Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Supporting Information for

Asymmetric Total Synthesis of *Lycopodium alkaloids* α-obscurine, N-desmethyl-α-obscurine, β-obscurine, N-desmethyl-β-obscurine

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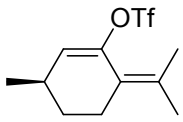
Table of contents

General Information

All non-aqueous reactions were run under a positive pressure of nitrogen. Anhydrous solvents were obtained using standard drying techniques. Commercial grade reagents were used without further purification unless stated otherwise. Flash chromatography was performed on 300-400 mesh silica gel with the indicated solvent systems. ^{1}H NMR were recorded on a Bruker 400 (400 MHz) spectrometer and chemical shifts are reported in ppm down field from TMS, using TMS (0.00 ppm) or residual $CDCl_3$ (7.26 ppm) as an internal standard. Data are reported as: (s = singlet, br = broad, d = doublet, t = triplet, q = quartet, m = multiplet; *J* = coupling constant in Hz, integration.). ^{13}C NMR spectra were recorded on a Bruker 400 (100 MHz) spectrometer, using proton decoupling unless otherwise noted. Chemical shifts are reported in ppm down field from TMS, using the central resonance of $CDCl_3$ (77.00 ppm) as the internal standard. HRMS were recorded by using either FTMS-7 or IonSpec 4.7 spectrometers. IR spectra were recorded on Nicolet iN 10 MX.

Experimental Procedures and Spectral Data

(*R*)-3-methyl-6-(propan-2-ylidene)cyclohex-1-en-1-yl trifluoromethanesulfonate

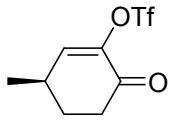


S1

To a solution of diisopropylamine (20.9 mL, 149 mmol) in THF (150 mL) was added *n*-butyllithium (2.5M in hexanes, 59 mL, 149 mmol) dropwise at 0 °C and the mixture was stirred at the temperature for 10 min before cooling down to -78 °C. (*R*)-Pulegone (22.4 g, 135 mmol, 92% purity) in THF (100 mL) was added dropwise over 20 min, and the solution was stirred for 30 min at -78 °C. Tf_2NPh (53.3 g, 149 mmol) in THF (200 mL) was added over 20 min, and then the mixture was allowed to warm to room temperature. A saturated solution of NH_4Cl was added and the mixture was extracted with CH_2Cl_2 for three times. The combined organic layers were dried over anhydrous Na_2SO_4 before the solvent was removed under reduced pressure. The residual was subjected to column chromatography on silica gel (Hexane) to give a 6/1 mixture of **S1** and its isomer as a colorless oil (39.8 g, 94% overall).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.58 (d, J = 3.3 Hz, 1H), 2.59-2.46 (m, 2H), 2.30-2.18 (m, 1H), 1.93 (s, 3H), 1.91-1.81 (m, 1H), 1.78 (s, 3H), 1.35-1.22 (m, 1H), 1.08 (d, J = 7.0 Hz, 3H); **LRMS** (EI) *m/z* (%): 284 (M^+, 24), 151 (55), 138 (100), 125 (99).

(*R*)-3-methyl-6-oxocyclohex-1-en-1-yl trifluoromethanesulfonate

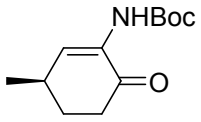


S2

The mixture of **S1** and its isomer (66.0 g, 232 mmol) was dissolved in CH_2Cl_2 (3600 mL) and MeOH (900 mL) before cooling down to -78 °C. The mixture was subjected to ozone until the solution color became blue. The mixture was then flushed with Ar for 10 min; following this, PPh_3 (72.9 g, 278 mmol) was added and the mixture was stirred at room temperature for 4 h. The mixture was then concentrated to a thick oil, which was subjected to column chromatography on silica gel (Hexane / EtOAc = 10 / 1) to give **S2** (40.3 g) as a colorless oil in 78% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.75 (d, J = 2.6 Hz, 1H), 2.92-2.81 (m, 1H), 2.70 (dt, J_1 = 17.1 Hz, J_2 = 4.9 Hz, 1H), 2.53 (ddd, J_1 = 17.1 Hz, J_2 = 12.3 Hz, J_3 = 4.8 Hz, 1H), 2.25-2.13 (m, 1H), 1.84-1.71 (m, 1H), 1.26 (d, J = 7.3 Hz, 3H); **LRMS** (ESI): 281 $(M+Na)^+$.

tert-butyl (*R*)-(3-methyl-6-oxocyclohex-1-en-1-yl)carbamate

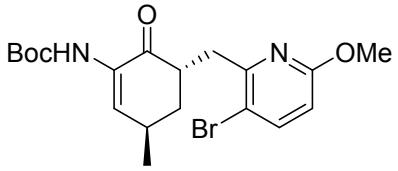


S3

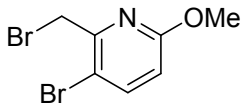
K_2CO_3 (17.9 g, 129 mmol) and *tert*-butylcarbamate (7.45 g, 62.3 mmol) were added to an oven-dried flask charged with $Pd_2(dba)_3$ (1.21 g, 1.30 mmol) and *t*Bu-XPhos (2.87 g, 6.75 mmol) under Ar. The flask was flushed with Ar and a solution of triflate **S2** (13.4 g, 51.9 mmol) in toluene (260 mL) was added and the reaction was heated at 80 °C for 12 h. After cooling down, the reaction mixture was poured into a saturated solution of aq. NH_4Cl and was extracted with CH_2Cl_2 for three times. The combined organic layers were dried over anhydrous Na_2SO_4 before the solvent was removed under reduced pressure. The residue was purified via flash chromatography on silica gel (Hexane/EtOAc = 60/1) to give **S3** (11.70 g, 90%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (s, 1H), 7.10 (s, 1H), 2.74-2.64 (m, 1H), 2.60 (dt, J_1 = 17.1 Hz, J_2 = 4.5 Hz, 1H), 2.42 (ddd, J_1 = 17.1 Hz, J_2 = 13.0 Hz, J_3 = 4.8 Hz, 1H), 2.11-2.01 (m, 1H), 1.69-1.57 (m, 1H), 1.47 (s, 9H), 1.18 (d, J = 7.0 Hz, 3H); **LRMS** (ESI): 248 $(M+Na)^+$.

***tert*-butyl ((3*R*,5*S*)-5-((3-bromo-6-methoxypyridin-2-yl)methyl)-3-methyl-6-oxocyclohex-1-en-1-yl)carbamate**



7

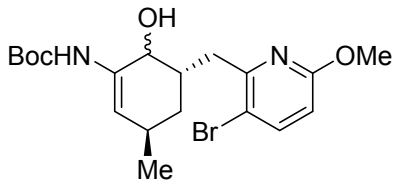


S4

To a solution of diisopropylamine (10.9 mL, 77.7 mmol) in THF (50 mL) was added *n*-butyllithium (2.5M in hexanes, 31 mL, 77.7 mmol) dropwise at 0 °C and the mixture was stirred at the temperature for 10 min before cooling down to -78 °C. Ketone **S3** (7.0 g, 31.1 mmol) in THF (30 mL) was added dropwise over 10 min followed by adding DMPU (10.0 g, 77.7 mmol), and the solution was stirred for 20 min. Then bromopyridine **S4** (13.1 g, 46.6 mmol) in THF (30 mL) was added over 10 min. Then the mixture was stirred at -78 °C over 18 hours. The mixture was then quenched with a saturated aq. solution of NH_4Cl (50 mL). Then it was diluted with ethyl acetate, washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (Hexane/EtOAc = 20/1) to afford carbamate **7** (9.9 g) in 75% yield (84% brsm) as a thick oil, along with recovered ketone **S3** (0.63 g).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, *J* = 8.7 Hz, 1H), 7.27 (s, 1H), 7.13 (s, 1H), 6.49 (d, *J* = 8.7 Hz, 1H), 3.85 (s, 3H), 3.38-3.25 (m, 2H), 3.07-3.97 (m, 1H), 2.93-2.82 (m, 1H), 2.03-1.93 (m, 1H), 1.76-1.67 (m, 1H), 1.48 (s, 9H), 1.19 (d, *J* = 7.2 Hz, 3H); **LRMS** (ESI): 447 $(M+Na)^+$.

***tert*-butyl ((3*R*,5*S*)-5-((3-bromo-6-methoxypyridin-2-yl)methyl)-6-hydroxy-3-methylcyclohex-1-en-1-yl)carbamate**



8-a: α-OH
8-b: β-OH

To a solution of carbamate **7** (4.60 g, 10.8 mmol) in MeOH (54 mL) was added $NaBH_4$ (408 mg, 10.8 mmol) at 0 ^oC and the mixture was stirred at the temperature for 10 min before quenched with saturated aq NH_4Cl (20 mL). The mixture was extracted with CH_2Cl_2. The organic layers were combined and dried over sodium sulfate. The dried solution was filtered and concentrated under reduced pressure. The crude products **8-a** and **8-b** (3.82 g) were found unstable towards purification by flash-column chromatography, so they were used for next step without further purification. Analytically pure samples of **8-a** and **8-b** were obtained by preparative thin layer chromatography.

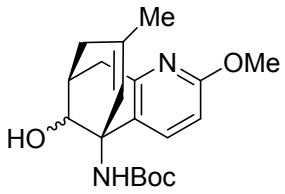
8-a:

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, *J* = 8.7 Hz, 1H), 6.53 (d, *J* = 8.7 Hz, 1H), 6.18 (s, 1H), 5.98 (d, *J* = 4.2 Hz, 1H), 4.61 (s, 1H), 3.90 (s, 3H), 3.87 (s, 1H), 3.09 (dd, J_1 = 14.3 Hz, J_2 = 4.8 Hz, 1H), 2.96 (dd, J_1 = 14.3 Hz, J_2 = 9.5 Hz, 1H), 2.56-2.36 (m, 2H), 1.92-1.81 (m, 1H), 1.45 (s, 9H), 1.37-1.30 (m, 1H), 1.04 (d, *J* = 7.0 Hz, 3H); **LRMS** (ESI): 449 $(M+Na)^+$.

8-b:

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, *J* = 8.7 Hz, 1H), 6.50 (d, *J* = 8.7 Hz, 1H), 6.46 (s, 1H), 5.75 (d, *J* = 3.7 Hz, 1H), 4.29 (s, 1H), 4.03 (d, *J* = 6.1 Hz, 1H), 3.89 (s, 3H), 2.94 (d, *J* = 6.4 Hz, 2H), 2.54-2.40 (m, 2H), 1.73-1.52 (m, 2H), 1.46 (s, 9H), 1.05 (d, *J* = 7.1 Hz, 3H); **LRMS** (ESI): 449 $(M+Na)^+$.

***tert*-butyl ((5*S*,9*S*)-11-hydroxy-2-methoxy-7-methyl-9,10-dihydro-5,9-methanocycloocta[b]pyridin-5(8H)-yl)carbamate**



S5-a: α-OH
S5-b: β-OH

To a solution of **11-a** and **11-b** (4.60 g, 10.8 mmol) (assuming quantitative yield in the preceding step) in DMA (2000 mL) was added $Pd(PPh_3)_4$ (1.25 g, 1.08 mmol) and TEA (5.98 mL, 43.2 mmol). The flask was flushed with Ar. Then the solution was heated at 130 °C for 3 hours. After cooled to room temperature, the DMA was removed using vacuum distillation and the residual was diluted with water (100 mL) and extracted with dichloromethane for three times. After dried over sodium sulfate the solution was filtered and concentrated under reduced pressure. The crude products **S5-a** and **S5-b** were used directly in the following step.

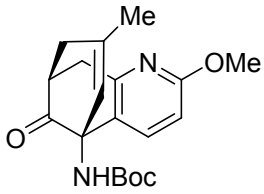
S5-a:

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (d, J = 8.5 Hz, 1H), 6.50 (d, J = 8.5 Hz, 1H), 5.35 (br, 1H), 5.08 (s, 2H), 4.22 (d, J = 3.5 Hz, 1H), 3.88 (s, 3H), 3.46 (dd, J_1 = 18.8 Hz, J_2 = 8.3 Hz, 1H), 2.69-2.61 (m, 1H), 2.57-2.45 (m, 2H), 2.02 (d, J = 18.1 Hz, 1H), 1.60 (s, 3H), 1.46 (s, 9H); **LRMS** (ESI): 347 $(M+H)^+$.

S5-b:

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, J = 8.5 Hz, 1H), 6.50 (d, J = 8.5 Hz, 1H), 5.11 (s, 1H), 4.84 (s, 1H), 4.64 (s, 1H), 3.86 (s, 3H), 3.34 (dd, J_1 = 18.8 Hz, J_2 = 7.3 Hz, 1H), 2.77 (d, J = 18.8 Hz, 1H), 2.74-2.67 (m, 1H), 2.66-2.56 (m, 1H), 2.47 (br s, 1H), 1.84 (d, J = 18.7 Hz, 1H), 1.64 (s, 3H), 1.40 (s, 9H); **LRMS** (ESI): 347 $(M+H)^+$.

***tert*-butyl ((5*S*,9*S*)-2-methoxy-7-methyl-11-oxo-9,10-dihydro-5,9-methanocycloocta[b]pyridin-5(8H)-yl)carbamate**



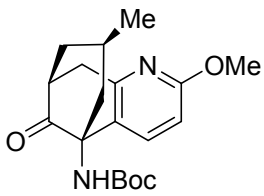
10

To a solution of unpurified **S5-a** and **S5-b** (10.8 mmol, assuming quantitative yield in the preceeding step) in dichloromethane (50 mL) was added NMO (1.89 g, 16.2 mmol), TPAP (380 mg, 1.08 mmol), 4Å molecular sieve (200 mg) under Ar. The mixture was stirred at room temperature for 3 hours before concentrated under reduced pressure. The residual was purified by flash chromatography (Hexane/EtOAc = 8/1) to afford ketone **10** (2.30 g, 62% from **7**) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, J = 8.7 Hz, 1H), 6.58 (d, J = 8.7 Hz, 1H), 6.01 (br s, 1H), 5.59 (br s, 1H), 3.88 (s, 3H), 3.50 (dd, J_1 = 18.1 Hz, J_2 = 7.6 Hz, 1H),

3.21-3.09 (m, 2H), 2.85 (dd, J_1 = 18.1 Hz, J_2 = 6.6 Hz, 1H), 2.50 (d, J = 17.9 Hz, 1H), 1.68 (s, 3H), 1.45 (s, 9H); **LRMS** (ESI): 345 $(M+H)^+$.

***tert*-butyl ((5*S*,7*R*,9*S*)-2-methoxy-7-methyl-11-oxo-7,8,9,10-tetrahydro-5,9-methanocycloocta[b]pyridin-5(6H)-yl)carbamate**

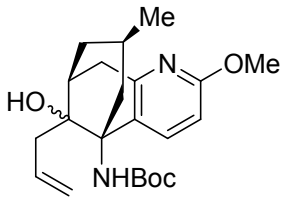


6

To a solution of **10** (414 mg, 1.2 mmol) in EtOH (6 mL) was added Pd/C (10%) catalyst (256 mg, 0.24 mmol). Then the mixture was allowed to stir at room temperature under balloon pressure of H_2 for 12 h. The insoluble solid was filtered, and the solvent was removed under reduced pressure. The residue was purified via flash chromatography on silica gel (Hexane/EtOAc = 10/1) to give **6** (353 mg, 86%, dr > 6/1) as a white solid.

[α]$_D^{26}$ 59.6 (*c* = 0.28, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.68 (d, J = 8.5 Hz, 1H), 6.63 (d, J = 8.5 Hz, 1H), 5.38 (s, 1H), 3.90 (s, 3H), 3.45 (m, 1H), 3.15 (d, J = 18.4 Hz, 1H), 2.98 (br s, 1H), 2.47 (br d, J = 8.0 Hz, 1H), 2.08 (br dd, J_1 = 13.1 Hz, J_2 = 2.6 Hz, 1H), 1.91-1.86 (m, 1H), 1.71 (br td, J_1 = 13.1 Hz, J_2 = 4.3 Hz, 1H), 1.59 (t, J = 12.0 Hz, 1H), 1.45 (s, 9H), 0.89 (d, J = 6.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 209.1, 162.9, 155.0, 151.9, 136.9, 128.1, 109.6, 79.7, 63.1, 53.4, 49.7, 44.9, 44.5, 40.4, 28.3, 25.3, 20.2; **IR** (thin film): 3355, 2973, 2930, 1741, 1716, 1600, 1578, 1478, 1422, 1366, 1314, 1264, 1170, 1030, 827 cm^{-1}; **LRMS** (ESI): 347 $(M+H)^+$; **HRMS** (MALDI): calcd for $C_{19}H_{27}N_2O_4$ $(M+H)^+$: 347.1965, found: 347.1966; mp: 140-142 ^oC.

***tert*-butyl ((5*S*,7*R*,9*S*)-11-allyl-11-hydroxy-2-methoxy-7-methyl-7,8,9,10-tetrahydro-5,9-methanocycloocta[b]pyridin-5(6H)-yl)carbamate**



11: β-OH
12-*epi*-**11**: α-OH

To a solution of ketone **6** (133 mg, 384 μmol) in THF (4 mL) was added a solution of allylmagnesium chloride (0.6 mL, 2.0 M in THF) slowly at −78 °C. After the mixture was stirred at that temperature for 3 h, the reaction was quenched with saturated aqueous NH_4Cl (10 mL). The resulting mixture was then allowed to warm to room temperature, extracted with CH_2Cl_2 (20 mL × 3), dried over Na_2SO_4, concentrated, and purified by

chromatography (hexane/EtOAc = 30/1) to give **11** (101 mg, 68%) and 12-*epi*-**11** (37 mg, 25%) as white solids.

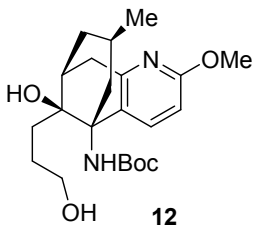
11:

[α]$_D^{26}$ -26.9 (*c* = 0.105, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.50 (d, *J* = 8.5 Hz, 1H), 6.59 (d, *J* = 8.5 Hz, 1H), 6.14-6.03 (m, 1H), 5.12 (d, *J* = 11.8 Hz, 1H), 5.08 (d, *J* = 19.1 Hz, 1H), 4.92 (s, 1H), 4.79 (br, 1H), 3.92 (s, 3H), 3.13 (dd, J_1 = 19.0 Hz, J_2 = 6.8 Hz, 1H), 2.71-2.62 (m, 1H), 2.64 (d, *J* = 19.0 Hz, 1H), 2.36 (dd, J_1 = 14.3 Hz, J_2 = 5.3 Hz, 1H), 2.20 (br s, 1H), 2.13 (dd, J_1 = 14.3 Hz, J_2 = 8.8 Hz, 1H),1.90 (td, J_1 = 12.6 Hz, J_2 = 4.3 Hz, 1H), 1.46 (s, 9H), 1.37 (br d, *J* = 14.3 Hz, 1H), 1.30 (dd, J_1 = 12.6 Hz, J_2 = 4.0 Hz, 1H), 1.23-1.13 (m, 1H), 0.82 (d, *J* = 6.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 162.5, 157.0, 155.0, 135.3, 134.7, 127.6, 117.6, 108.5, 80.6, 75.4, 63.0, 53.4, 41.9, 40.9, 36.8, 36.7, 36.4, 28.4, 26.1, 21.6; **IR** (thin film): 3445, 2927, 1688, 1600, 1478, 1423, 1392, 1367, 1314, 1258, 1163, 1035 cm^{-1}; **LRMS** (ESI): 389 (M+H) $^+$; **HRMS** (MALDI): calcd for $C_{22}H_{33}N_2O_4$ (M+H) $^+$: 389.2435, found: 389.2440; mp: 202-204 °C.

12-*epi*-**11**:

[α]$_D^{26}$ -8.7 (*c* = 1.38, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.36 (d, *J* = 8.3 Hz, 1H), 6.53 (d, *J* = 8.3 Hz, 1H), 6.13-6.07 (m, 1H), 5.83 (br, 1H), 5.15 (s, 1H), 5.12 (d, *J* = 7.0 Hz, 1H), 4.86 (s, 1H), 3.90 (s, 3H), 3.48 (dd, J_1 = 18.1 Hz, J_2 = 7.0 Hz, 1H), 2.59-2.53 (m, 2H), 2.51 (d, *J* = 18.1 Hz, 1H), 2.34-2.33 (m, 1H), 1.58 (d, *J* = 11.7 Hz, 1H), 1.52-1.31 (m, 4H), 1.44 (s, 9H), 0.82 (d, *J* = 5.0 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 162.3, 156.8, 156.7, 134.8, 134.7, 126.3, 117.0, 107.7, 81.0, 75.1, 62.8, 53.3, 47.3, 39.2, 37.6, 36.9, 36.5, 28.3, 24.0, 21.2; **IR** (thin film): 3307, 2953, 2925, 2870, 1682, 1639, 1596, 1582, 1526, 1476, 1426, 1368, 1310, 1290, 1255, 1166, 1009, 823, 738 cm^{-1}; **LRMS** (ESI): 389 (M+H) $^+$; **HRMS** (MALDI): calcd for $C_{22}H_{33}N_2O_4$ (M+H) $^+$: 389.2435, found: 389.2437; mp: 188-190 °C.

***tert*-butyl ((5*S*,7*R*,9*S*,11*S*)-11-hydroxy-11-(3-hydroxypropyl)-2-methoxy-7-methyl-7,8,9,10-tetrahydro-5,9-methanocycloocta[b]pyridin-5(6H)-yl)carbamate**



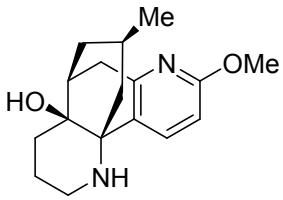
12

To a solution of **14a** (100 mg, 384 μmol) in THF (1.3 mL) was added borane tetrahydrofuran complex solution (0.52 mL, 1.0 M in THF) at 0 °C. After consumption of the starting material, 1 N NaOH (2 mL) and H_2O_2 (2 mL, 30%) was added

to the reaction mixture. After the mixture was stirred at room temperature for 3 h, the reaction was quenched with saturated aqueous $Na_2S_2O_3$ (1 mL), and the resulting mixture was extracted with CH_2Cl_2 (20 mL×3), dried over Na_2SO_4, concentrated, and purified by chromatography (hexane/EtOAc = 3/1) to give **12** (102 mg, 97%) as a white solid.

[α]$_D^{28}$ -36.8 (*c* = 2.02, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.50 (d, *J* = 8.5 Hz, 1H), 6.59 (d, *J* = 8.5 Hz, 1H), 5.64 (br, 1H), 5.05 (s, 1H), 3.90 (s, 3H), 3.69-3.65 (m, 1H), 3.62-3.56 (m, 1H), 3.07 (dd, J_1 = 18.8 Hz, J_2 = 6.8 Hz, 1H), 2.74-2.67 (m, 1H), 2.69 (d, *J* = 18.8 Hz, 1H), 2.37 (br s, 1H), 1.93 (td, J_1 = 13.3 Hz, J_2 = 4.3 Hz, 1H), 1.90-1.82 (m, 1H), 1.68-1.58 (m, 2H), 1.60 (d, *J* = 13.0 Hz, 1H), 1.47 (s, 9H), 1.40 (br d, *J* = 13.3 Hz, 1H), 1.31 (dd, J_1 = 12.3 Hz, J_2 = 2.0 Hz, 1H), 1.20-1.16 (m, 1H), 0.82 (d, *J* = 6.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 162.4, 157.4, 154.8, 135.1, 127.8, 108.6, 80.9, 75.3, 63.7, 63.4, 53.4, 41.6, 37.0, 36.7, 35.4, 33.4, 28.4, 26.6, 26.2, 21.6; **IR** (thin film): 3386, 2927, 2869, 1683, 1599, 1579, 1478, 1426, 1367, 1314, 1260, 1165, 1007, 735 cm^{-1}; **LRMS** (ESI): 407 $(M+H)^+$; **HRMS** (DART): calcd for $C_{22}H_{35}N_2O_5$ $(M+H)^+$: 407.2540, found: 407.2537; mp: 172-174 °C..

(4a*S*,5*S*,10b*S*,12*R*)-8-methoxy-12-methyl-1,2,3,4,5,6-hexahydro-4aH-5,10b-propano-1,7-phenanthrolin-4a-ol



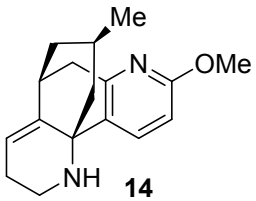
13

To a solution of **12** (220 mg, 0.54 mmol) in DCM (5 mL) were added triethylamine (0.23 mL, 1.63 mmol) and methanesulfonyl chloride (63 μL, 0.82 mmol) at room temperature. After consumption of the starting material, trifluoromethanesulfonic acid (0.14 mL, 1.63 mmol) was added to the reaction mixture. After the mixture was stirred at room temperature for 30 min, triethylamine (0.45 mL, 3.25 mmol) was added. After 3 h of further reaction, 1 N NaOH (10 mL) was added, and the resulting solution was vigorously stirred overnight, extracted with CH_2Cl_2 (20 mL×3), dried over Na_2SO_4, concentrated, and purified by chromatography (EtOAc) to give **13** (145 mg, 93%) as a white solid.

[α]$_D^{26}$ -22.4 (*c* = 0.86, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.45 (d, *J* = 8.6 Hz, 1H), 6.60 (d, *J* = 8.6 Hz, 1H), 3.91 (s, 3H), 3.13 (dd, J_1 = 18.6 Hz, J_2 = 7.0 Hz, 1H), 2.81 (s, 1H), 2.75 (d, *J* = 18.6 Hz, 1H), 2.73-2.69 (m, 1H), 2.55 (td, J_1 = 12.6 Hz, J_2 = 2.6 Hz, 1H), 2.07 (m, 1H), 1.93-1.86 (m, 2H), 1.67-1.59 (m, 3H), 1.45-1.42 (m, 2H),

1.36 (br d, J = 12.6 Hz, 1H), 1.32-1.24 (m, 1H), 1.00 (br d, J = 12.0 Hz, 1H), 0.79 (d, J = 6.5 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 162.3, 155.5, 135.8, 127.2, 108.3, 69.0, 59.5, 53.3, 44.1, 40.3, 38.1, 37.5, 37.5, 31.2, 25.0, 21.9, 21.7; **IR** (thin film): 3446, 2947, 2925, 2867, 1596, 1578, 1477, 1421, 1311, 1263, 1116, 1031, 827, 738 cm^{-1}; **LRMS** (ESI): 289 (M+H)$^+$; **HRMS** (ESI): calcd for $C_{17}H_{25}N_2O_2$ (M+H)$^+$: 289.1911, found: 289.1908; mp: 148-150 °C.

(5*S*,10b*R*,12*R*)-8-methoxy-12-methyl-2,3,5,6-tetrahydro-1H-5,10b-propano-1,7-phenanthroline

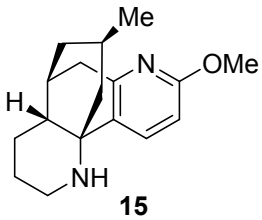


14

To a solution of **13** (67 mg, 233 μmol) in DCM (2.3 mL) was added triethylamine (97 μL, 1.63 mmol) and $SOCl_2$ (51 μL, 0.70 mmol) at room temperature. The mixture was stirred at this temperature for 9 h and then poured into a saturated aqueous solution of Na_2CO_3 and extracted with CH_2Cl_2 three times. The combined organic layers were dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified via flash chromatography on silica gel (hexane/EtOAc = 3/1) to give **14** (45 mg, 80%) as a colorless oil.

[α]$_D^{26}$ 31.2 (c = 1.55, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.80 (d, J = 8.5 Hz, 1H), 6.55 (d, J = 8.5 Hz, 1H), 5.60 (br s, 1H), 3.88 (s, 3H), 3.14 (dd, J_1 = 18.1 Hz, J_2 = 7.6 Hz, 1H), 2.92 (dt, J_1 = 13.3 Hz, J_2 = 4.2 Hz, 1H), 2.80 (d, J = 18.1 Hz, 1H), 2.78-2.75 (m, 1H), 2.60 (ddd, J_1 = 13.1 Hz, J_2 = 9.0 Hz, J_3 = 4.4 Hz, 1H), 2.10-2.05 (m, 1H), 1.88 (m, 1H), 1.80 (br d, J = 12.5 Hz, 1H), 1.62 (br d, J = 11.8 Hz, 1H), 1.54-1.50 (m, 1H), 1.38 (s, 1H), 1.33 (dd, J_1 = 12.8 Hz, J_2 = 4.0 Hz, 1H), 1.26 (t, J = 12.8 Hz, 1H), 0.80 (d, J = 6.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 162.3, 155.9, 142.9, 135.0, 131.8, 115.9, 107.9, 55.0, 53.2, 50.9, 43.9, 41.5, 39.3, 38.8, 26.6, 26.1, 21.6; **IR** (thin film): 3324, 2948, 2910, 2837, 1593, 1577, 1474, 1417, 1320, 1308, 1261, 1136, 1110, 1075, 1032, 827 cm^{-1}; **LRMS** (ESI): 271 (M+H)$^+$; **HRMS** (MADLI): calcd for $C_{17}H_{23}N_2O_1$ (M+H)$^+$: 271.1805, found: 271.1803.

(4a*R*,5*S*,10b*R*,12*R*)-8-methoxy-12-methyl-2,3,4,4a,5,6-hexahydro-1H-5,10b-propano-1,7-phenanthroline

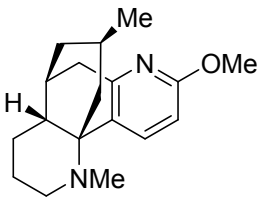


15

To a solution of **14** (18 mg, 68 μmol) in EtOH (1 mL) was added Pd/C (10%) catalyst (15 mg, 14 μmol). Then the mixture was allowed to stir at room temperature under balloon pressure of H_2 for 24 h. The insoluble solid was filtered, and the solvent was removed under reduced pressure. The residue was purified via flash chromatography on silica gel (EtOAc/MeOH = 10/1) to give **15** (17.4 mg, 96%) as a white solid.

[α]$_D^{27}$ -18.1 (c = 0.54, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.65 (d, J = 8.5 Hz, 1H), 6.58 (d, J = 8.5 Hz, 1H), 3.90 (s, 3H), 3.04 (dd, J_1 = 18.6 Hz, J_2 = 7.0 Hz, 1H), 2.76 (br d, J = 13.8 Hz, 1H), 2.56 (d, J = 18.6 Hz, 1H), 2.45 (td, J_1 = 12.3 Hz, J_2 = 4.0 Hz, 1H), 2.04 (br d, J = 3.7 Hz, 1H), 1.75 ((br d, J = 8.8 Hz, 1H), 1.55-1.43 (m, 5H), 1.32-1.22 (m, 4H), 1.11 (t, J = 11.3 Hz, 1H), 0.78 (d, J = 5.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 162.0, 155.9, 136.2, 128.0, 108.2, 55.7, 53.2, 51.2, 44.9, 43.9, 41.4, 35.3, 34.0, 28.0, 26.1, 25.9, 22.0; **IR** (thin film): 2914, 1383, 1577, 1475, 1457, 1419, 1328, 1311, 1252, 1033, 827, 724 cm^{-1}; **LRMS** (ESI): 273 $(M+H)^+$; **HRMS** (ESI): calcd for $C_{17}H_{25}N_2O_1$ $(M+H)^+$: 273.1961, found: 273.1962; mp: 96-98 °C.

(4a*R*,5*S*,10b*R*,12*R*)-8-methoxy-1,12-dimethyl-2,3,4,4a,5,6-hexahydro-1H-5,10b-propano-1,7-phenanthroline



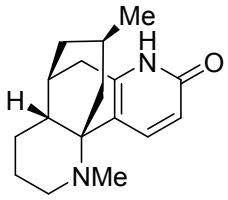
16

To a solution of **15** (12 mg, 44 μmol) in THF (0.3 mL) was added a solution of Lithium Hexamethyldisilazide (66 μL, 1.0 M in THF) and iodomethane (9 μL, 132 μmol) at −78 °C. After the mixture was stirred at that temperature for 3 h, the reaction was quenched with H_2O (0.5 mL). The resulting mixture was then allowed to warm to room temperature, extracted with CH_2Cl_2 (10 mL×3), dried over Na_2SO_4, concentrated, and purified by chromatography (EtOAc/MeOH = 10/1) to give **16** (10.6 mg, 84%) as a white solid.

[α]$_D^{25}$ 11.2 (c = 0.40, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.90 (d, J = 8.5 Hz, 1H), 6.55 (d, J = 8.5 Hz, 1H), 3.90 (s, 3H), 3.06 (dd, J_1 = 18.6 Hz, J_2 = 7.1 Hz, 1H), 2.70 (td, J_1 = 13.3 Hz, J_2 = 2.0 Hz, 1H), 2.61 (s, 3H), 2.53 (br d, J = 12.0 Hz, 1H), 2.50 (d, J = 18.6 Hz, 1H), 2.04 (m,1H), 1.89 (dt, J_1 = 12.6 Hz, J_2 = 3.3 Hz, 1H), 1.80 (dt, J_1 = 13.3 Hz, J_2 = 3.8 Hz, 1H), 1.73 (br d, J = 7.8 Hz, 1H), 1.50-1.46 (m, 1H), 1.42-1.21 (m, 5H), 1.10 (br d, J = 13.3 Hz, 1H), 0.78 (t, J = 5.5 Hz, 3H); **^{13}C NMR**

(100 MHz, $CDCl_3$): δ 161.9, 155.4, 137.4, 130.0, 108.1, 59.2, 53.2, 50.4, 47.8, 43.9, 36.3, 35.3, 34.7, 34.0, 26.8, 26.5, 22.4, 19.7; **IR** (thin film): 3419, 2925, 2794, 1594, 1577, 1474, 1420, 1312, 1260, 1034, 803 cm^{-1}; **LRMS** (ESI): 287 $(M+H)^+$; **HRMS** (ESI): calcd for $C_{18}H_{27}N_2O_1$ $(M+H)^+$: 287.2118, found: 287.2128; mp: 124-126 °C.

(4a*R*,5*S*,10b*R*,12*R*)-1,12-dimethyl-2,3,4,4a,5,6-hexahydro-1H-5,10b-propano-1,7-phenanthrolin-8(7H)-one

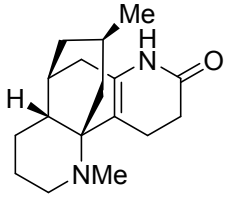


β-Obscurine (**2**)

To a solution of **16** (8 mg, 28 μmol) in $CHCl_3$ (0.5 mL) was added TMSI (20 μL, 140 μmol), and the mixture was refluxed for 2 h. After removal the solvent under reduced pressure, the residue was dissolved in MeOH (0.5 mL) and heated under reflux for 2 h. The mixture was cooled to room temperature, 1 N NaOH (2 mL) was added, and the resulting solution was vigorously stirred overnight, extracted with CH_2Cl_2 (20 mL × 3), dried over Na_2SO_4, concentrated, and purified by chromatography (DCM/MeOH = 10/1) to give β-obscurine (**2**) (6.2 mg, 81%) as a white solid.

[α]$_D^{28}$ -26.4 (*c* = 0.31, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 13.15 (br, 1H), 7.81 (d, *J* = 9.3 Hz, 1H), 6.43 (d, *J* = 9.3 Hz, 1H), 2.96 (dd, J_1 = 18.6 Hz, J_2 = 6.8 Hz, 1H), 2.70 (br t, *J* = 12.8 Hz, 1H), 2.56 (s, 3H), 2.56 (m, 1H), 2.41 (d, *J* = 18.6 Hz, 1H), 2.01 (br d, *J* = 3.0 Hz 1H), 1.84 (br d, *J* = 12.3 Hz, 1H), 1.78 (dt, J_1 = 13.1 Hz, J_2 = 3.8 Hz, 1H), 1.68 (br d, *J* = 12.8 Hz, 1H), 1.47-1.10 (m, 6H), 0.82 (t, *J* = 4.5 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 165.0, 144.3, 141.1, 119.9, 117.2, 58.0, 50.4, 46.4, 43.2, 36.1, 34.6, 33.4, 28.7, 26.5, 26.5, 22.2, 19.4; **IR** (thin film): 2926, 2849, 1665, 1626, 1557, 1469, 1364, 1324, 1260, 1122, 851 cm^{-1}; **LRMS** (ESI): 273 $(M+H)^+$; **HRMS** (ESI): calcd for $C_{17}H_{25}N_2O_1$ $(M+H)^+$: 273.1961, found: 273.1967; mp: 280-282 °C.

(4a*R*,5*S*,10b*R*,12*R*)-1,12-dimethyl-2,3,4,4a,5,6,9,10-octahydro-1H-5,10b-propano-1,7-phenanthrolin-8(7H)-one



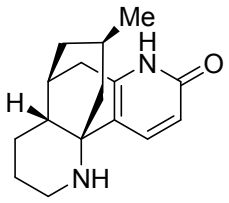
α-Obscurine (**1**)

To a solution of **2** (1.1 mg, 4 μmol) in 20% HCl (2 mL) at 0 °C was added Sm powder (66 mg, 0.44 mmol), and the solution was

stirred at room temperature for 6 h. Then aqueous NaOH solution was added until the pH reached 14. Water was removed under reduced pressure, and the residue was dissolved in MeOH. The insoluble solid was filtered, and the MeOH was removed under reduced pressure. The residue was purified via flash chromatography on silica gel (EtOAc/MeOH = 5/1) to give α-obscurine (**1**) (0.8 mg, 73%) as a white solid.

[α]$_D^{28}$ -23.9 (*c* = 0.21, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.71 (td, J_1 = 13.2 Hz, J_2 = 2.4 Hz, 1H), 2.65-2.61 (m, 1H), 2.52 (m, 1H), 2.45 (s, 3H), 2.52-2.33 (m, 3H), 2.26-2.19 (m, 1H), 1.85 (m, 1H), 1.79-1.57 (m, 5H), 1.51-1.42 (m, 3H), 1.22-1.10 (m, 3H), 0.87 (t, *J* = 6.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 171.4, 130.2, 114.4, 58.8, 51.4, 43.6, 42.9, 36.0, 35.4, 33.6, 31.3, 30.1, 27.1, 26.5, 22.3, 19.4, 19.4; **IR** (thin film): 3215, 3097, 2924, 2853, 1670, 1457, 1376, 1261, 1213, 1081, 1021, 801 cm^{-1}; **LRMS** (ESI): 275 (M+H)$^+$; **HRMS** (ESI): calcd for $C_{17}H_{27}N_2O_1$ (M+H)$^+$: 275.2118, found: 275.2114; mp: 260-262 °C.

(4a*R*,5*S*,10b*R*,12*R*)-12-methyl-2,3,4,4a,5,6-hexahydro-1H-5,10b-propano-1,7-phenanthrolin-8(7H)-one



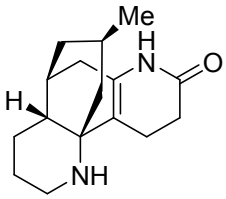
N–desmethyl-β-Obscurine (**4**)

To a solution of **15** (135 mg, 496 μmol) in $CHCl_3$ (2.5 mL) was added TMSI (350 μL, 2.48 mmol), and the mixture was refluxed for 2 h. After removal the solvent under reduced pressure, the residue was dissolved in MeOH (2.5 mL) and heated under reflux for 2 h. The mixture was cooled to room temperature, 1 N NaOH (2 mL) was added, and the resulting solution was vigorously stirred overnight, extracted with CH_2Cl_2 (20 mL×3), dried over Na_2SO_4, concentrated, and purified by chromatography (DCM/MeOH = 10/1) to give *N*-desmethyl-β-obscurine (**4**) (95 mg, 74%) as a white solid.

[α]$_D^{26}$ -29.2 (*c* = 1.60, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.62 (d, *J* = 9.3 Hz, 1H), 6.47 (d, *J* = 9.3 Hz, 1H), 2.96 (dd, J_1 = 18.9 Hz, J_2 = 7.1 Hz, 1H), 2.80 (br d, *J* = 12.8 Hz, 1H), 2.47 (d, *J* = 18.9 Hz, 1H), 2.47-2.41 (m, 1H), 2.03 (br d, *J* = 2.5 Hz, 1H), 1.73 ((br d, *J* = 12.6 Hz, 1H), 1.60-1.39 (m, 6H), 1.33-1.26 (m, 2H), 1.07 (dd, J_1 =J_2 = 11.6 Hz, 1H), 0.82 (d, *J* = 6.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 164.9, 144.9, 140.0, 117.9, 117.4, 54.7, 49.6, 44.6, 43.2, 41.4, 33.3, 29.9, 27.7, 25.9, 25.8, 21.9; **IR** (thin film): 2906, 2846, 1662, 1622, 1553, 1463, 1410, 1322, 1262, 1142,

1096, 869 cm^{-1}; **LRMS** (ESI): 259 $(M+H)^+$; **HRMS** (DART): calcd for $C_{16}H_{23}N_2O_1$ $(M+H)^+$: 259.1805, found: 259.1804; mp: 250-252 °C.

(4a*R*,5*S*,10b*R*,12*R*)-12-methyl-2,3,4,4a,5,6,9,10-octahydro-1H-5,10b-propano-1,7-phenanthrolin-8(7H)-one

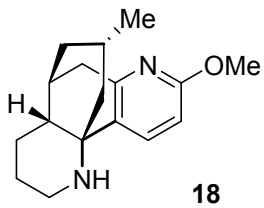


N–desmethyl-α-Obscurine (**3**)

To a solution of **4** (11.3 mg, 44 μmol) in 20% HCl (2 mL) at 0 °C was added Sm powder (66 mg, 0.44 mmol), and the solution was stirred at room temperature for 6 h. Then aqueous NaOH solution was added until the pH reached 14. Water was removed under reduced pressure, and the residue was dissolved in MeOH. The insoluble solid was filtered, and the MeOH was removed under reduced pressure. The residue was purified via flash chromatography on silica gel (EtOAc/MeOH = 5/1) to give *N*-desmethyl-α-obscurine (**3**) (10 mg, 86%) as a white solid.

[α]$_D^{26}$ -12.0 (*c* = 1.40, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.36 (br, 1H), 2.82 (br d, *J* = 13.0 Hz, 1H), 2.51-2.40 (m, 4H), 2.35-2.27 (m, 1H), 2.24-2.16 (m, 1H), 1.88 (br s, 1H), 1.70-1.54 (m, 5H), 1.51-1.41 (m, 5H), 1.23-1.19 (m, 1H), 0.87 (d, *J* = 6.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 171.3, 131.0, 112.2, 55.5, 46.2, 44.6, 43.5, 42.7, 33.5, 31.2, 30.2, 27.3, 26.6, 26.6, 22.0, 18.7; **IR** (thin film): 3220, 3097, 2922, 1695, 1667, 1456, 1377, 1312, 1263, 1219, 803, 734 cm^{-1}; **LRMS** (ESI): 261 $(M+H)^+$; **HRMS** (DART): calcd for $C_{16}H_{25}N_2O_1$ $(M+H)^+$: 261.1961, found: 261.1961; mp: 220-222 °C.

(4a*R*,5*S*,10b*R*,12*S*)-8-methoxy-12-methyl-2,3,4,4a,5,6-hexahydro-1H-5,10b-propano-1,7-phenanthroline



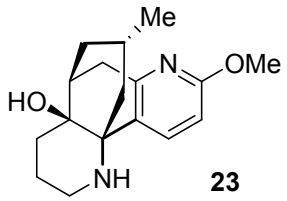
18

To a solution of **17** (27.2 mg, 102 μmol) in EtOH (4 mL) was added Pd/C (10%) catalyst (21.6 mg, 20 μmol). Then the mixture was allowed to stir at room temperature under balloon pressure of H_2 for 18 h. The insoluble solid was filtered, and the solvent was removed under reduced pressure. The residue

was purified via flash chromatography on silica gel (DCM/MeOH = 10/1) to give **18** (23.0 mg, 84%) as a white solid.

[α]$_D^{23}$ -65.5 (*c* = 0.15, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 8.5 Hz, 1H), 6.60 (d, *J* = 8.5 Hz, 1H), 3.90 (s, 3H), 3.09 (dd, J_1 = 18.8 Hz, J_2 = 7.0 Hz, 1H), 2.75 (br d, *J* = 12.3 Hz, 1H), 2.60 (d, *J* = 18.8 Hz, 1H), 2.45-2.38 (m, 1H), 2.12-2.03 (m, 3H), 1.78 (dd, J_1 = 12.8 Hz, J_2 = 6.5 Hz, 1H), 1.62-1.47 (m, 6H), 1.34-1.27 (m, 1H), 0.40 (d, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 162.3, 155.1, 136.8, 128.8, 108.4, 54.5, 53.3, 48.2, 43.7, 40.9, 39.3, 35.8, 33.1, 27.7, 26.2, 25.8, 22.4; **IR** (thin film): 3316, 2919, 1596, 1577, 1477, 1420, 1313, 1262, 1231, 1196, 1127, 1032, 927, 828, 732, 663, 522 cm^{-1}; **LRMS** (ESI): 273 $(M+H)^+$; **HRMS** (ESI): calcd for $C_{17}H_{25}N_2O_1$ $(M+H)^+$: 273.1961, found: 273.1964.

(4a*S*,5*S*,10b*S*,12*R*)-8-methoxy-12-methyl-1,2,3,4,5,6-hexahydro-4aH-5,10b-propano-1,7-phenanthrolin-4a-ol

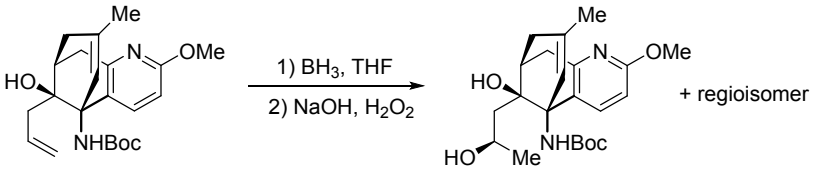


23

To a solution of **22** (14.5 mg, 51 μmol) in EtOH (2 mL) was added Raney Ni catalyst. Then the mixture was allowed to stir at room temperature under balloon pressure of H_2 for 6 h. The insoluble solid was filtered, and the solvent was removed under reduced pressure. The residue was purified via flash chromatography on silica gel (DCM/MeOH = 10/1) to give **23** (9.5 mg, 65%) as a white solid.

[α]$_D^{25}$ 16.6 (*c* = 0.425, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.18 (d, *J* = 8.5 Hz, 1H), 6.71 (d, *J* = 8.5 Hz, 1H), 3.91 (s, 3H), 3.90-3.88 (m, 1H), 3.28-3.21 (m, 1H), 2.84 (d, *J* = 18.8 Hz, 1H), 2.79 (td, J_1 = 12.8 Hz, J_2 = 3.0 Hz, 1H), 2.74-2.69 (m, 1H), 2.65-2.61 (m, 1H), 2.45 (m, 1H), 2.23-2.14 (m, 2H), 1.78 (td, J_1 = 13.0 Hz, J_2 = 4.8 Hz, 1H), 1.64-1.57 (m, 3H), 1.33 (d, *J* = 4.3 Hz, 1H), 0.36 (d, *J* = 8.0 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 163.3, 154.5, 136.8, 124.0, 109.6, 69.4, 62.8, 53.5, 39.7, 39.3, 38.1, 37.7, 33.0, 29.6, 24.8, 22.7, 18.9; **IR** (thin film): 3334, 2943, 1604, 1576, 1487, 1424, 1326, 1282, 1106, 1006, 822 cm^{-1}; **LRMS** (ESI): 289 $(M+H)^+$; **HRMS** (ESI): calcd for $C_{17}H_{25}N_2O_2$ $(M+H)^+$: 289.1911, found: 289.1909; mp: 173-175°C.

The procedure for preparation of **19**

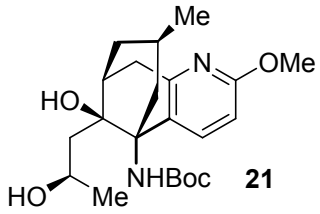


S6 **19**

To a solution of **S6** (638 mg, 1.65 mmol) in THF (16 mL) was added borane tetrahydrofuran complex solution (3.3 mL, 1.0 M in THF) at 0 °C. After consumption of the starting material, 1 N NaOH (5 mL) and H_2O_2 (5 mL, 30%) was added to the reaction mixture. After the mixture was stirred at room temperature for 3 h, the reaction was quenched with saturated aqueous $Na_2S_2O_3$ (1 mL), and the resulting mixture was extracted with CH_2Cl_2 (20 mL×3), dried over Na_2SO_4, concentrated, and purified by chromatography (hexane/EtOAc = 3/1) to give **19** (52.4 mg, 8%) as a white solid.

[α]$_D^{26}$ -0.5 (*c* = 1.11, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.51 (d, *J* = 8.6 Hz, 1H), 6.53 (d, *J* = 8.6 Hz, 1H), 5.40 (br, 2H), 5.18 (s, 1H), 4.76 (br, 1H), 4.26 (m, 1H), 3.88 (s, 3H), 3.08 (dd, J_1 = 18.8 Hz, J_2 = 6.6 Hz, 1H), 2.82-2.77 (m, 3H), 1.89-1.85 (m, 1H), 1.76-1.69 (m, 1H), 1.69 (s, 3H), 1.64 (s, 9H), 1.47 (d, *J* = 14.3 Hz, 1H), 1.15 (d, *J* = 6.0 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 162.1, 157.4, 153.3, 133.9, 133.9, 129.7, 126.8, 108.1, 81.2, 77.7, 64.0, 61.8, 53.4, 40.4, 39.6, 37.2, 34.4, 28.4, 24.2, 22.7; **IR** (thin film): 3276, 2968, 2918, 1680, 1597, 1578, 1542, 1476, 1426, 1369, 1297, 1164, 1092, 917, 845, 754 cm^{-1}; **LRMS** (ESI): 405 $(M+H)^+$; **HRMS** (MALDI): calcd for $C_{22}H_{33}N_2O_5$ $(M+H)^+$: 405.2384, found: 405.2380; mp: 172-174 °C.

***tert*-butyl ((5*S*,7*R*,9*S*,11*S*)-11-hydroxy-11-(2-hydroxypropyl)-2-methoxy-7-methyl-7,8,9,10-tetrahydro-5,9-methanocycloocta[b]pyridin-5(6H)-yl)carbamate**



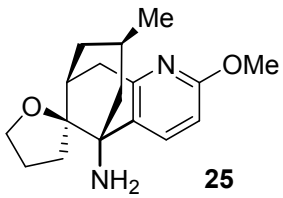
21

To a solution of **19** (6.3 mg, 16 μmol) in MeOH (0.5 mL) was added Pd/C (10%) catalyst (2 mg, 2 μmol). Then the mixture was allowed to stir at room temperature under balloon pressure of H_2 for 20 h. The insoluble solid was filtered, and the solvent was removed under reduced pressure. The residue was purified via flash chromatography on silica gel (hexane/EtOAc = 1/1) to give **21** (6.1 mg, 96%) as a white solid.

[α]$_D^{24}$ -22.4 (*c* = 0.305, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.50 (d, *J* = 8.6 Hz, 1H), 6.61 (d, *J* = 8.6 Hz, 1H), 6.10 (br, 1H), 5.05 (s, 1H), 4.72 (br, 1H), 4.22 (m, 1H),

3.91 (s, 3H), 3.02 (dd, J_1 = 19.0 Hz, J_2 = 6.7 Hz, 1H), 2.74 (d, J = 19.0 Hz, 1H), 2.73-2.67 (m, 1H), 2.52 (m, 1H), 1.97 (dd, J_1 = 12.8 Hz, J_2 = 4.3 Hz, 1H), 1.68-1.65 (m, 2H), 1.48 (s, 9H), 1.45-1.42 (m, 2H), 1.33-1.28 (m, 1H), 1.14 (d, J = 6.0 Hz, 3H), 0.83 (d, J = 6.5 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 162.6, 157.5, 154.3, 135.1, 127.4, 108.8, 81.2, 77.2, 64.3, 63.2, 53.4, 41.7, 40.9, 37.3, 36.7, 35.6, 28.4, 26.0, 24.3, 21.6; **IR** (thin film): 3393, 2926, 2869, 1728, 1684, 1600, 1578, 1478, 1424, 1316, 1260, 1165, 1102, 1035, 1001, 827 cm^{-1}; **LRMS** (ESI): 407 (M+H)$^+$; **HRMS** (MALDI): calcd for $C_{22}H_{33}N_2O_5$ (M+H)$^+$: 407.2540, found: 407.2538.

(2*S*,5'*S*,7'*R*,9'*S*)-2'-methoxy-7'-methyl-4,5,7',8',9',10'-hexahydro-3H-spiro[furan-2,11'-[5,9]methanocycloocta[b]pyridin]-5'(6'H)-amine

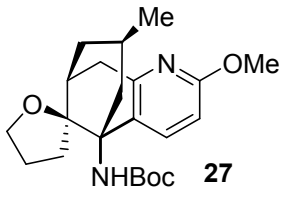


25

To a solution of **24** (28.8 mg, 100 μmol) in MeOH (0.5 mL) was added Pd/C (10%) catalyst (11 mg, 10 μmol). Then the mixture was allowed to stir at room temperature under balloon pressure of H_2 for 20 h. The insoluble solid was filtered, and the solvent was removed under reduced pressure. The residue was purified via flash chromatography on silica gel (hexane/EtOAc = 1/1) to give **25** (14.4 mg, 50%) as a colorless oil.

[α]$_D^{24}$ -9.9 (c = 0.215, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.79 (d, J = 8.5 Hz, 1H), 6.56 (d, J = 8.5 Hz, 1H), 4.02 (m, 1H), 3.89 (s, 3H), 3.84 (m, 1H), 3.16 (dd, J_1 = 19.1 Hz, J_2 = 7.5 Hz, 1H), 2.80 (d, J = 19.1 Hz, 1H), 2.20 (m, 1H), 1.96-1.93 (m, 1H), 1.88-1.81 (m, 1H), 1.72-1.62 (m, 3H), 1.48-1.45 (m, 1H), 1.35-1.27 (m, 2H), 1.06 (m, 1H), 0.80 (d, J = 6.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 162.2, 154.3, 136.1, 130.7, 107.9, 85.8, 68.0, 56.5, 53.3, 47.2, 38.1, 38.1, 37.5, 31.0, 27.0, 25.7, 21.6; **IR** (thin film): 3378, 2948, 2923, 1596, 1577, 1475, 1421, 1309, 1257, 1148, 1062, 1031, 931, 828 cm^{-1}; **LRMS** (ESI): 289 (M+H)$^+$; **HRMS** (ESI): calcd for $C_{17}H_{25}N_2O_2$ (M+H)$^+$: 289.1911, found: 289.1912.

***tert*-butyl ((2*S*,5'*S*,7'*R*,9'*S*)-2'-methoxy-7'-methyl-4,5,7',8',9',10'-hexahydro-3H-spiro[furan-2,11'-[5,9]methanocycloocta[b]pyridin]-5'(6'H)-yl)carbamate**



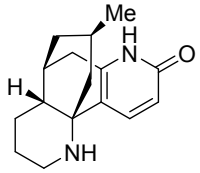
27

To a solution of **26** (6.0 mg, 15 μmol) in MeOH (0.5 mL) was added Pd/C (10%) catalyst (2 mg, 2 μmol). Then the mixture was allowed to stir at room temperature under

balloon pressure of H_2 for 20 h. The insoluble solid was filtered, and the solvent was removed under reduced pressure. The residue was purified via flash chromatography on silica gel (hexane/EtOAc = 5/1) to give a diastereomeric mixture (4.6 mg, 77%) as a colorless oil with a dr of 4/1 favoring **27**.

[α]$_D^{24}$ -4.9 (*c* = 0.155, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.44 (d, *J* = 8.8 Hz, 1H), 6.55 (d, *J* = 8.8 Hz, 1H), 4.69 (br, 1H), 4.96 (br s, 1H), 4.06 (m, 1H), 3.88 (s, 3H), 3.82-3.79 (m, 1H), 3.22 (dd, J_1 = 18.8 Hz, J_2 = 7.0 Hz, 1H), 2.73 (d, *J* = 18.8 Hz, 1H), 2.50-2.44 (m, 1H), 2.38-2.30 (m, 1H), 2.07 (m, 1H), 1.89-1.81 (m, 3H), 1.70-1.62 (m, 3H), 1.59 (s, 9H), 1.42-1.33 (m, 1H), 0.79 (d, *J* = 6.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 162.3, 154.4, 153.4, 137.5, 127.0, 107.7, 86.1, 79.0, 68.2, 61.1, 53.3, 45.6, 39.5, 38.0, 37.7, 32.6, 28.3, 26.8, 24.7, 21.4; **IR** (thin film): 3445, 3370, 2951, 2925, 1728, 1600, 1500, 1478, 1390, 1315, 1241, 1166, 1067, 824 cm^{-1}; **LRMS** (ESI): 389 $(M+H)^+$; **HRMS** (ESI): calcd for $C_{22}H_{33}N_2O_4$ $(M+H)^+$: 389.2435, found: 389.2436.

Comparison of ^{1}H NMR Data of Synthetic and Natural N-demethyl-β-obscurine



N–desmethyl-β-Obscurine (**4**)

	Synthetic (400 MHz, $CDCl_3$)		**Natural (400 MHz, $CDCl_3$)**	
1	7.62	d, J = 9.3 Hz, 1H	7.61	d, J = 9.2 Hz, 1H
2	6.47	d, J = 9.3 Hz, 1H	6.47	d, J = 9.5 Hz, 1H
3	2.96	dd, J_1 = 18.9 Hz, J_2 = 7.1 Hz, 1H	2.95	dd, J_1 = 18.9 Hz, J_2 = 7.0 Hz, 1H
4	2.80	br d, J = 12.8 Hz, 1H	2.79	br d, J = 13.1 Hz, 1H
5	2.47	d, J = 18.9 Hz, 1H	2.46	d, J = 18.6 Hz, 1H
6	2.47-2.41	m, 1H	2.44	ddd, J_1 = 12.7 Hz, J_2 = 12.7 Hz, J_3 = 3.2, 1H
7	2.03	br d, J = 2.5 Hz, 1H	2.03	br d, J =3.1 Hz, 1H
8	1.73	br d, J = 12.6 Hz, 1H	1.72	br d, J = 13.1 Hz, 1H
9	1.60-1.39	m, 6H	1.61-1.38	m, 6H
10	1.33-1.26	m, 2H	1.31-1.25	m, 2H
11	1.07	dd, J_1 = J_2 = 11.6 Hz, 1H	1.06	dd, J_1 = J_2 = 11.7 Hz, 1H
12	0.82	d, J = 6.2 Hz, 3H	0.82	d, J = 6.4 Hz, 3H

Comparison of ^{13}C NMR Data of Synthetic and Natural N-demethyl-β-obscurine

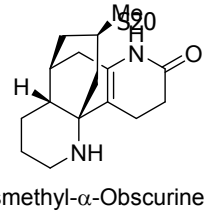
	Synthetic **(100 MHz, $CDCl_3$)**	**Natural** **(100 MHz, $CDCl_3$)**
1	164.9	164.8
2	144.9	144.8
3	140.0	139.9
4	117.9	117.9
5	117.4	117.4
6	54.7	54.6
7	49.6	49.6
8	44.6	44.5
9	43.2	43.1
10	41.4	41.4
11	33.3	33.2
12	29.9	29.8
13	27.7	27.7
14	25.9	25.9
15	25.8	25.8
16	21.9	21.9

* Data for natural N-demethyl-β-obscurine were obtained from the following reference:

1) W. A. Ayer,; G. C. Kasitu, *Can J. Chem.* **1986**, *67*, 1077.

2) K. Katakawa,; N. Kogure,; M. Kitajima,; H. Takayama, *Helv. Chim. Acta* **2009**, *92*, 445

Comparison of ^{1}H NMR Data of Synthetic and Natural N-demethyl-α-obscurine



N–desmethyl-α-Obscurine (**3**)

	Synthetic (400 MHz, $CDCl_3$)		Natural (400 MHz, $CDCl_3$)	
1	7.36	br s, 1H	7.45	br s, 1H
2	2.82	d, *J* = 13.0 Hz, 1H	2.82	d, *J* = 12.5 Hz, 1H
3	2.51-2.40	m, 4H	2.50-2.15	m, 6H
4	2.35-2.27	m, 1H		
5	2.24-2.16	m, 1H		
6	1.88	br s, 1H	1.87	br s, 1H
7	1.70-1.54	m, 5H	1.71-1.55	m, 5H
8	1.51-1.41	m, 5H	1.55-1.34	m, 5H
9	1.23-1.19	m, 1H	1.21	t, *J* =13.5 Hz, 1H
10	0.87	d, *J* = 6.1 Hz, 3H	0.85	d, *J* = 6.0 Hz, 3H

Comparison of ^{13}C NMR Data of Synthetic and Natural N-demethyl-α-obscurine

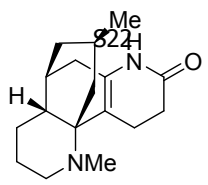
	Synthetic **(100 MHz, $CDCl_3$)**	**Natural** **(100 MHz, $CDCl_3$)**
1	171.3	172.0
2	131.0	131.4
3	112.2	112.1
4	55.5	55.5
5	46.2	46.4
6	44.6	44.8
7	43.5	43.7
8	42.7	42.8
9	33.5	33.7
10	31.2	31.2
11	30.2	30.0
12	27.3	27.5
13	26.6	26.6
14	26.6	26.1
15	22.0	22.0
16	18.7	

* Data for natural N-demethyl-α-obscurine were obtained from the following reference:

1) D. Schumann,; A. Naumann, *Libigs Ann. Chem.* **1983**, 220.

2) D. F. Fischer,; R. Sarpong, *J. Am. Chem. Soc*. **2010**, *132*, 5926.

Comparison of ^{13}C NMR Data of Synthetic and Natural α-obscurine



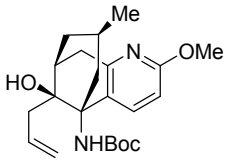
α-Obscurine (**1**)

	Synthetic **(100 MHz, $CDCl_3$)**	**Natural** **(100 MHz, $CDCl_3$)**
1	171.4	171.8
2	130.2	130.6
3	114.4	114.2
4	58.8	59.0
5	51.4	51.4
6	43.6	43.6
7	42.9	43.0
8	36.0	36.0
9	35.4	35.6
10	33.6	33.7
11	31.3	31.4
12	30.1	30.1
13	27.1	27.2
14	26.5	26.5
15	22.3	22.3
16	19.4	19.5
17	19.4	19.5

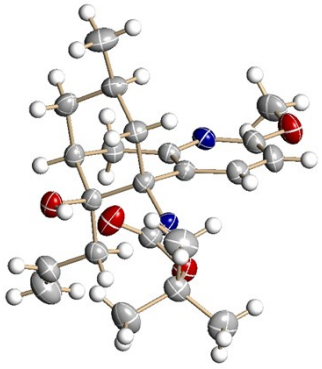
* Data for natural α-obscurine were obtained from the following reference:

1) T. T. Nakashima,; W. A. Ayer, *Can. J. Chem.* **1975**, 1936.

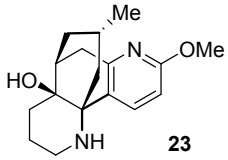
X-Ray structure of 14a



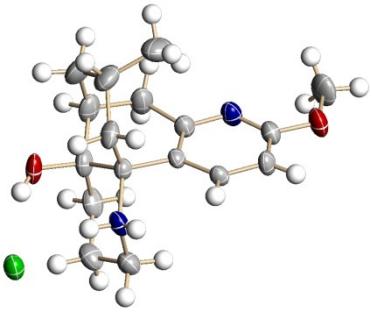
11



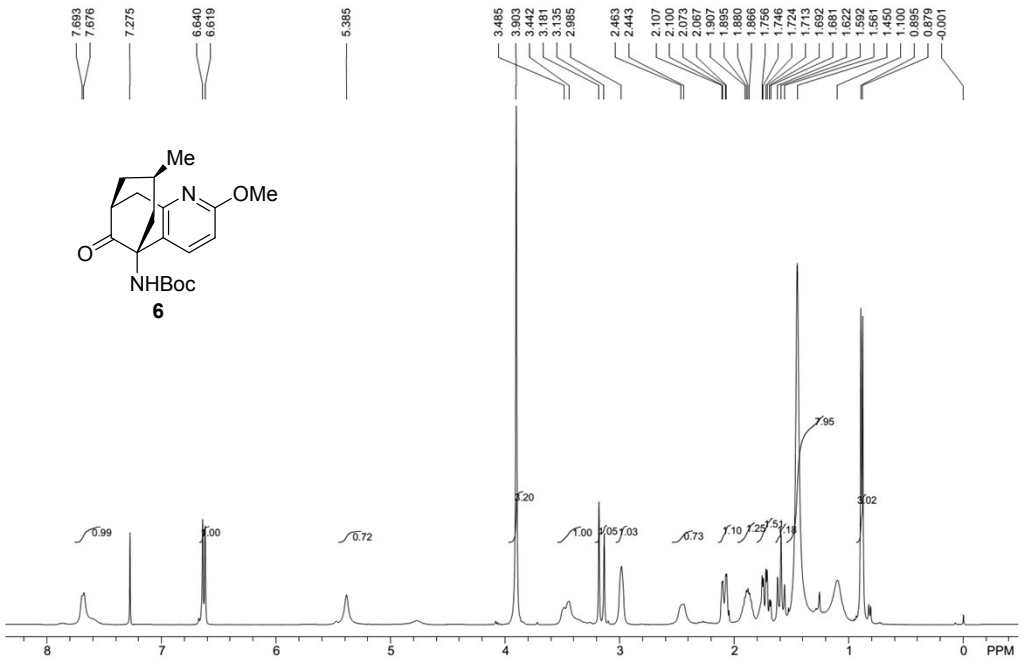
X-Ray structure of 23

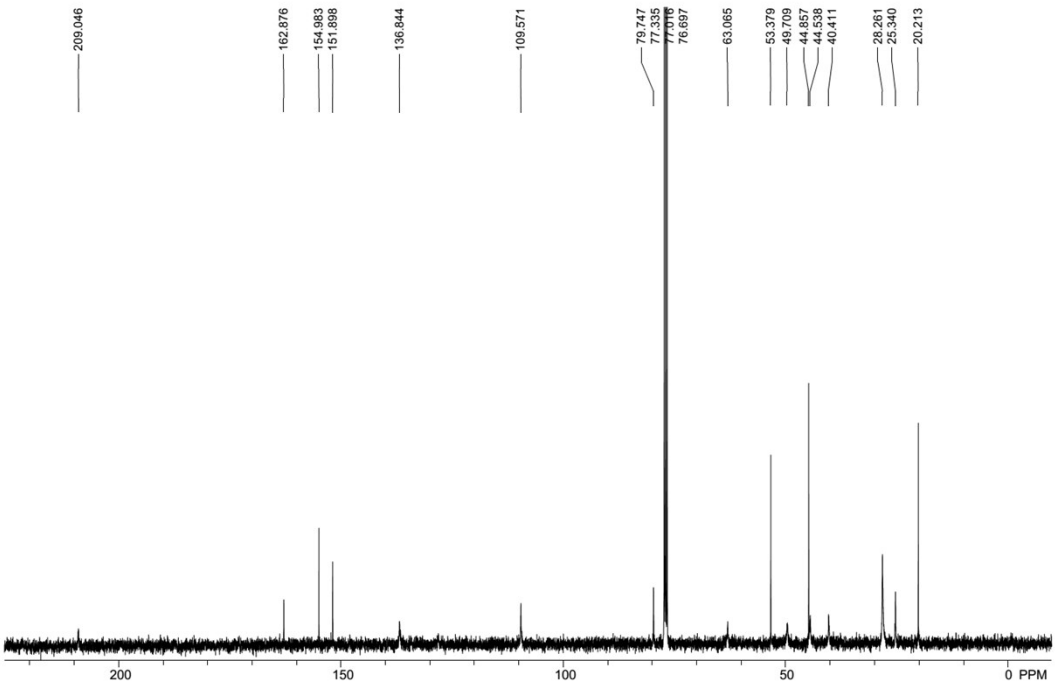


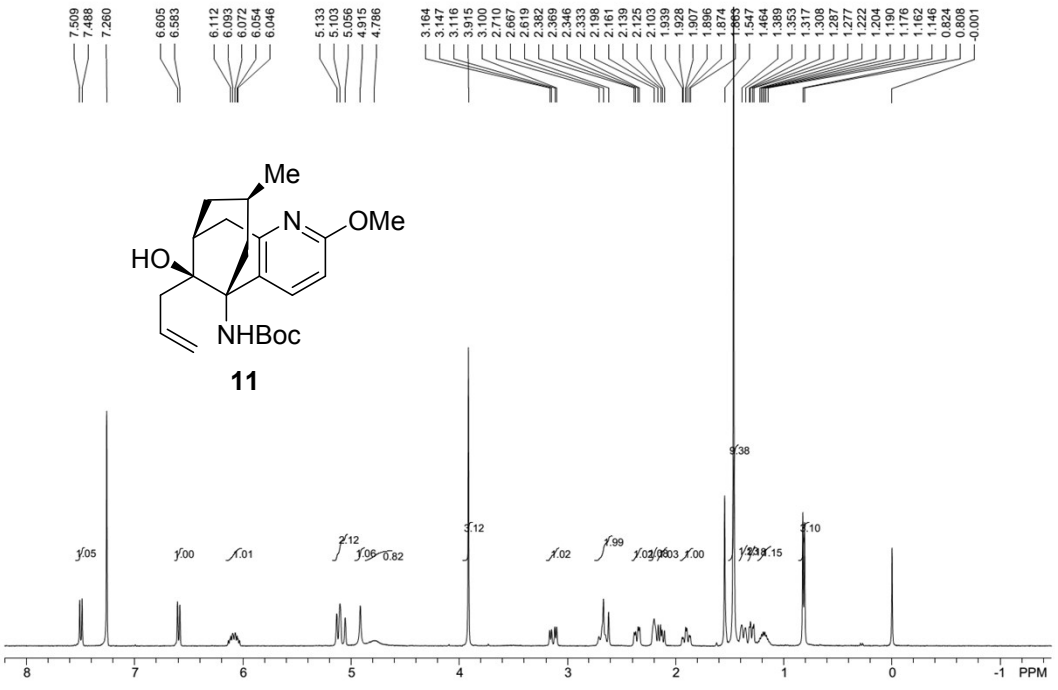
23



NMR spectra






Me
N
OMe
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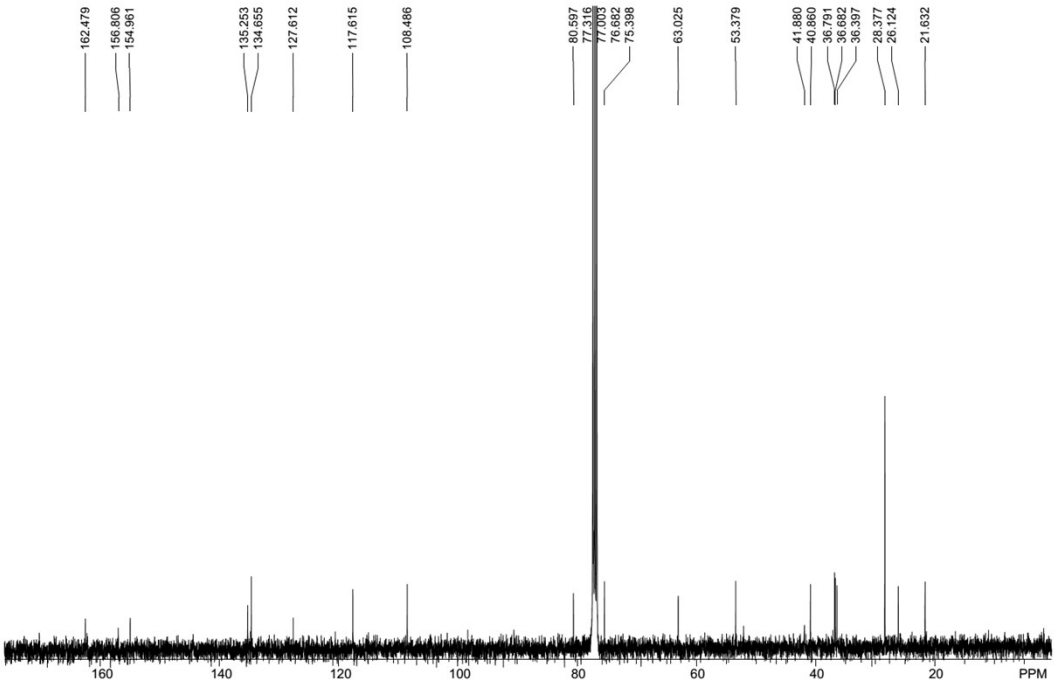
NHBoc
11
PPM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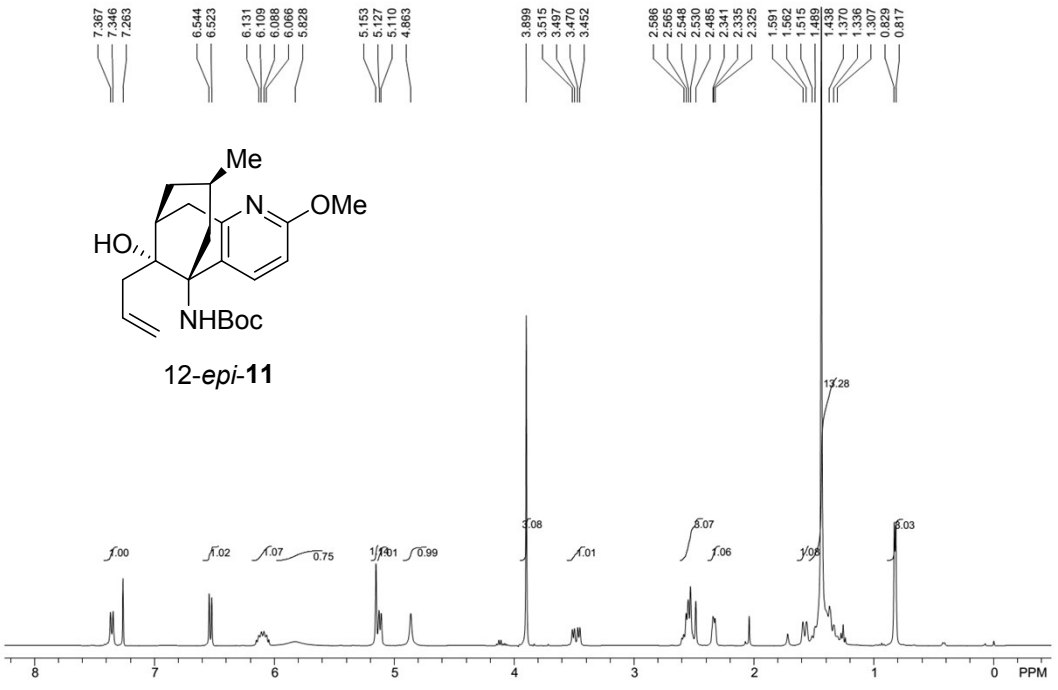
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12-*epi*-**11**
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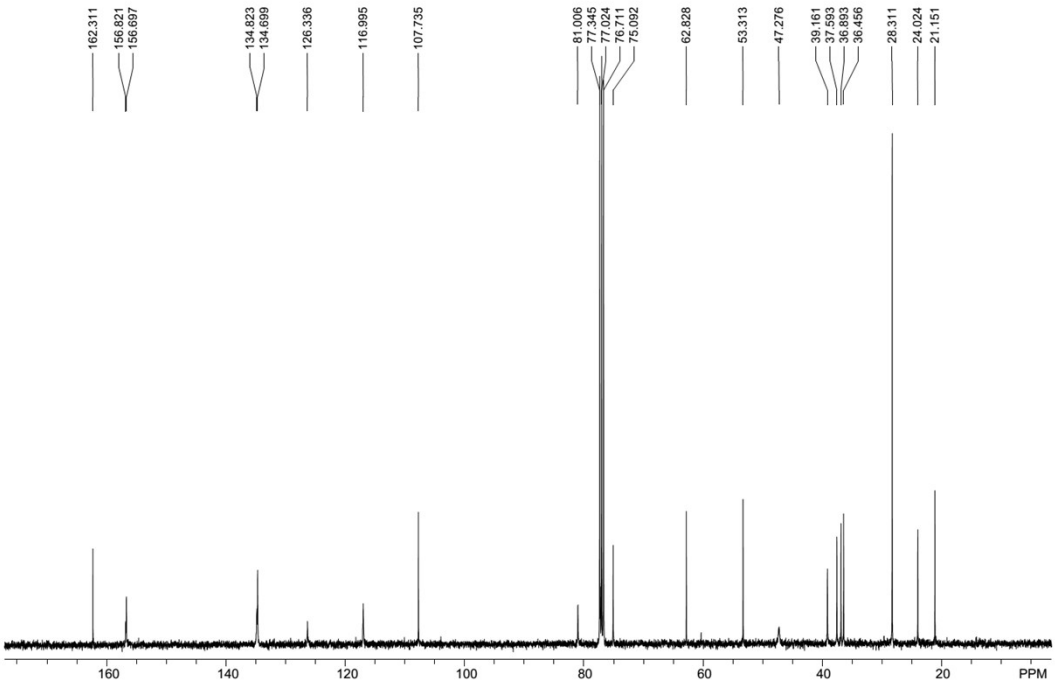
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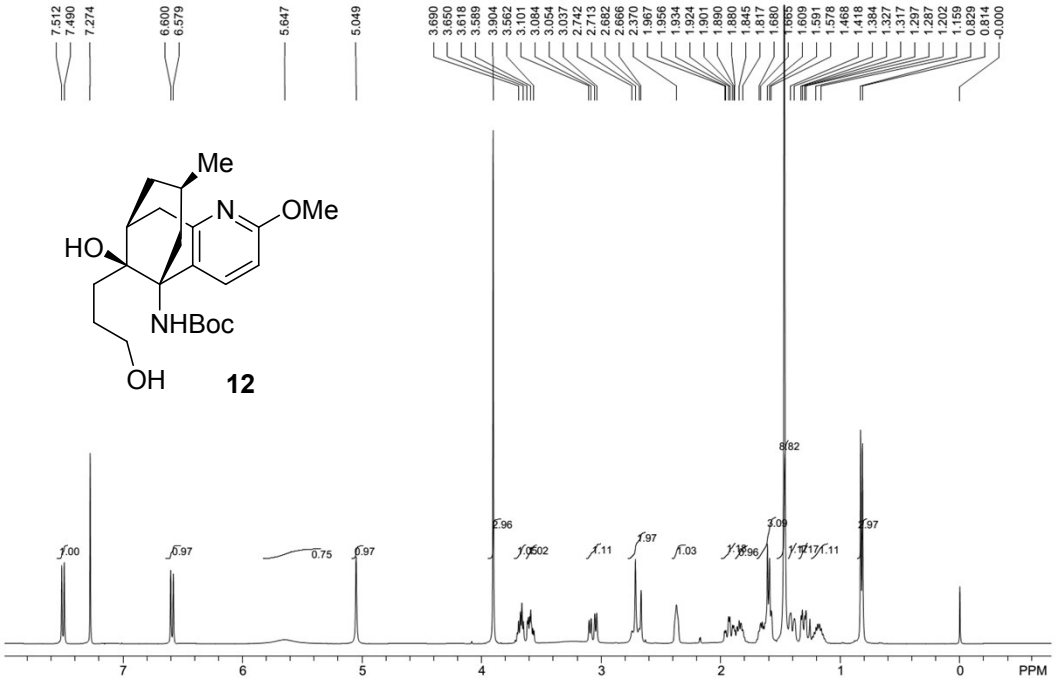
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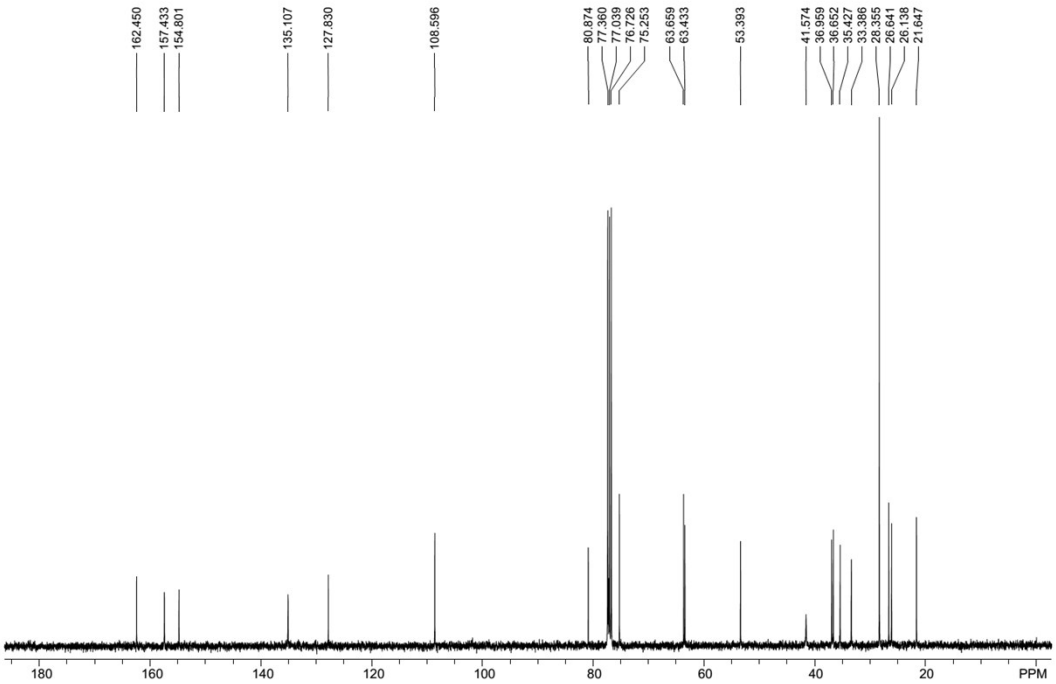
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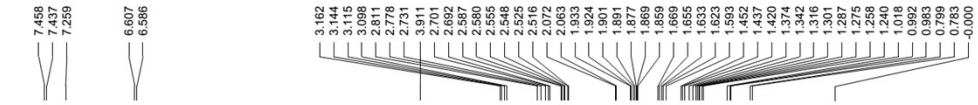
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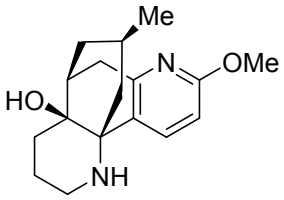
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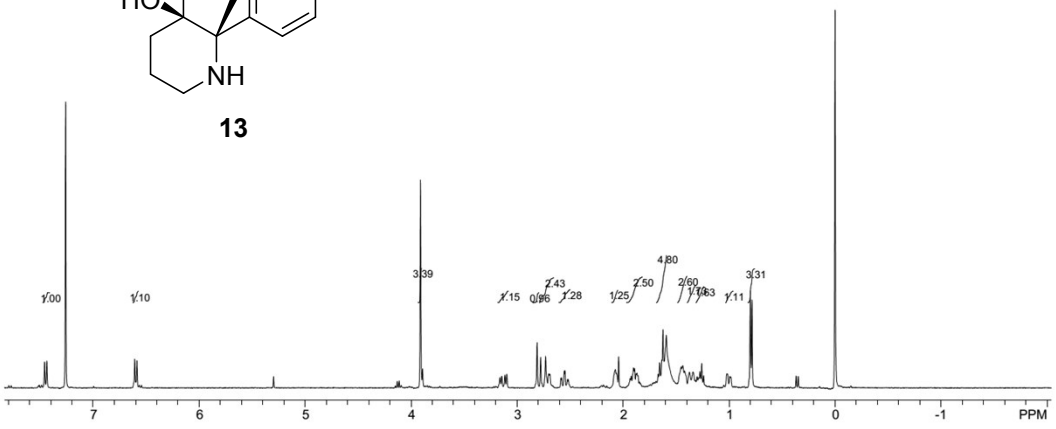
OMe
HO
NH

13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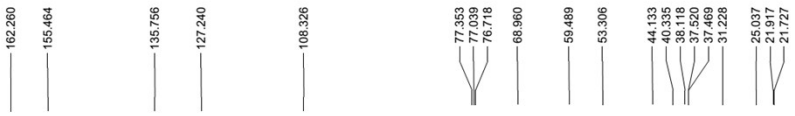
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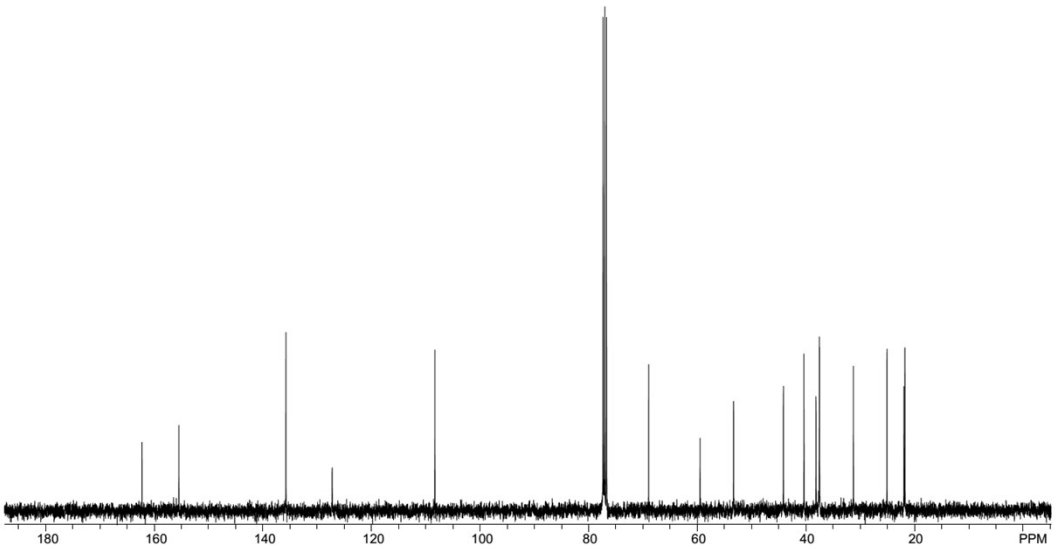
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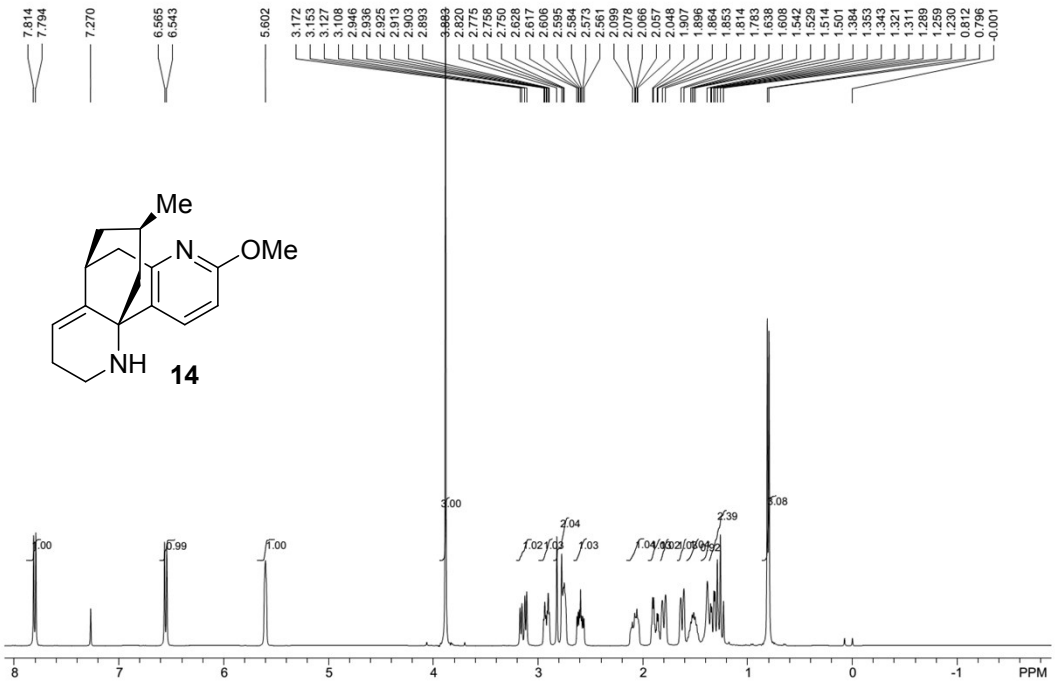
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2.573
2.561
2.099
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1.783
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1.542
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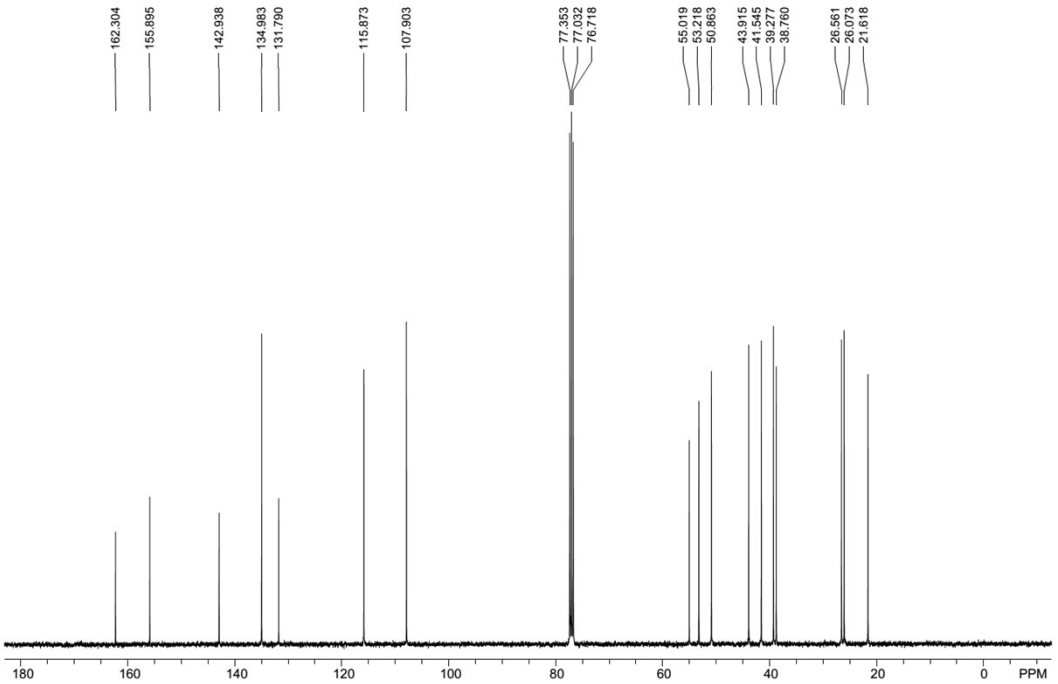
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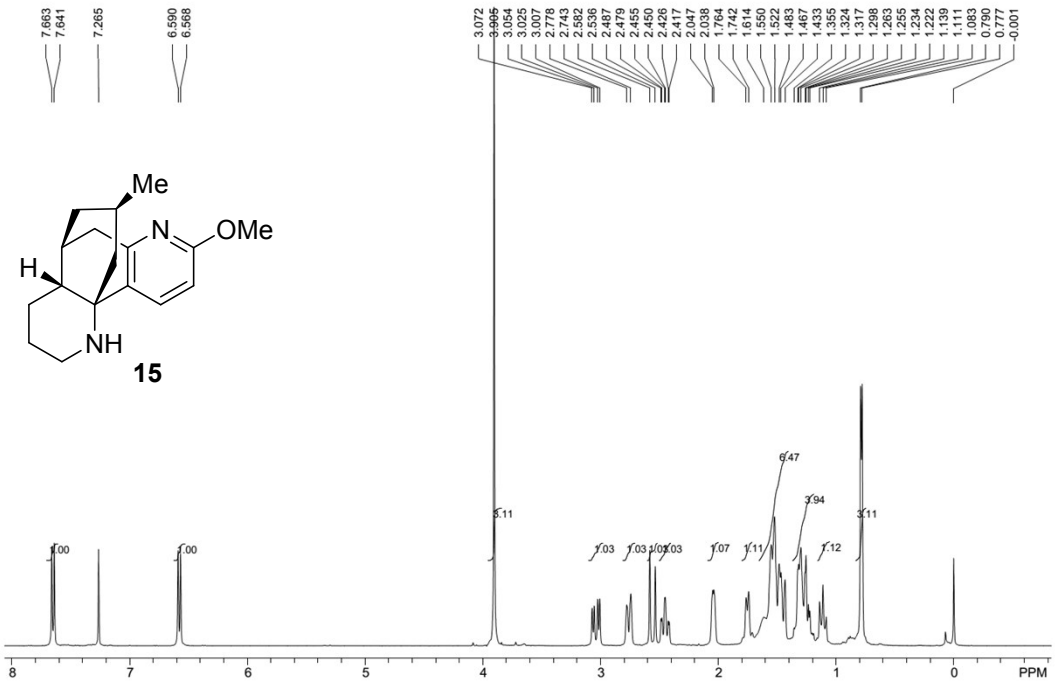
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OMe
H
NH
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1.00
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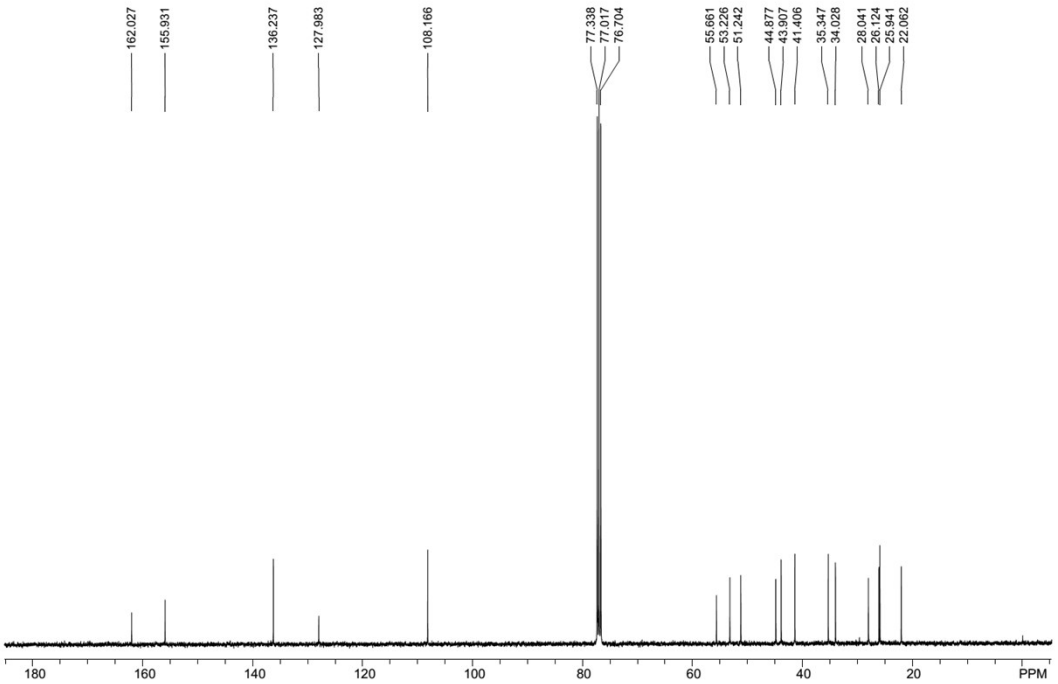
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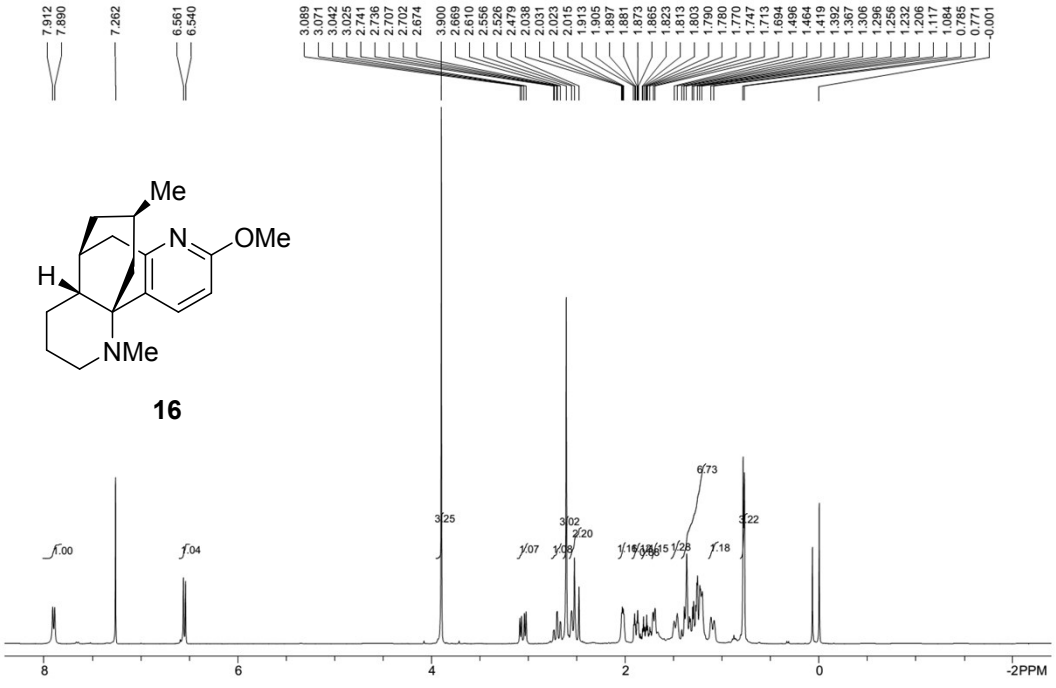
PPM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3.025
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2.674
3.900
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2.610
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2.479
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2.031
2.023
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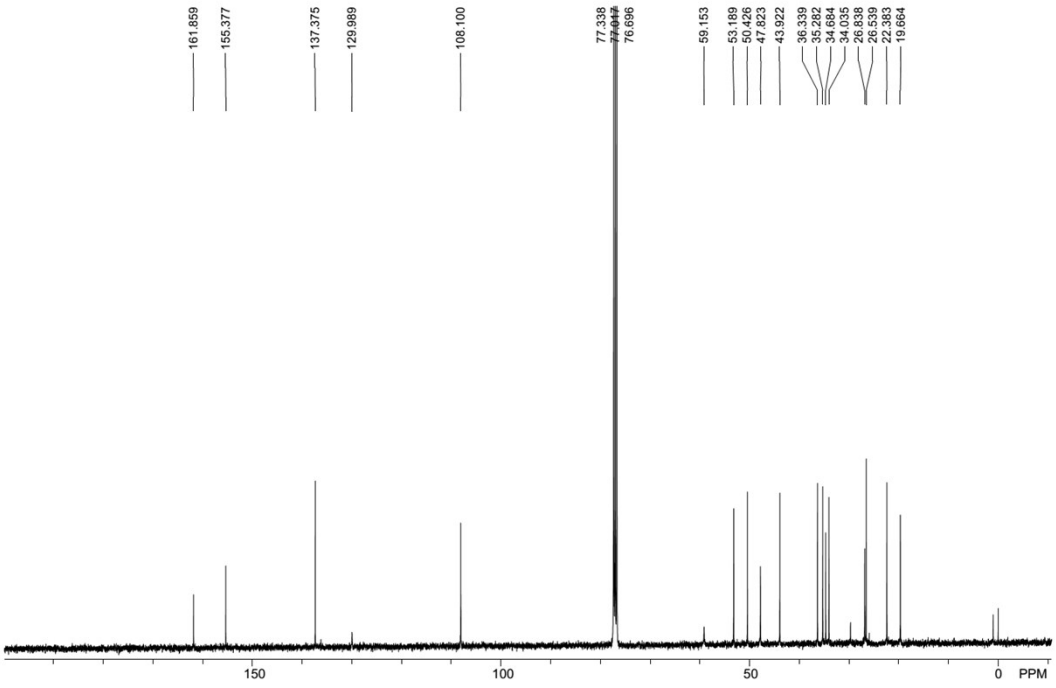
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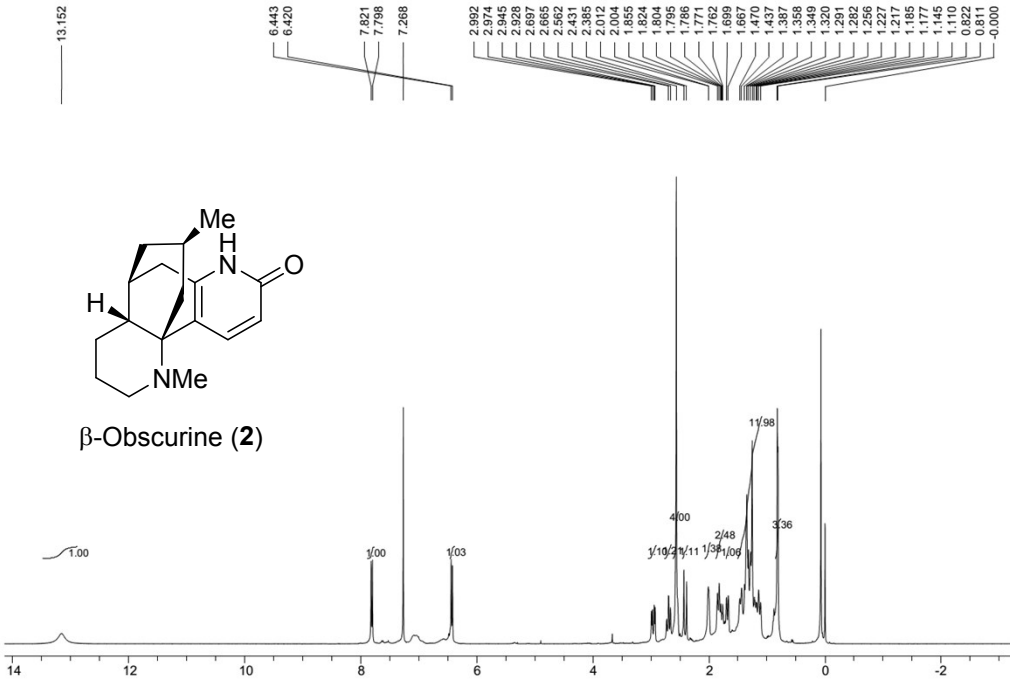
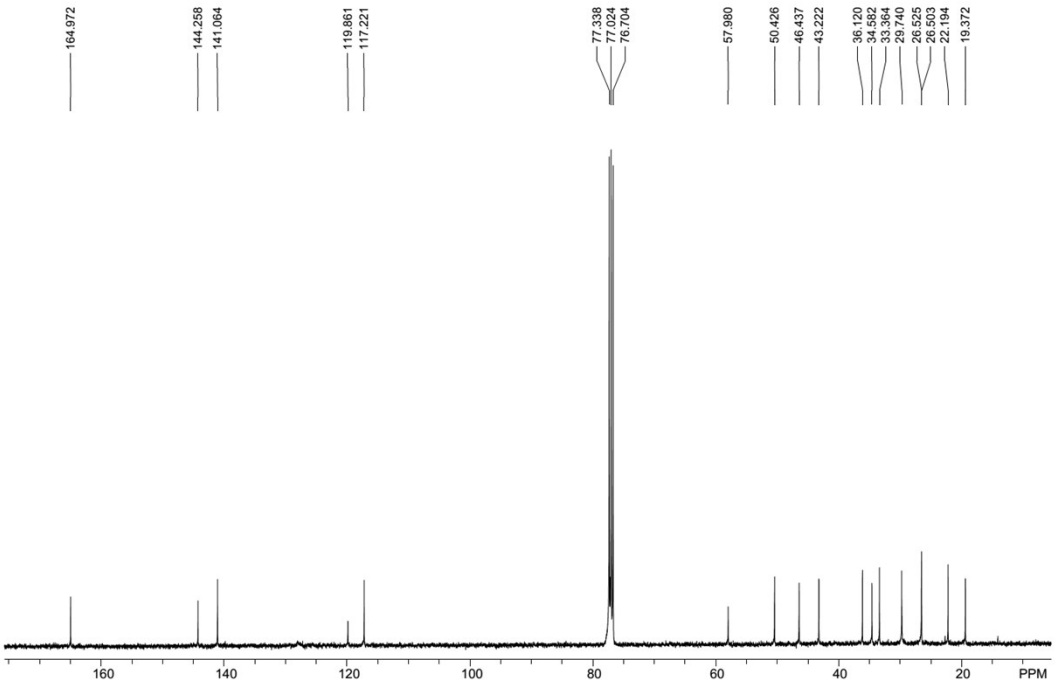
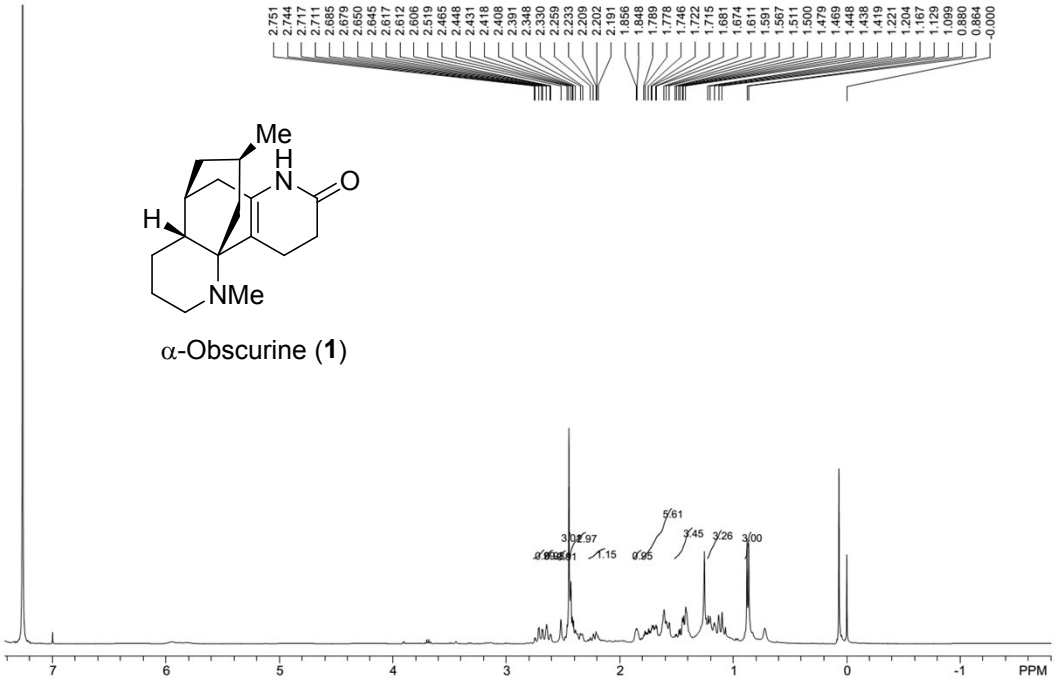
PPM

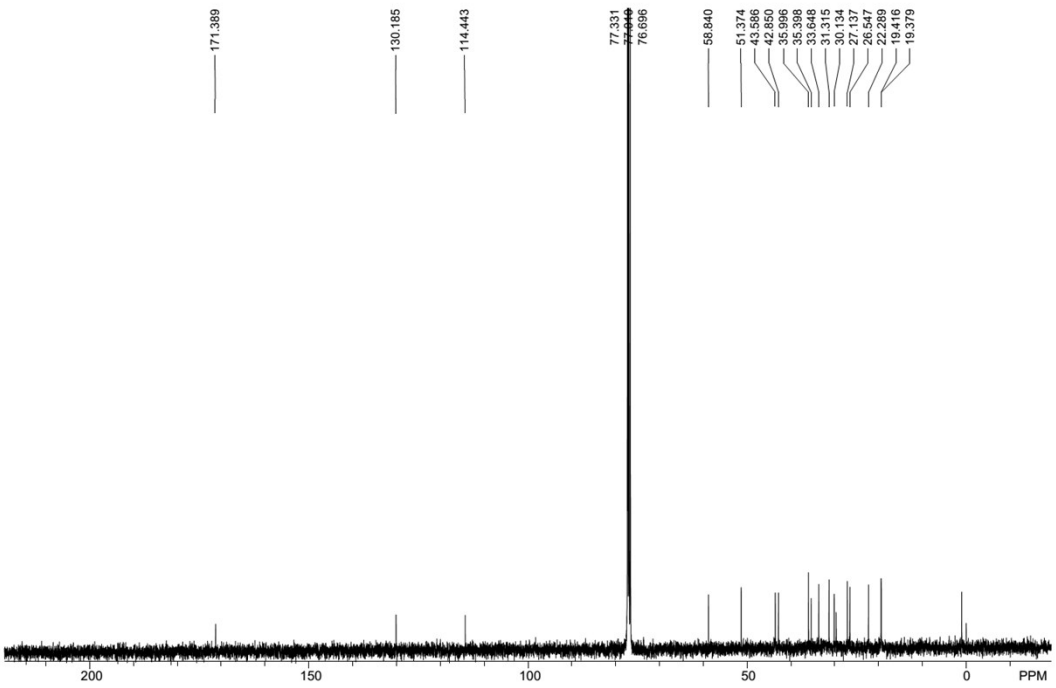


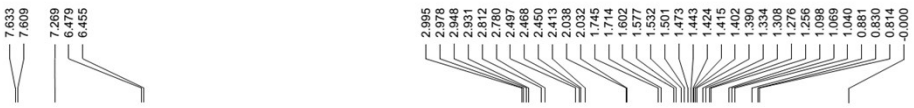
β-Obscurine (**2**)

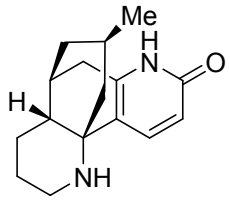




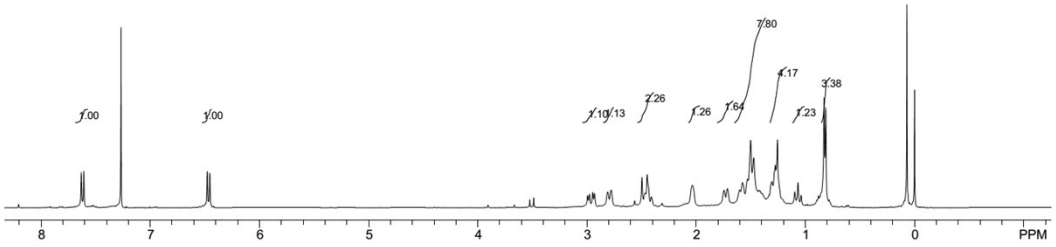
α-Obscurine (**1**)

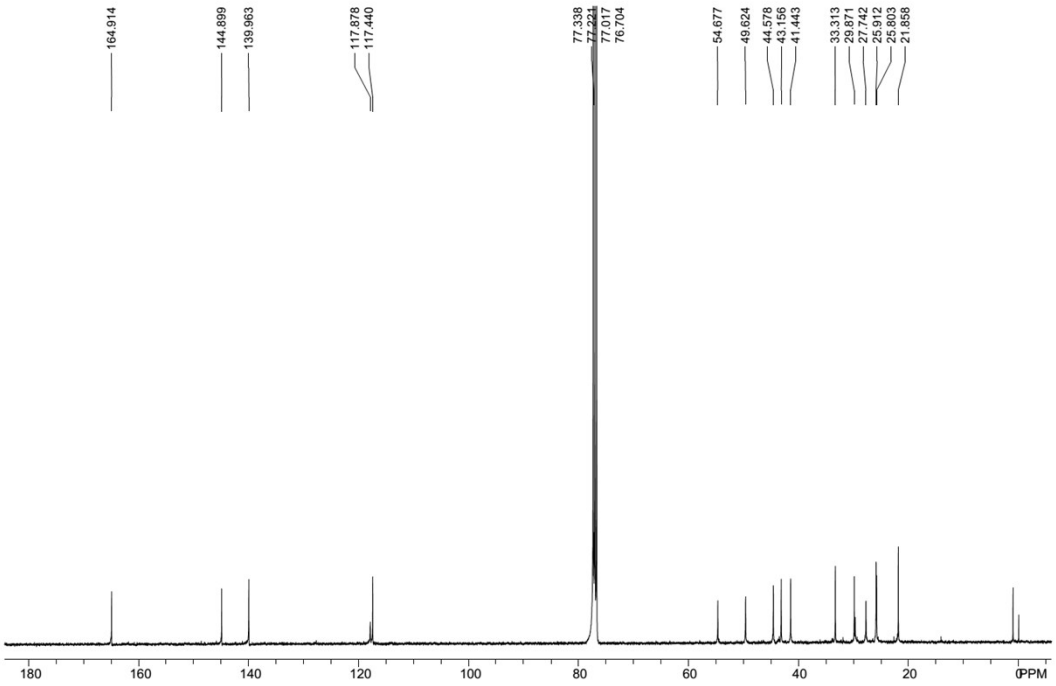


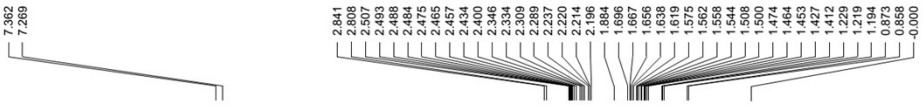


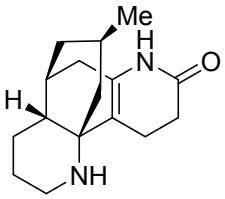


N–desmethyl-β-Obscurine (**4**)

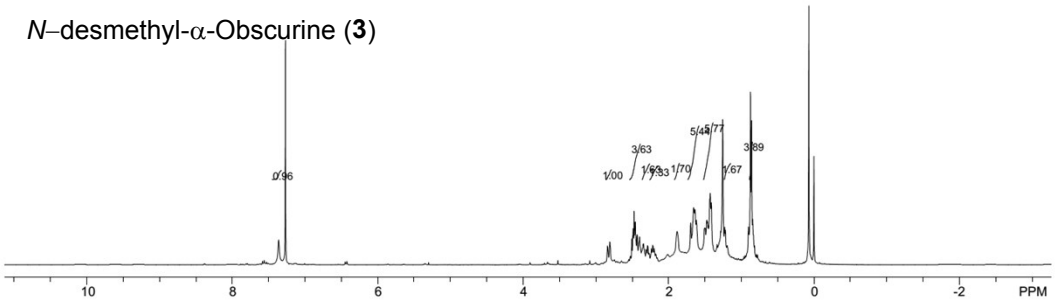


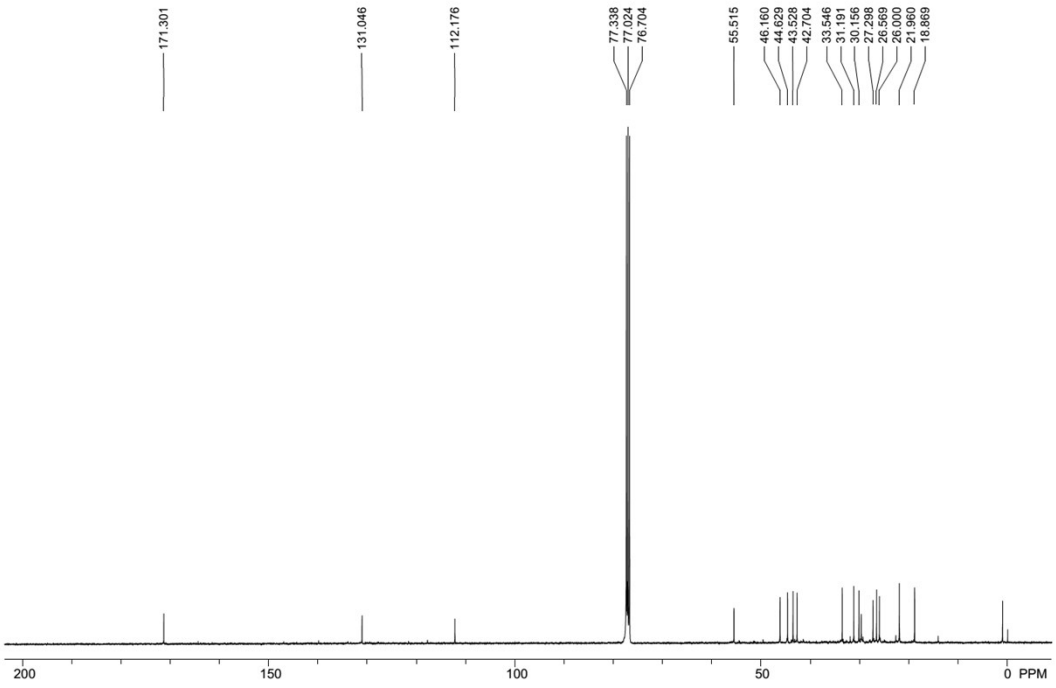


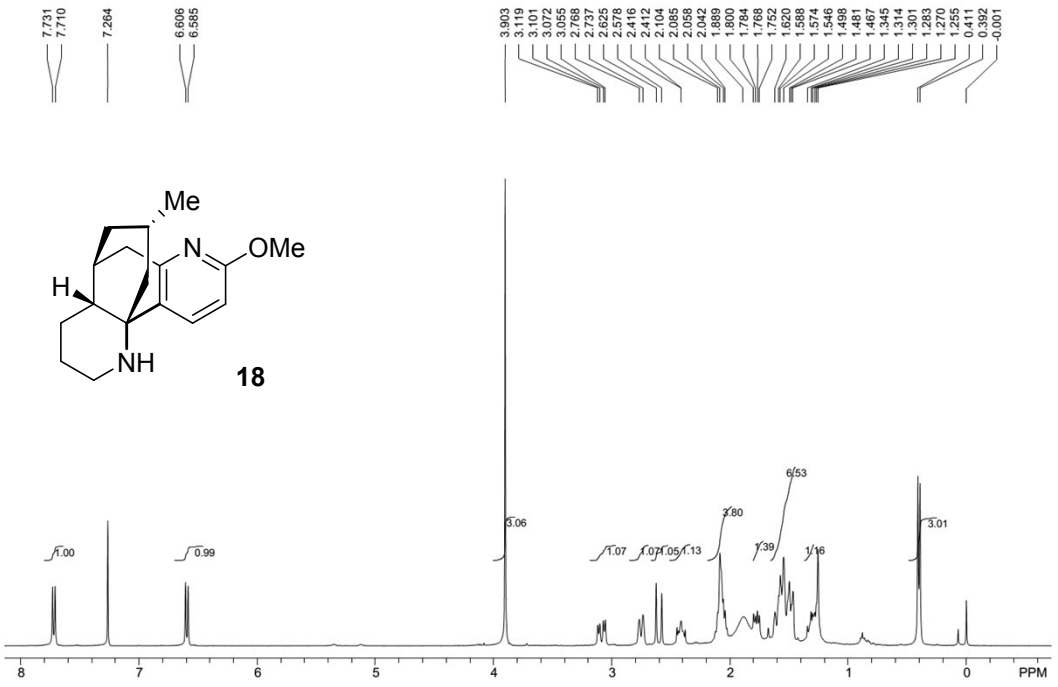




N–desmethyl-α-Obscurine (**3**)



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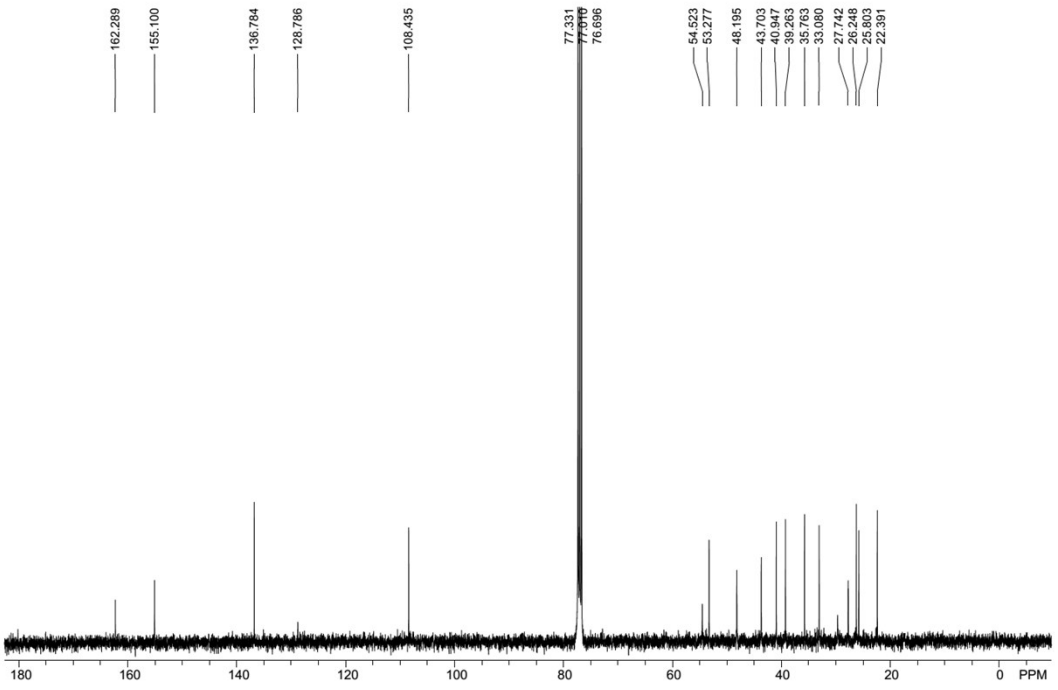
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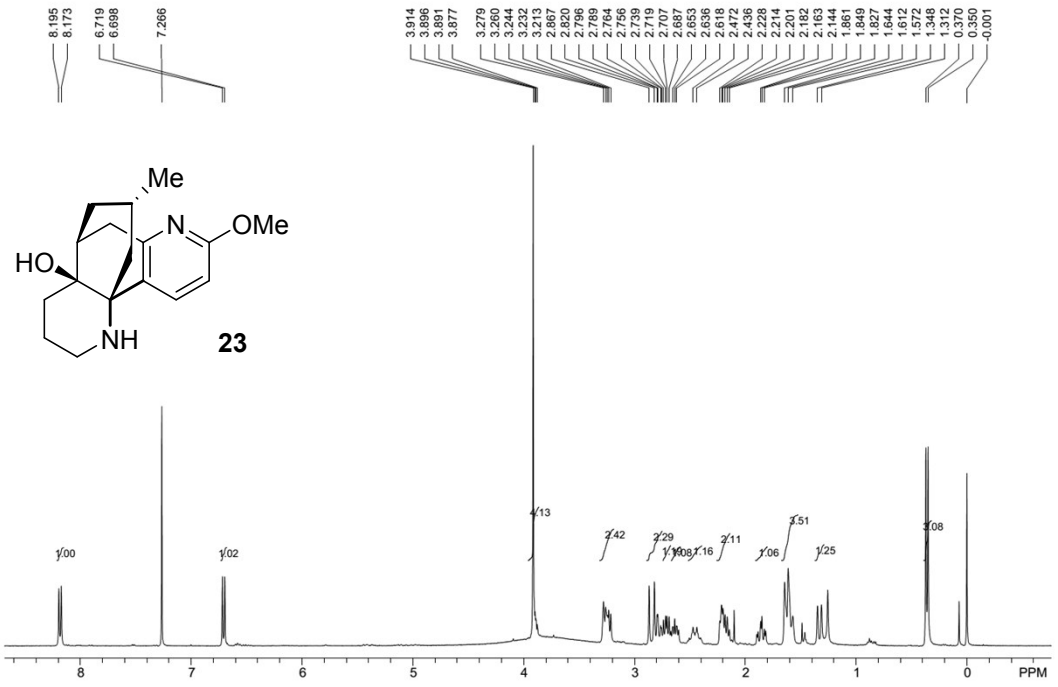
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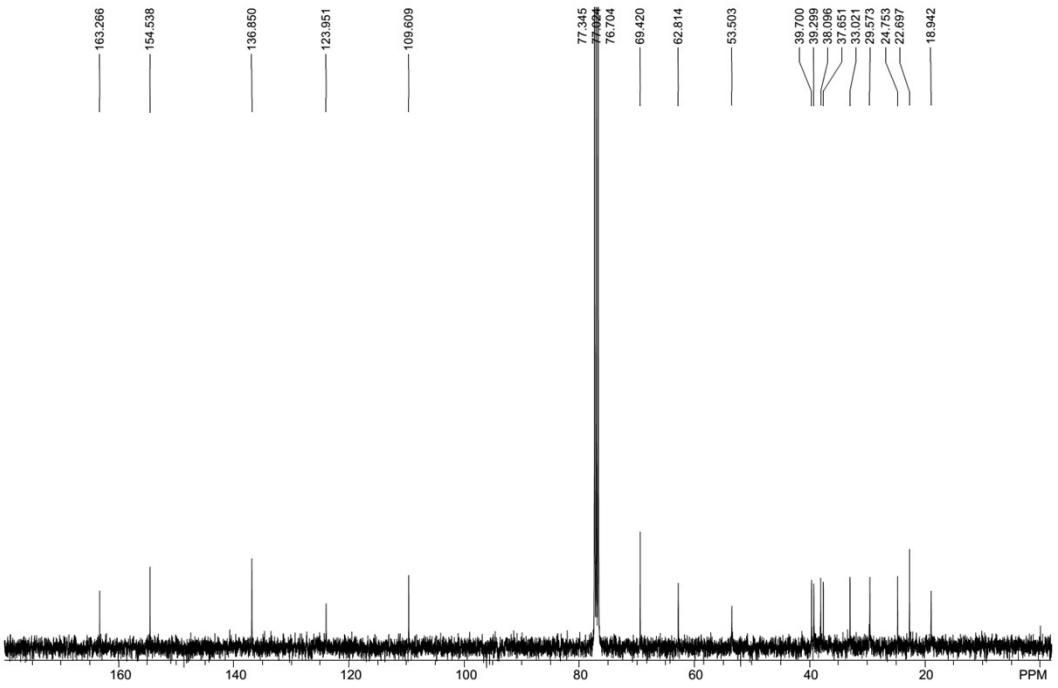
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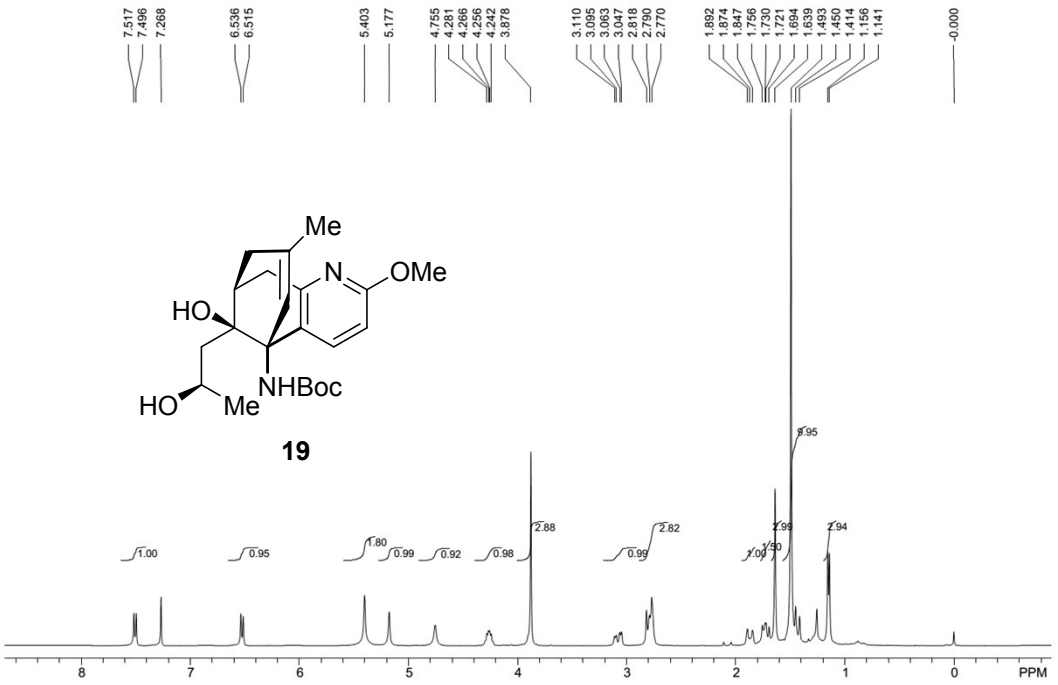
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NHBoc
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1.80
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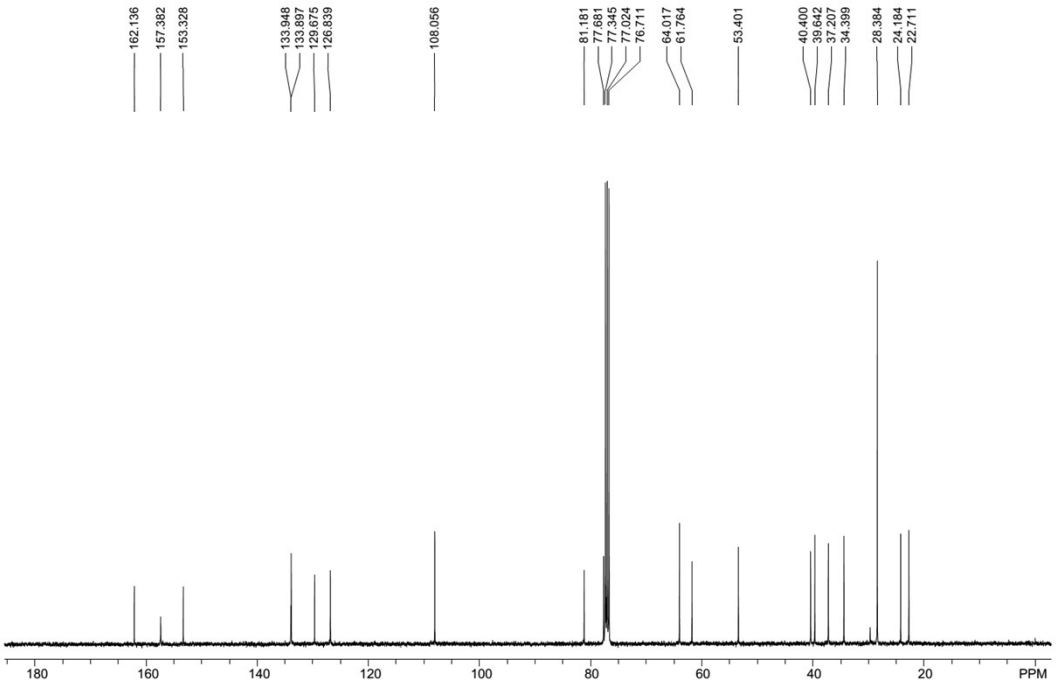
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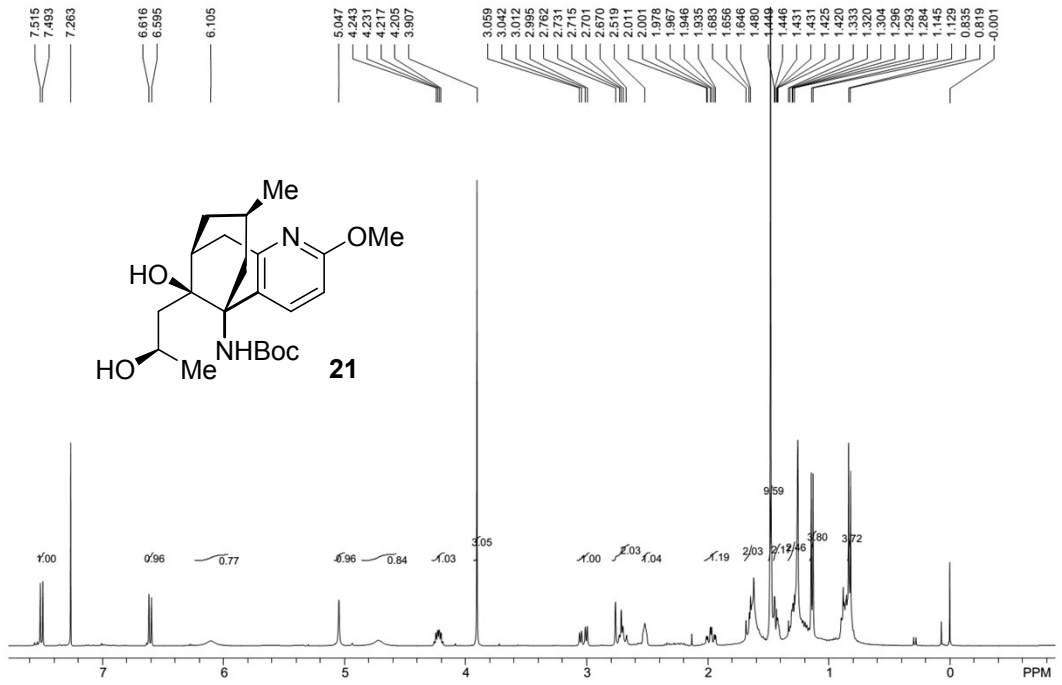
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NHBoc
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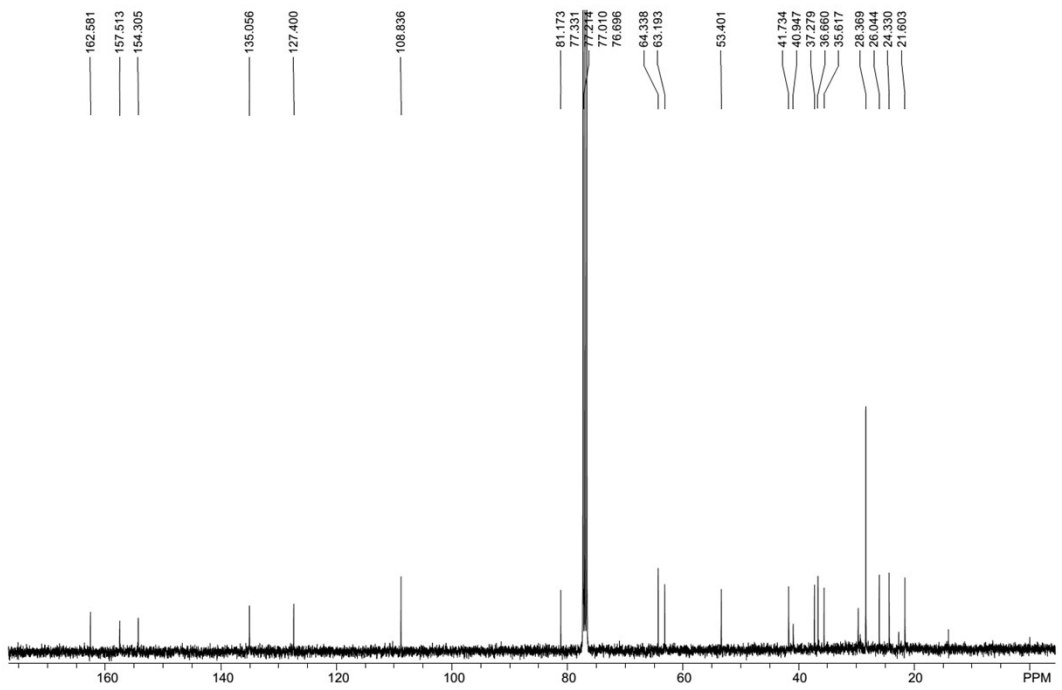
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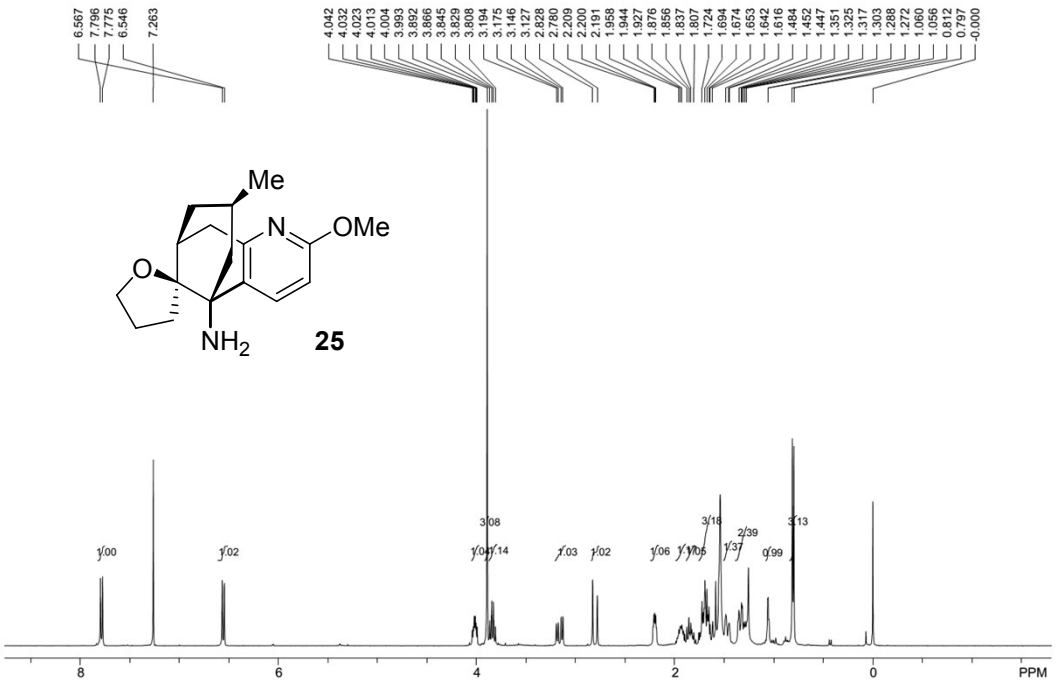
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-0.000
Me
N
OMe
O
NH2
25
1.00
1.02
3.08
1.04
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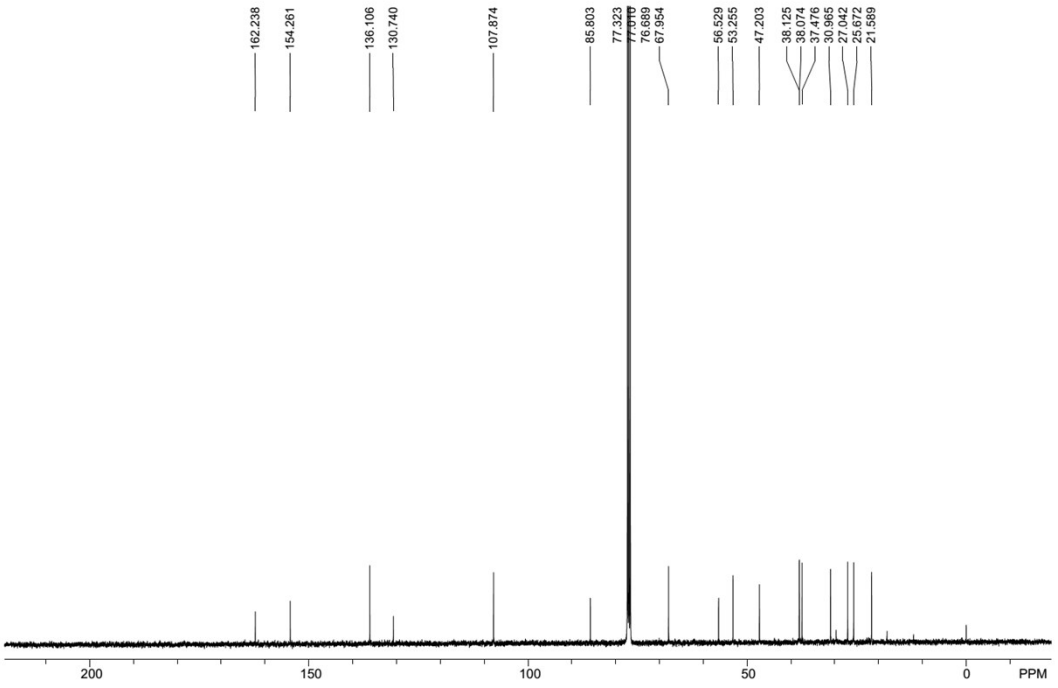
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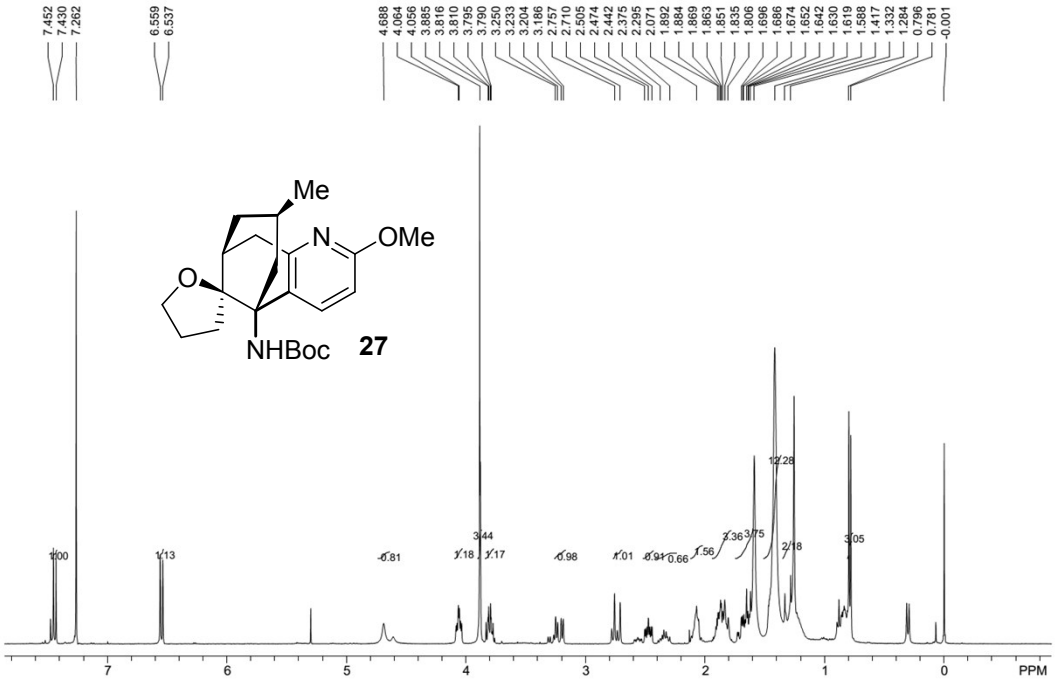
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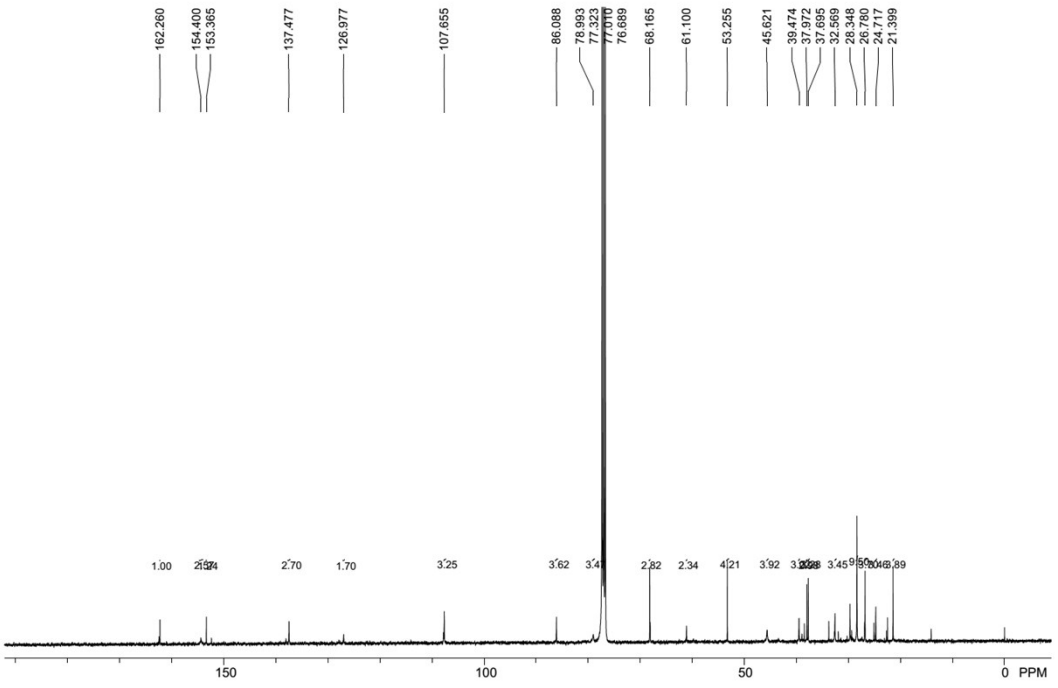
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