboom, F. Kaspersen and G. Kemperman, *Eur. J. Org. Chem.*, 2008, 2989–2997.

3-Benzylmorpholine (Table 3, entry 7)[8]

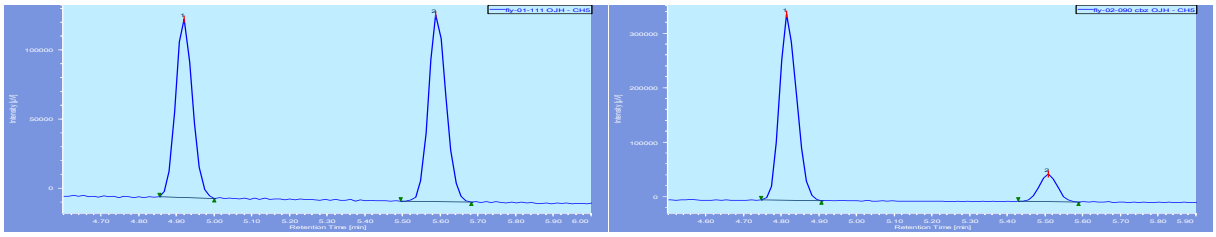


Racemic 3-benzylmorpholine (88.6 mg, 0.5 mmol) was resolved according to the general procedure. Recovered amine: 40 mg (45 %, *er* = 87:13); acylated product: 76 mg (43 %, *er* = 93:7); calculated conversion: 46 %; **s = 29**;

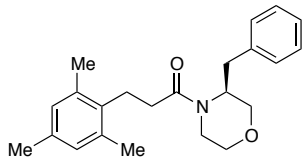
Recovered amine: **(3*R*)-3-Benzylmorpholine**



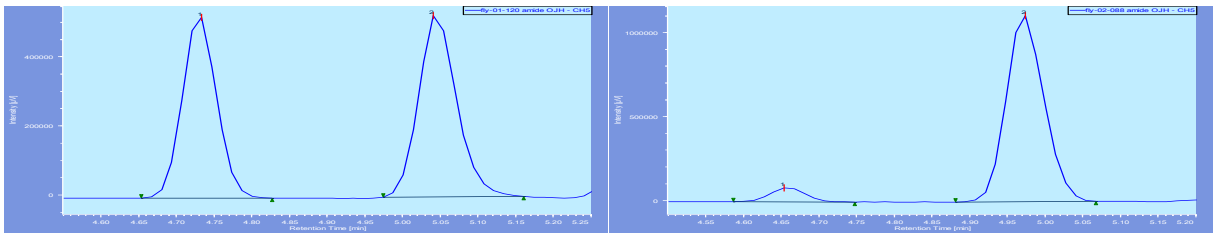
The amine was protected with benzyl chloroformate to determine the *er*: $[\alpha]^{25}_{D}$ (c = 1.0, $CHCl_3$): +23.1; **SFC**: column: Daicel Chiralpak OJH (4.6 × 250 mm); gradient: 5 % *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: t_R = 4.9 min (major) and 5.6 min (minor).



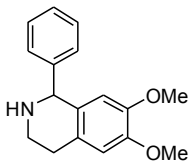
Acylated product: **(3*S*)-3-Benzyl-4-(3-mesitylpropanoyl)morpholine**



$[\alpha]^{25}_{D}$ (c = 1.0, $CHCl_3$): –21.8; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.33–7.07 (m, 5 H), 6.84 (s, 1 H), 6.80 (s, 1 H), 4.69 (ddd, *J* = 9.1, 5.7, 2.9 Hz, 0.5 H), 4.46 (dd, *J* = 13.8, 2.5 Hz, 0.5 H), 3.97 (dd, *J* = 11.4, 3.7 Hz, 0.5 H), 3.84 (dd, *J* = 11.1, 2.9 Hz, 0.5 H), 3.71 (dd, *J* = 16.8, 11.6 Hz, 0.5 H), 3.62 (apparent td, *J* = 8.6, 2.6 Hz, 0.5 H), 3.50–3.33 (m, 2 H), 3.29 (apparent td, *J* = 11.6, 2.9 Hz, 1.0 H), 3.19 (apparent td, *J* = 13.1, 3.9 Hz, 0.5 H), 3.10 (dd, *J* = 13.3, 8.6 Hz, 0.5 H), 3.07 (dd, *J* = 12.7, 9.9 Hz, 0.5 H), 2.98–2.79 (m, 2 H), 2.75–2.65 (m, 0.5 H), 2.49–2.38 (m, 0.5 H), 2.35–2.12 (m, 11 H), 1.89 (ddd, *J* = 15.8, 11.0, 5.2 Hz, 0.5 H); **SFC**: column: Daicel Chiralpak OJH (4.6 × 250 mm); gradient: 5 % *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: t_R = 5.4 min (minor) and 5.7 min (major).

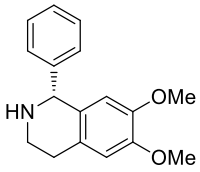


6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline (Table 2, entry 8)[8]

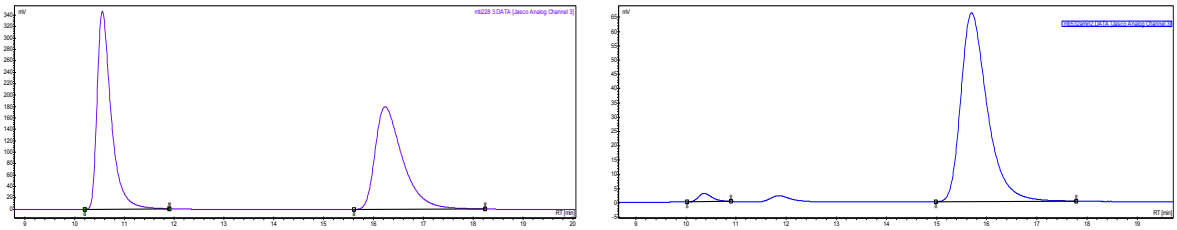


Racemic 6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline (134.7 mg, 0.50 mmol) was resolved according to the general procedure. Recovered amine: 48 mg (36 %, *er* = 98:2); acylated product: 113 mg (51 %, *er* = 97:3); calculated conversion: 51 %; **s = 127**;

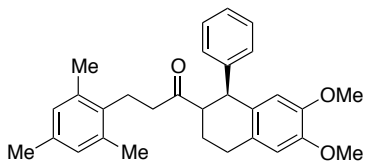
Recovered amine: **(1*R*)-6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline**



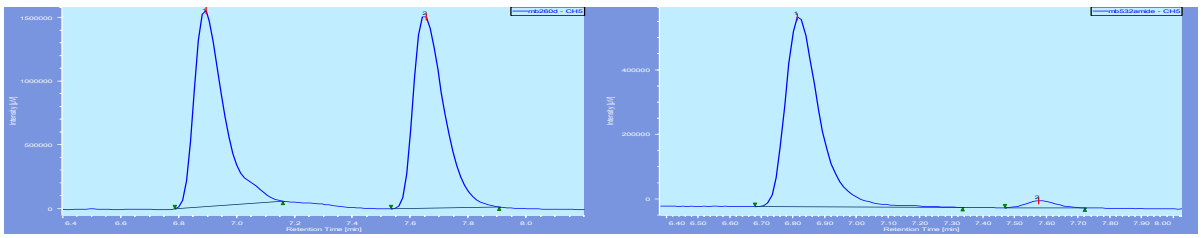
$[\alpha]^{28}_{D}$ (c = 1.0, $CHCl_3$): +20.2; lit.: $[\alpha]^{23}_{D}$ (c = 0.5, $CHCl_3$): +23.8;[20a] $[\alpha]^{22}_{D}$ (c = 1.0, $CHCl_3$): +20.4;[20b] **Chiral HPLC:** column: Daicel Chiralpak OJH (4.6 × 250 mm); eluent: 60 % *i*PrOH in hexane + 0.1 % Et_3N, flow: 0.5 mL/min; detection: 254 nm. Retention time: t_R = 10.5 min (minor) and 16.2 min (major).



Acylated product: **(1*S*)-2-(3-Mesitylpropanoyl)-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydro-isoquinoline**

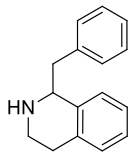


$[\alpha]^{28}_{D}$ (c = 5.6, $CHCl_3$): +140.7; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.33–7.23 (m, 4.5 H), 7.15–7.10 (m, 0.5 H), 6.93 (s, 0.8 H), 6.84 (s, 1.6 H), 6.81 (s, 0.4 H), 6.68 (s, 0.2 H), 6.65 (s, 0.8 H), 6.55 (s, 0.8 H), 6.50 (0.2 H), 5.85 (s, 0.2 H) 4.41–4.32 (m, 0.2 H), 3.88 (s, 3 H), 3.79 (s, 2.4 H), 3.76 (s, 0.6 H), 3.72–3.62 (m, 0.8 H), 3.34 (ddd, *J* = 13.7, 11.6, 4.4 Hz, 0.8 H), 3.25–3.15 (m, 0.2 H), 3.14–2.39 (m, 6 H), 2.29 (s, 4.8 H), 2.27 (s, 1.2 H), 2.25 (2.4 H), 2.22 (s, 0.6 H); **SFC**: column: Daicel Chiralpak ASH (4.6 × 250 mm); gradient: 5 % *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: t_R = 6.9 min (major) and 7.7 min (minor).



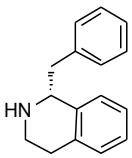
[20] (a) P. Allef and H. Kunz, *Heterocycles*, 2007, **74**, 421–436; (b) A. Krasiński, Z. Radić, R. Manetsch, J. Raushel, P. Taylor, K. B. Sharpless and H. C. Kolb, *J. Am. Chem. Soc.*, 2005, **127**, 6686–6692.

1-Benzyl-1,2,3,4-tetrahydroisoquinoline (Table 3, entry 9)

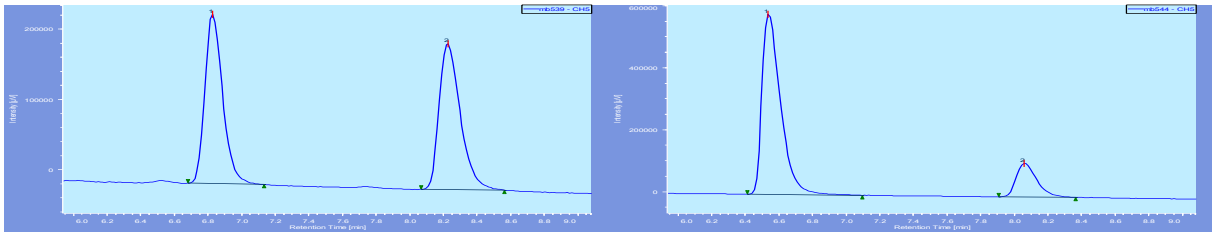


Racemic 1-benzyl-1,2,3,4-tetrahydroisoquinoline (116.7 mg, 0.5 mmol) was resolved according to the general procedure. Recovered amine: 50 mg (45 %, *er* = 83:17); acylated product: 85 mg (43 %, *er* = 89:11); calculated conversion: 46 %; **s = 16**;

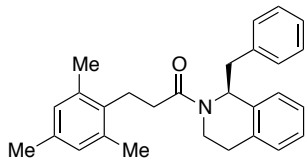
Recovered amine: **(1*R*)-1-Benzyl-1,2,3,4-tetrahydroisoquinoline**



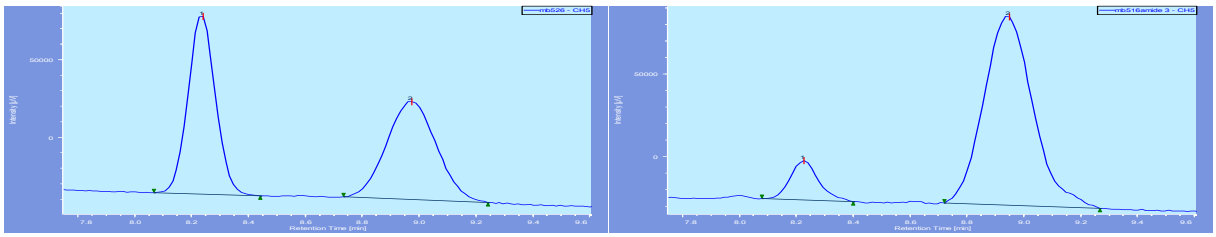
$[\alpha]^{27}_{D}$ (c = 0.6, THF): +33.8; lit.: $[\alpha]_D$ (c = 1.11, THF): +60.1;[21] The amine was protected with benzoyl chloride to determine the *er*;[22] **SFC**: column: Daicel Chiralpak ASH (4.6 × 250 mm); gradient: 5 % *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: t_R = 6.9 min (major) and 8.3 min (minor).



Amide product: **(1*S*)-1-Benzyl-2-(3-mesitylpropanoyl)-1,2,3,4-tetrahydroisoquinoline**

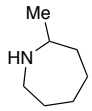


$[\alpha]^{29}_{D}$ (c = 4.0, $CHCl_3$): +33.5; at room temperature the ratio of rotamers was about 55:45 as determined by ^{1}H NMR; **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] = 171.6, 171.2, 138.0, 137.7, 136.5, 136.4, 136.01, 135.96, 135.4, 135.1, 134.8, 134.6, 134.4, 133.8, 129.7, 129.4, 129.2, 128.9, 128.7, 128.6, 128.1, 128.0, 127.7, 126.99, 126.97, 126.94, 126.7, 126.3, 126.1, 126.0, 58.2, 54.7, 42.8, 42.5, 41.0, 34.9, 32.9, 32.0, 28.8, 28.1, 24.7, 24.5, 20.73, 20.69, 19.7, 19.6; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 7.39–7.05 (m, 9 H), 6.91 (s, 1 H), 6.77 (s, 1 H), 5.86 (apparent t, *J* = 7.8 Hz, 0.5 H), 4.97–4.89 (m, 0.5 H), 4.87 (dd, *J* = 10.5, 3.7 Hz, 0.5 H), 3.70–3.61 (m, 0.5 H), 3.53 (ddd, *J* = 12.9, 8.0, 5.1 Hz, 0.5), 3.25-2.93 (m, 3.5 H), 2.90–2.73 (m, 2 H), 2.67–2.38 (m, 2 H), 2.35 (s, 2.7 H), 2.32 (s, 1.3 H), 2.24 (m, 1.7 H), 2.11 (s, 3.3 H), 2.10-2.03 (m, 0.5 H), 1.74 (ddd, *J* = 16.3, 11.4, 5.1 Hz, 0.5 H); **HRMS** (ESI): calculated for $[C_{28}H_{32}NO]^+$: m/z = 398.2478, found: m/z = 398.2477; **IR** ($\tilde{\nu}$ /cm^{-1}, neat): 3028, 3002, 2938, 2915, 2863, 1640, 1492, 1450, 1424, 1218, 1028, 948; **SFC**: column: Daicel Chiralpak ODH (4.6 × 250 mm); gradient: 5 % *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm; retention time: t_R = 8.2 min (minor) and 9.0 min (major); **mp:** 125–128 °C.



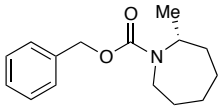
[21] I. M. P. Huber and D. Seebach, *Helv. Chim. Acta*, 1987, **70**, 1944–1954.
[22] Y. M. Al-Hiari, S. J. Bennett, B. Cox, R. J. Davies, A. I. Khalaf, R. D. Waigh and A. J. Worsley, *J. Heterocyclic Chem*., 2005, **42**, 647–659.

2-Methylazepane (Table 3, entry 10)[8]

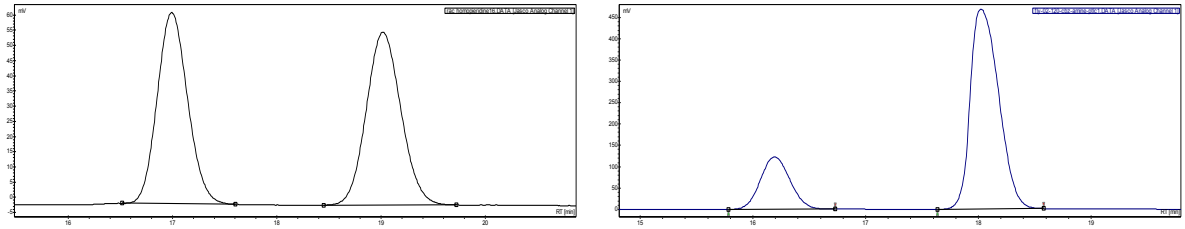


Racemic 2-methylazepane (56.6 mg, 0.5 mmol) was resolved according to the general procedure. Recovered (Cbz-protected) amine: 29 mg (24 %, *er* = 79:21); acylated product: 51 mg (35 %, *er* = 84:16); calculated conversion: 46 %; **s = 9**;

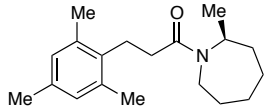
The recovered amine was characterized as its Cbz-derivative: **Benzyl (2*R*)-2-methylazepane-1-carboxylate**



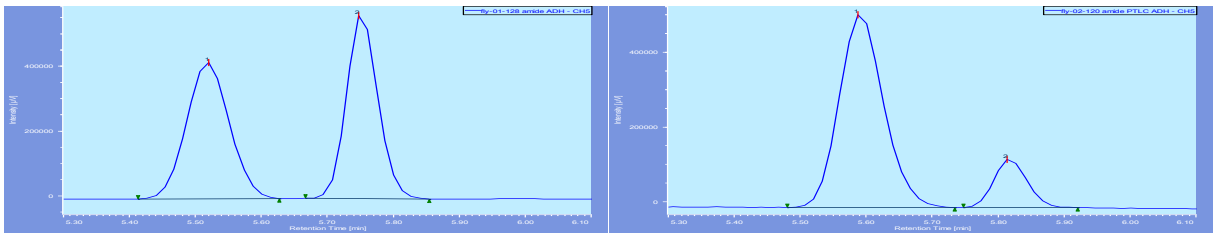
[α]$^{25}_{D}$ (c = 1.0, $CHCl_3$): –44.9; **Chiral HPLC**: column: Daicel Chiralpak ADH (4.6 × 250 mm); eluent: 1 % *i*PrOH in hexane, flow: 1.0 mL/min; detection: 254 nm. Retention time: t_R = 16.99 min (minor) and 19.02 min (major).



Acylated product: **(2*S*)-1-(3-Mesitylpropanoyl)-2-methylazepane**

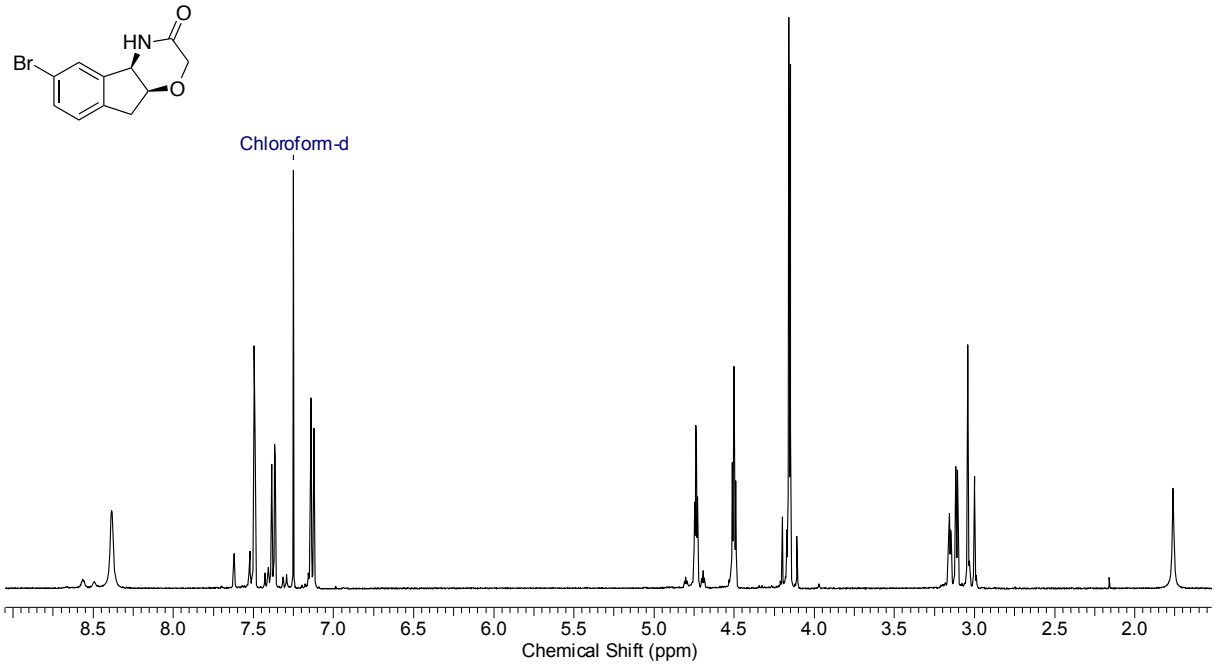


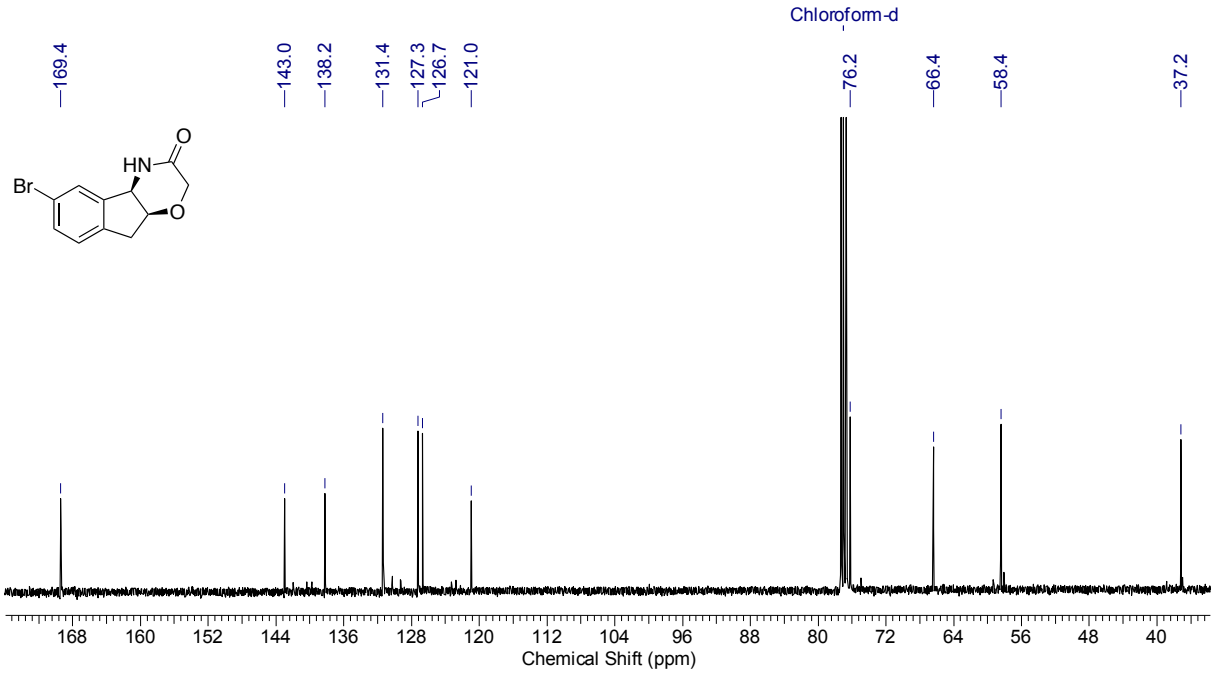
[α]$^{25}_{D}$ (c = 1.0, $CHCl_3$): +29.4; **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] = 6.84 (s, 2 H), 4.59–4.48 (m, 0.5 H), 4.11 (d, *J* = 13.8 Hz, 0.5 H), 3.73 (ddd, *J* = 17.6, 12.6, 6.5 Hz, 0.5 H), 3.42 (d, *J* = 15.0, 3.0 Hz, 0.5 H), 3.07–2.87 (m, 3 H), 2.61 (ddd, *J* = 13.5, 12.0, 1.3 Hz, 0.5 H), 2.54–2.32 (m, 2.5 H), 2.31–2.29 (m, 6 H), 2.25–2.23 (m, 3 H), 2.10–1.95 (m, 1 H), 1.85–1.68 (m, 3.5 H), 1.62–1.49 (m, 0.5 H), 1.38–1.11 (m, 2 H), 1.08 (d, *J* = 6.4 Hz, 1.3 H), 1.05 (d, *J* = 6.4 Hz, 1.7 H); **SFC**: column: Daicel Chiralpak ADH (4.6 × 250 mm); gradient: 5 % *i*PrOH in CO_2 to 50 % *i*PrOH in CO_2 over 10 min; flow: 3.0 mL/min; detection: 254 nm. Retention time: t_R = 5.59 min (major) and 5.81 min (minor).



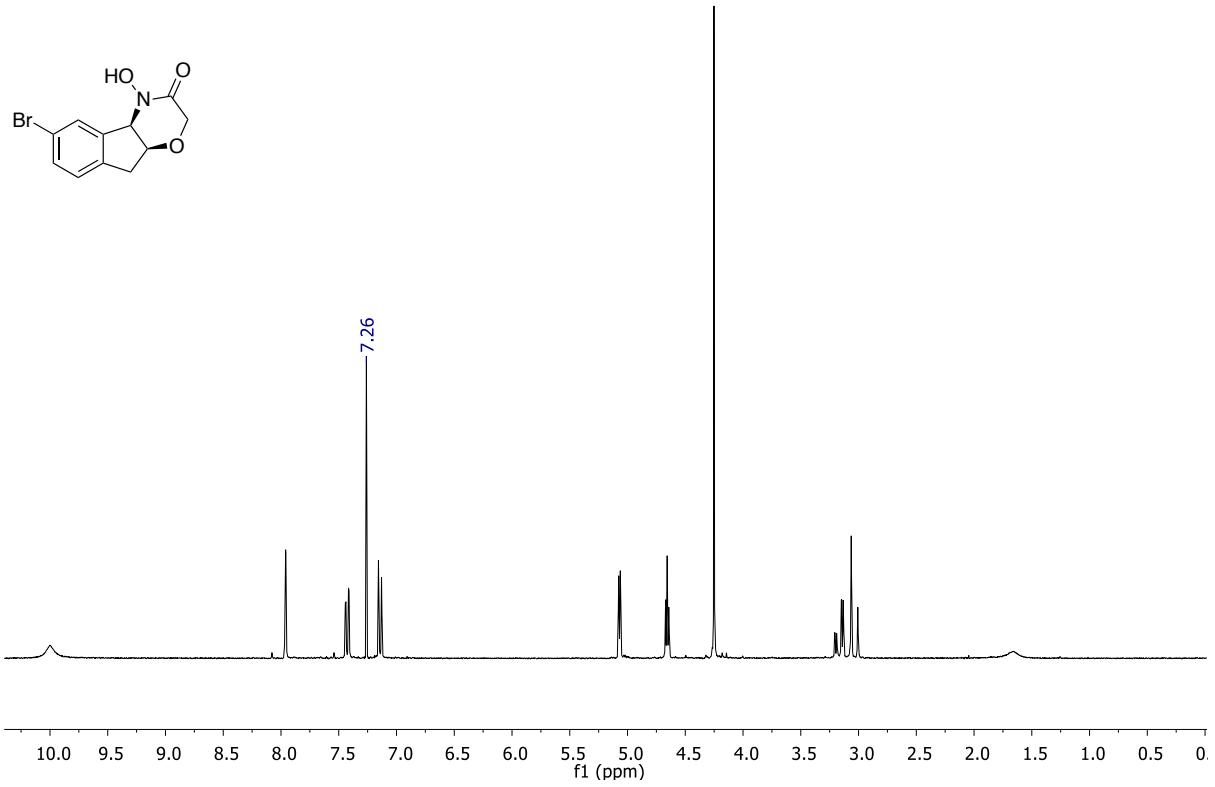
6. ^{1}H and ^{13}C NMR Spectra

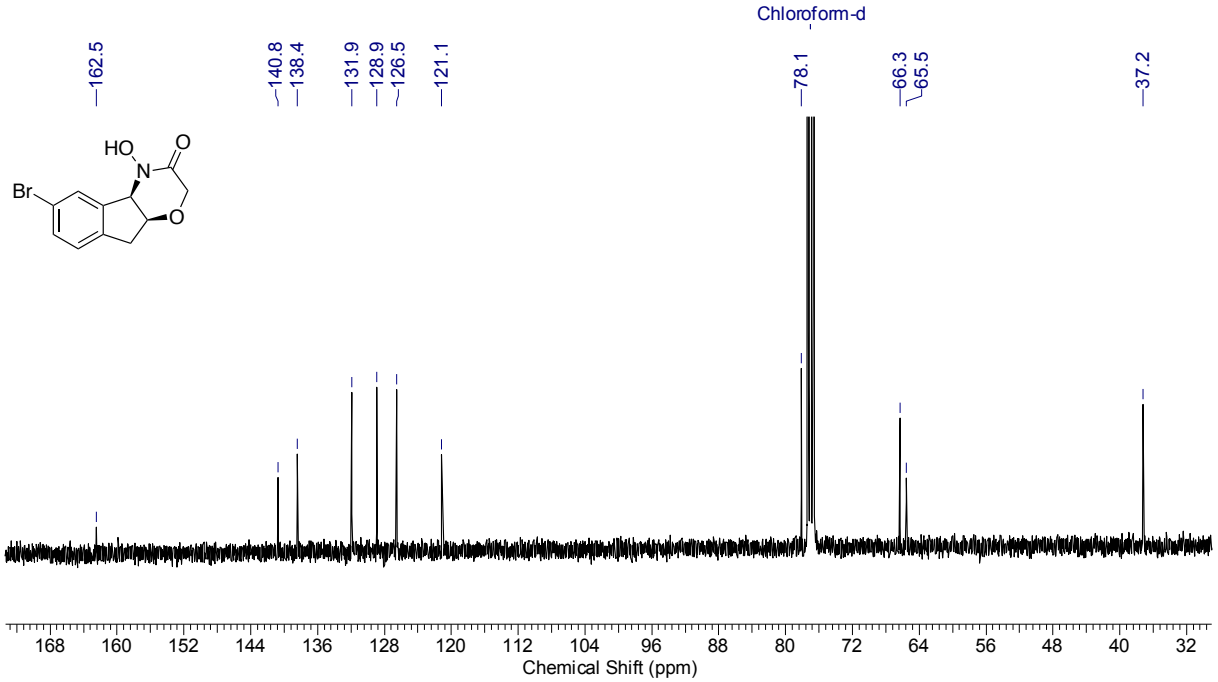
(4a*R*,9a*S*)-6-Bromo-4,4a,9,9a-tetrahydroindeno[2,1-*b*][1,4]oxazin-3(2*H*)-one (10)



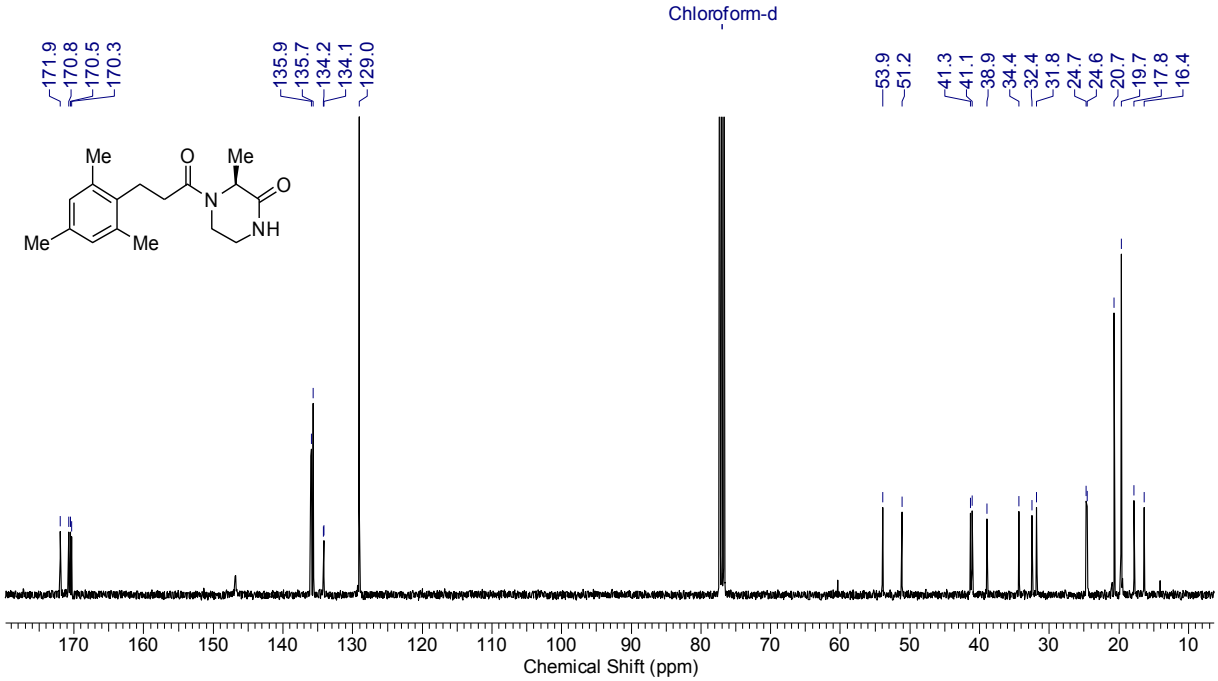


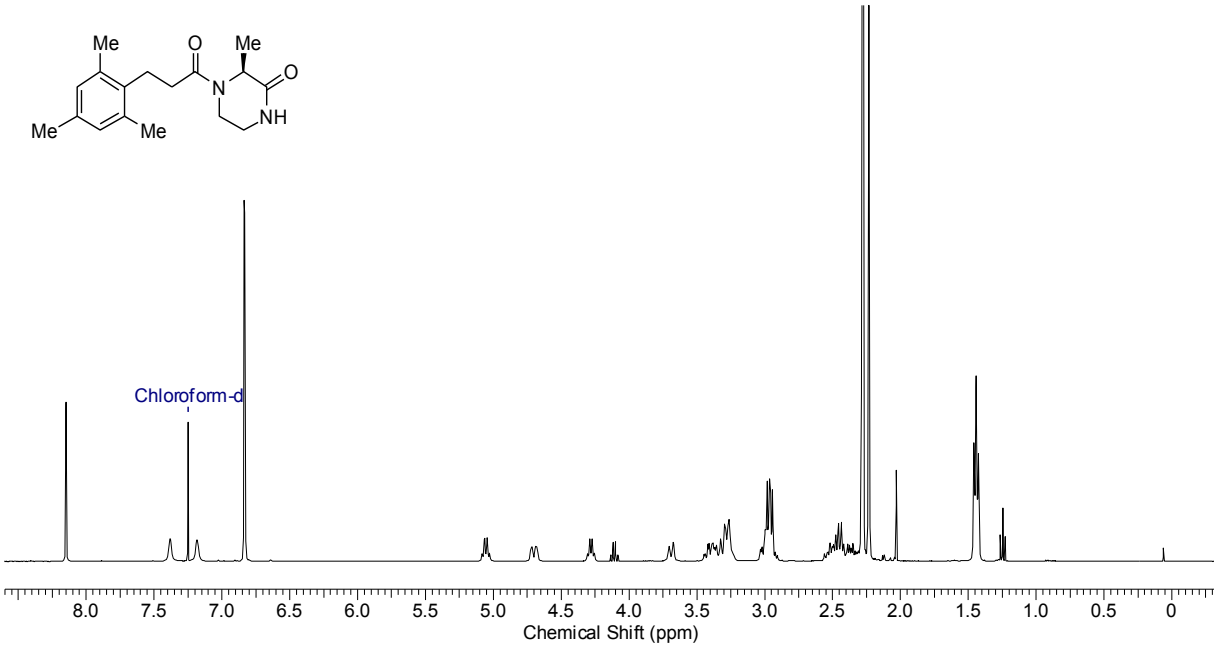
(4a*R*,9a*S*)-6-Bromo-4-hydroxy-4,4a,9,9a-tetrahydroindeno[2,1-*b*][1,4]oxazin-3(2*H*)-one (2)



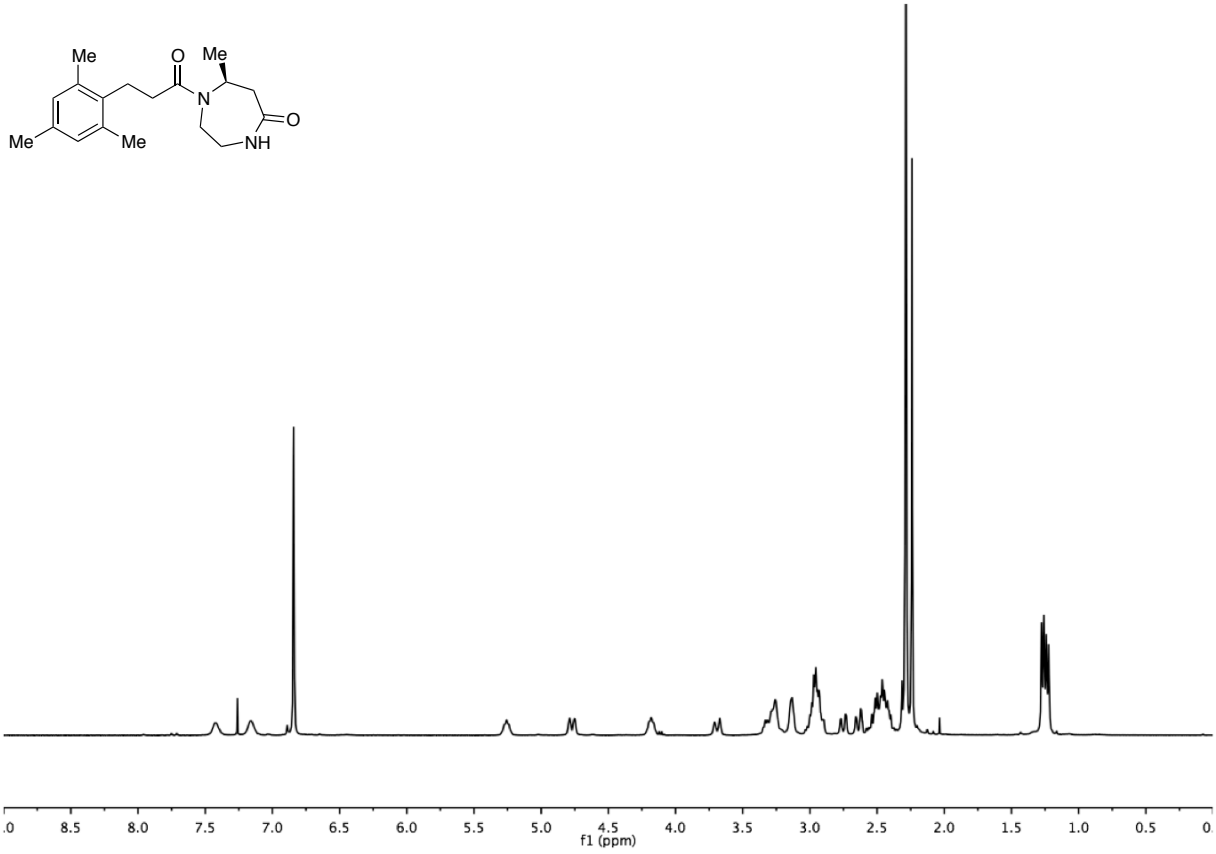


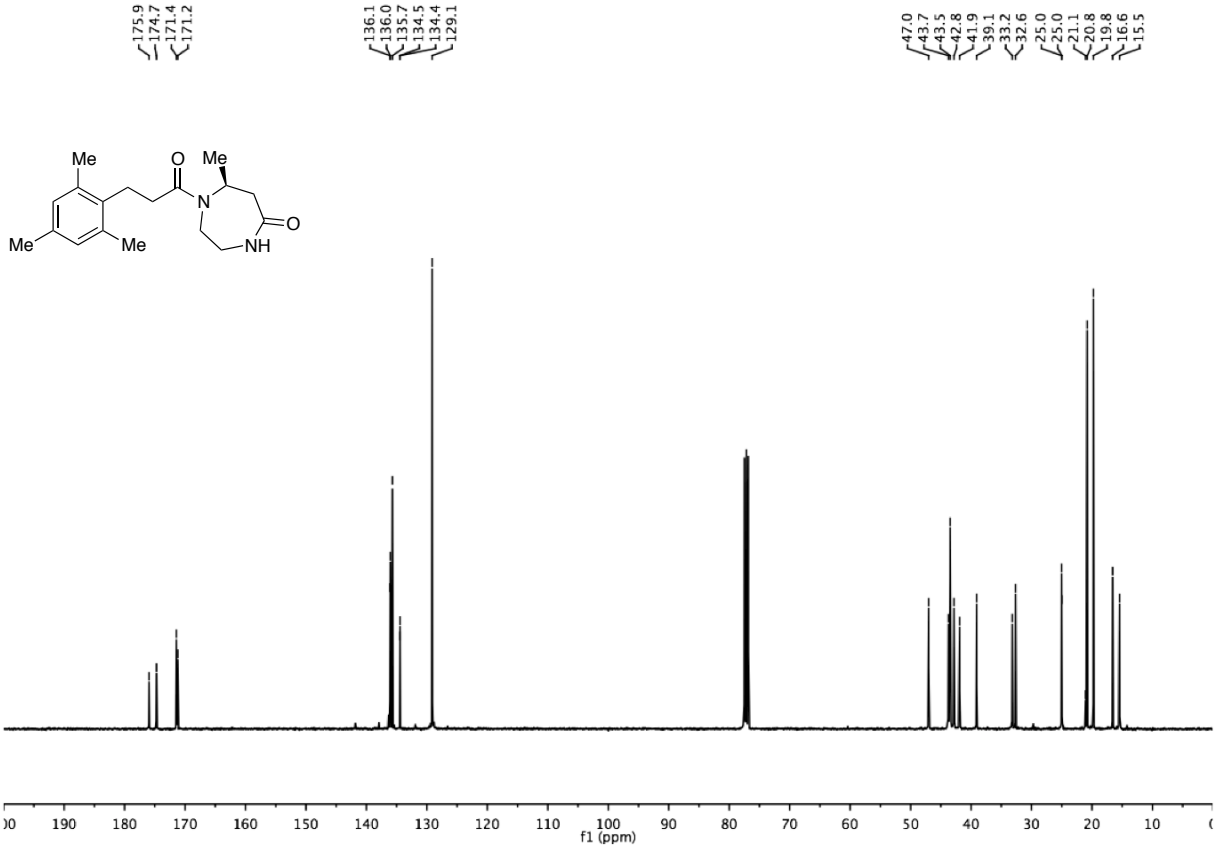
(3*S*)-4-(3-Mesitylpropanoyl)-3-methylpiperazin-2-one (Table 2, entry 1)



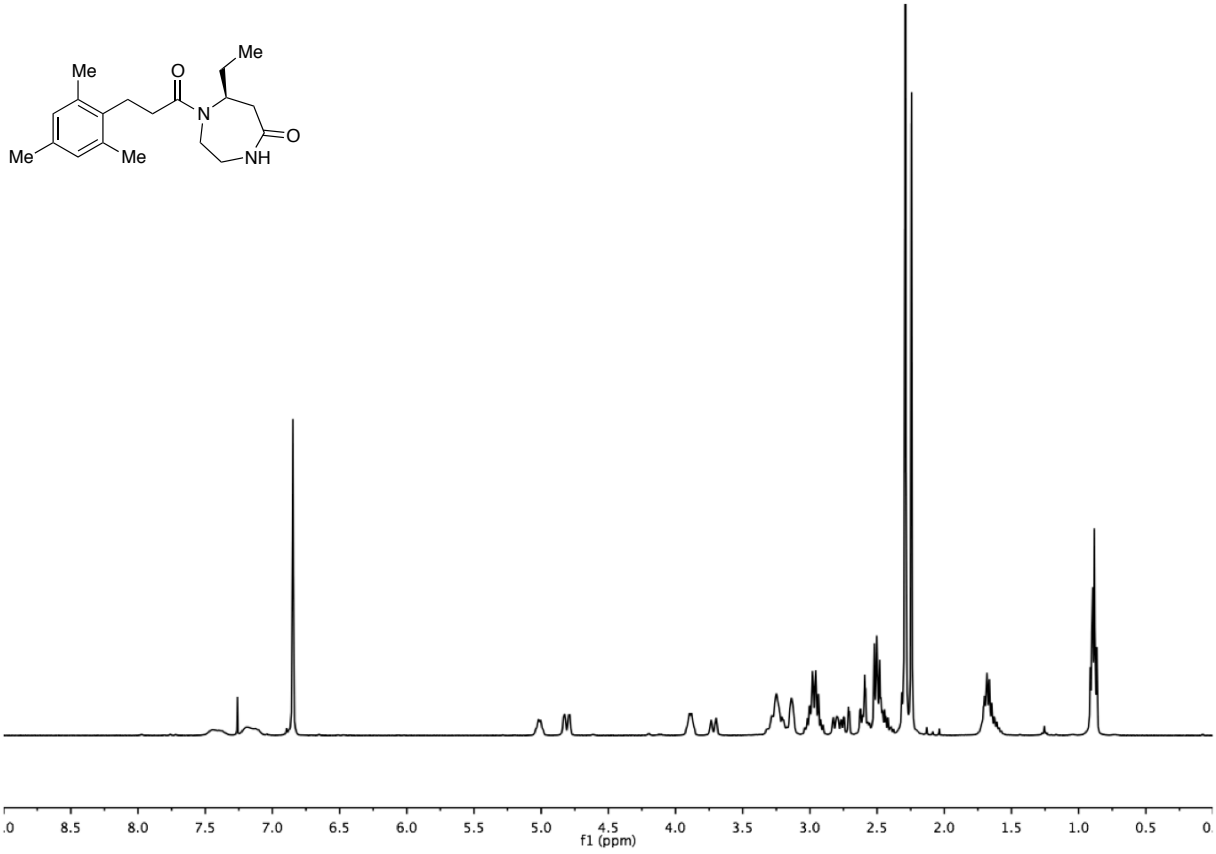


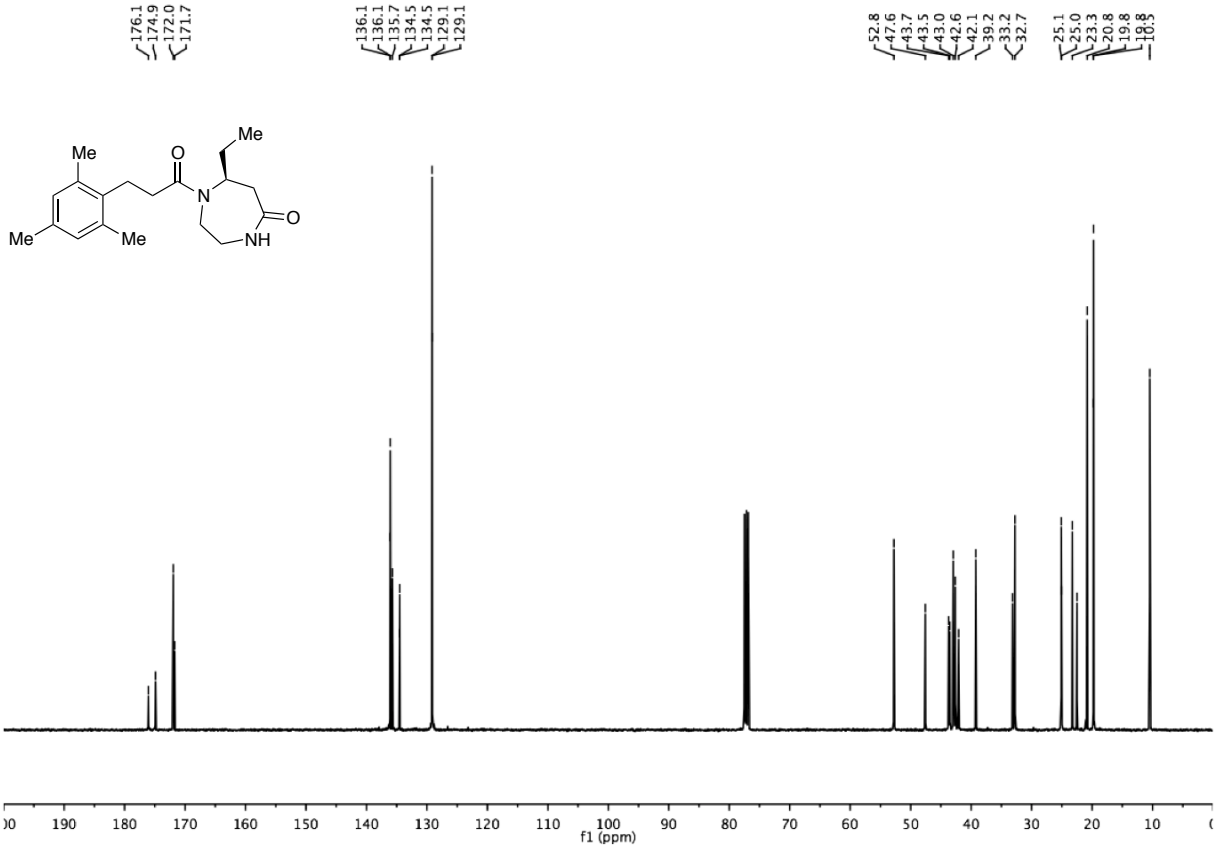
(7*S*)-1-(3-Mesitylpropanoyl)-7-methyl-1,4-diazepan-5-one (Table 2, entry 2)



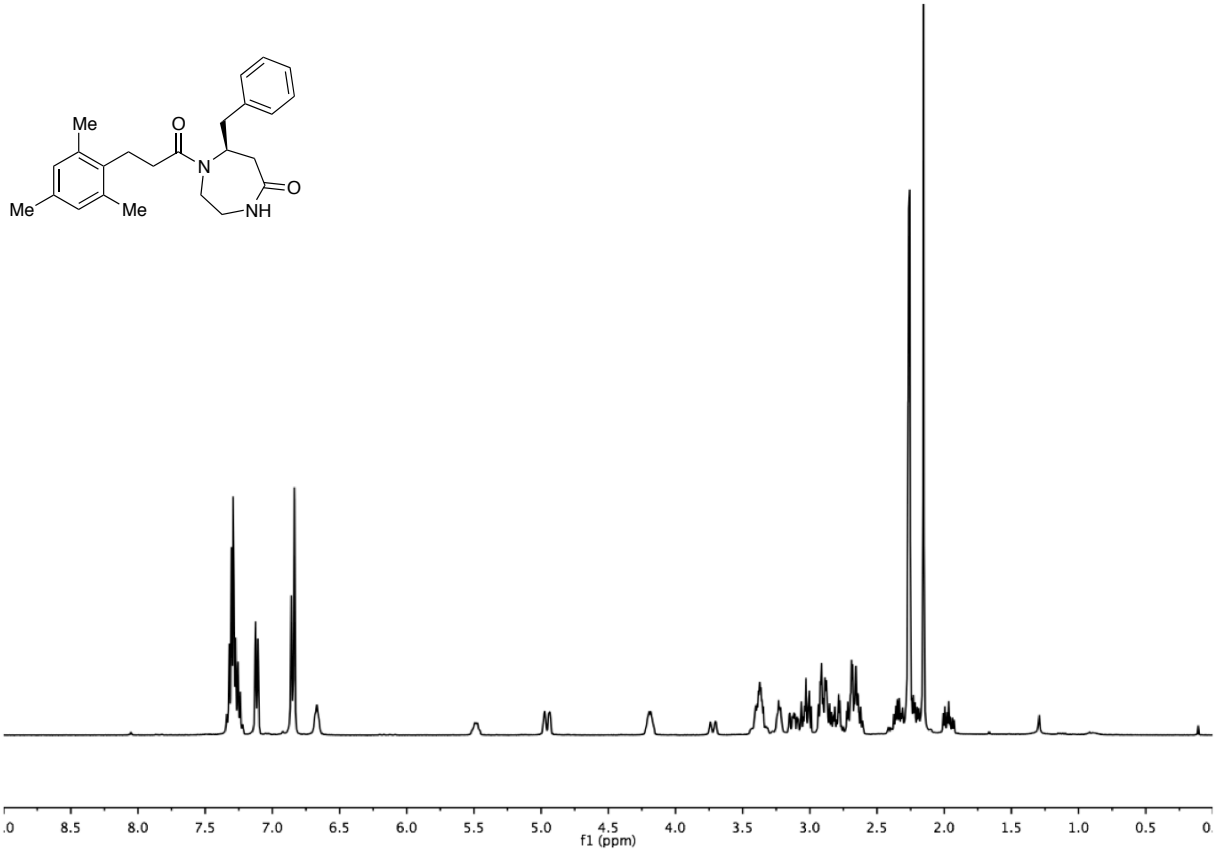


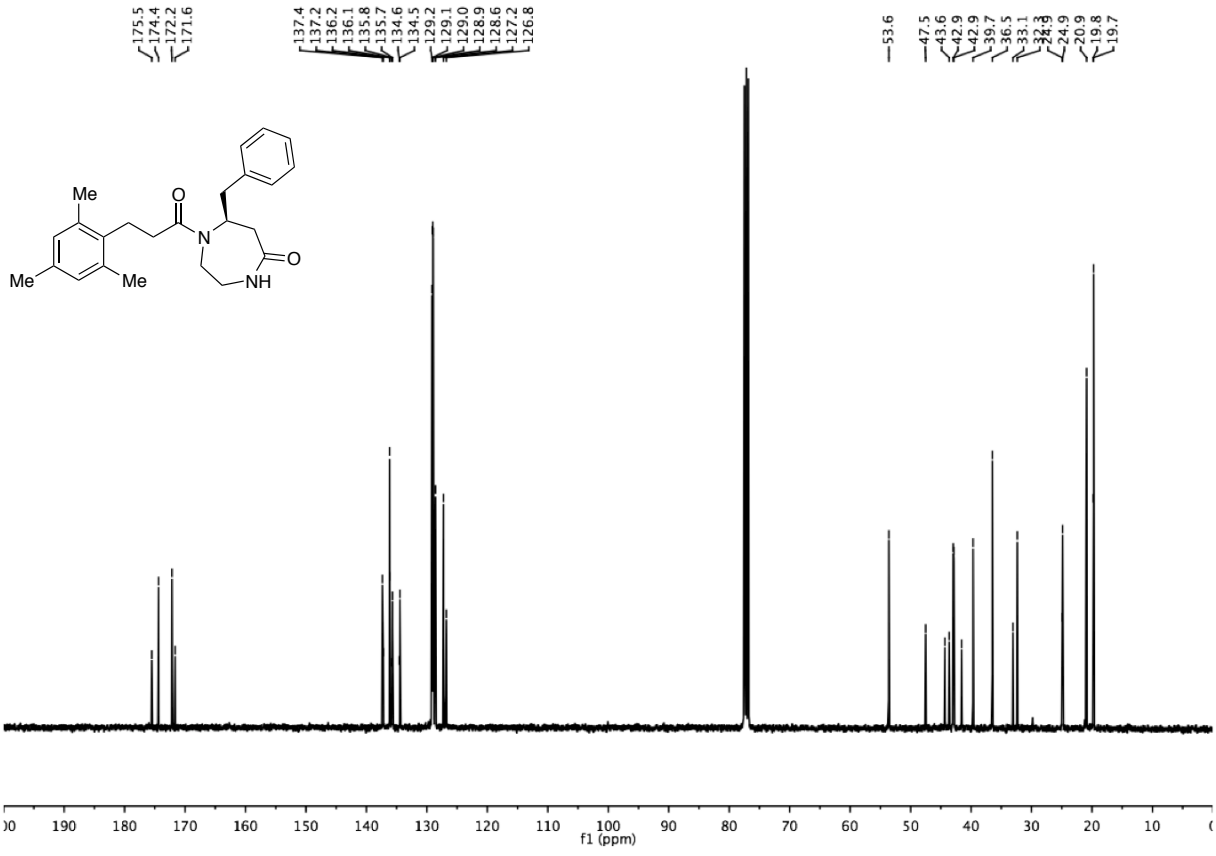
(7*S*)-7-Ethyl-1-(3-mesitylpropanoyl)-1,4-diazepan-5-one (Table 2, entry 3)



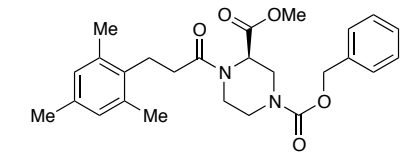


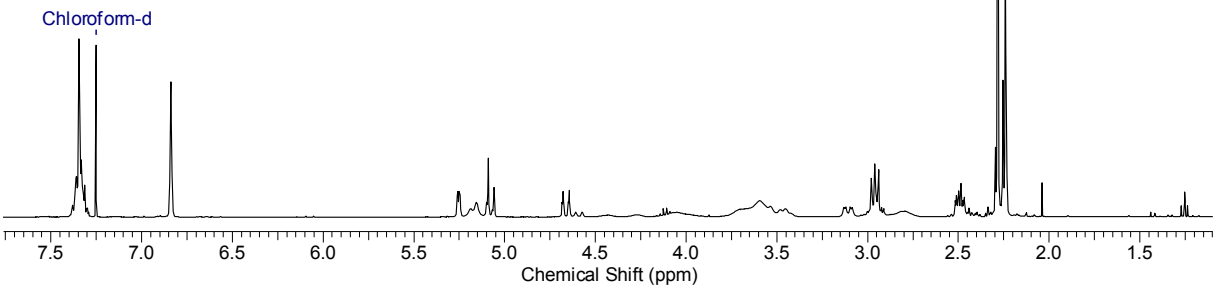
(7*S*)-7-benzyl-1-(3-mesitylpropanoyl)-1,4-diazepan-5-one (Table 2, entry 4)

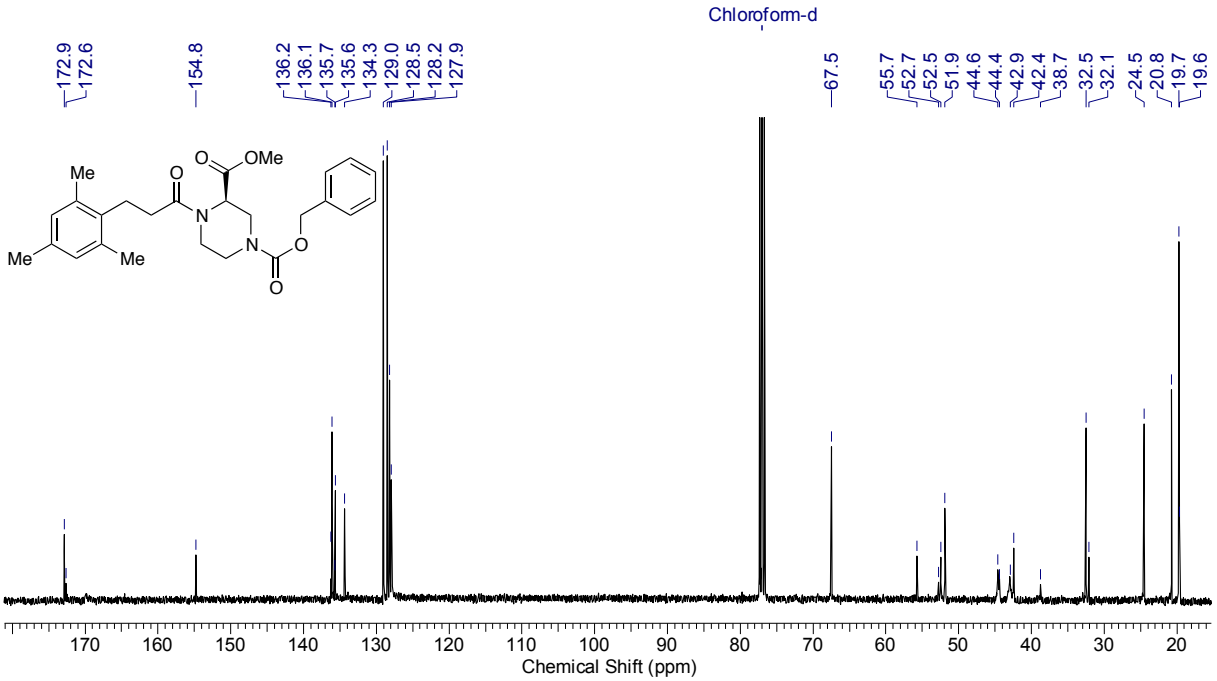




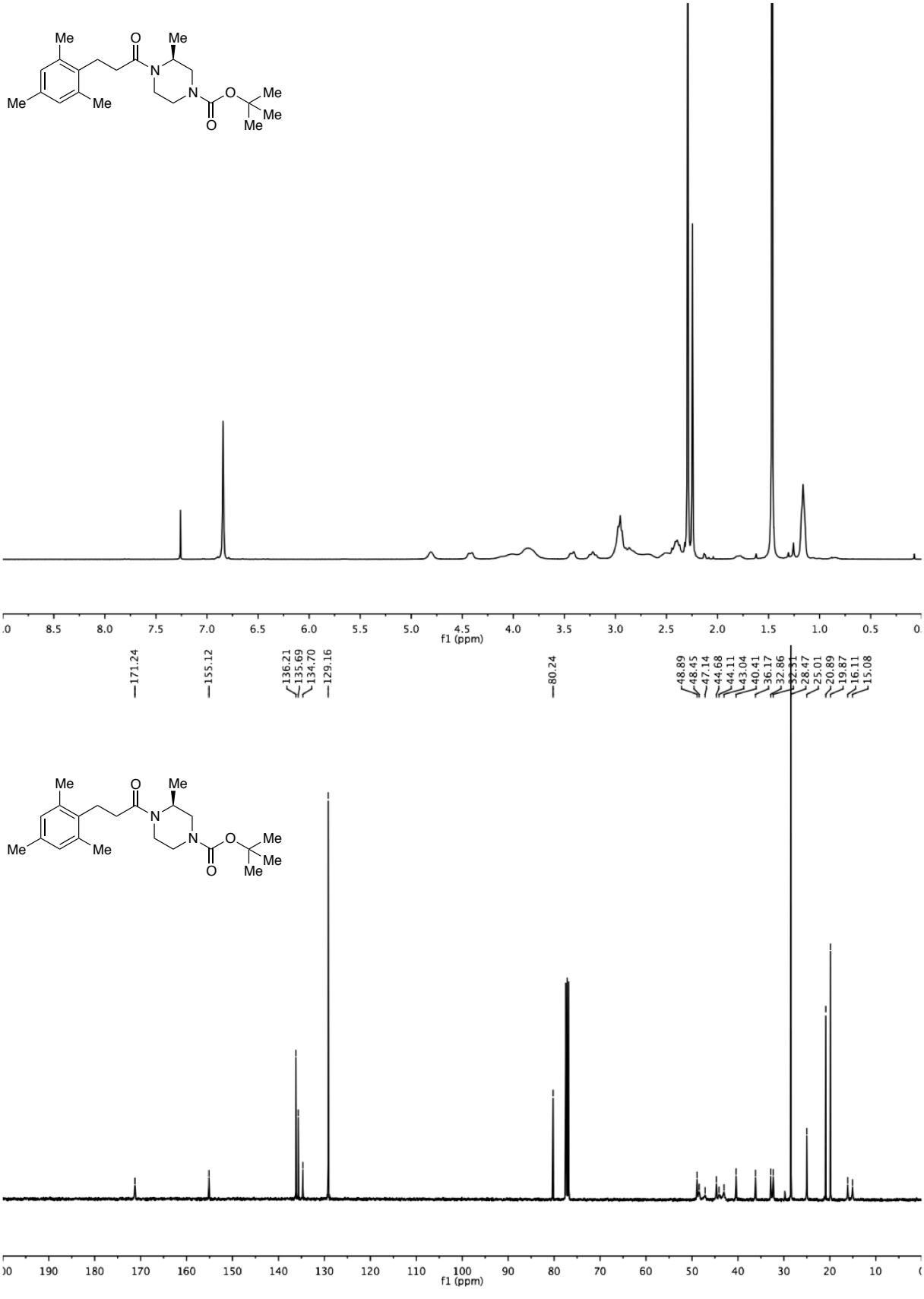
1-Benzyl 3-methyl (3*R*)-4-(3-mesitylpropanoyl)piperazine-1,3-dicarboxylate (Table 2, entry 5)



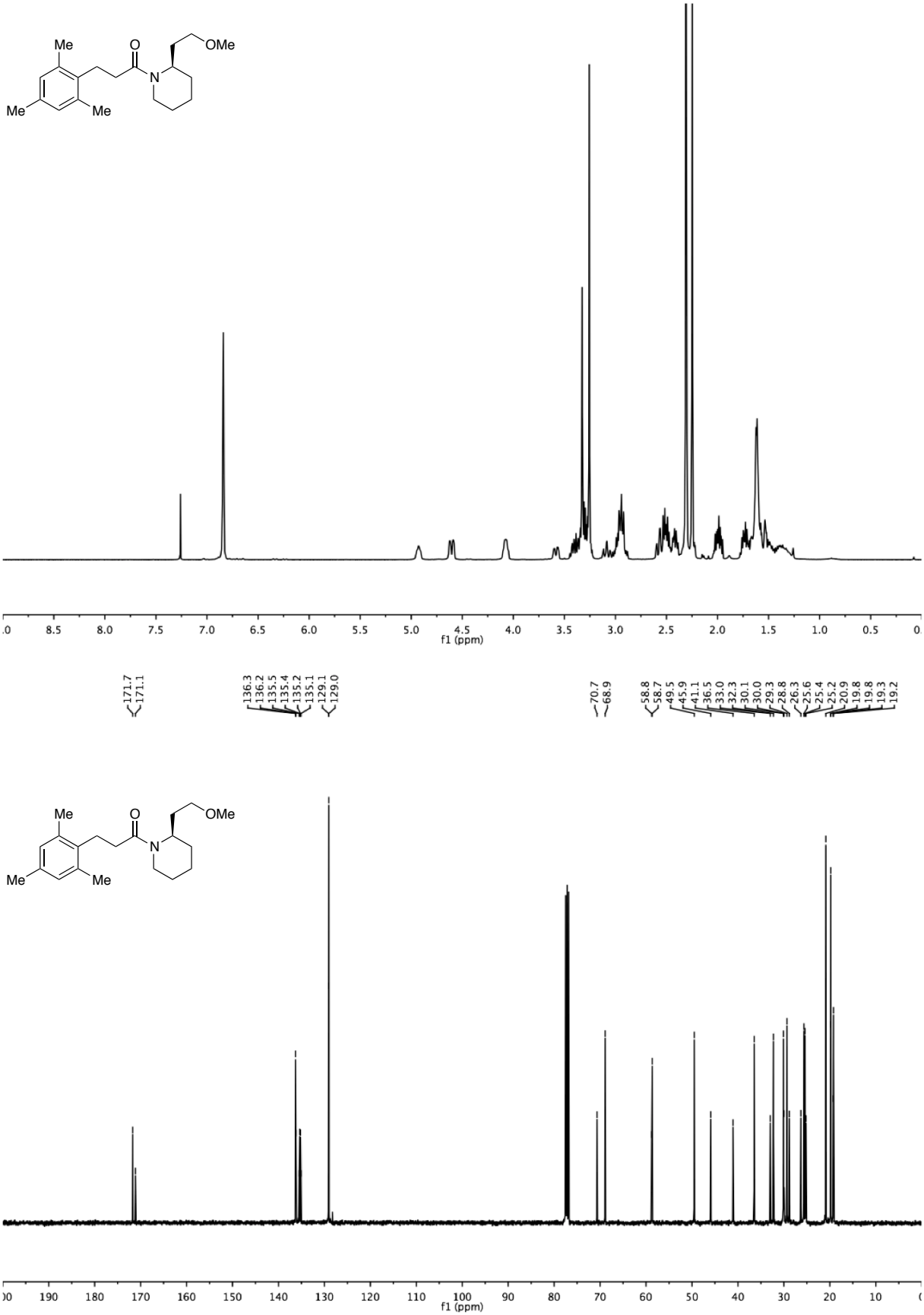




tert-Butyl (3*S*)-4-(3-mesitylpropanoyl)-3-methylpiperazine-1-carboxylate (Table 2, entry 6)



(2*R*)-1-(3-Mesitylpropanoyl)-2-(2-methoxyethyl)piperidine (Table 3, entry 4)



(1*S*)-1-Benzyl-2-(3-mesitylpropanoyl)-1,2,3,4-tetrahydroisoquinoline (Table 3, entry 9)