Oxidative Coupling of Amines and Ketones by Combined Vanadium- and Organocatalysis

Abhishek Sud, Devarajulu Sureshkumar and Martin Klussmann

Max-Planck-Institut für Kohlenforschung, Kaiser-Wilhelm-Platz 1,
45470 Mülheim an der Ruhr, Germany.
email: klusi@mpi-muelheim.mpg.de

Supporting Information

Experimental details

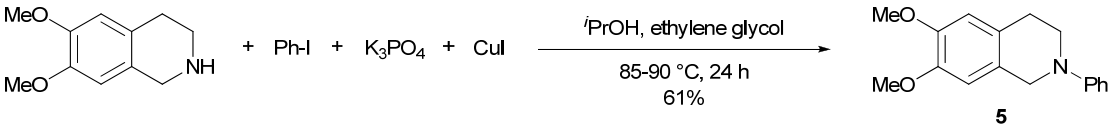
Except when indicated otherwise, all reagents and solvents were purchased from commercial sources and used as received. All reactions and workup were conducted under air, except when noted otherwise. Flash column chromatography was performed using Merck Silica Gel 60 (0.040-0.063mm). TLC was performed on Macherey Nagel Polygram Sil G/UV_{254} plates and visualised by UV-light and $KMnO_4$-solution. Yields refer to pure isolated substances.

NMR spectra were recorded on a Bruker AV500 MHz spectrometer. The chemical shifts are reported in ppm downfield of internal standard tetramethylsilane for ^{1}H NMR and ^{13}C NMR. Chemical shifts are designated using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Peaks were assigned based on ^{13}C-DEPT- or 2D-NMR spectra or by analogy with derivatives. Mass spectra were recorded on a Finnigan MAT 8200 or a Finnigan SSQ 7000 instrument, high resolution mass determinations were performed on a Bruker APEX III FT-MS or a Finnigan MAT 95 instrument. High performance liquid chromatography (HPLC) was performed on a Shimadzu LC-10A HPLC-system. For preparative HPLC, a Shimadzu LC-8A FRC-10A fraction sampler was used. Racemic samples for determination of the separation conditions were synthesised according to the synthetic procedures described below using racemic proline as the organic cocatalyst.

Substrates

The substrates 2-phenyl-1,2,3,4-tetrahydro-isoquinoline (**1**) and 2-(*p*-methoxyphenyl)-1,2,3,4-tetrahydro-isoquinoline (**4**) were synthesized according to literature procedures.[S1]

6,7-Dimethoxy-2-phenyl-1,2,3,4-tetrahydro-isoquinoline (5)



5

In accordance with a literature procedure.[S1] Copper(I) iodide (200 mg, 1.0 mmol) and potassium phosphate (4.25 g, 20.0 mmol) were put into a Schlenk tube. The tube was evacuated and refilled with nitrogen. 2-Propanol (10.0 ml), ethylene glycol (1.11 ml, 20.0 mmol), 6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline (2.9 g, 15 mmol) and iodobenzene (1.12 ml, 10.0 mmol) were added successively. The reaction mixture was stirred at 85-90 °C for 24 h and then allowed to cool to room temperature. Diethyl ether (20 ml) and water (20 ml) were then added to the reaction mixture and the aqueous layer was extracted another two times with diethyl ether (20 ml each). The combined organic phases were washed with brine and dried over magnesium sulfate. The solvent was removed by rotary evaporation and purified by column chromatography on silica gel (hexane/ethyl acetate=20:1), giving the product **5** as while solid with 61 % (2.5 g) isolated yield.

R_f = 0.60 (EtOAc/pentane, 3 : 7); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29 (dd, *J* = 8.7, 7.4 Hz, 2H), 6.99 (d, *J* = 5.0 Hz, 2H), 6.83 (t, *J* = 5.0 Hz, 1H), 6.64 (d, *J* = 5.0 Hz, 2H), 4.33 (bs, 2H), 3.87 (s, 3H), 3.86 (s, 3H), 3.55 (t, *J* = 5.0 Hz, 2H), 2.90 (t, *J* = 5.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.6, 147.5, 129.2, 126.7, 126.2, 118.8, 115.4, 111.3, 109.4, 56.0, 54.7, 55.9, 50.5, 46.8, 28.5; HR - MS m/z: calcd for $C_{17}H_{19}NO_2[M^+]$: 269.1416; found: 269.1413.

Oxidative coupling - general procedure A (tetrahydroisoquinolines)

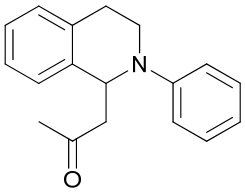
The amine (0.12 mmol), $VO(acac)_2$ (0.012 mmol, 10 mol%) and L-proline (0.012 mmol, 10 mol%) are dissolved in 1.0 ml MeOH and acetone (0.60 mmol, 5.0 eq.). A 5.5M solution of *tert*-butyl hydroperoxide in decane (0.033 ml, 0.18 mmol, 1.5 eq.) is added and the reaction mixture is stirred at room temperature until full conversion of the amine is achieved. Then, water and CH_2Cl_2 are added and the mixture is extracted with CH_2Cl_2. The combined organic phases are dried over $MgSO_4$ and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (5-10% EtOAc in pentane) gave the corresponding products.

Oxidative coupling - general procedure B (*N*-methyl pyrrolidines)

To a suspension of $VO(acac)_2$ (0.05 mmol, 5 mol%) and L-proline (0.1 mmol, 10 mol%) in 1.0 ml iso-hexane, *N*-methyl pyrrolidine (1.0 mmol) and ketone (5.0 mmol, 5.0 eq.) were added. A 5.5M solution of *tert*-butyl hydroperoxide in decane (0.27 ml, 1.5 mmol, 1.5 eq.) was added carefully and the reaction mixture was stirred at room temperature until full conversion of the amine was achieved. The reaction mixture was then filtered over a short pad of silica gel (basified by washing with a solution of 5% $NEtMe_2$ in pentane) which was further washed with CH_2Cl_2/MeOH. Concentration of the eluted solution in vacuo and purification of the residue by flash column chromatography on basified silica gel (0.5-1% MeOH in CH_2Cl_2) gave the corresponding products.

Products

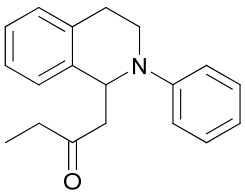
1-(2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)propan-2-one (3)



Synthesized according to general procedure A. White solid, r_f = 0.50 (EtOAc/pentane, 1 : 9); Yield : 22 mg, 69%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24 (t, J = 8.5 Hz, 2H), 7.18-7.12 (m, 4H), 6.93 (d, J = 8.1 Hz, 2H), 6.77 (t, J = 7.2 Hz, 1H), 5.93 (t, J = 6.3 Hz, 1H), 3.66-3.62 (m, 1H), 3.56-3.49 (m, 1H), 3.07-3.01 (m, 2H), 2.82 (dd, J = 16.4, 7.0 Hz, 1H), 2.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 207.3, 148.8, 138.2, 134.4, 129.3, 128.7, 126.8, 126.3, 118.3, 114.8, 54.8, 50.2, 42.1, 31.1, 27.2; HR - MS m/z: calcd for $C_{18}H_{19}NNaO[M^+$+Na]: 288.1364; found: 288.1368. Determination of ee by HPLC: Chiralpak IB (250x4.6mm), n-heptane/2-propanol 97:3, 0.5 ml/min, 25°C, 220nm, r_t (**3**) = 16 min, r_t (ent-**3**) = 33 min (chromatogram: see page S20).

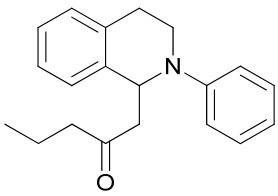
Preparative separation of enantiomers by HPLC was performed using a Chiralpak IA column (200x48mm), a mobile phase of iso-hexan/2-propanol (97:3) at 35 ml/min and a temperature of 35°C.

1-(2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)butan-2-one (6)



Synthesized according to general procedure A. Colourless oil, r_f = 0.70 (EtOAc/pentane, 1:9); Yield : 22 mg, 65%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25-7.22 (m, 2H), 7.17-7.12 (m, 4H), 6.94 (d, J = 8.2 Hz, 2H), 6.76 (t, J = 7.3 Hz, 1H), 5.41 (t, J = 6.4 Hz, 1H), 3.66-3.61 (m, 1H), 3.56-3.50 (m, 1H), 3.09-3.01 (m, 2H), 2.86-2.75 (m, 2H), 2.39-2.21 (m, 2H), 0.97 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 209.9, 148.8, 138.4, 134.4, 129.3, 128.6, 126.8, 126.7, 118.1, 114.6, 55.1, 48.9, 41.9, 37.3, 27.3, 7.5; HR - MS m/z: calcd for $C_{19}H_{21}NNaO[M^+$+Na]: 302.1515; found: 302.1511.

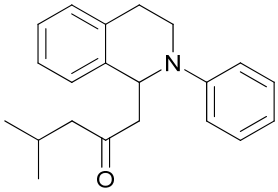
1-(2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)pentan-2-one (7)



Synthesized according to general procedure A. Colourless oil, r_f = 0.70 (EtOAc/pentane, 1:9); Yield : 15 mg, 41%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24 (t, J = 6.2 Hz, 2H), 7.18-7.12 (m, 4H), 6.94 (d, J = 7.0 Hz, 2H), 6.77 (t, J = 6.2 Hz, 1H), 5.43 (t, J = 6.3 Hz, 1H), 3.67-3.62 (m,

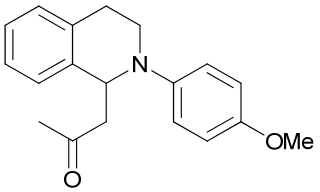
1H), 3.56-3.51 (m, 1H), 3.09-3.01 (m, 2H), 2.85-2.75 (m, 2H), 2.34-2.19 (m, 2H), 1.56-1.49 (m, 2H), 0.84 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 209.5, 148.8, 138.4, 134.4, 129.3, 128.6, 126.9, 126.8, 126.2, 118.1, 114.6, 54.9, 49.3, 46.0, 41.9, 27.3, 16.9, 13.6; HR - MS m/z: calcd for $C_{20}H_{23}NNaO[M^+$+Na]: 316.1672; found: 316.1669.

4-methyl-1-(2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)pentan-2-one (8)



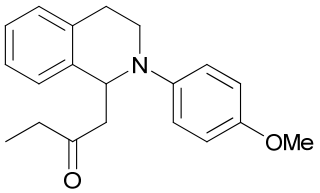
Synthesized according to general procedure A. Colourless oil, r_f = 0.60 (EtOAc/pentane, 1:9); Yield : 11 mg, 32%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25 (t, J = 6.7 Hz, 2H), 7.15-7.12 (m, 4H), 6.94 (bs, 2H), 6.77 (bs, 1H), 5.44 (t, J = 6.3 Hz, 1H), 3.67-3.62 (m, 1H), 3.56-3.51 (m, 1H), 3.09-3.00 (m, 2H), 2.85-2.74 (m, 2H), 2.23-2.01 (m, 3H), 0.84 (t, J = 3.9 Hz, 3H), 0.83 (t, J = 3.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 209.2, 138.5, 134.4, 129.3, 128.6, 126.9, 126.8, 126.3, 118.1, 114.6, 54.7, 53.0, 49.7, 42.0, 27.3, 24.4, 22.6, 22.5; HR - MS m/z: calcd for $C_{21}H_{25}NNaO[M^+$+Na]: 330.1828; found: 330.1825.

1-(2-(*p*-methoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)propan-2-one (9)



Synthesized according to general procedure A. Colourless oil, r_f = 0.50 (EtOAc/pentane, 3:7); Yield : 18 mg, 51%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.17-7.09 (m, 4H), 6.91 (bd, J = 8.2 Hz, 2H), 6.81 (d, J = 8.2 Hz, 2H), 5.24 (t, J = 6.4 Hz, 1H), 3.75 (s, 3H), 3.58-3.53 (m, 1H), 3.49-3.43 (m, 1H), 3.03-2.96 (m, 2H), 2.77 (dd, J = 16.1, 6.3 Hz, 1H), 2.72 (bs, 1H), 2.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 207.3, 138.3, 134.3, 128.9, 126.8, 126.7, 126.2, 118.4, 114.6, 56.0, 55.6, 49.9, 42.9, 30.9, 26.7; HR - MS m/z: calcd for $C_{19}H_{21}NNaO_2[M^+$+Na]: 318.1464; found: 318.1466.

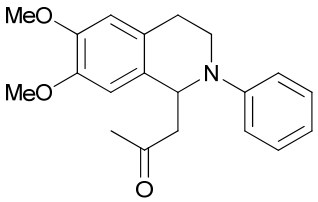
1-(2-(*p*-methoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)butan-2-one (10)



Synthesized according to general procedure A. Colourless oil, r_f = 0.70 (EtOAc/pentane, 3:7); Yield : 15 mg, 40%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.16-7.10 (m, 4H), 6.91 (d, J = 8.3 Hz, 2H), 6.81 (d, J = 9.1 Hz, 2H), 5.27 (t, J = 6.2 Hz, 1H), 3.75 (s, 3H), 3.58-3.44 (m, 2H), 3.05-2.98 (m, 2H), 2.75-2.71 (m, 2H), 2.36-2.23 (m, 2H), 0.97 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125

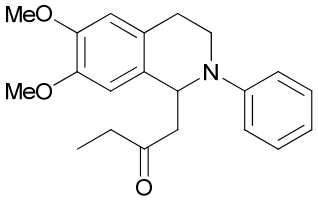
MHz, $CDCl_3$): δ 210.1, 153.1, 143.7, 138.4, 134.3, 128.9, 126.8, 126.6, 126.2, 118.1, 114.7, 56.1, 55.6, 48.7, 42.7, 37.1, 26.8, 7.5; HR - MS m/z: calcd for $C_{20}H_{23}NNaO_2[M^+ + Na]$: 332.1621; found: 332.1624.

1-(6,7-dimethoxy-2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)propan-2-one (11)



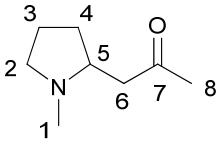
Synthesized according to general procedure A. Colourless oil, r_f = 0.30 (EtOAc/pentane, 3:7); Yield : 24 mg, 61%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24 (t, J = 8.4 Hz, 2H), 6.94 (d, J = 6.5 Hz, 2H), 6.79 (t, J = 6.5 Hz, 1H), 6.69 (s, 1H), 6.61 (s, 1H), 5.30 (t, J = 6.3 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.69-3.64 (m, 1H), 3.52-3.47 (m, 1H), 3.06-2.94 (m, 2H), 2.83 (dd, J = 16.3, 6.9 Hz, 1H), 2.72-2.69 (m, 1H), 2.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 207.7, 149.0, 147.8, 147.4, 130.2, 129.3, 126.3, 118.4, 115.1, 111.3, 109.8, 55.9, 55.8, 54.6, 50.2, 41.9, 31.2, 26.6; HR - MS m/z: calcd for $C_{20}H_{23}NO_3[M^+]$: 325.1678; found: 325.1675.

1-(6,7-dimethoxy-2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)butan-2-one (12)



Synthesized according to general procedure A. Colourless oil, r_f = 0.40 (EtOAc/pentane, 3:7); Yield : 15 mg, 36%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24 (t, J = 7.7 Hz, 2H), 6.95 (d, J = 6.0 Hz, 2H), 6.78 (t, J = 6.0 Hz, 1H), 6.65 (s, 1H), 6.61 (s, 1H), 5.32 (t, J = 6.4 Hz, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.68-3.63 (m, 1H), 3.52-3.48 (m, 1H), 3.03-2.95 (m, 2H), 2.79-2.69 (m, 2H), 2.39-2.24 (m, 2H), 0.99 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.8, 147.4, 130.5, 129.3, 126.3, 118.3, 114.9, 111.3, 109.7, 55.9, 55.8, 54.9, 48.8, 42.1, 37.4, 26.7, 7.6; HR - MS m/z: calcd for $C_{21}H_{25}NNaO_3[M^+ + Na]$: 362.1727; found: 362.1729.

Hygrine (14)



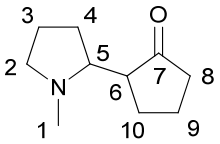
Synthesized according to general procedure B. Yellowish oil, r_f = 0.42 (CH_2Cl_2/MeOH/conc. NH_3 50:50:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.06-3.01 (ddd, J = 2.4 Hz, J = 7.3 Hz, J = 9.6 Hz, 1H, H^2), 2.79 (dd, J = 3.8 Hz, J = 16.2 Hz, 1H, H^6), 2.56-2.49 (m, 1H, H^5), 2.42 (dd, J = 8.8 Hz, J = 16.2 Hz, 1H, H^6), 2.30 (s, 3H, H^1), 2.21-2.15 (m, 1H, H^2), 2.18 (s, 3H, H^8), 2.13-2.05 (m, 1H, H^4), 1.81-1.66 (m, 2H, H^3), 1.45-1.36 (m, 1H, H^4); ^{13}C NMR (125

MHz, $CDCl_3$): δ 208.0 (C7), 61.7 (C5), 56.7 (C2), 48.4 (C6), 40.4 (C1), 31.3 (C4), 30.9 (C8), 22.1 (C3); HR – MS (EI) m/z: calcd for $C_8H_{15}NO[M^+]$: 141.115363 ; found: 141.115516.

Spectroscopic data for the hydrochloric acid salt were identical with those reported in the literature.[S2]

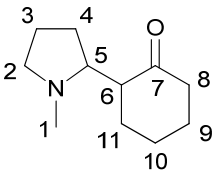
Enantiomeric excess was determined by ^{1}H-NMR spectroscopy in $CDCl_3$ using 35 mol% (+)-di-*O*-4-toluoyl-D-tartaric acid monohydrate as a chiral shift reagent and integrating the C1-methyl signals of the enantiomers at ca. 2.62 and 2.66 ppm (also see the NMR spectra below).

2-(1-methylpyrrolidin-2-yl)cyclopentanone (17)



Synthesized according to general procedure B. Yellowish oil, diastereomeric ratio (**17**:**17'**) ca. 1.8:1, determined by ^{1}H-NMR spectroscopy; inseparable by column chromatography; r_f = 0.4 (CH_2Cl_2/MeOH/conc. NH_3 90:10:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.09-3.03 (m, 1H, $H^{2,2'}$), 2.75-2.70 (m, ca. 0.4H, $H^{5'}$), 2.68-2.62 (m, ca. 0.6H, H^5), 2.54-2.48 (m, ca. 0.6H, H^6), 2.37-1.9 (m, ca. 9H [2.31/2.17 (2s, 3H, $H^{1,1'}$)]), 1.82-1.66 (m, ca. 4.4H), 1.64-1.57 (m, ca. 0.4H, $H^{4'}$), 1.44-1.36 (m, ca. 0.6H, H^4); ^{13}C NMR (125 MHz, $CDCl_3$): δ 220.9 (C7), 220.4 (C7'), 64.9 (C5), 64.4 (C5'), 57.7 (C2'), 56.7 (C2), 52.6 (C6'), 49.9 (C6), 42.0 (C1'), 40.0 (C1), 39.2 (C8), 30.6 (C4'), 25.5 (C4), 24.5, 23.5, 22.6, 22.2, 20.80, 20.77; HR – MS (EI) m/z: calcd for $C_{10}H_{17}NO[M^+]$: 167.131014 ; found: 167.130846.

2-(1-methylpyrrolidin-2-yl)cyclohexanone (18)



Synthesized according to general procedure B. Yellowish oil, diastereomeric ratio (**18**:**18'**) ca. 2.8:1, determined by ^{1}H-NMR spectroscopy; inseparable by column chromatography; r_f = 0.3 (CH_2Cl_2/MeOH/conc. NH_3 90:10:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.06-2.99 (m, 1H, $H^{2,2'}$), 2.75-2.70 (m, ca. 0.3H, $H^{5'}$), 2.70-2.65 (m, ca. 0.7H, H^5), 2.59-2.53 (m, ca. 0.7H, H^6), 2.42-2.21 (m, ca. 6H [2.31/2.24 (2s, 3H, $H^{1',1}$)]), 2.19-2.12 (m, ca. 1.3H), 2.08-1.89 (m, ca. 3H), 1.77-1.42 (m, ca. 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 212.74 (C7), 212.70 (C7'), 64.0 (C5), 63.6 (C5'), 58.0 (C2'), 57.0 (C2), 56.1 (C6'), 51.7 (C6), 43.5 (C1'), 42.7 (C8'), 42.5 (C8), 40.7 (C1), 30.9, 30.2, 27.9, 27.3, 26.6, 26.5, 25.1, 24.9, 23.6, 23.0; HR – MS (EI) m/z: calcd for $C_{11}H_{19}NO[M^+]$: 181.146665; found: 181.146512.

Racemisation of 3 under reaction conditions

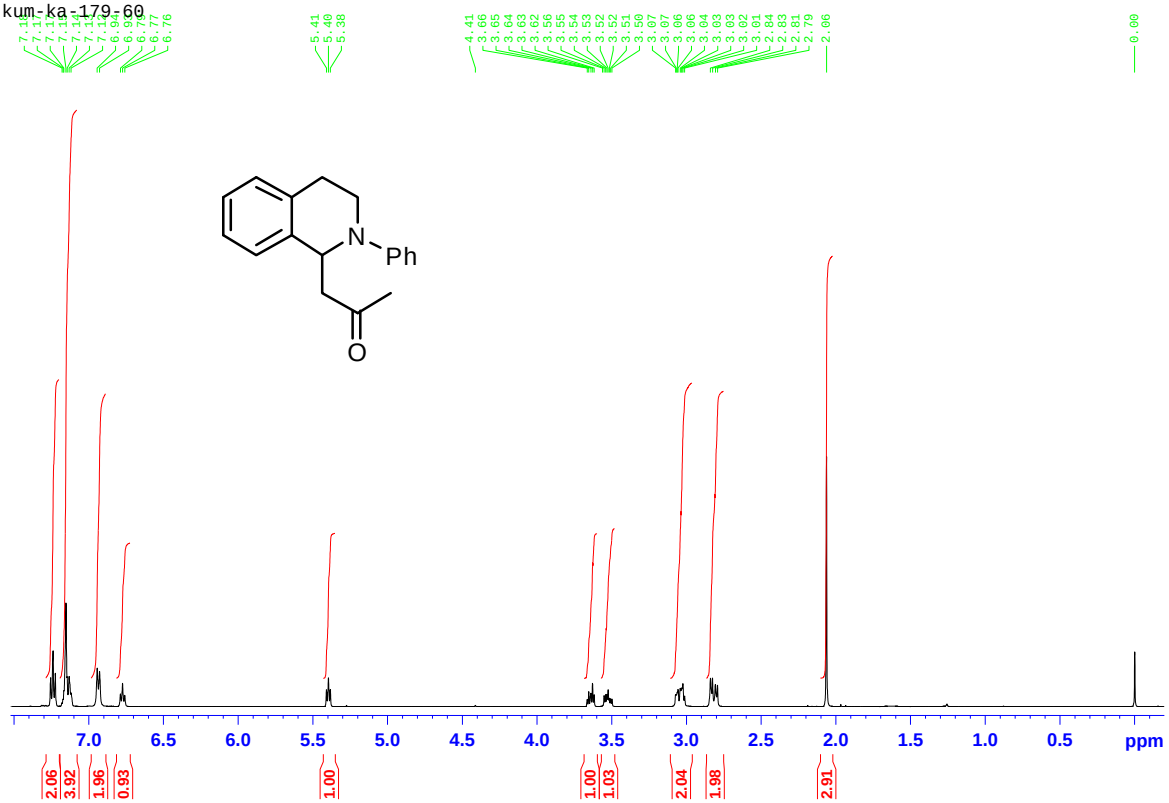
Isolated samples of basically enantiopure **3** (by preparative HPLC) were subjected to the reaction conditions of its synthesis, except that no substrate amine **1** was added. Aliquots for analysis were taken after certain time intervals and worked up by addition to a mixture of water and CH_2Cl_2 and extracting it with CH_2Cl_2. The combined organic phases are dried over $MgSO_4$, concentrated in vacuo and directly analysed for ee by HPLC:

t	% ee
0	99
15h	89
2d	85
3d	83

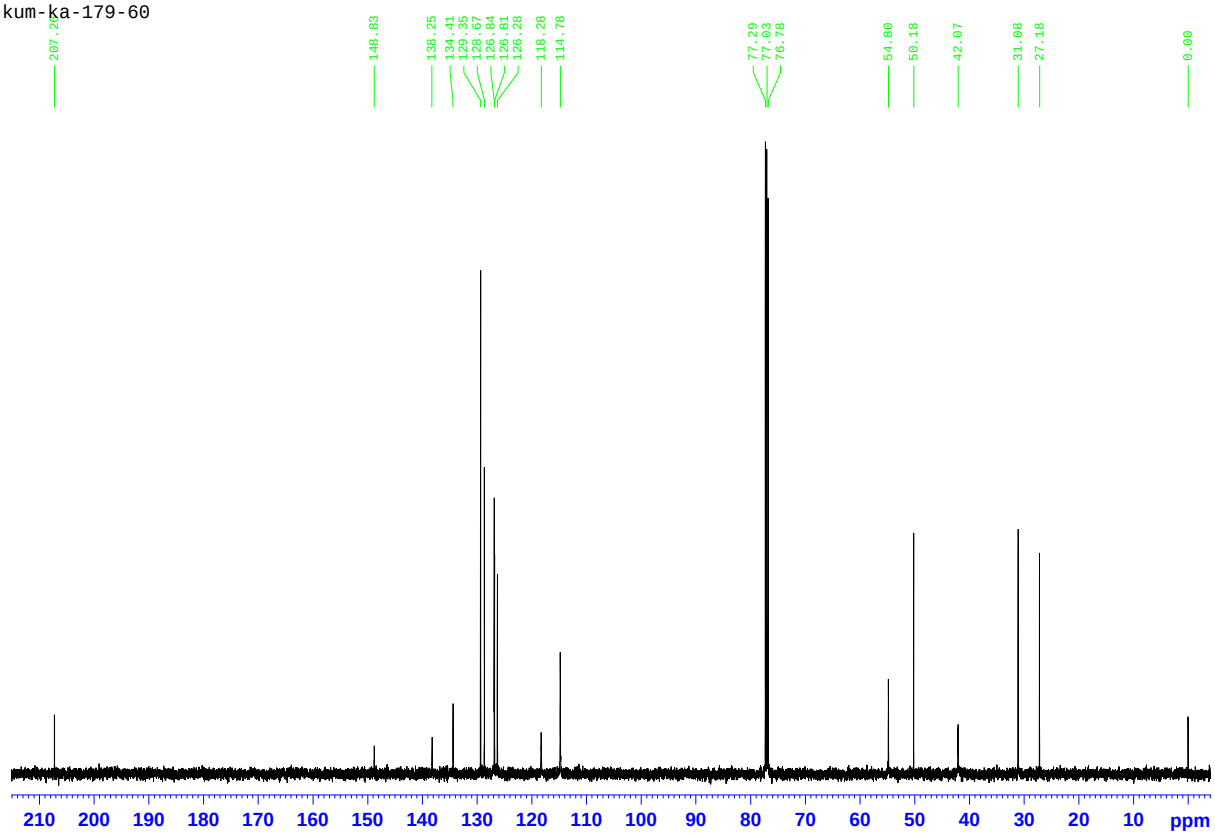
No further racemisation of the isolated samples occurred after keeping them at room temperature for two days.

NMR-spectra

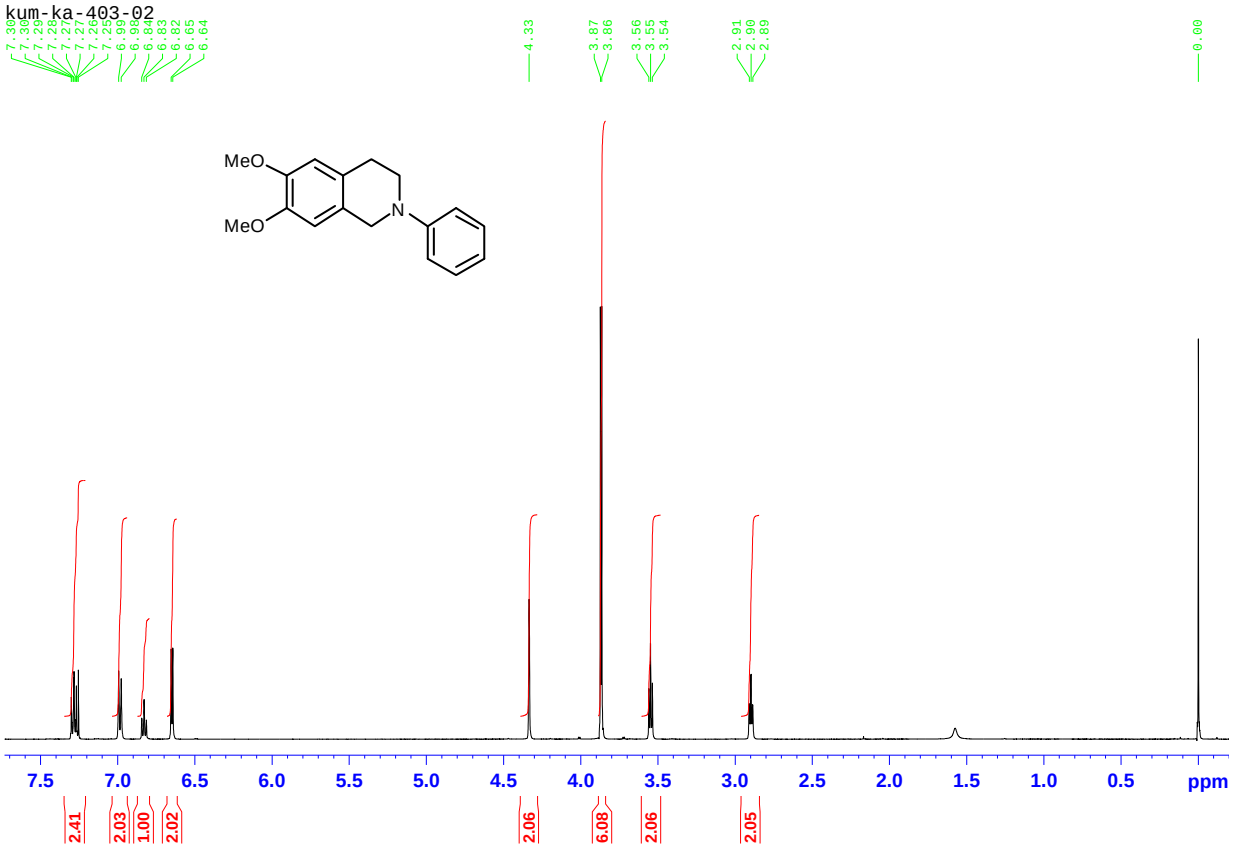
Compound 3: ^{1}H-NMR – $CDCl_3$ (500 MHz)



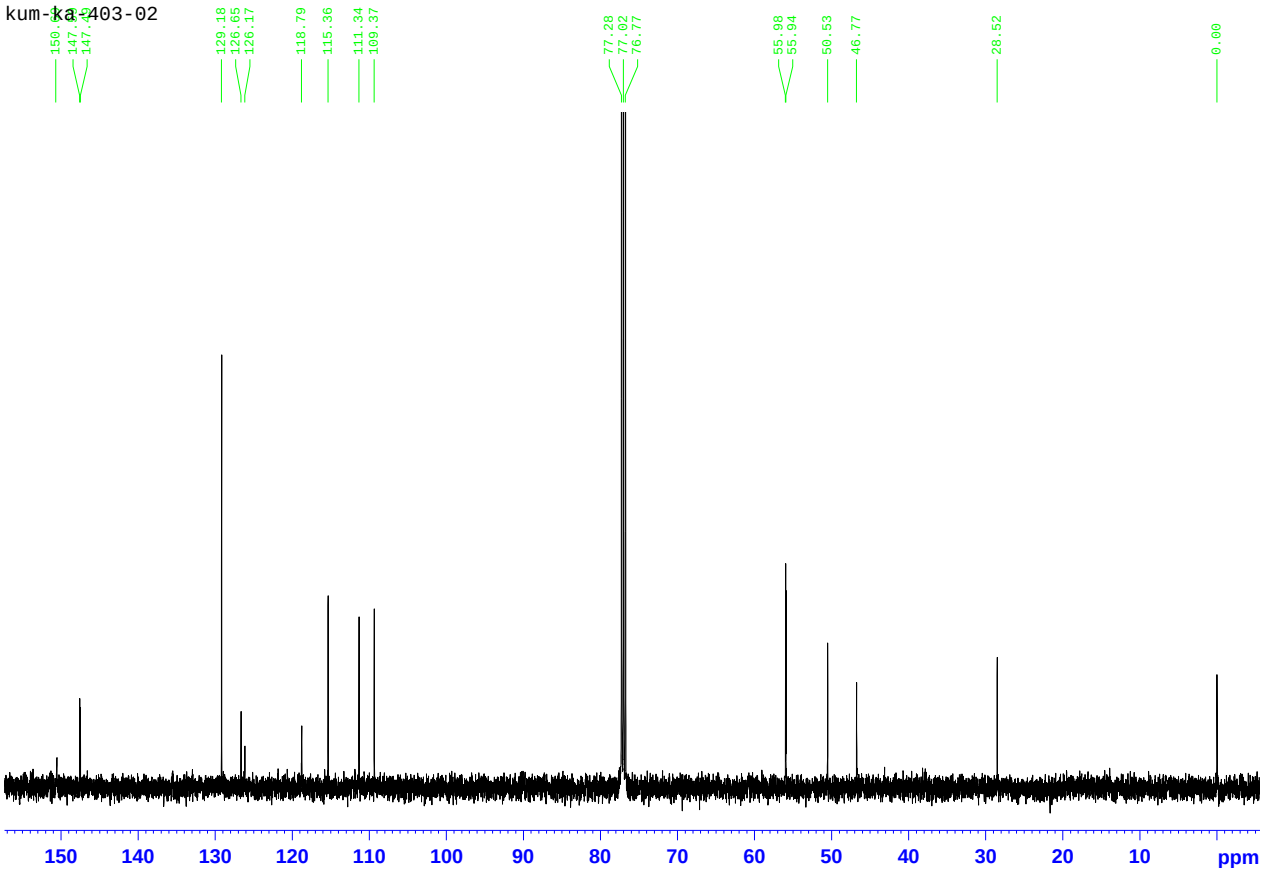
Compound 3: ^{13}C-NMR – $CDCl_3$ (125 MHz)



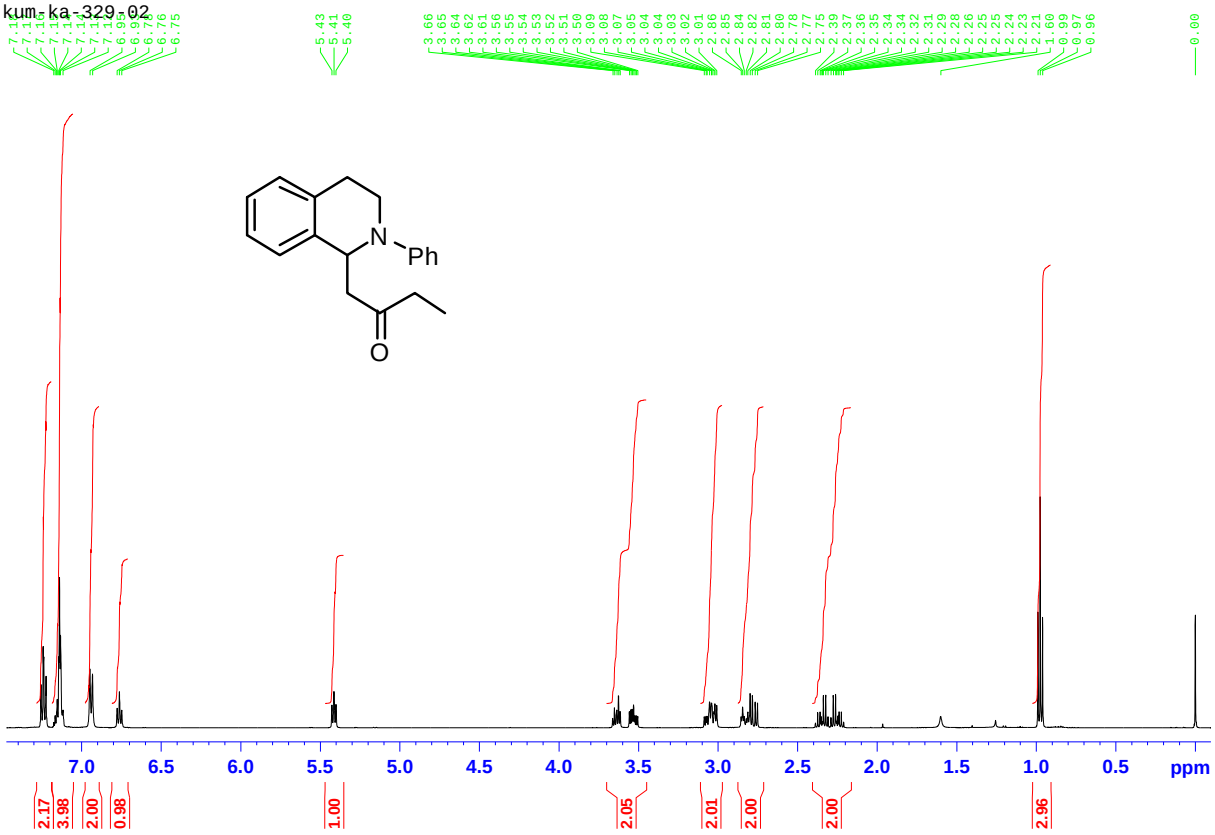
Compound 5: ^{1}H-NMR – $CDCl_3$ (500 MHz)



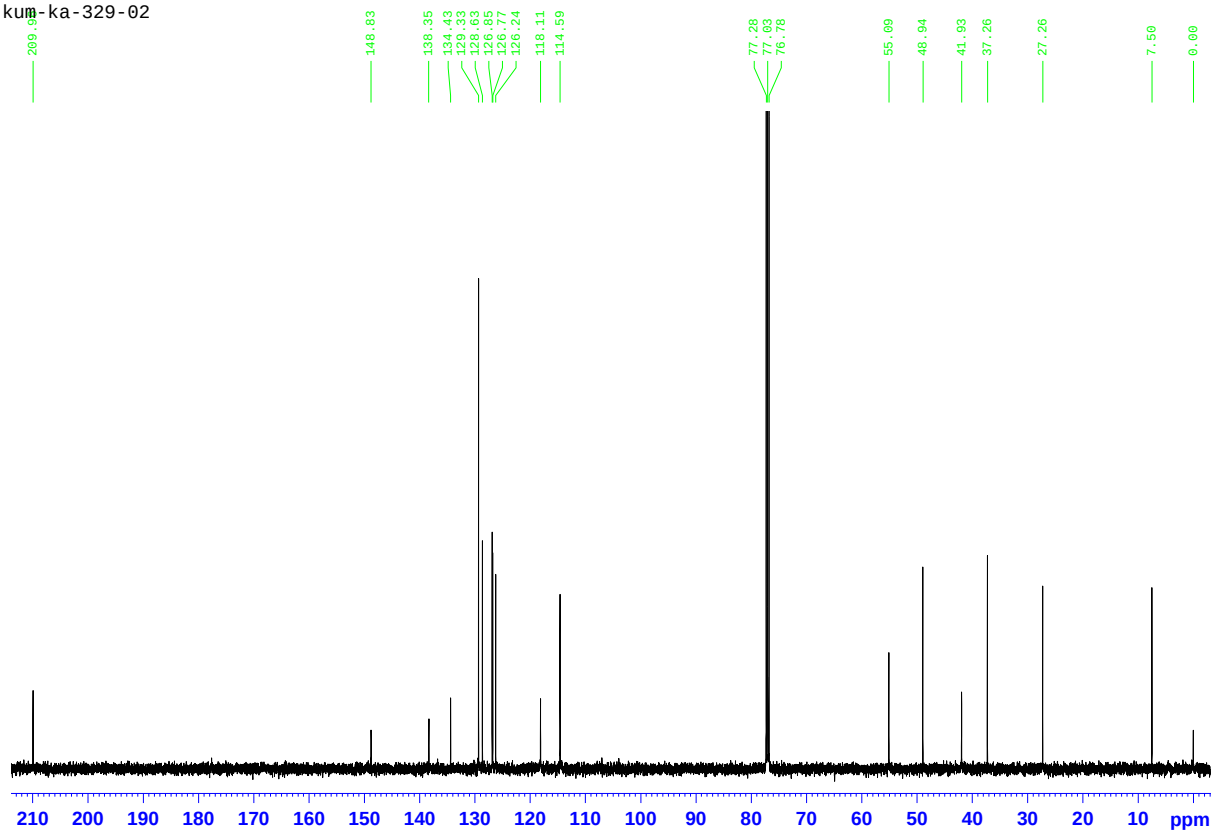
Compound 5: ^{13}C-NMR – $CDCl_3$ (125 MHz)



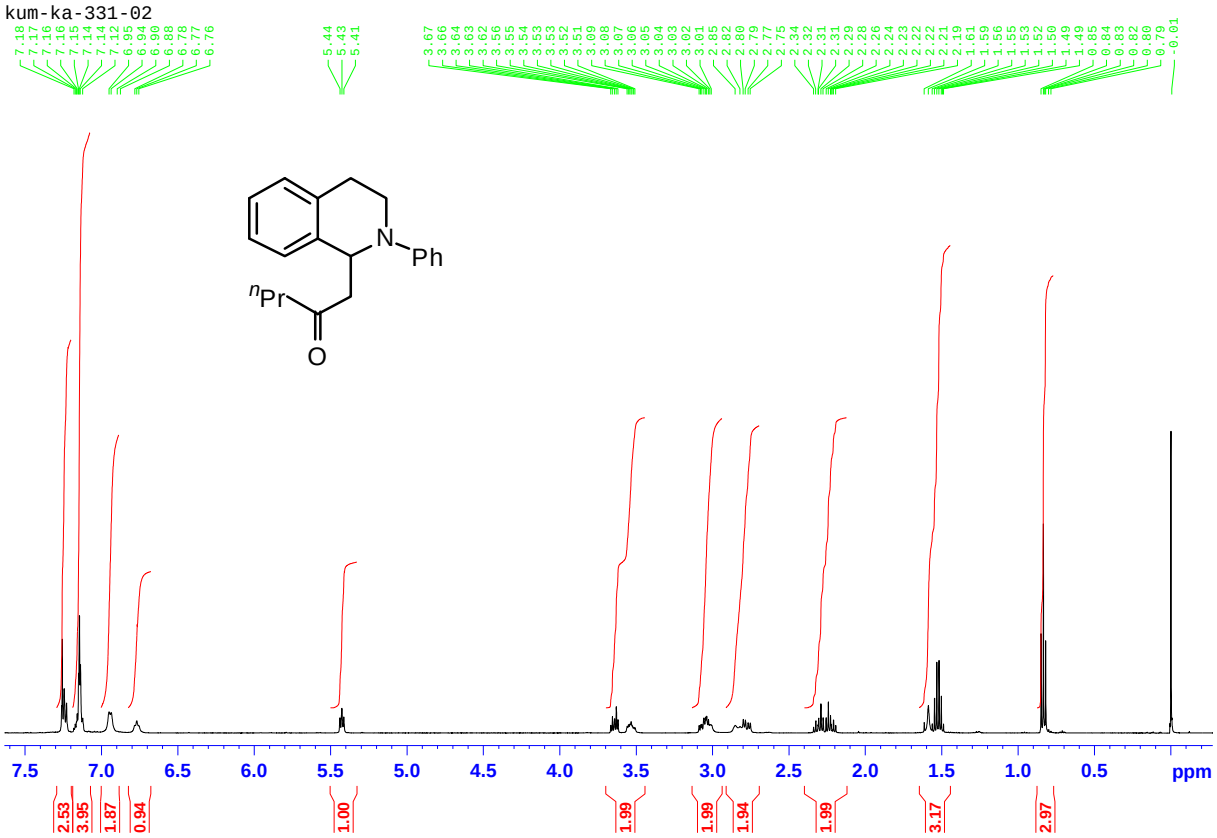
Compound 6: ^{1}H-NMR – $CDCl_3$ (500 MHz)



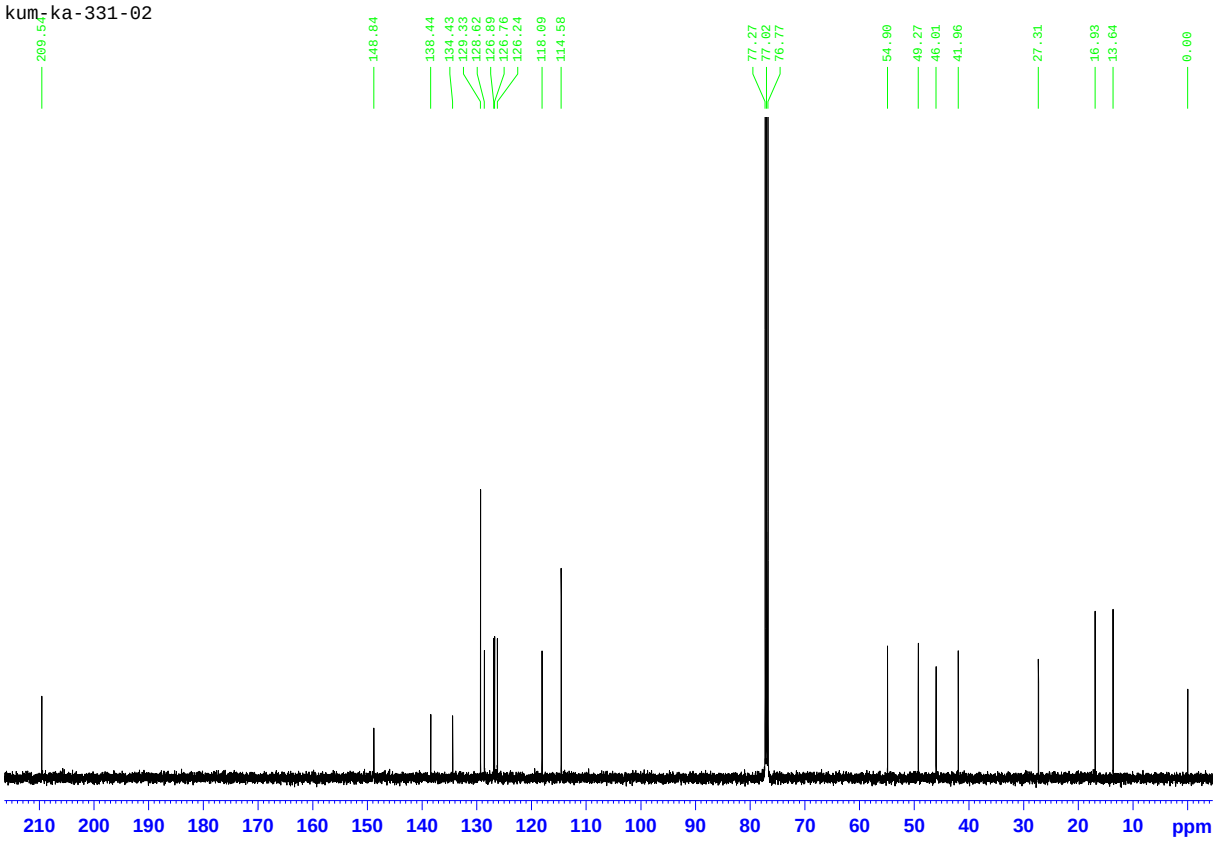
Compound 6: ^{13}C-NMR – $CDCl_3$ (125 MHz)



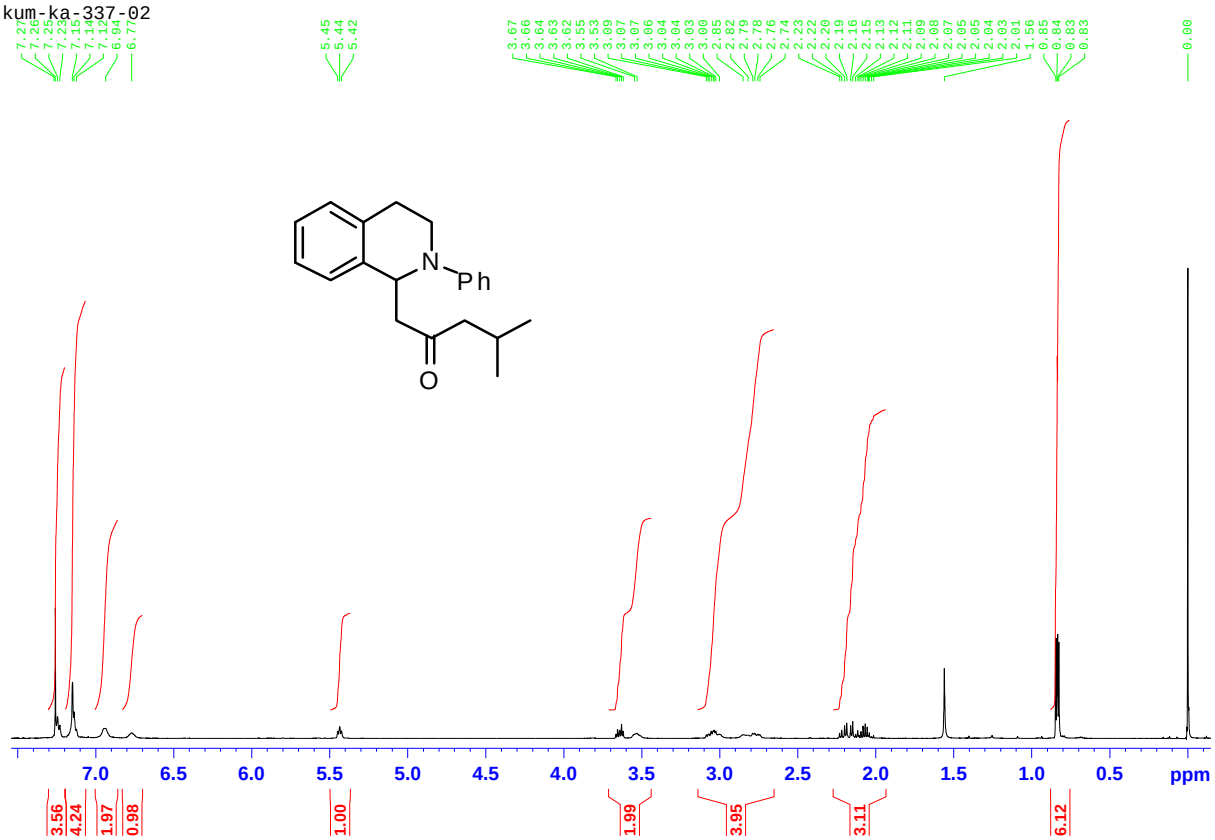
Compound 7: ^{1}H-NMR – $CDCl_3$ (500 MHz)



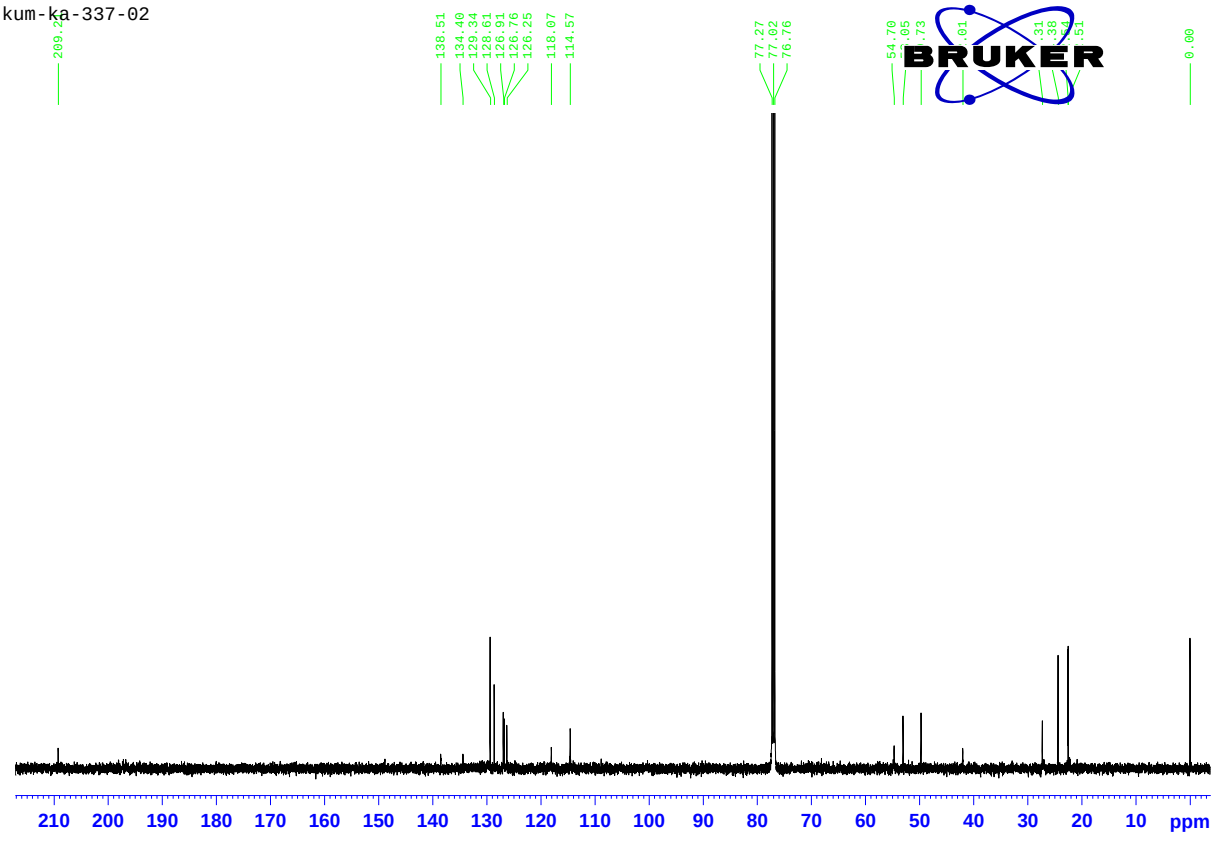
Compound 7: ^{13}C-NMR – $CDCl_3$ (125 MHz)



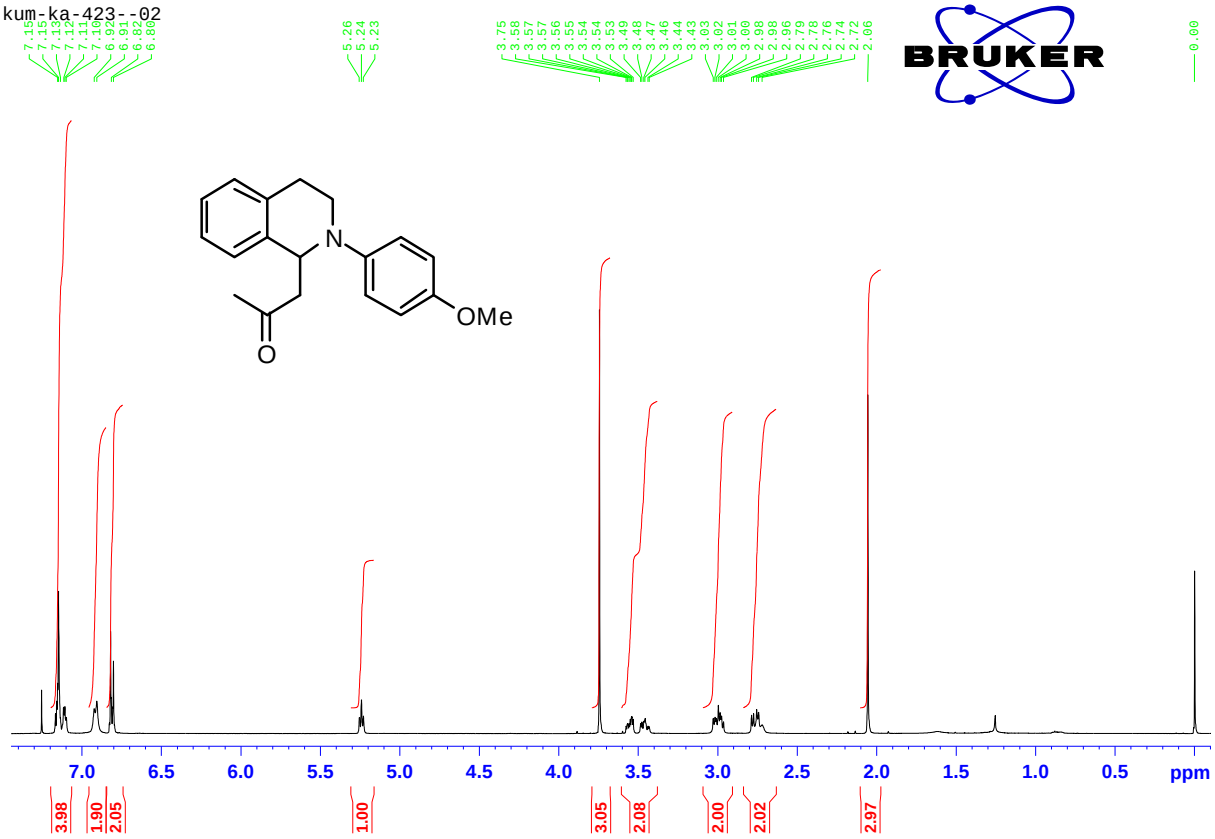
Compound 8: ^{1}H-NMR – $CDCl_3$ (500 MHz)



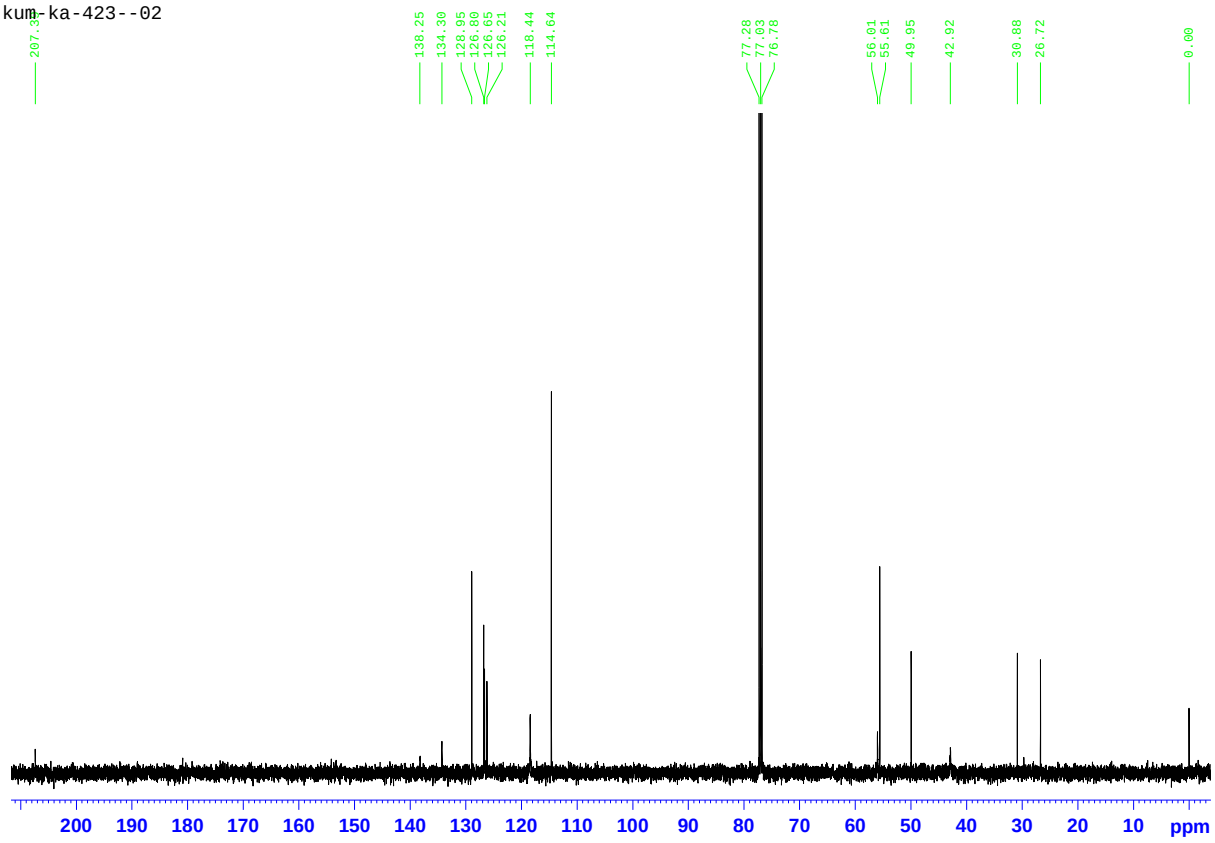
Compound 8: ^{13}C-NMR – $CDCl_3$ (125 MHz)



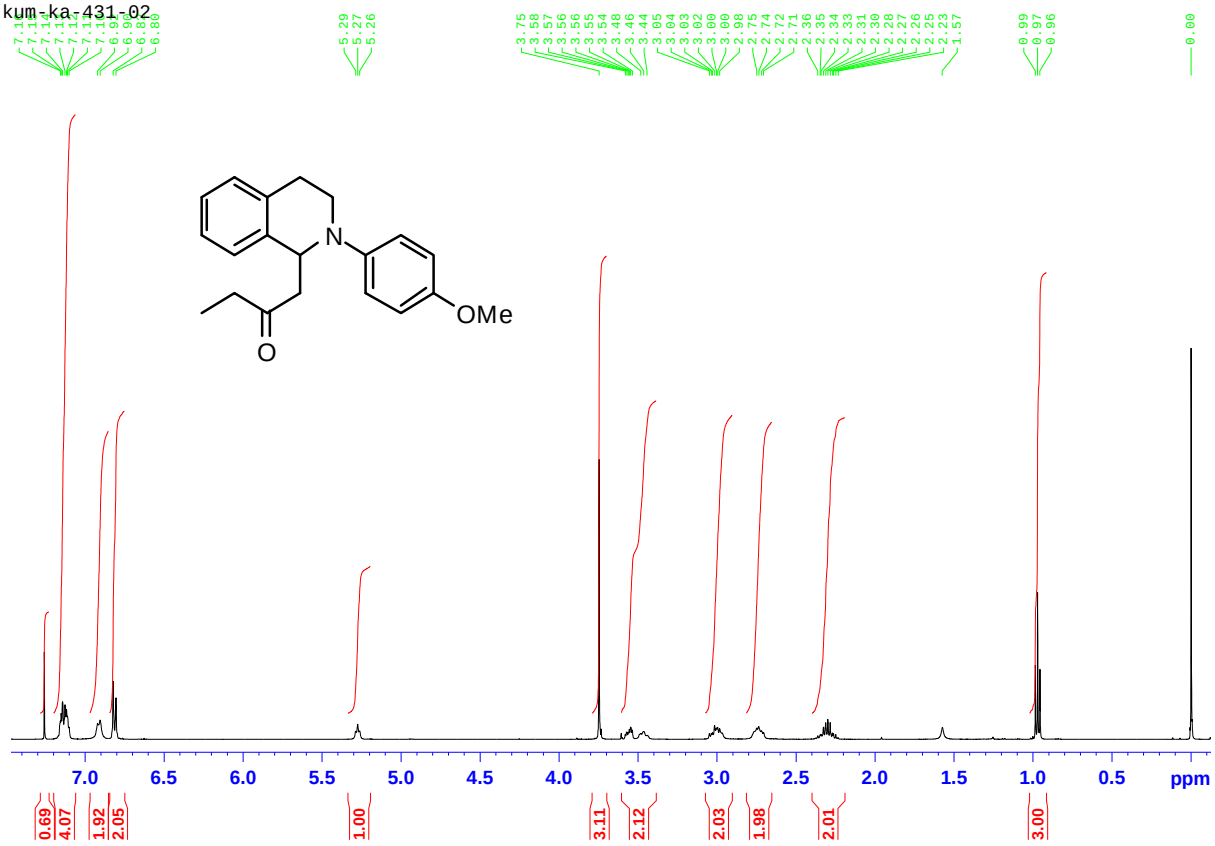
Compound 9: ^{1}H-NMR – $CDCl_3$ (500 MHz)



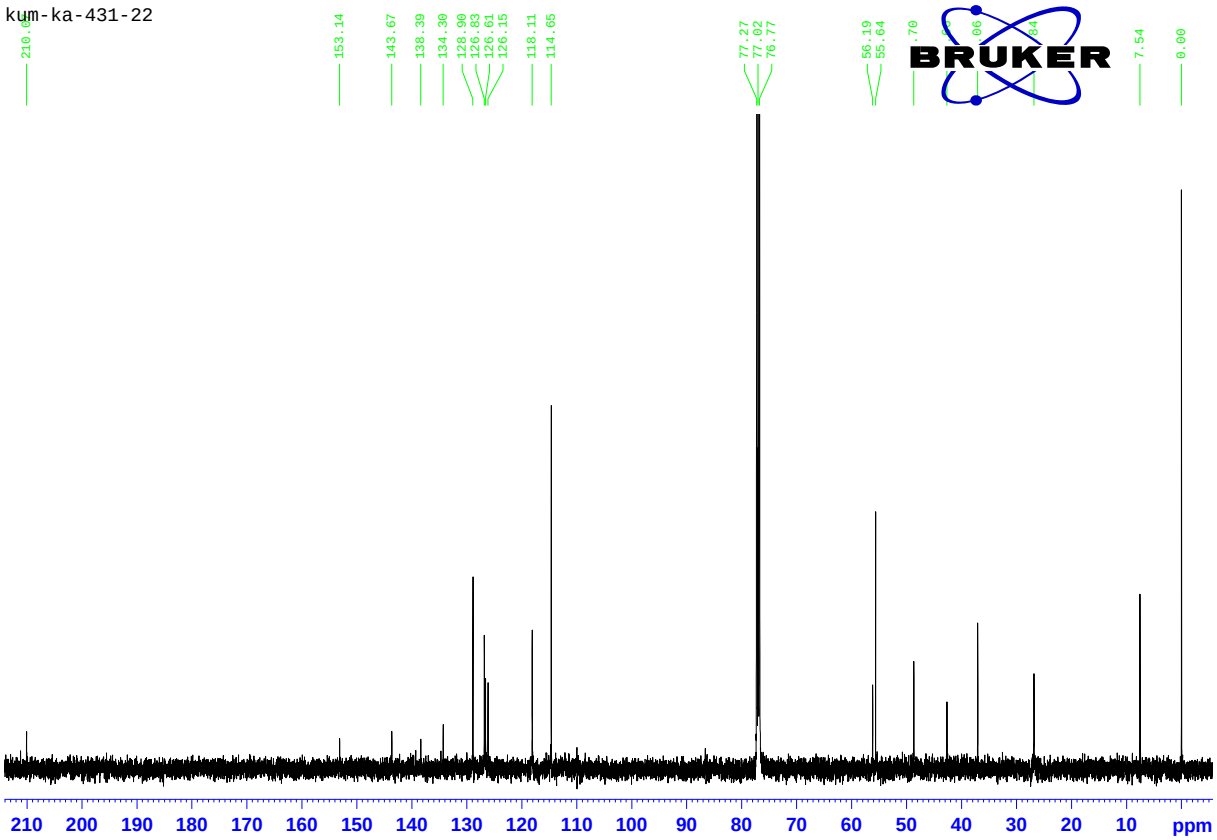
Compound 9: ^{13}C-NMR – $CDCl_3$ (125 MHz)



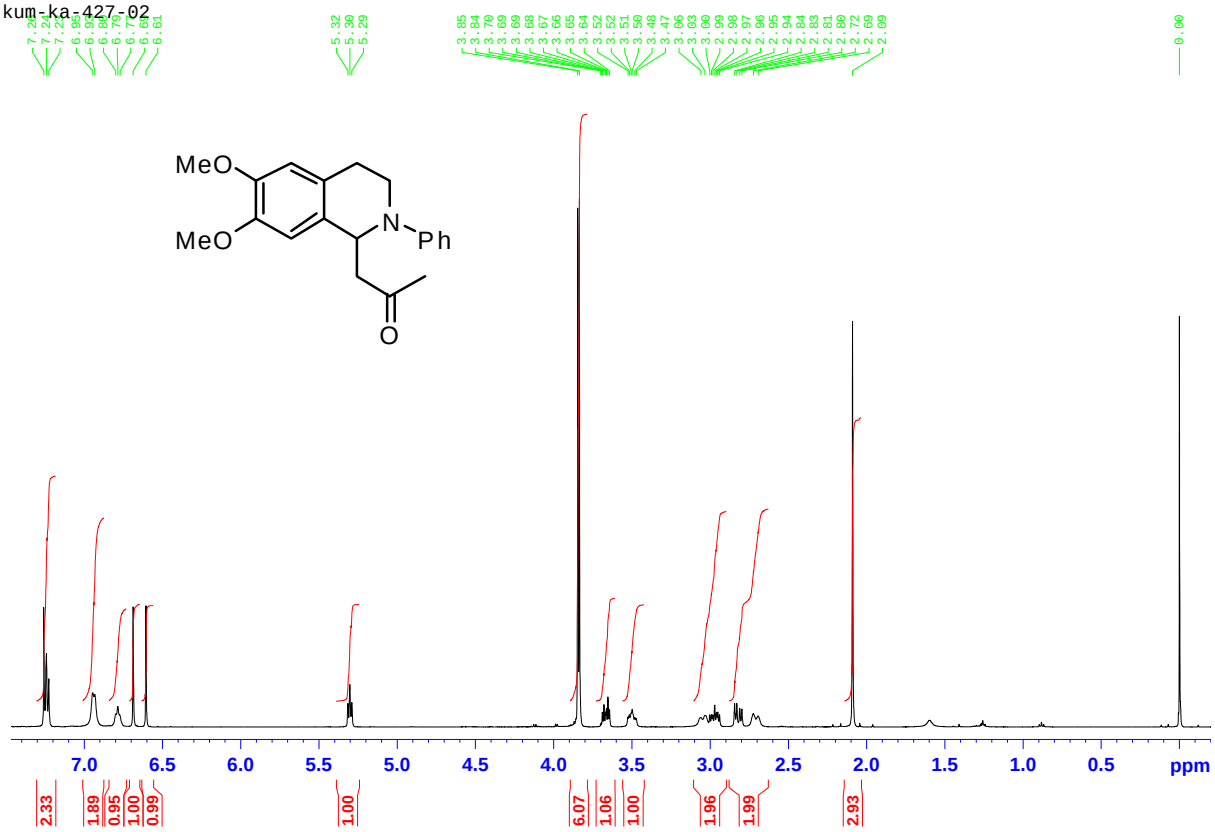
Compound 10: ^{1}H-NMR – $CDCl_3$ (500 MHz)



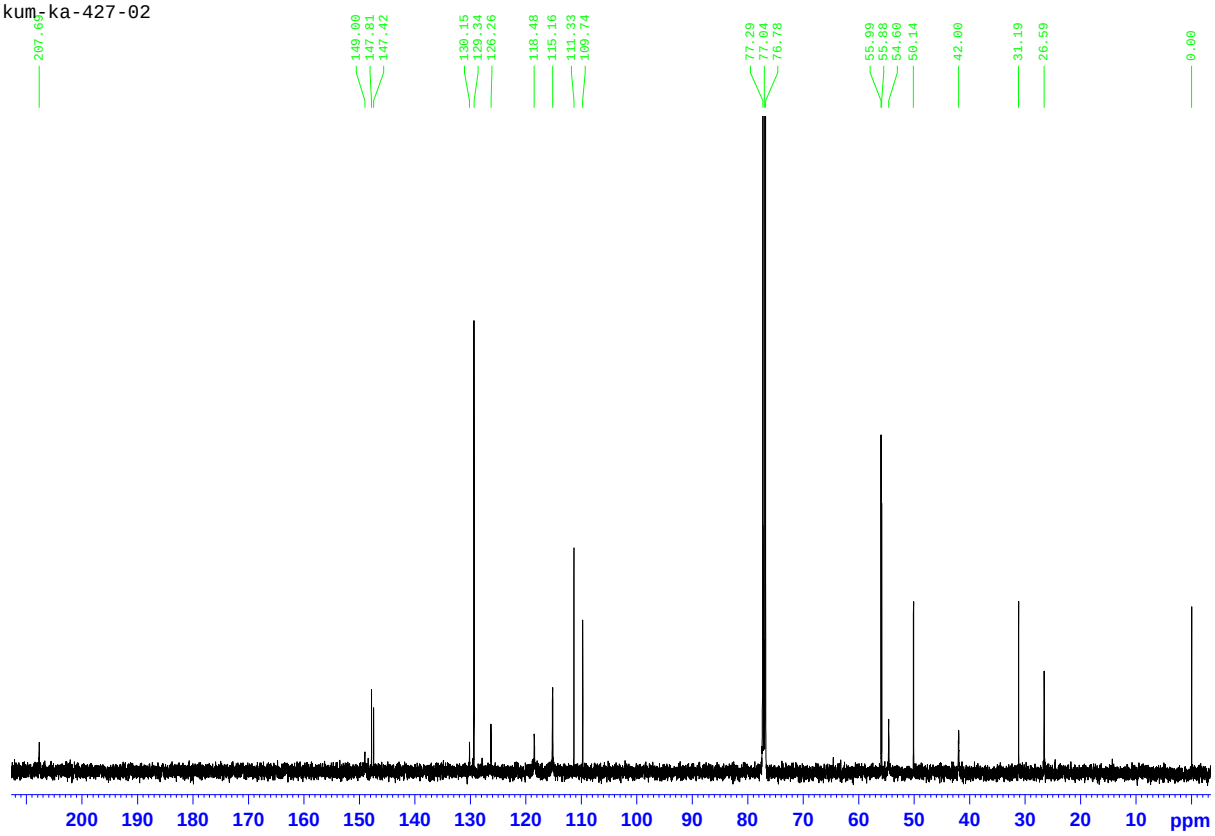
Compound 10: ^{13}C-NMR – $CDCl_3$ (125 MHz)



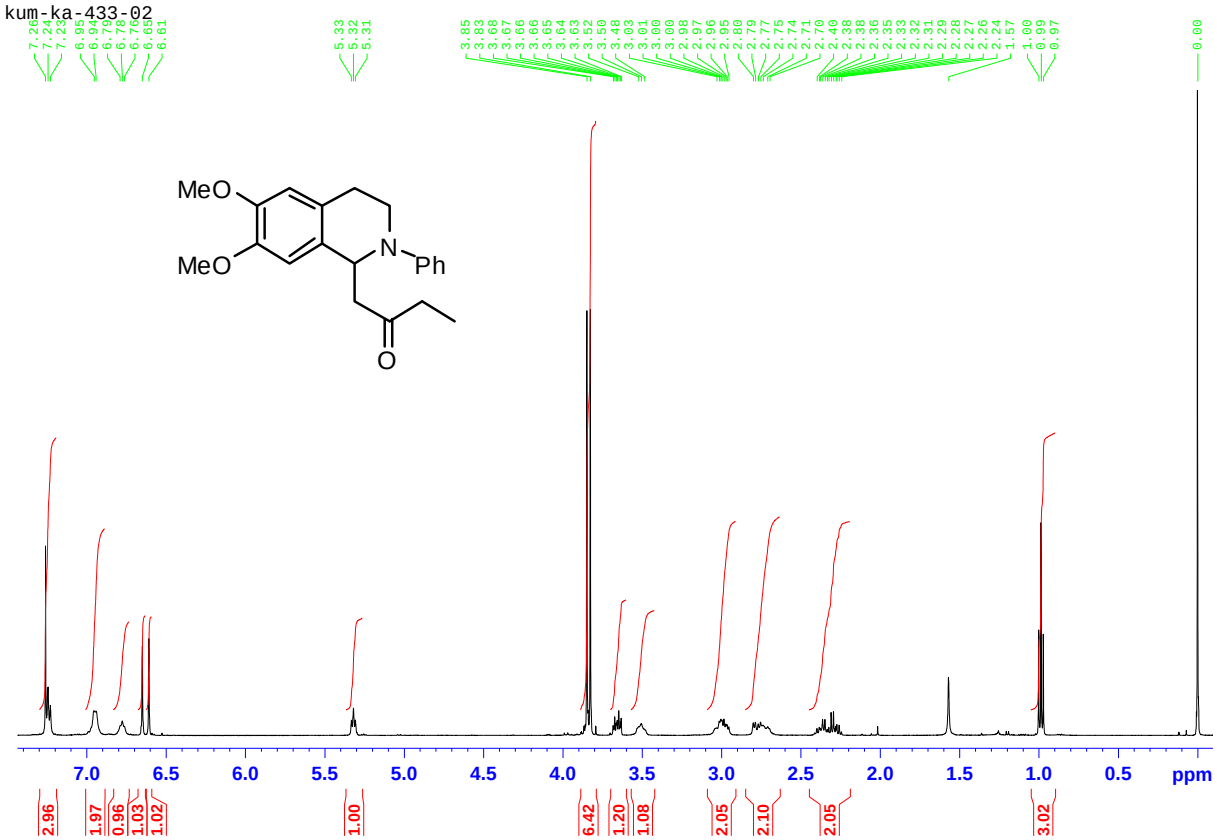
Compound 11: ^{1}H-NMR – $CDCl_3$ (500 MHz)



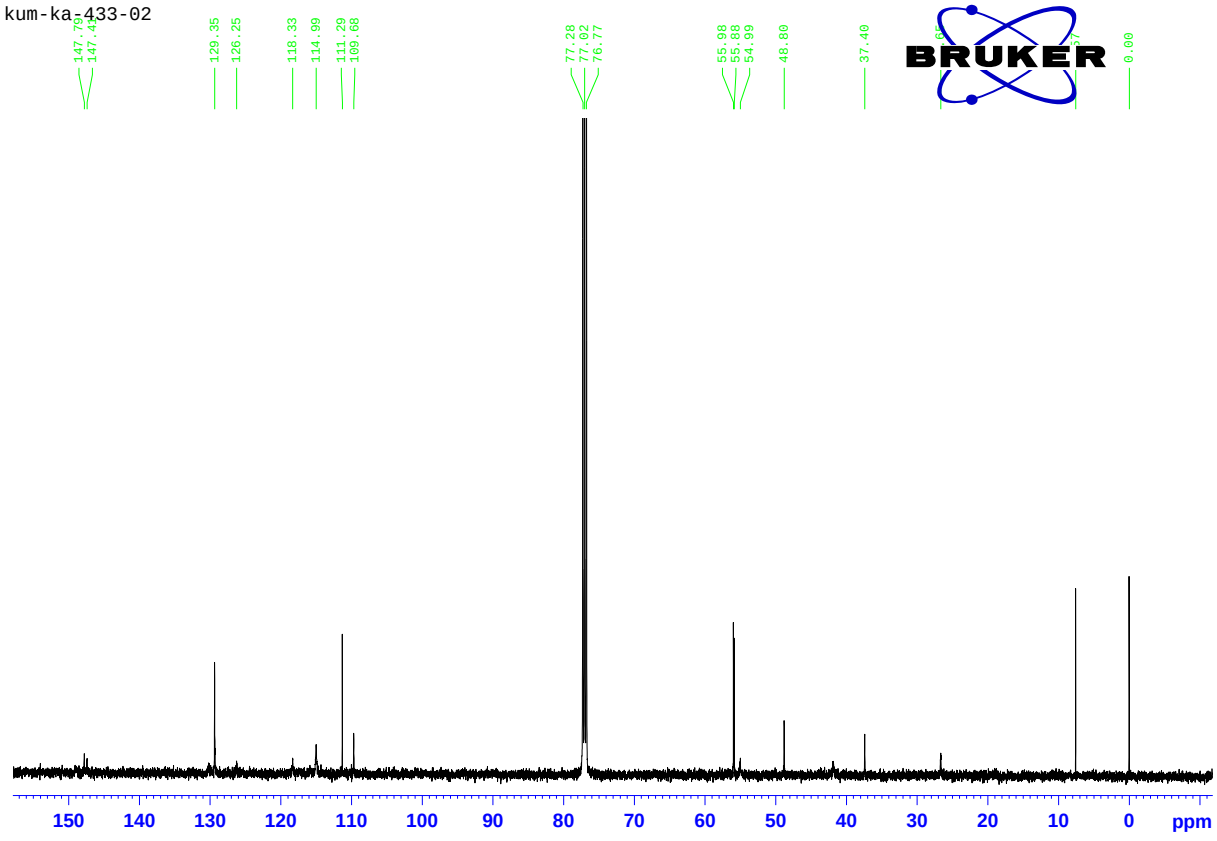
Compound 11: ^{13}C-NMR – $CDCl_3$ (125 MHz)



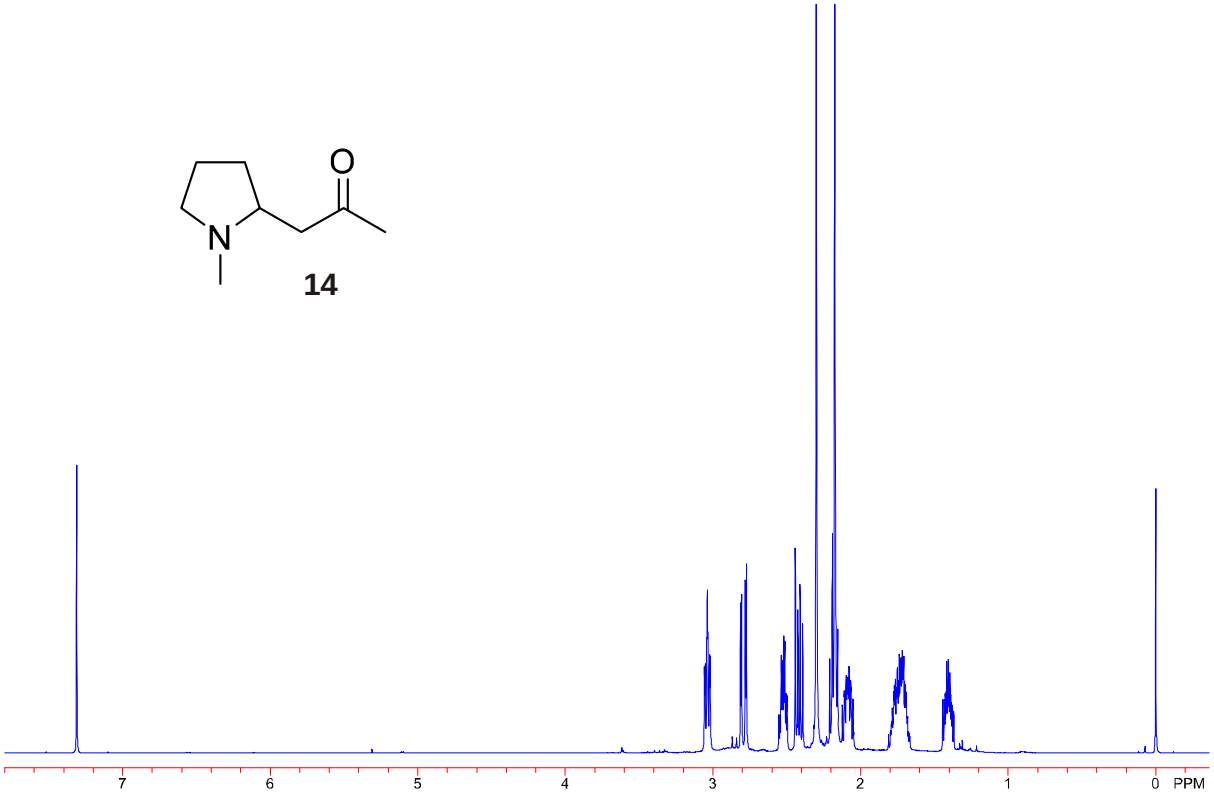
Compound 12: ^{1}H-NMR – $CDCl_3$ (500 MHz)



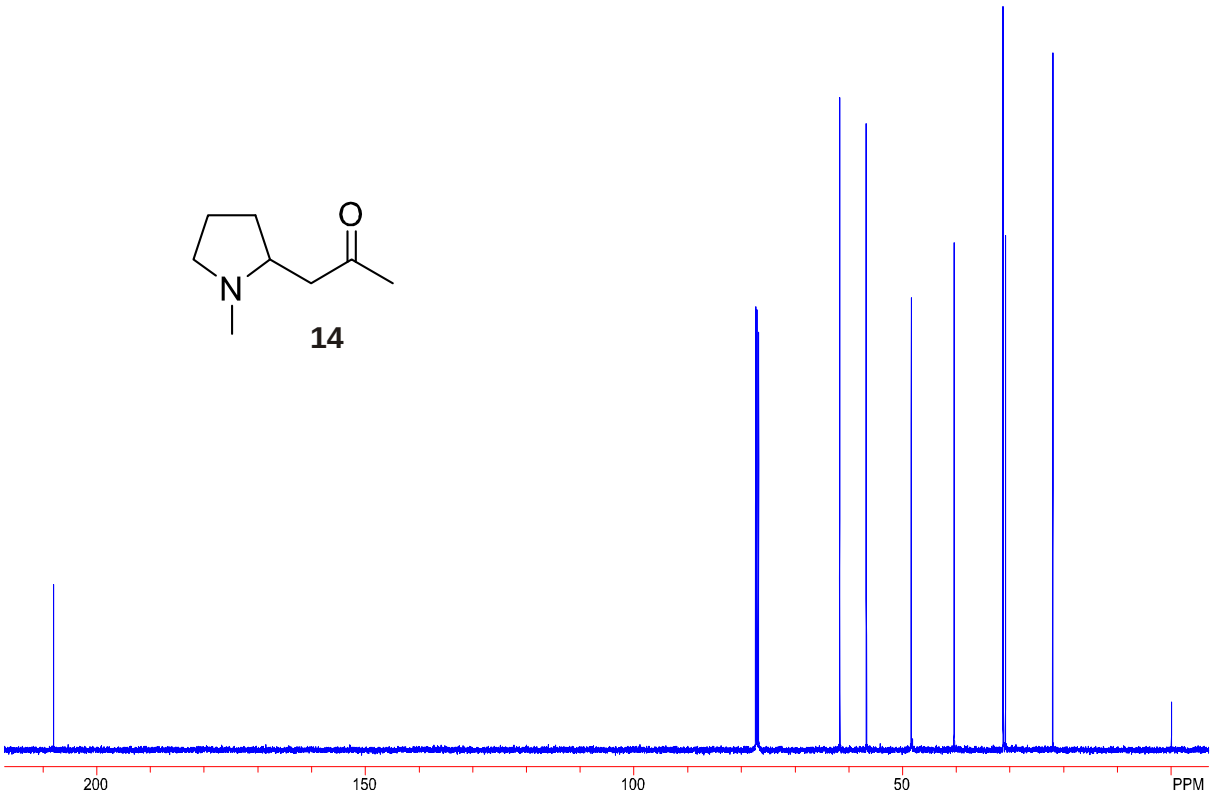
Compound 12: ^{13}C-NMR – $CDCl_3$ (125 MHz)



Compound 14: ^{1}H-NMR – $CDCl_3$ (500 MHz)



Compound 14: ^{13}C-NMR – $CDCl_3$ (125 MHz)



Determination of enantiomeric purity of 14 by ^{1}H-NMR

Using (+)-di-*O*-4-toluoyl-D-tartaric acid monohydrate (DTTA) as a chiral shift reagent in $CDCl_3$.

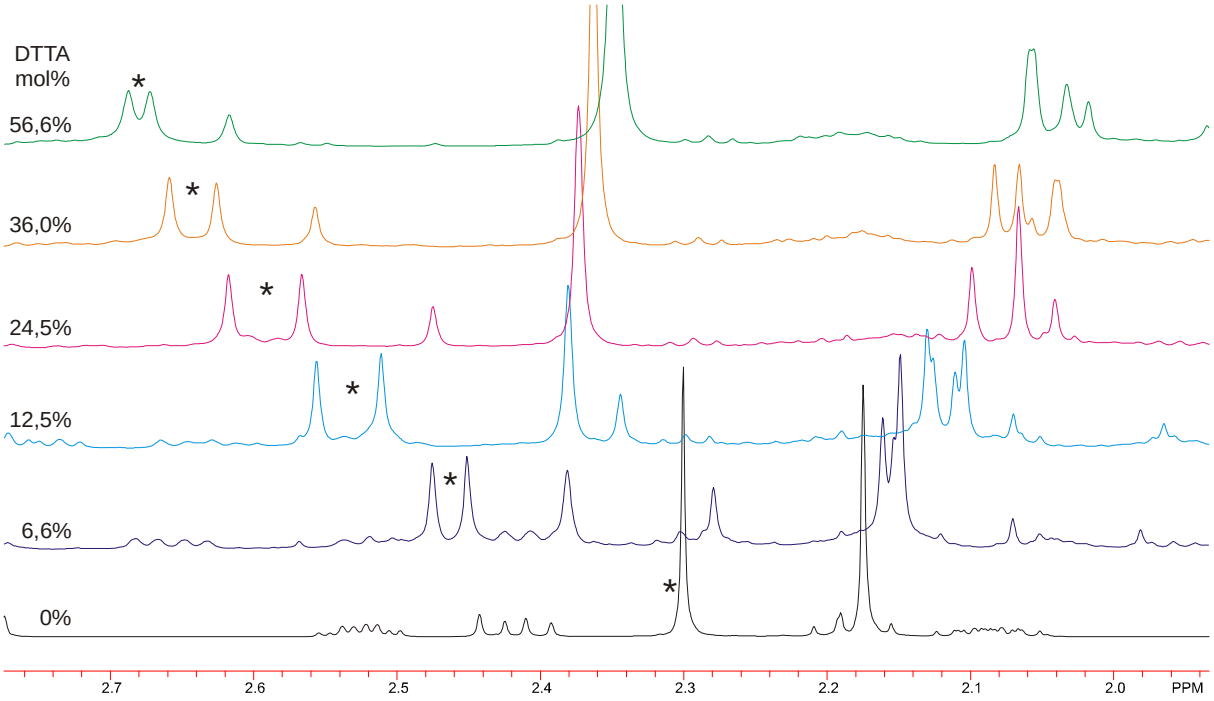
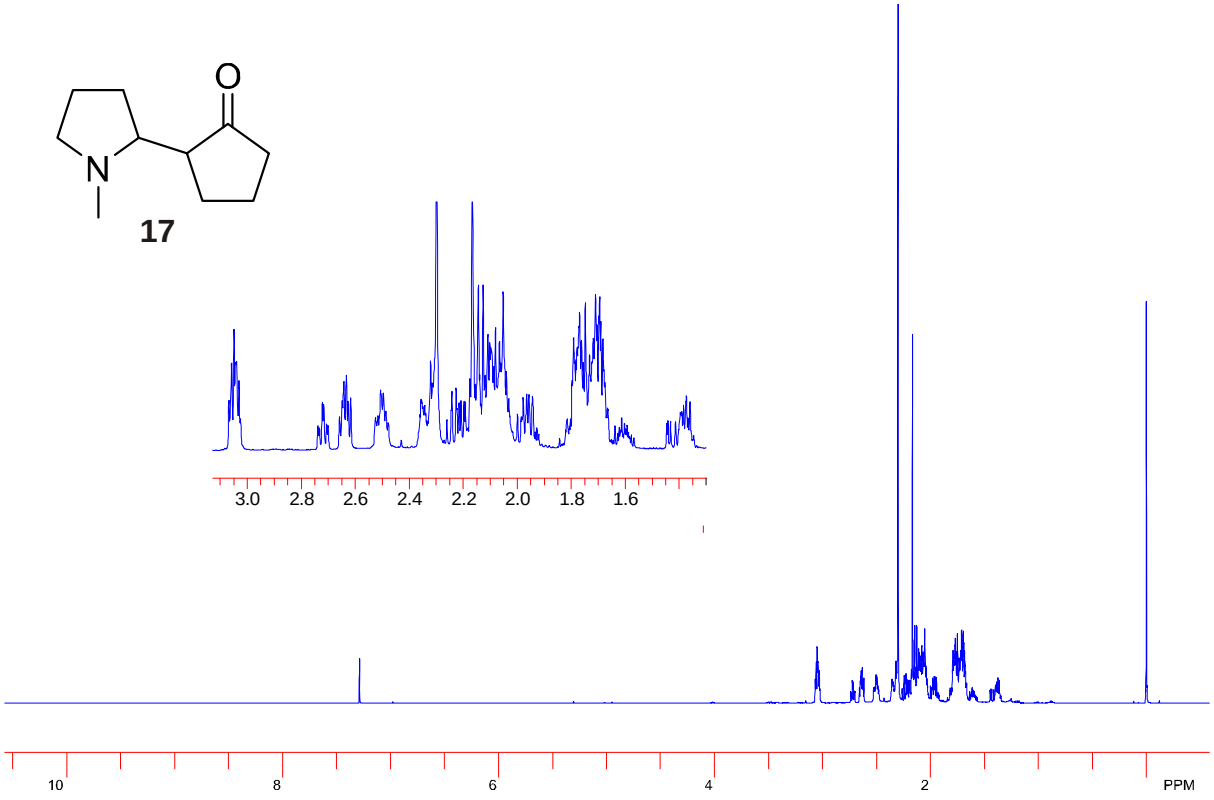
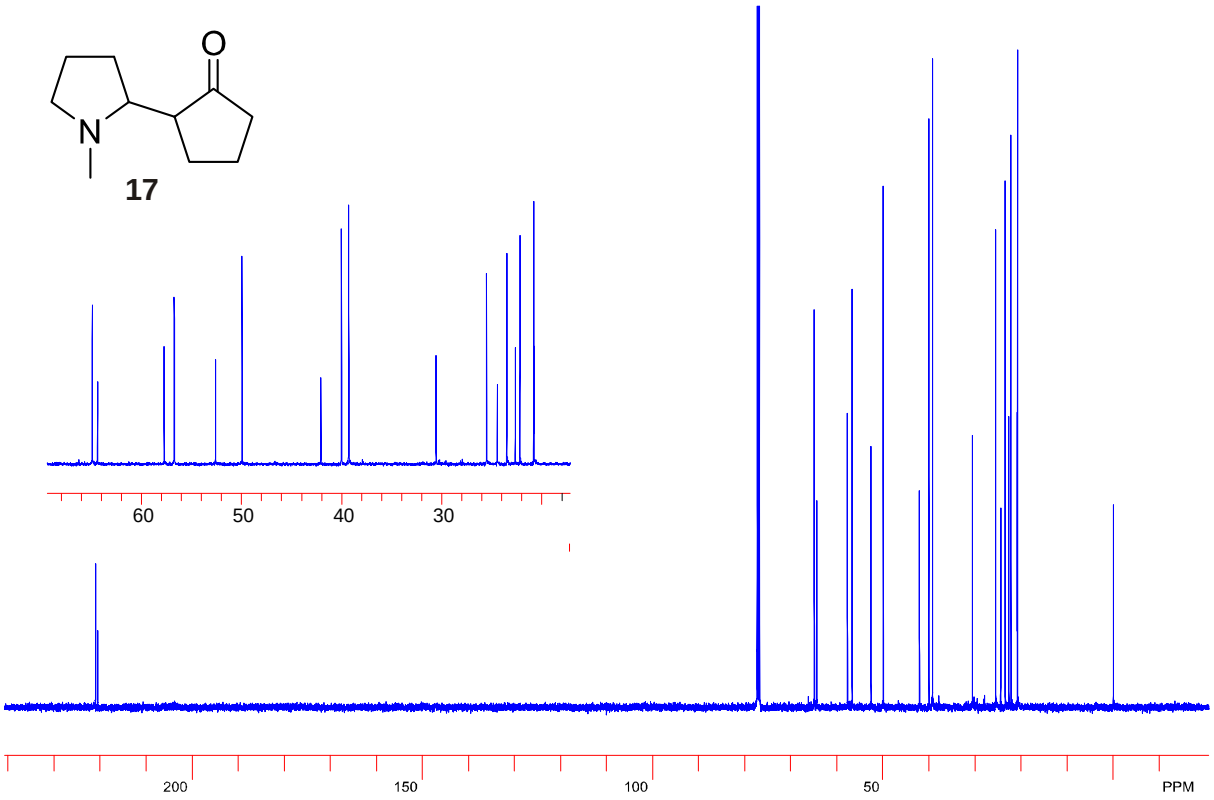


Figure 1: Shift of hygrine peaks upon addition of different amount of DTTA; taken with a racemic sample of **14** in $CDCl_3$. An asterisk denotes the methyl group signals of **14** used to determine the enantiomeric ratio.

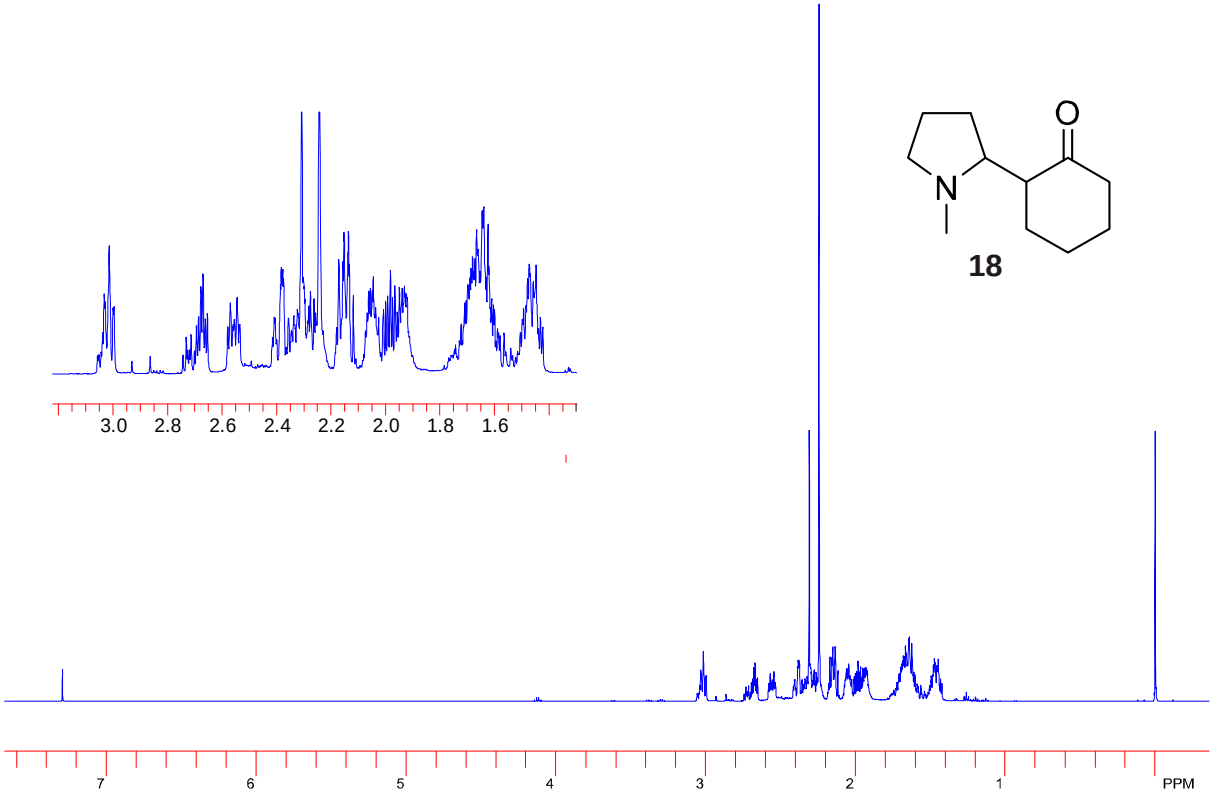
Compound 17: ^{1}H-NMR – $CDCl_3$ (500 MHz)



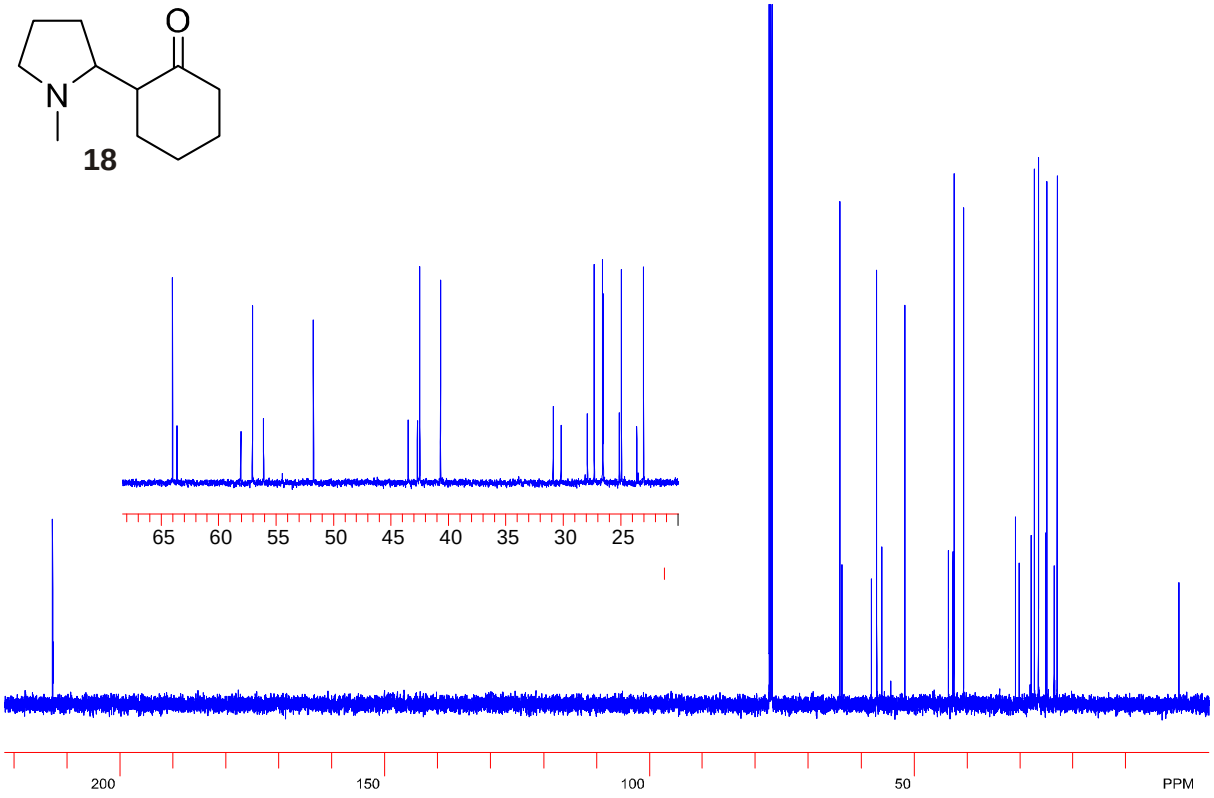
Compound 17: ^{13}C-NMR – $CDCl_3$ (125 MHz)



Compound 18: ^{1}H-NMR – $CDCl_3$ (500 MHz)

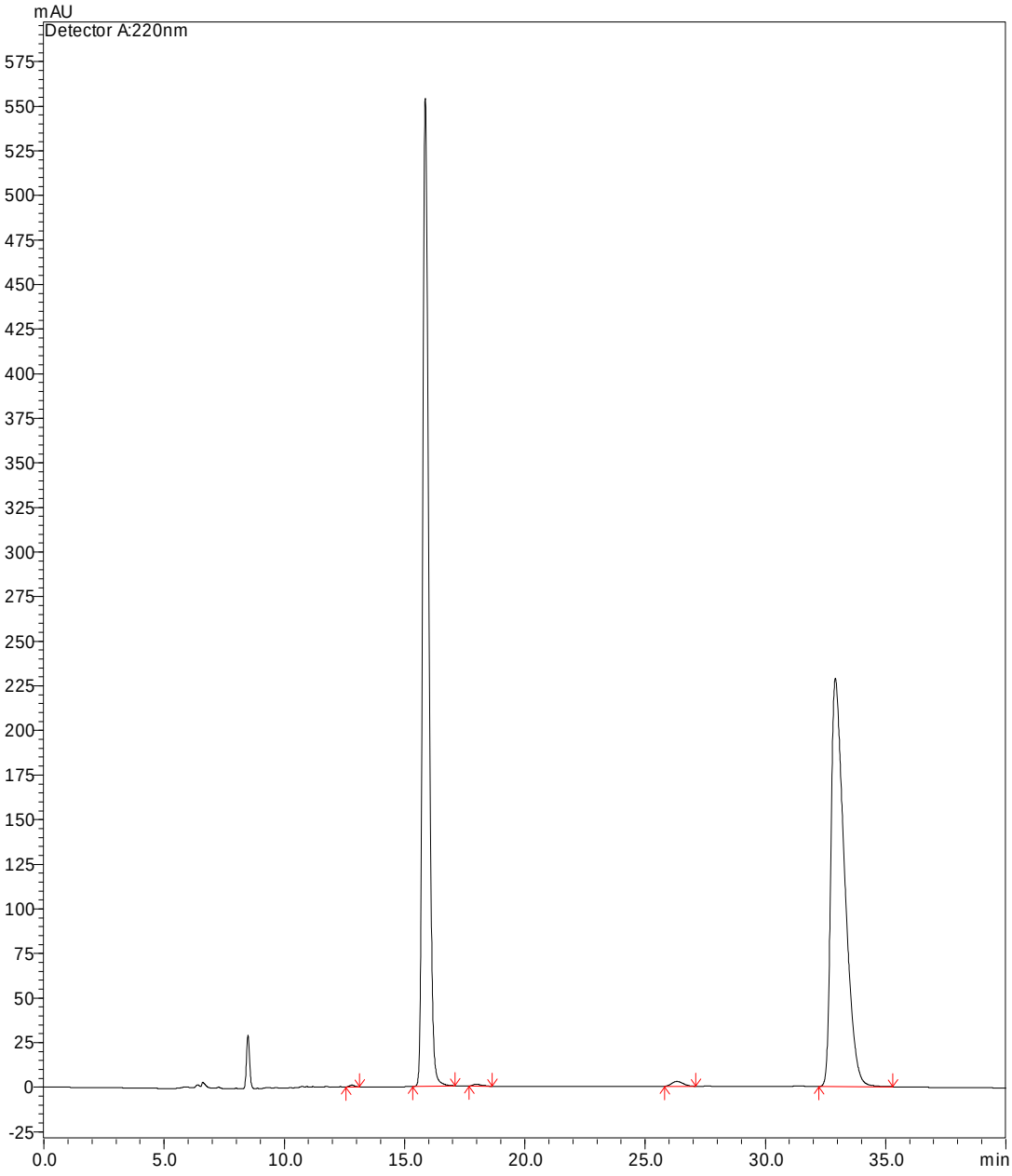


Compound 18: ^{13}C-NMR – $CDCl_3$ (125 MHz)



HPLC of rac-3

250 mm Chiralpak IB 4.6 mm i.D.
n-Heptan/2-Propanol = 97:3, 0.5 ml/min, 2.8 MPa, 298 K
UV, 220 nm



Supporting references

S1 Z. Li and C.-J. Li, *J. Am. Chem. Soc.*, 2005, **127**, 6968.

S2 J.-H. Lee, B.-S. Jeong, J.-M. Goo, S.-S. Jew and H.-G. Park, *J. Org. Chem.*, 2006, **71**, 6690.