

Synthesis of Syn-1,3-aminoalcohols via a Ru-Catalyzed *N*-Demethylative Rearrangement of Isoxazolidines and Its application in Three-Step Total Synthesis of HPA-12

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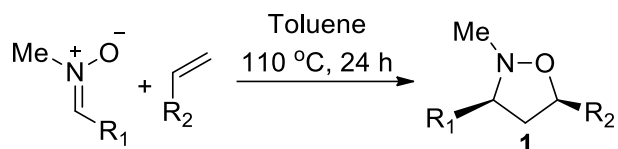
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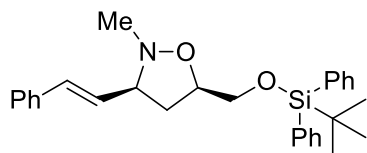
1. General information and experiments

Solvents were pre-dried over activated 4Å molecular sieves and heated to reflux over sodium (toluene, THF) or calcium hydride (CH₂Cl₂) under a nitrogen atmosphere and collected by distillation. ¹H, ¹³C NMR spectra were recorded on a Bruker 400 MHz spectrometer; Chemical shifts are reported in δ units relative to [CDCl₃, ¹H δ = 7.26, ¹³C δ = 77.36]. What should be noted is that all petroleum ether and ethyl acetate using for flash chromatography purchased from commercial sources were redistilled twice before using, even though the trace amount of residue of impurities such as H-grease and silicone grease could still be seen on NMR spectra of some products (¹H NMR: δ 1.25/0.84-0.87 and 0.07; ¹³C NMR δ 29.7 and 1.19). HRMS were recorded by the mass spectrometry service at University of Science and Technology of China. All alkenes were purchased from commercial sources and nitrones were prepared according to literatural procedures.¹

(1) General procedure for preparation of starting materials

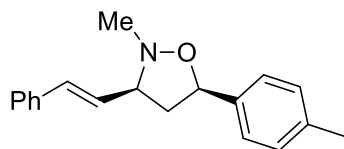


Styrene (4 equiv.) was added into the solution of a nitronium (2.0 mmol) in toluene (0.25 M) and the resulting reaction solution was stirred at 110 °C under argon for corresponding time (typically 24 hours). After cooling to room temperature, the reaction solution was concentrated by a rotary evaporator, followed by isolation using flash column chromatography on silica gel to give the *cis*-isoxazolidines **1**.



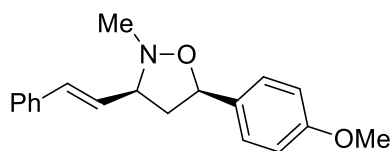
***cis*-5-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-methyl-3-((*E*)-styryl)isoxazolidine (**1a**)**

¹H NMR (400 MHz, CDCl₃) δ 7.72 - 7.69 (m, 4H), 7.45 - 7.29 (m, 10H), 7.26 - 7.22 (m, 1H), 6.54 (d, *J* = 16.0 Hz, 1H), 6.03 (dd, *J* = 16.0, 9.0 Hz, 1H), 4.33 - 4.26 (m, 1H), 3.89 (dd, *J* = 10.2, 6.2 Hz, 1H), 3.64 - 3.60 (m, 1H), 3.17 - 3.15 (m, 1H), 2.64 (s, 3H), 2.61 - 2.54 (m, 1H), 2.00 - 1.94 (m, 1H), 1.07 (s, 9H). **¹³C NMR** (100 MHz, CDCl₃) δ 136.7, 135.9, 135.8, 133.9, 133.8, 133.3, 129.8, 128.7, 128.1, 128.0, 127.9, 127.8, 126.6, 77.0, 71.9, 66.6, 43.3, 40.0, 27.1, 19.5. **HRMS (ESI)** calcd for C₂₉H₃₆NO₂Si [M+H]⁺ 458.2515, found 458.2514.



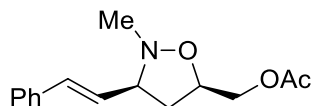
***cis*-2-methyl-3-((*E*)-styryl)-5-(*p*-tolyl)isoxazolidine (**1b**)**

¹H NMR (400 MHz, CDCl₃) δ 7.36 - 7.25 (m, 6H), 7.22 - 7.17 (m, 1H), 7.14 - 7.12 (m, 2H), 6.56 (d, *J* = 15.8 Hz, 1H), 6.14 (dd, *J* = 15.8, 8.2 Hz, 1H), 5.14 (dd, *J* = 7.6, 7.6 Hz, 1H), 3.38 (br s, 1H), 2.88 - 2.81 (m, 1H), 2.74 (s, 3H), 2.30 (s, 3H), 2.32 - 2.23 (m, 1H). **¹³C NMR** (100 MHz, CDCl₃) δ 139.8, 137.3, 136.7, 133.3, 129.4, 128.8, 128.0 (2 peaks), 126.7, 126.2, 78.1, 72.8, 46.3, 44.1, 21.4. **HRMS (ESI)** calcd for C₁₉H₂₂NO [M+H]⁺ 280.1701, found 280.1703.



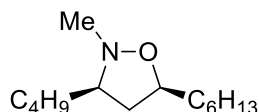
***cis*-5-(4-methoxyphenyl)-2-methyl-3-((*E*)-styryl)isoxazolidine (**1c**)**

¹H NMR (400 MHz, CDCl₃) δ 7.40 - 7.36 (m, 4H), 7.34 - 7.30 (m, 2H), 7.27 - 7.23 (m, 1H), 6.91 - 6.87 (m, 2H), 6.61 (d, *J* = 16.0 Hz, 1H), 6.19 (dd, *J* = 16.0, 8.0 Hz, 1H), 5.17 (t, *J* = 7.6 Hz, 1H), 3.81 (s, 3H), 3.45 (brs, 1H), 2.92 - 2.85 (m, 1H), 2.77 (m, 3H), 2.34 - 2.27 (m, 1H). **¹³C NMR** (100 MHz, CDCl₃) δ 159.4, 136.8, 134.7, 133.4, 128.9, 128.2, 128.1, 127.8, 126.8, 114.2, 78.1, 73.0, 55.6, 46.4, 44.2. **HRMS (ESI)** calcd for C₁₉H₂₂NO₂ [M+H]⁺ 296.1651, found 296.1654.



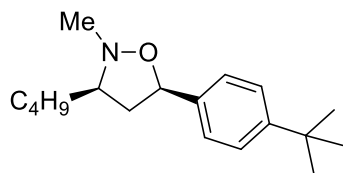
***cis*-(2-methyl-3-((*E*)-styryl)isoxazolidin-5-yl)methyl acetate (1d)**

¹H NMR (400 MHz, CDCl₃) δ 7.40 - 7.38 (m, 2H), 7.33 (t, *J* = 7.4 Hz, 2H), 7.29 - 7.25 (m, 1H), 6.59 (d, *J* = 16.0 Hz, 1H), 6.08 (dd, *J* = 16.0, 8.2 Hz, 1H), 4.42 - 4.36 (m, 1H), 4.21 - 4.12 (m, 2H), 3.23 - 3.17 (m, 1H), 2.68 (s, 3H), 2.65 - 2.60 (m, 1H), 2.12 (s, 3H), 1.93 - 1.86 (m, 1H). **¹³C NMR** (100 MHz, CDCl₃) δ 170.8, 136.3, 133.6, 128.6, 127.9, 127.1, 126.4, 74.1, 71.5, 66.2, 43.0, 39.4, 20.9. **HRMS (ESI)** calcd for C₁₅H₂₀NO₃ [M+H]⁺ 262.1443, found 262.1441.



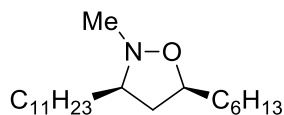
***cis*-3-butyl-5-hexyl-2-methylisoxazolidine (1e)**

¹H NMR (400 MHz, CDCl₃) δ 4.11 - 4.07 (m, 1H), 2.68 - 2.61 (m, 1H), 2.64 (s, 3H), 2.49 (dd, *J* = 7.2, 6.8 Hz, 1H), 1.70 - 1.63 (m, 1H), 1.59 - 1.51 (m, 2H), 1.48 - 1.39 (m, 2H), 1.38 - 1.27 (m, 12H), 0.90 (t, *J* = 6.8 Hz, 3H), 0.87 (t, *J* = 6.8 Hz, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 76.4, 69.2, 45.0, 42.0, 35.8, 34.2, 32.1, 29.6 (2 peaks), 26.7, 23.1, 22.9, 14.4 (2 peaks); **HRMS (ESI)** calcd for C₁₄H₃₀NO [M+H]⁺ 228.2327, found 228.2336.



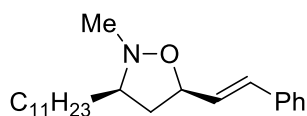
***cis*-3-butyl-5-(4-(*tert*-butyl)phenyl)-2-methylisoxazolidine (1f)**

¹H NMR (400 MHz, CDCl₃) δ 7.37 - 7.26 (m, 4H), 5.15 (t, *J* = 7.6 Hz, 1H), 2.83 - 2.77 (m, 5H), 2.03 - 1.95 (m, 1H), 1.69 - 1.62 (m, 1H), 1.48 - 1.34 (m, 6H), 1.30 (s, 9H), 0.90 (t, *J* = 7.2 Hz, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 150.8, 139.0, 126.3, 125.7, 69.9, 45.3, 45.0, 34.8, 34.0, 31.7, 30.0, 29.6, 23.1, 14.3; **HRMS (ESI)** calcd for C₁₈H₃₀NO [M+H]⁺ 276.2327, found 276.2325.



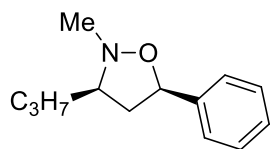
***cis*-5-hexyl-2-methyl-3-undecylisoxazolidine (1g)**

¹H NMR (400 MHz, CDCl₃) δ 4.14 - 4.07 (m, 1H), 2.67 - 2.61 (m, 1H), 2.64 (s, 3H), 2.52 - 2.45 (m, 1H), 1.69 - 1.62 (m, 1H), 1.57 - 1.50 (m, 2H), 1.49 - 1.39 (m, 2H), 1.31 - 1.26 (m, 26H), 0.88 (t, *J* = 6.8 Hz, 3H), 0.87 (t, *J* = 7.0 Hz, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 76.4, 69.2, 53.7, 45.0, 42.0, 35.9, 34.5, 32.3, 32.1, 30.1, 30.0 (2 peaks), 29.9, 29.7, 29.6, 27.4, 26.7, 23.0, 22.9, 14.4 (2 peaks); **HRMS (ESI)** calcd for C₂₁H₄₄NO [M+H]⁺ 326.3423, found 326.3422.



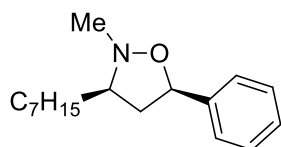
***cis*-2-methyl-5-((*E*)-styryl)-3-undecylisoxazolidine (1h)**

¹H NMR (400 MHz, CDCl₃) δ 7.39 - 7.37 (m, 2H), 7.32 - 7.28 (m, 2H), 7.26 - 7.21 (m, 1H), 6.56 (d, *J* = 15.6 Hz, 1H), 6.24 (dd, *J* = 15.8, 7.8 Hz, 1H), 4.75 (q, *J* = 7.6 Hz, 1H), 2.71 (s, 3H), 2.67 - 2.63 (m, 1H), 1.87 - 1.80 (m, 1H), 1.63 - 1.58 (m, 1H), 1.44 - 1.36 (m, 2H), 1.30 - 1.26 (m, 18H), 0.88 (t, *J* = 6.8 Hz, 3H). **¹³C NMR** (100 MHz, CDCl₃) δ 136.9, 132.0, 129.8, 128.8, 128.0, 126.9, 77.3, 69.5, 45.0, 42.7, 34.2, 32.2, 30.0 (2 peaks), 29.9 (3 peaks), 29.7, 27.3, 23.0, 14.4. **HRMS (ESI)** calcd for C₂₃H₃₈NO [M+H]⁺ 344.2953, found 344.2946.



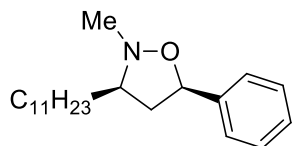
***cis*-2-methyl-5-phenyl-3-propylisoxazolidine (1i)**

¹H NMR (400 MHz, CDCl₃) δ 7.41 - 7.39 (m, 2H), 7.35 - 7.32 (m, 2H), 7.28 - 7.24 (m, 1H), 5.17 (t, *J* = 7.6 Hz, 1H), 2.88 - 2.83 (m, 2H), 2.79 (s, 3H), 2.01 - 1.93 (m, 1H), 1.67 - 1.59 (m, 1H), 1.47 - 1.34 (m, 3H), 0.95 (t, *J* = 7.2 Hz, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 142.3, 128.7, 127.7, 126.4, 77.8, 69.6, 45.2, 36.4, 30.0, 20.5, 14.4; **HRMS (ESI)** calcd for C₁₃H₂₀NO [M+H]⁺ 206.1545, found 206.1541.



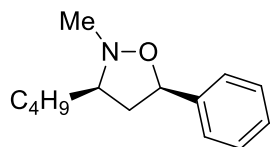
***cis*-3-heptyl-2-methyl-5-phenylisoxazolidine (1j)**

¹H NMR (400 MHz, CDCl₃) δ 7.41 - 7.39 (m, 2H), 7.35 - 7.31 (m, 2H), 7.27 - 7.23 (m, 1H), 5.17 (t, *J* = 7.6 Hz, 1H), 2.87 - 2.82 (m, 2H), 2.78 (s, 3H), 2.01 - 1.93 (m, 1H), 1.69 - 1.58 (m, 1H), 1.45 - 1.38 (m, 2H), 1.38 - 1.25 (m, 9H), 0.88 (t, *J* = 6.8 Hz, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 142.4, 128.7, 127.7, 126.4, 77.8, 69.9, 45.2 (2 peaks), 34.2, 32.1, 30.0, 29.5, 27.4, 22.9, 14.4.; **HRMS (ESI)** calcd for C₁₇H₂₈NO [M+H]⁺ 262.2171, found 262.2166.



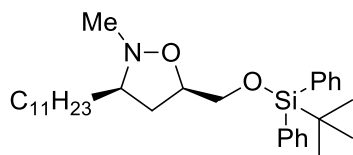
***cis*-2-methyl-5-phenyl-3-undecylisoxazolidine (1k)**

¹H NMR (400 MHz, CDCl₃) δ 7.41 - 7.39 (m, 2H), 7.35 - 7.31 (m, 2H), 7.27 - 7.23 (m, 1H), 5.17 (t, *J* = 8.0 Hz, 1H), 2.88 - 2.78 (m, 2H), 2.78 (s, 3H), 2.00 - 1.93 (m, 1H), 1.68 - 1.59 (m, 1H), 1.47 - 1.26 (m, 19H), 0.89 (t, *J* = 7.8 Hz, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 142.3, 128.6, 127.6, 126.3, 77.7, 69.8, 45.2, 45.1, 34.2, 32.1, 30.0, 29.9, 29.8 (3 peaks), 29.6, 27.3, 22.9, 14.3; **HRMS (ESI)** calcd for C₂₁H₃₆NO [M+H]⁺ 318.2797, found 318.2796.



***cis*-3-butyl-2-methyl-5-phenylisoxazolidine (1l)**

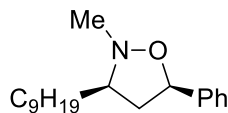
¹H NMR (400 MHz, CDCl₃) δ 7.41 - 7.39 (m, 2H), 7.35 - 7.31 (m, 2H), 7.28 - 7.23 (m, 1H), 5.17 (t, *J* = 7.6 Hz, 1H), 2.89 - 2.83 (m, 2H), 2.78 (s, 3H), 2.01 - 1.94 (m, 1H), 1.69 - 1.62 (m, 1H), 1.48 - 1.26 (m, 5H), 0.91 (t, *J* = 7.2 Hz, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 142.3, 128.7, 127.7, 126.4, 77.8, 69.9, 45.2 (2 peaks), 33.9, 29.5, 23.1, 14.3; **HRMS (ESI)** calcd for C₁₄H₂₂NO [M+H]⁺ 220.1701, found 220.1697.



***cis*-5-(((*tert*-butyl) diphenylsilyl)oxy)methyl-2-methyl-3-undecylisoxazolidine (1m)**

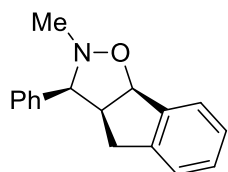
¹H NMR (400 MHz, CDCl₃) δ 7.73 - 7.70 (m, 4H), 7.45 - 7.37 (m, 6H), 4.30 - 4.24 (m, 1H), 3.84 (dd, *J* = 10.4, 6.0 Hz, 1H), 3.61 (dd, *J* = 10.4, 5.6 Hz, 1H), 2.65 (s, 3H), 2.59 - 2.54 (m, 1H), 2.52 - 2.45 (m, 1H), 1.74 - 1.67 (m, 1H), 1.56 - 1.51 (m, 1H), 1.34 - 1.24 (m, 19H), 1.09 (s, 9H), 0.91 (t, *J* = 6.8 Hz, 1H). **¹³C NMR** (100 MHz, CDCl₃) δ 136.0, 135.9, 134.1, 133.9, 129.9, 127.9 (2 peaks), 76.6, 68.9, 66.4,

44.4, 38.4, 33.8, 32.2, 30.1, 30.0, 29.9 (3 peaks), 29.7, 27.2 (2 peaks), 23.0, 19.6, 14.4. **HRMS (ESI)** calcd for C₃₂H₅₂NO₂Si [M+H]⁺ 510.3767, found 510.3783.



***cis*-2-methyl-3-nonyl-5-phenylisoxazolidine (1n)**

¹H NMR (400 MHz, CDCl₃) δ 7.41 - 7.38 (m, 2H), 7.35 - 7.31 (m, 2H), 7.27 - 7.23 (m, 1H), 5.16 (t, *J* = 7.8 Hz, 1H), 2.87 - 2.82 (m, 2H), 2.77 (s, 3H), 2.00 - 1.93 (m, 1H), 1.67 - 1.58 (m, 1H), 1.46 - 1.36 (m, 2H), 1.30 - 1.26 (m, 13H), 0.88 (t, *J* = 6.8 Hz, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 142.4, 128.7, 127.7, 126.4, 77.8, 69.9, 45.3 (2 peaks), 34.3, 32.2, 30.0, 29.9, 29.8, 29.6, 27.4, 23.0, 14.4; **HRMS (ESI)** calcd for C₁₉H₃₂NO [M+H]⁺ 290.2484, found 290.2487.

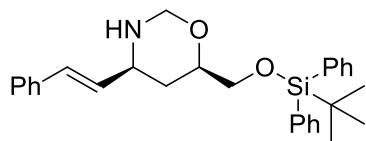


***cis*-2-methyl-3-phenyl-3,3a,4,8b-tetrahydro-2H-indeno[2,1-*d*]isoxazole (1o)**

¹H NMR (400 MHz, CDCl₃) δ 7.48 - 7.43 (m, 3H), 7.41 - 7.37 (m, 2H), 7.36 - 7.33 (m, 2H), 7.30 - 7.26 (m, 2H), 5.71 (d, *J* = 7.6 Hz, 1H), 3.53 - 3.39 (m, 1H), 3.17 - 3.08 (m, 2H), 3.00 (dd, *J* = 14.8, 2.4 Hz, 1H), 2.55 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 142.7, 141.3, 138.7, 129.4, 129.1, 128.5, 128.3, 127.5, 126.2, 125.8, 86.0, 81.9, 56.0, 43.2, 35.1.; **HRMS (ESI)** calcd for C₁₇H₁₈NO [M+H]⁺ 252.1388, found 252.1388.

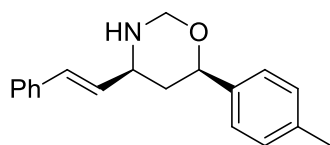
(2) General procedure for standard conditions

The isolated *cis*-isoxazolidine intermediate **1** (0.5 mmol) was directly dissolved into 2 mL toluene and then transferred by syringe into a Schlenk tube charged with [RuCl₂(*p*-cymene)]₂ (0.0125 mmol, 7.6 mg), *p*-TsOH·H₂O (0.0375 mmol, 14.2 mg) and K₂CO₃ (0.5 mmol, 68 mg). Under stirring, water (1 mmol, 18 μL) was added. The reaction mixture was heated to 110 °C. The reaction was monitored by TLC and quenched by filtration through a thin pad of silica gel, followed by washing with ethyl acetate. After concentrated by a rotary evaporator under reduced pressure, the crude reaction residue was examined on ¹H NMR spectrometer to determine conversion and selectivity using nitromethane and methyl *tert*-butyl ether as internal standards. The crude product was purified by flash column chromatography on silica gel using petroleum ether and ethyl acetate as eluent to give the *cis*-1,3-isoxazolidine **2**.



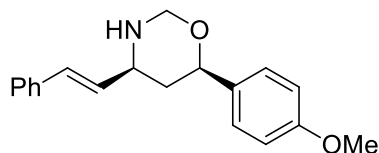
***cis*-6-(((*tert*-butyldiphenylsilyl)oxy)methyl)-4-((*E*)-styryl)-1,3-oxazinane (2a)**

Prepared according to the general procedure, solid, 82%. **¹H NMR** (400 MHz, CDCl₃) δ 7.69 (dd, *J* = 6.4, 1.0 Hz, 4H), 7.46 - 7.38 (m, 8H), 7.32 (t, *J* = 7.4 Hz, 2H), 7.26 - 7.22 (m, 1H), 6.53 (dd, *J* = 16.0, 1.4 Hz, 1H), 6.21 (dd, *J* = 16.0, 5.0 Hz, 1H), 4.72 (d, *J* = 10.4 Hz, 1H), 4.35 (d, *J* = 10.4 Hz, 1H), 3.79 - 3.72 (m, 2H), 3.64 - 3.57 (m, 2H), 1.86 (ddd, *J* = 13.2, 2.4, 2.4 Hz, 1H), 1.33 - 1.23 (m, 1H), 1.08 (s, 9H). **¹³C NMR** (100 MHz, CDCl₃) δ 137.2, 135.9, 133.9, 133.8, 131.6, 130.0, 129.5, 128.9, 128.0, 127.8, 126.6, 79.5, 77.1, 67.6, 55.5, 35.7, 27.2, 19.6. **HRMS (ESI)** calcd for C₂₉H₃₆NO₂Si [M+H]⁺ 458.2515, found 458.2522.



***cis*-4-((*E*)-styryl)-6-(*p*-tolyl)-1,3-oxazinane (2b)**

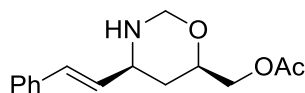
Prepared according to the general procedure, solid, 79%. **¹H NMR** (400 MHz, CDCl₃) δ 7.38 - 7.36 (m, 2H), 7.33 - 7.29 (m, 2H), 7.28 - 7.21 (m, 3H), 7.19 - 7.17 (m, 2H), 6.57 (dd, *J* = 16.0, 1.8 Hz, 1H), 6.24 (dd, *J* = 16.0, 4.8 Hz, 1H), 4.88 (d, *J* = 10.4 Hz, 1H), 4.62 (dd, *J* = 11.2, 2.0 Hz, 1H), 4.54 (d, *J* = 10.8 Hz, 1H), 3.79 - 3.73 (m, 1H), 2.35 (s, 3H), 2.02 (ddd, *J* = 13.2, 2.6, 2.6 Hz, 1H), 1.58 (ddd, *J* = 13.2, 12.8, 11.2 Hz, 1H). **¹³C NMR** (100 MHz, CDCl₃) δ 139.7, 137.6, 137.1, 131.3, 129.6, 129.4, 128.9, 127.9, 126.6, 126.0, 80.0, 78.8, 56.0, 40.9, 21.4. **HRMS (ESI)** calcd for C₁₉H₂₂NO [M+H]⁺ 280.1701, found 280.1697.



***cis*-6-(4-methoxyphenyl)-4-((*E*)-styryl)-1,3-oxazinane (2c)**

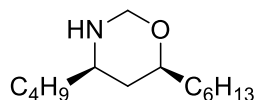
Prepared according to the general procedure, solid, 87%. **¹H NMR** (400 MHz, CDCl₃) δ 7.38 - 7.36 (m, 2H), 7.33 - 7.30 (m, 4H), 7.26 - 7.22 (m, 1H), 6.93 - 6.89 (m, 2H), 6.57 (dd, *J* = 16.4, 1.6 Hz, 1H), 6.25 (dd, *J* = 16.4, 4.8 Hz, 1H), 4.87 (d, *J* = 10.4 Hz, 1H), 4.60 (dd, *J* = 10.8, 2.2 Hz, 1H), 4.54 (d, *J* = 10.4 Hz, 1H), 3.81 (s, 3H), 3.78 - 3.72 (m, 1H), 2.01 (ddd, *J* = 13.2, 2.4, 2.4 Hz, 1H), 1.59 (ddd, *J* = 13.2, 12.8, 11.4 Hz, 1H). **¹³C NMR** (100 MHz, CDCl₃) δ 159.4, 137.1, 134.9, 131.2, 129.7, 128.9,

127.9, 127.4, 126.6, 114.2, 80.0, 78.6, 56.1, 55.6, 40.8; **HRMS (ESI)** calcd for C₁₉H₂₂NO₂ [M+H]⁺ 296.1651, found 296.1653.



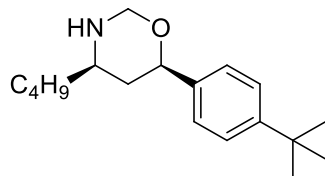
***cis*-4-((*E*)-styryl)-1,3-oxazinan-6-yl)methyl acetate (2d)**

Prepared according to the general procedure, solid, 90%. **¹H NMR** (400 MHz, CDCl₃) δ 7.38 - 7.36 (m, 2H), 7.33 - 7.28 (m, 2H), 7.26 - 7.21 (m, 1H), 6.55 (dd, *J* = 16.0, 2.0 Hz, 1H), 6.19 (dd, *J* = 16.0, 4.8 Hz, 1H), 4.76 (d, *J* = 10.4 Hz, 1H), 4.37 (d, *J* = 10.8 Hz, 1H), 4.14 (dd, *J* = 11.6, 3.6 Hz, 1H), 4.08 (dd, *J* = 11.6, 6.4 Hz, 1H), 3.91 - 3.85 (m, 1H), 3.65 - 3.60 (m, 1H), 2.11 (s, 3H), 1.76 (ddd, *J* = 12.8, 2.8, 2.8 Hz, 1H), 1.66 (br s, 1H), 1.34 (ddd, *J* = 12.8, 11.6, 11.6 Hz, 1H). **¹³C NMR** (100 MHz, CDCl₃) δ 171.3, 137.0, 130.9, 129.8, 128.9, 128.0, 126.6, 79.6, 74.4, 67.5, 55.3, 34.8, 21.2. **HRMS (ESI)** calcd for C₁₅H₂₀NO₃ [M+H]⁺ 262.1443, found 262.1439.



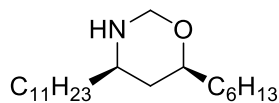
***cis*-4-butyl-6-hexyl-1,3-oxazinane (2e)**

Prepared according to the general procedure, oil, 95%. **¹H NMR** (400 MHz, CDCl₃) δ 4.63 (d, *J* = 10.4 Hz, 1 H), 4.22 (d, *J* = 10.4 Hz, 1 H), 3.47 - 3.41 (m, 1 H), 2.75 - 2.68 (m, 1 H), 1.60 (ddd, *J* = 12.8, 2.4, 2.4 Hz, 1 H), 1.51 - 1.28 (m, 16 H), 0.98 - 0.80 (m, 7 H); **¹³C NMR** (100 MHz, CDCl₃) δ 79.8, 76.8, 54.6, 40.0, 37.1, 37.0, 32.1, 29.6, 28.1, 25.3, 23.0, 22.9, 14.4, 14.3. **HRMS (ESI)** calcd for C₁₄H₃₀NO [M+H]⁺ 228.2327, found 228.2333.



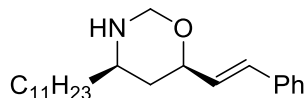
***cis*-4-butyl-6-(4-(*tert*-butyl)phenyl)-1,3-oxazinane (2f)**

Prepared according to the general procedure, oil, 81%. **¹H NMR** (400 MHz, CDCl₃) δ 7.39 - 7.36 (m, 2H), 7.29 - 7.26 (m, 2H), 4.80 (d, *J* = 10.4 Hz, 1H), 4.52 (dd, *J* = 11.2, 2.0 Hz, 1H), 4.44 (d, *J* = 10.4 Hz, 1H), 2.96 - 2.89 (m, 1H), 1.86 (ddd, *J* = 12.8, 2.4 Hz, 1H), 1.50 - 1.32 (m, 8H), 1.32 (s, 9H), 0.91 (t, *J* = 6.8 Hz, 1H); **¹³C NMR** (100 MHz, CDCl₃) δ 150.8, 140.0, 125.9, 125.6, 80.2, 78.9, 54.9, 41.5, 36.9, 34.8, 31.7, 28.0, 23.0, 14.3; **HRMS (ESI)** calcd for C₁₈H₃₀NO [M+H]⁺ 276.2327, found 276.2330.



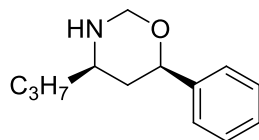
***cis*-6-hexyl-4-undecyl-1,3-oxazinane (2g)**

Prepared according to the general procedure, solid (mp 31-34 °C), 93%. **¹H NMR** (400 MHz, CDCl₃) δ 4.62 (d, *J* = 10.6 Hz, 1 H), 4.22 (d, *J* = 10.6 Hz, 1 H), 3.47 - 3.40 (m, 1 H), 2.74 - 2.68 (m, 1H), 1.59 (ddd, *J* = 12.8, 2.4, 2.4 Hz, 1 H), 1.53 - 1.25 (m, 30 H), 0.97-0.90 (m, 1 H), 0.89 - 0.86 (m, 6 H); **¹³C NMR** (100 MHz, CDCl₃) δ 79.9, 76.9, 54.7, 40.0, 37.4, 37.2, 32.2, 32.1, 30.0 (3 peaks), 29.9 (2 peaks), 29.7, 25.9, 25.3, 23.0, 22.9, 14.4 (2 peaks); **HRMS (ESI)** calcd for C₂₁H₄₄NO [M+H]⁺ 326.3423, found 326.3431.



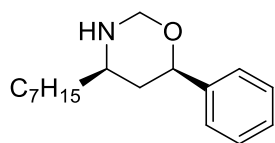
***cis*-6-((*E*)-styryl)-4-undecyl-1,3-oxazinane (2h)**

Prepared according to the general procedure, solid, 84%. **¹H NMR** (400 MHz, CDCl₃) δ 7.38 (d, *J* = 7.2 Hz, 2H), 7.31 (t, *J* = 7.2 Hz, 2H), 7.23 - 7.21 (m, 1H), 6.59 (d, *J* = 16.0 Hz, 1H), 6.18 (dd, *J* = 16.0, 5.6 Hz, 1H), 4.73 (d, *J* = 10.8 Hz, 1H), 4.36 (d, *J* = 10.8 Hz, 1H), 4.22 - 4.18 (m, 1H), 2.90 - 2.82 (m, 1H), 1.80 - 1.71 (m, 1H), 1.46 - 1.35 (m, 20H), 1.21 - 1.09 (m, 1H), 0.88 (t, *J* = 6.8 Hz, 3H). **¹³C NMR** (100 MHz, CDCl₃) δ 137.2, 130.5, 130.2, 128.8, 127.9, 126.8, 79.8, 77.1, 54.5, 39.9, 37.3, 32.2, 30.0 (2 peaks), 29.9 (3 peaks), 29.7, 25.8, 23.0, 14.4. **HRMS (ESI)** calcd for C₂₃H₃₈NO [M+H]⁺ 344.2953, found 344.2949.



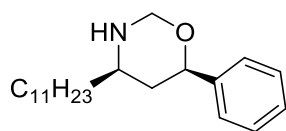
***cis*-6-phenyl-4-propyl-1,3-oxazinane (2i)**

Prepared according to the general procedure, oil, 77%. **¹H NMR** (400 MHz, CDCl₃) δ 7.38 - 7.32 (m, 4 H), 7.30 - 7.25 (m, 1 H), 4.81 (d, *J* = 10.8 Hz, 1 H), 4.55 (dd, *J* = 11.2, 2.4 Hz, 1 H), 4.44 (d, *J* = 10.8 Hz, 1 H), 2.97 - 2.91 (m, 2 H), 1.85 (ddd, *J* = 13.2, 2.6, 2.6 Hz, 1 H), 1.55 (br s, 1 H), 1.50 - 1.33 (m, 4 H), 1.33 - 1.24 (m, 1 H), 0.94 (t, *J* = 7.2 Hz, 3 H); **¹³C NMR** (100 MHz, CDCl₃) δ 143.0, 128.7, 127.8, 126.0, 80.2, 79.0, 54.6, 41.7, 39.3, 18.9, 14.4; **HRMS (ESI)** calcd for C₁₃H₂₀NO [M+H]⁺ 206.1539, found 206.1535.



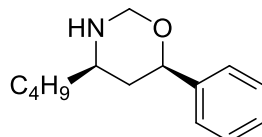
***cis*-4-heptyl-6-phenyl-1,3-oxazinane (2j)**

Prepared according to the general procedure, oil, 71%. **¹H NMR** (400 MHz, CDCl₃) δ 7.38 - 7.33 (m, 4 H), 7.30 - 7.25 (m, 1 H), 4.81 (d, *J* = 10.4 Hz, 1 H), 4.55 (dd, *J* = 11.2, 2.4 Hz, 1 H), 4.44 (d, *J* = 10.4 Hz, 1 H), 2.96 - 2.89 (m, 1 H), 1.86 (ddd, *J* = 12.8, 2.4, 2.4 Hz, 1 H), 1.59 (br s, 1 H), 1.51 - 1.35 (m, 3 H), 1.34 - 1.24 (m, 10 H), 0.88 (t, *J* = 6.8 Hz, 3 H); **¹³C NMR** (100 MHz, CDCl₃) δ 143.0, 128.7, 127.8, 126.0, 80.2, 79.1, 54.9, 41.8, 37.2, 32.1, 29.9, 29.5, 25.8, 23.0, 14.4; **HRMS (ESI)** calcd for C₁₇H₂₈NO [M+H]⁺ 262.2165, found 262.2162.



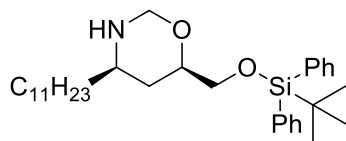
***cis*-6-phenyl-4-undecyl-1,3-oxazinane (2k)**

Prepared according to the general procedure, oil, 79%. **¹H NMR** (400 MHz, CDCl₃) δ 7.38 - 7.33 (m, 4 H), 7.31 - 7.26 (m, 1 H), 4.82 (d, *J* = 10.8 Hz, 1 H), 4.55 (dd, *J* = 11.6, 2.4 Hz, 1 H), 4.45 (d, *J* = 10.8 Hz, 1 H), 2.97 - 2.91 (m, 1 H), 1.87 (ddd, *J* = 13.2, 2.6, 2.6 Hz, 1 H), 1.69 (br s, 1 H), 1.49 - 1.36 (m, 3 H), 1.35 - 1.27 (m, 18 H), 0.89 (t, *J* = 6.8 Hz, 3 H); **¹³C NMR** (100 MHz, CDCl₃) δ 143.0, 128.7, 127.8, 126.0, 80.2, 79.0, 54.9, 41.7, 37.2, 32.2, 30.0 (2 peaks), 29.9 (3 peaks), 29.6, 25.8, 23.0, 14.4; **HRMS (ESI)** calcd for C₂₁H₃₆NO [M+H]⁺ 318.2791, found 318.2787.



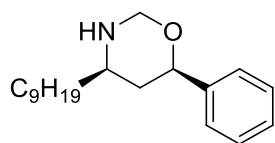
***cis*-4-butyl-6-phenyl-1,3-oxazinane (2l)**

Prepared according to the general procedure, oil, 75%. **¹H NMR** (400 MHz, CDCl₃) δ 7.38 - 7.33 (m, 4 H), 7.31 - 7.26 (m, 1 H), 4.82 (d, *J* = 10.8 Hz, 1 H), 4.55 (dd, *J* = 11.2, 2.4 Hz, 1 H), 4.44 (d, *J* = 10.8 Hz, 1 H), 2.95 - 2.89 (m, 1 H), 1.86 (ddd, *J* = 13.2, 2.4, 2.4 Hz, 1 H), 1.59 (br s, 1 H), 1.50 - 1.45 (m, 1 H), 1.40 - 1.24 (m, 6 H), 0.92 (t, *J* = 6.9 Hz, 3 H); **¹³C NMR** (100 MHz, CDCl₃) δ 143.0, 128.7, 127.8, 126.0, 80.2, 79.0, 54.8, 41.7, 36.9, 28.0, 23.0, 14.3; **HRMS (ESI)** calcd for C₁₄H₂₂NO [M+H]⁺ 220.1696, found 220.1691.



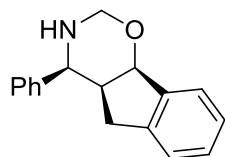
***cis*-6-(((*tert*-butyldiphenylsilyl)oxy)methyl)-4-undecyl-1,3-oxazinane (2m)**

Prepared according to the general procedure, solid, 75%. **¹H NMR** (400 MHz, CDCl₃) δ 7.71 - 7.67 (m, 4H), 7.45 - 7.36 (m, 6H), 4.64 (d, *J* = 10.4 Hz, 1H), 4.24 (d, *J* = 10.8 Hz, 1H), 3.72 (dd, *J* = 10.0, 5.2 Hz, 1H), 3.67 - 3.61 (m, 1H), 3.56 (dd, *J* = 10.0, 5.2 Hz, 1H), 2.78 - 2.70 (m, 1H), 1.65 (ddd, *J* = 13.2, 2.4, 2.4 Hz, 1H), 1.43 - 1.23 (m, 20H), 1.07 (s, 9H), 1.02 - 0.90 (m, 1H), 0.89 (t, *J* = 6.8 Hz, 3H). **¹³C NMR** (100 MHz, CDCl₃) δ 136.0, 134.1, 134.0, 130.0, 128.0, 79.8, 77.3, 67.8, 54.4, 37.4, 36.4, 32.3, 30.0 (3 peaks), 29.9 (2 peaks), 29.7, 27.2, 25.9, 23.0, 19.6, 14.5. **HRMS (ESI)** calcd for C₃₂H₅₂NO₂Si [M+H]⁺ 510.3767, found 510.3778.



***cis*-4-nonyl-6-phenyl-1,3-oxazinane (2n)**

Prepared according to the general procedure, oil, 81%. **¹H NMR** (400 MHz, CDCl₃) δ 7.38-7.33 (m, 4 H), 7.31-7.26 (m, 1 H), 4.82 (d, *J* = 10.8 Hz, 1 H), 4.55 (dd, *J* = 11.2, 2.0 Hz, 1 H), 4.45 (d, *J* = 10.8 Hz, 1 H), 2.97-2.91 (m, 1 H), 1.87 (ddd, *J* = 13.2, 2.6, 2.6 Hz, 1 H), 1.70 (br s, 1 H), 1.52-1.36 (m, 4 H), 1.34-1.27 (m, 13 H), 0.89 (t, *J* = 6.6 Hz, 3 H); **¹³C NMR** (100 MHz, CDCl₃) δ 143.0, 128.7, 127.8, 126.0, 80.2, 79.0, 54.9, 41.7, 37.2, 32.2, 30.0, 29.9, 29.8, 29.6, 25.8, 23.0, 14.4; **HRMS (ESI)** calcd for C₁₉H₃₂NO [M+H]⁺ 290.2478, found 290.2476.

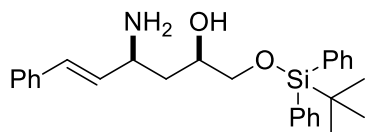


***cis*-4-phenyl-2,3,4,4a,5,9b-hexahydroindeno[2,1-*e*][1,3]oxazine (2o)**

Prepared according to the general procedure, oil, 71%. **¹H NMR** (400 MHz, CDCl₃) δ 7.44 (d, *J* = 7.2 Hz, 1H), 7.39 - 7.27 (m, 7H), 7.26 - 7.23 (m, 2H), 5.53 (d, *J* = 6.4 Hz, 1H), 4.53 (d, *J* = 6.4 Hz, 1H), 4.48 (d, *J* = 10.0 Hz, 1H), 3.54 (d, *J* = 9.6 Hz, 1H), 2.88 - 2.77 (m, 1H), 2.53 (d, *J* = 14.8 Hz, 1H). **¹³C NMR** (100 MHz, CDCl₃) δ 142.1, 141.8, 141.4, 129.0, 128.3, 127.9 (2 peaks), 127.2, 126.1, 124.3, 80.0, 74.3, 59.2, 42.6, 33.6. **HRMS (ESI)** calcd for C₁₇H₁₈NO [M+H]⁺ 252.1388, found 252.1389.

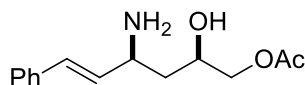
(3) General procedure for Synthesis of *N*-H 1,3-aminoalcohols from 2.

To a solution of **2** (0.3 mmol) and $\text{NH}_2\text{OH HCl}$ (208.5 mg, 3.0 mmol) in MeOH (3 mL) was added H_2O (11.0 μL , 0.6 mmol) and the resulting reaction mixture was heated under reflux until the starting material completely disappeared (monitored by TLC).² The solution was quenched with sat. Na_2CO_3 (aq.) and extracted with CH_2Cl_2 (10 mL \times 3). The combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated under vacuum. The residue was purified by flash column chromatography to give the corresponding 1,3-aminoalcohol **3**.



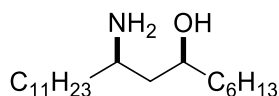
(syn, E)-4-amino-1-((tert-butyldiphenylsilyl)oxy)-6-phenylhex-5-en-2-ol (3a)

Prepared according to the general procedure, solid, 70%. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.68 - 7.66 (m, 4H), 7.44 - 7.30 (m, 11H), 6.48 (d, J = 16.0 Hz, 1H), 6.18 (dd, J = 16.0, 7.0 Hz, 1H), 3.98 - 3.92 (m, 1H), 3.74 - 3.68 (m, 1H), 3.64 (dd, J = 10.0, 6.0 Hz, 1H), 3.57 (dd, J = 10.0, 6.0 Hz, 1H), 2.41 (br s, 3H), 1.83 - 1.78 (m, 1H), 1.55 - 1.50 (m, 1H), 1.07 (s, 9H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 137.2, 135.9, 135.1, 133.8, 130.0, 128.9 (2 peaks), 128.0, 127.9, 126.7, 72.5, 68.5, 54.0, 40.1, 27.2, 19.6. **HRMS (ESI)** calcd for $\text{C}_{28}\text{H}_{36}\text{NO}_2\text{Si}$ $[\text{M}+\text{H}]^+$ 446.2515, found 446.2516.



(syn, E)-4-amino-2-hydroxy-6-phenylhex-5-en-1-yl acetate (3d)

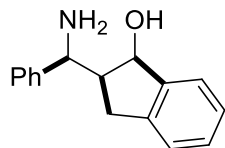
Prepared according to the general procedure, solid, 87%. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.35 - 7.20 (m, 5H), 6.54 (d, J = 15.6 Hz, 1H), 6.54 (br s, 1H), 6.10 (dd, J = 15.6, 6.8 Hz, 1H), 4.75 - 4.68 (m, 1H), 3.80 (br s, 1H), 3.64 (dd, J = 11.2, 2.8 Hz, 1H), 3.48 (dd, J = 11.2, 6.8 Hz, 1H), 2.00 (s, 3H), 1.85 - 1.69 (m, 2H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 171.0, 136.9, 131.3, 129.5, 129.0, 128.1, 126.8, 70.2, 66.9, 49.7, 38.7, 23.7. **HRMS (ESI)** calcd for $\text{C}_{14}\text{H}_{20}\text{NO}_3$ $[\text{M}+\text{H}]^+$ 250.1443, found 250.1442.



syn-9-aminoicosan-7-ol (3g)

Prepared according to the general procedure, solid, 96%. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 3.81 - 3.74 (m, 1H), 2.82 - 2.77 (m, 1H), 2.80 (br s, 3H), 1.57 (ddd, J = 14.0, 2.0, 2.0 Hz, 1H), 1.48 - 1.26 (m, 30H), 1.15 (ddd, J = 14.0, 10.8, 10.8 Hz, 1H), 0.90 - 0.86 (m, 6H). $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 73.4, 53.6, 42.6, 41.4, 38.6, 32.2 (2 peaks), 30.0, 29.9 (4 peaks), 29.8, 29.7, 26.0, 25.8, 23.0 (2 peaks), 14.4 (two peaks).

HRMS (ESI) calcd for C₂₀H₄₄NO [M+H]⁺ 314.3423, found 314.3427.

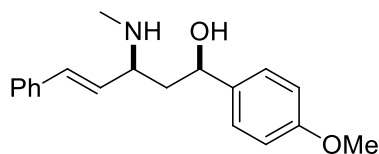


2-amino(phenyl)methyl-2,3-dihydro-1H-inden-1-ol (3o)

Prepared according to the general procedure, solid, 87%. ¹H NMR (400 MHz, CDCl₃) δ 7.49 - 7.47 (m, 1H), 7.41 - 7.29 (m, 5H), 7.24 - 7.20 (m, 2H), 7.13 - 7.11 (m, 1H), 5.35 (d, *J* = 5.6 Hz, 1H), 4.07 (d, *J* = 5.6 Hz, 1H), 2.70 - 2.62 (m, 5H), 2.60 - 2.55 (m, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 145.7, 144.7, 142.9, 129.0, 128.6, 127.6, 127.0, 126.9, 125.4, 125.0, 76.2, 57.4, 50.7, 35.1; **HRMS (ESI)** calcd for C₁₆H₁₈NO [M+H]⁺ 240.1388, found 240.1388.

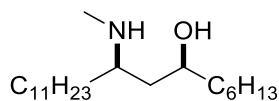
(4) General procedure for synthesis of *N*-Me 1,3-aminoalcohols from 2.

To the solution of **2** (0.3 mmol) in dried THF (4 mL) was added LiAlH₄ (34.2 mg, 0.9 mmol) portion-wise at 0 °C under a nitrogen atmosphere.³ The resulting reaction mixture was stirred at 0 °C for 4 hours. The reaction was quenched by the addition of water (35 μL), followed by the addition of 15% NaOH aqueous solution (35 μL) and additional water (105 μL). The mixture was allowed to warm to room temperature and MgSO₄ was added. The reaction was stirred for 30 min and filtered through a short pad of Celite with CH₂Cl₂-MeOH (20:1) as the eluent. The filtrate was concentrated under vacuum and the crude residue was purified by flash chromatography to give the product **4**.



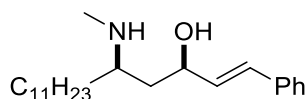
(*syn, E*)-1-(4-methoxyphenyl)-3-(methylamino)-5-phenylpent-4-en-1-ol (4c)

Prepared according to the general procedure, solid, 84%. ¹H NMR (400 MHz, CDCl₃) δ 7.38 - 7.30 (m, 5H), 7.26 - 7.23 (m, 1H), 6.87 (d, *J* = 8.8 Hz, 1H), 6.48 (d, *J* = 8.6 Hz, 1H), 6.48 (d, *J* = 15.6 Hz, 1H), 5.97 (dd, *J* = 15.6, 8.2 Hz, 1H), 4.94 (dd, *J* = 10.4, 2.4 Hz, 1H), 3.79 (s, 3H), 3.47 - 3.41 (m, 1H), 2.78 (br s, 2H), 2.46 (s, 3H), 1.88 - 1.73 (m, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 159.0, 137.7, 136.8, 131.9, 130.2, 128.9, 128.1, 127.1, 126.7, 114.0, 74.8, 63.6, 55.6, 44.3, 33.4. **HRMS (ESI)** calcd for C₁₉H₂₄NO₂ [M+H]⁺ 298.1807, found 298.1804.



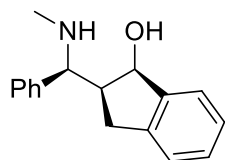
***syn*-9-(methylamino)icosan-7-ol (4g)**

Prepared according to the general procedure, solid, 92%. **¹H NMR** (400 MHz, CDCl₃) δ 3.79 - 3.73 (m, 1H), 2.65 - 2.58 (m, 1H), 2.37 (s, 3H), 1.61 - 1.56 (m, 1H), 1.50 (ddd, *J* = 14.2, 2.0, 2.0 Hz, 1H), 1.45 - 1.40 (m, 2H), 1.37 - 1.14 (m, 29H), 0.89 - 0.86 (m, 6H). **¹³C NMR** (100 MHz, CDCl₃) δ 73.5, 60.6, 39.7, 38.7, 33.8, 32.2, 32.1, 30.1, 29.9 (4 peaks), 29.8, 29.6, 25.8, 25.7, 23.0, 22.9, 14.4 (2 peaks). **HRMS (ESI)** calcd for C₂₁H₄₆NO [M+H]⁺ 328.3574, found 328.3569.



(*syn*, *E*)-5-(methylamino)-1-phenylhexadec-1-en-3-ol (4h)

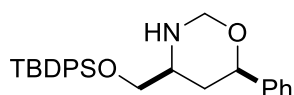
Prepared according to the general procedure, solid, 95%. **¹H NMR** (400 MHz, CDCl₃) δ 7.37 (br d, *J* = 7.6 Hz, 2H), 7.29 (t, *J* = 7.6 Hz, 2H), 7.23 - 7.19 (m, 1H), 6.61 (d, *J* = 16.0 Hz, 1H), 6.14 (dd, *J* = 16.0, 6.0 Hz, 1H), 4.54 - 4.50 (m, 1H), 3.19 (br s, 2H), 2.87 - 2.76 (m, 1H), 2.47 (s, 3H), 1.72 - 1.64 (m, 2H), 1.55 - 1.46 (m, 1H), 1.33 - 1.20 (m, 20H), 0.88 (t, *J* = 6.4 Hz, 3H). **¹³C NMR** (100 MHz, CDCl₃) δ 137.4, 133.0, 129.2, 128.8, 127.6, 126.7, 73.9, 60.4, 39.6, 33.3, 32.2, 31.8, 30.0, 29.9 (4 peaks), 29.6, 25.8, 23.0, 14.4. **HRMS (ESI)** calcd for C₂₃H₄₀NO [M+H]⁺ 346.3110, found 346.3104.



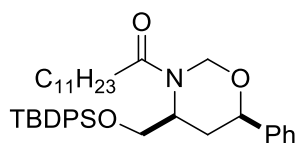
2-((methylamino)(phenyl)methyl)-2,3-dihydro-1H-inden-1-ol (4o)

Prepared according to the general procedure, solid, 93%. **¹H NMR** (400 MHz, CDCl₃) δ 7.43 - 7.39 (m, 3H), 7.32 - 7.29 (m, 3H), 7.22 (s, 3H), 5.11 (d, *J* = 6.0 Hz, 1H), 4.14 (d, *J* = 4.8 Hz, 1H), 3.10 (dd, *J* = 15.6, 9.6 Hz, 1H), 2.75 (dd, *J* = 15.6, 8.0 Hz, 1H), 2.65 - 2.58 (m, 1H), 2.30 (s, 1H). **¹³C NMR** (100 MHz, CDCl₃) δ 146.0, 142.8, 141.9, 129.0, 128.6, 127.5, 127.2, 127.1, 125.2, 125.0, 77.7, 64.7, 49.5, 34.0, 31.4. **HRMS (ESI)** calcd for C₁₇H₂₀NO [M+H]⁺ 254.1545, found 254.1535.

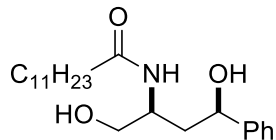
(5) Synthesis of HPA-12



[RuCl₂(*p*-cymene)]₂ (0.355 mmol, 215.8 mg), *p*-TsOH H₂O (1.42 mmol, 272.6 mg) and K₂CO₃ (14.2 mmol, 1.93 g) were directly weighed into a Schlenk tube and purged with argon. Toluene (30 mL) and H₂O (28.4 mmol, 511 μL) were added and the mixture was stirred for about 15 minutes until the color changed from dark brown to yellow. Nitron **5** (14.2 mmol, 4.65g) and styrene (56.8 mmol, 6.8 mL) were added. The mixture was stirred at 110 °C for 48 h. After cooling to room temperature, the reaction mixture was filtered through a pad of silica gel and washed with ethyl acetate. The filtrate was concentrated and the residue was purified by flash column chromatography to give the oil product as oil in 56% (3.43 g). **¹H NMR** (400 MHz, CDCl₃) δ 7.68-7.63 (m, 4 H), 7.43-7.34 (m, 10 H), 7.32-7.29 (m, 1 H), 4.86 (d, *J* = 10.4 Hz, 1 H), 4.56 (dd, *J* = 11.2, 2.4 Hz, 1 H), 4.48 (d, *J* = 10.8 Hz, 1 H), 3.79 (dd, *J* = 10.2, 4.2 Hz, 1 H), 3.65 (dd, *J* = 10.4, 2.8 Hz, 1 H), 3.08-3.03 (m, 1 H), 2.10 (br s, 1 H), 1.86 (ddd, *J* = 13.0, 11.2, 11.2 Hz, 1 H), 1.73 (ddd, *J* = 13.2, 2.8, 2.8 Hz, 1 H), 1.07 (s, 9 H); **¹³C NMR** (100 MHz, CDCl₃) δ 142.9, 135.9, 133.5, 130.1, 128.8, 128.1 (2 peaks), 127.9, 126.3, 80.1, 79.1, 67.2, 56.1, 37.1, 27.2, 19.7. **HRMS (ESI)** calcd for C₂₇H₃₄NO₂Si [M+H]⁺ 432.2367, found 432.2366.



To a stirred solution of 1,3-oxazinane **2p** (2.62 g, 6.02 mmol) in CH₂Cl₂ (20 mL) was added Et₃N (18 mmol, 2.7 mL) and 4-dimethylaminopyridine (DMAP, 0.3 mmol, 36.6 mg). The solution of lauroyl chloride (9.0 mmol, 1.97 g) in CH₂Cl₂ (10 mL) was added dropwise at 0 °C over 30 min. The resulting reaction mixture was then allowed to warm to room temperature, stirred for 17 hours, and poured into water (30 mL), then extracted with CH₂Cl₂ (30 mL × 2). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated under vacuum. The residue was purified by flash column chromatography to give the product **6** as an oil in 86% yield (3.16 g). **¹H NMR** (400 MHz, acetone-d₆) δ 7.69-7.65 (m, 4 H), 7.48-7.34 (m, 10 H), 7.30-7.25 (m, 1 H), 5.31 (br s, 2 H), 4.81 (dd, *J* = 11.8, 3.0 Hz, 1 H), 4.50 (br s, 1 H), 3.93-3.89 (m, 1 H), 3.81 (dd, *J* = 10.4, 4.4 Hz, 1 H), 2.82 (br s, 1 H), 2.43-2.20 (m, 3 H), 1.64-1.58 (m, 2 H), 1.28 (br s, 16 H), 1.04 (s, 9 H), 0.88 (t, *J* = 6.9 Hz, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 173.9, 142.4, 135.8 (2 peaks), 133.5, 133.4, 130.1 (2 peaks), 128.8, 128.1 (2 peaks), 128.0, 126.2, 74.6, 71.9, 65.2, 52.7, 33.8, 32.5, 32.2, 29.9, 29.8, 29.7, 29.6, 27.2, 25.5, 23.0, 19.5, 14.4. **HRMS (ESI)** calcd for C₃₉H₅₆NO₃Si [M+H]⁺ 614.4024, found 614.4025.

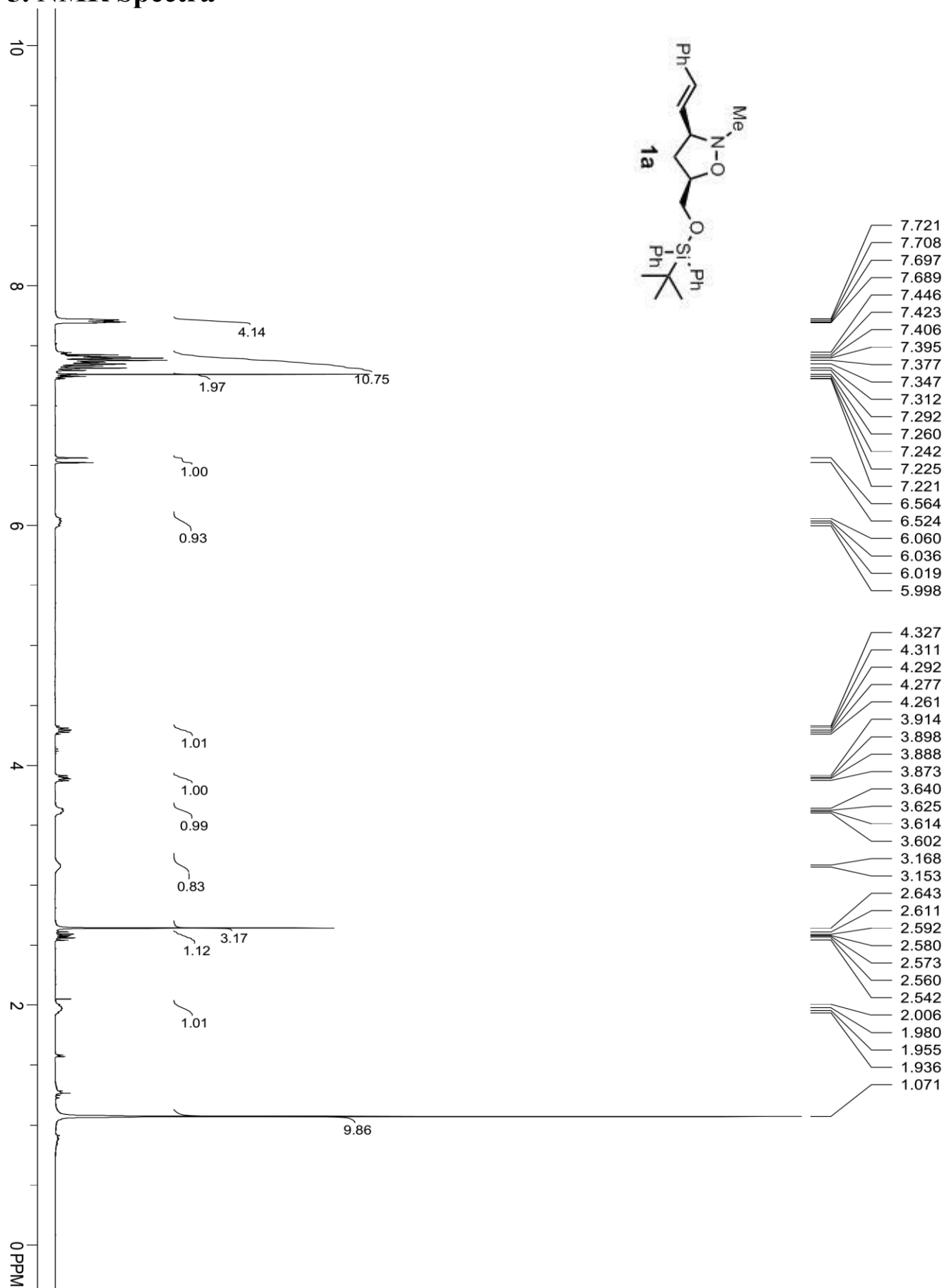


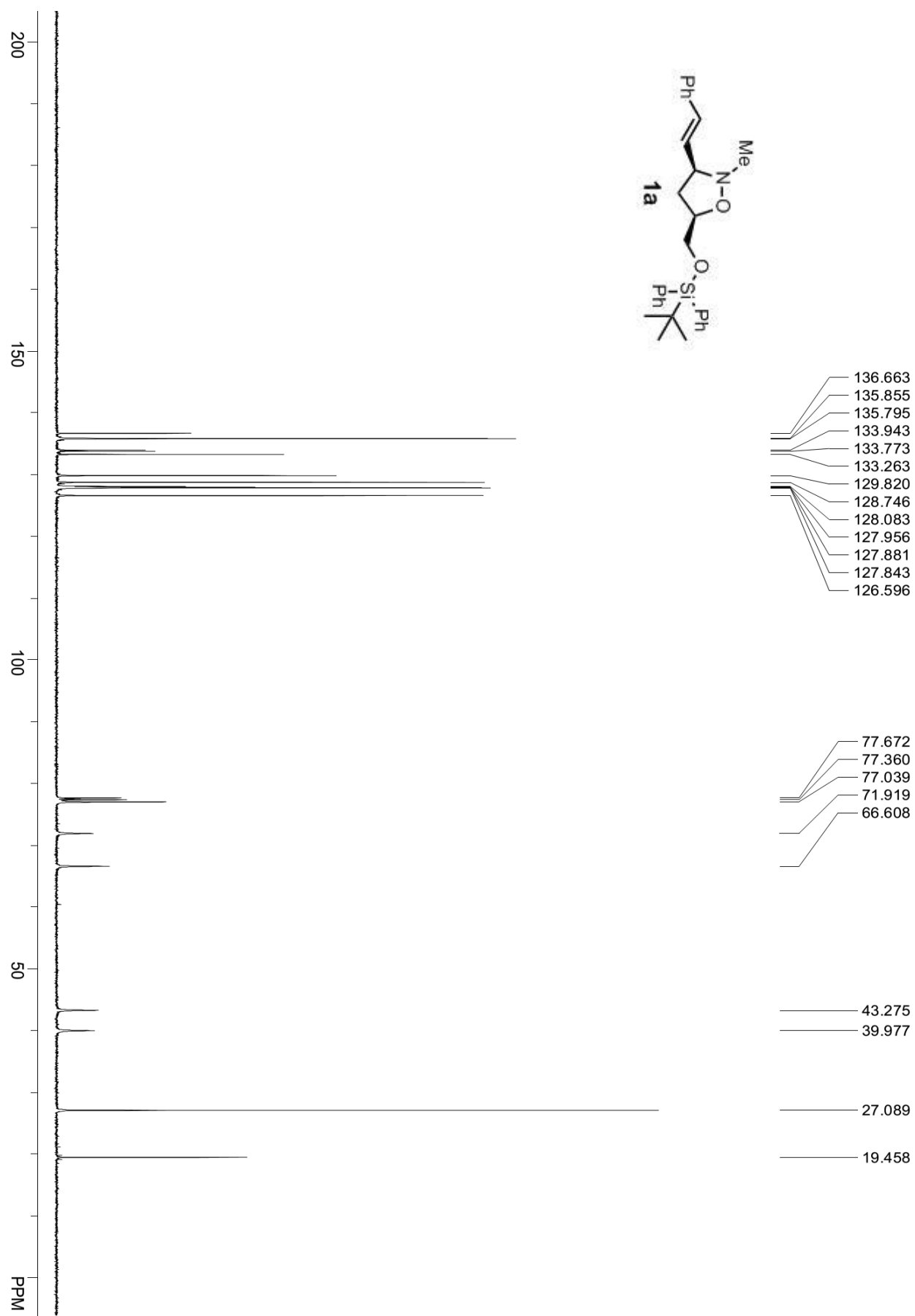
To the mixture of N-lauroyl 1,3-oxazinane **8** (4.72 mmol, 2.9 g) and NH₂OH HCl (47.2 mmol, 3.28 g) in MeOH (25 mL) was added H₂O (18.9 mmol, 340 μ L). The resulting reaction solution was heated under reflux for 4 hours and quenched with sat. Na₂CO₃ and extracted with CH₂Cl₂ (30 mL \times 2). The combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The residue was purified by flash column chromatography to give the final racemic **HPA-12 ((\pm)-7)** as a white solid product (1.20 g, 70%). **¹H NMR** (400 MHz, CDCl₃) δ 7.34-7.33 (m, 4 H), 7.30-7.24 (m, 1 H), 6.44 (d, *J* = 6.0 Hz, 1 H), 4.81 (dd, *J* = 8.8, 3.2 Hz, 1 H), 4.05 (br s, 1 H), 3.70-3.64 (m, 2 H), 2.85 (br s, 2 H), 2.16 (t, *J* = 7.6 Hz, 2 H), 2.04 (ddd, *J* = 14.6, 5.2, 3.4 Hz, 1 H), 1.97-1.89 (m, 1 H), 1.61-1.58 (m, 2 H), 1.36-1.22 (m, 16 H), 0.87 (t, *J* = 6.8 Hz, 3 H);⁴ **¹³C NMR** (100 MHz, CDCl₃) δ 174.7, 144.6, 128.8, 127.9, 125.9, 72.0, 65.6, 50.6, 41.1, 37.1, 32.2, 30.0 (2 peaks), 29.9, 29.7 (2 peaks), 29.6, 26.1, 23.0, 14.4. ⁴ **HRMS (ESI)** calcd for C₂₂H₃₈NO₃ [M+H]⁺ 364.2846, found 364.2851.

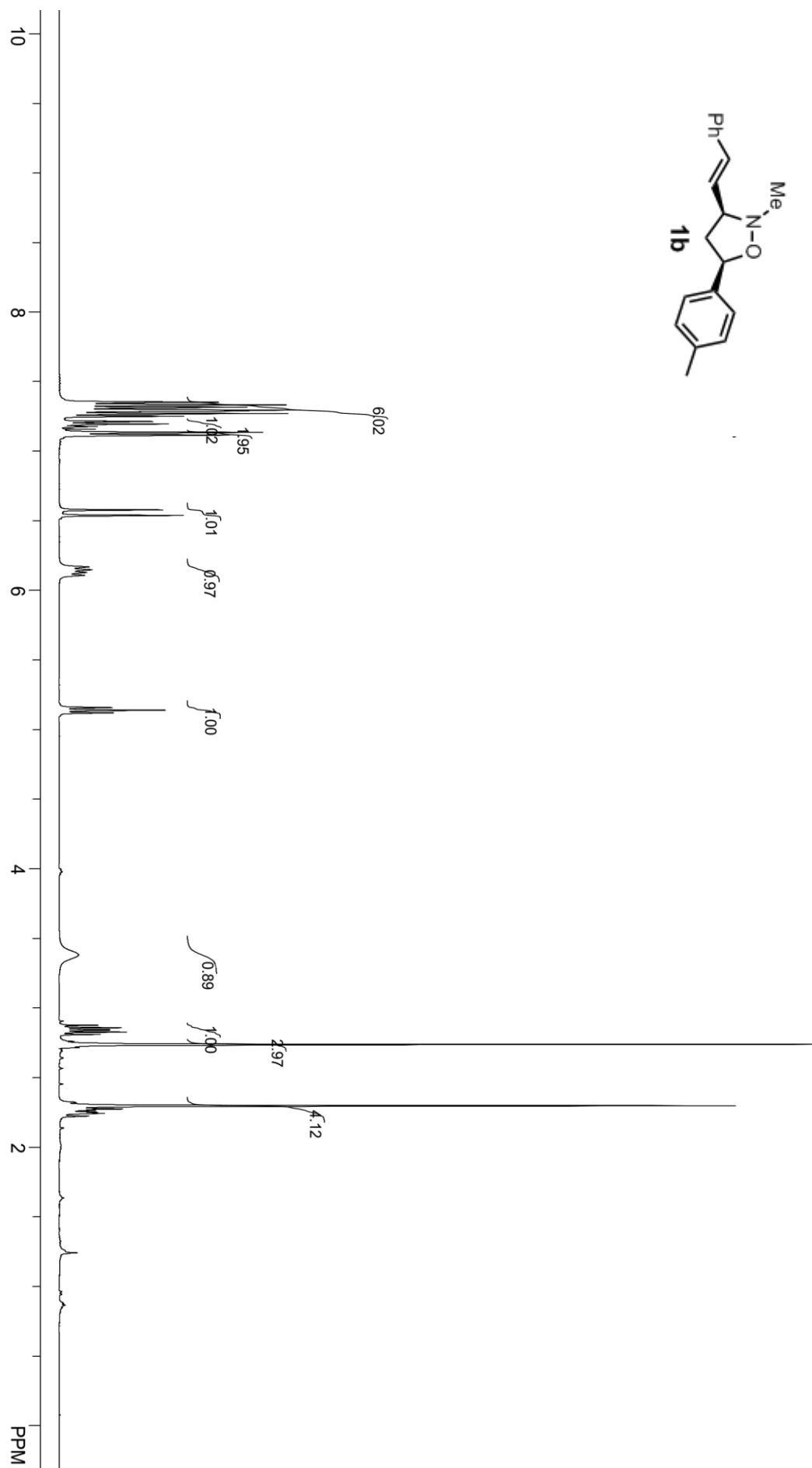
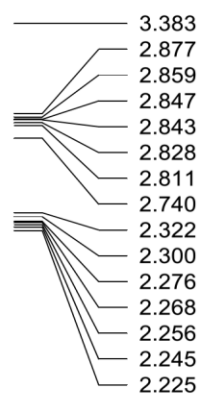
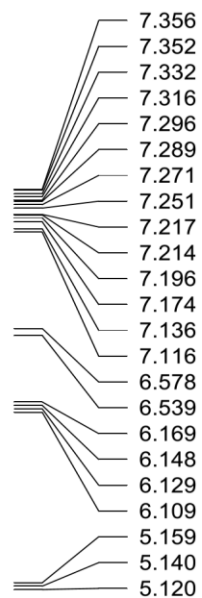
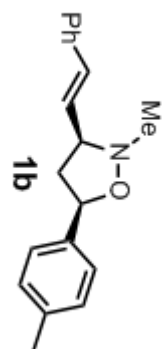
2. References

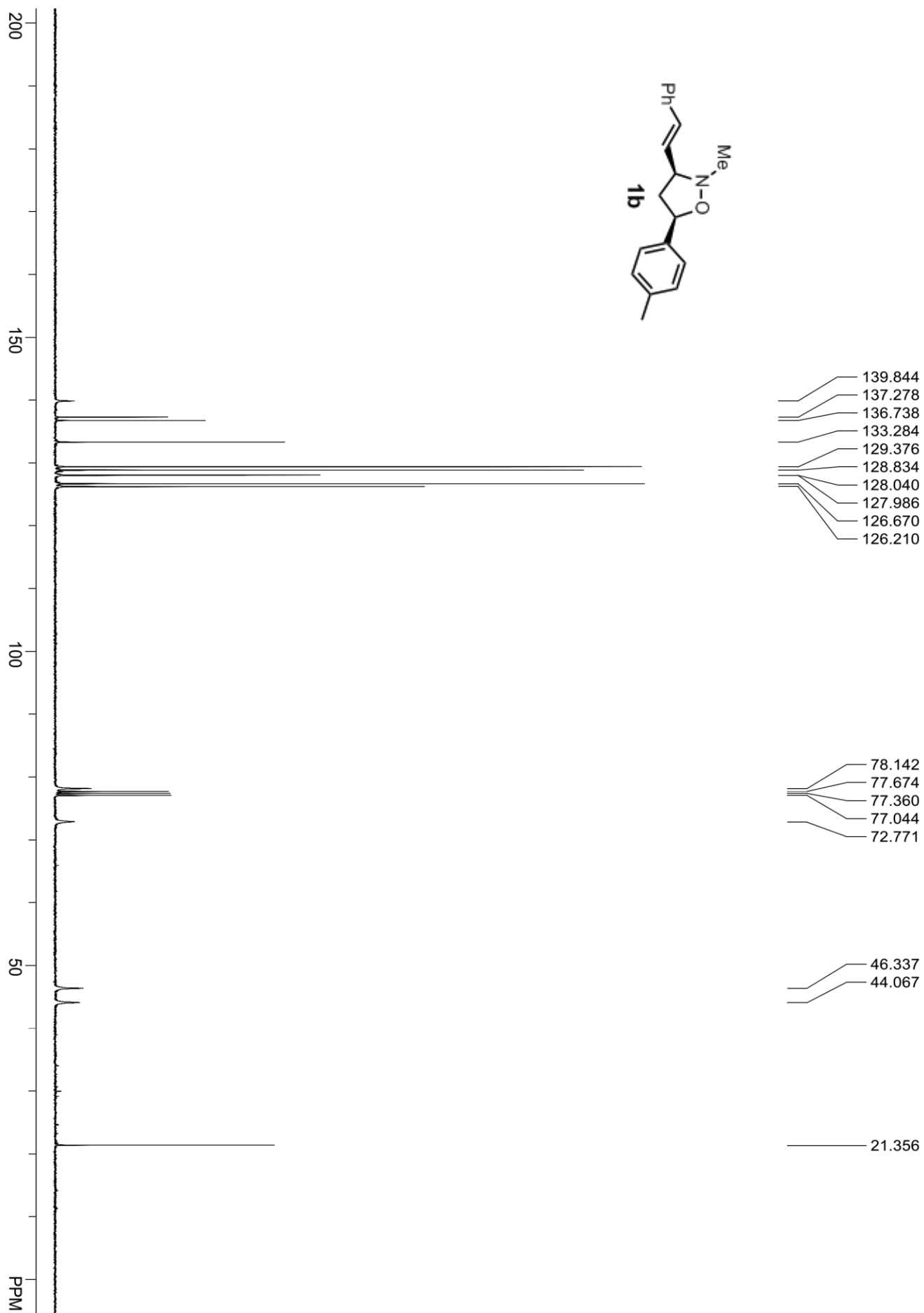
1. (a) Cho, S. J.; Jensen, N. H.; Kurome, T.; Kadari, S.; Manzano, M. L.; Malberg, J. E.; Caldarone, B.; Roth, B. L.; Kozikowski, A. P. *J. Med. Chem.* **2009**, *52*, 1885. (b) Revuelta, J.; Cicchi, S.; Meijere, A. D.; Brandi, A. *Eur. J. Org. Chem.* **2008**, *6*, 1085. (c) Cawkill, E.; Clark, N. G. *J. Chem. Soc., Perkin Trans.* **1980**, *1*, 244.
2. Harding, K. E.; Marman, T. H.; Nam, D. *Tetrahedron* **1988**, *44*, 5605.
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4. (a) Duris, A.; Wiesenganger, T.; Moravcikova, D.; Baran, P.; Kozisek, J.; Daich, A.; Berkes, D. *Org. Lett.* **2011**, *13*, 1642. (b) Ueno, M.; Huang, Y.-Y.; Yamano, A.; Kobayashi, S. *Org. Lett.* **2013**, *15*, 2869.

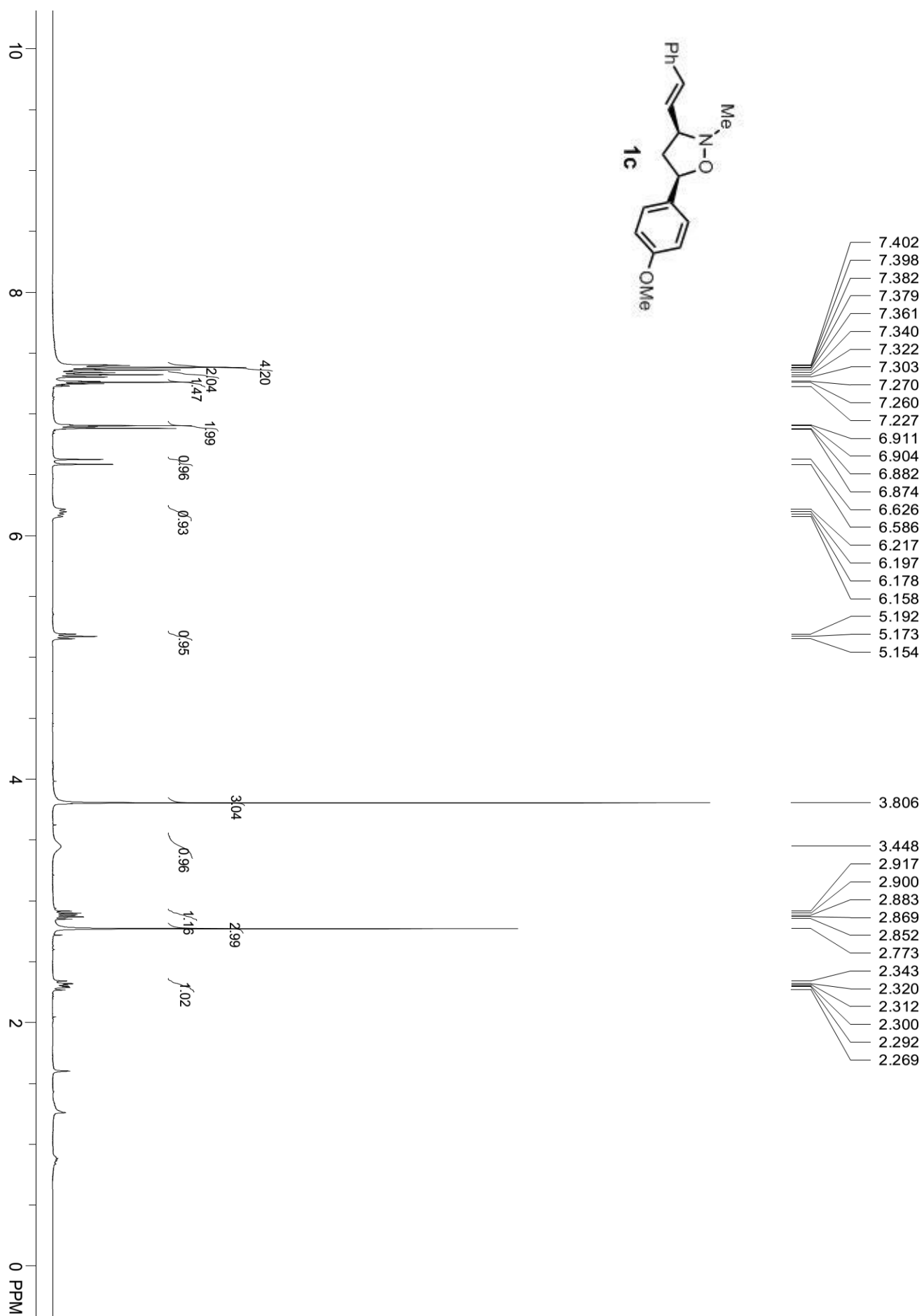
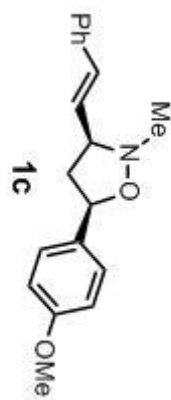
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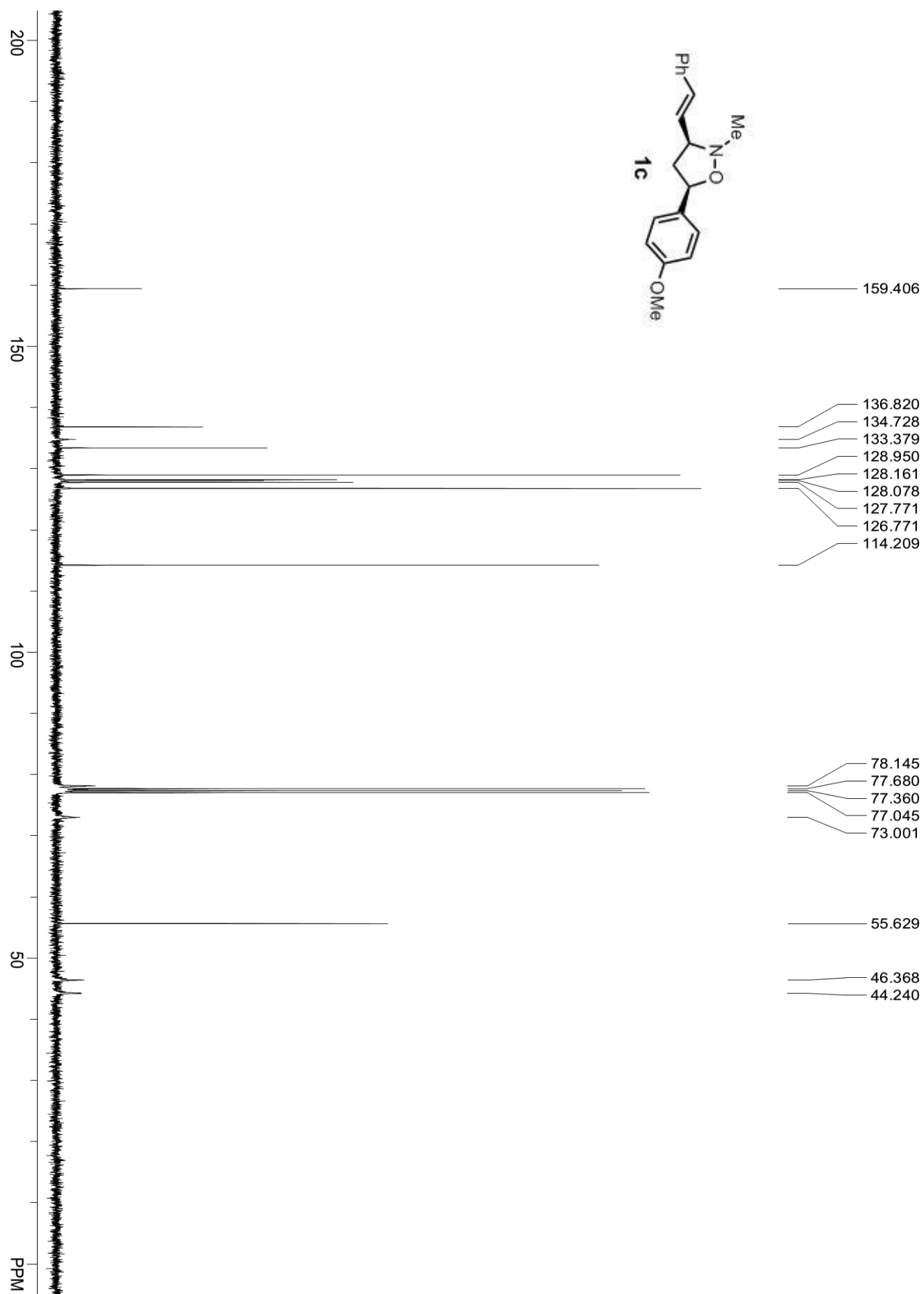


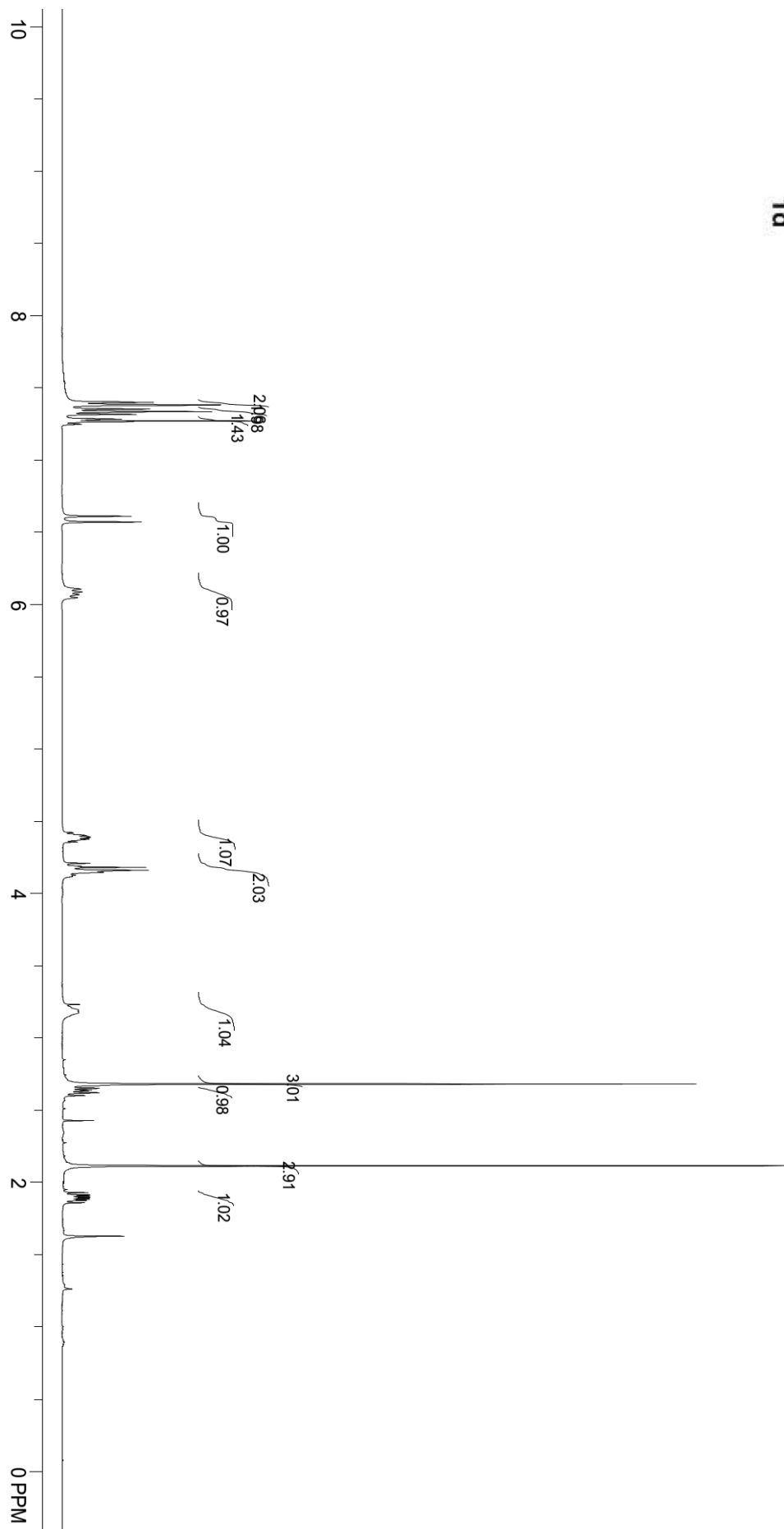
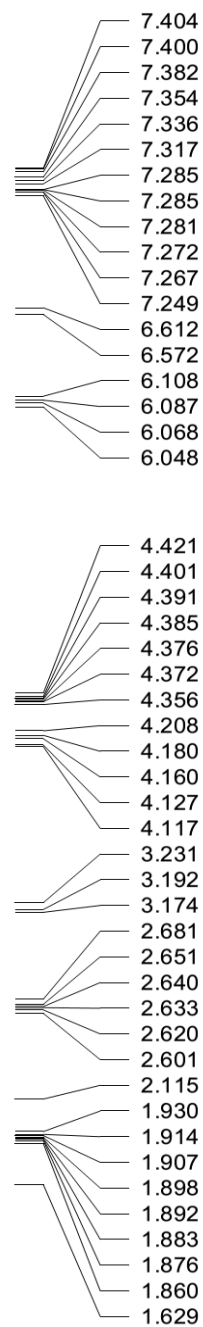
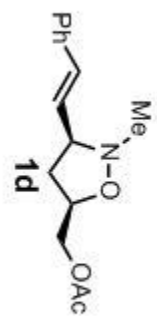


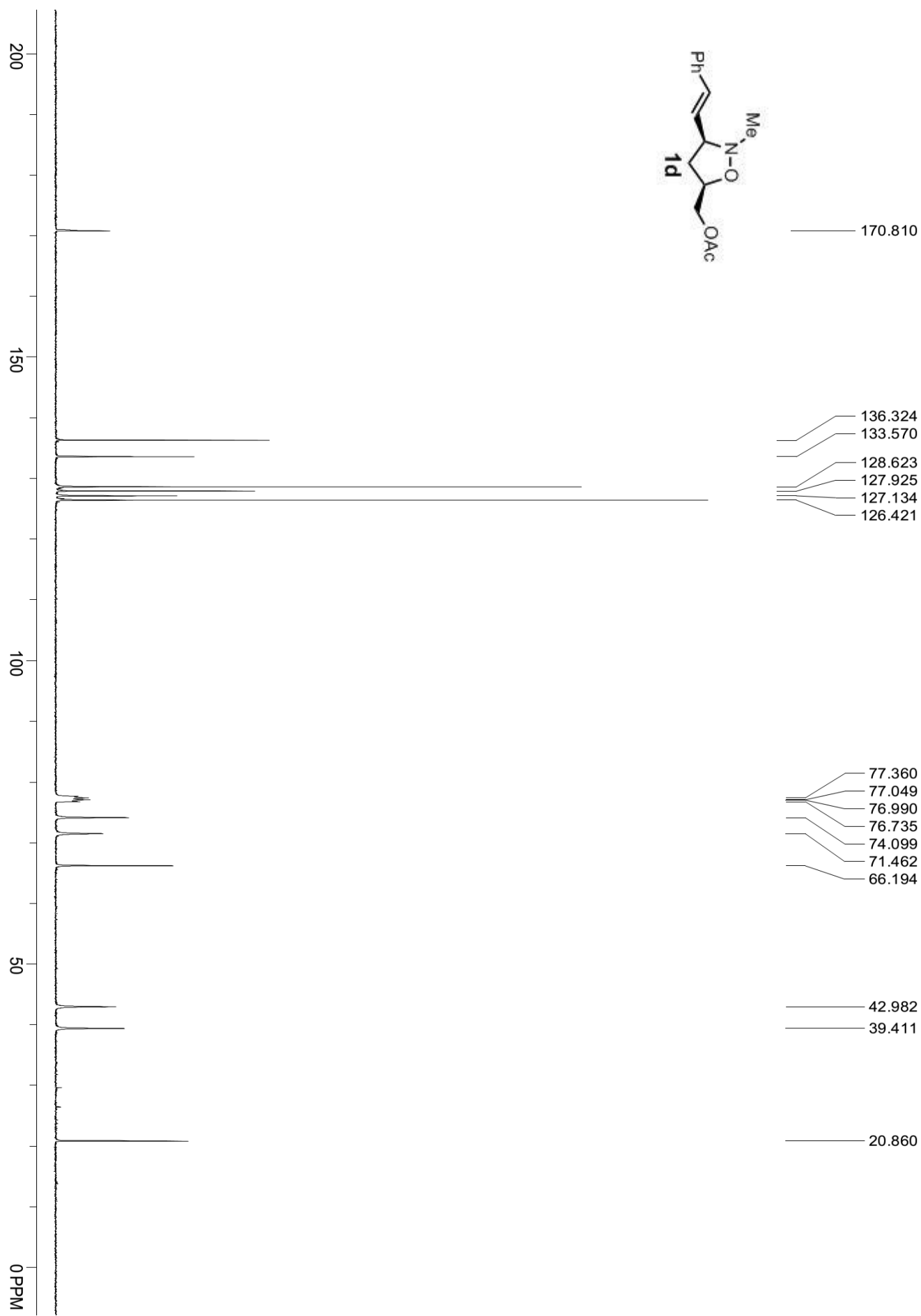


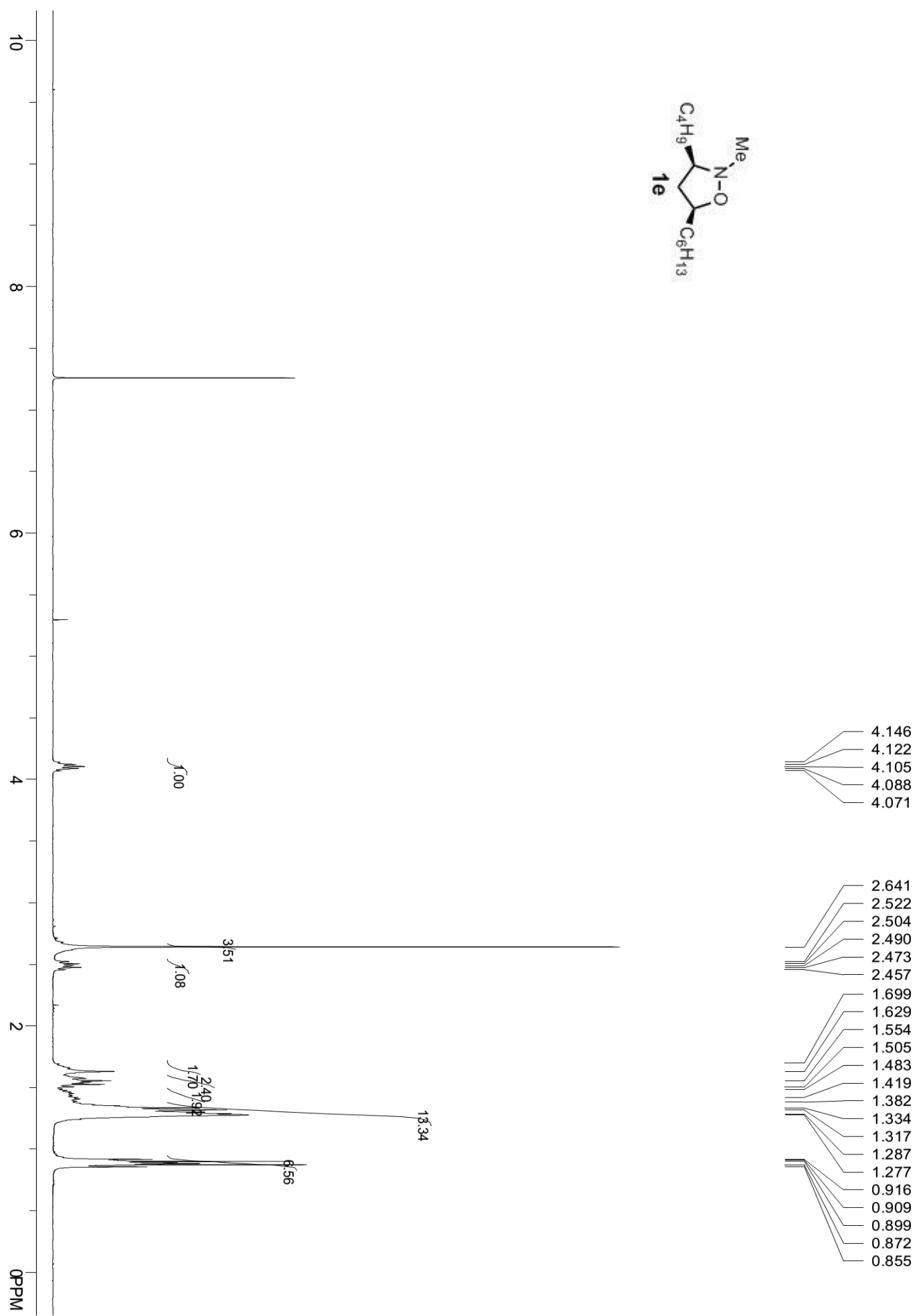
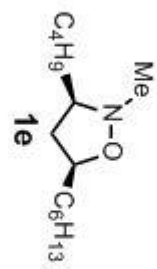


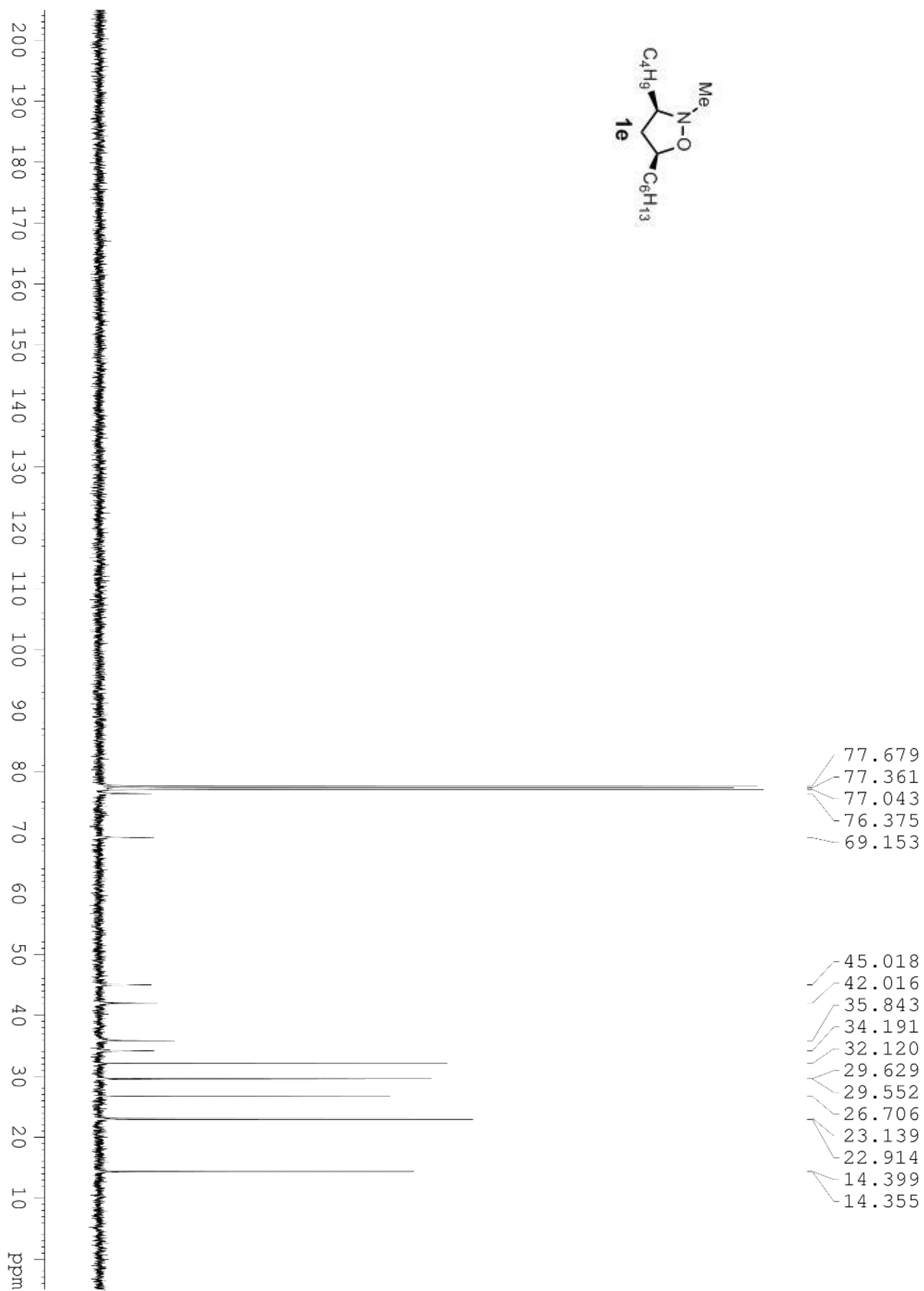
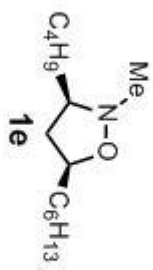


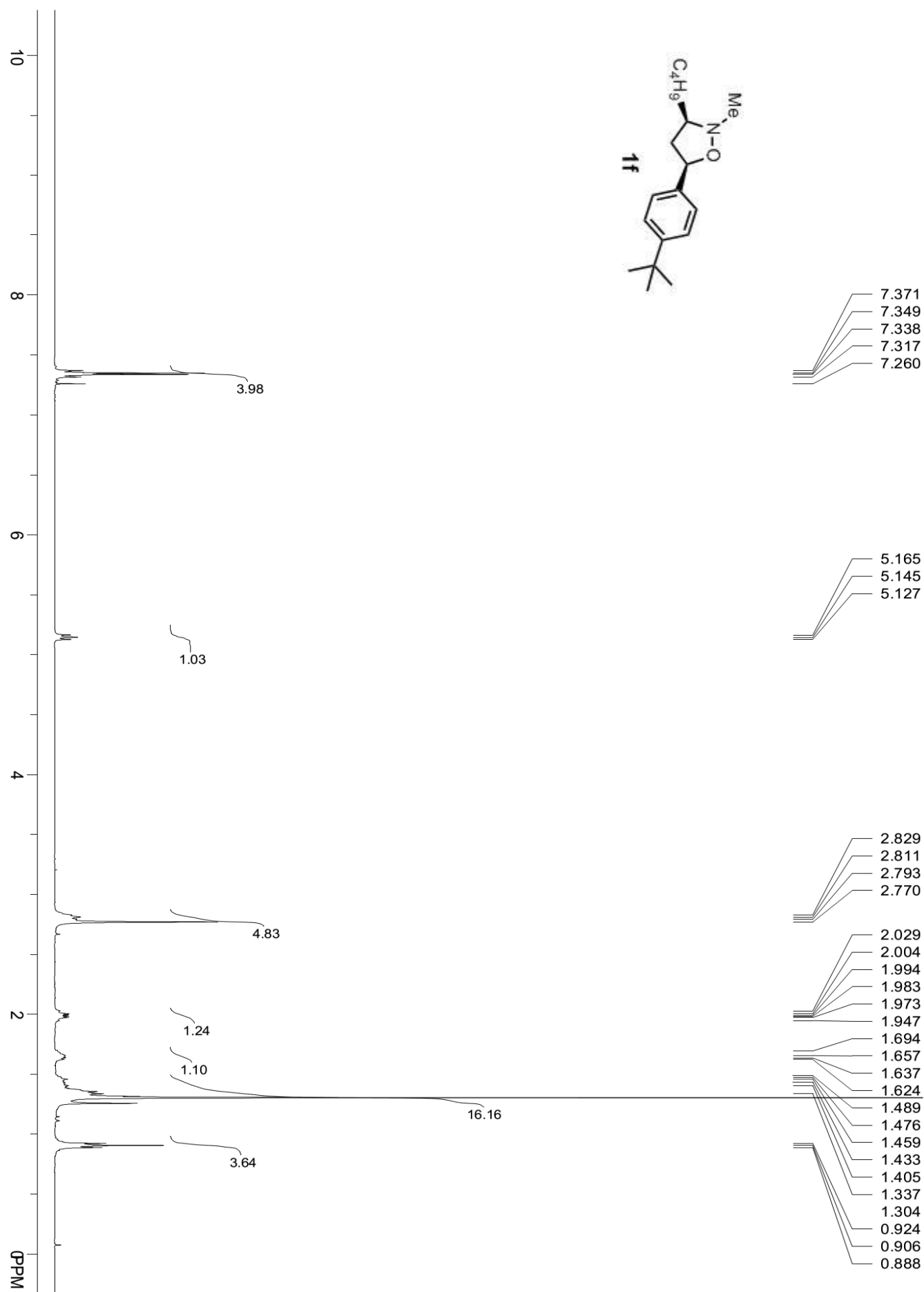


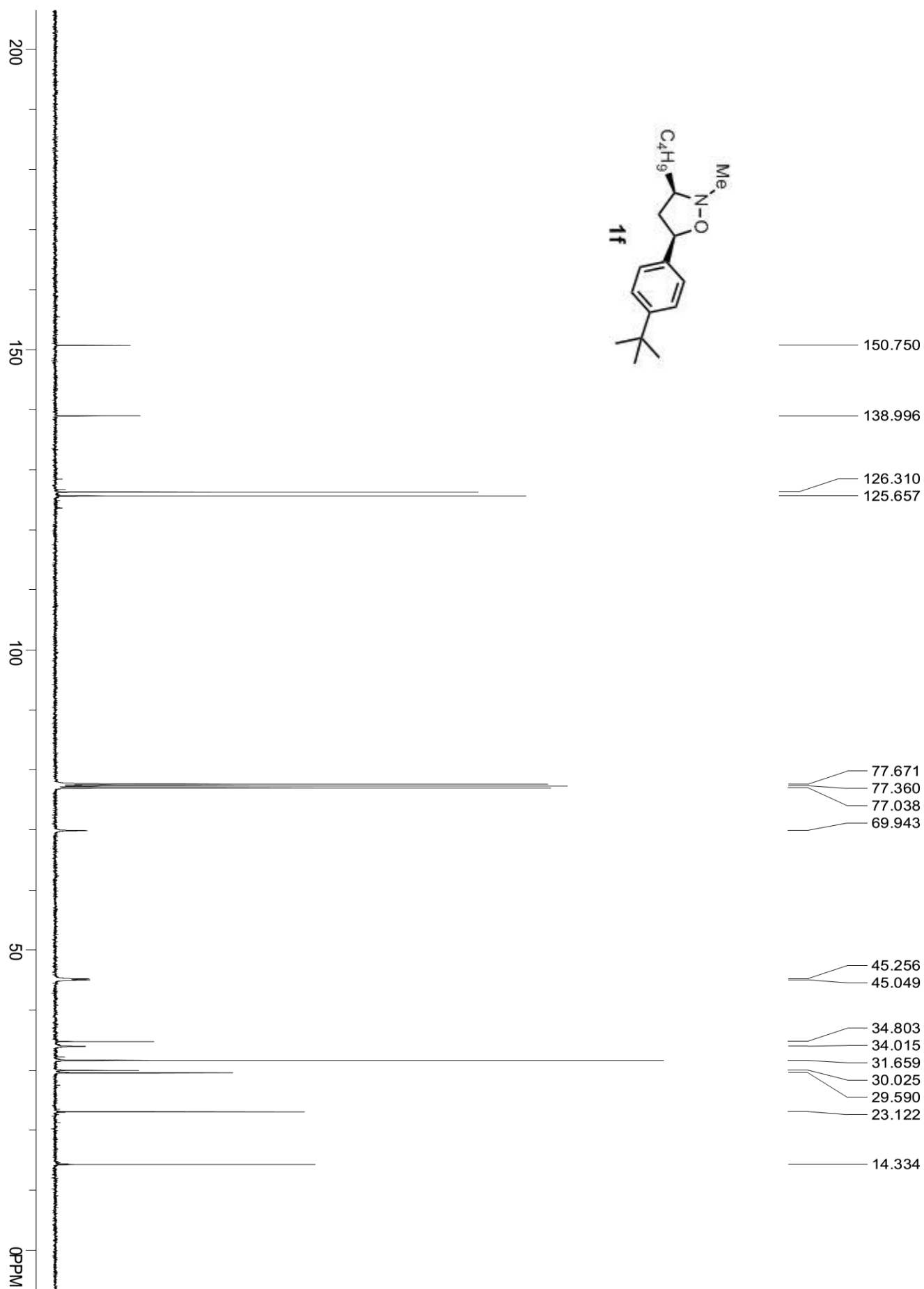


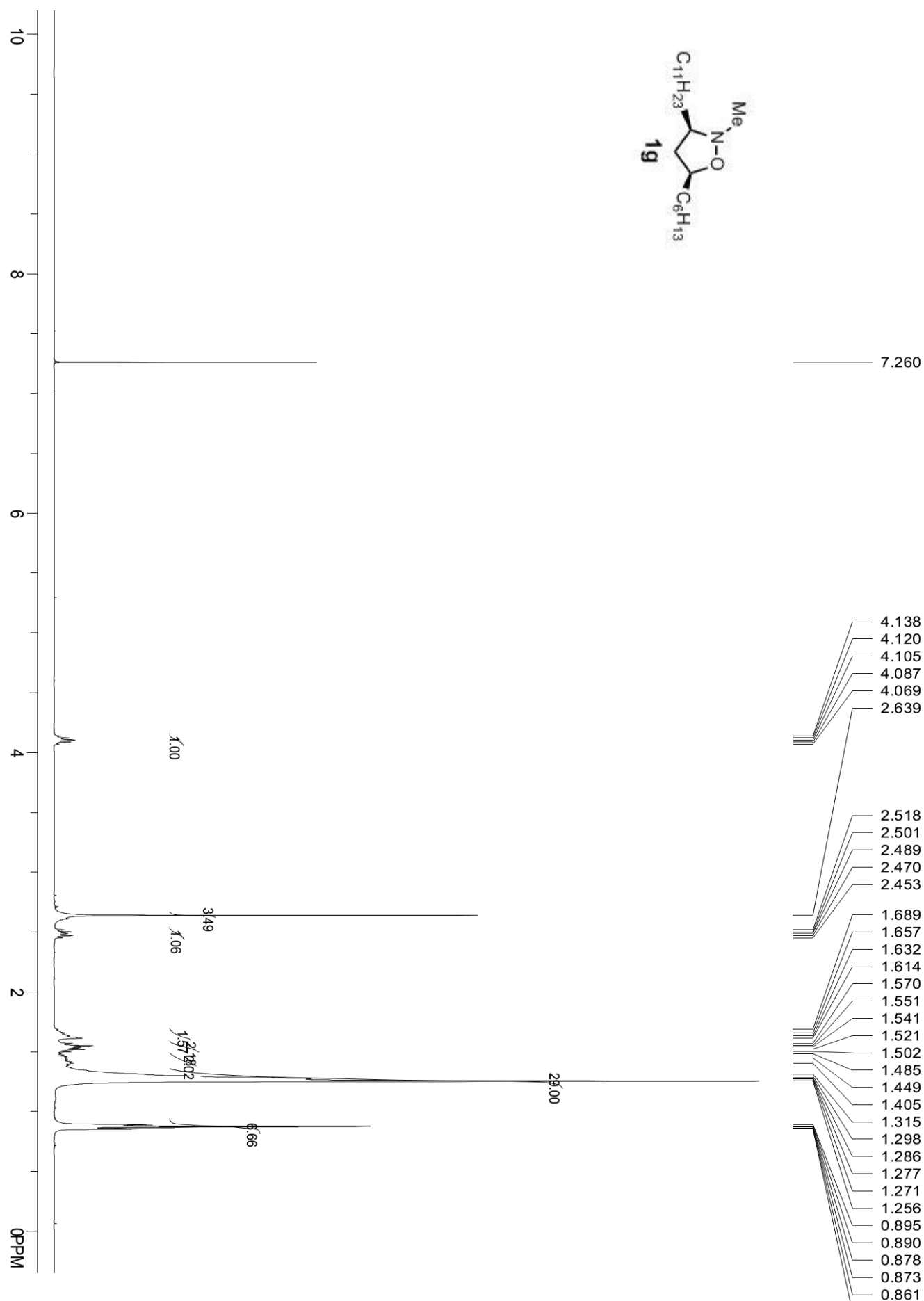
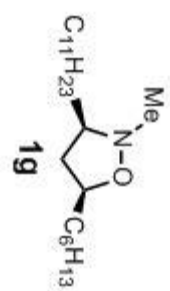


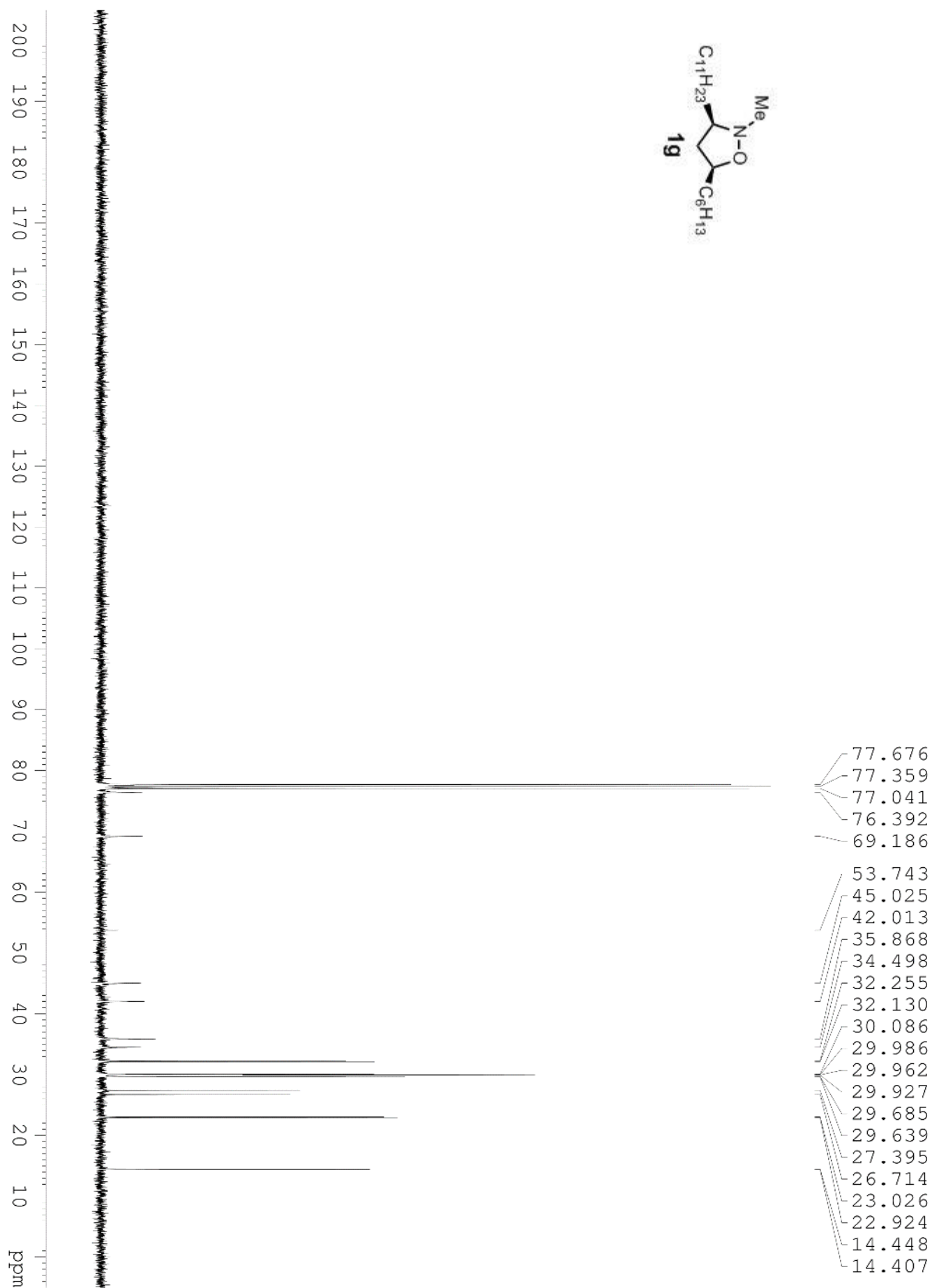
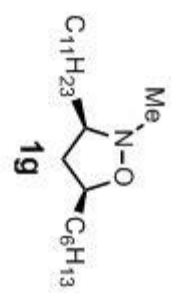


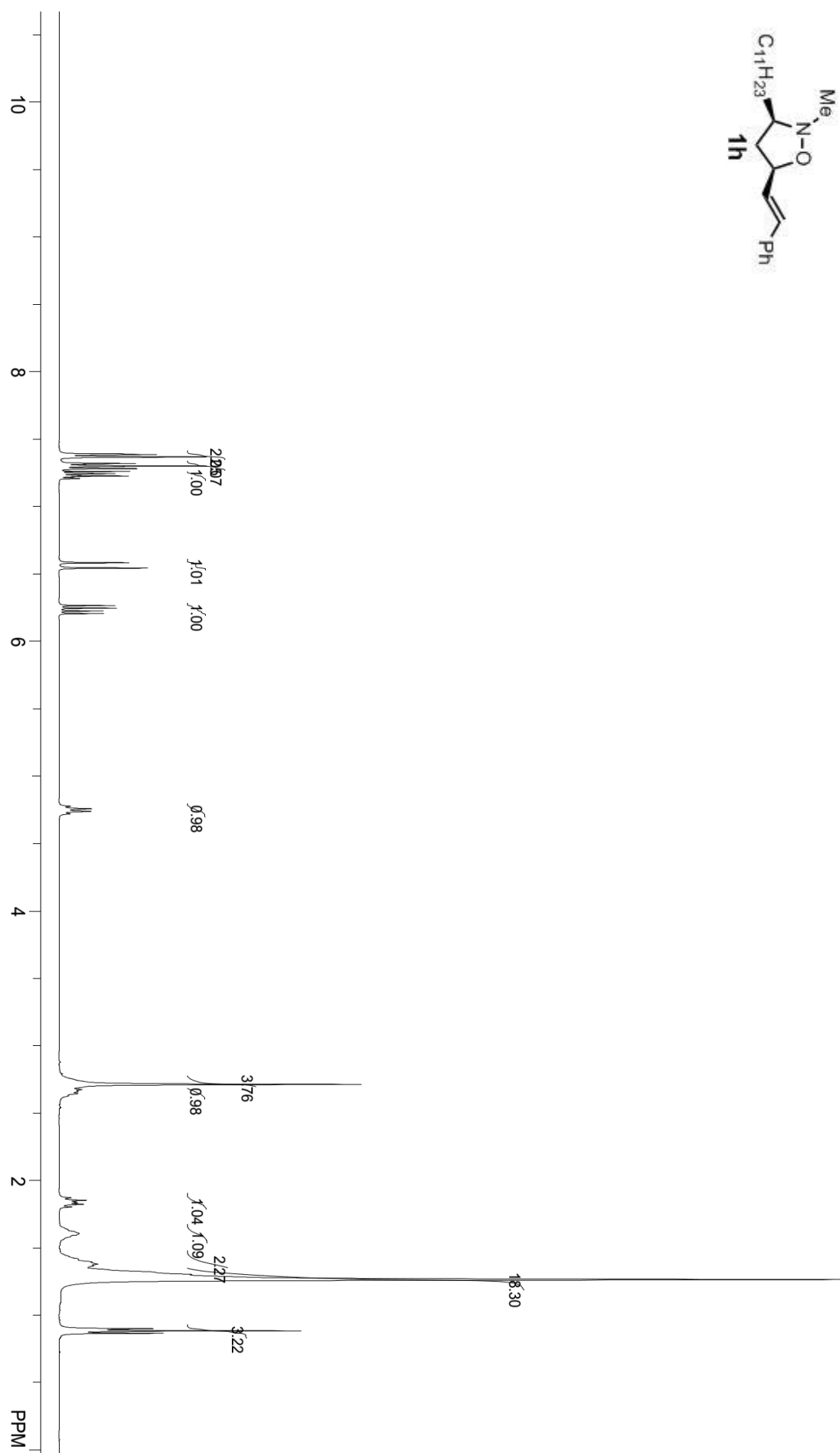
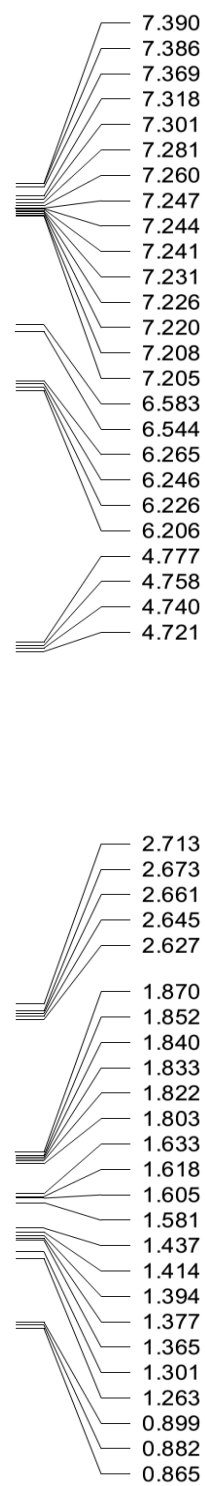
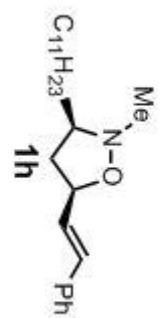


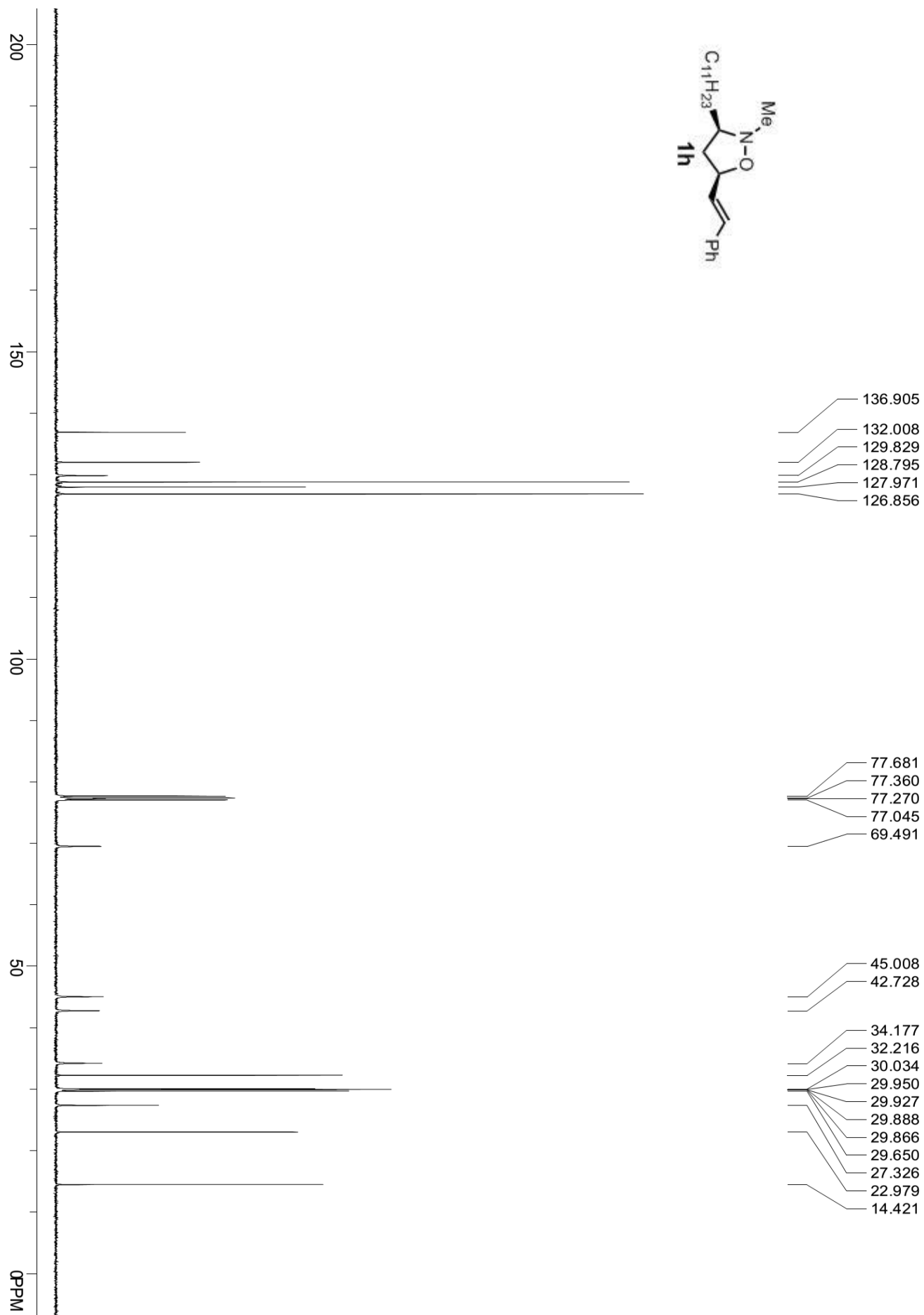


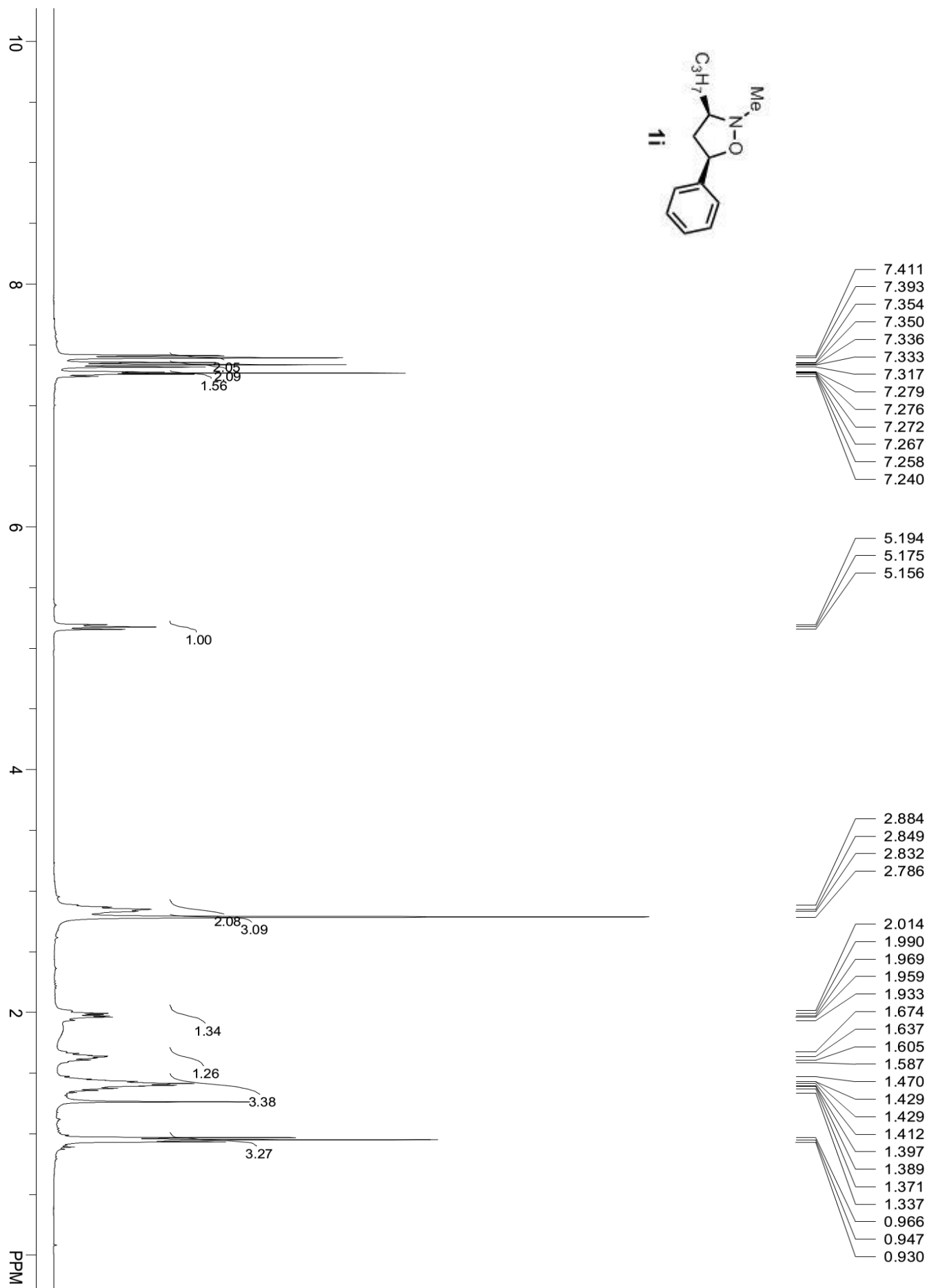


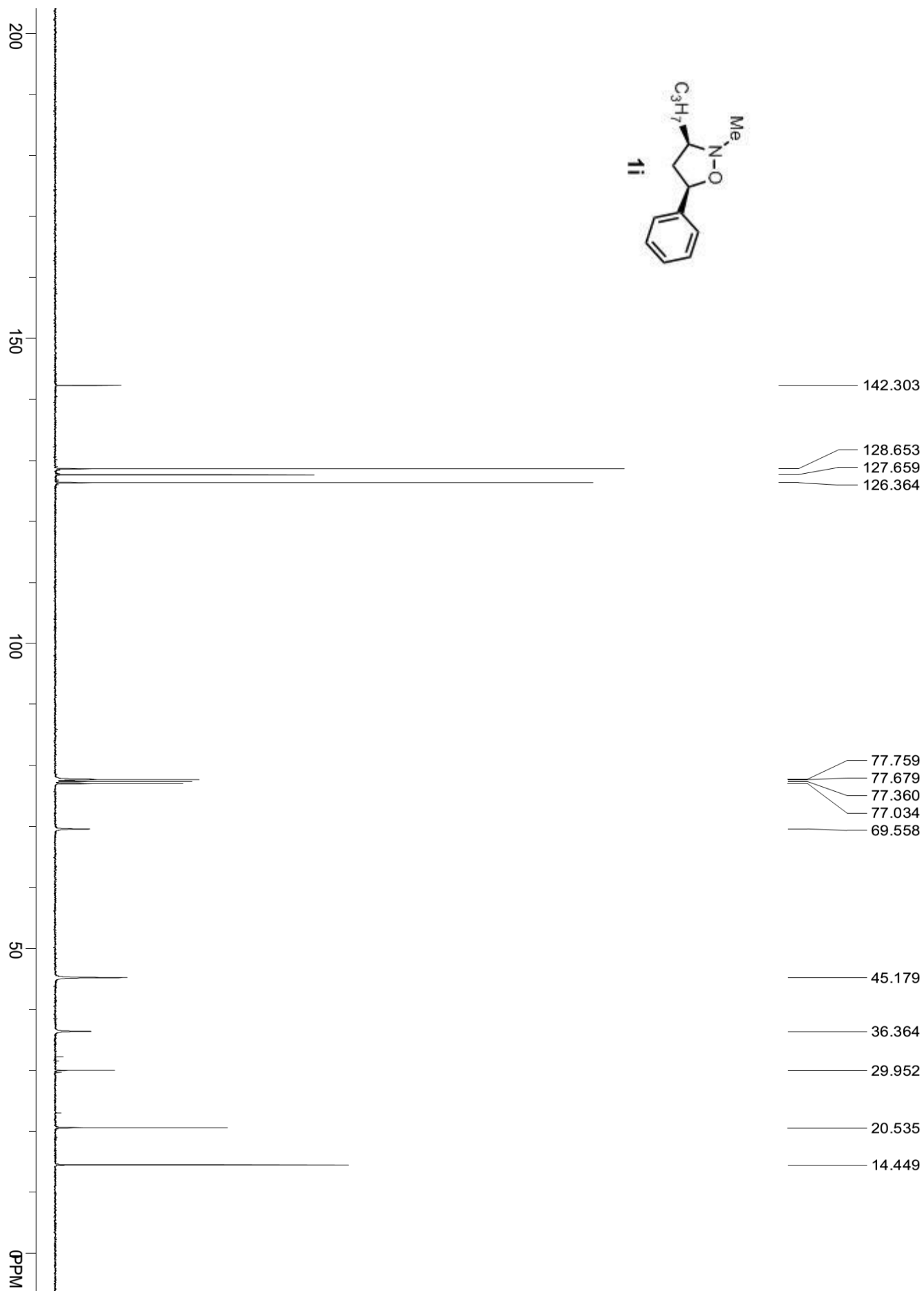


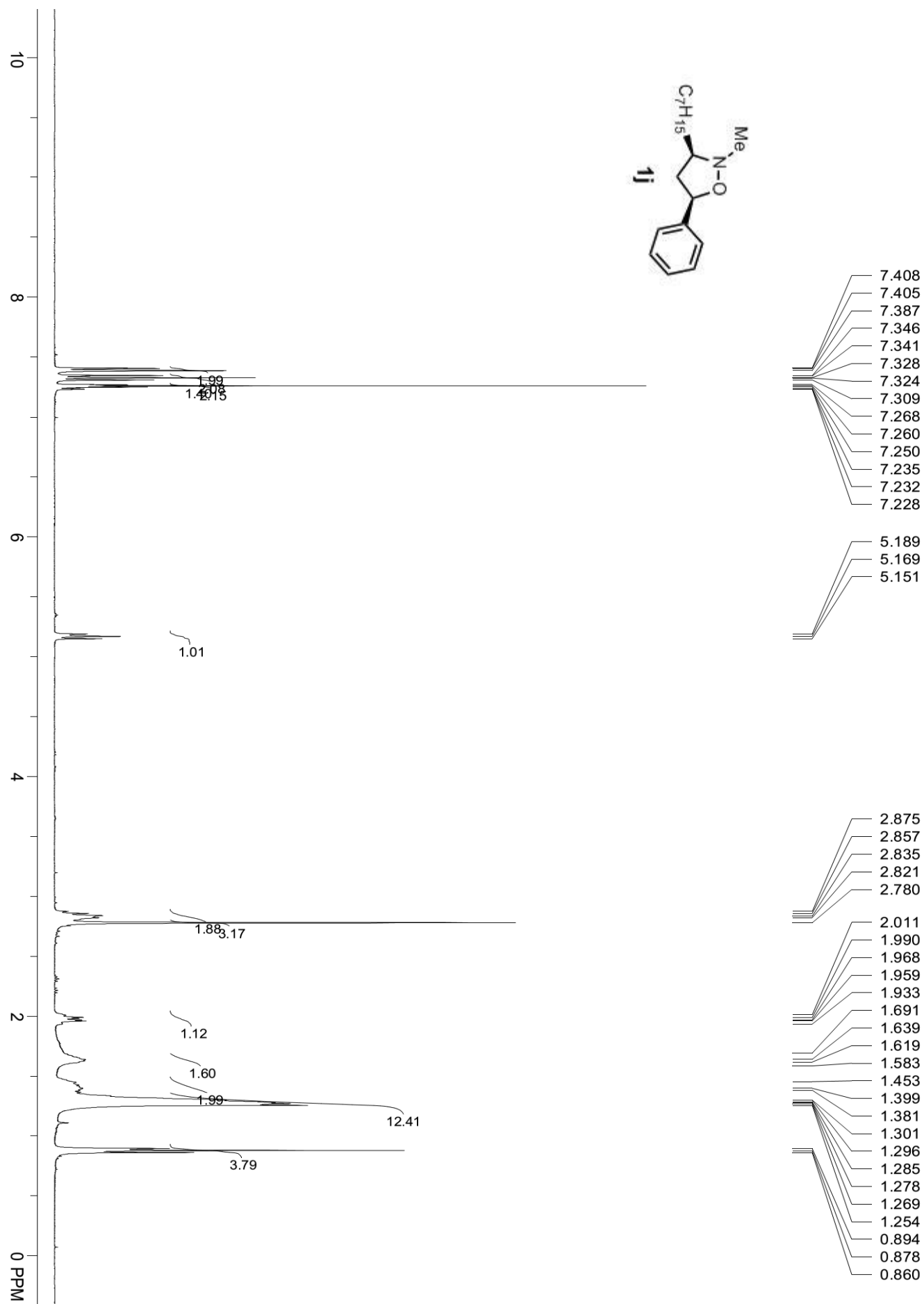


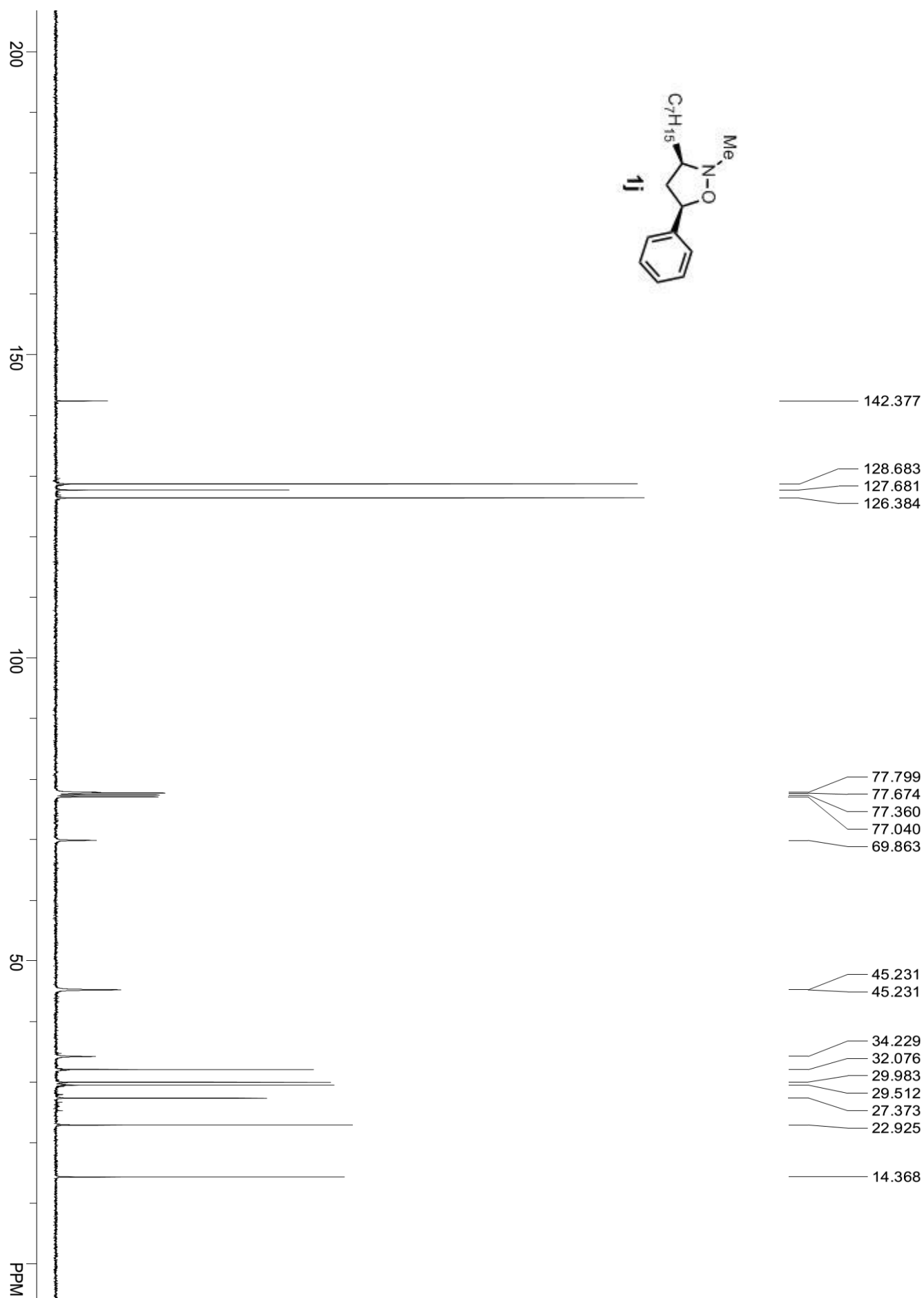


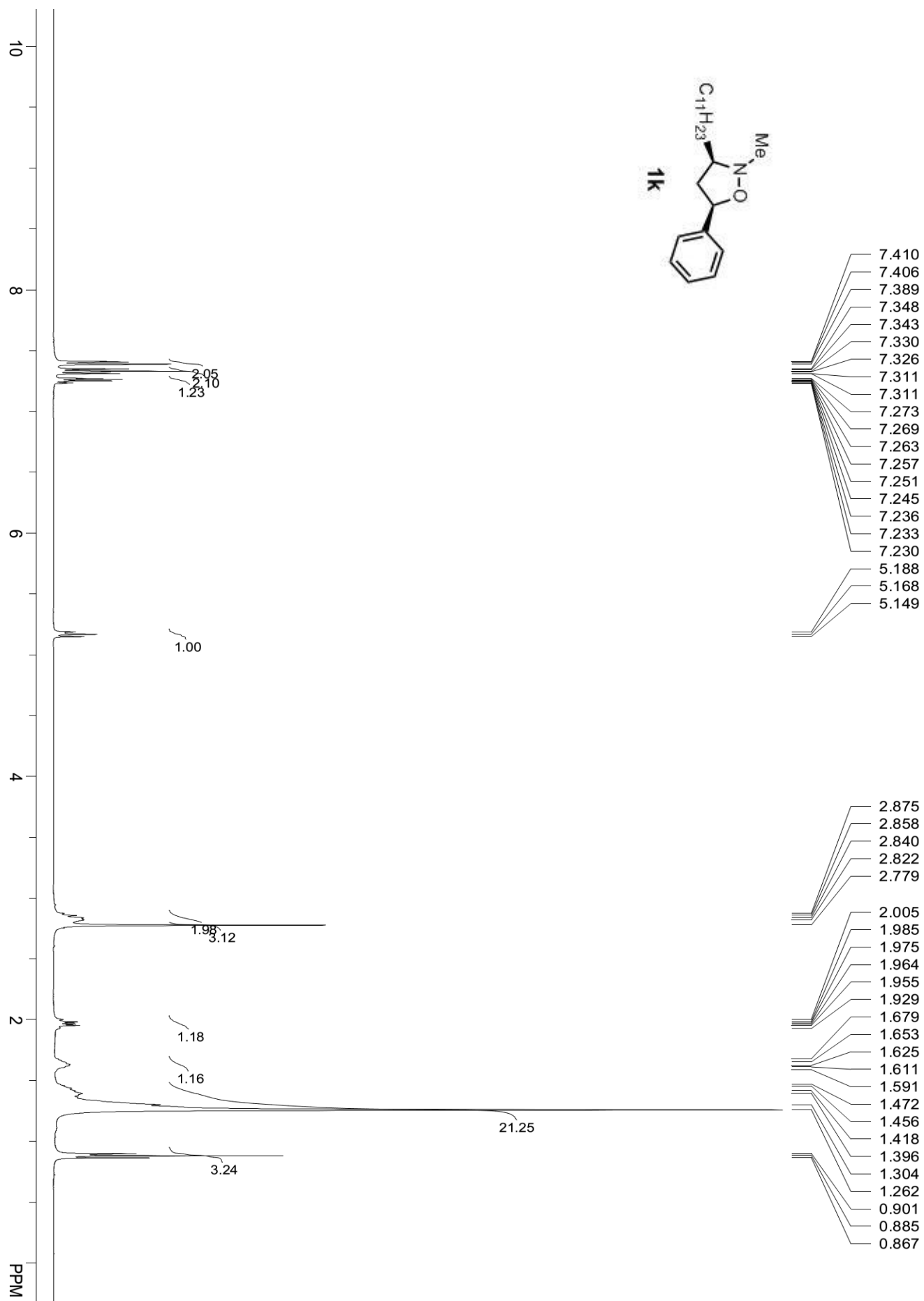


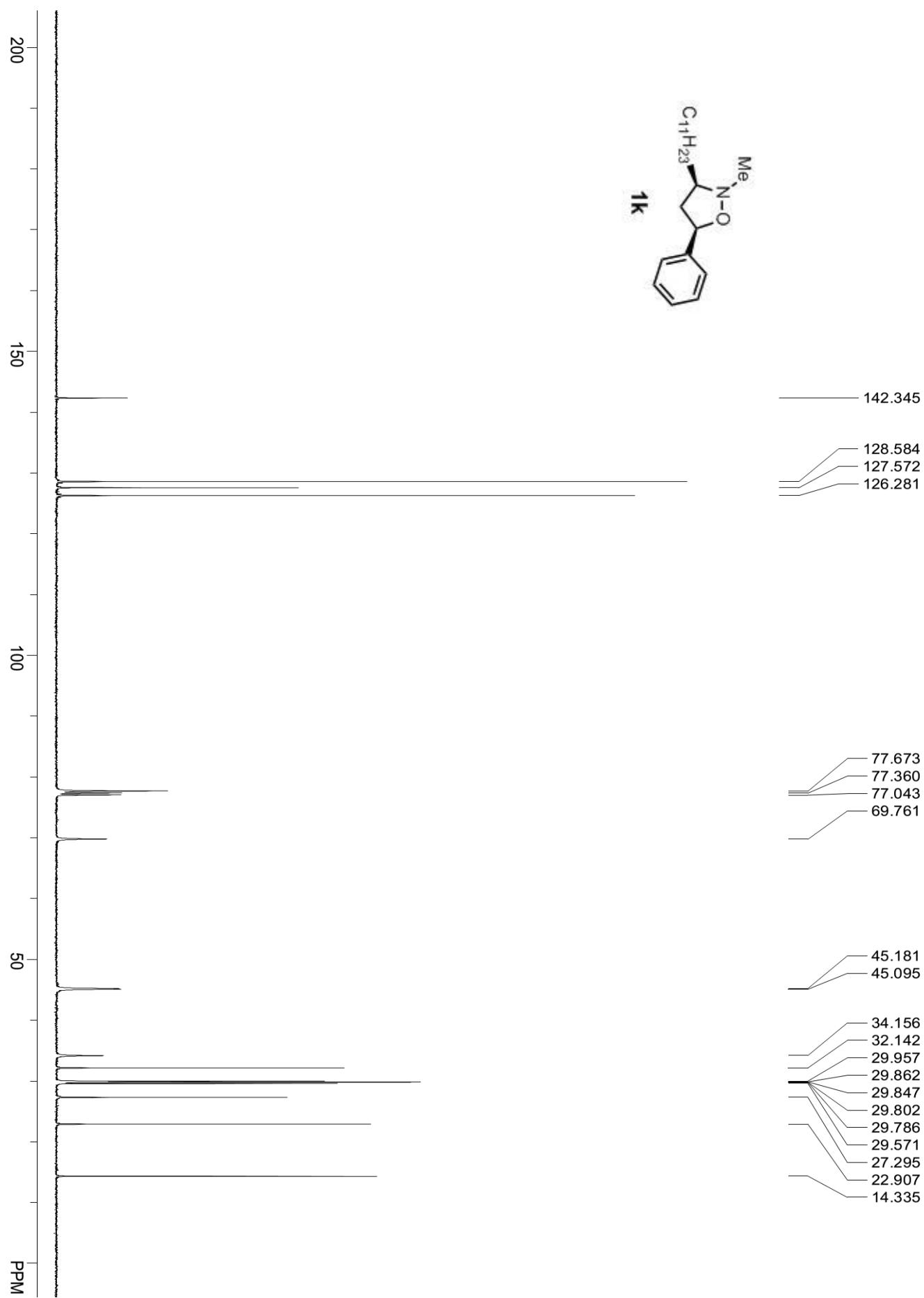


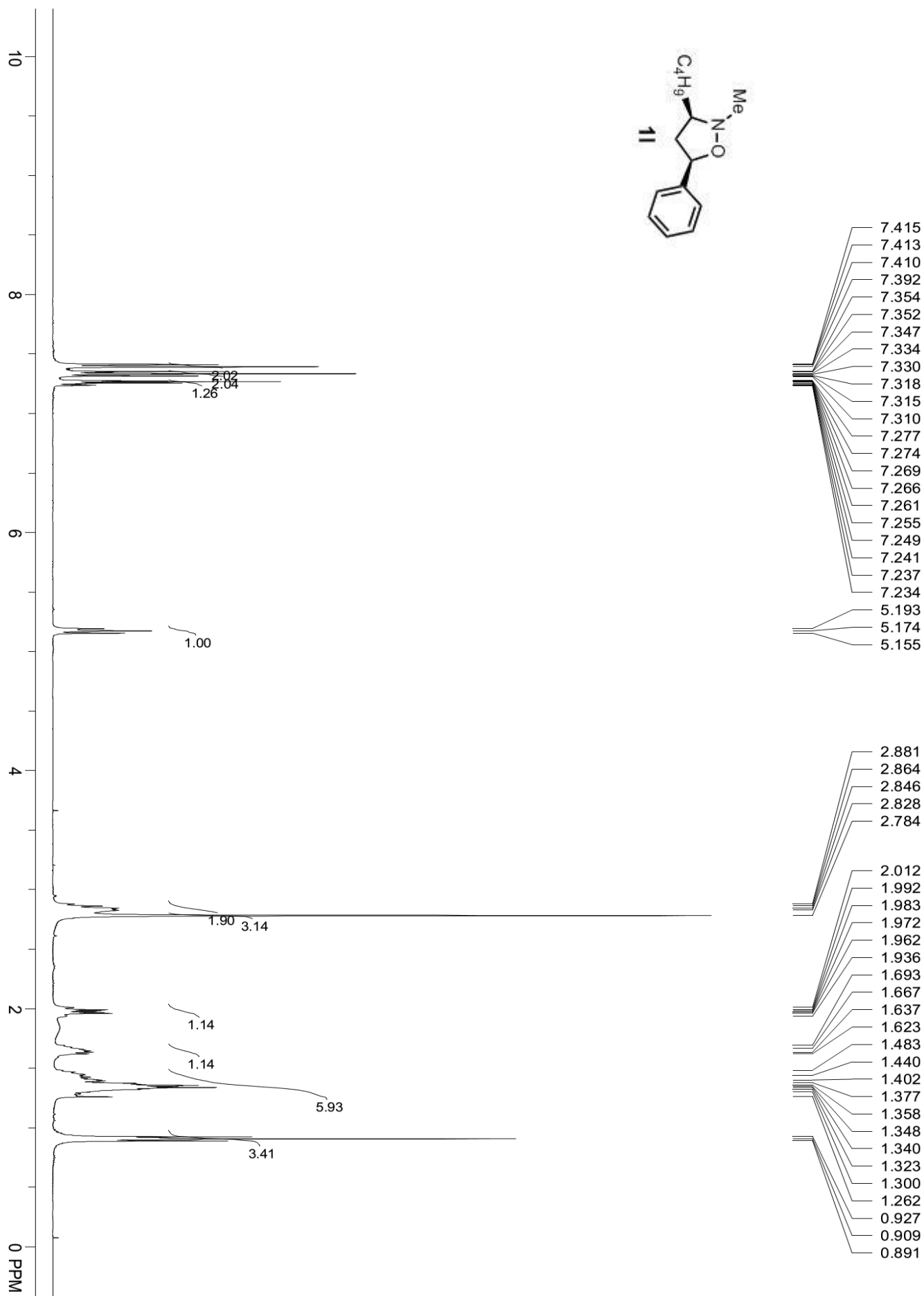


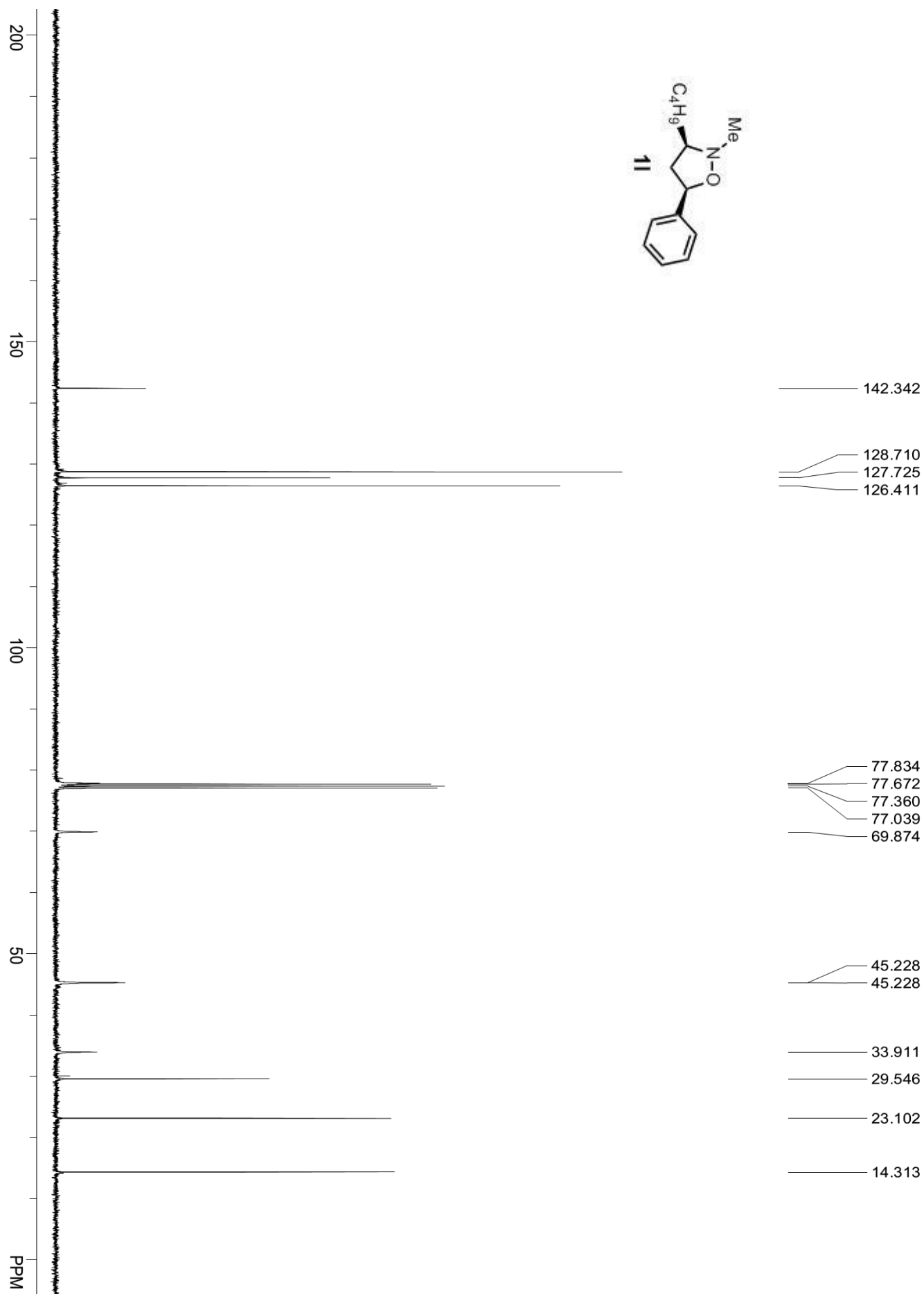


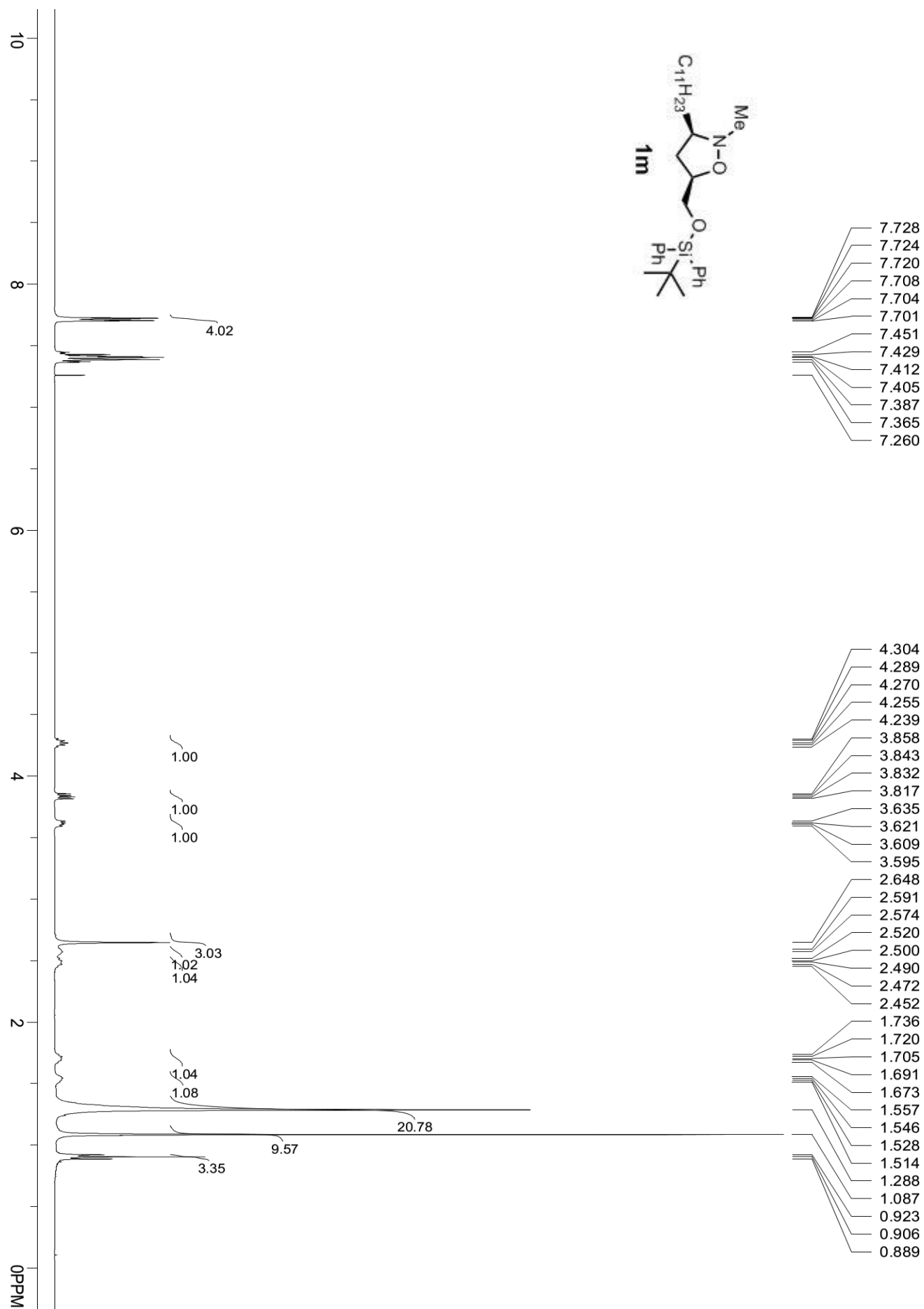


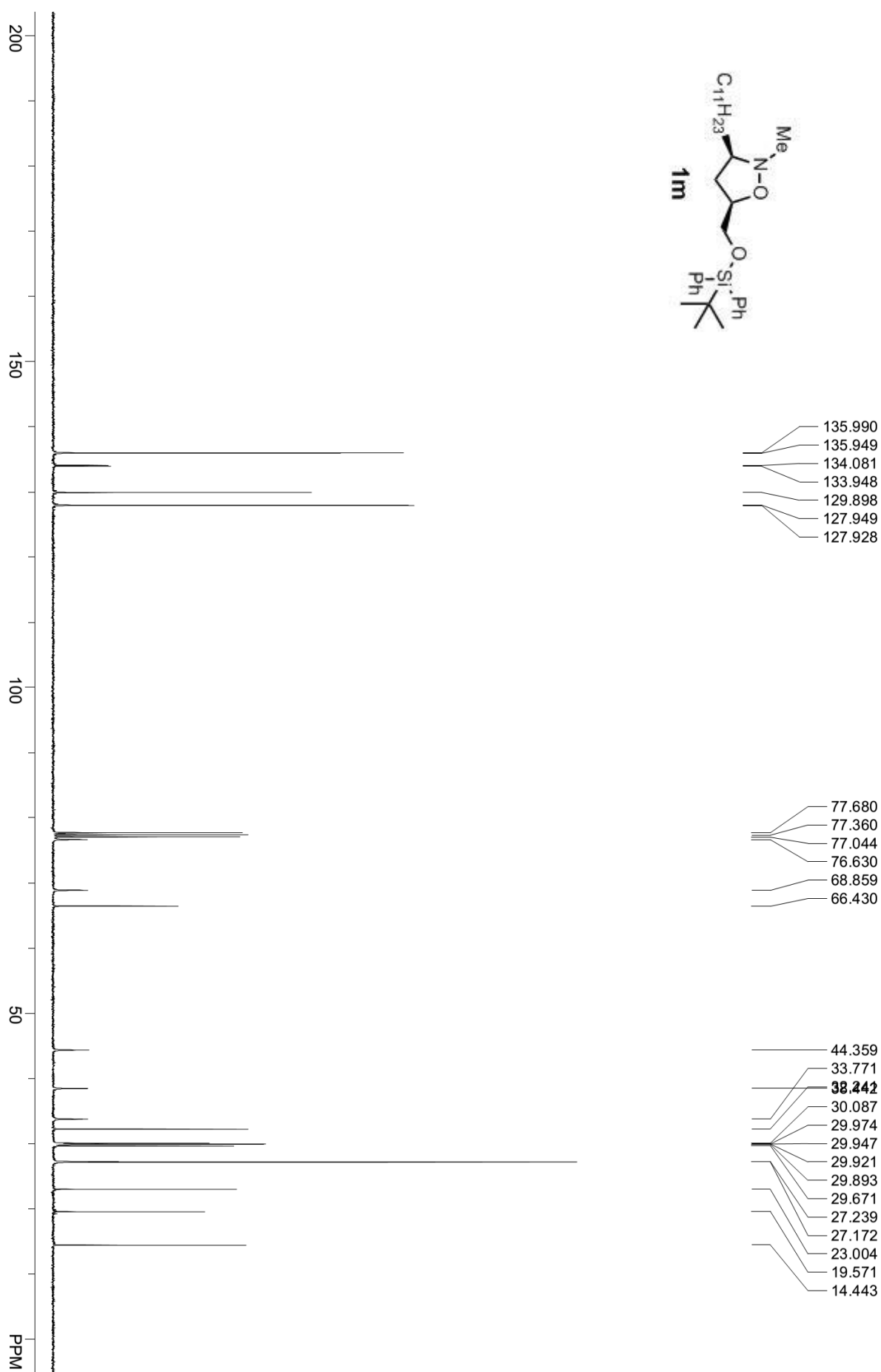
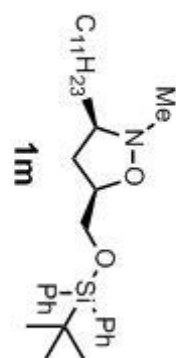


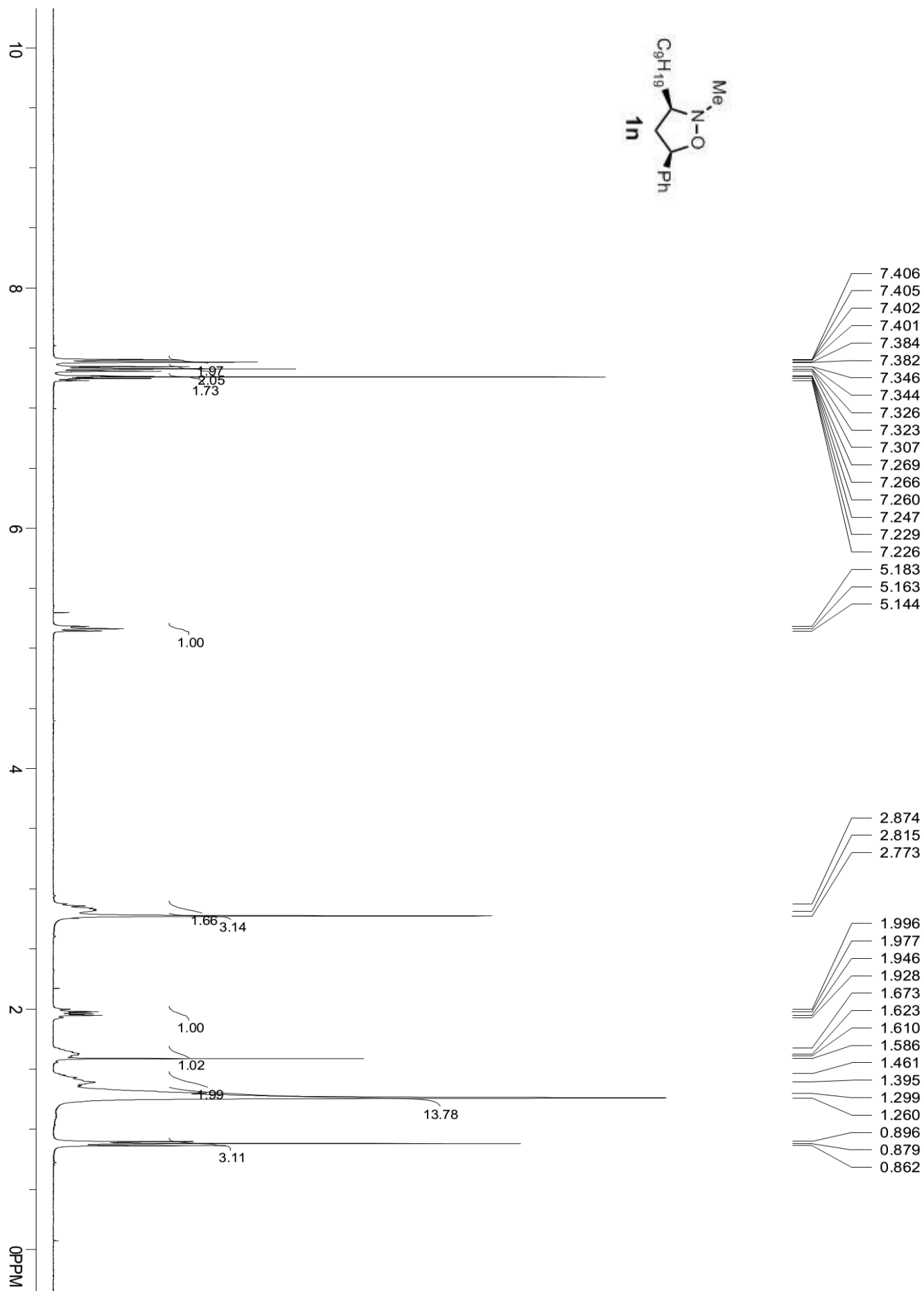


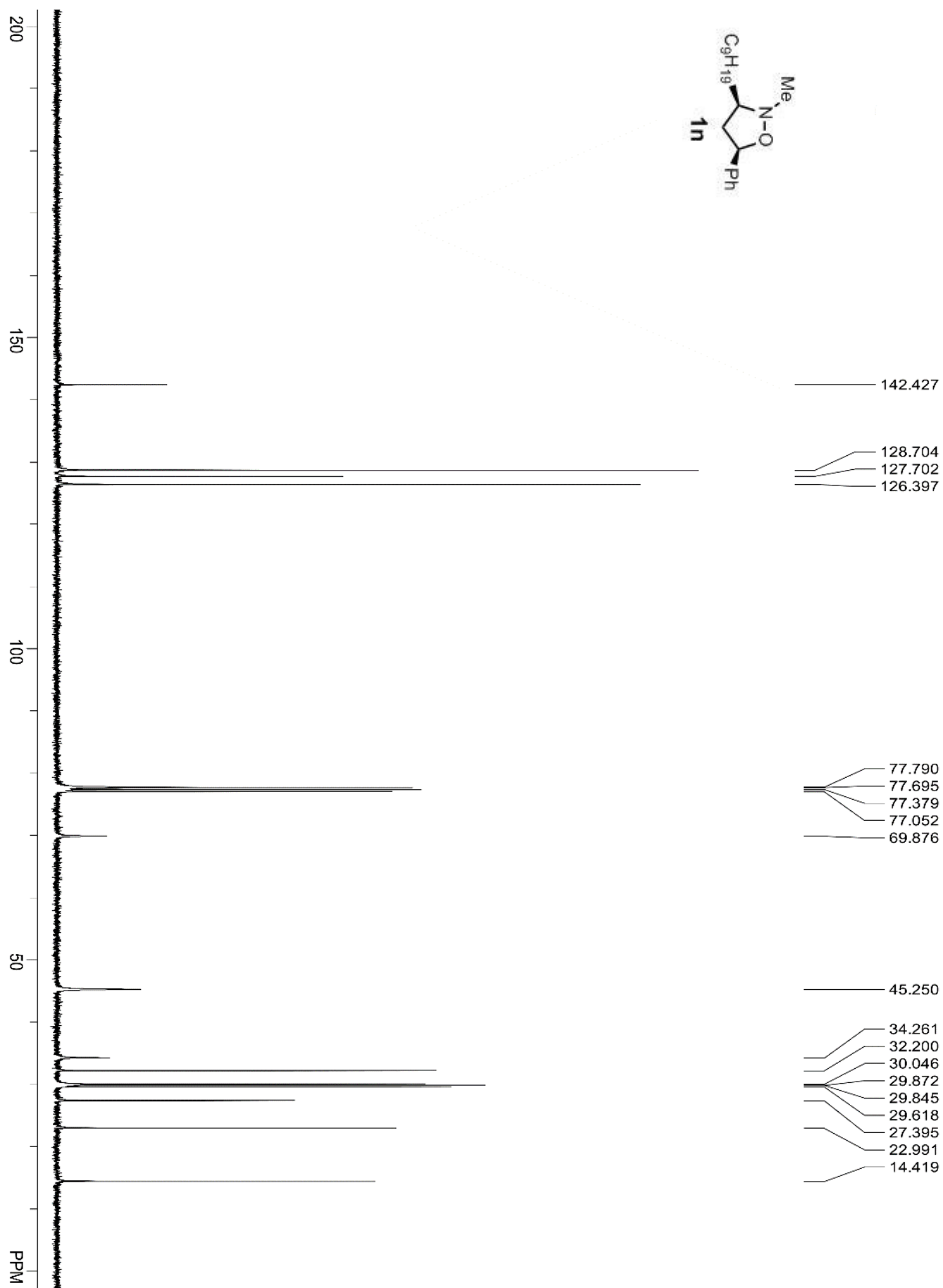


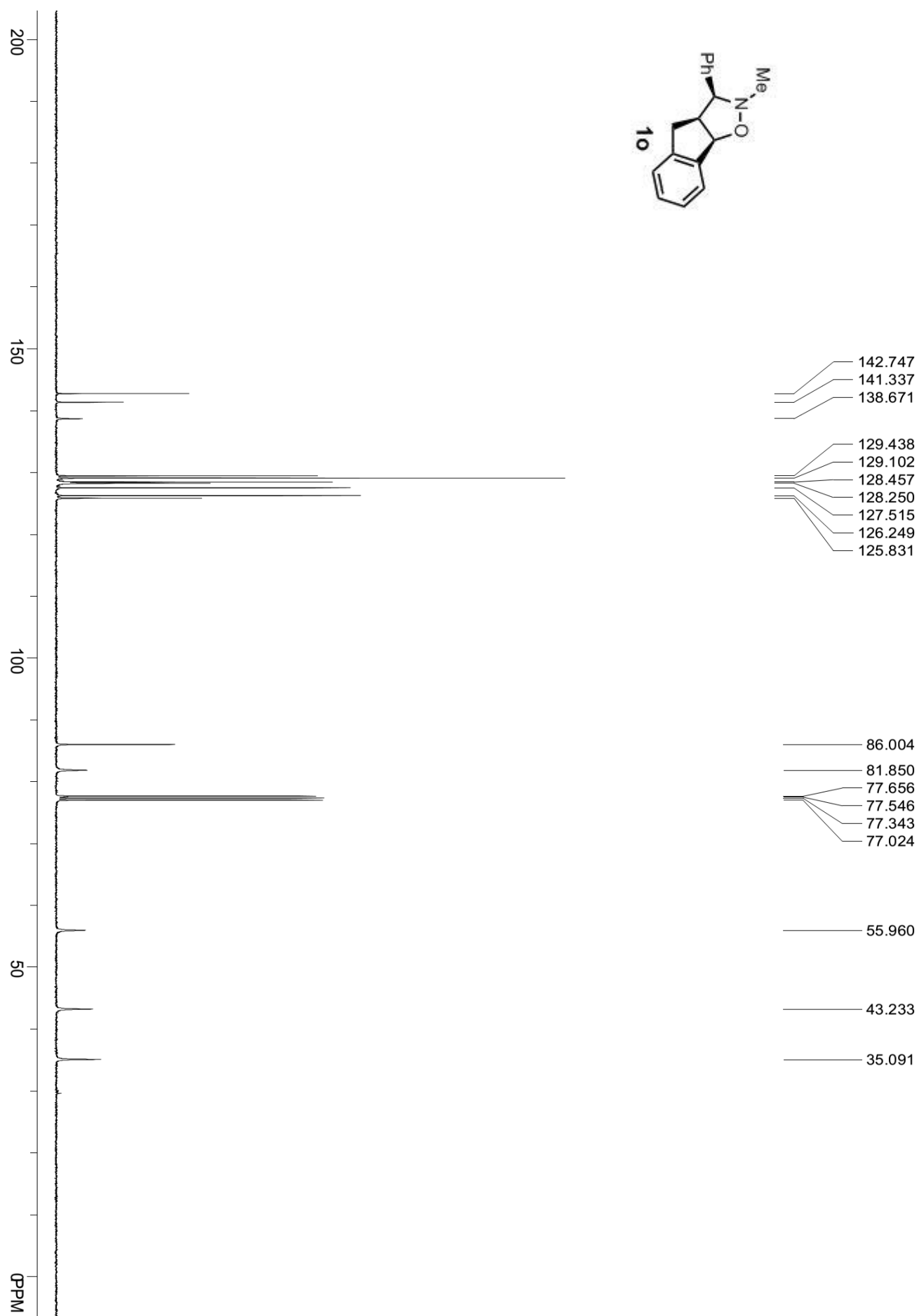
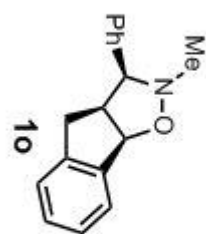


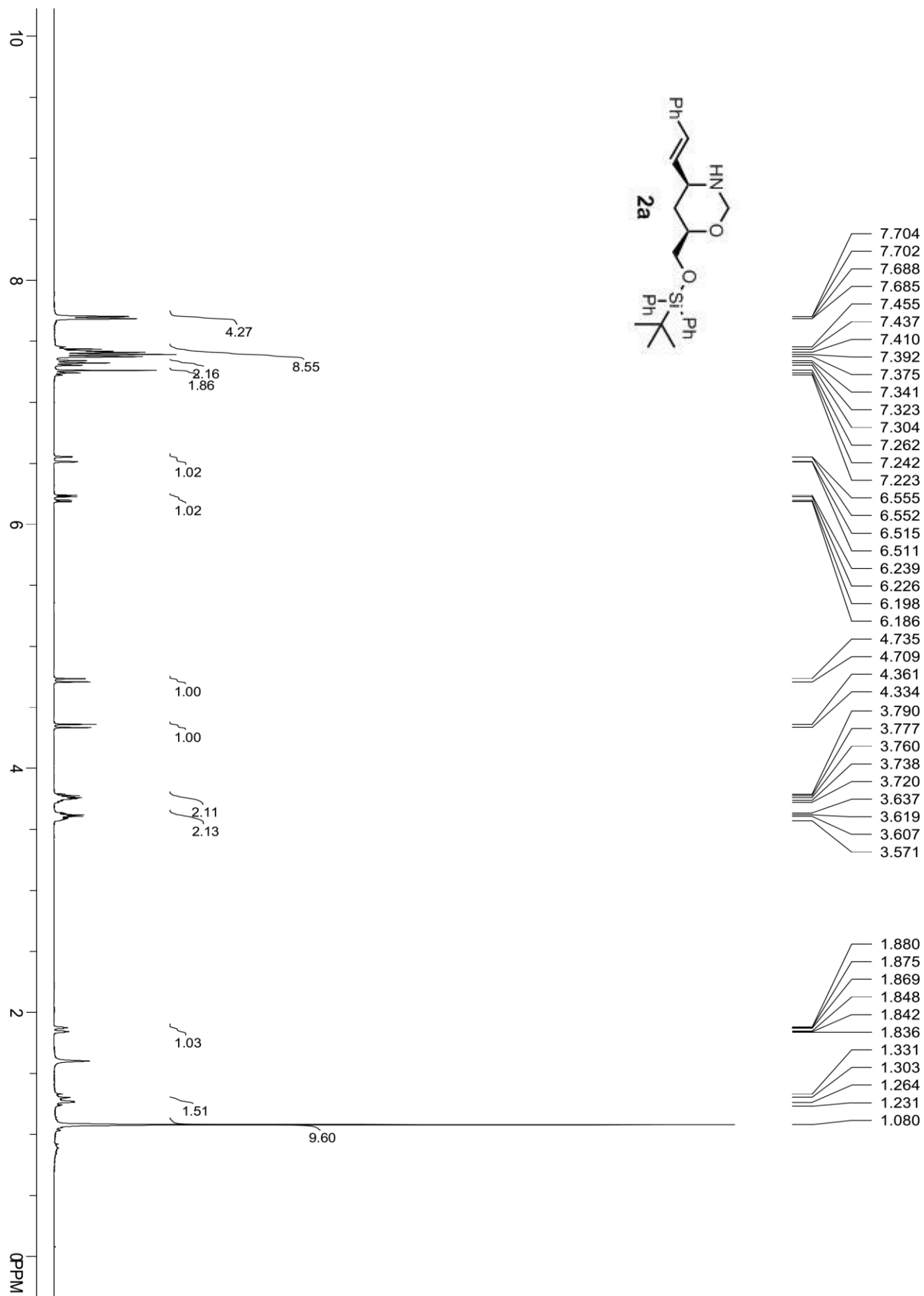


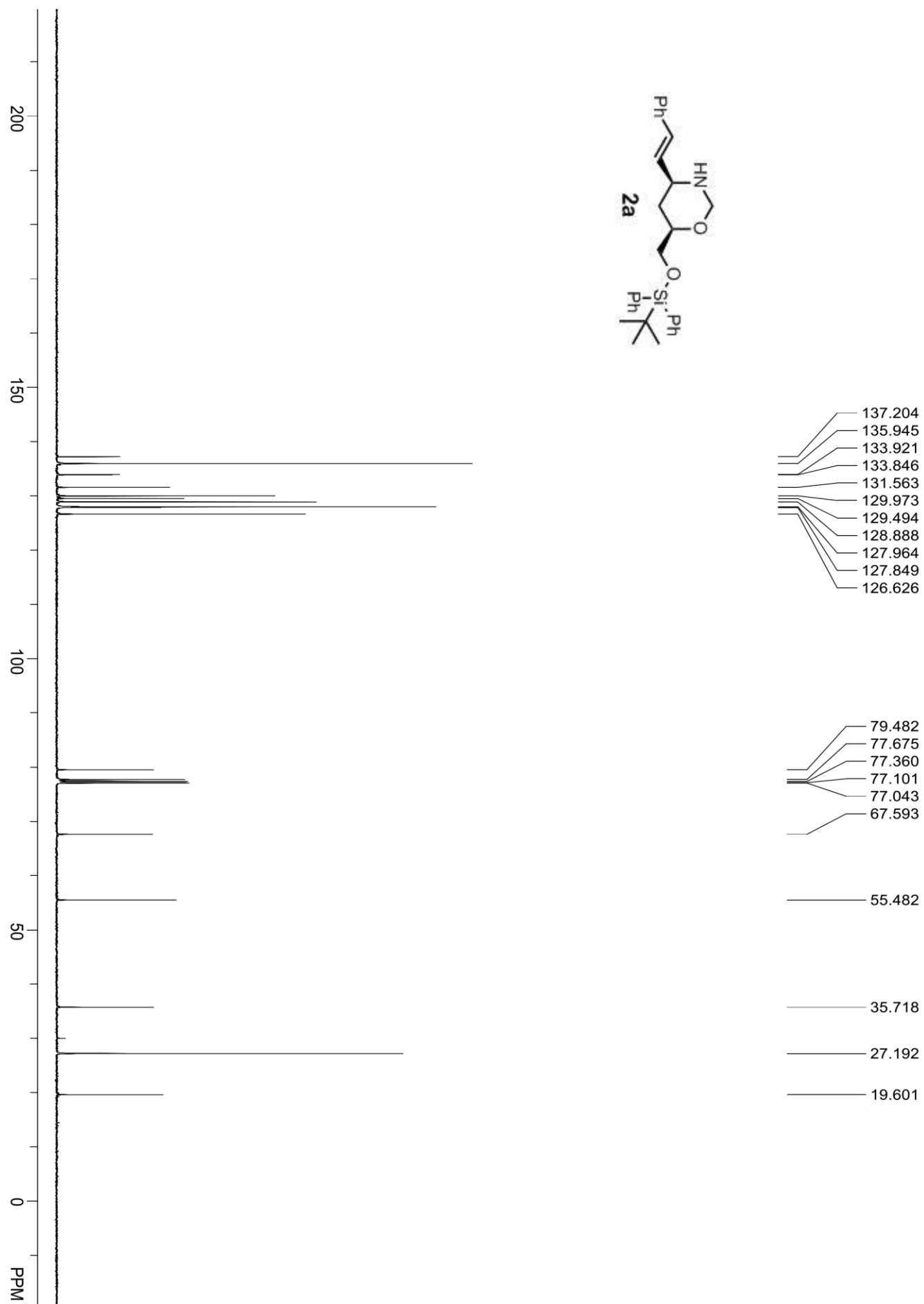


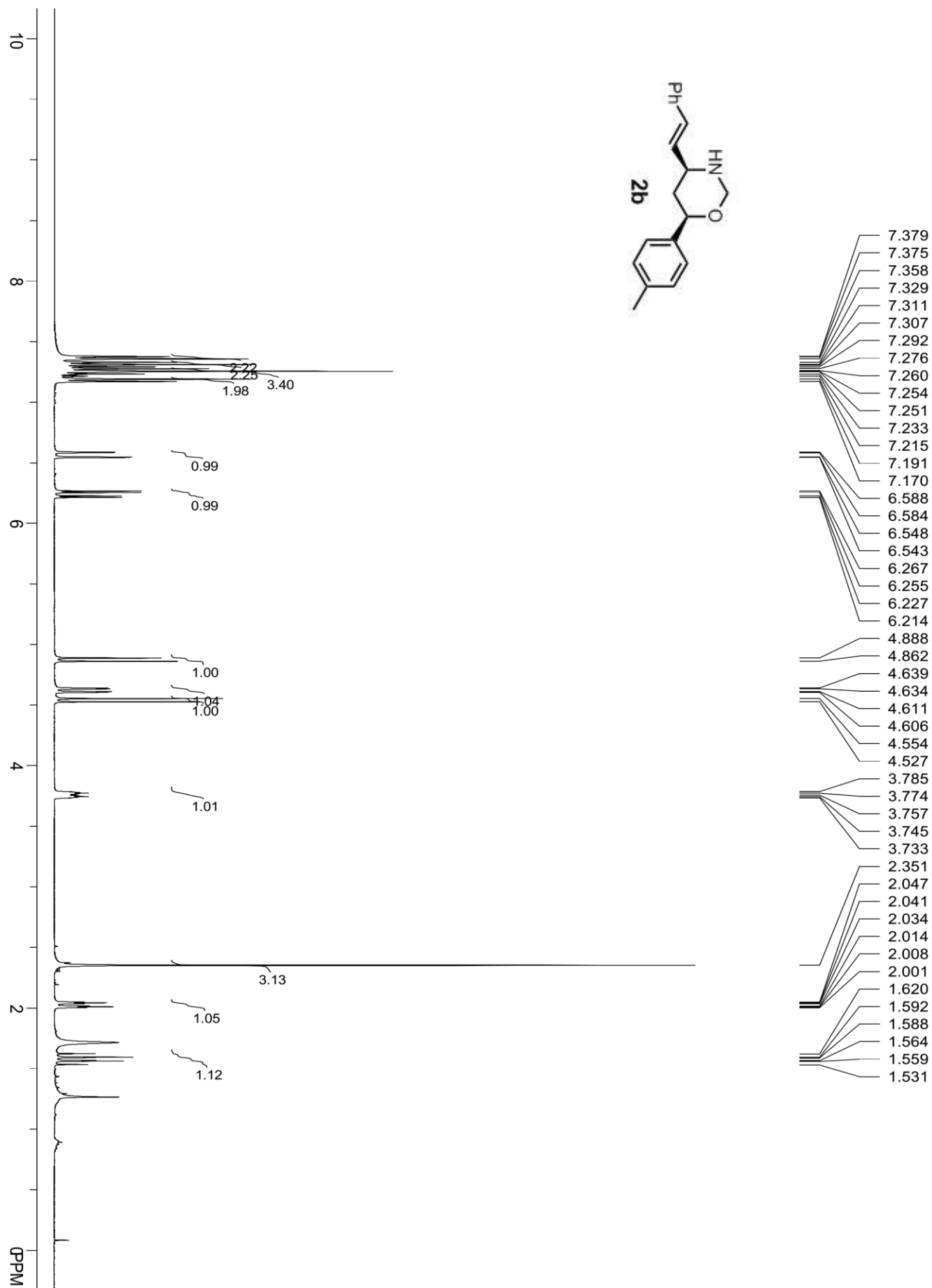


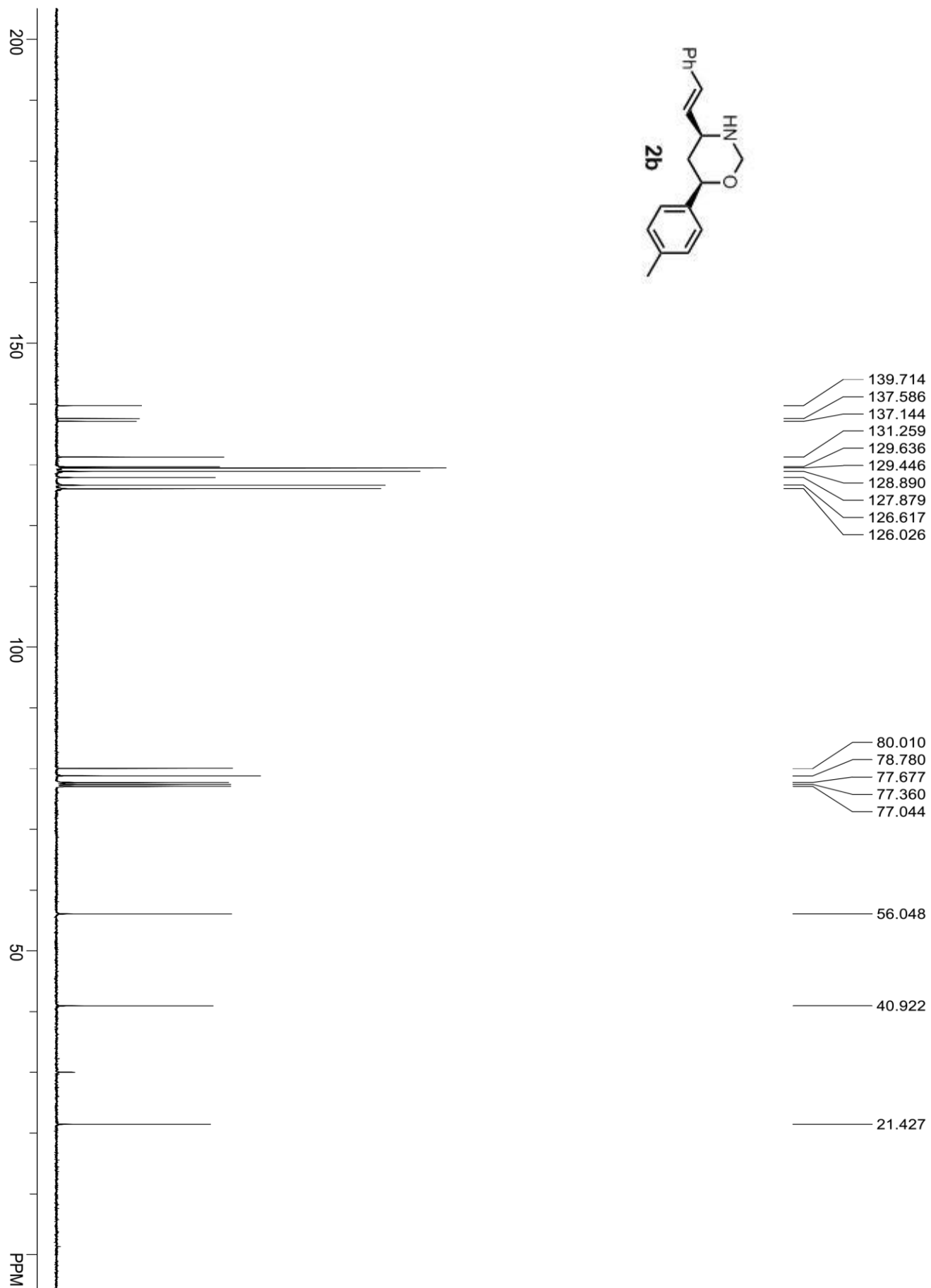


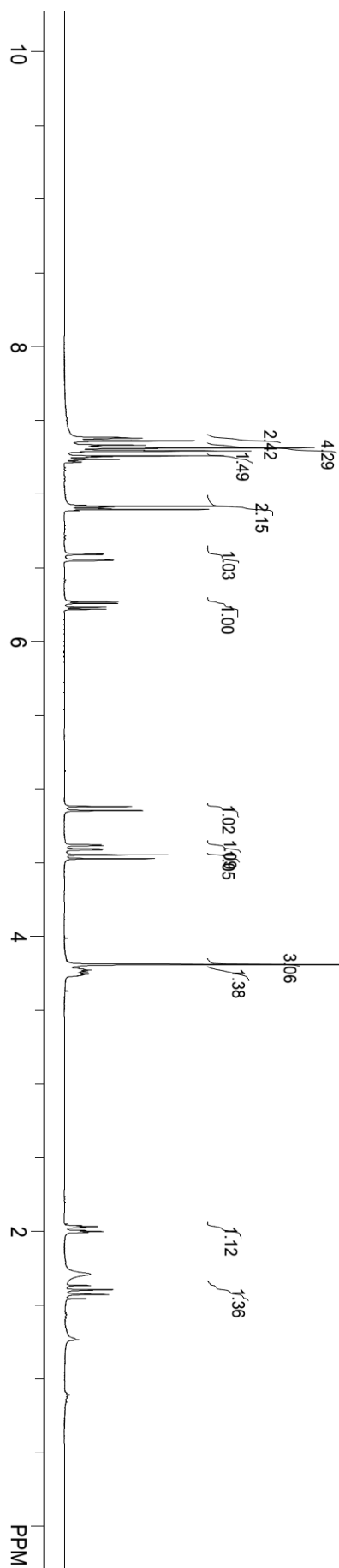
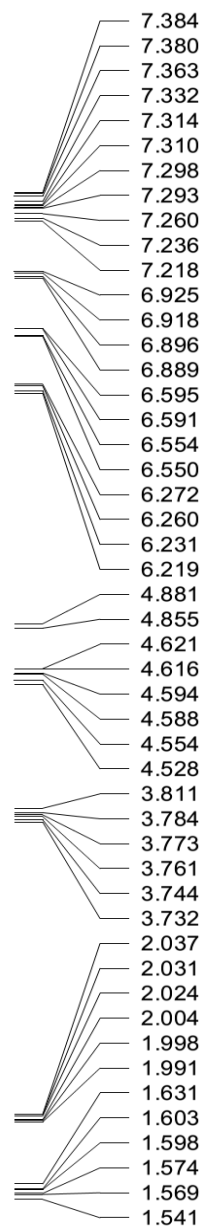
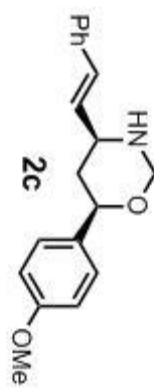


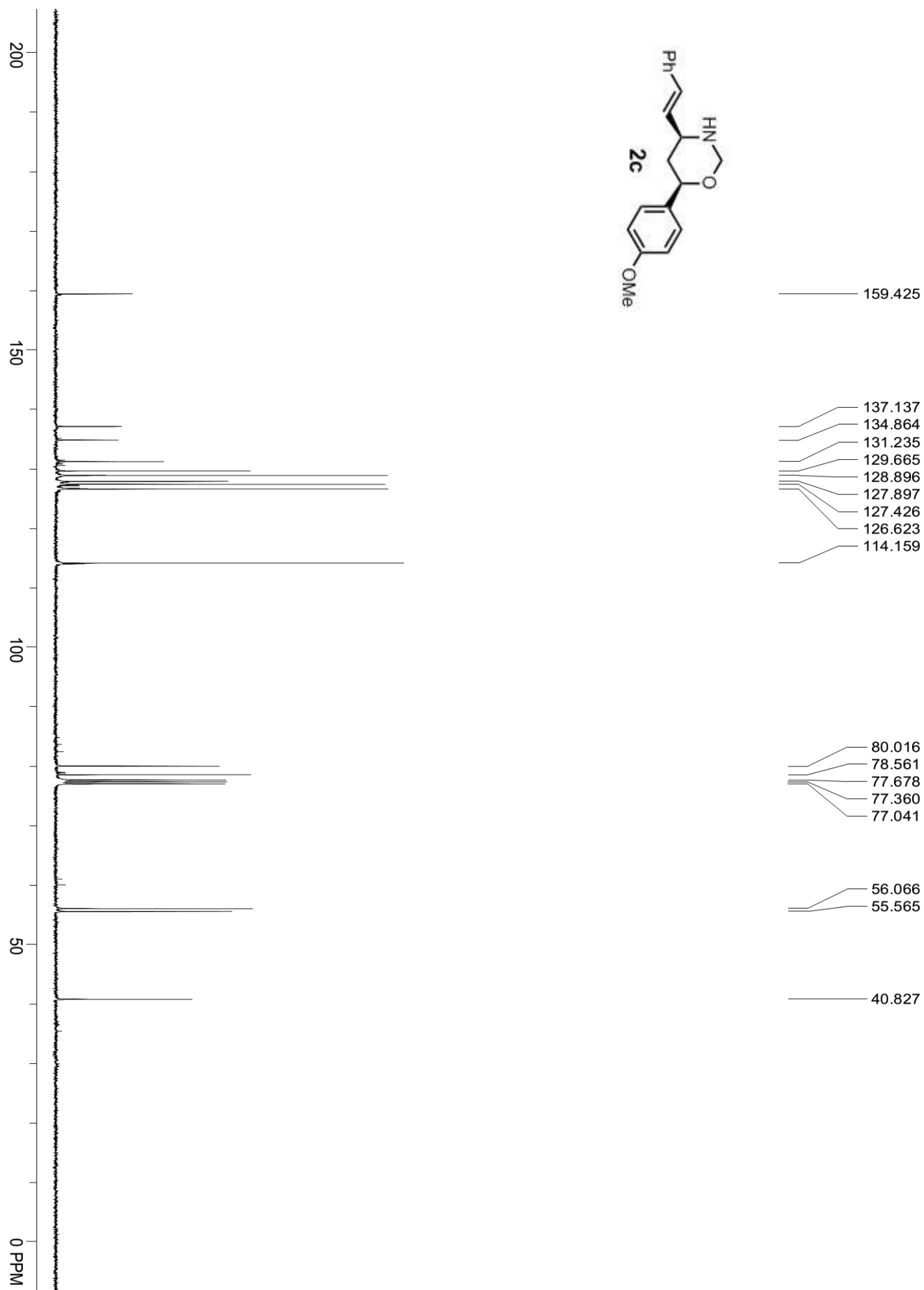


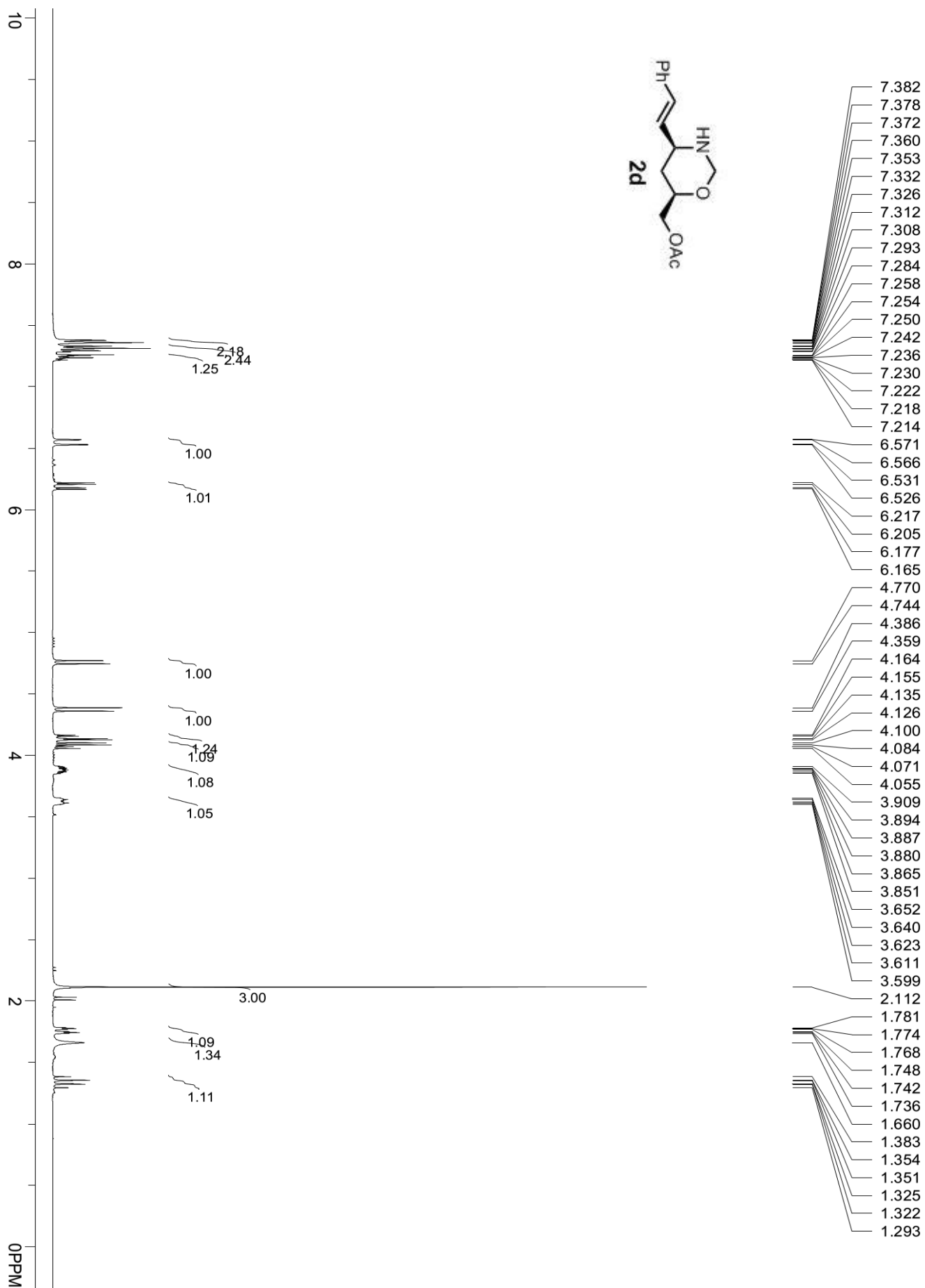


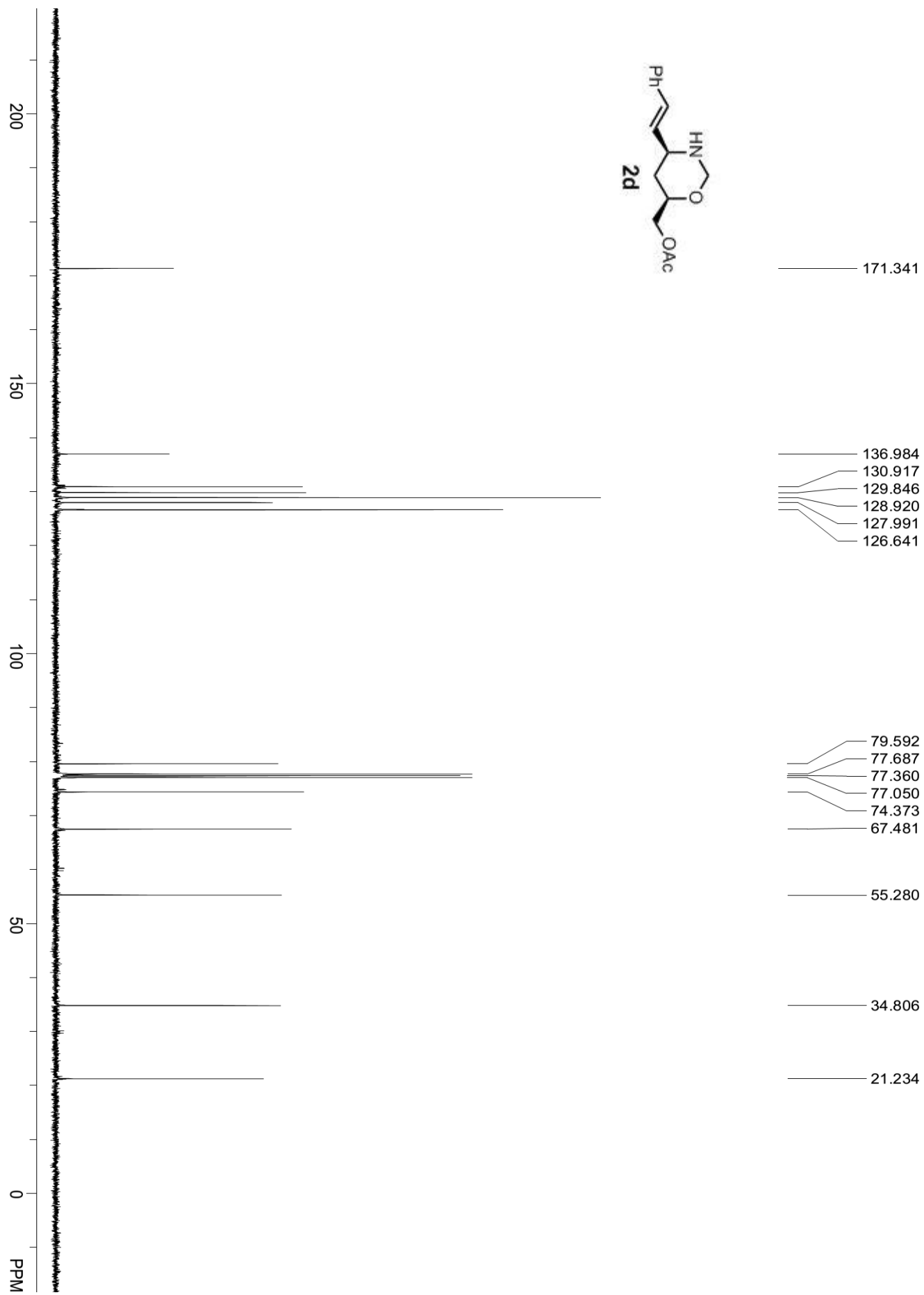


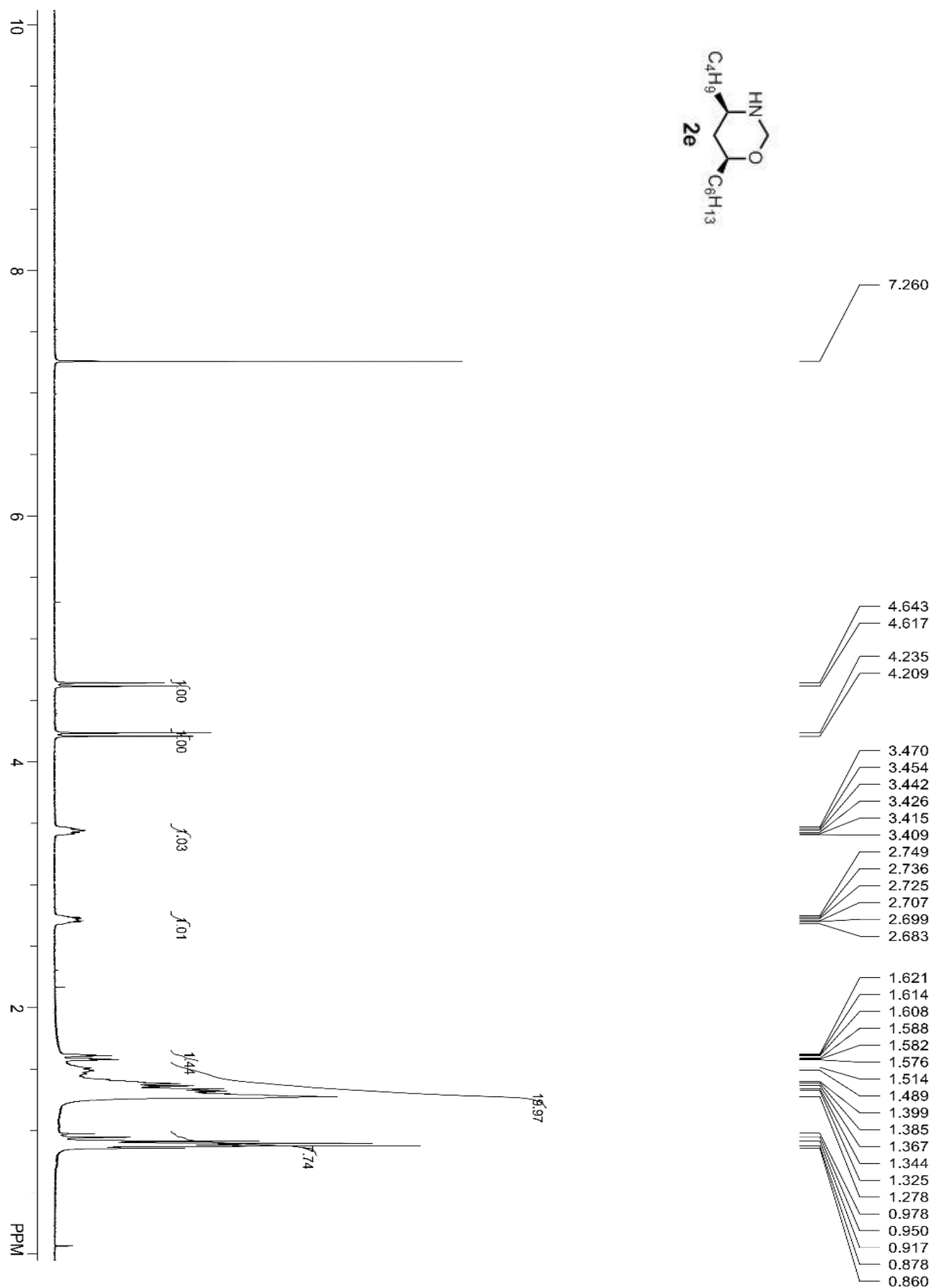
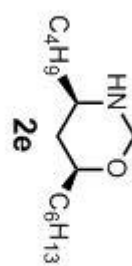


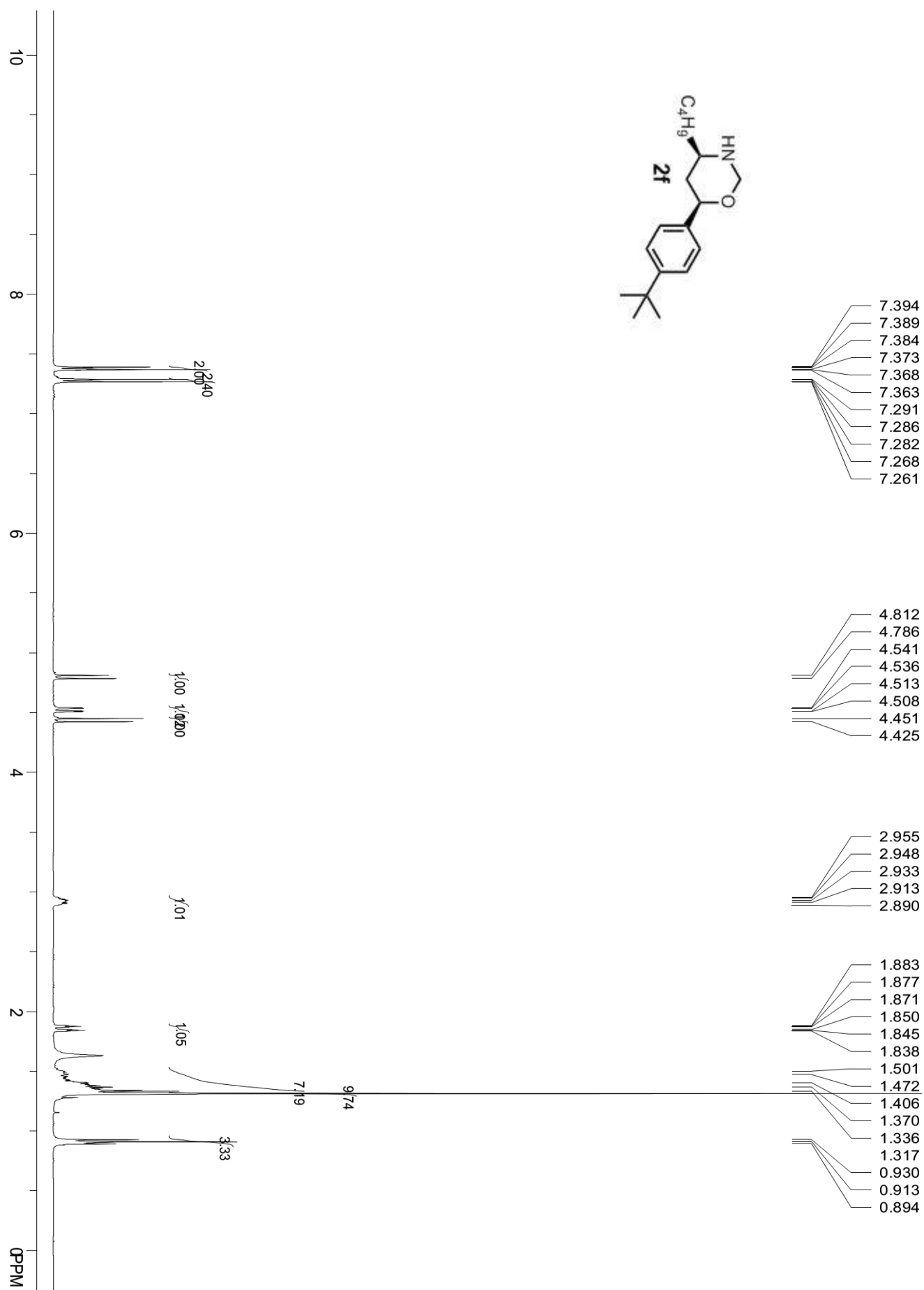


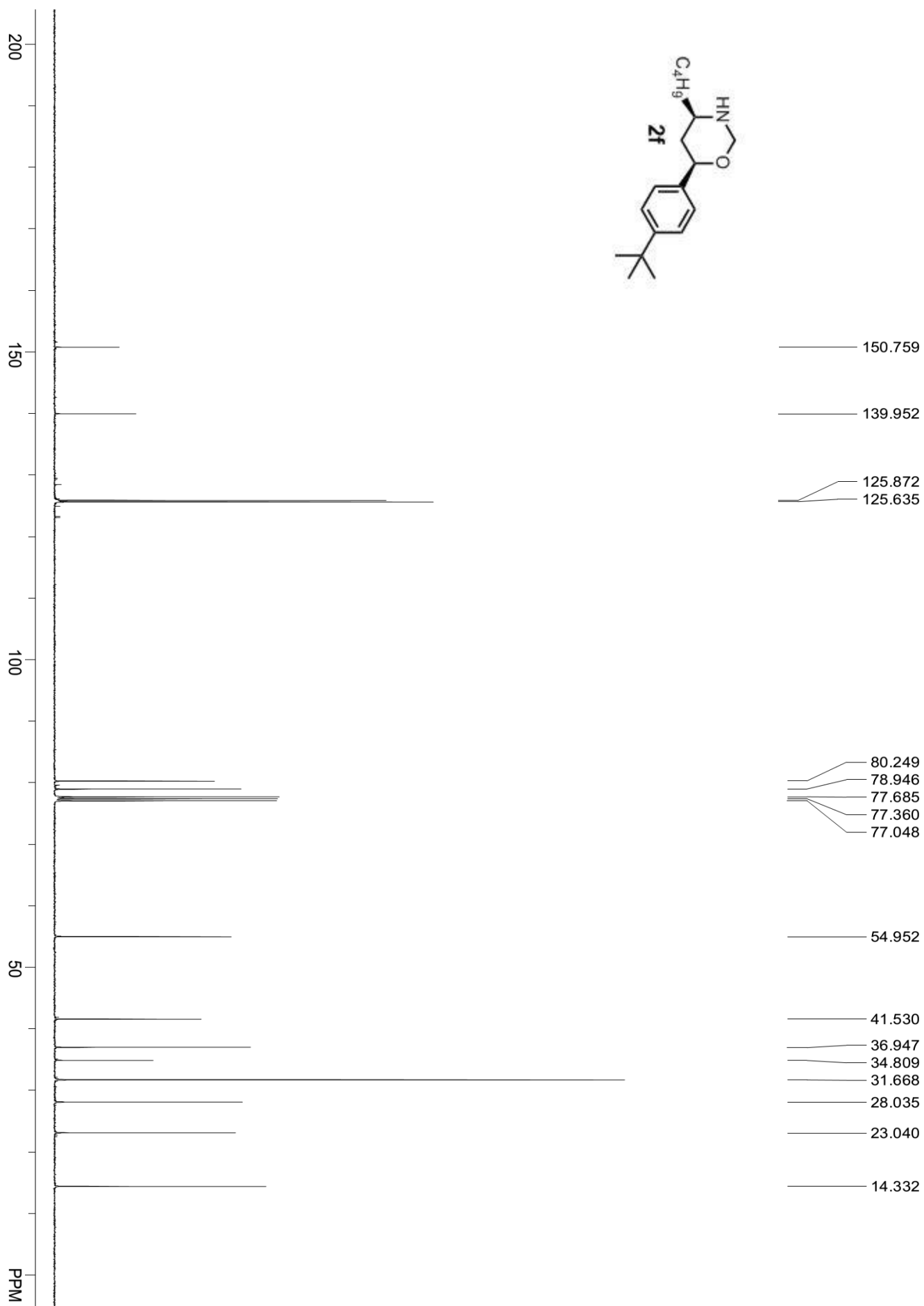


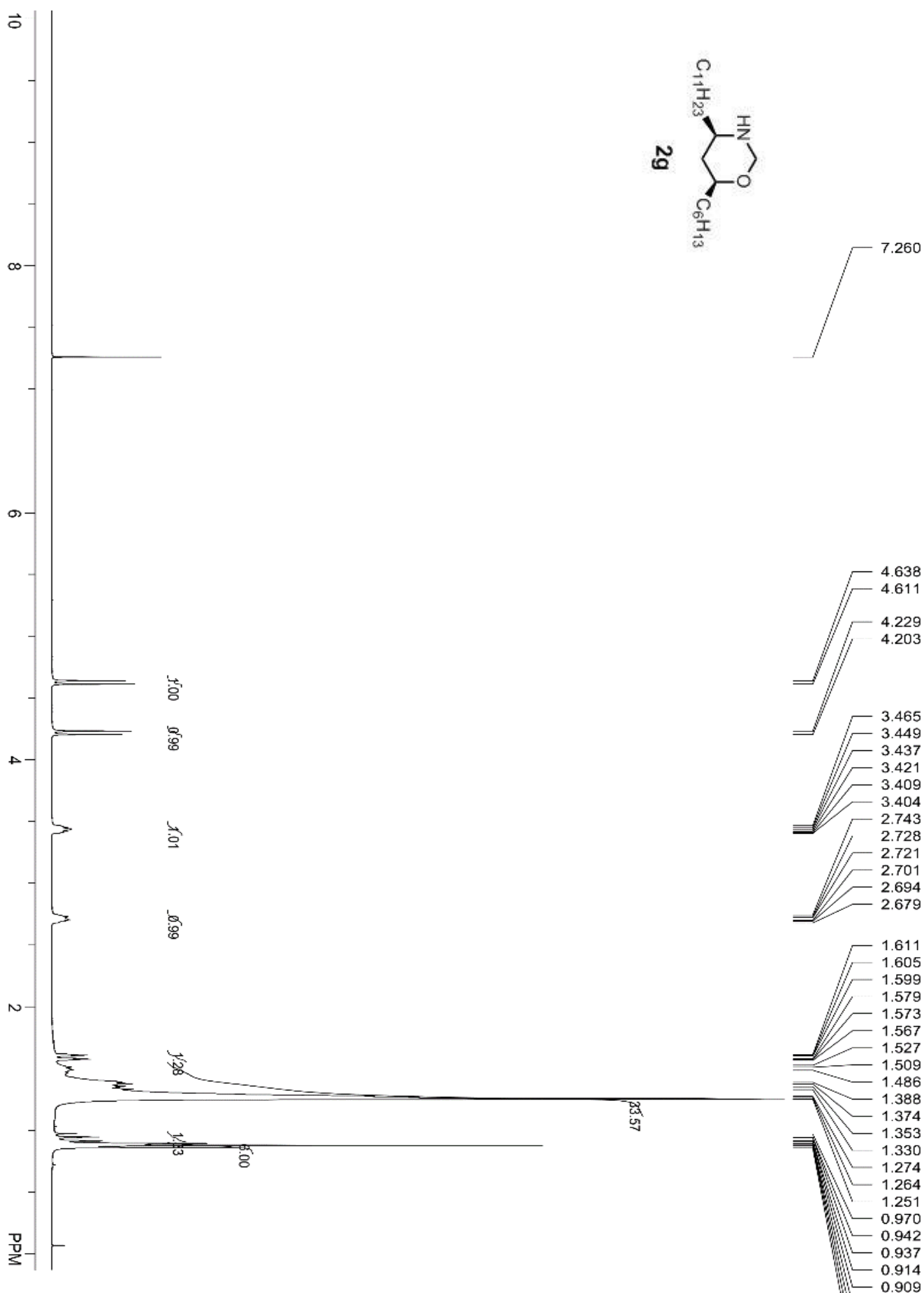
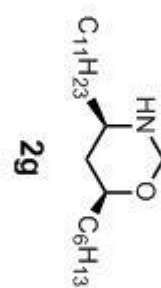


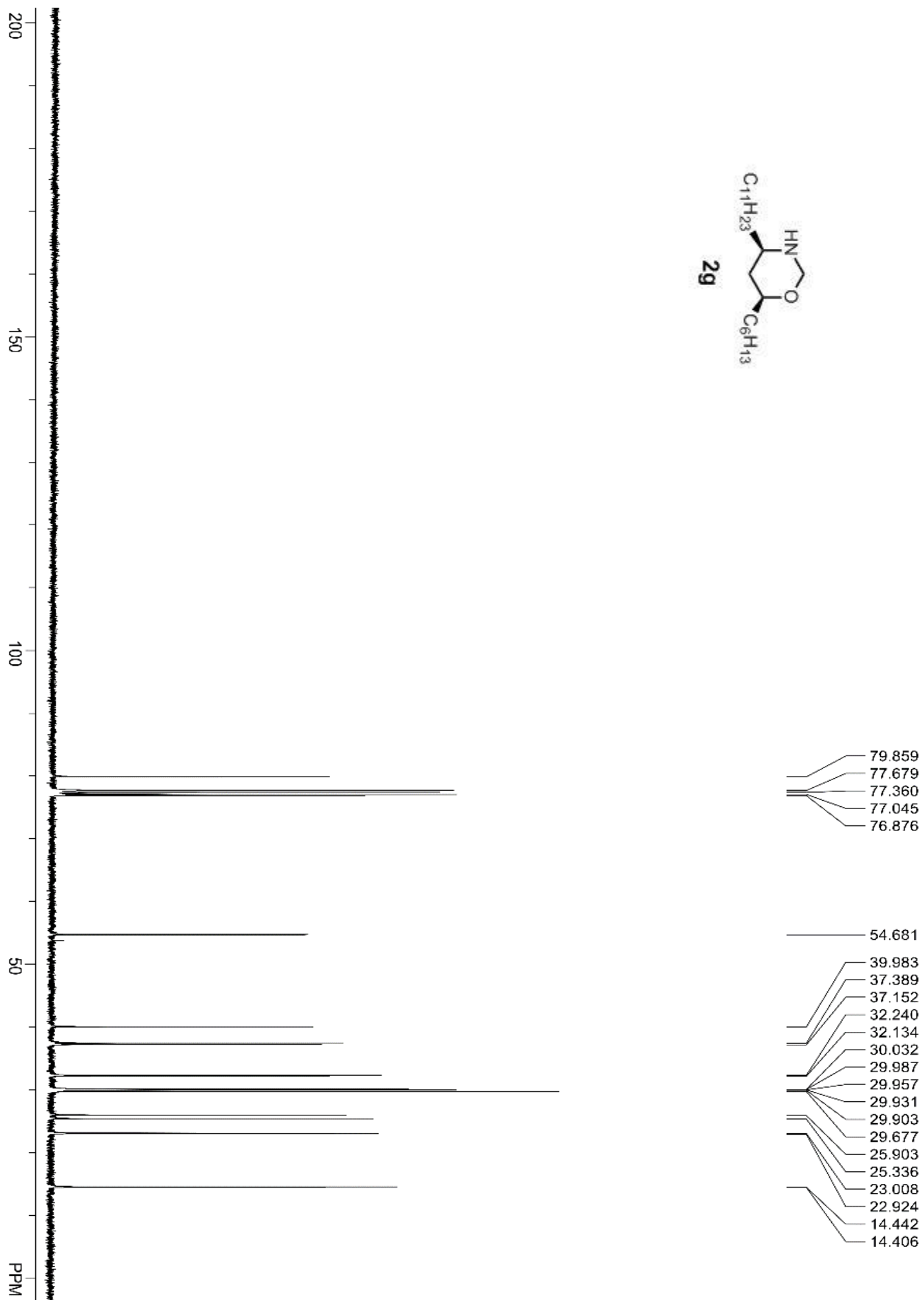
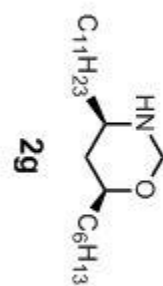


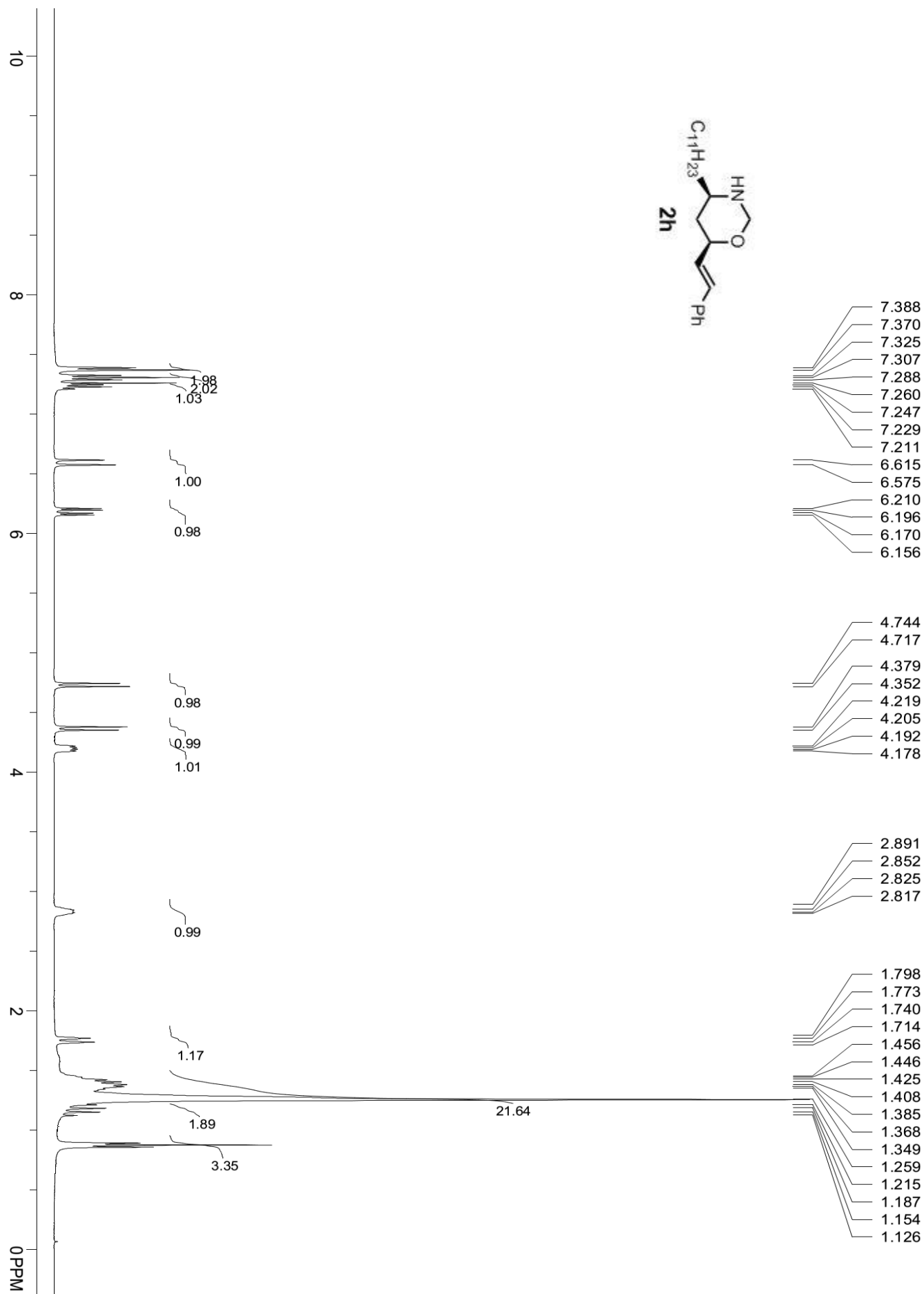


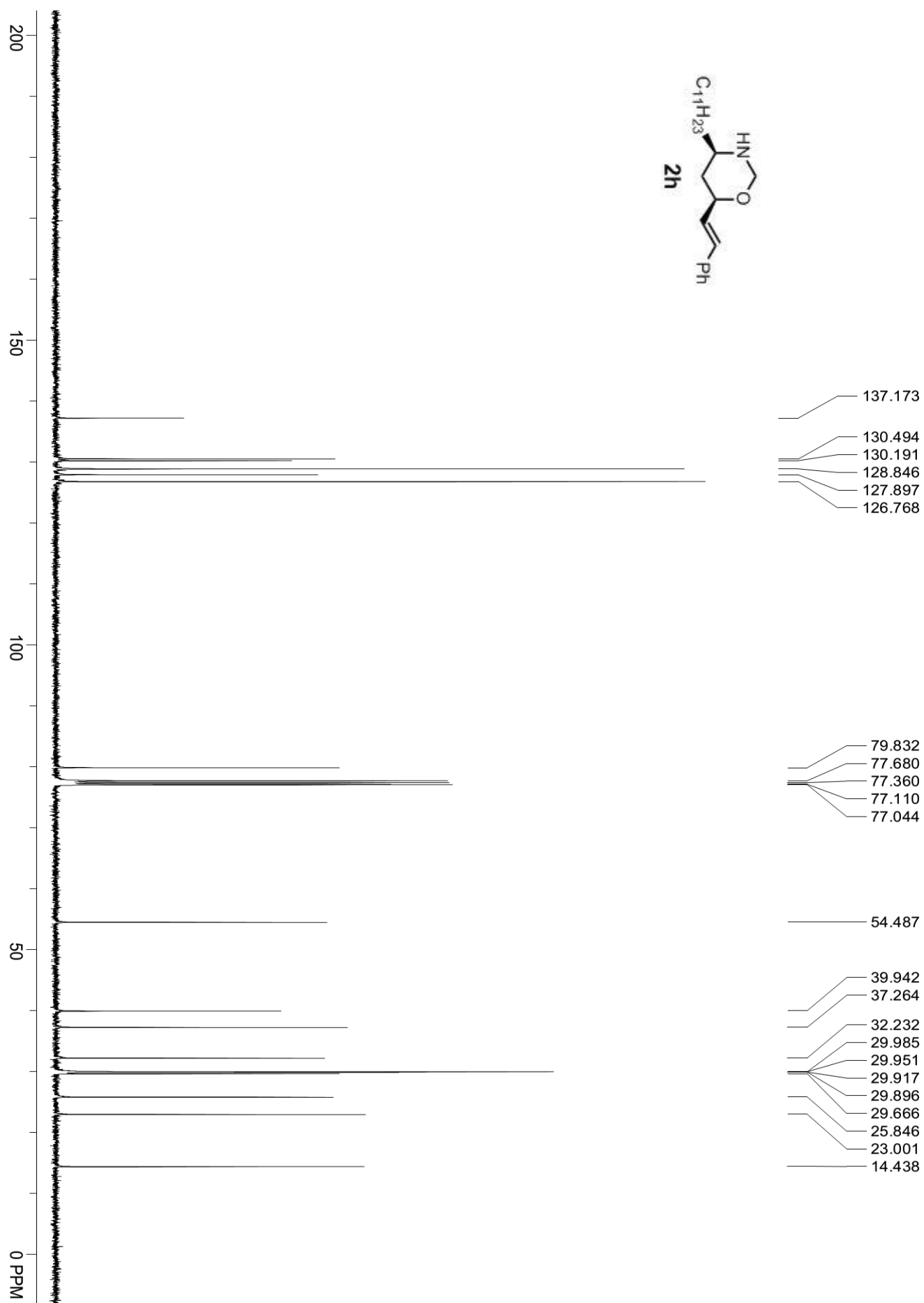
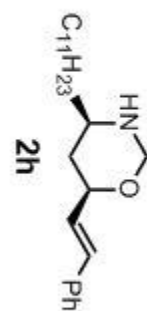


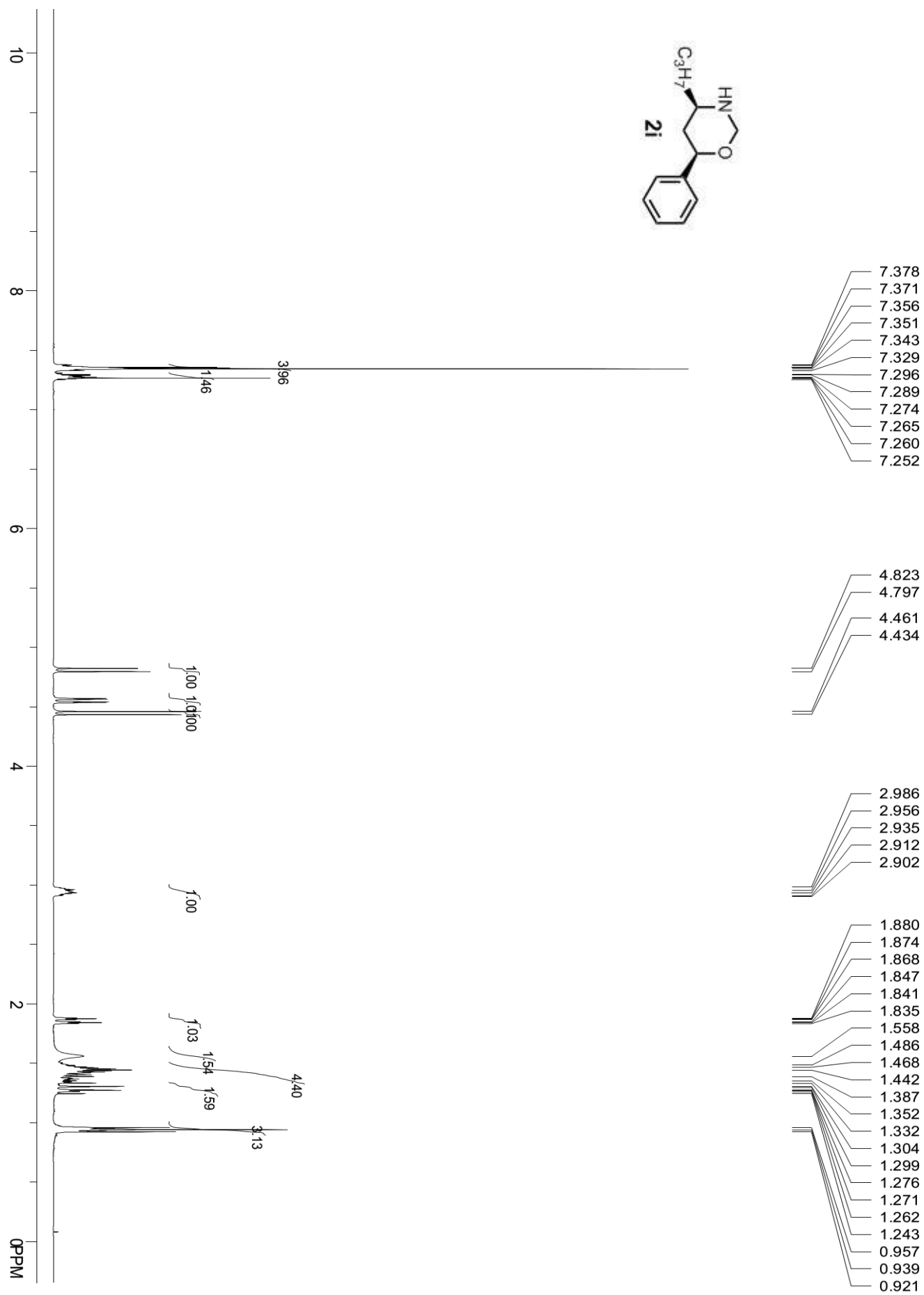


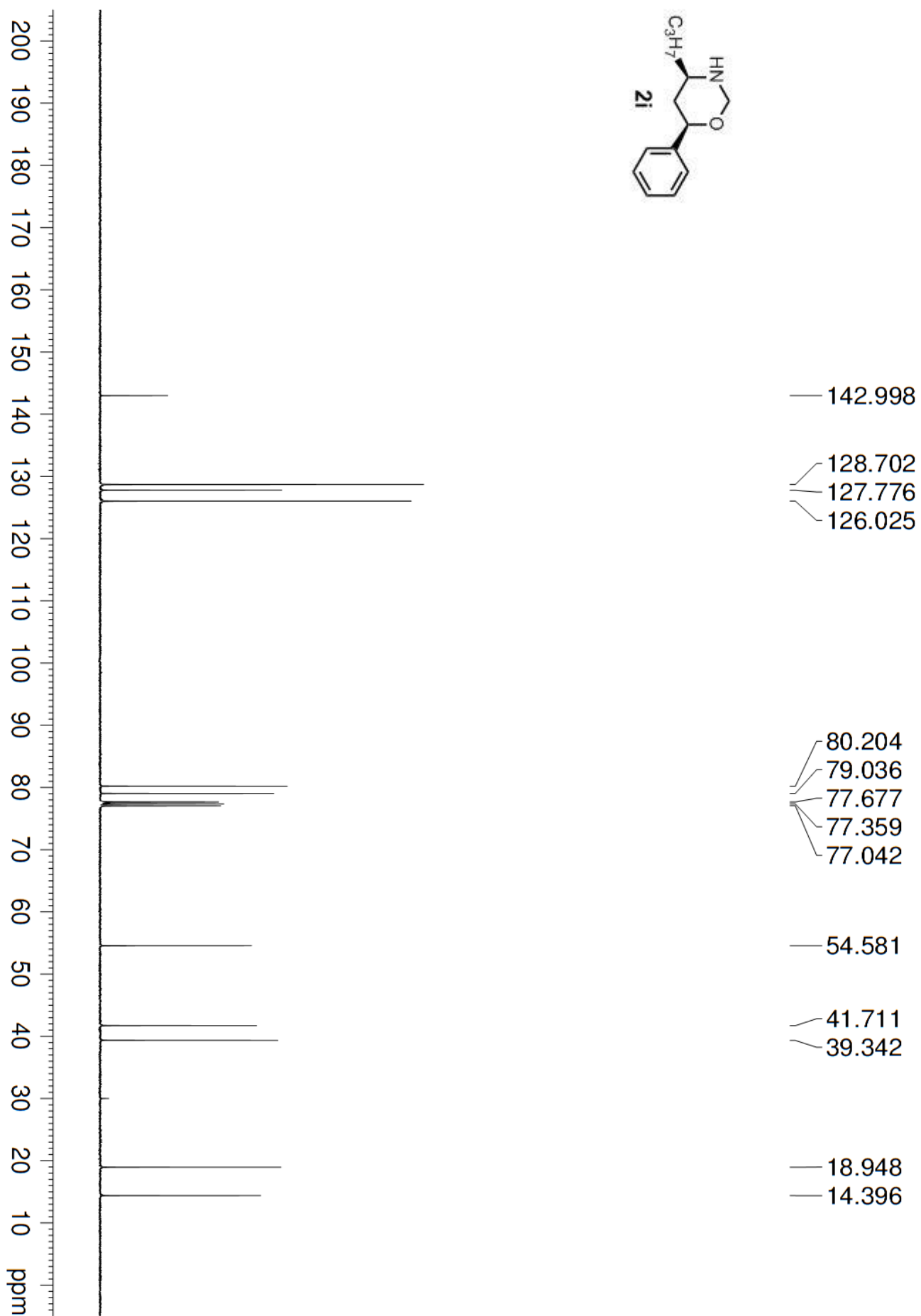
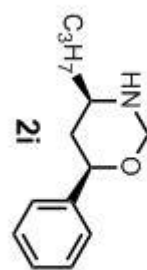


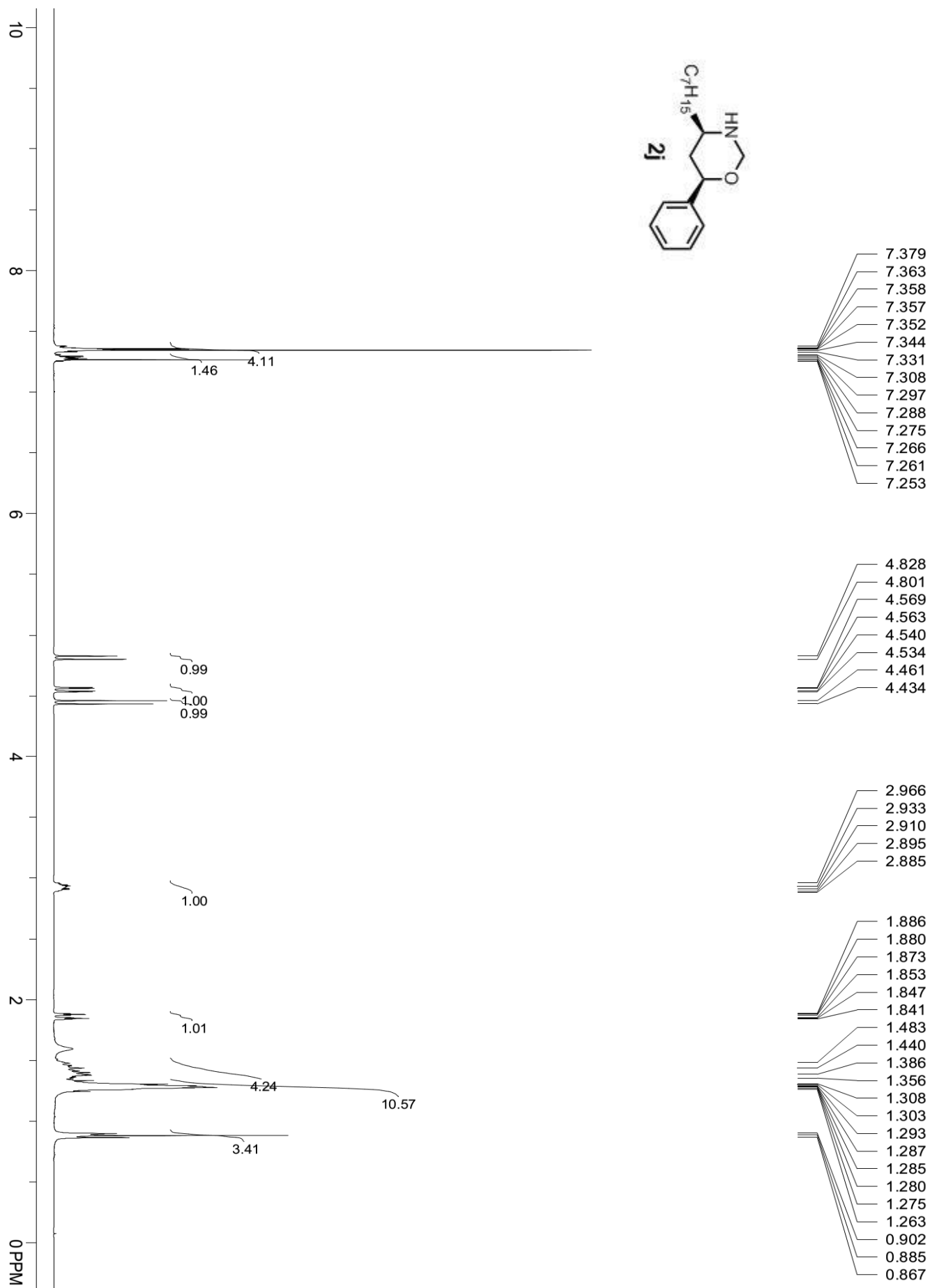


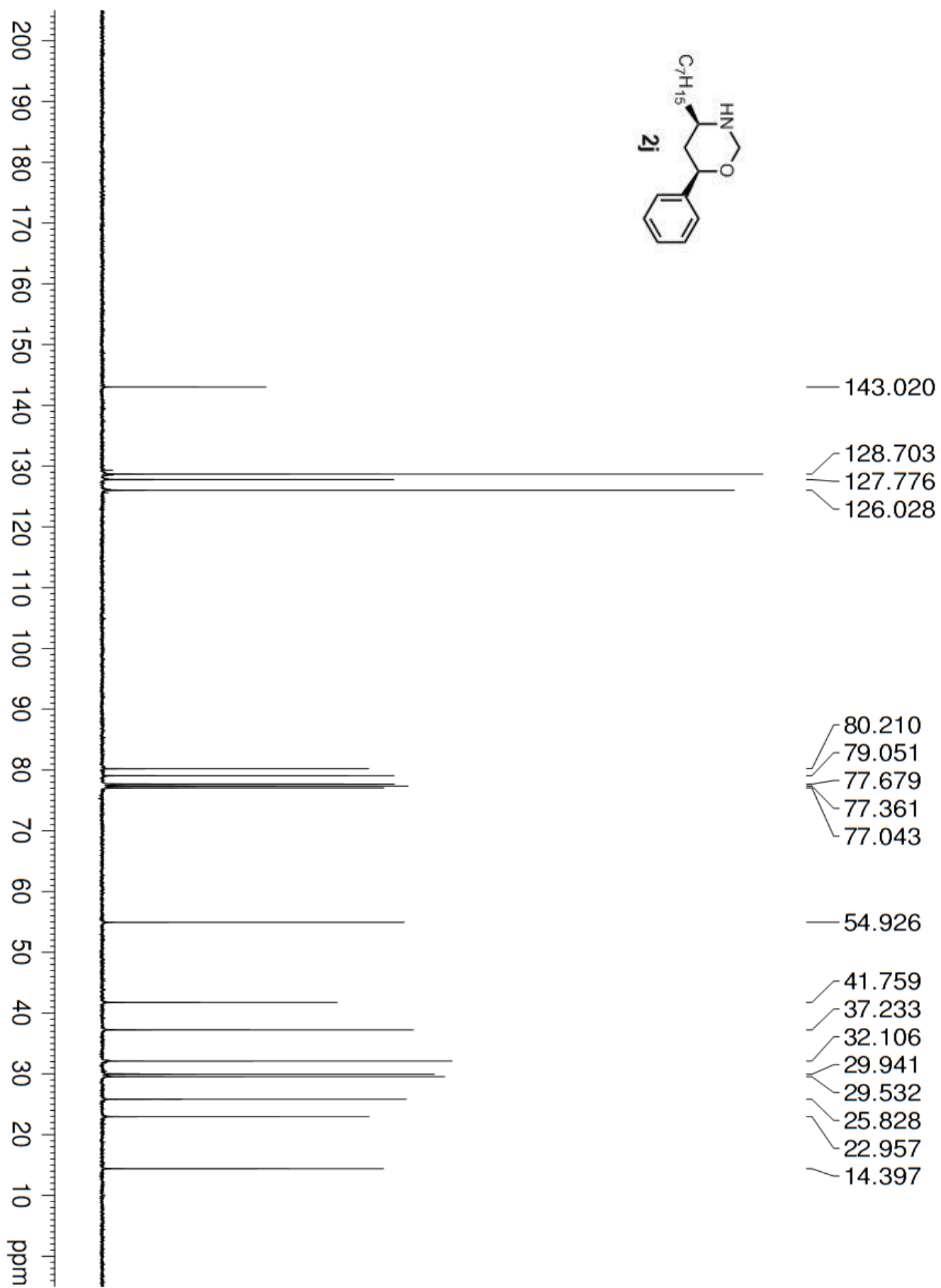


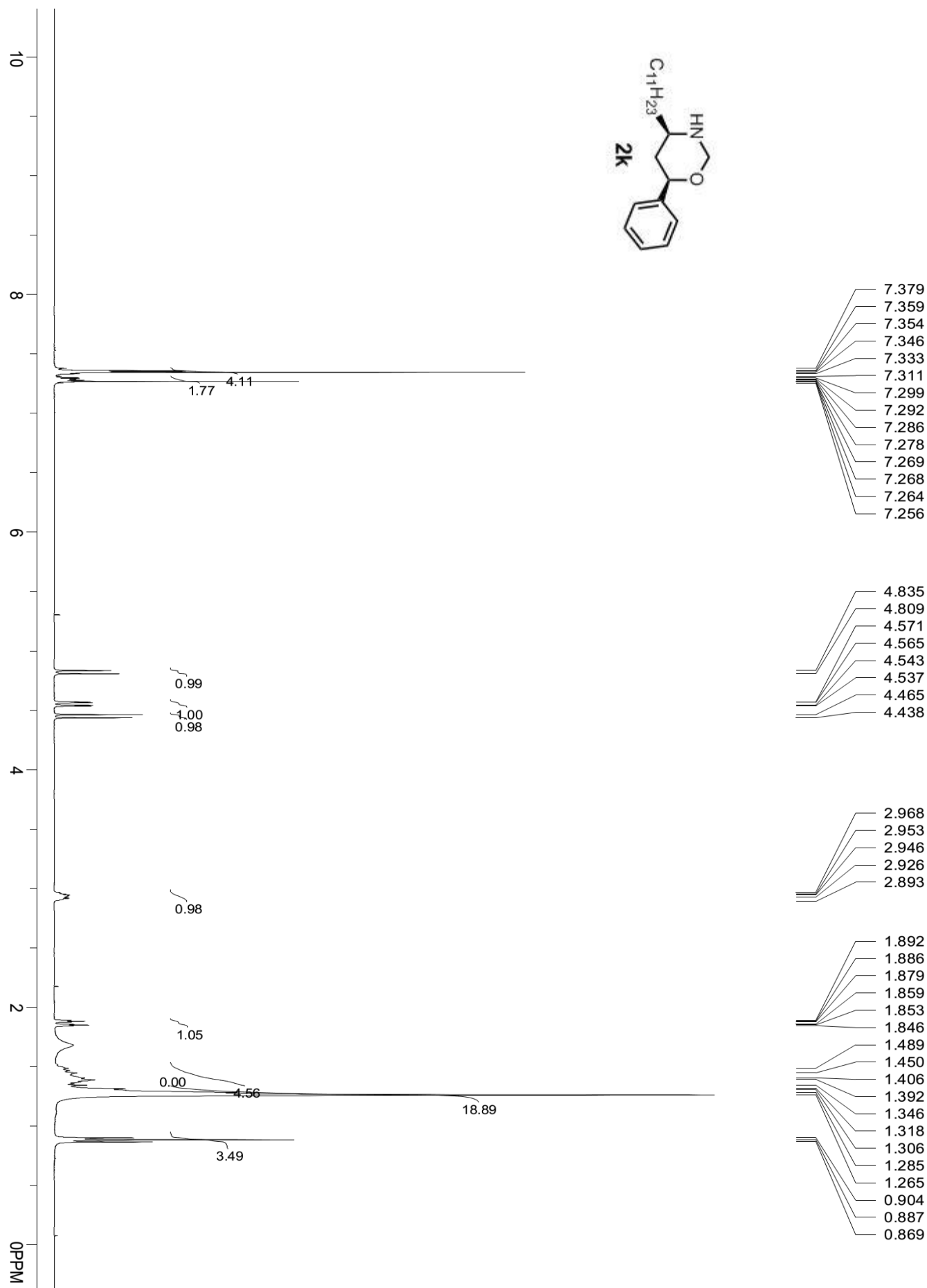


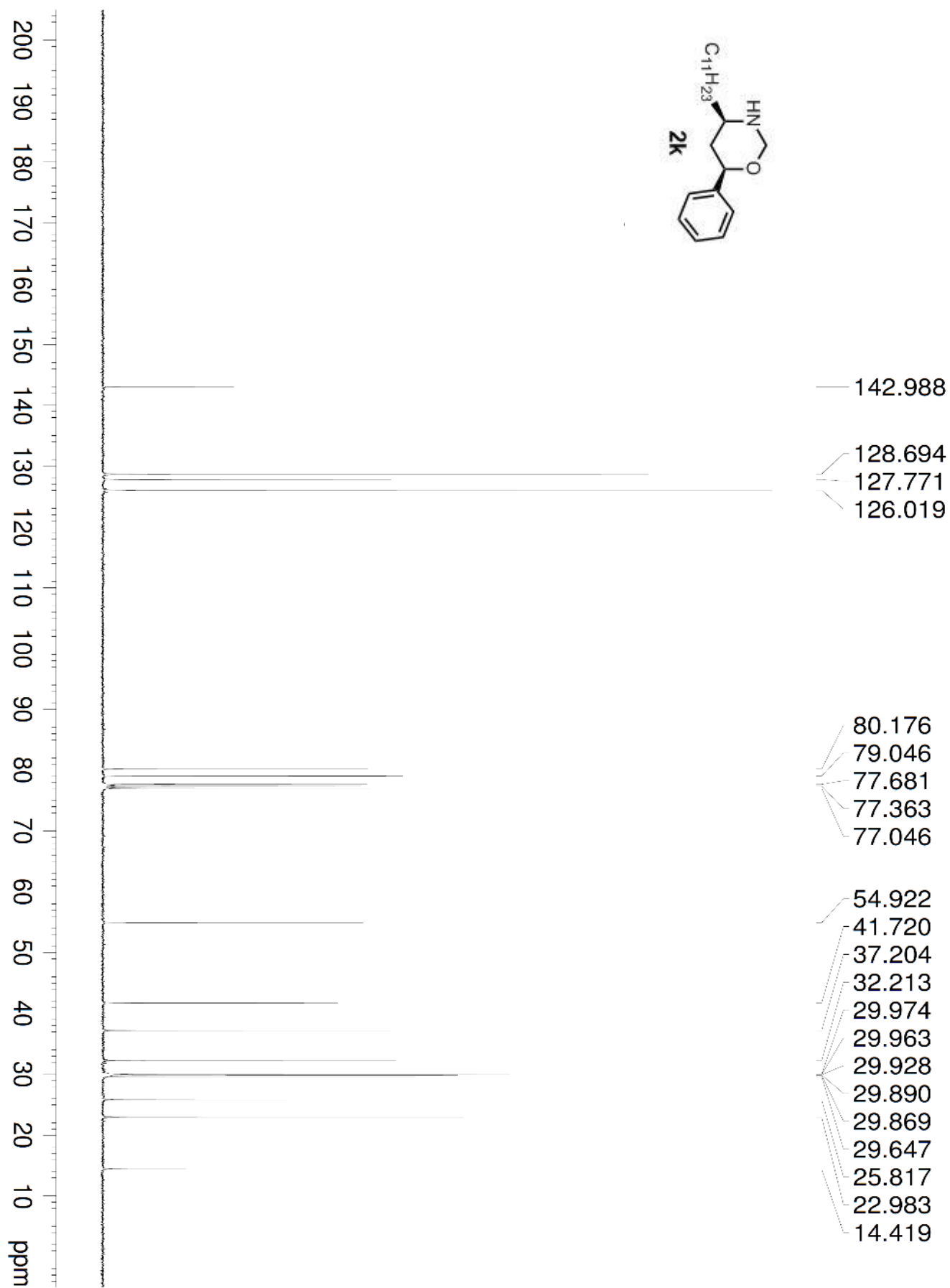
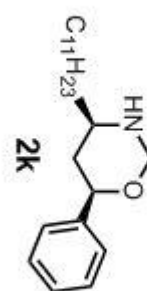


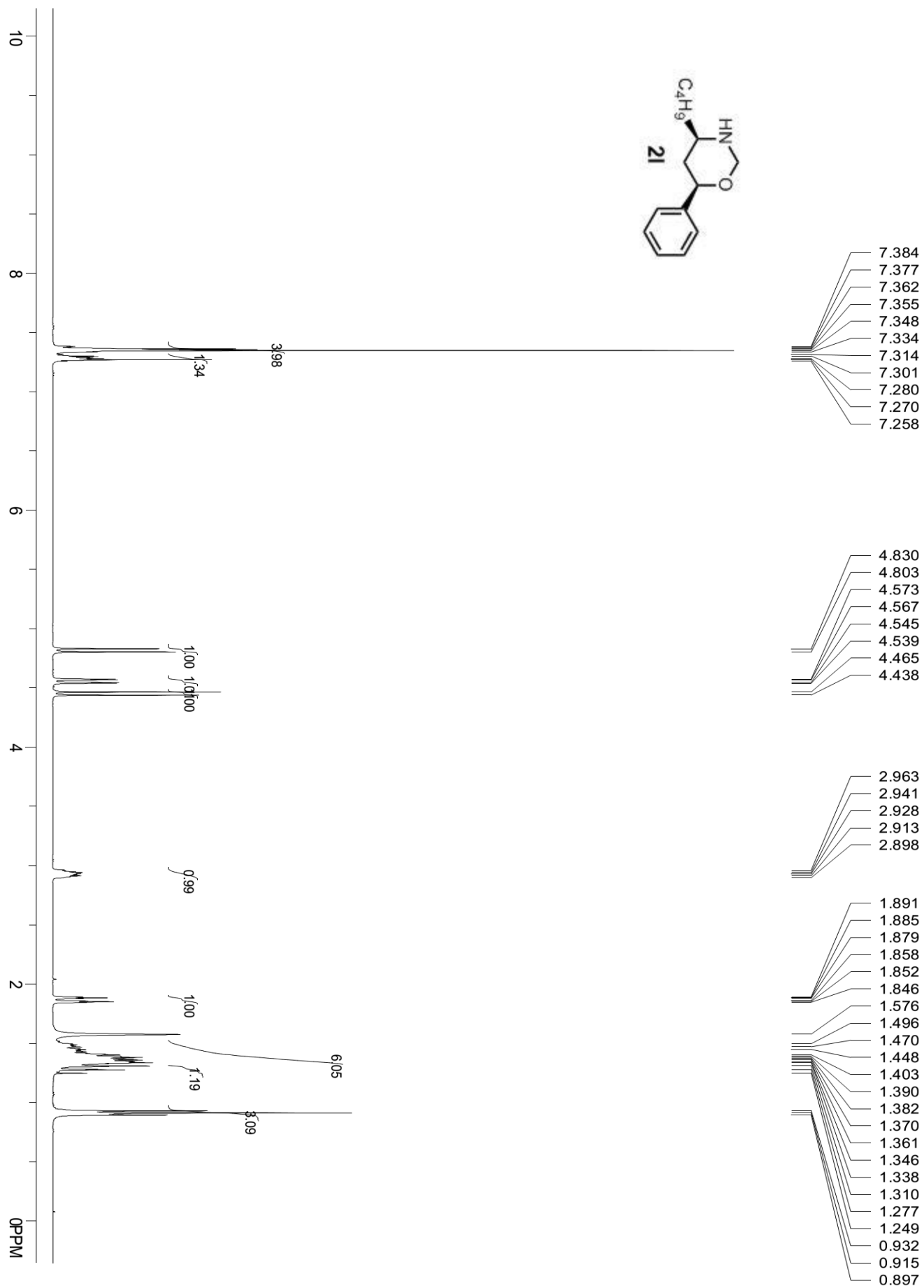


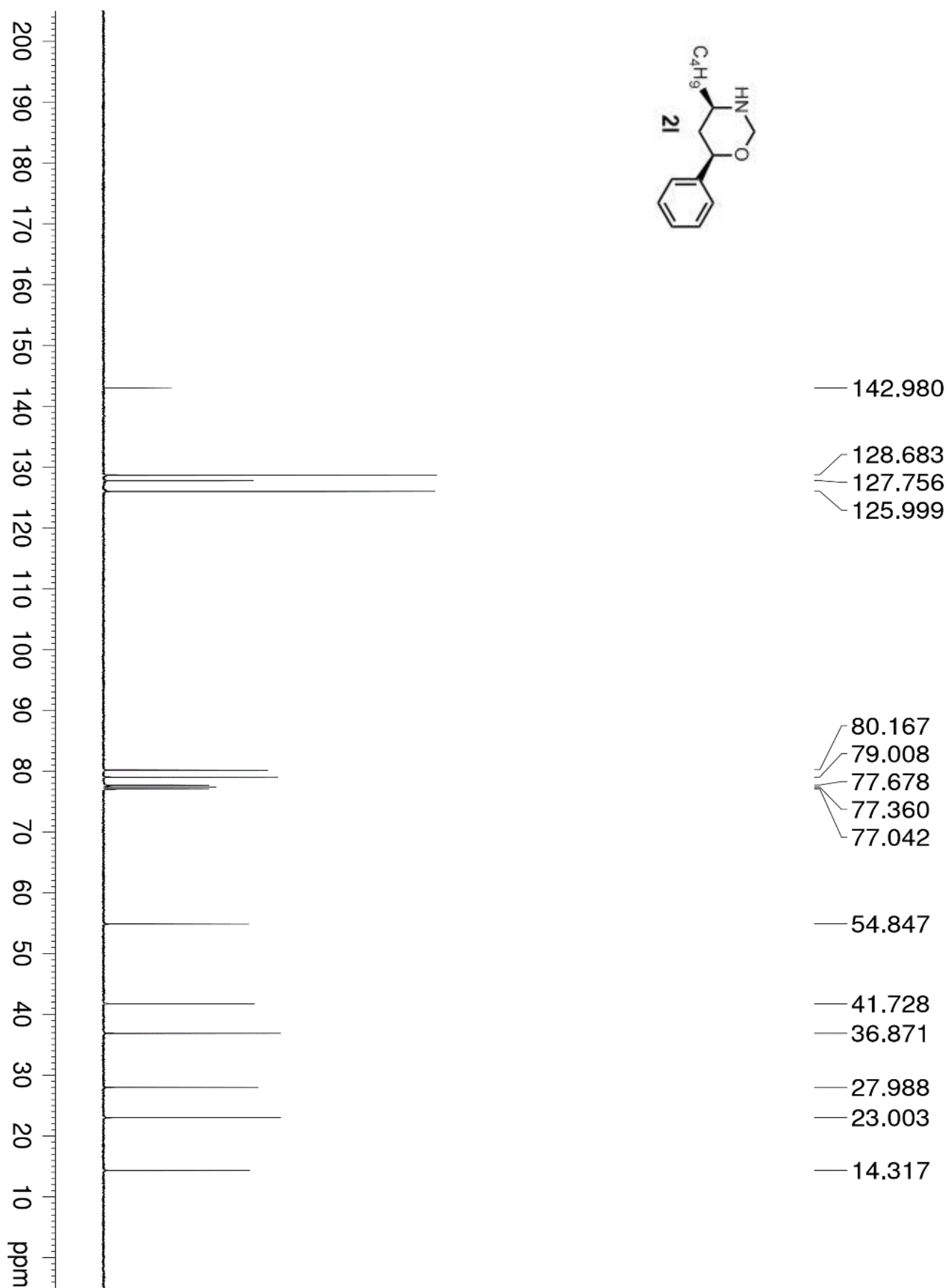
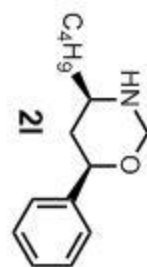


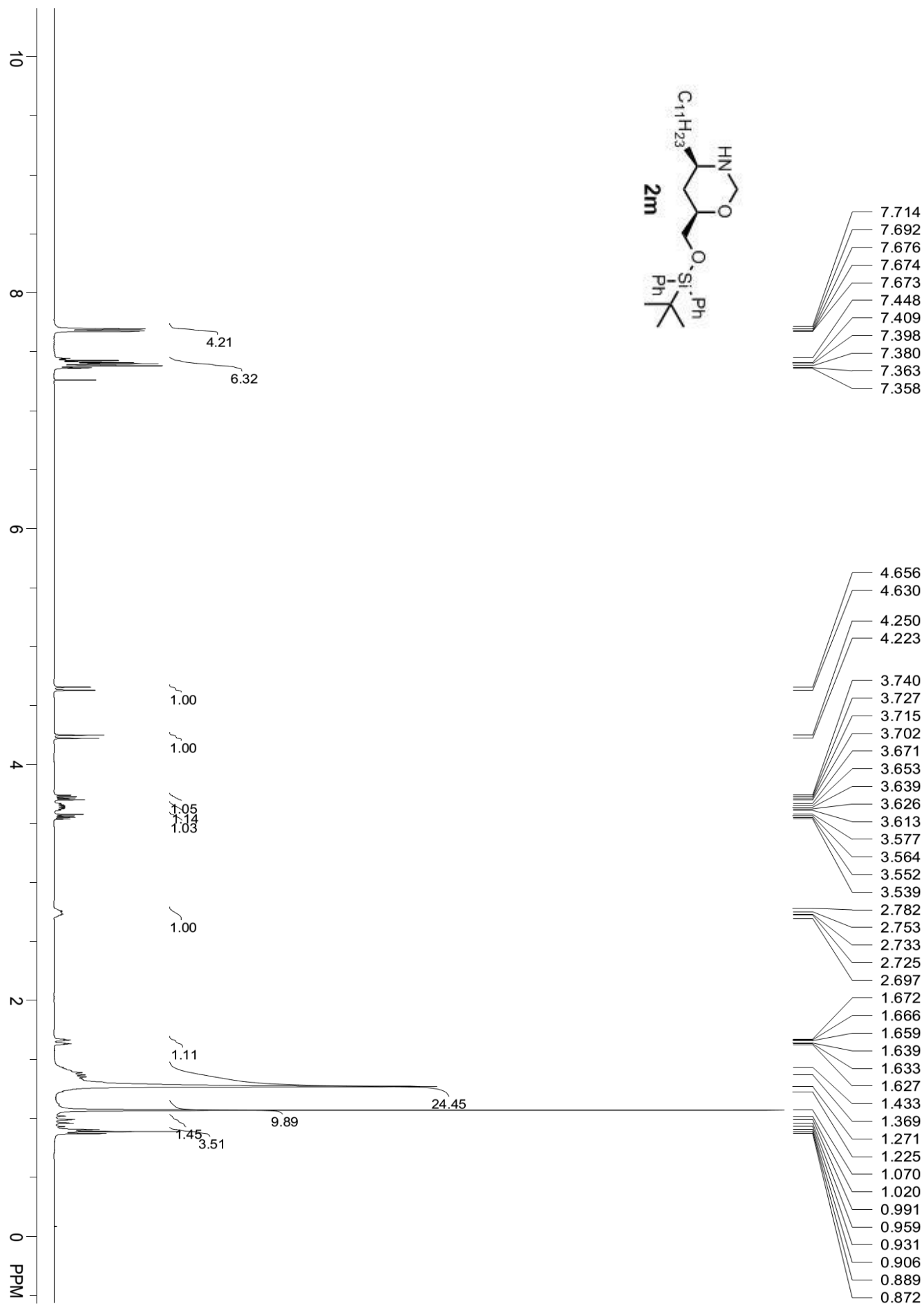


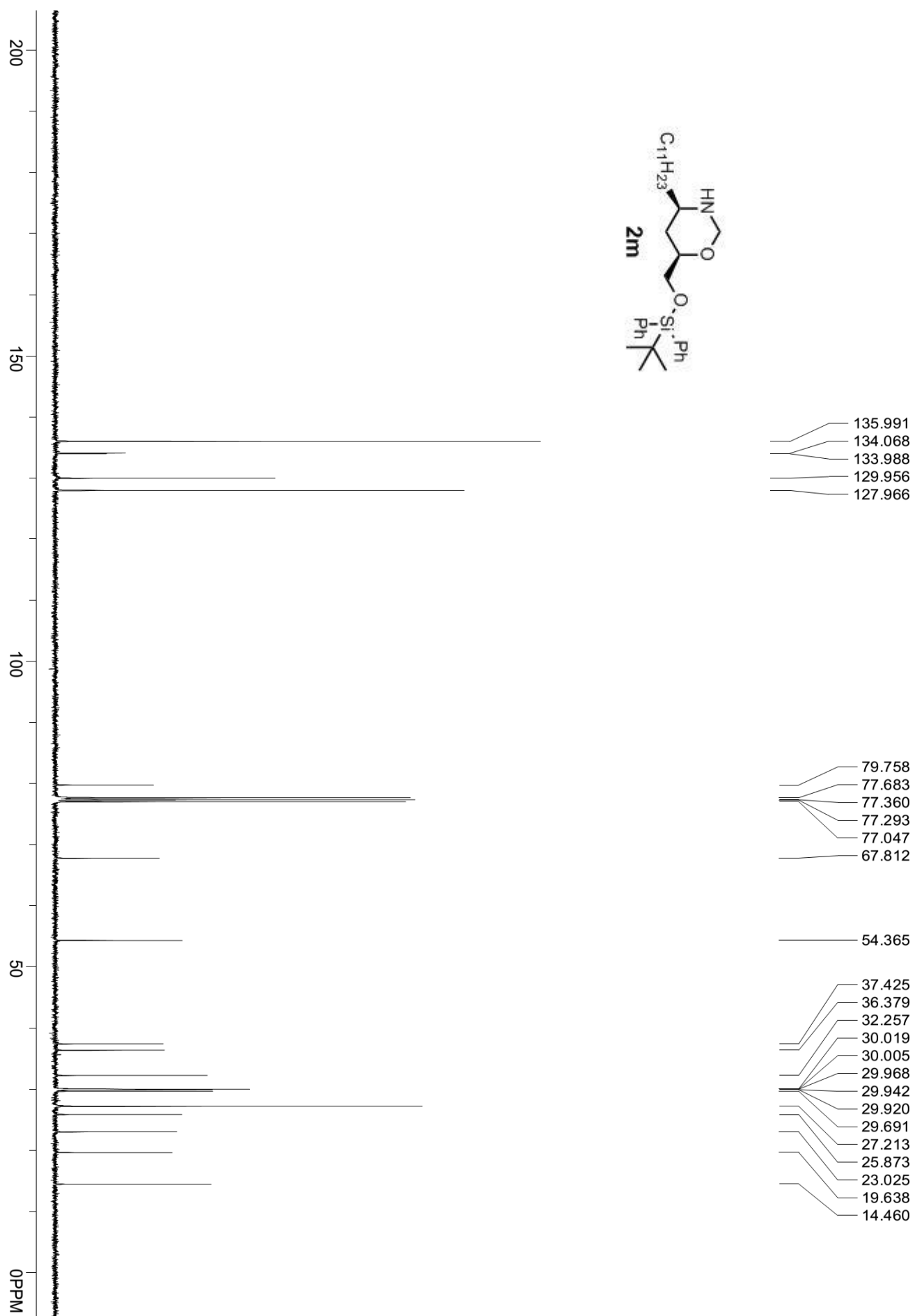


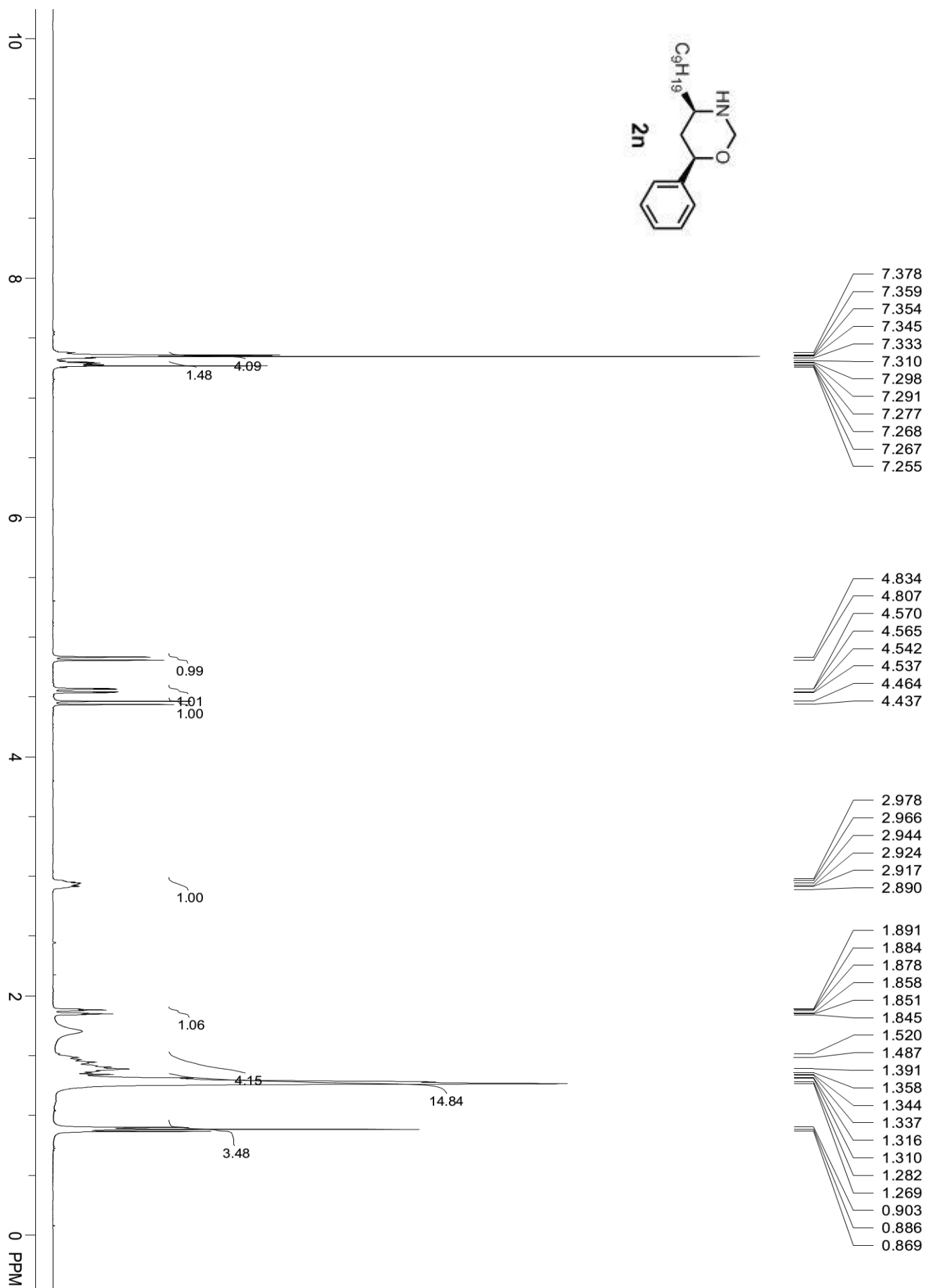


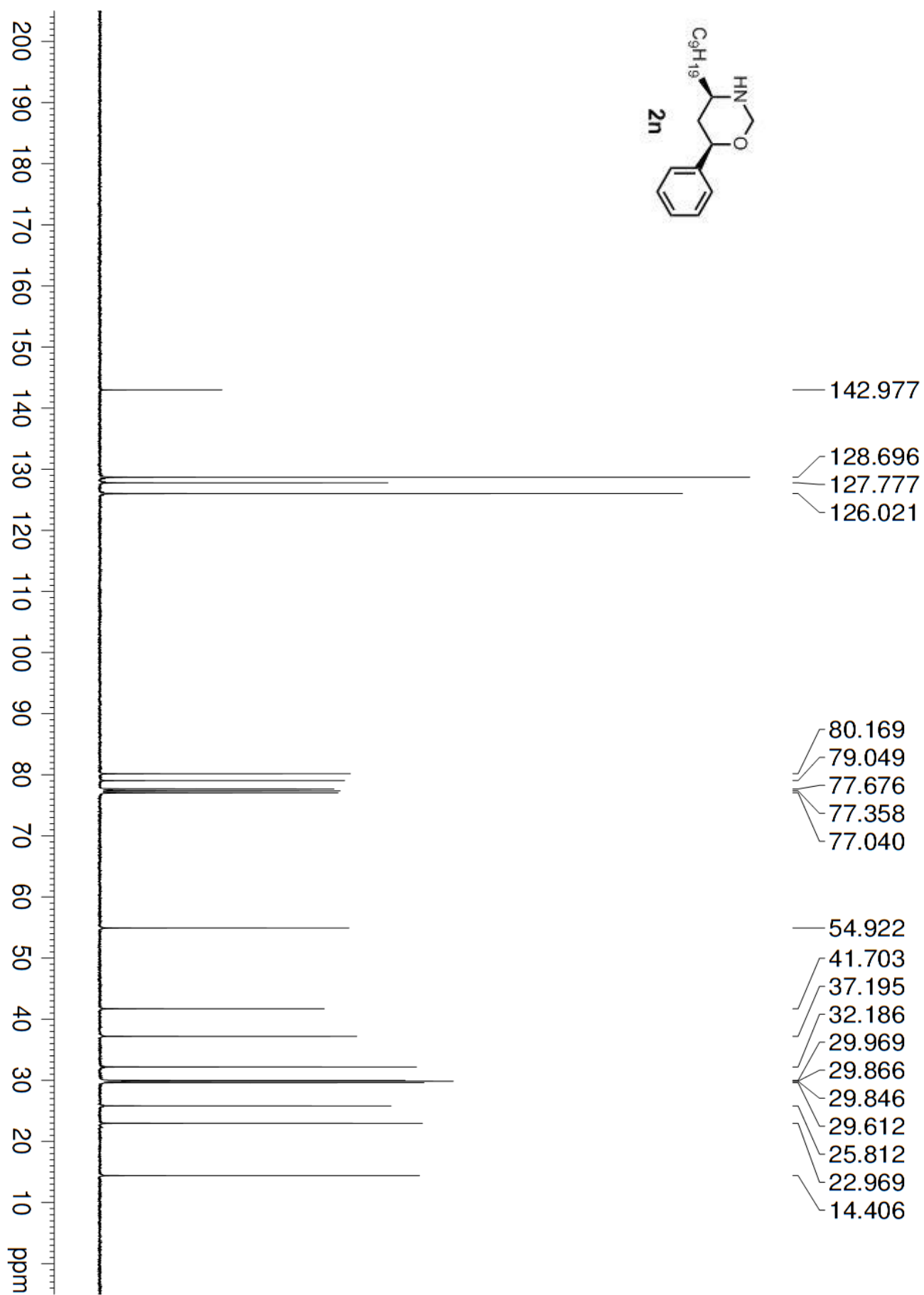
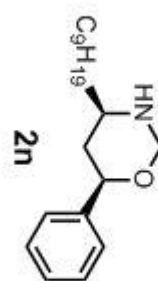


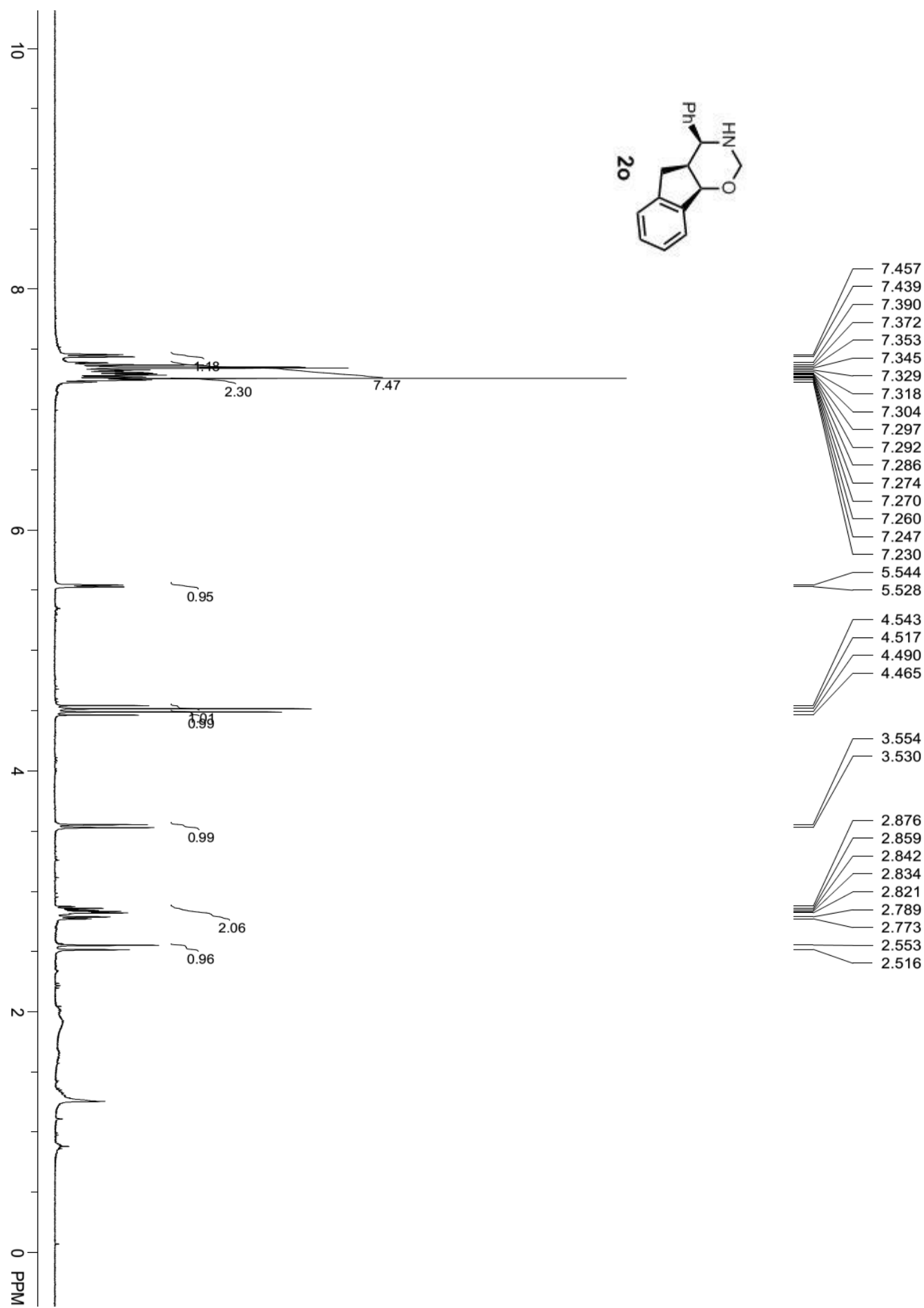


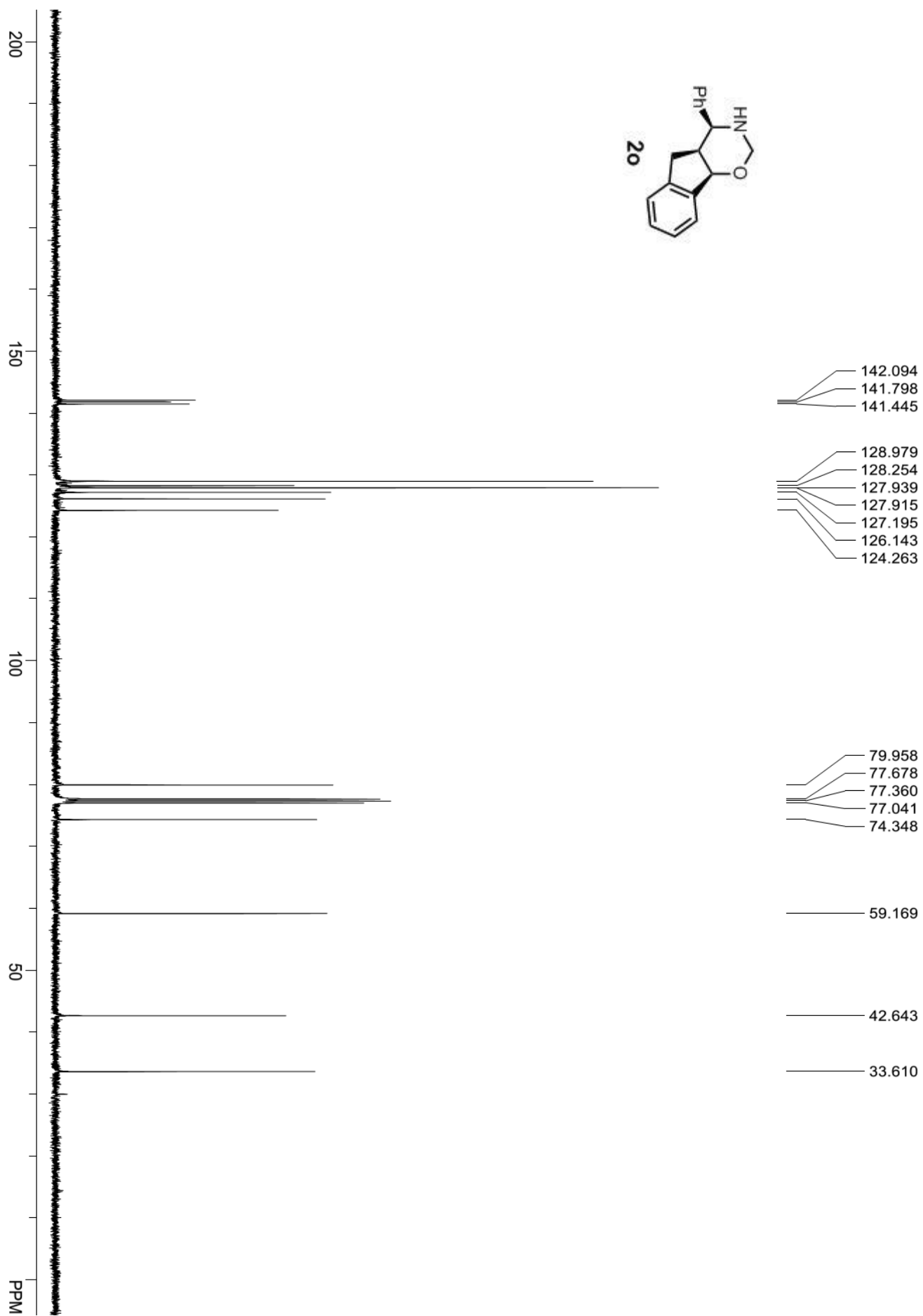


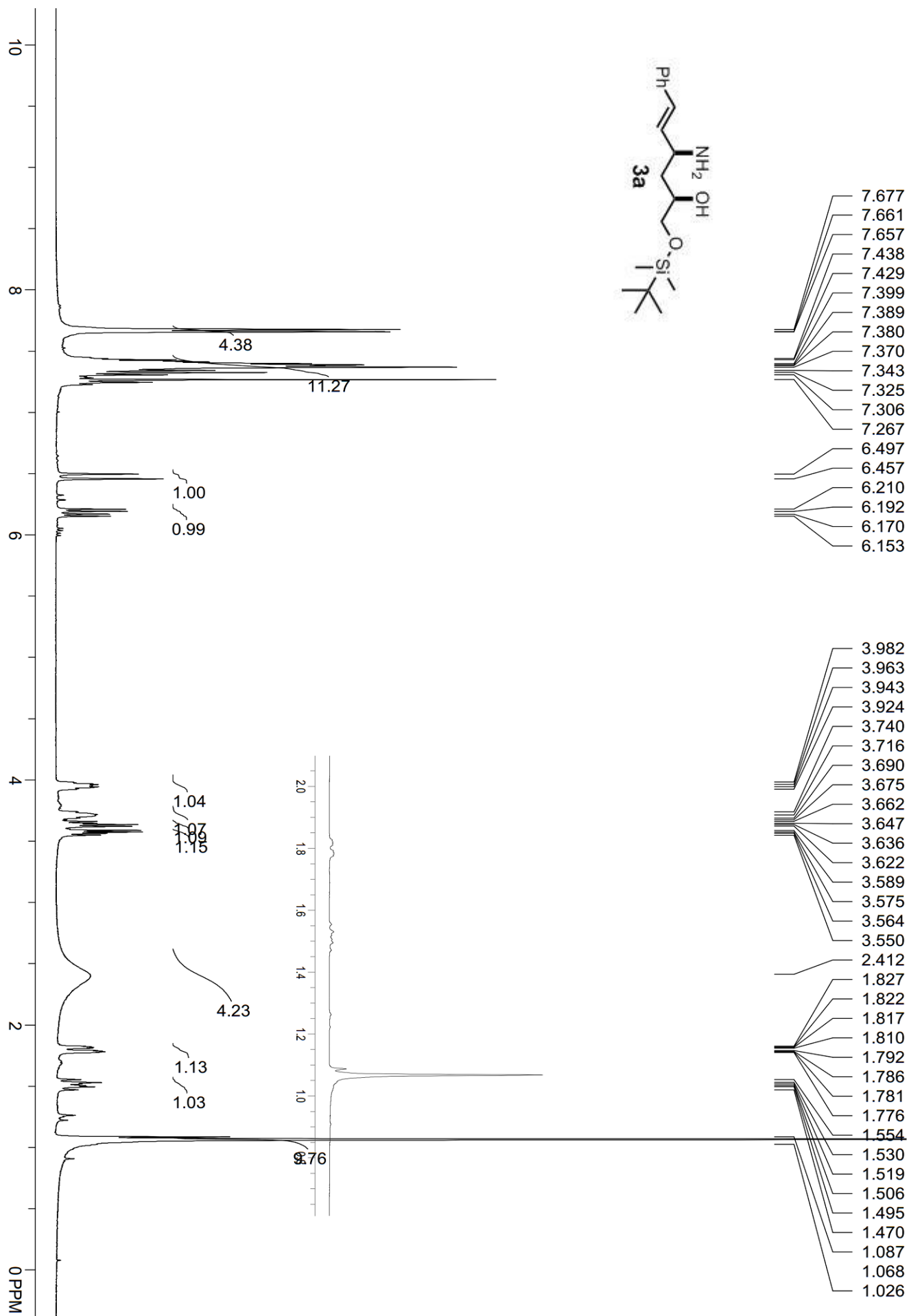
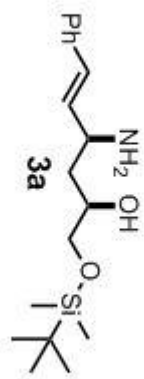


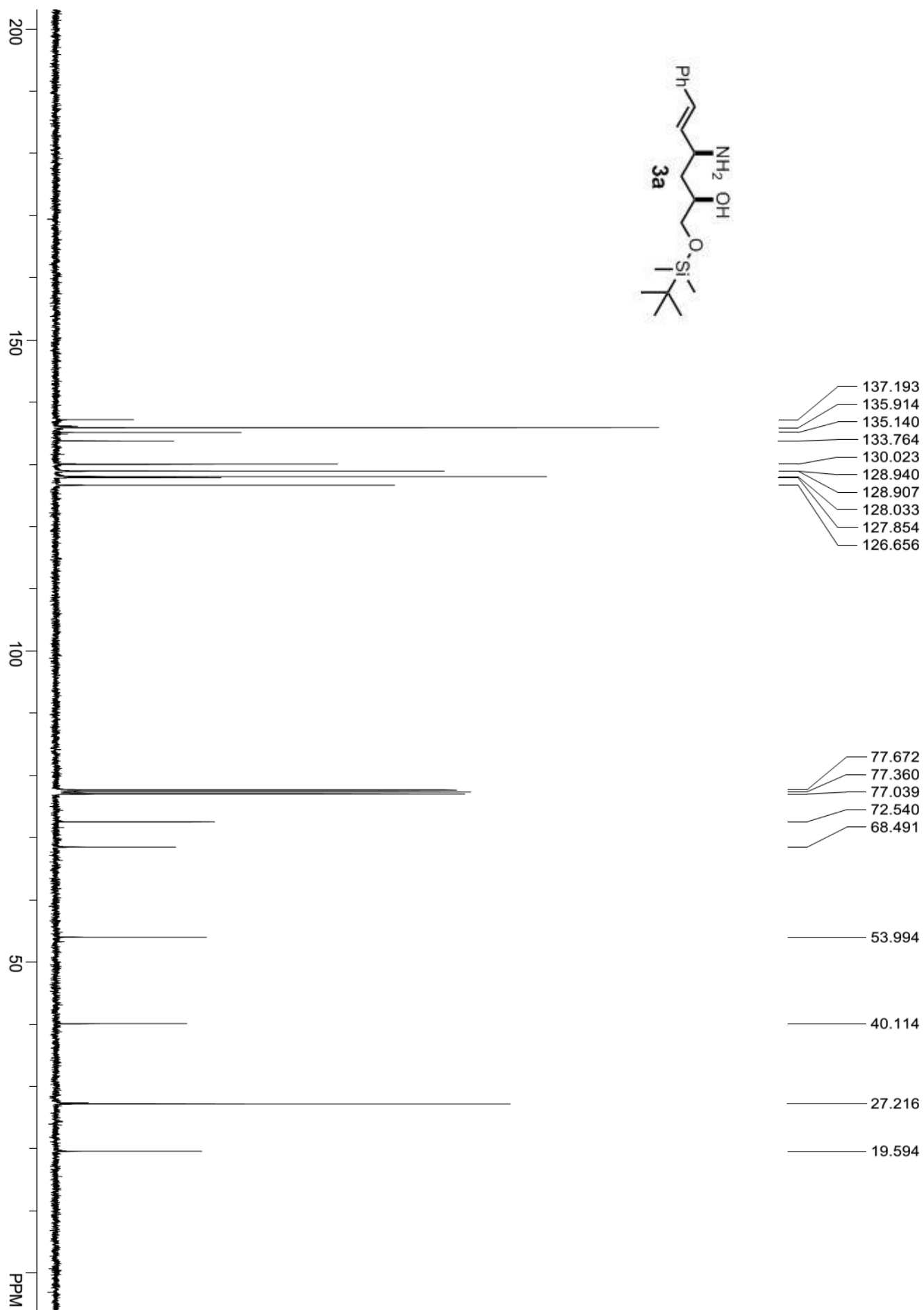


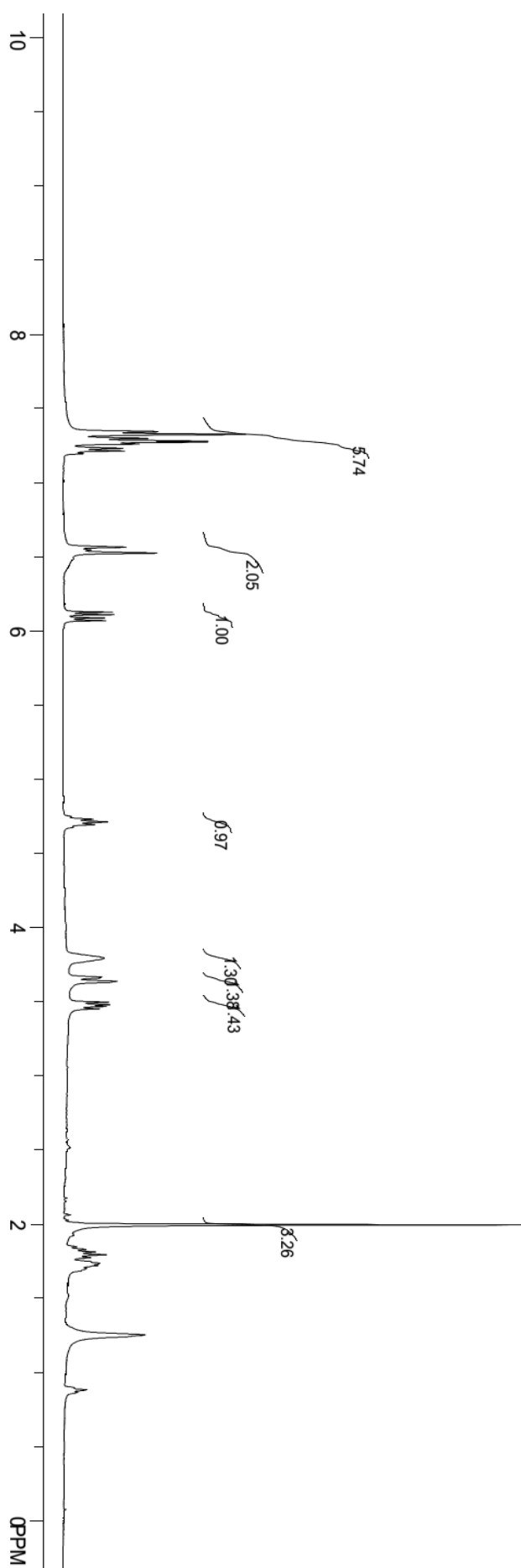
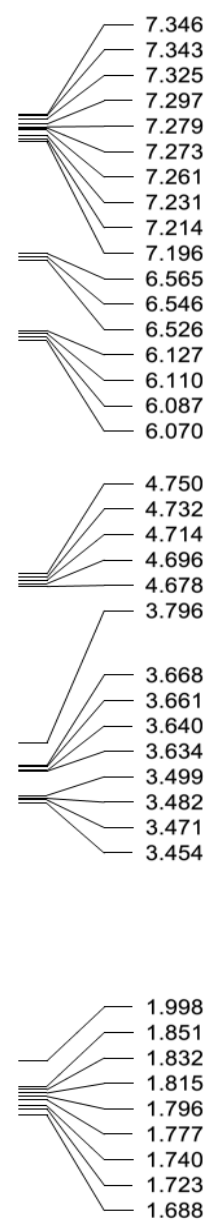
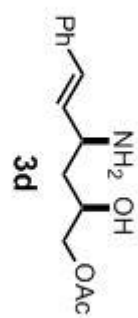


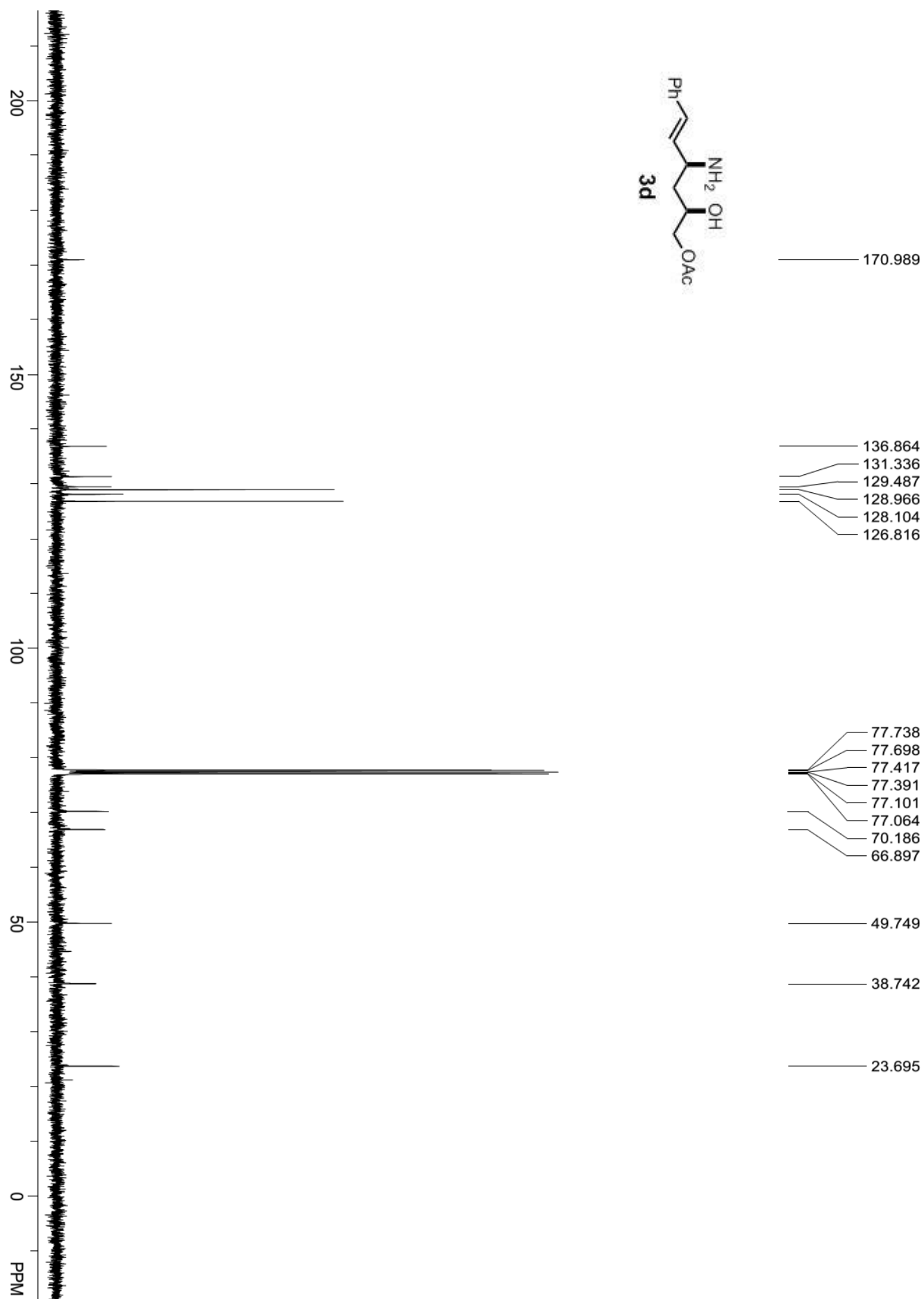


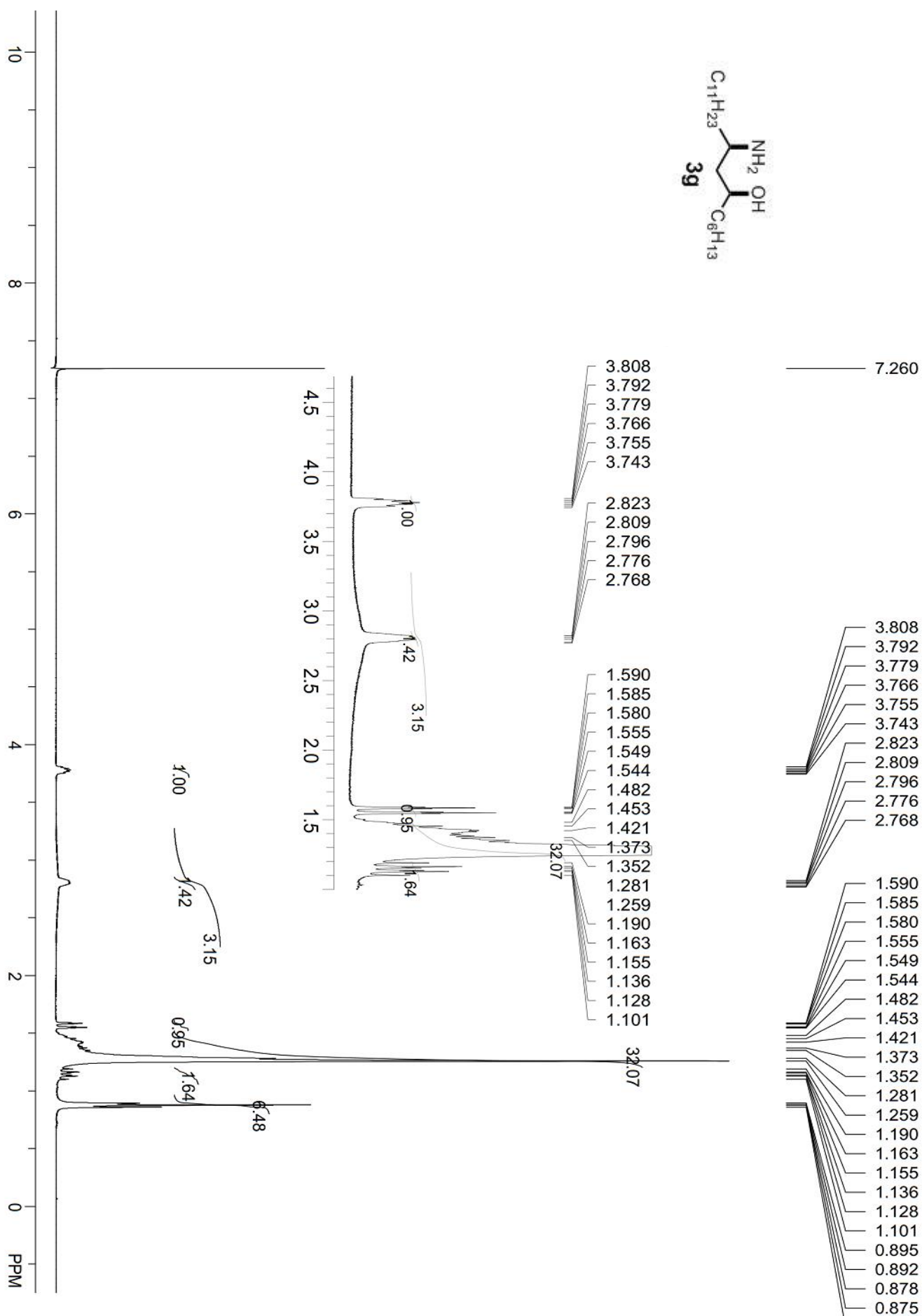
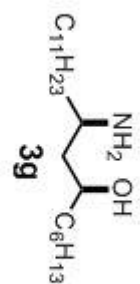


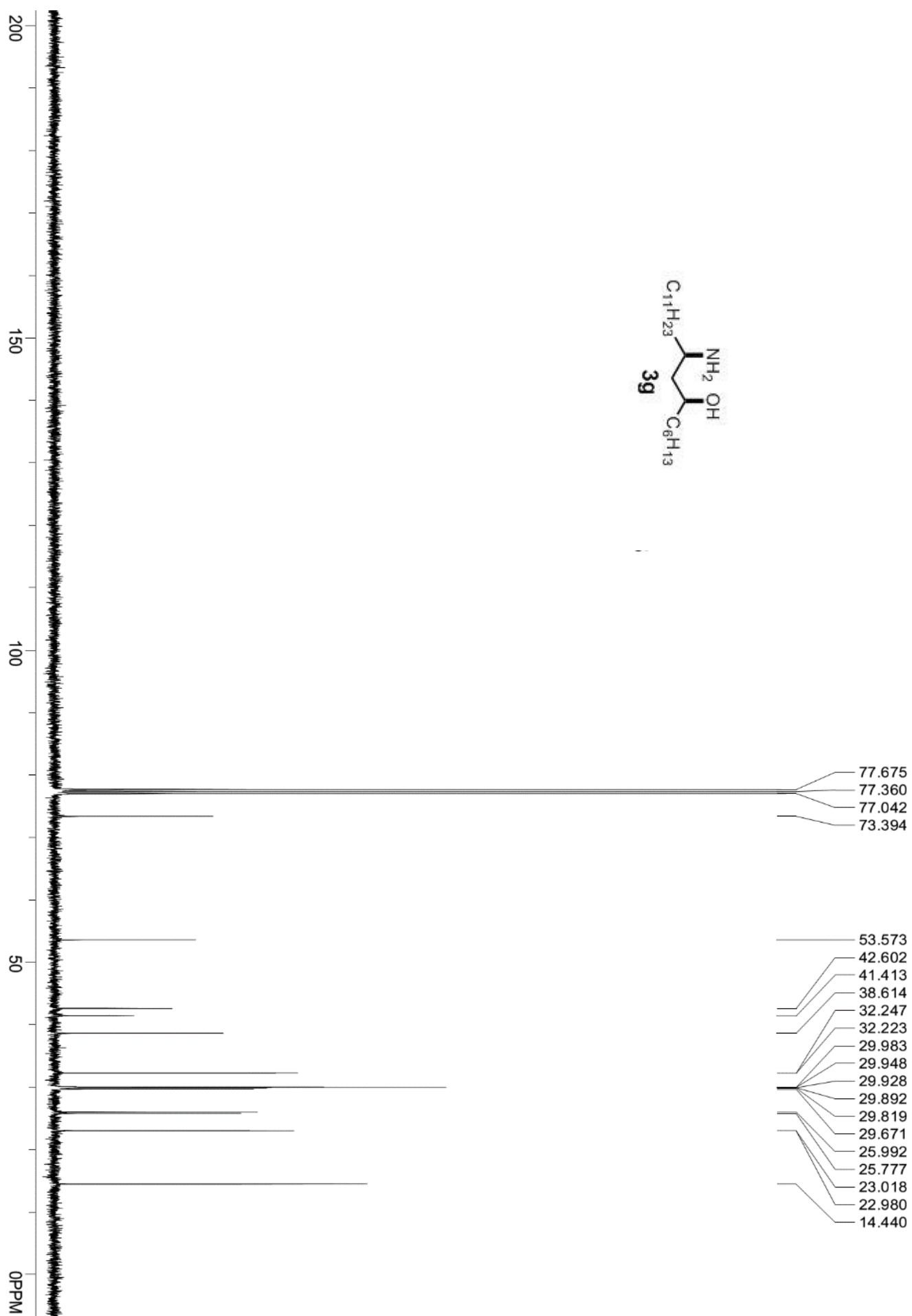


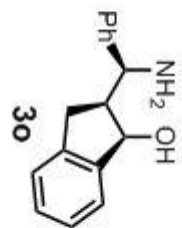
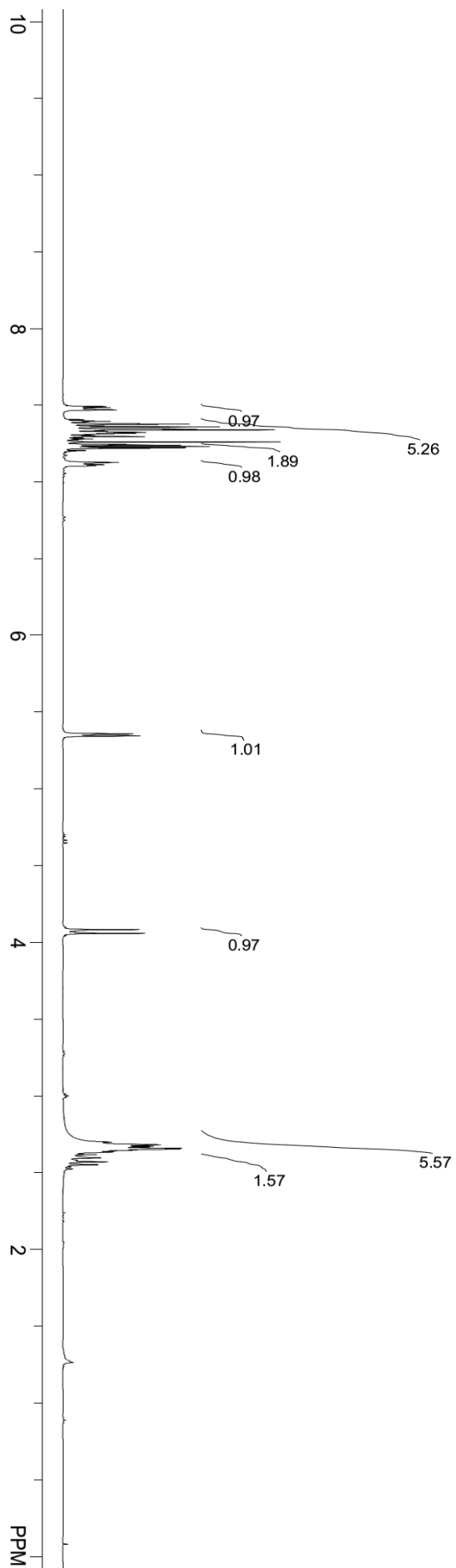


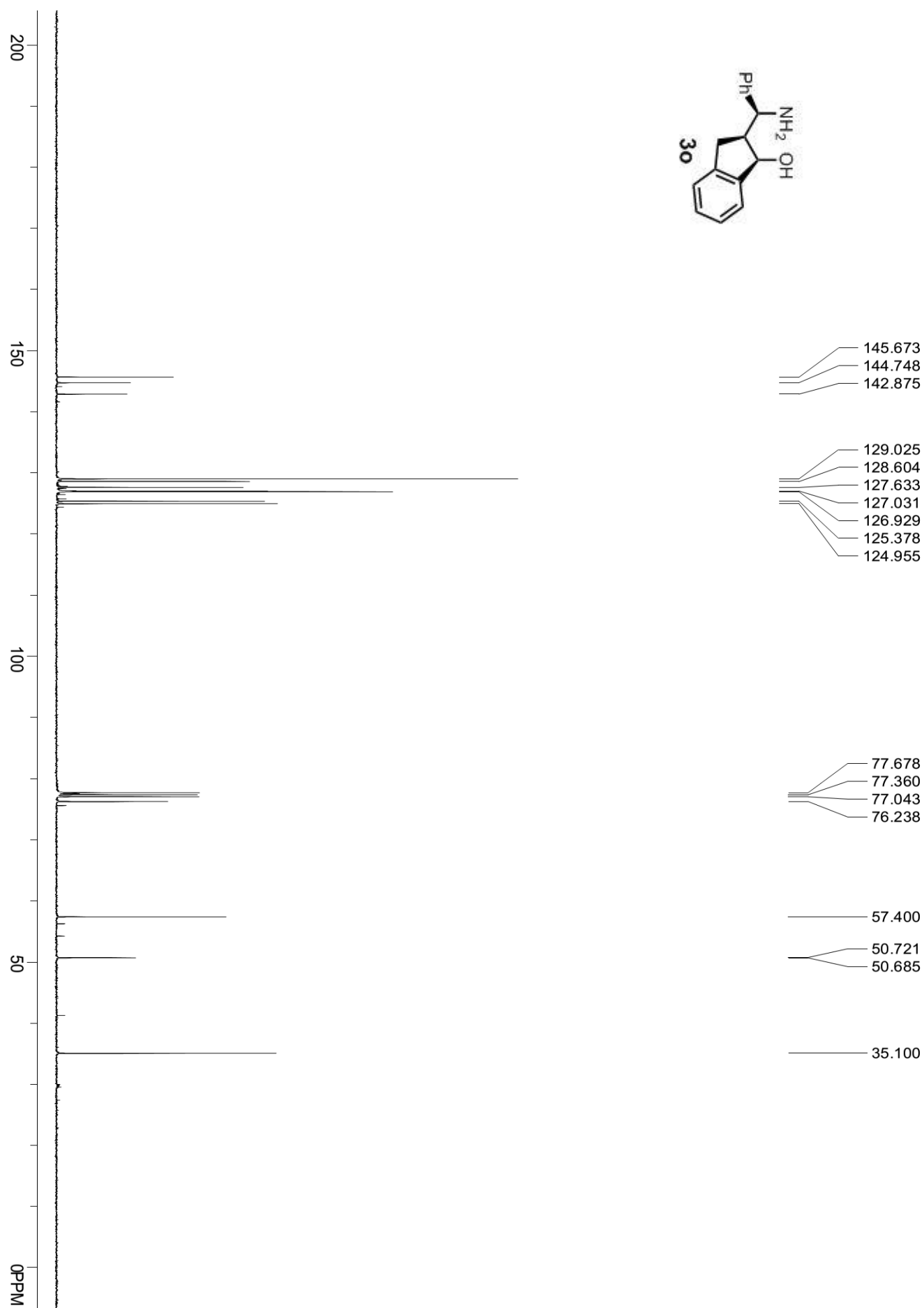
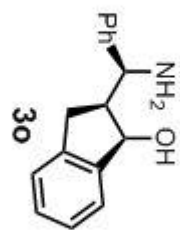


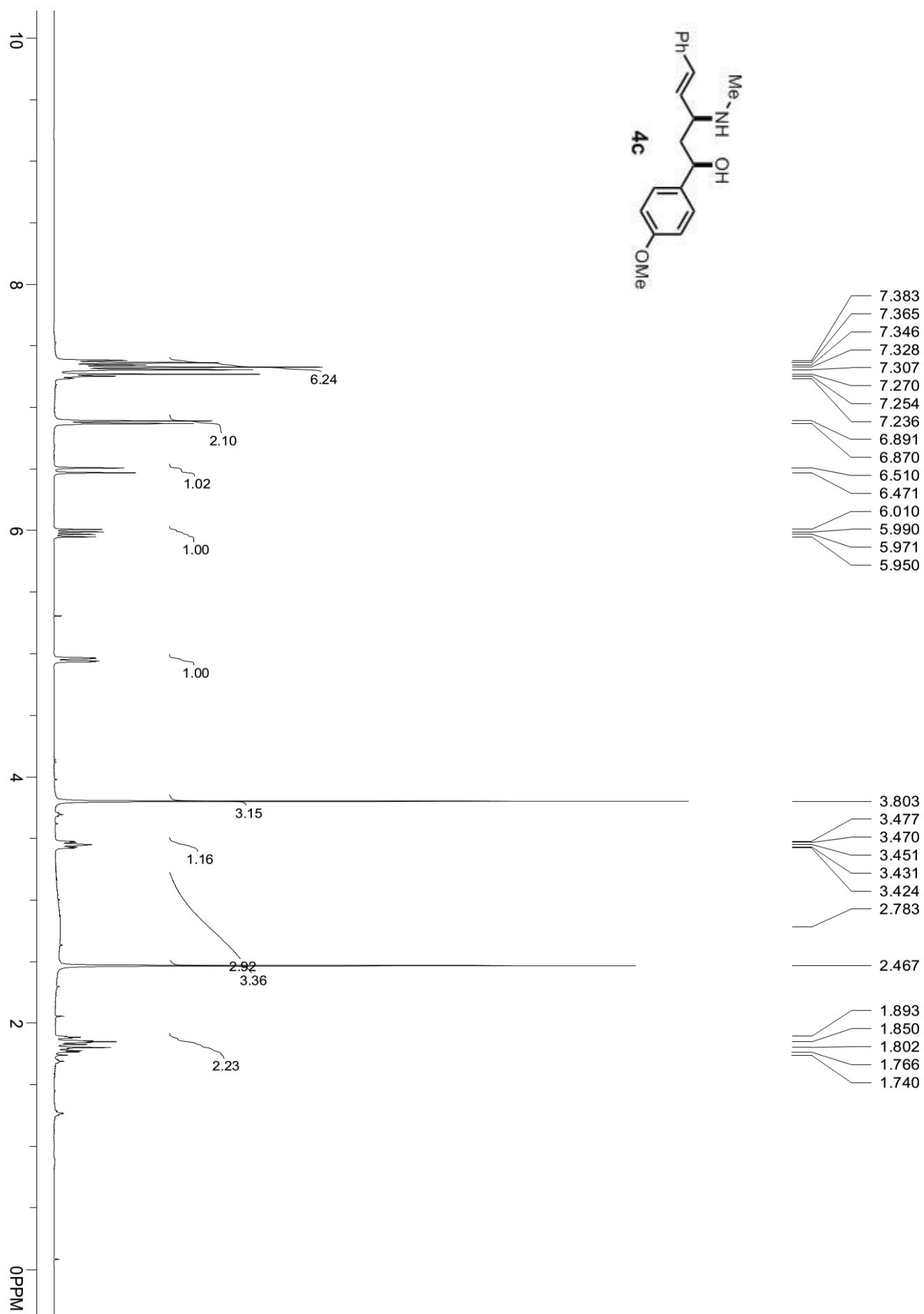


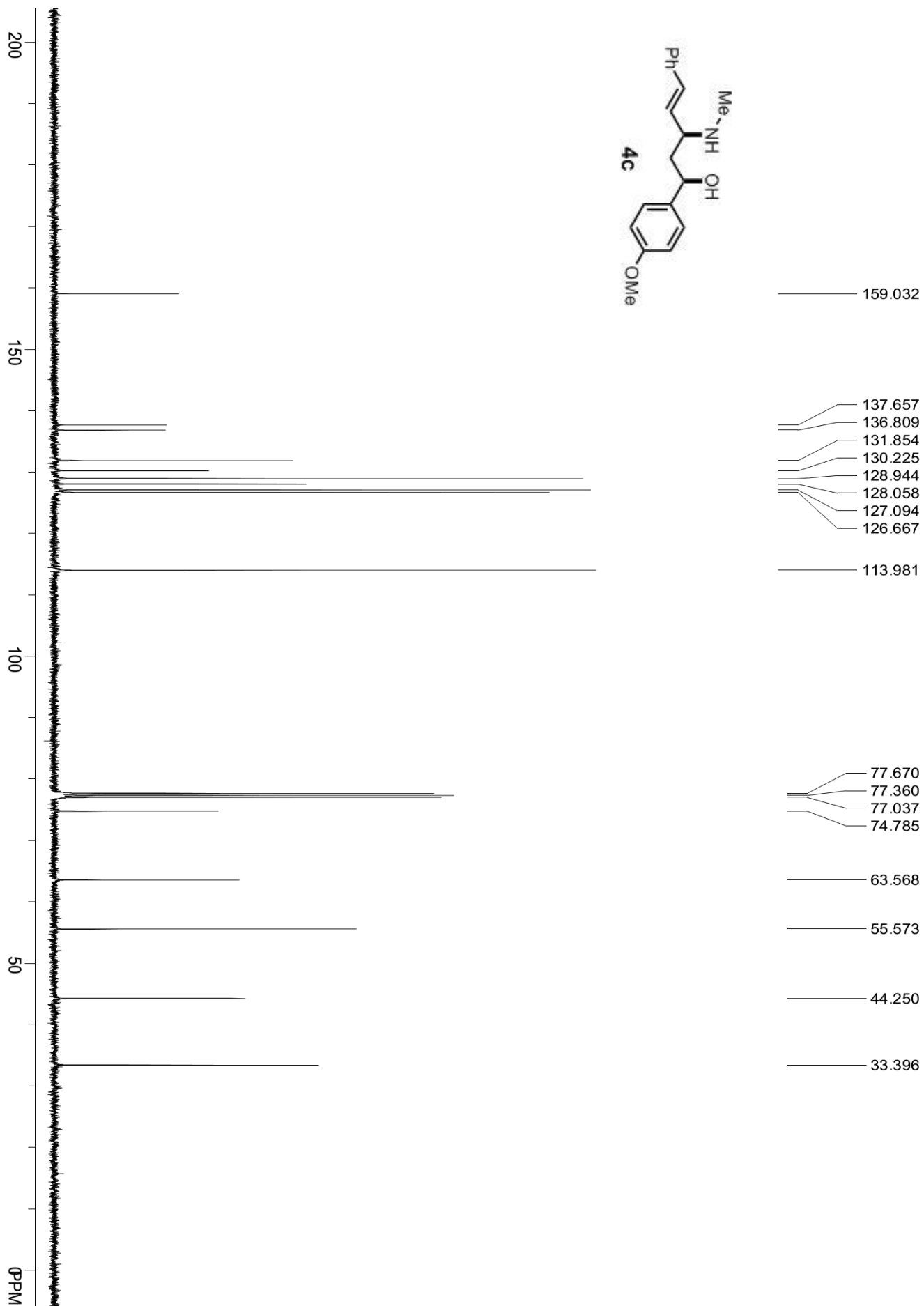


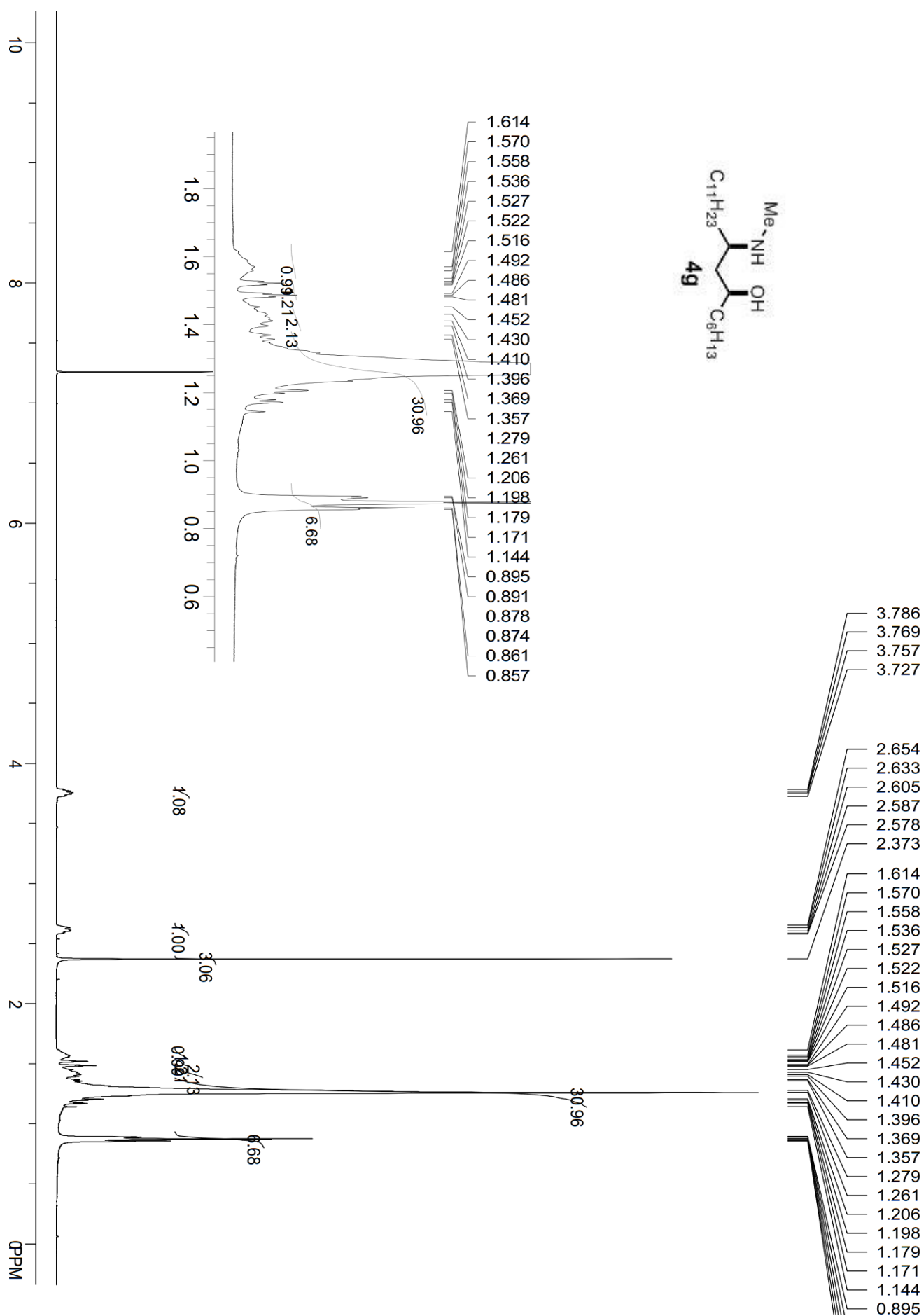
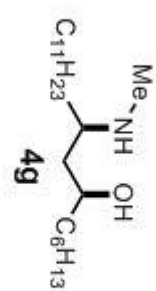


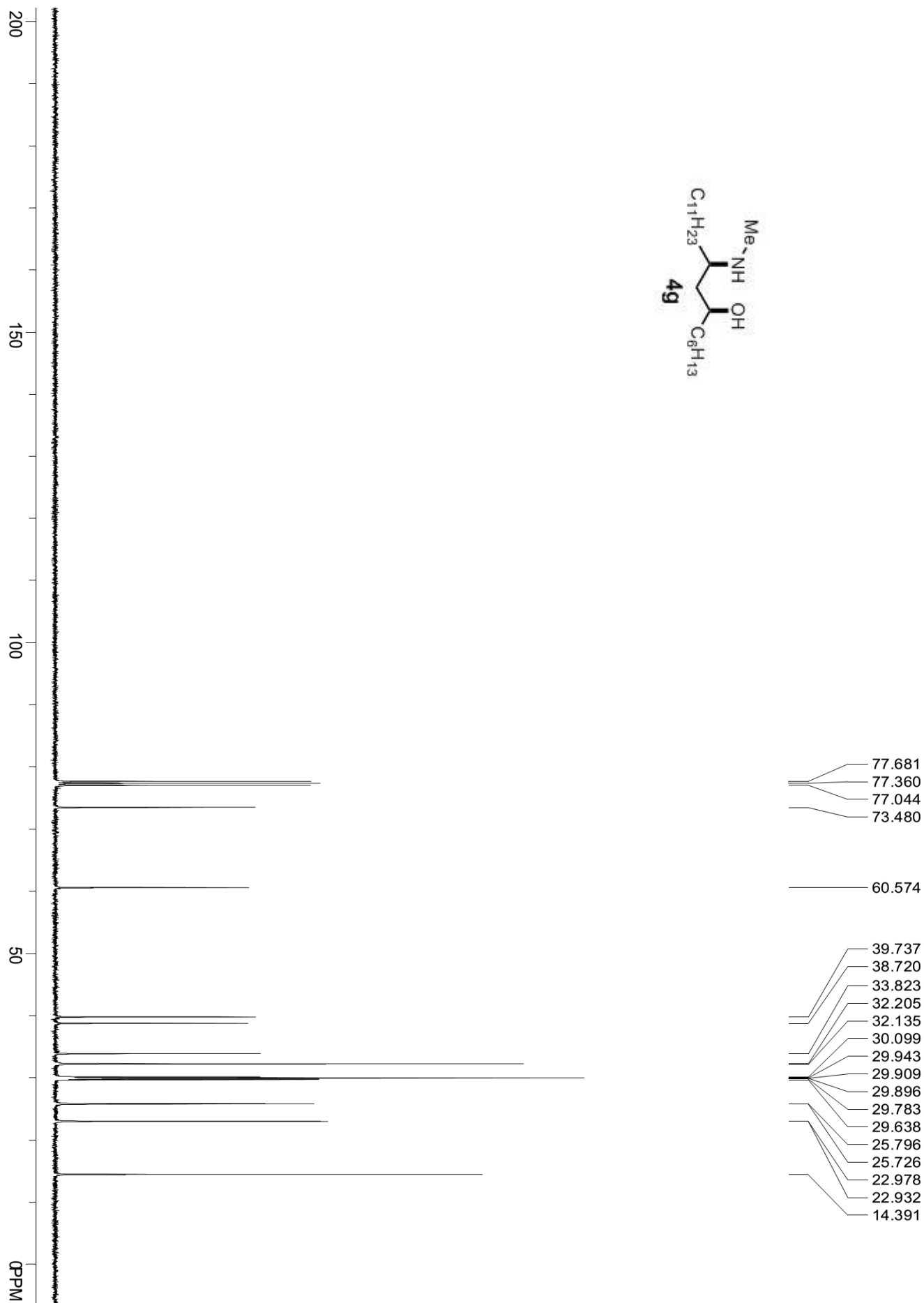
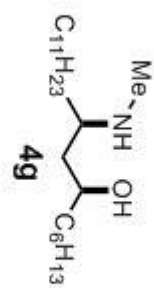


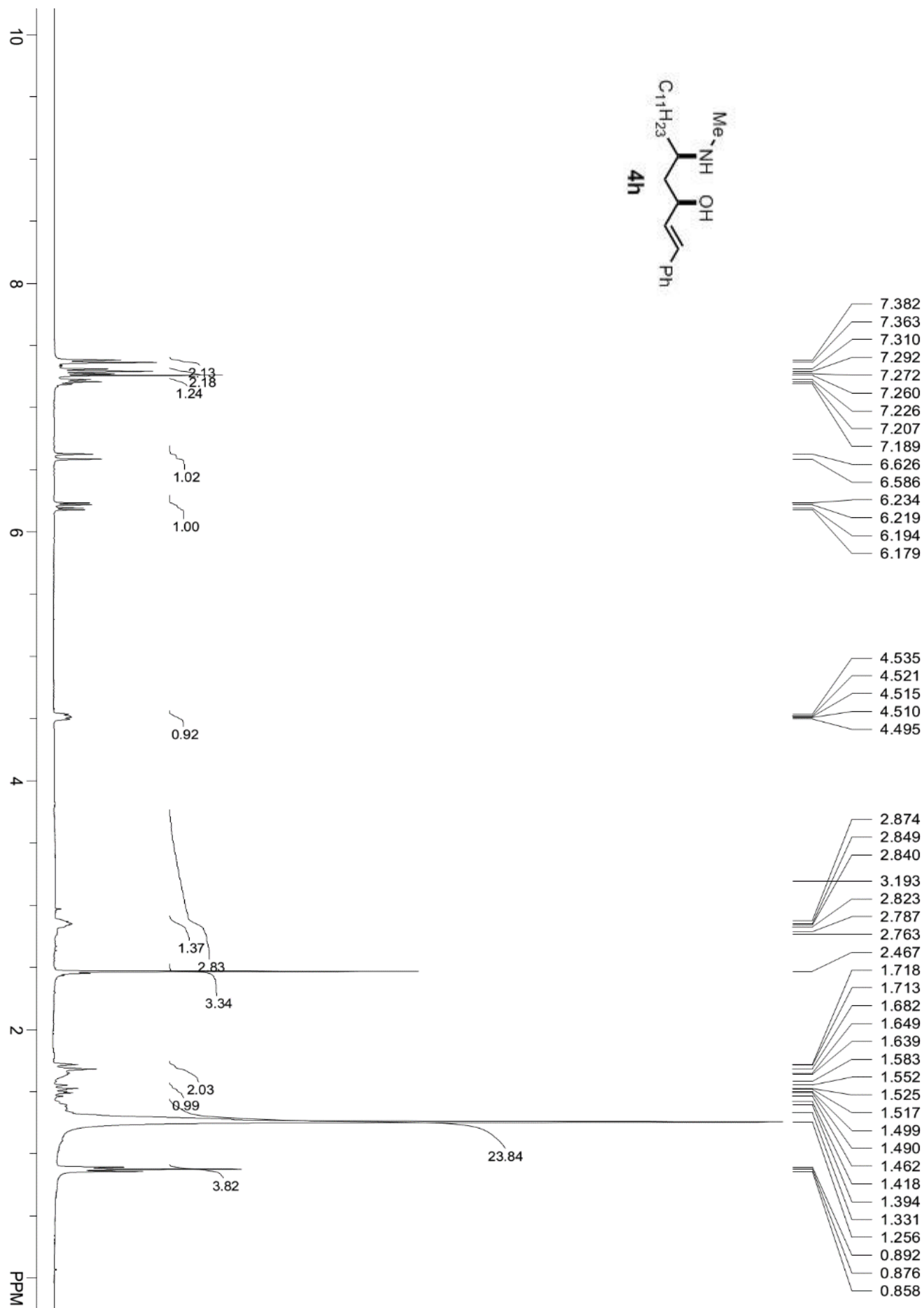


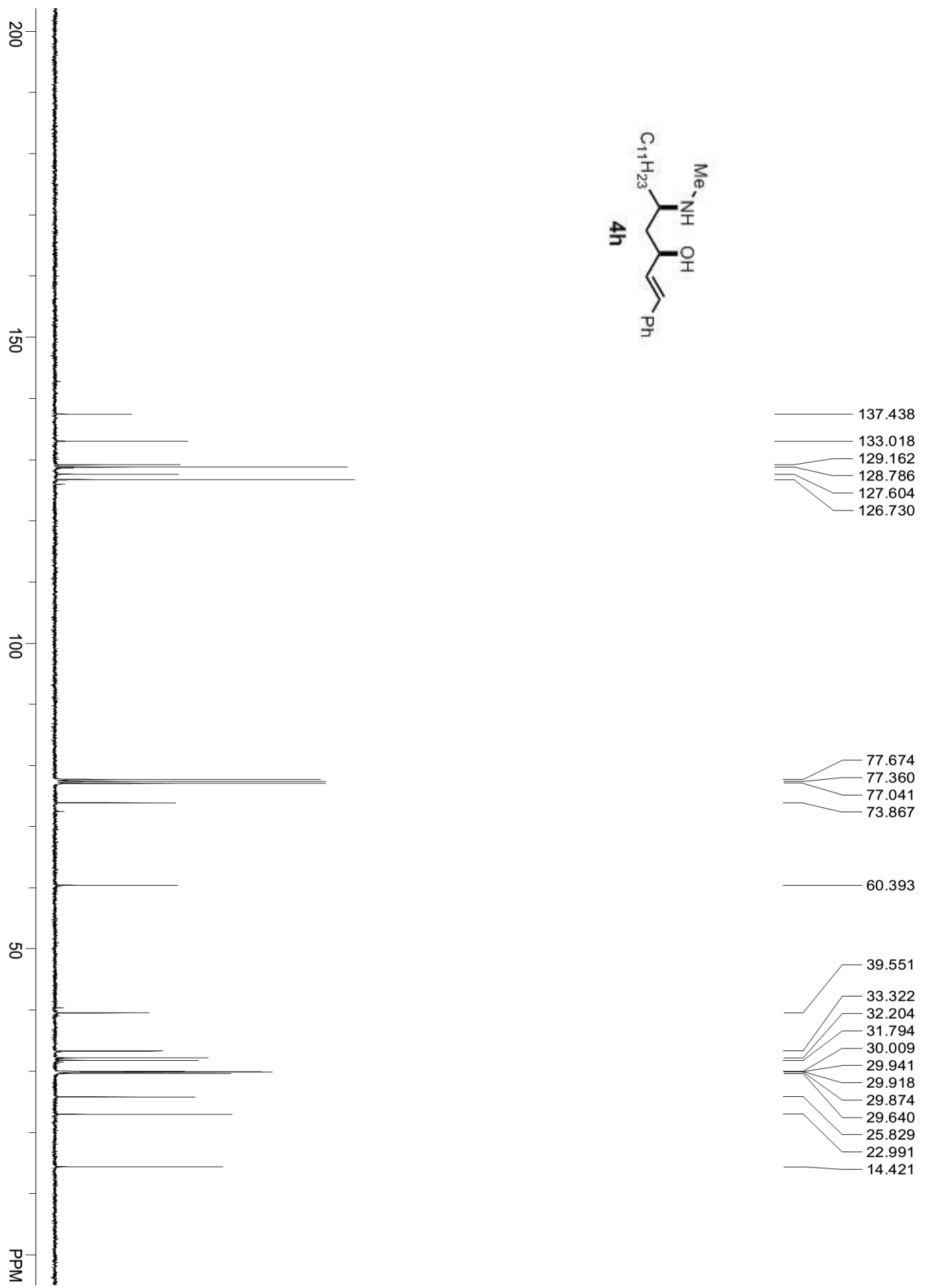
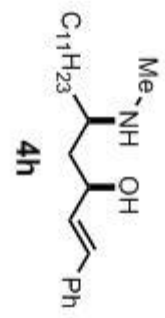


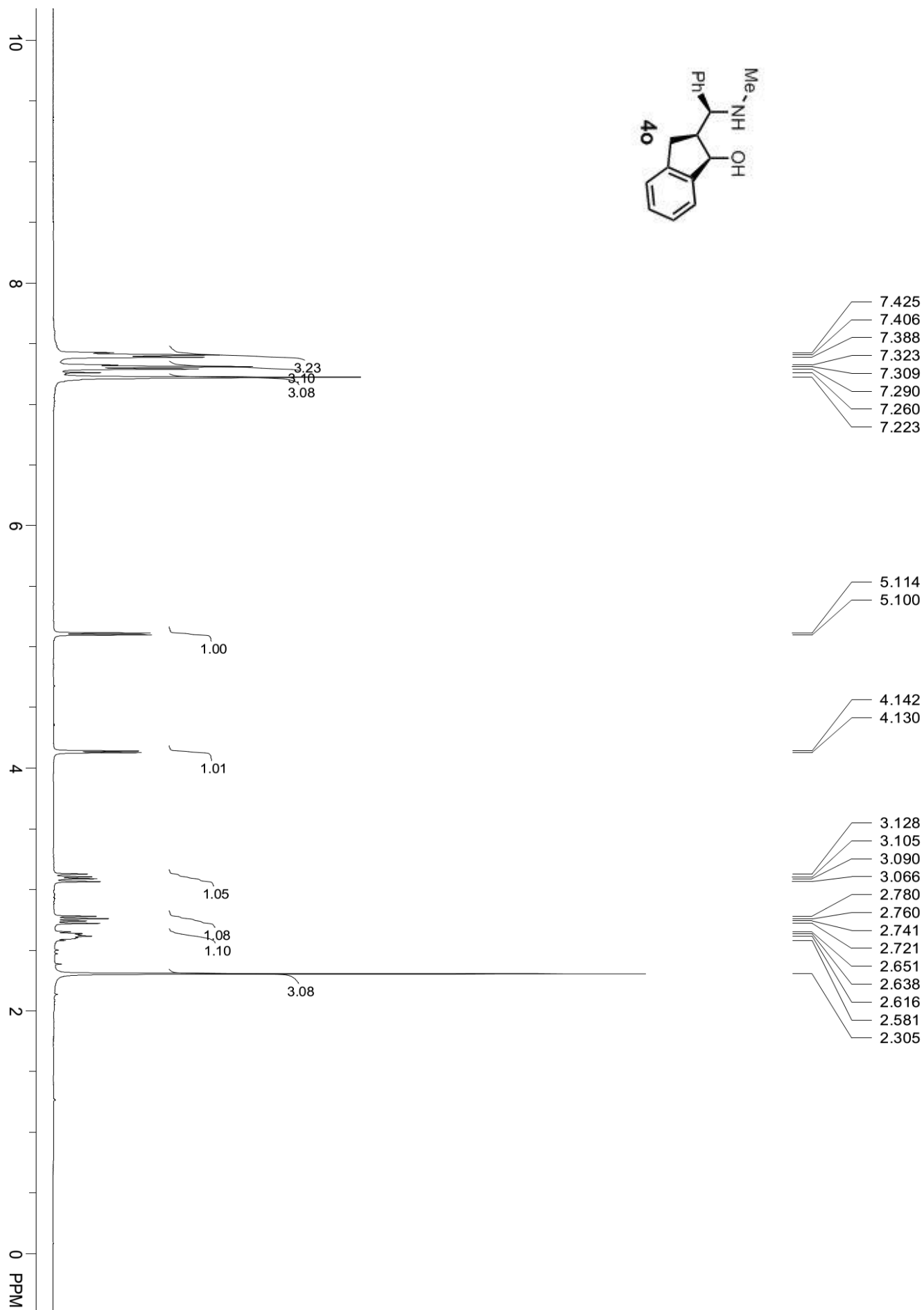


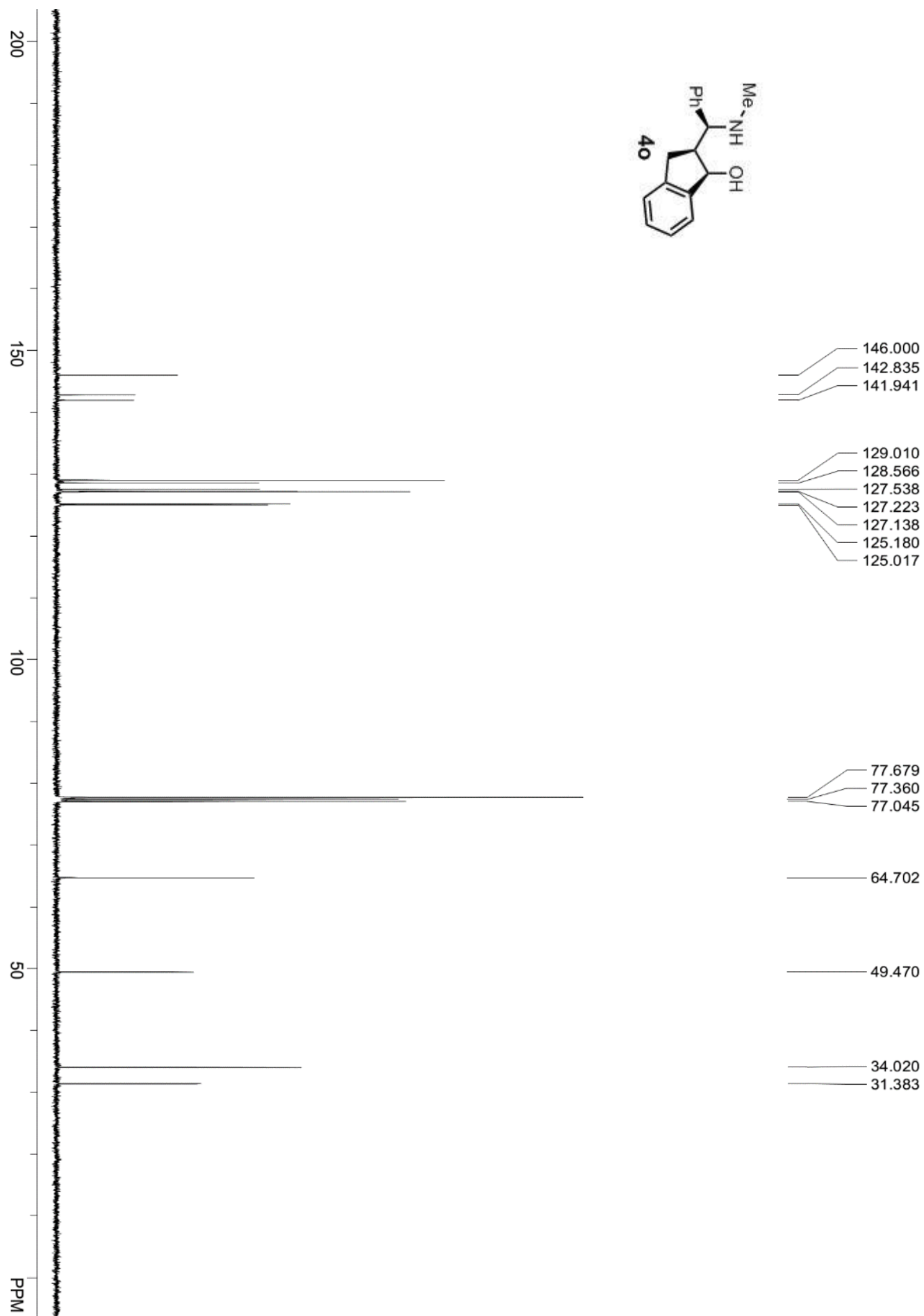
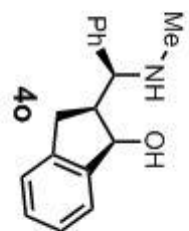


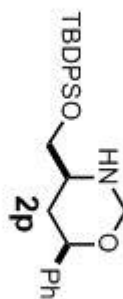
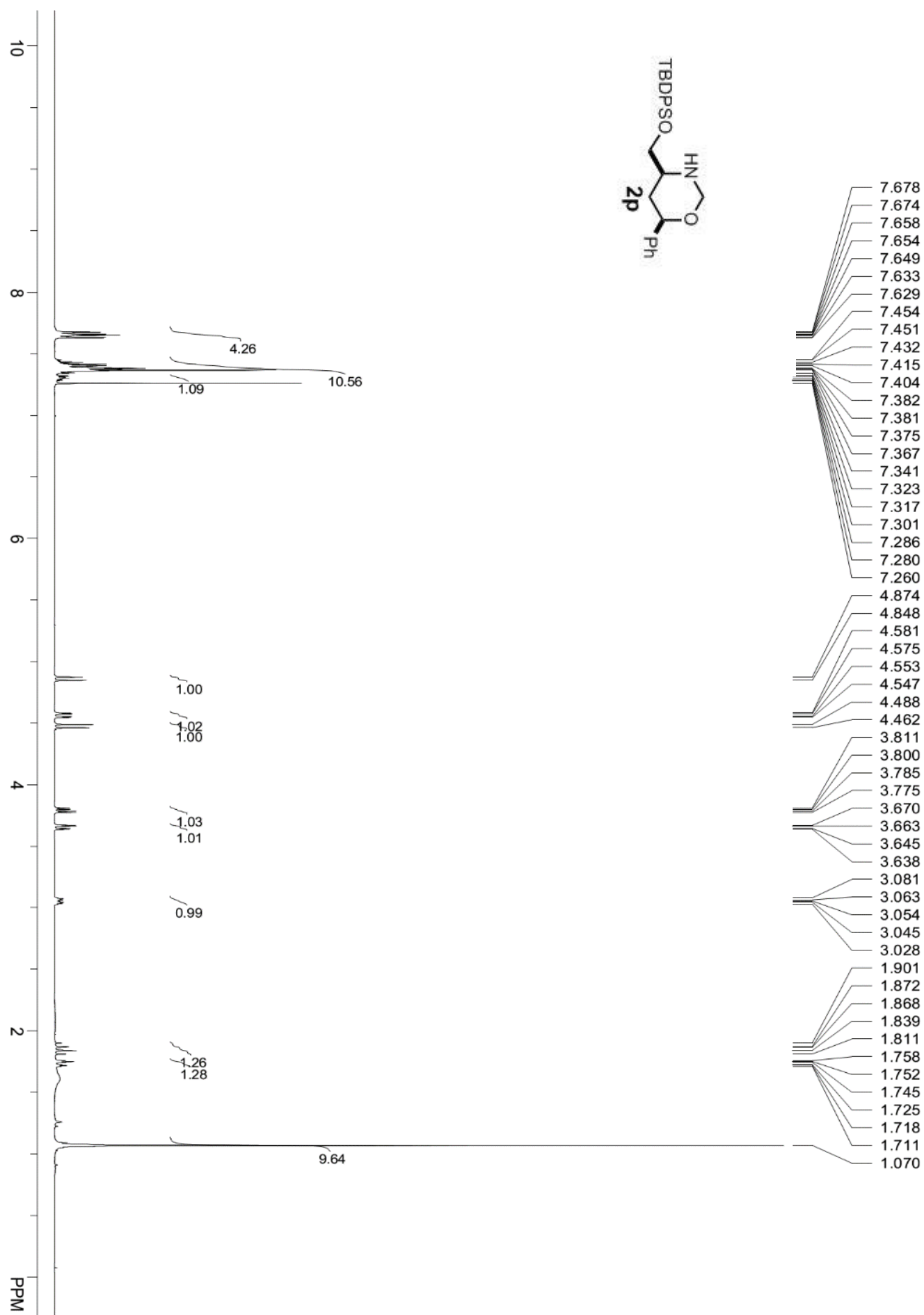


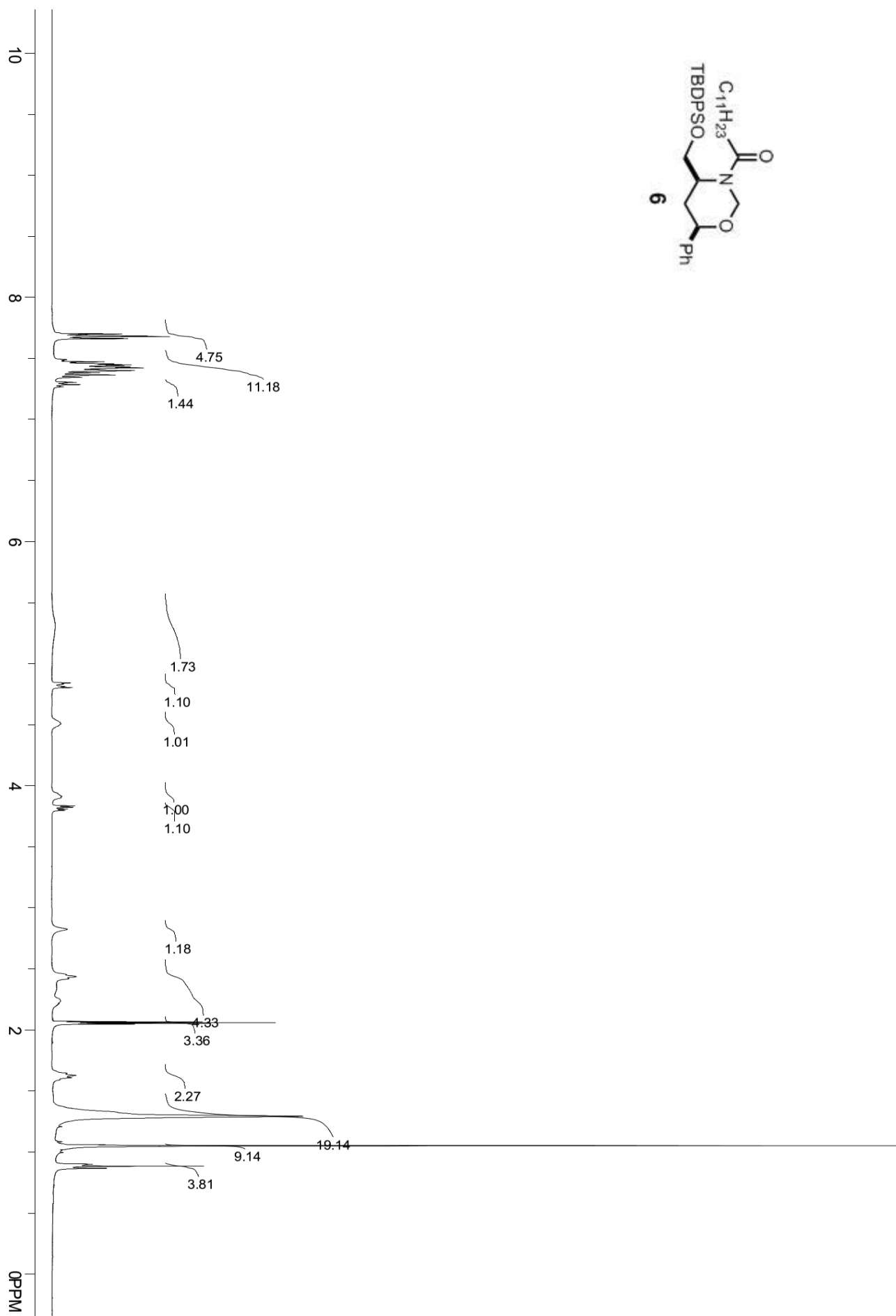
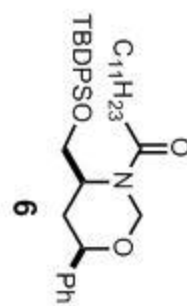


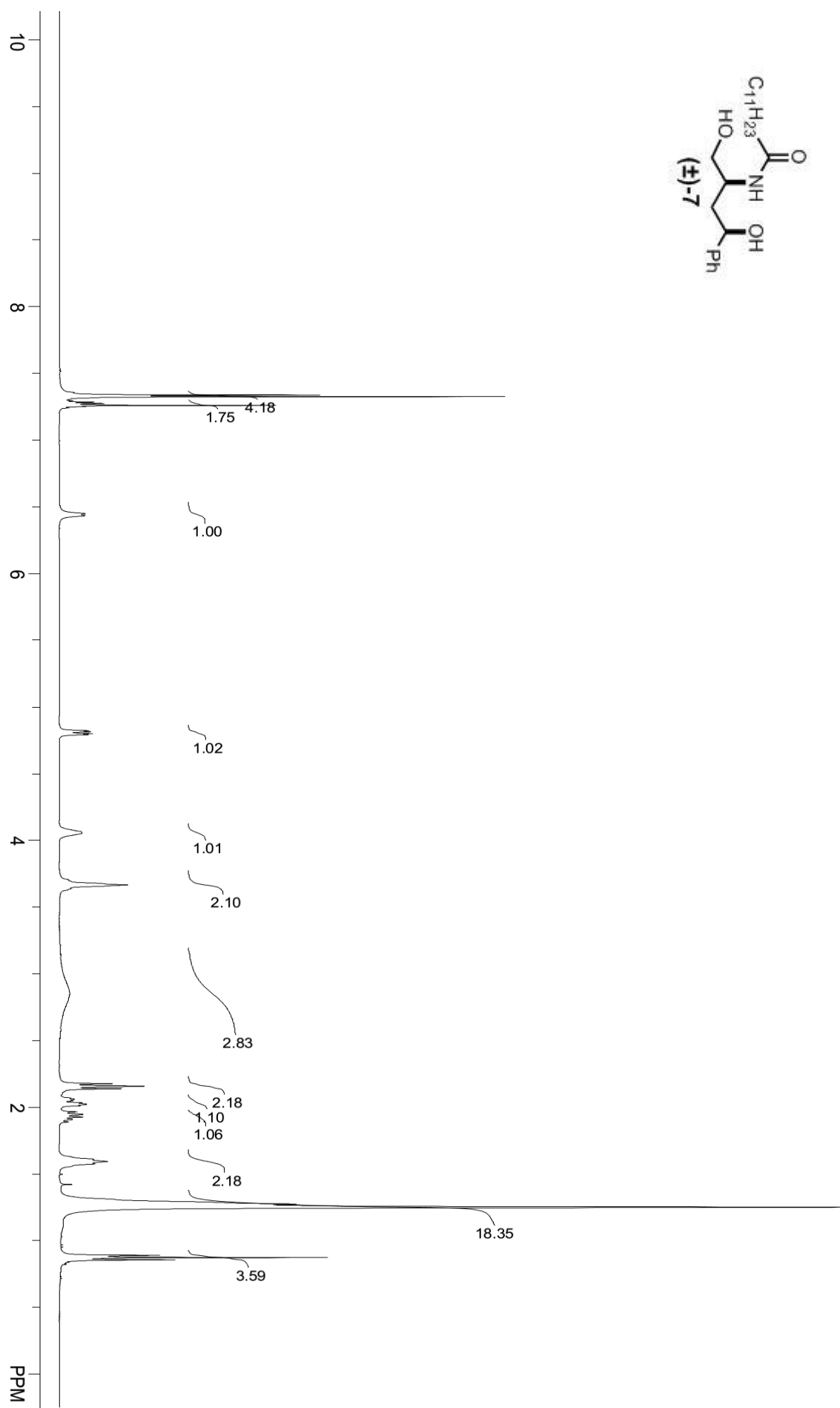
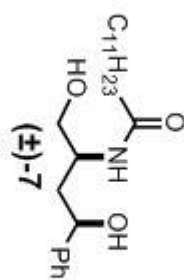


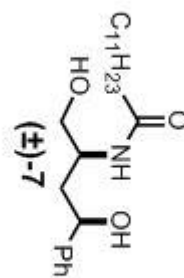












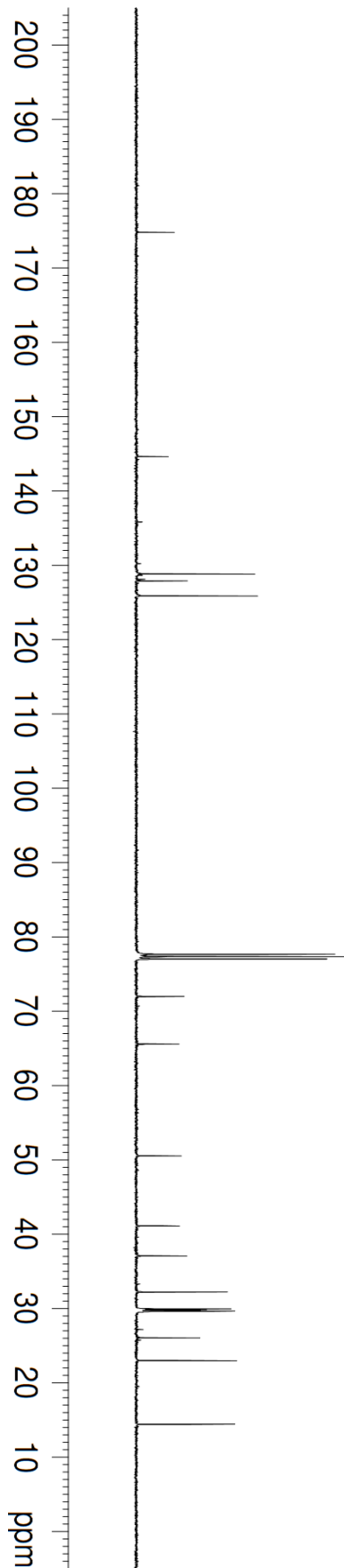
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THE END

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