Modular Syntheses of Phenanthroindolizidine Natural Products

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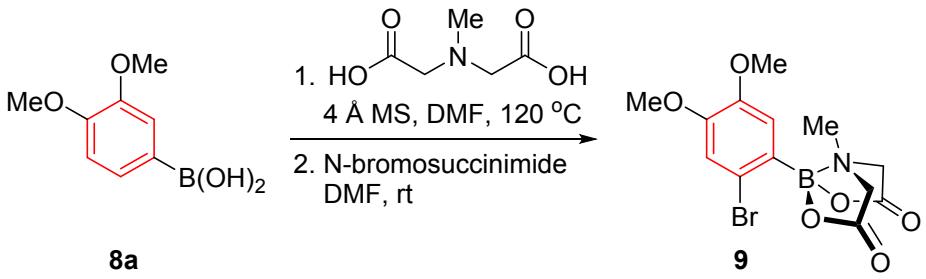
1. General Information

All reactions were carried out in oven-dried glassware in an open flask, unless otherwise noted. Except as otherwise indicated, all reactions were magnetically stirred and monitored by analytical thin layer chromatography (TLC) using pre-coated silica gel glass plates (0.25 mm) with F254 indicator. Visualization was accomplished by UV light (254 nm), with a combination of potassium permanganate and/or phosphomolybdic acid solution as an indicator. Flash column chromatography was performed using silica gel 60 (230 – 400 mesh). Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise noted. Commercial grade reagents and solvents were used without further purification. Boronic acids **8** and dibromopyridines **11** were purchased from commercial suppliers and used without further purification unless otherwise noted. *ortho*-Brominated MIDA (N-methyliminodiacetic acid) boronate **9** was prepared via the procedure reported in the literature.[1] ^{1}H NMR and ^{13}C NMR spectra were recorded at 500 MHz and 125 MHz spectrometers, respectively. Tetramethylsilane (δ: 0.0 ppm) and residual NMR solvents, either $CDCl_3$ (δ_H: 7.26 ppm, δ_C: 77.16 ppm) or DMSO-d_6 (δ_H: 2.50 ppm, δ_C: 39.52 ppm), were used as internal standards for ^{1}H NMR and ^{13}C NMR spectra, respectively. The proton spectra are reported as follows: *δ* (position of proton, multiplicity, coupling constant *J*, number of protons). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (quintet), h (septet), m (multiplet) and br (broad). High resolution mass spectra (HRMS) were recorded on quadrupole time-of-flight mass spectrometer (QTOF-MS) using electrospray ionization (ESI) as an ionization method. Infrared spectra were measured by using attenuated total reflectance (ATR) mounted Bruker Alpha FT-IR spectrometer.

2. Synthesis of Building Blocks

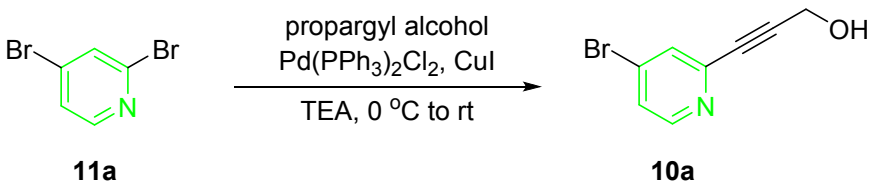
2-1. Synthesis of *ortho*-Bromoaryl MIDA Boronate 9



To a solution of **8a** (3.6 g, 20 mmol) in 200 mL of DMF were added N-methyliminodiacetate (4.4 g, 30 mmol) and molecular sieves (4 Å, 10 g). The reaction mixture was heated to 120 °C under nitrogen atmosphere and monitored by TLC. After complete consumption of boronic acid **8a**, the reaction mixture was cooled to room temperature and molecular sieves were filtered off. Then the reaction mixture was concentrated to provide a crude mixture of MIDA boronate of boronic acid **8a**, which was used for the next step without further purification. To a solution of a crude mixture of MIDA boronate of **8a** in DMF (200 mL) was added a solution of N-bromosuccinimide (NBS, 5.3 g, 30 mmol) in DMF (20 mL). The reaction mixture was stirred at room temperature until all MIDA boronate of **8a** was consumed. After the complete consumption of MIDA boronate of **8a**, the reaction mixture was quenched with 100 mL of saturated $Na_2S_2O_3$ aqueous solution. Upon addition of additional 200mL of H_2O to the reaction mixture, the white precipitate was formed, collected by filtration and washed with H_2O. The resulting white solid was identified as compound **9** (7.0 g, 94%). Spectroscopic data was in good agreement with the literature.[1]

^{1}H NMR (500 MHz, DMSO-d_6, ppm): δ 7.12 (s, 1H), 7.04 (s, 1H), 4.39 (d, J = 17.39 Hz, 2H), 4.13 (d, J = 17.40 Hz, 2H), 3.78 (s, 3H), 3.76 (s, 3H), 2.67 (s, 3H).

2-2. Synthesis of 3-(4-Bromopyridin-2-yl)prop-2-yn-1-ol (10a)

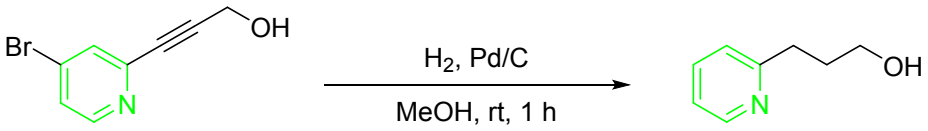


A solution of **11a** (2.4 g, 10 mmol), propargyl alcohol (0.58 mL, 10 mmol), $Pd(PPh_3)_2Cl_2$ (0.21 g, 0.30 mmol) and copper(I) iodide (57 mg, 0.30 mmol) in 20 mL of triethylamine was stirred at 0 °C under nitrogen atmosphere. The reaction mixture was warmed to room temperature and allowed to stir at the same temperature. After 2 h, H_2O was added to the reaction mixture to quench the reaction and the reaction mixture was extracted with dichloromethane. The organic layers were combined, dried over $MgSO_4$, and concentrated. The crude mixture was purified by flash column chromatography on silica gel using a 1:3 mixture of ethyl acetate and hexanes as the eluent to provide the desired product **10a** (1.7 g, 78%) as a brown solid.

^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 8.37 (d, J = 5.5 Hz, 1H), 7.61 (d, J = 1.5 Hz, 1H), 7.43 (dd, J = 5.3, 1.7 Hz, 1H), 4.52 (d, J = 5.2 Hz, 2H), 2.80 (br, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$, ppm): δ 150.5, 143.9, 133.0, 130.4, 126.7, 89.4, 83.6, 51.3. **IR** (film): 3264, 2226, 1567, 1540, 1464, 1373, 1052, 826, 686 cm^{-1}; **HRMS** (ESI) calcd for $C_8H_6BrNONa$ [M+Na] 233.9531, found 233.9538.

To confirm the structure of the desired product **10a**, compound **10a** was further converted into its reduced analogue ***red*-10a**.

3-(Pyridin-2-yl)propan-1-ol (*red*-10a)



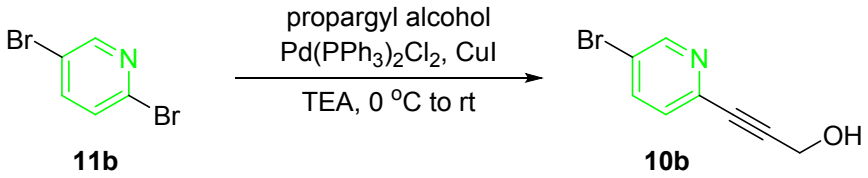
10a ***red*-10a**

To a solution of **10a** (21 mg, 0.10 mmol) in methanol (1.0 mL) was added Pd/C (21 mg). The mixture was stirred at room temperature under 1.0 atm of hydrogen atmosphere and monitored by TLC. After 1 h, the reaction mixture was filtered through celite to remove the undissolved solid. The filtrate was concentrated and purified by flash column chromatography on silica gel using a 1:1 mixture of ethyl acetate and hexanes as the eluent to afford compound ***red*-10a** (13 mg, 92%) as yellow oil. Spectroscopic data was in good match with one obtained from a commercial source. **^{1}H NMR** (500 MHz, $CDCl_3$, ppm): δ 8.50 (d, J = 4.6 Hz, 1H), 7.61 (td, J = 7.6, 1.5 Hz, 1H), 7.19 (d, J

= 7.6 Hz, 1H), 7.13 (dd, *J* = 7.0, 5.2 Hz, 1H), 4.12 (br, 1H), 3.72 (t, *J* = 5.8 Hz, 2H), 2.98 (t, *J* = 6.7 Hz, 2H), 1.96 - 2.04 (m, 2H).

Based on this ^{1}H NMR result, we reached the conclusion that the Sonogashira coupling reaction would take place at the bromide at the 2-position of rather than one at the 4-position.

2-3. 3-(5-Bromopyridin-2-yl)prop-2-yn-1-ol (10b)



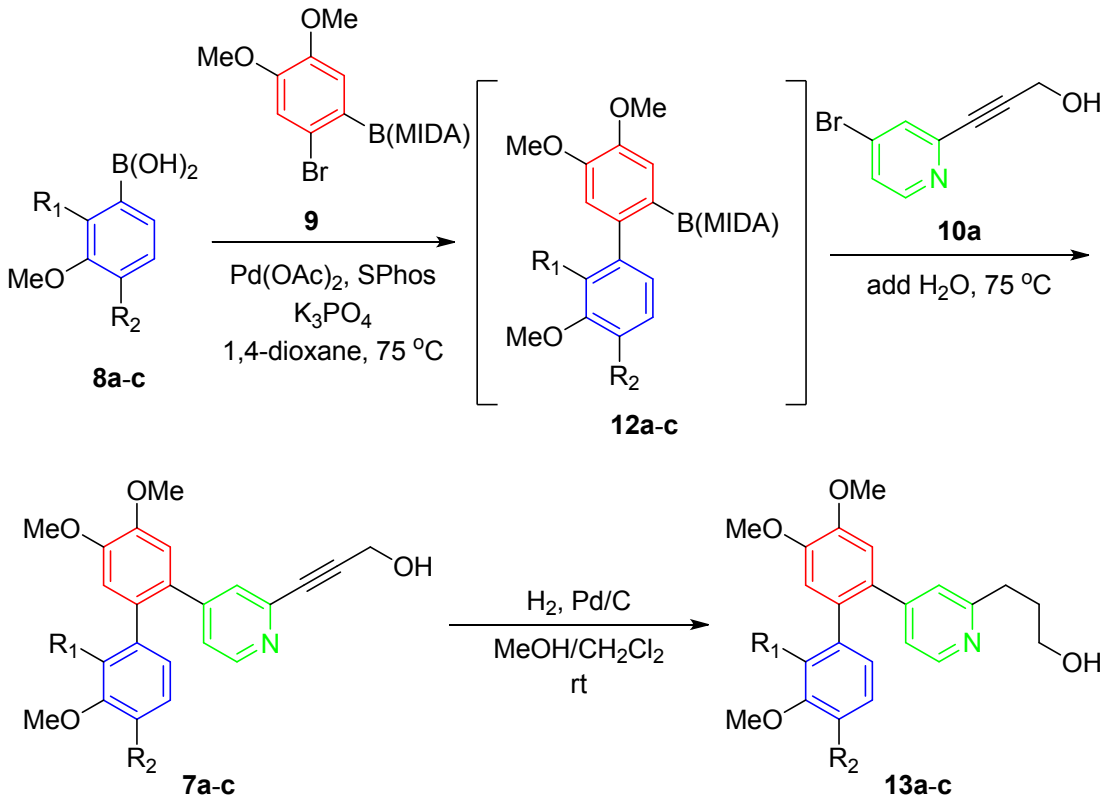
11b **10b**

To a solution of compound **11b** (2.4 g, 10 mmol), $Pd(PPh_3)_2Cl_2$ (0.21 g, 0.30 mmol) and copper(I) iodide (57 mg, 0.30 mmol) in triethylamine (20 mL) was added propargyl alcohol (0.58 mL, 10 mmol). The above mixture was stirred at 0 °C under nitrogen atmosphere for 10 min, then warmed up to room temperature and stirred for 2 h. After complete consumption of **11b**, the reaction mixture was quenched by H_2O, and extracted with dichloromethane. The organic layers were combined, dried over $MgSO_4$, and concentrated. The residue was purified by flash column chromatography on silica gel using a 1:3 mixture of ethyl acetate and hexanes as the eluent to afford compound **10b** (1.8 g, 83%) as a white solid. Spectroscopic data was in good match with a reported value in the literature.[2] **^{1}H NMR** (500 MHz, $CDCl_3$, ppm): δ 8.62 (s, 1H), 7.78 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.31 (d, *J* = 8.2 Hz, 1H), 4.51 (s, 2H), 3.27 (br, 1H).

3. Total Synthesis of Phenanthroindolizidine Alkaloids

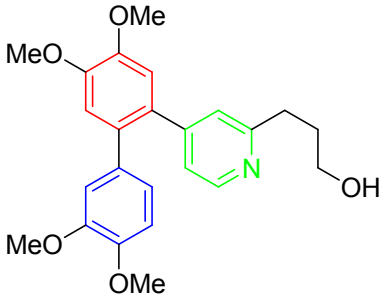
3-1. Total Synthesis of Natural Products in Group A

Synthesis of Compound 13



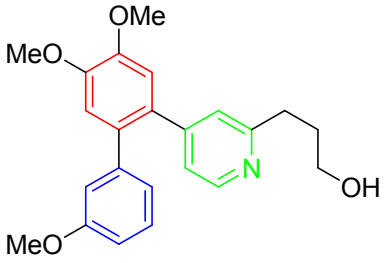
In a one-neck round bottom flask were placed **8** (2.4 mmol), **9** (0.74 g, 2.0 mmol), $Pd(OAc)_2$ (45 mg, 0.20 mol), SPhos (0.16 g, 0.40 mmol), and K_3PO_4 (1.3 g, 6.0 mmol) under argon atmosphere. To the flask was added 20 mL of 1,4-dioxane and the reaction mixture was heated to 75 °C and monitored by TLC. After 3 h, **10a** (0.51 g, 2.4 mmol) and water (4.0 mL) were directly added to the reaction mixture and the reaction mixture was further stirred for 3 h. After 3 h, the reaction mixture was cooled to room temperature, quenched with water (20 mL) and extracted with dichloromethane. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Without further purification, the crude mixture was re-dissolved in a mixture of methanol and dichloromethane (2:1, 20 mL) and Pd/C powder (0.40 g) was added to the solution. The mixture was stirred at room temperature under 1.0 atm of hydrogen. After 3 h, the mixture was filtered to remove insoluble solid. The filtrate was concentrated and purified by flash column chromatography on silica gel using a 1:1 mixture of tetrahydrofuran and hexanes as the eluent to afford compound **13**.

Compound 13a



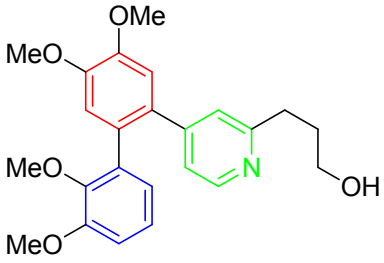
A white solid; 0.51 g, 62% yield. **^{1}H NMR** (500 MHz, $CDCl_3$, ppm): δ 8.35 (d, J = 4.9 Hz, 1H), 6.95 (s, 2H), 6.91 (d, J = 10.1 Hz, 2H), 6.76 - 6.81 (m, 1H), 6.69 - 6.75 (m, 1H), 6.54 (s, 1H), 3.96 (s, 6H), 3.87 (s, 3H), 3.62 (s, 3H), 3.59 (t, J = 5.8 Hz, 2H), 2.83 (t, J = 6.7 Hz, 2H), 1.81 - 1.88 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$, ppm): δ 161.1, 150.6, 149.3, 148.5, 148.5, 148.2, 133.4, 130.1, 124.5, 122.4, 122.2, 113.7, 113.6, 113.0, 111.1, 62.3, 56.4, 56.3, 56.1, 55.9, 35.4, 31.7; **IR** (film): 3309, 2928, 2852, 1602, 1507, 1250, 1025, 801 cm^{-1}; **HRMS** (ESI) calcd for $C_{24}H_{27}NO_5Na$ [M+Na] 432.1787, found 432.1784.

Compound 13b



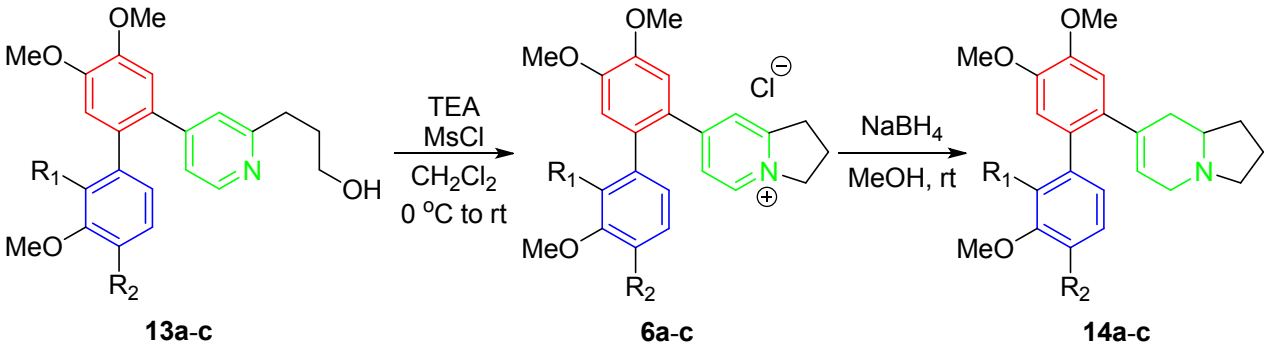
A white solid; 0.36 g, 47% yield. **^{1}H NMR** (500 MHz, $CDCl_3$, ppm): δ 8.32 (d, J = 5.2 Hz, 1H), 7.15 (t, J = 7.9 Hz, 1H), 6.94 (s, 2H), 6.90 (d, J = 5.5 Hz, 2H), 6.77 (dd, J = 8.1, 1.7 Hz, 1H), 6.70 (d, J = 7.6 Hz, 1H), 6.64 (s, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 3.66 (s, 3H), 3.57 (t, J = 5.8 Hz, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$, ppm): δ 161.0, 159.3, 150.2, 149.1, 148.6, 148.4, 142.2, 133.4, 130.1, 129.3, 124.4, 122.5, 122.3, 115.7, 113.7, 112.9, 112.4, 62.1, 56.3, 56.2, 55.2, 35.2, 31.7; **IR** (film): 3311, 2935, 2852, 1602, 1517, 1478, 1248, 1204, 1155, 1031, 774 cm^{-1}; **HRMS** (ESI) calcd for $C_{23}H_{25}NO_4Na$ [M+Na] 402.1681, found 402.1678.

Compound 13c



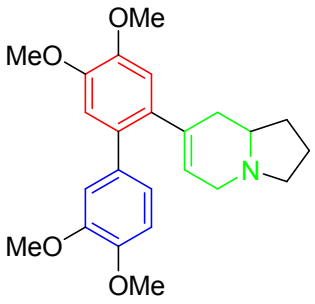
A white solid; 0.39 g, 24% yield. **^{1}H NMR** (500 MHz, $CDCl_3$, ppm): δ 8.29 (d, J = 4.9 Hz, 1H), 6.89 - 6.98 (m, 5H), 6.84 (d, J = 8.2 Hz, 1H), 6.62 (d, J = 7.6 Hz, 1H), 3.95 (s, 3H), 3.91 (s, 3H), 3.82 (s, 3H), 3.54 (t, J = 5.7 Hz, 2H), 3.50 (s, 3H), 2.81 (t, J = 6.7 Hz, 2H), 1.77 - 1.86 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$, ppm): δ 160.8, 152.9, 150.3, 148.8, 148.6, 148.3, 146.6, 134.9, 130.9, 129.6, 123.9, 123.8, 123.6, 121.8, 114.3, 112.4, 111.8, 62.1, 60.4, 56.2, 56.2, 55.9, 35.2, 31.6; **IR** (film): 3303, 2924, 2852, 1507, 1462, 1248, 1174, 1025, 859, 764 cm^{-1}; **HRMS** (ESI) calcd for $C_{24}H_{27}NO_5Na$ [M+Na] 432.1787, found 432.1782.

Synthesis of Compound 14



To a solution of **13** (1.0 mmol) in dichloromethane (10 mL) were added MsCl (0.15 mL, 2.0 mmol) and TEA (0.41 mL, 3.0 mmol) at 0 °C. The reaction mixture was warmed up to room temperature and stirred for 2 h. After 2 h, the reaction mixture was concentrated under reduced pressure. recrystallization in a mixture of dichloromethane and ethyl acetate provided the crude mixture of compound **6**, which was directly used for the next step. To a solution of the resulting solid in methanol (10 mL) was added $NaBH_4$ (0.15 g, 4.0 mmol) and the reaction mixture was stirred at room temperature. After 30 min, the reaction mixture was quenched with water (10 mL) and extracted with ethyl acetate. The organic layers were combined, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using a 10:1 mixture of dichloromethane and methanol as the eluent to provide the product **14**.

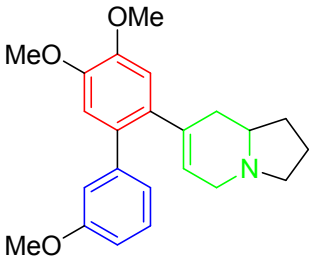
Compound 14a



A white solid; 0.32 g, 81% yield. Spectroscopic data was in good match with a reported value in the literature.[3] **^{1}H NMR** (500 MHz, $CDCl_3$, ppm): δ 6.97 (s, 1 H), 6.94 (d, J = 8.2 Hz, 1H), 6.89 (d, J = 8.2 Hz, 1H), 6.82 (s, 1H), 6.81 (s, 1H), 5.74 (d, J = 2.8 Hz, 1H), 3.92 (s, 3H), 3.89 (s, 3H), 3.89 (s,

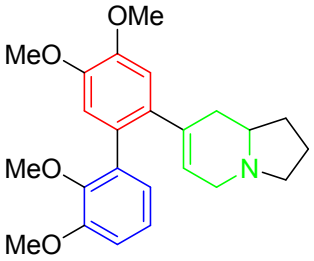
3H), 3.88 (s, 3H), 3.67 (d, J = 14.7 Hz, 1H), 3.25 (m, 1H), 2.93 (d, J = 13.4 Hz, 1H), 2.17 - 2.27 (m, 1H), 2.12 (m, 1H), 1.98 (m, 2H), 1.85 (m, 2H), 1.73 (m, 1H), 1.37 (m, 1H).

Compound 14b



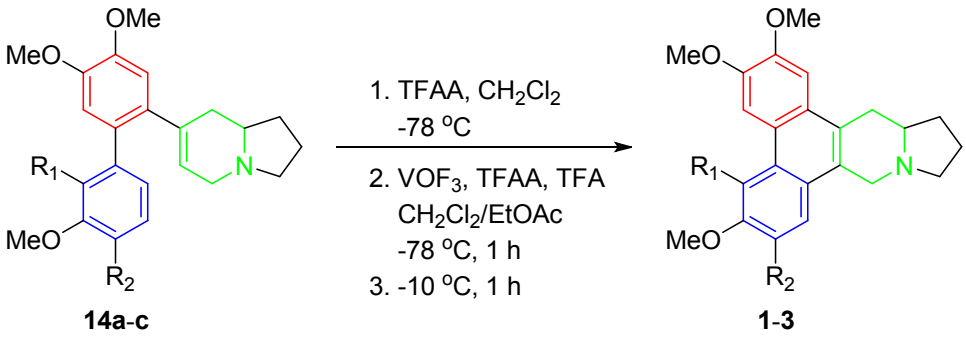
A white solid; 0.31 g, 86% yield. Spectroscopic data was in good match with a reported value in the literature.[3] **^{1}H NMR** (500 MHz, $CDCl_3$, ppm): δ 7.25 - 7.29 (t, J = 7.8 Hz, 1H), 6.94 - 7.01 (m, 2H), 6.82 - 6.86 (m, 2H), 6.82 (s, 1H), 5.71 (d, J = 3.1 Hz, 1H), 3.89 (s, 6H), 3.82 (s, 3H), 3.57 - 3.66 (m, 1H), 3.21 (m, 1H), 2.89 (m, 1H), 2.17 (m, 1H), 1.90 - 2.11 (m, 3H), 1.82 (m, 2H), 1.71 (m, 1 H), 1.29 - 1.37 (m, 1 H).

Compound 14c



A white solid; 0.33 g, 84% yield. Spectroscopic data was in good match with a reported value in the literature.[3] **^{1}H NMR** (500 MHz, $CDCl_3$, ppm): δ 7.01 (t, J = 7.9, 1H), 6.87 (d, J = 7.9, 1H), 6.86 (s, 1H), 6.82 (d, J = 7.9, 1H), 6.82 (s, 1H), 5.50 (br, 1H), 3.89 (s, 6H), 3.85 (s, 3H), 3.58 (s, 3H), 3.53 (d, J = 16.2 Hz, 1H), 3.19 (br, 1H), 2.80 (br, 1H), 2.04 - 2.28 (m, 4H), 1.80 - 1.95 (m, 2H), 1.73 (br, 1H), 1.42 (br, 1 H).

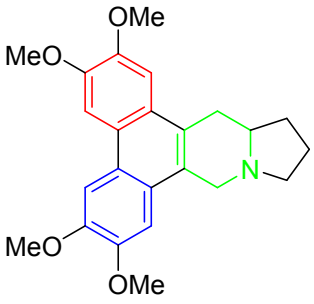
Synthesis of Natural Products in Group A



Preparation of VOF_3 solution : To a solution of the VOF_3 (1.0 g, 8.0 mmol) in anhydrous dichloromethane (20 mL) and anhydrous ethyl acetate (10 mL) were added trifluoroacetic acid (TFA, 1.0 mL, 13 mmol) and trifluoroacetic anhydride (TFAA, 4 drops) under nitrogen atmosphere and the mixture was stirred at room temperature.

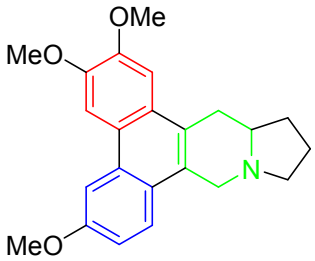
A solution of **14** (0.50 mmol) and TFAA (2 drops) in anhydrous dichloromethane (100 mL) was stirred at -78 °C under nitrogen atmosphere. To the solution was added the prepared VOF_3 solution (4.9 mL, 1.3 mmol) over 10 minutes. After 1 h, the reaction mixture was warmed to -10 °C and further stirred for additional 1 h at the same temperature. After 1 h, 50 mL of 10% NaOH solution was directly added to the reaction mixture and the reaction mixture was vigorously stirred for 1 h at room temperature. Then, the reaction mixture was extracted with dichloromethane, and the organic layers were combined, dried over $MgSO_4$, and concentrated. The crude mixture was purified by flash column chromatography on silica gel using a 10:1 mixture of dichloromethane and methanol as the eluent to provide the natural product in group A.

Tylophorine (1)



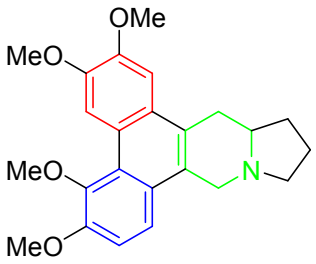
A yellow solid; 0.16 g, 82% yield. Spectroscopic data was in good match with a reported value in the literature.[3] **^{1}H NMR** (500 MHz, $CDCl_3$, ppm): δ 7.83 (s, 1H), 7.83 (s, 1H), 7.32 (s, 1H), 7.16 (s, 1H), 4.63 (d, J = 14.7 Hz, 1H), 4.12 (s, 6H), 4.06 (s, 3H), 4.05 (s, 3H), 3.68 (d, J = 14.3 Hz, 1H), 3.49 (t, J = 7.9 Hz, 1H), 3.38 (dd, J = 15.9, 2.4 Hz, 1H), 2.87 - 2.97 (m, 1H), 2.43 - 2.56 (m, 2H), 2.22 - 2.30 (m, 1H), 2.05 (dd, J = 11.6, 8.6 Hz, 1H), 1.89 - 1.98 (m, 1H), 1.74 - 1.83 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$, ppm): δ 148.9, 148.7, 148.6, 126.5, 126.0, 124.5, 123.8, 123.6, 104.1, 103.6, 103.5, 103.3, 60.4, 56.2, 56.1, 56.0, 55.3, 54.2, 34.0, 31.4, 21.8; **IR** (film): 2922, 2852, 1619, 1514, 1470, 1427, 1248, 1213, 1151, 1017, 842, 750 cm^{-1}; **HRMS** (ESI) calcd for $C_{24}H_{27}NO_4Na$ [M+Na] 416.1838, found 416.1835.

Antofine (2)



A yellow solid; 0.14g, 79% yield. Spectroscopic data was in good match with a reported value in the literature.[3] **^{1}H NMR** (500 MHz, $CDCl_3$, ppm): δ 7.90 (s, 1H), 7.89 (d, J = 2.1 Hz, 1H), 7.81 (d, J = 8.9 Hz, 1H), 7.30 (s, 1H), 7.20 (dd, J = 8.9, 2.1 Hz, 1H), 4.69 (d, J = 14.7 Hz, 1H), 4.10 (s, 3H), 4.06 (s, 3H), 4.01 (s, 3H), 3.69 (d, J = 15.0 Hz, 1H), 3.46 (t, J = 8.1 Hz, 1H), 3.33 (dd, J = 15.6, 2.1 Hz, 1H), 2.85 - 2.94 (m, 1H), 2.41 - 2.55 (m, 2H), 2.20 - 2.28 (m, 1H), 1.99 - 2.08 (m, 1H), 1.88 - 1.96 (m, 1H), 1.73 - 1.82 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$, ppm): δ 157.6, 149.5, 148.5, 130.3, 127.2, 126.7, 125.7, 124.4, 124.2, 123.7, 115.0, 104.8, 104.1, 103.9, 60.4, 56.1, 56.0, 55.7, 55.2, 53.9, 33.8, 31.4, 21.7; **IR** (film): 2916, 1615, 1512, 1468, 1256, 1205, 1126, 1042, 842, 735 cm^{-1}; **HRMS** (ESI) calcd for $C_{23}H_{25}NO_3Na$ [M+Na] 386.1732, found 386.1735.

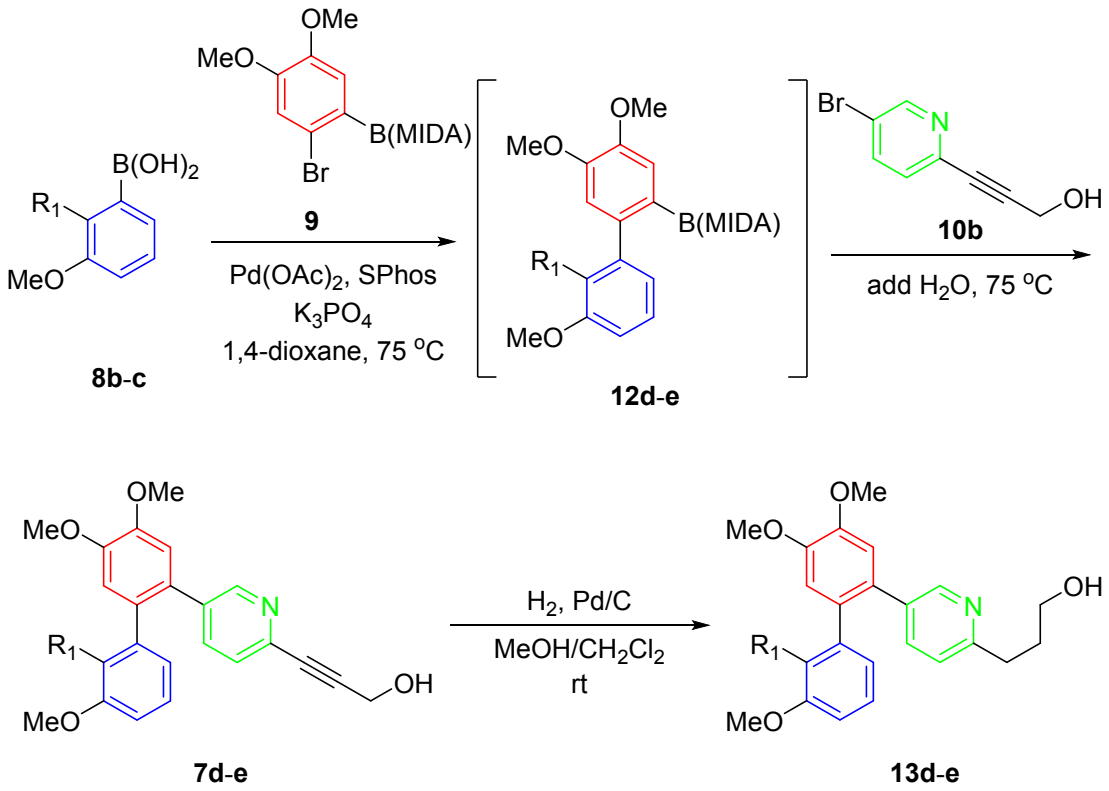
Tylocrebrine (3)



A yellow solid; 0.13g, 65% yield. Spectroscopic data was in good match with a reported value in the literature.[3] **^{1}H NMR** (500 MHz, $CDCl_3$, ppm): δ 9.33 (s, 1H), 7.66 (d, J = 9.2 Hz, 1H), 7.33 (s, 1H), 7.29 (d, J = 9.2 Hz, 1H), 4.67 (d, J = 15.0 Hz, 1H), 4.07 (s, 6H), 4.04 (s, 3H), 3.92 (s, 3H), 3.69 (d, J=14.7 Hz, 1H), 3.44 - 3.50 (m, 1H), 3.34 (dd, J = 15.7, 2.3 Hz, 1H), 2.88 - 2.97 (m, 1H), 2.43 - 2.54 (m, 2H), 2.21 - 2.29 (m, 1H), 2.00 - 2.08 (m, 1H), 1.88 - 1.98 (m, 1H), 1.75 - 1.84 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$, ppm): δ 150.7, 148.8, 147.9, 146.4, 126.6, 125.9, 123.7, 123.4, 119.0, 112.2, 109.3, 103.6, 60.4, 60.2, 56.6, 55.9, 55.3, 54.4, 34.1, 31.4, 21.8; **IR** (film): 2928, 1717, 1569, 1445, 1255, 1182, 1114, 1027, 823, 739 cm^{-1}; **HRMS** (ESI) calcd for $C_{24}H_{27}NO_4Na$ [M+Na] 416.1838, found 416.1833.

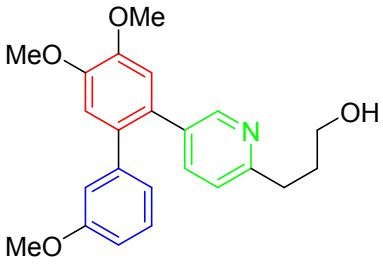
3-2. Total Synthesis of Natural Products in Group B

Synthesis of Compound 13



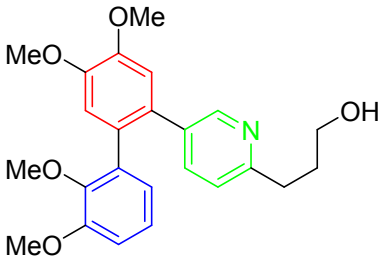
In a one-neck round bottom flask were placed **8** (2.4 mmol), **9** (0.74 g, 2.0 mmol), $Pd(OAc)_2$ (45 mg, 0.20 mol), SPhos (0.16 g, 0.40 mmol), and K_3PO_4 (1.3 g, 6.0 mmol) under argon atmosphere. To the flask was added 1,4-dioxane (20 mL) and the reaction mixture was heated to 75 °C and was stirred for 3 h. After 3 h, **10b** (0.51 g, 2.4 mmol) and 4.0 mL of water were directly added to the reaction mixture and the reaction mixture was further stirred at the same temperature. After 3 h, the reaction mixture was cooled to room temperature, quenched with water (20 mL) and extracted with dichloromethane. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Without further purification, the crude mixture was re-dissolved in a mixture of methanol and dichloromethane (2:1, 20 mL) and Pd/C powder (0.40 g) was added to the solution. The mixture was stirred at room temperature under 1.0 atm of hydrogen for 3 h and then filtered to remove insoluble solid. The filtrate was concentrated and purified by flash column chromatography on silica gel using a 1:1 mixture of tetrahydrofuran and hexanes as the eluent to afford compound **13**.

Compound 13d



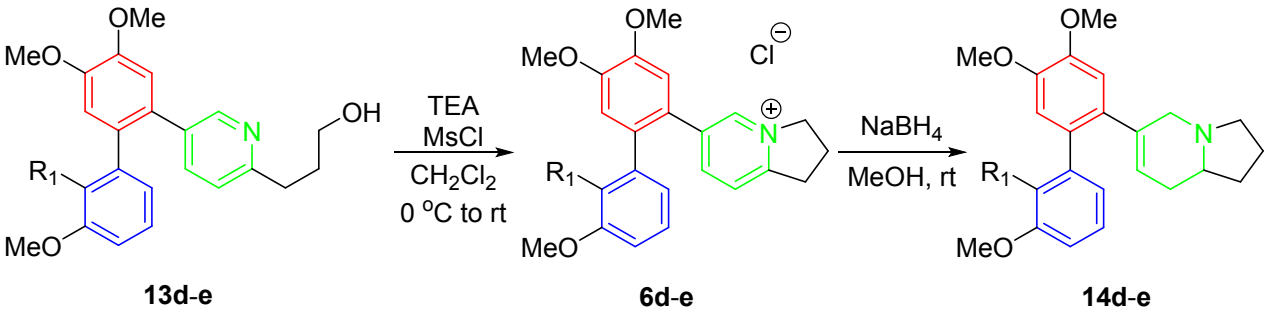
A white solid; 0.34 g, 45% yield. **^{1}H NMR** (500 MHz, $CDCl_3$, ppm): δ 8.39 (s, 1H), 7.37 (d, J = 7.5 Hz, 1H), 7.15 (t, J = 7.9 Hz, 1H), 7.05 (d, J = 7.8 Hz, 1H), 6.96 (s, 1H), 6.89 (s, 1H), 6.77 (dd, J = 7.9, 2.1 Hz, 1H), 6.68 (d, J = 7.5 Hz, 1H), 6.66 (d, J = 2.3 Hz, 1H), 3.96 (s, 3H), 3.95 (s, 3H), 3.70 (t, J = 5.7 Hz, 2H), 3.68 (s, 3H), 2.99 (t, J = 6.4 Hz, 2H), 2.03 (br, 1 H), 1.94 - 2.01 (m, 2 H); **^{13}C NMR** (125 MHz, $CDCl_3$, ppm): δ 159.4, 159.2, 149.2, 148.8, 148.7, 142.3, 138.1, 134.8, 133.5, 129.3, 129.0, 122.7, 122.3, 115.8, 113.8, 113.4, 112.5, 62.6, 56.3, 56.3, 55.3, 35.2, 31.5; **IR** (film): 3309, 2924, 2852, 1600, 1485, 1244, 1202, 1157, 1027, 856, 778, 733, 700 cm^{-1}; **HRMS** (ESI) calcd for $C_{23}H_{25}NO_4Na$ [M+Na] 402.1681, found 402.1683.

Compound 13e



A white solid; 0.36 g, 22% yield. **^{1}H NMR** (500 MHz, $CDCl_3$, ppm): δ 8.32 (d, J = 1.8 Hz, 1H), 7.38 (dd, J = 8.1, 2.3 Hz, 1H), 6.99 (d, J = 8.2 Hz, 1H), 6.94 (s, 1H), 6.92 (t, J = 7.9 Hz, 1H), 6.90 (s, 1H), 6.82 (dd, J = 8.2, 1.2 Hz, 1H), 6.61 (dd, J = 7.6, 1.2 Hz, 1H), 4.12 (br, 1H), 3.95 (s, 3H), 3.91 (s, 3H), 3.82 (s, 3H), 3.67 (t, J = 5.8 Hz, 2H), 3.50 (s, 3H), 2.90 (t, J = 6.7 Hz, 2H), 1.90 - 1.97 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$, ppm): δ 159.0, 153.0, 148.9, 148.6, 148.4, 146.7, 137.4, 135.0, 134.9, 129.9, 129.6, 124.1, 123.7, 122.3, 114.4, 112.9, 111.7, 62.6, 60.4, 56.2, 55.9, 35.3, 31.5; **IR** (film): 3322, 2926, 2850, 1520, 1468, 1260, 1241, 1110, 1017, 801, 768 cm^{-1}; **HRMS** (ESI) calcd for $C_{24}H_{27}NO_5Na$ [M+Na] 432.1787, found 432.1791.

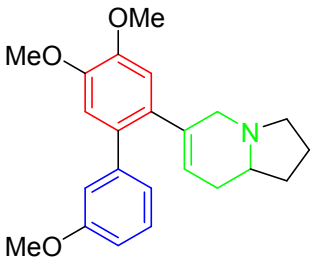
Synthesis of Compound 14



13d-e **6d-e** **14d-e**

To a solution of **13** (1.0 mmol) in dichloromethane (10 mL) were added MsCl (0.15 mL, 2.0 mmol) and TEA (0.41 mL, 3.0 mmol) at 0 °C. The reaction mixture was warmed up to room temperature and stirred for 2 h. After 2 h, the reaction mixture was concentrated under reduced pressure to provide a crude product of compound **6**. Recrystallization of **6** in a mixture of dichloromethane and ethyl acetate afforded the crude product of 6 as a yellow solid. To a solution of the resulting solid in methanol (10 mL) was added $NaBH_4$ (0.15 g, 4.0 mmol) and the reaction mixture was stirred at room temperature. After 30 min, the reaction mixture was quenched with water (10 mL) and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using a 10:1 mixture of dichloromethane and methanol as the eluent to provide the product **14**.

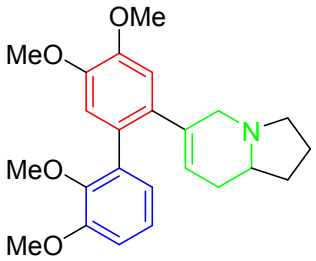
Compound 14d



A white solid; 0.30 g, 82% yield. **^{1}H NMR** (500 MHz, $CDCl_3$, ppm): δ 7.23 - 7.28 (t, J = 7.6 Hz, 1H), 6.97 (d, J = 7.6 Hz, 1H), 6.95 (d, J = 1.8 Hz, 1H), 6.82 - 6.85 (m, 1H), 6.82 (s, 1H), 6.81 (s, 1H), 5.66 (d, J = 4.3 Hz, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 3.81 (s, 3H), 3.36 (d, J = 15.6 Hz, 1H), 3.07 (t, J = 8.1 Hz, 1H), 2.58 (d, J = 15.6 Hz, 1H), 2.24 - 2.34 (m, 1H), 1.91 - 2.10 (m, 4H), 1.77 - 1.87 (m,

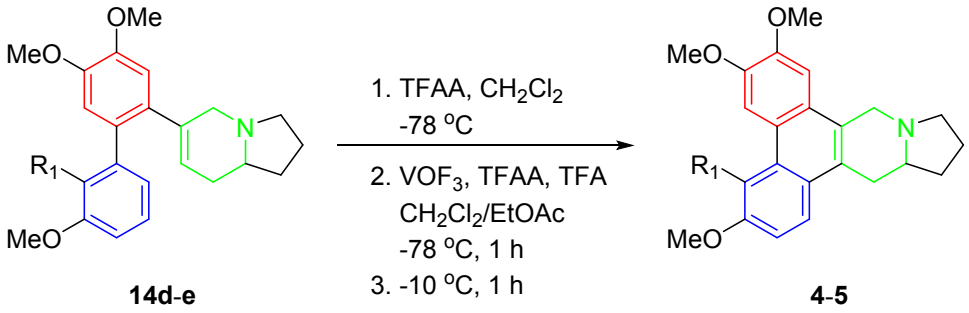
1H), 1.64 - 1.75 (m, 1H), 1.35 - 1.47 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$, ppm): δ 159.3, 148.0, 147.9, 143.3, 137.5, 133.1, 132.5, 129.1, 125.8, 121.9, 114.9, 113.2, 112.8, 112.3, 59.2, 56.3, 56.1, 56.1, 55.4, 54.3, 32.8, 30.6, 21.4; **IR** (film): 2925, 2854, 1598, 1505, 1462, 1378, 1256, 1208, 1173, 1025, 764 cm^{-1}; **HRMS** (ESI) calcd for $C_{23}H_{25}NO_3Na$ [M+Na] 388.1889, found 388.1891.

Compound 14e



A white solid; 0.34 g, 87% yield. **^{1}H NMR** (500 MHz, $CDCl_3$, ppm): δ 7.01 (t, J = 7.9 Hz, 1H), 6.79 - 6.91 (m, 4H), 5.54 (br, 1H), 3.90 (s, 6H), 3.85 (s, 3H), 3.58 (s, 3H), 3.15 (br, 1H), 2.76 (br, 1H), 1.82 - 2.25 (m, 7H), 1.74 (br, 1H), 1.45 (br, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$, ppm): δ 152.9, 148.1, 147.4, 146.8, 136.0, 128.7, 125.3, 123.9, 123.4, 113.8, 112.1, 111.3, 60.6, 56.1, 56.0, 54.1, 31.1, 30.4, 21.3; **IR** (film): 2928, 2848, 1514, 1466, 1256, 1202, 1161, 1108, 1007, 766 cm^{-1}; **HRMS** (ESI) calcd for $C_{24}H_{27}NO_4Na$ [M+Na] 418.1994, found 418.1995.

Synthesis of Natural Products in Group B

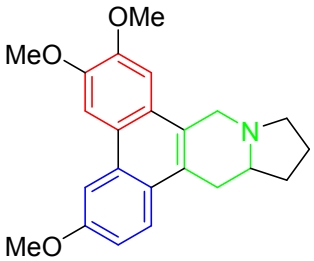


14d-e **4-5**

Preparation of VOF_3 solution : To a solution of the VOF_3 (1.0 g, 8.0 mmol) in anhydrous dichloromethane (20 mL) and anhydrous ethyl acetate (10 mL) were added trifluoroacetic acid (TFA, 1.0 mL, 13 mmol) and trifluoroacetic anhydride (TFAA, 4 drops) under nitrogen atmosphere and the mixture was stirred at room temperature.

A solution of **14** (0.50 mmol), TFAA (2 drops) in anhydrous dichloromethane (100 mL) was stirred at -78 °C under nitrogen atmosphere. To the above solution was added the prepared VOF_3 solution (4.9 mL, 1.3 mmol) over 10 minutes. After 1 h, the reaction mixture was warmed to -10 °C and further stirred for additional 1 h at the same temperature. After 1 h, 50 mL of 10% NaOH solution were directly added to the reaction mixture and the reaction mixture was vigorously stirred at room temperature. After 1 h, the reaction mixture was extracted with dichloromethane, and the organic layers were combined, dried over $MgSO_4$, and concentrated. The crude mixture was purified by flash silica gel column chromatography using a 10:1 mixture of dichloromethane and methanol as the eluent to provide the natural product in group B.

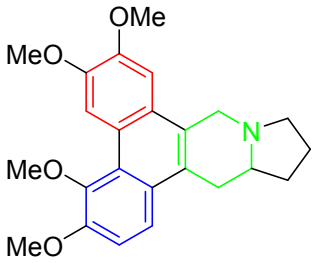
Deoxytylophorine (4)



A yellow solid; 0.14 g, 78% yield. Spectroscopic data was in good match with a reported value in the literature.[3] **^{1}H NMR** (500 MHz, $CDCl_3$, ppm): δ 7.87 - 7.99 (m, 3H), 7.22 (d, J = 9.2 Hz, 1H),

7.17 (s, 1H), 4.62 (d, J = 14.7 Hz, 1H), 4.11 (s, 3H), 4.06 (s, 3H), 4.02 (s, 3H), 3.68 (d, J = 14.7 Hz, 1H), 3.49 (t, J = 8.2 Hz, 1H), 3.4 (d, J = 15.0 Hz, 1H), 2.91 - 3.00 (m, 1H), 2.44 - 2.55 (m, 2H), 2.20 - 2.28 (m, 1H), 2.00 - 2.08 (m, 1H), 1.88 - 1.97 (m, 1H), 1.72 - 1.82 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$, ppm): δ 157.7, 149.6, 148.4, 130.5, 127.2, 125.8, 125.7, 125.4, 125.3, 123.5, 114.9, 104.8, 104.1, 103.3, 60.4, 56.2, 56.1, 55.7, 55.3, 54.1, 33.7, 31.4, 21.8; **IR** (film): 2924, 2852, 1616, 1512, 1468, 1414, 1260, 1204, 1166, 1032, 840, 750 cm^{-1}; **HRMS** (ESI) calcd for $C_{23}H_{25}NO_3Na$ [M+Na] 386.1732, found 386.1737.

Isotylocrebrine (5)



A yellow solid; 0.11g, 58% yield. Spectroscopic data was in good match with a reported value in the literature.[3] **^{1}H NMR** (500 MHz, $CDCl_3$, ppm): δ 9.33 (s, 1H), 7.66 (d, J = 9.2 Hz, 1H), 7.33 (s, 1H), 7.29 (d, J = 9.2 Hz, 1H), 4.67 (d, J = 15.0 Hz, 1H), 4.07 (s, 6H), 4.04 (s, 3H), 3.92 (s, 3H), 3.69 (d, J=14.7 Hz, 1H), 3.44 - 3.50 (m, 1H), 3.34 (dd, J = 15.7, 2.3 Hz, 1H), 2.88 - 2.97 (m, 1H), 2.43 - 2.54 (m, 2H), 2.21 - 2.29 (m, 1H), 2.00 - 2.08 (m, 1H), 1.88 - 1.98 (m, 1H), 1.75 - 1.84 (m, 1H); **^{13}C NMR** (125 MHz, $CDCl_3$, ppm): δ 150.7, 148.8, 147.9, 146.4, 126.6, 125.9, 123.7, 123.4, 119.0, 112.2, 109.3, 103.6, 60.4, 60.2, 56.6, 55.9, 55.3, 54.4, 34.1, 31.4, 21.8; **IR** (film): 2918, 2846, 1515, 1466, 1260, 1064, 790 cm^{-1}; **HRMS** (ESI) calcd for $C_{24}H_{27}NO_4Na$ [M+Na] 416.1838, found 416.1839.

4. References

1. Lee, C.-Y.; Cheon, C.-H. *Adv. Synth. Catal*. **2017**, *359*, 3831.

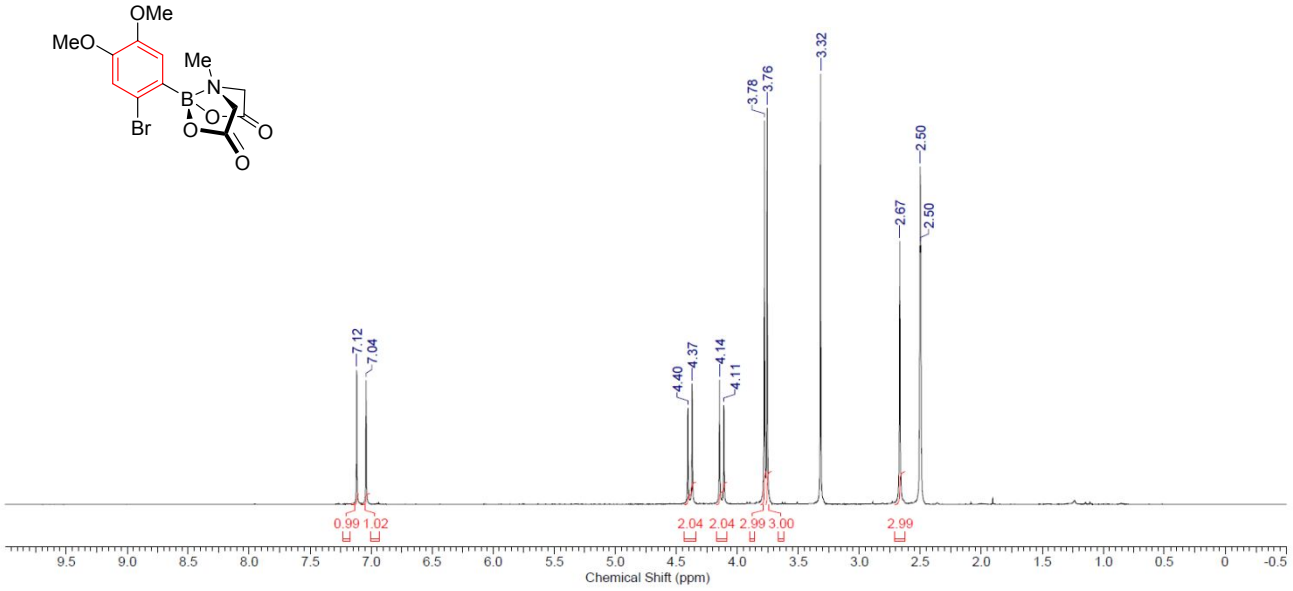
2. Zhang, B.; Chen, R.; Jiang, H.; Zhou, Q.; Qiu, F.; Han, D.; Li, R.; Tang, W.; Zhong, A.; Zhang, J.; Yu, X. *Tetrahedron* **2016**, *72*, 2813.

3. Niphakis, M. J.; Georg, G. I. *Org. Lett.* **2011**, *13*, 196.

5. Spectroscopic Data

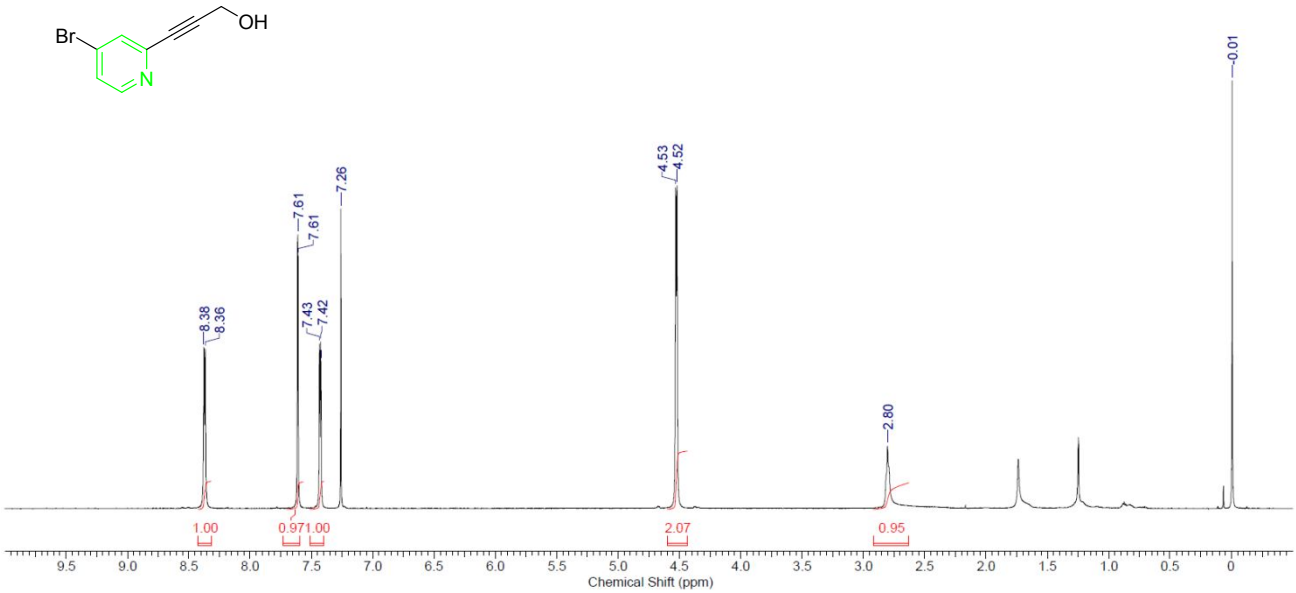
5-1. NMR Spectrum of *ortho*-Bromoaryl MIDA Boronate **9**

a) ^{1}H NMR Spectrum (in DMSO-d_6, 500 MHz)

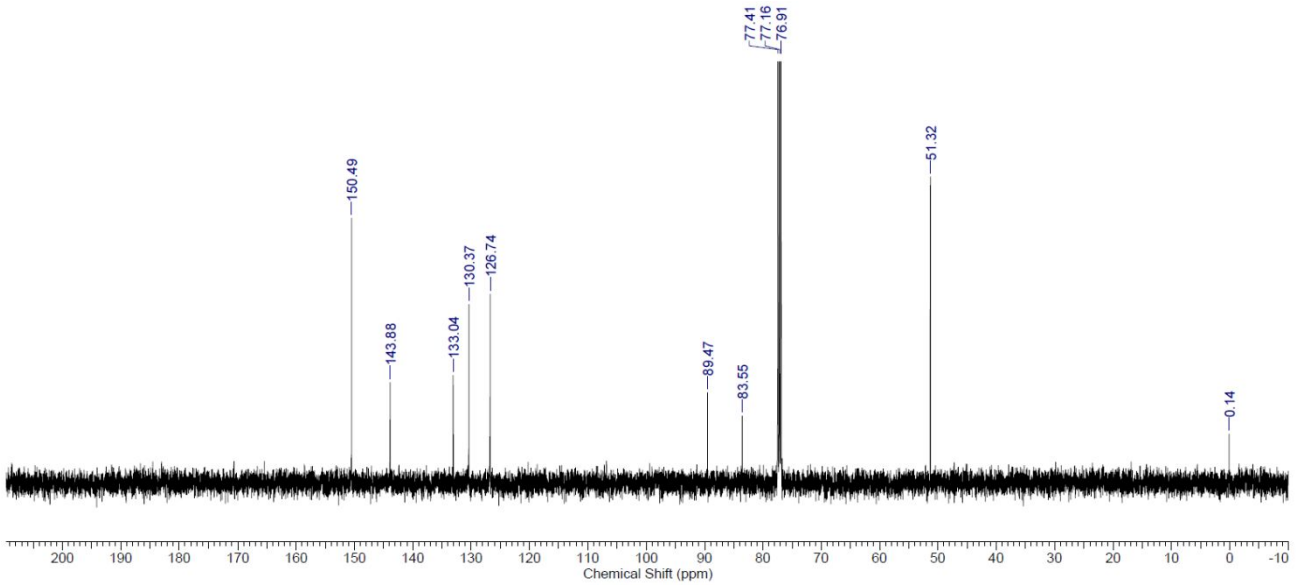


5-2. NMR Spectra of 3-(4-Bromopyridin-2-yl)prop-2-yn-1-ol (**10a**)

a) ^{1}H NMR Spectrum (in $CDCl_3$, 500 MHz)

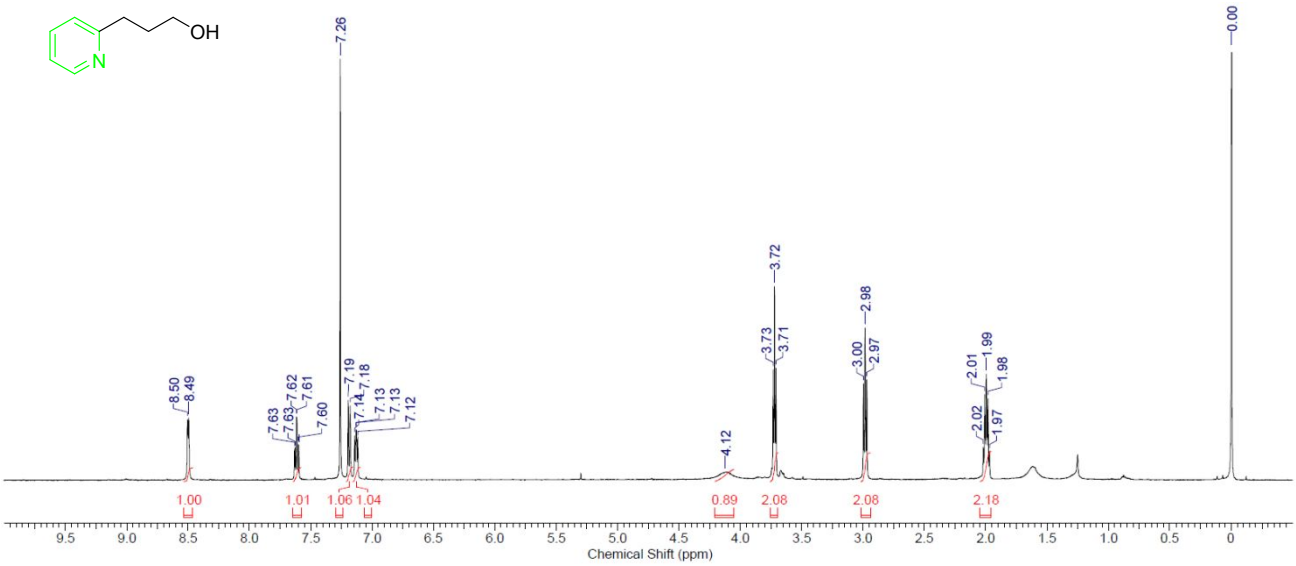


b) ^{13}C NMR Spectrum (in $CDCl_3$, 125 MHz)



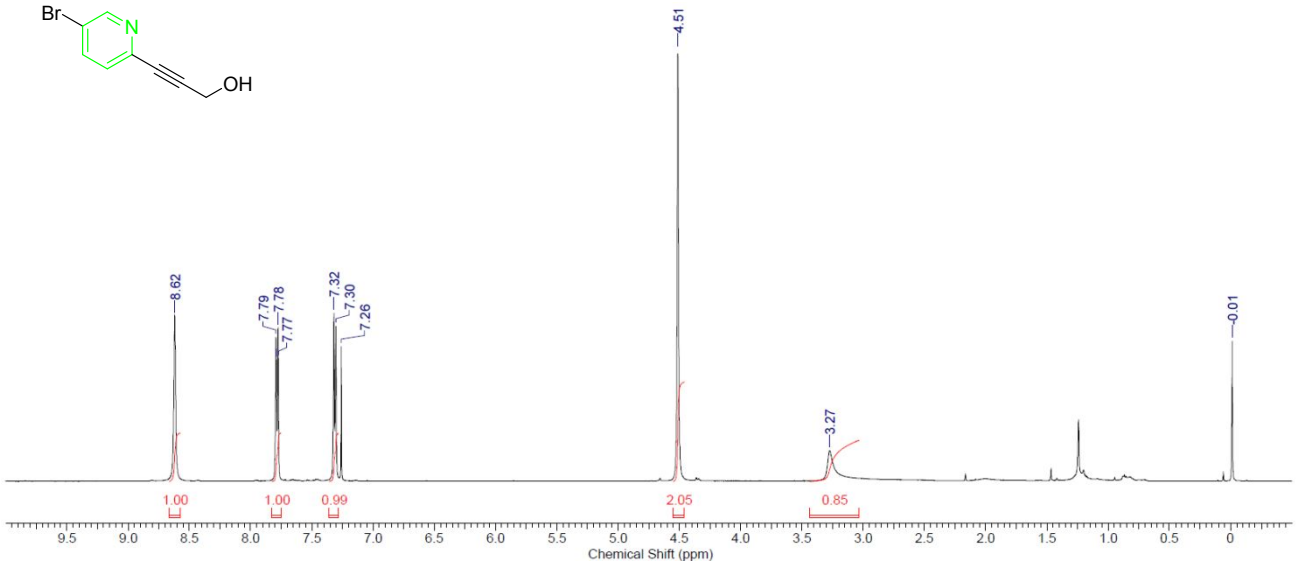
5-3. NMR Spectrum of 3-(Pyridin-2-yl)propan-1-ol (***red*-10a**)

a) ^{1}H NMR Spectrum (in $CDCl_3$, 500 MHz)



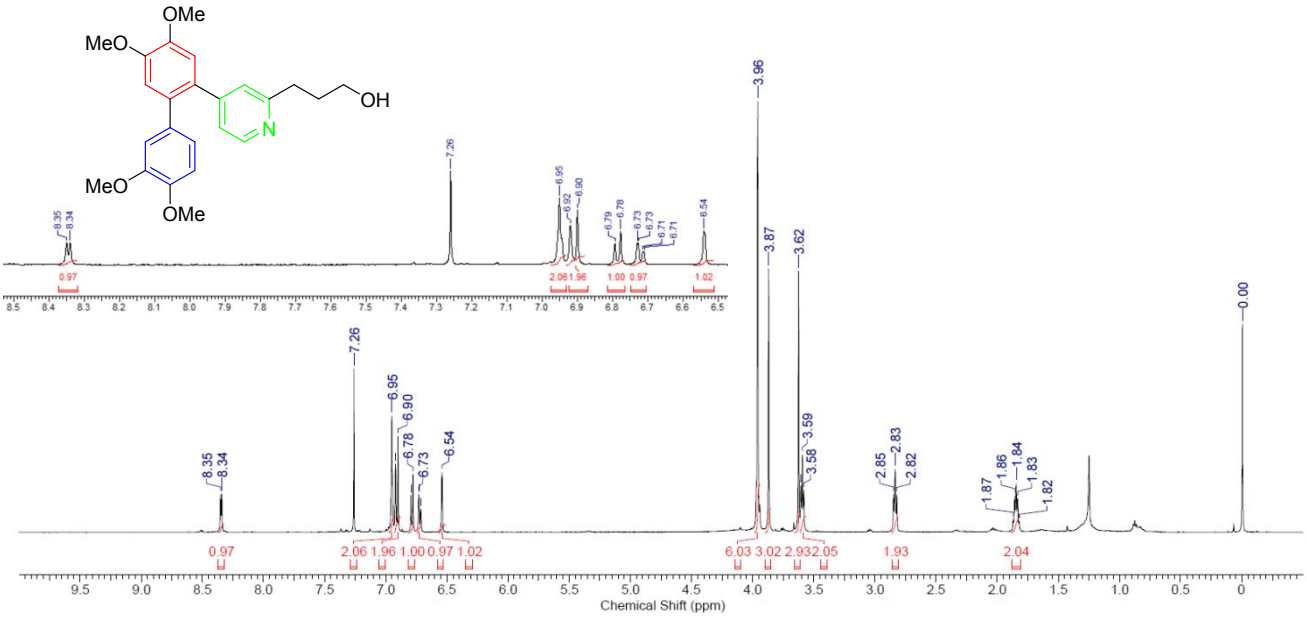
5-4. NMR Spectrum of 3-(5-Bromopyridin-2-yl)prop-2-yn-1-ol (**10b**)

a) ^{1}H NMR Spectrum (in $CDCl_3$, 500 MHz)

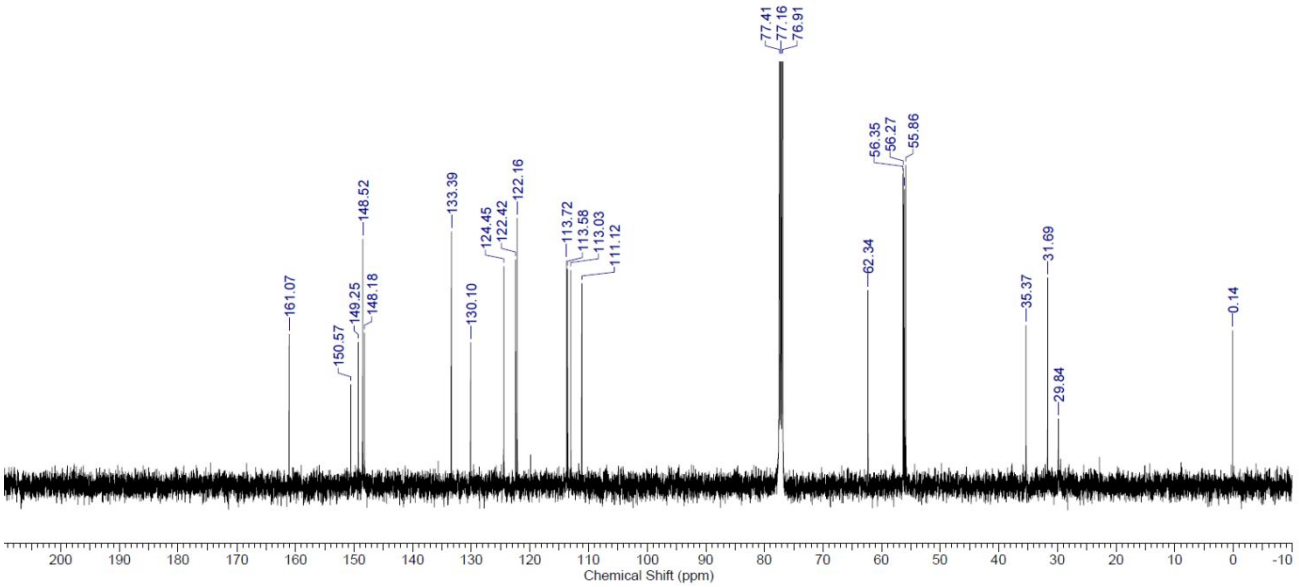


5-5. NMR Spectra of Compound **13a**

a) ^{1}H NMR Spectrum (in $CDCl_3$, 500 MHz)

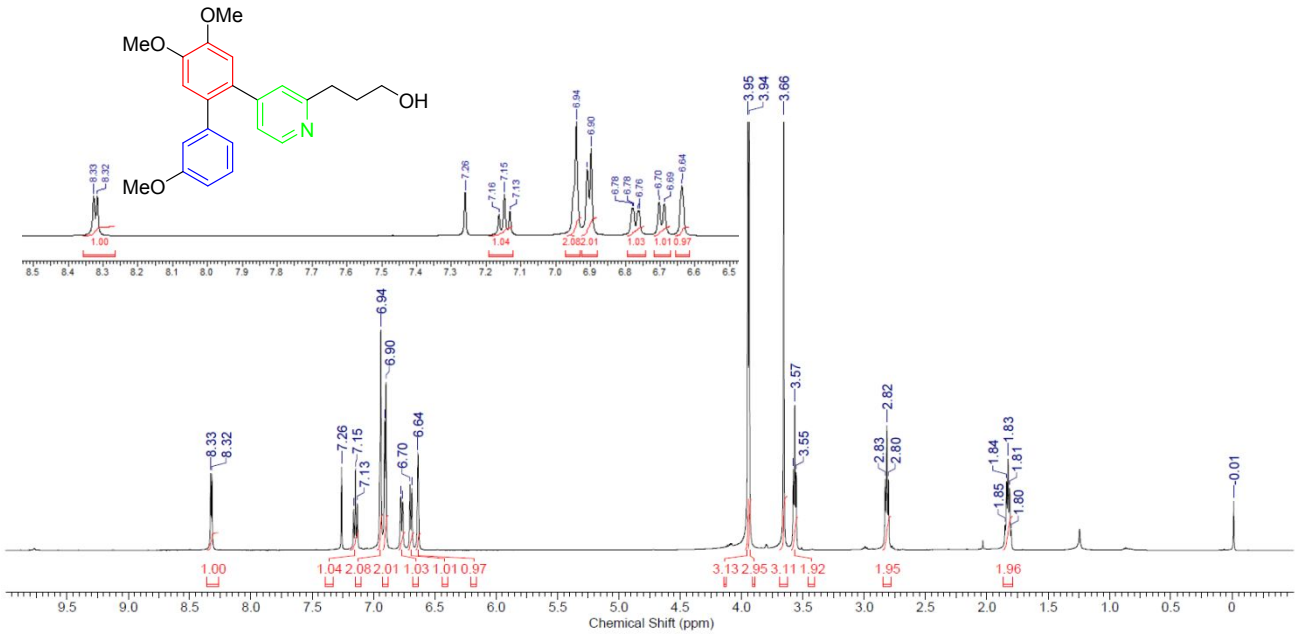


b) ^{13}C NMR Spectrum (in $CDCl_3$, 125 MHz)

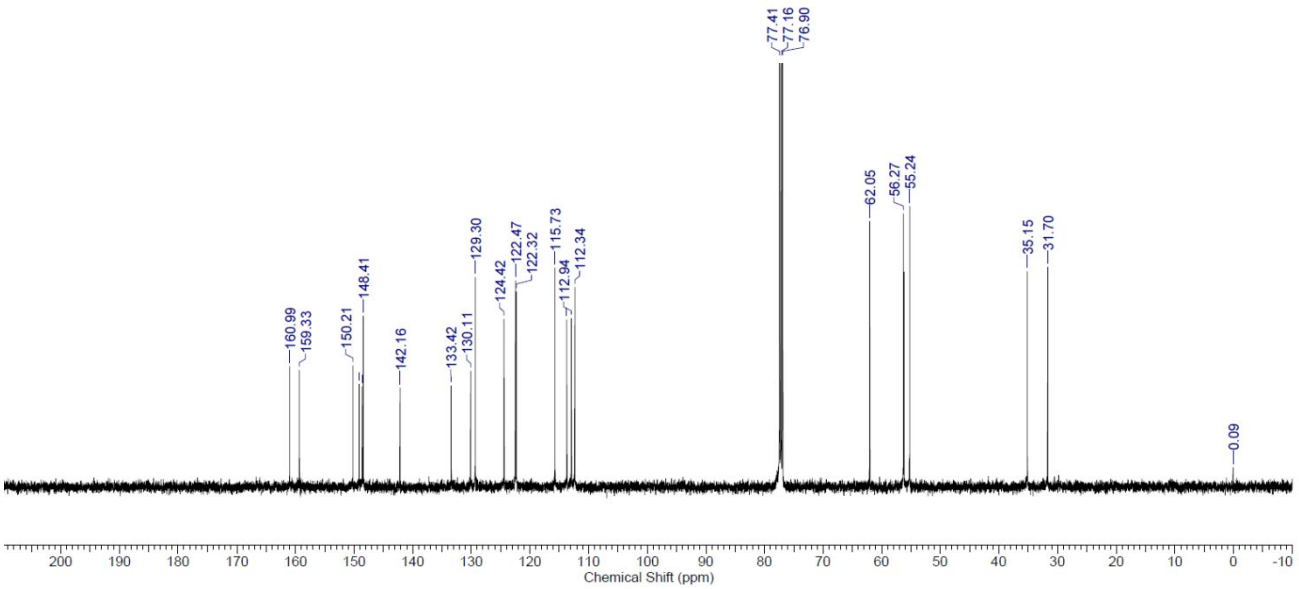


5-6. NMR Spectra of Compound **13b**

a) ^{1}H NMR Spectrum (in $CDCl_3$, 500 MHz)

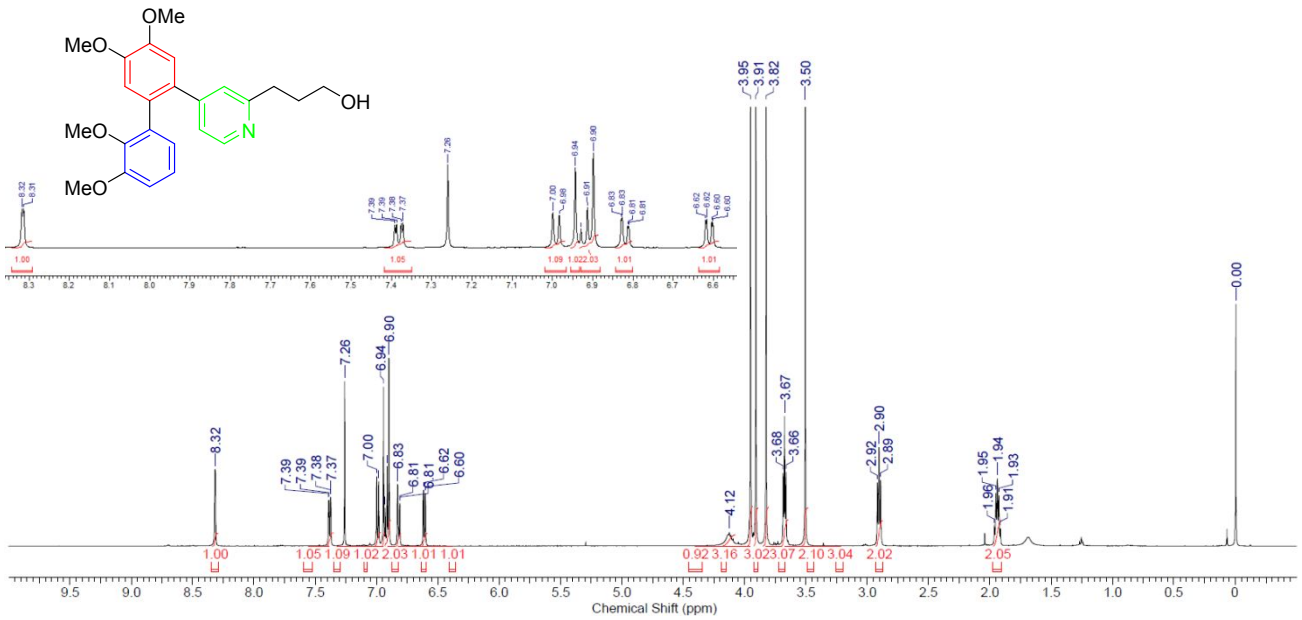


b) ^{13}C NMR Spectrum (in $CDCl_3$, 125 MHz)

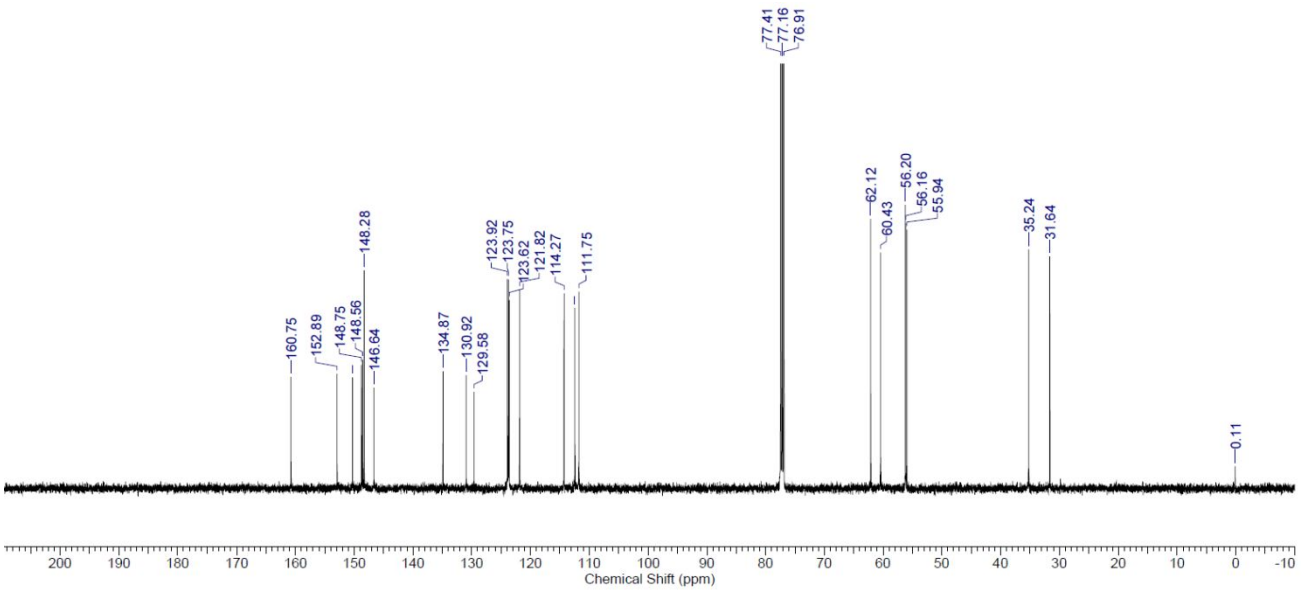


5-7. NMR Spectra of Compound **13c**

a) ^{1}H NMR Spectrum (in $CDCl_3$, 500 MHz)

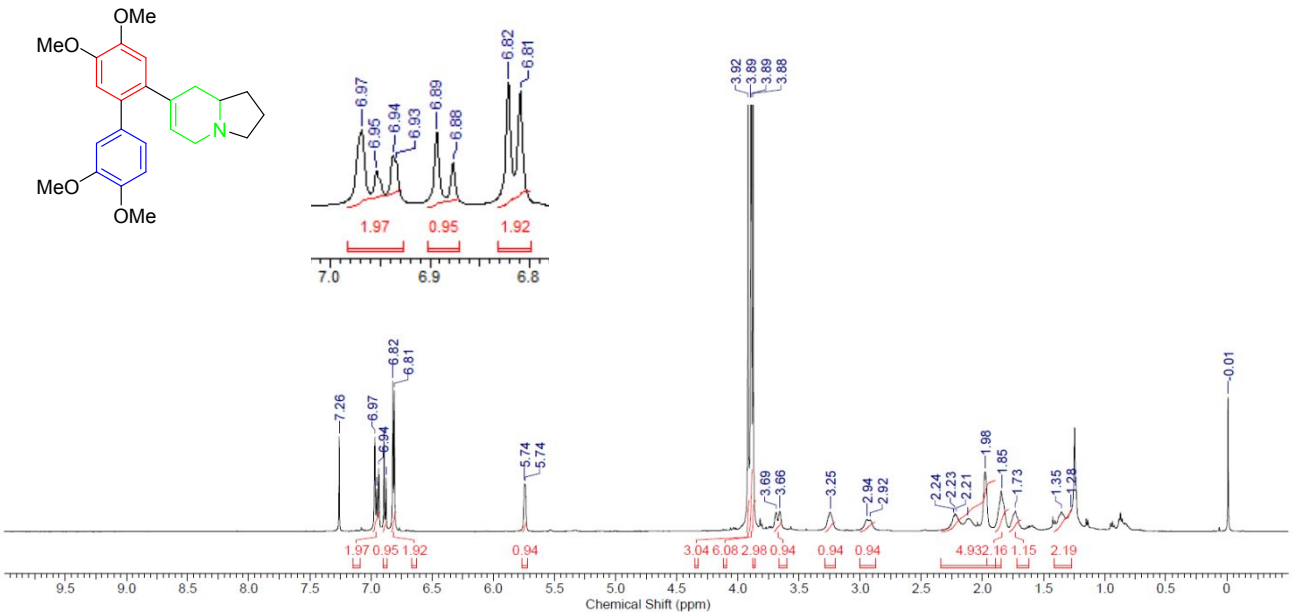


b) ^{13}C NMR Spectrum (in $CDCl_3$, 125 MHz)



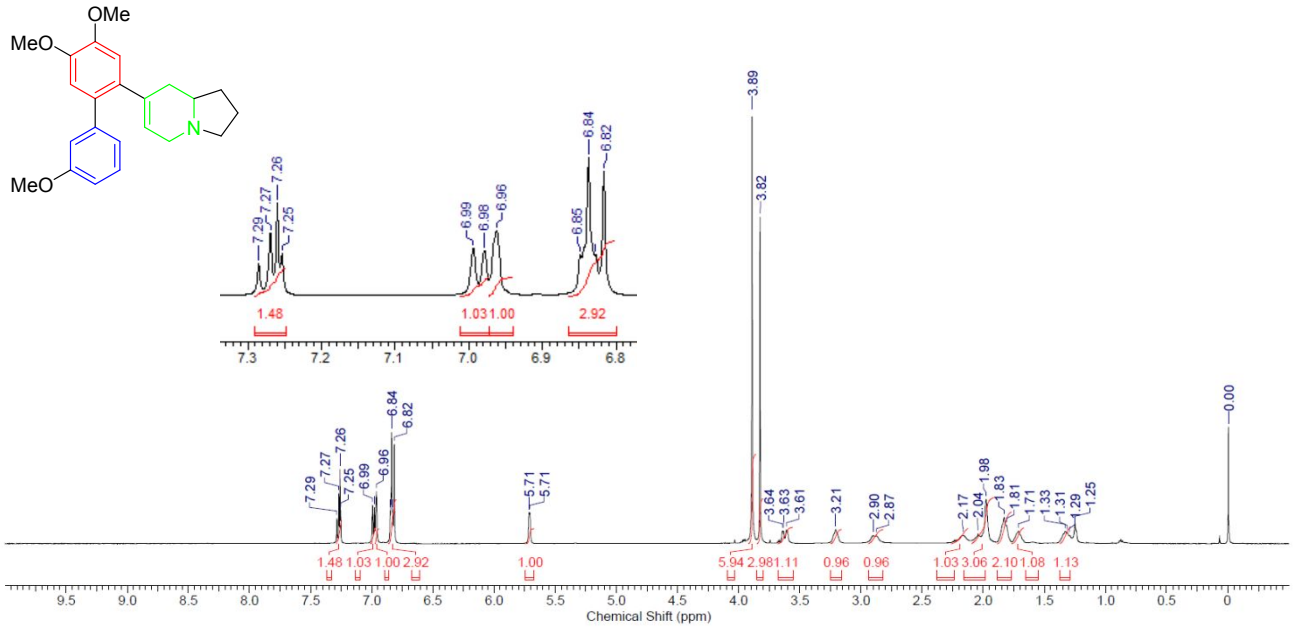
5-8. NMR Spectrum of Compound **14a**

a) ^{1}H NMR Spectrum (in $CDCl_3$, 500 MHz)



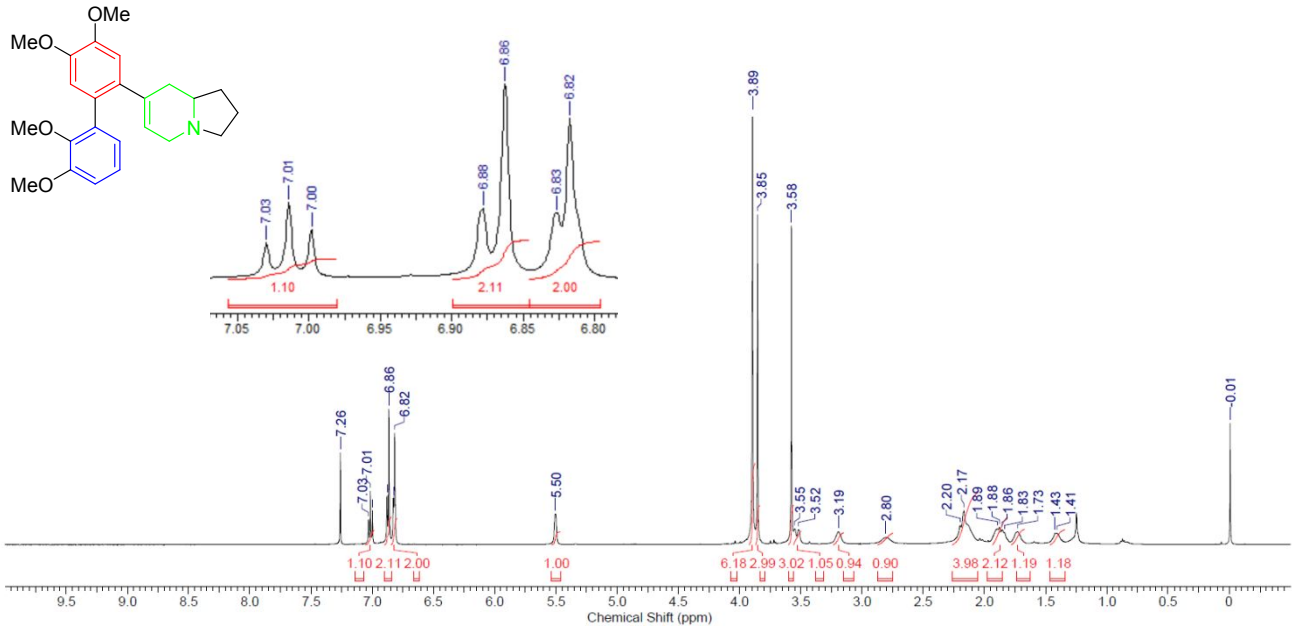
5-9. NMR Spectrum of Compound **14b**

a) ^{1}H NMR Spectrum (in $CDCl_3$, 500 MHz)



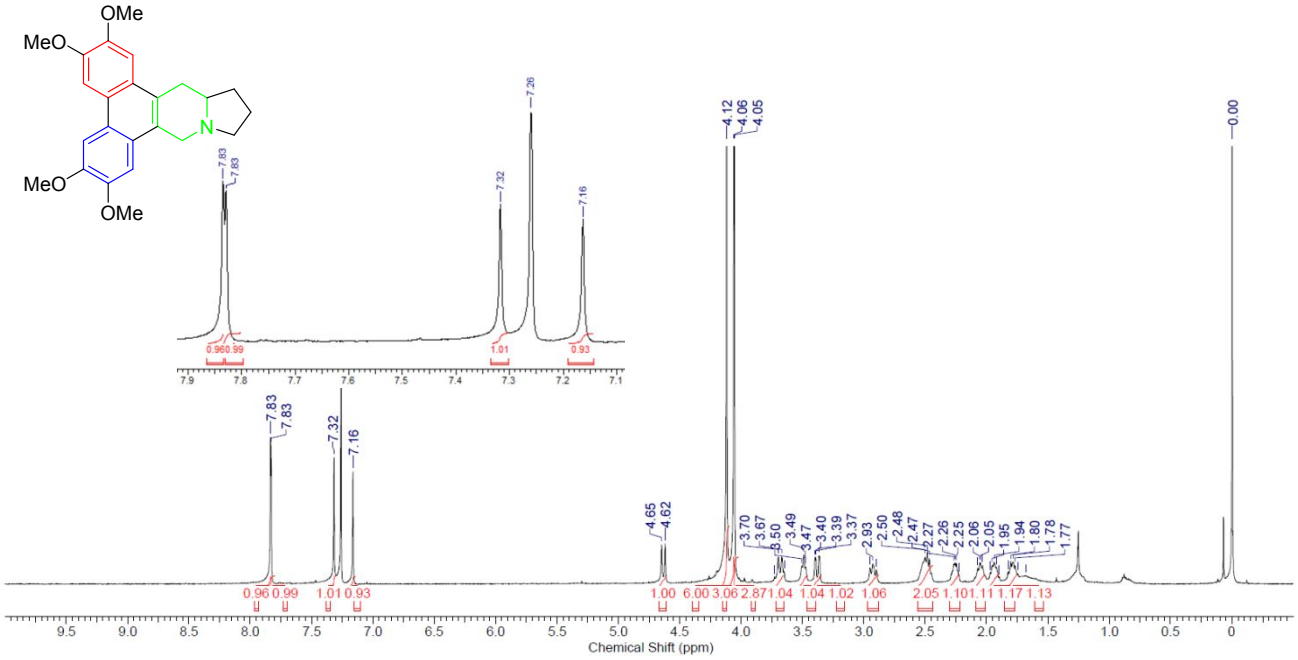
5-10. NMR Spectrum of Compound **14c**

a) ^{1}H NMR Spectrum (in $CDCl_3$, 500 MHz)

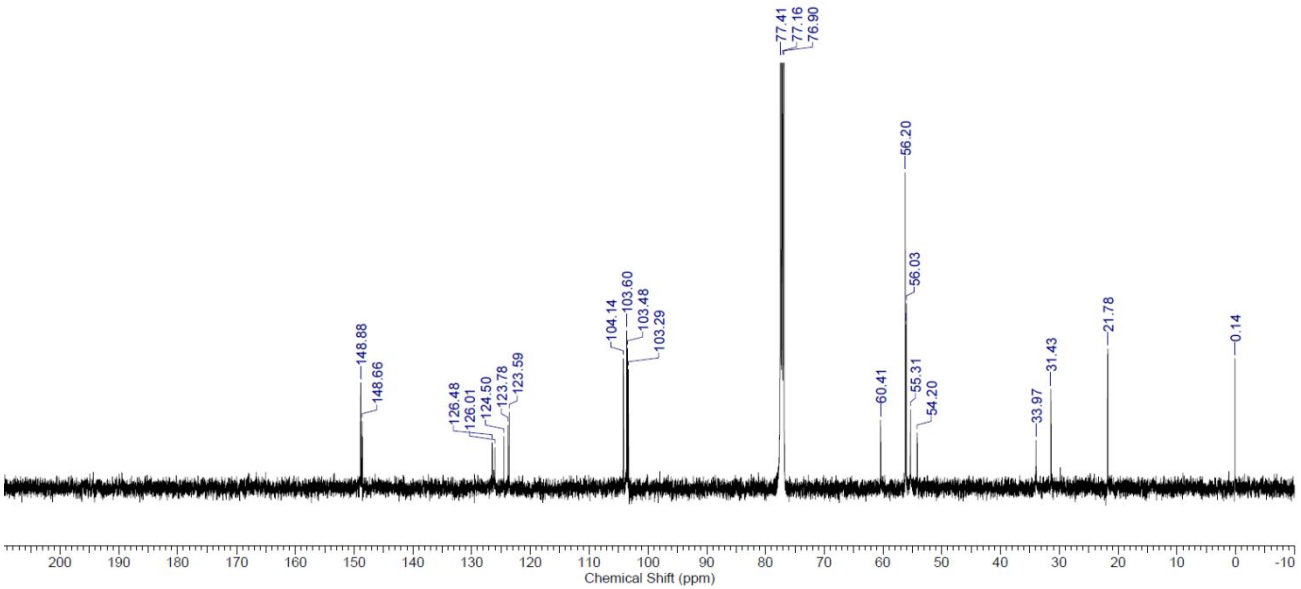


5-11. NMR Spectra of Tylophorine (**1**)

a) ^{1}H NMR Spectrum (in $CDCl_3$, 500 MHz)

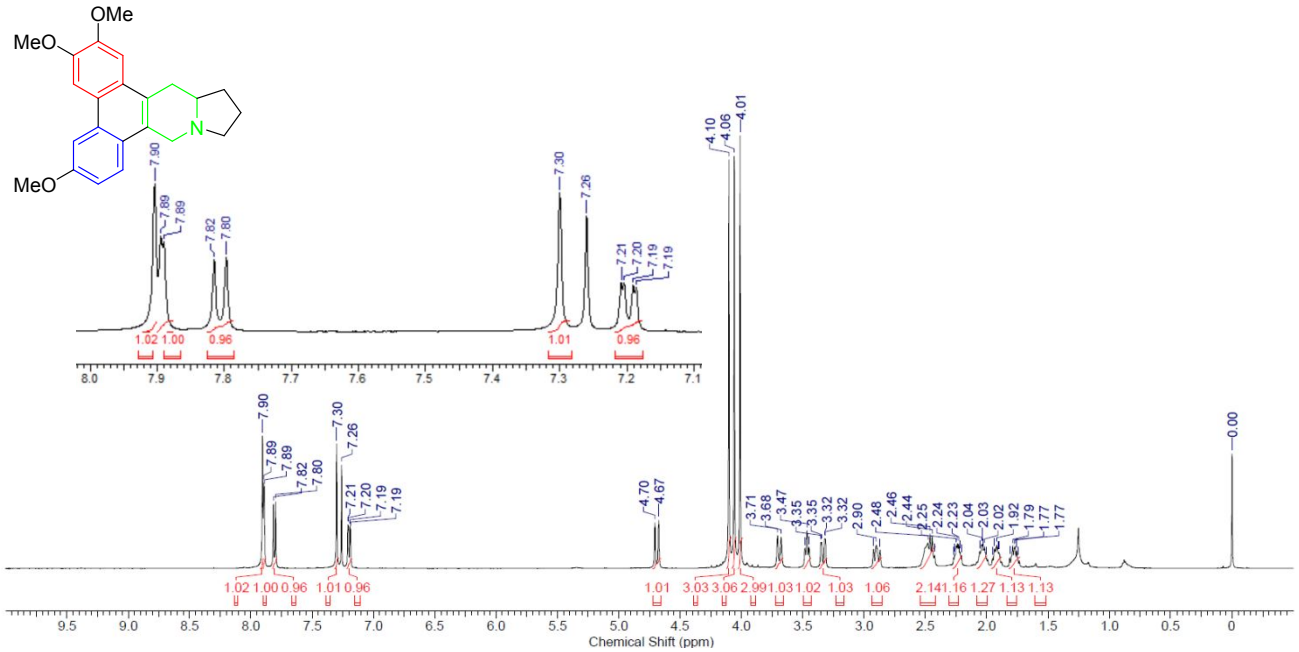


b) ^{13}C NMR Spectrum (in $CDCl_3$, 125 MHz)

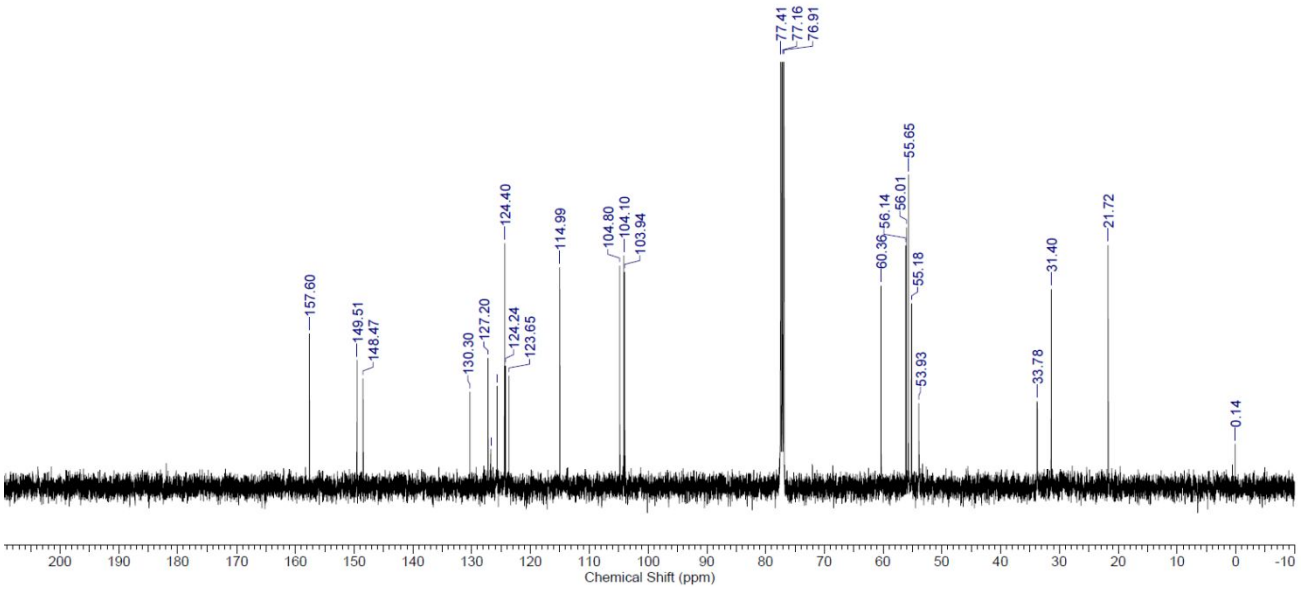


5-12. NMR Spectra of Antofine (**2**)

a) ^{1}H NMR Spectrum (in $CDCl_3$, 500 MHz)

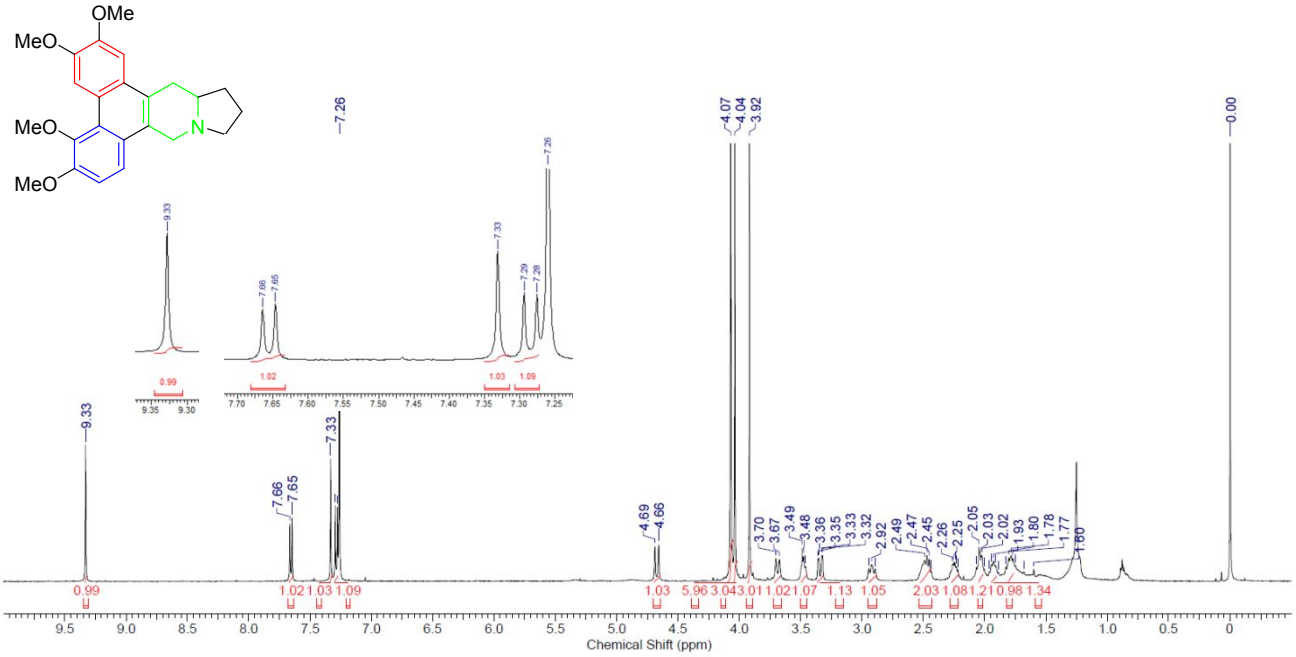


b) ^{13}C NMR Spectrum (in $CDCl_3$, 125 MHz)

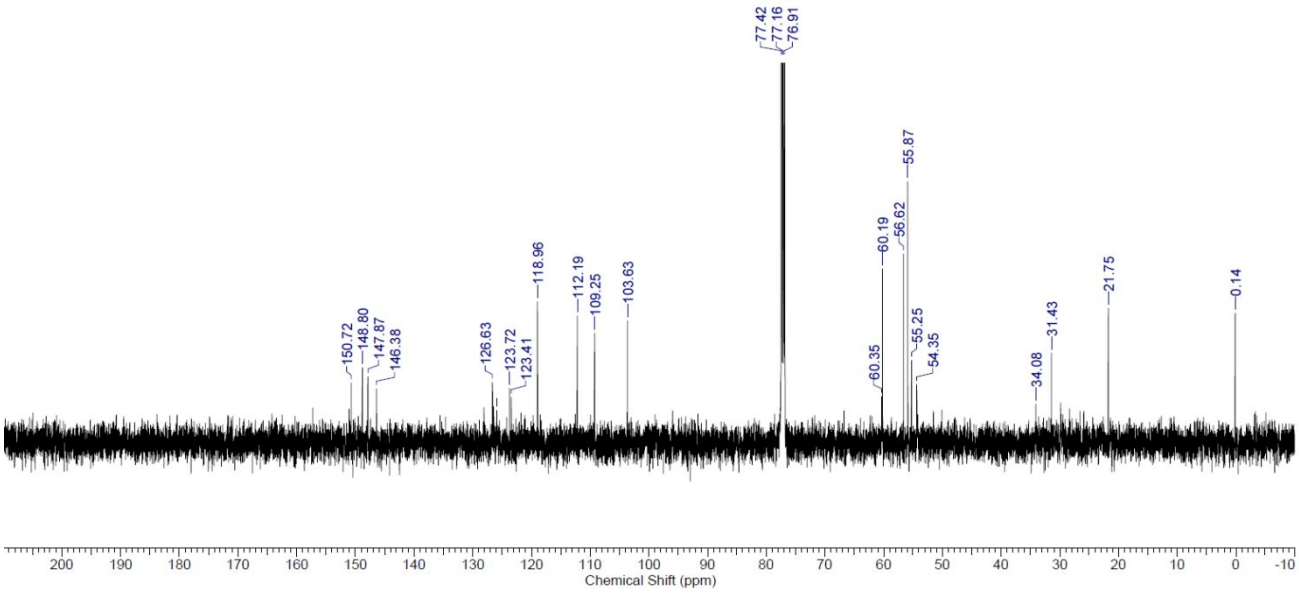


5-13. NMR Spectra of Tylocrebrine (**3**)

a) ^{1}H NMR Spectrum (in $CDCl_3$, 500 MHz)

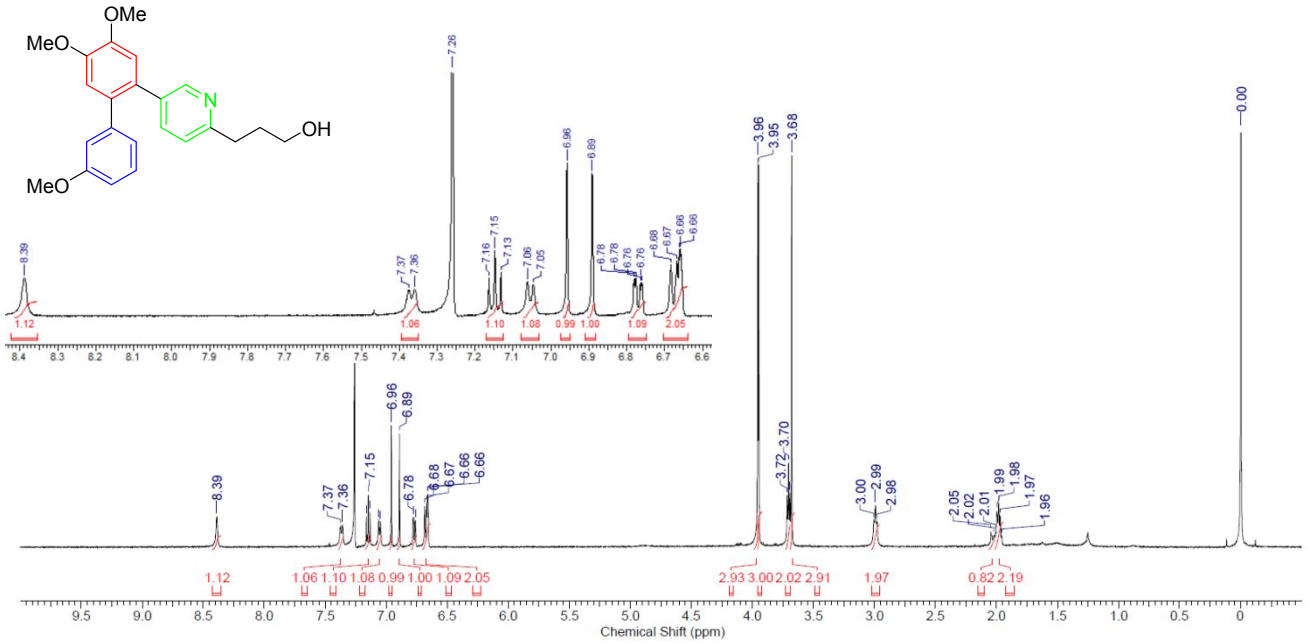


b) ^{13}C NMR Spectrum (in $CDCl_3$, 125 MHz)

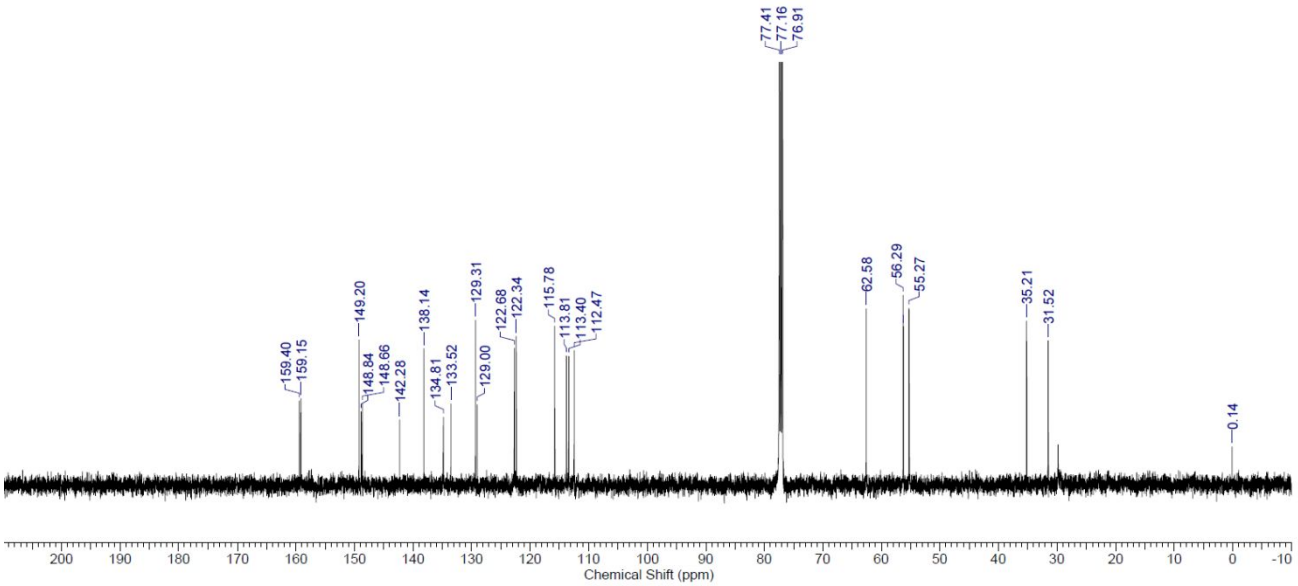


5-14. NMR Spectra of Compound **13d**

a) ^{1}H NMR Spectrum (in $CDCl_3$, 500 MHz)

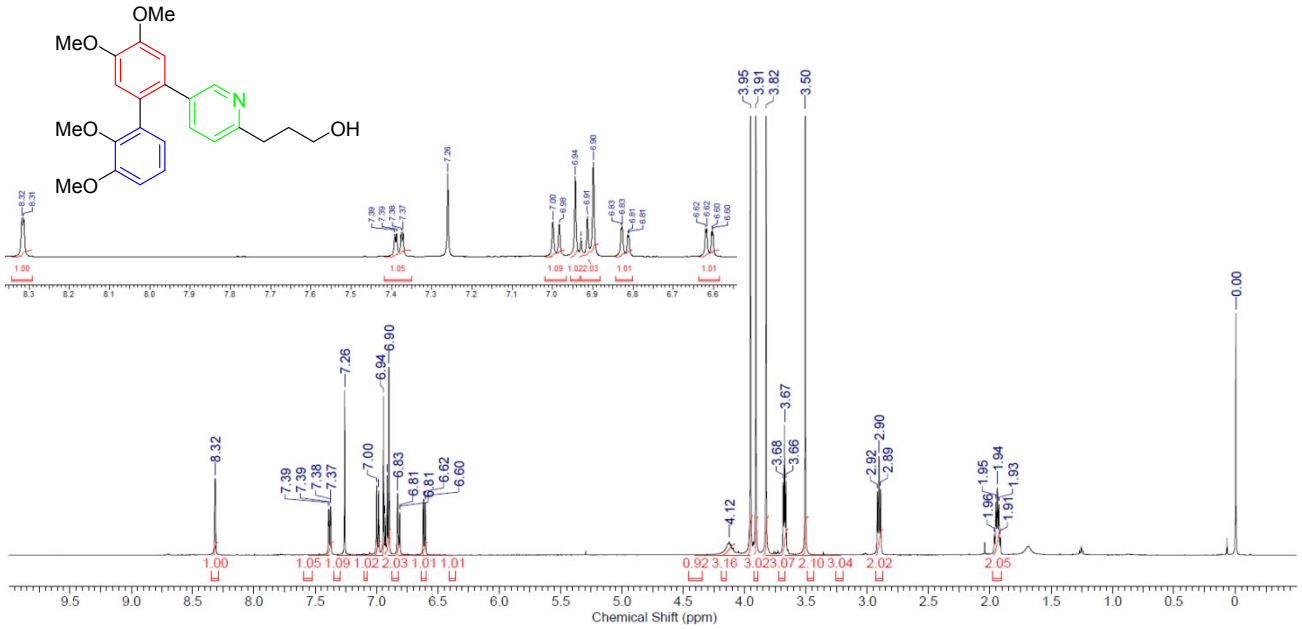


b) ^{13}C NMR Spectrum (in $CDCl_3$, 125 MHz)

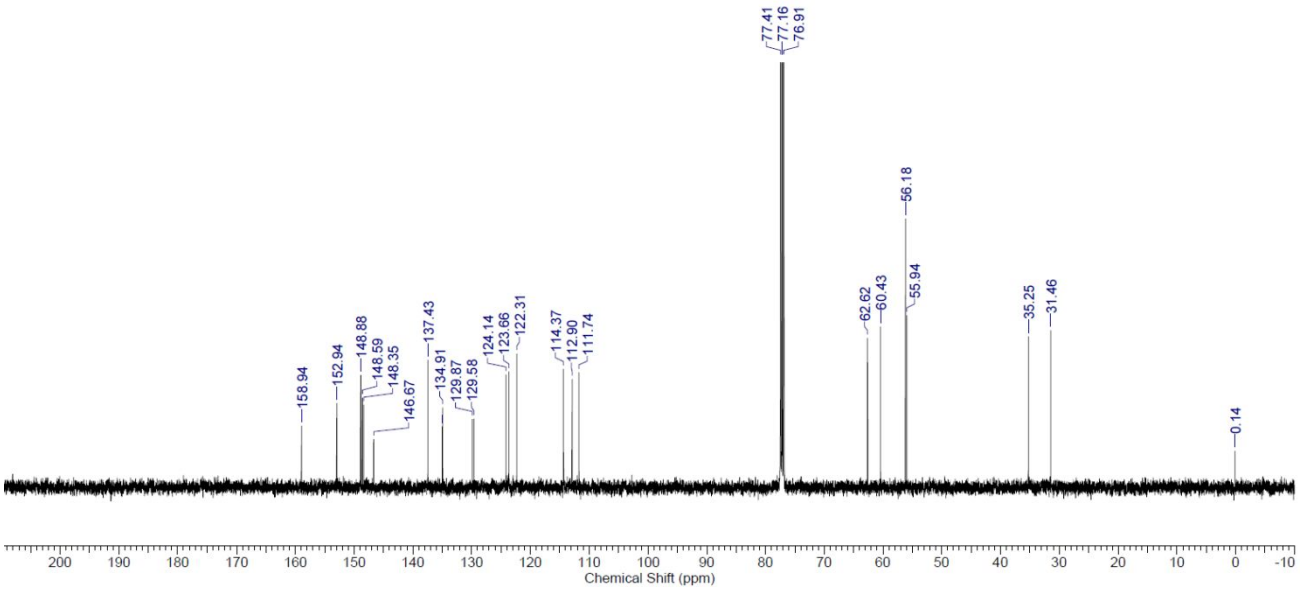


5-15. NMR Spectra of Compound **13e**

a) ^{1}H NMR Spectrum (in $CDCl_3$, 500 MHz)

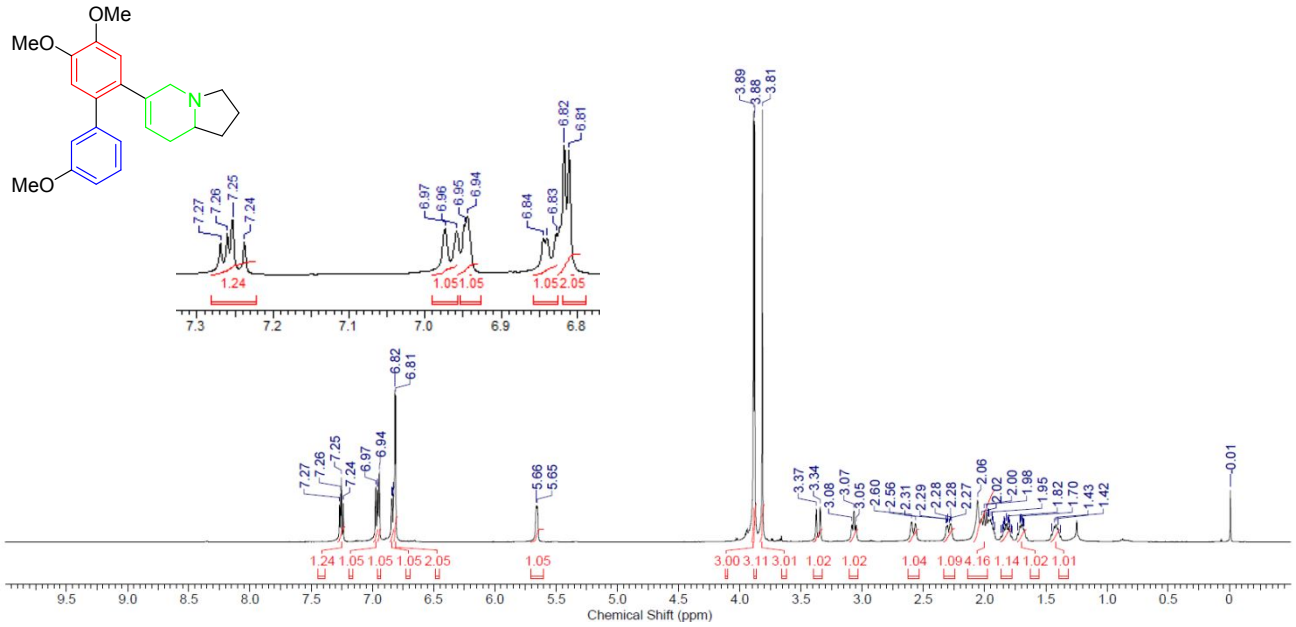


b) ^{13}C NMR Spectrum (in $CDCl_3$, 125 MHz)

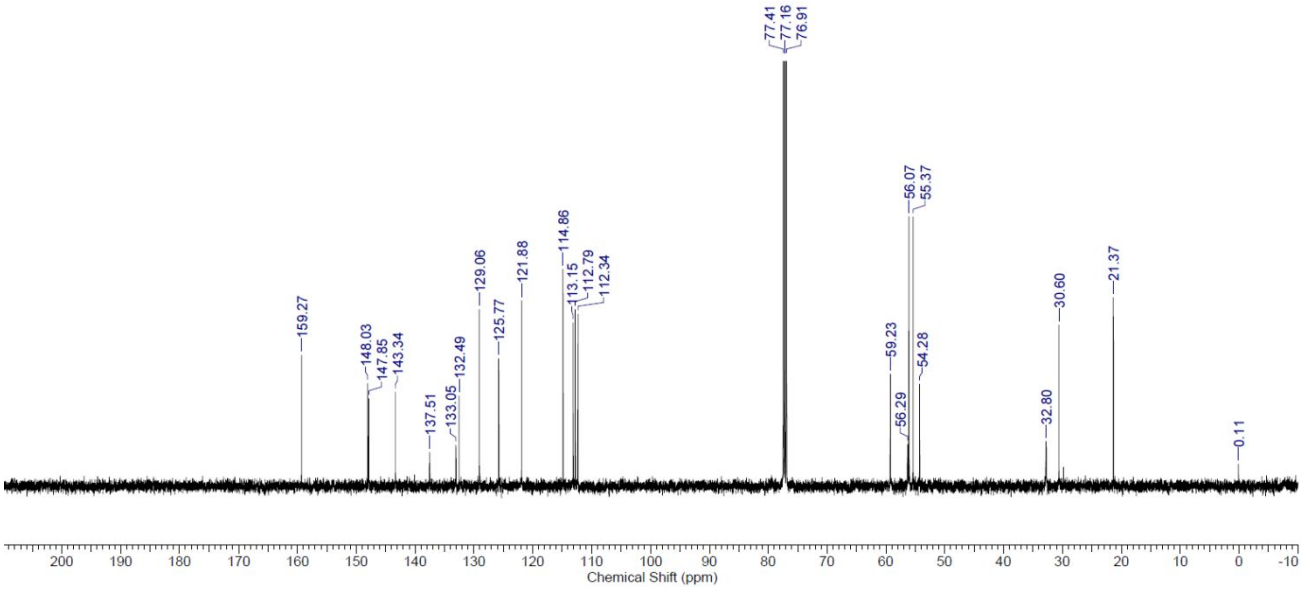


5-16. NMR Spectra of Compound **14d**

a) ^{1}H NMR Spectrum (in $CDCl_3$, 500 MHz)

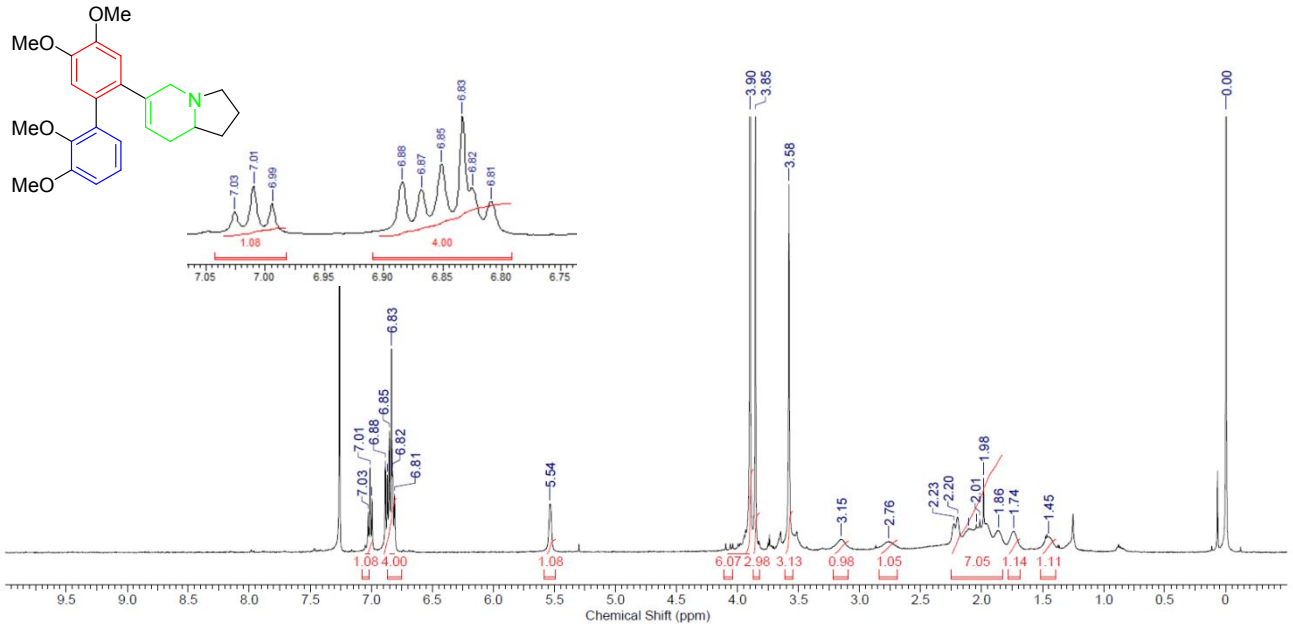


b) ^{13}C NMR Spectrum (in $CDCl_3$, 125 MHz)

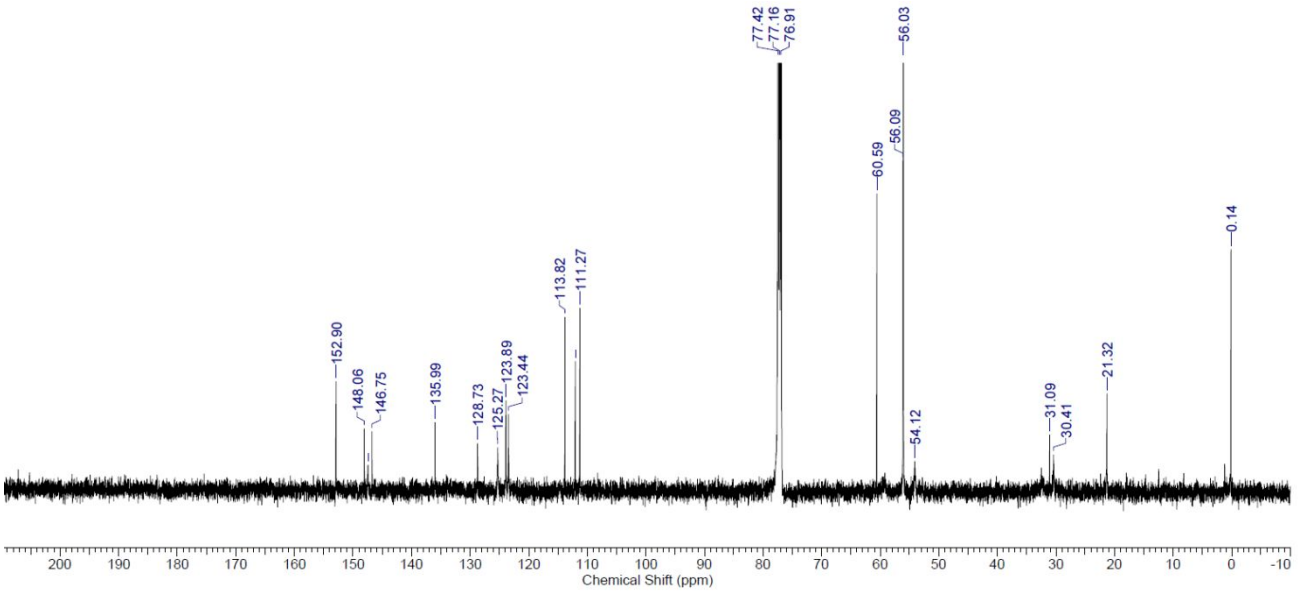


5-17. NMR Spectra of Compound **14e**

a) ^{1}H NMR Spectrum (in $CDCl_3$, 500 MHz)

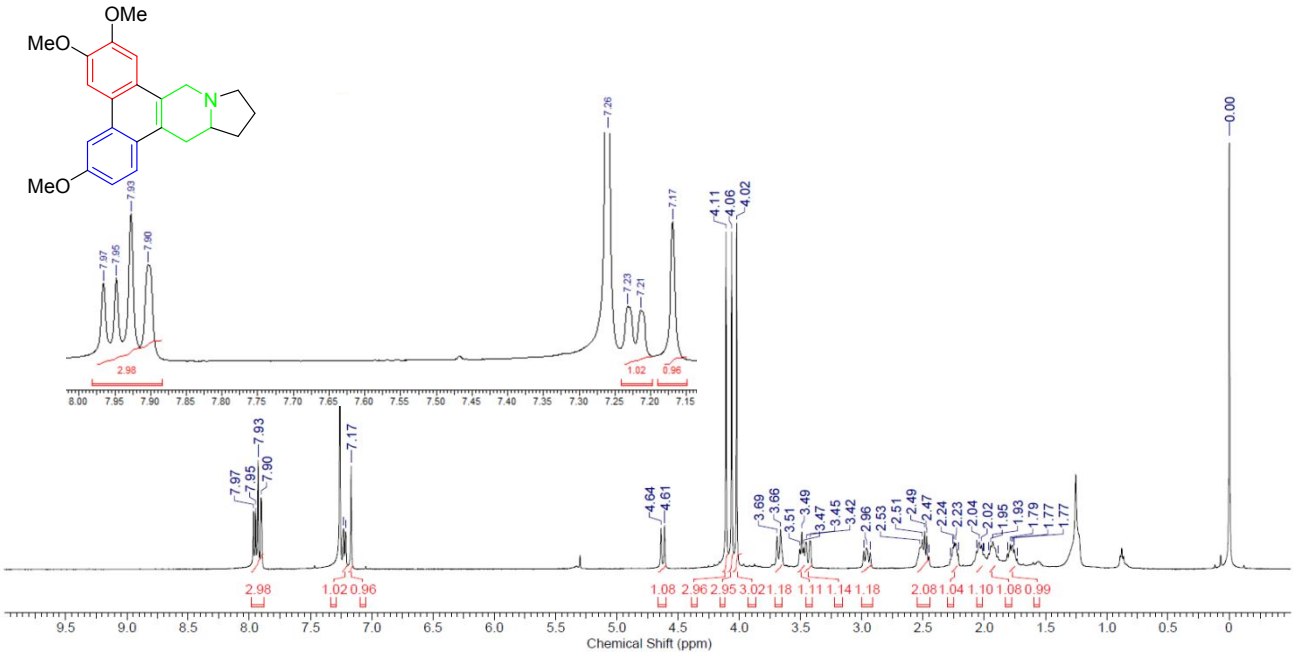


b) ^{13}C NMR Spectrum (in $CDCl_3$, 125 MHz)

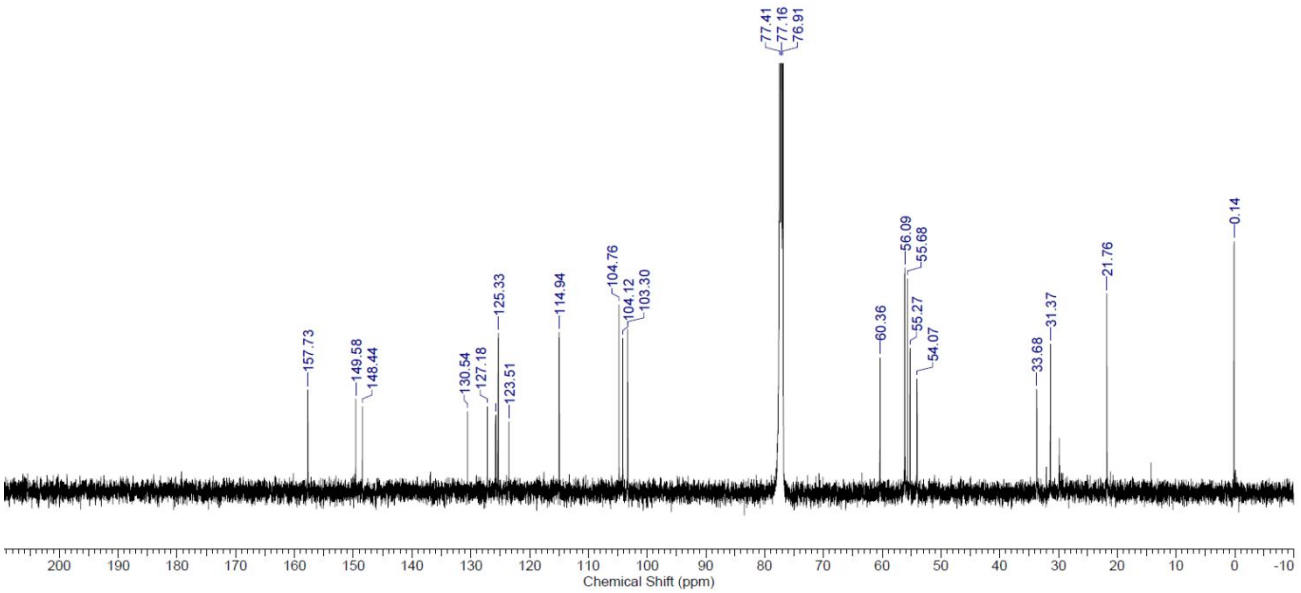


5-18. NMR Spectra of Deoxytylophorine (**4**)

a) ^{1}H NMR Spectrum (in $CDCl_3$, 500 MHz)

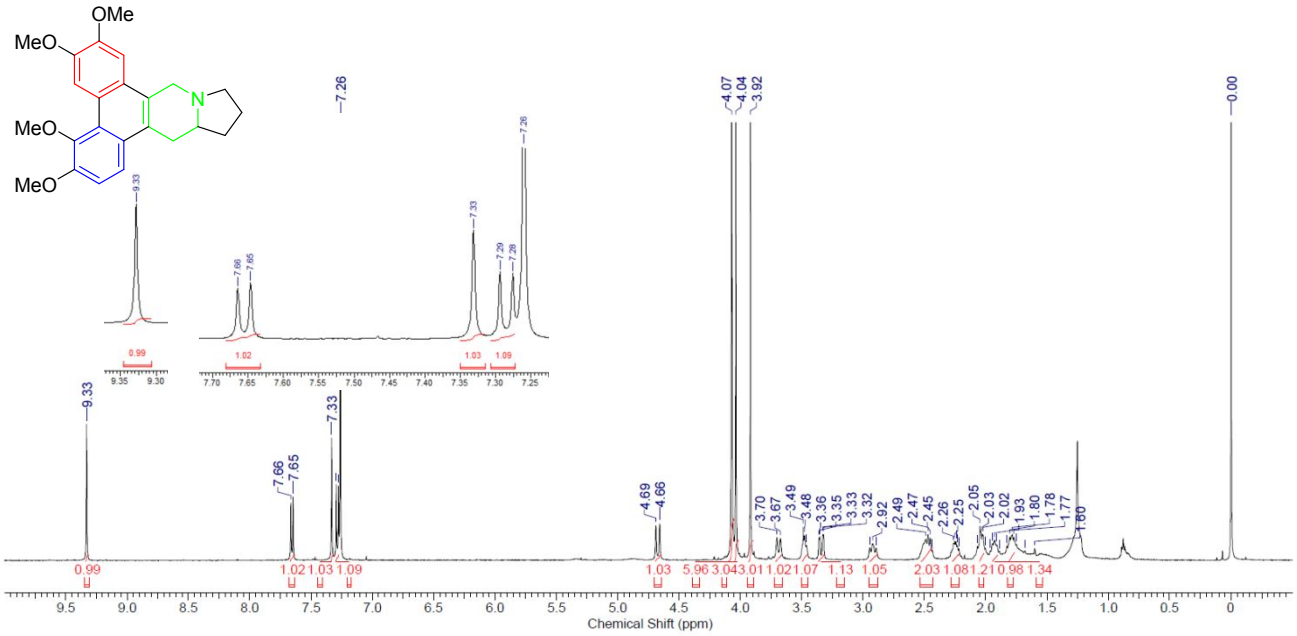


b) ^{13}C NMR Spectrum (in $CDCl_3$, 125 MHz)



5-19. NMR Spectra of Isotylocrebrine (**5**)

a) ^{1}H NMR Spectrum (in $CDCl_3$, 500 MHz)



b) ^{13}C NMR Spectrum (in $CDCl_3$, 125 MHz)