Electronic Supplementary Material (ESI) for ChemComm.

The Asymmetric Alkylation of Dimethylhydrazones; Intermolecular Chirality Transfer using Sparteine as Chiral Ligand

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Supporting Information

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I. General Information

Solvents employed were distilled prior to use as follows: cyclohexane was distilled from calcium hydride, tetrahydrofuran (THF), diethyl ether (Et_2O) and toluene were distilled from sodium benzophenone ketyl, methyl *tert*-butyl ether, benzene and cumene were purchased as anhydrous solvents from Sigma Aldrich. Sparteine was distilled prior to use, using a Kugelrohr distillation apparatus. (-)-Sparteine was purchased from Santa Cruz Technologies Inc. (+)-sparteine was purchased from Beta Pharma. All other reagents were purchased from Sigma Aldrich unless otherwise noted.

All non-aqueous reactions were carried out under oxygen-free nitrogen using oven-dried glassware.

Wet flash column chromatography was carried out using Kieselgel silica gel 60, 0.040-0.063 mm (Merck). Thin layer chromatography (TLC) was carried out on pre-coated silica gel plates (Merck 60 PF254)). Visualisation was achieved by potassium permanganate staining.

Melting points were measured in a Thomas Hoover Capillary Melting Point apparatus.

Infrared (IR) spectra were recorded on a Perkin-Elmer FT-IR Paragon 1000 spectrophotometer. Liquid samples were examined as thin films interspersed between sodium chloride plates. Solid samples were dispersed in potassium bromide and recorded as pressed discs. The intensity of peaks were expressed as strong (s), medium (m) and weak (w).

NMR spectra were run in $CDCl_3$ using tetramethylsilane (TMS) as the internal standard, unless otherwise specified. ^{1}H NMR spectra were recorded at 300 MHz on a Bruker AVANCE 300 spectrometer and ^{13}C NMR spectra were recorded at 75 MHz on a Bruker AVANCE 300 instrument, unless otherwise stated. All spectra were recorded at University College Cork. Chemical shifts δ_H and δ_C are expressed as parts per million (ppm), positive shift being downfield from TMS; coupling constants (*J*) are expressed in hertz (Hz). Splitting patterns in ^{1}H NMR spectra are designated as s (singlet), br s (broad singlet), d (doublet), dd (doublet of doublets), dt (doublet of triplets), t (triplet), q (quartet), quin (quintet), sext (sextet), sept (septet), and m (multiplet). For ^{13}C NMR spectra, the number of attached protons for each signal was determined using the DEPT pulse sequence run in the DEPT-90 and DEPT-135 modes.

Low resolution mass spectra (LRMS) were recorded on a Waters Quattro Micro triple quadrupole instrument in electrospray ionization (ESI) mode using 50% acetonitrile- water containing 0.1% formic acid as eluent; samples were made up in acetonitrile. High resolution precise mass spectra (HRMS) were recorded on a Waters LCT Premier Tof LC-MS instrument

in electrospray ionization (ESI) mode using 50% acetonitrile-water containing 0.1% formic acid as eluent; samples were prepared in acetonitrile.

Enantiopurity of the chiral compounds was determined by chiral gas chromatography (GC) performed on an Astec CHIRALDEX^{TM} G-TA, fused silica capillary column, 20m x 0.25mm x 0.12µm film thickness. GC analysis was performed on an Agilent Technologies 7820 A GC system. All chiral columns were purchased from Sigma-Aldrich Supelco. Conditions for separation were determined using the following operating conditions as standard, flow rate: 1 mL/min, injection volume: 0.2 µL, split ratio: 10:1, front inlet temp.: 150°C, detector temp: 155°C.

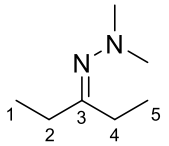
Optical rotations were measured on a Perkin-Elmer 141 polarimeter at 589 nm in a 10 cm cell; concentrations (c) are expressed in g/100 mL. α_D^T is the specific rotation of a compound and is expressed in units of 10^{-1} deg cm^2 g^{-1}.

^{1}H NMR spectra, ^{13}C NMR spectra, LRMS and melting point (if solid) analyses were recorded for all previously prepared compounds. For novel compounds, in addition to the previously mentioned analysis, IR and HRMS were also obtained. Optical rotations were used to assign absolute stereochemistry for known compounds.

II. Synthesis and characterisation of hydrazones 1 and 2

General procedure for the synthesis of hydrazones

The **ketone**, neat, was treated with non-symmetric N,N-dimethylhydrazine (1.5 eq) and acetic acid (few drops), and the reaction mixture was refluxed for 24 h. After cooling, water (10 mL) was added and the mixture extracted with Et_2O (3 x 30 mL). The organic layers were combined and dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure.

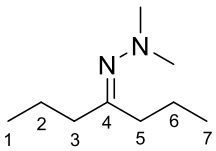


1,1-dimethyl-2-(pentan-3-ylidene)hydrazine 1

Prepared following the general procedure outlined above using 3-pentanone and N,N-dimethylhydrazine. The crude product (>98%) was then purified using Kugelrohr distillation to give the title compound **1** as a clear oil (5.01 g, 83%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.08 (6H, t, *J* = 7.6 Hz, H-1, H-5), 2.24 (2H, q, *J* = 7.6, H-2), 2.42 (6H, s, N-$(CH_3)_2$), 2.45 (2H, q, *J* = 7.6 Hz, H-4) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 11.1 (C-1), 11.6 (C-5), 22.5 (C-2), 28.7 (C-4), 47.6 (N-$(CH_3)_2$), 174.5 (C-3) ppm; MS (ESI) *m/z*: 129 $[M + H]^+$.

Spectral characteristics were consistent with previously reported data.[1]



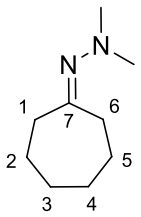
2-(heptan-4-ylidene)-1,1-dimethylhydrazine 2

Prepared following the general procedure outlined above using 4-heptanone and N,N-dimethylhydrazine. The crude product (>98%) was then purified using Kugelrohr distillation to give the title compound **2** as a clear oil (5.60g, 82%).

^{1}H NMR (300 MHz, CDCl3): δ 0.93 (3H, t, *J* = 7.4 Hz, H-1), 0.95 (3H, t, *J* = 7.4 Hz, H-7), 1.47-1.58 (4H, m, H-2, H-6), 2.15-2.20 (2H, m, H-3), 2.38-2.42 (8H, m, H-5, N-$(CH_3)_2$) ppm; ^{13}C NMR (75.5 MHz, CDCl3): δ 13.8 (C-1), 14.4 (C-7), 19.9 (C-2), 20.6 (C-6), 31.7 (C-3), 38.0 (C-5), 47.6 (N-(CH3)2), 172.5 (C-3) ppm; MS (ESI) m/z: 157 $[M + H]^+$.

Spectral characteristics were consistent with previously reported data.[2]

2-cycloheptylidene-1,1-dimethylhydrazine 3



Prepared following the general procedure outlined above using cycloheptanone and N,N-dimethylhydrazine. The crude product (>98%) was then purified using Kugelrohr distillation to give the title compound **3** as a clear oil (4.13 g, 75%).

Spectral characteristics were consistent with previously reported data.[3]

^{1}H NMR (300 MHz, CDCl3): δ 1.54-1.72 (8H, m, H-2, H-3, H-4, H-5), 2.39-2.43 (8H, m, H-1, N-$(CH_3)_2$), 2.61-2.65 (2H, m, H-6) ppm; ^{13}C NMR (75.5 MHz, CDCl3): δ 25.0, 27.2, 29.9, 30.4, 30.9 (C-1,C-2, C-3, C4, C5), 37.0 (C-6), 47.1 (N-(CH3)2), 174.2 (C-7) ppm; MS (ESI) *m/z*: 155 $[M + H]^+$.

III. Asymmetric alkylations via intermolecular chiral transfer

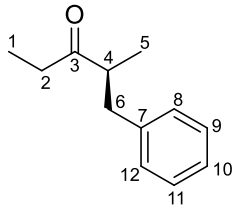
General Procedure for Asymmetric Alkylations with (+)- or (-)-sparteine

To a schlenk tube, under a N_2 atmosphere, anhydrous solvent (1 mL) and (+)- or (-)-sparteine (0.281 g, 1.2 mmol) were added at room-temperature. *Sec*-BuLi (1.4 M, 1.1 mmol, 0.78 mL) was then added at -78°C and allowed to stir for 30 minutes. Hydrazone (1 mmol, 1 eq.) was added drop-wise at -78°C, allowed to warm to room-temperature and stirred at room-temperature for 6 h. The reaction was cooled to -30°C and electrophile (1.2 mmol, 1.2 eq.) was added drop-wise, very slowly. This mixture was allowed to stir at -30°C for 22 h.

At -30°C, saturated NH_4Cl (0.5 mL) was added and the mixture allowed warm to room-temperature. Et_2O (30 mL) was added and the mixture extracted with NH_4Cl (3 x 10 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to afford the crude hydrazone. This crude hydrazone was used in the next step without further purification.

Hydrazone cleavage

The resulting oil was hydrolyzed, by adding Et_2O (5 mL), followed by 4 M HCl (0.5 mL) and stirring vigorously. Once TLC (5:1, hexane / Et_2O) showed the reaction had gone to completion, water (10 mL) and Et_2O (10 mL) were added and the mixture extracted with Et_2O (3 x 20 mL). The organic layers were combined and dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. This crude product was then purified using column chromatography on silica gel to give the pure ketone.



(S)-2-methyl-1-phenylpentan-3-one 4 (entry 2, Table 1 and entry 3, Table 2)

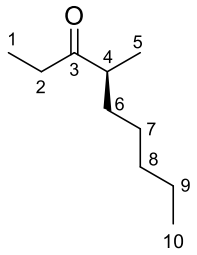
Prepared following the general procedure outlined above using 1,1-dimethyl-2-(pentan-3-ylidene)hydrazine **1** and benzyl bromide. The crude product was purified using column chromatography (10:1, hexane / Et_2O) on silica gel to give the title compound 4 as a clear oil (0.098 g, 57% over two steps, 52% ee, S enantiomer).

R_f = 0.45 (5:1, hexane / Et_2O). $[\alpha]_D^{23}$ + 31.7 (c 1.1, $CHCl_3$) (lit.[1] $[\alpha]_D^{23}$ + 70.9 (c 1.1, $CHCl_3$, for 99% ee, S enantiomer). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.95 (3H, t, *J* = 7.5 Hz, H-1), 1.08 (3H, d, *J* = 6.0 Hz, H-5), 2.25 (1H, dq, *J* = 7.2, 17.8 Hz, H-2), 2.44 (1H, dq, *J* = 7.3, 17.9 Hz, H-2),

2.57 (1H, dd, *J* = 7.2, 14.2 Hz, H-6), 2.78-2.89 (1H, m, H-4), 2.97 (1H, dd, *J* = 7.2, 14.2 Hz, H-6), 7.12-7.30 (5H, m, Ar-H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 7.6 (C-1), 16.6 (C-5), 35.2 (C-2), 39.3 (C-6), 47.9 (C-4), 120.2 (C-10), 128.4 (C-8, C-12), 128.9 (C-9, C-11), 139.9 (C-7), 214.8 (C-3) ppm; MS (ESI) *m/z*: 177 $[M + H]^+$.

Spectral characteristics were consistent with previously reported data.[4]

Enantioselectivity was determined by GC analysis: 24 : 76 er, t_R = 7.6 (R-enantiomer) and 7.9 min (S-enantiomer) (120°C hold for 10 min, ramp 10°C/min to 140°C, hold for 5 min).

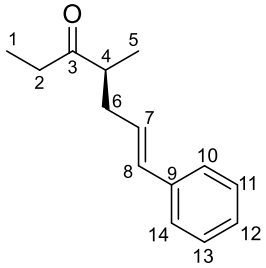


(S)-4-methylnonan-3-one 5 (entry 6, Table 1 and entry 1, Table 2)

Prepared following the general procedure outlined above using 1,1-dimethyl-2-(pentan-3-ylidene)hydrazine **1** and 1-iodopentane. The crude product was purified using column chromatography (10:1, hexane / Et_2O) on silica gel to give the title compound **5** as a clear oil (0.07 g, 46% over two steps, 66% ee).

R_f = 0.68 (4:1, hexane / Et_2O). $[\alpha]_D^{20}$ + 4.9 (c 0.528, Et_2O). IR (NaCl) $\bar{\nu}_{max}$: 2960-2858 (C-H stretch, s), 1716 (C=O stretch, s), 1460 (C-H bend, s) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.88 (3H, t, *J* = 6.9 Hz, H-10), 1.04 (3H, t, *J* = 7.3 Hz, H-1), 1.06 (3H, d, *J* = 6.8 Hz, H-5), 1.13-1.41 (7H, m, H-6, H-7, H-8, H-9), 1.52-1.73 (1H, m, H-6), 2.35-2.61 (3H, m, H-2, H-4) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 7.8 (C-1), 14.0 (C-10), 16.5 (C-5), 22.5, 27.0, 31.9, 33.1 (4 x CH_2, C-6, C-7, C-8, C-9), 34.2 (C-2) 46.1 (C-4), 215.5 (C-3) ppm; HRMS (ESI) *m/z* calcd for $C_{10}H_{21}O$ $[M + H]^+$: 157.1592, found 157.1588.

Enantioselectivity was determined by GC analysis: 17 : 83 er, t_R = 3.6 (R-enantiomer) and 3.8 min (S-enantiomer) (105°C hold for 10 min, ramp 10°C/min to 140°C, hold for 5 min).



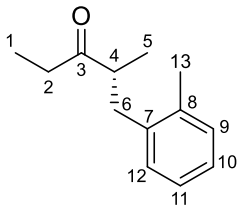
(S)-(E)-4-methyl-7-phenylhept-6-en-3-one 6 (entry 4, Table 2)

Prepared following the general procedure outlined above using 1,1-dimethyl-2-(pentan-3-ylidene)hydrazine **1** and 3-bromo-1-phenyl-1-propene. The crude product was purified using column chromatography (15:1, hexane / Et_2O) on silica gel to give the title compound **6** as a clear oil (0.061 g, 30% over two steps, 58% ee).

R_f = 0.4 (10:1, hexane / Et_2O). $[\alpha]_D^{20}$ + 9.7 (c 0.36, Et_2O). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.05 (3H, t, *J* = 7.2 Hz, H-1), 1.13 (3H, d, *J* = 6.9 Hz, H-5), 2.19-2.29 (1H, m, H-6), 2.40-2.59 (3H, m, H-2, H-6), 2.63-2.74 (1H, m, H-4), 6.06-6.17 (1H, m, H-7), 6.40 (1H, d, *J* = 15.9 Hz, H-8), 7.25-7.33 (5H, m, Ar-H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 7.7 (C-1), 16.4 (C-5), 34.6 (C-2), 36.3 (C-6), 46.1 (C-4), 126.1 (C-10, C-14), 127.2 (C-7), 127.6 (C-8), 128.5 (C-11, C-13), 131.9 (C-12), 137.4 (C-9), 214.6 (C-3) ppm; MS (ESI) *m/z*: 203 $[M + H]^+$.

Spectral characteristics were consistent with previously reported data.[5]

Enantioselectivity was determined by GC analysis: 21 : 79 er, t_R = 25.2 (R-enantiomer) and 26.5 min (S-enantiomer) (130°C hold for 30 min, ramp 10°C/min to 140°C, hold for 5 min).



(R)-2-methyl-1-(o-tolyl)pentan-3-one 7 (entry 5, Table 2)

Prepared following the general procedure outlined above using 1,1-dimethyl-2-(pentan-3-ylidene)hydrazine **1** and 2-methylbenzyl bromide, on 5 mmol scale. The crude product was purified using column chromatography (10:1, hexane / Et_2O) on silica gel to give the title compound **7** as a clear oil (0.52 g, 55% over two steps, 52% ee).

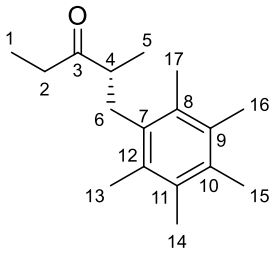
R_f = 0.55 (5:1, hexane / Et_2O). $[\alpha]_D^{20}$ – 45.9 (c 1, Et_2O). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.97 (3H, t, *J* = 7.3 Hz, H-1), 1.09 (3H, d, *J* = 6.9 Hz, H-5), 2.23 (1H, dq, *J* = 7.3, 17.9 Hz, H-2), 2.31 (3H, s, H-13), 2.42 (1H, dq, *J* = 7.3, 17.9 Hz, H-2), 2.57 (1H, dd, *J* = 6.9, 13.4 Hz, H-6), 2.77-2.90 (1H, m, H-4), 2.97 (1H, dd, *J* = 6.9, 13.4 Hz, H-6), 6.97-7.19 (4H, m, Ar-H) ppm;

^{13}C NMR (75.5 MHz, $CDCl_3$): δ 7.6 (C-1), 16.6 (C-5), 19.4 (C-13), 35.2 (C-2), 36.5 (C-6), 46.4 (C-4), 125.9 (Ar-CH), 126.4 (Ar-CH), 129.7 (Ar-CH), 130.4 (Ar-CH), 136.0 (Ar-C), 138.0 (Ar-C), 214.8 (C-3) ppm; MS (ESI) *m/z*: 191 $[M + H]^+$.

Spectral characteristics were consistent with previously reported data.[6]

*Note: opposite stereochemistry due to the use of (+)-sparteine used as chiral ligand.

Enantioselectivity was determined by GC analysis: 76 : 24 er, t_R = 11.4 (R-enantiomer) and 11.9 min (S-enantiomer) (120°C hold for 20 min, ramp 10°C/min to 140°C, hold for 5 min).



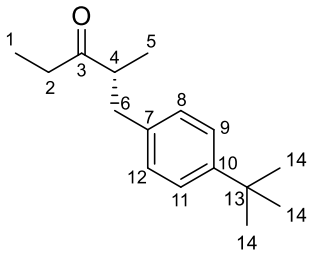
(R)-2-methyl-1-(2,3,4,5,6-pentamethylphenyl)pentan-3-one 8 (entry 6, Table 2)

Prepared following the general procedure outlined above using 1,1-dimethyl-2-(pentan-3-ylidene)hydrazine **2** and 1-(bromomethyl)-2,3,4,5,6-pentamethylbenzene. The crude product was purified using column chromatography (30:1, hexane/ Et_2O) on silica gel to give the title compound **8** as a white solid (0.147 g, 60% over two steps, 60% ee). Mp 57-60°C.

R_f = 0.70 (4:1, hexane / Et_2O). $[\alpha]_D^{20}$ − 53.2 (c 1.0, CH_2Cl_2). IR (NaCl) $\bar{\nu}_{max}$: 2928 (C-H stretch, s), 1714 (C=O stretch, s), 1456 (Aromatic C=C stretch, s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98 (3H, t, *J* = 7.3 Hz, H-1), 1.06 (3H, d, *J* = 6.7 Hz, H-5), 2.21-2.22 (2 x 6H, s, H-13, H-14, H-16, H-17), 2.23 (3H, s, H-15), 2.26 (1H, dq, *J* = 7.3, 18.0 Hz, H-2), 2.40 (1H, dq, *J* = 7.3, 17.9 Hz, H-2), 2.73-2.82 (2H, m, H-6), 2.98-3.06 (1H, m, H-4) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 7.7 (C-1), 16.1 (C-5), 16.9 (C-15), 16.9, 17.1 (4 x CH_3, C-14, C-16, C-13, C-17), 33.3 (C-2), 35.4 (C-6), 46.6 (C-4), 132.2, 132.7, 132.9, 133.7 (6 x Ar-C, C-7, C-8, C-9, C-10, C-11, C-12), 215.4 (C-3) ppm; HRMS (ESI) *m/z* calcd for $C_{17}H_{27}O$ $[M + H]^+$: 247.2062, found 247.2052.

*Note: opposite stereochemistry due to the use of (+)-sparteine used as chiral ligand.

Enantioselectivity was determined by GC analysis: 81 : 19 er, t_R = 60.0 (R-enantiomer) and 60.9 min (S-enantiomer) (140°C hold for 45 min, ramp 10°C/min to 120°C and hold for 10 min, ramp 10°C/min to 140°C and hold for 10 min).



(R)-1-(4-(tert-butyl)phenyl)-2-methylpentan-3-one 9 (entry 7, Table 2)

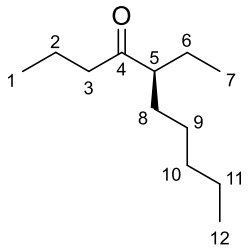
Prepared following the general procedure outlined above using 1,1-dimethyl-2-(pentan-3-ylidene)hydrazine **1** and 4-*tert*-butylbenzyl bromide. The crude product was purified using column chromatography (10:1, hexane / Et_2O) on silica gel to give the title compound **9** as a clear oil (0.143 g, 62% over two steps, 42% ee).

R_f = 0.45 (5:1, hexane / Et_2O). $[\alpha]_D^{20}$ – 25.1 (c 1, Et_2O). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.98 (3H, t, *J* = 7.3 Hz, H-1), 1.07 (3H, d, *J* = 6.9 Hz, H-5), 1.29 (9H, s, H-14), 2.28 (1H, dq, *J* = 7.3, 17.9 Hz, H-2), 2.43 (1H, dq, *J* = 7.3, 17.9 Hz, H-2), 2.52 (1H, dd, *J* = 6.9, 13.4 Hz, H-6), 2.74-2.89 (1H, m, H-4), 2.95 (1H, dd, *J* = 6.9, 13.4 Hz, H-6), 7.06 (2H, d, *J* = 8.2 Hz, Ar-H), 7.28 (2H, d, *J* = 8.2 Hz, Ar-H) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 7.6 (C-1), 16.6 (C-5), 31.4 (C-14), 34.4 (C-13), 34.9 (C-2) 38.7 (C-6), 47.9 (C-4), 125.3 (C-8, C-12), 128.6 (C-9, C-11), 136.7 (C-7), 149.0 (C-10), 214.8 (C-3) ppm; MS (ESI) *m/z*: 233 $[M + H]^+$.

Spectral characteristics were consistent with previously reported data.[6]

*Note: opposite stereochemistry due to the use of (+)-sparteine used as chiral ligand.

Enantioselectivity was determined by GC analysis: 71 : 29 er, t_R = 12.9 (R-enantiomer) and 13.2 min (S-enantiomer) (140°C hold for 20 min).

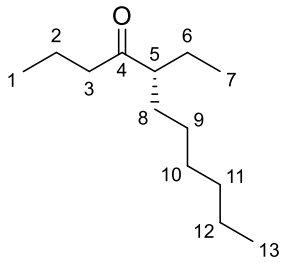


(S)-5-ethyldecan-4-one 10 (entry 8, Table 2)

Prepared following the general procedure outlined above using 2-(heptan-4-ylidene)-1,1-dimethylhydrazine and 1-iodopentane. The crude product was then purified using column chromatography (30:1, hexane / Et_2O) on silica gel to give the title compound **10** as a clear oil (0.071 g, 39% over two steps, 64% ee).

R_f = 0.75 (4:1, hexane / Et_2O). $[\alpha]_D^{20}$ + 16.5 (c 0.1, Et_2O). IR (NaCl) $\bar{\nu}_{max}$: 2961-2860 (C-H stretch, s) 1711 (C=O stretch, s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.82-0.94 (9H, m, H-1, H-7, H-12), 1.2-1.65 (12H, m, H2, H-6, H-8, H-9, H-10, H-11), 2.33-2.42 (3H, m, H-3, H-5) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 11.9 (C-1), 13.8 (C-7), 14.0 (C-12), 16.9, 22.5, 24.7, 27.2, 31.3, 32.0 (6 x CH_2, C-2, C-6, C-8, C9, C-10, C-11), 44.2 (C-3), 53.9 (C-5), 215.0 (C-4) ppm; HRMS (ESI) *m/z* calcd for $C_{12}H_{25}O$ $[M + H]^+$: 185.1905, found 185.1912.

Enantioselectivity was determined by GC analysis: 18 : 82 er, t_R = 14.5 (R-enantiomer) and 14.9 min (S-enantiomer) (90°C hold for 20 min, ramp 5°C/min to 140°C, hold for 5 min).



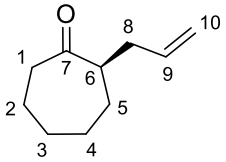
(R)-5-ethylundecan-4-one 11 (entry 9, Table 2)

Prepared following the general procedure outlined above using 2-(heptan-4-ylidene)-1,1-dimethylhydrazine **2** and 1-iodohexane. The crude product was purified using column chromatography (30:1 hexane / Et_2O) on a silica gel to give the title compound **11** as a clear oil (0.105g, 53% over two steps, 60% ee).

R_f = 0.56 (4:1, hexane / Et_2O). $[\alpha]_D^{20}$ − 4.083 (c 0.6, CH_2Cl_2). IR (NaCl) $\bar{\nu}_{max}$: 2857-2960 (C-H stretch, s), 1712 (C=O stretch, s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.77 (3H, t, *J* = 7.6 Hz, H-13), 0.80 (3H, t, *J* = 6.8 Hz, H-1), 0.84 (3H, t, *J* = 7.4 Hz, H-7), 1.10-1.58 (14H, m, H-2, H-6, H-8, H-9, H-10, H-11, H-12), 2.26-2.35 (3H, m, H-3, H-5) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 11.9 (C-1), 13.8 (C-7), 14.0 (C-13), 16.9, 22.6, 24.7, 27.5, 29.4, 31.4, 31.7 (7 x CH_2, C-2, C-6, C-8, C-9, C-10, C-11, C-12), 44.2 (C-3), 53.9 (C-5), 214.91 (C-4) ppm; HRMS (ESI) *m/z* calcd for $C_{13}H_{27}O$ $[M + H]^+$: 199.2062, found 199.2058.

*Note: opposite stereochemistry due to the use of (+)-sparteine used as chiral ligand.

Enantioselectivity was determined by GC analysis: 80 : 20 er, t_R = 33.9 (R-enantiomer) and 34.2 min (S-enantiomer) (80°C hold for 30 min, ramp 5°C/min to 140°C, hold for 5 min).



(R)-2-pentylcycloheptan-1-one 12 (entry 10, Table 2)

Prepared following the general procedure outlined above using (2-cycloheptylidene-1,1-dimethylhydrazine **3** and allyl bromide. The crude product was purified using column chromatography (30 : 1, hexane / Et_2O) on silica gel to give the title compound **12** as a clear oil (0.029 g, 19% over two steps, 36% ee).

R_f = 0.78 (4 : 1, hexane / Et_2O). $[\alpha]_D^{20}$ − 20.5 (c 0.2, Et_2O). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.27-2.49 (12H, m, H-1, H-2, H-3, H-4, H-5, H-8), 2.53-2.62 (1H, m, H-6), 4.98-5.06 (2H, m, H-10), 5.67-5.81 (1H, m, H-9) ppm; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 24.3, 28.7, 29.5, 30.5, 36.2, 43.1 (C1, C-2, C-3, C-4, C-5, C-8) 51.6 (C-6), 116.5 (C-10), 136.2 (C-9), 215.5 (C-7) ppm; MS (ESI) *m/z*: 153 $[M + H]^+$.

Spectral characteristics were consistent with previously reported data.[7]

Enantioselectivity was determined by GC analysis: 68 : 32 er, t_R = 17.6. (R-enantiomer) and 18.9 min (S-enantiomer) (50°C hold for 20 min, ramp 5°C/min to 140°C and hold for 5 min).

* Note: Exact configuration not determined.

Optimisation Studies of Alkylation temperature

Table S-1 details optimisation studies carried out in order to determine the best temperature for alkylation.

Ligand	Electrophile	Deprot. Temp.	Alkyl. Temp.	Solvent	Yield[a]	Ketone	er R:S	% ee
(-)-sp **1**	BnBr	RT	-70°C	Toluene	no reaction occurred			
(-)-sp **1**	BnBr	RT	-55°C	Toluene	50%	**3**	28 : 72	44%
(-)-sp **1**	BnBr	RT	-30°C	Toluene	57%	**3**	24 : 76	52%
(-)-sp **1**	BnBr	RT	0°C	Toluene	50%	**3**	27 : 73	46%
(-)-sp **1**	BnBr	RT	RT	Toluene	55%	**3**	29 : 71	42%

Table S-1

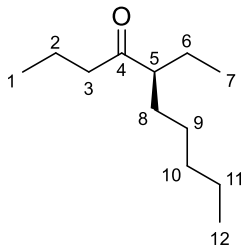
General Procedure for Asymmetric Alkylations with (-)-sparteine and LDA

To diisopropylamine (0.121 g, 0.17 mL, 1.2 mmol) in anhydrous toluene (2 mL), under N_2 atmosphere, was added *n*-BuLi (1.4 M, 0.79 mL, 1.1 mmol) at -78°C. The mixture was allowed to stir at 0°C for 30 minutes. The reaction was cooled to -78°C, 2-(heptan-4-ylidene)-1,1-dimethylhydrazine (0.156 g, 1 mmol) was added drop-wise. The reaction mixture was allowed to warm to room temperature and stirred for 6 h at room temperature. The reaction was cooled to -78°C, (-)-sparteine (0.281 g, 1.2 mmol) was added and left to stir at room temperature for 1 h. The reaction mixture was then cooled to -30°C and 1-iodopentane (0.23g, 0.15 mL, 1.2 mmol) was added drop-wise, very slowly. The mixture was allowed to stir at -30°C for 22 h.

At -30°C, saturated NH_4Cl (0.5 mL) was added and the mixture allowed to warm to room-temperature. Et_2O (30 mL) was added and the mixture extracted with NH_4Cl (3 x 10 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to afford the crude hydrazone. The crude hydrazone was used in the next step without further purification.

Hydrazone cleavage

The resulting oil was hydrolyzed, by adding Et_2O (5 mL), followed by 4 M HCl (0.5 mL) and stirring vigorously. Once TLC (5:1, hexane / Et_2O) showed the reaction had gone to completion, water (10 mL) and Et_2O (10 mL) were added and the mixture extracted with Et_2O (3 x 20 mL). The organic layers were combined and dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. This crude product was purified using column chromatography on silica gel to give the pure ketone.



(S)-5-ethyldecan-4-one 9 (Scheme 3)

Prepared following the general procedure outlined above using 2-(heptan-4-ylidene)-1,1-dimethylhydrazine and 1-iodopentane. The crude product was purified using column chromatography (30:1, hexane / Et_2O) on silica gel to give the title compound as a clear oil (0.046 g, 25% over two steps, 58% ee).

Spectral characteristics were consistent with that of **9** shown above previously.

Enantioselectivity was determined by GC analysis: 21 : 79 er, t_R = 14.5 (R enantiomer) and 14.9 min (S enantiomer) (90°C hold for 20 min, ramp 5°C/min to 140°C, hold for 5 min).

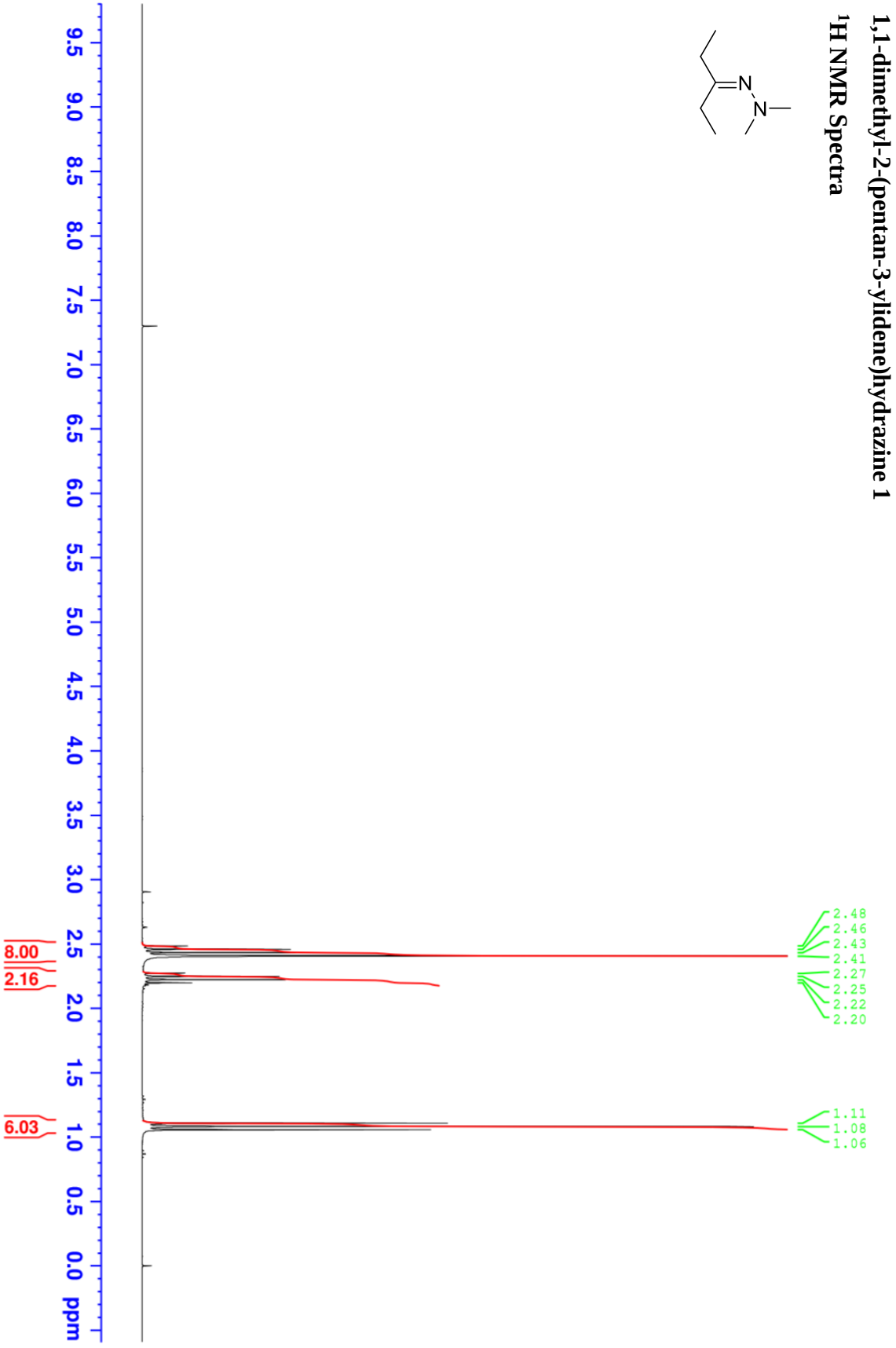
IV. References for supporting information

1. Stankovic, S.; Espenson, J. H. *J. Org. Chem.* 2000, **65**, 2218-2221.
2. Neuman, R.C.; Holmes, G. D. *J. Org. Chem.* 1968, **33**, 4317-4322.
3. Lin, H. H.; Chang, W. S.; Luo, S. Y.; Sha, C. K.. *Org. Lett.* 2004, **6**, 3289-3292
4. Lu, S. M.; Bolm, C. *Angew. Chem. Int. Ed.* 2008, **47**, 8920-8923.
5. Katritzky, A. R.; Huang, Z.; Fang, Y. *J. Org. Chem.* 1999, **64**, 7625-7627.
6. Berthiol, F.; Doucet, H.; Santelli, M. *Tetrahedron* 2006, **62**, 4372-4383.
7. Huo, X.; Quan, M.; Yang, G.; Zhao, X.; Liu, D.;Liu, Y.; Zhang, W. *Org. Lett.* 2014, **16**, 1570-1573.

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

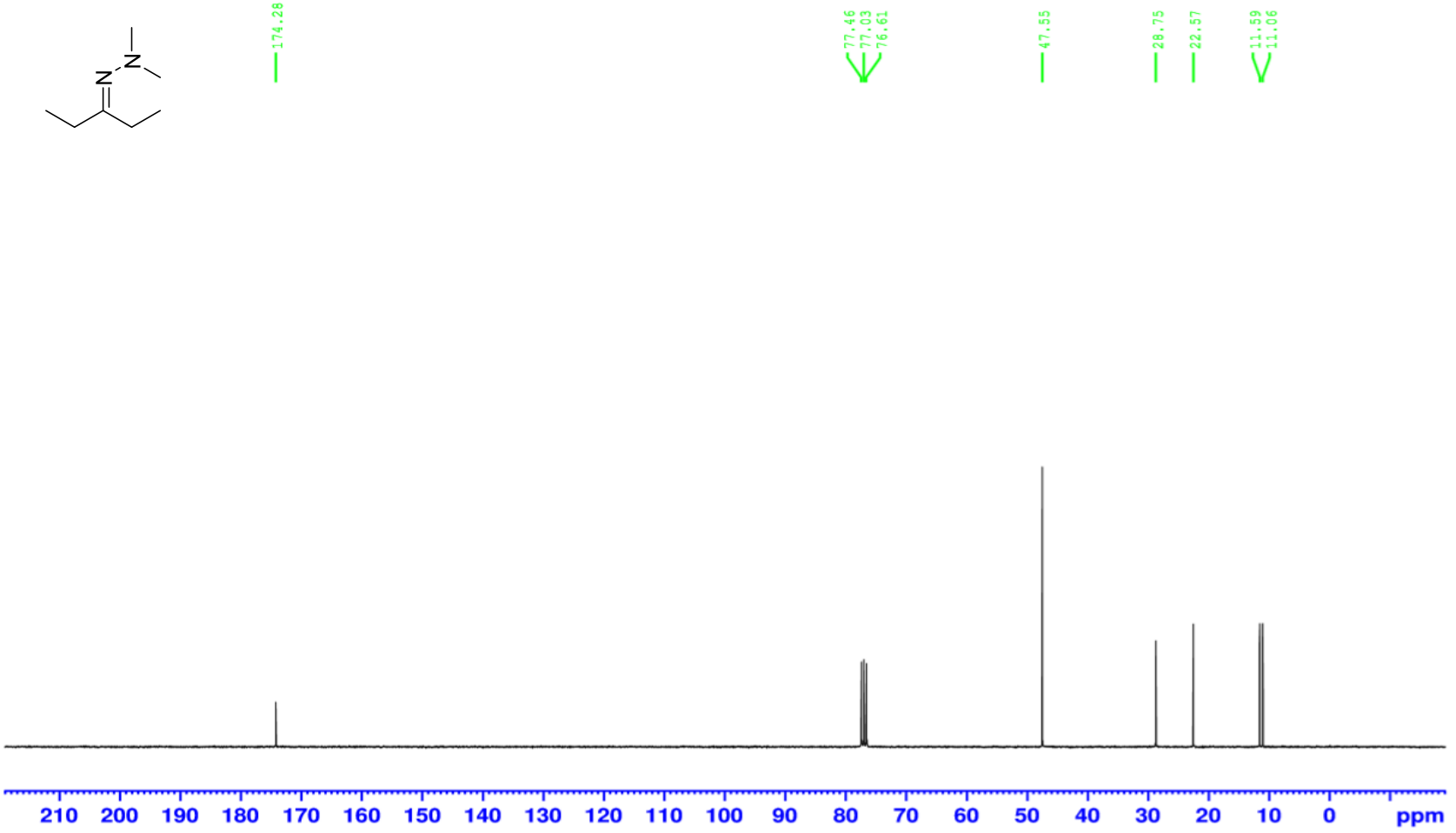
1,1-dimethyl-2-(pentan-3-ylidene)hydrazine 1

^{1}H NMR Spectra



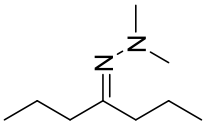
1,1-dimethyl-2-(pentan-3-ylidene)hydrazine 1

^{13}C NMR Spectra



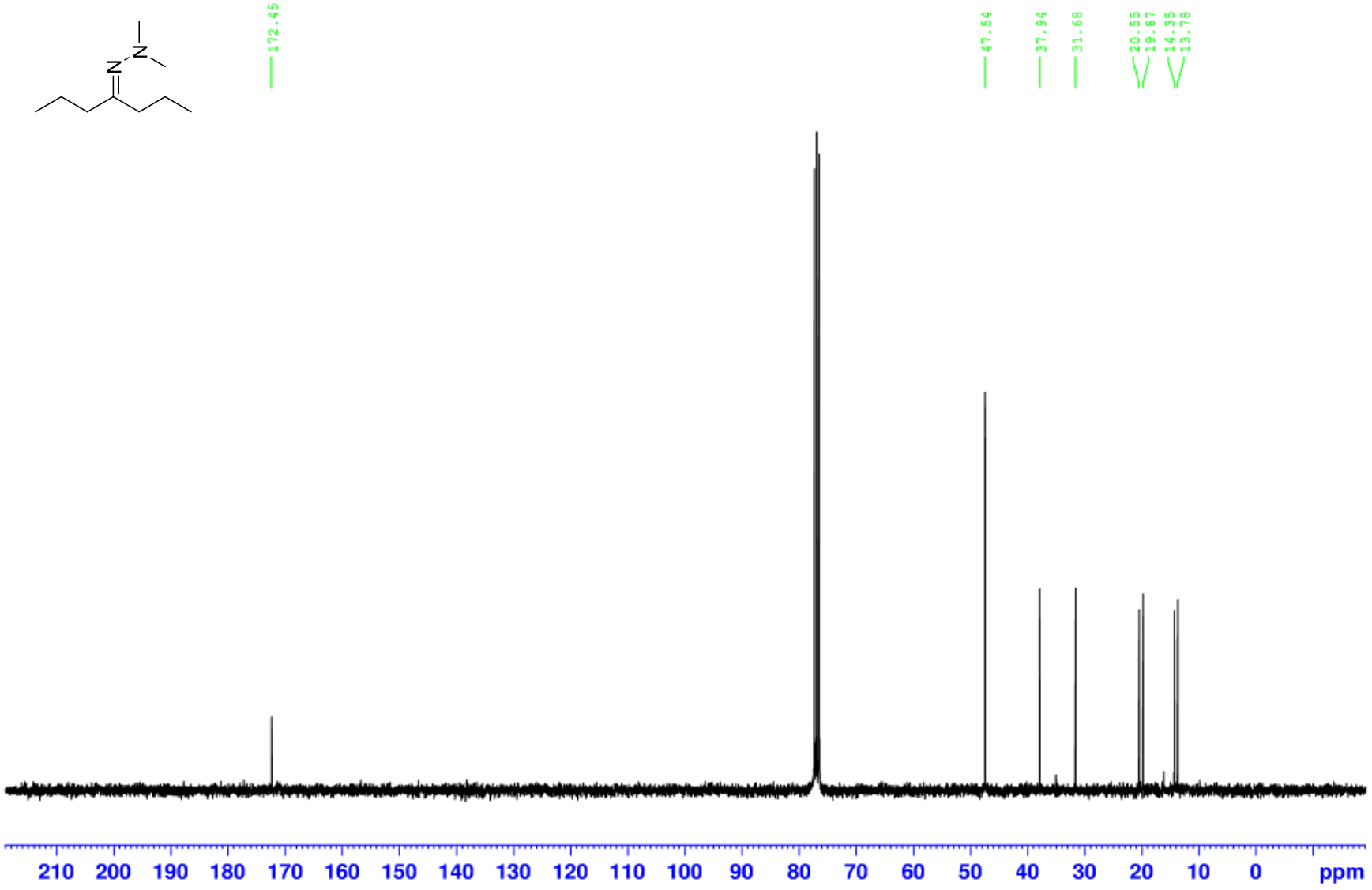
2-(heptan-4-ylidene)-1,1-dimethylhydrazine 2

^{1}H NMR Spectra



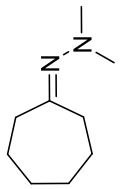
2-(heptan-4-ylidene)-1,1-dimethylhydrazine 2

^{13}C NMR Spectra



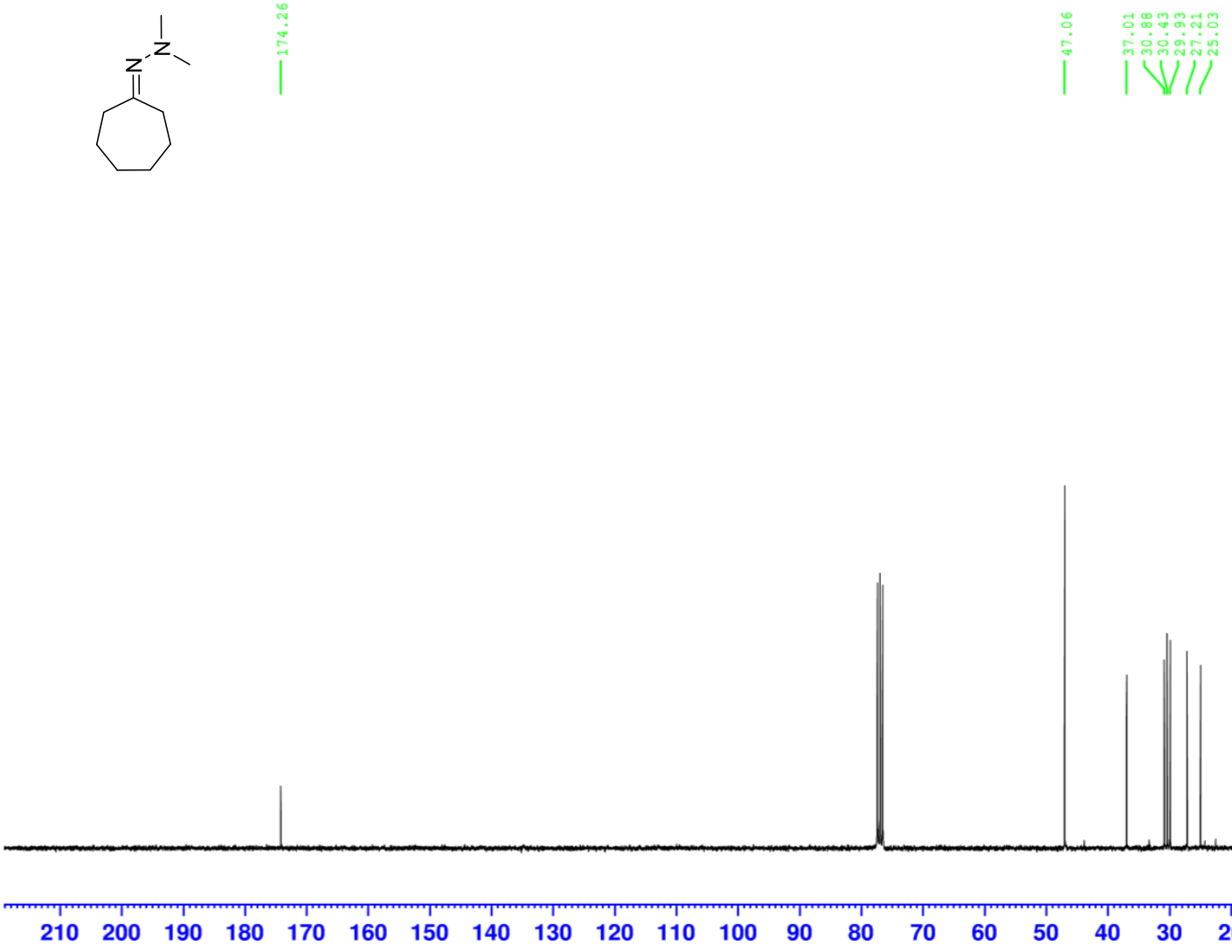
2-cycloheptylidene-1,1-dimethylhydrazine 3

^{1}H NMR Spectra



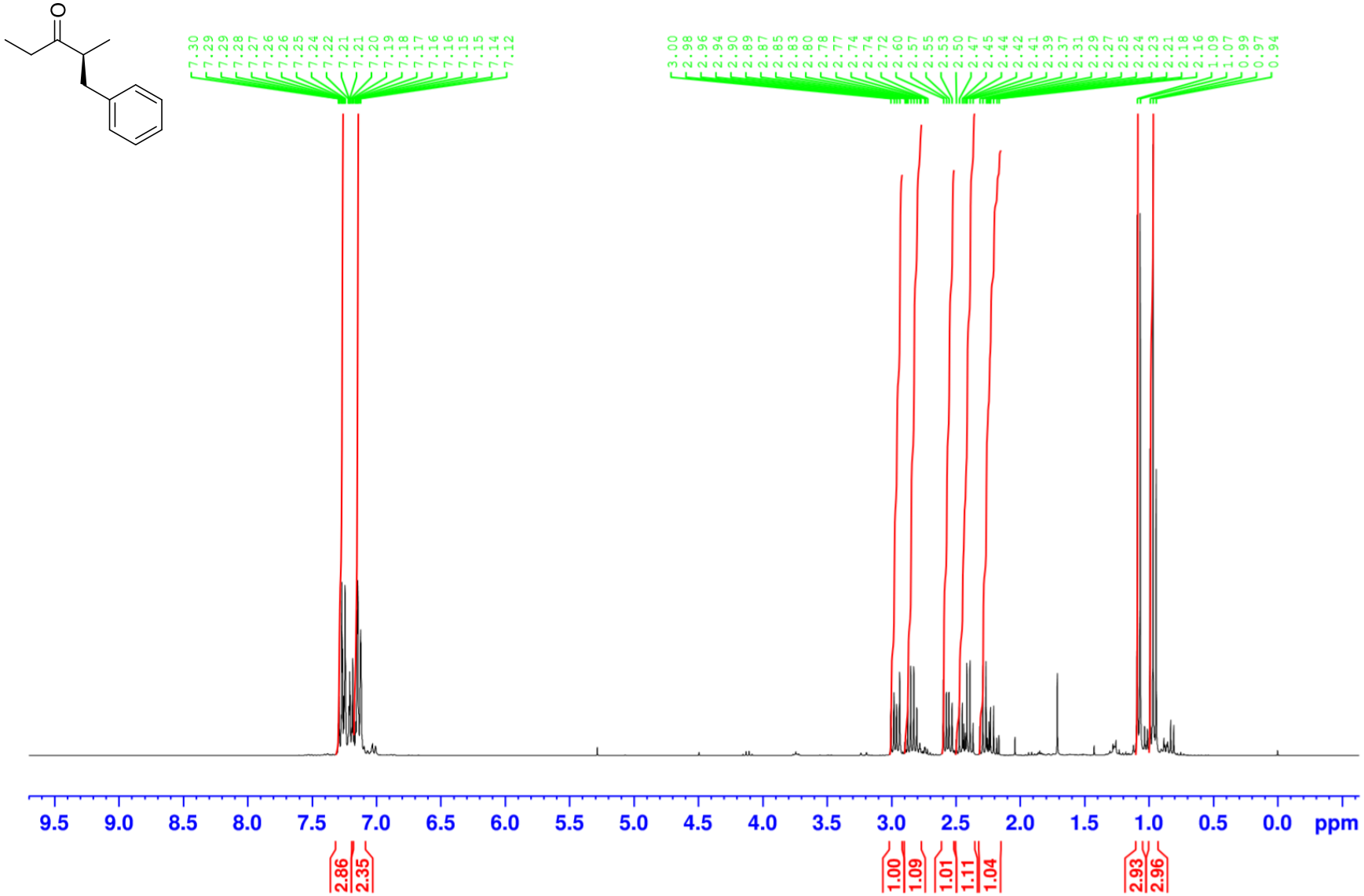
2-cycloheptylidene-1,1-dimethylhydrazine 3

^{13}C NMR Spectra



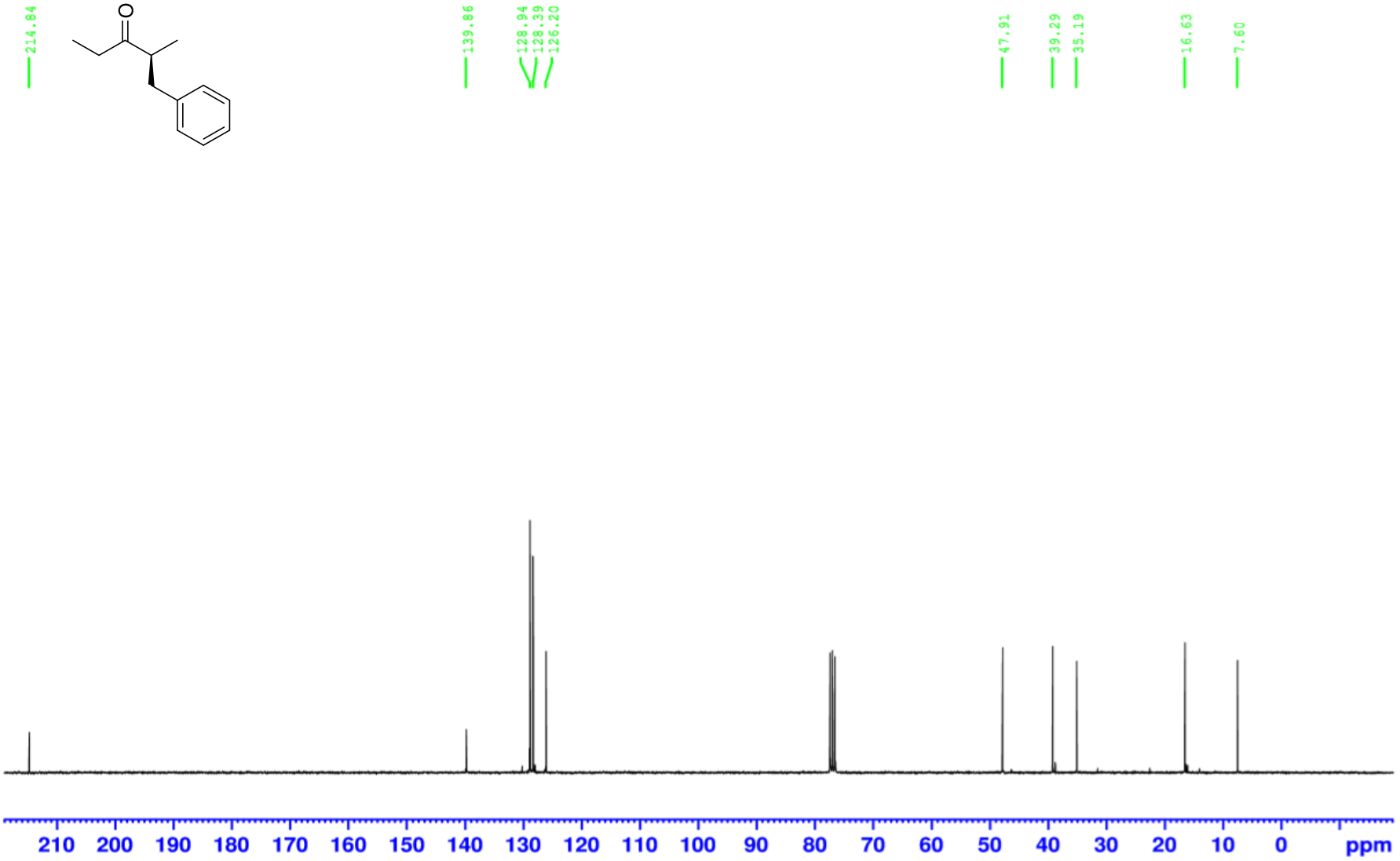
(S)-2-methyl-1-phenylpentan-3-one 3

^{1}H NMR Spectra



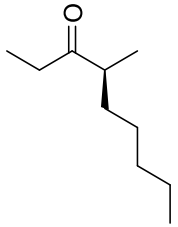
(S)-2-methyl-1-phenylpentan-3-one 3

^{13}C NMR Spectra



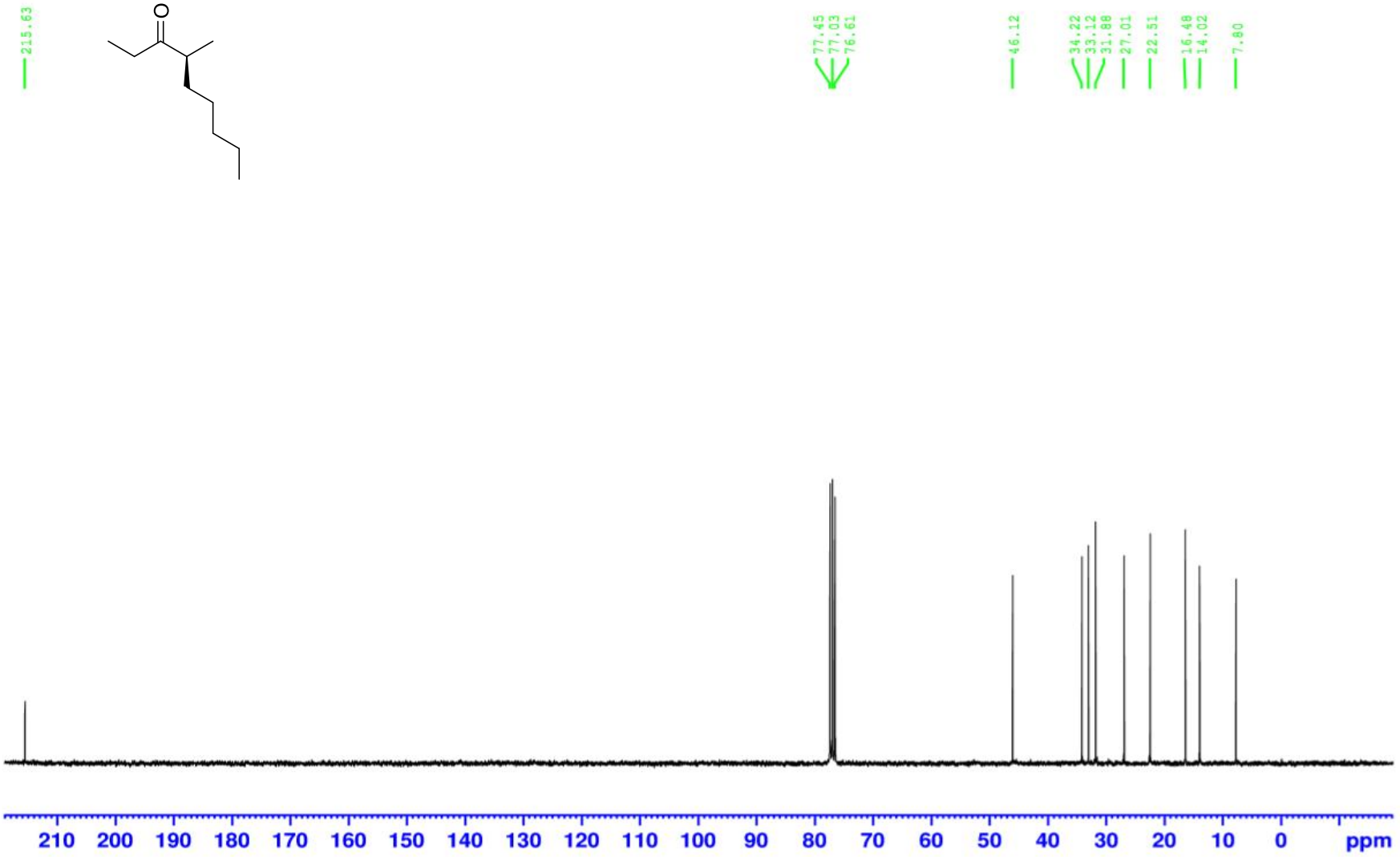
(S)-4-methylnonan-3-one 4

^{1}H NMR Spectra



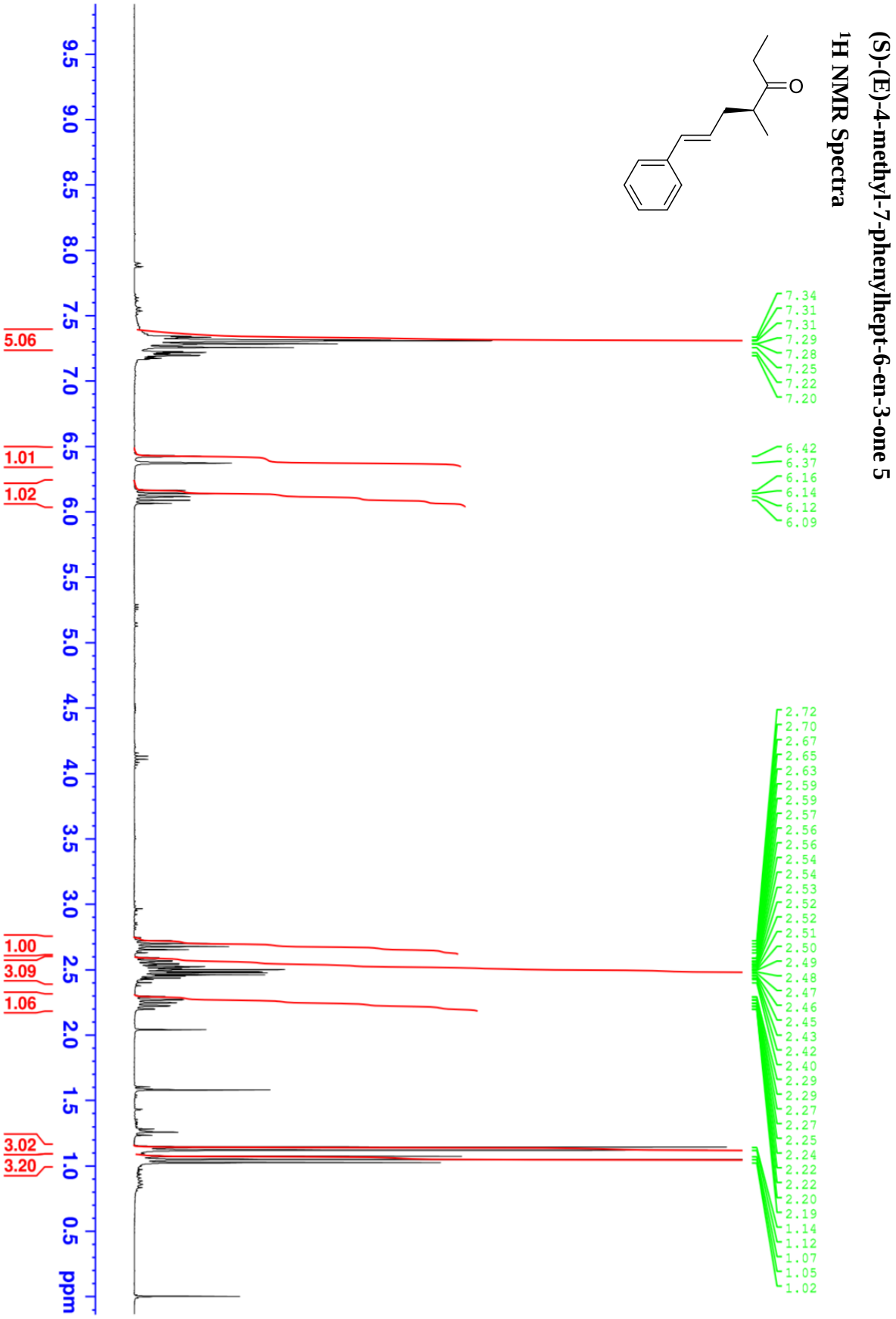
(S)-4-methylnonan-3-one 4

^{13}C NMR Spectra



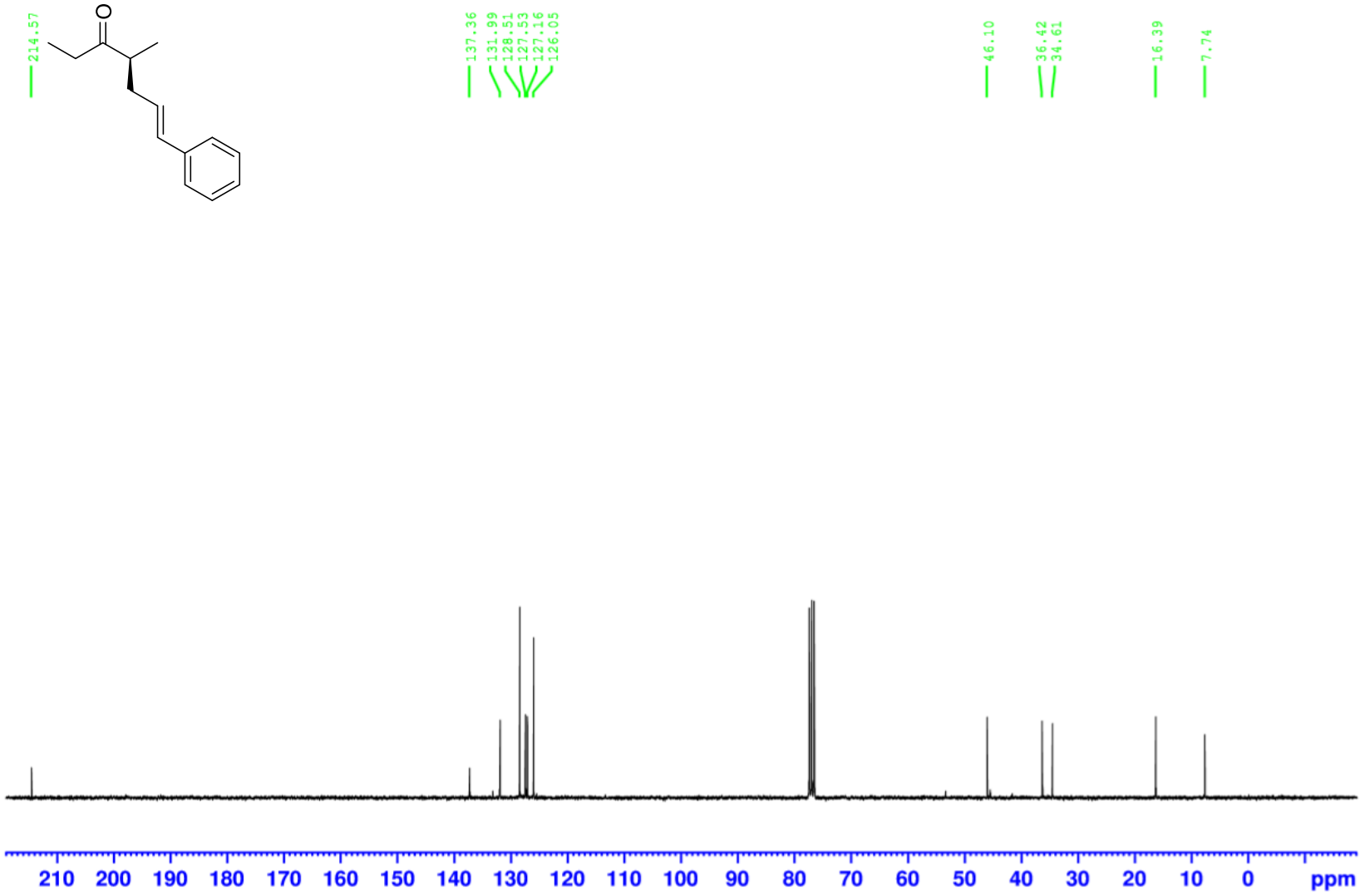
(S)-(E)-4-methyl-7-phenylhept-6-en-3-one 5

^{1}H NMR Spectra



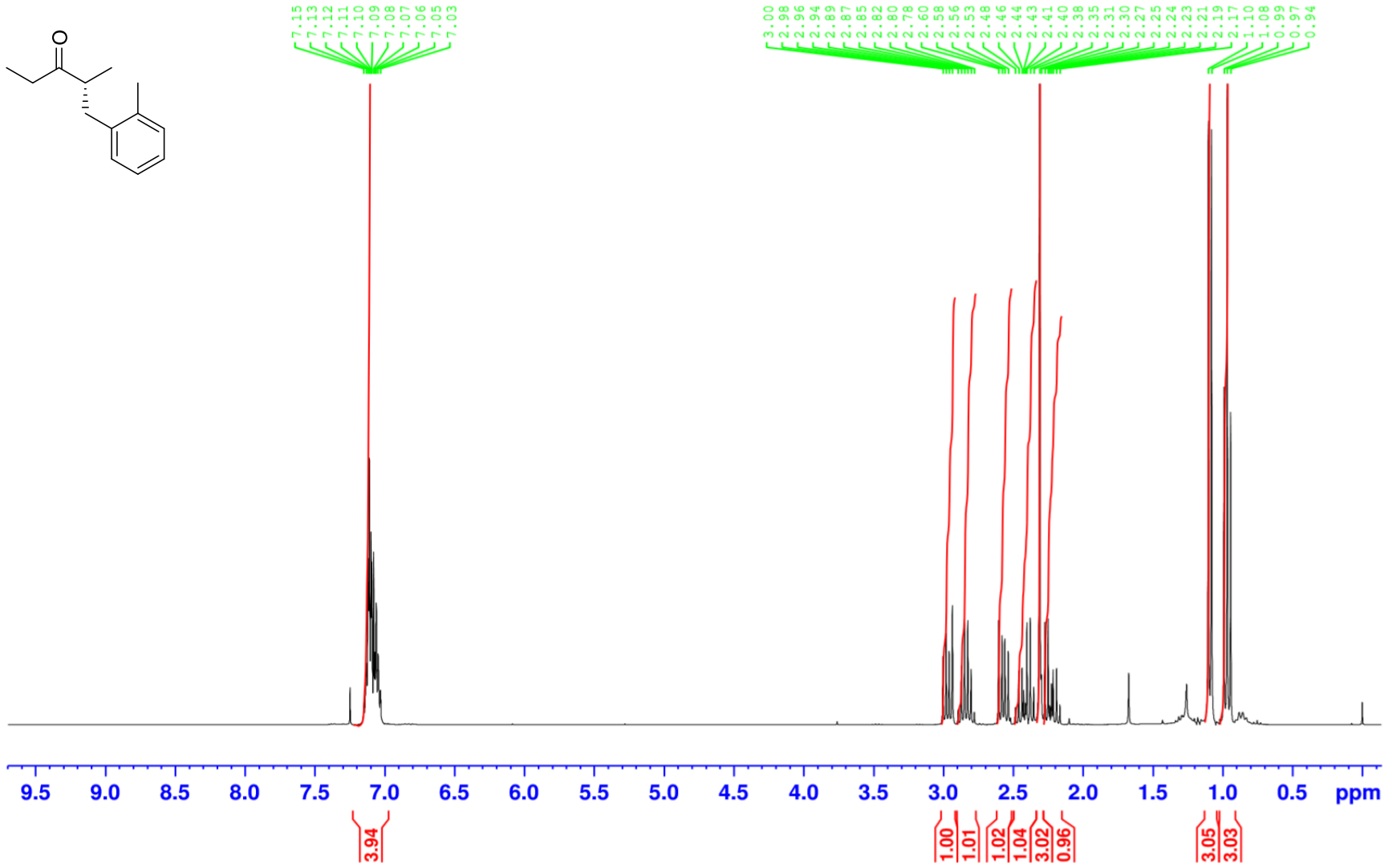
(S)-(E)-4-methyl-7-phenylhept-6-en-3-one 5

^{13}C NMR Spectra



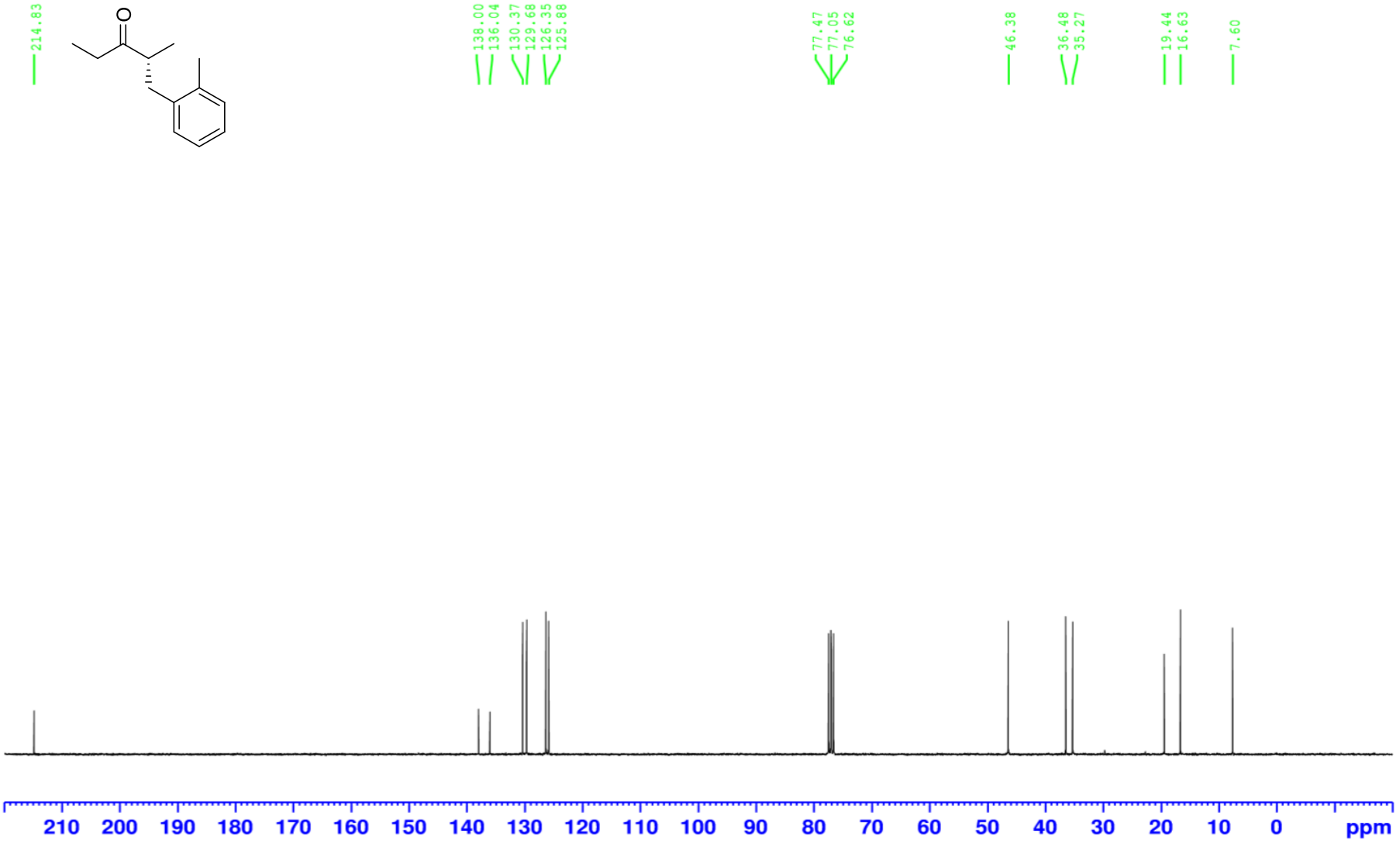
(R)-2-methyl-1-(o-tolyl)pentan-3-one 6

^{1}H NMR Spectra



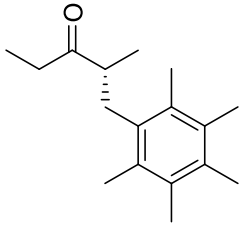
(R)-2-methyl-1-(o-tolyl)pentan-3-one 6

^{13}C NMR Spectra



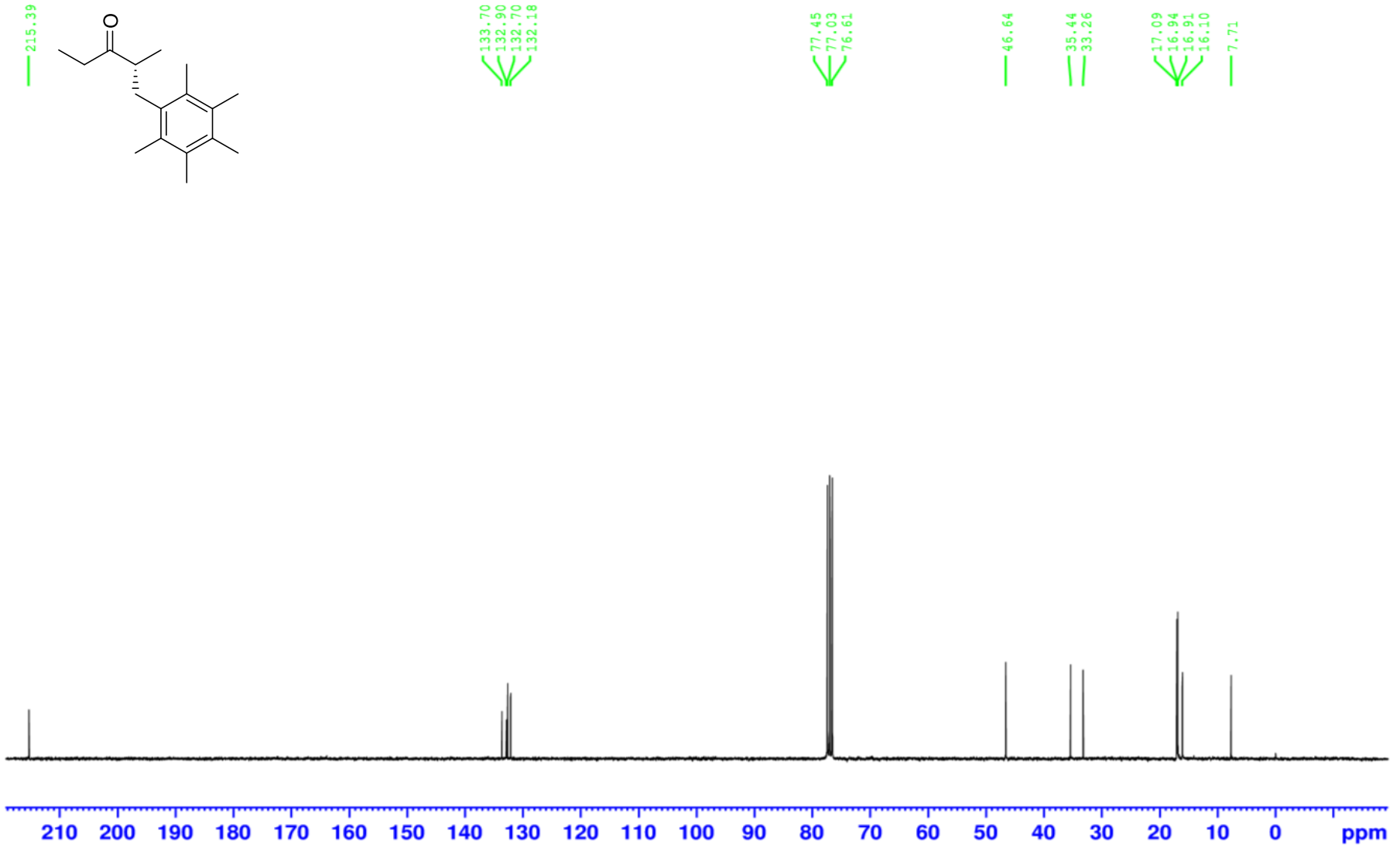
(R)-2-methyl-1-(2,3,4,5,6-pentamethylphenyl)pentan-3-one 7

^{1}H NMR Spectra



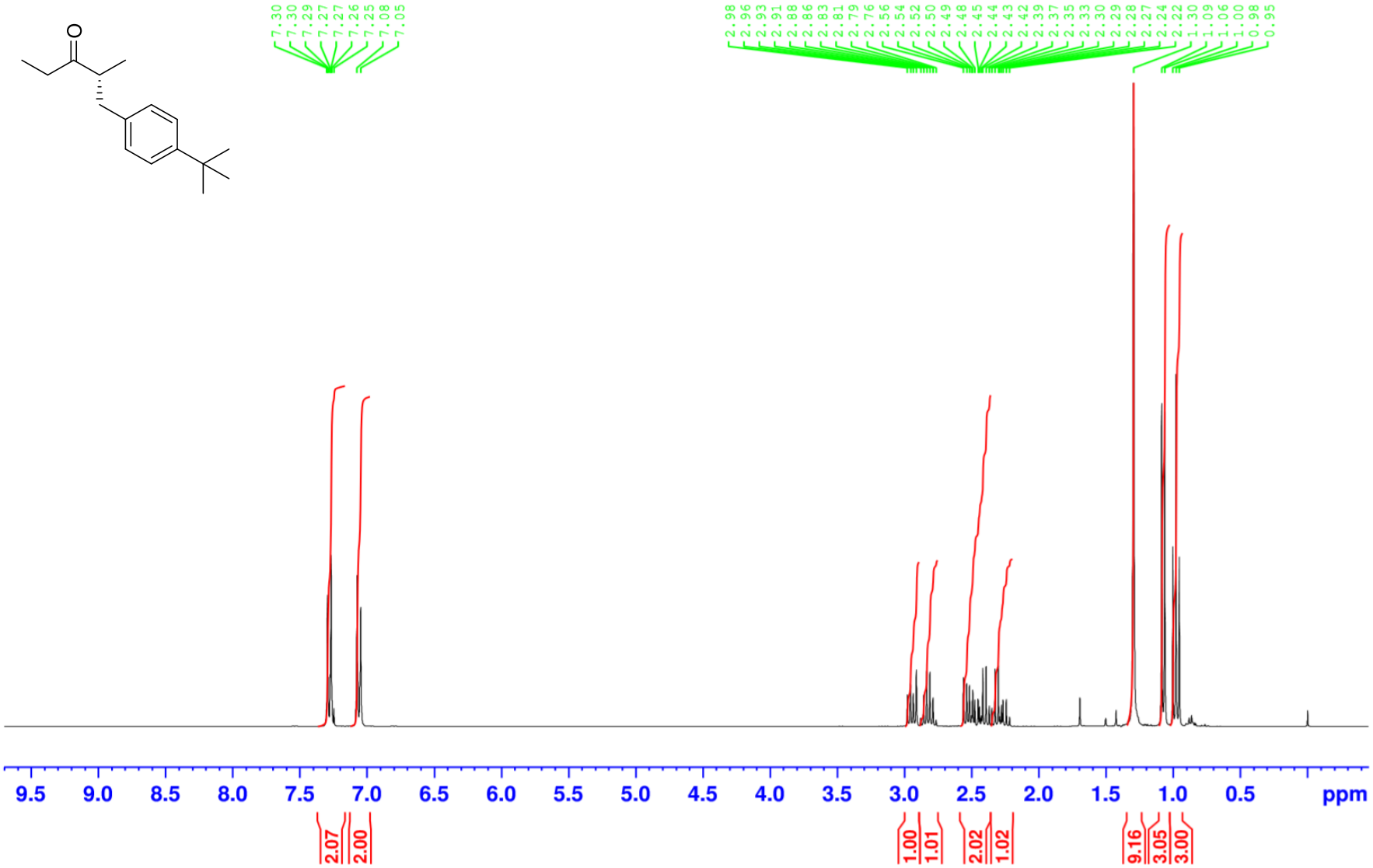
(R)-2-methyl-1-(2,3,4,5,6-pentamethylphenyl)pentan-3-one 7

^{13}C NMR Spectra



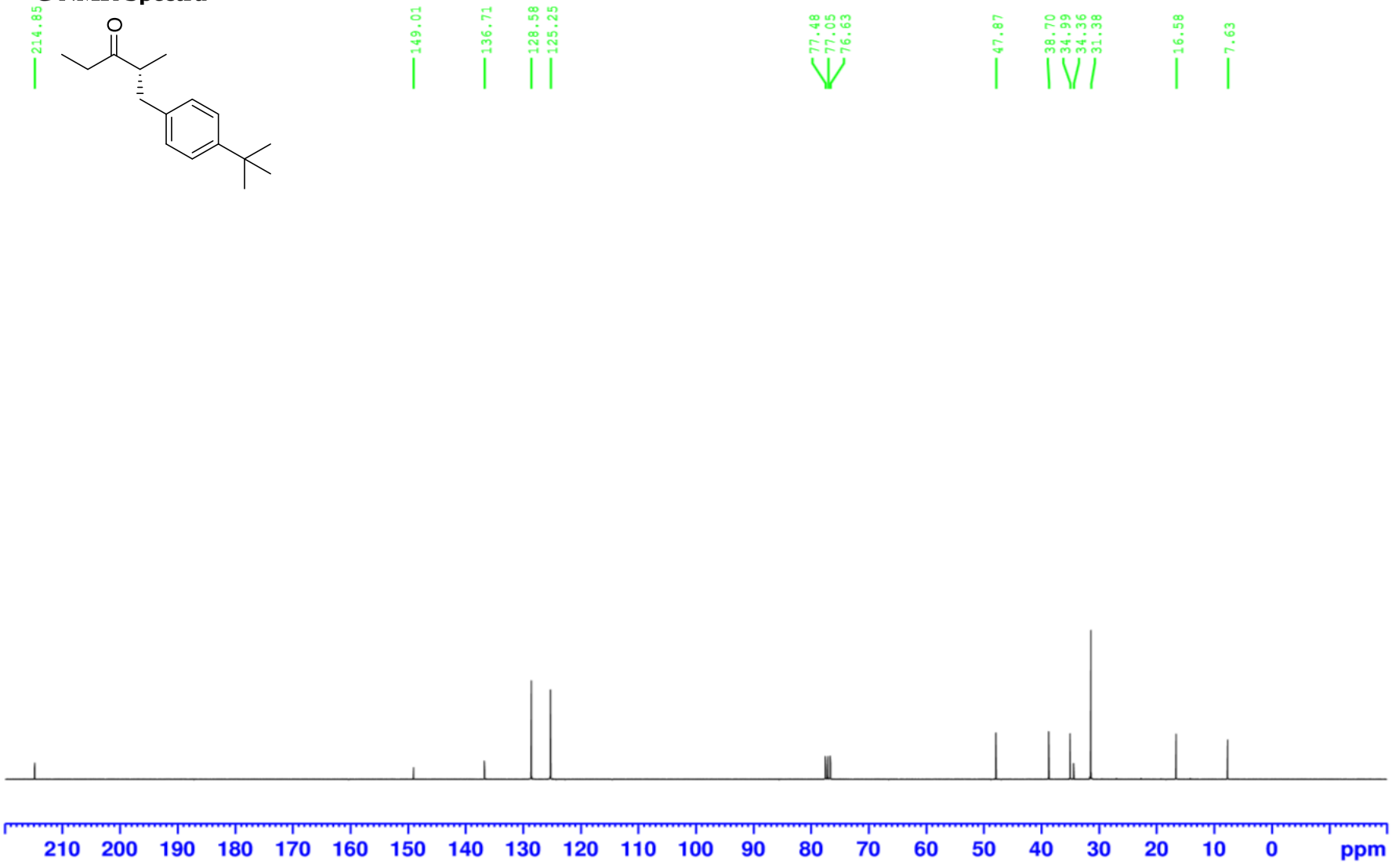
(R)-1-(4-(tert-butyl)phenyl)-2-methylpentan-3-one 8

^{1}H NMR Spectra



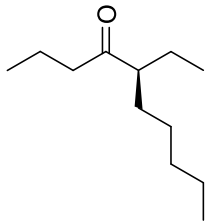
(R)-1-(4-(tert-butyl)phenyl)-2-methylpentan-3-one 8

^{13}C NMR Spectra



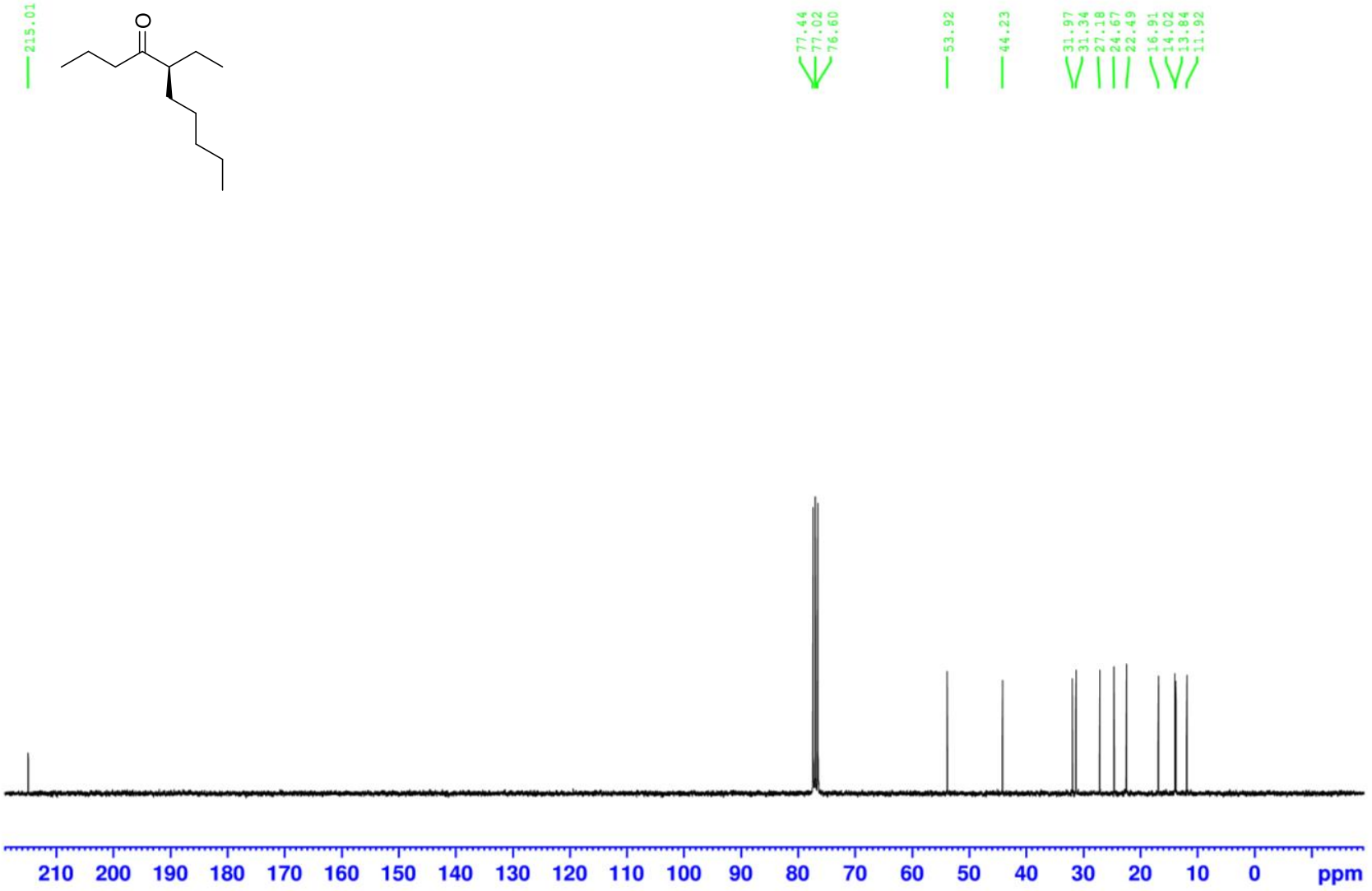
(S)-5-ethyldecan-4-one 9

^{1}H NMR Spectra



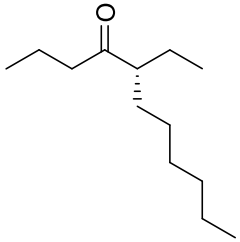
(S)-5-ethyldecan-4-one 9

^{13}C NMR Spectra



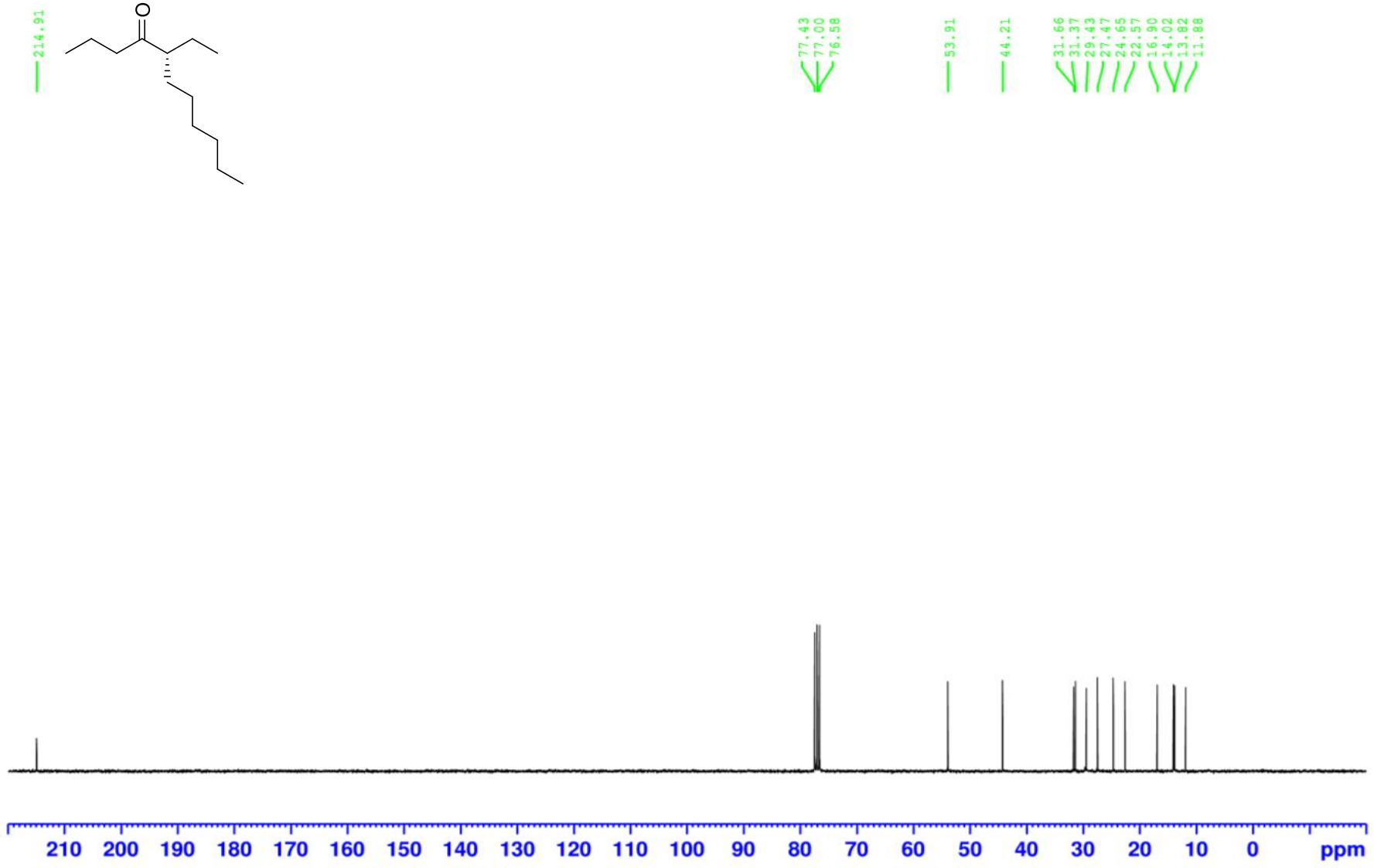
(R)-5-ethylundecan-4-one 10

^{1}H NMR Spectra



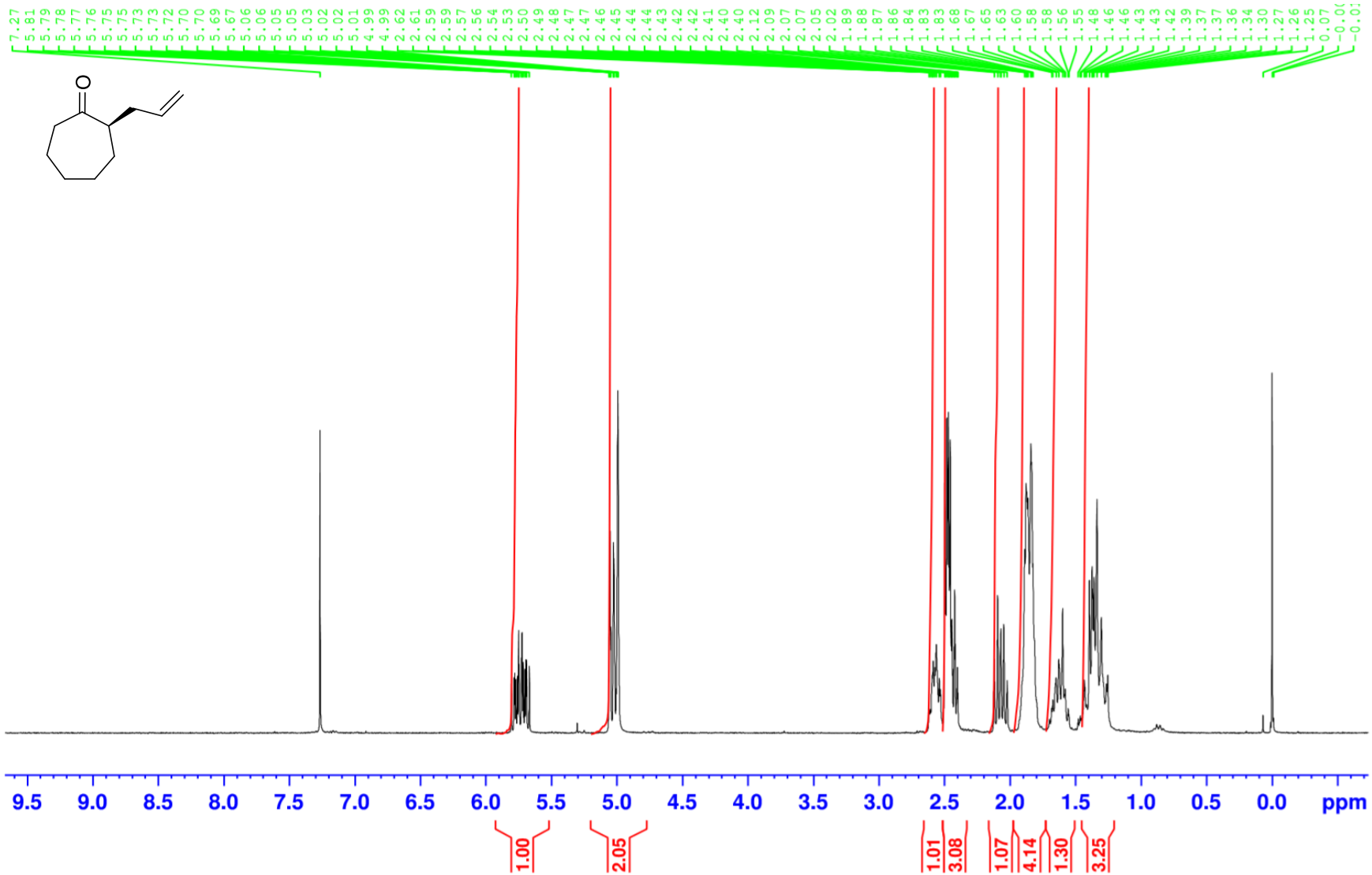
(R)-5-ethylundecan-4-one 10

^{13}C NMR Spectra



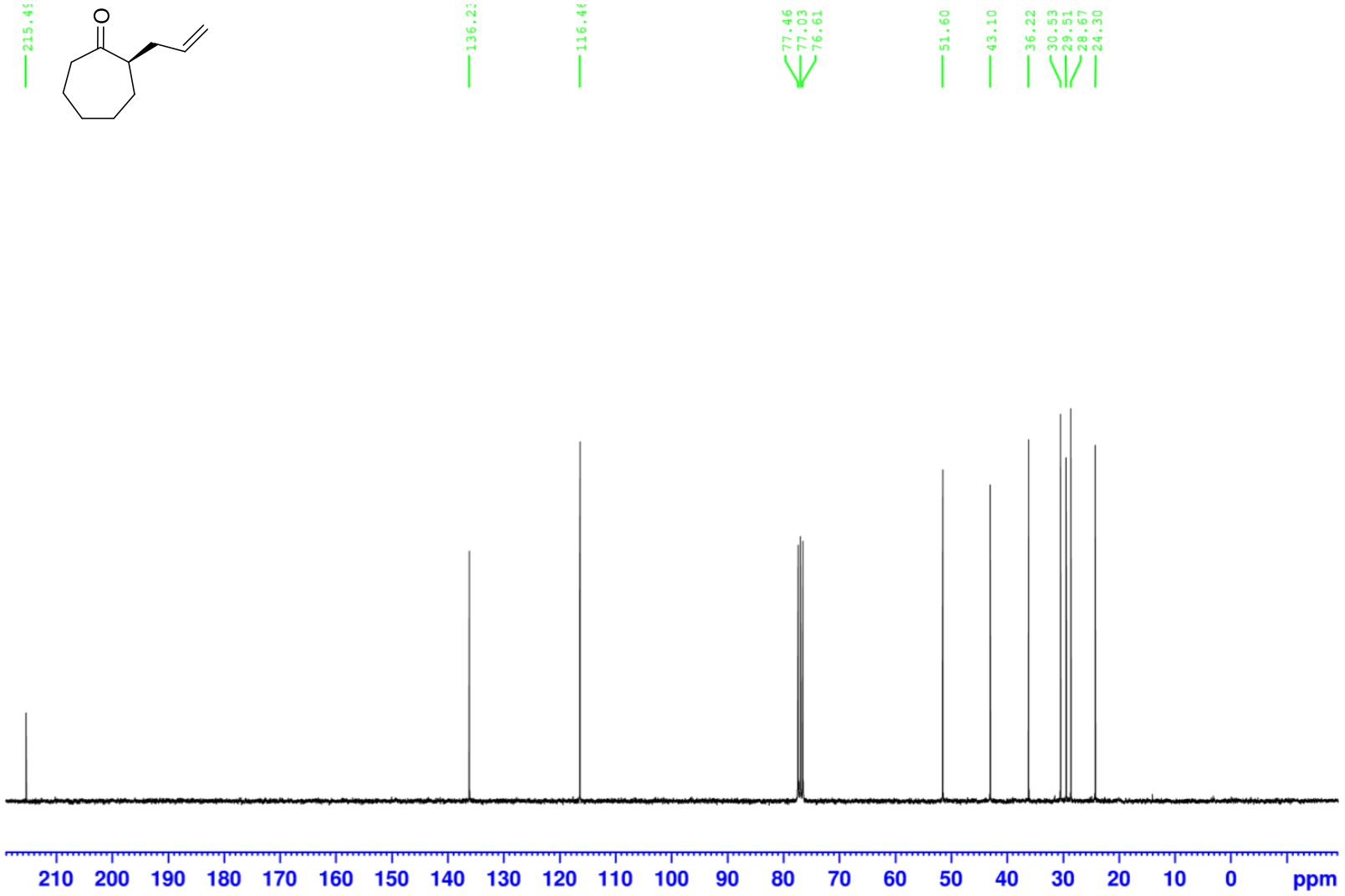
(R)-2-allylcycloheptan-1-one 12

^{1}H NMR Spectra



(R)-2-allylcycloheptan-1-one 12

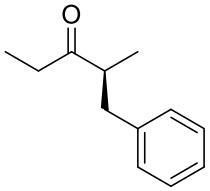
^{13}C NMR Spectra



VI. Chiral Gas chromatography chromatograms

Note: Optimum separation conditions determined using racemic samples of each substrate. In some cases (entry 1 and entry 4, Table 2) crude samples were used to facilitate rapid GC analysis.

(S)-2-methyl-1-phenylpentan-3-one 4 (entry 3, Table 2)



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Sample Info     : 120C hold 10min ramp 10C/min to 140C hold 5min, flow 1m
                  l/min, Inj vol. 0.2ul, split ratio 10:1, front inlet 15
                  0C, detector 155C
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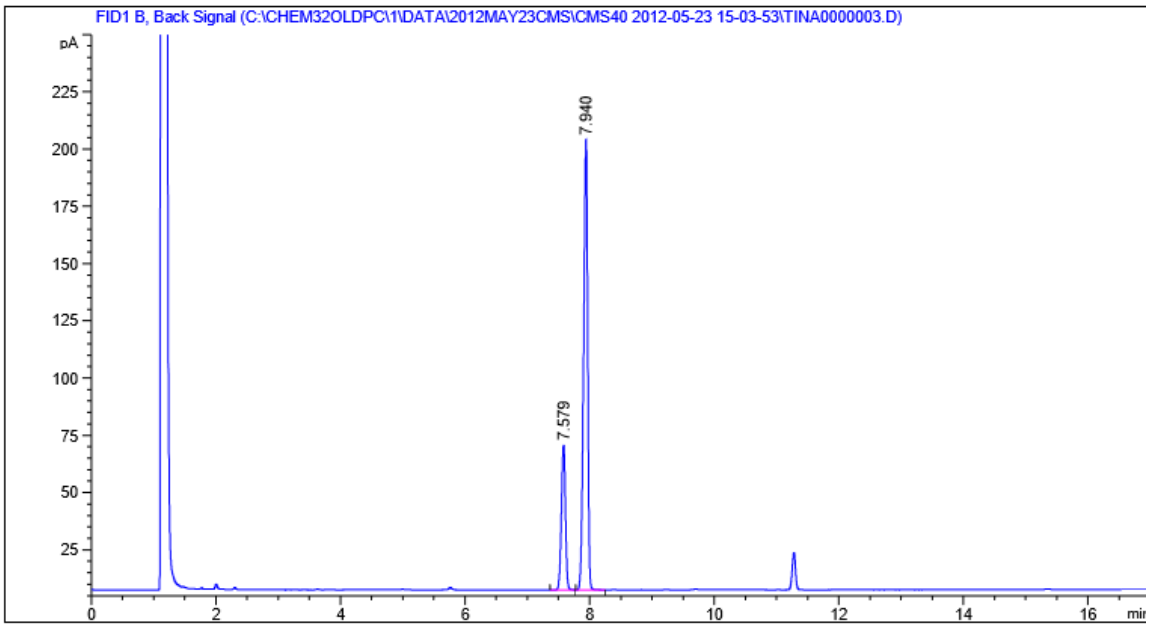


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=====================================================================
                        Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 B, Back Signal

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]         %
----|-------|----|-------|----------|----------|--------|
   1   7.579 BV    0.0708  286.51343   63.31395 24.19896
   2   7.940 VB    0.0713  897.47748  196.58499 75.80104
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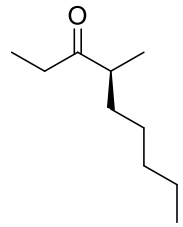
(S)-4-methylnonan-3-one 5 (entry 1, Table 2)



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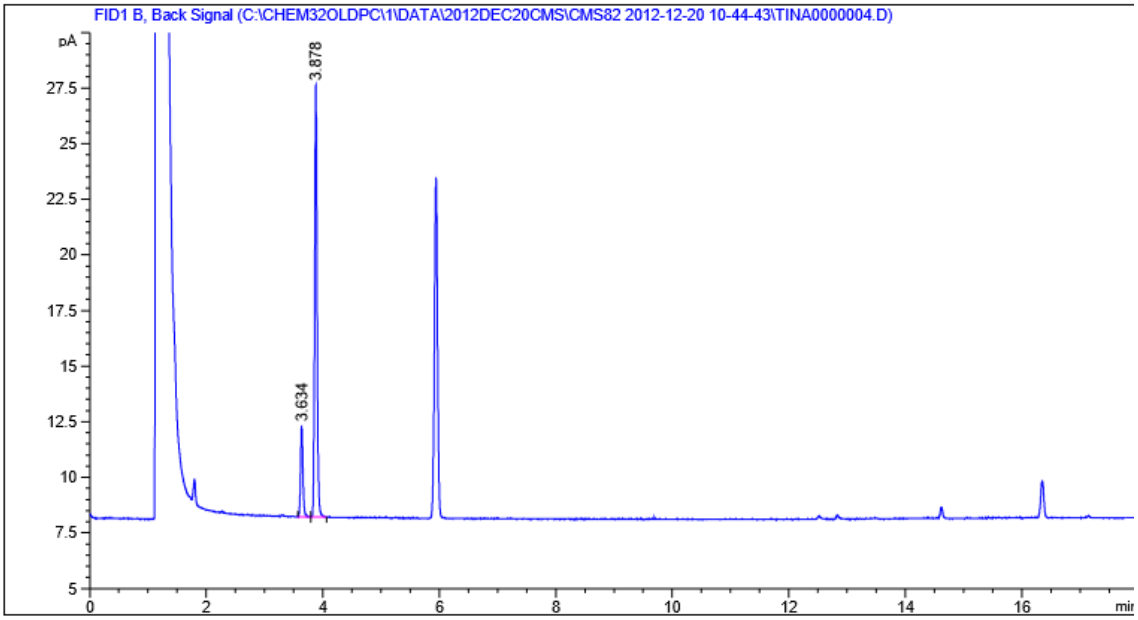


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=====================================================================
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=====================================================================

Sorted By             :      Signal
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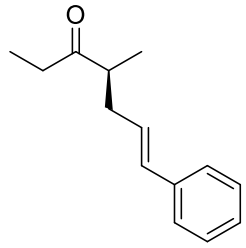
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs

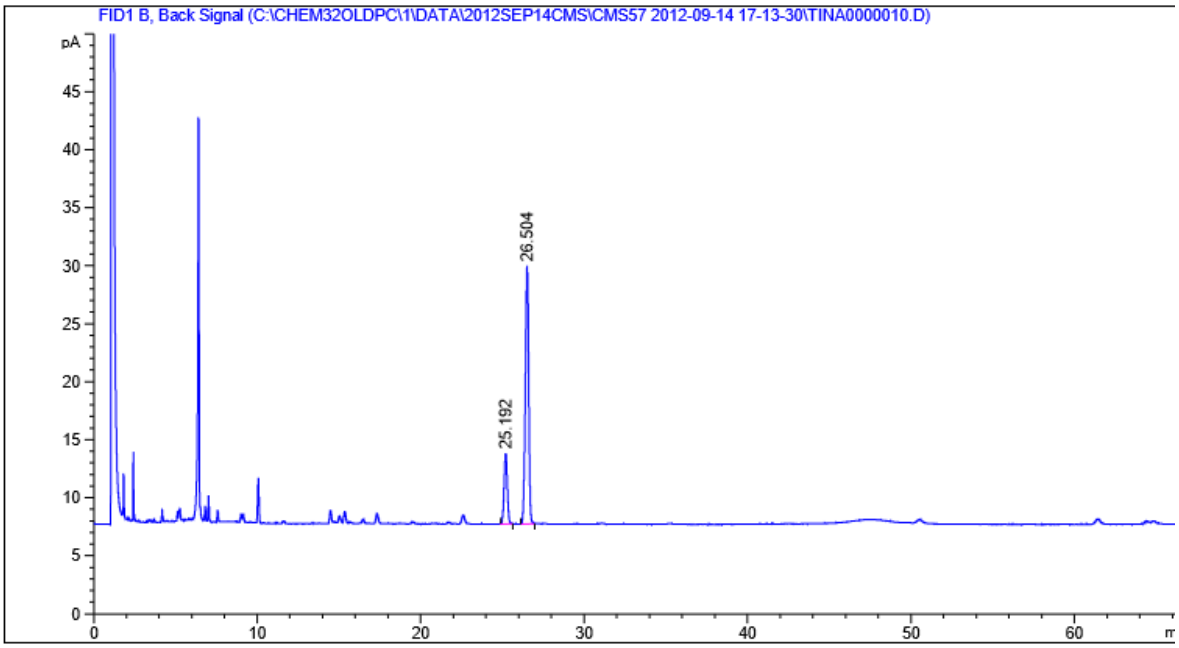

Signal 1: FID1 B, Back Signal

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]        %
----|-------|----|-------|----------|----------|--------|
   1   3.634 BV    0.0438   11.51704    4.09046 17.00971
   2   3.878 VB    0.0447   56.19158   19.42904 82.99029
```

(S)-(E)-4-methyl-7-phenylhept-6-en-3-one 6 (entry 4, Table 2)



```
Sample Info     : 130C HOLD 1H, RAMP 10/MIN 10 140 HOLD 5MIN, flow 1ml/mi
                  n, Inj vol. 0.2ul, split ratio 10:1, front inlet 150C,
                  detector 155C
```



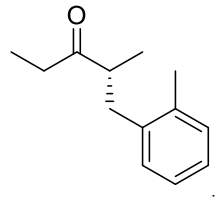

```
=====================================================================
                        Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs

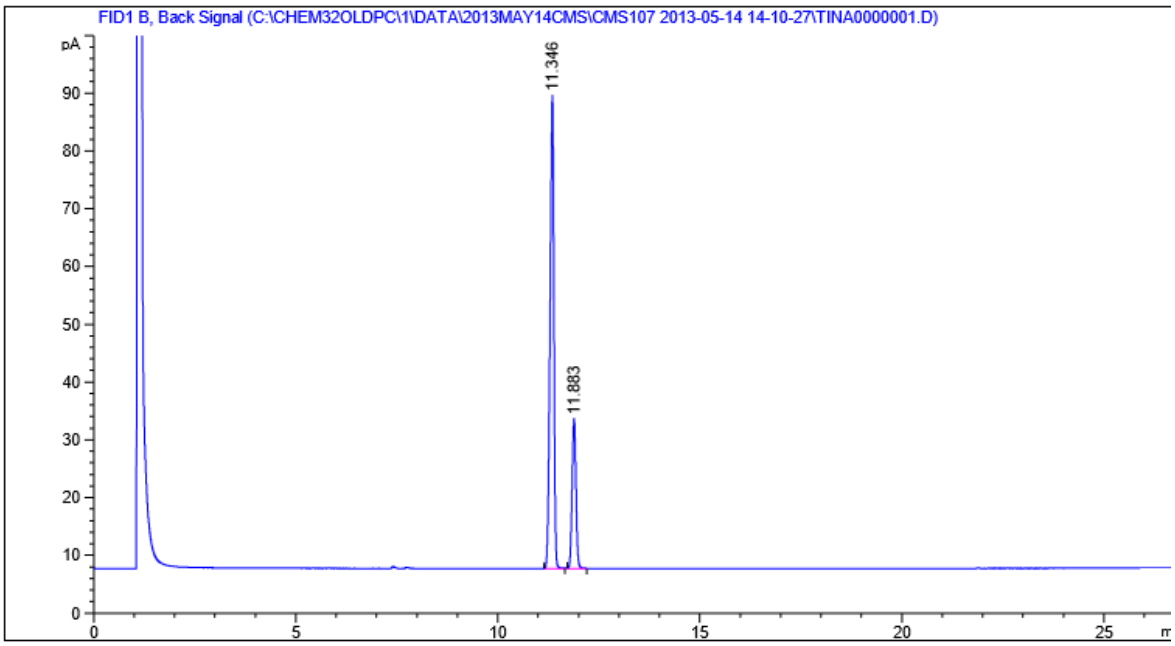

Signal 1: FID1 B, Back Signal

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]        %
----|-------|----|-------|----------|----------|--------|
   1  25.192 BB    0.2105   83.39989    6.09977 20.84473
   2  26.504 BB    0.2162  316.70065   22.23346 79.15527
```

(R)-2-methyl-1-(o-tolyl)pentan-3-one 7 (entry 5, Table 2)



```
Sample Info     : 120 HOLD 20 MIN, RAMP 10C/MIN TO 140, HOLD 5MIN, flow 1
                  ml/min, Inj vol. 0.2ul, split ratio 10:1, front inlet 1
                  50C, detector 155C
```



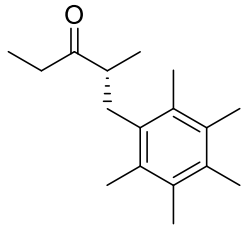

```
=====================================================================
                        Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 B, Back Signal

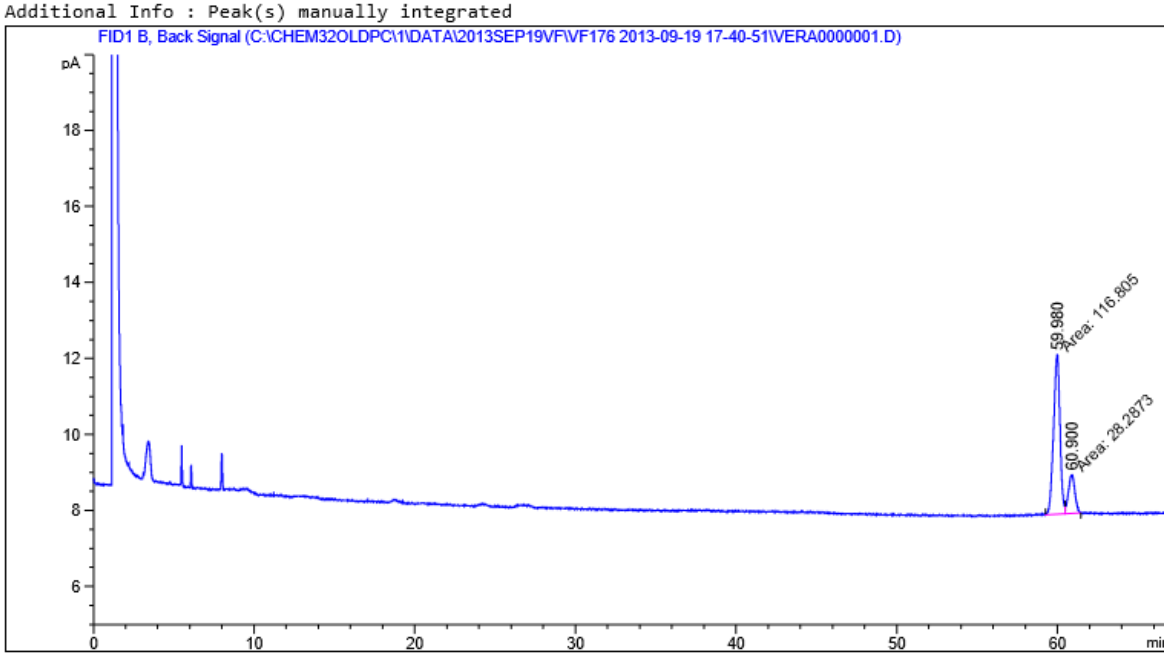
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]        %
----|-------|----|-------|----------|----------|--------|
   1  11.346 BB    0.1015  543.51331   81.81093 75.92652
   2  11.883 BB    0.1049  172.32788   25.81181 24.07348
```

(R)-2-methyl-1-(2,3,4,5,6-pentamethylphenyl)pentan-3-one 8 (entry 6, Table 2)



```
Sample Info     :  flow 1ml/min, Inj vol. 0.2ul, split ratio 10:1, front
                   inlet 150C, detector 155C

Additional Info : Peak(s) manually integrated
```



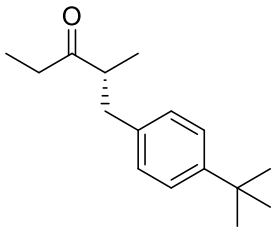

```
======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs

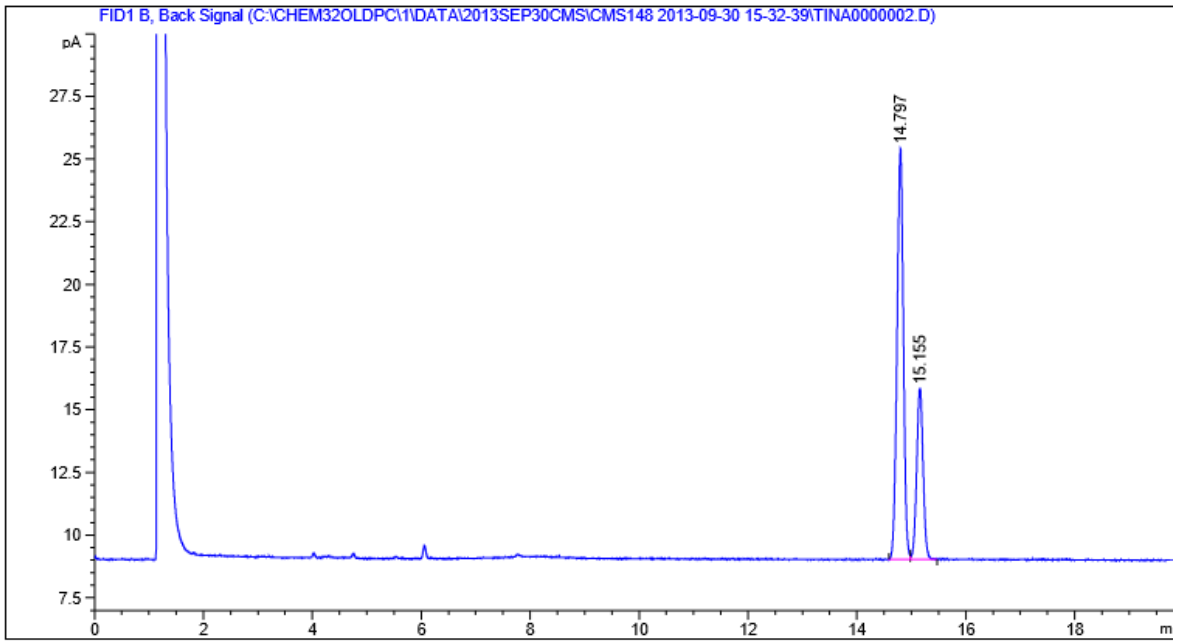

Signal 1: FID1 B, Back Signal

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]        %
----|-------|----|-------|----------|----------|--------|
   1  59.980 MF    0.4649  116.80544    4.18716 80.50398
   2  60.900 FM    0.4647   28.28730    1.01447 19.49602
```

(R)-1-(4-(tert-butyl)phenyl)-2-methylpentan-3-one 9 (entry 7, Table 2)



```
Sample Info     : 140C HOLD 20MIN flow 1ml/min, Inj vol. 0.2ul, split rat
                  io 10:1, front inlet 150C, detector 155C
```



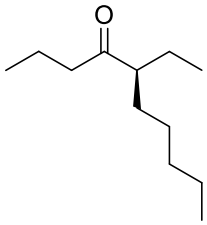

```
=====================================================================
                        Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs

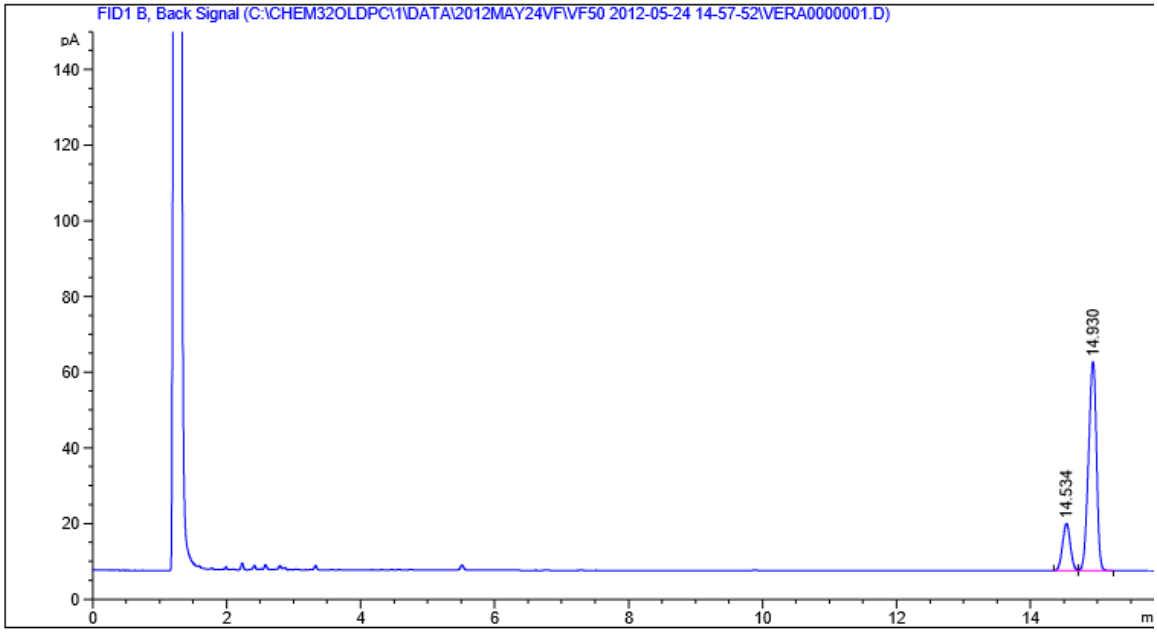

Signal 1: FID1 B, Back Signal

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]        %
----|-------|----|-------|----------|----------|--------|
   1  14.797 BV    0.1246  132.89465   16.39598 70.48133
   2  15.155 VB    0.1264   55.65833    6.80694 29.51867
```

(S)-5-ethyldecan-4-one 10 (entry 8, Table 2)



```
Sample Info     : 90C hold 20min ramp 5C/min to 140C hold 5min, flow 1ml/
                  min, Inj vol. 0.2ul, split ratio 10:1, front inlet 150C
                  , detector 155C
```



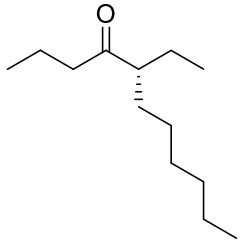

```
=====================================================================
                        Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 B, Back Signal

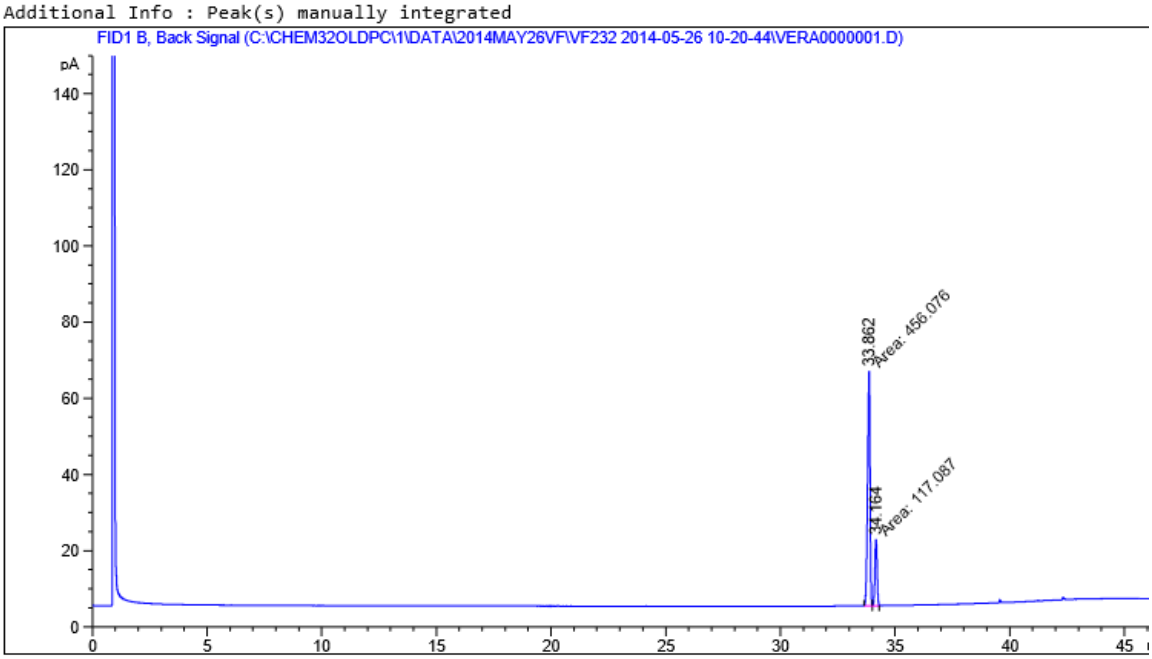
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]        %
----|-------|----|-------|----------|----------|--------|
   1  14.534 BV    0.1262  101.22231   12.53708 18.17876
   2  14.930 VB    0.1272  455.59396   55.24330 81.82124
```

(R)-5-ethylundecan-4-one 11 (entry 9, Table 2)



```
Sample Info     : 80 HOLD 30MIN, RAMP 5C/MIN TO 140 HOLD 5MIN flow 1ml/mi
                  n, Inj vol. 0.2ul, split ratio 10:1, front inlet 150C,
                  detector 155C

Additional Info : Peak(s) manually integrated
```



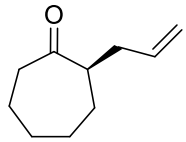

```
=====================================================================
                        Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 B, Back Signal

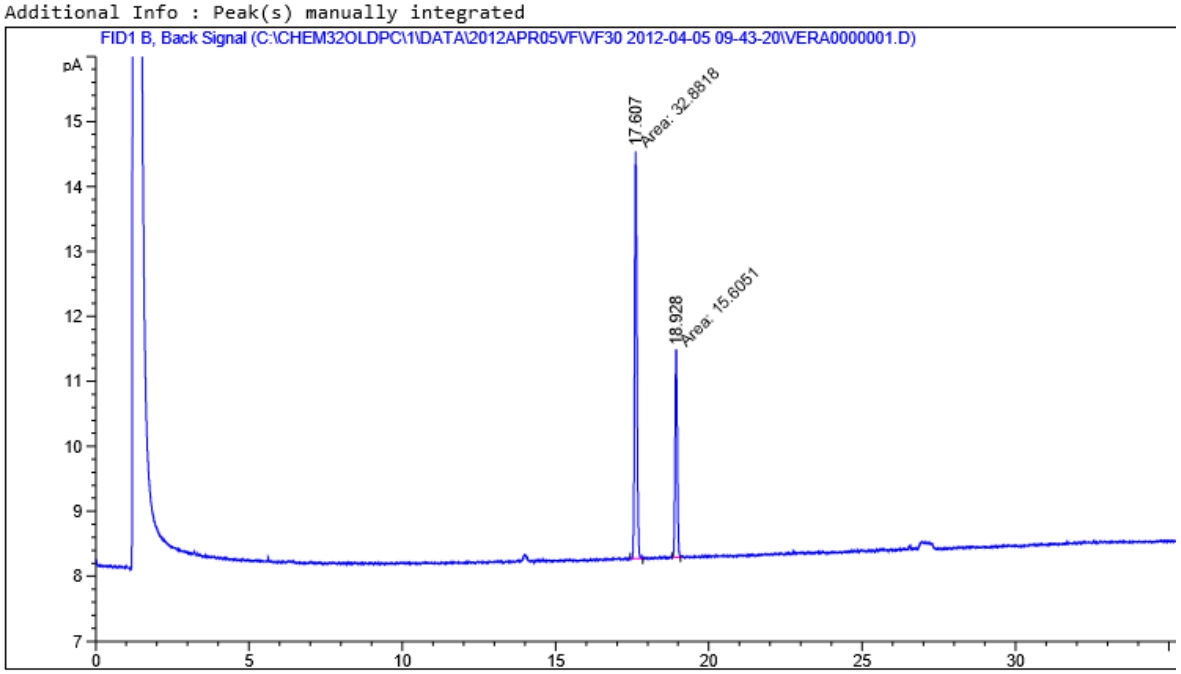
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]        %
----|-------|----|-------|----------|----------|--------|
   1  33.862 FM    0.1232  456.07623   61.68636 79.57181
   2  34.164 MF    0.1122  117.08681   17.39379 20.42819
```

(R)-2-allylcycloheptan-1-one 12 (entry 10, Table 2)



```
Sample Info     : 50C FOR 20MIN, RAMP 5C/MIN TO 140C HOLD FOR 5 MIN

Additional Info : Peak(s) manually integrated
```



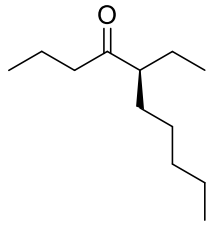

```
=====================================================================
                        Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 B, Back Signal

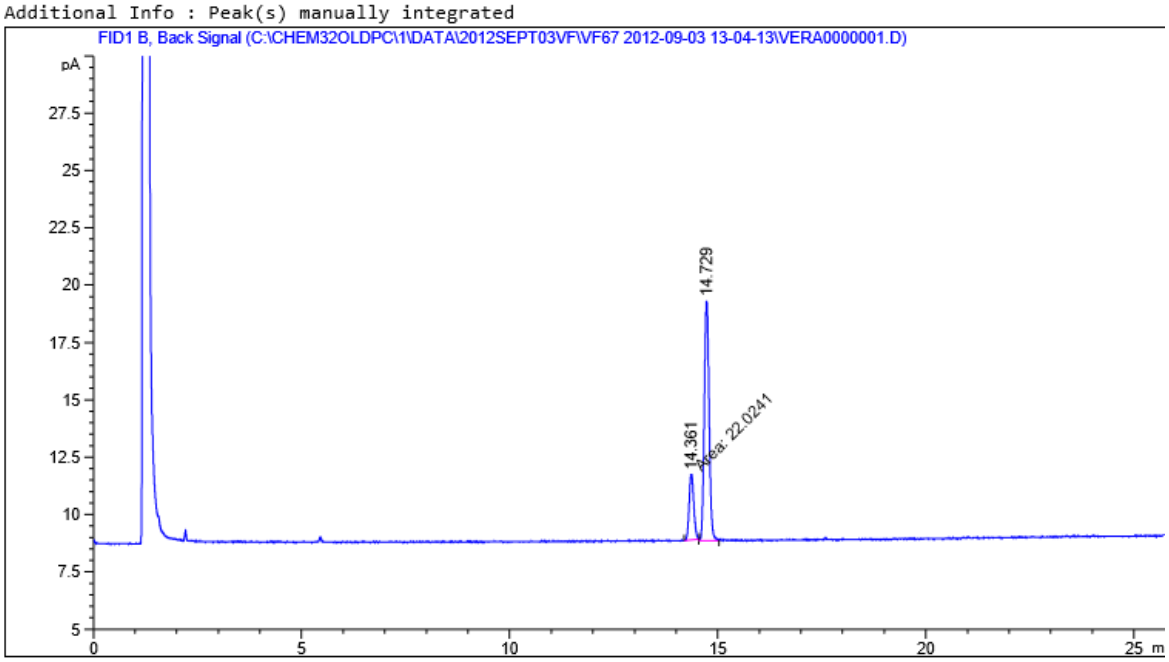
Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]        %
----|-------|----|-------|----------|----------|--------|
   1  17.607 MM    0.0874   32.88176    6.27052 67.81579
   2  18.928 MM    0.0816   15.60512    3.18581 32.18421
```

(S)-5-ethyldecan-4-one 10 (Scheme 3)



```
Sample Info     : 90C FOR 16MIN, RAMP 10C/MIN TO 140, HOLD FOR 5MIN , flo
                  w 1ml/min, Inj vol. 0.2ul, split ratio 10:1, front inle
                  t 150C, detector 155C

Additional Info : Peak(s) manually integrated
```




```
=====================================================================
                        Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 B, Back Signal

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]        %
----|-------|----|-------|----------|----------|--------|
   1  14.361 MM    0.1282   22.02409    2.86327 20.68530
   2  14.729 VBA   0.1253   84.44807   10.45032 79.31470
```