Supplementary Information

Combination of Organocatalytic Oxidation of Alcohols and Organolithium Chemistry (RLi) in Aqueous Media, at Room Temperature and Under Aerobic Conditions

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1.- General Methods

All reagents were obtained from commercial suppliers and used without further purification. Alcohol 1-phenylpropan-1-ol (**3a**) was purchased from commercial source. Secondary alcohols **3b-f** were prepared according to conventional procedures (addition of EtMgBr to the corresponding aromatic aldehyde). Organolithium and organomagnesium reagents were purchased from Sigma Aldrich: *i*) *n*-butyllithium (1.6 M solution in hexanes); *ii*) methyllithium (1.6 M solution in diethyl ether); *iii*) *sec*-butyllithium (1.4 M solution in cyclohexane); *iv*) phenyllithium (1.9 M solution in di-*n*-butylether); and *v*) butylmagnesium chloride (2.0 M solution in THF). All the rest of reagents and solvents were of the highest quality available.

^{1}H-NMR spectra ($CDCl_3$) were obtained using a Bruker DPX-300 (^{1}H, 300.13 MHz; $^{13}C\{^{1}H\}$, 75.4 MHz) spectrometer and employing the δ scale (ppm) for chemical shifts. Calibration was made on the signal of the solvent (^{1}H: $CDCl_3$, 7.26 ppm; ^{13}C: $CDCl_3$, 77.0 ppm). Gas chromatography (GC) analyses were performed on an Agilent Technologies 7820A chromatograph equipped with a HP-5 (30 m x 0.32 mm x 0.25 μm) column. The employed program started at an initial temperature of 170 ºC (3 min) and then a slope of 10 ºC/min until to reach a final temperature of 220 ºC.

Spectroscopic data of ketones **4a-f**[1] and tertiary alcohols **5a**, **5b**, **5c**, **5d**, **5g**, and **5i**[2] are in agreement with those reported in the literature.

2.- Protocols

General Procedure for Organocatalytic Oxidation of Racemic Alcohols 3a-f.

To a sample of commercially available NaClO solution (1.95 M as determined by titration),[3] were added KH_2PO_4 and water in such amounts that the resulting solution was 0.125 M in phosphate and 0.40 M in NaClO (pH 7.9). Then, the required amount of this NaClO solution (1.2-1.3 equiv.), 1 mmol of the desired alcohol **3a-f** and AZADO (1 mol%)[4] were consecutively added. The mixture was vigorously stirred (magnetic stirring) at room temperature for 1 hour under air (the oxidation reaction was monitored by GC analysis), and the reaction mixture was extracted with ethyl acetate (3 x 5 mL). The organic layers were combined, dried with Na_2SO_4 and the solvents evaporated under vacuum. The identity of the resulting ketones **4a-f** was confirmed by ^{1}H-RMN analysis of the crude product after comparison with reported spectra.[1]

Procedure for direct conversion of 1-phenylpropan-1-ol (3a) into tertiary alcohols 5a-d through one-pot combination of oxidation and addition of RLi/RMgX reagents in water, at room temperature and under air.

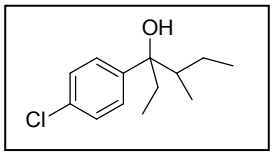
In a round-bottom flask, at room temperature and under air, the commercially available alcohol **3a** (1 mmol), the aqueous solution of NaOCl (3.7 mL) and AZADO (1 mol%, 1.5 mg) were mixed. The obtained aqueous mixture was vigorously stirred for 1 hour and once the oxidation was completed (GC analysis), 3 equivalents of the corresponding organolithium (RLi) or Grignard (RMgX) reagents were quickly spread out through the mixture at room temperature, under air and with vigorous stirring. After 3 s, 2 mL of saturated aqueous solution of Rochelle salt were added, and the mixture was extracted with 2-MeTHF (3 x 5 mL). The combined organic phases were dried over anhydrous $MgSO_4$, and the solvent was concentrated *in vacuo*. The crude product was purified by flash chromatography (silica gel 60 Å, hexane:ethyl acetate mixtures) to give **5a-d** products (23-83% yields).

Procedure for direct conversion of secondary alcohols 3a-f into tertiary alcohols 5a,c-n through one-pot combination of oxidation and addition reactions of *n*-BuLi or *sec*-BuLi in water, at room temperature and under air.

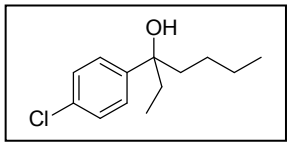
In a round-bottom flask, at room temperature and under air the desired alcohol **3a-f** (1 mmol), the aqueous solution of NaOCl (3.7 mL) and AZADO (1 mol%, 1.5 mg) were

mixed. The obtained aqueous mixture was vigorously stirred for 1 hour and once the oxidation was completed (GC analysis), 3 equivalents of the corresponding organolithium reagent (*n*-BuLi or *sec*-BuLi, respectively) were quickly spread out through the mixture at room temperature, under air and with vigorous stirring. After 3 s, 2 mL of saturated aqueous solution of Rochelle salt were added, and the mixture was extracted with 2-MeTHF (3 x 5 mL). The combined organic phases were dried over anhydrous $MgSO_4$, and the solvent was concentrated *in vacuo*. The crude product was purified by flash chromatography (silica gel 60 Å, hexane:ethyl acetate mixtures) to give **5a,c-n** products (39-95% yields).

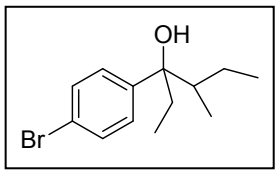
3.- Characterization of new compounds 5e, 5f, 5h, 5k, 5l, 5m and 5n



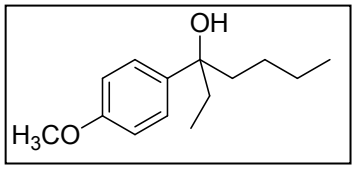
3-(4-chlorophenyl)-4-methylhexan-3-ol (5e): dr 1/1 (inseparable mixture of diastereomers), colorless oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (m, 4H), 1.81 (m, 2H), 1.61 (m, 2H), 1.28 (m, 1H), 0.95-0.64 (m, 9H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 7.9, 12.6, 12.7, 13.7, 23.3, 24.1, 32.0, 32.9, 44.8, 44.9, 79.6, 79.8, 127.6, 127.7, 127.9, 128.0, 132.7, 143.8, 144.2; FT-IR (film, cm^{-1}): 3411, 2951, 2923, 2855, 2364, 2345, 2035, 1710, 1460, 1378, 1373, 1131.



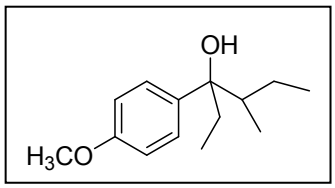
3-(4-chlorophenyl)heptan-3-ol (5f): colorless oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (m, 4 H), 1.87 (m, 4H), 1.23 (m, 4H), 0.94 (t, *J* = 6.0 Hz, 3H), 0.74 (t, *J* = 6.0 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 7.8, 14.1, 23.2, 25.7, 35.7, 42.5, 77.1, 127.1, 128.21, 132.13, 144.8; FT-IR (film, cm^{-1}): 3460, 2921, 2842, 1711, 1596, 1491, 1463, 1381, 1377, 1157, 1094, 1014.



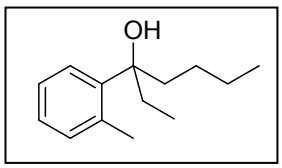
3-(4-bromophenyl)-4-methylhexan-3-ol (5h): dr 1/1 (inseparable mixture of diastereomers), colorless oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (m, 3H), 7.21 (m, 1H), 1.96 (m, 2H), 1.79 (m, 2H), 1.38 (m, 1H), 0.96-0.65 (m, 9H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 8.0, 12.7, 13.8, 23.3, 24.2, 31.9, 32.2, 44.8, 45.0, 79.9, 80.0, 126.0, 126.2, 126.3, 127.8, 127.9, 145.3, 145.6; FT-IR (film, cm^{-1}): 3480, 2960, 2852, 2354, 2332, 1611, 1582, 1511, 1463, 1377, 1299, 1249, 1179, 1039, 959.



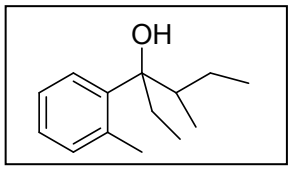
3-(4-methoxyphenyl)heptan-3-ol (5k): colorless oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.1 Hz, 2H), 7.12 (d, *J* = 8.1 Hz, 2H), 2.36 (s, 3H), 1.97-1.72 (m, 4H), 1.33-1.06 (m, 4H), 0.87 (t, *J* = 6.0 Hz, 3H), 0.80 (t, *J* = 6.0 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 7.9, 14.1, 21.0, 23.2, 25.8, 35.4, 42.3, 77.0, 125.4, 128.8, 135.7, 143.3; FT-IR (film, cm^{-1}): 3447, 2853, 2818, 2729, 1711, 1513, 1463, 1377, 1157, 1111.



3-(4-methoxyphenyl)-4-methylhexan-3-ol (5l): dr 1/1 (inseparable mixture of diastereomers), colorless oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.1 Hz, 2H), 6.85 (d, *J* = 8.1 Hz, 2H), 3.80 (s, 3H), 1.86 (m, 2H), 1.68 (m, 2H), 1.32 (m, 1H), 0.963-0.66 (m, 9 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 5.7, 6.8, 16.3, 17.2, 24.8, 25.1, 37.8, 38.0, 48.3, 72.5, 72.7, 120.2, 120.3, 103.3, 130.6, 151.0; FT-IR (film, cm^{-1}): 3605, 2970, 2936, 2877, 1512, 1462, 1380, 1262, 1159, 965.



3-(o-tolyl)heptan-3-ol (5m): colorless oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (m, 1H), 7.14 (m, 3H), 2.50 (m, 3H), 2.01 (m, 2H), 1.86 (m, 2H), 1.27 (m, 4 H), 0.86 (t, J = 6.0 Hz, 3H), 0.78 (t, J = 6.0 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 8.0, 14.0, 22.5, 23.1, 26.0, 33.8, 40.7, 78.6, 125.5, 126.6, 127.2, 132.2, 134.9, 143.2; FT-IR (film, cm^{-1}): 3450, 2950, 2910, 2852, 2724, 1715, 1636, 1576, 1512, 1462, 1377, 1309, 1156, 1111.



4-methyl-3-(o-tolyl)hexan-3-ol (5n): dr 1/1 (inseparable mixture of diastereomers), colorless oil, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (m, 1H), 7.15 (m, 3H), 2.50 (s, 3H), 2.05-1.96 (m, 2 H), 1.59 (m, 2H), 1.00 (m, 1H), 1.02-0.65 (m, 9 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 8.2, 8.3, 12.7, 13.5, 22.8, 24.0, 30.1, 30.6, 42.7, 42.9, 81.3, 81.5, 125.2, 125.3, 126.3, 127.7, 127.8, 132.5, 143.1; FT-IR (film, cm^{-1}): 3450, 3058, 2930, 2852, 2724, 1709, 1601, 1508, 1459, 1376, 1371, 1273, 1150, 1130.

4.- NMR spectra data

^{1}H and ^{13}C NMR spectra of 3-phenyl-heptan-3-ol (5a)

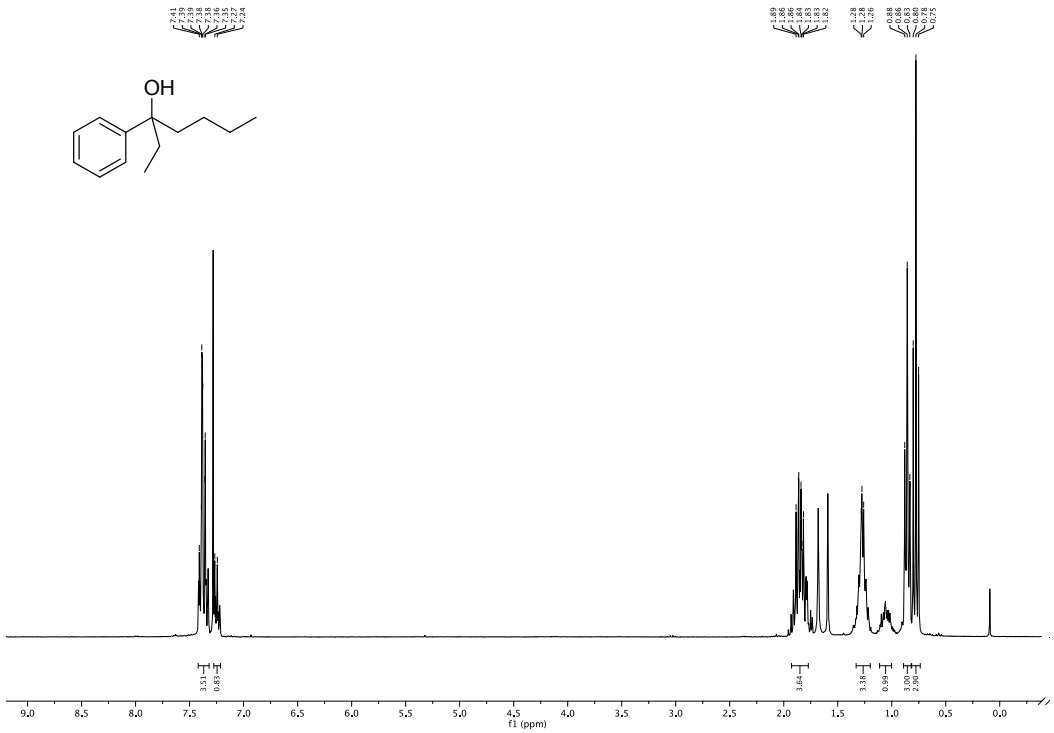


Figure S1. ^{1}H-NMR full chart for **5a** in $CDCl_3$.

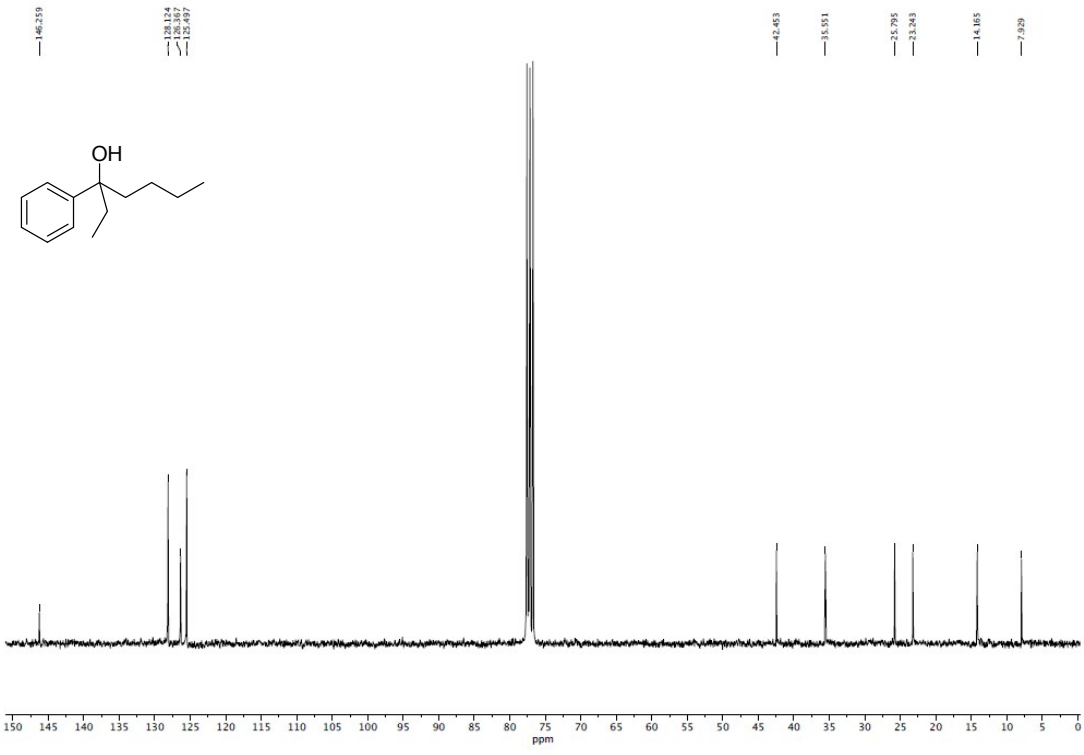


Figure S2. $^{13}C\{^{1}H\}$-NMR full chart for **5a** in $CDCl_3$.

^{1}H and ^{13}C NMR spectra of 2-phenylbutan-2-ol (5b)

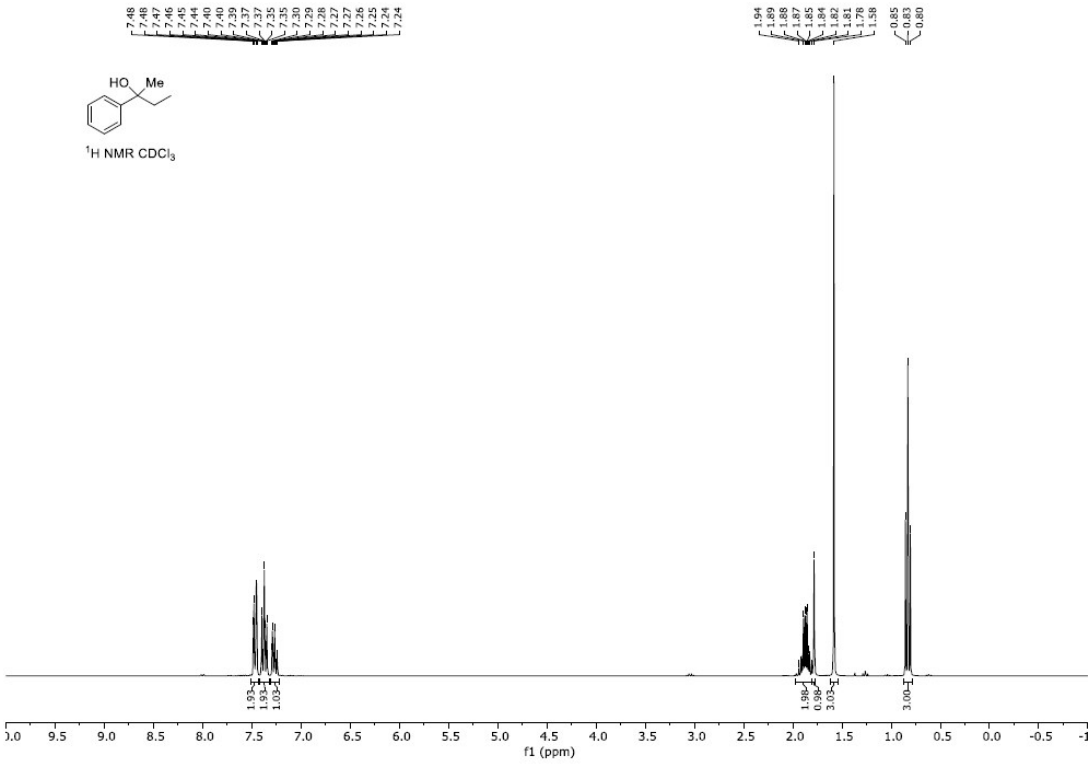


Figure S3. ^{1}H-NMR full chart for **5b** in $CDCl_3$.

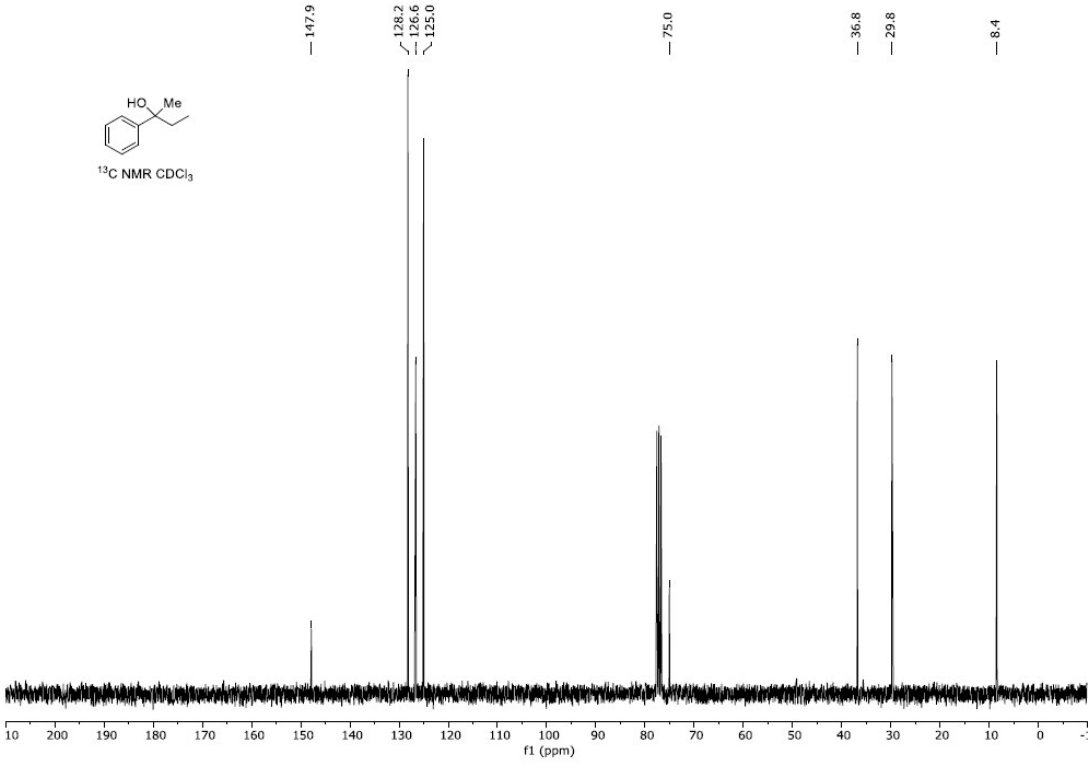


Figure S4. ^{13}C{^{1}H}-NMR full chart for **5b** in $CDCl_3$.

^{1}H and ^{13}C NMR spectra of 4-methyl-3-phenyl-hexan-3-ol (5c)

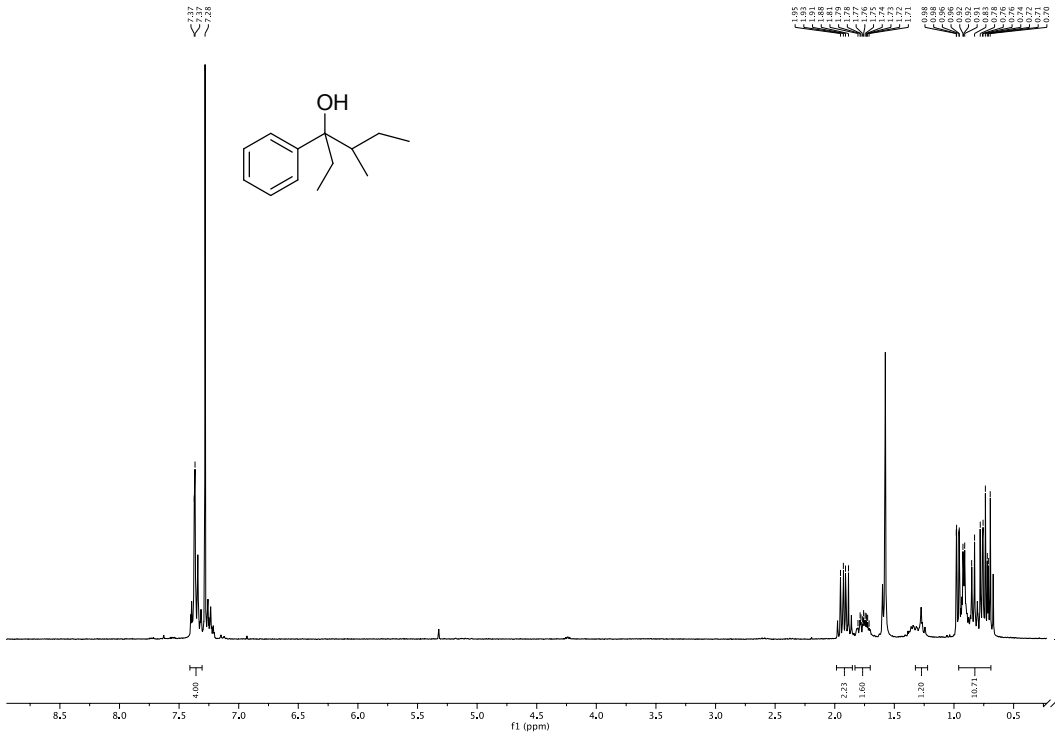


Figure S5. ^{1}H-NMR full chart for **5c** in $CDCl_3$.

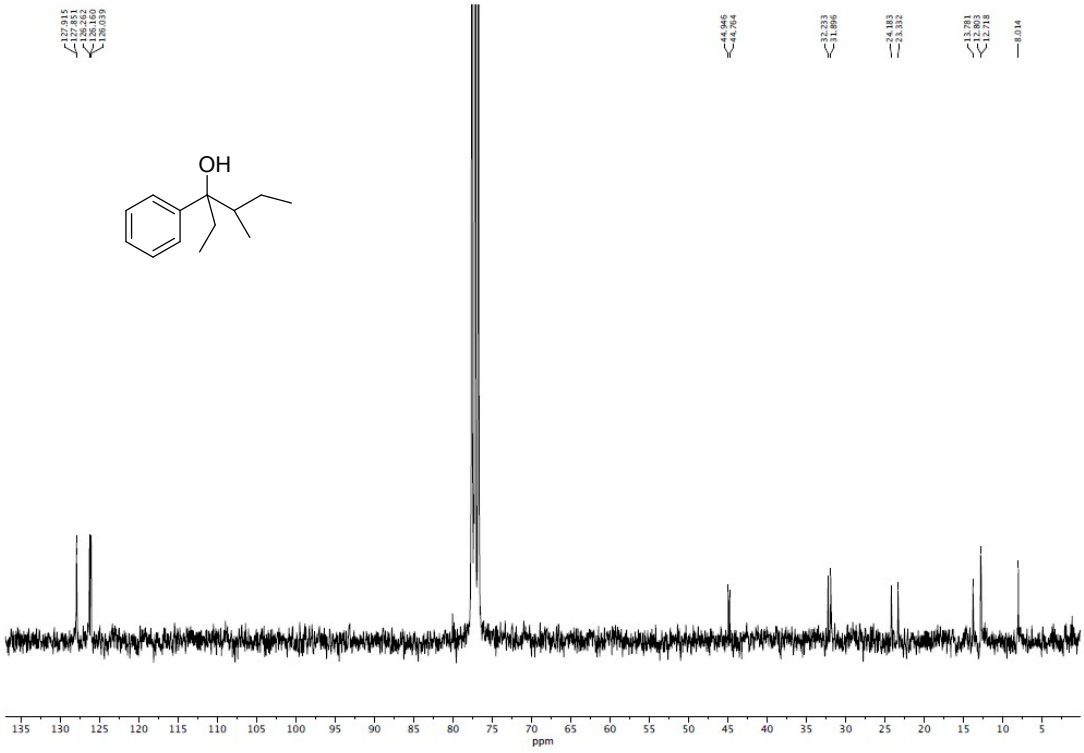


Figure S6. ^{13}C{^{1}H}-NMR full chart for **5c** in $CDCl_3$.

^{1}H and ^{13}C NMR spectra of 1,1-diphenylpropan-1-ol (5d)

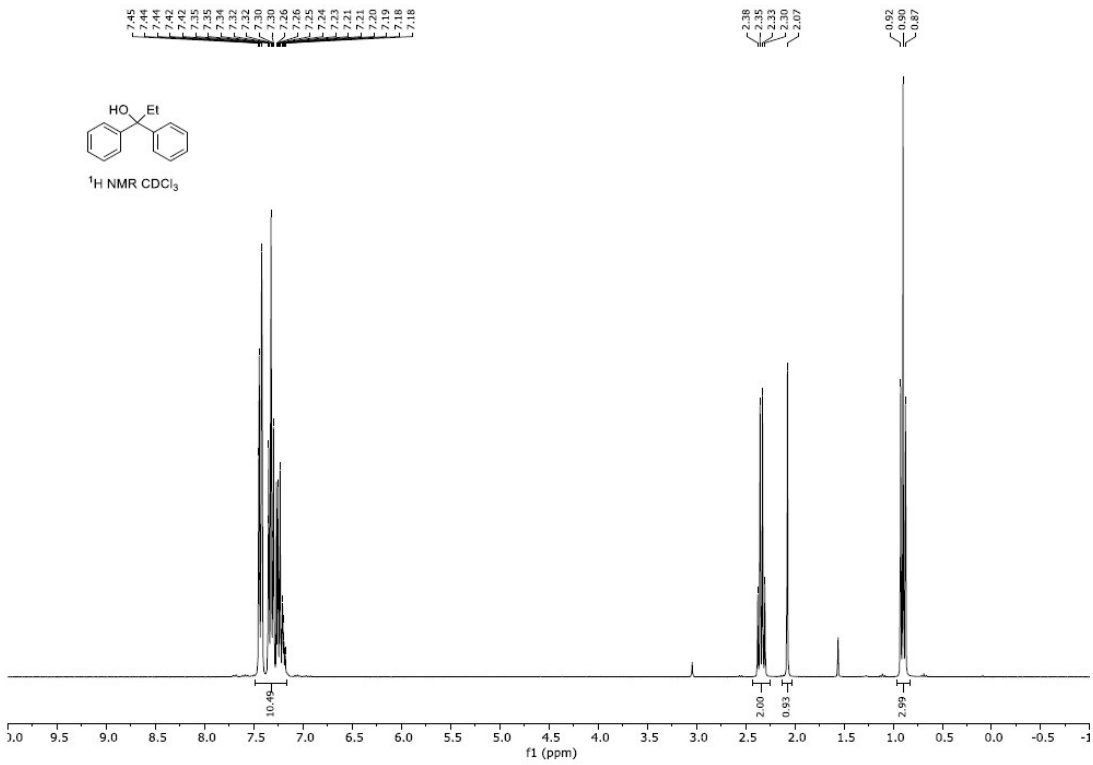


Figure S7. ^{1}H-NMR full chart for **5d** in $CDCl_3$.

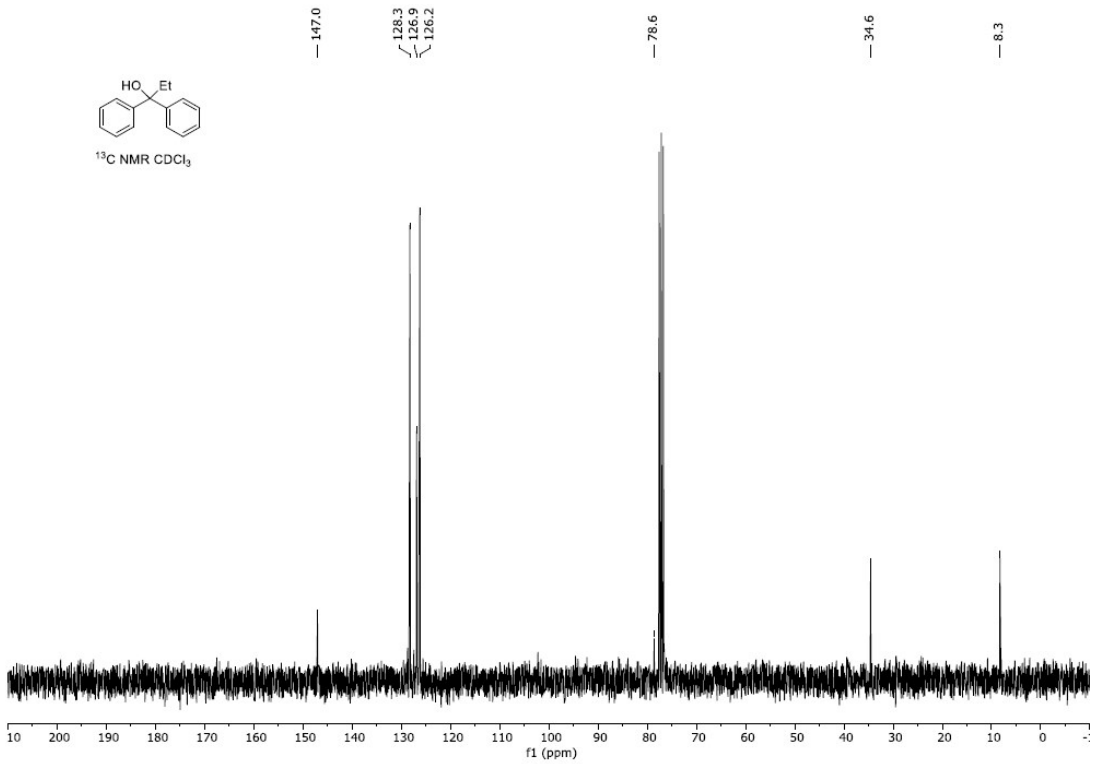


Figure S8. ^{13}C{^{1}H}-NMR full chart for **5d** in $CDCl_3$.

^{1}H and ^{13}C NMR spectra of 3-(4-chlorophenyl)-4-methylhexan-3-ol (5e)

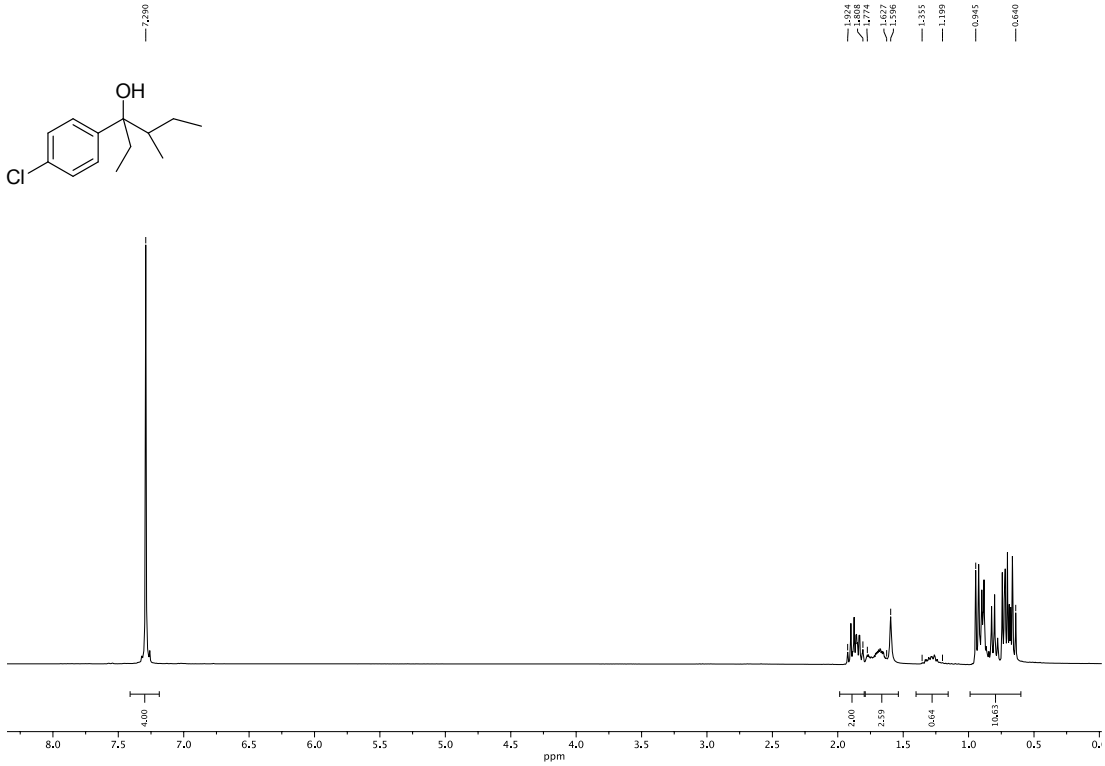


Figure S9. ^{1}H-NMR full chart for **5e** in $CDCl_3$.

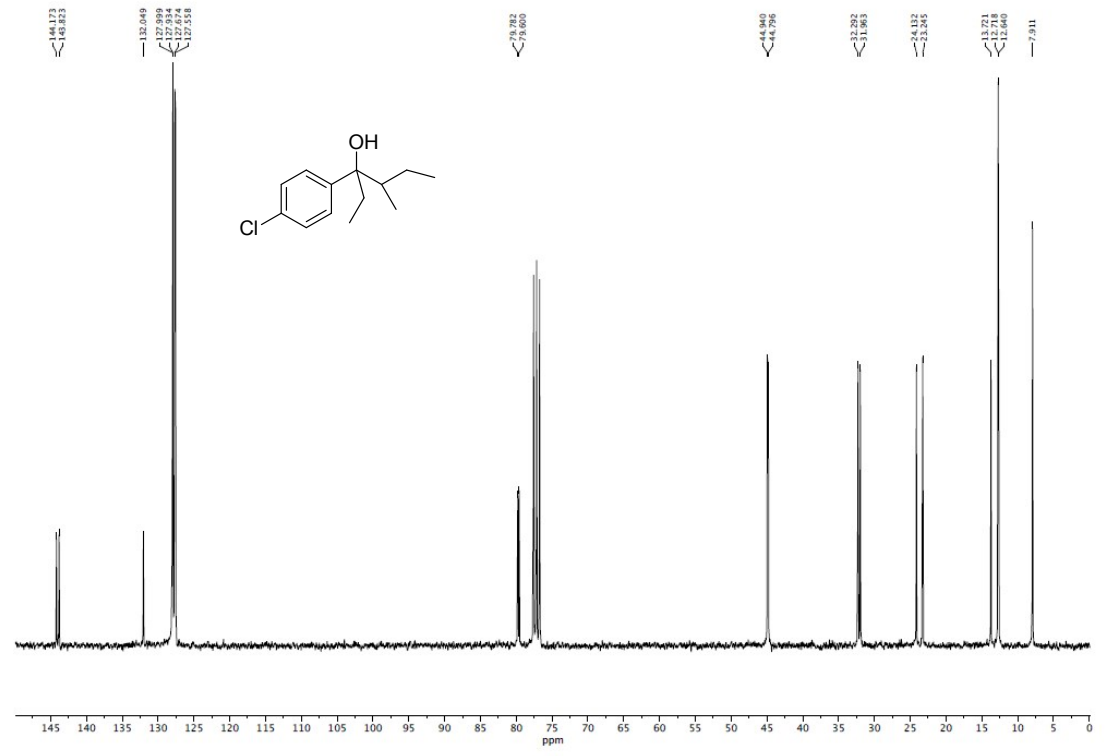


Figure S10. ^{13}C{^{1}H}-NMR full chart for **5e** in $CDCl_3$.

^{1}H and ^{13}C NMR spectra of 3-(4-chlorophenyl)heptan-3-ol (5f)

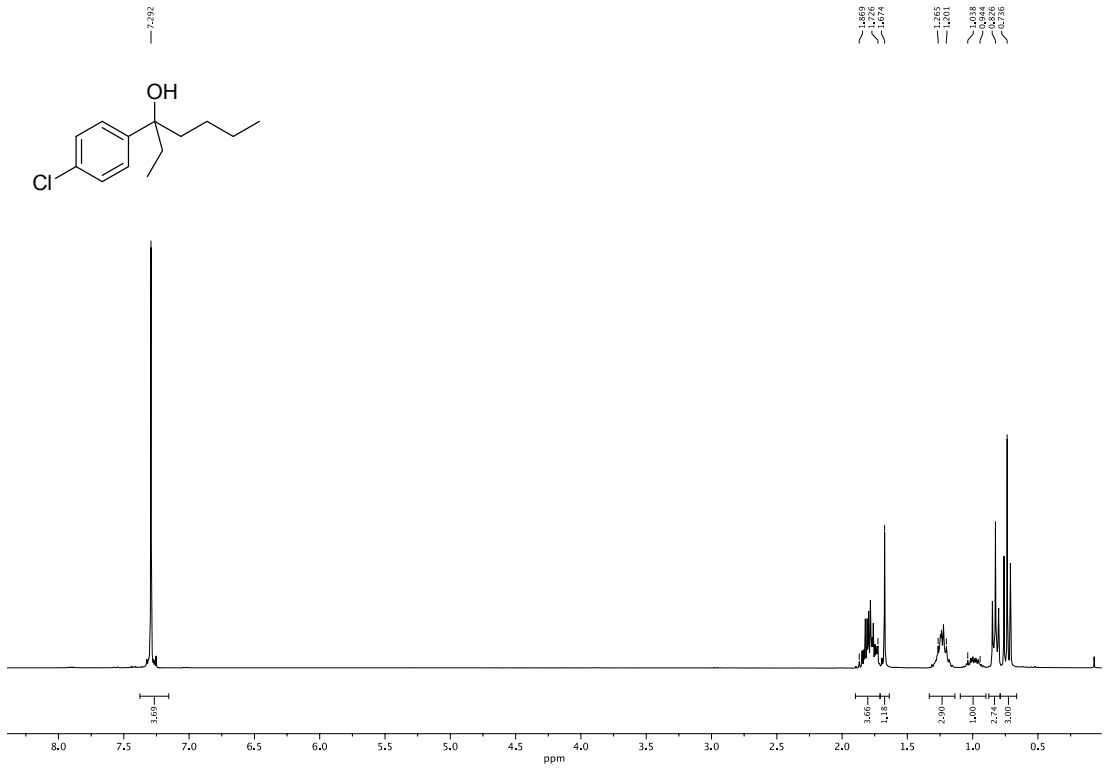


Figure S11. ^{1}H-NMR full chart for **5f** in $CDCl_3$.

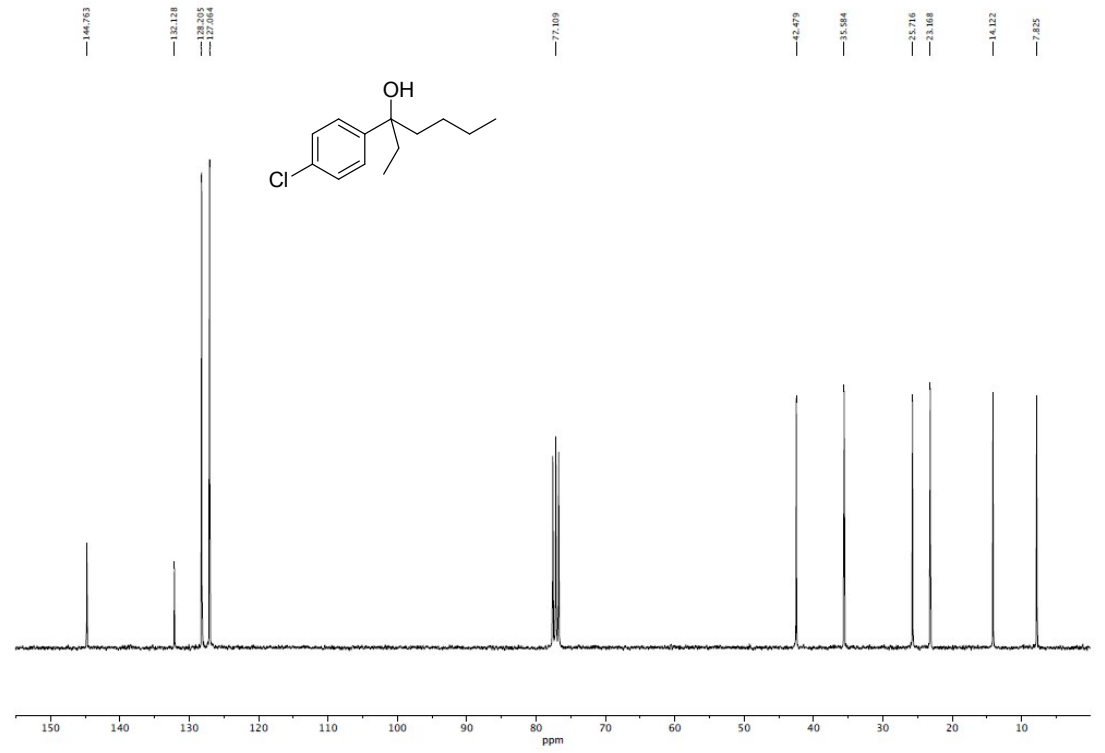


Figure S12. ^{13}C{^{1}H}-NMR full chart for **5f** in $CDCl_3$.

^{1}H and ^{13}C NMR spectra of 3-(4-bromophenyl)heptan-3-ol (5g)

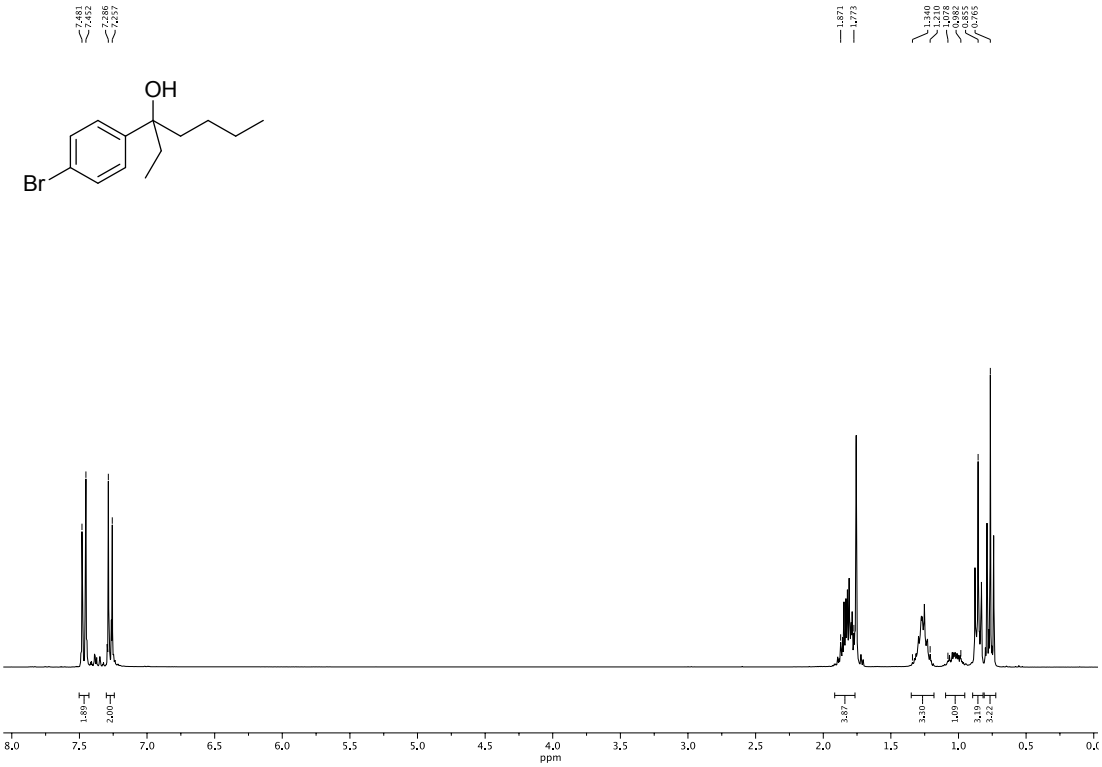


Figure S13. ^{1}H-NMR full chart for **5g** in $CDCl_3$.

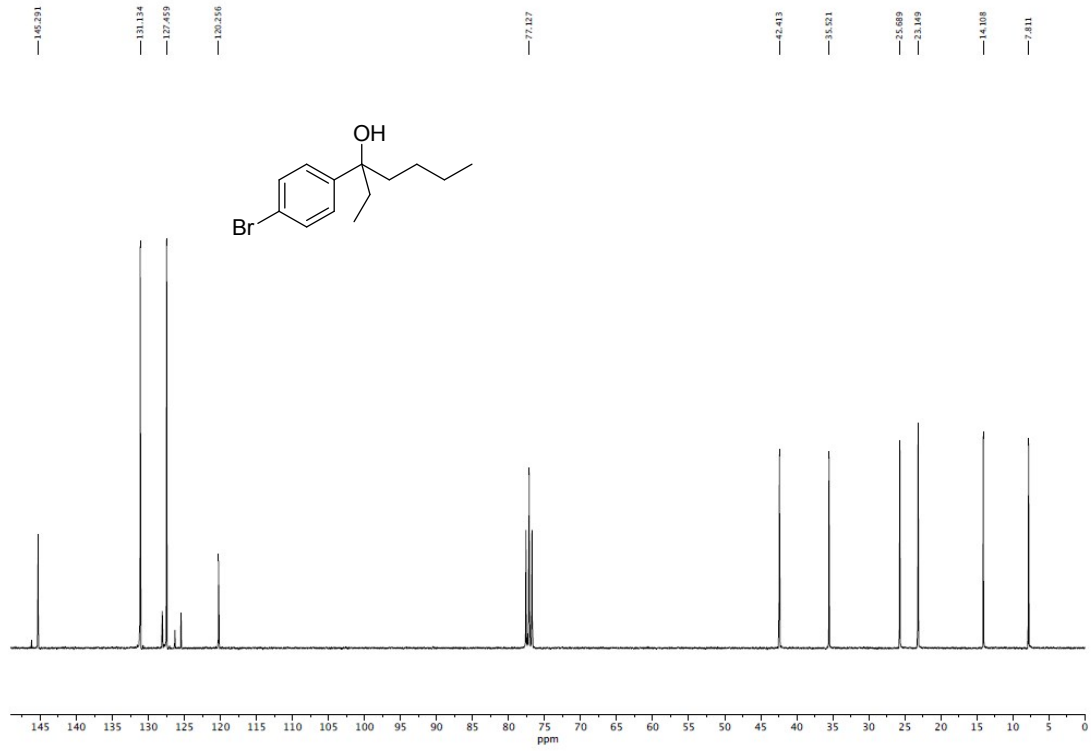


Figure S14. ^{13}C{^{1}H}-NMR full chart for **5g** in $CDCl_3$.

^{1}H and ^{13}C NMR spectra of 3-(4-bromophenyl)-4-methylhexan-3-ol (5h)

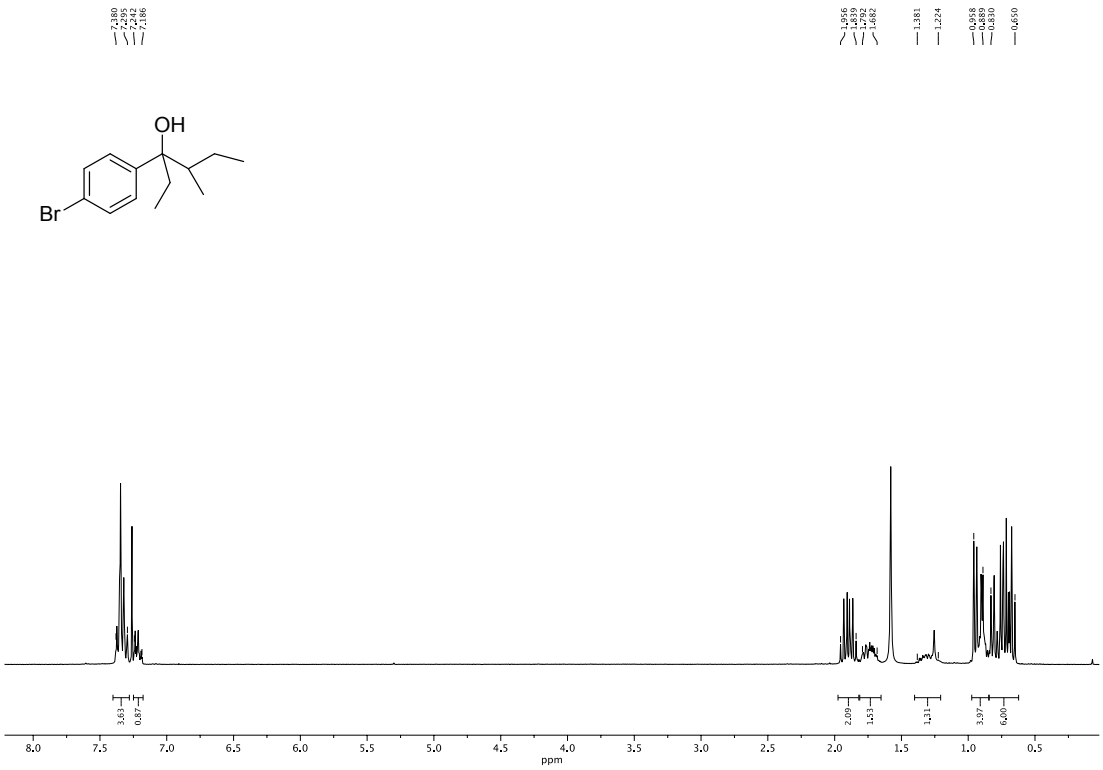


Figure S15. ^{1}H-NMR full chart for **5h** in $CDCl_3$.

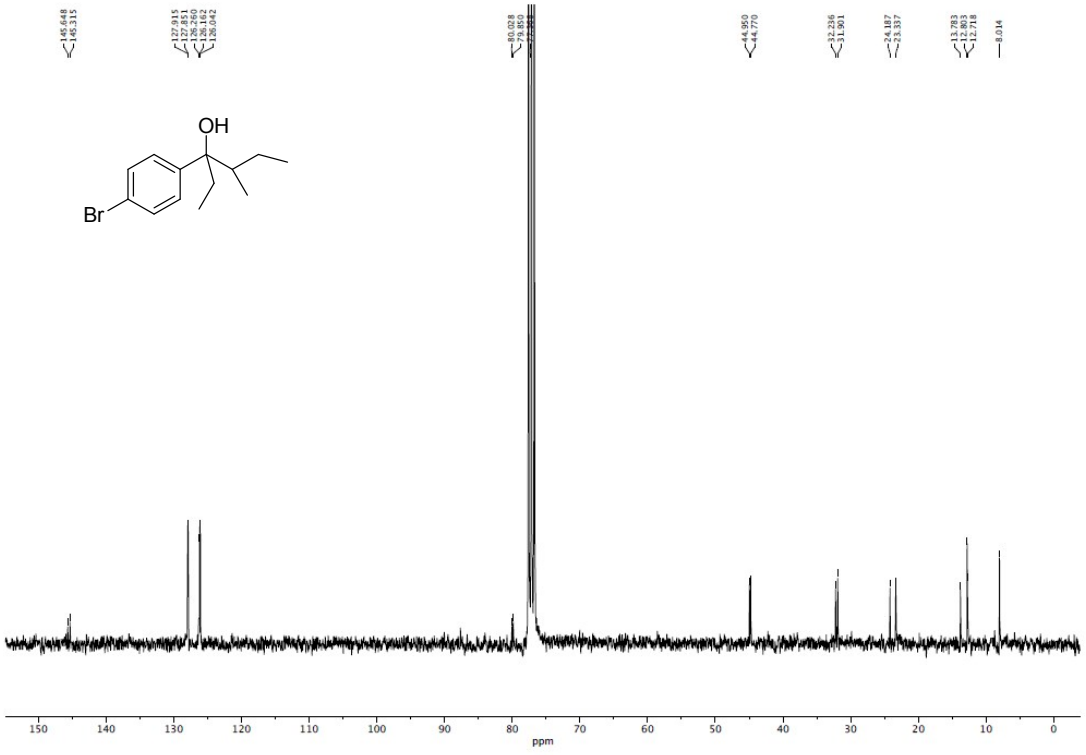


Figure S16. ^{13}C{^{1}H}-NMR full chart for **5h** in $CDCl_3$.

^{1}H and ^{13}C NMR spectra of 3-(p-tolyl)heptan-3-ol (5i)

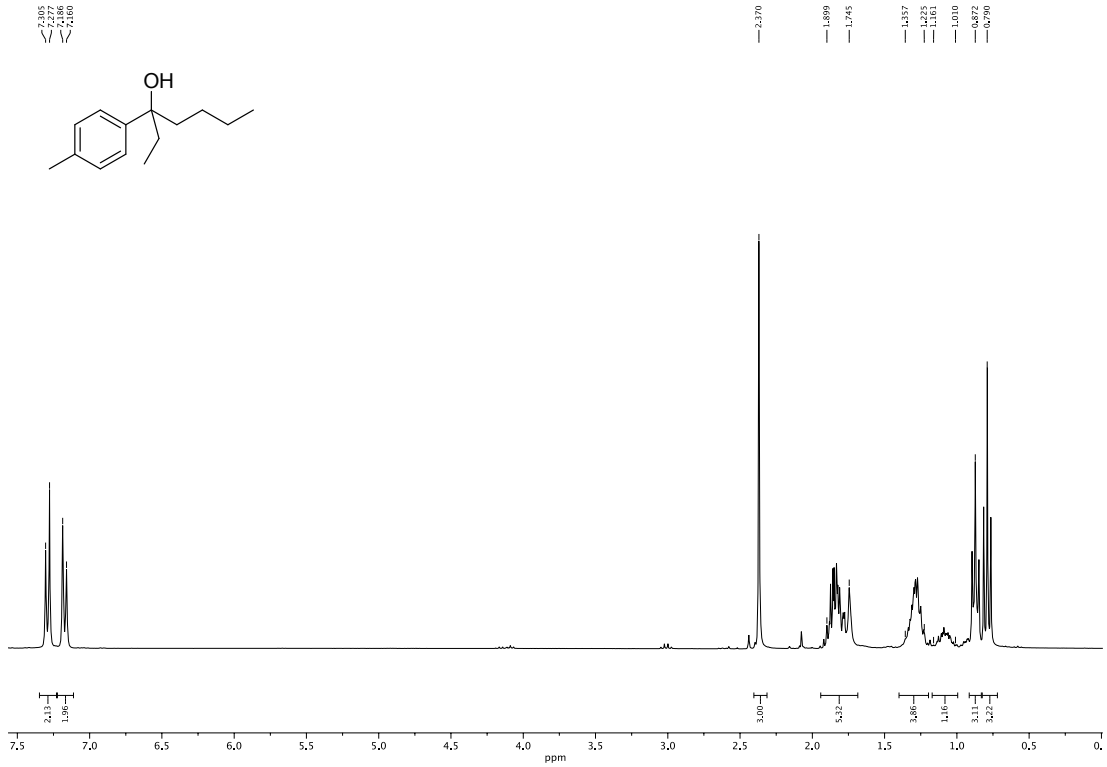


Figure S17. ^{1}H-NMR full chart for **5i** in $CDCl_3$.

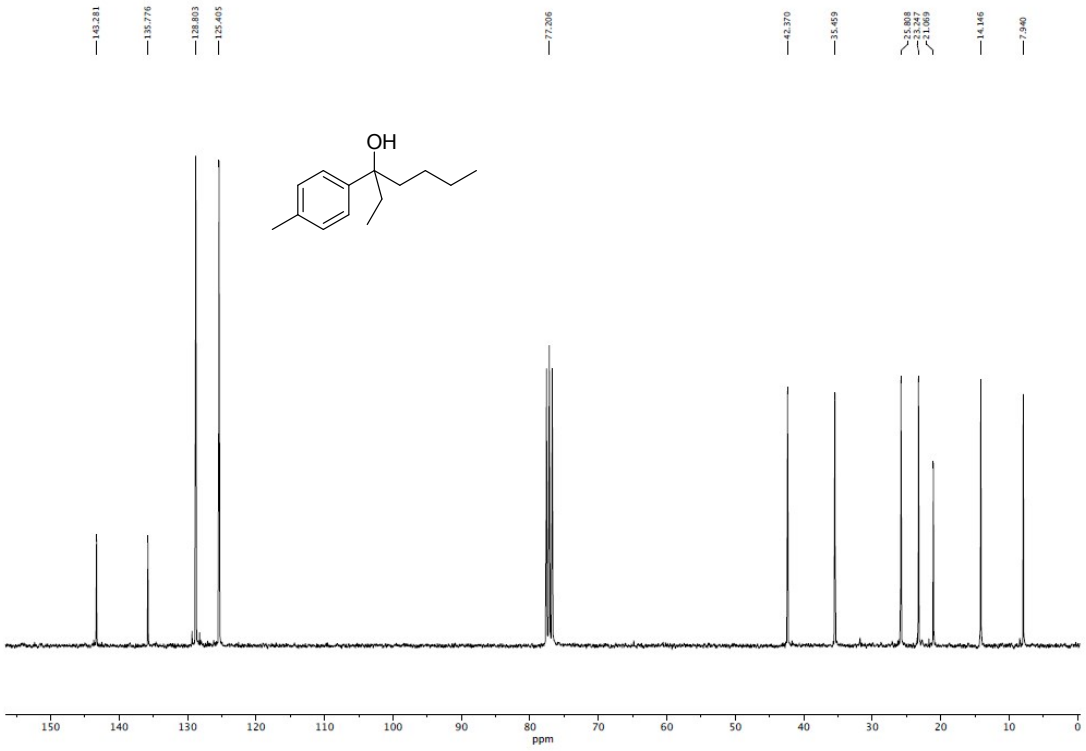


Figure S18. $^{13}C\{^{1}H\}$-NMR full chart for **5i** in $CDCl_3$.

^{1}H and ^{13}C NMR spectra of 4-methyl-3-(p-tolyl)hexan-3-ol (5j)

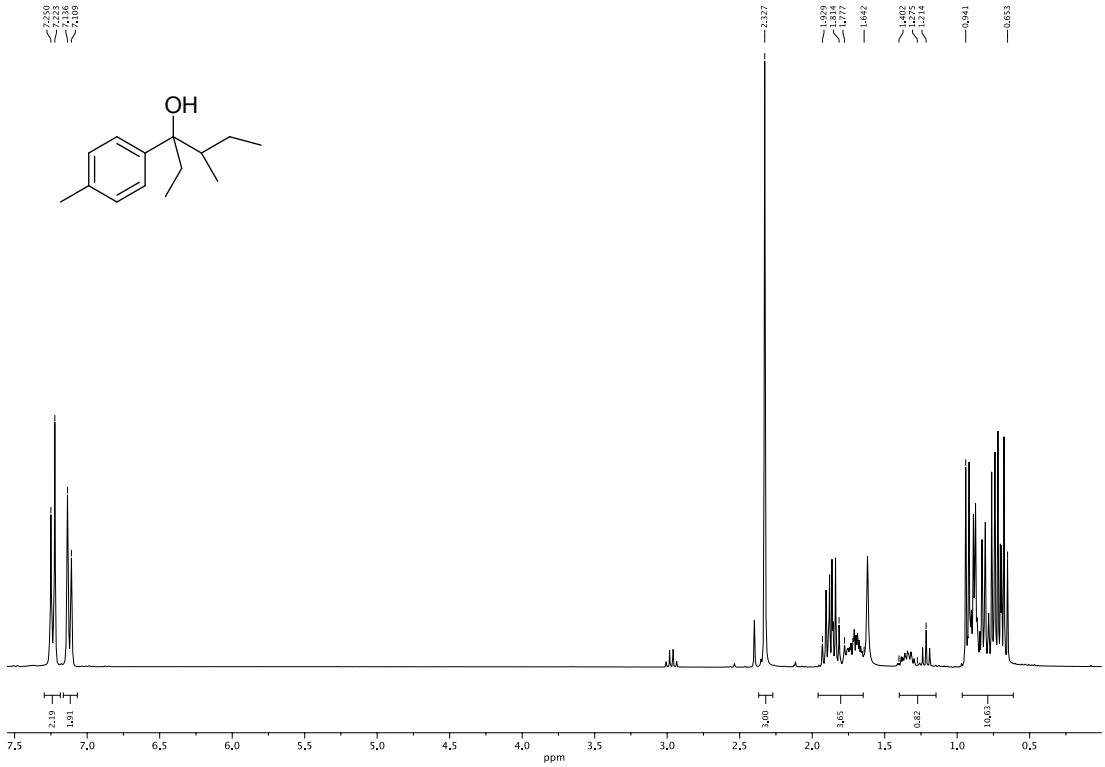


Figure S19. ^{1}H-NMR full chart for **5j** in $CDCl_3$.

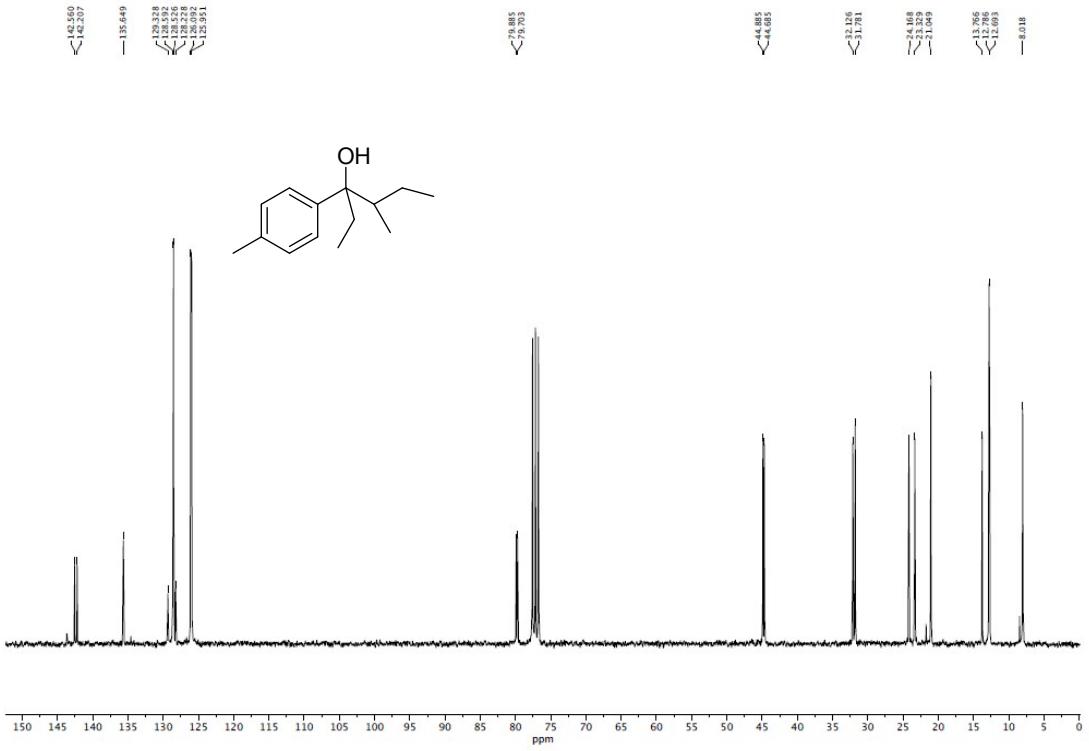


Figure S20. ^{13}C{^{1}H}-NMR full chart for **5j** in $CDCl_3$.

^{1}H and ^{13}C NMR spectra of 3-(4-methoxyphenyl)heptan-3-ol (5k)

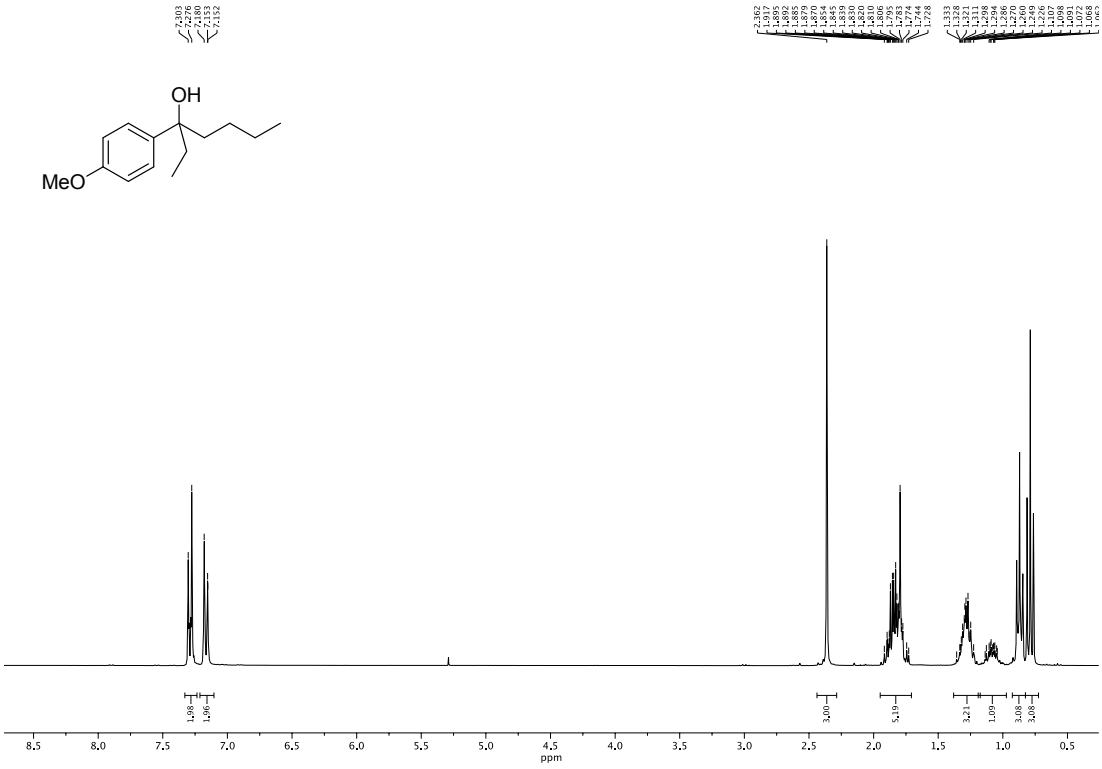


Figure S21. ^{1}H-NMR full chart for **5k** in $CDCl_3$.

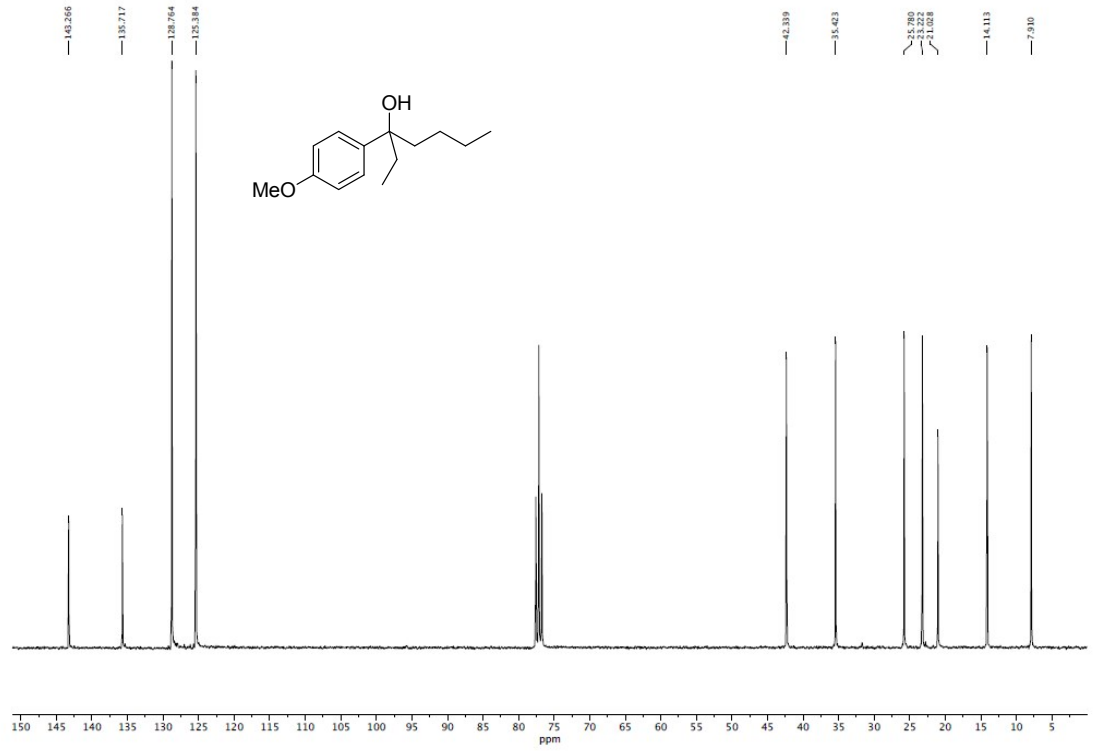


Figure S22. $^{13}C\{^{1}H\}$-NMR full chart for **5k** in $CDCl_3$.

^{1}H and ^{13}C NMR spectra of 3-(4-methoxyphenyl)-4-methylhexan-3-ol (5l)

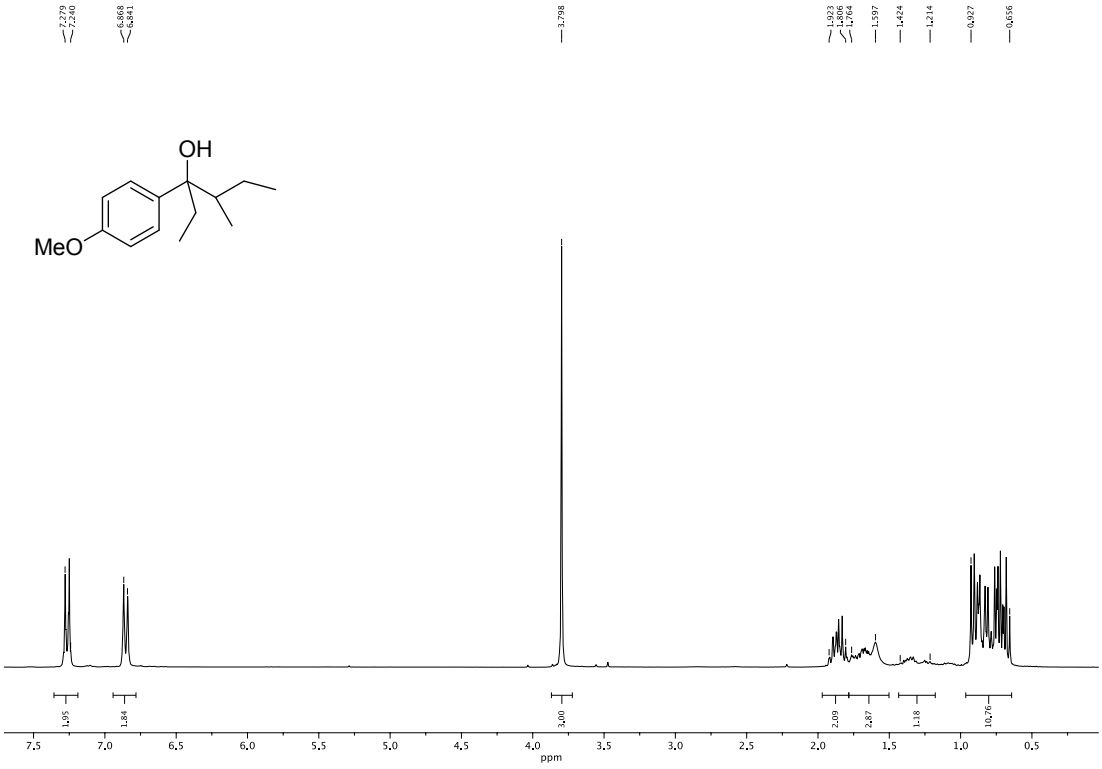


Figure S23. ^{1}H-NMR full chart for **5l** in $CDCl_3$ (300 MHz).

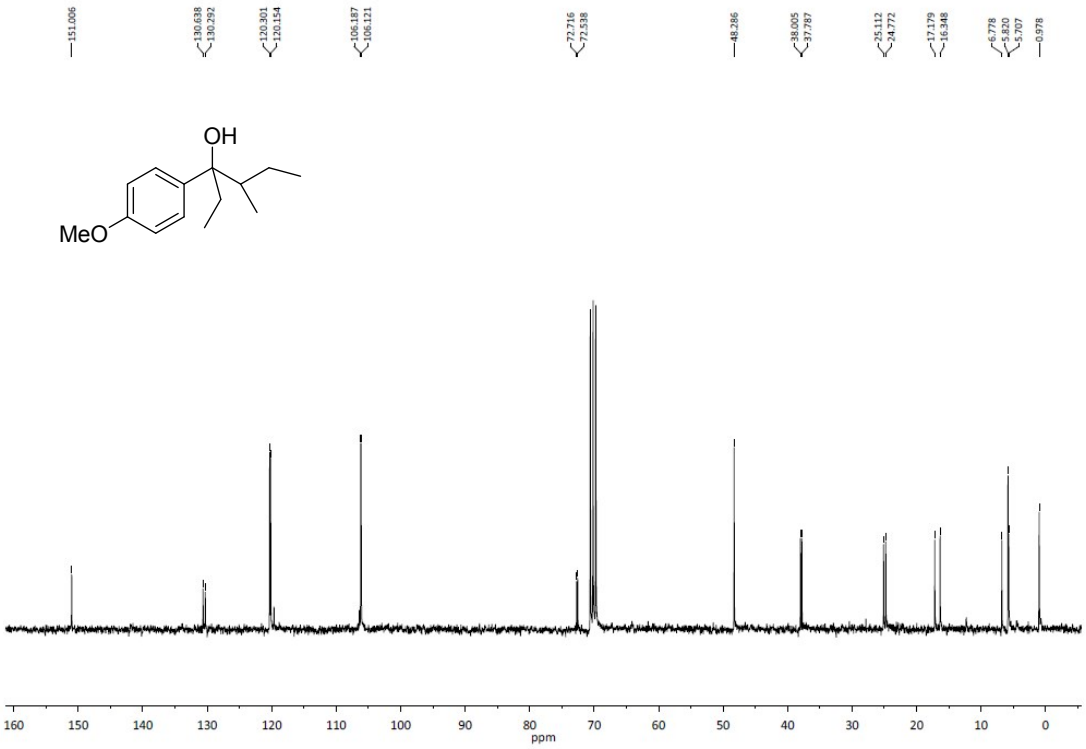


Figure S24. ^{13}C{^{1}H}-NMR full chart for **5l** in $CDCl_3$.

^{1}H and ^{13}C NMR spectra of 3-(o-tolyl)heptan-3-ol (5m)

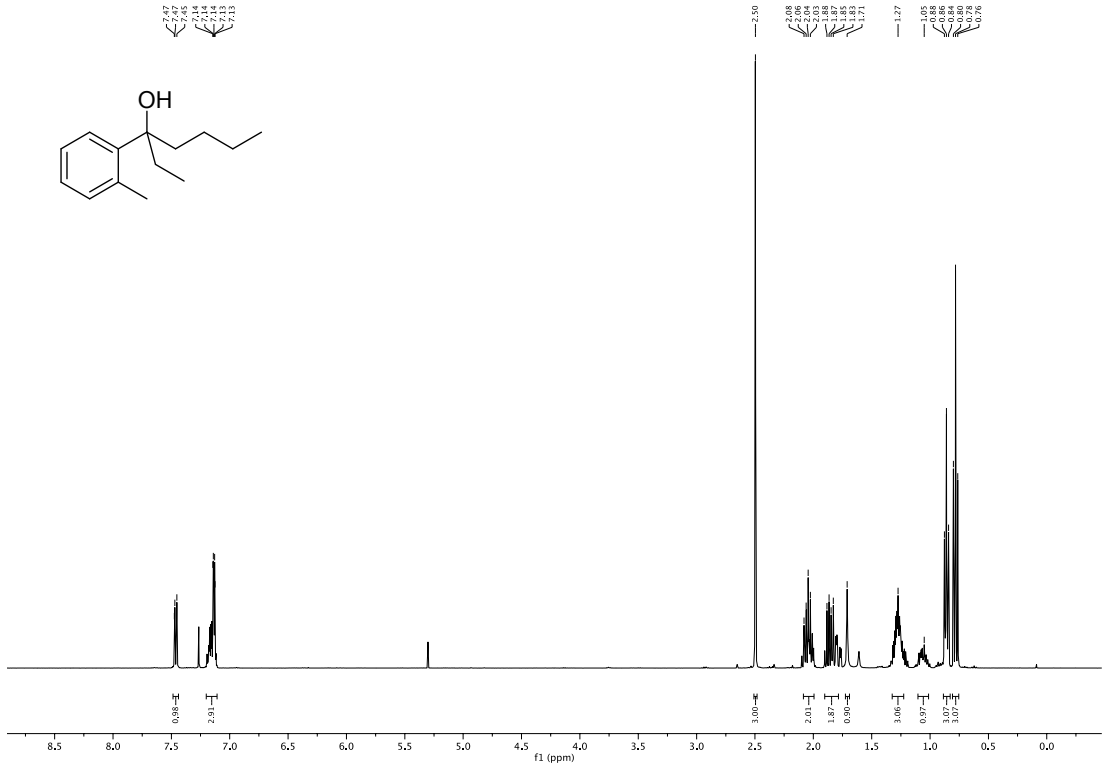


Figure S25. ^{1}H-NMR full chart for **5m** in $CDCl_3$.

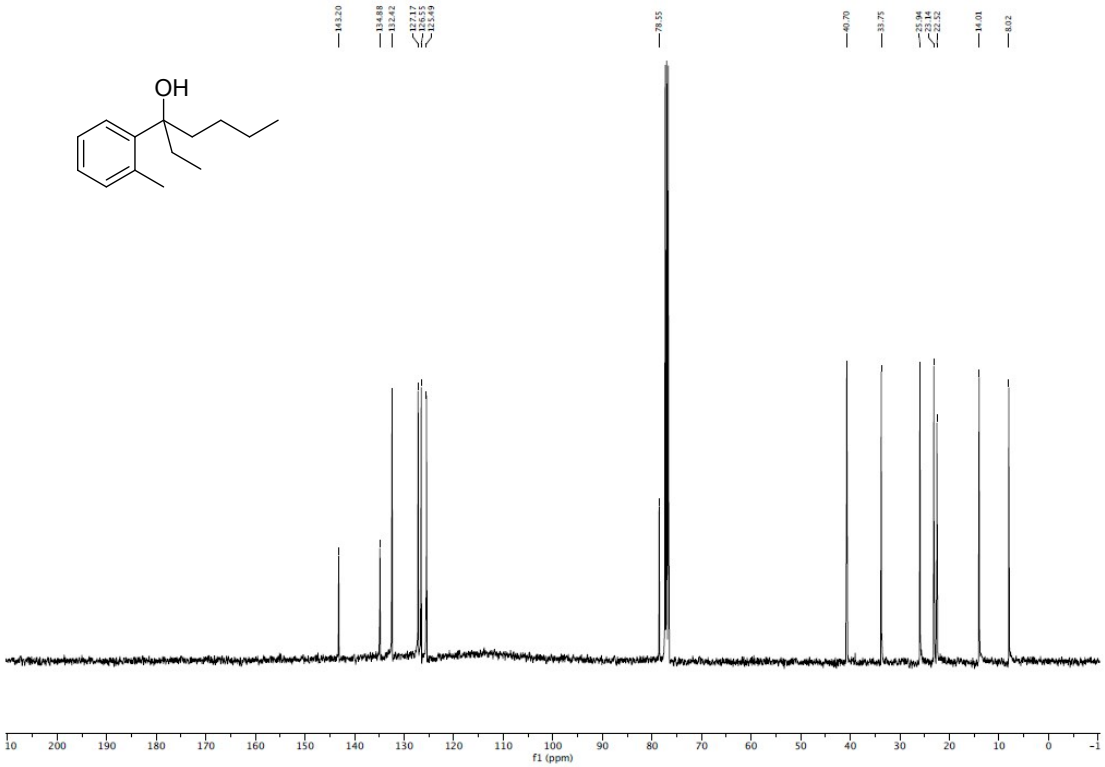


Figure S26. ^{13}C{^{1}H}-NMR full chart for **5m** in $CDCl_3$.

^{1}H and ^{13}C NMR spectra of 4-methyl-3-(o-tolyl)hexan-3-ol (5n)

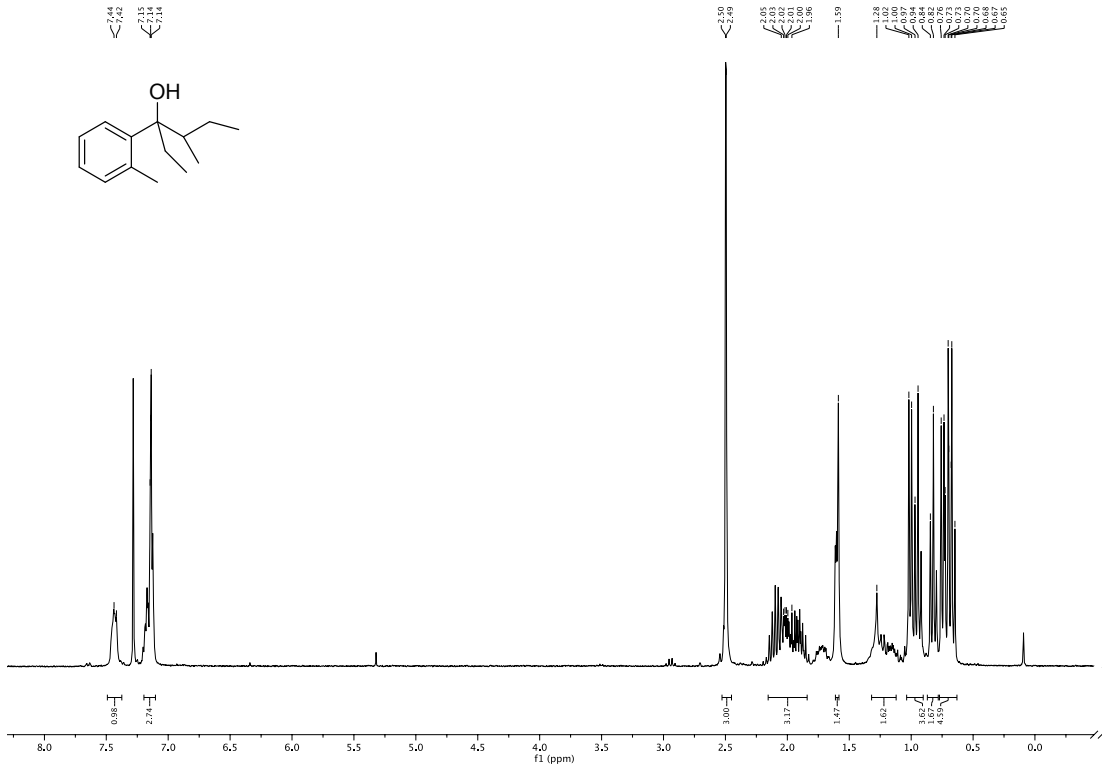


Figure S27. ^{1}H-NMR full chart for **5n** in $CDCl_3$.

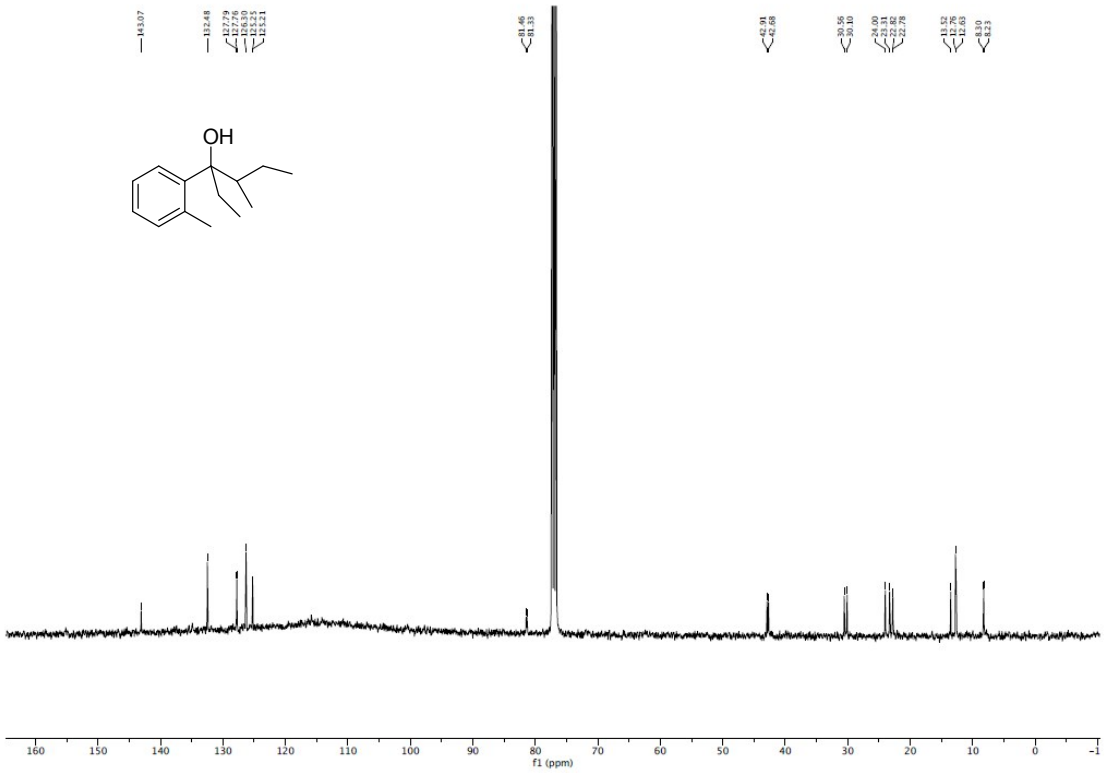


Figure S28. ^{13}C{^{1}H}-NMR full chart for **5n** in $CDCl_3$.

5.- References

[1] E. Liardo, N. Ríos-Lombardía, F. Morís, J. González-Sabín and F. Rebolledo, *Eur. J. Org. Chem.,* 2018, 3031.

[2] L. Cicco, M. J. Rodríguez-Álvarez, F. M. Perna, J. García-Álvarez and V. Capriati, *Green Chem.,* 2017, **19**, 3069.

[3] T. Okada, T. Asawa, Y. Sugiyama, T. Iwai, M. Kirihara and Y. Kimura, *Tetrahedron*, 2016, **72**, 2818.

[4] (2-azaadamantane *N*-oxyl) AZADO was supplied by Sigma-Aldrich.