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Supporting Information

Total synthesis of (±)-vinoxine: construction of the bridged pyrido[1,2-*a*]indole skeleton *via* Tf_2O-mediated Bischler-Napieralski reaction and stereoselective radical cyclization

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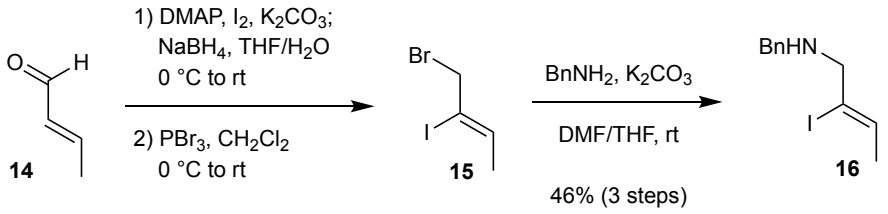
1. General Remarks

Materials were obtained from commercial suppliers and used without further purification unless otherwise mentioned. All reactions were carried out in oven-dried glassware under a slight positive pressure of argon unless otherwise noted. Anhydrous THF, CH_2Cl_2, and MeCN were purchased from Kanto Chemical Co., Inc. Anhydrous toluene, benzene, EtOAc, DMF, and 99% AcOH were purchased from FUJIFILM Wako Pure Chemical Corporation. Anhydrous MeOH was dried and distilled according to the standard protocols. Column chromatography was performed on Silica Gel 60N (Kanto Chemical Co., Inc., spherical neutral, 40–50 μm) using the indicated eluent. Preparative TLC and analytical TLC were performed on Merck 60 F_{254} glass plates precoated with a 0.25 mm thickness of silica gel. IR spectra were measured on a SHIMADZU FT/IR-4100 spectrometer. NMR spectra were recorded on a JEOL ECA600 spectrometer and a JNM-AL400 spectrometer with tetramethylsilane (0 ppm) or chloroform (7.26 ppm) as an internal standard. Chemical shifts were expressed in δ (ppm) values, and coupling constants were expressed in hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, q = quartet, and m = multiplet. Mass spectra were recorded on a BRUKER micrOTOF II spectrometer.

2. Experimental Procedures

Benzyl amine 16



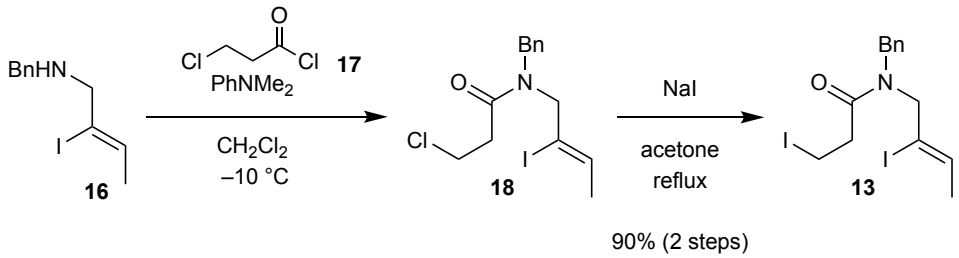
To a stirred suspension of crotonaldehyde (**14**) (10.0 mL, 120 mmol), K_2CO_3 (20.0 g, 144 mmol) and DMAP (3.00 g, 2.40 mmol) in THF/H_2O (1/1 v/v, 600 mL) was added iodine (46.0 g, 180 mmol) at 0 °C. After stirring at room temperature for 2 hours, $NaBH_4$ (5.00 g, 132 mmol) was added to the reaction mixture at 0 °C. After stirring at room temperature for 1 hour, the reaction was quenched with saturated aqueous NH_4Cl and the resulting mixture was extracted with EtOAc three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was subjected to the next reaction without further purification.

To a stirred solution of the above crude allyl alcohol in CH_2Cl_2 (600 mL) was added PBr_3 (17.1 mL, 180 mmol) at 0 °C. After stirring at room temrepature for 2 hours, the reaction was quenched with saturated aqueous $NaHCO_3$ and the resulting mixture was extracted with petroleum ether three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was subjected to the next reaction without further purification.

To a stirred suspension of benzyl amine (65.0 mL, 600 mmol) and K_2CO_3 (33.1 g, 240 mmol) in DMF/THF (1/1 v/v, 400 mL) was added a solution of the above crude allyl bromide **15** in DMF/THF (1/1 v/v, 200 mL) at 0 °C. After stirring at the same temperature for 20 minutes, water was added to the reaction mixture and the resulting mixture was extracted with EtOAc three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure (10 torr) at 80 °C to remove the excess amount of benzyl amine. The residue was purified by flash column chromatography on silica gel (hexane-EtOAc = 4:1) to afford allyl amine **16** (16.0 g, 55.7 mmol, 46% for 3 steps) as a pale yellow oil. R_f = 0.45 (hexane-EtOAc = 3:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39–7.34 (m, 4H), 7.30–7.23 (m, 1H), 5.82 (q, J = 6.4, Hz, 1H), 3.68 (s, 2H), 3.48 (s, 2H), 1.80 (d, J = 6.4 Hz, 3H), 1.87–1.78 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.9, 131.9, 128.44, 128.37, 127.0, 112.0, 60.3, 51.2, 21.8; IR (neat, cm^{-1}): 3331, 3026, 2913, 2826, 1644, 1454, 1294, 1112, 946, 803, 735, 697; HRMS (EI) m/z: calcd. for $C_{11}H_{15}IN$

([M+H]$^+$) 288.0244, found 288.0234.

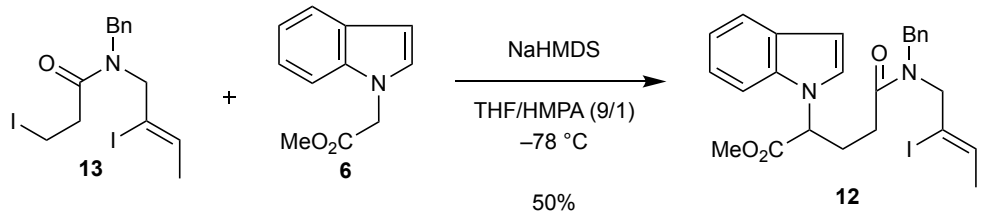
Amide 13



To a stirred solution of 3-chloropropionyl chloride **17** (5.3 mL, 55 mmol) and *N,N*-dimethylaniline (8.7 mL, 69 mmol) in CH_2Cl_2 (307 mL) was added a solution of allyl amine (13.2 g, 46.0 mmol) in CH_2Cl_2 (100 mL) at –10 °C. After stirring at the same temperature for 10 minutes, the reaction was quenched with saturated aqueous $NaHCO_3$ and the resulting mixture was extracted with EtOAc three times. The combined organic extracts were washed with brine, dried over $NaSO_4$, filtered, and concentrated under reduced pressure. The residue was subjected to the next reaction without further purification.

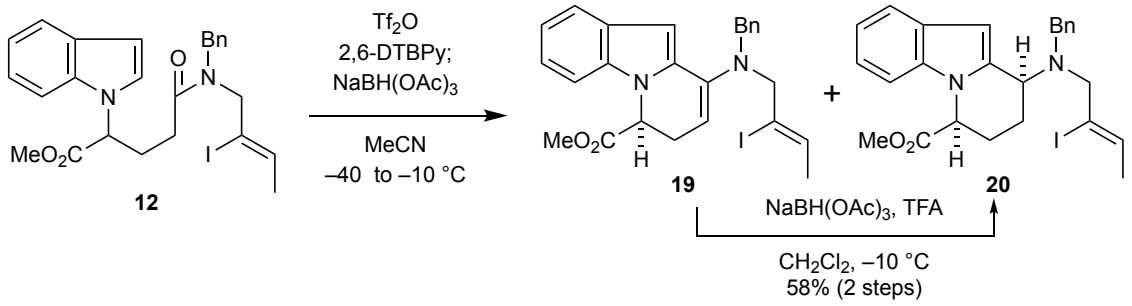
To a solution of the above crude alkyl chloride **18** in acetone (300 mL) was added NaI (41.4 g, 276 mmol). After stirring at reflux for 2.5 hours, the reaction mixture was cooled to room temperature and concentrated under the reduced pressure. To the residue was added saturated aqueous $Na_2S_2O_3$ and the resulting mixture was extracted with EtOAc three times. The combined organic extracts were washed with brine, dried over $NaSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane-EtOAc = 5:1) to afford alkyl iodide **13** (19.5 g, 41.6 mmol, 90% for 2 steps) as a colorless oil. R_f = 0.41 (hexane-EtOAc = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$, a mixture of rotamers): δ 7.40–7.23 (m, 4.2H), 7.16 (d, J = 0.8H), 5.86–6.78 (m, 1H), 4.60 (s, 1.2H), 4.52 (s, 0.8H), 4.39 (s, 0.8H), 4.07 (s, 1.2H), 3.50–3.43 (m, 2H), 3.11–3.04 (m, 2H), 1.84 (d, J = 6.4 Hz, 1.8H), 1.80 (d, J = 6.4 Hz, 1.2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 170.8, 136.8, 135.9, 133.3, 132.6, 129.1, 128.7, 128.3, 127.9, 127.6, 126.5, 104.3, 104.2, 57.3, 55.7, 49.4, 47.6, 37.5, 37.2, 22.1, 21.9, 21.9; IR (neat, cm^{-1}): 3024, 2913, 1653, 1419, 1216, 1169, 758, 699; HRMS (ESI) m/z: calcd. for $C_{14}H_{18}INO$ ([M+H]$^+$) 469.9472, found 469.9490.

Tertiary amide 12



To a stirred solution of indole ester **6** (2.48 g, 13.1 mmol) and alkyl iodide **13** (4.10 g, 8.74 mmol) in THF/HMPA (9/1 v/v, 87 mL) was NaHMDS (1.8 M in THF, 6.2 mL, 10.4 mmol) at –78 °C. After stirring at the same temperature for 30 minutes, the reaction was quenched with saturated aqueous NH_4Cl and the resulting mixture was extracted with EtOAc three times. The combined organic extracts were washed with water and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane-EtOAc = 94:6 to 65:35, gradient) to afford tertiary amide **12** (2.32 g, 4.38 mmol, 50%) as colorless oil. R_f = 0.28 (hexane-EtOAc = 3:1); ^{1}H NMR (400 MHz, $CDCl_3$, a mixture of rotamers): δ 7.64–7.60 (m, 1H), 7.40–7.08 (m, 7H), 6.80–6.79 (m, 1H), 6.57 (d, J = 3.6 Hz, 0.5H), 6.55 (d, J = 3.2 Hz, 0.5H), 5.67 (q, J = 6.4 Hz, 0.5H), 5.51–5.44 (m, 1H), 5.46 (q, J = 6.0 Hz, 0.5H), 4.53 (d, J = 14.8 Hz, 0.5H), 4.47 (d, J = 14.8 Hz, 0.5H), 4.37–4.17 (m, 2H), 3.77–3.75 (m, 1H), 3.71 (s, 1.5H), 3.69 (s, 1.5H), 2.79–2.68 (m, 1H), 2.51–2.32 (m, 2H), 2.18–2.05 (m ,1H), 1.77 (d, J = 6.0 Hz), 1.63 (d, J = 6.4 Hz, 1.5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8, 171.7, 171.4, 171.3, 136.9, 136.6, 136.5, 135.8, 133.3, 132.3, 128.9, 128.7, 128.6, 128.5, 128.3, 127.6, 127.5, 126.3, 125.8, 125.6, 122.1, 121.13, 121.11, 120.0, 109.6, 109.5, 104.2, 103.8, 103.05, 102.99, 57.2, 56.8, 56.7, 55.4, 52.6, 49.3, 47.4, 28.2, 28.1, 27.3, 27.1, 21.8, 21.5 (two signal is missing due to overlap); IR (neat, cm^{-1}): 3028, 2950, 1743, 1652, 1460, 1437, 1311, 1215, 743; HRMS (ESI) m/z: calcd. for $C_{25}H_{28}IN_2O_3$ ($[M+H]^+$) 531.1139, found 531.1127.

Pyrido[1,2,*a*]indole 20

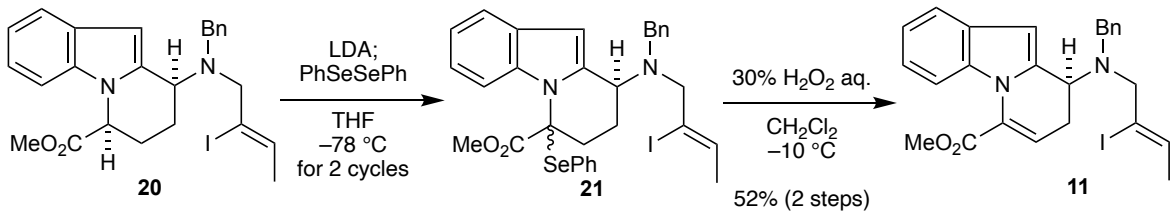


To a stirred solution of tertiary amide **12** (952 mg, 1.79 mmol) and 2,6-di-*tert*-butylpyridine (1.21 mL, 5.39 mmol) in MeCN (18 mL) was added Tf_2O (600 μL, 3.58 mmol) at –40 °C. After stirring at –10 °C for 30 minutes, $NaBH(OAc)_3$ (1.90 g, 8.95 mmol) was added to the reaction mixture at the same temperature. After stirring for 15 minutes –10 °C, the reaction was quenched with saturated aqueous $NaHCO_3$ and the resulting mixture was extracted with EtOAc three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was filtered through a pad of silica gel and filtered cake was washed with hexane-EtOAc = 95:5 to 73:27, gradient. The eluent was concentrated under the reduced pressure to afford a mixture of enamine **19** and tertiary amine **20**. The residue was subjected to the next reaction without further purification.

To a suspension of the above crude mixture of enamine **19** and tertiary amine **20** and $NaBH(OAc)_3$ (600 mg, 2.84 mmol) in CH_2Cl_2 was added TFA (57 μL, 0.74 mmol) at –10 °C. After strirrig for 15 minutes at the same temperature, the reaction was quenched with saturated aqueous $NaHCO_3$ and the resulting mixture was extracted with EtOAc three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane-EtOAc = 95:5 to 75:25, gradient) to afford tertiary amide **20** (513 mg, 1.03 mmol, 58% for 2 steps) as white foam. R_f = 0.55 (hexane-EtOAc = 3:1); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.62 (d, J = 7.8 Hz, 1H), 7.54 (d, J = 7.2 Hz, 2H), 7.32 (dd, J = 7.2, 7.2 Hz, 2H), 7.23 (dd, J = 7.8, 7.2 Hz, 1H), 7.14–7.07 (m, 3H), 6.89 (s, 1H), 6.02 (q, J = 6.0 Hz, 1H), 5.00 (d, J = 6.0 Hz, 1H), 4.20 (dd, J = 11.4, 6.0 Hz, 1H), 4.00 (d, J =14.4 Hz, 1H), 3.70 (s, 3H), 3.58 (d, J =14.4 Hz, 1H), 3.55 (d, J = 14.4 Hz, 1H), 2.49–2.46 (m,1H), 2.14 (dddd, J = 14.4, 14.4, 6.0, 3.0 Hz, 1H), 2.08–2.03 (m, 1H), 1.87–1.80 (m, 1H), 1.79 (d, J = 6.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 171.9, 139.5, 137.9, 136.4, 131.8, 128.6, 128.2, 127.0, 121.1, 120.4, 120.2, 110.3, 108.3, 100.1, 61.3, 53.9, 53.8, 53.4, 52.5, 26.0, 21.8, 17.9; IR (neat,

cm^{-1}): 3057, 2950, 2807, 1747, 1460, 1371, 1200, 994, 921, 752; HRMS (EI) m/z: calcd. for $C_{25}H_{27}IN_2O_2$ ([M]$^+$) 514.1111, found 514.1105.

α,β-Unsaturated ester 11



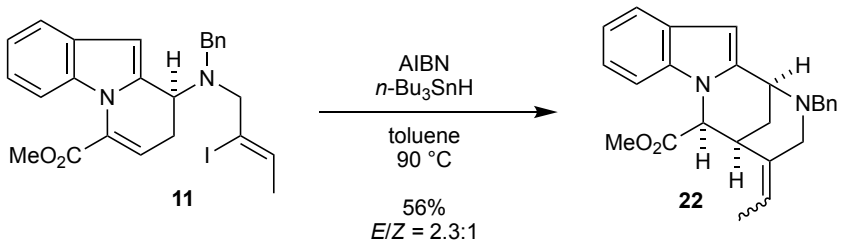
To a solution of *i*-Pr_2NH (1.5 mL, 11 mmol) in THF (4.5 mL) was added *n*-BuLi (2.34 M in hexane, 4.0 mL, 9.4 mmol) at 0 °C and stirred for 30 minutes. After cooling to –78 °C, to the resulting solution was added a solution of tertiary amine **20** (3.70 g, 7.20 mmol) in THF (100 mL) and the mixture was stirred for 30 minutes at the same temperature. To the reaction mixture was added a solution of PhSeSePh (2.92 g, 9.36 mmol) in THF (40 mL) at –78 °C. After stirring at the same temperature for 30 minutes, the reaction was quenched with saturated aqueous NH_4Cl and the resulting mixture was extracted with EtOAc three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was filtered off through a pad of silica gel and the filtered cake was washed with (hexane-EtOAc = 5:1) to separate the crude phenyl selenide **21** and starting material **20**. The filtrate was concentrated under the reduced pressure to give a crude phenyl selenide and starting material **20** (1.70 g, 3.30 mmol, 46%). This reaction was repeated with the recovered starting material **20**.

To a solution of *i*-Pr_2NH (1.1 mL, 7.8 mmol) in THF (3.0 mL) was added *n*-BuLi (2.34 M in hexane, 3.0 mL, 7.0 mmol) at 0 °C and stirred for 30 minutes. After cooling to –78 °C, to the resulting solution was added a solution of recovered **20** (1.70 g, 3.30 mmol) in THF (30 mL) and stirred for 30 minutes at the same temperature. To the reaction mixture was added a solution of PhSeSePh (2.06 g, 6.60 mmol) in THF (36 mL) at –78 °C. After stirring at the same temperature for 30 minutes, the reaction was quenched with saturated aqueous NH_4Cl and the resulting mixture was extracted with EtOAc three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was filtered off through a pad of silica gel and the filtered cake was washed with (hexane-EtOAc = 5:1). The filtrate was concentrated under the reduced pressure to give a crude phenyl selenide **21**. The combined crude phenyl selenide **21** was subjected to the next reaction without further purification.

To a solution of the crude phenyl selenide **21** in CH_2Cl_2 (74 mL) was added 30% aqueous

H_2O_2 (1.3 mL, 11 mmol) at –10 °C. After stirring for 20 minutes at the same temperature, the reaction was quenched with saturated aqueous $Na_2S_2O_3$ and the resulting mixture was extracted with EtOAc three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under the reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane-EtOAc = 5:1) to afford the α,β-unsaturated ester **11** (1.91 g, 3.72 mmol, 52% for 2 steps) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, *J* = 7.2 Hz, 1H), 7.53 (d, *J* = 7.6 Hz, 2H), 7.35 (dd, *J* = 7.6, 7.2 Hz, 2H), 7.18–7.08 (m, 3H), 6.83 (s, 1H), 6.45 (dd, *J* = 5.6, 4.8 Hz, 1H), 6.05 (q, *J* = 6.4 Hz, 1H), 4.20 (dd, *J* = 6.4, 5.6 Hz, 1H), 3.98 (d, *J* = 14.8 Hz, 1H), 3.93 (s, 3H), 3.68 (d, *J* = 14.8 Hz, 1H), 3.59 (d, *J* = 14.8 Hz, 1H), 3.40 (d, *J* = 14.8 Hz, 1H), 2.60 (ddd, *J* = 6.4, 5.6, 5.6 Hz, 1H), 2.49 (ddd, *J* = 6.4, 6.4, 4.8 Hz, 1H), 1.81 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.6, 139.2, 136.6, 134.7, 132.2, 130.2, 129.0, 128.50, 128.46, 127.2, 122.0, 121.5, 120.8, 120.6, 111.9, 109.8, 102.2, 61.6, 53.7, 52.6, 52.5, 23.0, 22.0; IR (neat, cm^{-1}): 3025, 2807, 1731, 1635, 1458, 1281, 1154, 753; HRMS (ESI) m/z: calcd. for $C_{25}H_{26}IN_2O_2$ ([M+H]$^+$) 513.1033, found 513.1023.

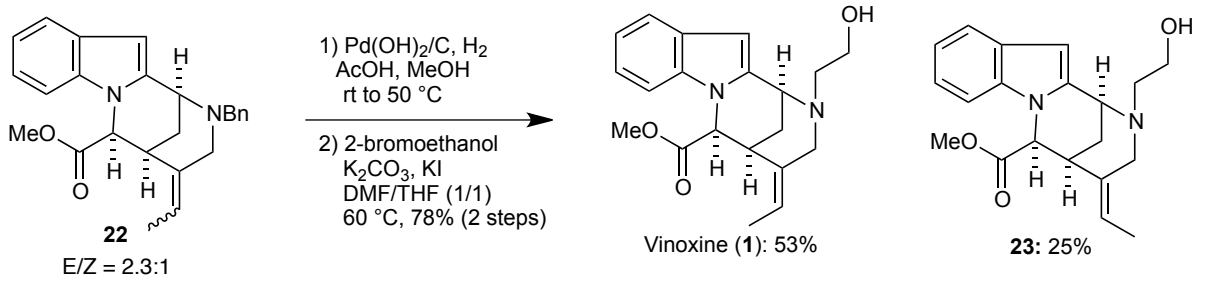
Bicyclic amines 22



A solution of α,β-unsaturated ester **11** (1.15 g, 2.24 mmol) in toluene (200 mL) was degassed by freeze-pump-thaw cycles for twice. The resultant solution was heated to reflux, and the degassed solution of AIBN (197 mg, 1.29 mmol) and *n*-Bu_3SnH (2.6 mL, 9.6 mmol) in toluene (20 mL) was added to the reaction mixture via a syringe pump over an hour. After stirring for more 1.5 hours at reflux, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was filtered a pad of 10% w/w K_2CO_3 in silica gel and the filtered cake was washed with hexane to EtOAc. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexanes-EtOAc = 4:1) to afford bicyclic amines **22** (486 mg, 1.26 mmol, 56%) as pale yellow foams. R_f = 0.28 (hexanes-EtOAc = 4:1); ^{1}H NMR (400 MHz, $CDCl_3$, a mixture of isomers): δ 7.81–7.79 (m, 1H), 7.63–7.58 (m, 1H), 7.54–7.45

(m, 2H), 7.43–7.40 (m, 2H), 7.34–7.28 (m, 2H), 7.12–7.10 (m, 1H), 5.61 (q, J = 6.8 Hz, 0.7H), 5.55 (q, J = 6.8 Hz, 0.3H), 5.18 (d, J = 6.0 Hz, 0.7H), 5.11 (d, J = 6.4 Hz, 0.3H), 4.26–4.25 (m, 1H), 4.01–3.94 (m, 0.7H), 3.95 (d, J = 13.2 Hz, 0.3H), 3.89 (s, 2.1H), 3.88 (d, J = 13.6 Hz, 0.7H), 3.87 (s, 0.9H), 3.73 (d, J =13.2 Hz, 0.3H), 3.65 (d, J = 13.4 Hz, 0.7H), 3.61 (d, J = 13.2 Hz, 0.3H), 3.38–3.36 (m, 0.3H), 3.13 (d, J = 13.2 Hz, 0.7H), 3.09 (d, J = 13.2 Hz, 0.7H), 2.83 (d, J = 13.2 Hz, 0.3H), 2.49 (ddd, J = 12.0, 3.2, 3.2 Hz, 0.3H), 2.41 (ddd, J = 12.4, 3.2, 3.2 Hz, 0.7H), 2.23–2.15 (m, 1H), 1.82 (d, J = 6.8 Hz, 2.1H), 1.70 (d, J = 6.8 Hz, 0.9H); ^{13}C NMR (100 MHz, $CDCl_3$, a mixture of isomers): δ 1704, 139.0, 138.9, 136.6, 134.4, 133.54, 133.47, 129.3, 129.1, 128.54, 128.52, 128.2, 127.2, 122.0, 121.58, 121.55, 120.64, 120.60, 120.4, 120.3, 110.1, 102.1, 102.0, 61.5, 60.3, 59.65, 59.56, 55.9, 52.3, 52.4, 50.7, 50.4, 47.9, 40.4, 31.5, 31.34, 31.28, 13.0, 12.7 (six signals are missing due to the overlap); IR (neat, cm^{-1}): 3027, 2950, 2810, 1759, 1459, 1331, 1172, 1017, 753; HRMS (ESI) m/z: calcd. for $C_{25}H_{27}N_2O_2$ ([M+H]$^+$) 387.2067, found 387.2050.

Vinoxine (1) and its geometric isomer 23

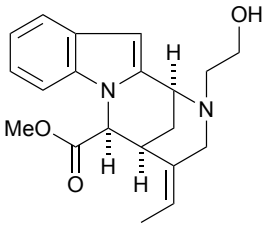


To a stirred suspension of bicyclic amines **22** (68.3 mg, 0.176 mmol) and in MeOH (8.8 mL) was added 20% wet 5% $Pd(OH)_2/C$ (12.5 mg, 8.80 μmol). After stirring under the hydrogen atmosphere (1 atm) at room temperature for an hour, AcOH (20 μL, 0.35 mmol) was added to the reaction mixture and heated at 50 °C. After stirring for additional 3 hours, the resulting suspension was filtered through a pad of Celite and the filter cake was washed with EtOAc. The filtrated was washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was subjected to the next reaction without further purification.

To a suspension of the above crude amine, KI (146 mg, 0.880 mmol) and K_2CO_3 (73.0 mg, 0.528 mmol) in DMF/THF (1/1 v/v, 2 mL) was added 2-bromoethanol (37 μL, 0.53 mmol). After stirring at 60 °C for 3 hours, additional 2-bromoethanol (18 μL, 0.26 mmol) was added. After stirring for additional 2 hours at the same temperature, the reaction mixture was cooled at room temperature and water was added to the mixture. The resultant mixture was extracted with EtOAc

three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC (CH_2Cl_2-MeOH = 20:1) to afford vinoxine **1** (32.0 mg, 0.0941 mmol, 53% for 2 steps) and geometric isomer **23** (14.2 mg, 0.388 mmol, 25% for 2 steps) as white foams, respectively.

Vinoxine (1)

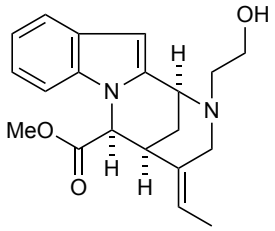


Vinoxine (**1**)

R_f = 0.38 (CH_2Cl_2-MeOH = 10:1); ^{1}H NMR (400 MHz, C_6D_6): δ 7.71–7.68 (m, 1H), 7.24–7.19 (m, 2H), 7.06–7.02 (m, 1H), 6.14 (s, 1H), 5.17 (q, *J* = 6.4 Hz, 1H), 4.60 (d, *J* = 6.0 Hz, 1H), 3.72–3.71 (m, 1H), 3.59–3.49 (m, 2H), 3.29–3.28 (m, 1H), 3.20 (s, 3H), 2.96 (d, *J* = 12.4 Hz, 1H), 2.83 (d, *J* =12.4 Hz, 1H), 2.62 (ddd, *J* = 12.0, 7.2, 4.8 Hz, 1H), 2.48–2.17 (m, 1H), 2.14 (ddd, *J* = 12.0, 4.8, 4.8 Hz, 1H), 1.80 (ddd, *J* = 12.8, 3.6, 3.6 Hz, 1H), 1.45–1.42 (m, 1H), 1.41 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (150 MHz, C_6D_6): δ 169.9, 137.2, 134.8, 133.3, 128.9, 121.8, 121.44, 121.41, 121.0, 110.5, 102.0, 60.1, 58.0, 56.9, 55.2, 52.0, 51.4, 31.3, 30.9, 12.4.

^{1}H NMR (600 MHz, $CHCl_3$): δ 7.60 (d, *J* = 7.2 Hz, 1H), 7.17–7.12 (m, 2H), 6.93 (d, *J* = 7.2 Hz, 1H), 6.34 (s, 1H), 5.51 (q, *J* = 6.0 Hz, 1H), 4.13 (dd, *J* = 3.6, 3.0 Hz, 1H), 3.80 (ddd, *J* = 6.0, 3.6, 3.0 Hz, 1H) , 3.74 (s, 3H), 3.71–3.68 (m, 1H), 3.64 (ddd, *J* = 10.8, 7.2, 3.6 Hz, 1H), 3.00 (d, *J* = 12.6 Hz, 1H), 2.95 (d, *J* = 12.6 Hz, 1H), 2.89 (ddd, *J* =12.6, 7.2, 4.8 Hz, 1H), 2.77–2.63 (m, 1H), 2.45 (ddd, *J* = 12.6, 4.8, 3.6 Hz, 1H), 2.25 (ddd, *J* = 12.6, 3.6, 3.0 Hz, 1H), 2.09 (ddd, *J* = 12.6, 3.0, 3.0 Hz, 1H), 1.68 (d, *J* = 6.0 Hz, 1H); δ 170.2, 136.5, 133.9, 133.3, 128.1, 122.2, 121.6, 120.6, 120.3, 110.0, 101.7, 60.1, 57.9, 56.4, 54.9, 52.2, 51.8, 31.2, 31.1, 12.5. IR (neat, cm^{-1}): 3436, 2949, 1758, 1460, 1202, 1173, 1009, 752,; HRMS (ESI) m/z: calcd. For $C_{20}H_{24}N_2O_3$ ([M+H]$^+$) 341.1860, found 341.1857.

19,20-Z-vinoxine (**23**)

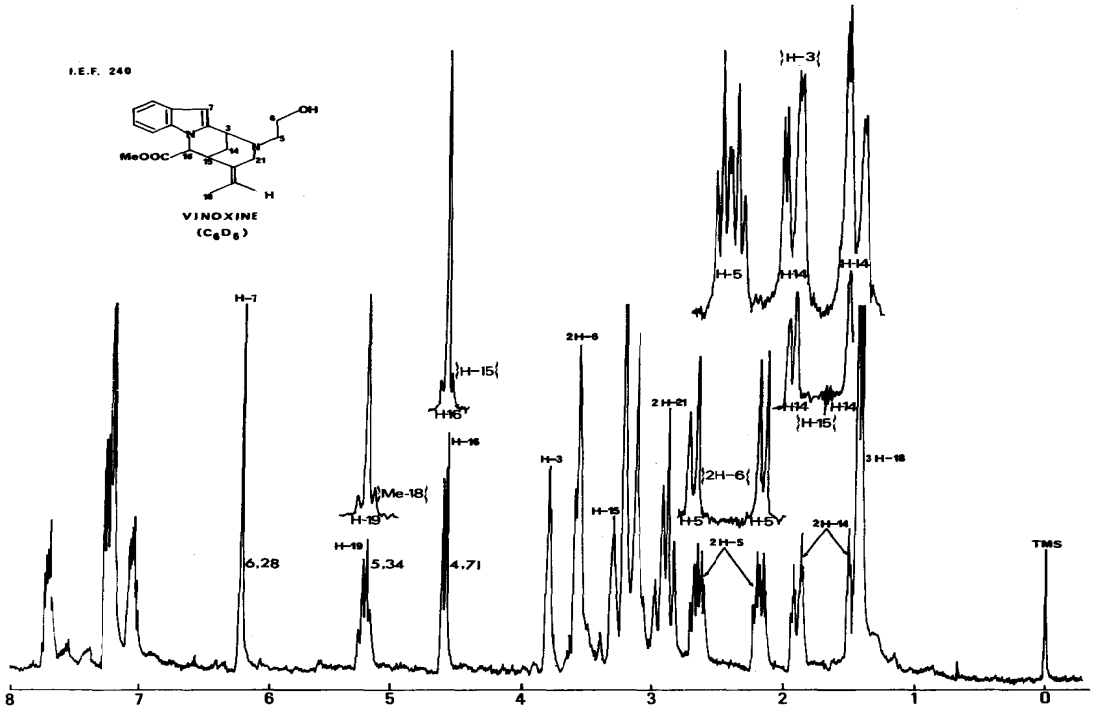


23

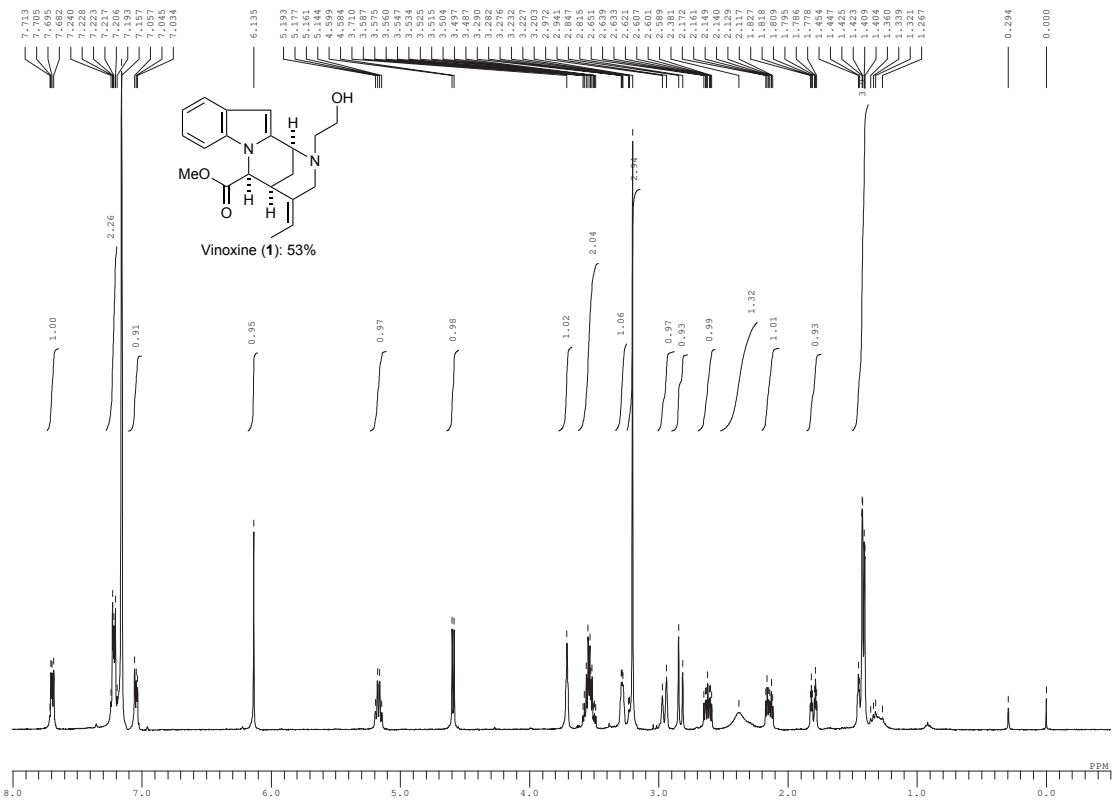
R_f = 0.41 (CH_2Cl_2-MeOH = 10:1); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.60 (d, *J* = 7.2 Hz, 1H), 7.17–7.08 (m, 2H), 6.94 (d, *J* = 7.8 Hz, 1H), 6.34 (s, 1H), 5.42 (d, *J* = 7.2 Hz, 1H), 4.96 (d, *J* = 6.0 Hz, 1H), 4.14 (dd, *J* = 3.6, 2.4 Hz, 1H), 3.75–3.67 (m, 2H), 3.72 (s, 3H), 3.47 (d, *J* = 13.8 Hz, 1H), 3.22 (ddd, *J* = 6.0, 3.6, 2.4 Hz, 1H), 2.94 (ddd, *J* = 12.6, 7.2, 4.2 Hz, 1H), 2.69 (d, *J* = 13.8 Hz, 1H), 2.51 (ddd, *J* = 12.6, 6.0, 4.2 Hz, 1H), 2.33 (ddd, *J* = 12.6, 3.6, 3.6 Hz, 1H), 2.08 (ddd, *J* = 12.6, 2.4, 2.4 Hz, 1H), 1.61 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 170.2, 136.5, 133.7, 133.3, 128.1, 122.3, 121.6, 120.5, 120.3, 110.0, 101.7, 61.2, 57.9, 56.6, 52.1, 51.5, 46.9, 40.2, 31.4, 12.9; IR (neat, cm^{-1}): 3413, 2949, 1758, 1460, 1201, 1173, 1017, 752; HRMS (ESI) m/z: calcd. for $C_{20}H_{24}N_2O_3$ ($[M+H]^+$) 341.1860, found 341.1877.

3. Comparision of Natural and Synthetic (±)-Vinoxine

Natural vinoxine (**1**)[1], ^{1}H-NMR (240 MHz, C_6D_6)



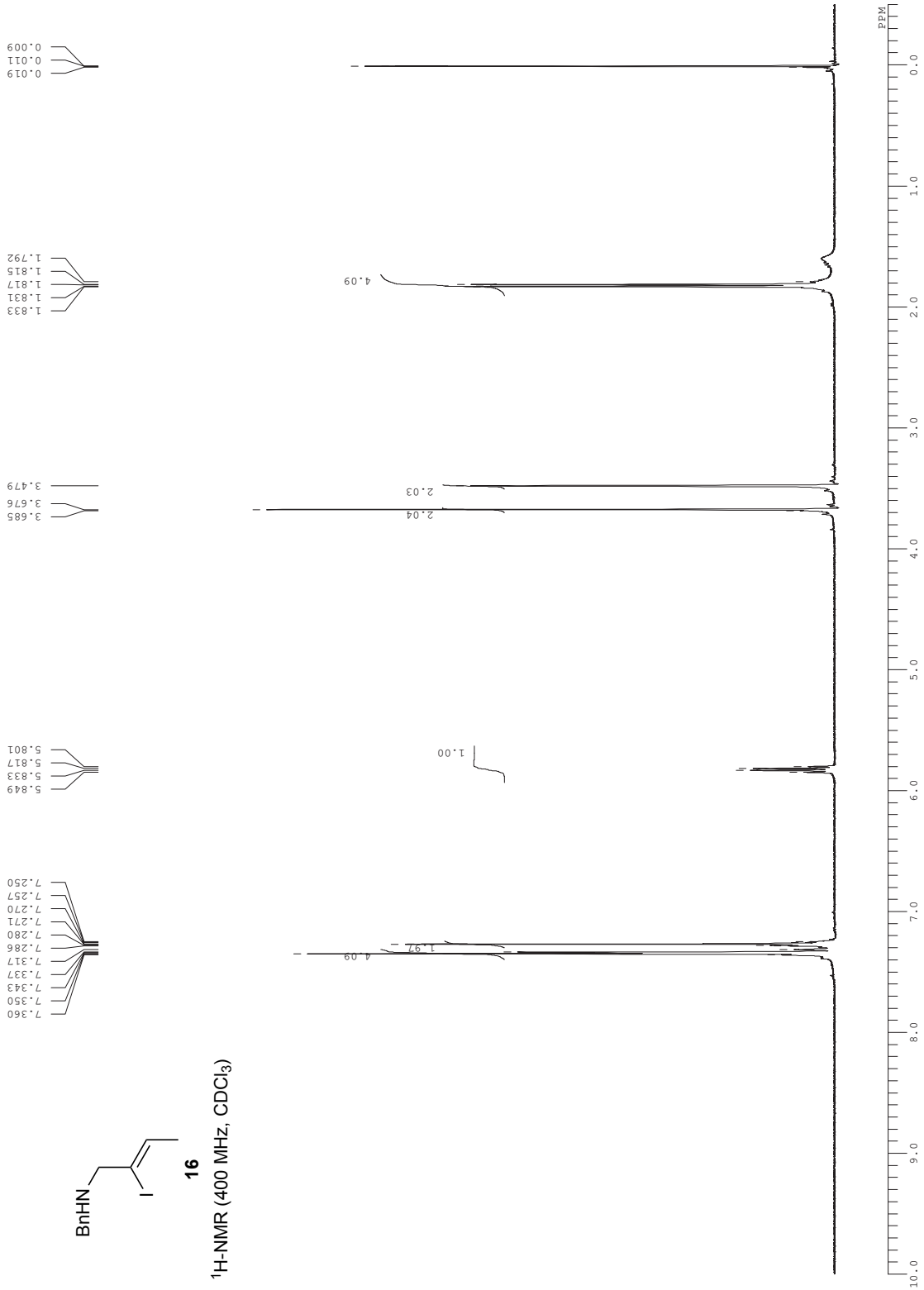
Synthetic vinoxine (**1**), ^{1}H-NMR (400 MHz, C_6D_6)

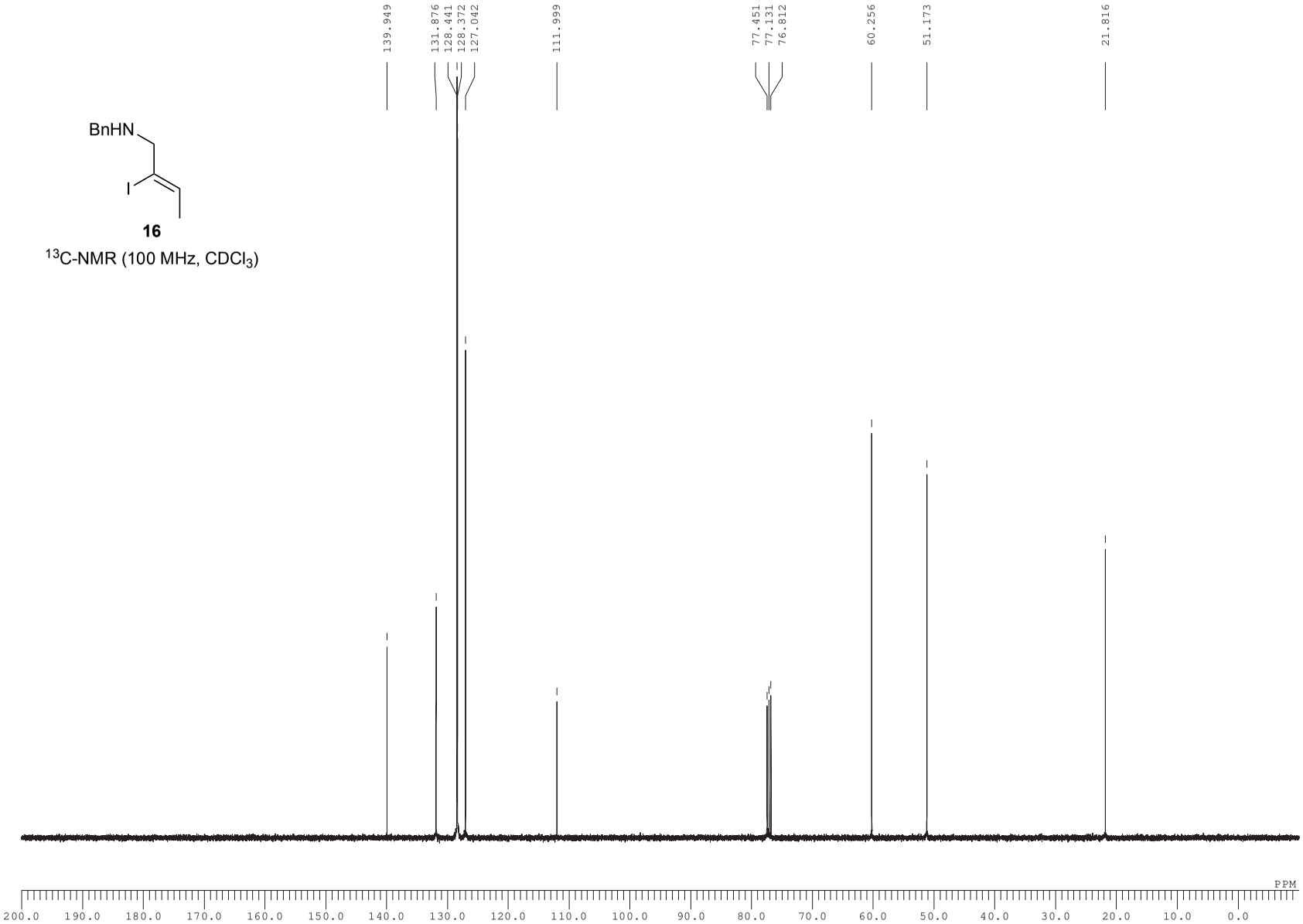


Chemical shifts of ^{13}C NMR for synthetic vinoxine (**1**)

Our synthetic (150 MHz, $CDCl_3$)	Bosch's synthetic[2] (60 MHz, $CDCl_3$)	Natural[1] (60 MHz, the deuterated solvent is unclear)	$\Delta\delta = \delta$ Bosch's report	$\Delta\delta = \delta$ Tomko's report
170.2	170.1	169.4	0.1	0.6
136.5	136.5	136.0	0.0	0.5
133.9	133.8	133.3	0.1	0.6
133.3	133.2	132.7	0.1	0.6
128.1	128.1	127.6	0.0	0.5
122.2	122.3	121.9	–0.1	0.3
121.6	121.6	120.0	0.0	1.6
120.6	120.6	119.3	0.0	1.6
120.3	120.3	118.9	0.0	0.4
110.0	110.0	108.5	–0.1	0.5
101.7	101.8	101.5	–0.1	0.2
60.1	60.0	59.9	0.1	0.2
57.9	58.0	57.7	–0.1	0.2
56.4	56.5	56.2	–0.1	0.2
54.9	55.0	54.7	–0.1	0.2
52.2	52.2	51.7	0.0	0.5
51.8	51.8	51.5	0.0	0.3
31.2	31.1	31.1	0.1	0.1
31.1	31.0	31.1	0.1	0.0
12.5	12.6	12.4	–0.1	0.1

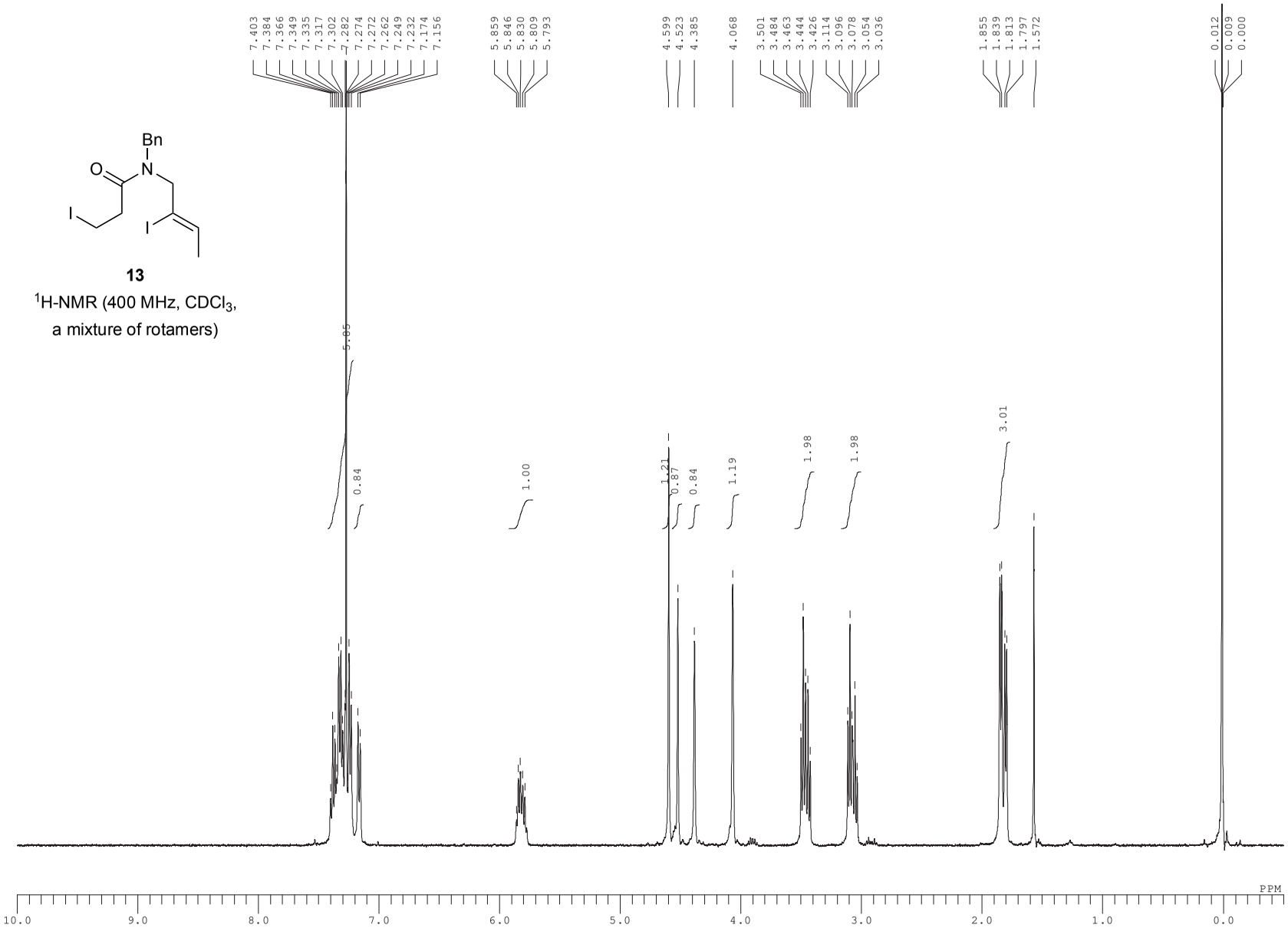
4. NMR chart

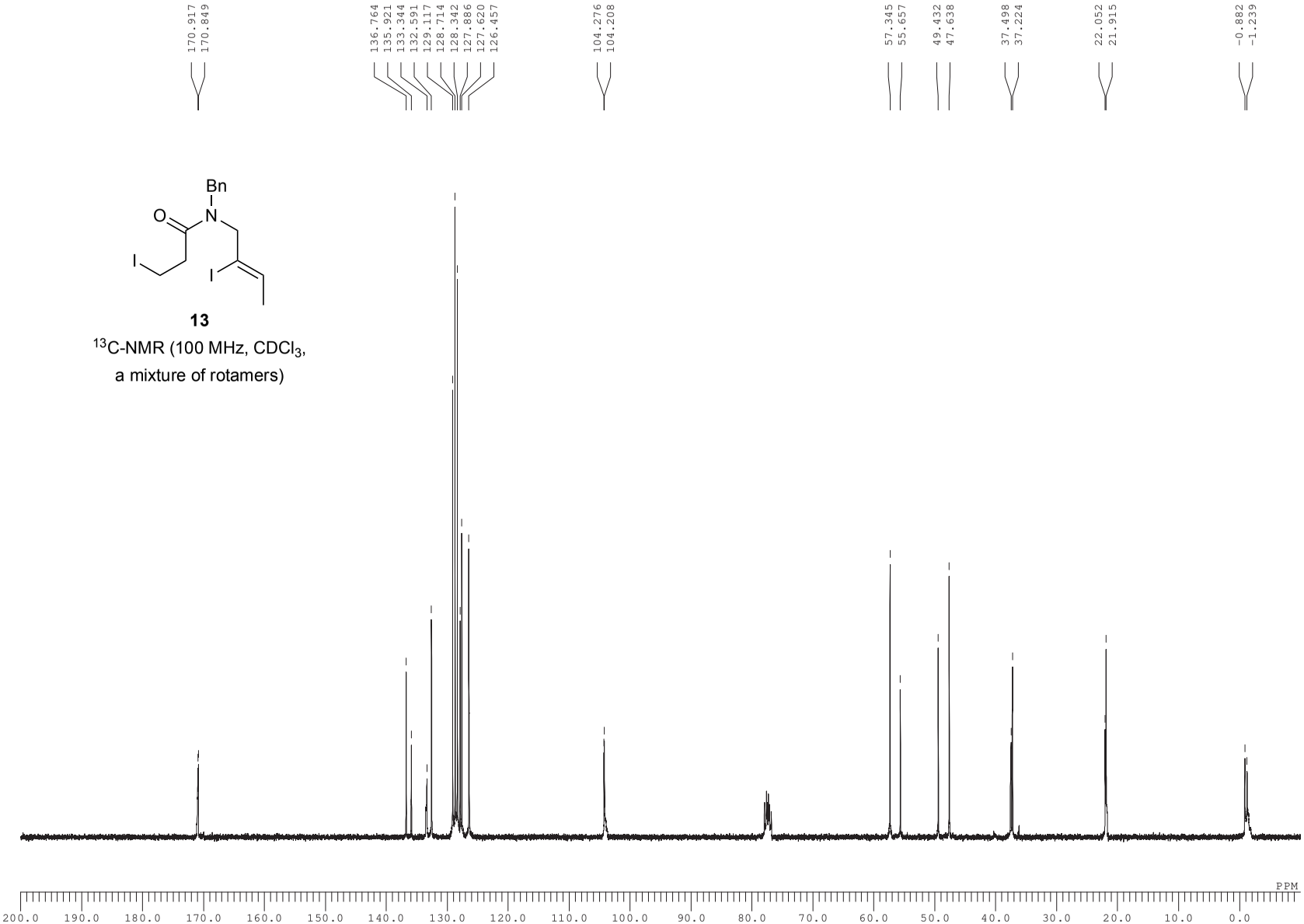

BnHN
I
16
1H-NMR (400 MHz, CDCl3)
7.360
7.350
7.343
7.337
7.317
7.286
7.280
7.271
7.270
7.257
7.250
5.849
5.833
5.817
5.801
3.685
3.676
3.479
1.833
1.831
1.817
1.815
1.792
0.019
0.011
0.009
4.09
1.97
4.09
1.00
2.04
2.03
PPM


BnHN
I
16
^{13}C-NMR (100 MHz, $CDCl_3$)
139.949
131.876
128.441
128.372
127.042
111.999
77.451
77.131
76.812
60.256
51.173
21.816
PPM
200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0.0

13

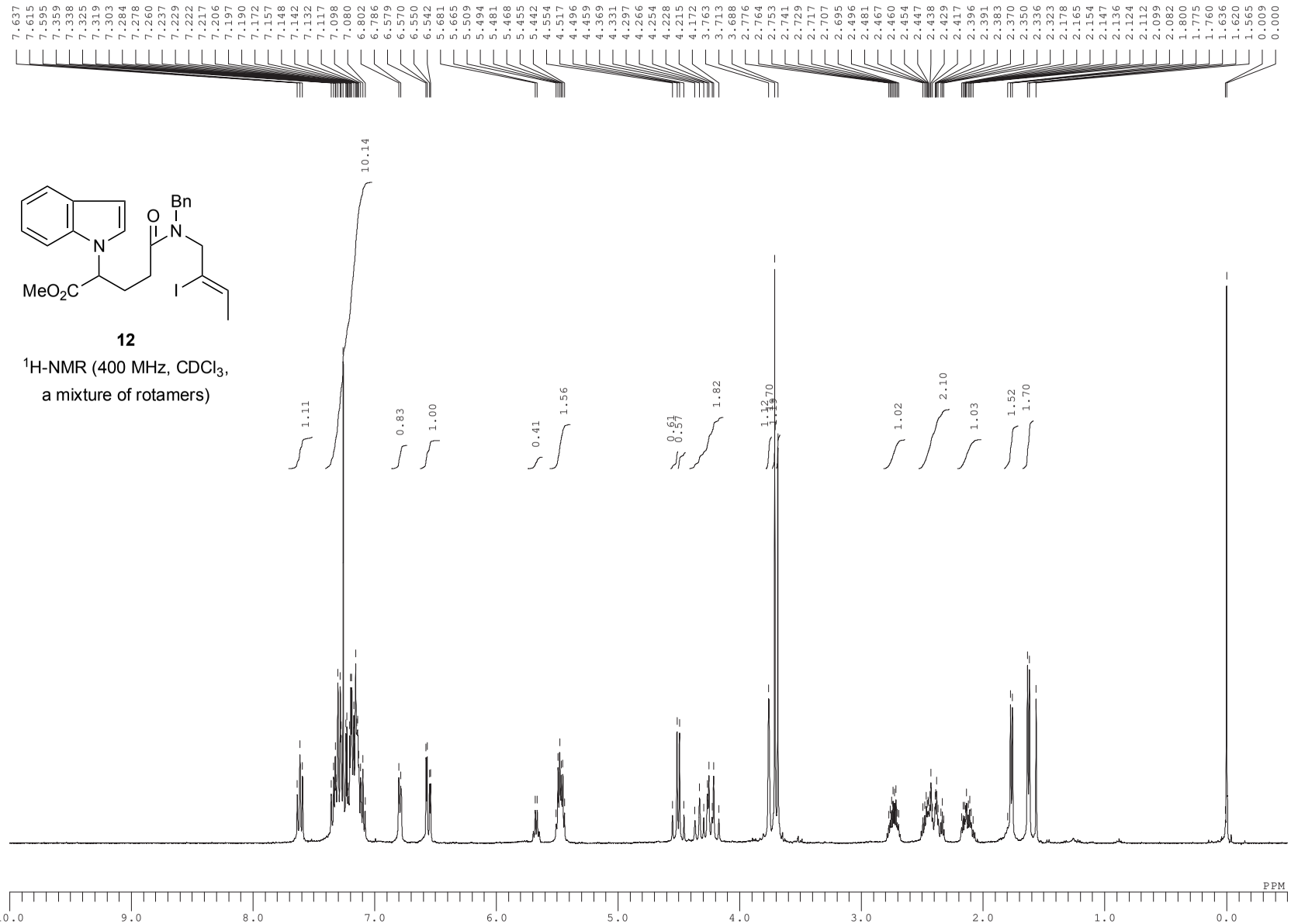
^{1}H-NMR (400 MHz, $CDCl_3$,
a mixture of rotamers)

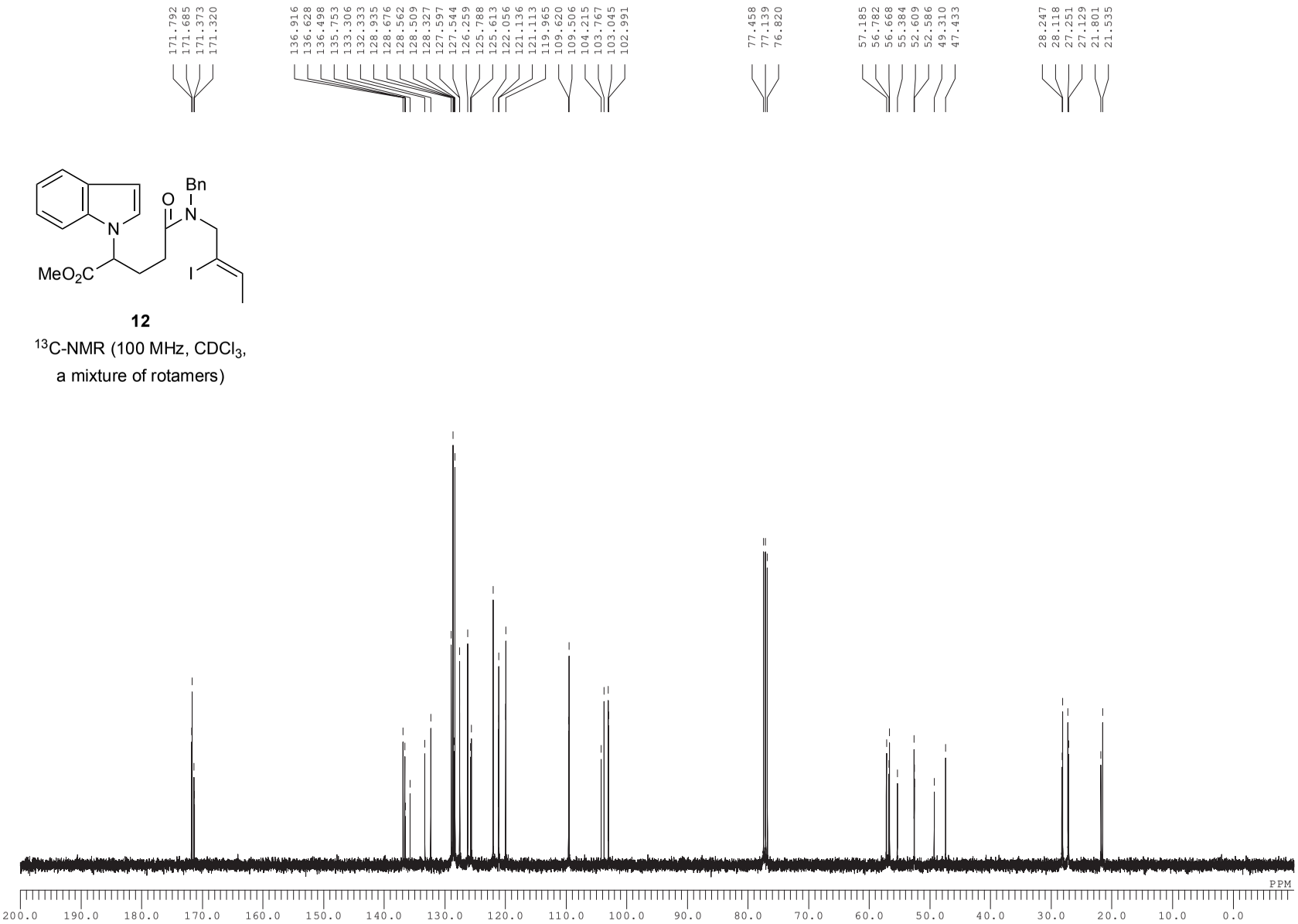




13

^{13}C-NMR (100 MHz, $CDCl_3$, a mixture of rotamers)


Bn
O
N
N
MeO2C
I
12
1H-NMR (400 MHz, CDCl3,
a mixture of rotamers)
10.14
1.11
0.83
1.00
0.41
1.56
0.61
0.57
1.82
1.12
1.10
1.70
1.02
2.10
1.03
1.52
1.70
PPM
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

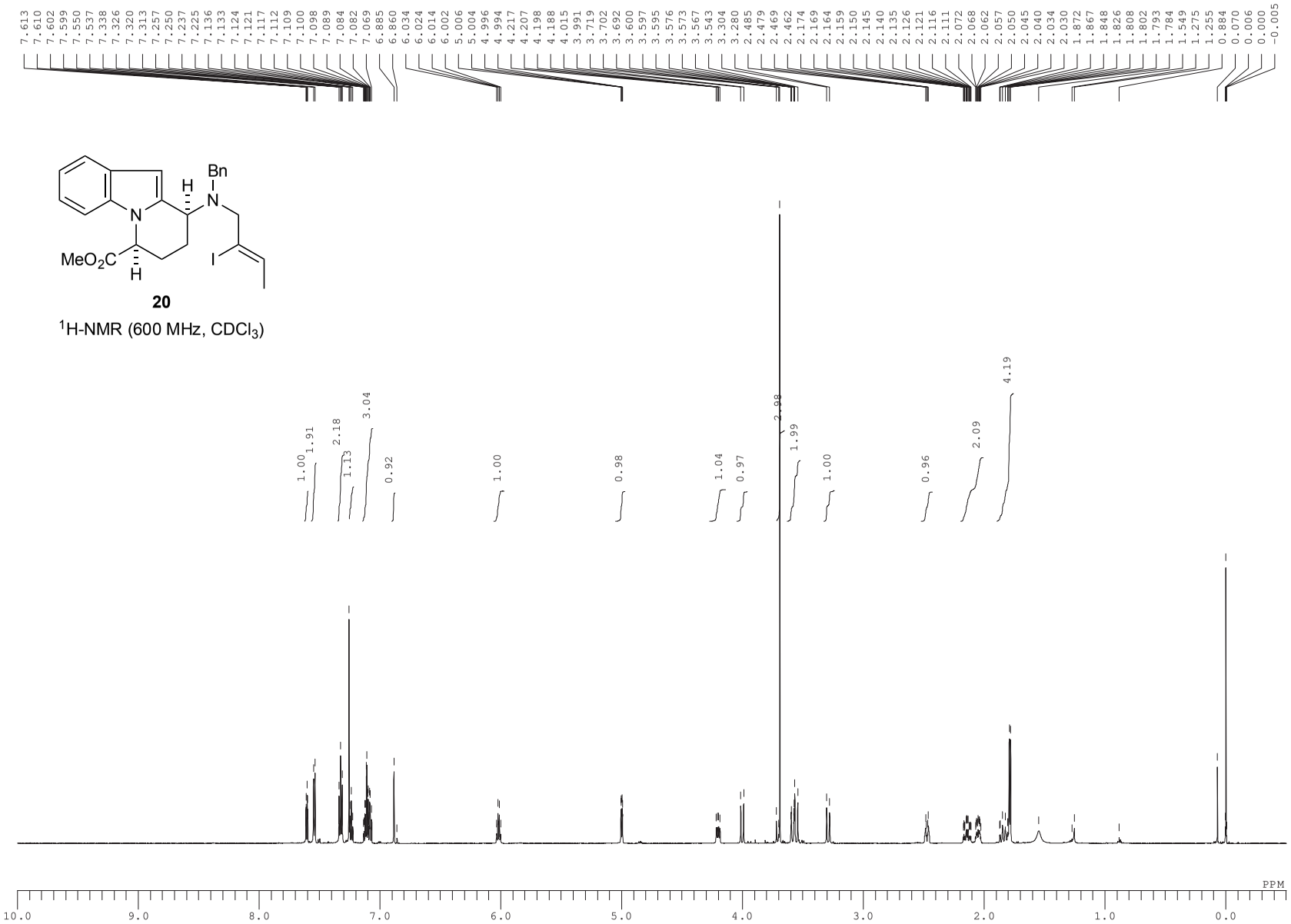


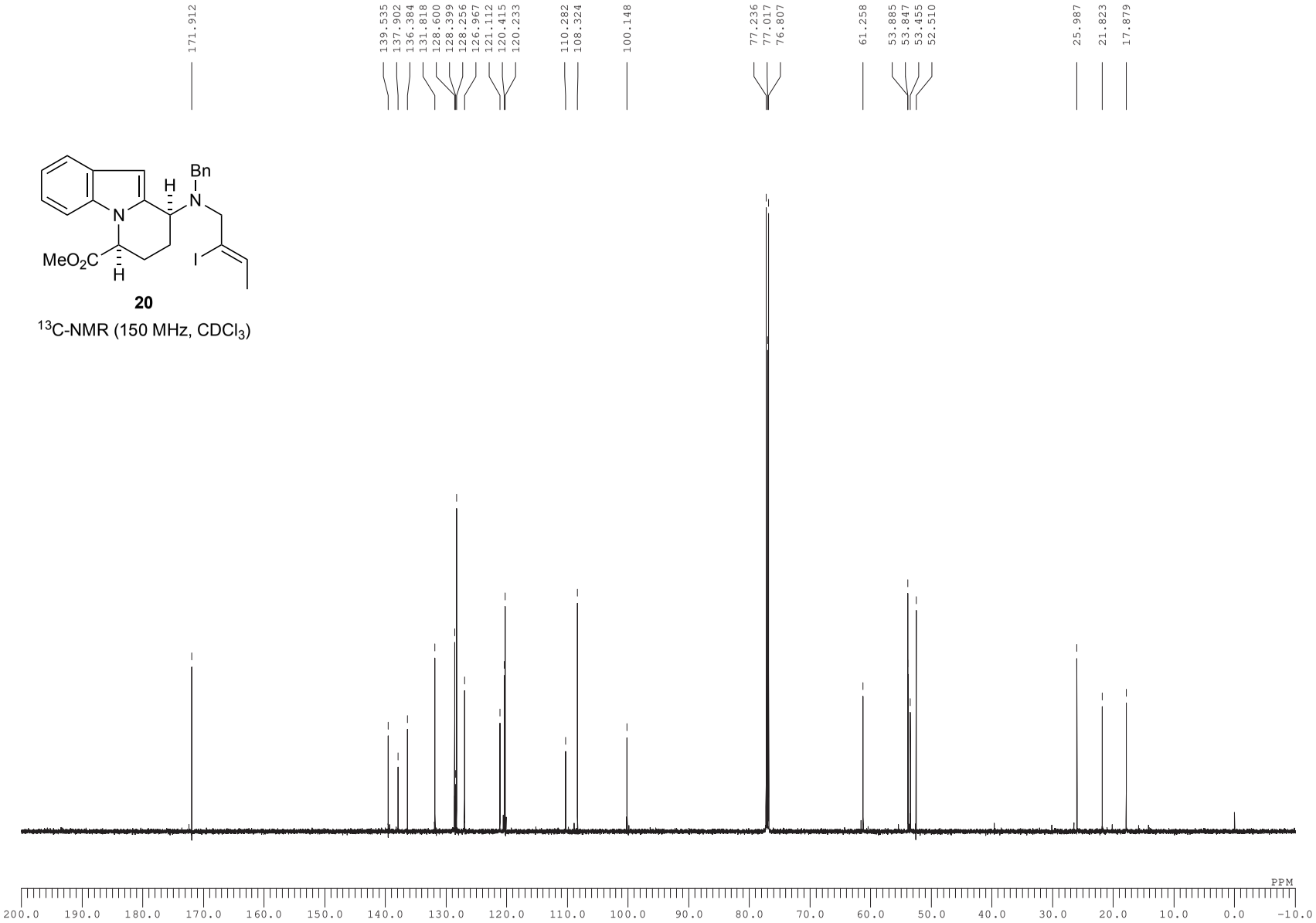
12

^{13}C-NMR (100 MHz, $CDCl_3$, a mixture of rotamers)

20

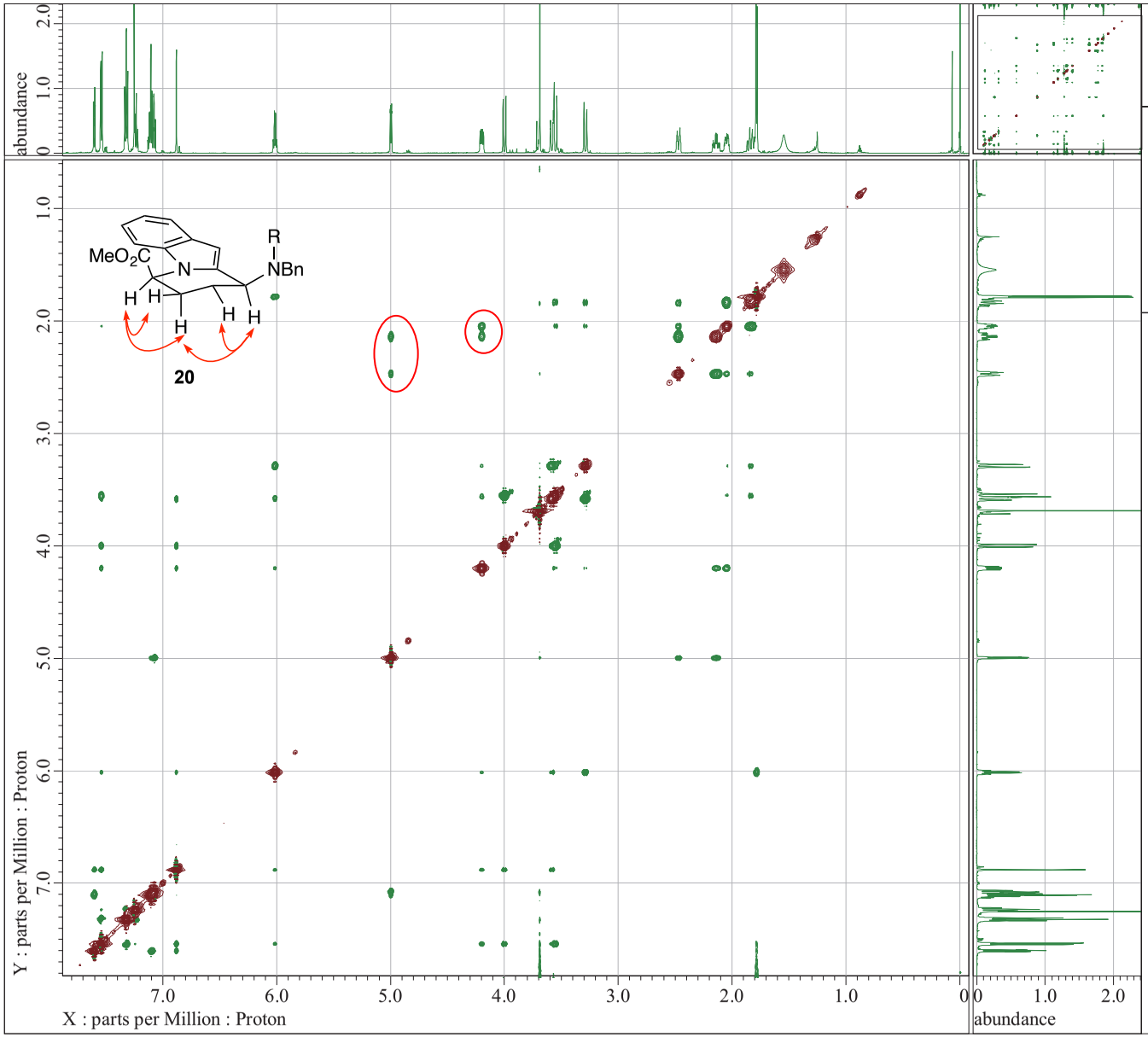
^{1}H-NMR (600 MHz, $CDCl_3$)





20

^{13}C-NMR (150 MHz, $CDCl_3$)



JEOL RESONANCE

```
---- PROCESSING PARAMETERS ----
sexp( 5.0[Hz], 0.0[s] )
trapezoid( 0[%], 0[%], 80[%], 100[%] )
zerofill( 1 )
fft( 1, TRUE, TRUE )
ppm
machinephase
[transpose]
sexp( 5.0[Hz], 0.0[s] )
trapezoid( 0[%], 0[%], 80[%], 100[%] )
zerofill( 2 )
fft( 1, TRUE, TRUE )
ppm
```

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Filename          = ko_11_111_noesy-1-2.jdf
Author            = delta
Experiment        = noesy.jxp
Sample_Id         = ko_11_111
Solvent           = CHLOROFORM-D
Creation_Time     = 25-OCT-2021 20:58:29
Revision_Time     =  4-FEB-2022 15:24:16
Current_Time      =  4-FEB-2022 15:29:00

Comment           = phase sensitive noesy
Data_Format       = 2D COMPLEX COMPLEX
Dim_Size          = 819, 512
Dim_Title         = Proton Proton
Dim_Units         = [ppm] [ppm]
Dimensions        = X Y
Site              = JNM-ECA600
Spectrometer      = DELTA2_NMR

Field_Strength    = 14.02588743[T] (600[MHz])
X_Acq_Duration    = 0.16719872[s]
X_Domain          = 1H
X_Freq            = 597.17144293[MHz]
X_Offset          = 4[ppm]
X_Points          = 1024
X_Prescans        = 4
X_Resolution      = 5.98090703[Hz]
X_Sweep           = 6.1244488[kHz]
X_Sweep_Clipped   = 4.89955904[kHz]
Y_Domain          = 1H
Y_Freq            = 597.17144293[MHz]
Y_Offset          = 4[ppm]
Y_Points          = 256
Y_Prescans        = 0
Y_Resolution      = 19.12952987[Hz]
Y_Sweep           = 4.89715965[kHz]
Irr_Domain        = Proton
Irr_Freq          = 597.17144293[MHz]
Irr_Offset        = 5[ppm]
Tri_Domain        = Proton
Tri_Freq          = 597.17144293[MHz]
Tri_Offset        = 5[ppm]
Clipped           = FALSE
Scans             = 27
Total_Scans       = 6912

Relaxation_Delay  = 1.5[s]
Recvr_Gain        = 44
Temp_Get          = 24.3[dC]
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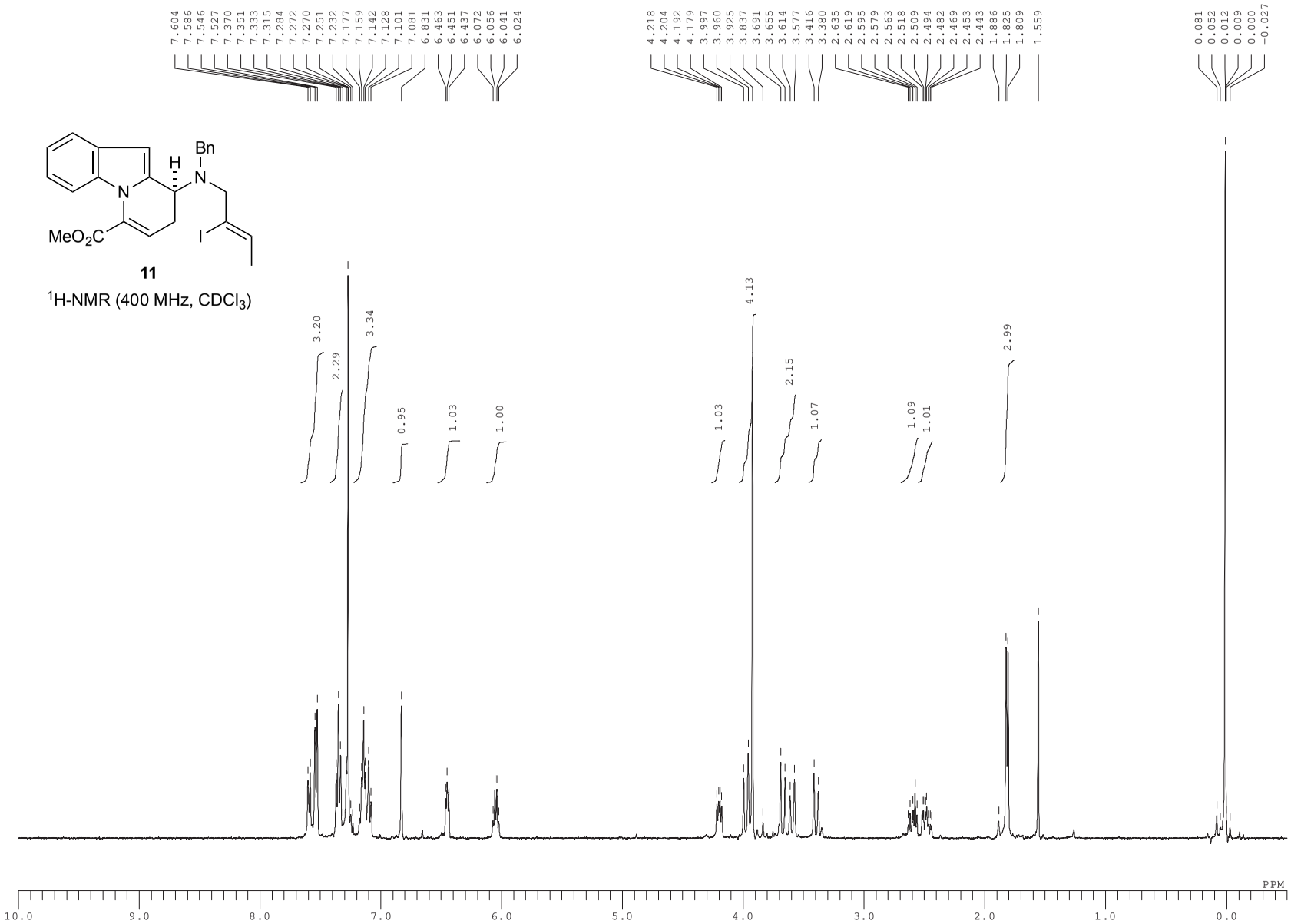
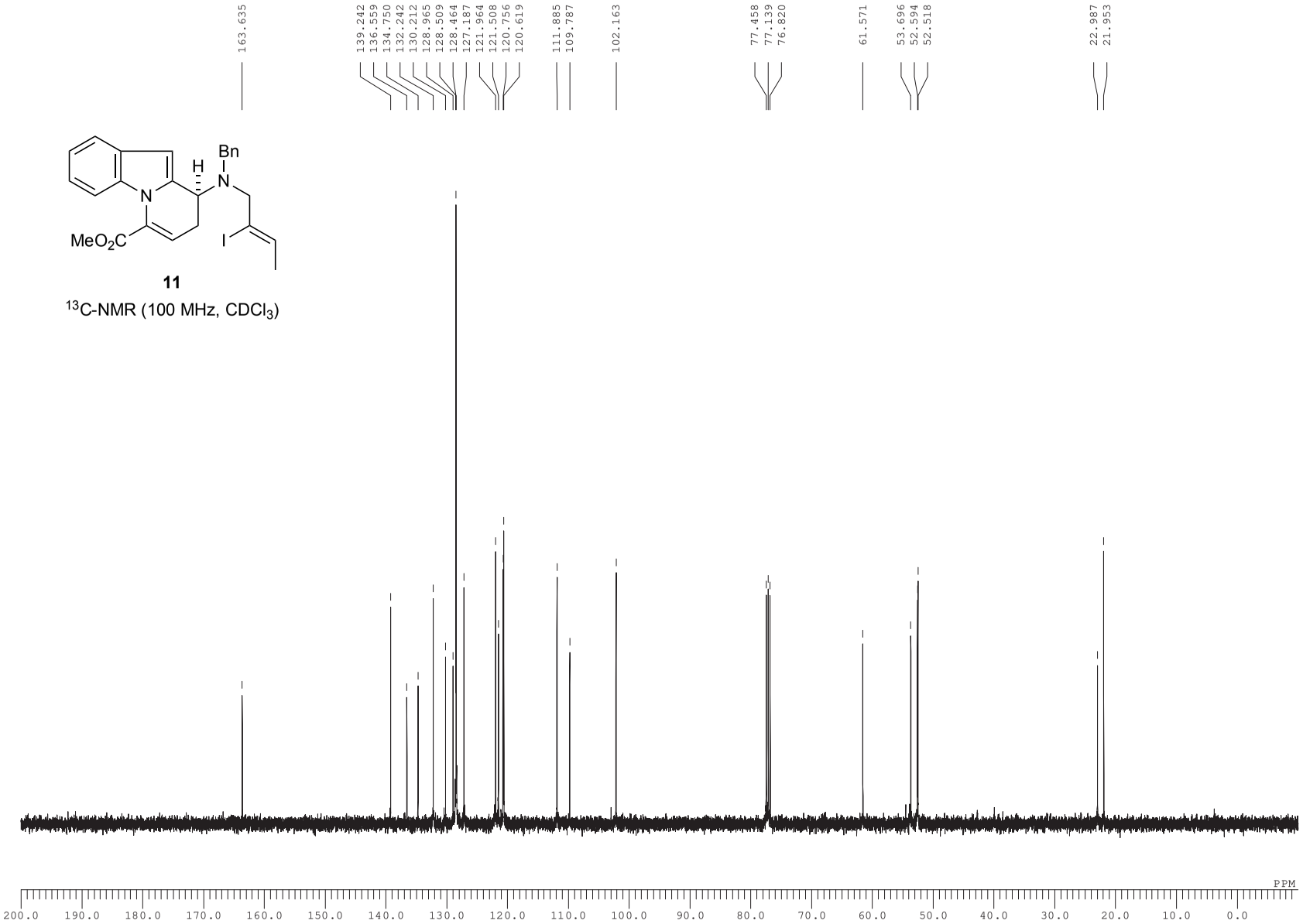
11

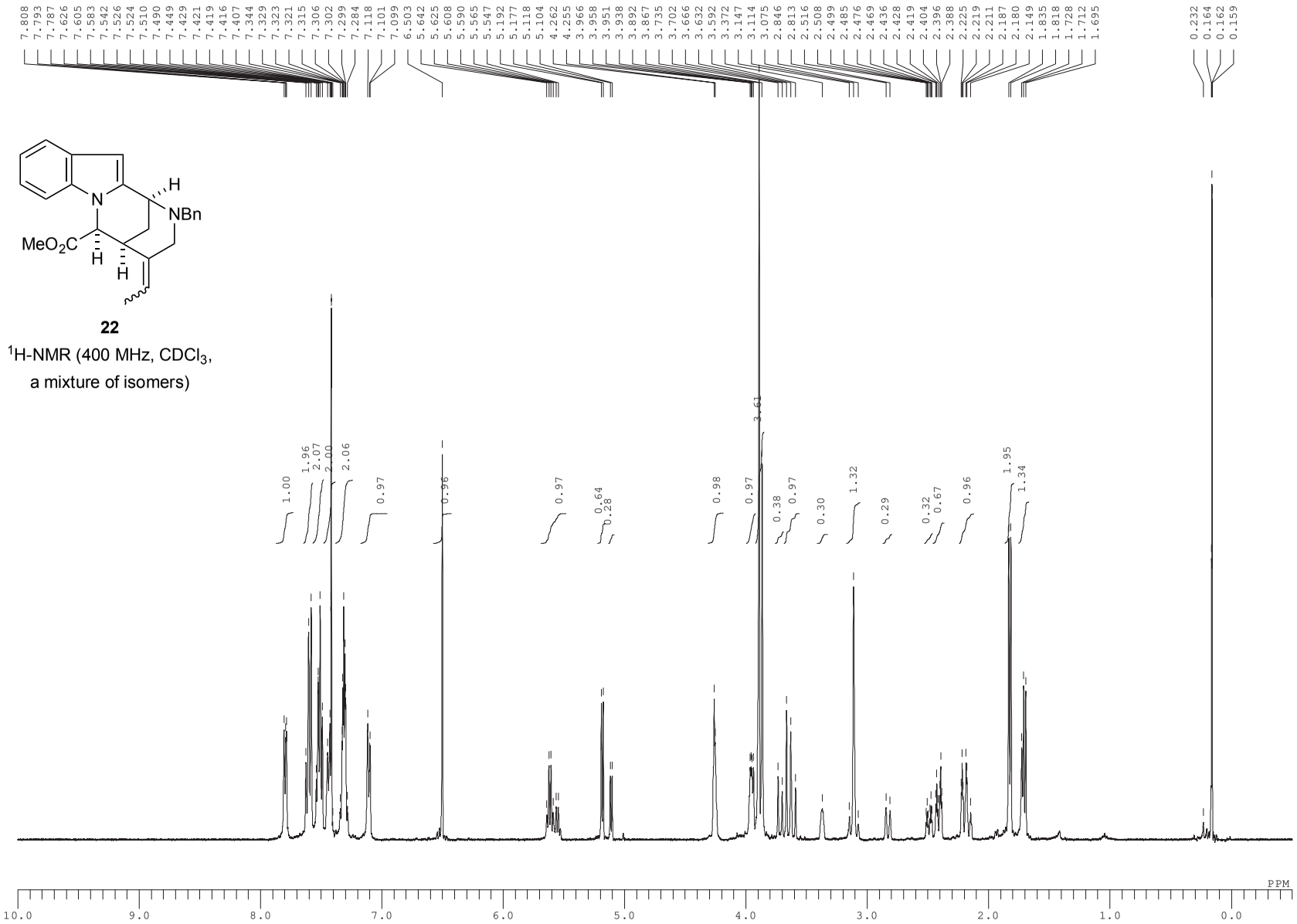
^{1}H-NMR (400 MHz, $CDCl_3$)





11

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

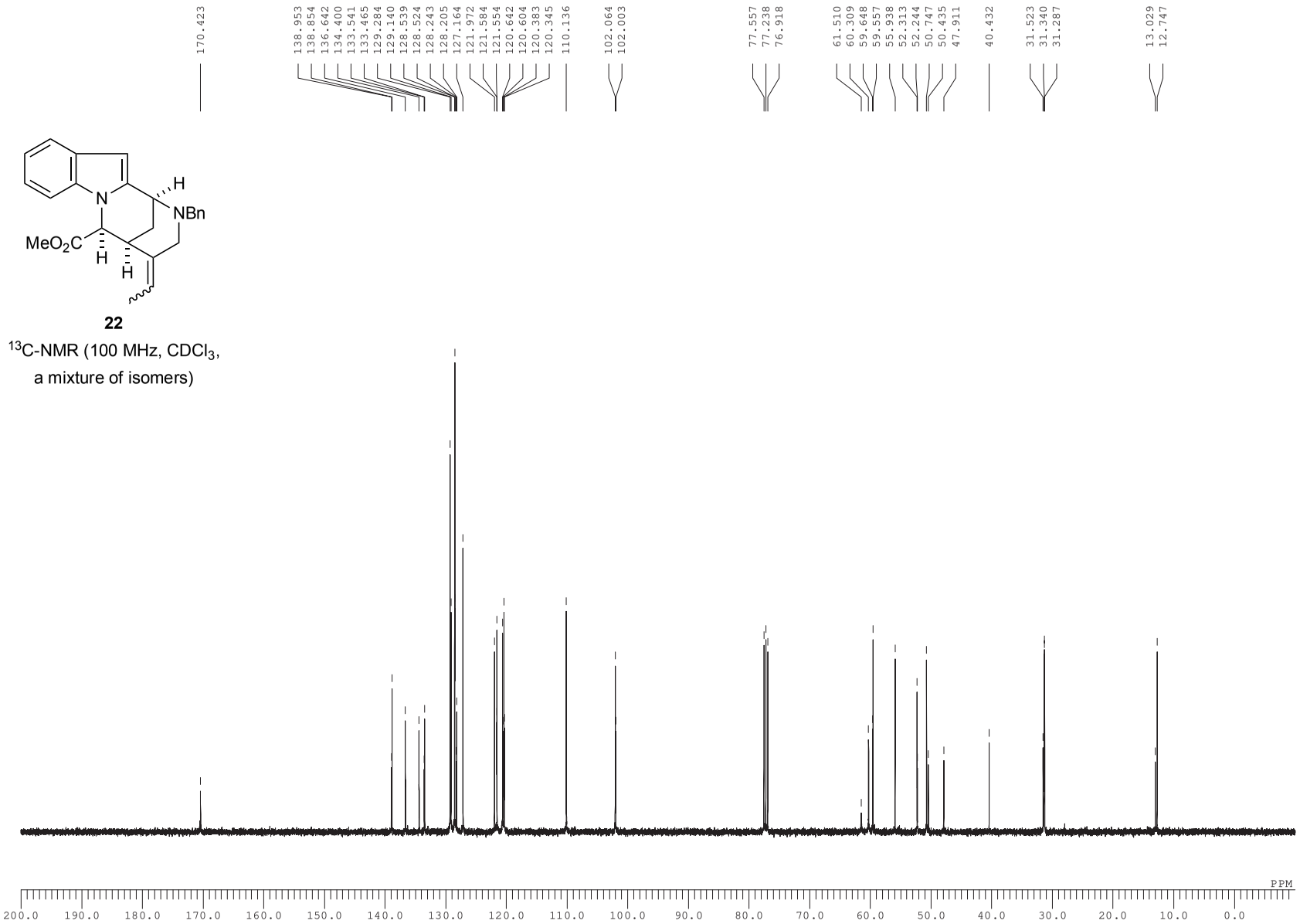


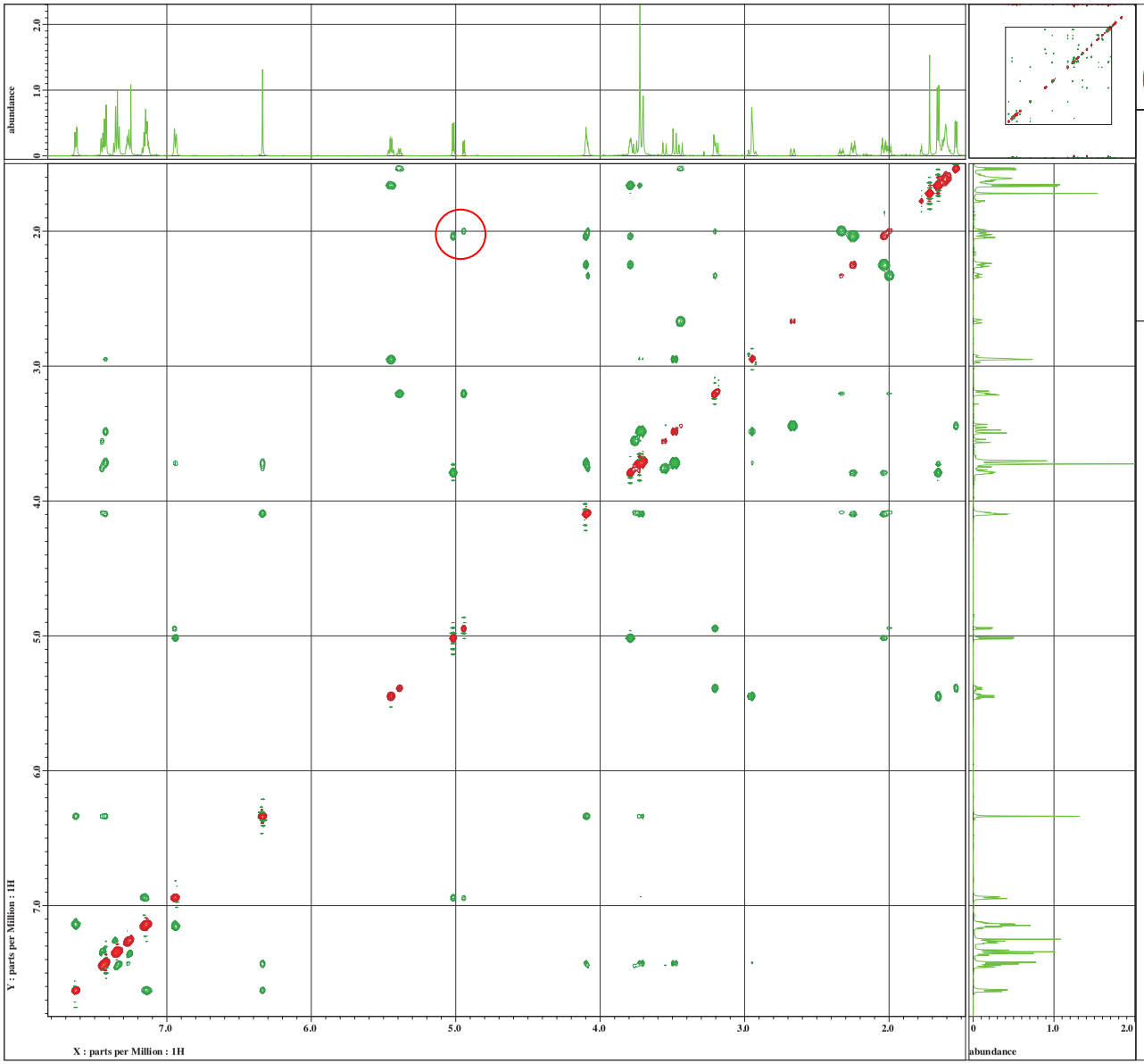
22

^{1}H-NMR (400 MHz, $CDCl_3$, a mixture of isomers)

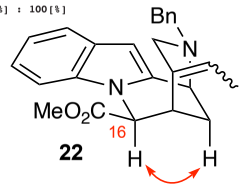
22

^{13}C-NMR (100 MHz, $CDCl_3$, a mixture of isomers)





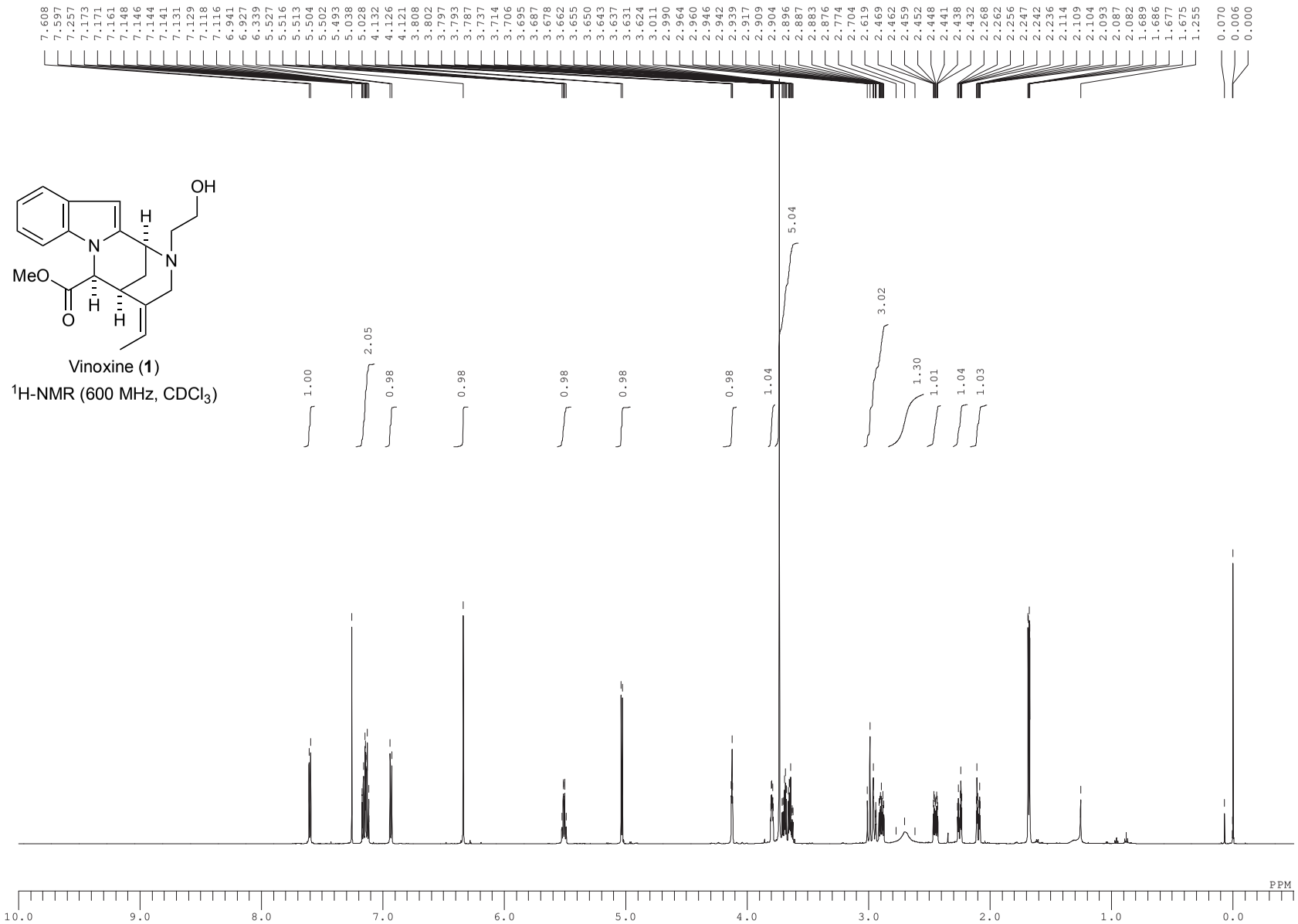
---- PROCESSING PARAMETERS ----
dc_balance : 0 : FALSE
sexp : 0.2[Hz] : 0.0[s]
trapezoid3 : 0[%] : 80[%] : 100[%]
zerofill : 1
fft : 1 : TRUE : TRUE
machinephase
ppm

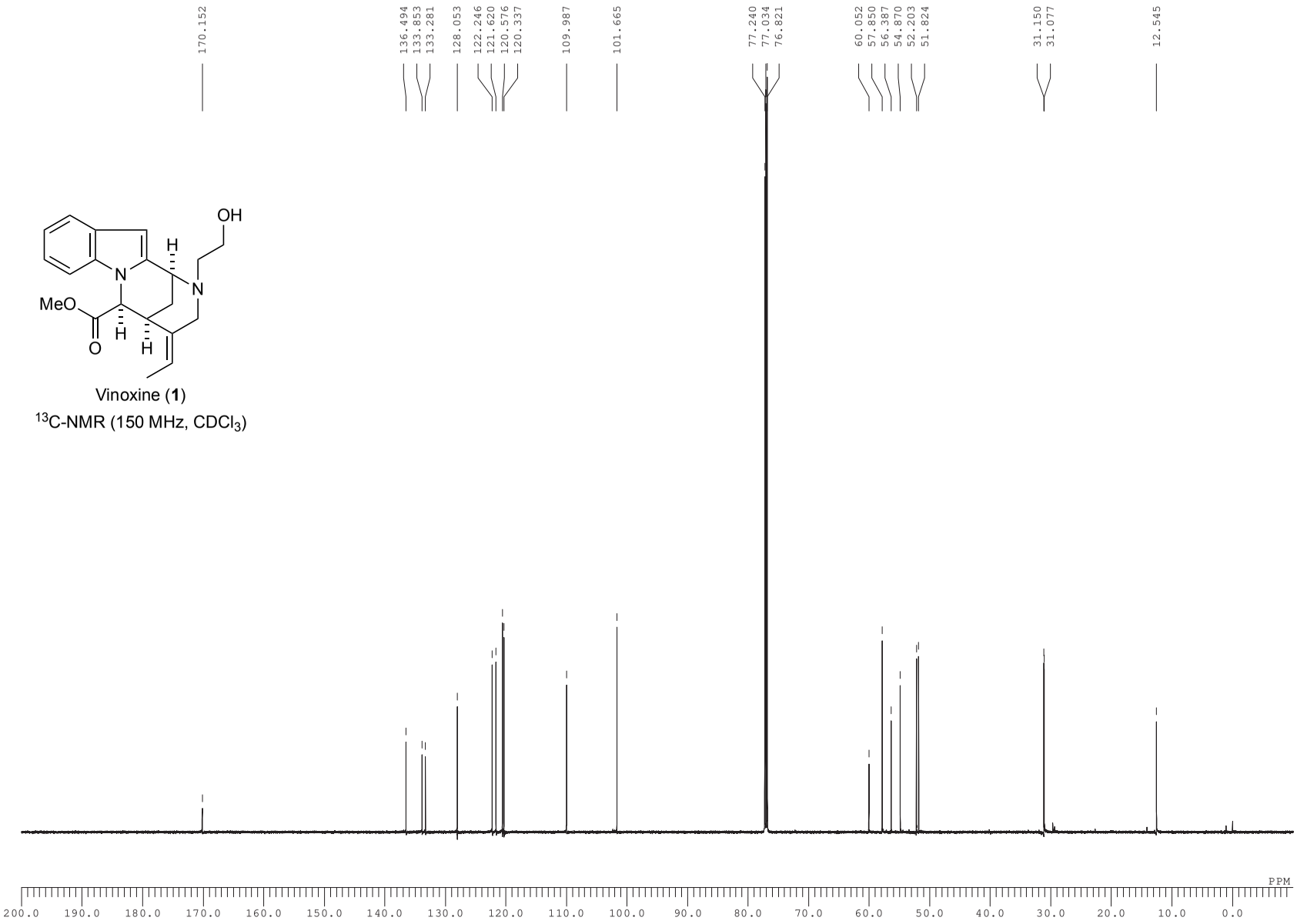


Filename	= ko_10_155_noesy_phase
Author	= yakkou
Experiment	= noesy_phase.ex2
Sample_id	= 1
Solvent	= CHLOROFORM-D
Creation_time	= 16-JUN-2021 08:20:33
Revision_time	= 17-JUN-2021 09:33:03
Current_time	= 4-FEB-2022 15:33:58
Comment	= phase sensitive noesy
Data_format	= 2D COMPLEX COMPLEX
Dim_size	= 819, 512
Dim_title	= 1H 1H
Dim_units	= [ppm] [ppm]
Dimensions	= X Y
Site	= ECA600
Spectrometer	= JNM-ECA600
Field_strength	= 14.09636928[T] (600[M
X_acq_duration	= 0.1363968[s]
X_domain	= 1H
X_freq	= 600.1723046[MHz]
X_offset	= 5[ppm]
X_points	= 1024
X_prescans	= 4
X_resolution	= 7.3315503[Hz]
X_sweep	= 7.50750751[kHz]
Y_domain	= 1H
Y_freq	= 600.1723046[MHz]
Y_offset	= 5[ppm]
Y_points	= 256
Y_prescans	= 0
Y_resolution	= 23.44687875[Hz]
Y_sweep	= 6.00240096[kHz]
Irr_domain	= 1H
Irr_freq	= 600.1723046[MHz]
Irr_offset	= 5[ppm]
Tri_domain	= 1H
Tri_freq	= 600.1723046[MHz]
Tri_offset	= 5[ppm]
Clipped	= FALSE
Mod_return	= 1
Scans	= 25
Total_scans	= 6382
X_acq_time	= 0.1363968[s]
X_atn	= 3[dB]
X_pulse	= 15.1[us]
Y_acq_time	= 42.6496[ms]
Y_p0_correction	= 0
Y_p1_correction	= 180
Irr_mode	= Off
Tri_mode	= Off
Dante_presat	= FALSE
Initial_wait	= 1[s]
Mix_time	= 1.505[s]
Recvr_gain	= 42
Relaxation_delay	= 1.5[s]
Repetition_time	= 1.6363968[s]
Scramble	= 1[ms]
T1	= 63.972[us]
T1_cal1	= 63.972[us]
T1_cal2	= 0.147272[ms]
T1_cal3	= 0.230572[ms]
T1_cal4	= 0.313872[ms]
T1_cal5	= 0.397172[ms]
T1_cal6	= 0.480472[ms]
Temp_get	= 24.7[dC]

Vinoxine (**1**)

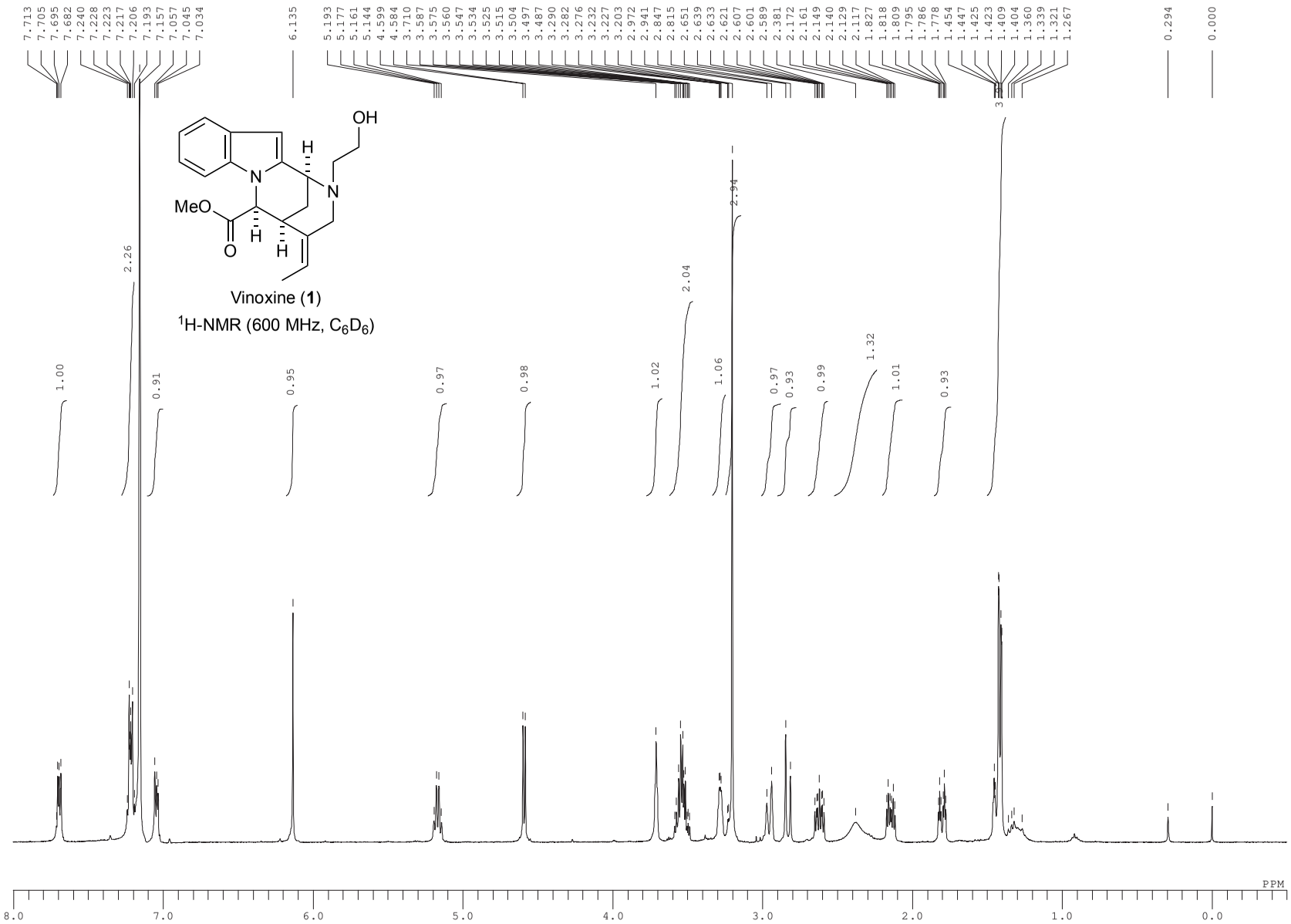
^{1}H-NMR (600 MHz, $CDCl_3$)

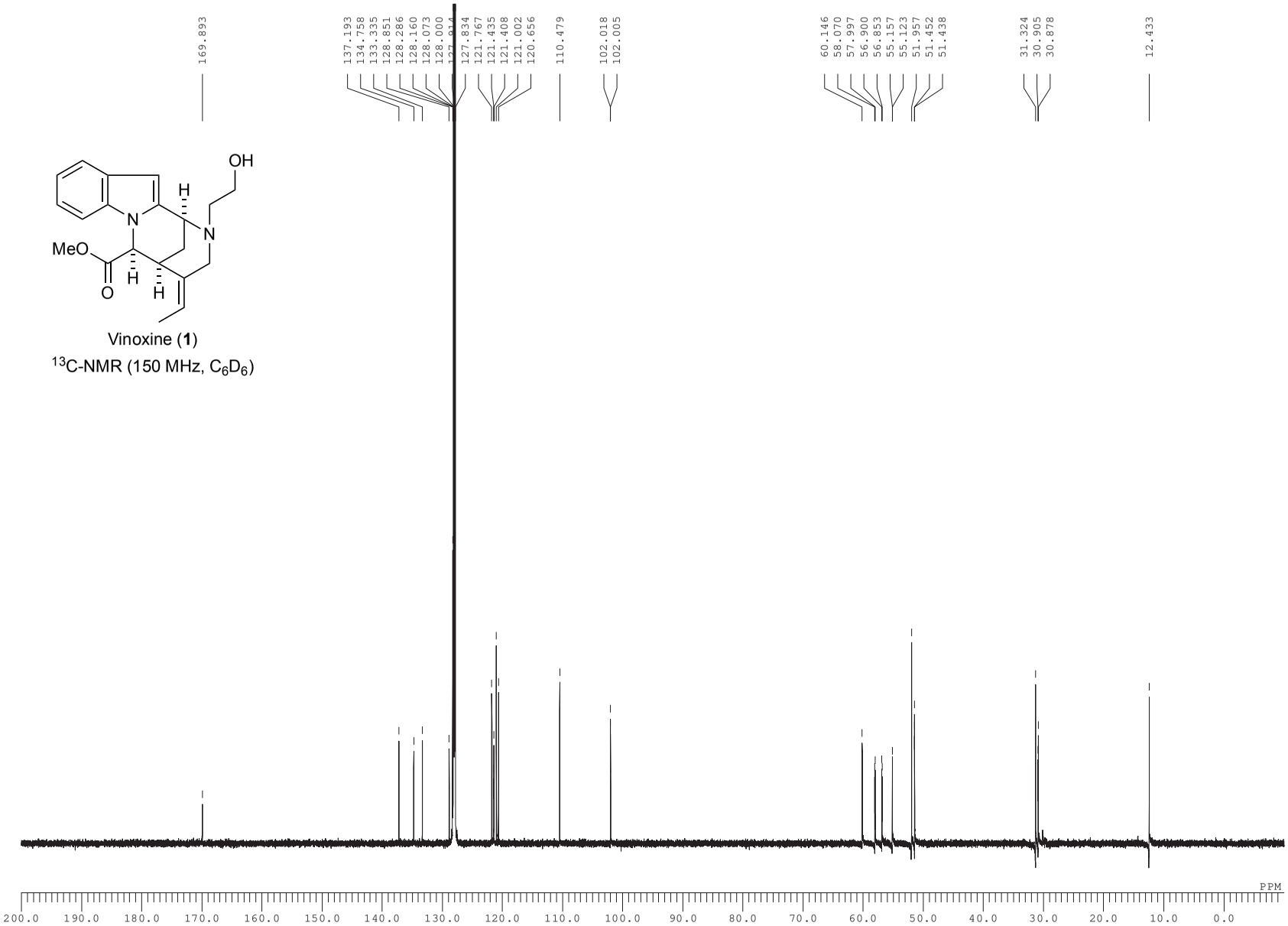




Vinoxine (**1**)

^{13}C-NMR (150 MHz, $CDCl_3$)


OH
H
N
N
MeO
O
H
H
Vinoxine (1)
1H-NMR (600 MHz, C6D6)
PPM
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

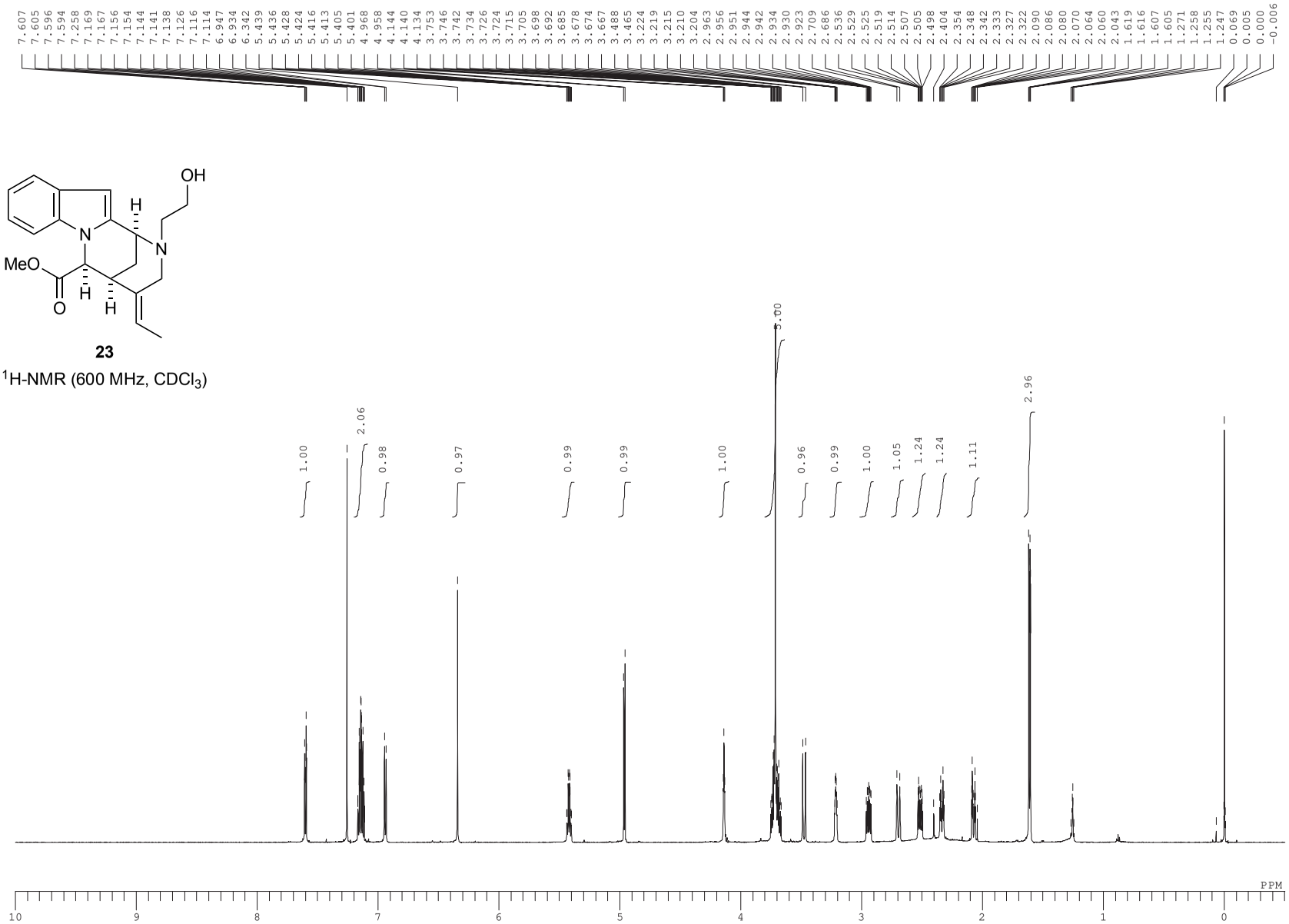


Vinoxine (**1**)

^{13}C-NMR (150 MHz, C_6D_6)

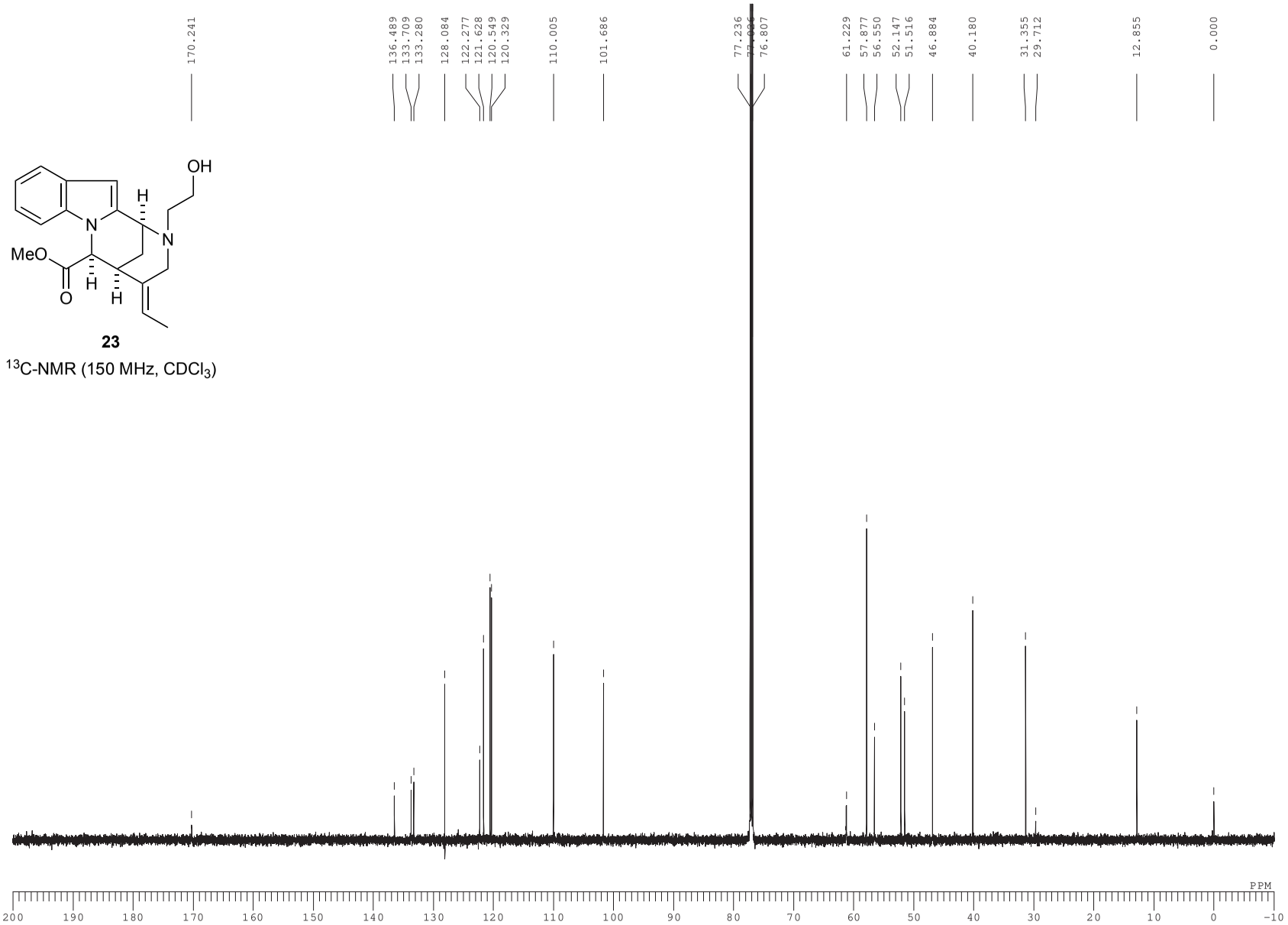
23

^{1}H-NMR (600 MHz, $CDCl_3$)



23

^{13}C-NMR (150 MHz, $CDCl_3$)



5. References

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