Supporting Information

for

An Efficient Total Synthesis of (-)-Huperzine A

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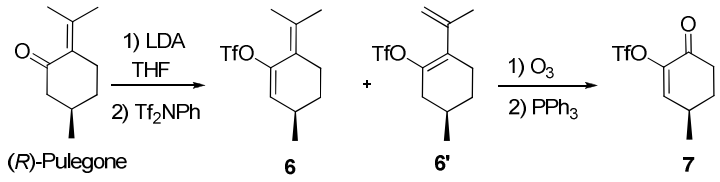
1. General Information

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.

2. Experimental Procedures and Spectral Data

*t*Bu-XPhos and 2-hydroxy-6-methylpyridine were purchased from Aldrich. (+)-(*R*)-Pulegone (92% purity) was purchased from Acros. $Pd_2(dba)_3$ was purchased from Alfa. Tf_2NPh [1], H_2NBoc [2] and bromide **5** [3,4] were prepared as described in literature.

Compound 7



To a solution of diisopropylamine (15.4 mL, 110 mmol) in THF (150 mL) was added *n*-butyllithium (2.5M in hexanes, 44 mL, 110 mmol) dropwise at 0 ^{o}C and the mixture was stirred at the temperature for 10 min before cooling down to -78 ^{o}C. (*R*)-Pulegone (16.5 g, 100 mmol, 92% purity) in THF (100 mL) was added dropwise over 20 min, and the solution was stirred for 30 min at -78 ^{o}C. Tf_2NPh (39.3 g, 110 mmol) in THF (200 mL) was added over 20 min, and then the mixture

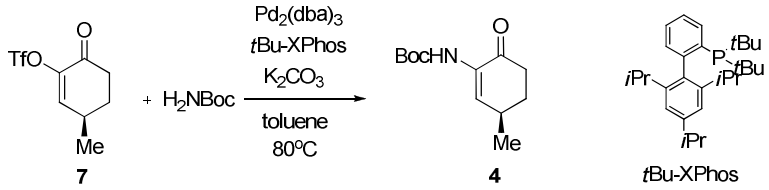
was allowed to warm to room temperature. A saturated solution of NH_4Cl was added and the mixture was extracted with CH_2Cl_2 for three times. The combined organic layers were dried over anhydrous Na_2SO_4 before the solvent was removed under reduced pressure. The residual was subjected to column chromatography on silica gel (Hexane) to give an inseparable mixture of **6** and **6'** (ca. 6 : 1) as a colorless oil (27.3 g).

The mixture was dissolved in CH_2Cl_2 (1440 mL) and MeOH (360 mL) before cooling down to -78 ^oC. The mixture was subjected to ozone until the solution color became blue. The mixture was then flushed with O_2 gas for 10 min; following this, PPh_3 (37.8 g, 144 mmol) was added and the mixture was stirred at r.t. 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 **7** (17.9 g) as a colorless oil in 69% yield from (*R*)-pulegone.

For **6**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.58 (d, *J* = 3.3 Hz, 1H), 2.53 (m, 2H), 2.23 (m, 1H), 1.93 (s, 3H), 1.87 (m, 1H), 1.78 (s, 3H), 1.28 (m, 1H), 1.08 (d, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ147.0, 131.5, 125.8, 123.3, 118.5 (q, *J* = 321 Hz), 31.0, 30.9, 27.6, 22.9, 22.4, 20.8; **LRMS** (EI): 284 (M^+).

For **7**: **$[\alpha]_D^{28}$** +44.8 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.75 (d, *J* = 2.6 Hz, 1H), 2.86 (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), 2.18 (m, 1H), 1.77 (m, 1H), 1.26 (d, *J* = 7.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 189.6, 144.2, 143.8, 118.6 (q, *J* = 319 Hz), 36.4, 31.3, 30.0, 19.9; **IR** (thin film): 2969, 2879, 1708, 1459, 1211, 1142, 1012, 905, 820, 606 cm^{-1}; **LRMS** (ESI): 281 $(M+Na)^+$; **HRMS** (ESI): calcd for $C_8H_9F_3NaO_4S$ $(M+Na)^+$: 281.0066, found: 281.0063.

Compound 4

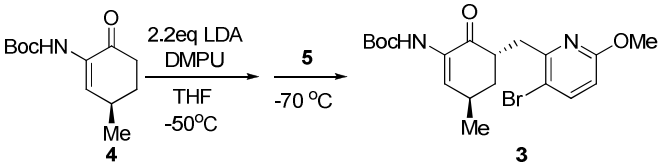


K_2CO_3 (15.0 g, 109 mmol) and *tert*-butylcarbamate (6.11 g, 51.2 mmol) were added to an oven-dried

flask charged with $Pd_2(dba)_3$ (995 mg, 1.09 mmol) and *t*Bu-XPhos (2.40 g, 5.65 mmol) under Ar. The flask was flushed with Ar and a solution of triflate **7** (11.2 g, 43.5 mmol) in toluene (220 mL) was added and the reaction was heated at 80 °C for 9 h. After cooling, 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 ketone **4** (8.92 g, 91%) as a colorless oil.

[α]$_D^{26}$ +22.9 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.23 (s, 1H), 7.10 (s, 1H), 2.69 (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), 2.06 (m, 1H), 1.63 (m, 1H), 1.47 (s, 9H), 1.18 (d, *J* = 7.0 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 193.9, 152.9, 132.9, 131.6, 80.3, 36.0, 30.6, 30.5, 28.3, 21.3; **IR** (thin film): 3401, 2975, 1725, 1677, 1510, 1351, 1231, 1158, 997, 870 cm^{-1}; **LRMS** (ESI): 248 $(M+Na)^+$; **HRMS** (ESI): calcd for $C_{12}H_{19}NNaO_3$ $(M+Na)^+$: 248.1257, found: 248.1266.

Compound 3

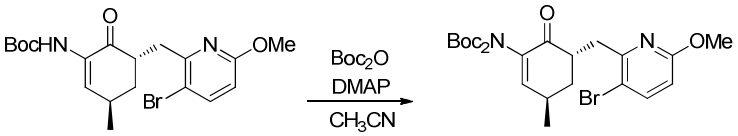


To a solution of diisopropylamine (20.0 mL, 142 mmol) in THF (100 mL) was added n-butyllithium (2.5M in hexanes, 57 mL, 142 mmol) dropwise at 0 °C and the mixture was stirred at the temperature for 10 min before cooling down to -50 °C. ketone **4** (12.8 g, 56.9 mmol) in THF (30 mL) was added dropwise over 10 min followed by adding DMPU (18.3 g, 142 mmol), and the solution was stirred for 20 min at -50 °C. Then the yellow mixture was cooled down to -70 °C and bromopyridine **5** (24.0g, 85.4 mmol) in THF (40 mL) was added over 10 min during which the reaction turned red. After addition, the mixture was stirred at -70 °C over 18 hours and the color turned back to yellow. It was then quenched with a saturated aq. solution of NH_4Cl (50 mL). The resulting mixture 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 **3** (18.1 g) in 75% yield (83% brsm) as a thick oil, along with recovered ketone **4** (1.27 g).

[α]$_D^{25}$ +22.5 (*c* = 0.6, $CHCl_3$); **^{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), 3.31 (m, 2H), 3.02 (m, 1H), 2.87 (m, 1H), 1.98 (m, 1H), 1.72 (m, 1H), 1.48 (s, 9H), 1.19 (d, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 195.5, 162.3, 154.2, 153.0, 142.4, 131.8, 130.8, 112.3, 110.3, 80.3, 53.5, 41.4, 36.5, 33.9, 28.3, 27.4, 20.0; **IR** (thin film): 3400, 2976, 1726, 1673, 1575, 1506, 1462, 1367, 1297, 1230, 1159, 880, 822, 758, 620 cm^{-1}; **LRMS** (ESI): 447 $(M+Na)^+$; **HRMS** (ESI): calcd for $C_{19}H_{25}BrN_2NaO_4$ $(M+Na)^+$: 447.0890, found: 447.0883.

Compound 8



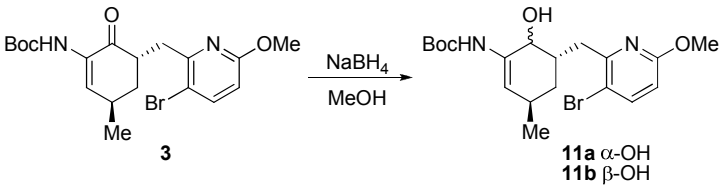
3 **8**

To a solution of carbamate **3** (1.35 g, 3.18 mmol) in anhydrous acetonitrile (13 mL) was added 4-(dimethylamino)pyridine (DMAP) (39 mg, 0.32 mmol) followed by di-*tert*-butyl dicarbonate (1.53 g, 7.02 mmol). The yellow solution was stirred under Ar at RT for 36 h. Solvent was removed under reduced pressure, then diethyl ether (150 mL) and water (100 mL) was added to the resultant residue. The organic layer was removed and the aqueous phase was extracted with diethyl ether for three times. The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified via flash chromatography on silica gel (Hexane / EtOAc = 10 / 1) to give enone **8** (1.44 g, 86%) as a colorless thick oil, along with recovered carbamate **3** (182 mg, 14%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, *J* = 8.7 Hz, 1H), 6.64 (d, *J* = 3.6 Hz, 1H), 6.50 (d, *J* = 8.7 Hz, 1H), 3.88 (s, 3H), 3.36 (m, 2H), 2.94 (m, 2H), 1.94 (m, 1H), 1.77 (m, 1H), 1.46 (s, 18H), 1.20 (d, *J* = 7.2 Hz, 3H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ 195.2, 162.4, 154.5, 150.9, 149.7, 142.5, 135.3, 112.3, 110.3, 82.6, 53.5, 42.3, 36.0, 33.8, 28.6, 27.9, 18.7; **IR** (thin film): 2977, 2932, 1797, 1757, 1693, 1576, 1460, 1368, 1276, 1156, 1115, 892, 854, 778, 736 cm^{-1}; **LRMS** (ESI): 547 $(M+Na)^+$; **HRMS**

(ESI): calcd for $C_{24}H_{33}BrN_2NaO_6$ $(M+Na)^+$: 547.1414, found: 547.1433.

Compound 11a and 11b (Data in red corresponding to a parallel set of experiments)



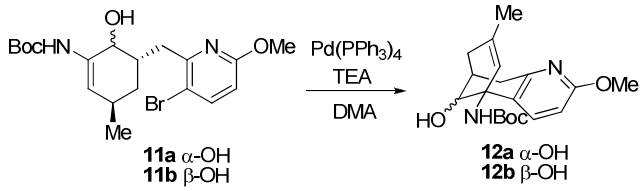
To a solution of carbamate **3** (418 mg, 0.983 mmol) (3.81 g, 8.96 mmol) in MeOH (5 mL) (40 mL) was added $NaBH_4$ (38 mg, 1.0 mmol) (338 mg, 8.96 mmol) at 0 ^oC and the mixture was stirred at the temperature for 10 min before quenched with saturated aq NH_4Cl (20 mL). The mixture was transferred to a separatory funnel and 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 product **11a** and **11b** (420 mg) (3.82 g) were found to be unstable towards purification by flash-column chromatography, so they were used for next step without further purification.

Analytically pure sample of the alcohol **11a** and **11b** were obtained by preparative thin layer chromatography.

For **11a**: **^{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), 2.46 (m, 2H), 1.87 (m, 1H), 1.45 (s, 9H), 1.33 (m, 1H), 1.04 (d, J = 7.0 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 162.4, 156.2, 153.4, 143.2, 132.6, 116.6, 112.1, 110.5, 79.8, 67.3, 53.9, 37.9, 35.1, 32.1, 28.4, 28.0, 20.9; **LRMS** (ESI): 449 $(M+Na)^+$; **HRMS** (ESI): calcd for $C_{19}H_{27}N_2O_4BrNa$ $(M+Na)^+$: 449.1046, found: 449.1041.

For **11b**: **^{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), 2.47 (m, 2H), 1.62 (m, 2H), 1.46 (s, 9H), 1.05 (d, J = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 162.4, 156.0, 153.7, 142.8, 133.1, 116.1, 112.3, 110.2, 80.0, 71.0, 53.8, 39.7, 37.4, 32.7, 28.4, 27.6, 21.6; **LRMS** (ESI): 449 $(M+Na)^+$; **HRMS** (ESI): calcd for $C_{19}H_{27}N_2O_4BrNa$ $(M+Na)^+$: 449.1046, found: 449.1049.

Compound 12a and 12b (Data in red corresponding to a parallel set of experiments)



11a α-OH
11b β-OH

12a α-OH
12b β-OH

To a solution of **11a** and **11b** (420 mg, 0.983 mmol) (3.82 g, 8.96 mmol) (assuming quantitative yield in the preceeding step) in DMA (200 mL) (1800 mL) was added $Pd(PPh_3)_4$ (114 mg, 0.0983 mmol) (1.03 g, 0.896 mmol) and TEA (544 μL, 3.93 mmol) (4.90 mL, 35.8 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 product **12a** and **12b** were used directly in the following step.

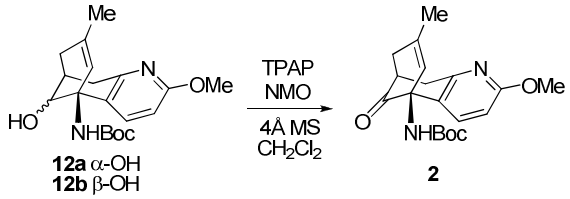
Analytically pure sample of the product **12a** and **12b** were obtained by flash-column chromatography.

For **12a**: **^{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), 2.65 (m, 1H), 2.51 (m, 2H), 2.02 (d, J = 18.1 Hz, 1H), 1.60 (s, 3H), 1.46 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 162.1, 157.1, 155.5, 134.6, 134.2, 127.6, 126.2, 107.3, 81.0, 74.3, 59.9, 53.4, 39.2, 36.3, 32.9, 28.3, 22.6; **IR** (thin film): 3320, 2975, 2924, 1687, 1593, 1474, 1288, 1161, 1095, 982, 879, 820, 755 cm^{-1}; **LRMS** (ESI): 347 $(M+H)^+$; **HRMS** (ESI): calcd for $C_{19}H_{27}N_2O_4$ $(M+H)^+$: 347.1965, found: 347.1967.

For **12b**: **^{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), 2.71 (m, 1H), 2.61 (m, 1H), 2.47 (br, 1H), 1.84 (d, J = 18.7 Hz, 1H), 1.64 (s, 3H), 1.40 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 162.1, 154.9, 152.8, 135.8, 134.2, 129.8, 124.9, 107.8, 80.2, 69.1, 58.7, 53.4, 40.3, 34.6, 32.4, 28.3, 23.0; **IR** (thin film): 3385, 2975, 2925, 1701, 1596, 1475, 1367, 1311, 1252, 1164, 1067, 1037, 824, 756 cm^{-1}; **LRMS** (ESI): 347 $(M+H)^+$; **HRMS** (ESI): calcd

for $C_{19}H_{27}N_2O_4$ $(M+H)^+$: 347.1965, found: 347.1970.

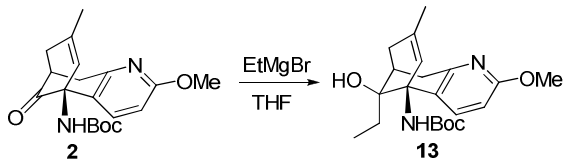
Compound 2 (Data in red corresponding to a parallel set of experiments)



To a solution of unpurified **12a** and **12b** (0.983 mmol, assuming quantitative yield in the preceeding step) (8.96 mmol) in dichloromethane (7 mL) (50 mL) was added NMO (173 mg, 1.47 mmol) (1.57 g, 13.4 mmol), TPAP (35 mg, 0.10 mmol) (315mg, 0.896 mmol), 4Å molecular sieve (50 mg) (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 **2** (213 mg, 63% from **3**) (1.88 g, 61% from **3**) as a white solid.

[α]$_D^{27}$ +126.3 (c = 1.4, $CHCl_3$); **^{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, 1H), 5.59 (br, 1H), 3.88 (s, 3H), 3.50 (dd, J_1 = 18.1 Hz, J_2 = 7.6 Hz, 1H), 3.15 (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); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 206.2, 162.7, 155.3, 151.2, 135.9, 134.7, 129.6, 127.1, 109.0, 79.9, 61.4, 53.4, 43.2, 42.1, 41.0, 28.3, 22.2; **IR** (thin film): 3425, 2970, 1735, 1709, 1596, 1476, 1348, 1311, 1248, 1166, 1031, 836, 768, cm^{-1}; **LRMS** (ESI): 345 $(M+H)^+$; **HRMS** (ESI): calcd for $C_{19}H_{25}N_2O_4$ $(M+H)^+$: 345.1809, found: 345.1822.

Compound 13

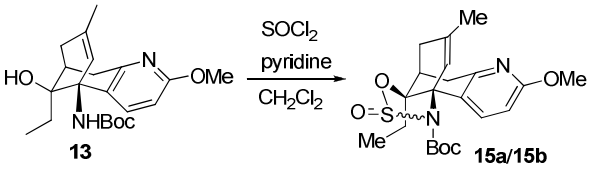


A solution of **2** (320 mg, 0.930 mmol) in THF (1 mL) was added to a solution of EtMgBr (2.0 mL, 1.0 M in THF) slowly over 2.5 h at -25°C. After addition, the mixture was stirred at this temperature

for 2 h before quenched with saturated aq NH_4Cl (10 mL). The mixture was transferred to a separatory funnel and 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 residual was purified by flash chromatography (Hexane / EtOAc = 15 / 1) to afford alcohol **13** (258 mg, 74%, dr = 7/1) as a white solid, and a mixture of **12a** and **12b** (63 mg, 20%).

For **13**: $[\alpha]_D^{26}$ -14.5 (*c* = 1.4, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.52 (d, *J* = 8.6 Hz, 1H), 6.50 (d, *J* = 8.6 Hz, 1H), 6.49 (s, 1H), 4.95 (s, 1H), 4.27 (br, 1H), 3.88 (s, 3H), 3.11 (dd, J_1 = 19.0 Hz, J_2 = 7.2 Hz, 1H), 2.73 (m, 2H), 2.58 (t, *J* = 7.0 Hz, 1H), 1.84 (d, *J* = 18.3 Hz, 1H), 1.66 (m, 1H), 1.63 (s, 3H), 1.48 (s, 9H), 1.38 (m, 1H), 1.04 (t, *J* = 7.5 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 161.9, 156.9, 154.0, 134.1, 133.6, 130.4, 127.6, 107.7, 80.6, 75.8, 62.1, 53.4, 39.7, 37.2, 33.6, 28.4, 26.3, 22.8, 7.4; **IR** (thin film): 3285, 2976, 2935, 1683, 1597, 1578, 1529, 1476, 1425, 1365, 1309, 1285, 1254, 1169, 1090, 1041, 987, 916, 825, 667, 623 cm^{-1}; **LRMS** (ESI): 397 $(M+Na)^+$; **HRMS** (ESI): calcd for $C_{21}H_{30}N_2Na_1O_4$ $(M+Na)^+$: 397.2098, found: 397.2115.

Compound 15a and 15b



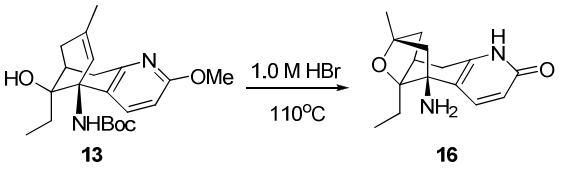
Pyridine (194 μL, 2.41 mmol) was added to a solution of alcohol **13** (45 mg, 0.12 mmol) in CH_2Cl_2 (1 mL), followed by adding $SOCl_2$ (43 μL, 0.59 mmol). Then the solution was stirred at room temperature for 4 h, before quenched by water (10 mL). The mixture was transferred to a separatory funnel and 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 residual was purified by flash chromatography (Hexane / EtOAc = 50 / 1) to afford imides **15a** and **15b** (47 mg, 92%) as a mixture in 3/1 ratio.

For **15a**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.77 (d, *J* = 8.6 Hz, 1H), 6.50 (d, *J* = 8.6 Hz, 1H), 5.81 (s, 1H), 3.86 (s, 3H), 3.24 (q, *J* = 9.4 Hz, 1H), 2.79 (m, 2H), 2.53 (d, *J* = 17.2 Hz, 1H), 2.08 (m, 1H), 1.91 (dd, J_1 = 17.4 Hz, J_2 = 1.7 Hz, 1H), 1.68 (s, 3H), 1.60 (s, 9H), 1.09 (m, 1H), 0.99 (t, *J* = 7.1 Hz,

3H); **LRMS** (ESI): 421 $(M+H)^+$; **HRMS** (ESI): calcd for $C_{21}H_{29}N_2O_5S_1$ $(M+H)^+$: 421.1792, found: 421.1795.

For **15b**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 8.6 Hz, 1H), 6.48 (d, *J* = 8.6 Hz, 1H), 5.93 (s, 1H), 3.86 (s, 3H), 3.21 (q, *J* = 9.5 Hz, 1H), 2.80 (m, 2H), 2.64 (d, *J* = 17.2 Hz, 1H), 1.96 (dd, J_1 = 17.0 Hz, J_2 = 1.5 Hz, 1H), 1.71 (s, 3H), 1.60 (s, 9H), 1.46 (m, 1H), 1.09 (m, 1H), 0.92 (t, *J* = 7.4 Hz, 3H); **LRMS** (ESI): 421 $(M+H)^+$; **HRMS** (ESI): calcd for $C_{21}H_{29}N_2O_5S_1$ $(M+H)^+$: 421.1792, found: 421.1795

Compound 16

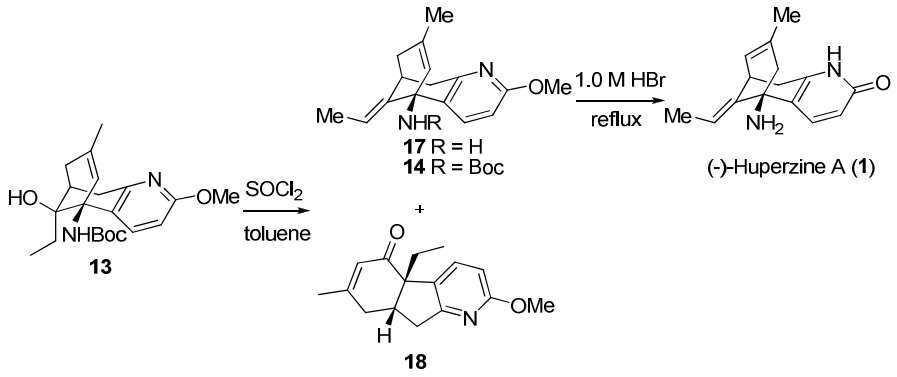


13 **16**

Alcohol **13** (36 mg, 0.096 mmol) was dissolved in 1.0 M HBr (1 mL), and was refluxed for 10 h. After cooling down to room temperature, a solution of saturated aq $NaHCO_3$ was added, and the mixture was extracted with dichloromethane for 3 times. After dried over sodium sulfate, the solution was concentrated under reduced pressure, and the residual was purified by flash chromatography (EtOAc / MeOH = 10 / 1) to afford **16** (25 mg, 100%) as a white solid.

[α]$_D^{28}$ -84.3 (*c* = 0.4, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.98 (d, *J* = 9.5 Hz, 1H), 6.45 (d, *J* = 9.5 Hz, 1H), 2.87 (m, 2H), 2.65 (m, 1H), 2.00 (td, J_1 = 11.9 Hz, J_2 = 2.9 Hz, 1H), 1.91 (m, 1H), 1.86 (d, *J* = 12.2 Hz, 1H), 1.60 (dd, J_1 = 12.2 Hz, J_2 = 2.7 Hz, 1H), 1.42 (m, 1H), 1.39 (s, 3H), 1.32 (dd, J_1 = 12.0 Hz, J_2 = 5.8 Hz, 1H), 1.00 (t, *J* = 7.5 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 165.2, 141.5, 139.6, 120.8, 117.8, 86.6, 81.1, 61.5, 58.4, 43.0, 35.7, 28.1, 21.0, 20.9, 8.1; **IR** (thin film): 3371, 3284, 3129, 2968, 1660, 1623, 1556, 1463, 1385, 1335, 1255, 1182, 1129, 965, 943, 835, 754, 674, 625, 605, 521cm^{-1}; **LRMS** (ESI): 261 $(M+H)^+$; **HRMS** (ESI): calcd for $C_{15}H_{21}N_2O_2$ $(M+H)^+$: 261.1598, found: 261.1598.

(-)-Huperzina A (1)



Alcohol **13** (62 mg, 0.17 mmol) was dissolved in toluene (3 mL), and $SOCl_2$ (36 μL, 0.50 mmol) was added. The mixture was stirred at room temperature for 36 h before quenched with saturated aq $NaHCO_3$ (10 mL). The mixture was transferred to a separatory funnel and 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 mixture of crude product **14**, **17** and **18** was used directly in the following step. (An analytically pure sample of the product **17** and **18** was obtained by flash-column chromatography.)

The residual was dissolved in 1.0 M HBr (1 mL) and refluxed at 110°C for 10 h. After cooling down to room temperature, a solution of saturated aq $NaHCO_3$ was added, and the mixture was extracted with dichloromethane for 3 times. After dried over sodium sulfate, the solution was concentrated under reduced pressure, and the residual was purified by flash chromatography (EtOAc / MeOH = 10 / 1) to afford **1** (23 mg, 57% from **13**) as a white solid.

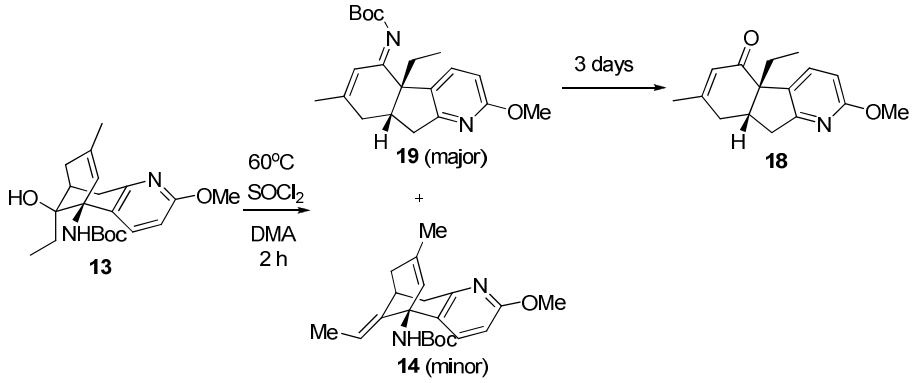
For **17**: $[\alpha]_D^{28}$ 108.8 (*c* = 0.6, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.84 (d, *J* = 8.5 Hz, 1H), 6.49 (d, *J* = 8.5 Hz, 1H), 5.49 (q, *J* = 6.7 Hz, 1H), 5.37 (s, 1H), 3.86 (s, 3H), 3.58 (t, *J* = 7.4 Hz, 1H), 3.27 (dd, J_1 = 18.5 Hz, J_2 = 8.4 Hz, 1H), 2.83 (d, *J* = 18.5 Hz, 1H), 2.46 (dd, J_1 = 17.6 Hz, J_2 = 6.1 Hz, 1H), 2.08 (d, *J* = 17.7 Hz, 1H), 1.73 (d, *J* = 6.7 Hz, 3H), 1.58 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 162.0, 154.7, 143.5, 133.9, 133.8, 133.6, 132.7, 110.3, 107.1, 55.2, 53.3, 41.6, 41.5, 29.4, 22.6, 12.2; **IR** (thin film): 3373, 2931, 2857, 1593, 1577, 1472, 1423, 1308, 1246, 1191, 1123, 1034, 923, 904, 825, 774, 732, 656 cm^{-1}; **LRMS** (ESI): 257 $(M+H)^+$; **HRMS** (ESI): calcd for $C_{16}H_{21}N_2O$ $(M+H)^+$: 257.1648, found: 257.1637.

For **18**: $[\alpha]_D^{27}$ -47.3 (*c* = 0.4, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.09 (d, *J* = 8.6 Hz, 1H), 6.63 (d, *J* = 8.6 Hz, 1H), 5.27 (s, 1H), 3.99 (s, 1H), 3.14 (dd, J_1 = 17.0 Hz, J_2 = 6.0 Hz, 1H), 2.92 (dd, J_1 =

17.0 Hz, J_2 = 3.9 Hz, 1H), 2.80 (m, 1H), 2.50 (dd, J_1 = 16.0 Hz, J_2 = 8.5 Hz, 1H), 2.07 (m, 1H), 2.00 (m, 1H), 1.70 (m, 1H), 1.68 (s, 3H), 0.89 (t, J = 7.5 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 199.9, 166.5, 161.6, 141.9, 138.1, 130.2, 124.1, 109.7, 62.1, 53.9, 43.1, 39.7, 34.0, 30.2, 16.7, 9.3; **IR** (thin film): 2963, 2917, 2849, 1667, 1594, 1574, 1479, 1416, 1349, 1325, 1267, 1095, 944, 870, 836, 792 cm^{-1}; **LRMS** (ESI): 280 $(M+Na)^+$; **HRMS** (ESI): calcd for $C_{16}H_{19}N_1Na_1O_2$ $(M+Na)^+$: 280.1308, found: 280.1302.

For huperzine A (**1**): **[α]**$_D^{28}$ -144 (c = 1.10, $CHCl_3$), lit. **[α]**$_D^{25}$ -150 (c = 0.12, $CHCl_3$)[5]; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 13.0 (br s, 1H), 7.90 (d, J = 9.4 Hz, 1H), 6.41 (d, J = 9.4 Hz, 1H), 5.49 (q, J = 6.8 Hz, 1H), 5.41 (d, J = 4.6 Hz, 1H), 3.61 (m, 1H), 2.89 (dd, J_1 = 16.9 Hz, J_2 = 5.1 Hz, 1H), 2.74 (dd, J_1 = 16.9 Hz, J_2 = 1.3 Hz, 1H), 2.13 (m, 2H), 1.68 (d, J = 6.8 Hz, 3H), 1.55 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 165.2, 142.9, 142.5, 140.3, 134.2, 124.3, 122.8, 117.2, 111.3, 54.3, 49.2, 35.4, 32.9, 22.6, 12.3; **IR** (thin film): 2927, 1656, 1614, 1554, 1459, 1378, 1305, 1120, 932, 834, 754, 662, 520 cm^{-1}; **LRMS** (ESI): 243 $(M+H)^+$; **HRMS** (ESI): calcd for $C_{15}H_{19}N_2O$ $(M+H)^+$: 243.1492, found: 243.1483.

Compound 19

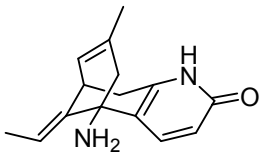


Alcohol **13** (18 mg, 0.048 mmol) was dissolved in DMA (1 mL), and $SOCl_2$ (14 μL, 0.19 mmol) was added. The mixture was stirred at 60°C for 2 h followed by stirred at RT for 3 days before being quenched with saturated aq $NaHCO_3$ (10 mL). The mixture was diluted with EtOAc, and washed with water for 3 times, then the organic layer was dried over sodium sulfate. The dried solution was filtered and concentrated under reduced pressure. The residual was purified by flash chromatography (Hexane / EtOAc = 30 / 1) to afford enone **18** (6.3 mg, 51%) as a white solid (55% as determined by

crude ^{1}H NMR). [If the reaction was heated for 2 h and then quenched, compound **19** could be isolated, which is highly liable to hydrolysis to give **18** even in $CDCl_3$.]

For **19**: **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.93 (d, J = 8.6 Hz, 1H), 6.57 (d, J = 8.6 Hz, 1H), 5.45 (s, 1H), 3.96 (s, 3H), 2.95 (dd, J_1 = 15.8 Hz, J_2 = 5.4 Hz, 1H), 2.78 (dd, J_1 = 15.8 Hz, J_2 = 6.7 Hz, 1H), 2.57 (m, 2H), 1.92 (m, 2H), 1.70 (s, 3H), 1.66 (m, 1H), 1.51 (s, 9H), 0.87 (t, J = 7.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) (mixed with minor amount of **19**): δ 169.3, 165.3, 161.9, 159.0, 141.1, 137.9, 129.2, 122.9, 108.8, 81.5, 61.6, 53.7, 42.9, 40.8, 36.0, 32.1, 28.1, 16.7, 9.3; **LRMS** (ESI): 357 $(M+H)^+$;

Comparison of NMR Data of Synthetic and Natural (−)-Huperzine A (**1**)



(-)-Huperzine A (**1**)

	^{1}H NMR Synthetic **1** (400 MHz, $CDCl_3$)	^{1}H NMR Natural **1*** (100 MHz, $CDCl_3$)	^{13}C NMR Synthetic **1** (100 MHz, $CDCl_3$)	^{13}C NMR Natural **1*** (22.63 MHz, $CDCl_3$)
1	13.00 (br s, 1H)	13.20 (bs, 1H)	165.2	165.5
2	7.90 (d, J = 9.4 Hz, 1H)	7.84 (d, J = 9 Hz, 1H)	142.9	143.3
3	6.41 (d, J = 9.4 Hz, 1H)	6.38 (d, J = 9 Hz, 1H)	142.5	142.6
4	5.49 (q, J = 6.8 Hz, 1H)	5.46 (q, J = 7 Hz, 1H)	140.3	140.2
5	5.41 (d, J = 4.6 Hz, 1H)	5.38 (d, J = 5 Hz, 1H)	134.2	134.1
6	3.61 (m, 1H)	3.56 (m, 1H)	124.3	124.4
7	2.89 (dd, J_1 = 16.9 Hz, J_2 = 5.1 Hz, 1H)	2.76 (AB of ABX, J_1 = 16 Hz, J_2 = 3 Hz, $J_3 \approx 0$ Hz, 2H)	122.8	123.0
8	2.74 (dd, J_1 = 16.9 Hz, J_2 = 1.3 Hz, 1H)		117.2	117.0
9	2.13 (m, 2H)	2.12 (s, 2H)	111.3	111.2
10	1.68 (d, J = 6.8 Hz, 3H)	1.62 (d, J = 7 Hz, 3H)	54.3	54.4
11	1.55 (s, 3H)	1.46 (s, 3H)	49.2	49.3
12			35.4	35.2
13			32.9	33.0
14			22.6	22.6
15			12.3	12.3

* Data for natural (-)-huperzine A (**1**) were obtained from the following reference: J.-S. Liu, Y.-L. Zhu, C.-M. Yu, Y.-Z. Zhou, Y.-T. Han, F.-W. Wu, B.-F. Qi, *Can J. Chem.* **1986**, *64*, 837.

3. References

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[2] Y. Tsuzuki, K. Chiba, K. Mizuno, K. Tomita, K. Suzuki, *Tetrahedron: Asymmetry* **2001**, *12*, 2989.

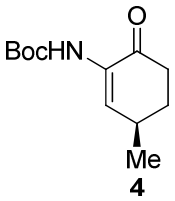
[3] A. Haudrechy, C. Chassaing, C. Richeb, Y. Langlois, *Tetrahedron* **2000**, *56*, 3181.

[4] S. A. Kelly, Y. Foricher, J. Mann, J. M. Bentley, *Org.Biomol.Chem*. **2003**, *1*, 2865.

[5] F. Yamada, A. P. Kozikowski, E. R. Reddy, Y. P. Pang, J. H. Miller, M. McKinney, *J. Am. Chem. Soc.* 1991, **113**, 4695.

4. Chiral HPLC Chromatogram

HPLC trace of racemic ketone **4**



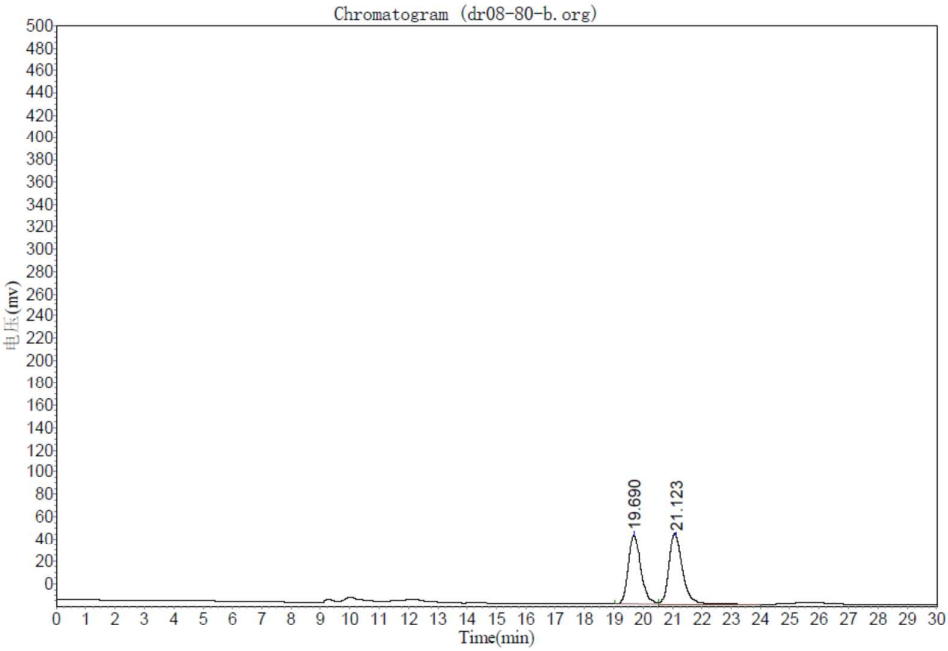
4

rac ketone 4

Company: sioc
Date/Time: 2012-02-08,16:29:17
Data File: D:\dr\buchwald product\dr08-80-b.org
Method File: D:\HZT\Method\HZT AD-H 90-10 1.0 214.mtd

Analyst: dr
Date/Time: 2012-06-26,8:48:34
Quantification: Area/Area%

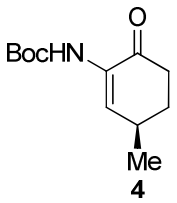
Sample Description:
AD-H, hex/iPrOH = 99/1, 224nm, 0.3mL/min



Results

Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		19.690	61462.746	1803928.500	47.4318
2		21.123	62722.906	1999278.875	52.5682
Total			124185.652	3803207.375	100.0000

HPLC trace of enantioenriched ketone **4**



4

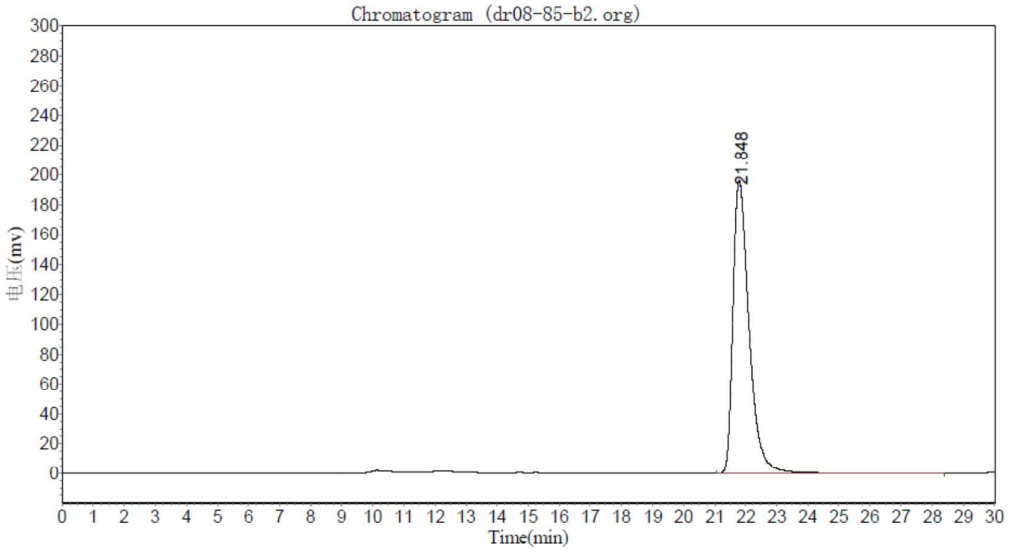
ketone 4

Company: sioc
Date/Time: 2012-02-11,18:56:02
Data File: D:\dr\buchwald product\dr08-85-b2.org
Method File: D:\HZT\Method\HZT AD-H 90-10 1.0 214.mtd

Analyst: dr
Date/Time: 2012-06-26,8:58:21
Quantification: Area/Area%

Type of Instrument: LC Gradient:High Presure Detector:UV

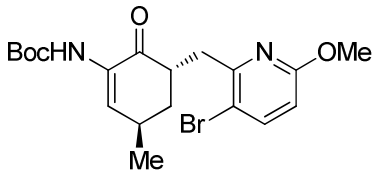
Sample Description:
AD-H ;hex/iPrOH = 99/1, 224nm, 0.3ml/min



Results

Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		21.848	194337.938	7161515.500	100.0000
Total			194337.938	7161515.500	100.0000

HPLC trace of racemic carbamate **3**



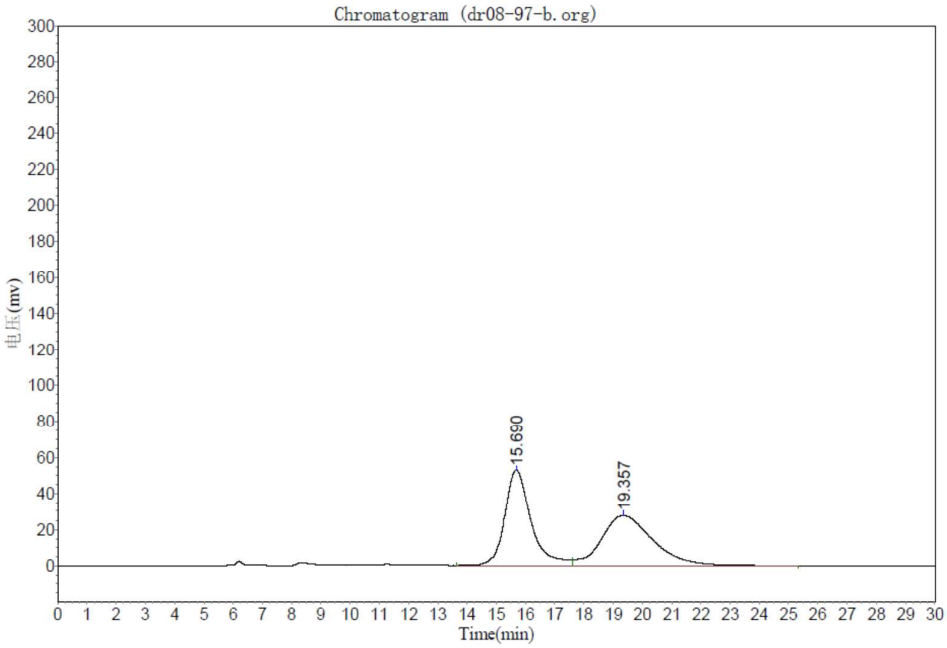
3

rac carbamate 3

Company: sioc
Date/Time: 2012-03-26, 18:28:08
Data File: D:\dr\alkylation\dr08-97-b.org
Method File: D:\HZT\Method\HZT AD-H 90-10 1.0 214.mtd

Analyst: dr
Date/Time: 2012-06-25, 19:45:14
Quantification: Area/Area%

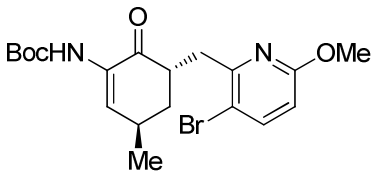
Sample Description:
AS-H, hex/iPrOH = 99/1, 214nm, 0.5mL/min



Results

Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		15.690	52728.965	3287989.000	49.2557
2		19.357	27640.625	3387352.750	50.7443
Total			80369.590	6675341.750	100.0000

HPLC trace of enantioenriched carbamate **3**



3

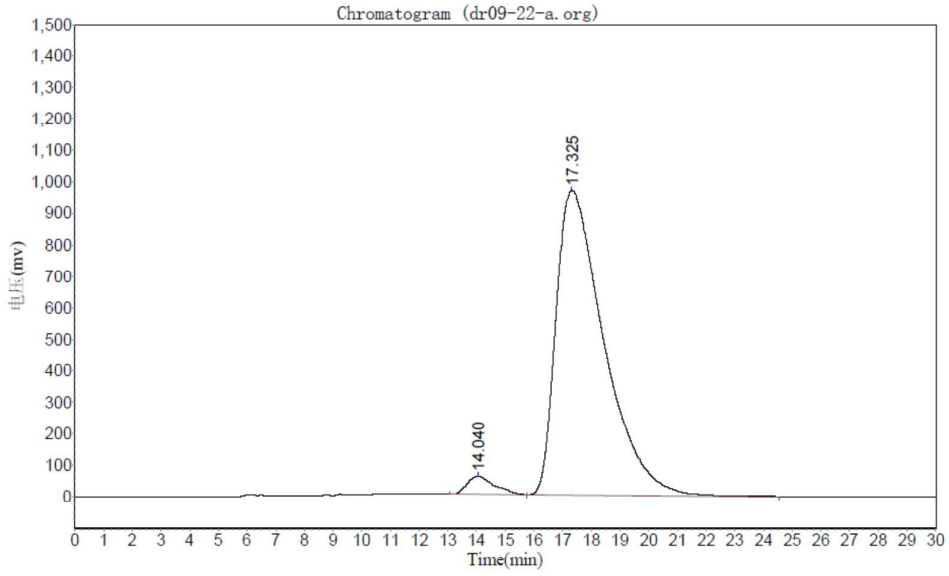
carbamate 3

Date/Time: 2012-03-28,9:54:18
Data File: D:\dr\alkylation\dr09-22-a.org
Method File: D:\HZT\Method\HZT AD-H 90-10 1.0 214.mtd

Analyst: dr
Date/Time: 2012-06-25,19:42:16
Quantification: Area/Area%

Type of Instrument: LC Gradient:High Presure Detector:UV

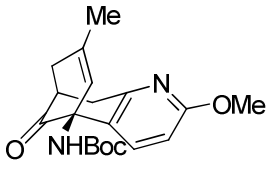
Sample Description:
AS-H; n-Hexane/iPrOH = 99/1; 0.5mL/min; 214nm



Results

Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		14.040	55588.602	3632341.250	3.1517
2		17.325	968168.188	111618200.000	96.8483
Total			1023756.789	115250541.250	100.0000

HPLC trace of racemic ketone **2**



2

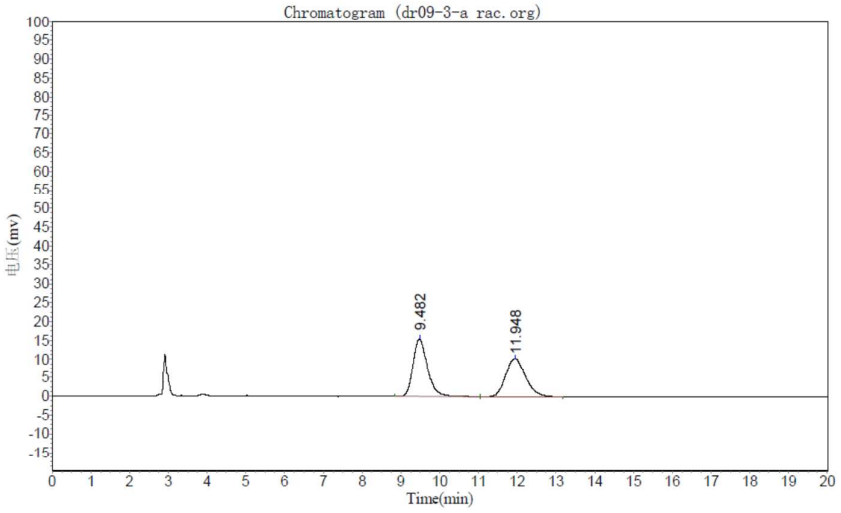
rac ketone 2

Date/Time: 2012-03-03,22:09:15
Data File: D:\dr\Ley\dr09-3-a rac.org
Method File: D:\HZT\Method\HZT AD-H 99-1 1.0 254.mtd

Analyst: dr
Date/Time: 2012-05-29,16:51:19
Quantification: Area/Area%

Type of Instrument: LC Gradient:High Presure Detector:UV

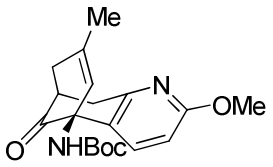
Sample Description:
OD-H; n-Hexane/iPrOH = 95/5; 1.0mL/min; 214nm



Results

Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		9.482	15504.228	400533.094	52.3916
2		11.948	10316.484	363965.813	47.6084
Total			25820.712	764498.906	100.0000

HPLC trace of enantioenriched ketone **2**



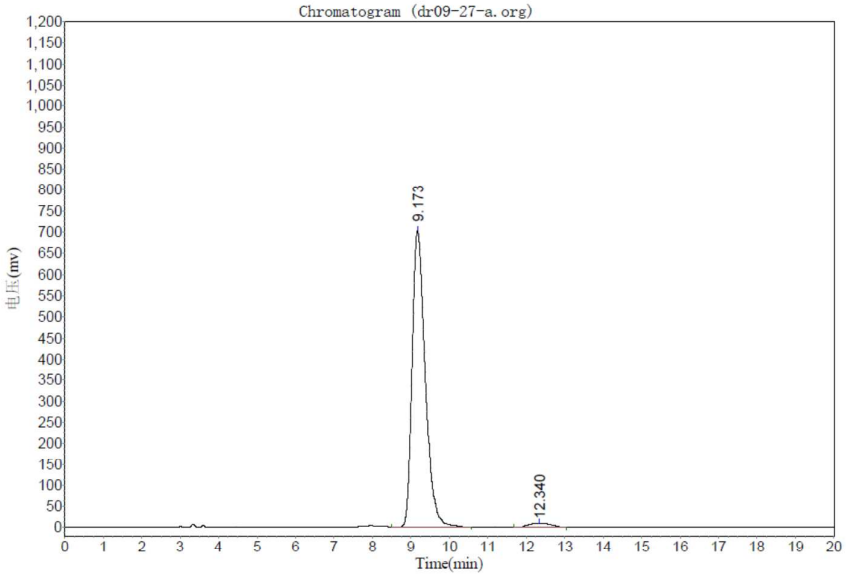
2

ketone 2

Company: sioc
Date/Time: 2012-4-5, 19:04:28
Data File: D:\dr\Ley\dr09-27-a.org
Method File: D:\HZT\Method\HZT AD-H 99-1 1.0 254.mtd

Analyst: dr
Date/Time: 2012-5-29, 16:59:53
Quantification: Area/Area%

Sample Description:
OD-H, Hex/iPrOH = 95/5, 214nm, 1.0mL/min



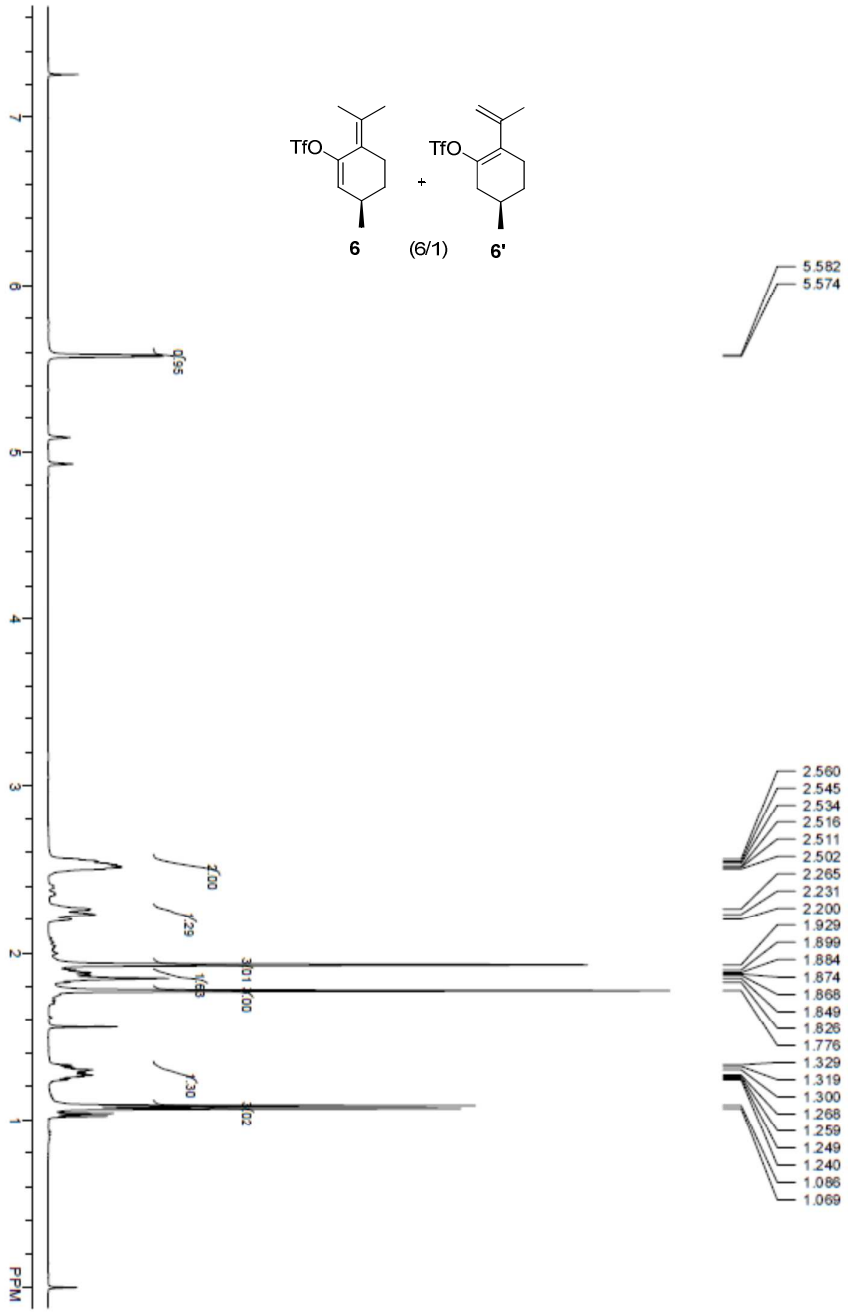
Results

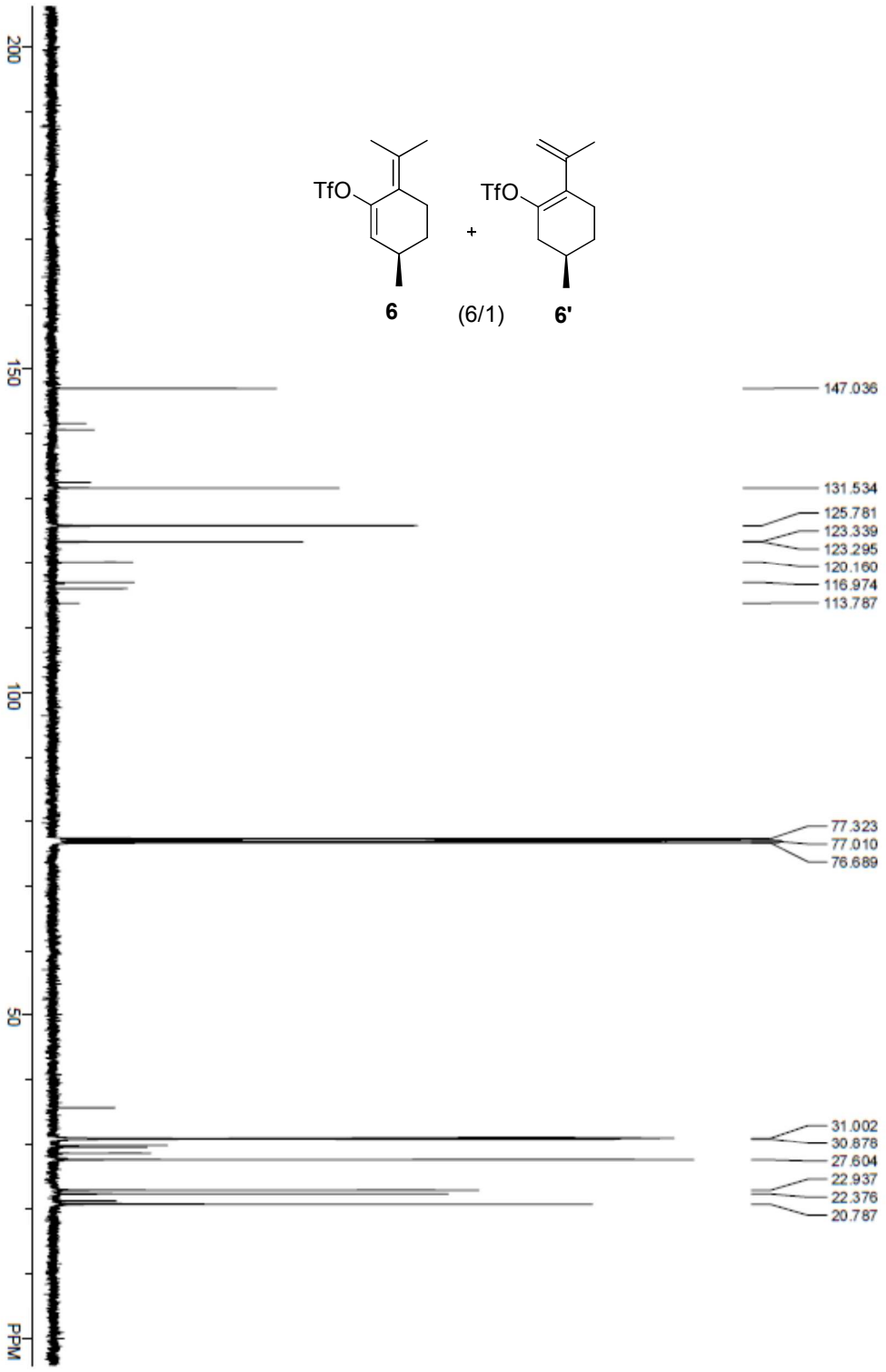
Peak No.	Peak ID	Ret Time	Height	Area	Conc.
1		9.173	702447.875	16578014.000	97.9118
2		12.340	9875.574	353569.156	2.0882
Total			712323.449	16931583.156	100.0000

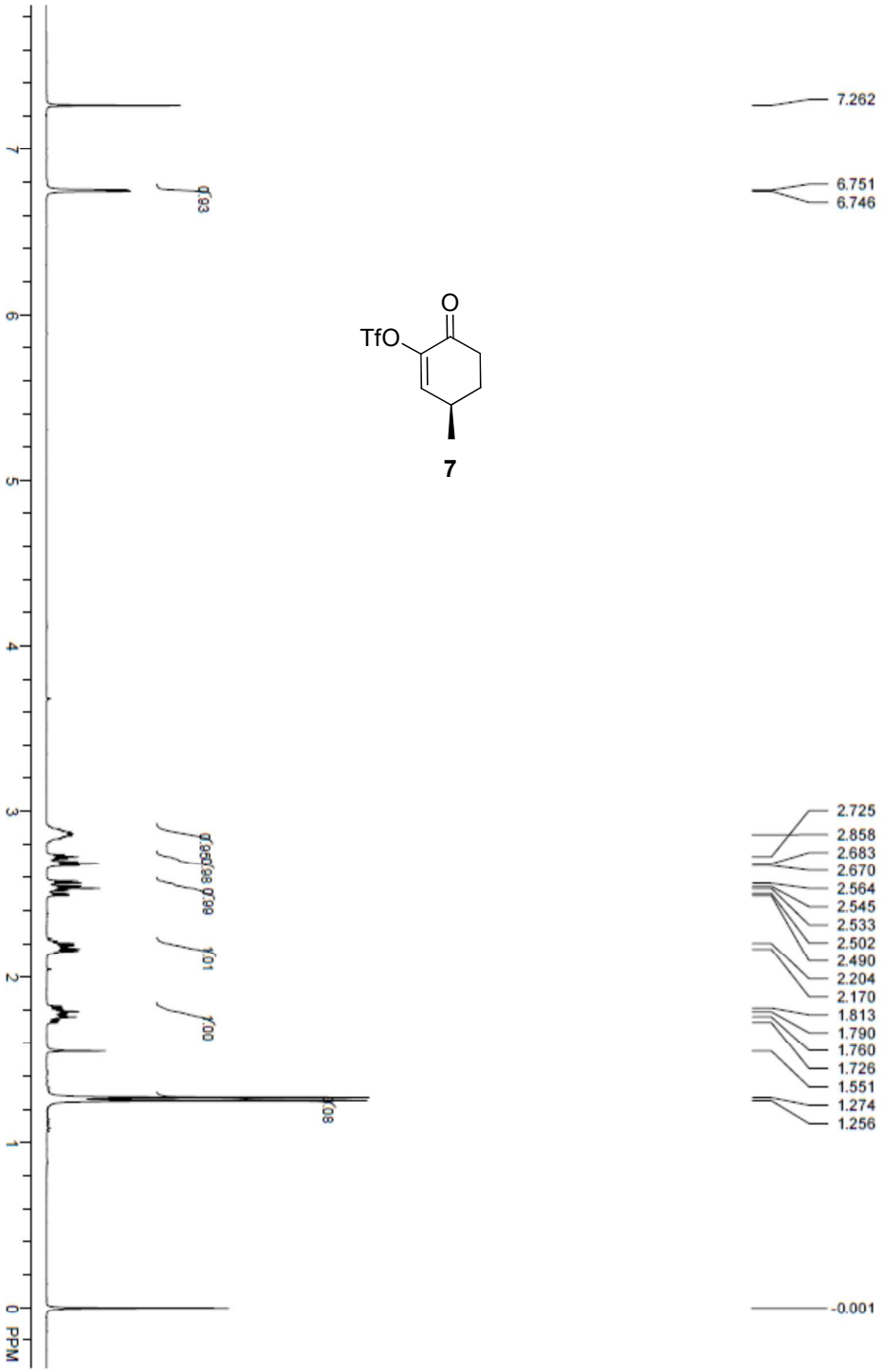
System Evaluation

Peak No.	Peak ID	Ret. Time	Half-Peak Width	Theoretical levels	Resolution	Tail Factor	Asymmetry
1		9.173	0.360	3603.692	0.000	1.378	1.643
2		12.340	0.582	2503.511	3.381	1.162	1.255

5. NMR Spectra




TfO
TfO
+
6
(6/1)
6'
200
150
100
50
PPM
147.036
131.534
125.781
123.339
123.295
120.160
116.974
113.787
77.323
77.010
76.689
31.002
30.878
27.604
22.937
22.376
20.787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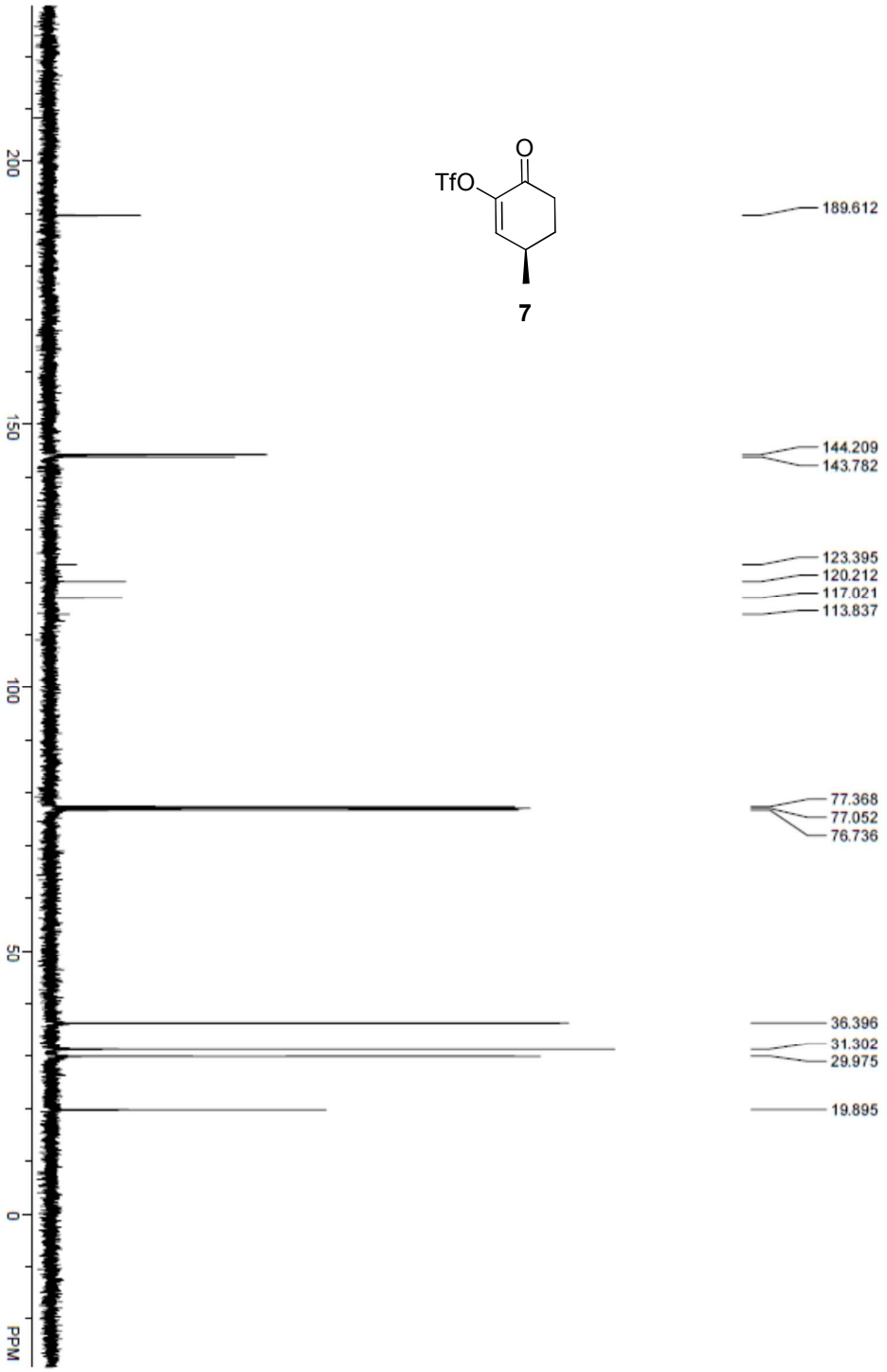
6.751
6.746
2.725
2.858
2.683
2.670
2.564
2.545
2.533
2.502
2.490
2.204
2.170
1.813
1.790
1.760
1.726
1.551
1.274
1.256
-0.001
PPM

7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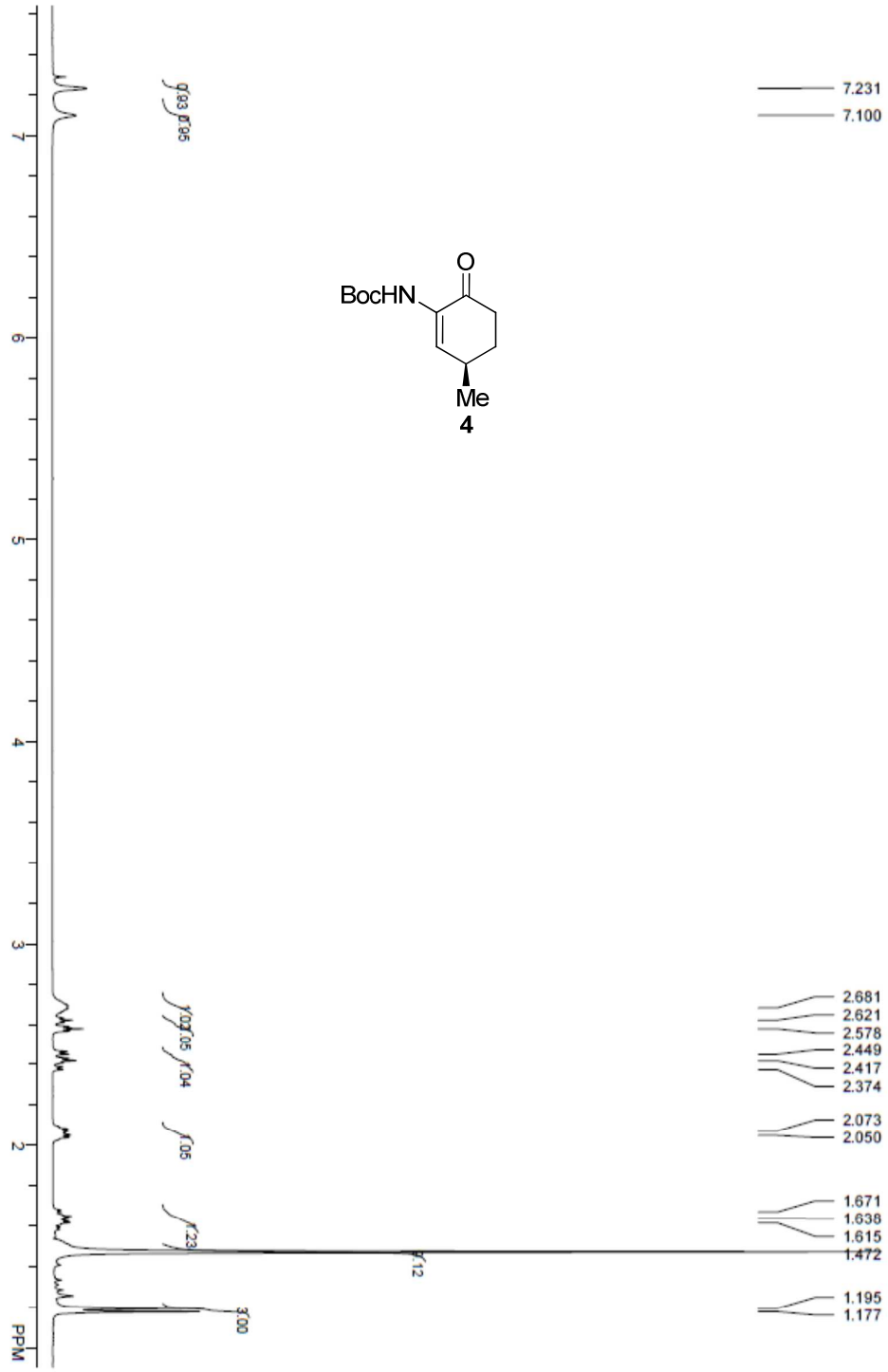
O
7
189.612
144.209
143.782
123.395
120.212
117.021
113.837
77.368
77.052
76.736
36.396
31.302
29.975
19.895
200
150
100
50
0
PPM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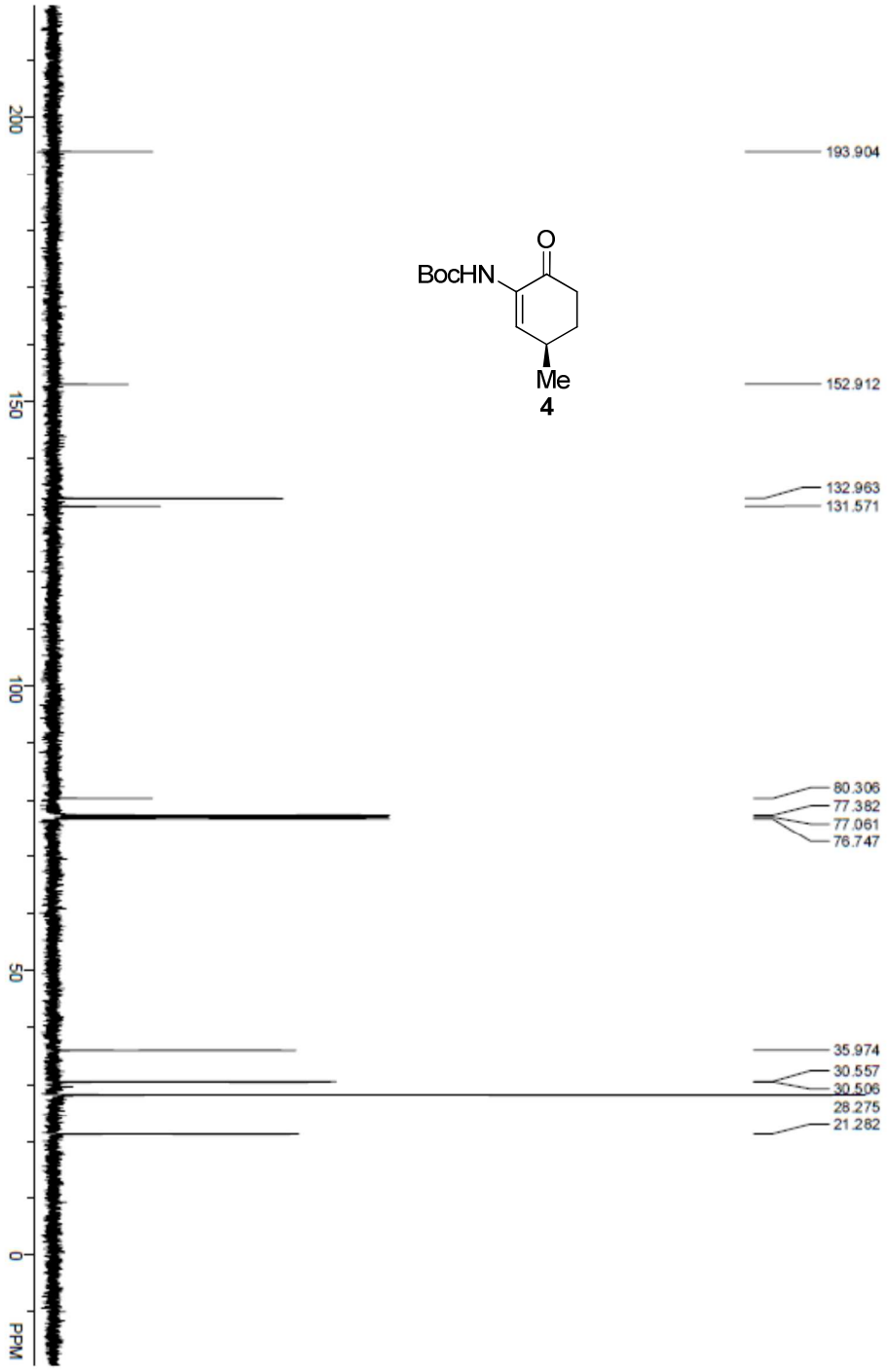
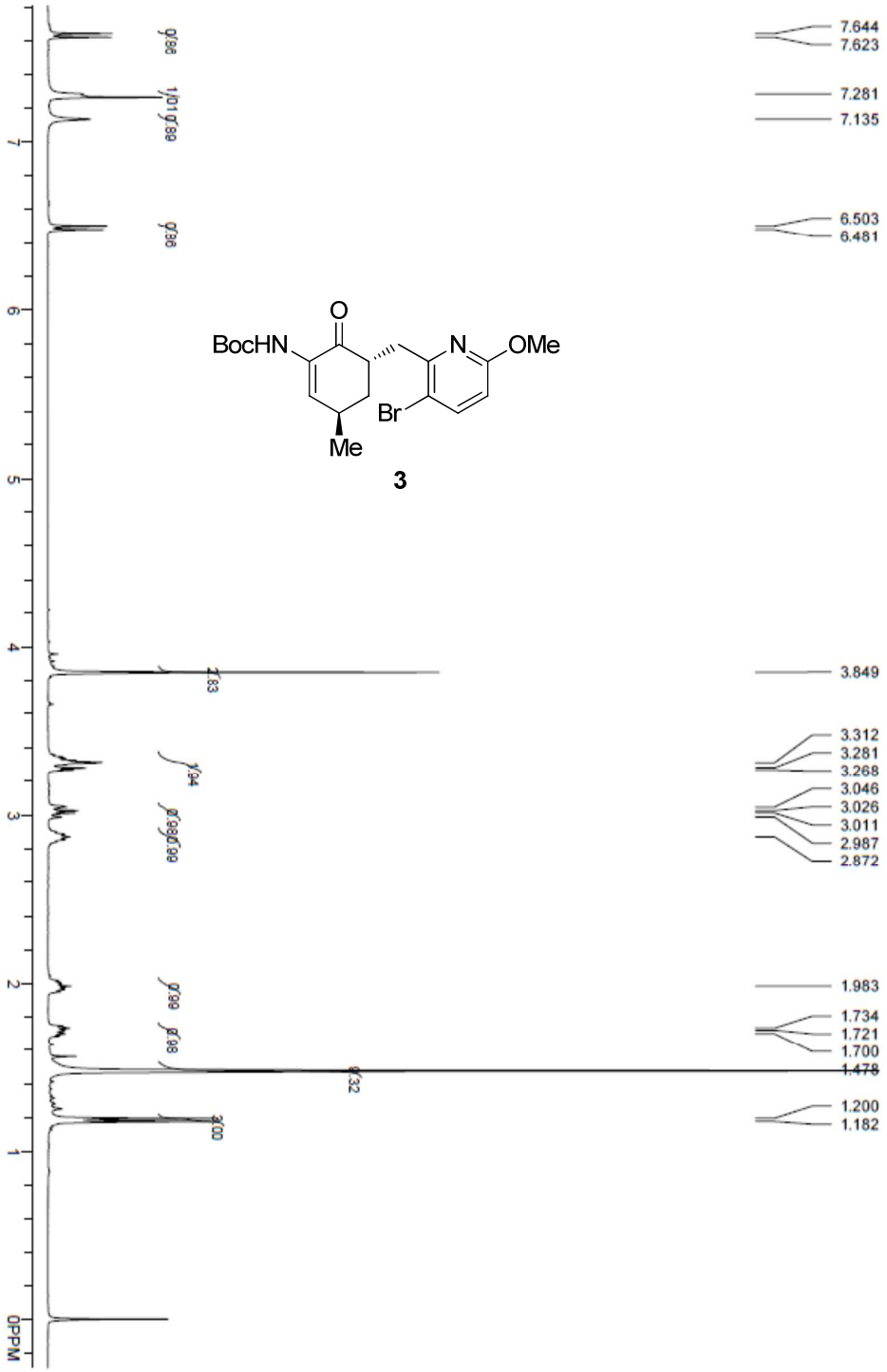
7.100
2.681
2.621
2.578
2.449
2.417
2.374
2.073
2.050
1.671
1.638
1.615
1.472
1.195
1.177
PPM

O
BocHN
Me

4


200
150
100
50
0
PPM
193.904
152.912
132.963
131.571
80.306
77.382
77.061
76.747
35.974
30.557
30.506
28.275
21.282
O
BocHN
Me
4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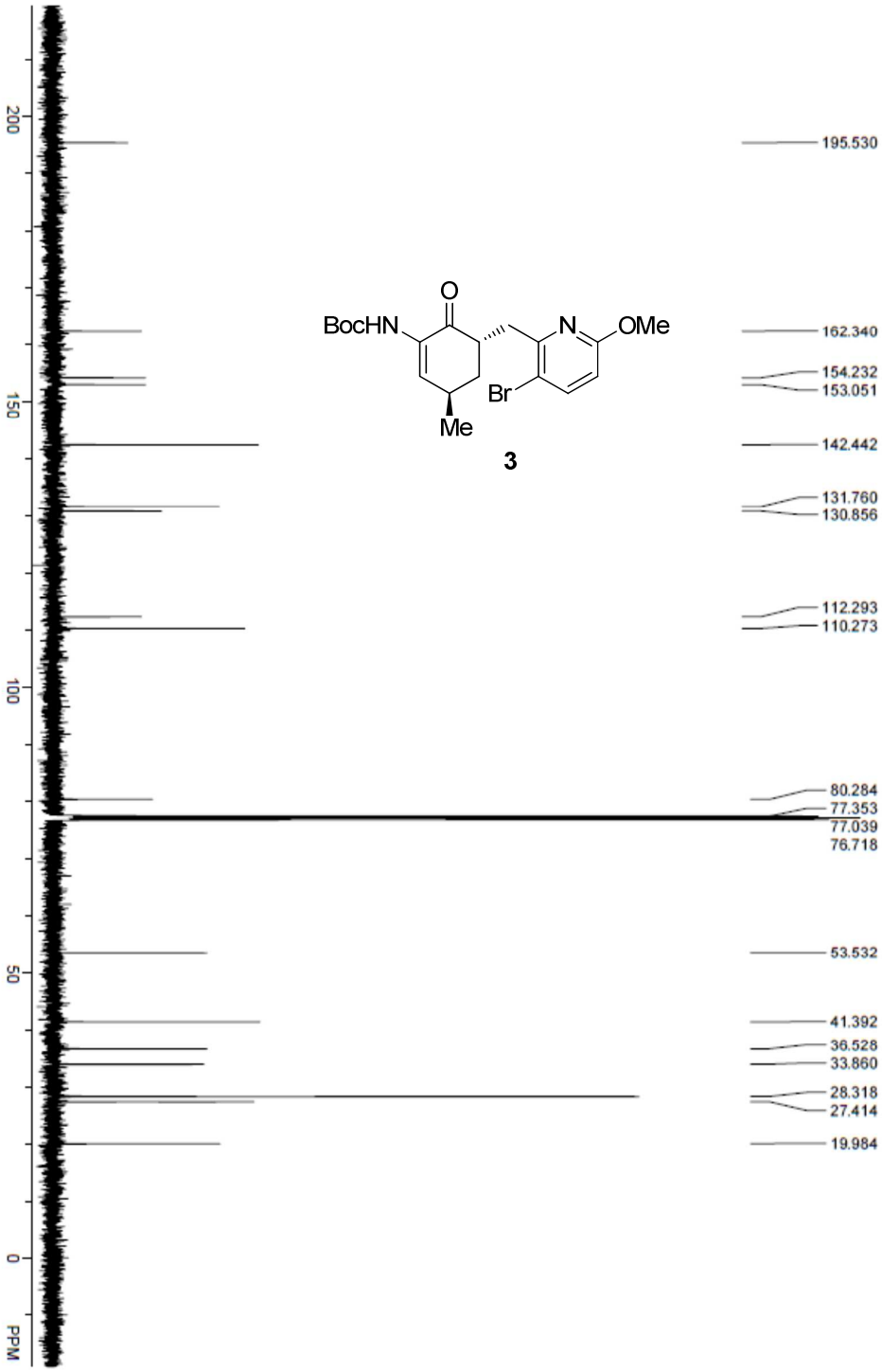
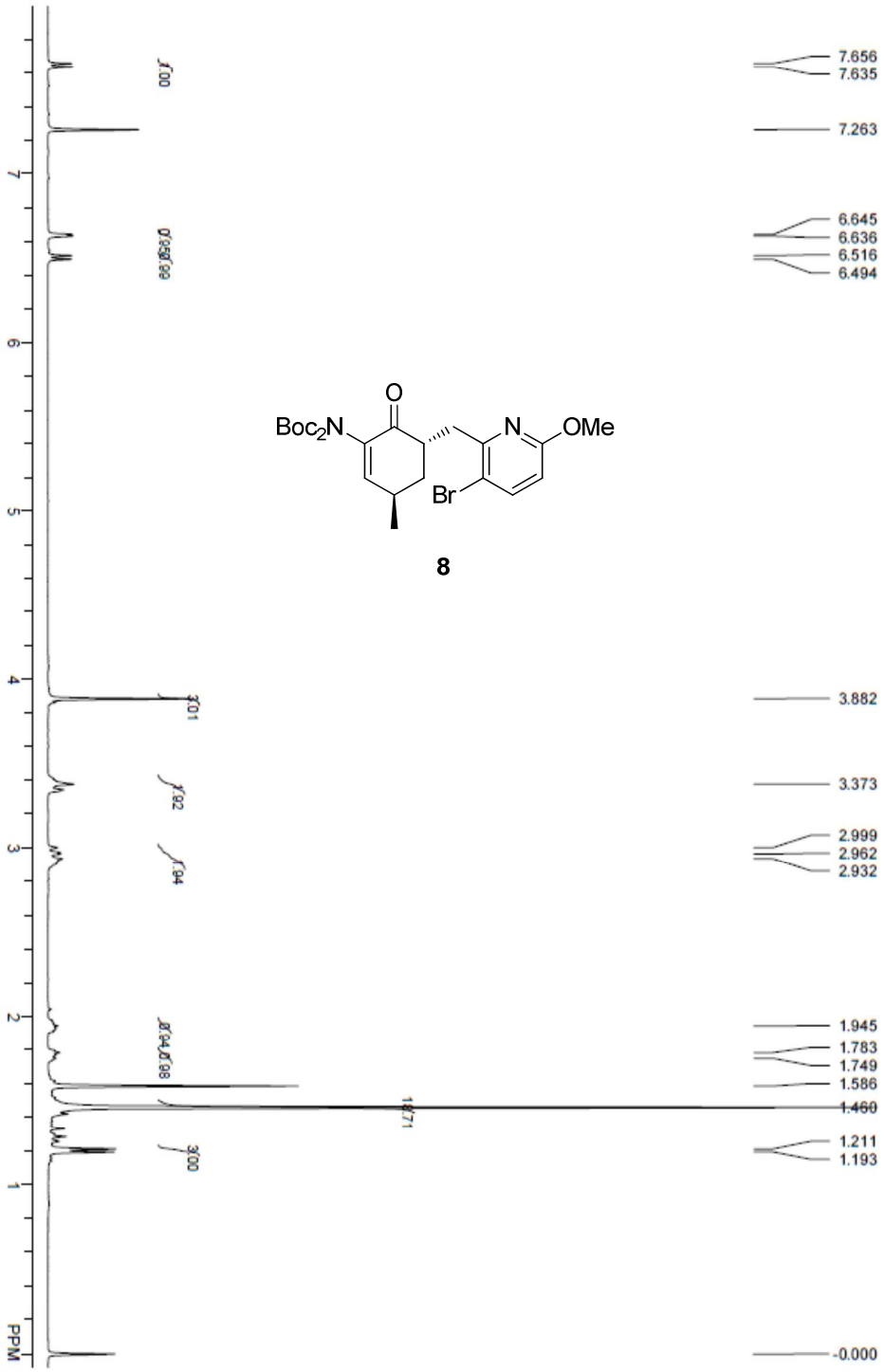
7.623
7.281
7.135
6.503
6.481
3.849
3.312
3.281
3.268
3.046
3.026
3.011
2.987
2.872
1.983
1.734
1.721
1.700
1.478
1.200
1.182
BocHN
O
N
OMe
Br
Me

3

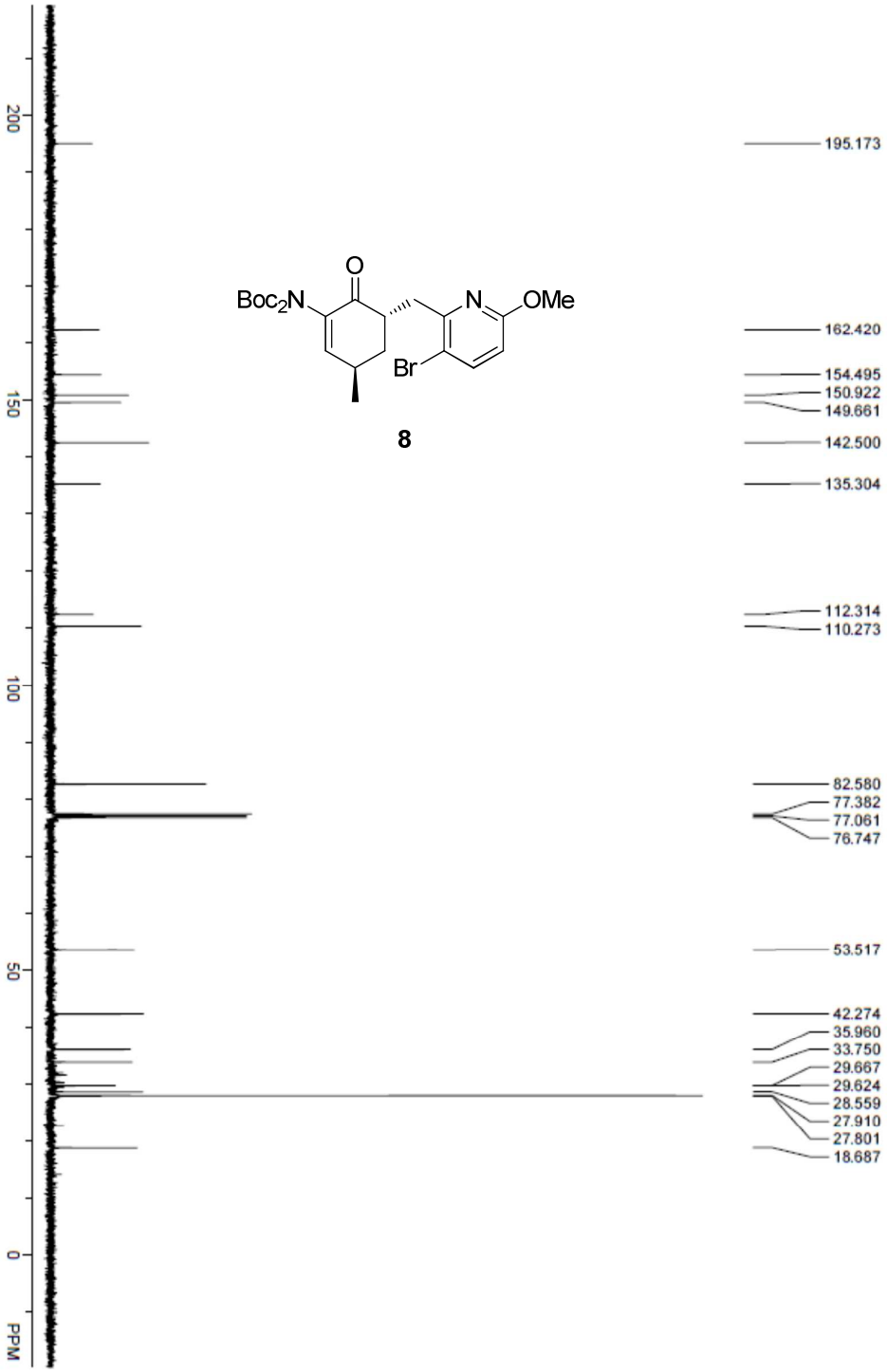

195.530
162.340
154.232
153.051
142.442
131.760
130.856
112.293
110.273
80.284
77.353
77.039
76.718
53.532
41.392
36.528
33.860
28.318
27.414
19.984
200
150
100
50
0
PPM
O
BocHN
N
OMe
Br
Me

3


7.656
7.635
7.263
6.645
6.636
6.516
6.494
3.882
3.373
2.999
2.962
2.932
1.945
1.783
1.749
1.586
1.460
1.211
1.193
-0.000
PPM

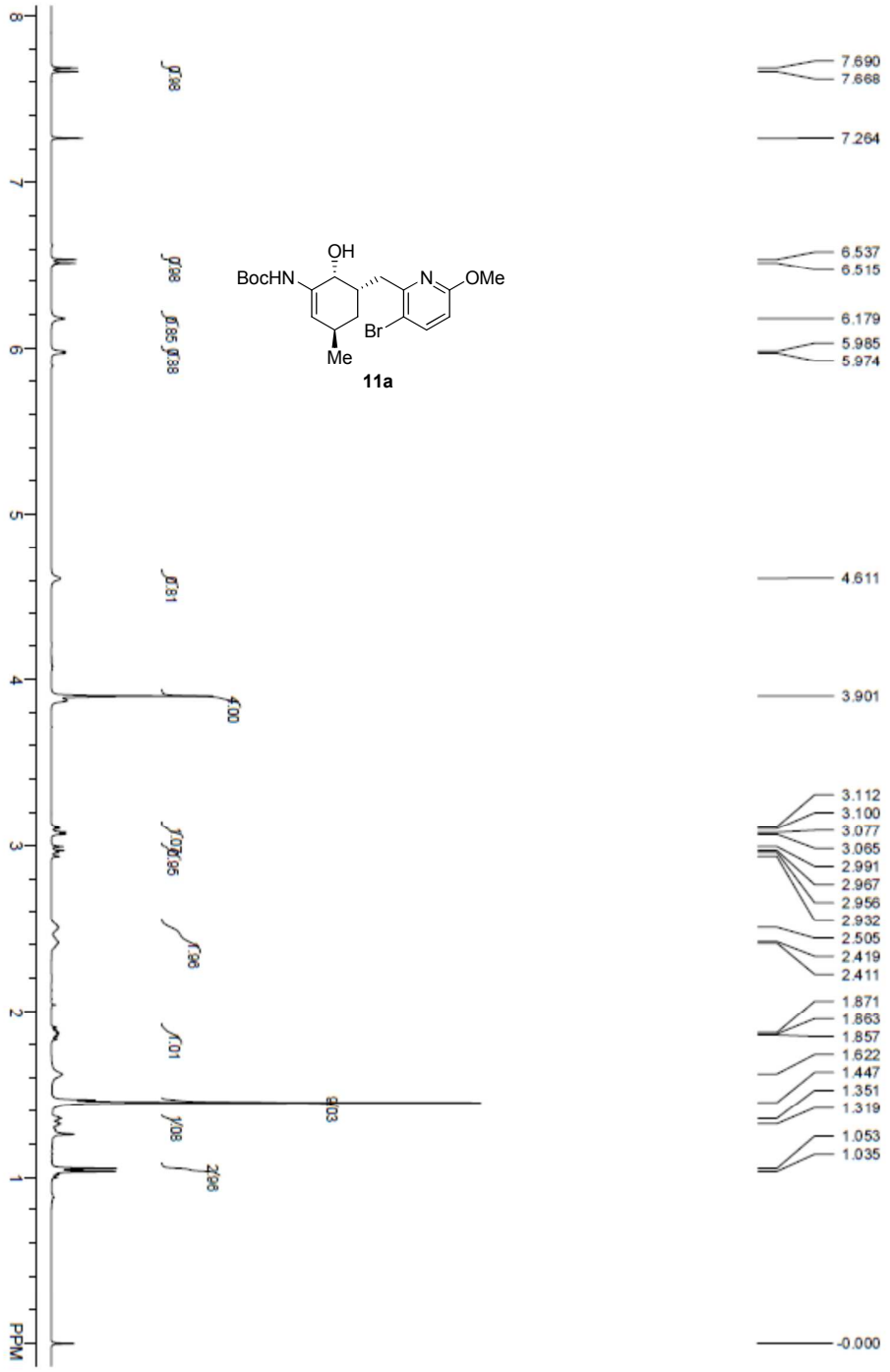
O
Boc2N
N
OMe
Br

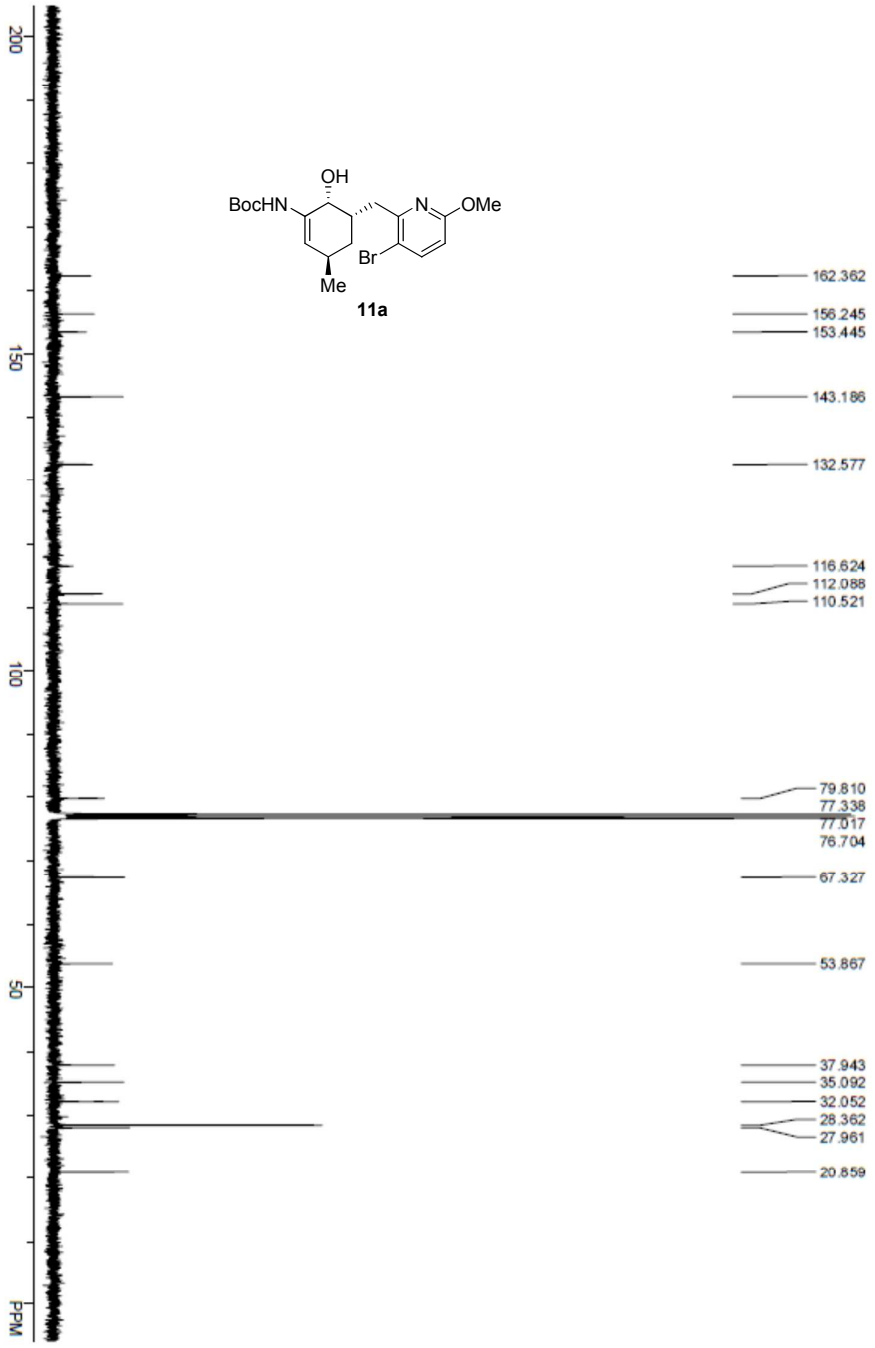
8


195.173
162.420
154.495
150.922
149.661
142.500
135.304
112.314
110.273
82.580
77.382
77.061
76.747
53.517
42.274
35.960
33.750
29.667
29.624
28.559
27.910
27.801
18.687
200
150
100
50
0
PPM

O
Boc2N
N
OMe
Br

8


OH
BocHN
N
OMe
Br
Me
11a
7.690
7.668
7.264
6.537
6.515
6.179
5.985
5.974
4.611
3.901
3.112
3.100
3.077
3.065
2.991
2.967
2.956
2.932
2.505
2.419
2.411
1.871
1.863
1.857
1.622
1.447
1.351
1.319
1.053
1.035
-0.000
PPM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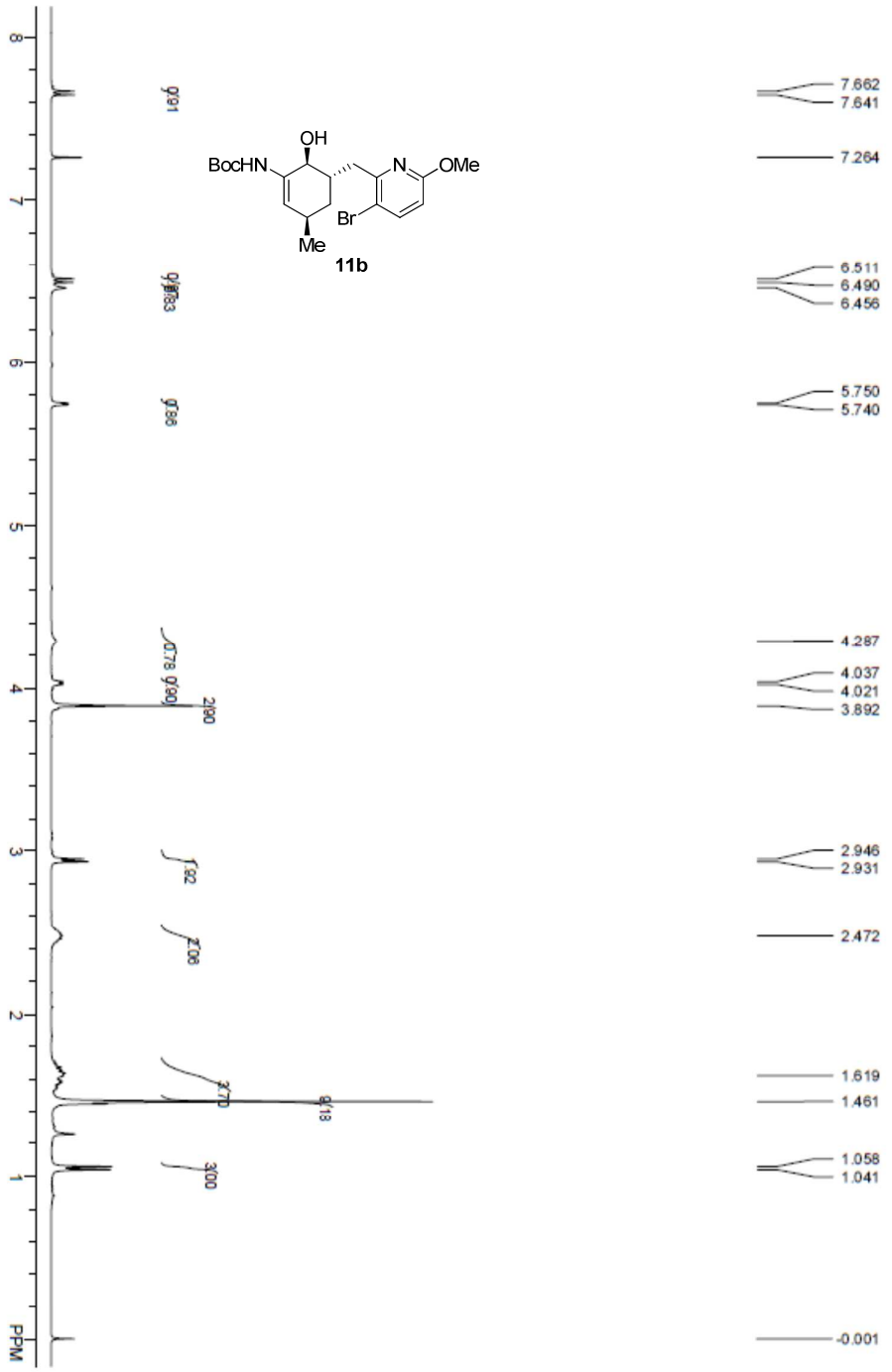
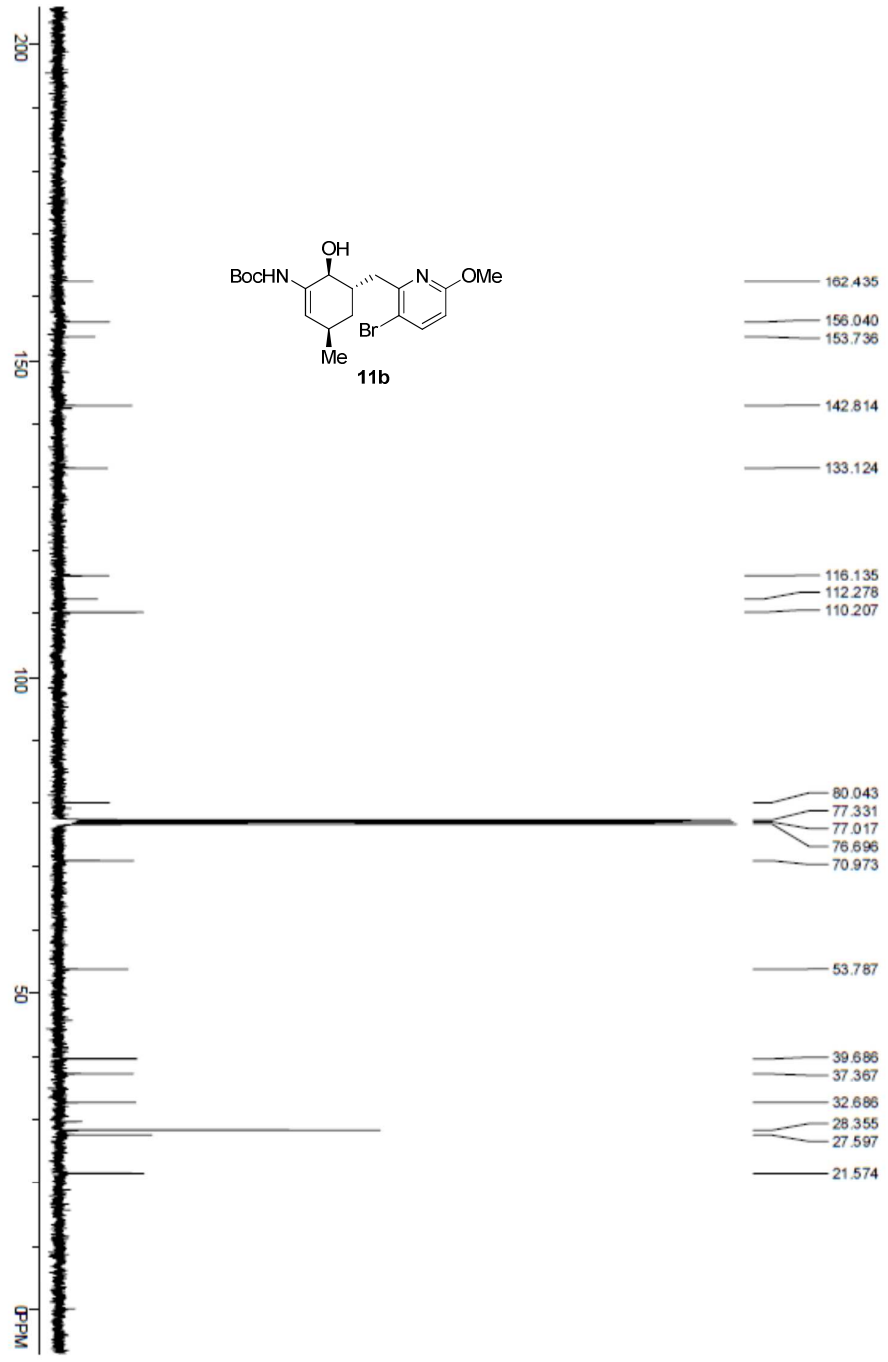
BocHN
N
OMe
Br
Me
11a
162.362
156.245
153.445
143.186
132.577
116.624
112.088
110.521
79.810
77.338
77.017
76.704
67.327
53.867
37.943
35.092
32.052
28.362
27.961
20.859
200
150
100
50
PPM


OH
BocHN
N
OMe
Br
Me
11b
7.662
7.641
7.264
6.511
6.490
6.456
5.750
5.740
4.287
4.037
4.021
3.892
2.946
2.931
2.472
1.619
1.461
1.058
1.041
-0.001
PPM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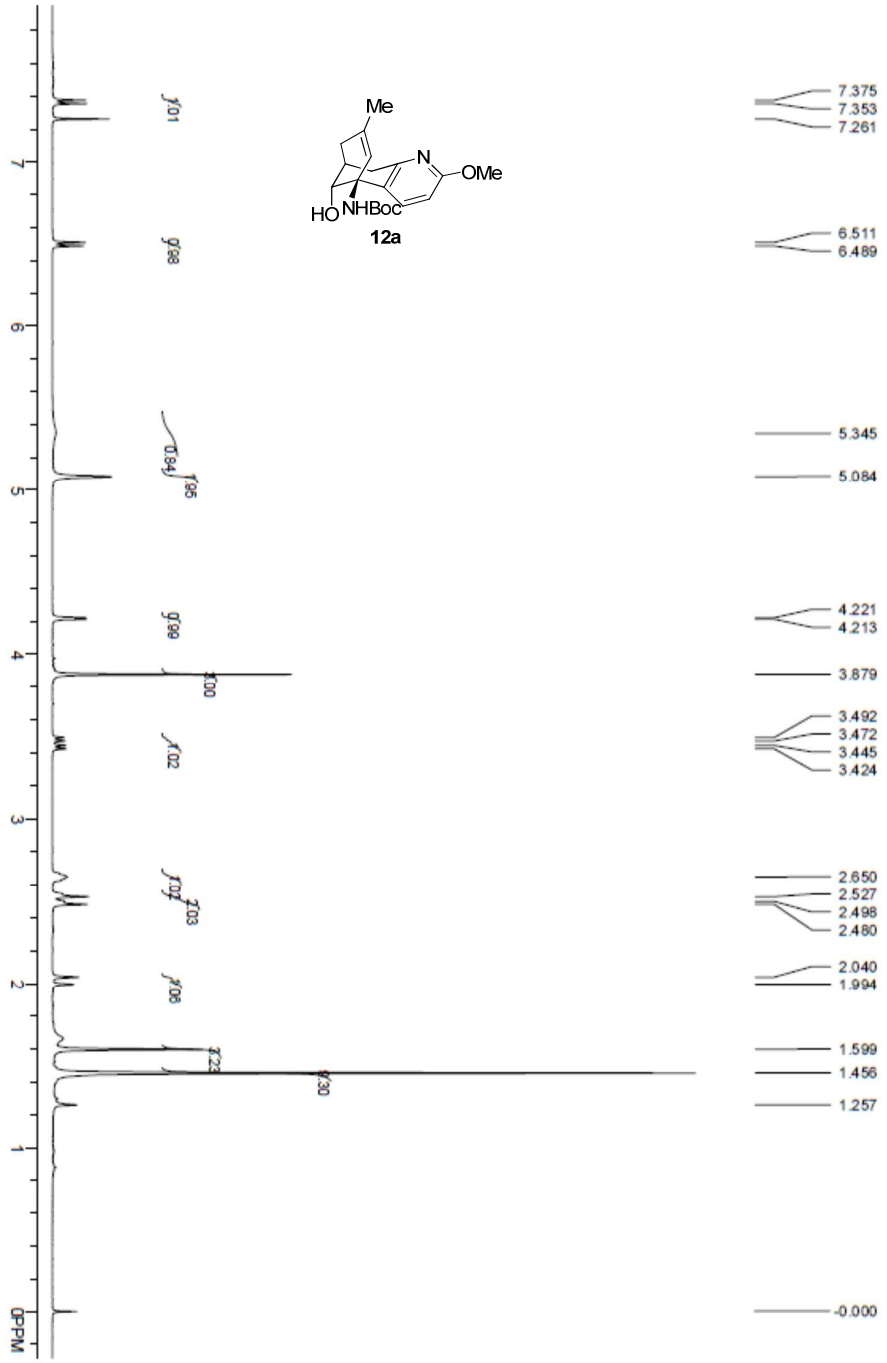
BocHN
N
OMe
Br
Me
11b
162.435
156.040
153.736
142.814
133.124
116.135
112.278
110.207
80.043
77.331
77.017
76.696
70.973
53.787
39.686
37.367
32.686
28.355
27.597
21.574
200
150
100
50
0PPM


Me
N
OMe
HO
NHBoc
12a
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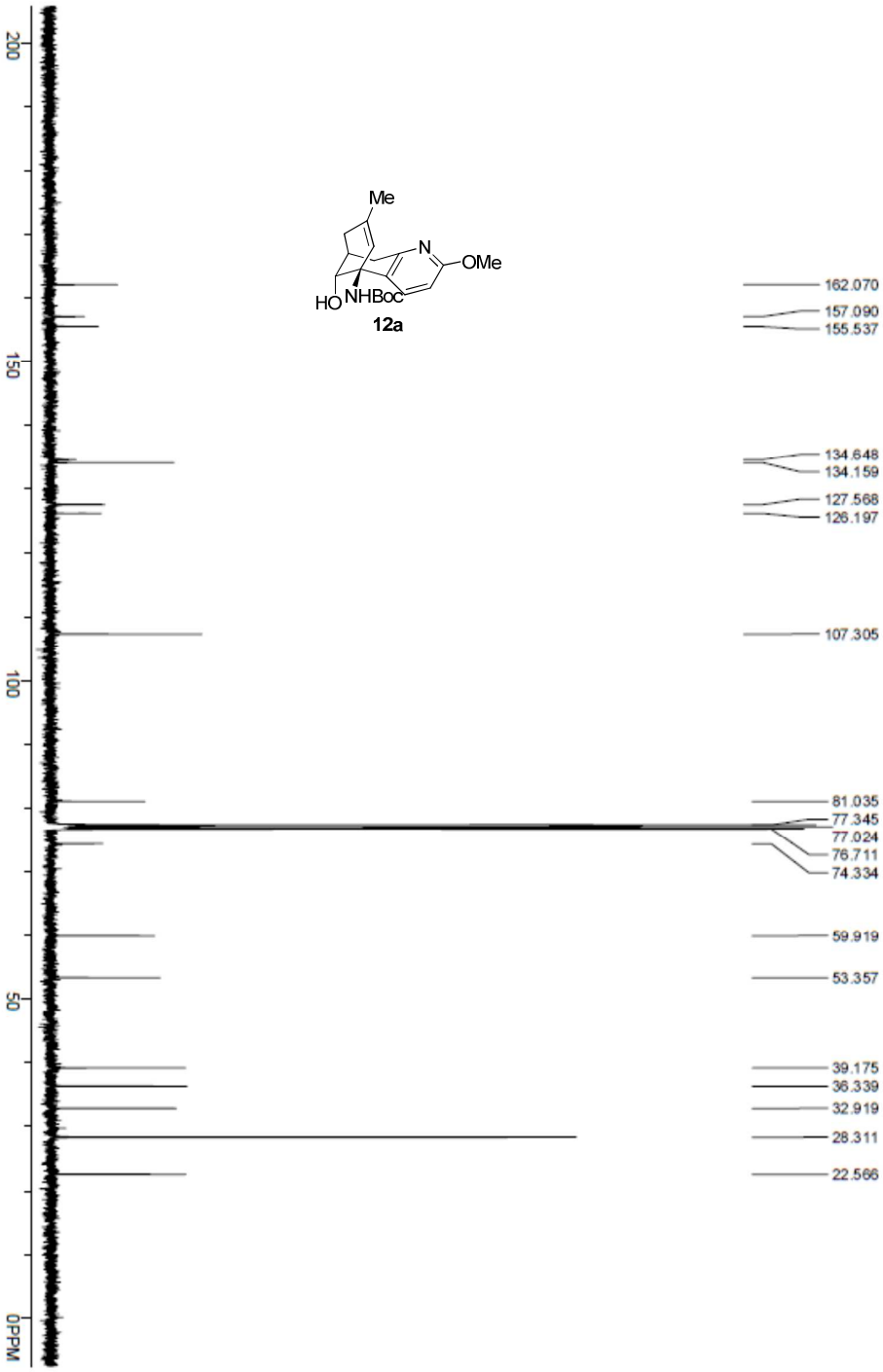
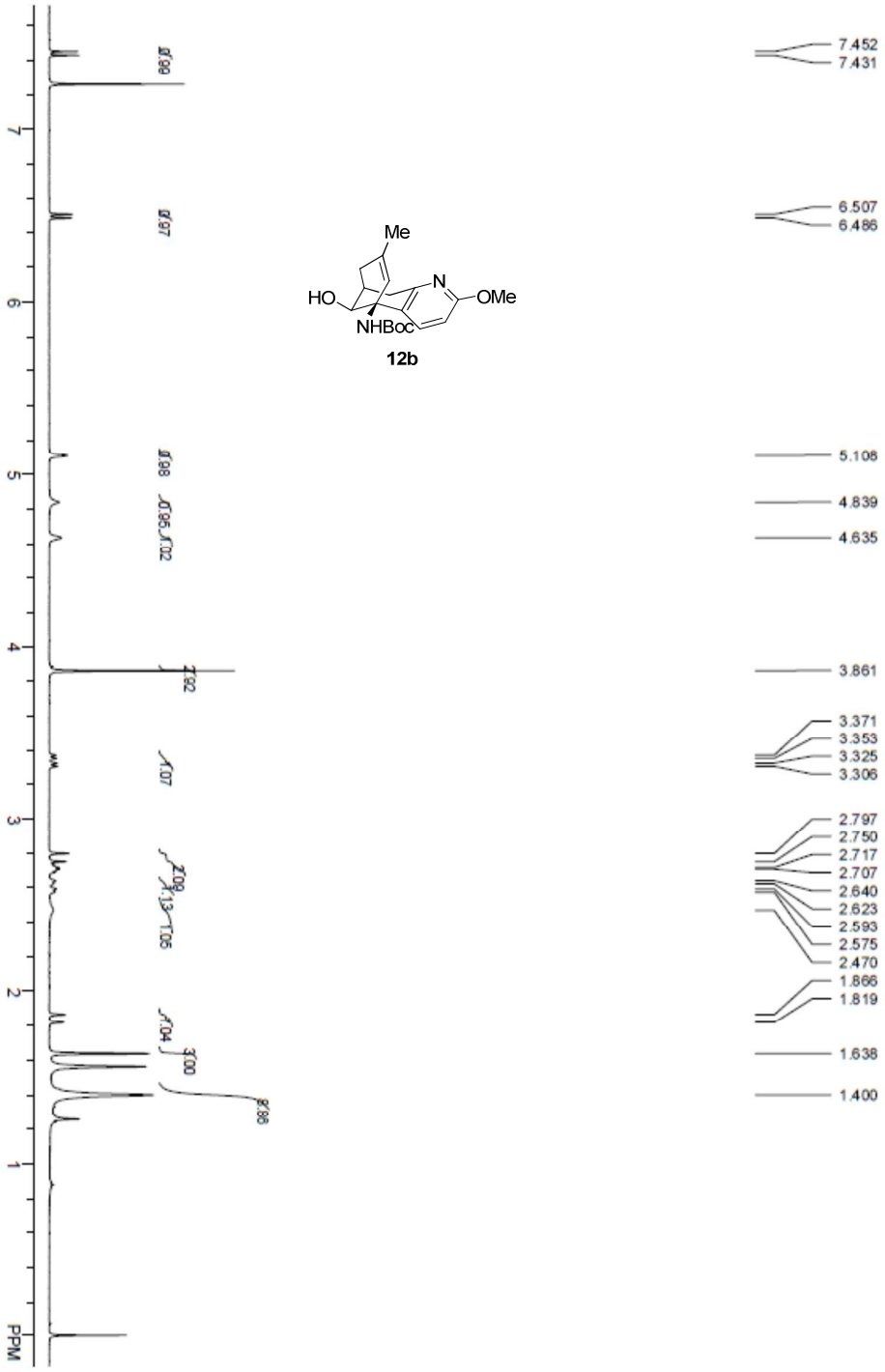
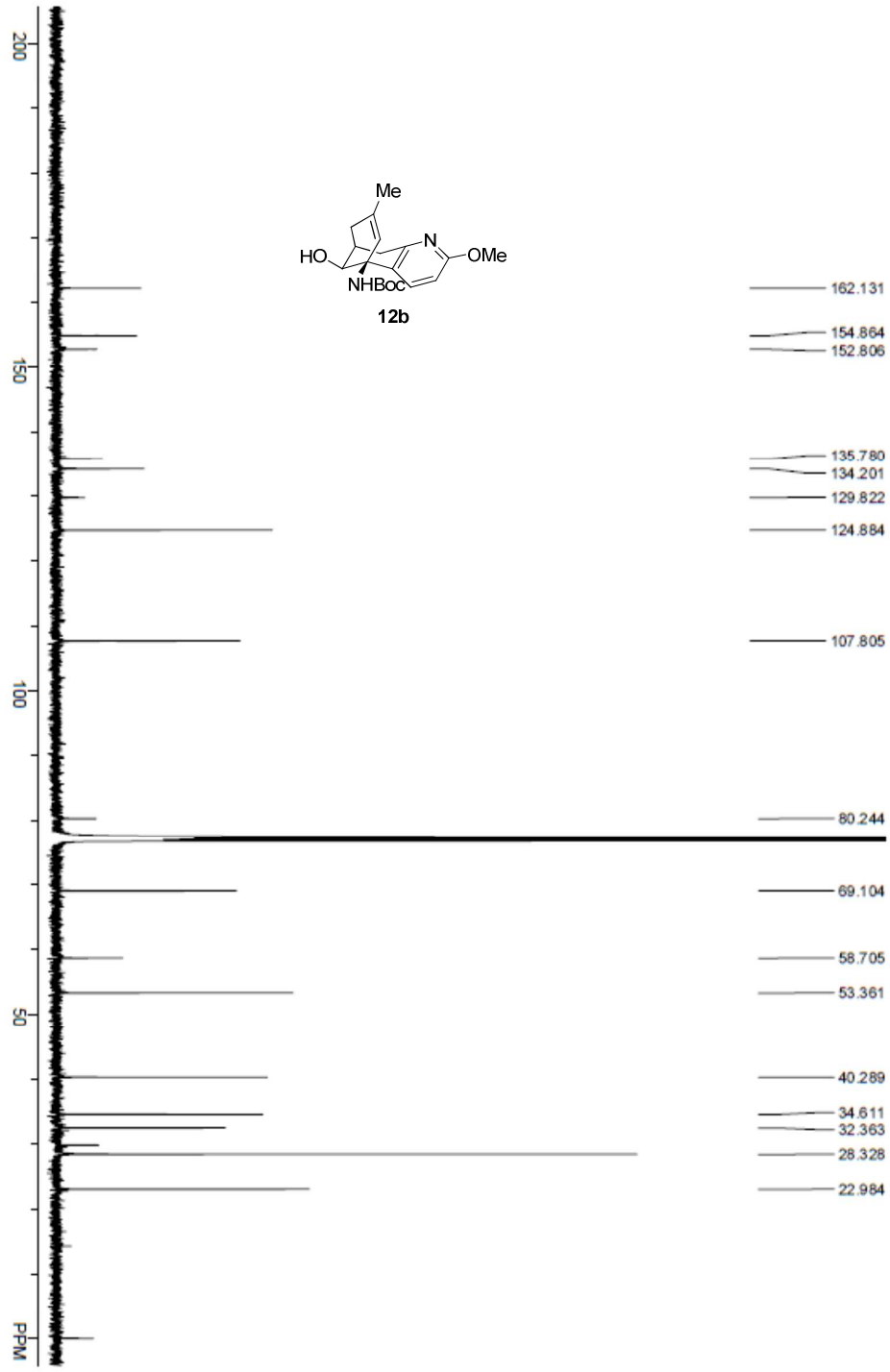
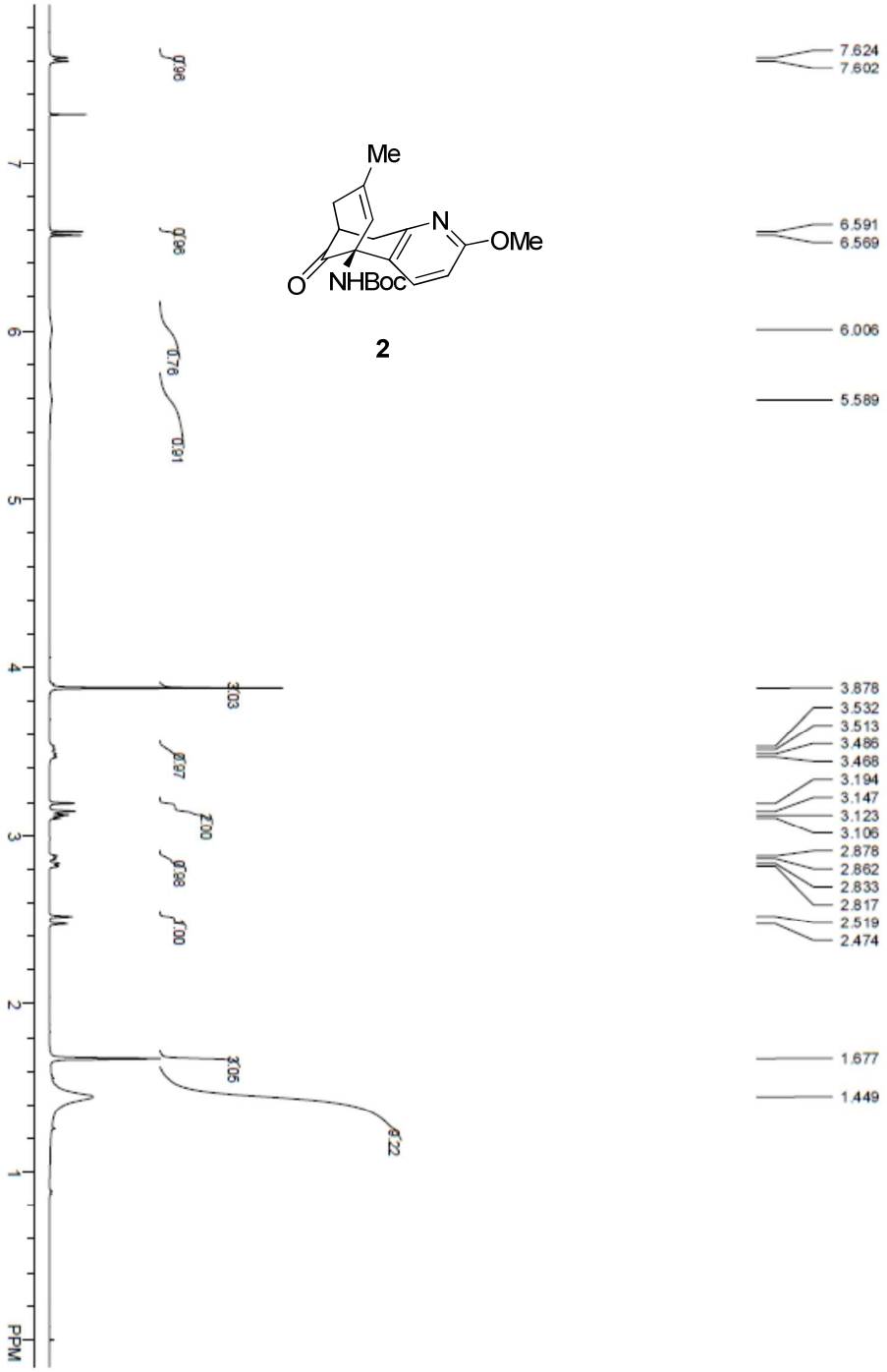
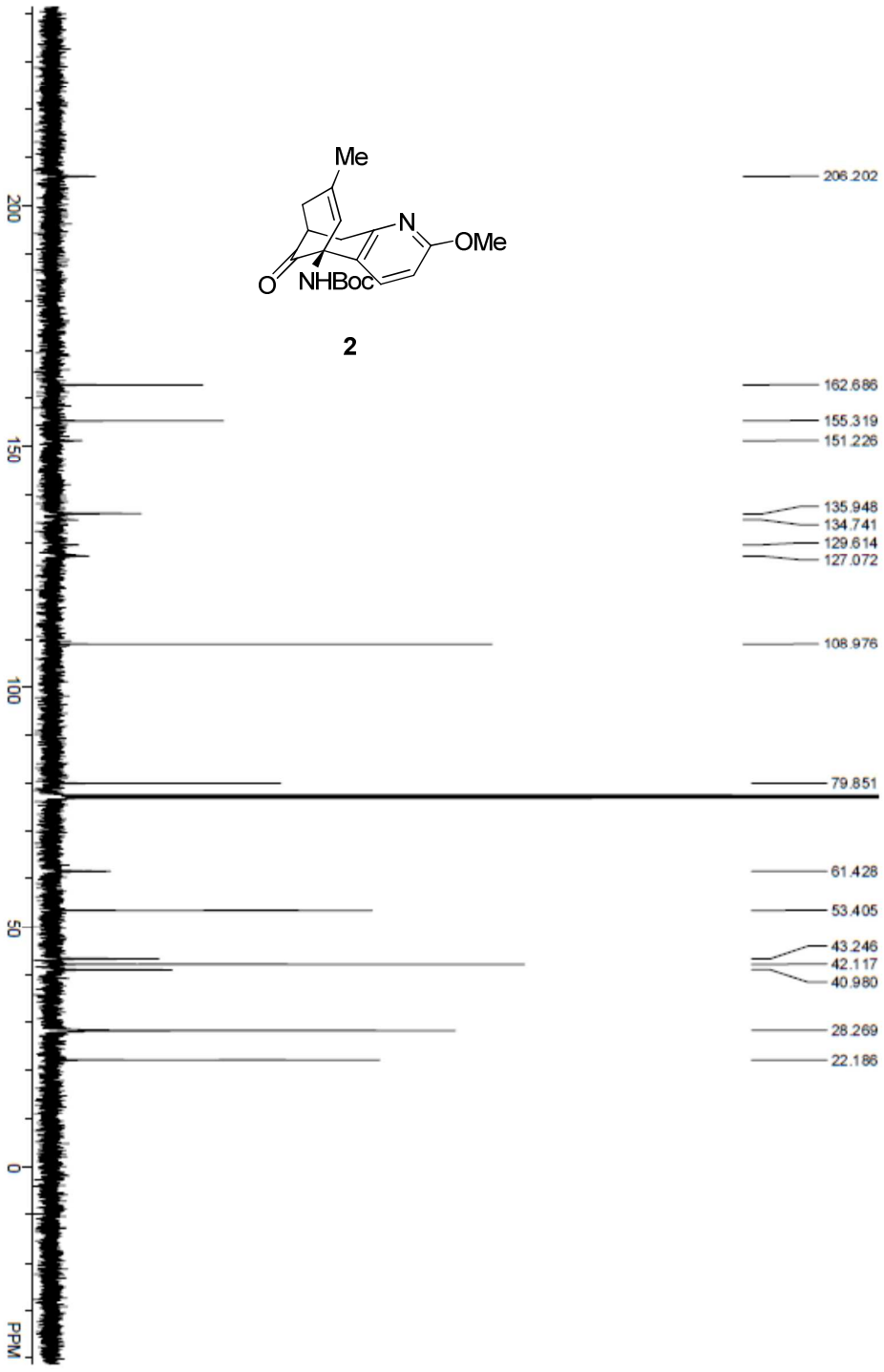
7.353
7.261
6.511
6.489
5.345
5.084
4.221
4.213
3.879
3.492
3.472
3.445
3.424
2.650
2.527
2.498
2.480
2.040
1.994
1.599
1.456
1.257
-0.000
PPM


Me
N
OMe
HO
NHBoc
12a
162.070
157.090
155.537
134.648
134.159
127.568
126.197
107.305
81.035
77.345
77.024
76.711
74.334
59.919
53.357
39.175
36.339
32.919
28.311
22.566
200
150
100
50
0PPM


Me
HO
N
OMe
NHBoc
12b
7.452
7.431
6.507
6.486
5.106
4.839
4.635
3.861
3.371
3.353
3.325
3.306
2.797
2.750
2.717
2.707
2.640
2.623
2.593
2.575
2.470
1.866
1.819
1.638
1.400
PPM


Me
HO
N
OMe
NHBoc
12b
162.131
154.864
152.806
135.780
134.201
129.822
124.884
107.805
80.244
69.104
58.705
53.361
40.289
34.611
32.363
28.328
22.984
200
150
100
50
PPM


Me
N
OMe
O
NHBoc
2
7.624
7.602
6.591
6.569
6.006
5.589
3.878
3.532
3.513
3.486
3.468
3.194
3.147
3.123
3.106
2.878
2.862
2.833
2.817
2.519
2.474
1.677
1.449
PPM


Me
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OMe
O
NHBoc
206.202
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155.319
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134.741
129.614
127.072
108.976
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43.246
42.117
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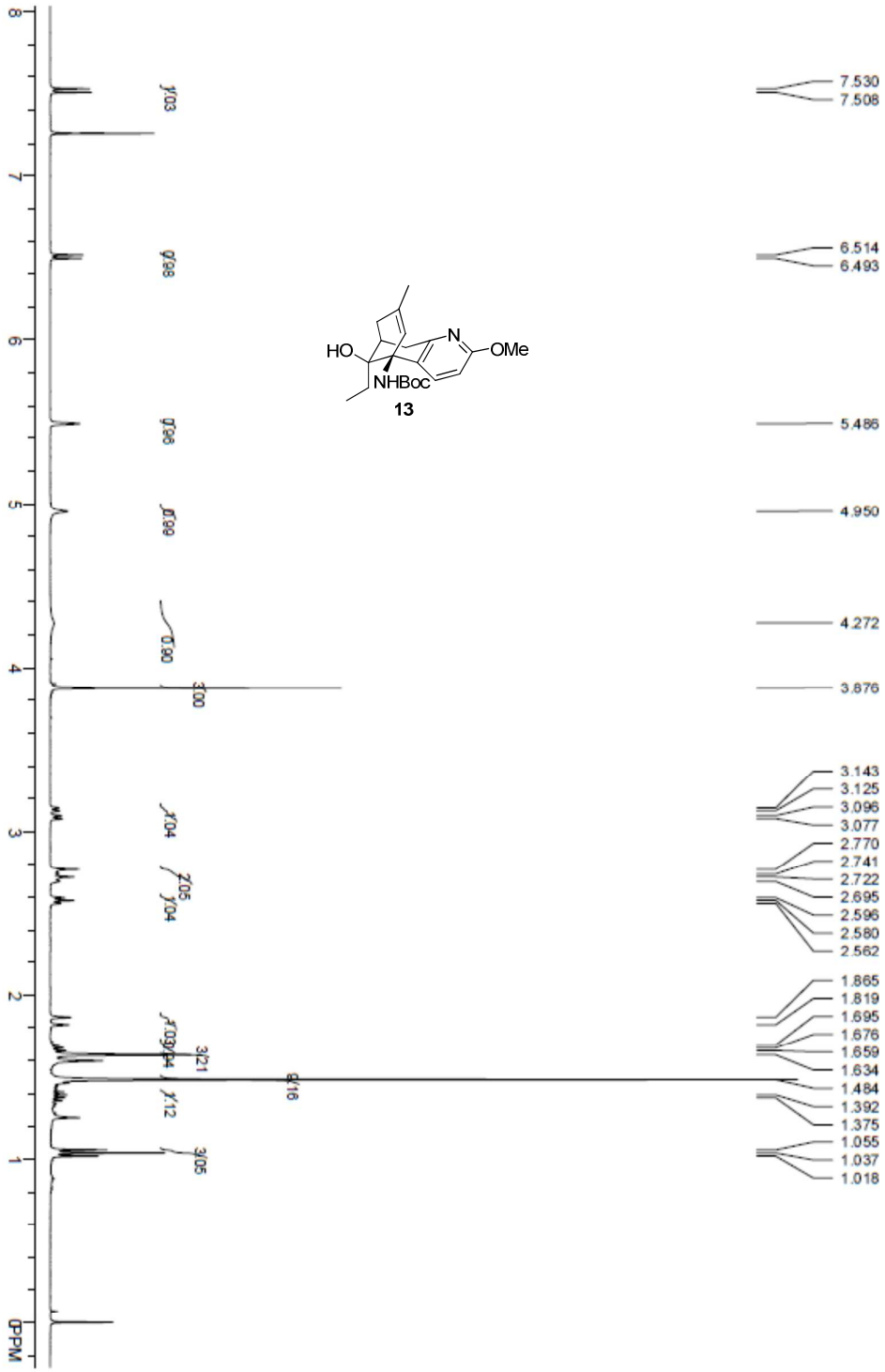
200
150
100
50
0
PPM

2


HO
N
OMe
NHBoc
13
7.530
7.508
6.514
6.493
5.486
4.950
4.272
3.876
3.143
3.125
3.096
3.077
2.770
2.741
2.722
2.695
2.596
2.580
2.562
1.865
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1.375
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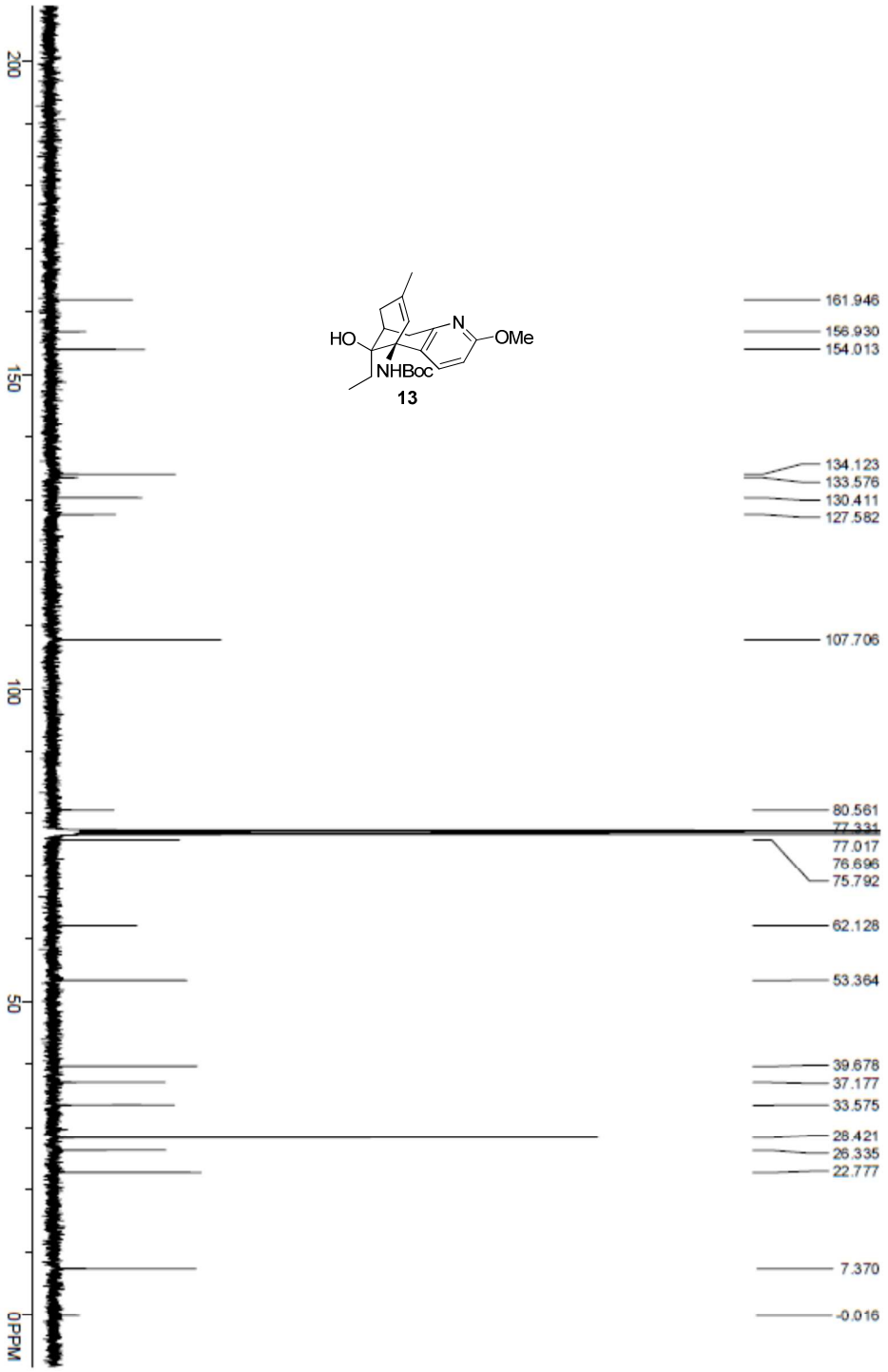
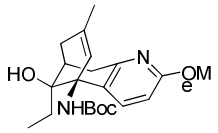
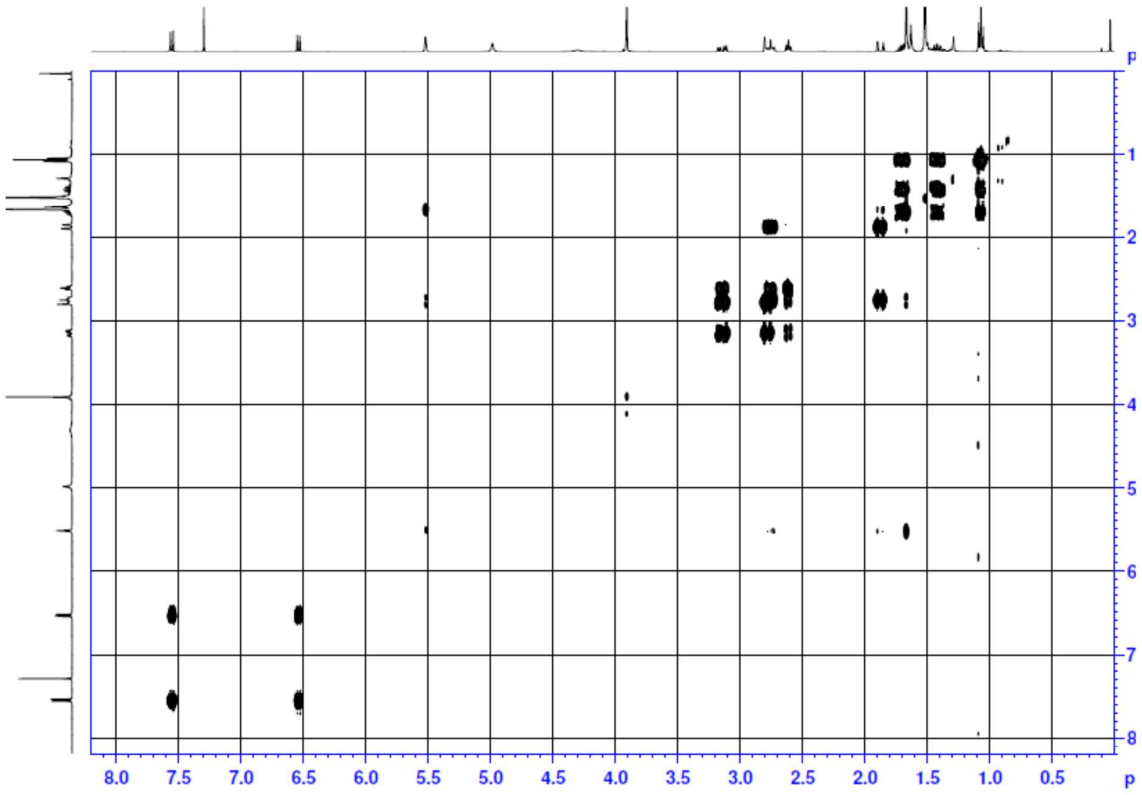
1.018
PPM


HO
N
OMe
NHBoc
13
161.946
156.930
154.013
134.123
133.576
130.411
127.582
107.706
80.561
77.331
77.017
76.696
75.792
62.128
53.364
39.678
37.177
33.575
28.421
26.335
22.777
7.370
-0.016
200
150
100
50
0PPM

COSY


HO
N
OMe
NHBoc

13


p
1
2
3
4
5
6
7
8
8.0
7.5
7.0
6.5
6.0
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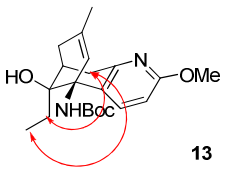
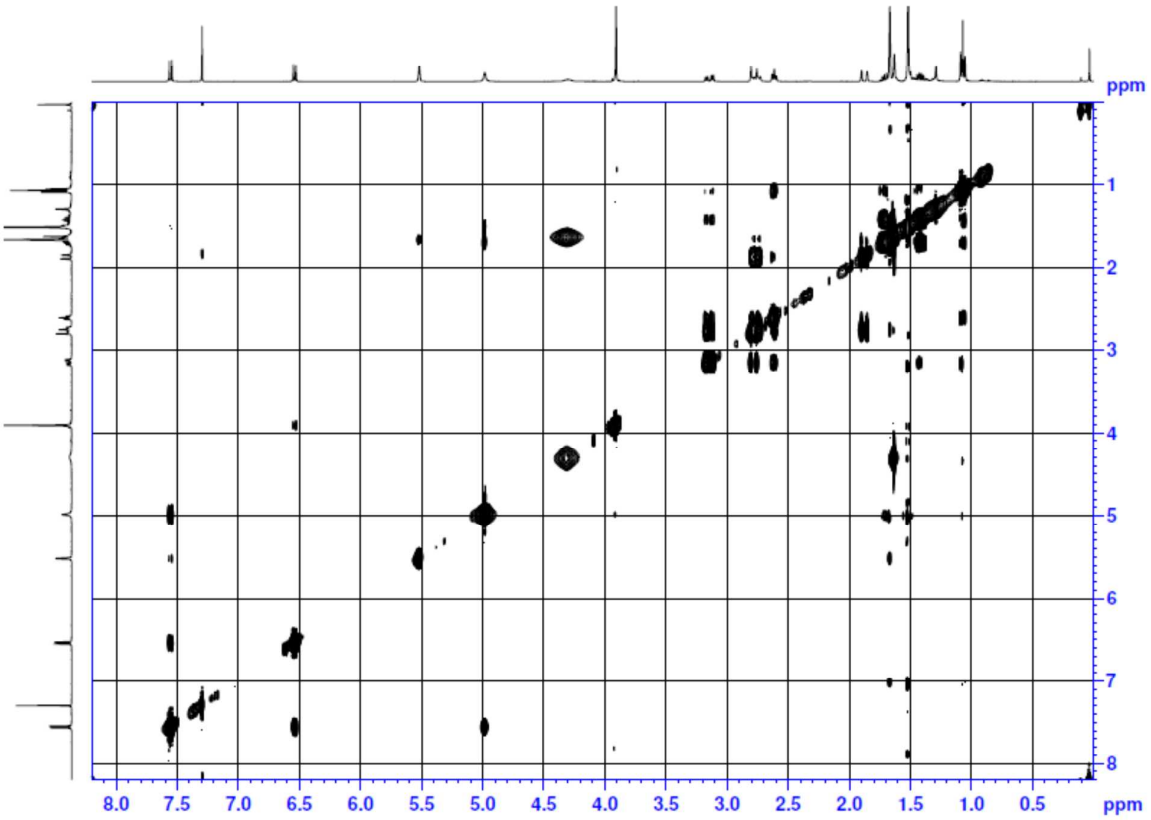
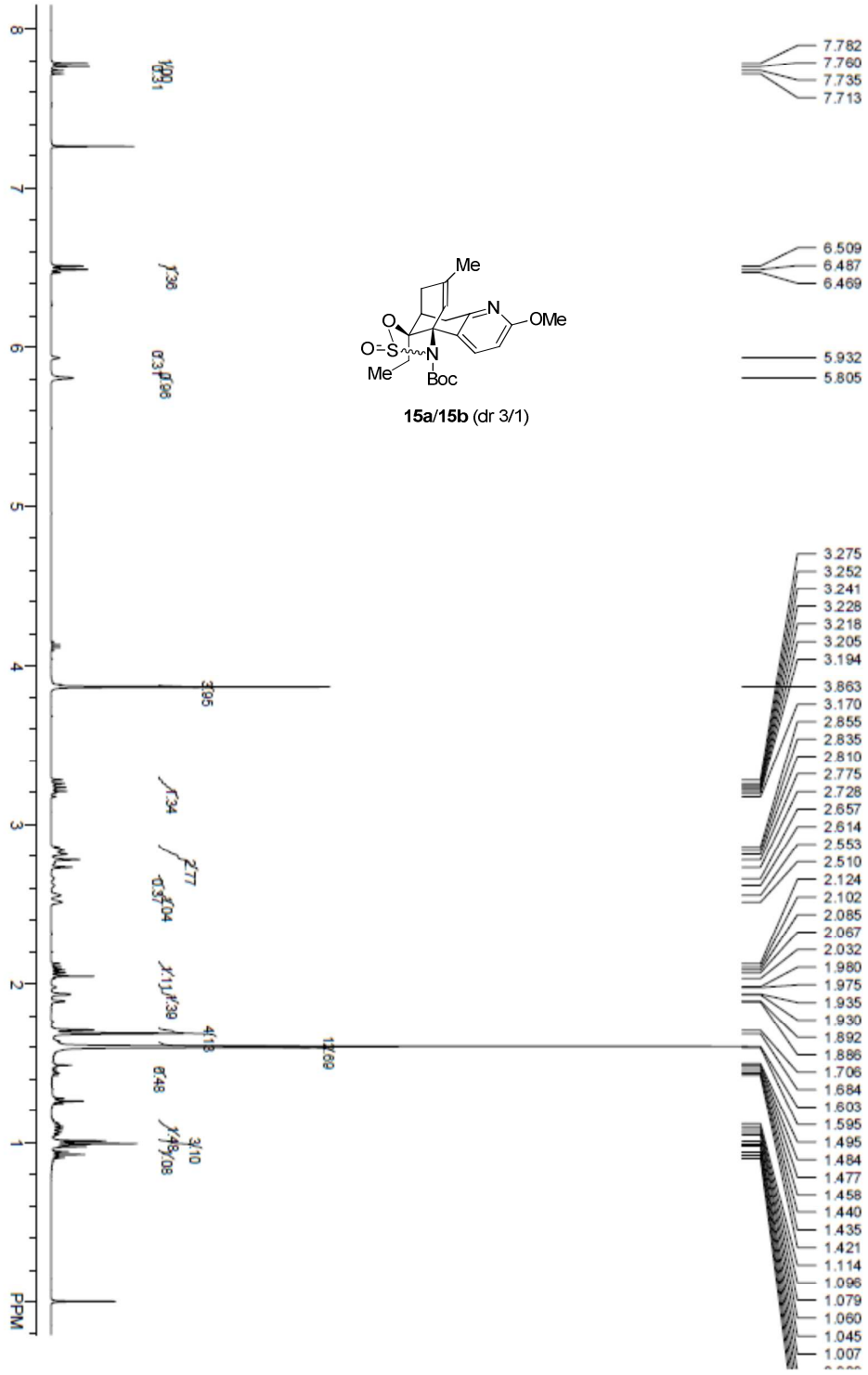
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
p

NOESY


HO
N
OMe
NHBoc

13


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


Me
O
O=S
Me
N
Boc
N
OMe
15a/15b (dr 3/1)
7.782
7.760
7.735
7.713
6.509
6.487
6.469
5.932
5.805
3.275
3.252
3.241
3.228
3.218
3.205
3.194
3.863
3.170
2.855
2.835
2.810
2.775
2.728
2.657
2.614
2.553
2.510
2.124
2.102
2.085
2.067
2.032
1.980
1.975
1.935
1.930
1.892
1.886
1.706
1.684
1.603
1.595
1.495
1.484
1.477
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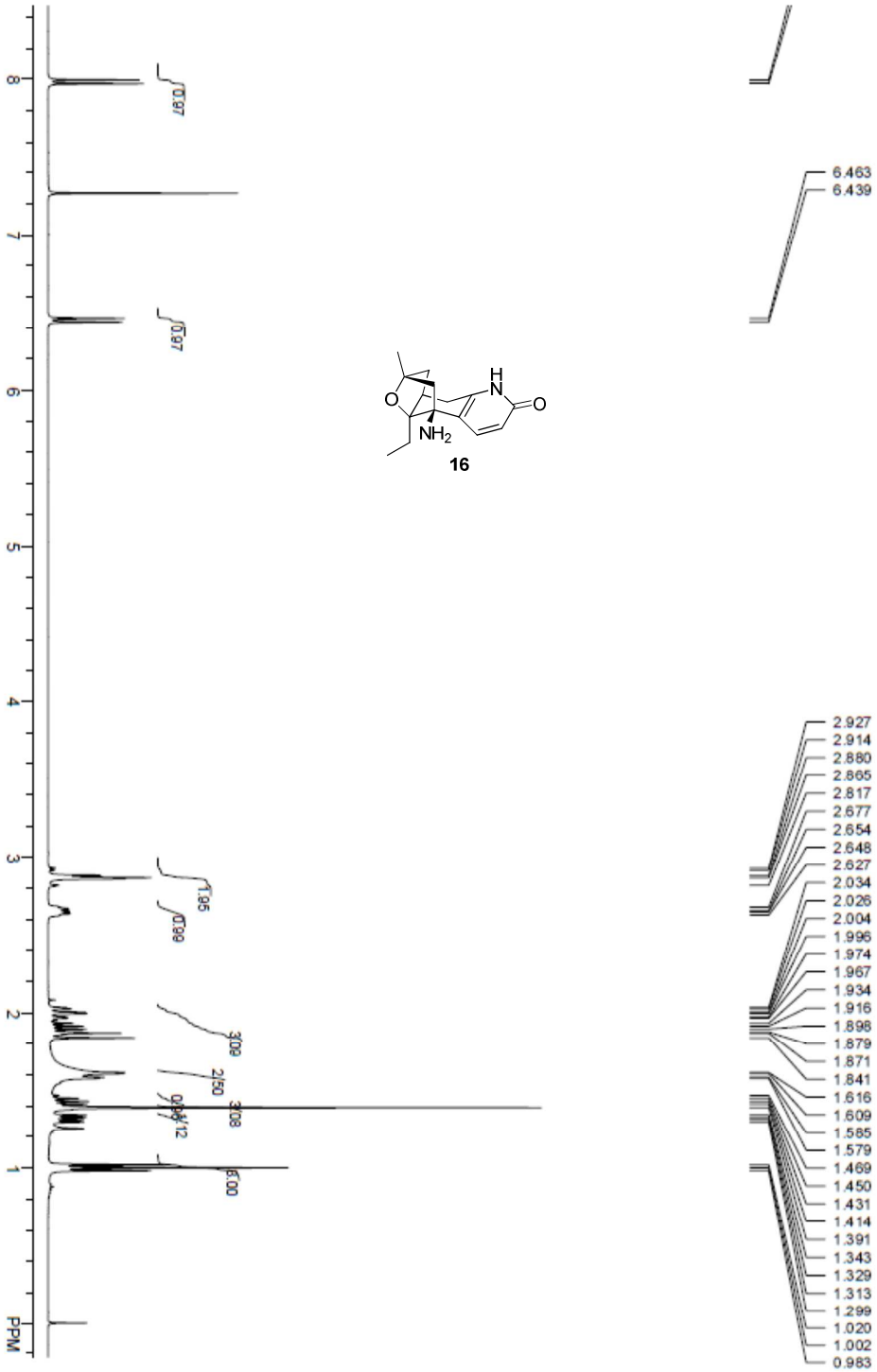
1.440
1.435
1.421
1.114
1.096
1.079
1.060
1.045
1.007
PPM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0.97
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0.99
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2.50
3.08
0.94
2.12
6.00
PPM
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6.439
2.927
2.914
2.880
2.865
2.817
2.677
2.654
2.648
2.627
2.034
2.026
2.004
1.996
1.974
1.967
1.934
1.916
1.898
1.879
1.871
1.841
1.616
1.609
1.585
1.579
1.469
1.450
1.431
1.414
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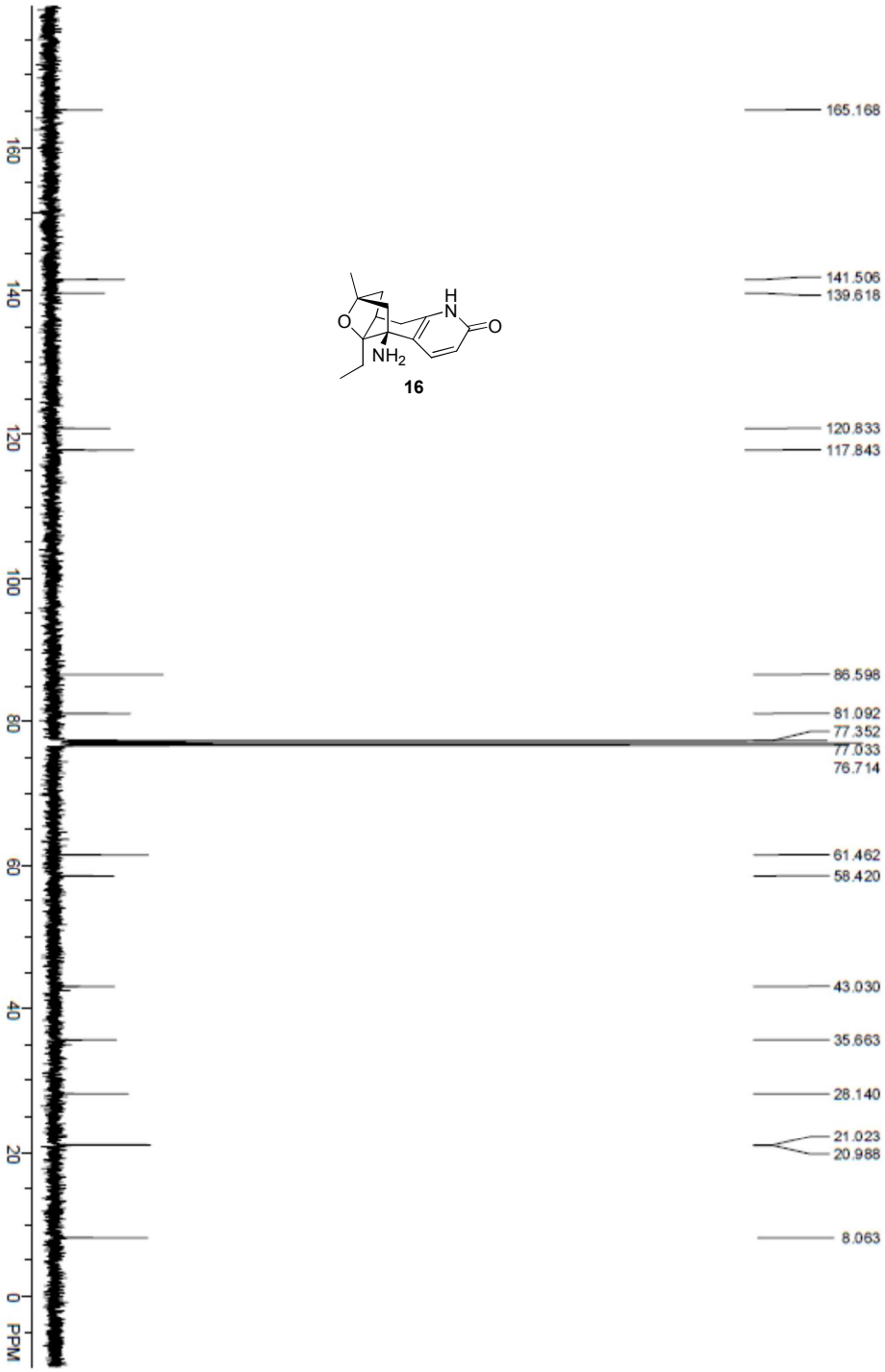
1.299
1.020
1.002
0.983

H
N
O
O
NH2

16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117.843
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81.092
77.352
77.033
76.714
61.462
58.420
43.030
35.663
28.140
21.023
20.988
8.063
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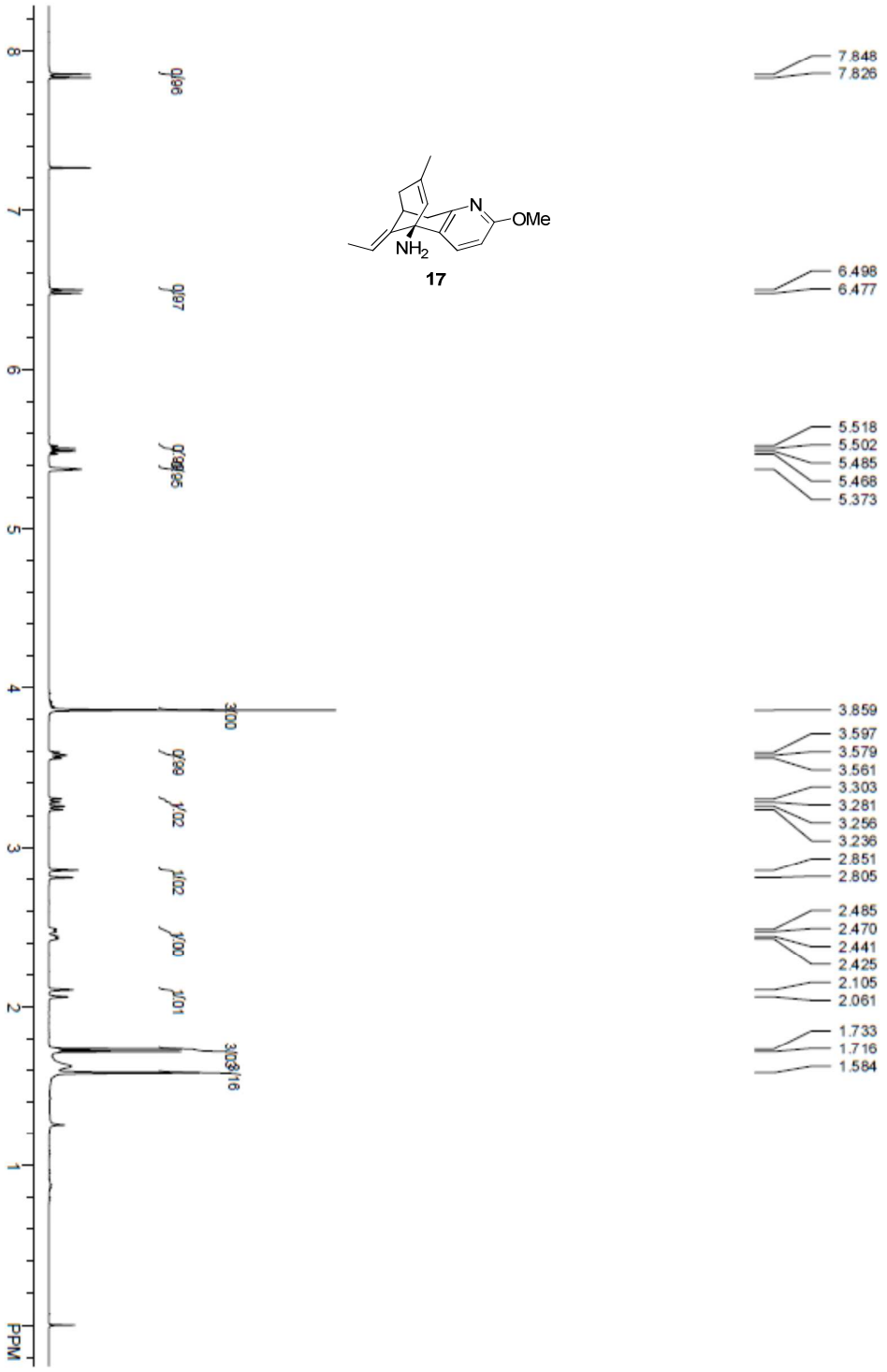
140
120
100
80
60
40
20
0
PPM
H
N
O
O
NH2

16

f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7.826
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6.477
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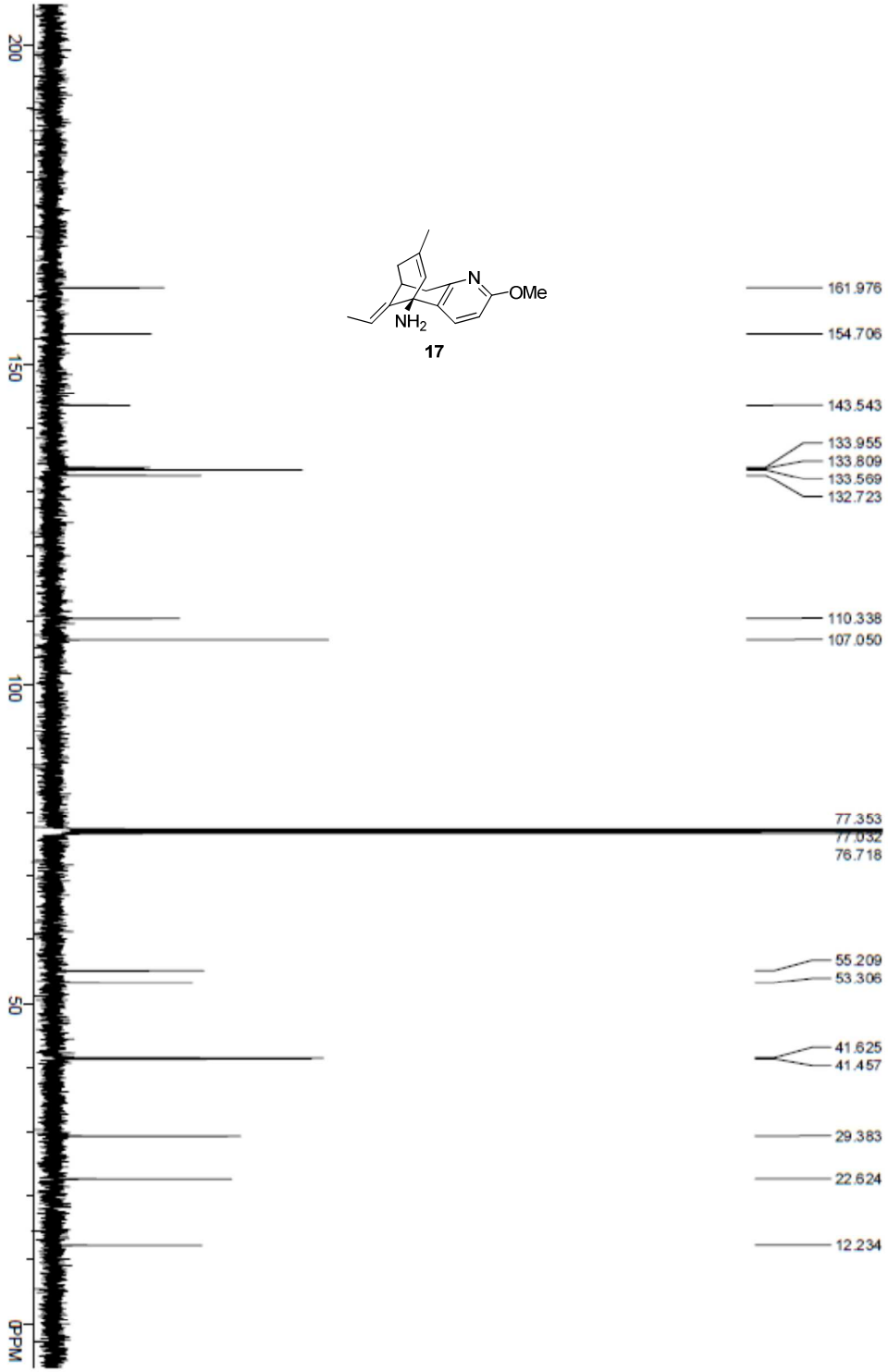
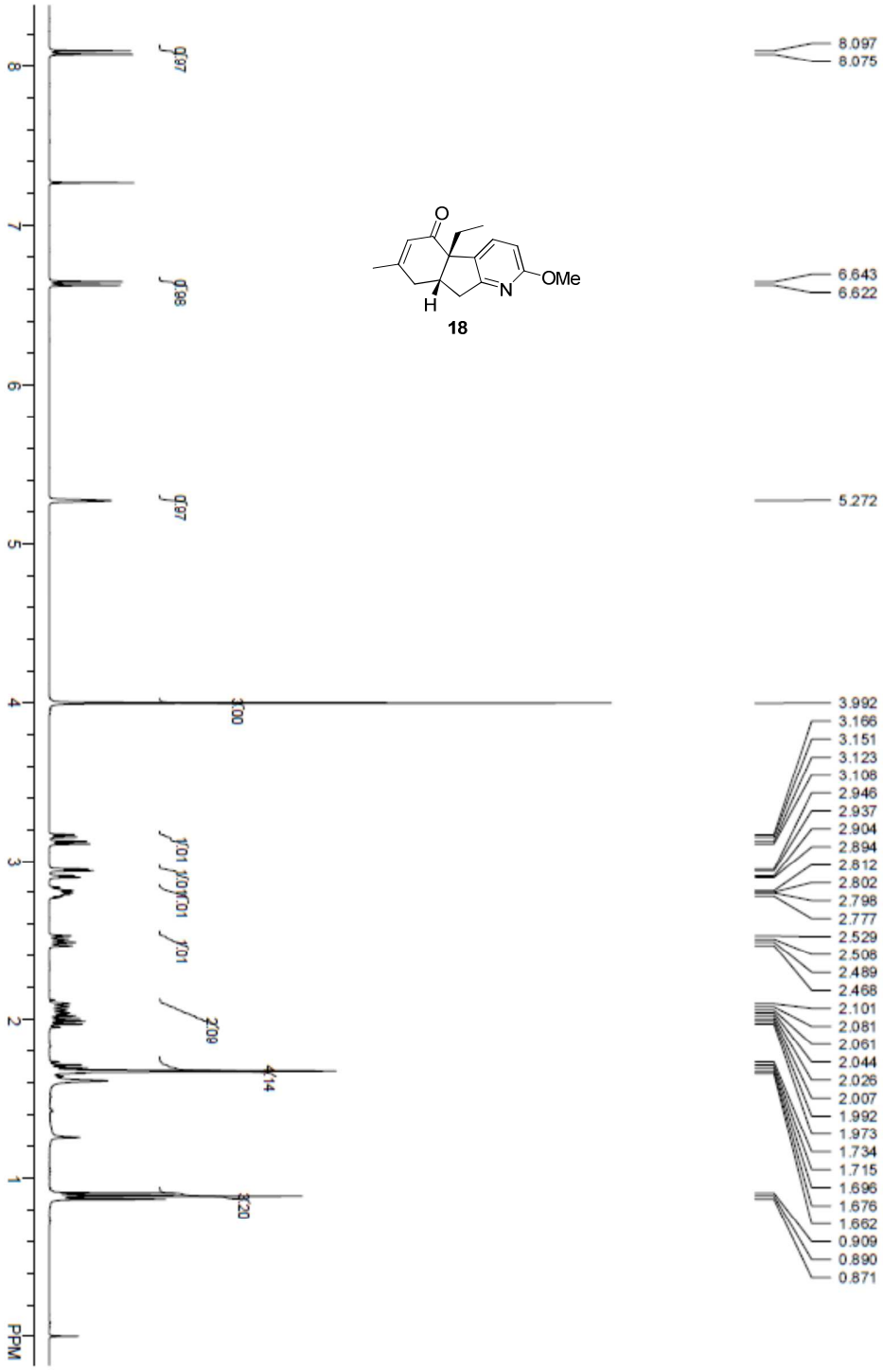
5.502
5.485
5.468
5.373
3.859
3.597
3.579
3.561
3.303
3.281
3.256
3.236
2.851
2.805
2.485
2.470
2.441
2.425
2.105
2.061
1.733
1.716
1.584
0.96
0.97
0.98
0.95
3.00
0.99
1.02
1.02
1.00
1.01
3.03
3.16
PPM

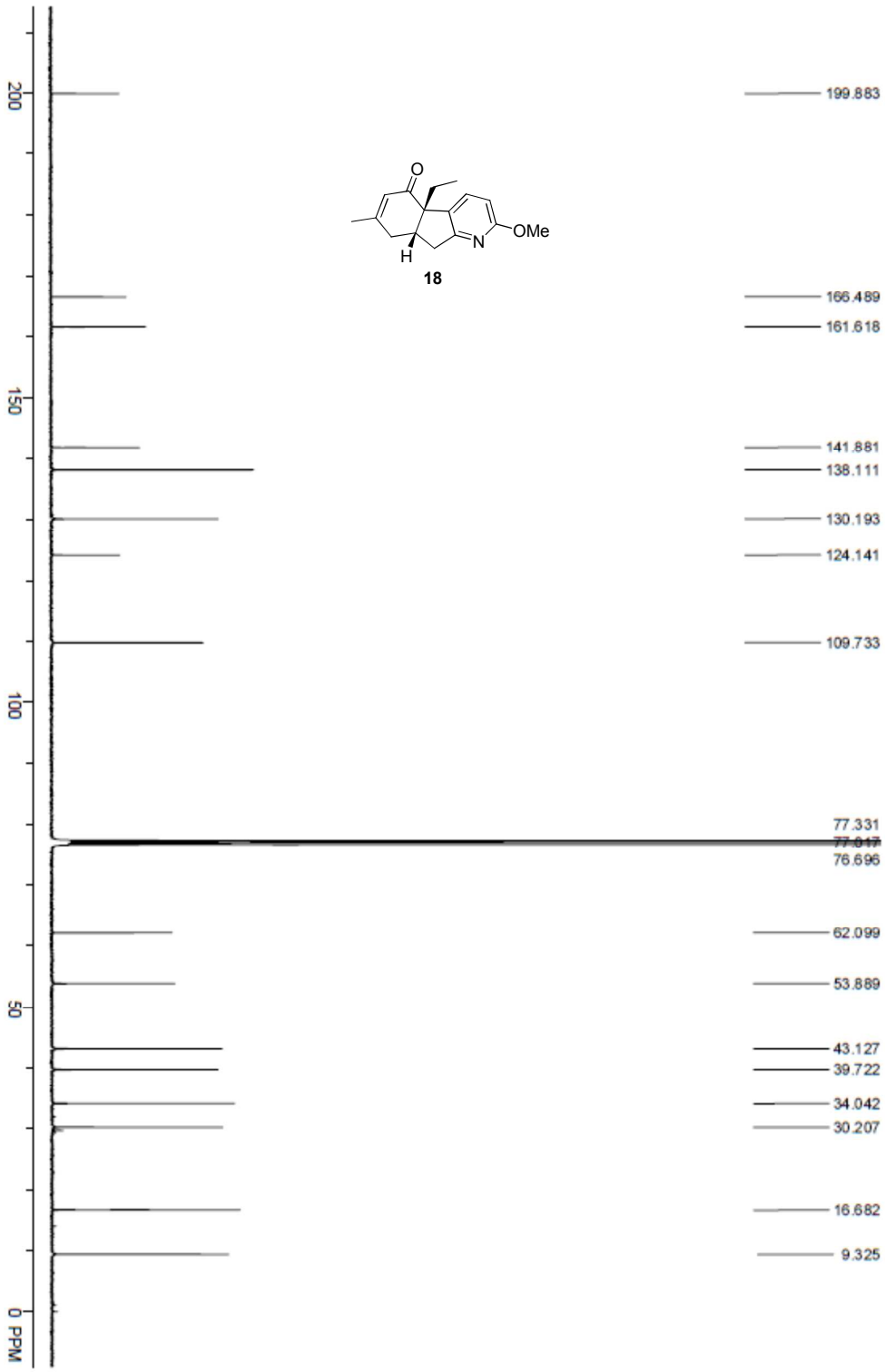
N
OMe
NH2

17


200
150
100
50
0PPM
N
OMe
NH2
161.976
154.706
143.543
133.955
133.809
133.569
132.723
110.338
107.050
77.353
77.032
76.718
55.209
53.306
41.625
41.457
29.383
22.624
12.234

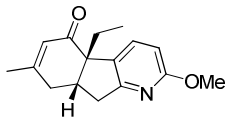
17


8.097
8.075
6.643
6.622
5.272
3.992
3.166
3.151
3.123
3.106
2.946
2.937
2.904
2.894
2.812
2.802
2.798
2.777
2.529
2.508
2.489
2.468
2.101
2.081
2.061
2.044
2.026
2.007
1.992
1.973
1.734
1.715
1.696
1.676
1.662
0.909
0.890
0.871
O
OMe
N
H
18
PPM

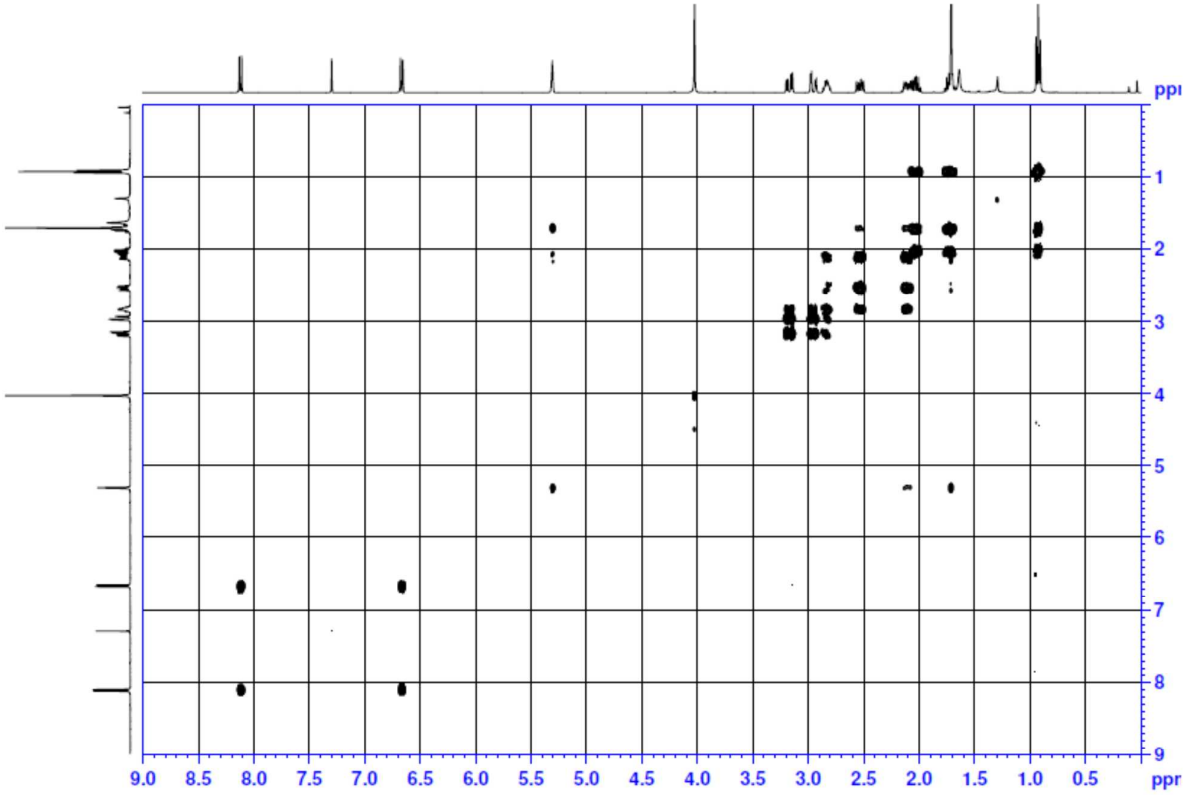

200
150
100
50
0 PPM
199.883
166.489
161.618
141.881
138.111
130.193
124.141
109.733
77.331
77.017
76.696
62.099
53.889
43.127
39.722
34.042
30.207
16.682
9.325
O
OMe
N
H

18

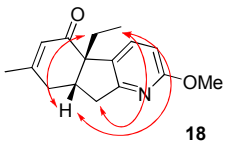
COSY


O
OMe
N
H

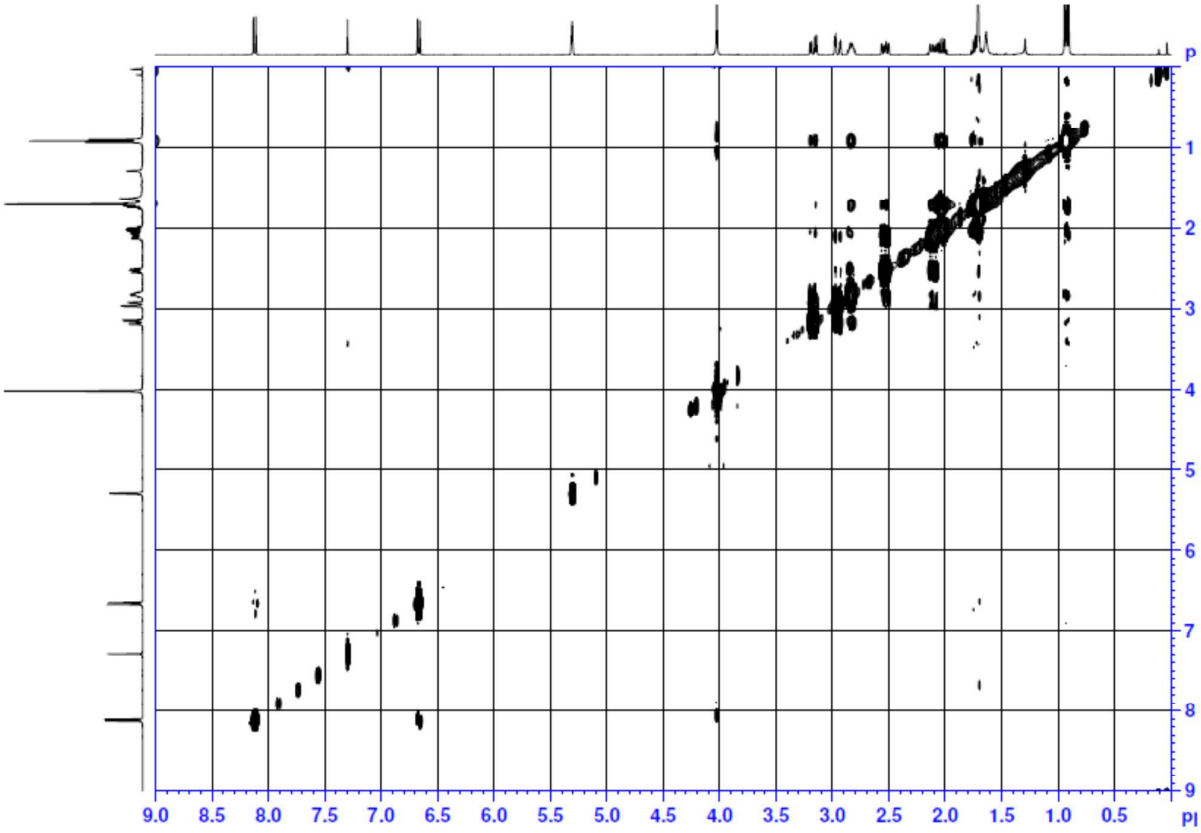
18

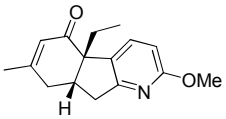

ppm
1
2
3
4
5
6
7
8
9
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

NOESY

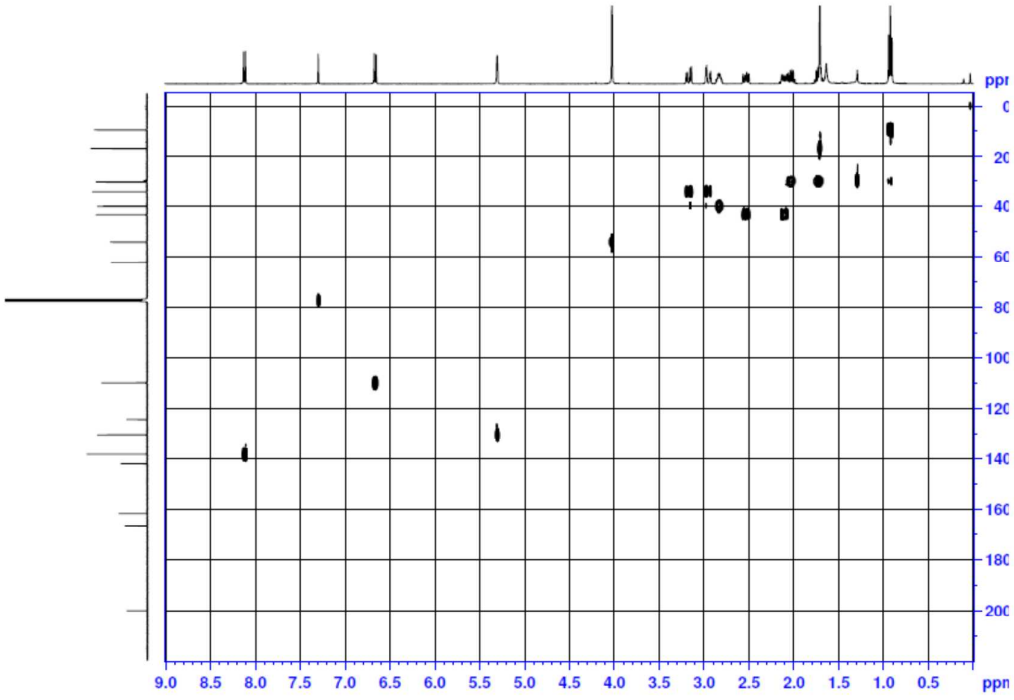

O
OMe
N
H

18

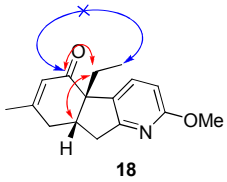

P
1
2
3
4
5
6
7
8
9
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
pl


O
OMe
N
H

HMQC **18**

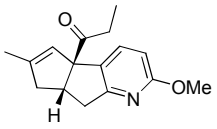

ppm
0
20
40
60
80
100
120
140
160
180
200
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
ppm

HMBC

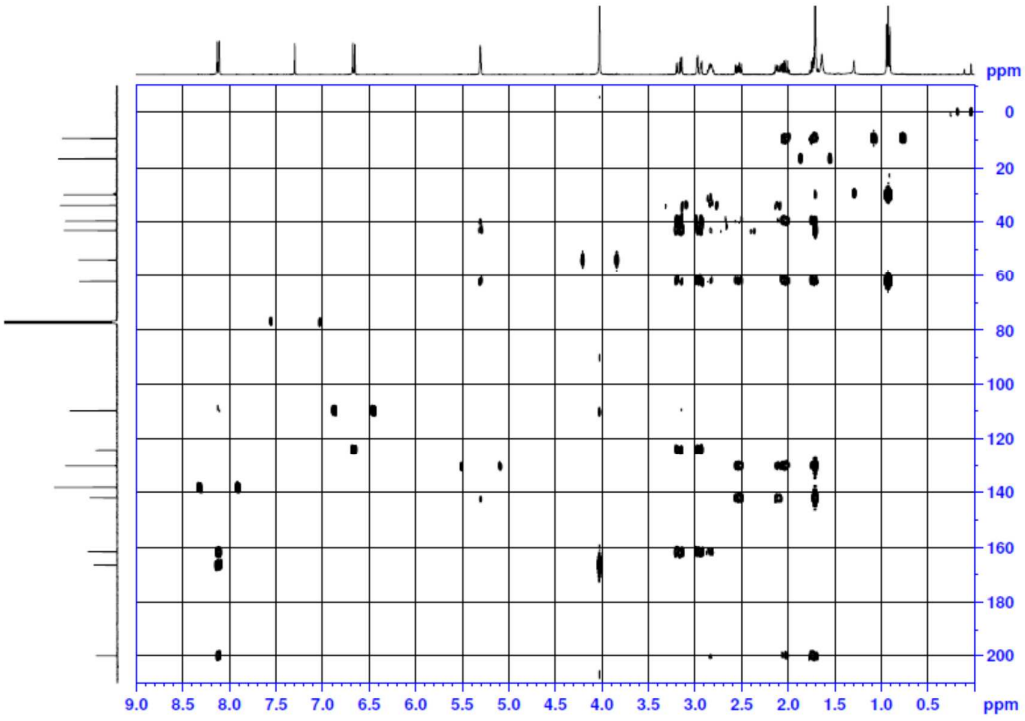


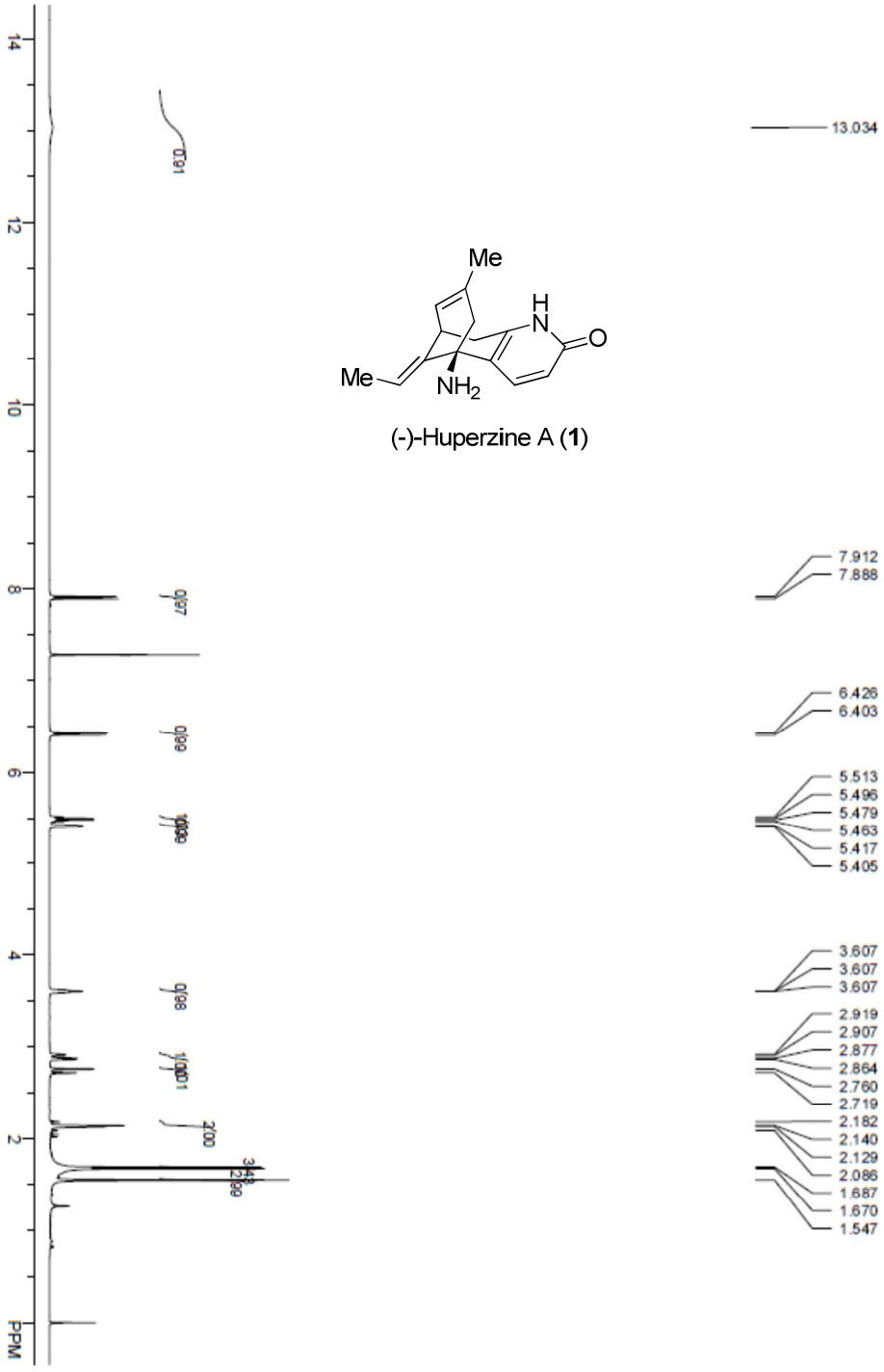
18

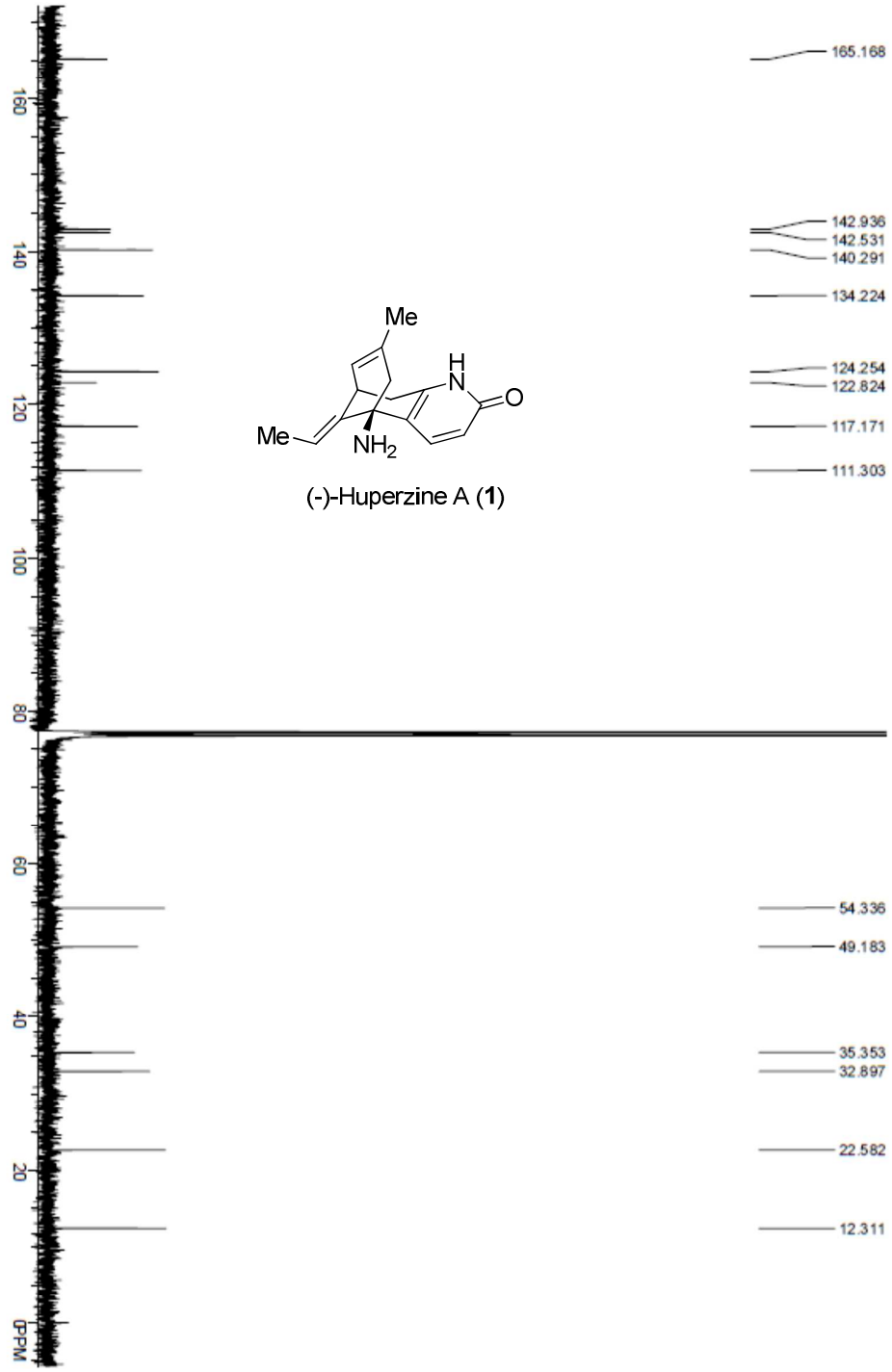
YES



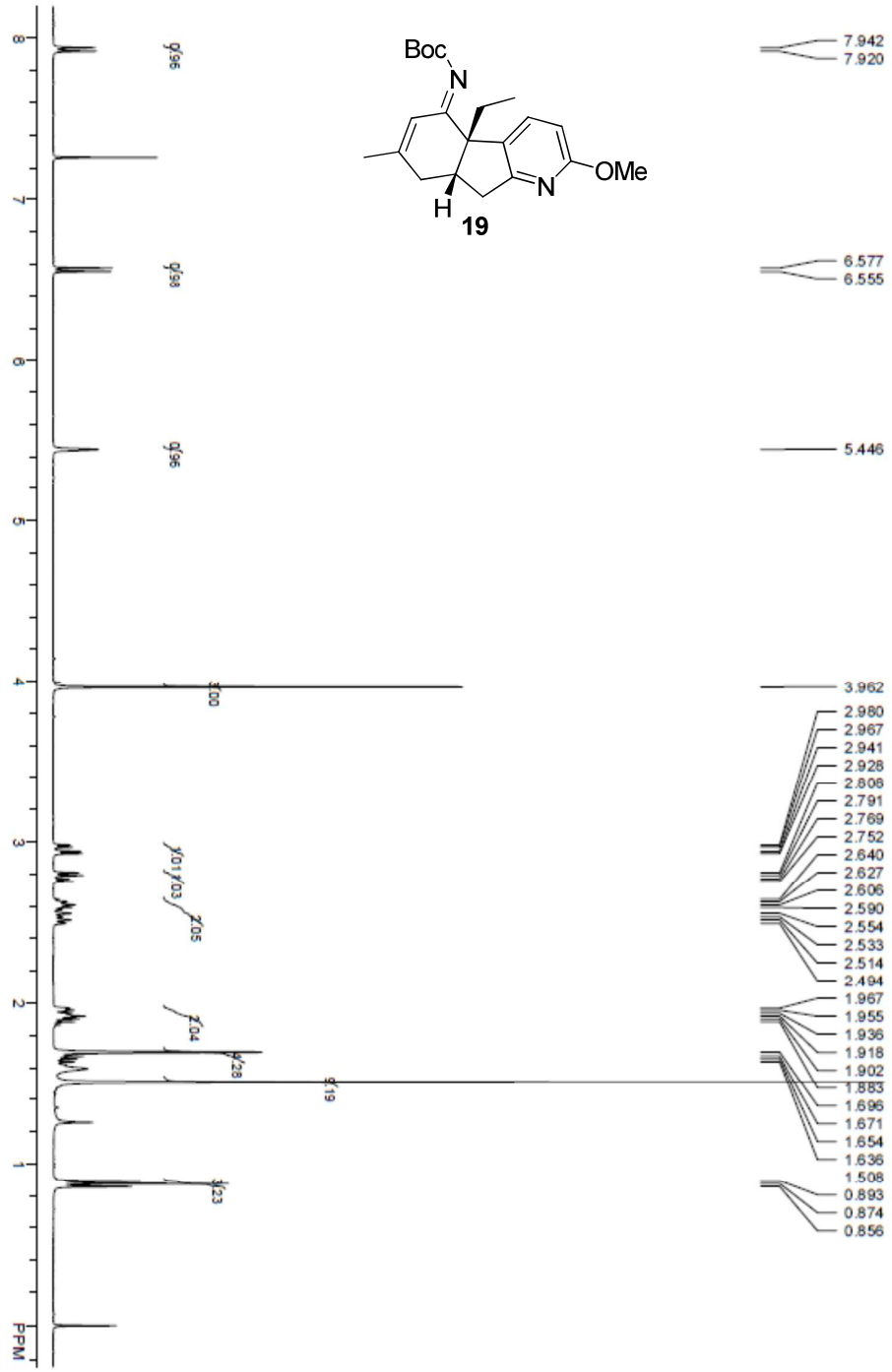
NO

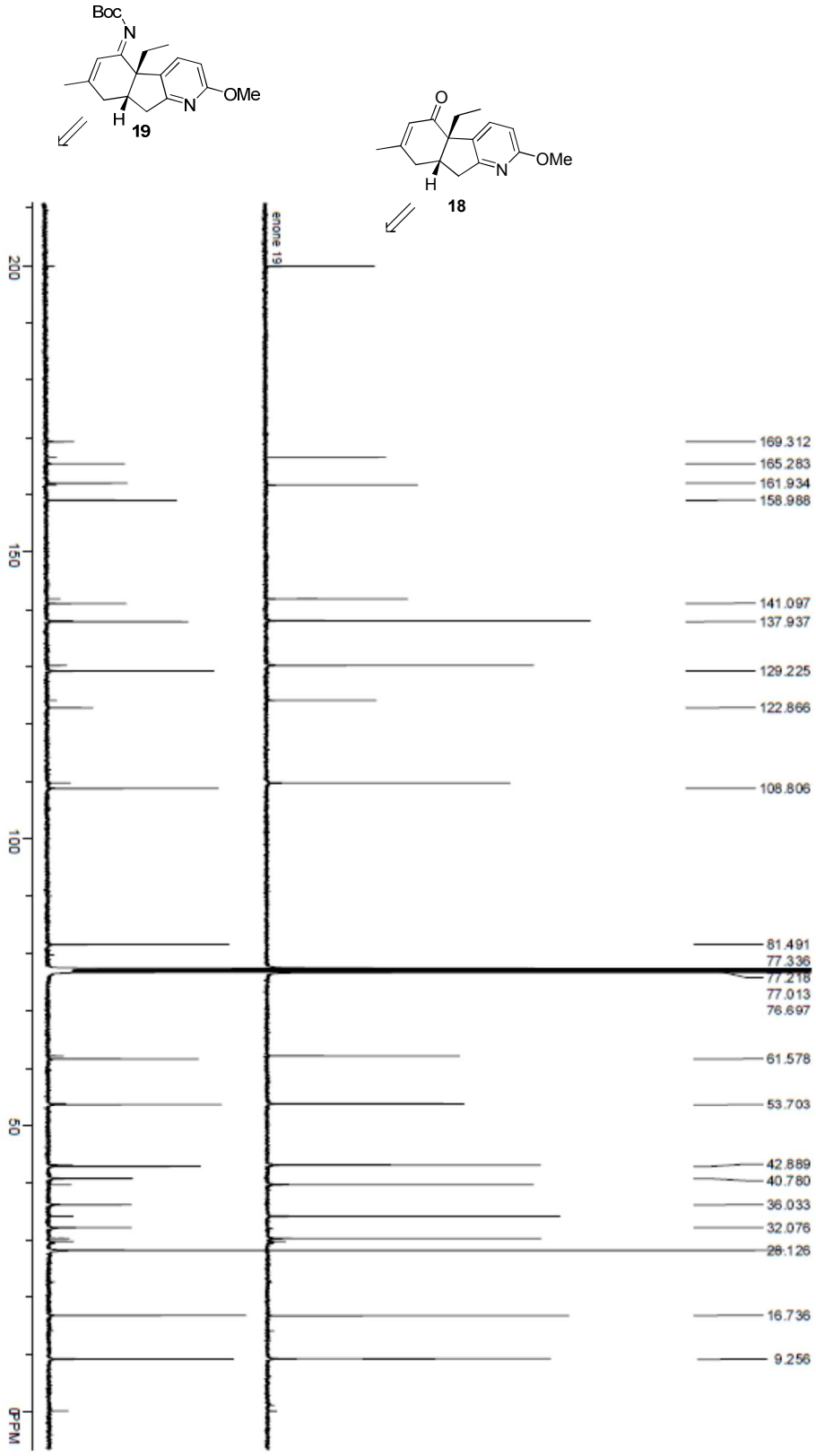



13.034
7.912
7.888
6.426
6.403
5.513
5.496
5.479
5.463
5.417
5.405
3.607
3.607
3.607
2.919
2.907
2.877
2.864
2.760
2.719
2.182
2.140
2.129
2.086
1.687
1.670
1.547
Me
H
N
O
Me
NH2
(-)-Huperzine A (1)
PPM



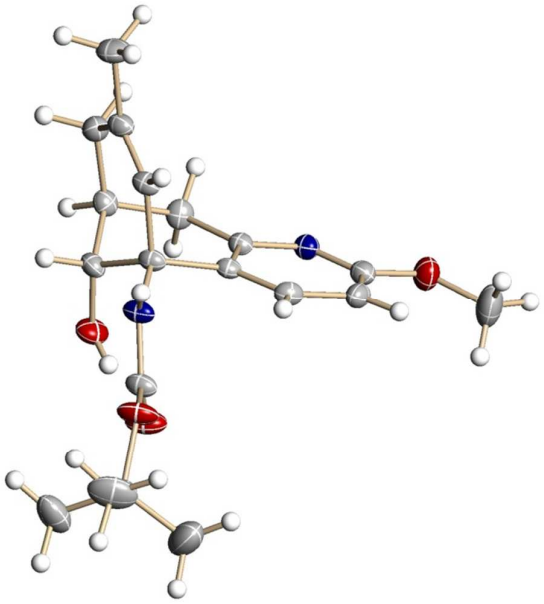
(-)-Huperzine A (**1**)

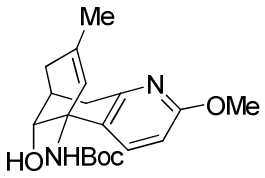

Boc
N
N
OMe
H
19
7.942
7.920
6.577
6.555
5.446
3.962
2.980
2.967
2.941
2.928
2.808
2.791
2.769
2.752
2.640
2.627
2.606
2.590
2.554
2.533
2.514
2.494
1.967
1.955
1.936
1.918
1.902
1.883
1.696
1.671
1.654
1.636
1.508
0.893
0.874
0.856
PPM


Boc
N
OMe
N
H
19
O
OMe
N
H
18
enone 19
200
150
100
50
0
PPM
169.312
165.283
161.934
158.988
141.097
137.937
129.225
122.866
108.806
81.491
77.336
77.218
77.013
76.697
61.578
53.703
42.889
40.780
36.033
32.076
28.126
16.736
9.256

6. X-ray Structures

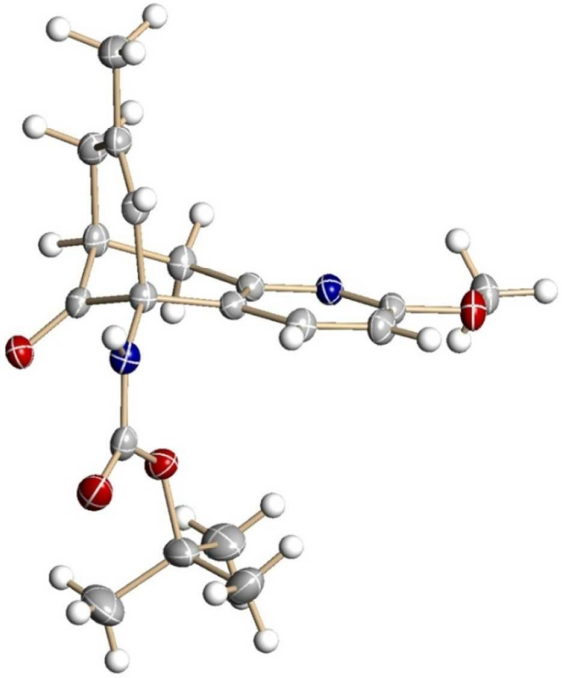
Compound 12a

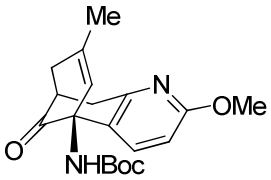




12a

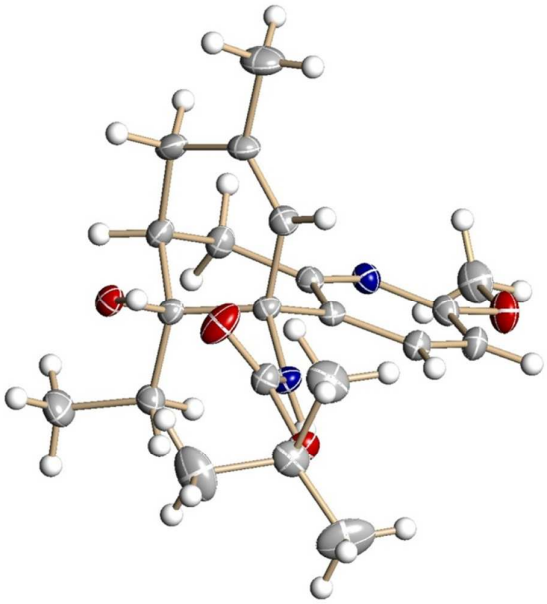
Compound 2

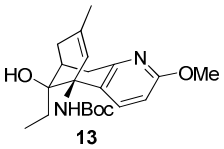




2

Compound 13





13