General Strategy for the Synthesis of Antirhine Alkaloids: Divergent Total Syntheses of (±)-Antirhine, (±)-18,19-Dihydroantirhine, and Their 20-Epimers

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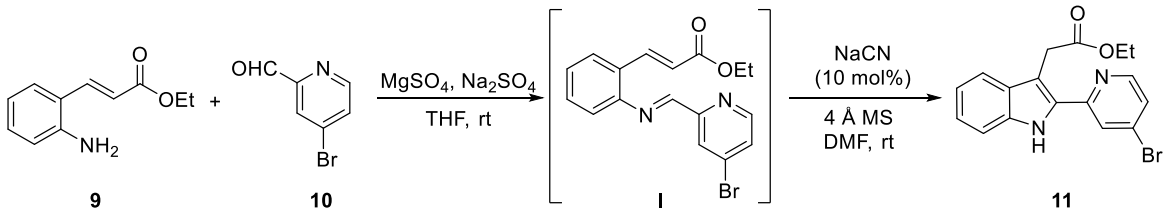
Table of Contents

1. General Information

All reactions were carried out in an oven-dried glassware under an argon atmosphere 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). Flash column chromatography was performed using silica gel 60 (230 – 400 mesh). Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise noted. (E)-ethyl 2-aminocinnamate **9** was prepared by the reported procedures.[1] ^{1}H NMR and ^{13}C NMR spectra were recorded on 500 MHz and 125 MHz spectrometers, respectively. Residual NMR solvents ($CDCl_3$ (δ_H: 7.26 ppm, δ_C: 77.16 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.

2. Synthesis of Preparation of Tetracyclic Core Structure (18)

ethyl 2-(2-(4-bromopyridin-2-yl)-1H-indol-3-yl) acetate (**11**)

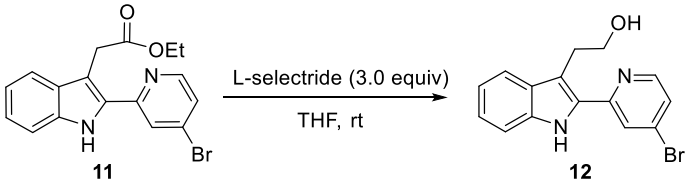


To a solution of (*E*)-ethyl-2-aminocinnamate (**9**) (4.8 g, 25 mmol) in anhydrous THF (250 mL) were added aldehyde **10** (4.7 g, 25 mmol), Na_2SO_4 (7.5 g) and $MgSO_4$ (7.5 g) at room temperature. The mixture was stirred at room temperature and monitored by ^{1}H NMR analysis of the crude mixture. After the complete conversion of amine **9** and aldehyde **10** into aldimine **I**, the reaction mixture was filtered to remove $MgSO_4$ and Na_2SO_4. The filtrate was concentrated in vacuo to furnish the crude product of aldimine **I**, which was used in the next step without further purification.

To a solution of the crude mixture in anhydrous DMF (250 mL) were added NaCN (120 mg; 2.5 mmol) and 4 Å molecular sieves (7.5 g) at room temperature. After the complete consumption of aldimine I, the reaction mixture was filtered to remove molecular sieves and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (ethyl acetate:hexanes = 1:7) to afford indole **11** as a pale yellow solid (8.2 g, 23 mmol, 92%).

Compound 11: ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 9.40 (br, 1H), 8.45 (dd, *J* = 5.3, 0.4 Hz, 1H), 8.23 (d, *J* = 1.4 Hz, 1H), 7.73 (dd, *J* = 8.1, 0.8 Hz, 1H), 7.42 - 7.36 (m, 2H), 7.28 - 7.26 (m, 1H), 7.17 (ddd, *J* = 7.9, 7.0, 0.9 Hz, 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 4.05 (s, 2H), 1.28 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR (125 MHz, $CDCl_3$, ppm)** δ = 171.5, 151.6, 150.2, 135.6, 133.6, 132.6, 129.6, 125.2, 124.7, 124.2, 120.3, 119.8, 111.5, 108.2, 61.3, 31.6, 14.4; **HRMS (ESI)** calcd for $C_{17}H_{16}BrN_2O_2$ 359.0395, found 359.0401.

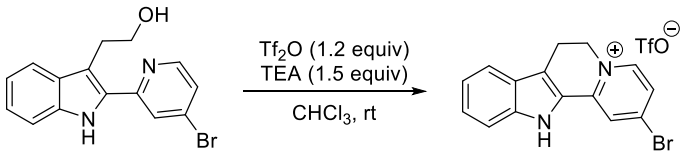
2-(2-(4-bromopyridin-2-yl)-1H-indol-3-yl)ethan-1-ol (**12**)



To a solution of the indole **11** (8.2 g, 23 mmol) in anhydrous THF (240 mL) was slowly added L-selectride solution (71 mL, 1.0 M THF solution) at 0 °C. The mixture was stirred and monitored by TLC. After the complete consumption of indole **11**, the reaction mixture was quenched with water and stirred vigorously for 15 min. The crude mixture was extracted with ethyl acetate. The organic layers were combined, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (ethyl acetate:hexanes = 1:2) to afford alcohol **12** as a white solid (5.3 g, 22 mmol, 96%).

Compound 12: ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 9.13 (br, 1H), 8.35 (dd, *J* = 5.3, 0.3 Hz, 1H), 7.89 (d, *J* = 1.4 Hz, 1H), 7.59 (d, *J* = 7.9 Hz, 1H), 7.33 - 7.28 (m, 2H), 7.20 (ddd, *J* = 8.2, 7.0, 1.1 Hz, 1H), 7.10 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 4.08 (t, *J* = 6.1 Hz, 2H), 4.00 (br, 1H), 3.33 (t, *J* = 6.0 Hz, 2H); **^{13}C NMR (125 MHz, $CDCl_3$, ppm)** δ 151.9, 149.5, 136.4, 133.8, 132.3, 129.2, 125.1, 124.3, 124.2, 120.1, 119.5, 114.2, 111.6, 63.4, 27.8; **HRMS (ESI)** calcd for $C_{15}H_{14}BrN_2O$ 317.0290, found 317.0286.

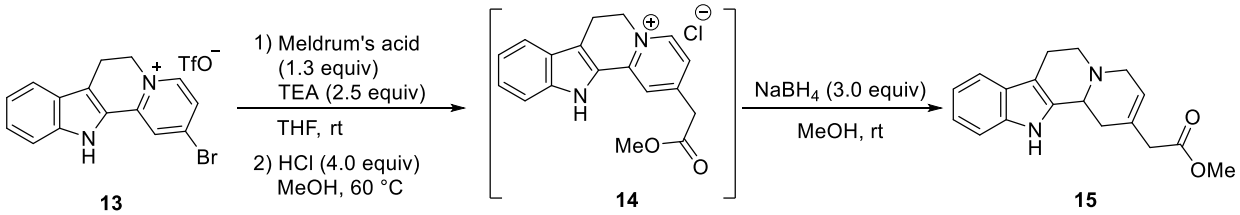
2-bromo-7,12-dihydro-6H-indolo[2,3-a]quinolizin-5-ium trifluoromethanesulfonate (**13**)



To a solution of alcohol **12** (5.0 g, 21 mmol) and triethylamine (4.4 mL, 32 mmol) in dry $CHCl_3$ (210 mL) at room temperature was slowly added trifluoromethanesulfonic anhydride (5.3 mL, 25 mmol). After stirring for 15 min, the resulting yellow precipitate was collected by filtration and washed with $CHCl_3$. The yellow solid was identified as compound **13** (8.7 g, 19 mmol,88%).

Compound 13: ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 12.23 (s, 1H), 8.82 (d, J = 6.7 Hz, 1H), 8.54 (d, J = 2.1 Hz, 1H), 8.11 (dd, J = 6.7, 2.1 Hz, 1H), 7.74 (d, J = 8.10 Hz, 1H), 7.56 (d, J = 8.40 Hz, 1H), 7.40 (ddd, J = 8.2, 7.0, 1.1 Hz, 1H), 7.19 (ddd, J = 8.0, 7.0, 0.8 Hz, 1H), 4.82 (t, J = 7.4 Hz, 2H), 3.38 (t, J = 7.4 Hz, 2H); **^{13}C NMR (125 MHz, $CDCl_3$, ppm)** δ 145.9, 143.3, 141.3, 139.6, 126.8, 126.1, 124.6, 124.3, 123.7, 121.0, 120.9, 118.8, 112.7, 55.3, 18.8; **HRMS (ESI)** calcd for $C_{15}H_{12}BrN_2$ 299.0178, found 299.0179.

methyl 2-(1,4,6,7,12,12b-hexahydroindolo[2,3-a]quinolizin-2-yl)acetate (**15**)



To a solution of compound **13** (8.6 g, 19 mmol) and Meldrum's acid (3.6 g, 25 mmol) in anhydrous THF (190 mL) was added triethylamine (6.7 mL, 47 mmol). The mixture was stirred at room temperature and monitored by TLC. After the complete consumption of the starting material **13**, the reaction mixture was quenched with water ant stirred for 30 min. The crude mixture was extracted with ethyl acetate. The organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo* to furnish the crude product of the compound. Without complete isolation, the crude mixture was used in the next step.

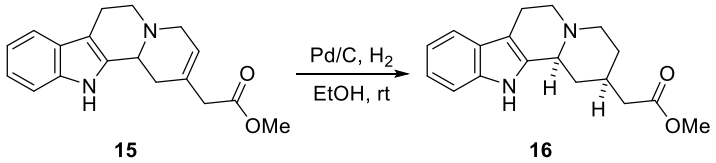
To a solution of the crude mixture of compound in anhydrous MeOH (190 mL) were added HCl (61 mL, 1.25 M solution in MeOH). The reaction mixture was stirred at 60 ^{o}C and monitored by TLC. After the complete consumption of starting material, the reaction mixture was cooled to room temperature and concentrated *in vacuo*. The resulting crude mixture **14** was used in the next step without purification.

To a solution of the crude mixture of compound **14** in MeOH (190 mL) was added $NaBH_4$ (2.2 g, 57 mmol) in three portions. The mixture was stirred at room temperature and monitored by TLC. After the complete consumption of the starting material **14**, the reaction mixture was quenched with water ant stirred for 15 min and diluted with ethyl acetate. The crude mixture was extracted with ethyl acetate. The organic layers were combined, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (100% ethyl acetate) to afford **15** as a white solid (4.0 g, 14 mmol, 70%).

Compound 15: ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.80 (br, 1H), 7.50 (d, J = 7.8 Hz, 1H), 7.37 - 7.28 (m, 1H), 7.15 (td, J = 7.5, 1.3 Hz, 1H), 7.13 - 7.08 (m, 1H), 5.70 (dd, J = 2.6, 1.1 Hz, 1H), 3.71 (s, 3H), 3.63 - 3.57 (m, 1H), 3.53 - 3.45 (m, 1H), 3.19 (dd, J = 11.4, 4.7 Hz, 1H), 3.11 (t, J = 14.6 Hz, 3H), 3.04 - 2.97 (m, 1H), 2.80 - 2.73 (m, 1H), 2.65 (td, J = 11.4, 4.1 Hz, 1H), 2.56 (d, J = 16.5 Hz, 1H), 2.39 - 2.30 (m, 1H); **^{13}C NMR (125 MHz, $CDCl_3$, ppm)** δ 171.9, 136.4, 134.6, 128.8, 127.3,

124.6, 121.7, 119.6, 118.4, 110.9, 108.7, 55.5, 54.5, 52.1, 52.1, 42.3, 34.4, 21.6; **HRMS (ESI)** calcd for $C_{18}H_{21}N_2O_2$ 297.1603, found 297.1608.

tert-butyl 2-(2-methoxy-2-oxoethyl)-1,3,4,6,7,12b-hexahydroindolo[2,3-a]quinolizine-12(2H)-carboxylate (**16**)

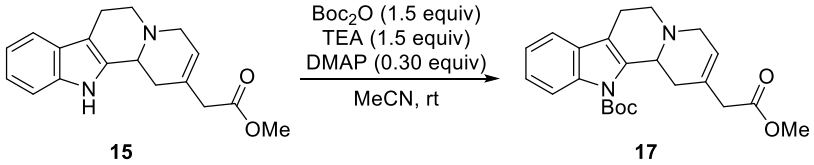


15 **16**

The starting material **15** (89 mg, 0.30 mmol) was dissolved in EtOH (130 mL) and Pd/C (32 mg, 10 wt%) was added to the reaction mixture. The above mixture was stirred at room temperature under a hydrogen atmosphere and monitored by TLC. After complete consumption of compound **15**, the reaction mixture was filtered in celite to remove an insoluble solid. Then, the filtrate was concentrated, and the crude mixture was purified by column chromatography on silica (diethylether:MeOH = 20:1 to 10:1) to afford **16** as transparent oil (86 mg, 29 mmol, 96%).

Compound 16: ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.76 (br, 1H), 7.49 - 7.44 (m, 1H), 7.30 (d, J = 7.93 Hz, 1H), 7.13 (td, J = 7.52, 1.14 Hz, 1H), 7.10 - 7.05 (m, 1H), 3.72 (s, 3H), 3.28 (dd, J = 11.37, 1.91 Hz, 1H), 3.12 - 3.04 (m, 2H), 3.04 - 2.96 (m, 1H), 2.77 - 2.68 (m, 1H), 2.62 (td, J = 11.33, 4.35 Hz, 1H), 2.46 (td, J = 11.90, 2.75 Hz, 1H), 2.41 - 2.27 (m, 2H), 2.24 - 2.17 (m, 1H), 2.15 - 2.04 (m, 1H), 1.85 - 1.75 (m, 1H), 1.53 (qd, J = 12.51, 4.27 Hz, 1H), 1.33 (q, J = 11.80 Hz, 1H); **^{13}C NMR (125 MHz, $CDCl_3$, ppm)** δ 173.2, 136.1, 134.7, 127.6, 121.5, 119.5, 118.3, 110.9, 108.4, 59.6, 55.4, 53.3, 51.8, 41.1, 36.2, 33.2, 32.2, 21.9; **HRMS (ESI)** calcd for $C_{18}H_{23}N_2O_2$ 299.1760, found 299.1758.

tert-butyl 2-(2-methoxy-2-oxoethyl)-1,6,7,12b-tetrahydroindolo[2,3-a]quinolizine-12(4H)-carboxylate (**17**)

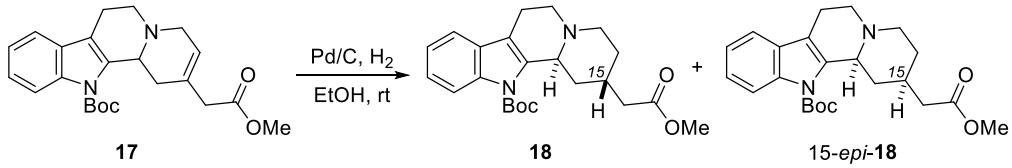


15 **17**

To a solution of compound **15** (4.0 g, 14 mmol), Boc_2O (4.6 g, 21 mmol) and DMAP (510 mg, 4.2 mmol) in acetonitrile (140 mL) was added TEA (2.9 mL, 21 mmol) at room temperature. The reaction mixture was stirred at room temperature and monitored by TLC. After the complete conversion of starting material **15,** the reaction mixture was concentrated *in vacuo*, quenched with water and extracted with ethyl acetate. The organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (ethyl acetate:hexanes = 1:2) to afford compound **17** as a yellow solid (5.3 g, 13 mmol, 95%).

Compound 17: ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.07 (d, J = 8.2 Hz, 1H), 7.46 - 7.39 (m, 1H), 7.29 - 7.26 (m, 1H), 7.24 - 7.20 (m, 1H), 5.71 - 5.63 (m, 1H), 4.23 - 4.16 (m, 1H), 3.67 (s, 3H), 3.52 - 3.37 (m, 2H), 3.17 - 3.08 (m, 1H), 3.03 (s, 2H), 2.88 (dtd, J = 9.7, 4.9, 4.9, 2.8 Hz, 1H), 2.79 - 2.71 (m, 2H), 2.66 (d, J = 16.8 Hz, 1H), 2.21 (d, J = 2.4 Hz, 1H), 1.66 (s, 9H); **^{13}C NMR (125 MHz, $CDCl_3$, ppm)** δ 171.8, 150.5, 137.0, 136.9, 129.6, 129.4, 124.1, 123.6, 122.8, 118.2, 116.4, 115.6, 84.0, 56.0, 54.5, 51.9, 48.4, 42.8, 33.5, 28.3, 22.4; **HRMS (ESI)** calcd for $C_{23}H_{29}N_2O_4$ 397.2127, found 397.2124.

tert-butyl 2-(2-methoxy-2-oxoethyl)-1,3,4,6,7,12b-hexahydroindolo[2,3-a]quinolizine-12(2H)-carboxylate (**18**)



17 **18** 15-*epi*-**18**

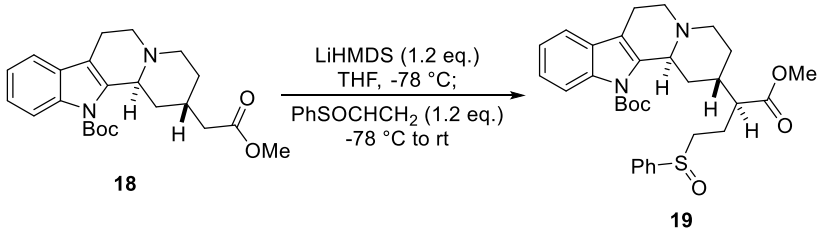
The starting material **17** (5.3 g, 13 mmol) was dissolved in EtOH (130 mL) and Pd/C (1.4 g, 10 wt%) was added to the reaction mixture. The above mixture was stirred at room temperature under a hydrogen atmosphere and monitored by TLC. After complete consumption of compound **17**, the reaction mixture was filtered in celite to remove an insoluble solid. Then, the filtrate was concentrated, and the crude mixture was purified by column chromatography on silica (diethylether:MeOH:acetone = 200:1:1 to 100:1:1) to afford **18** (4.5 g, 11 mmol, 85%) and 15-**epi**-**18** (730 mg, 1.8 mmol, 14%) as yellowish oil.

Compound 18: ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.92 (dd, J = 7.3, 0.9 Hz, 2H), 7.42 - 7.38 (m, 2H), 7.26 - 7.18 (m, 5H), 4.26 (d, J = 9.6 Hz, 1H), 3.71 (s, 3H), 3.20 - 3.13 (m, 1H), 3.00 - 2.94 (m, 1H), 2.93 - 2.84 (m, 2H), 2.84 - 2.76 (m, 1H), 2.71 - 2.60 (m, 3H), 2.45 - 2.38 (m, 1H), 2.06 - 1.96 (m, 2H), 1.84 (dd, J = 10.1, 4.5 Hz, 1H), 1.66 (s, 9H), 1.43 (d, J = 13.6 Hz, 1H); **^{13}C NMR (125 MHz, $CDCl_3$, ppm)** δ 173.6, 150.5, 137.7, 136.4, 129.5, 123.7, 122.5, 118.0, 116.3, 115.3, 83.6, 54.6, 51.5, 50.2, 48.5, 36.5, 33.2, 29.0, 28.2, 27.7, 21.8; **HRMS (ESI)** calcd for $C_{23}H_{31}N_2O_4$ 399.2284, found 399.2282.

Compound 15-*epi*-**18: ^{1}H NMR (500 MHz, $CDCl_3$, ppm)** δ 8.10 (d, J = 8.1 Hz, 1H), 7.40 (dd, J = 7.5, 0.8 Hz, 1H), 7.28 - 7.24 (td, J = 8.4, 1.5 Hz, 1H), 7.21 (td, J = 7.4, 1.1 Hz, 1H), 4.06 (d, J = 10.5 Hz, 1H), 3.67 (s, 3H), 3.16 - 3.10 (m, 2H), 2.92 (td, J = 12.7, 2.9 Hz, 1H), 2.87 - 2.79 (m, 1H), 2.79 - 2.69 (m, 2H), 2.31 - 2.21 (m, 2H), 2.20 - 2.13 (m, 2H), 1.67 (s, 9H), 1.62 (d, J = 13.0 Hz, 1H), 1.54 - 1.43 (m, 1H), 1.30 - 1.21 (m, 1H); **^{13}C NMR (125 MHz, $CDCl_3$, ppm)** δ 173.0, 150.5, 137.0, 137.0, 129.4, 124.1, 122.7, 118.0, 116.1, 115.6, 83.9, 58.9, 55.1, 51.6, 47.3, 41.6, 34.9, 33.8, 29.4, 28.3, 22.5; **HRMS (ESI)** calcd for $C_{23}H_{31}N_2O_4$ 399.2284, found 399.2281.

3. Total Synthesis of (±)-20-epi-Antirhine (3) and (±)-20-*epi*-18,19-Dihydroantirhine (4)

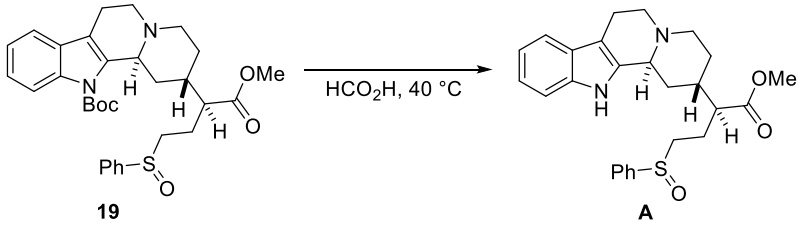
tert-butyl 2-(1-methoxy-1-oxo-4-(phenylsulfinyl)butan-2-yl)-1,3,4,6,7,12b-hexahydroindolo[2,3-a]quinolizine-12(2H)-carboxylate (**19**)



To a flame-dried flask were added compound **18** (120 mg, 0.30 mmol) and distilled THF (3.0 mL). To a solution of mixture was slowly added LiHMDS solution (0.36 mL, 1.0 M THF solution) at -78 °C. The resulting mixture was stirred for 30 minutes. Then, phenyl vinyl sulfoxide (48 μL, 0.36 mmol) was added dropwise by syringe to the reaction mixture. The reaction mixture was allowed to warm to room temperature, stirred for 5 hours. The mixture was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica (diethyl ether:MeOH = 50:1 to 20:1) to afford the **19** (50 mg, 0.091 mmol, 30%, 44% de) and the starting material **18** (61 mg, 0.15 mmol, 50%).

Compound 19: ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.94 (d, J = 8.09 Hz, 1H), 7.63 (dd, J = 7.71, 1.75 Hz, 2H), 7.54 - 7.48 (m, 3H), 7.40 (d, J = 7.32 Hz, 1H), 7.28 - 7.19 (m, 2H), 4.37 (d, J = 7.17 Hz, 1H), 3.65 (s, 2.16H), 3.63 (s, 0.84H)*, 3.22 - 3.14 (m, 1H), 3.03 - 2.92 (m, 3H), 2.90 - 2.79 (m, 3H), 2.77 - 2.62 (m, 2H), 2.47 (br, 0.28H)*, 2.41 - 2.32 (m, 0.72H), 2.17 - 2.07 (m, 1H), 2.07 - 1.82 (m, 4H), 1.72 (s, 2.52H)*, 1.71 (s, 6.48H), 1.29 - 1.22 (m, 1H); **^{13}C NMR (125 MHz, $CDCl_3$, ppm)** δ 175.3, 175.2, 150.7, 150.7, 144.4, 144.3, 137.1, 136.4, 136.3, 131.2, 131.0, 129.6, 129.3, 129.3, 124.2, 124.0, 124.0, 122.7, 118.1, 116.7, 115.6, 115.5, 84.2, 84.1, 55.9, 55.8, 54.3, 54.2, 51.7, 51.7, 50.1, 49.8, 48.0, 46.2, 35.0, 34.7, 29.9, 29.7, 28.4, 27.0, 23.7, 23.7, 21.5, 21.2; **HRMS (ESI)** calcd for $C_{31}H_{39}N_2O_5S$ 551.2580, found 551.2575.

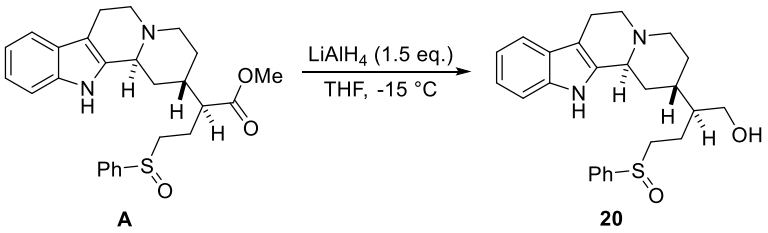
methyl 2-(1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizin-2-yl)-4-(phenylsulfinyl)butanoate



To a solution of compound **19** (110 mg, 0.20 mmol) was added formic acid (2.0 mL). To a solution of mixture was heated to 40 °C, stirred and monitored by TLC. Upon complete consumption of starting material **19**, the mixture was neutralized with NaOH to pH 7, and extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was used in the next step without more purification.

Compound A: crude ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 9.51 (br, 0.72H), 9.38 (br, 0.28H)*, 7.71 - 7.57 (m, 2H), 7.57 - 7.46 (m, 4H), 7.42 (d, J = 8.09 Hz, 0.72H), 7.39 (d, J = 8.09 Hz, 0.28H)*, 7.18 - 7.12 (m, 1H), 7.12 - 7.07 (m, 1H), 4.34 (br, 1H), 3.62 (s, 0.84H)*, 3.60 (s, 2.16H), 3.29 - 3.22 (m, 1H), 3.17 (t, J = 10.91 Hz, 1H), 3.11 - 2.99 (m, 2H), 2.91 - 2.77 (m, 2H), 2.75 - 2.65 (m, 2H), 2.62 (dd, J = 15.49, 3.28 Hz, 1H), 2.54 (br, 1H), 2.47 - 2.37 (m, 1H), 2.34 - 2.24 (m, 1H), 1.76 - 1.67 (m, 2H), 1.65 - 1.53 (m, 2H), 1.47 - 1.35 (m, 1H); **HRMS (ESI)** calcd for $C_{26}H_{31}N_2O_3S$ 451.2055, found 451.2053.

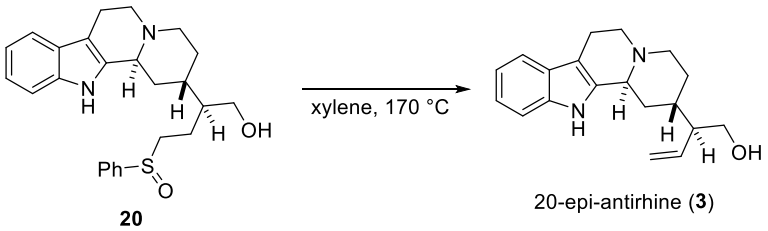
2-(1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizin-2-yl)-4-(phenylsulfinyl)butan-1-ol (**20**)



To a solution of the ester **A** (81 mg, 0.18 mmol) in anhydrous THF (1.8 mL) was slowly added lithium aluminum hydride solution (0.11 mL, 2.4 M hexane solution) at -15 °C. The mixture was stirred and monitored by TLC. After the complete consumption of ester **A**, the reaction mixture was diluted with ether and warmed to 0 °C. Then it was slowly added 10 μL of water, 10 μL of 15% *aq*. NaOH and 30 μL of water again. The reaction mixture stirred at room temperature for 15 minutes and dried over $MgSO_4$. The resulting suspension was stirred vigorously for 15 minutes and filtered to remove salts. After NMR analysis to determine the diastereomeric ratio (72:28), the crude residue was used in the next step without purification.

Compound 20: crude ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 9.69 (br, 0.72H), 9.66 (br, 0.28H)*, 7.68 - 7.62 (m, 0.56H)*, 7.58 - 7.53 (m, 1.44H), 7.53 - 7.44 (m, 4H), 7.43 - 7.36 (m, 1H), 7.15 - 7.10 (m, 1H), 7.10 - 7.04 (m, 1H), 4.33 (br, 1H), 3.74 (d, *J* = 4.12 Hz, 0.28H)*, 3.69 (dd, *J* = 10.99, 3.81 Hz, 0.72H), 3.49 (dd, *J* = 10.99, 7.02 Hz, 0.72H), 3.45 (d, *J* = 7.48 Hz, 0.28H), 3.30 - 3.21 (m, 1H), 3.19 - 3.11 (m, 1H), 3.06 - 2.96 (m, 2H), 2.84 - 2.73 (m, 2H), 2.73 - 2.65 (m, 1H), 2.62 (dd, *J* = 15.41, 4.27 Hz, 1H), 2.49 (d, *J* = 12.97 Hz, 1H), 2.24 - 2.07 (m, 1H), 1.80 - 1.62 (m, 2H), 1.60 - 1.49 (m, 2H); **HRMS (ESI)** calcd for $C_{25}H_{31}N_2O_2S$ 423.2106, found 423.2104.

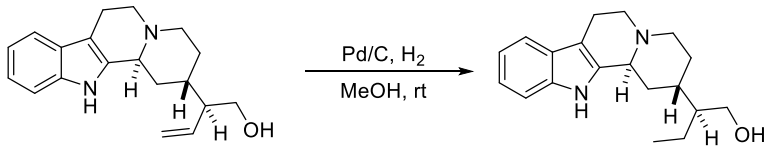
(±)-20-epi-antirhine (**3**)



To a solution of the sulfoxide **20** (54 mg, 0.13 mmol) in xylene (240 mL) was stirred at 170 °C and monitored by TLC. After the complete consumption of sulfoxide xx, the reaction mixture was concentrated in vacuo. The mixture was purified by column chromatography (diethyl ether:MeOH = 10:1) to afford 20-*epi*-antirhine (**3**) (32 mg, 0.11 mmol, 84%). Spectroscopic data were in good agreement with the literature.[2]

Compound 3: ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.92 (br, 1H), 7.47 (d, *J* = 7.63 Hz, 1H), 7.34 (d, *J* = 7.93 Hz, 1H), 7.17 - 7.12 (m, 1H), 7.12 - 7.07 (m, 1H), 5.66 (dt, *J* = 17.09, 9.84 Hz, 1H), 5.30 (dd, *J* = 10.30, 1.75 Hz, 1H), 5.21 (dd, *J* = 17.09, 1.37 Hz, 1H), 4.15 (br. s., 1H), 3.74 (dd, *J* = 10.68, 5.04 Hz, 1H), 3.47 (dd, *J* = 10.68, 8.09 Hz, 1H), 3.28 - 3.19 (m, 1H), 3.10 - 2.97 (m, 2H), 2.87 - 2.79 (m, 1H), 2.76 - 2.69 (m, 1H), 2.64 (d, *J* = 10.53 Hz, 1H), 2.30 (d, *J* = 4.73 Hz, 1H), 2.08 - 2.01 (m, 1H), 1.91 (ddd, *J* = 13.35, 8.85, 4.04 Hz, 1H), 1.76 (d, *J* = 11.75 Hz, 1H), 1.65 - 1.53 (m, 2H); **^{13}C NMR (125 MHz, $CDCl_3$, ppm)** δ 138.2, 136.0, 133.2, 127.7, 121.7, 119.7, 119.2, 118.2, 111.1, 108.1, 63.5, 54.4, 51.9, 49.7, 47.4, 31.5, 31.1, 28.8, 18.7; **HRMS (ESI)** calcd for $C_{19}H_{25}N_2O$ 297.1967, found 297.1964.

(±)-20-epi-18,19-dihydroantirhine (**4**)

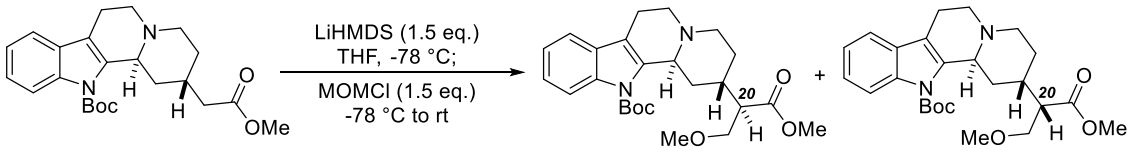


20-epi-antirhine (**3**) 20-epi-18,19-dihydroantirhine (**4**)

The starting material **3** (15 mg, 0.050 mmol) was dissolved in MeOH (0.50 mL), and Pd/C (5.3 mg, 10 wt% on carbon) was added to the reaction mixture. The above mixture was stirred at room temperature under a hydrogen atmosphere and monitored by TLC. After complete consumption of compound **3**, the reaction mixture was filtered in celite to remove an insoluble solid. Then, the filtrate was concentrated, and the crude mixture was purified by column chromatography on silica (diethylether:MeOH = 10:1) to afford **4** (14 mg, 0.049 mmol, 98%). Spectroscopic data were in good agreement with the literature.[3,4] **Compound 4: ^{1}H NMR (500 MHz, $CDCl_3$, ppm)** δ 8.12 (br, 1H), 7.47 (d, J = 7.63 Hz, 1H), 7.35 (d, J = 7.93 Hz, 1H), 7.18 - 7.13 (m, 1H), 7.13 - 7.07 (m, 1H), 4.36 (br, 1H), 3.69 (d, J = 5.49 Hz, 2H), 3.32 - 3.24 (m, 1H), 3.17 (td, J = 12.32, 5.26 Hz, 1H), 3.03 (dddd, J = 15.54, 9.06, 6.14, 3.13 Hz, 1H), 2.85 - 2.79 (m, 1H), 2.77 - 2.71 (m, 1H), 2.63 (dd, J = 15.56, 4.43 Hz, 1H), 2.14 (d, J = 13.58 Hz, 1H), 1.97 - 1.88 (m, 1H), 1.68 - 1.58 (m, 2H), 1.58 – 1.46 (m, 2H) 1.45 - 1.38 (m, 1H), 1.36 - 1.28 (m, 2H), 0.92 (t, J = 7.40 Hz, 3H); **^{13}C NMR (125 MHz, $CDCl_3$, ppm)** δ 136.1, 133.0, 127.7, 121.6, 119.6, 118.1, 111.2, 107.8, 62.8, 54.6, 51.5, 46.7, 45.0, 31.7, 30.3, 28.9, 20.4, 17.8, 12.2; **HRMS (ESI)** calcd for $C_{19}H_{27}N_2O$ 299.2123, found 299.2120.

4. Total Synthesis of (±)-Antirhine (1) and (±)-18,19-Dihydroantirhine (2)

tert-butyl 2-(1,3-dimethoxy-1-oxopropan-2-yl)-1,3,4,6,7,12b-hexahydroindolo[2,3-a]quinolizine-12(2H)-carboxylate



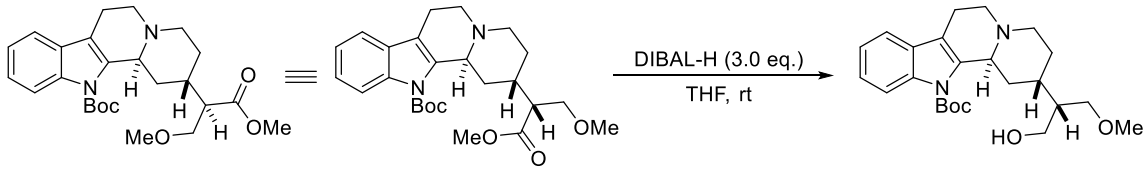
18 **21** 20-*epi*-**21**

To a flame-dried flask were added compound **18** (240 mg, 0.60 mmol) and distilled THF (6.0 mL). To a solution of mixture was slowly added LiHMDS solution (0.90 mL, 1.0 M THF solution) at -78 °C. The resulting mixture was stirred for 30 minutes. Then, chloromethyl methyl ether (68 μL, 0.90 mmol) was added dropwise by syringe to the reaction mixture. The reaction mixture was allowed to warm to room temperature, stirred and monitored by TLC. After the complete consumption of starting material **18**, the mixture was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica (diethyl ether:MeOH = 50:1 to 20:1) to afford **21** (170 mg, 0.38 mmol, 64%) and 20-*epi*-**21** (42 mg, 0.096 mmol, 16%).

Compound 21: ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.91 (dd, J = 7.40, 1.14 Hz, 1H), 7.42 - 7.38 (m, 1H), 7.26 - 7.19 (m, 2H), 4.40 (d, J = 9.00 Hz, 1H), 3.93 (dd, J = 8.85, 4.27 Hz, 1H), 3.73 (s, 3H), 3.72 - 3.64 (m, 1H), 3.41 (s, 3H), 3.32 (td, J = 10.49, 4.20 Hz, 1H), 3.22 - 3.14 (m, 1H), 3.13 - 3.04 (m, 1H), 2.97 - 2.78 (m, 3H), 2.73 - 2.63 (m, 1H), 2.11 - 2.00 (m, 2H), 1.98 - 1.88 (m, 1H), 1.81 (ddd, J = 13.73, 10.07, 4.12 Hz, 1H), 1.69 (s, 9H), 1.65 (d, J = 3.05 Hz, 1H), 1.32 - 1.26 (m, 1H); **^{13}C NMR (125 MHz, $CDCl_3$, ppm)** δ 175.4, 150.7, 137.4, 136.3, 129.6, 124.0, 122.8, 118.2, 116.6, 115.5, 83.9, 72.7, 59.0, 54.2, 51.7, 50.3, 47.8, 46.6, 32.4, 30.1, 28.4, 26.6, 21.6; **HRMS (ESI)** calcd for $C_{25}H_{35}N_2O_5$ 443.2546, found 443.2542.

Compound 20-*epi*-**21: ^{1}H NMR (500 MHz, $CDCl_3$, ppm)** δ 7.97 - 7.92 (m, 1H), 7.42 - 7.37 (m, 1H), 7.26 - 7.23 (m, 1H), 7.23 - 7.19 (m, 1H), 4.43 - 4.33 (m, 1H), 3.77 (s, 3H), 3.63 - 3.54 (m, 2H), 3.31 (s, 3H), 3.24 - 3.14 (m, 1H), 2.97 - 2.87 (m, 3H), 2.83 (t, J = 5.65 Hz, 2H), 2.65 - 2.56 (m, 1H), 2.06 - 1.96 (m, 3H), 1.85 (td, J = 6.98, 4.20 Hz, 1H), 1.66 (s, 9H), 1.52 (dd, J = 13.50, 5.26 Hz, 1H); **^{13}C NMR (125 MHz, $CDCl_3$, ppm)** δ 174.4, 150.6, 137.0, 136.8, 129.6, 124.0, 122.7, 118.0, 116.9, 115.5, 83.8, 72.6, 59.2, 55.1, 51.8, 49.1, 49.0, 47.6, 32.0, 31.3, 28.3, 26.7, 20.3; **HRMS (ESI)** calcd for $C_{25}H_{35}N_2O_5$ 443.2546, found 443.2544.

tert-butyl 2-(1-hydroxy-3-methoxypropan-2-yl)-1,3,4,6,7,12b-hexahydroindolo[2,3-a]quinolizine-12(2H)-carboxylate (**22**)

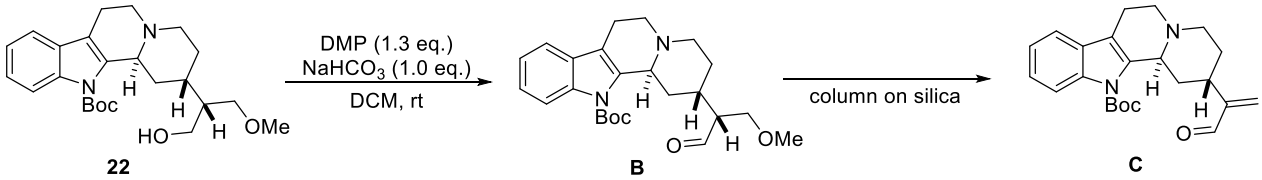


21 **21** **22**

To a solution of compound **21** (170 mg, 0.38 mmol) in distilled THF (3.8 mL) was added DIBAL-H solution (1.1 mmol, 1.0 M THF solution). The mixture was stirred at room temperature and monitored by TLC. After the complete consumption of ester **21**, the reaction mixture was diluted with ether and cooled to 0°C. Then it was slowly added 48 μL of water, 48 μL of 15% *aq*. NaOH and 120 μL of water again. The reaction mixture was warmed to room temperature and stirred for 15 minutes, dried over $MgSO_4$ and stirred vigorously for 15 minutes. After filtered to remove salts, the mixture was purified by column chromatography (diethyl ether:MeOH = 5:1) to afford the **22** (150 mg, 0.36 mmol, 95%).

Compound 22: ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.91 (dd, J = 7.25, 1.14 Hz, 1H), 7.42 - 7.38 (m, 1H), 7.26 - 7.19 (m, 2H), 4.36 (d, J = 7.93 Hz, 1H), 3.93 - 3.86 (m, 2H), 3.79 - 3.71 (m, 2H), 3.40 (s, 3H), 3.23 - 3.17 (m, 1H), 2.98 - 2.81 (m, 5H), 2.69 - 2.62 (m, 1H), 2.16 (td, J = 6.22, 3.13 Hz, 1H), 2.08 - 2.00 (m, 1H), 1.94 - 1.81 (m, 3H), 1.69 (s, 9H), 1.66 – 1.60 (m, 1H); **^{13}C NMR (125 MHz, $CDCl_3$, ppm)** δ 150.8, 137.8, 136.6, 129.7, 123.9, 122.7, 118.1, 116.9, 115.4, 83.7, 75.7, 65.2, 59.3, 54.8, 50.2, 48.3, 39.4, 30.7, 29.6, 28.4, 25.6, 21.4; **HRMS (ESI)** calcd for $C_{24}H_{35}N_2O_4$ 415.2597, found 415.2592.

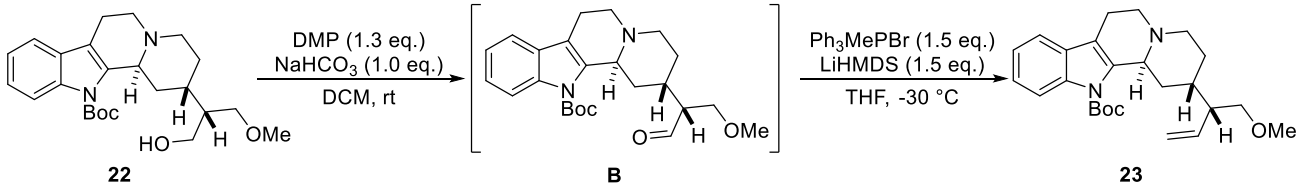
tert-butyl 2-(3-oxoprop-1-en-2-yl)-1,3,4,6,7,12b-hexahydroindolo[2,3-a]quinolizine-12(2H)-carboxylate (**B**)



To a solution of compound **22** (150 mg, 0.36 mmol) in distilled DCM (3.6 mL) were added Dess-Martin periodinane (200 mg, 0.46 mmol) and sodium bicarbonate (30 mg, 0.36 mmol) at room temperature. The resulting mixture was stirred at room temperature monitored by TLC. After the complete consumption of starting material **22**, the reaction mixture was quenched with sodium thiosulfate and stirred for 30 minutes. Then the crude mixture was extracted with brine, combined organic layer was dried over $MgSO_4$ and concentrated in vacuo to furnish the crude product of aldehyde **B.** The mixture was purified by column chromatography (diethyl ether:MeOH = 5:1) to afford the α,β-unsaturated aldehyde **C**.

Compound C: ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 9.56 (s, 1H), 7.91 (dd, J = 7.32, 0.92 Hz, 1H), 7.43 - 7.38 (m, 1H), 7.26 - 7.19 (m, 2H), 6.83 (d, J = 1.37 Hz, 1H), 6.23 (d, J = 0.76 Hz, 1H), 4.30 (d, J = 8.09 Hz, 1H), 3.18 (dt, J = 11.25, 4.75 Hz, 1H), 2.97 - 2.86 (m, 4H), 2.86 - 2.78 (m, 1H), 2.70 - 2.62 (m, 1H), 2.23 (d, J = 13.73 Hz, 1H), 2.15 - 2.06 (m, 1H), 2.03 – 1.95(m, 1H), 1.72 (dt, J = 12.28, 1.95 Hz, 1H), 1.66 (s, 9H); **^{13}C NMR (125 MHz, $CDCl_3$, ppm)** δ 195.1, 152.5, 150.7, 137.5, 136.5, 135.3, 129.6, 123.9, 122.7, 118.2, 116.7, 115.4, 84.0, 55.2, 50.6, 48.5, 31.2, 30.6, 28.4, 26.1, 21.5; **HRMS (ESI)** calcd for $C_{23}H_{29}N_2O_3$ 381.2178, found 381.2175.

tert-butyl 2-(1-methoxybut-3-en-2-yl)-1,3,4,6,7,12b-hexahydroindolo[2,3-a]quinolizine-12(2H)-carboxylate



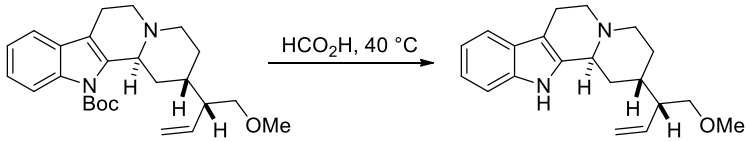
To a solution of compound **22** (150 mg, 0.36 mmol) in distilled DCM (3.6 mL) were added Dess-Martin periodinane (200 mg, 0.46 mmol) and sodium bicarbonate (30 mg, 0.36 mmol) at room temperature. The resulting mixture was stirred at room temperature monitored by TLC. After the complete consumption of starting material **22**, the reaction mixture was quenched with sodium thiosulfate and stirred for 30 minutes. Then it was extracted with brine and combined organic layer was dried over $MgSO_4$ and concentrated in vacuo to furnish the crude product of aldehyde **B**, which was used in the next step without further purification.

To a flame-dried flask were added methyltriphenylphosphonium bromide (190 mg, 0.54 mmol), distilled THF (1.0 mL) and LiHMDS solution (0.54 mL, 1.0 M THF solution) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 30 minutes. Meanwhile, the crude mixture of **B** was dissolved in THF (2.6 mL) in a flame-dried round-bottom flask under argon and cooled to -30 °C. The freshly prepared Wittig reagent solution was transferred to the solution of **B** in THF slowly dropwise via syringe, and the mixture was allowed to stir at the same temperature and monitored by TLC. After the complete

consumption of starting material **B**, the mixture was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica (diethyl ether:MeOH = 50:1 to 20:1) to afford the **23** (61 mg, 0.15 mmol, 41%).

Compound 23: ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.93 (dd, J = 7.32, 0.92 Hz, 1H), 7.43 - 7.38 (m, 1H), 7.26 - 7.19 (m, 2H), 5.73 - 5.64 (m, 1H), 5.16 - 5.14 (m, 1H), 5.14 - 5.10 (m, 1H), 4.45 (br, 1H), 3.68 (dd, J = 9.31, 3.66 Hz, 1H), 3.56 (dd, J = 9.16, 7.48 Hz, 1H), 3.40 - 3.35 (m, 3H), 3.26 - 3.18 (m, 1H), 2.99 - 2.79 (m, 4H), 2.77 - 2.64 (m, 2H), 2.09 (d, J = 13.58 Hz, 1H), 1.89 - 1.71 (m, 4H), 1.66 - 1.71 (m, 9H), 1.58 (d, J = 13.89 Hz, 1H); **^{13}C NMR (125 MHz, $CDCl_3$, ppm)** δ 150.7, 140.3, 138.0, 136.6, 129.8, 123.8, 122.7, 118.1, 116.7, 116.4, 115.4, 83.7, 74.7, 58.9, 54.6, 49.8, 48.3, 44.7, 32.4, 30.6, 28.4, 25.8, 21.4; **HRMS (ESI)** calcd for $C_{25}H_{35}N_2O_3$ 411.2648, found 411.2644.

2-(1-methoxybut-3-en-2-yl)-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine (**24**)

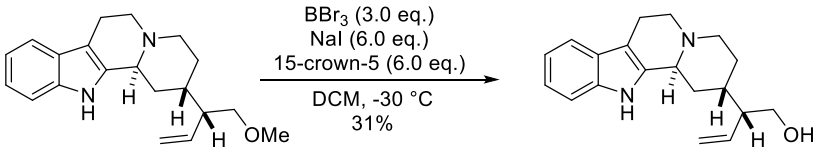


23 **24**

To a solution of compound **23** (44 mg, 0.11 mmol) was added formic acid (1.1 mL). To a solution of mixture was heated to 40 °C, stirred and monitored by TLC. Upon complete consumption of starting material **23**, the mixture was neutralized with NaOH to pH 7, and extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica (diethyl ether:MeOH = 10:1) to afford the **24** (29 mg, 0.094 mmol, 85%).

Compound 24: crude ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.87 (br, 1H), 7.48 (d, J = 7.63 Hz, 1H), 7.34 (d, J = 7.93 Hz, 1H), 7.16 (td, J = 7.55, 1.22 Hz, 1H), 7.13 - 7.08 (m, 1H), 5.70 - 5.60 (m, 1H), 5.12 (dd, J = 10.30, 1.91 Hz, 1H), 5.08 (dt, J = 17.20, 0.86 Hz, 1H), 4.24 (br, 1H), 3.51 - 3.46 (m, 1H), 3.44 - 3.39 (m, 1H), 3.36 (s, 3H), 3.27 - 3.21 (m, 1H), 3.10 (d, J = 4.43 Hz, 1H), 3.03 (ddd, J = 15.34, 5.95, 2.52 Hz, 1H), 2.75 (dd, J = 9.46, 3.20 Hz, 1H), 2.67 (ddd, J = 11.41, 5.30, 3.43 Hz, 1H), 2.64 - 2.58 (m, 1H), 2.34 - 2.26 (m, 1H), 2.09 - 2.01 (m, 1H), 1.96 (dd, J = 9.38, 4.35 Hz, 1H), 1.71 - 1.64 (m, 1H), 1.57 - 1.45 (m, 2H); **HRMS (ESI)** calcd for $C_{20}H_{27}N_2O$ 311.2123, found 311.2122.

*(±)-antirhine (**1**)*



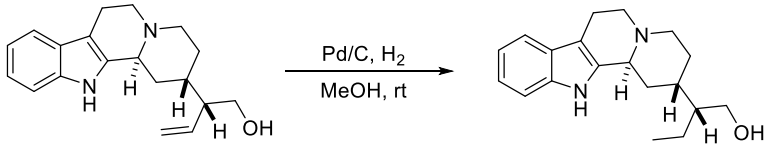
24 antirhine (**1**)

To a flask were added sodium iodide (85 mg, 0.56 mmol), distilled DCM (0.10 mL) and 15-crown-5 (124 mg, 0.56 mmol) at room temperature. The iodide reagent mixture was stirred for 30 minutes. Meanwhile, compound **24** (29 mg, 0.094 mmol) was dissolved in distilled DCM (1.0 mL) under argon and cooled to -30 °C. The freshly prepared reagent iodide solution was transferred to the solution of **24** in DCM rapidly dropwise via syringe. To the reaction mixture was added slowly the boron tribromide solution (0.28 mL, 1.0 M DCM solution) at -30 °C. The reaction mixture was stirred and monitored by TLC. After the complete consumption of starting material **24**, the mixture was quenched with sodium bicarbonate aqueous solution and extracted with DCM. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was

purified by column chromatography on silica (diethyl ether:MeOH = 10:1) to afford antirhine (**1**) (8.3 mg, 0.028 mmol, 30%). Spectroscopic data were in good agreement with the literature.[5]

Compound 1: ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.99 (br, 1H), 7.47 (d, J = 7.63 Hz, 1H), 7.33 (d, J = 7.78 Hz, 1H), 7.18 - 7.12 (m, 1H), 7.12 - 7.07 (m, 1H), 5.60 (dt, J = 17.36, 9.63 Hz, 1H), 5.22 (d, J = 10.22 Hz, 1H), 5.16 (d, J = 17.09 Hz, 1H), 4.16 (br, 1H), 3.74 (dd, J = 10.76, 4.20 Hz, 1H), 3.59 (dd, J = 10.45, 7.55 Hz, 1H), 3.25 - 3.17 (m, 1H), 3.10 - 2.96 (m, 2H), 2.81 - 2.72 (m, 1H), 2.69 - 2.56 (m, 2H), 2.25 (br, 1H), 2.10 - 2.02 (m, 1H), 1.97 - 1.89 (m, 1H), 1.71 (d, J = 5.95 Hz, 1H), 1.56 - 1.45 (m, 2H); **^{13}C NMR (125 MHz, $CDCl_3$, ppm)** δ 138.3, 135.9, 133.7, 127.8, 121.5, 119.6, 118.7, 118.2, 111.1, 108.2, 63.8, 54.5, 52.0, 49.8, 47.2, 31.9, 31.9, 28.9, 18.6; **HRMS (ESI)** calcd for $C_{19}H_{25}N_2O$ 297.1967, found 297.1964.

*(±)-18,19-dihydroantirhine (**2**)*



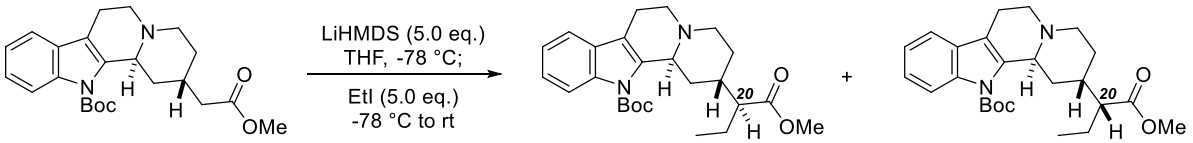
antirhine (**1**) 18,19-dihydroantirhine (**2**)

The starting material **1** (8.3 mg, 0.028 mmol) was dissolved in MeOH (0.30 mL), and Pd/C (3.0 mg, 10 wt% on carbon) was added to the reaction mixture. The above mixture was stirred at room temperature under a hydrogen atmosphere and monitored by TLC. After complete consumption of compound **1**, the reaction mixture was filtered in celite to remove an insoluble solid. Then, the filtrate was concentrated, and the crude mixture was purified by column chromatography on silica (diethylether:MeOH = 10:1) to afford 18,19-dihydroantirhine (**2**) (8.1 mg, 0.027 mmol, 97%). Spectroscopic data were in good agreement with the literature.[4]

Compound 2: ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.21 (br, 1H), 7.46 (d, J = 7.63 Hz, 1H), 7.33 (d, J = 7.78 Hz, 1H), 7.16 - 7.11 (m, 1H), 7.11 - 7.05 (m, 1H), 4.28 (br, 1H), 3.79 - 3.66 (m, 2H), 3.30 - 3.18 (m, 1H), 3.10 (br, 1H), 3.06 - 2.96 (m, 1H), 2.84 - 2.74 (m, 1H), 2.70 (d, J = 11.29 Hz, 1H), 2.60 (dd, J = 15.56, 4.27 Hz, 1H), 2.13 (d, J = 12.82 Hz, 1H), 1.96 (br, 1H), 1.71 (d, J = 10.99 Hz, 1H), 1.56 - 1.41 (m, 3H), 1.37 - 1.20 (m, 3H), 0.90 (t, J = 7.32 Hz, 3H); **^{13}C NMR (125 MHz, $CDCl_3$, ppm)** δ 136.0, 133.3, 127.7, 121.5, 119.5, 118.1, 111.2, 107.6, 62.3, 54.6, 51.6, 46.9, 44.9, 32.0, 31.6, 28.8, 21.2, 18.0, 12.1; **HRMS (ESI)** calcd for $C_{19}H_{27}N_2O$ 299.2123, found 299.1758.

5. Syntheses of 20-*epi*-18,19-Dihydroantirhine (4) and 18,19-Dihydroantirhine (2) via Ethylation of Enolate

tert-butyl-2-(1-methoxy-1-oxobutan-2-yl)-1,3,4,6,7,12b-hexahydroindolo[2,3-a]quinolizine-12(2H)-carboxylate (**26**)



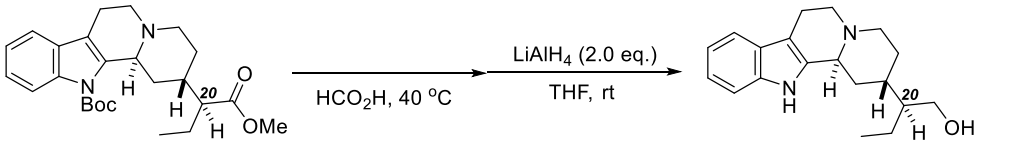
18 **26** 20-*epi*-**26**

To a flame-dried flask were added compound **18** (80 mg, 0.20 mmol) and distilled THF (2.0 mL). To a solution of mixture was slowly added LiHMDS solution (1.0 mL, 1.0 M THF solution) at -78 °C. The resulting mixture was stirred for 30 minutes. Then, iodoethane (80 μL, 1.0 mmol) was added dropwise by syringe to the reaction mixture, and the mixture was allowed to warm to room temperature, stirred at room temperature and monitored by TLC. Upon complete consumption of starting material **18**, the mixture was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica (diethyl ether:MeOH = 50:1) to afford compound **26** (54 mg, 0.13 mmol, 64%) and its 20-*epi*-**26** (14 mg, 0.031 mmol, 16%).

Compound 26: ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.93 - 7.88 (m, 1H), 7.42 - 7.38 (m, 1H), 7.25 - 7.18 (m, 2H), 4.37 - 4.30 (m, 1H), 3.70 (s, 2H), 3.21 - 3.13 (m, 1H), 3.03 - 2.94 (m, 1H), 2.92 - 2.75 (m, 4H), 2.70 - 2.60 (m, 1H), 2.12 - 2.03 (m, 1H), 1.93 (br, 3H), 1.87 - 1.78 (m, 1H), 1.67 (s, 9H), 1.62 - 1.52 (m, 1H), 1.33 - 1.24 (m, 1H), 0.95 (t, J = 7.4 Hz, 3H); **^{13}C NMR (125 MHz, $CDCl_3$, ppm)** δ 176.8, 150.7, 137.6, 136.5, 129.7, 123.8, 122.7, 118.1, 116.6, 115.3, 83.8, 54.6, 51.3, 50.2, 48.5, 48.3, 34.9, 30.4, 28.3, 27.6, 23.6, 21.5, 12.0.

Compound 20-*epi*-26: ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.95 (d, J = 8.1 Hz, 1H), 7.40 (d, J = 7.9 Hz, 1H), 7.26 - 7.18 (m, 2H), 4.41 (br, 1H), 3.77 - 3.72 (m, 1H), 3.74 (s, 3H), 3.24 - 3.18 (m, 1H), 3.26 - 3.17 (m, 1H), 2.97 - 2.90 (m, 2H), 2.82 (d, J = 4.7 Hz, 2H), 2.62 (dt, J = 9.3, 4.3 Hz, 2H), 1.98 (d, J = 5.0 Hz, 2H), 1.93 - 1.80 (m, 2H), 1.68 - 1.64 (m, 9H), 1.49 (d, J = 4.0 Hz, 1H), 0.87 (t, J = 7.5 Hz, 3H); **^{13}C NMR (125 MHz, $CDCl_3$, ppm)** δ 175.9, 150.6, 137.0, 136.8, 129.6, 124.0, 122.7, 118.0, 116.8, 115.5, 83.7, 55.1, 51.4, 49.0, 48.8, 48.3, 32.9, 32.1, 28.3, 26.3, 23.5, 20.3, 11.3.

*20-epi-18,19-Dihydroantirhine (**4**) and 18,19-Dihydroantirhine (**2**)*



26 20-*epi*-18,19-dihydroantirhine (**4**)
(84% over two steps)

To a solution of compound **26** (42.7 mg, 0.10 mmol) was added formic acid (1.0 mL). To a solution of mixture was heated to 40 °C, stirred and monitored by TLC. Upon complete consumption of **26**, the mixture was neutralized with NaOH to pH 7, and extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was used in the next step without more purification.

To a solution of the crude mixture from the above reaction in anhydrous THF (1.0 mL) was slowly added lithium aluminum hydride solution (0.083 mL, 2.4 M hexane solution) at room temperature. The mixture was stirred and monitored by TLC. After the complete reduction of the ester group, the reaction mixture was diluted with ether and cooled to 0 °C. Then it was slowly added 8.0 μL of water, 8.0 μL of 15% *aq*. NaOH and 20 μL of water again. The reaction mixture stirred at room temperature for 15 minutes and dried over $MgSO_4$. The crude residue was purified by column chromatography on silica (diethyl

ether:MeOH = 10:1) to afford 20-*epi*-18,19-dihydroantirhine (**4**) (25 mg, 0.084 mmol, 84% yield over two steps). The spectroscopic data were in good agreement with those in the literature.[3,4]

With compound 20-*epi*-**26**, 18,19-dihydroantirhine (**2**) was obtained through the same procedure with similar efficiency. The spectroscopic data of the resulting product were in good agreement with those of 18,19-dihydroantirhine (**2**).[4]

6. References

1. Lee, S. J.; Seo, H.-A.; Cheon, C.-H. *Adv. Synth. Catal.* **2016**, *358*, 1566-1570.

2. Weniger, B.; Anton, R.; Varea, T.; Quirion, J.-C.; Bastida, J.; Garcia, R. *J. Nat. Prod.* **1994**, *57*, 287-290.

3. Tietze, L. F.; Bachmann, J.; Wichmann, J.; Zhou, Y.; Raschke T. Liebigs Ann. 1997, 881-886.

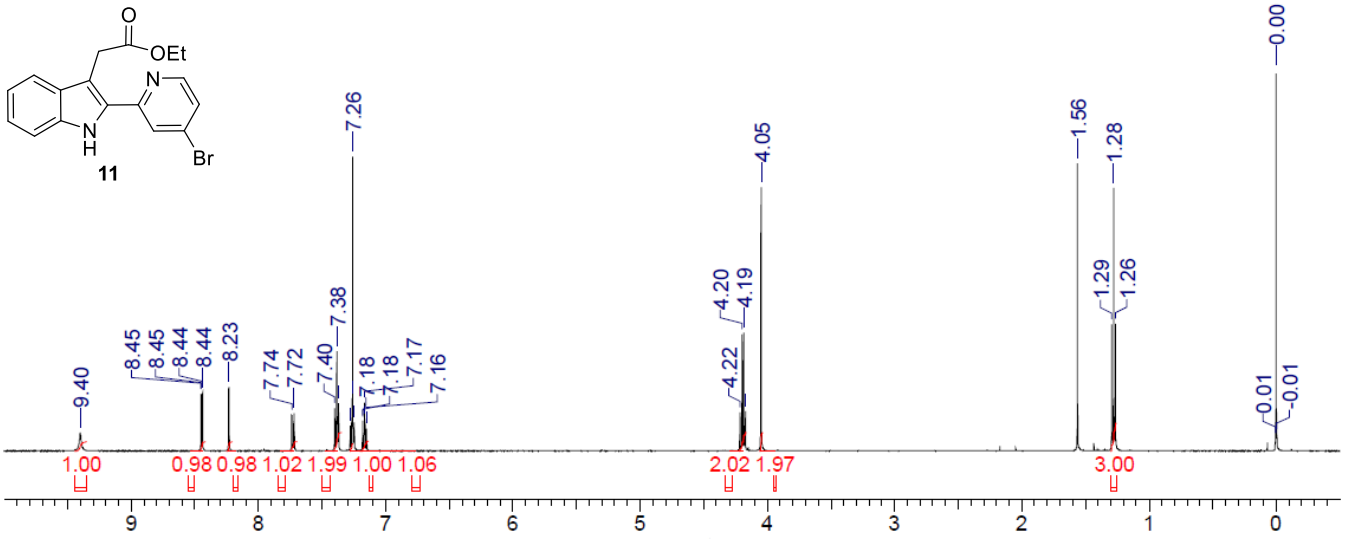
4. Robert, G. M. T.; Ahond, A.; Poupat, C.; Potier. P.; Jollès, C.; Jousselin, A.; Jacquemin, H. *J. Nat. Prod.* **1983**, *46*, 694-707.

5. Suzuki, T.; Sato, E.; Unno, K.; Kametani, T. *Chem. Pharm. Bull.* **1986**, *34*, 3135-3141.

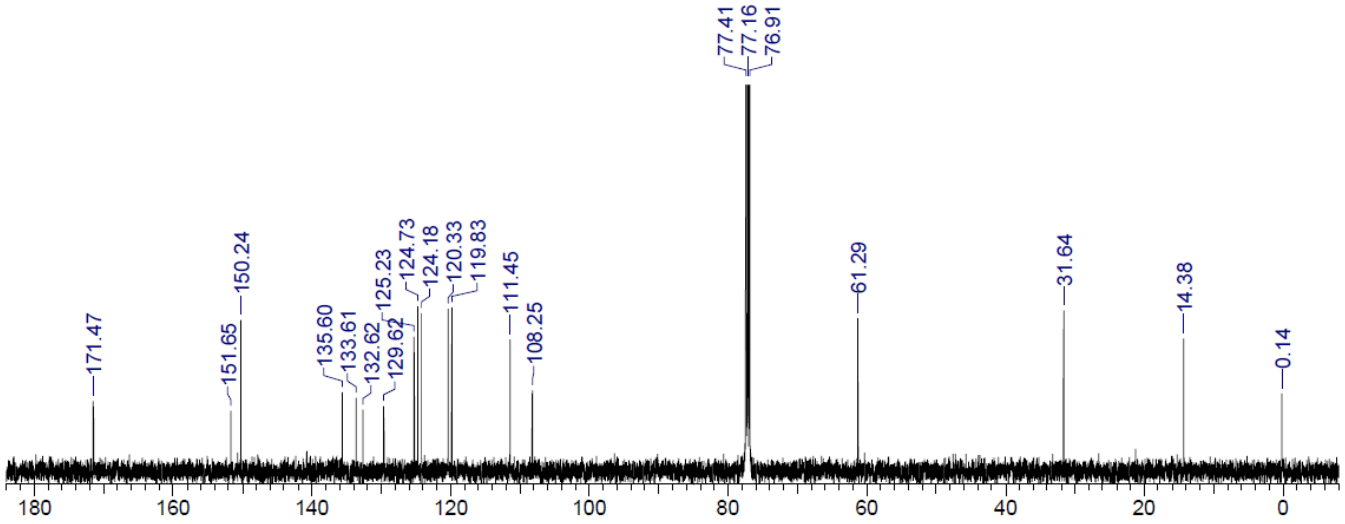
7. Spectroscopic Data

7-1. NMR Spectra of ethyl 2-(2-(4-bromopyridin-2-yl)-1H-indol-3-yl) acetate (**11**)

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

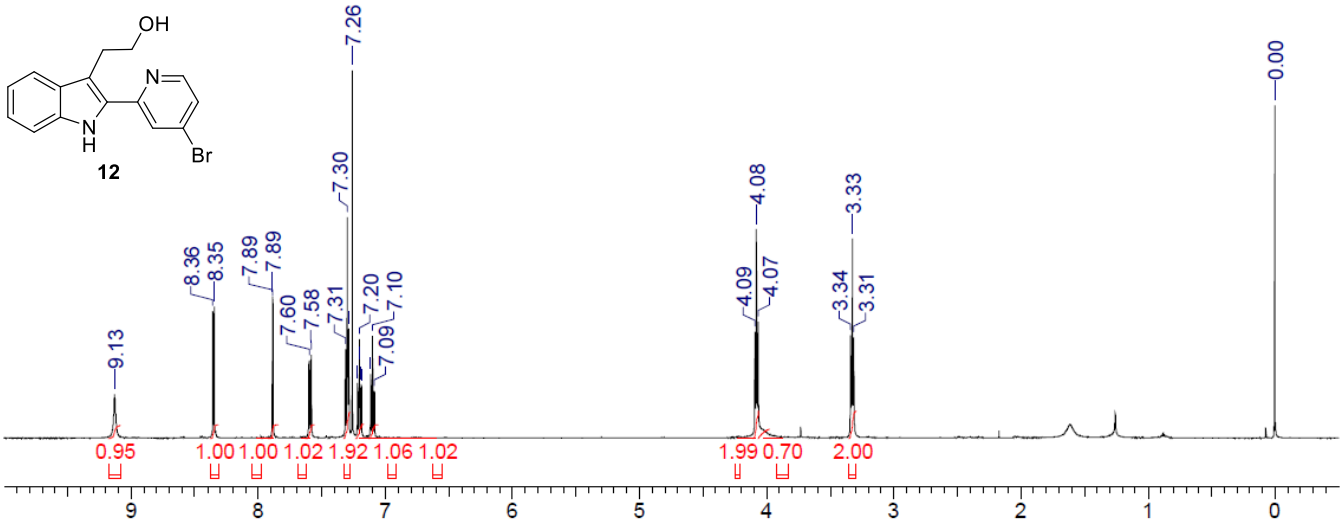


b) ^{13}C NMR Spectrum (in $CDCl_3$, 125 MHz)

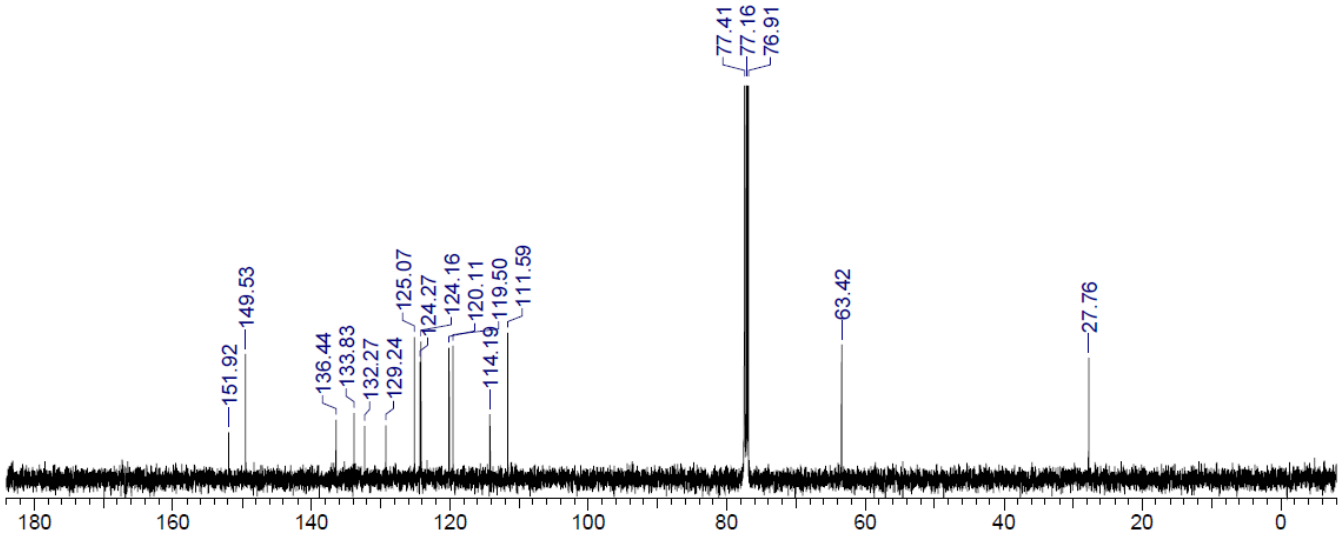


7-2. NMR Spectra of 2-(2-(4-bromopyridin-2-yl)-1H-indol-3-yl)ethan-1-ol (**12**)

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

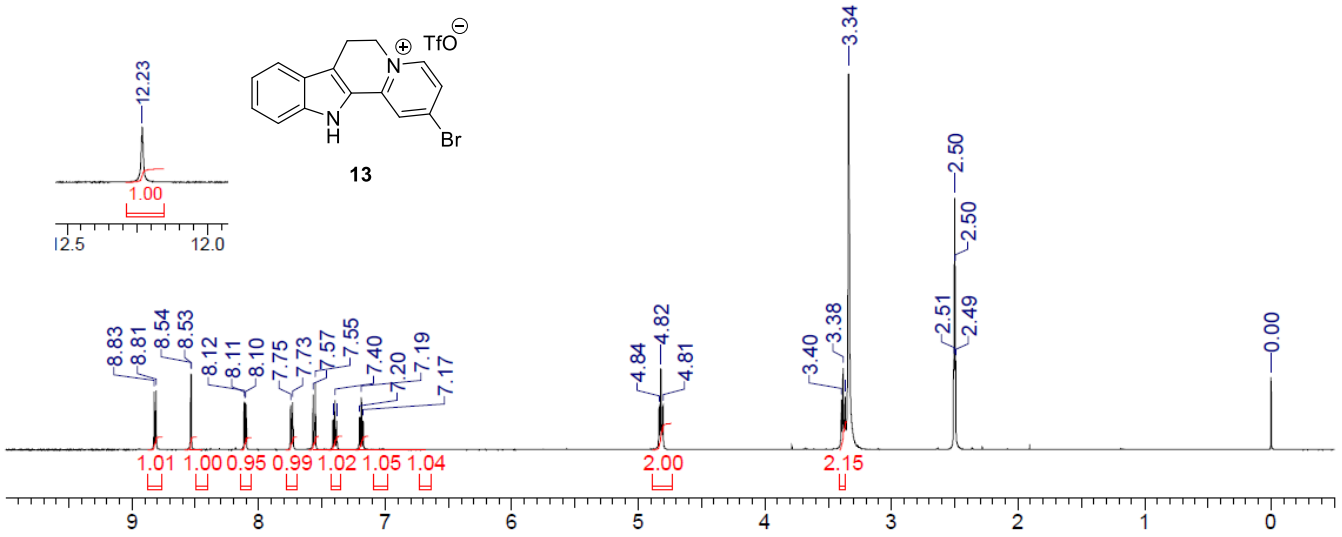


b) ^{13}C NMR Spectrum (in $CDCl_3$, 125 MHz)

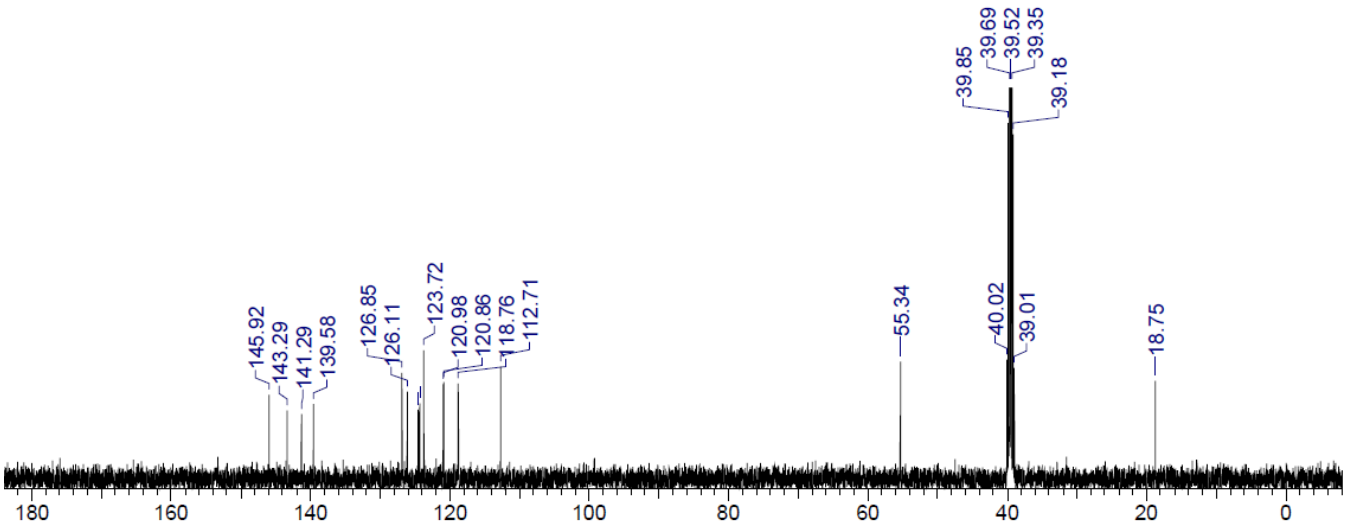


7-3. NMR Spectra of 2-bromo-7,12-dihydro-6H-indolo[2,3-a]quinolizin-5-ium trifluoromethanesulfonate (**13**)

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

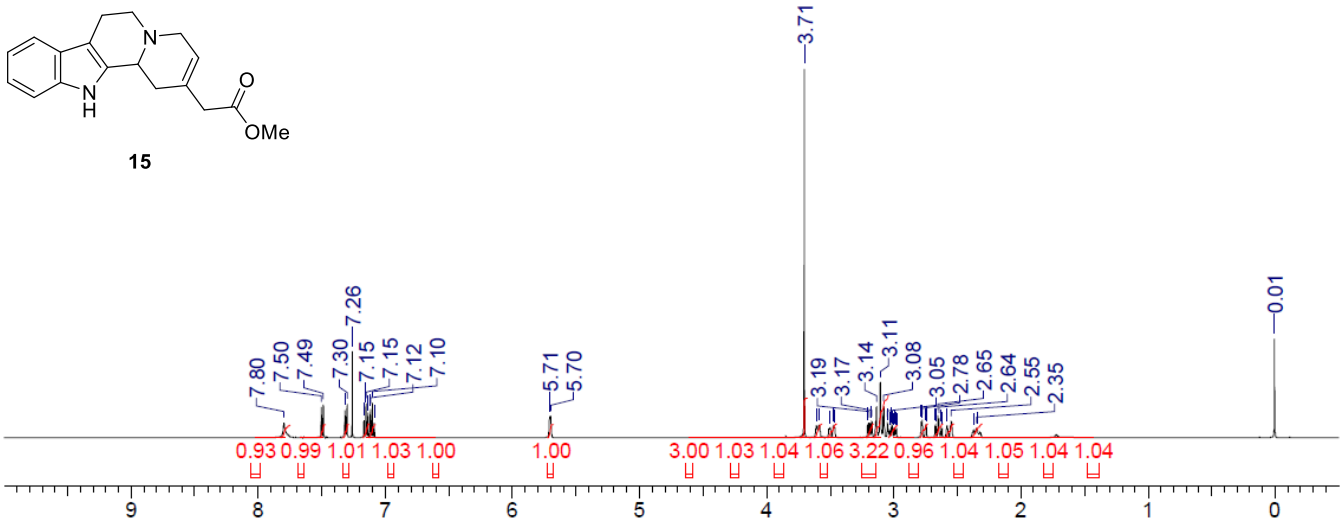


b) ^{13}C NMR Spectrum (in DMSO-d_6, 125 MHz)

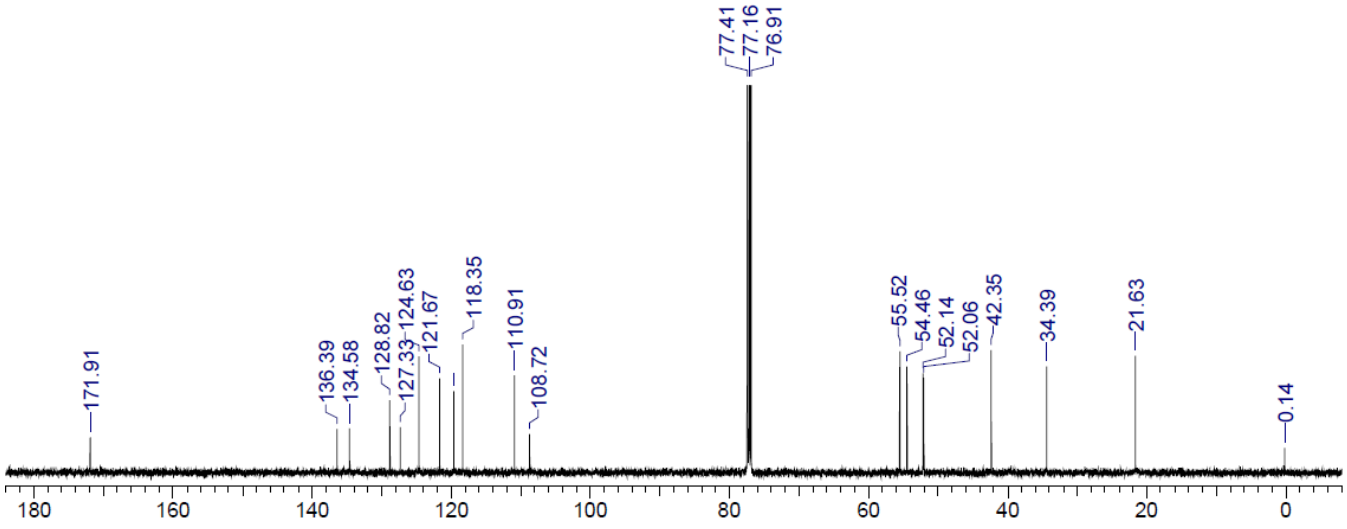


7-4. NMR Spectra of methyl 2-(1,4,6,7,12,12b-hexahydroindolo[2,3-a]quinolizin-2-yl)acetate (**15**)

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

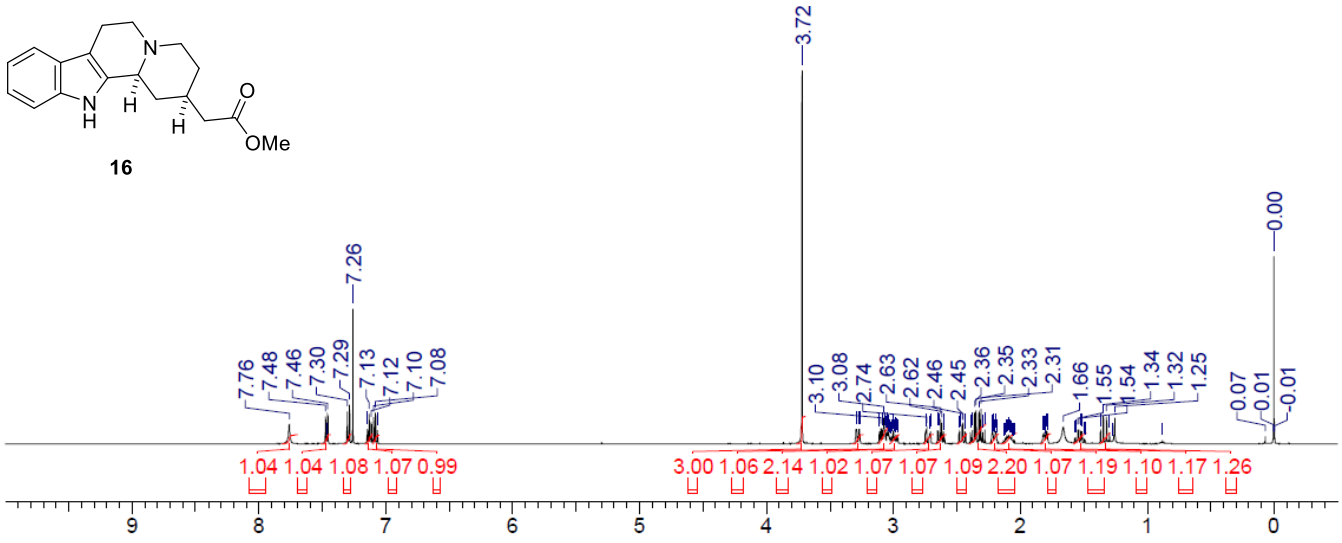


b) ^{13}C NMR Spectrum (in $CDCl_3$, 125 MHz)

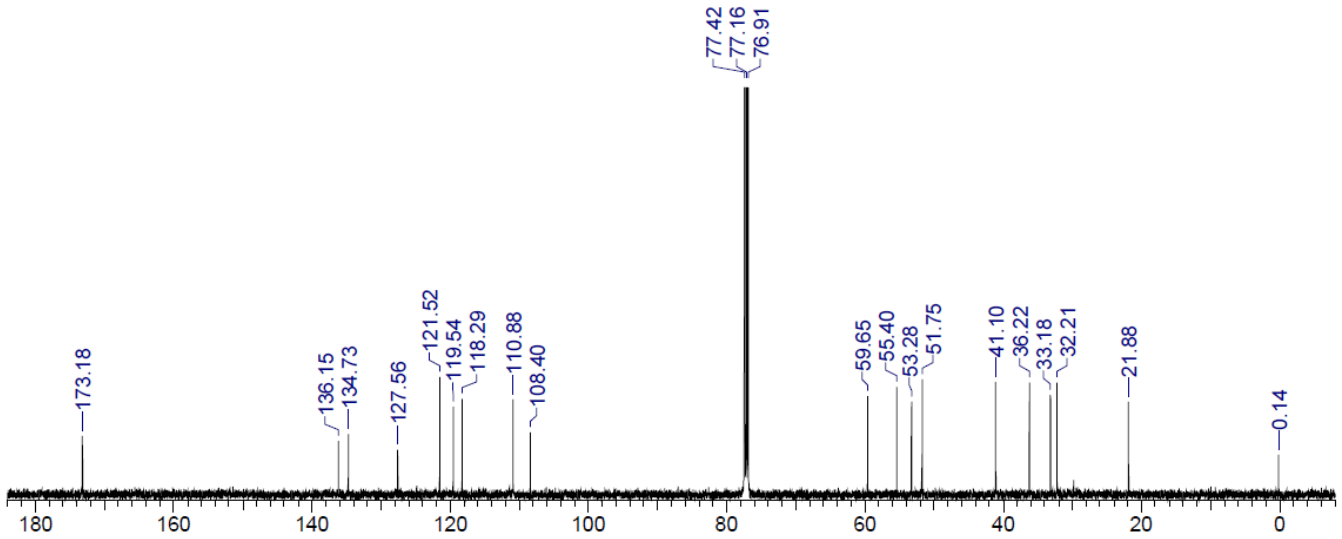


7-5. NMR Spectra of methyl 2-(1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizin-2-yl)acetate (**16**)

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

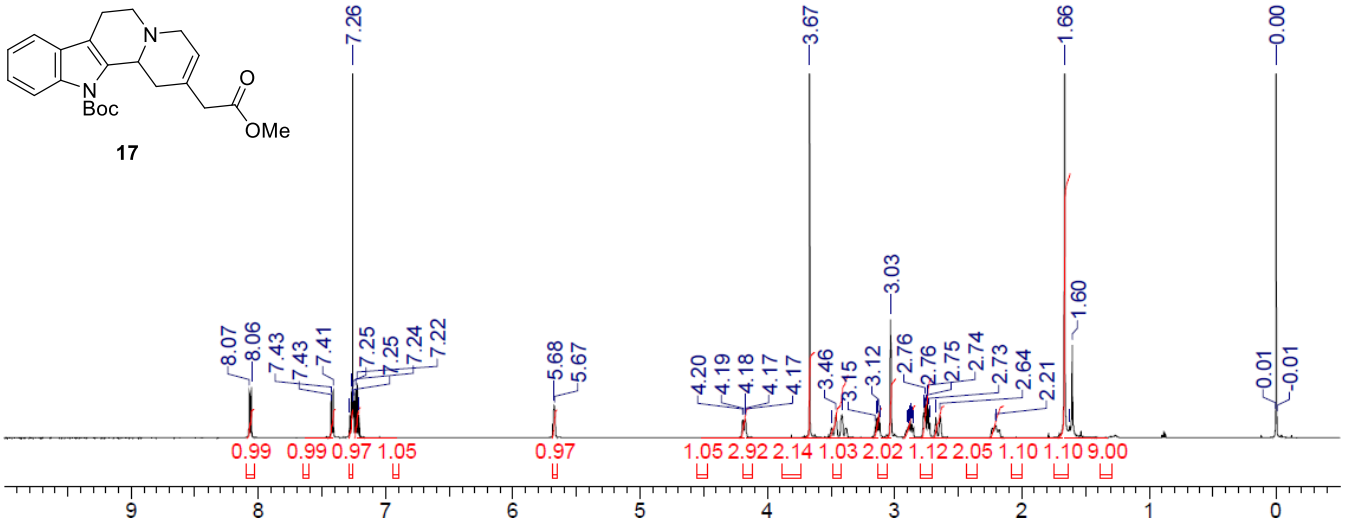


b) ^{13}C NMR Spectrum (in $CDCl_3$, 125 MHz)

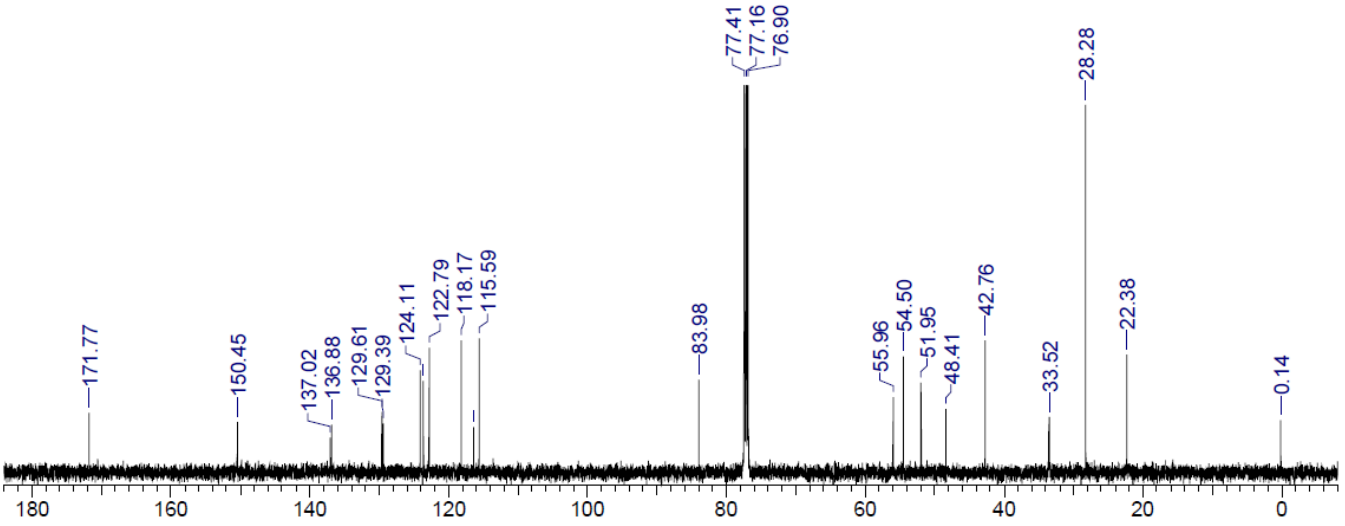


7-6. NMR Spectra of tert-butyl 2-(2-methoxy-2-oxoethyl)-1,6,7,12b-tetrahydroindolo[2,3-a]quinolizine-12(4H)-carboxylate (**17**)

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

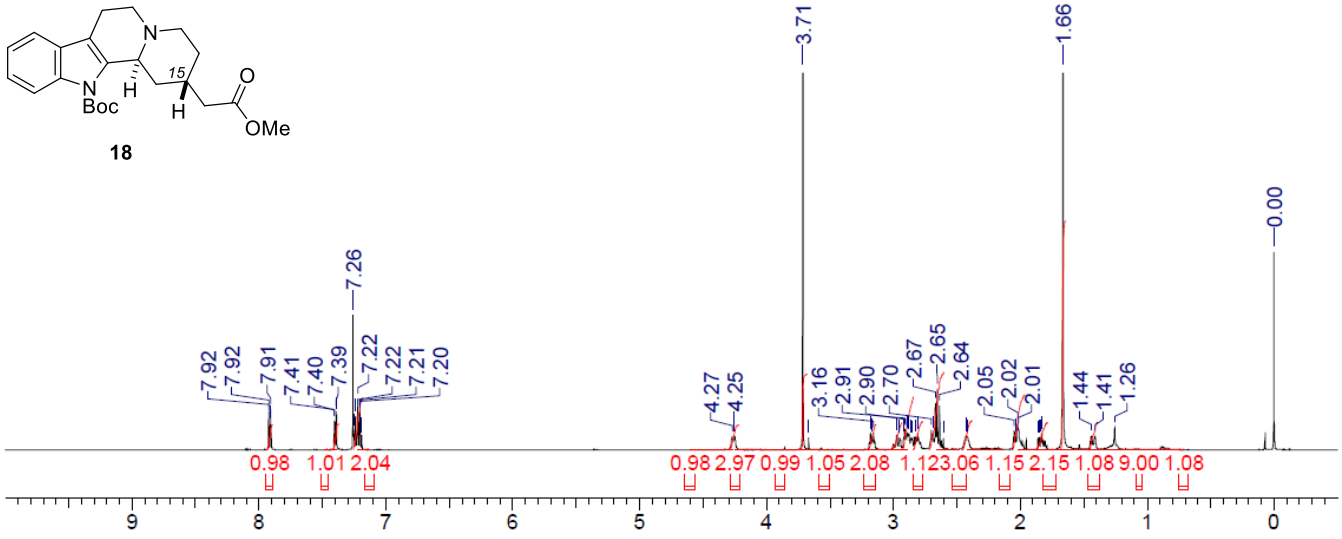


b) ^{13}C NMR Spectrum (in $CDCl_3$, 125 MHz)

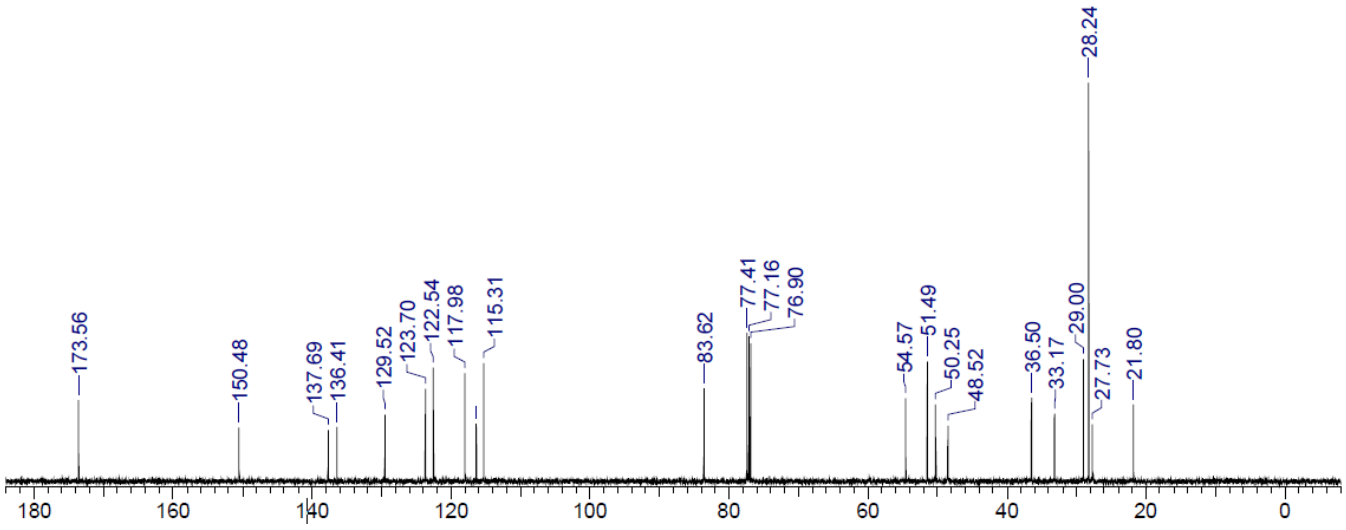


7-7. NMR Spectra of 2,12b-*trans*-tert-butyl 2-(2-methoxy-2-oxoethyl)-1,3,4,6,7,12b-hexahydroindolo[2,3-a]quinolizine-12(2H)-carboxylate (**18**)

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

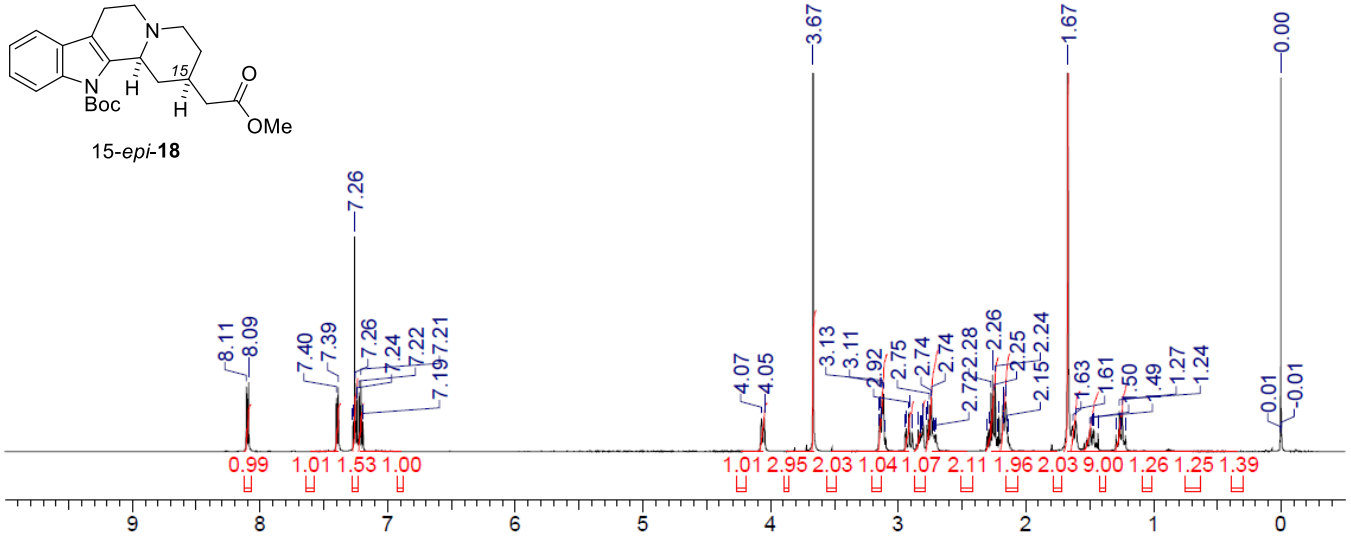


b) ^{13}C NMR Spectrum (in $CDCl_3$, 125 MHz)

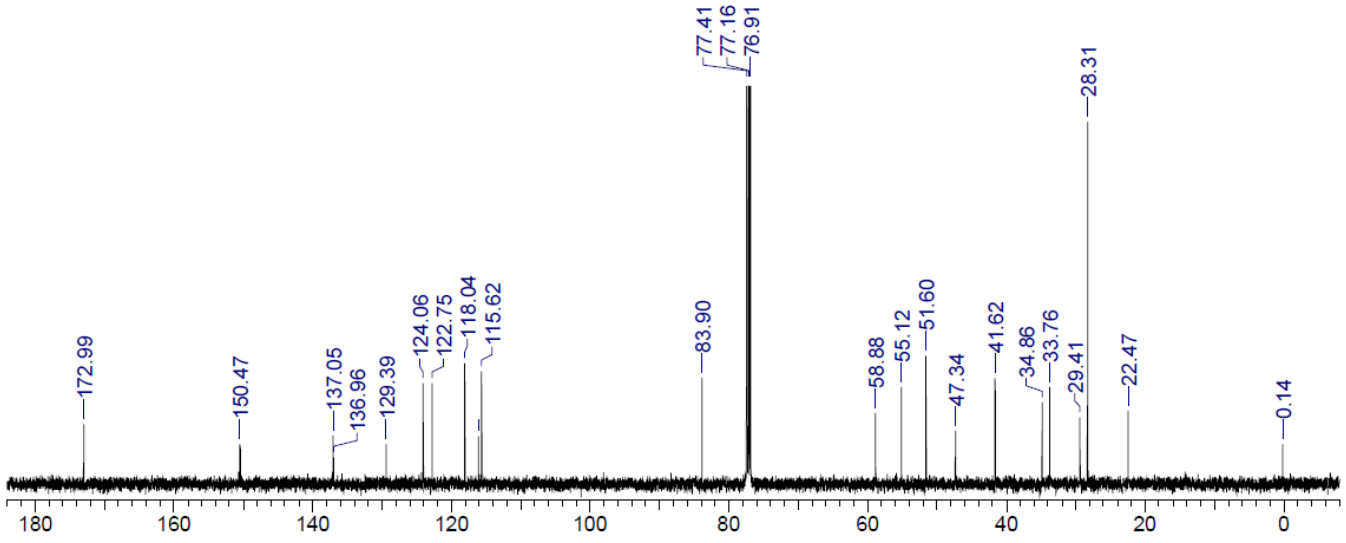


7-8. NMR Spectra of 2,12b-*cis*-tert-butyl 2-(2-methoxy-2-oxoethyl)-1,3,4,6,7,12b-hexahydroindolo[2,3-a]quinolizine-12(2H)-carboxylate (15-*epi*-**18**)

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

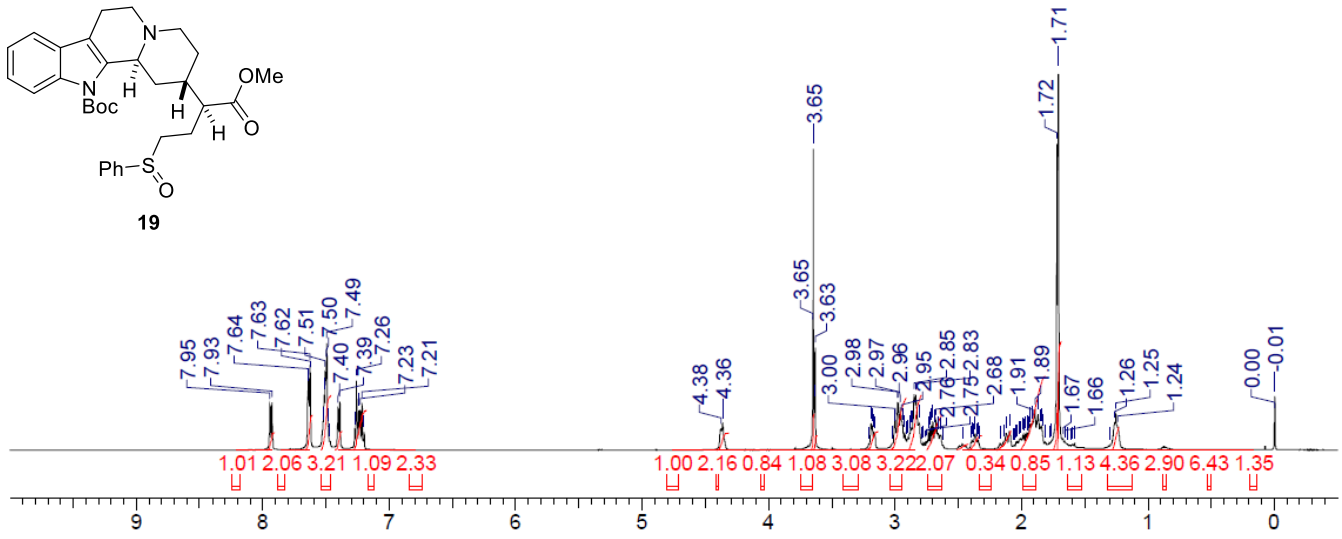


b) ^{13}C NMR Spectrum (in $CDCl_3$, 125 MHz)

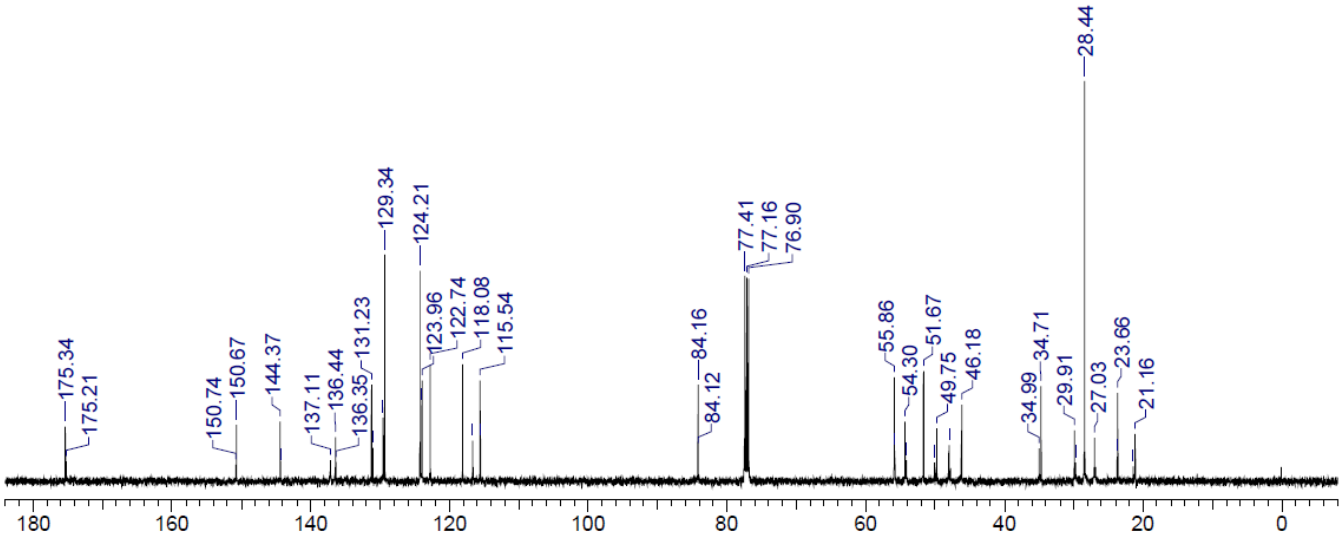


7-9. NMR Spectra of tert-butyl 2-(1-methoxy-1-oxo-4-(phenylsulfinyl)butan-2-yl)-1,3,4,6,7,12b-hexahydroindolo[2,3-a]quinolizine-12(2H)-carboxylate (**19**)

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

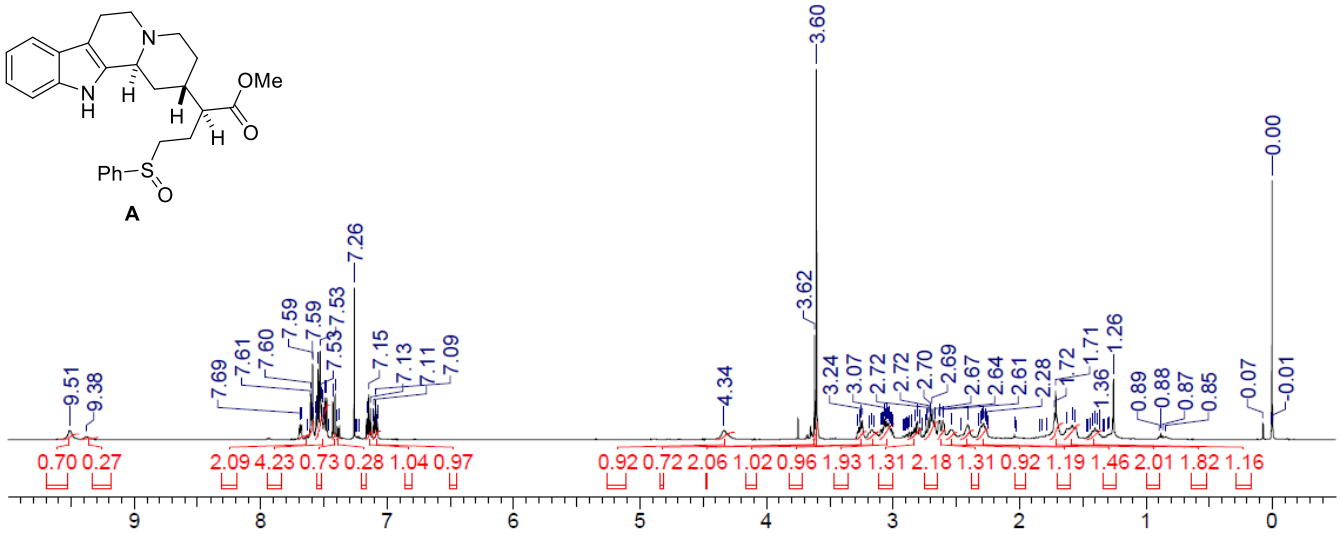


b) ^{13}C NMR Spectrum (in $CDCl_3$, 125 MHz)



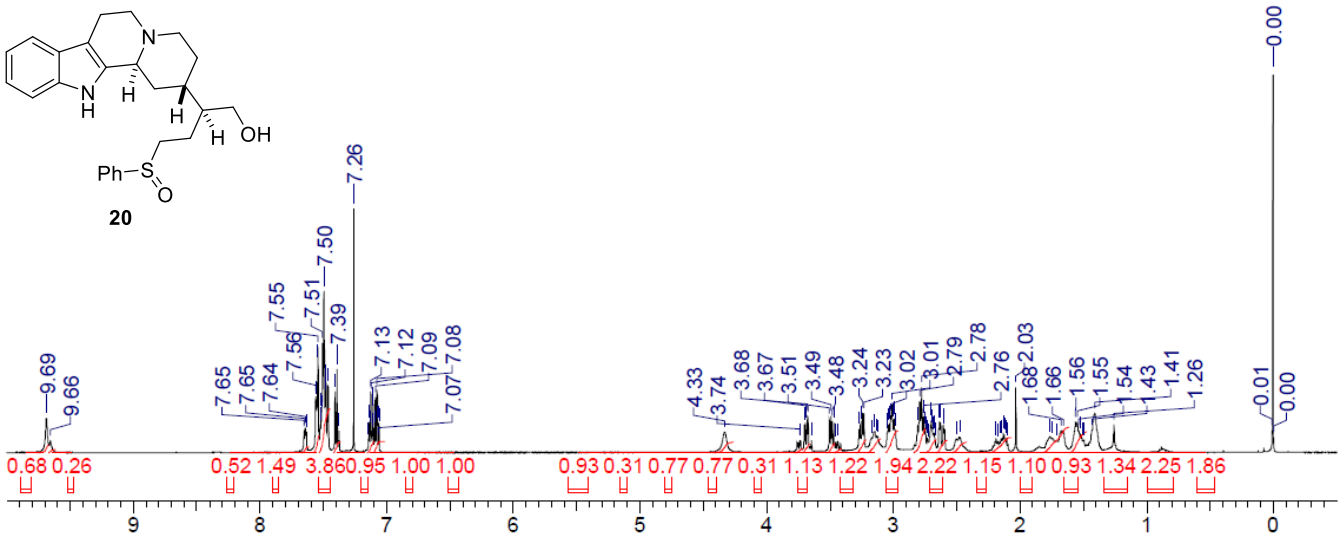
7-10. NMR Spectra of methyl 2-(1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizin-2-yl)-4-(phenylsulfinyl)butanoate (**A**)

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



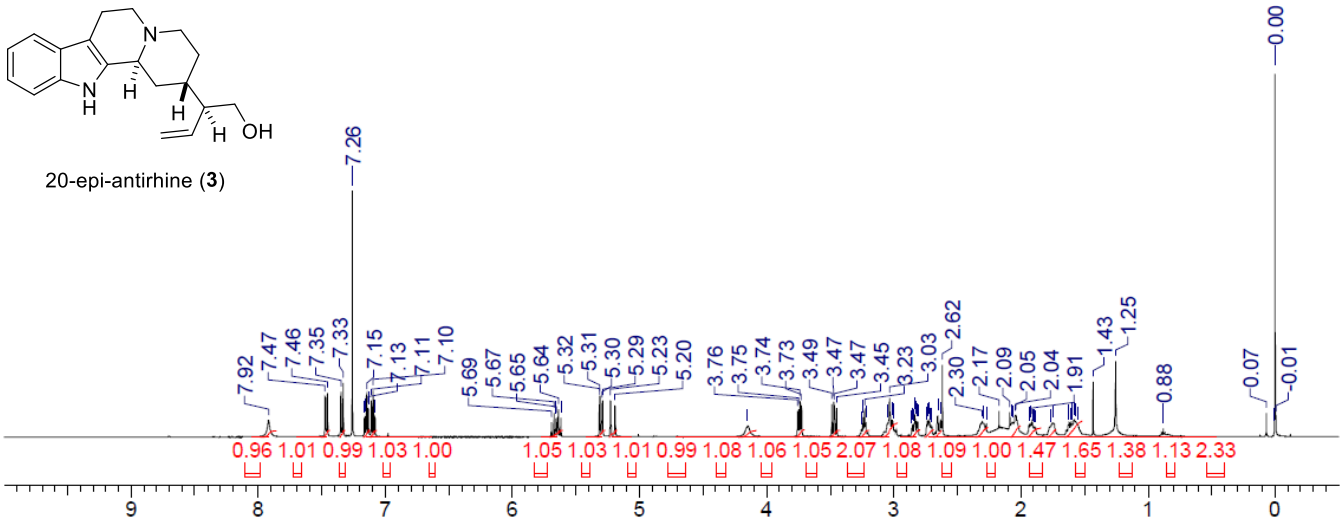
7-11. NMR Spectra of 2-(1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizin-2-yl)-4-(phenylsulfinyl)butan-1-ol (**20**)

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

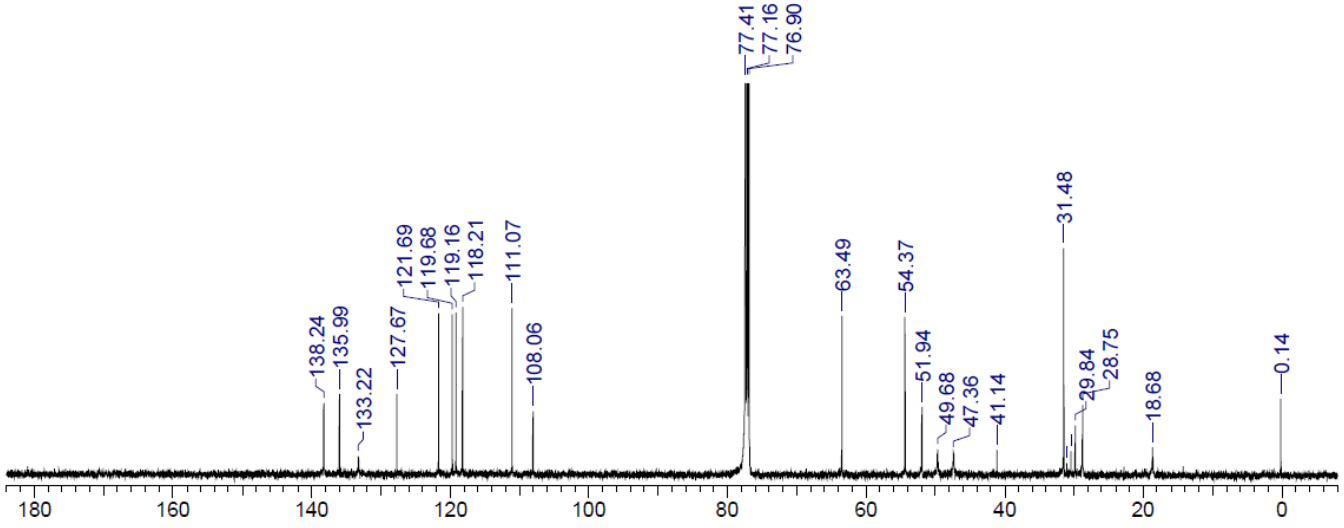


7-12. NMR Spectra of (±)-20-*epi*-antirhine (**3**)

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

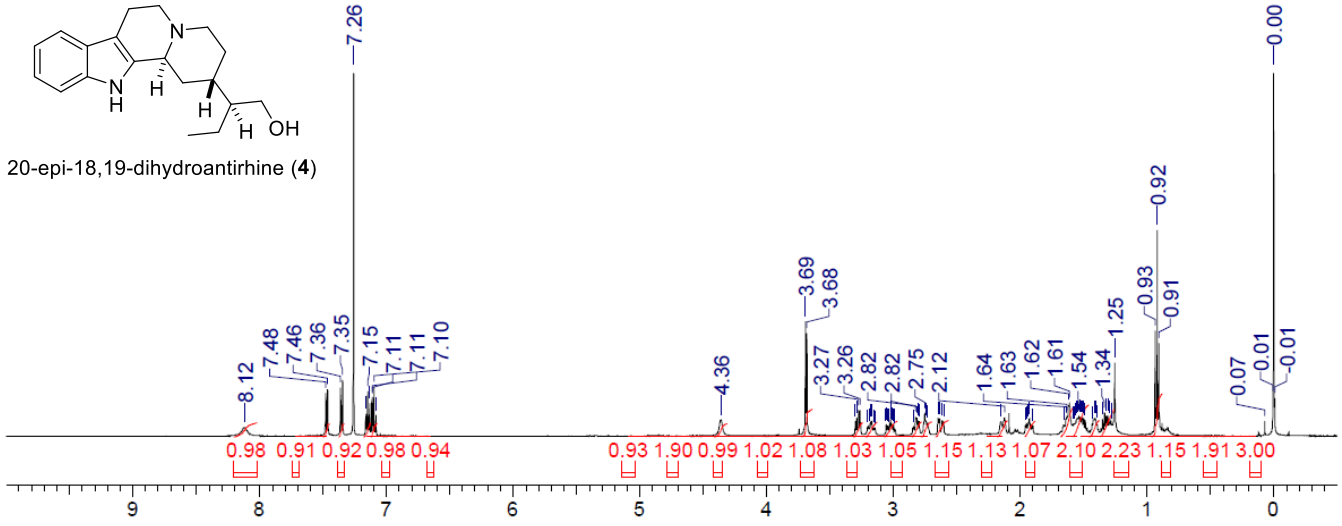


b) ^{13}C NMR Spectrum (in $CDCl_3$, 125 MHz)

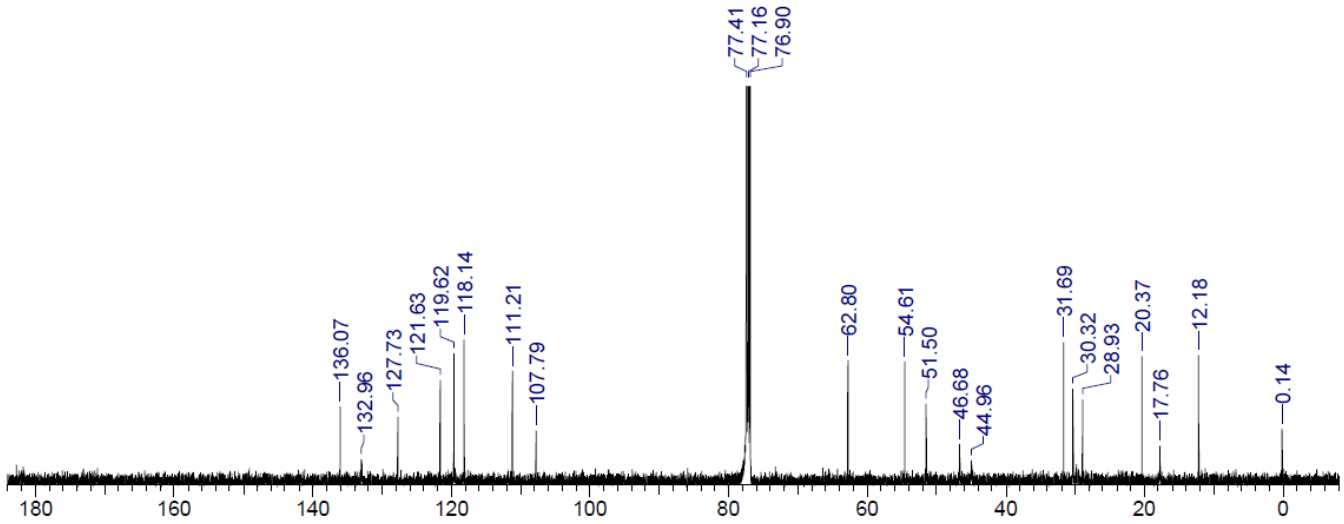


7-13. NMR Spectra of (±)-20-*epi*-18,19-dihydroantirhine (**4**)

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

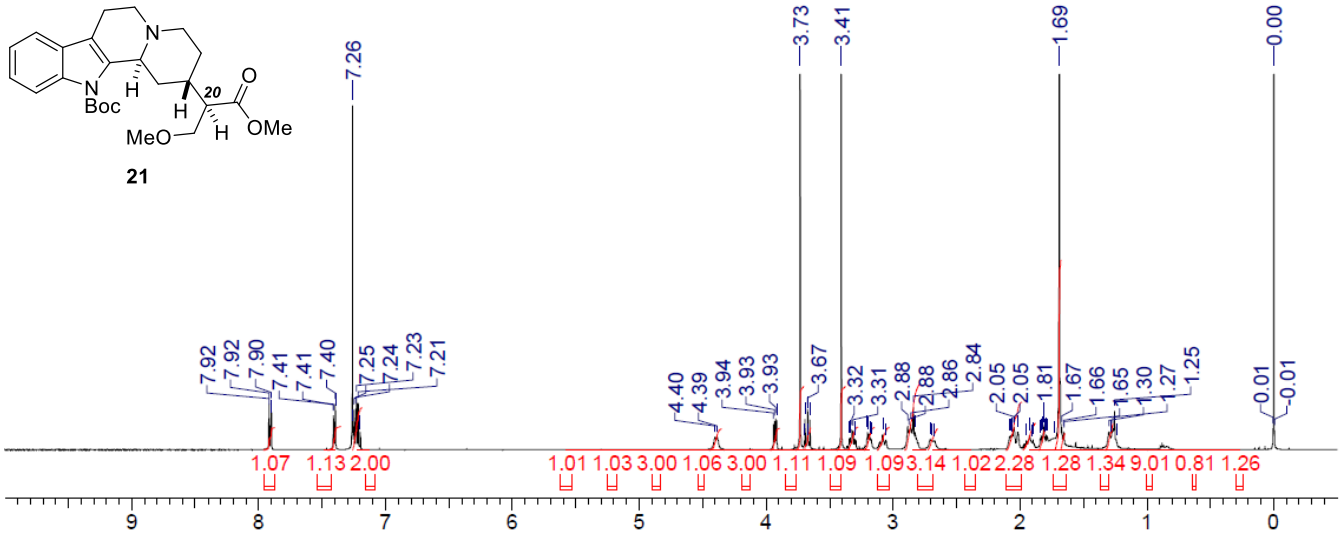


b) ^{13}C NMR Spectrum (in $CDCl_3$, 125 MHz)

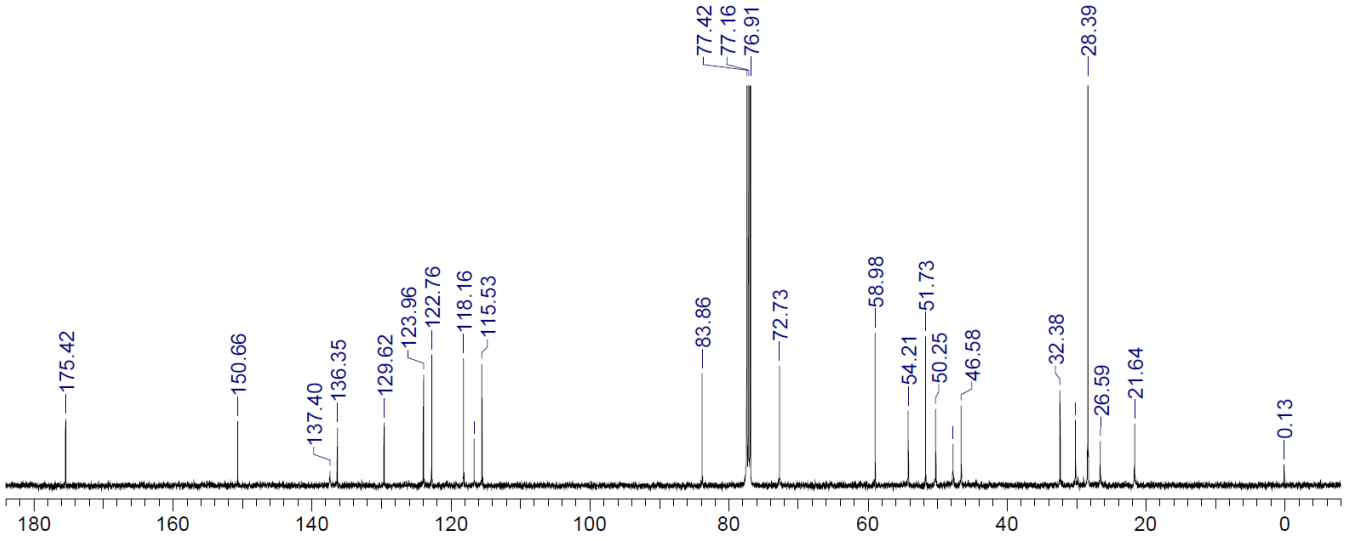


7-14. NMR Spectra of tert-butyl 2-(1,3-dimethoxy-1-oxopropan-2-yl)-1,3,4,6,7,12b-hexahydroindolo[2,3-a]quinolizine-12(2H)-carboxylate (**21**)

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

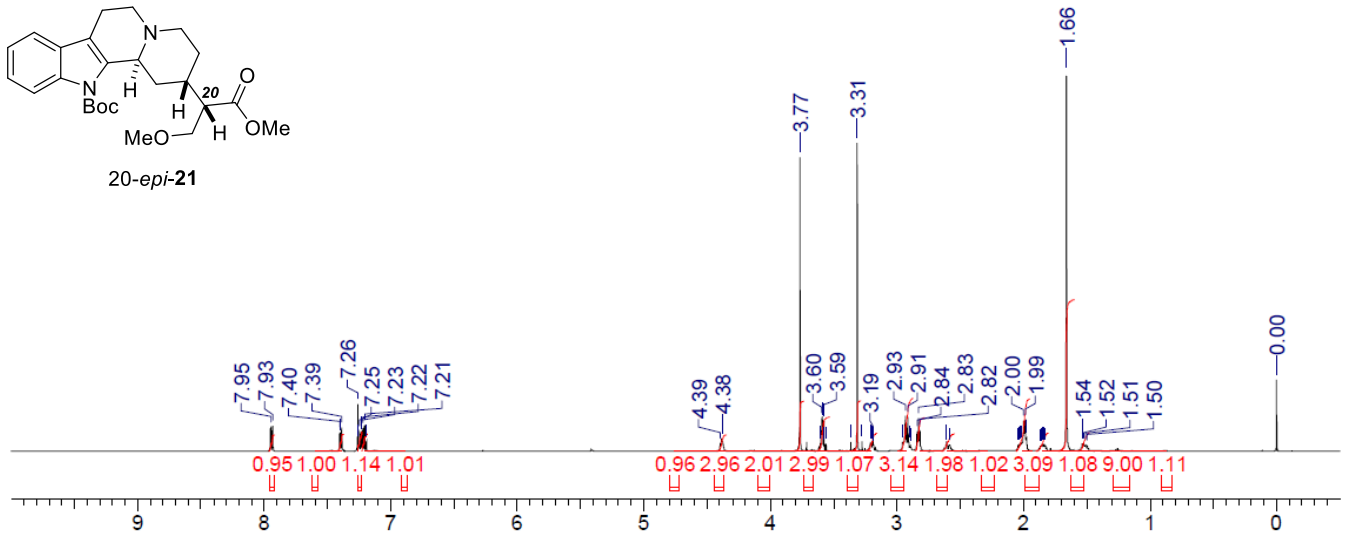


b) ^{13}C NMR Spectrum (in $CDCl_3$, 125 MHz)

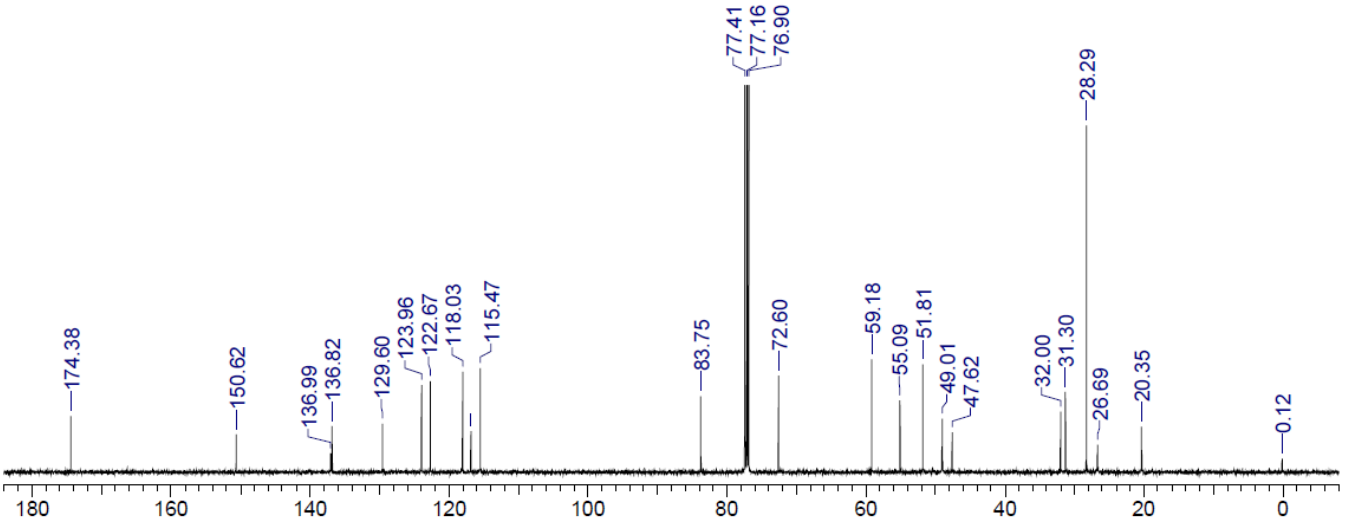


7-15. NMR Spectra of tert-butyl 2-(1,3-dimethoxy-1-oxopropan-2-yl)-1,3,4,6,7,12b-hexahydroindolo[2,3-a]quinolizine-12(2H)-carboxylate (20-*epi*-**21**)

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

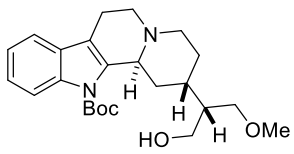


b) ^{13}C NMR Spectrum (in $CDCl_3$, 125 MHz)



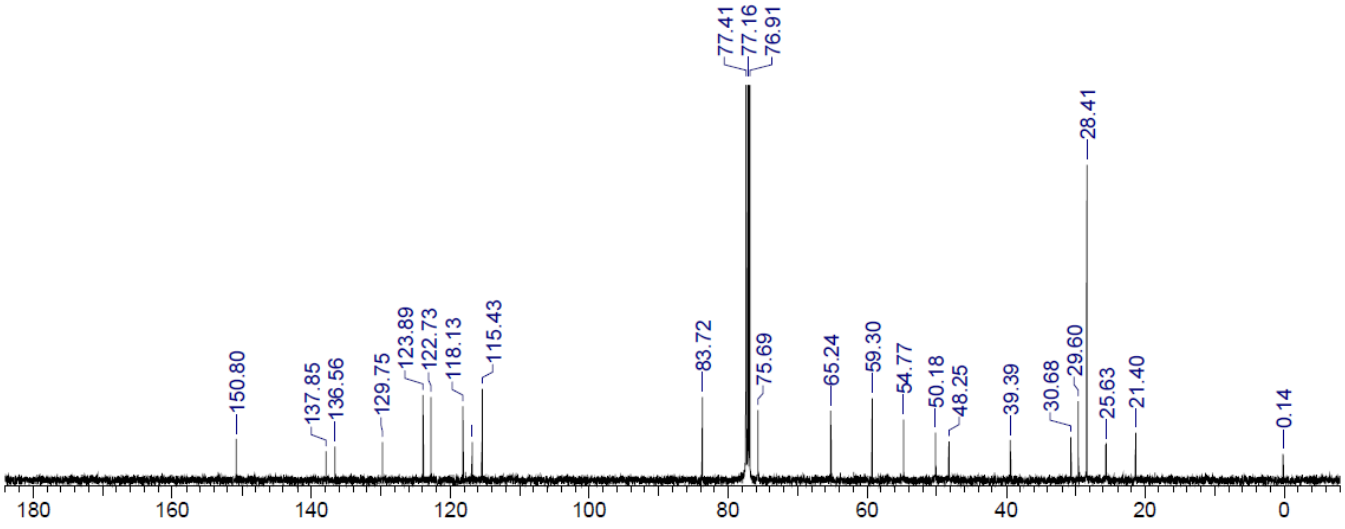
7-16. NMR Spectra of tert-butyl 2-(1-hydroxy-3-methoxypropan-2-yl)-1,3,4,6,7,12b-hexahydroindolo[2,3-a]quinolizine-12(2H)-carboxylate (**22**)

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



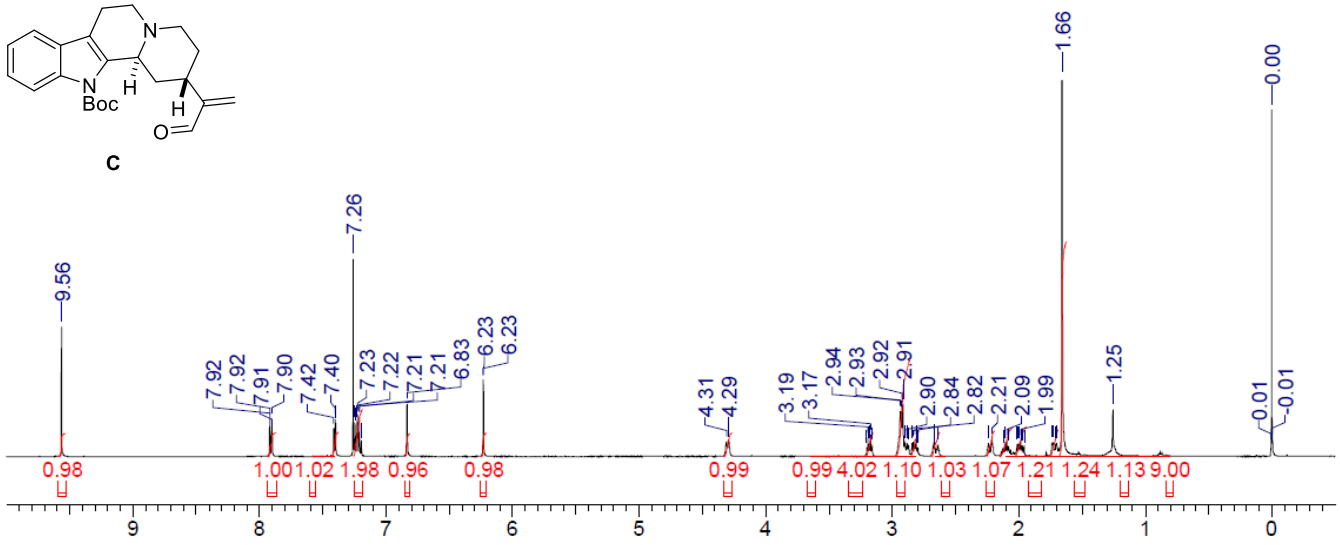
22

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

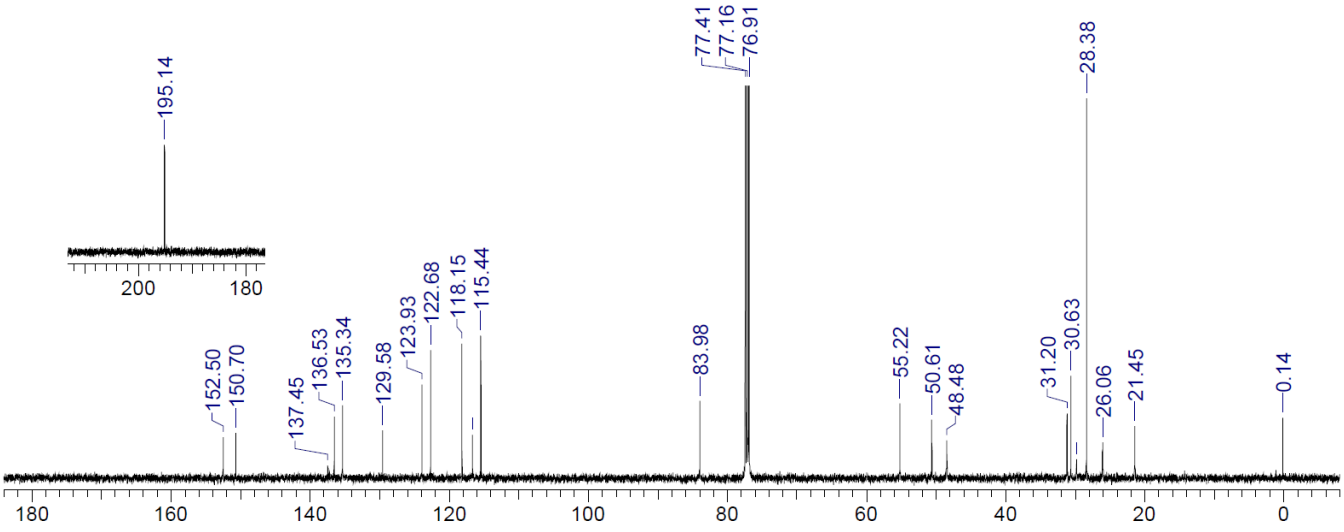


7-17. NMR Spectra of tert-butyl 2-(3-oxoprop-1-en-2-yl)-1,3,4,6,7,12b-hexahydroindolo[2,3-a]quinolizine-12(2H)-carboxylate (**C**)

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

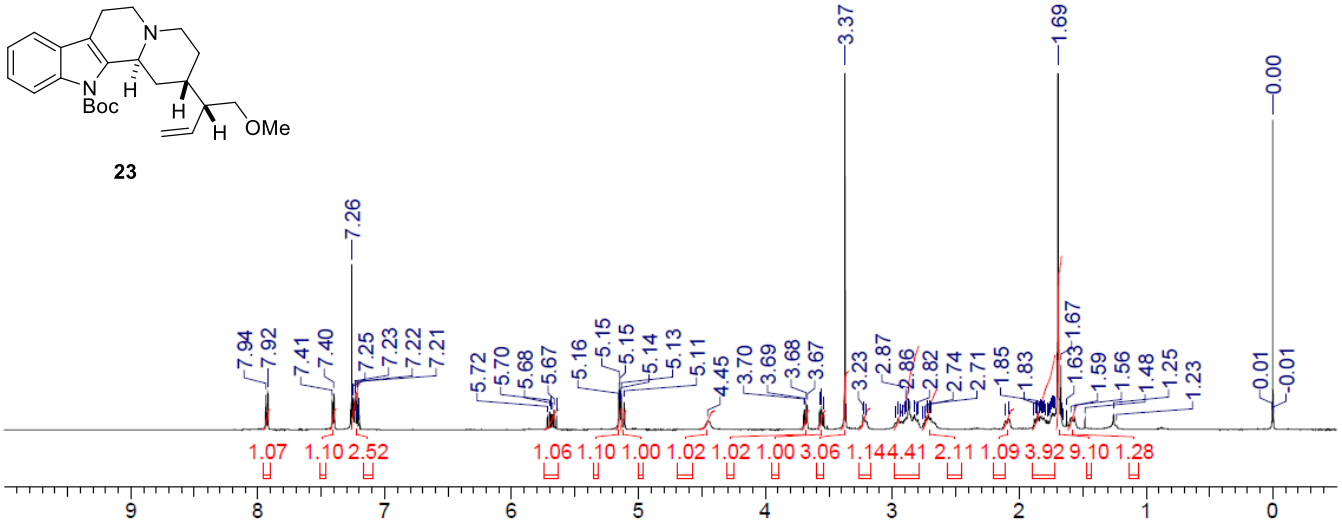


b) ^{13}C NMR Spectrum (in $CDCl_3$, 125 MHz)

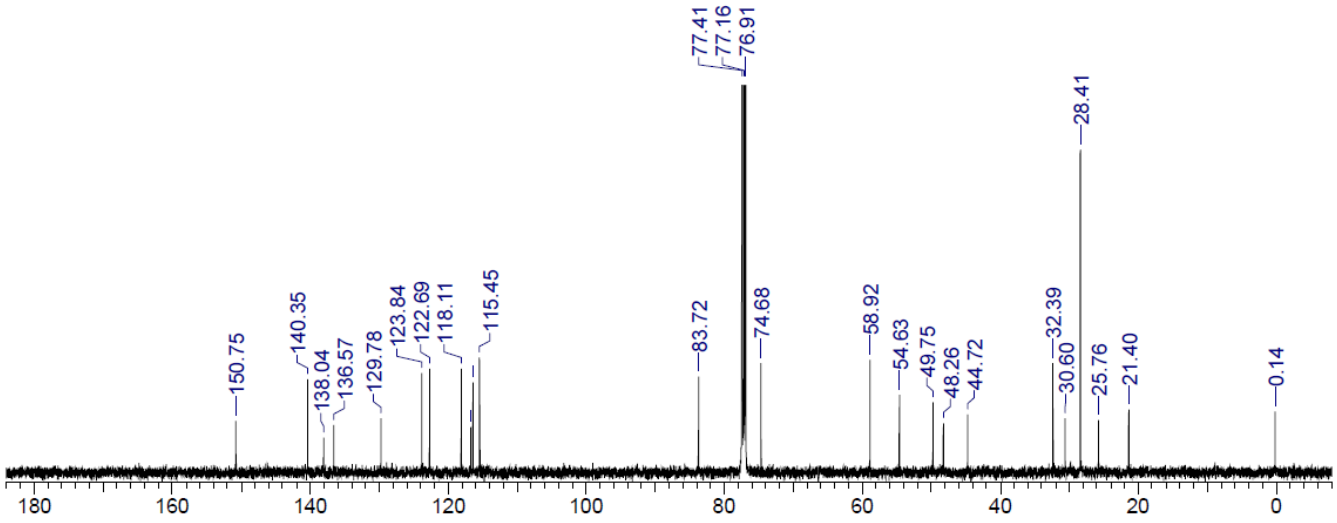


7-18. NMR Spectra of tert-butyl 2-(1-methoxybut-3-en-2-yl)-1,3,4,6,7,12b-hexahydroindolo[2,3-a]quinolizine-12(2H)-carboxylate (**23**)

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

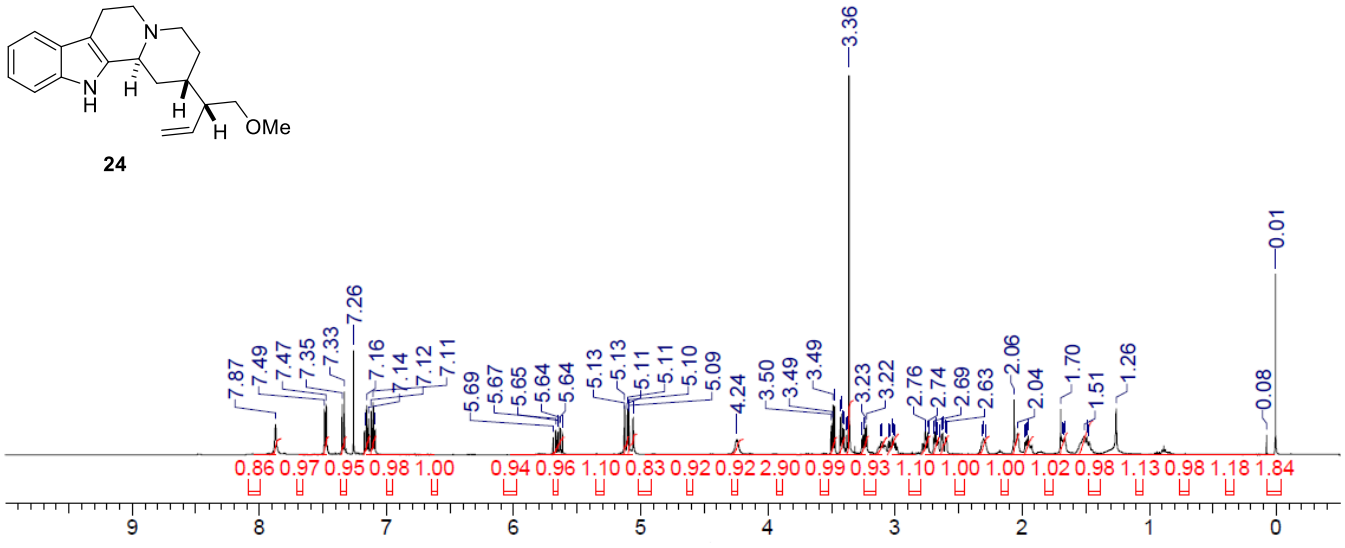


b) ^{13}C NMR Spectrum (in $CDCl_3$, 125 MHz)



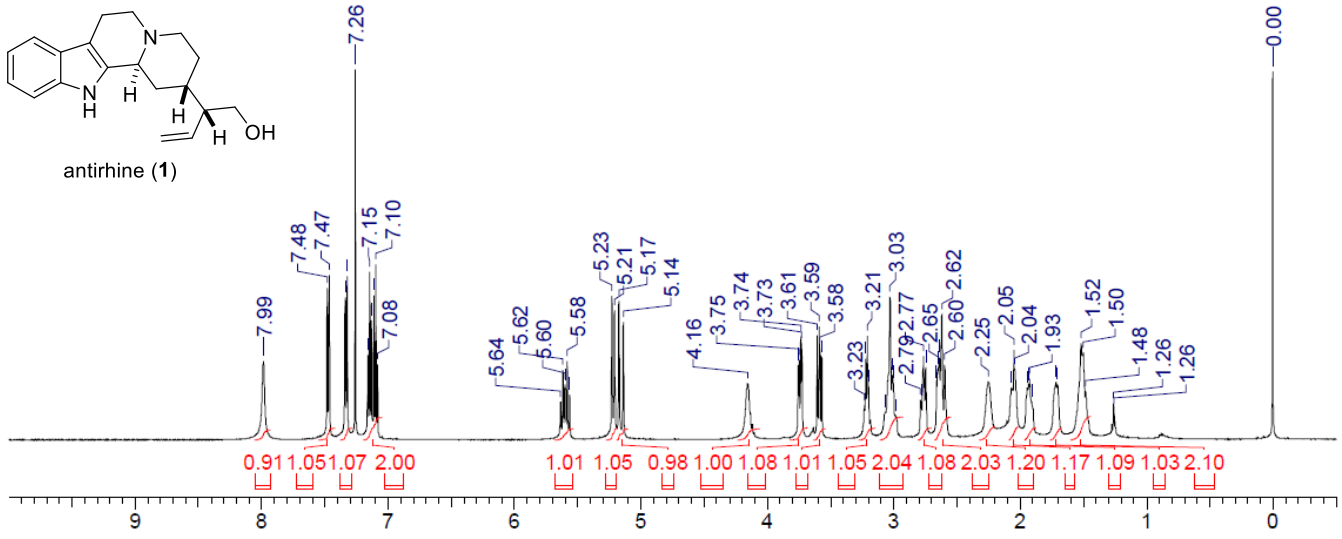
7-19. NMR Spectra of 2-(1-methoxybut-3-en-2-yl)-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine (**24**)

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

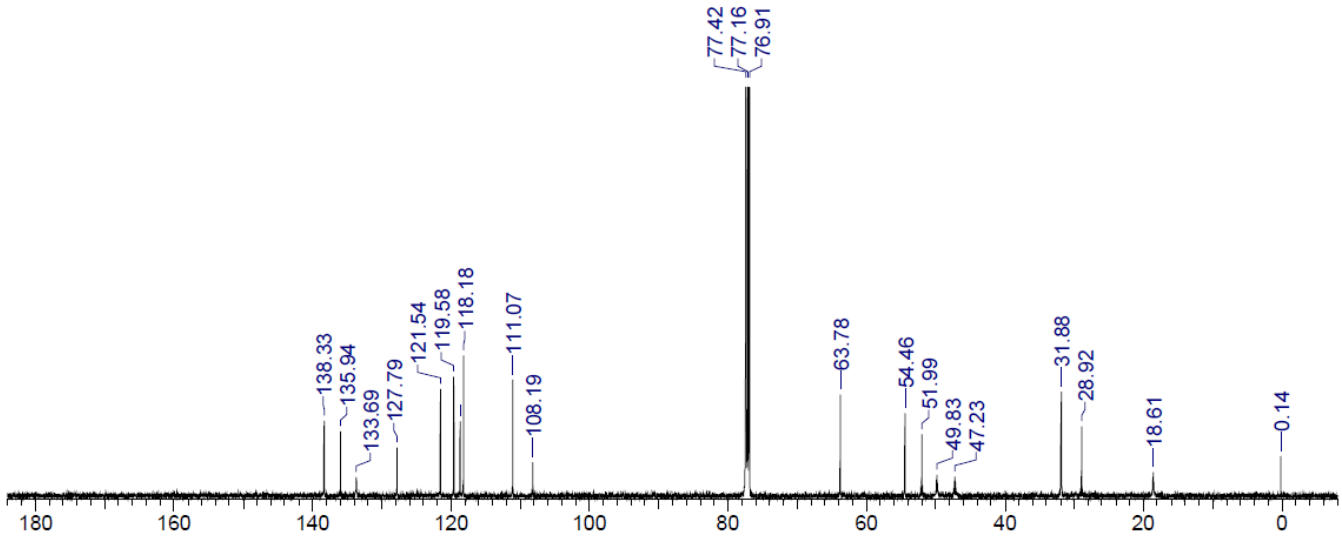


7-20. NMR Spectra of (±)-antirhine (**1**)

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

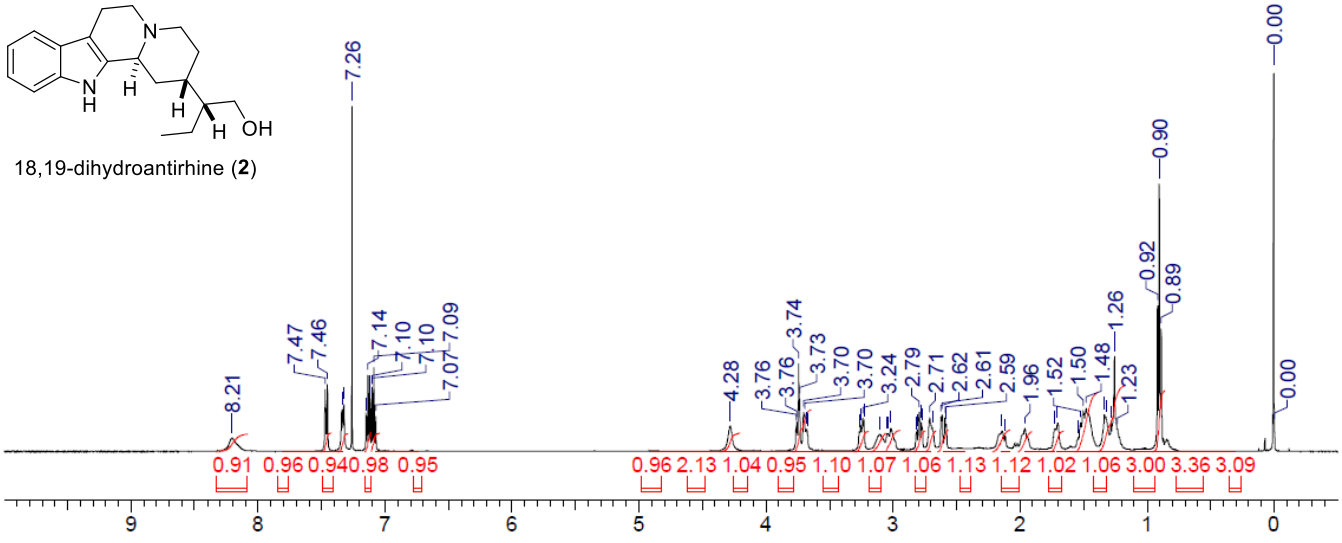


b) ^{13}C NMR Spectrum (in $CDCl_3$, 125 MHz)

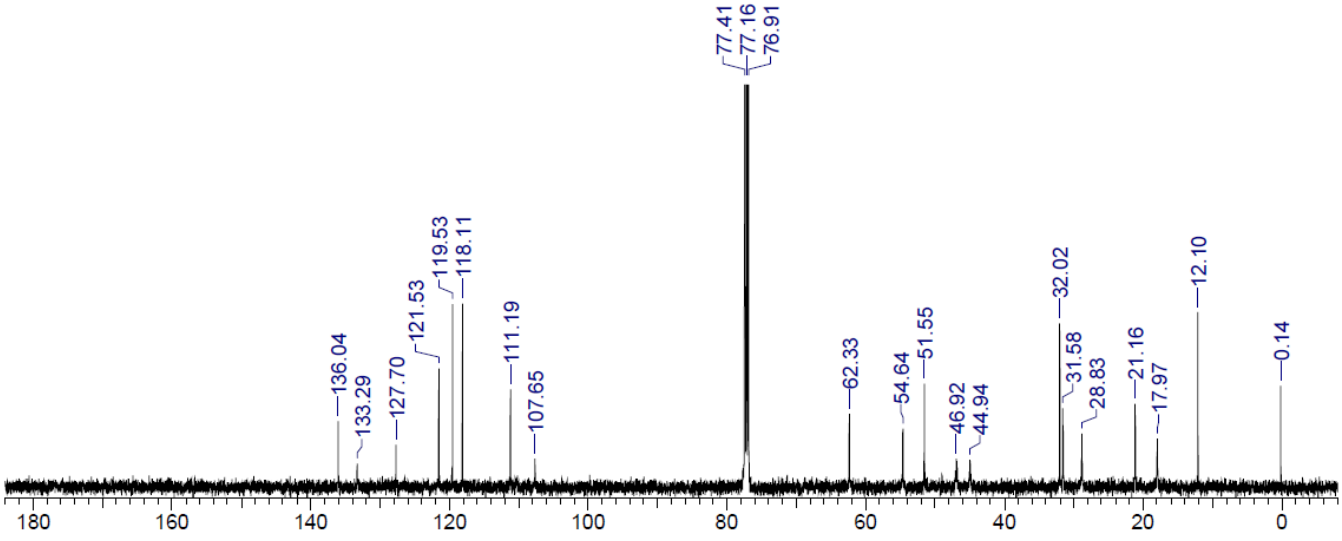


7-21. NMR Spectra of (±)-18,19-dihydroantirhine (**2**)

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

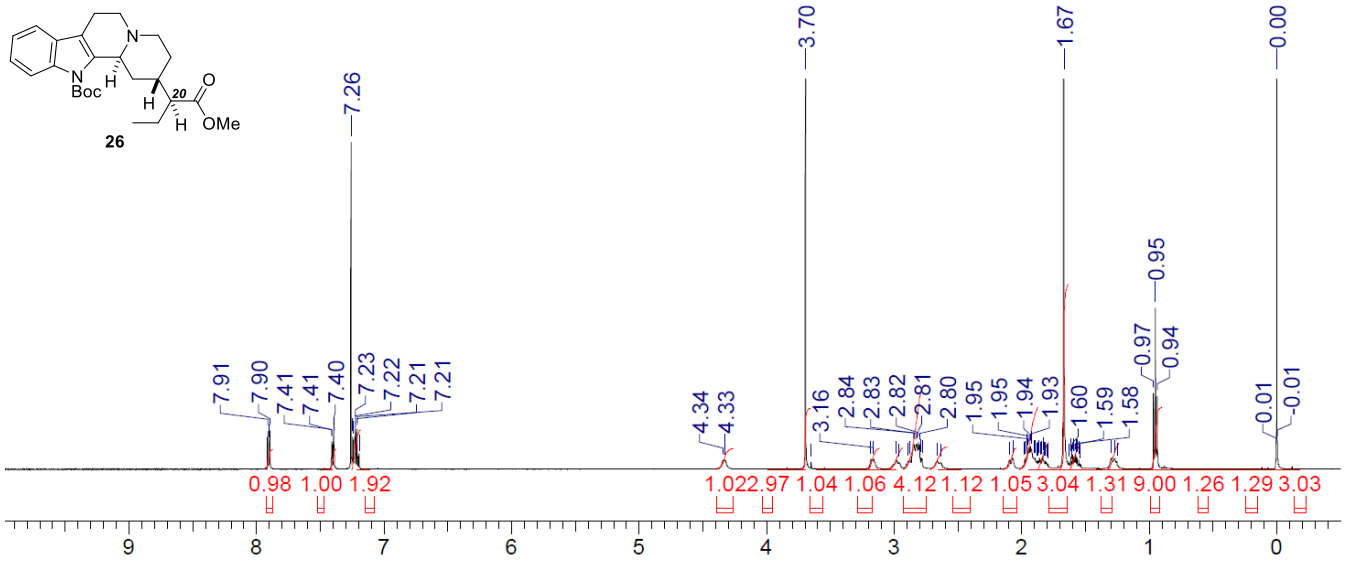


b) ^{13}C NMR Spectrum (in $CDCl_3$, 125 MHz)

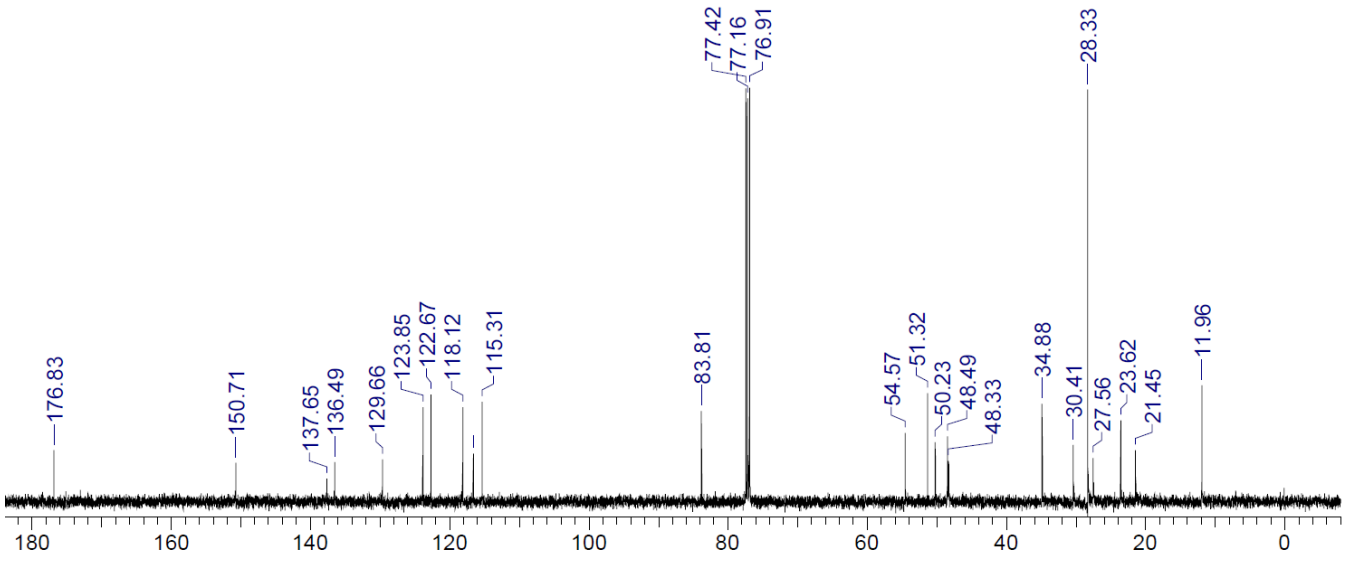


7-22. NMR Spectra of tert-butyl-2-(1-methoxy-1-oxobutan-2-yl)-1,3,4,6,7,12b-hexahydroindolo[2,3-a]quinolizine-12(2H)-carboxylate (**26**)

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

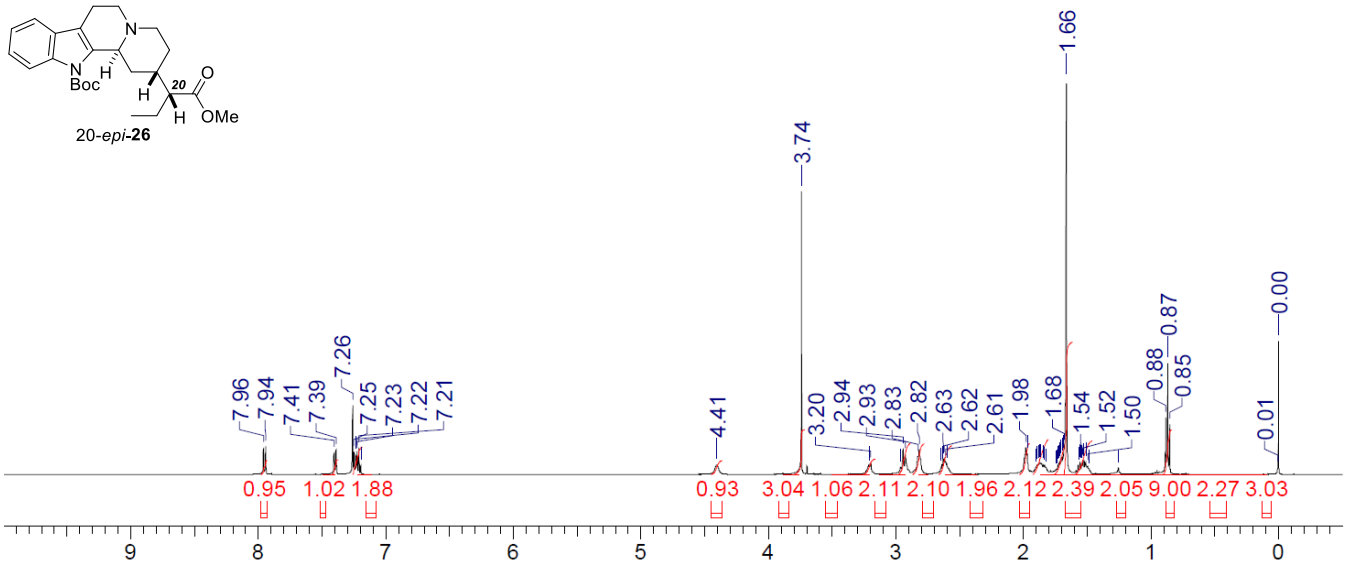


b) ^{13}C NMR Spectrum (in $CDCl_3$, 125 MHz)



7-23. NMR Spectra of tert-butyl-2-(1-methoxy-1-oxobutan-2-yl)-1,3,4,6,7,12b-hexahydroindolo[2,3-a]quinolizine-12(2H)-carboxylate (20-*epi*-**26**)

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



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