

SUPPORTING INFORMATION

Title: TBD-Catalyzed Direct 5- and 6-*enolexo* Aldolization of Ketoaldehydes

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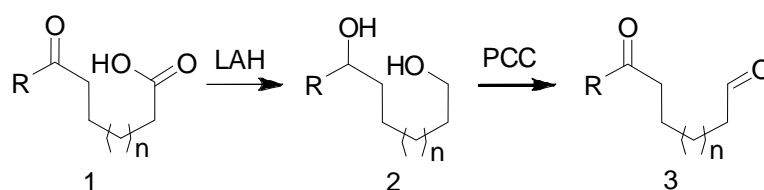
Ref. No.: O200800539

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I. General information

All reactions were performed under an Argon atmosphere. The following solvents were distilled from the indicated drying agents: CH₂Cl₂ (CaH₂), THF (Na), CH₃CN (CaH₂), or dried over 4 Å molecular sieves. All commercially available reagents were used without further purification. Analytical thin-layer chromatography (TLC) was performed on glass-backed silica gel plates. Visualization of the developed chromatogram was performed using UV absorbance and a vanillin solution. Flash column chromatography was performed with silica gel (40-63 μm) according to a standard technique. Nuclear magnetic resonance spectra (¹H and ¹³C) were recorded on a 200 or 300 MHz spectrometer equipped with a BBI or a DUAL probe. Chemical shifts for ¹H and ¹³C spectra are recorded in parts per million using the residual chloroform as internal standard (¹H, δ = 7.26 ppm; ¹³C, δ = 77.16 ppm). Multiplicities are indicated by s (singlet), bs (broad singlet), d (doublet), t (triplet), q (quadruplet), qt (quintuplet) and m (multiplet). Coupling constants, *J*, are reported in Hertz. Infrared spectra were recorded on a FT-IR spectrometer equipped with KRS-5 (ThI/ThBr) lenses and are reported in reciprocal centimetres (cm⁻¹). Melting points were uncorrected.

II. A representative procedure for the synthesis of ketoaldehydes substrates 3

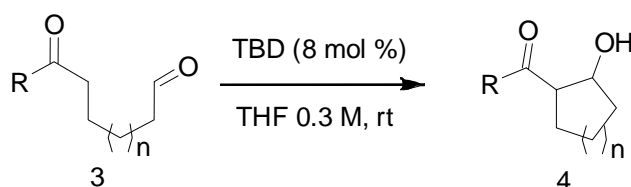


To a suspension of lithium aluminium hydride (3.7 equiv) in anhydrous THF, was added dropwise *via* an addition funnel a solution of the oxocarboxylic acid **1** in THF. The reaction was stirred for 1h at room temperature then cooled to 0°C. The excess hydride was cautiously quenched by the sequential addition of water and 15% of sodium hydroxide. The resulting white suspension was warmed to room temperature and stirred for 30 min. Filtration through Celite afforded filtrate, which was dried over magnesium sulfate. Filtration, followed by

concentration *in vacuo*, provided the crude that was purified by flash chromatography to give the diol **2** as oil or a solid.

To a solution of **2** in anhydrous CH₂Cl₂ was added PCC (3 equiv) at room temperature. The mixture was stirred for 4h then the medium was concentrated and the crude directly purified by silica gel chromatography to give the ketolaldehyde substrates **3**. These ketoaldehydes must be used directly for the intramolecular aldol reactions because they are unstable and undergo oxidation rapidly to give the oxocarboxylic acid derivatives. Due to oxidation problems, the melting points of the solid ketoaldehydes were not measured.

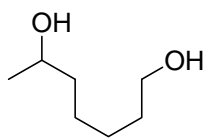
A representative procedure for the TBD-catalyzed intramolecular aldolization.



To a solution of ketoaldehyde **3** in anhydrous THF (0.3 M) was added 8 mol % of TBD at room temperature. The reaction mixture was stirred for 30 min and then quenched with saturated ammonium chloride solution. The organic layer was separated. The aqueous layer was extracted 3 times with diethyl ether. The organic layers were dried over magnesium sulfate, filtered, concentrated *in vacuo* to afford a crude that was purified by flash chromatography to give the desired aldol products **4** as a mixture of two diastereoisomers.

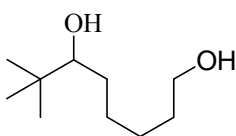
The relative stereochemistry of the diastereoisomers was assigned by analogy to our results and to reported data.^[1]

Characterization data



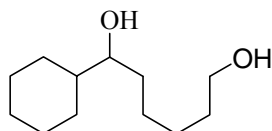
Heptane-1,6-diol (2a)

81% as colorless oil after purification by flash chromatography (EtOAc/cyclohexane 80/20); ^1H NMR (300 MHz, CDCl_3) δ 3.65 (m, 3H), 3.46 (t, $J = 6.4$ Hz, 2H), 1.48-1.4 (m, 2H), 1.38-1.19 (m, 6H), 1.05 (d, $J = 6.3$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 67.5, 62.0, 39.0, 32.4, 25.7, 25.4, 23.2; IR (neat): 3356, 2929, 2858, 1463, 1376, 1135, 1057, 1018, 947 cm^{-1} ; exact mass calculated for $\text{C}_7\text{H}_{16}\text{Li}_1\text{O}_2$ ($\text{M}+\text{Li}^+$): 139.1305 ; found 139.1302.



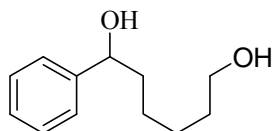
7,7-Dimethyl-octane-1,6-diol (2b)

97% as colorless oil after purification by flash chromatography (EtOAc/cyclohexane 70/30); ^1H NMR (200 MHz, CDCl_3) δ 3.65 (t, $J = 6.4$, 2H), 3.19 (dd, $J = 10$ Hz, $J = 1.6$ Hz, 1H), 1.62-1.20 (m, 8H), 1.41 (s, 2H), 0.88 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 79.8, 62.5, 35.0, 32.7, 31.4, 26.8, 25.8, 25.8; IR (neat): 3369, 2944, 2867, 1648, 1478, 1465, 1393, 1364, 1071, 1053, 1004, 652 cm^{-1} ; exact mass calculated for $\text{C}_{10}\text{H}_{22}\text{Li}_1\text{O}_2$ ($\text{M}+\text{Li}^+$): 181.1775 ; found 181.1773.



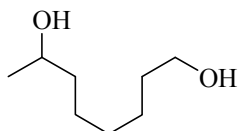
1-Cyclohexyl-hexane-1,6-diol (2c)

99% as colorless oil after purification by flash chromatography (EtOAc/cyclohexane 80/20); ^1H NMR (300 MHz, CDCl_3) δ 3.65 (t, $J = 6$ Hz, 2H), 3.38-3.33 (m, 1H), 1.18-1.01 (m, 19H), 1.40 (bs, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 76.0, 62.5, 43.7, 34.0, 32.6, 29.3, 27.9, 26.6, 26.4, 26.3, 25.8, 25.7; IR (neat): 3368, 2928, 2853, 1651, 1450, 1055, 683 cm^{-1} ; exact mass calculated for $\text{C}_{12}\text{H}_{24}\text{Li}_1\text{O}_2$ ($\text{M}+\text{Li}^+$) : 207.1931 ; found 207.1928.



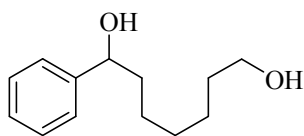
1-Phenyl-hexane-1,6-diol (2d)

94% as white solid after purification by flash chromatography (EtOAc/cyclohexane 50/50); ^1H NMR (200 MHz, CDCl_3) δ 7.36-7.26 (m, 5H), 4.68 (dd, $J = 7.2$ Hz, $J = 5.8$ Hz, 1H), 3.62 (t, $J = 6.4$ Hz, 2H), 1.77-1.18 (m, 10H); ^{13}C NMR (75 MHz, CDCl_3) δ 144.0, 128.4, 127.4, 125.9, 74.3, 62.5, 39.0, 32.5, 25.6, 25.56; IR (neat): 3339, 2935, 2860, 1651, 1493, 1453, 1055, 1015, 762, 701 cm^{-1} ; mp : 54-57 $^{\circ}\text{C}$; exact mass calculated for $\text{C}_{12}\text{H}_{18}\text{Li}_1\text{O}_2$ ($\text{M}+\text{Li}^+$) : 201.1462 ; found 201.1460.



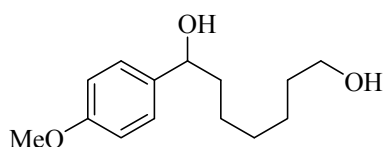
Octane-1,7-diol (2e)

91% as colorless oil after flash chromatography (EtOAc/cyclohexane 80:20) ; ^1H NMR (200 MHz, CDCl_3) δ 3.87-3.72 (m, 1H), 3.64 (t, $J = 6.6$ Hz, 2H), 1.60-1.53 (m, 2H), 1.45-1.33 (m, 10H), 1.18 (d, $J = 6$ Hz, 3H) ; ^{13}C NMR (75 MHz, CDCl_3) δ 67.5, 62.0, 38.9, 32.4, 29.3, 25.6, 23.1; IR (neat): 3339, 2931, 2858, 1460, 1374, 1132, 1058 cm^{-1} ; exact mass calculated for $\text{C}_8\text{H}_{18}\text{Li}_1\text{O}_2$ ($\text{M}+\text{Li}^+$) : 153.1462 ; found 153.1459.



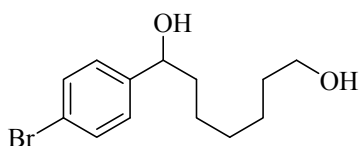
1-Phenyl-heptane-1,7-diol (2f)

96% as white solid after purification by flash chromatography (EtOAc/cyclohexane 50:50); ^1H NMR (200 MHz, CDCl_3) δ 7.36-7.26 (m, 5H), 4.67 (dd, $J = 7$ Hz, $J = 5.8$ Hz, 1H), 3.62 (t, $J = 6.4$ Hz, 2H), 1.85-1.31 (m, 12H); ^{13}C NMR (75 MHz, CDCl_3) δ 145.0, 128.4, 127.5, 126.0, 74.6, 62.8, 39.0, 32.6, 29.3, 25.8, 25.7; IR (neat): 3351, 2933, 2858, 1493, 1454, 1056, 763, 701 cm^{-1} ; mp : 40-43 $^\circ\text{C}$; exact mass calculated for $\text{C}_{13}\text{H}_{20}\text{Li}_1\text{O}_2$ ($\text{M}+\text{Li}^+$) : 215.1618 ; found 215.1619.



1-(4-Methoxy-phenyl)-heptane-1,7-diol (2g)

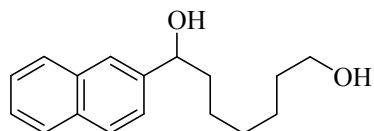
73% as white solid after purification by flash chromatography (EtOAc 100%); ^1H NMR (200 MHz, CDCl_3) δ 7.30-7.21 (m, 3H), 6.91-6.86 (m, 2H), 4.63 (t, $J = 6.4$ Hz, 1H), 3.82 (s, 3H), 3.63 (t, $J = 6.4$ Hz, 2H), 1.90-1.20 (m, 12H); ^{13}C NMR (75 MHz, CDCl_3) δ 159.0, 137.2, 127.2, 113.9, 74.3, 63.0, 55.4, 39.0, 32.7, 29.4, 25.9, 25.7; IR (neat): 3391, 2934, 2851, 1651, 1611, 1513, 1247, 833 cm^{-1} ; mp : 80-81 $^\circ\text{C}$; exact mass calculated for $\text{C}_{14}\text{H}_{22}\text{Li}_1\text{O}_3$ ($\text{M}+\text{Li}^+$) : 245.1724 ; found 245.1718.



1-(4-Bromo-phenyl)-heptane-1,7-diol (2h)

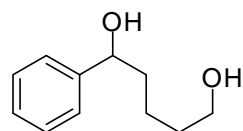
83% as white solid after purification by flash chromatography (EtOAc/cyclohexane 70:30); ^1H NMR (200 MHz, CDCl_3) δ 7.53-7.23 (m, 4H), 4.67 (t, $J = 6.4$ Hz, 1H), 3.66 (t, $J = 6.4$ Hz, 2H), 1.90-1.30 (m, 12H); ^{13}C NMR (75 MHz, CDCl_3) δ 144.0, 131.5, 127.7, 121.2, 73.9,

62.9, 39.1, 32.6, 29.3, 25.8, 25.7; IR (neat): 3359, 2933, 2857, 1486, 1070, 1010, 826, 701 cm^{-1} ; mp : 53.5-56 °C; exact mass calculated for $\text{C}_{13}\text{H}_{19}\text{BrLiO}_2$ ($\text{M}+\text{Li}^+$) : 293.0723 ; found 293.0718.



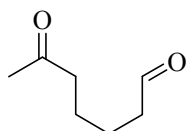
1-Naphthalen-2-yl-heptane-1,7-diol (2i)

75% as white solid after purification by flash chromatography (EtOAc/cyclohexane 70:30); ^1H NMR (200 MHz, CDCl_3) δ 7.85-7.78 (m, 4H), 7.50-7.45 (m, 3H), 4.84 (t, $J = 6.6$ Hz, 1H), 3.61 (t, $J = 6.6$ Hz, 2H), 1.57-1.35 (m, 12H); ^{13}C NMR (75 MHz, CDCl_3) δ 142.3, 133.4, 133.1, 128.4, 128.0, 127.8, 126.2, 125.9, 124.7, 124.2, 74.8, 63.0, 39.0, 32.7, 29.4, 25.9, 25.7; IR (neat): 3390, 2934, 1644, 820, 749 cm^{-1} ; mp : 87-88 °C; exact mass calculated for $\text{C}_{17}\text{H}_{22}\text{LiO}_2$ ($\text{M}+\text{Li}^+$) : 265.1775 ; found 265.1765.



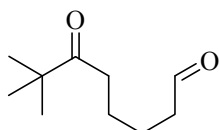
1-Phenyl-pentane-1,5-diol (2k)

96% as white solid after purification by flash chromatography (EtOAc/cyclohexane 90/10); ^1H NMR (200 MHz, CDCl_3) δ 7.35-7.26 (m, 5H), 4.68 (dd, $J = 7.6$ Hz, $J = 5.6$ Hz, 1H), 3.63 (t, $J = 6.4$ Hz, 2H), 1.93-1.32 (m, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 145.0, 128.4, 127.4, 125.9, 74.3, 62.3, 38.7, 32.3, 22.0; IR (neat): 3351, 2939, 2864, 1455, 1070, 1056, 1029, 701 cm^{-1} ; mp : 52-54 °C ; exact mass calculated for $\text{C}_{11}\text{H}_{16}\text{LiO}_2$ ($\text{M}+\text{Li}^+$) : 187.1305 ; found 187.1299.



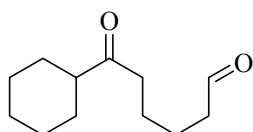
6-Oxo-heptanal (3a)

65% as colorless oil after purification by flash chromatography (EtOAc/cyclohexane 50:50); ^1H NMR (200 MHz, CDCl_3) δ 9.77 (s, 1H), 2.48-2.44 (m, 4H), 2.14 (s, 3H), 1.64-1.57 (m, 4H); ^{13}C NMR (75 MHz, CDCl_3) δ 208.5, 202.3, 43.7, 43.3, 30.0, 23.1, 21.5; IR (neat): 2941, 2868, 2727, 1717, 1412, 1365, 1174, 1162, 735 cm^{-1} ; exact mass calculated for $\text{C}_7\text{H}_{12}\text{Li}_1\text{O}_2$ ($\text{M}+\text{Li}^+$) : 135.0992 ; found 135.0992.



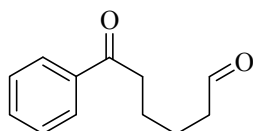
7,7-Dimethyl-6-oxo-octanal (3b)

82% as yellow pale oil after purification by flash chromatography (cyclohexane/EtOAc 80:20); ^1H NMR (300 MHz, CDCl_3) δ 9.68 (t, $J = 1.5$ Hz, 1H), 2.46-2.35 (m, 4H), 1.51 (m, 4H), 0.88 (s, 9H) ; ^{13}C NMR (75 MHz, CDCl_3) δ 215.3, 202.3, 44.0, 43.8, 36.0, 26.4, 23.3, 21.6; IR (neat): 2967, 2871, 2825, 1725, 1705, 1479, 1366, 1169, 1060, 736 cm^{-1} ; exact mass calculated for $\text{C}_{10}\text{H}_{18}\text{Li}_1\text{O}_2$ ($\text{M}+\text{Li}^+$) : 177.1462 ; found 177.1454.



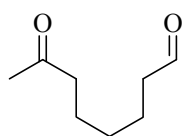
6-Cyclohexyl-6-oxo-hexanal (3c)

84% as yellow pale oil after purification by flash chromatography (cyclohexane/EtOAc 80:20); ^1H NMR (200 MHz, CDCl_3) δ 9.73 (t, $J = 1.5$ Hz, 1H), 2.21-2.12 (m, 4H), 2.10-1.96 (m, 1H), 1.56-1.43 (m, 4H), 1.34-1.24 (m, 4H), 1.12-0.89 (m, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 213.7, 202.4, 50.9, 43.8, 40.2, 28.6, 25.9, 25.7, 23.1, 21.7; IR (neat): 2931, 2855, 2720, 1724, 1707, 1450, 1410, 1375, 1145 cm^{-1} ; exact mass calculated for $\text{C}_{12}\text{H}_{20}\text{Li}_1\text{O}_2$ ($\text{M}+\text{Li}^+$) : 203.1618 ; found 203.1614.



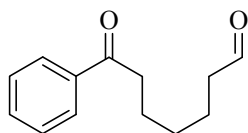
6-Oxo-6-phenyl-hexanal (3d)

74% as white solid after purification by flash chromatography (cyclohexane/EtOAc 80:20); ^1H NMR (300 MHz, CDCl_3) δ 9.79 (t, $J = 1.5$ Hz, 1H), 7.96-7.93 (m, 2H), 7.59-7.53 (m, 1H), 7.49-7.43 (m, 2H), 3.01 (t, $J = 6.9$ Hz, 2H), 2.51 (td, $J = 7.2$ Hz, $J = 1.5$ Hz, 2H), 1.79-1.70 (m, 4H); ^{13}C NMR (75 MHz, CDCl_3) δ 202.3, 199.7, 136.9, 133.1, 128.6, 128.0, 43.8, 38.2, 23.6, 21.7; IR (neat): 2945, 2934, 2868, 1713, 1678, 1459, 1449, 1405, 733, 692 cm^{-1} ; exact mass calculated for $\text{C}_{12}\text{H}_{14}\text{Li}_1\text{O}_2$ ($\text{M}+\text{Li}^+$) : 197.1149 ; found 197.1152.



7-Oxo-octanal (3e)

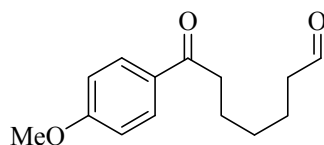
68% as colorless oil after purification by flash chromatography (cyclohexane/EtOAc 50:50); ^1H NMR (300 MHz, CDCl_3) δ 9.76 (t, $J = 1.5$ Hz, 1H), 2.43 (t, $J = 7.5$ Hz, 4H) 2.13 (s, 3H), 1.68-1.54 (m, 4H), 1.37-1.29 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 208.6, 202.3, 43.4, 43.1, 29.7, 28.4, 23.2, 21.6; IR (neat): 2938, 2863, 2725, 1716, 1460, 1411, 1361, 1163 cm^{-1} ; exact mass calculated for $\text{C}_8\text{H}_{14}\text{Li}_1\text{O}_2$ ($\text{M}+\text{Li}^+$) : 149.1149 ; found 149.1145.



7-Oxo-7-phenyl-heptanal (3f)

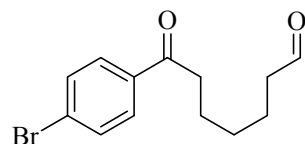
73% as white solid after purification by flash chromatography (cyclohexane/EtOAc 50:50); ^1H NMR (300 MHz, CDCl_3) δ 9.78 (t, $J = 1.5$ Hz, 1H), 7.95 (d, $J = 7.2$ Hz, 2H), 7.59-7.43 (m, 3H), 2.98 (t, $J = 7.2$ Hz, 2H), 2.46 (td, $J = 7.2$ Hz, $J = 1.5$ Hz, 2H), 1.82-1.65 (m, 4H), 1.48-1.40 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 202.5, 200.1, 137.0, 133.0, 128.6, 128.0, 43.7,

38.2, 28.8, 23.9, 21.9; IR (neat): 2938, 2863, 2724, 1723, 1686, 1597, 1580, 1449, 1218, 755, 692 cm^{-1} ; exact mass calculated for $\text{C}_{13}\text{H}_{16}\text{Li}_1\text{O}_2$ ($\text{M}+\text{Li}^+$) : 211.1305; found 211.1309.



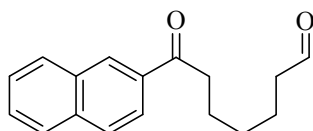
7-(4-Methoxy-phenyl)-7-oxo-heptanal (3g)

83% as white solid after purification by flash chromatography (EtOAc/cyclohexane 60:40); ^1H NMR (300 MHz, CDCl_3) δ 9.76 (t, $J = 1.5$ Hz, 1H), 7.92 (d, $J = 8.7$ Hz, 2H), 6.92 (d, $J = 8.7$ Hz, 2H), 3.86 (s, 3H), 2.92 (t, $J = 7.2$ Hz, 2H), 2.45 (td, $J = 7.2$ Hz, $J = 1.5$ Hz, 2H), 1.79-1.62 (m, 4H), 1.46-1.38 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 202.7, 198.8, 163.5, 130.4, 130.1, 113.8, 55.6, 43.8, 38.0, 28.9, 24.2, 22.0; IR (neat): 2937, 2851, 2722, 1721, 1676, 1601, 1575, 1510, 1259, 1172, 1029, 837 cm^{-1} ; exact mass calculated for $\text{C}_{14}\text{H}_{18}\text{Li}_1\text{O}_3$ ($\text{M}+\text{Li}^+$) : 241.1411 ; found 241.1400.



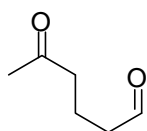
7-(4-Bromo-phenyl)-7-oxo-heptanal (3h)

85% as white solid after purification by flash chromatography (EtOAc/cyclohexane 60:40); ^1H NMR (200 MHz, CDCl_3) δ 9.81 (t, $J = 1.5$ Hz, 1H), 8.01-7.82 (m, 2H), 7.66-7.45 (m, 2H), 3.00 (t, $J = 7.4$ Hz, 2H), 2.5 (td, $J = 7$ Hz, $J = 1.5$ Hz, 2H), 1.89-1.65 (m, 4H), 1.54-1.40 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 202.6, 199.1, 132.0, 129.6, 128.7, 128.1, 43.8, 38.3, 28.8, 23.9, 21.9; IR (neat): 2940, 2862, 2717, 1722, 1685, 1584, 1397, 1215, 1008, 692 cm^{-1} ; exact mass calculated for $\text{C}_{13}\text{H}_{15}\text{Br}_1\text{Li}_1\text{O}_2$ ($\text{M}+\text{Li}^+$) : 289.0410 ; found 289.0403.



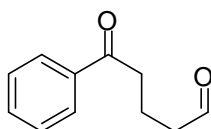
7-Naphthalen-2-yl-7-oxo-heptanal (3i)

87% as white solid after purification by flash chromatography (cyclohexane/EtOAc 80/20); ^1H NMR (200 MHz, CDCl_3) δ 9.76 (t, $J = 1.5$ Hz, 1H), 8.45 (s, 1H), 8.04-7.84 (m, 4H), 7.63-7.49 (m, 2H), 3.09 (t, $J = 7.2$ Hz, 2H), 2.46 (td, $J = 7.2$ Hz, $J = 1.5$ Hz, 2H), 1.88-1.62 (m, 4H), 1.52-1.36 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 202.7, 200.1, 135.6, 134.3, 132.6, 129.7, 129.6, 128.5, 127.8, 126.8, 123.9, 43.8, 38.3, 28.9, 24.1, 22.0; IR (neat): 3061, 2938, 2863, 1719, 1682, 1461, 1410, 816 cm^{-1} ; exact mass calculated for $\text{C}_{17}\text{H}_{18}\text{Li}_1\text{O}_2$ ($\text{M}+\text{Li}^+$): 261.1462 ; found 261.1458.



5-Oxo-hexanal (3j)

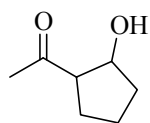
Synthesized according to literature^[2]: colorless oil after purification by flash chromatography (cyclohexane/EtOAc 70/30); ^1H NMR (300 MHz, CDCl_3) δ 9.76 (t, $J = 1.5$ Hz, 1H), 2.52-2.45 (m, 4H), 2.13 (bs, 3H), 1.89 (qt, $J = 7.2$ Hz, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 207.7, 201.7, 42.6, 41.9, 29.6, 15.7.



5-Oxo-5-phenyl-pentanal (3k)

51% as yellow pale oil after purification by flash chromatography (cyclohexane/EtOAc 50/50) ; ^1H NMR (300 MHz, CDCl_3) δ 9.79 (t, $J = 1.5$ Hz, 1H), 7.94 (m, 2H), 7.58-7.42 (m, 3H), 3.03 (t, $J = 7.2$ Hz, 2H), 2.58 (td, $J = 7.2$ Hz, $J = 1.5$ Hz, 2H), 2.06 (qt, $J = 7.2$ Hz, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 181.0, 178.8, 126.8, 123.8, 120.0, 119.5, 48.9, 44.1, 26.8; IR

(neat): 2942, 2896, 2823, 2726, 1722, 1685, 1598, 1580, 1449, 1372, 1230, 748, 692 cm^{-1} ;
exact mass calculated for $\text{C}_{11}\text{H}_{12}\text{LiO}_2$ ($\text{M}+\text{Li}^+$) : 183.0992 ; found 183.0984.



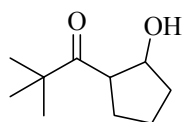
1-(2-Hydroxy-cyclopentyl)-ethanone (4a)

The product was partly lost in the aqueous phase thus no work up was used and the reaction medium was directly poured on the column for purification.

Ratio of diastereoisomers (anti/syn): 69/31

93% as colorless oil after purification by flash chromatography (cyclohexane/EtOAc 80:20);

Syn diastereoisomer: $R_f = 0.42$ (cyclohexane/EtOAc 60:40); ^1H NMR (300 MHz, CDCl_3) δ 4.48 (q, $J = 3.6$ Hz, 1H), 2.77 (td, $J = 9.06$ Hz, $J = 4.38$ Hz, 1H), 2.21 (s, 3H), 2.02-1.89 (m, 3H), 1.79-1.64 (m, 3H) ; ^{13}C NMR (75 MHz, CDCl_3) δ 212.2, 74.0, 57.2, 34.5, 30.5, 25.8, 22.2; IR (neat): 3448, 2962, 2877, 1706, 1364, 1184, 595 cm^{-1} ; Anti diastereoisomer: $R_f = 0.36$ (cyclohexane/EtOAc 60:40); ^1H NMR (300 MHz, CDCl_3) δ 4.36 (q, $J = 6.24$ Hz, 1H), 2.78 (td, $J = 8.43$ Hz, $J = 6.24$ Hz, 1H), 2.20 (s, 3H), 2.05-1.57 (m, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 210.9, 75.1, 60.5, 34.7, 29.6, 27.0, 22.3; IR (neat): 3402, 2963, 2876, 1698, 1365, 1184, 665 cm^{-1} ; exact mass calculated for $\text{C}_7\text{H}_{12}\text{O}_2$ (M^+) : 128.08373 ; found 128.0832.



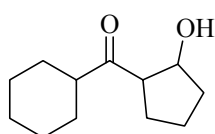
1-(2-Hydroxy-cyclopentyl)-2,2-dimethyl-propan-1-one (4b)

Ratio of diastereoisomers (anti/syn): 23/77

60% as colorless oil after purification by flash chromatography (cyclohexane/EtOAc 80:20);

Syn diastereoisomer: $R_f = 0.51$ (cyclohexane/EtOAc 70:30); ^1H NMR (300 MHz, CDCl_3) δ 4.21 (s, 1H), 3.72 (s, 1H), 3.07 (td, $J = 9.3$ Hz, $J = 4.1$ Hz, 1H), 1.90-1.50 (m, 6H), 1.08 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 221.5, 75.4, 49.1, 44.9, 35.3, 29.2, 25.7, 22.3; IR (neat):

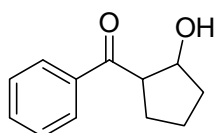
3464, 2969, 2873, 1699, 1680, 1478, 1396, 1366, 1085 cm^{-1} ; Anti diastereoisomer: $R_f = 0.36$ (cyclohexane/EtOAc 70:30); ^1H NMR (300 MHz, CDCl_3) δ 4.36 (q, $J = 6$ Hz, 1H), 3.20 (td, $J = 8.7$ Hz, $J = 5.7$ Hz, 1H), 2.01-1.93 (m, 2H), 1.78-1.70 (m, 3H), 1.65-1.49 (m, 2H), 1.14 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 218.9, 77.6, 54.3, 44.5, 35.3, 30.5, 26.0, 23.2; IR (neat): 3455, 2957, 2871, 1731, 1449, 1365, 1287, 1261, 1169, 1140, 1059, 1015 cm^{-1} ; exact mass calculated for $\text{C}_{10}\text{H}_{16}\text{O}$ ($\text{M}-\text{H}_2\text{O}^+$): 152.12012; found 152.1208.



Cyclohexyl-(2-hydroxy-cyclopentyl)-methanone (4c)

Ratio of diastereoisomers (anti/syn): 77/23

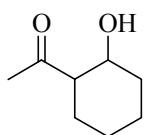
59% as colorless oil after purification by flash chromatography (cyclohexane/EtOAc 80:20); Syn diastereoisomer: $R_f = 0.51$ (cyclohexane/EtOAc 70:30); ^1H NMR (300 MHz, CDCl_3) δ 4.40 (m, 1H), 3.48 (s, 1H), 2.89 (td, $J = 9.3$ Hz, $J = 3.9$ Hz, 1H), 2.48-2.39 (m, 1H), 2.00-1.10 (m, 17H); ^{13}C NMR (75 MHz, CDCl_3) δ 218.7, 74.6, 53.9, 51.3, 34.7, 28.6, 28.1, 26.9, 25.9, 25.8, 25.6, 22.3; IR (neat): 3482, 2932, 2855, 1705, 1450 cm^{-1} ; Anti diastereoisomer: $R_f = 0.4$ (cyclohexane/EtOAc 70:30); ^1H NMR (300 MHz, CDCl_3) δ 4.31 (q, $J = 6$ Hz, 1H), 2.92 (td, $J = 8.4$ Hz, $J = 5.4$ Hz, 1H), 2.49-2.39 (m, 2H), 2.03-1.51 (m, 10H), 1.38-1.09 (m, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 216.3, 75.6, 58.0, 50.6, 34.8, 28.5, 28.3, 27.8, 25.9, 25.7, 25.7, 22.6; IR (neat): 3423, 2930, 2855, 1701, 1449, 1375, 1347, 1004 cm^{-1} ; exact mass calculated for $\text{C}_{12}\text{H}_{18}\text{O}$ ($\text{M}-\text{H}_2\text{O}^+$): 178.13577; found 178.1362.



(2-Hydroxy-cyclopentyl)-phenyl-methanone (4d)

Ratio of diastereoisomers (anti/syn): 83/17

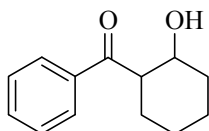
90% as colorless oil after purification by flash chromatography (cyclohexane/EtOAc 80:20); Syn diastereoisomer: $R_f = 0.51$ (cyclohexane/EtOAc 60:40); ^1H NMR (300 MHz, CDCl_3) δ 7.95 (m, 2H), 7.61-7.45 (m, 3H), 4.59 (m, 1H), 3.83 (s, 1H), 3.58 (td, $J = 9.3$ Hz, $J = 3.9$ Hz, 1H), 2.13-1.75 (m, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 204.5, 137.2, 133.6, 128.9, 128.5, 75.1, 51.1, 34.8, 28.2, 22.5; IR (neat): 3443, 2962, 1681, 1597, 1580, 1448, 1261, 1223, 1096, 1024, 798, 693 cm^{-1} ; Anti diastereoisomer: $R_f = 0.42$ (cyclohexane/EtOAc 60:40); ^1H NMR (300 MHz, CDCl_3) δ 8.01 (m, 2H), 7.59-7.44 (m, 3H), 4.60 (q, $J = 5.4$ Hz, 1H), 3.66 (m, 1H), 2.21-1.68 (m, 7H); ^{13}C NMR (75 MHz, CDCl_3) δ 202.2, 136.7, 133.1, 128.6, 75.8, 55.3, 35.0, 28.9, 23.0; IR (neat): 3409, 2960, 1676, 1448, 1219, 1004, 701 cm^{-1} ; exact mass calculated for $\text{C}_{12}\text{H}_{12}\text{O}$ ($\text{M}-\text{H}_2\text{O}^+$) : 172.08882 ; found 172.0881.



1-(2-Hydroxy-cyclohexyl)-ethanone (4e)

Ratio of diastereoisomers (anti/syn): 83/17

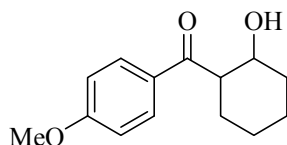
33% as colourless oil for both diastereoisomers after purification by flash chromatography (cyclohexane/EtOAc 60:40); Syn diastereoisomer: ^1H NMR (300 MHz, CDCl_3) δ 3.73 (m, 1H), 2.71 (bs, 1H), 2.31 (m, 1H), 2.15 (s, 3H), 1.93 (m, 2H), 1.72 (m, 2H), 1.21 (m, 4H); ^{13}C NMR (75 MHz, CDCl_3) δ 213.0, 70.8, 58.9, 33.8, 29.2, 28.0, 25.4, 24.5; IR (neat): 3422, 2934, 2859, 1702, 1450, 1424, 1356, 1172, 1066, 962, 609 cm^{-1} ; Anti diastereoisomer: ^1H NMR (300 MHz, CDCl_3) δ 3.76 (td, $J = 9.6$ Hz, $J = 4.5$ Hz, 1H), 2.53 (bs, 1H), 2.33 (m, 1H), 2.16 (s, 3H), 1.96 (m, 2H), 1.73 (m, 2H), 1.25 (m, 4H); ^{13}C NMR (75 MHz, CDCl_3) δ 212.9, 70.8, 59.0, 33.8, 29.2, 28.0, 25.4, 24.5; IR (neat): 3415, 2934, 2859, 1702, 1450, 1424, 1357, 1172, 1066, 609 cm^{-1} ; exact mass calculated for $\text{C}_8\text{H}_{14}\text{O}_2$ (M^+) : 142.09938 ; found 142.1001.



(2-Hydroxy-cyclohexyl)-phenyl-methanone (4f)

Ratio of diastereoisomers (anti/syn): 83/17

91% as white solid after purification by flash chromatography (cyclohexane/EtOAc 80:20); During purification the syn isomer ($R_f = 0.6$ (cyclohexane/EtOAc 60:40)) epimerized to the anti one. Isolated diastereoisomer (Anti): $R_f = 0.53$ (cyclohexane/EtOAc 60:40); ^1H NMR (300 MHz, CDCl_3) δ 7.96 (m, 2H), 7.59-7.43 (m, 3H), 4.08 (m, 1H), 3.26 (m, 1H), 2.40 (bs, 1H), 2.12-1.96 (m, 2H), 1.86-1.74 (m, 2H), 1.51-1.27 (m, 4H); ^{13}C NMR (75 MHz, CDCl_3) δ 203.8, 136.7, 133.1, 128.6, 128.5, 70.8, 53.8, 33.7, 29.7, 25.5, 24.6; IR (neat): 3436, 2934, 2858, 1676, 1597, 1580, 1448, 1211, 1063, 942, 701 cm^{-1} ; mp : 75-77 $^\circ\text{C}$; exact mass calculated for $\text{C}_{13}\text{H}_{16}\text{O}_2$ (M^+) : 204.11503 ; found 204.1158.

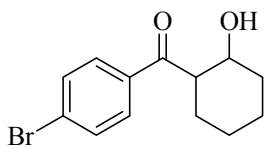


(2-Hydroxy-cyclohexyl)-(4-methoxy-phenyl)-methanone (4g)

Ratio of diastereoisomers (anti/syn): 55/45

85% as white solid after purification by flash chromatography (cyclohexane/EtOAc 50:50); Syn diastereoisomer: $R_f = 0.59$ (cyclohexane/EtOAc 40:60); ^1H NMR (300 MHz, CDCl_3) δ 7.94-7.90 (m, 2H), 6.96-6.93 (m, 2H), 4.26 (m, 1H), 3.88 (s, 3H), 3.32-3.29 (m, 1H), 1.99-1.66 (m, 5H), 1.57-1.40 (m, 4H); ^{13}C NMR (75 MHz, CDCl_3) δ 204.6, 163.9, 130.8, 128.6, 113.9, 66.5, 55.5, 47.6, 32.0, 25.7, 24.9, 19.6; IR (neat): 3483, 2935, 2859, 1655, 1600, 1510, 1420, 1253, 1171, 978, 847 cm^{-1} ; mp : 74.5-77 $^\circ\text{C}$; Anti diastereoisomer: $R_f = 0.46$ (cyclohexane/EtOAc 40:60); ^1H NMR (300 MHz, CDCl_3) δ 7.96 (m, 2H), 6.94 (m, 2H), 4.07 (m, 1H), 3.87 (s, 3H), 3.22 (m, 1H), 2.34 (bs, 1H), 2.07-1.96 (m, 2H), 1.86-1.74 (m, 2H), 1.45-1.20 (m, 4H); ^{13}C NMR (75 MHz, CDCl_3) δ 202.2, 163.6, 130.8, 129.6, 113.8, 70.8, 55.5, 53.5, 33.7, 29.9, 25.5, 24.7; IR (neat): 3449, 2935, 2858, 1667, 1601, 1510, 1421, 1253,

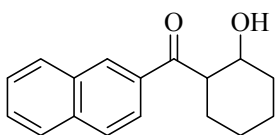
1172, 942, 838 cm^{-1} ; mp : 100-102 $^{\circ}\text{C}$; exact mass calculated for $\text{C}_{14}\text{H}_{18}\text{O}_3$ (M^+) : 234.12559 ; found 234.1263.



(4-Bromo-phenyl)-(2-hydroxy-cyclohexyl)-methanone (4h)

Ratio of diastereoisomers (anti/syn): 83/17

66% as colorless oil of the first diastereoisomer and white solid of the second one, after purification by flash chromatography (cyclohexane/EtOAc 90:10); Syn diastereoisomer coelutes with an unidentified minor compound : $R_f = 0.54$ (cyclohexane/EtOAc 70:30); ^1H NMR (300 MHz, CDCl_3) δ 7.80-7.77 (m, 2H), 7.64-7.60 (m, 2H), 4.27 (bs, 1H), 3.77 (bs, 1H), 3.29 (m, 1H), 2.04-1.4 (m, 8H); ^{13}C NMR (75 MHz, CDCl_3) δ 205.2, 132.5, 130.3, 129.1, 128.8, 66.8, 48.6, 32.3, 25.9, 25.0, 20.0; IR (neat): 3495, 2934, 2860, 1682, 1667, 1585, 1566, 1447, 1397, 1251, 1211, 1176, 1071, 1010, 978, 848, 704, 517 cm^{-1} ; Anti diastereoisomer : $R_f = 0.43$ (cyclohexane/EtOAc 70:30); ^1H NMR (300 MHz, CDCl_3) δ 7.83-7.79 (m, 2H), 7.61-7.57 (m, 2H), 4.08-4.00 (m, 1H), 3.24-3.16 (m, 1H), 2.35 (bs, 1H), 2.10-1.74 (m, 4H), 1.44-1.27 (m, 4H); ^{13}C NMR (75 MHz, CDCl_3) δ 202.8, 135.4, 132.0, 130.0, 128.4, 70.9, 53.8, 33.8, 29.6, 25.5, 24.6; IR (neat): 3423, 2934, 2858, 1675, 1585, 1397, 1070, 941 cm^{-1} ; mp : 106-107.5 $^{\circ}\text{C}$; exact mass calculated for $\text{C}_{13}\text{H}_{15}\text{Br}_1\text{O}_2$ (M^+) : 282.02554 ; found 282.0257.

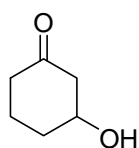


(2-Hydroxy-cyclohexyl)-naphthalen-2-yl-methanone (4i)

Ratio of diastereoisomers (anti/syn): 77/23

87% as colorless oil of the first diastereoisomer and white solid of the second one, after purification by flash chromatography (cyclohexane/EtOAc 80:20); Syn diastereoisomer

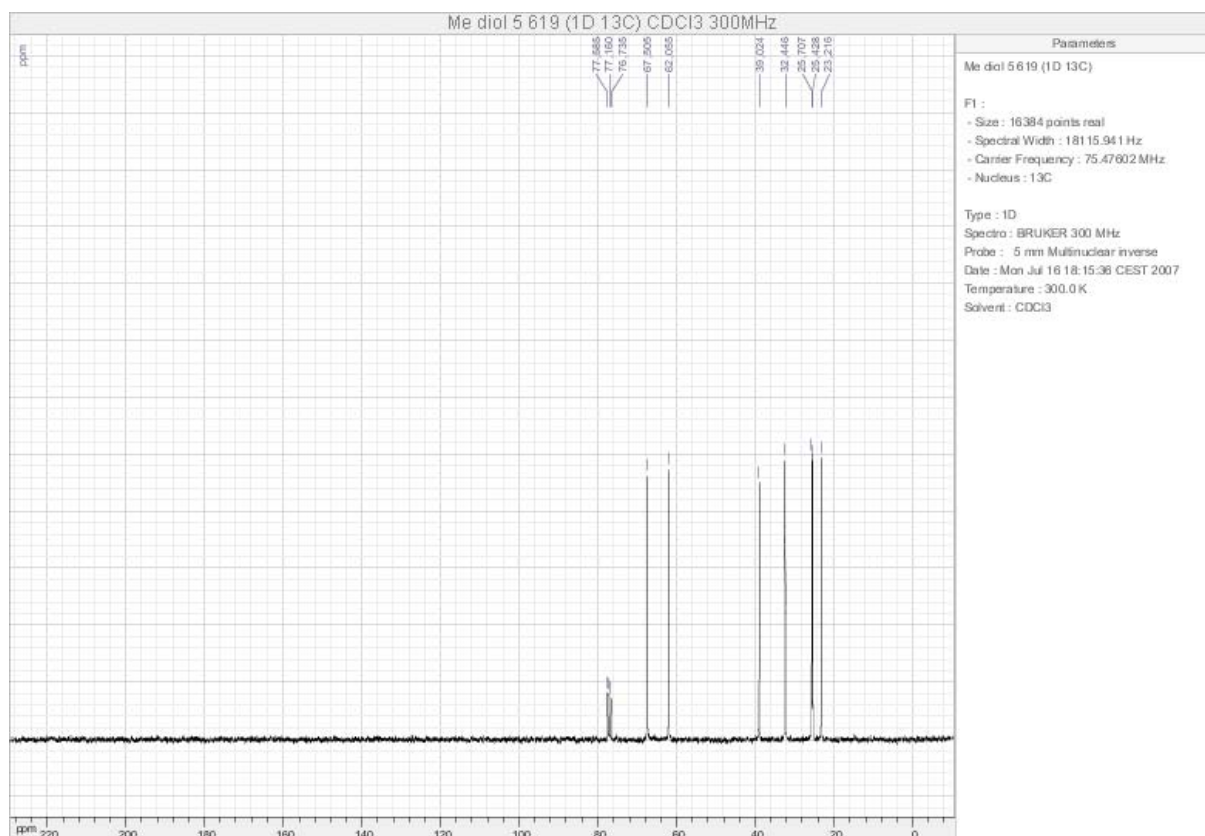
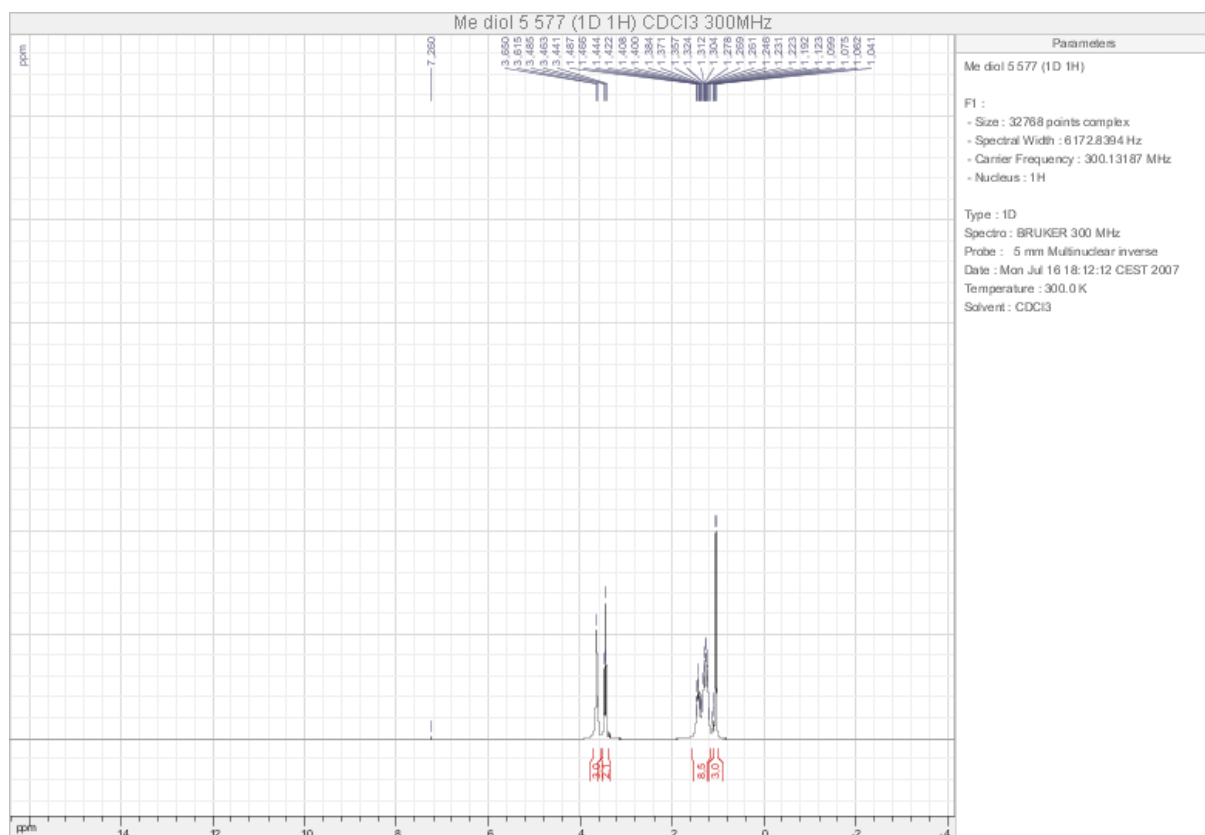
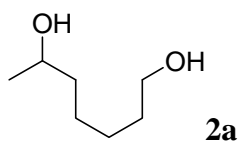
coelutes with an unidentified minor compound : $R_f = 0.58$ (cyclohexane/EtOAc 70:30); ^1H NMR (300 MHz, CDCl_3) δ 8.44 (s, 1H), 8.00-7.85 (m, 4H), 7.59 (m, 2H), 4.34 (bs, 1H), 4.05 (bs, 1H), 3.53 (m, 1H), 2.05-1.43 (m, 8H); ^{13}C NMR (75 MHz, CDCl_3) δ 206.1, 135.9, 133.2, 132.6, 130.3, 129.8, 128.8, 128.3, 127.9, 127.0, 124.1, 66.6, 48.3, 32.1, 25.8, 25.0, 19.8; IR (neat): 3498, 2934, 2859, 1677, 1626, 1467, 1446, 1259, 1174, 1127, 981, 776, 476 cm^{-1} ; Anti diastereoisomer : $R_f = 0.39$ (cyclohexane/EtOAc 70:30); ^1H NMR (300 MHz, CDCl_3) δ 8.47 (s, 1H), 8.00 (dd, $J = 8.7$ Hz, $J = 1.8$ Hz, 1H), 7.94 (d, $J = 7.8$ Hz, 1H), 7.84 (m, 2H), 7.55 (m, 2H), 4.12 (td, $J = 9.9$ Hz, $J = 3.9$ Hz, 1H), 3.44 (m, 1H), 2.69 (bs, 1H), 2.06 (m, 2H), 1.81 (m, 2H), 1.56-1.26 (m, 4H) ; ^{13}C NMR (75 MHz, CDCl_3) δ 203.8, 135.6, 134.0, 132.6, 130.2, 129.7, 128.5, 127.8, 126.8, 124.2, 70.9, 53.9, 33.8, 29.9, 25.6, 24.7; IR (neat): 3443, 2934, 2858, 1672, 1627, 1467, 1450, 1182, 1126, 1064, 934, 755, 476 cm^{-1} ; m.p.: 100-102 $^\circ\text{C}$; exact mass calculated for $\text{C}_{17}\text{H}_{18}\text{O}_2$ (M^+) : 254.13068 ; found 254.1310.

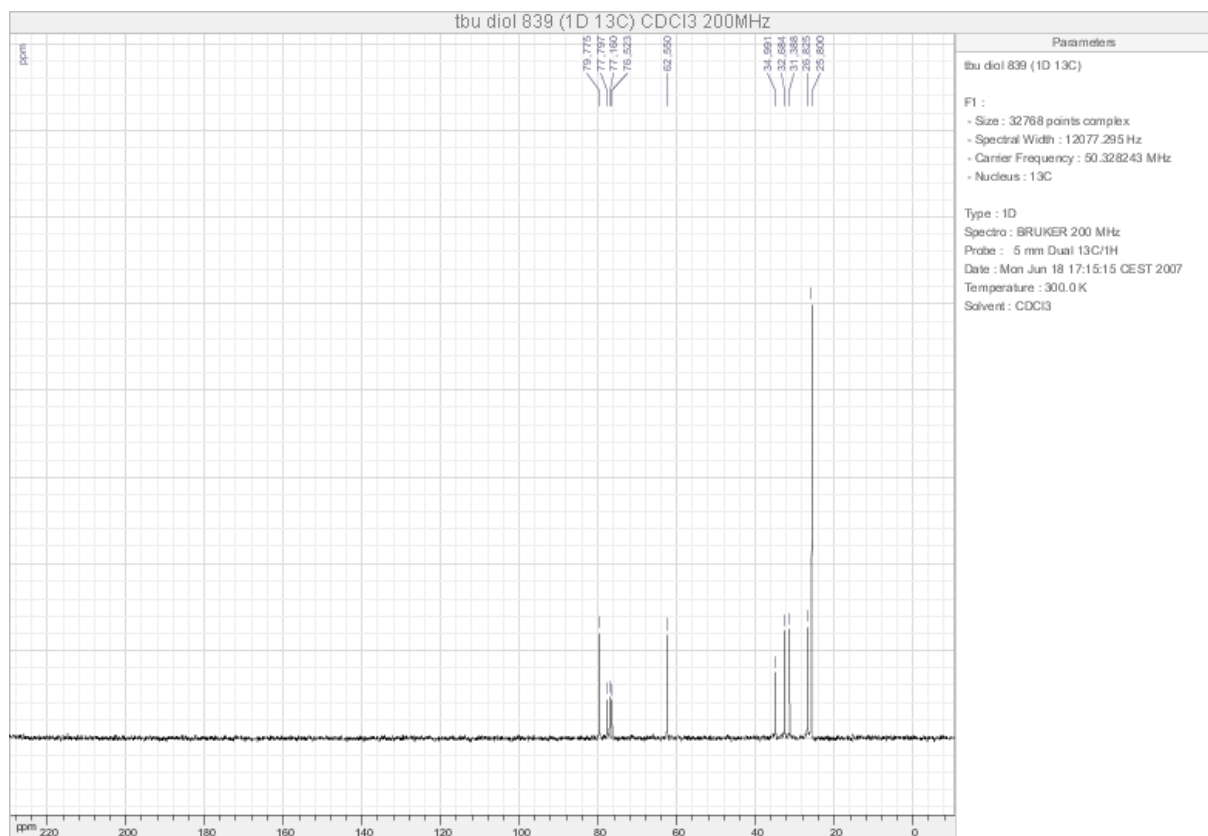
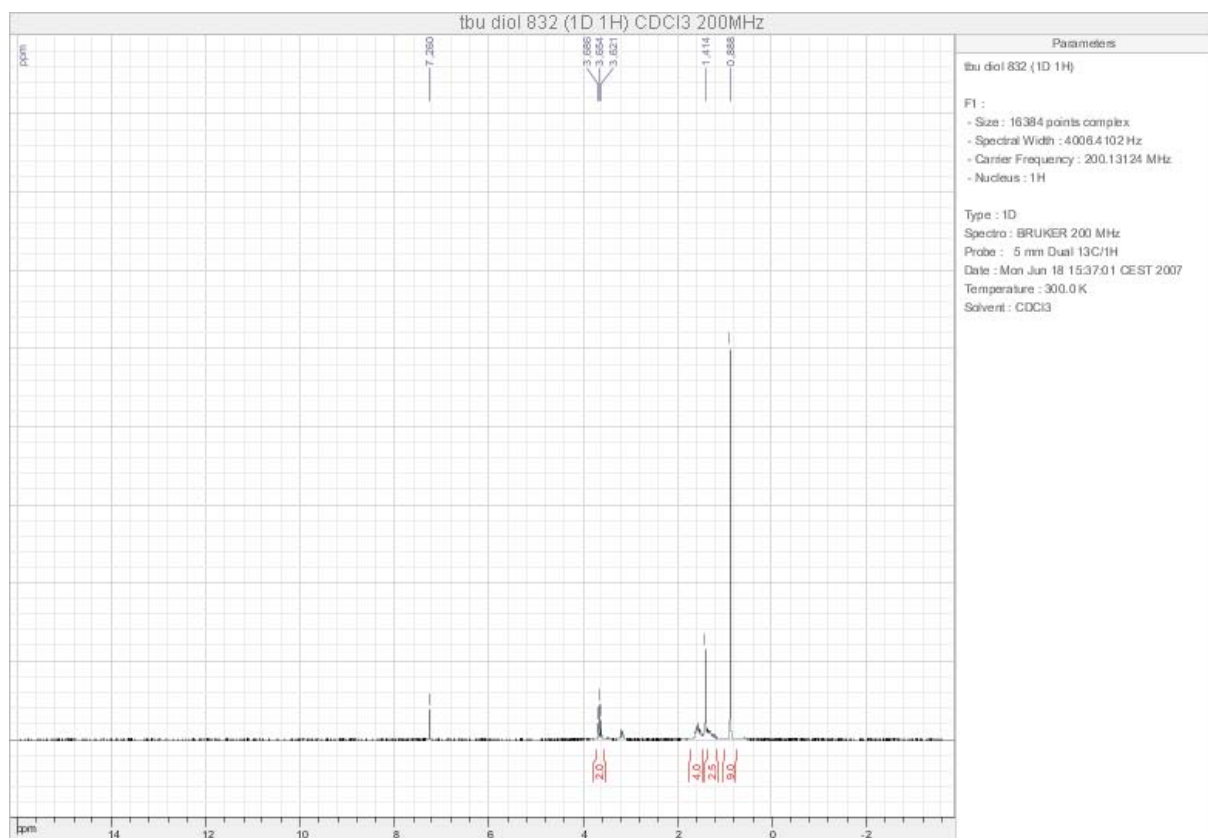
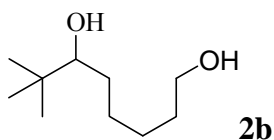


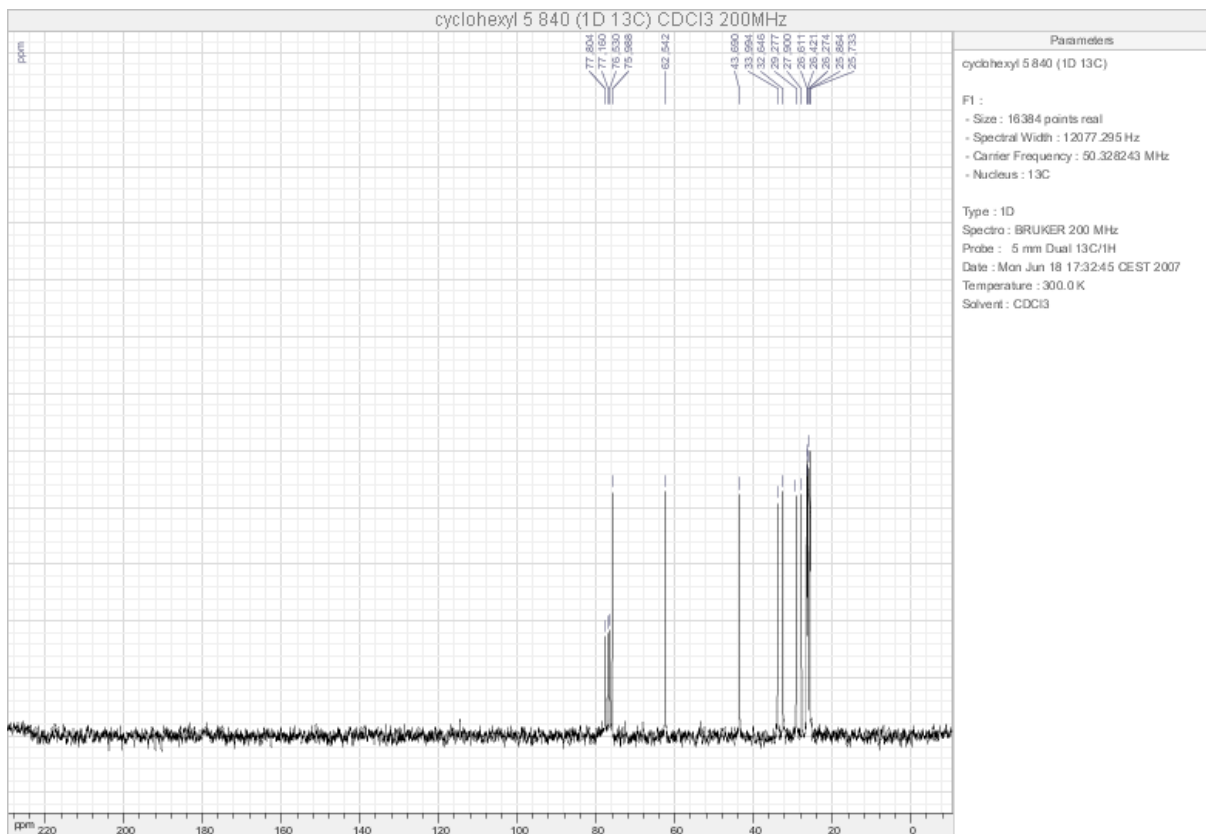
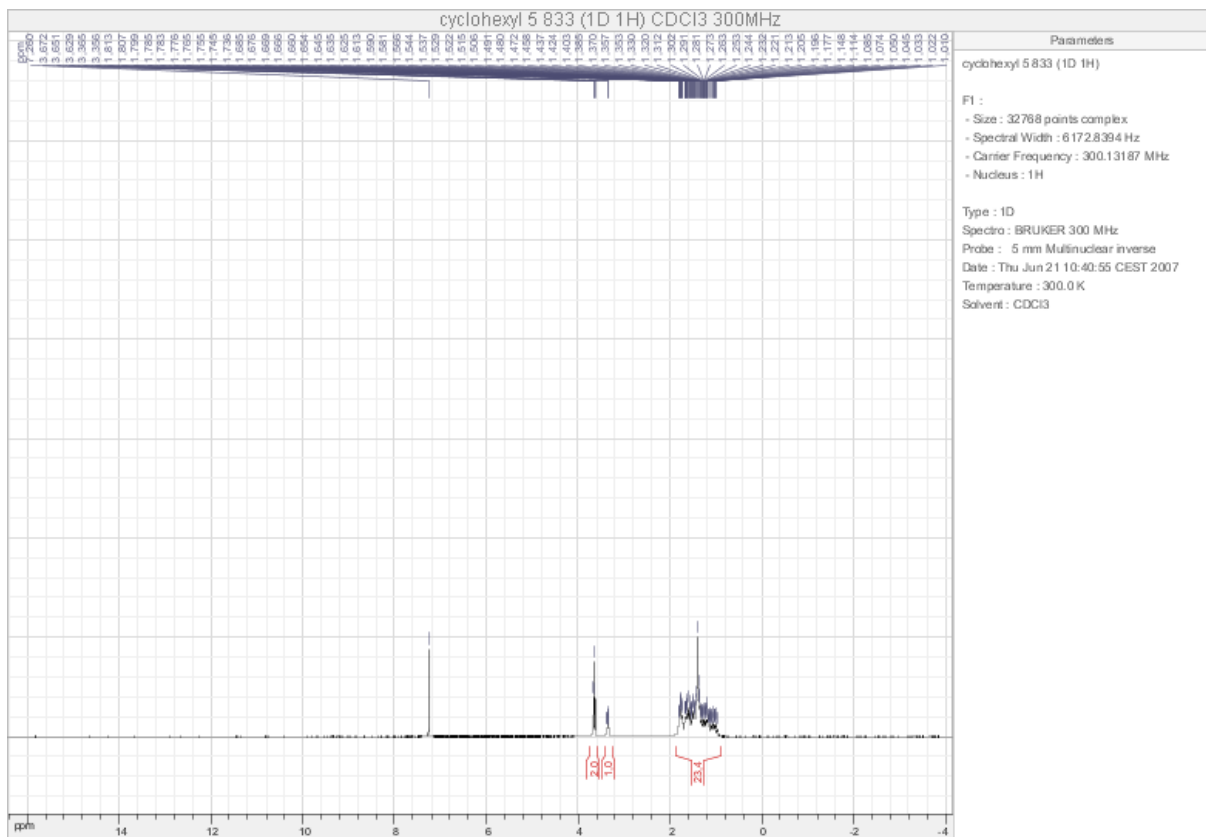
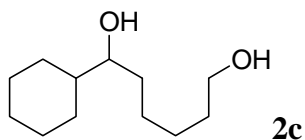
3-Hydroxy-cyclohexanone (4j)

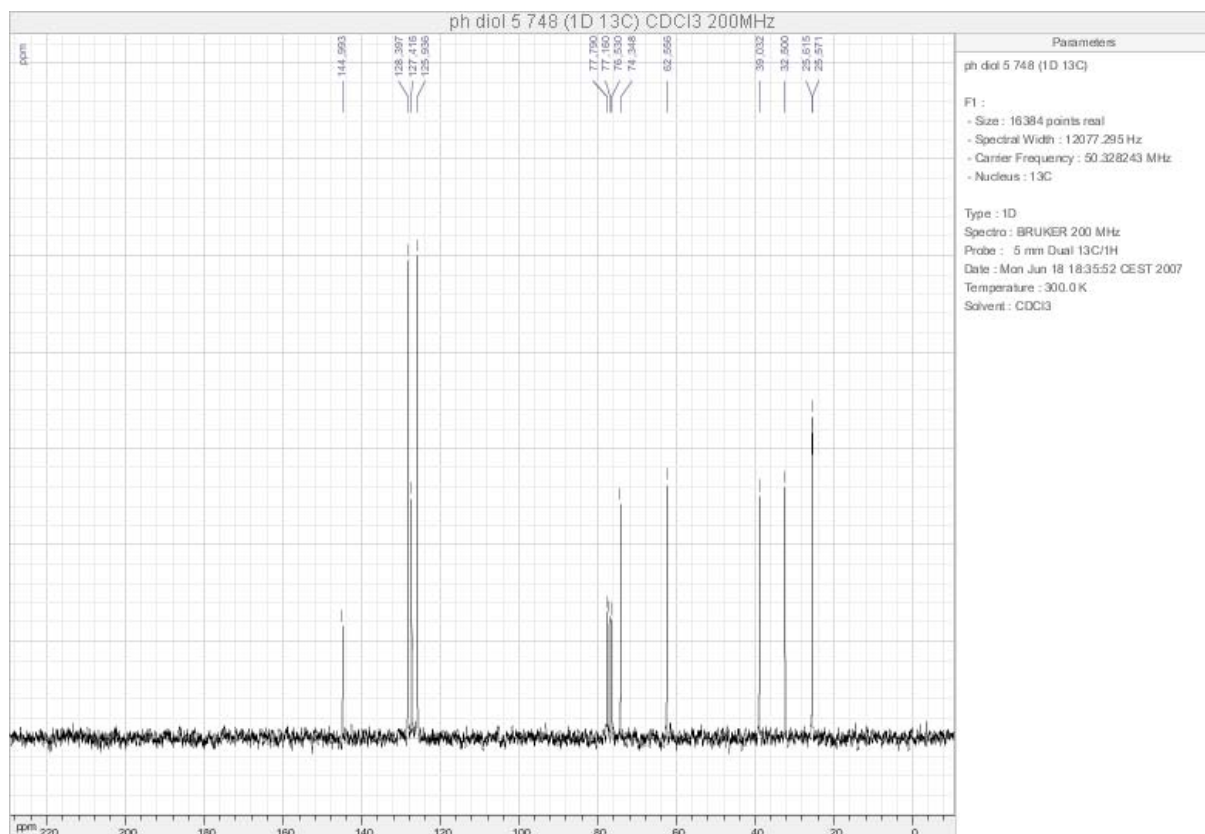
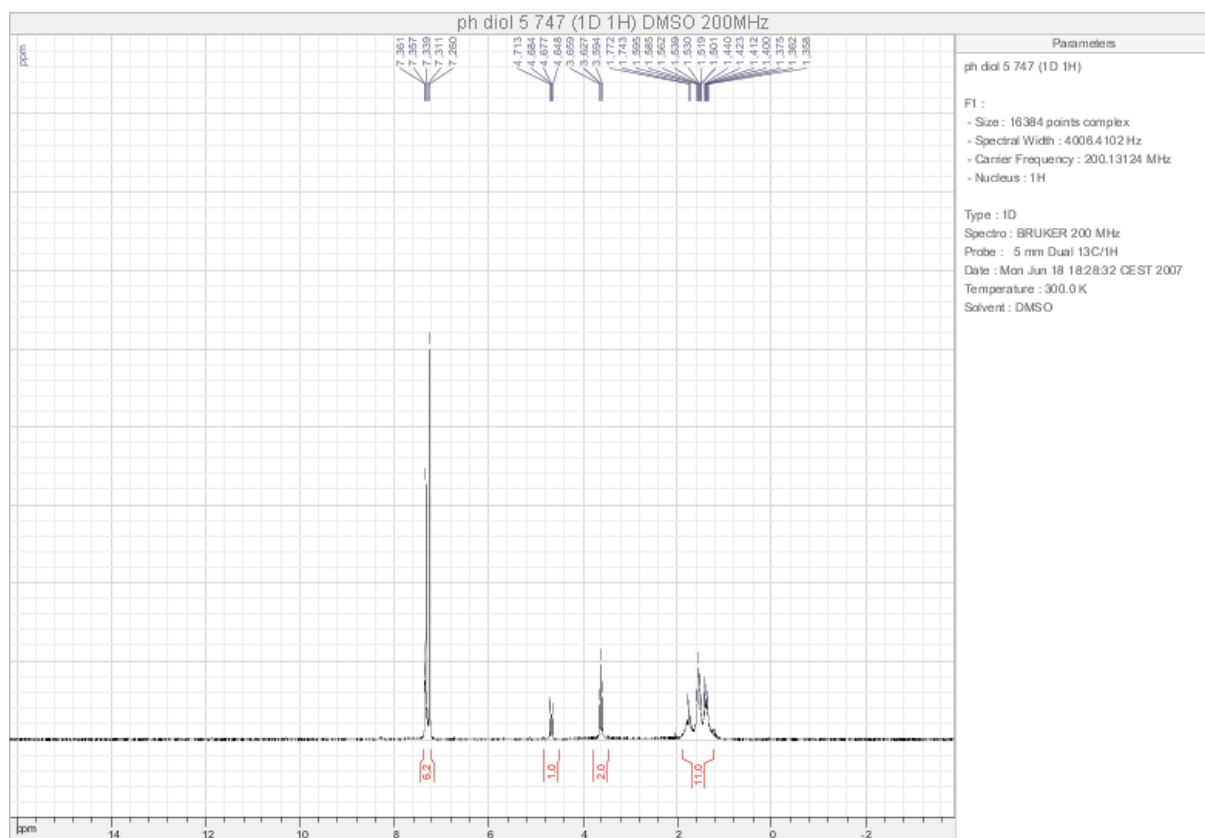
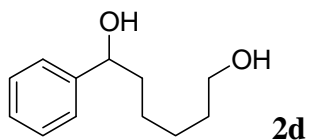
82% as colorless oil after purification by flash chromatography (cyclohexane/EtOAc 50/50); $R_f = 0.26$ (cyclohexane/EtOAc 30:70); ^1H NMR (300 MHz, CDCl_3) δ 4.14-4.07 (m, 1H), 3.34 (bs, 1H), 2.56 (dd, $J = 14.1$ Hz, $J = 4.2$ Hz, 1H), 2.33 (dd, $J = 13.8$ Hz, $J = 7.4$ Hz, 1H), 2.23 (t, $J = 6.6$ Hz, 2H), 2.06-1.88 (m, 2H), 1.77-1.57 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 210.9, 69.5, 50.3, 40.9, 32.6, 20.6; IR (neat): 3407, 2949, 2885, 1704, 1452, 1423, 1363, 1347, 1315, 1269, 1224, 1105, 1094, 1064, 965, 531 cm^{-1} ; exact mass calculated for $\text{C}_6\text{H}_{10}\text{O}_2$ (M^+) : 114.06808 ; found 114.0688.

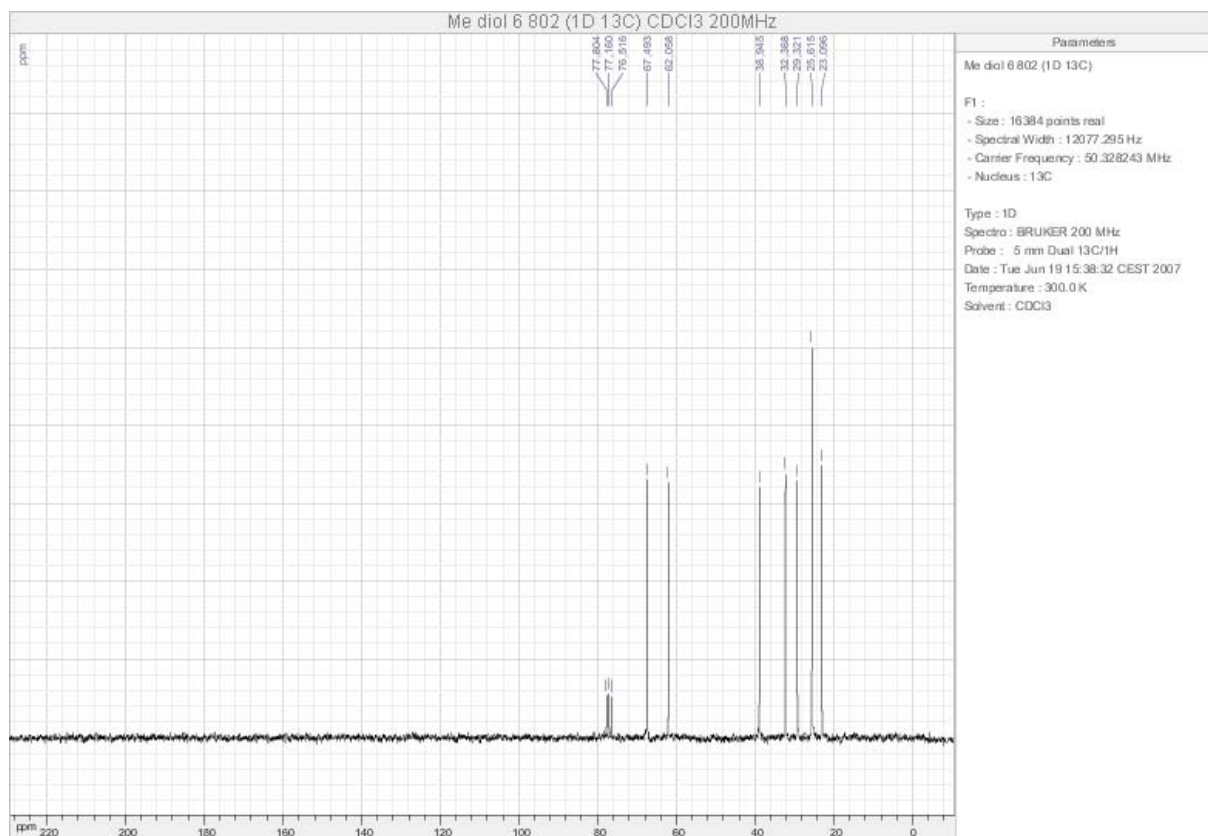
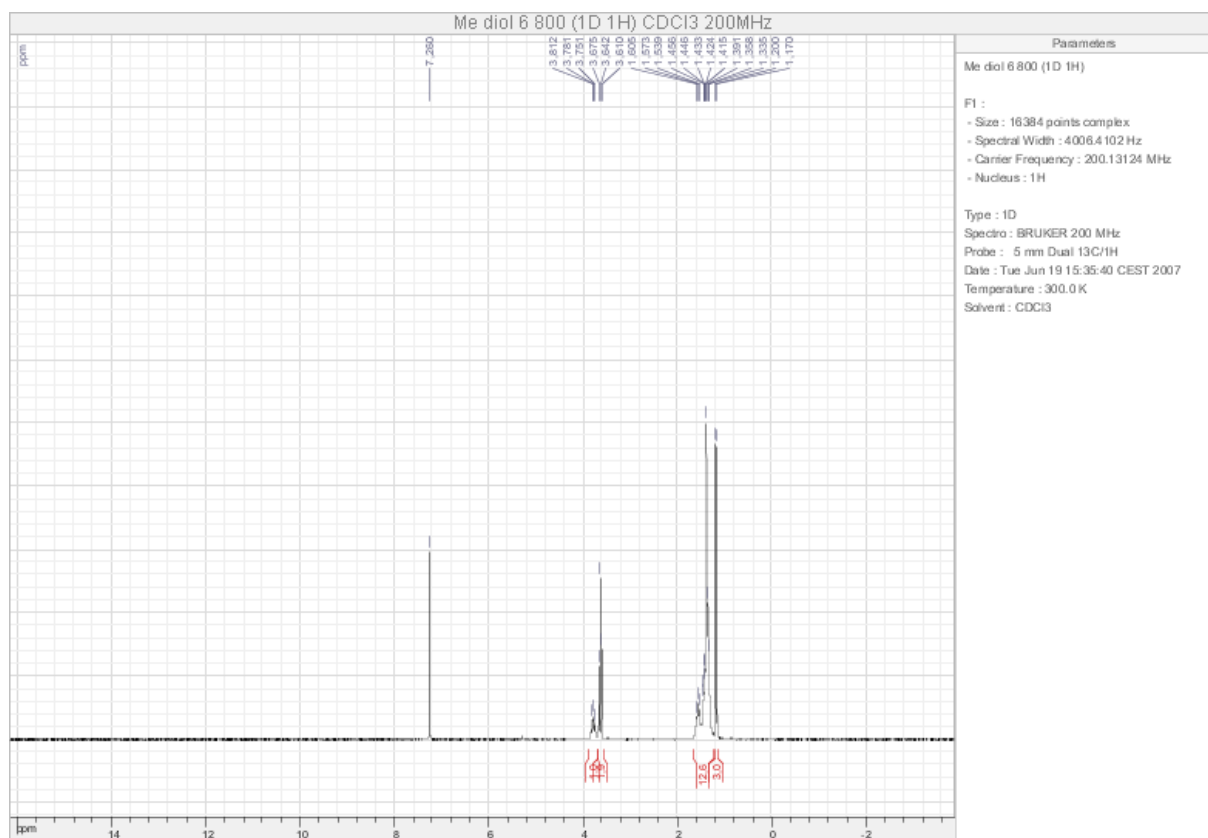
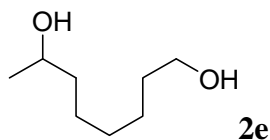
IV. NMR spectras

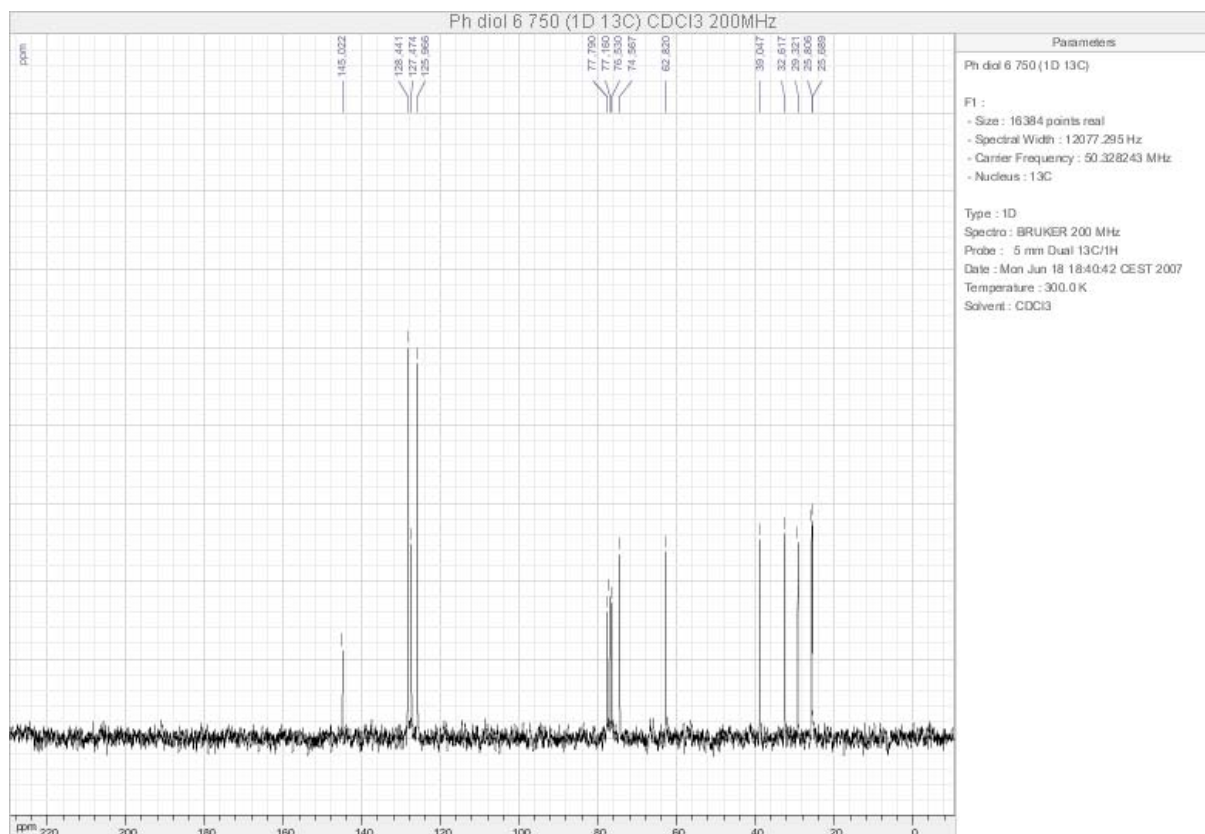
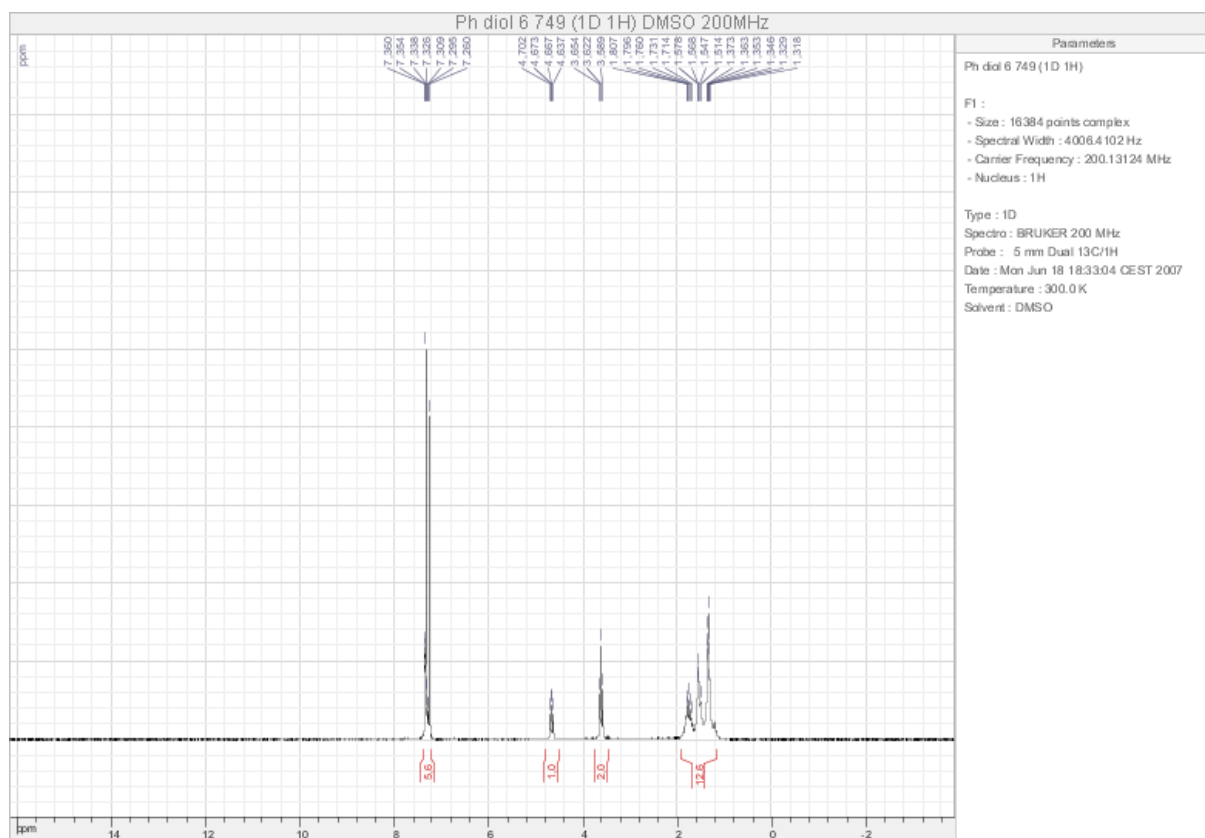
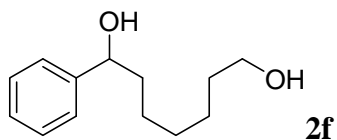


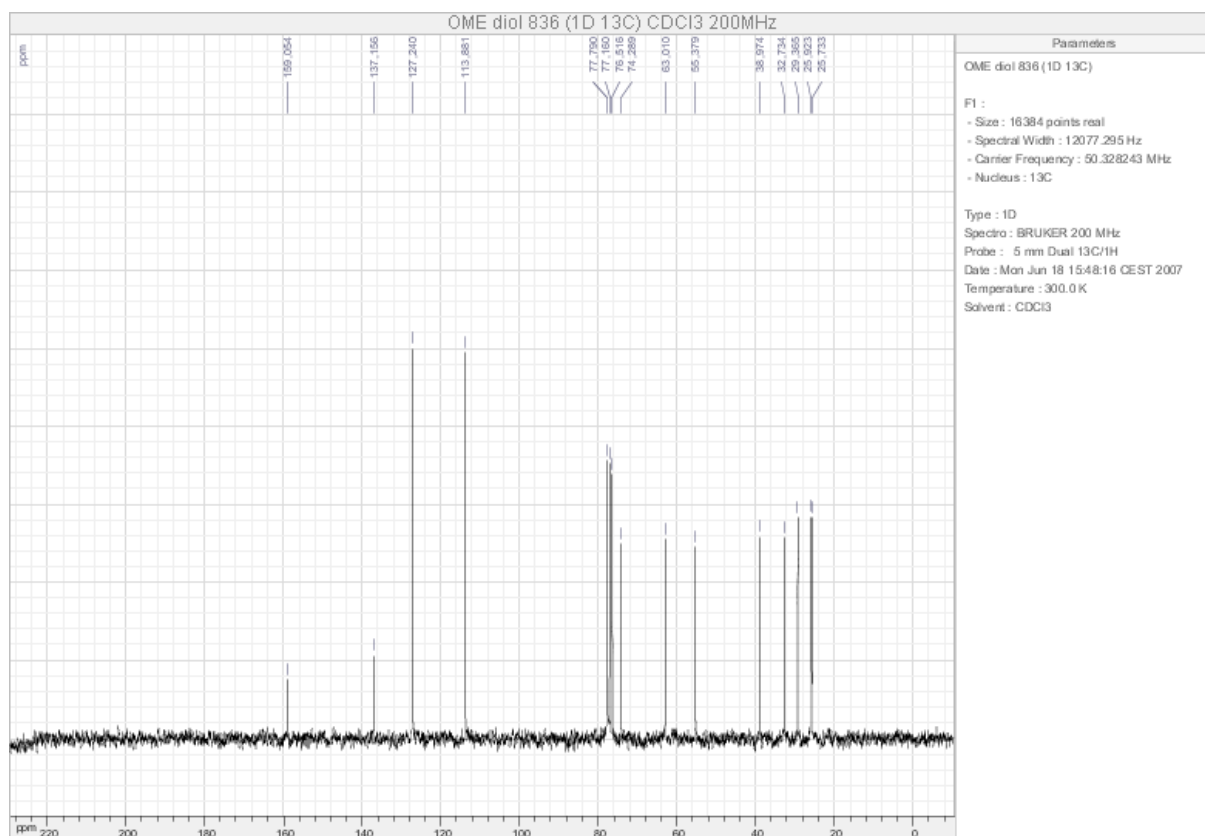
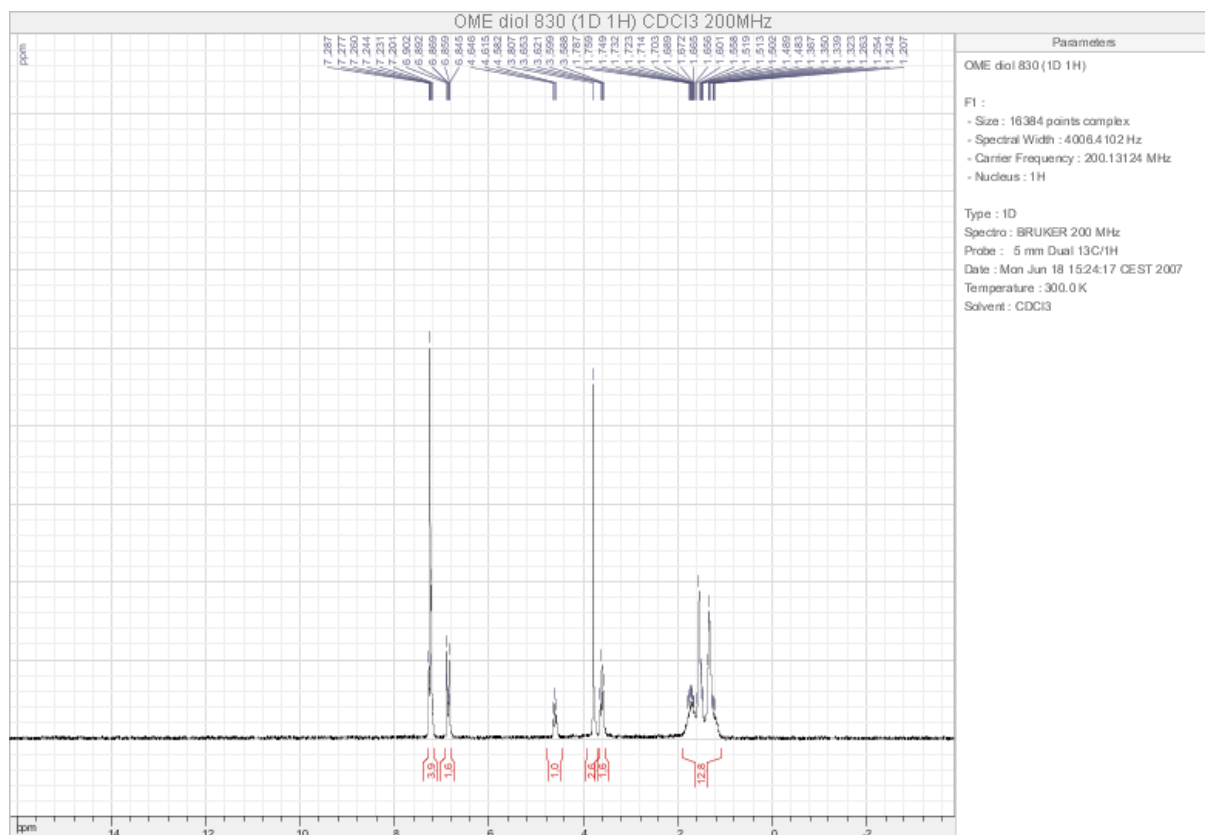
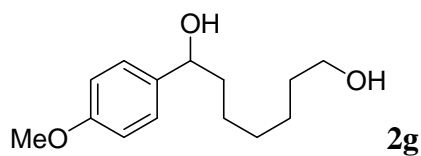


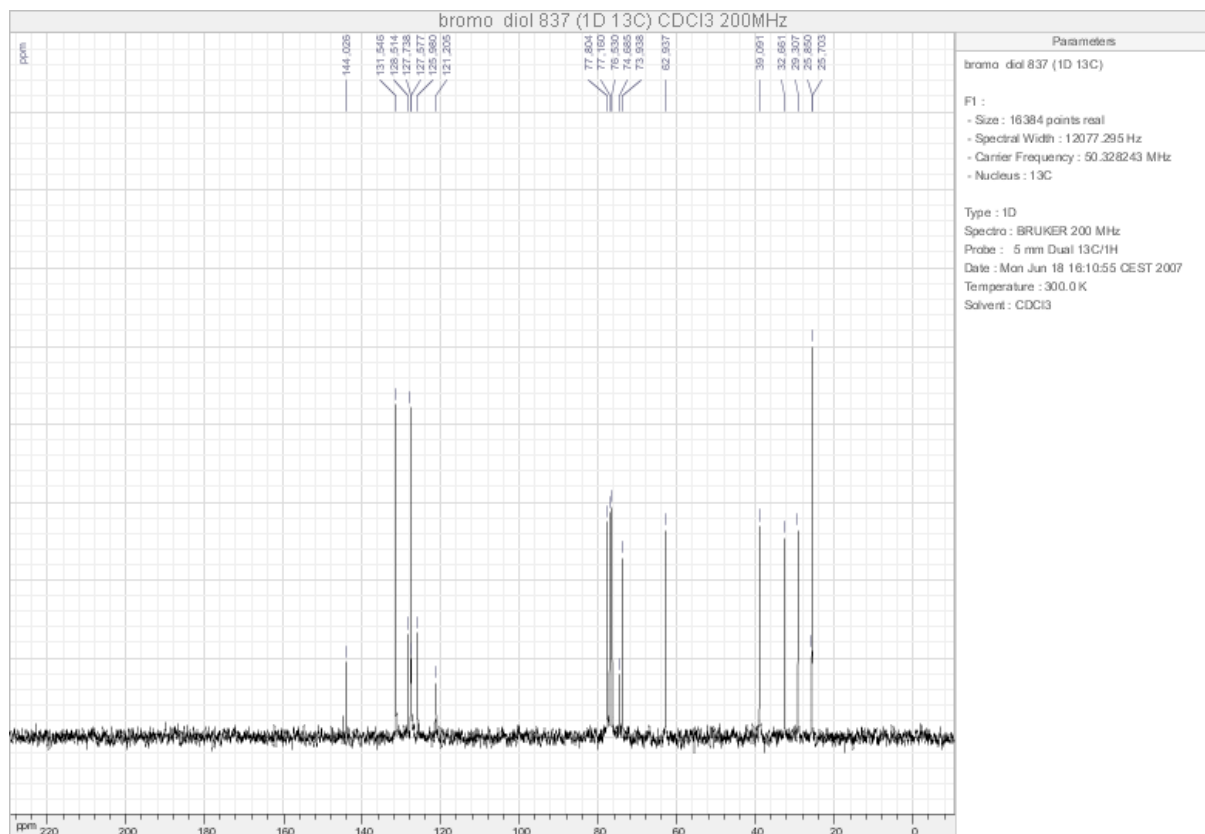
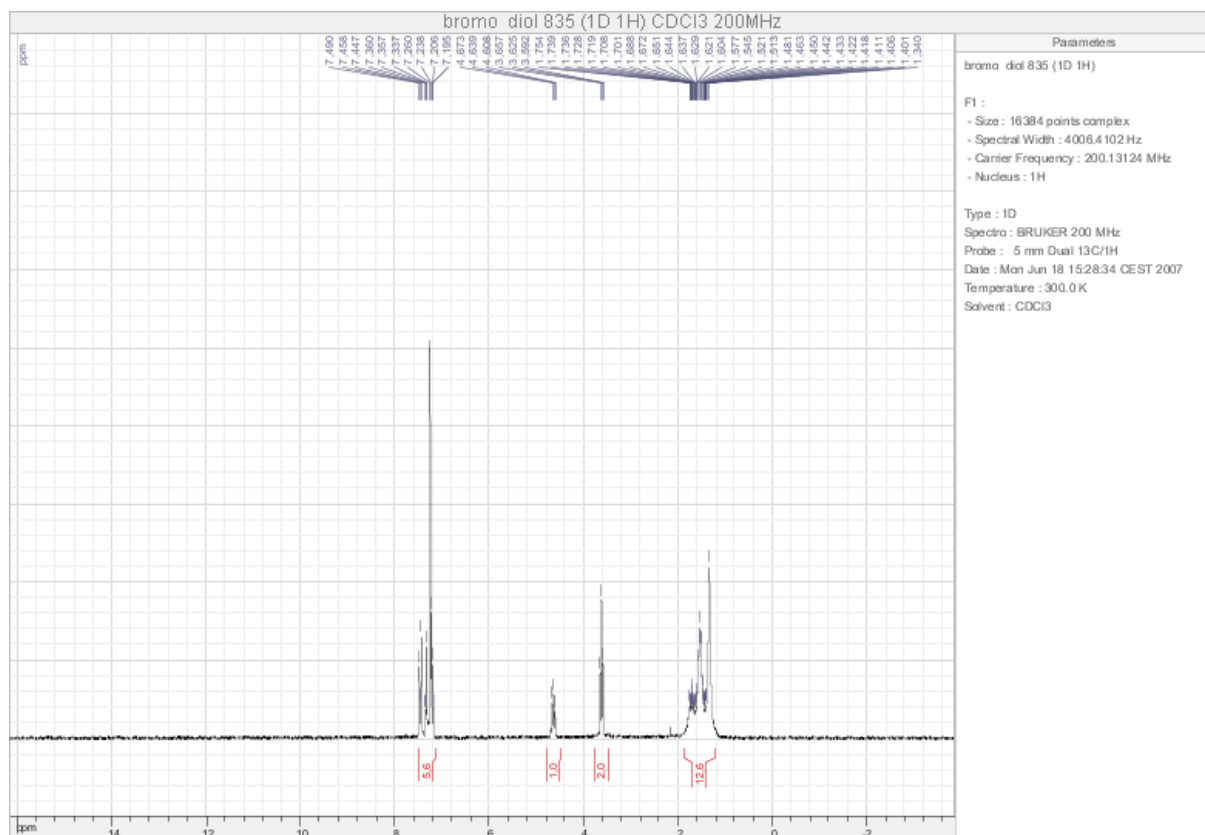
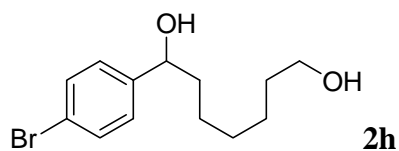


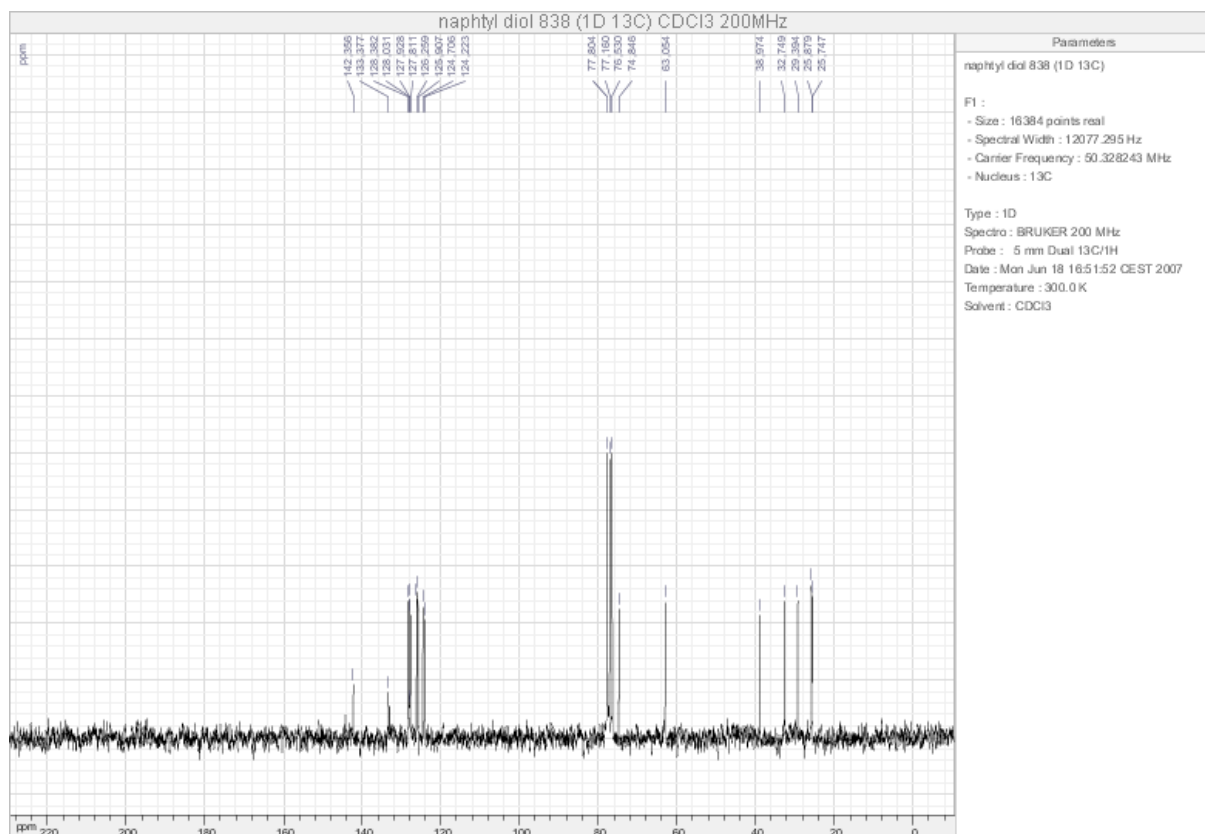
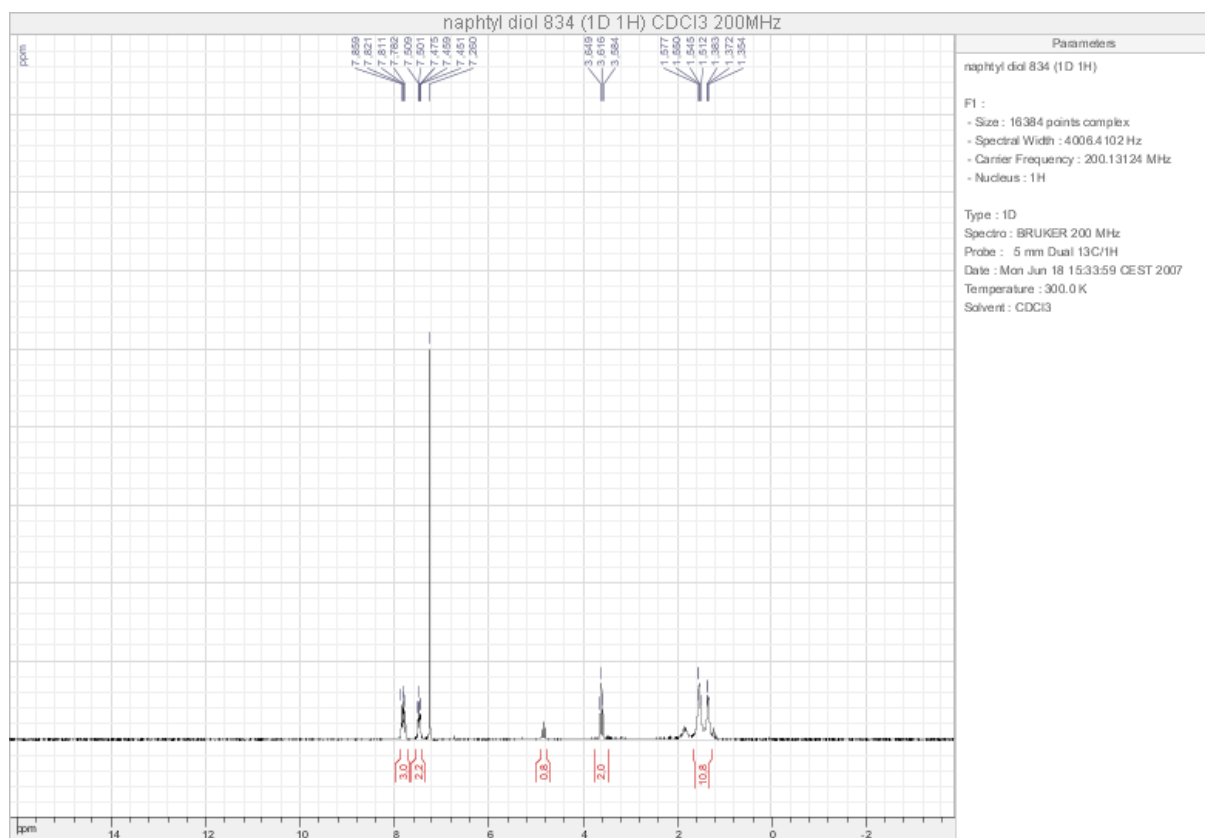
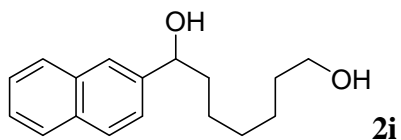


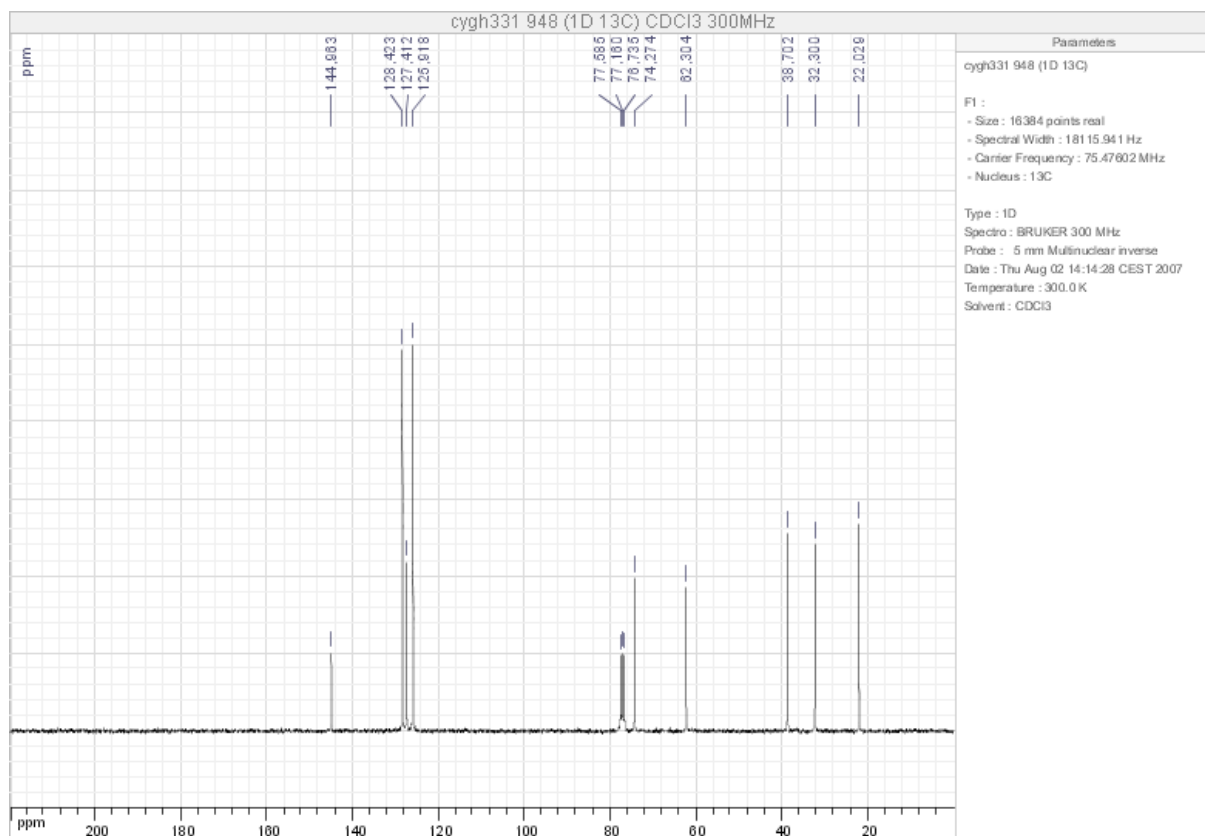
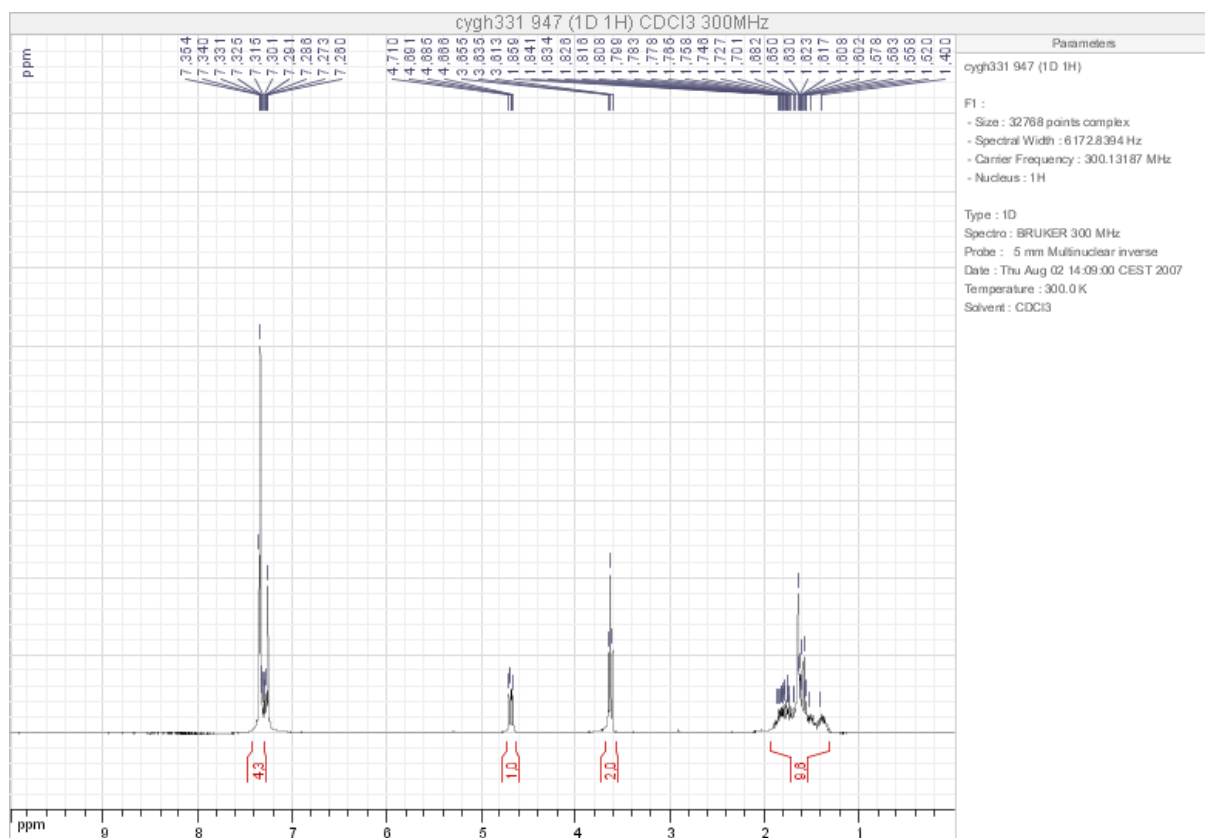
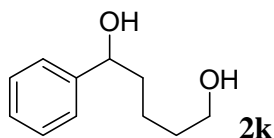


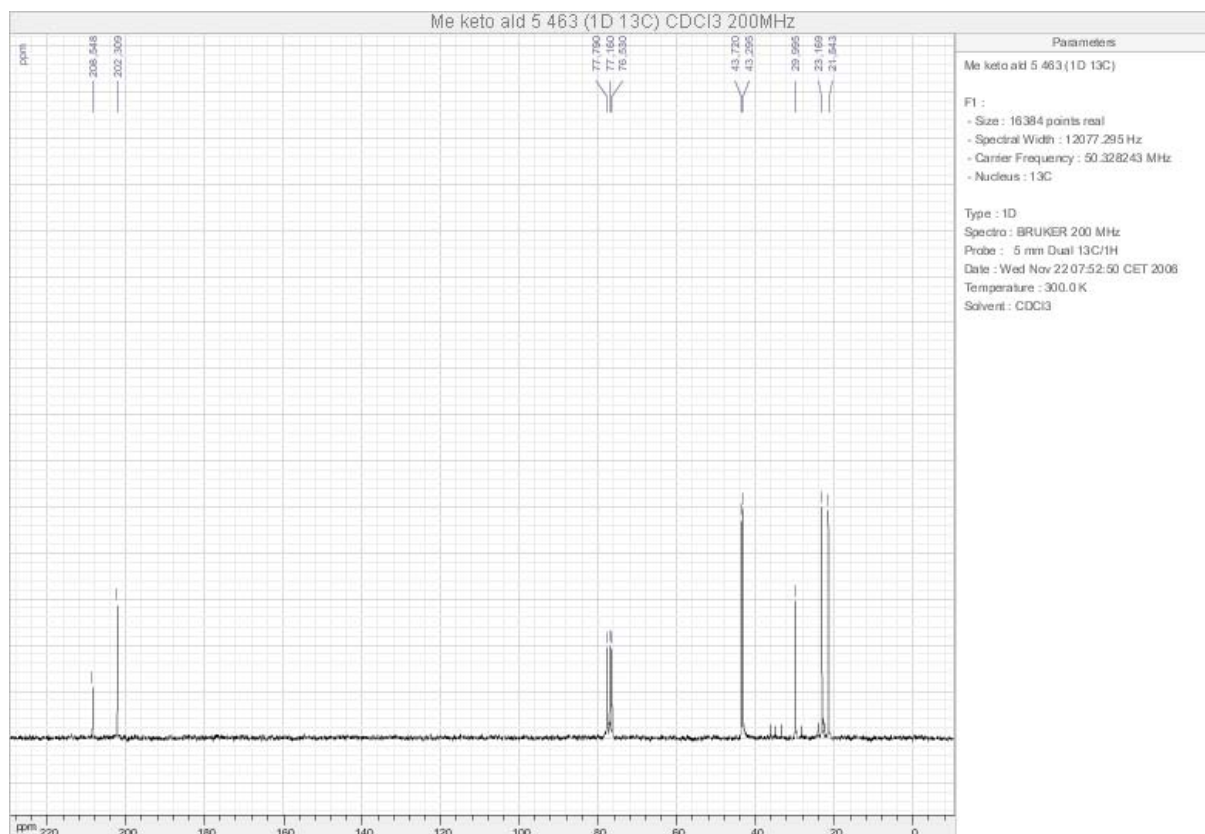
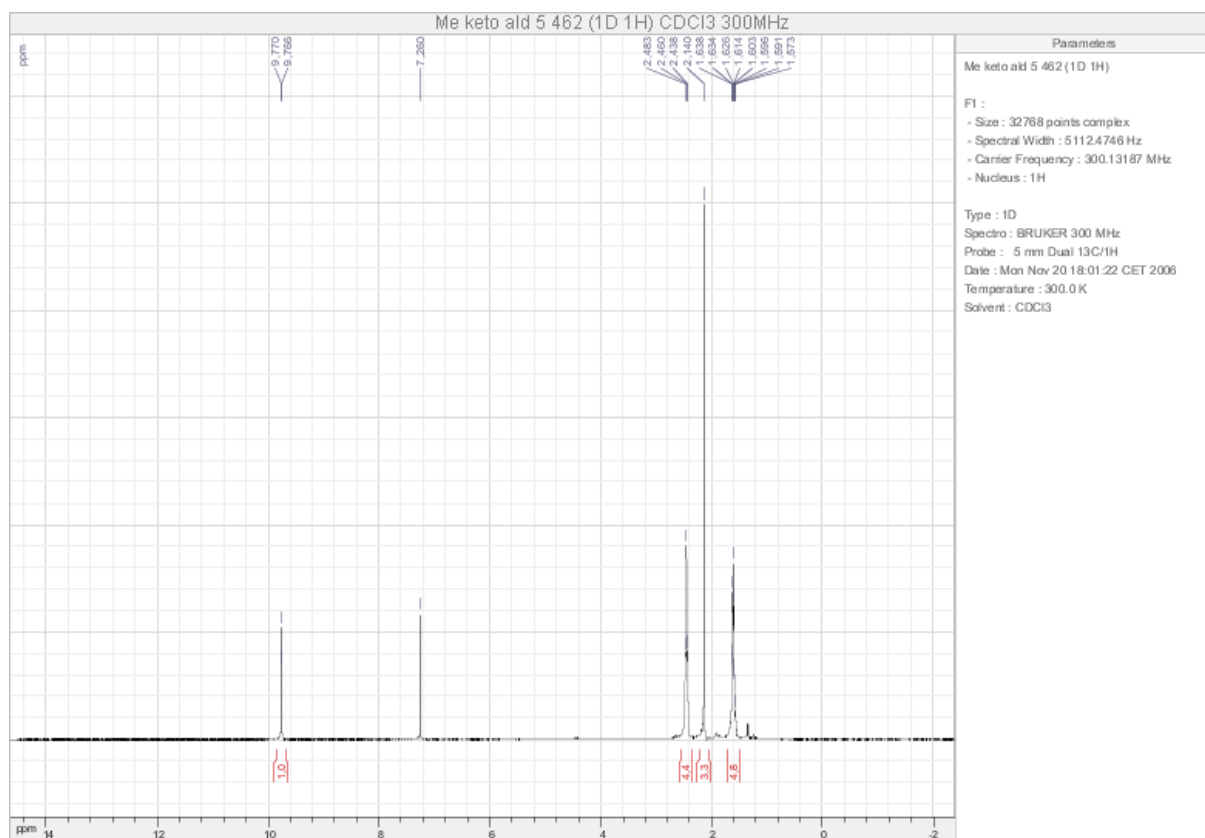
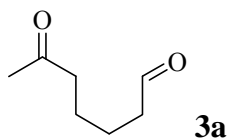


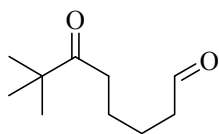




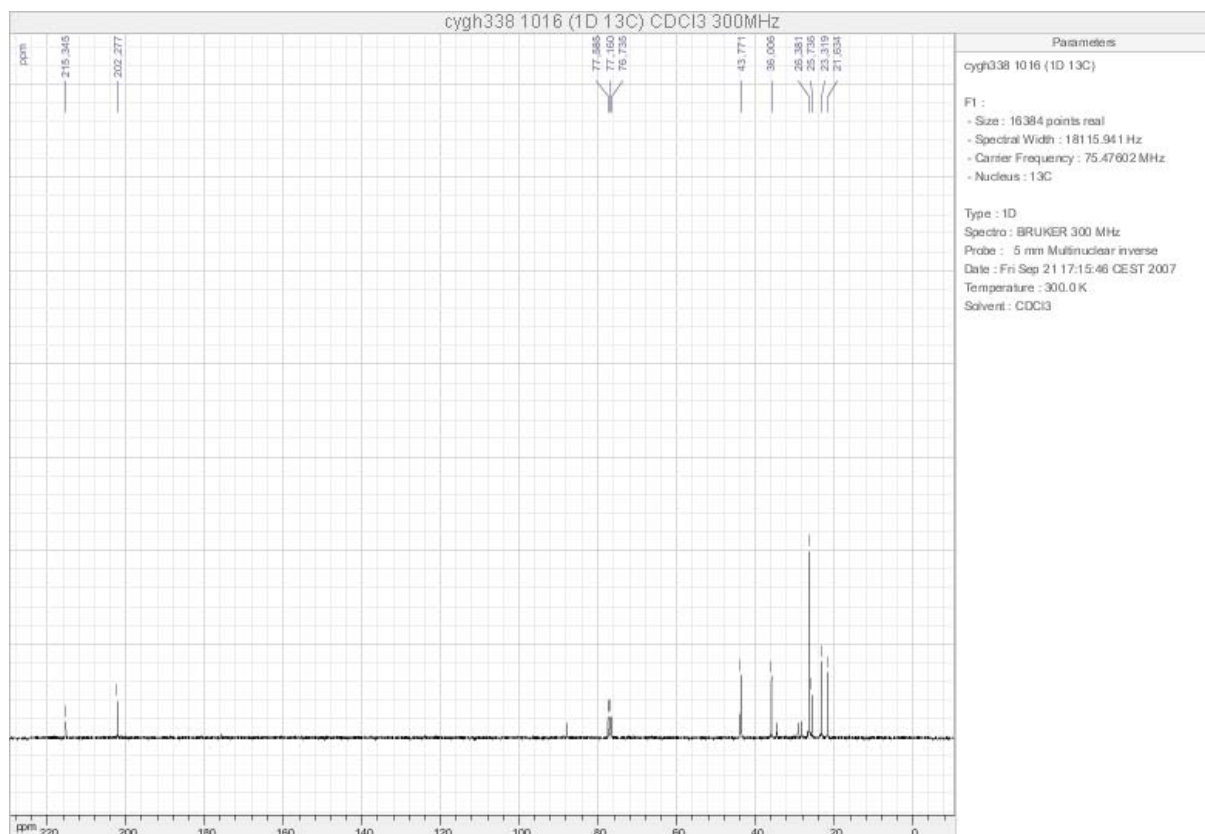
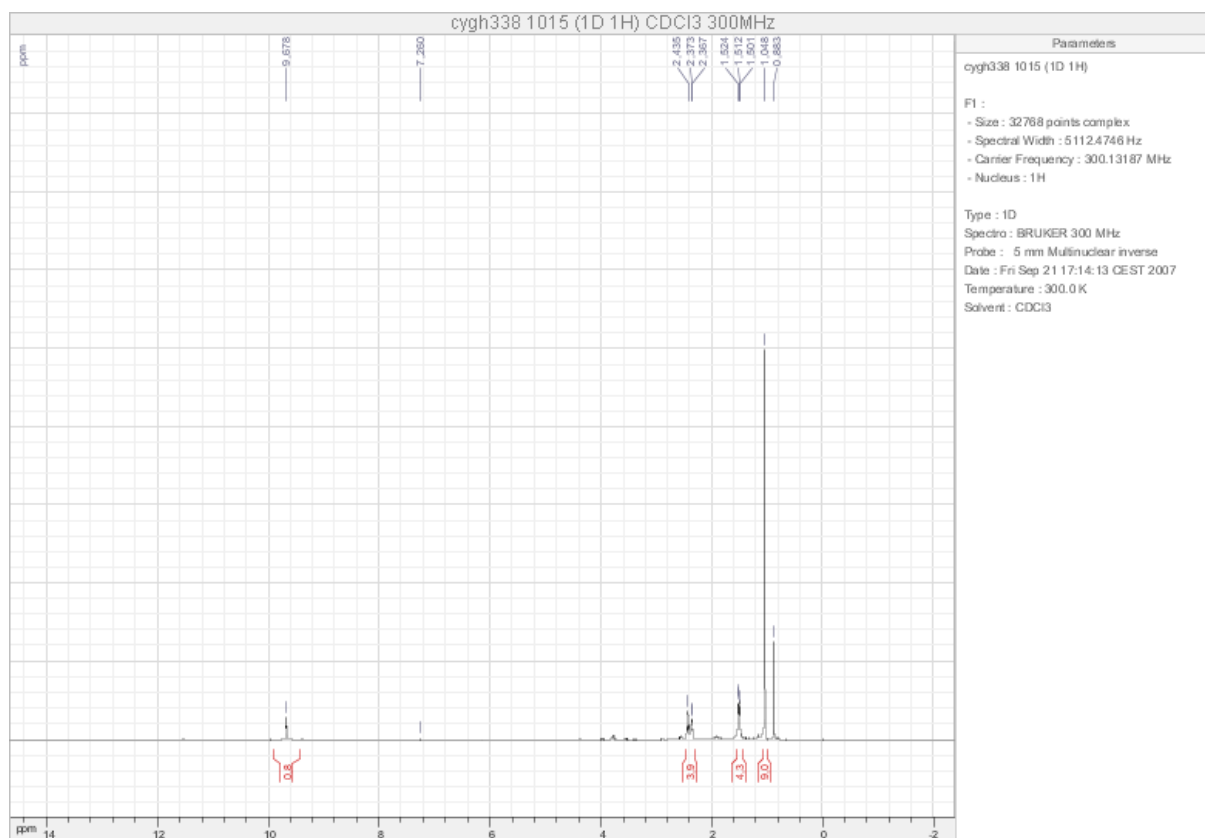


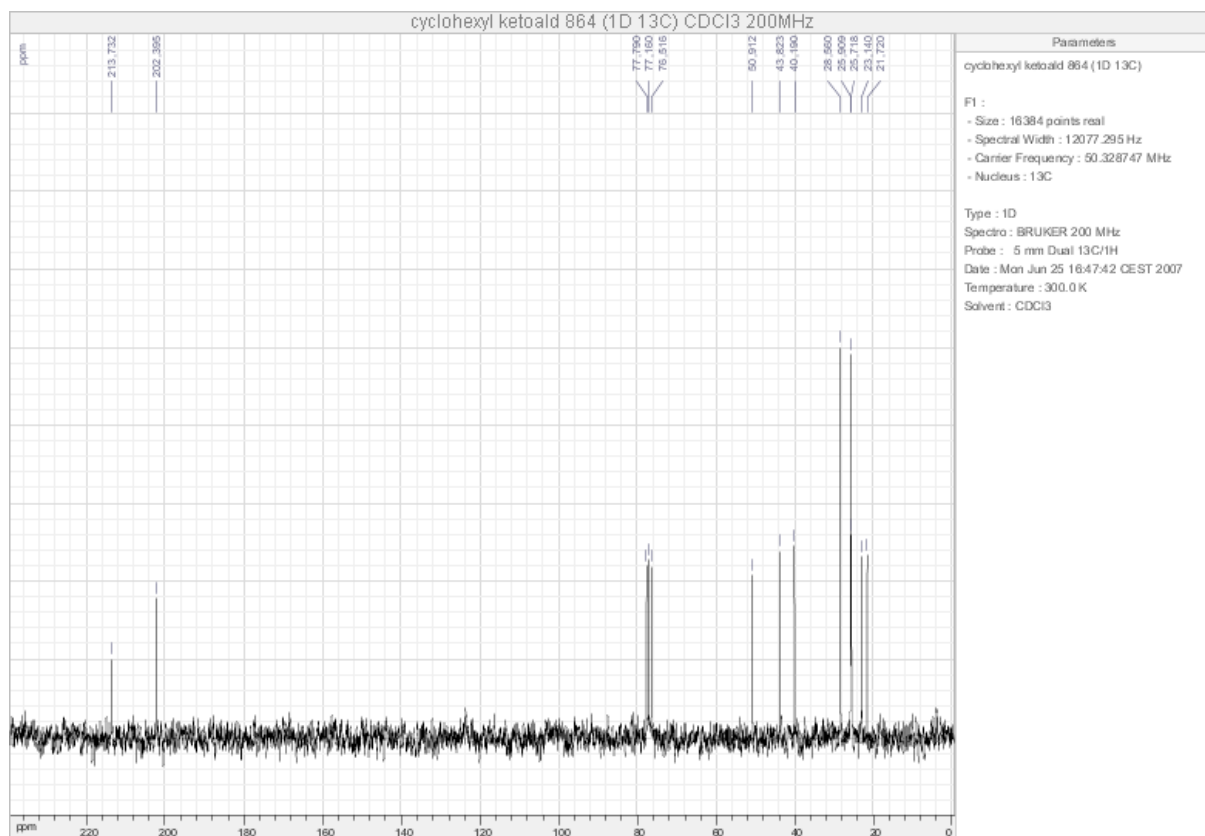
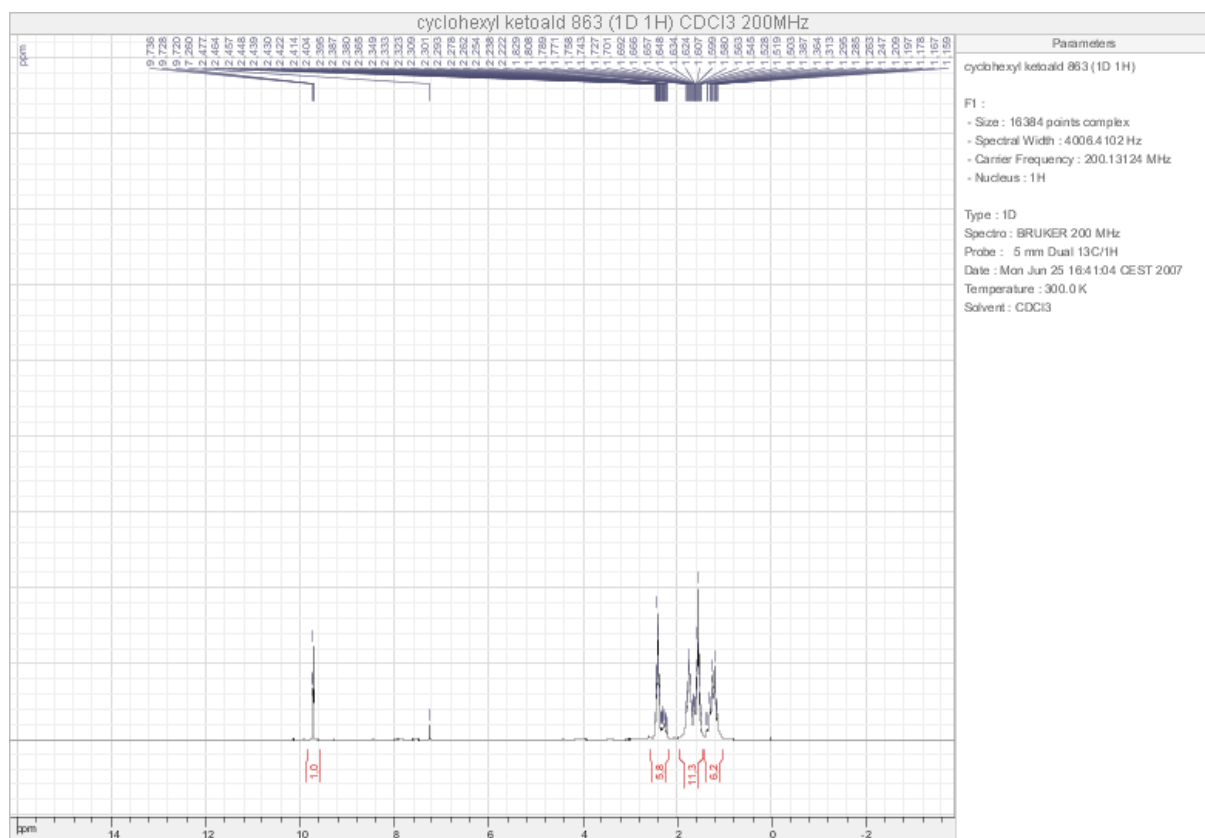
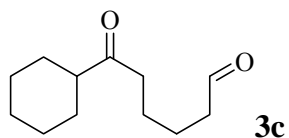


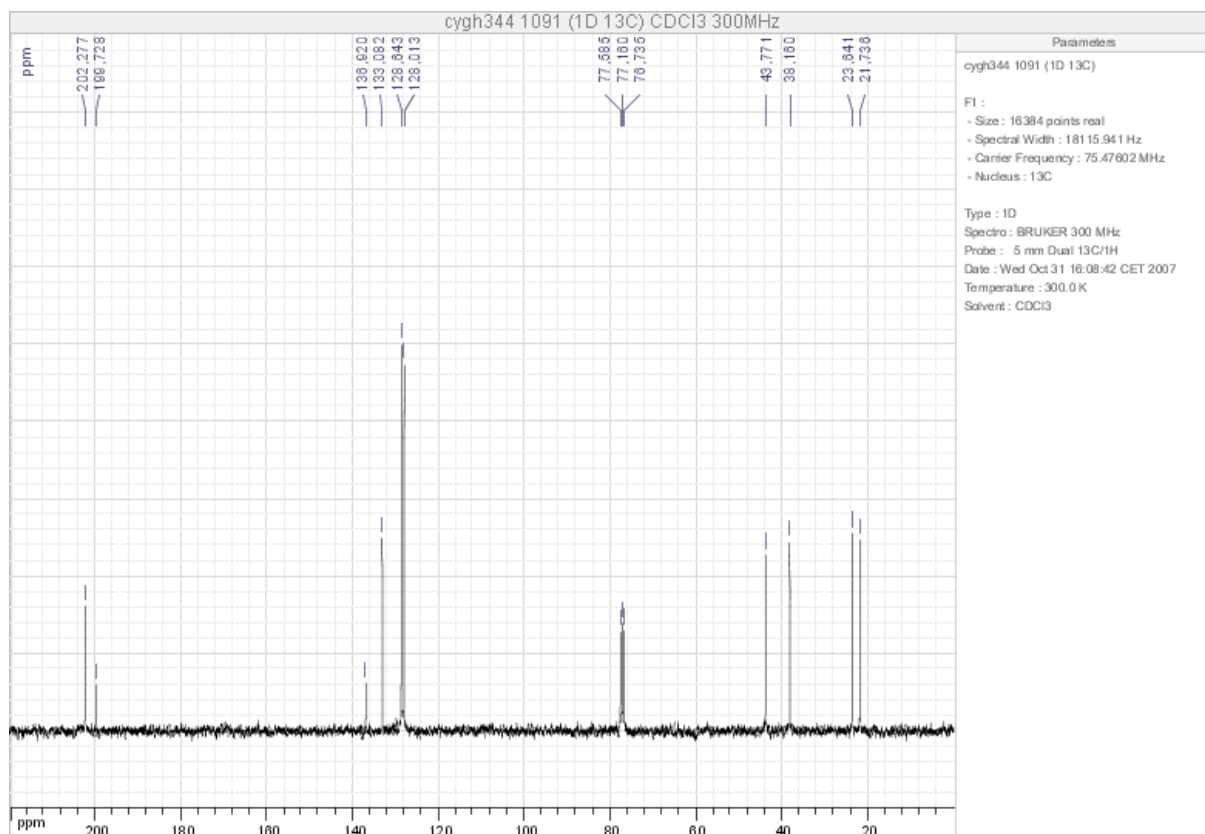
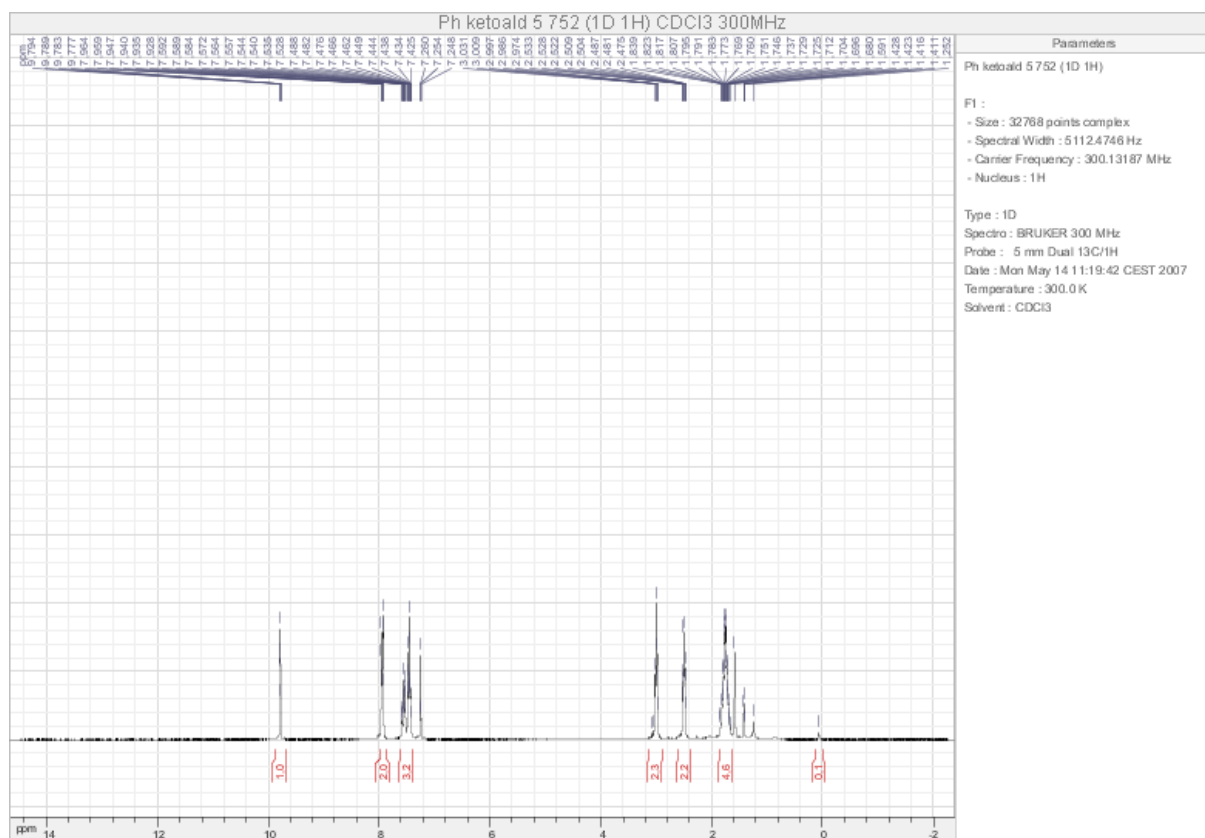
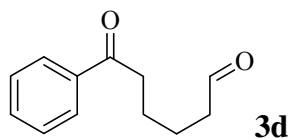


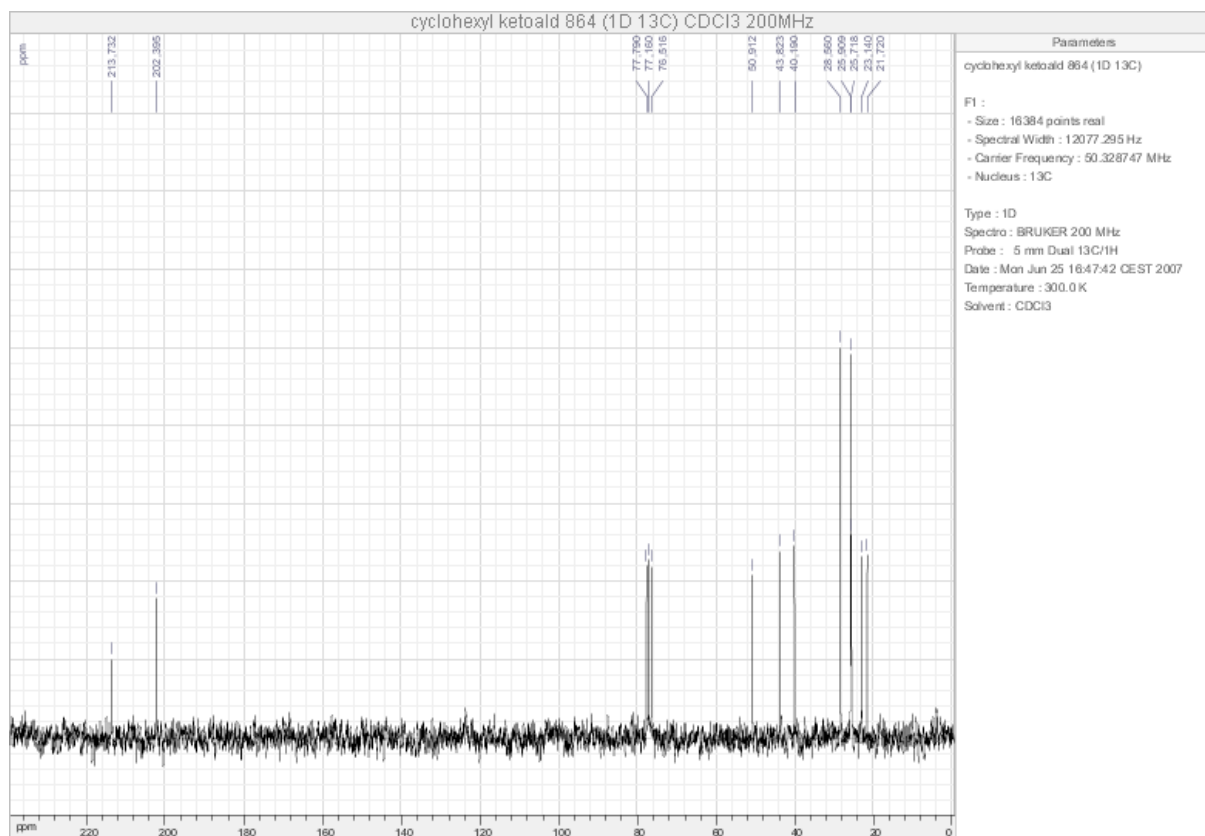
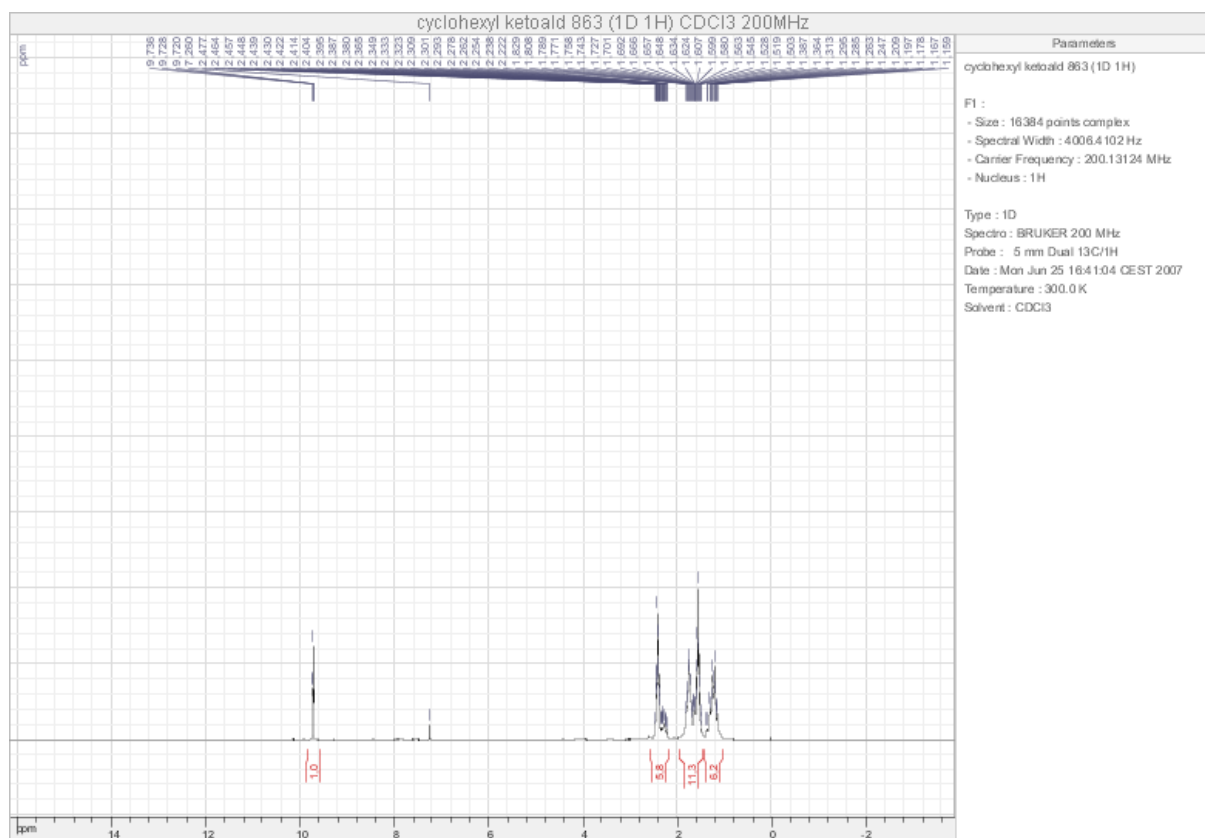
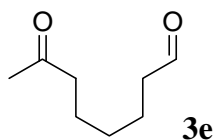


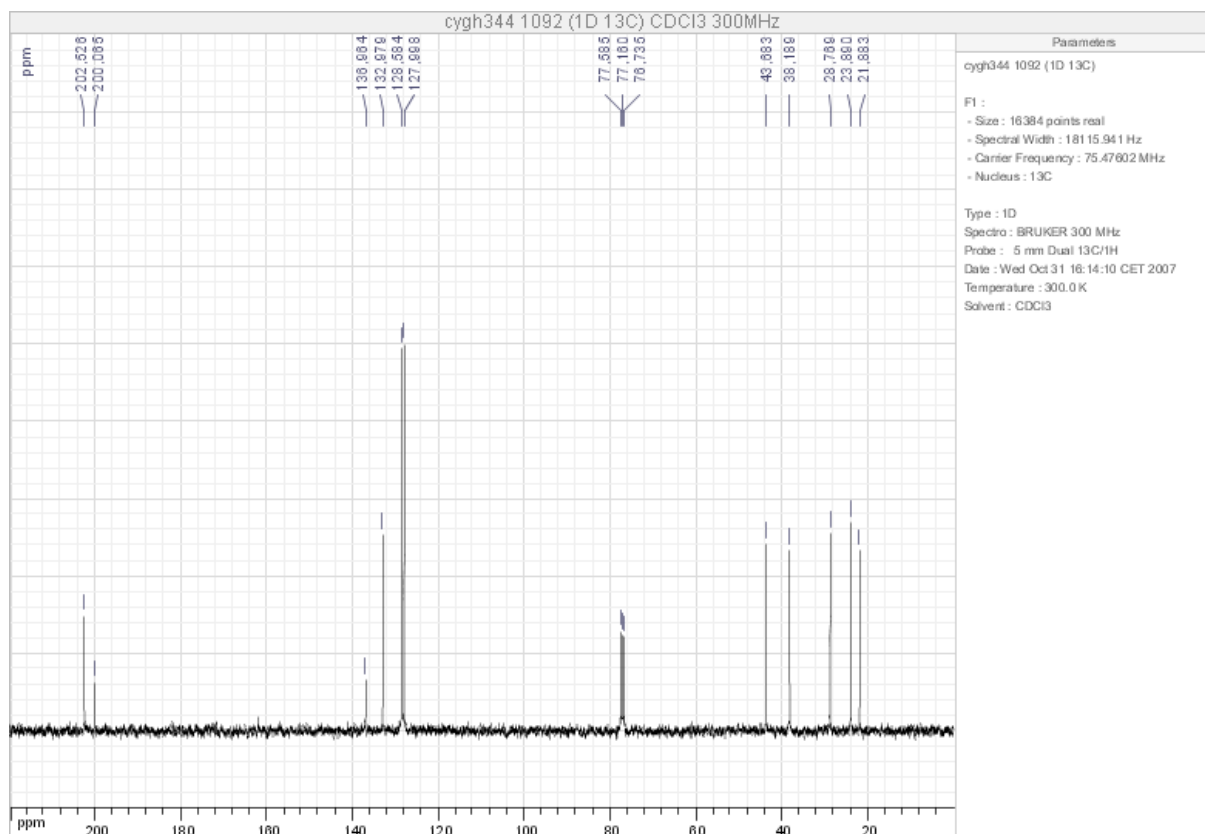
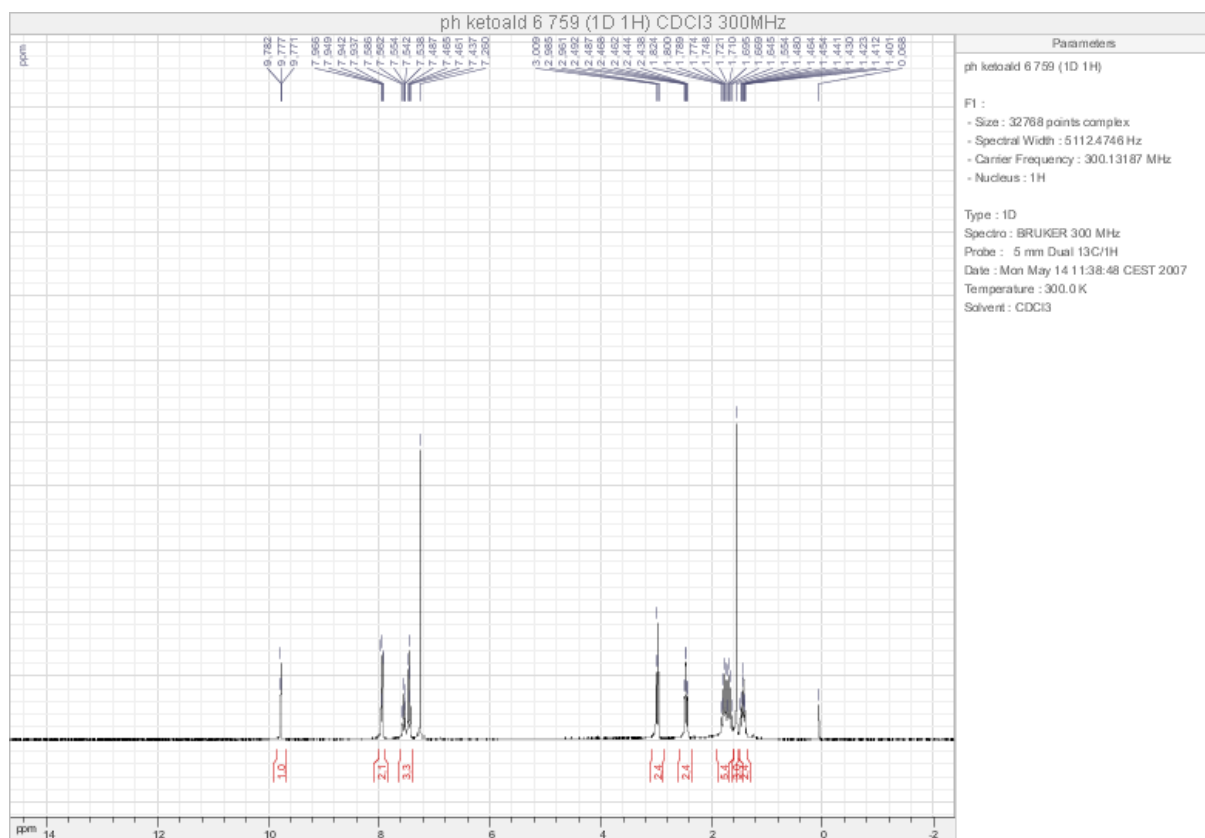
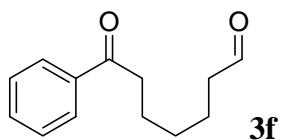
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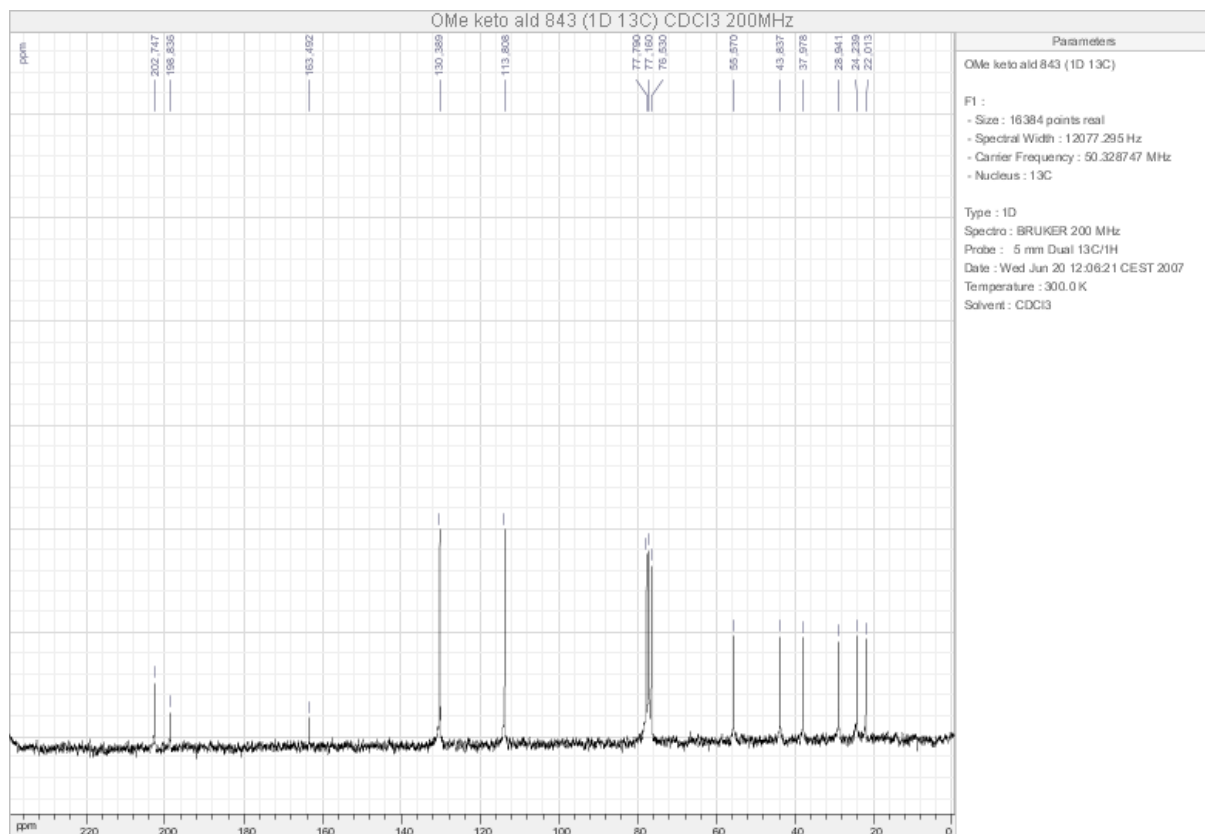
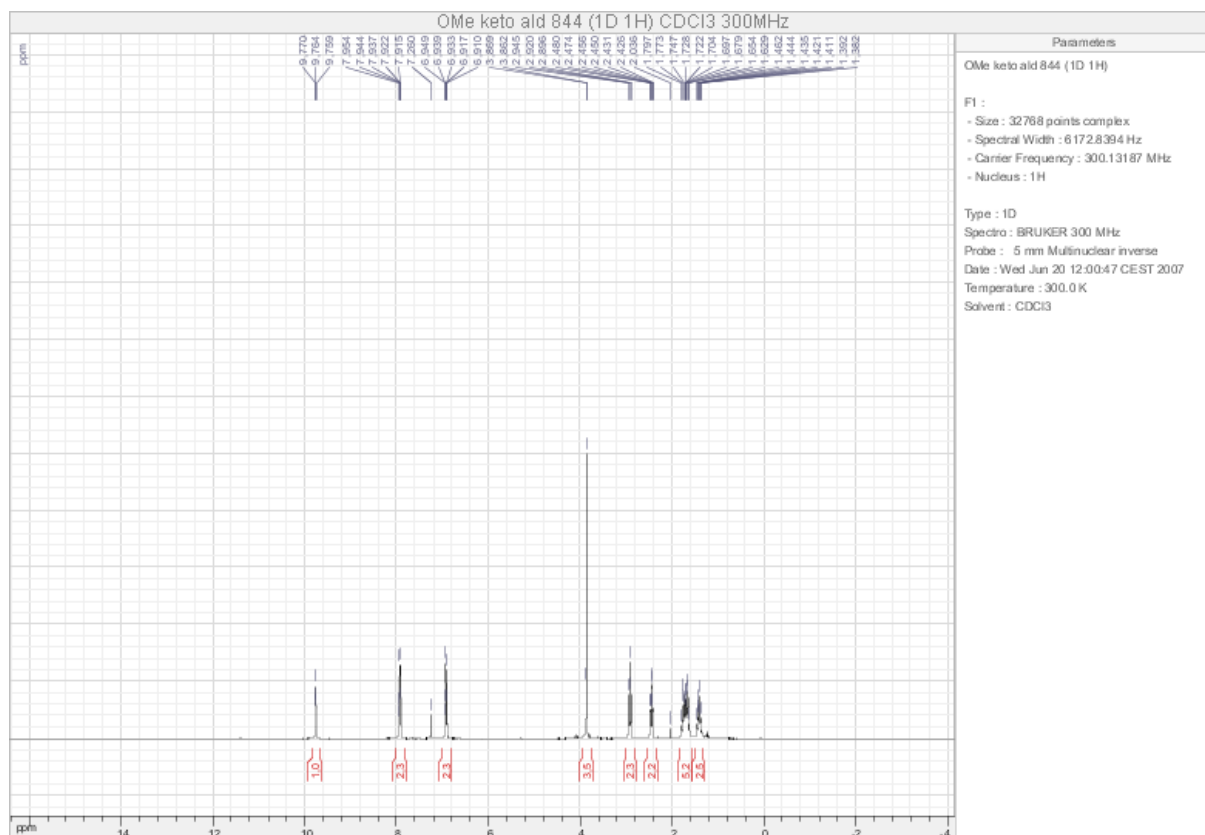
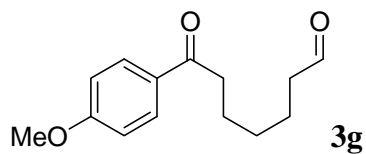


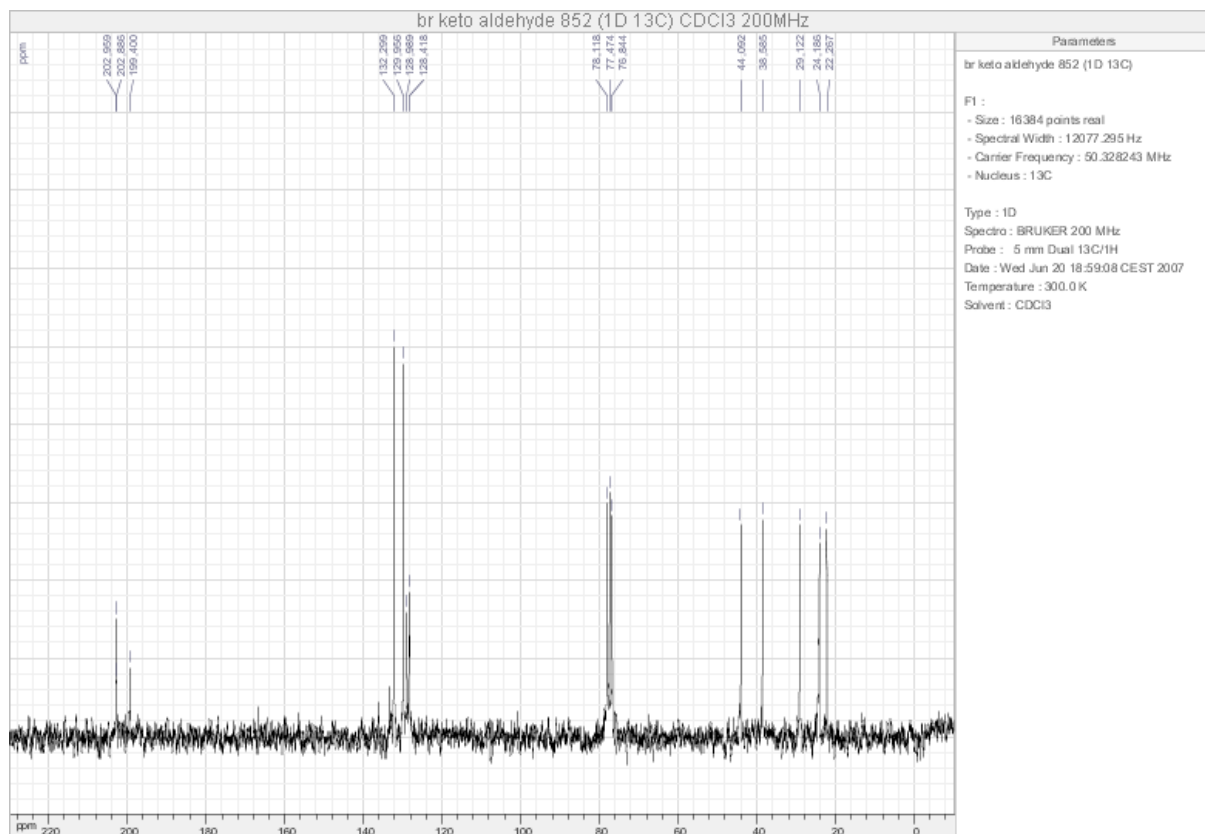
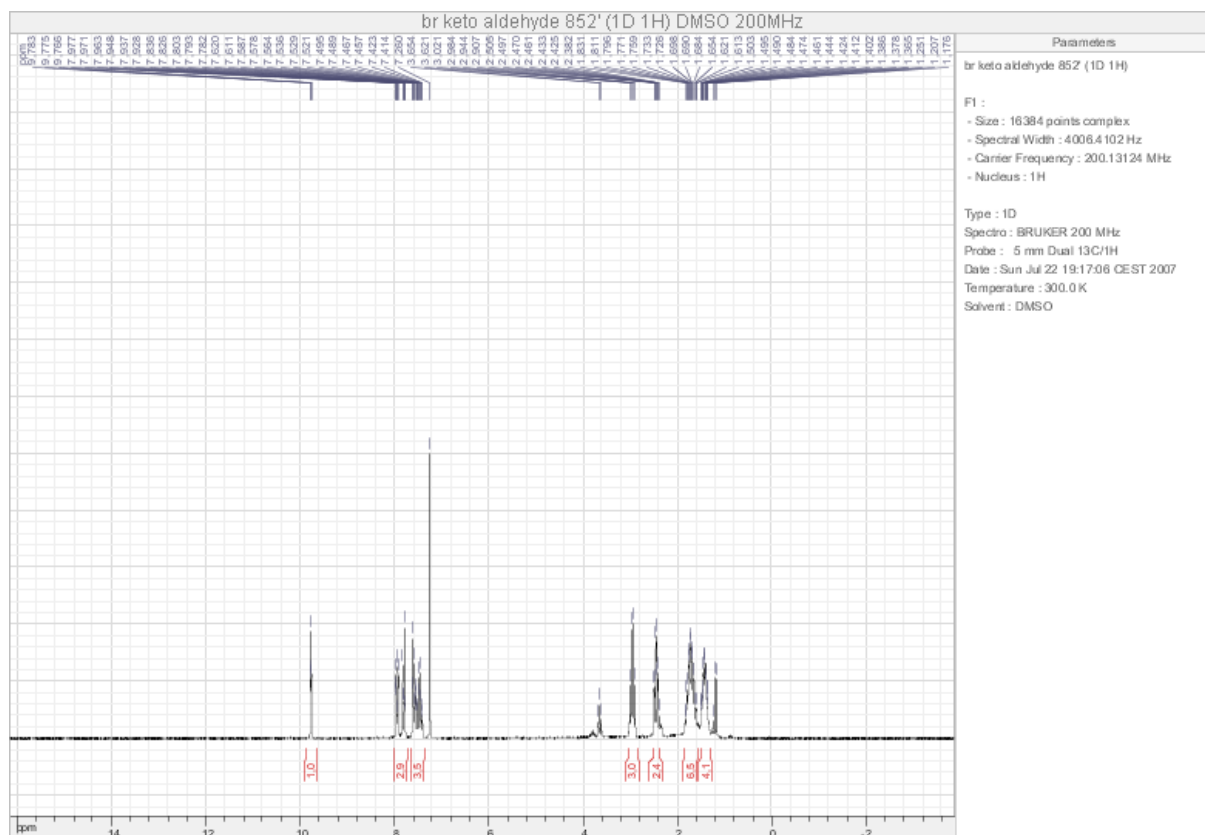
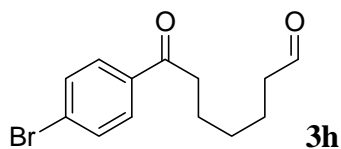


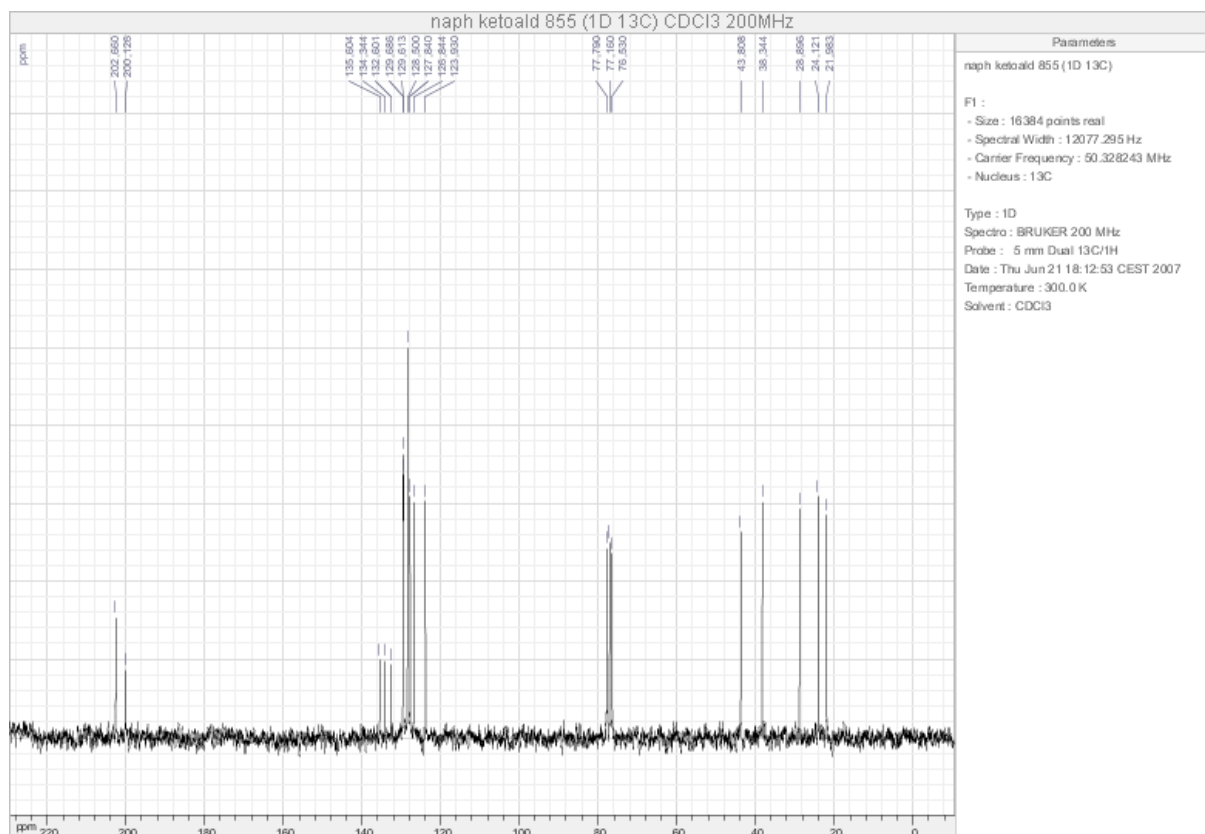
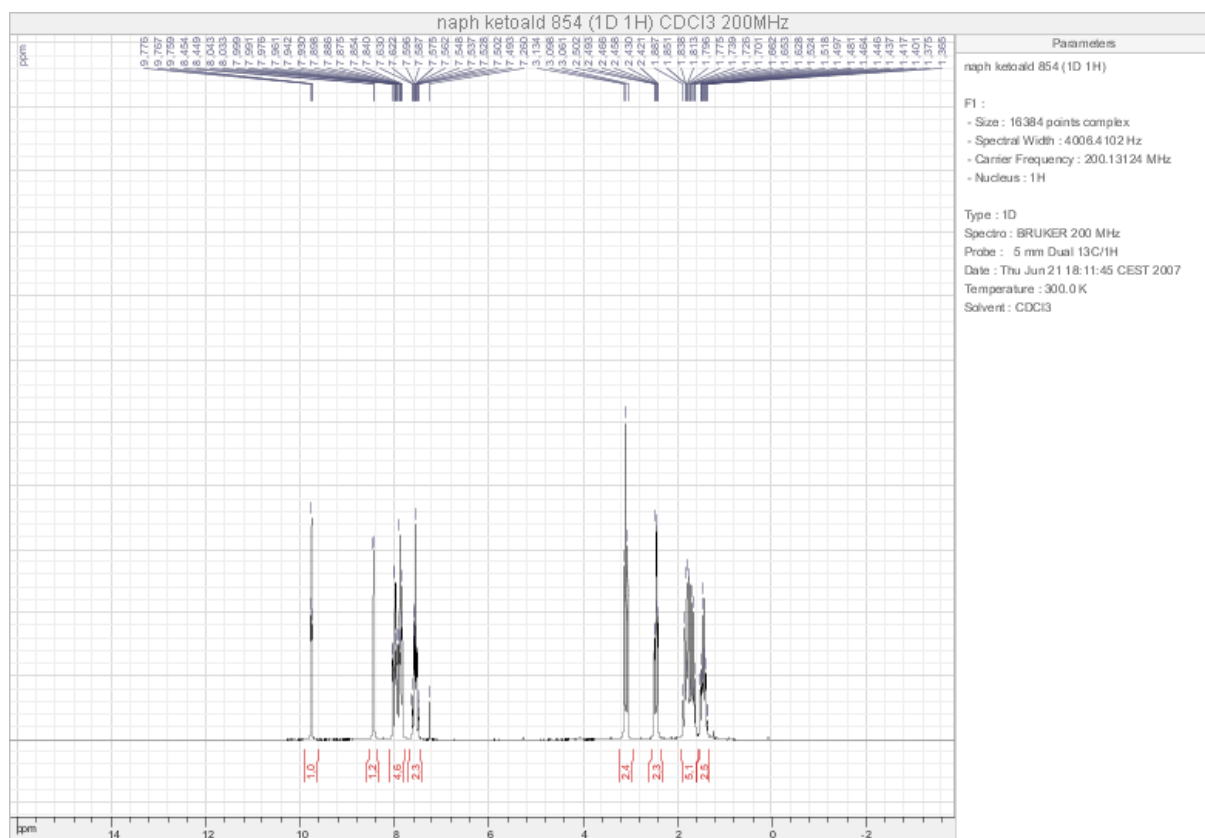
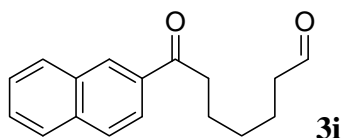


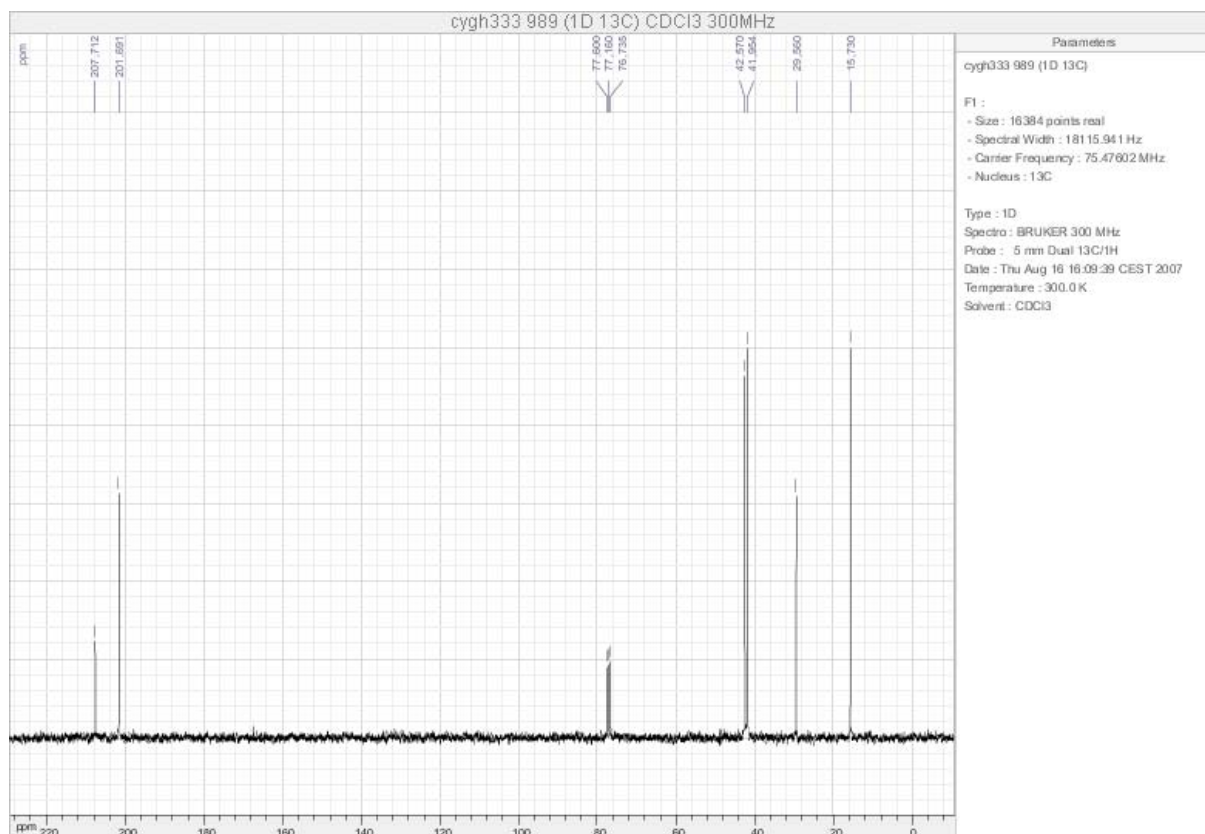
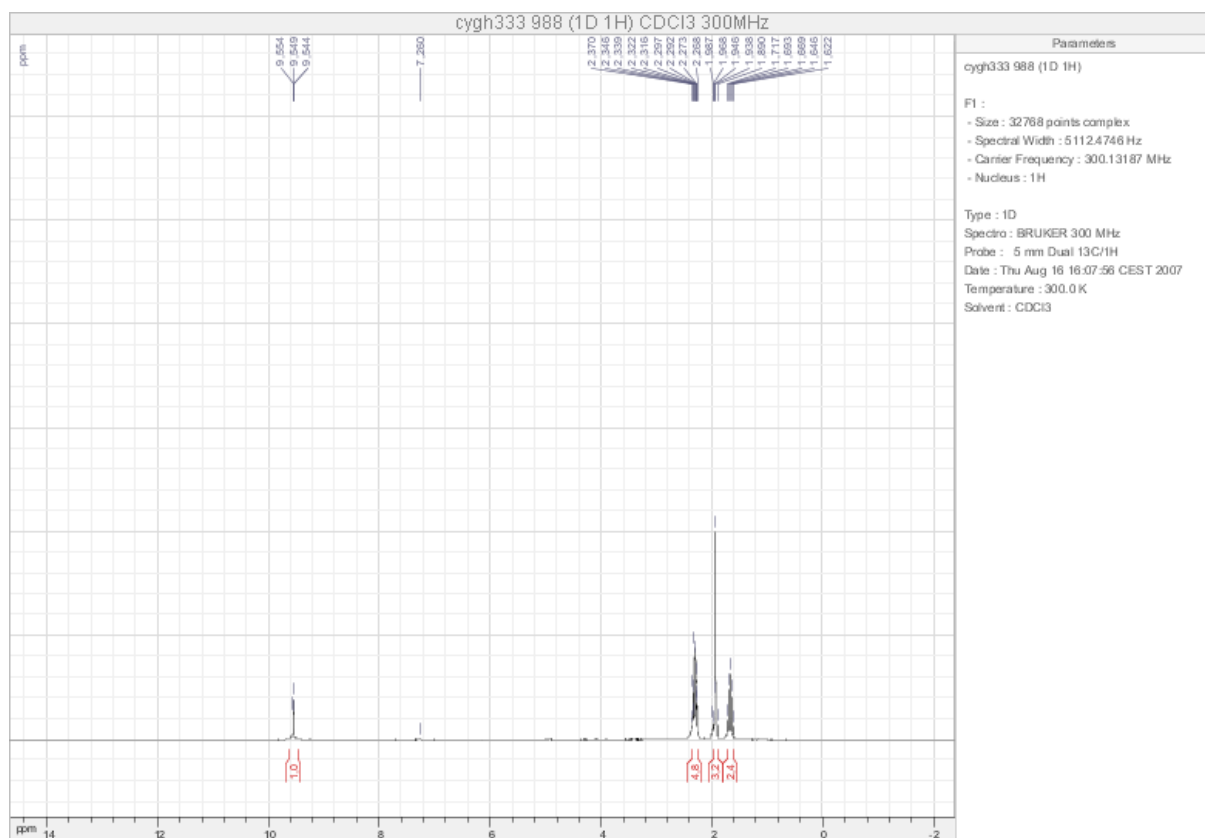
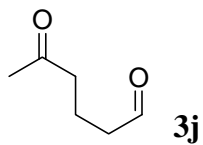


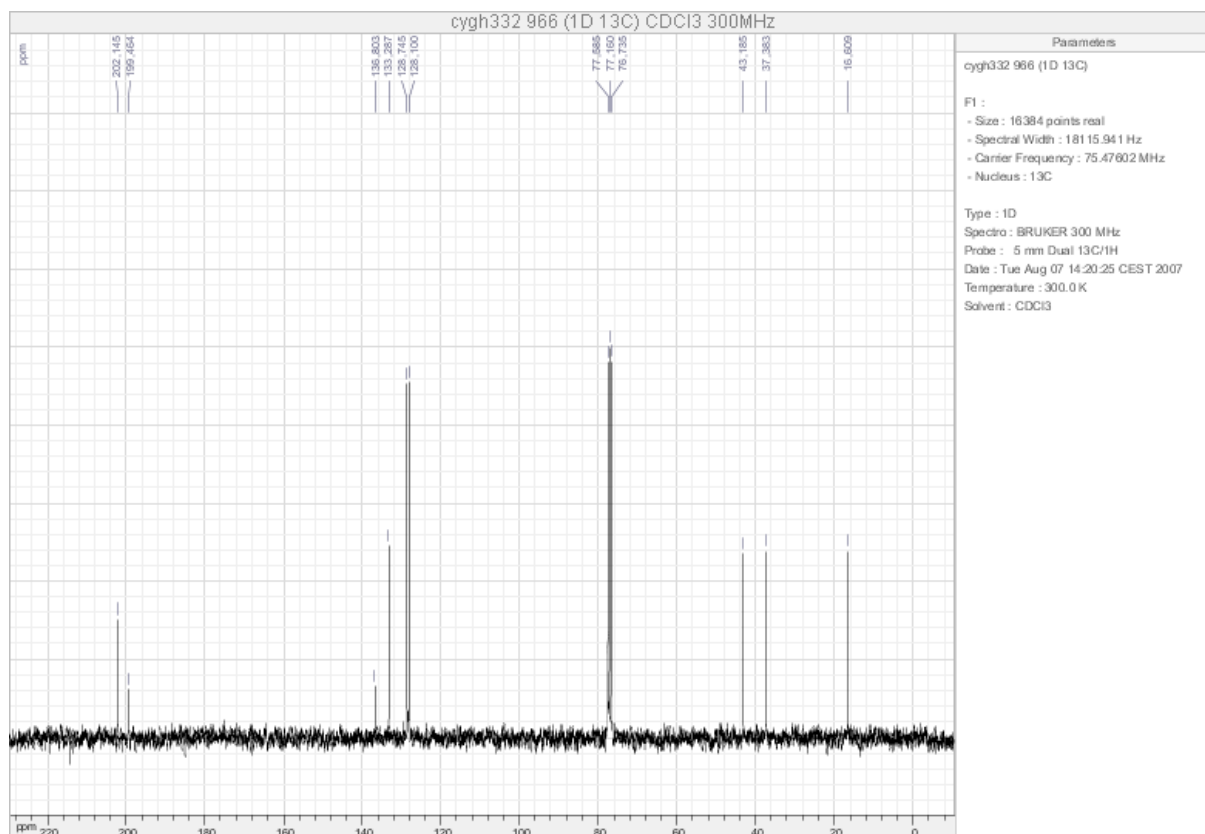
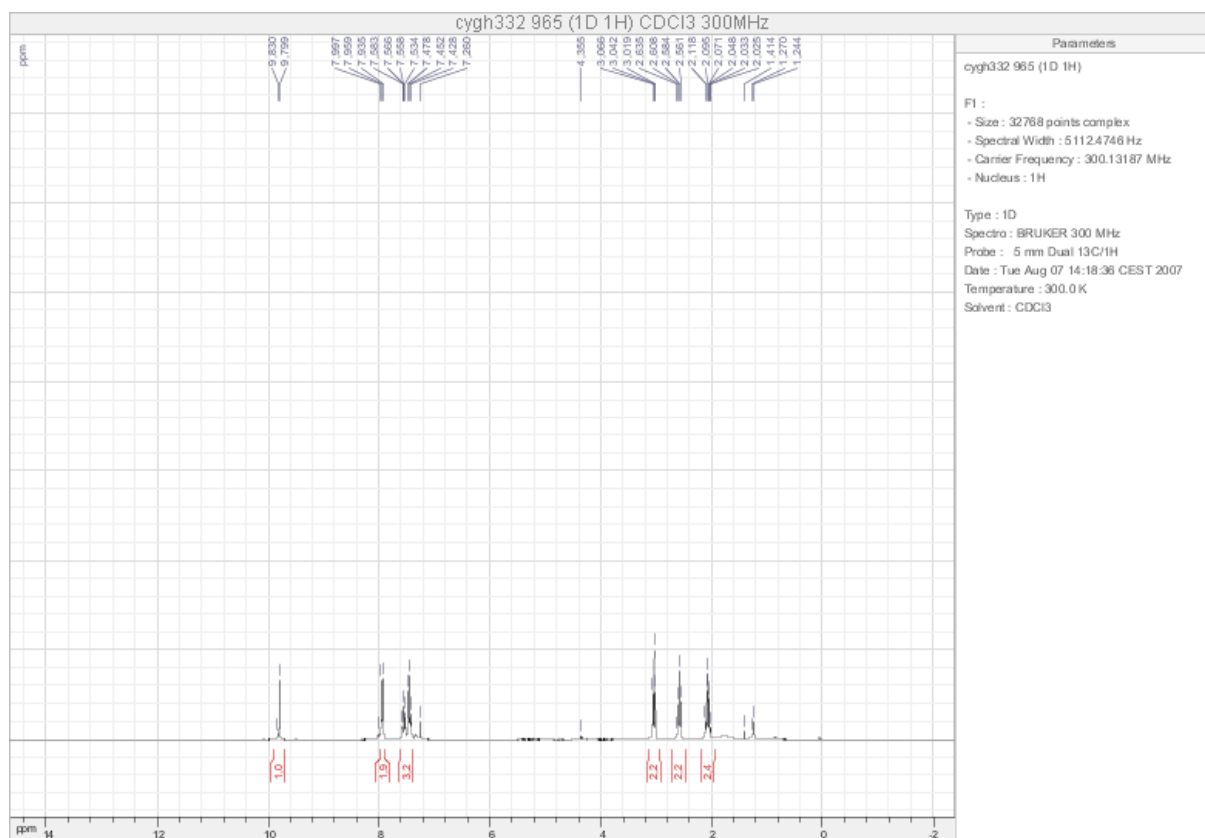
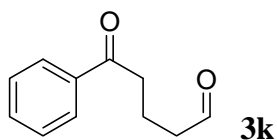


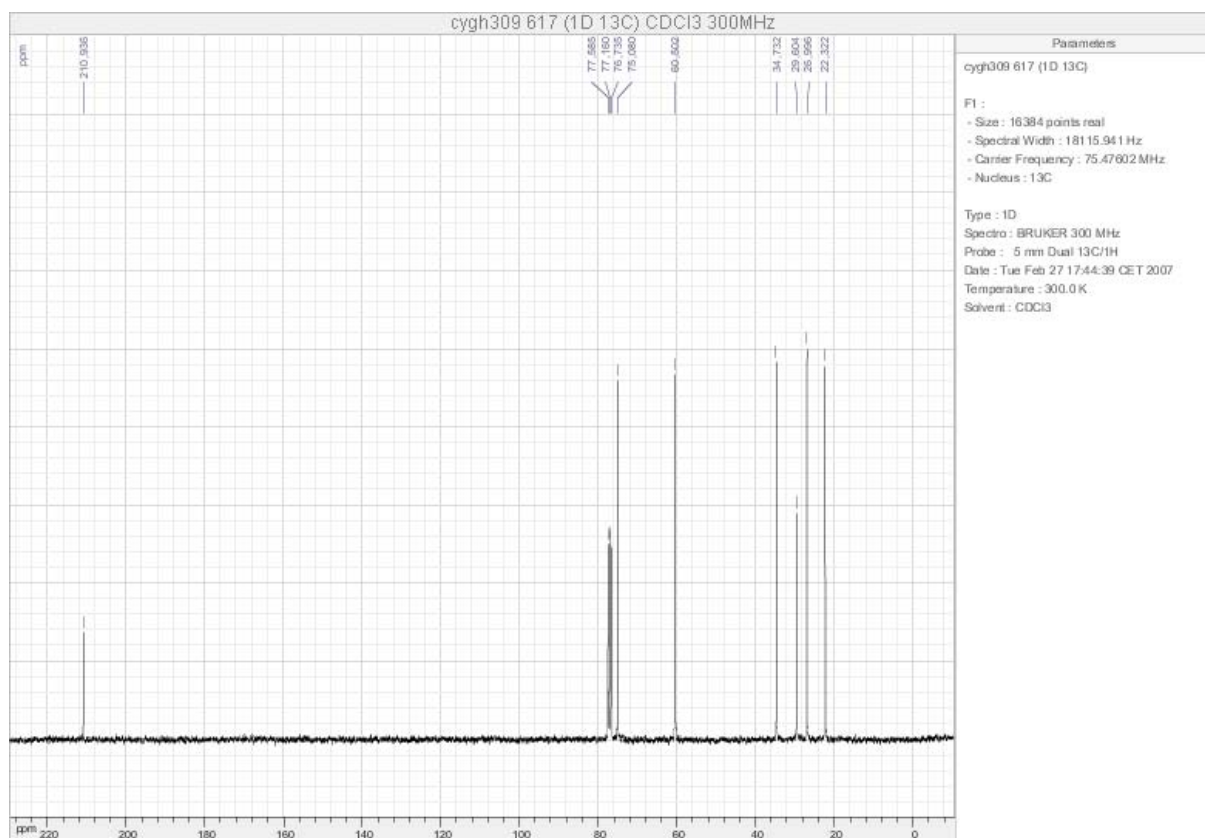
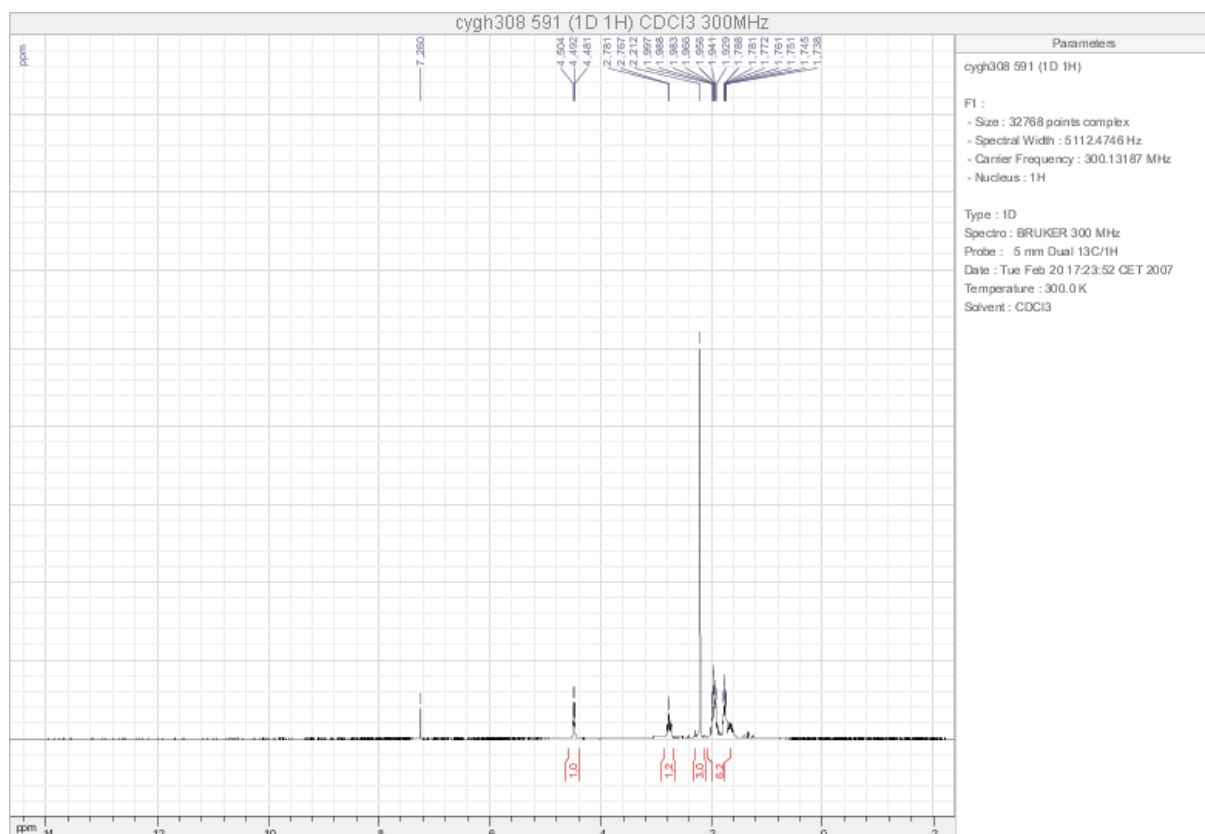
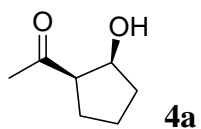


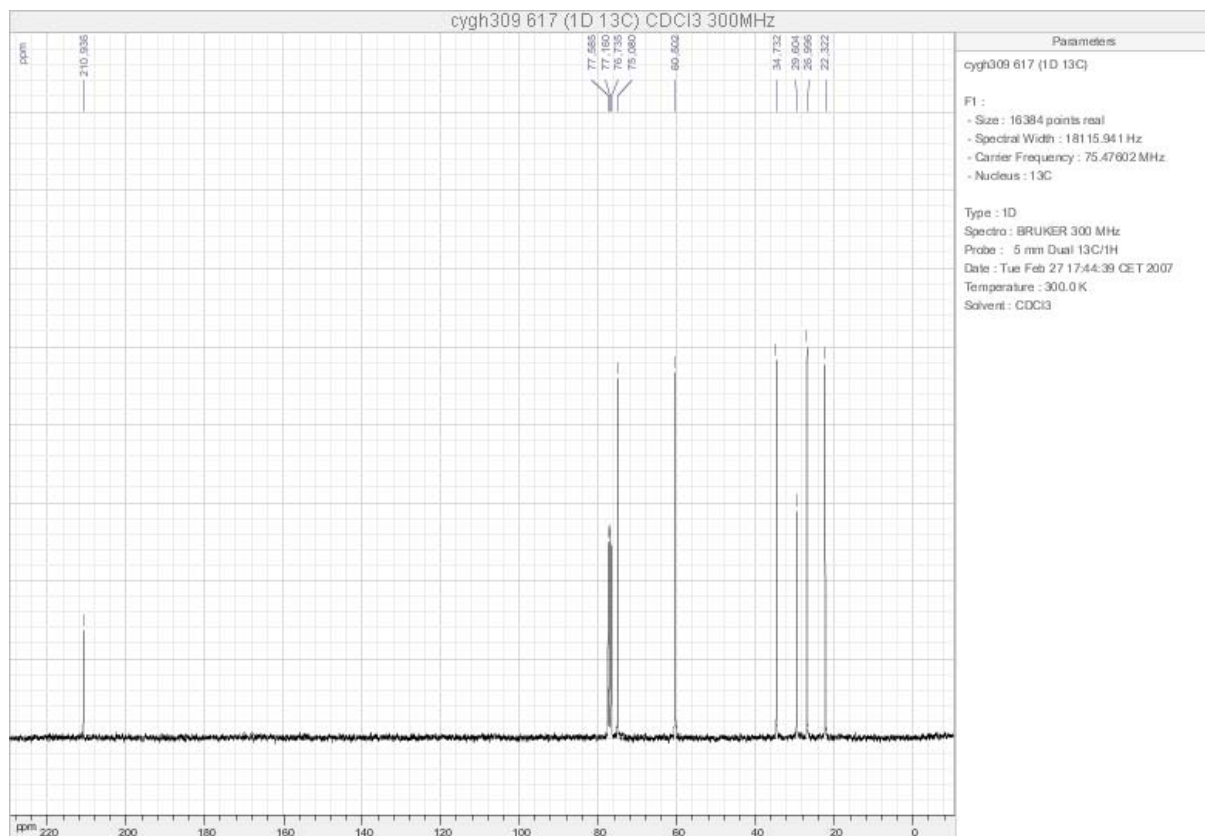
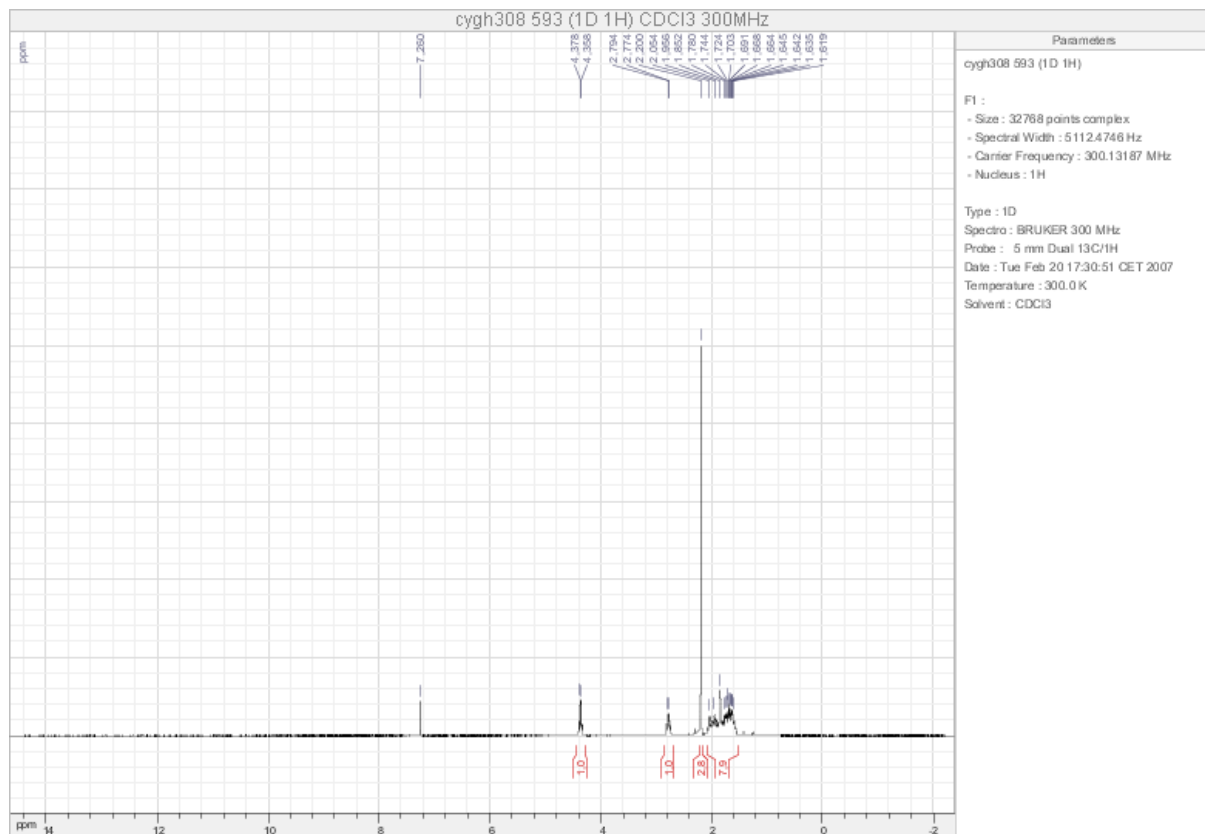
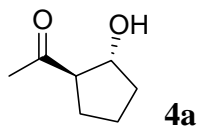


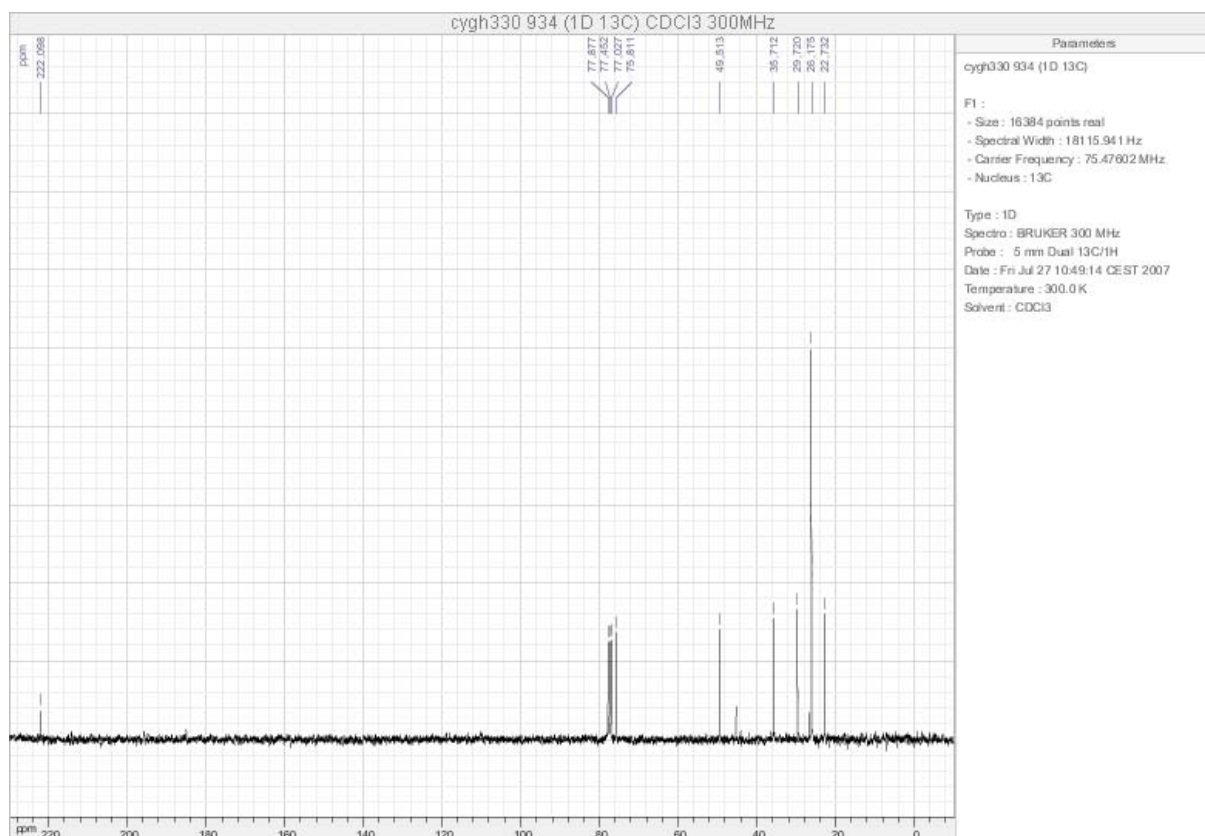
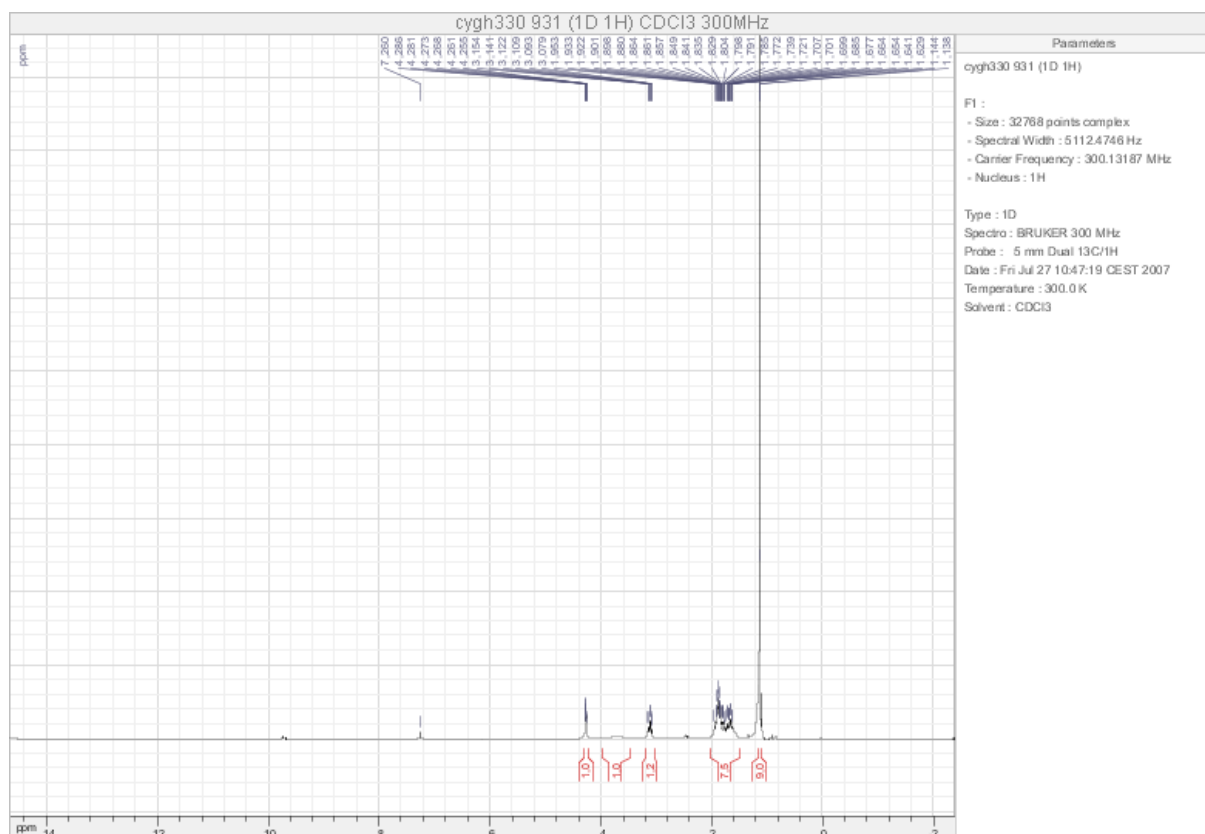
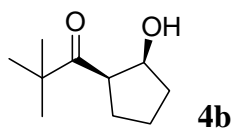


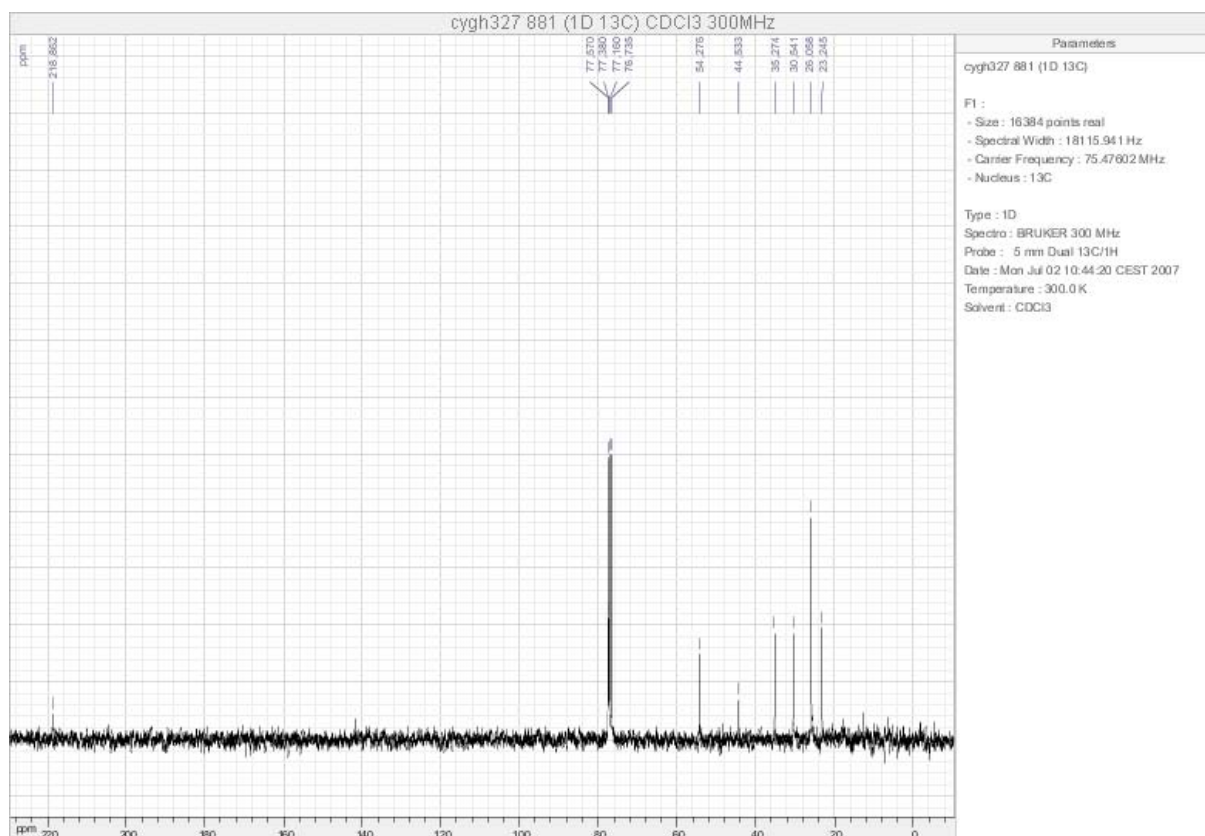
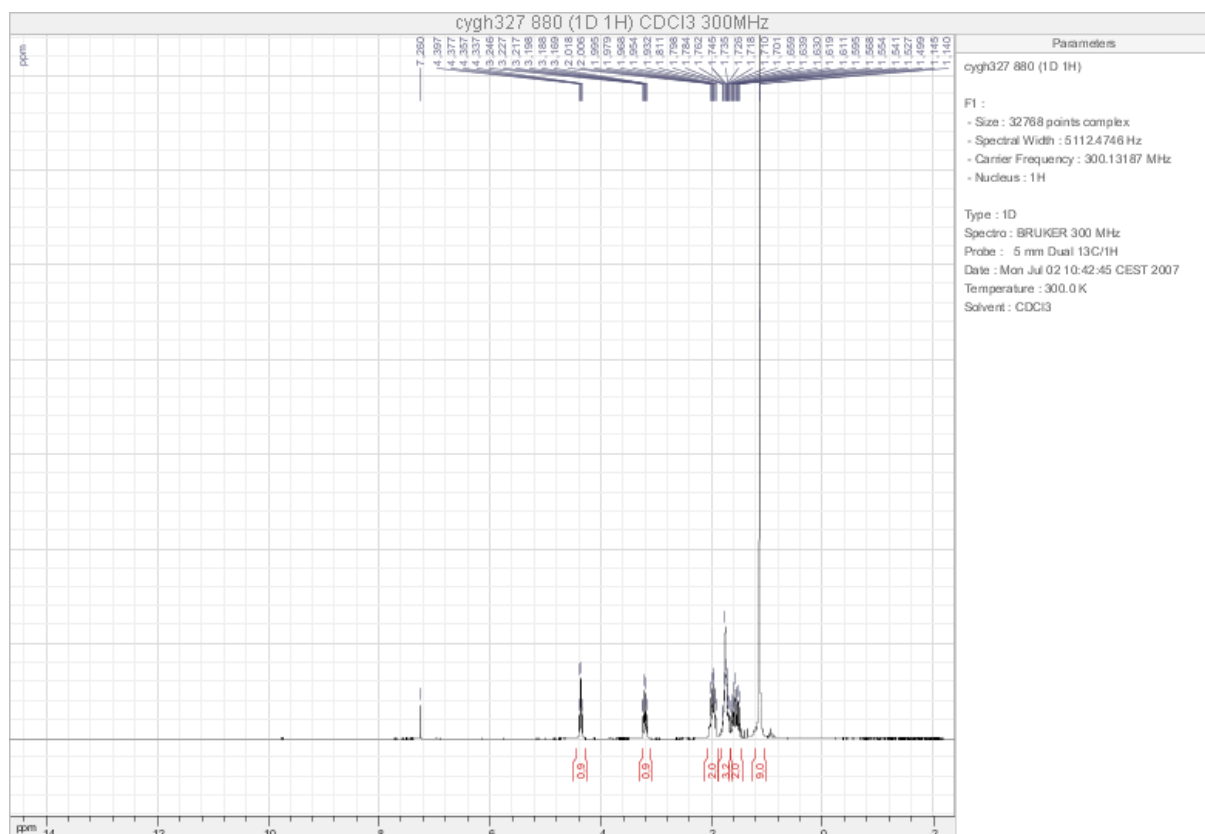
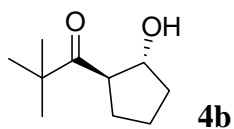




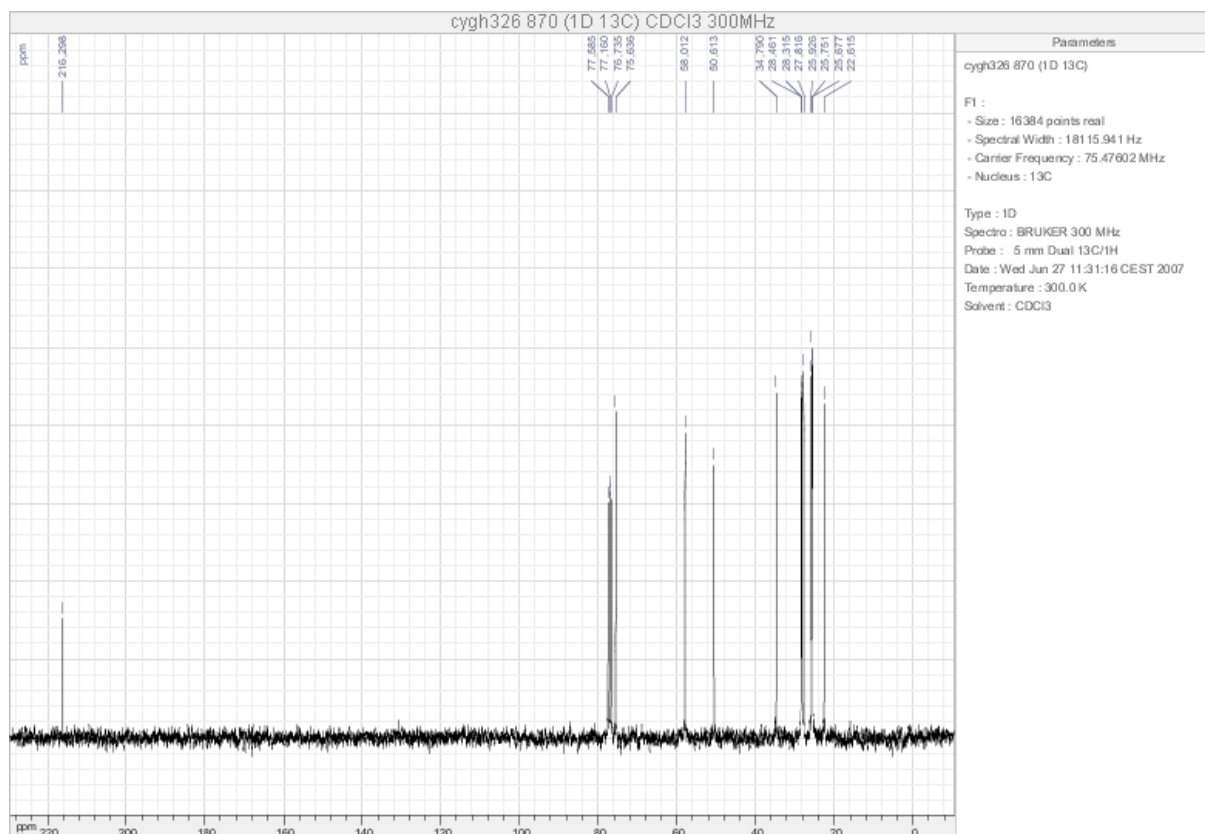
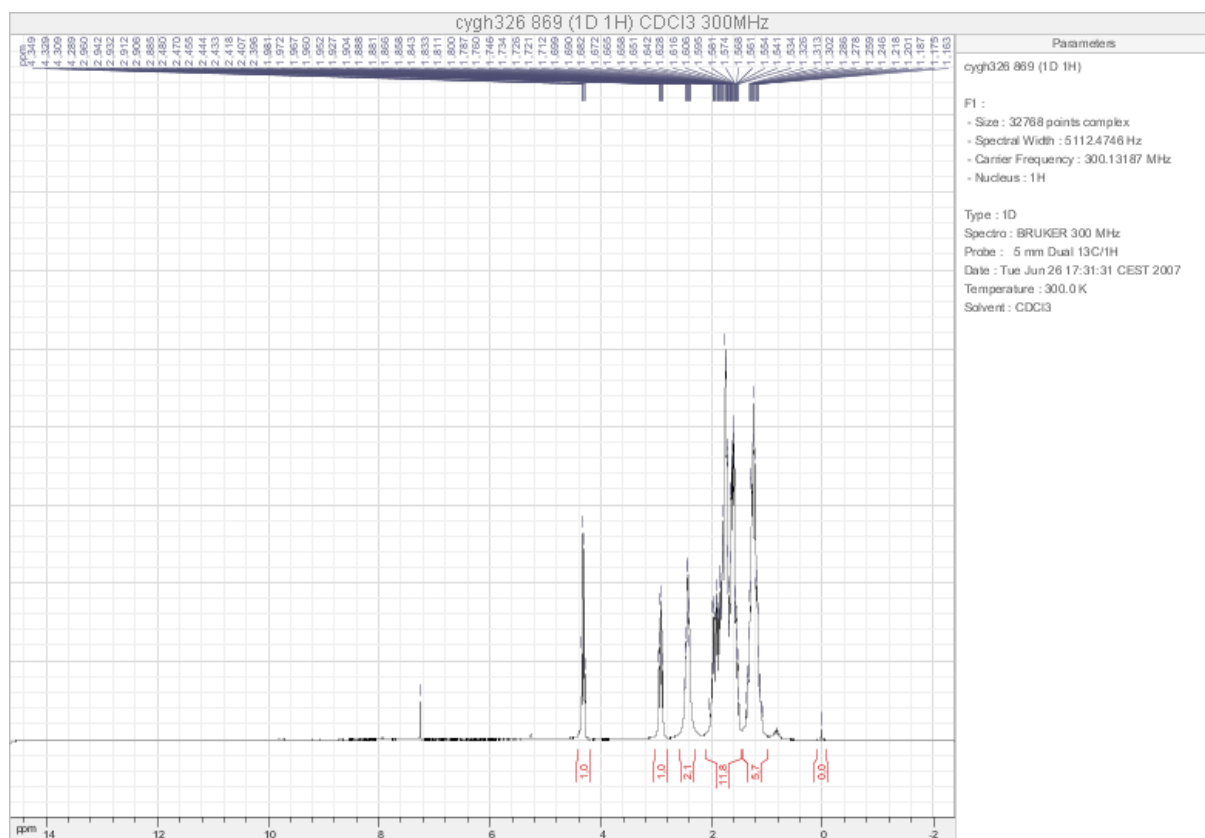
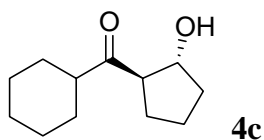


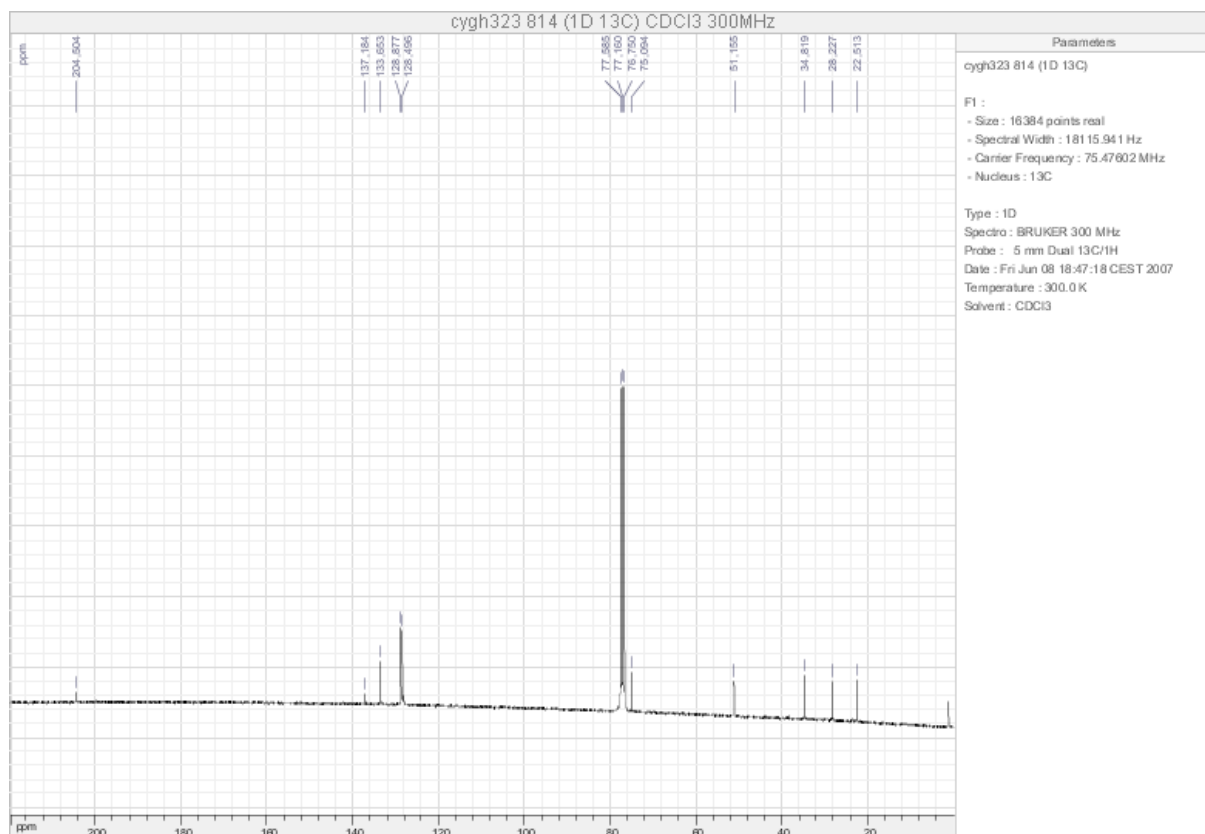
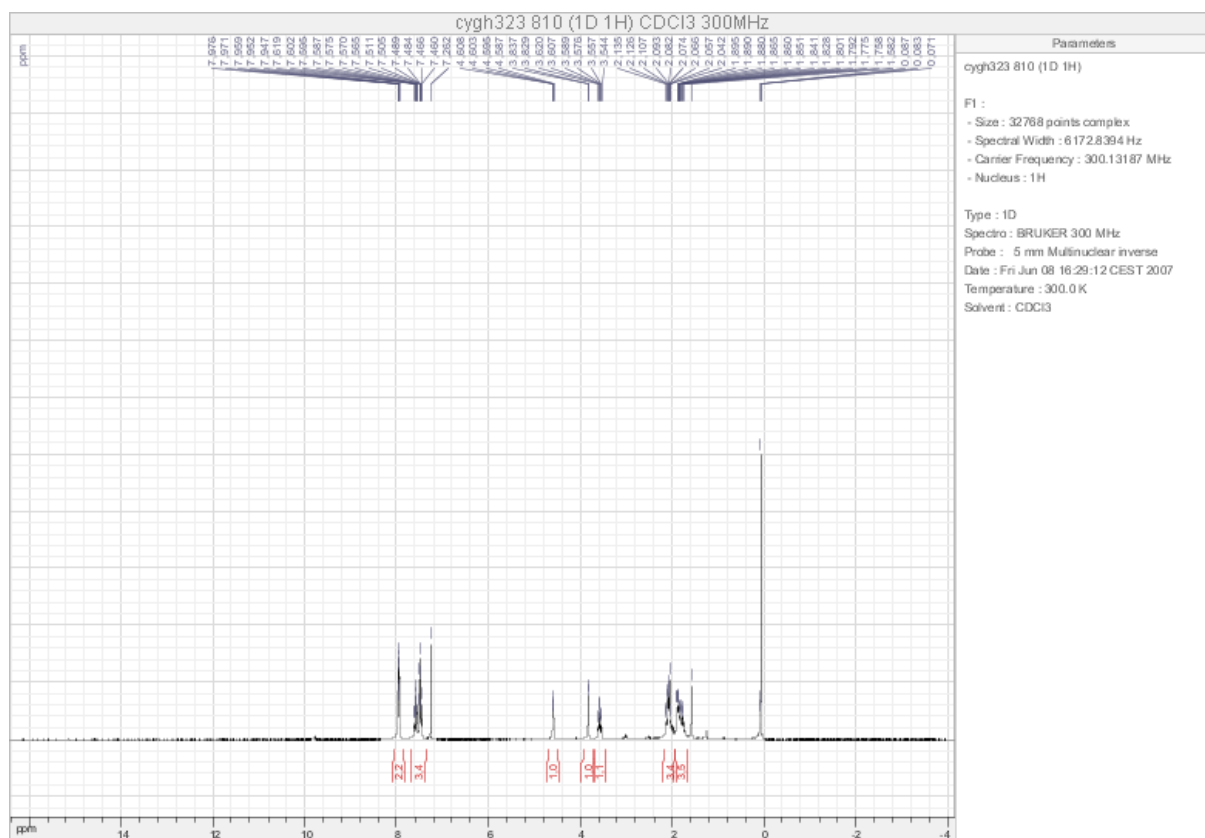
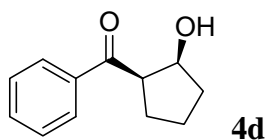


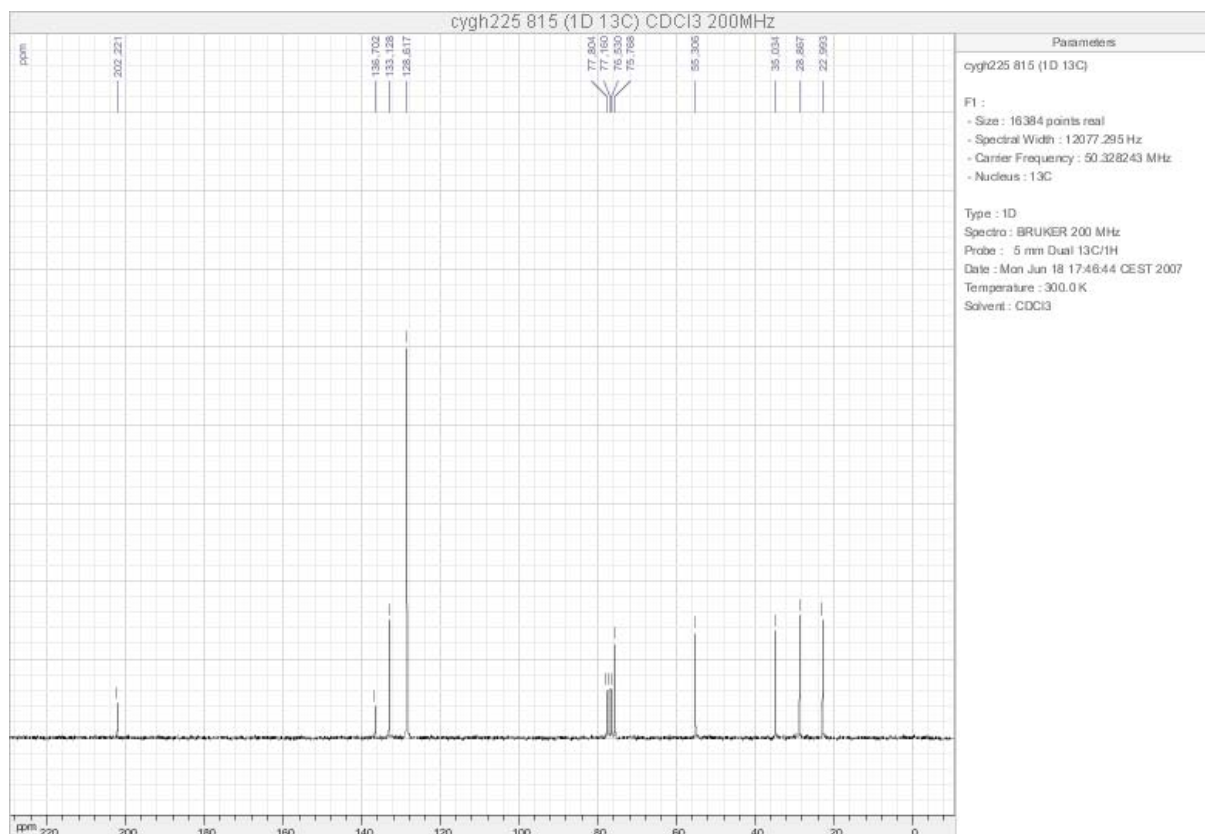
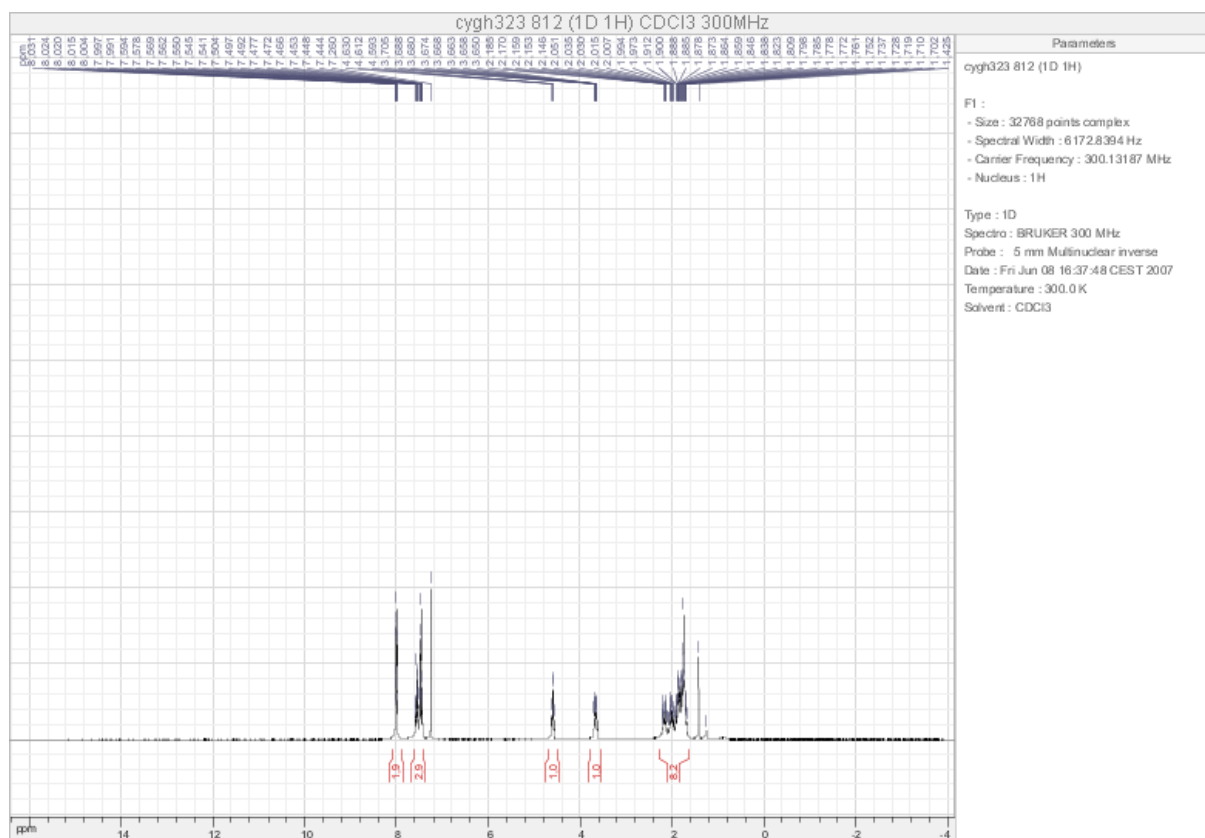
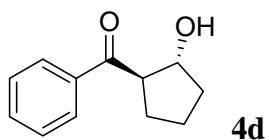


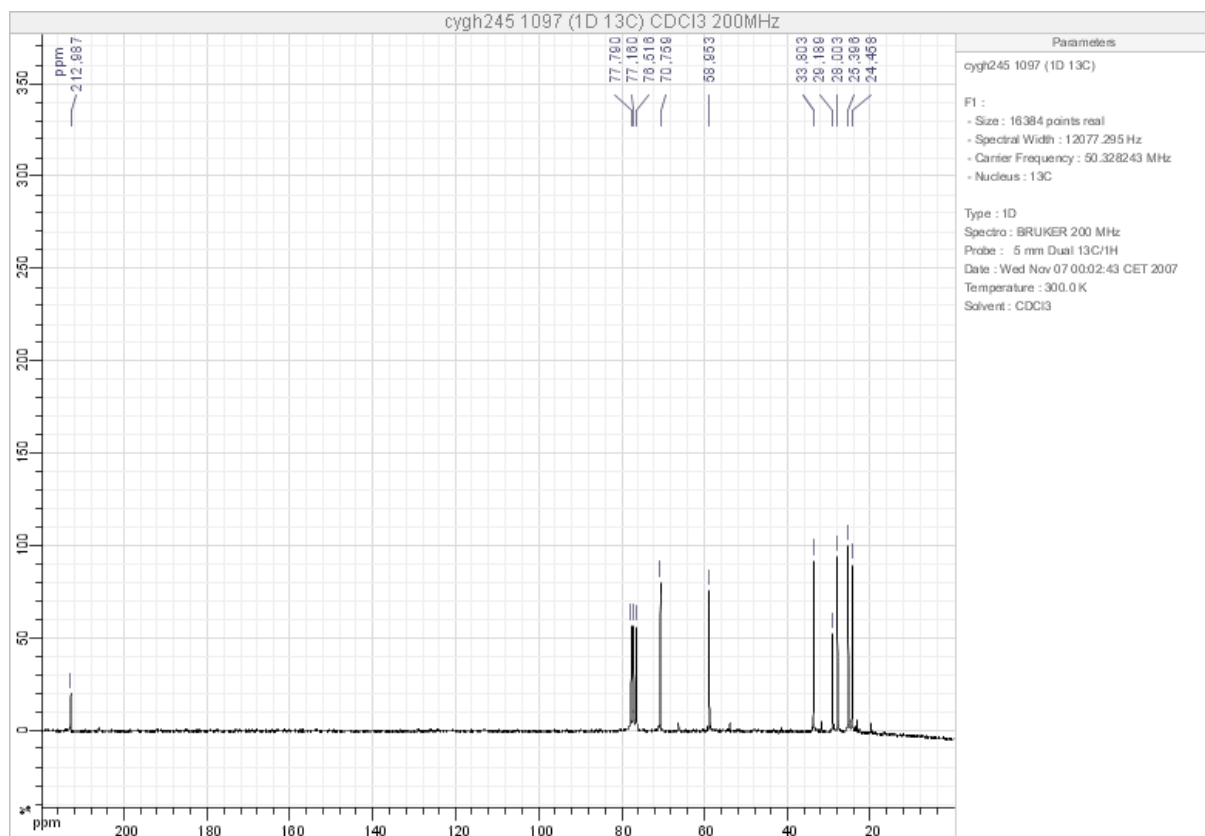
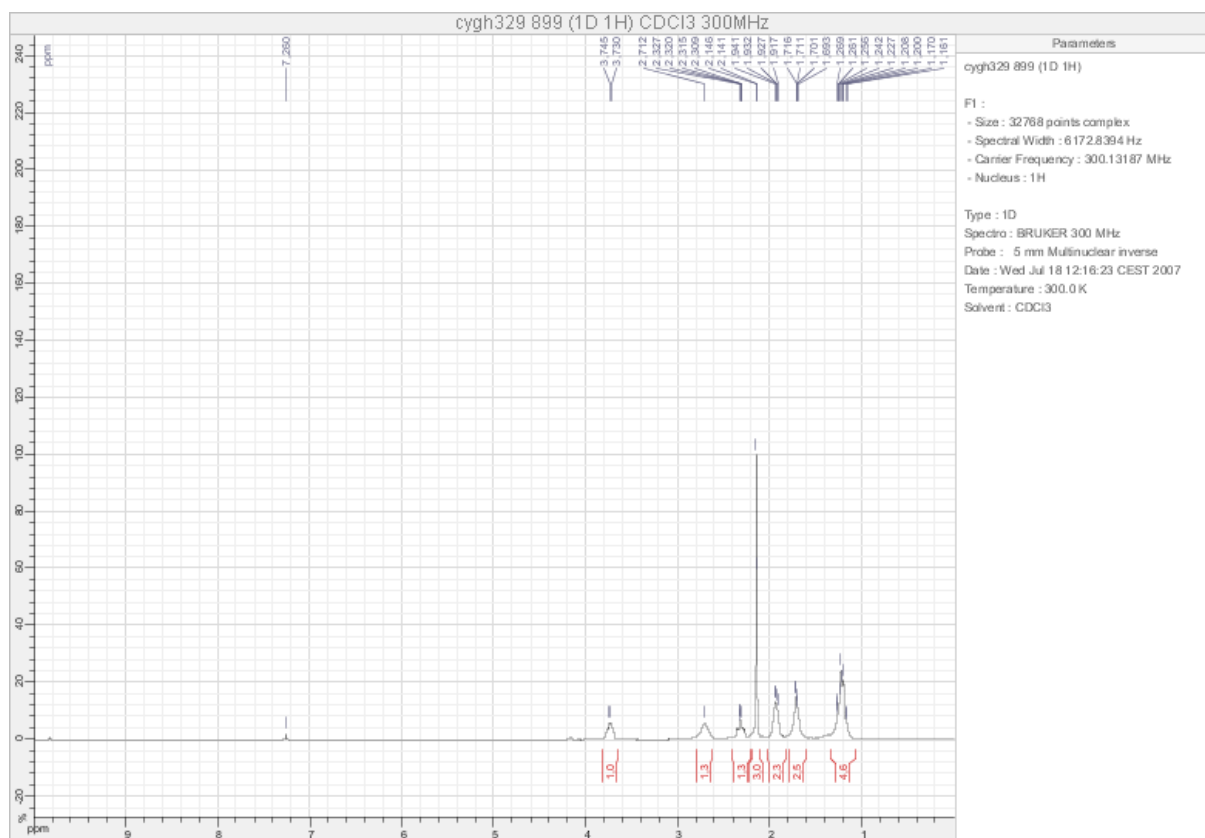
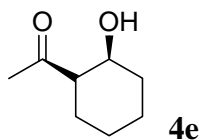




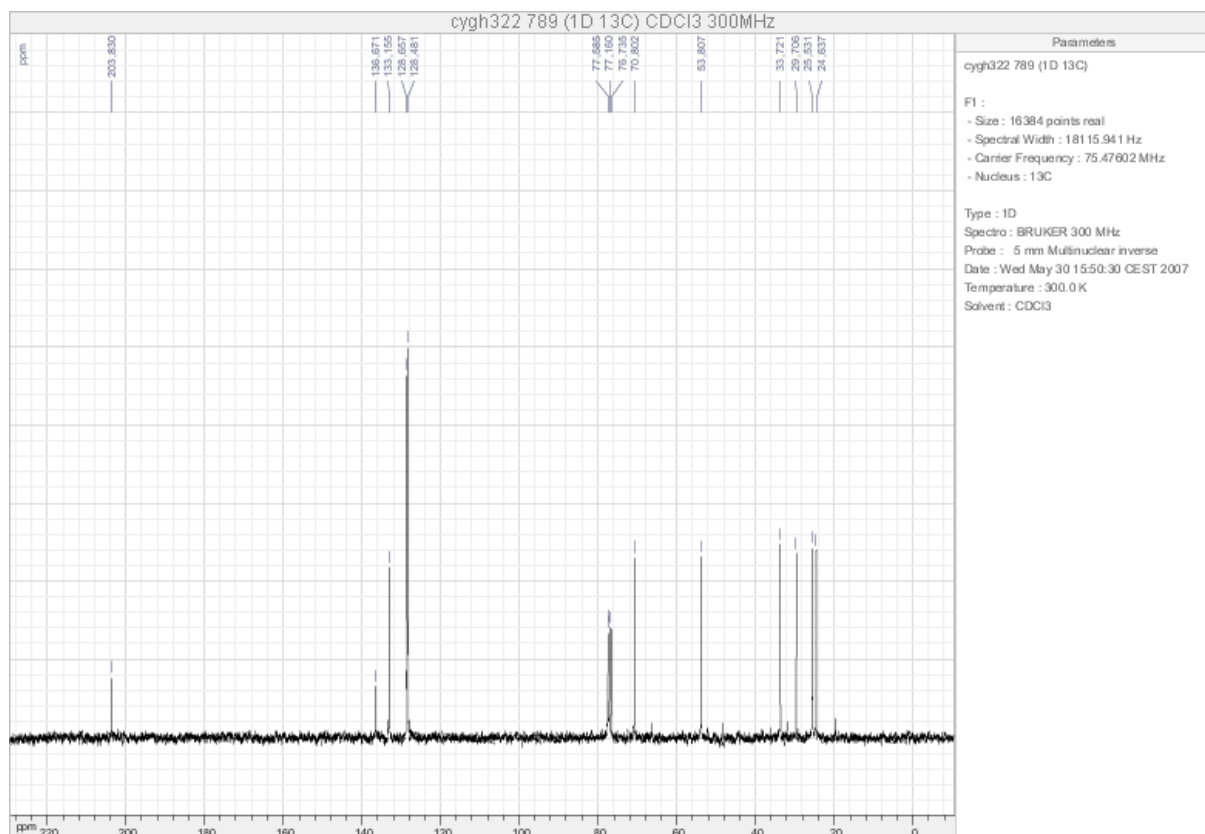
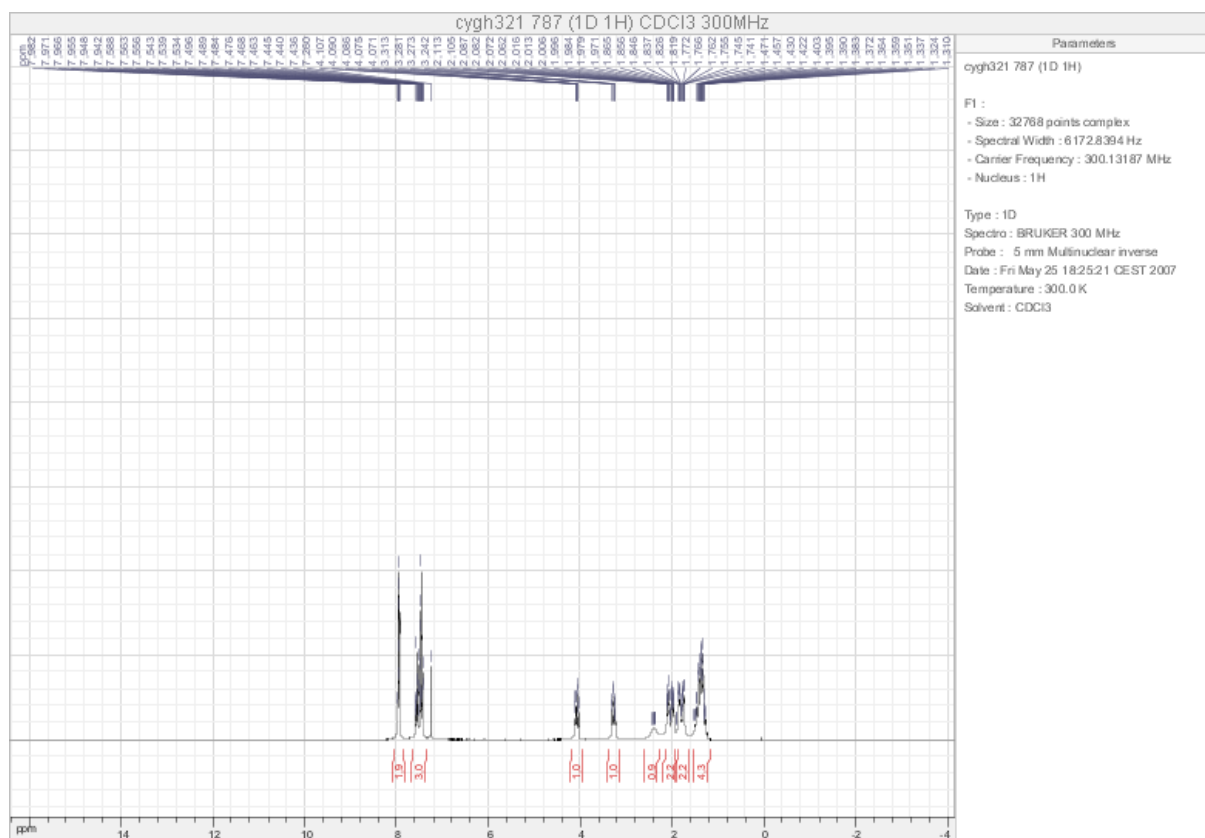
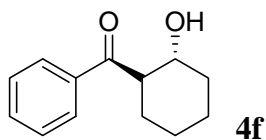


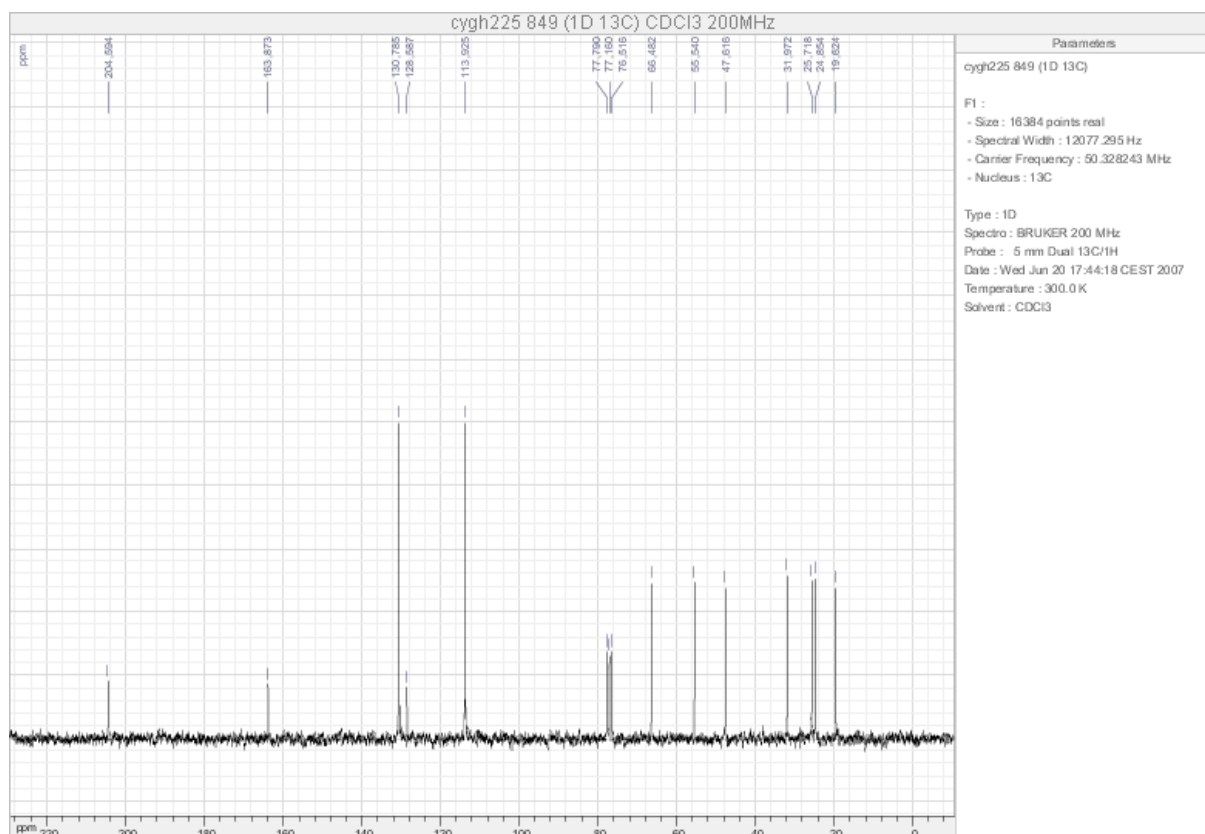
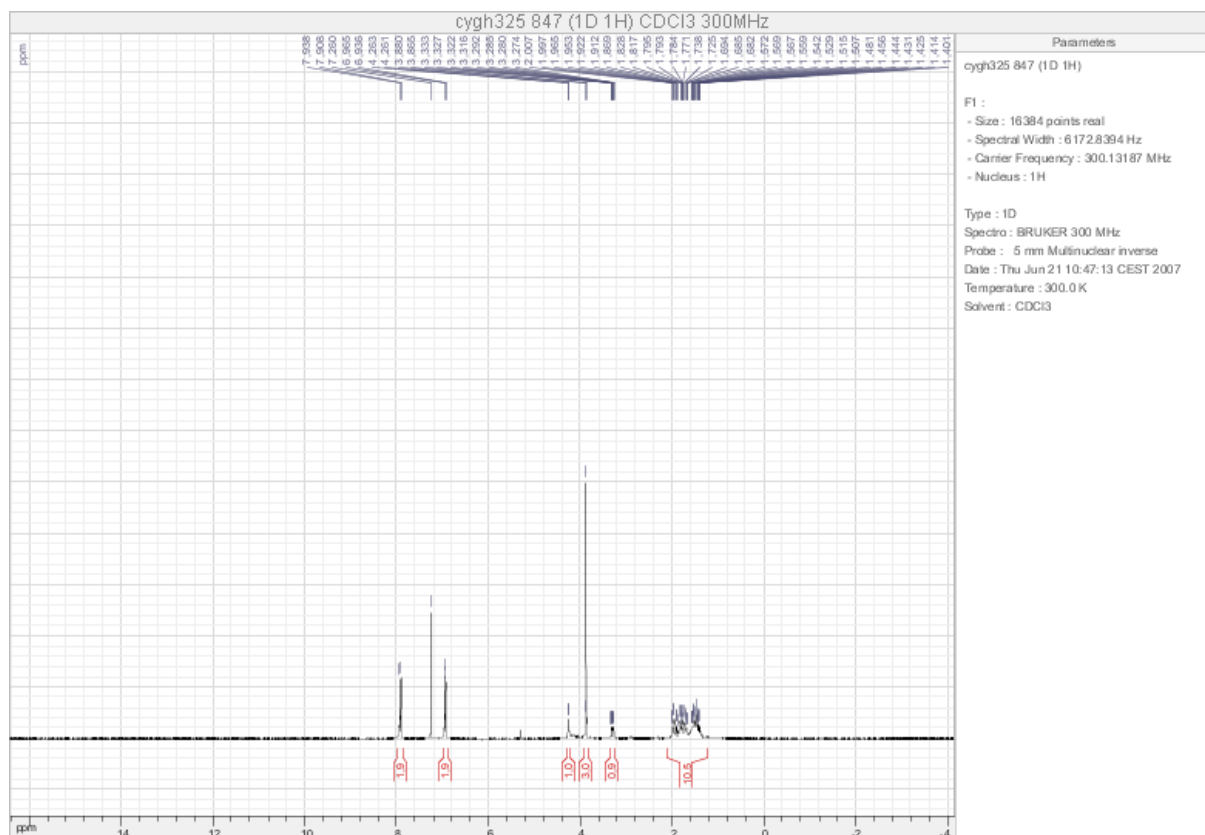
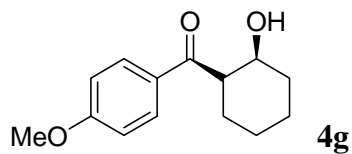


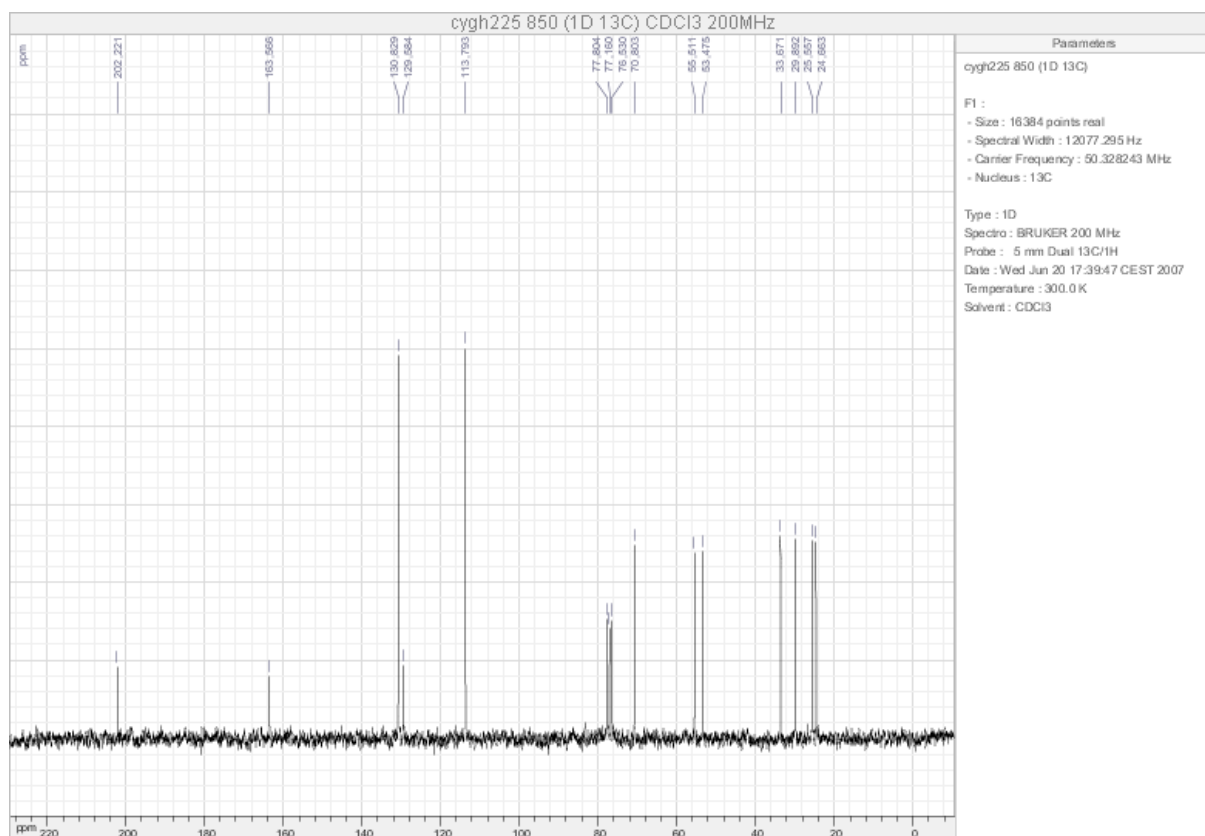
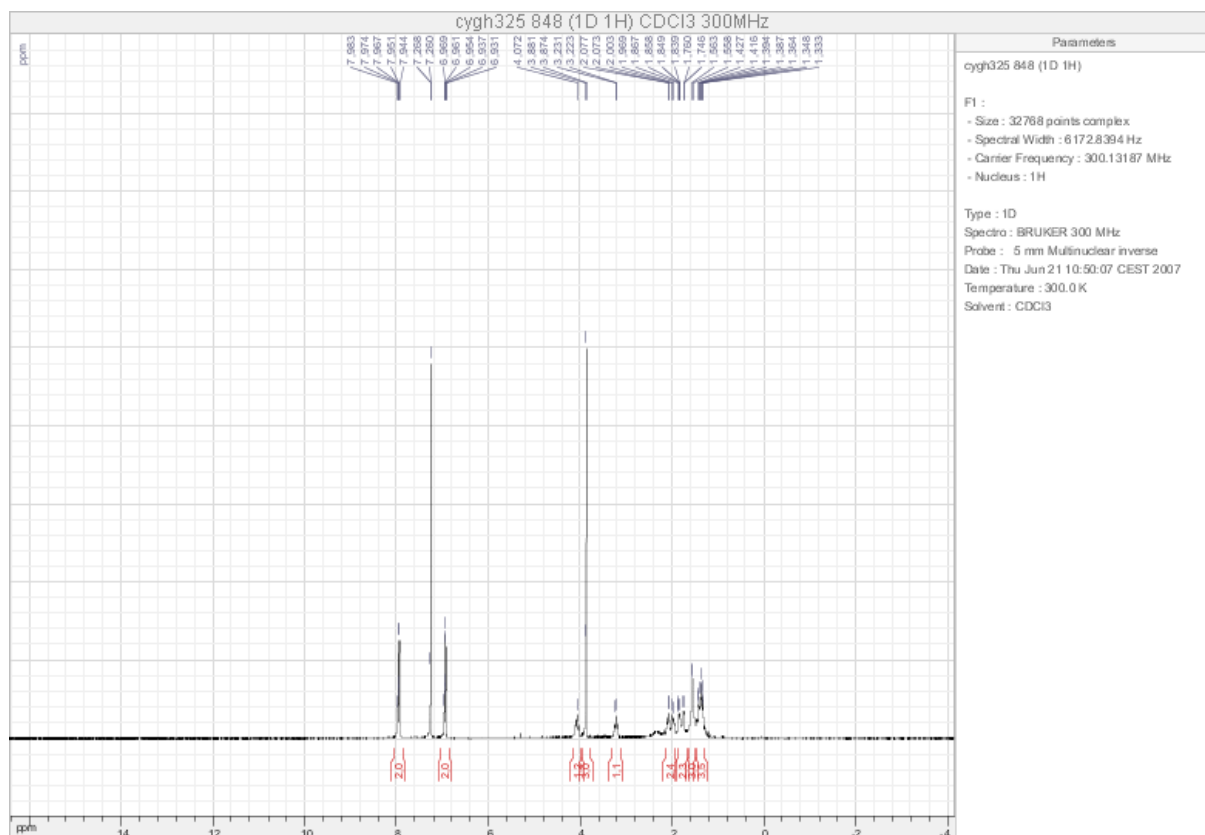
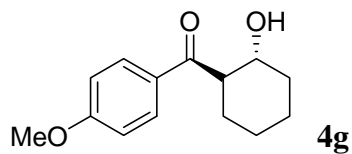


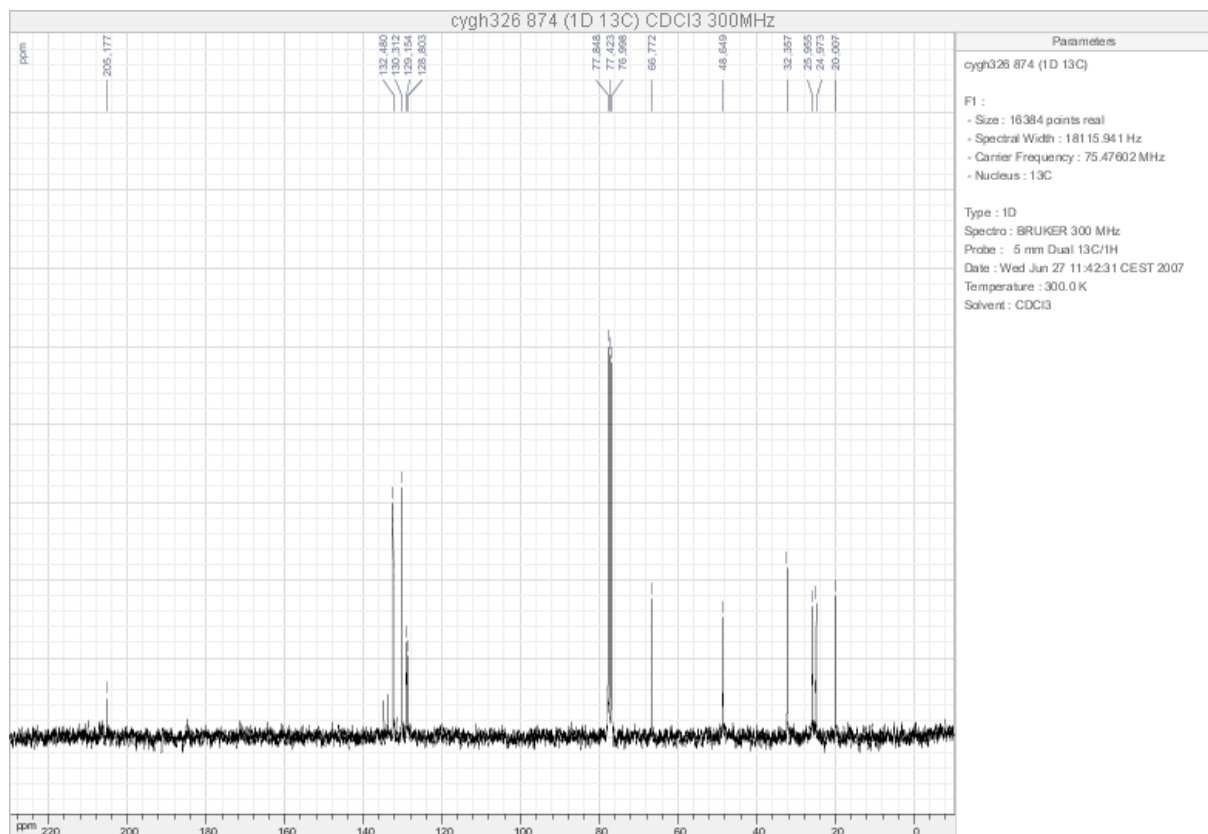
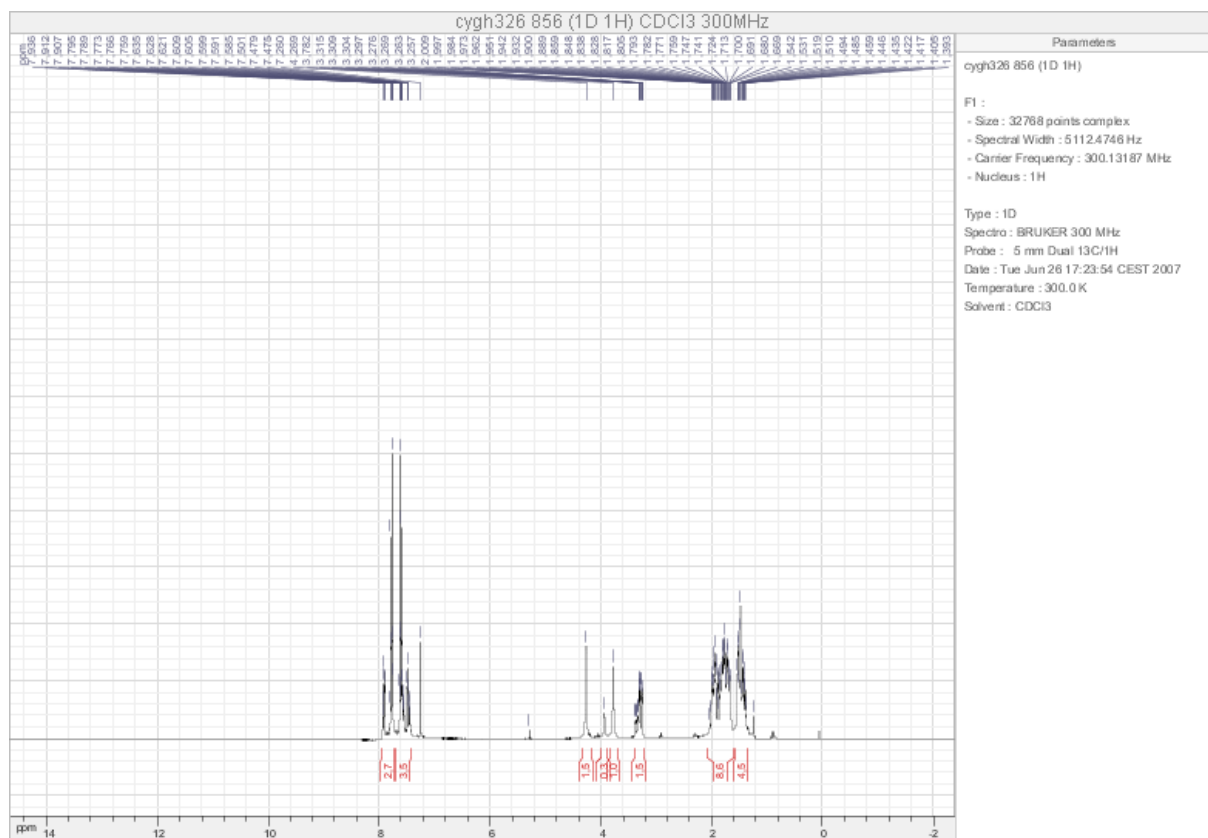
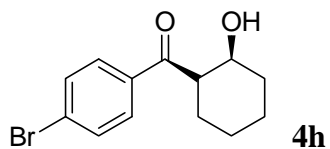


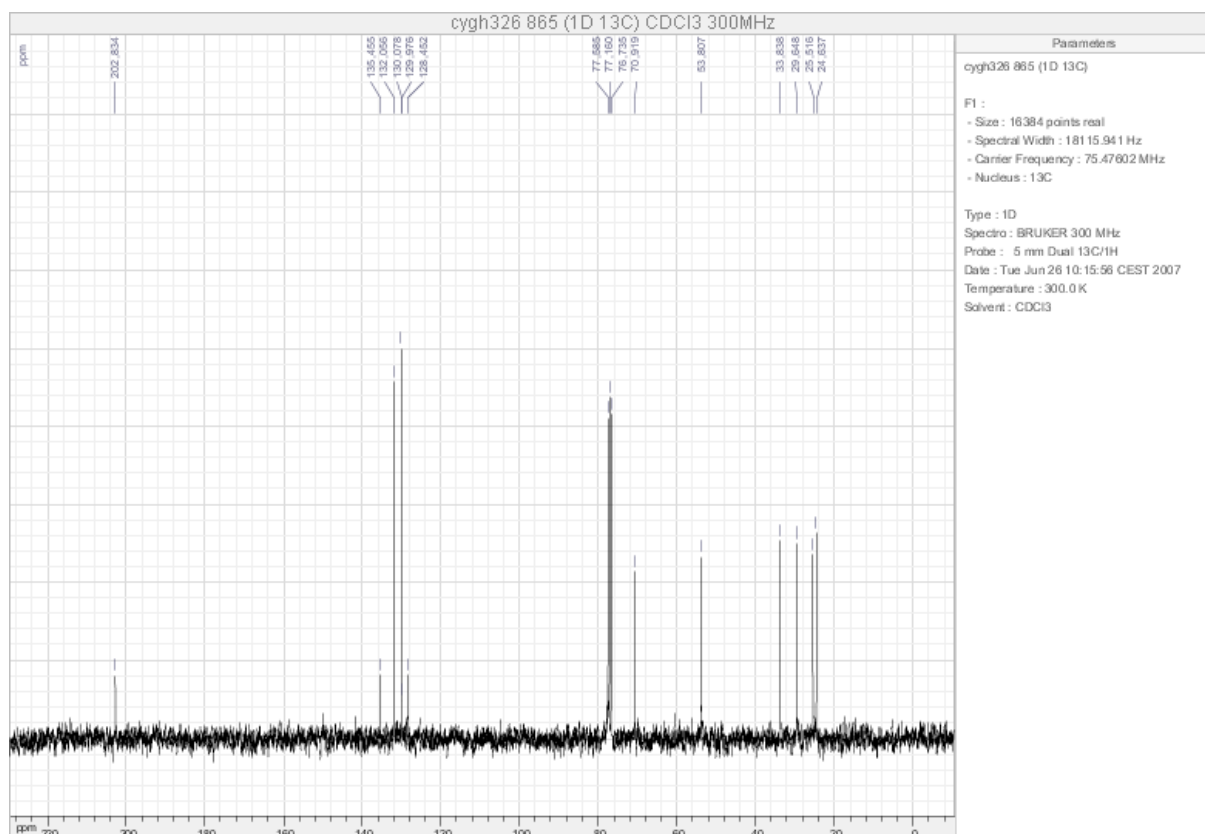
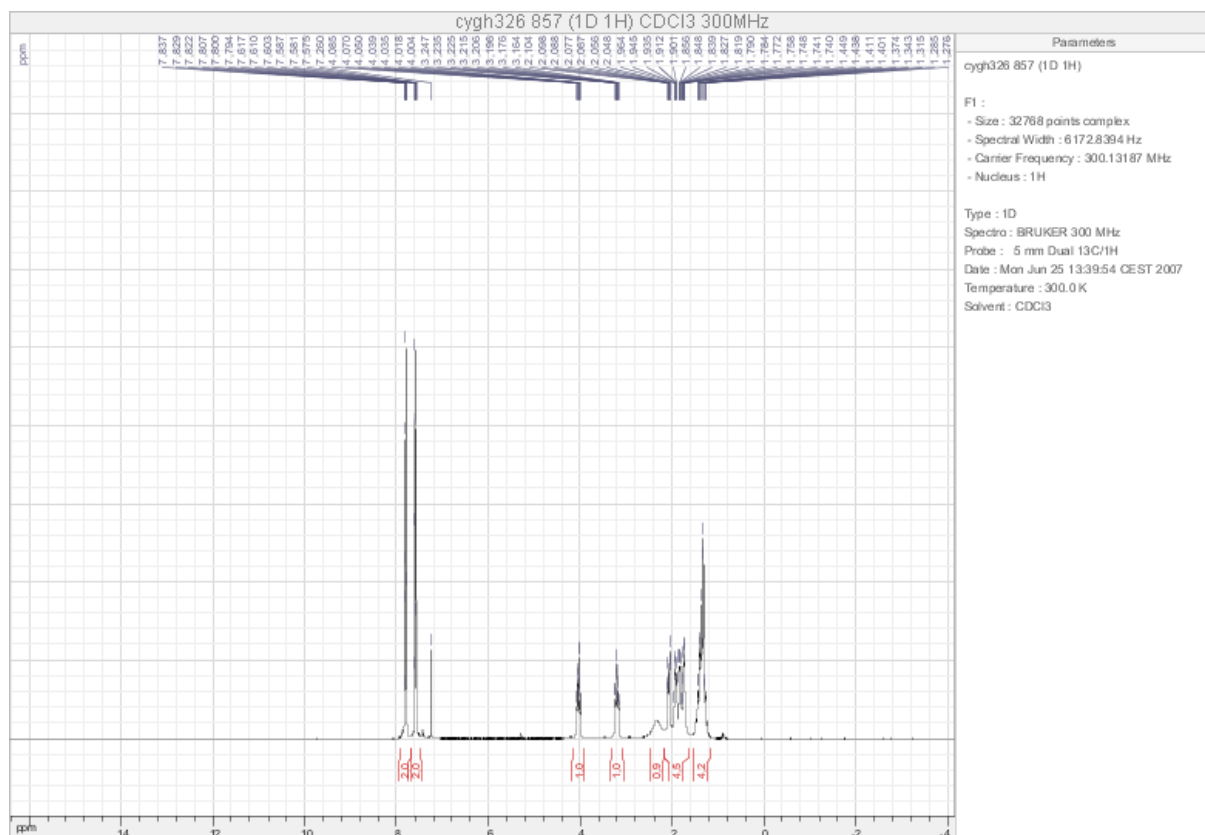
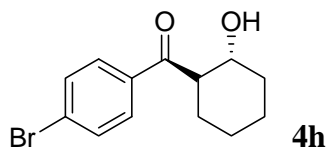


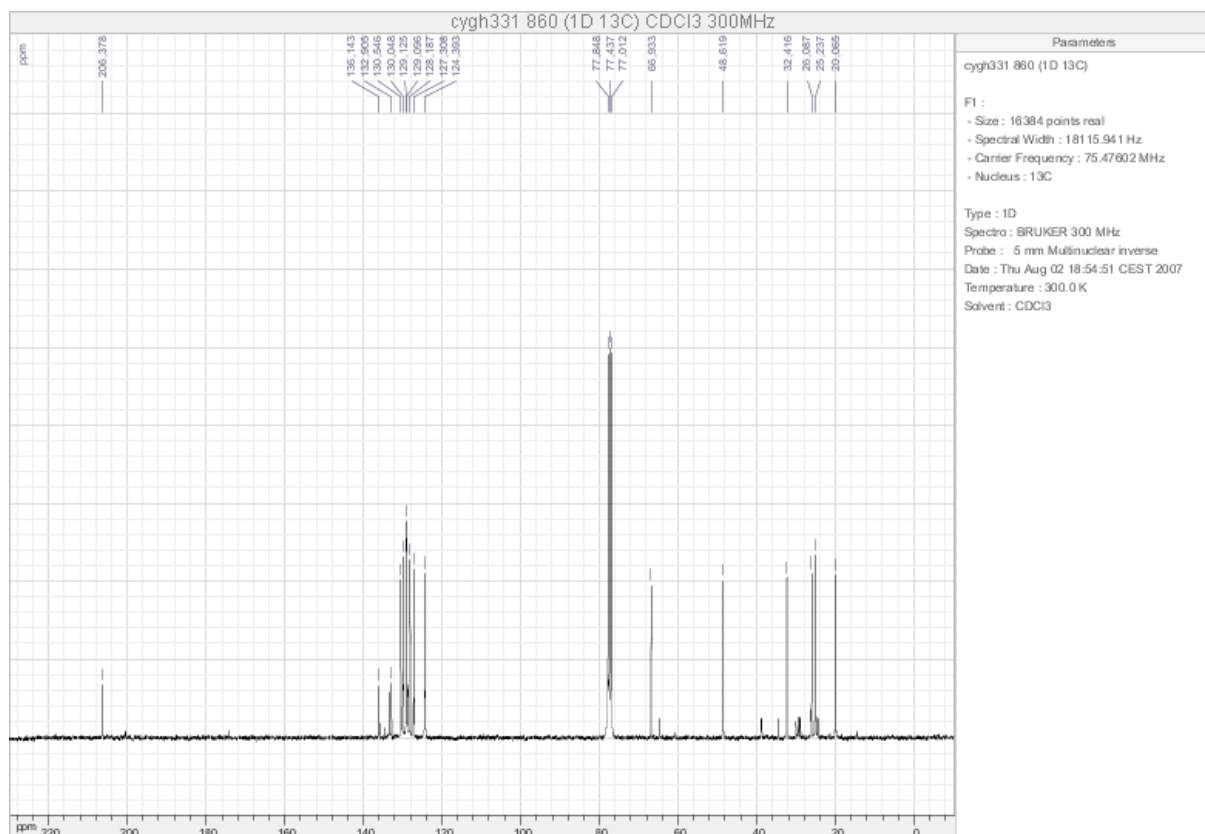
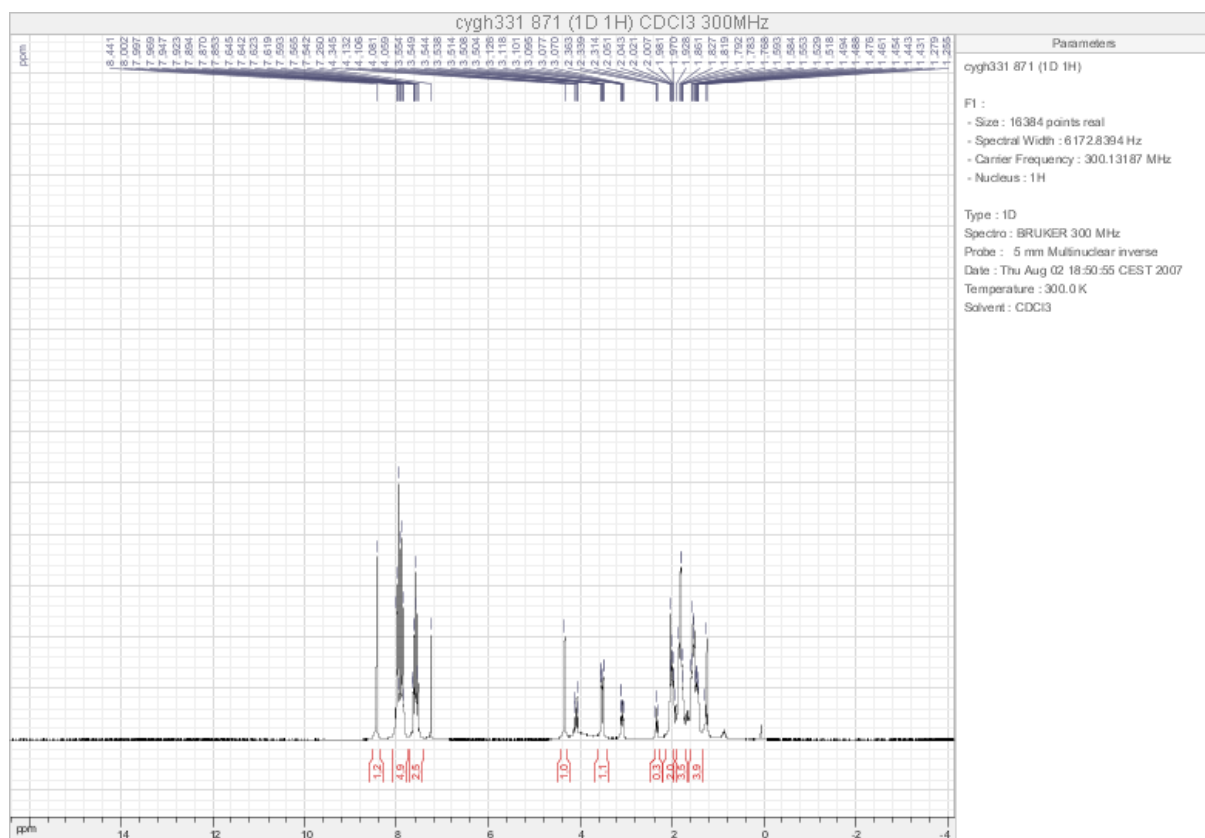
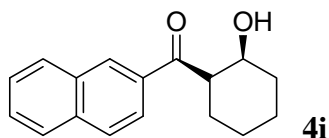


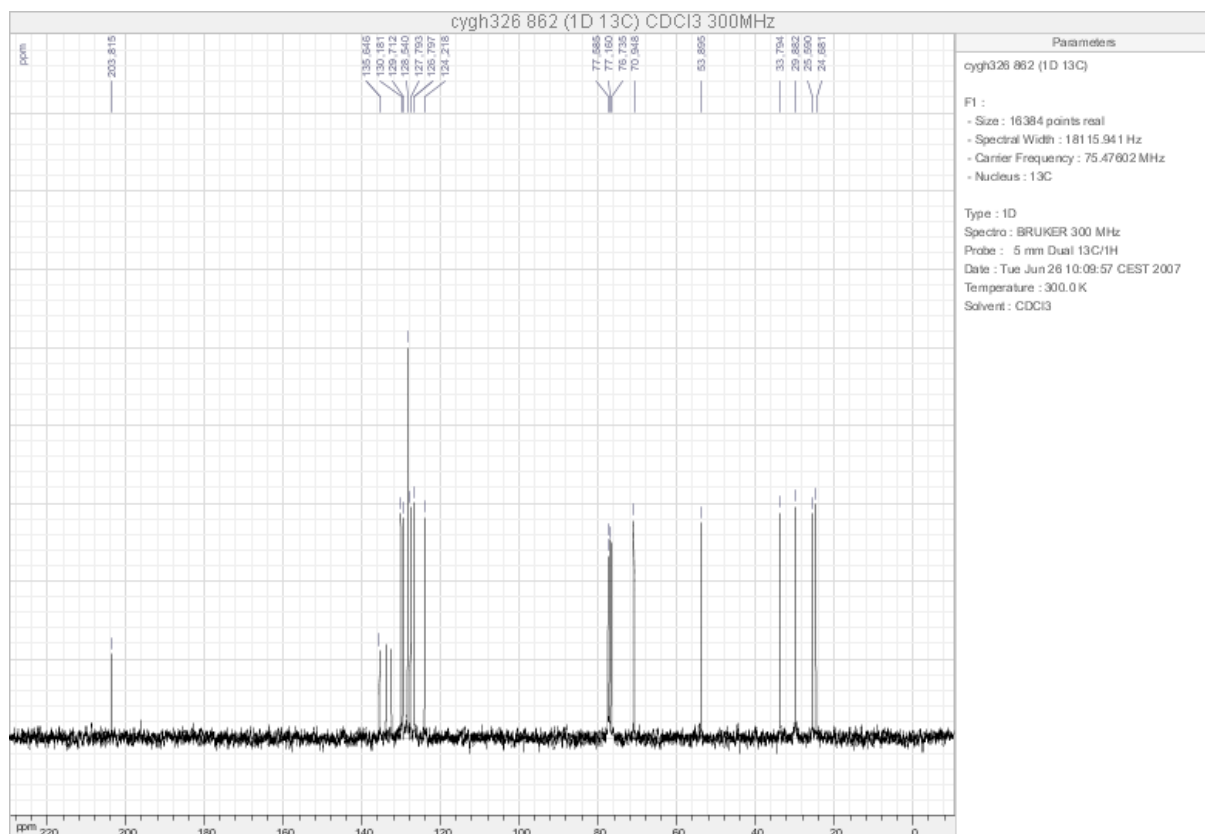
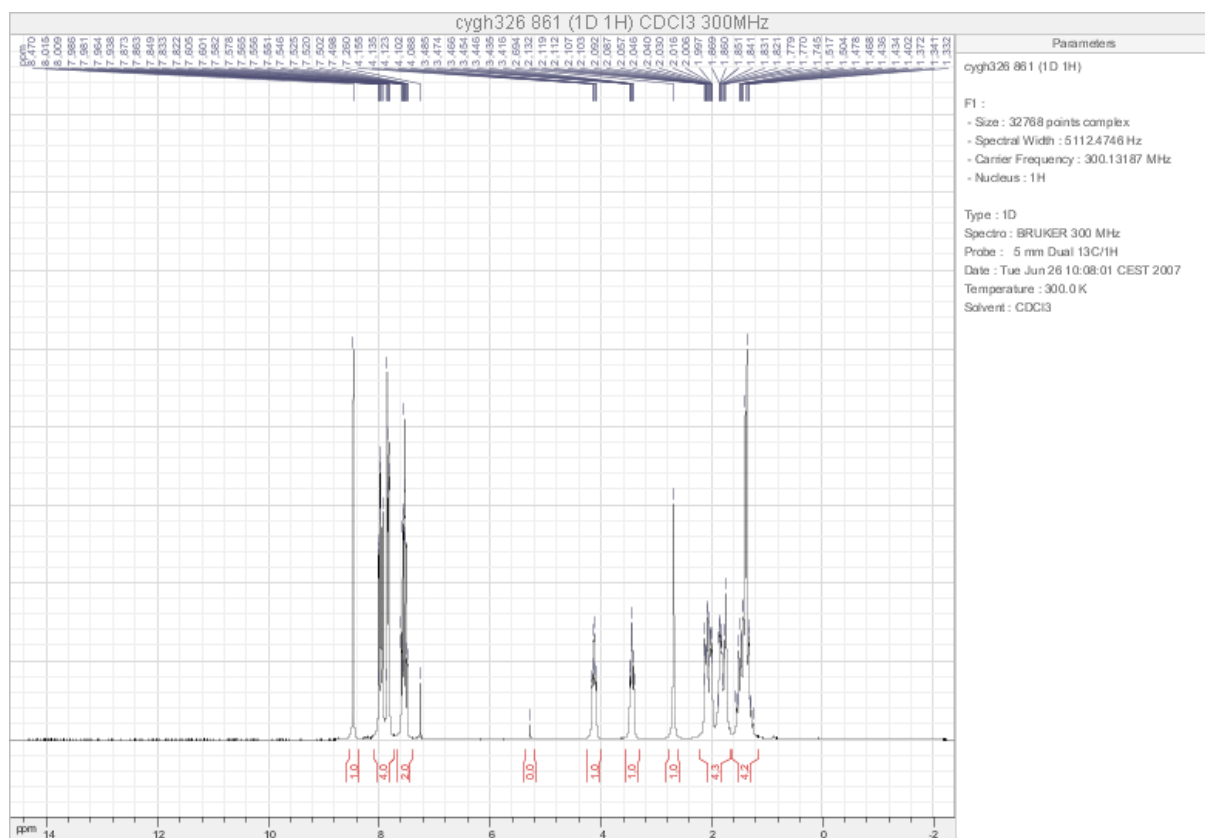
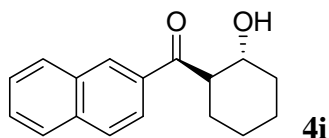


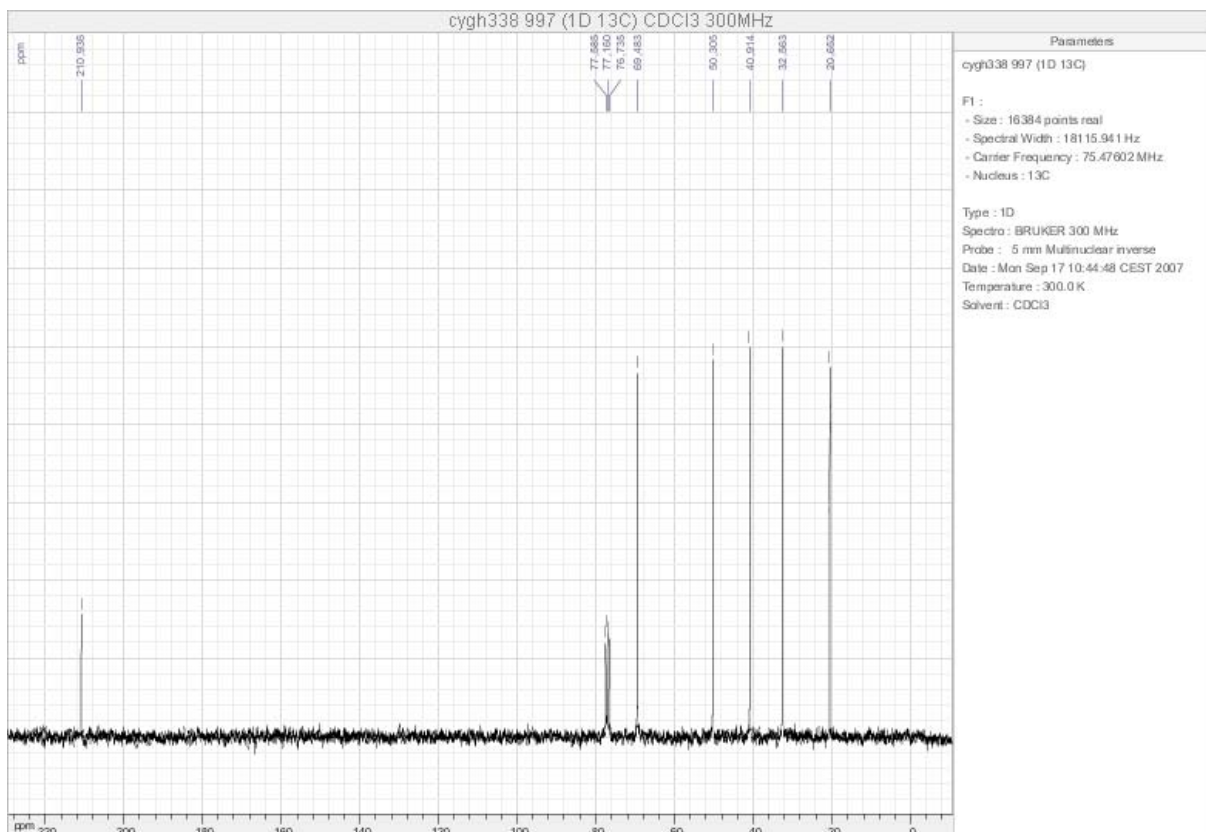












V. References

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- [2] B. Hong, F.-L. Chen, S.-H. Chen, J.-H. Liao, G.-H. Lee, *Org. Lett.* **2005**, *7*, 557-560.