Enantioselective Synthesis of Indolizidines Bearing Quaternary Substituted Stereocenters via Rhodium-Catalyzed [2+2+2] Cycloaddition of Alkenyl Isocyanates and Terminal Alkynes

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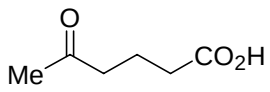
I.1 General Methods

Toluene, tetrahydrofuran, ether, and dichloromethane were degassed with argon and passed through one column of neutral alumina and one column of Q5 reactant. Triethylamine (peptide synthesis grade) was purchased from Fisher Scientific and used without further purification. Flash column chromatography was carried out on silica gel (60 Å, 230 - 400 mesh, obtained from Silicycle Inc.) and was performed with reagent grade solvents. Analytical thin-layer chromatography (TLC) was performed on Silicycle glass-backed silica gel plates (60 Å, 0.25 mm, purchased from Silicycle Inc.), visualized with a UV lamp (254 nm) and/or potassium permanganate.

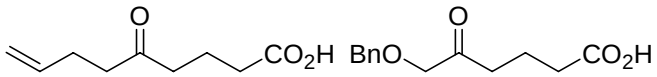
Infrared spectra (IR) were obtained on a Nicolet Avatar 320 FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR were obtained on Varian Unity 300 and Unity 400 spectrometers. Chemical shifts are expressed in ppm values. Proton chemical shifts in $CDCl_3$ were referenced to 7.26 ppm ($CHCl_3$) or 0.00 ppm (TMS). Carbon chemical shifts were referenced to 77.2 ppm ($CDCl_3$). Peak multiplicities are designated by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublets; dt, doublet of triplet; b, broad; *J*, coupling constant in Hz. Low resolution mass spectra (MS) and high resolution mass spectra (HRMS) were recorded on a Fisons VG Autospec spectrometer. HPLC spectra were obtained on an Angilent 1100 series system. Optical rotation was obtained with an Autopol-III automatic polarimeter. Melting points were obtained on a Fisher-Johns melting point apparatus and are uncorrected. References following the compound names indicate literature articles where the compound has been previously been reported.

Unless otherwise indicated, commercially available starting materials were purchased from Aldirch Chemicals. $[Rh(ethylene)_2Cl]_2$ was purchased from Strem Chemicals. Commercially available ligand **L3** was prepared from diethyl-tartrate according to literature procedures.

I.1 Starting material synthesis

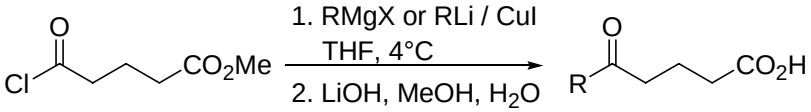


5-Oxo-hexanoic acid: commercially available.



5-Oxo-non-8-enoic acid and **5-Benzyloxymethyl-hex-5-enoic acid** were prepared as described: Meyers, A. I.; Andres, C. J.; Resek, J. E.; Woodall, C. C.; McLaughlin, M. A.; Lee, P. H.; Price, D. A. *Tetrahedron* **1999**, *55*, 8931-8952.

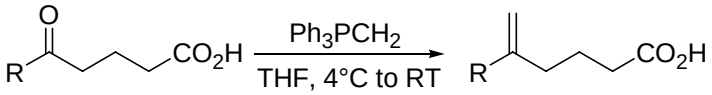
The remaining keto-acids were synthesized as follows:



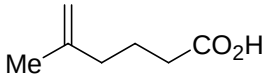
R = *n*Bu, *i*Bu, *i*Pent, Bn, $Ph(CH_2)_2$, Chx, $AllylCH_2$, $TBSO(CH_2)_4$, Ph

In a flame dried flask under Ar atmosphere, a solution of Grignard (1.0M in THF or Et_2O, 14.5 mL, 14.5 mmol) or *n*-BuLi (for R = *n*Bu, 1.6M, 9.0 mL) was slowly added to a stirring suspension of copper(I) iodide (1.38 g, 7.24 mmol) in THF (30 mL) at 4 ^oC. After 30 minutes, methyl 5-chloro-5-oxo-valerate (1.00 mL, 7.24 mmol) was added. The reaction was stirred at 4 ^oC for 3 hours and then quenched with 1M HCl, extracted (Et_2Ox3), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The keto-ester was purified by flash chromatography (Hexanes:EtOAc;93:7). The keto-ester (0.2 M) was then added to a stirring suspension of LiOH (5 eq) in MeOH/H_2O (3/1) and stirred at room temperature for 16 hours. The reaction was then quenched with 1M HCl, extracted (Et_2Ox3), dried over $MgSO_4$, filtered and concentrated *in vacuo*. If suitably pure, the crude keto-acid was carried forward to the next step. If not suitably pure, the keto-acid was purified by silica gel flash chromatography (Hexanes:EtOAc4:1).

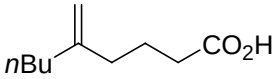
I.2 Procedures for alkenyl acid synthesis



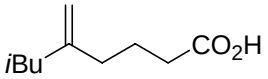
In a flame dried flask under Ar atmosphere, *n*-BuLi (1.6M in hexanes, 5.63 mL, 9.0 mmol) was added to a stirring solution of methyltriphenylphosphonium bromide (3.21 g, 9.0 mmol) in THF (40 mL) at 4 °C. After stirring for 1 hour, ketoacid (3.0 mmol) was added dropwise to the bright orange solution. The reaction was then warmed to room temperature and stirred overnight. The reaction was then quenched with 1M HCl, extracted (Et_2Ox3), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was then purified by silica gel flash chromatography.



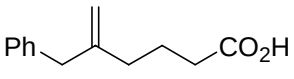
5-Methyl-hex-5-enoic acid: Flash Chromatography (Hexanes:EtOAc;4:1) yielded a clear liquid (67%). R_f = 0.32 (Hexanes:EtOAc;3:1); IR (Thin Film) ν 3076, 2939, 1709, 1414, 1292, 1239, 890 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.72 (1H, s), 4.67 (1H, s), 2.33 (2H, t, *J* = 7.5 Hz), 2.04 (2H, t, *J* = 7.5 Hz), 1.76 (2H, tt, *J* = 7.5, 7.5 Hz), 1.69 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.6, 144.7, 111.0, 37.1, 33.6, 22.6, 22.4.



5-Methylene-nonanoic acid: Flash Chromatography (Hexanes:EtOAc;4:1) yielded a clear liquid (47%). R_f = 0.25 (Hexanes:EtOAc;3:1); ^1H NMR (400 MHz, $CDCl_3$) δ 4.72 (1H, s), 4.69 (1H, s), 2.33 (2H, t, *J* = 7.0 Hz), 2.04 (2H, t, *J* = 7.5 Hz), 1.98 (2H, t, *J* = 7.5 Hz), 1.75 (2H, tt, *J* = 7.5, 7.5 Hz), 1.41-1.22 (4H, m), 0.88 (3H, t, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.5, 148.9, 109.7, 35.7, 35.4, 33.7, 30.1, 22.8, 22.7, 14.2.

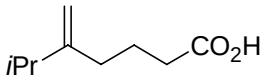


7-Methyl-5-methylene-octanoic acid: Flash Chromatography (Hexanes:EtOAc;4:1) yielded a clear liquid (56%). R_f = 0.20 (Hexanes:EtOAc;3:1); IR (Thin Film) ν 2958, 1709, 1410, 1368 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.73 (1H, s), 4.70 (1H, s), 2.34 (2H, t, *J* = 7.0 Hz), 2.01 (2H, t, *J* = 7.5 Hz), 1.85 (2H, d, *J* = 7.0 Hz), 1.79-1.67 (3H, m), 0.84 (6H, d, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.1, 147.6, 111.2, 45.9, 35.0, 33.7, 26.2, 22.7, 22.7.

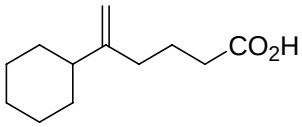


5-Benzyl-hex-5-enoic acid: Flash Chromatography (Hexanes:EtOAc;4:1) yielded a clear liquid (60%). R_f = 0.35 (Hexanes:EtOAc;4:1); IR (Thin Film) ν 3027, 2934, 1708, 1495,

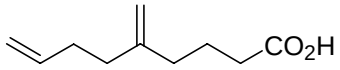
1453, 1243, 896 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31-7.26 (2H, m), 7.24-7.17 (3H, m), 4.86 (1H, s), 4.81 (1H, s), 3.34 (2H, s), 2.34 (2H, t, *J* = 7.0 Hz), 2.03 (2H, t, *J* = 7.5 Hz), 1.79 (2H, tt, *J* = 7.0, 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.5, 147.9, 139.7, 129.2, 128.5, 126.4, 112.3, 43.0, 34.7, 33.7, 22.6.



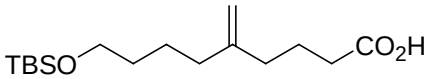
6-Methyl-5-methylene-heptanoic acid: Flash Chromatography (Hexanes:EtOAc;4:1) yielded a clear liquid (35%). R_f = 0.20 (Hexanes:EtOAc;3:1); IR (Thin Film) ν 2963, 1709, 1462, 1288 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.76 (1H, s), 4.67 (1H, s), 2.35 (2H, t, *J* = 7.5 Hz), 2.20 (1H, sext, *J* = 7.5 Hz), 2.06 (2H, t, *J* = 7.5 Hz), 1.77 (2H, tt, *J* = 7.0, 7.0 Hz), 1.00 (6H, d, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.6, 154.8, 107.3, 33.8, 33.7, 23.1, 21.9.



5-Cyclohexyl-hex-5-enoic acid: Flash Chromatography (Hexanes:EtOAc;4:1) yielded a clear liquid (38%). R_f = 0.22 (Hexanes:EtOAc;3:1); IR (Thin Film) ν 2926, 2852, 1709, 1640, 1449, 1262 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.80 (1H, s), 4.75 (1H, s), 2.42 (2H, t, *J* = 7.5 Hz), 2.12 (2H, t, *J* = 7.5 Hz), 1.88-1.68 (7H, m), 1.34-1.14 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.6, 154.1, 107.8, 44.1, 34.3, 33.8, 32.6, 26.9, 26.5, 23.2.

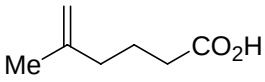


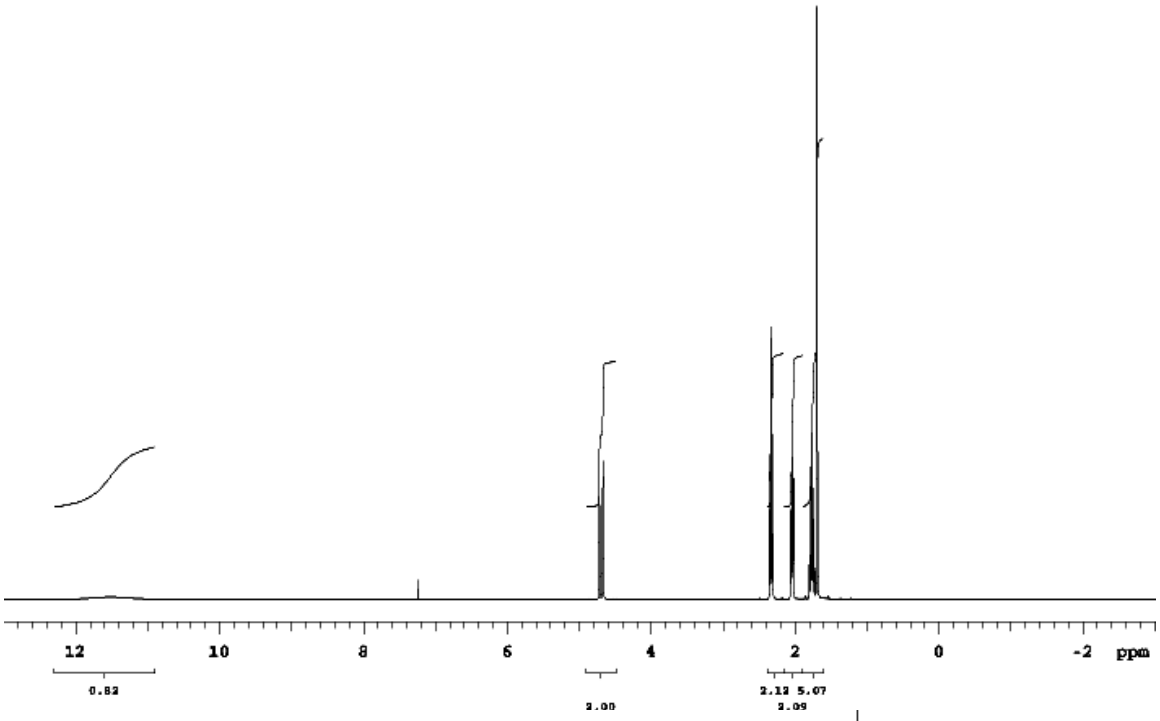
5-Methylene-non-8-enoic acid: Flash Chromatography (Hexanes:EtOAc;4:1) yielded a clear liquid (58%). R_f = 0.26 (Hexanes:EtOAc;3:1); IR (Thin Film) ν 2934, 1709, 1643, 1414, 1289 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.79 (1H, ddd, *J* = 17.0, 10.0 Hz), 5.00 (1H, dt, *J* = 17.0, 1.0 Hz), 4.93 (1H, d, *J* = 10.0 Hz), 4.75 (1H, s), 4.73 (1H, s), 2.34 (2H, t, *J* = 8.0 Hz), 2.16 (2H, dt, *J* = 7.5, 7.5 Hz), 2.09 (2H, t, *J* = 8.0 Hz), 2.05 (2H, t, *J* = 8.0 Hz), 1.76 (2H, tt, *J* = 7.5, 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.4, 147.9, 138.5, 114.8, 110.2, 35.4, 35.3, 33.7, 32.1, 22.7; HRMS (EI) *m/e* calcd (M^+) 169.1233, found 169.1229.

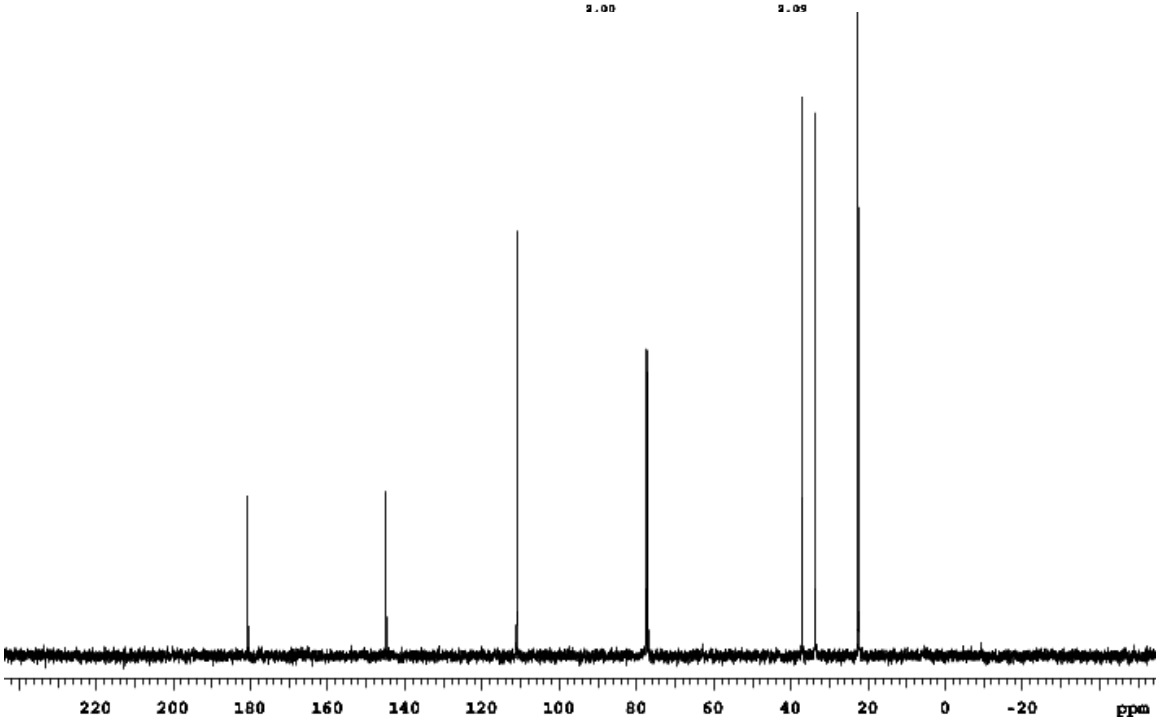


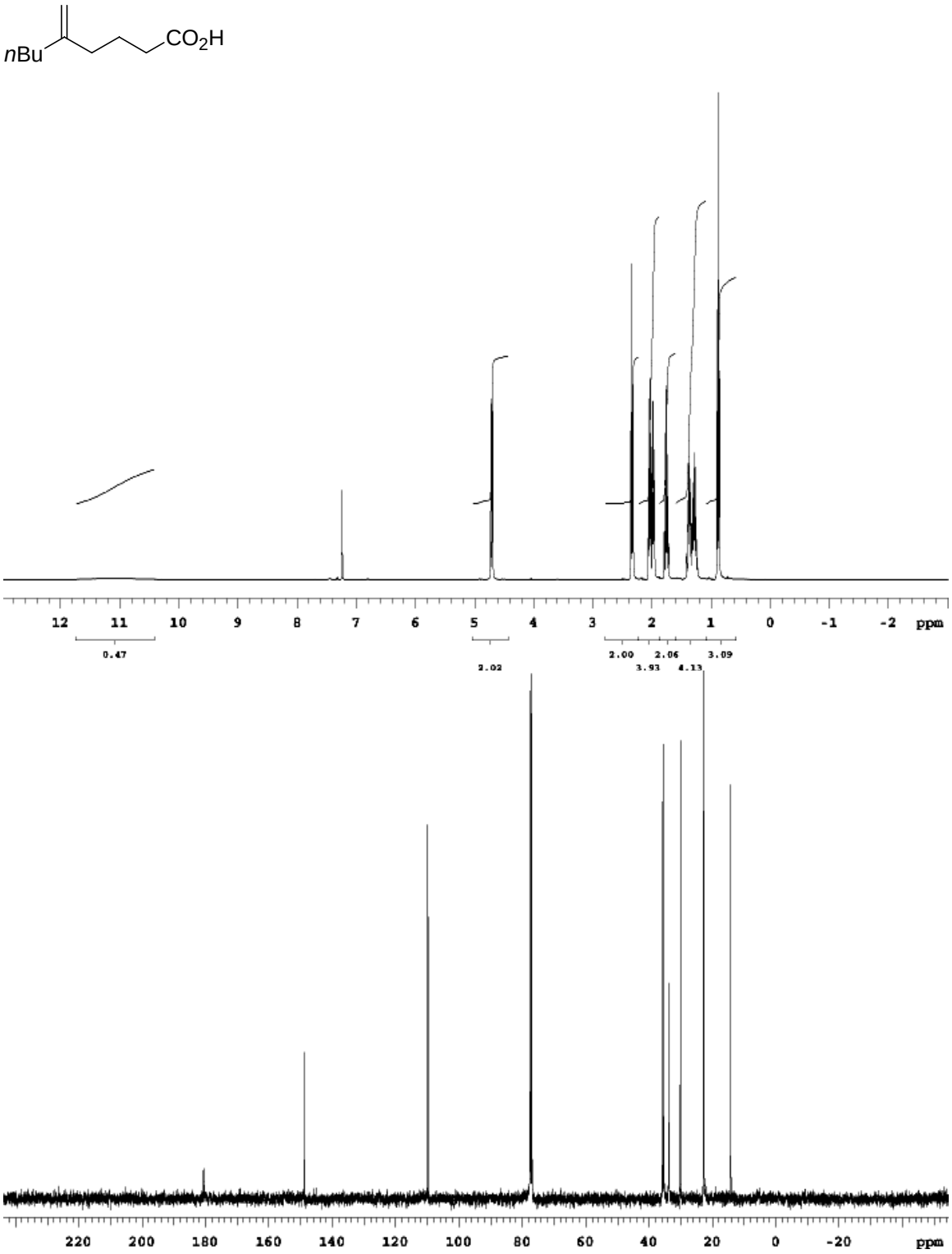
9-(tert-Butyl-dimethyl-silanyloxy)-5-methylene-nonanoic acid: Flash Chromatography (Hexanes:EtOAc;4:1) yielded a clear liquid (60%). R_f = 3.20 (Hexanes:EtOAc;3:1); IR (Thin Film) ν 2930, 1710, 1412, 1255, 1104, 836 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.77 (1H, s), 4.75 (1H, s), 3.63 (2H, t, *J* = 8.0 Hz), 2.37 (2H, t, *J* = 7.5 Hz), 2.08 (2H, t, *J* = 7.5 Hz), 2.03 (2H, t, *J* = 7.5 Hz), 1.80 (2H, tt, *J* = 7.5, 7.5 Hz), 1.60-1.40 (4H, m), 0.91 (9H, s), 0.06 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.2, 148.6, 110.0, 63.3, 35.7, 35.3, 33.7, 32.7, 26.2, 24.2, 22.9, 18.6, -5.0; HRMS (EI) *m/e* calcd (M^+) 301.2199, found 301.2188.

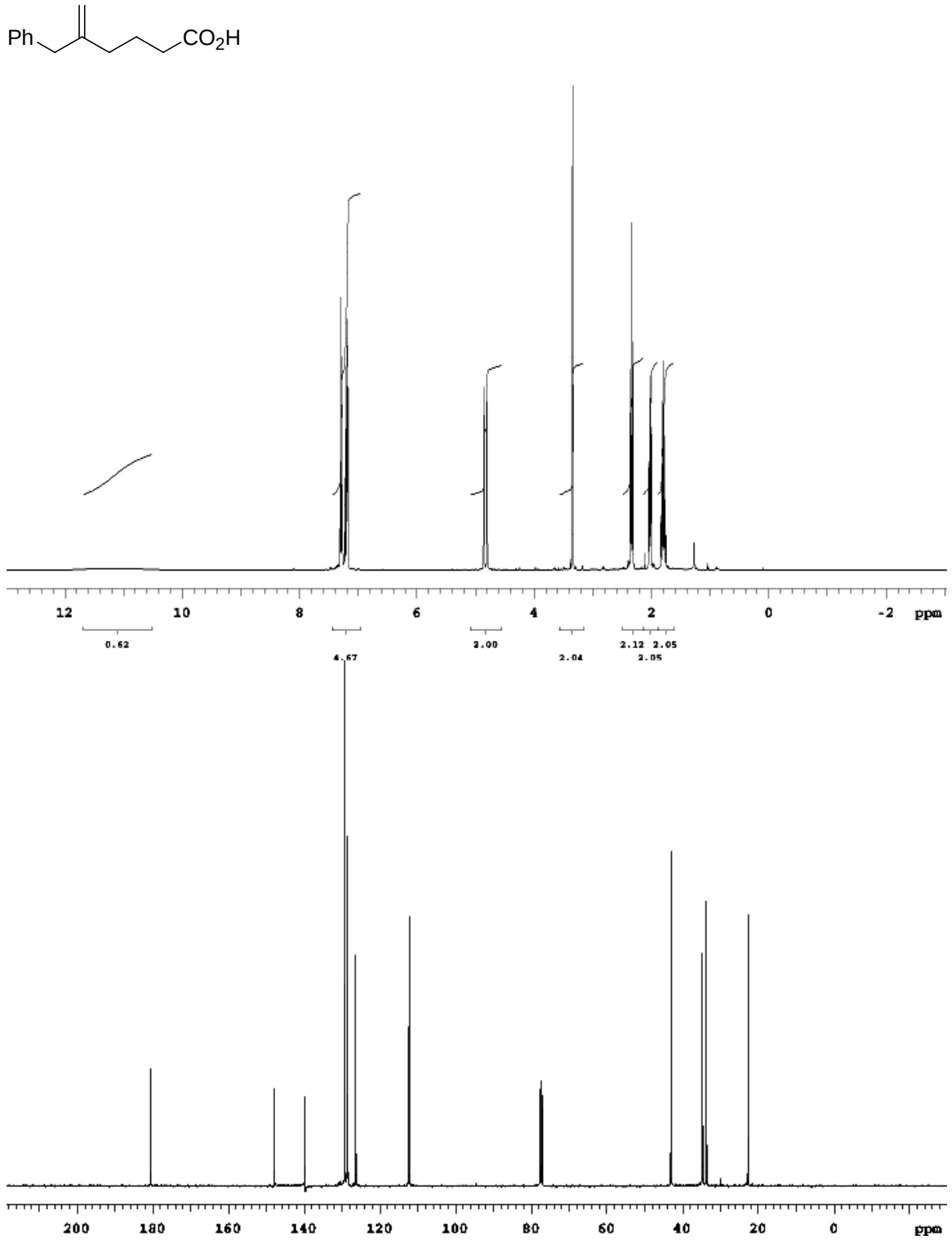
I.3 ^{1}H and ^{13}C NMR Spectra for new carboxylic acids








nBu
CO2H
12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 ppm
0.47
2.02
2.00 2.06 3.09
3.93 4.13
220 200 180 160 140 120 100 80 60 40 20 0 -20 ppm


Ph
CO2H
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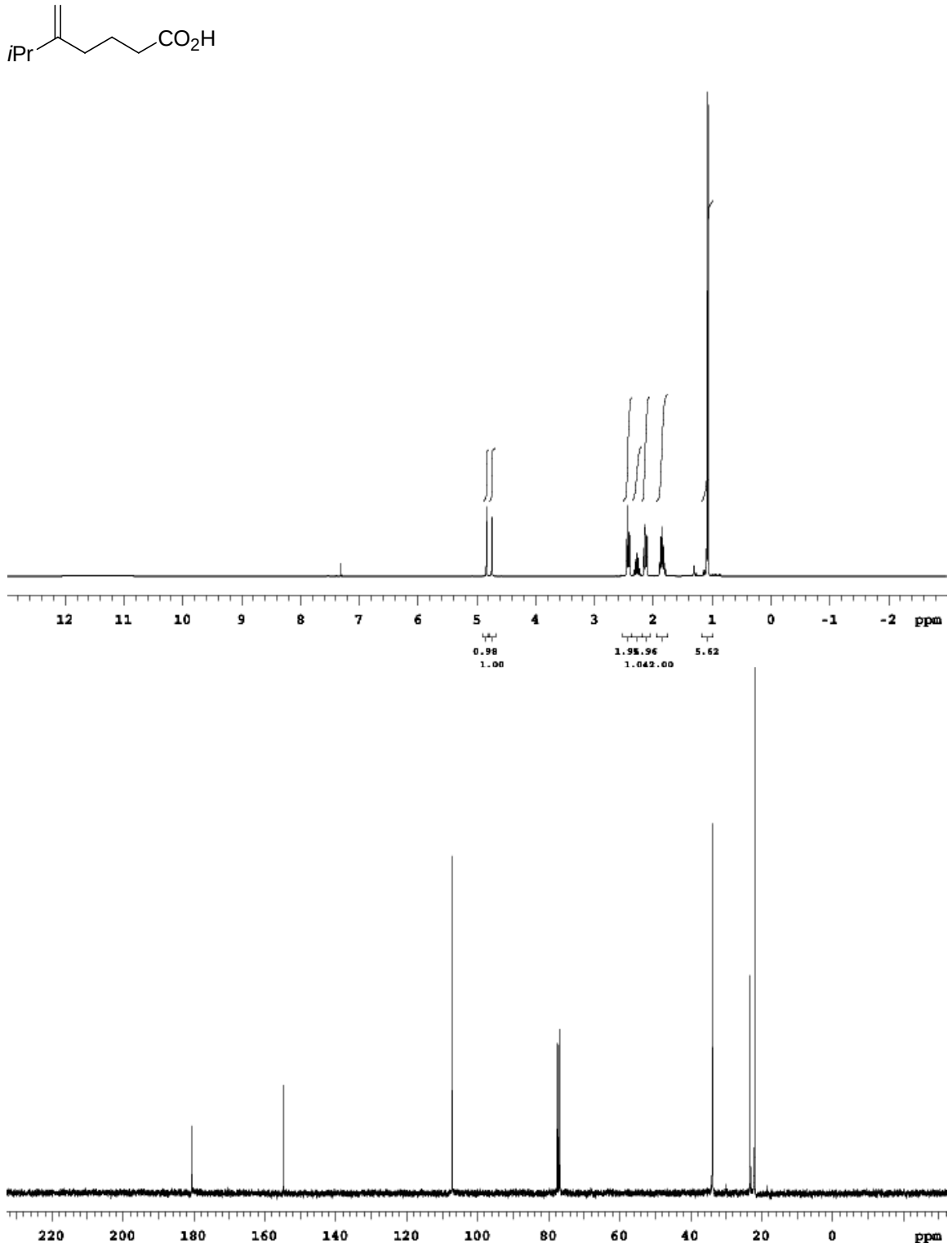
10
8
6
4
2
0
-2
ppm
0.62
4.67
2.00
2.04
2.12
2.05
2.05
200
180
160
140
120
100
80
60
40
20
0
ppm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CO2H
12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 ppm
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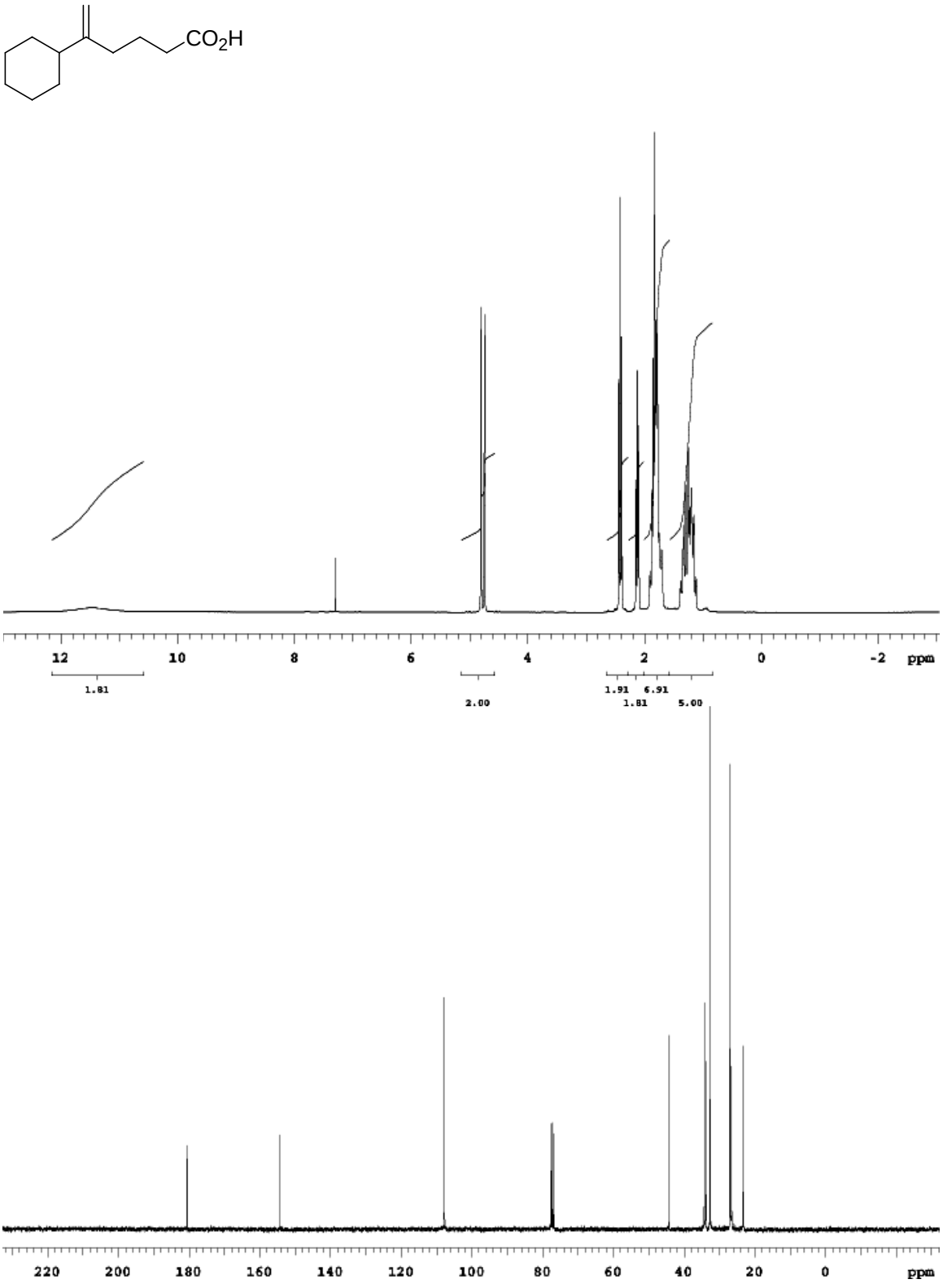
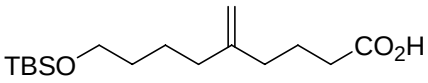
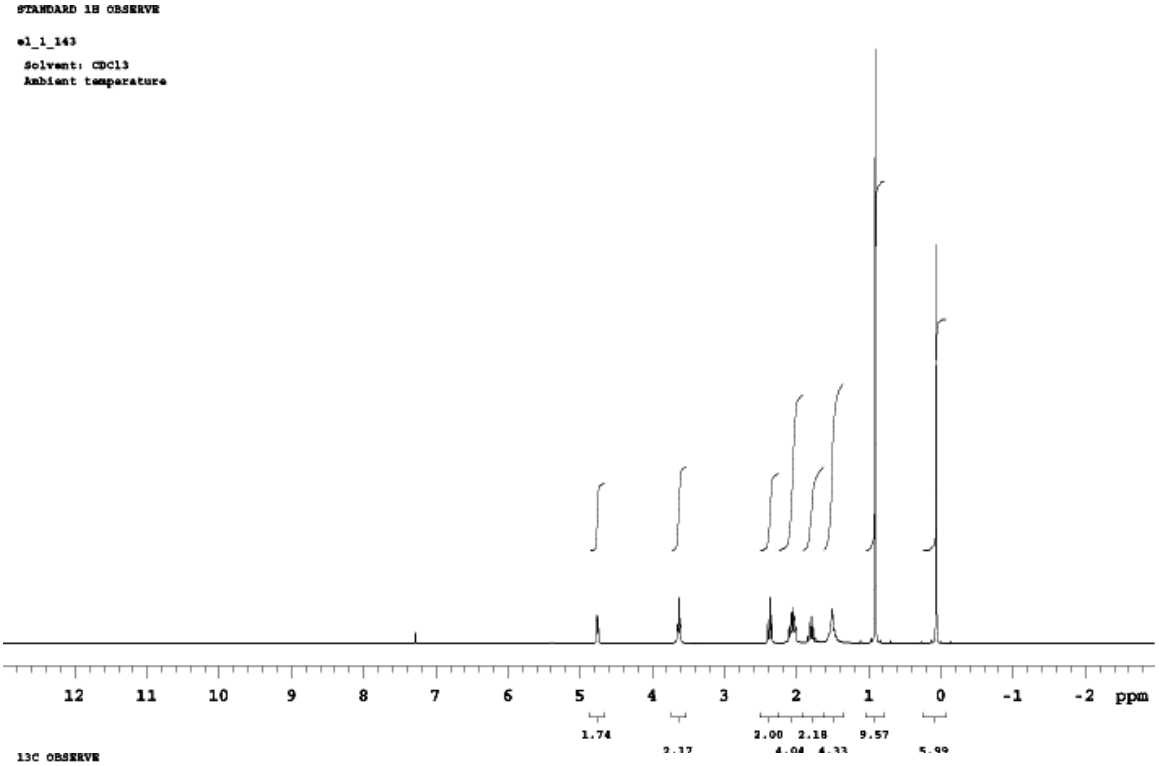
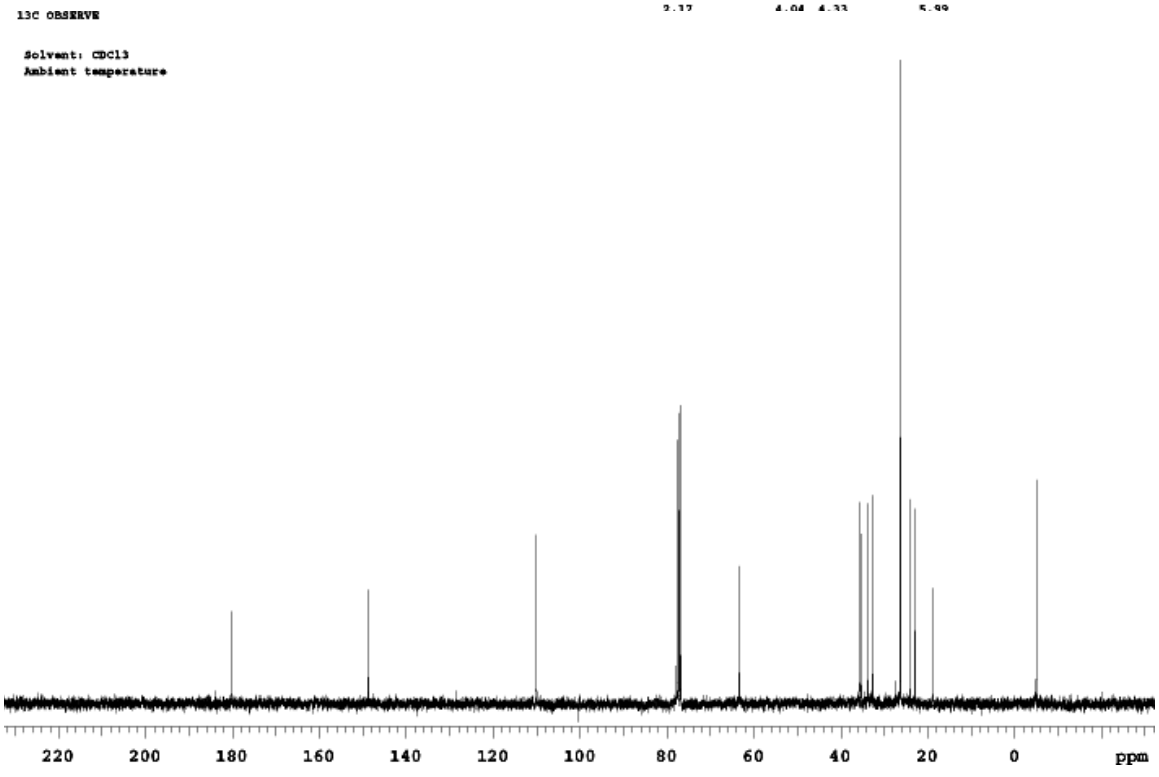
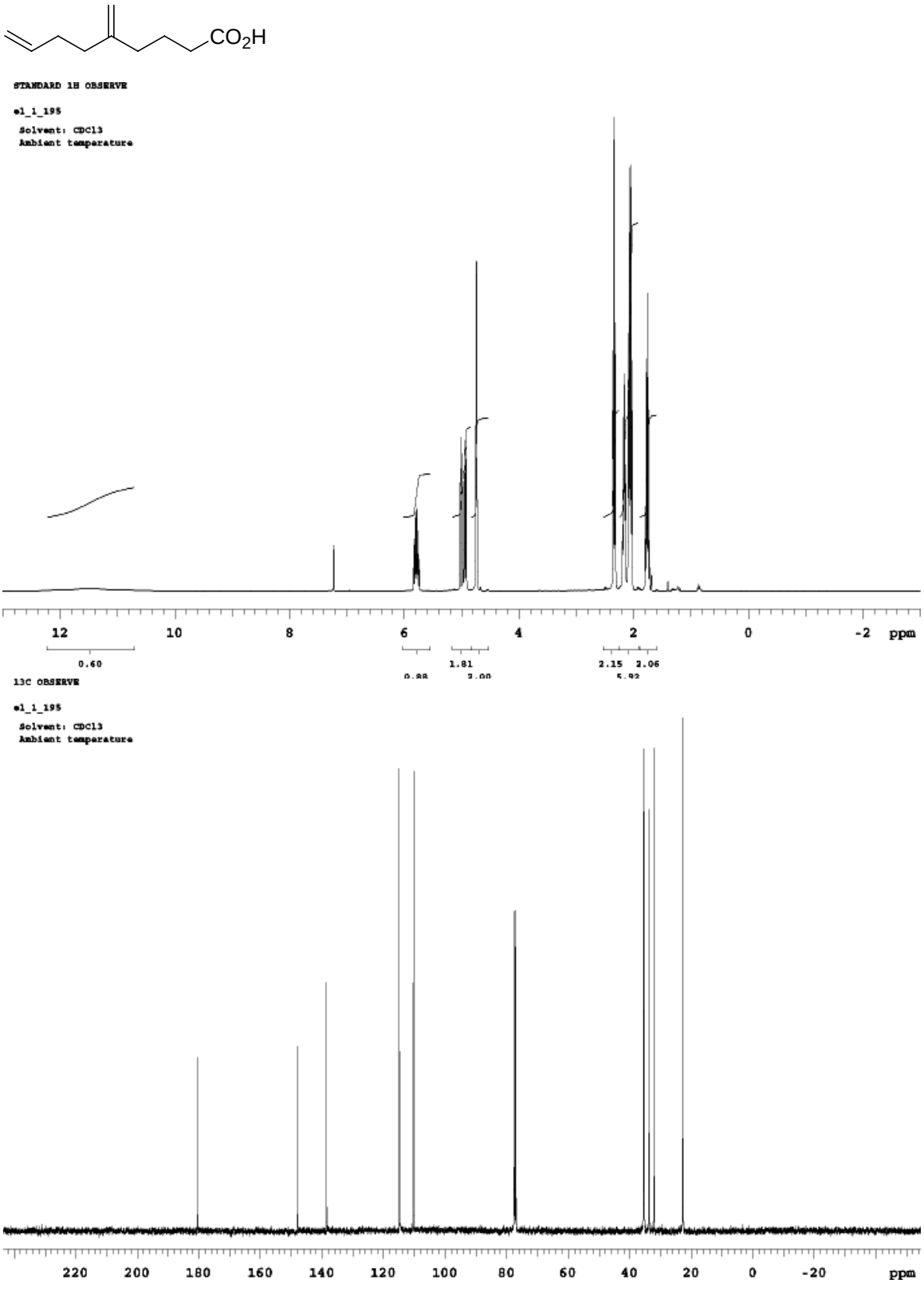
1.00
1.95
1.96
1.042.00
5.62
220 200 180 160 140 120 100 80 60 40 20 0 ppm


CO2H
12
10
8
6
4
2
0
-2
ppm
1.81
2.00
1.91
6.91
1.81
5.00
220
200
180
160
140
120
100
80
60
40
20
0
ppm

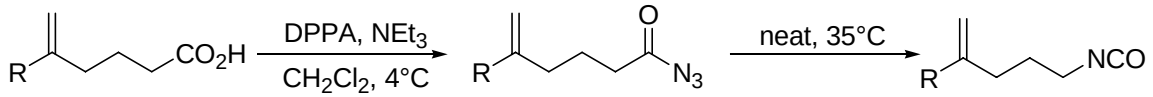

TBSO
CO2H


STANDARD 1H OBSERVE
el_1_143
Solvent: CDCl3
Ambient temperature
12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 ppm
1.74
2.00 2.18
9.57

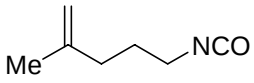

13C OBSERVE
Solvent: CDCl3
Ambient temperature
220 200 180 160 140 120 100 80 60 40 20 0 ppm


CO2H
STANDARD 1H OBSERVE
el_1_195
Solvent: CDCl3
Ambient temperature
12
10
8
6
4
2
0
-2
ppm
0.60
1.81
2.15
2.06
13C OBSERVE
el_1_195
Solvent: CDCl3
Ambient temperature
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

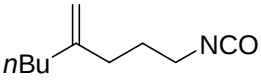
I.4 General procedure for isocyanate synthesis.



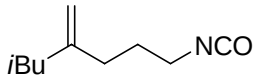
In a flame dried flask under Ar atmosphere, diphenylphosphoryl azide (8.88 mmol, 1.2 eq) was added to a stirring solution of carboxylic acid (7.4 mmol) in dichloromethane (25 mL) at 4 ^{o}C. Triethylamine (8.88 mmol, 1.2 eq) was then slowly added. After 4 hours, the reaction was concentrated under vacuum and rapidly purified by flash chromatography (solvent removal was carried out with the rotovap bath temperature less than 23 ^{o}C). The resulting acyl azide was then gently heated to 35^{o}C for 16-24 hours to afford the desired isocyanate.



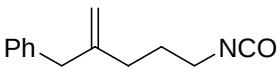
5-Isocyanato-2-methyl-pent-1-ene (5a): Flash chromatography of the acyl azide (Hex:EtOAc;98:2) and subsequent thermal conversion yielded a clear liquid (78%). IR (Thin Film) ν 2941, 2275, 1651, 1447, 1355, 891 cm^{-1}; ^{1}H NMR (400 MHz, CDCl $_{3}$) δ 4.76 (1H, s), 4.71 (1H, s), 3.31 (2H, t, *J* = 6.5 Hz), 2.11 (2H, t, *J* = 7.5 Hz), 1.75 (2H, tt, *J* = 7.0, 7.0 Hz), 1.73 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.2, 111.2, 42.6, 34.7, 29.2, 22.4.



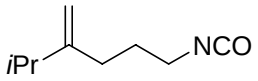
1-Isocyanato-4-methylene-octane (5b): Flash chromatography of the acyl azide (Hex:EtOAc;98:2) and subsequent thermal conversion yielded a clear liquid (70%). IR (Thin Film) ν 2929, 2170, 1644, 1489, 1270, 1183, 966 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.74 (1H, s), 4.70 (1H, s), 3.28 (2H, t, *J* = 6.5 Hz), 2.08 (2H, t, *J* = 8.0 Hz), 1.98 (2H, t, *J* = 7.5 Hz), 1.72 (2H, tt, *J* = 7.5, 7.0 Hz), 1.43-1.24 (4H, m), 0.88 (3H, t, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.3, -653904.0, 42.7, 35.8, 32.9, 30.1, 29.4, 22.6, 14.2.



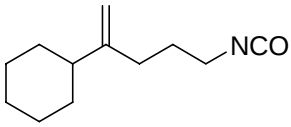
1-Isocyanato-6-methyl-4-methylene-heptane (5c): Flash chromatography of the acyl azide (Hex:EtOAc;98:2) and subsequent thermal conversion yielded a clear liquid (54%). IR (Thin Film) ν 2955, 2870, 2277, 1644, 1465, 1367 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.73 (1H, s), 4.71 (1H, s), 3.27 (2H, td, *J* = 6.5, 0.5 Hz), 2.04 (2H, t, *J* = 7.0 Hz), 1.85 (2H, d, *J* = 7.0 Hz), 1.75-1.66 (3H, m), 0.84 (2H, d, *J* = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.0, 111.4, 45.9, 42.7, 32.6, 29.3, 26.2, 22.6.



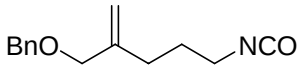
(5-Isocyanato-2-methylene-pentyl)-benzene (5d): Flash chromatography of the acyl azide (Hex:EtOAc;98:2) and subsequent thermal conversion yielded a clear liquid (75%). IR (Thin Film) ν 2948, 2277, 1645, 1494, 1452, 897 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.15 (5H, m), 4.84 (1H, s), 4.81 (1H, s), 3.33 (2H, s), 3.26 (2H, t, *J* = 6.5 Hz), 2.04 (2H, t, *J* = 7.5 Hz), 1.72 (2H, tt, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.4, 139.5, 129.1, 128.6, 126.5, 112.4, 43.2, 42.6, 32.3, 29.2.



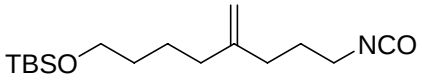
1-Isocyanato-5-methyl-4-methylene-hexane (5e): Flash chromatography of the acyl azide (Hex:EtOAc;98:2) and subsequent thermal conversion yielded a clear liquid (80%). IR (Thin Film) ν 2930, 2852, 2270, 1641, 1448, 1355, 888 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.78 (1H, s), 4.66 (1H, s), 3.30 (2H, t, *J* = 6.5 Hz), 2.20 (1H, sept, *J* = 7.0 Hz), 2.09 (2H, t, *J* = 8.0 Hz), 1.74 (2H, tt, *J* = 7.0, 7.0 Hz), 1.00 (6H, d, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 107.5, 42.8, 33.9, 31.3, 29.7, 22.0.



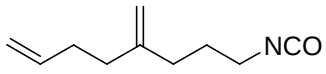
(4-Isocyanato-1-methylene-butyl)-cyclohexane (5f): Flash chromatography of the acyl azide (Hex:EtOAc;98:2) and subsequent thermal conversion yielded a clear liquid (77%). IR (Thin Film) ν 2926, 2852, 2276, 1641, 1448, 1355, 888 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.74 (1H, s), 4.67 (1H, s), 3.28 (2H, t, *J* = 7.5 Hz), 2.08 (2H, t, *J* = 7.5 Hz), 1.84-1.62 (8H, m), 1.30-1.06 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 108.0, 44.2, 42.8, 32.6, 31.8, 29.8, 27.0, 26.5.



(5-Isocyanato-2-methylene-pentyloxymethyl)-benzene (5g): Flash chromatography of the acyl azide (Hex:EtOAc;98:2) and subsequent thermal conversion yielded a clear liquid (61%). IR (Thin Film) ν 2933, 2856, 2277, 1650, 1453, 1096, 1072, 906 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.24 (mH, 5), 5.09 (1H, s), 4.95 (1H, s), 4.48 (2H, s), 3.95 (2H, s), 3.31 (2H, t, *J* = 6.5 Hz), 2.18 (2H, t, *J* = 7.0 Hz), 1.76 (2H, tt, *J* = 7.0, 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.6, 138.4, 128.6, 127.9, 127.9, 113.1, 73.1, 72.2, 42.7, 30.2, 29.2.

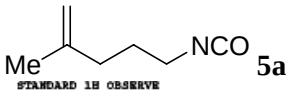


tert-Butyl-(8-isocyanato-5-methylene-octyloxy)-dimethyl-silane (5i): Flash chromatography of the acyl azide (Hex:EtOAc;98:2) and subsequent thermal conversion yielded a clear liquid (59%). IR (Thin Film) ν 2931, 2858, 2277, 1472, 1256, 1103, 909, 734 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.75 (1H, s), 4.72 (1H, s), 3.59 (2H, t, *J* = 6.5 Hz), 3.28 (2H, t, *J* = 6.5 Hz), 2.08 (2H, t, *J* = 7.5 Hz), 2.00 (2H, t, *J* = 6.5 Hz), 1.72 (2H, tt, *J* = 7.5, 7.0 Hz), 1.51-1.43 (4H, m), 0.87 (9H, s), 0.02 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.1, 110.2, 63.2, 42.7, 35.8, 32.9, 32.6, 29.3, 26.2, 24.1, 18.6, -5.1.



8-Isocyanato-5-methylene-oct-1-ene (5i): Flash chromatography of the acyl azide (Hex:EtOAc;98:2) and subsequent thermal conversion yielded a clear liquid (87%). IR (Thin Film) ν 2936, 2277, 1643, 1446, 1356, 911 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78 (1H, ddd, *J* = 17.0, 10.5, 6.5 Hz), 4.99 (1H, dd, *J* = 17.0, 1.5 Hz), 4.94 (1H, dd, *J* = 10.5, 1.5 Hz), 4.77 (1H, s), 4.74 (1H, s), 3.29 (2H, td, *J* = 6.5, 1.0 Hz), 2.17 (2H, tdd, *J* = 7.0, 7.0, 1.0 Hz), 2.11-2.05 (4H, m), 1.72 (2H, tt, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.4, 138.4, 122.2, 114.9, 110.4, 42.6, 35.3, 33.0, 32.1, 29.3.

I.5 Isocyanate ^{1}H and ^{13}C NMR Spectra



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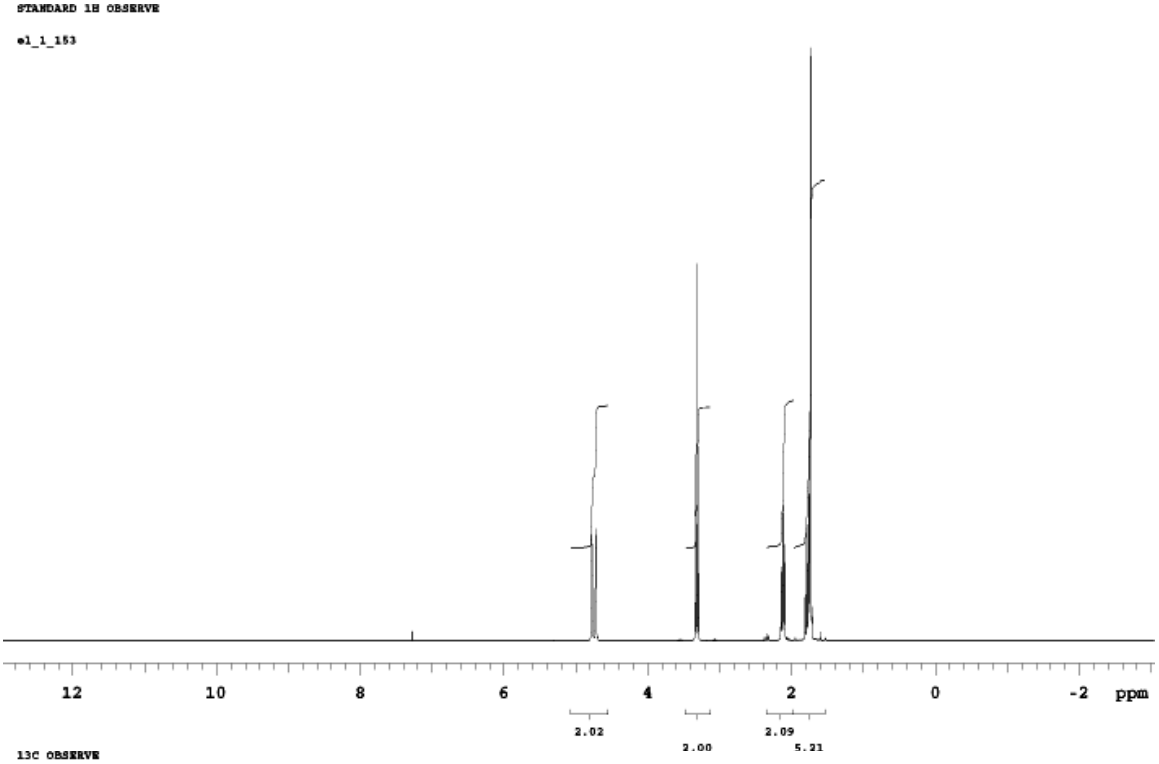

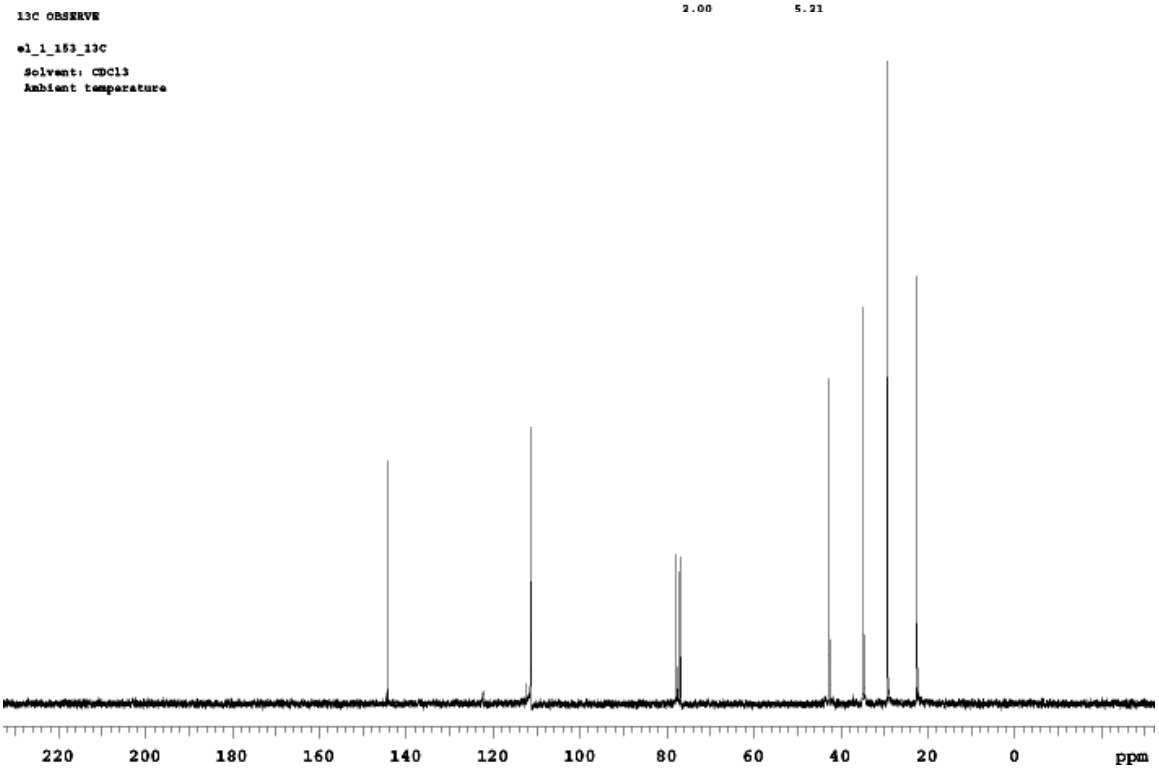

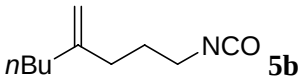
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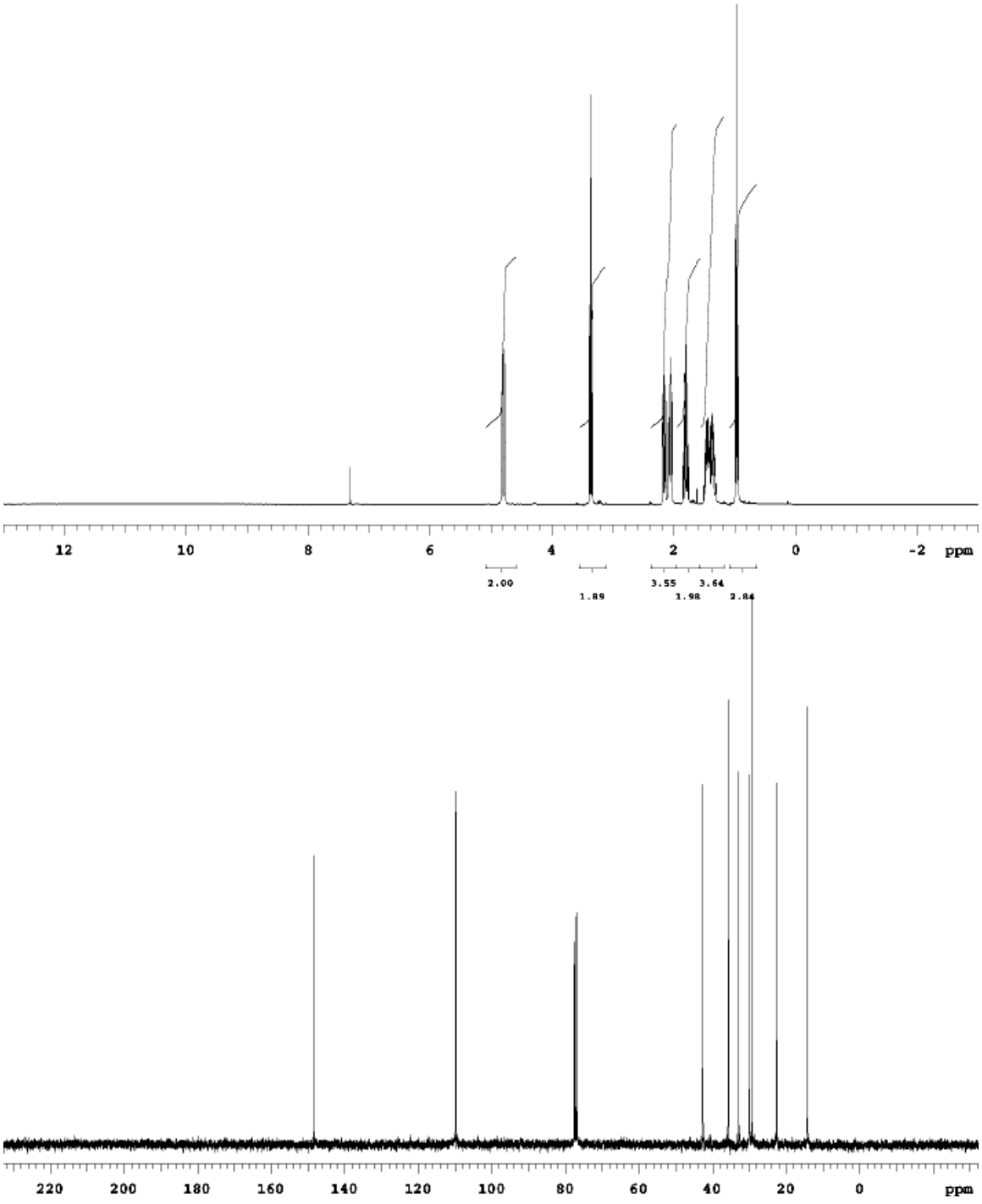
NCO

5b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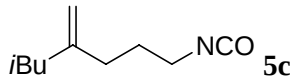
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NCO

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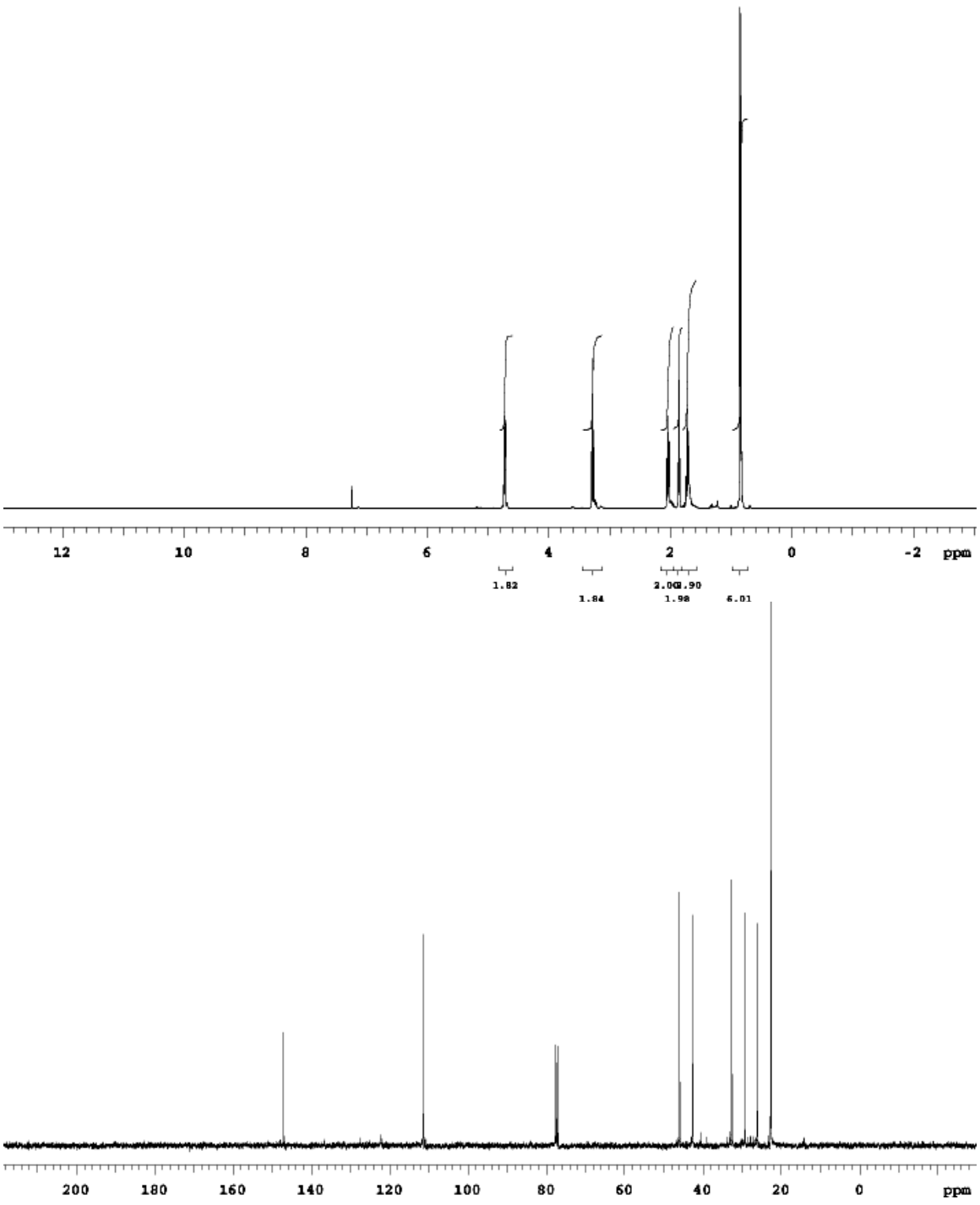
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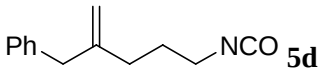
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NCO

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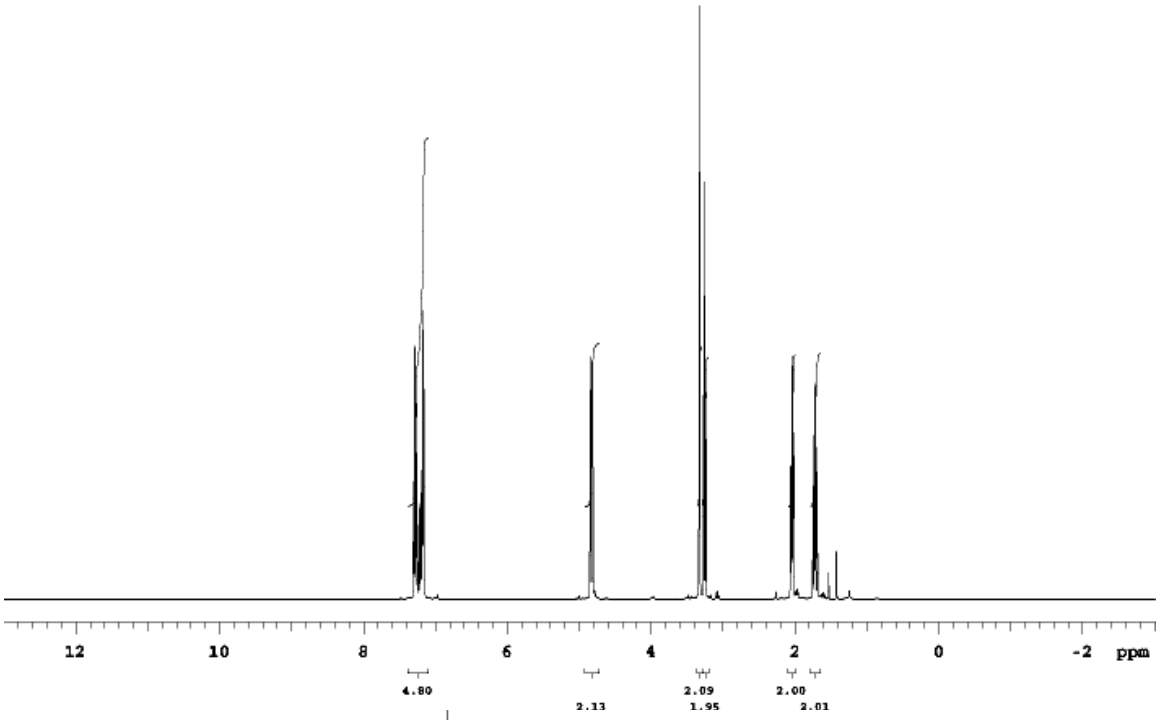
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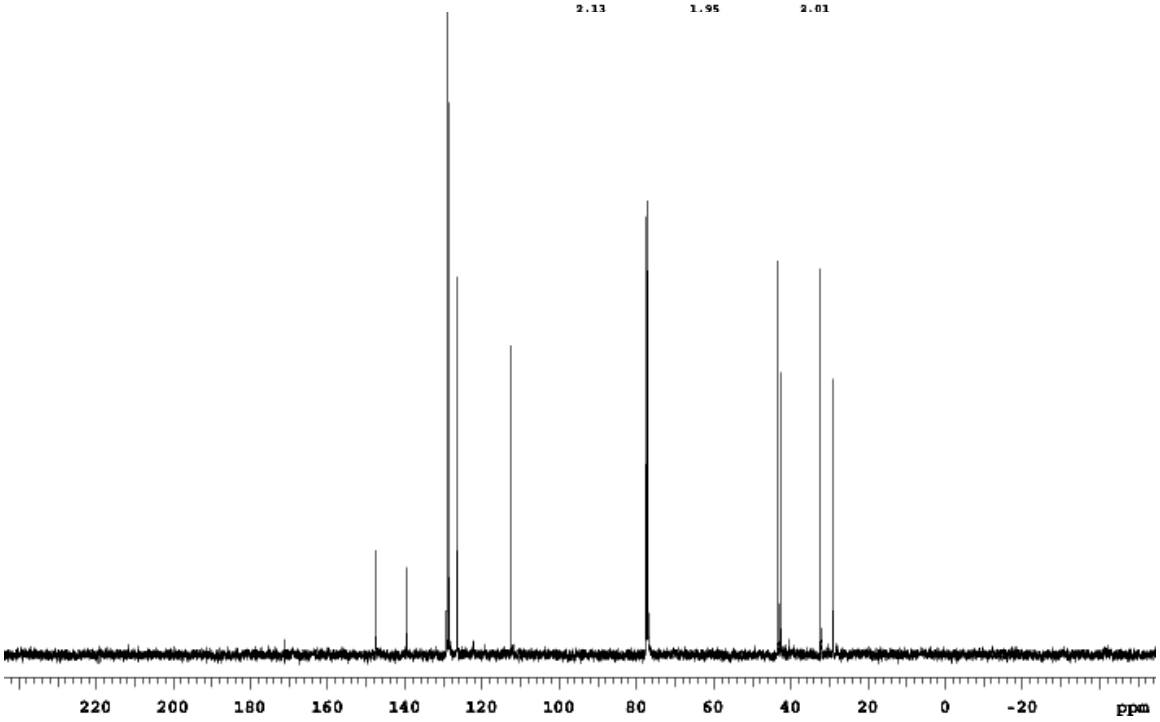
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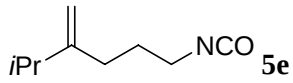
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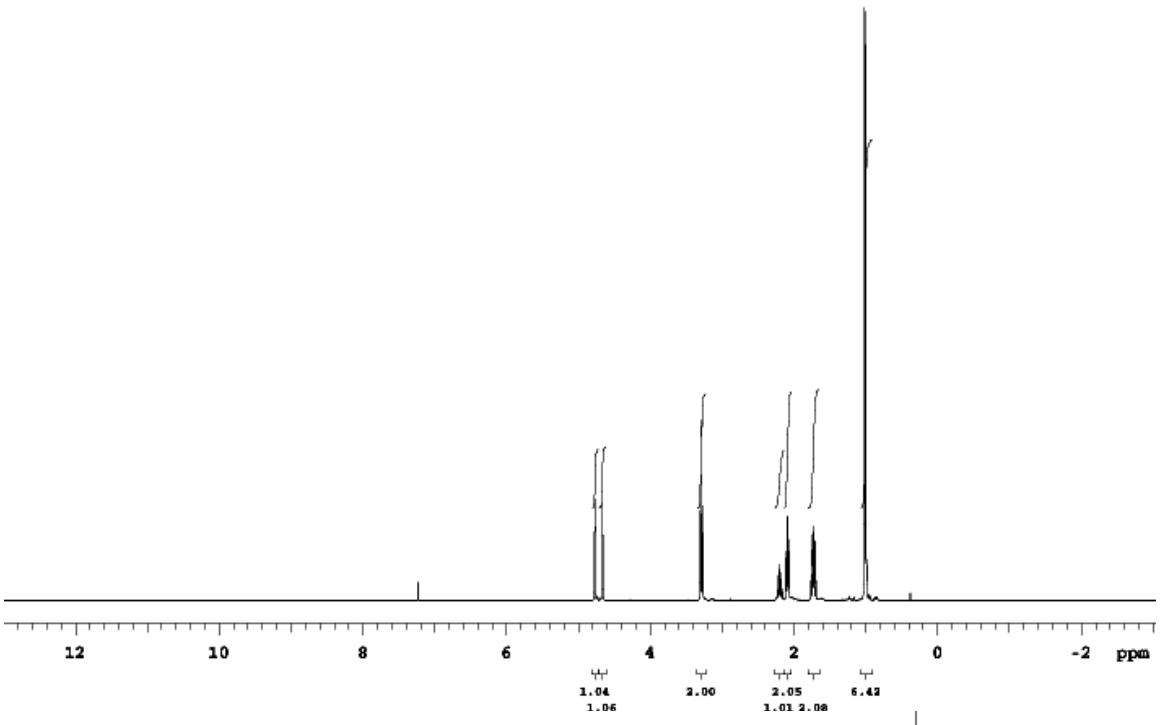
NCO

5e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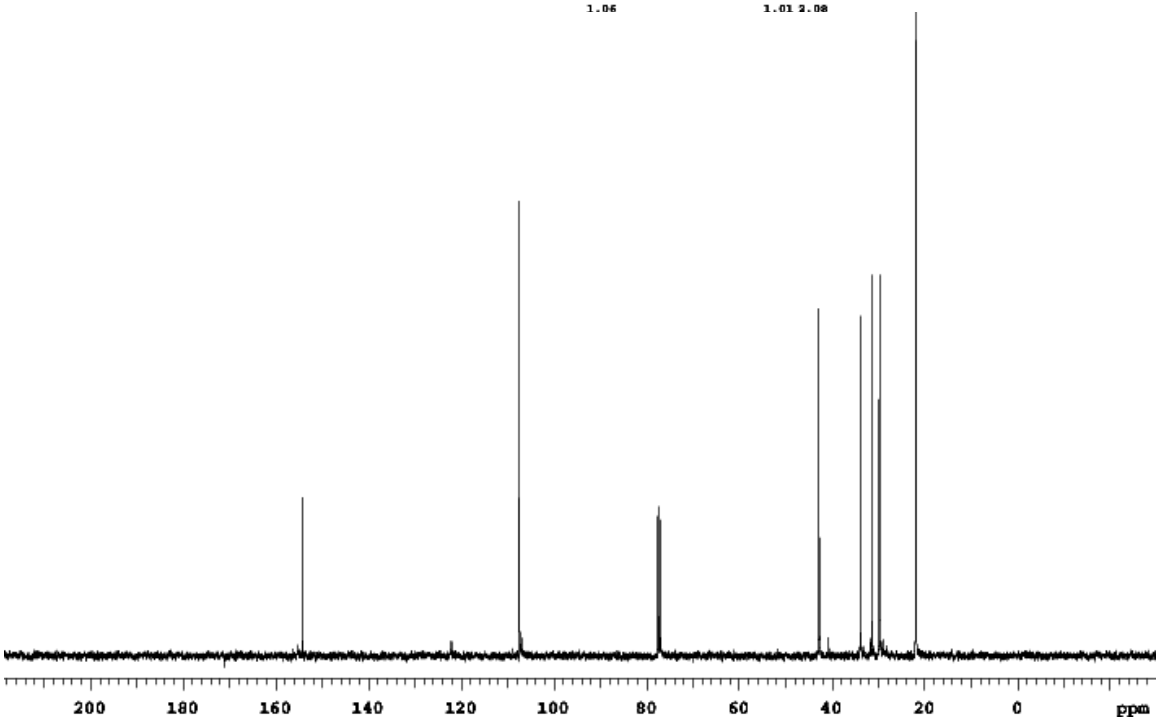
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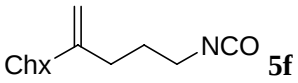
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NCO

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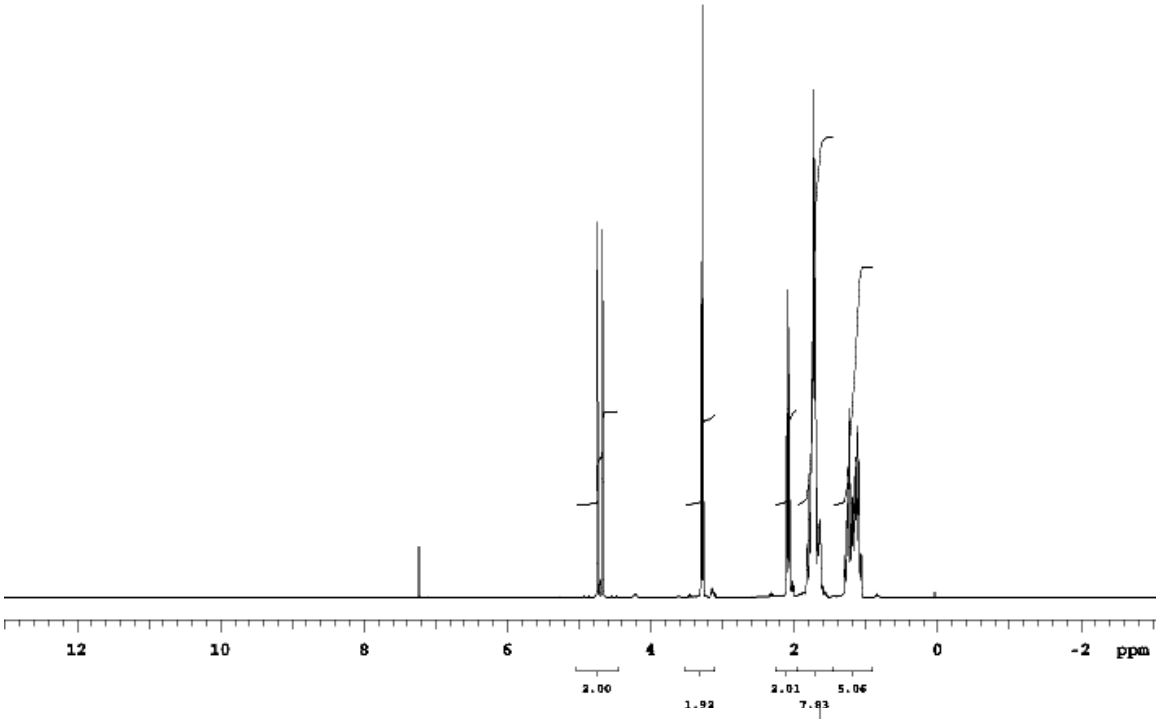
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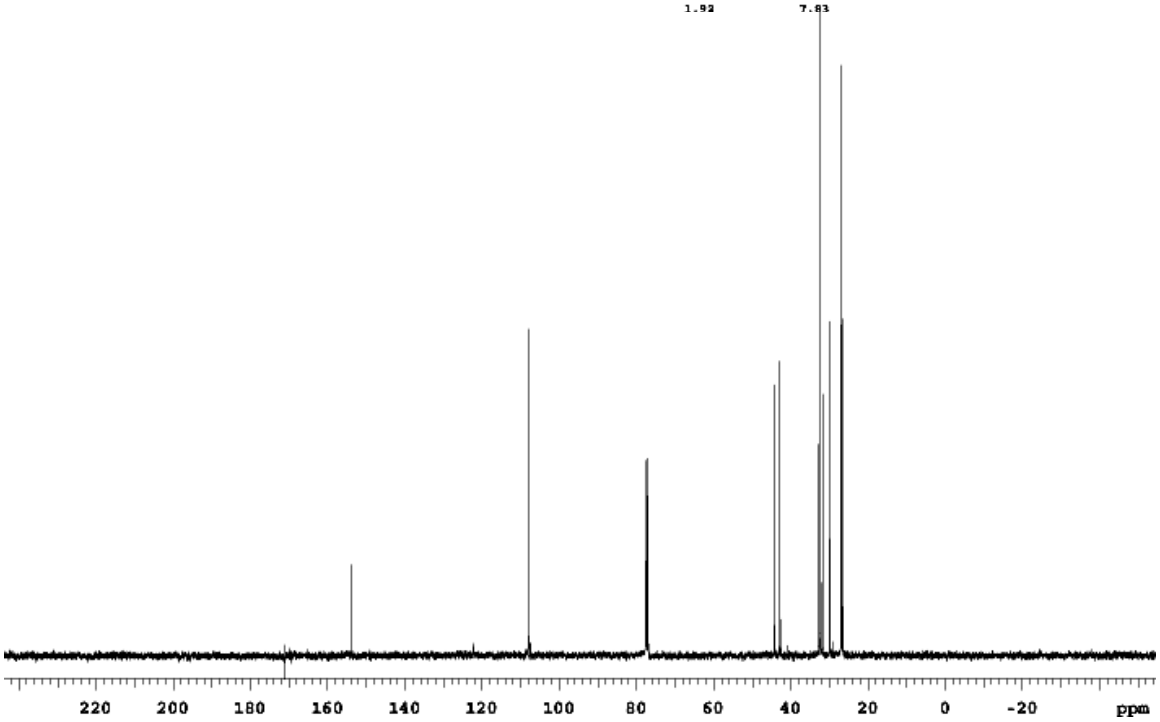
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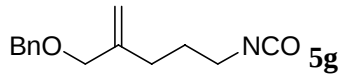
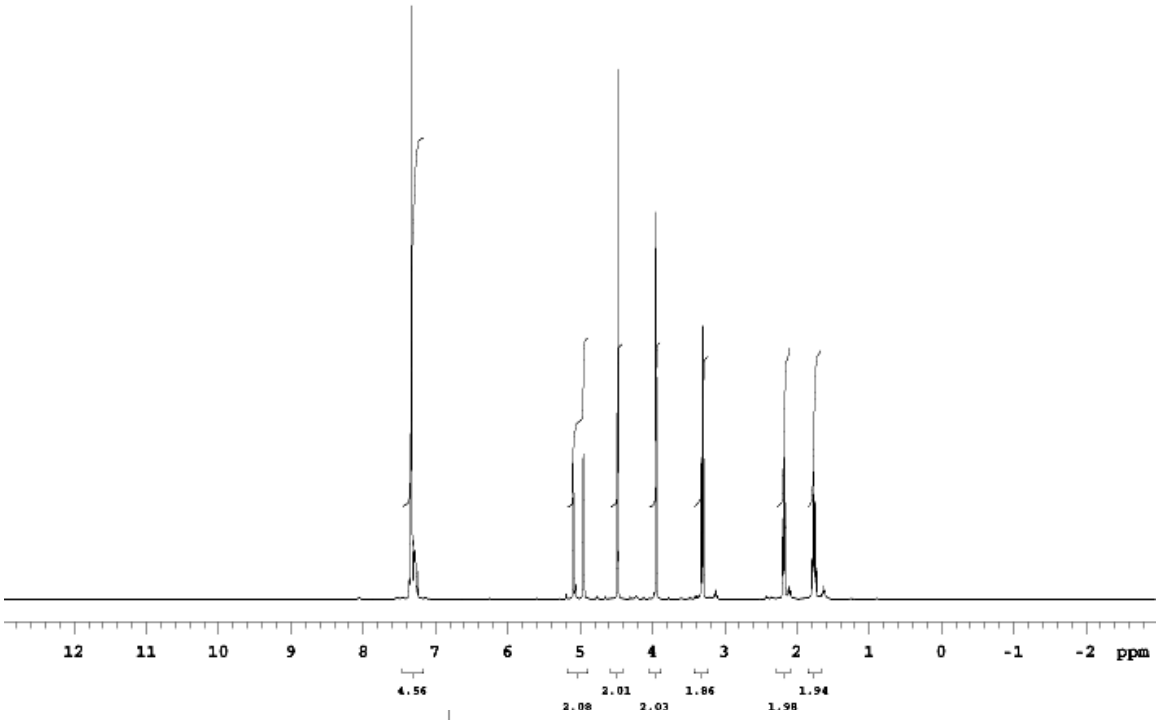

BnO
NCO

5g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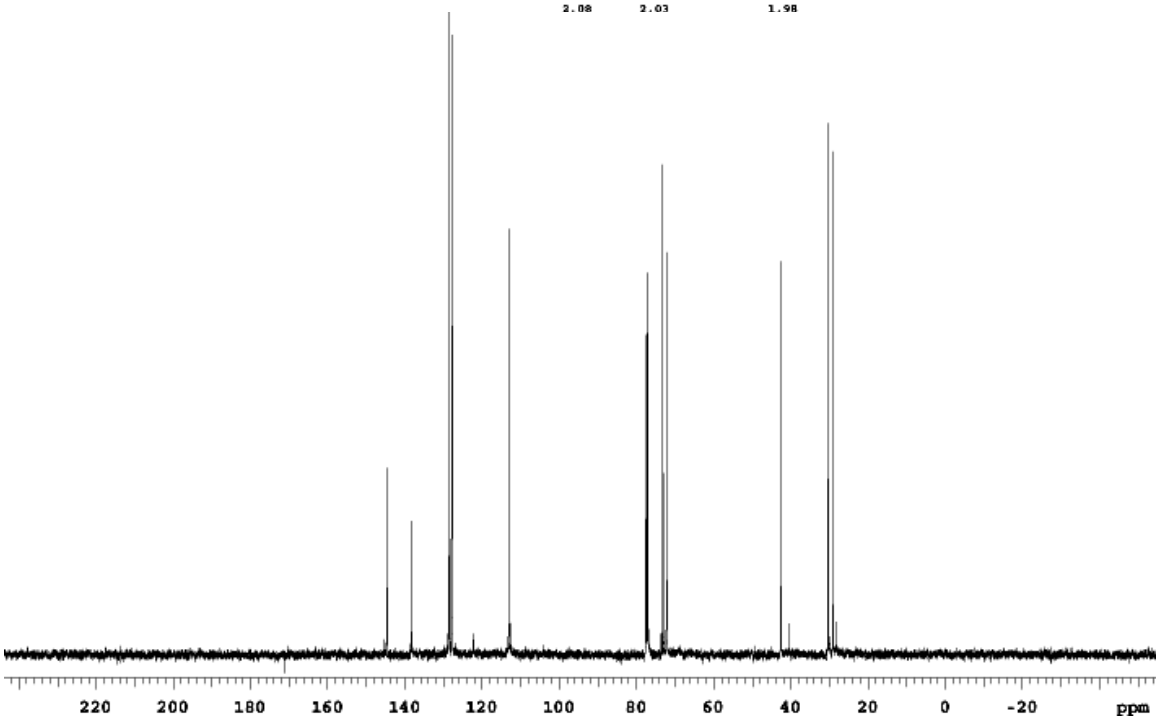
1.94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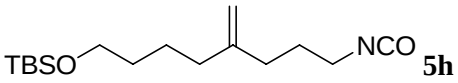
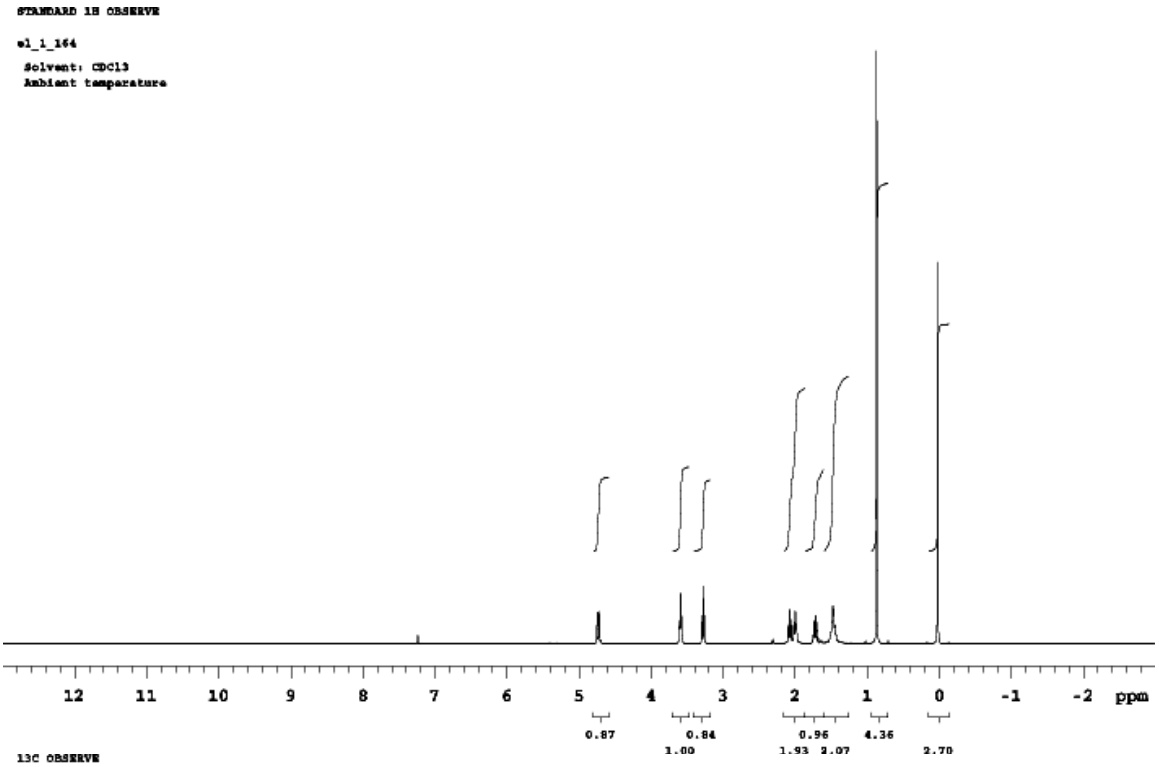

TBSO
NCO

5h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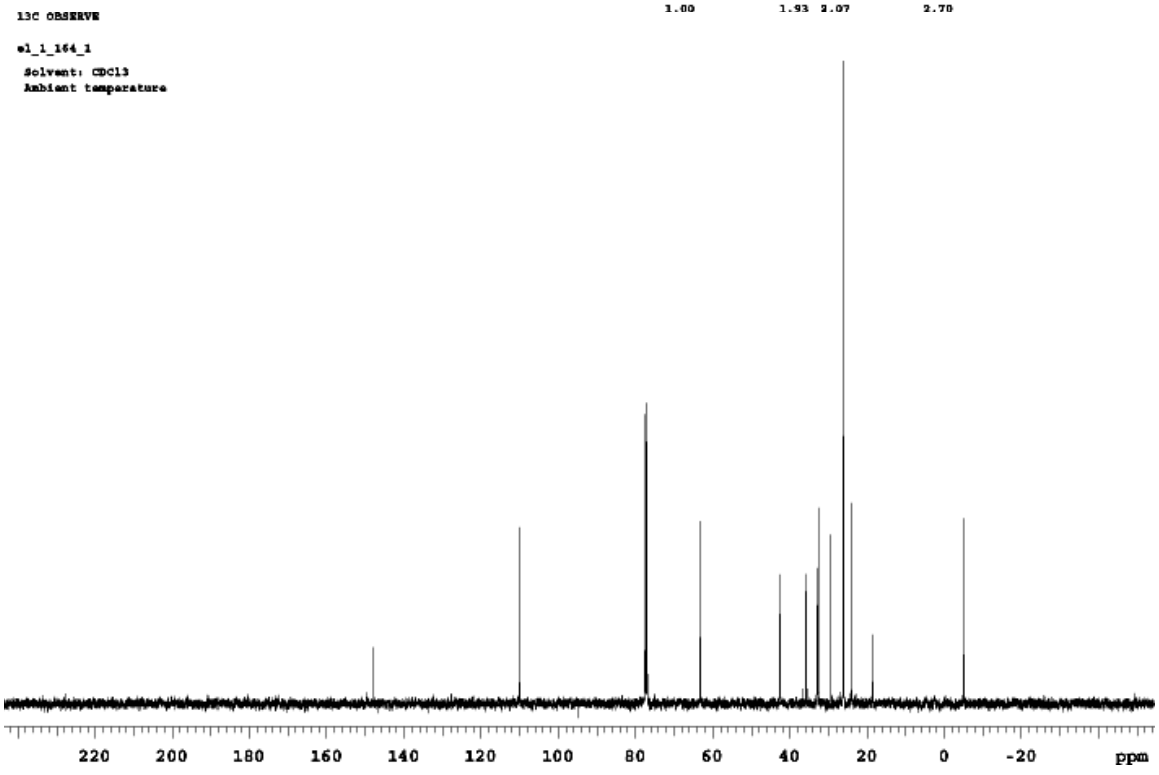
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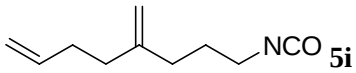
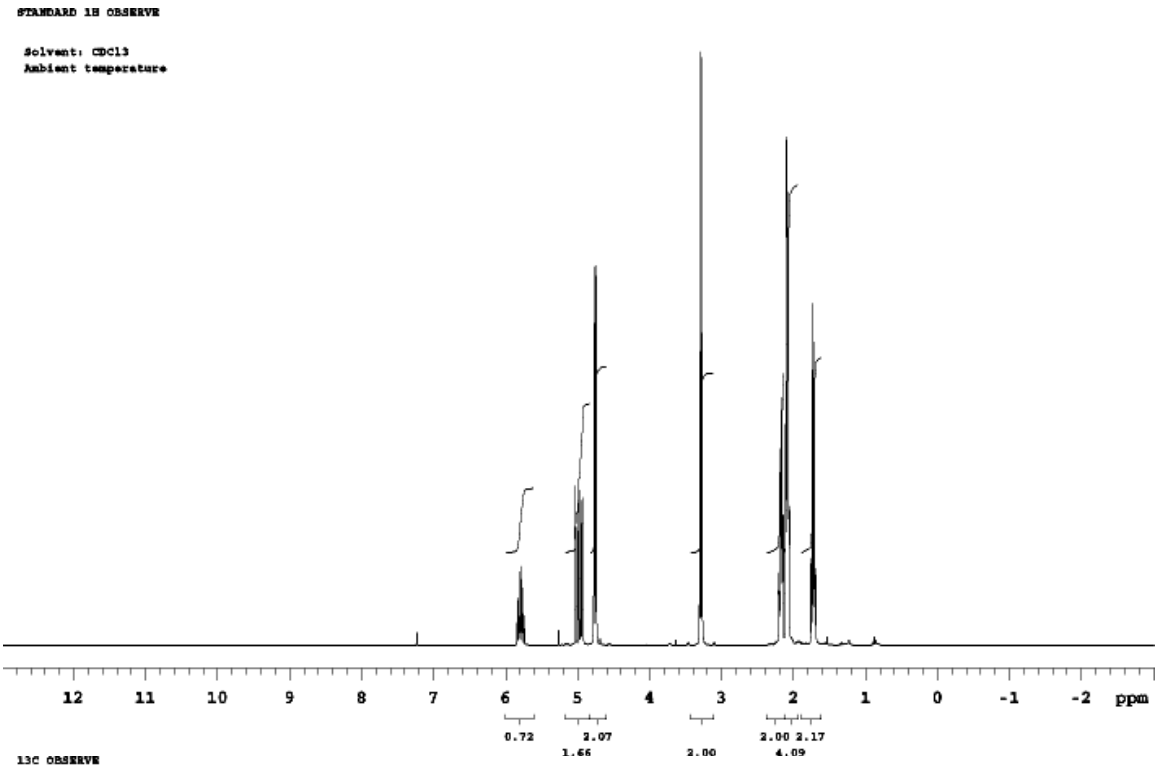

NCO

5i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2.00 2.17
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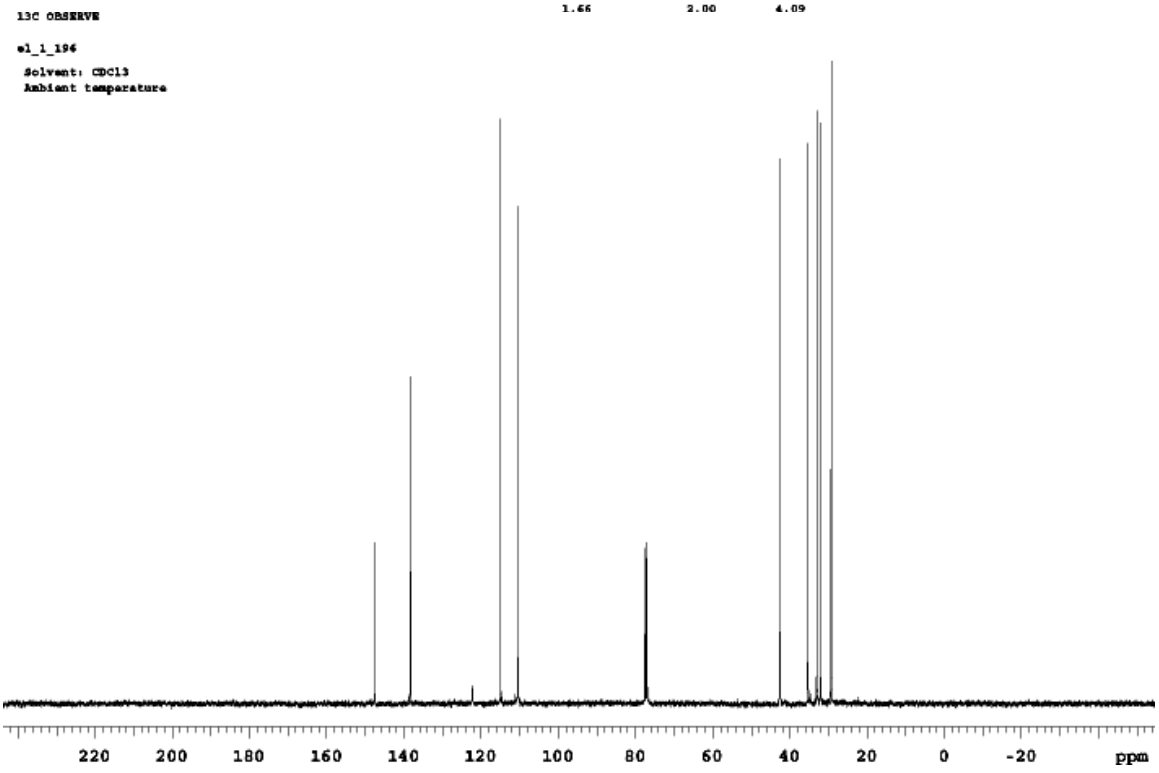
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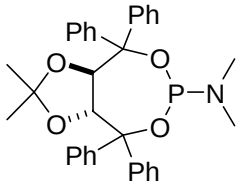
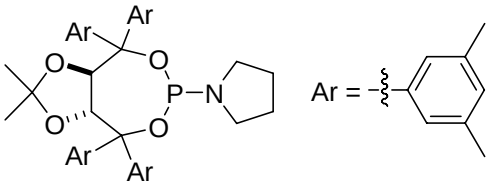
I.6 Synthesis of Ligands

Procedure A (**L3**, **L4** and **L5**): to a solution of diol in ether at 0°C, triethylamine (3 eq) then phosphorous trichloride (1.2 eq) were added. After 6 hours, amine (10 eq) were added, and the reaction warmed to room temperature and left for 2 hours. Filtration, concentration and purification by flash chromatography provides the desired product (after chromatography and concentration, products are dissolved in ether and concentrated again).

Procedure B (alternatively used for **L3**): to a solution of diol in toluene, hexamethyl phosphorous triamide (1.2 eq) was added. The reaction was then heated at reflux for 48 hours under a slow, dynamic flow of argon. The clear yellow solution was then cooled and diluted with hexanes. The white solid was filtered off, washed with hexanes and dried under vacuum.

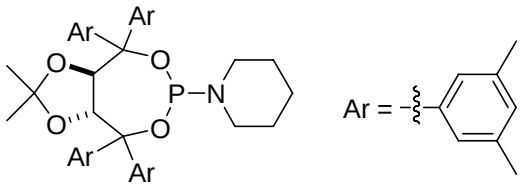


(2,2-Dimethyl-4,4,8,8-tetraphenyl-tetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepin-6-yl)-dimethyl-amine (L3): Flash Chromatography (Hexanes:EtOAc;95:5) yielded a white solid (Procedue A: 54%, Procedure B without chromatography: 74%). R_f = 0.50 (Hexanes:EtOAc;90:10); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (2H, d, *J* = 11.0 Hz), 7.63 (2H, d, *J* = 12.0 Hz), 7.51 (2H, d, *J* = 11.0 Hz), 7.48 (2H, d, *J* = 11.0 Hz), 7.38-7.20 (12H, m), 5.22 (1H, dd, *J* = 12.0, 4.5 Hz), 4.86 (1H, d, *J* = 11.0 Hz), 2.76 (6H, d, *J* = 14.5 Hz), 1.32 (3H, s), 0.33 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.1, 146.7, 142.4, 142.4, 142.0, 129.2, 129.0, 128.9, 128.4, 128.0, 127.8, 127.7, 127.5, 127.4, 127.3, 112.0, 82.8 (d, *J* = 3.5 Hz), 82.5, 82.1, 81.4 (d, *J* = 7.3 Hz), 25.6 (d, *J* = 21.0 Hz), 27.9, 25.6.
First Report: Keller, E.; Maurer, J.; Naasz, R.; Schader, T.; Meetsma, A.; Feringa, B. L. *Tetrahedron Asymmetry*, **1998**, *9*, 2409, 2413.



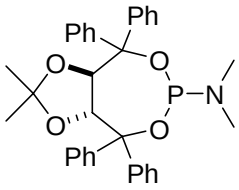
1-[4,4,8,8-Tetrakis-(3,5-dimethyl-phenyl)-2,2-dimethyl-tetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepin-6-yl]-pyrrolidine (L4): Flash Chromatography (Hexanes:EtOAc;95:5) yielded a white solid (50%). R_f = 0.50 (Hexanes:EtOAc;90:10); IR (Thin Film) ν 2917, 2866, 1601, 1456, 1379, 1214, 1159, 1042, 854 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (2H, s), 7.16 (2H, s), 7.04 (2H, s), 7.02 (2H, s), 6.84 (3H, s), 6.80 (1H, s), 5.08 (1H, dd, *J* = 8.5, 2.5 Hz), 4.74 (1H, d, *J* = 8.0 Hz), 3.47-3.35 (2H, m), 3.35-3.15 (2H, m), 2.27 (6H, s), 2.25 (12H, s), 2.24 (6H, s), 1.86-1.72 (4H, m), 1.32 (3H, s), 0.25 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$)

δ 147.2, 146.9, 142.2, 142.1, 137.3, 136.9, 136.7, 136.3, 129.2, 128.9, 128.7, 127.9, 127.0, 126.8, 125.3, 125.2, 111.7, 83.1 (d, *J* = 4.5 Hz), 82.9, 82.7, 81.8, 81.1 (d, *J* = 5.5 Hz), 45.1 (d, *J* = 19.0 Hz), 27.9, 26.3, 16.2, 25.7, 21.9, 21.8; ^{31}P NMR (75 MHz, $CDCl_3$) δ 138.40; HRMS (ESI) *m/e* calcd ($M+H^+$) 678.3707, found 678.3702.

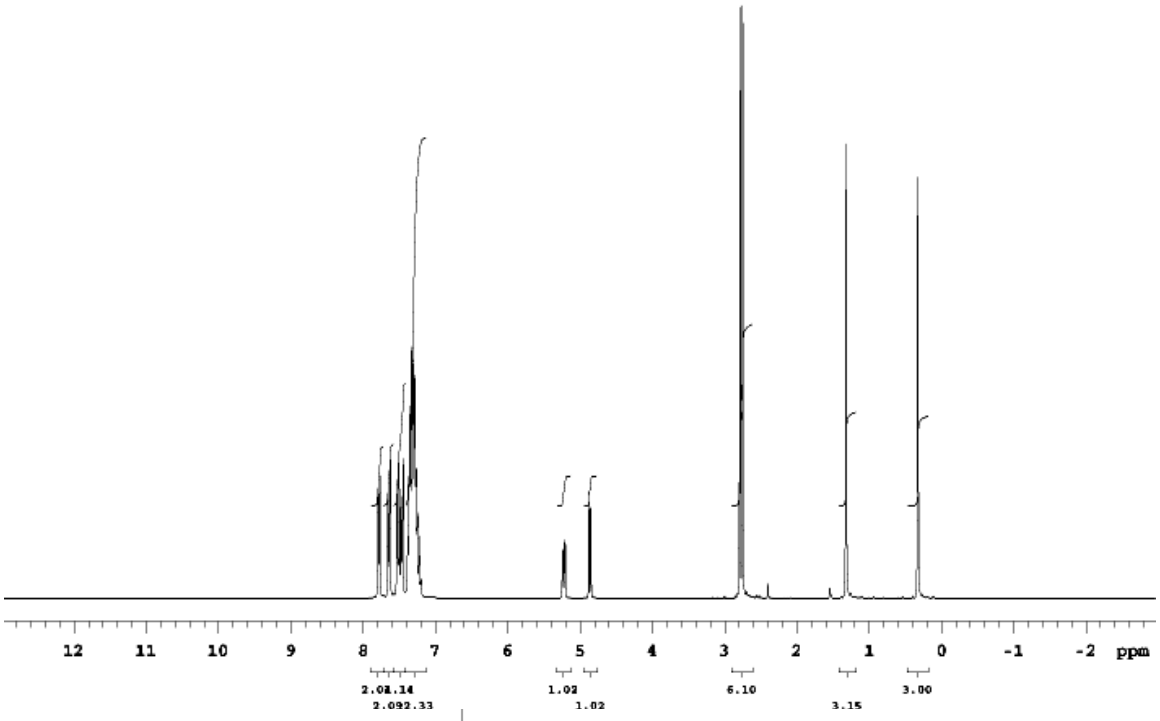


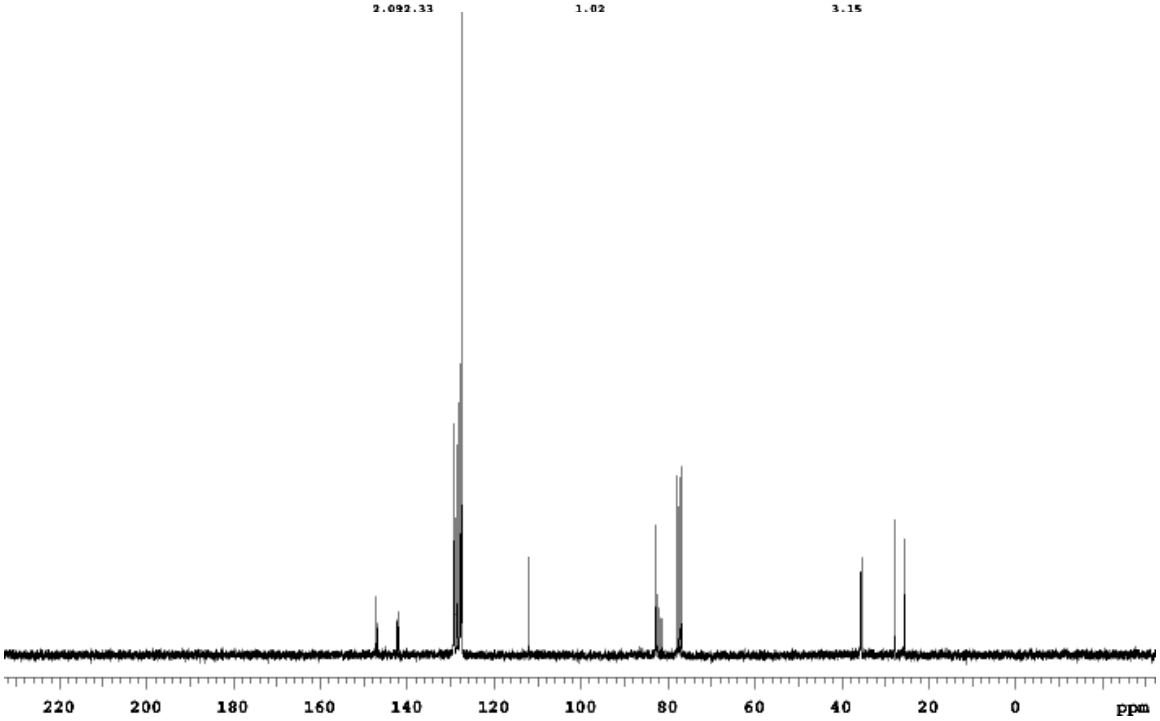
(*R*,*R*)-1-[4,4,8,8-Tetrakis-(3,5-dimethyl-phenyl)-2,2-dimethyl-tetrahydro-[1,3]dioxolo[4,5-e][1,3,2]dioxaphosphepin-6-yl]-piperidine (L5): Flash Chromatography (Hexanes:EtOAc;95:5) yielded a white solid (52%); $[\alpha]_D$ = -108.0^o ($CHCl_3$, c=1.0); R_f = 0.50 (Hexanes:EtOAc;90:10); IR (Thin Film) ν 2931, 2851, 1600, 1448, 1370, 1215, 1159, 1040, 940 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (2H, s), 7.20 (2H, s), 7.04 (4H, s), 6.84 (3H, s), 6.79 (1H, s), 5.02 (1H, dd, *J* = 8.5, 3.0 Hz), 4.67 (1H, d, *J* = 8.5 Hz), 3.34-3.27 (2H, m), 3.20-3.08 (2H, m), 2.26 (6H, s), 2.26 (6H, s), 2.25 (6H, s), 2.24 (6H, s), 1.65-1.50 (6H, m), 1.37 (3H, s), 0.25 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.5, 147.0, 142.1, 137.3, 136.9, 136.7, 136.4, 129.2, 128.9, 128.8, 128.7, 127.1, 126.8, 125.3, 111.5, 83.3, 82.9, 82.7, 81.4, 81.3, 81.2, 77.4, 45.3, 45.1, 27.9, 27.2, 27.2, 25.7, 25.5, 21.9, 21.8, 21.7; ^{31}P NMR (75 MHz, $CDCl_3$) δ 138.76; HRMS (ESI) *m/e* calcd ($M+H^+$) 692.3863, found 692.3843.

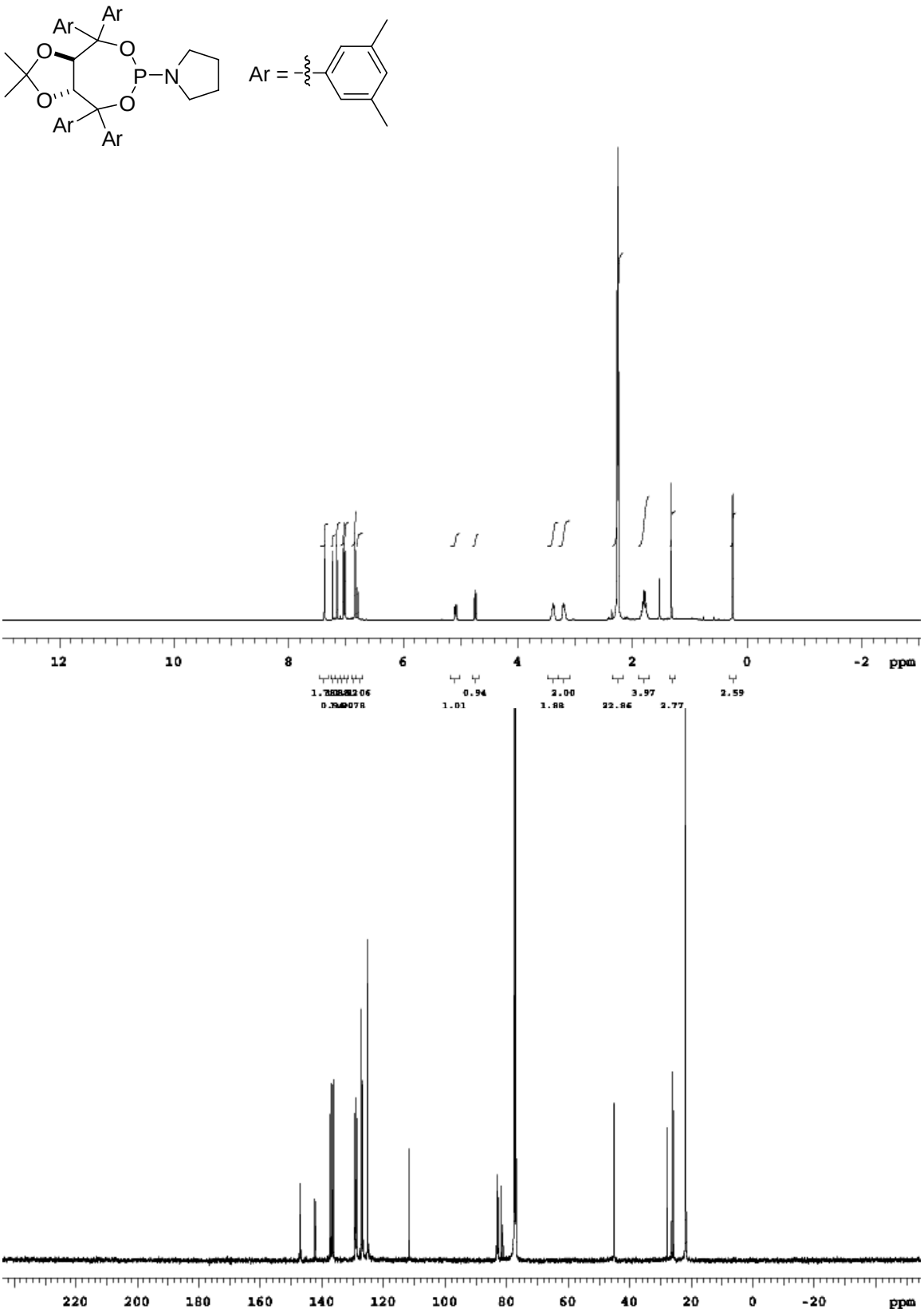
I.7 ^{1}H and ^{13}C NMR Spectra for New Ligands

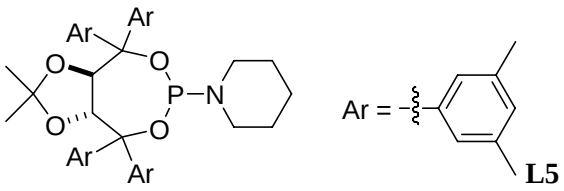


L3

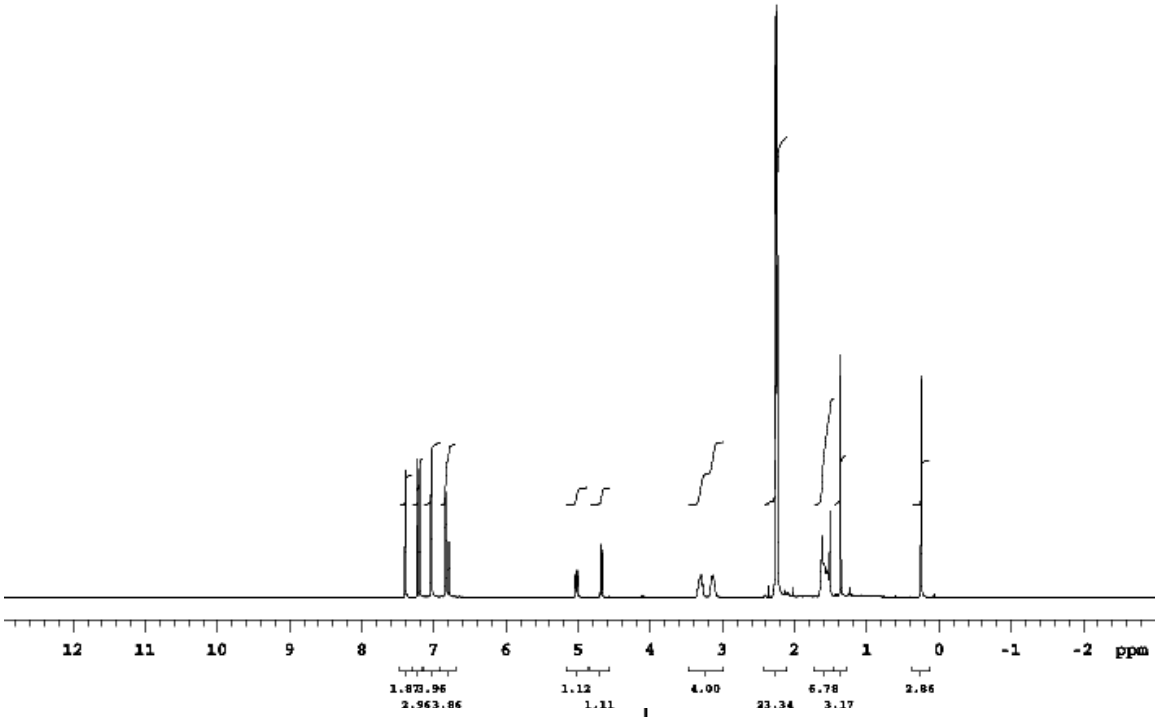


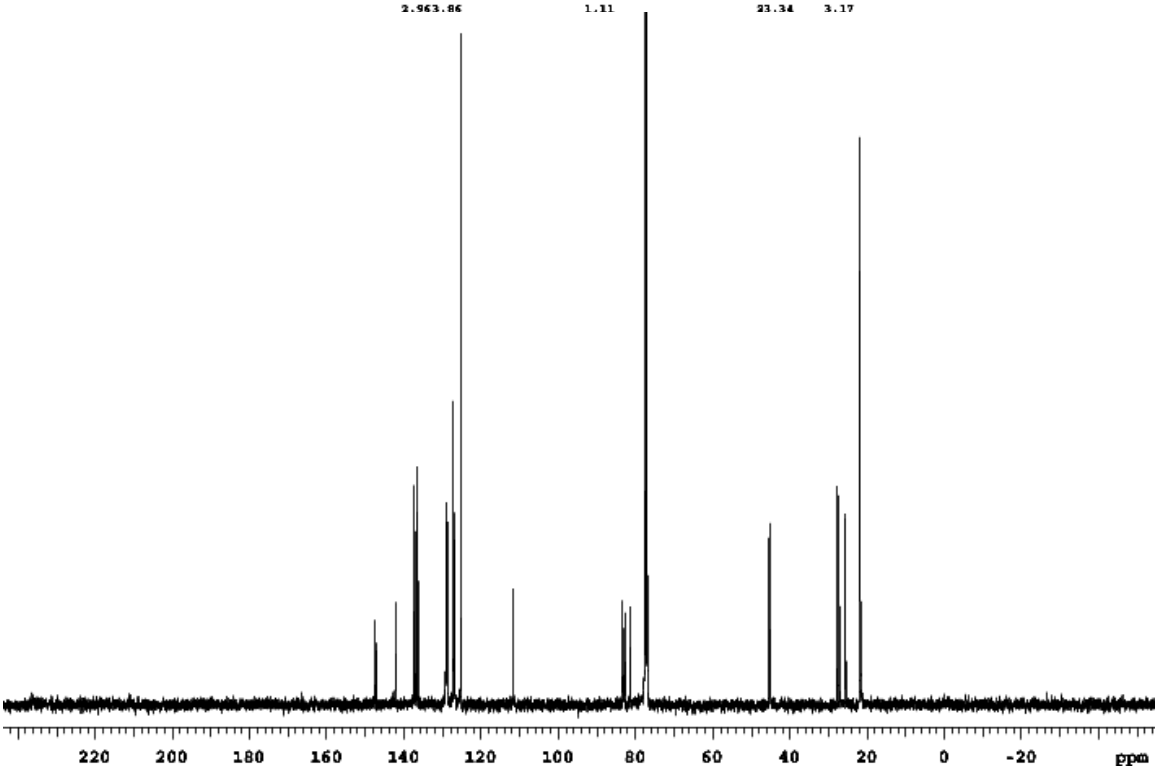



Ar
Ar
O
O
P
N
O
O
Ar
Ar
Ar =
12
10
8
6
4
2
0
-2
ppm
1.00
0.94
2.00
3.97
2.59
1.01
1.88
22.86
2.77
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

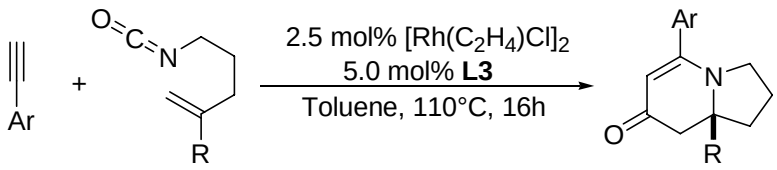

Ar
Ar
O
O
P
N
O
O
Ar
Ar
Ar =

L5


12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
ppm
1.00
3.96
2.96
3.86
1.12
1.11
4.00
23.34
6.78
3.17
2.86

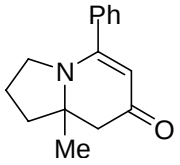

220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

I.8 General procedure for [2+2+2] cycloadditions with Aryl Alkynes.

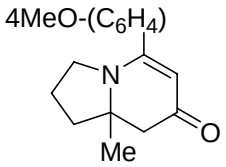


2b (2 eq) **5** (*S*)-**9**

In a glovebox under N_2 atmosphere, chlorobis(ethylene)rhodium(I) dimer (2.3 mg, 0.006 mmol) and dimethyl-TADDOL-phosphoramidite **L3** (6.5 mg, 0.012 mmol) were transferred into a round bottom flasked fitted with a reflux condenser. The system was sealed with a standard septum, removed from the glovebox and flushed with Ar. A solution of alkyne (0.48 mmol) and isocyanate (0.24 mmol) in toluene (7 mL) was then added. The brown-black solution was then heated to 110 ^{o}C (bath temperature), stirred at reflux for 16 hours under a static atmosphere of Ar, and cooled. The crude mixture was then concentrated and purified by silica gel, column chromatography.

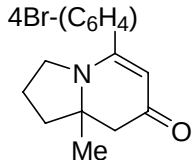


(*S*)-8a-Methyl-5-phenyl-2,3,8,8a-tetrahydro-1H-indolizin-7-one (7a): Flash Chromatography (Hexanes:EtOAc;1:6) yielded a clear syrup (76% yield); 91% ee by HPLC (Chiralcel ODH, Hex:*i*PrOH;85:15, 1 ml/min, RT_{major} = 20.9 min, RT_{minor} = 15.0 min); $[\alpha]_D$ = +285.0^{o} ($CHCl_3$, c=0.9); R_f = 0.20 (100% EtOAc); IR (Thin Film) ν 2962, 2871, 1628, 1533, 1461, 1265, 1119 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.25 (5H, m), 5.01 (1H, s), 3.59-3.51 (1H, m), 3.22-3.13 (1H, m), 2.69 (1H, d, *J* = 16.5 Hz), 2.32 (1H, d, *J* = 16.5 Hz), 2.10-1.90 (4H, m), 1.41 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.8, 161.5, 136.8, 130.1, 128.6, 127.9, 99.3, 62.9, 50.2, 48.0, 40.0, 24.1, 22.0; MS (EI) *m/e* (rel intensity) 228 (100), 227 (27), 226 (11), 212 (19), 154 (9), 136 (12); HRMS (EI) *m/e* calcd (M^+) 228.1388, found 228.1400.



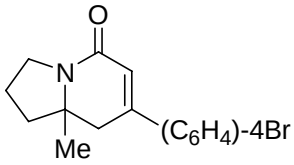
(*S*)-5-(4-Methoxy-phenyl)-8a-methyl-2,3,8,8a-tetrahydro-1H-indolizin-7-one (7b): Flash Chromatography (Hexanes:EtOAc;1:6) yielded a clear syrup (80%); 91% ee by HPLC (Chiralcel ODH, Hex:*i*PrOH;85:15, 1 ml/min, RT_{major} = 11.2 min, RT_{minor} = 14.9 min); $[\alpha]_D$ = +225.0^{o} ($CHCl_3$, c=0.6); R_f = 0.25 (100% EtOAc); IR (Thin Film) ν 2964, 1606, 1578, 1508, 1461, 1245, 1174, 1028 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (2H, d, *J* = 8.5 Hz), 6.88 (2H, d, *J* = 8.5

Hz), 5.06 (1H, s), 3.81 (3H, s), 3.56 (1H, ddd, *J* = 10.5, 6.5, 6.5 Hz), 3.18 (1H, m), 2.65 (1H, d, *J* = 16.5 Hz), 2.26 (1H, d, *J* = 16.5 Hz), 2.04-1.85 (4H, m), 1.38 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.0, 161.6, 161.2, 129.8, 129.2, 114.0, 99.0, 62.7, 55.6, 50.6, 47.8, 39.9, 24.2, 22.3; MS (EI) *m/e* (rel intensity) 258 (100), 257 (34), 242 (14), 154 (10), 136 (7); HRMS (ESI) *m/e* calcd (M^+) 258.1494, found 258.1485.

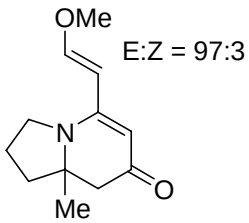


Flash Chromatography (Hex:EtOAc;1:4) yielded an off white solid **6c** (19%) followed by an off white solid **7c** (58%):

(*S*)-5-(4-Bromo-phenyl)-8a-methyl-2,3,8,8a-tetrahydro-1H-indolizin-7-one (7c): 88% ee by HPLC (Chiralcel ODH, Hex:*i*PrOH;85:15, 1 ml/min, RT_{major} = 10.1 min, RT_{minor} = 14.5 min); $[\alpha]_D$ = $[\alpha]_D$ = +153.0° ($CHCl_3$, c=0.5); R_f = 0.35 (EtOAc 100%); IR (Thin Film) ν 2929, 2858, 1625, 1526, 1445, 1262, 1212 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (2H, d, *J* = 8.5 Hz), 7.24 (2H, d, *J* = 8.5 Hz), 5.04 (1H, s), 3.53-3.47 (1H, m), 3.17-3.10 (1H, m), 2.65 (1H, d, *J* = 16.0 Hz), 2.30 (1H, d, *J* = 16.0 Hz), 2.03-1.89 (4H, m), 1.37 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.9, 160.5, 135.7, 132.1, 132.0, 129.7, 127.6, 124.6, 99.4, 63.0, 50.2, 47.7, 39.9, 24.0, 22.0; MS (FAB) *m/e* (rel intensity) 308 (20), 306 (22), 221 (18), 207 (17), 154 (16), 147 (29), 136 (23), 133 (100); HRMS (FAB) *m/e* calcd (M^+) 306.0494, found 306.0487.

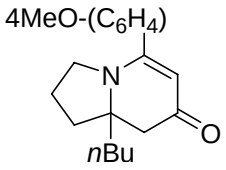


(*R*)-7-(4-Bromo-phenyl)-8a-methyl-2,3,8,8a-tetrahydro-1H-indolizin-5-one (6c): 82% ee by HPLC (Chiralcel ODH, Hex:*i*PrOH;85:15, 1 ml/min, RT_{major} = 7.5 min, RT_{minor} = 8.2 min); $[\alpha]_D$ = +107.0° ($CHCl_3$, c=0.3); R_f = 0.45 (EtOAc 100%); IR (Thin Film) ν 2967, 2882, 1645, 1595, 1459, 1434 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (2H, d, *J* = 8.5 Hz), 7.32 (2H, d, *J* = 8.5 Hz), 6.26 (1H, d, *J* = 1.5 Hz), 3.66-3.54 (2H, m), 2.77 (1H, d, *J* = 16.5 Hz), 2.71 (1H, dd, *J* = 16.5, 1.5 Hz), 2.10-1.70 (4H, m), 1.22 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1, 146.5, 137.4, 132.1, 127.6, 123.7, 120.4, 61.0, 43.9, 41.0, 40.2, 23.7, 21.6.

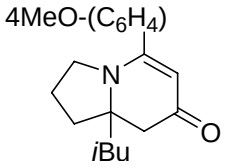


(*S*)-5-(2-Methoxy-vinyl)-8a-methyl-2,3,8,8a-tetrahydro-1H-indolizin-7-one (7d): Flash Chromatography (Hex:EtOAc;1:6) yielded a yellow syrup (58%); 91% ee by HPLC (Chiralcel ODH, Hex:*i*PrOH;80:20, 1 ml/min, RT_{major} = 9.3 min, RT_{minor} = 14.4 min);: $[\alpha]_D$ = +342.0° ($CHCl_3$, c=1.3); R_f = 0.25 (EtOAc 100%); IR (Thin Film) ν 2965, 2871, 1627, 1530, 1495, 1277,

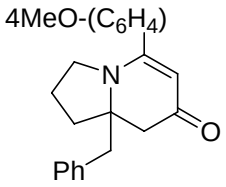
1009 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.11 (1H, d, *J* = 12.5 Hz), 5.26 (1H, d, *J* = 12.5 Hz), 5.03 (1H, s), 3.65 (3H, s), 3.62-3.55 (1H, m), 3.43-3.35 (1H, m), 2.50 (1H, d, *J* = 16.0 Hz), 2.26 (1H, d, *J* = 16.0 Hz), 2.05-1.93 (3H, m), 1.84-1.75 (1H, m), 1.21 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.4, 157.5, 156.8, 99.5, 91.5, 62.6, 57.8, 48.5, 47.7, 40.0, 22.6, 20.5; MS (FAB) *m/e* (rel intensity) 208 (100), 207 (39), 155 (23), 154 (76), 139 (10), 138 (25), 137 (46), 136 (43); HRMS (FAB) *m/e* calcd ($M+H^+$) 208.1332, found 208.1337.



(*S*)-8a-Butyl-5-(4-methoxy-phenyl)-2,3,8,8a-tetrahydro-1H-indolizin-7-one (9b): Flash Chromatography (Hexanes:EtOAc;1:6) yielded a clear syrup (71%); 90% ee by HPLC (Chiralcel ODH, Hex:*i*PrOH; 80:20, 1 ml/min, RT_{major} = 6.6 min, RT_{minor} = 9.5 min); $[\alpha]_D = 305.0^o$ ($CHCl_3$, c=0.8); R_f = 0.35 (100% EtOAc); IR (Thin Film) ν 2956, 1605, 1626, 1578, 1508, 1453, 1243, 1173 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (2H, d, *J* = 8.0 Hz), 6.88 (2H, d, *J* = 8.0 Hz), 5.07 (1H, s), 3.81 (3H, s), 3.48 (1H, ddd, *J* = 11.0, 7.5, 7.5 Hz), 3.23 (1H, ddd, *J* = 11.0, 5.0, 5.0 Hz), 2.62 (1H, d, *J* = 16.5 Hz), 2.31 (1H, d, *J* = 16.5 Hz), 2.11-2.04 (1H, m), 1.90-1.72 (5H, m), 1.44-1.16 (4H, m), 0.87 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.2, 161.9, 161.4, 129.9, 129.4, 114.1, 99.1, 65.5, 55.6, 52.1, 45.8, 36.8, 34.2, 26.6, 25.0, 23.3, 14.3; HRMS (ESI) *m/e* calcd (M^+) 300.1958, found 300.1960.

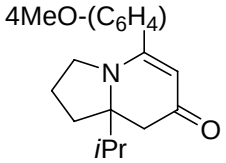


(*S*)-8a-Isobutyl-5-(4-methoxy-phenyl)-2,3,8,8a-tetrahydro-1H-indolizin-7-one (9c): Flash Chromatography (Hexanes:EtOAc;1:6) yielded a clear syrup (75%); 94% ee by HPLC (Chiralcel ODH, Hex:*i*PrOH; 80:20, 1 ml/min, RT_{major} = 6.7 min, RT_{minor} = 10.4 min); $[\alpha]_D = 314.0^o$ ($CHCl_3$, c=1.0); R_f = 0.33 (100% EtOAc); IR (Thin Film) ν 2955, 1606, 1627, 1508, 1456, 1246, 1174 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (2H, d, *J* = 7.0 Hz), 6.88 (2H, d, *J* = 7.0 Hz), 5.11 (1H, s), 3.81 (3H, s), 3.52 (1H, ddd, *J* = 11.0, 7.5, 7.5 Hz), 3.23 (1H, ddd, *J* = 11.0, 5.5, 5.5 Hz), 2.62 (1H, d, *J* = 16.0 Hz), 2.31 (1H, d, *J* = 16.0 Hz), 2.15-2.08 (1H, m), 1.91-1.81 (4H, m), 1.77-1.68 (1H, m), 1.60 (1H, dd, *J* = 14.0, 7.0 Hz), 0.95 (3H, d, *J* = 6.5 Hz), 0.93 (3H, d, *J* = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.3, 161.9, 161.4, 129.9, 129.3, 114.1, 99.4, 65.8, 55.6, 45.7, 42.7, 37.7, 25.4, 25.0, 24.8, 24.3; HRMS (ESI) *m/e* calcd (M^+) 300.1958, found 300.1944.

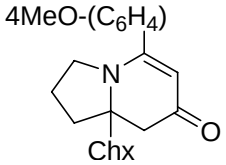


(*S*)-8a-Benzyl-5-(4-methoxy-phenyl)-2,3,8,8a-tetrahydro-1H-indolizin-7-one (9d): Flash Chromatography (Hex:EtOAc;1:6) yielded a light yellow solid (80%); 92% ee by HPLC (Chiralcel ODH, Hex:*i*PrOH;85:15, 1 ml/min, RT_{major} = 13.4 min, RT_{minor} = 19.5 min); $[\alpha]_D = 235.0^o$ ($CHCl_3$, c=1.1); R_f = 0.25 (EtOAc 100%); IR (Thin Film) ν 2962, 1625, 1605, 1508, 1454,

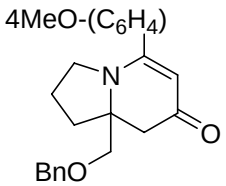
1245, 1175, 1027 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (2H, d, *J* = 7.0 Hz), 7.32-7.23 (3H, m), 7.18 (2H, d, *J* = 8.0 Hz), 6.89 (2H, d, *J* = 8.0 Hz), 5.25 (1H, s), 3.81 (3H, s), 3.34 (1H, d, *J* = 13.5 Hz), 3.13-3.10 (1H, m), 3.15-2.97 (1H, m), 2.78 (1H, d, *J* = 13.0 Hz), 2.65 (1H, d, *J* = 16.0 Hz), 2.34 (1H, d, *J* = 16.0 Hz), 2.30-2.22 (1H, m), 1.78-1.69 (2H, m), 1.65-1.60 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.2, 161.8, 161.6, 137.1, 131.2, 130.2, 128.9, 128.3, 126.9, 114.1, 99.4, 65.9, 55.6, 52.4, 46.5, 39.0, 35.7, 24.5; HRMS (FAB) *m/e* calcd ($M+H^+$) 334.1786, found 334.1795.



(*S*)-8a-Isopropyl-5-(4-methoxy-phenyl)-2,3,8,8a-tetrahydro-1H-indolizin-7-one (9e): Flash Chromatography (Hexanes:EtOAc;1:3) yielded a yellow syrup (50%); 91% ee by HPLC (Chiralcel ODH, Hex:*i*PrOH; 85:15, 1 ml/min, RT_{major} = 8.8 min, RT_{minor} = 10.3 min); $[\alpha]_D$ = +320.0° ($CHCl_3$, c=0.9); R_f = 0.40 (100% EtOAc); IR (Thin Film) ν 2966, 2874, 1627, 1606, 1508, 1453, 1243 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (2H, d, *J* = 8.0 Hz), 6.88 (2H, d, *J* = 8.0 Hz), 5.14 (1H, s), 3.81 (3H, s), 3.41 (1H, ddd, *J* = 10.5, 8.5, 8.0 Hz), 3.31 (1H, ddd, *J* = 10.5, 5.5, 3.5 Hz), 2.65 (1H, sept, *J* = 7.0 Hz), 2.64 (1H, d, *J* = 16.5 Hz), 2.50 (1H, d, *J* = 16.5 Hz), 2.12-2.01 (1H, m), 1.90-1.82 (2H, m), 1.64-1.58 (1H, m), 0.98 (3H, d, *J* = 7.0 Hz), 0.90 (3H, d, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.1, 162.4, 161.6, 130.1, 129.4, 114.1, 99.3, 69.0, 55.6, 54.0, 44.1, 31.5, 28.7, 25.5, 17.6, 17.5; MS (EI) *m/e* (rel intensity) 286 (100), 285 (15), 242 (48); HRMS (ESI) *m/e* calcd (M^+) 286.1807, found 286.1808.

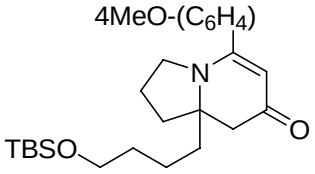


8a-Cyclohexyl-5-(4-methoxy-phenyl)-2,3,8,8a-tetrahydro-1H-indolizin-7-one (9f): Flash Chromatography (Hexanes:EtOAc;1:4) yielded a light yellow syrup (19%); 87% ee by HPLC (Chiralcel ODH, Hex:*i*PrOH; 85:15, 1 ml/min, RT_{major} = 8.6 min, RT_{minor} = 15.9 min); $[\alpha]_D$ = 206.0° ($CHCl_3$, c=0.8); R_f = 0.25 (EtOAc 100%); IR (Thin Film) ν 2928, 2851, 1605, 1577, 1535, 1507, 1452, 1247, 1174 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (2H, d, *J* = 8.5 Hz), 6.89 (2H, d, *J* = 8.5 Hz), 5.10 (1H, s), 3.82 (3H, s), 3.37 (1H, ddd, *J* = 10.0, 8.0, 8.0 Hz), 3.28 (1H, m, *J* = 10.0, 3.5, 3.5 Hz), 2.60 (1H, d, *J* = 16.5 Hz), 2.51 (1H, d, *J* = 16.5 Hz), 2.28-2.20 (1H, m), 2.11 (1H, ddd, *J* = 12.0, 9.0, 9.0 Hz), 1.90-1.56 (8H, m), 1.25-0.90 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.3, 162.3, 161.6, 130.2, 129.5, 114.1, 99.2, 68.6, 55.6, 53.9, 43.9, 39.4, 33.1, 27.6, 27.3, 26.7, 26.6, 26.5, 25.7; HRMS (ESI) *m/e* calcd (M^+) 326.2115, found 326.2100.

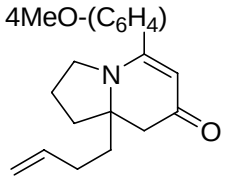


(*S*)-8a-Benzyloxymethyl-5-(4-methoxy-phenyl)-2,3,8,8a-tetrahydro-1H-indolizin-7-one (9g): Flash Chromatography (Hex:EtOAc;1:6) yielded a yellow syrup (77%); 92% ee by HPLC

(Chiralcel ODH, Hex:*i*PrOH; 80:20, 1 ml/min, RT_{major} = 11.3 min, RT_{minor} = 14.1 min); $[\alpha]_D$ = 165.0° ($CHCl_3$, c=1.0); R_f = 0.26 (EtOAc 100%); IR (Thin Film) ν 2965, 2870, 1626, 1606, 1509, 1453, 1246, 1175, 1106, 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33-7.24 (7H, m), 6.87 (2H, d, *J* = 8.0 Hz), 5.05 (1H), 4.54 (1H, d, *J* = 12.0 Hz), 4.50 (1H, d, *J* = 12.0 Hz), 3.82 (1H, d, *J* = 10.0 Hz), 3.80 (3H, s), 3.60-3.52 (1H, m), 3.47 (1H, d, *J* = 10.0 Hz), 3.23-3.17 (1H, m), 2.63 (1H, d, *J* = 16.0 Hz), 2.45 (1H, d, *J* = 16.0 Hz), 2.44-2.35 (1H, m), 2.00-1.75 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.5, 162.1, 161.4, 138.4, 130.0, 129.1, 128.6, 127.8, 127.6, 114.0, 99.0, 73.7, 70.3, 65.5, 55.6, 52.2, 43.6, 35.5, 24.6; HRMS (FAB) *m/e* calcd ($M+H^+$) 364.1907, found 364.1907.

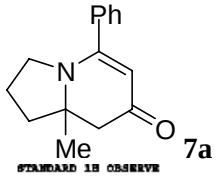


(*S*)-8a-[4-(tert-Butyl-dimethyl-silanyloxy)-butyl]-5-(4-methoxy-phenyl)-2,3,8,8a-tetrahydro-1H-indolizin-7-one (9h): Flash Chromatography (Hexanes:EtOAc;1:6) yielded a clear syrup (74%); 88% ee by HPLC (Chiralcel ADH, Hex:*i*PrOH; 90:10, 1 ml/min, RT_{major} = 8.3 min, RT_{minor} = 7.8 min); $[\alpha]_D$ = +138.0° ($CHCl_3$, c=0.9); R_f = 0.23 (100% EtOAc); IR (Thin Film) ν 2933, 1605, 1507, 1461, 1246, 1174, 1026 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37 (2H, d, *J* = 8.5 Hz), 6.90 (2H, d, *J* = 8.5 Hz), 5.12 (1H, s), 3.84 (3H, s), 3.66-3.58 (2H, m), 3.56-3.46 (1H, m), 3.27 (1H, ddd, *J* = 11.0, 5.0, 5.0 Hz), 2.68 (1H, d, *J* = 16.5 Hz), 2.35 (1H, d, *J* = 16.5 Hz), 2.20-2.04 (1H, m), 1.95-1.76 (5H, m), 1.60-1.35 (4H, m), 0.89 (9H, s), 0.04 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.2, 162.2, 161.5, 130.0, 129.3, 114.1, 99.2, 65.6, 63.1, 55.6, 52.4, 45.9, 36.7, 34.3, 33.3, 26.2, 25.0, 20.9, 18.6, -5.0; MS (EI) *m/e* (rel intensity) 431 (32), 430 (100), 428 (13), 372 (18), 243 (21), 242 (53); HRMS (EI) *m/e* calcd (M^+) 430.2777, found 430.2765.

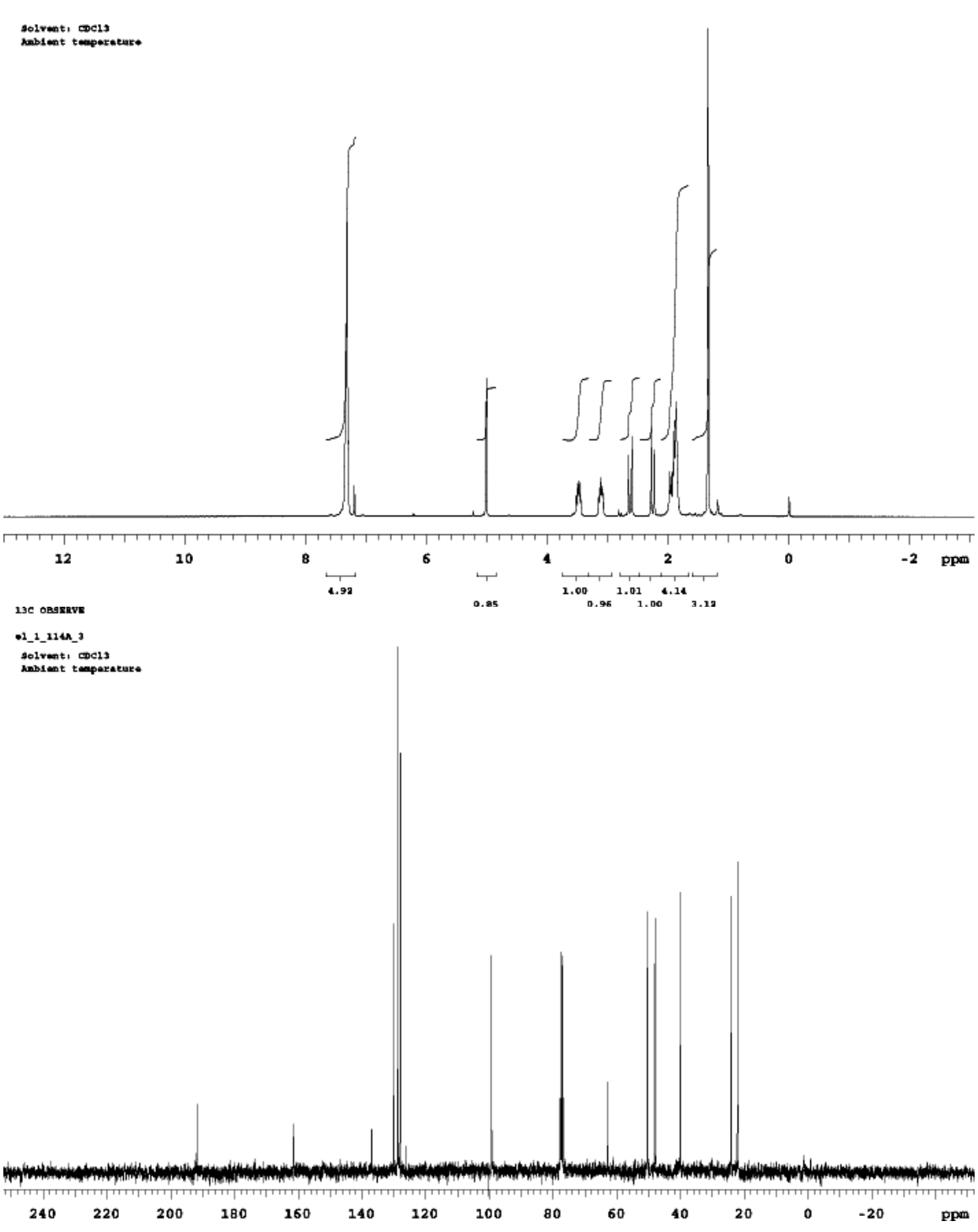


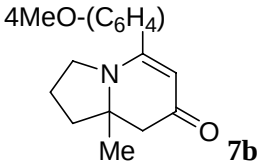
(*S*)-8a-But-3-enyl-5-(4-methoxy-phenyl)-2,3,8,8a-tetrahydro-1H-indolizin-7-one (9i): Flash Chromatography (Hexanes:EtOAc;1:6) yielded a clear syrup (75%); 91% ee by HPLC (Chiralcel ODH, Hex:*i*PrOH;85:15, 1 ml/min, RT_{major} = 9.6 min, RT_{minor} = 15.5 min); $[\alpha]_D$ = +288.0° ($CHCl_3$, c=1.0); R_f = 0.20 (100% EtOAc); IR (Thin Film) ν 2969, 2872, 1605, 1578, 1537, 1508, 1454, 1244, 1175, 1028, 913 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (2H, d, *J* = 8.0 Hz), 6.87 (2H, d, *J* = 8.0 Hz), 5.76 (1H, ddt, *J* = 17.0, 10.5, 6.5 Hz), 5.09 (1H, s), 5.00 (1H, dd, *J* = 17.0, 1.5 Hz), 4.92 (1H, dd, *J* = 10.5, 1.0 Hz), 3.80 (3H, s), 3.49 (1H, ddd, *J* = 11.0, 7.5, 3.5 Hz), 3.24 (1H, ddd, *J* = 11.0, 5.5, 5.5 Hz), 2.64 (1H, d, *J* = 16.5 Hz), 2.31 (1H, d, *J* = 16.5 Hz), 2.25-2.00 (3H, m), 1.94-1.75 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.0, 162.1, 161.5, 138.1, 130.0, 129.2, 115.1, 114.1, 99.4, 65.3, 55.6, 52.3, 45.7, 36.8, 33.7, 28.9, 25.0; MS (EI) *m/e* (rel intensity) 298 (100), 297 (23), 243 (20), 242 (18), 154 (22), 137 (13), 136 (13); HRMS (ESI) *m/e* calcd (M^+) 298.1807, found 298.1808.

I.9 ^{1}H and ^{13}C NMR Spectra for [2+2+2] Products from Aryl Alkynes

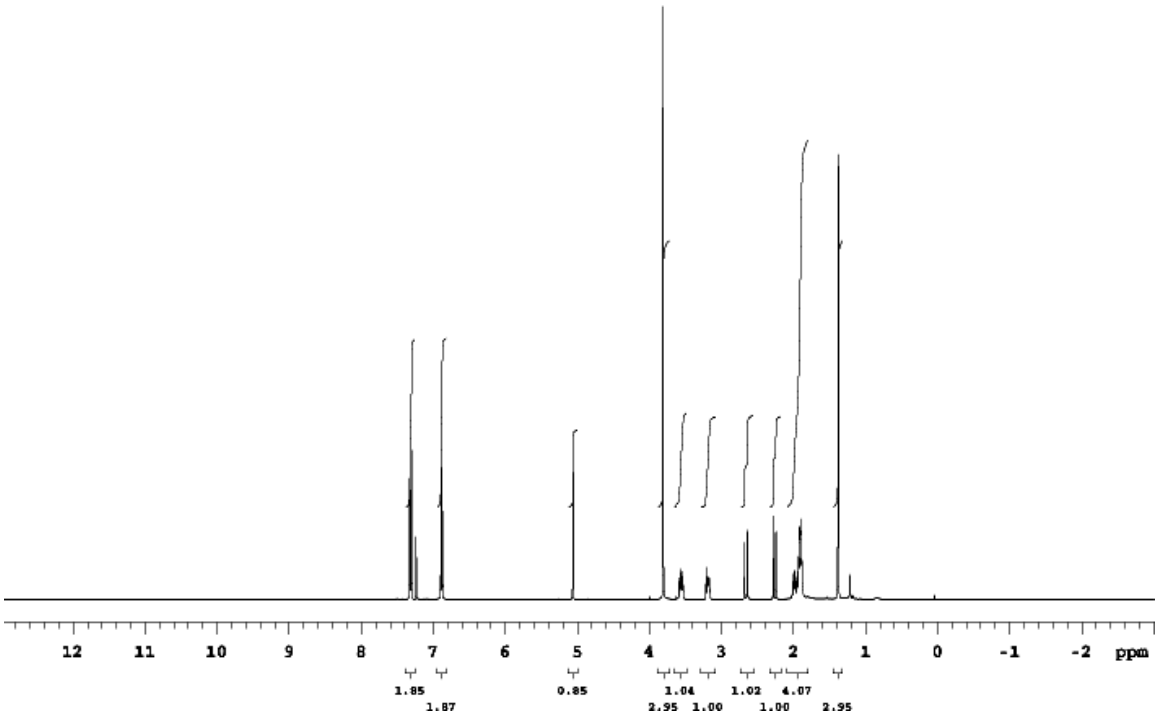


7a




4MeO-(C6H4)
N
O
Me

7b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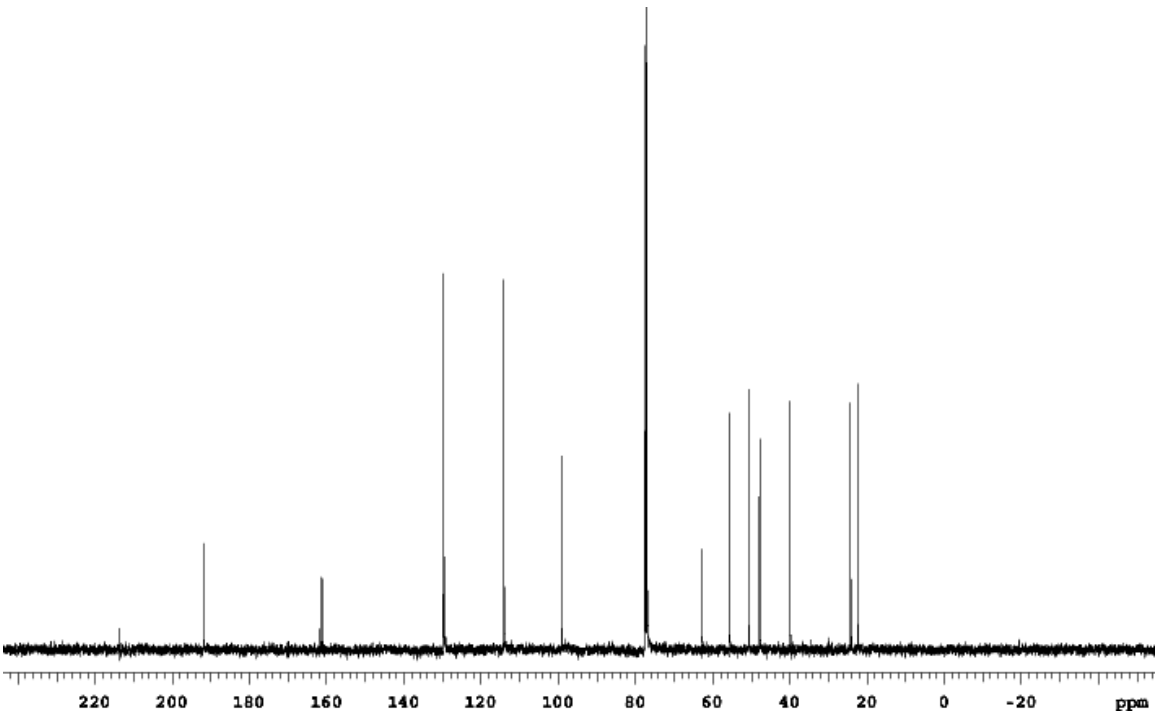
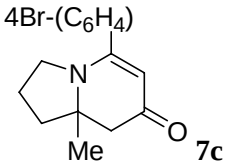
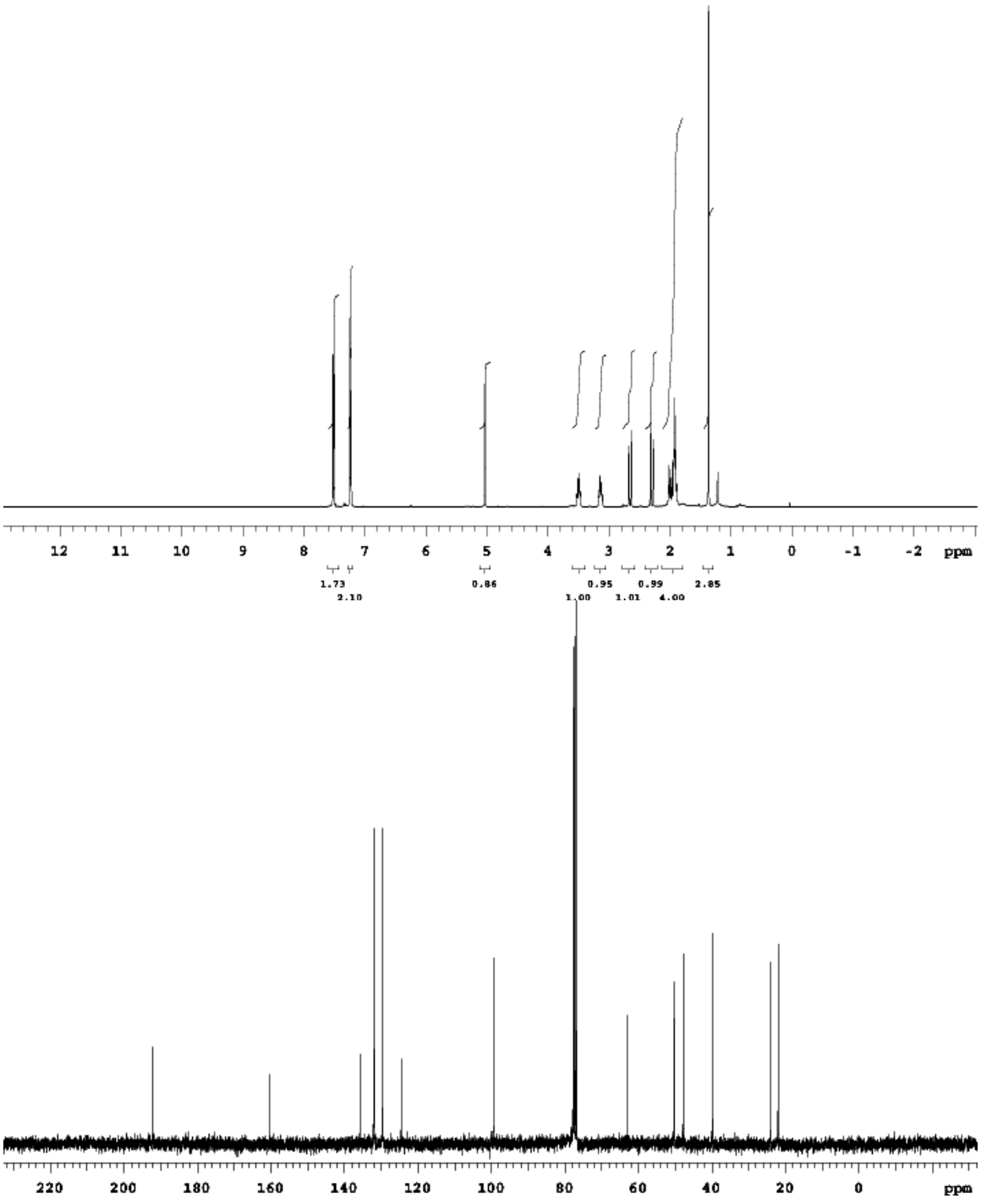
1.87
0.85
2.95
1.04
1.00
1.02
1.00
4.07
2.95


220 200 180 160 140 120 100 80 60 40 20 0 -20 ppm


4Br-(C6H4)
N
O
Me

7c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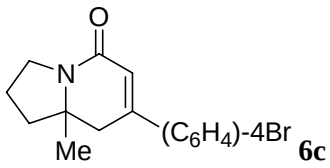
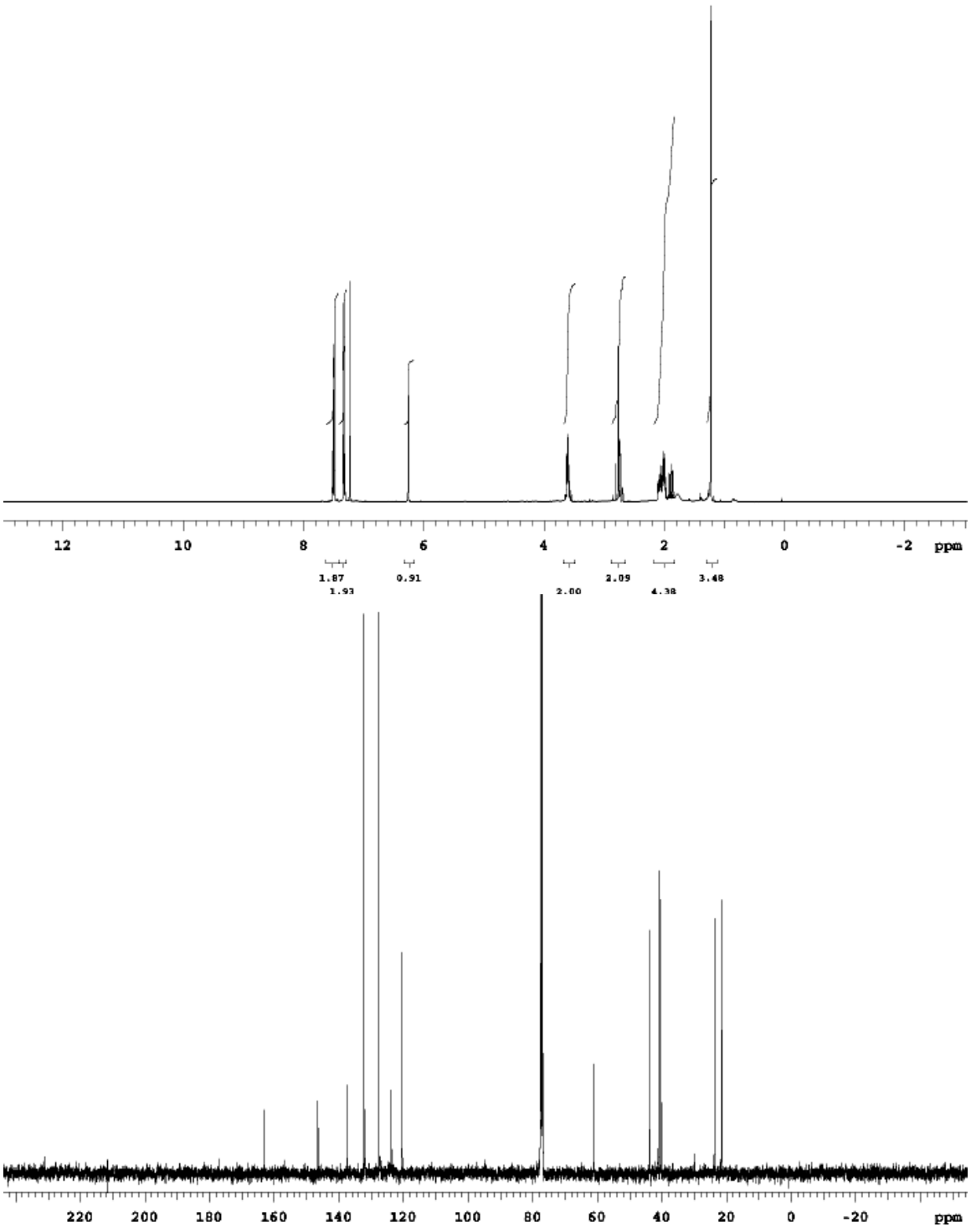
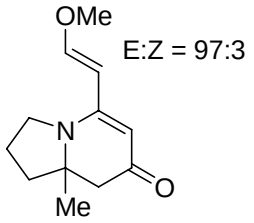
2.10
0.86
0.95
1.00
1.01
0.99
4.00
2.85
220 200 180 160 140 120 100 80 60 40 20 0 ppm


O
N
Me
(C6H4)-4Br

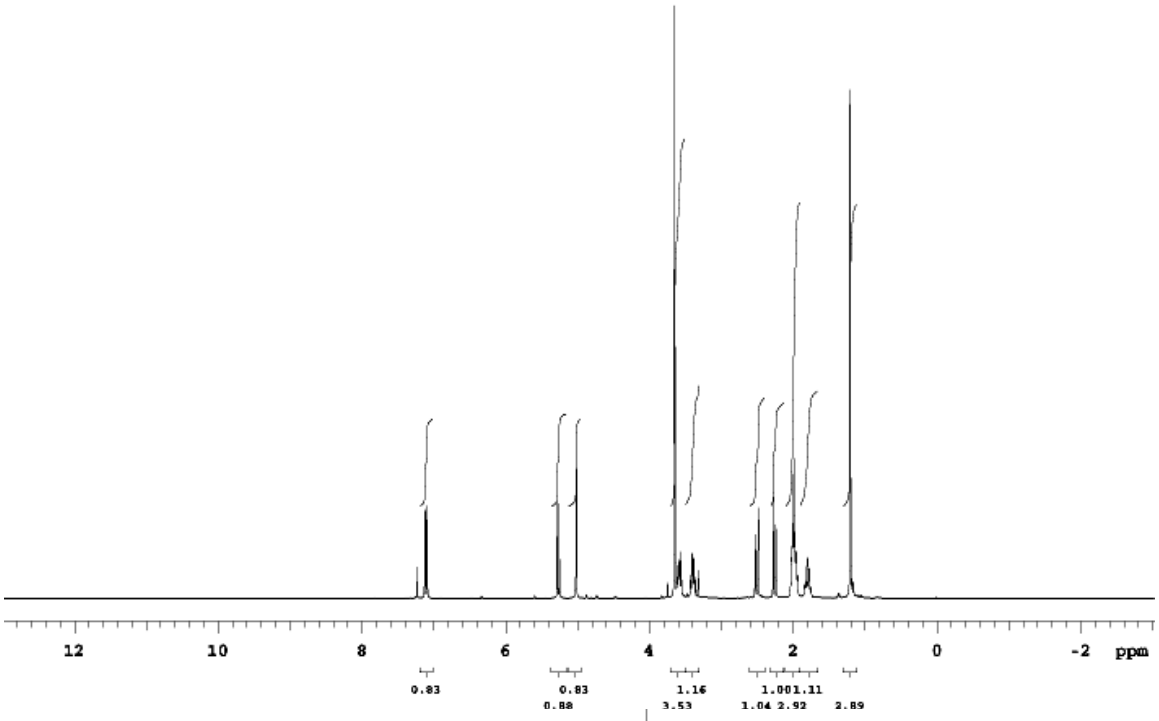
6c


12
10
8
6
4
2
0
-2
ppm
1.87
1.93
0.91
2.00
2.09
4.38
3.48
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm


OMe
N
O
Me

E:Z = 97:3

7d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10
8
6
4
2
0
-2
ppm
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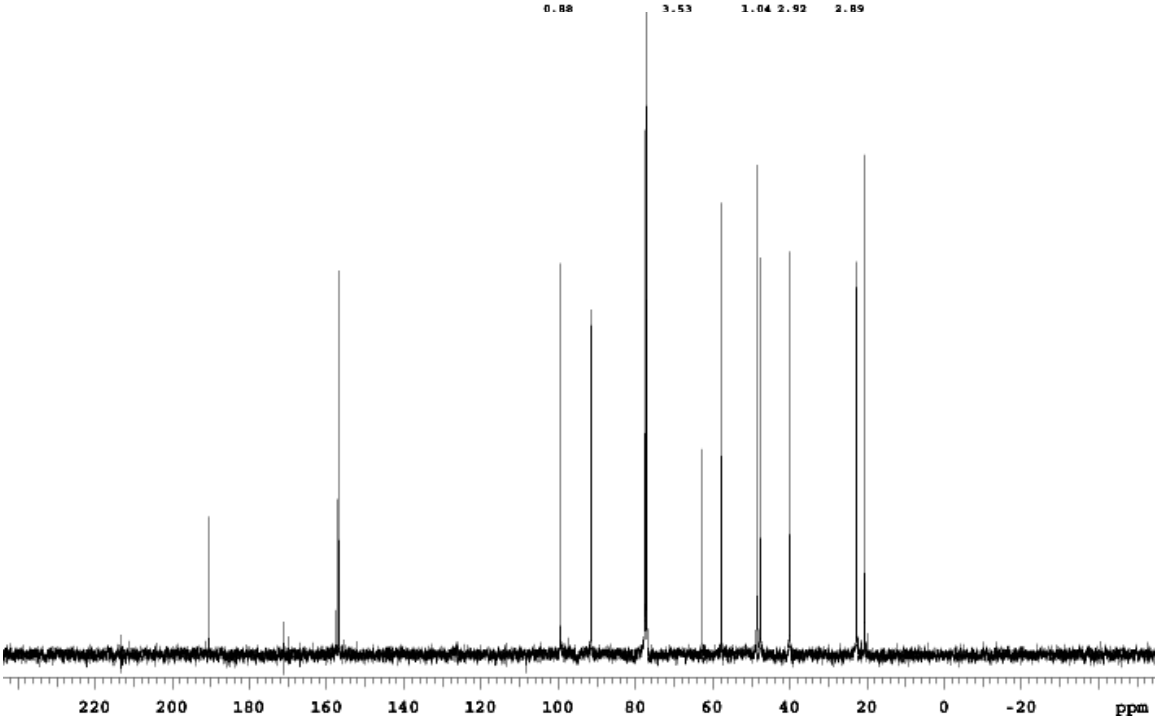
0.83
0.88
1.16
3.53
1.00
1.11
1.04
2.92
2.89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200
180
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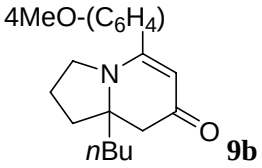
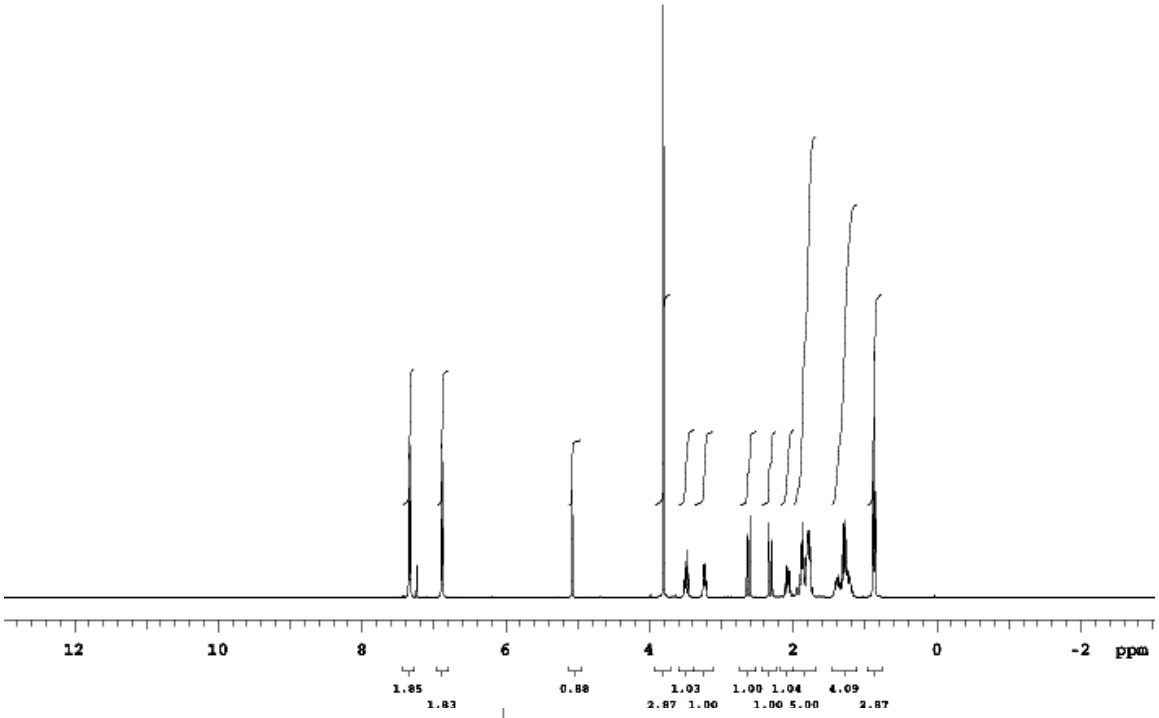
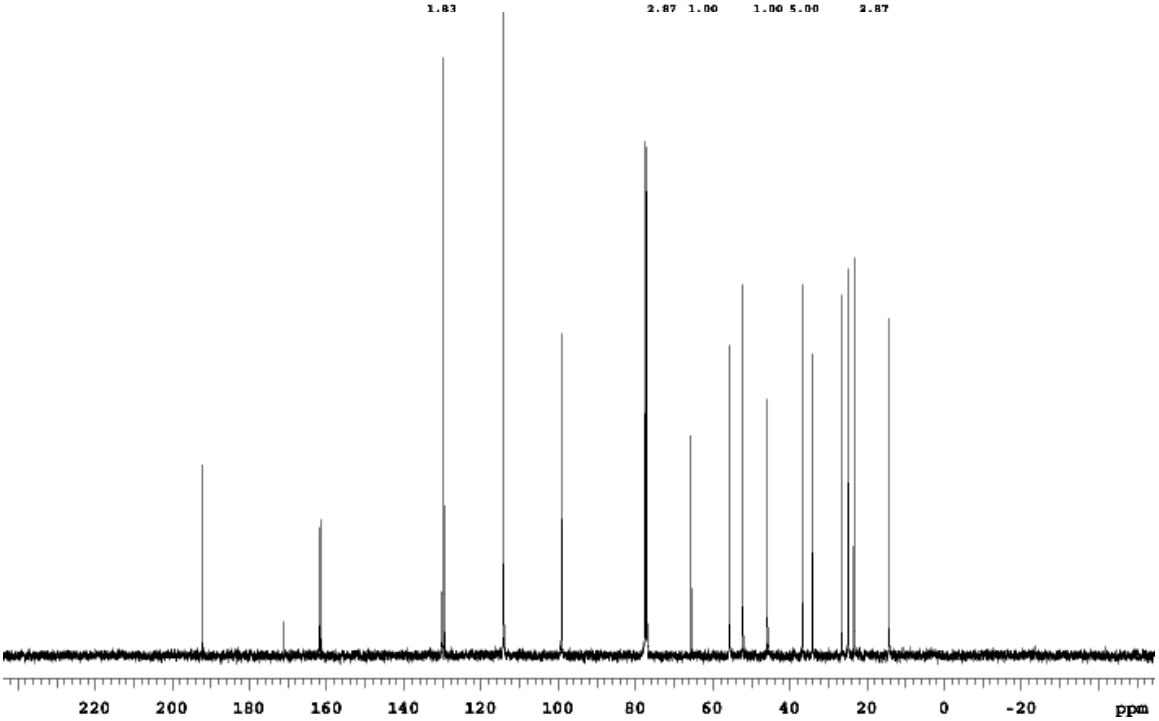
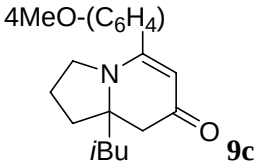
140
120
100
80
60
40
20
0
-20
ppm


4MeO-(C6H4)
N
O
nBu

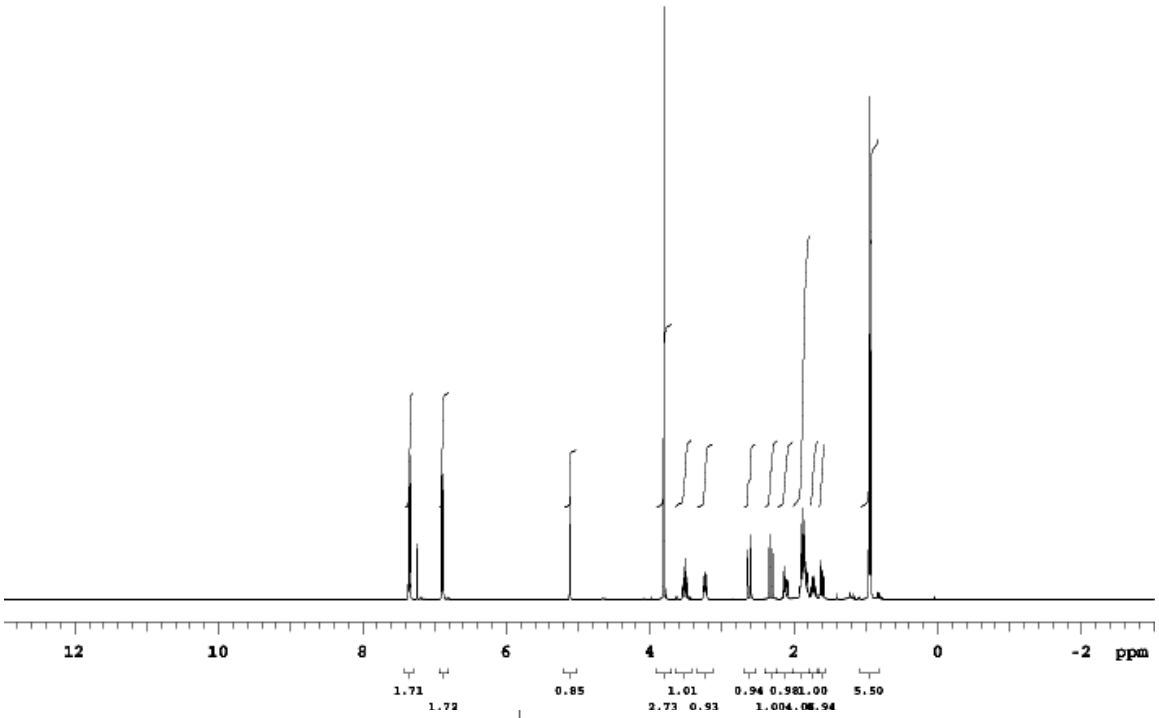
9b


12
10
8
6
4
2
0
-2
ppm
1.85
1.83
0.88
1.03
2.87 1.00
1.00 1.04
1.00 5.00
4.09
2.87


220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm


4MeO-(C6H4)
N
O
iBu

9c


12
10
8
6
4
2
0
-2
ppm
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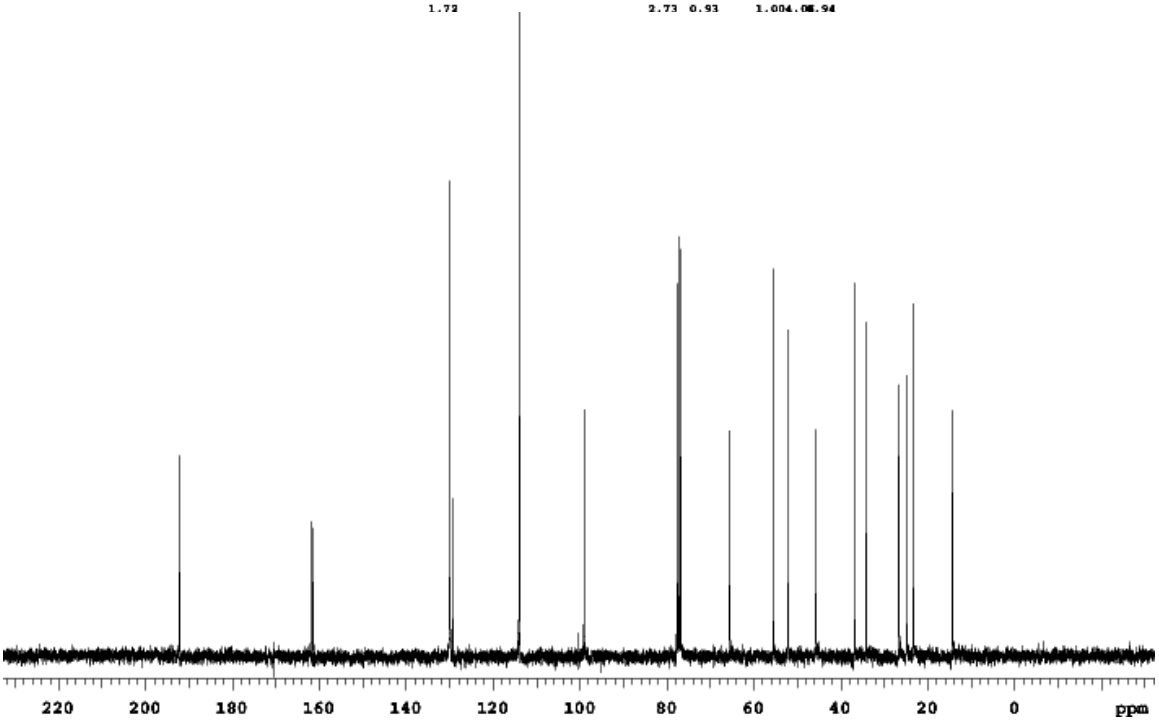
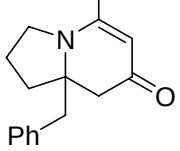
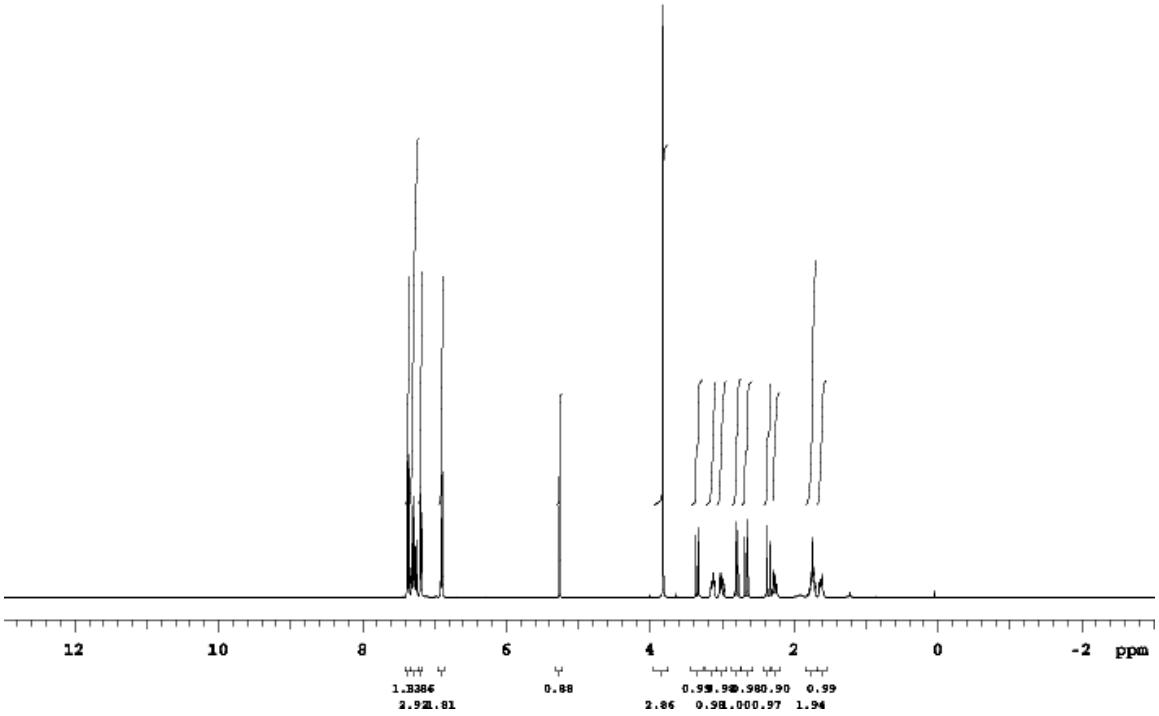
2.73
0.93
0.94
0.98
1.00
1.00
4.94
5.50


220
200
180
160
140
120
100
80
60
40
20
0
ppm

4MeO-(C_6H_4)


N
O
Ph

9d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10
8
6
4
2
0
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ppm
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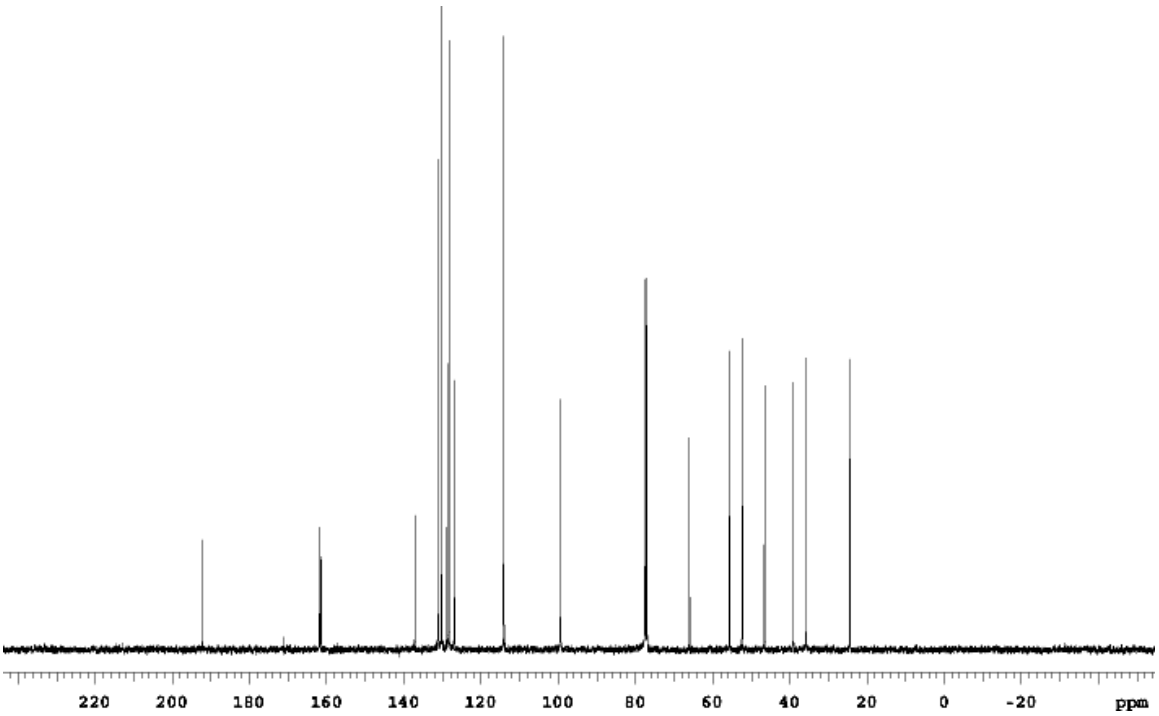
2.92
1.81
0.88
2.86
0.98
1.00
0.97
1.94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100
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20
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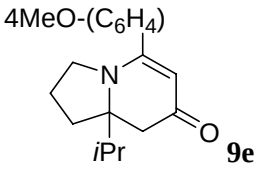
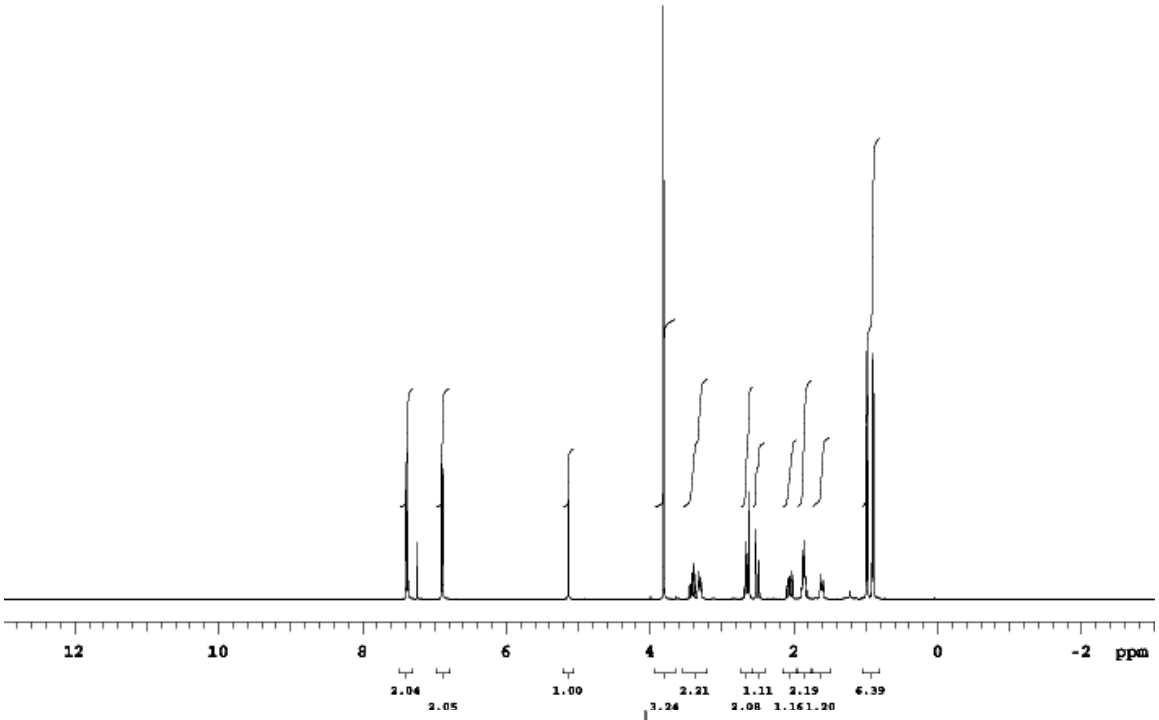
-20
ppm


4MeO-(C6H4)
N
O
iPr

9e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6
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0
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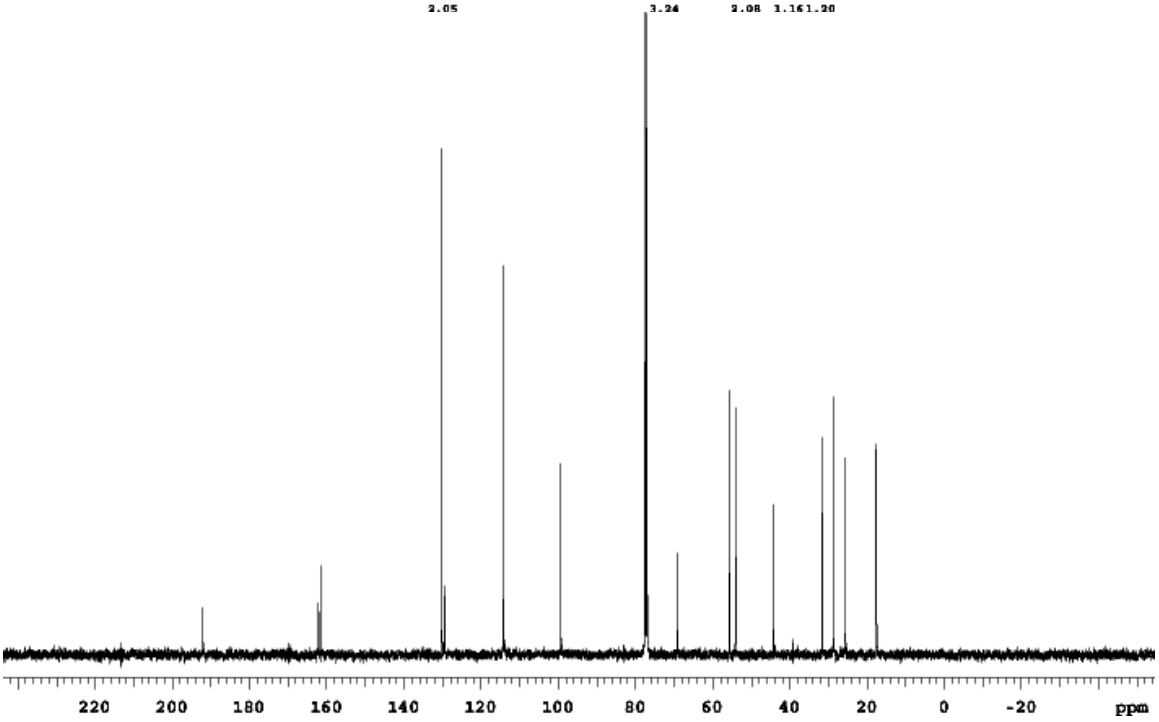
1.00
3.24
2.21
1.11
2.08
2.19
1.16
1.20
6.39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80
60
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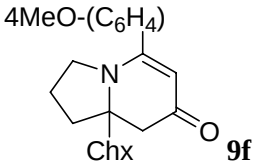
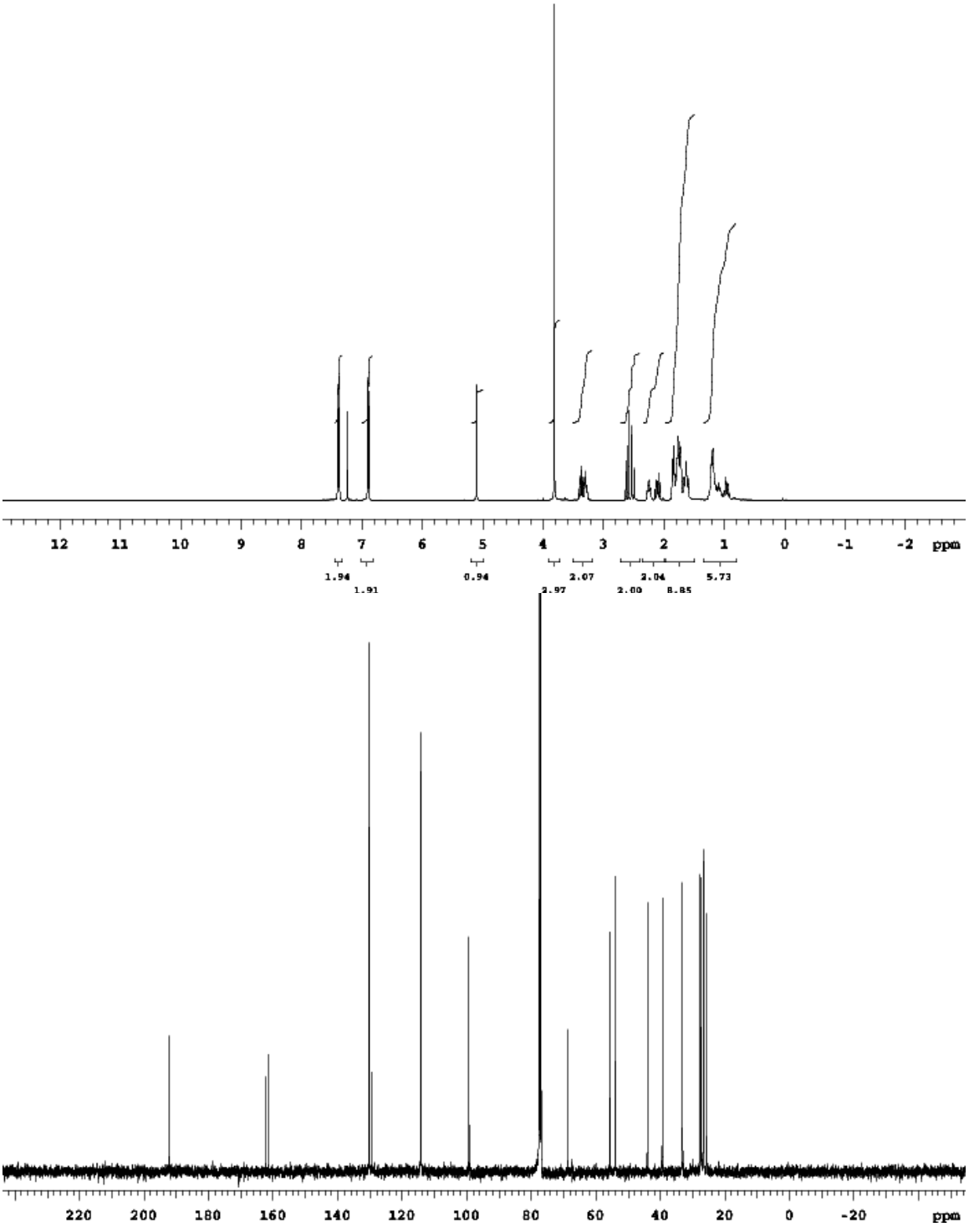
20
0
-20
ppm


4MeO-(C6H4)
N
O
Chx

9f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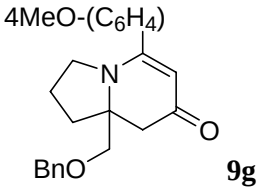
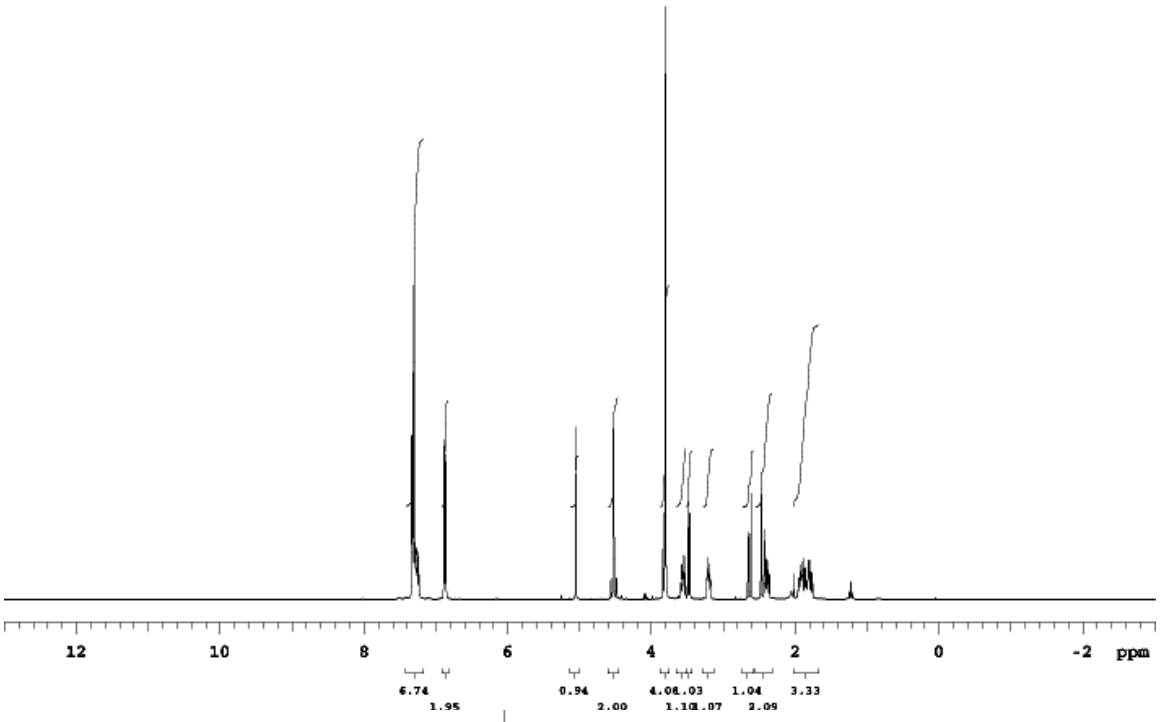
1.91
0.94
2.07
2.97
2.04
2.00
8.85
5.73
220 200 180 160 140 120 100 80 60 40 20 0 -20 ppm


4MeO-(C6H4)
N
O
BnO

9g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8
6
4
2
0
-2
ppm
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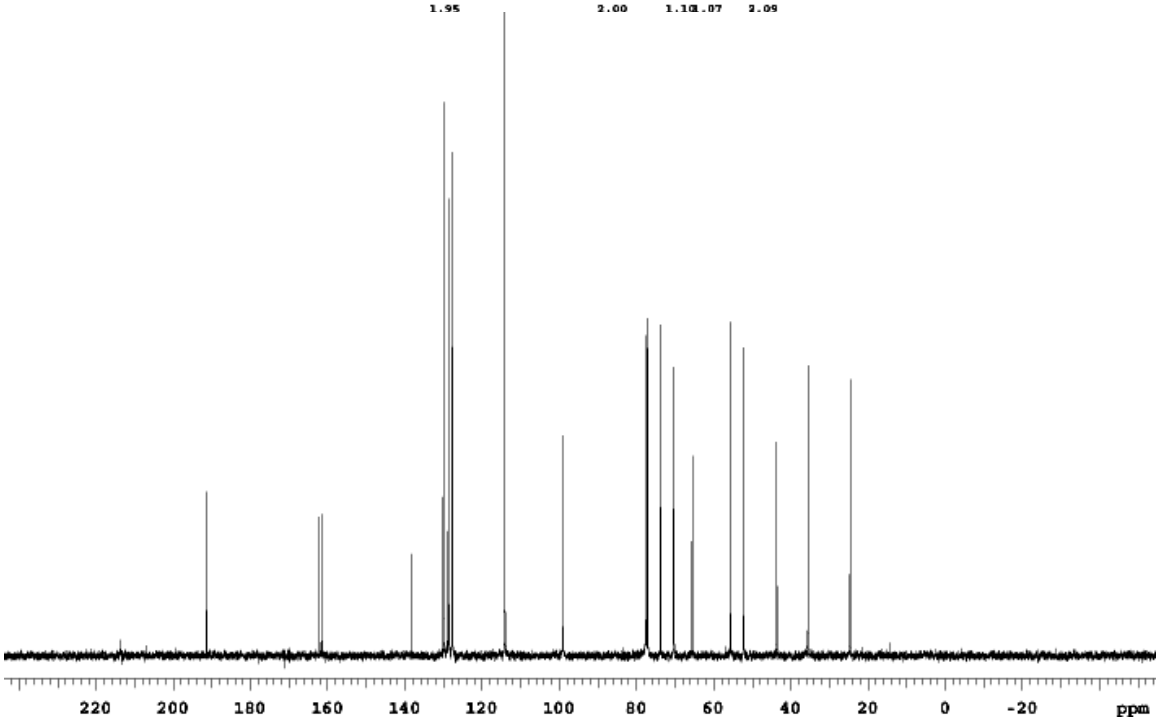
0.94
2.00
4.06
1.03
1.10
1.07
1.04
2.09
3.33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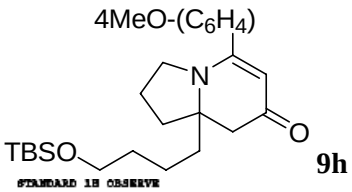
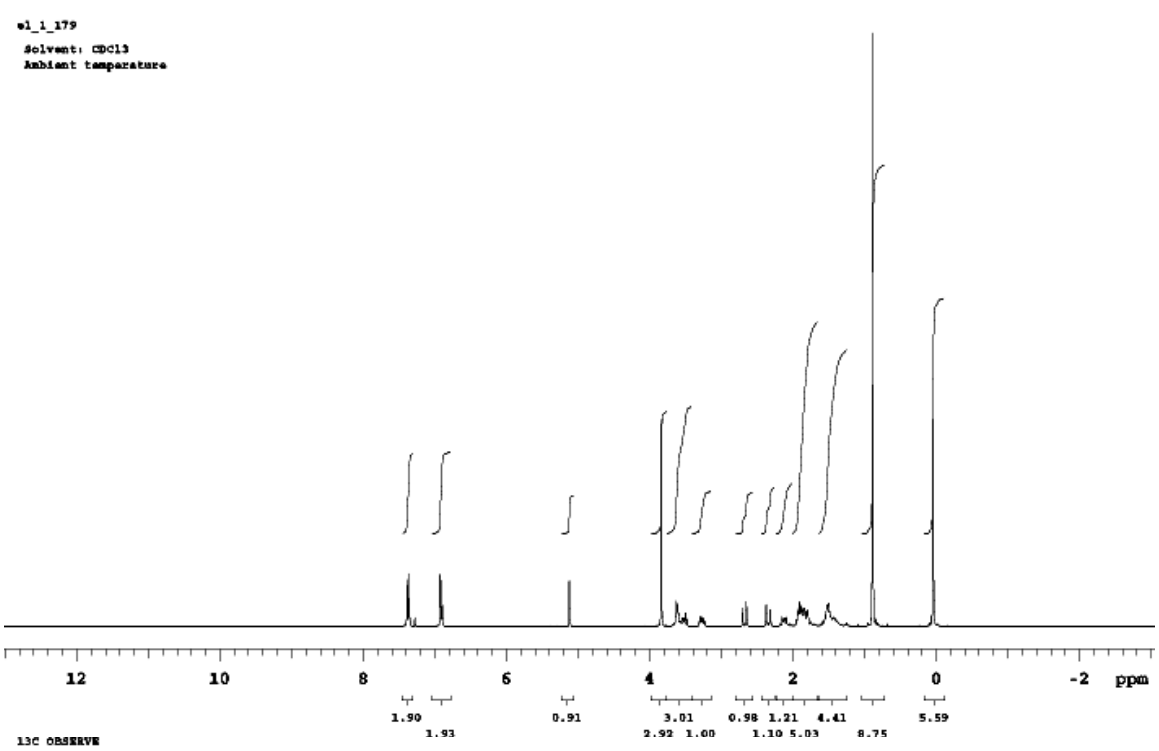
200
180
160
140
120
100
80
60
40
20
0
-20
ppm


4MeO-(C6H4)
N
O
TBSO

9h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el_1_179
Solvent: CDCl3
Ambient temperature
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8
6
4
2
0
-2
ppm
1.90
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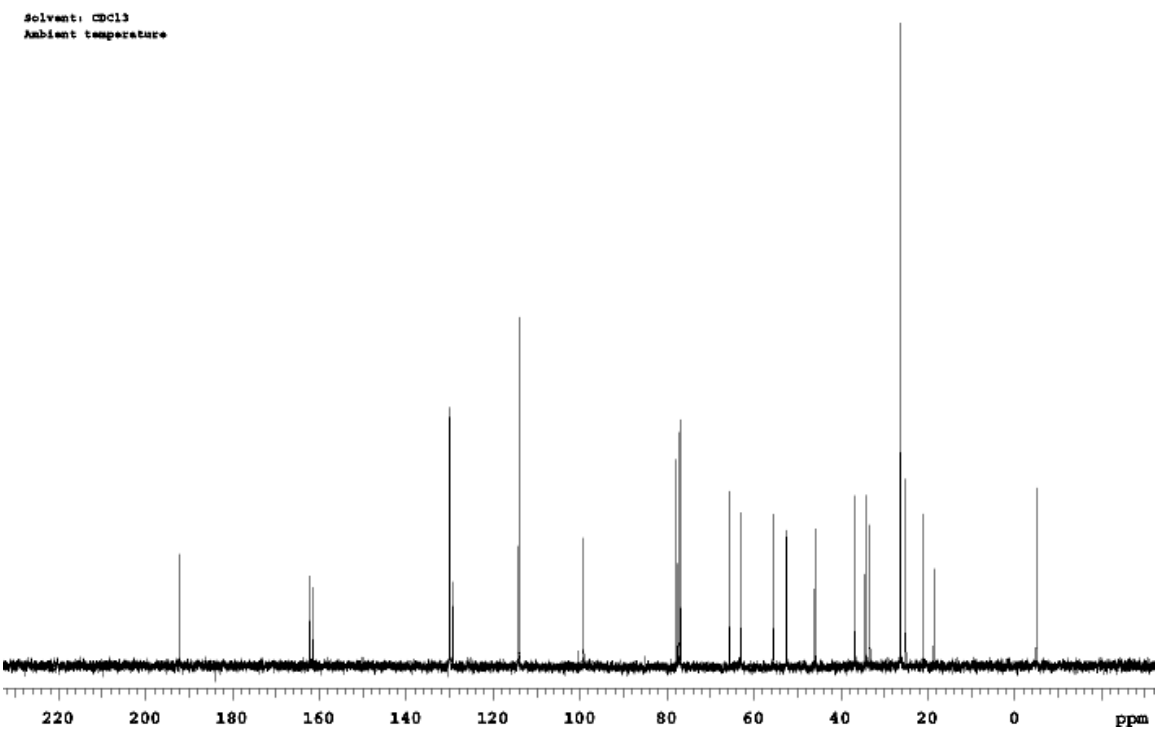
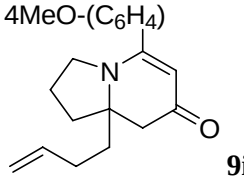
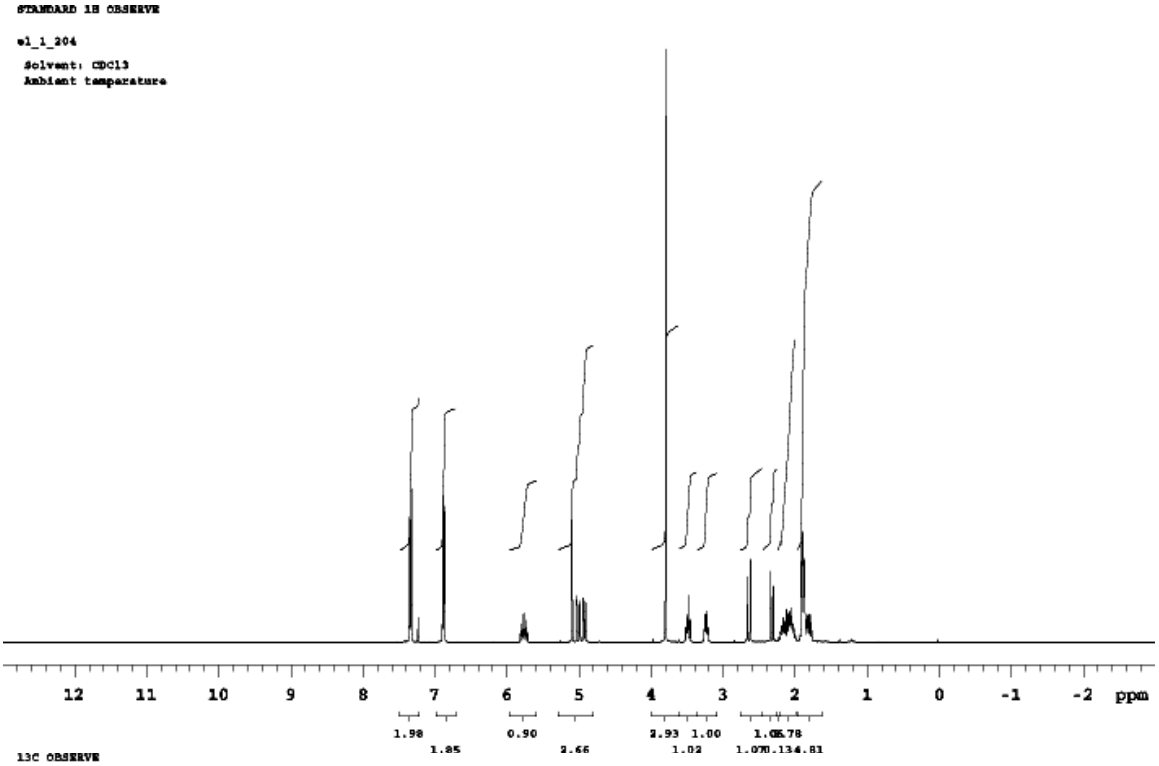
0.91
3.01
2.92
1.00
0.98
1.10
1.21
5.03
4.41
8.75
5.59


13C OBSERVE
Solvent: CDCl3
Ambient temperature
220
200
180
160
140
120
100
80
60
40
20
0
ppm

4MeO-(C_6H_4)


N
O

9i


STANDARD 1H OBSERVE
el_1_204
Solvent: CDCl3
Ambient temperature
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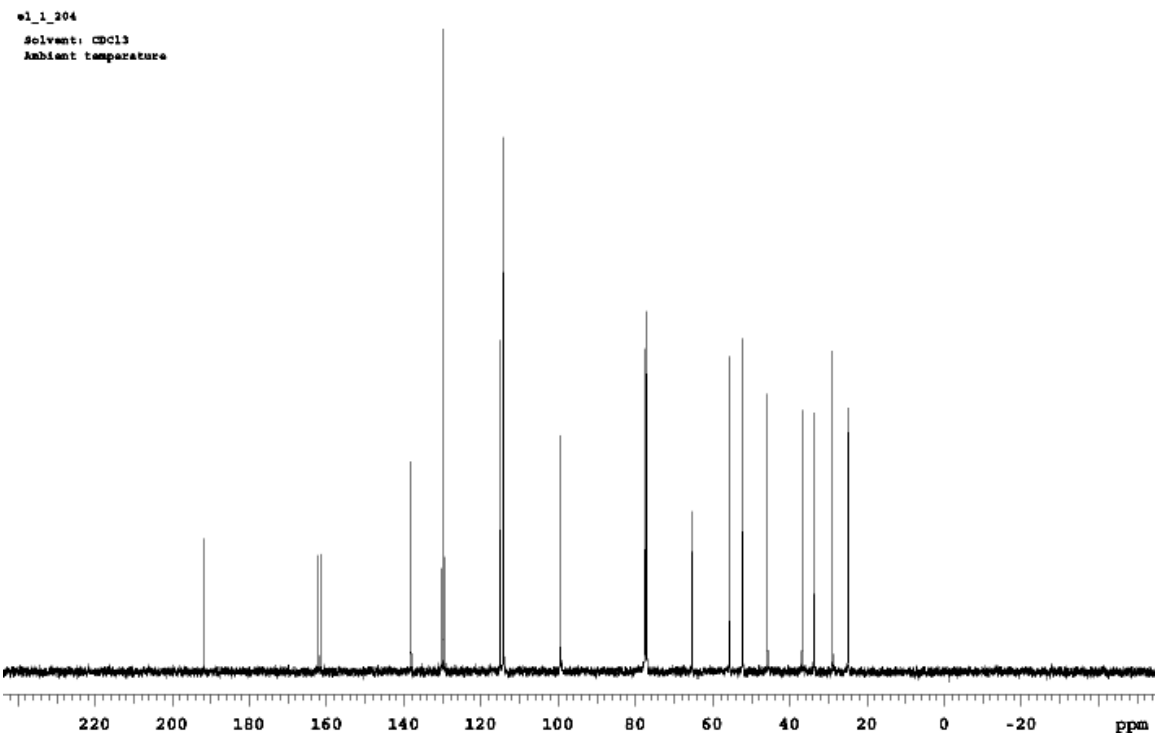
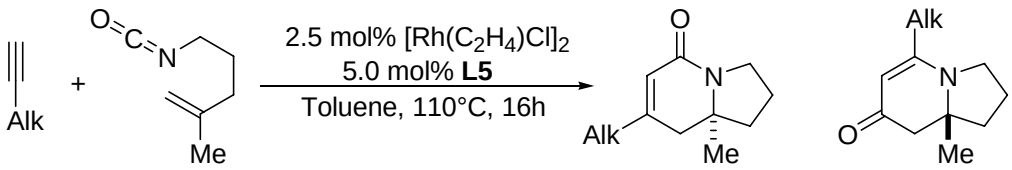
1.85
0.90
2.66
2.93
1.00
1.02
1.07
0.78
1.13
4.81

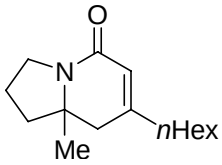

13C OBSERVE
el_1_204
Solvent: CDCl3
Ambient temperature
220 200 180 160 140 120 100 80 60 40 20 0 -20 ppm

I.10 General procedure for [2+2+2] cycloadditions with Alkyl Alkynes.



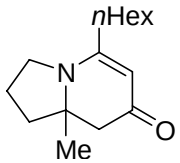
2 (2 eq) **5a** (*R*)-**6** (*S*)-**7**

In a glovebox under N_2 atmosphere, chlorobis(ethylene)rhodium(I) dimer (2.3 mg, 0.006 mmol) and piperidyl-(xylyl-TADDOL)-phosphoramidite **L5** (8.3 mg, 0.012 mmol) were transferred into a round bottom flasked fitted with a reflux condenser. The system was sealed with a standard septum, removed from the glovebox and flushed with Ar. A solution of alkyne (0.48 mmol) and isocyanate **5a** (0.24 mmol) in toluene (7 mL) was then added. The brown-black solution was then heated to 110 ^{o}C (bath temperature), stirred at reflux for 16 hours under a static atmosphere of Ar, and cooled. The crude mixture was then concentrated and purified by silica gel, column chromatography.



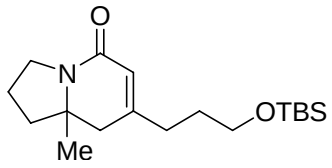
Flash Chromatography (Hexanes:EtOAc;1:3 to 1:8) yielded a clear syrup **6e** (76%) followed by a clear syrup **7h** (12%):

(*R*)-7-Hexyl-8a-methyl-2,3,8,8a-tetrahydro-1H-indolizin-5-one (6e): 91% ee by HPLC (Chiralcel ODH, Hex:*i*PrOH;85:15, 1 ml/min, RT_{major} = 5.2 min, RT_{minor} = 5.7 min); $[\alpha]_D$ = +96.2^{o} ($CHCl_3$, c=1.3); R_f = 0.35 (100% EtOAc); IR (Thin Film) ν 2928, 2858, 1664, 1615, 1426, 1374, 1338 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.67 (1H, m), 3.53-3.48 (2H, m), 2.33 (1H, d, *J* = 16.5 Hz), 2.18 (1H, d, *J* = 16.5 Hz), 2.15-2.08 (2H, m), 2.00-1.86 (3H, m), 1.80-1.72 (1H, m), 1.46-1.38 (2H, m), 1.30-1.20 (6H, m), 1.12 (3H, s), 0.84 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6, 152.3, 119.4, 60.8, 43.7, 41.7, 40.9, 36.9, 31.8, 29.0, 26.7, 23.5, 22.7, 21.6, 14.3; MS (EI) *m/e* (rel intensity) 236 (100), 234 (14), 220 (11), 178 (3), 154 (4), 149 (4), 136 (5); HRMS (ESI) *m/e* calcd (M^+) 236.2014, found 236.2004.



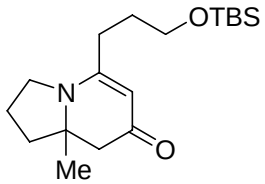
(*S*)-5-Hexyl-8a-methyl-2,3,8,8a-tetrahydro-1H-indolizin-7-one (7e): Flash Chromatography (Hexanes:EtOAc;1:8) yielded a clear syrup (12%); 56% ee by HPLC (Chiralcel ODH, Hex:*i*PrOH;85:15, 1 ml/min, RT_{major} = 7.5 min, RT_{minor} = 8.4 min); $[\alpha]_D$ = +99.0^{o} ($CHCl_3$, c=0.8); R_f = 0.15 (100% EtOAc); IR (Thin Film) ν 2957, 2928, 2870, 1625, 1544, 1487, 1267, 1213,

1100 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.89 (1H, s), 3.60-3.52 (1H, m), 3.47-3.39 (1H, m), 2.48 (1H, d, *J* = 16.0 Hz), 2.28 (1H, d, *J* = 16.0 Hz), 2.20-2.10 (2H, m), 2.08-1.94 (3H, m), 1.84-1.74 (1H, m), 1.52-1.40 (2H, m), 1.35-1.20 (6H, m), 1.17 (3H, s), 0.85 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.1, 163.2, 96.2, 63.1, 48.0, 46.5, 39.7, 34.1, 31.7, 29.1, 27.3, 22.7, 22.4, 20.0, 14.2; MS (EI) *m/e* (rel intensity) 236 (100), 234 (15), 220 (12), 165 (14), 150 (8), 132 (16); HRMS (ESI) *m/e* calcd (M^+) 236.2014, found 236.2011.

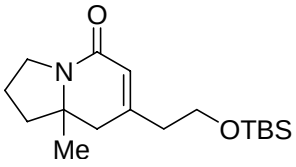


Flash Chromatography (Hex:EtOAc;1:2 to EtOAc 100%) yielded a brown syrup **6f** (63%) followed by a light yellow syrup **7i** (7%):

(*R*)-7-[3-(tert-Butyl-dimethyl-silanyloxy)-propyl]-8a-methyl-2,3,8,8a-tetrahydro-1H-indolizin-5-one (6f): 95% ee by HPLC (Chiralcel ODH, Hex:*i*PrOH;85:15, 1 ml/min, RT_{major} = 8.7 min, RT_{minor} = 10.1 min);: $[\alpha]_D$ = +90.0° ($CHCl_3$, c=0.8); R_f = 0.45 (EtOAc 100%); IR (Thin Film) ν 2954, 2928, 2857, 1664, 1616, 1461, 1427, 1103, 835 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.69 (1H, t, *J* = 1.0 Hz), 3.59 (2H, t, *J* = 6.0 Hz), 3.55-3.46 (2H, m), 2.36 (1H, d, *J* = 17.0 Hz), 2.20 (1H, d, *J* = 17.0 Hz), 2.20-2.15 (2H, m), 1.99-1.89 (3H, m), 1.75-1.63 (3H, m), 1.13 (3H, s), 0.85 (9H, s), 0.00 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 151.9, 119.4, 62.5, 60.8, 43.7, 41.9, 40.9, 33.3, 30.0, 26.1, 23.6, 21.6, 18.5, -5.1; HRMS (ESI) *m/e* calcd ($M+H^+$) 324.2353, found 324.2350.

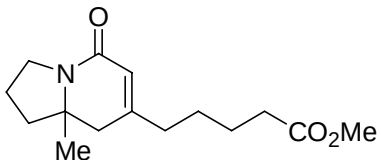


(*S*)-5-[3-(tert-Butyl-dimethyl-silanyloxy)-propyl]-8a-methyl-2,3,8,8a-tetrahydro-1H-indolizin-7-one (7f): 64% ee by HPLC (Chiralcel ODH, Hex:*i*PrOH;90:10, 1 ml/min, RT_{major} = 7.9 min, RT_{minor} = 9.0 min); $[\alpha]_D$ = +74.0° ($CHCl_3$, c=0.4); R_f = 0.15 (EtOAc 100%); IR (Thin Film) ν 2955, 2928, 1626, 1545, 1472, 1099 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.88 (1H, s), 3.62 (2H, t, *J* = 6.0 Hz), 3.62-2.56 (1H, m), 3.49-3.41 (1H, ddd, *J* = 10.0, 8.0, 8.0 Hz), 2.48 (1H, d, *J* = 16.0 Hz), 2.28 (1H, d, *J* = 16.0 Hz), 2.26 (2H, ddd, *J* = 12.0, 7.5, 3.0 Hz), 2.07-1.95 (3H, m), 1.84-1.75 (1H, m), 1.71-1.65 (2H, m), 1.18 (3H, s), 0.86 (9H, s), 0.02 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.2, 162.9, 96.0, 63.1, 62.0, 48.0, 46.5, 39.7, 30.5, 30.4, 29.9, 26.1, 22.4, 20.0, -5.2; HRMS (ESI) *m/e* calcd (M^+) 324.2353, found 324.2355.



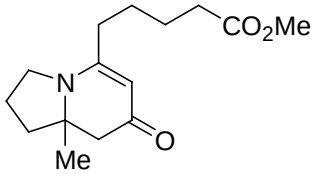
(*R*)-7-[2-(tert-Butyl-dimethyl-silanyloxy)-ethyl]-8a-methyl-2,3,8,8a-tetrahydro-1H-indolizin-5-one (6g): Flash Chromatography (Hexanes:EtOAc;1:5) yielded a light yellow syrup (77%); 93% ee by HPLC (Chiralcel ADH, Hex:*i*PrOH;90:10, 1 ml/min, RT_{major} = 5.9 min, RT_{minor} = 5.2 min); $[\alpha]_D$ = +104.0° ($CHCl_3$, c=1.1); R_f = 0.48 (EtOAc 100%); IR (Thin Film) ν 2955, 2928,

2857, 1664, 1616, 1427, 1255, 1096, 837 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.71 (1H, d, *J* = 1.0 Hz), 3.73 (2H, t, *J* = 6.5 Hz), 3.55-3.50 (2H, m), 2.40-2.27 (4H, m), 2.00-1.89 (3H, m), 1.78-1.70 (1H, m), 1.14 (3H, s), 0.84 (9H, s), 0.02 (3H, s), 0.01 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 149.6, 121.0, 61.2, 60.9, 43.7, 42.0, 40.9, 40.6, 26.1, 23.6, 21.6, 18.4, -5.2; HRMS (ESI) *m/e* calcd (M^+) 310.2197, found 310.2187.

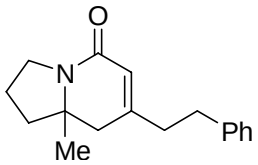


Flash Chromatography (Hexanes:EtOAc;1:5 then EtOAc 100%) yielded a light yellow syrup **6k** (74%) followed by a light yellow syrup **7h** (9%):

(*R*)-5-(8a-Methyl-5-oxo-1,2,3,5,8,8a-hexahydro-indolizin-7-yl)-pentanoic acid methyl ester (6h): 93% ee by HPLC (Chiralcel ODH, Hex:*i*PrOH;90:10, 1 ml/min, RT_{major} = 16.4 min, RT_{minor} = 18.0 min); $[\alpha]_D$ = +111.0° ($CHCl_3$, c=0.9); R_f = 0.48 (EtOAc 100%); IR (Thin Film) ν 2949, 2877, 1736, 1660, 1612, 1432 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.68 (1H, s), 3.62 (3H, s), 3.53-3.47 (2H, m), 2.34 (1H, d, *J* = 17.0 Hz), 2.29 (2H, ddd, *J* = 7.0, 7.0, 4.0 Hz), 2.18 (1H, d, *J* = 17.0 Hz), 2.13 (2H, dd, *J* = 7.5, 7.5 Hz), 1.99-1.87 (3H, m), 1.78-1.73 (1H, m), 1.65-1.57 (2H, m), 1.52-1.44 (2H, m), 1.12 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 163.4, 151.4, 119.7, 60.8, 51.7, 43.7, 41.7, 40.9, 36.5, 33.9, 26.2, 24.6, 23.6, 21.5; HRMS (ESI) *m/e* calcd (M^+) 266.1751, found 266.1764.

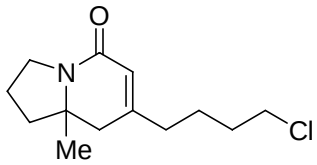


(*S*)-5-(8a-Methyl-7-oxo-1,2,3,7,8,8a-hexahydro-indolizin-5-yl)-pentanoic acid methyl ester (7h): 49% ee by HPLC (Chiralcel ADH, Hex:*i*PrOH;80:20, 1 ml/min, RT_{major} = 8.6 min, RT_{minor} = 8.1 min); $[\alpha]_D$ = 49.0° ($CHCl_3$, c=0.5); R_f = 0.19 (EtOAc 100%); IR (Thin Film) ν 2953, 2871, 1736, 1621, 1555, 1484, 1269, 1212, 1168 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.87 (1H, s), 3.64 (3H, s), 3.55 (1H, ddd, *J* = 11.0, 8.0, 6.0 Hz), 3.42 (1H, ddd, *J* = 11.0, 8.0, 8.0 Hz), 2.46 (1H, d, *J* = 16.0 Hz), 2.31 (2H, t, *J* = 7.0 Hz), 2.28 (1H, d, *J* = 16.0 Hz), 2.24-2.14 (2H, m), 2.06-1.95 (3H, m), 1.83-1.74 (1H, m), 1.70-1.62 (2H, m), 1.57-1.49 (2H, m), 1.17 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.4, 173.9, 162.2, 96.2, 63.2, 51.8, 48.1, 46.5, 39.7, 33.8, 33.7, 26.7, 24.7, 22.5, 20.0; HRMS (ESI) *m/e* calcd ($M+H^+$) 266.1751, found 266.1739.



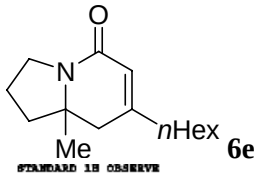
(*R*)-8a-Methyl-7-phenethyl-2,3,8,8a-tetrahydro-1H-indolizin-5-one (6i): Flash Chromatography (Hexanes:EtOAc;1:4) yielded a light yellow syrup (71%); 95% ee by HPLC (Chiralcel ADH, Hex:*i*PrOH;90:10, 1 ml/min, RT_{major} = 12.9 min, RT_{minor} = 10.4 min); $[\alpha]_D$ = +110.0° ($CHCl_3$, c=0.8); R_f = 0.44 (EtOAc 100%); IR (Thin Film) ν 2967, 2925, 2881, 1661, 1613, 1429 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28-7.23 (2H, m), 7.19-7.15 (3H, m), 5.75 (1H,

bs), 3.55-3.50 (2H, m), 2.78 (2H, ddd, *J* = 9.0, 9.0, 4.5 Hz), 2.45 (2H, td, *J* = 9.0, 1.0 Hz), 2.38 (1H, d, *J* = 16.0 Hz), 2.24 (1H, d, *J* = 16.0 Hz), 2.00-1.88 (3H, m), 1.81-1.70 (1H, m), 1.12 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 151.3, 141.0, 128.7, 128.4, 126.4, 119.8, 60.9, 43.7, 41.9, 40.9, 38.4, 33.2, 23.6, 21.5; HRMS (ESI) *m/e* calcd ($M+H^+$) 256.1696, found 256.1696.

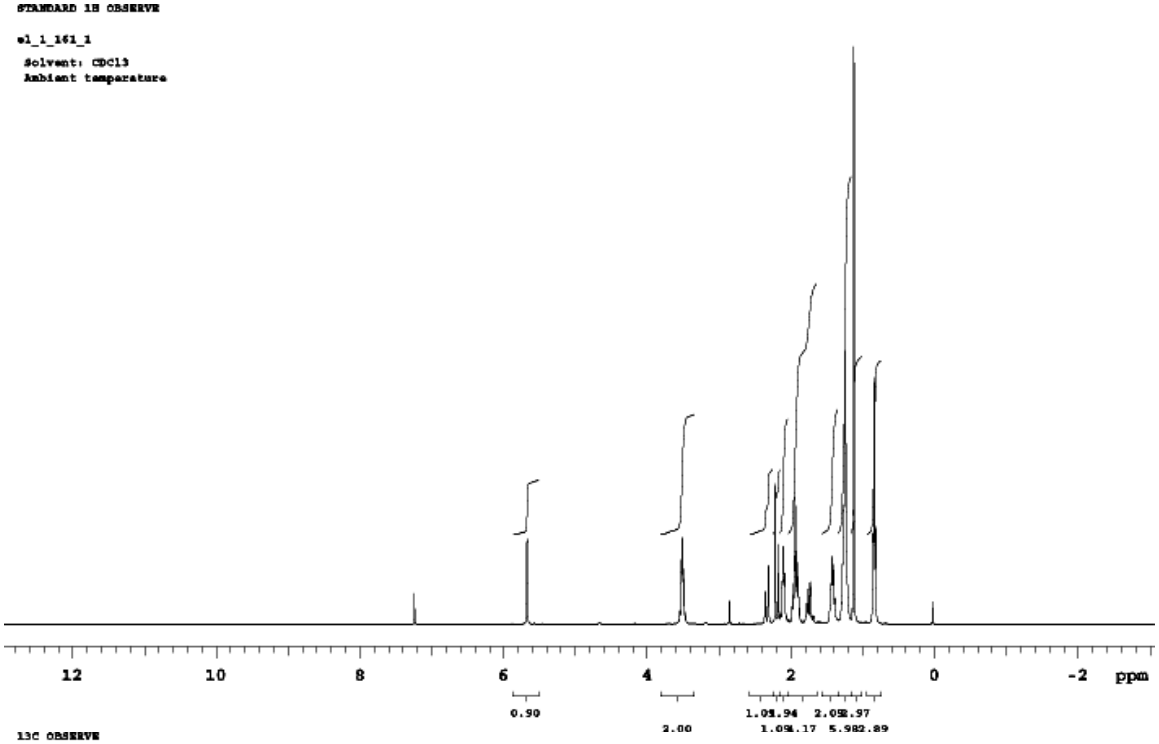


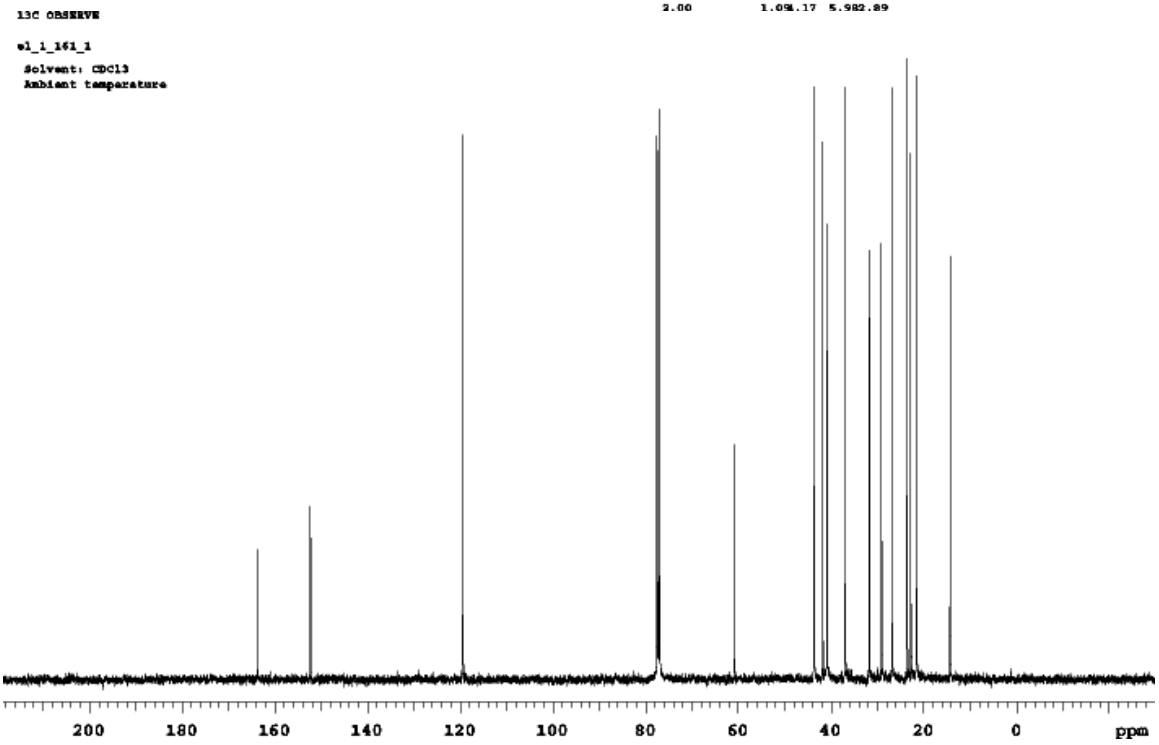
(*R*)-7-(4-Chloro-butyl)-8a-methyl-2,3,8,8a-tetrahydro-1H-indolizin-5-one (6j): Flash Chromatography (Hex:EtOAc;1:2) yielded a yellowish syrup (60%); 92% ee by HPLC (Chiralcel ODH, Hex:*i*PrOH;85:15, 1 ml/min, RT_{major} = 8.7 min, RT_{minor} = 10.1 min); $[\alpha]_D$ = +106.0^o ($CHCl_3$, c=0.53); R_f = 0.52 (EtOAc 100%); IR (Thin Film) ν 2967, 1660, 1605, 1433 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.71 (1H, t, *J* = 1.0 Hz), 3.58-3.47 (4H, m), 2.36 (1H, d, *J* = 17.0 Hz), 2.21 (1H, d, *J* = 17.0 Hz), 2.17 (2H, t, *J* = 7.5 Hz), 2.01-1.89 (2H, m), 1.82-1.73 (4H, m), 1.66-1.57 (2H, m), 1.14 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 151.2, 119.9, 60.8, 44.8, 43.7, 41.6, 40.9, 36.0, 32.0, 23.9, 23.6, 21.6; HRMS (ESI) *m/e* calcd ($M+H^+$) 242.1306, found 242.1308.

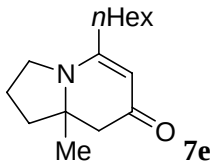
I.11 ^{1}H and ^{13}C NMR Spectra for [2+2+2] Products from Alkyl Alkynes



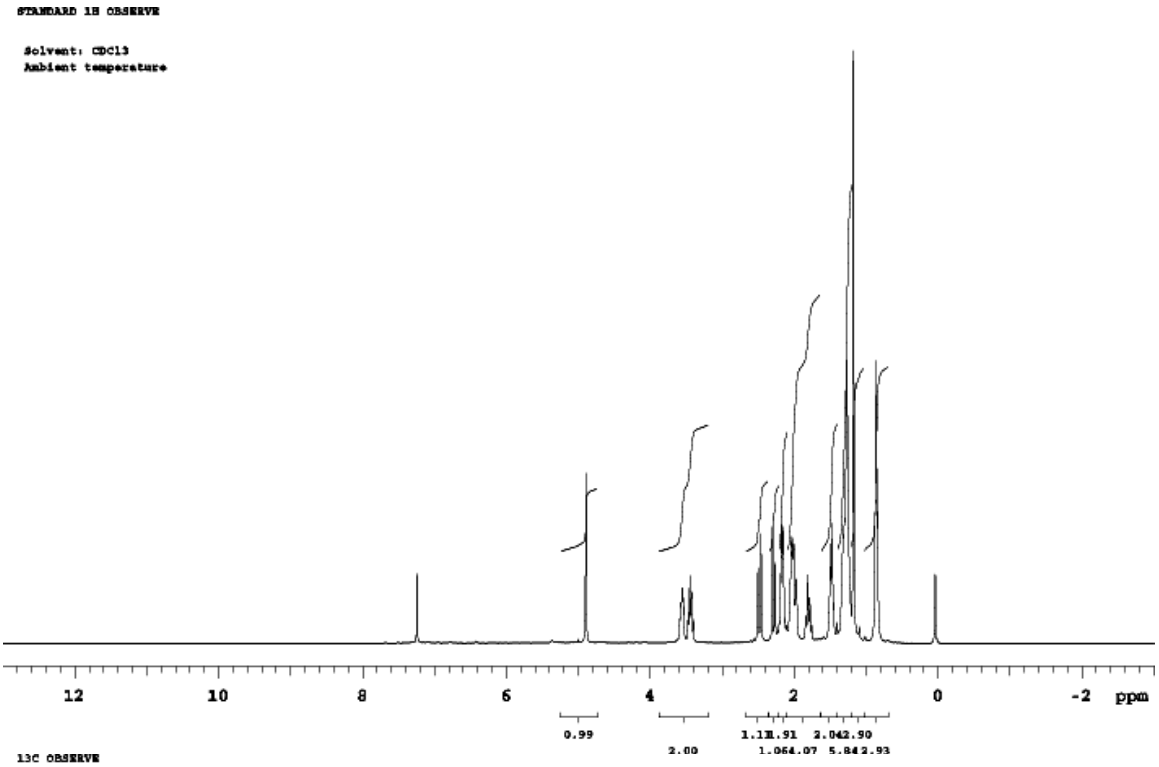
6e

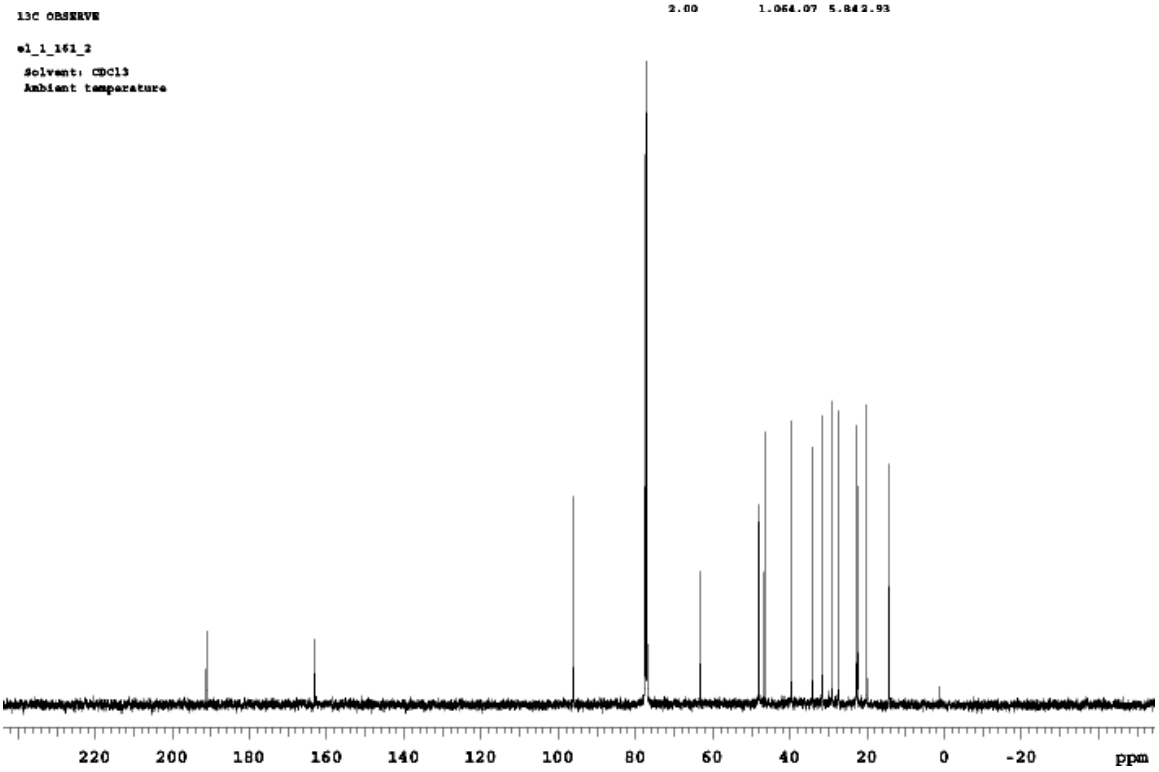


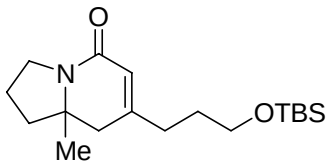



nHex
N
O
Me

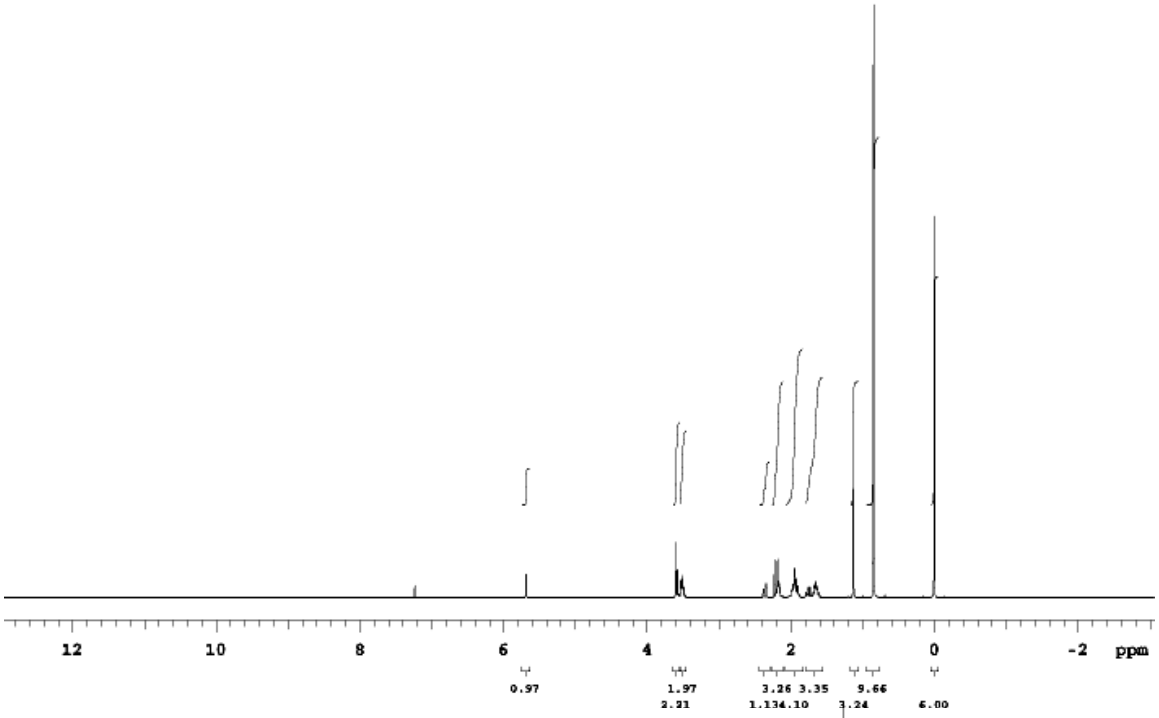
7e

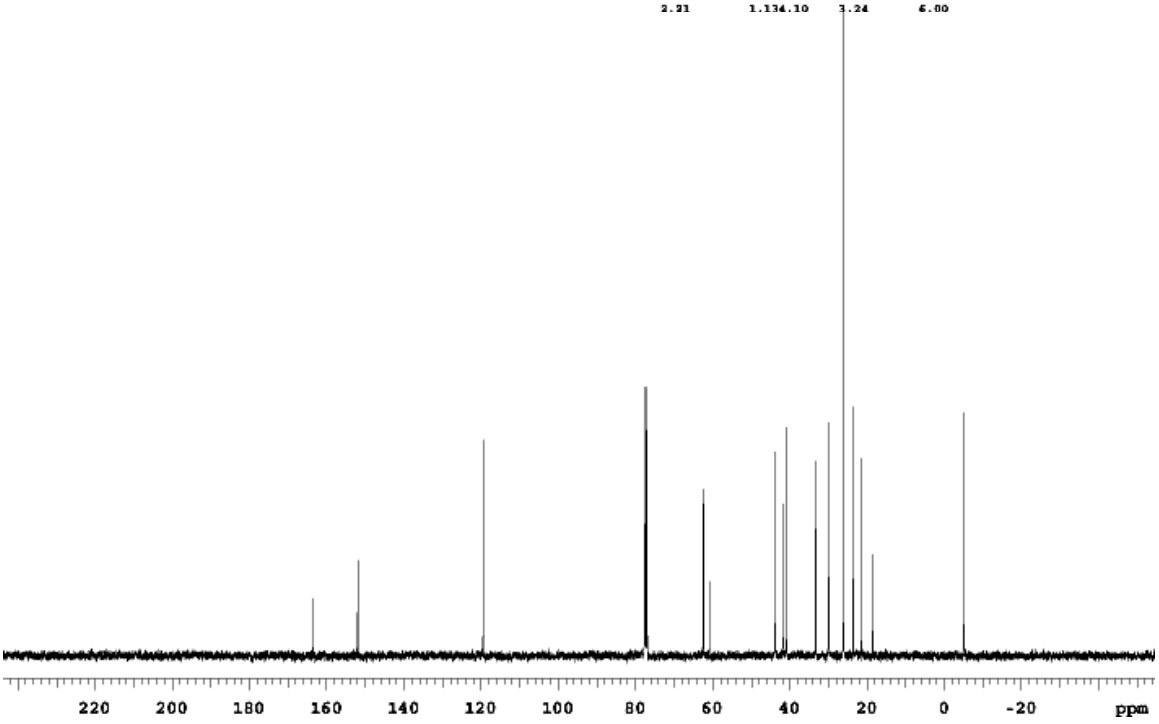

STANDARD 1H OBSERVE
Solvent: CDCl3
Ambient temperature
12
10
8
6
4
2
0
-2
ppm
0.99
2.00
1.13
1.91
2.04
2.90
1.06
4.07
5.84
2.93

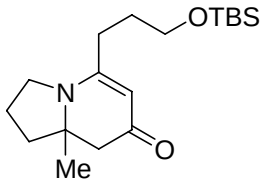

13C OBSERVE
el_1_161_2
Solvent: CDCl3
Ambient temperature
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm


O
N
OTBS
Me

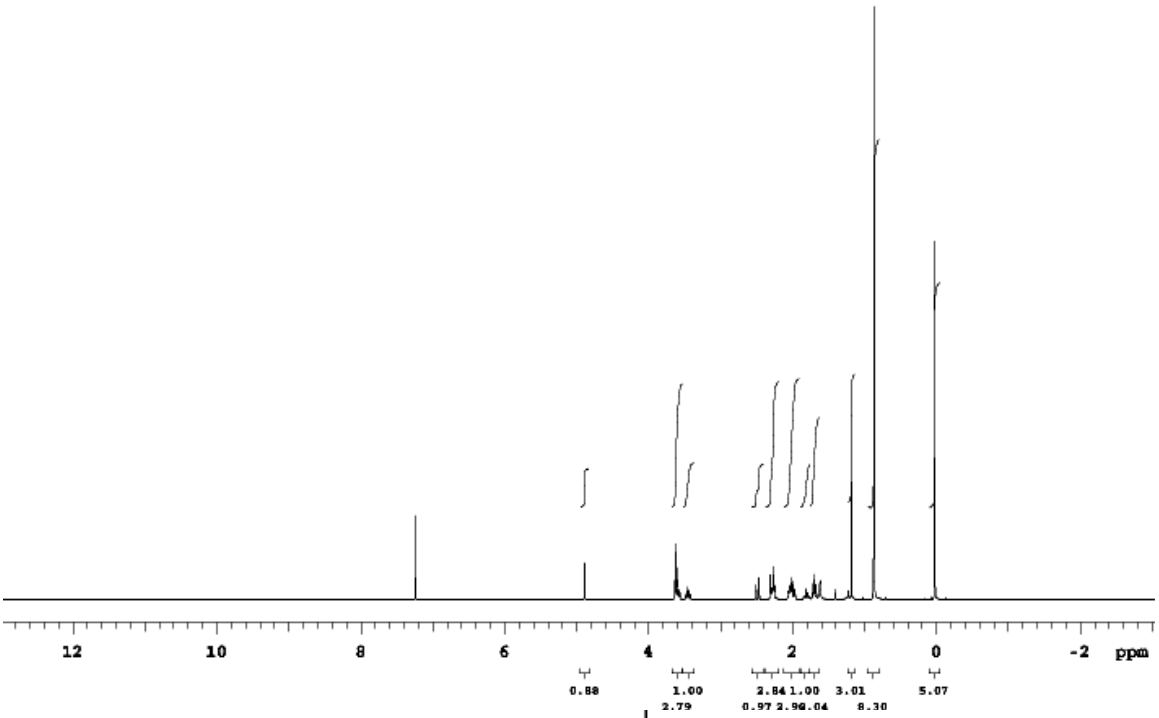
6f


12
10
8
6
4
2
0
-2
ppm
0.97
1.97
2.21
3.26
3.35
1.13
4.10
9.66
3.24
6.00


220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm


OTBS
N
O
Me

7f


12
10
8
6
4
2
0
-2
ppm
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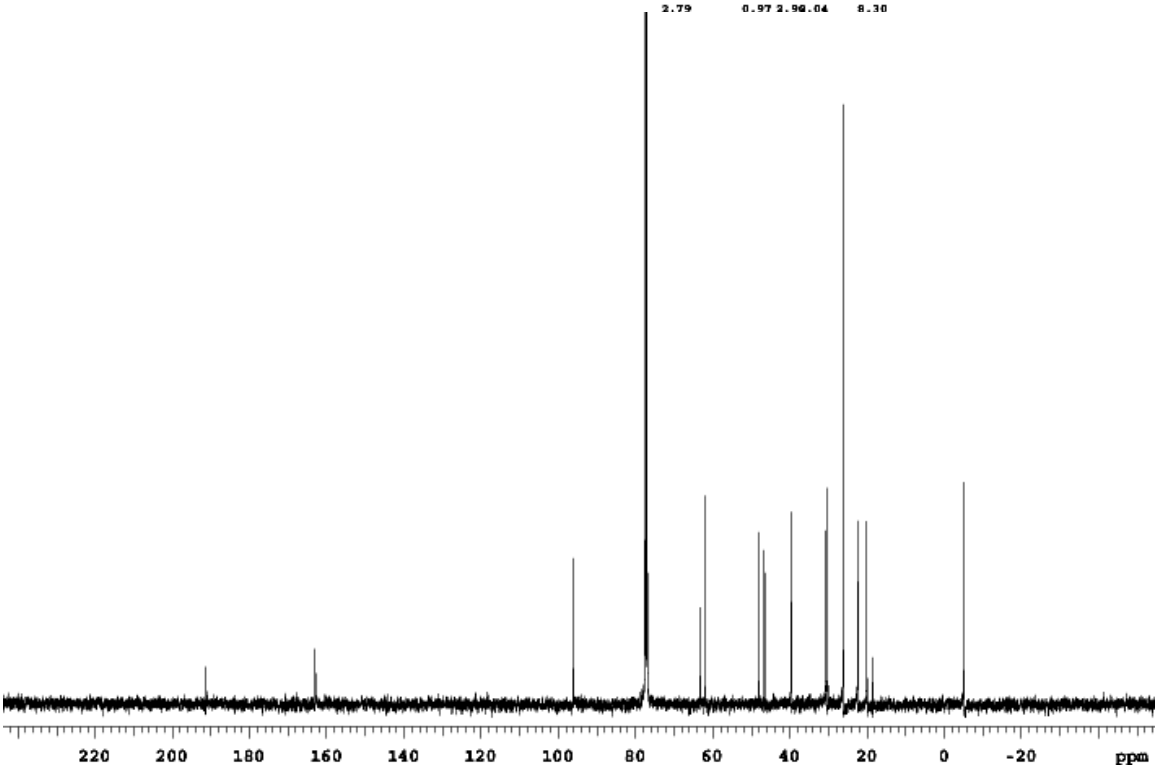
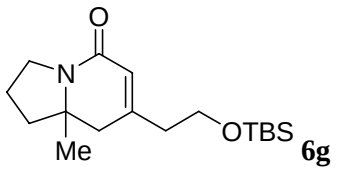
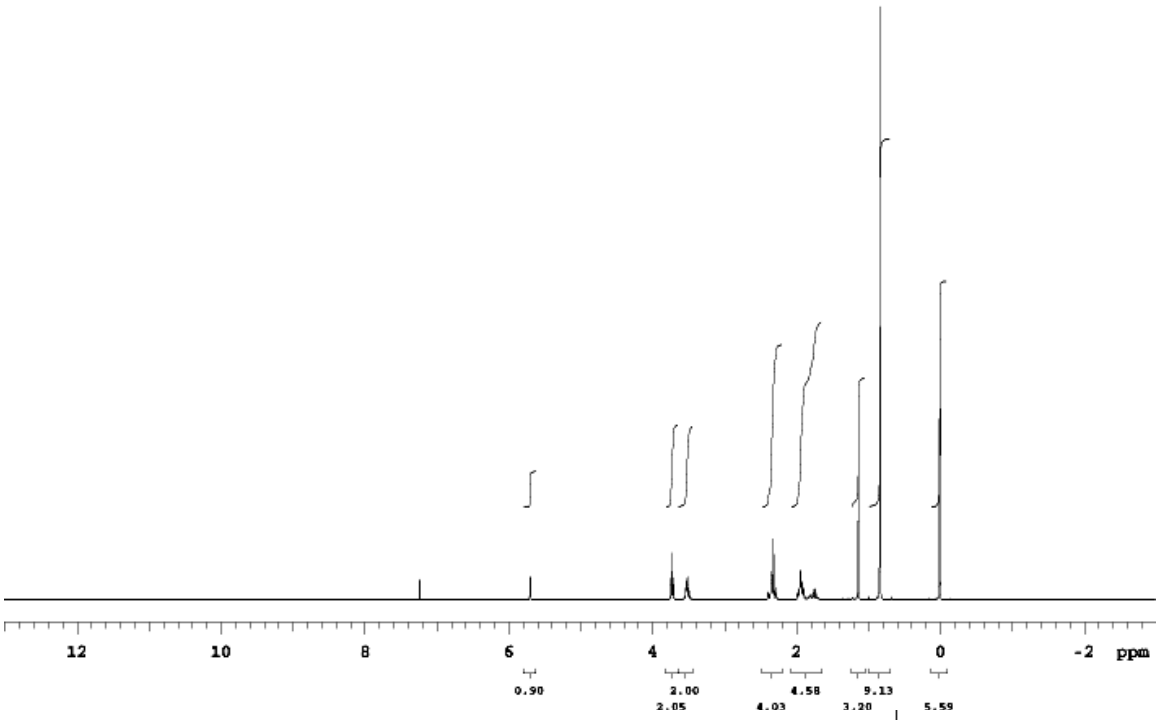
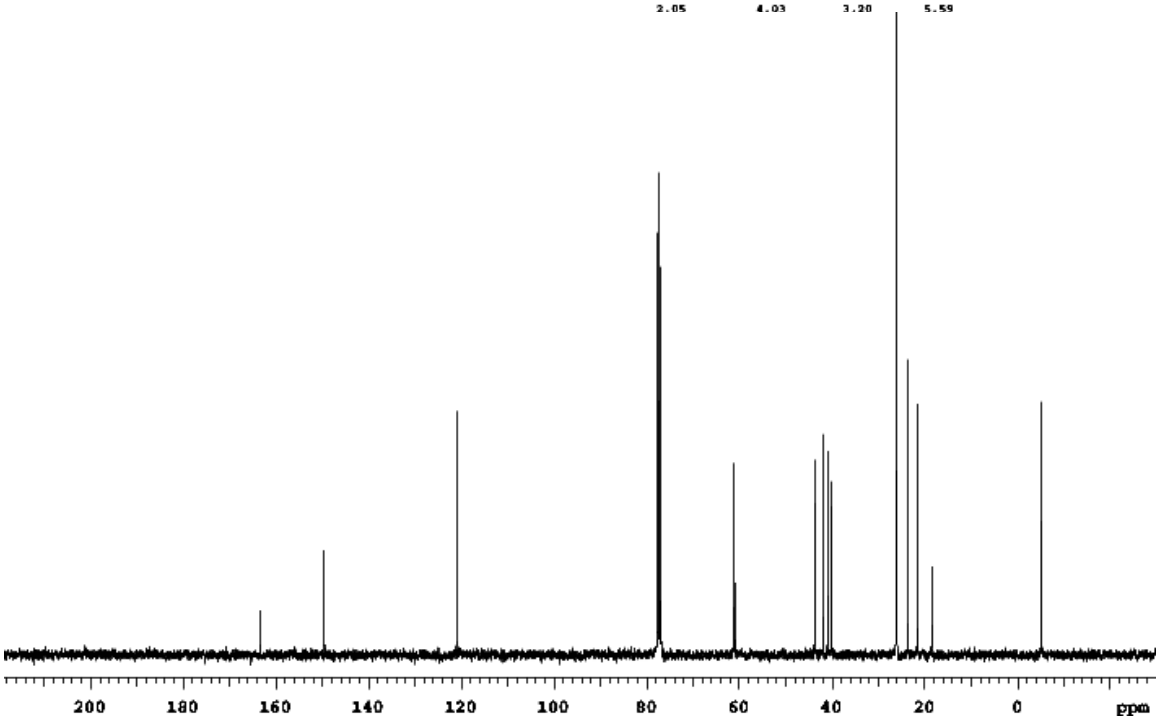
1.00
2.79
2.84
1.00
0.97
3.01
5.07

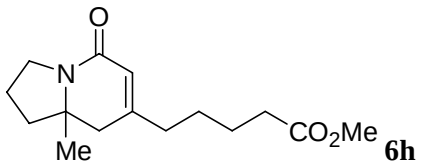

220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm


O
N
Me
OTBS

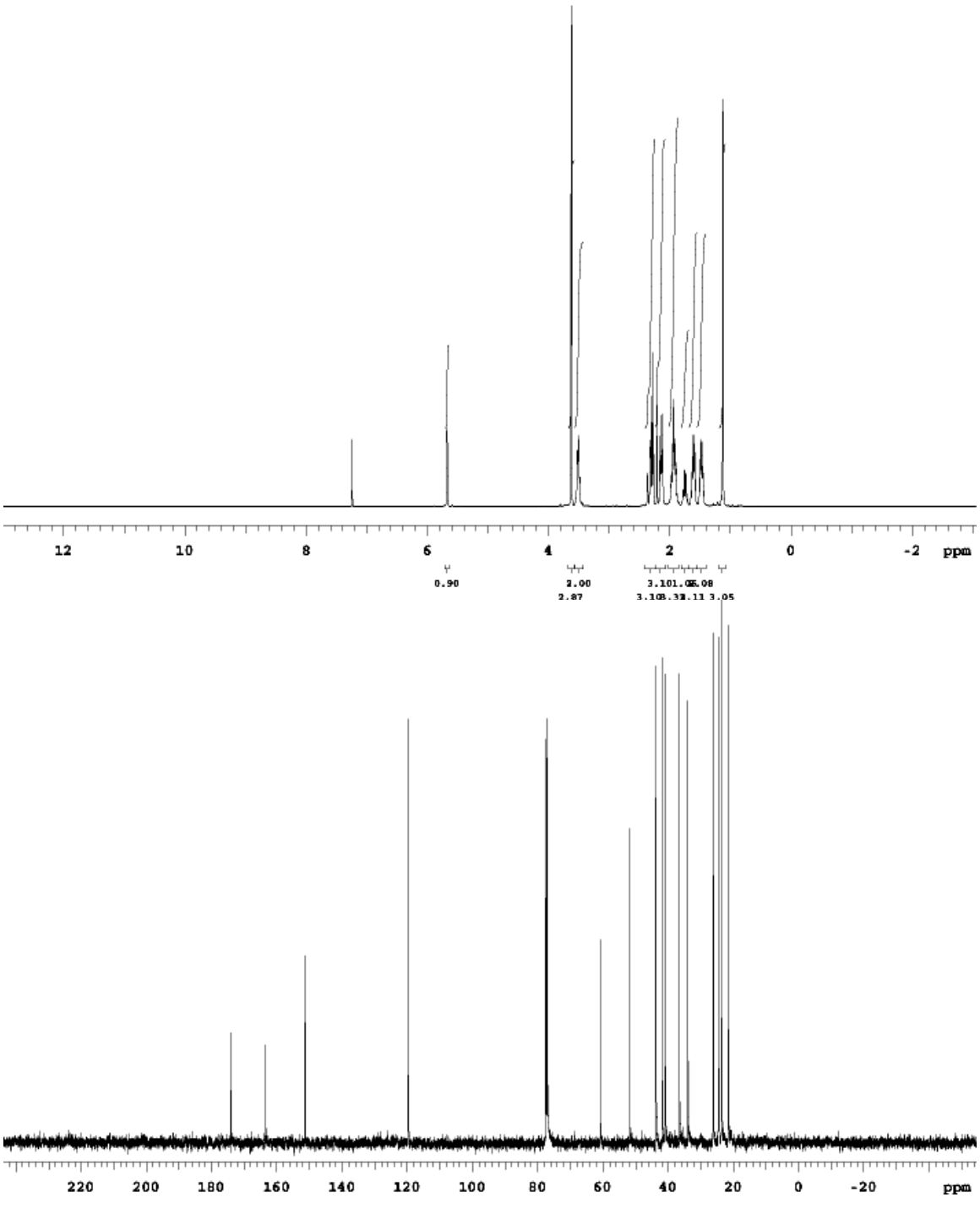
6g

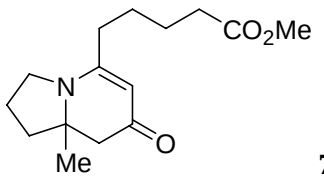

12
10
8
6
4
2
0
-2
ppm
0.90
2.00
2.05
4.58
4.03
9.13
3.20
5.59


200
180
160
140
120
100
80
60
40
20
0
ppm

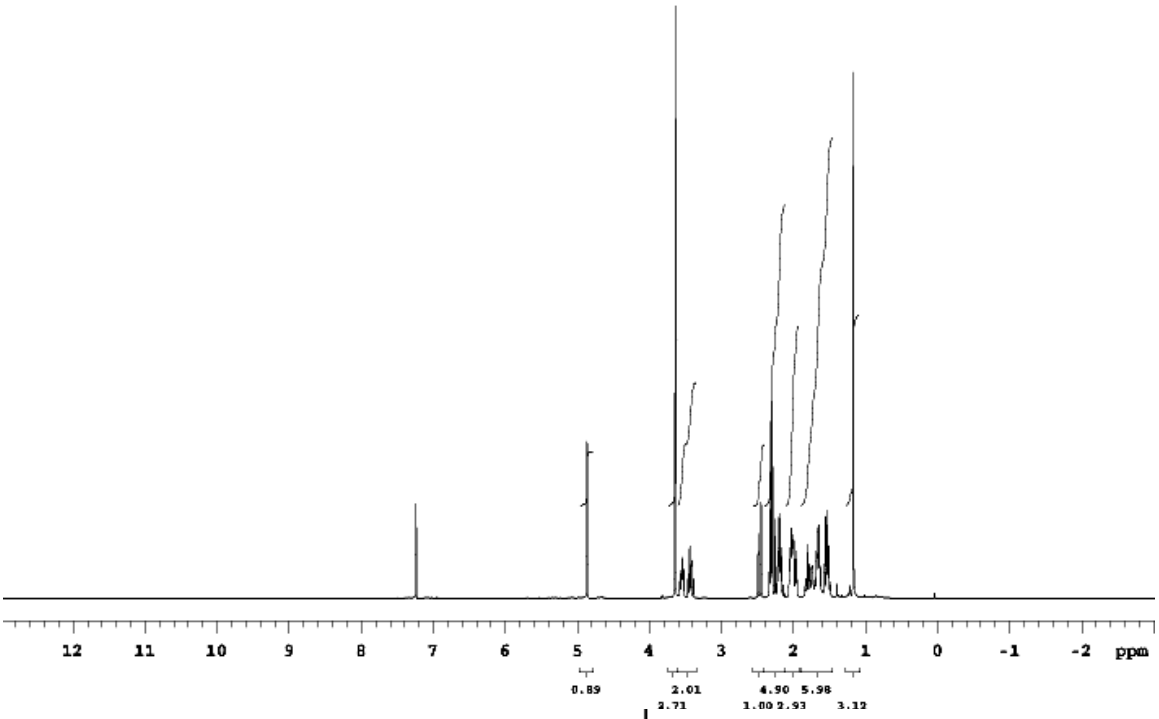

O
N
Me
CO2Me

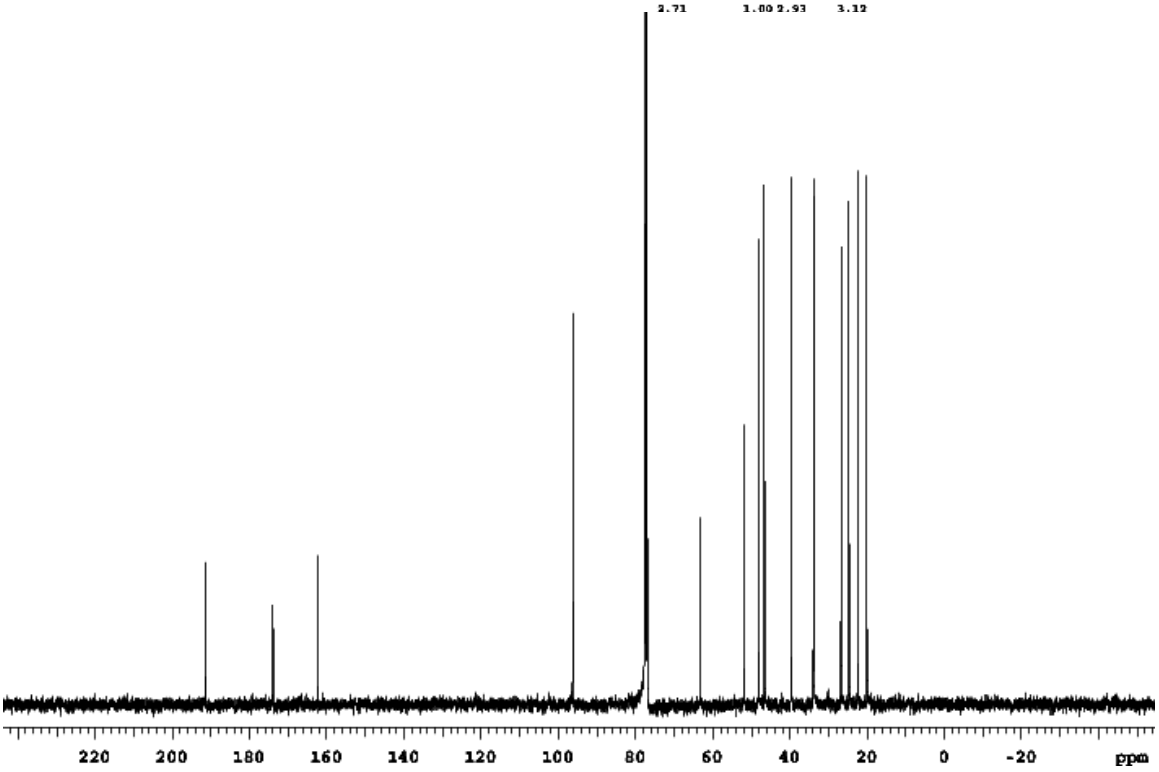
6h

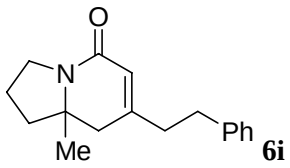

12
10
8
6
4
2
0
-2
ppm
0.90
2.00
2.87
3.10
3.11
3.05
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm


CO2Me
N
O
Me

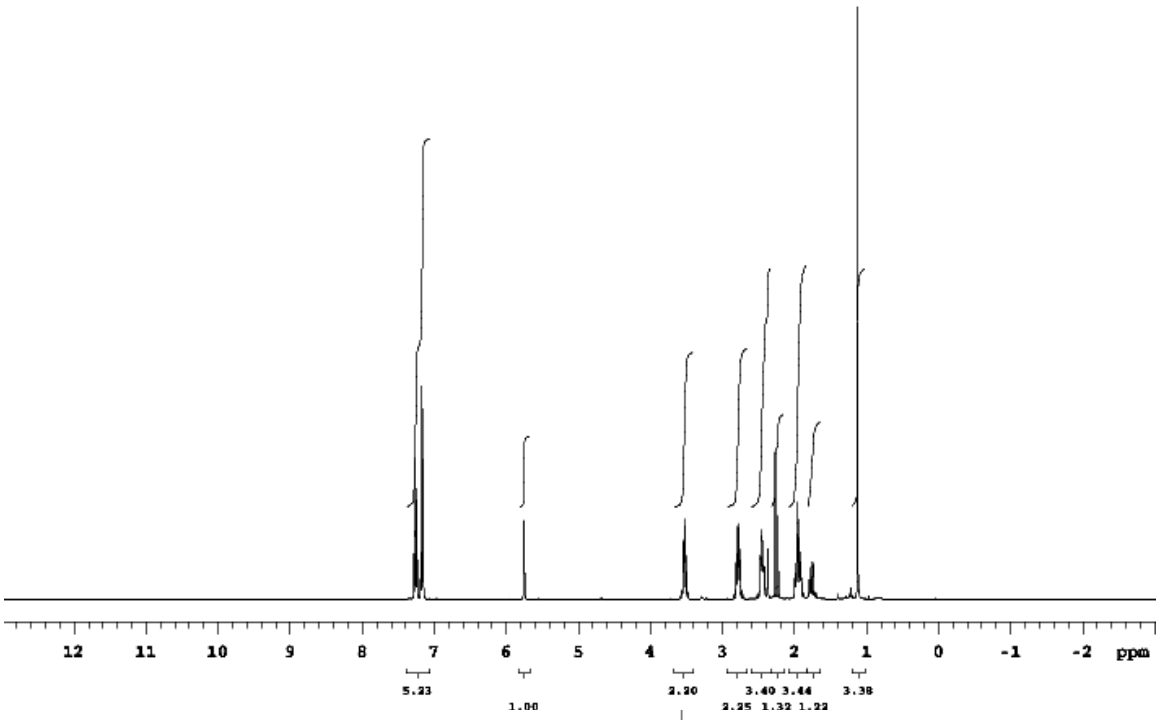
7h

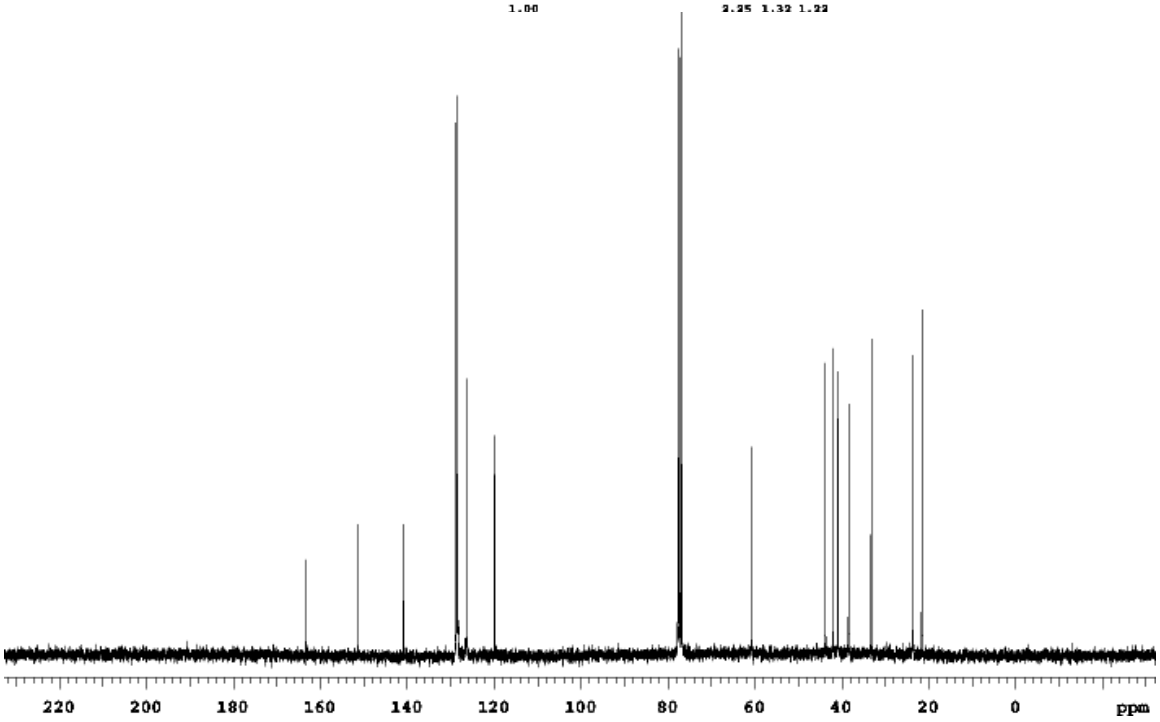

12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 ppm
0.89
2.01
2.71
4.90
1.80
5.98
2.93
3.12

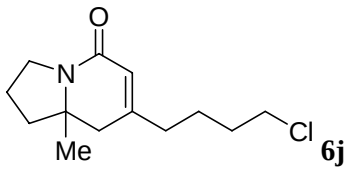

220 200 180 160 140 120 100 80 60 40 20 0 -20 ppm


O
N
Ph
Me

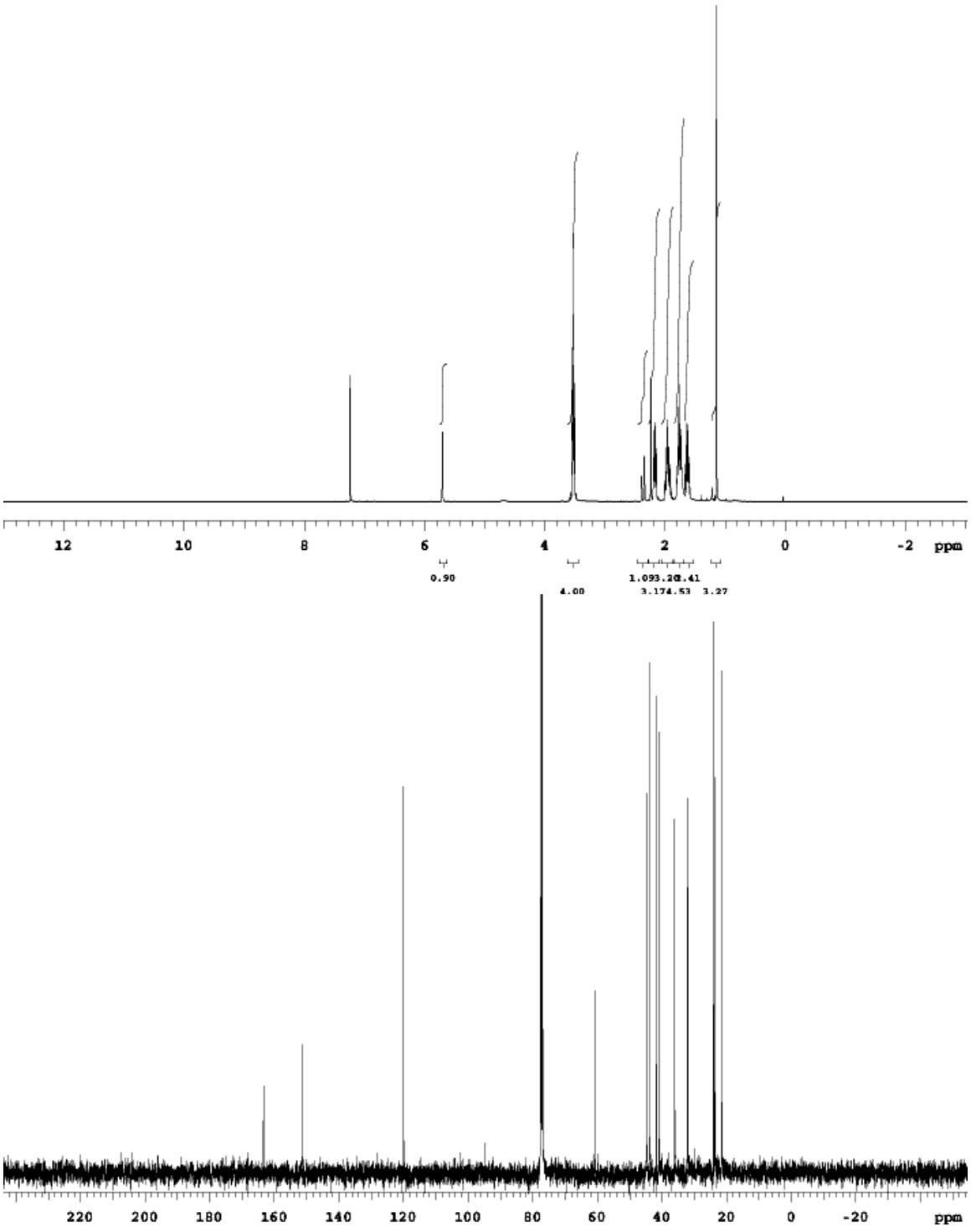
6i


12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 ppm
5.23
1.00
2.20
3.40 3.44
2.25 1.32 1.22
3.38

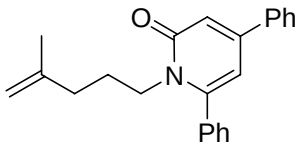

220 200 180 160 140 120 100 80 60 40 20 0 ppm


O
N
Me
Cl

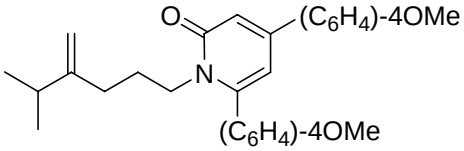
6j


12
10
8
6
4
2
0
-2
ppm
0.90
4.00
3.174.53
3.27
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm

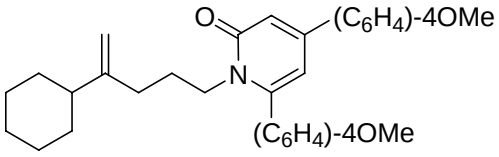
I.12 Characterization of Pyridone Side Products.



1-(4-Methyl-pent-4-enyl)-4,6-diphenyl-1H-pyridin-2-one (8a): R_f = 0.62 (EtOAc(100%)); IR (Thin Film) ν 3059, 2935, 1654, 1602, 1537, 1490 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60-7.55 (2H, m), 7.48-7.35 (8H, m), 6.79 (1H, d, *J* = 2.0 Hz), 6.32 (1H, d, *J* = 2.0 Hz), 4.55 (1H, s), 4.47 (1H, s), 3.86 (2H, m), 1.85 (2H, t, *J* = 7.0 Hz), 1.70 (2H, tt, *J* = 7.0 Hz), 1.51 (sH, 3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6, 150.5, 149.7, 144.6, 137.7, 135.9, 129.5, 129.4, 129.1, 128.9, 128.8, 127.0, 115.9, 110.5, 107.8, 45.5, 35.1, 26.5, 22.2; MS (EI) *m/e* (rel intensity) 330 (100), 260 (19), 248 (40), 247 (24), 179 (19), 167 (14); HRMS (EI) *m/e* calcd (M^+) 330.1858, found 330.1853.

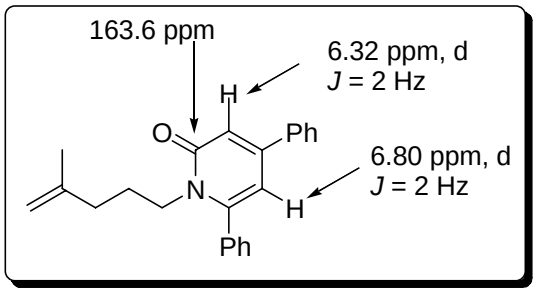


4,6-Bis-(4-methoxy-phenyl)-1-(5-methyl-4-methylene-hexyl)-1H-pyridin-2-one (10g): R_f = 0.60 (EtOAc(100%)); IR (Thin Film) ν 2960, 1651, 1609, 1512, 1250, 1180, 1030 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (2H, d, *J* = 9.0 Hz), 7.28 (2H, d, *J* = 8.5 Hz), 6.96 (2H, d, *J* = 9.0 Hz), 6.91 (2H, d, *J* = 9.0 Hz), 6.72 (1H, d, *J* = 2.0 Hz), 6.27 (1H, d, *J* = 2.0 Hz), 4.59 (1H, s), 4.47 (1H, s), 3.89-3.83 (2H, m), 3.84 (3H, s), 3.80 (3H, s), 2.00 (1H, sept, *J* = 6.5 Hz), 1.87 (2H, t, *J* = 7.5 Hz), 1.69 (2H, tt, *J* = 7.5, 7.5 Hz), 0.88 (6H, d, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 160.9, 160.3, 154.5, 149.8, 149.5, 130.2, 129.9, 128.3, 128.2, 114.5, 114.1, 107.8, 106.9, 55.6, 55.5, 45.6, 33.4, 31.8, 27.1, 21.9; HRMS (ESI) *m/e* calcd ($M+H^+$) 418.2377, found 418.2379.

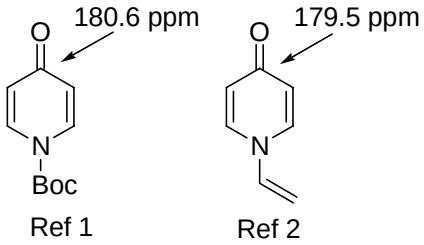


1-(4-Cyclohexyl-pent-4-enyl)-4,6-bis-(4-methoxy-phenyl)-1H-pyridin-2-one (10h): R_f = 0.60 (EtOAc(100%)); IR (Thin Film) ν 2926, 2850, 1651, 1609, 1509, 1250, 1179, 1031, 824 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (2H, d, *J* = 9.0 Hz), 7.28 (2H, d, *J* = 8.5 Hz), 6.95 (2H, d, *J* = 9.0 Hz), 6.91 (2H, d, *J* = 8.5 Hz), 6.73 (1H, d, *J* = 1.5 Hz), 6.27 (1H, d, *J* = 1.5 Hz), 4.57 (1H, s), 4.48 (1H, s), 3.89-3.84 (2H, m), 3.85 (3H, s), 3.81 (3H, s), 1.87 (2H, t, *J* = 7.5 Hz), 1.71-1.56 (8H, m), 1.23-0.96 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 160.9, 160.3, 153.9, 149.8, 149.4, 130.2, 129.9, 128.4, 128.2, 114.5, 114.1, 107.8, 107.4, 55.6, 45.6, 43.8, 32.5, 32.4, 27.3, 26.9, 26.6; HRMS (ESI) *m/e* calcd ($M+H^+$) 458.2690, found 458.2667.

I.13 Determination of Pyridone Isomer.

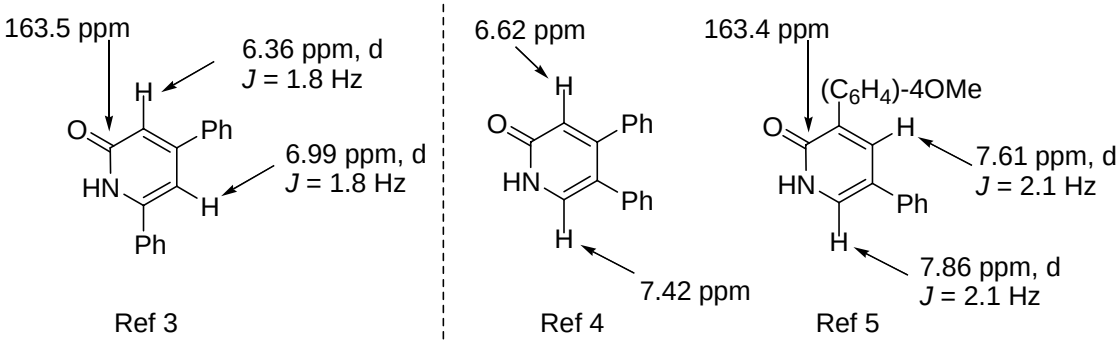


4-Pyridones



Ref 1 Ref 2

Matching isomer *Non-matching isomers*

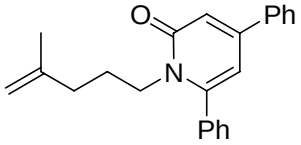


Ref 3 Ref 4 Ref 5

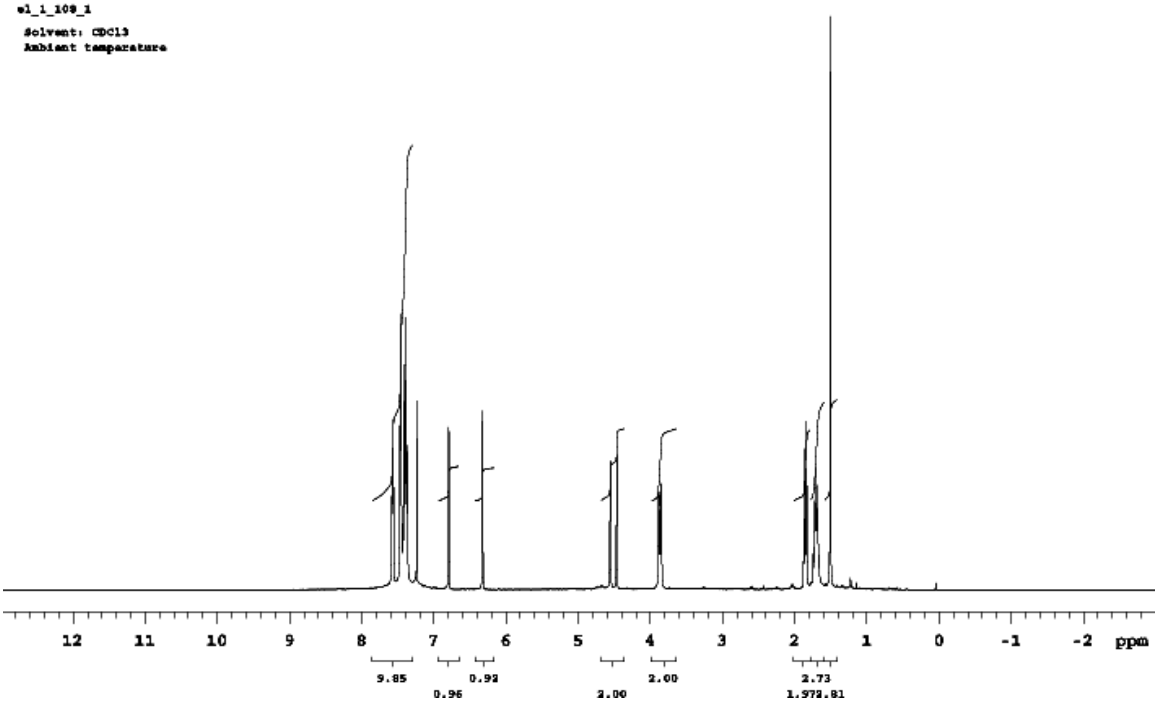
References

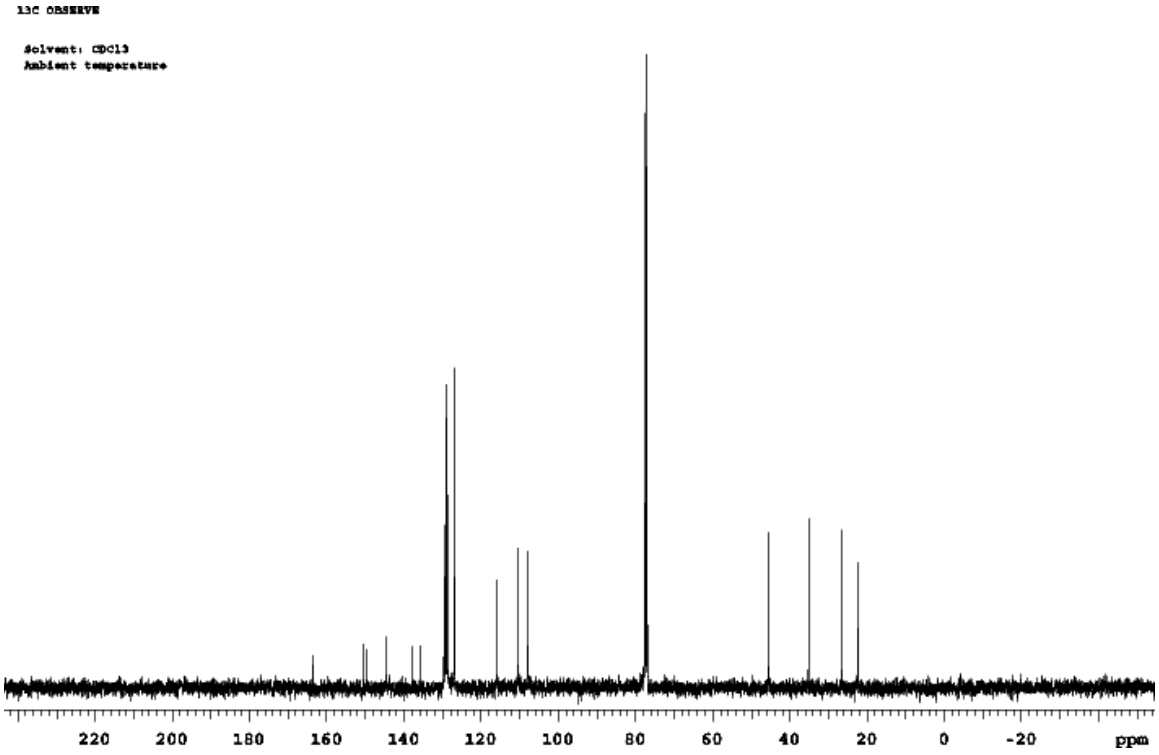
1. Lim, S. H.; Curtis, M. D.; Beak, P. *Org. Lett.* **2001**, *3*, 711-714.
2. Blouin, M.; Frenette, R. *J. Org. Chem.* **2001**, *66*, 9043-9045.
3. Carles, L.; Narkunam, K.; Penlou, S.; Rousset, L.; Bouchu, D.; Ciufolini, M. A. *J. Org. Chem.* **2002**, *67*, 4304-4308.
4. Yamamoto, K.; Yamazaki, S.; Murata, I. *J. Org. Chem.* **1987**, *52*, 5239-5243.
5. Sutherland, A.; Gallagher, T. *J. Org. Chem.* **2003**, *68*, 3352-3355.

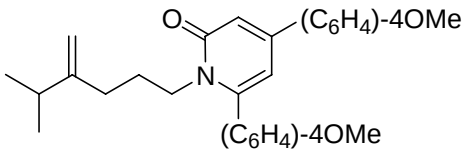
I.14 Pyridone Byproduct ^{1}H and ^{13}C NMR Spectra



10a



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N
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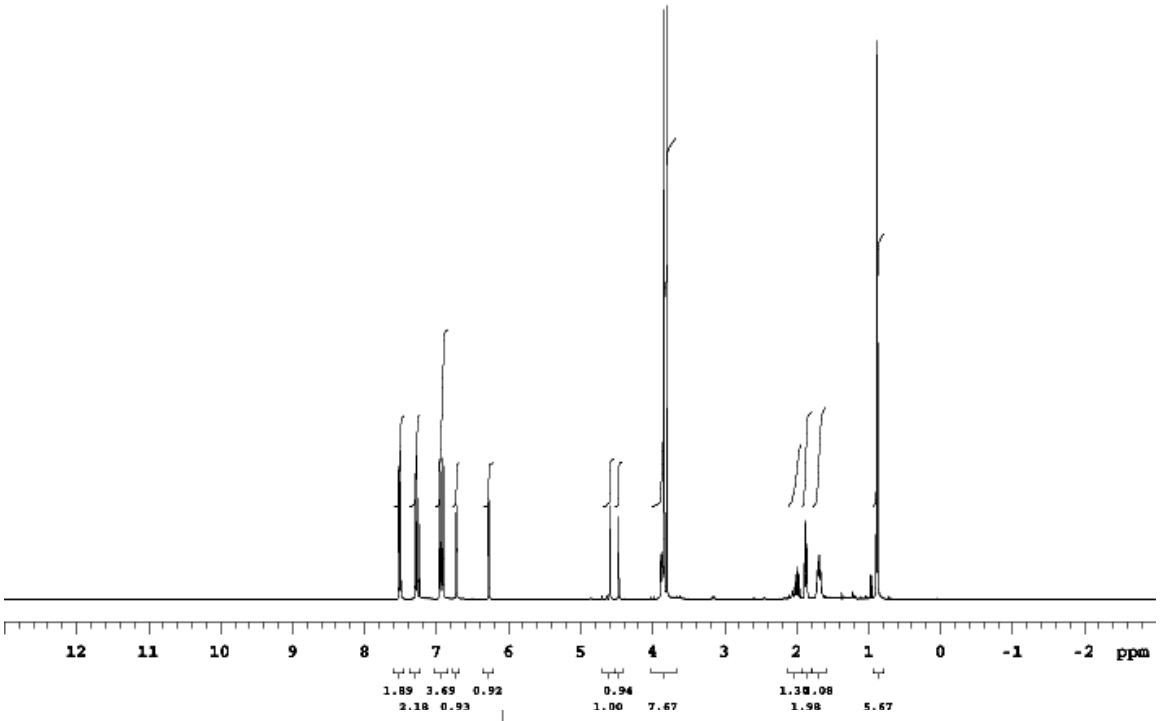
(C6H4)-4OMe

10g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4
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-2
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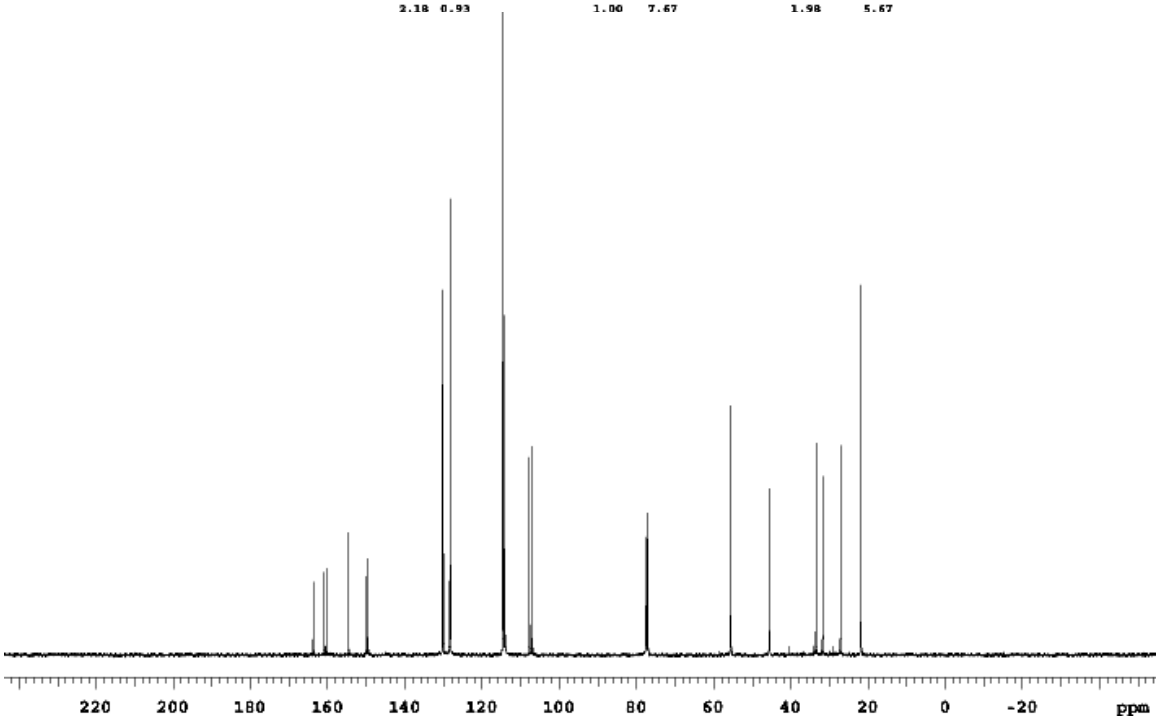
5.67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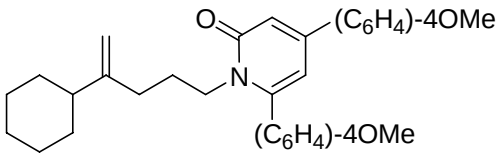
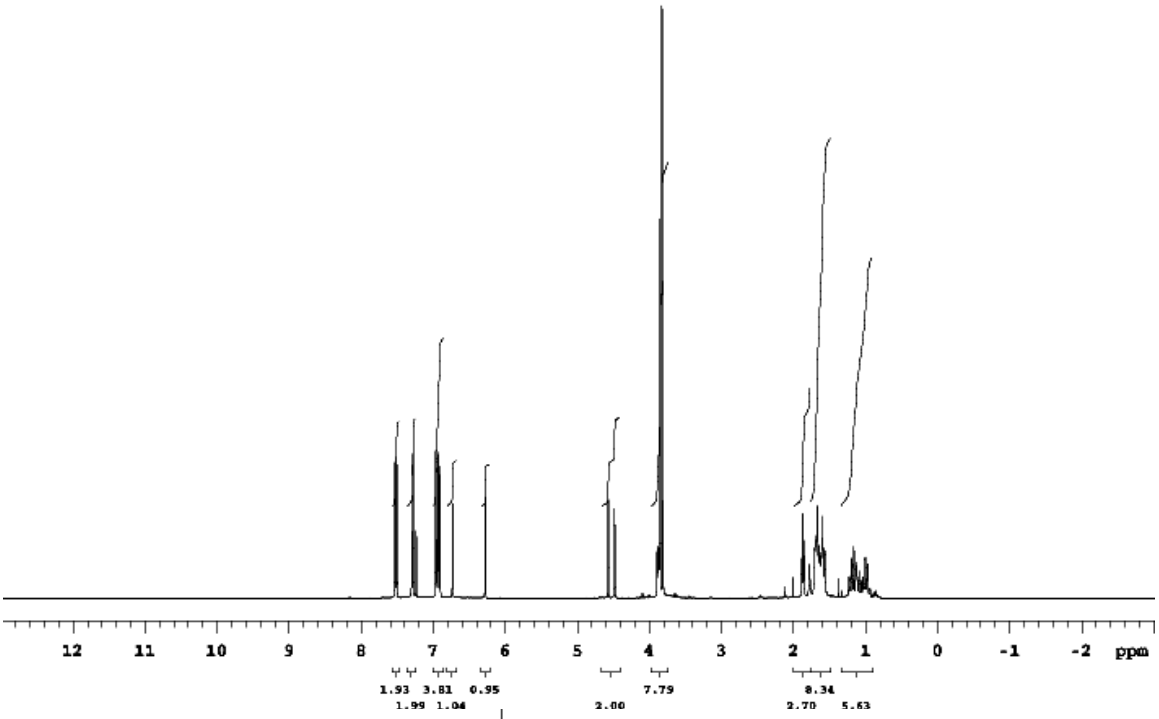

O
N
(C6H4)-4OMe
(C6H4)-4OMe

10h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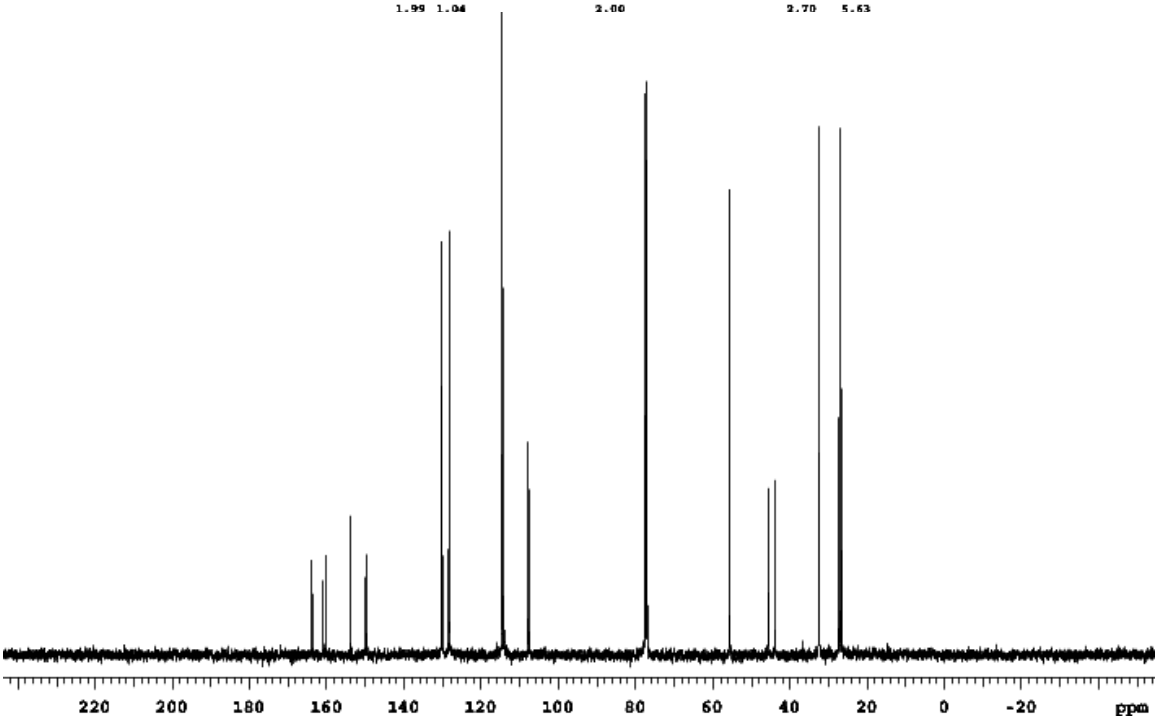
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