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Electronic Supplementary Information

Microwave-assisted telescoped cross metathesis-ring closing aza-Michael reaction sequence: a step-economical access to nicotine-lobeline hybrid analogues

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1. General and materials:

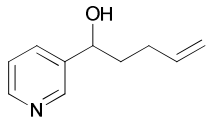
Commercially available reagents were used throughout without further purification other than those detailed below. Prior to use, THF and CH_2Cl_2 were dried by means of a SP-1 Stand Alone Solvent Purification System apparatus (LC Technology Solutions Inc). DMF was dried by fractioned distillation over CaH_2. All anhydrous reactions were carried out under argon atmosphere. Microwave experiments were carried out in a CEM Discover Labmate microwave oven using 10 mL pressurized vials. Analytical thin layer chromatography was performed on Merck 60F-254 precoated silica (0.2 mm) on glass and was revealed by UV light or Kägi-Misher or Dragendorf reagent. Flash chromatography separations were performed on Merck Kieselgel (40-63µm) or on Merck neutral activated Aluminiumoxid 90 (63-200µm). Infrared (IR) spectra were obtained as neat films on Bruker Vector22 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC 300 or ARX 400 apparatus respectively at 300 or 400 MHz and 75 or 100 MHz unless otherwise specified. The chemical shifts for ^1H NMR were recorded in ppm downfield from tetramethylsilane (TMS) with the solvent resonance as the internal standard. Coupling constants (*J*) are reported in Hz and refer to apparent peak multiplications. NMR peak assignments have been made on the basis of HMBC, HMQC, nOesy, and ^1H-^1H COSY spectra. The electrospray impact (ESI) and the atmospheric pressure chemical ionisation (APCI) mass spectra were realized on an esquire-LC Brucker spectrometer. High resolution mass spectroscopy (HRMS) was performed at the “Service d’Analyses HRMS”, Institut Lavoisier, Versailles, France: HRMS were collected using a Q-TOF instrument supplied by WATERS with Leucine-Enkephalin as accurate mass reference. All data were processed using MassLynx v4.1 (WATERS) data analysis software. Elemental analyses were performed by the "Service Commun d’Analyses", UMR CNRS 8076, Châtenay-Malabry, France. Diastereomeric excesses (*de*) were evaluated by ^1H NMR spectroscopy.

2. Experimental procedures

General procedure for the preparation of the secondary alcohols 8a and 8b.

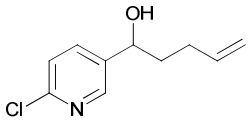
A small crystal of iodine was added to magnesium (150 mg, 6.25 mmol) in dry THF (5.5 mL) and the slurry was gently heated to reflux. A solution of 4-bromo-1-butene (665 mg, 4.92 mmol) in dry THF (5.5 mL) was added slowly, and the mixture was refluxed for 3 h until almost complete consumption of magnesium metal. The solution was cooled to -10 °C and pyridine-2-carboxaldehyde (376 mg, 3.52 mmol) or 6-chloropyridine-3-carboxaldehyde (500 mg, 3.52 mmol) in dry THF (2 mL) was added slowly. The solution was allowed to warm to room temperature over 3 h. The reaction mixture was then diluted with saturated NH_4Cl, extracted with EtOAc (3×20 mL). Organic layers were gathered, washed with brine, dried over $MgSO_4$ and, concentrated under reduced pressure to afford a crude oil which was purified by flash chromatography on silica gel using a 60:40 cyclohexane-AcOEt solvent mixture to provide 1-pyridine-3-yl-pent-4-ene-1-ol **8a** (573 mg, 90% yield) or 1-(6-chloro-pyridin-3-yl)-pent-4-en-1-ol **8b** (400 mg, 57% yield).

1-(pyridin-3-yl)-pent-4-en-1-ol (8a)



Orange oil; IR (neat): ν_{max}/cm^{-1} 3250, 1640, 1595, 1579, 1428; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.42 (1H , d, J = 1.9 Hz), 8.38 (1H, m), 7.70 (1H , d, J = 7.7 Hz), 7.24 (1H, m), 5.81 (1H, ddt, J = 16.8, 10.2, 6.6 Hz), 5.03 (2H, m), 4.71 (1H, m), 3.80 (1H, br), 2.14 (2H, m), 1.88 (1H, m), 1.71 (1H, m); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 148.22 (CH), 147.47 (CH), 140.54 (Cq), 137.77 (CH), 133.93 (CH), 123.55 (CH), 115.20 (CH_2), 71.14 (CH), 38.05 (CH_2), 29.82 (CH_2); APCI-MS *m/z* 164 $[M + H]^+$, 146. HRMS *m/z* calcd. for $C_{10}H_{14}NO$ ($[M+H]^+$) 164.1070, found 164.1071.

1-(6-Chloro-pyridin-3-yl)-pent-4-en-1-ol (8b)

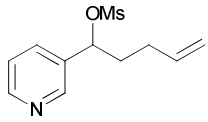


Orange oil; IR (neat): ν_{max}/cm^{-1} 3366, 1640, 1586, 1567, 1457, 837; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.25 (1H, br), 7.65 (1H , dd, J = 8.2, 2.3 Hz), 7.28 (1H, d, J = 8.2 Hz), 5.79 (1H, m), 5.03 (1H, s), 4.99 (1H, d, J = 10.2 Hz), 4.73 (1H, t, J = 5.5 Hz), 2.95 (1H, br), 2.12 (2H, m), 1.86 (1H, m), 1.76 (1H, m); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 150.21 (Cq), 148.46 (CH), 139.07 (Cq), 137.45 (CH), 136.63 (CH), 123.14 (CH), 115.50 (CH_2), 70.68 (CH), 37.97 (CH_2), 29.69 (CH_2); HRMS *m/z* calcd. for $C_{10}H_{13}ClNO$ ($[M+H]^+$) 198.0680, found 198.0686.

General procedure for alcohol mesylation:

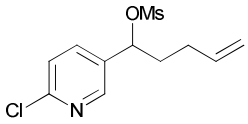
Under nitrogen, to a stirred solution of the alcohol **8a** or **8b** (1 eq) and triethylamine (1.3 eq) in CH_2Cl_2 (0.38 M) was added dropwise methanesulfonyl chloride (1.2 eq) over a period of 30 min. One hour after the completion of the methanesulfonyl chloride addition, the reaction was quenched with saturated NH_4Cl. The organic layer was separated, washed with a saturated $NaHCO_3$ solution and brine, dried over $MgSO_4$, and concentrated under reduced pressure to yield the mesylated compound **11a** or **11b** which was directly engaged in the following step without further purification.

1-(3-Pyridyl)-pent-4-en-1-yl-methanesulfonate (11a)



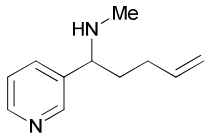
According to the typical procedure, the reaction using the 1-(3-pyridyl)-pent-4-en-1-ol **8a** (6.3 g, 38 mmol) gave **11a** (8.8 g, 96%) as an orange oil; IR (neat): ν_{max}/cm^{-1} 1639, 1568, 1352, 1168, 1038; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.62 (2H, br), 7.72 (1H, dd, *J* = 8.3, 2.3 Hz), 7.35 (1H, m), 5.79 (1H, m), 5.67 (1H, m), 5.07 (1H, d, *J* = 7.5 Hz), 5.02 (1H, s), 2.78 (3H, s), 2.15 (4H, m); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 150.48 (CH), 148.22 (CH), 136.12 (CH), 134.28 (CH), 134.12 (Cq), 123.78 (CH), 116.38 (CH_2), 81.17 (CH), 39.11 (CH_3), 36.00 (CH_2), 29.28 (CH_2). APCI-MS *m/z* 242 $[M + H]^+$, 146; HRMS calcd. for $C_{11}H_{16}NO_3S$ ($[M+H]^+$) 242.0845, found 242.0849.

1-(6-Chloro-pyridin-3-yl)-pent-4-en-1-yl-methanesulfonate (11b)



According to the typical procedure, the reaction using the 1-(6-chloro-pyridin-3-yl)-pent-4-en-1-ol **8b** (350 mg, 1.76 mmol) gave **11b** (450 mg, 92%) as an orange oil; IR (neat): ν_{max}/cm^{-1} 1681, 1567, 1461, 1358, 1173, 1104; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.38 (1H, s), 7.68 (1H, dd, *J* = 8.3, 2.4 Hz), 7.37 (1H, d, *J* = 8.3 Hz), 5.76 (1H, m), 5.55 (1H, m), 5.05 (2H, m), 2.85 (3H, s), 2.15 (3H, m), 1.91 (1H, m); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.08 (Cq), 148.02 (CH), 137.00 (CH), 135.87 (CH), 133.23 (Cq), 124.62 (CH), 116.50 (CH_2), 80.07 (CH), 39.03 (CH_3), 35.87 (CH_2), 29.12 (CH_2); HRMS calcd. for $C_{11}H_{15}ClNO_3S$ ($[M+H]^+$) 276.0456, found 276.0463.

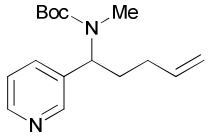
1-(3-pyridyl)-pent-4-en-1-yl-*N*-methylamine (14a)



To the mesylate **11b** (4.7 g, 0.019 mol) was added a 2.0 M methylamine solution in THF (40 mL, 0.080 mol). The reaction mixture was stirred at 50 °C overnight. The solvent was removed to give the desired product as a crude oil (2.5 g, 75% yield), which was directly engaged in the following step without further purification.

Orange oil, IR (neat): ν_{max}/cm^{-1} 3161, 2795, 1640, 1451, 1135, 1026; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.42 (2H, br), 7.58 (1H , dt, *J* = 7.7, 1.9 Hz), 7.15 (1H, dd, *J* = 7.8, 4.7 Hz), 5.69 (1H, ddt, *J* = 23.5, 10.2, 6.5 Hz), 4.90 (2H, m), 3.45 (1H, dd, *J* = 7.7, 5.9 Hz), 2.18 (3H, s), 1.97-1.50 (4H, m); ^{13}C NMR ($CDCl_3$, 75 MHz): δ149.30 (CH), 148.45 (CH), 138.74 (Cq), 137.83 (CH), 134.58 (CH), 123.57 (CH), 115.06 (CH_2), 62.27 (CH), 38.48 (CH_2), 34.26 (CH_3), 30.08 (CH_2); HRMS *m/z* calcd. for $C_{11}H_{17}N_2$ ($[M+H]^+$) 177.1386, found 177.1382.

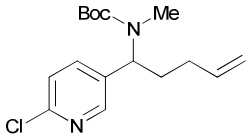
***N*-*tert*-butyloxycarbonyl-*N*-methyl-1-(3-pyridyl)-pent-4-en-1-yl-amine (6a)**



A solution of amine (530 mg, 3 mmol) and Et_3N (0.65 mL, 4.5 mmol) in CH_2Cl_2 (50 mL) at room temperature was treated with $(Boc)_2O$ (1.00 g, 4.5 mmol). The mixture was stirred at room temperature for 2 days, and the solvent was then evaporated under reduced pressure. The residue was diluted in EtOH (25 mL) and treated with imidazole (1.00 g, 14.7 mmol). The resulting mixture was then stirred for 30 min at room temperature, the solvent was evaporated and the residue was diluted with CH_2Cl_2 (25 mL), and washed with a 1 M HCl solution. The organic extract was dried over anhydrous $MgSO_4$, filtred and concentrated in vacuo. Purification by flash chromatography using a cyclohexane-AcOEt mixture (60:40, *c*Hex: EtOAc) gave **6a** (750 mg, 90%) as a yellow oil;

IR (neat): ν_{max}/cm^{-1} 2980, 1687, 1642, 1390, 1143; ^1H NMR ($CDCl_3$, 300 MHz): δ8.53 (2H, m), 7.58 (1H , d, *J* = 7.7 Hz), 7.24 (1H , m), 5.84 (1H, ddt, *J* = 16.9, 10.2, 6.5 Hz), 5.32 (1H, br), 5.04 (2H, dd, *J* = 20.6, 5.2 Hz), 2.59 (3H, s), 2.09 (2H, m), 2.00 (2H, m), 1.47 (9H, s); ^{13}C NMR ($CDCl_3$, 75 MHz): δ156.02 (Cq), 148.88 (CH), 148.46 (CH), 137.22 (CH), 136.04 (Cq), 134.679 (CH), 123.26 (CH), 115.50 (CH_2), 79.95 (Cq), 54.79 (CH), 30.23 (CH_2), 29.18 (CH_2), 28.37 (3xCH_3), 27.81 (CH_3); APCI-MS *m/z* 277 $[M+H]^+$, 211. HRMS *m/z* calcd. for $C_{16}H_{25}N_2O_2$ ($[M+H]^+$) 277.1911, found 277.1906.

***N*-*tert*-Butyloxycarbonyl-*N*-methyl-1-(6-chloro-3-pyridyl)-pent-4-en-1-yl-amine (6b)**



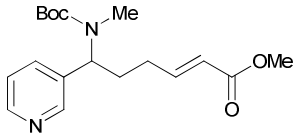
To the mesylate **11b** (450 mg, 1.6 mmol) was added a 2.0 M methylamine solution in THF (3.5 mL, 6.68 mmol) and the reaction mixture was stirred at 50 °C for 2 days. An equivalent volume of methylamine solution (3.5 mL, 6.68 mmol) was then added and the reaction mixture was stirred at 50 °C for 2 additional days. The solvent was removed to give the corresponding 1-(6-chloro-3-pyridyl)-pent-4-en-1-yl-*N*-methylamine **14b** as a red oil which was directly engaged in the *N*-protection reaction (**14b**; H NMR ($CDCl_3$, 400 MHz): δ 8.23 (1H, s), 7.58(1H , dt, dd, *J* = 8.3, 2.4 Hz), 7.24 (1H, d, *J* = 8.3 Hz), 5.79-5.52 (1H, m), 4.90 (2H, m), 3.49 (1H, dd, *J* = 7.5, 6.0 Hz), 2.19 (3H, s), 1.98-1.53 (4H, m)). A solution of **14b**, Et_3N (0.400 mL, 2.65 mmol) and $(Boc)_2O$ (580 mg, 2.65 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature during 24 h. The reaction was concentrated under reduced pressure. The residue was diluted with EtOH (15 mL) and treated with imidazole (800 mg, 11.7 mmol). The resulting mixture was then stirred for 30 min at room temperature. The solvent was removed under reduced pressure. The residue was diluted with CH_2Cl_2 (15 mL) and, washed with a 1 M HCl solution. The organic layer was separated and dried over $MgSO_4$, filtred and concentrated *in vacuo*. Purification by flash chromatography on silica gel using a 90:10 cyclohexane-AcOEt solvent mixture gave **6b** (300 mg, 58%) as a yellow oil.

IR (neat):): ν_{max}/cm^{-1} 1687, 1641, 1584, 1458, 1390, 1140; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.26 (1H, s), 7.52 (1H, d, *J* = 7.5 Hz), 7.25 (1H, m), 5.78 (1H, m), 5.25 (1H, br), 4.98 (2H, dd, *J* = 17.2, 10.1 Hz), 2.55 (3H, s), 2.05 (2H, m), 1.93 (2H, m), 1.42 (9H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.71 (Cq), 150.21 (Cq), 148.61 (CH), 137.95 (CH), 136.88 (CH), 135.01 (Cq), 123.88 (CH), 115.62 (CH_2), 80.06 (Cq), 58.60 (CH), 30.09 (CH_2), 29.12 (CH_2), 28.26 (4xCH_3); APCI-MS *m/z* 277 $[M+H]^+$, 211; HRMS *m/z* calcd. for $C_{16}H_{24}ClN_2O_2$ ($[M+H]^+$) 311.1521, found 311.1526.

General procedure for the cross-metathesis reaction:

To a stirred solution of the amine **6a** or **6b** in CH_2Cl_2 (0.5 M concentration) was subsequently added the Michael acceptor **7a-d** (1.3 eq) and the appropriate Ru-based metathesis precatalyst (5 mol%). The The vial was sealed, reaction mixture was heated with stirring at 100 °C using microwaves irradiation (100 W) for 45 to 60 min (the irradiation power was 100 W during the warm up period and 60 W, on average, during the constant phase). The internal pressure depended upon the head space of the vial (typically 2.0 bars). The reaction duration was determined by TLC analysis. The solvent was then evaporated under reduced pressure and the residue was purified by flash chromatography on silica gel.

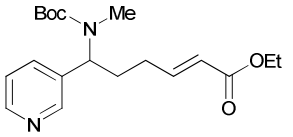
Methyl 6-(*N*-*tert*-butoxycarbonyl, *N*-methyl)amino-6-(pyridin-3-yl)-hex-2-enoate (15aa)



According to the typical procedure, the reaction using **6a** (100 mg, 0.36 mmol) gave **15aa** (85 mg, 70%) as a yellow oil after purification by flash chromatography on silica gel using a 60:40 cyclohexane-AcOEt solvent.

IR (neat): ν_{max}/cm^{-1} 3050, 1720, 1667, 1650, 1480, 1455, 1390, 1136; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.52 (2H, br), 7.57 (1H , br), 7.00 (1H, m), 5.88 (1H, d, *J* = 15.6 Hz), 5.40 (1H, br), 3.72 (3H, s), 2.27 (2H, m), 2.07 (2H, m), 1.48 (9H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.67 (Cq), 149.88 (Cq), 148.89 (CH), 148.82 (CH), 147.55 (CH), 135.5 (Cq), 134.70 (CH), 123.39 (CH), 121.81 (CH), 80.21 (Cq), 54.91 (CH), 51.45 (CH_3), 28.80 (2xCH_2), 28.39 (4xCH_3); HRMS *m/z* calcd. for $C_{18}H_{27}N_2O_4$ ($[M+H]^+$) 335.1965, found 335.1971.

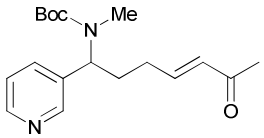
Ethyl 6-(*N*-*tert*-butoxycarbonyl, *N*-methyl)amino-6-(pyridin-3-yl)-hex-2-enoate (15ab)



According to the typical procedure, the reaction using **6a** (50 mg, 0.18 mmol) gave **15ab** (45 mg, 70%) as a yellow oil after purification by flash chromatography on silica gel using a 60:40 cyclohexane-AcOEt solvent.

IR (neat): ν_{max}/cm^{-1} 3055, 1718, 1668, 1653, 1479, 1458, 1390, 1136; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.53 (2H, br), 7.56 (1H , br), 6.99 (1H, m), 5.86 (1H, d, *J* = 15.4 Hz), 5.34 (1H, br), 4.16 (3H, m), 2.58 (3H, s), 2.26 (2H, m), 2.07 (2H, m), 1.47 (9H, s), 1.27 (3H, m); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.32 (Cq), 149.57 (Cq), 148.88 (2xCH), 147.15 (CH), 136.90 (CH), 135.53 (Cq), 134.61 (CH), 122.33 (CH), 80.35 (Cq), 60.23 (CH_2), 54.87 (CH), 28.75 (CH_2), 29.38 (4xCH_3), 28.26 (CH_2), 14.21 (CH_3); HRMS *m/z* calcd. for $C_{19}H_{29}N_2O_4$ ($[M+H]^+$) 349.2122, found 349.2127.

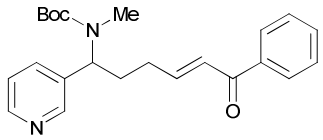
7-(*N*-*tert*-Butoxycarbonyl, *N*-methyl)amino-7-(pyridin-3-yl)-hept-3-en-2-one (15ac)



According to the typical procedure, the reaction using **6a** (50 mg, 0.18 mmol) gave crude **15ac** (57 mg, 70%) as a yellow oil which was directly used in the following step without further purification because of its instability.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.48 (2H, m), 7.52 (1H , d, *J* = 7.5 Hz), 7.12 (1H, br), 6.95 (1H, dt, *J* = 15.5, 6.9 Hz), 5.82 (1H, dd, *J* = 15.4, 3.0 Hz), 5.29 (1H, br), 3.66 (3H, s), 2.54 (3H, br), 2.22 (2H, m), 2.00 (2H, m), 1.42 (9H, s).

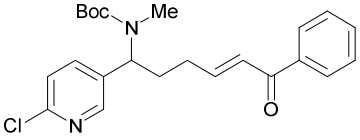
6-(*N*-*tert*-Butoxycarbonyl, *N*-methyl)amino-1-phenyl-6-(pyridin-3-yl)-hex-2-en-1-one (15ad)



According to the typical procedure, the reaction using **8a** (120 mg, 0.43 mmol) gave **15ad** (90 mg, 50%) as a yellow oil after purification by flash chromatography on silica gel using a 70:30 cyclohexane-AcOEt solvent.

IR (neat): ν_{max}/cm^{-1} 1689, 1667, 1618, 1596, 1578, 1450, 1390, 1139; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.58 (2H, m), 7.94 (1H, br), 7.64 (5H, m), 7.07 (1H, m), 6.95 (1H, d, *J* = 15.6 Hz), 5.40 (1H, br), 2.62 (3H, s), 2.40 (2H, m), 2.15 (2H, m), 1.48 (9H, s); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 190.42 (Cq), 151.11 (Cq), 148.84 (CH), 148.79 (CH), 147.57 (CH), 137.74 (Cq), 135.79 (Cq), 134.7 (CH), 132.71 (CH), 128.50 (4xCH), 128.16 (CH), 126.76 (CH), 80.23 (Cq), 50.73 (CH), 28.41 (2xCH_2), 28.39 (4xCH_3); Elemental analysis: found C, 70.87; H, 7.48; N, 7.29. Calc. for $C_{23}H_{28}N_2O_3 \cdot 1/2H_2O$: C, 70.93; H, 7.50; N, 7.19 %.

6-(*N*-*tert*-Butoxycarbonyl, *N*-methyl)amino-1-phenyl-6-(6-chloro-pyridin-3-yl)-hex-2-en-1-one (15bd)



According to the typical procedure, the reaction using **8b** (165 mg, 0.36 mmol) gave **15bd** (200 mg, 93%) as a yellow oil after purification by flash chromatography on silica gel using a 50:50 cyclohexane-AcOEt solvent.

IR (neat): ν_{max}/cm^{-1} 1687, 1668, 1620, 1597, 1578, 1447, 1391, 1140; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.33 (1H, s), 7.92 (2H, m), 7.56 (2H, t, *J* = 7.4Hz), 7.47 (2H, t, *J* = 7.6 Hz), 7.33 (1H, d, *J* = 7.5Hz), 7.08 (1H, m), 6.95 (1H, d, *J* = 15.4 Hz), 5.42 (1H, br), 2.61 (3H, s), 2.37 (2H, m), 2.09 (2H, m), 1.47 (9H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 190.42 (Cq), 150.65 (Cq), 148.64 (CH), 147.26 (CH), 137.71 (Cq), 137.71 (CH), 134.62 (Cq), 132.80 (CH), 128.56 (2xCH), 128.54 (2xCH), 126.89 (CH), 124.17 (CH), 80.45 (Cq), 54.38 (CH), 29.35 (2xCH_2), 28.40 (4xCH_3); HRMS *m/z* calcd. for $C_{23}H_{28}ClN_2O_3$ ($[M+H]^+$) 415.1783, found 415.1788.

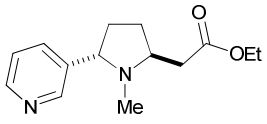
Typical procedure for the aza-Michael cyclisation:

To a stirred solution of the amino enone **15ab-ad** and **15bd** in *i*-PrOH (0.5 M concentration) was added few drops of concentrated HCl. The solution with **15ab** or **15ac** was heated at 100 °C using microwaves irradiation (100 W) for 45 min (the irradiation power was 100 W during the warm up period and 60 W, on average, during the constant phase). The internal pressure depended upon the head space of the vial (typically 2.0 bars). The solution with **15bd** was conventionally heated at 80 °C for 2 hours. With **15ad**, the solution was stirred under ultrasonic irradiation for 3 hours. Then the reaction media was neutralised with a saturated potassium carbonate solution and extracted with dichloromethane. The organic phases were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude reaction mixture was purified by flash chromatography on neutral alumina gel using the appropriate eluent.

Typical procedure for the tandem cross-metathesis-aza-Michael cyclisation:

To a stirred solution of the amine **6a** or **6b** in CH_2Cl_2 (0.5 M concentration) was subsequently added the Michael acceptor **7b-d** (1.2 eq) and the Ru-based metathesis precatalyst [Ru]-**IV** (5 mol%) (see Table 1). The vial was sealed and the mixture was heated with stirring at 100 °C using microwaves irradiation (100 W) for 45 to 60 min (the irradiation power was 100 W during the warm up period and 60 W, on average, during the constant phase). The internal pressure depended upon the head space of the vial (typically 2.0 bars). After reaction completion confirmed by TLC, concentrated HCl (1%) was added and the mixture was heated with stirring at 80 °C using microwaves irradiation (70 W) for 30 additional minutes. After cooling at room temperature, the solution was diluted with water and basified with solid $NaHCO_3$ until pH 9-10. The aqueous layer was extracted three times with CH_2Cl_2. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude reaction mixture was subsequently purified by flash chromatography on neutral alumina gel using the appropriate eluent.

Ethyl [(1-methyl-5-pyridin-3-yl-)pyrrolidin-2-yl] acetate (5ab)

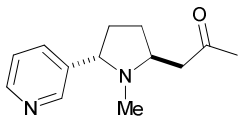


According to the typical procedure, the reaction using **6a** (100 mg, 0.36 mmol) and **7b** (43 mg, 0.43 mmol) gave, after purification by flash chromatography on neutral alumina gel using AcOEt as eluent**,** an inseparable mixture of two diastereoisomers **5ab** (89 mg, 60%) as a yellow oil.

IR (neat): ν_{max}/cm^{-1} 1718, 1670, 1650, 1390; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.50 (4H, br, minor *cis* and major *trans*), 7.69 (1H, d, *J* = 7.8 Hz, minor *cis*), 7.63 (1H, d, *J* = 7.8 Hz, major *trans*), 7.24 (2H, br, *cis* and *trans*), 4.16 (4H, q, *J* = 6.7 Hz, *cis* and *trans*), 3.70 (2H, m, major *trans*), 3.33 (1H, minor

cis), 2.86 (1H, m, minor *cis*), 2.64 (2H, m, major *trans*), 2.40 (1H, dd, *J* = 14.7, 8.5 Hz, major *trans*), 2.36-2.12 (5H, m, minor *cis* and major *trans*), 2.16 (3H, s, major *trans*) 2.14 (3H, s, minor *cis*) 1.72 (4H, m, minor *cis* and major *trans*), 1.27 (6H, m, minor *cis* and major *trans*); ^{13}C NMR $CDCl_3$, 100 MHz): δ 172.89 (Cq, minor *cis*), 172.25 (Cq, major *trans*), 149.37 (CH, major *trans*), 149.33 (CH, minor *cis*), 148.5 (CH, *cis* and *trans*), 139.30 (Cq, *cis* and *trans*), 134.88 (CH, major *trans*), 134.80 (CH, minor *cis*), 123.53 (CH, *cis* and *trans*), 69.28 (CH, minor *cis*), 64.46 (CH, major *trans*), 62.96 (CH, minor *cis*), 60.64 (CH, major *trans*), 60.43 (CH_2, minor *cis*), 60.29 (CH_2, major *trans*), 38.68 (CH_3, minor *cis*), 34.83 (CH_3, major *trans*), 34.39 (CH_2, minor *cis*), 34.06 (CH_2, major *trans*), 33.54 (CH_2, minor *cis*), 33.03 (CH_2, major *trans*), 29.7 (CH_2, minor *cis*), 29.3 (CH_2, major *trans*), 14.22 (CH_3, *cis* and *trans*); HRMS *m/z* calcd. for $C_{14}H_{21}N_2O_2$ ($[M+H]^+$) 249.1598, found 249.1603.

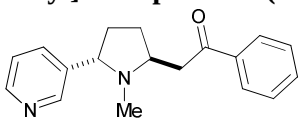
[(1-Methyl-5-pyridin-3-yl-)pyrrolidin-2-yl] acetone (5ac)



According to the typical procedure, the reaction using **6a** (100 mg, 0.36 mmol) and **7c** (30 mg, 0.43 mmol) gave **5ac** (50 mg, 65%) as a yellow oil after purification by flash chromatography on neutral alumina gel using AcOEt as eluent.

IR (neat): ν_{max}/cm^{-1} 1687, 1643, 1580, 1390, 1152; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.55 (1H, s), 8.49 (1H, d, *J* = 4.3 Hz), 7.69 (1H, br), 7.26 (1H, br), 3.31 (1H, m), 2.90 (1H, m), 2.85 (1H, m), 2.61 (1H, m), 2.21 (3H, s), 2.14 (2H, m), 2.13 (3H, s), 1.57 (2H, m); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 208.14 (Cq), 149.41 (CH), 148.68 (CH), 138.71 (Cq), 134.90 (CH), 123.55 (CH), 69.27 (CH), 62.43 (CH), 48.9 (CH_2), 38.71 (CH_3), 31.05 (CH_3), 29.88 (CH_2), 29.68 (CH_2). APCI-MS *m/z* 219 $[M+H]^+$. HRMS *m/z* calcd. for $C_{13}H_{19}N_2O$ ($[M+H]^+$) 219.1492, found 219.1500.

[(1-Methyl-5-pyridin-3-yl-)pyrrolidin-2-yl] acetophenone (5ad)

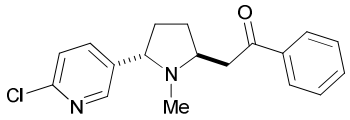


According to the typical procedure, the reaction using **6a** (165 mg, 0.36 mmol) and **7d** (57 mg, 0.43 mmol) gave **5ad** (85 mg, 50%) as a yellow oil after purification by flash chromatography on neutral alumina gel using AcOEt as eluent.

IR (neat): ν_{max}/cm^{-1} 1721, 1682, 1596, 1579, 1183; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.55 (1H, br), 8.49 (1H, d, *J* = 3.7 Hz), 8.00 (2H, d, *J* = 7.4 Hz), 7.69 (1H, d, *J* = 7.6 Hz), 7.58 (1H, d, *J* = 7.9 Hz), 7.48 (2H, d, *J* = 7.9 Hz), 7.25 (1H, dd, *J* = 4.7, 7.8 Hz), 3.35 (2H, m), 3.12 (2H, m), 2.22 (1H, m), 2.17 (3H, s), 2.14 (1H, m), 1.68 (1H, m), 1.62 (1H, m); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 199.42 (Cq), 149.43 (CH), 148.62 (CH), 137.28 (Cq), 137.04 (Cq), 134.96 (CH), 133.10 (CH), 128.61 (2xCH),

128.09 (2xCH), 123.51 (CH), 69.29 (CH), 62.89 (CH), 44.23 (CH_2), 38.90 (CH_3), 33.60 (CH_2), 30.28 (CH_2). HRMS *m/z* calcd. for $C_{18}H_{21}N_2O$ ($[M+H]^+$) 281.1648, found 281.1650.

{[1-Methyl-5-(6-chloro-pyridin-3-yl-)]pyrrolidin-2-yl} acetophenone (5bd)



According to the typical procedure, the reaction using **6b** (100 mg, 0.32 mmol) and **7d** (57 mg, 0.43 mmol) gave, after purification by flash chromatography on neutral alumina gel using a 50:50 cyclohexane-AcOEt solvent mixture as eluent**,** an inseparable mixture of two diastereoisomers **5bd** (85 mg, 70%) as a yellow oil.

IR (neat): ν_{max}/cm^{-1} 2152, 1681, 1587, 1560, 1450, 1373, 1179;

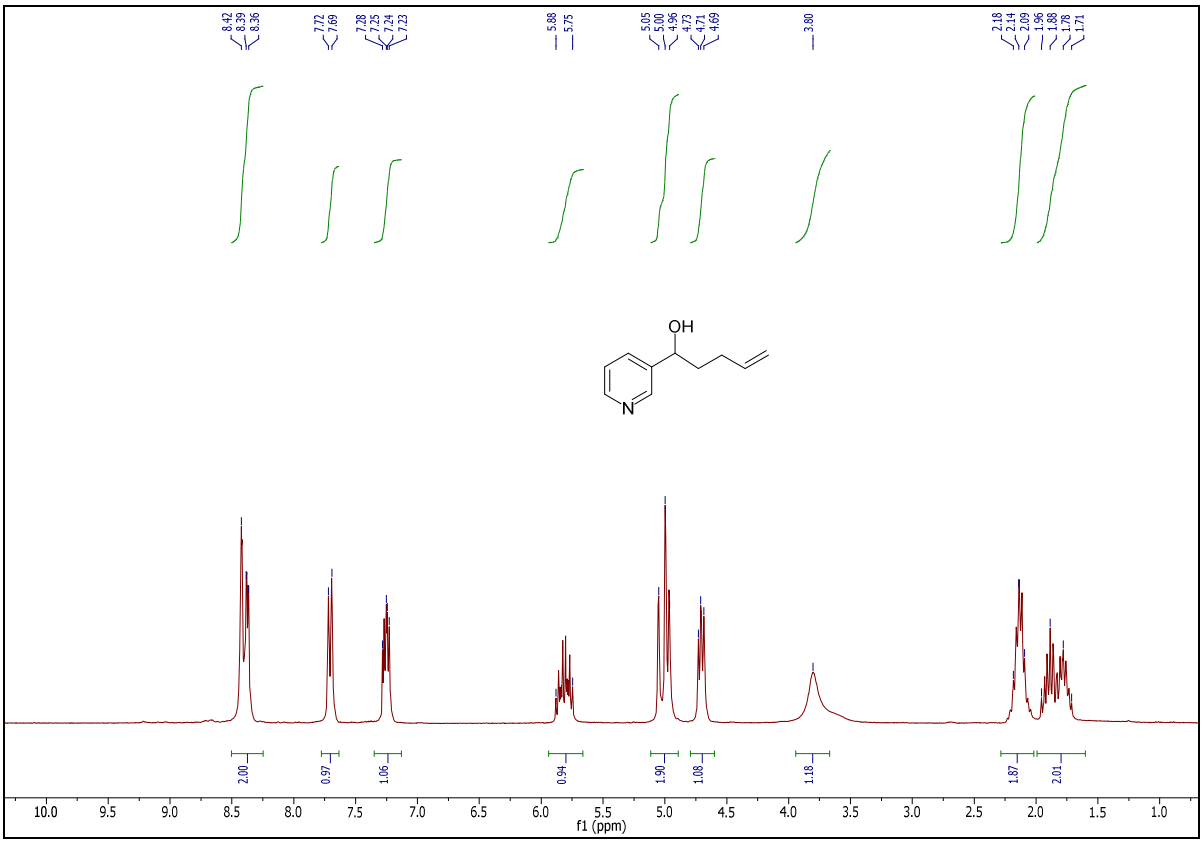
Minor isomer (*cis*): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.30 (1H, d, *J* = 2.0 Hz), 7.98 (2H, d, *J* = 7.3 Hz), 7.66 (1H, m), 7.57 (1H, t, *J* = 7.3 Hz), 7.47 (2H, m), 7.27 (1H, d, *J* = 8.5 Hz), 3.38 (1H, m), 3.35 (1H, m), 3.11 (1H, m), 3.09 (1H, m), 2.17 (3H, s), 2.22 (1H, m), 2.14 (1H, m), 1.62 (1H, m), 1.61 (1H, m); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 199.27 (Cq), 150.06 (CH), 149.08 (CH), 137.80 (CH), 137.18 (Cq), 136.35 (Cq), 133.25 (CH), 133.14 (2xCH), 128.11 (2xCH), 124.20 (CH), 68.49 (CH), 62.80 (CH), 44.51 (CH_2), 39.71 (CH_3), 34.03 (CH_2), 30.17 (CH_2).

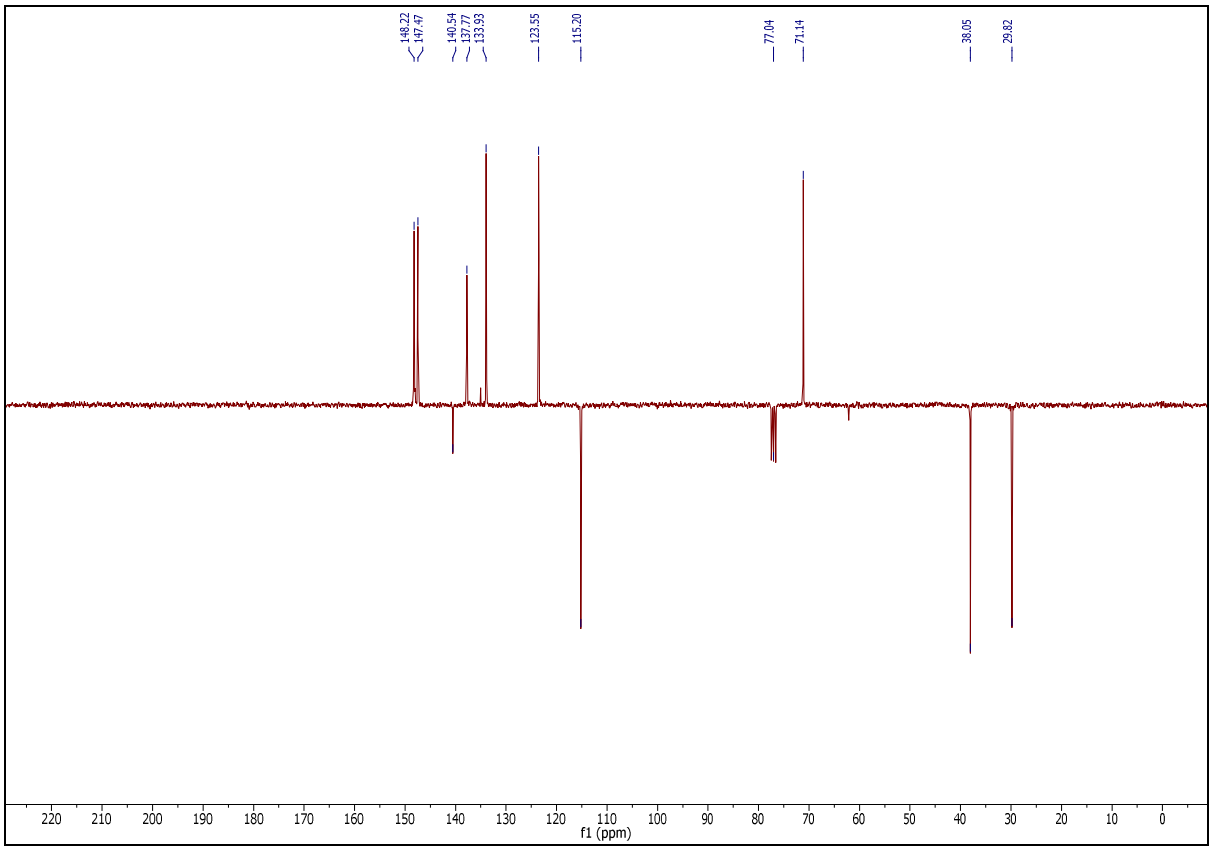
Major isomer (*trans*): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.31 (1H, dd, *J* = 2.1, 5.2 Hz), 7.98 (2H, t, *J* = 7.8 Hz), 7.67 (1H, d, *J* = 7.0 Hz), 7.58 (1H, m), 7.48 (2H, m), 7.29 (1H, d, *J* = 7.7 Hz), 3.39 (1H, m), 3.35 (1H, m), 3.10 (2H, m), 2.22 (1H, m), 2.17 (3H, s), 2.16 (1H, m), 1.63 (2H, m); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 199.30 (Cq), 150.11 (CH), 149.08 (CH), 137.81 (CH), 137.21 (Cq), 136.31 (Cq), 133.27 (CH), 128.63 (2xCH), 128.08 (2xCH), 124.31 (CH), 68.47 (CH), 62.82 (CH), 44.10 (CH_2), 38.82 (CH_3), 33.65 (CH_2), 29.69 (CH_2).

ESI-MS *m/z* 315 $[M+H]^+$. HRMS *m/z* calcd. for $C_{18}H_{20}ClN_2O$ ($[M+H]^+$) 315.1259, found 315.1264.

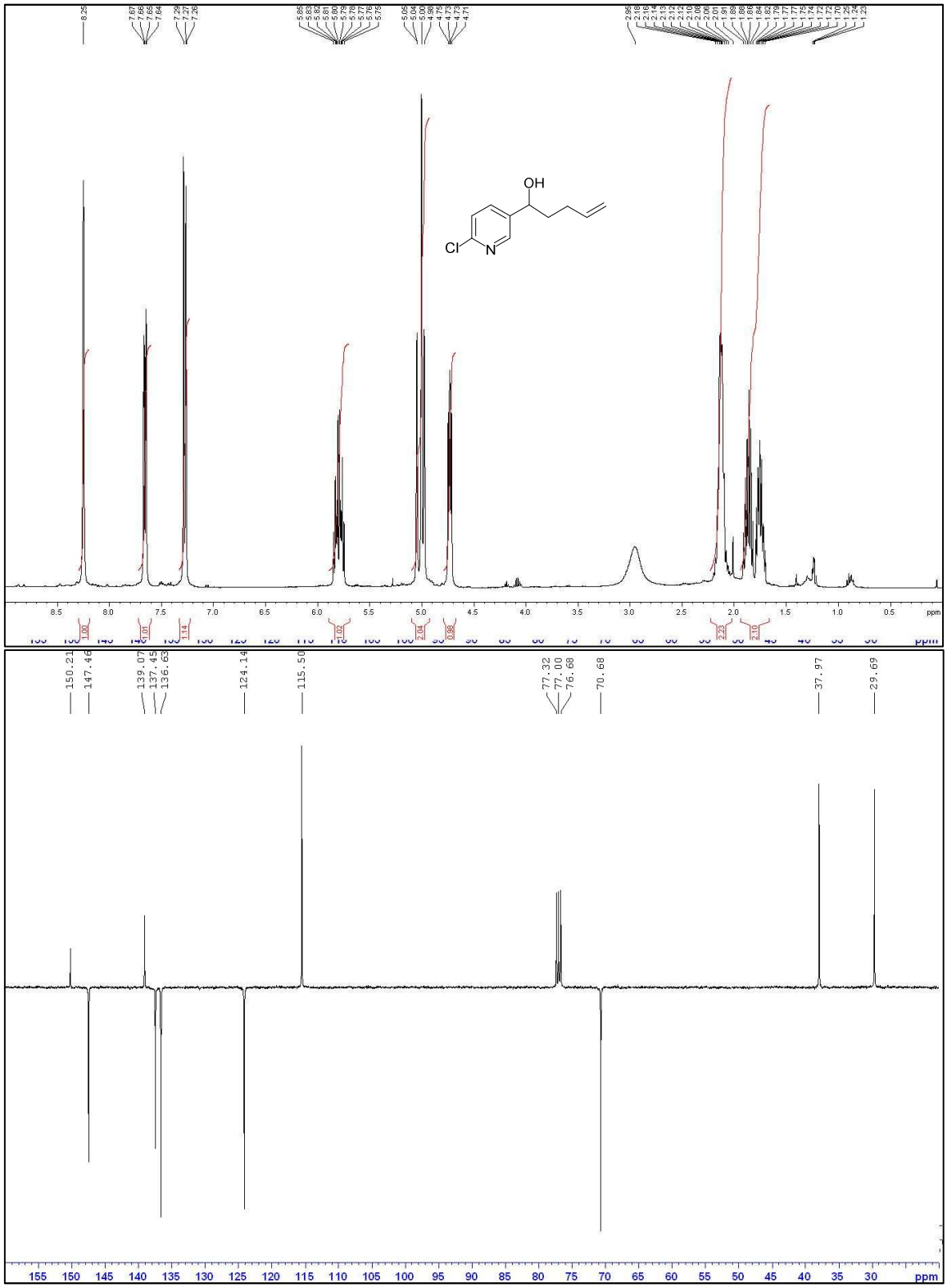
3. ^{1}H and ^{13}C NMR spectra in $CDCl_3$:

a. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra of compound (8a)

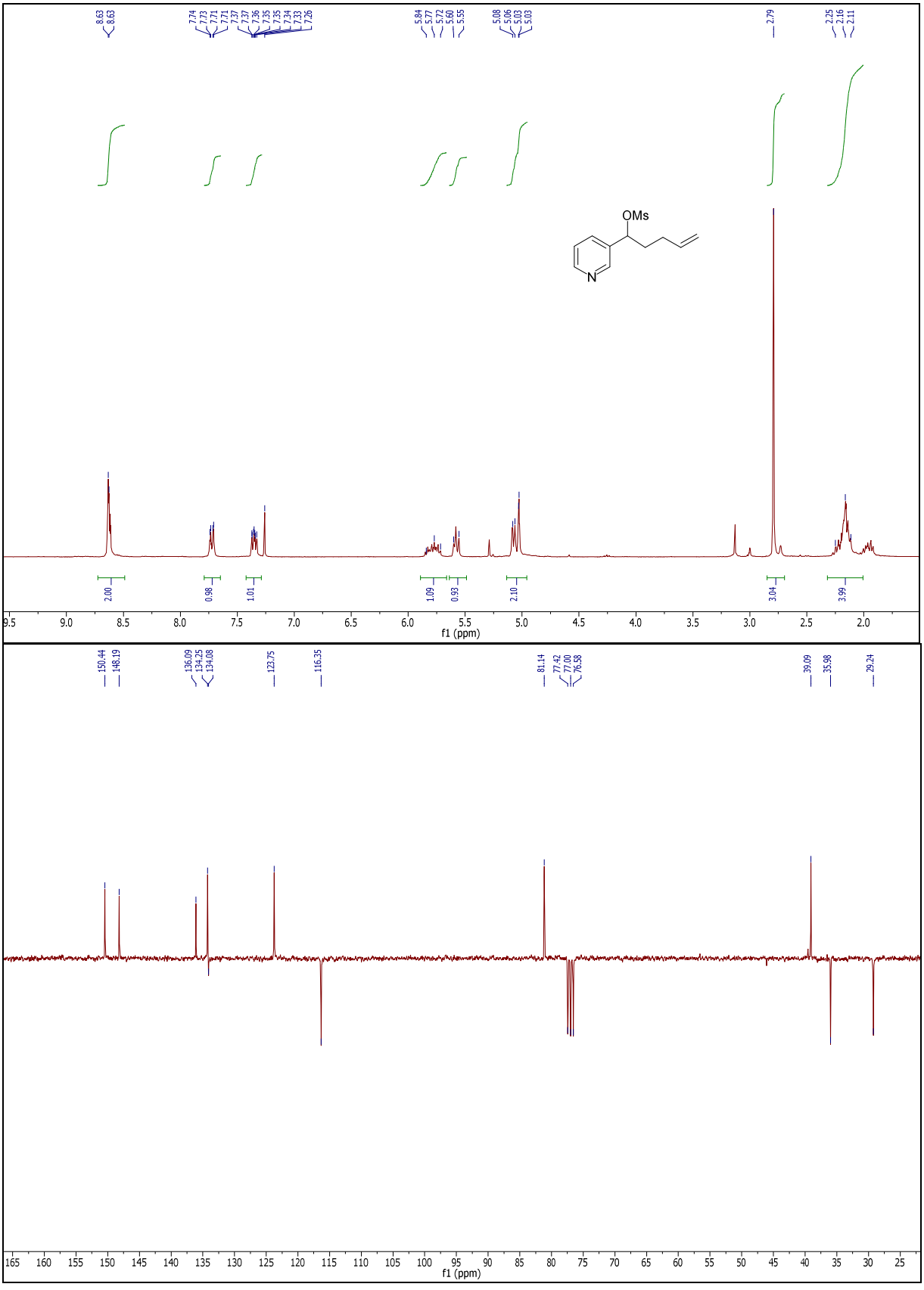




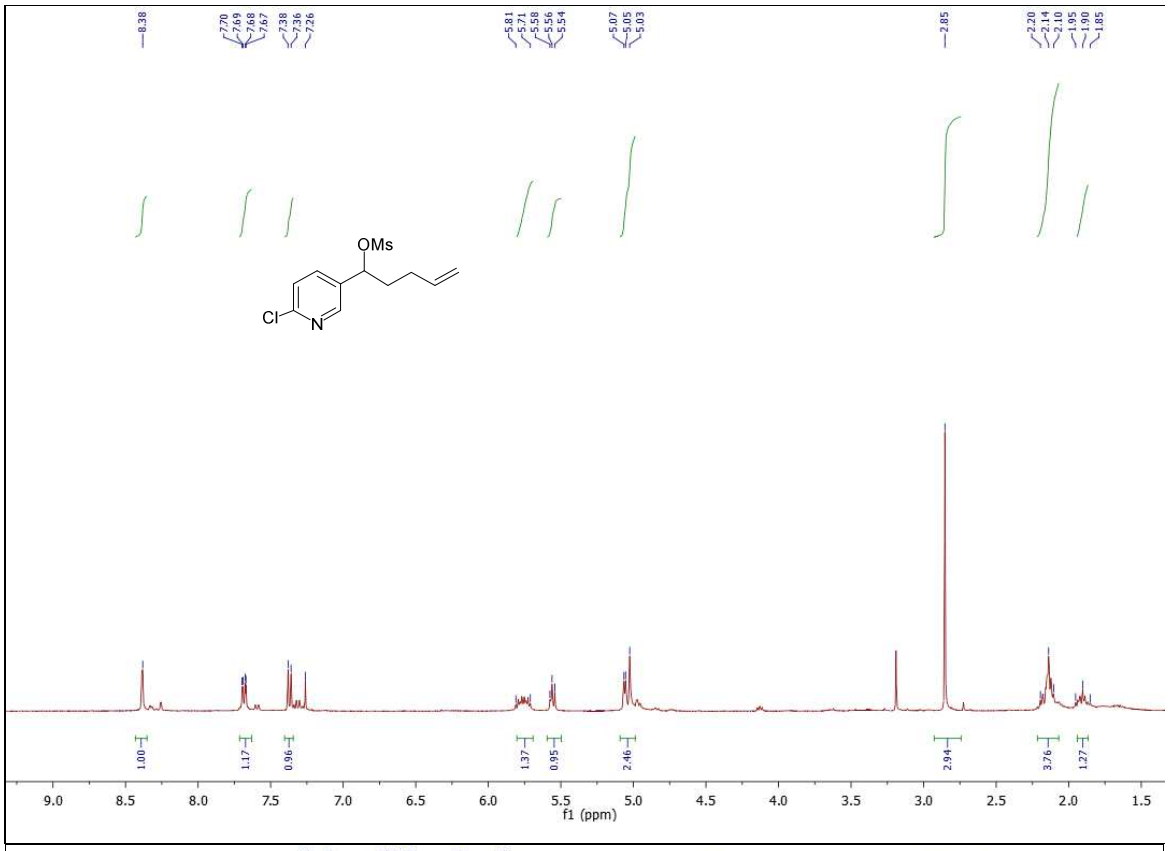
b. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra of compound (8b)

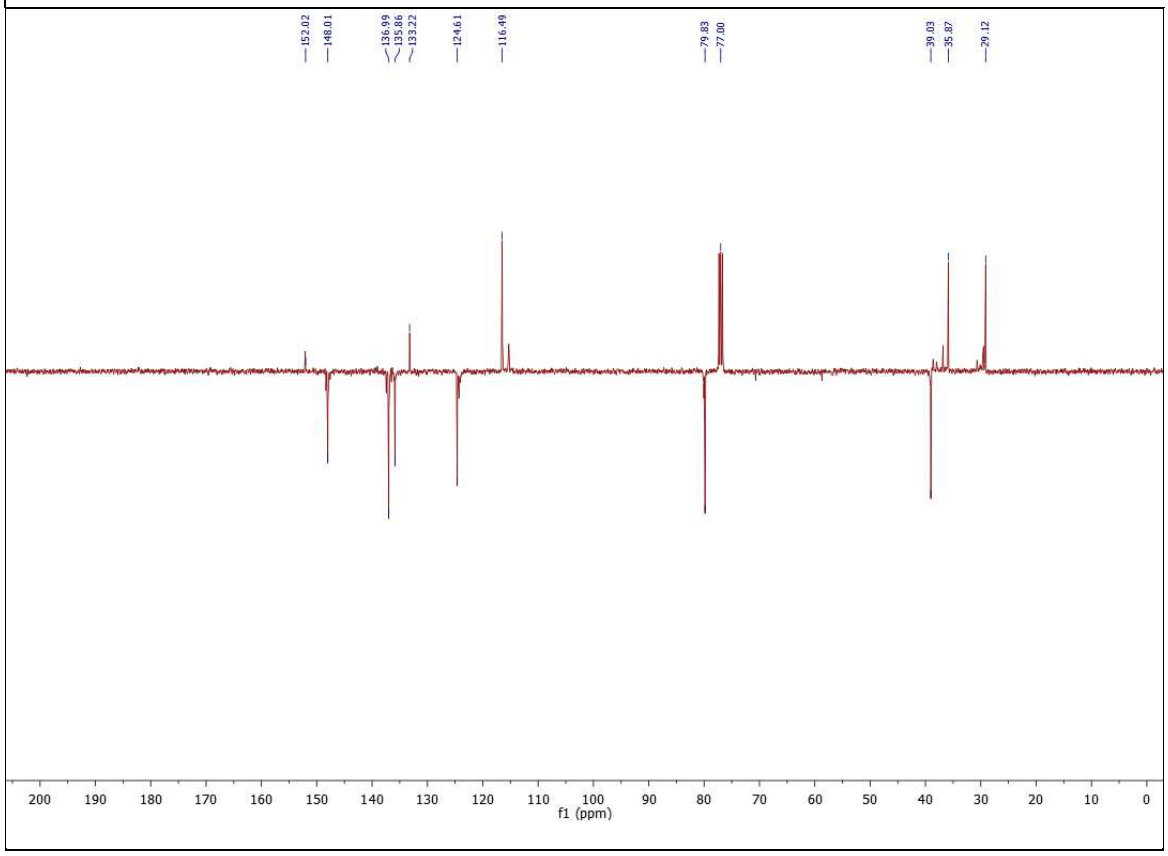


c. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra of compound (11a)

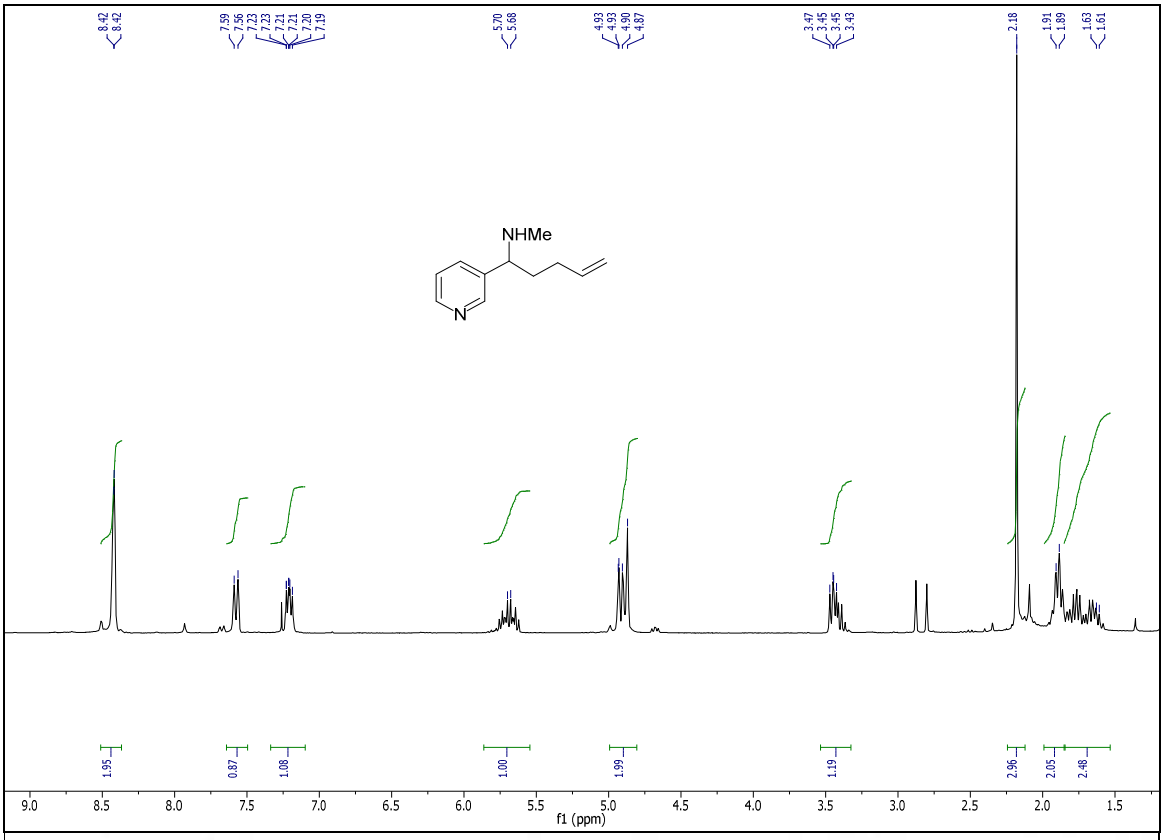


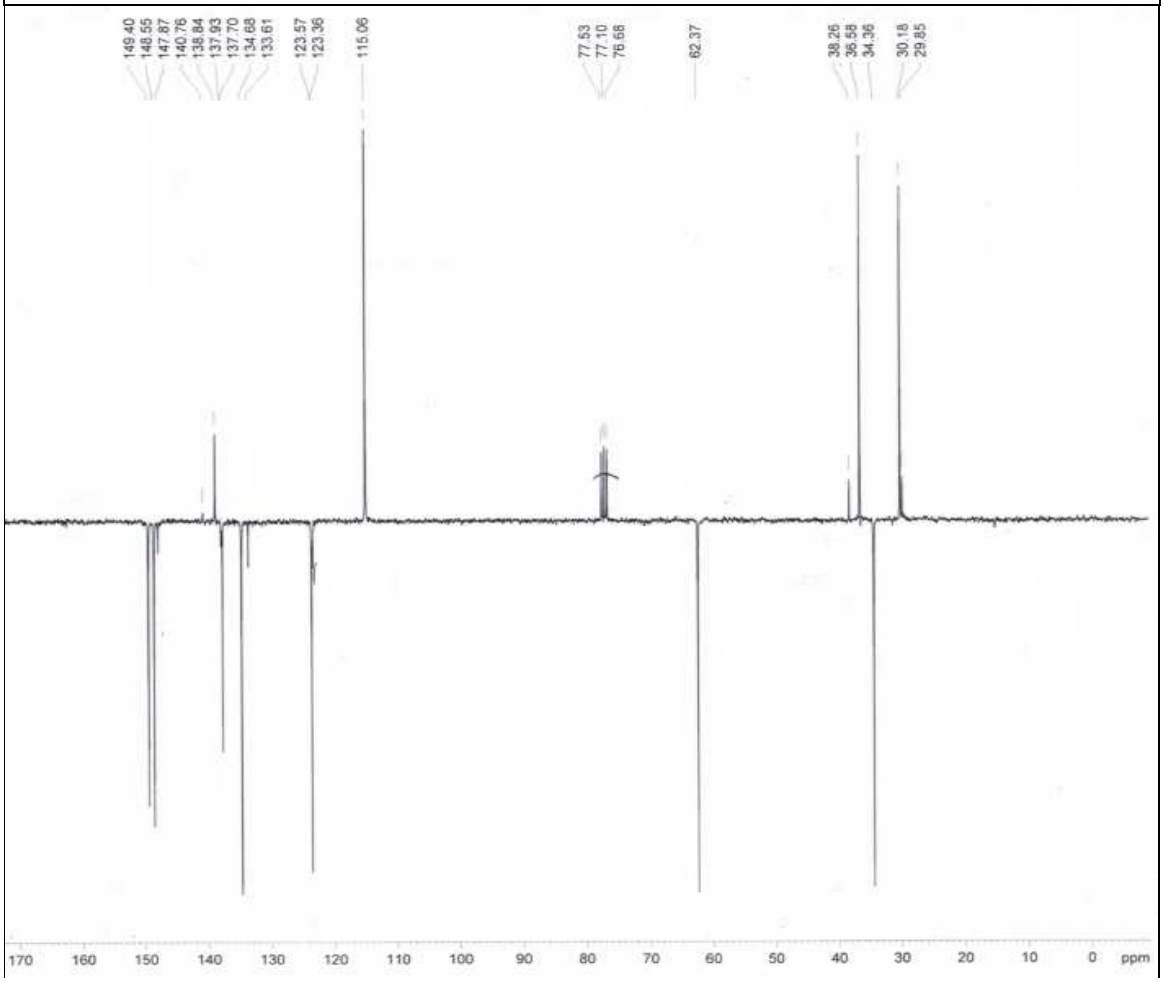
d. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra of compound (11b)



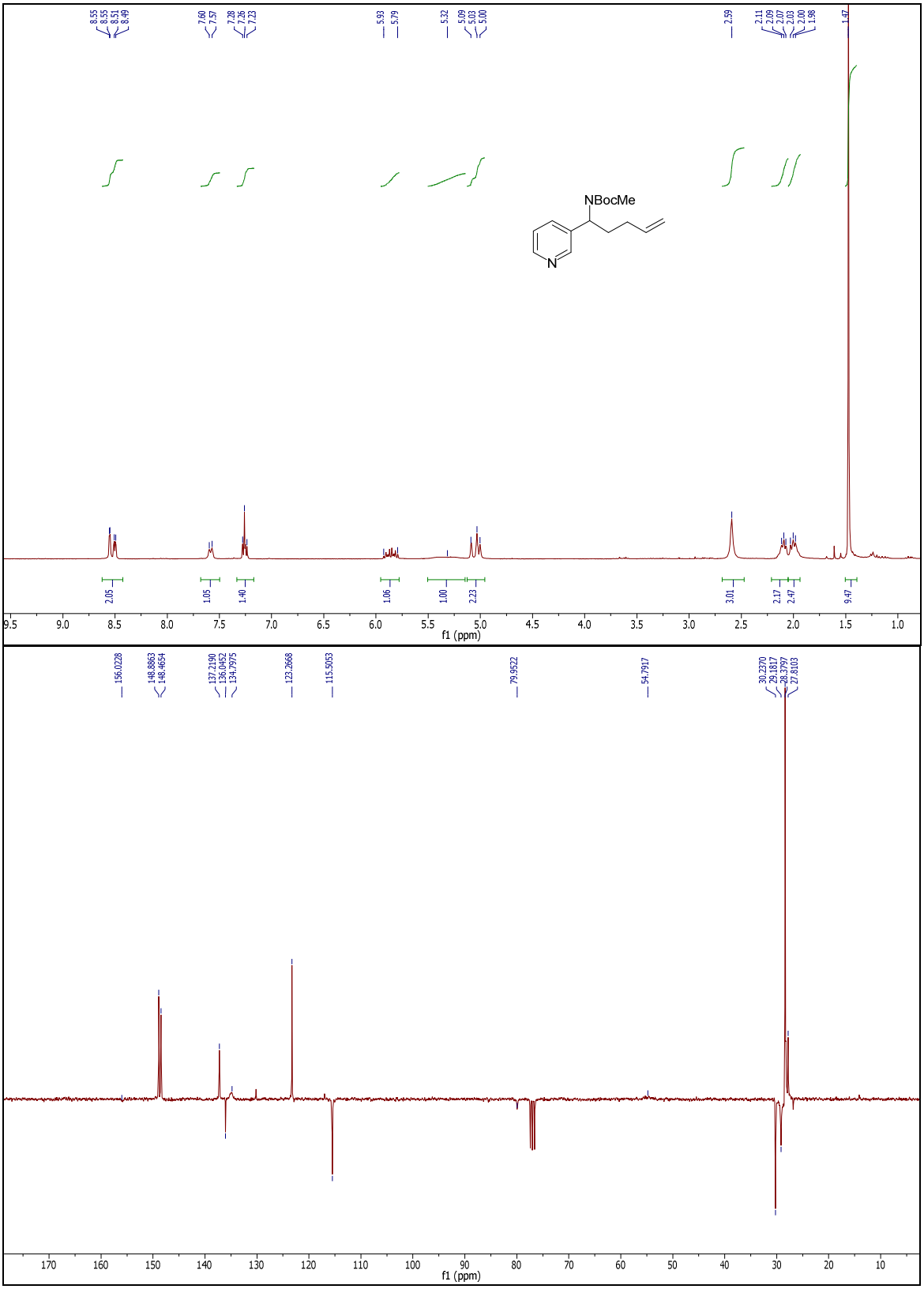


e. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra of compound (14a)

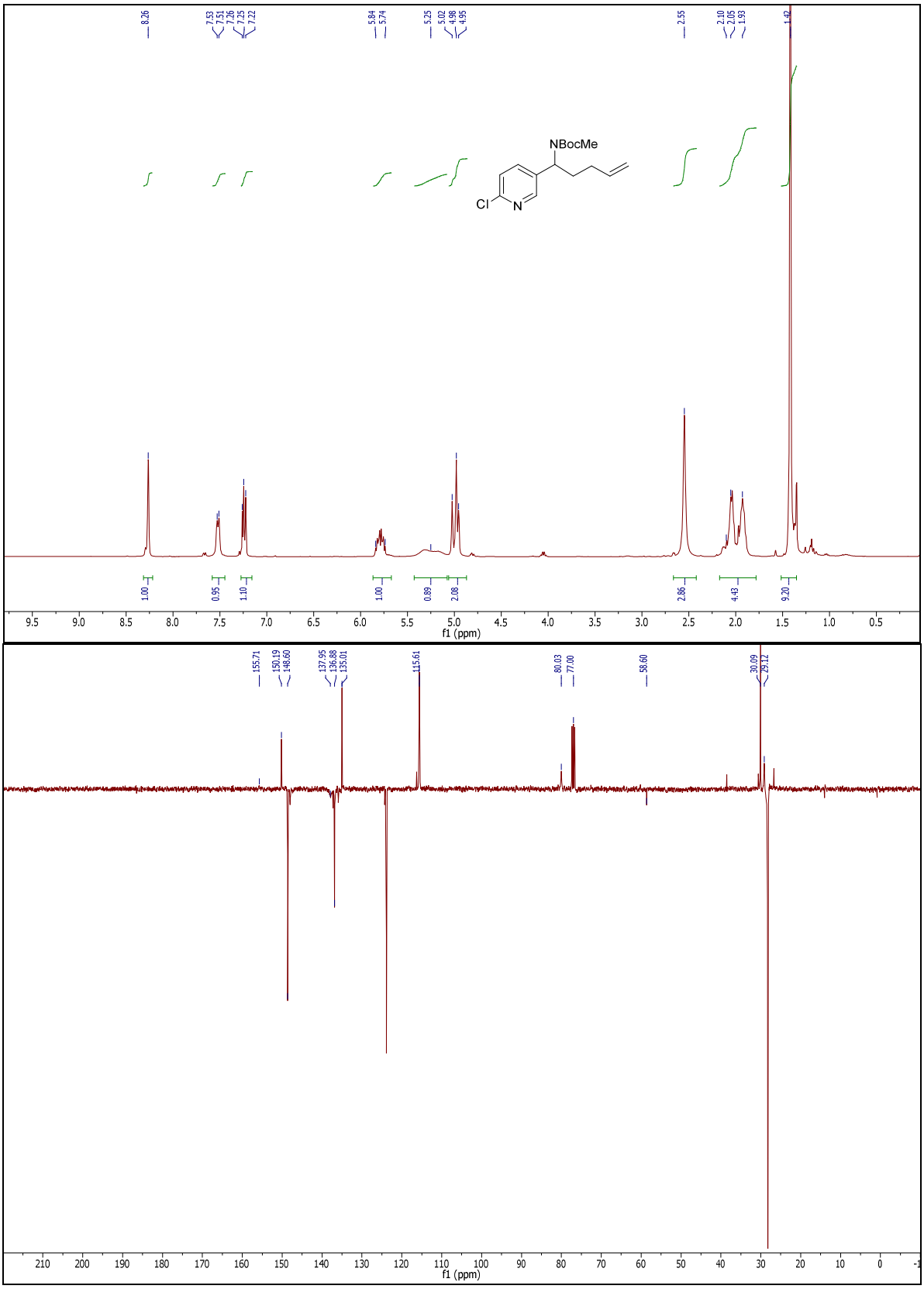


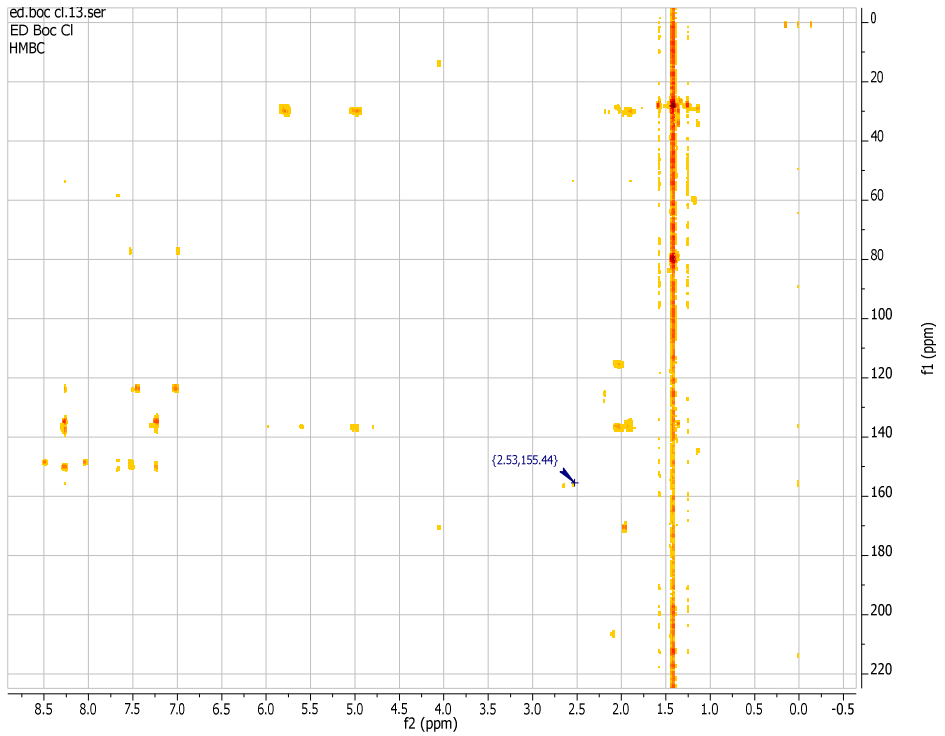


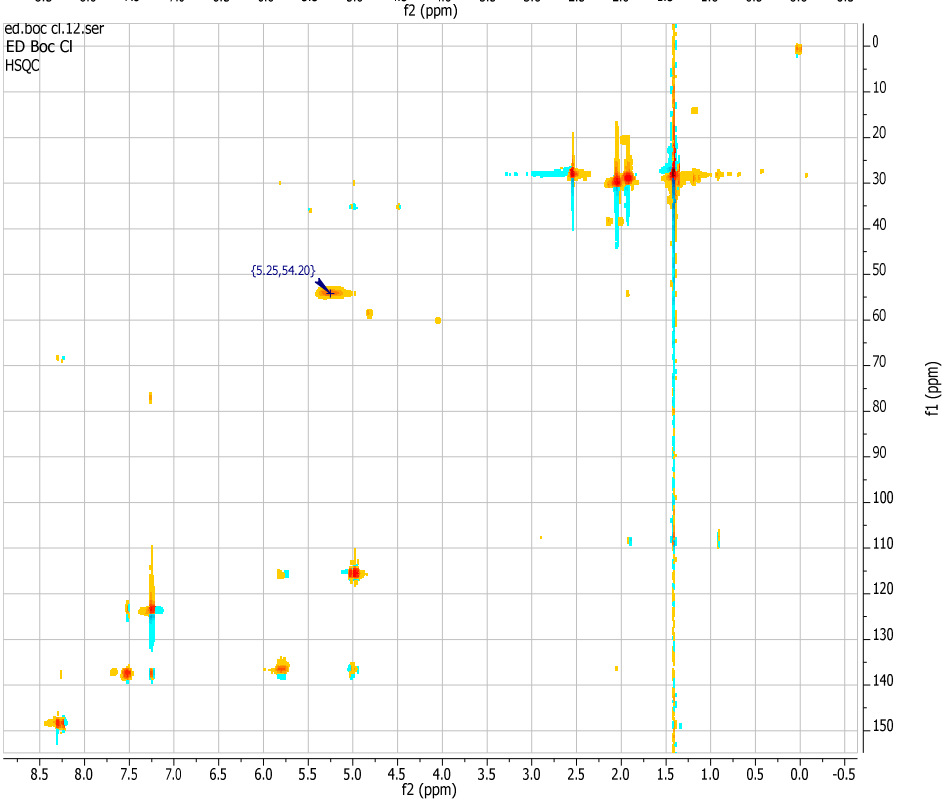
g. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra of compound (6a)



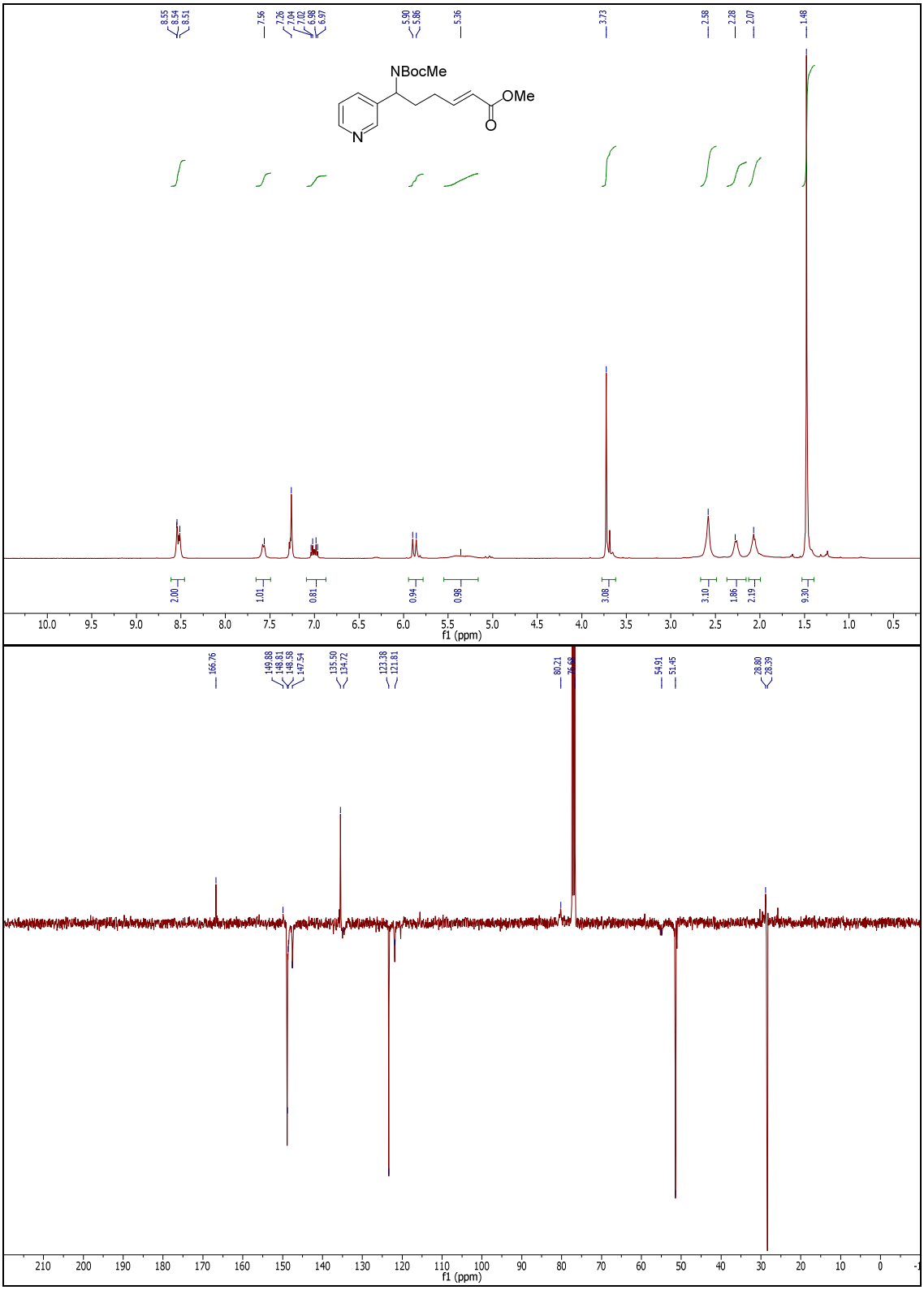
f. ^{1}H (400 MHz), ^{13}C (100 MHz) and HMBC NMR spectra of compound (6b)

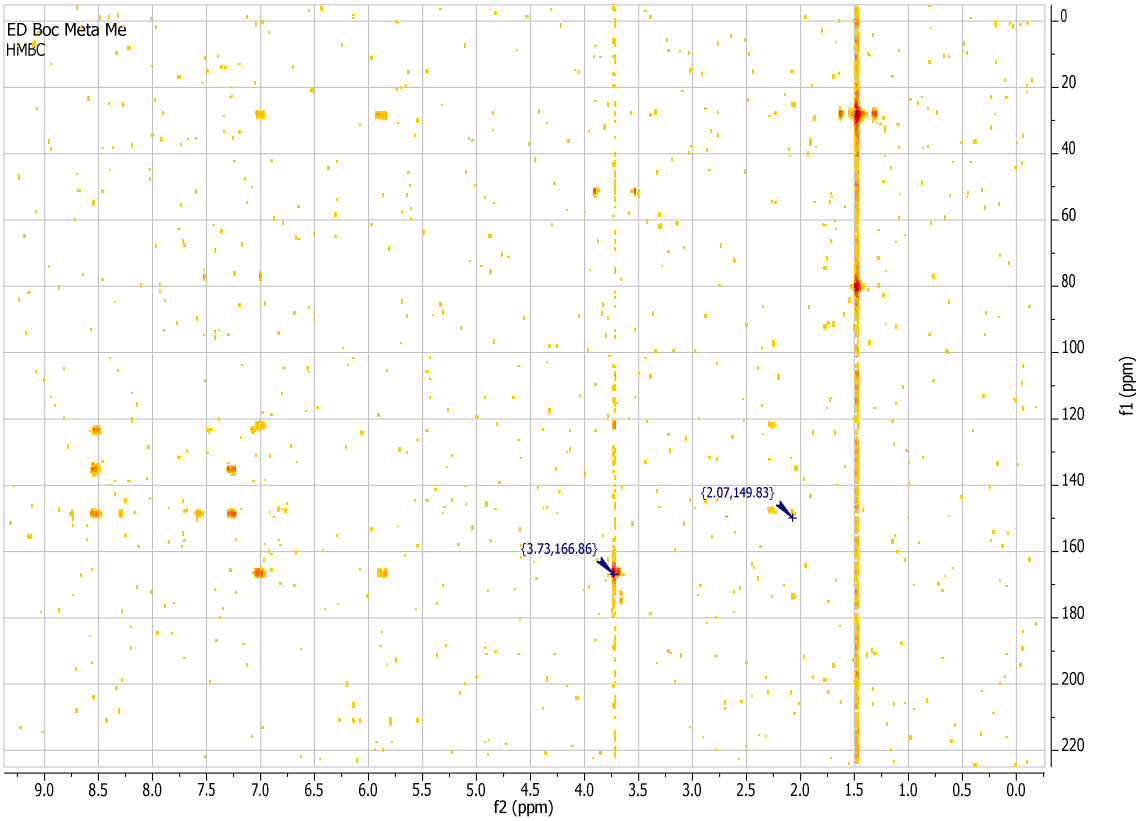



ed.boc cl.13.ser
ED Boc Cl
HMBC
{2.53,155.44}
f2 (ppm)
f1 (ppm)

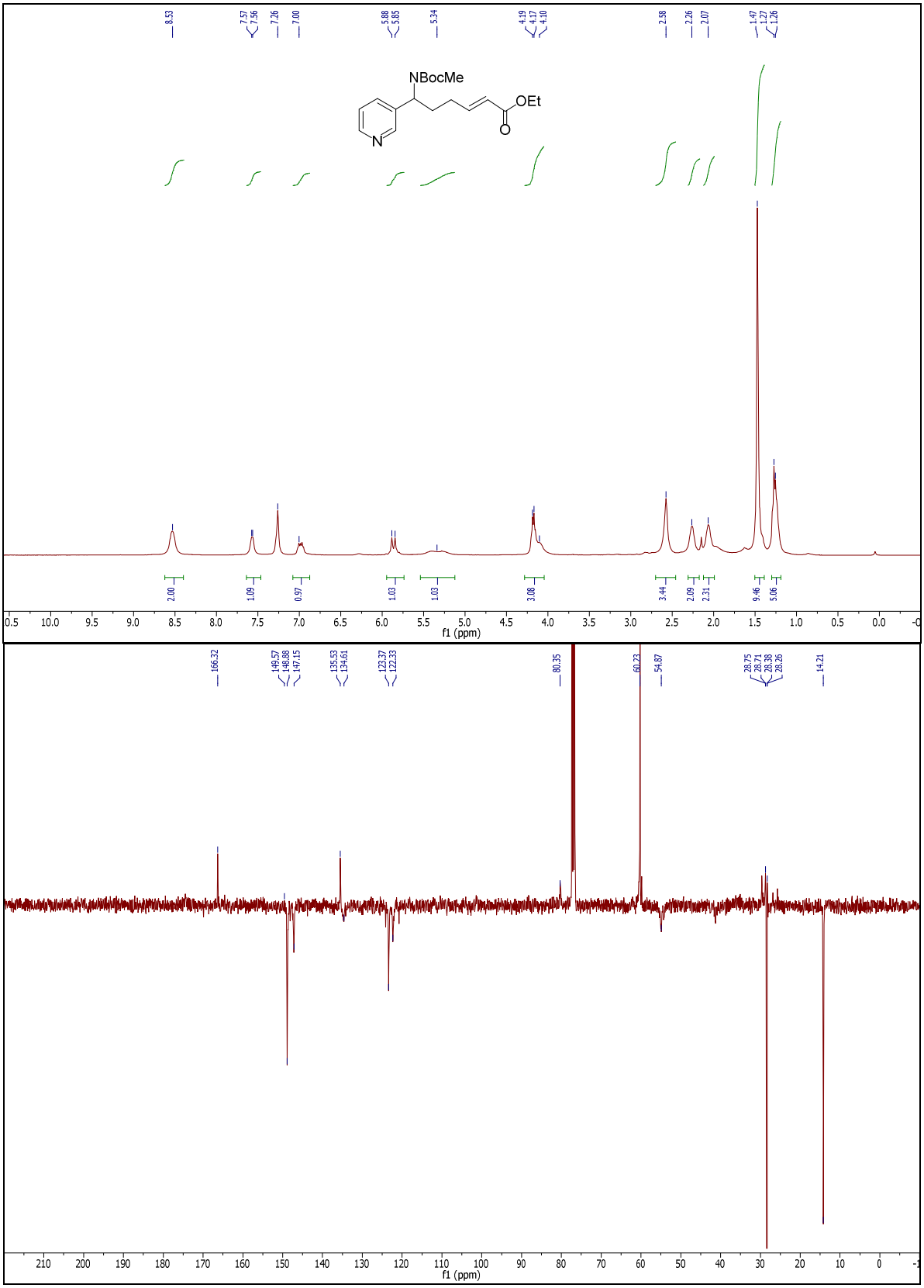

ed.boc cl.12.ser
ED Boc Cl
HSQC
{5.25,54.20}
f2 (ppm)
f1 (ppm)

h. ^{1}H (400 MHz), ^{13}C (100 MHz) and HMBC NMR spectra of compound (15aa)

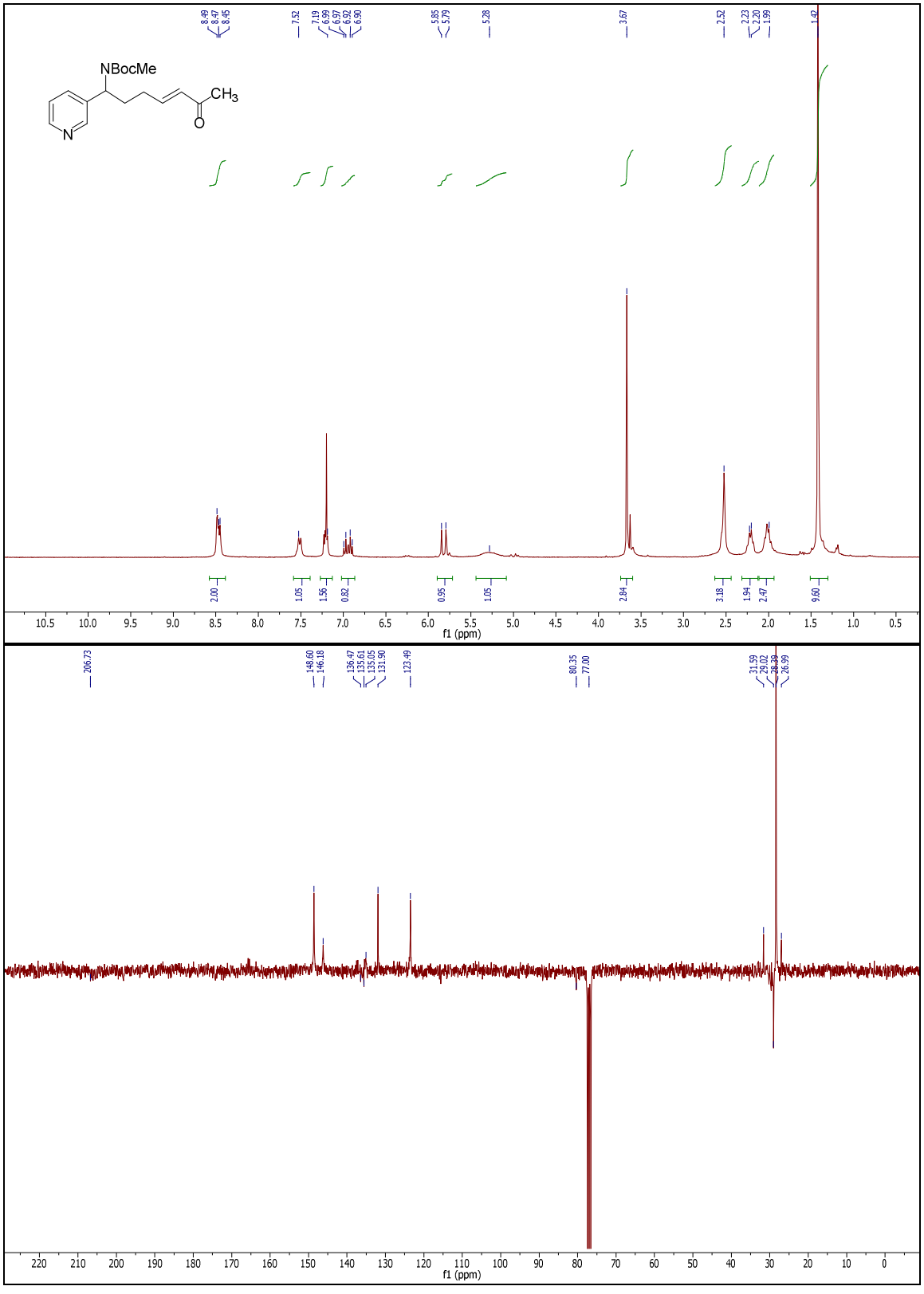



ED Boc Meta Me
HMBC
{2.07,149.83}
{3.73,166.86}
f2 (ppm)
f1 (ppm)

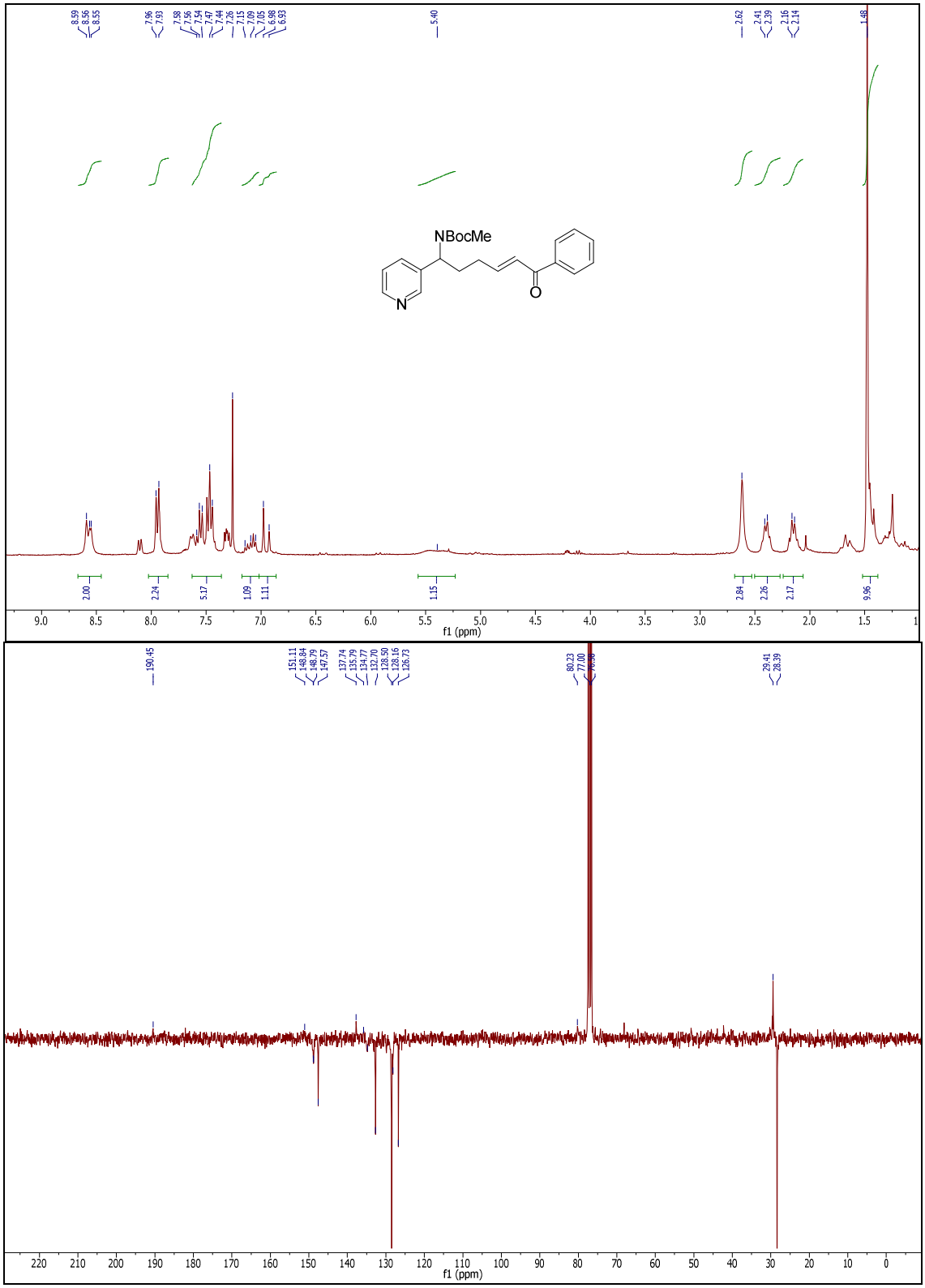
i. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra of compound (15ab)



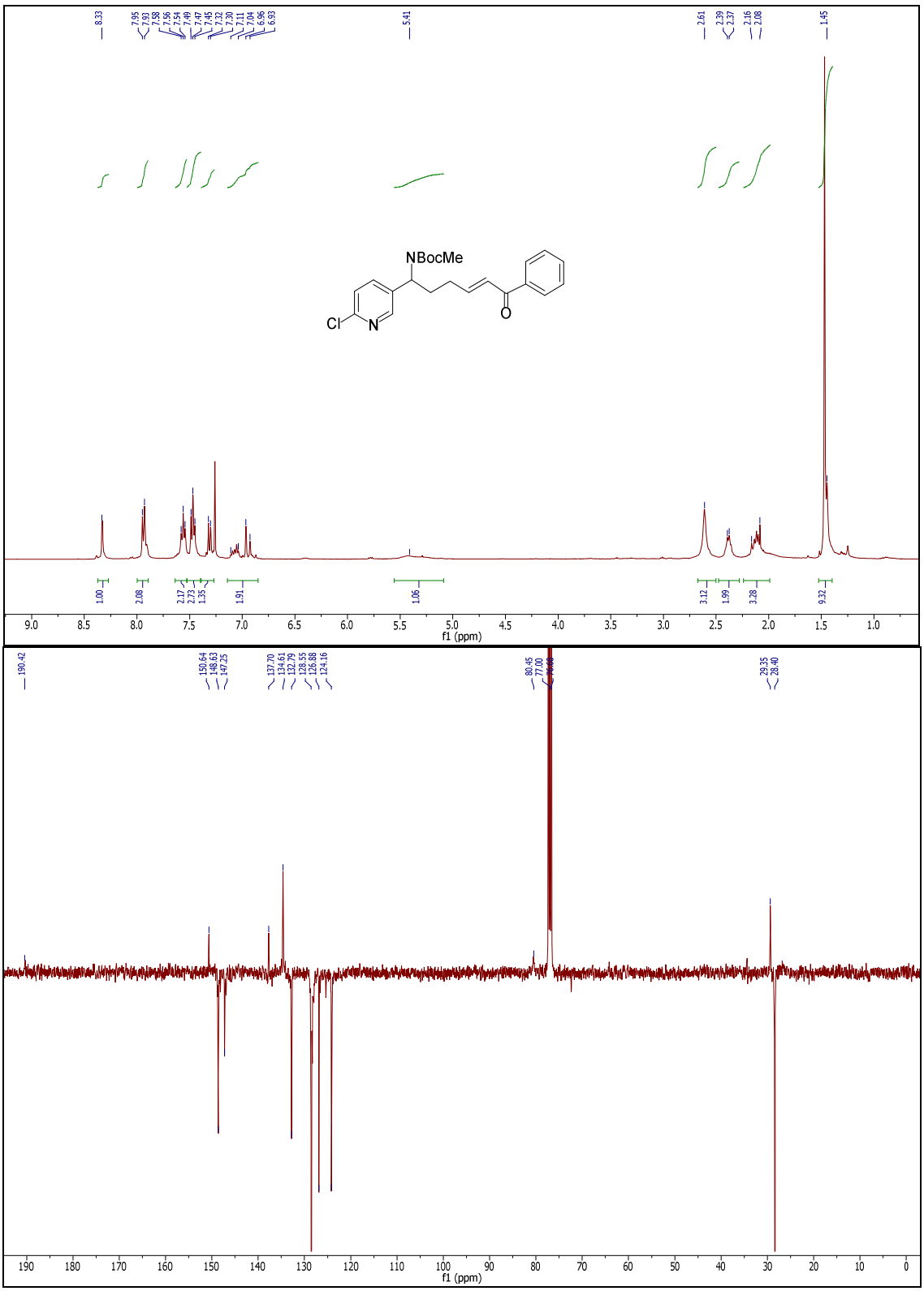
i. ^{1}H (300 MHz) NMR spectra of compound (15ac)

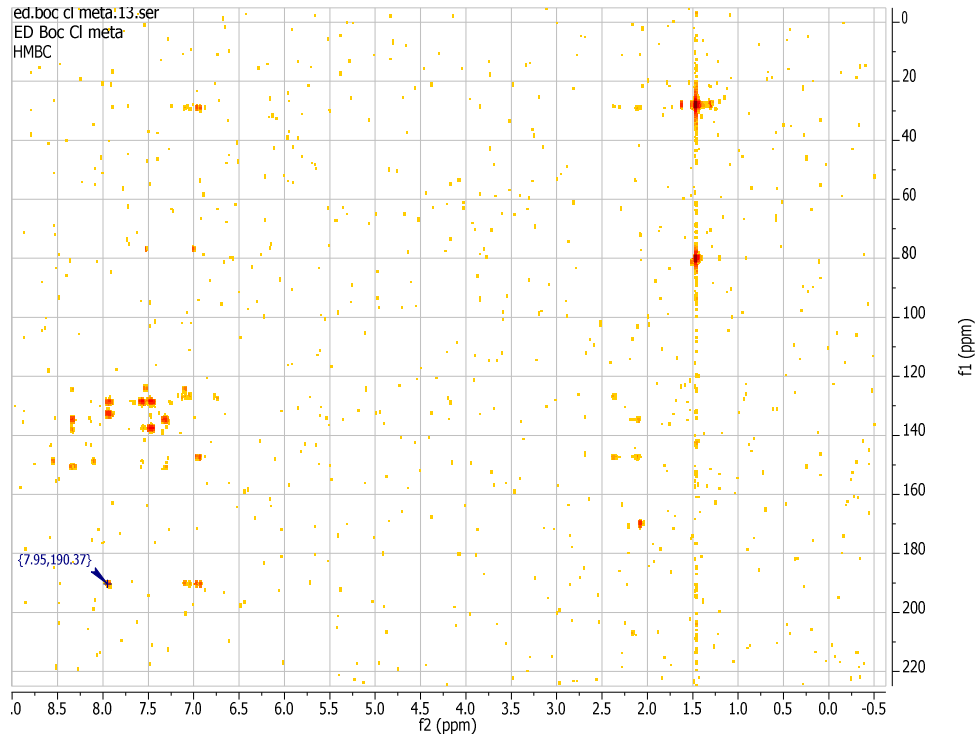


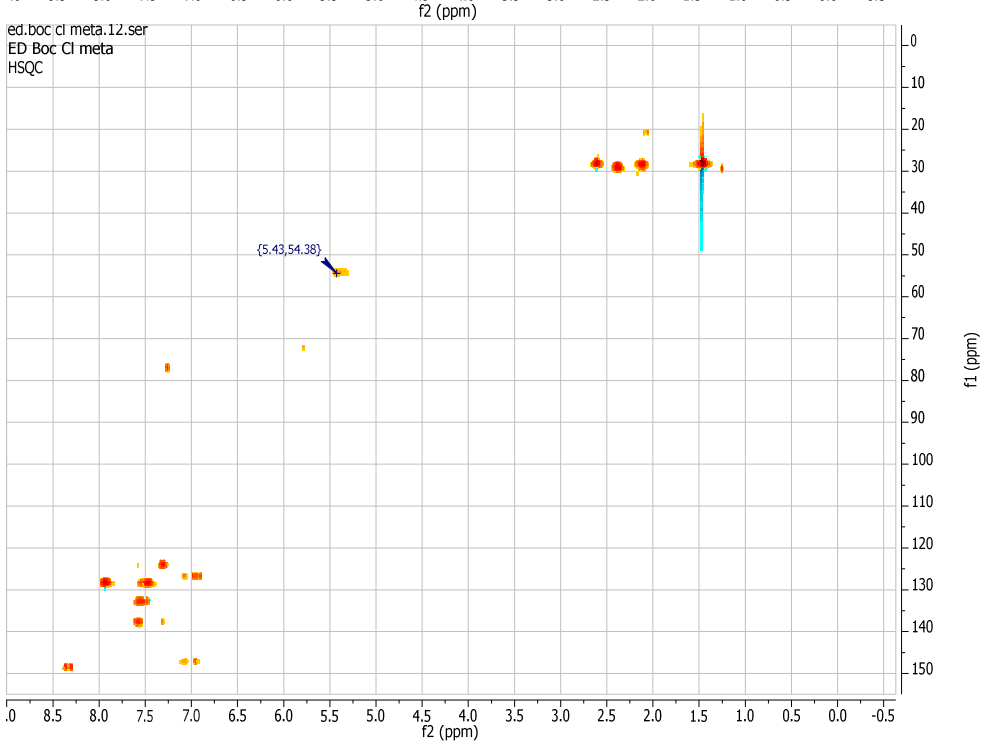
j. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra of compound (15ad)



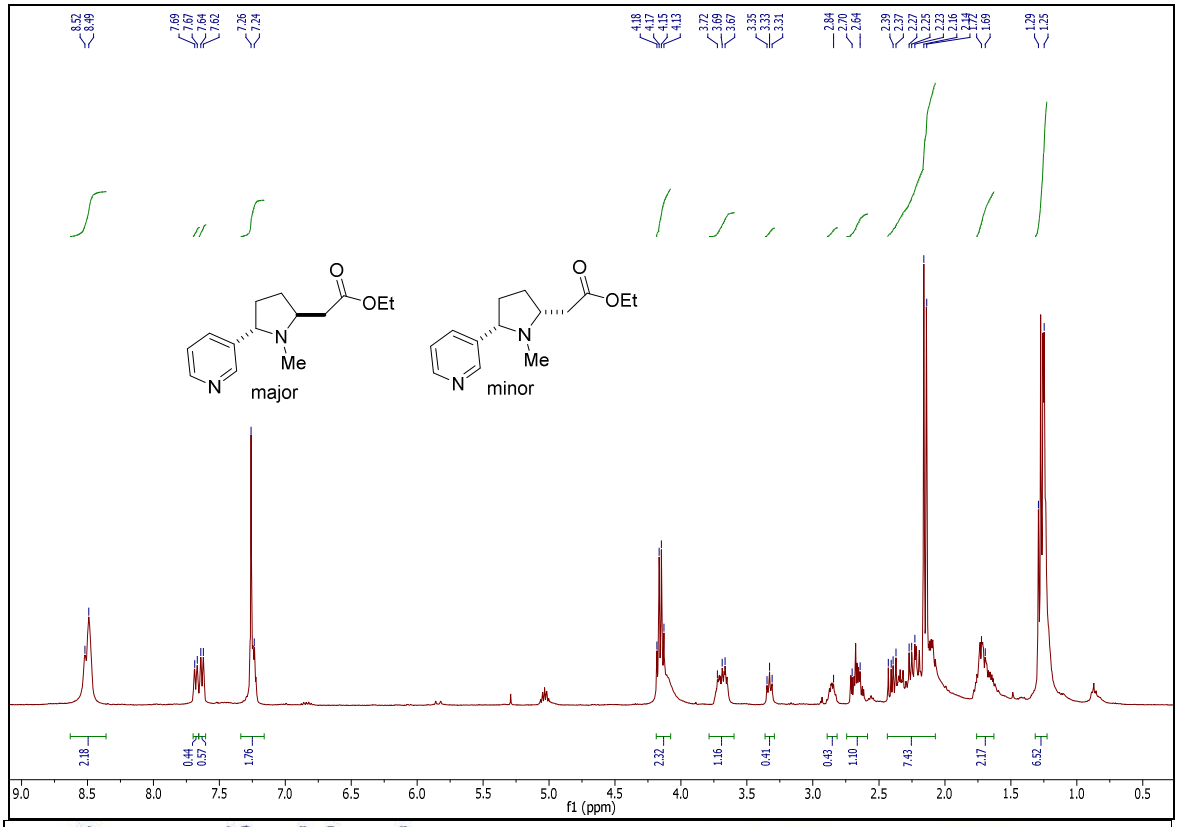
k. ^{1}H (400 MHz), ^{13}C (100 MHz), HMBC and HSQC NMR spectra of compound (15bd)

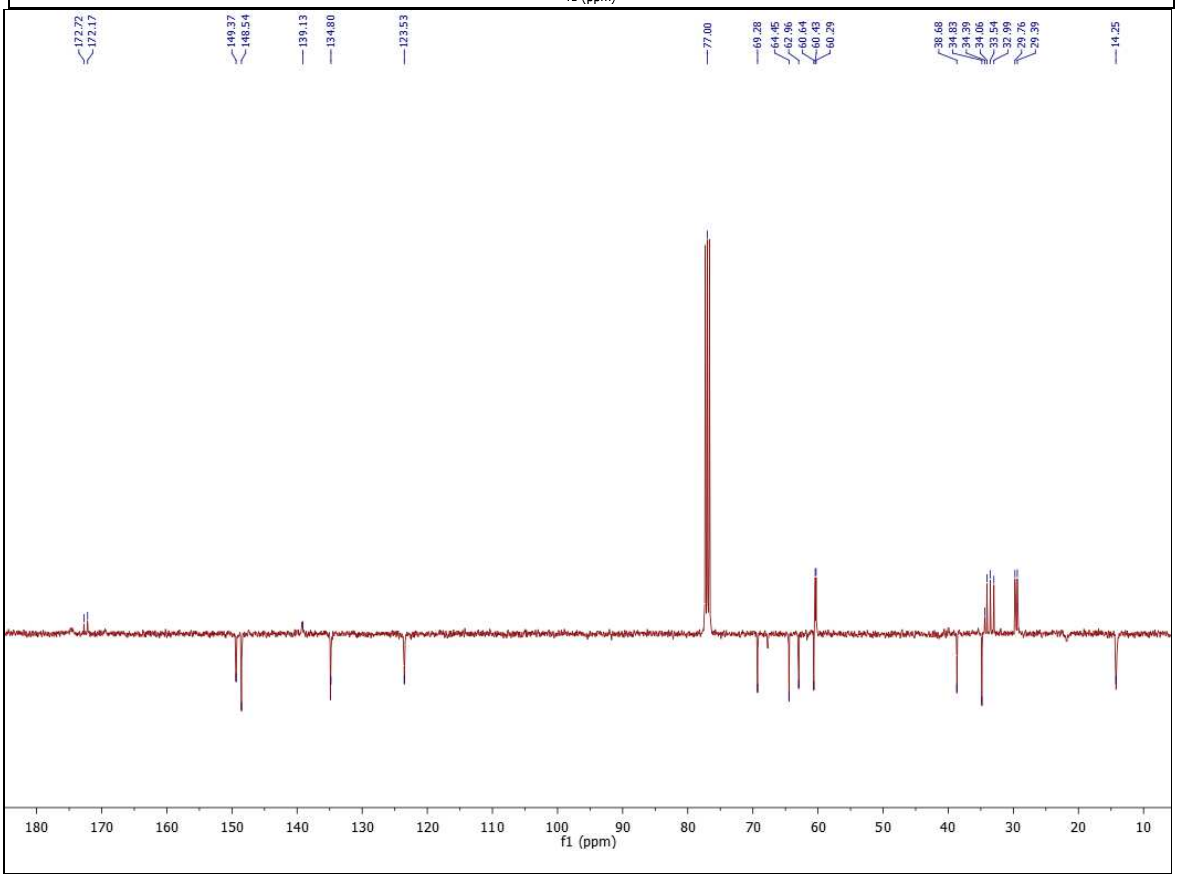



ed.boc cl meta.13.ser
ED Boc Cl meta
HMBC
{7.95,190.37}
f2 (ppm)
f1 (ppm)

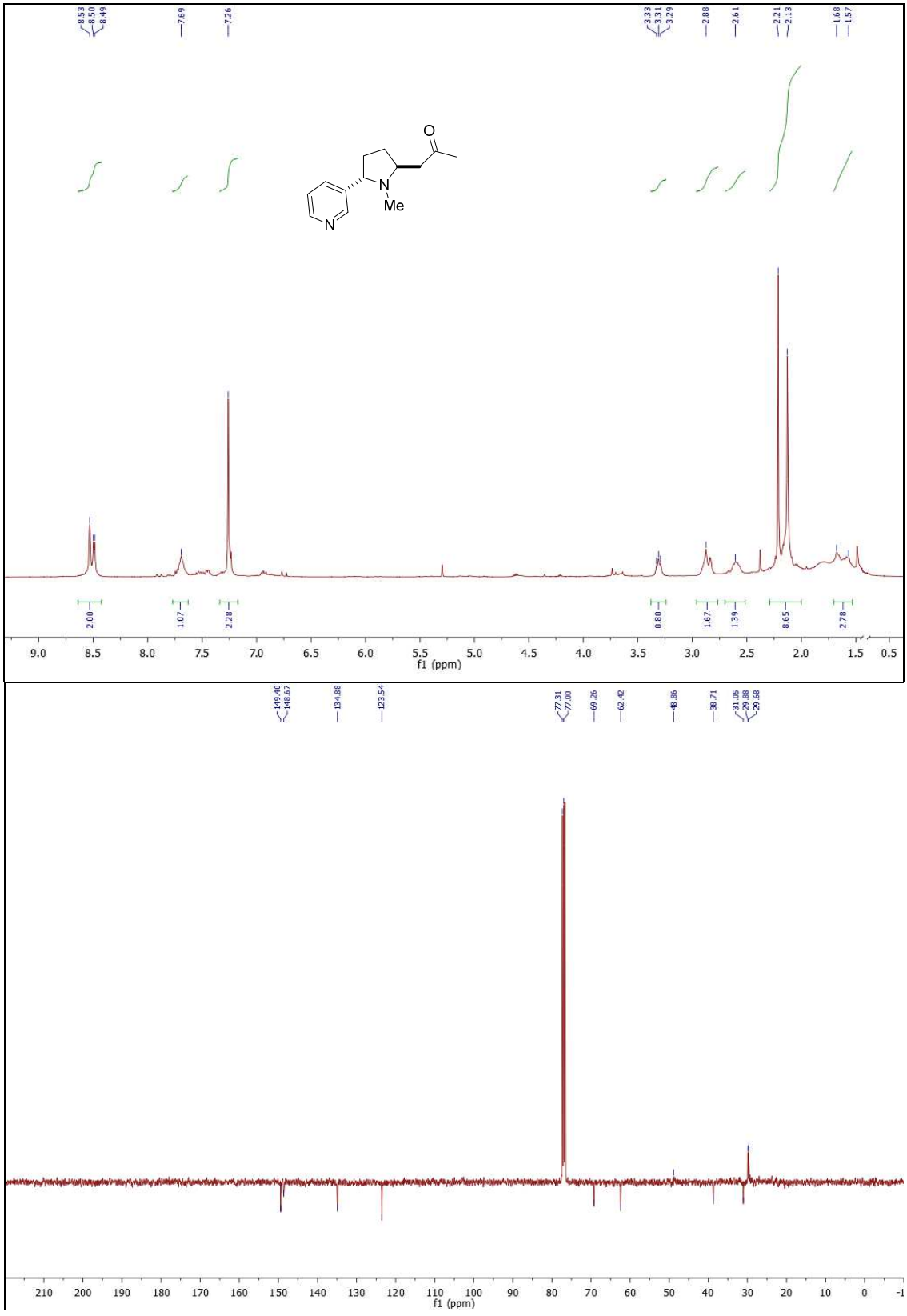

ed.boc cl meta.12.ser
ED Boc Cl meta
HSQC
{5.43,54.38}
f2 (ppm)
f1 (ppm)

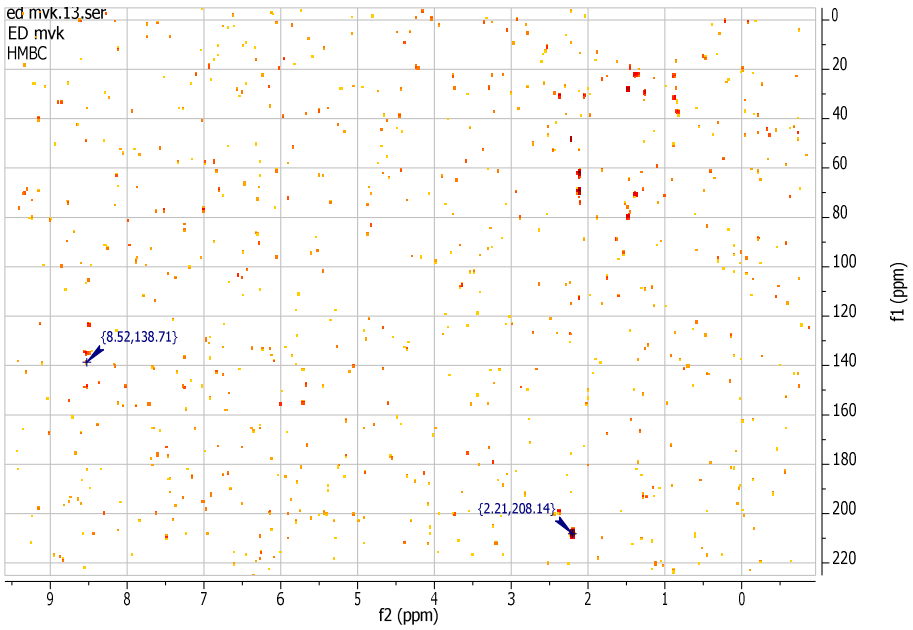
l. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra of compound (5ab)



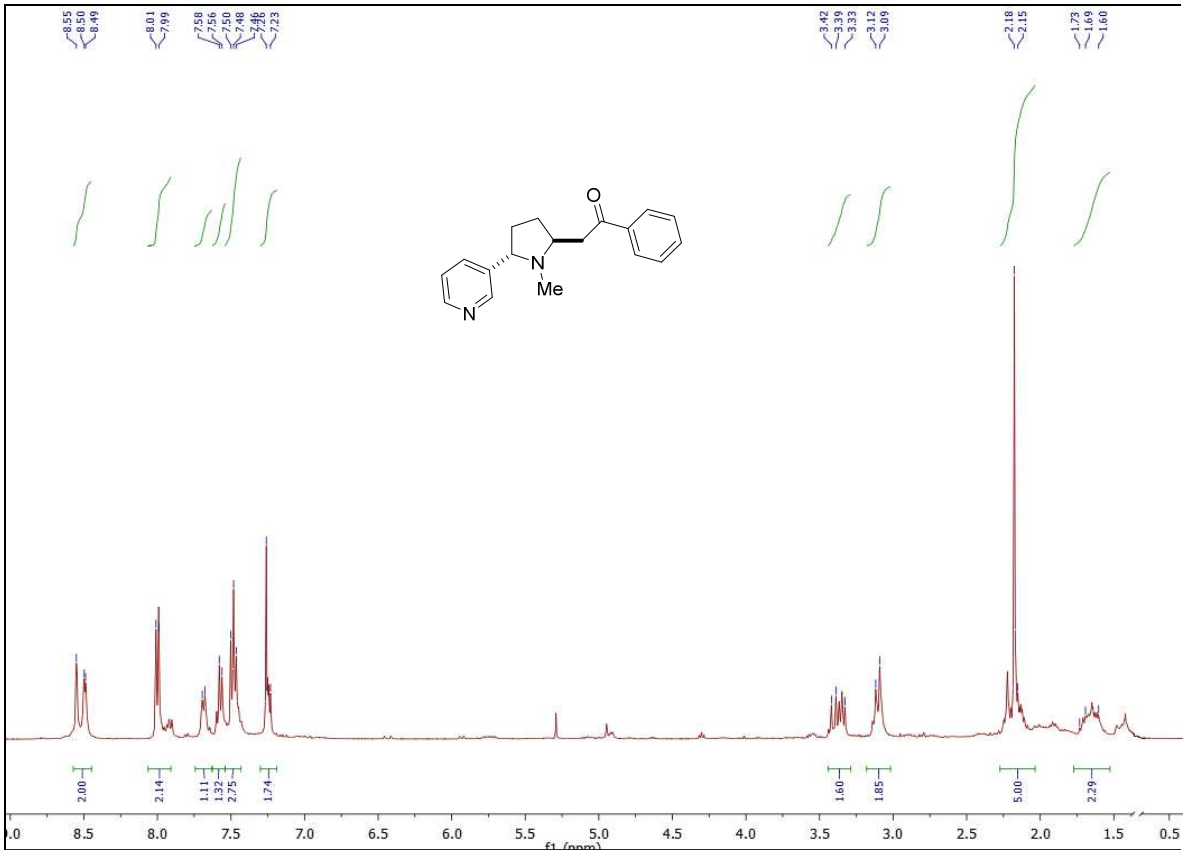


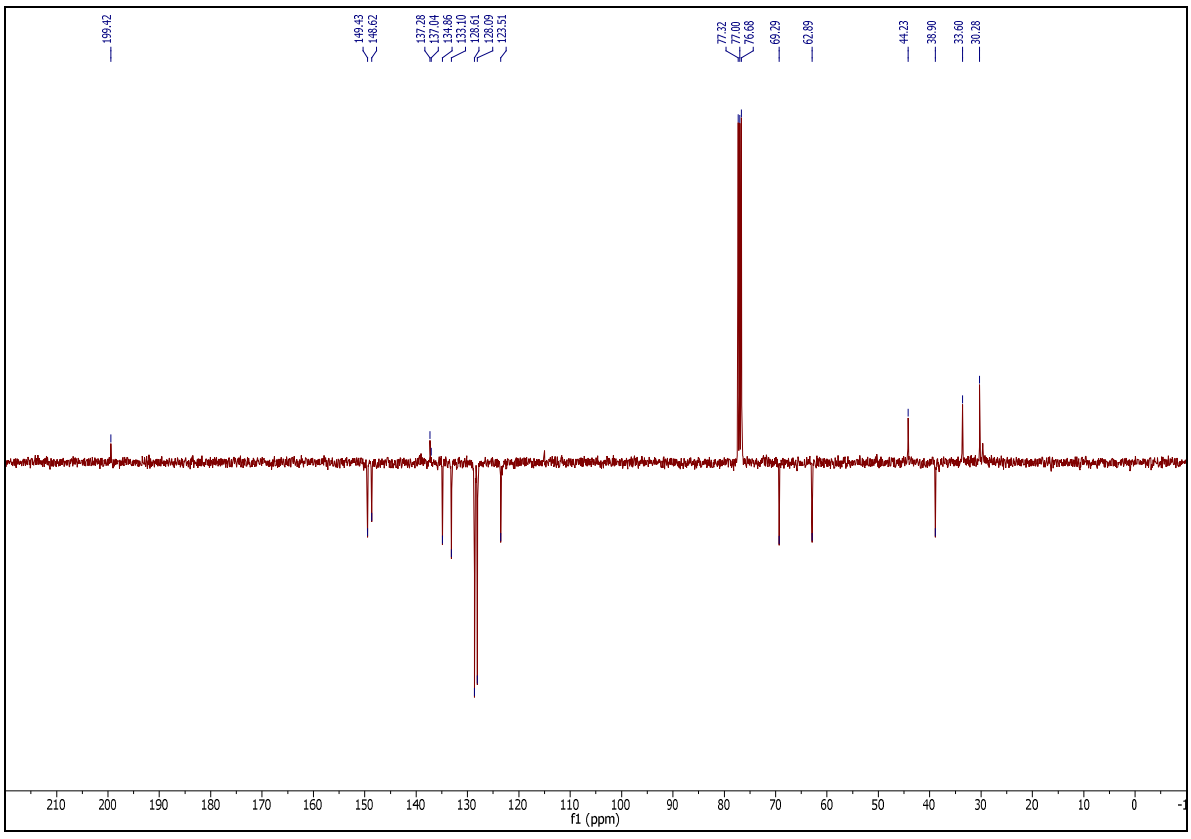
m. ^{1}H (400 MHz) ^{13}C (100 MHz) and HMBC NMR spectra of compound (5ac)

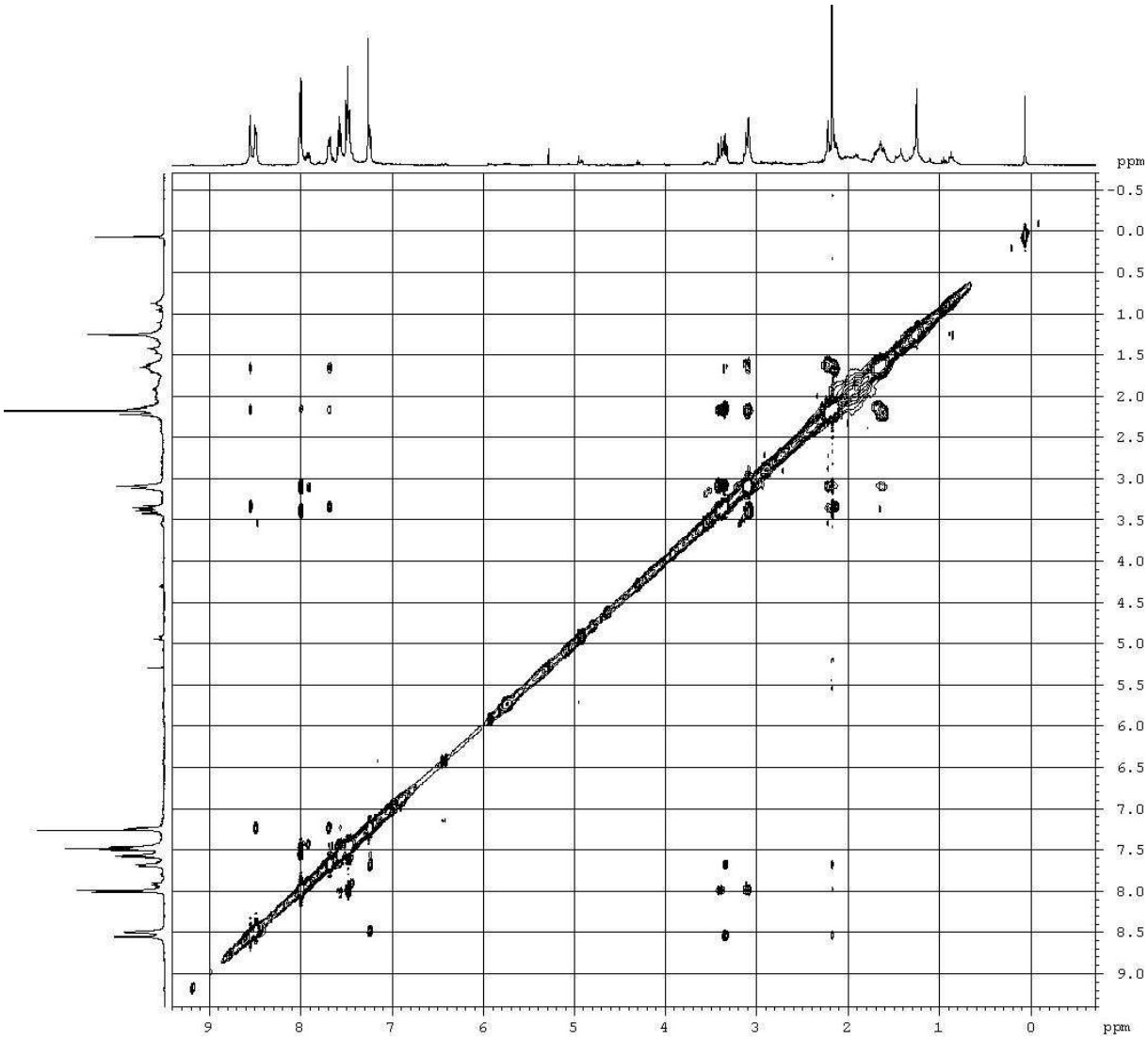



ed mvk.13.ser
ED mvk
HMBC
{8.52,138.71}
{2.21,208.14}
f2 (ppm)
f1 (ppm)

n. ^{1}H (400 MHz), ^{13}C (100 MHz) and NOESY NMR spectra of compound (5ad)

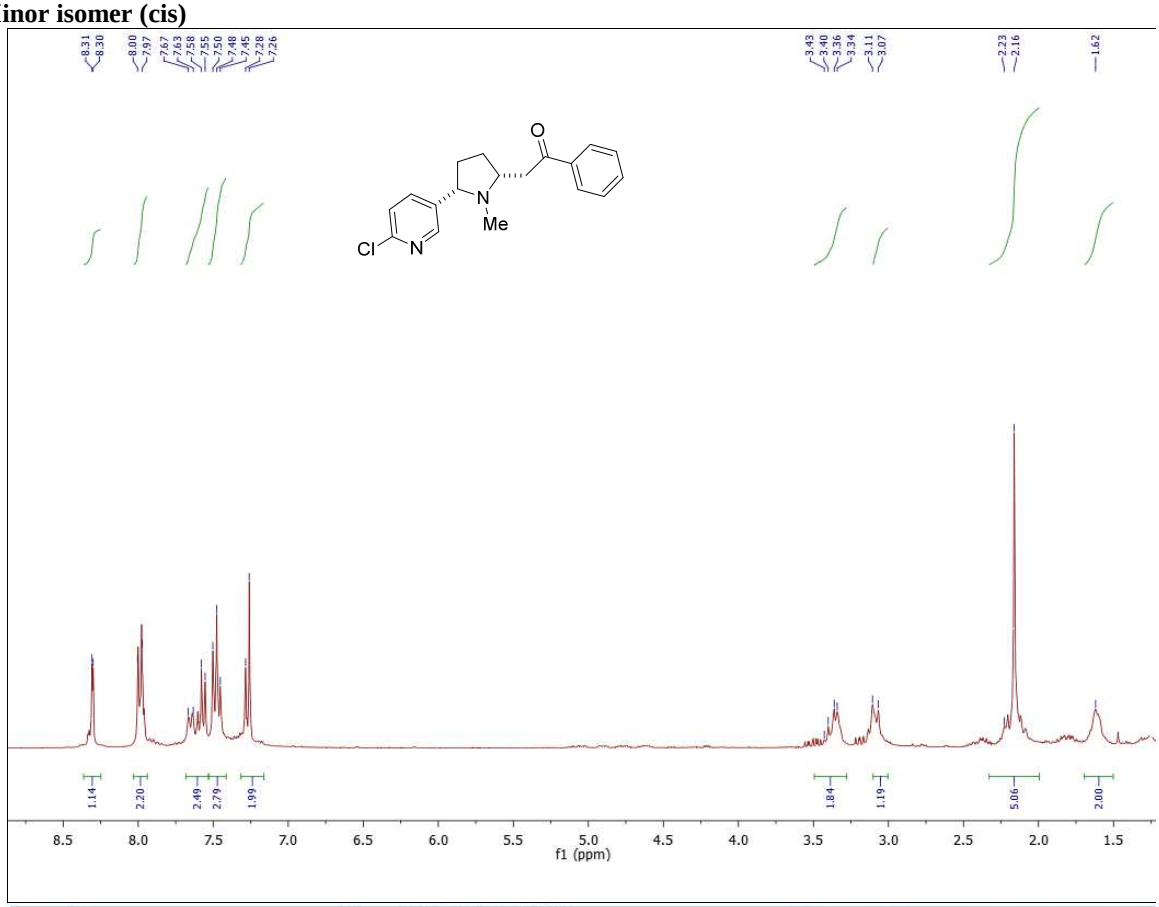


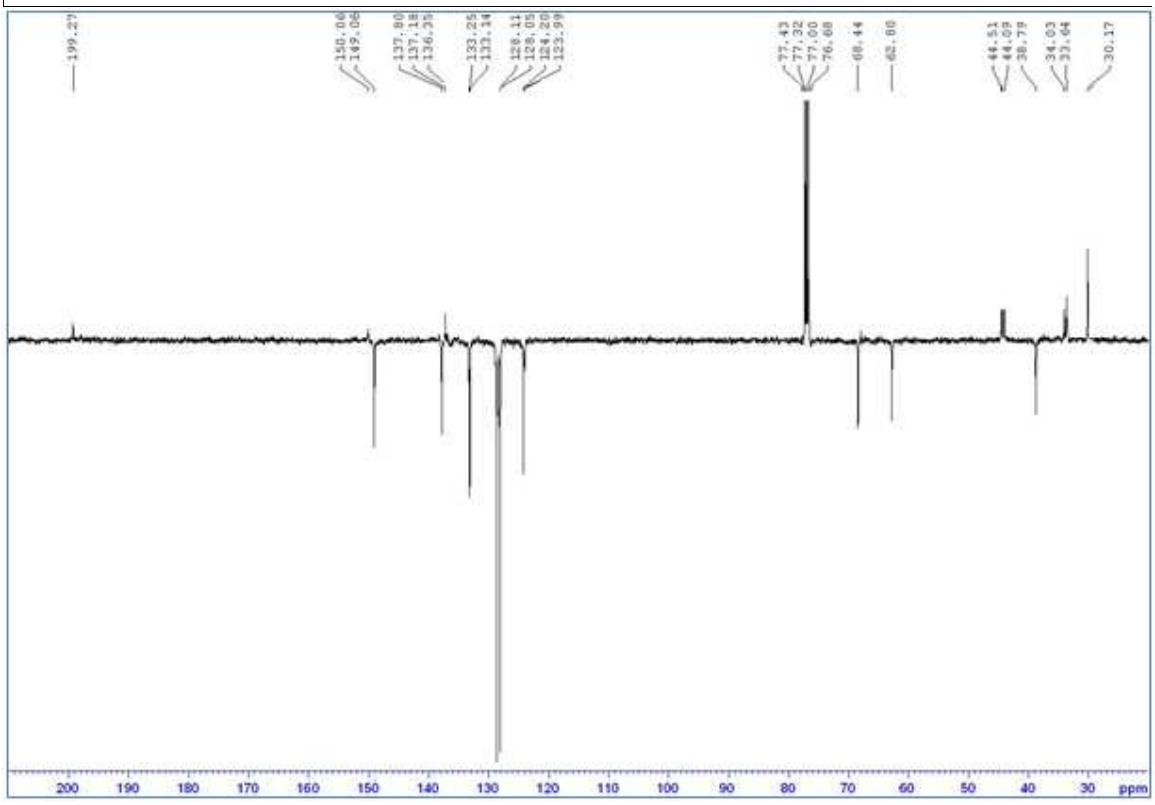



ppm
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9
8
7
6
5
4
3
2
1
0
ppm

o. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra of compound (5bd)

Minor isomer (cis)





Mixture of major (trans) and minor (cis)