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SUPPORTING INFORMATION

Title: Synthesis of the Bicyclic Core of Pumiliotoxins
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Ref. No.: O02179

European Journal of Organic Chemistry

Alexander Sudau, Winfried Münch, Jan-W. Bats and Udo Nubbemeyer

Title: **Total Synthesis of (+)-Pumiliotoxin 251D (Part 1): Synthesis of the Bicyclic Core**

Supporting Information

Contents:

Procedures

***L*-(-)-proline methylester hydrochloride**: A suspension of *L*-(-)-proline (100 g, 0.87 mol) in MeOH (600 m*L*) was treated with acetyl chloride (92.6 m*L*, 1.30 mol, 1.5 eq). The mixture was heated to reflux. After about 8 h, the solvent was removed in vacuum to give 171 g (0.87 mol, 100 %) of the *L*-proline methylester hydrochloride as a colorless oil. All spectral data of the product were in good accordance with those published in the literature.

(2S)-*N*-Benzylproline methylester: Proline methylester hydrochloride (171.4 g, 0.87 mol) in dry CH_2Cl_2 (700 m*L*, Al_2O_3) was subsequently treated with freshly distilled Et_3N (242.1 m*L*, 1.74 mol, 2 eq) and benzyl chloride (200.0 m*L*, 1.74 mol, 2 eq). While stirring with a mechanical stirrer the mixture was heated to reflux overnight. A pale yellow precipitate of triethylamine hydrochloride occurred. Work-up started by removal of the excess Et_3N under reduced pressure. The residue was dissolved in H_2O (300 m*L*) and 20 % aqueous HCl was added to adjust the pH to about 1 – 2. The mixture was extracted with Et_2O (3x 300 m*L*) to remove reactant benzyl chloride. Then, 1 M aqueous NaOH (~ 800 m*L*) was added raising the pH to about 11. The mixture was extracted with Et_2O (3x 300 m*L*), the combined organic layers were dried (Na_2SO_4) and the solvent was removed under reduced pressure. Yield: 155.9 g (0.72 mmol, 82%) of pure *N*-benzylproline methylester as a yellow oil. ^{1}H-NMR (270 MHz, $CDCl_3$): δ 1.70-2.23 (m, 4 H), 2.38 (dd, 1 H, H^5), 3.05 (m, 1 H, $H^{5'}$), 3.24 (m, 1 H, H^2), 3.54 (d, 1 H, N-Bn), 3.67 (s, 3 H), 3.86 (d, 1 H, N-Bn), 7.30 (m, 5 H). ^{13}C-NMR (67.9 MHz, $CDCl_3$): δ 22.82 (t), 29.21 (t), 51.55 (q), 53.13 (t), 58.62 (t), 65.14 (d), 126.96 (d), 128.02 (d),

129.10 (d), 138.12 (s), 174.42 (s). IR (KBr): υ = 2950 (m), 2798 (m), 1748 (s), 1733 (s), 1377 (m), 1198 (s), 1171 (s), 7447 (m), 699 (s) cm^{-1}. MS (80 eV, EI, 40 °C): m/z (%) = 219 M^+ (6), 160 (100), 91 (83), 65 (6). DC: R_f = 0.55 (hexane/EtOAc 1:1).

(2S)-*N*-Benzyl prolinol (1): Under argon, *N*-benzylproline methylester (155.9 g, 0.71 mol) in dry THF (600 m*L*) was cooled to 4 °C. $LiBH_4$ (20.0 g, 0.92 mol, 1.3 eq) was added and the mixture was stirred by means of a mechanical stirrer for 2 d at 4 °C. Work-up started by quenching subsequently with MeOH (100 m*L*) and H_2O (50 m*L*). After a further 30 min of stirring aqueous HCl was added until pH 1 was achieved. The mixture was stirred for about 1 h to complete the cleavage of the boron amine complexes. Then, the aqueous layer was extracted with Et_2O (2x 150 m*L*) to remove acid or neutral type impurities. After adding 1 M aqueous NaOH (→ pH 11) and extraction with Et_2O (3x 150 m*L*) the combined organic layers were dried (Na_2SO_4) and the solvent was removed to isolate pure amino alcohol **1** as a clear colorless oil. Yield: 99.6 g (0.52 mol, 73%). $[\alpha]_D^{20}$ = - 59 (c = 1.5, $CHCl_3$). ^{1}H-NMR (270 MHz, $CDCl_3$): δ 1.60-2.00 (m, 4 H), 2.26 (m, 1 H), 2.71 (m, 1 H), 2.96 (m, 1 H), 3.32 (d, 1 H), 3.41 (dd, 1 H), 3.60 (dd, 1 H), 3.96 (d, 1 H, N-Bn), 7.30 (m, 5 H). DC: R_f = 0.1 (n-hexane/EtOAc 1:1). ^{13}C-NMR (67.9 MHz, $CDCl_3$): δ 23.0 (t), 27.5 (t), 54.1 (t), 58.4 (t), 61.9 (d), 64.1 (d), 126.7 (d), 127.9 (d), 128.0 (d), 138.9 (s). IR (film): υ = 3409 (s, br), 3107 (w), 3062 (m), 2961 (s), 2873 (s), 1603 (w), 1495 (m), 1453 (s), 1252w (m), 1121 (m), 1075 (s), 1043 (s), 1028 (s), 740 (s) cm^{-1}. MS (70 eV, EI, 30 °C): m/z (%) 191 (1) [$M^{+\cdot}$], 161 (17), 160 (100), 91 (97), 65 (7). All spectral data of the product were in good accordance with those published in the literature.

(*2S*)-*N*-Benzyl-2-vinylpyrrolidine (2): *Swern oxidation*: Under argon, freshly distilled oxalyl chloride (89.9 m*L*, 132.2 g, 1.042 mol, 2 eq.) in dry CH_2Cl_2 (600 m*L*) was cooled to -78°C and treated dropwise with DMSO (75.8 m*L*, 83.4 g, 1.067 mol, 2.05 eq.) in dry CH_2Cl_2 (50 m*L*) keeping the internal temperature below –70 °C. After stirring for 3 h at about –60 °C, the mixture was cooled again to –78 °C and aminoalcohol **1** (99.6 g, 0.521 mol) in dry CH_2Cl_2 (50 m*L*) was added slowly. After a further stirring at –45 to –50 °C for 2 h Et_3N (266.0 m*L*, 2.6 mol, 5 eq.) were injected slowly at about –45 °C. The cooling bath was removed and the mixture was stirred for 1.5 h at –20 °C, then, the temperature was allowed to reach 20 °C (tlc monitoring to determine complete consumption of the reactant aminoalcohol **1**). Work-up started by cleavage with saturated aqueous $NaHCO_3$ (300 m*L*). The organic layer was washed with saturated aqueous $NaHCO_3$ (2x 100 m*L*) and brine (100 m*L*) and dried (Na_2SO_4). Finally, the solvent was removed to isolate the intermediate aldehyde as a red oil which was

used without any further purification. The crude aldehyde could be stored at -78°C for several days without epimerization.

Wittig reaction: Under argon, dry methyl triphenylphosphonium bromide (223.5 g, 0.625 mol, 1.2 eq.) was suspended in dry THF (600 m*L*) by means of a mechanical stirrer. After cooling to –60 °C *n*BuLi (391 m*L*, 0.625 mol, 1.6 M in *n*-heptane) was added slowly keeping the internal temperature below –50 °C. The mixture was stirred for 3.5 h at –60 to –45 °C. Then, the crude aldehyde (0.521 mol) in dry THF (200 m*L*) was added via dropping funnel. The reaction mixture was allowed to warm-up to room temperature, stirring was continued overnight, a white precipitate occurred. Work-up started by quenching with H_2O (300 m*L*), triphenylphoshine oxide dissolved. The organic layer was washed with H_2O (3x 300 m*L*) and brine (300 m*L*) and dried (Na_2SO_4). During the removal of the solvent remaining triphenylphoshine oxide precipitated. Thus, the residue was treated with Et_2O and the non-dissolved phosphorous compounds were filtered off. The solvent was removed and the remaining crude vinyl pyrrolidine was purified by Kugelrohr distillation (bp. 100 °C, 0.02 mbar). Yield: 67.7 g (0.36 mol, 69 %) as a colorless oil. $[\alpha]_D^{20}$ = - 54 (c = 3.14, $CHCl_3$). ^{1}H-NMR (270 MHz, $CDCl_3$): δ 1.60-1.05 (m, 4 H), 2.15 (m, 1 H), 2.78 (m, 1 H), 2.95 (m, 1 H), 3.08 (d, 1 ^2J = 15 Hz, Bn), 4.05 (d, 1 H, ^2J = 15 Hz, Bn), 5.12-5.28 (m, 2 H), 5.75-5.85 (m 1 H), 7.30 (m, 5 H). ^{13}C-NMR (67.9 MHz, $CDCl_3$): δ 21.9 (t), 31.4 (t), 53.2 (t), 58.0 (t), 68.4 (d), 116.6 (t), 126.7 (d), 128.1 (d), 128.9 (d), 139.4 (s), 140.9 (d). DC: R_f = 0.6, *n*-hexane/EtOAc 1:1). IR (film): υ = 3081 (m), 3063 (s), 3027 (m), 2967 (w), 2874 (m), 1642 (w), 1604 (w), 1584 (w), 1495 (m), 1453 (s), 1111 (m), 1073 (m), 1029 (m), 994 (m), 918 (s), 1050 (w), 847 (w), 738 (s) cm^{-1}. MS (70 eV, EI, 30 °C): m/z (%) 187 (45) [$M^{+\cdot}$], 186 (18), 160 (62), 96 (12), 91 (100), 68 (14).

This sequence did not suffer from racemization as proven, e.g., by X-ray analyses: 3-phenyl and 3-chloro azoninones type **3a/b** form racemic crystals from racemic lactams and enantiomerically pure crystals from enantiopure lactams.

Chloroacetyl fluoride: The synthesis was carried out using a Teflon apparatus! Finely powdered KF·HF (30 g, 0.38 mol) and chloroacetyl chloride (48.0 g, 0.43 mol) were heated to about 60 °C with vigorous magnetic stirring. Then, the temperature was raised to 100 °C and the product chloroacetyl fluoride was continuously collected as the distillate for a further 3 – 4 h, bp. 75 – 78 °C. Yield: 28.1 g (0.3 mol, 69%) of pure choroacetyl fluoride as a clear colorless liquid. The compound can be stored without decomposition at –20 °C in a PFA flask for several months. ^{1}H-NMR (270 MHz, $CDCl_3$): δ 4.25 (d, 2 H, ^3J(^{1}H, ^{19}F) = 1 Hz). ^{13}C-NMR

(67.9 MHz, $CDCl_3$): δ 38.6 (dt, C-2, $^2J(^{13}C, ^{19}F)$ = 76.9 Hz), 160.1 (d, C=O, $^1J(^{13}C, ^{19}F)$ = 356.5 Hz) .

(*pS*)*E*-3R-1-Benzyl-3-chloro-2,3,4,7,8,9-hexahydro-1H-azonin-2-one (3a) and **(*pS*)*E*-3S-1-Benzyl-3-chloro-2,3,4,7,8,9-hexahydro-1H-azonin-2-one (3b)**: (large scale preparation, zwitterionic aza-Claisen rearrangement): Vinyl pyrrolidine 2 (25 g, 0.133 mol) and K_2CO_3 (36.76 g, 0.266 mol, 2 eq.) in dry CH_2Cl_2 (400 m*L*) was cooled to 0 °C. Chloroacetyl fluoride (33.6 g, 0.346 mol, 2.6 eq) was added via dropping funnel. Then, Me_3Al (133 m*L*, 0.266 mol, 2 M in *n*-heptane) was added slowly maintaining the internal reaction temperature below 5 °C. A vigorous methane evolution occurred. Then, the mixture was stirred for 8.5 h at 0 °C. Work-up started by dilution with Et_2O (1.2 L). The resulting suspension was filtered through a short silica gel column (height: 40 mm, diameter: 70 mm). The remaining aluminum salts were removed from the surface of the column and the silica gel was eluted with Et_2O (3x 200 m*L*). The combined filtrates were dried (Na_2SO_4) and the solvent was removed under reduced pressure maintaining the temperature below 20 °C. The crude oil can be stored at –20 °C without any epimerization. Yield: 24.28 g (93.1 mmol, 70%) of the azoninones **3a** and **3b**.[1] Separation of the diastereomers via preparative HPLC.

(*3R,5R*)-5-(1*S*-2-Benzyl-pyrrolidinyl)-3-chloro-3,4,5-trihydro-furan-2-one (11): Epoxylactam **9a** (200 mg, 0.71 mmol) in dry $CHCl_3$ (10 m*L*) was treated with TMSCl (93 mg, 0.85 mmol, 1.2 eq.) at room temperature. After 1 h of vigorous stirring the reaction was stopped by addition of saturated aqueous $NaHCO_3$ and 10 % aqueous $Na_2S_2O_3$ (3:1). A clear colorless solution was obtained which was extracted with Et_2O (2x 15 m*L*). The organic layers were dried (Na_2SO_4) and the solvent was removed to give 200 mg (0.71 mmol, 100%) of pure lactone **11a** as a colorless oil. ^{1}H-NMR (270 MHz, $CDCl_3$): δ 1.80 - 1.60 (m, 3 H; H-7o, 8o, 8u), 2.04 - 1.91 (m, 1 H; H-7u), 2.41 - 2.31 (m, 1 H; H-9u), 2.59 - 2.46 (ddd, 1 H; H-4o; $^2J(H^{4o}, H^{4u})$ = 12.5 Hz, $^3J(H^{4o}, H^{3u})$ = 10.5 Hz, $^3J(H^{4o}, H^{5o})$ = 9.5 Hz), 2.86 - 2.76 (ddd, 1 H; H-4u; $^2J(H^{4u}, H^{4o})$ = 14.5 Hz, $^3J(H^{4u}, H^{3u})$ = 8.5 Hz, $^3J(H^{4u}, H^{5o})$ = 5.5 Hz), 3.00 - 2.90 (m, 1 H; H-9o), 3.17 - 3.10 (m, 1 H; H-6u), 3.54 - 3.48 (d, 1 H; H-N-Bn2; $^2J(H^{N\text{-}Bn2}, H^{N\text{-}Bn1})$ = 13 Hz), 4.08 - 4.02 (d, 1 H; H-N-Bn1; $^2J(H^{N\text{-}Bn1}, H^{N\text{-}Bn2})$ = 13 Hz), 4.42 - 4.34 (ddd, 1 H; H-5o; $^3J(H^{5o}, H^{4o})$ = 9.5 Hz, $^3J(H^{5o}, H^{4u})$ = 5 Hz, $^3J(H^{5o}, H^{6u})$ = 5 Hz), 4.60 - 4.52 (dd, 1 H; H-3u; $^3J(H^{3u}, H^{4o})$ = 10.5 Hz, $^3J(H^{3u}, H^{4u})$ = 8.5 Hz), 7.40 - 7.20 (m, 5 H; H-Ph). ^{13}C-NMR (67.9 MHz, $CDCl_3$): δ 23.8 (t, C-8), 27.1 (t, C-7), 34.6 (t, C-4), 51.6 (d, C-3), 60.7 (t, C-9), 64.2 (d,

[1] in some cases the crude product contained traces of the reactant vinyl pyrrolidine **2**. Removal by washing an Et_2O solution of the product with saturated aqueous $KHSO_4$.

C-6), 80.4 (d, C-5), 126.9 (d), 128.2 (d), 128.5 (d), 139.4 (s), 172.1 (s). IR (KBr): υ = 3085 (w), 3062 (m), 3028 (m), 2957 (s), 2877 (m), 2798 (m), 1786 (s, lactone C=O), 1653 (s), 1494 (m), 1453 (s), 1385 (m), 1368 (m), 1327 (m), 1276 (m), 1253 (m), 1188 (s), 1135 (m), 1101 (m), 1027 (m), 1012 (m), 935 (m), 885 (m), 844 (m), 701 (s) cm^{-1}.

(*5R,6S*)-5-Hydroxy-5-methyl-azabicyclo[4.3.0]nonan-2-one 17 and **(*5S,6S*)-5-Hydroxy-5-methyl-azabicyclo[4.3.0]nonan-2-one 18**: Data of the mixture of carbinols **17**/**18**: $[\alpha]_D^{20}$ = -48 (c = 1.78, $CHCl_3$). ^{1}H-NMR (270 MHz, $CDCl_3$): δ 1.08 (s, 3 H; H-CH_3'), 1.25 (s, 3 H; H-CH_3), 1.90 - 1.60 (m, 10 H; H-2x7',2x8, 2x8', 2x3, 2x3'), 2.08 - 1.89 (m, 2 H; H-7), 2.35 - 2.20 (m, 2 H; H-4'), 2.50 - 2.40 (m, 2 H; H-4), 3.00 - 2.90 (s, 2 H; H-OH), 3.20 - 3.10 (m, 1 H; H-6'), 3.30 - 3.25 (m, 1 H; H-6), 3.50 - 3.35 (m, 4 H; H-2x9,2x9'). ^{13}C-NMR (67.9 MHz, $CDCl_3$): δ 19.5 (q, Me), 21.9 (t, C-8'), 22.1 (t, C-8), 26.2 (t, C-7'), 26.3 (q, Me'), 27.1 (t, C-7), 28.0 (t, C-4'), 30.0 (t, C-4), 34.9 (t, C-3'), 36.6 (t, C-3), 45.8 (t, C-9,C-9'), 66.2 (d, C-6'), 66.4 (d, C-6), 67.3 (s, C-5'), 69.5 (s, C-5), 168.3 (s). IR ($CHCl_3$): υ = 3365 (m), 3053 (s), 2981 (s), 2882 (m), 1620 (s, C=O), 1471 (s), 1452 (s), 1418 (s), 1301 (m), 1265(s), 1149 (m), 1125 (m), 1050 (w), 972 (m), 896 (m) cm^{-1}. MS (80 eV, EI, 30 °C): m/z (%) 169 (73) [$M^{+\cdot}$], 154 (6), 152 (5), 140 (5), 112 (18), 111 (26), 99 (14), 83 (65), 70 (100). HRMS (80 eV, 70 °C): calc. 169.110279 (for $C_9H_{15}NO_2$ [M^+]), found 169.11355. For the synthesis of the carbinols see: (a) A. G. M. Barrett, F. Damiani, *J. Org. Che*m. **1999**, *64* 1410 – 1411. (b) S. F. Martin, S. K. Bur, *Tetrahedron* **1999**, *55*, 8905-8914, (c) Y. Ni, G. Zhao, Y. Ding, *J. Che*m. *Soc. Perkin Trans I*, **2000**, 3264–3266. (d - racemic) A. Azzouzi, M. Dufour, J.-C. Gramain, R. Remuson, *Heterocycles* **1988**, *27*, 133-148.

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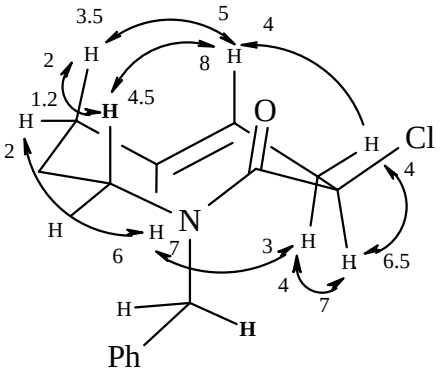
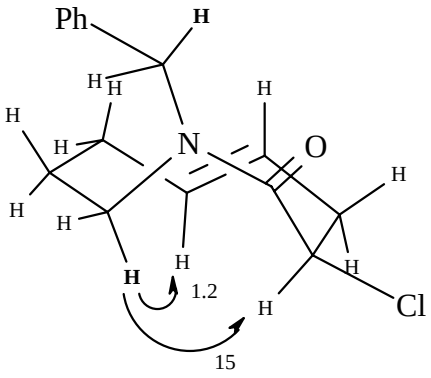
Total Synthesis of (+)-Pumiliotoxin 251D (Part 1): Synthesis of the Bicyclic Core

NOE Analyses 1



pS-**3a** (major conformer)



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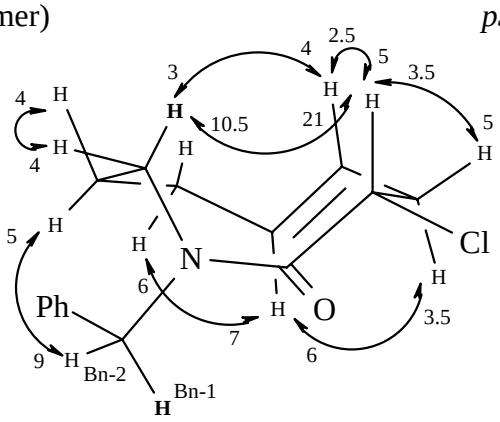

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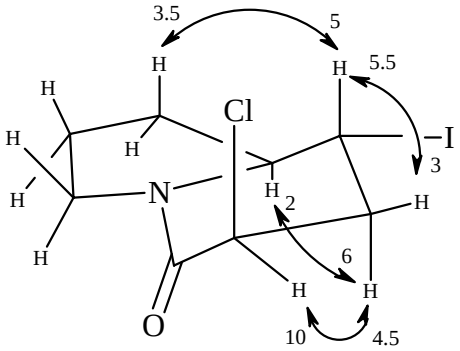
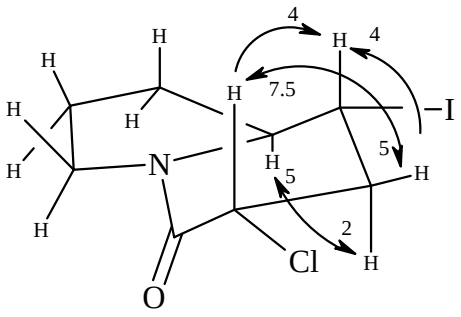


4a



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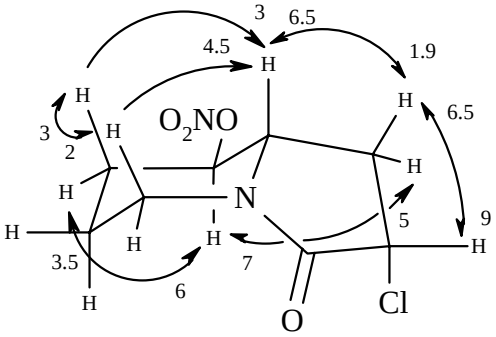
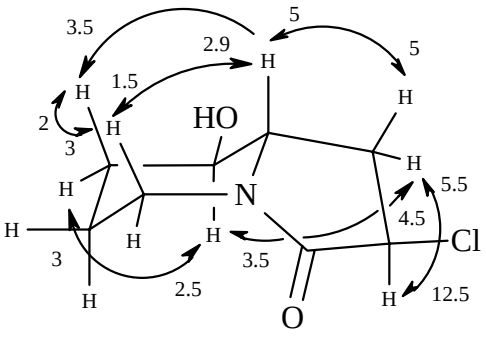


6b



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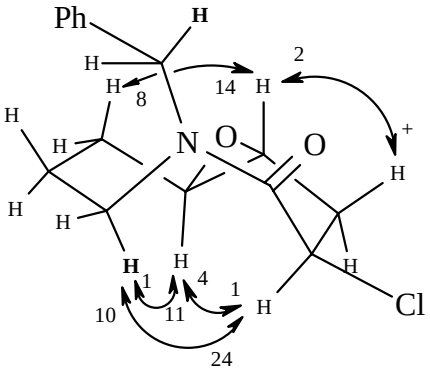
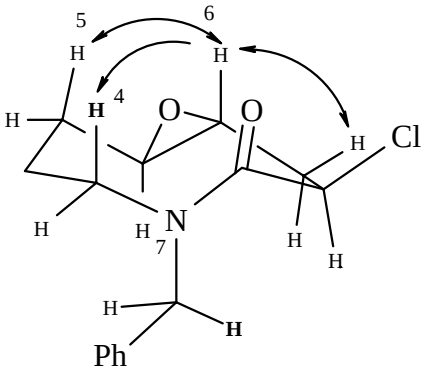
Total Synthesis of (+)-Pumiliotoxin 251D (Part 1): Synthesis of the Bicyclic Core

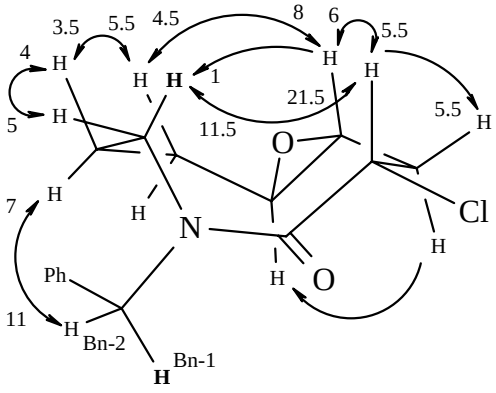
NOE Analyses 2



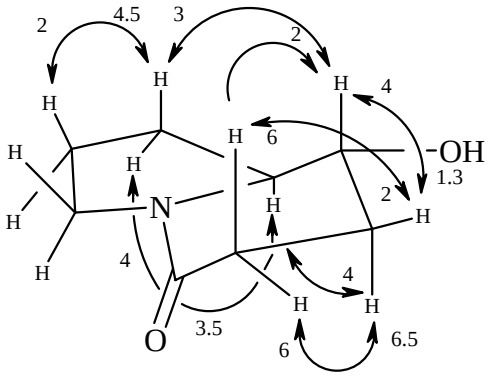
9a (major conformer 60 %)



9a (minor conformer, 40 %)



9b



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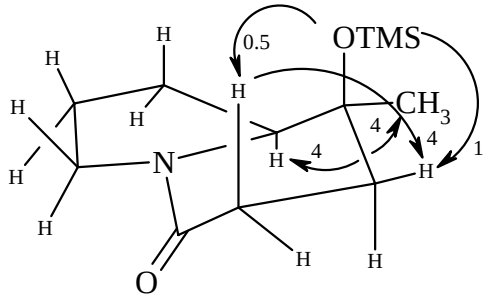

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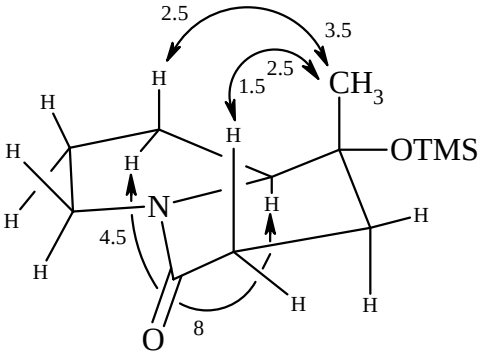

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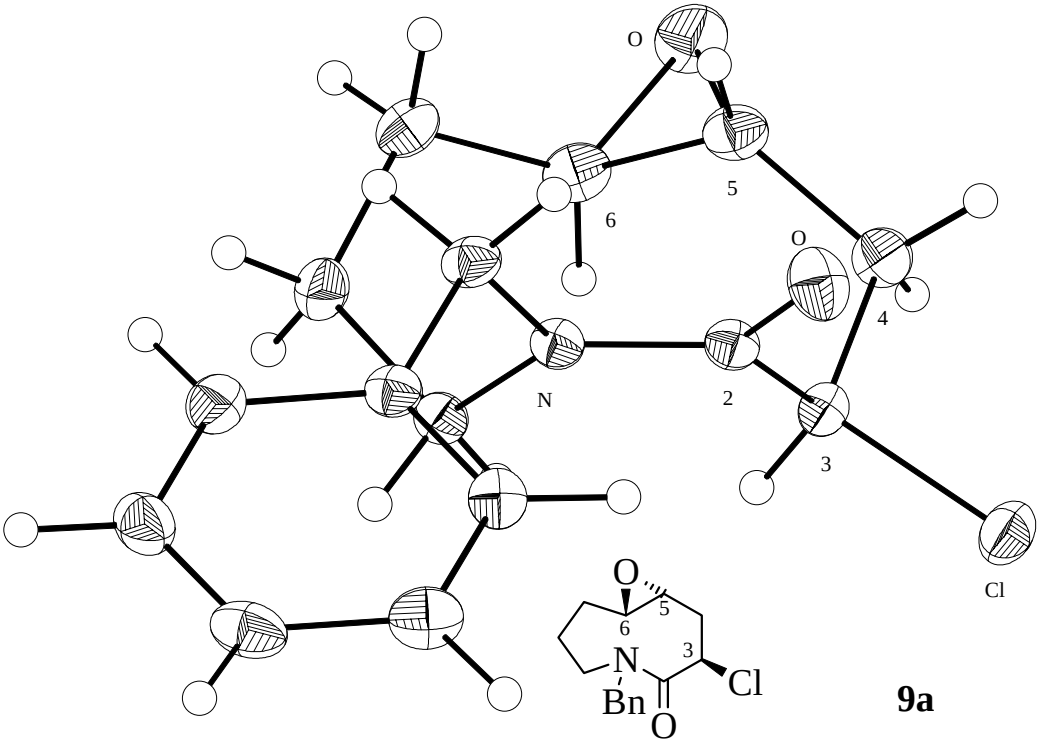
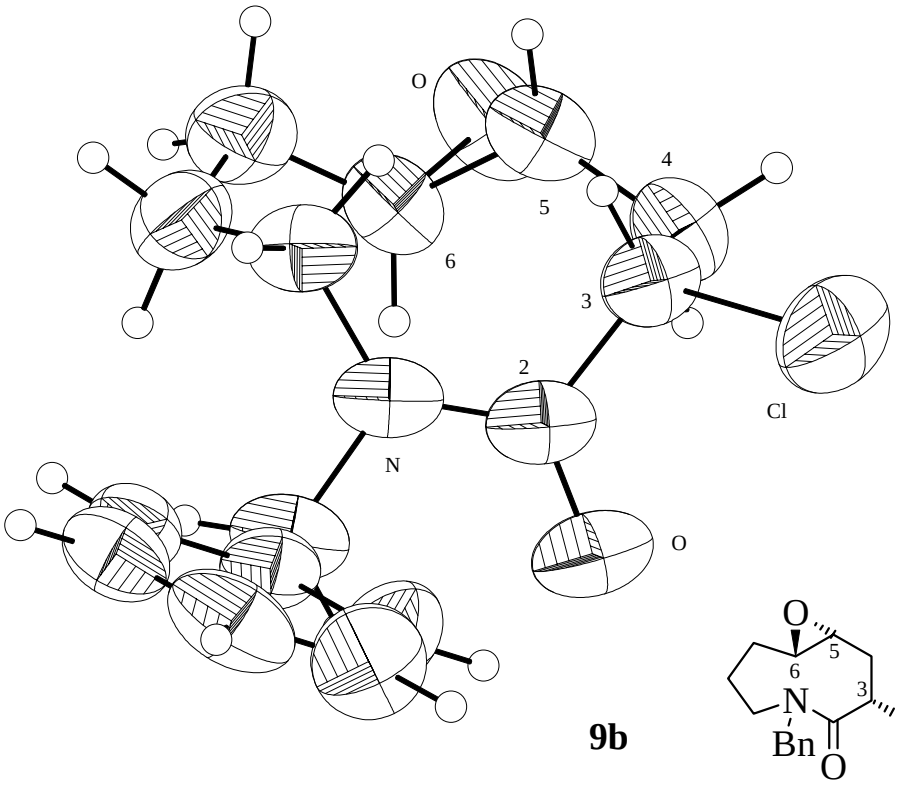
Total Synthesis of (+)-Pumiliotoxin 251D (Part 1): Synthesis of the Bicyclic Core

X-ray Analyses Epoxides 9a and 9b

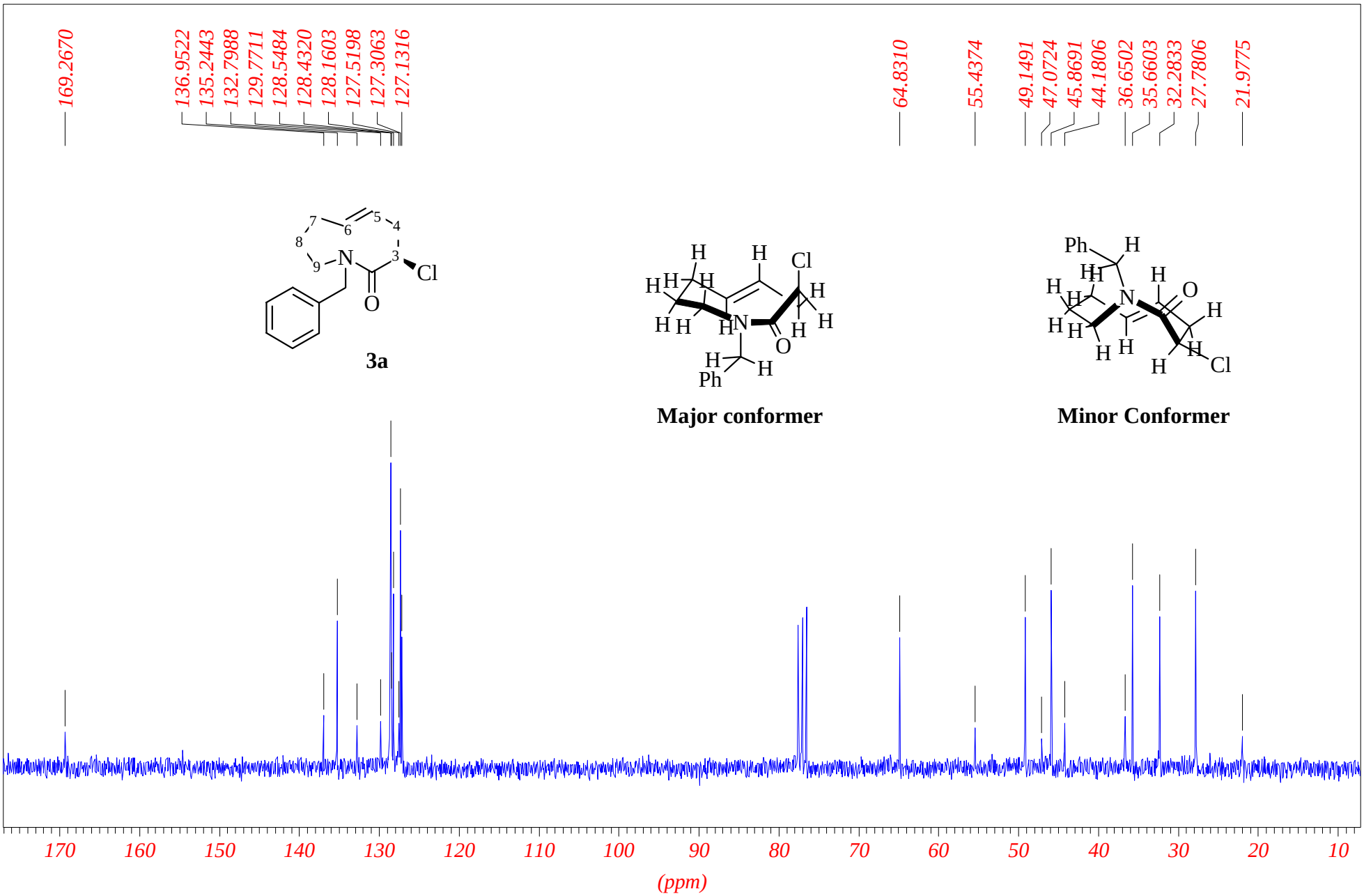


9a



9b

solvent: $CDCl_3$



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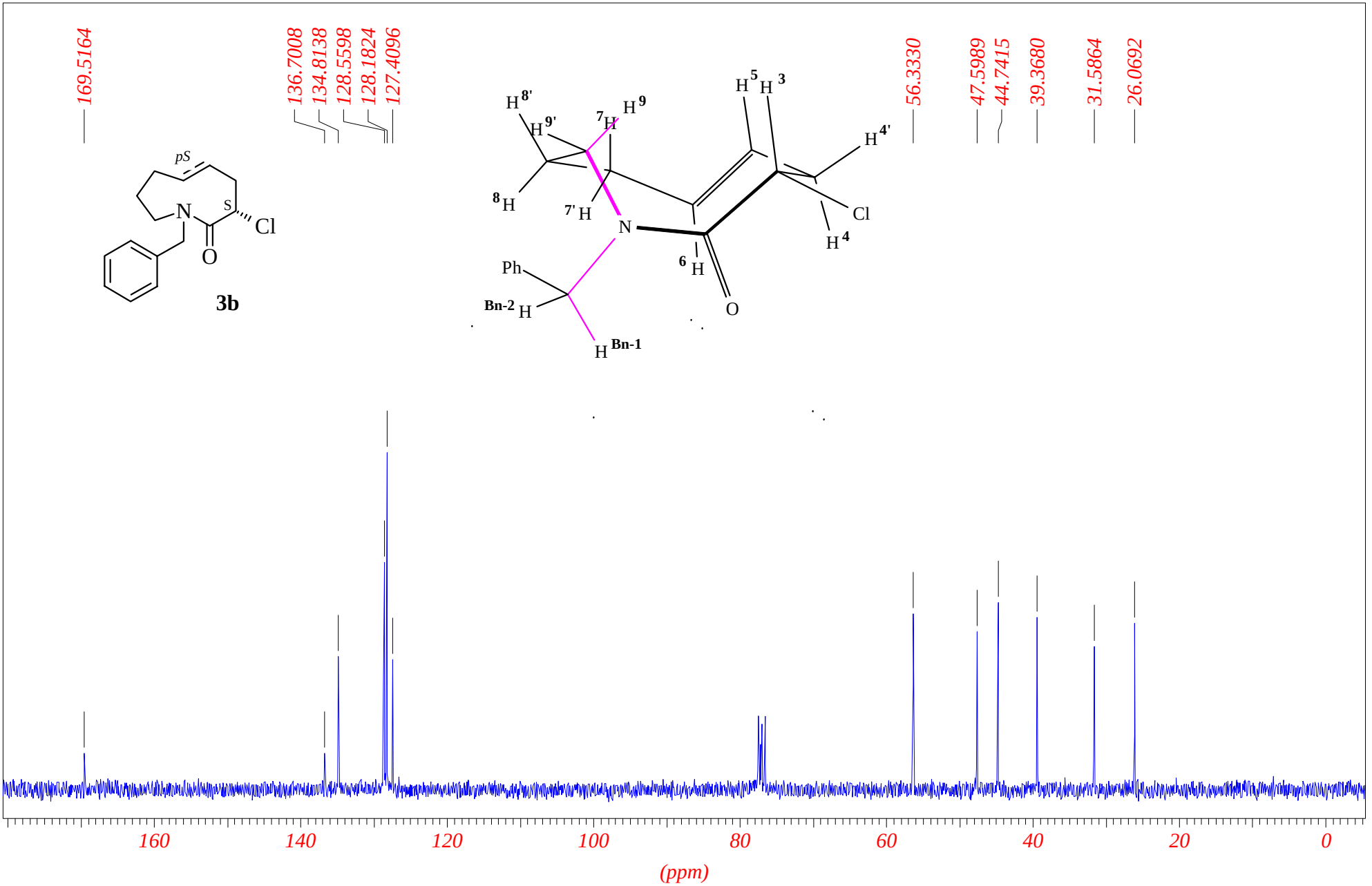

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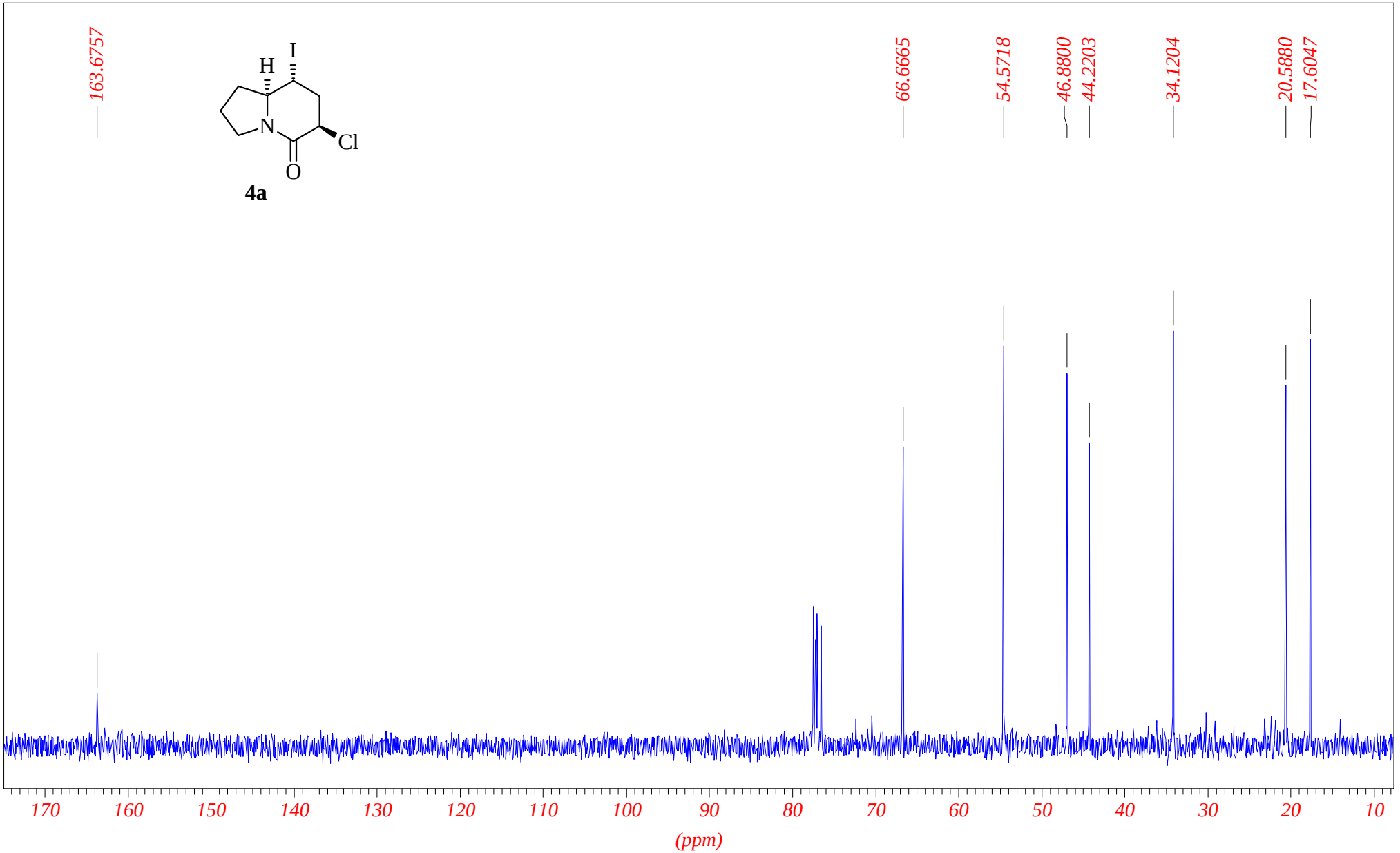
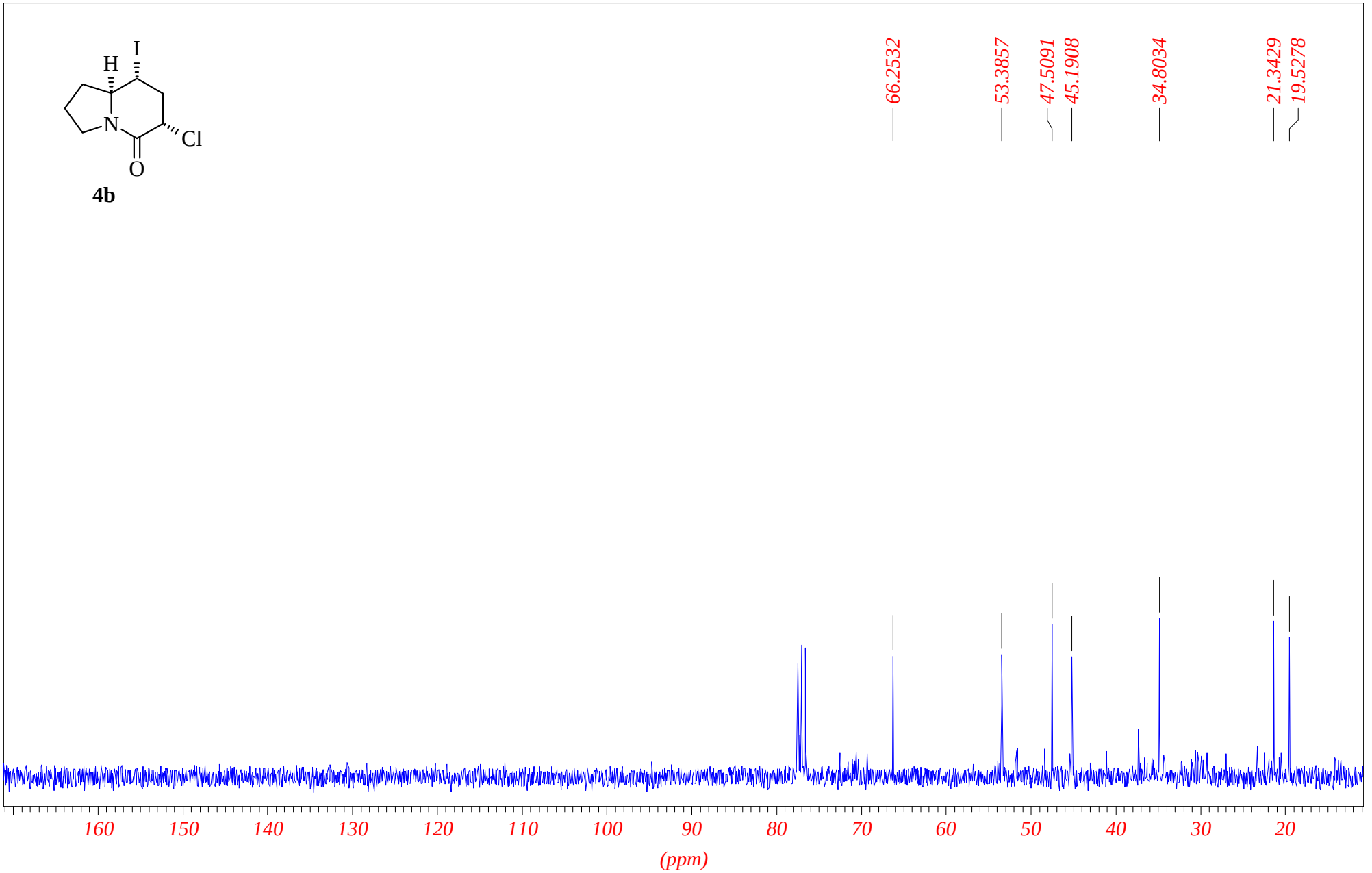
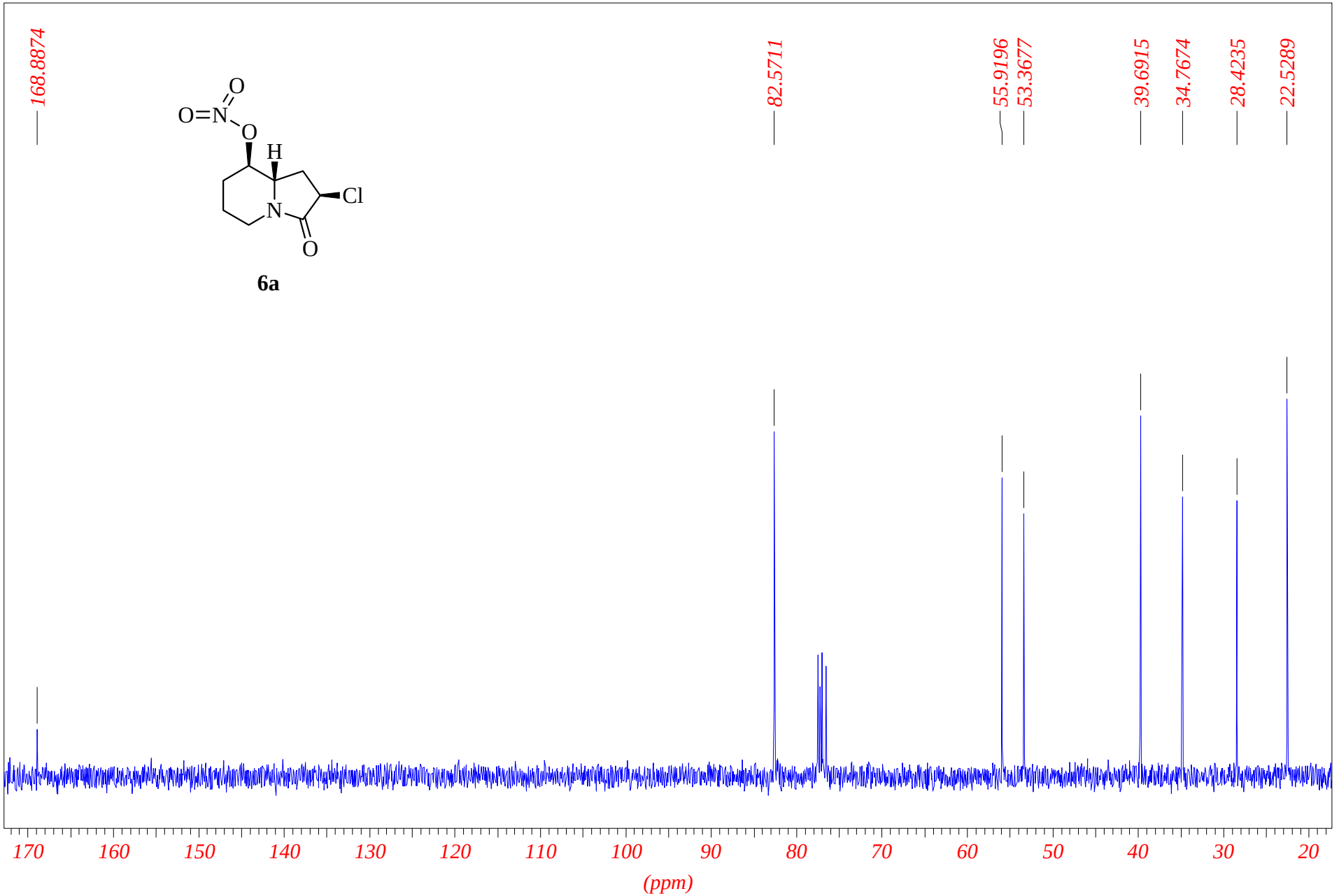


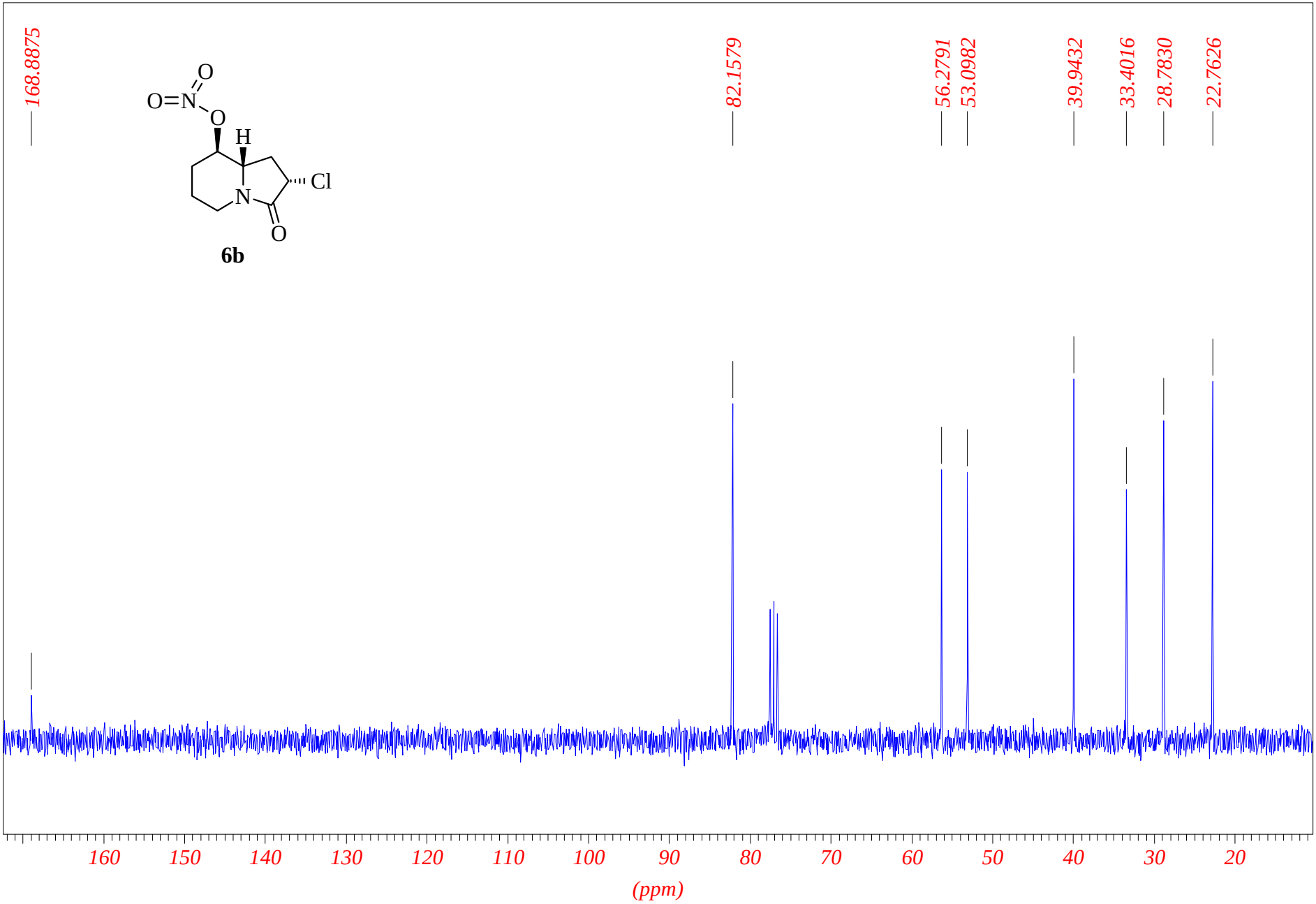
solvent: $CDCl_3$



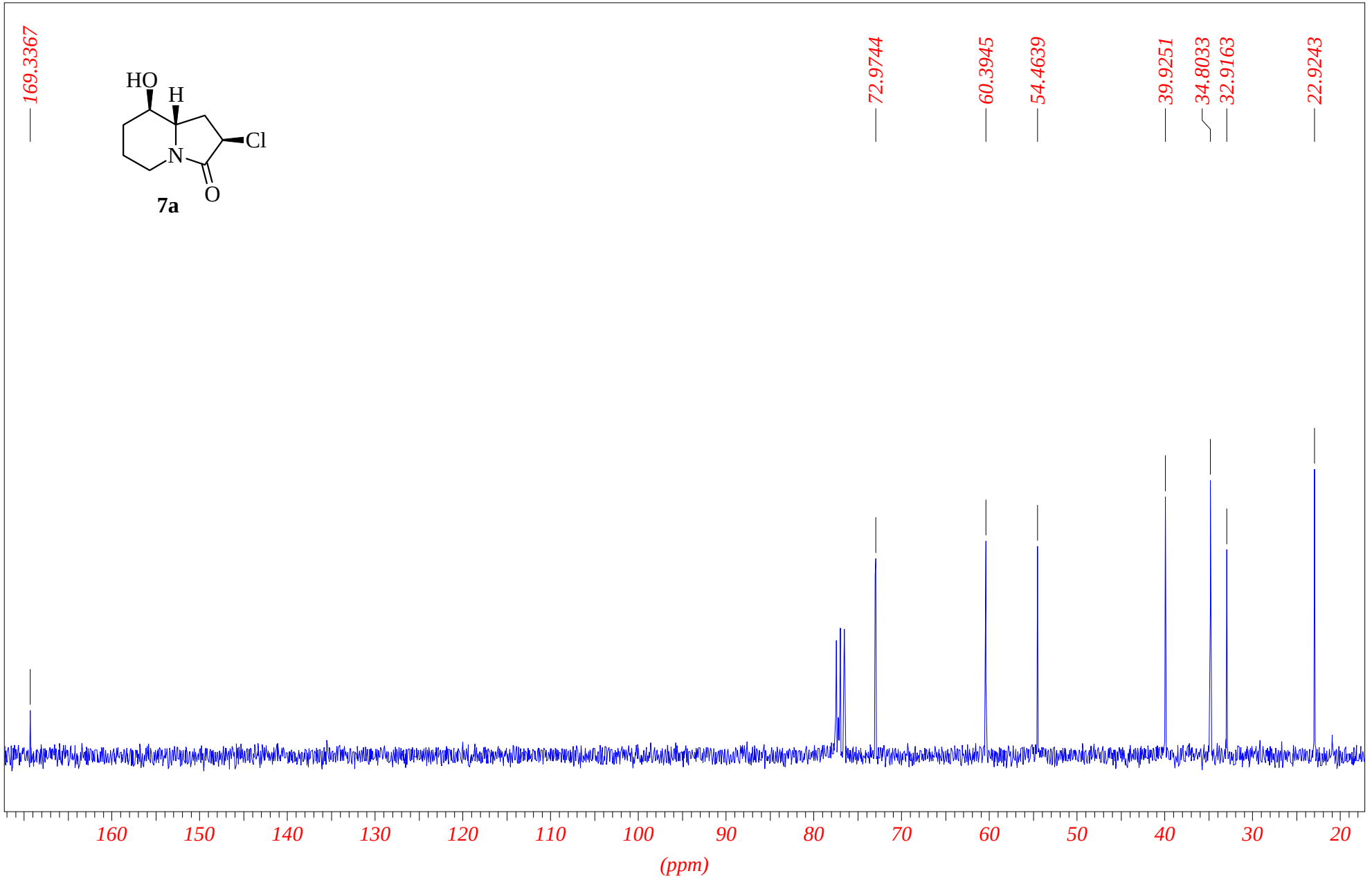
solvent: $CDCl_3$



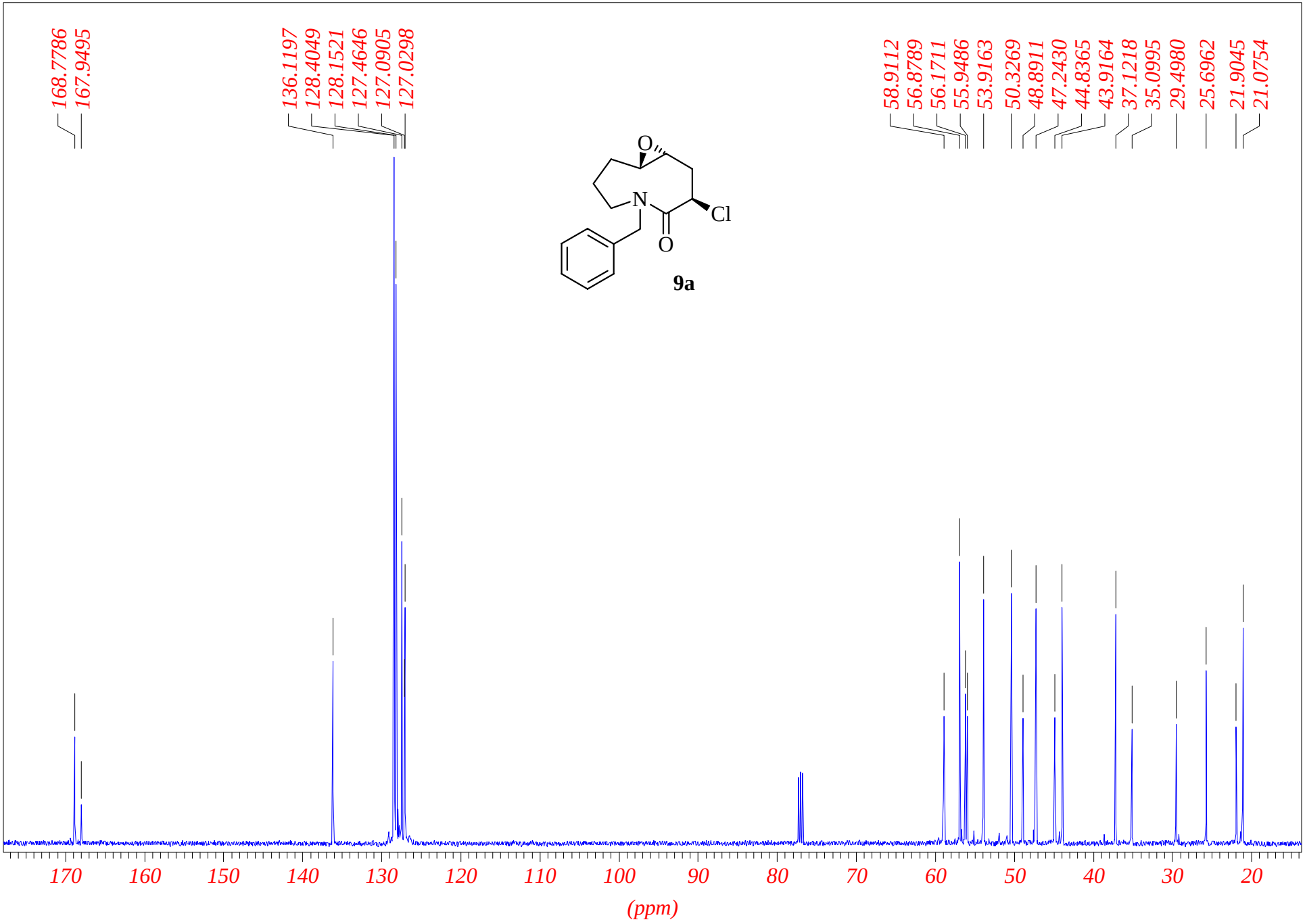
solvent: $CDCl_3$



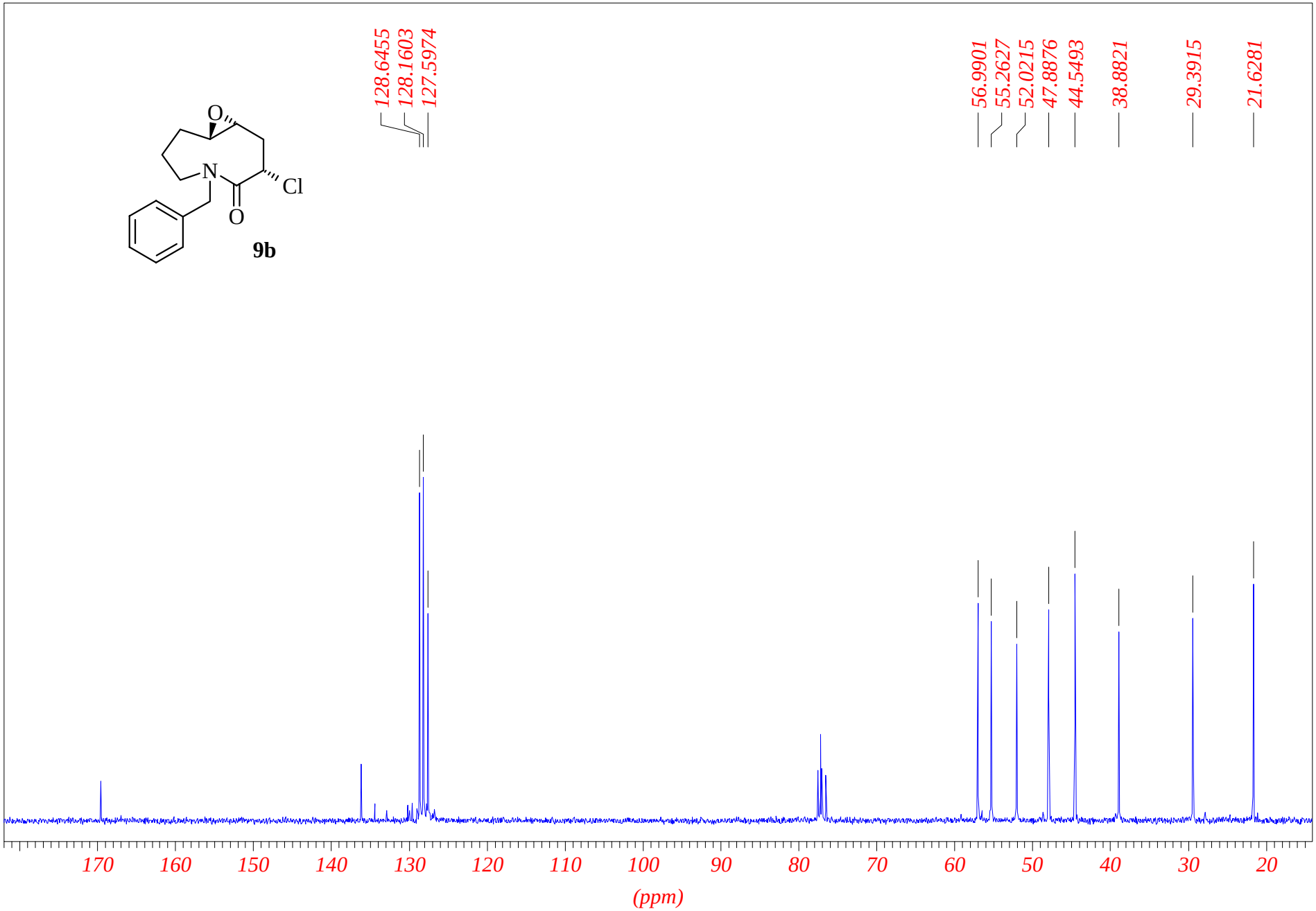
solvent: $CDCl_3$



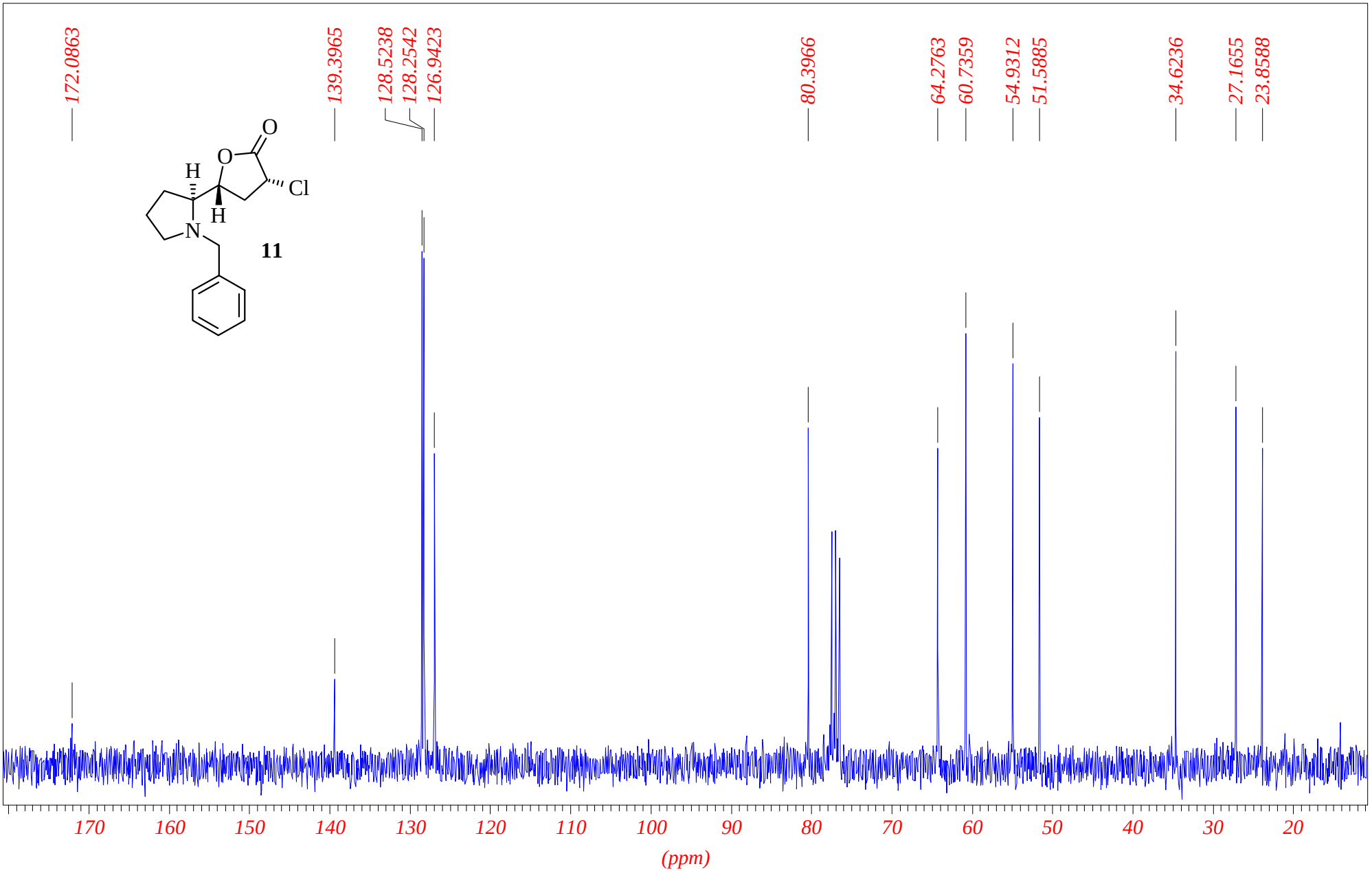
solvent: $CDCl_3$



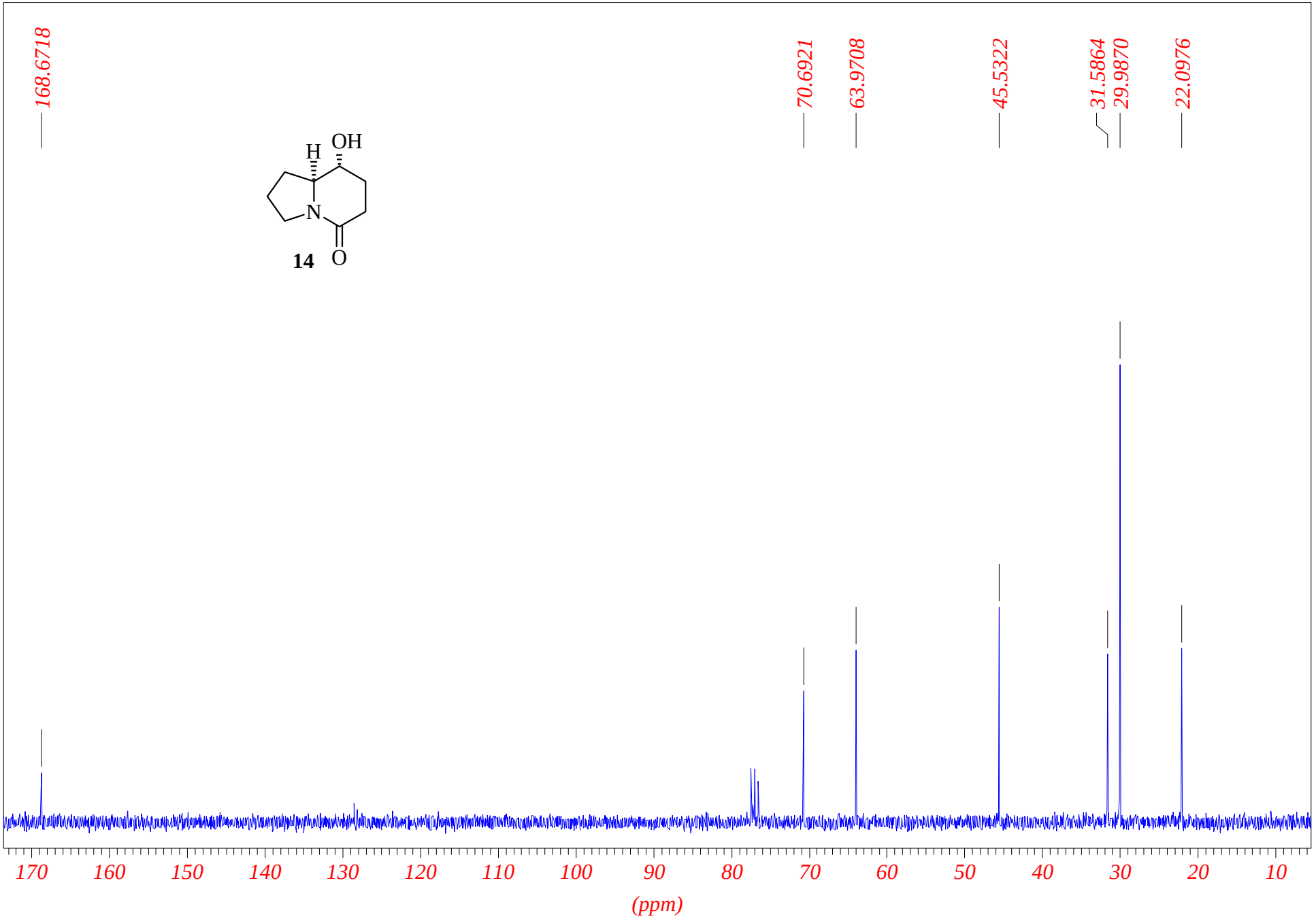
solvent: $CDCl_3$



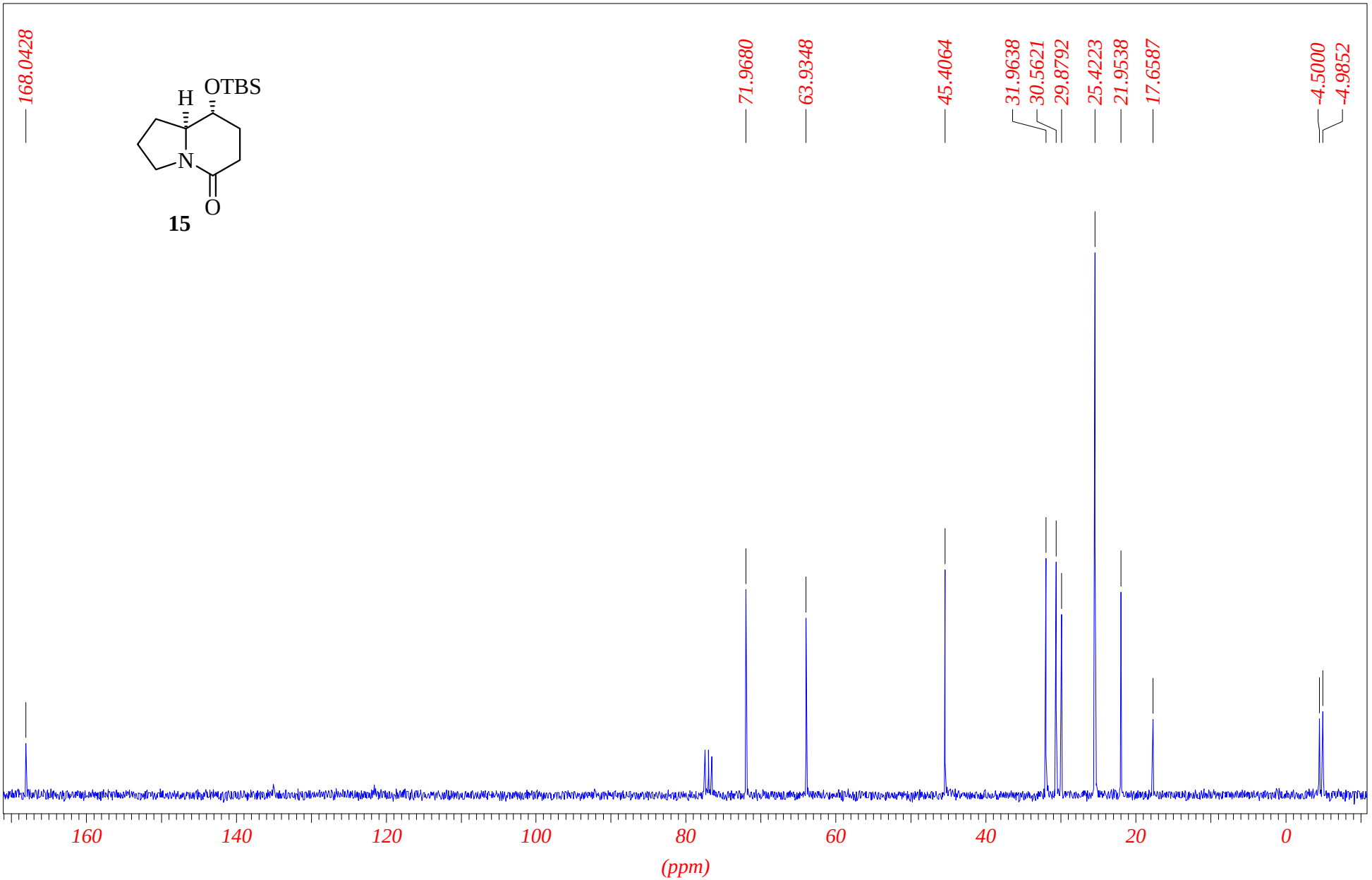
solvent: $CDCl_3$



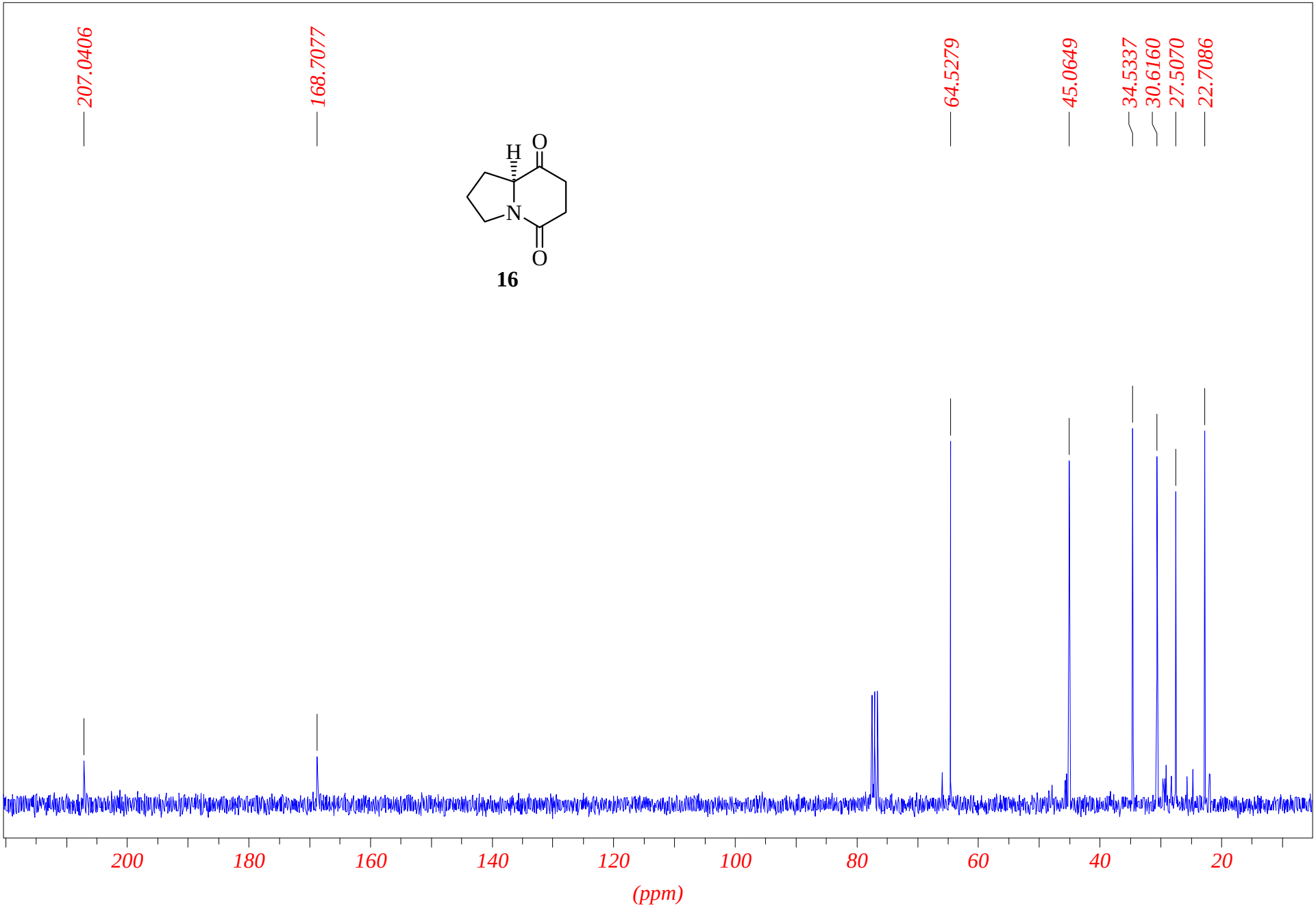
solvent: $CDCl_3$



solvent: $CDCl_3$

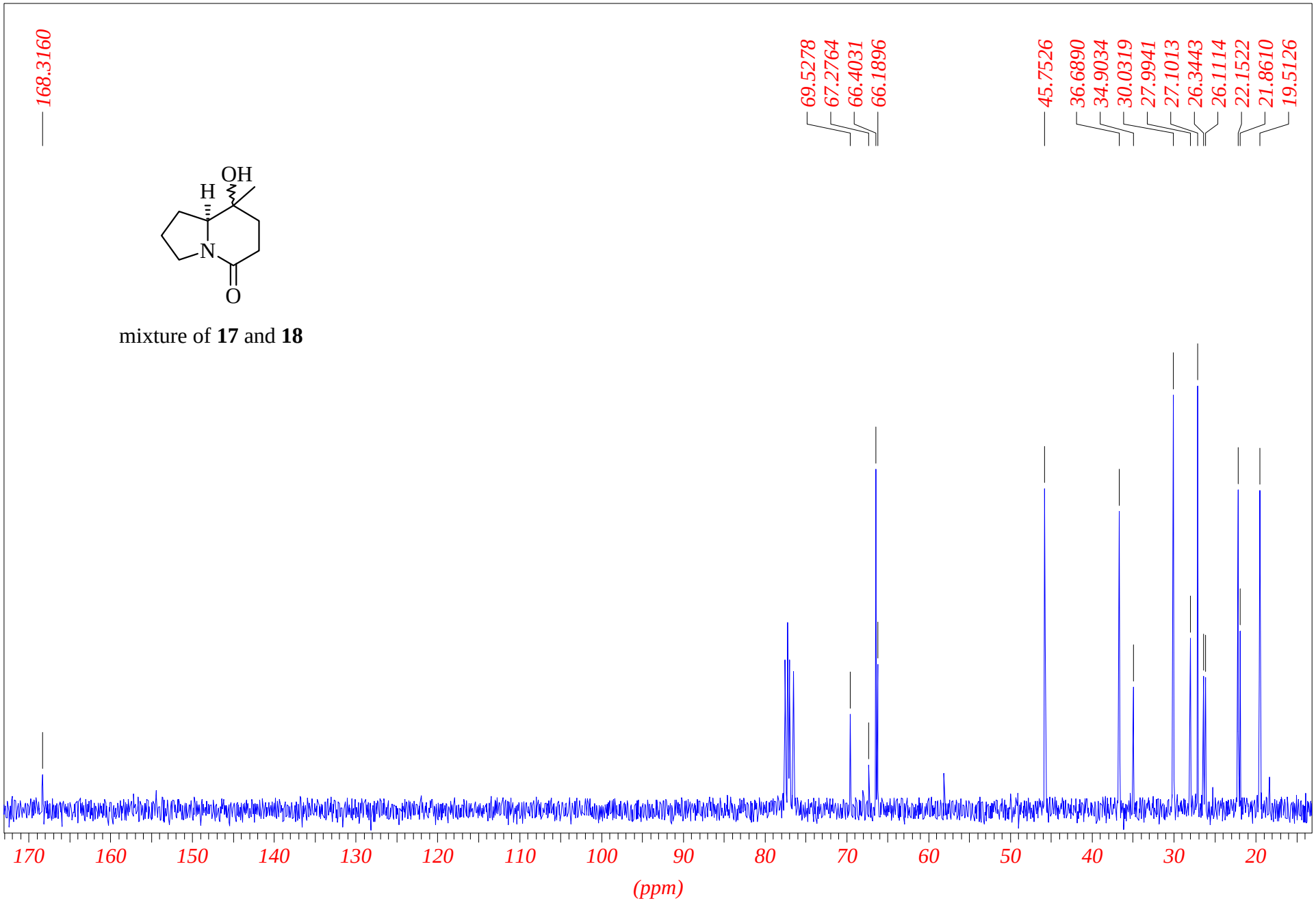


solvent: $CDCl_3$



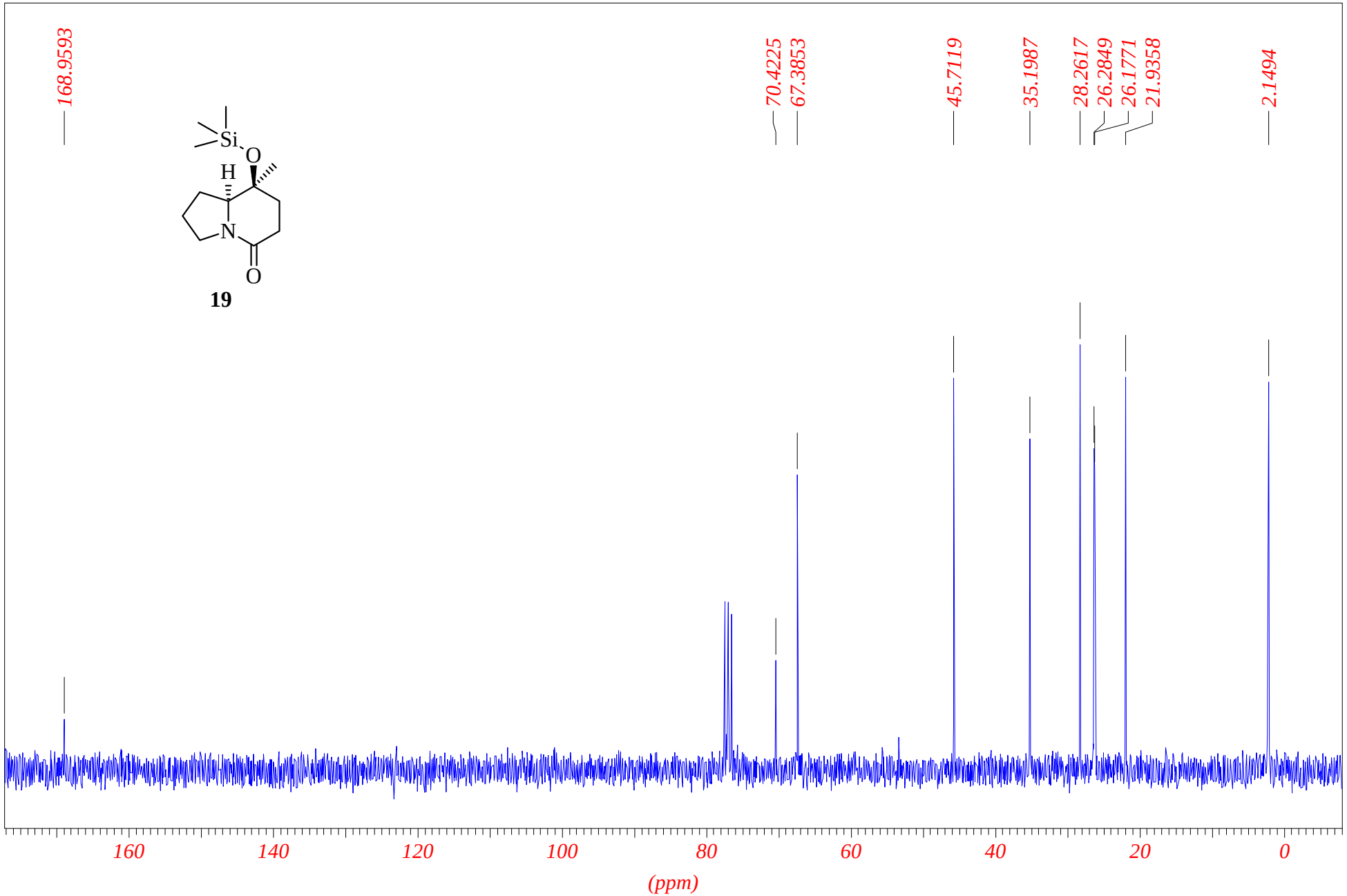
16

solvent: $CDCl_3$



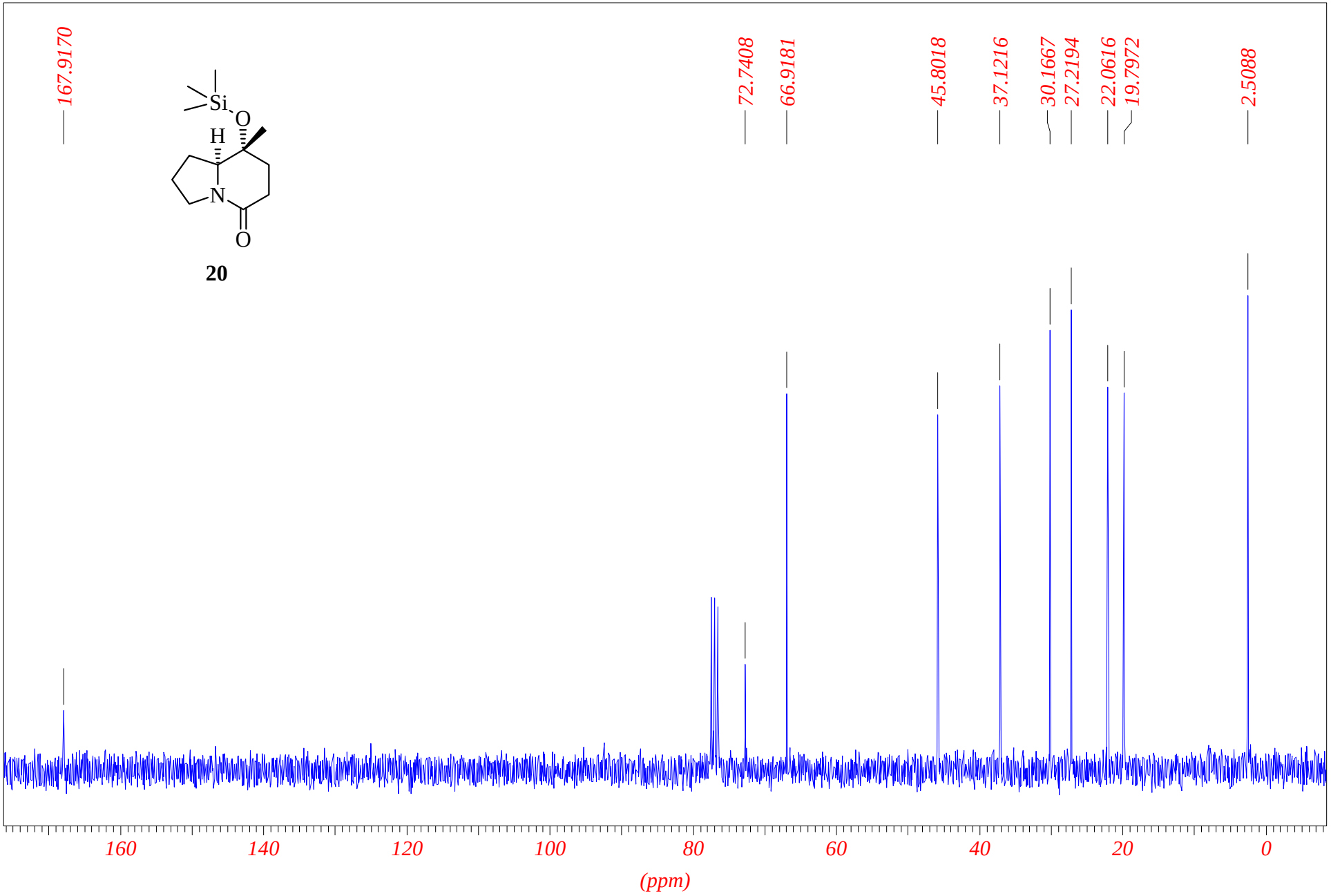
mixture of **17** and **18**

solvent: $CDCl_3$



19

solvent: $CDCl_3$



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