A Catalytic Asymmetric Total Synthesis of (–)-Perophoramidine

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Supporting Information

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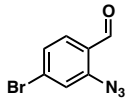
General Remarks:

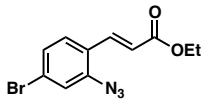
General Remarks: THF was distilled from Na(0)/benzophenone and degassed using the freeze-pump-thaw technique. All other anhydrous solvents were obtained from elution through alumina columns and degassed using the freeze-pump-thaw technique unless stated otherwise. Commercial reagents were used without further purification unless stated otherwise. Reactions were run under nitrogen or argon atmosphere and anhydrous conditions. TLC was performed on precoated glass plates (Merck). Flash chromatography was performed with silica gel 60, 230-400 mesh. ^{1}H- NMR (0 ppm for tetramethylsilane as internal standard) and ^{13}C-NMR (77.5 ppm for CDCl3 as internal standard) spectra were recorded on Varian UI- 600 (600 MHz), UI-500 (500 MHz), Varian MERC-400 (400 MHz), or Varian UI-300 (300 MHz). IR spectra (cm –1) were obtained with a Perkin-Elmer FT-IR Paragon 500 spectrometer or a Thermo Scientific Nicolet IR 100 FT- IR spectrometer using neat sample on a NaCl pad. Enantiomeric excess was determined using chiral HPLC analyses on a Themo Separation Products Spectra Series P-100 or 200 and UV100 (254 nm) using Chiralcell columns (OD-H, OB-H, AD-H, OJ-H OD, OB, OJ, AD, As, OC, IA, IB or IC) eluting with heptane / *iso*-propanol mixtures indicated. Optical rotations were measured on a Jasco DIP-1000 digital polarimeter using 5 cm cells and the sodium D line (589 nm) at ambient temperature in the solvent and concentration indicated.



2-azido-4-bromobenzaldehyde (**11**)

Sodium azide (7.80 g, 120.0 mmol, 1.20 eq.) was added to a solution of 4-bromo-2-fluorobenzaldehyde (20.3 g, 100 mmol, 1.00 eq.) in DMSO (100 mL, 1.0M). The reaction mixture was heated to 50 °C for 10 h. The mixture was allowed to cool to rt and was poured onto ice water (300 mL). The resulting white precipitate was collected and dried under vacuum. The Solids were dissolved in Et_2O (400 mL) and brine (100 mL) was added. The organic layer was collected, dried with anhydrous Mg_2SO_4, filtered through a plug of silica, eluting with additional Et_2O (250 mL), and concentrated *via* rotary evaporation. The product was >95% pure by ^{1}H NMR analysis and was used without further purification (18.74 g, 83%).

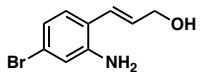
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 10.28 (s, 1H), 7.74 (d, *J* = 8.3, 1H), 7.43 (d, *J* = 1.5, 1H), 7.36 (d, *J* = 8.3, 1H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 187.80, 144.16, 130.41, 128.69, 125.92, 122.39. **IR** (film): 3087, 2122, 1684, 1585, 1391, 1279, 1196, 866, 810, 704, 432 cm $^{-1}$. **MP**: 89 ºC.



(*E*)-ethyl 3-(2-azido-4-bromophenyl)acrylate (**12**)

Triethyl phosphonoacetate (14.8 g, 66.0 mmol, 13.0 mL, 1.10 eq.) was added to a flask containing sodium hydride (1.58 g of 60% NaH dispersion in mineral oil, 66.0 mmol, 1.00 eq.) in THF (200 mL), at 0 ºC. The resulting reaction mixture was stirred for 30 min, was cooled to –78 °C, and 2-azido-4-bromobenzaldehyde (**11**) (13.56 g, 60.0 mmol, 1.00 eq.) in THF (150 mL, added at 0 °C, cooled in an ice bath) was added dropwise. The reaction mixture was stirred for 3 h at –78 °C, and was diluted with aqueous NH_4Cl with warming to rt. The phases were separated, and aqueous layer was then extracted three times with EtOAc. The combined organic layers where washed with brine and dried over $MgSO_4$. The solvent was removed *in vacuo*. The crude product was used directly since no significant impurities were observed in the ^{1}H NMR. A small portion of the crude was purified for analytical purposes *via* column chromatography (8% EtOAc/Pet. ether).[1]

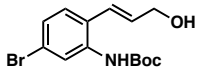
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.69 (d, *J* = 16.1, 1H), 7.31 (d, *J* = 8.55, 1H), 7.17 (m, 2H), 6.36 (d, *J* = 16.1, 1H), 4.20 (q, *J* = 7.1, 2H), 1.28 (t, *J* = 7.1, 3H). **^{13}C-NMR** (125 MHz, $CDCl_3$): δ = 166.66, 140.38, 137.74, 129.33, 128.35, 125.12, 124.95, 121.95, 120.47, 60.88, 14.55. **IR** (film): 2981, 2110, 1712, 1634, 1585, 1558, 1481, 1315, 1285, 1178, 1093, 1037, 984, 866, 812, 655, 568, 529, 440 cm $^{-1}$. **MP**: 44 ºC.



(E)-3-(2-amino-4-bromophenyl)prop-2-en-1-ol

To a solution of *E*-ethyl 3-(2-azido-4-bromophenyl)acrylate (**12**) (3.24 g, 11.0 mmol, 1.00 eq.) in THF (60.0 mL, 0.2 M), at –78 °C was added DIBAL-H solution (66.0 mL of a 1.0M solution, 6.00 eq.) dropwise. The reaction was allowed to warm to 0 °C over three hours and TLC indicated complete consumption of the starting material. The reaction was diluted slowly with saturate of sodium potassium tartrate (100 mL) and EtOAc (100 mL). The mixture was stirred overnight, whereupon two layers formed. The two phases were separated, and the aqueous layer was extracted two more times with ethyl acetate. The combined organic layers were dried over $MgSO_4$, and the solvent was evaporated *in vacuo* to give the desired product as a white solid 2.47 g (99%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.10 (d, *J* = 8.2, 1H), 6.85 (m, 2H), 6.58 (d, *J* = 15.7, 1H), 6.23 (dt, *J* = 15.7, 5.5, 1H), 4.33 (d, *J* = 4.8, 2H), 1.55 (brs, 1H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 145.16, 131.14, 129.06, 125.76, 122.28, 122.13, 122.06, 118.77, 63.99. **IR** (film): 3389, 3202, 2852, 1641, 1587, 1566, 1483, 1414, 1365, 1317, 1257, 1195, 1075, 974, 914, 880, 842, 776, 647, 579 cm $^{-1}$. **MP**: 108 ºC.

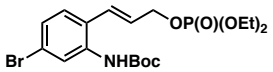


(*E*)-*tert*-butyl (5-bromo-2-(3-hydroxyprop-1-en-1-yl)phenyl)carbamate

E-3-(2-amino-5-bromophenyl)prop-2-en-1-ol (7.71 g, 33.8 mmol, 1.10 eq.), Boc_2O (9.39 g, 43.0 mmol, 1.40 eq.) and Na_2CO_3 (3.26 g, 30.7 mmol, 1.00 eq.) were suspended in dioxane/water. The reaction mixture was heated to 70 °C, for 3 h, after which the same amount of both Boc_2O and Na_2CO_3 were added. The reaction mixture was stirred for 15 h, followed by the addition of another amount of Boc_2O and Na_2CO_3. The same procedure was repeated after another 5 h. The

reaction mixture was diluted with water (100 mL) and ethyl acetate (100 mL). The layers were separated, and the aqueous phase was extracted with ethyl acetate (2x 100 mL). The combined organic phases were washed with brine, dried with anhydrous $MgSO_4$, and concentrated *via* rotary evaporation. The crude reaction mixture was purified *via* flash chromatography (50% EtOAc:Pet. ether) to provide the desired product as a white solid (1.0 g, 78%, 97% brsm). (R_f: 0.55 50% EtOAc:Pet. ether.

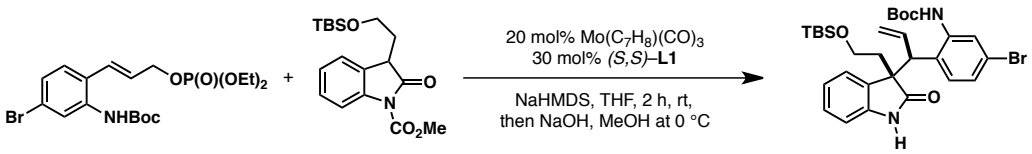
^{1}H-NMR (400 MHz, CDCl3): δ = 7.99 (brs, 1H), 7.12 (s, 2H), 6.69 (s, 1H), 6.57 (d, J = 15.7, 1H), 6.17 (dt, J = 15.7, 5.1, 1H), 4.28 (m, 2H), 2.77 (brs, 1H), 1.50 (s, 9H). **^{13}C-NMR** (100 MHz, CDCl3): δ = 152.96, 136.25, 133.14, 128.18, 127.04, 126.90, 124.43, 124.31, 121.75, 81.28, 63.15, 28.37. **IR** (film): 3309, 2978, 2928, 1700, 1571, 1512, 1458, 1411, 1393, 1367, 1273, 1236, 1157, 1119, 1085, 1052, 1024, 970, 861, 771, 580 cm $^{-1}$. **MP** = 104 ºC.



(*E*)-*tert*-butyl (5-bromo-2-(3-((diethoxyphosphoryl)oxy)prop-1-en-1-yl)phenyl)carbamate (9)

To a solution of *E*-tert-butyl (5-bromo-2-(3-hydroxyprop-1-en-1-yl)phenyl) carbamate (10.2 g, 31.0 mmol, 1.00 eq.) in DCM (155 mL, 0.24 M), and pyridine (7.00 mL) at 0 ºC was added diethylchlorophosphate (5.88 g, 34.1 mmol, 1.50 eq.). The reaction was stirred at 0 °C for 3 h was diluted with EtOAc (200 mL) and ice cold HCl (200 mL, 0.5M). The layers were separated and the organic layer was washed with ice cold 0.5M HCl (2x 100 mL). The organic layer was dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude reaction mixture was purified *via* column chromatography (50% EtOAc:PE) to afford the desired product as a pale yellow oil that solidifies upon cooling (10.9 g, 76% yield). (R_f = 0.31 (50% EtOAc:PE).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.07 (brs, 1H), 7.17 (s, 2H), 6.69 (d, *J* = 15.6, 1H), 6.60 (brs, 1H), 6.16 (dt, *J* = 15.7, 6.0, 1H), 4.69 (m, 2H), 4.13 (q, *J* = 7.4, 7.4, 4H), 1.51 (s, 9H), 1.34 (t, *J* = 7.1, 6H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 152.81, 136.81, 128.54, 128.28, 128.22, 128.07, 126.98, 124.33, 122.69, 81.37, 67.72, 67.67, 64.22, 64.16, 28.49, 16.42, 16.35. **IR** (film), cm^{-1}: 3236, 2981, 2933, 1723, 1591, 1572, 1515, 1478, 1411, 1392, 1368, 1269, 1160, 1100, 1029, 972, 872, 854, 799, 773, 511. **MP**: 80 °C.



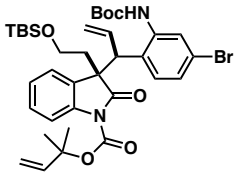
***tert*-butyl (5-bromo-2-((*S*)-1-((*S*)-3-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-2-oxoindolin-3-yl)allyl)phenyl)carbamate (8)**

To a solution of oxindole **10** (4.54 g, 13.0 mmol, 1.0 eq) in THF (40.0 mL) was added a solution of NaHMDS (26.0 mL, 0.5M/THF, 13 mmol) at 0 °C. The solution was allowed to warm to room temperature, and was stirred for 10 minutes. To the deprotonated oxindole solution was added a premixed, deep purple solution of the active catalyst consisting of ($Mo(C_7H_8)(CO)_3$, 704.9 mg, 2.6 mmol, 20 mol%) and ligand (*S,S,*)-**L1**, 1.26 g, 3.9 mmol, 30 mol%) in THF (8.0 mL) that was preheated at 60 °C for 15 min. Upon addition of the catalyst solution, a solution of phosphate **9** (6.10 g, 13.1 mmol, 1.01 eq) was added in THF (32.0 mL) over 20 minutes *via* syringe pump. After 2 h, the red/brown reaction mixture was cooled to 0 ºC and NaOH solution (26.0 mL, 1.0 M/MeOH, 26 mmol) was added, and the resulting solution was stirred for 30 minutes. The reaction mixture was diluted with Et_2O (100 mL), and was filtered thru a 4 cm plug of silica gel eluting with an additional 200 mL of Et_2O. The resulting solution was concentrated *via* rotary evaporation. The crude reaction mixture was purified *via* flash chromatography (10 % → 15 % EtOAc:Pet. ether.) providing the minor diastereomer (878.2 mg) R_f (minor) = 0.23 (15 % EtOAc:PE) as a white foam followed by the desired product and linear isomer (6.36 g) as a white foam R_f (major) = 0.23 (15 % EtOAc:PE) in 93 % yield for the mixture of regioisomers and diastereomers. The %ee of the major diastereomer was determined *via* chiral HPLC (97%, IA, 98:2 heptane:^{i}PrOH, 254 nM, 0.8 mL/min, t_{minor} = 21.9 min, t_{major} = 34.1 min).

Major Diastereomer:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.34 (s, 1H), 7.69 (brs, 1H), 7.18 (m, 1H), 7.10 (m, 1H), 7.0 (m, 3H), 6.76 (d, *J* = 7.7, 1H), 6.35 (s, 1H), 6.15 (m, 1H), 5.14 (d, *J* = 16.8, 1H), 5.06 (d, *J* = 10.3, 1H), 3.86 (d, *J* = 9.4, 1H), 3.24 (m, 2H), 2.44 (m, 1H), 1.88 (m, 1H), 1.53 (m, 9H), 0.77 (s, 1H), 0.73 (s, 9H), -0.19 (s, 3H), -0.23 (s, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$): δ = 181.17, 153.31, 141.60, 137.03, 135.05, 131.10, 129.41, 128.72, 127.45, 124.75, 123.77, 122.49, 122.00, 121.03, 118.86, 110.10, 81.08, 60.64, 59.48, 55.36, 51.09, 37.80, 28.58, 26.01, 21.28, 18.37, 14.42, -5.58, -5.62. **IR** (film): 3229, 2927, 2855, 1841, 1708, 1650, 1620, 1592, 1573, 1556, 1504, 1470, 1454, 1392, 1367, 1251, 1159, 1109, 1050, 1022, 922, 836, 776, 752 cm $^{-1}$. MP: 87 ºC. **HRMS**:

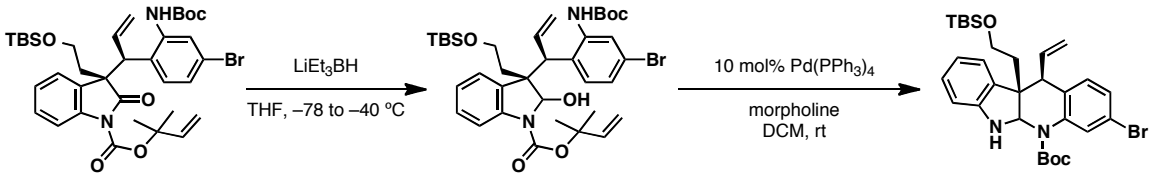
($C_{30}H_{41}BrN_2NaO_4Si$): calculated (M + Na): 623.1911, found (M + Na): 623.1913.



(*S*)-2-methylbut-3-en-2-yl 3-((*S*)-1-(4-bromo-2-((*tert*-butoxycarbonyl)amino)phenyl) allyl)-3-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-2-oxoindoline-1-carboxylate (14)

To a solution of oxindole (**8**) (3.01 g, 5.0 mmol) in THF (20.0 mL) at 0 ºC was added a solution of NaHMDS (6.0 mL, 1M/THF, 6.0 mmol). After 5 min, the reaction mixture was cooled to –78 ºC, and a solution of 2-methylbut-3-en-2-yl (4-nitrophenyl) carbonate (**13**) (1.38 g, 5.5 mmol) in THF (5.0 mL) was added dropwise. The reaction mixture was allowed to reach –20 ºC at which point TLC indicated the complete consumption of oxindole starting material. A saturated aqueous solution of $NaHCO_3$ (100 mL) was added to the reaction medium which was allowed to reach rt. The resulting biphasic reaction mixture was diluted with EtOAc (150 mL) and water (100 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (3x, 100 mL). The combined organic phases were dried over anhydrous $MgSO_4$ and the solvent was removed *en vacuo*. The crude reaction mixture was purified *via* column chromatography (10% Et_2O/pet. ether) to provide the desired product as a white foam (2.60 g, 73%). R_f = 0.3 (10% Et_2O/Pet. ether).

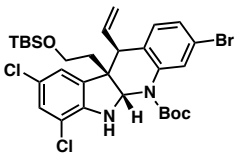
^{1}H-NMR (400 MHz; $CDCl_3$): δ 7.75 (d, *J* = 8.1 Hz, 1H), 7.62 (br s, 1H), 7.30-7.25 (m, 1H), 7.17-7.11 (m, 2H), 7.06 (d, *J* = 7.3 Hz, 1H), 6.98 (d, *J* = 8.4 Hz, 1H), 6.22-6.00 (m, 3H), 5.37 (d, *J* = 17.4 Hz, 1H), 5.20-5.12 (m, 3H), 3.77 (d, *J* = 9.6 Hz, 1H), 3.44-3.39 (m, 1H), 3.15 (td, *J* = 10.5, 4.0 Hz, 1H), 2.61-2.54 (m, 1H), 1.84-1.79 (m, 1H), 1.66 (ap d, *J* = 2.9 Hz, 6H), 1.51 (s, 9H), 0.68 (s, 9H), -0.24 (s, 3H), -0.33 (s, 3H). **^{13}C NMR** (101 MHz; CDCl3): δ 177.1, 153.3, 149.0, 141.9, 140.6, 136.9, 134.5, 130.7, 129.0, 127.82, 127.66, 123.95, 123.80, 121.1, 119.1, 115.6, 114.0, 83.9, 81.0, 59.2, 55.0, 52.4, 37.0, 28.5, 26.8, 26.6, 26.0, 18.3, -5.87, -5.92. **IR** (film): 3387, 2954, 2929, 2857, 1769, 1732, 1508, 1466, 1354, 1295, 1251, 1229, 1159, 1124, 835, 772 cm $^{-1}$. **HRMS**: ($C_{36}H_{49}BrN_2NaO_6Si$): calculated (M + Na): 735.2441, found (M + Na): 735.2443.



(10b*S*,11*S*)-*tert*-butyl 3-bromo-10b-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-11-vinyl-5a,6,10b,11-tetrahydro-5*H*-indolo[2,3-*b*]quinoline-5-carboxylate (7)

To a solution of carbamate (**14**) (5.00 g, 7.0 mmol) in THF (35 mL) at –78 ºC was added a solution of $LiEt_3BH$ (14.0 mL, 1M/THF). The reaction mixture was allowed to reach –40 ºC at which point TLC indicated the complete consumption of the carbamate starting material. The reaction mixture was diluted with MeOH (10 mL) and was warmed to rt. EtOAc (200 mL) and water (200 mL) were added and the biphasic mixture was stirred for 15 min. The organic layer was separated, and the aqueous layer was washed with EtOAc (3x 150 mL). The combined organic phases were dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuo*. The crude reaction mixture was dissolved in degassed DCM (35 mL), and morpholine (6.10 g, 70 mmol) was added followed by tetrakis(triphenylphosphine)palladium(0) (404.6 mg, 0.35 mmol, 5.0 mol%). The reaction mixture was stirred at rt for 16 h and was filtered through a 4 cm plug of silica washing with Et_2O (300 mL). The crude reaction mixture was concentrated *in vacuo* and was purified *via* column chromatography (10% Et_2O/pet. ether) to provide the desired product as a white foam (3.03 g, 74% over 2 steps) $R_f = 0.64$ (10% EtOAc/Pet. ether).

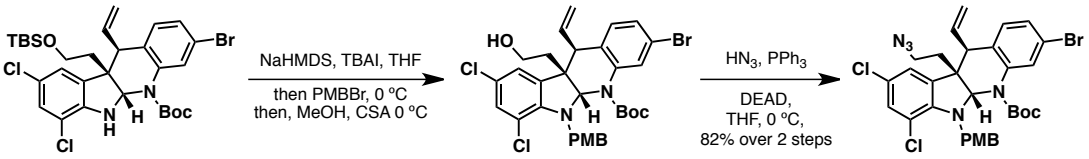
^{1}H-NMR (500 MHz; $CDCl_3$): δ 7.42 (s, 1H), 7.02 (dd, *J* = 8.0, 1.9 Hz, 1H), 6.89 (td, *J* = 7.6, 1.1 Hz, 1H), 6.83 (dd, *J* = 7.5, 0.7 Hz, 1H), 6.79 (d, *J* = 8.1 Hz, 1H), 6.58 (td, *J* = 7.4, 0.6 Hz, 1H), 6.44 (d, *J* = 7.8 Hz, 1H), 6.08 (ddd, *J* = 17.0, 10.1, 8.2 Hz, 1H), 5.68 (s, 1H), 5.18 (dd, *J* = 10.2, 0.5 Hz, 1H), 5.13 (d, *J* = 17.0 Hz, 1H), 4.44 (s, 1H), 3.84 (d, *J* = 8.2 Hz, 1H), 3.66 (ddd, *J* = 10.2, 8.4, 5.2 Hz, 1H), 3.54-3.49 (m, 1H), 2.13 (ddd, *J* = 13.7, 8.3, 6.7 Hz, 1H), 2.03 (ddd, *J* = 13.6, 8.2, 5.3 Hz, 1H), 0.89 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H). **^{13}C-NMR** (126 MHz; CDCl3): δ 149.0, 138.2, 135.7, 132.9, 130.7, 129.3, 128.17, 128.06, 127.7, 123.5, 119.6, 118.7, 118.1, 108.6, 82.1, 59.6, 55.1, 50.3, 40.3, 28.6, 26.2, 18.5, -5.12, -5.13. **IR** (film): 3375, 2954, 2930, 1685, 1609, 1594, 1486, 1470, 1392, 1369, 1334, 1255, 1221, 1162, 1099, 1077, 1038, 835, 811, 775, 740 cm $^{-1}$. **$[\alpha]^{22}_D$**: –96.8 (CH_2Cl_2, c 1.06). **HRMS**: ($C_{30}H_{42}BrN_2O_3Si$): calculated (M + H): 585.2148, found (M + H): 585.2140.



(10b*S*,11*S*)-*tert*-butyl 3-bromo-10b-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-7,9-dichloro-11-vinyl-5a,6,10b,11-tetrahydro-5*H*-indolo[2,3-*b*]quinoline-5-carboxylate (15)

To a solution tetracycle (**7**) (2.64 g, 4.5 mmol) in acetic acid (90 mL) was added NaH_2PO_4 (5.40 g, 45.0 mmol) followed by freshly recrystallized *N*-chlorosuccinimide (3.61 g, 27.0 mmol). The reaction mixture was stirred at rt for 16 h at which point saturated $Na_2S_2O_4$ (80 mL) and EtOAc (150 mL) were added. The biphasic mixture was stirred at rt for 15 min, and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (3x, 150 mL). The combined organic phases were dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuo*. The crude reaction mixture was purified *via* column chromatography (5% Et_2O/Pet. ether) to provide the desired product as a white foam (2.59 g, 88%). R_f = 0.66 (10% Et_2O/Pet. ether).

^{1}H-NMR (500 MHz; $CDCl_3$): δ 7.42 (s, 1H), 7.06 (dd, *J* = 8.0, 1.9 Hz, 1H), 6.89 (d, *J* = 1.9 Hz, 1H), 6.78 (d, *J* = 8.1 Hz, 1H), 6.71 (d, *J* = 1.9 Hz, 1H), 5.99 (ddd, *J* = 17.0, 10.2, 8.1 Hz, 1H), 5.79 (s, 1H), 5.17 (d, *J* = 10.3 Hz, 1H), 5.09 (d, *J* = 17.0 Hz, 1H), 4.64 (s, 1H), 3.75 (d, *J* = 8.1 Hz, 1H), 3.61-3.57 (m, 1H), 3.50 (dt, *J* = 10.5, 6.9 Hz, 1H), 2.10 (dt, *J* = 14.1, 7.0 Hz, 1H), 2.03-1.97 (m, 1H), 1.52 (s, 9H), 0.89 (s, 9H), 0.01 (d, *J* = 3.5 Hz, 6H). **^{13}C-NMR** (126 MHz; CDCl3): δ 153.18, 153.17, 144.9, 137.7, 135.0, 133.5, 132.2, 129.2, 128.5, 128.1, 127.5, 123.0, 122.2, 119.9, 118.6, 113.8, 82.4, 77.2, 76.7, 59.4, 56.8, 50.3, 39.7, 28.5, 26.1, 18.4, -5.35, -5.38. **IR** (film): 2954, 2930, 2857, 1692, 1594, 1485, 1471, 1391, 1369, 1332, 1255, 1225, 1161, 1104, 1022, 837, 776, 734 cm $^{-1}$. **$[\alpha]^{22}_D$**: –107.4 (CH_2Cl_2, c 1.06). **HRMS**: ($C_{30}H_{40}BrCl_2N_2O_3Si$): calculated (M + H): 653.1363, found (M + H): 653.1376.

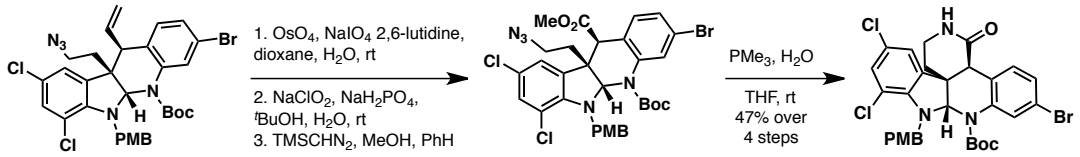


(5aS,10bS,11S)-tert-butyl 3-bromo-10b-(2-((tert-butyldimethylsilyl)oxy)ethyl)-7,9-dichloro-6-(4-methoxybenzyl)-11-vinyl-5a,6,10b,11-tetrahydro-5H-indolo[2,3-b]quinoline-5-carboxylate (6)

To a solution of dichloride **15** (2.62g, 4.0 mmol) and TBAI (147.7 mg, 0.40 mmol) in THF (40.0

mL) at 0 ºC was added a solution of NaHMDS (8.4 mL, 0.5M/THF, 4.2 mmol). The resulting reaction mixture was stirred for 5 min before PMBBr (844.5 mg, 4.2 mmol) was added. The resulting reaction mixture became heterogeneous after 5 min and TLC analysis indicated complete consumption of the starting material and a new, more polar spot. R_f = 0.5 (10% EtOAc/Pet Ether). The reaction mixture was diluted with MeOH (20 mL) at 0 ºC and CSA (1.86 g, 8.0 mmol) was added. The reaction mixture was stirred at 0 ºC for 6 h upon which TLC indicated the formation of a new polar product. The reaction mixture was diluted with saturate $NaHCO_3$ solution (200 mL), and the biphasic mixture was stirred with warming to rt. The layers were separated and the aqueous layer was extracted with EtOAc (3x 100 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and the solvent was removed *via* rotary evaporation. The crude product was purified *via* column chromatography (30% EtOAc/Pet. ether) to afford the desired product as a white foam with <5% PMBOH as an impurity. The primary alcohol product was dissolved in THF (40.0 mL) and to this solution was added PPh_3 (2.10 g, 8.0 mmol) and HN_3 solution (6.67 mL, 1.2M/PhMe, 8.0 mmol). The reaction mixture was cooled to 0 ºC and DEAD (1.39 g, 8.0 mmol, 40% solution in PhMe) was added. The resulting reaction mixture was stirred at 0 ºC for 15 min upon which TLC analysis indicated complete consumption of the alcohol starting material. The reaction mixture was concentrated *via* rotary evaporation and the crude reaction mixture was purified *via* column chromatography (5→10% Et_2O, Pet. ether.) to provide the desired product as a white foam. (2.25 g, 82% over 2 steps). R_f = 0.3 (10% Et_2O/Pet. ether).

^{1}H-NMR (500 MHz; $CDCl_3$): δ 7.29-7.25 (m, 2H), 7.12 (dd, *J* = 8.0, 1.4 Hz, 1H), 6.96 (d, *J* = 2.0 Hz, 1H), 6.93-6.90 (m, 2H), 6.78-6.76 (m, 2H), 6.00 (s, 1H), 5.77 (ddd, *J* = 16.7, 10.2, 8.8 Hz, 1H), 5.13 (t, *J* = 9.1 Hz, 2H), 4.94 (d, *J* = 16.1 Hz, 1H), 4.81 (d, *J* = 16.1 Hz, 1H), 3.84 (s, 3H), 3.45 (d, *J* = 8.7 Hz, 1H), 2.73-2.67 (m, 2H), 2.00 (ddd, *J* = 13.8, 10.0, 5.9 Hz, 1H), 1.82 (td, *J* = 0.8, 0.4 Hz, 1H), 1.43 (s, 9H). **^{13}C-NMR** (126 MHz, $CDCl_3$): δ 159.29, 153.19, 144.19, 137.54, 135.57, 135.02, 133.12, 131.31, 130.73, 130.55, 129.66, 129.06, 122.54, 121.84, 120.07, 118.88, 114.03, 112.69, 82.14, 79.46, 55.53, 54.67, 53.05, 48.91, 47.24, 39.24, 28.42. **IR** (film): 2935, 2892, 2069, 1676, 1491, 1461, 1372, 1350, 1309, 1231, 1148, 724 cm $^{-1}$. **$[\alpha]^{22}_D$**: –126.2 (CH_2Cl_2, c 1.09). **HRMS**: ($C_{32}H_{33}BrCl_2N_3O_3$): calculated (M –N_2 + H): 656.1082, found (M –N_2 + H): 656.1099.

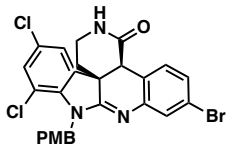


(4a*S*,9a*S*,14b*S*)-*tert*-butyl 12-bromo-6,8-dichloro-9-(4-methoxybenzyl)-1-oxo-1,3,4,9,9a,14b-hexahydrobenzo[*c*]indolo[3,2-*j*][2,6]naphthyridine-10(2*H*)-carboxylate (5)

To the tetrazyclic azide **6** (685 mg, 1.0 mmol) in dioxane (10 mL) was added 2,6-lutidine (214 mg, 2.0 mmol), $NaIO_4$ (856 mg, 4.0 mmol), water (3.3 mL) and OsO_4 (4% solution in water, 100 μL, 1 vol% relative to dioxane). The reaction mixture was stirred for 16 h at rt and TLC analysis indicated disappearance of the starting material and formation of a new polar spot. The reaction mixture was diluted with saturated $Na_2S_2O_4$ solution (15 mL), and EtOAc (50 mL). The biphasic mixture was stirred at rt for 15 min and the layers were separated. The aqueous layer was extracted with EtOAc (3x 50 mL), the combined organic phases were dried over anhydrous $MgSO_4$ and the solvent was removed *via* rotary evaporation. ^{1}H NMR analysis of the crude reaction mixture indicated clean formation of the desired aldehyde. The crude aldehyde was dissolved in ^{t}BuOH (20 mL), and 2-methyl-2-butene (1.40 g, 20 mmol) was added followed by a solution of $NaClO_2$ (904 mg, 10 mmol) and NaH_2PO_4 (10.9 g, 7.0 mmol) in water (10 mL). The reaction mixture was stirred at rt for 2 h upon which TLC analysis indicated no remaining aldehyde starting material. The reaction mixture was diluted with saturated $Na_2S_2O_4$ solution (25 mL), and EtOAc (50 mL) and the biphasic mixture was stirred at rt for 15 min. The layers were separated and the aqueous layer was extracted with EtOAc (3x 50 mL). The combined organic phases were dried over anhydrous $MgSO_4$ and the solvent was removed *via* rotary evaporation. ^{1}H NMR analysis of the crude reaction mixture indicated formation of the desired carboxylic acid. The crude carboxylic acid was dissolved in PhH (5.0 mL) and MeOH (5.0 mL). $TMSCHN_2$ solution (2.5 mL, 5.0 mmol, 2M/Et_2O) was added. Nitrogen evolution occurred, and the reaction mixture became yellow over 10 min. TLC analysis indicated no starting material after 15 min and silica gel was added to the reaction mixture to consume unreacted reagent (2.0 g). The slurry was stirred for 15 min and then filtered washing with EtOAc (100 mL). The filtrate was concentrated and the crude reaction mixture was purified *via* column chromatography (10% Et_2O/Pet. ether) to afford the desired ester as a white foam. (378 mg ~90% pure.) To the azido ester (378 mg, 0.527 mmol) in THF (5.3 mL) was added water (20 μL, 1.1 mmol) followed by a solution of PMe_3 (2.60 mL, 1M/PhMe). The resulting reaction mixture was stirred for 6 h at rt.

TLC analysis indicated complete consumption of the starting material and formation of a new polar spot. The reaction mixture was concentrated *via* rotary evaporation, and the crude material was purified *via* column chromatography (70→80% EtOAc/Pet. ether) to afford the desired product as an off-white foam (313.0 mg, 47% over 4 steps) $R_f = 0.3$ (85% EtOAc/Pet. ether).

^{1}H-NMR (600 MHz; $CDCl_3$): δ 7.15 (d, *J* = 6.4 Hz, 3H), 6.96 (d, *J* = 1.9 Hz, 1H), 6.92 (d, *J* = 8.0 Hz, 1H), 6.85 (d, *J* = 8.6 Hz, 3H), 6.78 (s, 1H), 6.38 (s, 1H), 6.17 (s, 1H), 4.76 (s, 2H), 3.80 (s, 3H), 3.63 (t, *J* = 10.6 Hz, 1H), 3.42 (s, 1H), 3.34-3.32 (m, 1H), 1.63-1.59 (m, 1H), 1.40 (d, *J* = 5.7 Hz, 1H), 1.36 (s, 9H). **^{13}C-NMR** (126 MHz, $CDCl_3$): δ 169.90, 159.18, 152.87, 143.93, 137.46, 137.45, 137.19, 137.18, 131.36, 130.66, 130.59, 130.33, 130.33, 130.17, 129.62, 129.57, 129.03, 123.30, 121.72, 121.02, 114.00, 113.92, 82.21, 78.94, 55.54, 53.10, 50.27, 50.10, 38.39, 33.71, 28.28. **IR** (film): 3202, 2935, 2892, 1675, 1648, 1575, 1491, 1464, 1400, 1370, 1350, 1308, 1230, 1157, 727, cm $^{-1}$. **$[\alpha]^{22}_D$**: –199.0 (CH_2Cl_2, c 2.67). **HRMS**: ($C_{31}H_{31}BrCl_2N_3O_4$): calculated (M + H): 658.0870, found (M + H): 658.0877.

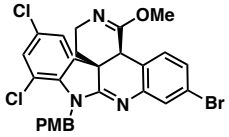


(4a*S*,14b*S*)-12-bromo-6,8-dichloro-9-(4-methoxybenzyl)-3,4,9,14b-tetrahydrobenzo[*c*]indolo[3,2-*j*][2,6]naphthyridin-1(2*H*)-one (18)

A vial containing the lactam **5** (248 mg, 0.378 mmol) was heated to 170 ºC under high vacuum. After 3 h, the vial was cooled to rt and TLC analysis indicated no remaining starting material. DCM (375 μL) and HOAc (375 μL) were added and the reaction mixture was cooled to 0 ºC and $PhI(OAc)_2$ (145.3 mg, 0.45 mmol) was added. The resulting reaction mixture was stirred for 5 h allowing to warm to rt. The reaction mixture was diluted with saturated $Na_2S_2O_4$ (20 mL) and EtOAc (50 mL) were added. The biphasic mixture was stirred at rt for 15 min, and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (3x, 50 mL). The combined organic phases were dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuo*. The crude reaction mixture was purified *via* column chromatography (35% EtOAc/Pet. ether) to provide the desired product as a yellow foam (136 mg, 65%).

^{1}H-NMR (600 MHz; $CDCl_3$): δ 7.42-7.41 (m, 2H), 7.23-7.18 (m, 5H), 6.83-6.82 (m, 2H), 6.66 (s, 1H), 5.47 (q, *J* = 12.8 Hz, 2H), 3.79 (s, 1H), 3.76 (s, 3H), 3.42 (td, *J* = 12.4, 5.3 Hz, 1H),

3.38-3.35 (m, 1H), 2.30 (ddd, *J* = 13.5, 12.3, 6.9 Hz, 1H), 1.34 (dd, *J* = 13.7, 4.6 Hz, 1H). **^{13}C-NMR** (126 MHz, $CDCl_3$): δ 169.38, 167.31, 159.05, 145.38, 139.73, 134.53, 131.50, 129.63, 128.85, 128.25, 128.22, 128.03, 127.50, 122.75, 122.66, 119.56, 116.15, 114.27, 55.49, 45.45, 45.04, 43.01, 38.28, 23.75. **IR** (film): 3167, 3028, 2890, 1648, 1626, 1551, 1492, 1475, 1434, 1346, 1326, 1295, 1231, 1188, 1150, 840, 724 cm $^{-1}$. **$[\alpha]^{22}_D$**: +233.2 (CH_2Cl_2, c 0.99). **HRMS**: ($C_{26}H_{21}BrCl_2N_3O_2$): calculated (M + H): 556.0189, found (M + Na): 556.0191.



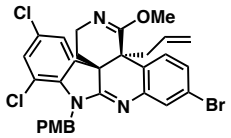
(4a*S*,14b*S*)-12-bromo-6,8-dichloro-1-methoxy-9-(4-methoxybenzyl)-3,4,9,14b-tetrahydrobenzo[*c*]indolo[3,2-*j*][2,6]naphthyridine (4)

To a solution of lactam **18** (139 mg, 0.25 mmol) in DCM (2.5 mL) was added $NaHCO_3$ solid (420 mg, 5.0 mmol). The reaction mixture was cooled to 0 ºC and freshly washed Me_3OBF_4 (370 mg, 2.5 mmol) was added.[1] The resulting reaction mixture was stirred overnight at 0 ºC upon which TLC analysis indicated the majority of the SM had been consumed. The reaction mixture was diluted with aqueous $NaHCO_3$ (20 mL) and EtOAc (50 mL) and the biphasic mixture was stirred with warming to rt. The layers were separated and the aqueous layer was extracted with EtOAc (3x 50 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and the solvent was removed *via* rotary evaporation. The crude product was purified *via* column chromatography (5→10% EtOAc/Pet. ether) to afford the desired product as a white foam (102 mg, 71 %).

^{1}H-NMR (600 MHz; $CDCl_3$): δ 7.37 (d, *J* = 2.0 Hz, 1H), 7.20-7.18 (m, 4H), 7.15 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.93 (d, *J* = 2.0 Hz, 1H), 6.82-6.80 (m, 2H), 5.49-5.43 (m, 2H), 3.94 (s, 3H), 3.75 (s, 3H), 3.68 (dd, *J* = 17.8, 6.5 Hz, 1H), 3.63 (s, 1H), 3.51 (ddd, *J* = 17.7, 11.6, 6.0 Hz, 1H), 2.07-2.02 (m, 1H), 1.14 (ddd, *J* = 13.5, 5.4, 1.3 Hz, 1H). **^{13}C-NMR** (126 MHz, $CDCl_3$): δ 168.30, 160.94, 159.00, 145.67, 139.60, 135.42, 131.08, 129.82, 128.80, 128.22, 127.71, 127.37, 122.76, 122.28, 122.17, 115.80, 114.23, 55.50, 53.28, 45.35, 42.40, 42.31, 39.84, 24.26. **IR** (film): 2901, 1657, 1625, 1551, 1492, 1432, 1348, 1317, 1304, 1276, 1230, 1184, 1148, 839, 727 cm $^{-1}$. **$[\alpha]^{22}_D$**: +242.8 (CH_2Cl_2, c 1.00). **HRMS**: ($C_{27}H_{23}BrCl_2N_3O_2$): calculated (M + H):

[1] Earle, M. J.; Fairhurst, R. A.; Giles, R. G.; Heaney, H. *Synlett,* **1991**, 728.

570.0345, found (M + Na): 570.0336.



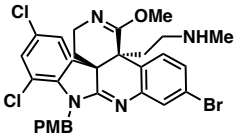
(4a*R*,14b*S*)-14b-allyl-12-bromo-6,8-dichloro-1-methoxy-9-(4-methoxybenzyl)-3,4,9,14b-tetrahydrobenzo[*c*]indolo[3,2-*j*][2,6]naphthyridine (3)

To a solution of imino ether **4** (123 mg, 0.215 mmol) in THF (2.15 mL) at 0 ºC was added allyl iodide (72.2 mg, 0.43 mmol) the reaction mixture was wrapped in foil and a solution of KHMDS (850 μL, 0.43 mmol, 0.5M/THF) was added dropwise over 10 min. The reaction mixture was stirred for 15 min upon which TLC analysis indicated complete consumption of the starting materials. The reaction mixture was diluted with Et_2O (5 mL) containing acetic acid (100 μL) to consume unreacted base and precipitate inorganic salt. The resulting slurry was filtered through a 2 cm plug of silica eluting with additional Et_2O (60 mL). The filtrate was concentrated *via* rotary evaporation, and the crude reaction mixture was purified using column chromatography (10→15% Et_2O/Pet. ether) to afford the desired product as a foam (129 mg, 98%).

^{1}H-NMR (500 MHz; $CDCl_3$): δ 7.37 (t, *J* = 2.1 Hz, 1H), 7.36-7.34 (m, 2H), 7.32 (d, *J* = 8.3 Hz, 1H), 7.24 (d, *J* = 2.0 Hz, 1H), 7.17 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.93 (d, *J* = 2.0 Hz, 1H), 6.89-6.86 (m, 2H), 5.49 (d, *J* = 15.7 Hz, 1H), 5.40-5.31 (m, 2H), 4.57-4.55 (m, 1H), 4.32 (d, *J* = 16.9 Hz, 1H), 3.92 (s, 3H), 3.80 (s, 3H), 3.66 (dd, *J* = 17.8, 6.0 Hz, 1H), 3.55 (ddt, *J* = 17.3, 11.4, 5.5 Hz, 1H), 2.67 (dd, *J* = 14.3, 5.4 Hz, 1H), 2.30-2.24 (m, 2H), 1.22 (dd, *J* = 13.6, 5.1 Hz, 1H).

^{1}H-NMR (600 MHz; $CDCl_3$): δ 7.34 (d, *J* = 2.1 Hz, 1H), 7.32 (d, *J* = 8.7 Hz, 2H), 7.28 (d, *J* = 8.3 Hz, 1H), 7.21 (d, *J* = 2.0 Hz, 1H), 7.14 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.90 (d, *J* = 2.0 Hz, 1H), 6.85-6.83 (m, 2H), 5.46 (d, *J* = 15.8 Hz, 1H), 5.36-5.29 (m, 2H), 4.53 (d, *J* = 10.0 Hz, 1H), 4.29 (d, *J* = 16.8 Hz, 1H), 3.89 (s, 3H), 3.77 (s, 3H), 3.63 (dd, *J* = 17.8, 6.1 Hz, 1H), 3.53 (ddd, *J* = 17.6, 11.8, 5.6 Hz, 1H), 2.64 (dd, *J* = 14.2, 5.4 Hz, 1H), 2.27-2.21 (m, 2H), 1.19 (dd, *J* = 13.6, 5.2 Hz, 1H). **^{13}C-NMR** (126 MHz, $CDCl_3$): δ 169.13, 162.03, 159.04, 145.54, 140.15, 133.92, 133.63, 130.89, 130.03, 128.80, 128.73, 128.25, 127.82, 126.95, 126.62, 123.76, 122.21, 118.18, 115.61, 114.10, 55.50, 53.44, 47.45, 46.57, 45.37, 41.93, 39.97, 29.96, 28.08. **IR** (film): 2879, 1647, 1625, 1550, 1492, 1443, 1344, 1328, 1230, 1147, 1020, 839, 724 cm $^{-1}$. **$[\alpha]^{22}_D$**: +271.2 (CH_2Cl_2, c 2.35). **HRMS**: ($C_{30}H_{27}BrCl_2N_3O_2$): calculated (M + H): 610.0658, found (M + H):

610.0660.

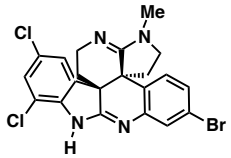


2-((4a*R*,14b*S*)-12-bromo-6,8-dichloro-1-methoxy-9-(4-methoxybenzyl)-3,4,9,14b-tetrahydrobenzo[*c*]indolo[3,2-*j*][2,6]naphthyridin-14b-yl)-*N*-methylethanamine (21)

To a solution of allyl imino ether **3** (18.3 mg, 0.03 mmol) in DCM (1.0 mL) at 0 ºC was added CSA (34.8 mg, 0.15 mmol). The resulting reaction mixture was cooled further to –78 ºC and sparged with a stream of ozone until a blue color persisted. At this point, TLC analysis indicated the complete consumption of starting material and MeOH (500 μL mL) was added followed by dimethyl sulfide (500 μL mL). The resulting reaction mixture was warmed to 0 ºC and was stirred for 15 min at which point a saturated aqueous solution of sodium bicarbonate (1.0 mL) was added. The biphasic mixture was stirred for 4 h allowing to warm to rt. The layers were separated and the aqueous layer was extracted with EtOAc (3x 20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and the solvent was removed *via* rotary evaporation. The crude product was dissolved in a EtOH containing $MeNH_2$ (600 μL, 33%/wt solution) and $Ti(O^iPr)_4$ (42.6 mg, 0.15 mmol) was added. The resulting solution was stirred at rt for 4 h upon which it was cooled to 0 ºC and $NaBH_4$ (11.3 mg, 0.3 mmol) was added. The resulting reaction mixture was stirred for 10 min and concentrated NH_4OH (2.0 mL) was added. The slurry was stirred for 10 min at 0 ºC and DCM (10 mL) was added. The layers were separated and the aqueous layer was extracted with DCM (3x 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and the organic solvent was removed *via* rotary evaporation. The crude reaction mixture was purified *via* prep TLC (5% MeOH/DCM) to afford the desired product as a white foam (9.6 mg, 51% over 2 steps).

^{1}H-NMR (500 MHz; $CDCl_3$): δ 7.37 (dd, *J* = 1.6, 0.8 Hz, 1H), 7.33-7.30 (m, 2H), 7.23 (d, *J* = 2.0 Hz, 1H), 7.17-7.13 (m, 2H), 6.90 (d, *J* = 2.0 Hz, 1H), 6.88-6.85 (m, 2H), 5.54 (d, *J* = 15.8 Hz, 1H), 5.40 (d, *J* = 15.8 Hz, 1H), 3.91 (s, 3H), 3.79 (s, 3H), 3.66 (dd, *J* = 17.7, 6.3 Hz, 1H), 3.54 (ddd, *J* = 17.7, 11.7, 5.8 Hz, 1H), 2.59 (td, *J* = 11.4, 4.0 Hz, 1H), 2.26 (ddd, *J* = 13.6, 11.6, 6.6 Hz, 1H), 2.13 (s, 3H), 1.97 (td, *J* = 11.2, 4.5 Hz, 1H), 1.89 (td, *J* = 12.3, 4.3 Hz, 1H), 1.62-1.56 (m, 1H), 1.23 (dd, *J* = 13.6, 5.2 Hz, 1H). **^{13}C-NMR** (126 MHz, $CDCl_3$): δ 168.72, 162.19,

159.06, 145.16, 139.77, 133.39, 131.17, 129.88, 128.77, 128.71, 128.47, 127.71, 127.48, 125.98, 123.63, 122.45, 115.95, 114.16, 55.49, 53.44, 48.50, 48.39, 45.35, 45.22, 41.90, 35.36, 32.24, 27.01. **IR** (film): 2887, 1648, 1623, 1590, 1550, 1492, 1432, 1344, 1230, 1148, 1021, 839, 803, 725 cm $^{-1}$. **[α]$^{22}_{D}$**: +155.8 (CH_2Cl_2, c 1.40). **HRMS**: ($C_{30}H_{30}BrCl_2N_4O_2$): calculated (M + H): 627.0924, found (M + H): 627.0926.



(3a*S*,13b*R*)-6-bromo-10,12-dichloro-1-methyl-1,2,3,9,14,15-hexahydrobenzo[*c*]indolo[3,2-*j*]pyrrolo[3,2-*e*][2,6]naphthyridine perophoramidine (2)

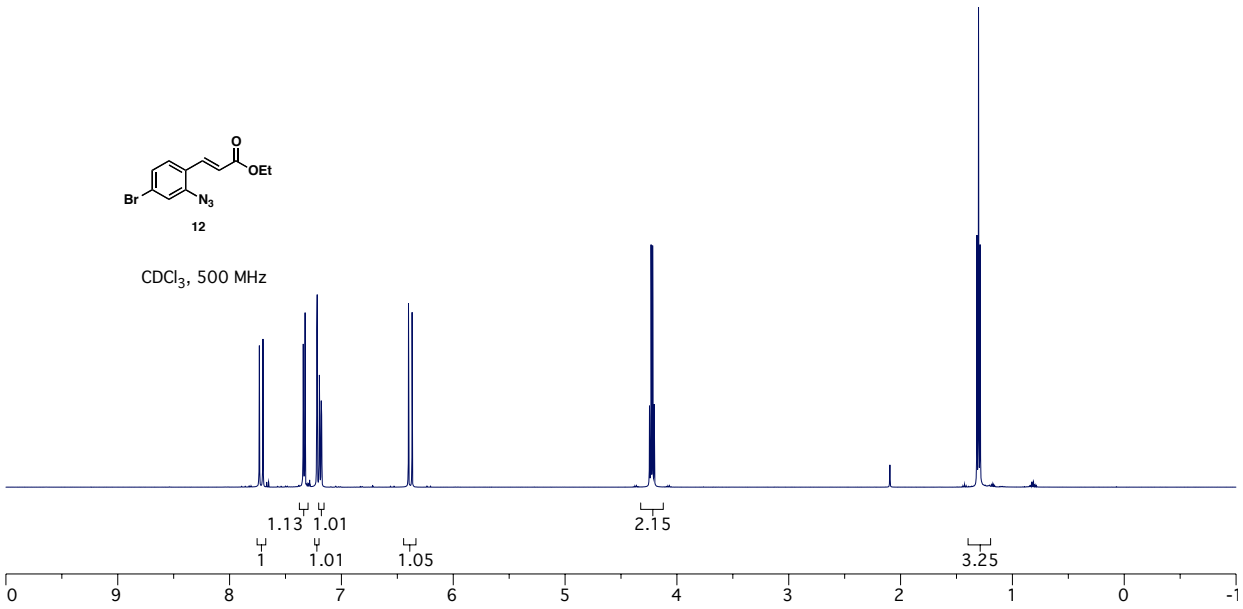
A solution of methylamine **21** (16.2 mg, 0.26 mmol) was heated to 120 ºC in anisole (0.52 mL) for 12 h at which point TLC analysis indicated the complete consumption of starting material. The reaction mixture was cooled to rt, and TFA (104 μL) was added. The resulting reaction mixture was heated to 90 ºC for 12 h upon which TLC analysis indicated the complete consumption of starting material. The reaction mixture was cooled to rt, and the volatiles were removed *via* vacuum. The resulting residue was purified *via* prep. TLC (5% MeOH/$CHCl_3$) to afford perophoramidine (**2**) as its TFA salt (8.0 mg, 62%, R_f = 0.35, 5% MeOH/$CHCl_3$).

^{1}H-NMR (600 MHz; $CDCl_3$): δ 7.35 (d, *J* = 1.8 Hz, 1H), 7.33 (d, *J* = 1.8 Hz, 1H), 7.19 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.06 (d, *J* = 1.7 Hz, 1H), 6.65 (d, *J* = 8.2 Hz, 1H), 3.77-3.67 (m, 2H), 3.58-3.54 (m, 1H), 3.50 (s, 3H), 3.42 (t, *J* = 9.6 Hz, 1H), 2.36 (ddd, *J* = 14.0, 10.7, 7.9 Hz, 1H), 2.01-1.96 (m, 1H), 1.87 (dd, *J* = 12.5, 5.7 Hz, 1H), 1.64 (dd, *J* = 14.1, 6.1 Hz, 1H). **^{13}C-NMR** (126 MHz, $CDCl_3$): δ 169.93, 163.07, 146.62, 139.05, 133.01, 130.23, 129.29, 127.95, 126.21, 124.88, 123.81, 122.51, 122.23, 120.65, 50.84, 50.38, 50.36, 50.33, 49.86, 49.83, 49.82, 39.59, 33.75, 30.21, 24.72. **IR** (film): 2882, 1679, 1642, 1611, 1543, 1469, 1390, 1184, 1162, 1114, 896, 722 cm $^{-1}$. The TFA salt could be liberated to the free amidine in by dissolving the material in DCM (3 mL) and stirring with saturated NH_4OH (3 mL) for 5 min followed by separating of the layers, extraction, drying over anhydrous $MgSO_4$ and concentration.

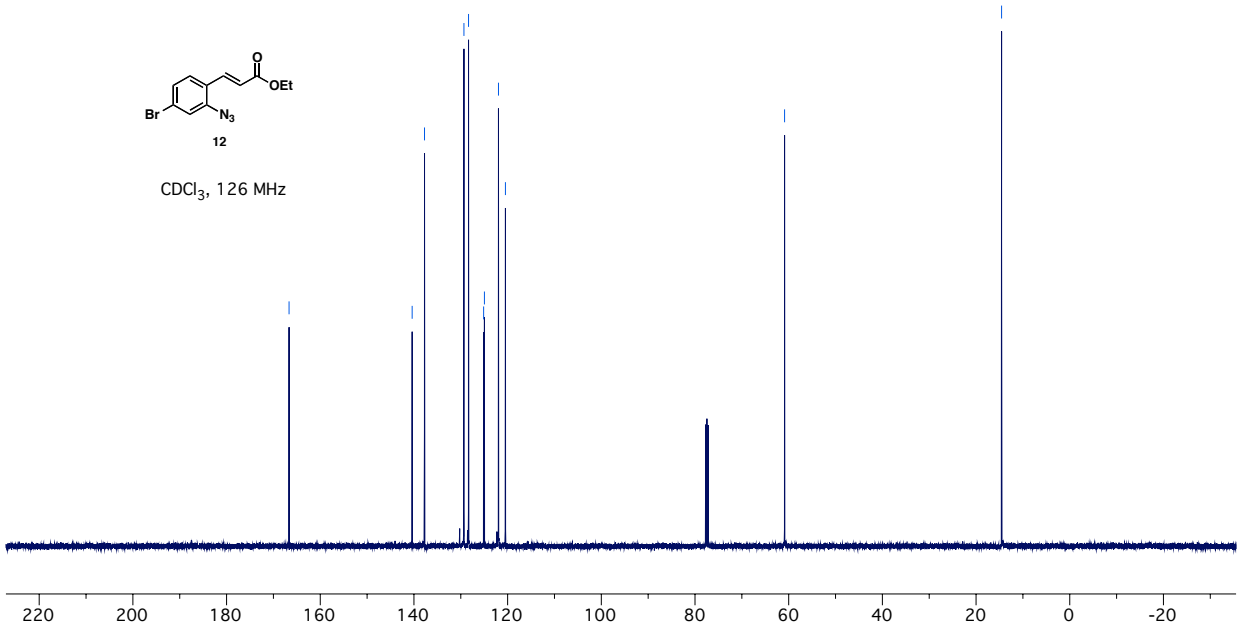
^{1}H-NMR (500 MHz; $CDCl_3$): δ 7.28 (d, *J* = 1.9 Hz, 1H), 7.23 (d, *J* = 1.8 Hz, 1H), 7.12 (dd, *J* = 8.2, 1.9 Hz, 1H), 6.97 (d, *J* = 1.9 Hz, 1H), 6.76 (d, *J* = 8.2 Hz, 1H), 3.75-3.61 (m, 2H), 3.28 (td, *J* = 9.7, 5.9 Hz, 1H), 3.14-3.11 (m, 3H), 3.11-3.08 (m, 1H), 2.20 (ddd, *J* = 13.5, 10.2, 7.7 Hz, 1H),

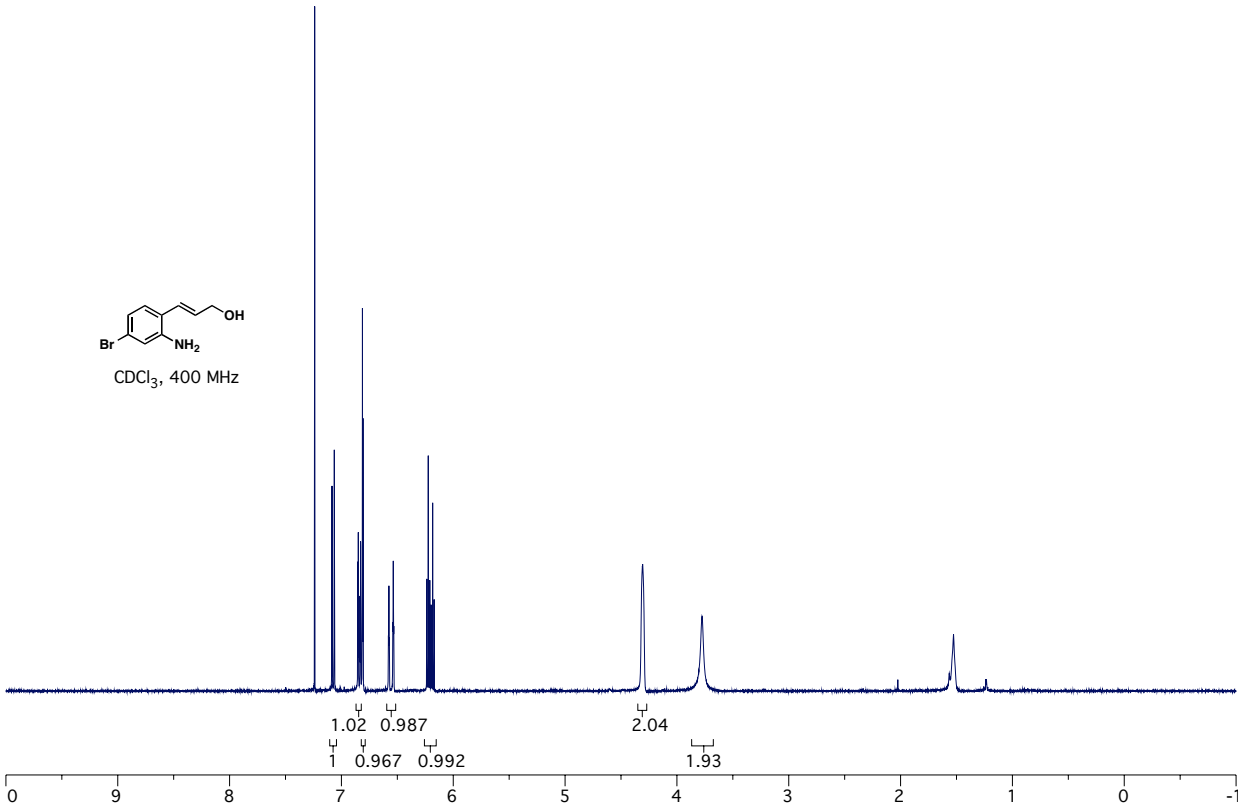
1.80-1.74 (m, 1H), 1.69 (dd, *J* = 12.2, 5.8 Hz, 1H), 1.37 (dd, *J* = 13.6, 6.2 Hz, 1H). **^{13}C-NMR** (126 MHz, $CDCl_3$): δ 172.41, 159.67, 147.82, 138.68, 135.71, 129.09, 128.33, 127.50, 127.05, 125.76, 122.99, 122.62, 121.97, 120.49, 52.35, 46.45, 45.65, 43.00, 31.15, 30.02, 25.23. **IR** (film): 2884, 2816, 1639, 1611, 1541, 1466, 1435, 1390, 1279, 1196, 1160, 1070, 932, 895, 850, 804, 722 cm^{-1}. **$[\alpha]^{22}_D$**: –26.4 ($CHCl_3$, c 1.10). **HRMS**: ($C_{21}H_{18}BrCl_2N_4$): calculated (M + H): 475.0086, found (M + H): 475.0078.

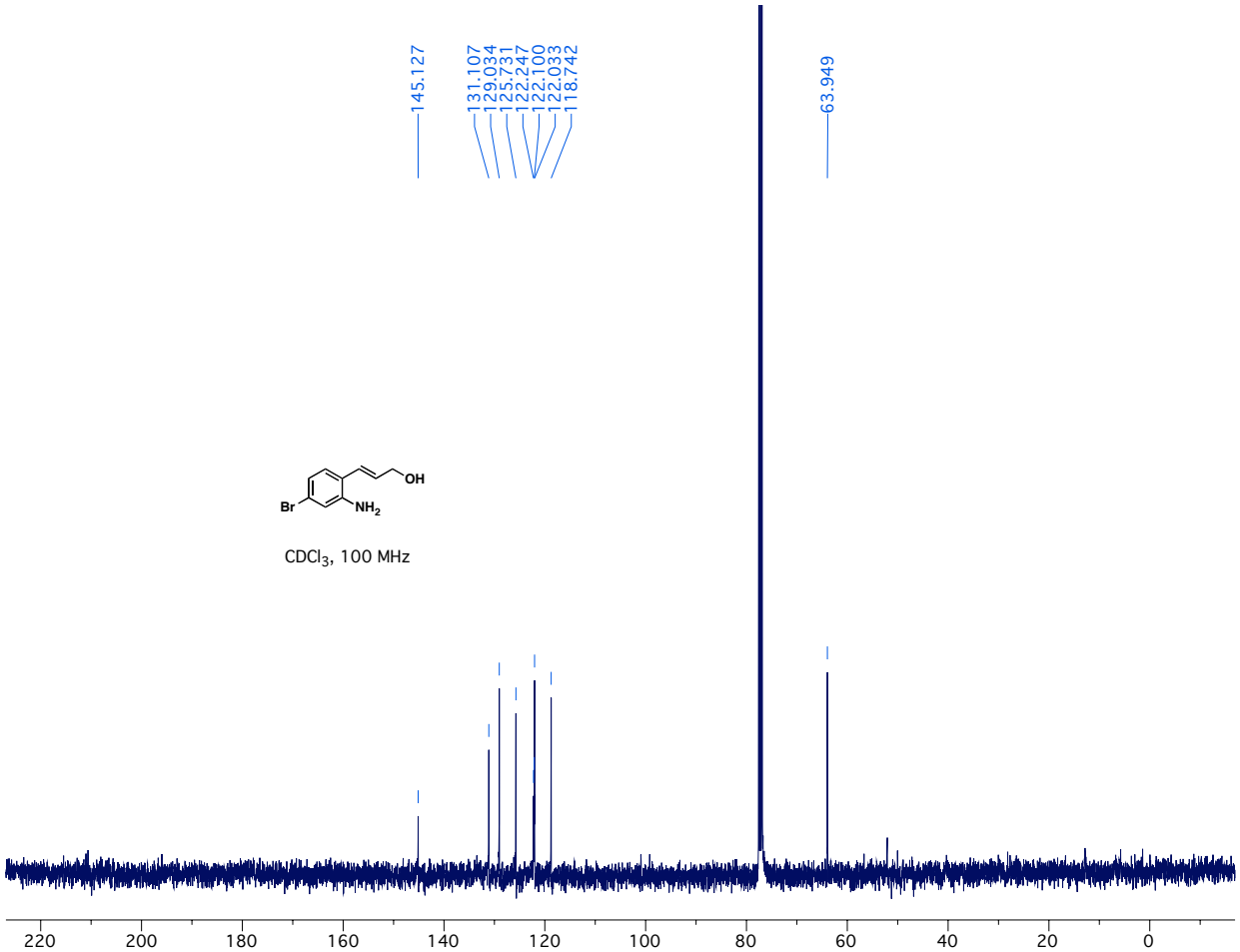
[1] On smaller scale, the entire reaction mixture was purified *via* column chromatography, and an 86% isolated yield was obtained.

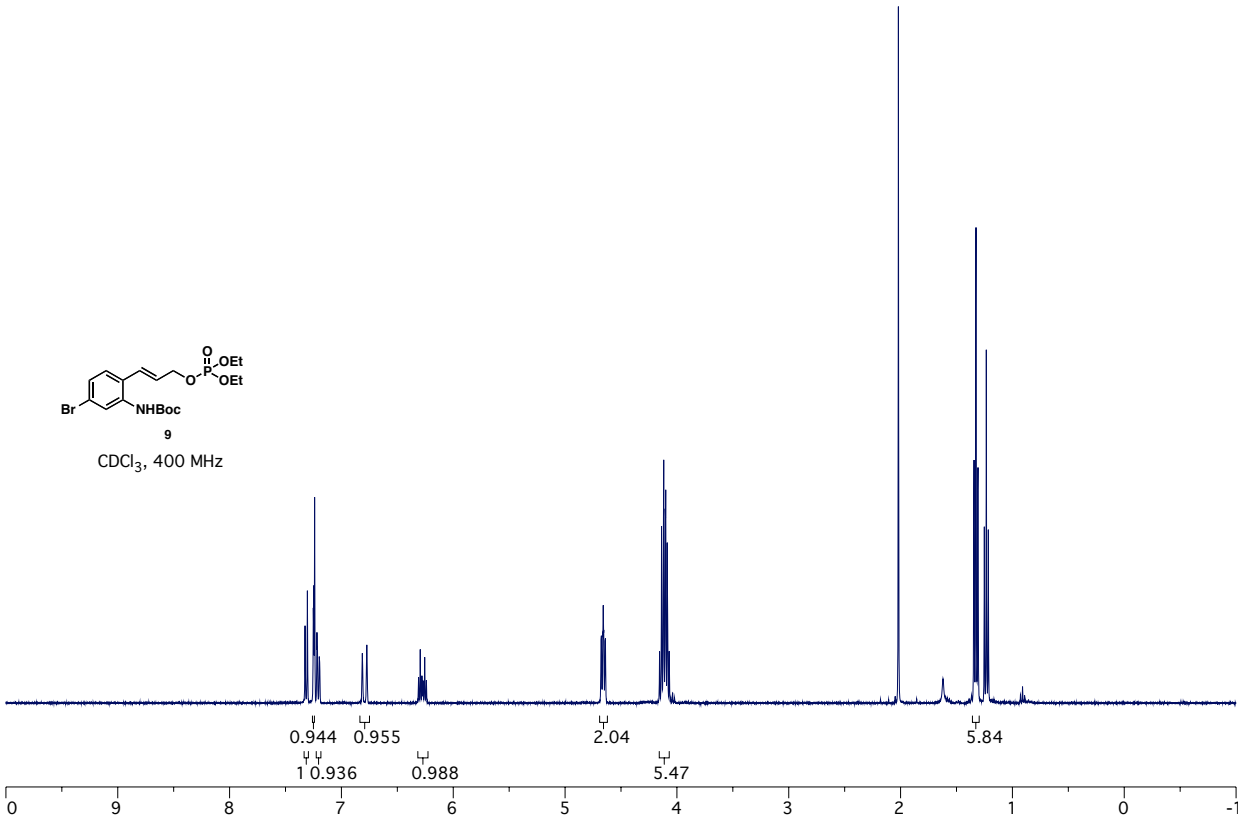

O
OEt
Br
N3
12
CDCl3, 500 MHz
1.13
1.01
2.15
1
1.01
1.05
3.25
0
9
8
7
6
5
4
3
2
1
0
-1

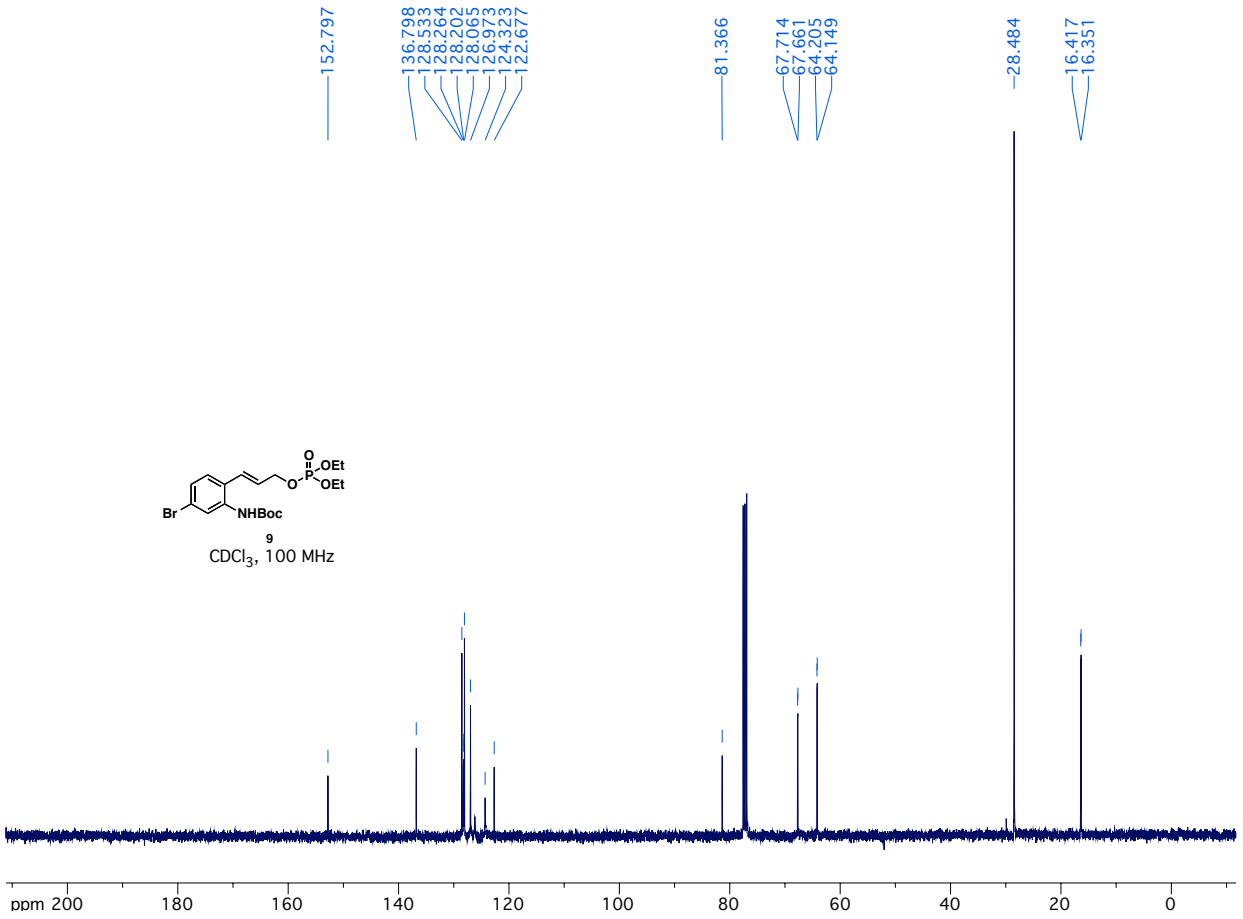

166.660
140.381
137.744
129.328
128.346
125.124
124.954
121.953
120.470
60.878
14.552

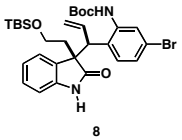

O
OEt
Br
N3
12
CDCl3, 126 MHz
220
200
180
160
140
120
100
80
60
40
20
0
-20


Br
NH2
OH
CDCl3, 400 MHz
1.02
0.987
2.04
1
0.967
0.992
1.93
0
9
8
7
6
5
4
3
2
1
0
-1


145.127
131.107
129.034
125.731
122.247
122.100
122.033
118.742
63.949
Br
NH2
OH
CDCl3, 100 MHz
220
200
180
160
140
120
100
80
60
40
20
0

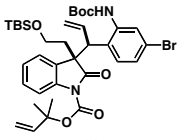

O
OEt
P
OEt
O
Br
NHBoc
9
CDCl3, 400 MHz
0.944
0.955
2.04
5.84
1
0.936
0.988
5.47
0
9
8
7
6
5
4
3
2
1
0
-1


152.797
136.798
128.533
128.264
128.202
128.065
126.973
124.323
122.677
81.366
67.714
67.661
64.205
64.149
28.484
16.417
16.351
O
OEt
P
OEt
O
Br
NHBoc
9
CDCl3, 100 MHz
ppm 200
180
160
140
120
100
80
60
40
20
0



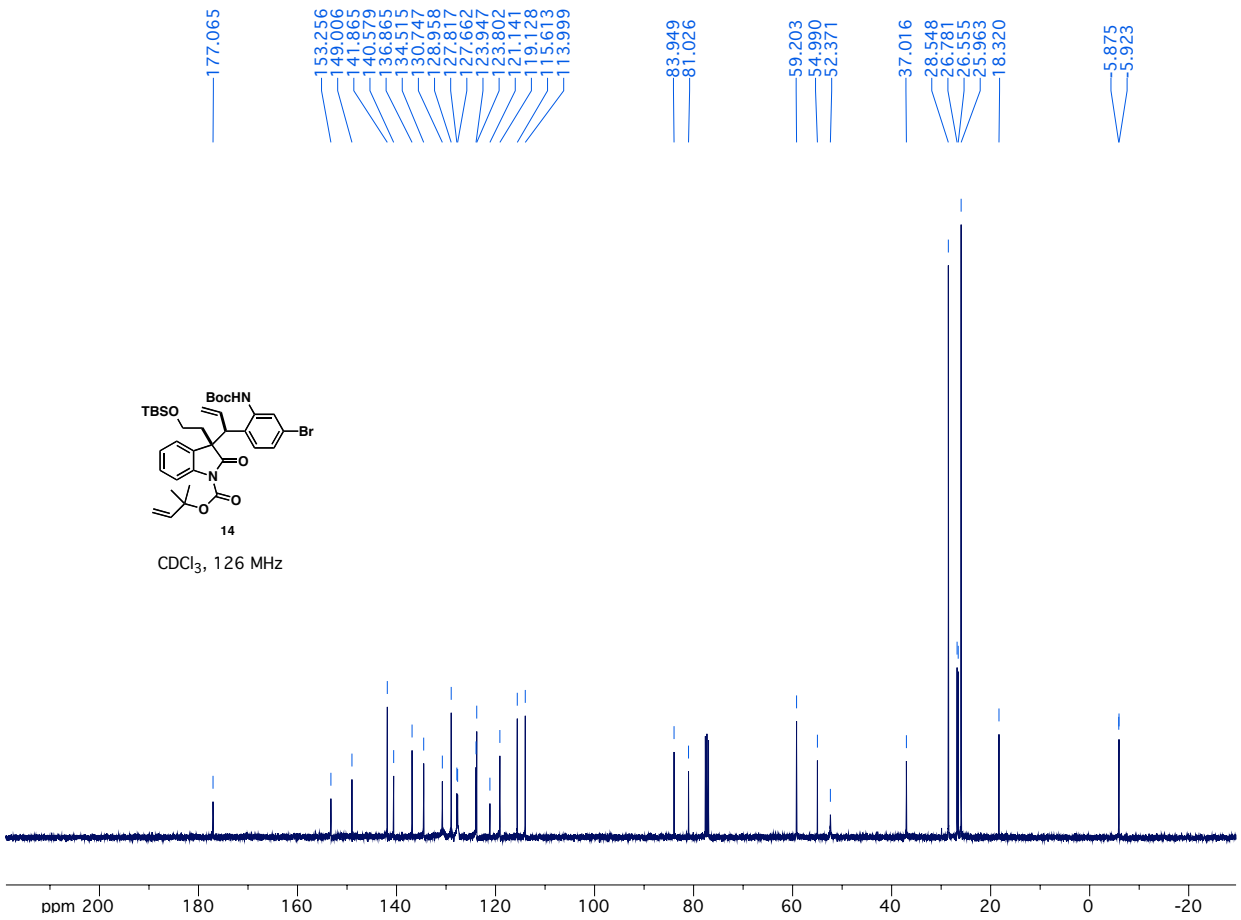
8

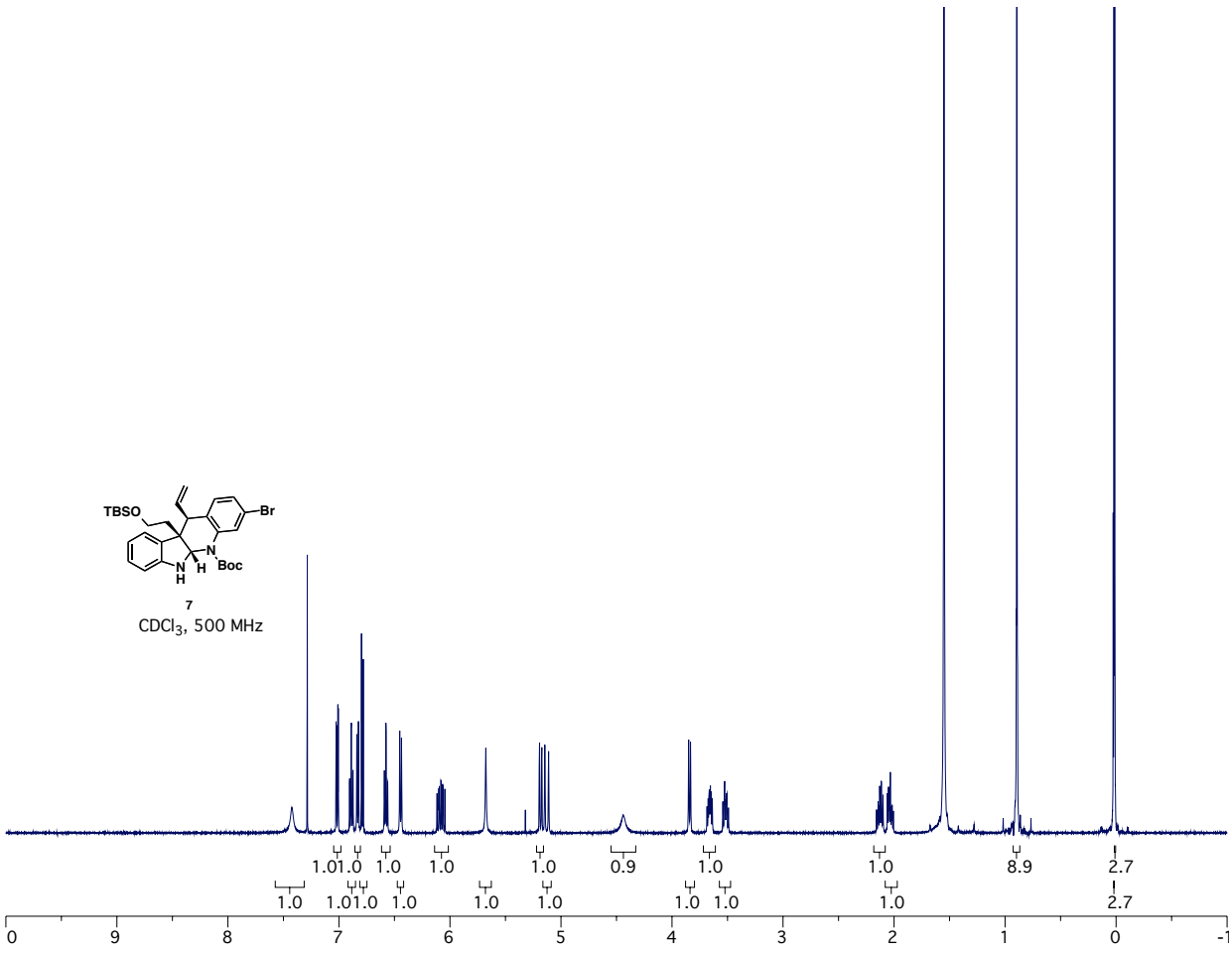
$CDCl_3$, 600 MHz
includes inseperable
linear isomer

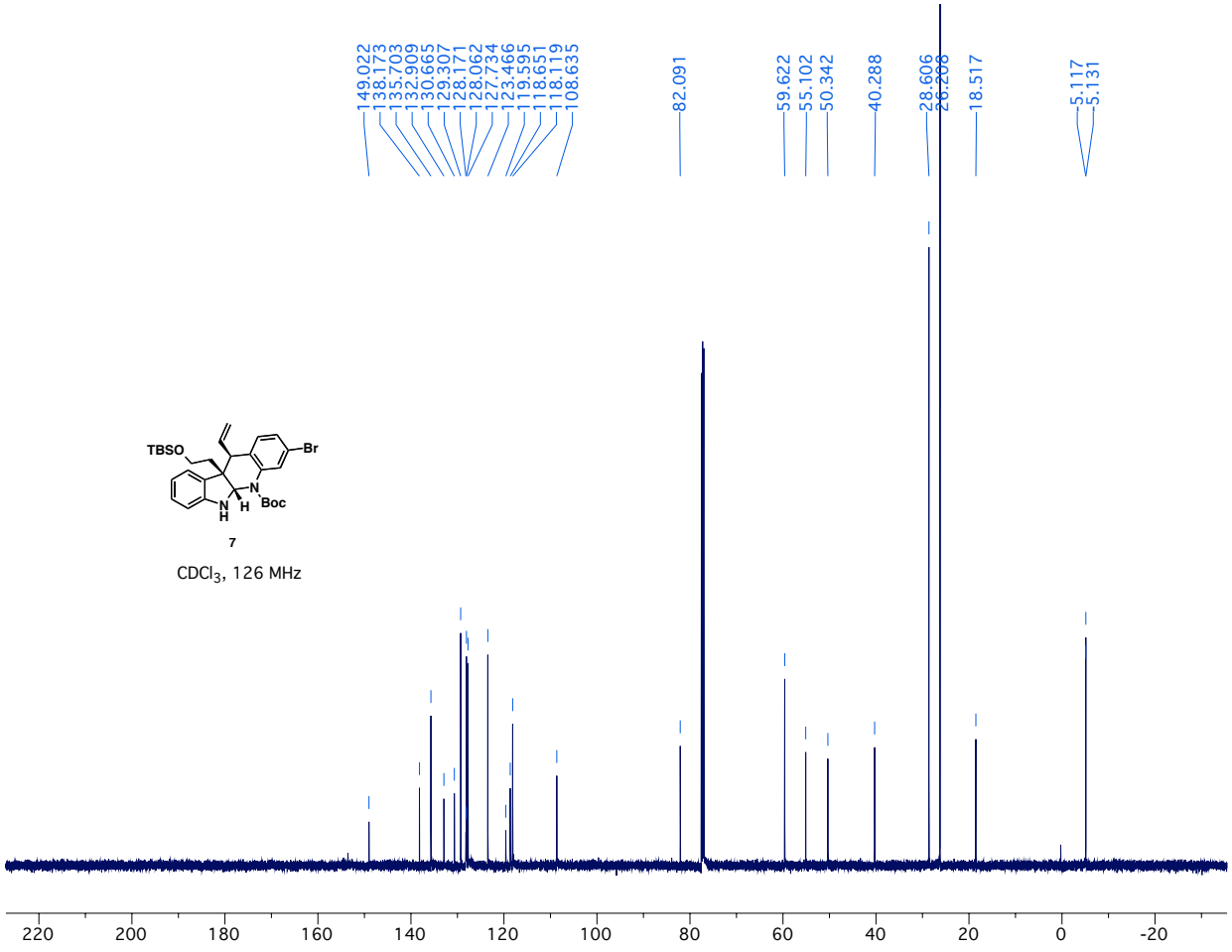


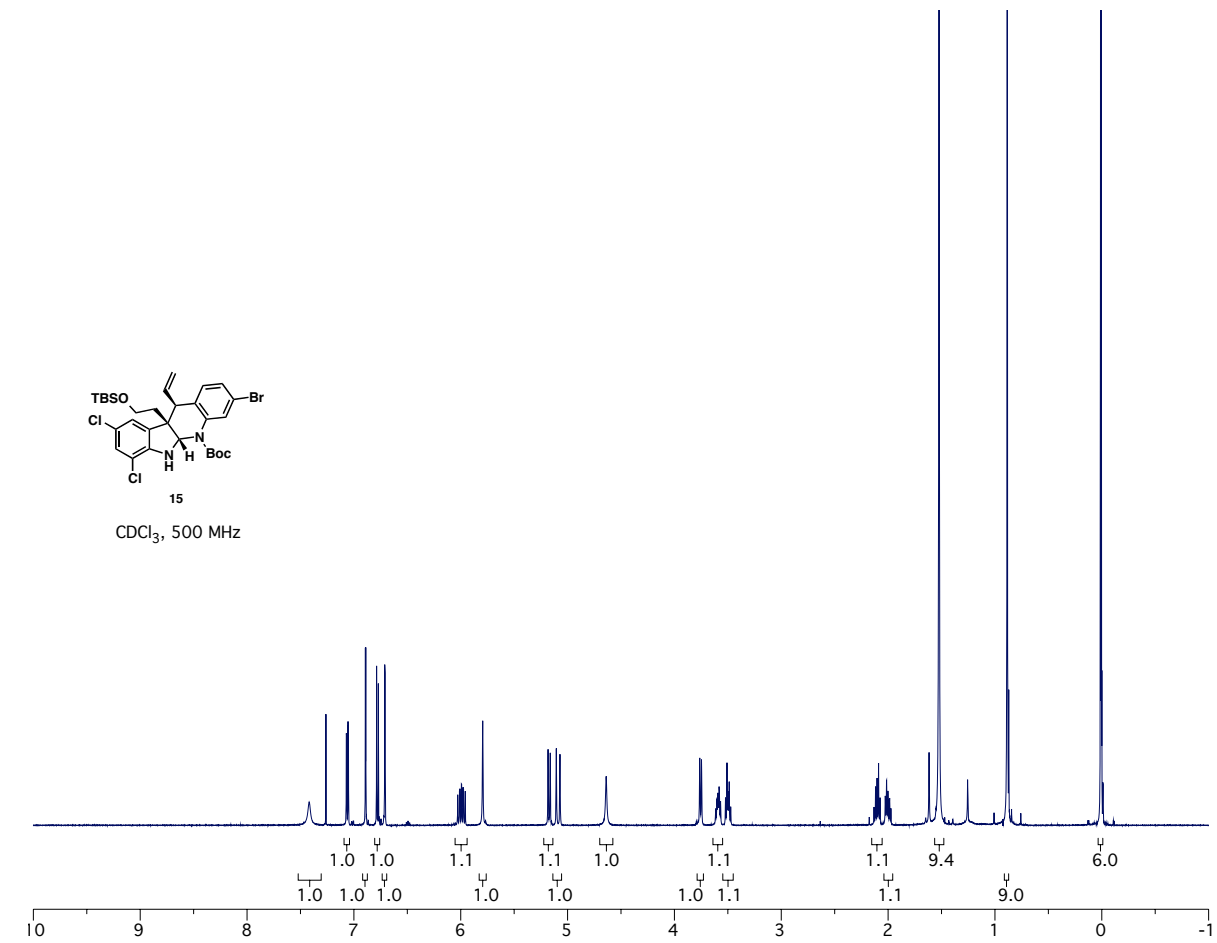
14

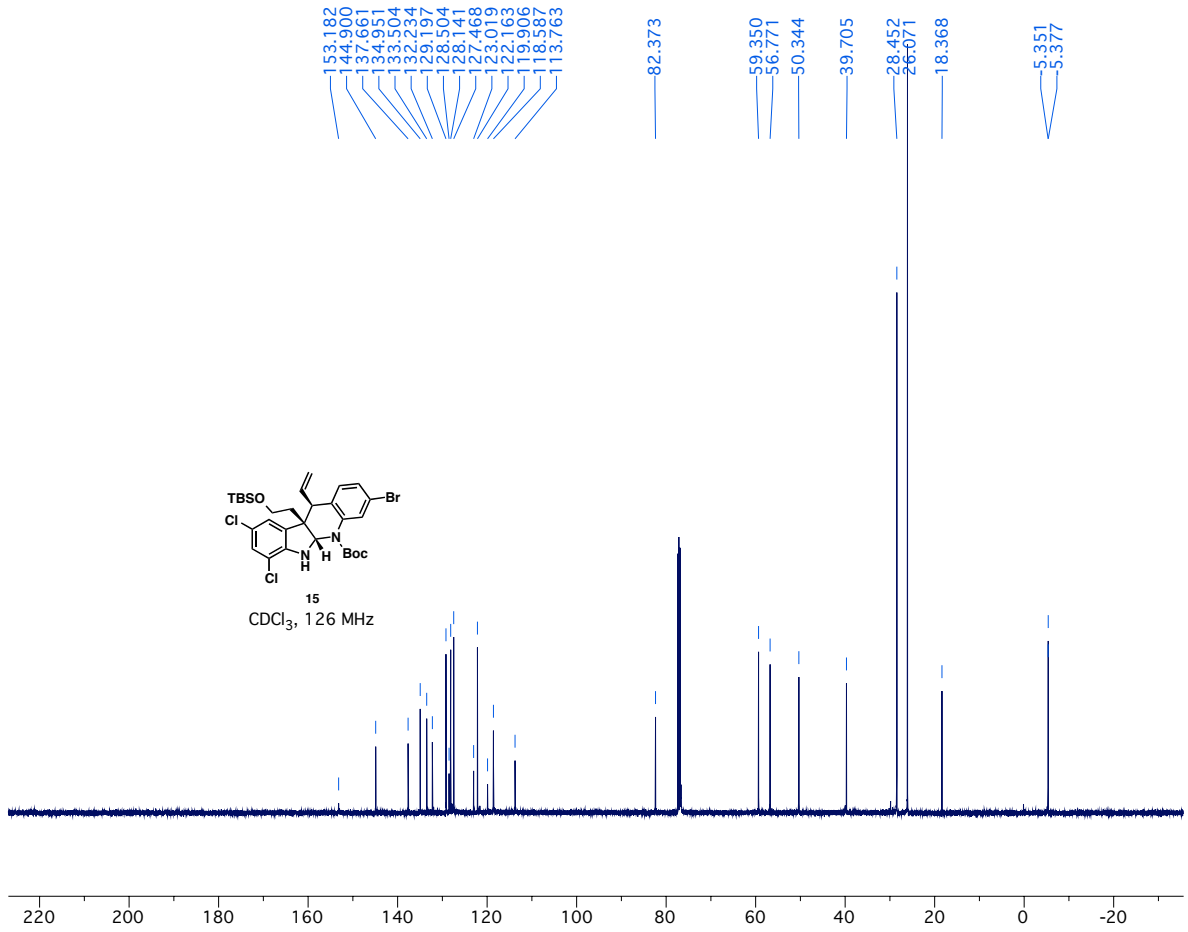
$CDCl_3$, 500 MHz

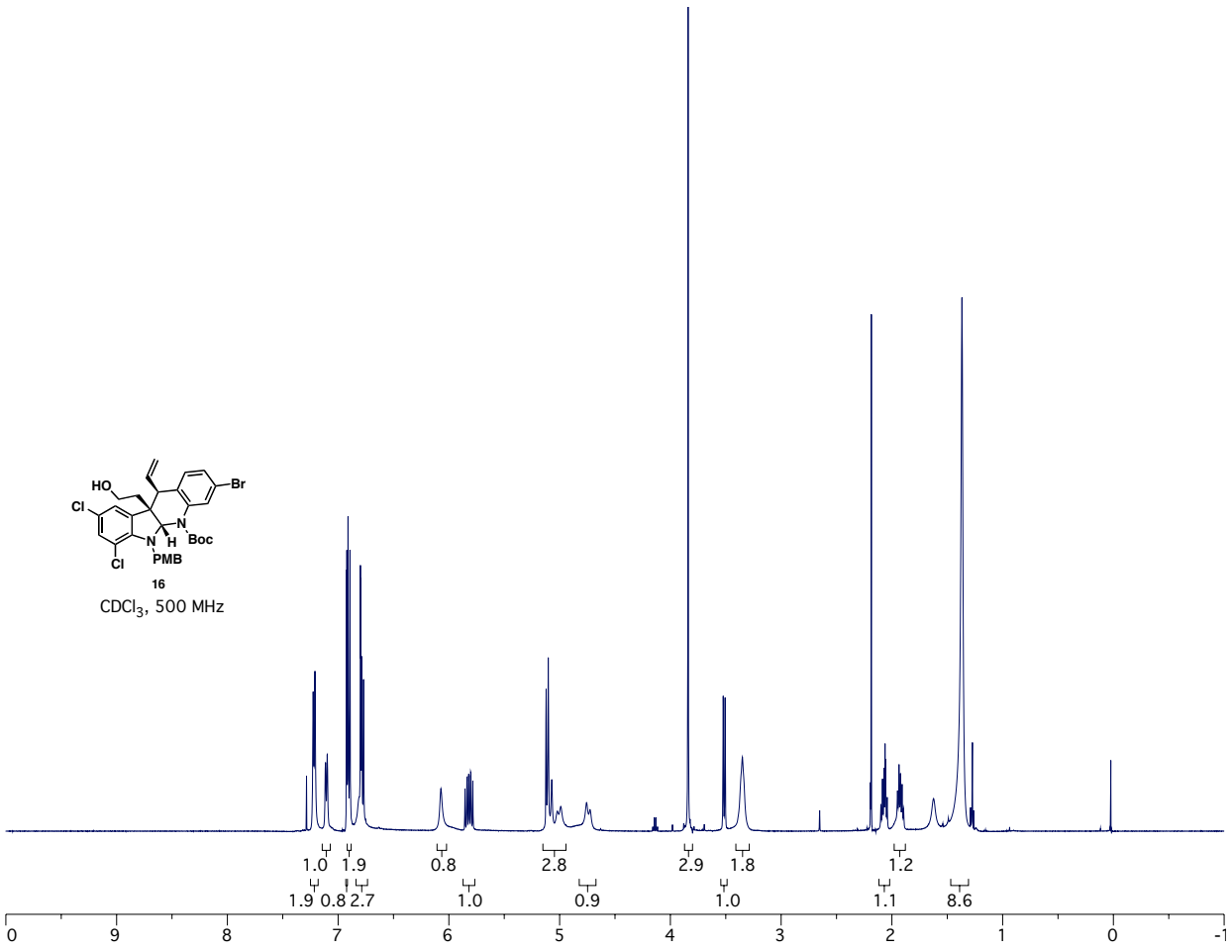

177.065
153.256
149.006
141.865
140.579
136.865
134.515
130.747
128.959
127.817
127.662
123.947
123.802
121.141
119.128
115.613
113.999
83.949
81.026
59.203
54.990
52.371
37.016
28.548
26.781
26.555
25.963
18.320
5.875
5.923
TBSO
BocHN
Br
O
N
O
O
14
CDCl3, 126 MHz
ppm 200
180
160
140
120
100
80
60
40
20
0
-20

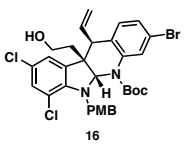

TBSO
Br
N
H
N
Boc
7
CDCl3, 500 MHz
1.0
1.01.0
1.0
1.0
1.0
0.9
1.0
1.0
8.9
2.7
1.0
1.01.0
1.0
1.0
1.0
1.0
1.0
1.0
2.7
0
9
8
7
6
5
4
3
2
1
0
-1


149.022
138.173
135.703
132.909
130.665
129.307
128.171
128.062
127.734
123.466
119.595
118.651
118.119
108.635
82.091
59.622
55.102
50.342
40.288
28.606
26.208
18.517
5.117
5.131
TBSO
Br
N
H
Boc
7
CDCl3, 126 MHz
220
200
180
160
140
120
100
80
60
40
20
0
-20


TBSO
Cl
Br
N
H
Boc
Cl
15
CDCl3, 500 MHz
1.0
1.0
1.0
1.0
1.0
1.1
1.0
1.1
1.0
1.0
1.1
1.1
1.1
9.4
1.1
9.0
6.0
10
9
8
7
6
5
4
3
2
1
0
-1

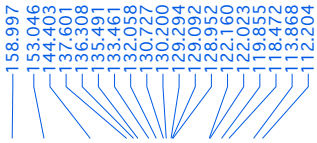

153.182
144.900
137.661
134.951
133.504
132.234
129.197
128.504
128.141
127.468
123.019
122.163
119.906
118.587
113.763
82.373
59.350
56.771
50.344
39.705
28.452
26.071
18.368
5.351
5.377
TBSO
Cl
Br
N
H
Boc
Cl
15
CDCl3, 126 MHz
220
200
180
160
140
120
100
80
60
40
20
0
-20

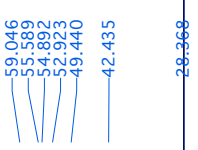

HO
Cl
Br
N
H
Boc
N
PMB
Cl
16
CDCl3, 500 MHz
1.0
1.9
0.8
1.9
2.7
0.8
1.0
2.8
0.9
2.9
1.8
1.0
1.2
1.1
8.6
0
9
8
7
6
5
4
3
2
1
0
-1

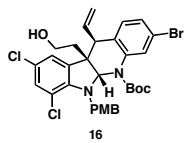


16

55 °C
$CDCl_3$, 500 MHz

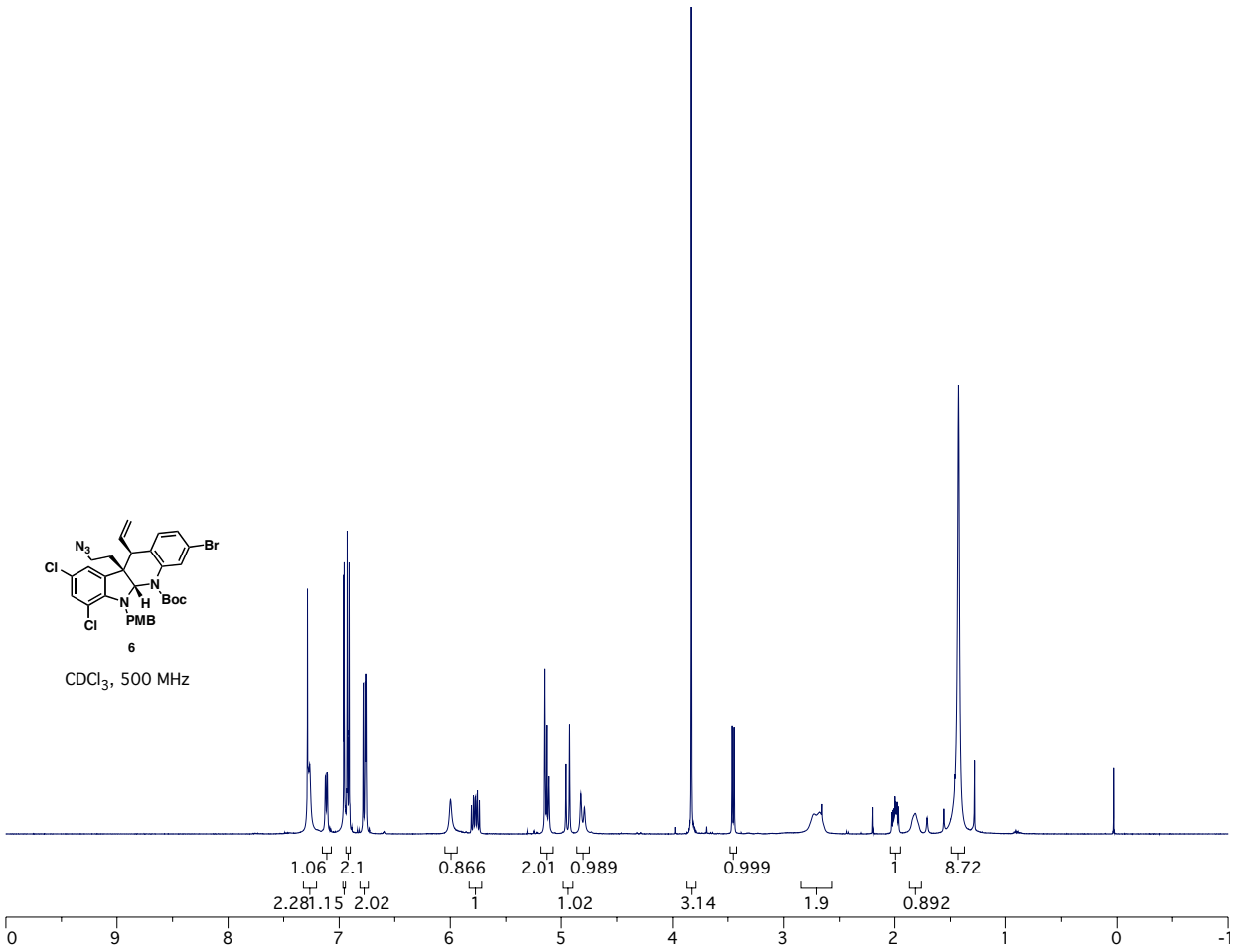


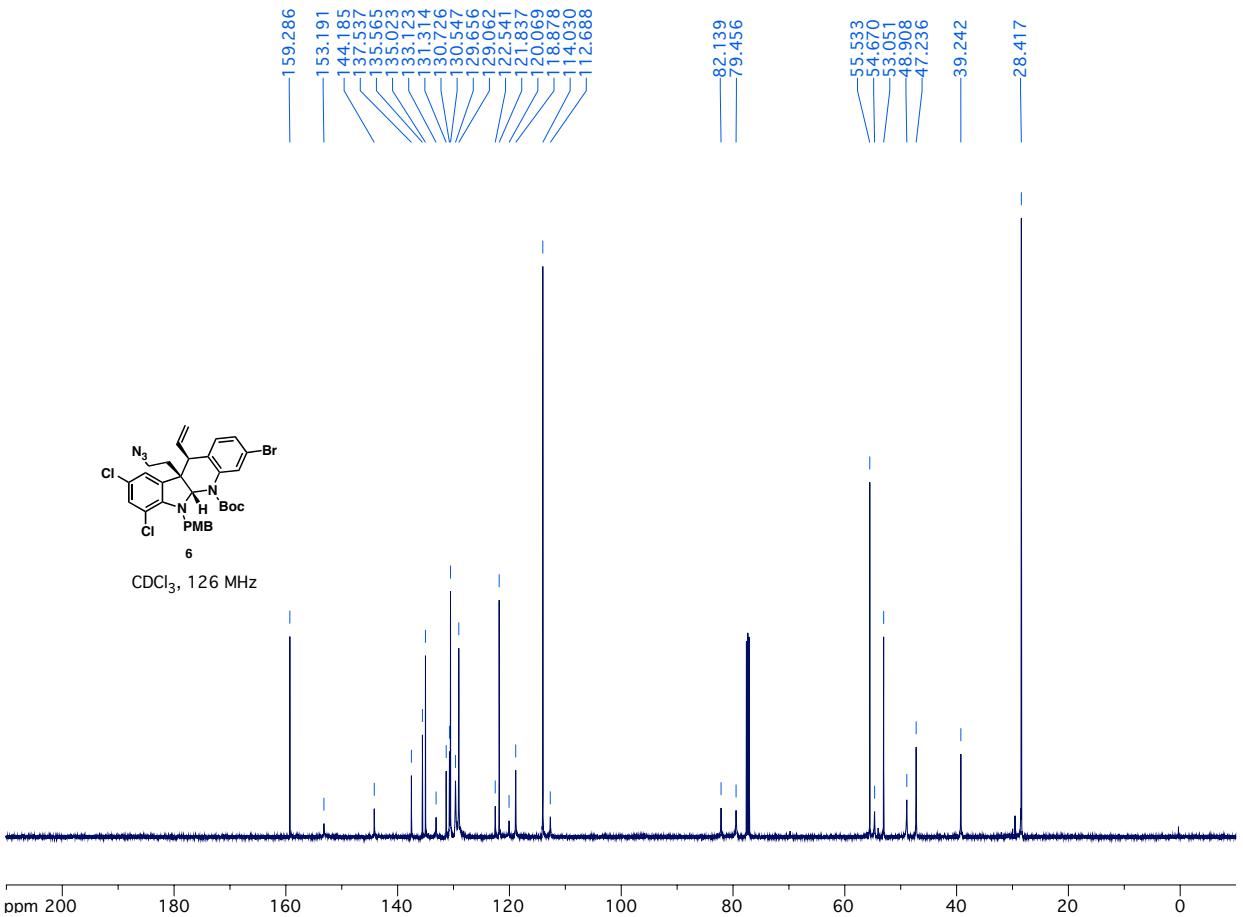


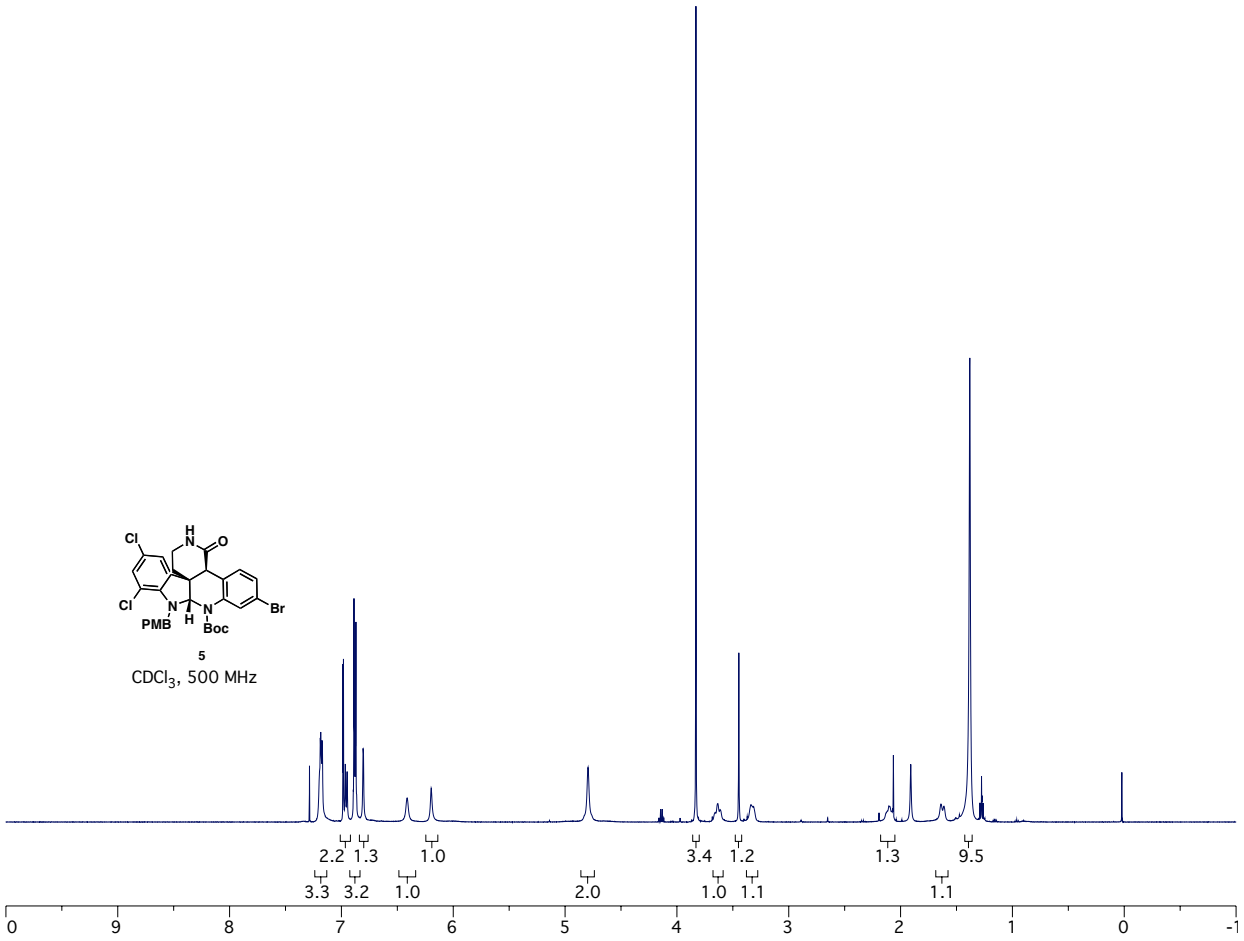


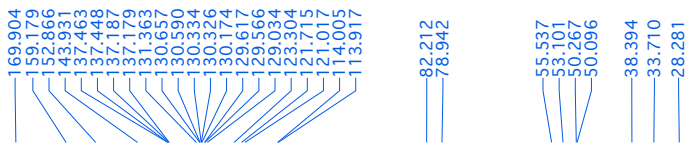
16

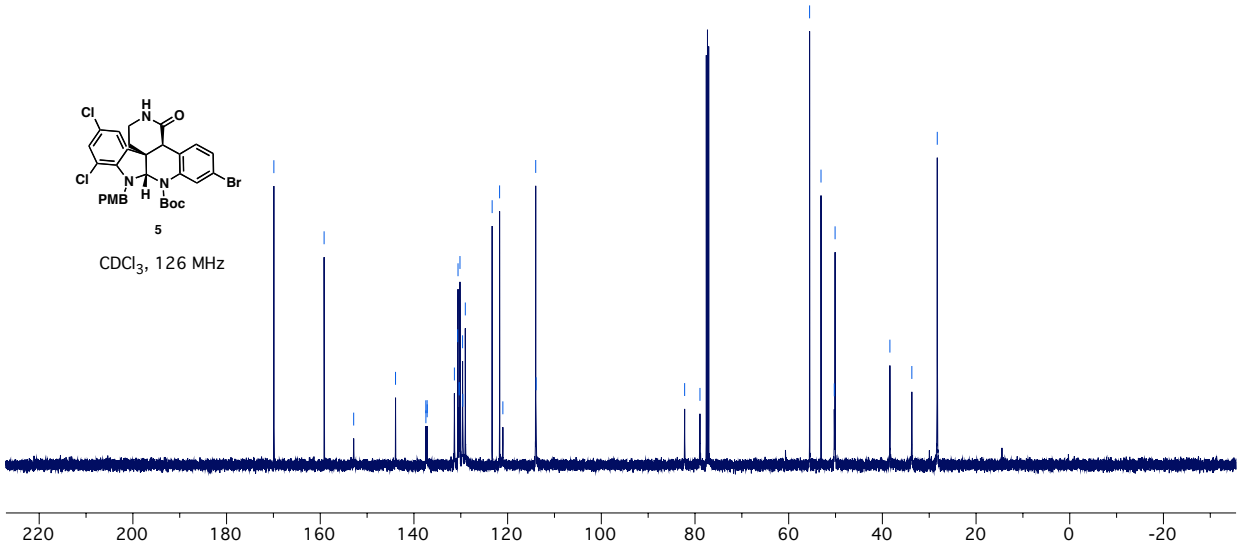
$CDCl_3$, 126 MHz

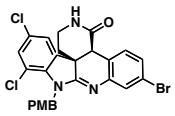

N3
Br
Cl
N
Boc
N
H
PMB
Cl
6
CDCl3, 500 MHz
1.06
2.1
0.866
2.01
0.989
0.999
1
8.72
2.28
1.15
2.02
1
1.02
3.14
1.9
0.892
0
9
8
7
6
5
4
3
2
1
0
-1


159.286
153.191
144.185
137.537
135.565
135.023
133.123
131.314
130.726
130.547
129.656
129.062
122.541
121.837
120.069
118.878
114.030
112.688
82.139
79.456
55.533
54.670
53.051
48.908
47.236
39.242
28.417
N3
Br
Cl
N
Boc
N
H
PMB
Cl
6
CDCl3, 126 MHz
ppm 200
180
160
140
120
100
80
60
40
20
0


Cl
H
N
O
Cl
N
N
H
Br
PMB
Boc
5
CDCl3, 500 MHz
2.2
1.3
1.0
3.4
1.2
1.3
9.5
3.3
3.2
1.0
2.0
1.0
1.1
1.1
0
9
8
7
6
5
4
3
2
1
0
-1

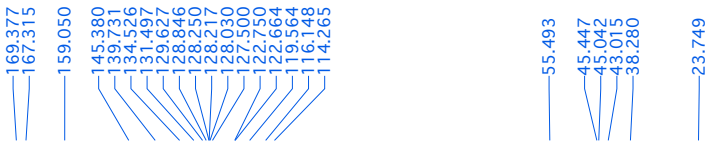

169.904
159.179
152.866
143.931
137.463
137.448
137.187
137.179
131.363
130.657
130.590
130.334
130.326
130.174
129.617
129.566
129.034
123.304
121.715
121.017
114.005
113.917
82.212
78.942
55.537
53.101
50.267
50.096
38.394
33.710
28.281

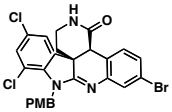

Cl
H
N
O
Cl
N
N
H
Br
PMB
Boc
5
CDCl3, 126 MHz
220
200
180
160
140
120
100
80
60
40
20
0
-20



18

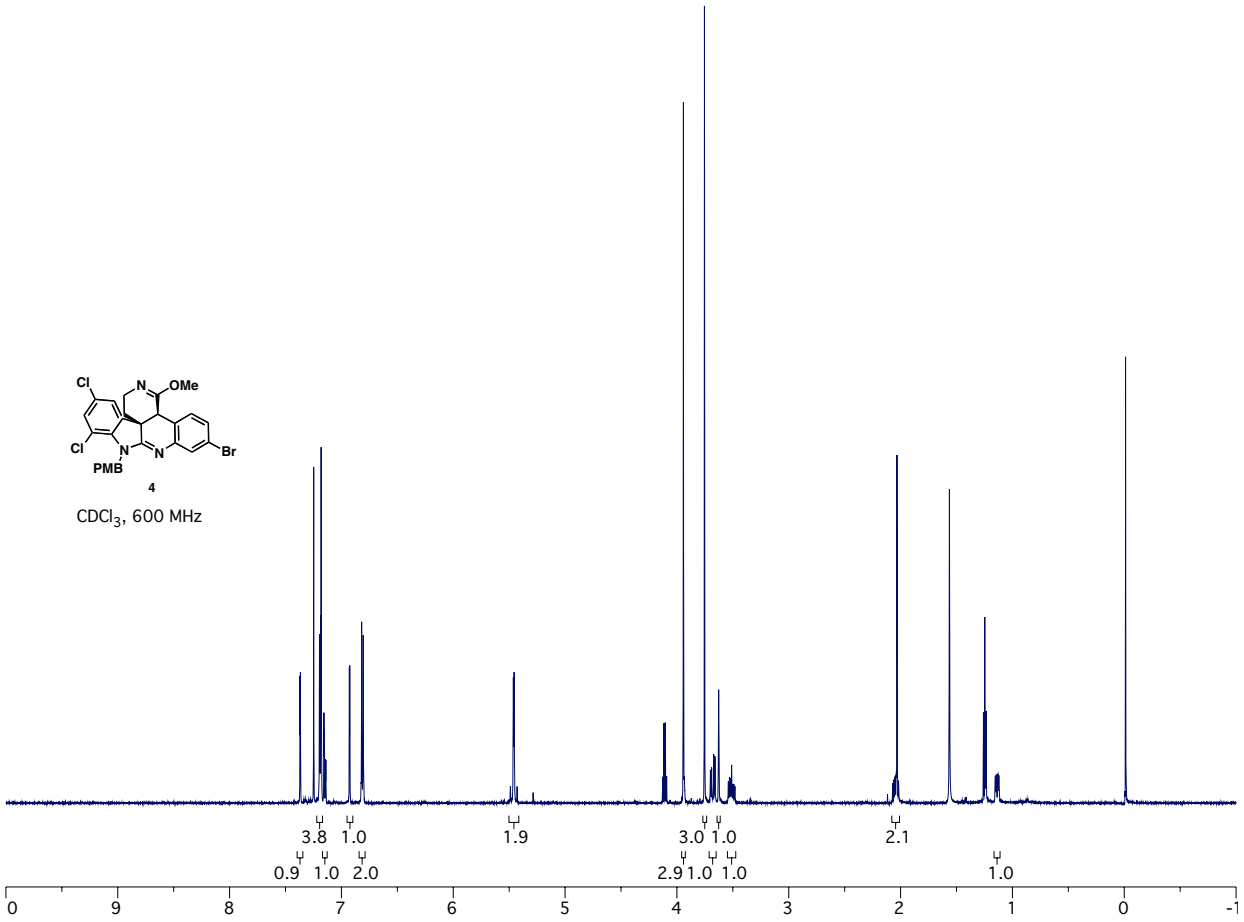
$CDCl_3$, 600 MHz

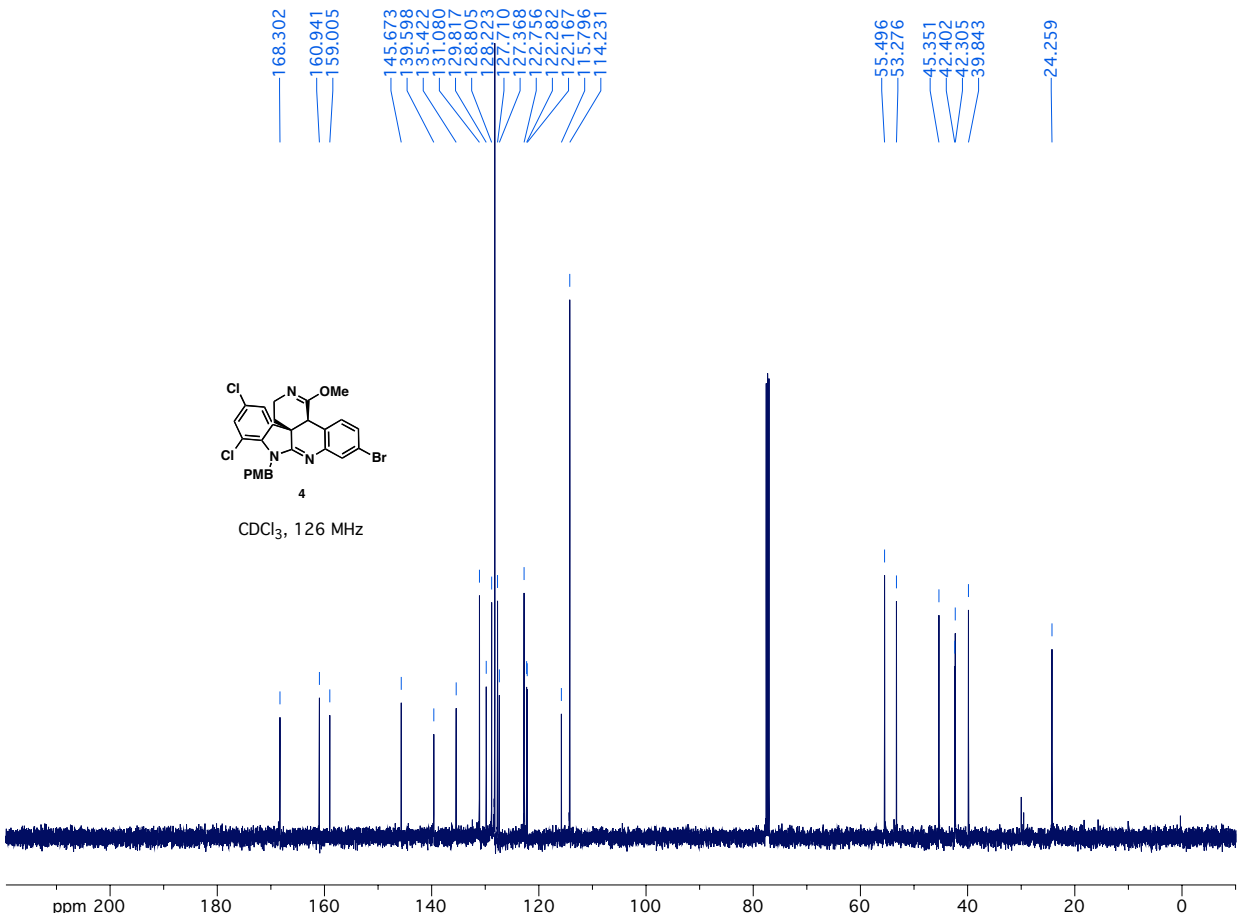


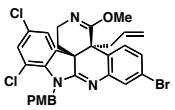


18

$CDCl_3$, 126 MHz

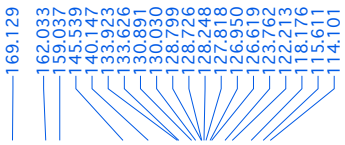

Cl
N
OMe
Cl
N
N
Br
PMB
4
CDCl3, 600 MHz
3.8
1.0
1.9
3.0
1.0
2.1
0.9
1.0
2.0
2.9
1.0
1.0
1.0
0
9
8
7
6
5
4
3
2
1
0
-1

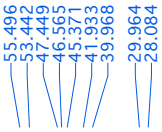

168.302
160.941
159.005
145.673
139.598
135.422
131.080
129.817
128.805
128.223
127.710
127.368
122.756
122.282
122.167
115.796
114.231
55.496
53.276
45.351
42.402
42.305
39.843
24.259
Cl
N
OMe
Cl
N
N
Br
PMB
4
CDCl3, 126 MHz
ppm 200
180
160
140
120
100
80
60
40
20
0

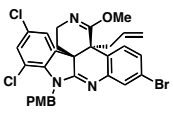


3

$CDCl_3$, 500 MHz

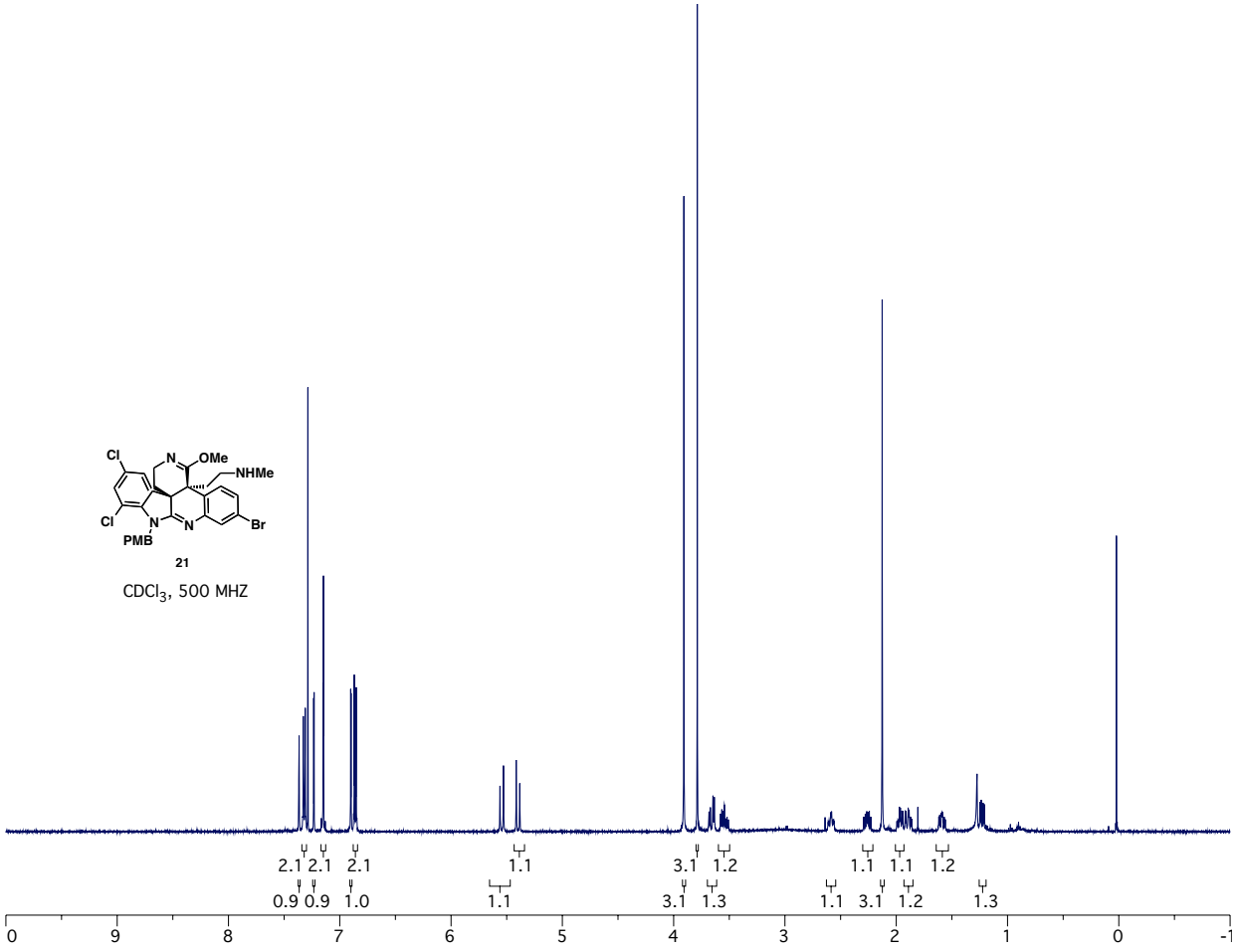


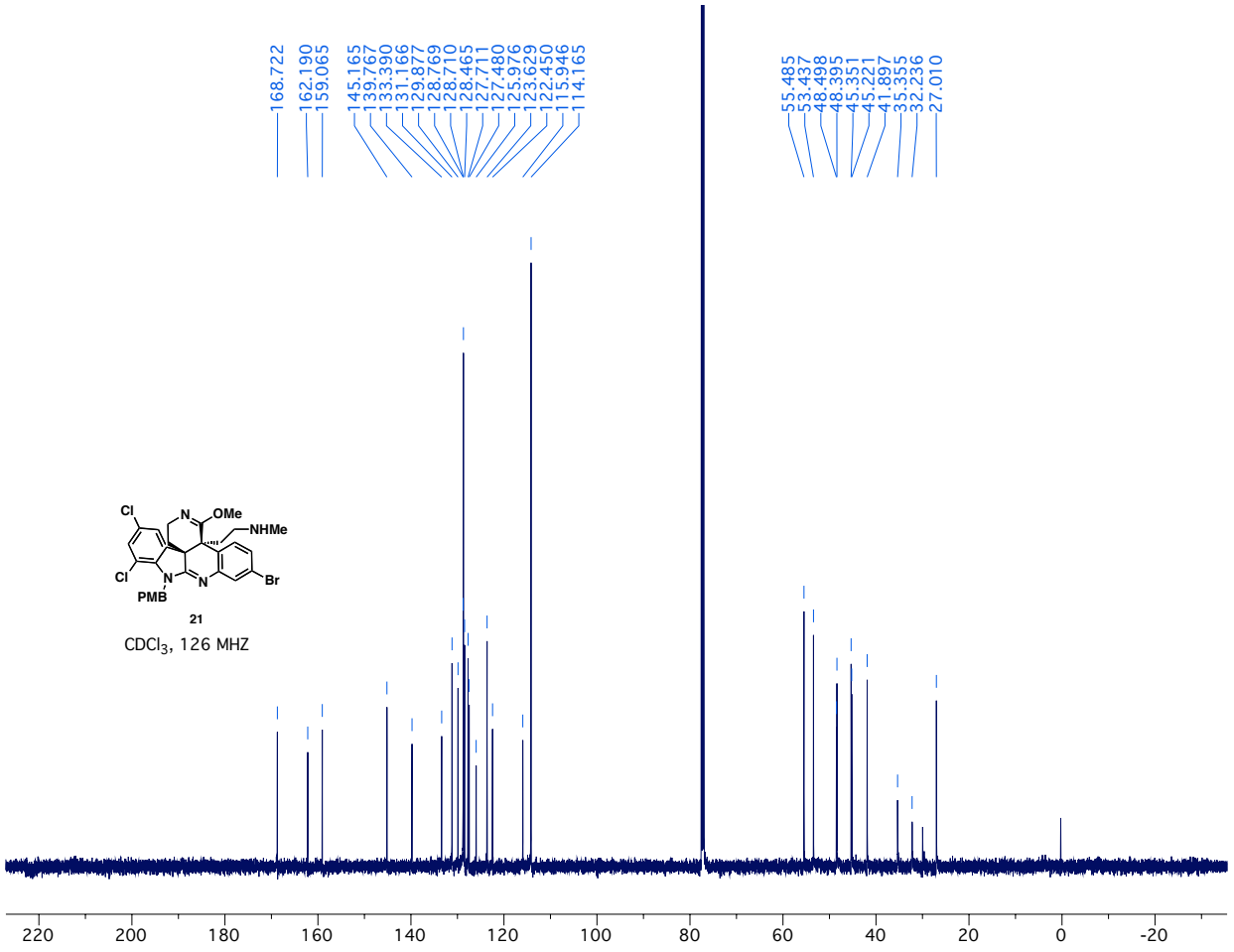


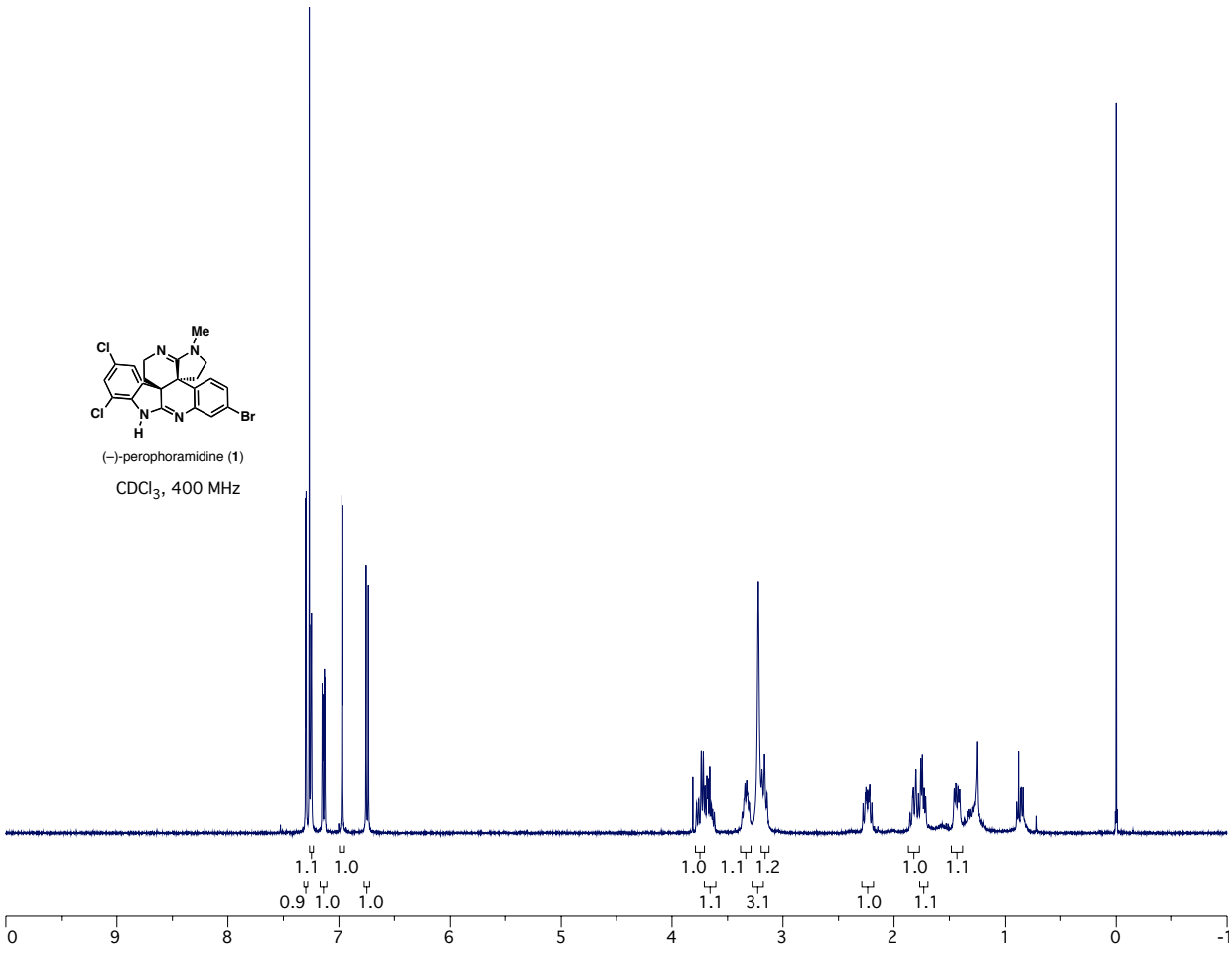


3

$CDCl_3$, 126 MHz

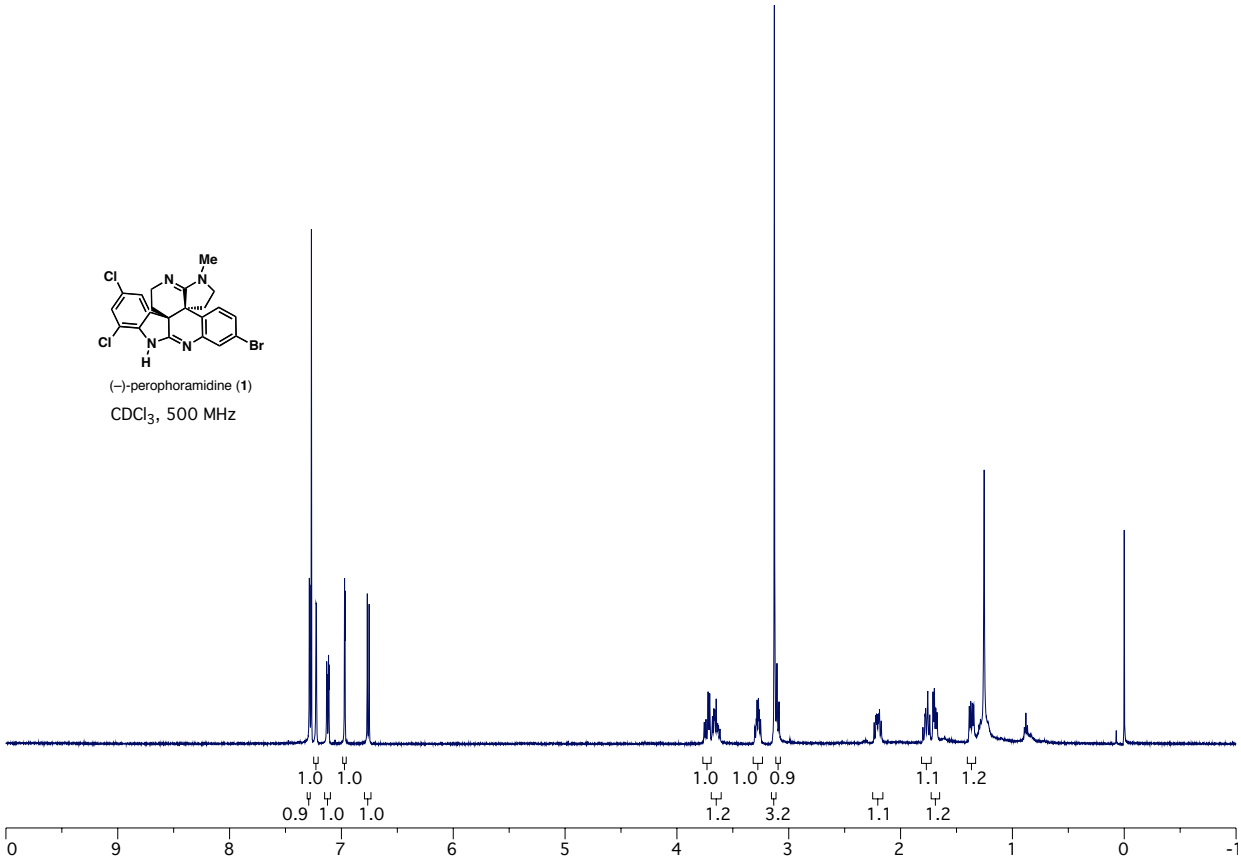

Cl
N
OMe
NHMe
Cl
N
N
Br
PMB
21
CDCl3, 500 MHZ
2.1 2.1 2.1 1.1 3.1 1.2 1.1 1.1 1.2
0.9 0.9 1.0 1.1 3.1 1.3 1.1 3.1 1.2 1.3
0 9 8 7 6 5 4 3 2 1 0 -1


168.722
162.190
159.065
145.165
139.767
133.390
131.166
129.877
128.769
128.710
128.465
127.711
127.480
125.976
123.629
122.450
115.946
114.165
55.485
53.437
48.498
48.395
45.351
45.221
41.897
35.355
32.236
27.010
Cl
N
OMe
NHMe
Cl
N
N
Br
PMB
21
CDCl3, 126 MHZ
220 200 180 160 140 120 100 80 60 40 20 0 -20



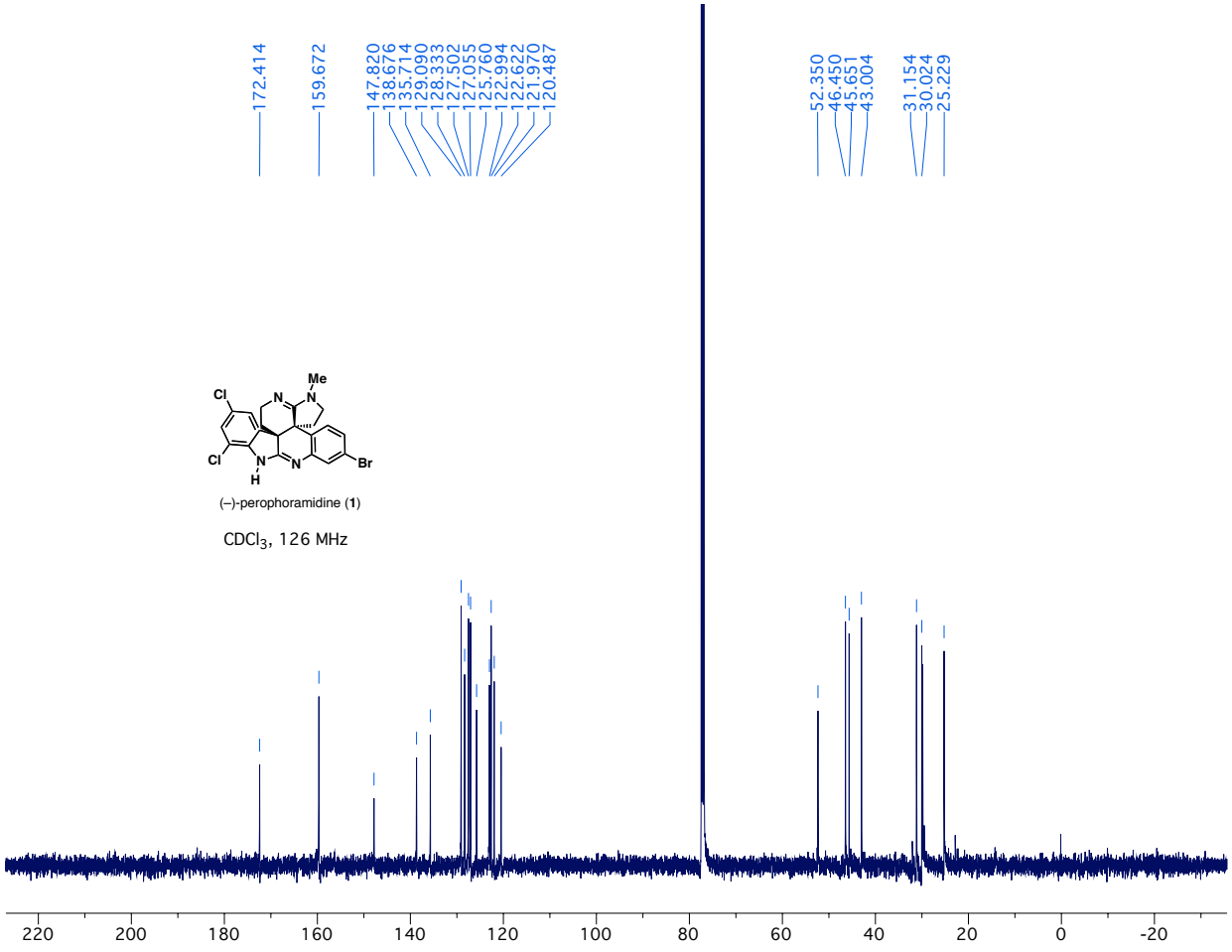
(–)-perophoramidine (**1**)

$CDCl_3$, 400 MHz



(–)-perophoramidine (**1**)

$CDCl_3$, 500 MHz



(–)-perophoramidine (**1**)

$CDCl_3$, 126 MHz