

Nucleophilic Carbene Catalyzed Synthesis of 1,2 Amino Alcohols Via Azidation of Epoxy Aldehydes

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General Methods

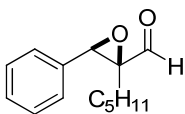
General Methods. All reactions were carried out under an atmosphere of argon in flame dried glassware with magnetic stirring. Toluene was degassed with argon and passed through one column of neutral alumina and one column of Q5 reactant. Column Chromatography was performed on 40-63 μ m 60A silica gel. Thin layer chromatography was performed on 250 μ m 60A plates. Visualization was accomplished with UV quench, KMNO₄, or aqueous ceric ammonium molybdate dips followed by heating. Data are reported as follows: chemical shift is parts per million (δ , ppm) from chloroform, (CHCl₃) taken as 7.26 ppm, integration, multiplicity (s = singlet, br s = broad singlet, br d = broad doublet, d = doublet, t = triplet, q = quartet, qint = quintet and m = multiplet), and coupling constants (Hz). ¹³C NMR spectra, chemical shifts are reported in ppm from CHCl₃ taken as 77.0 ppm. Mass spectra were obtained on a Fisions VG Autospec.

α,β -Epoxy aldehydes were prepared according to literature procedure from the corresponding allylic alcohol. Compounds **4a**,¹ **4g**,¹ match spectrometric data and physical properties to those previously reported in the literature. Azidotrimethylsilane (95%) and sodium azide were purchased from Aldrich Chemical Co. and used without further purification. Triethylamine was purified by distillation over Calcium hydride.

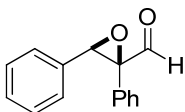
Hydrazoic acid is generated *in situ* by treatment of azidotrimethylsilane (0.042 g, 0.370 mmol, 1.05 equiv) and ethanol (0.018 g, 0.39 mmol, 1.1 equiv) in 1 ml of toluene which is stirred for 30 min in a sealed round bottom flask under an argon atmosphere prior to use.

Compounds **17a**,³ **17b**,³ and **17c**⁴ match spectroscopic data and physical properties to those previously reported in the literature.

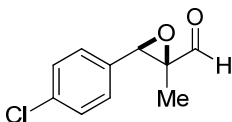
Substrate Characterization



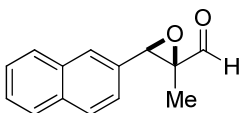
2-pentyl-3-phenyloxirane-2-carbaldehyde (4b): $R_f = 0.32$ (10:1 Hex/EtOAc); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 9.07 (s, 1H), 7.23-7.37 (m, 5H), 4.27 (s, 0.14H), 4.25 (s, 0.75H), 1.78-1.85 (m, 0.85H), 1.35-1.45 (m, 1H), 1.08-1.32 (m, 6H), 0.76-0.80 (t, 3H, $J = 7.03$ Hz); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 199.5, 133.3, 128.6, 128.5, 126.7, 126.7, 68.1, 60.9, 31.9, 24.5, 23.4, 22.4, 14.0; IR (NaCl, CH_2Cl_2), 2957, 2930, 2861, 1728, 1153 cm^{-1} . Mass was unobtainable.



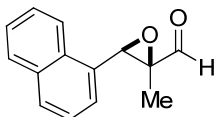
2,3-diphenyloxirane-2-carbaldehyde (4c): $R_f = 0.26$ (5:1 Hex/EtOAc); $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 9.43 (s, 1H), 7.24-7.25 (m, 5H), 7.14-7.17 (m, 3H), 7.07-7.08 (m, 2H), 4.53 (s, 1H); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 197.2, 132.4, 129.2, 128.8, 128.7, 128.3, 128.2, 126.9, 69.9, 62.9; IR (NaCl, CH_2Cl_2), 3066, 3032, 2815, 1726, 1448 cm^{-1} ; HRMS (FAB+) calcd for $\text{C}_{15}\text{H}_{12}\text{O}_2$, 224.0835. Found 224.0837.



3-(4-chlorophenyl)-2-methyloxirane-2-carbaldehyde (4d): $R_f = 0.30$ (10:1 Hex/EtOAc); $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 9.08 (s, 1H), 7.36-7.38 (d, 2H, $J = 8.42$ Hz), 7.22-7.25 (d, 2H, $J = 8.42$ Hz), 4.27 (s, 1H), 1.20 (s, 3H); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 198.9, 134.7, 131.7, 128.9, 128.2, 65.2, 60.1, 9.4; IR (NaCl, CH_2Cl_2) 2974, 2936, 2820, 1731, 1493 cm^{-1} ; HRMS (FAB+) calcd for $\text{C}_{10}\text{H}_9\text{ClO}_2$, 196.0281. Found 196.0291.

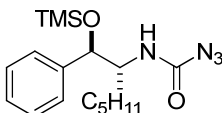


2-methyl-3-(naphthalene-2-yl) oxirane-2-carbaldehyde (4e): $R_f = 0.25$ (1:1 Hex/EtOAc); $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 9.16 (s, 1H), 7.84-7.88 (m, 3H), 7.79 (s, 1H), 7.50-7.53 (m, 2H), 7.37-7.41 (dd, 1H, $J = 1.83, 8.42$ Hz); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 199.4, 133.5, 133.2, 130.6, 128.5, 128.2, 128.1, 126.9, 126.7, 126.1, 124.1, 65.5, 60.9, 9.5; IR (NaCl, CH_2Cl_2), 3057, 2924, 2806, 1728, 1389 cm^{-1} ; HRMS (FAB+) calcd for $\text{C}_{14}\text{H}_{12}\text{O}_2$ 212.0837. Found 212.0842.

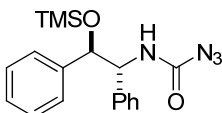


2-methyl-3-(naphthalen-1-yl) oxirane-2-carbaldehyde (4f): Rf = 0.19 (10:1 Hex/EtOAc); $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 9.31 (s, 1H), 7.85-7.93 (m, 2H), 7.73-7.76 (m, 1H), 7.52-7.56 (m, 4H), 4.77 (s, 1H), 1.14 (s, 1H); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 199.8, 133.5, 131.0, 129.3, 129.2, 129.1, 127.1, 125.6, 125.6, 124.8, 122.6, 65.4, 59.6, 9.9; IR (NaCl, CH_2Cl_2), 3037, 2986, 2825, 1727, 1378 cm^{-1} ; HRMS (FAB+) calcd for $\text{C}_{14}\text{H}_{12}\text{O}_2$ 212.0837. Found 212.0842.

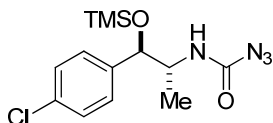
Carbamoyl Azide Characterization



1,2-anti-1-phenyl-1-(trimethylsiloxy) heptan-2-yl carbamoyl azide (16b): Title compound was prepared according to general procedure A. Rf = 0.2 (95:5 Hex:EtOAc); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.20-7.30 (m, 5H), 5.22 (br d, 1H), 4.72 (d, 1H, $J = 2.40$ Hz), 3.73-3.80 (m, 1H), 1.16 (d, 3H, $J = 6.80$ Hz), 0.03 (s, 9H); $^{13}\text{C NMR}$: (100 MHz, CDCl_3) δ 156.1, 141.9, 128.3, 126.2, 126.1, 75.1, 57.9, 32.6, 31.9, 25.9, 22.8, 14.3, 0.1; IR (NaCl, neat) 3432, 3317, 2956, 2930, 2860, 2445, 2134, 1693, 1504, 1251, 1228 cm^{-1} ; HRMS (FAB+) calcd for $\text{C}_{17}\text{H}_{28}\text{N}_4\text{O}_2\text{Si}$ 348.1981. Found 348.1983.

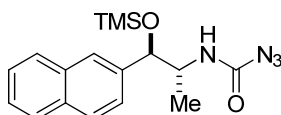


1,2-anti-1,2-diphenyl-2-(trimethylsiloxy) ethyl carbamoyl azide (16c): Title compound was prepared according to general procedure A. Rf = 0.4 (95:5 Hex:EtOAc); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.13-7.35 (m, 10H), 6.04 (br d, 1H), 8.47-4.92 (m, 2H), 0.013 (s, 9H); $^{13}\text{C NMR}$: (100 MHz, CDCl_3) δ 156.1, 141.5, 140.2, 128.6, 128.5, 128.0, 127.8, 126.8, 125.9, 77.8, 61.6, 0.1; IR (NaCl, neat) 3430, 3313, 3064, 3031, 2957, 2897, 2443, 2141, 1701, 1497, 1251, 1231 cm^{-1} ; HRMS (FAB+) calcd for $\text{C}_{18}\text{H}_{22}\text{N}_4\text{O}_2\text{Si}$ 354.151 Found 354.1511.



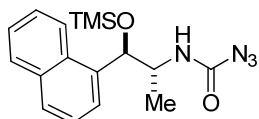
1,2-anti-1-(4-chlorophenyl)-1-(trimethylsilyloxy) propan-2-yl carbamoyl azide (16d):

Title compound was prepared according to general procedure A. R_f = 0.3 (95:5 Hex:EtOAc); ¹H NMR (400 MHz, CDCl₃) δ 7.15-7.30 (m, 4H), 5.27 (br d, 1H), 4.61 (d, 1H, *J* = 2.40 Hz), 3.90-3.93 (m, 1H), 1.16 (d, 3H, *J* = 6.80 Hz), 0.03 (s, 9H); ¹³C NMR: (100 MHz, CDCl₃) δ 155.9, 140.3, 133.5, 127.5, 75.7, 53.2, 18.2, 0.1; IR (NaCl, neat) 3317, 2958, 2444, 2139, 1689, 1491 cm⁻¹; HRMS (FAB+) calcd for C₁₃H₁₉ClN₄O₂Si 326.0965. Found 326.0962.



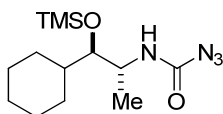
1,2-anti-1-(naphthalene-2-yl)-1-(trimethylsilyloxy) propan-2-yl carbamoyl azide (16e):

Title compound was prepared according to general procedure A. R_f = 0.35 (95:5 Hex:EtOAc); ¹H NMR (400 MHz, CDCl₃) δ 5.39 (br d, 1H), 3.92-3.97 (m, 1H), 3.36-3.39 (dd, 1H, *J* = 2.80, 8.8 Hz), 3.73-3.80 (m, 1H), 1.16 (d, 3H, *J* = 6.80 Hz), 0.03 (s, 9H); ¹³C NMR: (100 MHz, CDCl₃) δ 156.1, 141.9, 128.3, 126.2, 126.1, 75.1, 57.9, 32.6, 31.91, 25.9, 22.8, 14.3, 0.2; IR (NaCl, Neat) 3427, 3056, 2927, 2853, 2137, 1709, 1507 cm⁻¹.



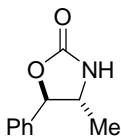
1,2-anti-1-(naphthalene-1-yl)-1-(trimethylsilyloxy) propan-2-yl carbamoyl azide (16f):

Title compound was prepared according to general procedure A. R_f = 0.35 (95:5 Hex:EtOAc); ¹H NMR (400 MHz, CDCl₃) δ 7.85-7.87 (m, 2H), 7.75-7.77 (m, 1H), 7.41-7.55 (m, 4H), 5.48 (br d, 1H), 5.42 (s, 1H), 4.11-4.16 (m, 1H), 1.34 (d, 3H, *J* = 6.80 Hz), 0.05 (s, 9H); ¹³C NMR: (100 MHz, CDCl₃) δ 155.9, 137.0, 133.9, 129.4, 128.4, 126.5, 125.7, 125.2, 124.1, 122.3, 52.2, 19.1, 0.2; IR (NaCl, neat) 3284, 2958, 2138, 1701, 1508, 1251, 1230 cm⁻¹; HRMS (FAB+) calcd for C₁₇H₂₂N₄O₂Si 342.1512. Found 342.1515.

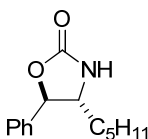


1,2-anti-1-cyclohexyl-1-(trimethylsilyloxy) propan-2-yl carbamoyl azide (16g):

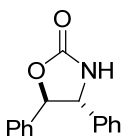
Title compound was prepared according to general procedure A. R_f = 0.2 (95:5 Hex:EtOAc); ¹H NMR (400 MHz, CDCl₃) δ 5.39 (br d, 1H), 3.92-3.97 (m, 1H), 3.38 (dd, 1H, *J* = 2.80, 8.8 Hz), 1.58-1.73 (m, 1H), 1.10 (d, 3H, *J* = 6.80 Hz), 0.84-1.22 (m, 10H), 0.10 (s, 9H); ¹³C NMR: (100 MHz, CDCl₃) δ 155.9, 80.4, 48.7, 41.8, 30.2, 29.3, 26.5, 26.3, 20.1, 0.9; IR (NaCl, neat) 3431, 3321, 2928, 3061, 2853, 2445, 2137, 1692, 1500, 1249, 1229, cm⁻¹; HRMS (FAB+) calcd for C₁₃H₂₇N₄O₂Si 298.1825 Found 298.1825.

Oxazolidinone Characterization

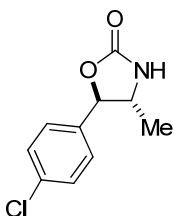
4,5-anti-4-methyl-5-phenyloxazolidin-2-one (17a): $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.33-7.39 (m, 5H), 6.38 (s, 1H), 5.01 (d, 1H, $J = 7.24$ Hz), 3.82 (quint, 1H, $J = 6.40$ Hz), 1.36 (d, 3H, $J = 6.18$ Hz).



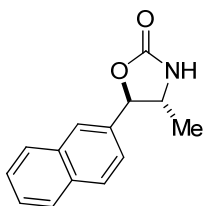
4,5-anti-4-pentyl-5-phenyloxazolidin-2-one (17b): Reported as a mixture of diastereomers: $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.32-7.39 (m, 5H), 7.23-7.31 (m, 0.46H), 6.78 (s, 1H), 6.74 (s, 0.21 H), 5.67 (d, 0.19 H, $J = 8.31$ Hz), 5.07 (d, 1H, $J = 6.40$ Hz), 3.99-4.01 (m, 0.22 H), 3.60 (q, 1H, $J = 6.18$ Hz), 1.83 (s, 0.27 H), 1.58-1.67 (m, 2H), 1.25-1.43 (m, 7H), 1.06-1.22 (m, 1H), 0.827-0.863 (m, 3H), 0.739-0.744 (m, 0.67 H).



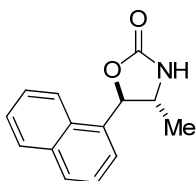
4,5-anti-4,5-diphenyloxazolidin-2-one (17c): $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.35-7.39 (m, 5H), 7.23-7.30 (m, 5H), 5.57 (s, 1H), 5.27 (d, 1H, $J = 7.46$ Hz), 4.73 (d, 1H, $J = 7.46$ Hz).



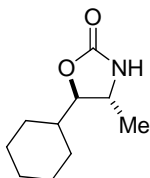
4,5-anti-5-(4-chlorophenyl)-4-methyloxazolidin-2-one (17d): $R_f = 0.30$ (1:1 Hex/EtOAc); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.33-7.37 (m, 2H) 7.27-7.29 (m, 2H), 6.33 (s, 1H), 4.98 (d, 1H, $J = 7.24$ Hz), 3.76 (quint, 1H, $J = 6.18$ Hz), 1.35 (d, 3H, $J = 6.18$ Hz); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 159.1, 136.3, 135.1, 129.3, 129.0, 127.5, 127.5, 84.8, 56.8, 20.1; IR (NaCl, neat) 2973, 2931, 1758, 1493, 1383 cm^{-1} ; HRMS (FAB⁺) calcd for $\text{C}_{10}\text{H}_{10}\text{ClNO}_2$ 211.0400. Found 211.0398.

**4,5-anti-4-methyl-5-(naphthalen-2-yl) oxazolidin-2-one (17e):**

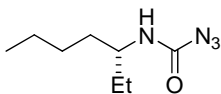
R_f = 0.24 (1:1 Hex/EtOAc); ¹H NMR (400 MHz, CDCl₃) δ 7.81-7.88 (m, 4H), 7.43-7.52 (m, 3H), 5.94 (s, 1H), 5.19 (d, 1H, *J* = 7.24 Hz), 3.90 (quint, 1H, *J* = 6.18 Hz), 1.42 (d, 3H, *J* = 6.18 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 159.1, 135.1, 133.7, 133.2, 129.3, 128.3, 128.0, 126.9, 125.7, 123.2, 85.7, 56.6, 20.3; IR (NaCl, neat) 3278, 2970, 1755, 1380, 1020 cm⁻¹; HRMS (FAB⁺) calcd for C₁₄H₁₃NO₂ 227.0951. Found 227.0946.

**4,5-anti-4-methyl-5-(naphthalen-1-yl) oxazolidin-2-one (17f):**

R_f = 0.30 (1:1 Hex/EtOAc); ¹H NMR (400 MHz, CDCl₃) δ 7.83-7.90 (m, 4H), 7.46-7.61 (m, 3H), 6.08 (s, 1H), 5.79 (d, 1H, *J* = 5.75 Hz), 3.98 (quint, 1H, *J* = 6.18 Hz), 1.51 (d, 3H, *J* = 6.18 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 159.3, 134.1, 133.3, 130.3, 129.6, 129.5, 126.9, 126.2, 125.6, 123.9, 122.6, 82.9, 55.8, 21.1; IR (NaCl, neat) 3278, 2971, 1754, 1380, 1234 cm⁻¹; HRMS (FAB⁺) calcd for C₁₄H₁₃N₄O₂ 227.0946. Found 227.0949.

**4,5-anti-5-cyclohexyl-4-methyloxazolidin-2-one (17g):**

R_f = 0.32 (10:1 Hex/EtOAc); ¹H NMR (400 MHz, CDCl₃) δ 6.56 (s, 1H), 6.35 (s, 0.29), 4.08-4.12 (dd, 0.32H, *J* = 3.62, 10.0 Hz), 3.79 (t, 1H), 3.75 (t, 0.32 H), 3.64 (quint, 1H, *J* = 6.18 Hz), 1.82 (d, 1H, *J* = 12.3 Hz), 1.70-1.58 (m, 5H), 1.47-1.52 (m, 1H), 1.09-1.23 (m, 8H), 0.972-1.09 (m, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 160.4, 159.8, 88.3, 84.5, 51.2, 51.2, 41.8, 36.9, 29.7, 28.9, 27.9, 26.4, 25.9, 25.7, 25.4, 25.4, 22.1, 15.8; IR (NaCl, neat) 3271, 2921, 2850, 1724, 1243 cm⁻¹. HRMS (FAB⁺) calcd for C₁₀H₁₇NO₂ 183.1259. Found 183.1259.

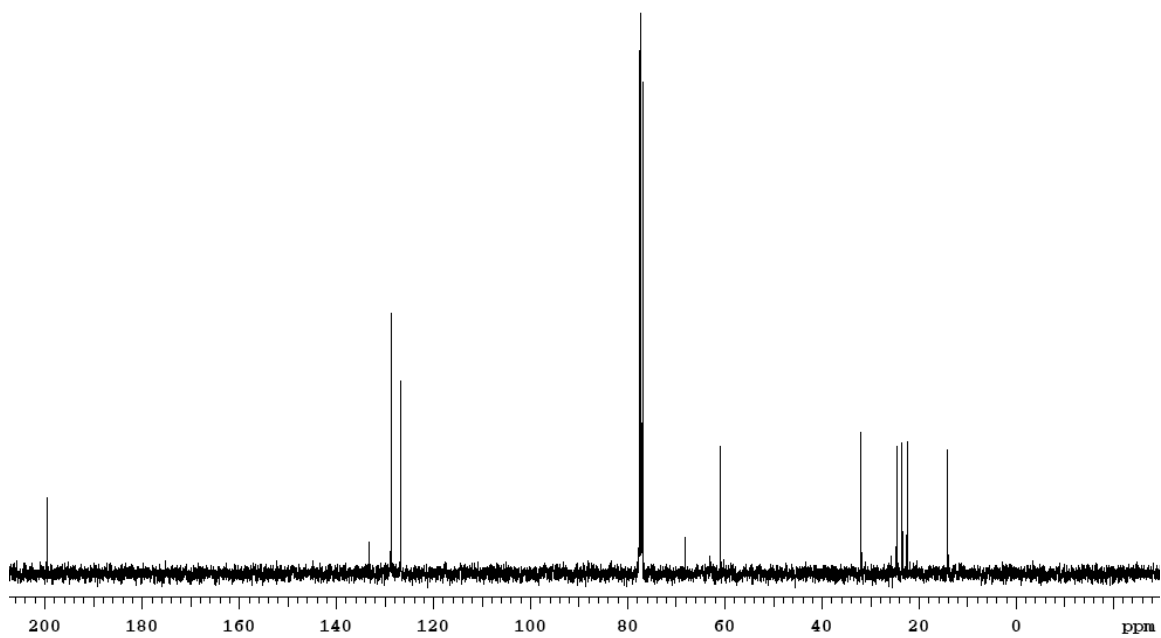
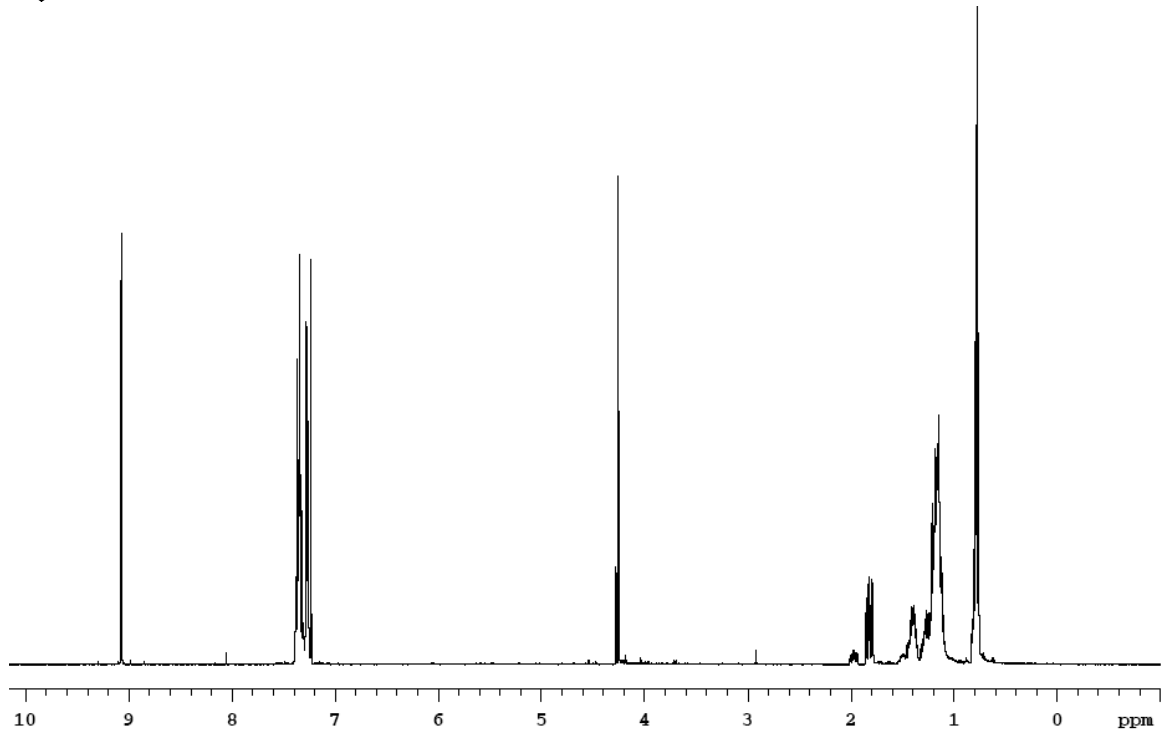
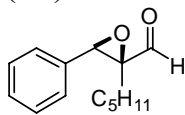
**(R)-heptan-3-ylcarbonyl azide (20):**

R_f = 0.20 (70:30 Hex/EtOAc); ¹H NMR (400 MHz, CDCl₃) δ 6.25 (s, 1H), 5.03 (m, 1H), 3.39 (d, 1H, *J* = 8.4 Hz), 3.24 (d, 1H, *J* = 8.4 Hz), 2.04-2.07 (m, 2 H), 1.58-1.71 (m, 9H), 1.42 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 160.0, 132.8, 123.1, 83.3, 51.3, 40.4, 25.9, 25.7, 22.3, 17.9; IR (NaCl, neat) 3271, 2921, 2850, 1724, 1243 cm⁻¹. [α]_D²³ = -30

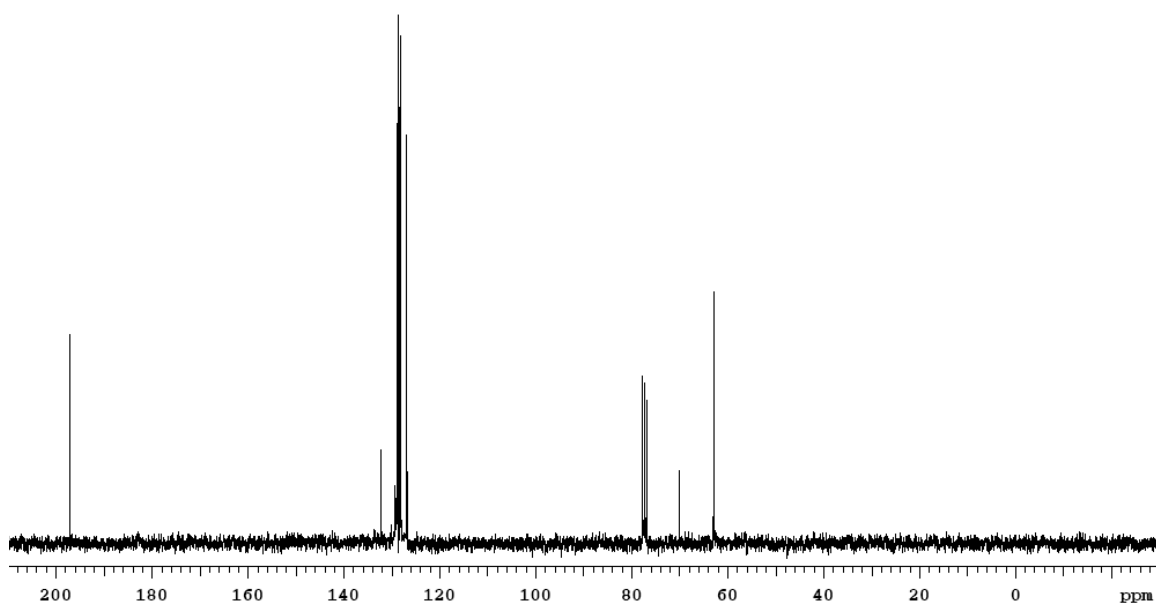
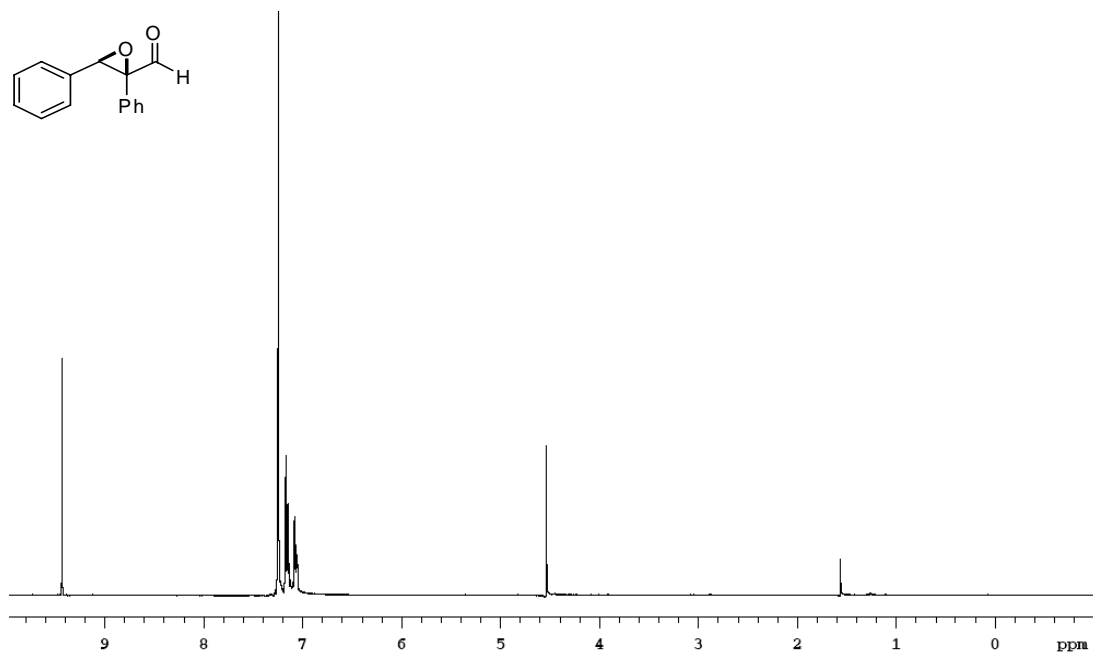
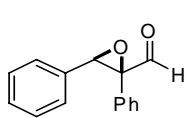
(CH₂Cl₂). HPLC Analysis CHIRACEL ADH column, 90:10 Hexanes: Isopropanol
1ml/min 30 min. Major 8.00, minor 7.61.

$^1\text{H NMR}$ and $^{13}\text{C NMR}$

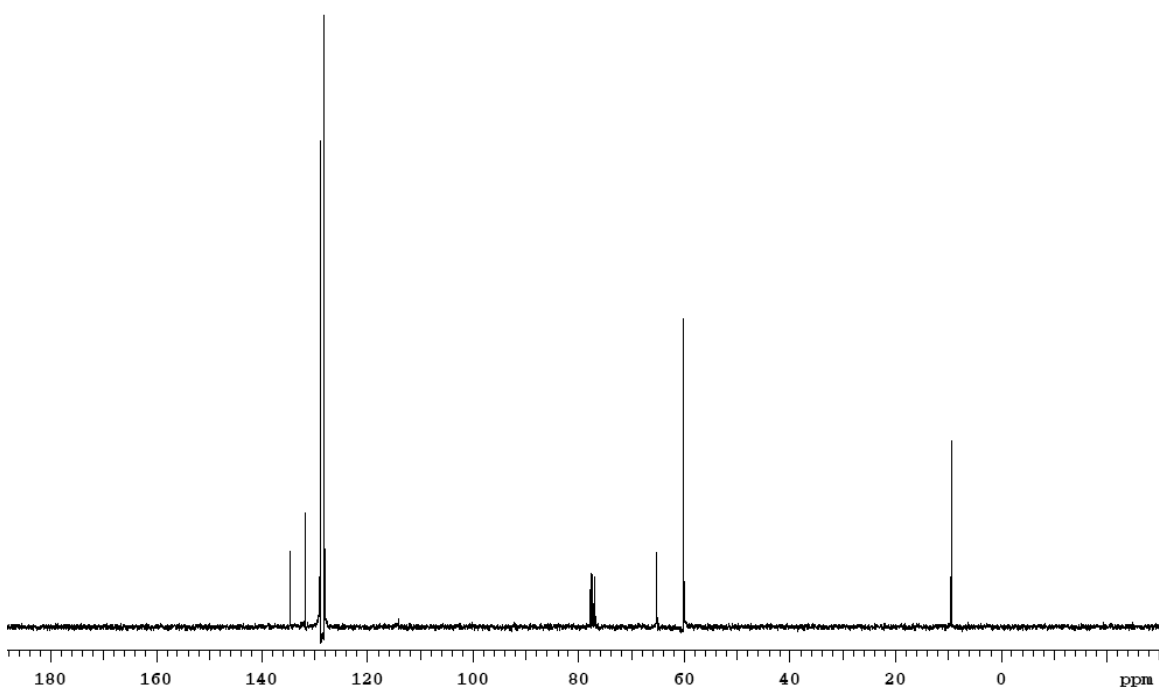
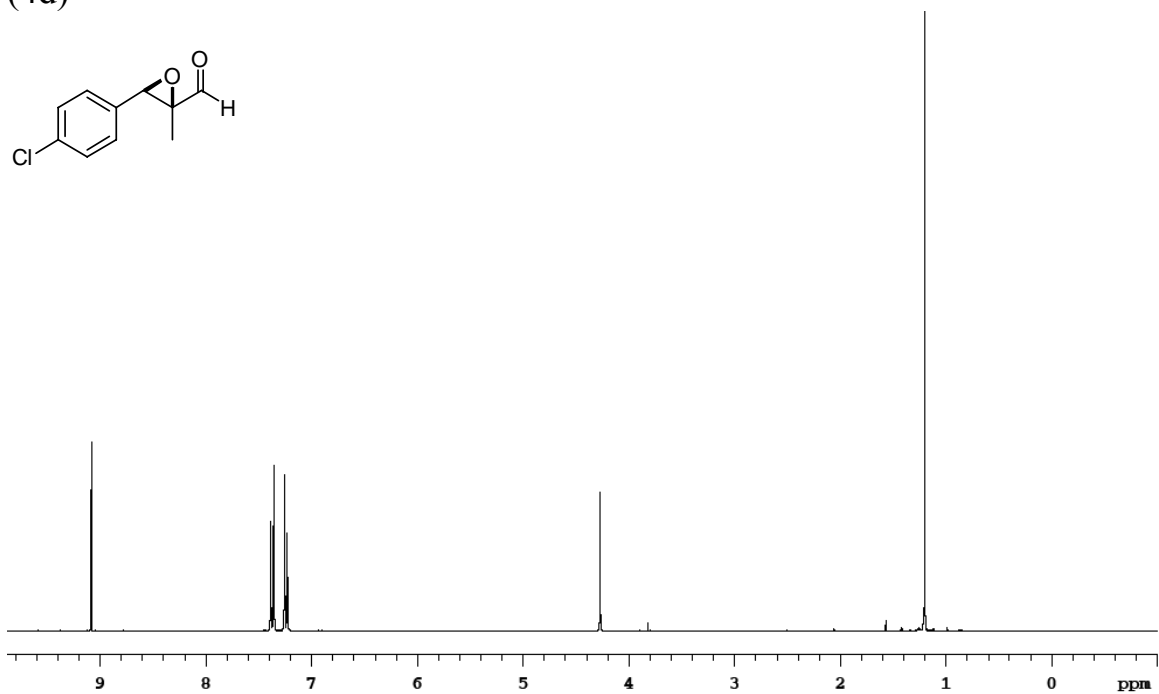
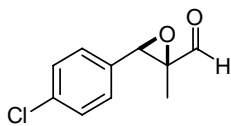
(4b)



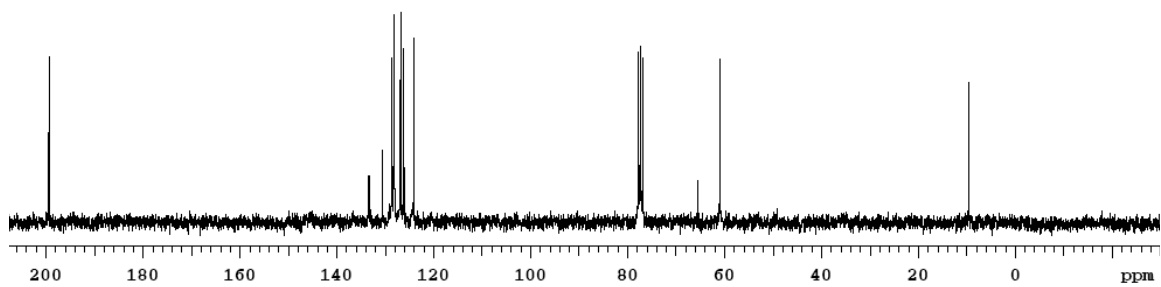
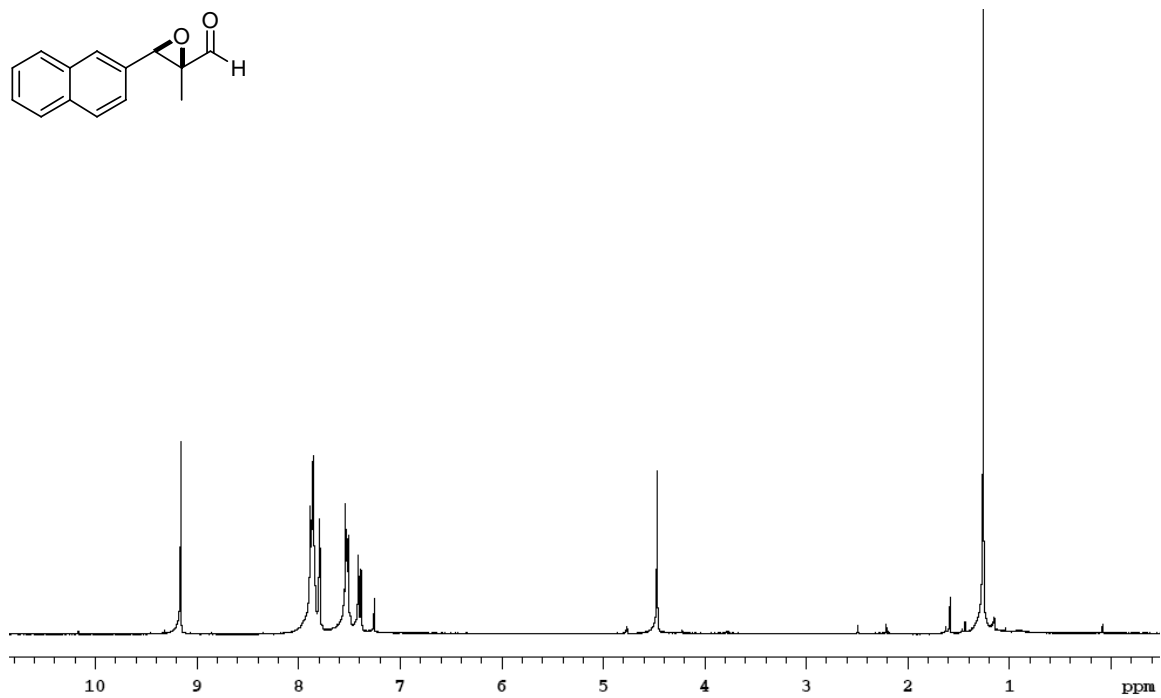
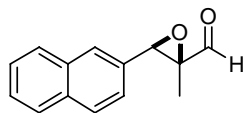
(4c)



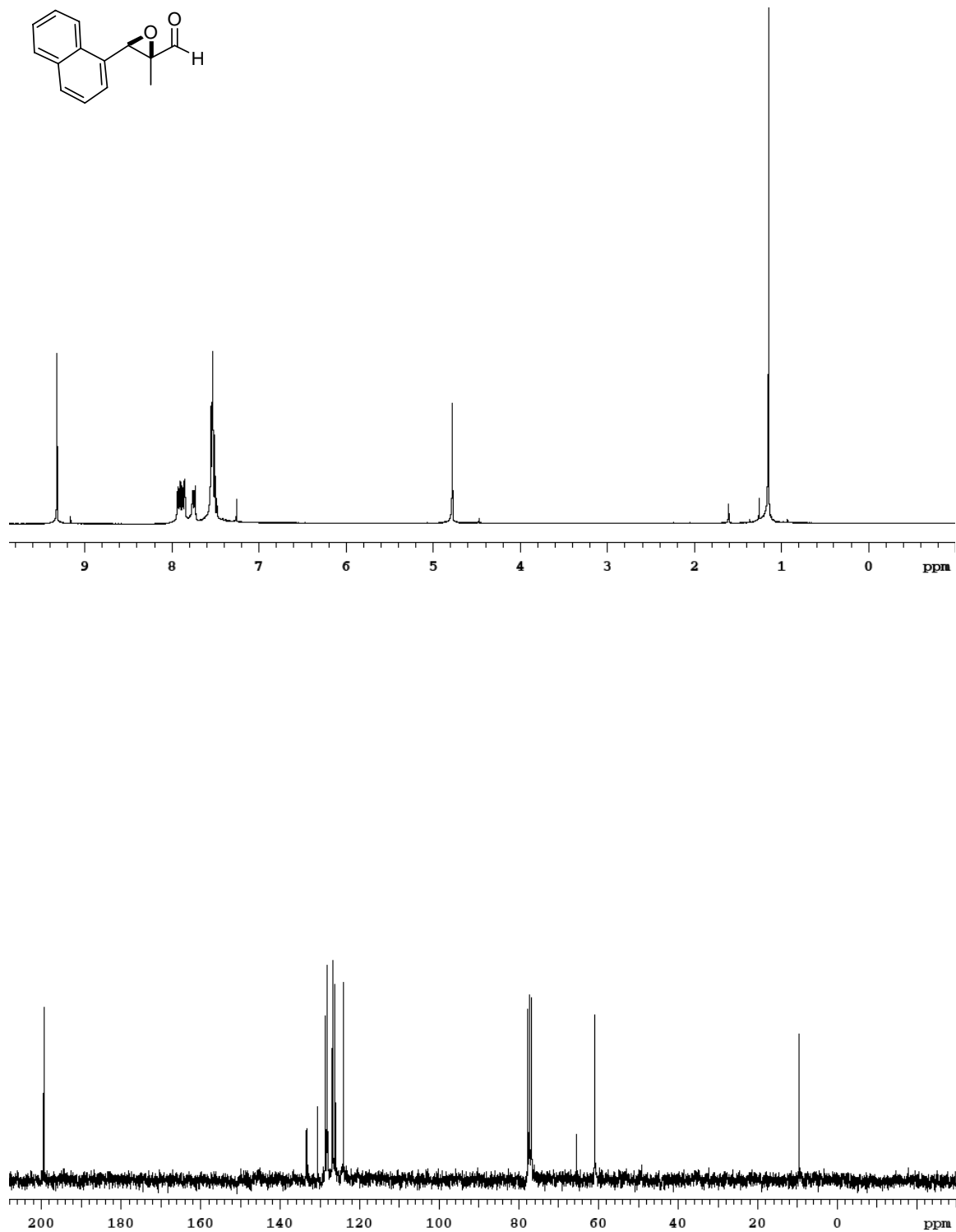
(4d)



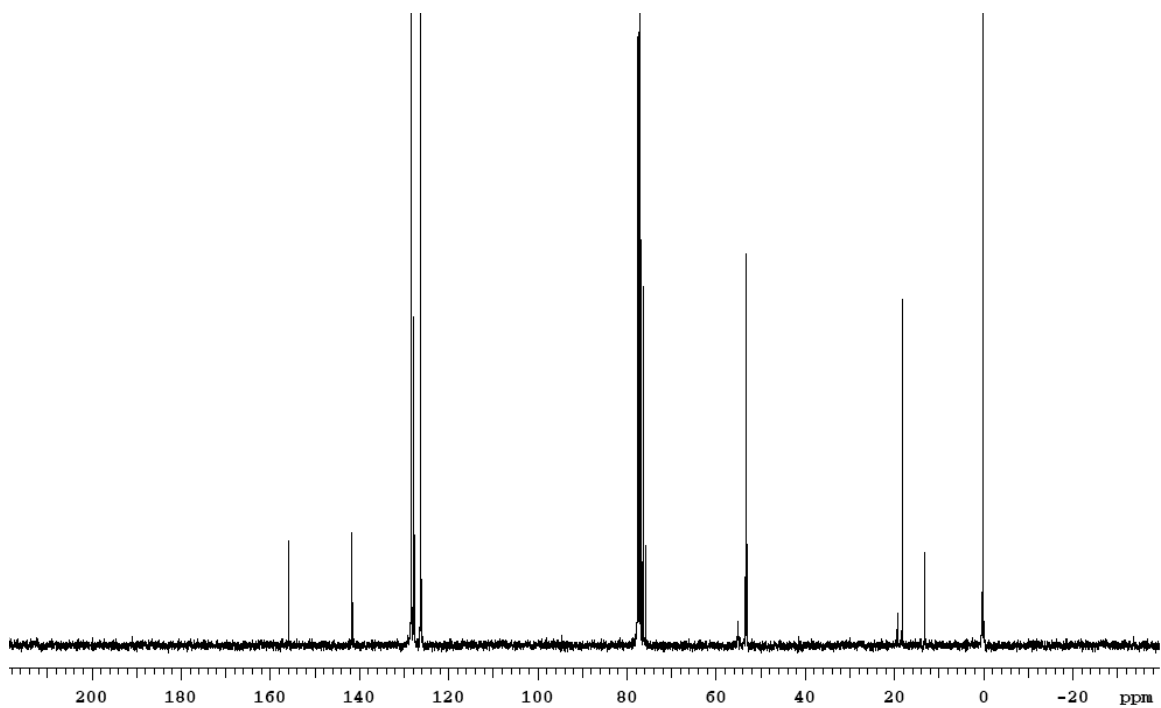
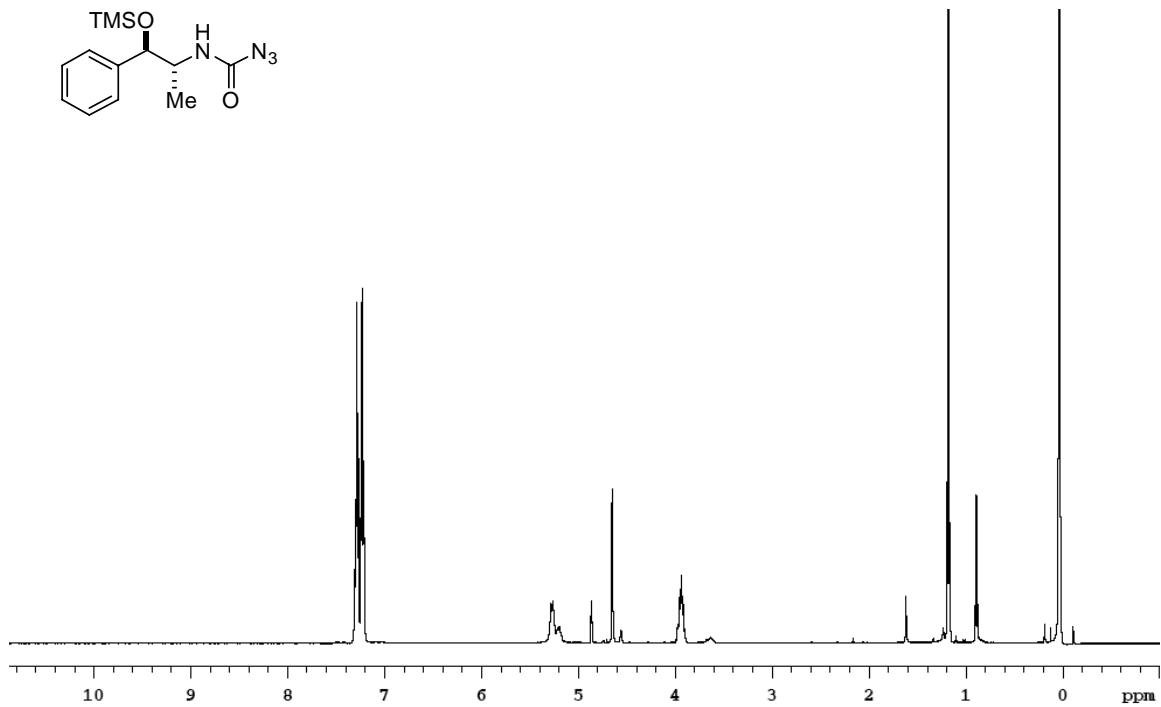
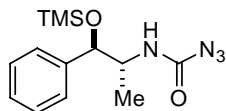
(4e)



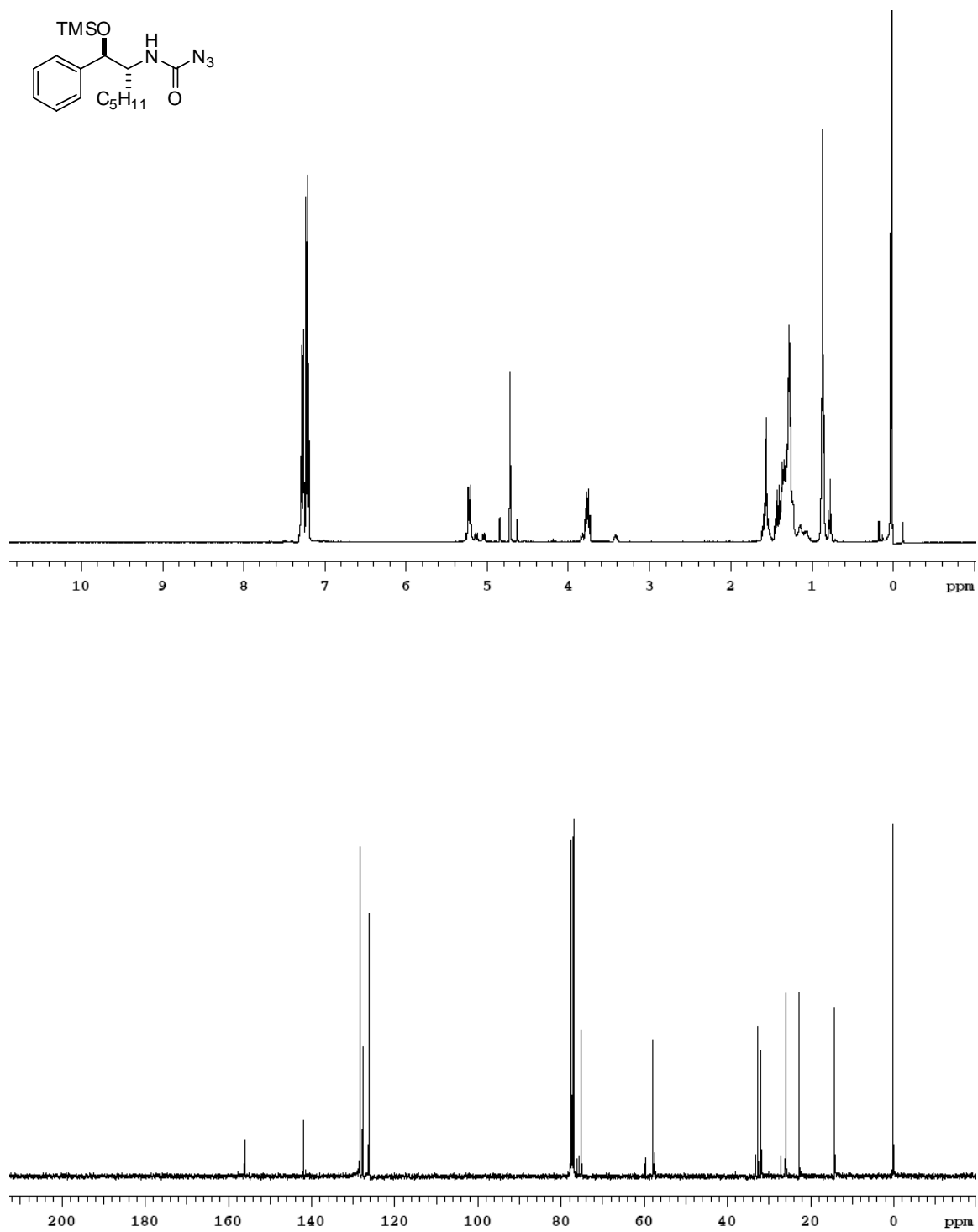
(4f)



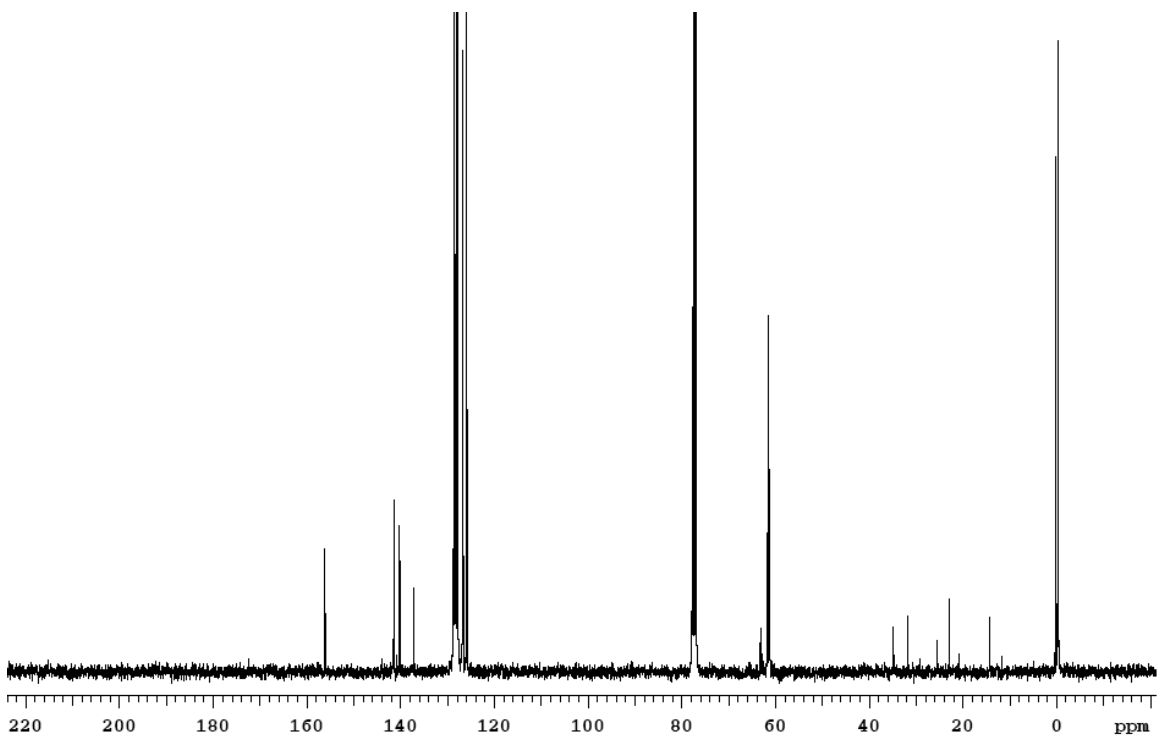
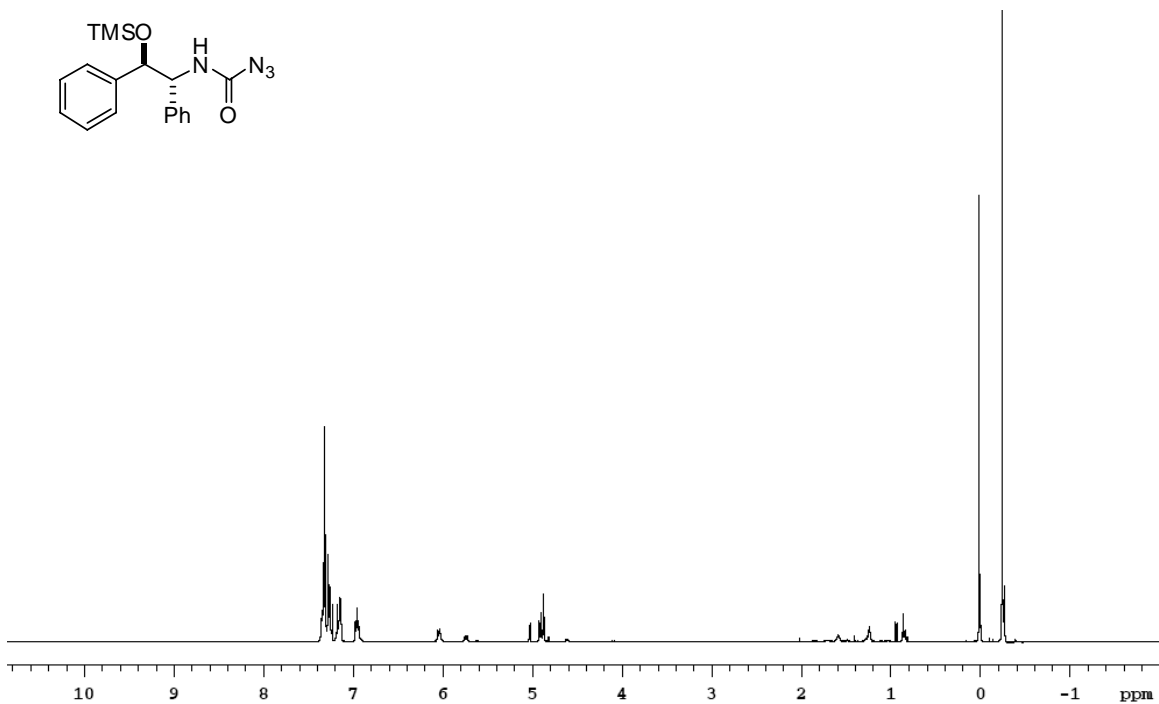
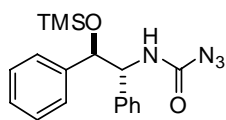
(16a)



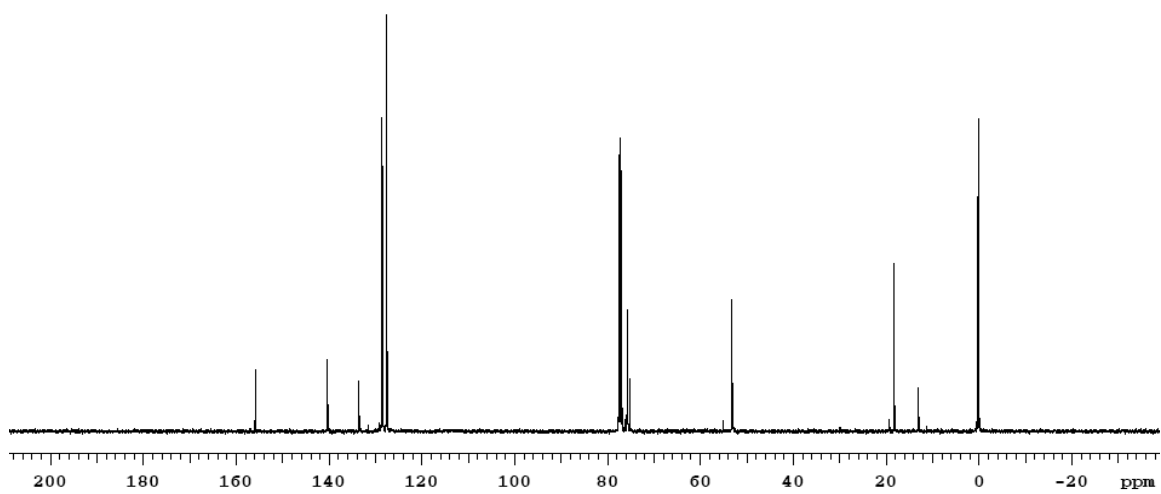
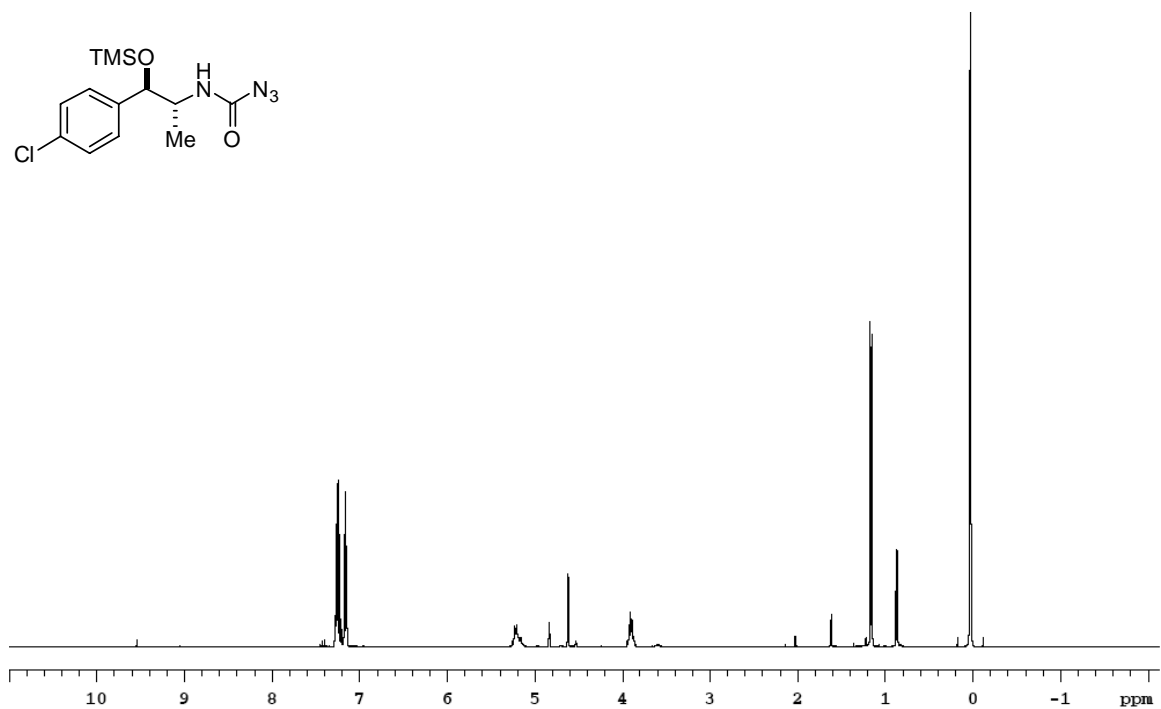
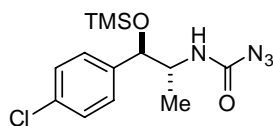
(16b)



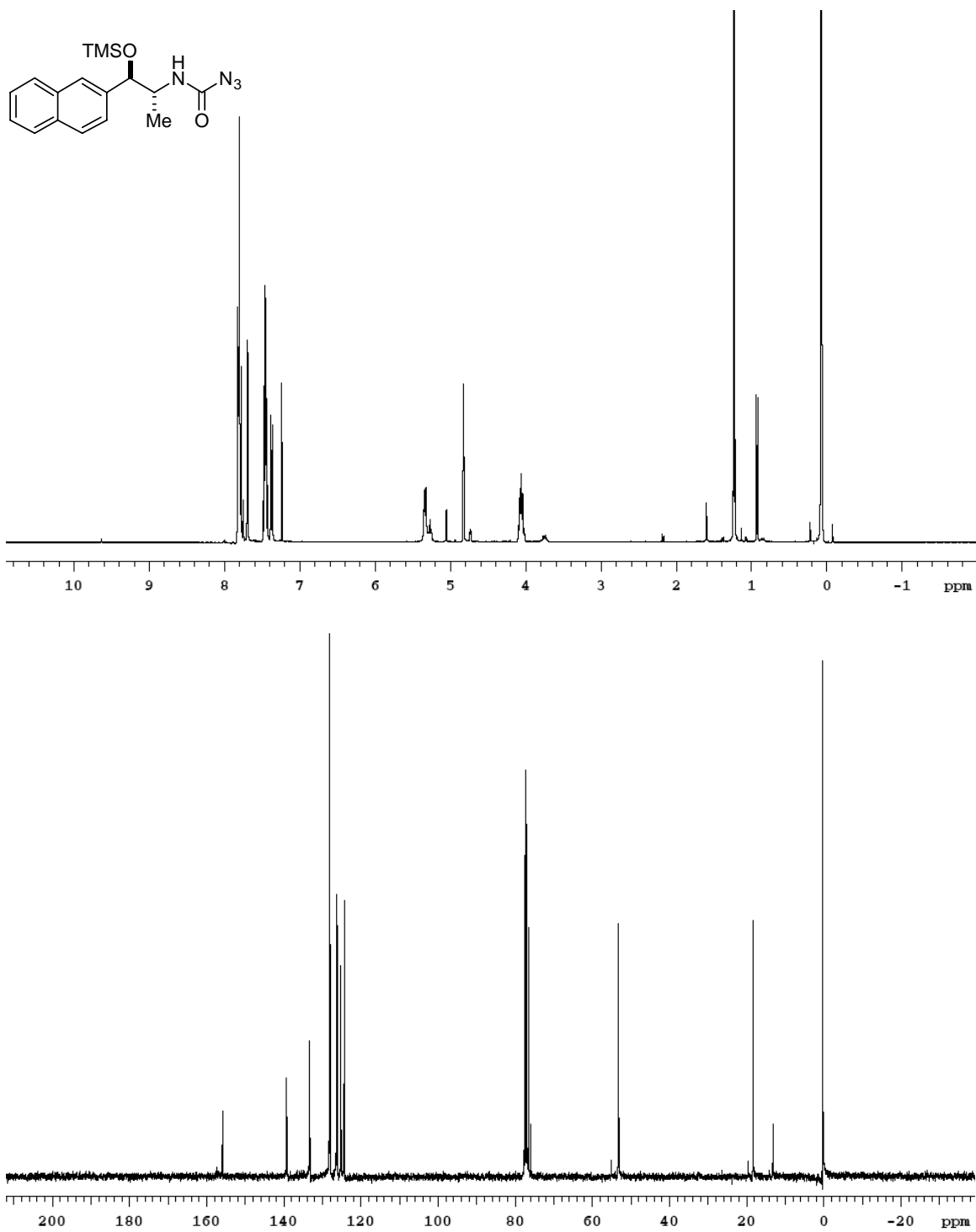
(16c)



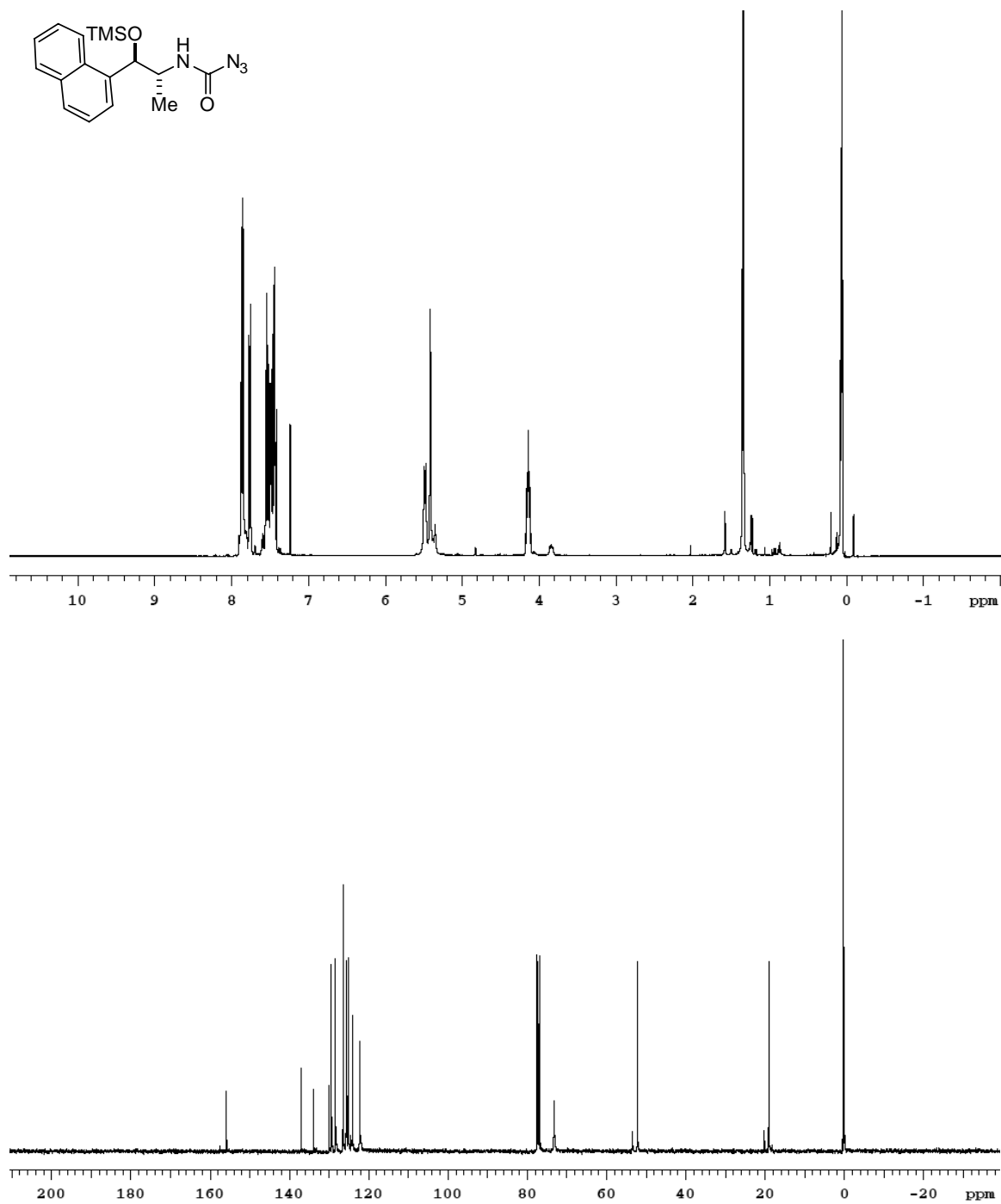
(16d)



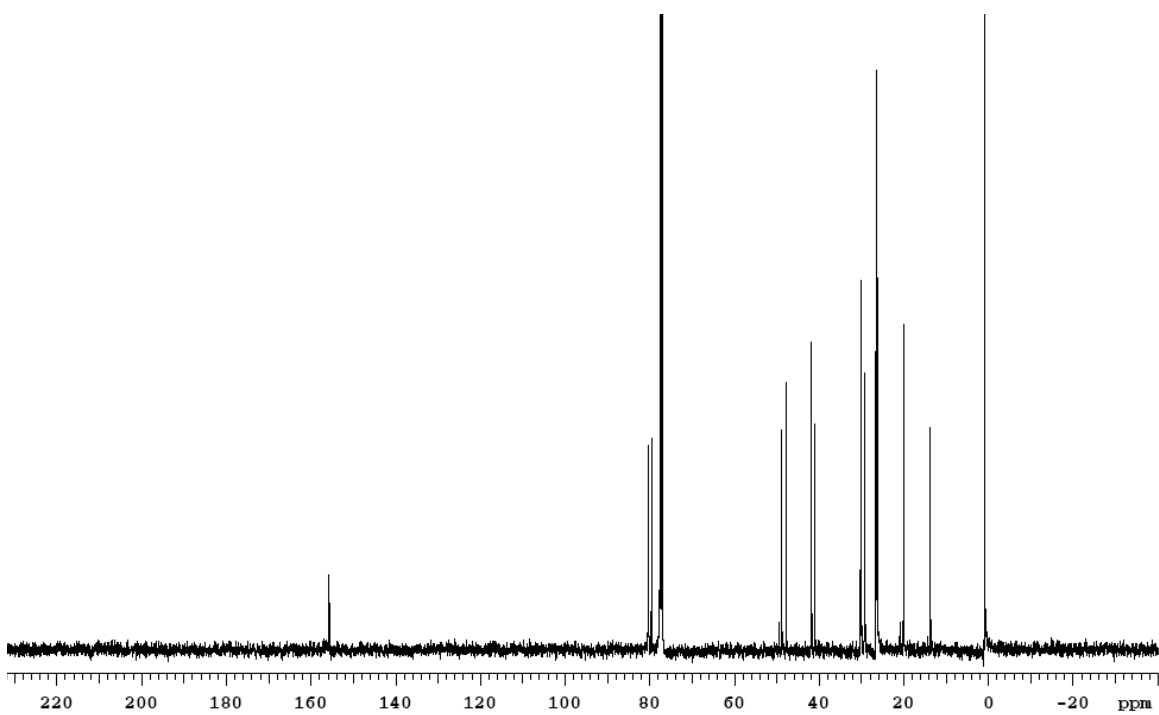
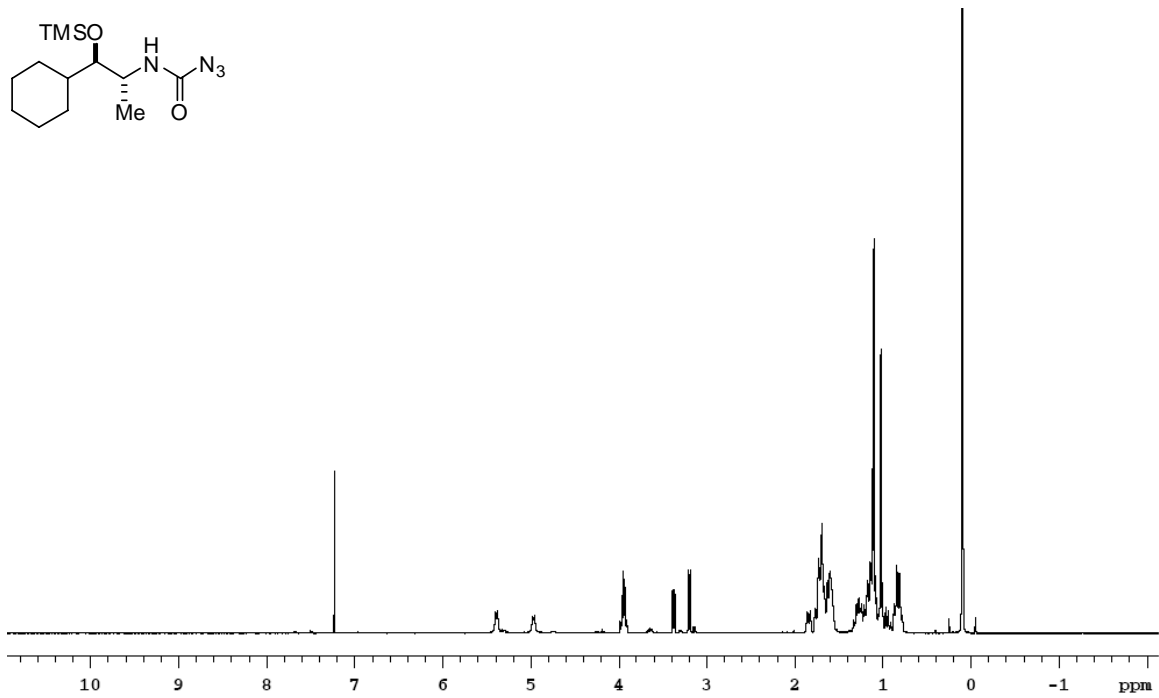
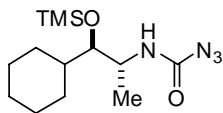
(16e)



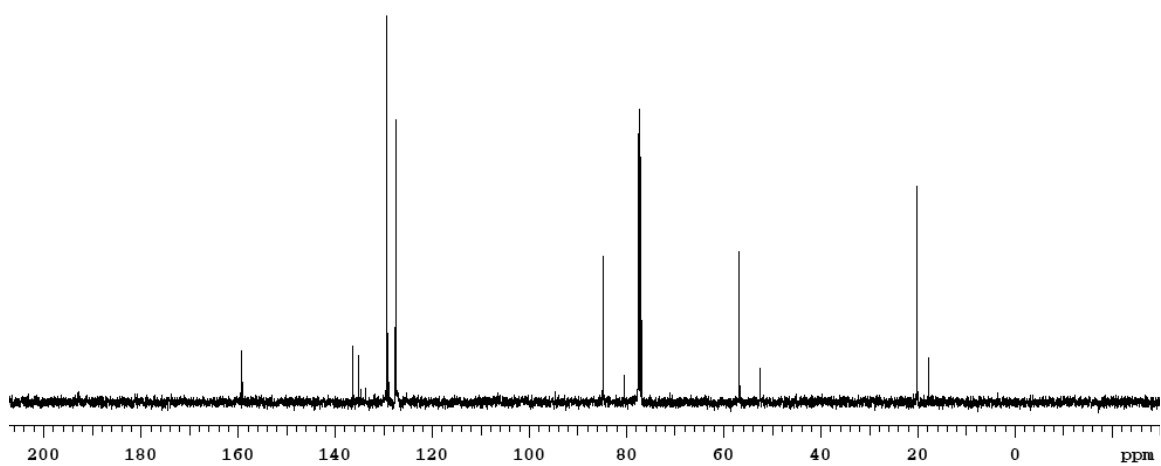
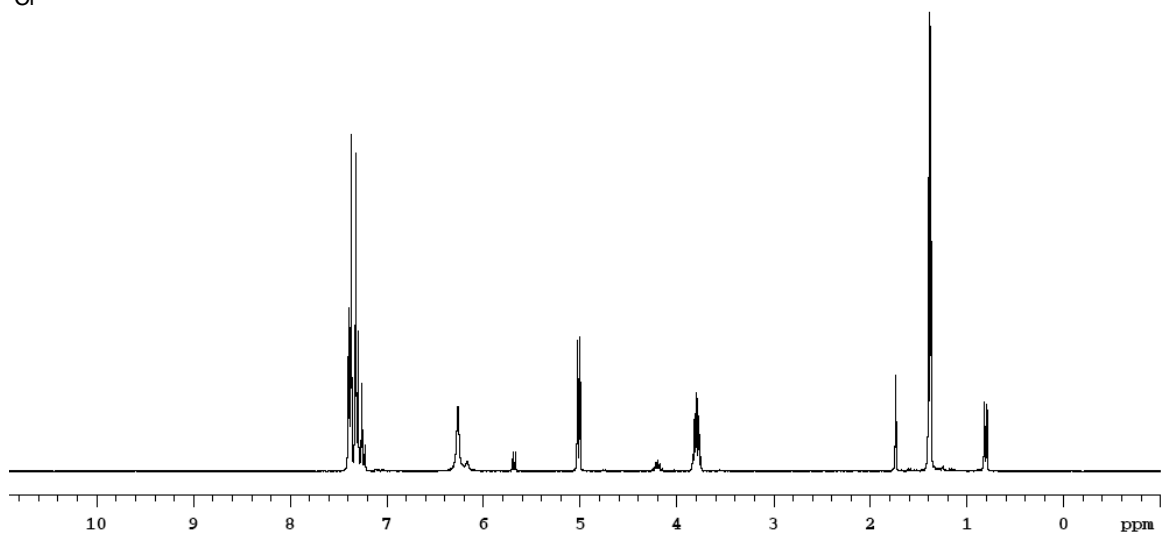
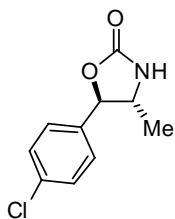
(16f)



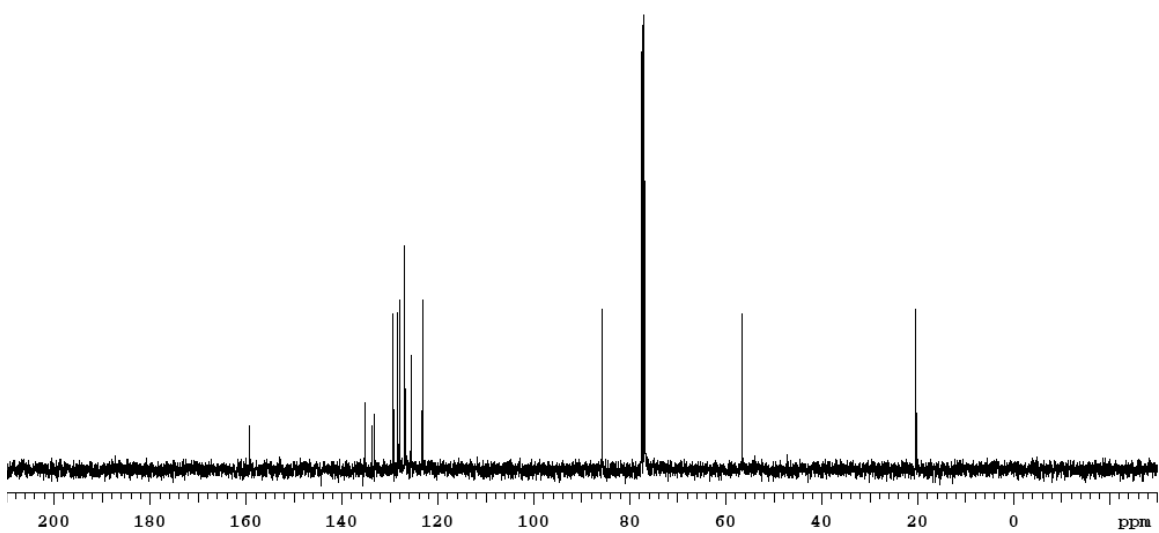
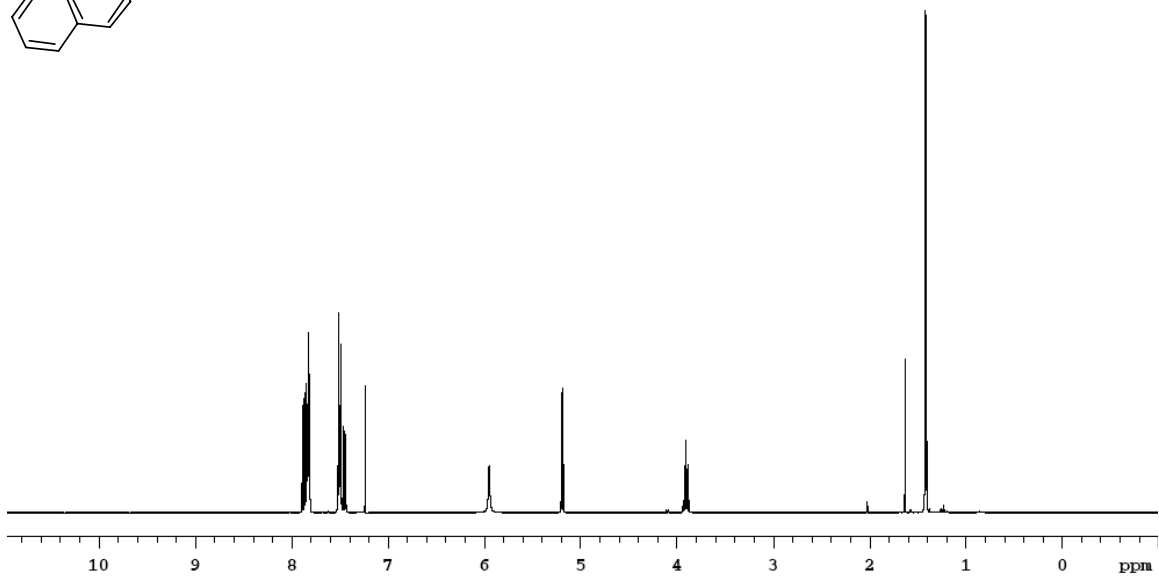
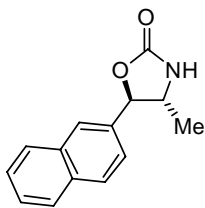
(16g)



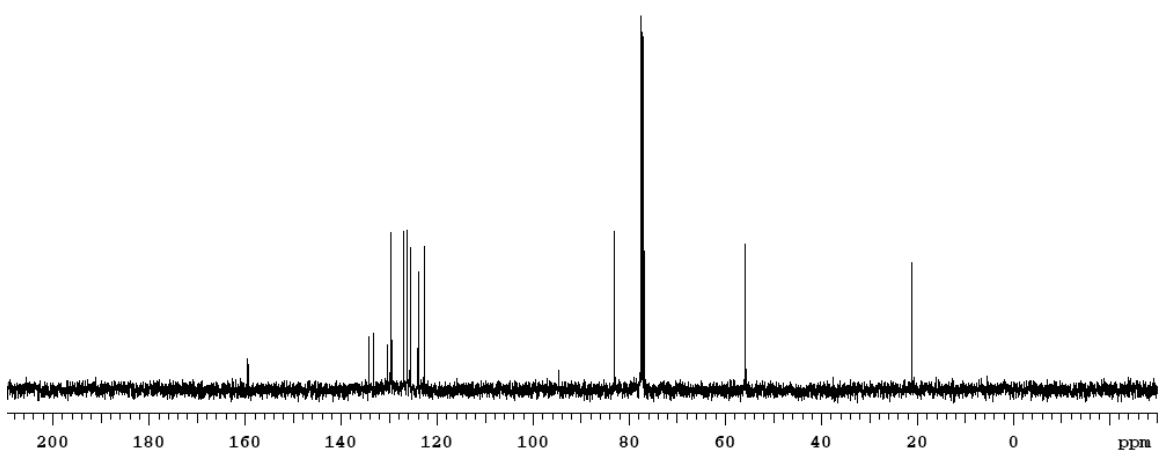
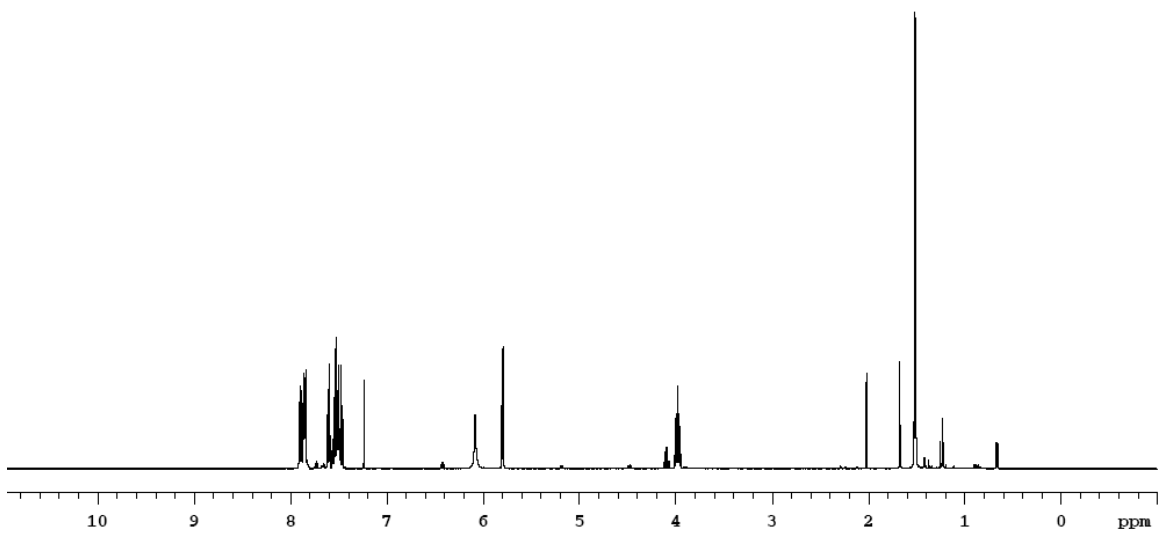
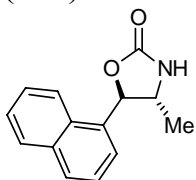
(17a)



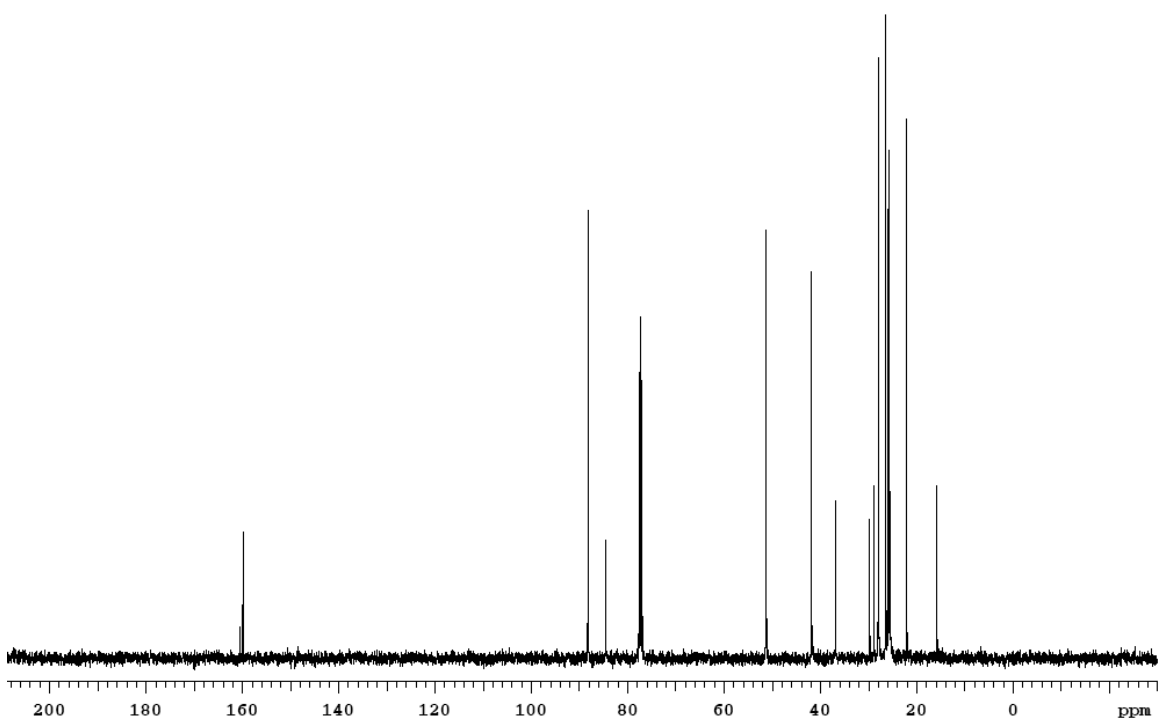
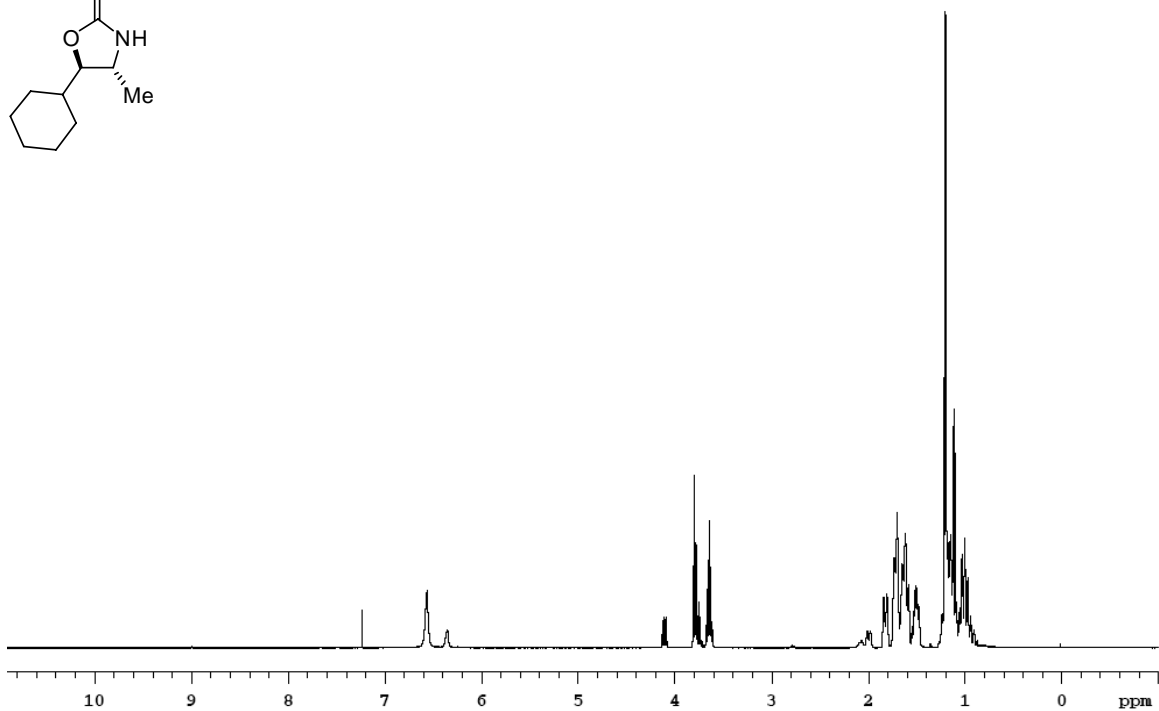
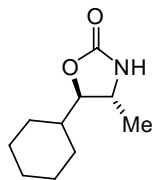
(17b)



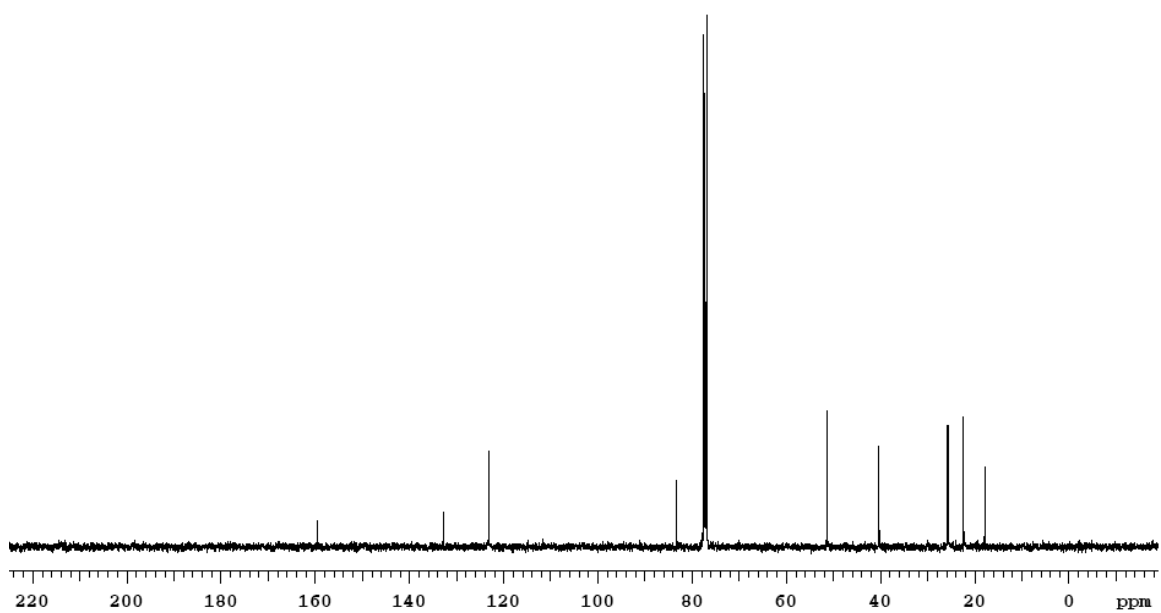
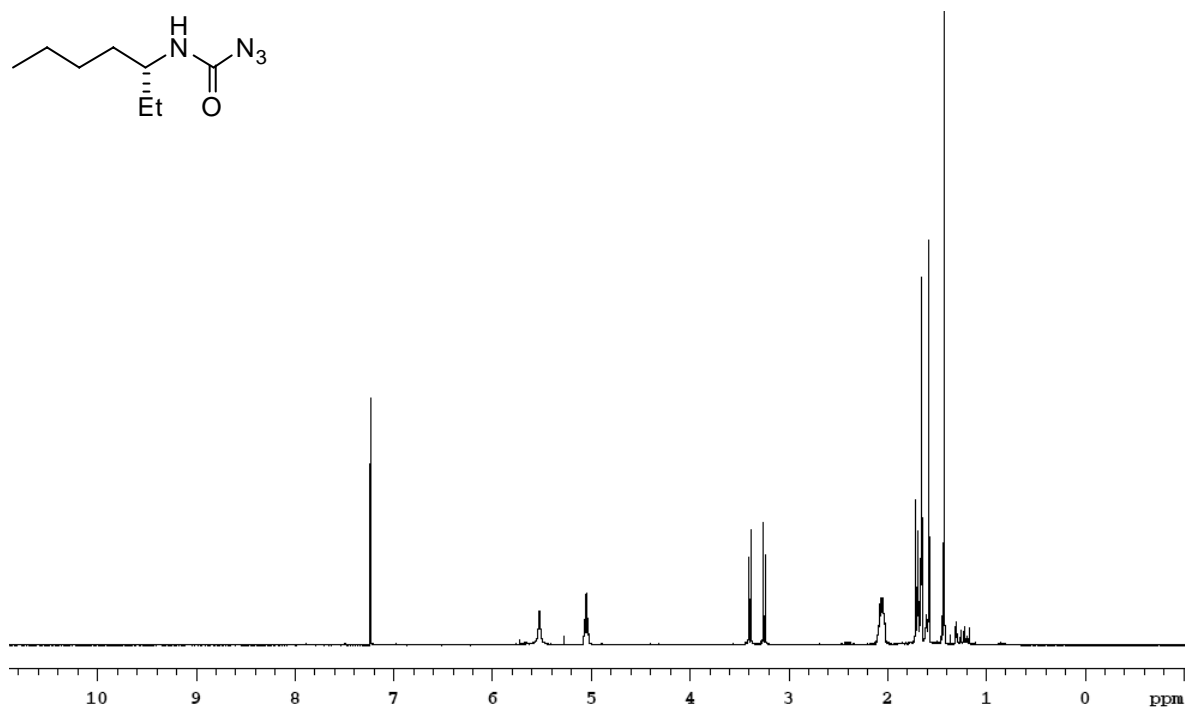
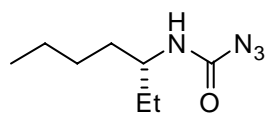
(17c)



(17d)



(20)



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