Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Total Synthesis of Incargranine A

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Supporting Information

1.1 TABLE OF CONTENTS

1.2 GENERAL EXPERIMENTAL CONDITIONS

NMR spectra

^{1}H NMR spectra were recorded at 600 MHz, 500MHz, and 400 MHz using a, Bruker AVANCE 600, Bruker AVANCE 500, Bruker PRO 500 or Bruker AVANCE 400 spectrometer. Residual solvent peaks were used as an internal reference for ^{1}H NMR spectra ($CDCl_3$ δ 7.26 ppm, CD_2Cl_2 δ 5.32ppm, CD_3OD δ 3.31 ppm). Coupling constants (*J*) are quoted to the nearest 0.1 Hz. Assignment of proton signals was assisted by ^{1}H-^{1}H COSY, HSQC and HMBC experiments. ^{13}C NMR spectra were recorded at 150 MHz or 125 MHz, using a Bruker AVANCE 600, or Bruker AVANCE 500 spectrometer. Solvent peaks were used as an internal reference for ^{13}C NMR spectra ($CDCl_3$ δ 77.16 ppm, CD_2Cl_2 δ 54.00 ppm CD_3OD δ 49.00 ppm). ^{13}C NMR peaks are generally reported to 1 decimal place. For compounds with several very close ^{13}C NMR signals, however, peaks are reported to 2 decimal places. Assignment of carbon signals was assisted by ^{1}H-^{1}H COSY, HSQC, HMBC and NOESY experiments.

IR spectra

IR spectra of solids and liquids were recorded as neat samples on a Shimadzu IRAffinity-1 FTIR spectrometer fitted with an ATR attachment.

Melting Point

Melting points were measured on a Gallenkamp Melting Point System.

Mass spectrometry

High resolution mass spectra were recorded either on a Bruker microTOF instrument using Electrospray Ionisation (ESI+) or on VG Autospec mass spectrometer using electron impact (EI+) ionization, operating at 70 eV.

Analytical TLC

Analytical TLC was performed with Merck silica gel plates, precoated with silica gel 60 F254 (0.2 mm). Visualisation was effected by quenching of UV fluorescence (λ_{max}= 254 nm) and by staining with *p*-anisaldehyde or $KMnO_4$ standard TLC stain solutions, followed by heating.

Flash chromatography

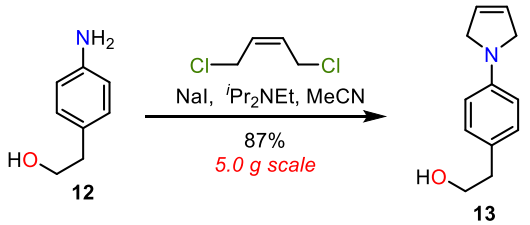
Flash chromatography employed Merck Kiesegel 60 (230–400 mesh) silica gel, or Merck aluminium oxide 90, active, neutral (70-230 mesh, activity I).

Experimental procedures, reagents and glassware

Reactions were conducted under a positive pressure of dry nitrogen in oven-dried glassware. Anhydrous solvents were either obtained from commercial sources or dried according to the procedure outlined by Grubbs and co-workers.[1] Commercially available chemicals were used as purchased. The yields reported in this paper are shown as a range of isolated yields obtained on various scales, we herein provide experimental details for the largest scale procedures conducted (note: the stated scale corresponds to the quantity of product isolated).

1.3 SPECIFIC EXPERIMENTAL CONDITIONS

1.3.1 Experimental Procedure for Compound **13**



2-(4-aminophenyl)ethanol **12** (5.00 g, 36.5 mmol), $^{i}Pr_2NEt$ (13.2 mL, 76.0 mmol), NaI (2.28 g, 15.2 mmol) and a trace quantity of BHT were dissolved in anhydrous CH_3CN (200 mL) at room temperature under a N_2 atmosphere. *Cis*-1,4-dichlorobut-2-ene (3.20 mL, 30.4 mmol) was added and the mixture heated to 60 °C with stirring. After 1.5 hours when TLC analysis indicated complete consumption of starting material, the reaction mixture was cooled to room temperature, water (250 mL) added and extracted with EtOAc (4 × 150 mL). The organic layers were combined, washed with brine, dried with Na_2SO_4 and concentrated under reduced pressure to give a brown solid. Flash chromatography (silica gel neutralised with Et_3N, CH_2Cl_2 + trace BHT) gave 2-(4-(2,5-dihydro-1H-pyrrol-1-yl)phenyl)ethan-1-ol 37 **13** as pale yellow solid (5.00 g, 26.3 mmol, 87% yield).

R_f 0.20 (CH_2Cl_2);

^{1}H NMR (500 MHz, $CDCl_3$); δ 7.12 (d, J =8.6 Hz, 2H), 6.51 (d, *J* = 8.6 Hz, 2H), 5.95 (s, 2H), 4.10 (s, 4H), 3.81 (q, J =6.5 Hz, 2H), 2.78 (t, *J* = 6.5 Hz, 2H), 1.39 (t, *J* = 6.0 Hz, 1H) ppm;

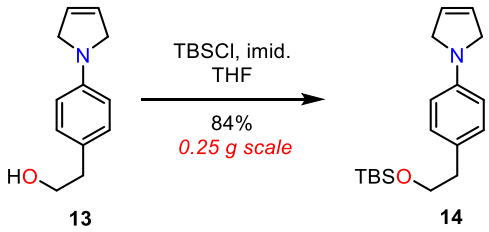
^{13}C NMR (126 MHz, $CDCl_3$); δ 146.1, 130.1, 126.6, 125.0, 111.5, 64.2, 54.7, 38.4 ppm;

IR (cm^{-1}) 3302(br), 2922, 2849, 2824, 1626, 1612, 1522, 1474, 1362, 1188, 1043, 1015, 1003;

HRMS (ESI^{+}) 190.1240 (calculated $[M+H]^{+}$ 190.1226);

M.p. 121-123 °C.

1.3.2 Experimental Procedure for Compound **14**



2-(4-(2,5-dihydro-1H-pyrrol-1-yl)phenyl)ethan-1-ol **13** (0.200 g, 1.06 mmol) and imidazole (0.080 g, 1.16 mmol) were dissolved in anhydrous THF (3 mL) at room temperature under an N_2 atmosphere. TBSCl (0.175 g, 1.16 mmol) was added with stirring at room temperature. After 1.5 hours, additional imidazole (0.014 g) and TBSCl (0.032 g) were added. After 2.5 hours, when TLC analysis showed complete consumption of starting material, Et_2O (10 mL) and saturated aqueous NH_4Cl (5 mL) were added, the organic fraction separated and the aqueous fraction extracted with Et_2O (2 × 10 mL). The organic fractions were combined, dried over Na_2SO_4 and concentrated under reduced pressure to give a pale yellow solid. Flash chromatography (silica gel, 19:1 petroleum ether/Et_2O) gave OTBS 2-(4-(2,5-dihydro-1H-pyrrol-1-yl)phenyl)ethanol **14** as a white solid (0.270 g, 0.890 mmol, 84% yield).

^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.07 (d, J = 8.5 Hz, 2H), 6.46 (d, J = 8.5 Hz, 2H), 5.96 (s, 2H), 4.07 (s, 4H), 3.73 (t, J = 7.2 Hz, 2H), 2.70 (t, J = 7.2 Hz, 2H), 0.89 (s, 9H), 0.02 (s, 6H) ppm;

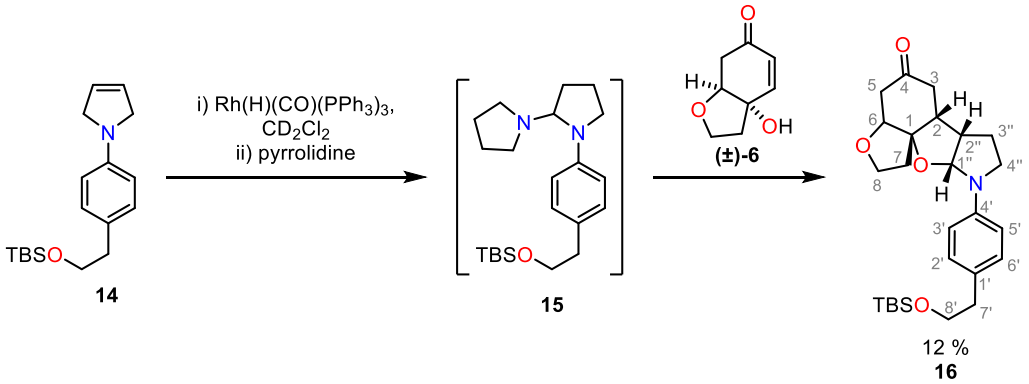
^{13}C NMR (126 MHz, CD_2Cl_2) δ 146.4, 130.4, 127.0, 126.5, 111.6, 65.6, 55.1, 39.3, 26.3, 18.8, −5.1 ppm;

IR (cm^{-1}) 2953, 2928, 2855, 2822, 1626, 1614, 1524, 1472, 1373, 1361, 1254, 1188, 1088;

HRMS (ESI^+) 304.2127 (calculated $[M+H]^+$ 304.2091);

M.p. 63-65 °C.

1.3.3 Experimental Procedure for Compound **16**



Dihydropyrrole **14** (42 mg, 0.14 mmol), durene (18 mg, 0.14 mmol) and a trace quantity of BHT were placed into an NMR tube fitted with a *J* Young valve. The tube was evacuated and flushed with N_2 three times, then anhydrous, degassed CD_2Cl_2 (0.5 mL) was added, followed by $Rh(H)(CO)(PPh_3)_3$ (6 mg, 7 µmol). The tube was sealed and heated to 40 °C for 30 minutes, then cooled to room temperature, pyrrolidine (7 µL, 93 µmol) was added. After 16 hours, when ^{1}H NMR analysis showed complete consumption of starting material (giving a 66 % yield of aminal **15**), (±)-rengyolone **6** (49 mg, 0.31 mmol) was added. After 10 days at room temperature, when ^{1}H NMR analysis showed complete consumption of aminal **15**, the reaction mixture was concentrated under reduced pressure and purified. Flash chromatography (silica gel, 19:1 CH_2Cl_2/MeOH) gave the cross-dimer **16** (7 mg, 15 µmol, 12 % yield) as a yellow oil.

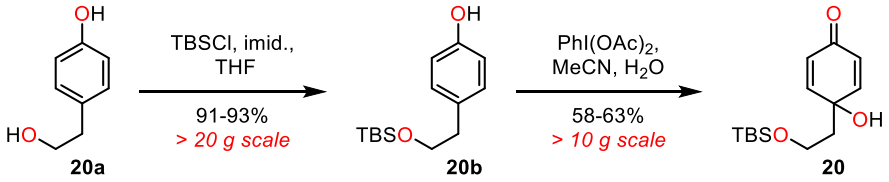
^{1}H NMR (601 MHz, CD_2Cl_2) δ 7.08 (d, *J* = 8.6 Hz, 2H, H-2′, H-6′), 6.74 (d, *J* = 8.6 Hz, 2H, H-3′, H-5′), 5.58 (d, *J* = 6.4 Hz, 1H, H-1″), 4.15 (dd, *J* = 9.3, 5.5 Hz, 1H, H-6), 4.02 – 3.95 (m, 2H, CH_2-7), 3.73 (td, *J* = 7.4, 1.6 Hz, 2H, CH_2-8′), 3.46 – 3.38 (m, 2H, CH_2-4″), 3.27 – 3.21 (m, 1H, H-2″), 2.71 (t, *J* = 7.2 Hz, 2H, CH_2-7′), 2.68 – 2.63 (m, 2H, H-5a, H-2), 2.47 (dd, *J* = 16.1, 5.8 Hz, 1H, H-3a), 2.35 (dd, *J* = 16.1, 9.7 Hz, 1H, H-3b), 2.31 – 2.24 (m, 2H, H-5b, H-8a), 2.08 – 1.98 (m, 2H, H-8b, H-3″a), 1.89 (ddt, *J* = 13.0, 7.4, 5.5 Hz, 1H, H-3″b), 0.89 (s, 9H, OTBS), 0.02 (s, 6H, OTBS) ppm;

^{13}C NMR (151 MHz, CD_2Cl_2) δ 209.39 (C-4), 144.92 (C-4′), 130.20 (C-2′, C-6′), 129.13 (C-1′), 113.77 (C-3′, C-5′), 94.68 (C-1″), 91.41 (C-1), 80.24 (C-6), 67.00 (C-7), 65.45 (C-8′), 49.46 (C-4″), 46.97 (C-2″), 44.31 (C-5), 42.94 (C-2), 39.48 (C-3), 39.27 (C-7′), 38.56 (C-8), 26.29 (3 × CH_3 OTBS), 24.82 (C-3″), 18.78 (C OTBS), −5.05 (2 × CH_3 OTBS) ppm;

IR (cm^{-1}) 2951, 2928, 2884, 2855, 1717, 1614, 1518, 1462, 1377, 1254, 1188;

HRMS (ESI^+) 458.2785 (calculated $[M+H]^+$ 458.272

1.3.4 Experimental Procedure for Compound **20**



Compound **20** was prepared according to the previously reported procedure.[2]

a) Tyrosol **20a** (15.0 g, 108.9 mmol) was dissolved in anhydrous THF (60 mL) at room temperature under an N_2 atmosphere. The solution was cooled to 0 °C and a solution of *tert*-butyldimethylsilylchloride (14.8 g, 98.1 mmol) in anhydrous THF (60 mL) was added dropwise over 45 minutes with vigorous stirring. The mixture was stirred at 0 °C until TLC analysis indicated complete consumption of the starting material (50 minutes). The reaction mixture was then diluted with Et_2O (150 mL) and saturated aqueous NH_4Cl (100 mL) added. The aqueous layer was separated and extracted with Et_2O (3 × 100mL). The organic layers were combined, dried with $MgSO_4$, filtered and concentrated under reduced pressure to give a white crystalline solid. Flash chromatography (silica gel, 3:1 Petroleum Ether 40-60/EtOAc) gave 4-(2-((tert-butyldimethylsilyl)oxy)ethyl)phenol **20b** as a white crystalline solid (25.0 g, 99.1 mmol, 91% yield); All data matched that previously reported.[2]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 - 7.04 (m, 2H), 6.78 - 6.72 (m, 2H), 3.76 (t, J = 7.1 Hz, 2H), 2.75 (t, J = 7.1 Hz, 2H), 0.87 (s, 9H), −0.01 (s, 6H) ppm;

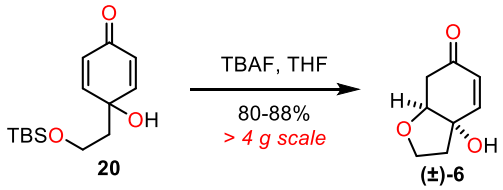
^{13}C NMR (101 MHz, $CDCl_3$) δ 154.0, 131.4, 130.2, 115.2, 65.0, 38.8, 26.1, 18.5, −5.2 ppm;

b) Phenol **20b** (24.4 g, 96.7 mmol) was dissolved in CH_3CN (480 mL) and H_2O (120 mL) at room temperature. The solution was cooled in an ice-water bath to an internal temperature of 2-3 °C and $PhI(OAc)_2$ (37.5 g, 116.4 mmol) was added portion-wise over 3 minutes with vigorous stirring. The mixture was stirred at 2-3 °C until TLC analysis indicated complete consumption of the starting material (20 minutes), then saturated aqueous Na_2SO_3 (300 mL) was added followed by Et_2O (300 mL). The organic layer was separated and the aqueous layer extracted with Et_2O (2 × 200 mL). The organic layers were combined, dried with $MgSO_4$ and concentrated under reduced pressure, giving a dark green/black oil. Flash chromatography (silica gel, gradient 9:1 Petroleum Ether 40-60/EtOAc to neat EtOAc) gave *4*-(2-((tert-butyldimethylsilyl)oxy)ethyl)-4-hydroxycyclohexa-2,5-dienone **20** (15.1 g, 56.3 mmol, 58% yield) as a pale yellow crystalline solid; All data matched that previously reported.[2]

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (d, *J* = 10.1 Hz, 2H), 6.15 (d, *J* = 10.1 Hz, 2H), 4.41 (s, 1H), 3.94 (t, *J* = 5.7 Hz, 2H), 1.94 (t, *J* = 5.7 Hz, 2H), 0.91 (s, 9H), 0.11 (s, 6H) ppm;

^{13}C NMR (101 MHz, $CDCl_3$) δ 185.7, 151.2, 127.5, 69.8, 60.9, 41.4, 25.9, 18.2, −5.3 ppm;

1.3.5 Experimental Procedure for Compound **6**



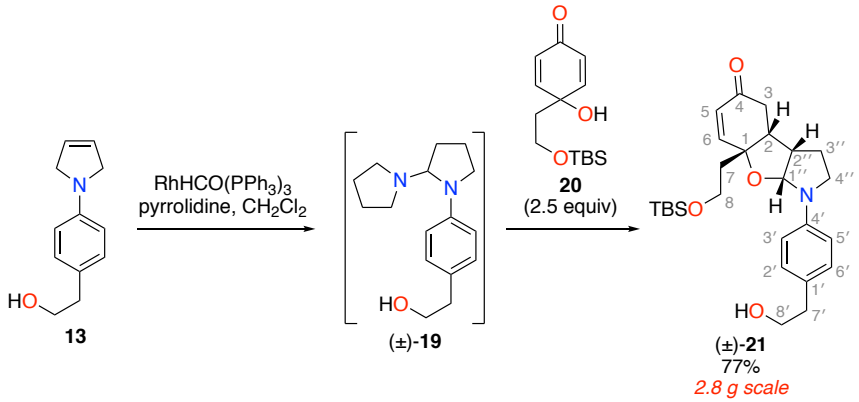
(±)-Rengyolone (**6**) was prepared according to the previously reported procedure.[2]

para-quinol **20** (10.5 g, 39.2 mmol) was dissolved in anhydrous THF (80 mL) at room temperature under an N_2 atmosphere. TBAF (1 M in THF, 78.4 mL, 78.4 mmol) was added with stirring over 10 minutes. The resulting mixture was stirred at room temperature until TLC analysis indicated complete consumption of the starting material (25 minutes), then cooled to 0 °C and saturated aqueous NH_4Cl (40 mL) and H_2O (20 mL) were added. The organic layer was separated and the aqueous layer extracted with EtOAc (10 × 50mL). The organic layers were combined, dried over Na_2SO_4 and concentrated under reduced pressure to give a pale yellow oil. Flash chromatography (silica gel 230-400 mesh, gradient 1:1 Petroleum Ether 40-60/EtOAc to neat EtOAc) gave (±)-rengyolone (**2**) as a pale yellow oil, that later solidified in the fridge (4.8 g, 31.4 mmol, 80 % yield);

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 (dd, J = 10.2, 1.4 Hz, 1H), 6.02 (d, J = 10.2 Hz, 1H), 4.24 (ddd, J ≈ 6.0, 4.8, 1.4 Hz, 1H), 4.08 (apparent td, J ≈ 8.5, 6.5 Hz, 1H), 3.96 (apparent td, J ≈ 8.5, 6.3 Hz, 1H), 2.78 (dd, J = 16.9, 4.8 Hz, 1H), 2.61 (dd, J = 16.9, 5.8 Hz, 1H), 2.33 (ddd, J = 13.0, 8.3, 6.4 Hz, 1H), 2.23 (ddd, J = 13.0, 8.2, 6.5 Hz, 1H), 2.01 (br. s, 1H);

^{13}C NMR (101 MHz, $CDCl_3$) δ 196.8, 147.8, 129.1, 81.8, 75.9, 66.4, 40.4, 39.7.

1.3.6 Experimental Procedure for Compound **21**



2,5-dihydropyrrole **13** (1.51 g, 7.96 mmol) was placed in a single neck Schlenk flask. The flask was evacuated and flushed with N_2 three times. Anhydrous CH_2Cl_2 (20 mL) was added and the resulting solution degassed by three freeze-pump-thaw cycles. Anhydrous, degassed pyrrolidine (0.730 mL, 8.76 mmol) was added, followed by $Rh(H)(CO)(PPh_3)_3$ (5 mol%, 0.368 g, 0.398 mmol). The tube was sealed and heated to 40 ºC with stirring. After 2 hours, when ^{1}H-NMR analysis showed complete conversion of starting material to aminal **19**, (for an example of ^{1}H NMR monitoring of this reaction, see **1.4.5**) the solution was cooled to room temperature, water (0.3 mL) added followed by *p*-quinol **20** (5.36 g, 19.9 mmol). The flask was re-sealed and stirred at room temperature. After 20 hours at room temperature, when ^{1}H-NMR analysis indicated consumption of starting material, the solvent was removed under reduced pressure to give a brown oil. Flash chromatography (silica gel neutralised with Et_3N, 4:1 → 1:1 petroleum ether/EtOAc) gave the desired compound **21** (2.81 g, 6.13 mmol, 77% yield) as a brown oil. The stereochemistry of dimer **21** was assigned as *cis-syn-cis* based on NOESY data, in particular NOESY cross-peaks between H(3b)-H(3″b) and H(1″)-H(2).

R_f 0.26 (1:1 petroleum ether:EtOAc);

^{1}H NMR (500 MHz, CD_2Cl_2); δ 7.09 (d, *J* = 8.6 Hz, 2H, H-2′, H-6′), 6.75 (d, *J* = 8.6 Hz, 2H, H-3′, H-5′), 6.50 (dd, *J* = 10.3, 1.7 Hz, 1H, H-6), 5.87 (dd, *J* = 10.3, 1.0 Hz, 1H, H-5), 5.69 (d, *J* = 6.2 Hz, 1H, H-1″), 3.90 – 3.84 (m, 1H, H-8a), 3.80 – 3.73 (m, 3H, H-8b, H-8′a, H-8′b), 3.26 (td, *J* = 8.9, 5.2 Hz, 1H, H-4″a), 3.19 – 3.11 (m, 2H, H-2″, H-4″b), 3.00 (ddt, *J* = 9.3, 7.2, 1.8 Hz, 1H, H-2), 2.80 – 2.73 (m, 3H, H-3a, CH_2-7′), 2.62 (dt, *J* = 18.2, 1.4 Hz, 1H, H-3b), 2.03 – 1.93 (m, 2H, H-3″a, H-H-7a), 1.93 – 1.87 (m, 1H, H-7b), 1.84 – 1.76 (m, 1H, H-3″b), 1.44 (d, *J* = 5.5 Hz, 1H, OH), 0.88 (s, 9H, OTBS), 0.05 (d, *J* = 6.2 Hz, 6H, OTBS) ppm;

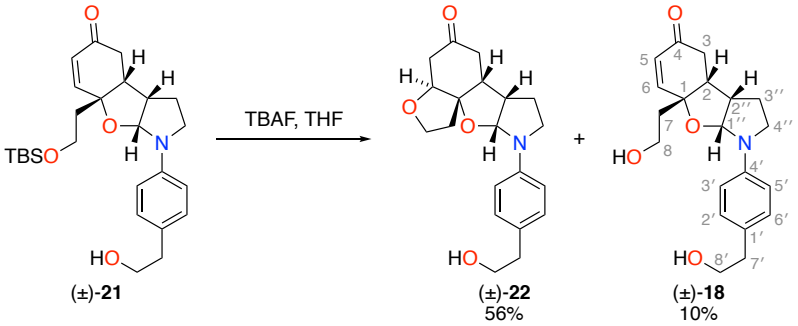
^{13}C NMR (126 MHz, CD_2Cl_2); δ 192.9 (C-4), 149.3 (C-6), 140.1 (C-4′), 125.1 (C-2′, C-6′), 122.3 (C-1′), 109.1 (C-3′, C-5′), 89.3 (C-1″), 75.7 (C-1), 59.4 (C-8′), 54.2 (C-8), 43.6 (C-4″),

43.0 (C-2″), 39.3 (C-2), 37.7 (C-7), 33.9 (C-7′), 31.2 (C-3), 21.2 (3C OTBS), 19.8 (C-3″), 13.6 (C OTBS), −10.1 (2C OTBS) ppm;

IR (cm^{-1}) 3495, 2953, 2930, 2893, 2857, 2843, 1670, 1614, 1518, 1485, 1462, 1369, 1248, 1088;

HRMS (ESI^+) 458.2742 (calculated $[M+H]^+$ 458.2721);

1.3.7 Experimental Procedure for Compounds **18** and **22**



OTBS dimer **21** (0.810 g, 1.77 mmol) was dissolved in anhydrous THF (20 mL) at room temperature. TBAF (2.65 mL, 1.0 M in THF, 2.65 mmol) was added with stirring at room temperature. After 3 hours, additional TBAF (0.885 mL, 1.0 M in THF, 0.885 mmol) was added and mixture stirred at room temperature for a further 30 minutes. When TLC analysis showed complete consumption of starting material (3.5 hours total), saturated NH_4Cl (25 mL) was added and the resulting mixture extracted with $CHCl_3$ (3 × 30 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to give a dark yellow oil. Flash chromatography (silica gel 230-400 mesh 96:4 → 95:5 $CHCl_3$/MeOH) gave the ring closed product **22** (0.344 g, 1.00 mmol, 56 % yield) allow with the ring opened product **18** (0.0628 g, 0.183 mmol, 10 % yield).

Ring-closed **22**

R_f 0.30 (96:4 CH_2Cl_2:MeOH);

^{1}H NMR (500 MHz,CD_2Cl_2) δ 7.09 (d, J = 8.5 Hz, 2H, H-2′, H-6′), 6.77 (d, J = 8.6 Hz, 2H, H-3′, H-5′), 5.59 (d, J = 6.4 Hz, 1H, H-1″)), 4.14 (dd, J = 9.4, 5.5 Hz, 1H, H-6), 4.01 – 3.93 (m, 2H, CH_2-8), 3.74 (td, J = 6.5, 3.1 Hz, 2H, CH_2-8′), 3.47 – 3.38 (m, 2H, CH_2-4″), 3.28-3.20 (m, 1H, H-2″), 2.74 (t, J = 6.7 Hz, 2H, CH_2-7′), 2.68 – 2.61 (m, 2H, H-5a, H-2), 2.47 (dd, J = 16.2, 5.8 Hz, 1H, H-3a), 2.34 (dd, J = 16.2, 9.7 Hz, 1H, H-3b), 2.31 – 2.22 (m, 2H, H-5b, H-7a), 2.10 – 1.97 (m, 2H, H-7b, H-3″a), 1.89 (ddt, J = 12.9, 7.3, 5.5 Hz, 1H, H-3″b), 1.58 (d, J = 5.2 Hz, 1H, OH) ppm;

^{13}C NMR (126 MHz, CD_2Cl_2) δ 209.4 (C-4), 145.1 (C-4′), 130.1 (C-2′, C-6′), 128.5 (C-1′), 114.0 (C-3′, C-5′), 94.6 (C-1″), 91.5 (C-1), 80.2 (C-6), 67.0 (C-8), 64.4 (C-8′), 49.4 (C-4″), 46.9 (C-2″), 44.3 (C-5), 42.9 (C-2), 39.4 (C-3), 38.9 (C-7′), 38.5 (C-7), 24.8 (3″) ppm;

IR (cm^{-1}) 3439, 2938, 2874, 1711, 1614, 1518, 1377, 1346, 1186, 1043;

HRMS (ESI^+); 366.1678 (calculated $[M+Na]^+$ 366.1676);

Ring-open **18**

R_f 0.20 (96:4 CH_2Cl_2:MeOH);

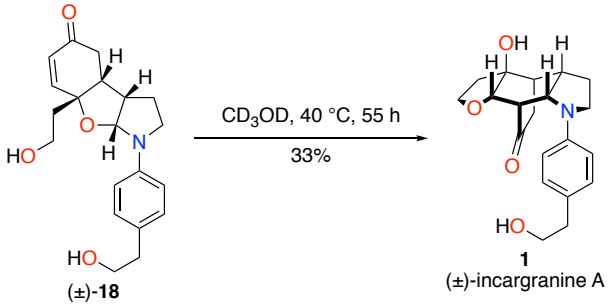
^{1}H NMR (601 MHz, CD_3OD) δ 7.09 – 7.04 (m, 2H, H-2′, H-6′), 6.77 – 6.73 (m, 2H, H-3′, H-5′), 6.57 (dd, *J* = 10.4, 1.7 Hz, 1H, H-6′), 5.91 (dd, *J* = 10.3, 1.0 Hz, 1H, H-6), 5.72 (d, *J* = 6.2 Hz, 1H, H-5), 3.82 – 3.71 (m, 2H, CH_2-8), 3.68 (t, *J* = 7.3 Hz, 2H, CH_2-8′), 3.27 (td, *J* = 9.0, 5.0 Hz, 1H, H-4″a), 3.21 (tt, *J* = 10.3, 5.6 Hz, 1H, H-2″), 3.12 (td, *J* = 8.5, 6.4 Hz, 1H, H-4″b), 2.96 (ddt, *J* = 9.5, 7.5, 1.7 Hz, 1H, H-2), 2.84 (dd, *J* = 18.4, 7.3 Hz, 1H, H-3a), 2.72 (t, *J* = 7.3 Hz, 2H, CH_2-7′), 2.69 – 2.63 (m, 1H, H-3b), 2.06 (dt, *J* = 13.8, 6.8 Hz, 1H, H-7a), 2.02 – 1.97 (m, 1H, H-3″a), 1.94 (dt, *J* = 14.2, 6.4 Hz, 1H, H-7b), 1.77 (ddt, *J* = 13.4, 8.1, 5.1 Hz, 1H, H-3″b) ppm;

^{13}C NMR (151 MHz, CD_3OD) δ 200.3 (C-4), 155.9 (C-6), 145.7 (C-4′), 130.4 (C-2′, C-6′), 129.3 (C-1′), 127.5 (C-5′), 114.7 (C-3′, C-5′), 95.1 (C-1″), 81.3 (C-1), 64.7 (C-8′), 58.7 (C-8), 49.3, 49.1 (C-3″ and C-2″ overlap with solvent), 45.3 (C-2), 42.9 (C-7), 39.4 (C-7′), 36.5 (C-3), 25.2 (C-3″) ppm;

IR (cm^{-1}) 3374, 2920, 2857, 1665, 1614, 1518, 1371, 1348, 1045, 1005;

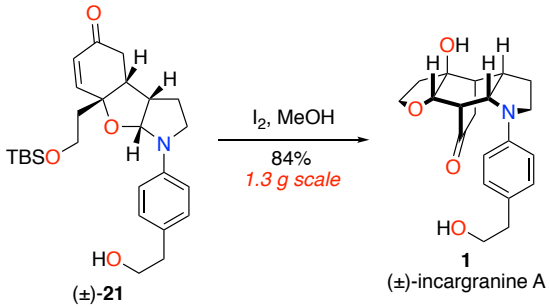
HRMS (ESI^+); 344.1849 (calculated $[M+H]^+$ 344.1856).

1.3.8 Experimental Procedure for Incargranine A **1**



Ring-open pre-incargranine A **18** (7 mg, 20 µmol) was dissolved in CD_3OD (0.6 mL) in an NMR tube. The resulting solution was heated to 40 °C and monitored by ^1H NMR. After 55 hours the reaction mixture was cooled to room temperature and purified by flash chromatography (silica gel 230-400 mesh 96:4 $CHCl_3$/MeOH) to give incargranine A (**1**) (2 mg, 7 µmol) in a 33% yield (43% brsm) along with unreacted starting material **18** (1 mg, 4 µmol). For characterisation data for incargranine A (**1**) see below.

1.3.9 Alternative Experimental Procedure for incargranine A **1**



Compound **21** (2.10 g, 4.58 mmol) was dissolved in anhydrous MeOH (50 mL) at room temperature. I_2 (1 % w/v in MeOH, 11.6 mL, 0.459 mmol) was added and the resulting solution stirred at room temperature. After 22 hours, when TLC analysis showed complete consumption of starting material, saturated aqueous $Na_2S_2O_3$ (9 mL) was added. The resulting suspension was concentrated under reduced pressure to remove the majority of the MeOH, then the aqueous residue was extracted with $CHCl_3$ (10 × 30 mL). The organic fractions were combined, washed with brine, dried with Na_2SO_4 and concentrated under reduced pressure to give a brown foaming oil. Flash chromatography (silica gel, $CHCl_3$ + 5% MeOH → 7% MeOH) gave incargranine A (**1**) (1.33 g, 3.87 mmol, 84% yield) as a pale yellow, foaming amorphous solid. All data matched that previously reported for isolated incargranine A.[3]

R_f 0.15 (19:1 $CHCl_3$:MeOH);

^{1}H NMR (600 MHz, CD_3OD); δ 7.06 (d, *J* = 8.6 Hz, 2H), 6.63 (d, *J* = 8.6 Hz, 2H), 4.06 (dd, *J* = 9.7, 3.0 Hz, 1H), 3.92 (td, *J* = 8.4, 1.7 Hz, 1H), 3.86 – 3.84 (m, 1H), 3.84 – 3.80 (m, 1H), 3.68 (t, *J* = 7.2 Hz, 2H), 3.44 (ddd, *J* = 9.4, 7.9, 5.5 Hz, 1H), 3.35 (dddd, *J* = 9.7, 8.1, 5.9, 1.9 Hz, 1H), 3.22 (dd, *J* = 3.9, 3.0 Hz, 1H), 3.14 (ddd, *J* = 9.5, 8.3, 6.4 Hz, 1H), 2.71 (t, *J* = 7.2 Hz, 2H), 2.49 (dd, *J* = 20.0, 3.4 Hz, 1H), 2.39 – 2.35 (m, 1H), 2.35 – 2.26 (m, 2H), 2.19 (dddd, *J* = 13.5, 10.1, 8.3, 5.5 Hz, 1H), 2.00 – 1.89 (m, 2H) ppm;

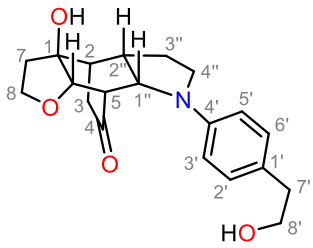
^{13}C NMR (151 MHz, CD_3OD); δ 213.9, 146.8, 130.6, 129.1, 115.4, 86.8, 81.7, 68.1, 64.6, 60.1, 53.9, 51.2, 42.8, 39.7, 39.4, 36.7, 36.1, 27.4 ppm;

IR (cm^{-1}); 3387(br), 2953, 2860, 1720, 1614, 1516, 1361, 1302, 1221, 1159, 1105, 1047;

HRMS (ESI^+); 344.1844 (calculated $[M+H]^+$ 344.1856);

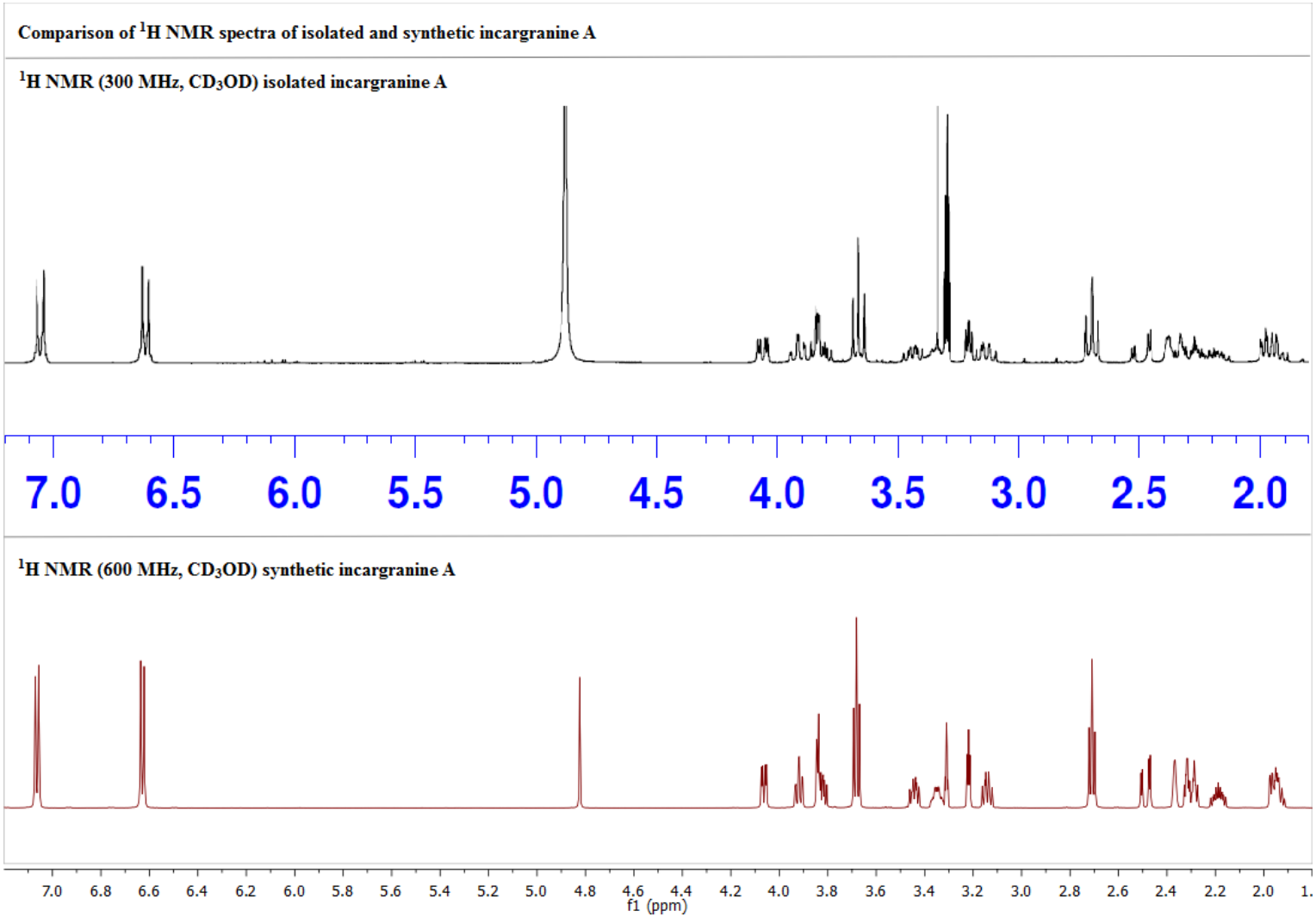
M.p. 78-80 °C (no lit. value available).

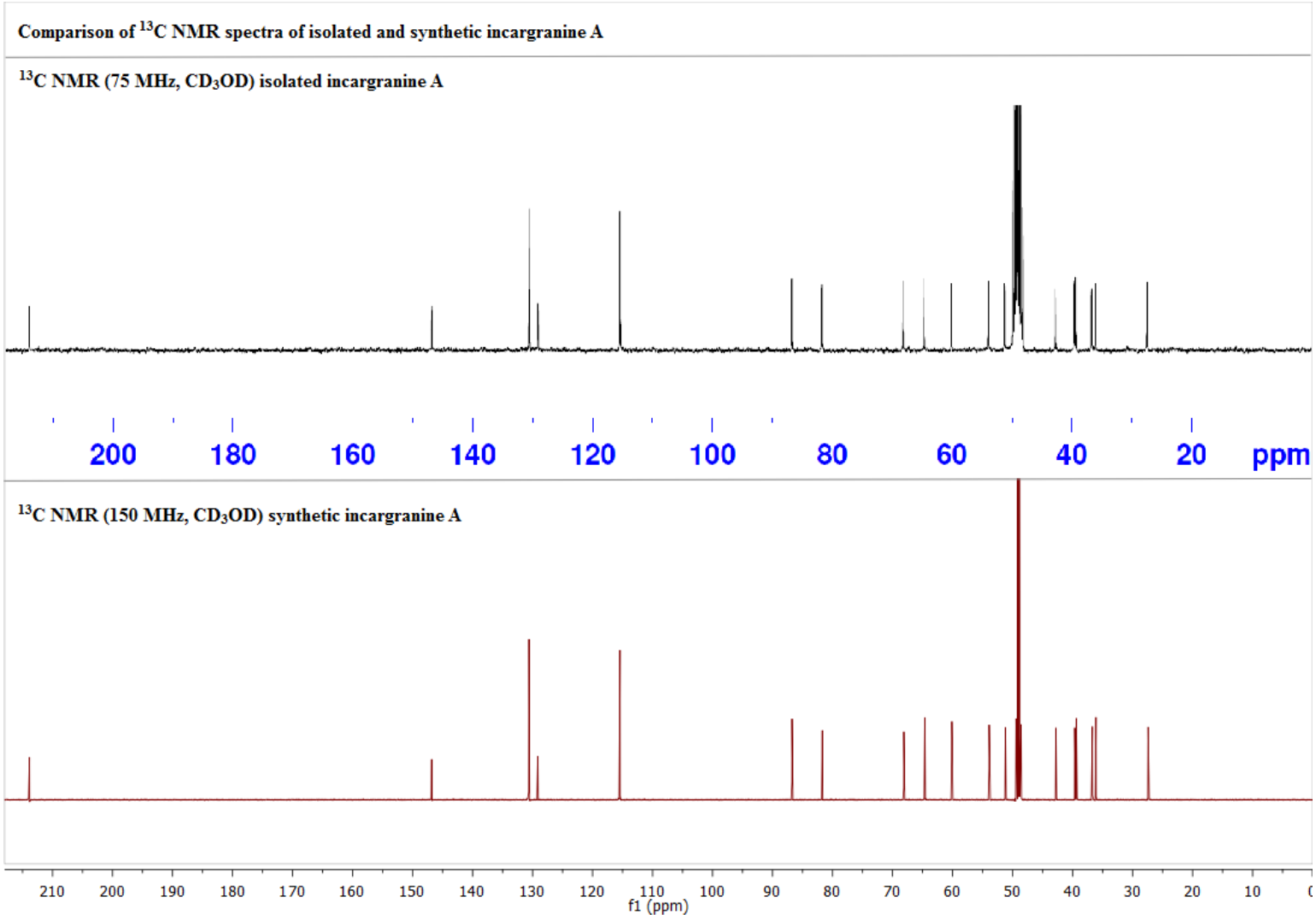
1.3.9.1 Comparison of NMR Spectra of Synthetic and Isolated Incargranine A **(1)**



Professor Zhang kindly provided the pdf copies of ^{1}H and ^{13}C spectra shown below. A comparison of ^{1}H and ^{13}C NMR data reported for synthetic incargranine A (**1**) (in CD_3OD) with the data for natural incargranine A (**1**)[3] is shown below. Note that the spectrometer frequency differs between the tabulated data (as published 600MHz, 150MHz)[3] and spectra provided in pdf form (300MHz, 75MHz).

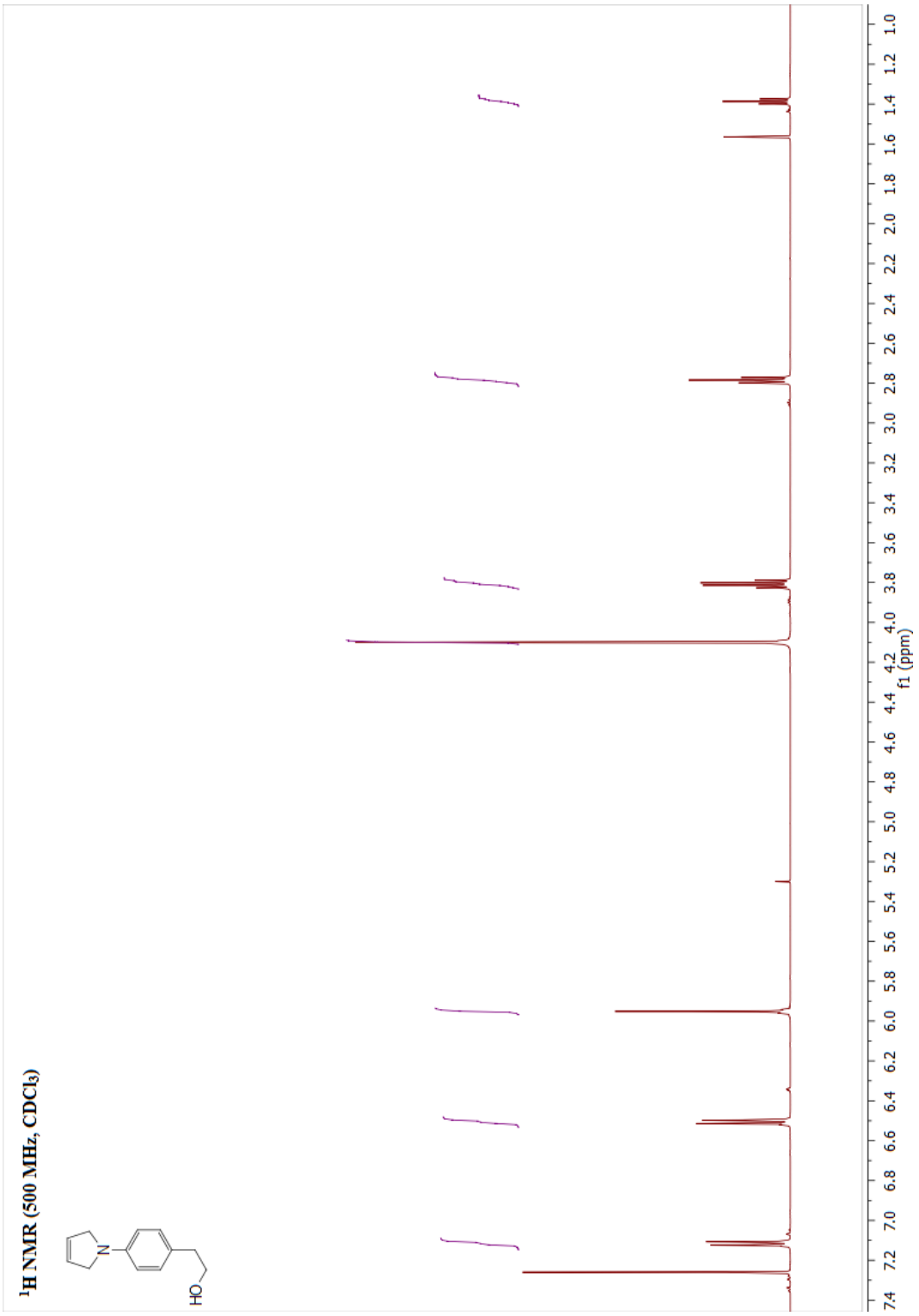
Atom #	Synthetic incargranine A (CD_3OD)			Natural incargranine A (CD_3OD)[3]		
	δ ^{1}H (600MHz)	m, *J* (Hz)	δ ^{13}C (150MHz)	δ ^{1}H (600MHz)	m, *J* (Hz)	δ ^{13}C (150MHz)
1	--	--	81.7	--	--	81.7
2	2.39-2.35	m	42.8	2.39-2.37	m	42.7
3a	2.49	dd (20.0, 3.4)	36.7	2.49	dd (18.9, 3.3)	36.7
3b	2.35-2.26	m (overlap)		2.31	dd (18.9, 3.1)	
4	--	--	213.9	--	--	214.1
5	3.22	dd (3.9, 3.0)	53.9	3.21	dd (3.6, 3.3)	53.9
6	3.86-3.84	m	86.8	3.83	d (3.6)	86.7
7a	2.35-2.26	m (overlap)	39.7	2.00-1.97	m	39.6
7b	2.00-1.89	m (overlap)				
8a	3.92	app. td (8.4, 1.7)	68.1	3.95-3.89	m	68.2
8b	3.84-3.80	m		3.83-3.78	m	
1′	--	--	129.1	--	--	129.1
2′, 6′	7.06	d (8.6)	130.6	7.05	d (8.4)	130.6
3′, 5′	6.63	d (8.6)	115.4	6.61	d (8.4)	115.5
4′	--	--	146.8	--	--	146.8
7′(CH_2)	2.71	d (7.2)	39.4	2.70	t (7.2)	39.4
8′ CH_2)	3.68	t (7.2)	64.6	3.67	t(7.2)	64.6
1″	4.06	dd (9.7, 3.0)	60.1	4.06	dd (8.6, 3.0)	60.1
2″	3.39-3.32	m	36.1	3.36-3.34	m	36.1
3″a	2.22-2.14	m	27.4	2.21-2.15	m	27.4
3″b	2.00-1.89	m(overlap)		1.95-1.92	m	
4″a	3.44	ddd (9.4, 7.9, 5.5)	51.2	3.48-3.40	m	51.2
4″b	3.14	ddd(9.5, 8.3, 6.4)		3.18-3.13	m	


Comparison of ^{1}H NMR spectra of isolated and synthetic incargranine A
^{1}H NMR (300 MHz, CD_3OD) isolated incargranine A
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
^{1}H NMR (600 MHz, CD_3OD) synthetic incargranine A
7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.
f1 (ppm)

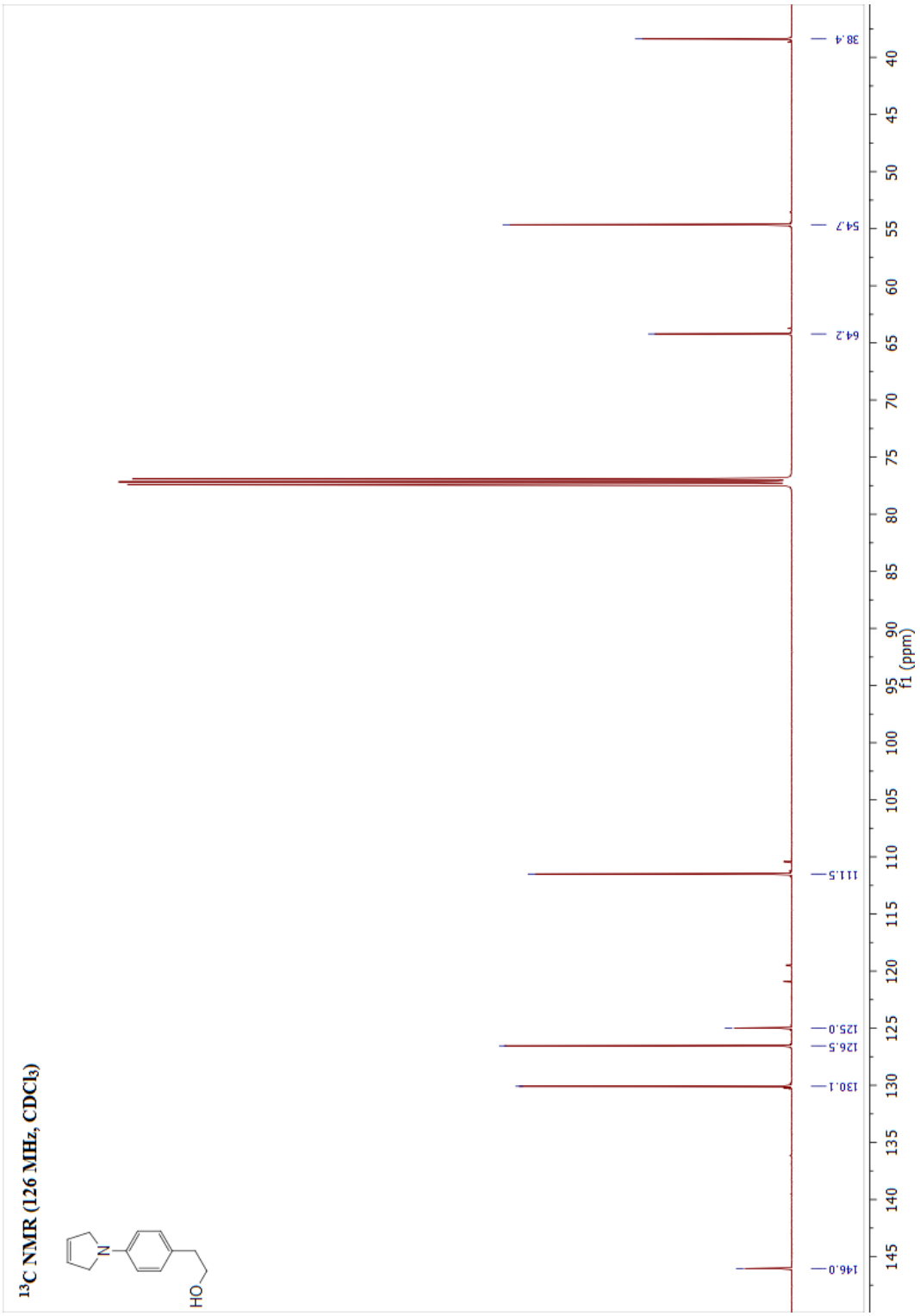

Comparison of ^{13}C NMR spectra of isolated and synthetic incargranine A
^{13}C NMR (75 MHz, CD_3OD) isolated incargranine A
200
180
160
140
120
100
80
60
40
20
ppm
^{13}C NMR (150 MHz, CD_3OD) synthetic incargranine A
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

1.4 NMR SPECTRA

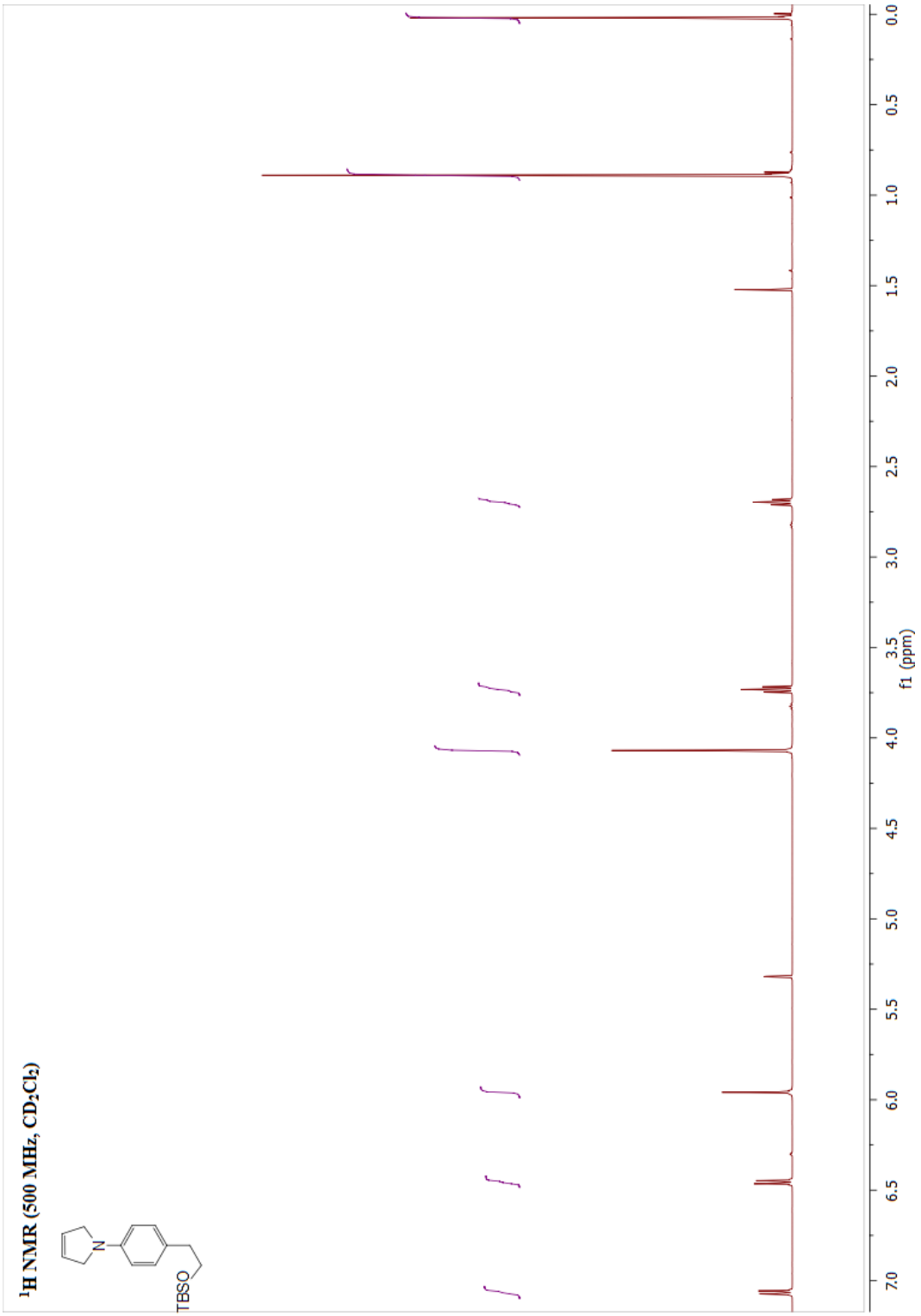
1.4.1 ^{1}H NMR Spectrum of Compound **13**



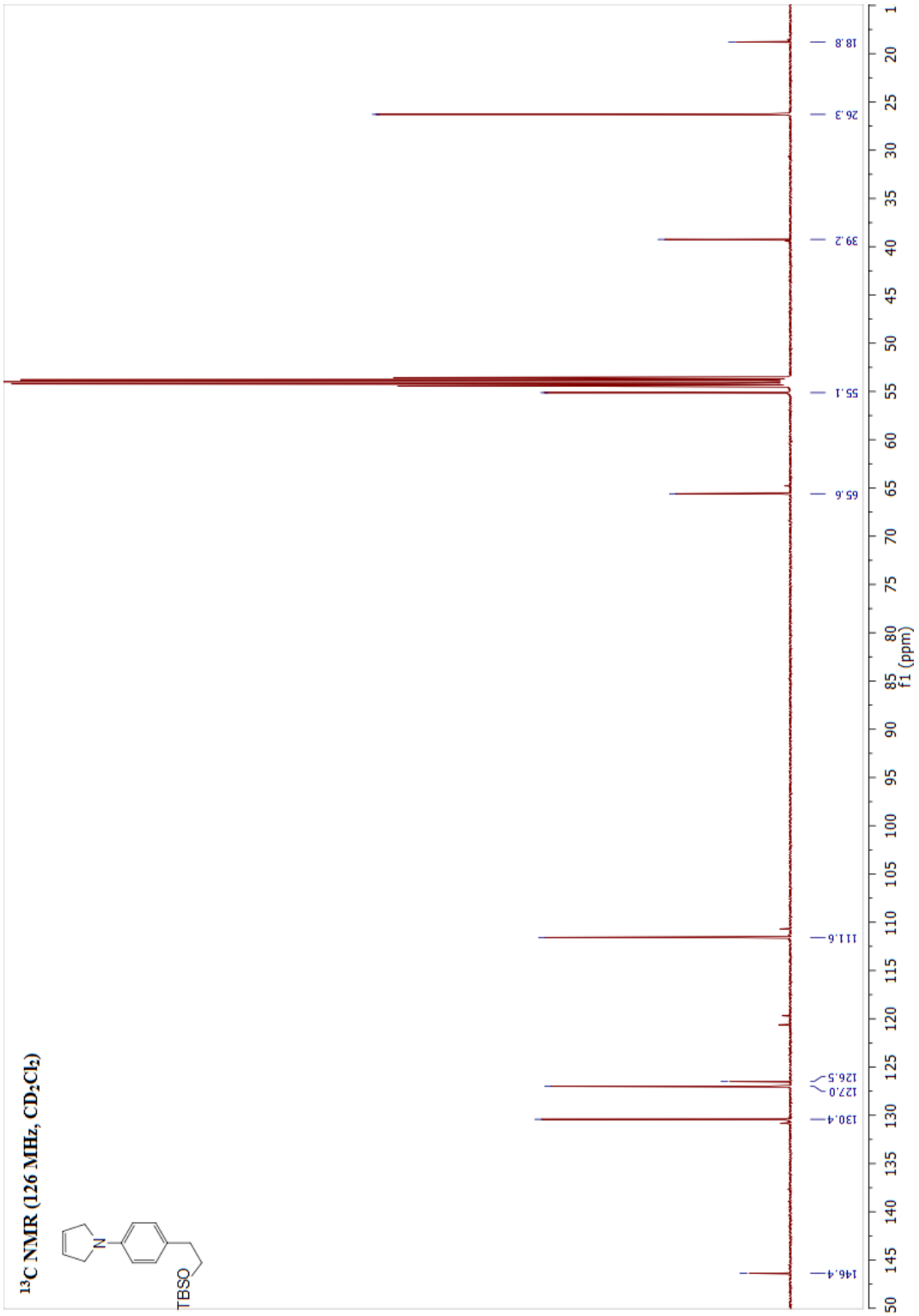
1.4.2 ^{13}C NMR Spectrum of Compound **13**



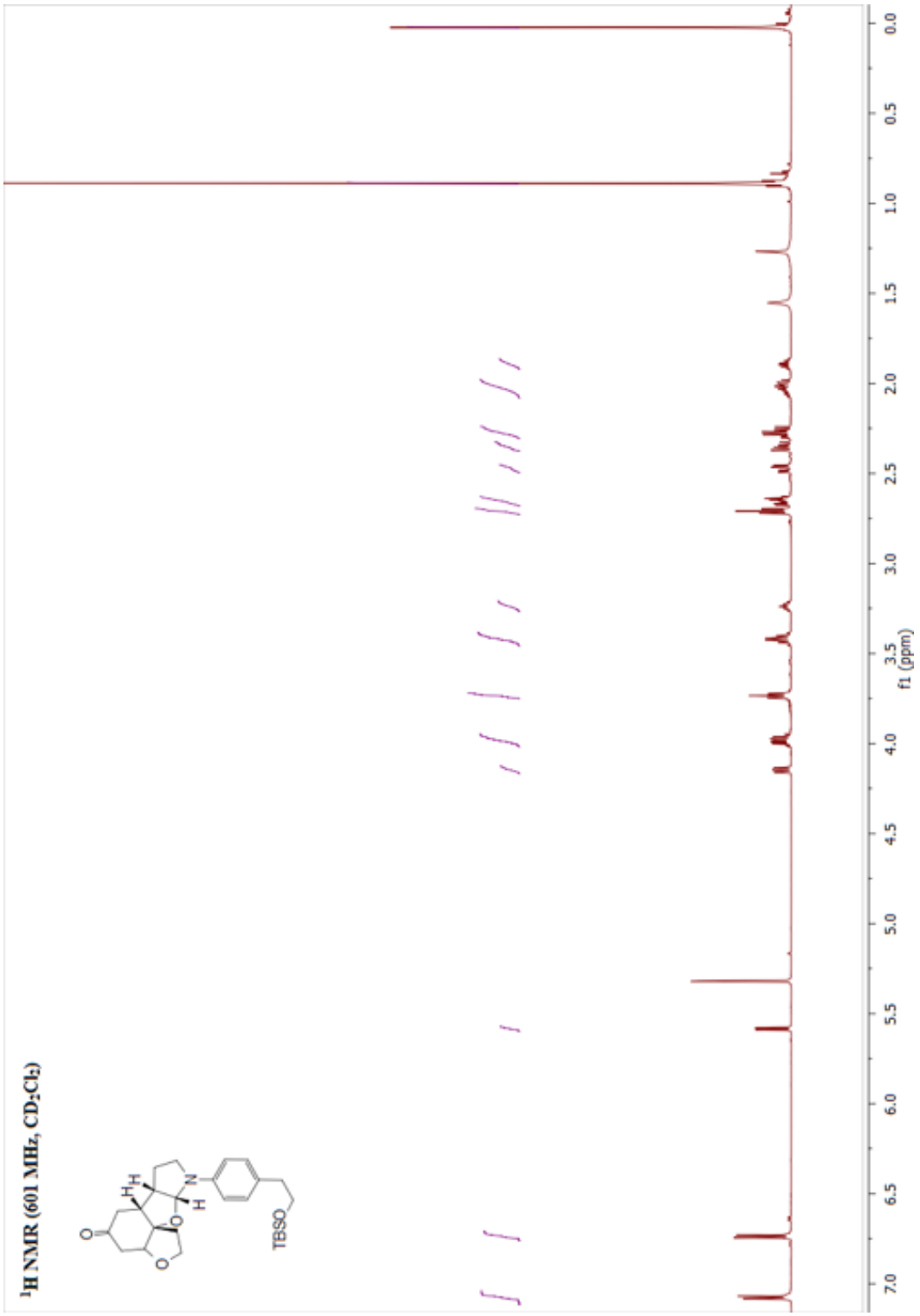
1.4.3 ^{1}H NMR Spectrum of Compound **14**



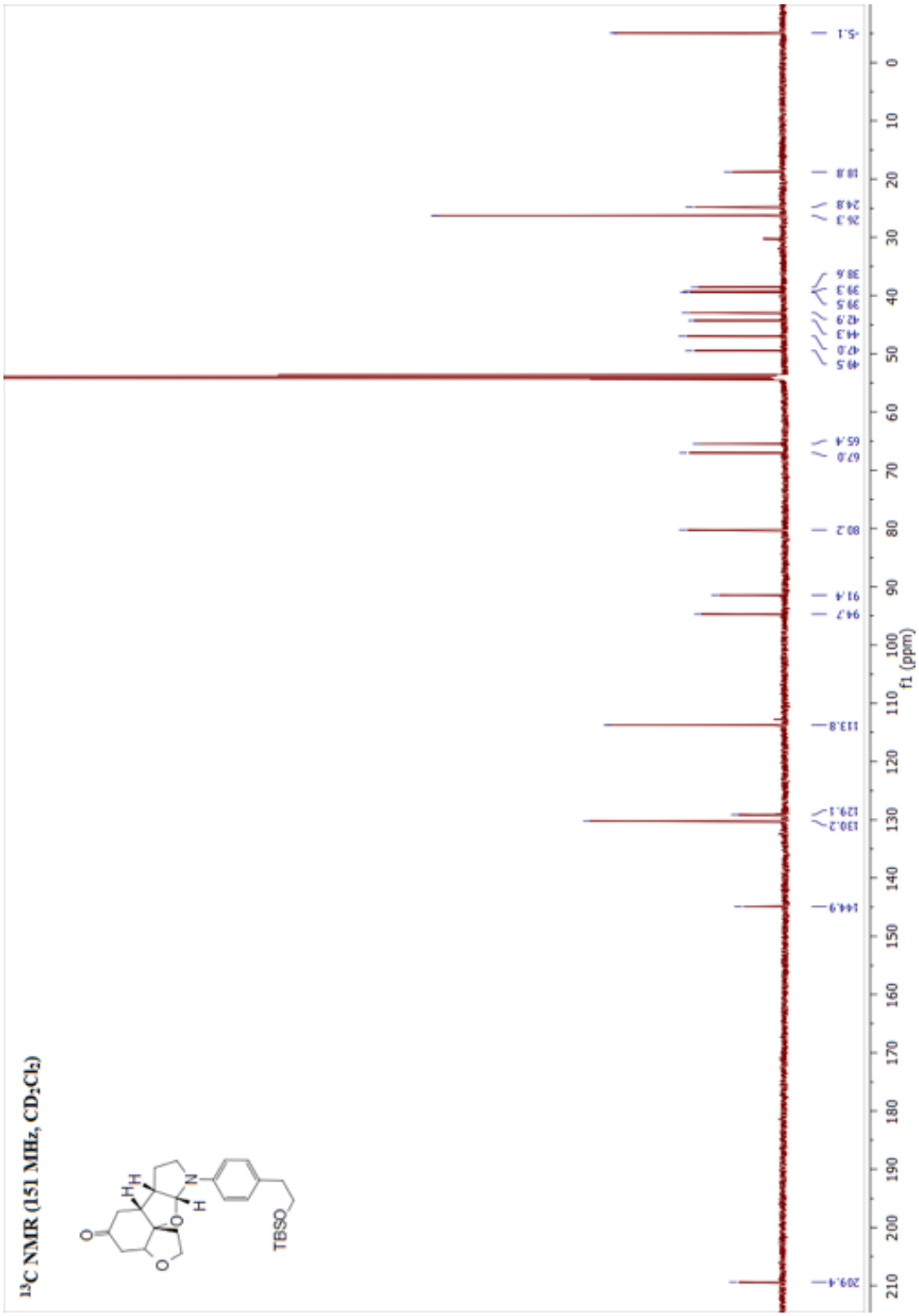
1.4.4 ^{13}C NMR Spectrum of Compound **14**



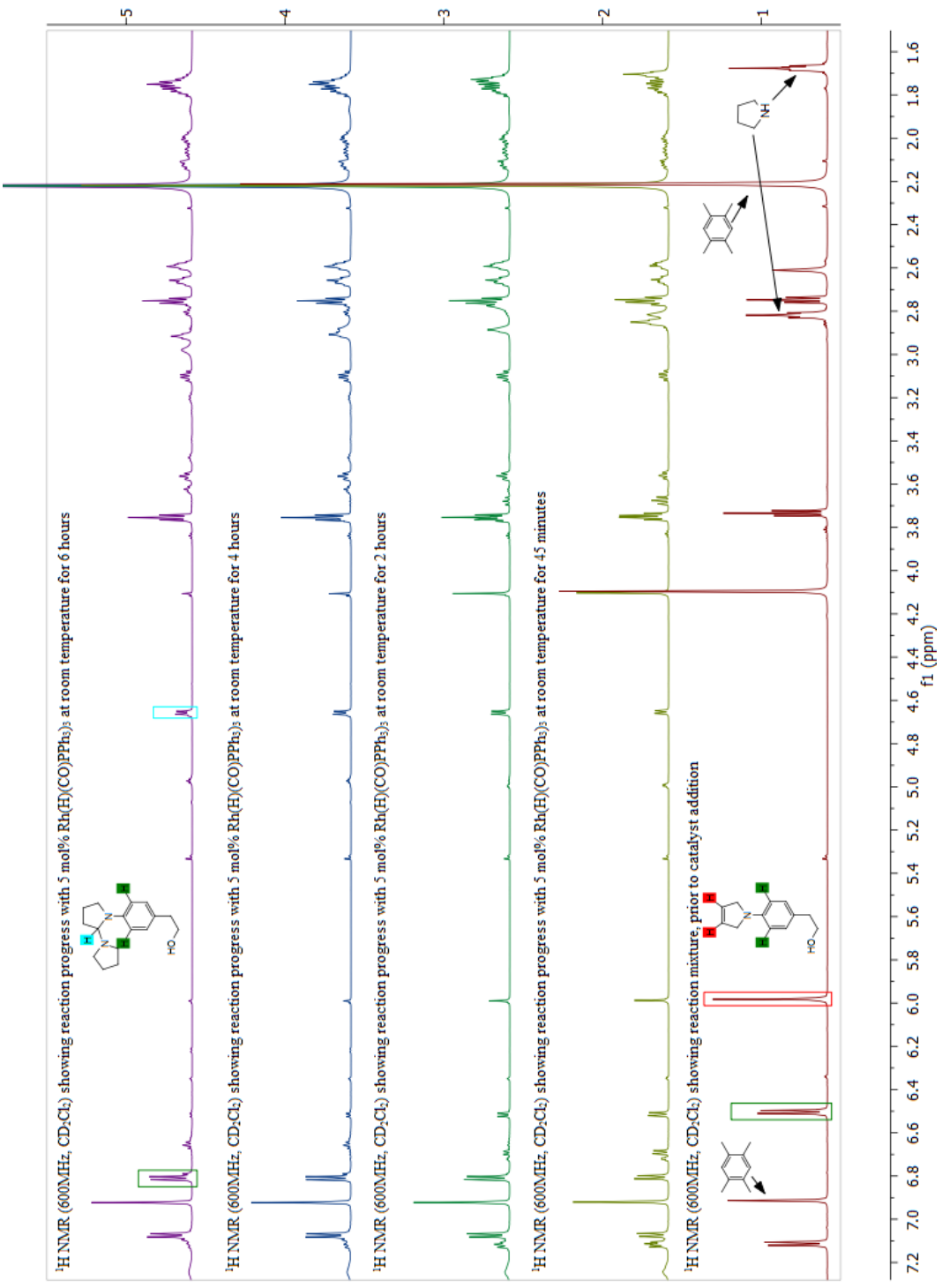
1.4.5 ^{1}H NMR Spectrum of Compound **16**



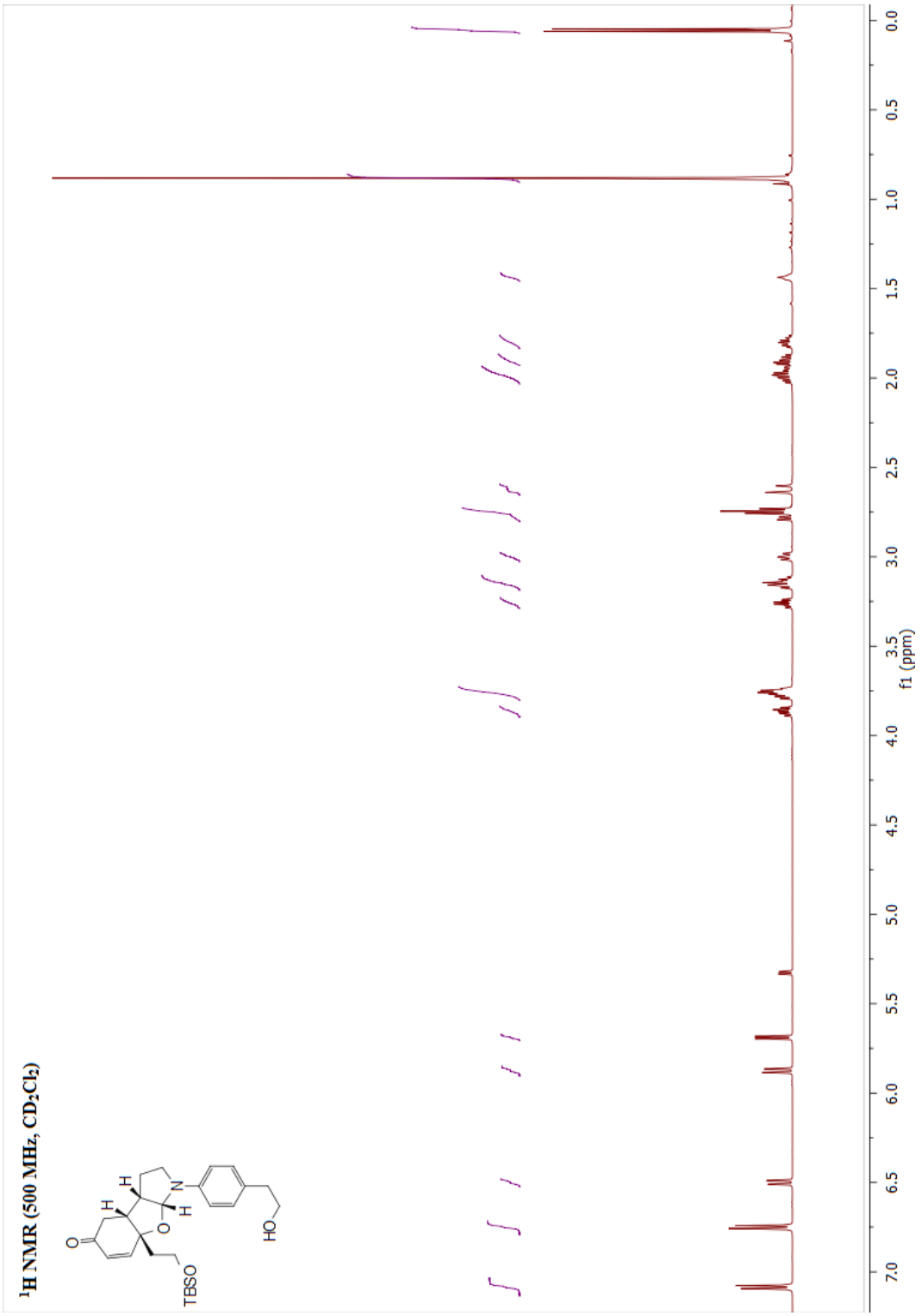
1.4.6 ^{13}C NMR Spectrum of Compound **16**



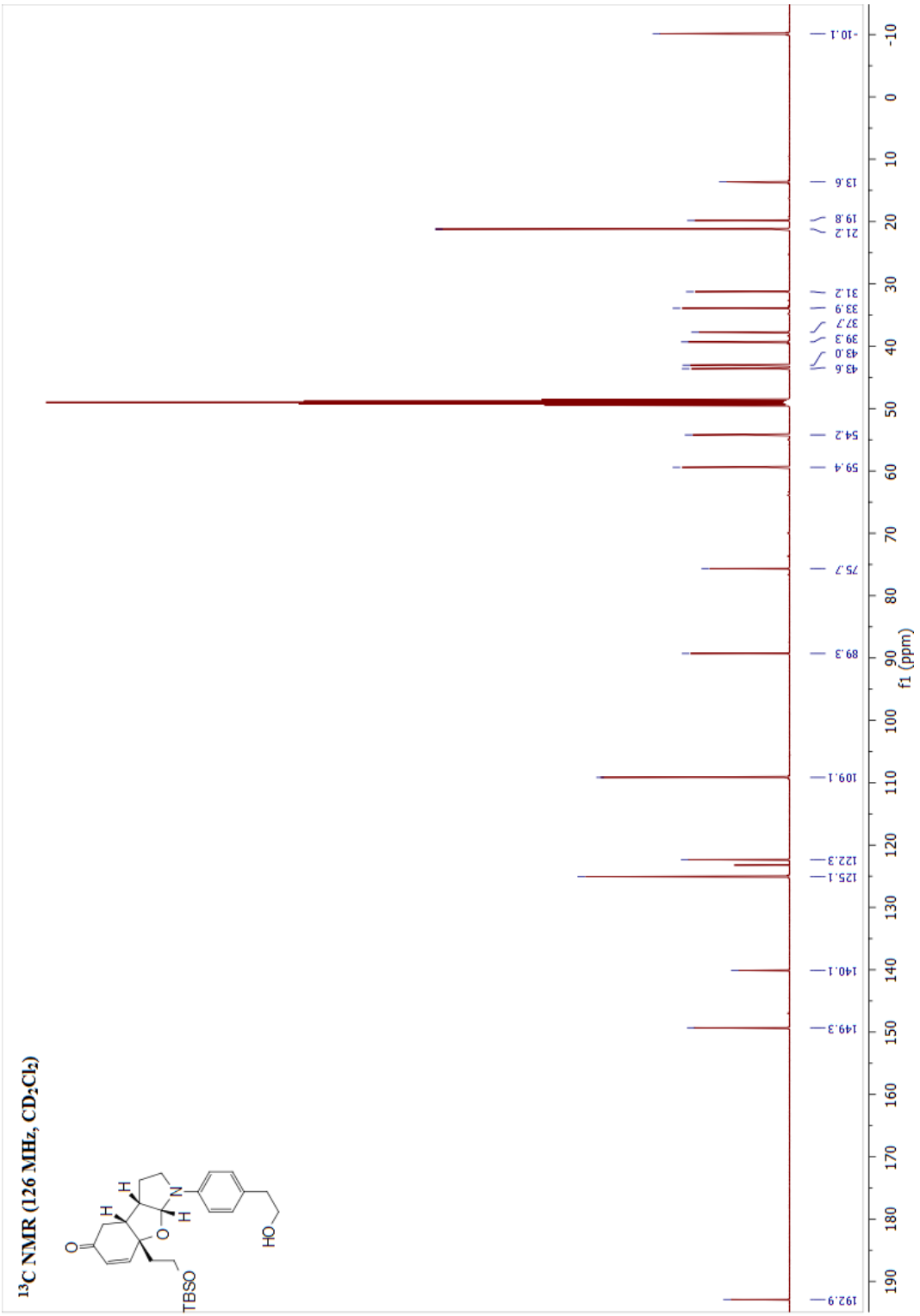
1.4.7 *In-situ* monitoring of the formation of aminal **19** by ^{1}H NMR Spectroscopy



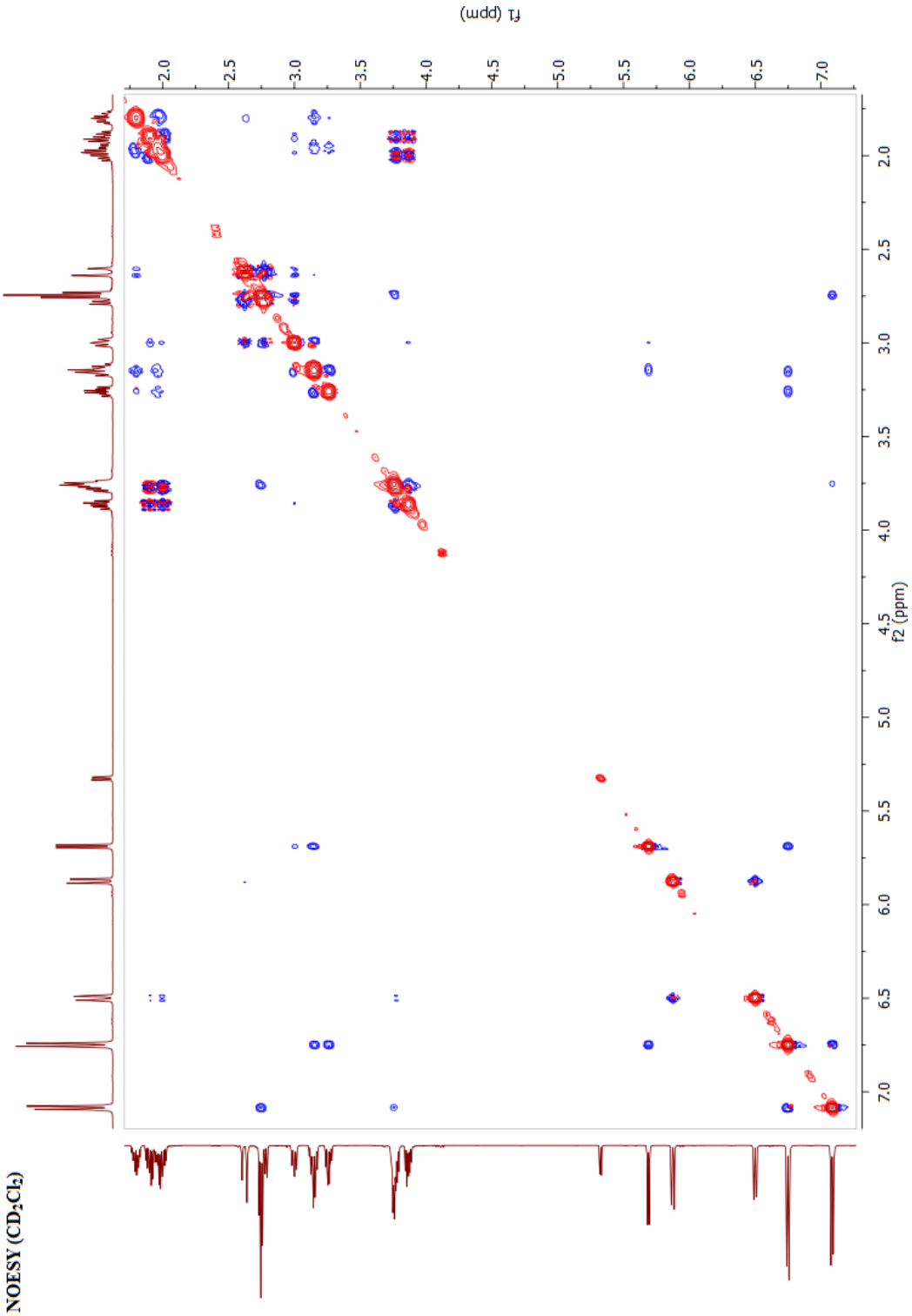
1.4.8 ^{1}H NMR Spectrum of Compound **21**



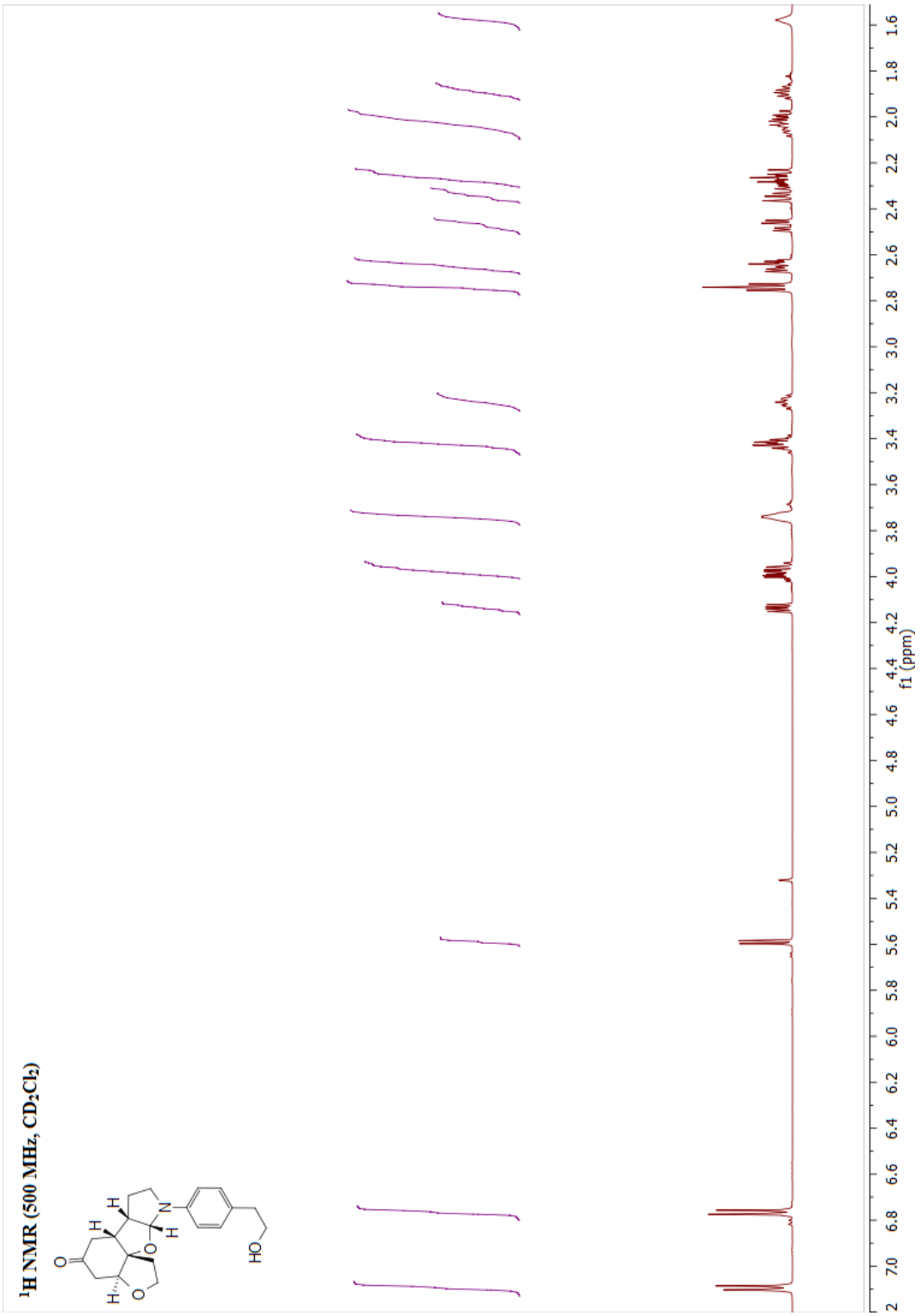
1.4.9 ^{13}C NMR Spectrum of Compound **21**



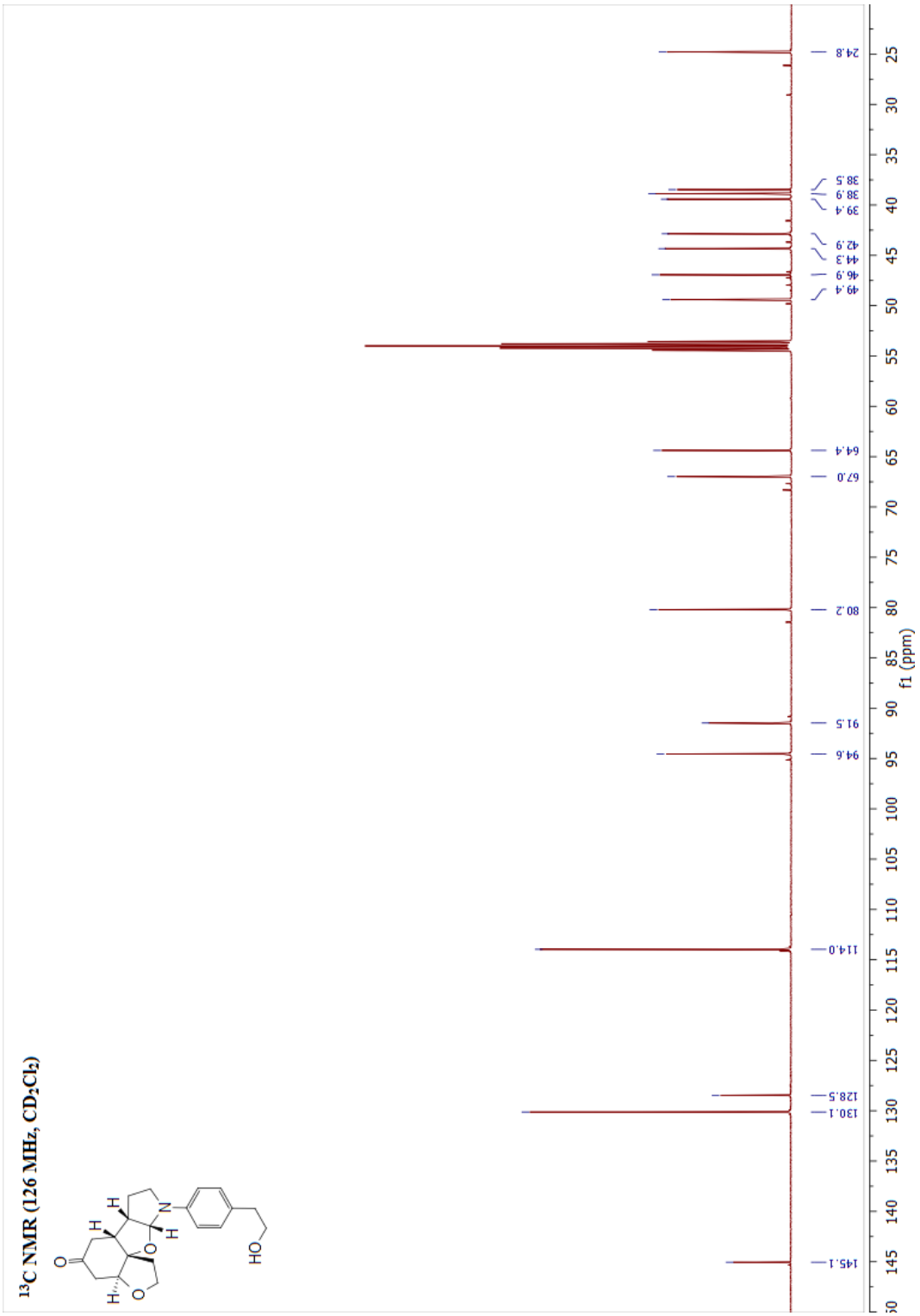
1.4.10 NOESY Spectrum of Compound **21**



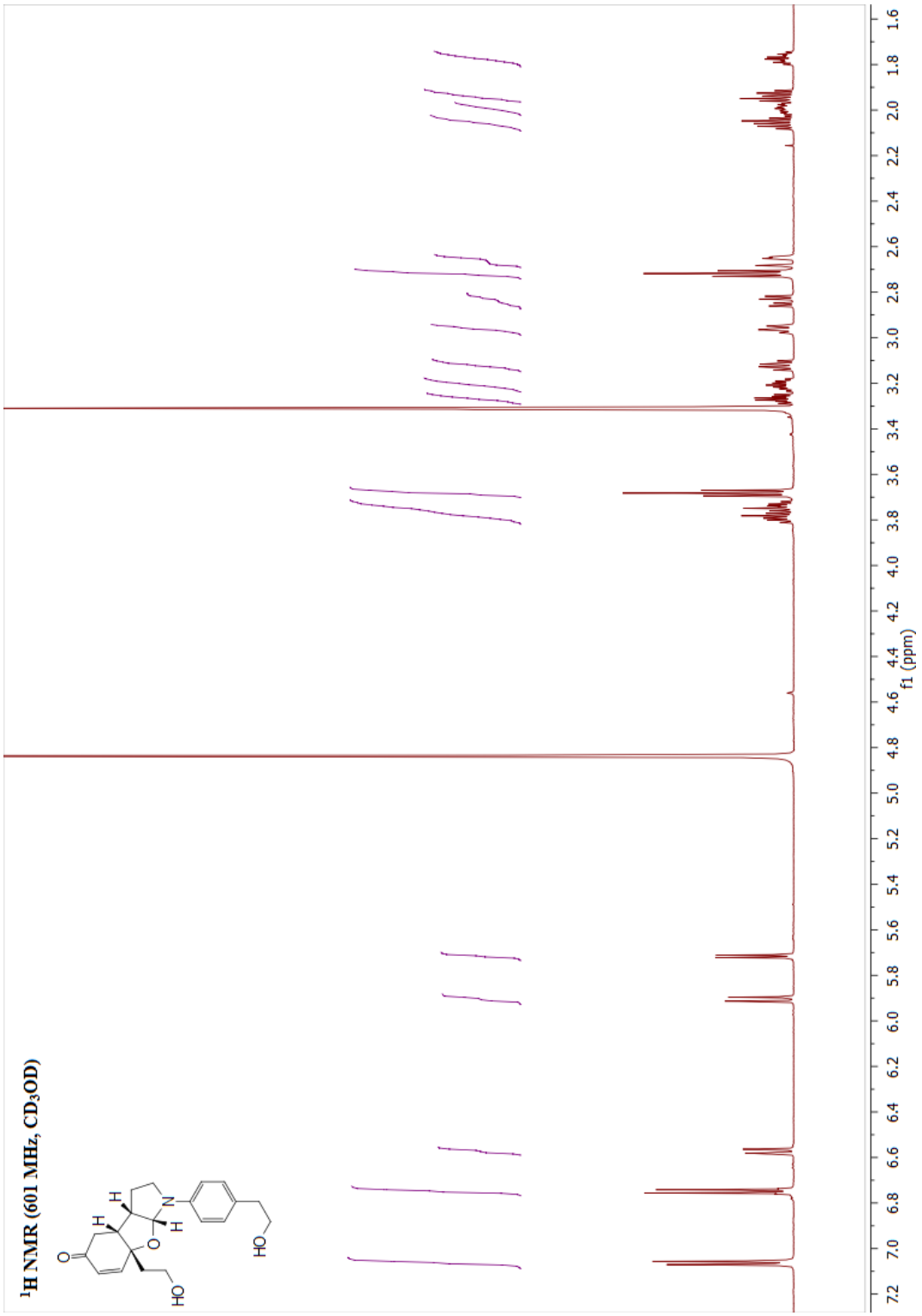
1.4.11 ^{1}H NMR Spectrum of Compound **22**



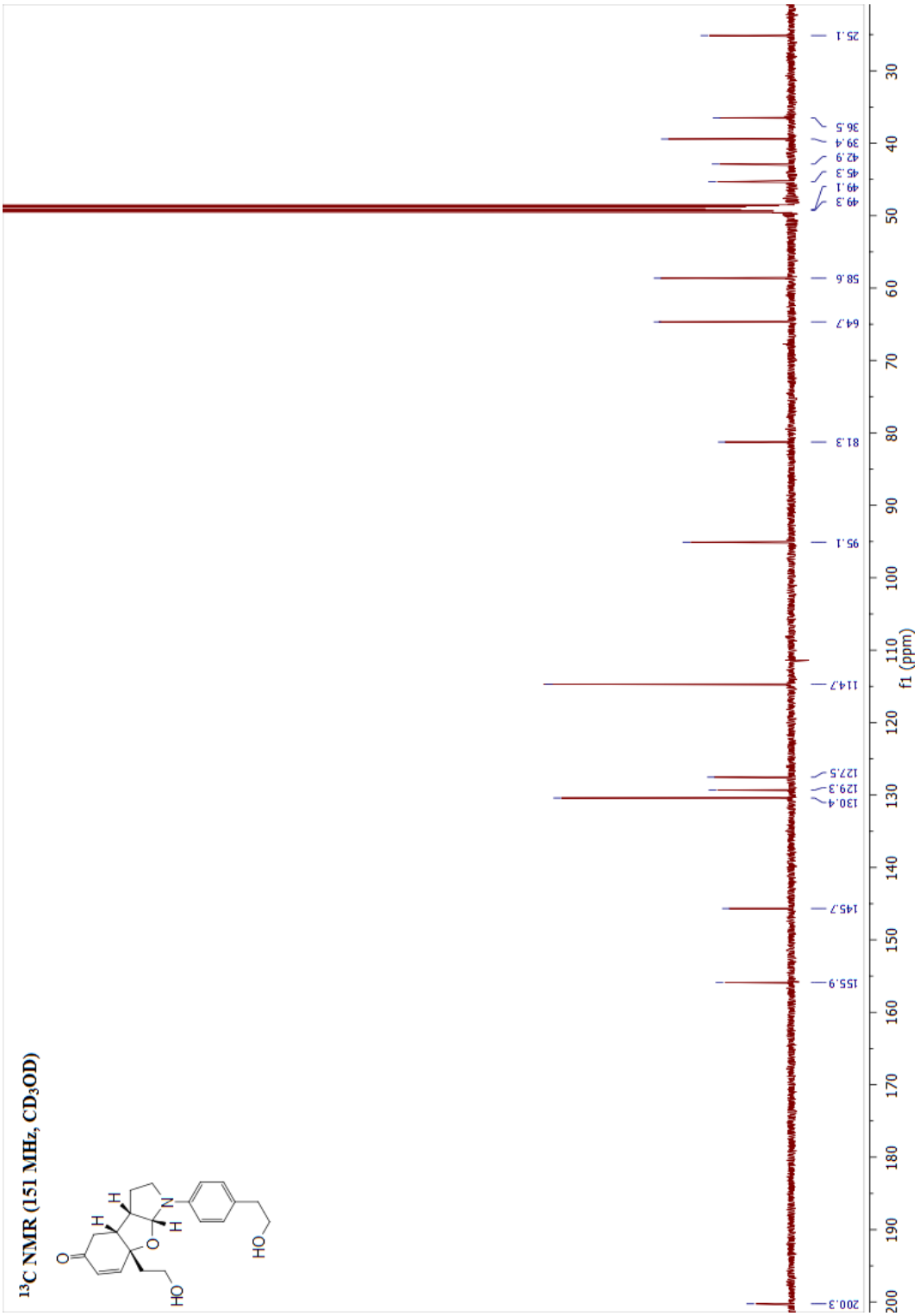
1.4.12 ^{13}C NMR Spectrum of Compound **22**



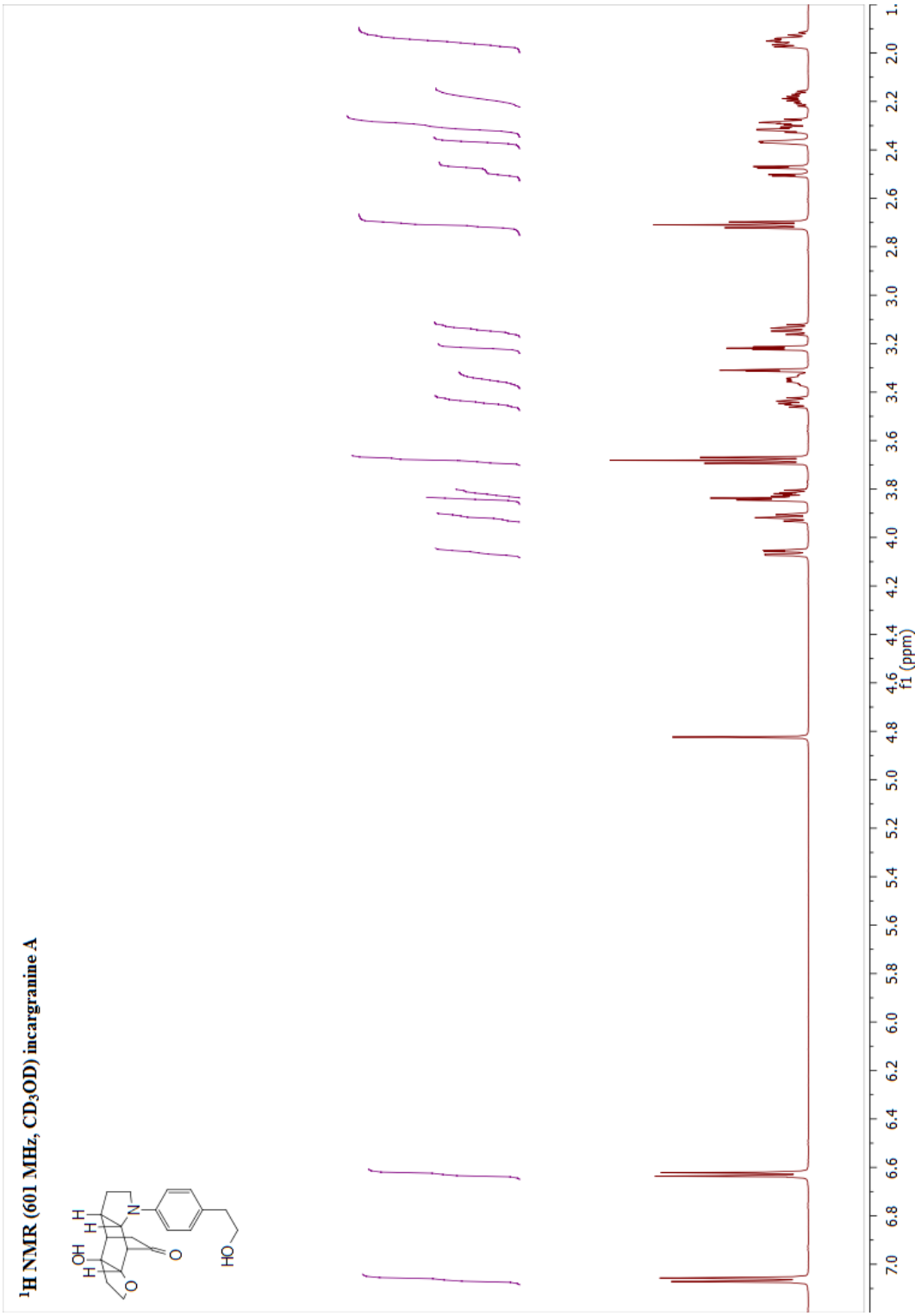
1.4.13 ^{1}H NMR Spectrum of Compound **18**



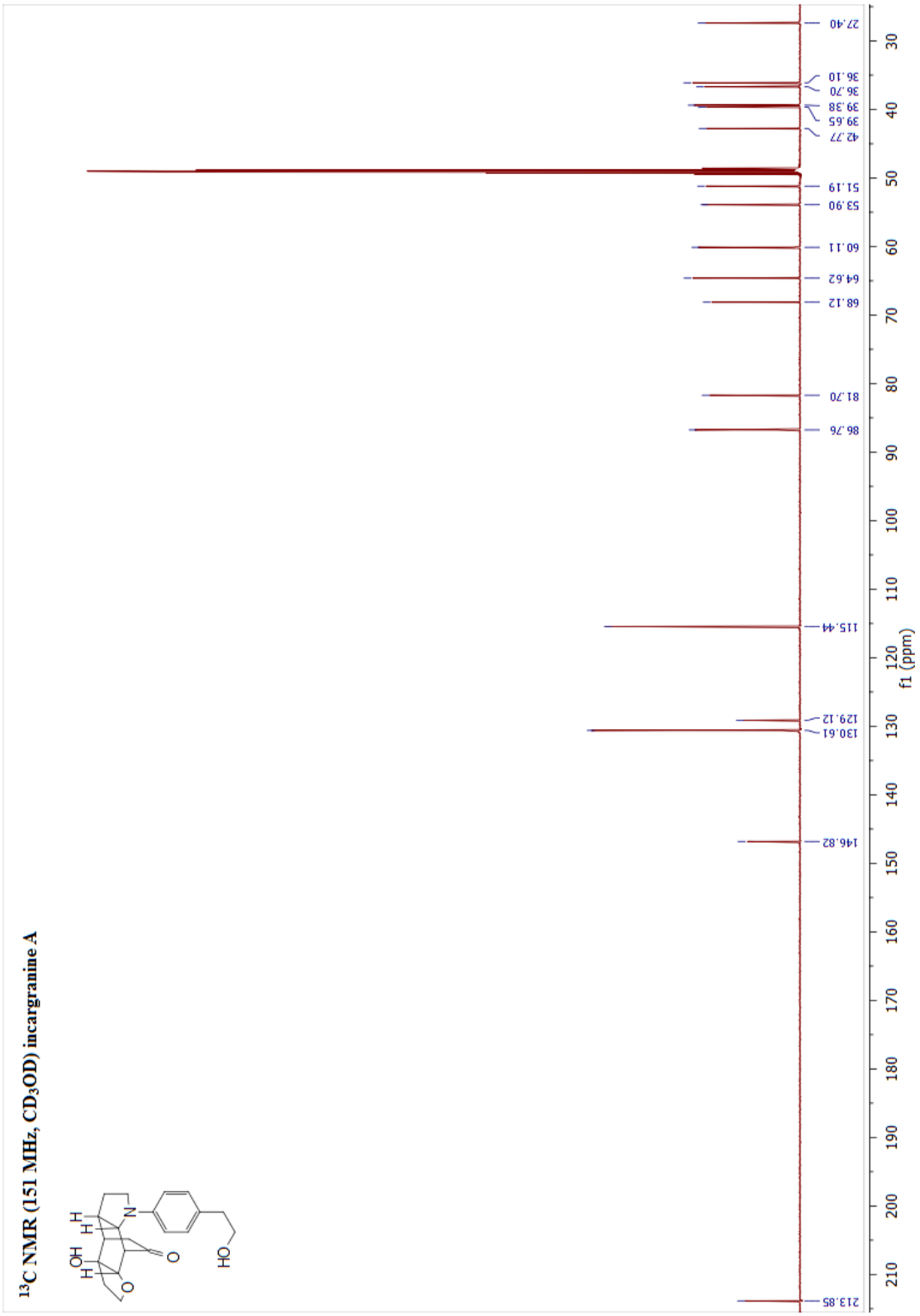
1.4.14 ^{13}C NMR Spectrum of Compound **18**



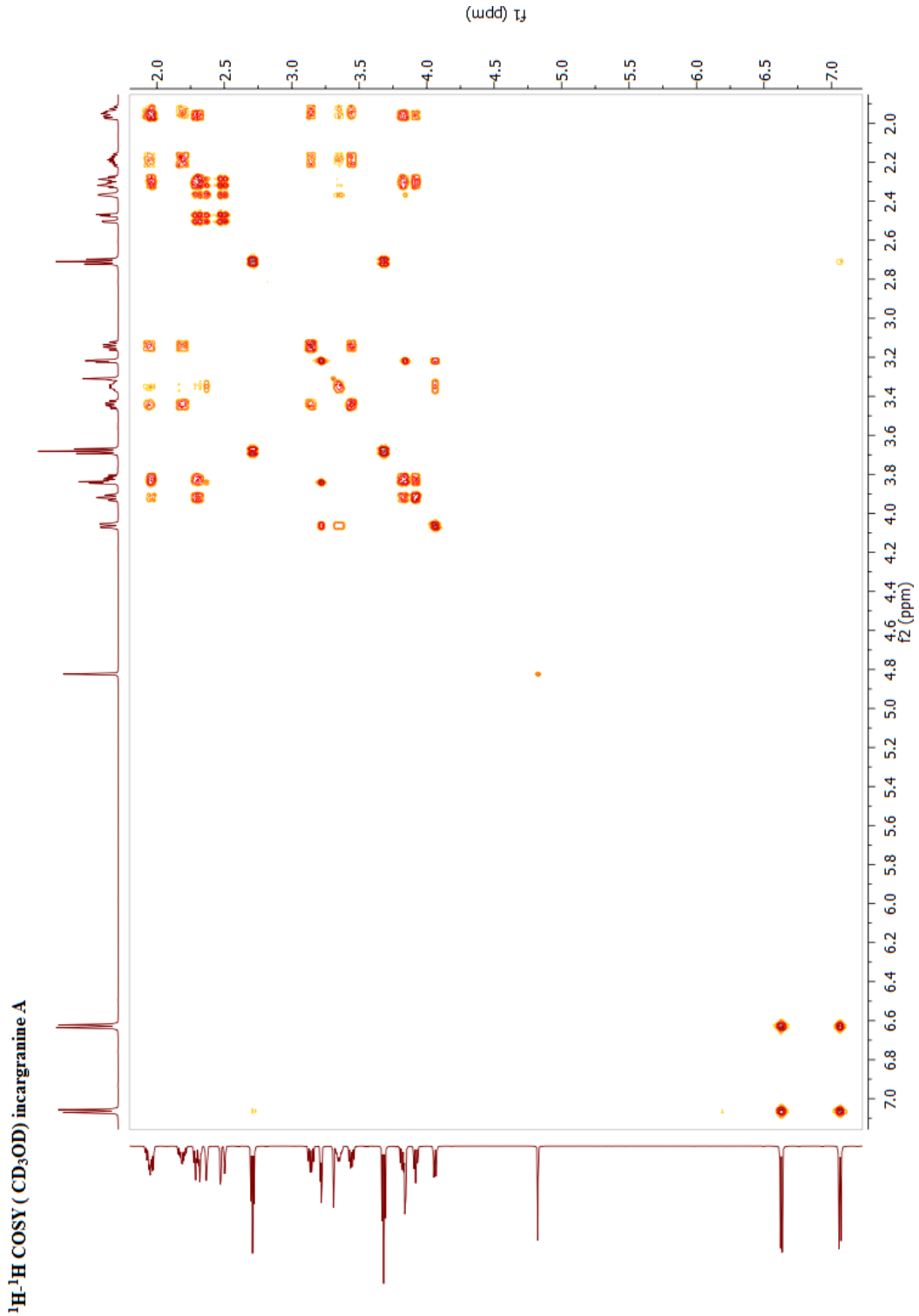
1.4.15 ^{1}H NMR Spectrum of Incargranine A **1**



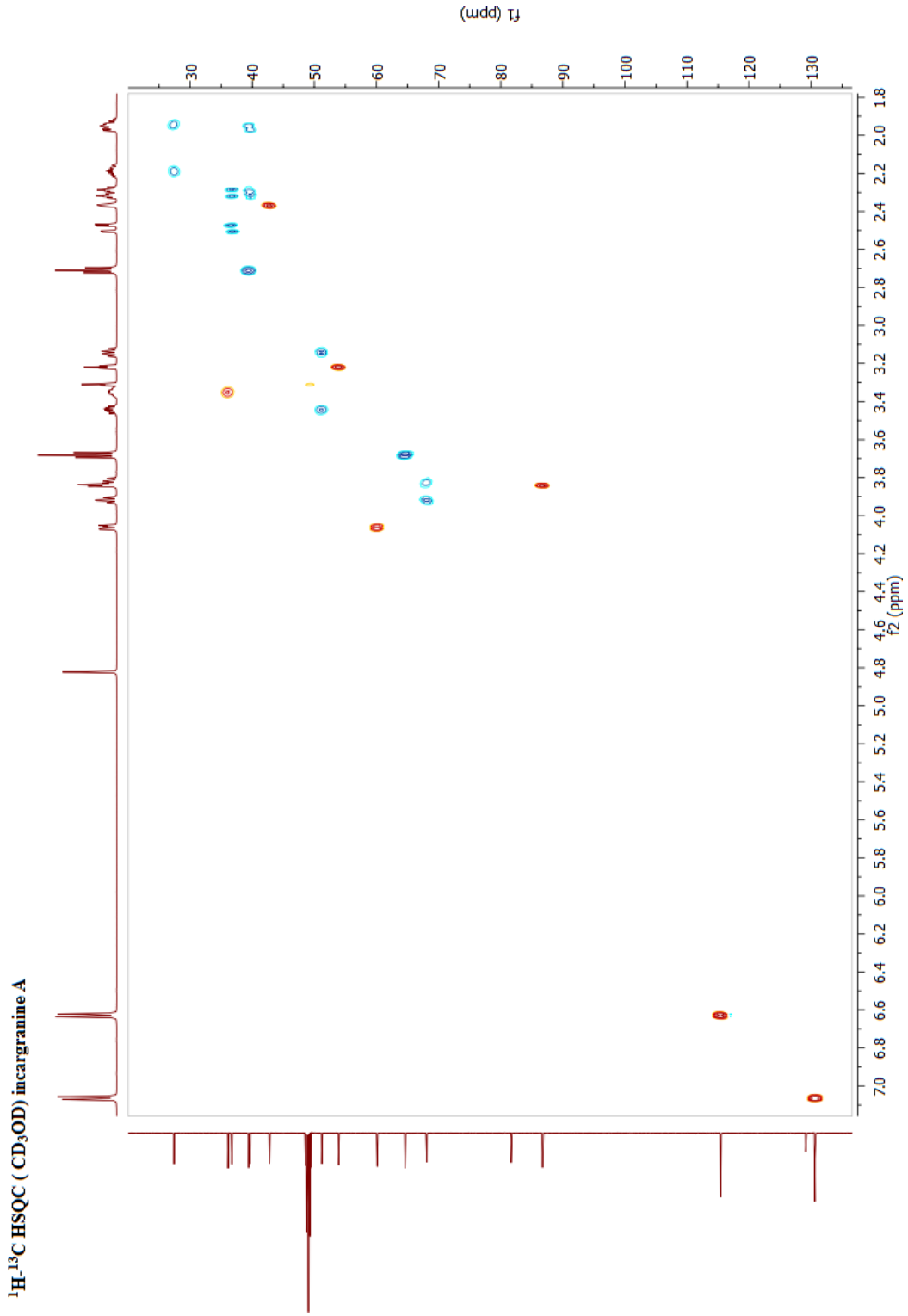
1.4.16 ^{13}C NMR Spectrum of Incargranine A **1**



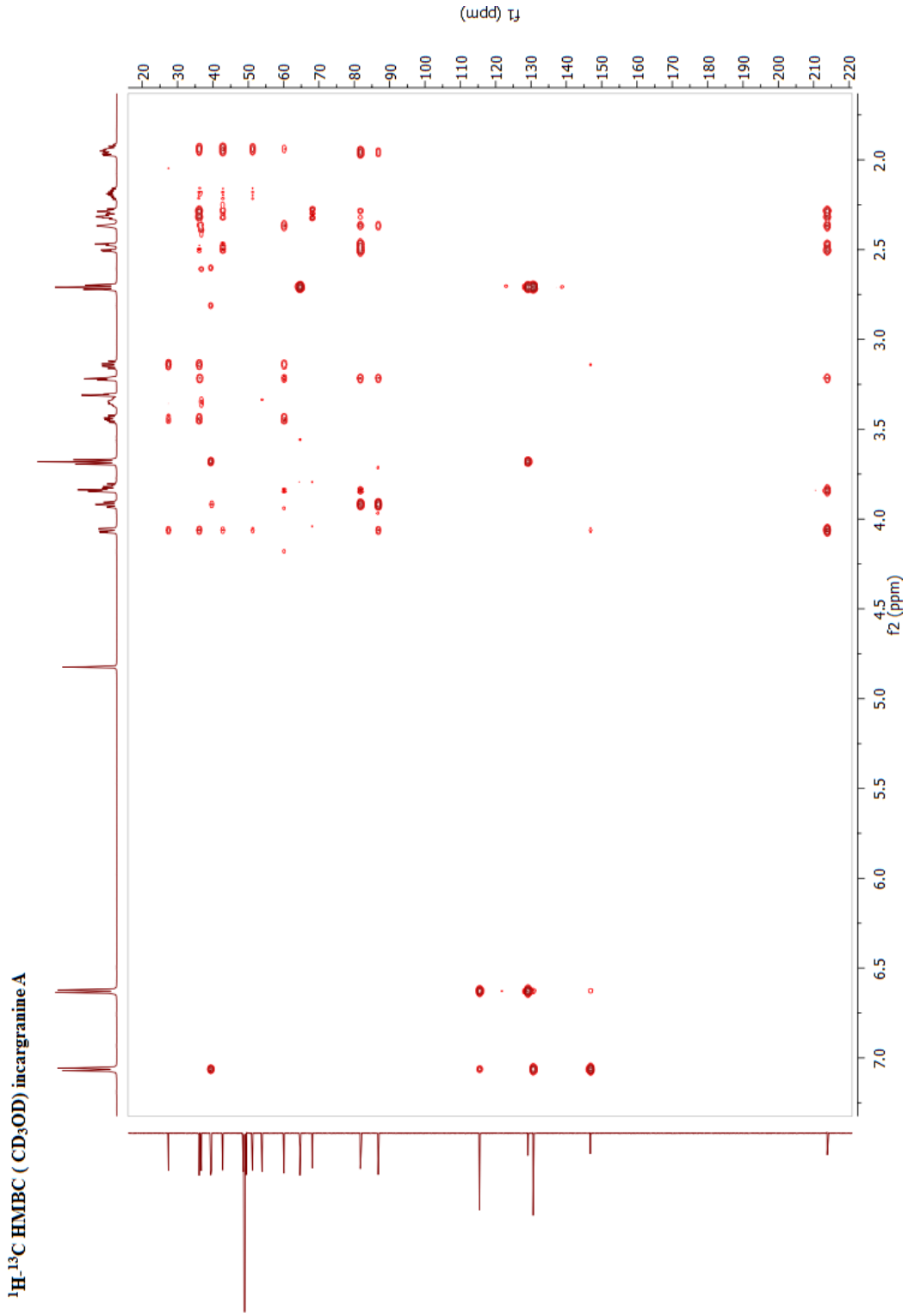
1.4.17 ^{1}H-^{1}H COSY Spectrum of Incargranine A **1**



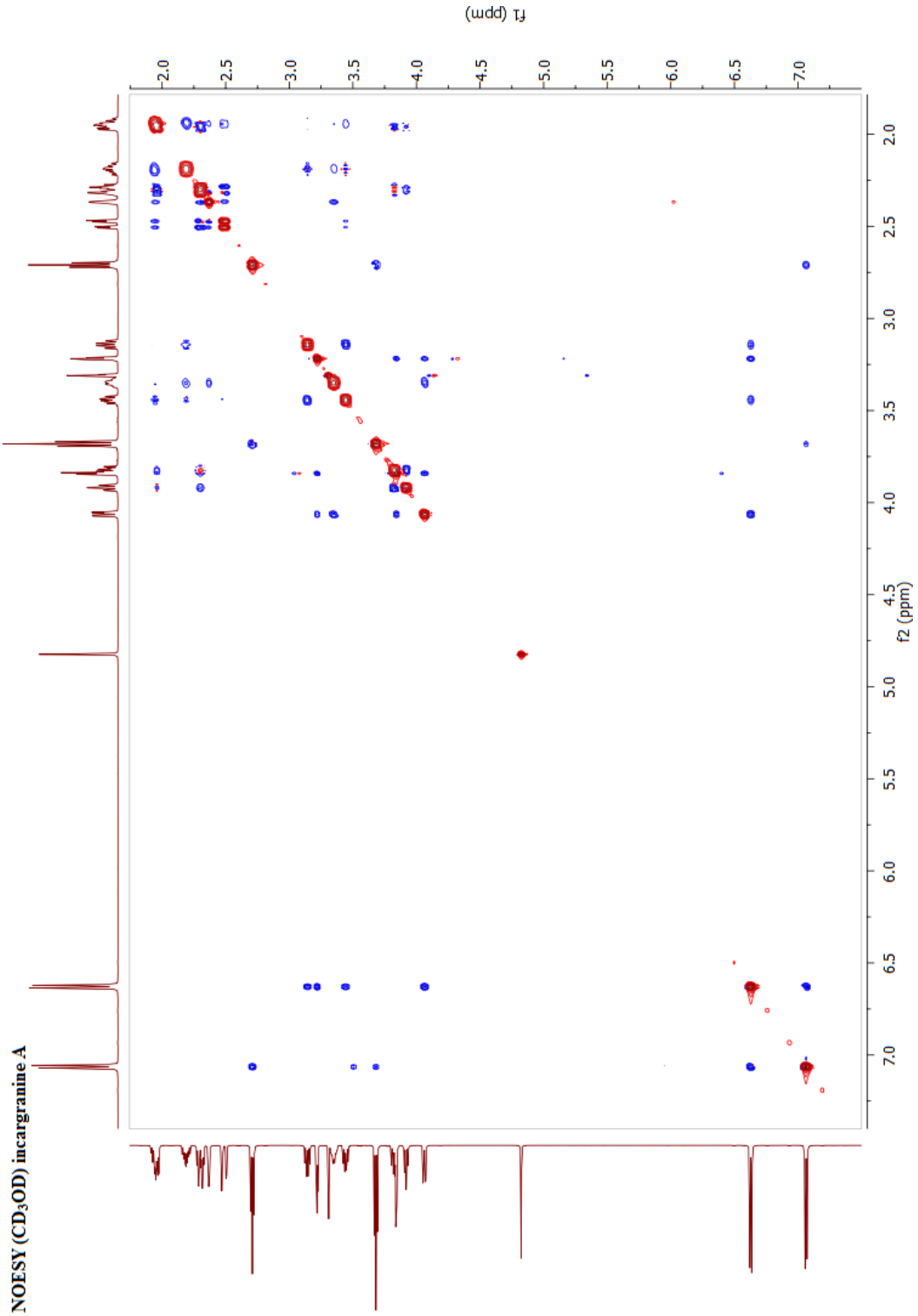
1.4.18 ^{1}H-^{13}C HSQC Spectrum of Incargranine A **1**



1.4.19 ^{1}H-^{13}C HMBC Spectrum of Incargranine A **1**



1.4.20 NOESY Spectrum of Incargranine A **1**



1.5 REFERENCES

(1) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15* (5), 1518.

(2) Brown, P. D.; Willis, A. C.; Sherburn, M. S.; Lawrence, A. L. *Org. Lett.* **2012**, *14* (17), 4537.

(3) Su, Y.-Q.; Shen, Y.-H.; Lin, S.; Tang, J.; Tian, J.-M.; Liu, X.-H.; Zhang, W.-D. *Helv. Chim. Acta* **2009**, *92* (1), 165.