Synthesis of 17- -Substituted Estradiol-Pyridin-2-yl Hydrazine Conjugates as Effective Ligands for Labeling with Alberto's Complex *fac*-$[Re(OH_2)_3(CO)_3]^+$ in Water

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SUPPORTING INFORMATION:

General Considerations: All experiments were performed in an efficient fume hood. Solvents and reagents were used without further purification. All air sensitive reagents were transferred in a dry-box, and the reactions were carried out under argon atmosphere. Silica gel 60, 70-230 mesh was used for column chromatography. Flash chromatography was performed using a medium pressure flash chromatography system utilizing prepacked silica gel columns. Deuterated solvents were used without further purification.

NMR spectra were acquired at ambient temperatures (18 ± 2 ^{o}C), unless otherwise noted. The ^{1}H NMR spectra in $CDCl_3$ were referenced to TMS unless otherwise noted. The ^{13}C {^{1}H} NMR spectra were recorded at 50 or 100 MHz and referenced relative to the ^{13}C {^{1}H} peaks of the solvent. Spectra are reported as ppm, (multiplicity, coupling constants (Hz), and number of protons). Melting points are uncorrected. Infrared spectra were recorded as KBr pellets or neat samples on NaCl plates and are reported in cm^{-1}

17 -[6-(chloro-pyridin-3-ylethynyl)]-estra-1,3,5(10)-triene-3,17 -diol (7a). A 2-neck flask was charged with Pd $(OAc)_2$ (5.7 mg, 0.026 mmol) and PPh_3 (13.4 mg, 0.051 mmol) and was flushed with argon. Contents were suspended in diethylamine (1.5 mL) and the solution was allowed to stir under argon for 10 minutes. **6** (121 mg, 0.51 mmol) and CuI (9.7 mg, 0.051 mmol) were added as solids. After an additional 10 minutes, **5a** (150mg, 0.51mmol) was added and the mixture was allowed to stir for 6 h. Volatiles were removed under vacuum and residue was dissolved in CH_2Cl_2 and filtered through celite. The filtrate was washed with H_2O and dried over Na_2SO_4. After removal of solvent under vacuum, the brown residue was chromatographed (2.5% MeOH / CH_2Cl_2) to yield **7a** (93%) as a yellow solid. Mp: 132.8-133.9. IR (KBr): 3406, 2931, 2870, 2361,2343, 1611, 1499, 1456, 1385, 1359, 1286 cm^{-1}. ^1H NMR ($CDCl_3$, 400MHz): 8.45 (d, *J* = 2.2 Hz, 1H), 7.69(dd, *J* = 8.6, 2.2 Hz, 1H), 7.30 (d, *J* = 8.6 Hz, 1H), 7.17 (d, *J* = 8.42 Hz, 1H), 6.64 (dd, *J* = 8.4, 2.9 Hz, 1H), 6.57(d, *J* = 2.9 Hz, 1H) 4.57 (s, 1H), 2.86-2.80 (m, 2H), 2.50-2.35 (m, 2H) 2.250-1.95 (m, 2H), 1.95-1.60 (m, 4H), 1.60-1.25 (m, 6H) 0.94 (s, 3H). ^{13}C ($CDCl_3$ 50MHz): 153.6, 152.0, 141.1, 138.1, 132.1, 126.5, 123.9, 115.3, 112.8, 97.6, 80.4, 76.3, 49.9, 47.7, 43.6, 39.4, 39.1, 38.9, 33.2, 29.6, 27.2, 26.4, 22.9, 14.1, 12.9.

17 -[6-(Chloro-pyridin-3-yl-(E)-ethenyl)]-estra-1,3,5(10)-triene-3,17 -diol (9b): A mixture of **8b** (200 mg, 0.58 mmol) and CsF (222 mg, 1.46 mmol) were stirred under vacuum for 30 min. To the above material, **6** (174 mg, 0.72 mmol) and tetrakis(triphenylphosphine)palladium(0) (68 mg, 0.058 mmol) were added and the contents were dissolved in DME (5 mL). The reaction mixture was heated at 90 °C for 18 h. The mixture was filtered, and rinsed with CH_2Cl_2. The solvents were removed in vacuo and the residue chromatographed (50% EtOAc / Hex) to yield **9b** (195 mg, 84%) as a white solid. Mp: 229-228°C. IR (KBr): 3292, 2923, 1585, 1461, 1023 cm^{-1}. ^1H (DMSO, 200 MHz,): 9.00 (s, 1H,), 8.45 (d, *J* = 4 Hz, 1H), 8.00 (dd, *J* = 2 Hz, *J* = 8 Hz, 1H), 7.41 (d, *J* = 8 Hz, 1H), 6.99 (d, *J* = 8 Hz, 1H), 6.85-6.35 (m, 4H),4.79(s,1H), 2.35-1.20 (m, 11H), 2.69 (s, 2H), 0.85 (s, 3H). ^{13}C (DMSO, 50 MHz,): 154.8, 154.7, 148.1, 147.8, 140.8, 137.1, 136.2, 132.5, 130.5, 125.8, 123.9, 121.0, 114.9,

112.6, 82.8, 48.7, 47.2, 43.1, 36.3, 32.3, 29.2, 27.1, 26.1, 23.1, 14.2. Anal. Calcd. for $C_{25}H_{28}ClNO_2$: C, 73.28; H, 6.88; N, 3.42. Found: C, 72.94; H, 7.08; N, 3.34.

General Procedure (Table 1): A Schlenk tube was charged with $Pd_2(dba)_3$ 1,1'-*bis*-(diphenylphosphanyl) ferrocene (dppf), di-*tert*-butyl hydrazodiformate **10** and aryl substrate **11a-11i** in a dry box. The tube was purged with argon and toluene (2 mL) was added. The reaction mixture was heated at 100 ^{0}C with stirring until the hydrazine derivative had been consumed, as judged by TLC. The reaction mixture was cooled, diluted with CH_2Cl_2, washed with water and concentrated under vacuum. The crude residue was purified by silica gel chromatography.

N,N'-Bis-*tert*-butoxycarbonyl-(pyridin-2-yl)-hydrazine (12a): The general procedure was followed with 2-bromopyridine **11b** (474 mg, 3 mmol), **10** (560 mg, 2.4 mmol), $Pd_2(dba)_3$ (109 mg, 0.12 mmol) dppf (200 mg, 0.36 mmol, 12 mol %), Cs_2CO_3 (1.05 g, 3 mmol). Column purification (20% EtOAc / Hex) gave (630 mg, 85%) of the coupled product **7a** as a white solid. Mp:: 80-82 ^{O}C. IR (KBr): 3171, 2975, 1731, 1595, 855, 771, cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): 8.58 (s, 1H), 8.34 (d, *J* = 4 Hz, 1H), 7.62 (m, 2H), 7.00 (dd, *J* = 8, 4 Hz, 1H), 1.40 (s, 9H), 1.36 (s, 9H). ^{13}C NMR ($CDCl_3$, 50 MHz): 154.9, 153.5, 153.1, 147.3, 137.3, 120.3, 118.7, 82.1, 80.7, 27.9, 27.8. FAB MS (M+1) calcd. for $C_{15}H_{23}N_3O_4$: .310.1766. Found: 310.1766.

N,N'-Bis-*tert*-butoxycarbonyl-(pyrazin-2-yl)-hydrazine (12d): The general procedure was followed with iodopyrazine **11d** (206 mg, 1 mmol), $Pd_2(dba)_3$ (37 mg, 0.04 mmol), dppf (67 mg, 0.12 mmol), Cs_2CO_3 (352 mg, 1 mmol), and **10** (186 mg, 0.8 mmol). Column purification (20% EtOAc / Hex) gave (210 mg, 85% yield) of the coupled product **12c** as a white solid. Mp: 102 °C. IR (KBr) 3191, 2998, 1737, 1347, 1020 cm^{-1}. ^{1}H ($CDCl_3$, 200 MHz): 9.12 (s, 1H), 8.35 (d, *J* = 2 Hz, 2H), 7.82 (s, 1H), 1.54 (s, 9H), 1.47 (s, 9H). ^{13}C ($CDCl_3$, 50 MHz,): 154.7, 152.6, 150.4, 141.5, 140.1, 139.9, 83.4, 81.5, 28.0, 27.91 Anal. Calcd. for $C_{14}H_{22}N_4O_4$: C, 54.18; H, 7.15; N, 18.05. Found: C, 54.20; H, 7.40; N, 18.03.

N,N'-Bis-*tert*-butoxycarbonyl-(pyridin-4-yl)-hydrazine (12e): The general procedure was followed with 4-bromopyridine hydrochloride **11e** (195 mg, 1 mmol), **10** (187 mg, 0.8 mmol), $Pd_2(dba)_3$ (37 mg, 0.04 mmol), DPPF (67 mg, 0.12 mmol), Cs_2CO_3 (704 mg, 2 mmol). Column purification (50% EtOAc / Hex) gave (200 mg, 80%) the coupled product **12e** as a white solid. IR (KBr) 3176, 2977, 1744, 1595, 839, 765 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): 8.50 (d, *J* = 4.0 Hz, 1H), 7.95 (s, 1H), 7.50 (d, *J* = 4 Hz, 2H),6.65(s,1H), 1.54 (s, 9H), 1.52(s,9H). ^{13}C ($CDCL_3$, 50 MHz): 155.0, 152.2, 149.9, 149.2, 114.2, 83.5, 81.9, 28.9 ppm.

N,N'-Bis-*tert*-butoxycarbonyl-(6-nitro-pyridin-3-yl)-hydrazine (12i). The general procedure was followed with 5-Bromo-2-nitro-pyridine **11i** (406 mg, 2 mmol), **10** (371 mg, 1.6 mmol), $Pd_2(dba)_3$ (73 mg, 0.08 mmol), dppf (133 mg, 0.24 mmol), Cs_2CO_3 (650 mg, 2.2 mmol). After 18 hrs. the reaction mixture was cool to r.t. diluted with CH_2Cl_2, filtered through celite and washed with H_2O. Solvent was dried over Na_2SO_4 and volatiles were removed in vacuo. Flash chromatography (20% EtOAc / Hex) was used to separate the most polar impurities from the resulting red solid. Column eluent was concentrated and the residual dissolved in a minimal volume of EtOAc. Hexanes were added until the solution began to cloud. Upon cooling to 0 C, a yellow solid crystallized from the solution that was collect by filtration and washed with cold hexanes. The solid was dried under vacuum yielding (188 mg, 33%) **12i** as a yellow solid. Mp: 121.0-122.3. IR (KBr) 3191, 2987, 1746, 1574, 1546, 1476, 1305, 1168 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): 8.79 (s, 1H), 8.23 (s, 2H), 7.16(s, 1H), 1.54 (s, 9H), 1.52(s, 9H). ^{13}C ($CDCl_3$, 100 MHz): 154.9, 151.9, 143.7, 140.7, 130.3, 118.1, 84.7, 82.9, 28.04, 27.92.

N,N'-Bis-*tert*-butoxycarbonyl-(4-nitro-phenyl)-hydrazine (15): The general procedure was followed with 1-bromo-4-nitrobezene **14** (150 mg, 0.74 mmol), **10** (172 mg, 0.74 mmol), $Pd_2(dba)_3$ (27 mg, 0.03 mmol), dppf (49 mg, 0.09 mmol), Cs_2CO_3 (268 mg, 0.82 mmol). Column chromatography (15% EtOAc / Hex) yielded (166 mg, 80%) **15** as a white solid. Mp: 121-122 C. IR (KBr) 3325,

2982, 1736, 1595, 856 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): 8.14 (d, *J* = 8.8 Hz, 2H), 7.66 (d, *J* = 8.8, 2H), 7.12 (s, 1H) 1.53 (s, 9H), 1.52 (s, 9H). ^{13}C ($CDCl_3$, 100 MHz): 155.0, 152.4, 147.6, 143.6, 123.9, 121.1, 83.6, 82.2, 28.0, 27.9.

2-Chloro-5-hex-1-ynyl-pyridine (21). $Pd(OAc)_2$ (22.4 mg, 0.1 mmol), PPh_3 (38 mg, 0.2 mmol) , and Et_2NH (2 mL) were charged into a two-neck flask and the suspension stirred for ten min. CuI (38mg, 0.2 mmol) and **5** (479 mg, 2mmol) were added, then after ten min 1-hexyne (0.23mL, 2mmol) was added and the reaction was stirred at rt overnight. Volatiles were removed under vacuum and the residue was dissolved in EtOAc, filtered through celite, washed with water, dried over Na_2SO_4 and concentrated under vacuum. The product was chromatographed (5%EtOAc / Hex) to yield (384mg, 90%) **21** as a colorless oil. IR (neat): 2959, 2933, 2234, 1581, 1545, 1456, 1358, 1135, 1109, 1025, 833 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): 8.39 (d, *J* = 2.4 Hz, 1H), 7.61 (dd, *J* = 2.4, 8.4 Hz, 1H), 7.24 (d, *J* = 8.4 Hz, 1H), 2.42(t, *J* = 7 Hz, 2H), 1.57(m, 2H), 1.46 (m, 2H), 0.95 (t, *J* = 7.2 Hz, 3H). ^{13}C ($CDCl_3$, 100 MHz): 151.8, 149.4, 140.7, 123.4, 119.9, 95.1, 75.9, 30.3, 21.8, 18.9, 13.4.

N,N'-Bis-*tert*-butoxycarbonyl-(5-Hex-1-ynyl-pyridin-2-yl)-hydrazine (22) A Schlenk tube was charged with **10** (225mg, 0.97 mmol) and **21** (235mg, 1.2 mmol). $Pd_2(dba)_3$ (44mg, 0.048 mmol), dppf (80 mg, 0.144 mmol) and Cs_2CO_3 (423 mg, 1.3 mmol) were added in a dry box. The tube was purged with argon and toluene (2.5 mL) was added. The reaction mixture was heated at 100 ^{0}C with stirring for 19 h. The reaction mixture was cooled, diluted with EtOAc, filtered through celite, washed with water, dried over Na_2SO_4 and concentrated under vacuum. The crude residue was purified by flash chromatography (20% EtOAc / Hex) to give (252 mg 67%) **22** as a colorless oil. IR (neat): 3331, 3191, 2979, 2361, 2254, 1724, 1716, 1482, 1176 cm^{-1}. 1H NMR ($CDCl_3$, 400 MHz): 8.57(s, 1H), 8.42 (s, 1H), 7.71 (d, *J* = 8 Hz, 1H), 7.65 (d *J* = 8Hz, 1H), 2.42 (t, *J* = 7.4Hz, 2H), 1.62-1.45 (m, 22H), 0.95 (t *J* = 7.3Hz, 3H). ^{13}C ($CDCl_3$, 100 MHz): 154.9, 152.9, 151.9 150, 139.8, 117.6, 93.2, 82.5, 80.9, 76.9, 30.5, 28.1, 27.9, 21.8, 19.0, 13.5.

2-Chloro-5-styryl-pyridine (23). *Trans*-vinylphenyl boronic acid (326 mg, 2.2 mmol), **5** (479mg, 2.0 mmol), $Pd(OAc)_2$ (45 mg, .0.2 mmol) tetrabutyl ammonium bromide (645 mg, 2 mmol), and K_2CO_3 (529 mg, 5 mmol) were suspended in degassed H_2O (2 mL) under argon. The mixture was heated to reflux for 16 hrs. Water (10 mL) was added, and extracted three times with CH_2Cl_2 (3 x 30 mL). The combined extracts were concentrated under vacuum and purified by silica gel column chromatography (5% EtOAc / Hex) to give (220mg, 51%) **23** as a white solid. Mp: 84–85 C. IR (KBr): 3434, 3029, 2362, 1553, 1459, 1372, 1146, 1099, 962 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): 8.38 (d, *J*=2.8 Hz, 1H), 7.67 (dd, *J*=2.8, 8.4 Hz, 1H), 7.44 (m, 2H) 7.33 (m, 2H) 7.28 (m, 1H) 7.22 (d, *J*=8.2 Hz, 1H), 7.03 (d, *J*=16.4 Hz, 1H), 6.91 (d, *J*=16.4 Hz, 1H). ^{13}C ($CDCl_3$, 100 MHz): 149.5, 147.8, 135.9, 134.9, 131.7, 130.1, 128.5, 128.16, 126.4, 123.9, 123.0.

N,N'-Bis-*tert*-butoxycarbonyl-(5-styryl-pyridin-2-yl) hydrazine (24). A Schlenk tube was charged with **10** (129mg, 0.56 mmol), **23** (150mg, 0.7 mmol). $Pd_2(dba)_3$ (26mg, 0.028 mmol), dppf (47 mg, 0.084 mmol), Cs_2CO_3 (247 mg, 0..76 mmol), and toluene (1.5 mL). The reaction mixture was heated at 100 ^{0}C with stirring for 29 hrs. The reaction mixture was cooled, diluted with EtOAc, filtered through celite ,washed with water, dried over Na_2SO_4 and concentrated under vacuum. The crude residue was purified by flash chromatography (30% EtOAc / Hex) to yield (130 mg, 57%) **24** as a white solid. IR (KBr): 3347, 2978, 2935, 1728, 1481, 1369, 1343, 1296, 1248, 1156 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): 8.47 (d *J* = 2.0 Hz, 1H), 7.86 (dd, *J* = 8.6, 2 Hz, 1H), 7.52 (m, 2H), 7.37(m, 2H), 7.29(m, 2H), 7.11(d, *J* = 16.4 Hz, 1H), 7.04(d, *J* = 16.4 Hz, 1H), 1.54 (s, 9H), 1.48(s, 9H). ^{13}C NMR ($CDCl_3$, 400 MHz): 155.0, 153.1, 152.6, 146.2, 136.6, 134.1, 130.0, 128.7, 127.5, 126.5, 124.2, 118.4, 82.6, 81.1, 28.

17 -[6-(Hydrazino-pyridin-3-ylethynyl)]-estra-1,3,5(10)-triene-3,17 -diol hydrochloride (25). Compound **1** (125 mg, 0.2 mmol) was dissolved in absolute ethanol (4 mL) and cooled to 0 C. To the stirred solution was added con. HCl (1 mL) dropwise over 2 min, then stirred at room temperature for

6 h. The volume of the solvent was decreased under vacuum to 1.0 mL and cold H_20 (45 mL) was added to precipitate a yellow solid that was collected by vacuum filtration. The solid was dried and residual water was removed under high vacuum affording (84mg, 95%) of **25**. IR (KBr): 3300-2200 (br), 1658 cm^{-1}. ^1H NMR (10%DMSO/$CDCl_3$, 400MHz): 7.96 (d, *J* = 2 Hz, 1H), 7.63 (dd, *J* = 2, 9.2 Hz, 1H), 7.22 (d, *J* = 9.2 Hz, 1H), 7.11 (d, *J* = 8 Hz, 1H), 6.63 (dd, *J* = 2.4, 8 Hz, 1H), 6.56 (d, *J* = 2.4 Hz, 1H) 4.55(s, 4H), 2.79 (m, 2H), 2.33 (m, 2H) 2.21-2.03 (m, 2H) 1.83 (m, 2H) 1.66 (m, 2H), 1.5-1.25 (m, 4H), 0.89(s, 3H). ^{13}C (DMSO, 100MHz): 154.96, 154.95, 148.3, 140.7, 137.1, 130.2, 126.1, 114.9, 112.8, 111.8, 109.3, 96.29, 80.9, 78.7, 49.4, 47.2, 43.3, 34.2, 32.9, 29.2, 27.0, 26.3, 22.6, 12.9.

17 -[6-(Hydrazino-pyridin-3-yl-(E)-ethenyl)]-estra-1,3,5,16(8)-tetraene-3-ol hydrochloride (26). Compound **2** (100 mg, 0.165mmol) was dissolved in EtOAc (1.5mL). To the stirred solution was added con. HCl (0.5 mL) dropwise over 1 min, then stirred for 2 h in which time the product precipitated out of solution. The solid was dried under high vacuum and triturated with Et_2O (10 mL). Drying under high vacuum yielded **26** (67.6 mg, 97%) as a yellow solid. IR (KBr): 3300-2200 (br) 1658 cm^{-1}. ^1H NMR (10%DMSO / $CDCl_3$, 400 MHz): 7.89(dd, *J* = 9.6, 1.2Hz, 1H), 7.73(d, *J* = 1.2Hz, 1H), 7.32(d, *J* = 8Hz, 1H), 7.10 (d, *J*=8 Hz, 1H), 6.60(m, 4H), 5.94(t, *J* = 3.2Hz, 1H), 2.84(s, 2H), 2.32(m 4H), 2.04(m,2H), 1.89(m, 2H), 1.69(m, 4H) 1.43(m,2H) 1.25(m, 1H) 0.96(s, 3H). ^{13}C NMR (DMSO, 100 MHz): 155.0, 154.1, 152.5, 146.4, 140.3, 137.0, 136.0, 130.3, 125.7, 125.2, 124.1, 122.3, 115.0, 112.8, 110.5, 56.1, 46.1, 43.7, 36.9, 34.8, 30.8, 29.1, 27.3, 26.3, 16.0.

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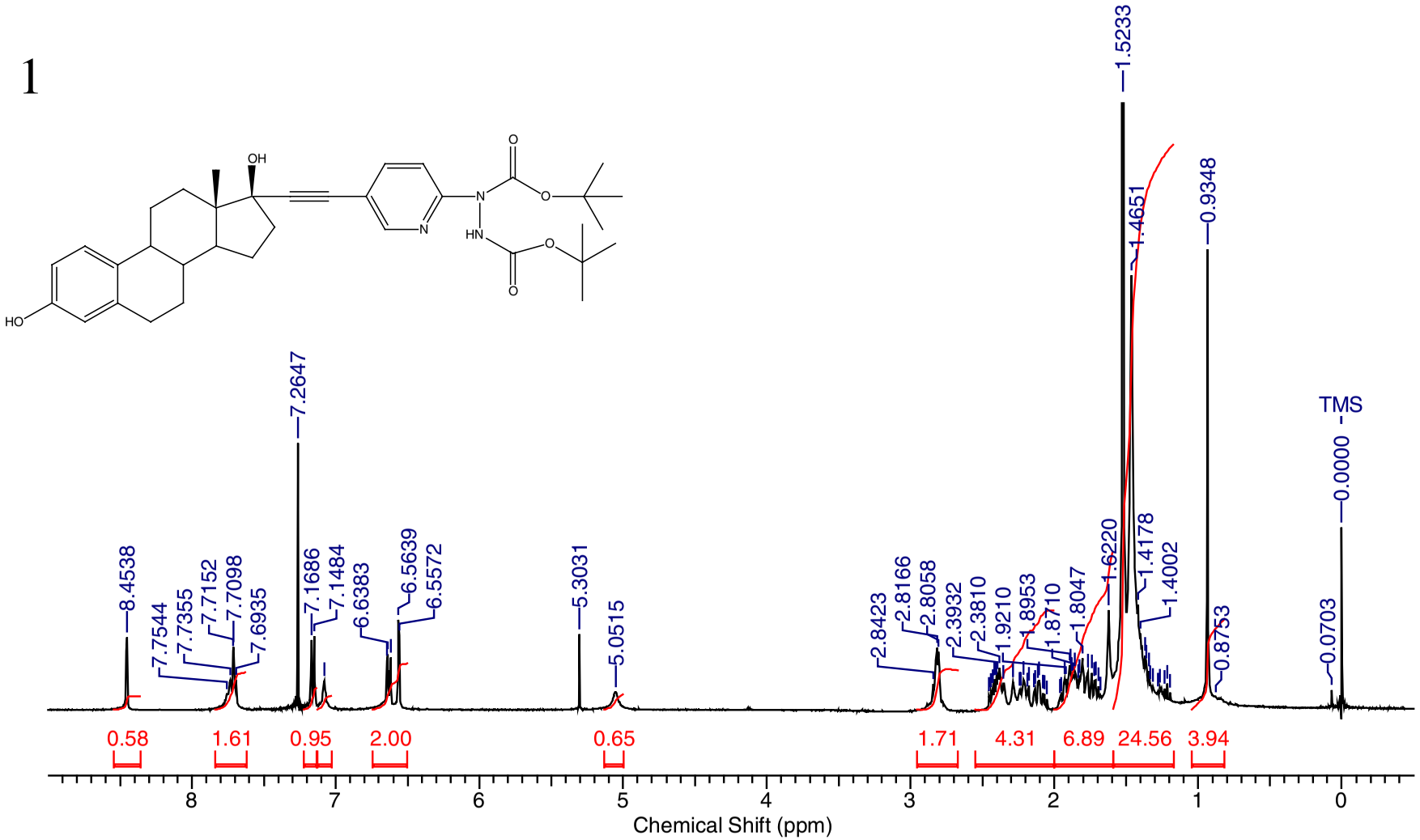
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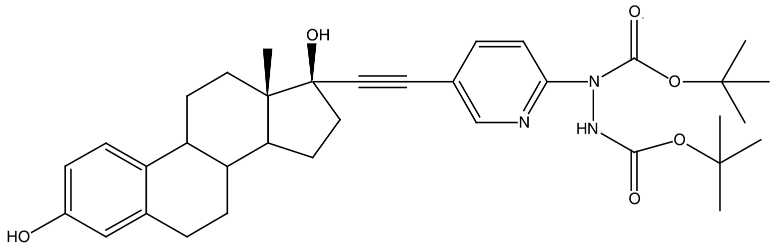

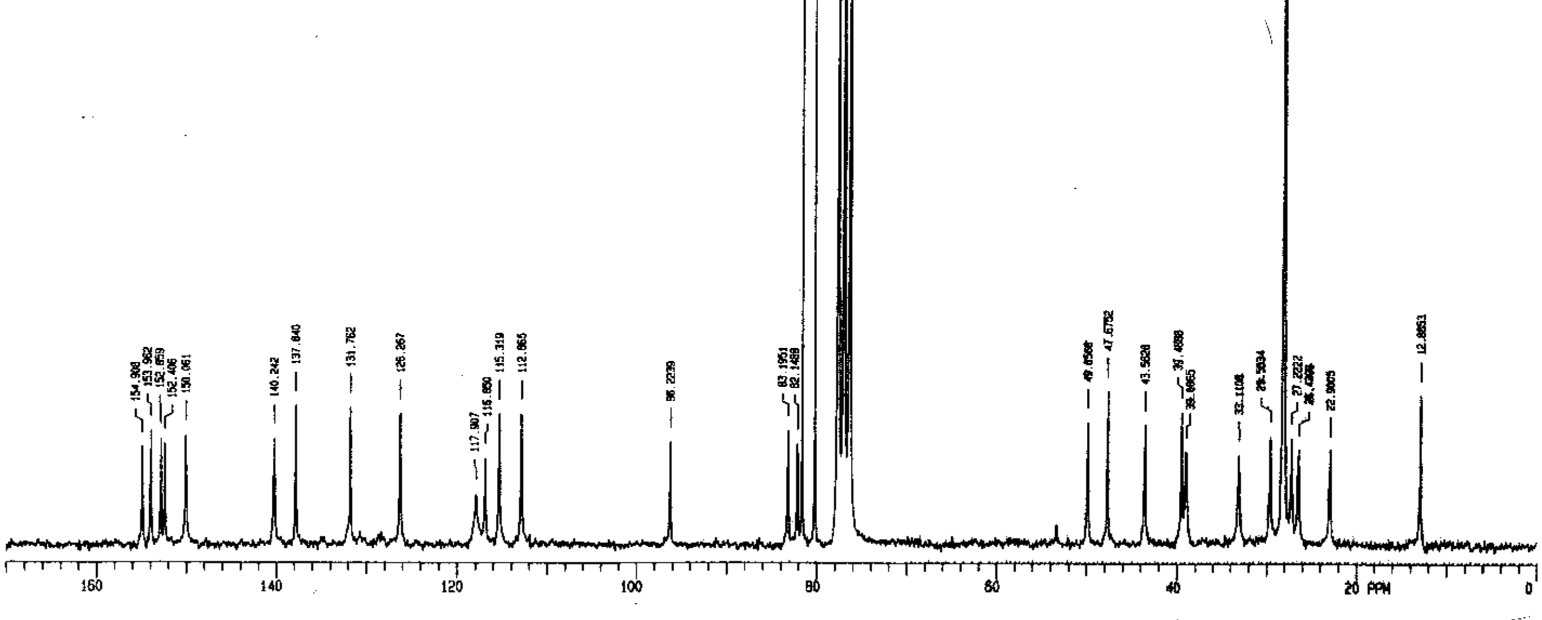

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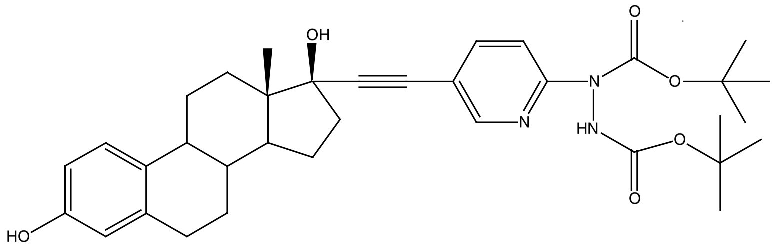
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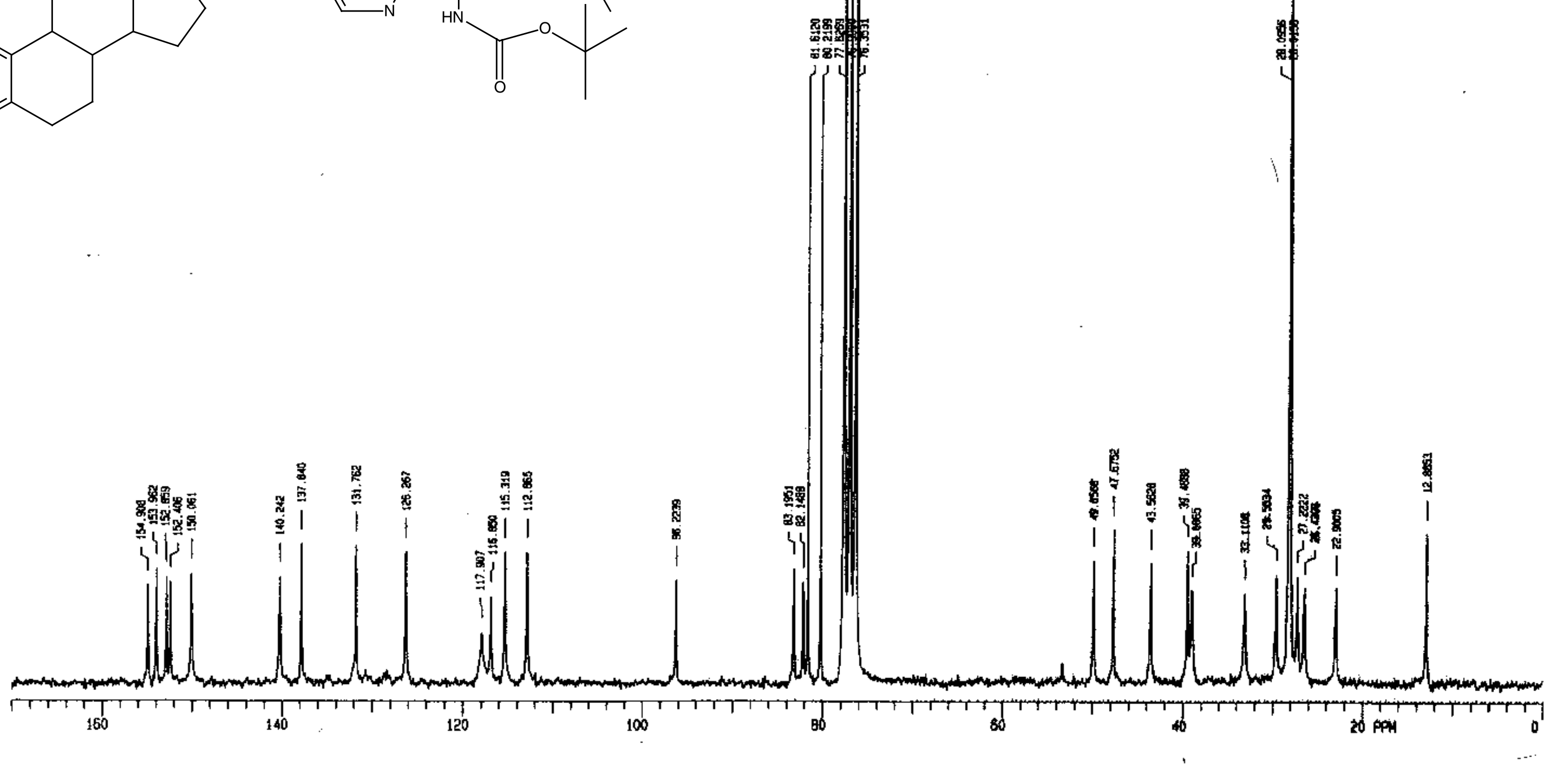
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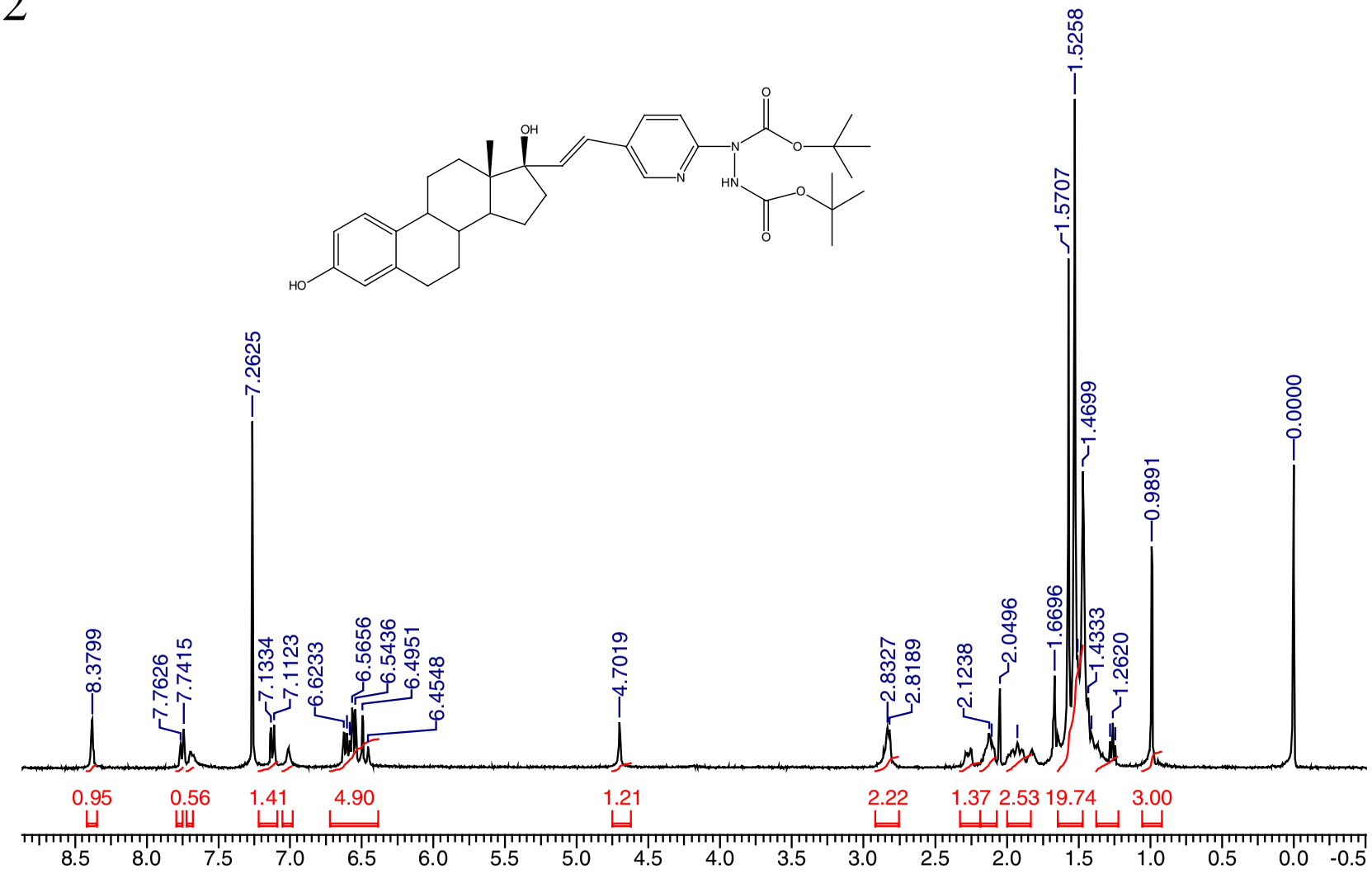
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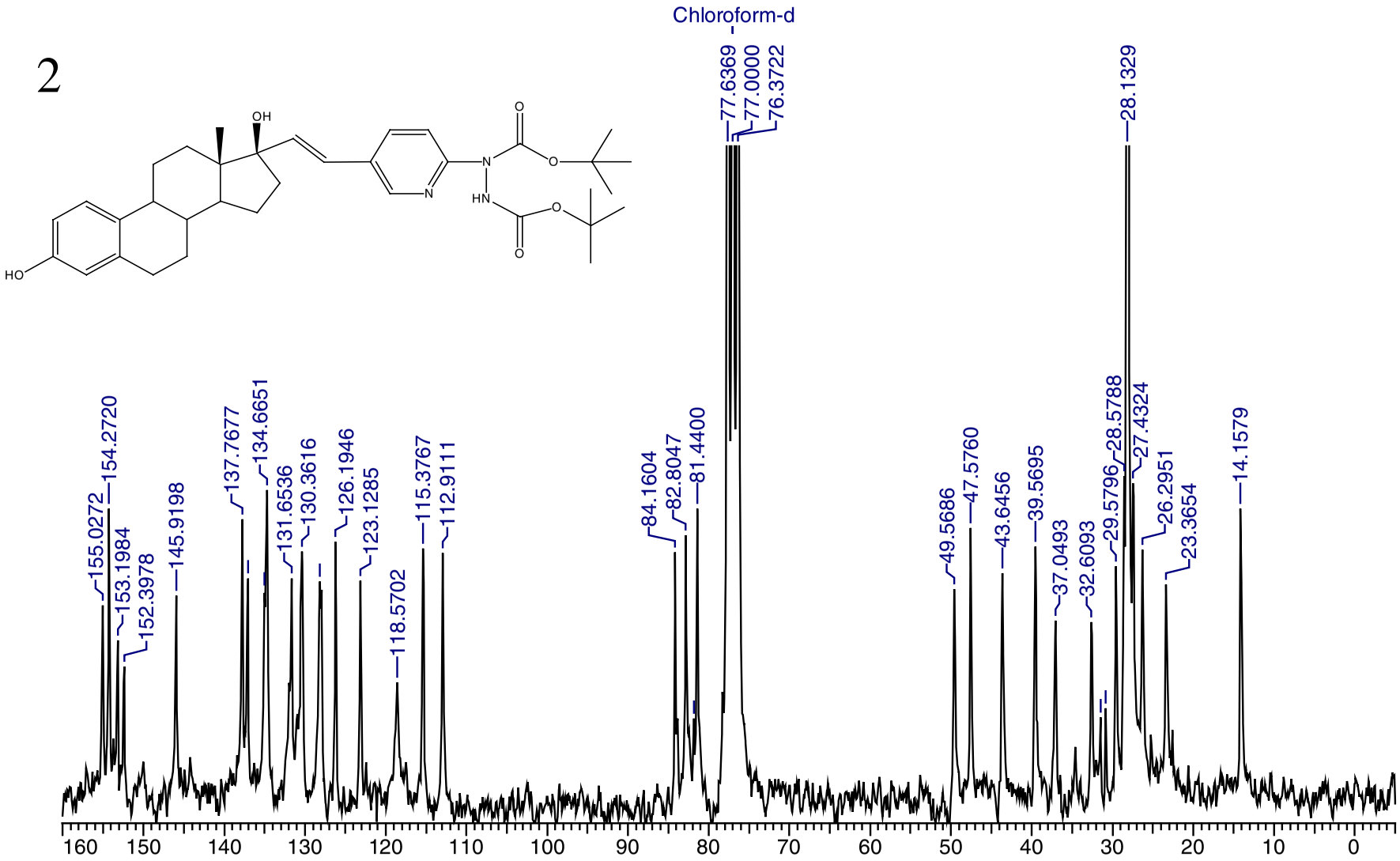
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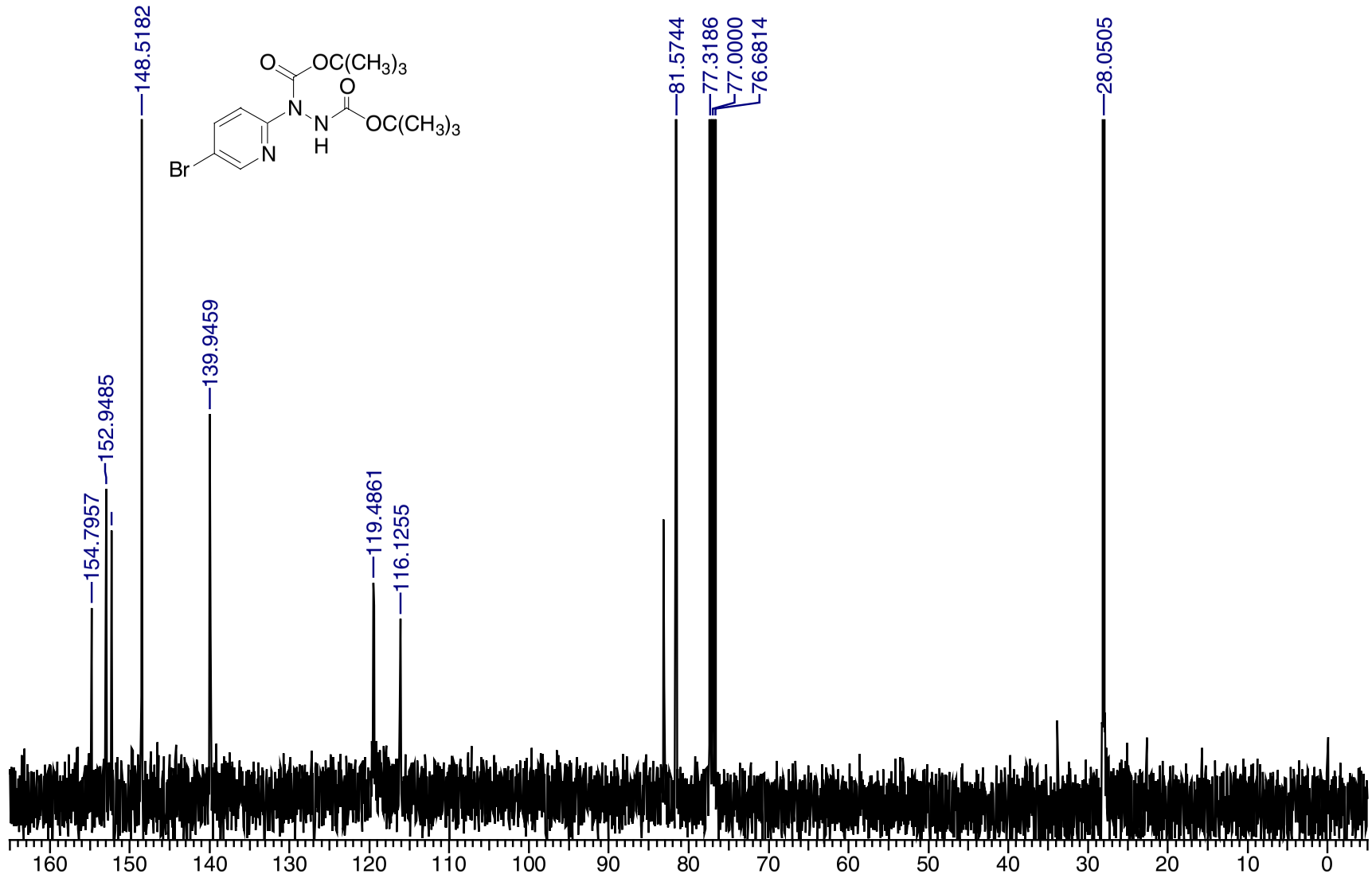
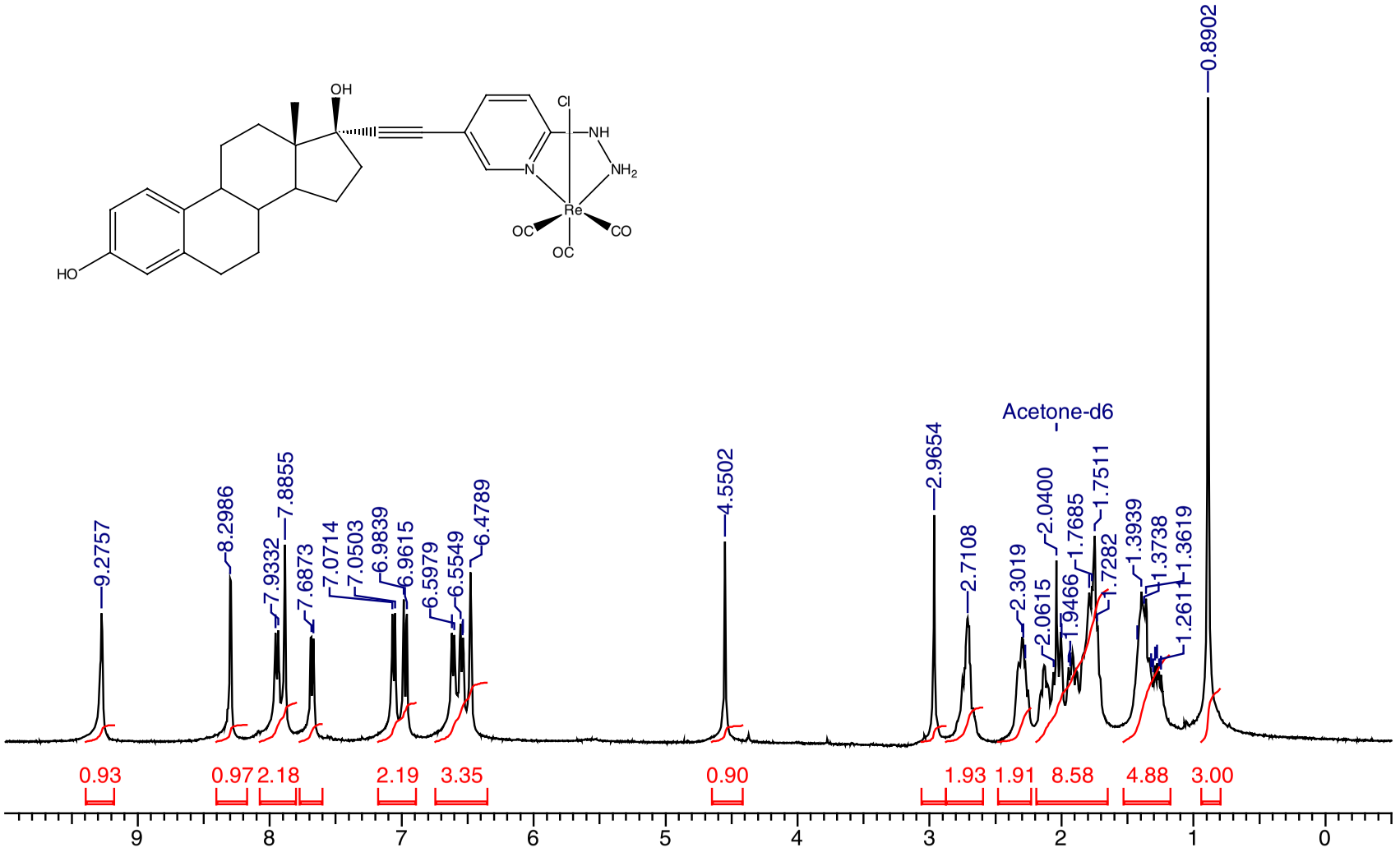
155.0272
154.2720
153.1984
152.3978
145.9198
137.7677
134.6651
131.6536
130.3616
126.1946
123.1285
118.5702
115.3767
112.9111
84.1604
82.8047
81.4400
49.5686
47.5760
43.6456
39.5695
37.0493
32.6093
29.5796
28.5788
27.4324
26.2951
23.3654
14.1579
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

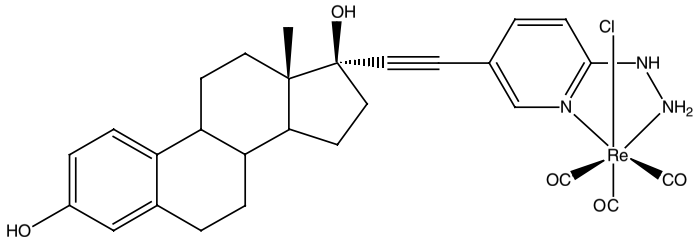
3


148.5182
81.5744
77.3186
77.0000
76.6814
28.0505
139.9459
154.7957
152.9485
119.4861
116.1255
O
OC(CH3)3
N
N
H
O
OC(CH3)3
Br
N
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

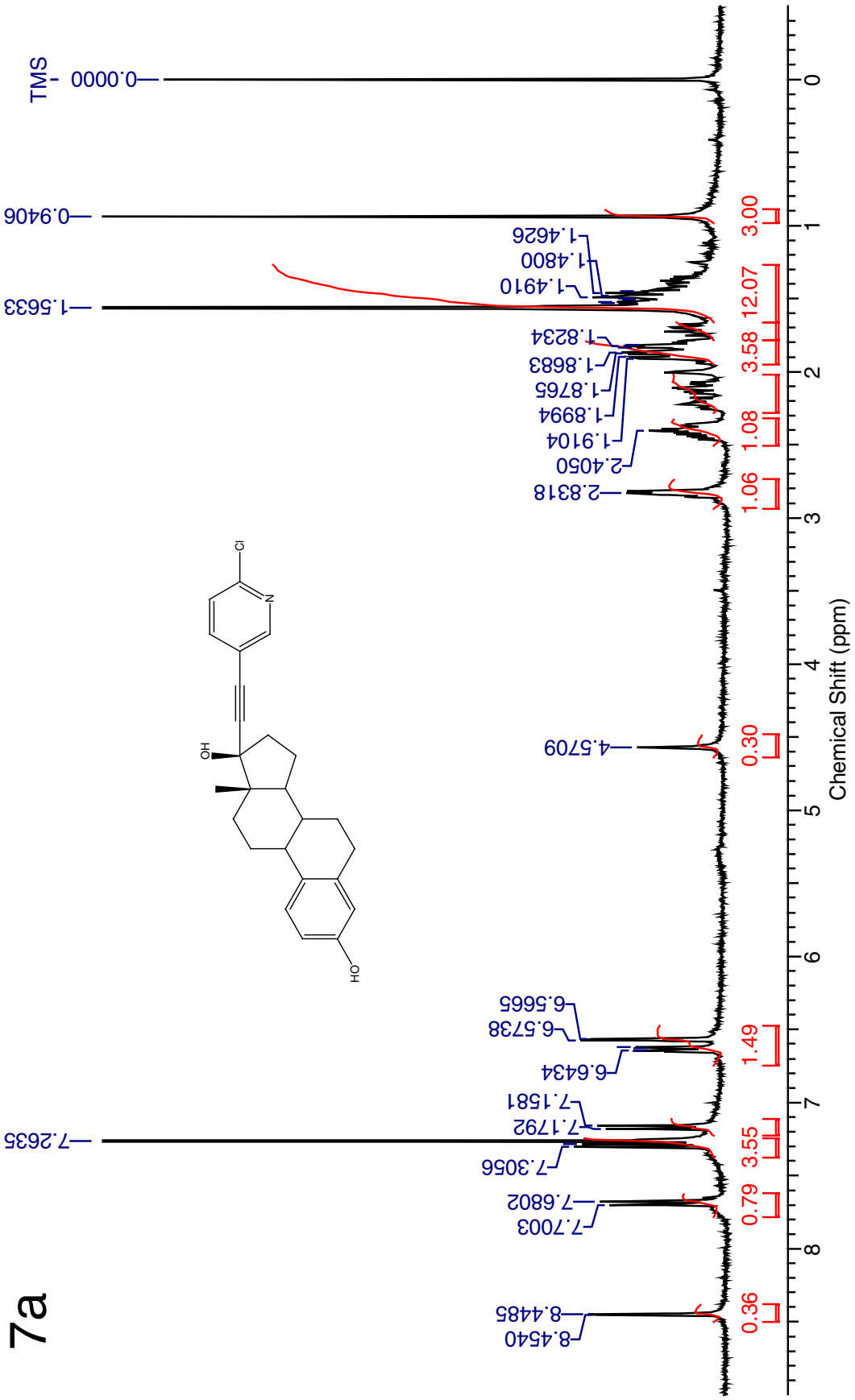
4


OH
HO
Cl
NH
NH2
N
Re
OC
CO
OC
9.2757
8.2986
7.9332
7.8855
7.6873
7.0714
7.0503
6.9839
6.9615
6.5979
6.5549
6.4789
4.5502
2.9654
Acetone-d6
2.7108
2.3019
2.0615
2.0400
1.9466
1.7685
1.7511
1.7282
1.3939
1.3738
1.3619
1.2611
0.8902
0.93
0.97
2.18
2.19
3.35
0.90
1.93
1.91
8.58
4.88
3.00
9
8
7
6
5
4
3
2
1
0

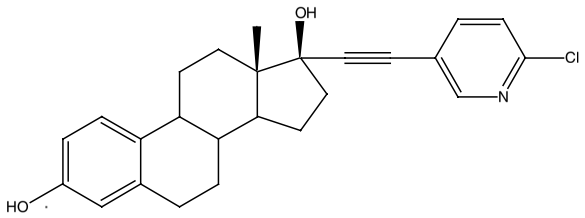
4

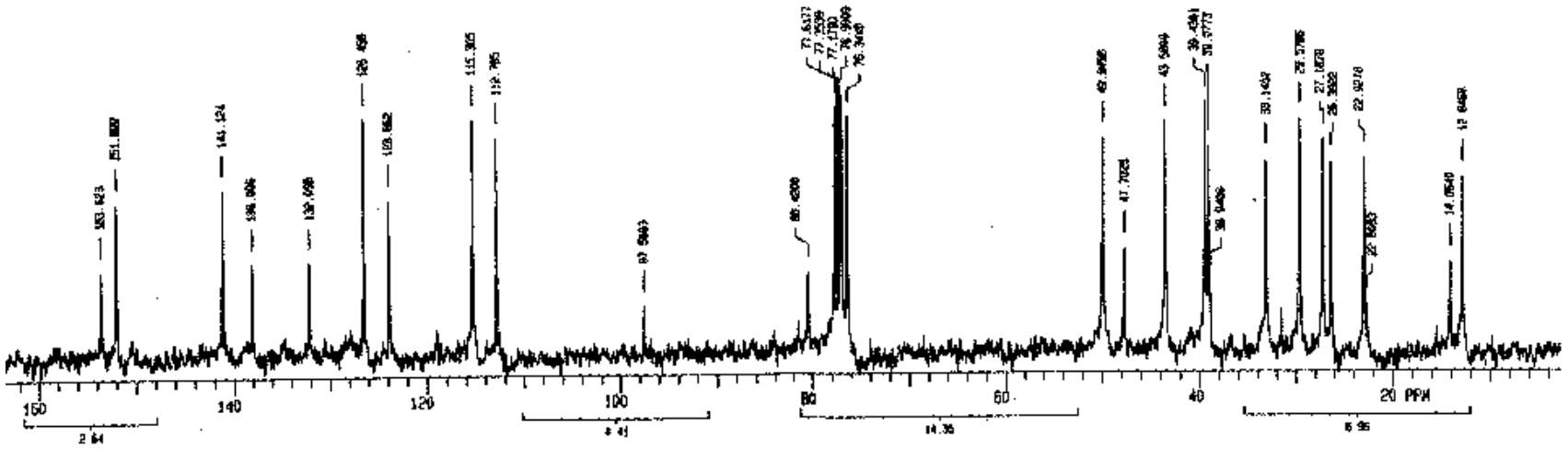

OH
HO
Cl
NH
NH2
N
Re
OC
CO
OC

Acetone-d6
30.1831
29.9897
29.8000
29.6066
29.2272
28.0893
27.3269
23.5301
13.3078
50.6277
48.3633
44.5474
40.5723
39.8668
34.0141
200.0972
198.3410
193.0952
159.6669
155.8284
152.2477
142.5488
138.3575
131.8600
127.0390
115.8798
113.5471
112.2271
108.4757
96.9524
80.7560
80.2288
200
150
100
50
0

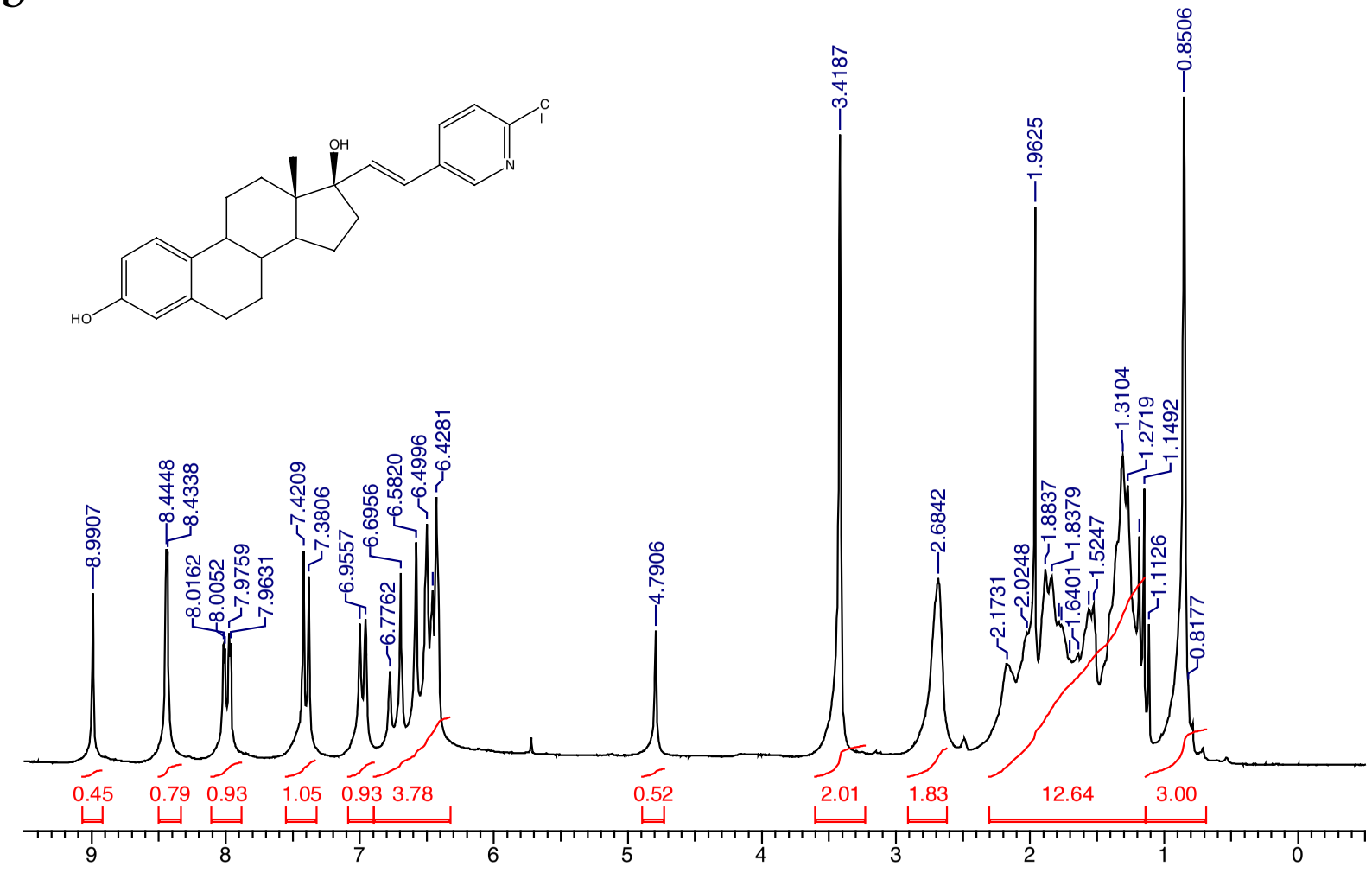

7a
TMS
0.0000
0.9406
1.5633
7.2635
8.4540
8.4485
7.7003
7.6802
7.3056
7.1792
7.1581
6.6434
6.5738
6.5665
4.5709
2.8318
2.4050
1.9104
1.8994
1.8765
1.8683
1.8234
1.4910
1.4800
1.4626
0.36
0.79
3.55
1.49
0.30
1.06
1.08
3.58
12.07
3.00
Chemical Shift (ppm)
0
1
2
3
4
5
6
7
8
Cl
N
OH
HO

7a

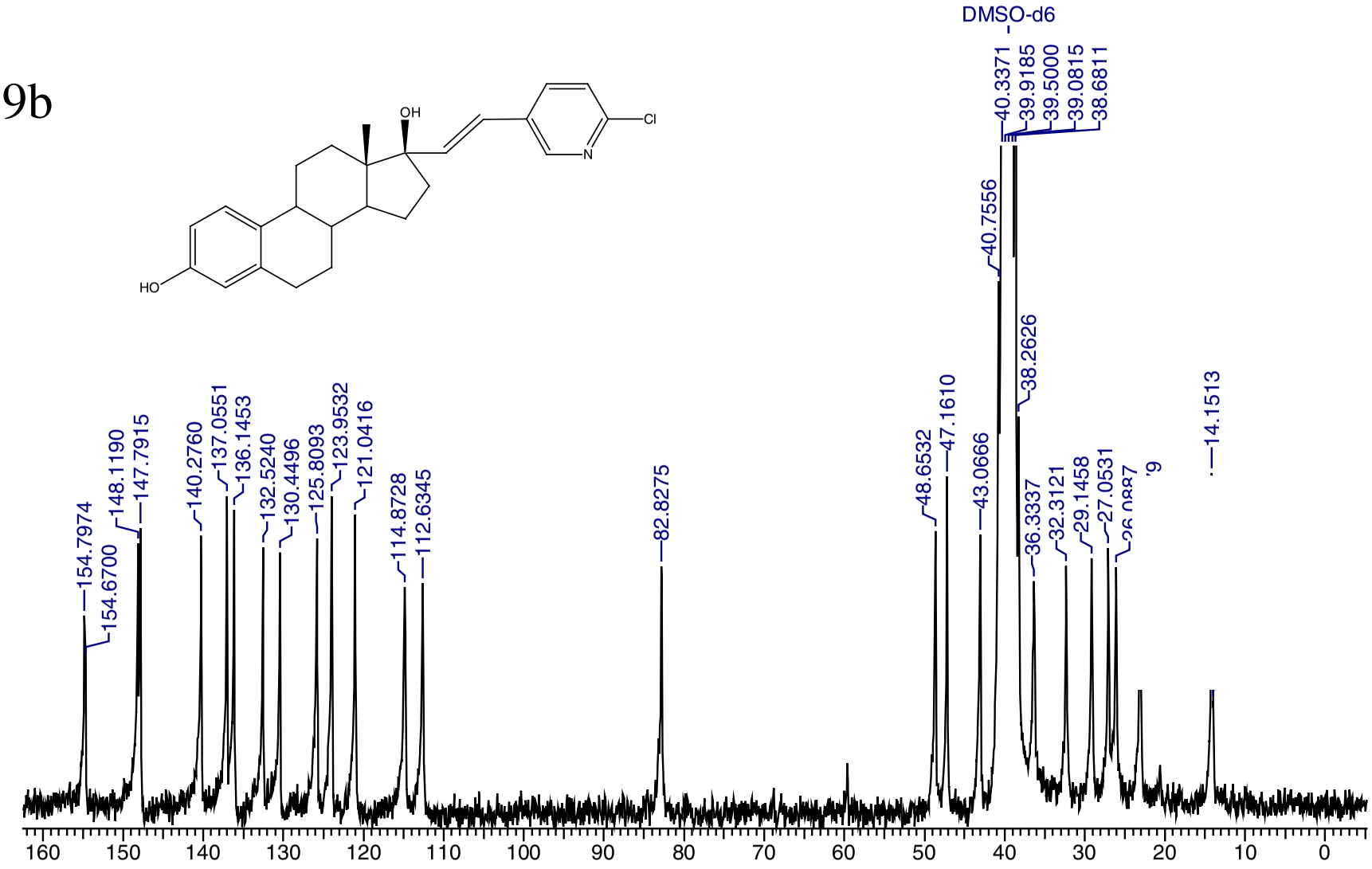




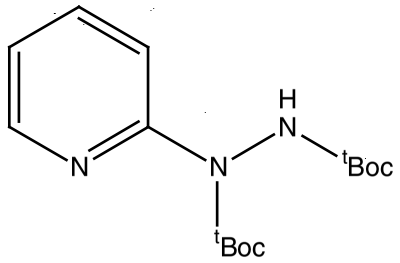
9b

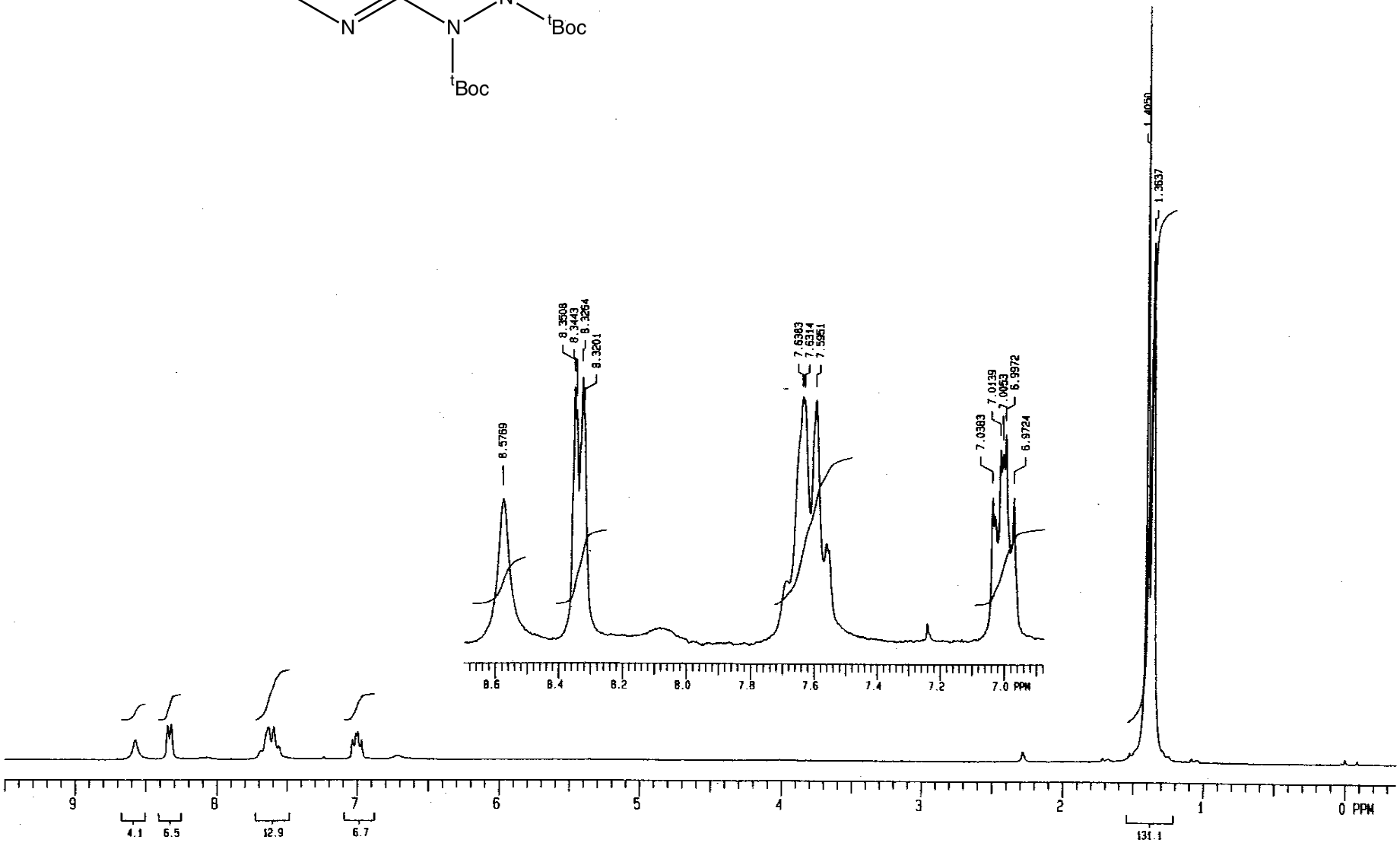

HO
OH
N
C
8.9907
8.4448
8.4338
8.0162
8.0052
7.9759
7.9631
7.4209
7.3806
6.9557
6.6956
6.7762
6.5820
6.4996
6.4281
4.7906
3.4187
2.6842
2.1731
2.0248
1.9625
1.8837
1.8379
1.6401
1.5247
1.3104
1.2719
1.1492
1.1126
0.8506
0.8177
0.45
0.79
0.93
1.05
0.93
3.78
0.52
2.01
1.83
12.64
3.00
9
8
7
6
5
4
3
2
1
0

9b

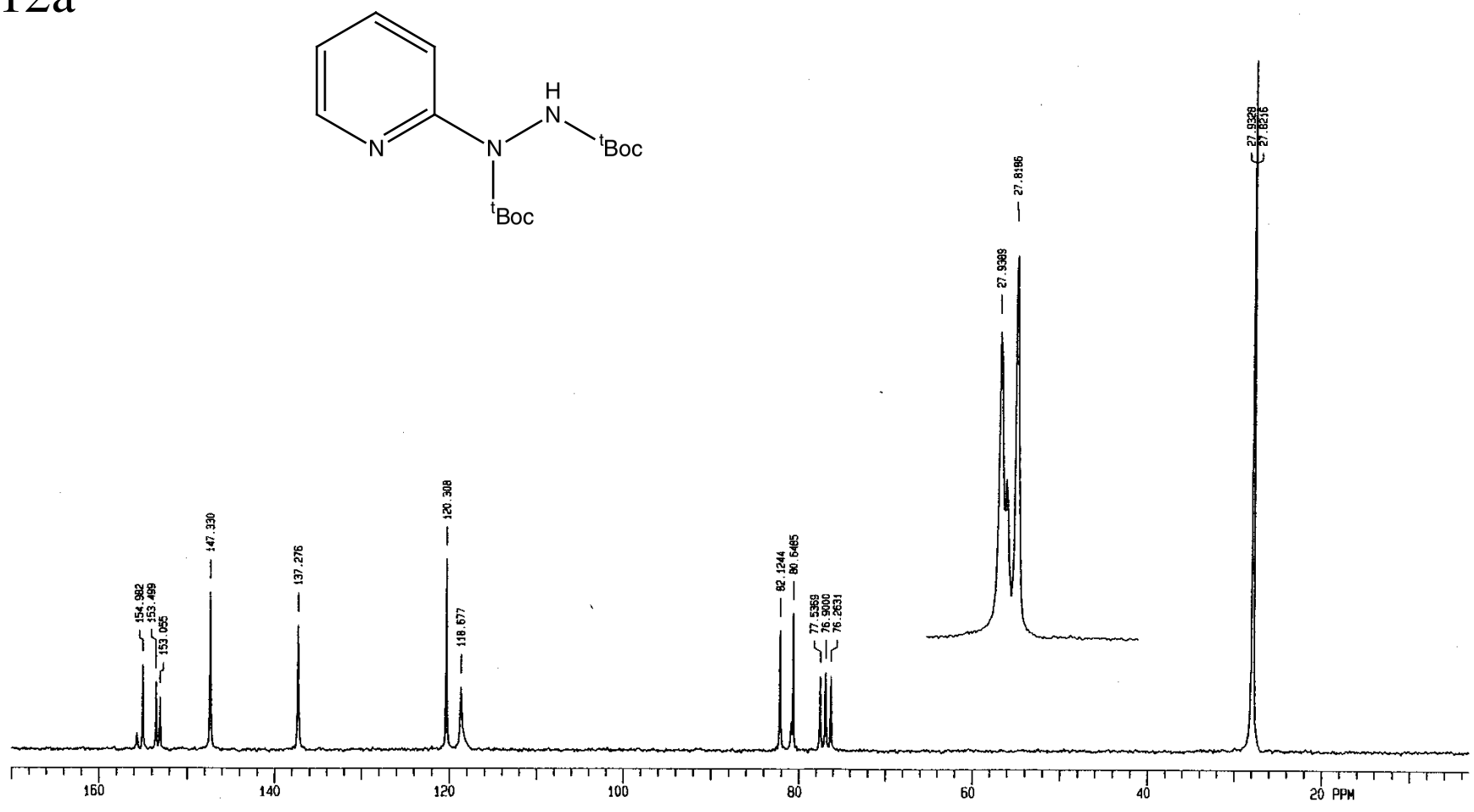

DMSO-d6
OH
Cl
N
HO
154.7974
154.6700
148.1190
147.7915
140.2760
137.0551
136.1453
132.5240
130.4496
125.8093
123.9532
121.0416
114.8728
112.6345
82.8275
48.6532
47.1610
43.0666
40.7556
40.3371
39.9185
39.5000
39.0815
38.6811
38.2626
36.3337
32.3121
29.1458
27.0531
14.1513
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

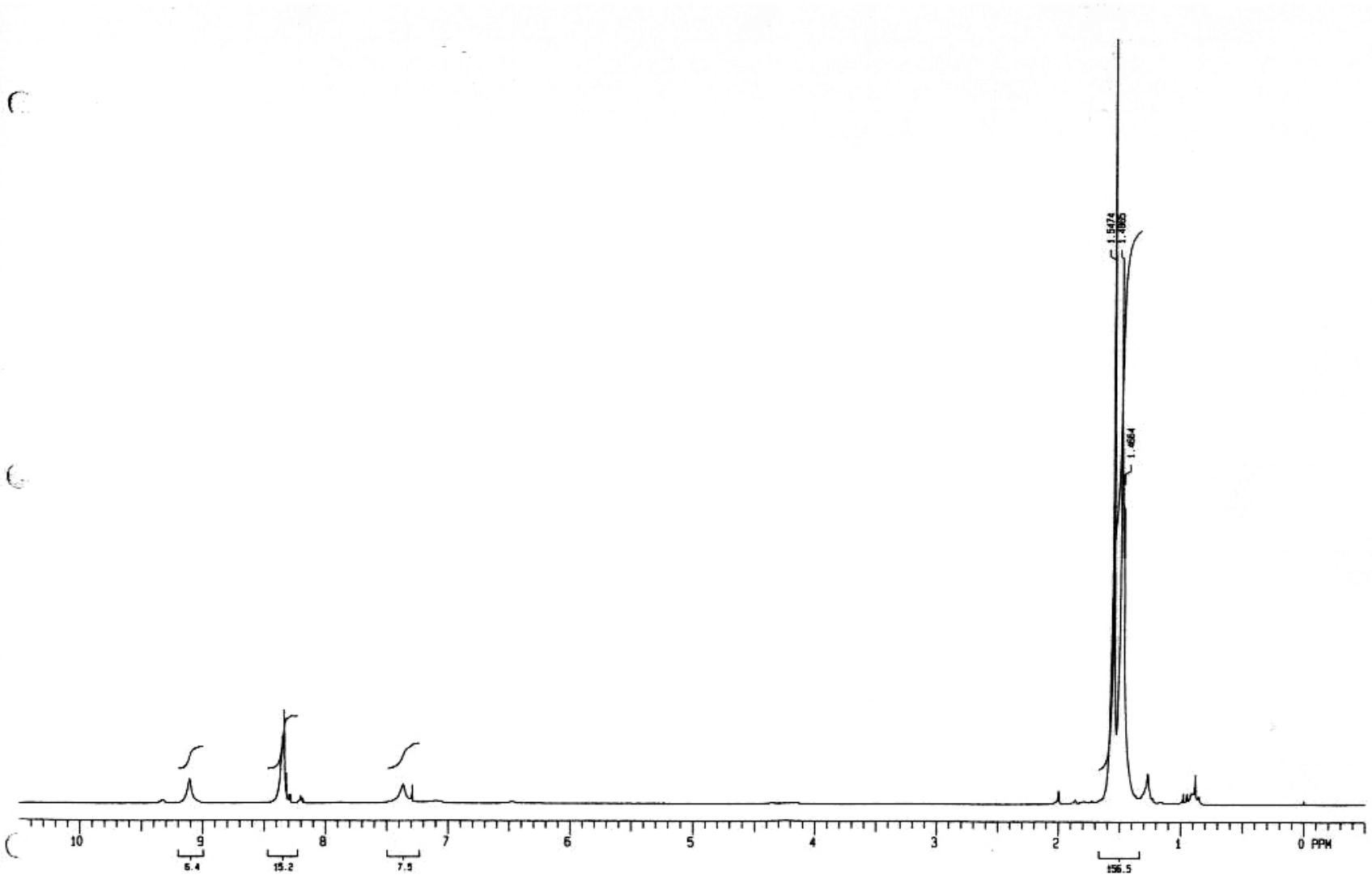
12a


H
N
N
N
tBoc
tBoc


8.5769
8.3508
8.3443
8.3264
8.3201
7.6383
7.6314
7.5951
7.0383
7.0139
7.0053
6.9972
6.9724
1.4050
1.3637
4.1
6.5
12.9
6.7
131.1
9
8
7
6
5
4
3
2
1
0 PPM

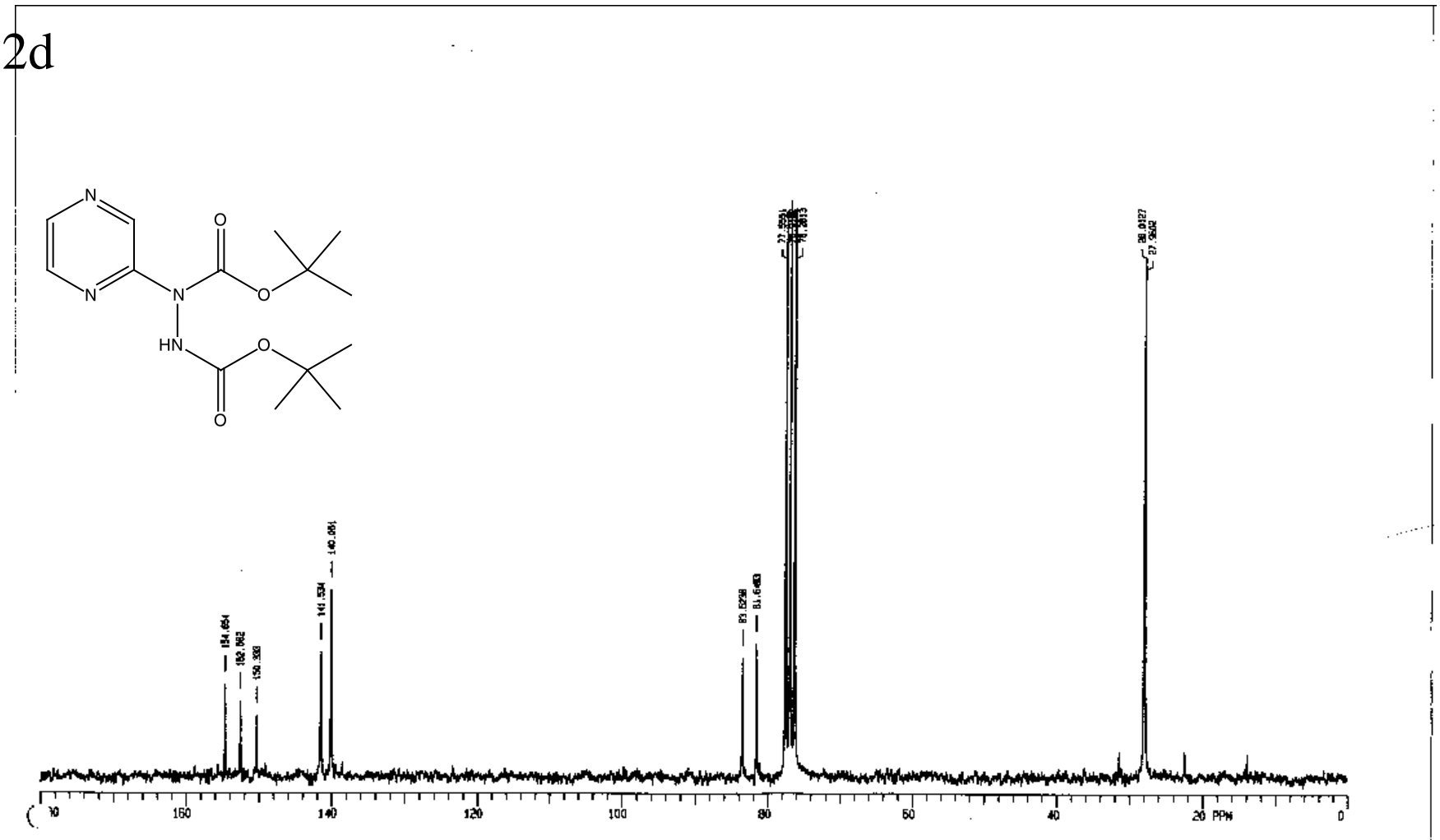
12a


H
N
N
N
tBoc
tBoc
154.982
153.499
153.055
147.330
137.276
120.308
118.677
82.1244
80.6485
77.5369
76.9000
76.2631
27.9389
27.8196
27.9389
27.8216
160
140
120
100
80
60
40
20 PPM

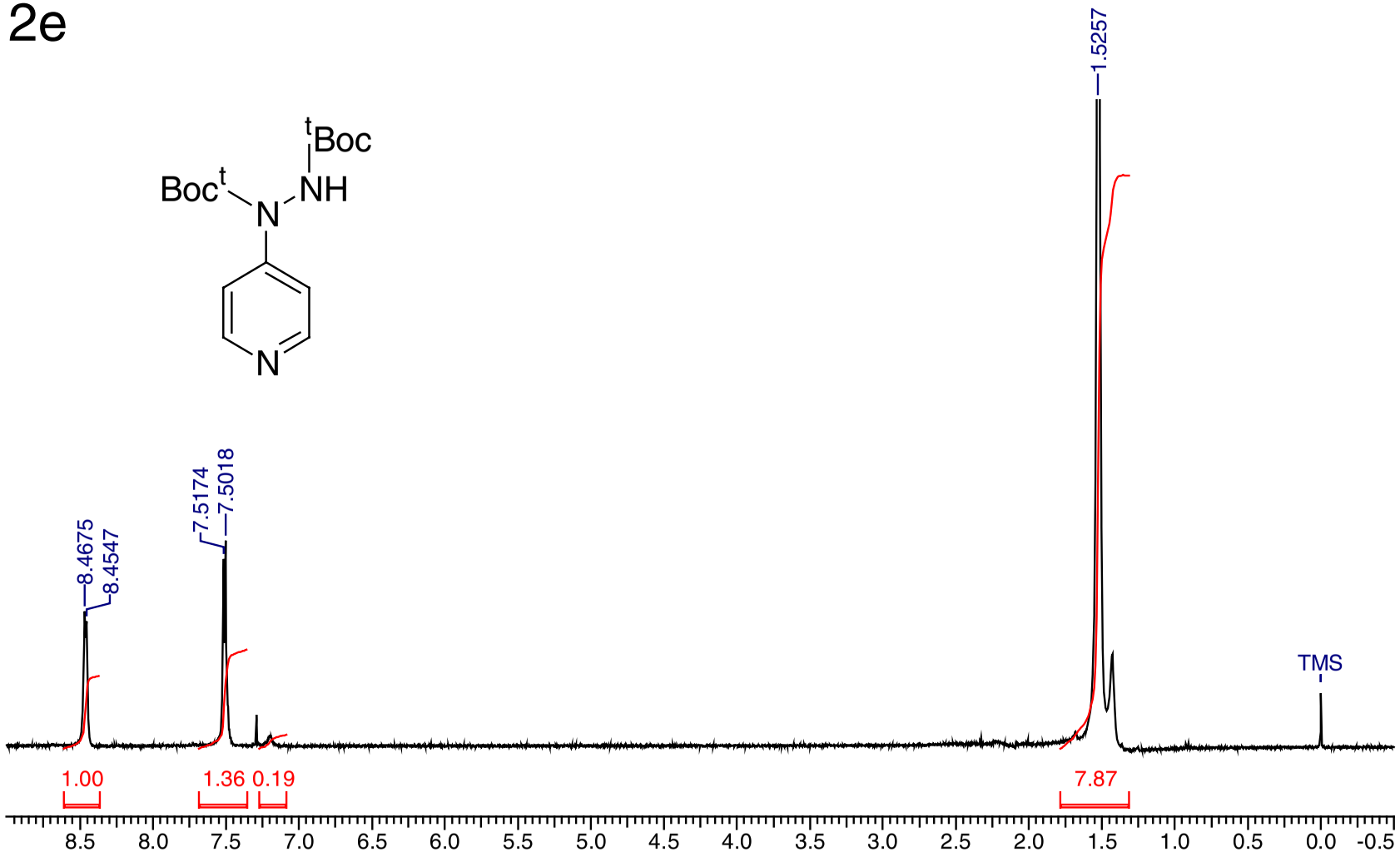

1.5474
1.4885
1.4684
10
9
8
7
6
5
4
3
2
1
0 PPM
6.4
15.2
7.5
156.5

12d

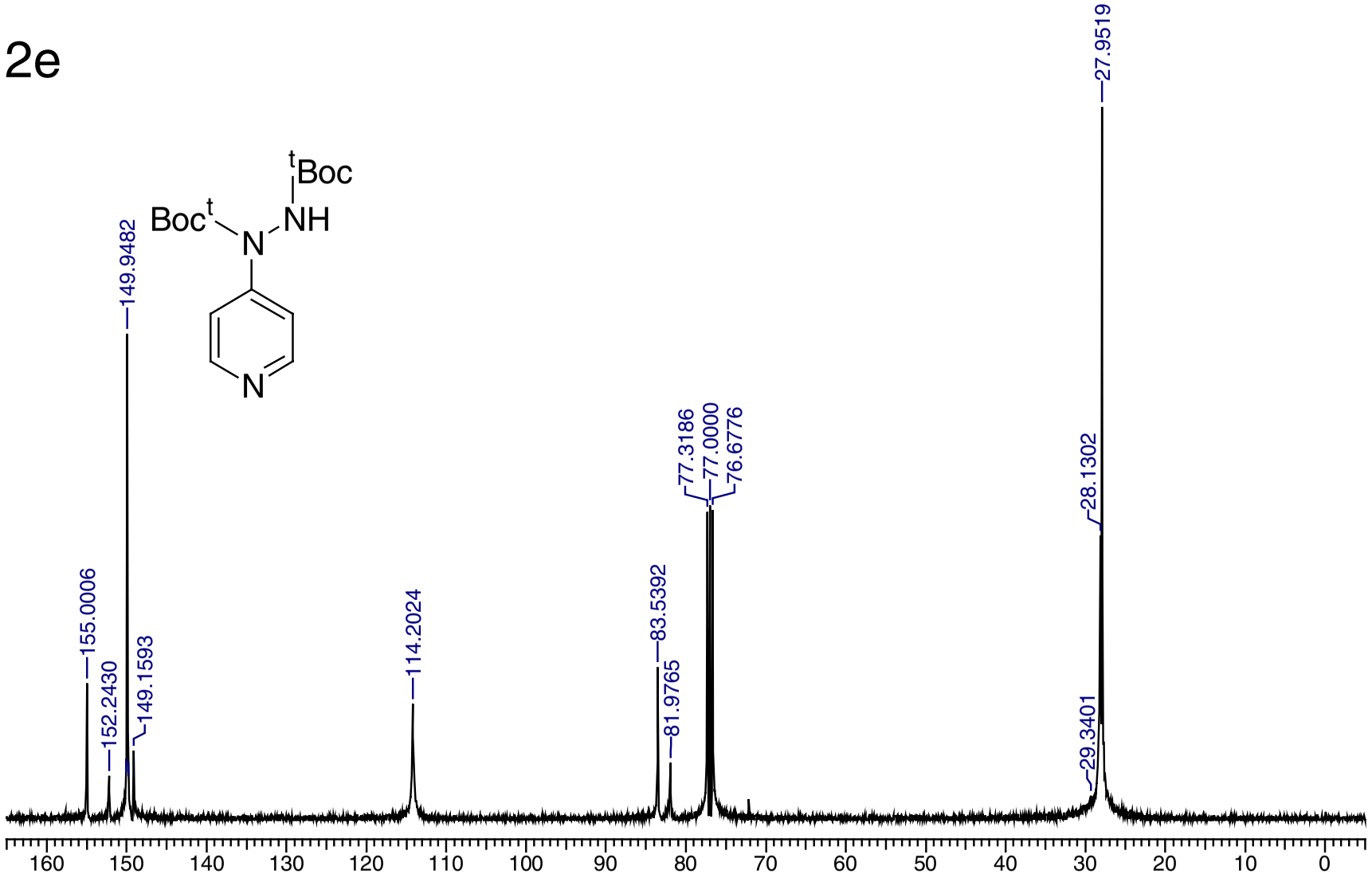
12d


N
N
N
O
O
HN
O
O
154.654
152.982
150.308
141.534
140.091
83.5298
81.6483
28.0127
27.9502
160
140
120
100
80
60
40
20 PPM
0

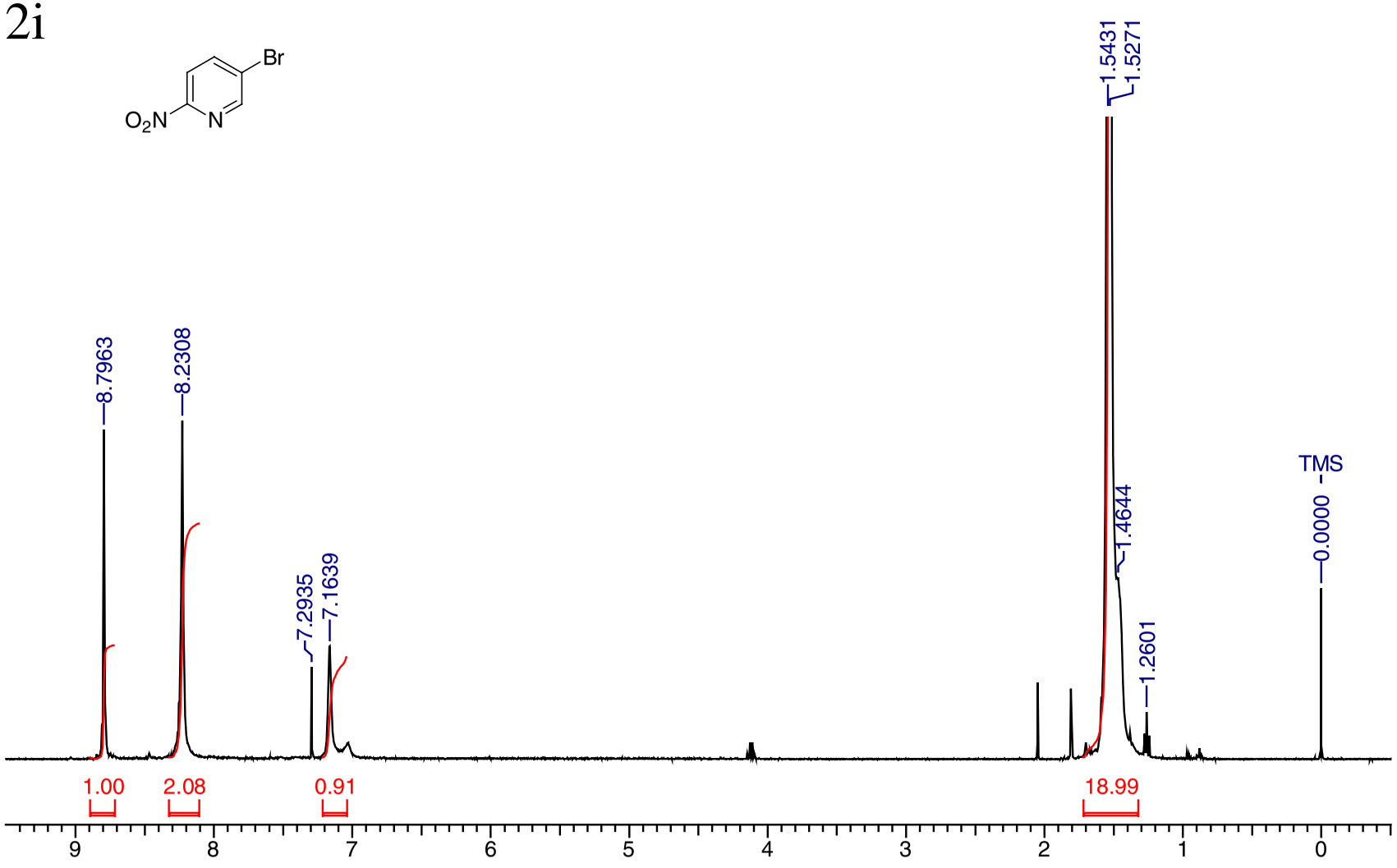
12e


tBoc
Boct
NH
N
N
1.5257
8.4675
8.4547
7.5174
7.5018
TMS
1.00
1.36
0.19
7.87
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

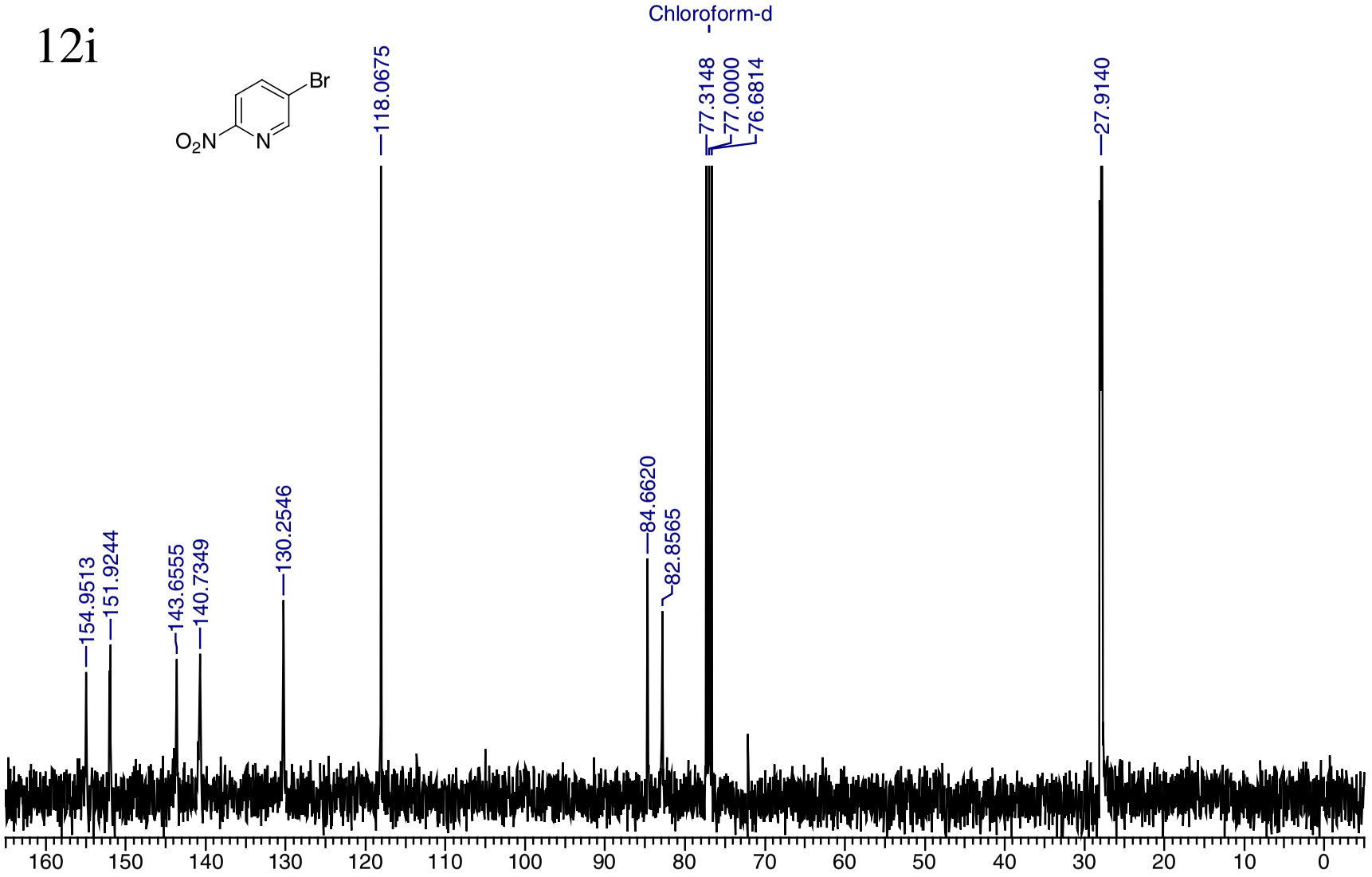
12e


tBoc
Boct
NH
N
N
155.0006
152.2430
149.9482
149.1593
114.2024
83.5392
81.9765
77.3186
77.0000
76.6776
28.1302
29.3401
27.9519
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

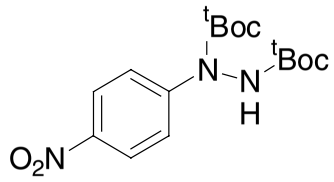
12i

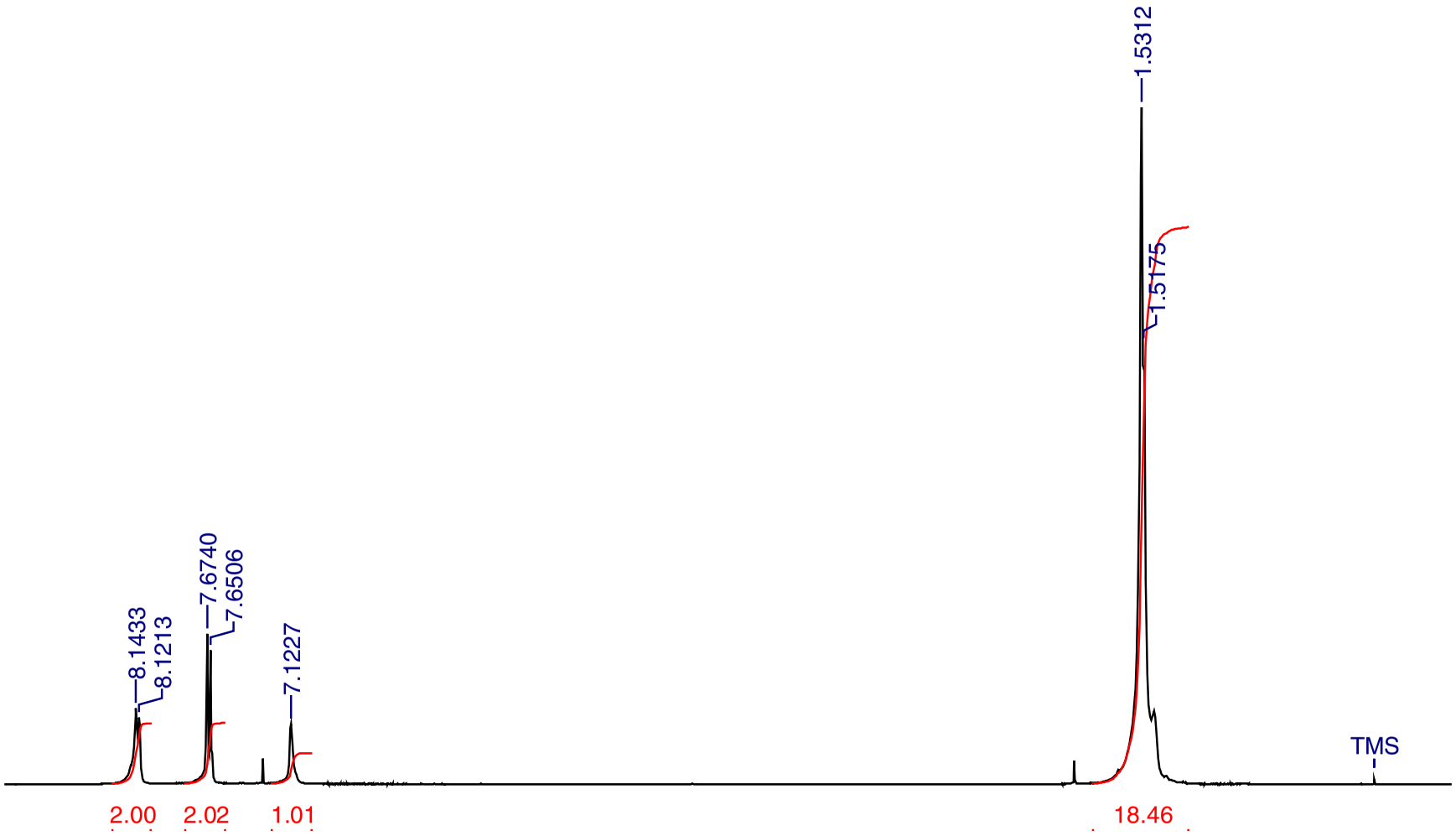

Br
O2N
N
8.7963
8.2308
7.2935
7.1639
1.5431
1.5271
1.4644
1.2601
TMS
0.0000
1.00
2.08
0.91
18.99
9
8
7
6
5
4
3
2
1
0

12i

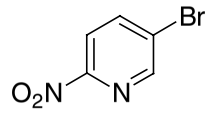

Chloroform-d
118.0675
77.3148
77.0000
76.6814
27.9140
154.9513
151.9244
143.6555
140.7349
130.2546
84.6620
82.8565
Br
O2N
N
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

15


tBoc
tBoc
N
N
H
O2N

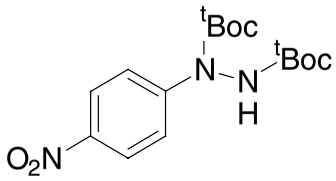

8.1433
8.1213
7.6740
7.6506
7.1227
1.5312
1.5175
TMS
2.00
2.02
1.01
18.46

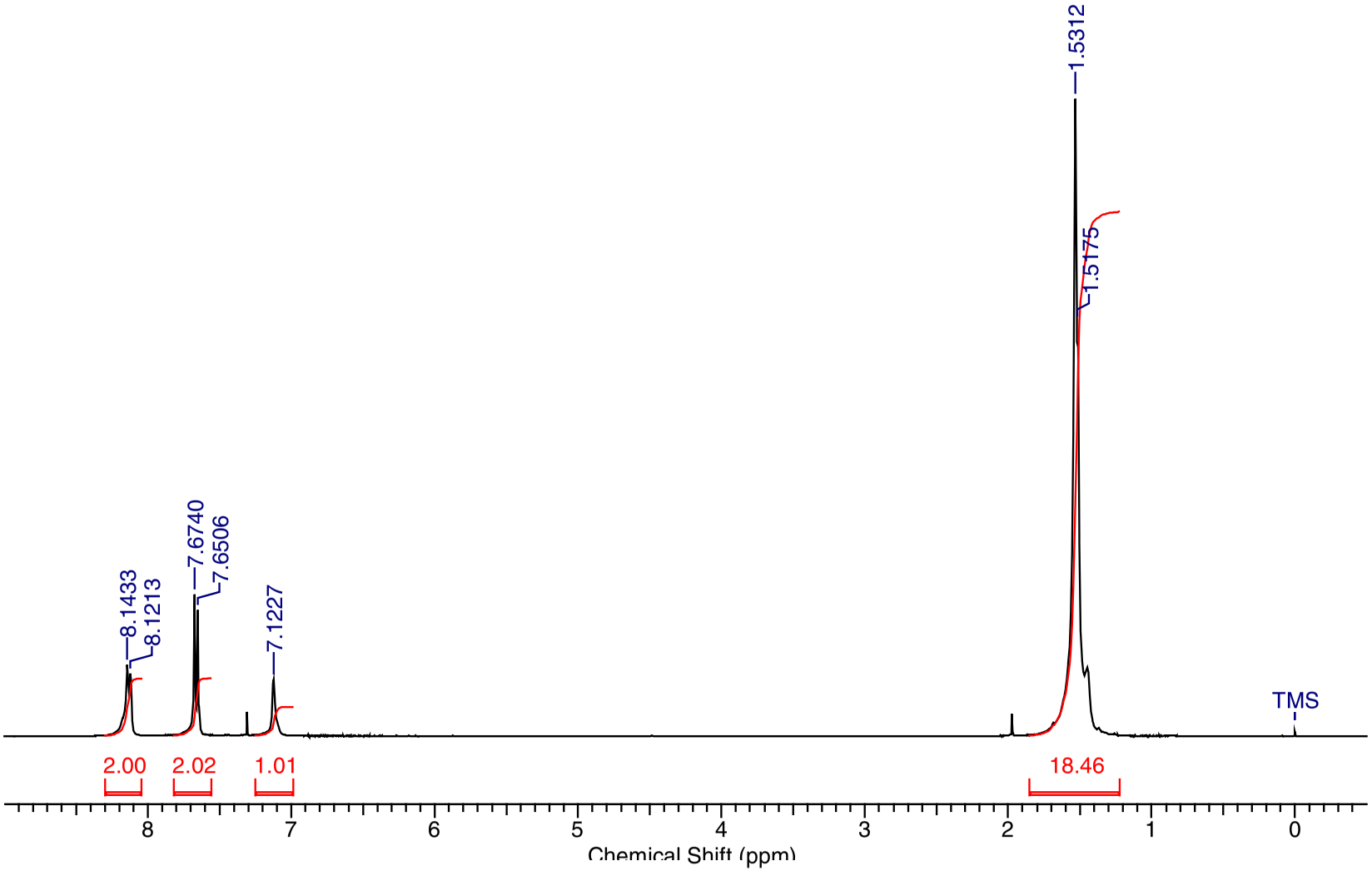
12i


Br
O_2N
N

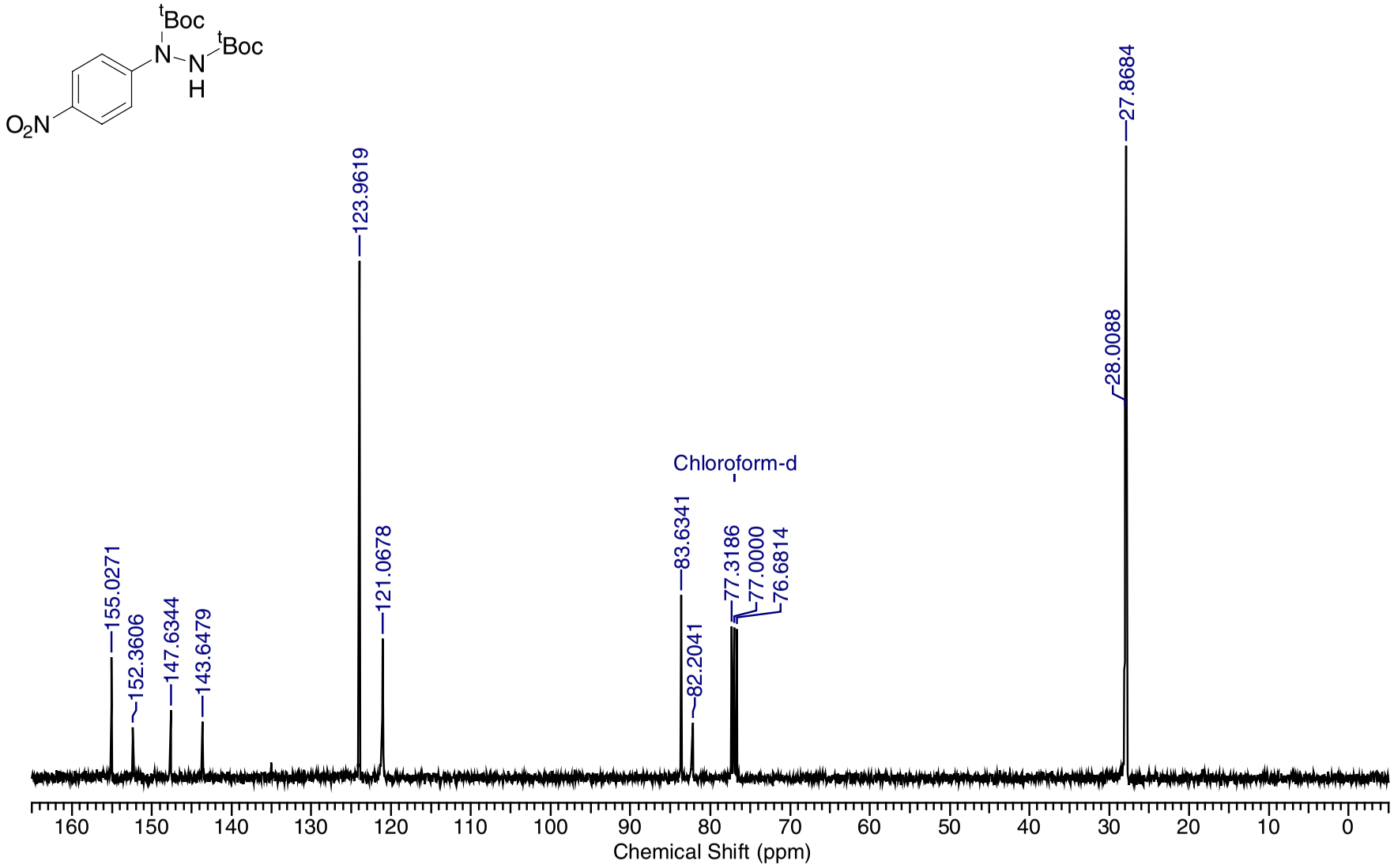
Chloroform-d
118.0675
77.3148
77.0000
76.6814
27.9140
154.9513
151.9244
143.6555
140.7349
130.2546
84.6620
82.8565
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

15


tBoc
N
N
tBoc
H
O2N

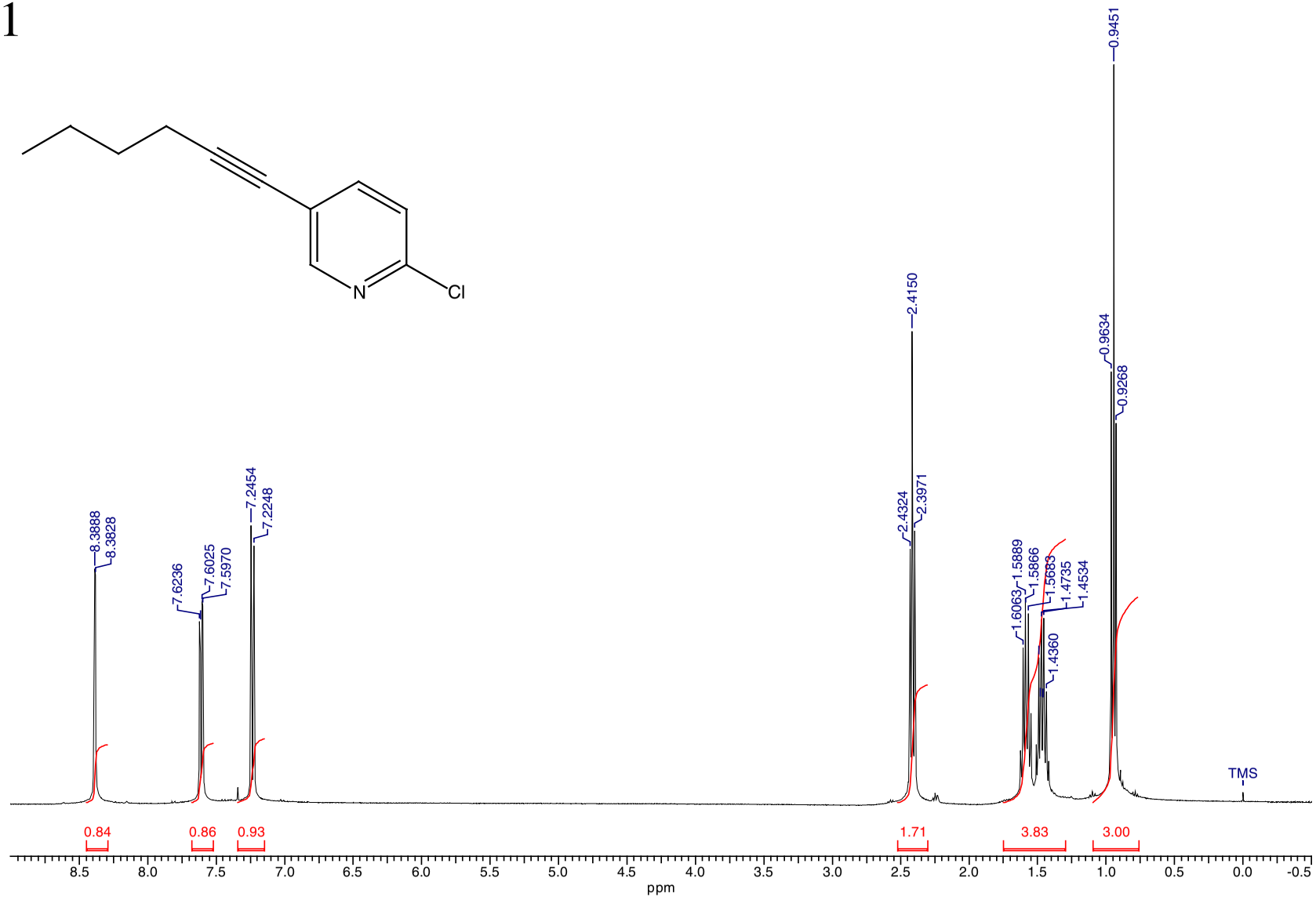

8.1433
8.1213
7.6740
7.6506
7.1227
1.5312
1.5175
TMS
2.00
2.02
1.01
18.46
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

15

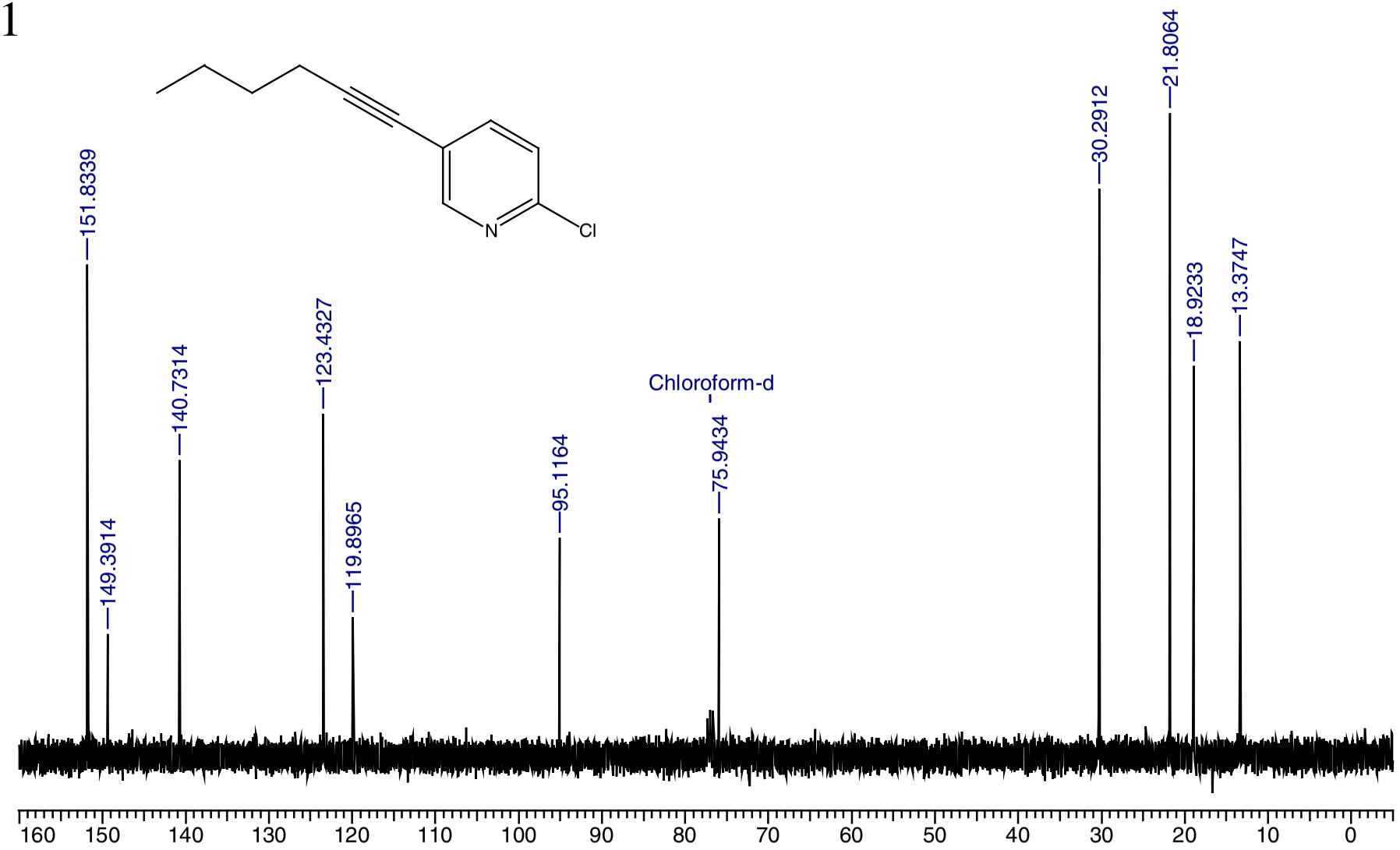

tBoc
tBoc
N
N
H
O2N
155.0271
152.3606
147.6344
143.6479
123.9619
121.0678
83.6341
82.2041
Chloroform-d
77.3186
77.0000
76.6814
28.0088
27.8684
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
Chemical Shift (ppm)

10 Apr 2003

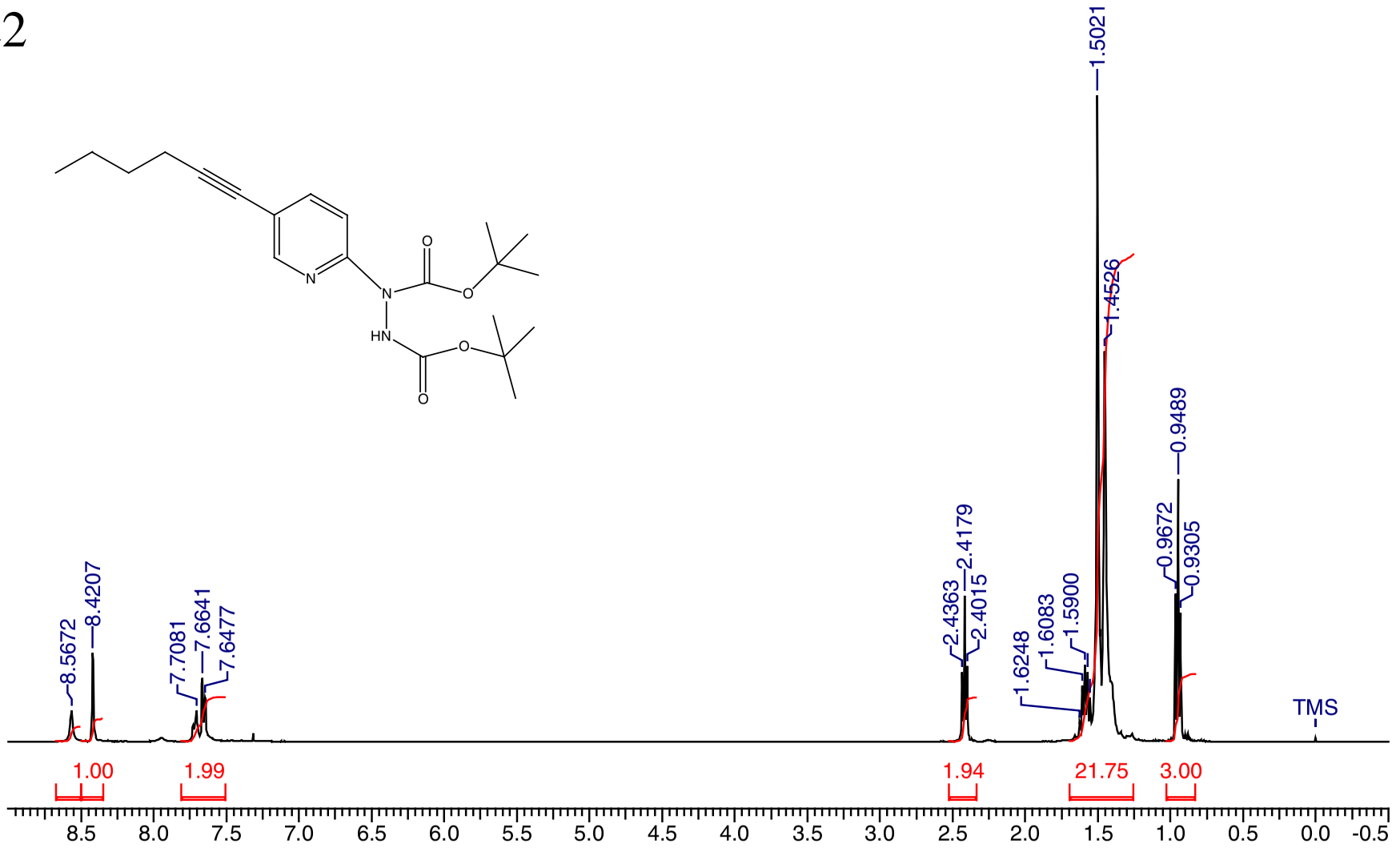
21



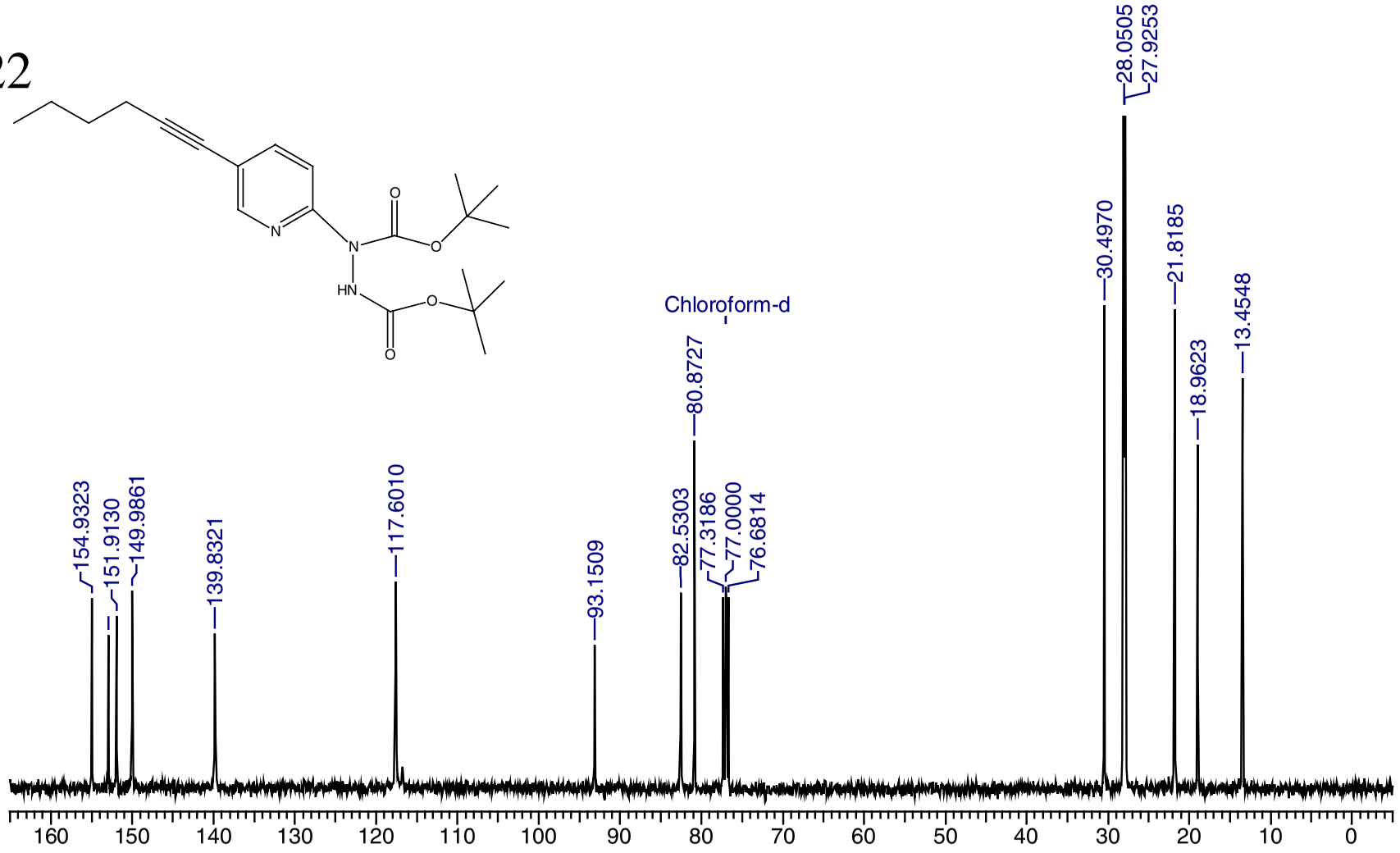
21


151.8339
149.3914
140.7314
123.4327
119.8965
95.1164
Chloroform-d
75.9434
30.2912
21.8064
18.9233
13.3747
N
Cl
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

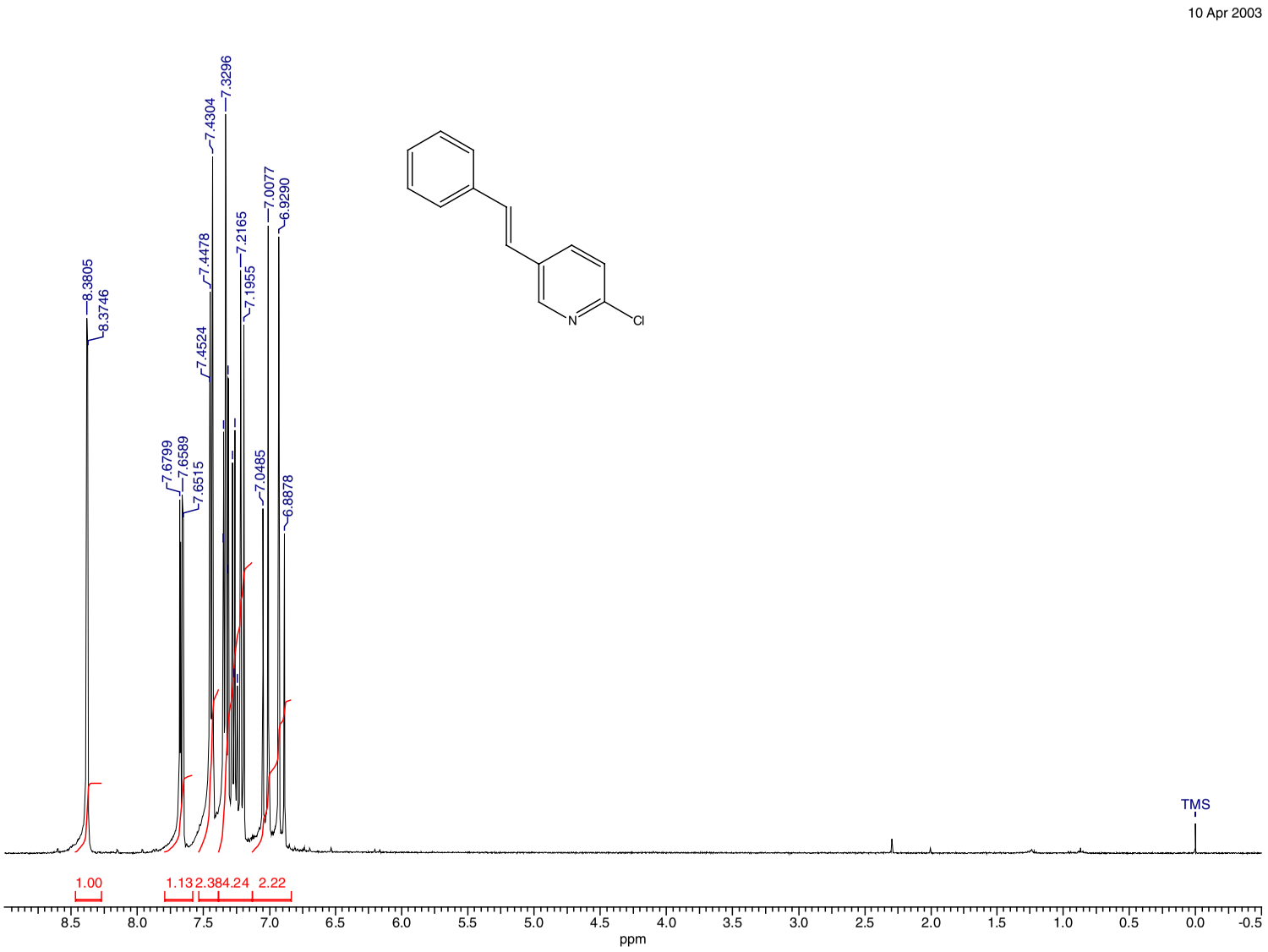
22


8.5672
8.4207
7.7081
7.6641
7.6477
2.4363
2.4179
2.4015
1.6248
1.6083
1.5900
1.5021
1.4526
0.9672
0.9489
0.9305
TMS
1.00
1.99
1.94
21.75
3.00
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

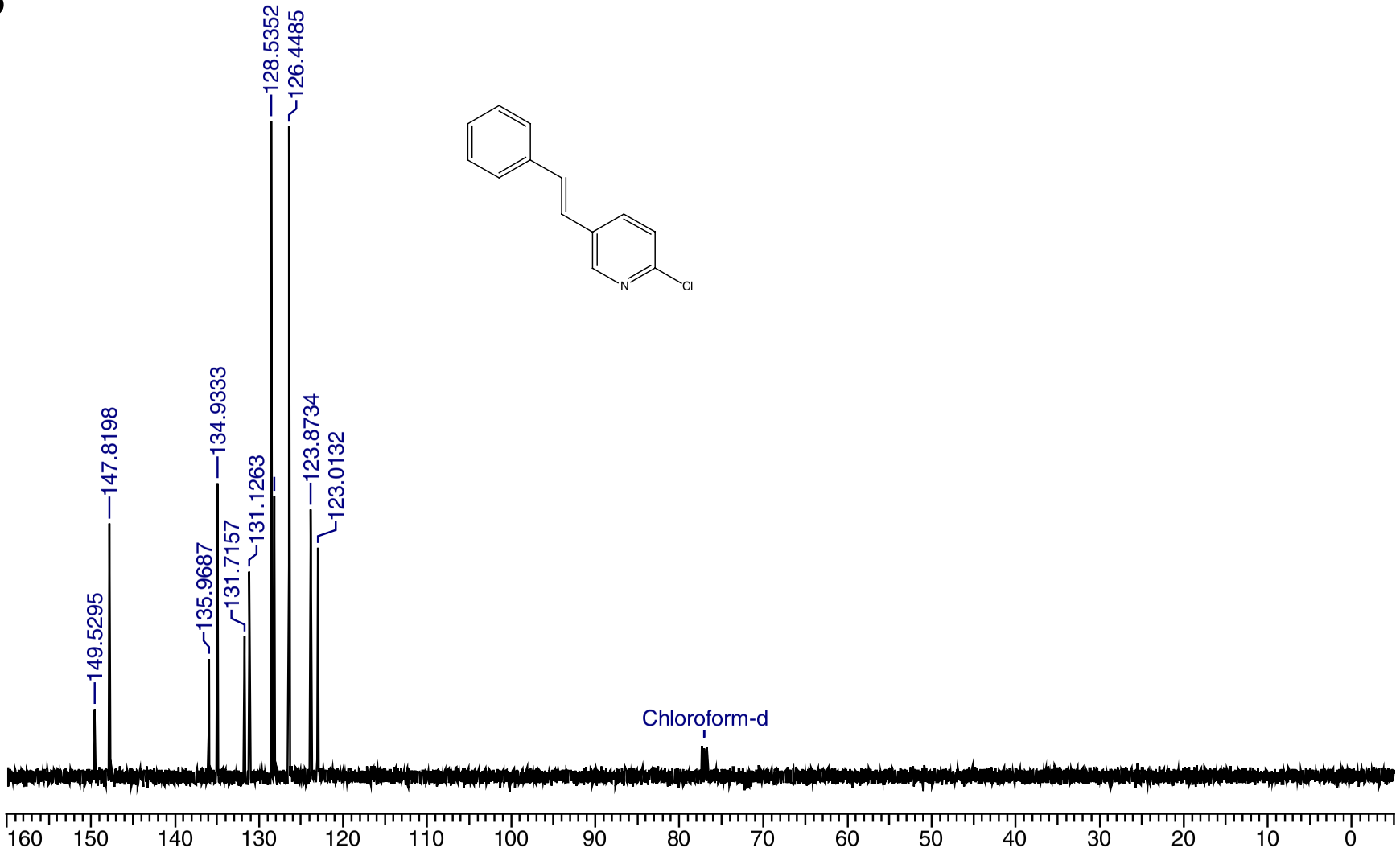
22

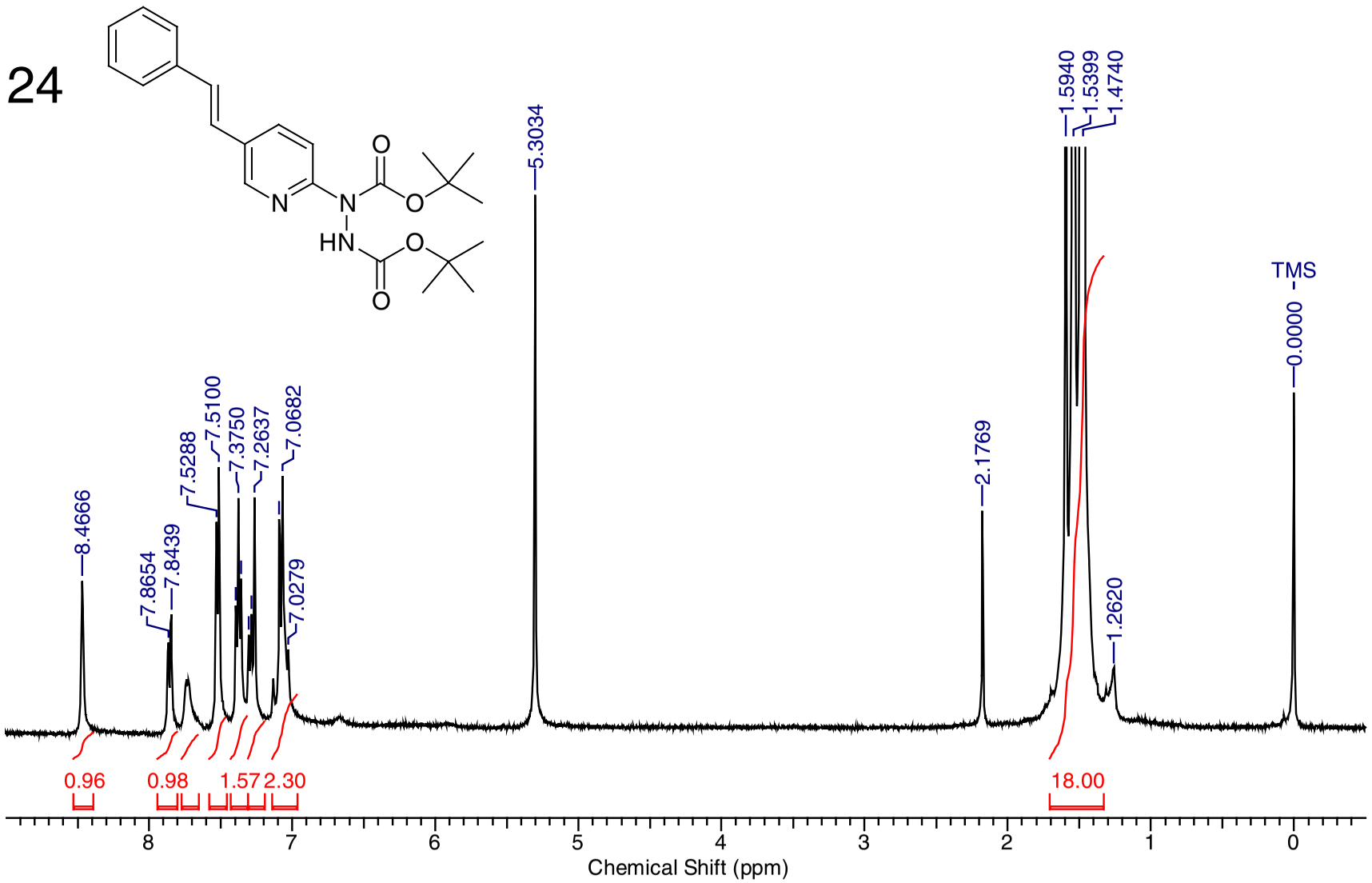

154.9323
151.9130
149.9861
139.8321
117.6010
93.1509
82.5303
80.8727
77.3186
77.0000
76.6814
Chloroform-d
30.4970
28.0505
27.9253
21.8185
18.9623
13.4548
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

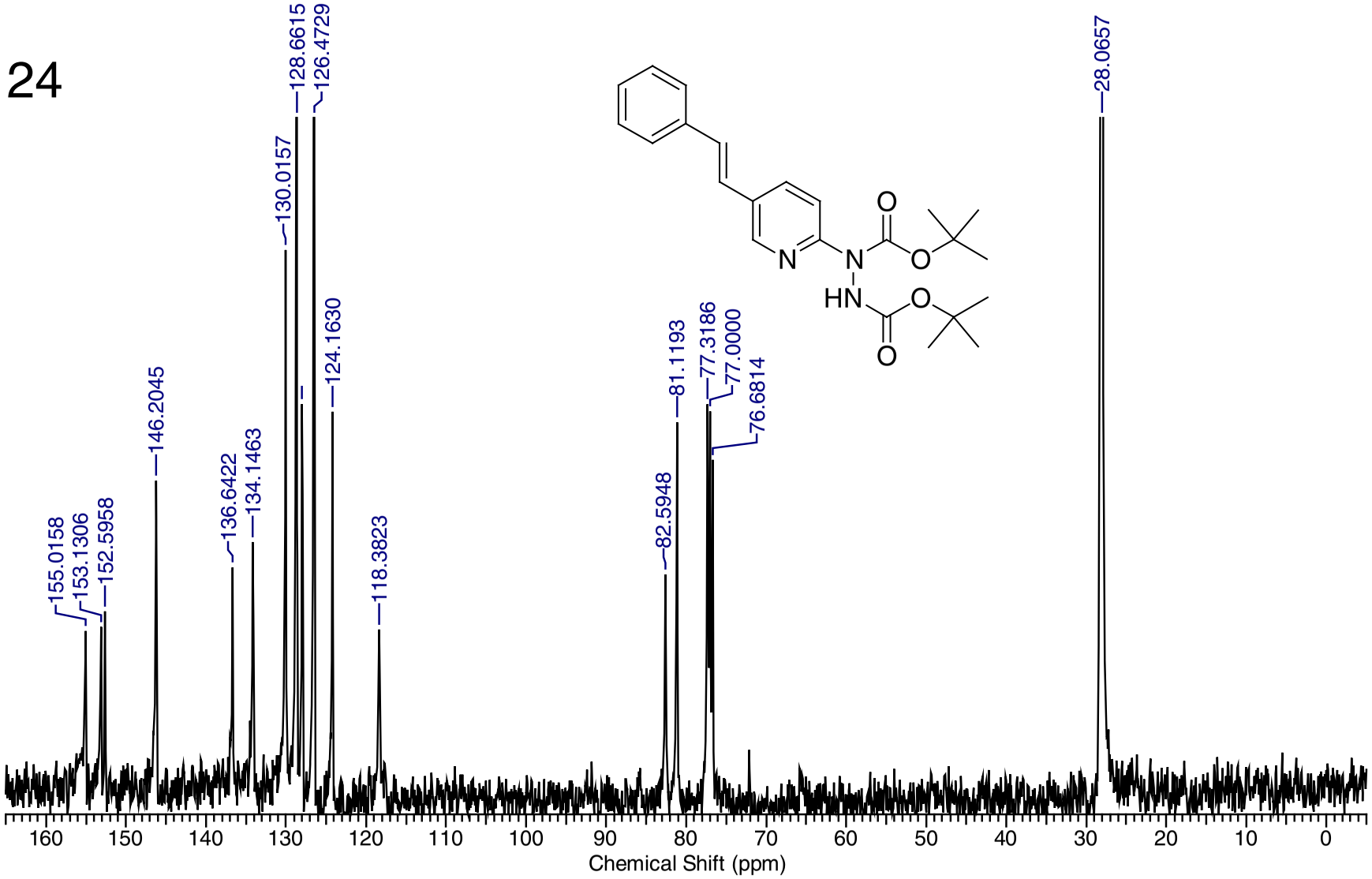
23


10 Apr 2003
8.3805
8.3746
7.6799
7.6589
7.6515
7.4524
7.4478
7.4304
7.3296
7.2165
7.1955
7.0485
7.0077
6.9290
6.8878
N
Cl
TMS
1.00
1.13
2.38
4.24
2.22
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm

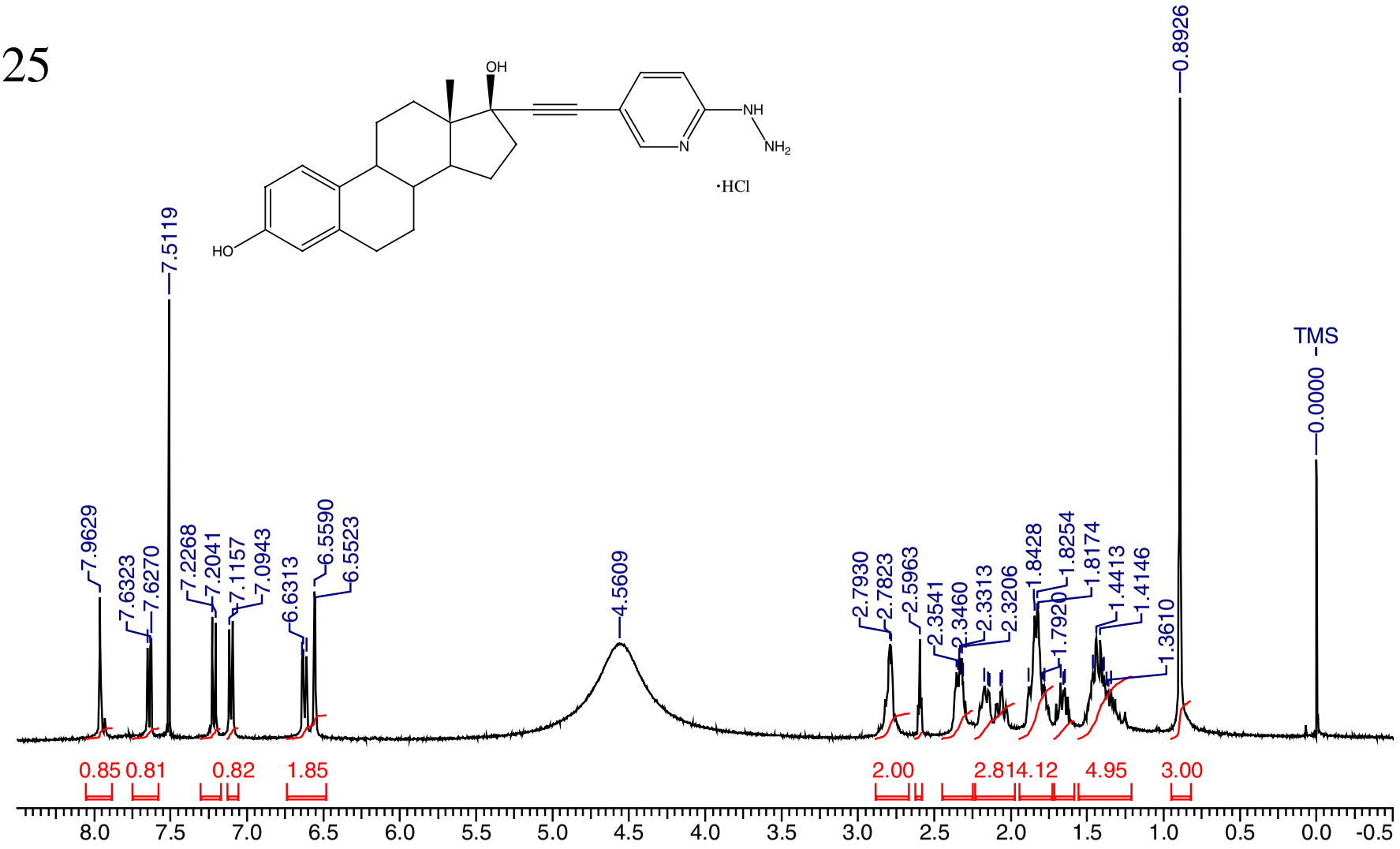
23


128.5352
126.4485
134.9333
147.8198
131.1263
123.8734
123.0132
135.9687
131.7157
149.5295
Chloroform-d
N
Cl
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

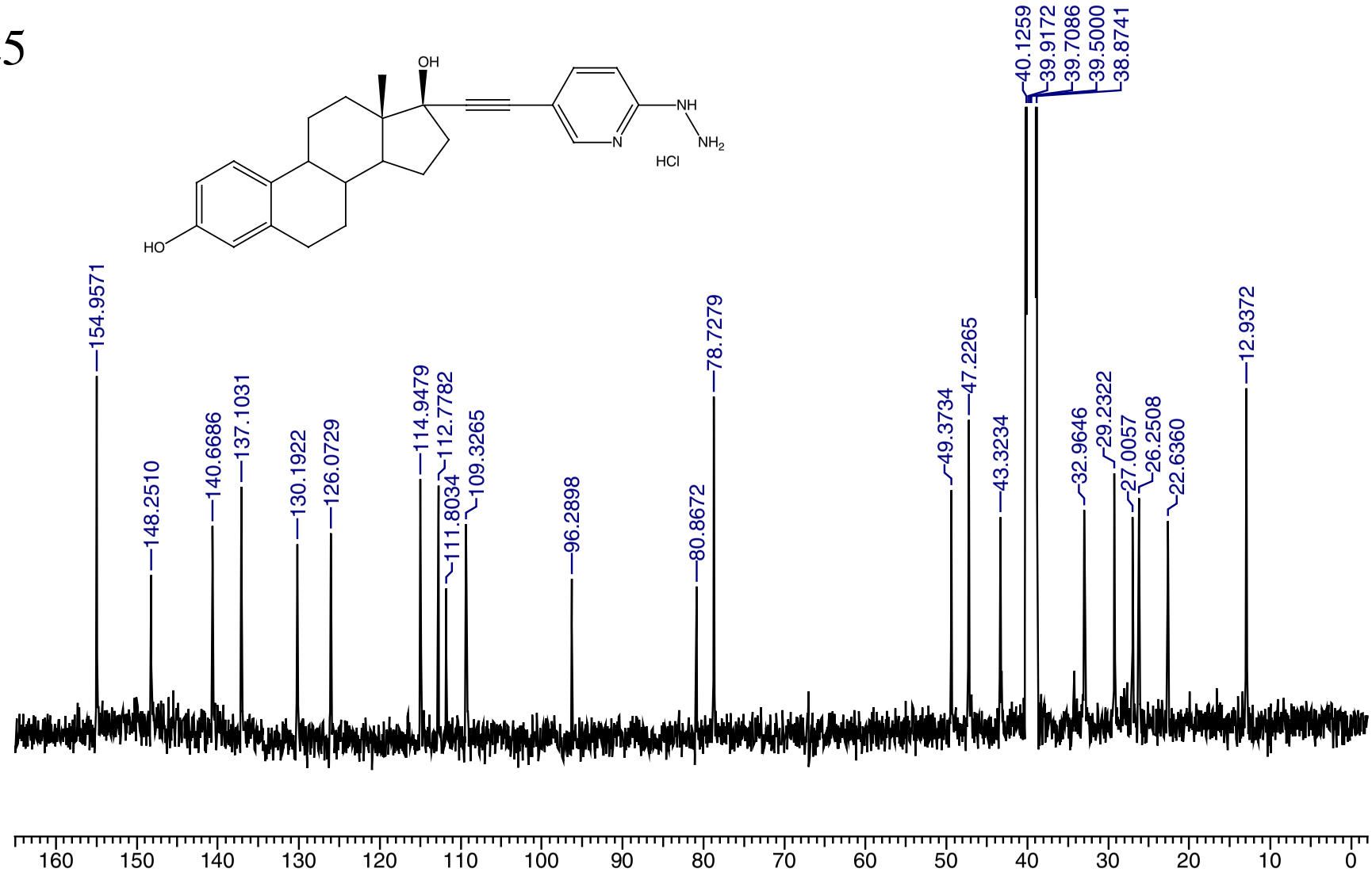

24
8.4666
7.8654
7.8439
7.5288
7.5100
7.3750
7.2637
7.0682
7.0279
5.3034
2.1769
1.5940
1.5399
1.4740
1.2620
TMS
0.0000
0.96
0.98
1.57
2.30
18.00
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

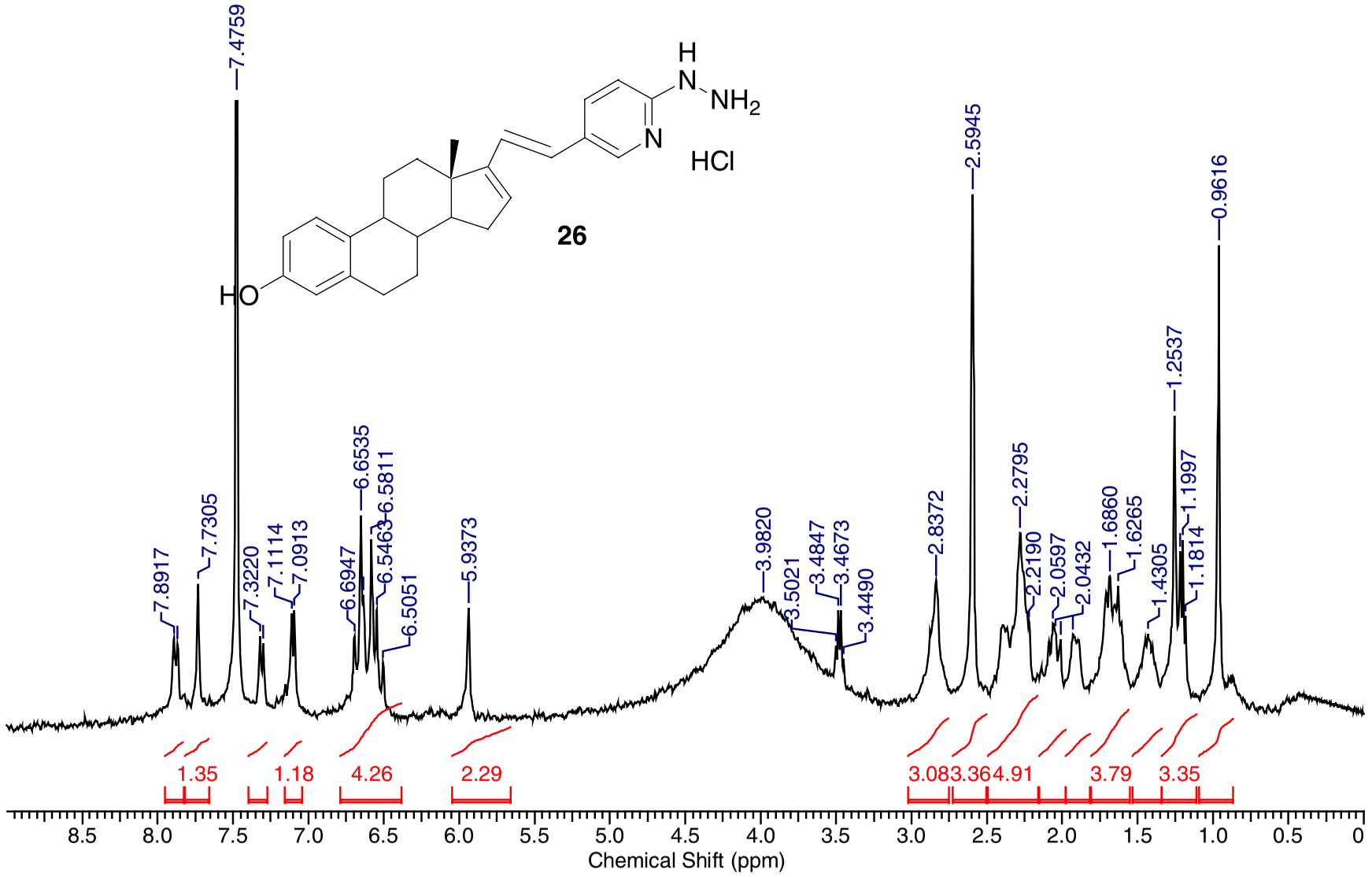

24
155.0158
153.1306
152.5958
146.2045
136.6422
134.1463
130.0157
128.6615
126.4729
124.1630
118.3823
82.5948
81.1193
77.3186
77.0000
76.6814
28.0657
O
N
N
O
HN
O
O
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
Chemical Shift (ppm)

25

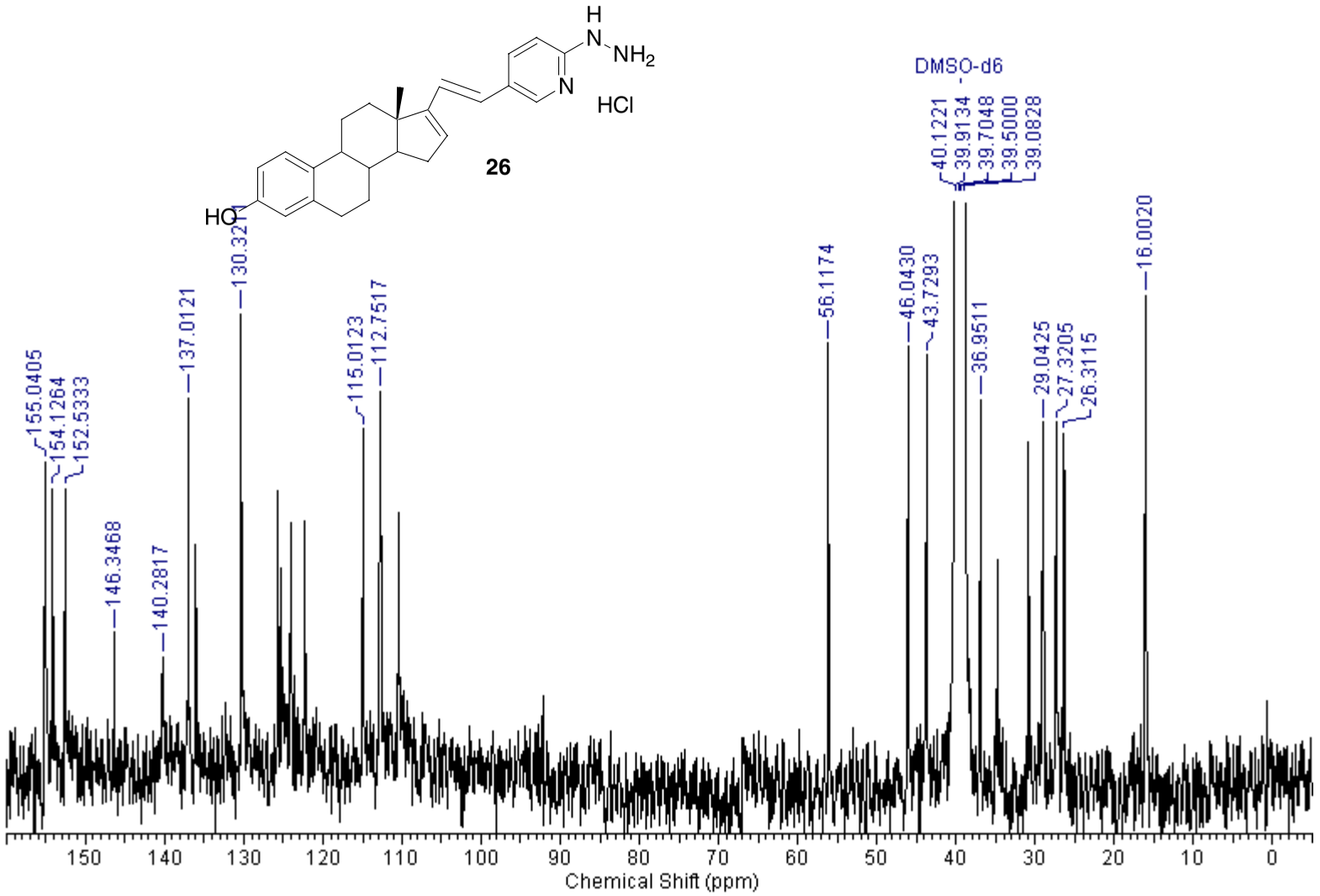

OH
NH
N
NH2
·HCl
HO
7.9629
7.6323
7.6270
7.5119
7.2268
7.2041
7.1157
7.0943
6.6313
6.5590
6.5523
4.5609
2.7930
2.7823
2.5963
2.3541
2.3460
2.3313
2.3206
1.8428
1.8254
1.8174
1.7920
1.4413
1.4146
1.3610
0.8926
TMS
0.0000
0.85
0.81
0.82
1.85
2.00
2.81
4.12
4.95
3.00
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5

25


OH
NH
N
NH2
HCl
HO
154.9571
148.2510
140.6686
137.1031
130.1922
126.0729
114.9479
112.7782
111.8034
109.3265
96.2898
80.8672
78.7279
49.3734
47.2265
43.3234
40.1259
39.9172
39.7086
39.5000
38.8741
32.9646
29.2322
27.0057
26.2508
22.6360
12.9372
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


7.4759
7.8917
7.7305
7.3220
7.1114
7.0913
6.6947
6.6535
6.5811
6.5463
6.5051
5.9373
3.9820
3.5021
3.4847
3.4673
3.4490
2.8372
2.5945
2.2795
2.2190
2.0597
2.0432
1.6860
1.6265
1.4305
1.2537
1.1997
1.1814
0.9616
1.35
1.18
4.26
2.29
3.08
3.36
4.91
3.79
3.35
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
Chemical Shift (ppm)
HO
H
N
NH2
N
HCl
26

26


H
N
NH2
N
HCl
HO
26
DMSO-d6
40.1221
39.9134
39.7048
39.5000
39.0828
155.0405
154.1264
152.5333
146.3468
140.2817
137.0121
130.3271
115.0123
112.7517
56.1174
46.0430
43.7293
36.9511
29.0425
27.3205
26.3115
16.0020
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
Chemical Shift (ppm)