Iminium ion cascade reaction in the total synthesis of (+)-Vincadifformine

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Supporting information available

I) Experimental Section

II) ^{1}H and ^{13}C spectra of compounds

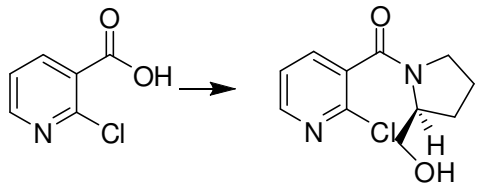
I) Experimental Section

General Procedures: All moisture-sensitive reactions were performed under an atmosphere of argon and glass wares were dried in an oven at 125 °C prior to use. Dry tetrahydrofuran (THF) and diethyl ether (Et_2O) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns and dried by distillation over sodium/benzophenone. Toluene, dimethylformamide (DMF) and dichloromethane (DCM) were distilled from calcium hydride and stored over 4Å molecular sieves. Pyridine and triethyl amine (TEA) were distilled over potassium hydroxide. Solvents used for chromatography were distilled at respective boiling points using known procedures.

All commercial reagents were obtained from Sigma-Aldrich Chemical Co and S. D. Fine Chemical Co. India. Reactions were monitored by thin layer chromatography (TLC, 0.25 mm E.Merck silica gel plates, $60F_{254}$) and visualized by using UV light, ethanolic solution of phosphomolybdic acid and iodine. Column chromatography was performed on silica gel 60-120/ 100-200/ 230-400 mesh obtained from S. D. Fine Chemical Co. India or SRL India. Typical syringe and cannula techniques were used to transfer air and moisture sensitive reagents.

All melting points were uncorrected in degree Celsius and were recorded on a Thermonik melting point apparatus. IR spectra were recorded on a Perkin-Elmer infrared spectrometer model 599-B and model 1620 FT-IR. ^{1}H NMR spectra were recorded on Bruker AC-200, Bruker AV-400 and Bruker DRX500 instruments using deuteriated solvent. Chemical shifts are reported in ppm. Proton coupling constants (*J*) are reported as absolute values in Hz and multiplicity (br, broadened; s, singlet; d, doublet; t, triplet; dd, doublet of doublet; dt, doublet of triplet; td, triplet of doublet; m, multiplet). ^{13}C NMR spectra were recorded on Bruker AC-200, AV-400 and Bruker DRX500 instruments operating at 50MHz, 100MHz and 125MHz respectively. ^{13}C NMR chemical shifts are reported in ppm relative to the central line of $CDCl_3$ (δ 77.0). Electro spray ionization (ESI) mass spectrometry (MS) experiments were performed on a Finnigan Mat-1020 spectrometer. High resolution mass spectrometric data were obtained using MSI Concept through direct insertion probe. Optical rotations were measured on a JASCO P-1030 polarimeter.

(*S*)- 2-Chloropyridin-3-yl) (2-(hydroxymethyl) pyrrolidin-1-yl)nicotinamide (II):



I **II**

To a stirred solution of 2-chloronicotinic acid (2.15 g, 13.667 mmol) and triethylamine (2.1 mL, 15.04 mmol) in anhydrous dichloromethane (65 mL) at –5 °C was added ethyl chloroformate (1.30 mL, 13.66 mmol). The resulting mixture was stirred at -5 °C for 45 minutes and (*S*) - Prolinol (1.52 g, 15.04 mmol) was added into it. The reaction mixture was allowed to warm to room temperature and stirred for additional 4 h, concentrated, purified by column chromatography (SiO_2, acetone-petroleumether,1:5→2:5) to afford **II** (3.22 g, 98%) as a colorless viscous oil which got crystallized from ethyl acetate/ petroleum ether as a colorless solid (mp = 61-62 °C); R_f = 0.3 (SiO_2, acetone-petroleum ether, 3:7); $[\alpha]^{26}_{D}$ = -78.023 ($CHCl_3$, *c* = 0.85);

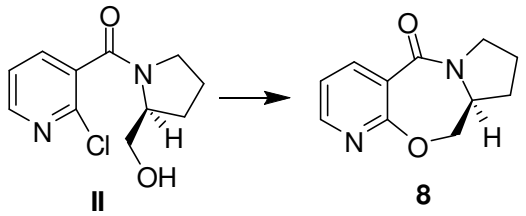
IR (film)ν_{max} = 3397, 2977, 1622, 1074 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$/ D_2O) = 8.44 (dd, *J* = 1.9, 4.9 Hz, 1H), 7.69 (dd, *J* = 1.9, 7.4 Hz, 1H), 7.32 (dd, *J* = 4.9, 7.7 Hz, 1H), 4.52-4.35 (m, 2H), 3.83-3.72 (m, 2H), 3.33-3.27 (m, 2H), 2.21-2.15 (m, 1H), 1.94-1.89 (m, 1H), 1.85-1.81 (m, 1H), 1.75-1.68 (m, 1H);

^{13}C NMR (50 MHz, $CDCl_3$) = 166.7, 150.1, 146.4, 136.4, 132.9, 122.7, 65.3, 61.1, 49.1, 28.1 24.2;

HR-MS (EI): calcd for $C_{11}H_{13}ClN_2O_2$:240.06656. Found: 240.06084.

1,2,3,10,11,11a,(*S*)-Hexahydro-5H-pyrrolo[2,1-*c*]pyrido-[3,2-*f*][1,4]oxazepin-5-one(8):



II **8**

A mixture of **II** (1.2 g, 4.98 mmol) and sodium hydride (0.131 g, 5.48 mmol) in 60 mL of anhydrous THF was refluxed under nitrogen for 16 h. Sodium chloride and unreacted NaH were removed by filtration, solvent evaporation and crystallization (ethyl acetate) afford analytically pure **8** as white crystals (1.0 g, 99%)**;** mp = 146-147 °C; **$[\alpha]^{25}_D$** = + 230.96° ($CHCl_3$, *c* = 1.55);

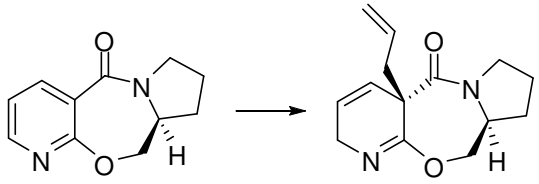
IR (film)ν_{max} = 3003, 1624, 1590, 1463, 1433, 1383, 1215 cm^{-1};

^{1}H NMR (200 MHz, $CDCl_3$) = 8.61 (dd, *J* = 2.0, 7.8 Hz, 1H), 8.36 (dd, *J* = 2.0, 4.5 Hz, 1H), 7.10 (dd, *J* = 4.6, 7.8 Hz, 1H), 4.6 (d, *J* = 11.5 Hz, 1H), 4.16-3.93 (m, 2H), 3.85-3.63 (m, 2H), 2.33-2.19 (m, 1H), 2.09-1.81 (m, 2H), 1.76-1.57 (m, 1H);

^{13}C NMR (50 MHz, $CDCl_3$) = 162.5, 160.4, 151.2, 143.5, 118.1, 115.8, 73.2, 57.2, 48.1, 29.2, 23.3;

HR-MS (EI): calcd for $C_{11}H_{12}N_2O_2$: 204.08988. Found: 204.08954.

(4a*S*, 9a*S*)-4a-Allyl-4a, 7, 8, 9, 9a, 10-hexahydropyrido [3, 2-*f*] pyrrolo [2, 1-*c*] [1, 4] oxazepin-5(2H)-one (9):



8 **9**

To a stirred solution of finely powdered **8** (0.25 g, 1.23 mmol) and *tert*-butyl alcohol (0.09 g, 0.11 mL, 1.23 mmol) in THF (2.5 mL) and ammonia (30 mL) was added sodium (0.104 g, 4.56 mmol) in small pieces at -78 °C. After 50 minutes, isoprene (few drops) was added until the blue coloration dissipated and a dark yellow solution resulted. Allyl bromide (3.2 mL, 36.99 mmol) was added into the flask in one portion. The resulting solution was vigorously stirred at -78 °C

for 3 h, quenched with water (5 mL). The reaction mixture was allowed to warm to room temperature while ammonia got evaporated. Extracted with dichloromethane (30 mL × 3), dried over Na_2SO_4 and concentrated. Purification by column chromatography (acetone-petroleum ether 2:8→3:7) afforded **9** as brown colored thick liquid (0.139 g, 46% yield and 97.9% de). Diastereomeric ratio was determined by HPLC analysis (Atlantis RP-18 (250 × 4.6mm) column, acetonitrile-water (40:60) as an eluent, 1.0 mL/min, λ = 224nm, 25 °C). The retention times of major isomer and minor isomer were 5.33 and 6.19 minutes, respectively. This compound upon crystallization with dichloromethane - *n*-pentane gave single diastereomer as colorless crystals.

(R_f = 0.3 acetone: petroleum ether 3:7) mp = 105.5-106.5 °C; $\mathbf{[\alpha]^{25}_D}$ = + 133.746° (*c* = 2.6, $CHCl_3$);

IR (film) ν_{max} = 1688, 1630, 1412, 1352 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) = 5.87-5.79 (m, 2H), 5.66-5.55 (m, 1H), 5.1-5.02 (m, 2H), 4.28 (dd, *J* = 10.8, 2.2 Hz, 1H), 4.2-4.07 (m, 3H), 3.9 (t, *J* = 10.5 Hz, 1H), 3.62-3.48 (m, 2H), 2.66 (d, *J* = 7.5 Hz, 2H), 2.11-2.03 (m, 1H), 1.90-1.73 (m, 2H), 1.6-1.51 (m, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) = 169.5, 161.6 132.1, 126.9, 125.1, 119.2, 72.7, 54.9, 52.1, 49.5, 48.1, 42.0, 29.2, 22.3;

HR-MS (EI): calcd for $C_{14}H_{18}N_2O_2$: 246.13683. Found: 246.13783.

X-ray Crystal Structure Analysis For 9 (C14H18N2O2) (CCDC-783953)

Crystal Data: Single crystals of the compound were grown by slow evaporation of compound **9** in dichloromethane and *n*-pentane. Colourless crystal of approximate size 0.30 x 0.26 x 0.14 mm, was used for data collection on *Bruker SMART APEX* CCD diffractometer using Mo K_α radiation with fine focus tube with 50kV and 30mA. Crystal to detector distance 6.05 cm, 512 x 512 pixels / frame, hemisphere data acquisition. Total frames = 1271, Oscillation / frame -0.3º, exposure / frame = 5.0 sec / frame, maximum detector swing angle = –30.0º, beam center = (260.2, 252.5), in plane spot width = 1.24, SAINT integration, θ range = 2.09 to 25.0º, completeness to θ of 25.0º is 100.0%. SADABS correction applied , C14H18N2O2, *M* = 246.30. Crystals belong to Tetragonal, space group $P4_32_12$, *a* = 11.0581(5), *b* = 11.0581(5), *c* = 20.481(4) Å, *V* = 2504.5(5) $Å^3$, *Z* = 8, D_c = 1.306 g /cc, μ (MoKα) = 0.088 mm^{-1}, *T* = 150(2) K, 17820 reflections measured, 2210 unique [I>2σ(I)], R value 0.0309, wR2 = 0.0815. All the data were corrected for Lorentzian, polarisation and absorption effects. SHELX-97 (ShelxTL)[ref] was used for structure solution and full matrix least squares refinement on F^2. Hydrogen atoms were

included in the refinement as per the riding model. X-ray analysis revealed the relative conformation of the molecule at C4a and C9a as *S* and *S* configuration.

The disordered atoms C13 and C14 have been refined with the split occupancies, C13 and $C13^1$ have 0.5 occupancies, while C14 has 0.6 and $C14^1$ has 0.4 occupancies respectively.

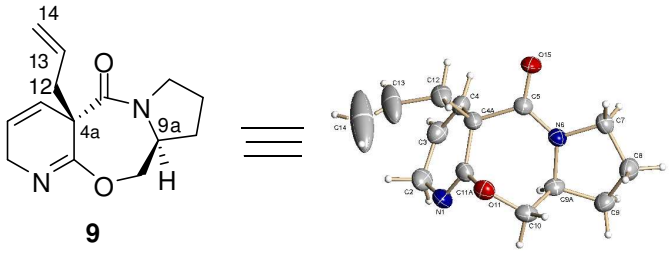
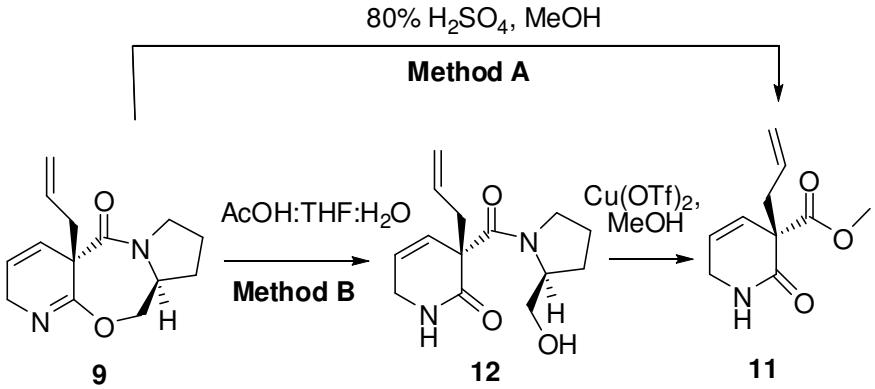


Figure 1: ORTEP diagram of **9**. Ellipsoids are drawn at 50% probability.

(*S*)-Methyl 3-allyl-2-oxo-1, 2, 3, 6-tetrahydropyridine-3-carboxylate (11):



Method A: A solution of **9** (0.39 g, 1.59 mmol) in methanol (8 mL) and 80% sulfuric acid (1 mL) was stirred at room temperature for 75 h. The methanol was evaporated under reduced pressure and the residue was basified with the saturated sodium bicarbonate solution, stirred for ten minutes. The mixture was extracted with dichloromethane (3 × 20 mL) and the combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification by column chromatography (SiO_2, ethyl acetate:petroleum ether, 2:3→3:2) afforded **11** (0.14 g) as a white solid (45% yield and 19% enantiomeric excess). Enantiomeric excess was determined by HPLC analysis {Chiralcel OD-H (250 × 4.6mm) column, isopropanol–petroleum ether (10:90) as an eluent}, 0.5 mL/min (265psi), λ = 220nm, 25 °C, the retention times of (+) - isomer and (-) - isomer being 27.36 and 52.35 minutes, respectively.

Method B: To a stirred solution of **9** (0.5 g, 2.03 mmol) in THF (8 mL) was added glacial acetic acid (1 mL) and water (1 mL) at room temperature. After stirring for 20 h, it was neutralized with

saturated $NaHCO_3$ solution, extracted with dichloromethane (3 × 25 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (acetone-petroleum ether 1:1) to afford pure **12** (0.477 g, 89%). mp = 141-142 °C; (R_f = 0.34 acetone: petroleum ether 7:3); $[\alpha]^{26}_{D}$ = + 28.82° ($CHCl_3$, *c* = 3.254);

IR (film) ν_{max}= 3401, 1679, 1658, 1412 cm^{-1};

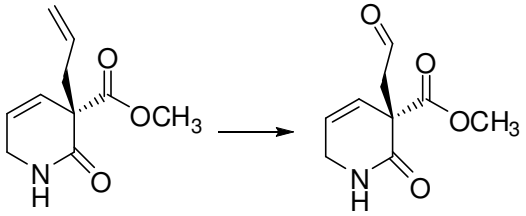
^{1}H NMR (200 MHz, $CDCl_3$) δ_H = 7.13 (bs, 1H), 5.96 (td, *J* = 2.9, 9.9 Hz, 1H), 5.82-5.58 (m, 2H), 5.12-5.01 (m, 2H), 4.52 (bs, 1H), 3.96 (bs, 2H), 3.59-3.5 (m, 2H), 3.42 (t, *J* = 6.6 Hz, 2H), 2.9(dd, *J* = 7.8, 13.7 Hz, 1H), 2.6 (dd, *J* = 7, 13.8 Hz, 1H), 2.02-1.74 (m, 3H), 1.62-1.49 (m, 1H);

^{13}C NMR (50 MHz, $CDCl_3$) δ_C =170.3, 169.9, 132.4, 125.4, 122.2, 119.0, 65.8, 61.7, 54.4, 46.7, 43.6, 41.9, 27.1, 24.5;

HR-MS (EI): calcd for $C_{14}H_{20}N_2O_3$: 264.14739. Found: 264.13514.

To a stirred solution of **12** (0.21 g, 0.8 mmol) in anhydrous methanol (20 mL) was added copper (II) triflate (0.29 g, 0.8 mmol) at room temperature, stirred for 48 h, concentrated and basified with saturated sodium bicarbonate solution. The aqueous layer was extracted with dichloromethane, dried over sodium sulfate, concentrated and purified by column chromatography (SiO_2, ethyl acetate: petroleum ether, 2:3→3:2) to afford **11** as a white solid (0.136 g, 87% yield as single enantiomer). Enantiomeric excess was determined by HPLC analysis {(Chiralcel OD-H (250×4.6mm) column, isopropanol- petroleum ether (10:90) as an eluent, 0.5 mL/min (265psi), λ = 220nm, 25 °C, the retention times of (+) - isomer being at 27.89 minutes}; mp = 88-91 °C; R_f = 0.4 (SiO_2, ethyl acetate:petroleum ether 4:1); $[\alpha]^{23}_{D}$ = + 82.812 ($CHCl_3$, *c* = 1.1);
IR (film) ν_{max} = 3226, 3078, 2952, 1731, 1660, 1236, 923 cm^{-1};
^{1}H NMR (200 MHz, $CDCl_3$) = 6.67 (bs, 1H), 6.0-5.92 (m, 1H), 5.76-5.55 (m, 2H), 5.18-5.04 (m, 2H), 4.12-3.85 (m, 2H), 3.71 (s, 3H), 2.98 (dd, *J* = 7.3, 13.7 Hz), 2.61 (dd, *J* = 7.2, 13.7 Hz), 2.0 (bs, 1H);
^{13}C NMR (50 MHz, $CDCl_3$) = 171.0, 168.8, 132.4, 125.5, 123.1, 119.1, 54.1, 52.8, 43.4, 39.5;
HR-MS (EI): calcd for $C_{10}H_{13}NO_3$: 195.08954. Found: 195.08821.

(*S*)-Methyl-2-oxo-3-(2-oxoethyl)-1, 2, 3, 6-tetrahydropyridine-3-carboxylate (11a):



11 **11a**

To a solution of **11** (0.15 g, 0.799 mmol) in dioxane-water (3:1, 8 mL) was added 2,6-lutidine (0.27 mL, 2.397 mmol), OsO_4 (2.14 % in 2-methyl-2-propanol, 4 mg, 0.0159 mmol), and $NaIO_4$ (0.683 g, 3.19 mmol).The reaction was stirred at 25 °C for 4 h and diluted with water (20 mL), extracted with CH_2Cl_2 (25 mL × 3). The combined organic layers were washed with brine and dried over Na_2SO_4, concentrated and purification by column chromatography (SiO_2, ethyl acetate- petroleum ether, 8:2→10:0) to obtain **11a** (0.11 g, 70%) as a colorless liquid. R_f = 0.3 (SiO_2, ethyl acetate-petroleum ether 6:4); $[\alpha]^{23}_D$ = + 3.88 (*c* = 1.15, $CHCl_3$);

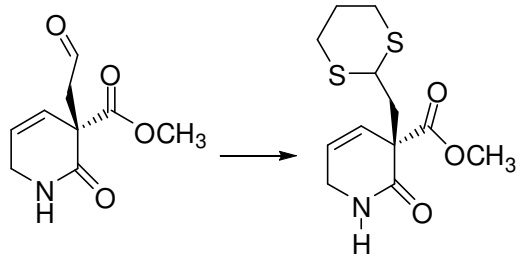
IR (neat) ν_{max} = 3319, 2955, 1726, 1682, 1660, 1487, 1334, 1235 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) = 9.72 (d, *J* = 1.6 Hz, 1H), 6.72 (bs, 1H), 6.01-5.97 (m, 1H), 5.68 (dt, *J* = 2.1, 9.9 Hz, 1H), 4.13-4.00 (m, 2H), 3.75 (s, 3H), 3.24 (d, *J* = 17.7 Hz, 1H), 3.02(dd, *J* = 2.0, 17.7 Hz);

^{13}C NMR (100 MHz, $CDCl_3$) = 198.7, 170.1, 168.4, 124.6, 124.0, 53.14, 51.2, 48.1, 43.29;

MS (ESI) (*m/z*) = 220.100 $(M + Na)^+$.

(*S*)-Methyl 3-((1,3-dithian-2-yl)-2-oxo-1,2,3,6-tetrahydropyridine-3-carboxylate (11b):



11a **11b**

To a solution containing **11a** (0.21 g, 1.085 mmol) in anhydrous CH_2Cl_2 (25 mL) were added 1,3-propanedithiol (0.152 g, 0.14 mL, 1.41 mmol) and boron trifluoride etherate (1.23 g, 1.1 mL, 8.68 mmol). The mixture was refluxed for 12 h, cooled to room temperature and quenched with aqueous $NaHCO_3$ (10 mL) . The aqueous layer was extracted with CH_2Cl_2, washed with water and dried over sodium sulfate, concentrated and purified by column chromatography (SiO_2,

ethyl acetate-petroleum ether, 6:4→7:3) to afford **11b** (0.251 g, 81%) as a gummy compound. R_f = 0.45 (SiO_2, EtOAc); $[\alpha]^{26}_D$ = + 102.42° (*c* = 2.75, $CHCl_3$);

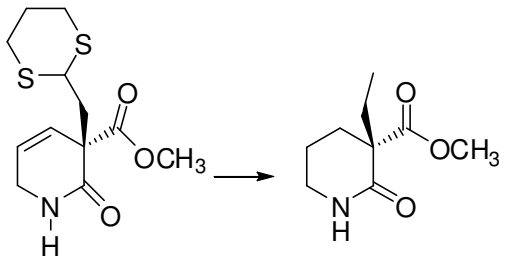
IR (neat) ν_{max} = 3213, 2902, 1738, 1682, 1662, 1488, 1433, 1229 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) = 6.87 (bs, 1H), 6.02- 5.97 (m, 1H), 5.67 (dt, *J* = 10.0, 2.1 Hz, 1H), 4.10-3.97 (m, 2H), 3.85 (dd *J* = 9.2, 5.5 Hz, 1H), 3.71 (s, 3H), 2.98 (dd, *J* = 14.6, 9.2 Hz, 1H), 2.95-2.84 (m, 2H), 2.67-2.61 (m, 1H), 2.46 (dd, *J* = 14.56, 5.40 Hz, 1H), 2.01-1.95 (m, 1H), 1.94-1.84 (m, 1H), 1.75 (s, 1H);

^{13}C NMR (50 MHz, $CDCl_3$) = 170.5, 168.7, 124.2, 123.8, 53.2, 52.8, 43.3, 41.7, 38.9, 28.5, 28.1, 25.1;

HR-MS(ESI): calcd for $C_{12}H_{17}NO_3S_2$: 287.06498. Found: 287.05690.

(*S*)- Methyl 3-ethyl-2-oxopiperidine-3-carboxylate (14):



To a solution of **11b** (0.423 g, 1.47 mmol) in absolute ethanol (65 mL) was added Raney-Ni (W-2, 2 g, prewashed with absolute ethanol) followed by refluxing under a hydrogen atmosphere (1 atm) for 7 h. The reaction mixture was filtrated through celite and the filtrate was concentrated under reduced pressure, purified by column chromatography (silica gel, eluting with ethyl acetate) to obtain **14** (0.25 g, 94%) as a colorless liquid. R_f = 0.33 (SiO_2, ethyl acetate);

$[\alpha]^{27}_D$ = - 48.3314 ($CHCl_3$, *c* = 2.45);

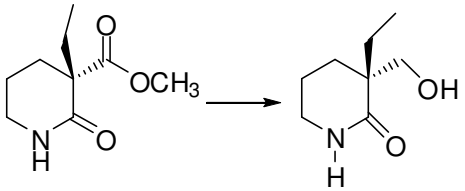
IR (neat) ν_{max} = 3300, 2953, 2880, 1732, 1666, 1491, 1449, 1247, 1199 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) = 6.0 (bs, 1H), 3.74 (s, 3H), 3.37-3.28 (m, 2H), 2.2-2.16 (1H, m), 2.07-1.99 (m, 1H), 1.97-1.92 (m, 1H), 1.9-1.78 (m, 3H), 1.66(s, 1H), 0.94 (t, *J* = 7.5 Hz, 3H);

^{13}C NMR (50 MHz, $CDCl_3$) =173.4, 171.1, 53.9, 52.3, 42.1, 28.8, 28.3, 19.4, 8.8;

HR-MS (EI): calcd for $C_9H_{15}NO_3$: 185.10519. Found: 185.10635.

(*R*)-3-Ethyl-3-(hydroxymethyl)piperidin-2-one (14a):



14 **14a**

To a suspension of $NaBH_4$ (0.18 g, 4.92 mmol) and cerium chloride heptahydrate (0.252 g, 0.677 mmol) in ethanol (4 mL) was added drop wise the solution of **14** (0.08 g, 0.464 mmol) in ethanol (3 mL) for 1h. The reaction mixture was stirred for 2 days at room temperature and poured into saturated aqueous NH_4Cl solution, extracted with dichloromethane (15 mL × 3). The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure, purified by column chromatography (SiO_2 acetone: petroleum ether 1:1) to afford **14a** (0.06 g, 87%) as colorless sticky liquid. R_f = 0.23 (SiO_2, acetone-petroleum ether 1:1); $[\alpha]^{27}_{D}$ = + 13.4667 ($CHCl_3$, *c* = 1.05);

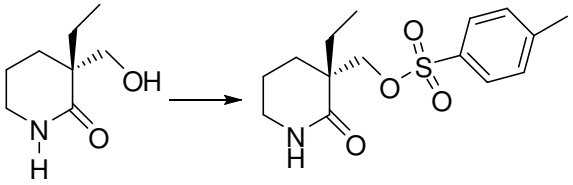
IR (neat) ν_{max} = 3297, 2940, 2875, 1644, 1492, 1054 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) = 6.38 (bs, 1H), 3.88 (dd, *J* = 8.9, 2.5 Hz, 1H), 3.57-3.47 (m, 2H), 3.29-3.25 (m, 2H), 1.9-1.68 (m, 5H), 1.49-1.43 (m, 1H), 0.89 (t, *J* = 7.5 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) = 178.2, 67.2, 45.1, 41.9, 26.6, 26.4, 19.1, 7.7;

HR-MS (EI): calcd for $C_8H_{15}NO_2$: 157.11028. Found: 157.11074.

(*R*)– (3-ethyl-2-oxopiperidin-3-yl)methyl 4-methylbenzenesulfonate (15):



14a **15**

p-Toluenesulfonyl chloride (0.11 g, 0.601 mmol) was added in small portions to a stirred and ice-cooled solution of **14a** (0.06 g, 0.4 mmol) in anhydrous pyridine (4 mL). The reaction mixture was stirred for 48 h at ambient temperature and poured into ice water. The aqueous layer was extracted with dichloromethane, washed with saturated $NaHCO_3$ solution, dried over Na_2SO_4, concentrated and purified by column chromatography (SiO_2, 6:4→10:0 ethyl acetate-petroleum ether) to afford **15** as white solid (0.138 g, 84%), which got crystallized from ethyl acetate–petroleum ether as colorless crystals. mp = 166-168 °C; R_f = 0.45 (SiO_2, EtOAc);

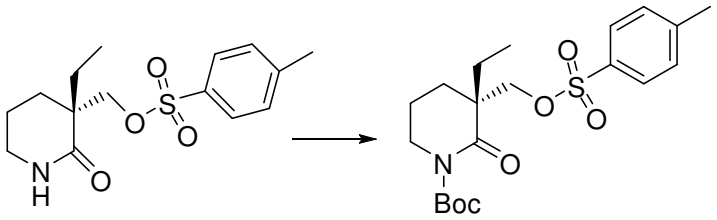
$[\alpha]^{23}_{D}$ = - 26.7586 ($CHCl_3$, *c* = 1.45); **IR** (neat) ν_{max} = 3020, 1661, 1359, 1215, 1176cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) = 7.76 (d, *J* = 8.2 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 6.03 (bs, 1H), 4.18 (d, *J* = 8.9 Hz, 1H), 3.91 (d, *J* = 9.0 Hz, 1H), 3.3-3.21 (m, 2H), 2.43 (s, 3H), 1.98-1.89 (m, 1H), 1.86-1.74 (m, 3H), 1.68-1.59 (m, 1H), 1.52-1.45 (m, 1H) 0.84 (t, *J* = 7.4 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) = 173.2, 144.7, 132.4, 129.7, 127.8, 75.0, 45.3, 42.3, 28.2, 27.2, 21.5, 19.6, 8.3;

HR-MS (EI): calcd for $C_{15}H_{21}NO_4S$: 311.11913. Found: 311.11887.

(*R*)-*tert*-Butyl 3-ethyl-2-oxo-3-(tosyloxymethyl)piperidine-1-carboxylate (15a):



15 **15a**

To a solution of **15** (0.64 g, 2.07 mmol) in dry dichloromethane (15 mL) was added triethylamine (0.72 mL, 5.17 mmol) and DMAP (0.025 g, 0.2 mmol). To this stirred mixture was added drop wise di-tertbutyl dicarbonate (0.7 mL, 3.1 mmol) over a period of 15 min and the mixture was stirred at ambient temperature for 12 h. The reaction mixture was concentrated under reduced pressure, purified by column chromatography (SiO_2, ethyl acetate-petroleum ether 2:8) to furnish **15a** as a colorless liquid (0.81 g, 95%). R_f = 0.27 (2:8 ethyl acetate:petroleum ether); $[\alpha]^{26}_D$ = - 62.8914 ($CHCl_3$ *c* = 1.05);

IR (neat) ν_{max}= 2976, 1765, 1717, 1367, 1177, 1150 cm^{-1};

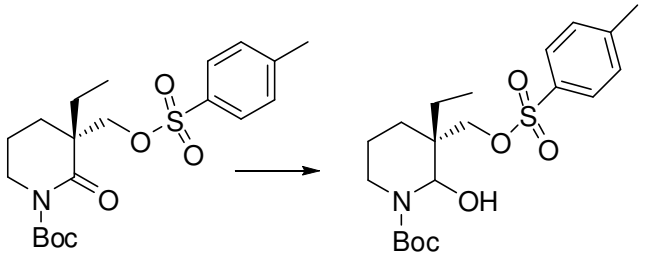
^{1}H NMR (200 MHz, $CDCl_3$) = 7.75 (d, *J* = 8.28 Hz, 2H), 7.33 (d, *J* = 8.03 Hz, 2H), 4.16 (d, *J* = 9.29 Hz, 1H), 3.97 (d, *J* = 9.28 Hz, 1H), 3.65-3.54 (m, 2H), 2.43 (s, 3H), 1.98-1.89 (m, 1H), 1.88-1.75 (m, 3H), 1.64-1.54 (m, 2H), 1.48 (s, 9H), 0.81 (t, *J* = 7.53 Hz, 3H);

^{13}C NMR (50 MHz, $CDCl_3$) = 173.2, 152.8, 144.8, 132.3, 129.8, 127.8, 82.7, 74.2, 48.3, 46.9, 28.7, 28.5, 27.8, 21.5, 19.7, 8.1;

MS (ESI): 412.1523 (M^++H), 434.1089 (M^++Na), 450.0987 (M^++K);

HR-MS (EI): calcd for $C_{20}H_{29}NO_6S$: 411.17156. Found: 311.11977 (-Boc).

(3*R*)-*tert*-Butyl 3-ethyl-2-hydroxy-3-(tosyloxymethyl)piperidine-1-carboxylate(15b):



15a **15b**

To a stirred solution of **15a** (0.137 g, 0.33 mmol) in anhydrous THF (4 mL) at -78 °C was added a solution of DIBAL-H (20 wt % solution in toluene, 0.8 mL, 0.99 mmol). After 4 h, the reaction was quenched by successive addition of saturated aqueous solution of NH_4Cl (3.5 mL) and an aqueous solution of Na_2CO_3 (10% wt/v, 2.5 mL). The mixture was extracted with dichloromethane, dried over Na_2SO_4, concentrated and purified by column chromatography (SiO_2, ethyl acetate-petroleum ether 2.5:7.5) to afford **15b** as colorless gum (0.133 g, 97%). R_f = 0.37, (2.5:7.5 ethyl acetate-petroleum ether); $[\alpha]^{26}_D$ = - 5.3059 ($CHCl_3$ *c* = 1.85);

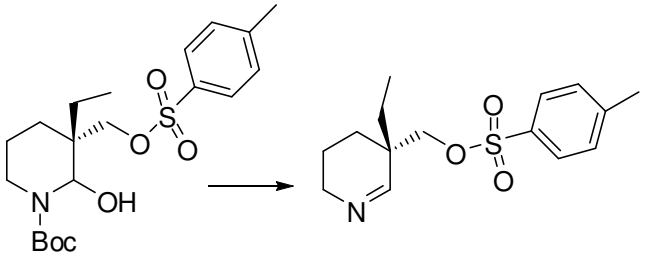
IR (neat) ν_{max} = 3414, 2972, 1673, 1366, 1176 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) = 7.77 (d, *J* = 8 Hz, 2H), 7.33 (d, *J* = 8 Hz, 2H), 5.3 (bs, 1H), 4.01-3.73 (m, 3H), 3.06-2.99 (m, 1H), 2.44(s, 3H), 1.78 (s, 1H), 1.49-1.34 (m, 15H), 0.66 (t, *J* = 7.5 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) = 155.5, 144.7, 132.4, 129.7, 127.8, 80.5, 75.4 71.8, 68.5, 40.4, 28.2, 26.2, 25.3, 21.5, 20.0, 6.4;

MS (ESI): 436.0946 (M^++Na), 452.0846 (M^++K).

(3-Ethyl-3, 4, 5, 6-tetrahydropyridin-3-yl) methyl 4-methylbenzenesulfonate (4):



15b **4**

To a stirred solution of **15b** (0.11 g, 0.278 mmol) in 5 mL of dry dichloromethane was added trifluoroacetic acid (0.2 mL, 2.78 mmol) drop by drop, stirred at ambient temperature for 4 h. Concentrated, neutralized with saturated aqueous sodium hydrogen carbonate and extracted with dichloromethane. The organic layer was separated, dried over sodium sulfate, concentrated under

reduced pressure and purified by column chromatography (SiO_2, ethyl acetate) to afford pure imine **4** as a colorless liquid (0.07 g, 90% yield, single enantiomer). Enantiomeric excess was determined by HPLC analysis and compared with the racemic imine (Chiralcel OJ-H (250×4.6mm) column, Isopropanol–petroleum ether (15:85) as an eluent), 0.7 mL/min (33 Kgf), λ = 254nm, 25 °C, the retention times of (-) – isomer and (+)-isomer being 21.408 and 23.867 minutes, respectively. (R_f : 0.4, ethyl acetate); $[\alpha]^{28.3}_D$ = - 42.2220 ($CHCl_3$ *c*= 2.0);

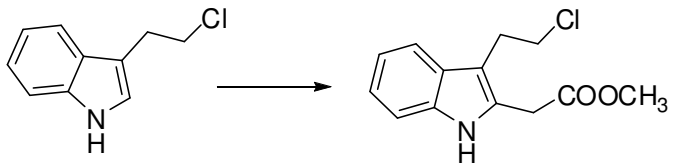
IR (neat) ν_{max} = 2941, 1654, 1363, 1176 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) = 7.77 (d, *J* = 8.0 Hz, 2H), 7.38 (bs, 1H), 7.34 (d, *J* = 8.0 Hz, 2H), 3.85, 3.81 (2 sets of doublet, *J* = 9.3 Hz, 2H), 3.53-3.42 (m, 2H), 2.44 (s, 3H), 1.56-1.39 (m, 6H), 0.81 (t, *J* = 7.3 Hz, 3H);

^{13}C NMR (125 MHz, $CDCl_3$) = 164.7, 145.0, 132.3, 129.8, 127.8, 127.8, 72.9, 49.1, 39.9, 27.2, 25.3, 21.6, 18.7, 7.6;

HR-MS (EI): calcd for $C_{15}H_{21}NO_3S$: 295.12421. Found: 295.11549.

Methyl 2-(3-(2-chloroethyl)-1H-indol-2-yl) acetate (5):



5

To a stirred solution of 3-(2-chloroethyl)-1H-indole (0.8 g, 4.46 mmol) and triethyl amine (0.74 mL, 5.35 mmol) in anhydrous THF (20 mL) was added drop wise *t*-BuOCl (0.63 mL, 5.35 mmol) dissolved in dry THF (2 mL) over a period of 10 minutes at-78 °C. After 40 minutes, the silylenol ether (1.9 mL, 8.92 mmol) was added followed by BF_3:OEt_2 (1.1 mL, 8.92 mmol). The solution was warmed to ambient temperature over 6 h and stirred at the same temperature for 6 h, quenched with aqueous $NaHCO_3$ (10 mL), extracted with dichloromethane, dried over sodium sulfate and concentrated under reduced pressure. The crude residue was purified by column chromatography (SiO_2, ethyl acetate-petroleum ether, 1.5:8.5) to obtain **5** (0.685 g, 61%) as a thick liquid. This compound upon crystallization with cyclohexane-ethyl acetate gave colorless crystalline solid; mp = 59-60 °C; R_f = 0.42 (SiO_2, ethyl acetate-petroleum ether 2.5: 7.5, Iodine/PMA);

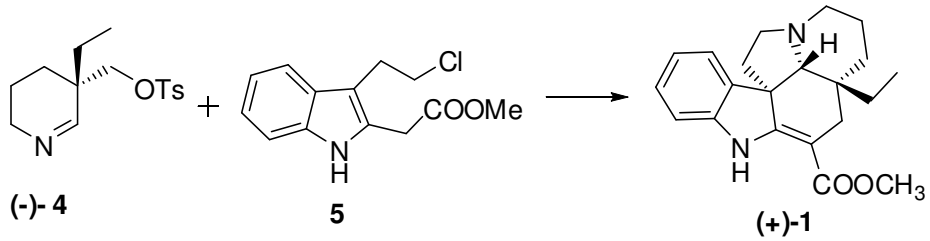
IR (neat) = 3457, 3019, 1735, 1438, 1460, 1216cm^{-1};

^{1}H NMR (200 MHz, $CDCl_3$) = 8.65 (brs, 1H), 7.53-7.51 (m, 1H), 7.37-7.33 (m, 1H), 7.23-7.08 (m, 2H), 3.84 (s, 2H), 3.76 (s, 3H), 3.72 (t, *J* = 7.4 Hz, 2H), 3.2 (t, *J* = 7.4 Hz, 2H);

^{13}C NMR (50 MHz, $CDCl_3$) = 170.8, 135.5, 127.7, 127.4, 122.0, 119.5, 117.9, 110.9, 109.6, 52.3, 44.5, 31.6, 27.8;

HR-MS (EI):calcd for $C_{13}H_{14}ClNO_2$:251.07131. Found: 251.05374

(+)-Vincadifformine (1):



The stirred solution of methyl-2-(3-(2-chloroethyl)-1H-indol-2-yl)acetate (**5)** (0.101g, 0.402 mmol) and potassium iodide (0.467 g, 2.81 mmol) in 4 mL of anhydrous DMF was degassed three to four times in presence of argon and heated at 90 °C for 3 h, cooled to room temperature. Imine **(-)-4** (0.119 g, 0.402 mmol) dissolved in 2 mL anhydrous DMF was added to the flask. After heating at 135 °C to 140 °C for 3 h, it was cooled to room temperature, diluted with dichloromethane, quenched with ice water. The organic layer was separated, dried over Na_2SO_4, concentrated, purified by column chromatography (SiO_2, ethyl acetate- petroleum ether 15:85) to afford vincadifformine **(1)** (0.04 g, 35%, >99% ee). Enantiomeric excess was determined by HPLC analysis by comparing with the racemic **1**(Chiralcel OD-H (250×4.6mm) column, ethanol:petroleum ether:TFA (15:85:0.1) as an eluent), 0.5 mL/min (26 Kgf), λ = 220 nm, 25 °C, the retention times of (+) – isomer and (-)-isomer being 14.942 and 18.983 minutes, respectively.

R_f : 0.37 (1.5:8.5 ethyl acetate: petroleum ether); $[\alpha]^{28}_D$ = + 550.760 (EtOH, *c* = 0.2);

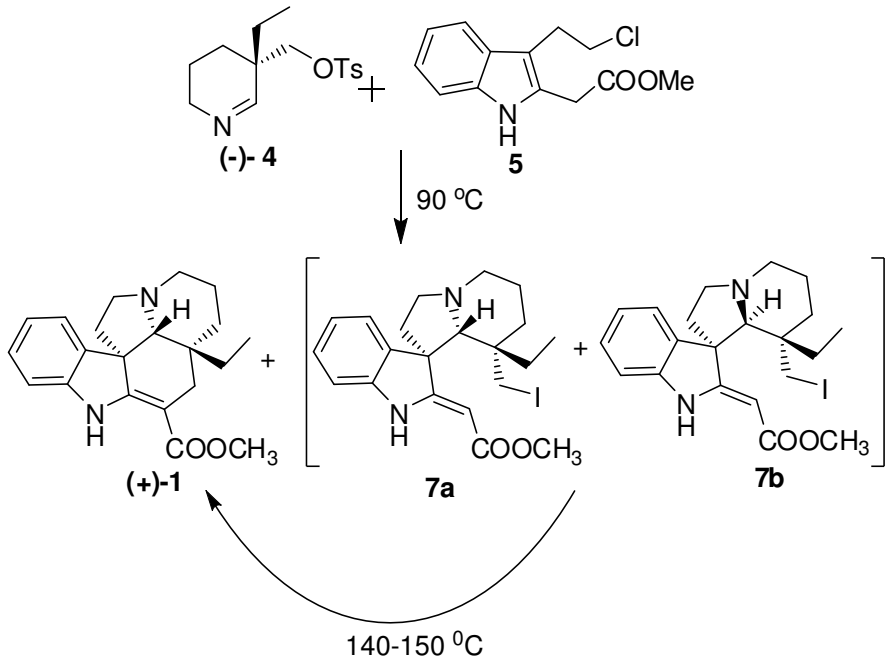
IR (neat) = 3368, 2934, 2774, 1674, 1608, 1463, 908, 733 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) = 8.89 (bs, 1H), 7.18 (d, *J* = 7.2 Hz, 1H), 7.11 (dt, *J* = 7.5, 1.0 Hz, 1H), 6.84 (dt, *J* = 7.3, 0.75 Hz, 1H), 6.78 (d, *J* = 7.7 Hz, 1H), 3.75 (s, 3H), 3.12 (br d, *J* = 9.3 Hz 1H), 2.91(t, *J* = 7.2 Hz, 1H), 2.71 (d, J = 15.1 Hz, 1H), 2.58-2.52 (m, 1H), 2.45 (s, 1H), 2.43-2.35 (m, 1H), 2.26 (dd, *J* = 15.1, 1.7Hz, 1H), 2.08-2.01 (m, 1H), 1.88-1.81 (m, 1H), 1.80-1.75 (m, 1H), 1.69 (dd, *J* = 11.5, 4.5 Hz, 1H), 1.56-1.50 (m, 1H), 1.27-1.20 (m, 1H), 0.96 (dd, *J* = 13.0, 6.7 Hz, 1H), 0.62 (m, 1H), 0.56 (t, *J* = 6.8 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) = 169.3, 167.9, 143.4, 138.1, 127.5, 121.1, 120.6, 109.4, 92.7, 72.8, 55.6, 51.8, 51.1, 50.8, 45.4, 38.3, 33.0, 29.4, 25.6, 22.3, 7.2;

HR-MS (EI): calcd for $C_{21}H_{26}N_2O_2$: 338.19943. Found: 338.20066.

Attempts towards the isolation of Spiro intermediate (7):



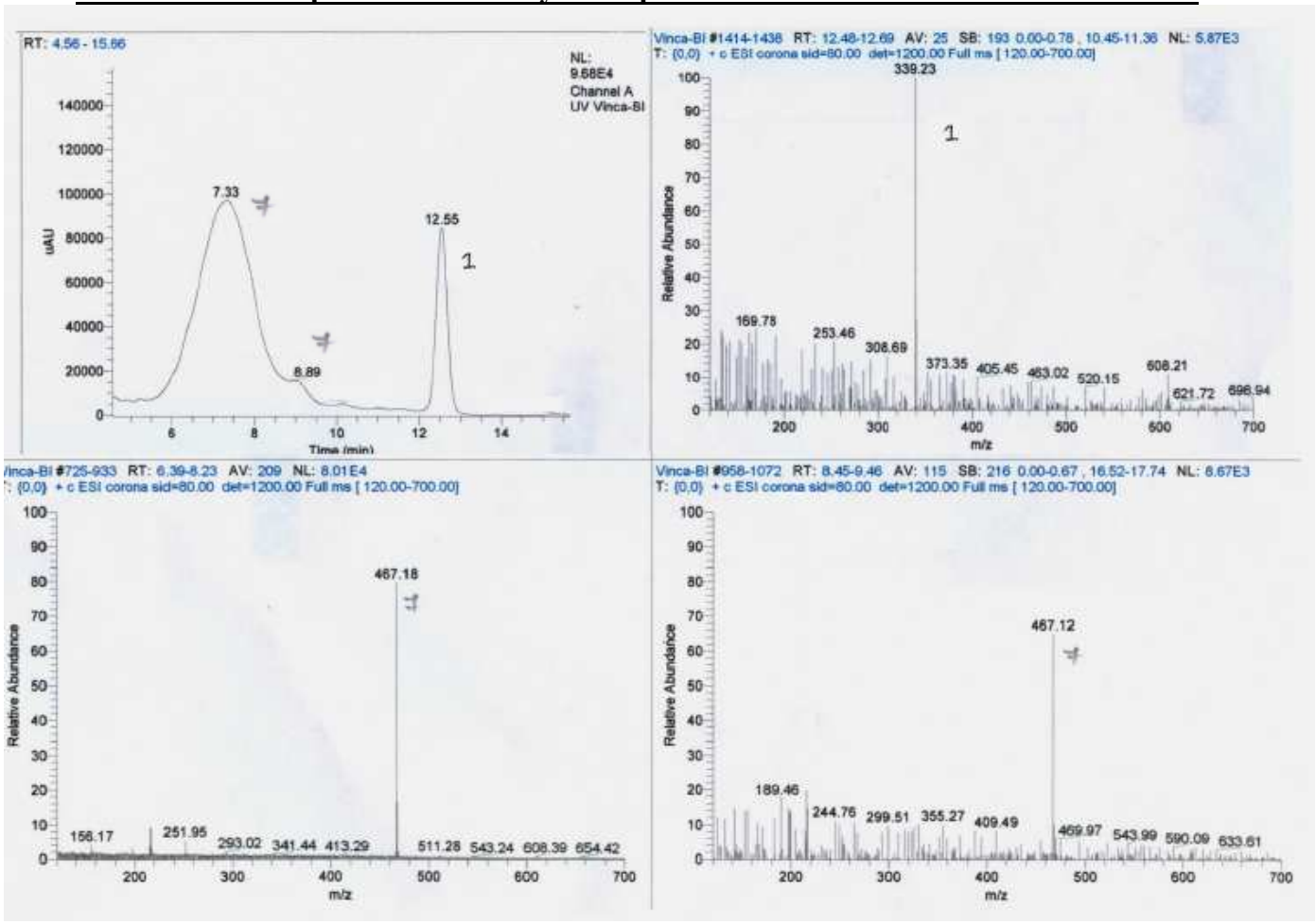
The stirred solution of methyl-2-(3-(2-chloroethyl)-1H-indol-2-yl)acetate (**5,** 0.07 g, 0.287 mmol), imine **(-)-4** (0.08 g, 0.287 mmol) and sodium iodide (0.258 g, 1.72 mmol) in 6 mL of anhydrous acetonitrile was degassed three to four times in presence of argon and refluxed for 12 h, cooled to room temperature and quenched the reaction with ice water. The aqueous layer was extracted with dichloromethane, dried over sodium sulfate and concentrated.

The isolation of the diastereomeric mixture of **7** through column chromatography by using silicagel or alumina was not successful due to their poor stability.

HPLC–LCMS analysis indicates the formation of (+)-vincadifformine (**1**), diastereomeric mixture (89:11) of (**7**) along with the indole fragment. The diastereomeric ratio of **7** was determined by HPLC analysis using Kromasil RP-18 (150×4.6mm) column, methanol:acetonitrile:triethyl ammonium acetate(0.1M. pH-7) (40:40:20) and (35:45:20) as an eluent, 1.0 mL/min (1140psi), λ = 254nm, 25 °C, the retention time of diastereomers being at 8.31 and 9.19 minutes.

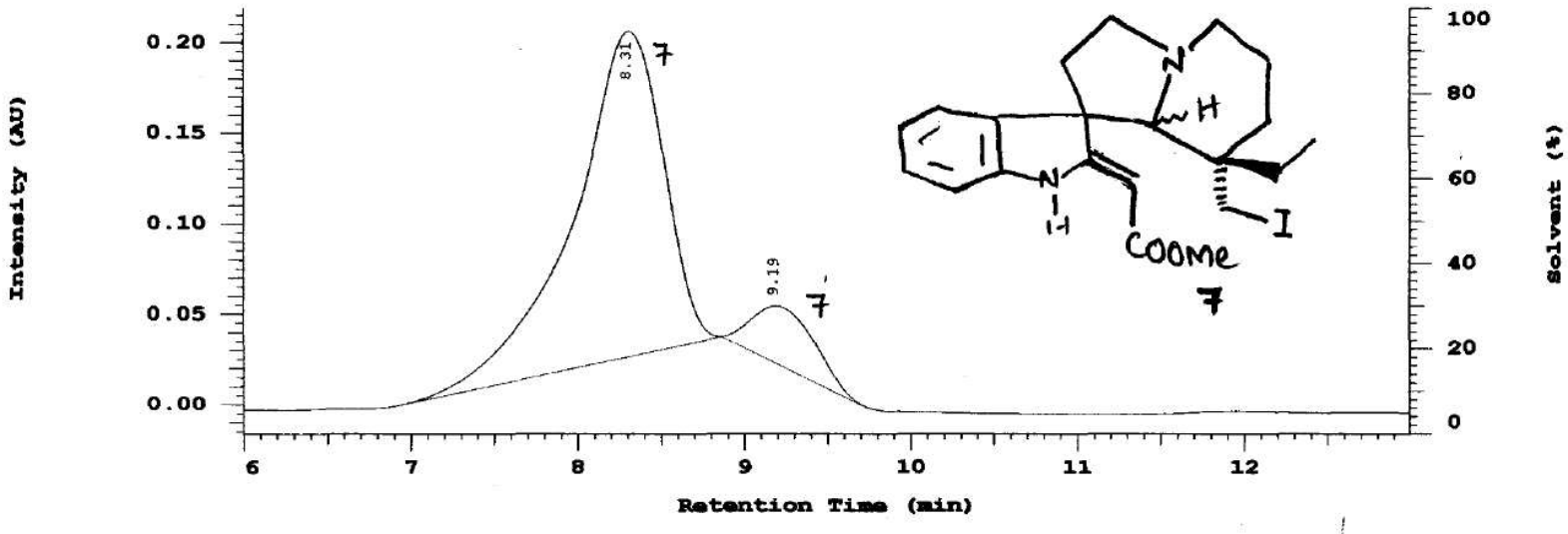
Diastereomeric mixture of **7** was found converting to **1** by heating at 145 °C in DMF for 3 h, determined by HPLC analysis using Kromasil RP-18 (150 × 4.6 mm) column, methanol:water (85:15) as an eluent, 1.0 mL/min (1260psi), λ = 254nm, 25 °C, the retention time of vincadifformine and spiro compound **7** being at 7.37 and 8.27 minutes, respectively.

HPLC and Mass spectrometric analysis of spiro intermediate 7 and Vincadifformine 1:



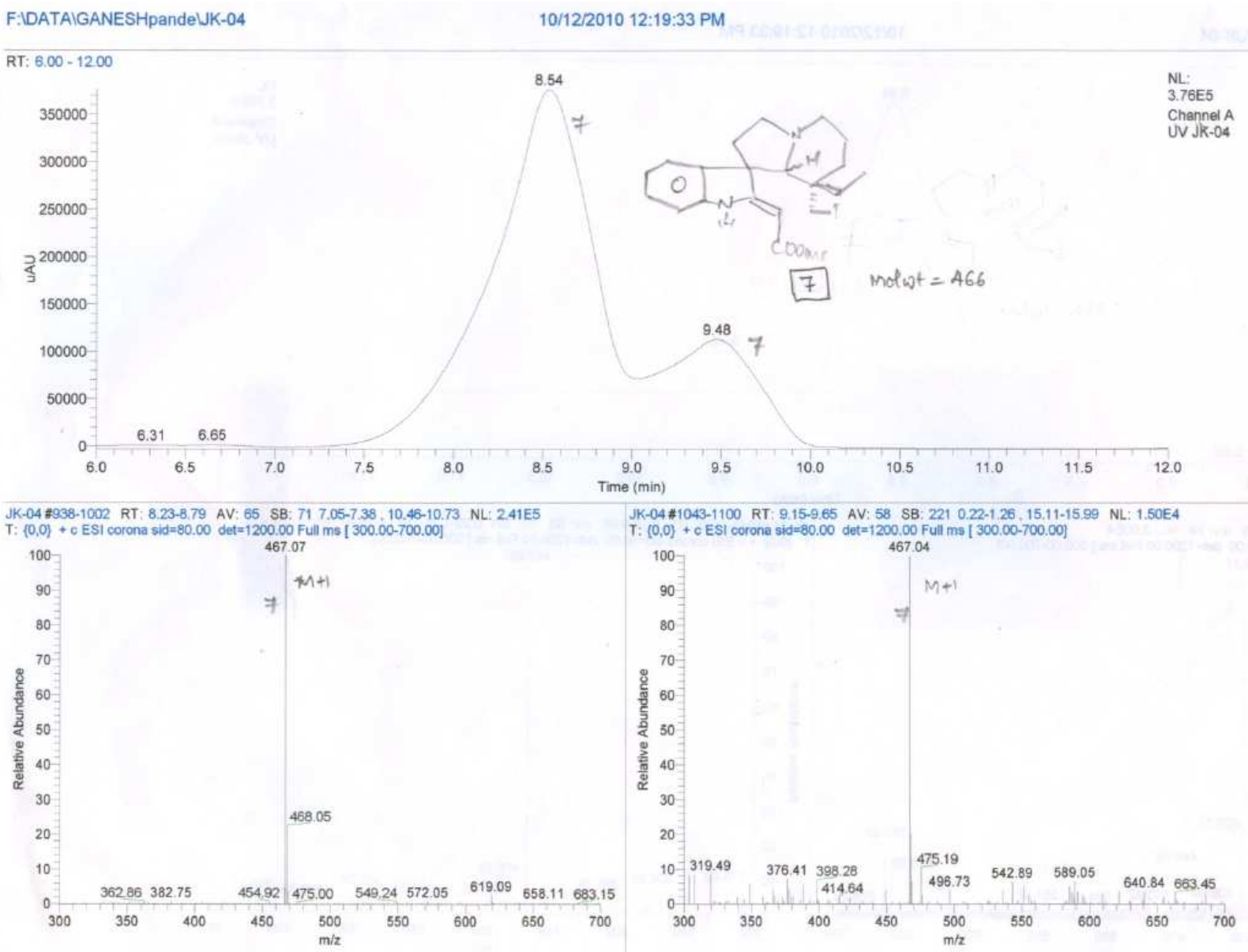
Column : Kromasil RP-18 (150×4.6mm)
Mobile Phase : MeOH:CH_3CN:TEAA(pH-7) (35:45:20)
Wavelength: 254nm
Flow rate : 1.0 mL/min (1140psi)
Sample conc : 1mg/1mL (inj vol-10µL)

Chrom Type: HPLC Channel : 1



No.	RT	Height	Area	Area %
1	8.31	89724	3356300	88.617
2	9.19	15882	431127	11.383
		105606	3787427	100.000

COLUMN :-Kromasil RP-18(150 X 4.6mm)
MOBILE PHASE :- MeOH:ACN:TEAA(PH-7)(40:40:20)
WAVELENGTH :- 254nm (D·IN)
FLOW RATE :- 1.0 ml/min (1140psi)
SAMPLE CONC :-1mg/1ml (Inj voL-10ul)


F:\DATA\GANESHpande\JK-04
10/12/2010 12:19:33 PM
RT: 6.00 - 12.00
NL:
3.76E5
Channel A
UV JK-04
8.54
9.48
6.31
6.65
uAU
Time (min)
mol wt = 466
JK-04 #938-1002 RT: 8.23-8.79 AV: 65 SB: 71 7.05-7.38 , 10.46-10.73 NL: 2.41E5
T: {0,0} + c ESI corona sid=80.00 det=1200.00 Full ms [300.00-700.00]
467.07
M+1
468.05
362.86 382.75 454.92 475.00 549.24 572.05 619.09 658.11 683.15
Relative Abundance
m/z
JK-04 #1043-1100 RT: 9.15-9.65 AV: 58 SB: 221 0.22-1.26 , 15.11-15.99 NL: 1.50E4
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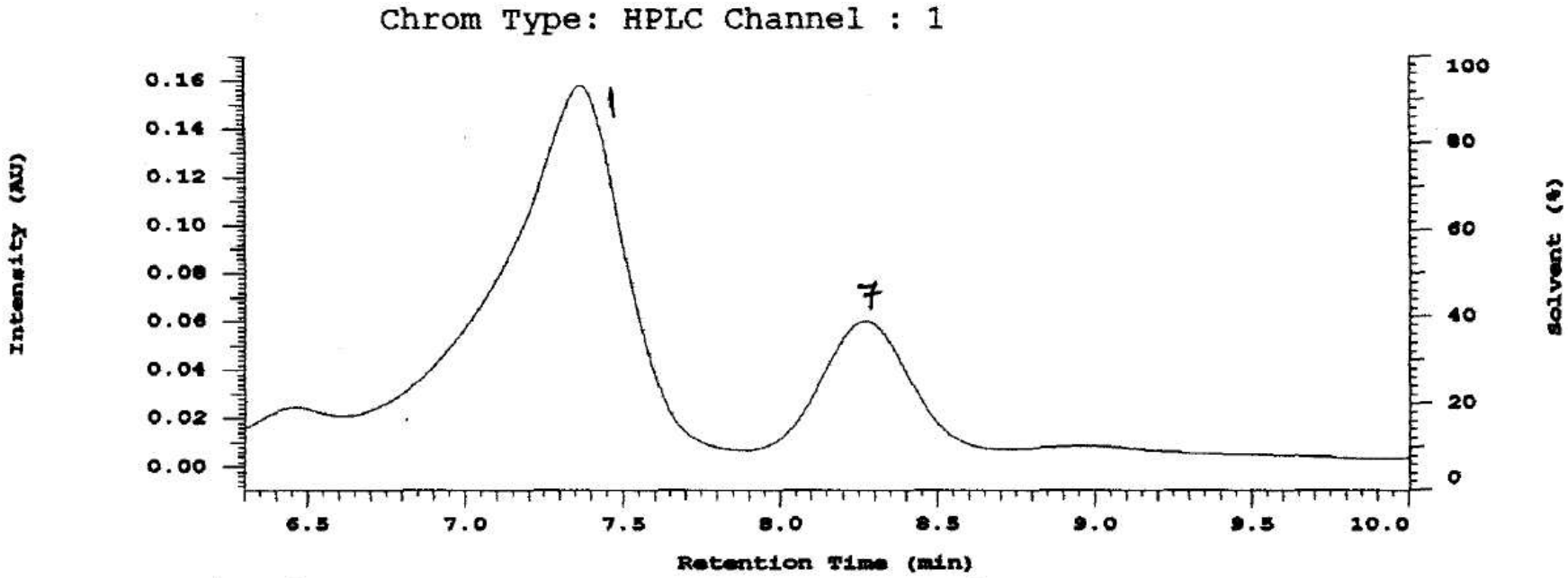
467.04
M+1
319.49 376.41 398.28 414.64 475.19 496.73 542.89 589.05 640.84 663.45
Relative Abundance
m/z

Conversion of Spiro 7 to Vincadifformine (1): HPLC and Mass spectrometric analysis of aliquots at different interval of times



Peak Quantitation: AREA Calculation Method: AREA%

No.	RT	Height	Area	Area %
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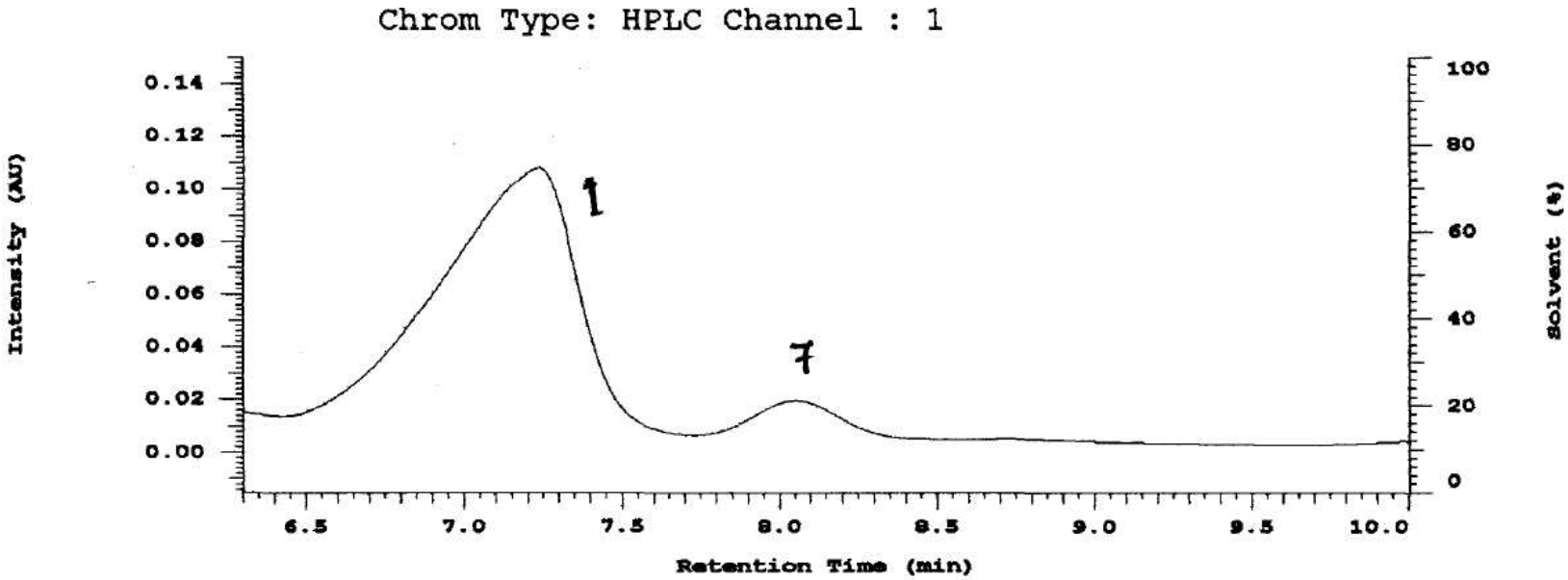
2	8.27	25605	466311	20.849
		97364	2236583	100.000



Peak Quantitation: AREA Calculation Method: AREA%

No.	RT	Height	Area	Area %
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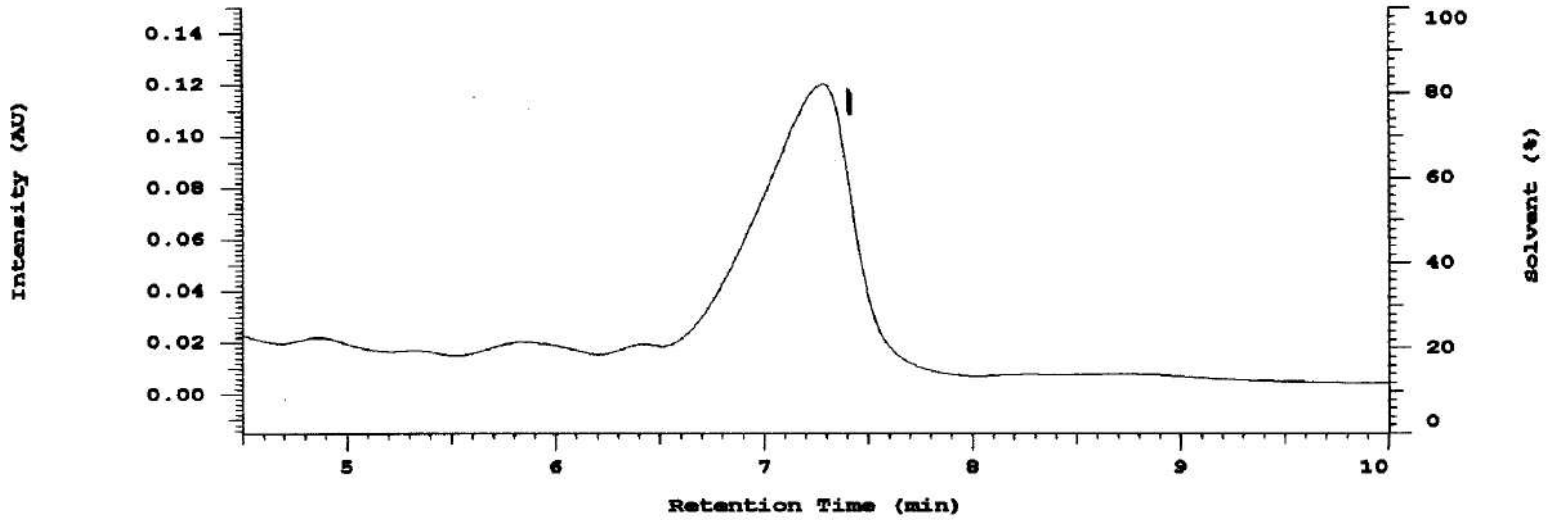
2	8.05	4336	54996	3.685
		53347	1492450	100.000

Chrom Type: HPLC Channel : 1



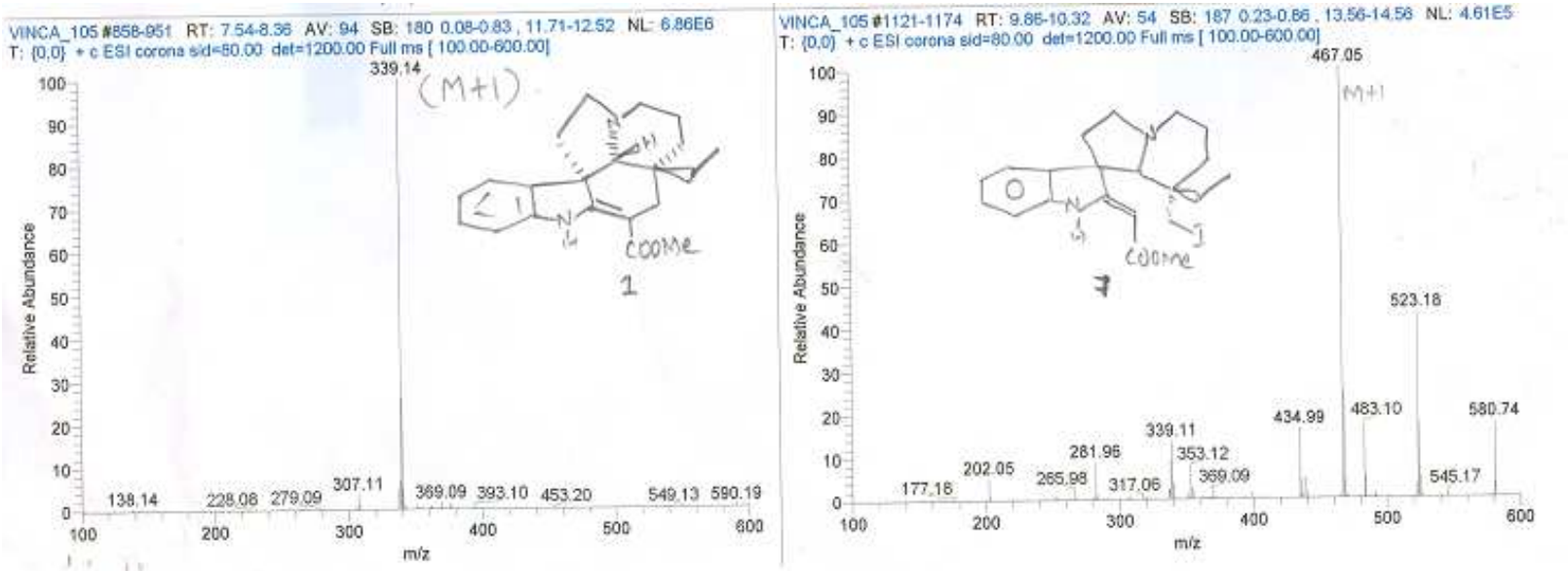
Peak Quantitation: AREA Calculation Method: AREA%

No.	RT	Height	Area	Area %
1	7.29	52165	1561137	100.000
		52165	1561137	100.000

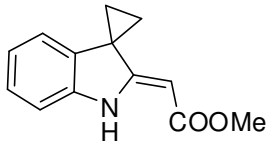
Group Leader :-Dr.Ganesh Pandey
COlumn :Kromasil RP-18(150 X 4.6mm)
M.P. :A)MEOH:H2O(85:15)

Flow Rate :-1.0ml/min (1260psi)
Sample conc :x mg/0.5 ml
Inj vol-10ul

WAVELENGTH :254nm



Methyl 2-(spiro[cyclopropane-1,3'-indoline]-2'-ylidene)acetate:



16

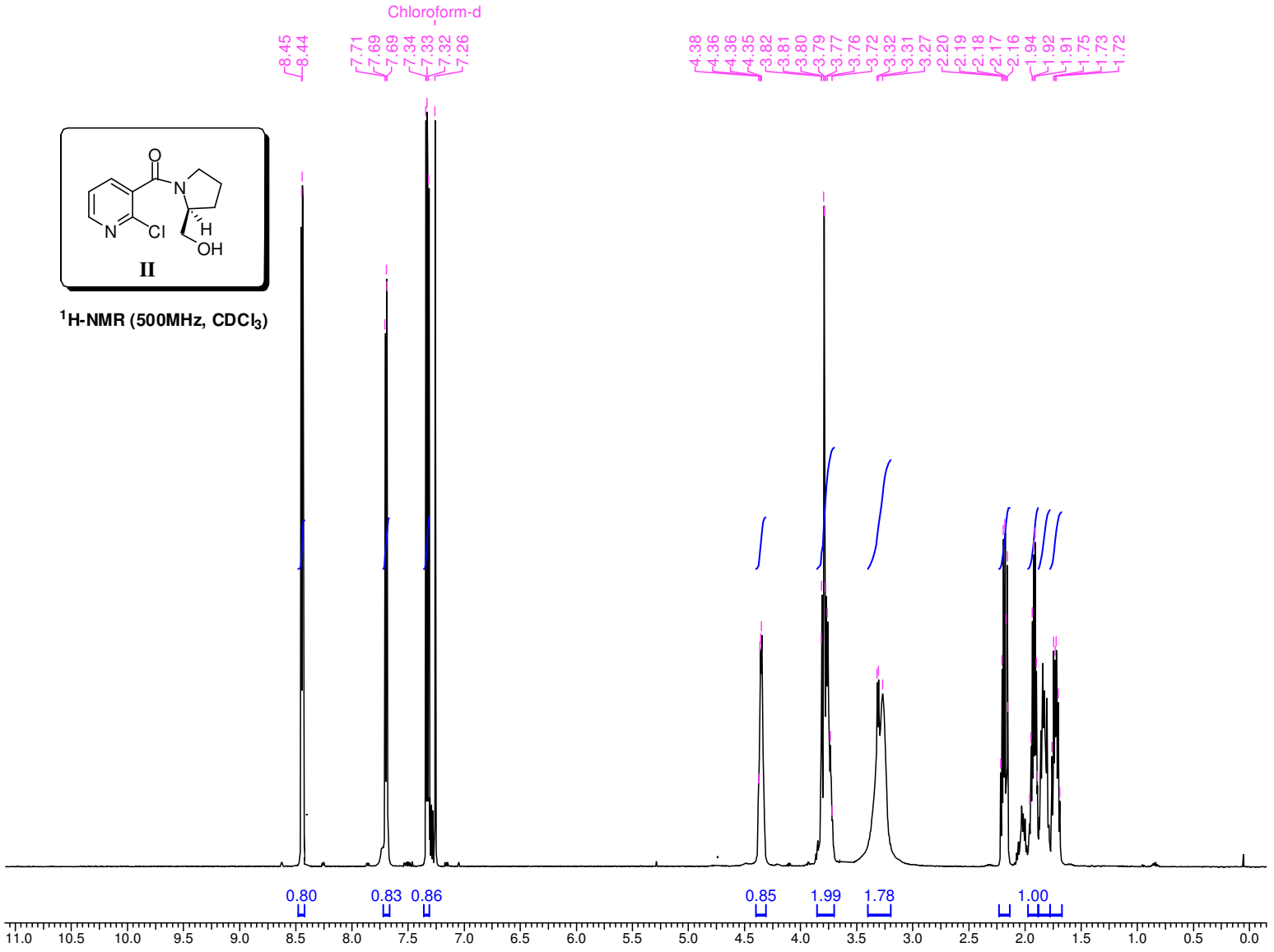
R_f : 0.4 (1.5:8.5 ethyl acetate: petroleum ether); **IR** (neat) = 3403, 2925, 1655, 1456, 743cm^{-1};

^{1}H NMR (200 MHz, $CDCl_3$) = 10.0 (brs, 1H), 7.2-7.12(m, 1H), 6.95-6.87(m, 2H), 6.81-6.77(m, 1H), 4.37(s, 1H), 3.69(s, 3H), 1.7-1.63(m, 2H), 1.45-1.39(m, 2H);

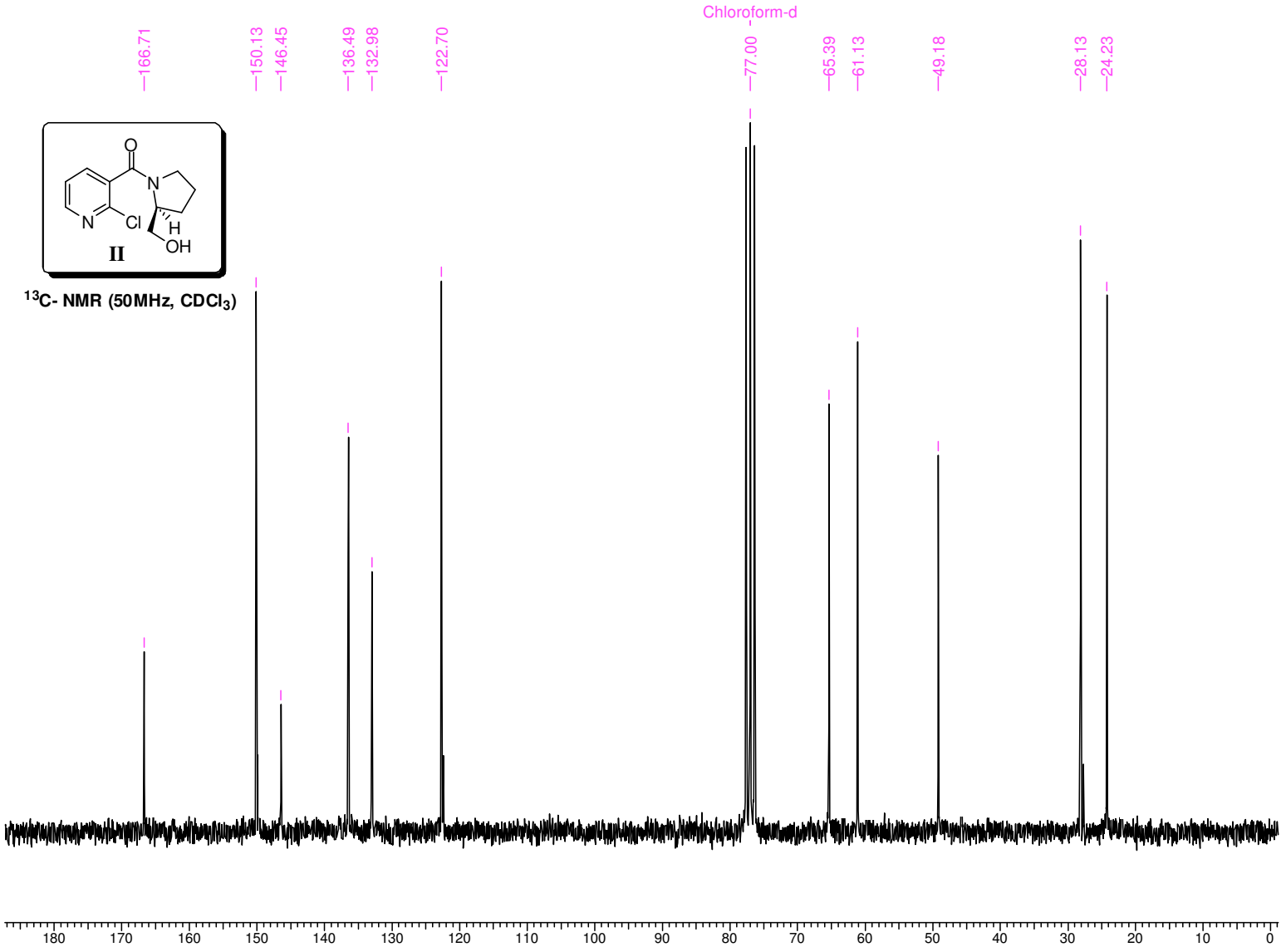
^{13}C NMR (50 MHz, $CDCl_3$) = 170.4, 167.7, 143.5, 132.7, 126.9, 121.0, 118.0, 109.0, 74.2, 50.4, 23.0:

MS (ESI): 216.09(M^++H)

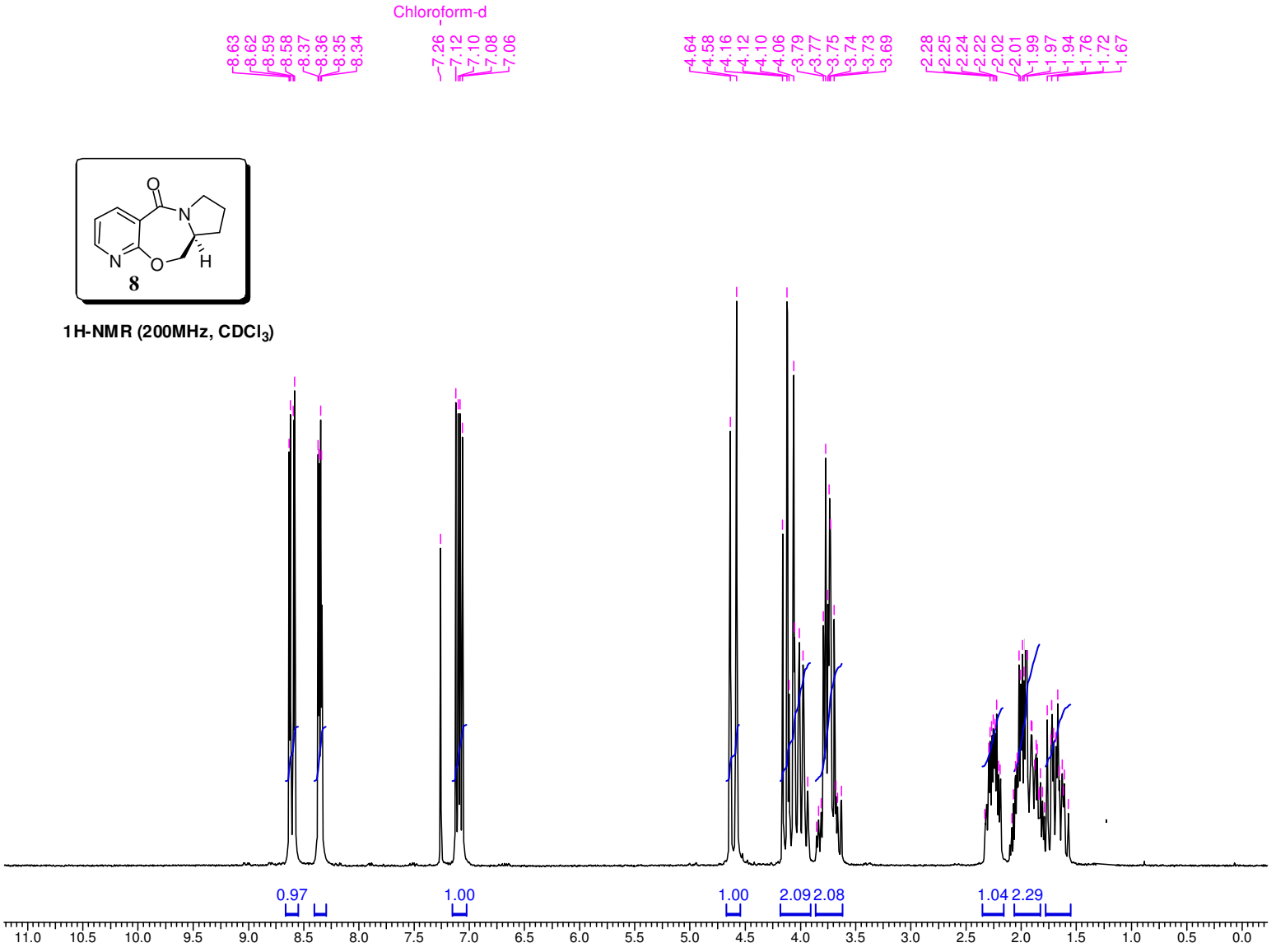
II) ^{1}H and ^{13}C spectra:

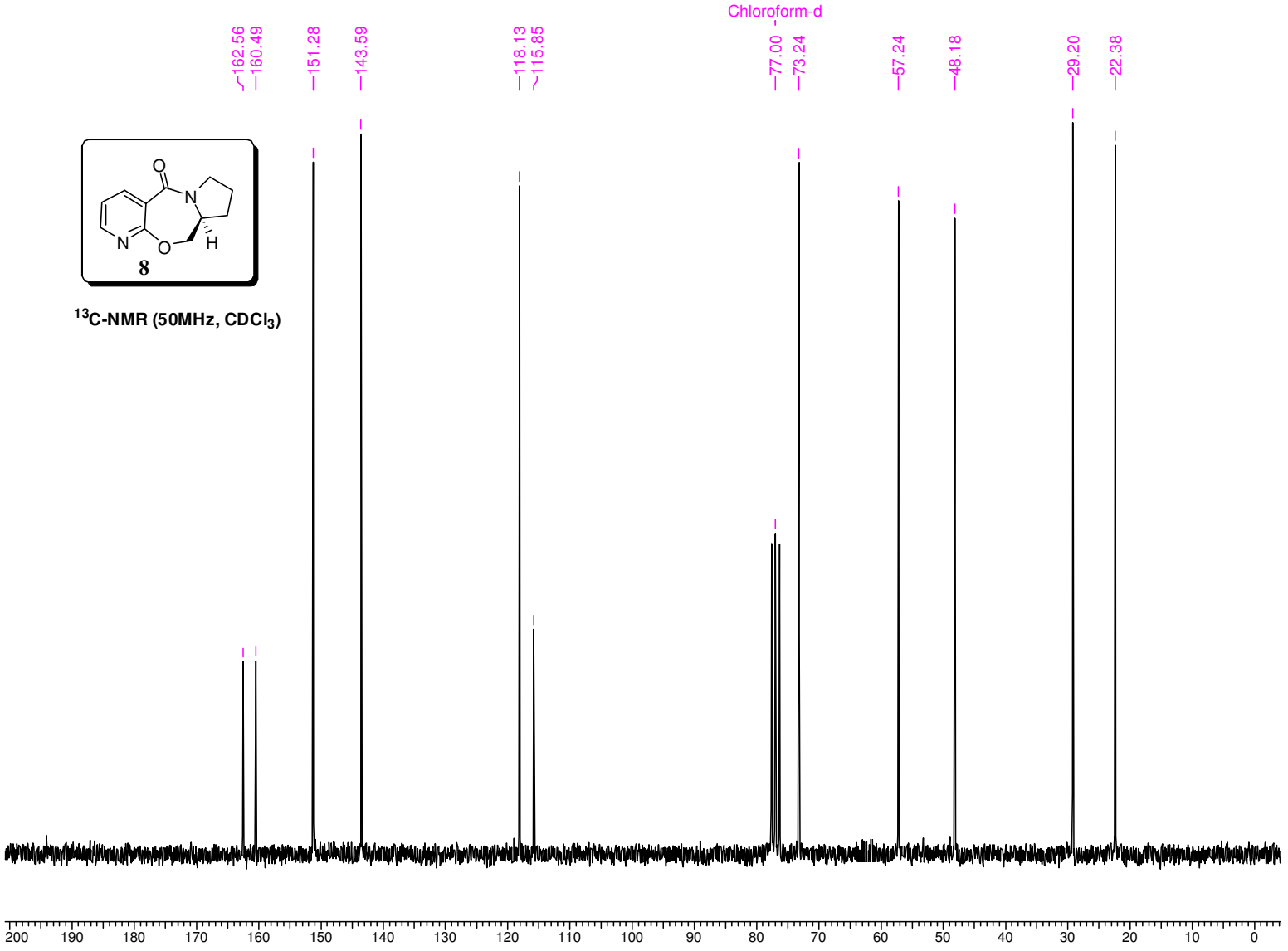


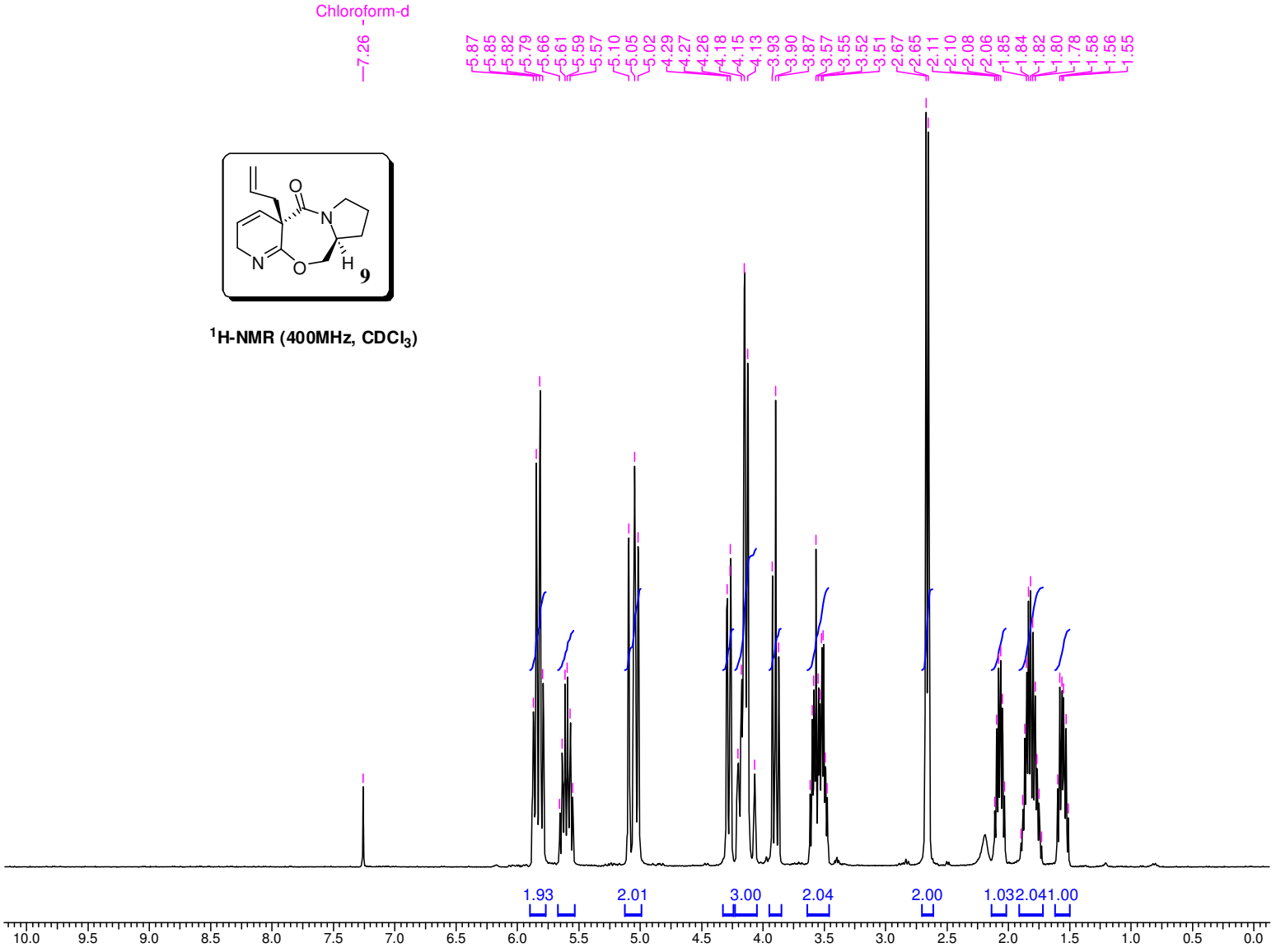
^{1}H-NMR (500MHz, $CDCl_3$)



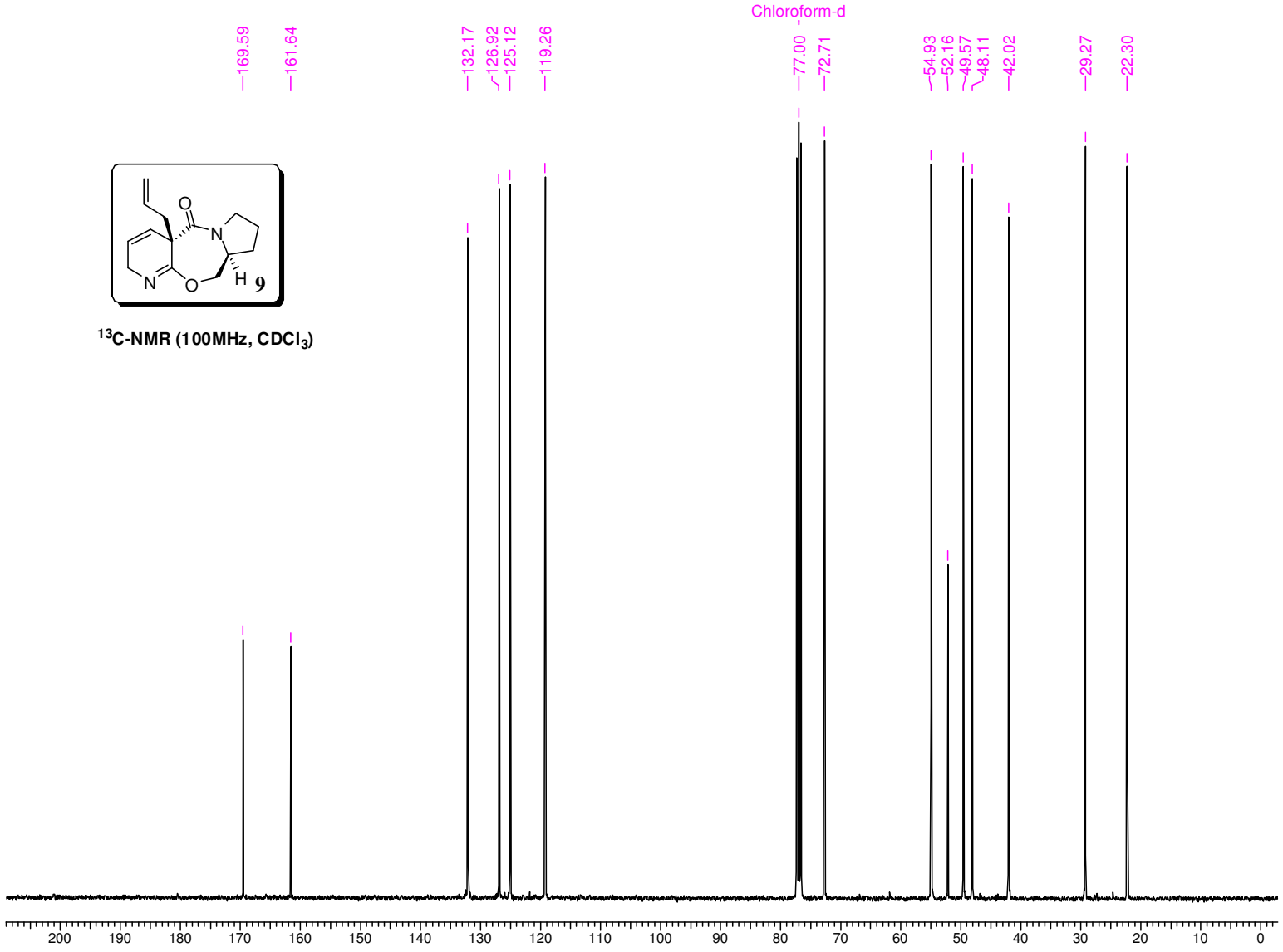
^{13}C- NMR (50MHz, $CDCl_3$)


Chloroform-d
8.63
8.62
8.59
8.58
8.37
8.36
8.35
8.34
7.26
7.12
7.10
7.08
7.06
4.64
4.58
4.16
4.12
4.10
4.06
3.79
3.77
3.75
3.74
3.73
3.69
2.28
2.25
2.24
2.22
2.02
2.01
1.99
1.97
1.94
1.76
1.72
1.67
O
N
N
O
H
8
1H-NMR (200MHz, CDCl3)
0.97
1.00
1.00
2.09
2.08
1.04
2.29
11.0
10.5
10.0
9.5
9.0
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


Chloroform-d
162.56
160.49
151.28
143.59
118.13
115.85
77.00
73.24
57.24
48.18
29.20
22.38
O
N
N
O
H
8
^{13}C-NMR (50MHz, CDCl$_3$)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

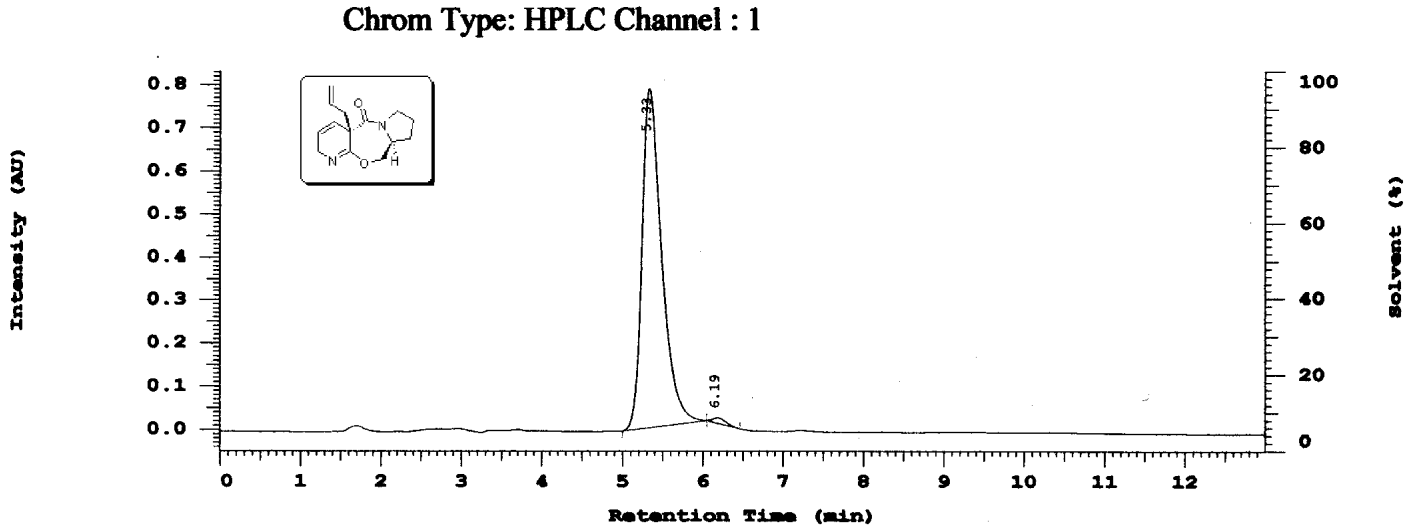


^{1}H-NMR (400MHz, $CDCl_3$)



^{13}C-NMR (100MHz, $CDCl_3$)

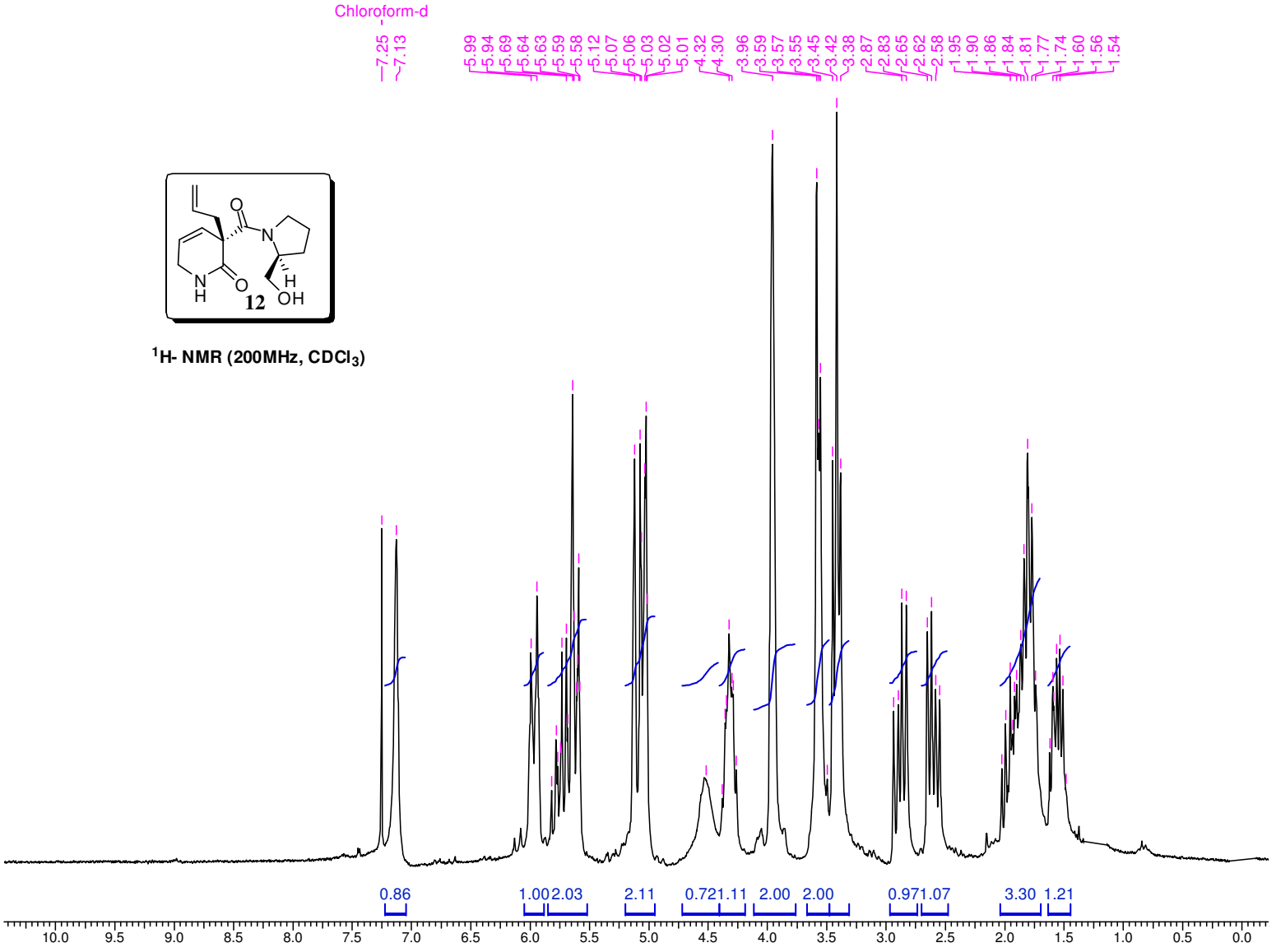
(4aS, 9aS)- 4a-Allyl-4a, 7, 8, 9a, 10-hexahydropyrido[3, 2-f] pyrrolo[2,1-c][1, 4] oxazepin-5(2H)-one: (9)



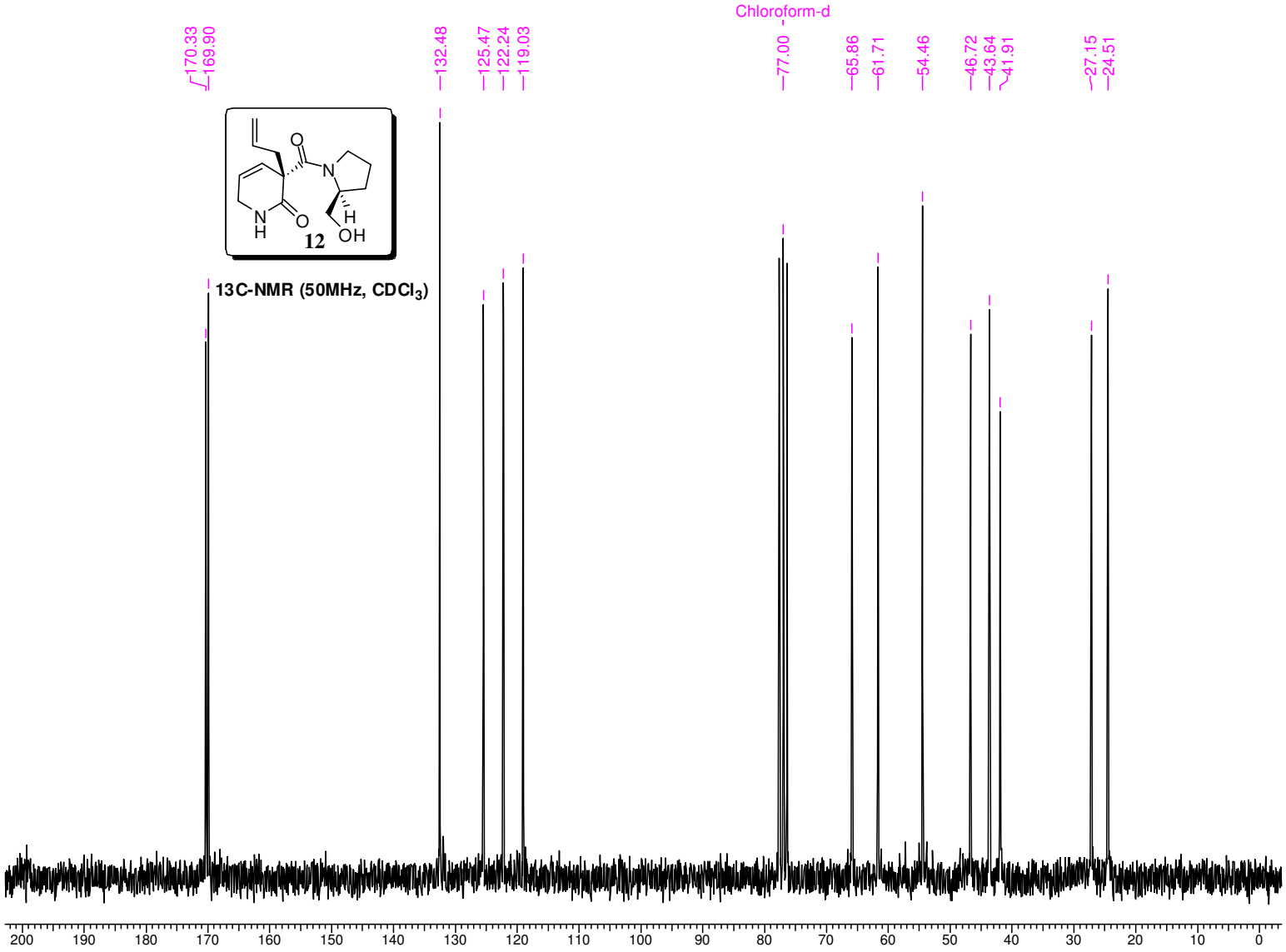
No.	RT	Height	Area	Area %
1	5.33	392937	6709760	98.938
2	6.19	6155	72044	1.062
		399092	6781804	100.000

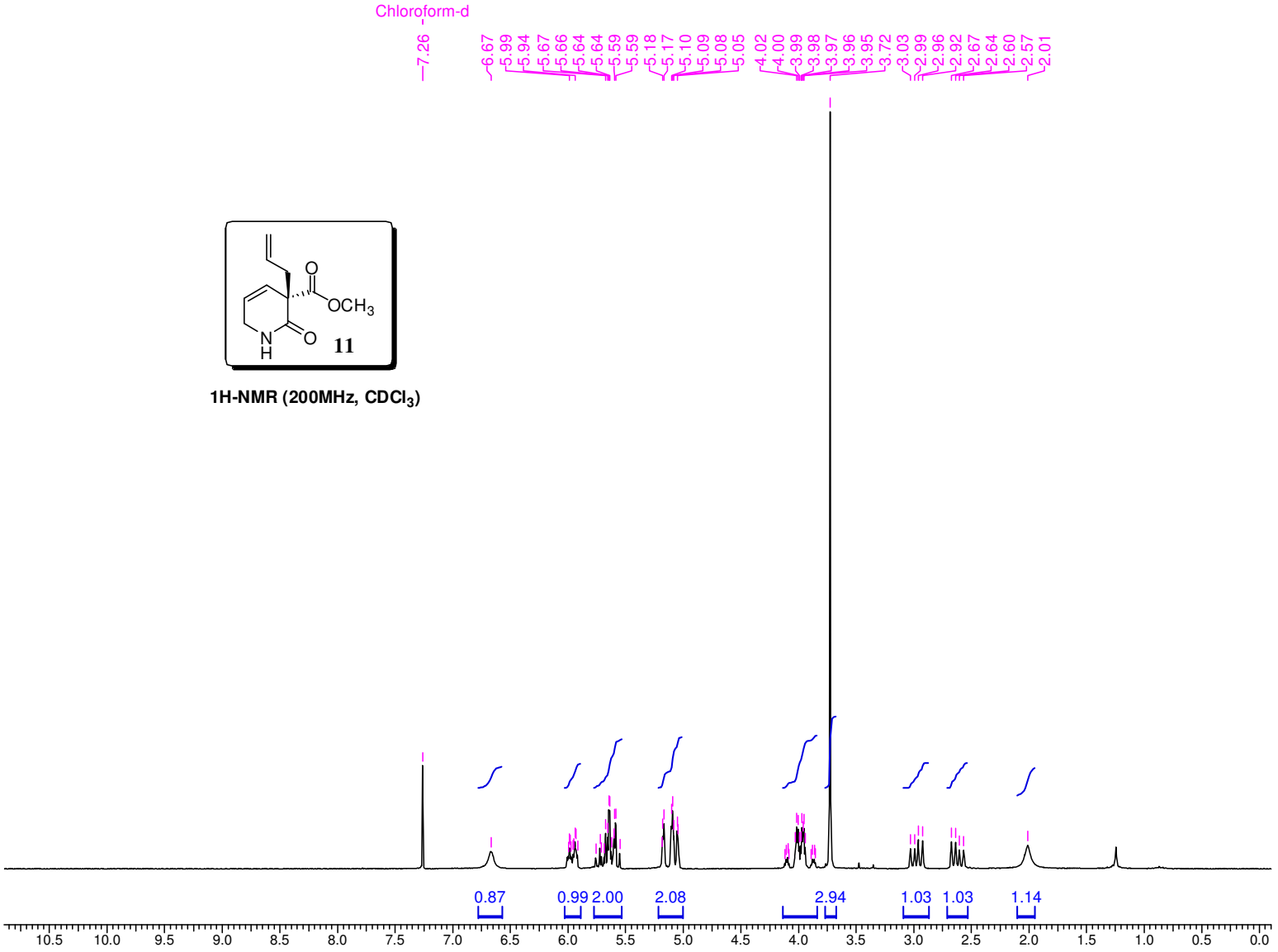
HPLC conditions:

Column : Atlantis RP-18(250×4.6mm)
Mobile Phase : Acetonitrile : Water (40:60)
Wavelength : 224nm
Flow rate : 1.0 mL/min (1200psi)
Sample conc : 2mg/1mL (Inj Vol-5µl)

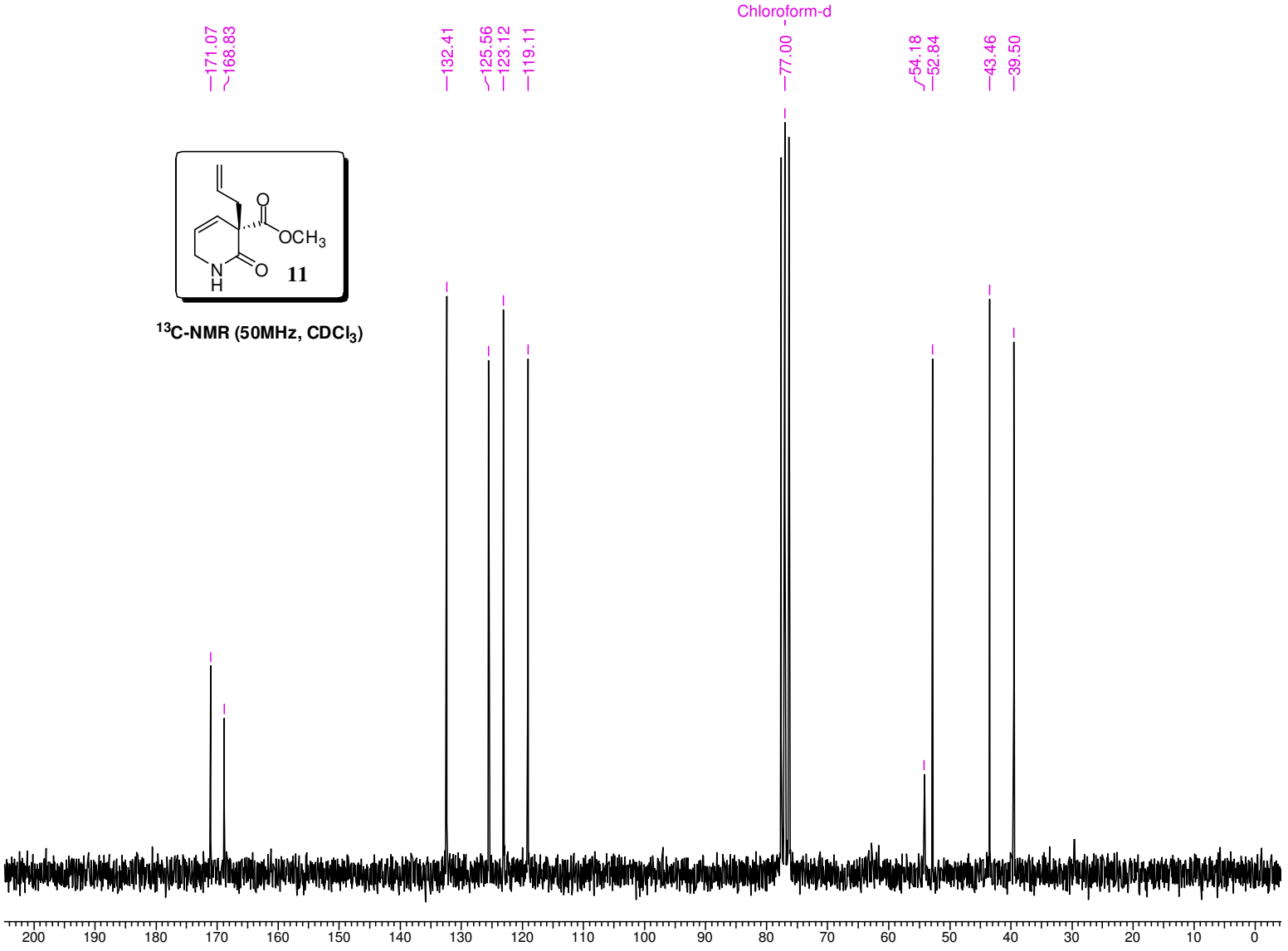


^{1}H- NMR (200MHz, $CDCl_3$)

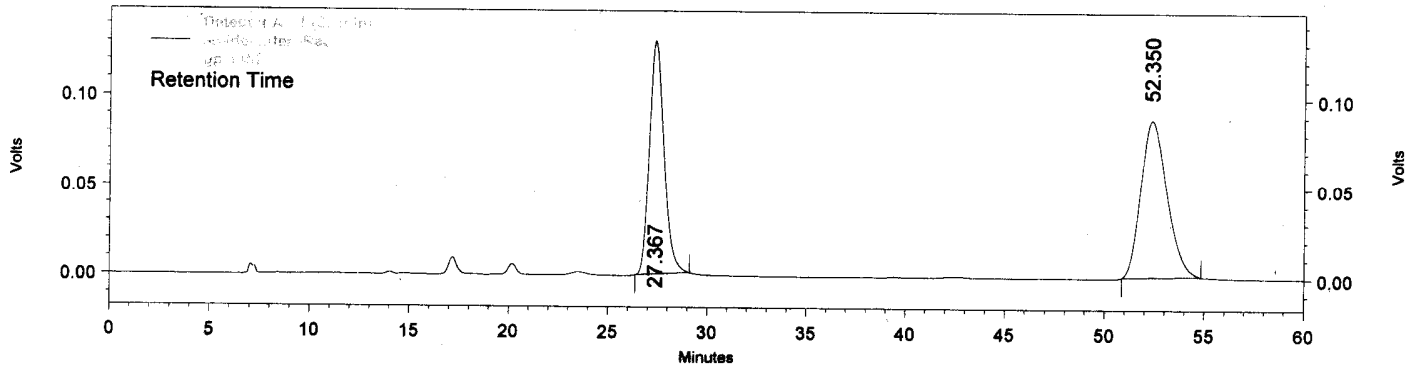

Chloroform-d
170.33
169.90
132.48
125.47
122.24
119.03
77.00
65.86
61.71
54.46
46.72
43.64
41.91
27.15
24.51
12
13C-NMR (50MHz, CDCl3)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0



1H-NMR (200MHz, $CDCl_3$)



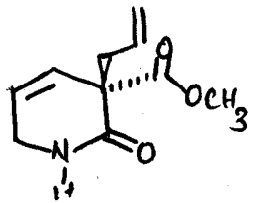
^{13}C-NMR (50MHz, $CDCl_3$)



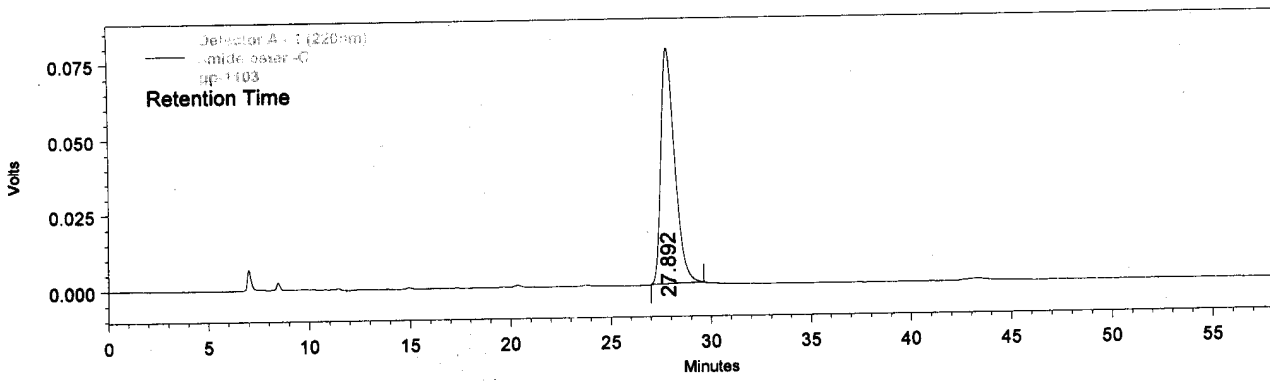
Detector A - 1
(220nm)

Pk #	Retention Time	Area	Area %	Height	Height Percent
1	27.367	6676591	45.529	130267	59.72
2	52.350	7987913	54.471	87868	40.28
Totals		14664504	100.000	218135	100.00

Column :-Chiralcel OD- H(250x4.6mm)
M.P. :IPA:P.E.(10:90)
Wavelength :- 220 nm
Flow :- 0.5ml/min(265psi)
conc. :- 2mg/2 ml
Injection vol : Inj Vol- 5ul



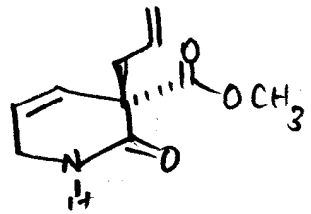
(S)-Ester (11) (19% ee)



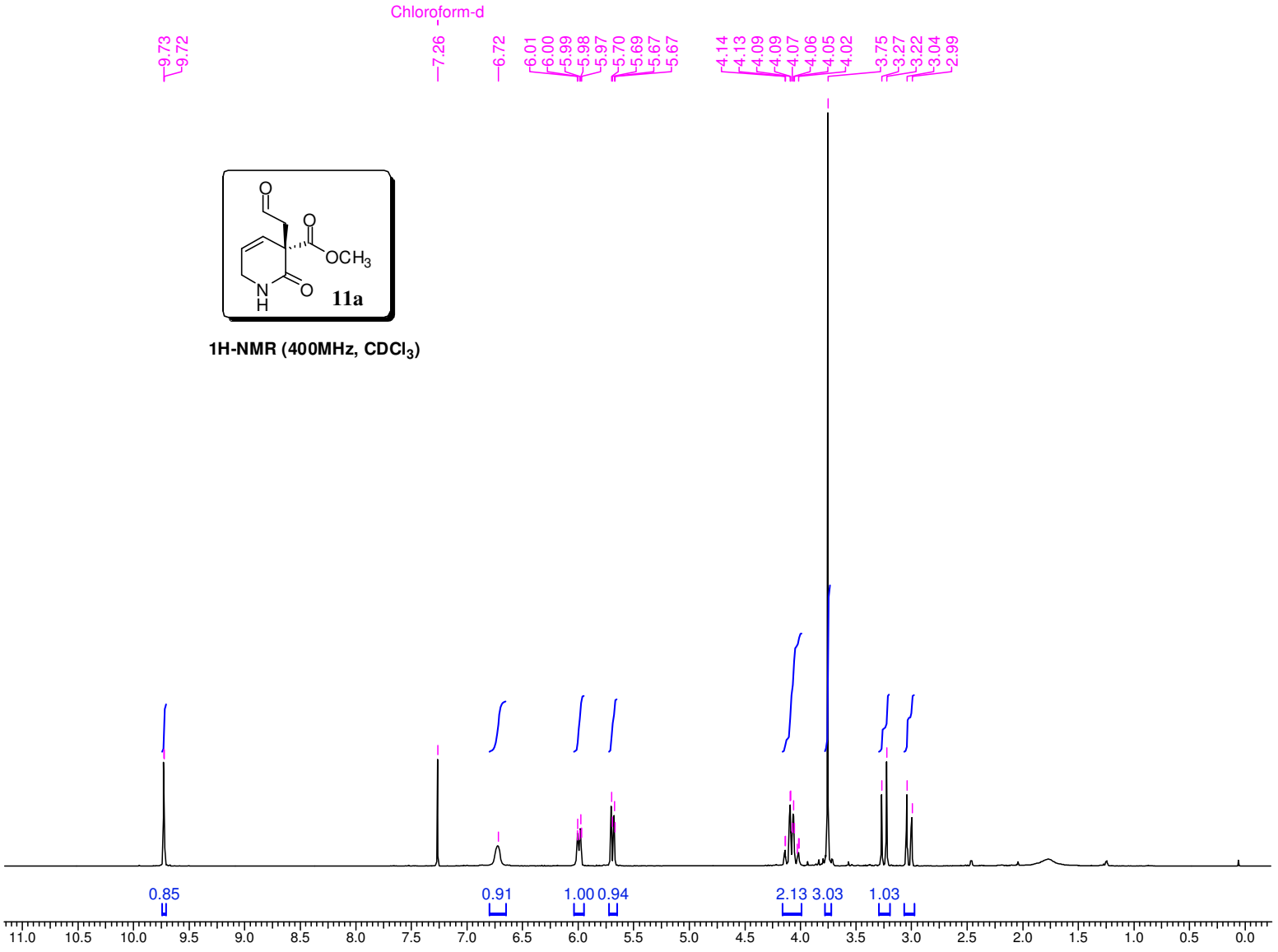
Detector A - 1
(220nm)

Pk #	Retention Time	Area	Area %	Height	Heig
1	27.892	3708490	100.000	78021	
Totals		3708490	100.000	78021	

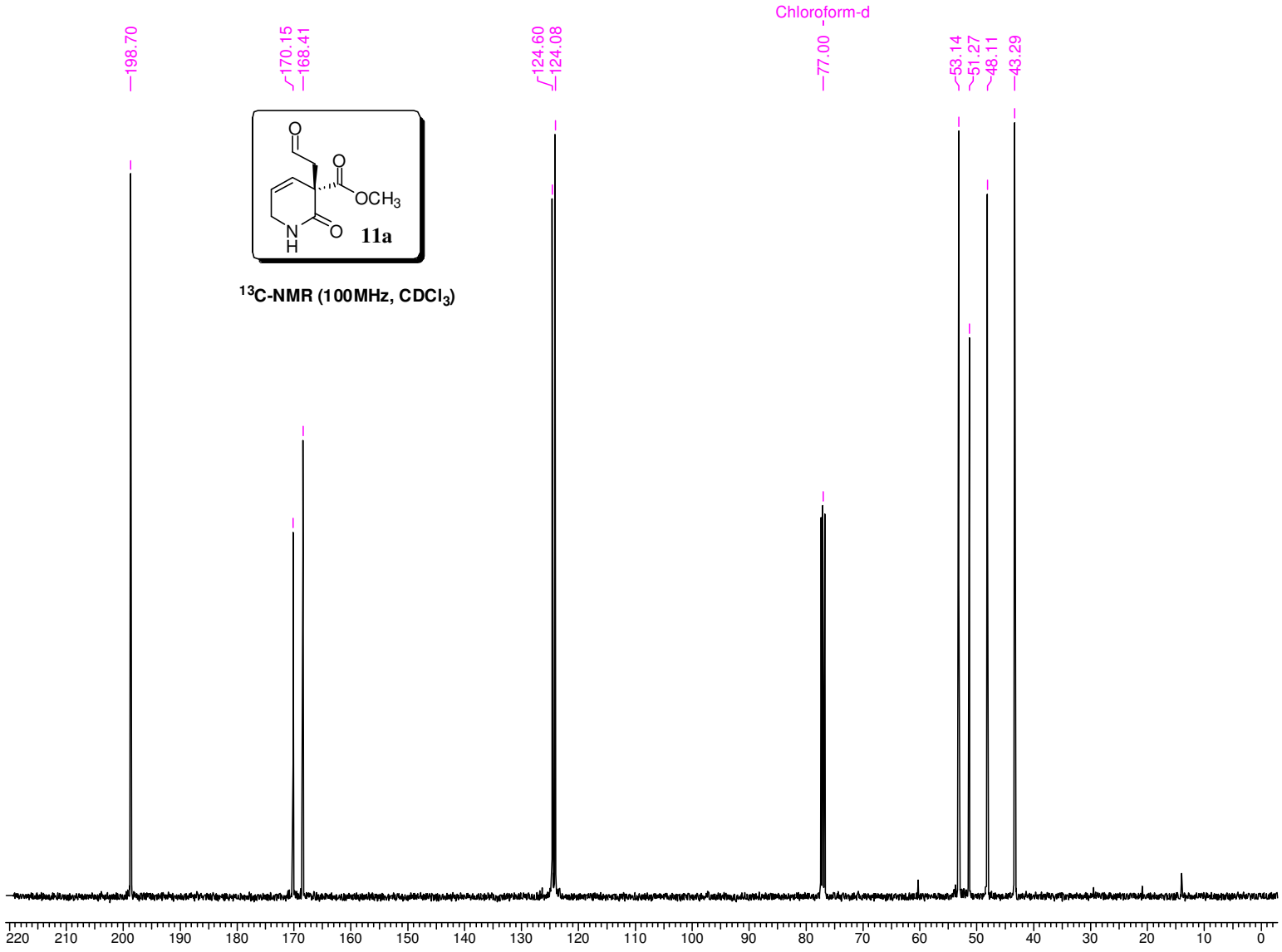
Column :-Chiralcel OD- H(250x4.6mm)
M.P. :IPA:P.E.(10:90)
Wavelength :- 220 nm
Flow :- 0.5ml/min(265psi)
conc. :- 2mg/2 ml
Injection vol : Inj Vol- 5ul

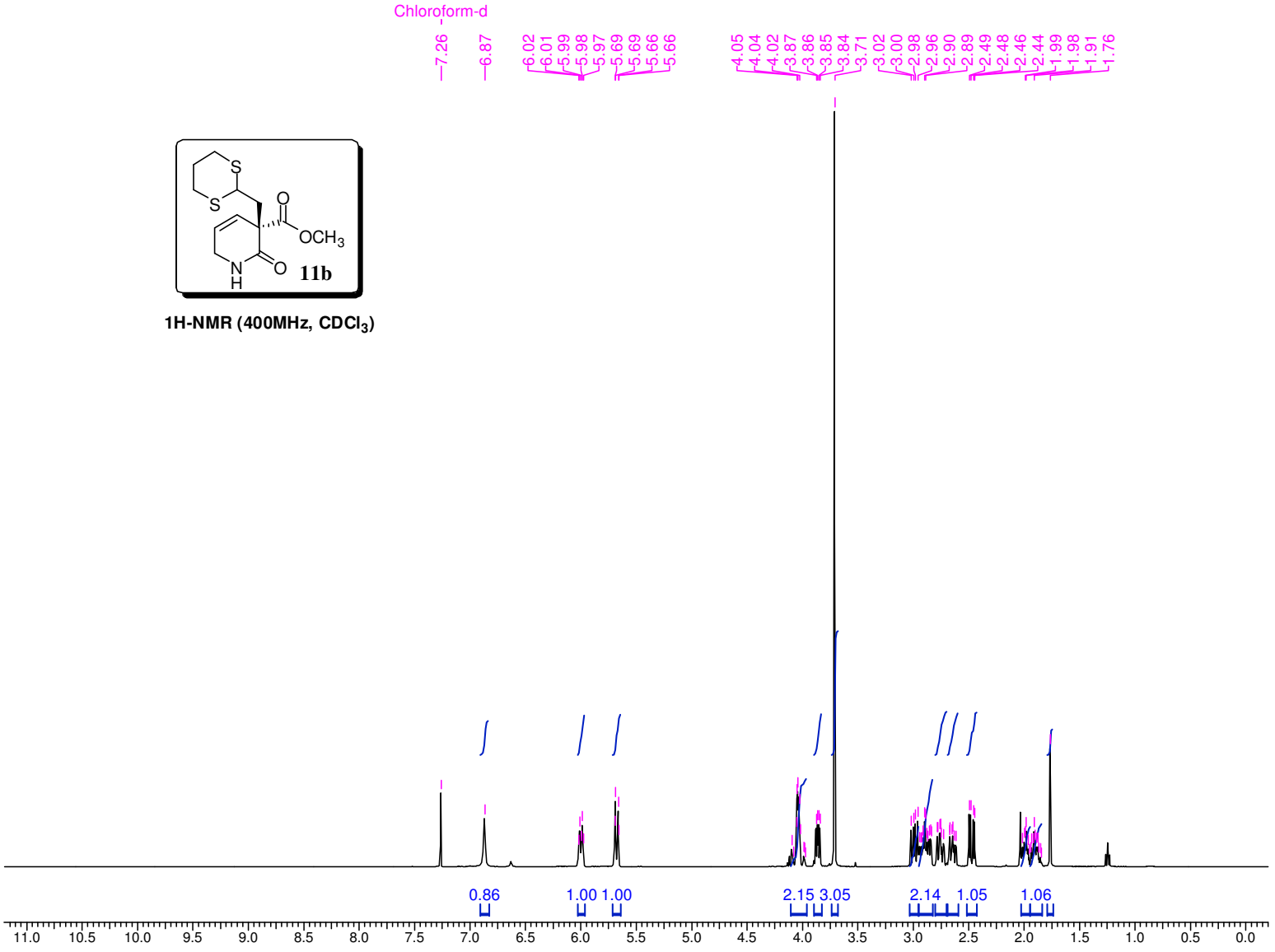


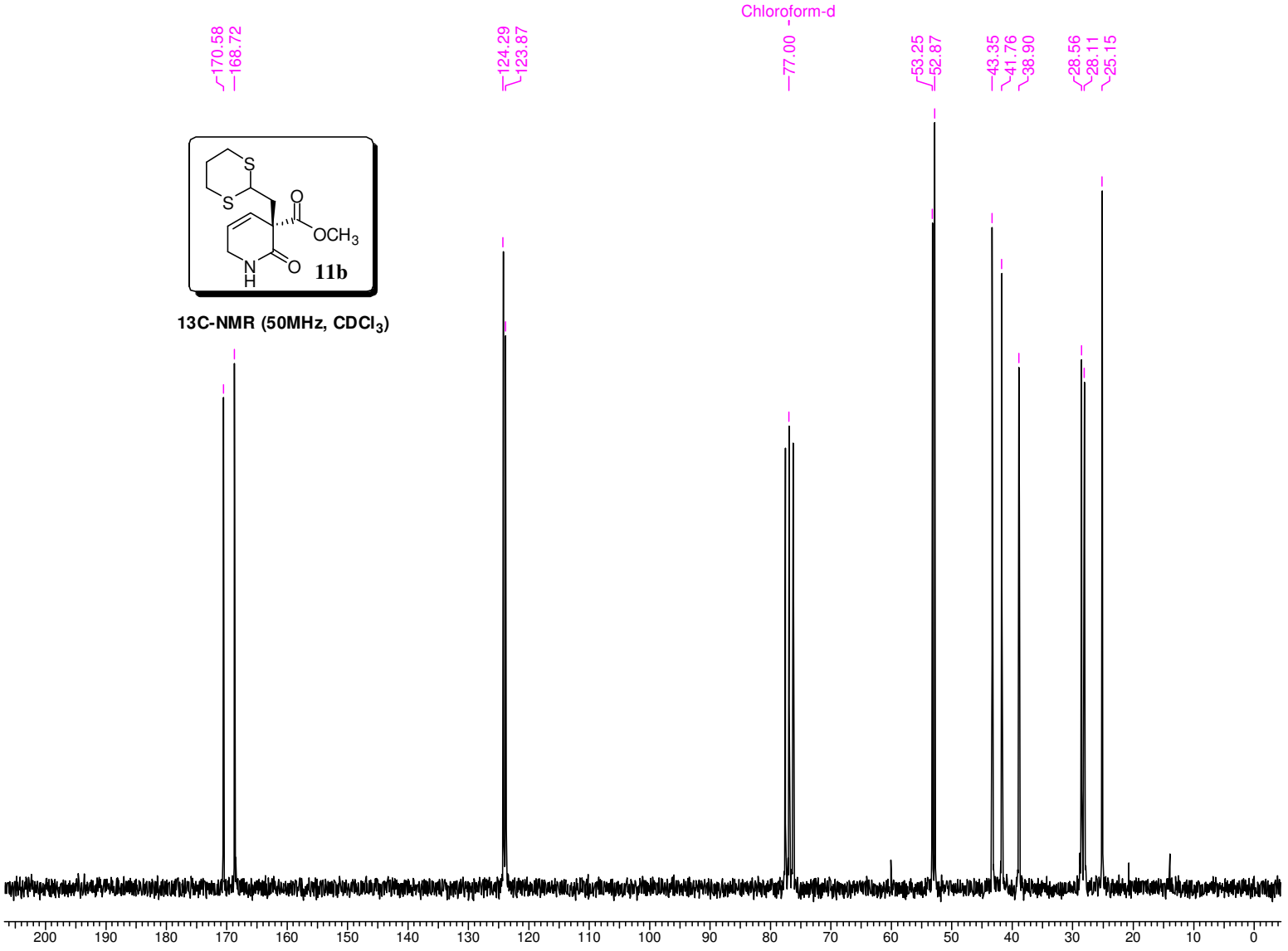
(S)-Ester (11) (>99% ee)

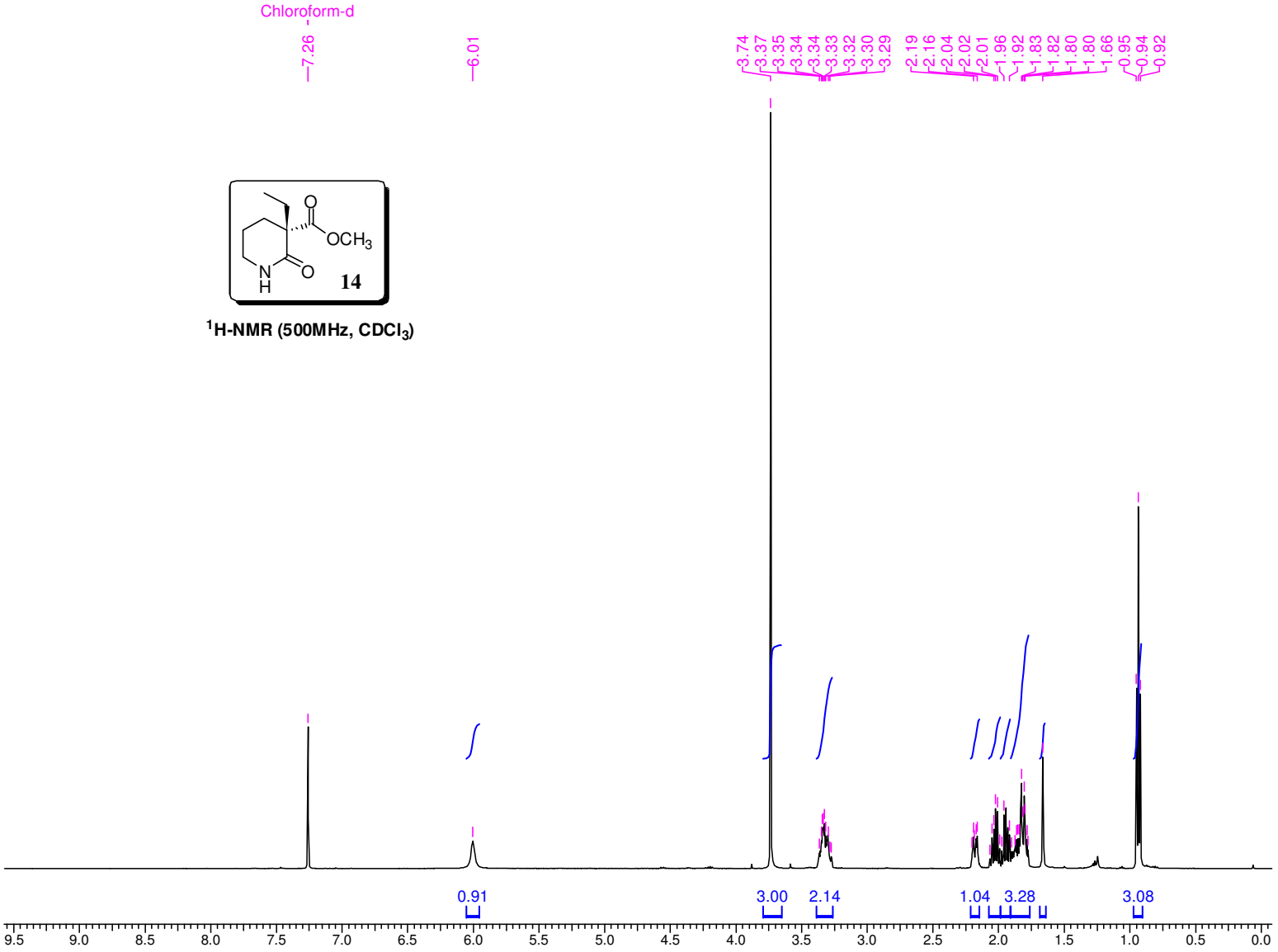


1H-NMR (400MHz, $CDCl_3$)

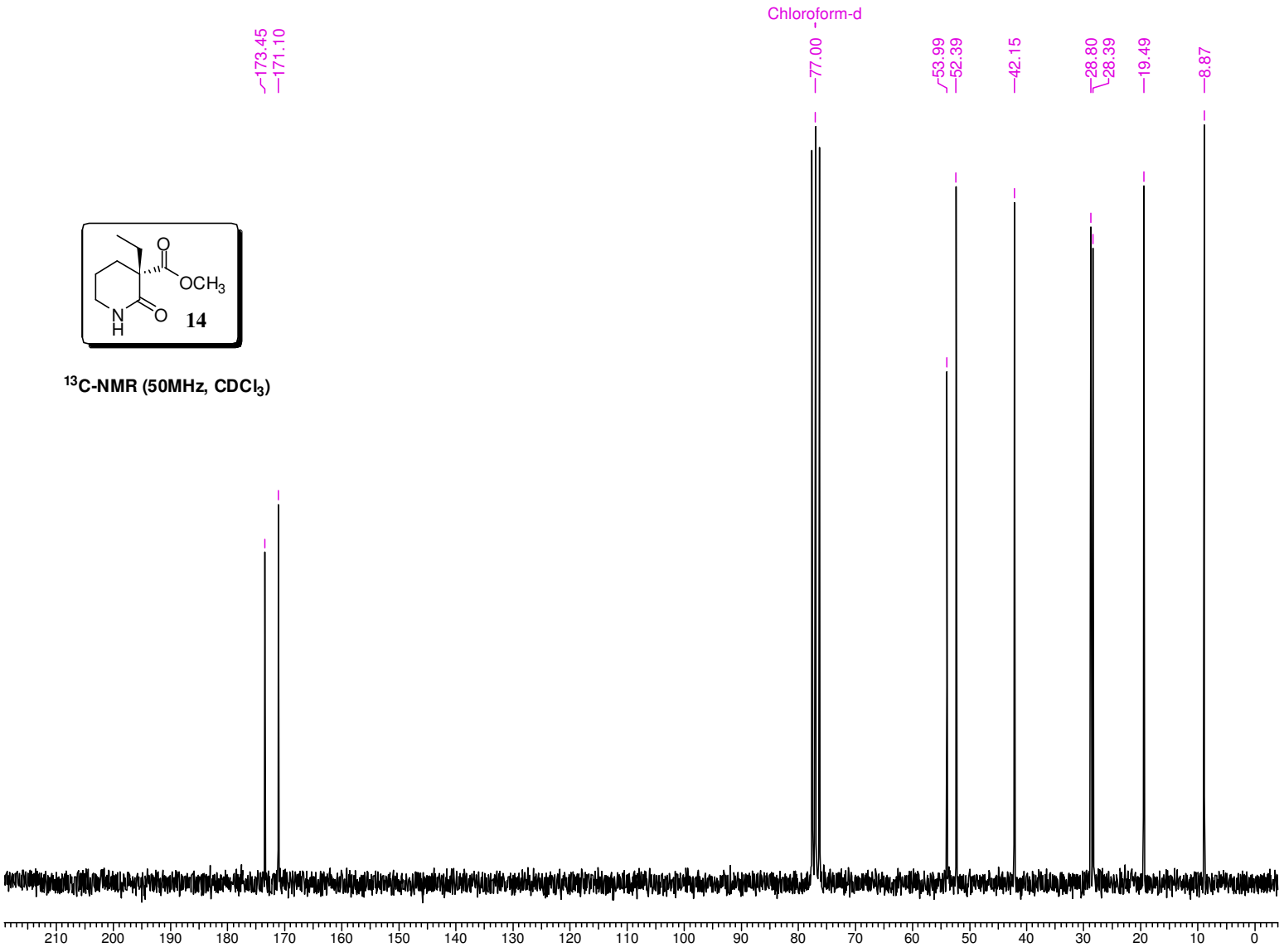

198.70
170.15
168.41
124.60
124.08
Chloroform-d
77.00
53.14
51.27
48.11
43.29
O
O
OCH3
N
H
O
11a
13C-NMR (100MHz, CDCl3)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0


Chloroform-d
7.26
6.87
6.02
6.01
5.99
5.98
5.97
5.69
5.69
5.66
5.66
4.05
4.04
4.02
3.87
3.86
3.85
3.84
3.71
3.02
3.00
2.98
2.96
2.90
2.89
2.49
2.48
2.46
2.44
1.99
1.98
1.91
1.76
S
S
O
OCH3
N
H
O
11b
1H-NMR (400MHz, CDCl3)
0.86
1.00
1.00
2.15
3.05
2.14
1.05
1.06
11.0
10.5
10.0
9.5
9.0
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

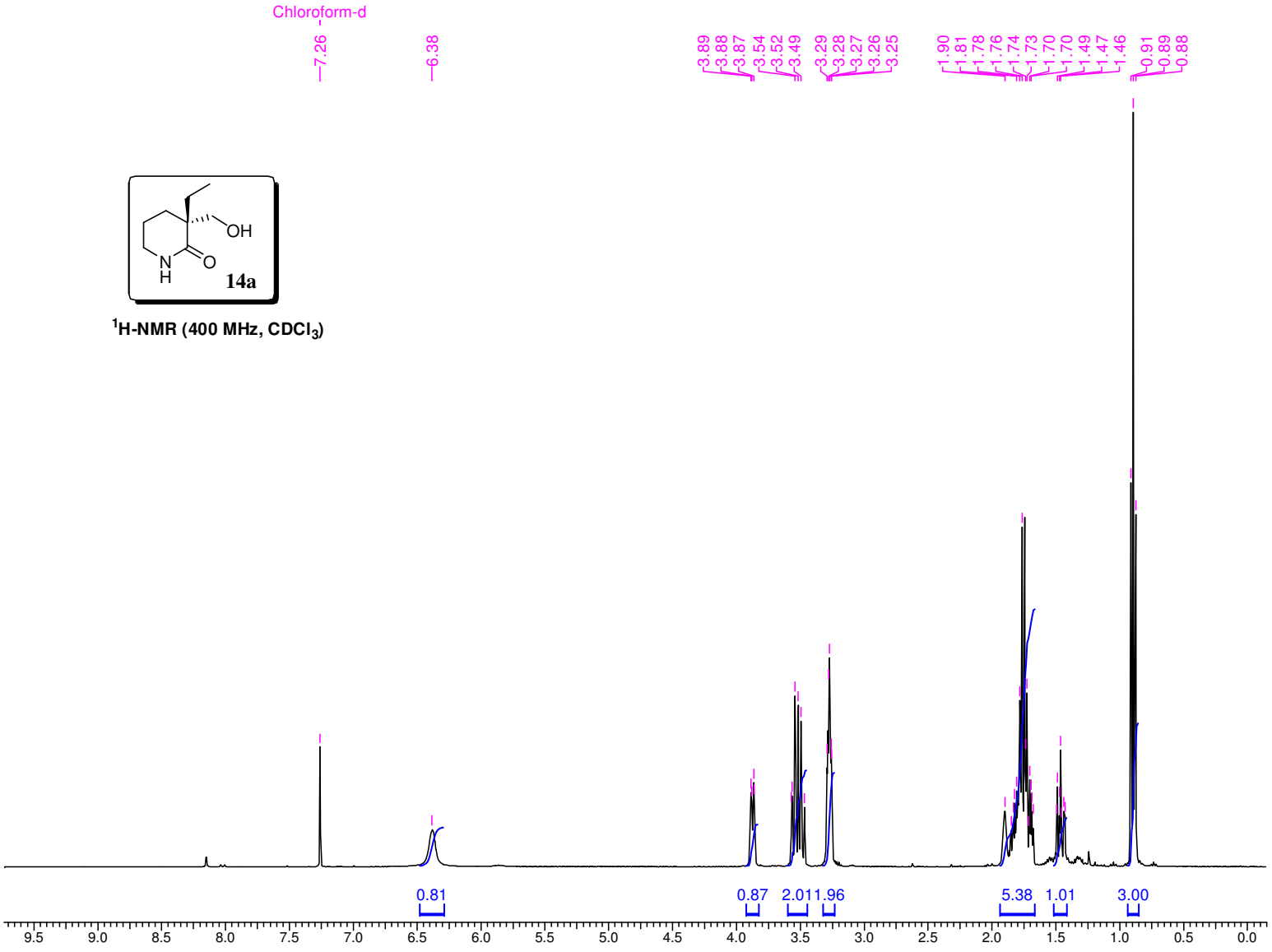

Chloroform-d
170.58
168.72
124.29
123.87
77.00
53.25
52.87
43.35
41.76
38.90
28.56
28.11
25.15
OCH3
11b
13C-NMR (50MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0



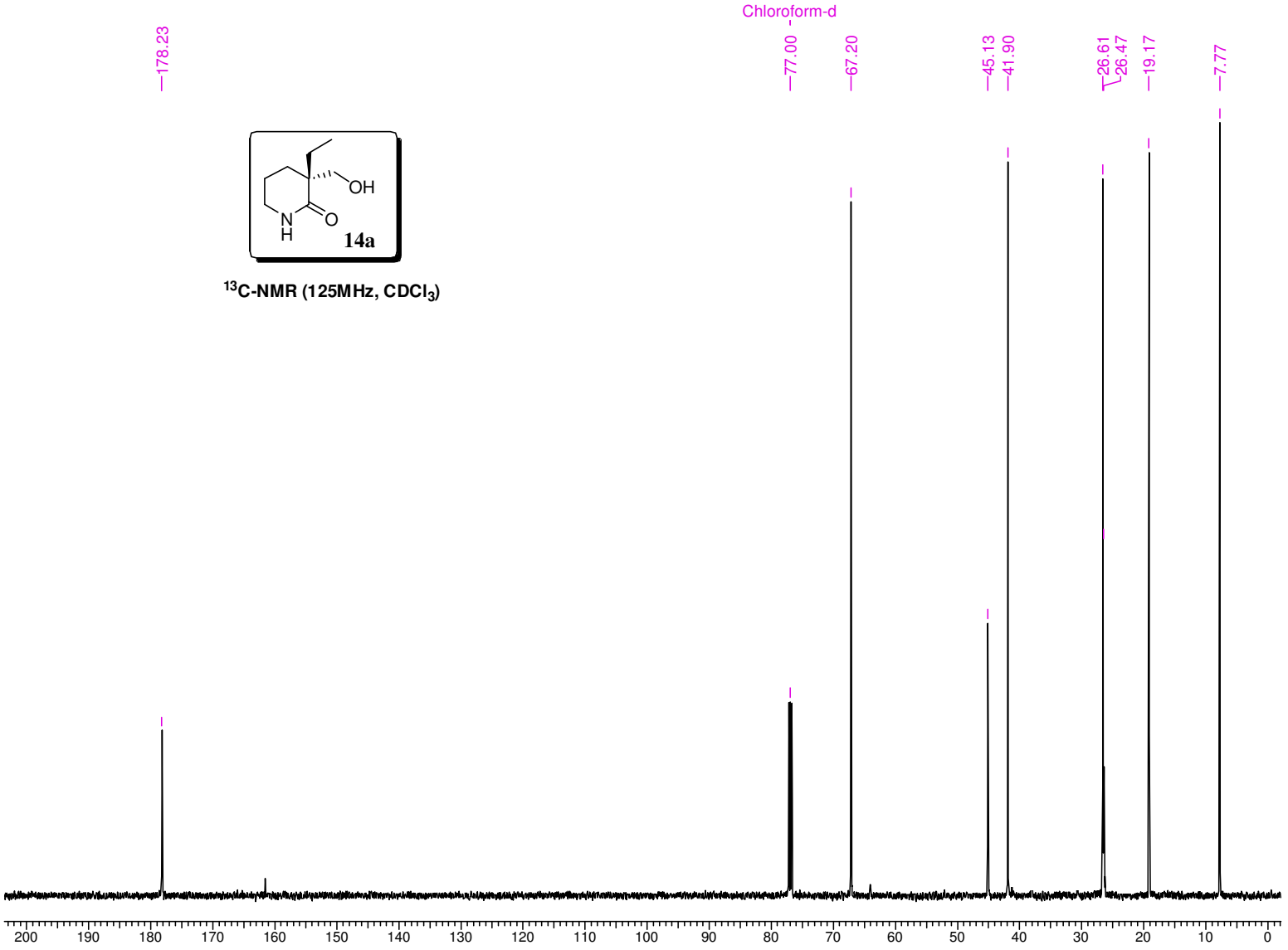
^{1}H-NMR (500MHz, $CDCl_3$)



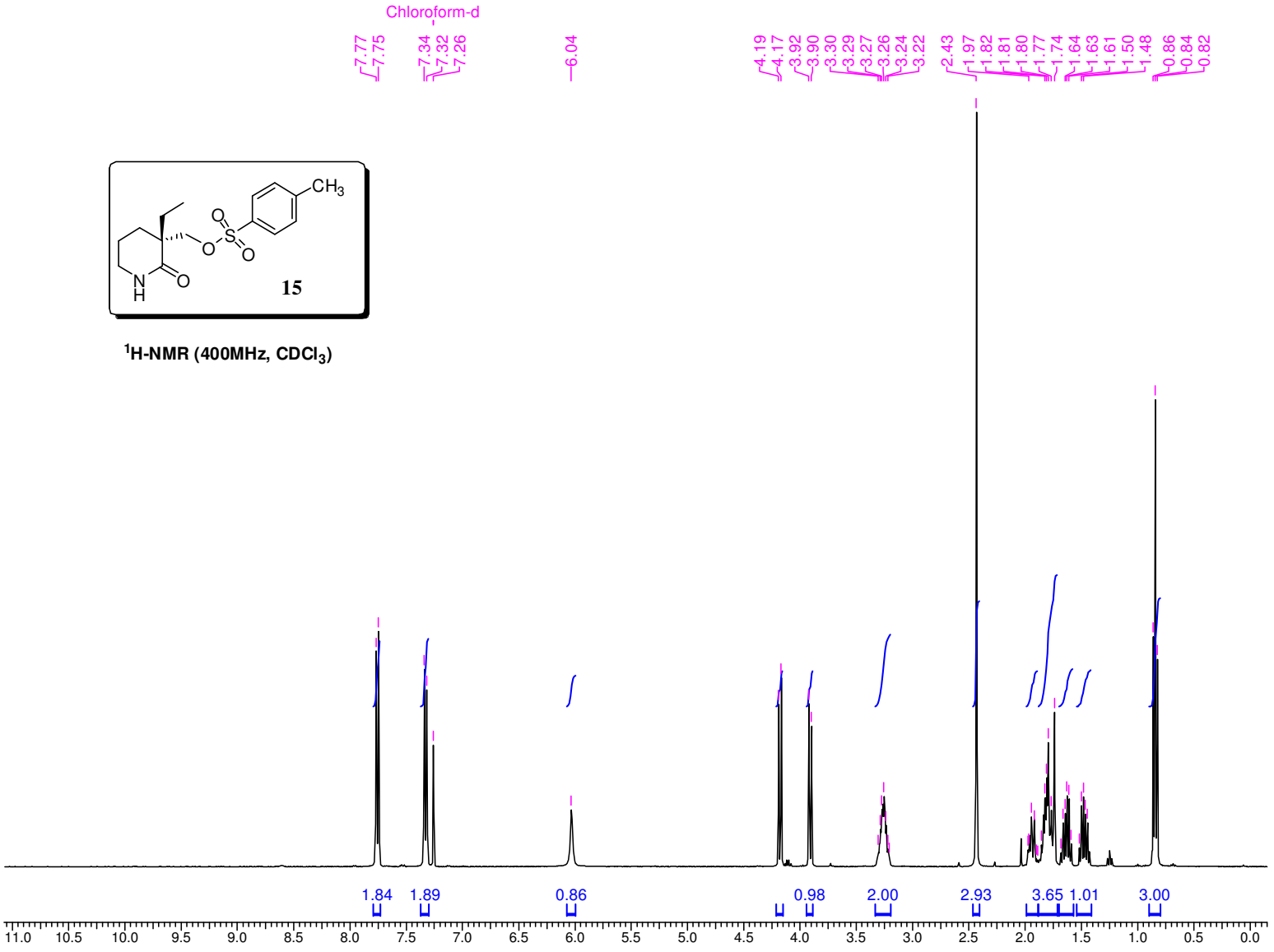
^{13}C-NMR (50MHz, $CDCl_3$)



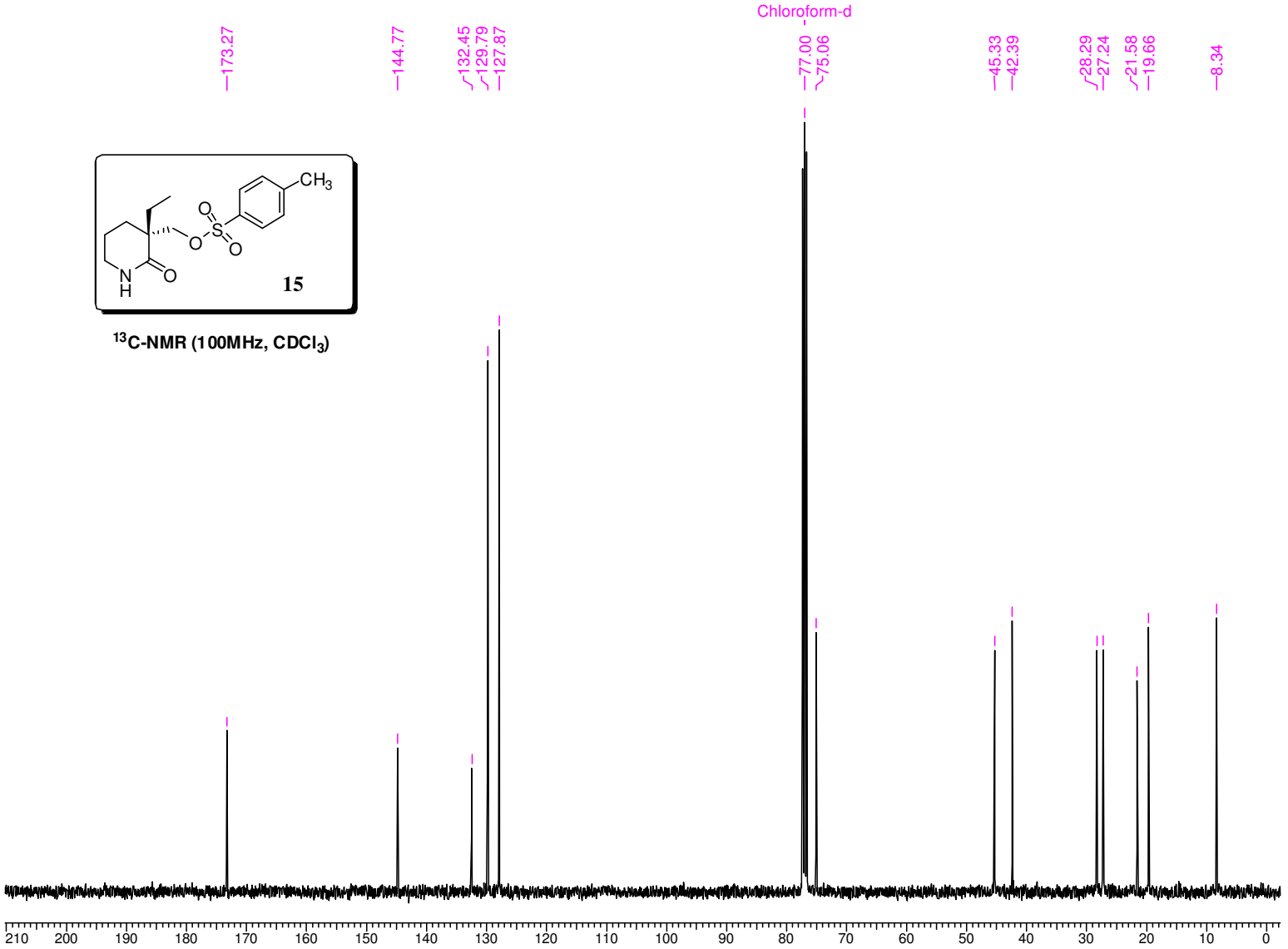
^{1}H-NMR (400 MHz, $CDCl_3$)



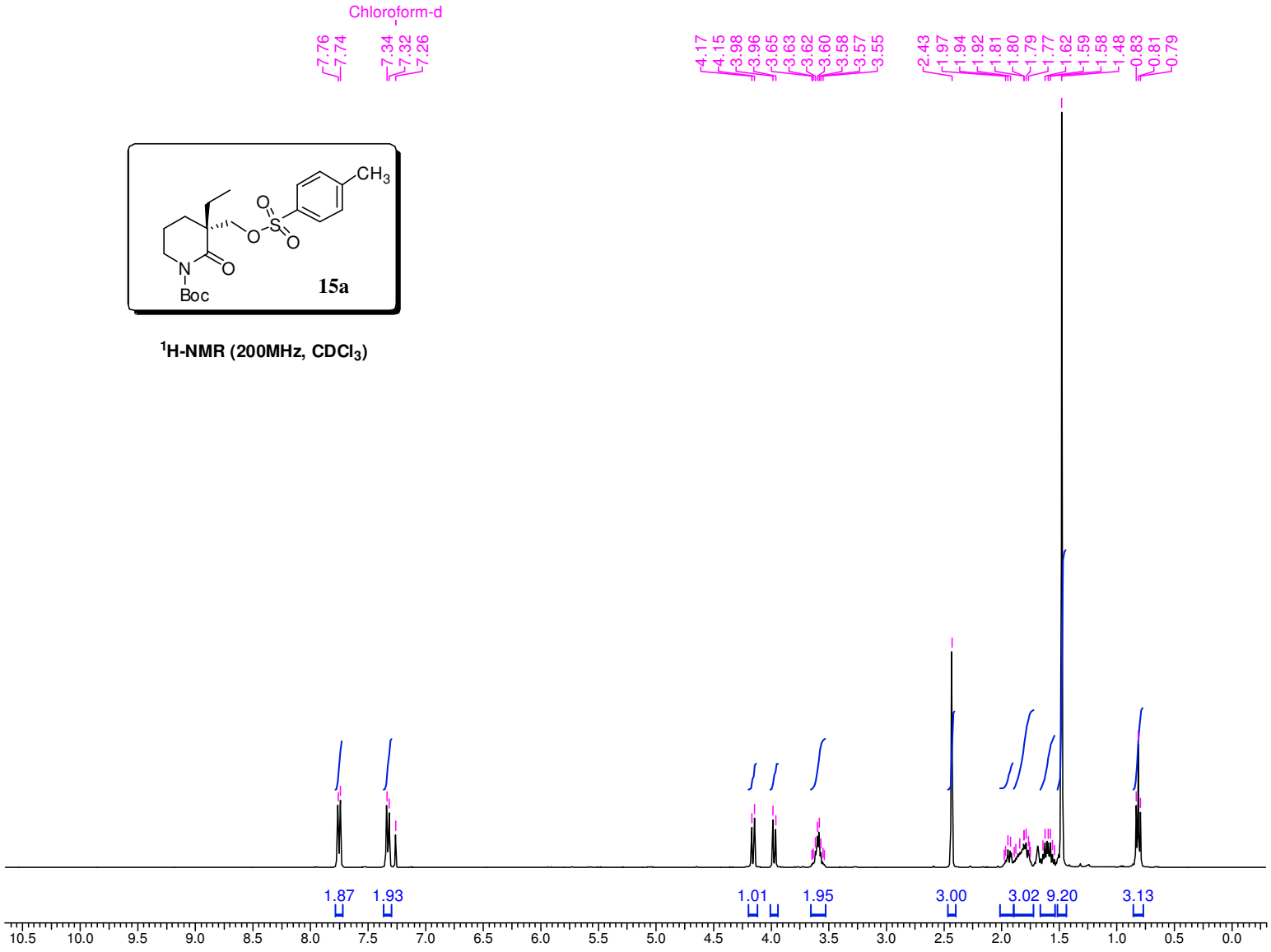
^{13}C-NMR (125MHz, $CDCl_3$)



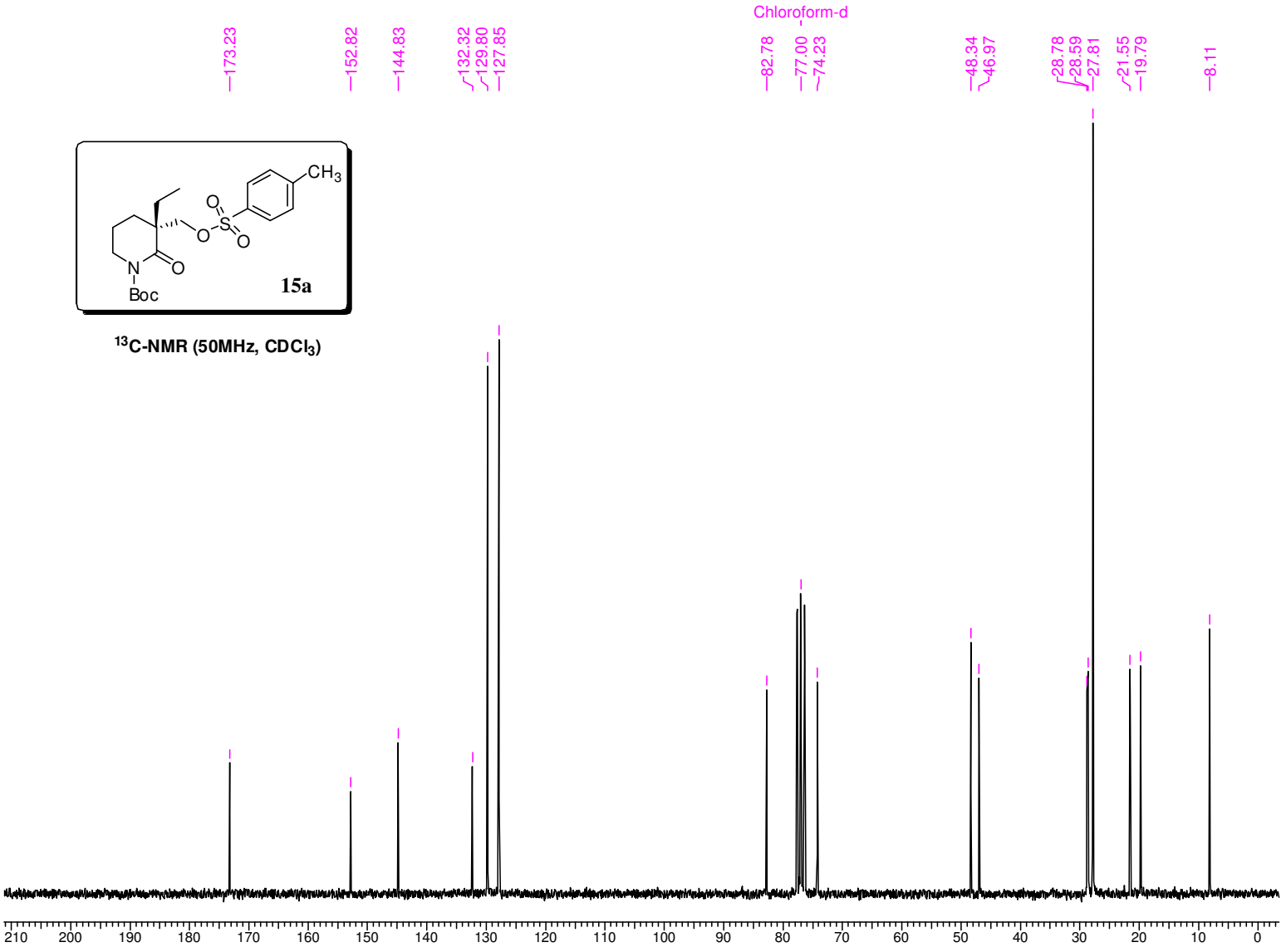
^{1}H-NMR (400MHz, $CDCl_3$)



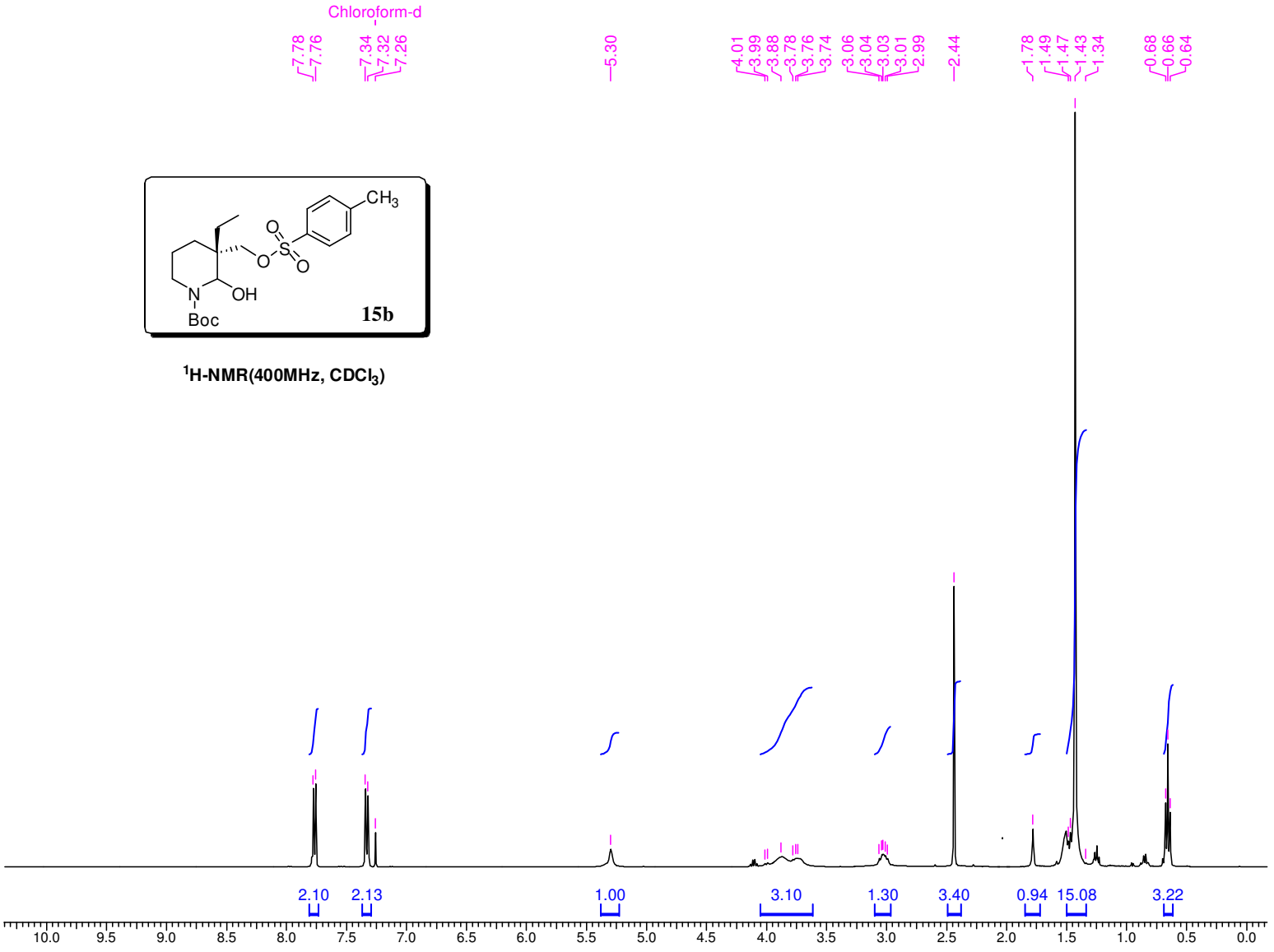
^{13}C-NMR (100MHz, $CDCl_3$)



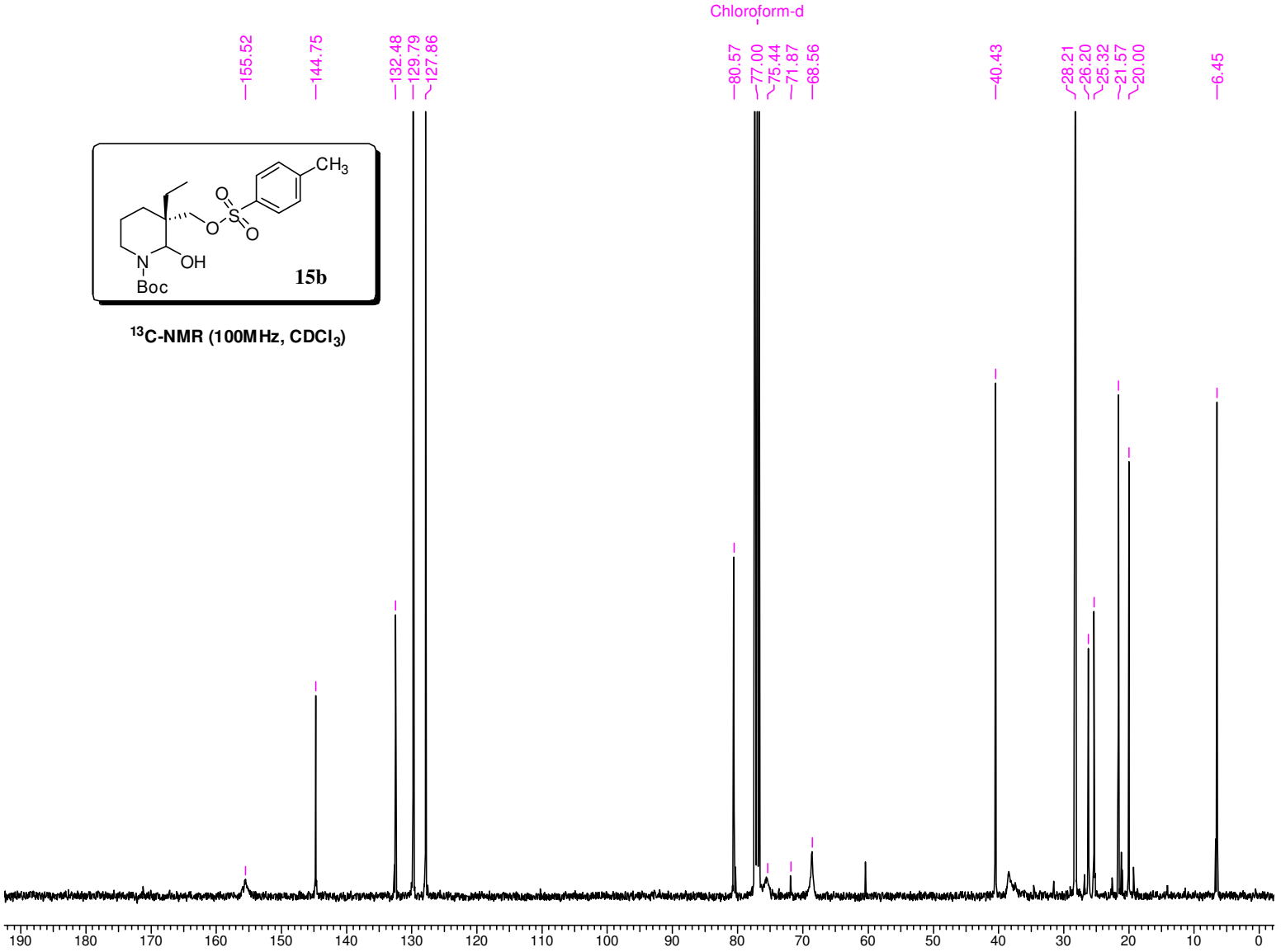
^{1}H-NMR (200MHz, $CDCl_3$)

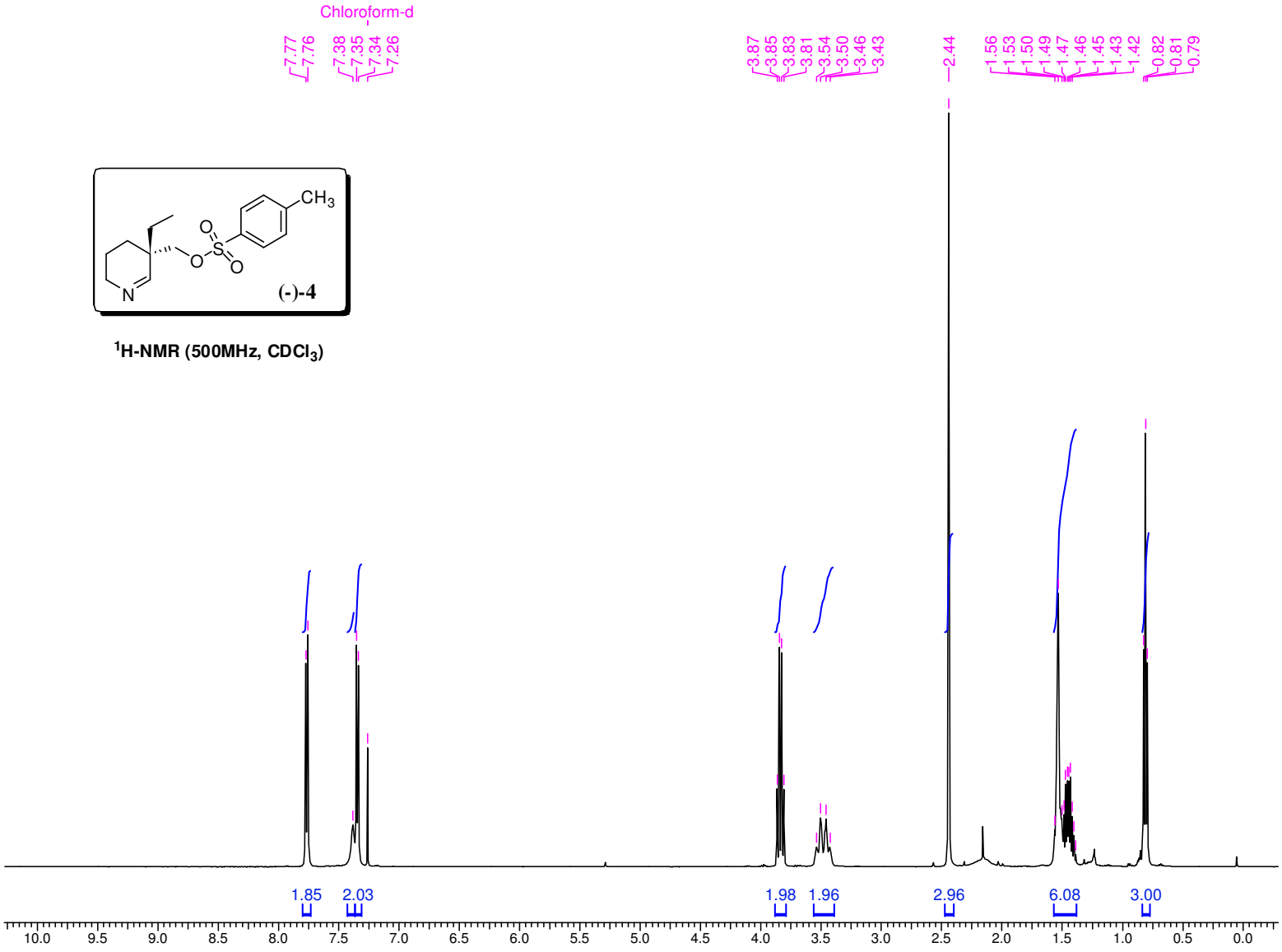


^{13}C-NMR (50MHz, $CDCl_3$)

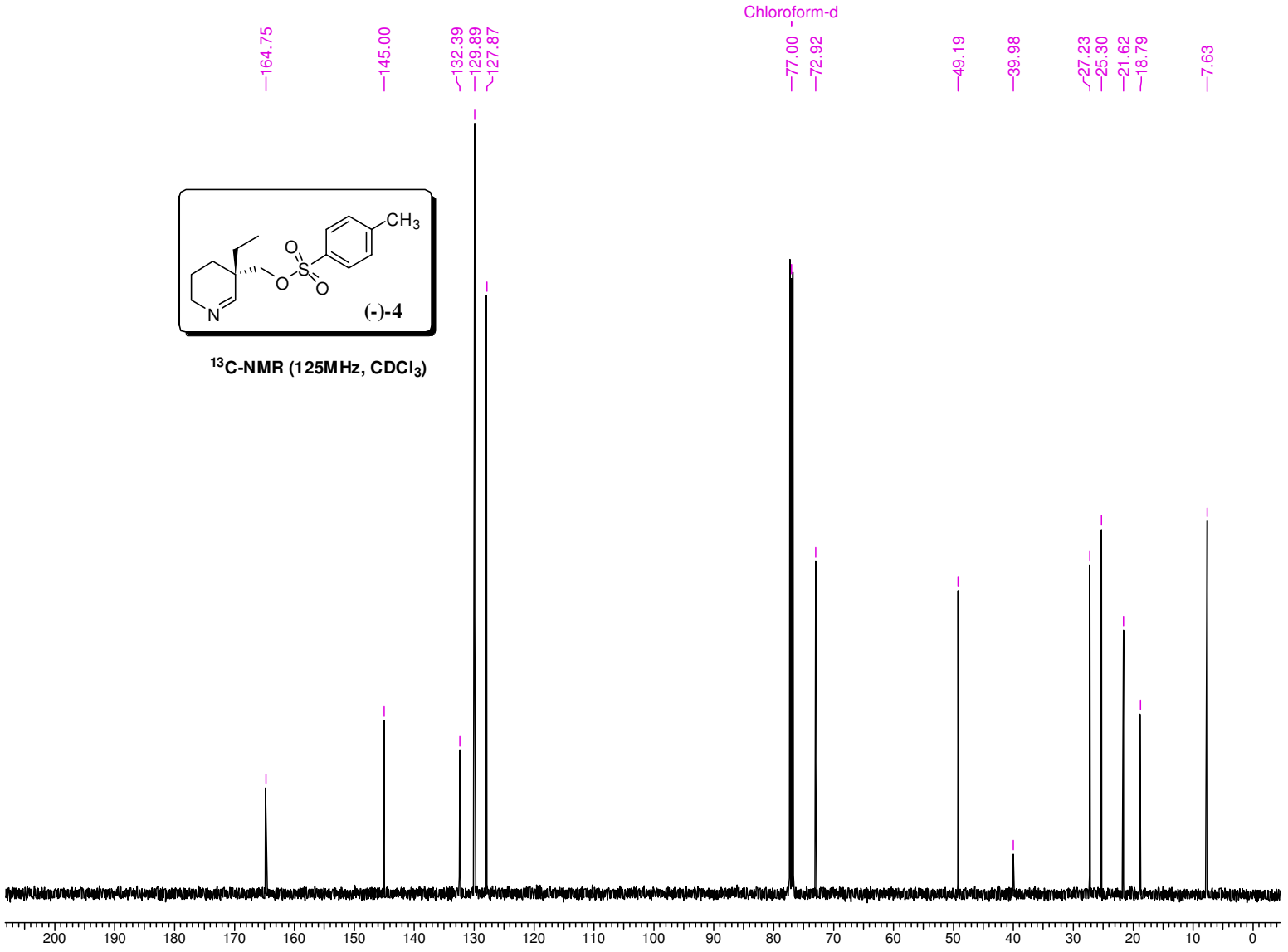


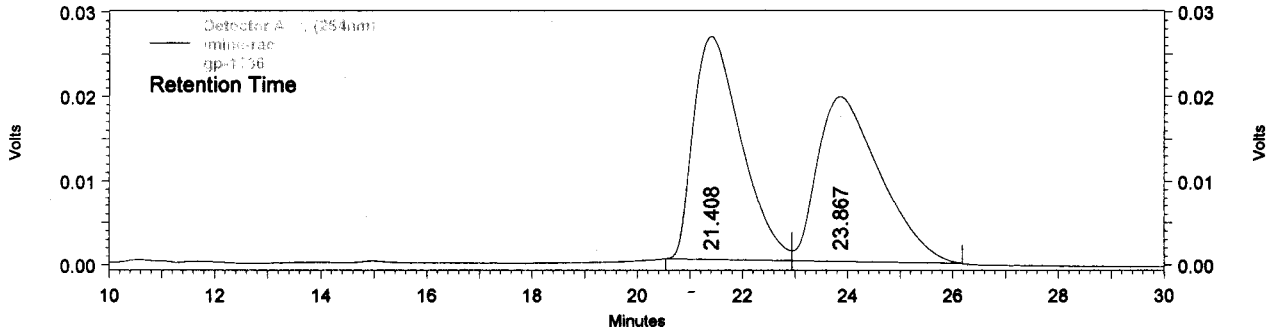
^{1}H-NMR(400MHz, $CDCl_3$)


Chloroform-d
155.52
144.75
132.48
129.79
127.86
80.57
77.00
75.44
71.87
68.56
40.43
28.21
26.20
25.32
21.57
20.00
6.45
CH3
O
S
O
O
N
OH
Boc
15b
13C-NMR (100MHz, CDCl3)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0



^{1}H-NMR (500MHz, $CDCl_3$)

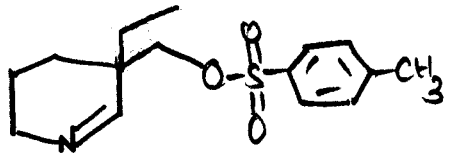

Chloroform-d
164.75
145.00
132.39
129.89
127.87
77.00
72.92
49.19
39.98
27.23
25.30
21.62
18.79
7.63
CH3
O
S
O
O
N
(-)-4
13C-NMR (125MHz, CDCl3)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0



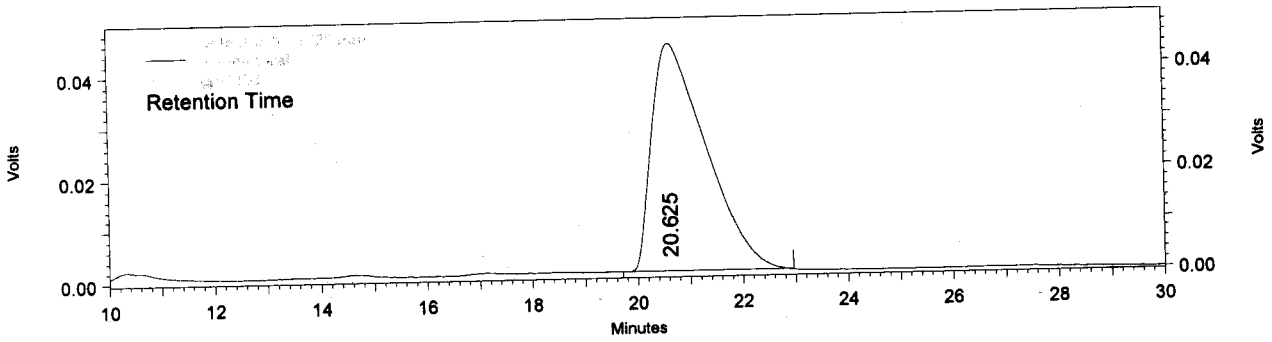
Detector A - 1 (254nm)

Pk #	Retention Time	Area	Area %
1	21.408	1674827	50.688
2	23.867	1629348	49.312
Totals		3304175	100.000

Column :Chiralcel OJ-H- (4.6x250mm)
Mobile Phase : IPA:Pet ether (15:85)
Wavelength : 254nm
Flow Rate : 0.7ml/min 33kgf
Sample Con :2.3mg/0.5ml Inj vol-10ul



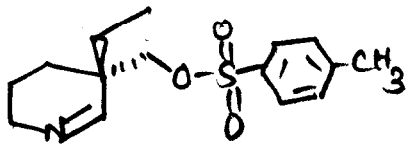
(Racemic)



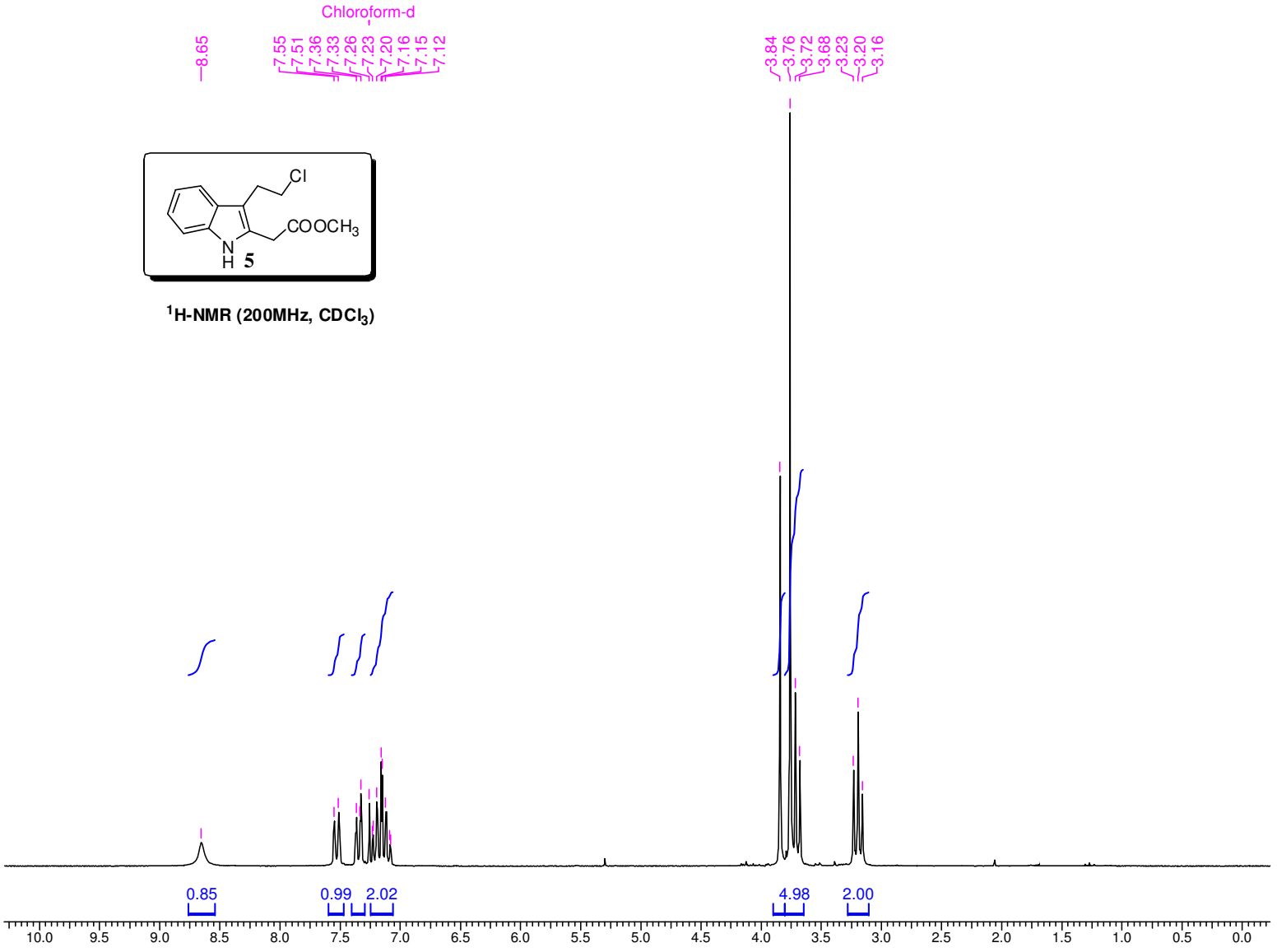
Detector A - 1 (254nm)

Pk #	Retention Time	Area	Area %
1	20.625	3155145	100.000
Totals		3155145	100.000

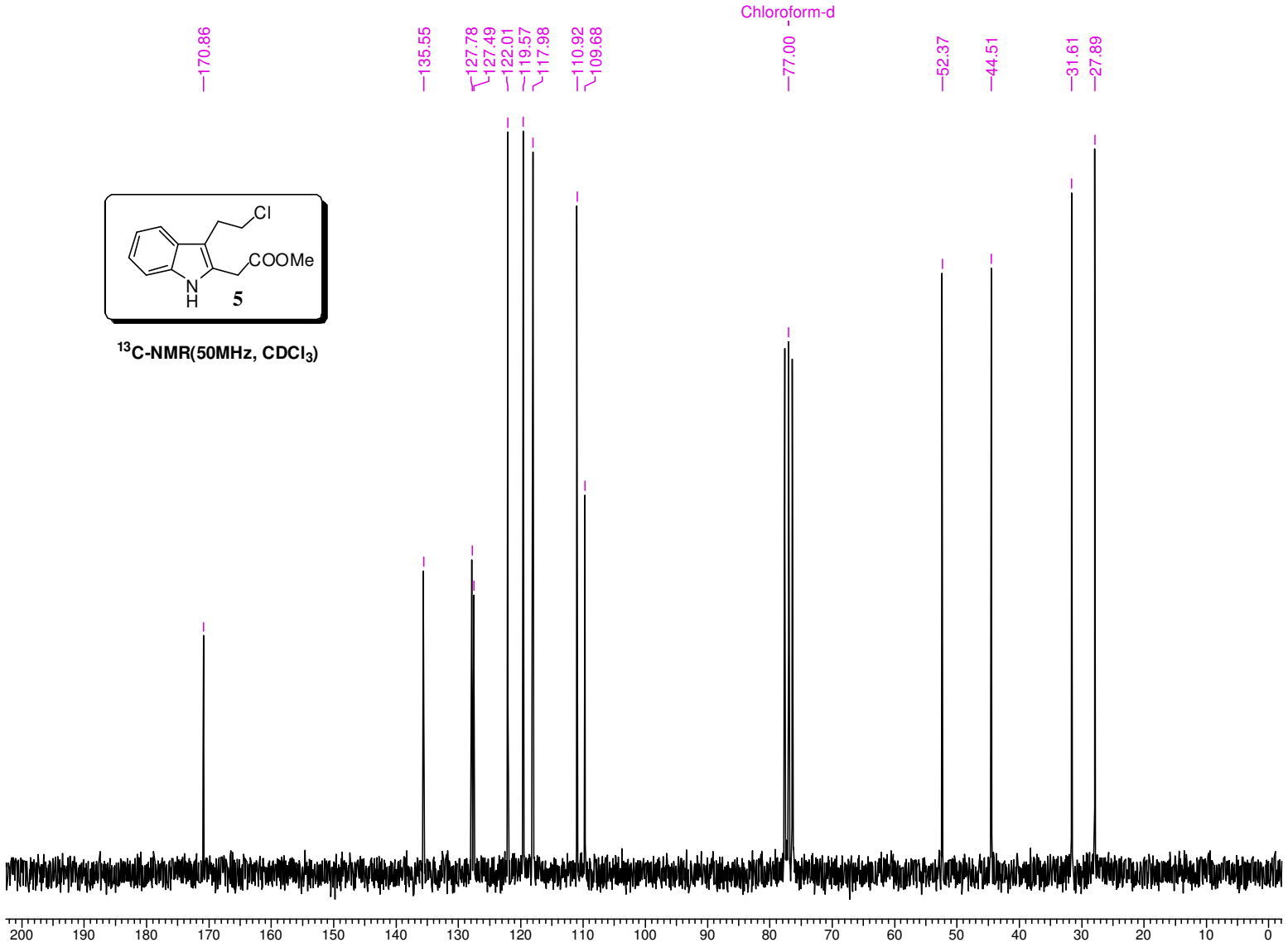
Column :Chiralcel OJ-H- (4.6x250mm)
Mobile Phase : IPA:Pet ether (15:85)
Wavelength : 254nm
Flow Rate : 0.7ml/min 33kgf
Sample Con :2.3mg/0.5ml Inj vol-10ul



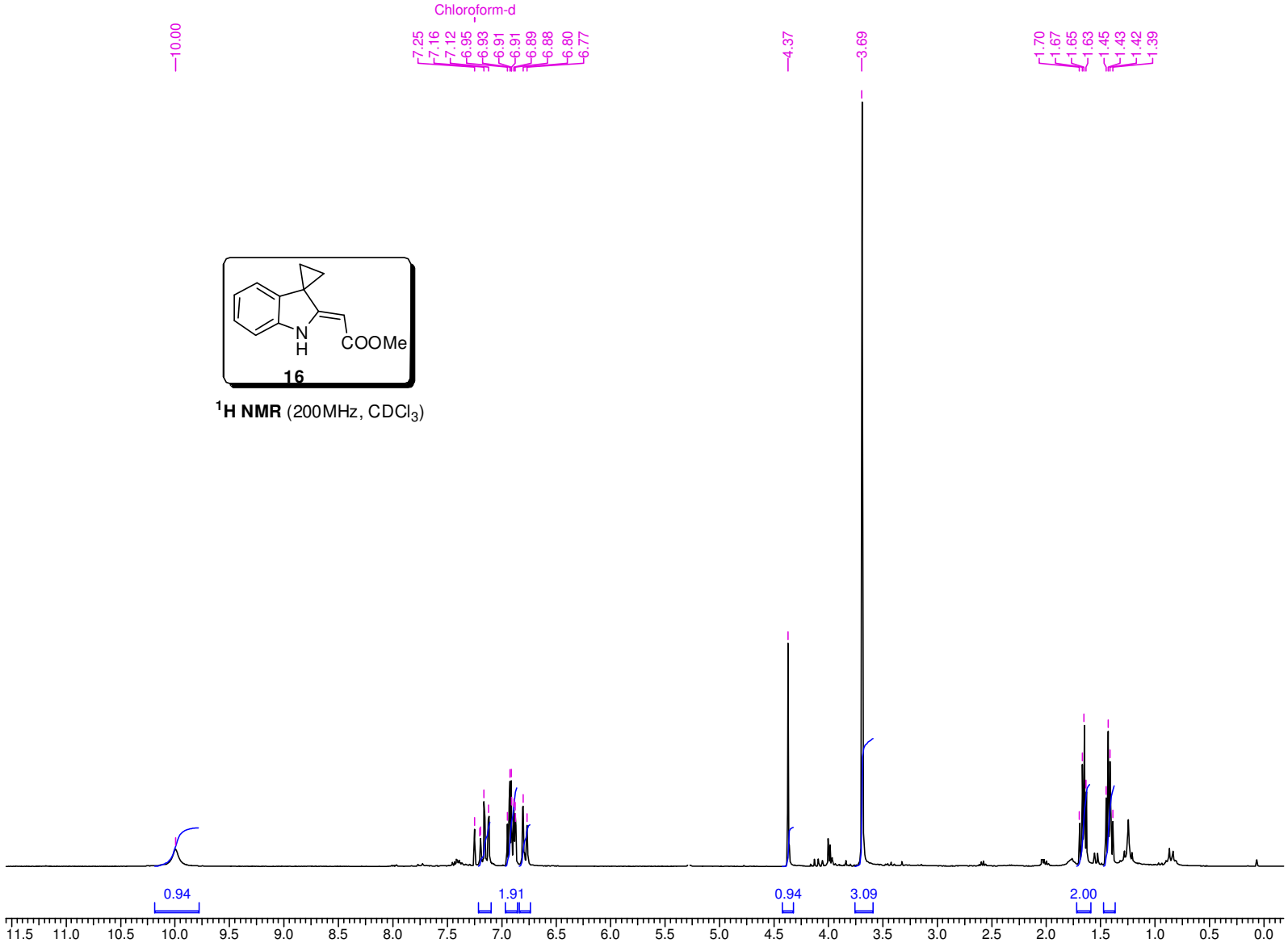
(chiral)



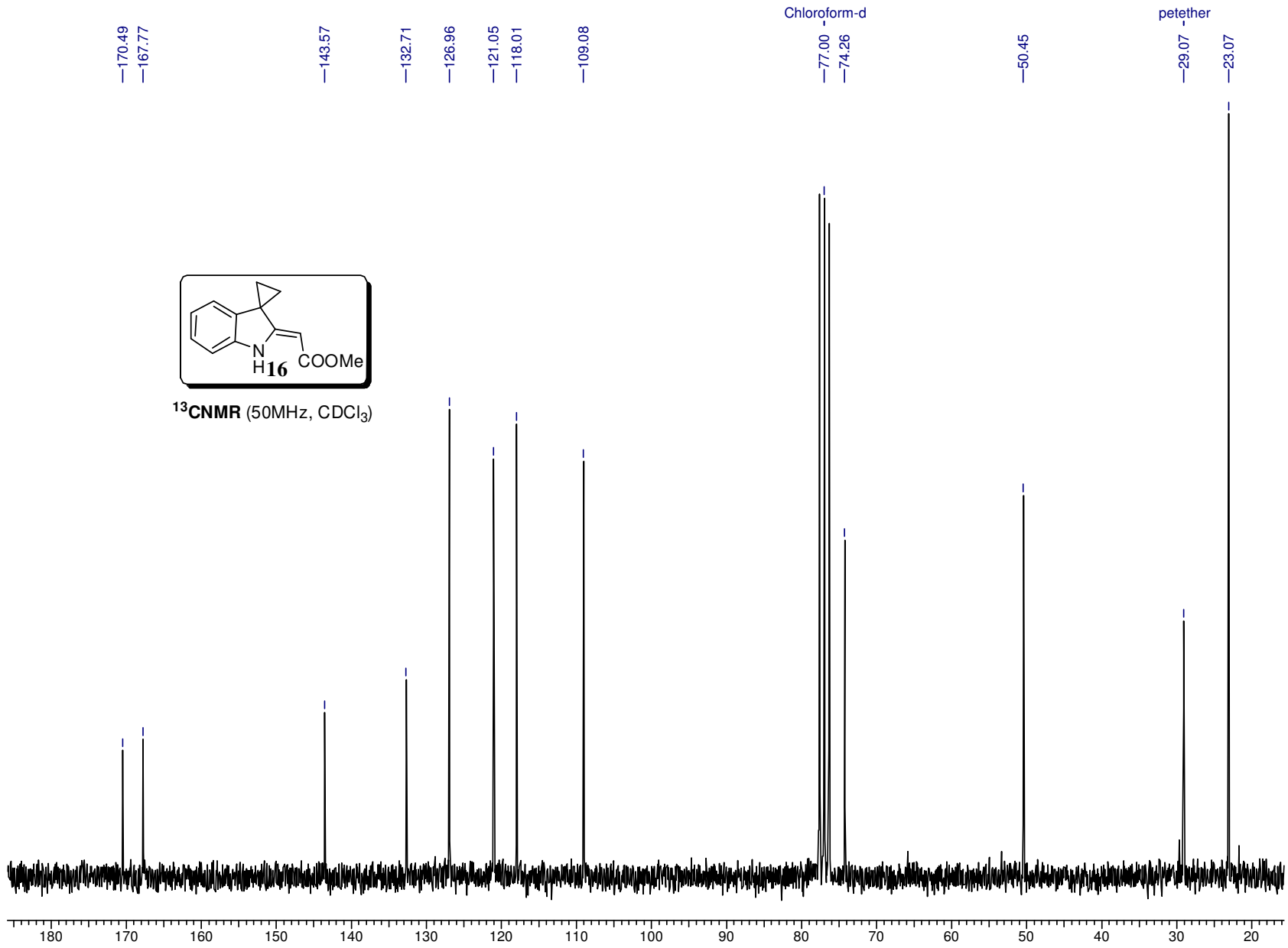
^{1}H-NMR (200MHz, $CDCl_3$)

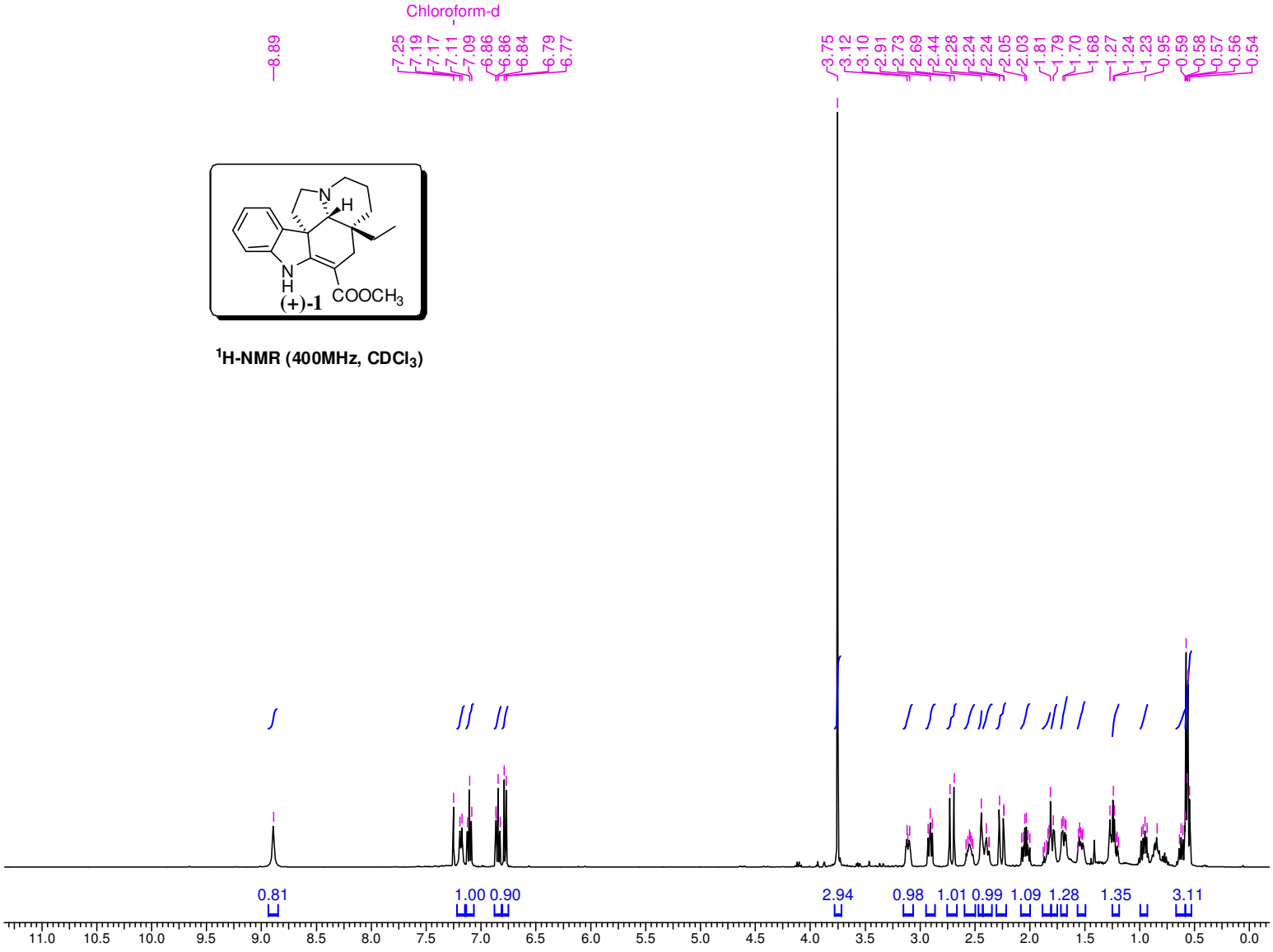


^{13}C-NMR(50MHz, $CDCl_3$)

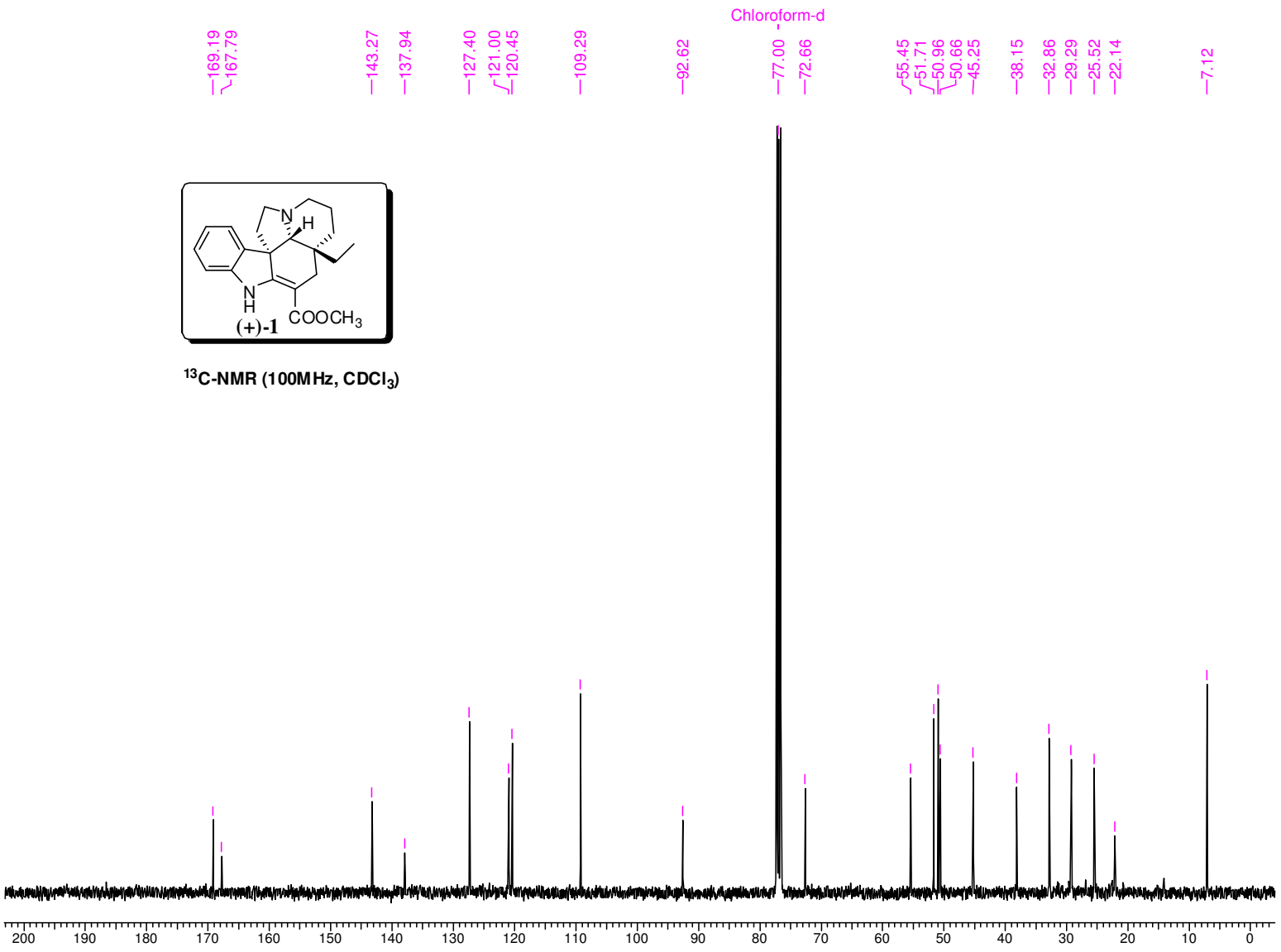


^{1}H NMR (200MHz, $CDCl_3$)

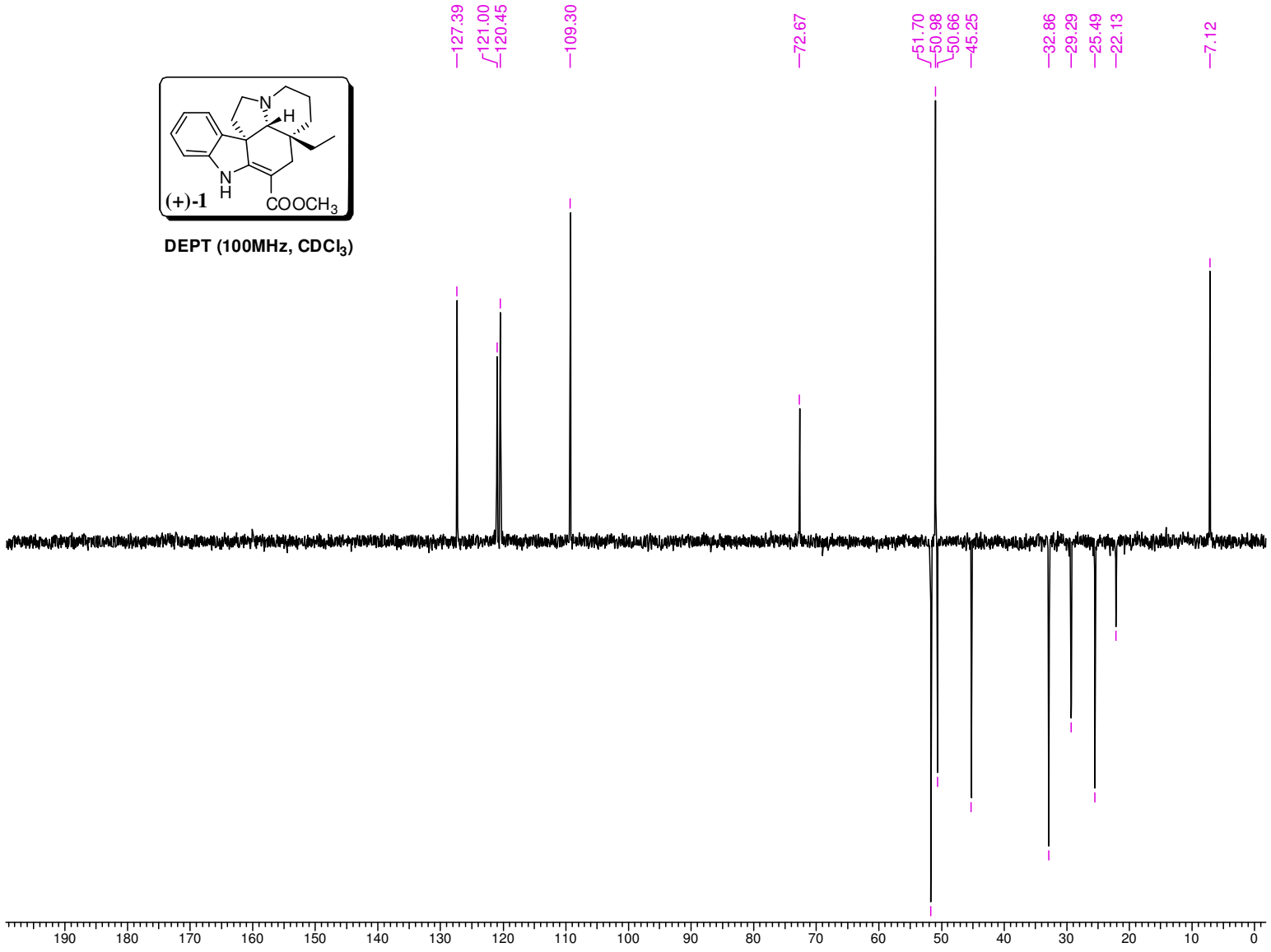

170.49
167.77
143.57
132.71
126.96
121.05
118.01
109.08
Chloroform-d
77.00
74.26
50.45
petether
29.07
23.07
N
H16
COOMe
13CNMR (50MHz, CDCl3)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20

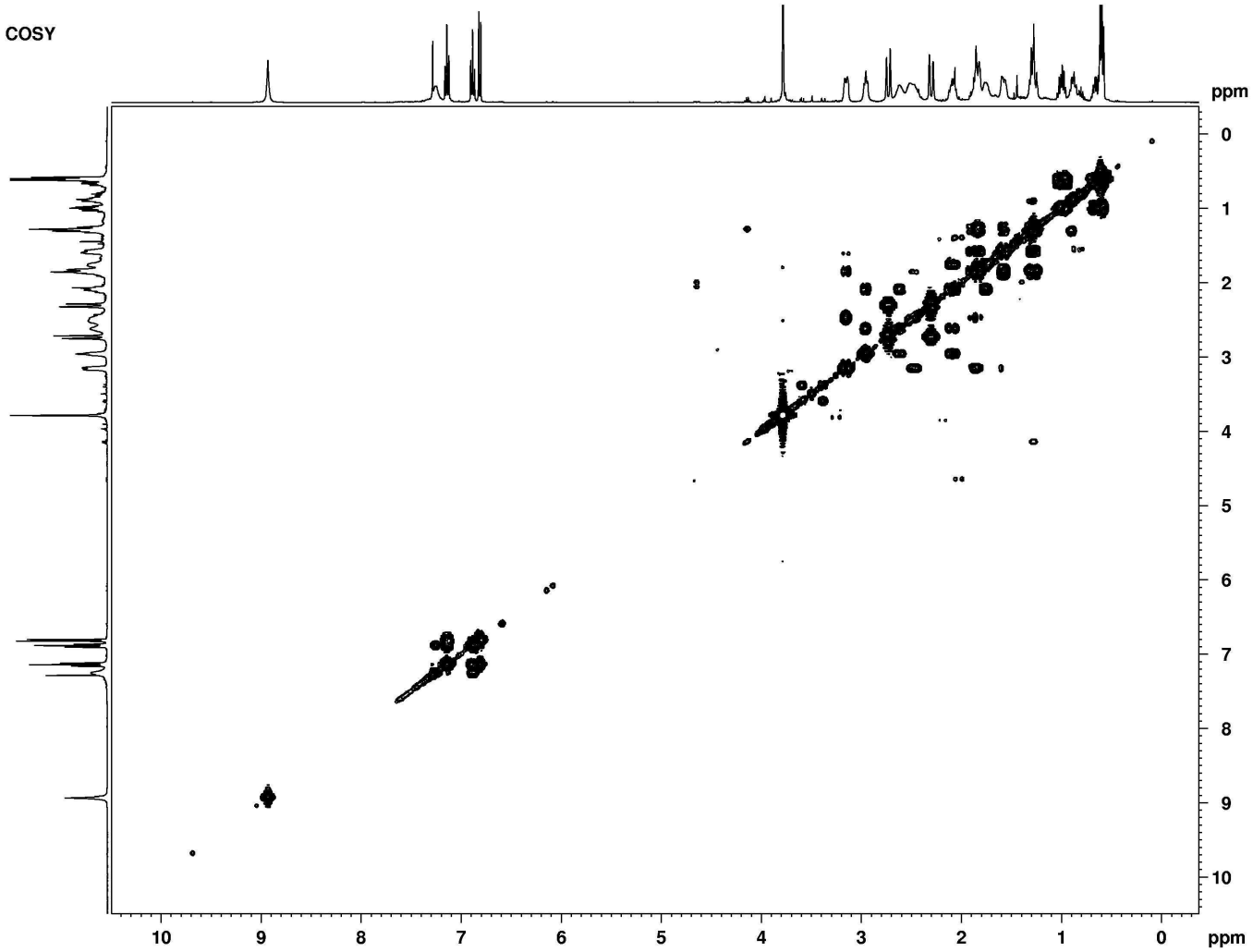


^{1}H-NMR (400MHz, $CDCl_3$)



^{13}C-NMR (100MHz, $CDCl_3$)


127.39
121.00
120.45
109.30
72.67
51.70
50.98
50.66
45.25
32.86
29.29
25.49
22.13
7.12
(+)-1
COOCH3
DEPT (100MHz, CDCl3)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0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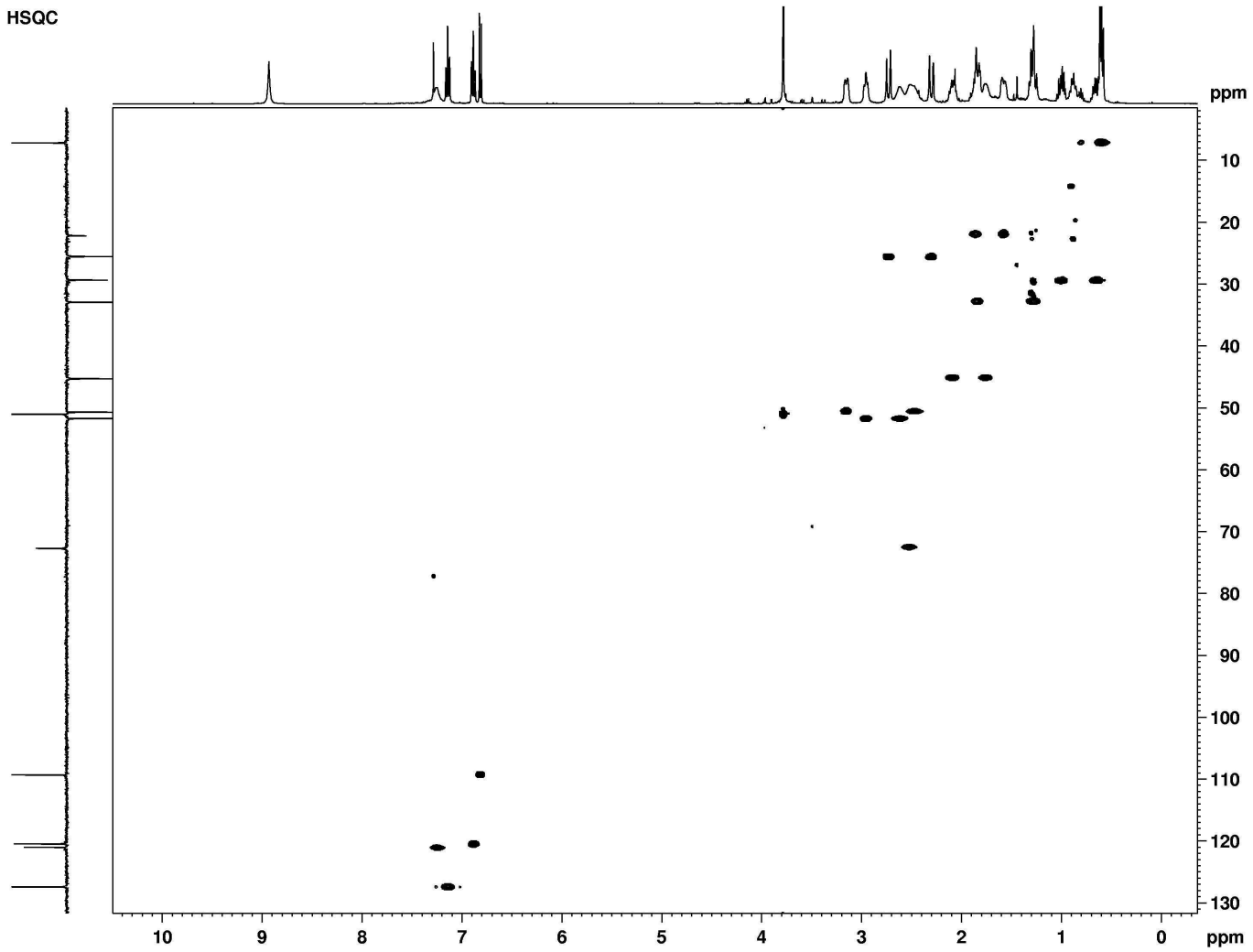
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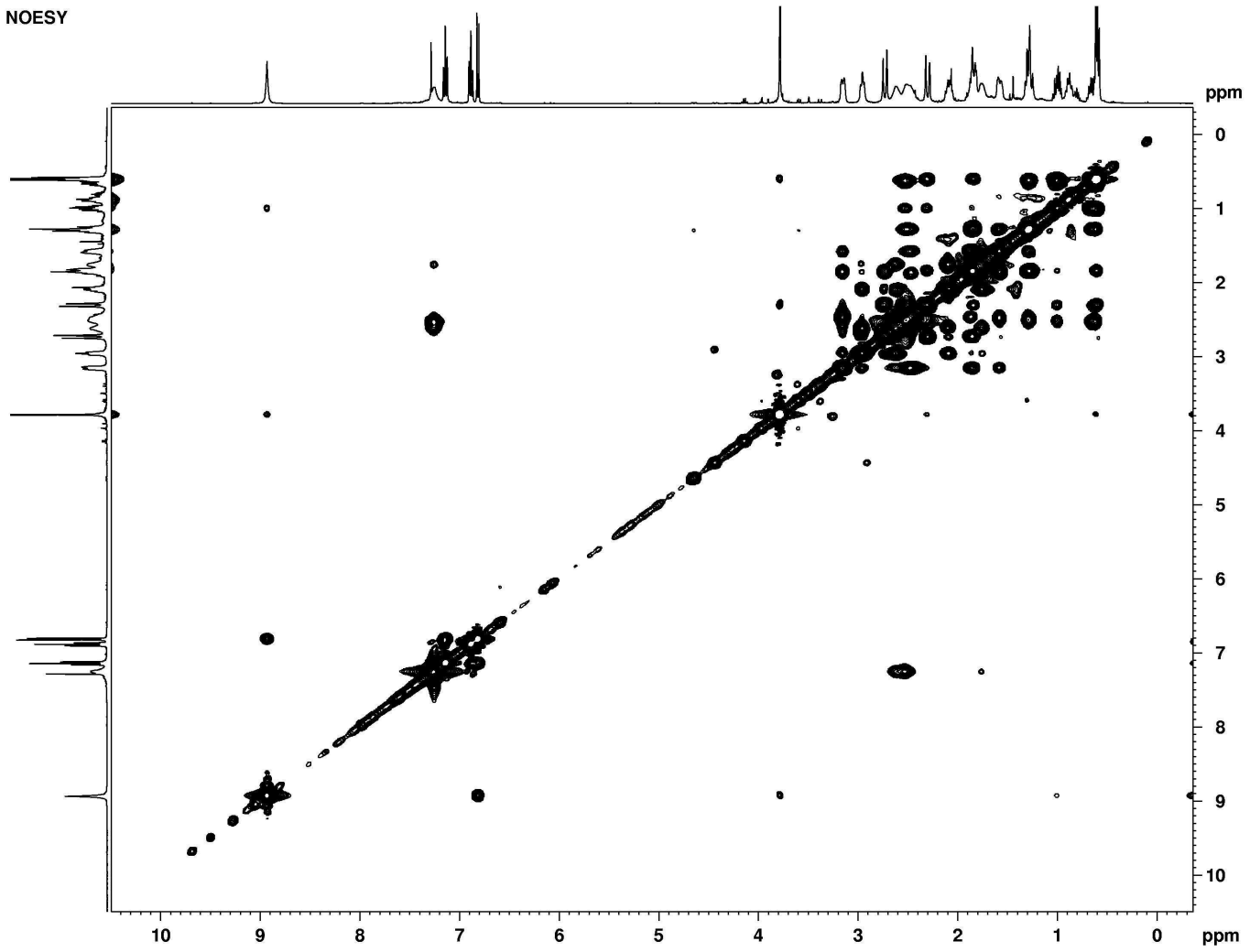
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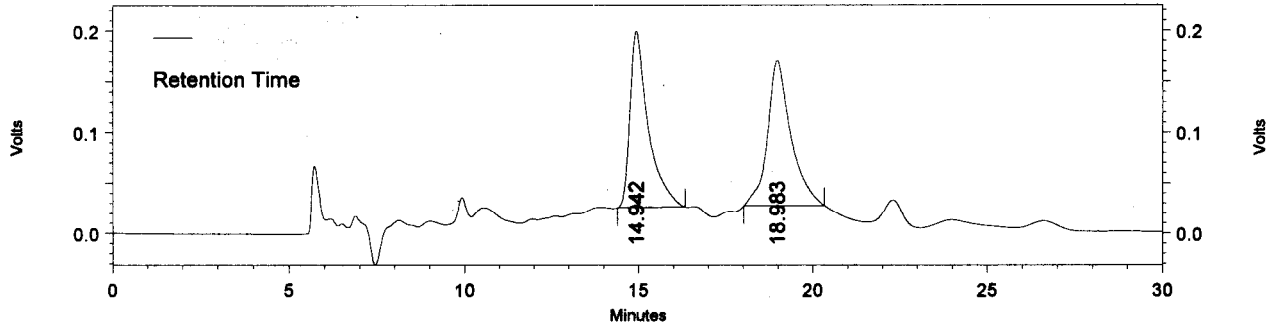
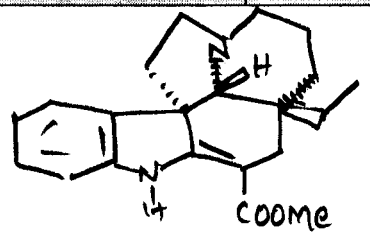


Detector A - 1 (220nm)

Pk #	Retention Time	Area	Area %
1	14.942	6337602	48.540
2	18.983	6718724	51.460
Totals		13056326	100.000

Column : Chiralcel OD-H (250x4.6mm)
Mobile Phase :Ethanol:Petether:TFA (15:85:0.1)
Wavelength : 220nm
Flow Rate : 0.5ml/min (26kgf)
Sample Con :1mg/0.5ml Inj vol-5ul



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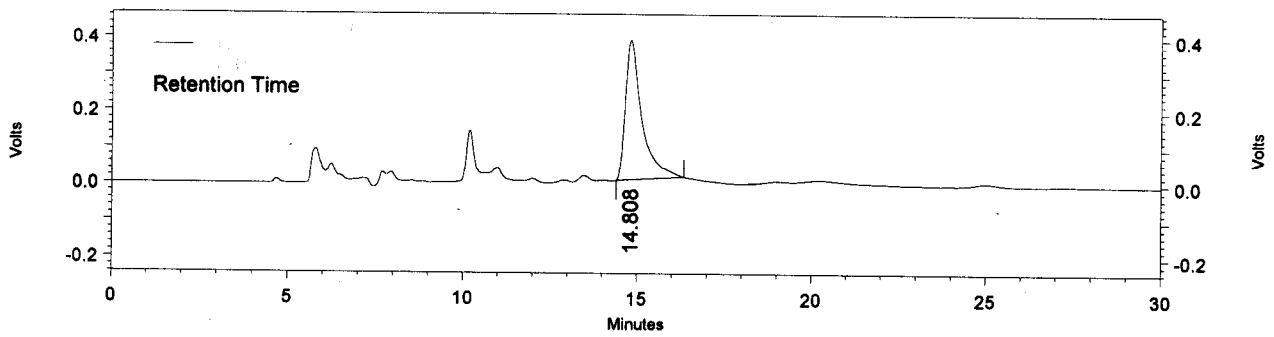
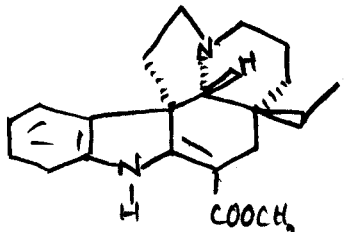


Detector A - 1 (220nm)

Pk #	Retention Time	Area	Area %
1	14.808	12586161	100.000
Totals		12586161	100.000

Column : Chiralcel OD-H (250x4.6mm)
Mobile Phase :Ethanol:Petether:TFA (15:85:0.1)
Wavelength : 220nm
Flow Rate : 0.5ml/min (26kgf)
Sample Con :1mg/0.5ml Inj vol-5ul



(+) - Vincadifformine.