Supplementary information

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Materials and methods

General informations

(*R*,*R*)-1,2-diaminocyclohexane·HCl and (*S*,*S*)-1,2-diaminocyclohexane·HCl were purchased from Arran Chemical Company LTD, 4-chlorobutyrophenone from Alfa Aesar, 4'-bromo-4-chlorobutyrophenone from Acros Organics and 4-bromophenyl isocyanate, 4-Chloro-1-(4-methylphenyl)-1-oxobutane and 5-chloro-1-(4-methylphenyl)-1-oxopentane from Fluorochem. All other reagents were purchased from Sigma-Aldrich and used as supplied, unless otherwise stated. Toluene, tetrahydrofuran and diethyl ether were dried with a Grubbs type Pure Solv-400-3-MD solvent purification system supplied by Innovative Technology Inc. Dichloromethane was dried over 4Å molecular sieves. Dry solvents were stored in J Young flasks over 4Å molecular sieves. The water content in all solvents was monitored before use by titration on an Aquamax KF instrument.

Oxygen-free nitrogen was obtained from BOC gases and passed over dry molecular sieves 4Å. Flash column chromatography was performed on Davisil silica with particle size 40-63 µm. Thin layer chromatography was performed on Merck pre-coated Kieselgel $60F_{254}$ aluminium plates with UV realisation.

NMR spectra were recorded on Varian VNMRS 400 and 500 spectrometers at 25 °C. Assignments were based on standard ^{1}H-^{1}H and ^{1}H-^{13}C two-dimensional techniques. Chemical shifts (δ) are reported in ppm relative to residual solvent signals for ^{1}H and ^{13}C NMR (^{1}H-NMR: 7.26 ppm and ^{13}C NMR: 77.16 ppm for $CDCl_3$). Coupling constants (*J*) are in Hz. Multiplicities are reported as follow: s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, m = multiplet and br = broad.

HPLC analysis was performed on Agilent Technologies 1260 Infinity system equipped with auto-sampler and Agilent UV-Vis detector operating at 210, 230 and 254 nm. Enantiomers were separated on chiral stationary phases Daicel Chiralpak® IA, IB, IC, AS-H, Chiracel® OJ-H, OB-H and Regis (S,S)-Whelk-O® 1 250 mm L x 4.6 mm ID, 5 µm particle size, coupled to a guard column 50 mm L x 4.6 mm ID.

Specific rotations were measured with a PerkinElmer Model 343 polarimeter, reported as [$100 \cdot deg \cdot dm^{-1} \cdot cm^{3} \cdot g^{-1}$] and are uncorrected for enantiomeric excess.

HRMS were measured with a LCT mass spectrometer Micromass/Waters corp. USA and a Waters GC/MS GCT premier mass spectrometer. The tertiary alcohols were unstable under both ESI and EI ionization methods. However, although the derived THF and THP were unstable under ESI ionization, their HRMS could be obtained under EI (at 35 eV) on the GC/MS system, which in all cases showed only one peak.

Grignard reagent solutions (MeMgBr 3.0 M in Et_2O, MeMgI 3.0 M in Et_2O, EtMgBr 3.0 M in Et_2O, *i*BuMgBr 2.0 M in Et_2O) were purchased from Sigma-Aldrich except for phenethylmagnesium bromide 1.7 M in Et_2O which was prepared from (2-bromoethyl)benzene and magnesium turnings. Grignard reagents solutions were titrated before use with 1.0 M menthol solution, using 1,10-phenantroline as indicator.[1] The solutions of ketones 0.5 M in dry toluene were stored in J Young flasks over 4Å molecular sieves.

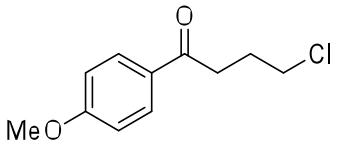
Ligands **L1** and **L2** were prepared according to our reported procedure.[2]

Experimental procedures and characterizations

General procedure for the preparation of ketones 2/3

In a 50 mL flame-dried Schlenk flask under nitrogen was prepared a solution of acyl chloride (10.0 mmol) in the selected arene (35.0 mmol). The solution was cooled to 0 °C and aluminium trichloride (11.0 mmol) was added portionwise over 10 minutes. The mixture was stirred at 0 °C for the indicated time and then poured into ice (75 g) and extracted with Et_2O (3 x 40 mL). The combined organic layers were dried over sodium sulfate, filtered and the solvent removed under reduced pressure. The crude material was purified by column chromatography on silica gel eluting with pentane/Et_2O 97:3 to obtain the pure ketone.

4'-methoxy-4-chlorobutyrophenone 2c

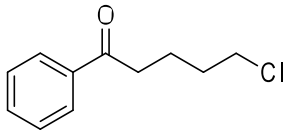


2c

Reaction conducted for 30 minutes at 0 °C. Off-white solid, 94% yield

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.97-7.94 (m, 2H), 6.95-6.92 (m, 2H), 3.87 (s, 3H), 3.68-3.65 (m, 2H), 3.14-3.10 (m, 2H), 2.25-2.18 (m, 2H); ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 197.6, 163.7, 130.4, 130.0, 113.9, 55.6, 44.9, 35.0, 27.1. Analytical data in accordance with literature reported results.[3]

5-chlorovalerophenone 3a

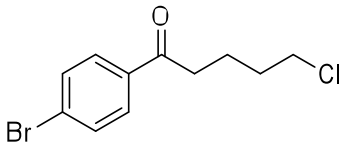


3a

Reaction conducted for 30 minutes at 0 °C. Off-white solid, 80% yield.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.97-7.94 (m, 2H), 7.59-7.54 (m, 1H), 7.49-7.45 (m, 2H), 3.60-3.57 (m, 2H), 3.04-3.00 (m, 2H), 1.95-1.83 (m, 4H); ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 199.8, 137.0, 133.2, 128.8, 128.1, 44.9, 37.7, 32.2, 21.7. Analytical data in accordance with literature reported results.[4]

4'-bromo-5-chlorovalerophenone 3b

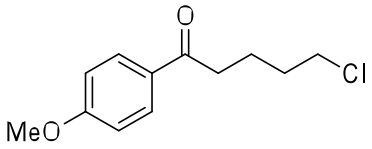


3b

Reaction conducted for 3 hours at room temperature. Off-white solid, 38% yield.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.83-7.79 (m, 2H), 7.61-7.58 (m, 2H), 3.59-3.56 (m, 2H), 2.99-2.96 (m, 2H), 1.93-1.83 (m, 4H); ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 198.6, 135.7, 132.1, 129.7, 128.4, 44.8, 37.7, 32.1, 21.5. Analytical data in accordance with literature reported results.[4]

4'-methoxy-5-chlorovalerophenone 3c



3c

Reaction conducted for 30 minutes at 0 °C. Off-white solid, 93% yield.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.96-7.92 (m, 2H), 6.95-6.91 (m, 2H), 3.87 (s, 3H), 3.59-3.56 (m, 2H), 2.98-2.94 (m, 2H), 1.93-1.82 (m, 4H); ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 198.3, 163.6, 130.4, 130.1, 113.9, 55.6, 44.9, 37.3, 32.3, 21.9. Analytical data in accordance with literature reported results.[4]

General procedure for the preparation of racemic tertiary alcohols

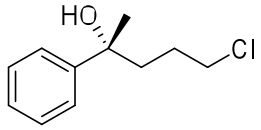
In a 50 mL flame-dried Schlenk flask under nitrogen was prepared a solution of ketone **2a-c/3a-c** (3.0 mmol) in dry toluene (10 mL). The solution was cooled to -78 °C and the Grignard reagent (4.5 mmol) was added dropwise. The mixture was stirred at -78 °C for 1 hour and then quenched with NH_4Cl sat. (3 mL) and H_2O (3 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3 x 15 mL). The combined organic phases were dried over sodium sulfate, filtered and the solvent removed under reduced pressure. The crude material was purified by column chromatography on silica gel, eluting with pentane/Et_2O 95:5 to 80:20 to obtain the pure tertiary alcohol.

General procedure for the preparation of chiral non-racemic tertiary alcohols

To a 25 mL flame-dried Schlenk flask under nitrogen was added a 0.5 M solution of ketone **2a-c/3a-c** in dry toluene (0.1 mmol, 0.200 mL) followed by dry toluene (1.3 mL). Ligand **L1** (50 mg, 0.133 mmol) was added, the solution was stirred magnetically at 750 rpm for 5 minutes at room temperature and then cooled to -78 °C. The Grignard reagent in Et_2O (0.243 mmol) was diluted with dry toluene (400 µL) and was added dropwise over 15 minutes. The reaction mixture was stirred at -78 °C for 1 hour and then quenched at that temperature with a solution of IPA/H_2O 1:1 (0.3 mL), followed by NH_4Cl sat. (0.3 mL) and diluted with heptane (1 mL). The cooling bath was removed and the mixture allowed to warm up to room temperature under vigorous stirring. The phases were separated and the aqueous phase was extracted with heptane (3 x 10 mL). The combined organic phases were washed with AcOH 20% solution (2 x 10 mL), H_2O (10 mL) and brine (10 mL), dried over sodium sulfate, filtered and the solvent removed under reduced pressure. The crude material was purified by column chromatography on silica gel, eluting with pentane/Et_2O 95:5 to

80:20 to obtain the pure scalemic tertiary alcohol **4/5**. The enantiomeric excess was determined by HPLC analysis on chiral stationary phase.

5-chloro-2-phenylpentan-2-ol 4aa



4 aa

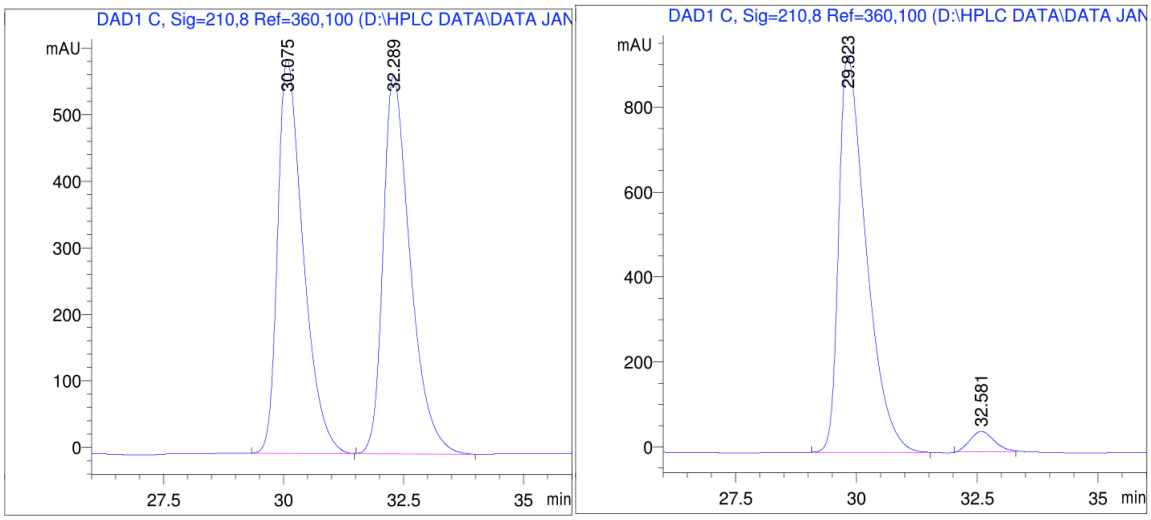
Colourless oil, 71% yield, 91% *ee*

HPLC analysis on chiral stationary phase: Column Chiralpak IB, Heptane/EtOH 99.7:0.3, flow 1 mL/min, 210 nm, 21 °C, t_M= 29.8 min, t_m= 32.6 min

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.45-7.42 (m, 2H), 7.37-7.33 (m, 2H), 7.27-7.23 (m, 1H), 2.01-1.88 (m, 2H), 1.85-1.74 (m, 2H), 1.72-1.61 (m, 2H), 1.59 (s, 3H)

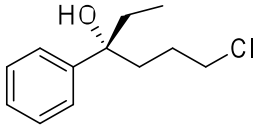
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 147.4, 128.4, 126.9, 124.8, 74.5, 45.6, 41.5, 30.7, 27.6

Analytical data were in accordance with literature reported results.[5]



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.823	BB	0.5871	3.67805e4	934.58868	95.6276
2	32.581	MM	0.5837	1681.71863	48.02130	4.3724
Totals :				3.84622e4	982.60999	

(*R*)-6-chloro-3-phenylhexan-3-ol 4ab



4ab

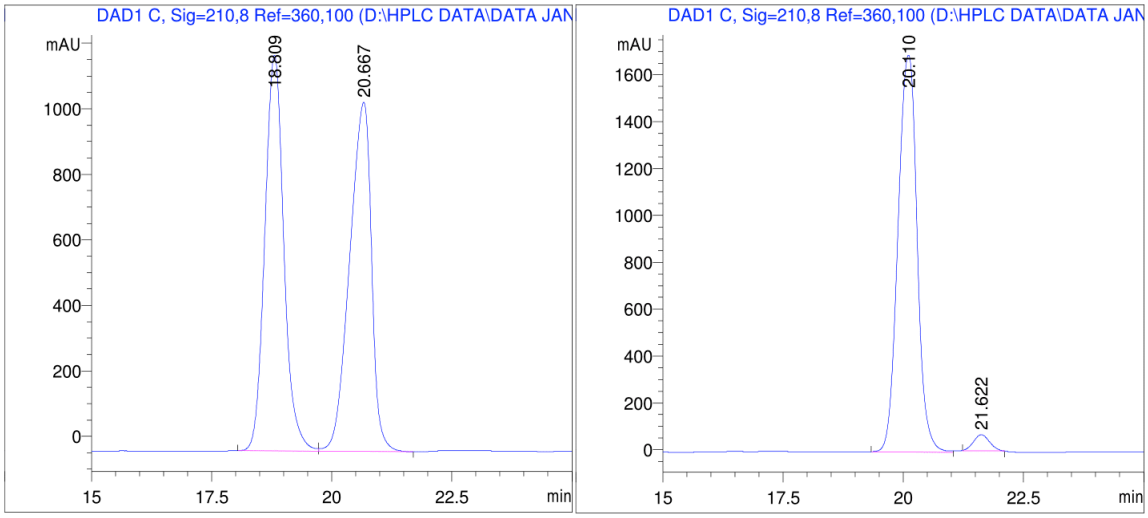
Colourless oil, 69% yield, 93% *ee*

HPLC analysis on chiral stationary phase: Column Chiralpak IB, Heptane/EtOH 99.7:0.3, flow 1 mL/min, 210 nm, 21 °C, t_M= 20.1 min, t_m= 21.6 min

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.39-7.32 (m, 4H), 7.26-7.22 (m, 1H), 3.52-3.43 (m, 2H), 2.02-1.75 (m, 5H), 1.66 (br s, 1H), 1.60-1.49 (m, 1H), 0.77 (t, *J* = 7.4 Hz, 3H)

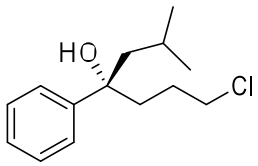
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 145.4, 128.3, 126.7, 125.4, 77.1, 45.8, 40.0, 35.9, 27.2, 7.8

Analytical data were in accordance with literature reported results.[5]



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.110	BB	0.4360	4.67509e4	1693.75146	96.7783
2	21.622	MM	0.3815	1556.30811	67.98848	3.2217
Totals :				4.83072e4	1761.73994	

1-chloro-6-methyl-4-phenylheptan-4-ol 4ac



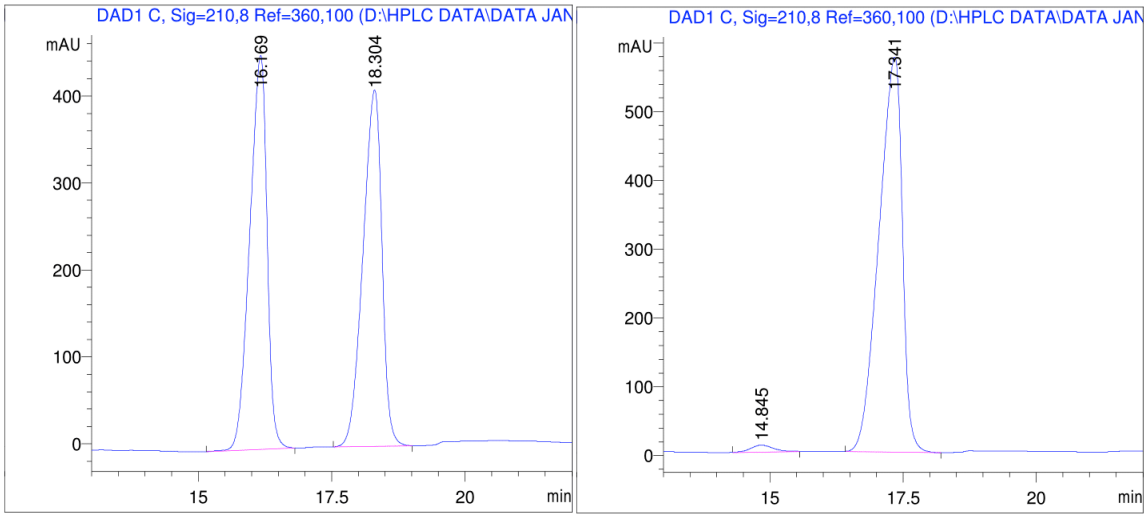
4ac

Colourless oil, 63% yield, 96% *ee*

HPLC analysis on chiral stationary phase: Column Chiralpak IB, Heptane/EtOH 99.7:0.3, flow 1 mL/min, 210 nm, 21 °C, t_m= 14.8 min, t_M= 17.3 min

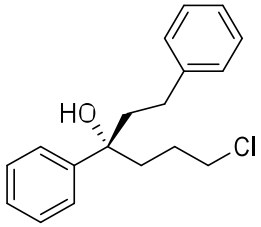
^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.40-7.31 (m, 4H), 7.26-7.20 (m, 1H), 3.52-3.40 (m, 2H), 2.02-1.42 (m, 8H), 0.91 (d, *J* = 6.6 Hz, 3H), 0.69 (d, *J* = 6.6 Hz, 3H)

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 145.8, 128.3, 126.5, 125.4, 77.4, 52.2, 45.8, 41.6, 27.0, 24.6, 24.5, 24.2



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.845	BB	0.4587	304.49869	10.07098	1.7050
2	17.341	BB	0.4864	1.75551e4	574.64240	98.2950
Totals :				1.78596e4	584.71337	

6-chloro-1,3-diphenylhexan-3-ol 4ad



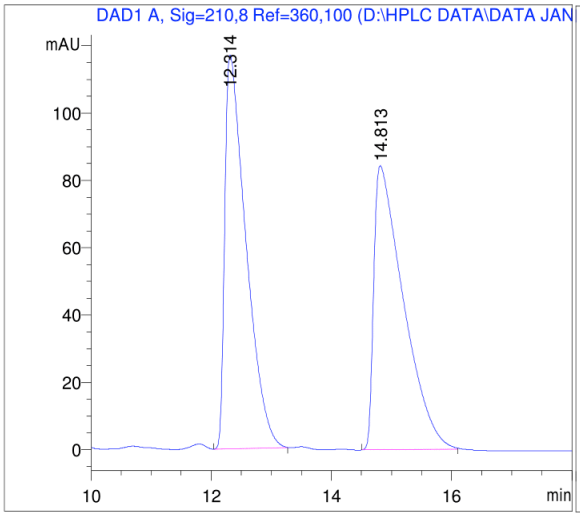
4ad

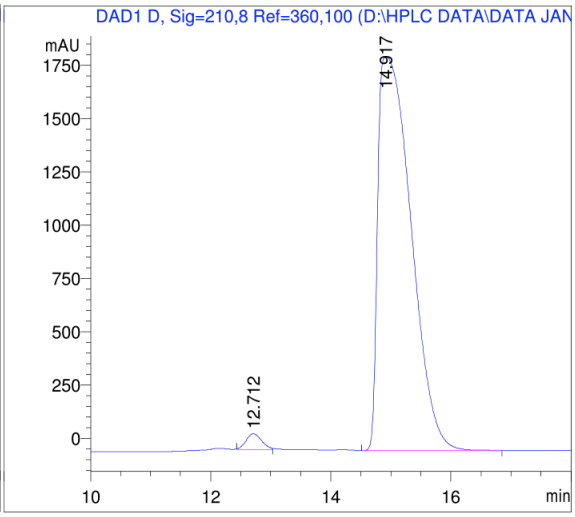
Colourless oil, 70% yield, 96% *ee*

HPLC analysis on chiral stationary phase: Column Chiralpak IA, Heptane/EtOH 95:5, flow 1 mL/min, 210 nm, 21 °C, t_m= 12.7 min , t_M= 14.9 min

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.45-7.36 (m, 4H), 7.31-7.09 (m, 6H), 3.53-3.42 (m, 2H), 2.67-2.57 (m, 1H), 2.43-2.33 (m, 1H), 2.26-1.92 (m, 4H), 1.89-1.75 (m, 1H), 1,72 (br s, 1H), 1.63-1.49 (m, 1H)

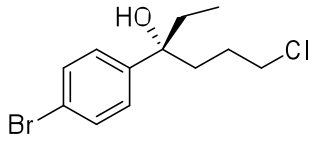
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 145.2, 142.2, 128.6, 128.5, 128.4, 126.9, 126.0, 125.3, 77.0, 45.6, 45.2, 40.7, 30.1, 27.1





Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.712	MM	0.2981	1311.56409	73.33271	1.8164
2	14.917	VB	0.6129	7.08954e4	1850.93774	98.1836
Totals :				7.22069e4	1924.27045	

3-(4-bromophenyl)-6-chlorohexan-3-ol 4bb



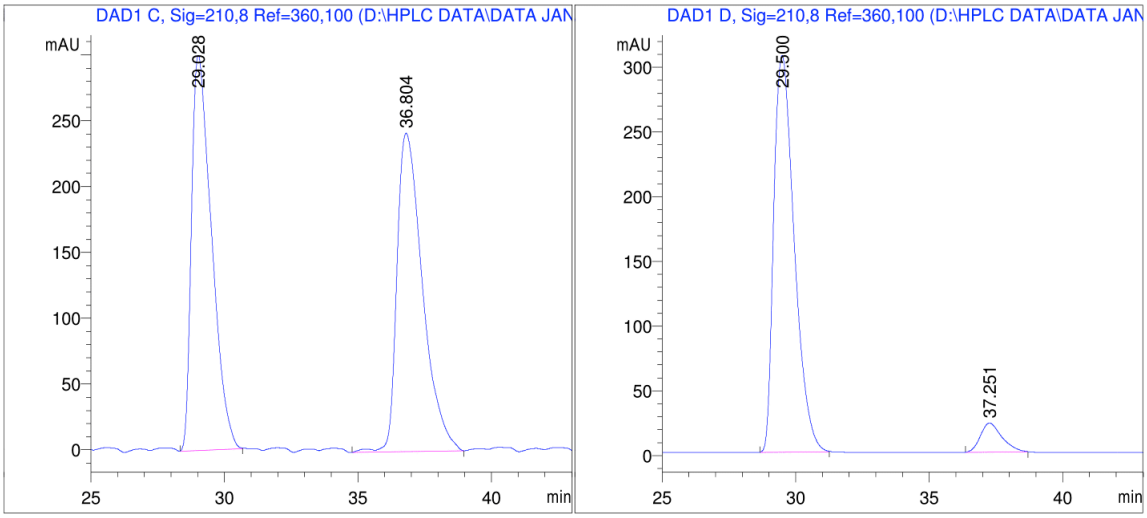
4bb

Colourless oil, 83% yield, 88% *ee*

HPLC analysis on chiral stationary phase: Column Chiralpak AS-H, Heptane/EtOH 99:1, flow 1 mL/min, 210 nm, 21 °C, t_M= 29.5 min, t_m= 37.3 min

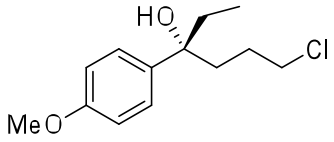
^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.47-7.44 (m, 2H), 7.26-7.23 (m, 2H), 3.51-3.42 (m, 2H), 1.98-1.73 (m, 5H), 1.65 (br s, 1H), 1.56-1.43 (m, 1H), 0.75 (t, *J* = 7.4 Hz, 3H);

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 144.4, 131.4, 127.4, 120.6, 76.9, 45.6, 40.0, 35.9, 27.0, 7.7



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.500	BB	0.8328	1.72259e4	321.67413	94.0501
2	37.251	MM	0.8201	1089.75647	22.14764	5.9499
Totals :				1.83156e4	343.82177	

6-chloro-3-(4-methoxyphenyl)hexan-3-ol 4cb



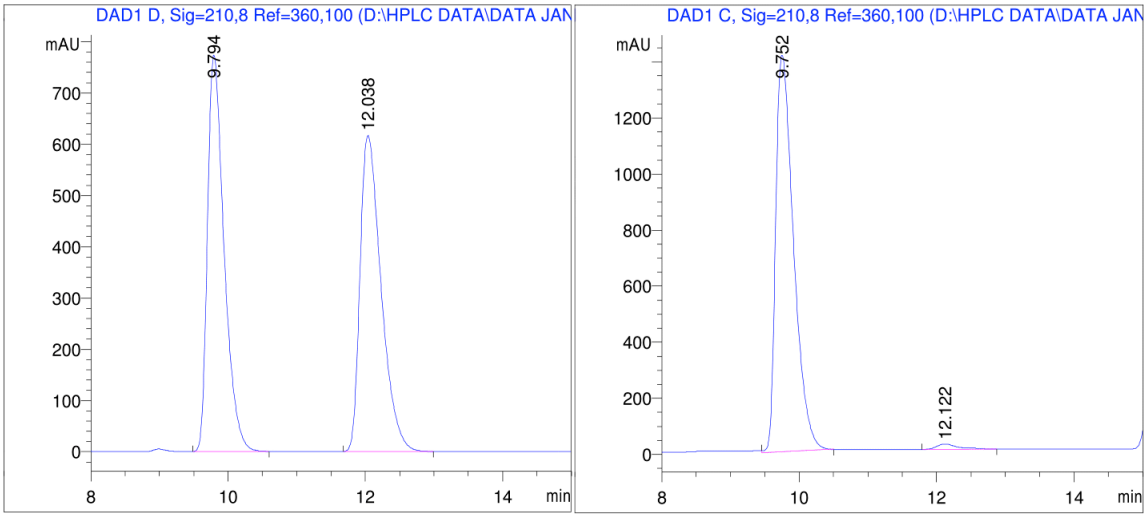
4cb

Colourless oil, 68% yield, 97% *ee*

HPLC analysis on chiral stationary phase: Column Chiracel OJ-H, Heptane/EtOH 90:10, flow 1 mL/min, 210 nm, 21 °C, t_M= 9.8 min, t_m= 12.1 min

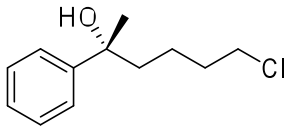
^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.30-7.26 (m, 2H), 6.89-6.86 (m, 2H), 3.81 (s, 3H), 3.52-3.43 (m, 2H), 1.98-1.73 (m, 5H), 1.62-1.51 (m, 2H), 0.76 (t, *J* = 7.4 Hz, 3H)

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 158.3, 137.5, 126.6, 113.6, 76.8, 55.4, 45.8, 40.0, 35.8, 27.2, 7.9



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.752	MM	0.3004	2.54841e4	1413.87439	98.6087
2	12.122	BB	0.3318	445.82925	19.42445	1.3913
Totals :				2.59300e4	1433.29884	

(*R*)-6-chloro-2-phenylhexan-2-ol 5aa



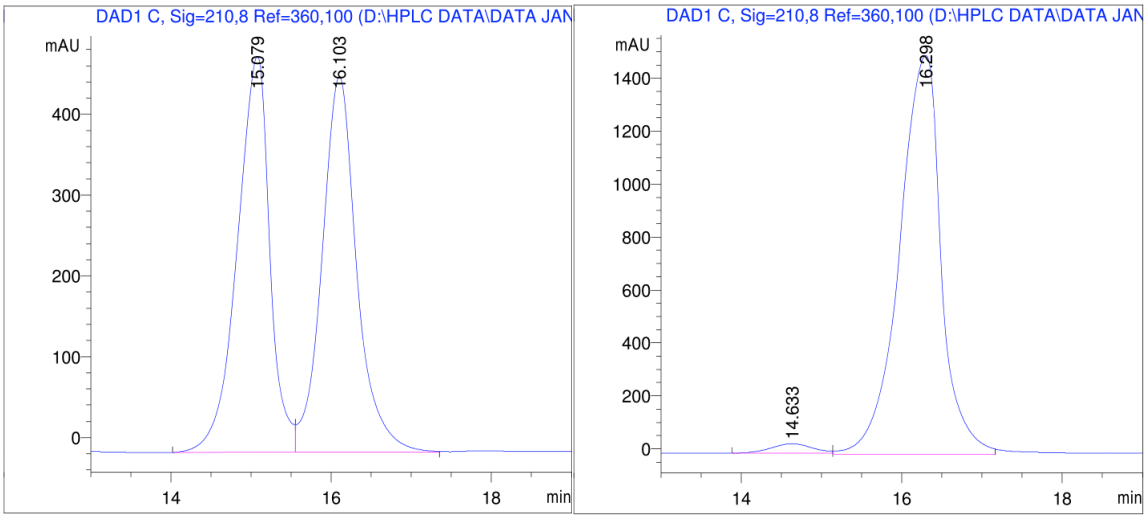
5aa

Colourless oil, 69% yield, 95% *ee*

HPLC analysis on chiral stationary phase: Column (*S*,*S*)-Whelk-O 1, Heptane/EtOH 99.7:0.3, flow 1 mL/min, 210 nm, 21 °C, t_m= 14.6 min, t_M= 16.3 min

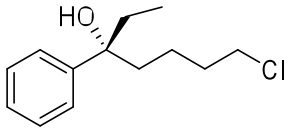
^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.44-7.41 (m, 2H), 7.37-7.32 (m, 2H), 7.27-7.23 (m, 1H), 3.47 (t, *J* = 6.8 Hz, 2H), 1.88-1.69 (m, 5H), 1.58 (s, 3H), 1.49-1.38 (m, 1H), 1.35-1.23 (m, 1H)

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 147.8, 128.4, 126.8, 124.9, 74.7, 45.0, 43.5, 33.0, 30.3, 21.6



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.633	BV	0.5610	1294.63440	35.70463	2.3274
2	16.298	MM	0.6006	5.43313e4	1507.58057	97.6726
Totals :				5.56259e4	1543.28519	

7-chloro-3-phenylheptan-3-ol 5ab



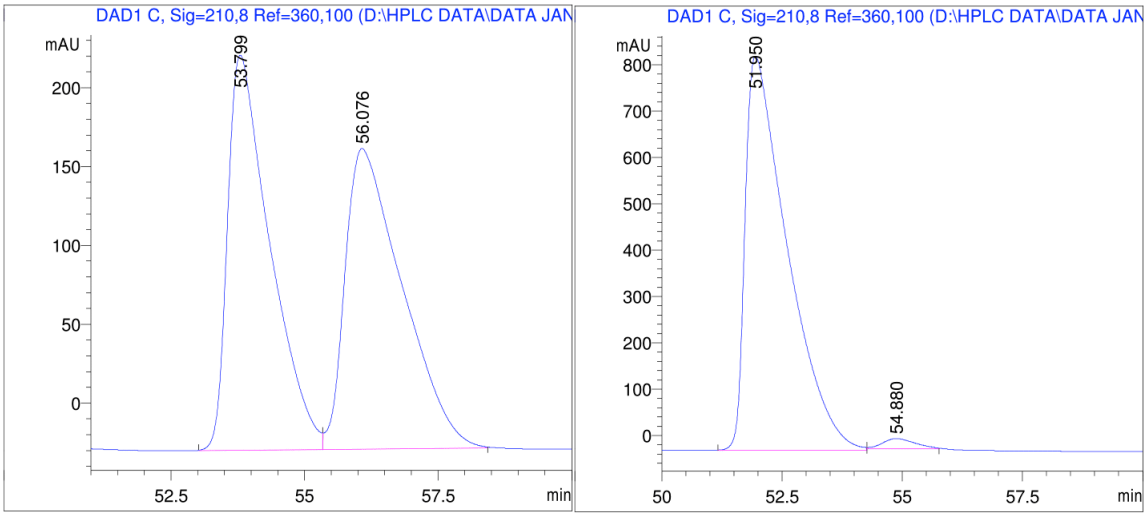
5ab

Colourless oil, 72% yield, 95% *ee*

HPLC analysis on chiral stationary phase: Column Chiralpak IB, Heptane/EtOH 99.9:0.1, flow 1 mL/min, 210 nm, 21 °C, t_M= 52.0 min, t_m= 54.9 min

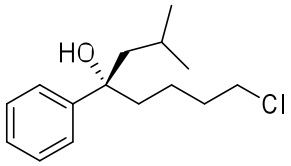
^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.39-7.32 (m, 4H), 7.26-7.21 (m, 1H), 3.50-3.41 (m, 2H), 1.94-1.66 (m, 7H), 1.51-1.39 (m, 1H), 1.26-1.14 (m, 1H), 0.76 (t, *J* = 7.4 Hz, 3H)

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 145.8, 128.2, 126.6, 125.4, 77.2, 44.9, 42.0, 35.5, 33.1, 21.2, 7.9



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	51.950	BV	0.8710	5.17038e4	850.75348	97.9291
2	54.880	MM	0.8081	1093.35901	22.55054	2.0709
Totals :				5.27971e4	873.30402	

8-chloro-2-methyl-4-phenyloctan-4-ol 5ac



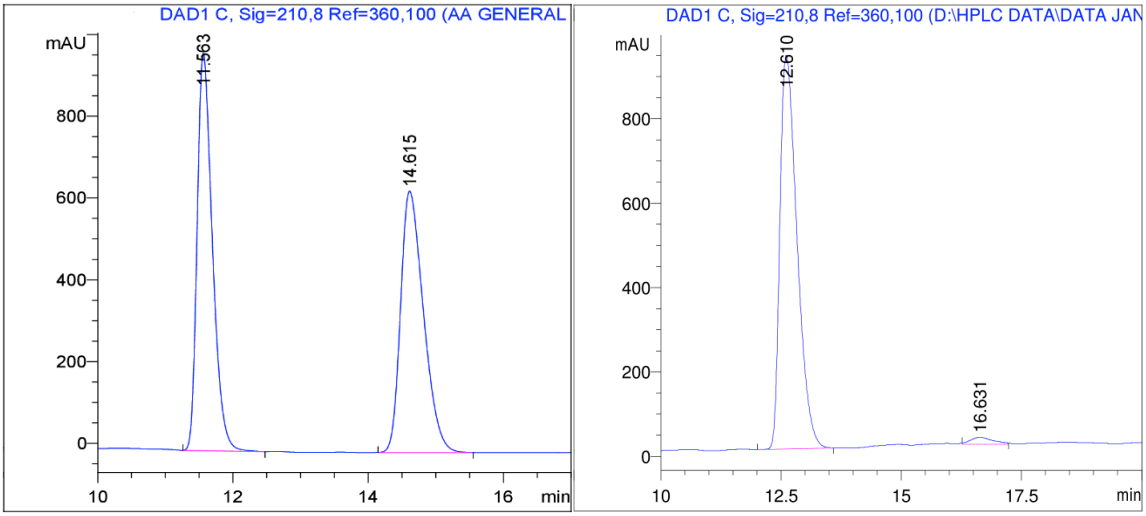
5ac

Colourless oil, 65% yield, 95% *ee*

HPLC analysis on chiral stationary phase: Column Chiracel OJ-H, Heptane/EtOH 99:1, flow 1 mL/min, 210 nm, 21 °C, t_M= 12.6 min, t_m= 16.6 min

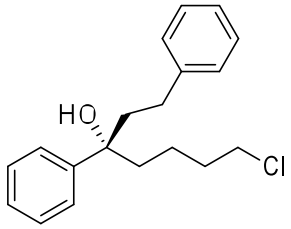
^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.39-7.31 (m, 4H), 7.25-7.20 (m, 1H), 3.49-3.40 (m, 2H), 1.87-1.64 (m, 7H), 1.62-1.39 (m, 2H), 1.19-1.08 (m, 1H), 0.90 (d, *J* = 6.6 Hz, 3H), 0.69 (d, *J* = 6.6 Hz, 3H)

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 146.2, 128.2, 126.4, 125.4, 77.6, 51.9, 44.9, 43.6, 33.0, 24.7, 24.5, 24.2, 21.0



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.610	VB	0.3832	2.31566e4	934.06403	97.7677
2	16.631	MM	0.5482	528.72235	16.07480	2.2323
Totals :				2.36853e4	950.13883	

7-chloro-1,3-diphenylheptan-3-ol 5ad



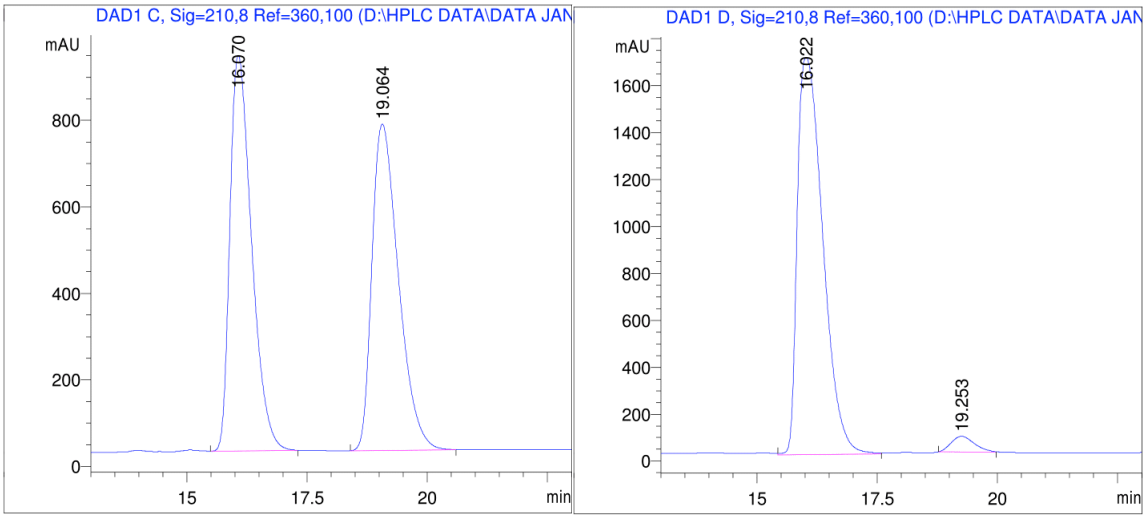
5ad

Colourless oil, 72% yield, 93% *ee*

HPLC analysis on chiral stationary phase: Column Chiralpak AS-H, Heptane/EtOH 95:5, flow 1 mL/min, 210 nm, 21 °C, t_M= 16.0 min, t_m= 19.3 min

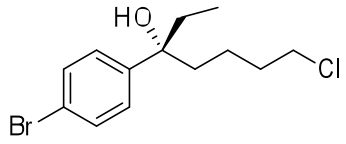
^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.44-7.37 (m, 4H), 7.30-7.24 (m, 3H), 7.19-7.14 (m, 1H), 7.12-7.10 (m, 2H), 3.49-3.43 (m, 2H), 2.62 (ddd, *J* = 13.6, 11.1, 6.3 Hz, 1H), 2.37 (ddd, *J* = 13.6, 11.2, 5.2 Hz, 1H), 2.22-2.09 (m, 2H), 1.93-1.80 (m, 2H), 1.79-1.64 (m, 3H), 1.53-1.42 (m, 1H), 1.27-1.16 (m, 1H)

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 145.6, 142.3, 128.6, 128.5, 128.4, 126.8, 126.0, 125.3, 77.1, 44.9, 44.9, 42.7, 33.0, 30.1, 21.1



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.022	VB	0.5815	6.23631e4	1693.98120	96.4563
2	19.253	MM	0.5684	2291.14697	67.18126	3.5437
Totals :				6.46543e4	1761.16246	

3-(4-bromophenyl)-7-chloroheptan-3-ol 5bb



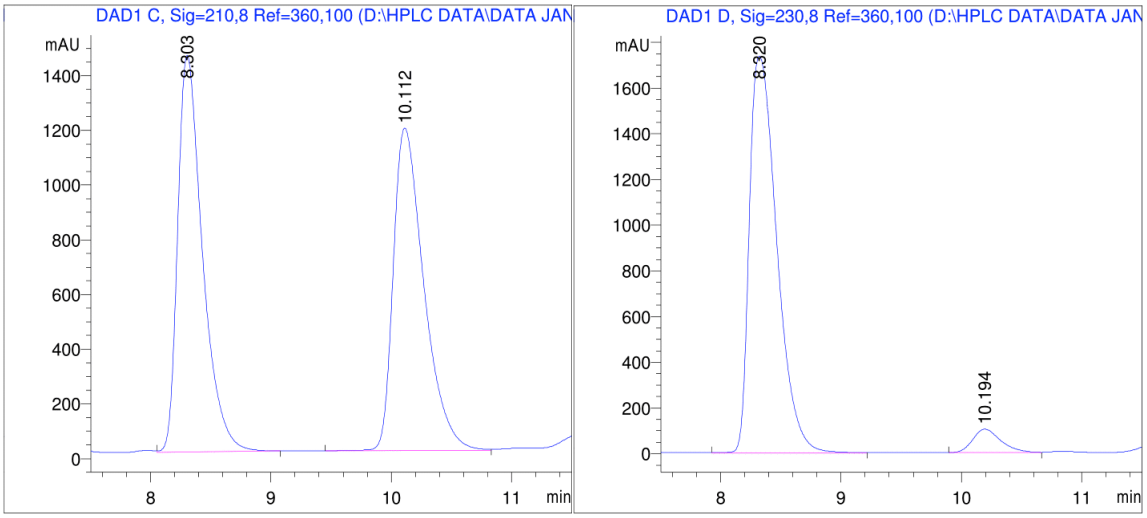
5bb

Colourless oil, 80% yield, 88% *ee*

HPLC analysis on chiral stationary phase: Column Chiralpak AS-H, Heptane/EtOH 95:5, flow 1 mL/min, 210 nm, 21 °C, t_M= 8.3 min, t_m= 10.2 min

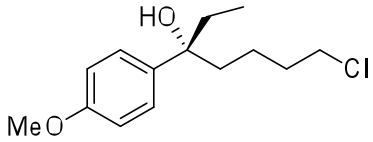
^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.47-7.44 (m, 2H), 7.26-7.23 (m, 2H), 3.50-3.41 (m, 2H), 1.90-1.65 (m, 6H), 1.62 (br s, 1H), 1.50-1.40 (m, 1H), 1.22-1.11 (m, 1H), 0.75 (t, *J* = 7.4 Hz, 3H)

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 144.8, 131.3, 127.4, 120.5, 77.0, 44.9, 42.0, 35.6, 32.9, 21.1, 7.8



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.320	MM	0.2644	2.75580e4	1737.25415	94.2565
2	10.194	BV	0.2464	1679.23865	102.88029	5.7435
Totals :				2.92373e4	1840.13445	

7-chloro-3-(4-methoxyphenyl)heptan-3-ol 5cb



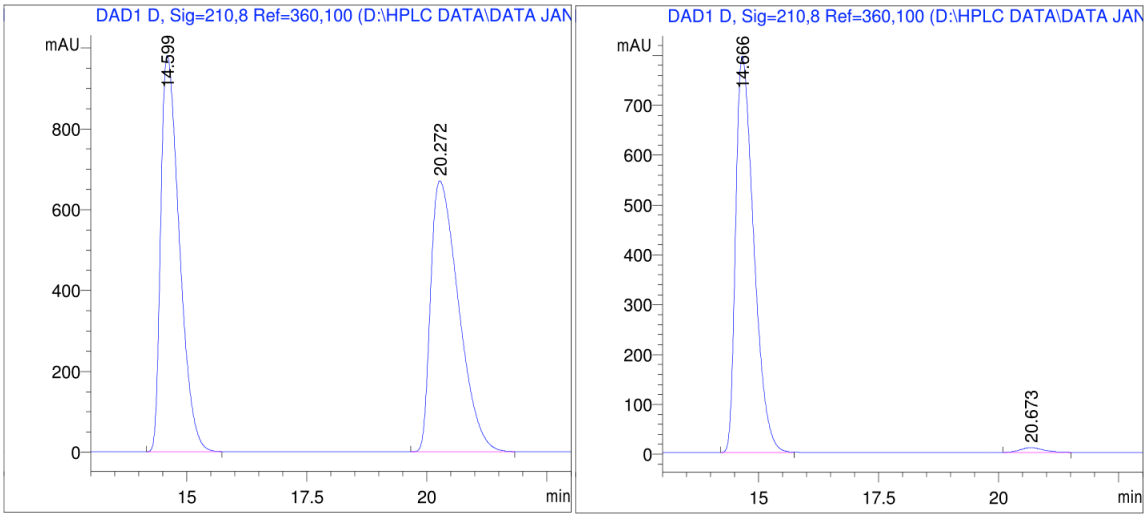
5cb

Colourless oil, 64% yield, 97% *ee*

HPLC analysis on chiral stationary phase: Column Chiracel OJ-H, Heptane/EtOH 95:5, flow 1 mL/min, 210 nm, 21 °C, t_M= 14.7 min, t_m= 20.7 min

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.30-7.26 (m, 2H), 6.89-6.85 (m, 2H), 3.81 (s, 3H), 3.50-3.42 (m, 2H), 1.90-1.67 (m, 6H), 1.63 (br s, 1H), 1.48-1.37 (m, 1H), 1.27-1.15 (m, 1H), 0.76 (t, *J* = 7.4 Hz, 3H)

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 158.2, 137.9, 126.6, 113.5, 76.9, 55.3, 45.0, 41.9, 35.4, 33.1, 21.2, 7.9



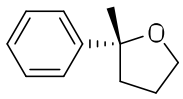
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.666	BB	0.4056	2.08464e4	795.81323	98.5342
2	20.673	BB	0.5061	310.10803	9.37131	1.4658
Totals :				2.11565e4	805.18454	

General procedure for the NaH-promoted cyclization to tetrahydrofurans (Method A)

In a 10 mL flame-dried Schlenk flask under nitrogen was prepared a solution of the γ-chloro alcohol **4** (0.1 mmol) in dry THF (1 mL). The solution was cooled to 0 °C and NaH 95% (13 mg, 0.5 mmol) was added. The reaction mixture was stirred for 18 hours at room temperature. The reaction was cooled to 0 °C and carefully quenched by adding H_2O (1 mL) drop wise under vigorous stirring. The mixture was extracted with Et_2O (3 x 5 mL) and the combined organic

phases were dried over sodium sulfate, filtered and the solvent removed under reduced pressure. The crude mixture was purified by column chromatography on silica gel eluting with pentane/Et_2O 99:1 to obtain pure 2,2-disubstituted tetrahydrofurans **6**. The enantiomeric excess was calculated by HPLC analysis on chiral stationary phase.

(*R*)-2-methyl-2-phenyltetrahydrofuran 6aa



6aa

Colourless oil, 93% yield, 91% *ee*

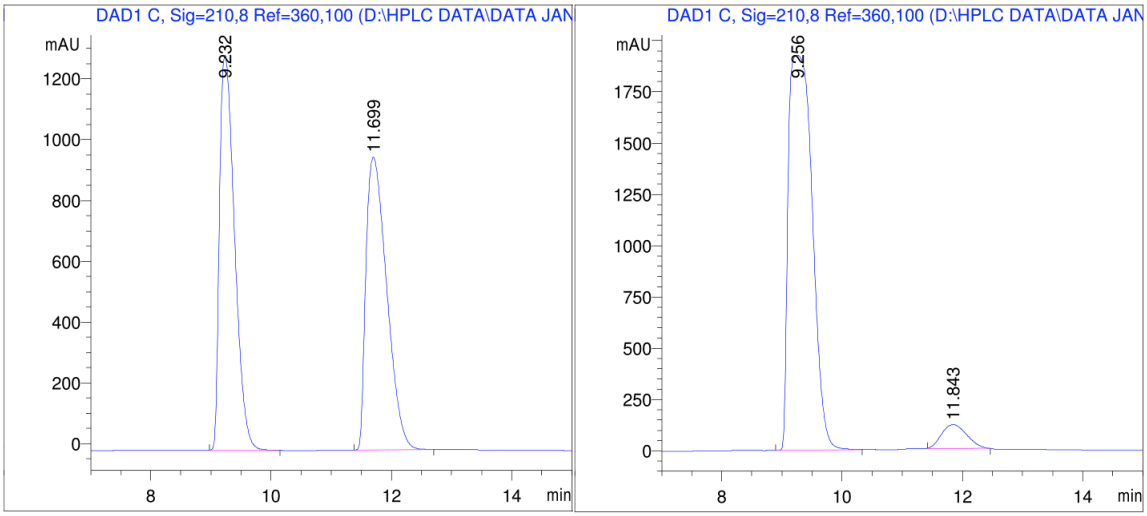
HPLC analysis on chiral stationary phase: Column Chiracel OJ-H, Heptane/EtOH 99.8:0.2, flow 1 mL/min, 210 nm, 21 °C, t_M= 9.3 min, t_m= 11.8 min

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.42-7.39 (m, 2H), 7.35-7.30 (m, 2H), 7.24-7.20 (m, 1H), 4.05-4.00 (m, 1H), 3.95-3.89 (m, 1H), 2.25-2.18 (m, 1H), 2.06-1.97 (m, 2H), 1.87-1.76 (m, 1H), 1.54 (s, 3H)

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 148.3, 128.2, 126.4, 124.8, 84.4, 67.7, 39.6, 29.8, 25.9

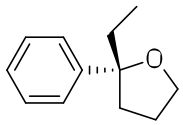
$[\alpha]_D^{20}$: + 4.7 (c. 0.8, $CHCl_3$); Lit. (for (S)-**8aa**) $[\alpha]_D^{25}$: - 4.1 (c. 0.64, CH_2Cl_2)[6]

Analytical data were in accordance with literature reported results.[5]



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.256	BB	0.4497	5.31047e4	1925.97913	95.4727
2	11.843	MM	0.4898	3448.91919	117.35313	4.5273
Totals :				5.65536e4	2043.33226	

(*R*)-2-ethyl-2-phenyltetrahydrofuran 6ab



6ab

Colourless oil, 91% yield, 93% *ee*

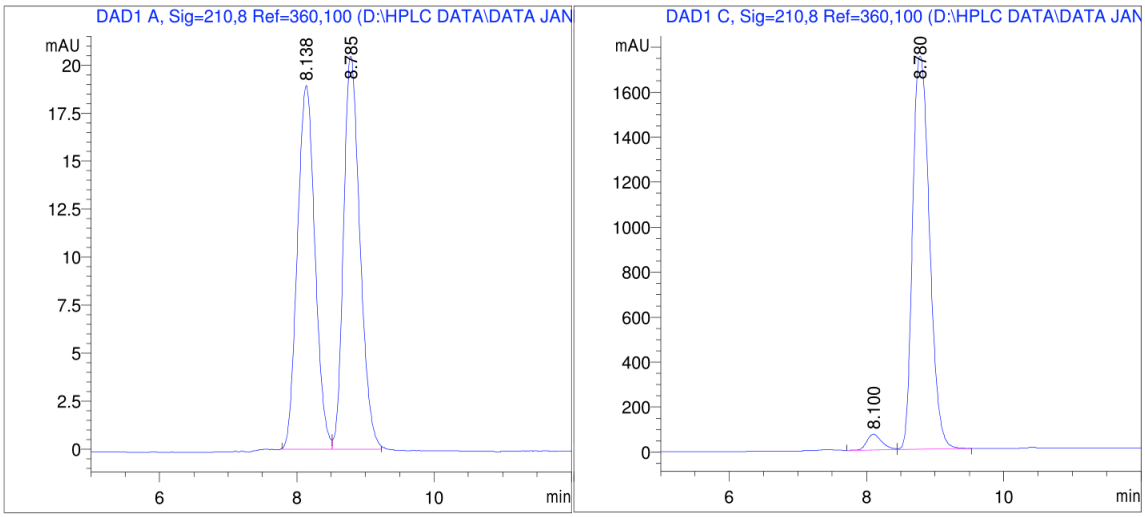
HPLC analysis on chiral stationary phase: Column Chiracel OJ-H, Heptane/EtOH 99.5:0.5, flow 1 mL/min, 210 nm, 21 °C, t_m= 8.1 min, t_M= 8.8 min

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.37-7.30 (m, 4H), 7.23-7.19 (m, 1H), 3.99-3.95 (m, 1H), 3.91-3.86 (m, 1H), 2.20-2.15 (m, 1H), 2.07-2.01 (m, 1H), 1.97-1.89 (m, 1H), 1.88-1.73 (m, 3H), 0.76 (t, *J* = 7.4 Hz, 3H)

^{13}C-NMR (125.7 MHz, $CDCl_3$): δ 146.8, 128.0, 126.3, 125.5, 87.3, 67.6, 37.9, 35.2, 25.8, 8.9

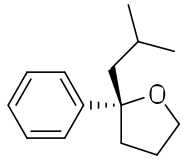
$[\alpha]_D^{20}$: - 9.0 (c. 0.7, $CHCl_3$)

Analytical data were in accordance with literature reported results.[5]



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.100	VV	0.2338	1066.71484	70.00732	3.4459
2	8.780	VB	0.2695	2.98895e4	1748.31543	96.5541
Totals :				3.09562e4	1818.32275	

2-isobutyl-2-phenyltetrahydrofuran 6ac



6 ac

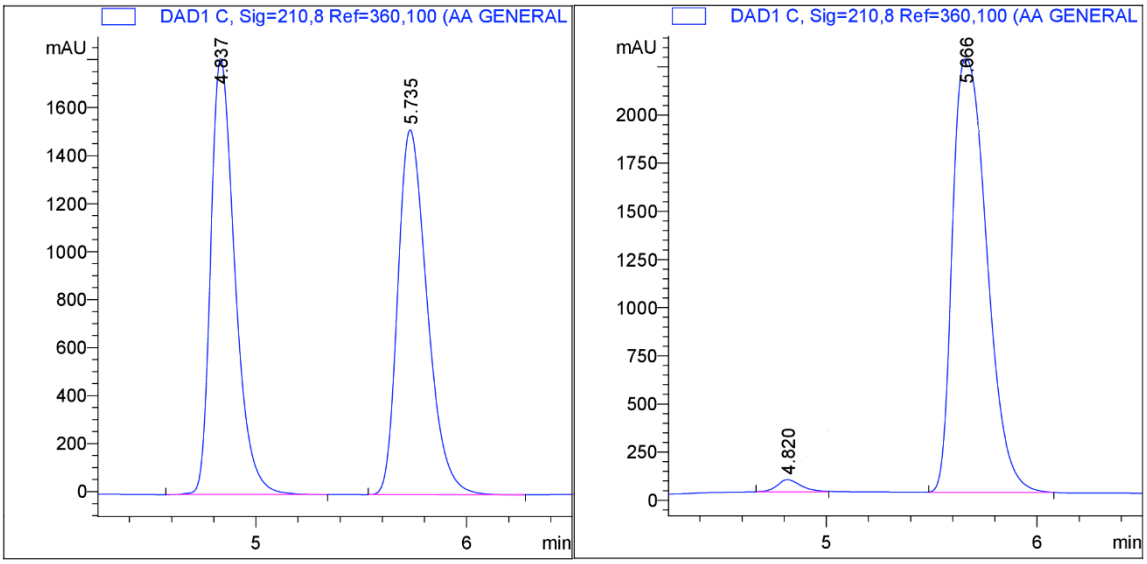
Colourless oil, 93% yield, 96% *ee*

HPLC analysis on chiral stationary phase: Column Chiracel OJ-H, Heptane/EtOH 99.7:0.3, flow 1 mL/min, 210 nm, 21 °C, t_m= 4.8 min, t_M= 5.7 min

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.38-7.29 (m, 4H), 7.23-7.18 (m, 1H), 4.00-3.87 (m, 2H), 2.21-2.15 (m, 1H), 2.03-1.80 (m, 3H), 1.76-1.66 (m, 2H), 1.51-1.41 (m, 1H), 0.88 (d, *J* = 6.6 Hz, 3H), 0.69 (d, *J* = 6.7 Hz, 3H)

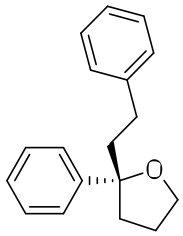
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 147.0, 128.0, 126.3, 125.5, 87.4, 67.4, 51.0, 39.8, 25.3, 24.9, 24.4, 24.1

$[\alpha]_D^{20}$: -7.6 (c. 1.1, $CHCl_3$)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.820	MM	0.1348	520.34540	64.35488	1.9948
2	5.666	MM	0.1889	2.55644e4	2255.30518	98.0052
Totals :				2.60847e4	2319.66006	

2-phenethyl-2-phenyltetrahydrofuran 6ad



6ad

Colourless oil, 94% yield, 94% *ee*

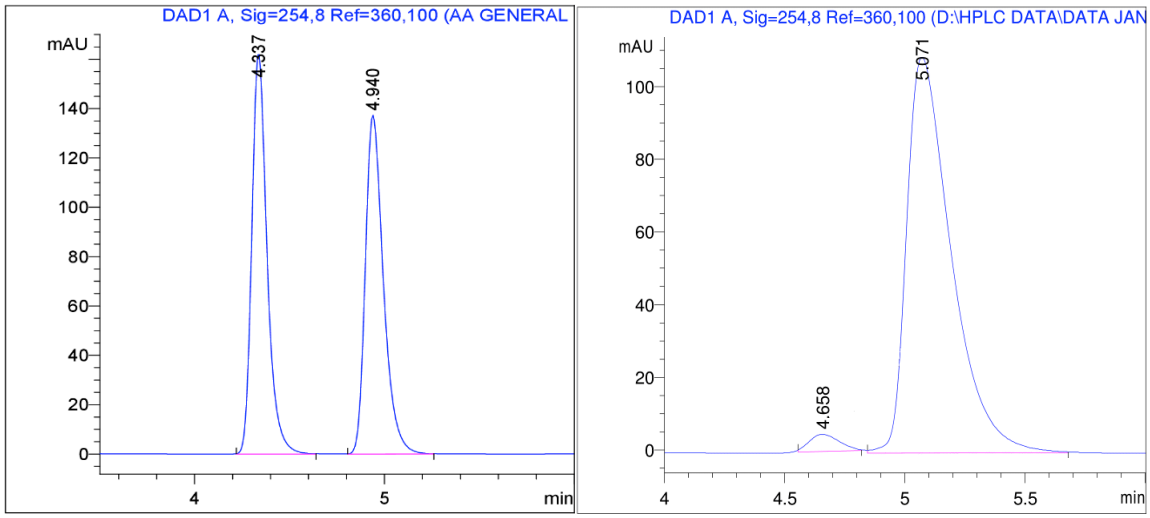
HPLC analysis on chiral stationary phase: Column Chiralpak IC, Heptane/EtOH 99.7:0.3, flow 1 mL/min, 210 nm, 21 °C, t_m= 4.7 min, t_M= 5.1 min

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.44-7.41 (m, 2H), 7.38-7.34 (m, 2H), 7.27-7.22 (m, 3H), 7.16-7.10 (m, 3H), 4.07-3.94 (m, 2H), 2.71-2.63 (m, 1H), 2.36-2.29 (m, 1H), 2.25-2.05 (m, 4H), 2.02-1.93 (m, 1H), 1.87-1.77 (m, 1H)

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 146.6, 142.8, 128.4, 128.4, 128.2, 126.5, 125.7, 125.4, 86.7, 67.8, 44.6, 38.9, 31.0, 25.7

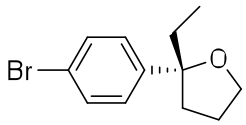
HRMS: (EI, 35 eV) Calculated for $C_{18}H_{20}O$ 252.1514 ($[M]^+$); found 252.1504

$[\alpha]_D^{20}$: + 12.3 (c. 1.0, $CHCl_3$)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.658	MM	0.1452	41.88210	4.80791	2.8912
2	5.071	VB	0.1946	1406.74805	109.01232	97.1088
Totals :				1448.63014	113.82023	

2-ethyl-2-(4-bromophenyl)tetrahydrofuran 6bb



6bb

Colourless oil, 95% yield, 87% *ee*

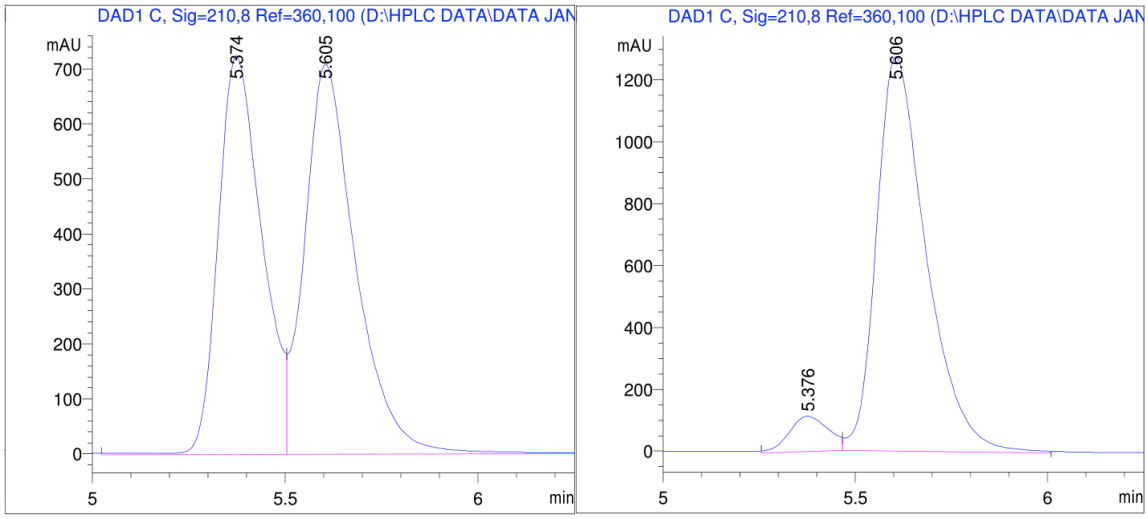
HPLC analysis on chiral stationary phase: Column Chiracel OJ-H, Heptane/EtOH 99.5:0.5, flow 1 mL/min, 210 nm, 21 °C, t_m= 5.4 min, t_M= 5.6 min

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.45-7.41 (m, 2H), 7.24-7.21 (m, 2H), 3.98-3.92 (m, 1H), 3.88-3.83 (m, 1H), 2.14-1.88 (m, 3H), 1.83-1.70 (m, 3H), 0.75 (t, *J* = 7.4 Hz, 3H)

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 145.9, 131.1, 127.5, 120.2, 87.0, 67.7, 38.0, 35.1, 25.7, 8.8

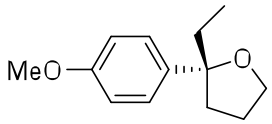
HRMS: (EI, 35 eV) Calculated for $C_{12}H_{15}OBr$ 254.0306 ($[M]^+$); found 254.0303

$[\alpha]_D^{20}$: - 3.1 (c. 1.0, $CHCl_3$)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.376	MM	0.1190	816.96680	114.41199	6.6600
2	5.606	MM	0.1493	1.14499e4	1278.02954	93.3400
Totals :				1.22668e4	1392.44153	

2-ethyl-2-(4-methoxyphenyl)tetrahydrofuran 6cb



6cb

Colourless oil, 91% yield, 96% *ee*

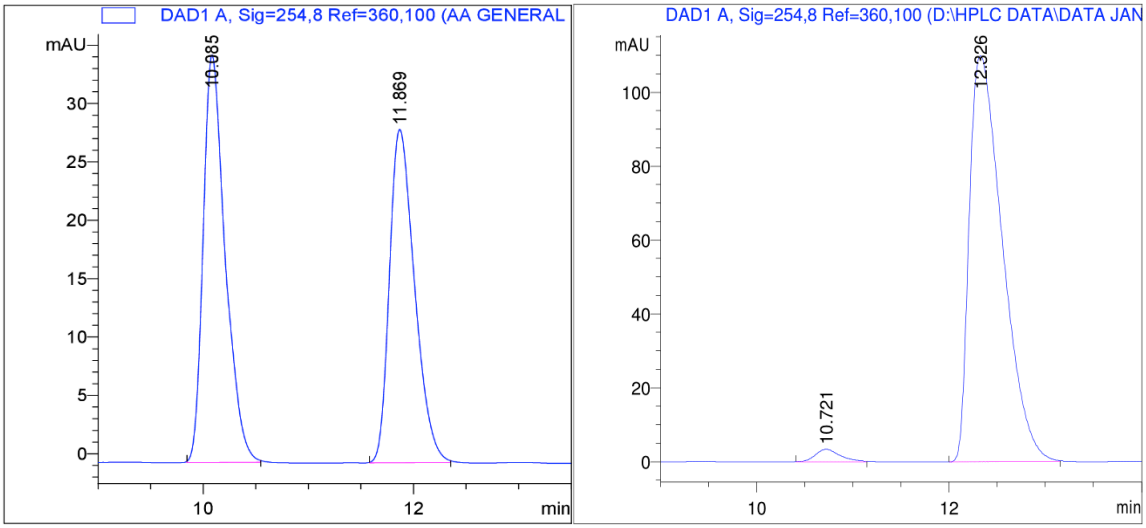
HPLC analysis on chiral stationary phase: Column Chiracel OJ-H, Heptane/EtOH 99:1, flow 1 mL/min, 254 nm, 21 °C, t_m= 10.7 min, t_M= 12.3 min

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.29-7.25 (m, 2H), 6.87-6.84 (m, 2H), 3.97-3.92 (m, 1H), 3.89-3.83 (m, 1H), 3.80 (s, 3H), 2.18-2.12 (m, 1H), 2.03-1.87 (m, 2H), 1.84-1.72 (m, 3H), 0.76 (t, *J* = 7.4 Hz, 3H)

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 158.2, 138.7, 126.6, 113.4, 87.0, 67.4, 55.4, 37.8, 35.3, 25.7, 9.0

HRMS: (EI, 35 eV) Calculated for $C_{13}H_{18}O_2$ 206.1307 ($[M]^+$); found 206.1309

$[\alpha]_D^{20}$: - 9.1 (c. 1.0, $CHCl_3$)

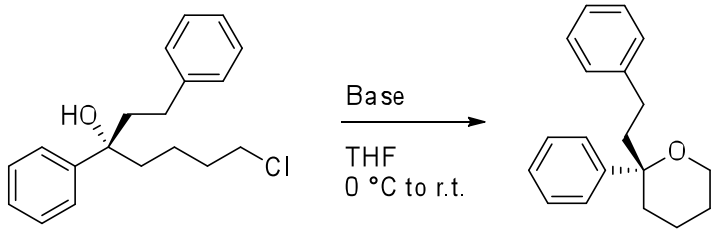


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.721	BB	0.2648	58.36172	3.32537	2.1675
2	12.326	BB	0.3695	2634.25024	109.96635	97.8325
Totals :				2692.61197	113.29172	

Conditions screening for the base-promoted cyclization to tetrahydropyrans

Alcohol **5ad** was chosen as model compound due to the lower volatility of the cyclized product **7ad** compared to other THP derivatives. A screening of different non-nucleophilic bases showed KHMDS in THF being the reagent of choice for the transformation, furnishing **7ad** in high yield after 1 hour (Table 1, entry 5).

Table 1 Optimization of conditions for base-promoted cyclization of δ-chloro tertiary alcohols to 2,2-disubstituted THPs.[a]



5ad **7ad**

Entry	Base (equiv.)	Time (h)	Yield (%)[b]	*ee* (%)[c]
1	NaH (5.0)	24	31	-
2	NaH (10.0)	48	43	-
3	*t*BuOK (1.5)	24	45	-
4	LDA (1.5)	24	14	-
5	KHMDS (1.5)	1	89	93

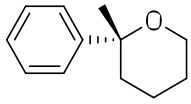
[a] Reactions were run on 0.1 mmol scale. [b] Isolated yields.

[c] Determined by HPLC analysis on chiral stationary phase.

General procedure for the KHMDS-promoted cyclization to tetrahydropyrans (Method B)

In a 10 mL flame-dried Schlenk flask under nitrogen was prepared a solution of the δ-chloro alcohol **5** (0.1 mmol) in dry THF (1 mL). The solution was cooled to 0 °C and KHMDS 1.0 M solution in THF (150 µL, 0.15 mmol) was added drop wise. The reaction mixture was allowed to warm up to room temperature, stirred for 1 hour and then quenched with NH_4Cl sat. (1 mL) and extracted with Et_2O (3 x 5 mL). The combined organic phases were dried over sodium sulfate, filtered and the solvent removed under reduced pressure. The crude mixture was purified by column chromatography on silica gel eluting with pentane/Et_2O 98:2 to obtain pure 2,2-disubstituted tetrahydropyrans **7**. The enantiomeric excess was calculated by HPLC analysis on chiral stationary phase.

(*R*)-2-methyl-2-phenyltetrahydro-2*H*-pyran 7aa



7aa

Colourless oil, 90% yield, 93% *ee*

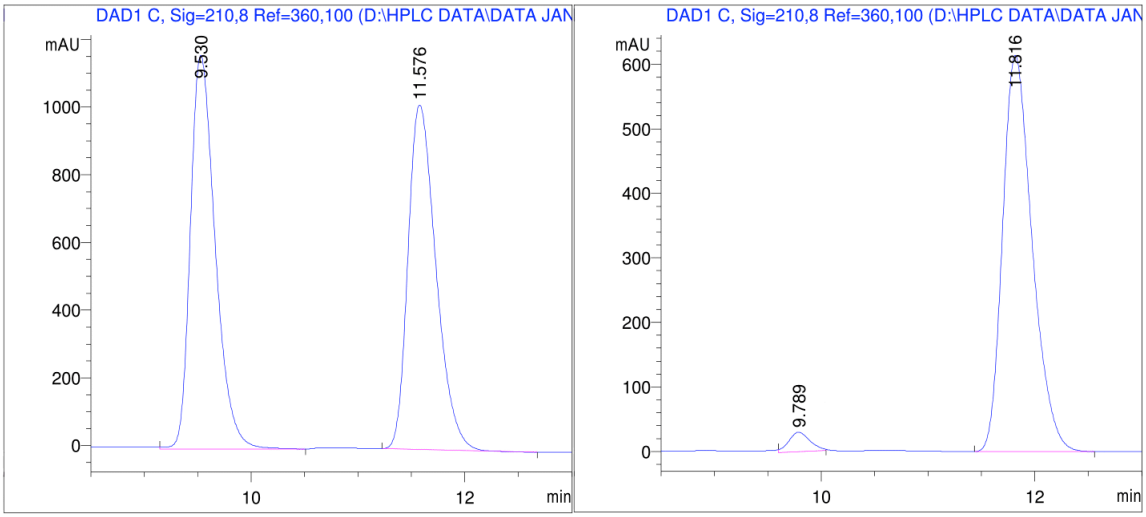
HPLC analysis on chiral stationary phase: Column Chiralpak AS-H, Heptane/EtOH 99.5:0.5, flow 1 mL/min, 210 nm, 21 °C, t_m= 9.8 min, t_M= 11.8 min

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.44-7.34 (m, 4H), 7.26-7.22 (m, 1H), 3.76-3.71 (m, 1H), 3.53-3.46 (m, 1H), 2.43-2.28 (m, 1H), 1.79-1.59 (m, 3H), 1.56-1.41 (m, 2H), 1.39 (s, 3H)

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 145.5, 128.6, 126.6, 126.1, 76.1, 62.9, 34.7, 32.9, 26.1, 20.2

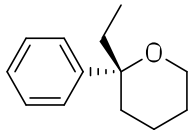
HRMS: (EI, 35 eV) Calculated for $C_{12}H_{16}O$ 176.1201 ($[M]^+$); found 176.1208

$[\alpha]_D^{20}$: - 48.2 (c. 0.6, $CHCl_3$); Lit. (for (*S*)-**9aa**) $[\alpha]_D^{25}$: + 59.1 (c. 0.34, CH_2Cl_2)[6]



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.789	MM	0.2293	414.54944	30.12720	3.3848
2	11.816	BB	0.2967	1.18327e4	614.39600	96.6152
Totals :				1.22472e4	644.52320	

2-ethyl-2-phenyltetrahydro-2*H*-pyran 7ab



7ab

Colourless oil, 88% yield, 95% *ee*

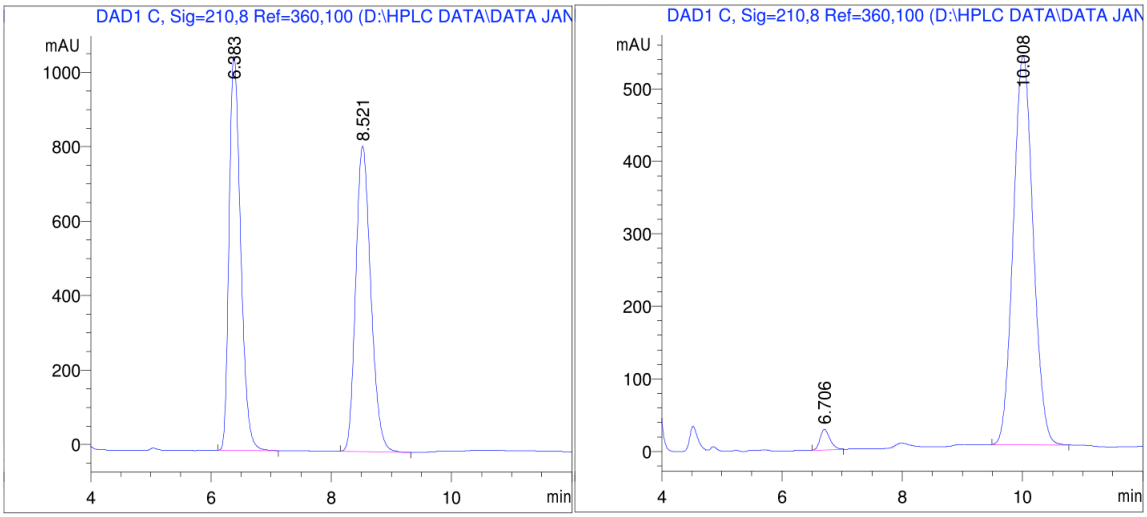
HPLC analysis on chiral stationary phase: Column Chiracel OJ-H, Heptane/EtOH 99.7:0.3, flow 1 mL/min, 210 nm, 21 °C, t_m= 6.7 min, t_M= 10.0 min

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.38-7.33 (m, 4H), 7.27-7.22 (m, 1H), 3.73-3.68 (m, 1H), 3.53-3.47 (m, 1H), 2.32-2.26 (m, 1H), 1.80-1.58 (m, 5H), 1.53-1.38 (m, 2H), 0.66 (t, *J* = 7.5 Hz, 3H)

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 143.4, 128.3, 127.1, 126.5, 78.8, 62.7, 37.6, 32.7, 26.4, 20.0, 7.8

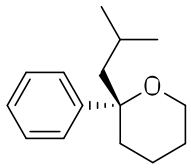
HRMS: (EI, 35 eV) Calculated for $C_{13}H_{18}O$ 190.1358 ($[M]^+$); found 190.1360

$[\alpha]_D^{20}$: - 11.4 (c. 1.0, $CHCl_3$)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.706	MM	0.1908	327.27475	28.58263	2.5893
2	10.008	MM	0.3818	1.23122e4	537.46356	97.4107
Totals :				1.26394e4	566.04619	

2-isobutyl-2-phenyltetrahydro-2*H*-pyran 7ac



7 ac

Colourless oil, 90% yield, 95% *ee*

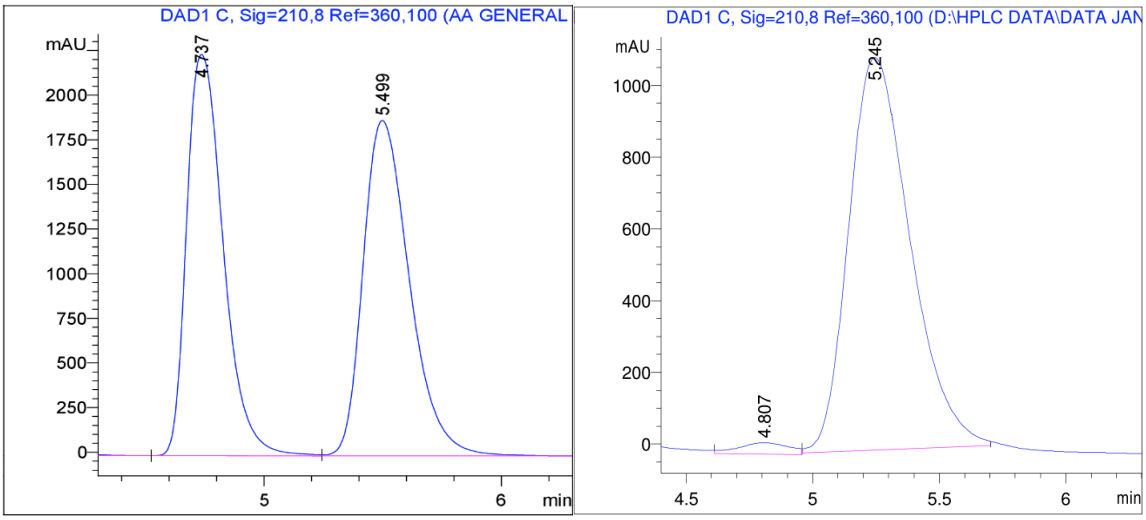
HPLC analysis on chiral stationary phase: Column Chiracel OJ-H, Heptane/EtOH 99.9:0.1, flow 1 mL/min, 210 nm, 21 °C, t_m= 4.8 min, t_M= 5.2 min

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.40-7.33 (m, 4H), 7.25-7.21 (m, 1H), 3.73-3.68 (m, 1H), 3.54-3.48 (m, 1H), 2.29-2.24 (m, 1H), 1.79-1.58 (m, 4H), 1.54-1.38 (m, 4H), 0.73-0.70 (m, 6H)

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 144.2, 128.3, 126.9, 126.4, 78.9, 62.5, 53.5, 34.1, 26.3, 24.8, 24.5, 23.7, 20.1

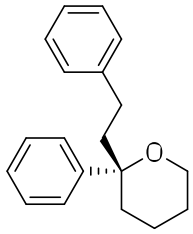
HRMS: (EI, 35 eV) Calculated for $C_{15}H_{22}O$ 218.1671 ($[M]^+$); found 218.1676

$[\alpha]_D^{20}$: - 54.3 (c. 1.5, $CHCl_3$)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.807	VV	0.2086	439.78687	31.55182	2.3284
2	5.245	MM	0.2806	1.84478e4	1095.72144	97.6716
Totals :				1.88876e4	1127.27326	

2-phenethyl-2-phenyltetrahydro-2*H*-pyran 7ad



7ad

Colourless oil, 89% yield, 93% *ee*

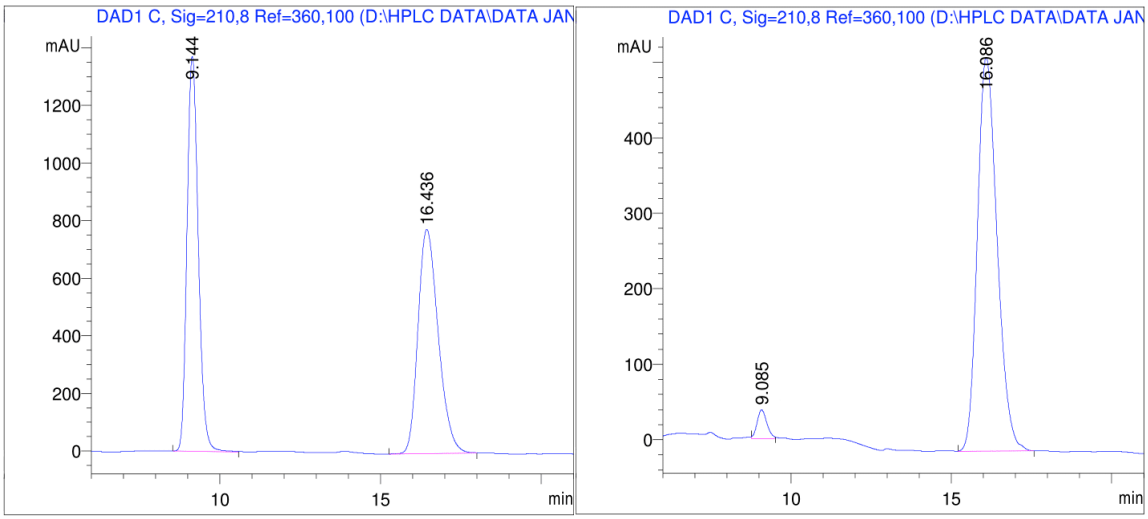
HPLC analysis on chiral stationary phase: Column Chiracel OJ-H, Heptane/EtOH 99.5:0.5, flow 1 mL/min, 210 nm, 21 °C, t_m= 9.1 min, t_M= 16.1 min

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.46-7.38 (m, 4H), 7.30-7.20 (m, 3H), 7.15-7.11 (m, 1H), 7.08-7.06 (m, 2H), 3.81-3.76 (m, 1H), 2.53-2.45 (m, 1H), 2.42-2.28 (m, 2H), 2.14-2.06 (m, 1H), 1.96-1.88 (m, 1H), 1.85-1.78 (m, 1H), 1.75-1.62 (m, 2H), 1.57-1.45 (m, 2H)

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 143.6, 142.7, 128.4, 128.4, 128.3, 126.8, 126.6, 125.7, 78.2, 62.7, 46.0, 33.7, 29.8, 26.3, 20.0

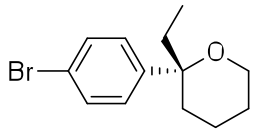
HRMS: (EI, 35 eV) Calculated for $C_{19}H_{22}O$ 266.1671 ($[M]^+$); found 266.1677

$[\alpha]_D^{20}$: + 4.0 (c. 1.0, $CHCl_3$)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.085	MM	0.3493	796.88702	38.02518	3.4366
2	16.086	BB	0.6643	2.23914e4	522.15582	96.5634
Totals :				2.31883e4	560.18100	

2-ethyl-2-(4-bromophenyl)tetrahydro-2*H*-pyran 7bb



7bb

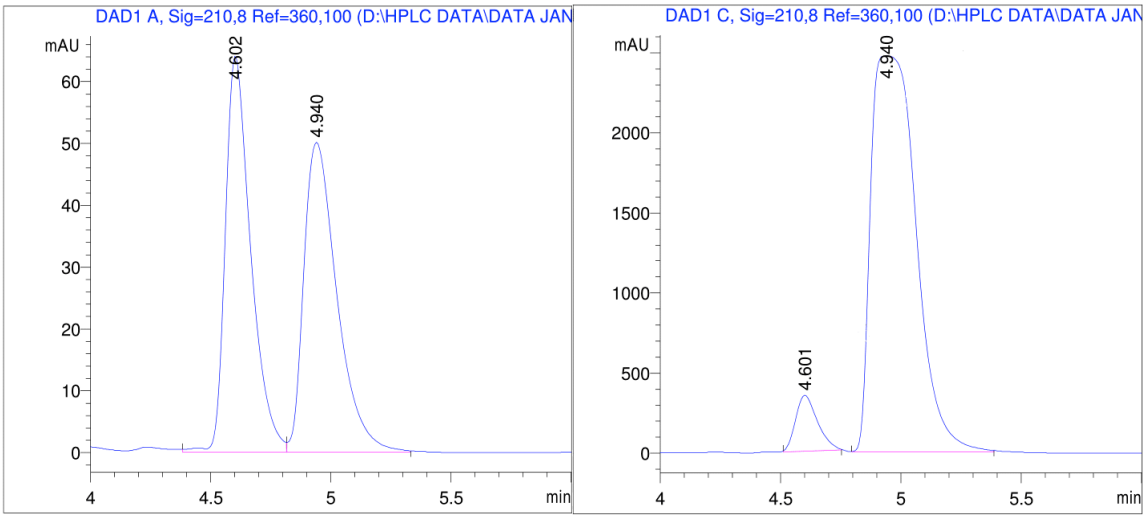
Colourless oil, 89% yield, 87% *ee*

HPLC analysis on chiral stationary phase: Column Chiralpak AS-H, Heptane/EtOH 99:1, flow 1 mL/min, 210 nm, 21 °C, t_m= 4.6 min, t_M= 4.9 min

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.49-7.45 (m, 2H), 7.25-7.21 (m, 2H), 3.72-3.68 (m, 1H), 3.48-3.42 (m, 1H), 2.23-2.18 (m, 1H), 1.78-1.56 (m, 5H), 1.49-1.37 (m, 2H), 0.65 (t, *J* = 7.5 Hz, 3H)

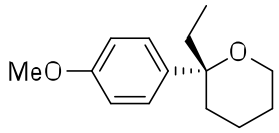
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 142.7, 131.4, 128.9, 120.5, 78.5, 62.7, 37.1, 32.7, 26.3, 19.9, 7.7

$[\alpha]_D^{20}$: - 36.0 (c. 1.0, $CHCl_3$)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.601	MM	0.1052	2213.96484	350.69925	6.4275
2	4.940	MM	0.2170	3.22310e4	2475.28223	93.5725
Totals :				3.44450e4	2825.98148	

2-ethyl-2-(4-methoxyphenyl)tetrahydro-2*H*-pyran 7cb



7cb

Colourless oil, 90% yield, 96% *ee*

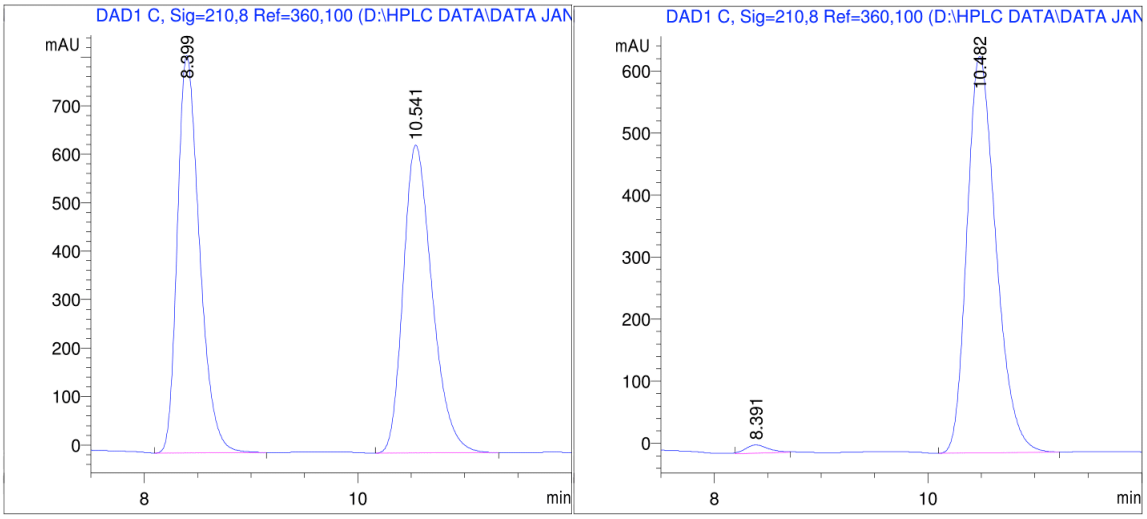
HPLC analysis on chiral stationary phase: Column Chiracel OJ-H, Heptane/EtOH 99:1, flow 1 mL/min, 210 nm, 21 °C, t_m= 8.4 min, t_M= 10.5 min

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.28-7.25 (m, 2H), 6.91-6.88 (m, 2H), 3.82 (s, 3H), 3.69-3.66 (m, 1H), 3.51-3.44 (m, 1H), 2.29-2.23 (m, 1H), 1.76-1.56 (m, 5H), 1.52-1.38 (m, 2H), 0.66 (t, *J* = 7.5 Hz, 3H)

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 158.2, 135.2, 128.3, 113.6, 78.6, 62.6, 55.3, 37.8, 32.6, 26.4, 20.0, 7.9

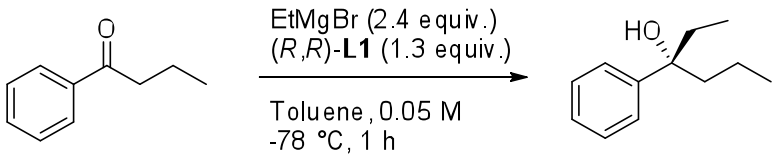
HRMS: (EI, 35 eV) Calculated for $C_{14}H_{20}O_2$ 220.1463 ($[M]^+$); found 220.1456

$[\alpha]_D^{20}$: - 28.3 (c. 1.0, $CHCl_3$)



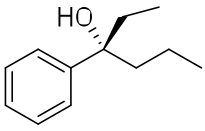
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.391	MM	0.2434	193.19537	13.23096	1.5818
2	10.482	BB	0.2894	1.20204e4	639.08350	98.4182
Totals :				1.22136e4	652.31445	

Asymmetric addition of ethylmagnesium bromide to butyrophenone.



Reaction of butyrophenone with EtMgBr in Et_2O, in the presence of ligand (*R*,*R*)-**L1**, followed the general procedure for the preparation of tertiary alcohols described above.

3-phenylhexan-3-ol

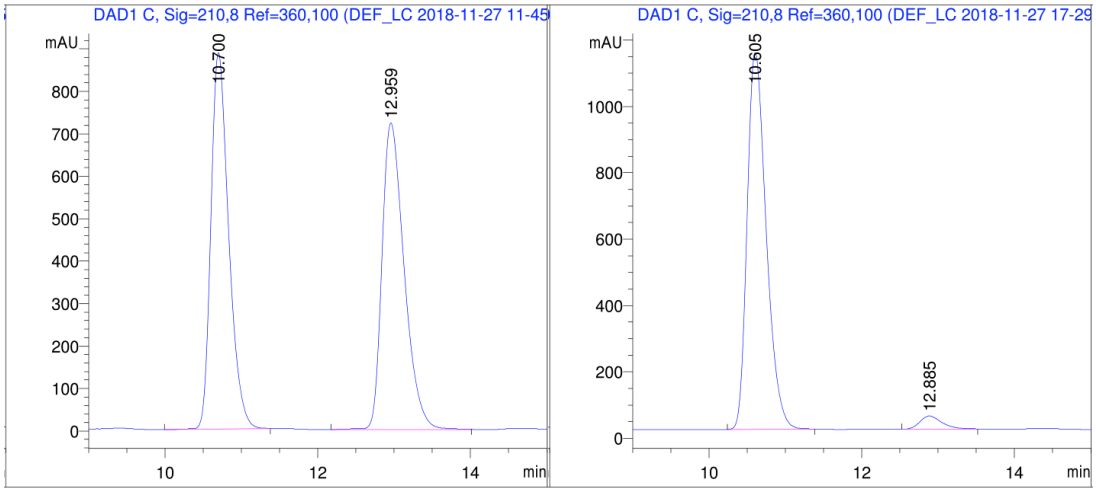


Colourless oil, 67% yield, 92% *ee*

HPLC analysis on chiral stationary phase: Column Chiralcel OJ-H, Heptane/EtOH 99:1, flow 1 mL/min, 210 nm, 21 °C, t_M= 10.6 min, t_m= 12.9 min

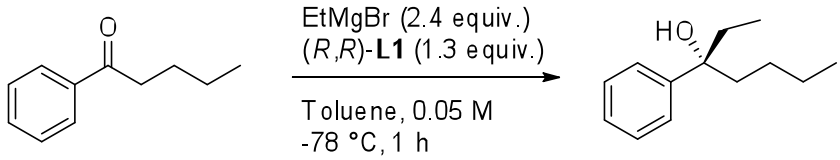
^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.37-7.30 (m, 4H), 7.23-7.19 (m, 1H), 1.91-1.70 (m, 4H), 1.66 (s, 1H), 1.35-1.22 (m, 1H), 1.12-1.01 (m, 1H), 0.84 (t, *J* = 7.3 Hz, 3H), 0.74 (t, *J* = 7.4 Hz, 3H)

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 146.2, 128.1, 126.4, 125.5, 77.4, 45.1, 35.5, 16.9, 14.6, 7.9



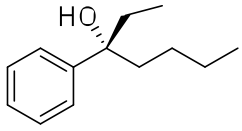
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.605	BB	0.2667	1.97347e4	1135.67139	96.1201
2	12.885	BB	0.3073	796.59833	39.50235	3.8799
Totals :				2.05313e4	1175.17374	

Asymmetric addition of ethylmagnesium bromide to valerophenone.



Reaction of valerophenone with EtMgBr in Et_2O, in the presence of ligand (*R*,*R*)-**L1**, followed the general procedure for the preparation of tertiary alcohols described above.

3-Phenylheptan-3-ol

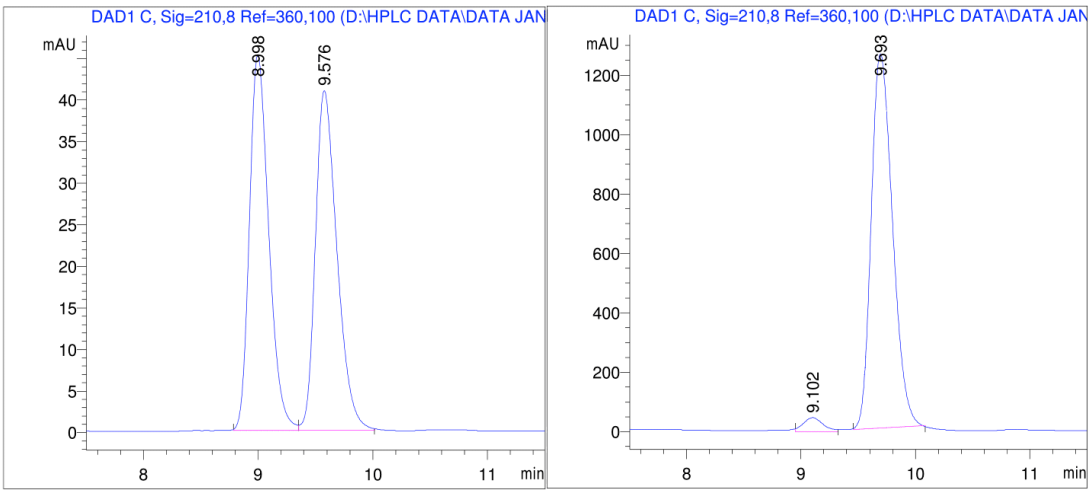


Colourless oil, 69% yield, 93% *ee*

HPLC analysis on chiral stationary phase: Column Chiralpak IA, Heptane/EtOH 99:1, flow 1 mL/min, 210 nm, 21 °C, t_m= 9.1 min, t_M= 9.7 min

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.40-7.32 (m, 4H), 7.25-7.21 (m, 1H), 1.91-1.74 (m, 4H), 1.70 (s, 1H), 1.30-1.22 (m, 3H), 1.06-1.02 (m, 1H), 0.84 (t, *J* = 7.2 Hz, 3H), 0.76 (t, *J* = 7.4 Hz, 3H)

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 146.3, 128.1, 126.3, 125.5, 77.3, 42.4, 35.5, 25.8, 23.2, 14.2, 7.9



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.102	MM	0.1995	555.09113	46.37671	3.2852
2	9.693	MM	0.2162	1.63414e4	1259.87537	96.7148
Totals :				1.68965e4	1306.25208	

Preparation of (*S*)-(-)-Gossonorol and (*R*)-(+)-Gossonorol

Preparation of 5-methyl-1-(4-methylphenyl)-1-oxo-hex-4-ene 1

Various bases and conditions were screened for the preparation of ketone **1** in one step by reaction of *p*-methylacetophenone with 3,3-dimethylallyl bromide (Table 2). Lithium bis(trimethylsilyl)amide (LiHMDS) showed the best selectivity between mono and bis alkylation, delivering the desired mono alkylate ketone **1** in high yield. On the other hand, the use of NaH or KHMDS yielded significant amounts of the bis alkylated ketone **1a**.

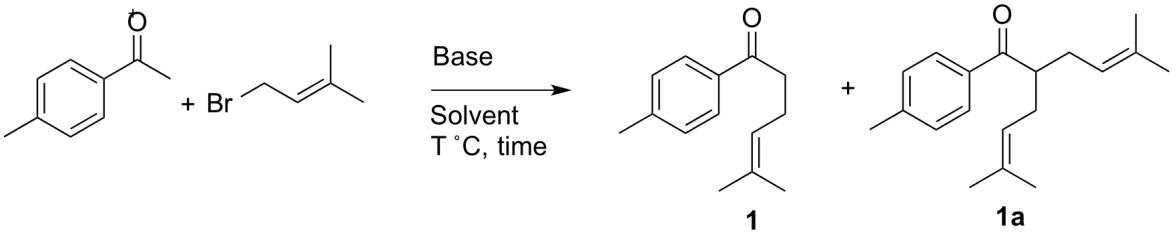


Table 2 Screening of conditions for the preparation of ketone **1**.[a]

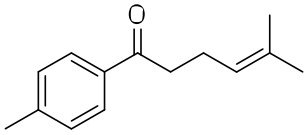
Entry	**Base** (equiv.)	**15** (equiv.)	**16** (equiv.)	**T** (°C)	**Solvent**	**1/1a** [b]	**Yield 1**
1	NaH (2.0)	1.0	2.0	-20 °C to r.t.	DMF	5:95	-
2	NaH (1.0)	1.0	1.0	-20 °C to r.t.	DMF	27:73	-
3	NaH (1.0)	5.0	1.0	-20 °C to r.t.	DMF	72:28	-
4	KHMDS (1.0)	1.1	1.0	0 °C	THF	38:62	-
5	LiHMDS (1.0)	1.1	1.0	0 °C	THF	96:4	63%
6	LiHMDS (1.0)	2.0	1.0	0 °C	THF	95:5	86%

[a] Reactions were run on 0.2 mmol scale. [b] Ratio calculated by ^{1}H-NMR analysis of the crude reaction mixture.

Procedure:

In a 25 mL flame-dried Schlenk flask under nitrogen was prepared a solution of *p*-methylacetophenone (0.139 mL, 0.987 mmol) in anhydrous THF (2 mL). The solution was cooled to 0 °C with an ice bath and LiHMDS 1.0 M solution in THF (0.987 mL, 0.987 mmol) was added dropwise. The yellow solution was stirred at 0 °C for 20 minutes, then 3,3-dimethylallyl bromide (0.057 mL, 0.493 mmol) was added dropwise and the mixture stirred at 0 °C for 2 hour. The reaction was quenched with NH_4Cl sat. solution (4 mL), the phases separated and the aqueous phase extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over sodium sulfate, filtered and the solvent removed under reduced pressure. The crude material was purified by column chromatography on silica gel eluting with pentane/Et_2O 98:2 to obtain pure ketone **1**.

5-methyl-1-(4-methylphenyl)-1-oxo-hex-4-ene 1



1

Colourless oil, 86% yield

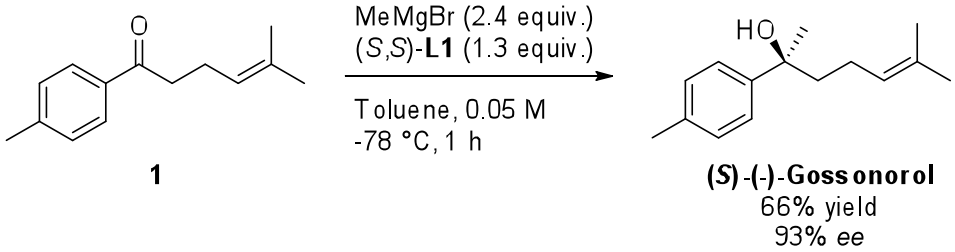
^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.88-7.86 (m, 2H), 7.27-7.25 (m, 2H), 5.20-5.17 (m, 1H), 2.99-2.96 (m, 2H), 2.44-2.40 (m, 5H), 1.70 (s, 3H), 1.64 (s, 3H)

^{13}C-NMR (125.7 MHz, $CDCl_3$): δ 199.9, 143.8, 134.7, 132.8, 129.4, 128.3, 123.2, 38.8, 25.8, 23.2, 21.8, 17.8

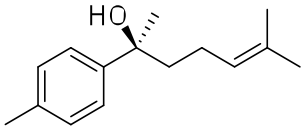
Analytical data were in accordance with literature reported results.[7]

Preparation of (*S*)-(-)-Gossonorol and (*R*)-(+)-Gossonorol

(*S*)-(-)-Gossonorol was prepared by reaction of ketone **1** with MeMgBr in the presence of ligand (*S*,*S*)-**L1**, following the general procedure for the preparation of chiral non-racemic tertiary alcohols described above.



(*S*)-(-)-Gossonorol



Colourless oil, 66% yield, 93% *ee*

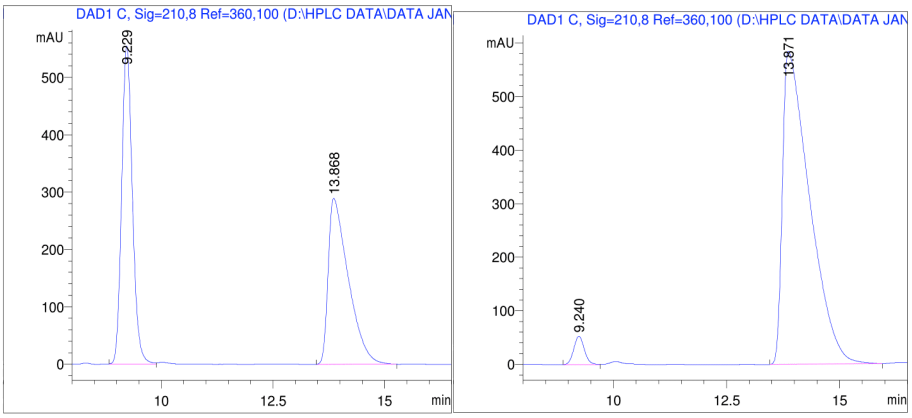
HPLC analysis on chiral stationary phase: Column Chiralpak IA, Heptane/EtOH 97:3, flow 1 mL/min, 210 nm, 21 °C, t_m= 9.2 min, t_M= 13.9 min

^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.33-7.30 (m, 2H), 7.16-7.14 (m, 2H), 5.11-5.08 (m, 1H), 2.34 (s, 3H), 1.98-1.81 (m, 5H), 1.65 (s, 3H), 1.53 (s, 3H), 1.50 (s, 3H)

^{13}C-NMR (125.7 MHz, $CDCl_3$): δ 145.1, 136.1, 132.3, 129.0, 124.8, 124.4, 75.0, 43.8, 30.7, 25.8, 23.1, 21.1, 17.8

$[\alpha]_D^{20}$: -11.9 (c. 1.0, $CHCl_3$); Lit. (for (*R*)-Gossonorol) $[\alpha]_D^{20}$: + 15.0 (c. 1.0, $CHCl_3$)[8]

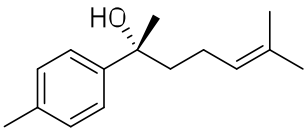
Analytical data were in accordance with literature reported results.[8]



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.240	BB	0.2540	872.63062	53.01289	3.4591
2	13.871	BB	0.6021	2.43544e4	584.53186	96.5409
Totals :				2.52270e4	637.54475	

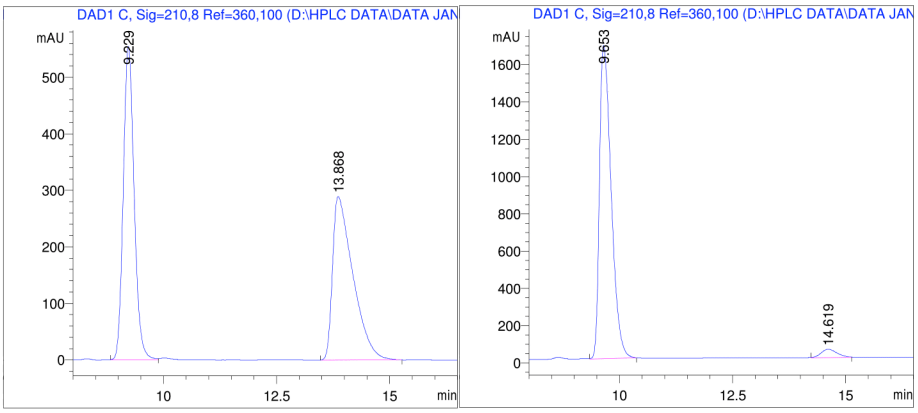
The opposite enantiomer **(*R*)-(+)-Gossonorol** was obtained by switching the ligand to (*R*,*R*)-**L1**.

(*R*)-(+)-Gossonorol



Colourless oil, 64% yield, 93% *ee*

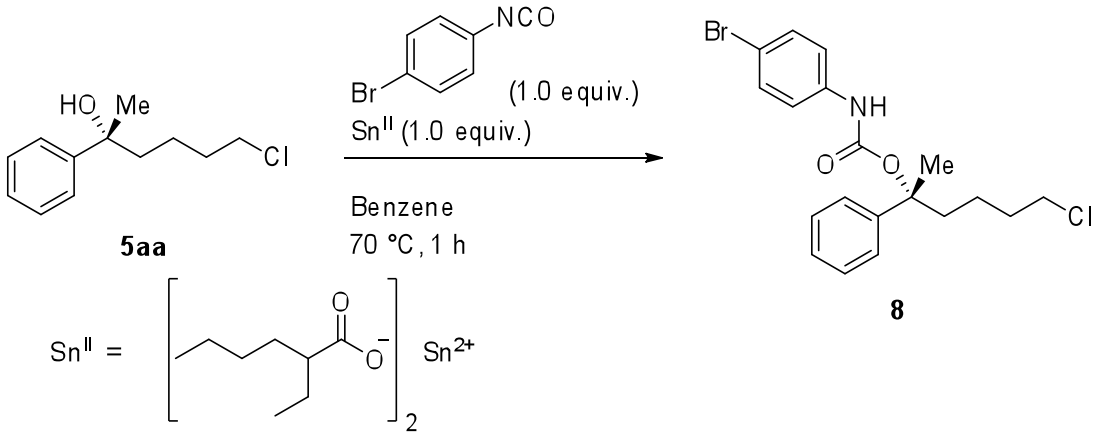
HPLC analysis on chiral stationary phase: Column Chiralpak IA, Heptane/EtOH 97:3, flow 1 mL/min, 210 nm, 21 °C, t_M= 9.7 min t_m= 14.6 min; $[\alpha]_D^{20}$: +15.1 (c. 1.3, $CHCl_3$); Lit.: $[\alpha]_D^{20}$: + 15.0 (c. 1.0, $CHCl_3$)[8]



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.653	MM	0.2993	3.01791e4	1680.40979	96.6124
2	14.619	MM	0.4025	1058.20740	43.81570	3.3876
Totals :				3.12373e4	1724.22549	

Carbamate Derivative for X-Ray analysis

Preparation of (*R*)-6-chloro-2-phenylhexan-2-yl (4-bromophenyl)carbamate 8



In a 15 mL flame-dried J Young flask, under nitrogen, tin(II) 2-ethylhexanoate (57 mg, 0.141 mmol) was dissolved in dry benzene (1 mL). To the solution was added 6-chloro-1,3-diphenylhexan-3-ol **5aa** (30 mg, 0.141 mmol, 95% *ee*) followed by 4-bromophenyl isocyanate (28 mg, 0.141 mmol). The reaction mixture was stirred at 70 °C for 1 hour and then diluted with H_2O (2 mL) and Et_2O (1 mL). The phases were separated and the aqueous phase extracted with Et_2O (2 x 5 mL). The combined organic layers were washed with $NaHCO_3$ sat. (2 x 5 mL), H_2O (5 mL) and brine (5 mL), dried over sodium sulfate, filtered and the solvent removed under reduced pressure. The crude material was purified by column chromatography on silica gel eluting with pentane/EtOAc 95:5 to obtain the pure carbamate **8**. Recrystallization from MeOH delivered suitable crystals for X-Ray analysis.

White solid, 72% yield, 96% *ee*

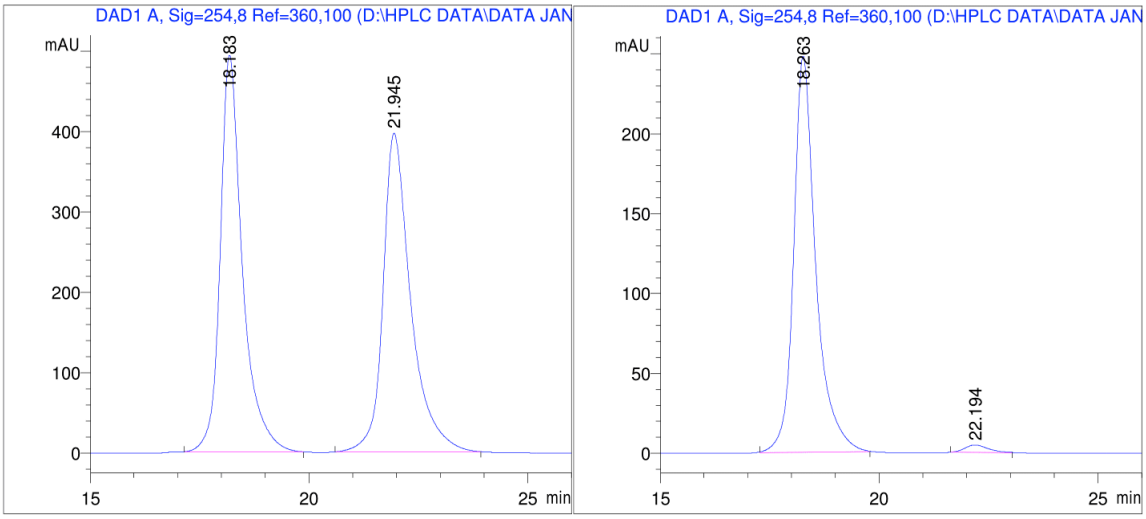
HPLC analysis on chiral stationary phase: Column (S,S)-Whelk-O 1, Heptane/EtOH 97:3, flow 1 mL/min, 254 nm, 21 °C, t_M= 18.3 min, t_m= 22.2 min

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.38-7.35 (m, 6H), 7.29-7.23 (m, 3H), 6.69 (br s, 1H), 3.51-3.48 (m, 2H), 2.07-2.03 (m, 2H), 1.92 (s, 3H), 1.77-1.70 (m, 2H), 1.46-1.37 (m, 2H)

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 151.8, 144.8, 137.3, 132.0, 128.5, 127.3, 124.6, 120.2, 115.8, 84.4, 44.9, 42.2, 32.7, 25.1, 21.4

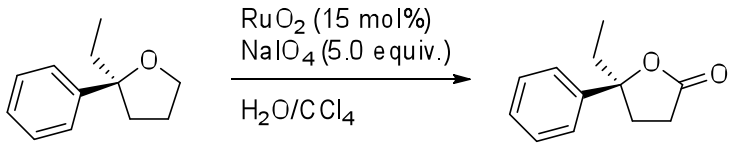
HRMS: (ESI) Calculated for $C_{19}H_{21}NO_2NaBrCl$ 432.0342 ($[M+Na]^+$); found 432.0341

$[\alpha]_D^{20}$: - 6.5 (c. 0.2, $CHCl_3$)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.263	BB	0.5224	8765.48633	247.95958	98.0671
2	22.194	BB	0.5315	172.76842	4.64922	1.9329
Totals :				8938.25475	252.60880	

Preparation of (*S*)-γ-ethyl-γ-phenylbutyrolactone 9

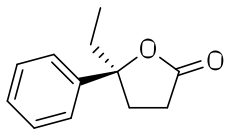


(*S*)-**6ab**
93% *ee*

(*S*)-**9**
66% yield
93% *ee*

(*S*)-γ-Ethyl-γ-phenylbutyrolactone **9** was prepared by oxidation of compound (*S*)-**6ab**, following the procedure reported by Capriati and co-workers.[9]

(*S*)-γ-Ethyl-γ-phenylbutyrolactone 9



9

Colourless oil, 66% yield, 93% *ee*

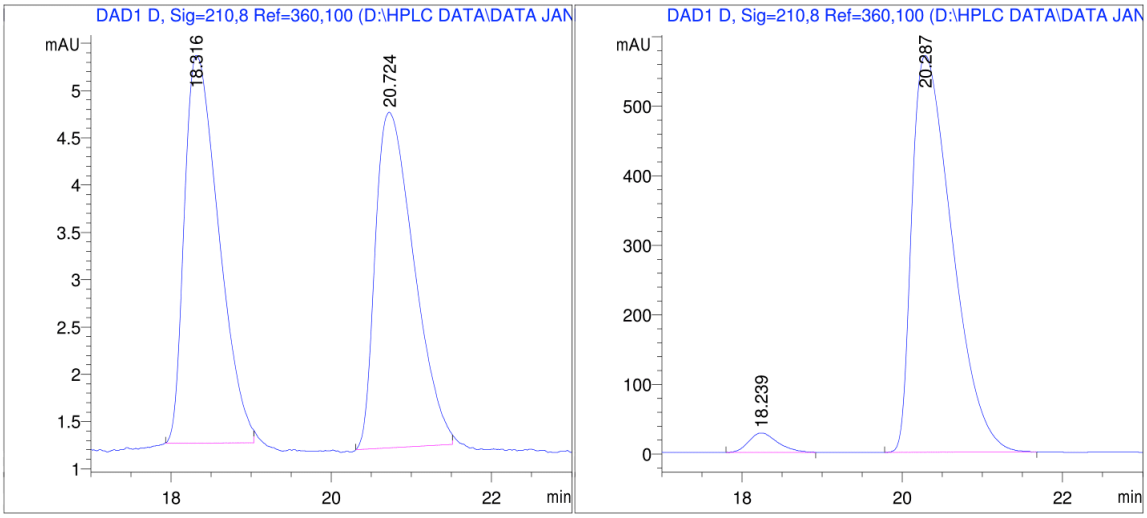
HPLC analysis on chiral stationary phase: Column Chiracel OJ-H, Heptane/EtOH 95:5, flow 1 mL/min, 210 nm, 21 °C, t_m= 18.2 min, t_M= 20.3 min

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.39-7.27 (m, 5H), 2.65-2.53 (m, 1H), 2.51-2.41 (m, 3H), 2.00 (q, *J* = 7.4 Hz, 2H), 0.82 (t, *J* = 7.4 Hz, 3H)

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 176.8, 142.8, 128.6, 127.6, 124.9, 90.0, 35.4, 34.7, 28.9, 8.4

$[\alpha]_D^{20}$: - 62 (c. 0.4 in CCl_4); Lit. (for (*S*)-**11**): $[\alpha]_D^{23}$: - 70 (c. 0.56, CCl_4)[10]

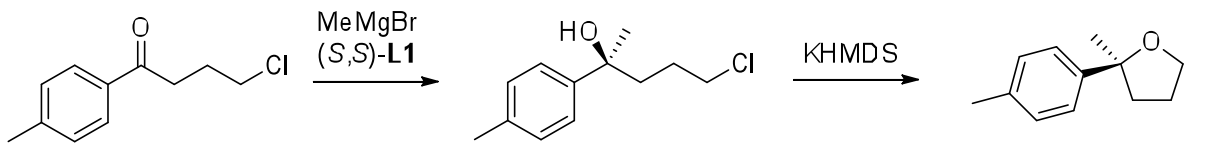
Analytical data were in accordance with previously reported results.[9]



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.239	BB	0.3825	703.89984	28.07863	3.4139
2	20.287	BB	0.5452	1.99150e4	570.57556	96.5861
Totals :				2.06189e4	598.65419	

Preparation of (*S*)-(-)-Boivinianin A

Preparation of (*S*)-2-methyl-2-(p-tolyl)tetrahydrofuran 10

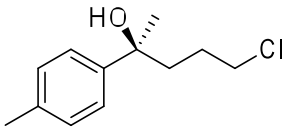


11 **11a** **10**

44%yield (over 2 steps)
96% *ee*

(*S*)-2-methyl-2-(p-tolyl)tetrahydrofuran **10** was prepared in two steps from 4-chloro-1-(4-methylphenyl)-1-oxobutane **11** following the procedures described above for chiral non-racemic tertiary alcohols. The intermediate tertiary alcohol (*S*)-5-chloro-2-(p-tolyl)pentan-2-ol **11a** was used immediately in the following cyclization (using Method A) due to racemization on standing.

(*S*)-5-chloro-2-(p-tolyl)pentan-2-ol 11a



11a

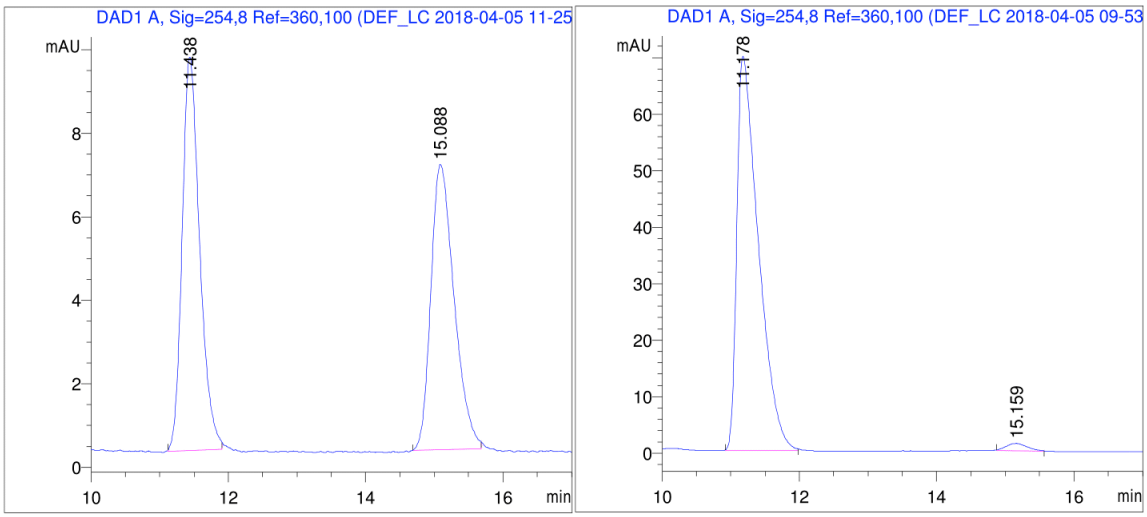
Colourless oil, 50% yield, 96% *ee* (the rest of the material was remaining starting ketone **11** recovered)

HPLC analysis on chiral stationary phase: Column Chiralpak IA, Heptane/EtOH 95:5, flow 1 mL/min, 254 nm, 21 °C, t_M= 11.1 min, t_m= 15.2 min

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.32-7.30 (m, 2H), 7.17-7.15 (m, 2H), 3.52-3.44 (m, 2H), 2.34 (s, 3H), 1.99-1.87 (m, 2H), 1.84-1.73 (m, 1H), 1.69-1.60 (m, 2H), 1.57 (s, 3H)

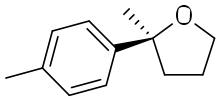
^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 144.5, 136.5, 129.1, 124.8, 74.4, 45.6, 41.5, 30.8, 27.6, 21.1

$[\alpha]_D^{20}$: -8.3 (c. 1.0, $CHCl_3$)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.178	BB	0.3223	1522.24634	69.84538	98.2111
2	15.159	BB	0.2994	27.72806	1.30754	1.7889
Totals :				1549.97440	71.15291	

(*S*)-2-methyl-2-(p-tolyl)tetrahydrofuran 10



10

Colourless oil, 88% yield, 96% *ee*

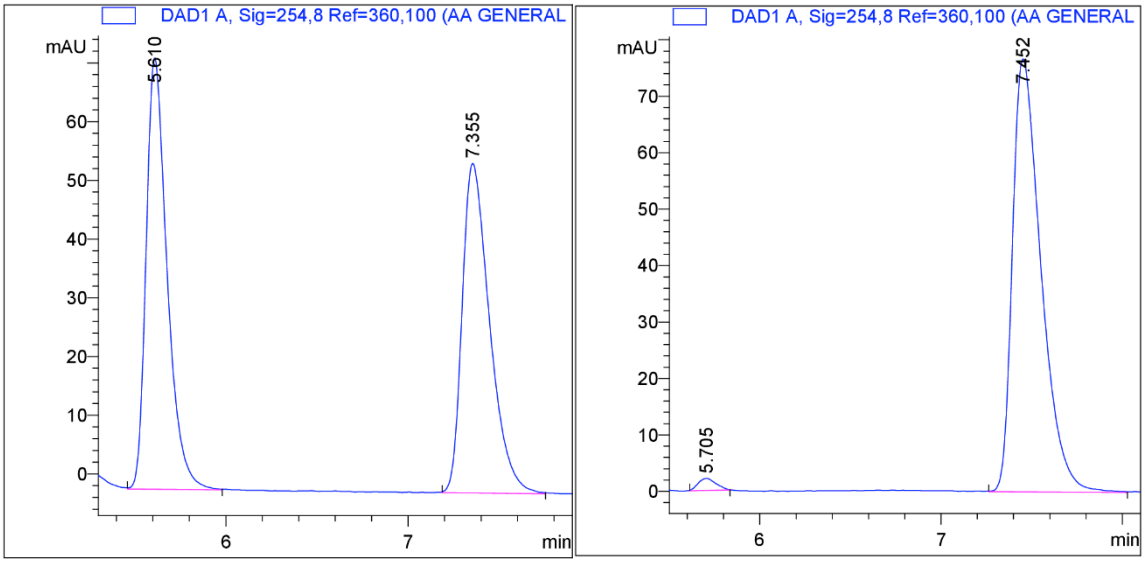
HPLC analysis on chiral stationary phase: Column Chiracel OJ-H, Heptane/EtOH 90:10, flow 1 mL/min, 254 nm, 21 °C, t_m= 5.7 min, t_M= 7.5 min

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.30-7.28 (m, 2H), 7.15-7.13 (m, 2H), 4.03-3.98 (m, 1H), 3.93-3.88 (m, 1H), 2.34 (s, 3H), 2.23-2.16 (m, 1H), 2.03-1.92 (m, 2H), 1.87-1.75 (m, 1H), 1.52 (s, 3H)

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 145.3, 136.0, 128.9, 124.8, 84.3, 67.6, 39.6, 29.9, 25.9, 21.1

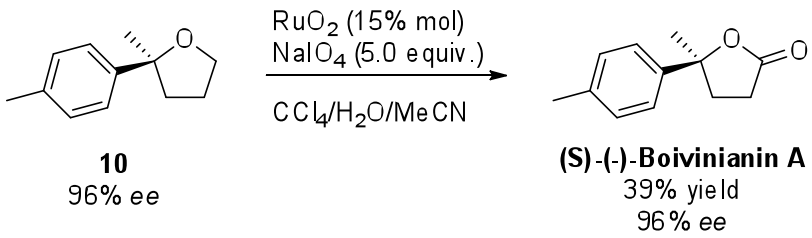
$[\alpha]_D^{20}$: +7.8 (c. 0.4, $CHCl_3$); Lit.: $[\alpha]_D^{25}$: + 6.5 (c. 0.28, CH_2Cl_2)[6]

Analytical data were in accordance with literature reported results.[6]



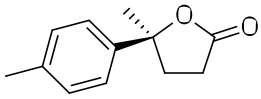
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.705	MM	0.1148	14.76613	2.14439	1.7290
2	7.452	MM	0.1822	839.28564	76.76058	98.2710
Totals :				854.05178	78.90498	

Oxidation of compound 10 to (*S*)-(-)-Boivinianin A



The oxidation of (*S*)-2-methyl-2-(p-tolyl)tetrahydrofuran **10** was performed applying the conditions reported by Sharpless and co-workers using $RuO_2/NaIO_4$ in $CCl_4/H_2O/MeCN$.[11]

(*S*)-(-)-Boivinianin A



Colourless oil, 39% yield, 96% *ee*

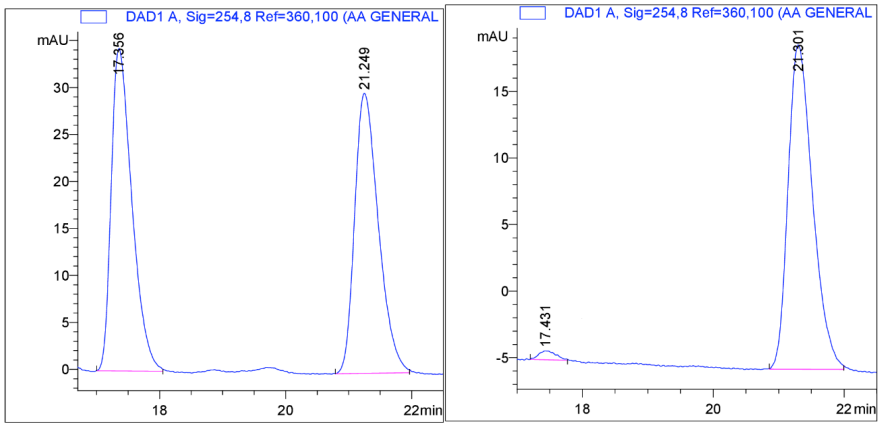
HPLC analysis on chiral stationary phase: Column Chiracel OJ-H, Heptane/EtOH 85:15, flow 0.5 mL/min, 254 nm, 21 °C, t_m= 17.4 min, t_M= 21.3 min

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.27-7.25 (m, 2H), 7.19-7.17 (m, 2H), 2.66-2.58 (m, 1H), 2.54-2.44 (m, 2H), 2.43-2.36 (m, 1H), 2.35 (s, 3H), 1.71 (s, 3H)

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 176.7, 141.5, 137.5, 129.4, 124.2, 87.2, 36.4, 29.6, 29.2, 21.1

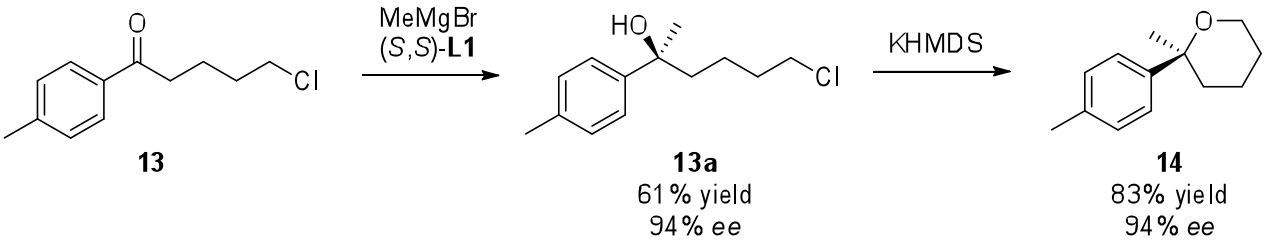
$[\alpha]_D^{20}$: -38.0 (c. 0.25, $CHCl_3$); Lit.: $[\alpha]_D^{25}$: -40 (c. 0.25, $CHCl_3$)[6]

Analytical data were in accordance with previously reported results.[6]



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.431	MM	0.3071	12.34708	6.70048e-1	1.9059
2	21.301	BB	0.3844	635.49646	24.36029	98.0941
Totals :				647.84354	25.03034	

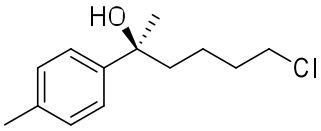
Preparation of 2-methyl-2-(p-tolyl)tetrahydro-2H-pyran 12



13 **13a** 61% yield 94% *ee* **14** 83% yield 94% *ee*

(*S*)-2-methyl-2-(p-tolyl)tetrahydro-2H-pyran **14** was prepared in two steps from 5-chloro-1-(p-tolyl)-1-oxopentane **13** following the procedures described above for chiral non-racemic tertiary alcohols and cyclisation (Method B). The intermediate tertiary alcohol (*S*)-6-chloro-2-(p-tolyl)hexan-2-ol **13a** was used immediately in the cyclization due to racemization on standing.

(*S*)-6-chloro-2-(p-tolyl)hexan-2-ol 13a



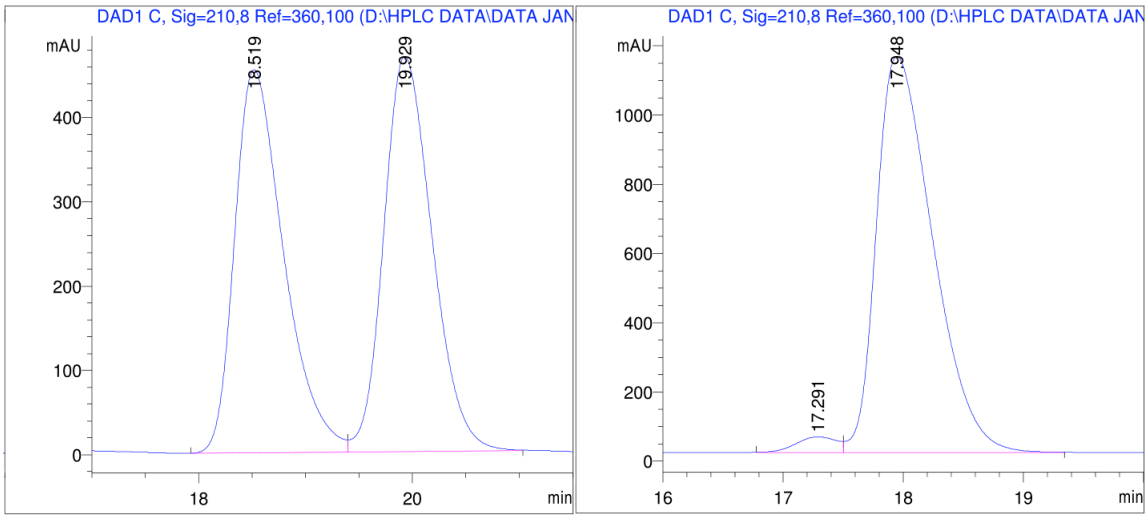
13a

Colourless oil, 61% yield, 94% *ee*

HPLC analysis on chiral stationary phase: Column Chiralpak IC, Heptane/EtOH 99.5:0.5, flow 1 mL/min, 210 nm, 21 °C, t_m= 17.3 min, t_M= 17.9 min

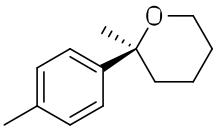
^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.32-7.30 (m, 2H), 7.17-7.15 (m, 2H), 3.47 (t, *J* = 6.8 Hz, 2H), 2.34 (s, 3H), 1.86-1.68 (m, 5H), 1.56 (s, 3H), 1.46-1.26 (m, 2H)

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 144.9, 136.3, 129.0, 124.8, 74.6, 45.0, 43.5, 33.0, 30.3, 21.7, 21.1



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.291	BV	0.3632	1046.04248	44.67373	2.7460
2	17.948	VB	0.4996	3.70469e4	1144.74109	97.2540
Totals :				3.80929e4	1189.41481	

(*S*)-2-methyl-2-(p-tolyl)tetrahydro-2H-pyran 14



14

Colourless oil, 83% yield, 94% *ee*

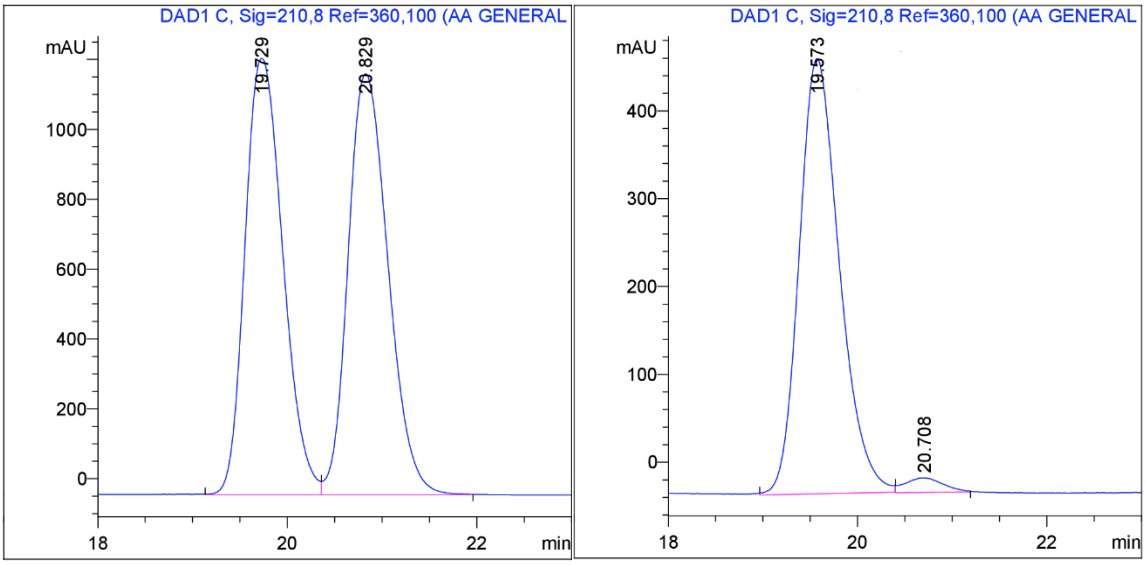
HPLC analysis on chiral stationary phase: Column Chiracel OJ-H, Heptane/EtOH 99.5:0.5, flow 0.5 mL/min, 210 nm, 21 °C, t_M= 19.6 min, t_m= 20.7 min

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.31-7.29 (m, 2H), 7.19-7.17 (m, 2H), 3.74-3.69 (m, 1H), 3.52-3.45 (m, 1H), 2.35 (s, 3H), 2.32-2.27 (m, 1H), 1.76-1.39 (m, 5H), 1.37 (s, 3H)

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 142.4, 136.1, 129.3, 126.1, 76.0, 62.9, 34.7, 33.1, 26.1, 21.1, 20.3

HRMS: (EI, 35 eV) Calculated for $C_{13}H_{18}O$ 190.1358 ($[M]^+$); found 190.1349

$[\alpha]_D^{20}$: +97.7 (c. 1.0, Acetone)

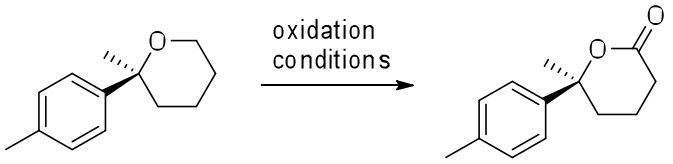


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.573	MM	0.4919	1.46288e4	495.64679	96.9673
2	20.708	MM	0.4666	457.52127	16.34122	3.0327
Totals :				1.50864e4	511.98801	

Oxidation of compound 14 to (*S*)-(-)-6-methyl-6-(p-tolyl)tetrahydro-2H-pyran-2-one 12

Various oxidation methods were tested for the preparation of compound **12** (Table 3). The $RuO_2/NaIO_4$ system in this case was not effective leading to degradation to mixtures of unidentified products. Methyltrioxorhenium/hydrogen peroxide[12] as well as sodium bromate/potassium hydrogen sulfate[13] showed no reactivity, with recovery of unreacted **14**. On the other hand, oxidation with iron (III) chloride/potassium permanganate[14] delivered the desired lactone **12**.

Table 3 Screening of conditions for the oxidation of tetrahydropyran **14** to lactone **12**.[a]



14 **(*S*)-12**

Entry	Oxidative system (equiv.)	Solvent	T (°C)	Time (h)	Yield 12 (%)[b]
1	RuO_2 (0.03) $NaIO_4$ (5.0)	CCl_4/H_2O	r.t.	18	-[c]
2	RuO_2 (0.03) $NaIO_4$ (5.0)	CCl_4/H_2O/MeCN	r.t.	18	-[c]
3	RuO_2 (0.15) $NaIO_4$ (5.0)	CCl_4/H_2O/MeCN	r.t.	6	-[c]
4	$MeReO_3$ (0.03) H_2O_2 (3.0)	MeOH	r.t.	24	-[d]
5	$NaBrO_3$ (1.0) $NaHSO_4$ (1.0)	Et_2O/H_2O	r.t.	24	-[d]
6	$FeCl_3$ (1.0) $KMnO_4$ (3.0)	Acetone	-78 to r.t	18	18
7	$FeCl_3$ (3.0) $KMnO_4$ (6.0)	Acetone	-78 to r.t	18	49

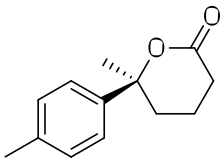
[a] Reactions were run on 0.2 mmol scale. [b] Isolated yields. [c] Degradation of compound **14.** [d] Recovery of compound **14**.

Procedure:

A solution of (*S*)-2-methyl-2-(p-tolyl)tetrahydro-2H-pyran **14** (38 mg, 0.2 mmol, 94% *ee*) in acetone (2 mL) was cooled to -78 °C and $KMnO_4$ (190 mg, 1.2 mmol) and $FeCl_3$ (97 mg, 0.6 mmol) were added. The temperature was slowly raised

to r.t. over 2 hours and the mixture was stirred at r.t. for 18 hours. The mixture was then diluted with DCM 15 mL and H_2O (5 mL), the phases were separated and the aqueous phase extracted with DCM (5 x 15 mL). The combined organic phases were dried over sodium sulfate, filtered and the solvent evaporated under reduced pressure. The crude was purified by flash column chromatography on silica gel eluting with pentane/EtOAc 80:20 to obtain compound **12** (49% yield, 91% *ee*)

(*S*)-(-)-6-methyl-6-(p-tolyl)tetrahydro-2H-pyran-2-one 12



12

White solid, 49% yield, 91% *ee*

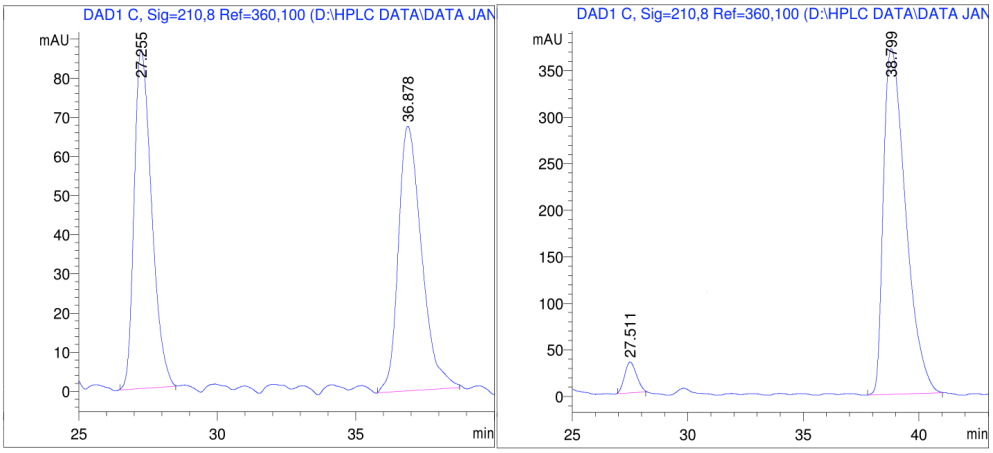
HPLC analysis on chiral stationary phase: Column Chiralpak AS-H, Heptane/EtOH 99:1, flow 1 mL/min, 210 nm, 21 °C, t_m= 27.5 min, t_M= 38.8 min

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.23-7.16 (m, 4H), 2.52-2.37 (m, 2H), 2.34 (s, 3H), 2.33-2.27 (m, 1H), 2.02-1.94 (m, 1H), 1.83-1.74 (m, 1H), 1.66 (s, 3H), 1.64-1.58 (m, 1H)

^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 171.8, 141.7, 137.2, 129.5, 124.5, 85.5, 34.4, 31.6, 29.2, 21.1, 16.7

$[\alpha]_D^{20}$: -32.5 (c. 0.2, MeOH); Lit.: $[\alpha]_D^{20}$: -38.0 (c. 0.17, MeOH)[15]

Analytical data were in accordance with literature reported results.[15]

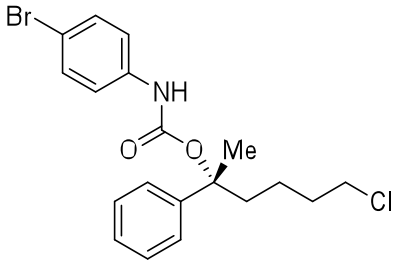


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	27.511	MM	0.6002	1195.22253	33.18724	4.5899
2	38.799	BB	1.0281	2.48452e4	371.55084	95.4101
Totals :				2.60404e4	404.73809	

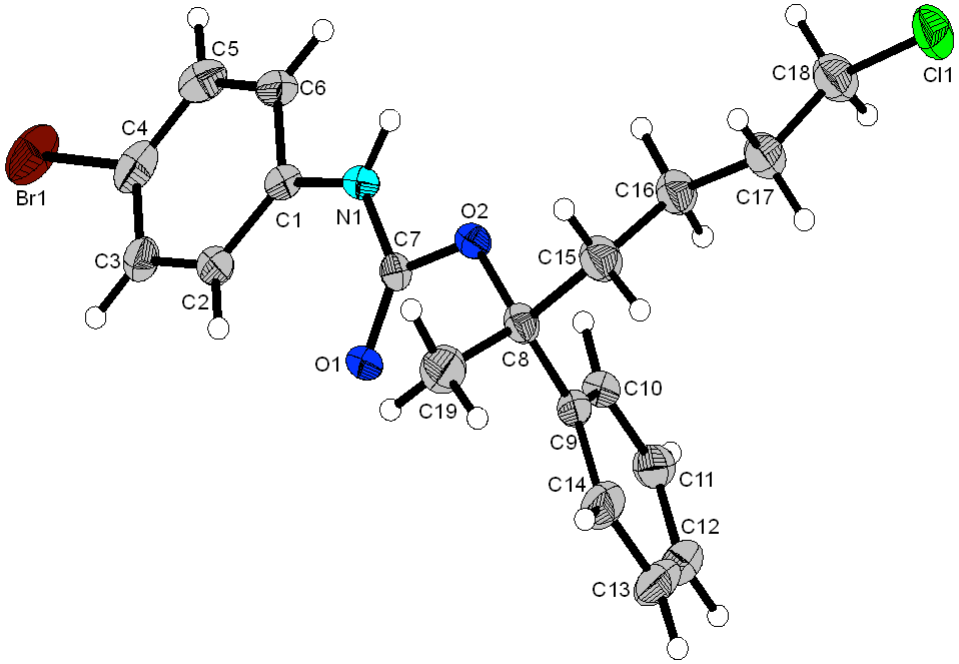
X-Ray analysis of compound 8

Crystal data were collected using a Rigaku Oxford Diffraction (former Agilent Technologies, former Oxford Diffraction) SuperNova A diffractometer, using Cu-K_α (1.54184 Å). An analytical absorption correction based on the shape of the crystal was performed.[16] The structures were solved by direct methods using SHELXS-97 and refined by full matrix least-squares on F^2 for all data using SHELXL-97.[17] Anisotropic thermal displacement parameters were used for all non-hydrogen atoms. Crystals were selected at low temperature.[18]

Crystallographic data for compound **8** have been deposited with the Cambridge Crystallographic Data Centre [CCDC 1883098]



8



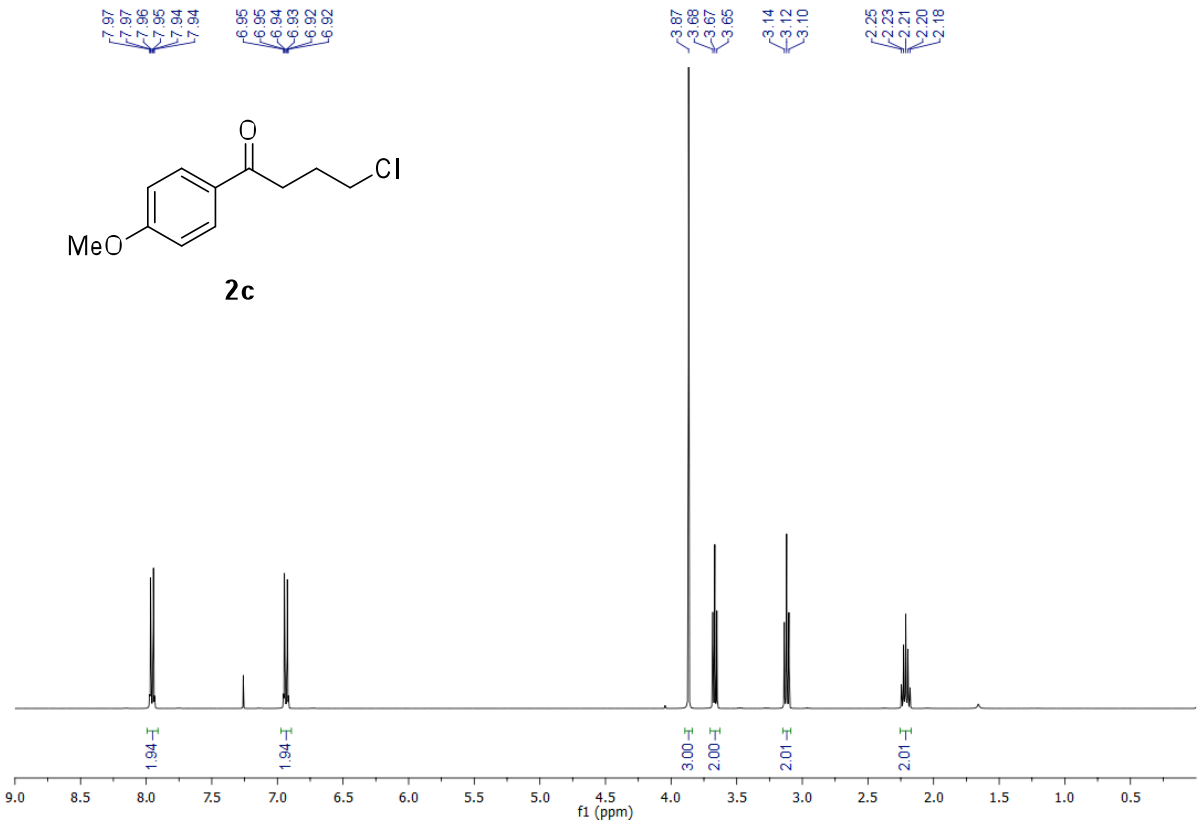
Crystallographic data

Table 4. Crystal data and structure refinement for compound **8**.

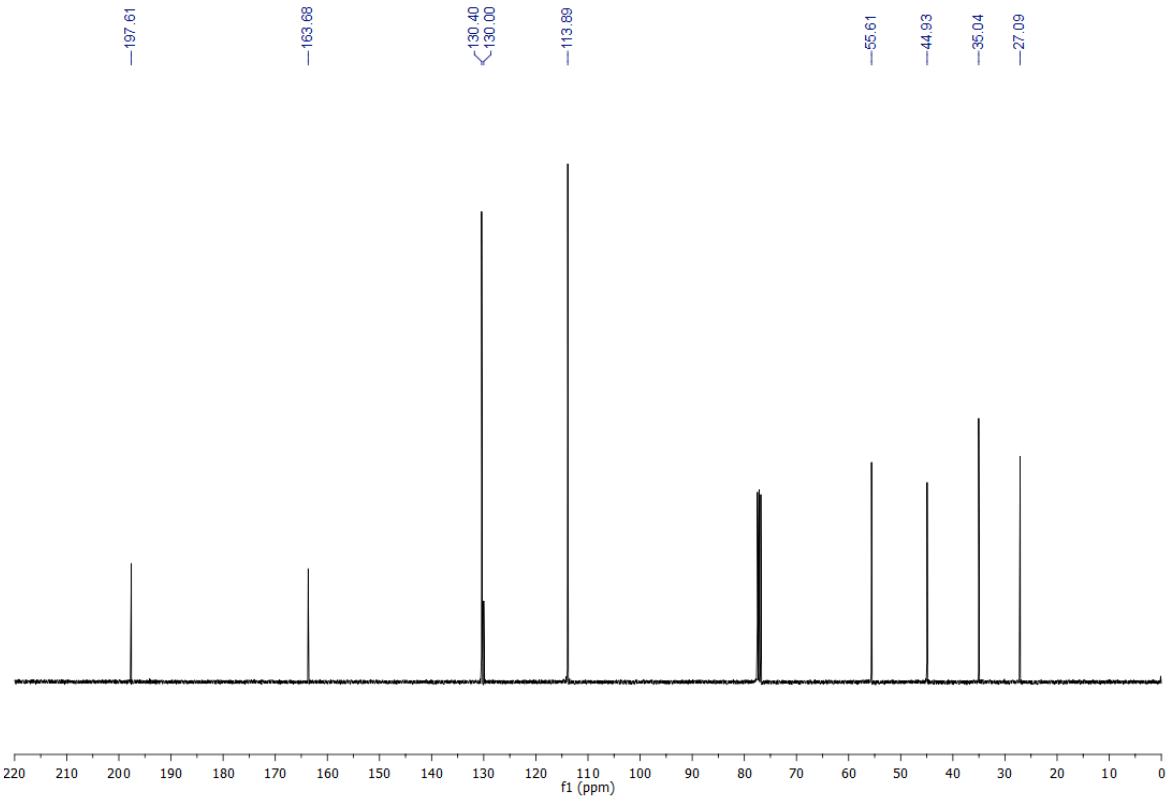
Identification code	gil104
Empirical formula	C_{19} H_{21} N O_2 Cl Br
Formula weight	410.73
Temperature	100(2) K
Wavelength	1.54184 Å
Crystal system	Monoclinic
Space group	$P2_1$ (#4)
Unit cell dimensions	a = 9.5181(2) Å α= 90°.
	b = 11.3448(2) Å β= 105.143(2)°.
	c = 18.2344(4) Å γ = 90°.
Volume	1900.60(7) $Å^3$
Z	4
Density (calculated)	1.435 Mg/m^3
Absorption coefficient	4.323 mm^{-1}
F(000)	840
Crystal size	0.191 x 0.160 x 0.024 mm^3
Theta range for data collection	3.896 to 77.106°.
Index ranges	–10<=h<=11, –14<=k<=14, –22<=l<=23
Reflections collected	20680
Independent reflections	7823 [R(int) = 0.0414]
Completeness to theta = 67.684°	100.0 %
Absorption correction	Gaussian
Max. and min. transmission	0.907 and 0.550
Refinement method	Full–matrix least–squares on F^2
Data / restraints / parameters	7823 / 1 / 436
Goodness–of–fit on F^2	1.016
Final R indices [I>2sigma(I)]	R1 = 0.0377, wR2 = 0.0965
R indices (all data)	R1 = 0.0389, wR2 = 0.0983
Absolute structure parameter	–0.012(15)
Extinction coefficient	n/a
Largest diff. peak and hole	0.929 and –0.595 $e.Å^{-3}$

NMR spectra

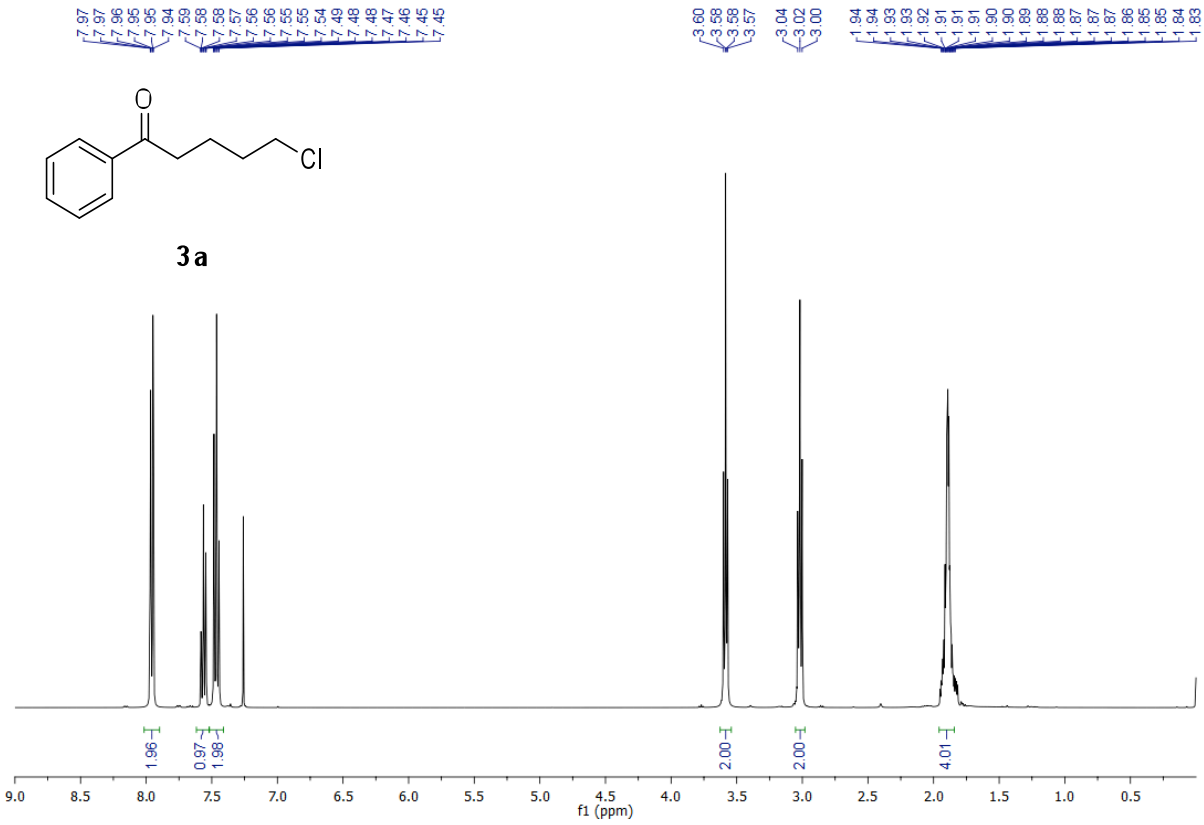
4’-methoxy-4-chlorobutyrophenone 2c

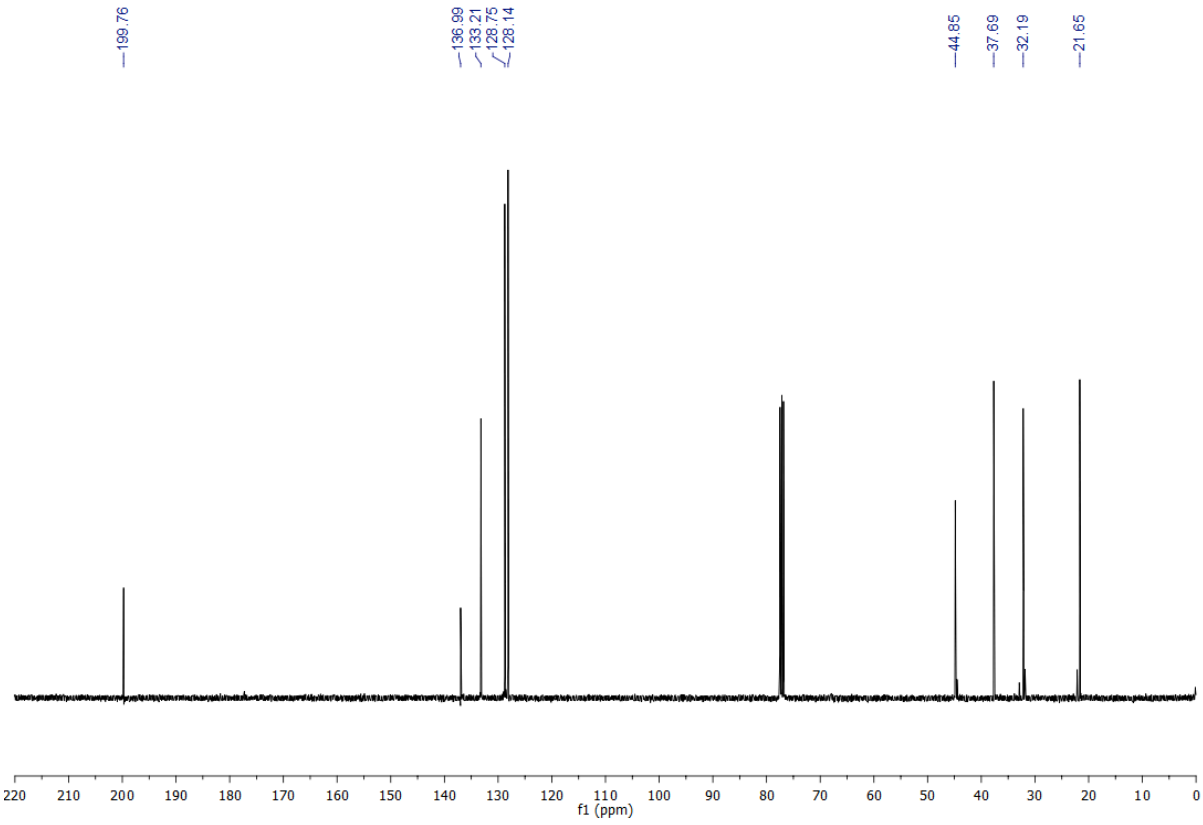


2c

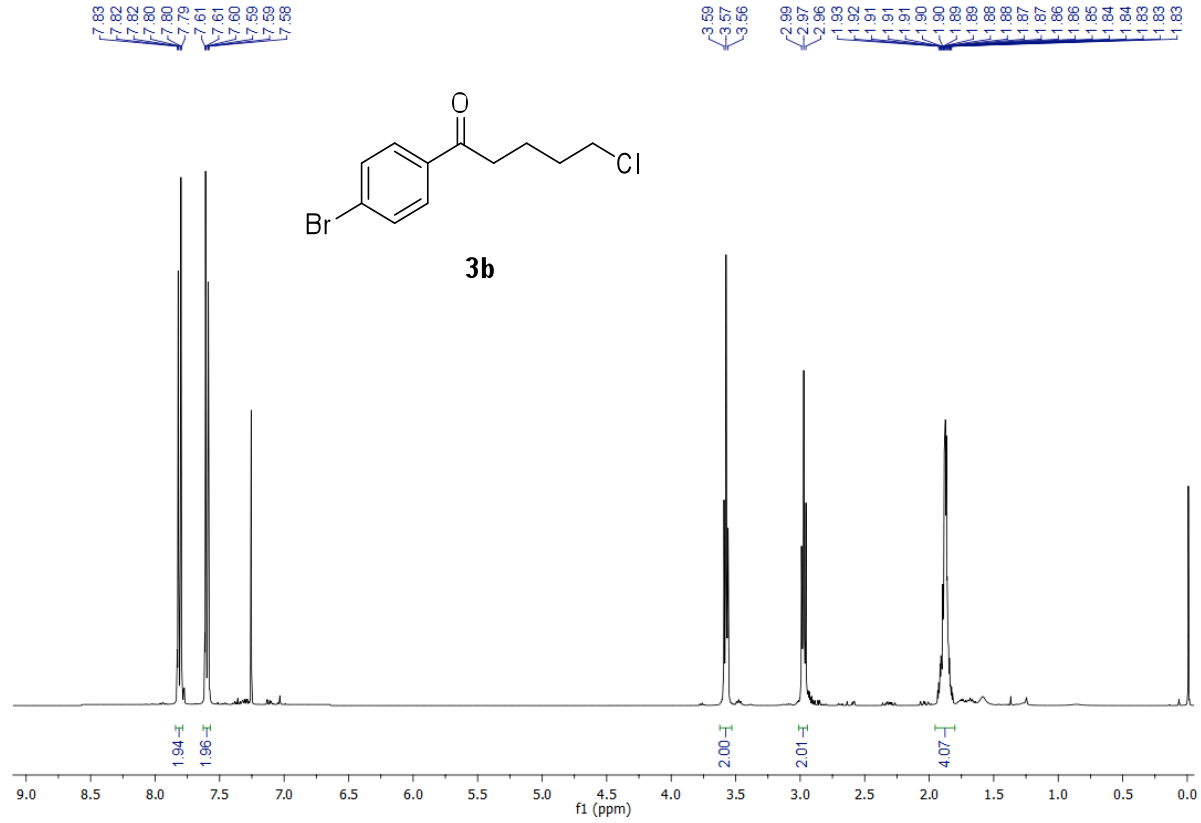


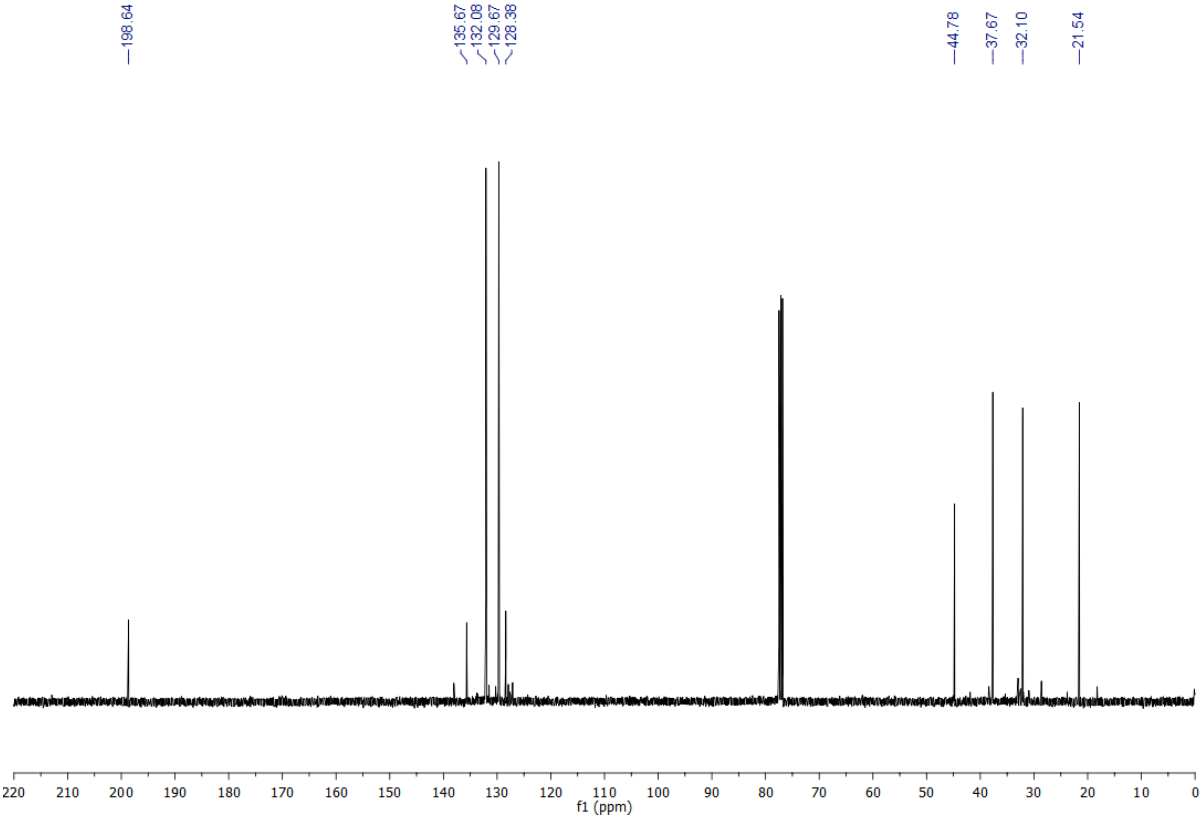
5-chlorovalerophenone 3a



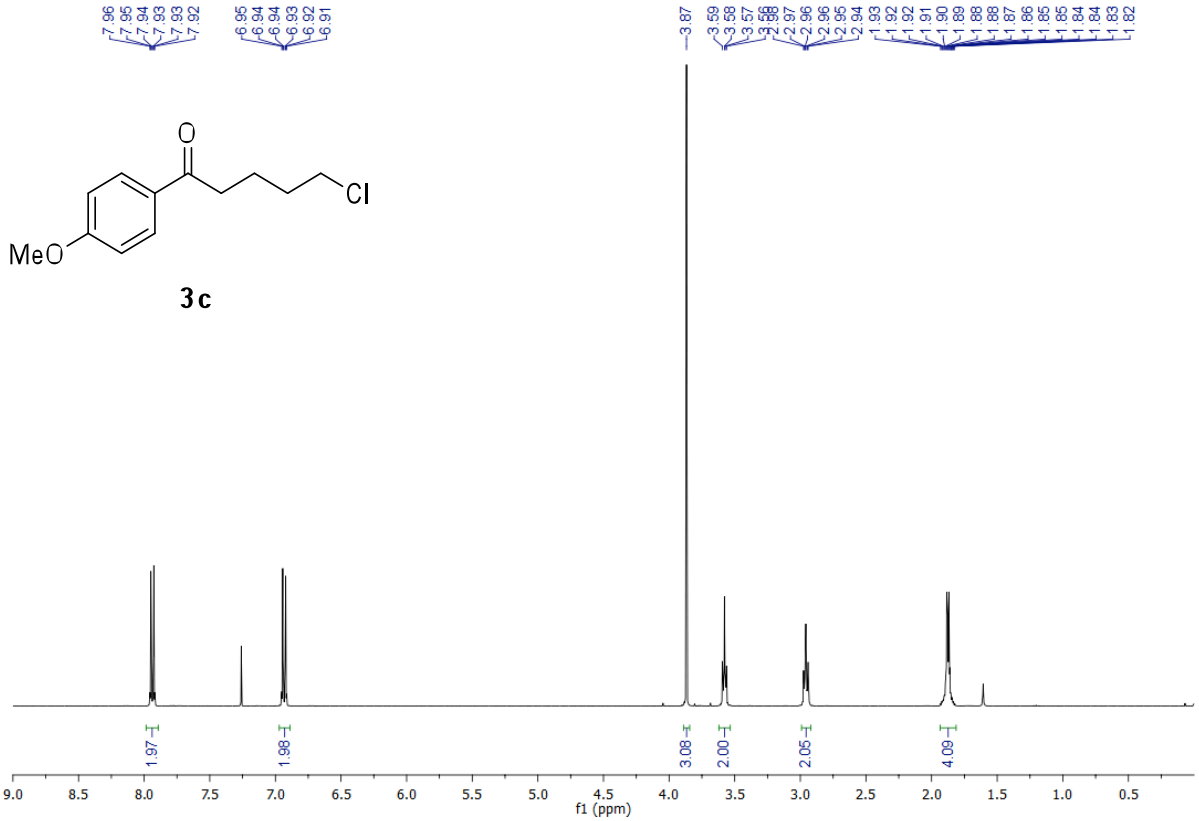


4’-bromo-5-chlorovalerophenone 3b

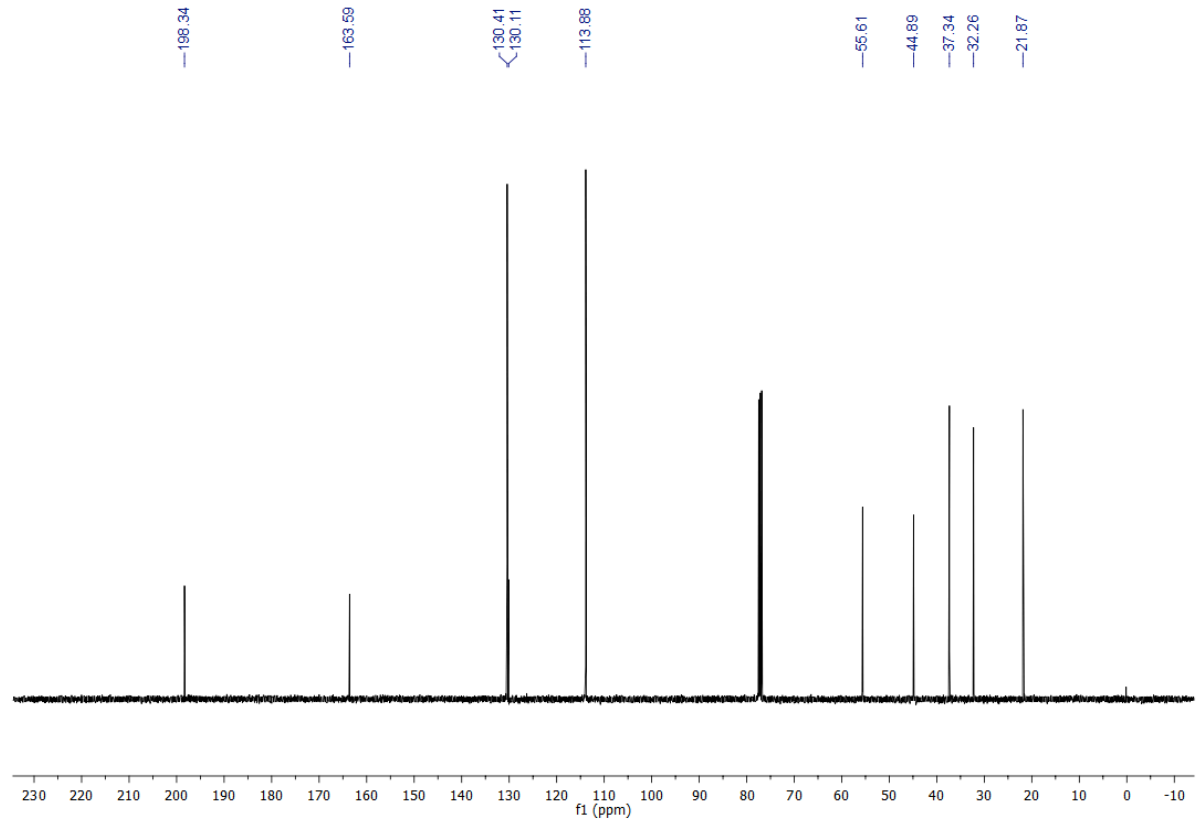




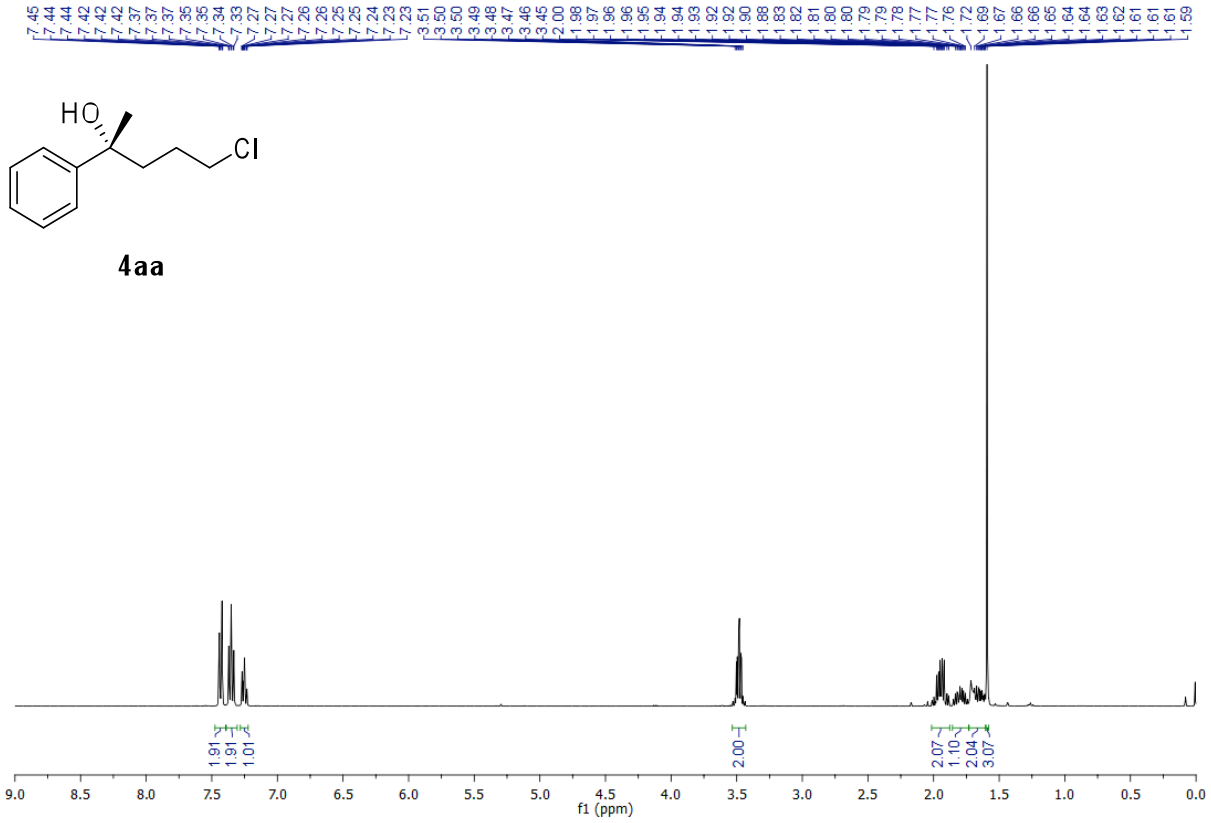
4’-methoxy-5-chlorovalerophenone 3c

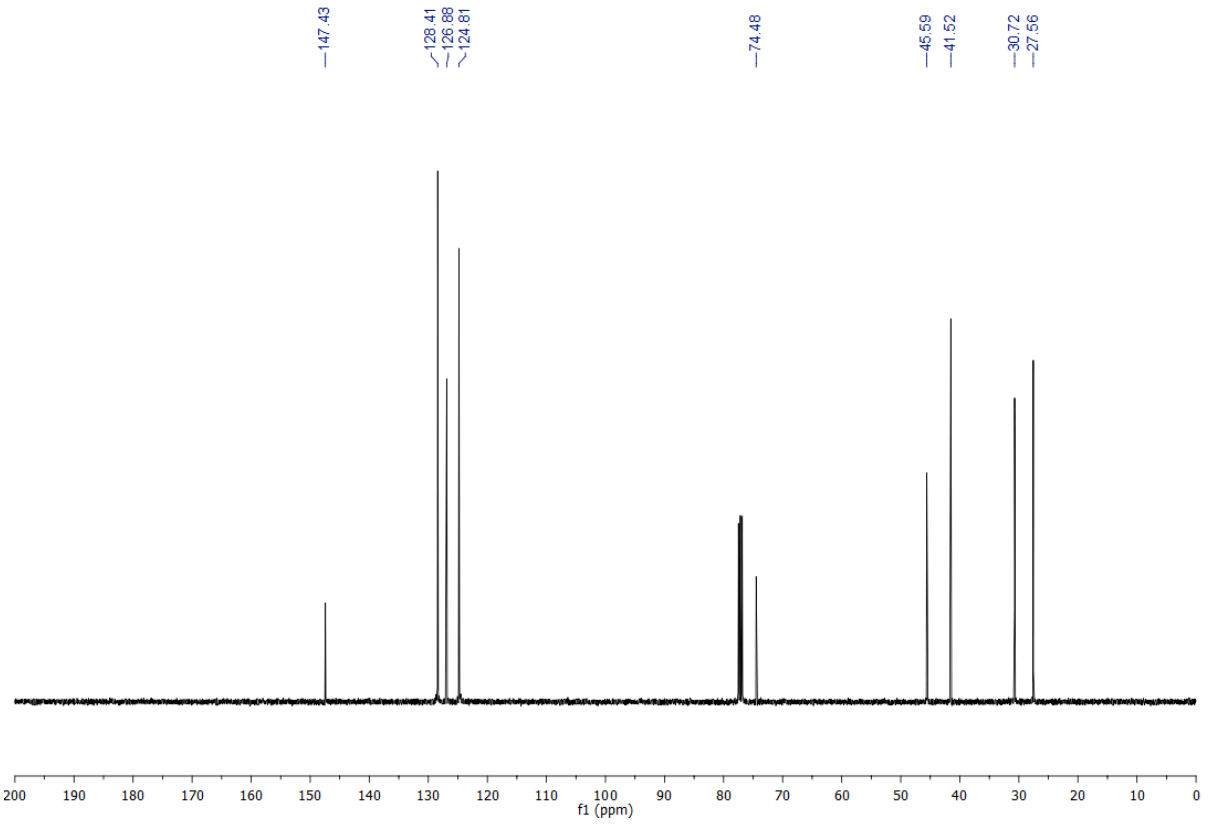


3c

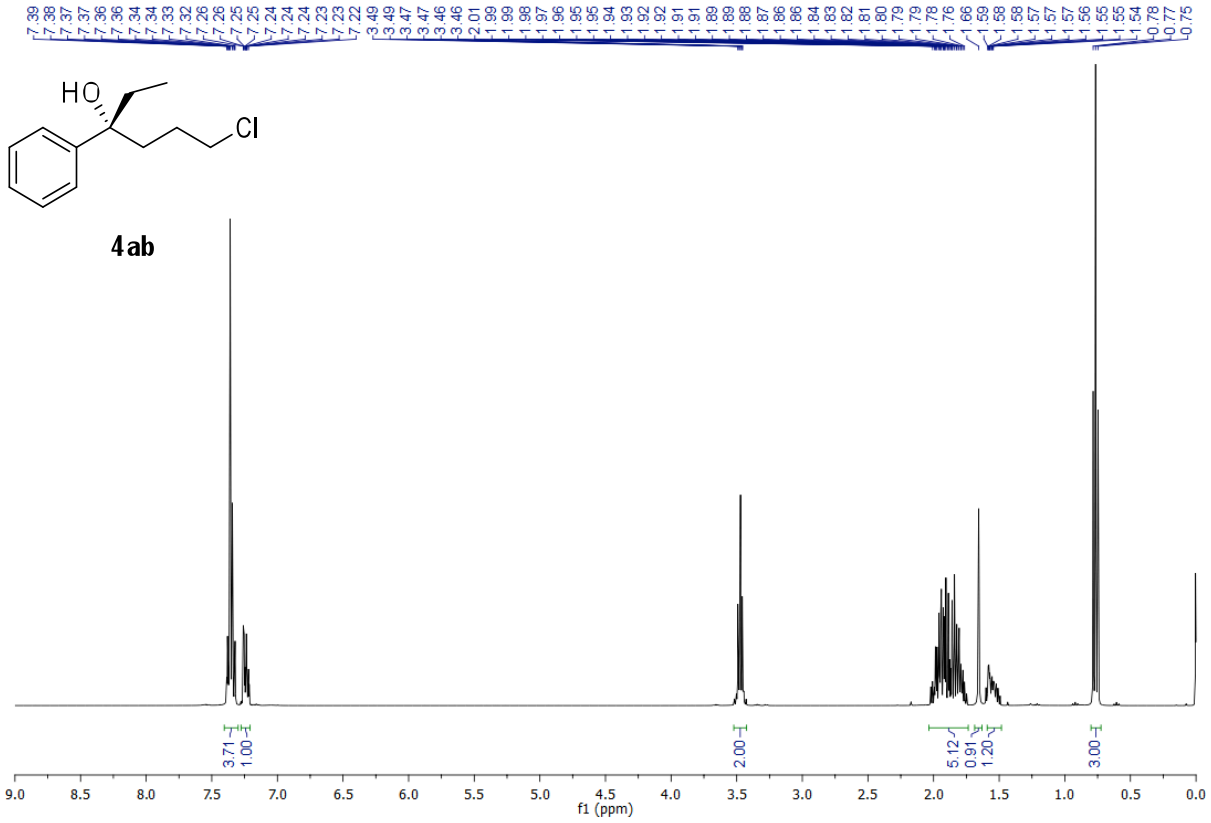


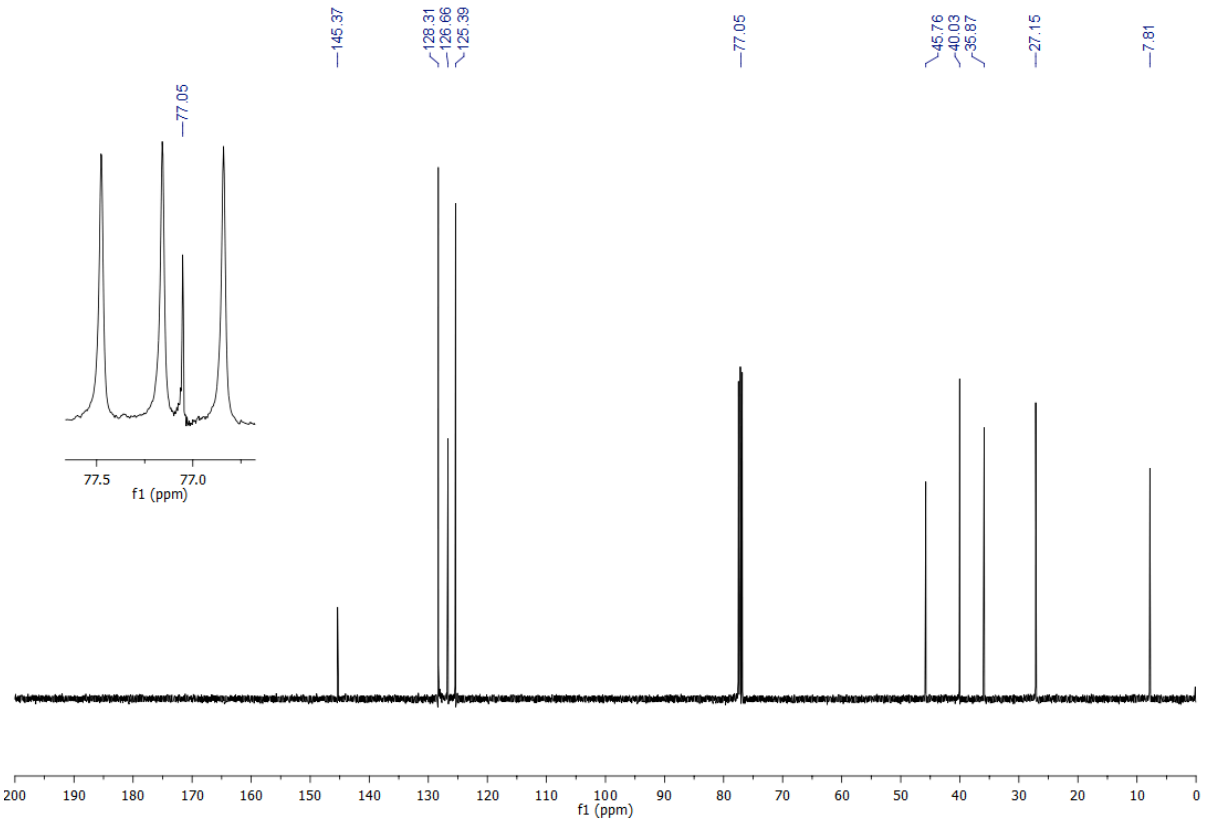
5-chloro-2-phenylpentan-2-ol 4aa



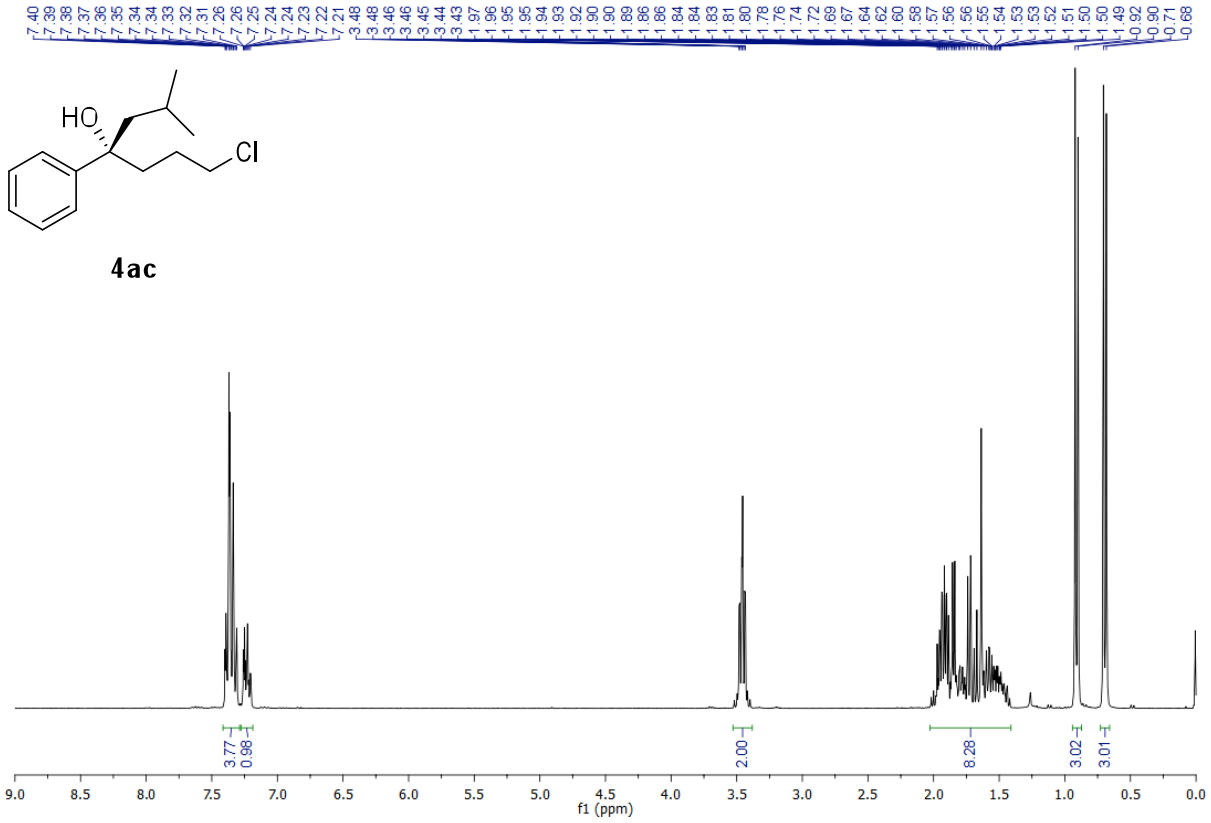


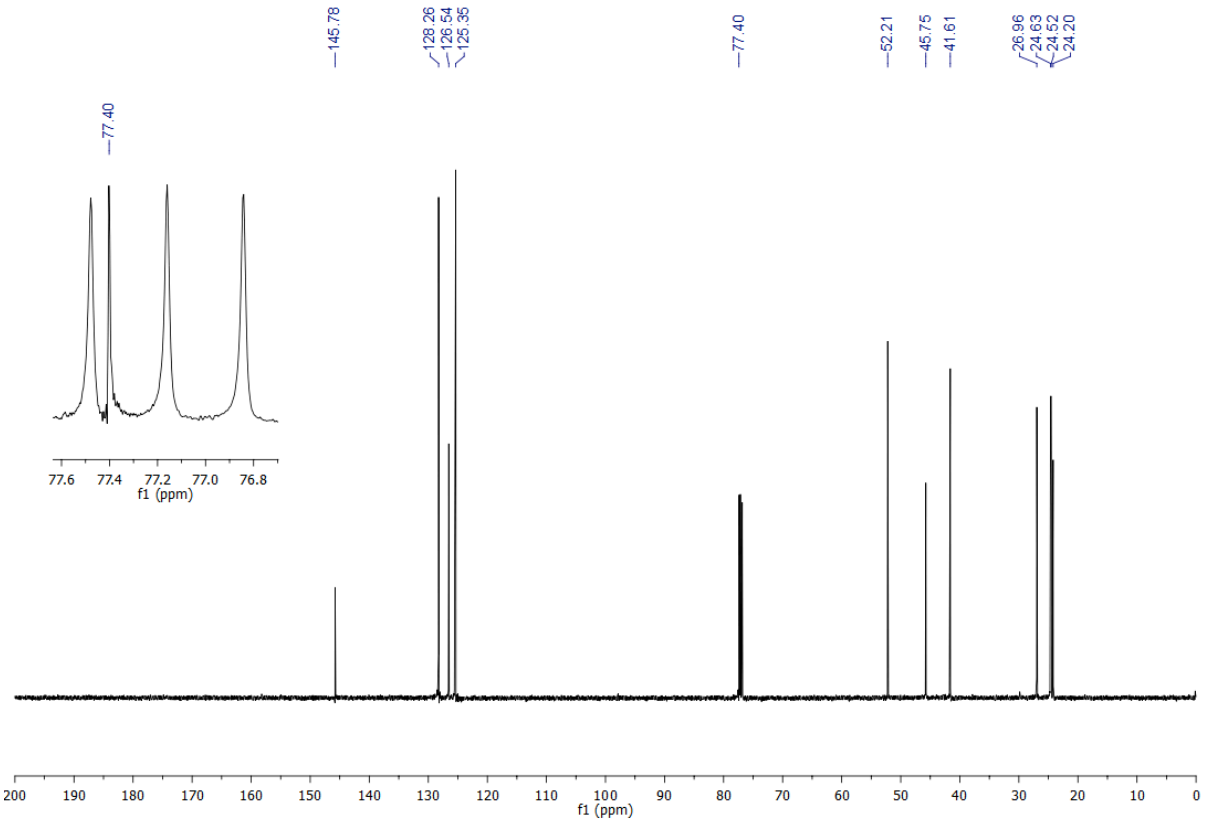
(*R*)-6-chloro-3-phenylhexan-3-ol 4ab



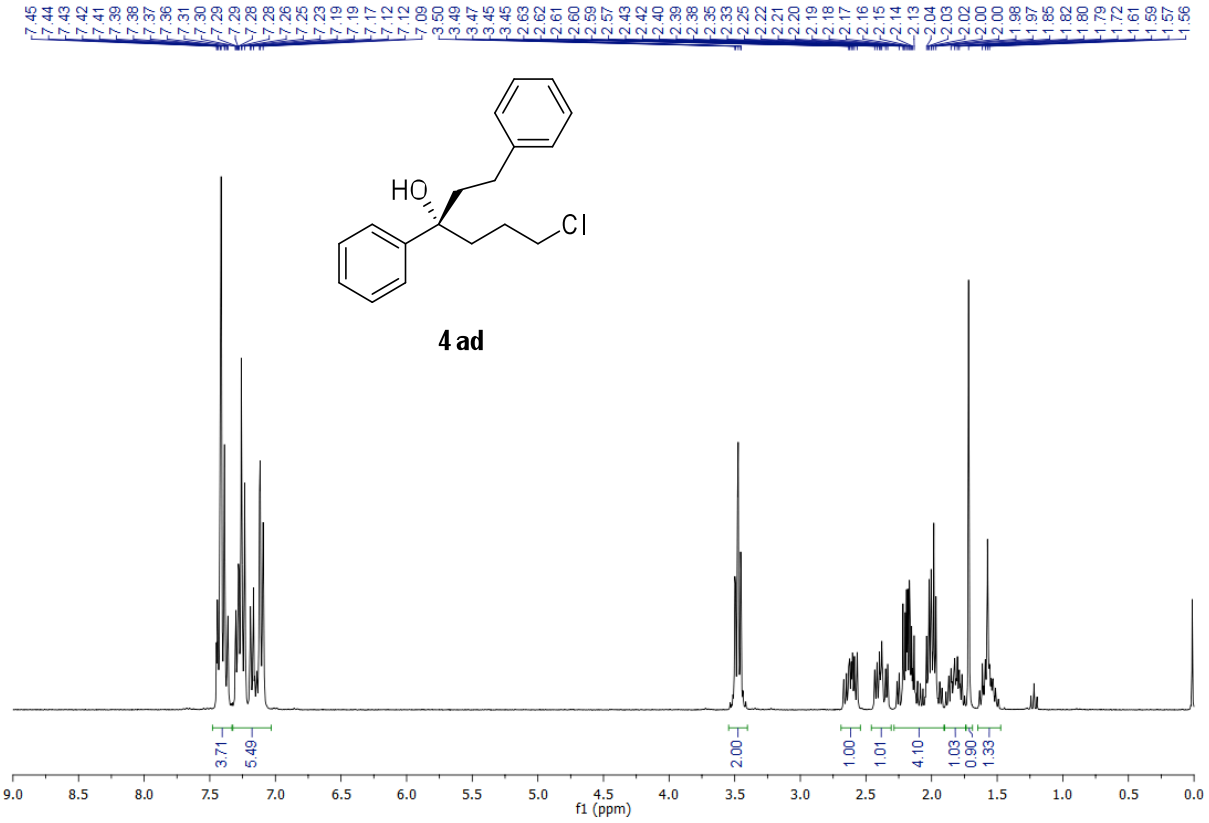


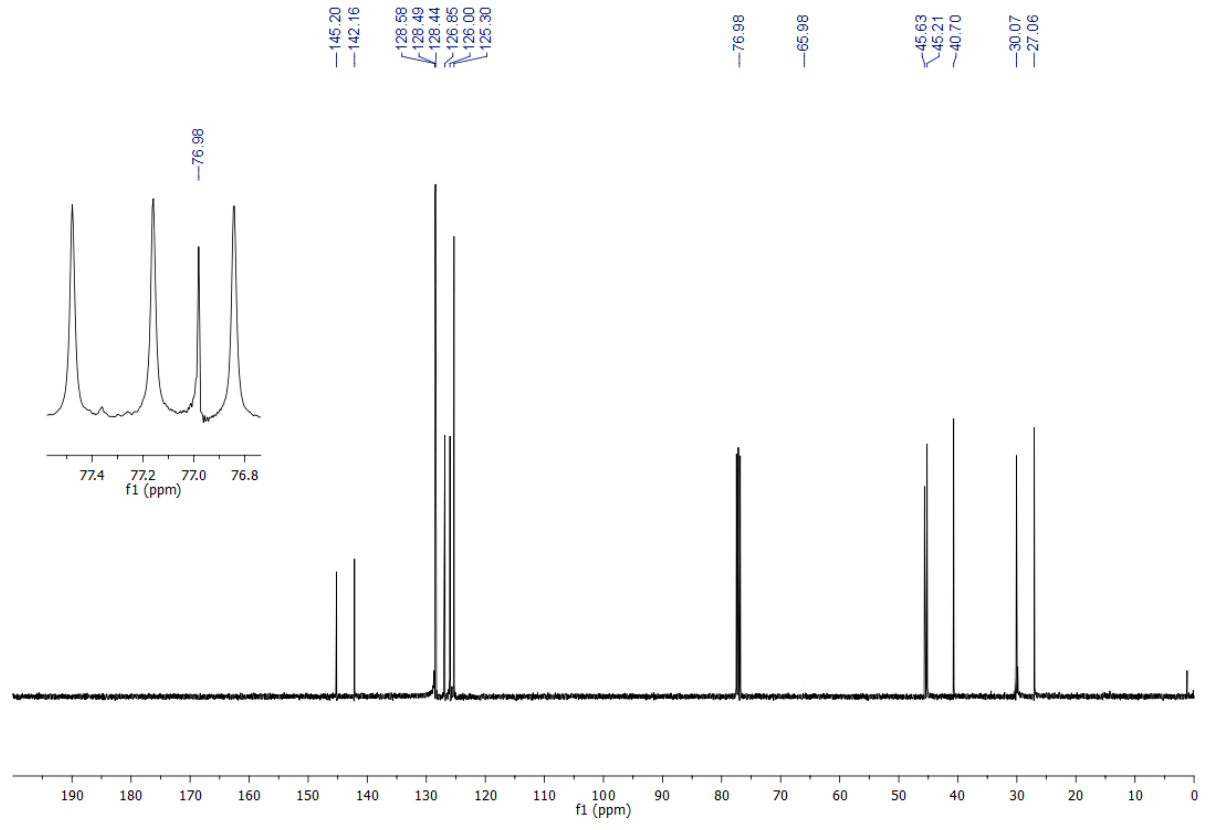
1-chloro-6-methyl-4-phenylheptan-4-ol 4ac



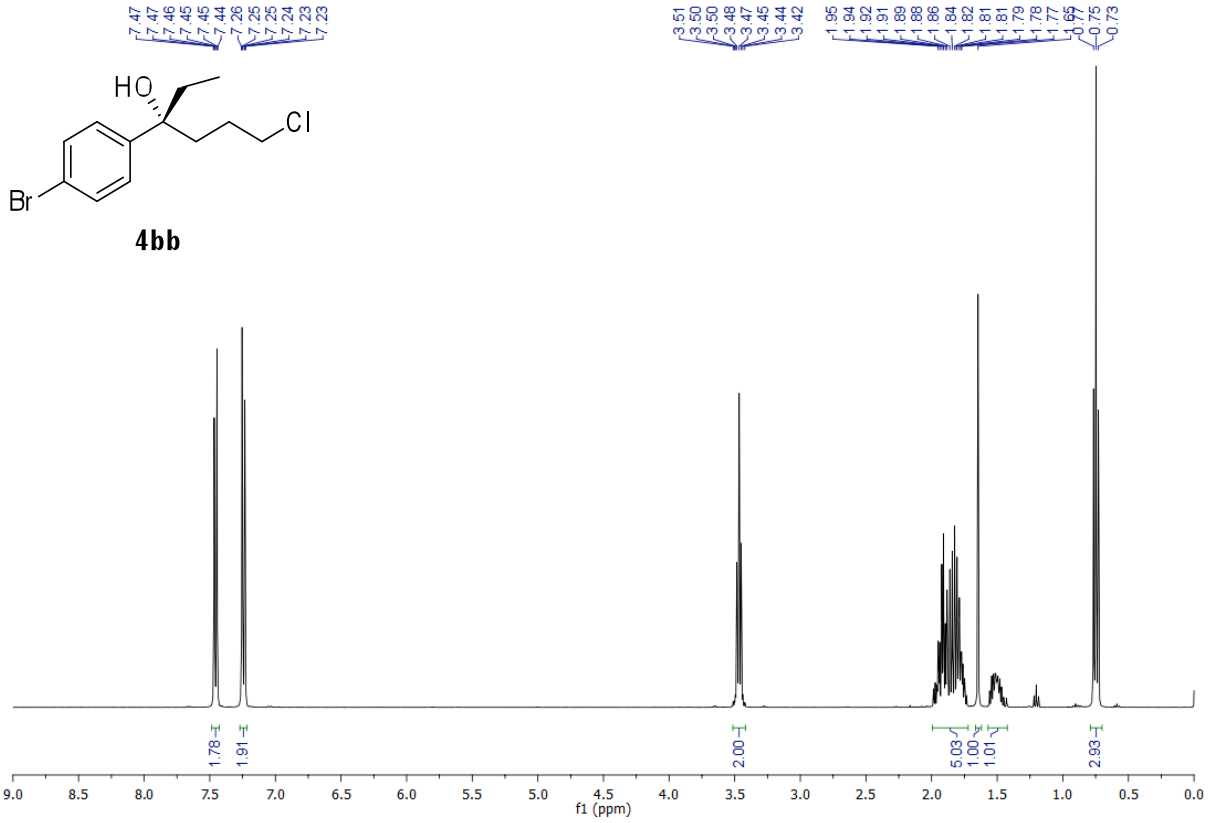


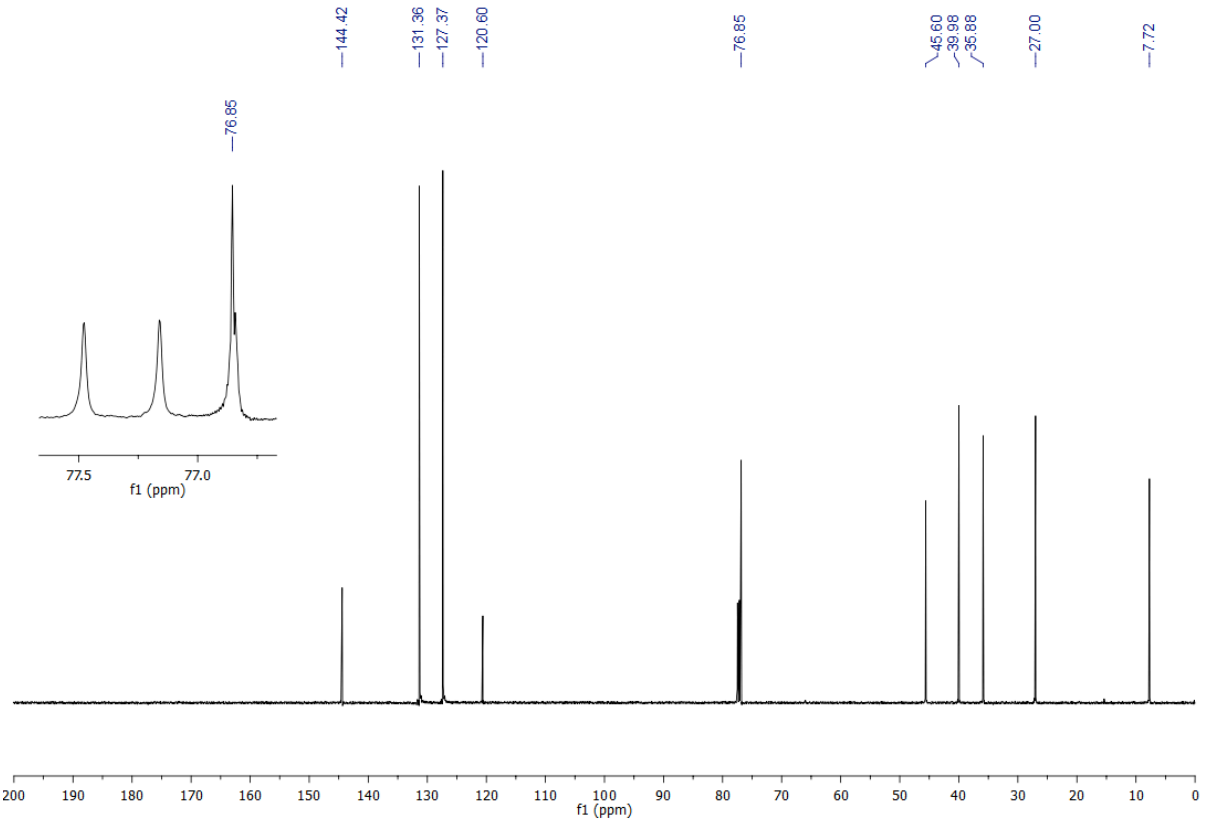
6-chloro-1,3-diphenylhexan-3-ol 4ad



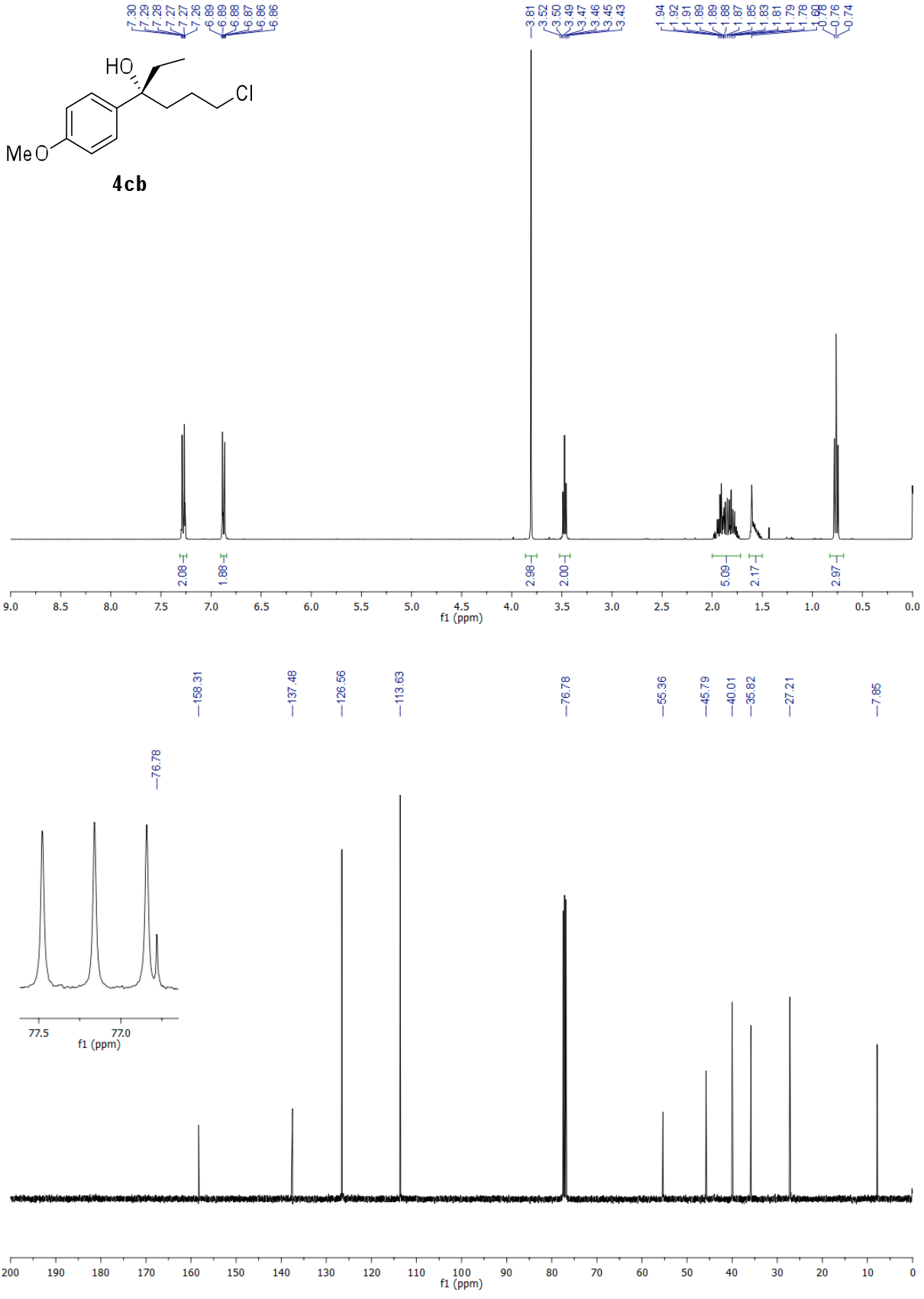


3-(4-bromophenyl)-6-chlorohexan-3-ol 4bb

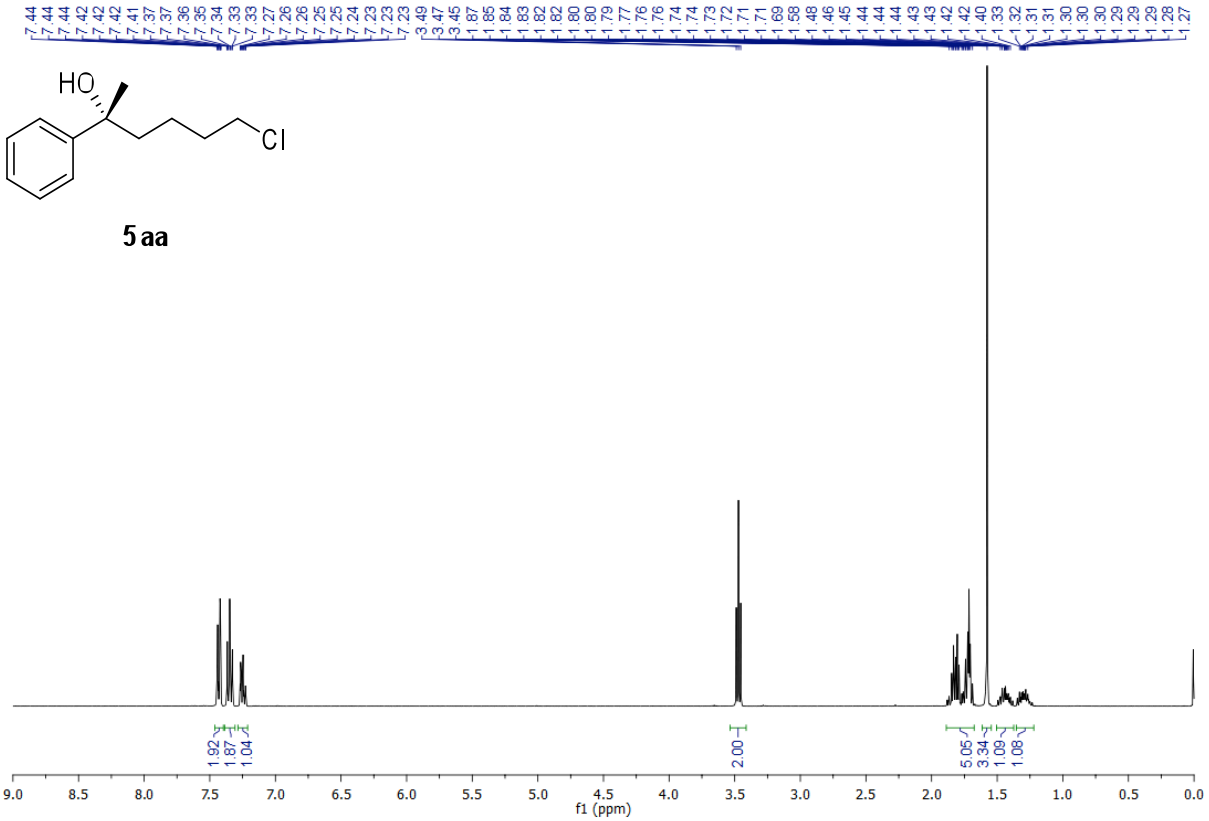


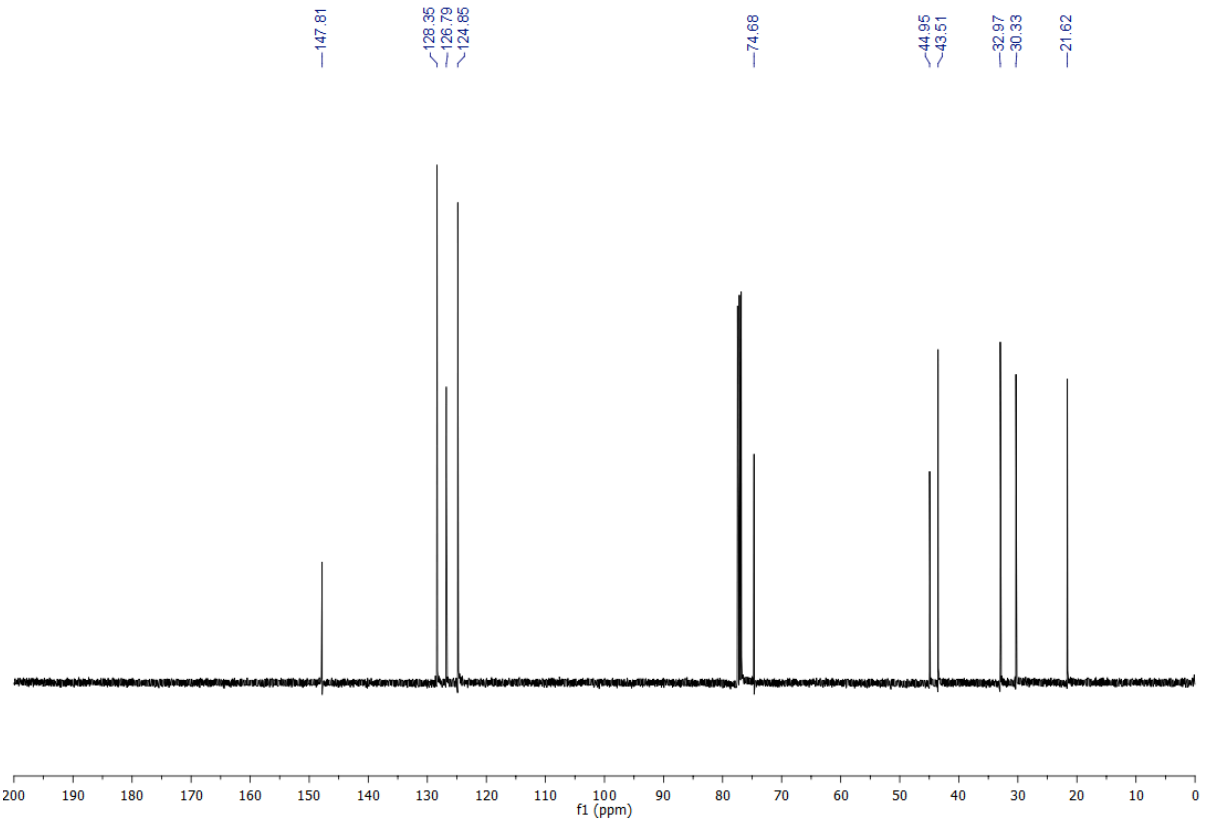


6-chloro-3-(4-methoxyphenyl)hexan-3-ol 4cb

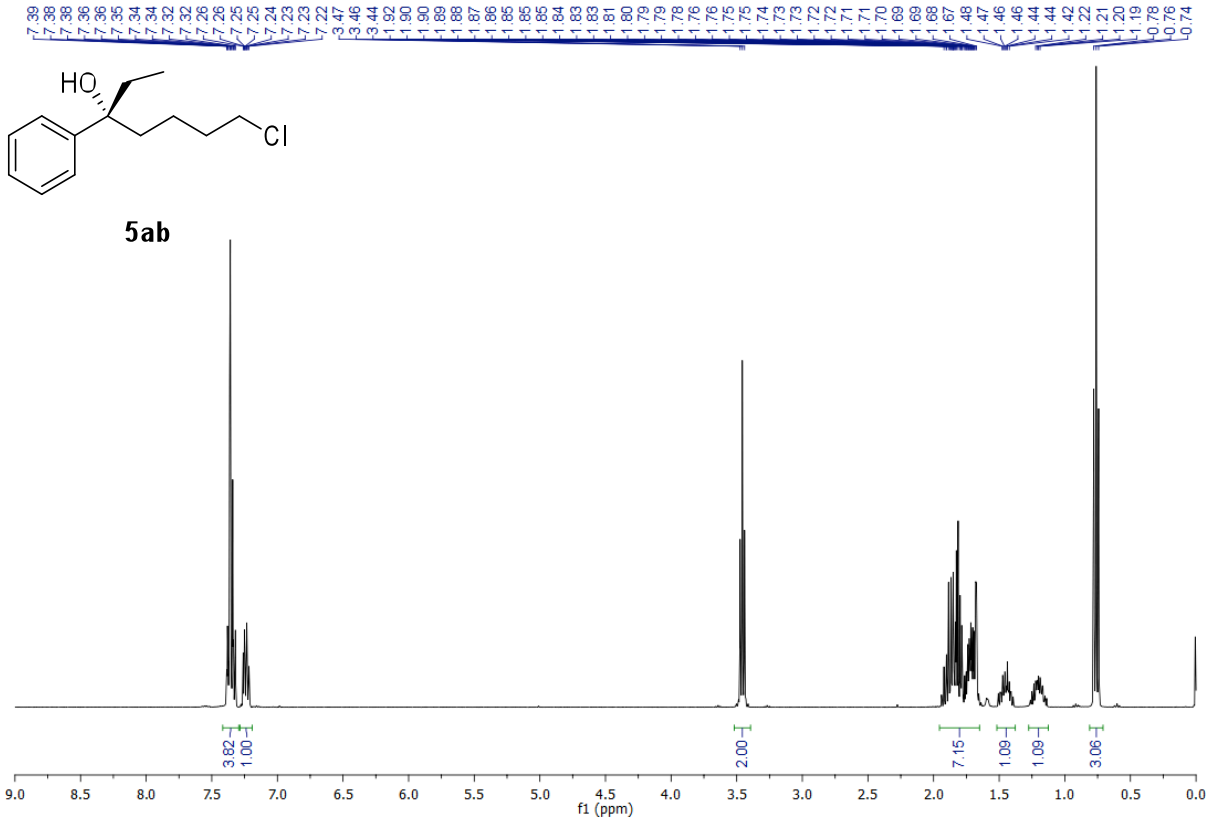


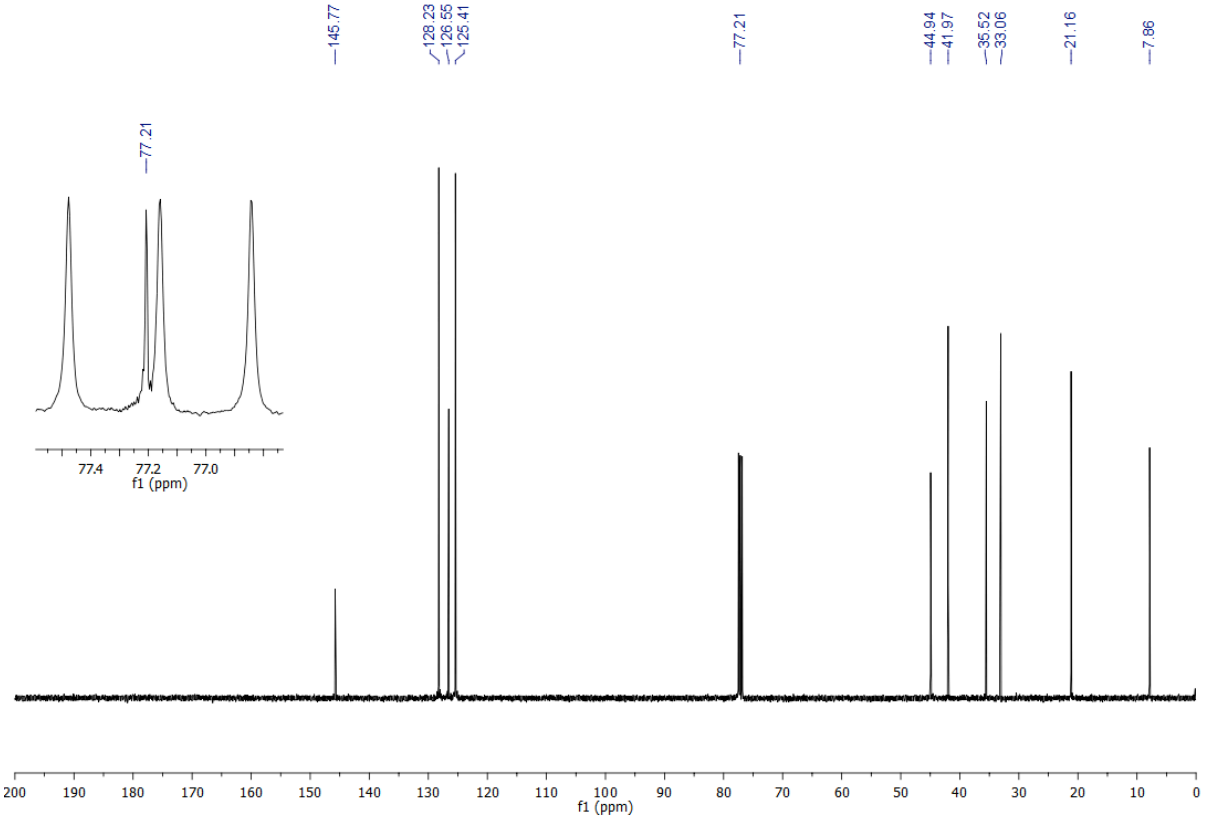
(*R*)-6-chloro-2-phenylhexan-2-ol 5aa



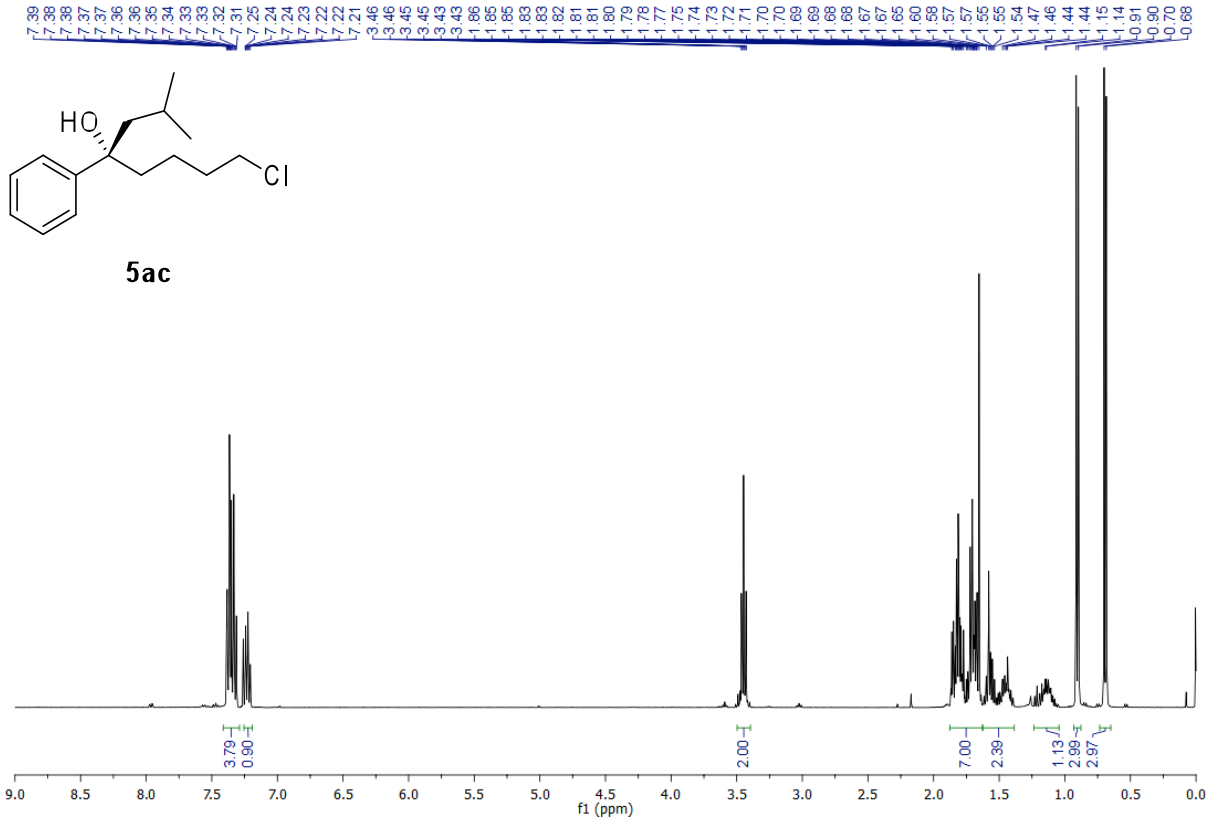


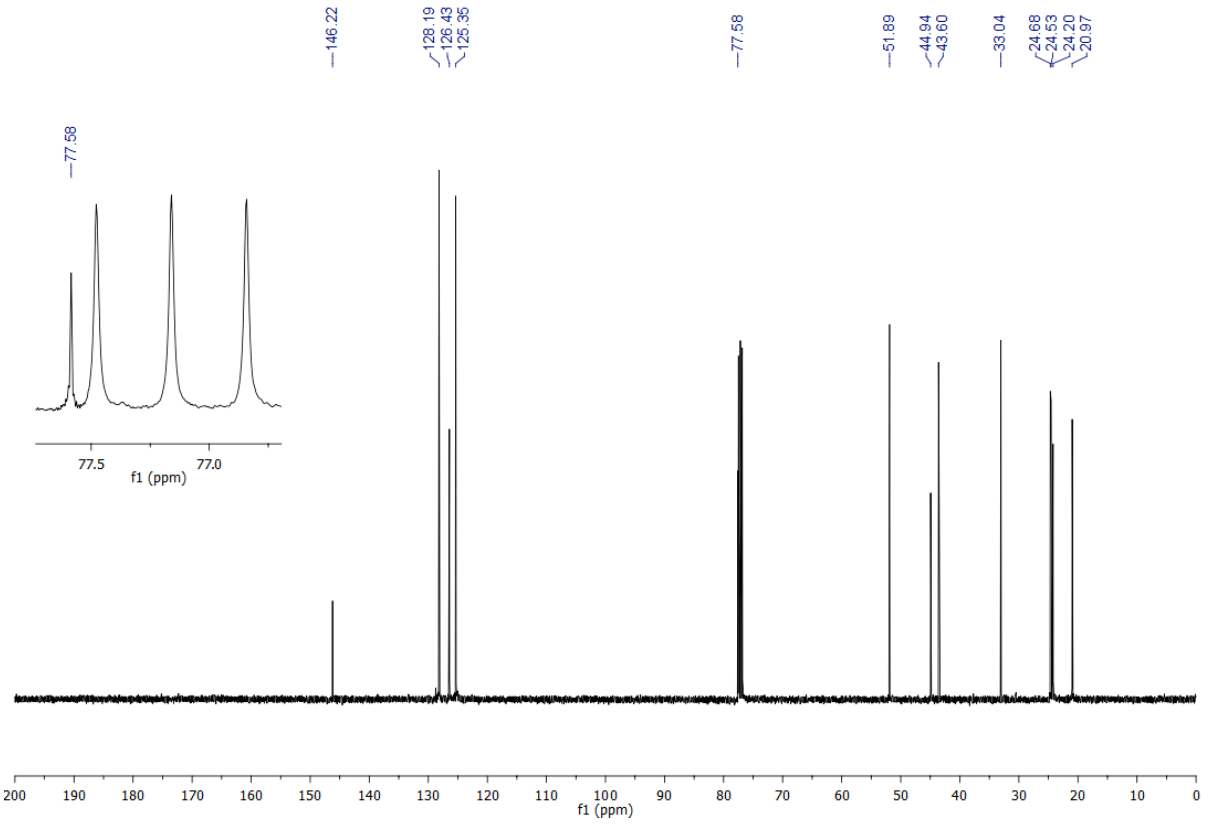
7-chloro-3-phenylheptan-3-ol 5ab



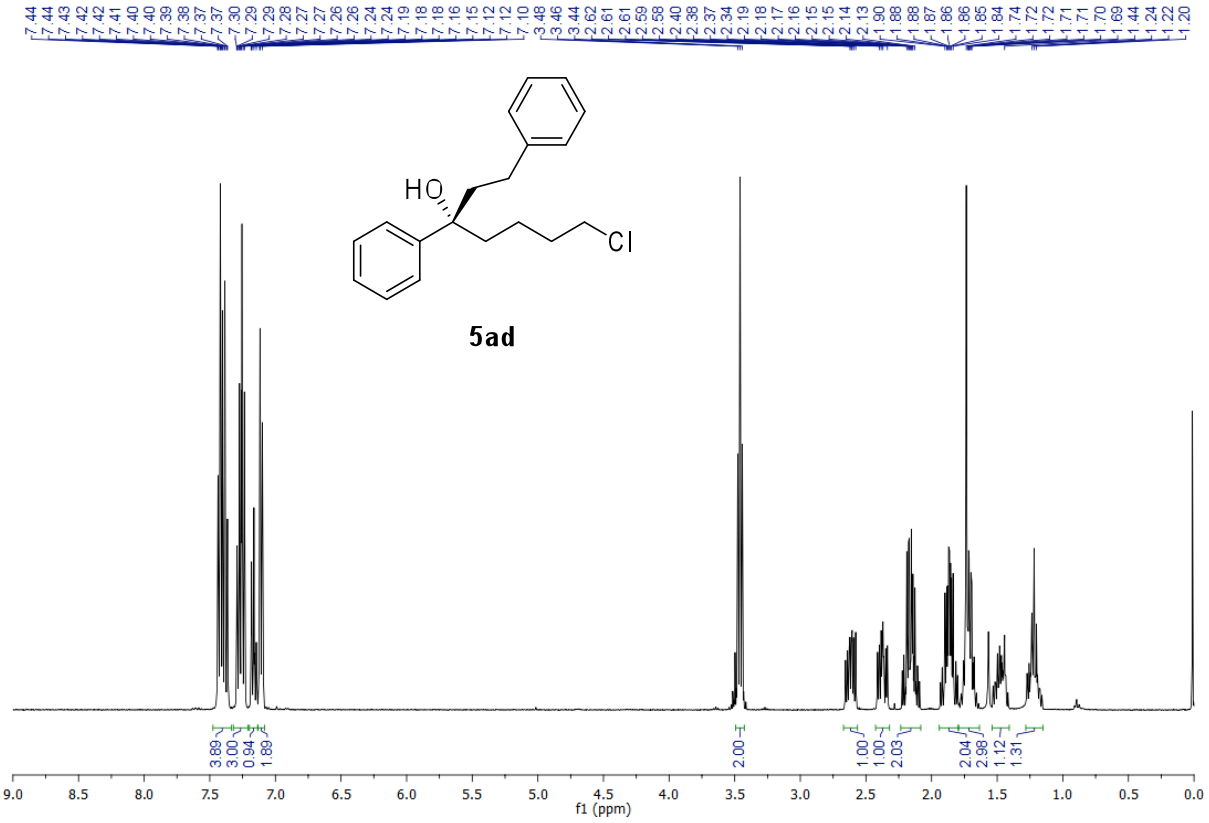


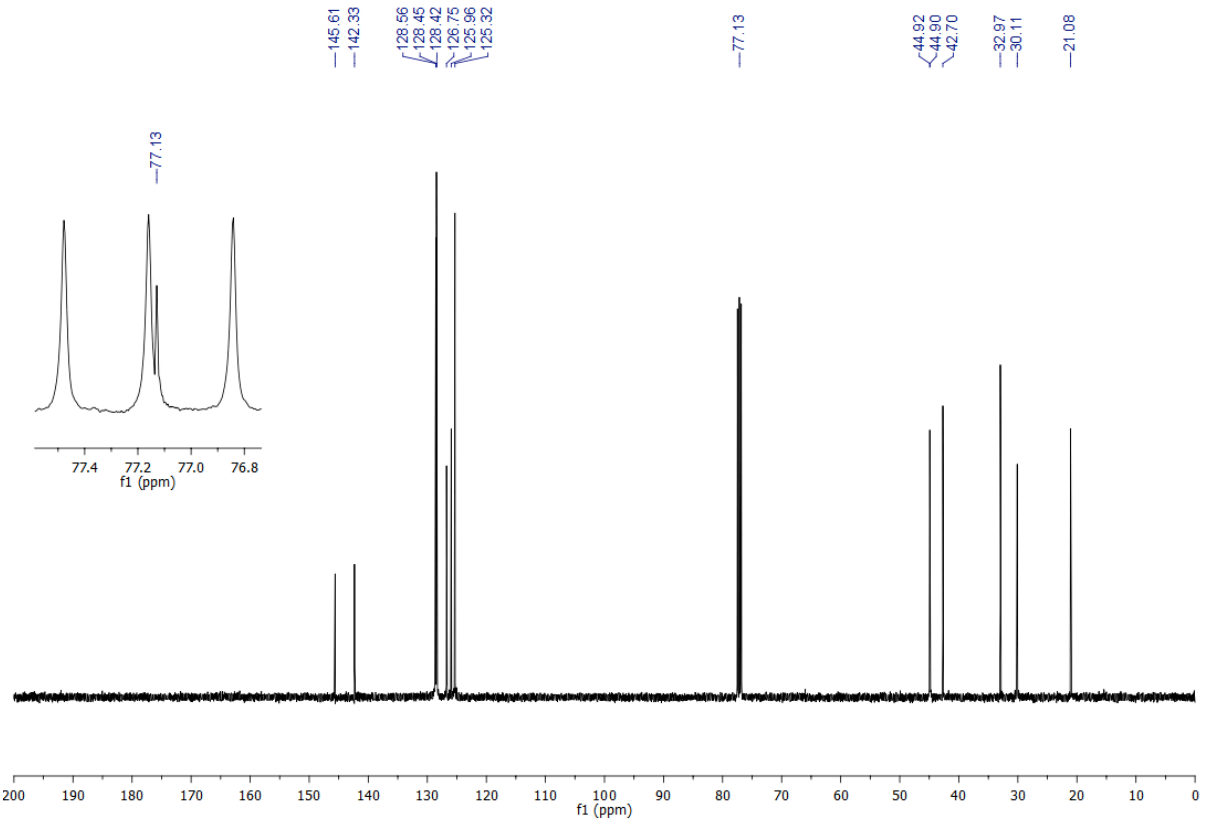
8-chloro-2-methyl-4-phenyloctan-4-ol 5ac



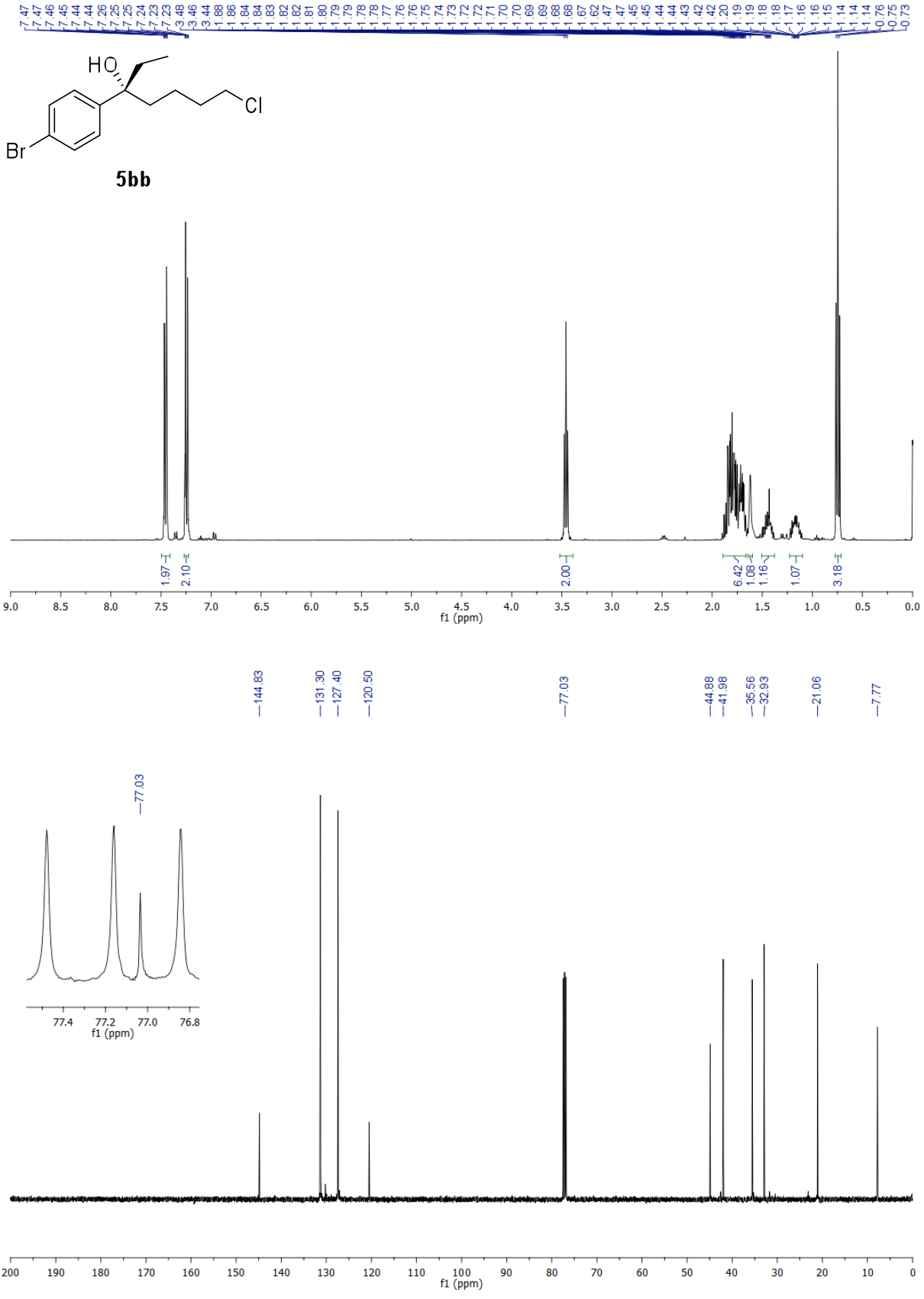


7-chloro-1,3-diphenylheptan-3-ol 5ad

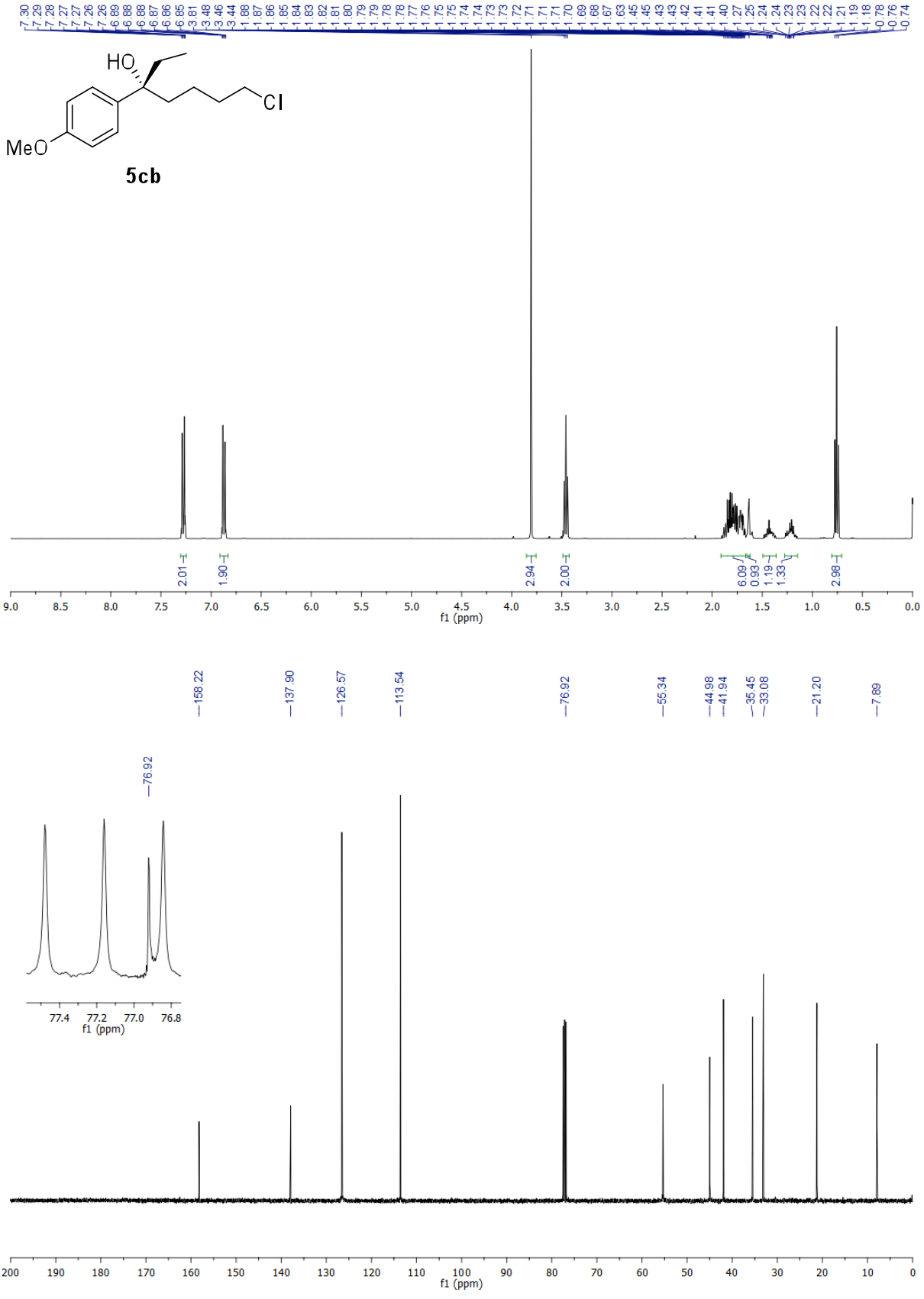




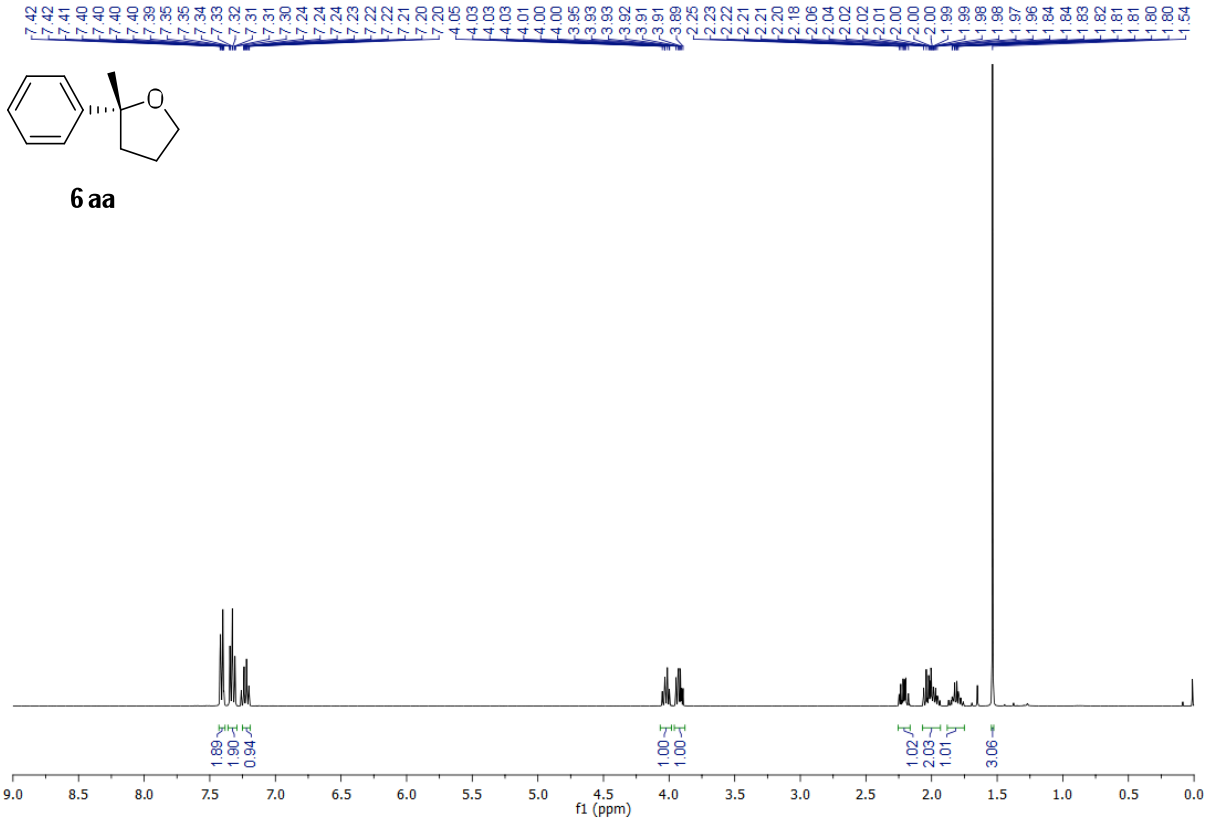
3-(4-bromophenyl)-7-chloroheptan-3-ol 5bb



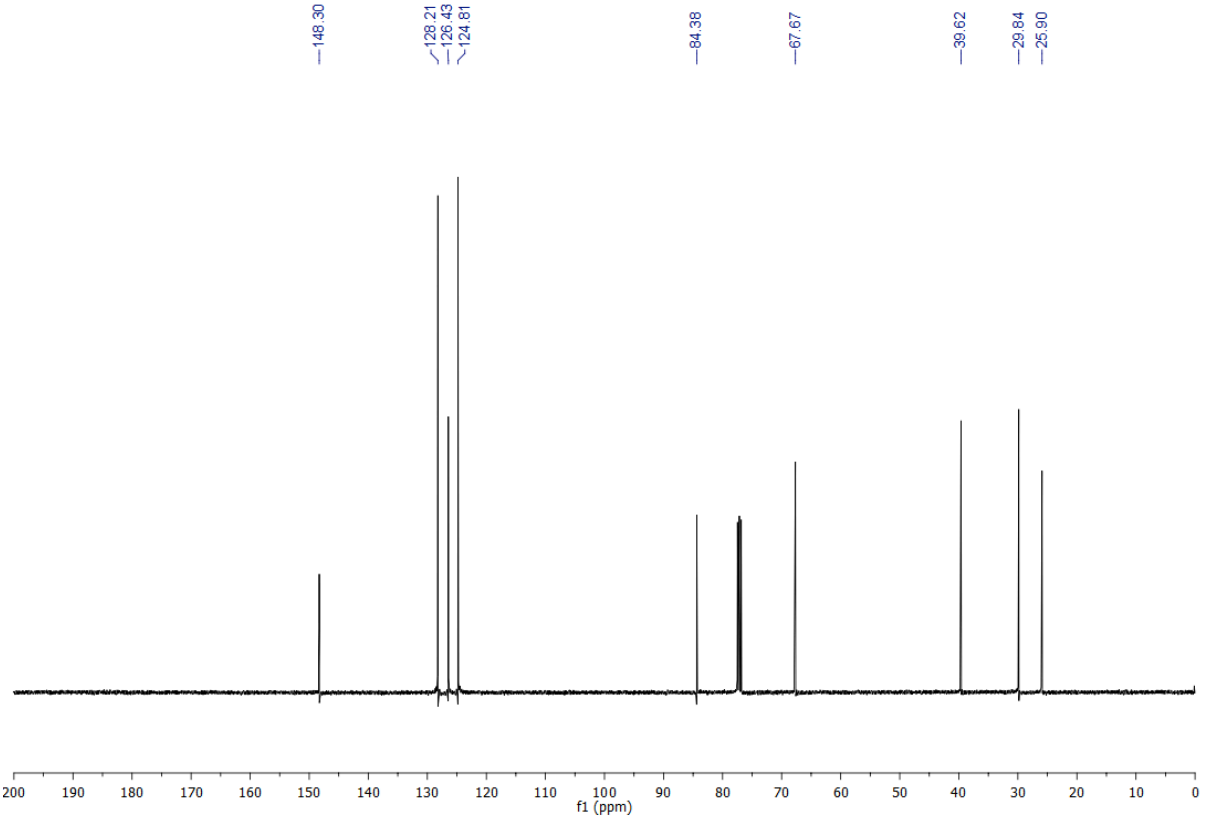
7-chloro-3-(4-methoxyphenyl)heptan-3-ol 5cb



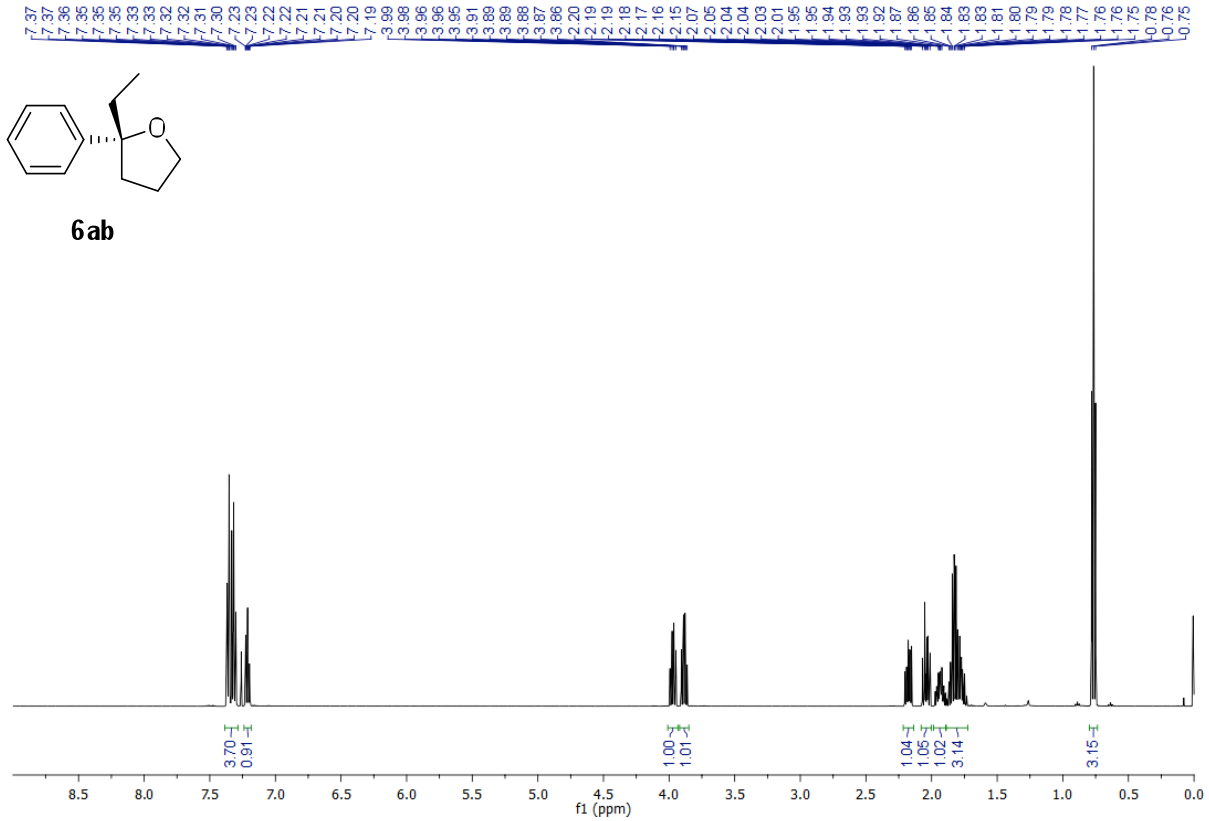
(*R*)-2-methyl-2-phenyltetrahydrofuran 6aa



6 aa



(*R*)-2-ethyl-2-phenyltetrahydrofuran 6ab



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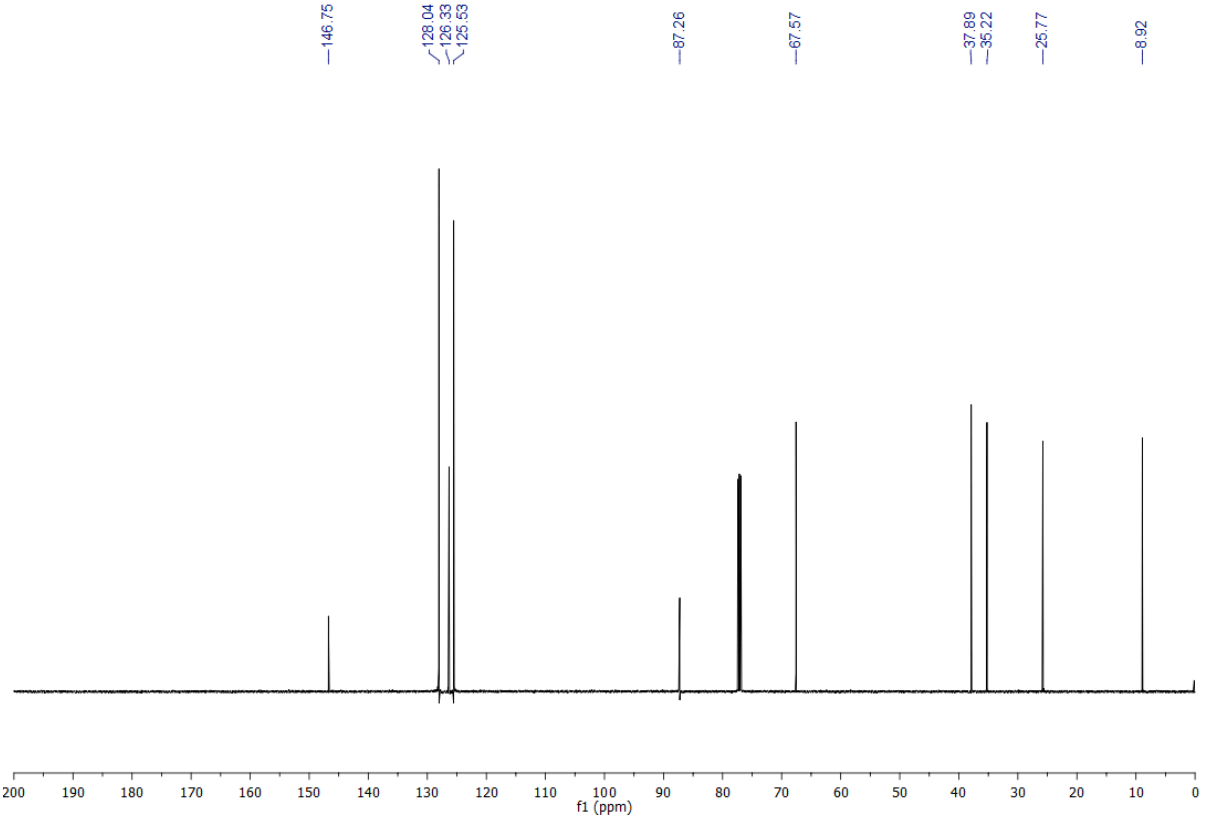
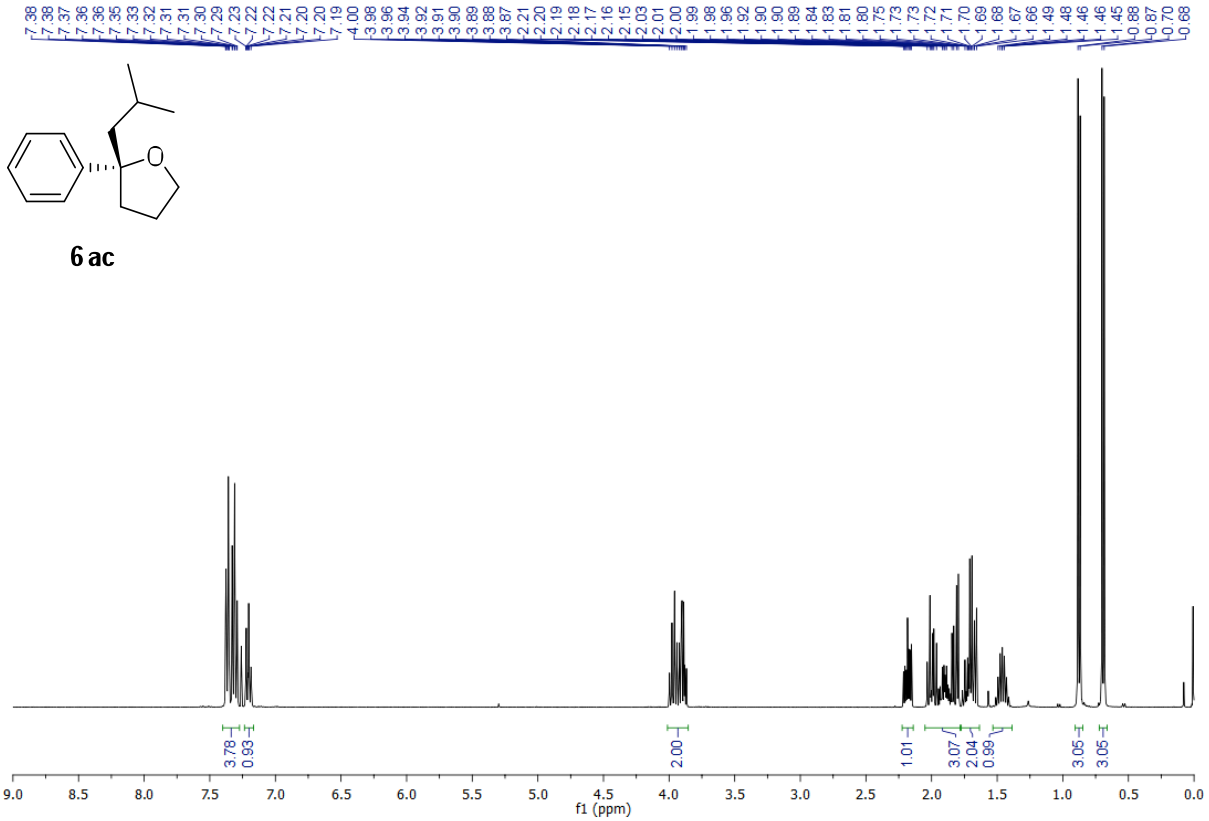


2-isobutyl-2-phenyltetrahydrofuran 6ac



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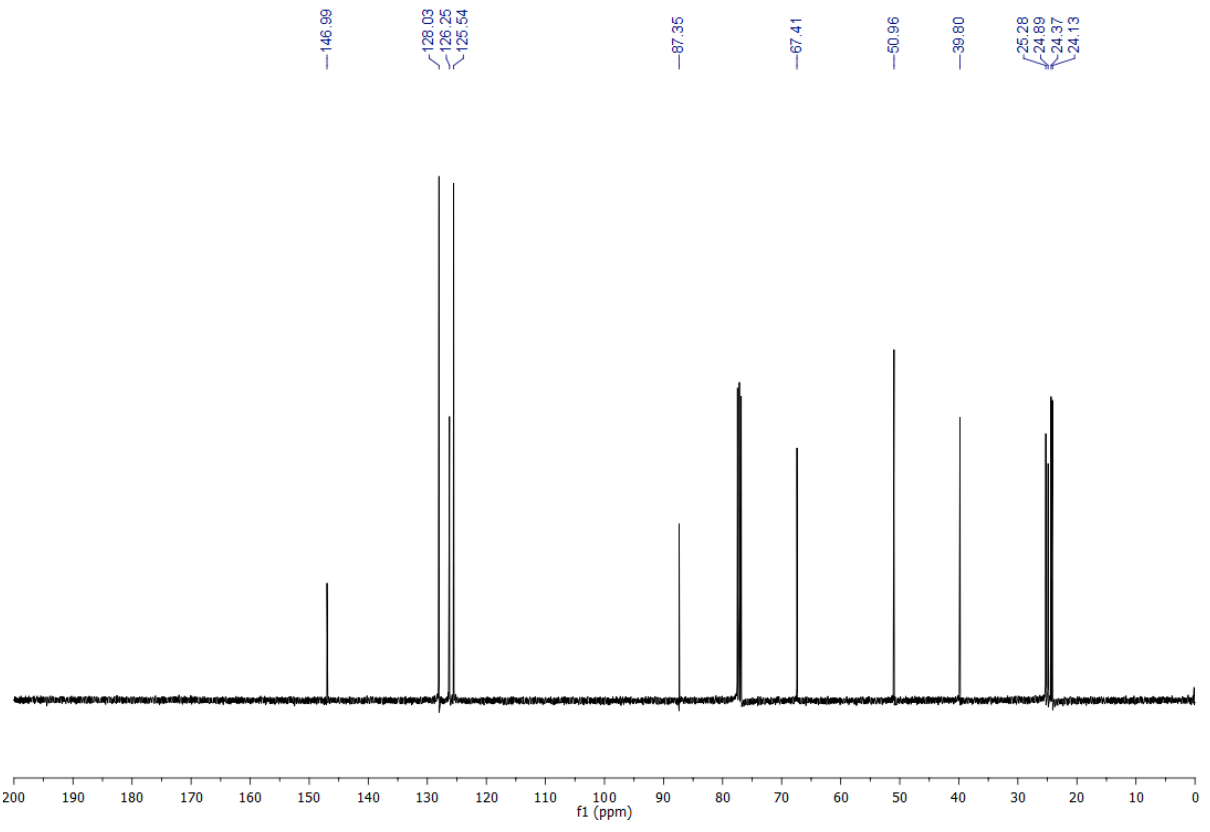
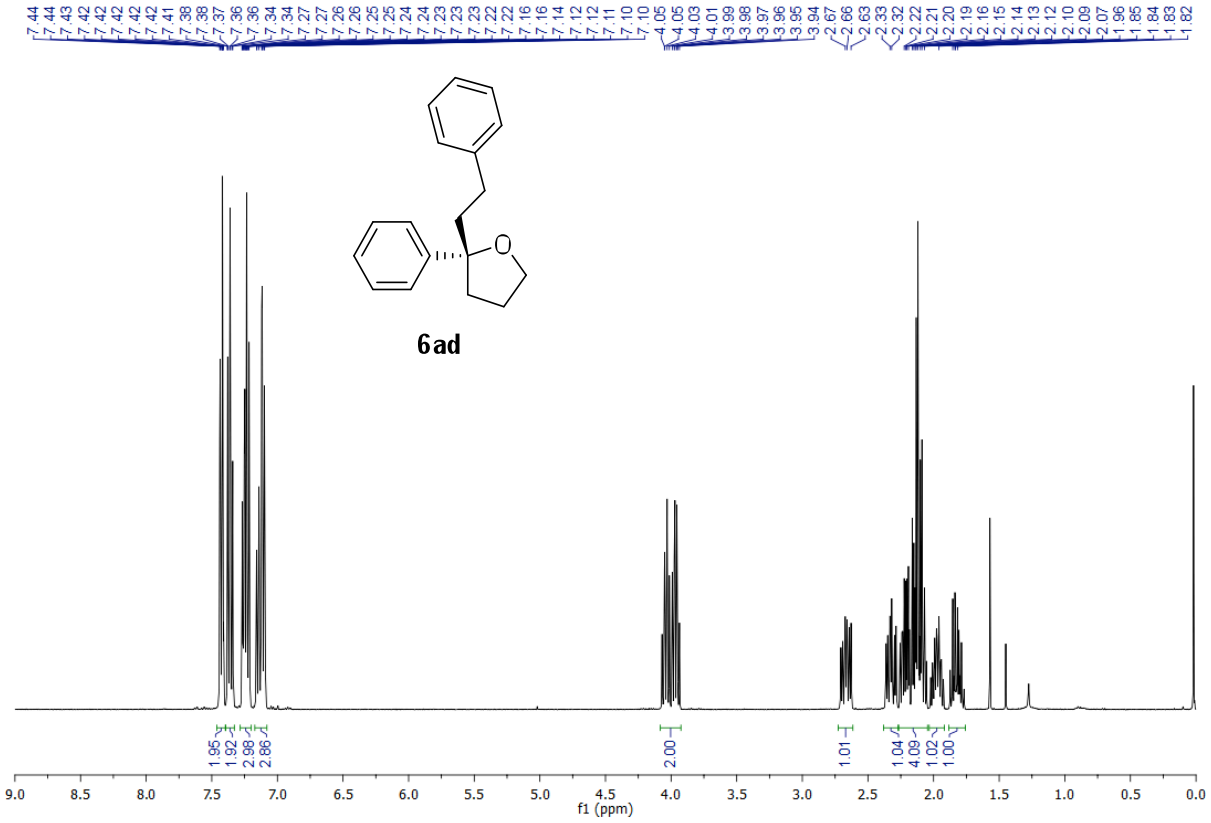
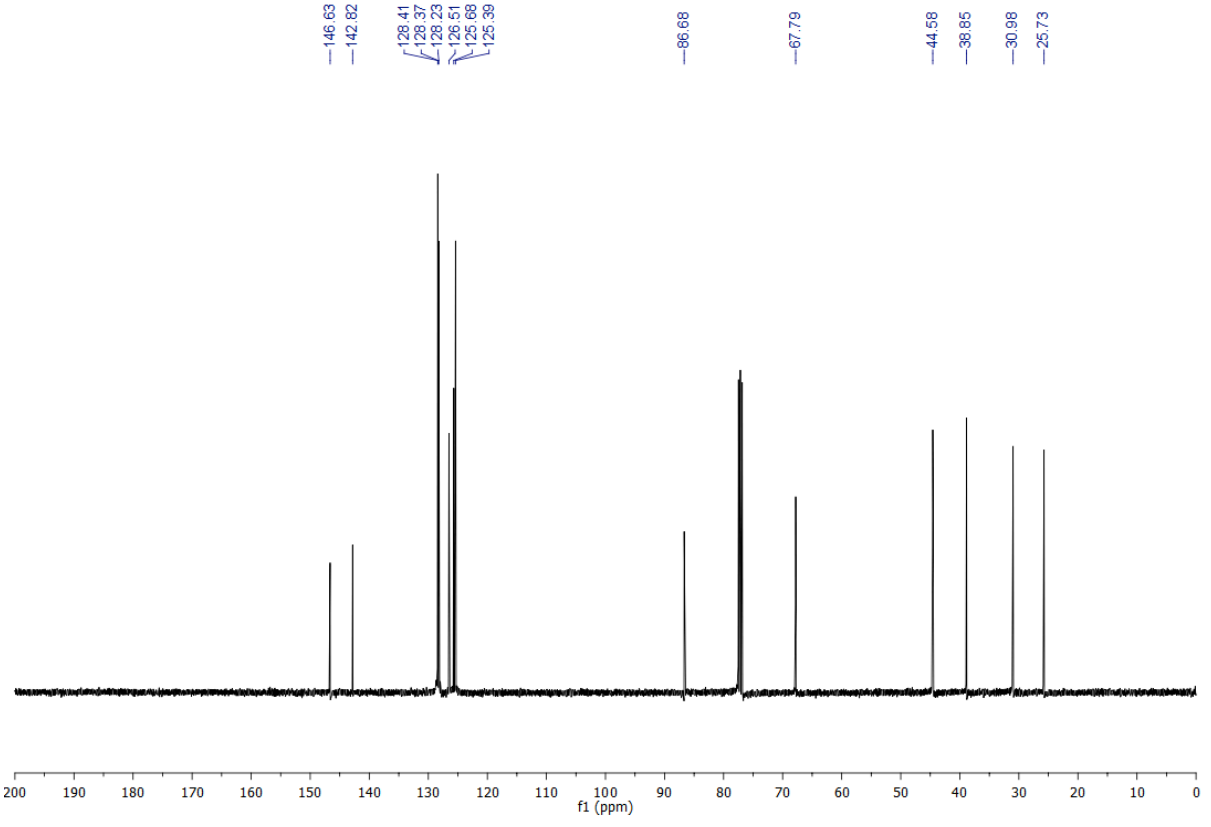
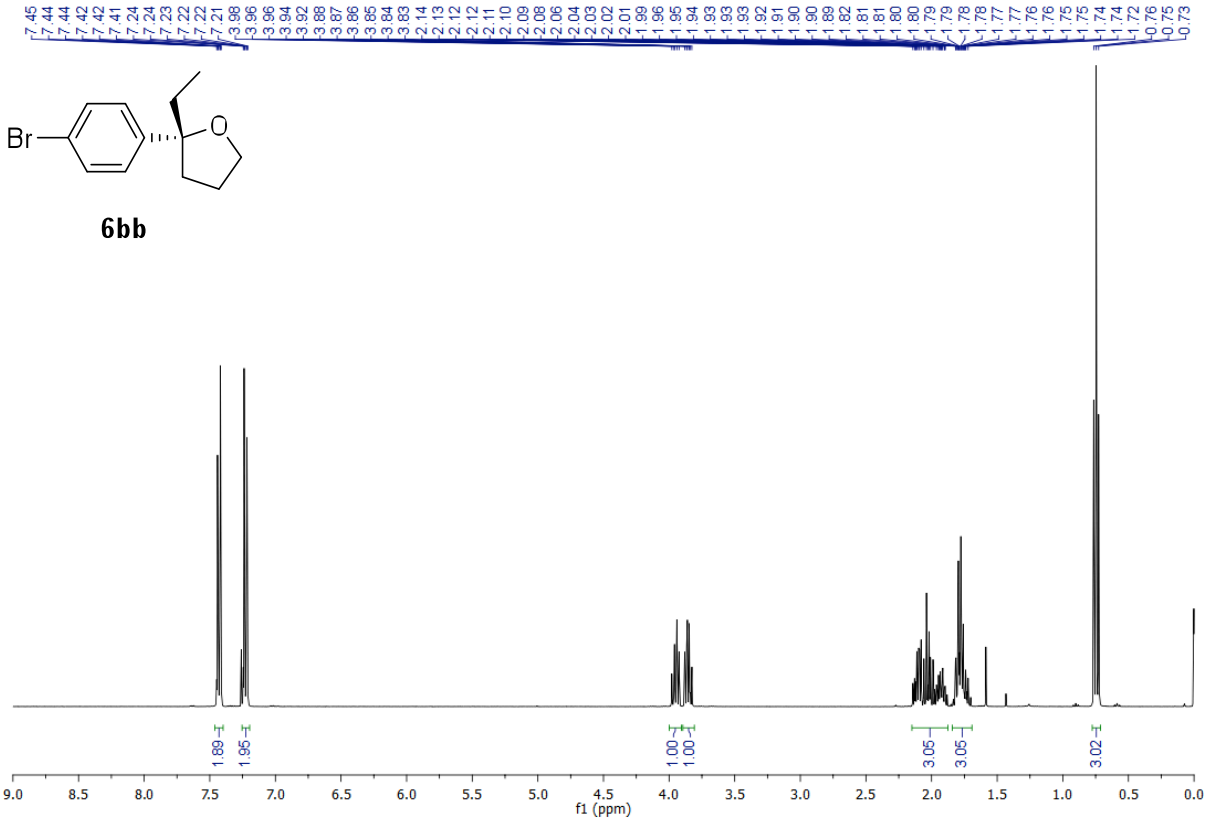


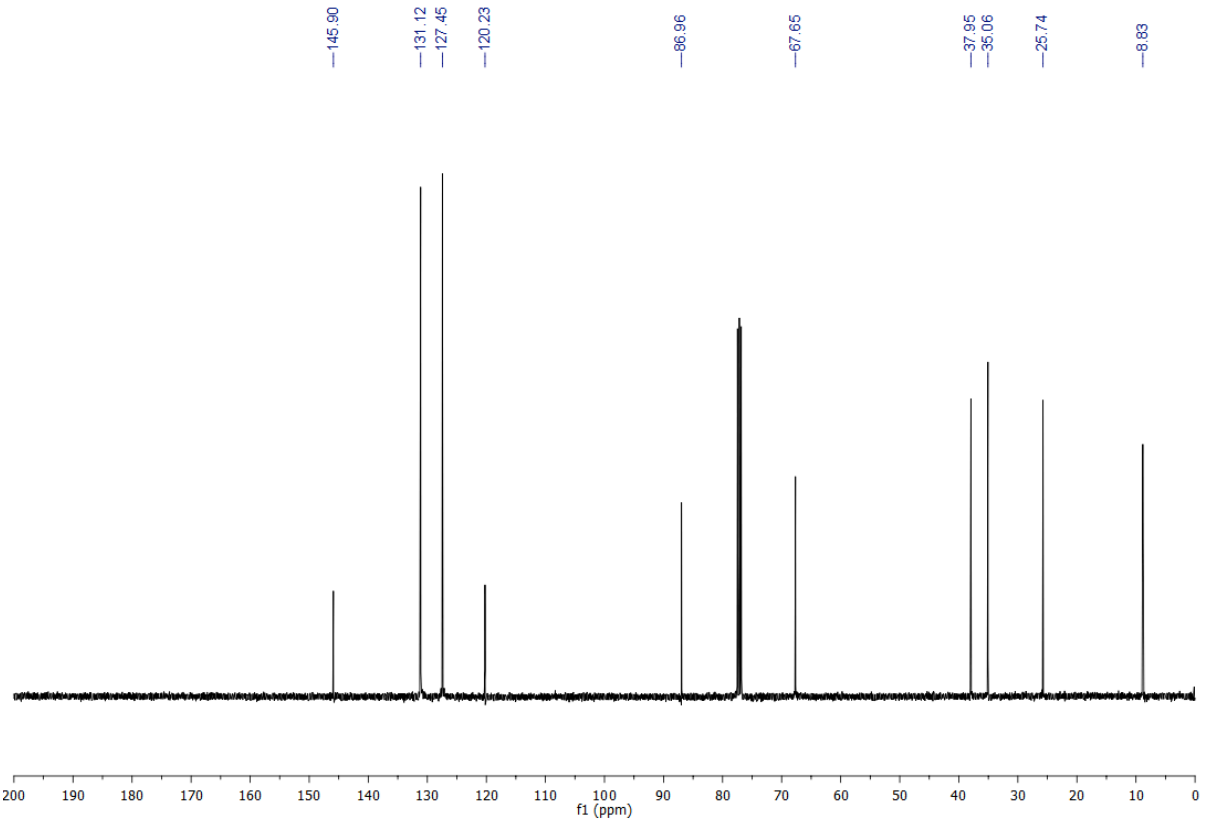
2-phenethyl-2-phenyltetrahydrofuran 6ad



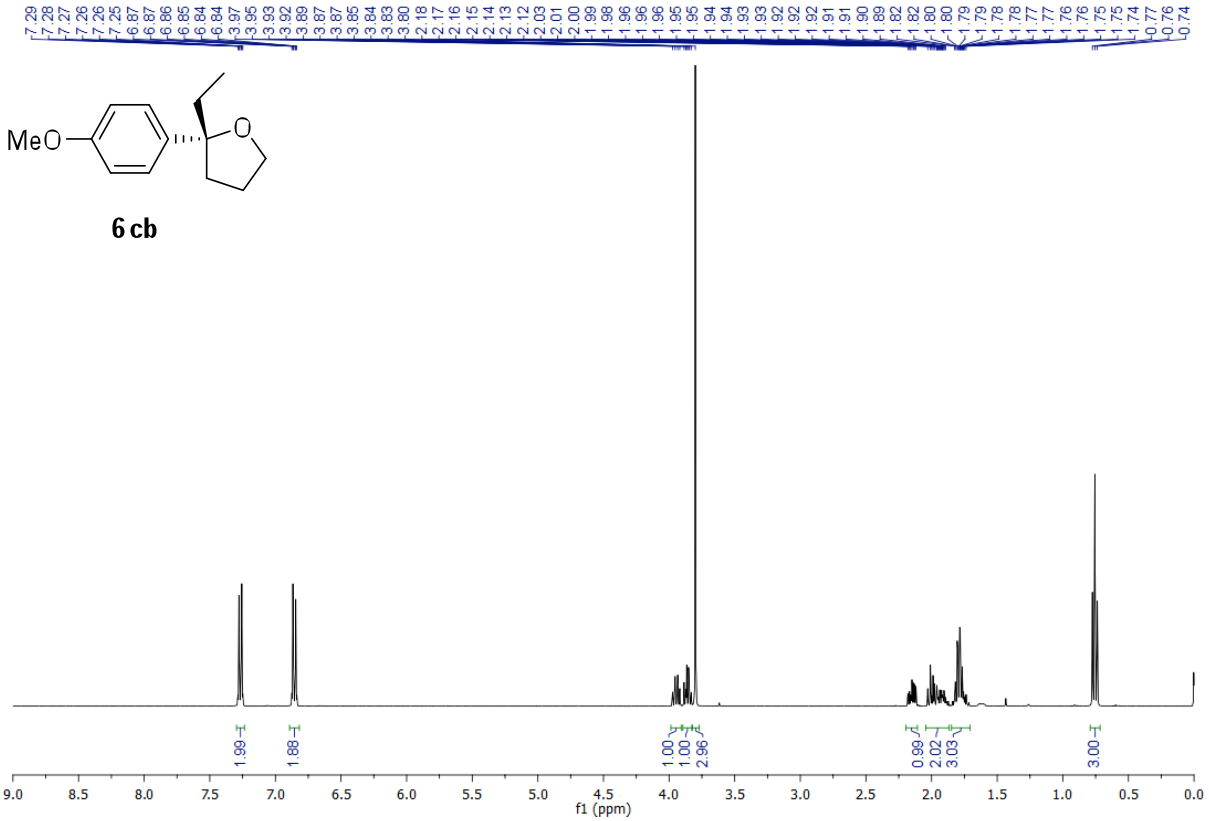


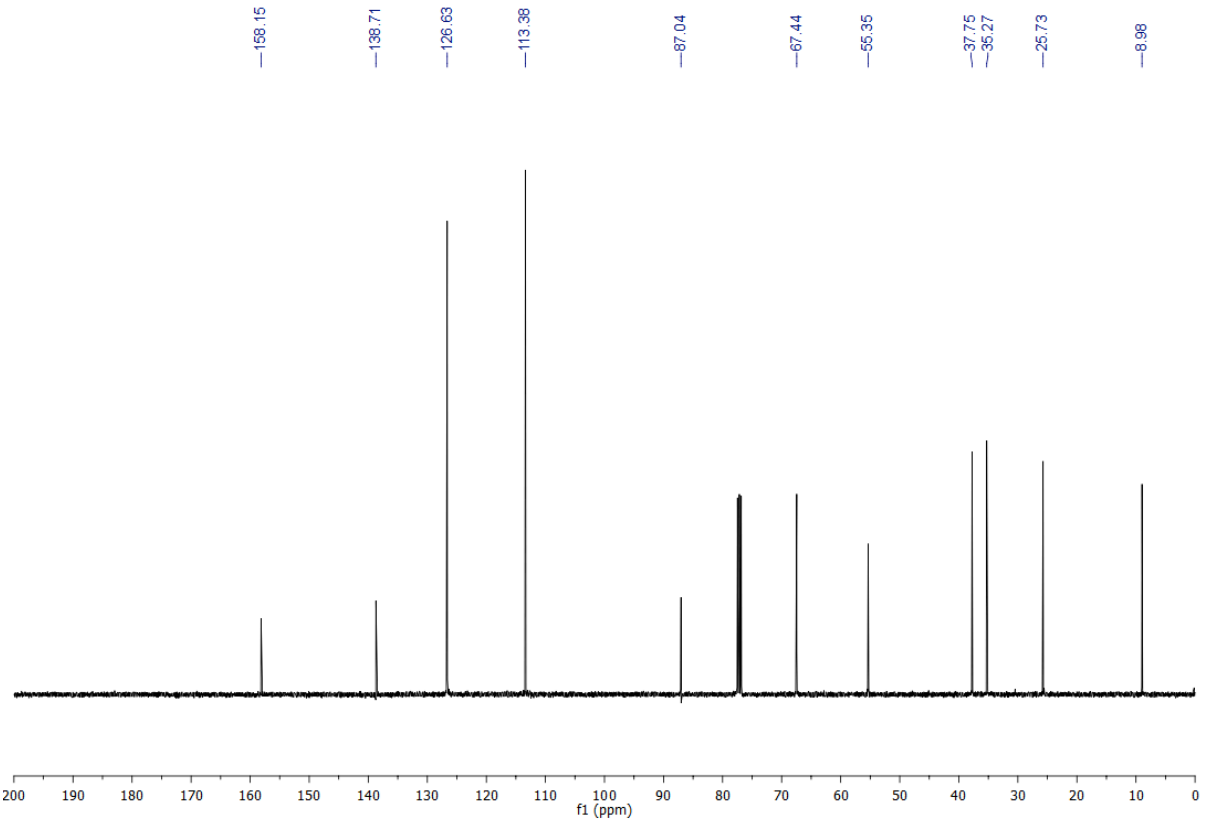
2-ethyl-2-(4-bromophenyl)tetrahydrofuran 6bb



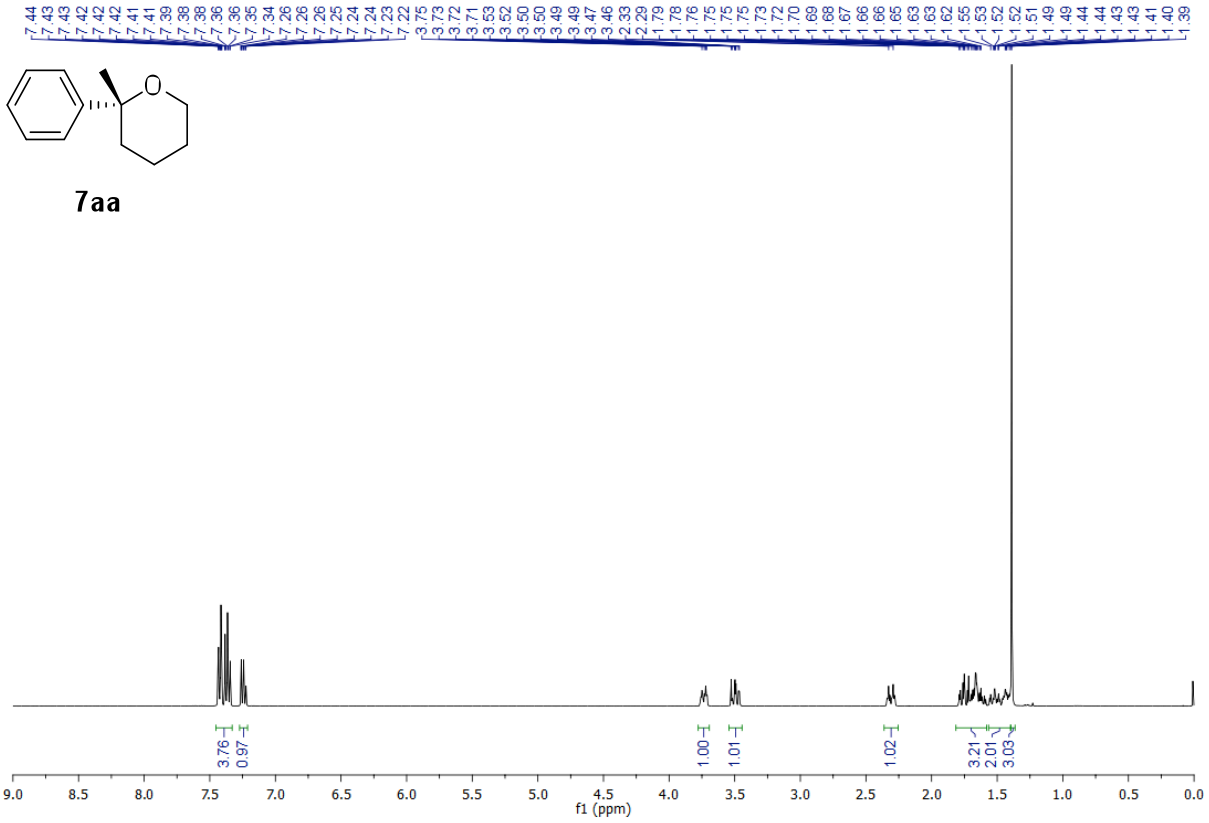


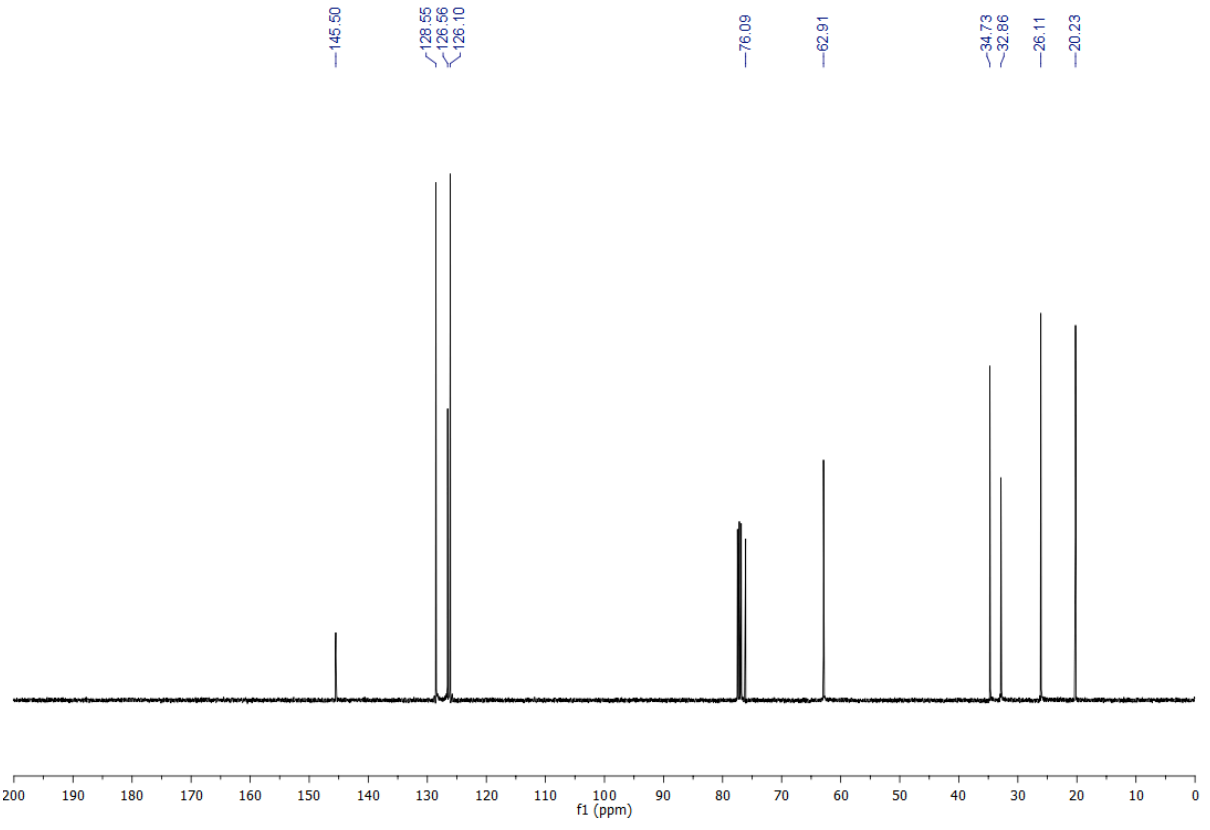
2-ethyl-2-(4-methoxyphenyl)tetrahydrofuran 6cb



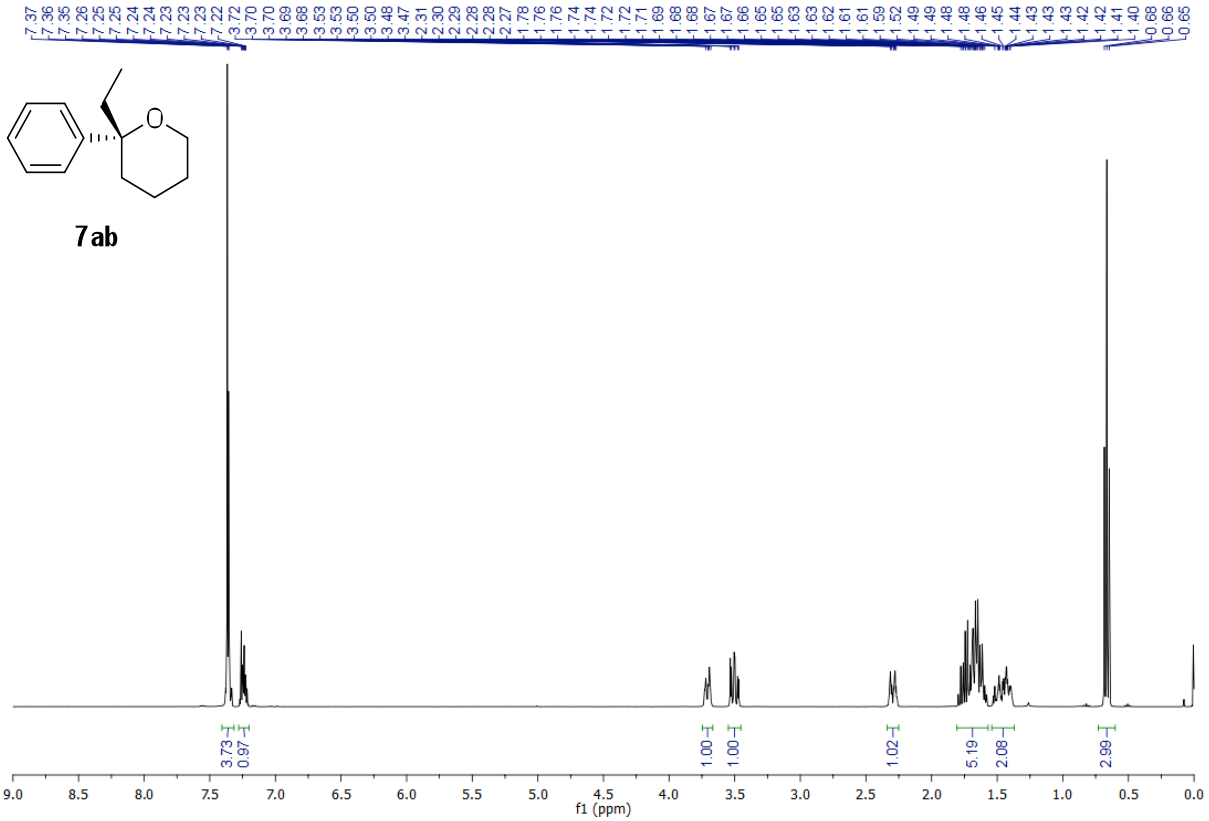


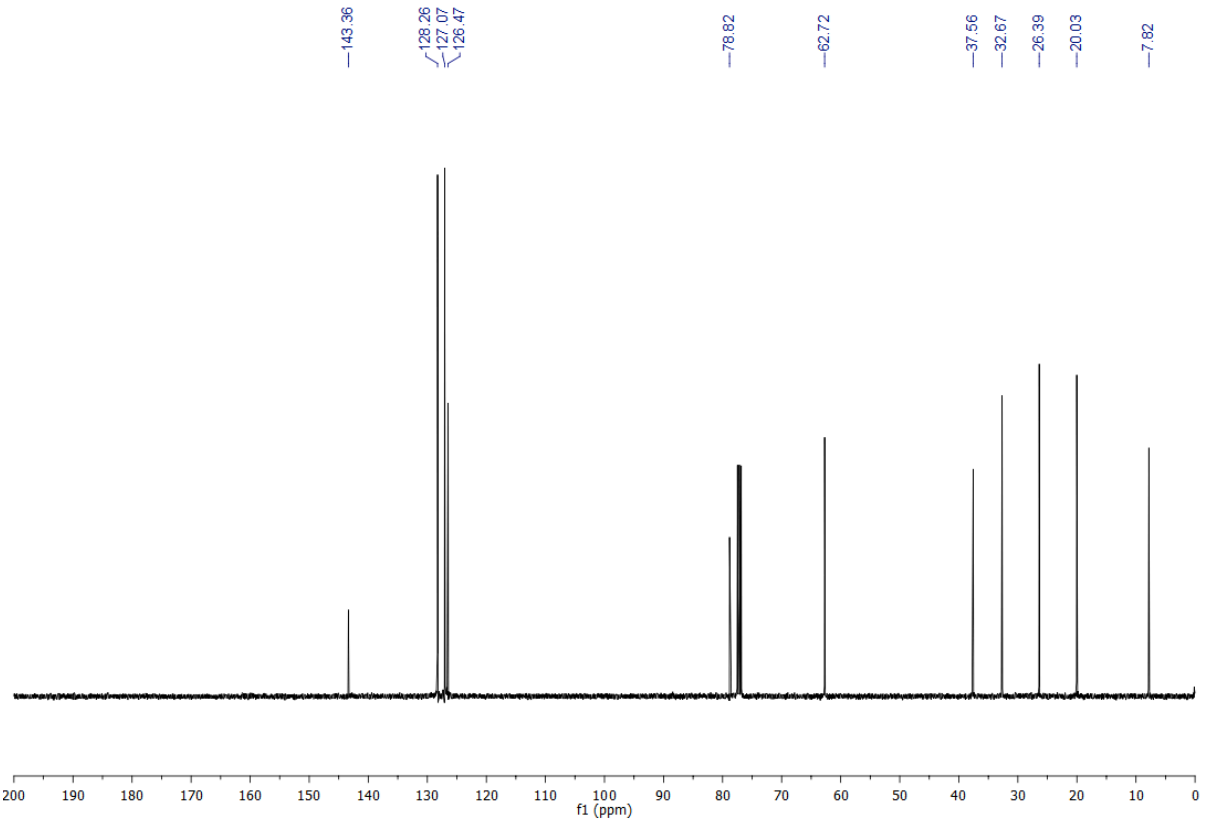
(*R*)-2-methyl-2-phenyltetrahydro-2*H*-pyran 7aa



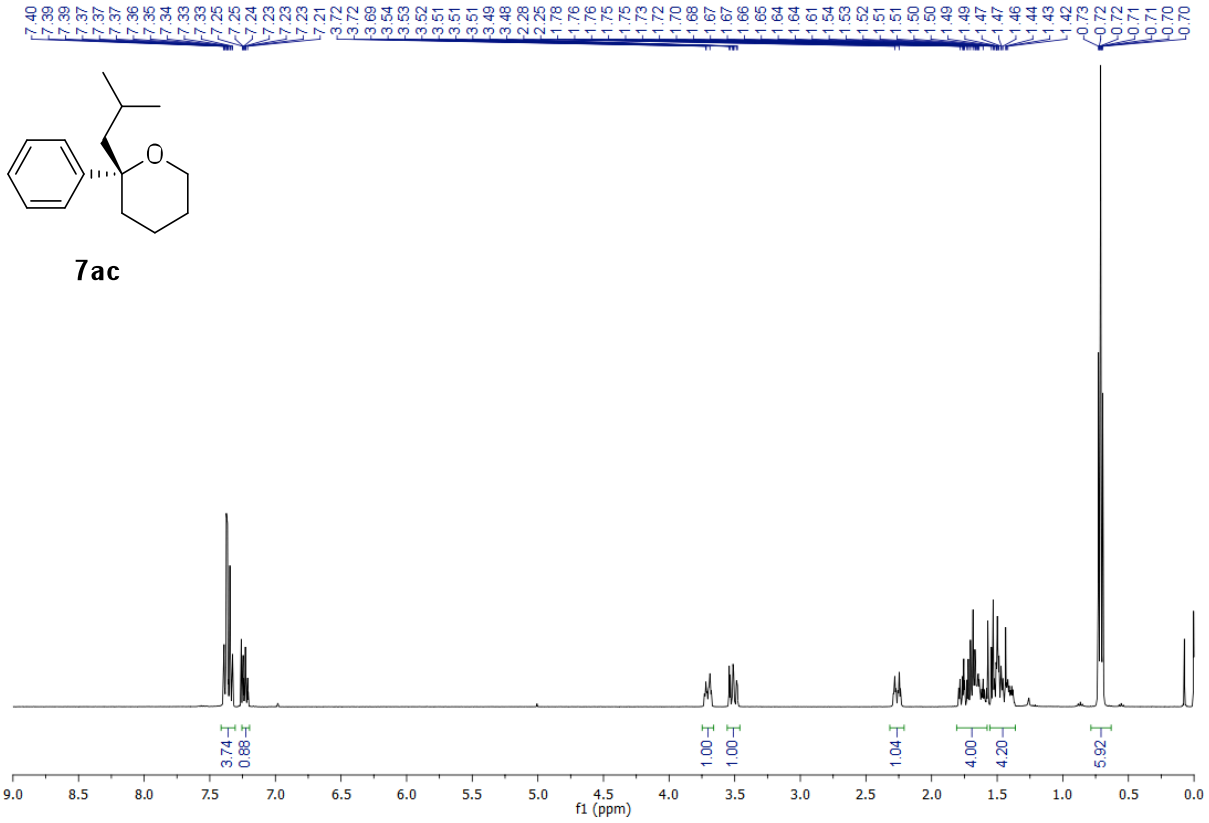


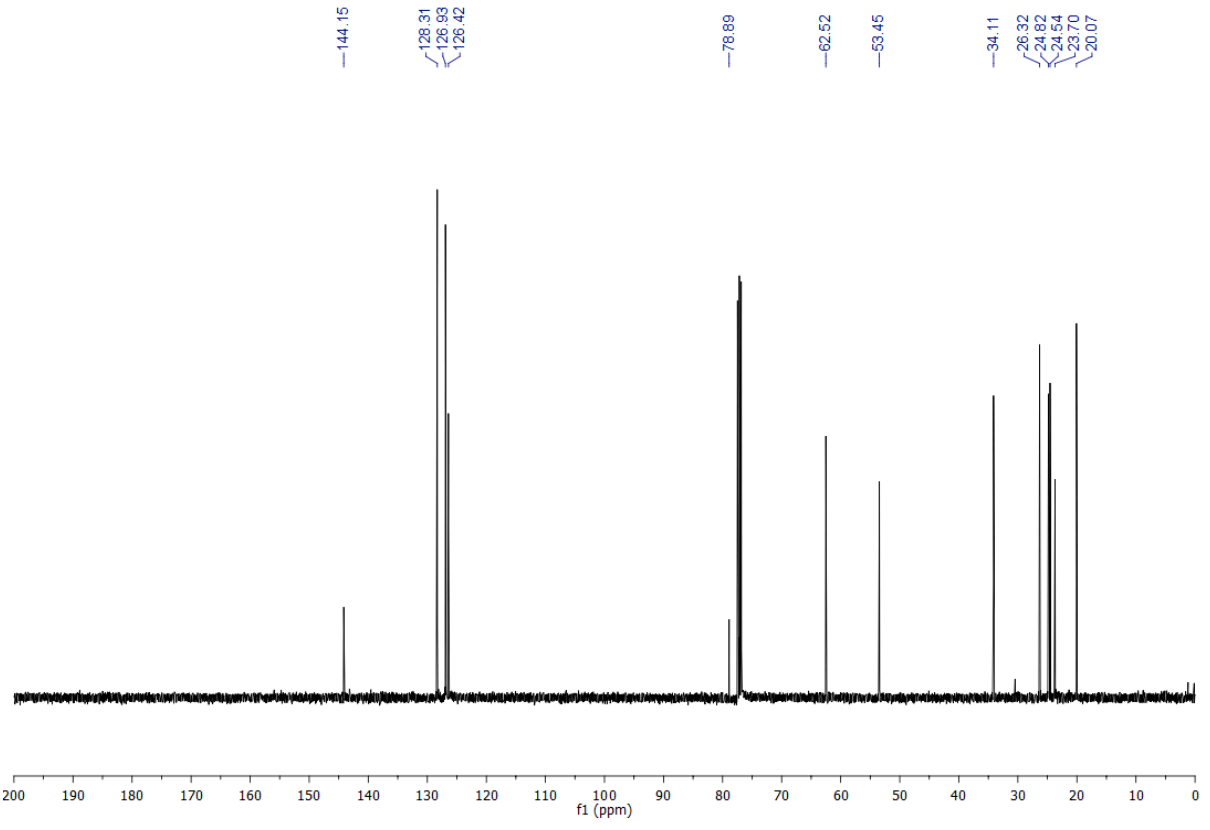
2-ethyl-2-phenyltetrahydro-2*H*-pyran 7ab



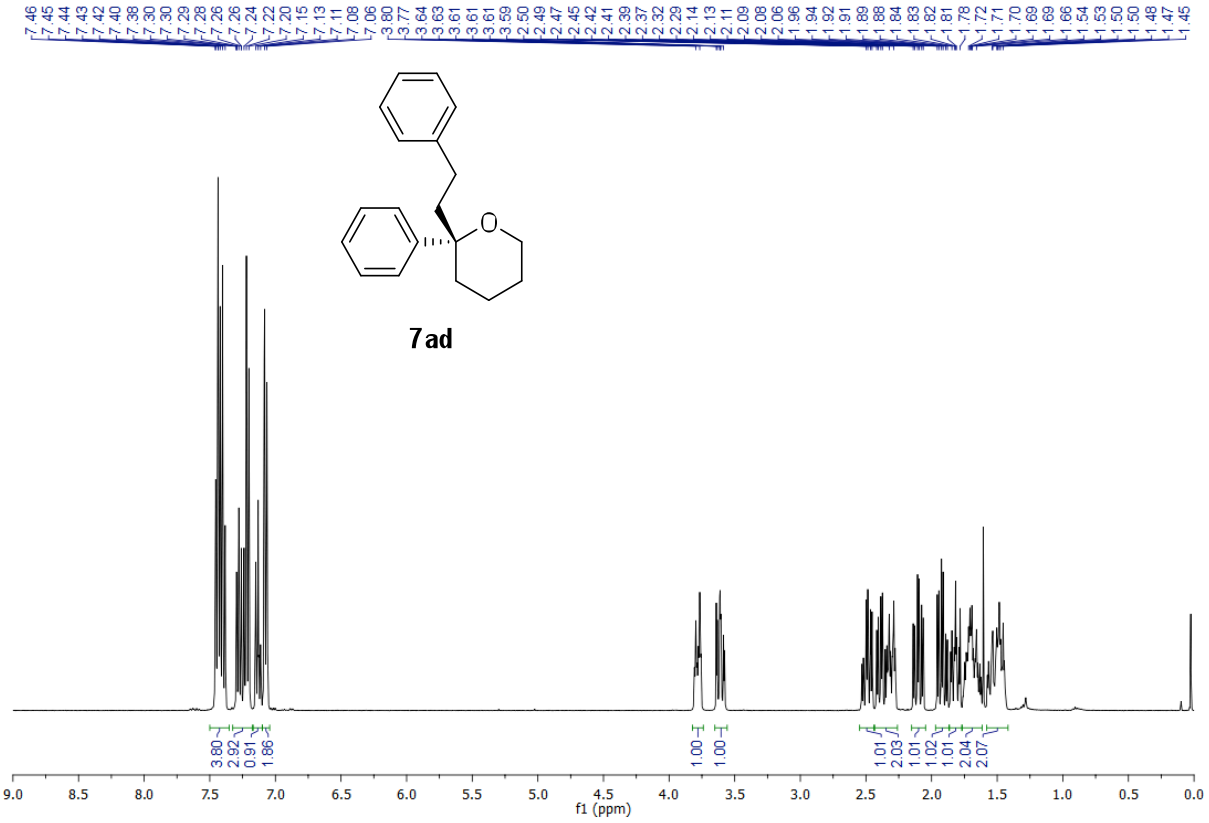


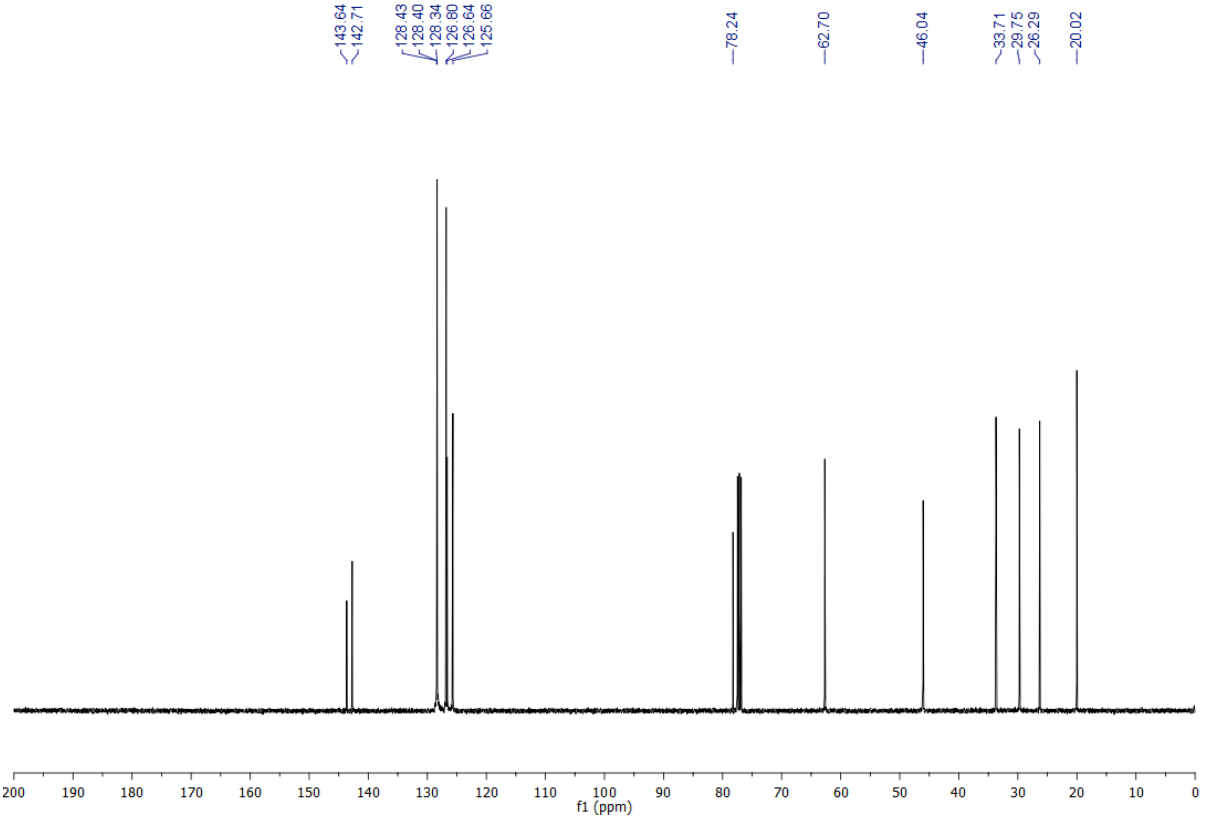
2-isobutyl-2-phenyltetrahydro-2*H*-pyran 7ac





2-phenethyl-2-phenyltetrahydro-2*H*-pyran 7ad





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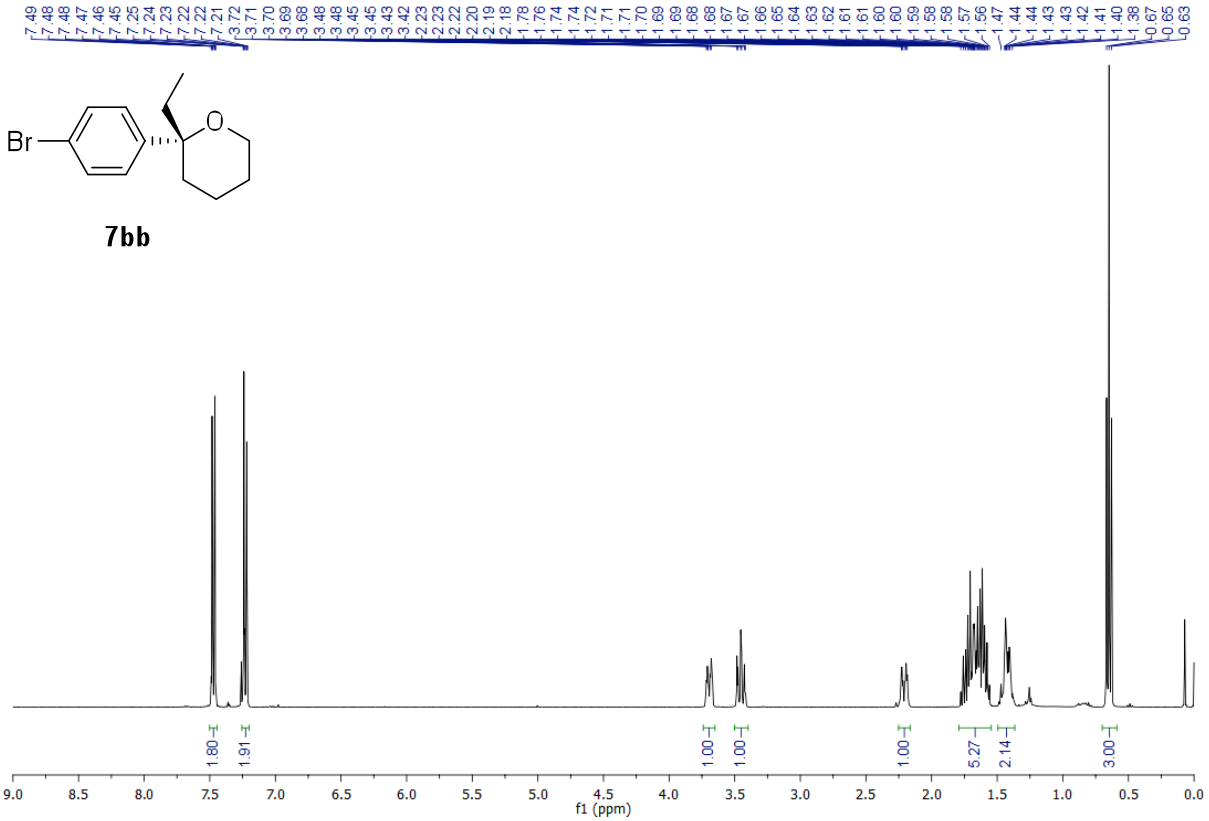
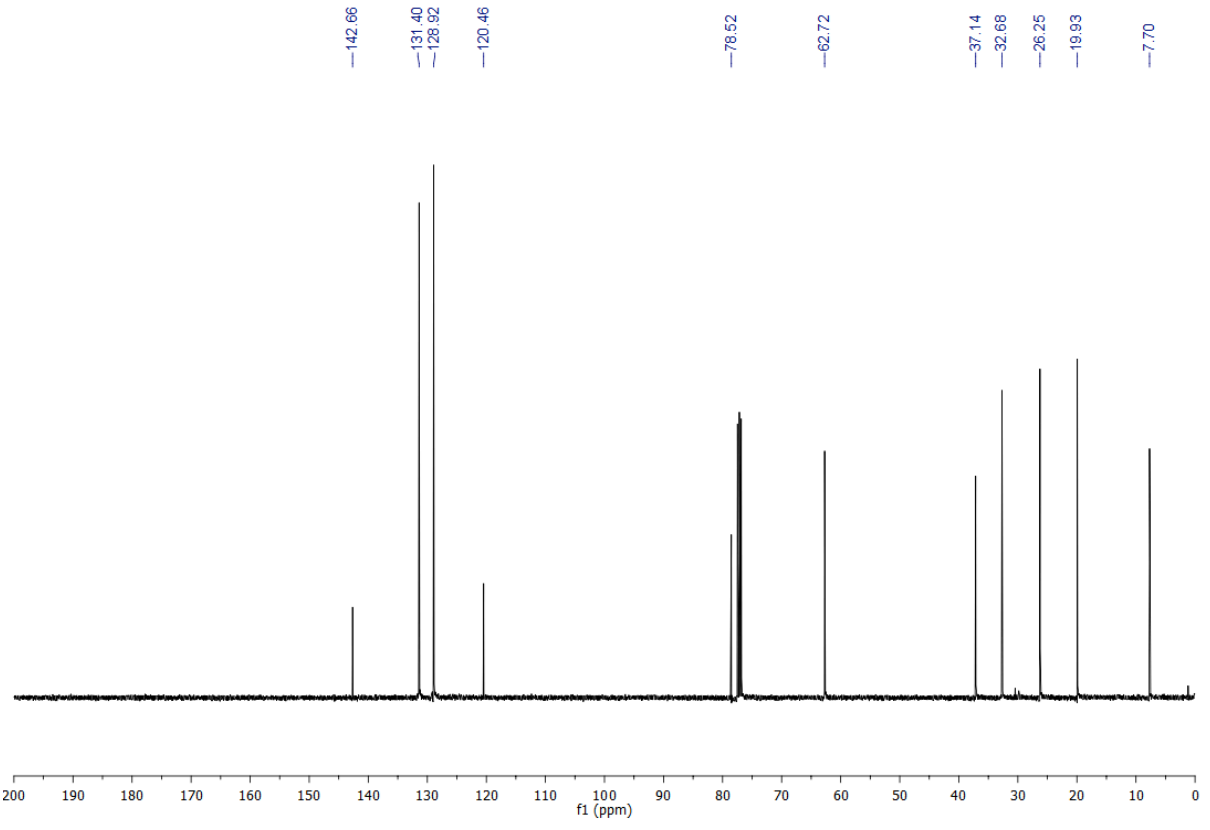
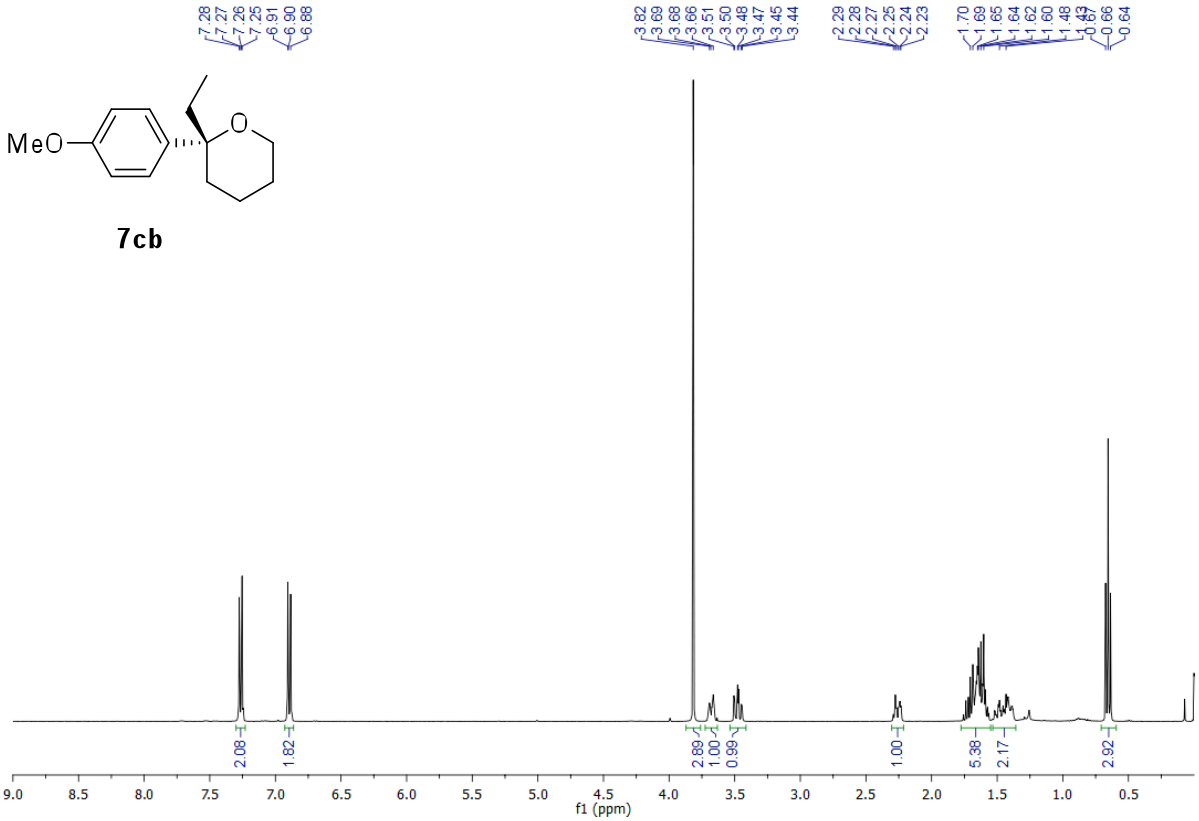
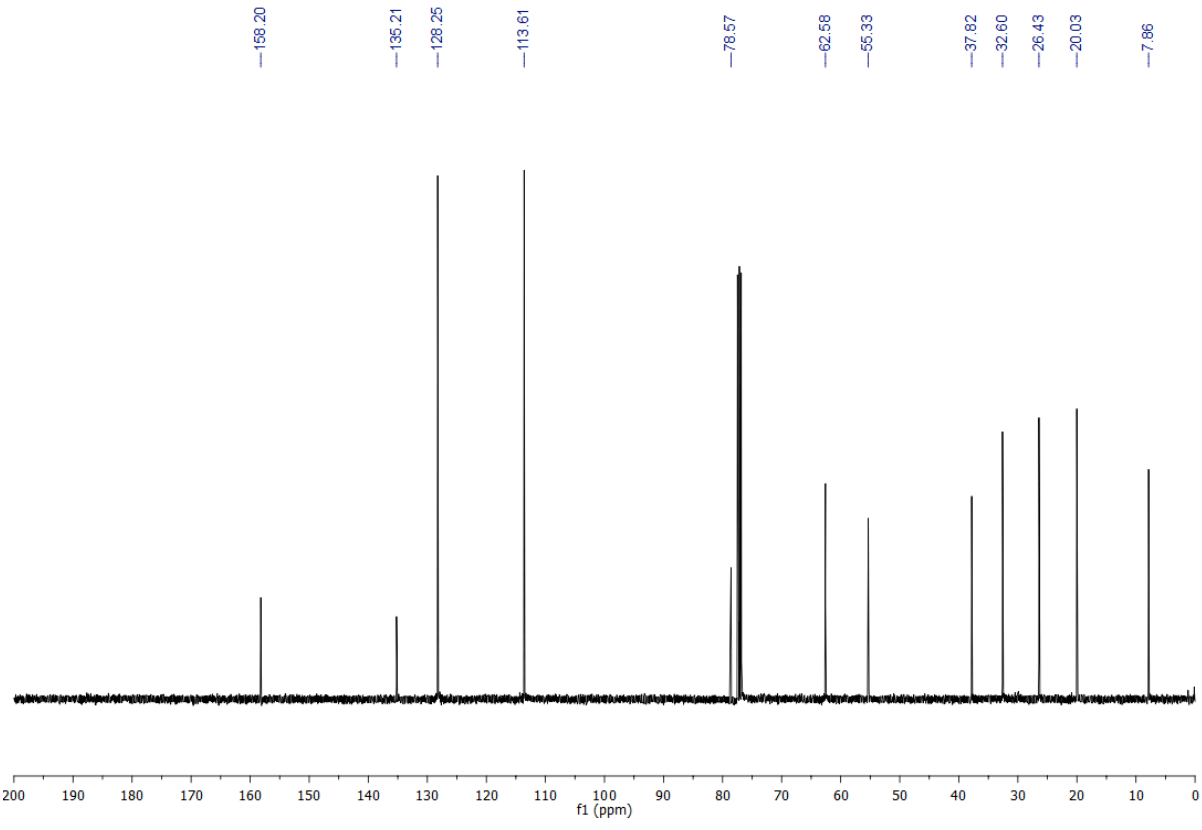


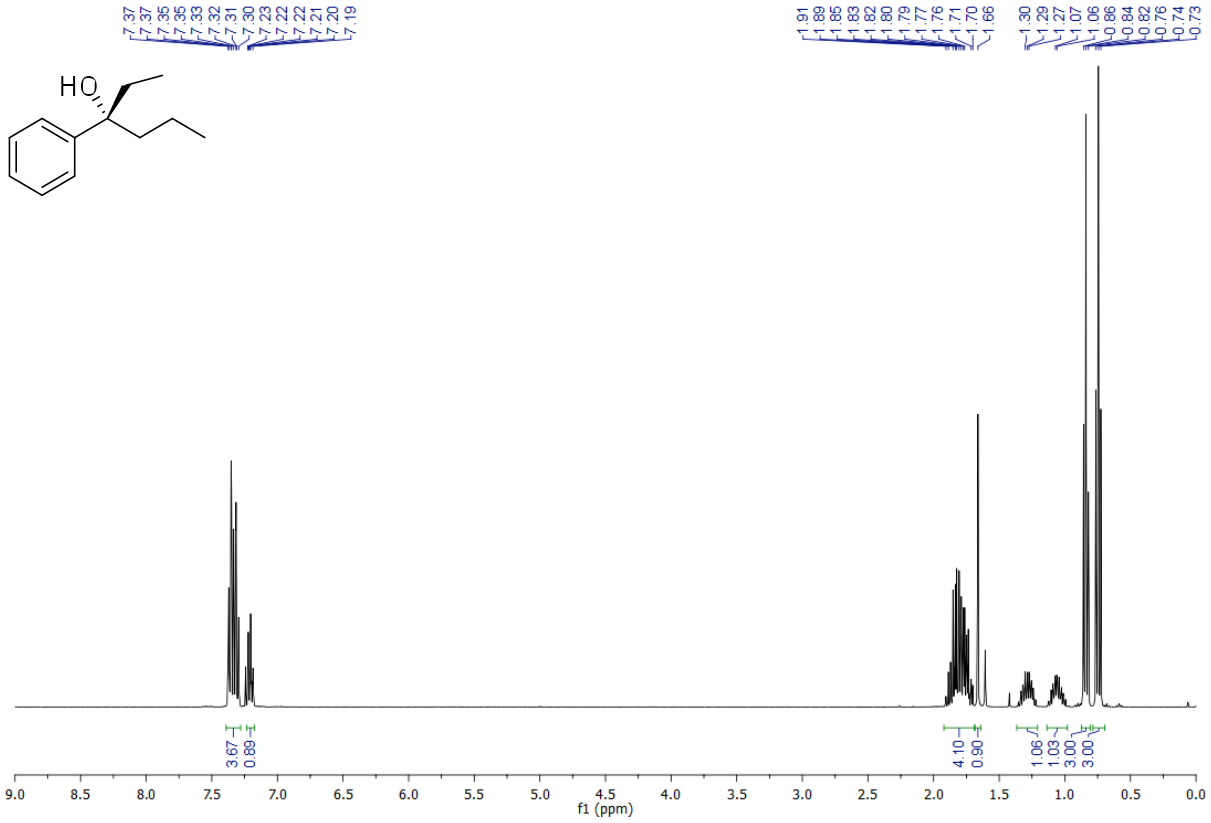


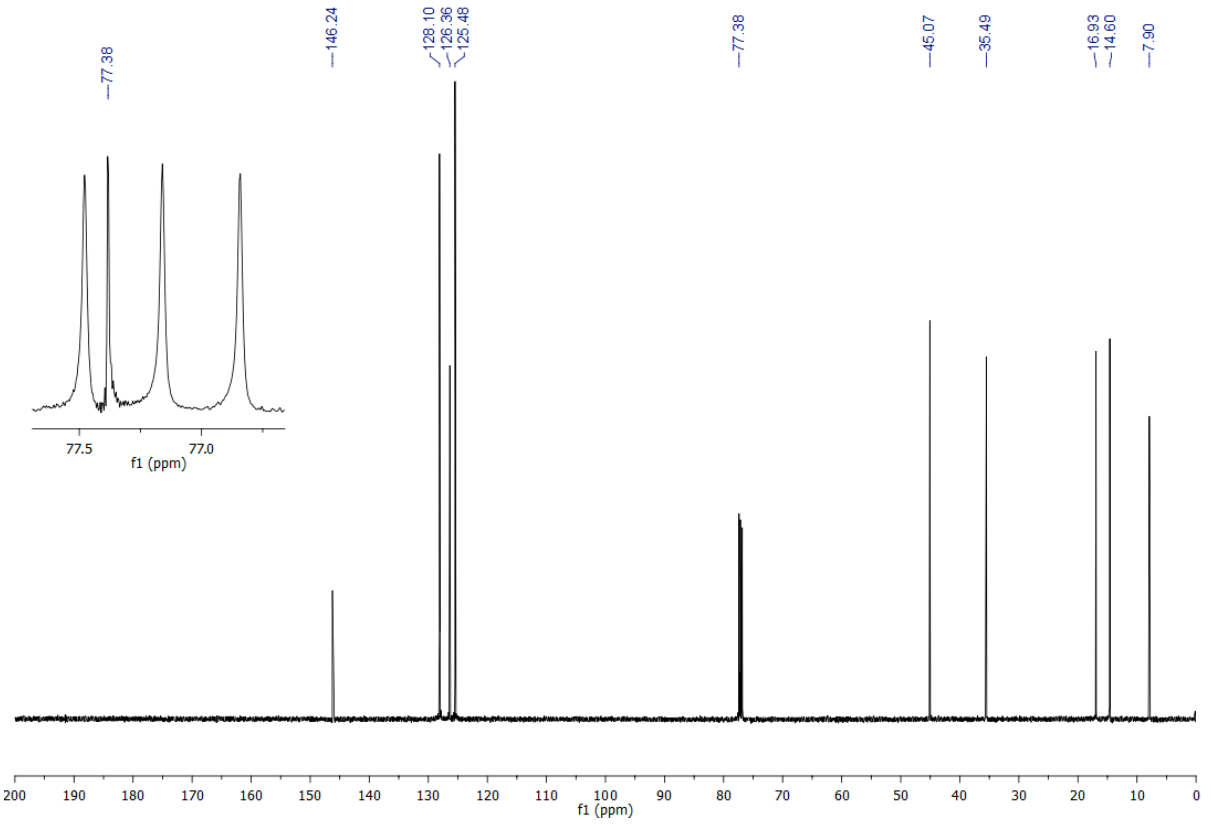
2-ethyl-2-(4-methoxyphenyl)tetrahydro-2*H*-pyran 7cb



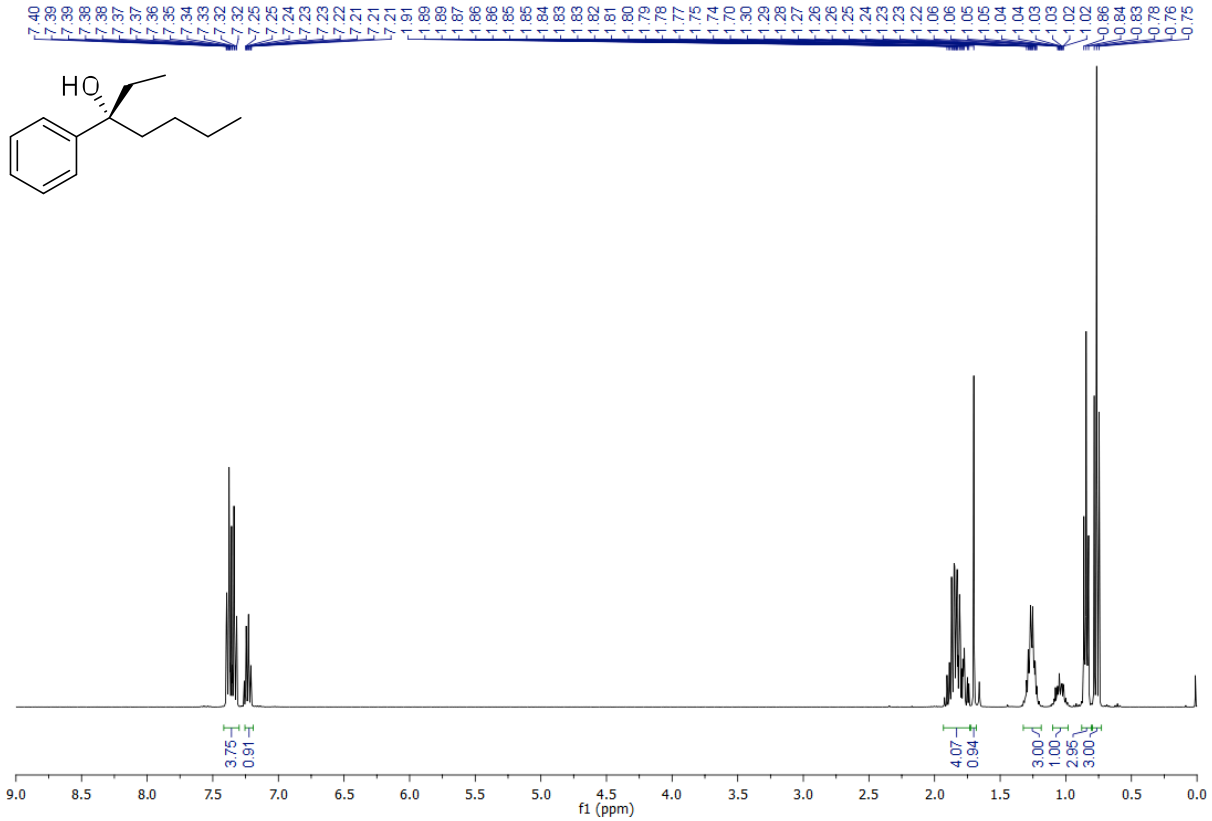


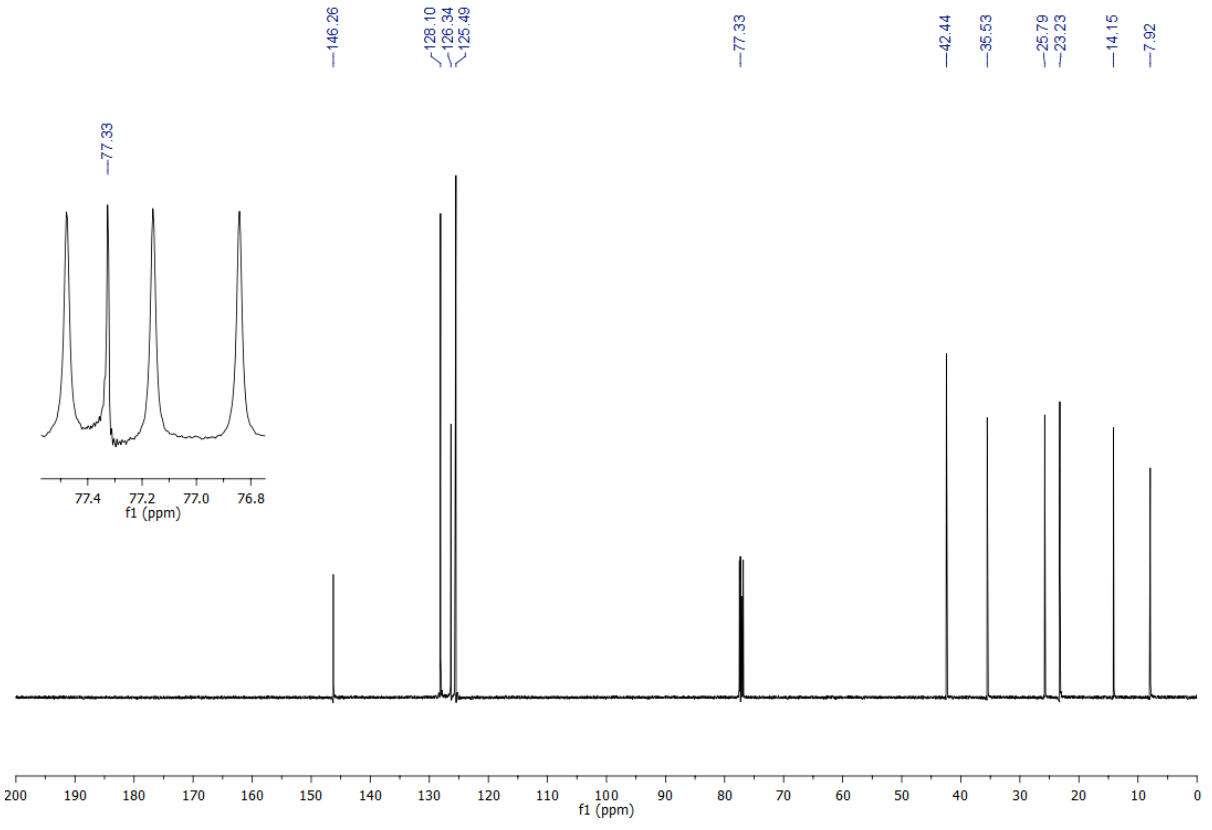
3-phenylhexan-3-ol



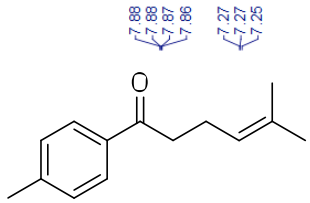


3-Phenylheptan-3-ol





5-methyl-1-(4-methylphenyl)-1-oxo-hex-4-ene 1



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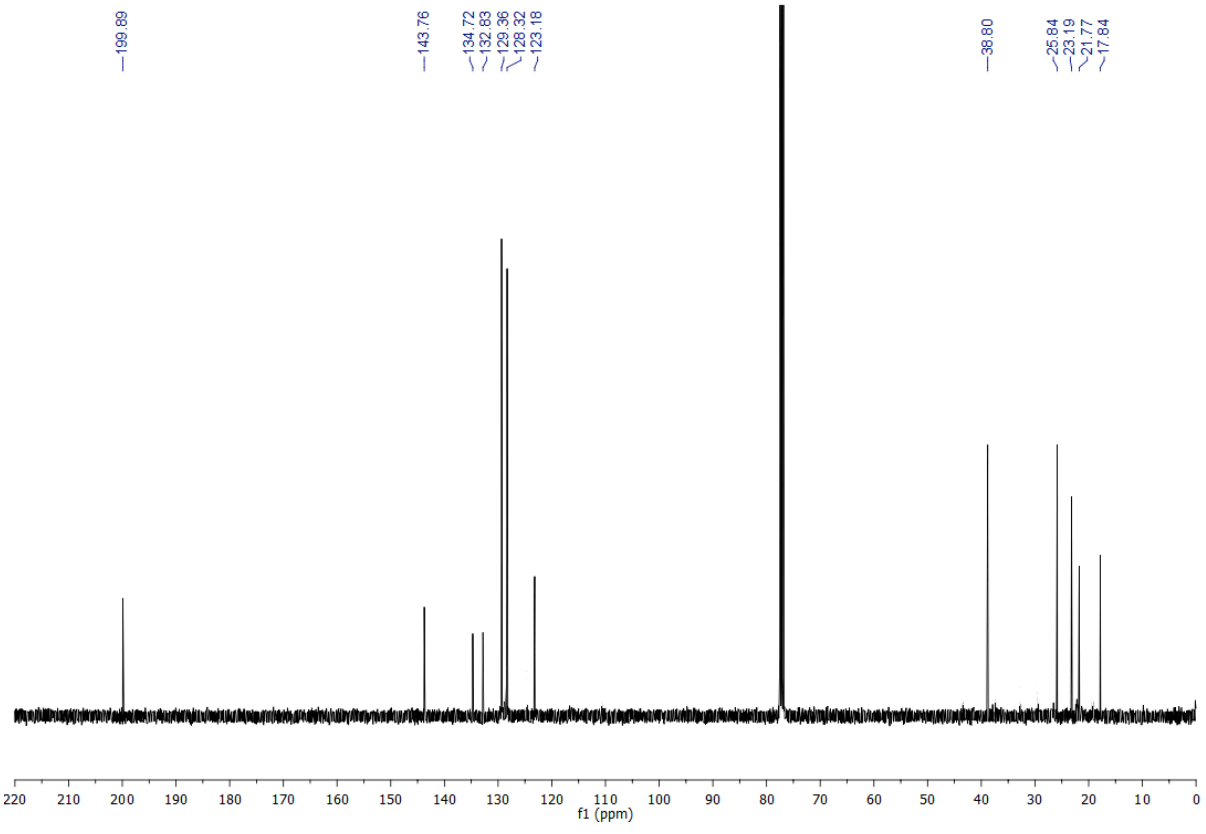
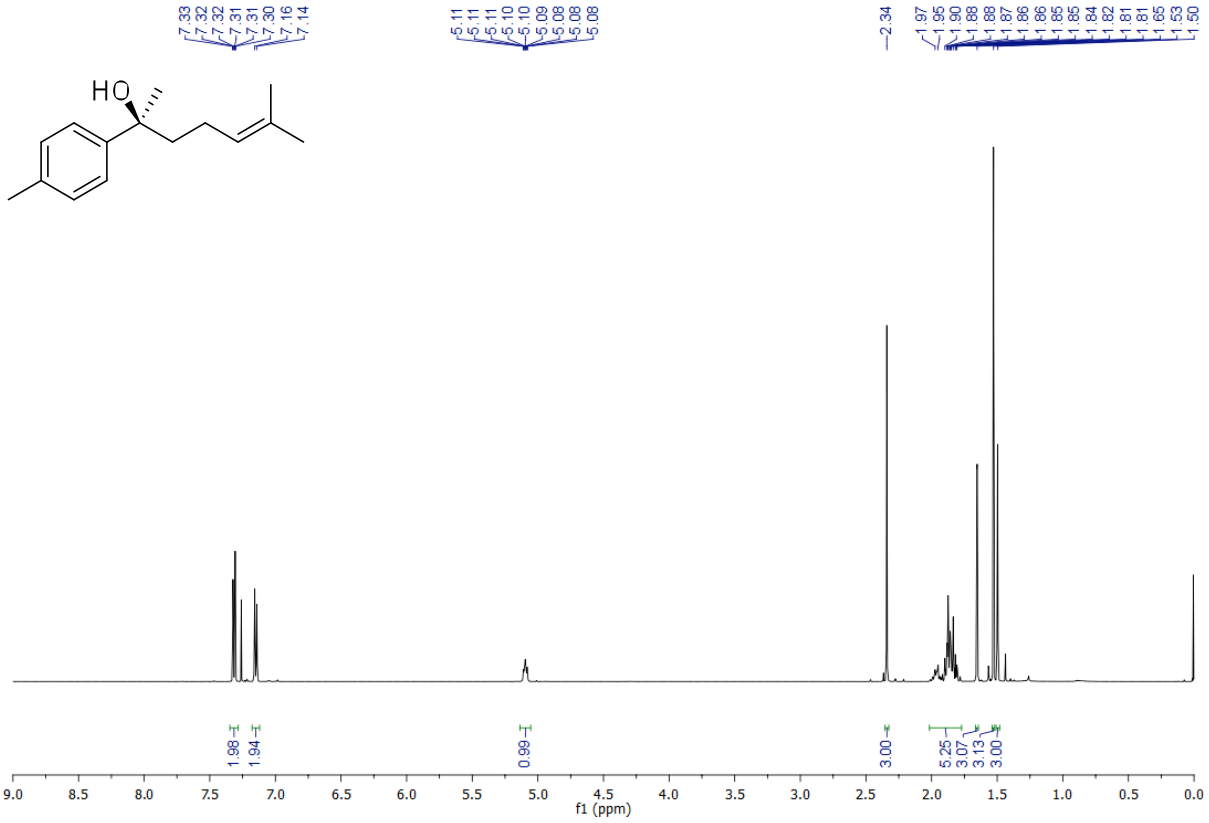
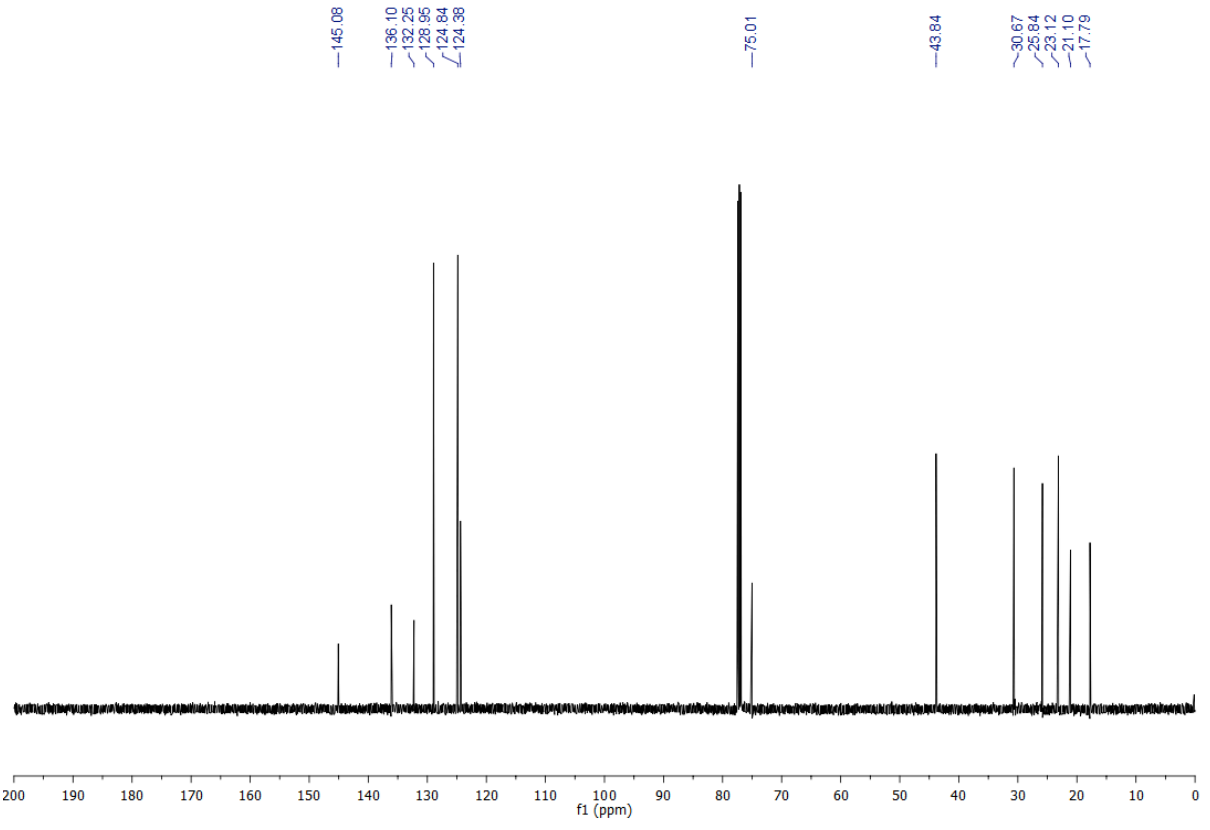
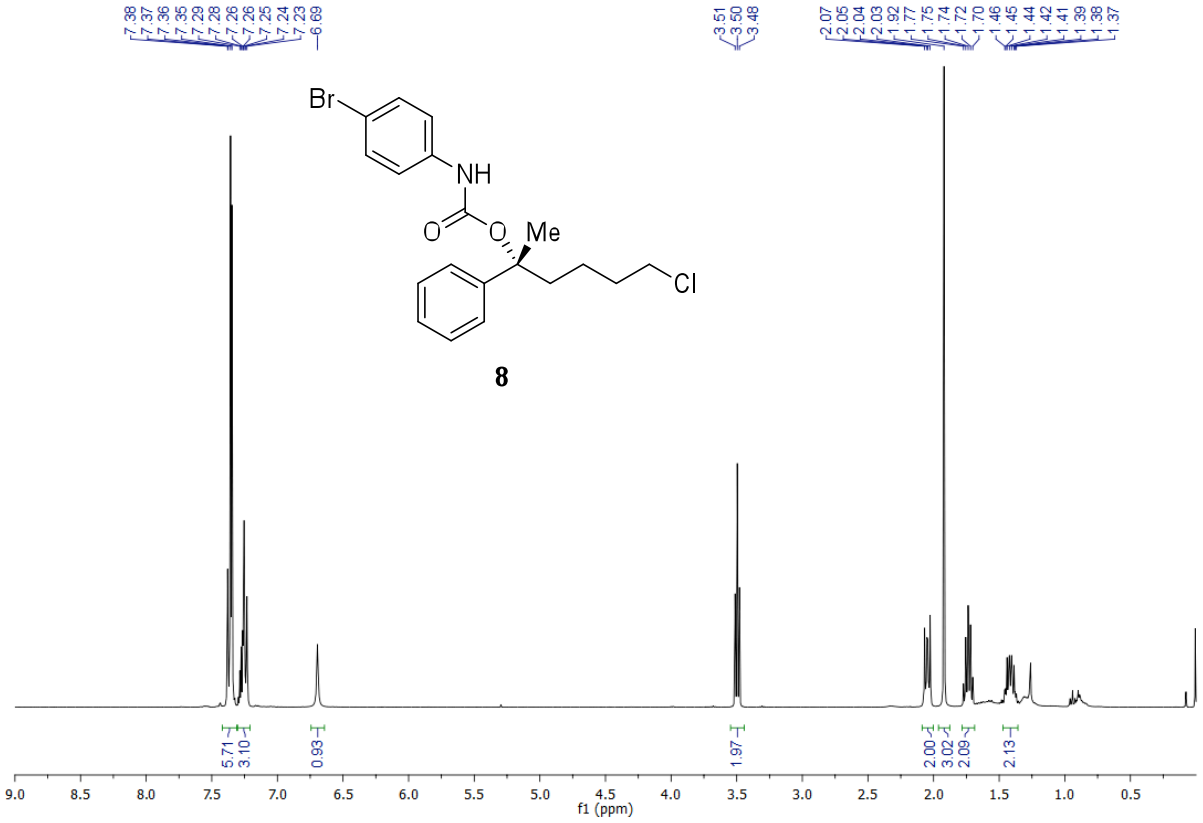


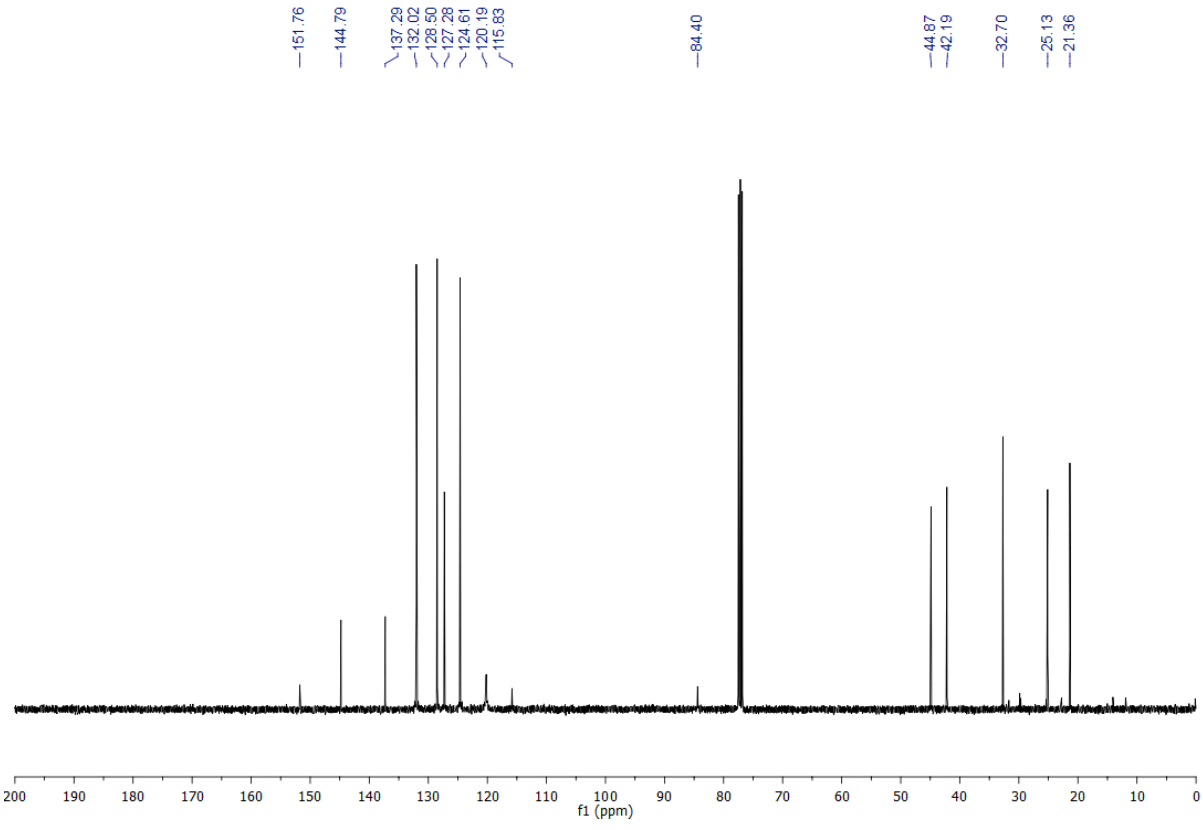
(*S*)-(-)-Gossonorol



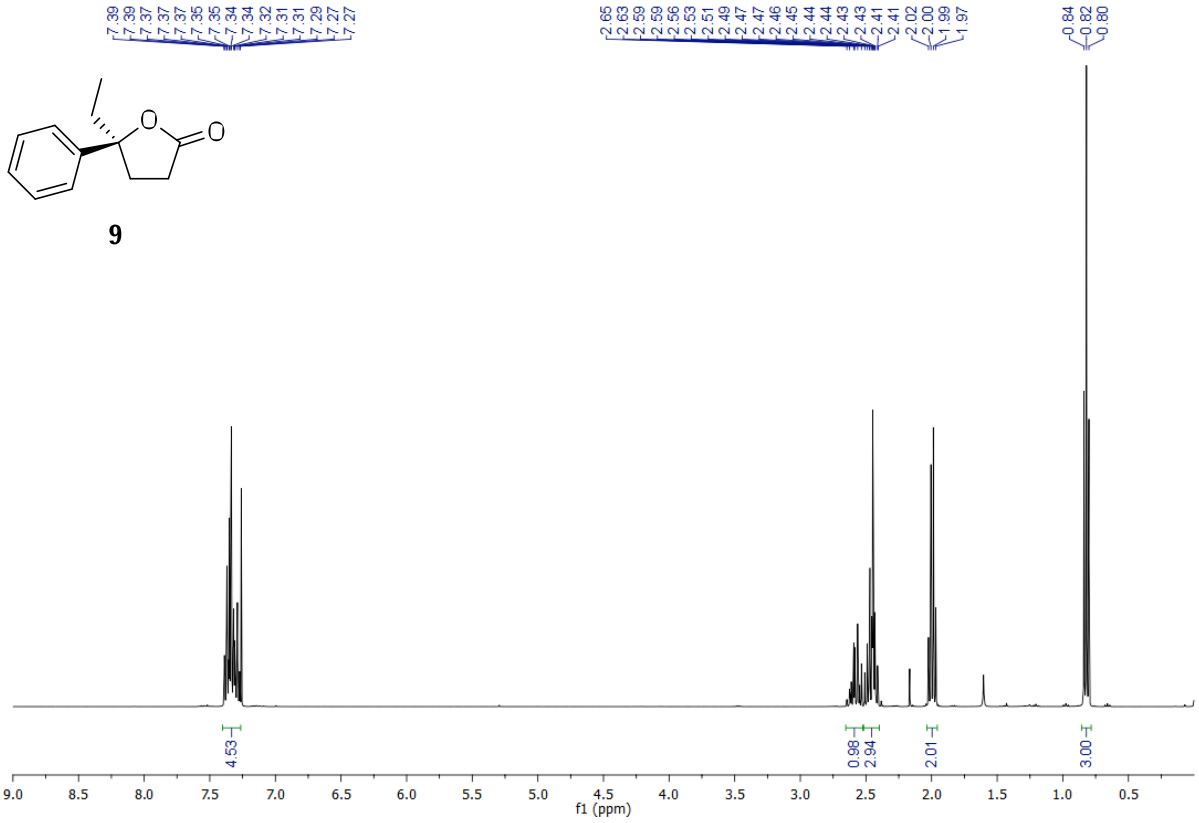


(*R*)-6-chloro-2-phenylhexan-2-yl (4-bromophenyl)carbamate 8





(*S*)-γ-ethyl-γ-phenylbutyrolactone 9



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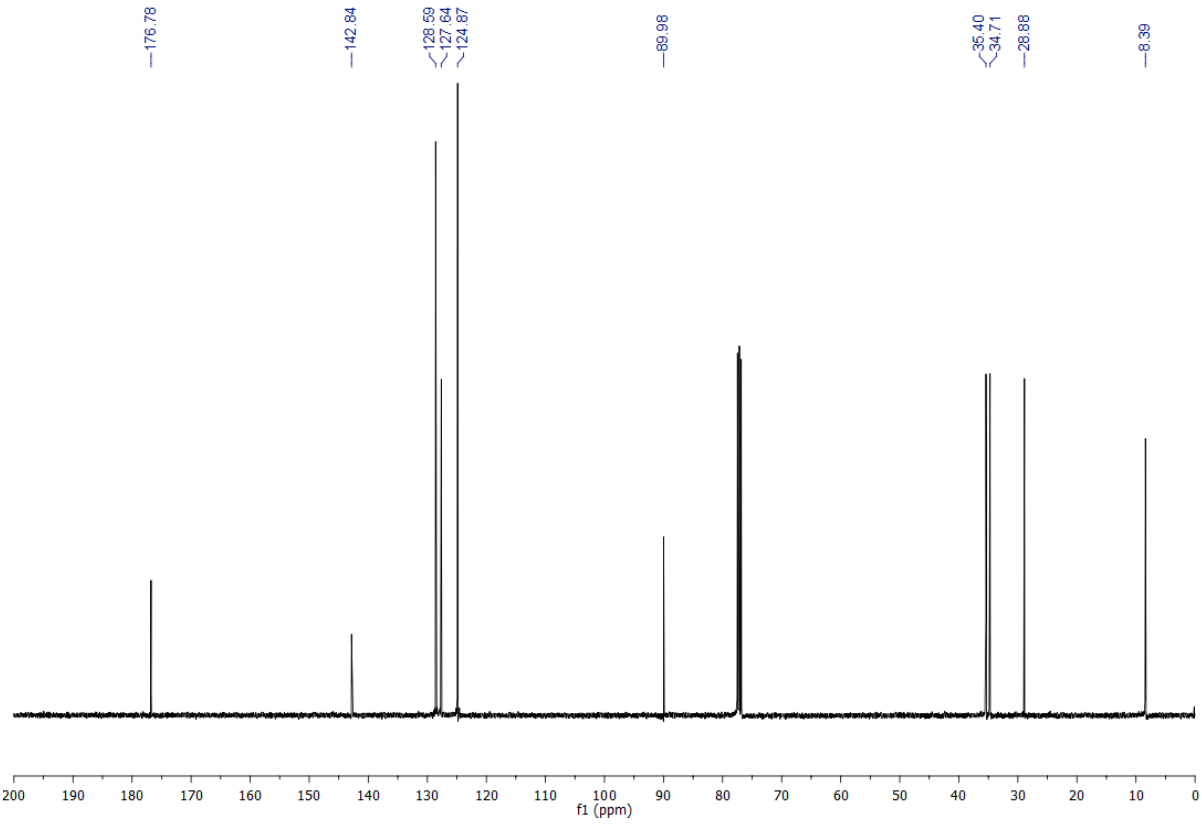

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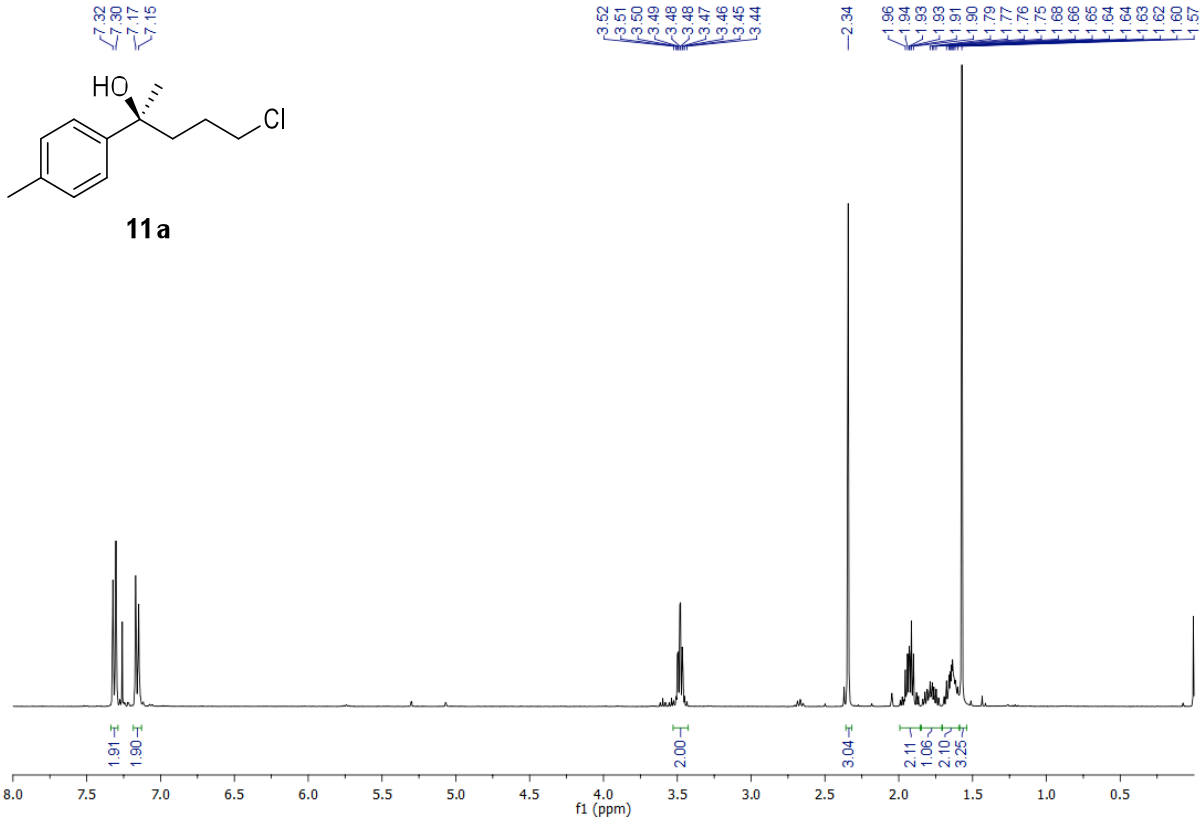
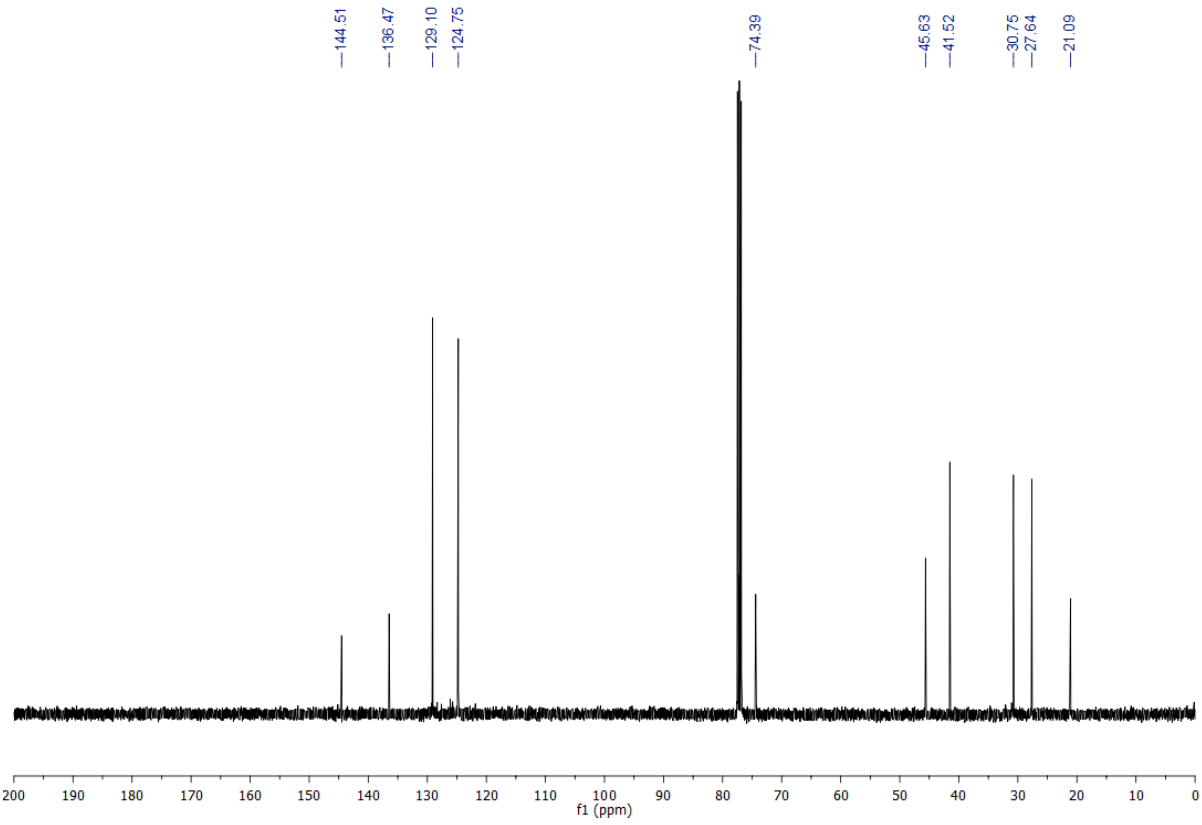
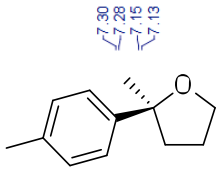




(*S*)-2-methyl-2-(p-tolyl)tetrahydrofuran 10



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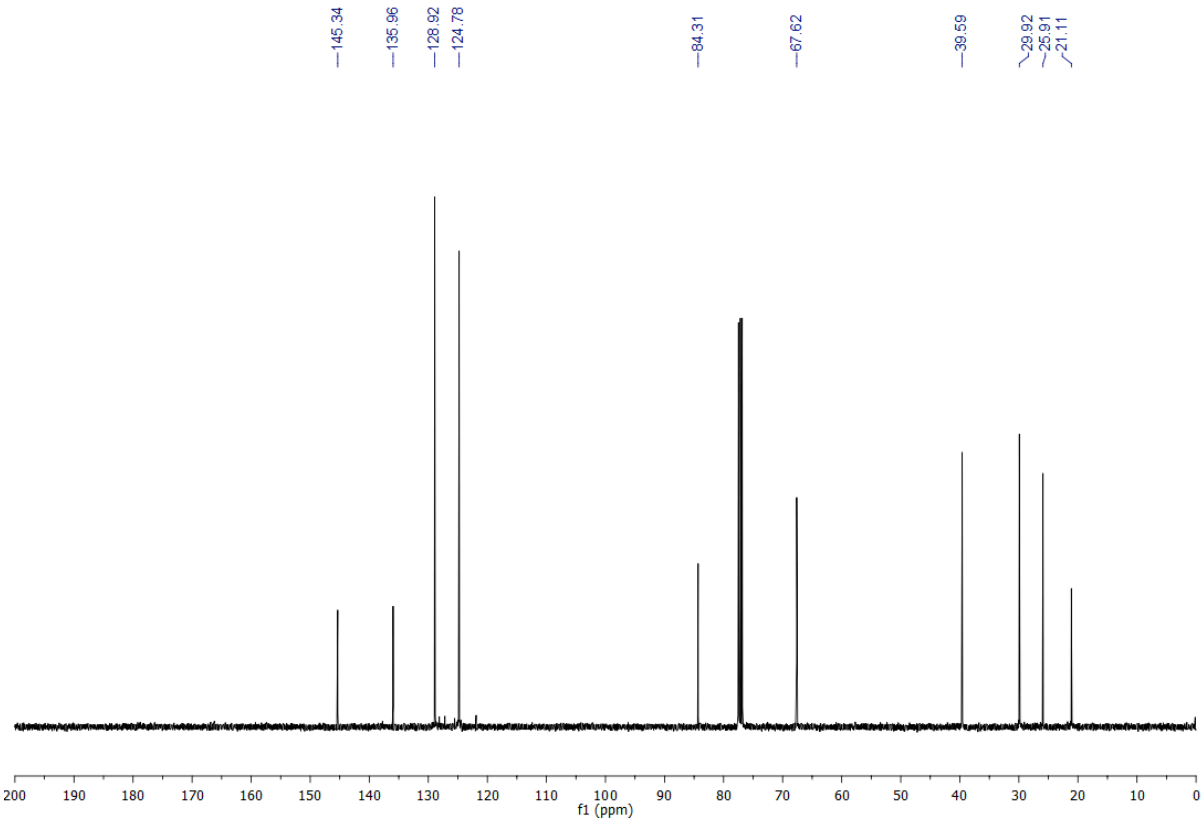
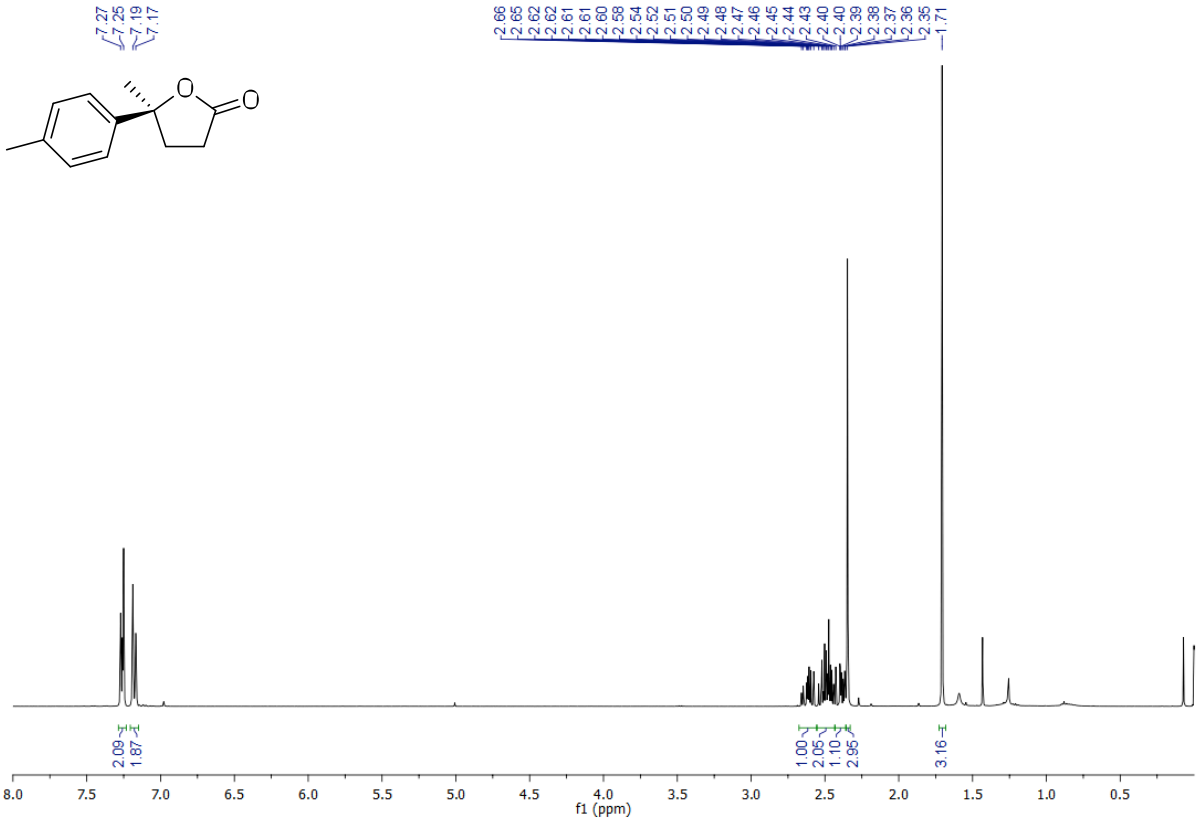
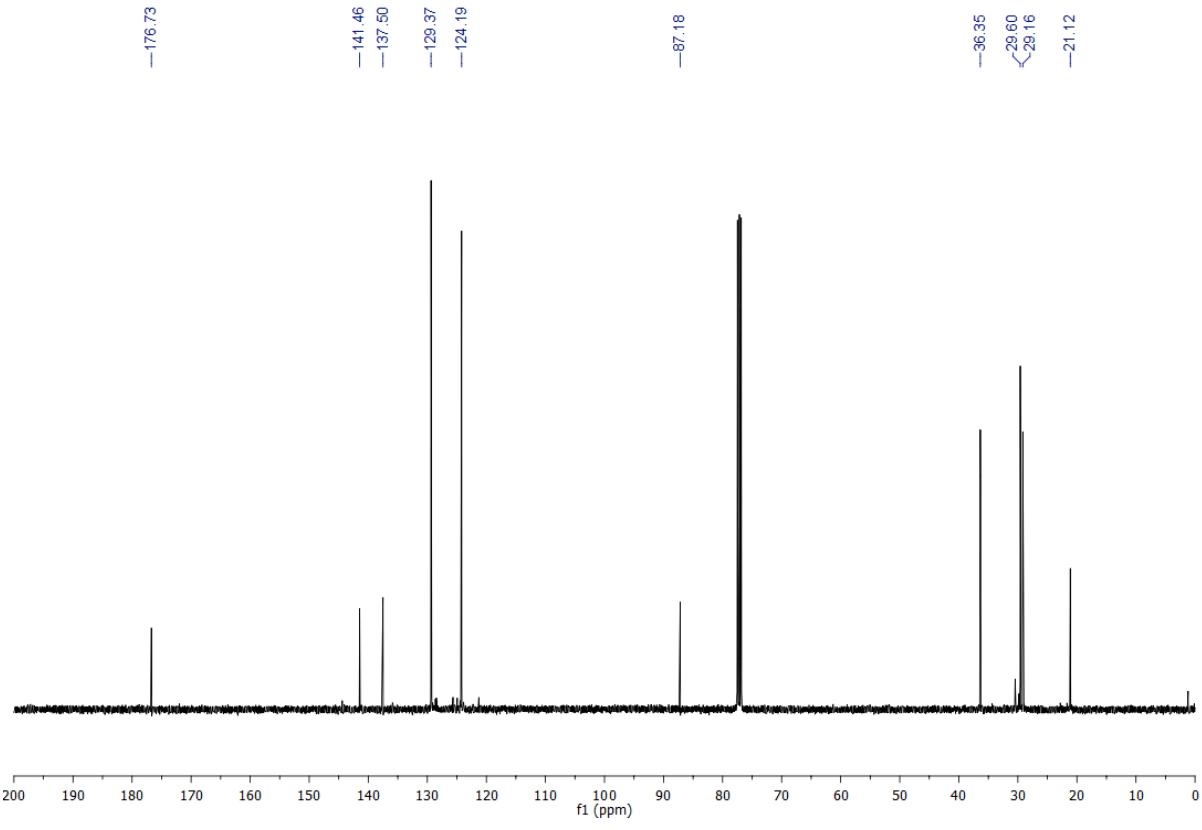
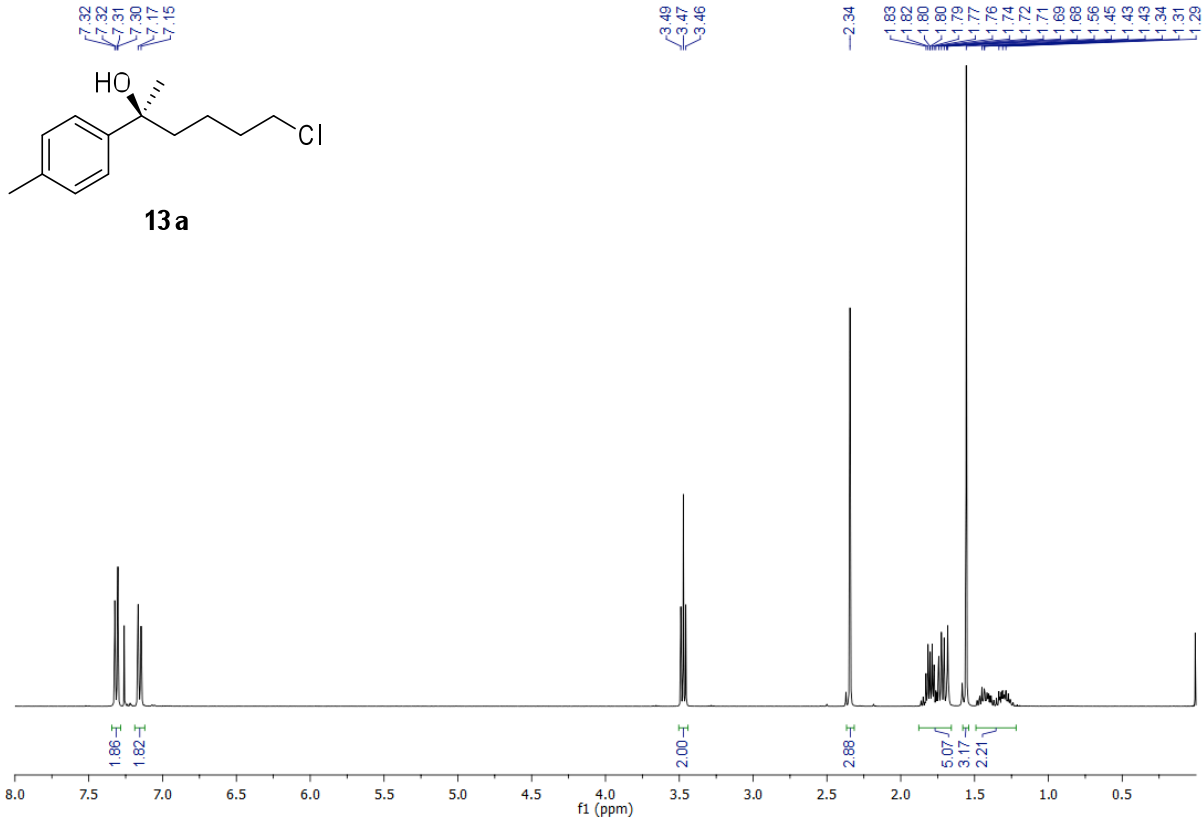


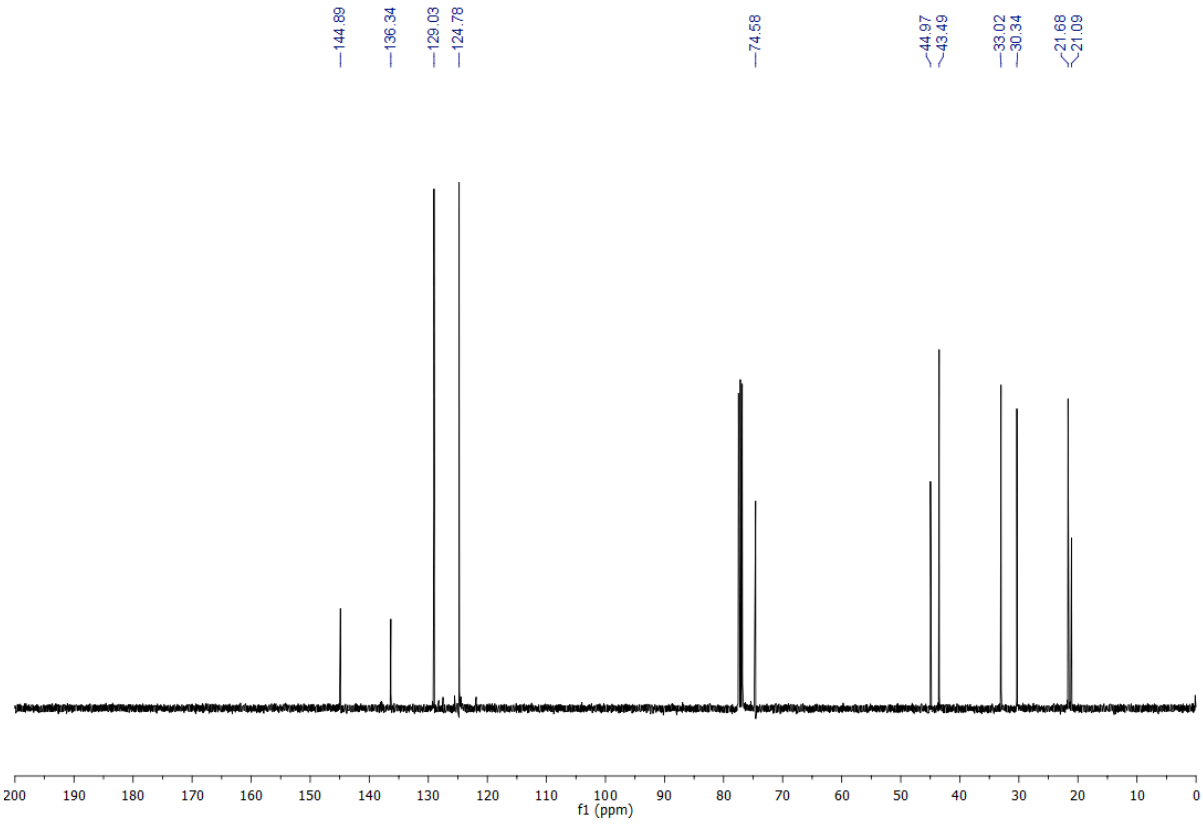
(*S*)-(-)-Boivinianin A



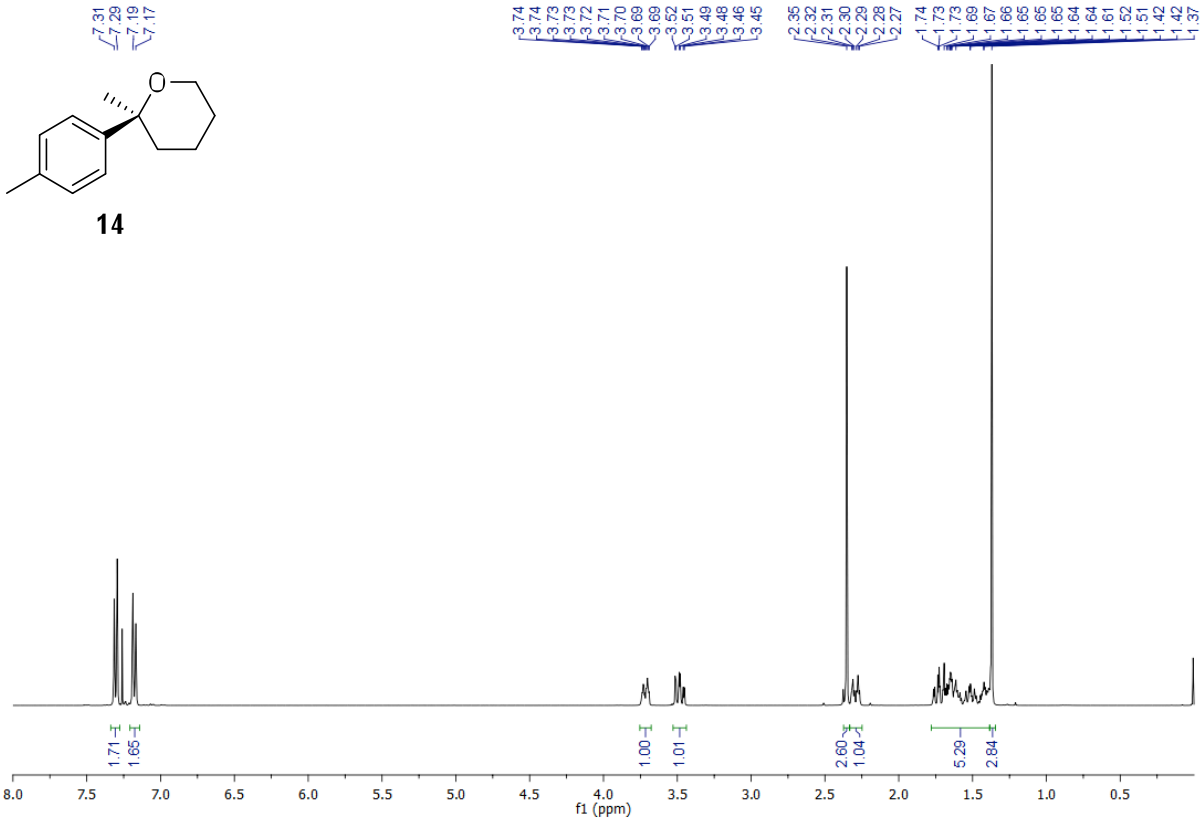


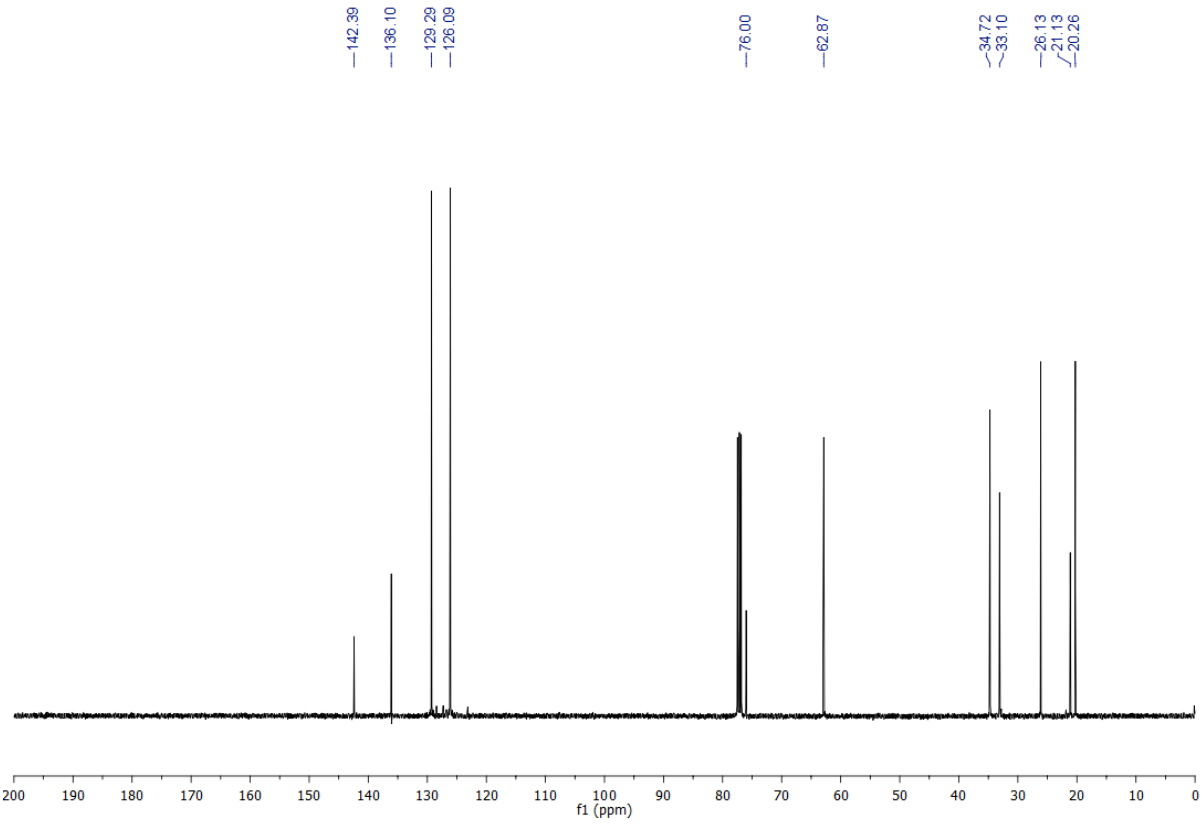
(*S*)-6-chloro-2-(p-tolyl)hexan-2-ol 13a



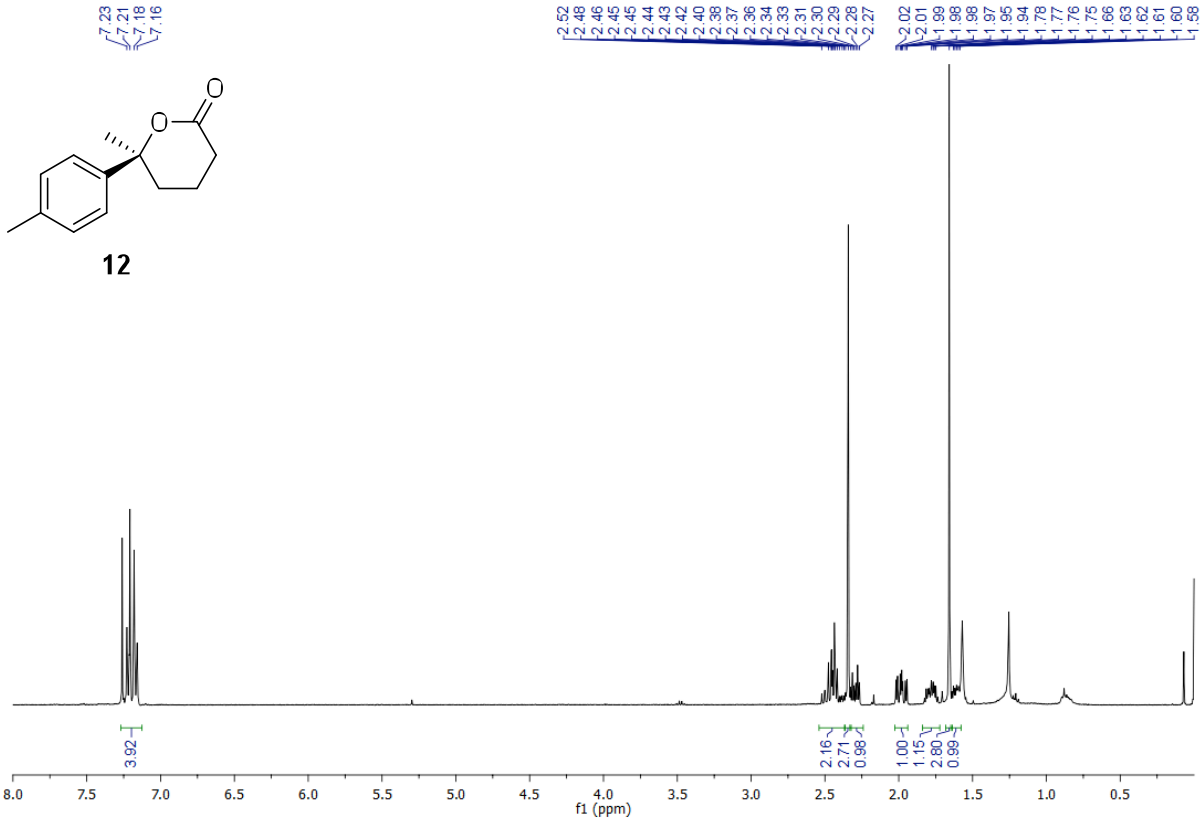


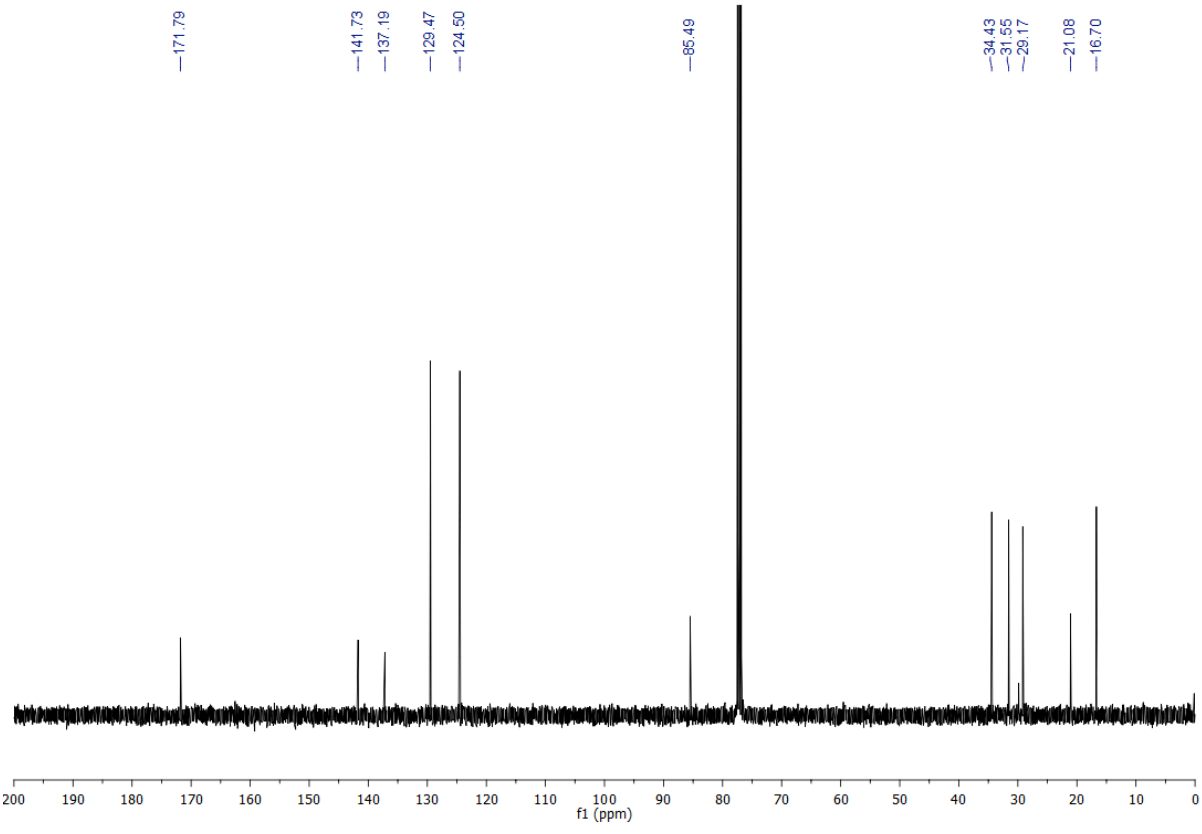
(*S*)-2-methyl-2-(p-tolyl)tetrahydro-2H-pyran 14





(S)-6-methyl-6-(p-tolyl)tetrahydro-2H-pyran-2-one 12





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