Convergent Synthesis of Piperidines by the Union of Conjugated Alkynes with Imines: A Unique Regioselective Bond Construction for Heterocycle Synthesis

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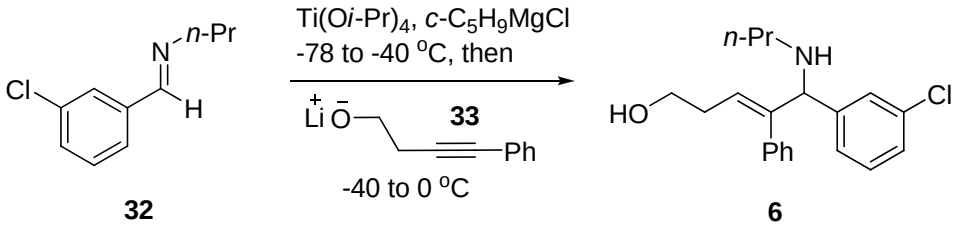
Supporting Information

Experimental Procedures and Spectral Data

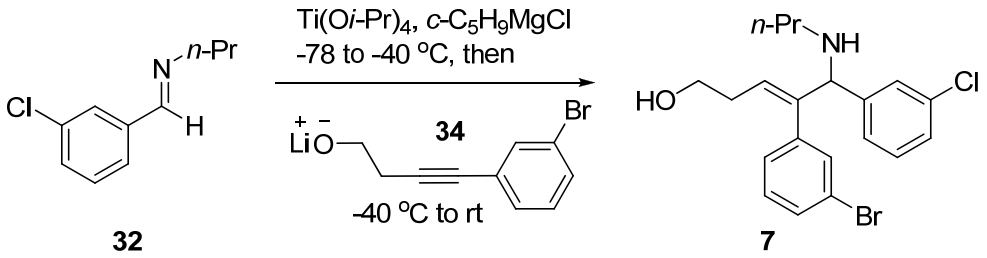
General. All reactions were conducted in flame-dried glassware under a nitrogen or argon atmosphere with anhydrous solvents, unless otherwise noted. Diethyl ether, dichloromethane, tetrahydrofuran and toluene were obtained by passing HPLC grade solvents through activated alumina columns. Acetonitrile was distilled over calcium hydride. Titanium tetraisopropoxide was purified by distillation at 250 millitorr. All conjugated homopropagylic alcohols were synthesized by known procedures.[1-4] Imines **40**, **42**, and all other known imines were prepared by stirring the aldehyde and amine in THF or DCM in the presence of anhydrous $MgSO_4$, followed by filtration and concentration. All imines were purified by distillation or recrystalization prior to use. All other commercially available reagents were used as received. Thin-layer chromatography was performed on 250 μm E. Merck silica gel plates (60F-254). Silica gel for flash column chromatography was purchased from Silicycle (P60, particle size 40-63 μm). All compounds purified by chromatography were sufficiently pure for use in further experiments except otherwise indicated.

^{1}H NMR and ^{13}C NMR data were recorded using a Bruker AM-400 or Bruker AM-500 instrument. ^{1}H NMR chemical shifts are reported relative to residual $CHCl_3$ (7.26 ppm). ^{13}C NMR chemical shifts were reported relative to the central line of $CDCl_3$ (77.23 ppm). Infrared spectra were recorded using a Thermo Electron Nicolet 6700 FT-IR spectrometer or Perkin Elmer Spectrum One 2000 FT-IR spectrometer. High-resolution mass spectrometry was performed on a 9.4T Bruker Qe FT-ICR Mass Spectrometer at the W. M. Keck Foundation Biotechnology and Resource Laboratory at Yale University. Low-resolution mass spectrometry was performed on a Varian 500-MS IT Mass Spectrometer using electrospray ionization. Optical rotations were measured on an Autopol IV Automatic Polarimeter (from Rudolph Research Analytical) using a quartz cell with a 0.5 mL capacity and a 10 cm path length. X-ray crystallography was performed using a Rigaku Mercury2 CCD area detector with graphite monochromated Mo-Kα radiation.



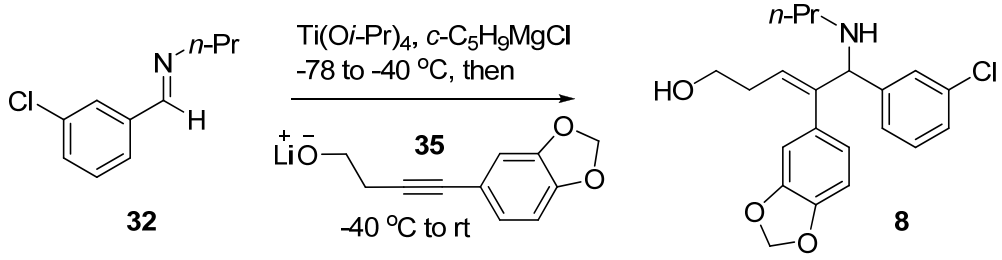
Synthesis of (*E*)-5-(3-chlorophenyl)-4-phenyl-5-(propylamino)pent-3-en-1-ol) (6). To a solution of imine **32** (83 μL, 90.8 mg, 0.50 mmol) and Ti(O*i*-Pr)$_4$ (222 μL, 213 mg, 0.75 mmol) in diethyl ether (2.5 mL) at –78 °C was added dropwise *c*-C_5H_9MgCl (2.18 M in diethyl ether, 1.50 mmol) via a gas-tight syringe. The mixture was warmed to –40 °C over 30 min and stirred at this temperature for another 1.5 h. Then a solution of lithium alkoxide **33** in diethyl ether (1 mL), generated from deprotonation of the corresponding alcohol (103 μL, 109.6 mg, 0.75 mmol) with *n*-BuLi (2.51 M in hexane, 0.80 mmol) at –78 °C followed by warming to 0 °C over 20 min, was added dropwise to the brown solution of imine-Ti complex at –40 °C via cannula. The resulting mixture was warmed to 0 °C over 30 min and stirred at this temperature for another 6 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL), and the resulting biphasic mixture was rapidly stirred until the precipitate became white in color. The mixture was further diluted with saturated aqueous $NaHCO_3$ (10 mL) and extracted with ethyl acetate (4 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (40→50% EtOAc/hexane) to afford amino alcohol **6** as an orange oil (103 mg, 63%).

Data for (*E*)-5-(3-chlorophenyl)-4-phenyl-5-(propylamino)pent-3-en-1-ol (6): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28-7.07 (m, 7H), 6.87 (d, *J* = 7.6 Hz, 2H), 5.83 (t, *J* = 7.4 Hz, 1H), 4.40 (s, 1H), 3.63 (t, *J* = 6.6 Hz, 2H), 2.64-2.59 (m, 1H), 2.53-2.47 (m, 1H), 2.20 (dt, *J* = 6.6, 6.6 Hz, 2H), 1.59-1.48 (m, 4H), 0.92 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.40, 144.82, 138.91, 134.41, 129.69, 129.47, 128.40, 128.14, 127.47, 127.39, 126.32, 125.14, 69.44, 62.83, 50.23, 32.76, 23.63, 12.24; IR (thin film, NaCl) ν_{max} 3328 (br), 3055, 3020, 2958, 2930, 2873, 1595, 1573, 1493, 1473, 1457, 1051, 770, 702 cm^{-1}; HRMS (EI, H) *m/z* calc'd for $C_{20}H_{24}ClNO$ $[M + H]^+$ 330.1619, found 330.1616.



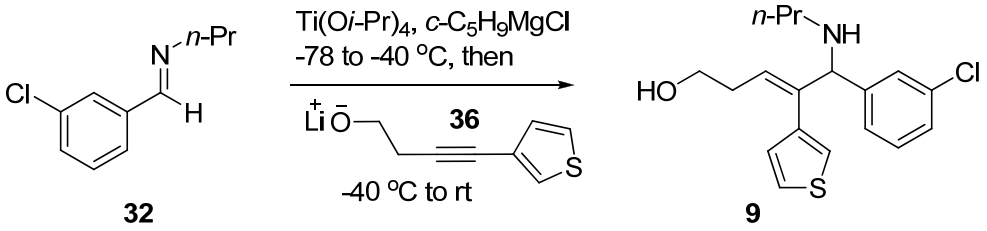
Synthesis of (*E*)-4-(3-bromophenyl)-5-(3-chlorophenyl)-5-(propylamino)pent-3-en-1-ol (7). To a solution of imine **32** (83 μL, 90.8 mg, 0.50 mmol) and Ti(O*i*-Pr)$_4$ (222 μL, 213 mg, 0.75 mmol) in diethyl ether (2.5 mL) at –78 °C was added dropwise *c*-C_5H_9MgCl (2.24 M in diethyl ether, 1.50 mmol) via a gas-tight syringe. The mixture was warmed to –40 °C over 30 min and stirred at this temperature for another 2 h. Then a solution of lithium alkoxide **34** in tetrahydrofuran (1 mL), generated from deprotonation of the corresponding alcohol (178 mg, 0.79 mmol) with *n*-BuLi (2.47 M in hexane, 0.87 mmol) at –78 °C followed by warming to 0 °C over 20 min, was added dropwise to the brown solution of imine-Ti complex at –40 °C via cannula. The resulting mixture was slowly warmed to room temperature over 15 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL), and the resulting biphasic mixture was rapidly stirred until the precipitate became white in color. The mixture was further diluted with saturated aqueous $NaHCO_3$ (10 mL) and extracted with ethyl acetate (4 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo.* The crude product was purified by column chromatography on silica gel (60→70% EtOAc/hexane) to afford amino alcohol **7** as an orange oil (126 mg, 62%).

Data for (*E*)-4-(3-bromophenyl)-5-(3-chlorophenyl)-5-(propylamino)pent-3-en-1-ol (7): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19-6.97 (m, 6H), 6.77 (d, *J* = 7.8 Hz, 2H), 5.74 (t, *J* = 7.4 Hz, 1H), 4.30 (s, 1H), 3.54 (t. *J* = 6.8 Hz, 2H), 2.55-2.49 (m, 1H), 2.43-2.38 (m, 1H), 2.10 (dt, *J* = 6.8, 6.8 Hz, 2H), 1.44-1.41 (m, 4H), 0.81 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.90, 145.37, 139.63, 135.18, 130.48, 130.23, 129.17, 128.90, 128.27, 128.16, 127.09, 126.09, 70.11, 63.46, 50.92, 33.50, 24.30, 12.99; IR (thin film, NaCl) ν_{max} 3308 (br), 3056, 3022, 2956, 2927, 2873, 1594, 1573, 1557, 1472, 1442, 1192, 1049, 770, 700 cm^{-1}; LRMS (EI, H) *m/z* calc'd for $C_{20}H_{23}BrClNO$ $[M + H]^+$ 408.1, found 408.2.



Synthesis of (*E*)-4-(benzo[*d*][1,3]dioxol-5-yl)-5-(3-chlorophenyl)-5-(propylamino) pent-3-en-1-ol (8). To a solution of imine **32** (83 μL, 90.8 mg, 0.50 mmol) and Ti(O*i*-Pr)$_4$ (222 μL, 213 mg, 0.75 mmol) in diethyl ether (2.5 mL) at –78 °C was added dropwise *c*-C_5H_9MgCl (2.24 M in diethyl ether, 1.50 mmol) via a gas-tight syringe. The mixture was warmed to –40 °C over 30 min and stirred at this temperature for another 2 h. Then a solution of lithium alkoxide **35** in tetrahydrofuran (1 mL), generated from deprotonation of the corresponding alcohol (145 mg, 0.75 mmol) with *n*-BuLi (2.47 M in hexane, 0.80 mmol) at –78 °C followed by warming to 0 °C over 20 min, was added dropwise to the brown solution of imine-Ti complex at –40 °C via cannula. The resulting mixture was slowly warmed to room temperature over 15 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL), and the resulting biphasic mixture was rapidly stirred until the precipitate became white in color. The mixture was further diluted with saturated aqueous $NaHCO_3$ (10 mL) and extracted with ethyl acetate (4 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo.* The crude product was purified by column chromatography on silica gel (60→70% EtOAc/hexane) to afford amino alcohol **8** as an orange oil (108 mg, 58%).

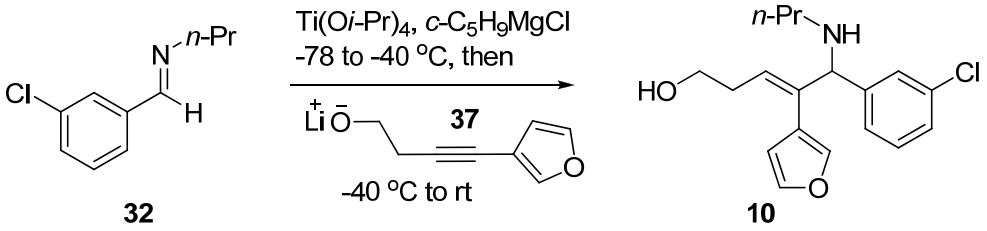
Data for (*E*)-4-(benzo[*d*][1,3]dioxol-5-yl)-5-(3-chlorophenyl)-5-(propylamino) pent-3-en-1-ol (8): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (s, 1H), 7.10 (app. d, *J* = 5.1 Hz, 2H), 7.01-6.99 (m, H), 6.61 (d, *J* = 7.9 Hz, 1H), 6.28 (s, 1H), 6.23 (d, *J* = 7.9 Hz, 1H), 5.85 (s, 2H), 5.71 (t, *J* = 7.4 Hz, 1H), 4.26 (s, 1H), 3.55 (t, *J* = 6.6 Hz, 2H), 1.47-1.39 (m, 4H), 0.83 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.19, 146.43, 144.52, 144.41, 134.00, 132.07, 129.29, 127.63, 127.07, 125.82, 124.95, 122.37, 109.51, 107.93, 100.85, 69.09, 62.42, 49.81, 32.32, 30.10 (residual acetone peak), 23.21, 11.83; IR (thin film, NaCl) ν_{max} 3331 (br), 3066, 2958, 2924, 1721, 1595, 1574, 1502, 1487, 1434, 1237, 1040, 937, 812, 734 cm^{-1}; HRMS (EI, H) *m/z* calc'd for $C_{21}H_{24}ClNO_3$ $[M + H]^+$ 374.1517, found 374.1516.



32 **9**

Synthesis of (*E*)-5-(3-chlorophenyl)-5-(propylamino)-4-(thiophen-3-yl)pent-3-en-1-ol (9). To a solution of imine **32** (83 μL, 90.8 mg, 0.50 mmol) and Ti(O*i*-Pr)$_4$ (222 μL, 213 mg, 0.75 mmol) in diethyl ether (2.5 mL) at –78 °C was added dropwise *c*-C_5H_9MgCl (2.24 M in diethyl ether, 1.50 mmol) via a gas-tight syringe. The mixture was warmed to –40 °C over 30 min and stirred at this temperature for another 2 h. Then a solution of lithium alkoxide **36** in diethyl ether (1 mL), generated from deprotonation of the corresponding alcohol (140 mg, 0.92 mmol) with *n*-BuLi (2.47 M in hexane, 1.01 mmol) at –78 °C followed by warming to 0 °C over 20 min, was added dropwise to the brown solution of imine-Ti complex at –40 °C via cannula. The resulting mixture was slowly warmed to room temperature over 15 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL), and the resulting biphasic mixture was rapidly stirred until the precipitate became white in color. The mixture was further diluted with saturated aqueous $NaHCO_3$ (10 mL) and extracted with ethyl acetate (4 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo.* The crude product was purified by column chromatography on silica gel (40→50% EtOAc/hexane) to afford amino alcohol **9** as an orange oil (93 mg, 55%).

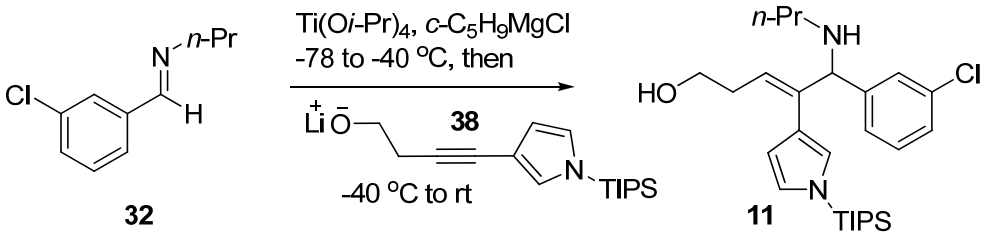
Data for (*E*)-5-(3-chlorophenyl)-5-(propylamino)-4-(thiophen-3-yl)pent-3-en-1-ol (9): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (s, 1H), 7.13-7.10 (m, 3H), 7.07-7.03 (m, 1H), 6.73 (dd, *J* = 3.0, 1.3 Hz, 1H), 6.60 (dd, *J* = 4.9, 1.3 Hz, 1H), 5.73 (t, *J* = 7.3 Hz, 1H), 4.30 (s, 1H), 3.56 (t, *J* = 6.7 Hz, 2H), 2.54-2.48 (m, 1H), 2.43-2.36 (m, 1H), 2.22 (dt, *J* = 6.7, 6.7 Hz, 2H), 1.59 (br, 2H), 1.47-1.37 (m, 2H), 0.82 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.57, 139.85, 137.98, 134.08, 129.36, 128.59, 127.60, 127.10, 126.38, 125.73, 124.85, 123.10, 68.76, 62.34, 49.74, 32.56, 23.23, 11.86; IR (thin film, NaCl) ν_{max} 3306 (br), 2958, 2931, 2873, 1594, 1573, 1471, 1428, 1192, 1077, 1049, 860, 785 cm^{-1}; LRMS (EI, H) *m/z* calc'd for $C_{18}H_{22}ClNOS$ $[M + H]^+$ 336.1, found 336.5.



32 10

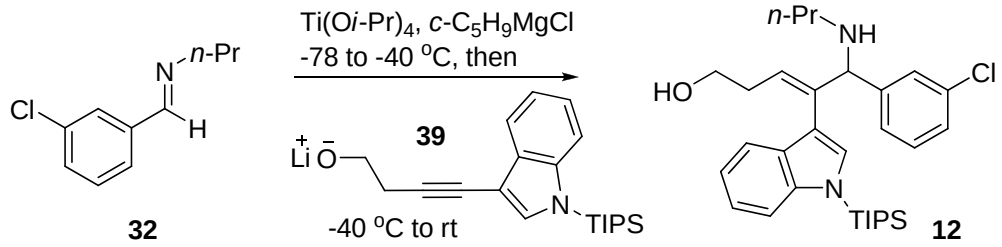
Synthesis of (*E*)-5-(3-chlorophenyl)-4-(furan-3-yl)-5-(propylamino)pent-3-en-1-ol (10). To a solution of imine **32** (50 μL, 54.4 mg, 0.30 mmol) and Ti(O*i*-Pr)$_4$ (133 μL, 128 mg, 0.45 mmol) in diethyl ether (1.5 mL) at –78 °C was added dropwise *c*-C_5H_9MgCl (2.28 M in diethyl ether, 0.90 mmol) via a gas-tight syringe. The mixture was warmed to –40 °C over 30 min and stirred at this temperature for another 2 h. Then a solution of lithium alkoxide **37** in diethyl ether (3 mL), generated from deprotonation of the corresponding alcohol (140 mg, 0.92 mmol) with *n*-BuLi (2.47 M in hexane, 1.01 mmol) at –78 °C followed by warming to 0 °C over 20 min, was added dropwise to the brown solution of imine-Ti complex at –40 °C via cannula. The resulting mixture was slowly warmed to room temperature over 15 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL), and the resulting biphasic mixture was rapidly stirred until the precipitate became white in color. The mixture was further diluted with saturated aqueous $NaHCO_3$ (10 mL) and extracted with ethyl acetate (4 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo.* The crude product was purified by column chromatography on silica gel (40→50% EtOAc/hexane) to afford amino alcohol **10** as an orange oil (53.5 mg, 56%).

Data for (*E*)-5-(3-chlorophenyl)-4-(furan-3-yl)-5-(propylamino)pent-3-en-1-ol (10): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25-7.24 (m, 2H), 7.16-7.08 (m, 3H), 7.03 (s, 1H), 6.02 (s, 1H), 5.76 (t, *J* = 7.3 Hz, 1H), 4.27 (s, 1H), 3.63 (t, *J* = 6.5 Hz, 2H), 2.53-2.48 (m, 1H), 2.43-2.38 (m, 1H), 2.34 (dt, *J* = 6.5, 6.5 Hz, 2H), 1.46-1.38 (m, 4H), 0.84 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.58, 142.35, 140.43, 129.35, 127.53, 127.10, 126.56, 125.66, 120.99, 111.41, 68.46, 62.28, 49.70, 32.50, 23.23, 11.85; IR (thin film, NaCl) ν_{max} 3334 (br), 3063, 2960, 2932, 2874, 1947, 1876, 1660, 1595, 1574, 1471, 1428, 1161, 1077, 1026, 873, 788 cm^{-1}; HRMS (EI, H) *m/z* calc'd for $C_{18}H_{22}ClNO_2$ $[M + H]^+$ 320.1412, found 320.1406.



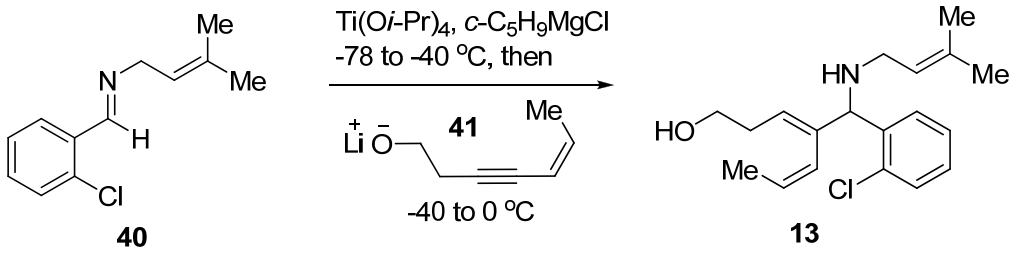
Synthesis of (*E*)-5-(3-chlorophenyl)-5-(propylamino)-4-(1-(triisopropylsilyl)-*1H*-pyrrol-3-yl)pent-3-en-1-ol (11). To a solution of imine **32** (50 μL, 54.4 mg, 0.30 mmol) and Ti(O*i*-Pr)$_4$ (133 μL, 128 mg, 0.45 mmol) in diethyl ether (1.5 mL) at –78 °C was added dropwise *c*-C_5H_9MgCl (2.28 M in diethyl ether, 0.90 mmol) via a gas-tight syringe. The mixture was warmed to –40 °C over 30 min and stirred at this temperature for another 2 h. Then a solution of lithium alkoxide **38** in diethyl ether (1.5 mL), generated from deprotonation of the corresponding alcohol (218 mg, 0.75 mmol) with *n*-BuLi (2.17 M in hexane, 0.83 mmol) at –78 °C followed by warming to 0 °C over 20 min, was added dropwise to the brown solution of imine-Ti complex at –40 °C via cannula. The resulting mixture was slowly warmed to room temperature over 15 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL), and the resulting biphasic mixture was rapidly stirred until the precipitate became white in color. The mixture was further diluted with saturated aqueous $NaHCO_3$ (10 mL) and extracted with ethyl acetate (4 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo.* The crude product was purified by column chromatography on silica gel (40→50% EtOAc/hexane) to afford amino alcohol **11** as an orange oil (94 mg, 66%).

Data for (*E*)-5-(3-chlorophenyl)-5-(propylamino)-4-(1-(triisopropylsilyl)-*1H*-pyrrol-3-yl)pent-3-en-1-ol (11): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (s, 1H), 7.16-7.06 (m, 3H), 6.58 (s, 1H), 6.29 (s, 1H), 5.95 (s, 1H), 5.53 (t, *J* = 7.2 Hz, 1H), 4.30 (s, 1H), 3.61 (t, *J* = 6.5 Hz, 2H), 2.53-2.48 (m, 1H), 2.42-2.36 (m, 3H), 1.48-1.34 (m, 4H), 1.28 (septex, *J* = 7.5 Hz, 3H), 0.96 (d, *J* = 7.5 Hz, 18H), 0.80 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.03, 139.87, 134.26, 129.51, 128.03, 127.01, 126.17, 124.20, 123.96, 123.77, 121.85, 111.70, 69.21, 63.27, 50.27, 33.07, 23.73, 18.26, 18.23, 12.28, 12.11; IR (thin film, NaCl) ν_{max} 3311 (br), 2947, 2868, 1595, 1572, 1473, 1385, 1263, 1092, 1017, 884, 785, 692 cm^{-1}; HRMS (EI, H) *m/z* calc'd for $C_{27}H_{43}ClN_2OSi$ $[M + H]^+$ 475.2906, found 475.2895.



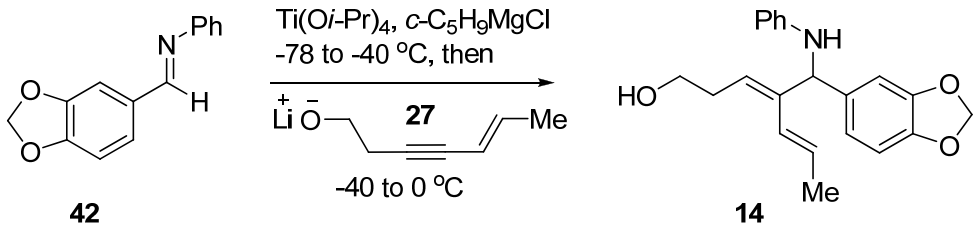
Synthesis of (*E*)-5-(3-chlorophenyl)-5-(propylamino)-4-(1-(triisopropylsilyl)-*1H*-indol-3-yl)pent-3-en-1-ol (12). To a solution of imine **32** (50 μL, 54.5 mg, 0.30 mmol) and Ti(O*i*-Pr)$_4$ (133 μL, 128 mg, 0.45 mmol) in diethyl ether (1.5 mL) at –78 °C was added dropwise *c*-C_5H_9MgCl (1.89 M in diethyl ether, 0.90 mmol) via a gas-tight syringe. The mixture was warmed to –40 °C over 30 min and stirred at this temperature for another 1.5 h. Then a solution of lithium alkoxide **39** in diethyl ether (1.5 mL), generated from deprotonation of the corresponding alcohol (256 mg, 0.75 mmol) with *n*-BuLi (2.57 M in hexane, 0.83 mmol) at –78 °C followed by warming to 0 °C over 20 min, was added dropwise to the brown solution of imine-Ti complex at –40 °C via cannula. The resulting mixture was slowly warmed to room temperature over 15 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL), and the resulting biphasic mixture was rapidly stirred until the precipitate became white in color. The mixture was further diluted with saturated aqueous $NaHCO_3$ (10 mL) and extracted with ethyl acetate (4 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo.* The crude product was purified by column chromatography on silica gel (20→30% EtOAc/hexane) to afford amino alcohol **12** as an orange oil (83.4 mg, 53%).

Data for (*E*)-5-(3-chlorophenyl)-5-(propylamino)-4-(1-(triisopropylsilyl)-*1H*-indol-3-yl)pent-3-en-1-ol (12): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.1 Hz, 1H), 7.24 (d, *J* = 8.6 Hz, 1H), 7.19 (s, 1H), 7.08-6.97 (m, 5H), 6.43 (s, 1H), 5.92 (t, *J* = 7.8 Hz, 1H), 4.38 (s, 1H), 3.54 (t, *J* = 6.5 Hz, 2H), 2.63-2.56 (m, 1H), 2.47-2.40 (m, 1H), 2.17 (dt, *J* = 6.6, 6.6 Hz, 2H), 1.52-1.35 (m, 7H), 0.98 (d, *J* = 7.5 Hz, 18H), 0.78 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.30, 140.70, 137.95, 133.95, 129.18, 126.76, 125.89, 121.41, 119.71, 119.40, 114.68, 113.93, 68.71, 62.63, 49.89, 32.96, 23.28, 18.08, 12.73, 11.82; IR (thin film, NaCl) ν_{max} 3325 (br), 3045, 2950, 2869, 1740, 1651, 1606, 1594, 1573, 1538, 1463, 1449, 1384, 1295, 1165, 1142, 1049, 1015, 883, 741 cm^{-1}; LRMS (EI, H) *m/z* calc'd for $C_{31}H_{45}ClN_2OSi$ $[M + H]^+$ 525.3, found 525.8.



Synthesis of (3*E*,5*Z*)-4-((2-chlorophenyl)(3-methylbut-2-enylamino)methyl)hepta-3,5-dien-1-ol (13). To a solution of imine **40** (310 μL, 343 mg, 1.65 mmol) and Ti(O*i*-Pr)$_4$ (444 μL, 426 mg, 1.5 mmol) in diethyl ether (5 mL) at –78 °C was added dropwise *c*-C_5H_9MgCl (2.26 M in diethyl ether, 3.0 mmol) via a gas-tight syringe. The mixture was warmed to –40 °C over 30 min and stirred at this temperature for another 3 h. Then a solution of lithium alkoxide **41** in diethyl ether (1 mL), generated from deprotonation of the corresponding alcohol (57 μL, 55 mg, 0.5 mmol) with *n*-BuLi (2.55 M in hexane, 0.55 mmol) at –78 °C followed by warming to 0 °C over 20 min, was added dropwise to the brown solution of imine-Ti complex at –40 °C via cannula. The resulting mixture was warmed to 0 °C over 30 min and stirred at this temperature for another 6 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL), and the resulting biphasic mixture was rapidly stirred until the precipitate became white in color. The mixture was further diluted with saturated aqueous $NaHCO_3$ (10 mL) and extracted with ethyl acetate (4 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo.* The crude product was purified by column chromatography on silica gel (40→50% EtOAc/hexane) to afford amino alcohol **13** as an orange oil (101 mg, 63%).

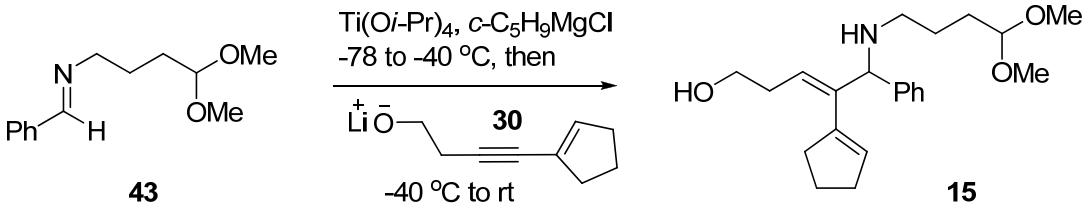
Data for (3*E*,5*Z*)-4-((2-chlorophenyl)(3-methylbut-2-enylamino)methyl)hepta-3,5-dien-1-ol (13): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, *J* = 7.7 Hz, 1H), 7.24-7.05 (m, 3H), 5.61-5.52 (m, 3H), 5.18 (t, *J* = 6.9 Hz, 1H), 4.64 (s, 1H), 3.56 (t, *J* = 6.5 Hz, 2H), 3.09-2.99 (m, 2H), 2.17-2.13 (m, 2H), 1.63 (s, 3H), 1.46 (s, 3H), 1.30 (d, *J* = 5.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.12, 138.44, 134.67, 133.89, 129.44, 129.11, 128.73, 127.85, 126.54, 125.64, 125.02, 122.69, 63.84, 62.20, 45.20, 32.69, 25.72, 17.79, 14.63; IR (thin film, NaCl) ν_{max} 3321 (br), 3064, 3006, 2968, 2912, 2871, 1673, 1571, 1471, 1442, 1376, 1050, 751 cm^{-1}; HRMS (EI, H) *m/z* calc'd for $C_{19}H_{26}ClNO$ $[M + H]^+$ 320.1776, found 320.1770.



42 **14**

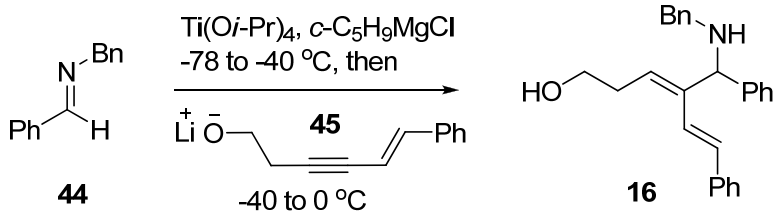
Synthesis of (3*E*,5*E*)-4-(benzo[*d*][1,3]dioxol-5-yl(phenylamino)methyl)hepta-3,5-dien-1-ol (14). To a solution of imine **42** (78.8 mg, 0.35 mmol) and Ti(O*i*-Pr)$_4$ (155 μL, 150 mg, 0.53 mmol) in diethyl ether (2.5 mL) at –78 °C was added dropwise *c*-C$_5$H$_9$MgCl (2.20 M in diethyl ether, 1.05 mmol) via a gas-tight syringe. The mixture was warmed to –40 °C over 30 min and stirred at this temperature for another 1.5 h. Then a solution of lithium alkoxide **27** in diethyl ether (1 mL), generated from deprotonation of the corresponding alcohol (80 μL, 77 mg, 0.70 mmol) with *n*-BuLi (2.55 M in hexane, 0.74 mmol) at –78 °C followed by warming to 0 °C over 20 min, was added dropwise to the brown solution of imine-Ti complex at –40 °C via cannula. The resulting mixture was warmed to 0 °C over 30 min and stirred at this temperature for another 6 h. The reaction was quenched with saturated aqueous NaHCO$_3$ (5 mL), and the resulting biphasic mixture was rapidly stirred until the precipitate became white in color. The mixture was further diluted with saturated aqueous NaHCO$_3$ (10 mL) and extracted with ethyl acetate (4 x 20 mL). The combined organic extracts were washed with brine, dried over MgSO$_4$, and concentrated *in vacuo.* The crude product was purified by column chromatography on silica gel (20% EtOAc/hexane) to afford amino alcohol **14** as an orange oil (71.6 mg, 61%).

Data for (3*E*,5*E*)-4-(benzo[*d*][1,3]dioxol-5-yl(phenylamino)methyl)hepta-3,5-dien-1-ol (14): ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.14 (d, *J* = 8.4 Hz, 2H), 6.86-6.84 (m, 2H), 6.76 (app. d, *J* = 8.6 Hz, 1H), 6.69 (t, *J* = 7.3 Hz, 1H), 6.50 (d, *J* = 7.7 Hz, 2H), 6.34 (d, *J* = 5.8 Hz, 1H), 5.95 (s, 2H), 5.80-5.72 (m, 1H), 5.57 (t, *J* = 7.6 Hz, 1H), 5.05 (s, 1H), 3.95 (br, 1H), 3.64-3.61 (m, 2H), 2.55-2.43 (m, 2H), 1.76 (d *J* = 7.6 Hz, 3H); ^{13}C NMR (126 MHz, CDCl$_3$) δ 148.28, 147.65, 147.24, 138.46, 136.31, 129.51, 127.86, 126.52, 125.58, 121.39, 117.89, 113.55, 108.72, 108.51, 101.45, 62.79, 60.85, 31.45, 19.50; IR (thin film, NaCl) ν_{max} 3555, 3414 (br), 3046, 2880, 2245, 1601, 1540, 1502, 1485, 1440, 1316, 1248, 1039, 963, 750 cm^{-1}; HRMS (EI, H) *m/z* calc'd for C$_{21}$H$_{23}$NO$_3$ [M + Na]$^+$ 360.1570, found 360.1573.



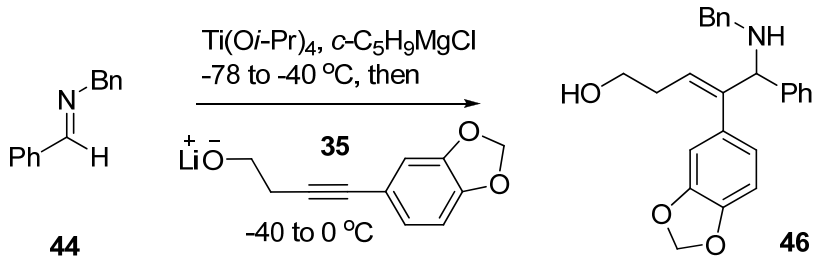
Synthesis of (*E*)-4-cyclopentenyl-5-(4,4-dimethoxybutylamino)-5-phenylpent-3-en-1-ol (15). To a solution of imine **43** (104 μL, 111 mg, 0.50 mmol) and Ti(O*i*-Pr)$_4$ (222 μL, 213 mg, 0.75 mmol) in diethyl ether (2 mL) at –78 °C was added dropwise *c*-C_5H_9MgCl (1.85 M in diethyl ether, 1.50 mmol) via a gas-tight syringe. The mixture was warmed to –40 °C over 30 min and stirred at this temperature for another 1.5 h. Then a solution of lithium alkoxide **30** in diethyl ether (1 mL), generated from deprotonation of the corresponding alcohol (170 mg, 1.25 mmol) with *n*-BuLi (2.44 M in hexane, 1.30 mmol) at –78 °C followed by warming to 0 °C over 20 min, was added dropwise to the brown solution of imine-Ti complex at –40 °C via cannula. The resulting mixture was slowly warmed to room temperature over 15 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL), and the resulting biphasic mixture was rapidly stirred until the precipitate became white in color. The mixture was further diluted with saturated aqueous $NaHCO_3$ (10 mL) and extracted with ethyl acetate (4 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo.* The crude product was purified by column chromatography on silica gel (90→100% EtOAc/hexane) to afford **15** as an orange oil (93.0 mg, 52%).

Data for (*E*)-4-cyclopentenyl-5-(4,4-dimethoxybutylamino)-5-phenylpent-3-en-1-ol (15): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.10 (m, 5H), 5.46 (t, *J* = 7.3 Hz, 1H), 5.28-5.26 (m, 1H), 4.28 (t, *J* = 5.5 Hz, 1H), 4.16 (s, 1H), 3.57 (t, *J* = 6.6 Hz, 2H), 3.22 (s, 6H), 2.57-2.39 (m, 2H), 2.29 (dt, *J* = 6.8, 6.8 Hz, 2H), 2.25-2.18 (m, 2H), 1.72-1.64 (m, 2H), 1.60-1.43 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.82, 142.75, 140.95, 129.71, 128.03, 127.45, 126.77, 122.95, 104.46, 67.54, 62.74, 52.70, 47.66, 36.54, 32.56, 30.36, 25.29, 23.60; IR (thin film, NaCl) ν_{max} 3401 (br), 3060, 3026, 2948, 2845, 1601, 1492, 1454, 1384, 1191, 1129, 1051, 702 cm^{-1}; LRMS (EI, H) *m/z* calc'd for $C_{22}H_{33}NO_3$ [M + H]$^+$ 360.3, found 360.7.



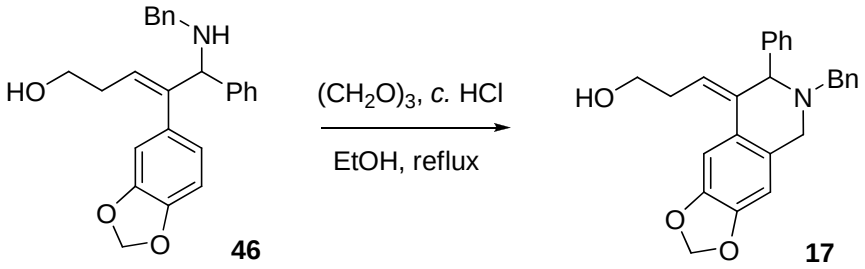
Synthesis of (3*E*,5*E*)-4-((benzylamino)(phenyl)methyl)-6-phenylhexa-3,5-dien-1-ol (16). To a solution of imine **44** (90 μL, 97.5 mg, 0.50 mmol) and Ti(O*i*-Pr)$_4$ (222 μL, 213 mg, 0.75 mmol) in diethyl ether (2.5 mL) at –78 °C was added dropwise *c*-C_5H_9MgCl (2.18 M in diethyl ether, 1.50 mmol) via a gas-tight syringe. The mixture was warmed to –40 °C over 30 min and stirred at this temperature for another 1.5 h. Then a solution of lithium alkoxide **45** in diethyl ether (2 mL), generated from deprotonation of the corresponding alcohol (129 mg, 0.75 mmol) with *n*-BuLi (2.51 M in hexane, 0.80 mmol) at –78 °C followed by warming to 0 °C over 20 min, was added dropwise to the brown solution of imine-Ti complex at –40 °C via cannula. The resulting mixture was warmed to 0 °C over 30 min and stirred at this temperature for another 6 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL), and the resulting biphasic mixture was rapidly stirred until the precipitate became white in color. The mixture was further diluted with saturated aqueous $NaHCO_3$ (10 mL) and extracted with ethyl acetate (4 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo.* The crude product was purified by column chromatography on silica gel (25→30% EtOAc/hexane) to afford amino alcohol **16** as an orange oil (95.5 mg, 52%).

Data for (3*E*,5*E*)-4-((benzylamino)(phenyl)methyl)-6-phenylhexa-3,5-dien-1-ol (16): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, *J* = 7.5 Hz, 2H), 7.29-7.09 (m, 13H), 6.91 (d, *J* = 16.5 Hz, 1H), 6.49 (d, *J* = 16.5 Hz, 1H), 5.79 (t, *J* = 7.6 Hz, 1H), 4.61 (s, 1H), 3.69 (s, 2H), 3.66 (t, *J* = 6.6 Hz, 2H), 2.58-2.49 (m, 2H), 1.57 (br, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.05, 140.81, 140.47, 137.95, 130.30, 128.95, 128.82, 128.75, 128.57, 128.03, 127.93, 127.50, 127.40, 126.80, 124.45, 64.29, 62.85, 52.44, 31.96; IR (thin film, NaCl) ν_{max} 3312 (br), 3082, 3059, 3025, 2918, 2874,1599, 1493, 1452, 1335, 1049, 1029, 959, 749, 699 cm^{-1}; HRMS (EI, H) *m/z* calc'd for $C_{26}H_{27}NO$ $[M + H]^+$ 370.2165, found 370.2153.



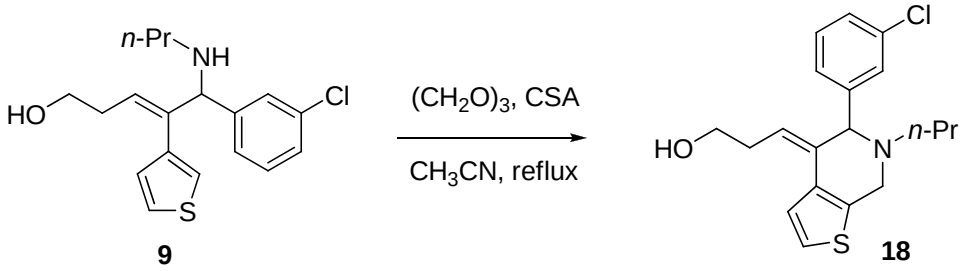
Synthesis of (*E*)-4-(benzo[*d*][1,3]dioxol-5-yl)-5-(benzylamino)-5-phenylpent-3-en-1-ol (46). To a solution of imine **44** (90 μL, 97.5 mg, 0.5 mmol) and Ti(O*i*-Pr)$_4$ (222 μL, 213 mg, 0.75 mmol) in diethyl ether (2.5 mL) at –78 °C was added dropwise *c*-C_5H_9MgCl (2.18 M in diethyl ether, 1.5 mmol) via a gas-tight syringe. The mixture was warmed to –40 °C over 30 min and stirred at this temperature for another 1.5 h. Then a solution of lithium alkoxide **35** in tetrahydrofuran (1 mL), generated from deprotonation of the corresponding alcohol (112 μL, 143 mg, 0.75 mmol) with *n*-BuLi (2.51 M in hexane, 0.80 mmol) at –78 °C followed by warming to 0 °C over 20 min, was added dropwise to the brown solution of imine-Ti complex at –40 °C via cannula. The resulting mixture was warmed to 0 °C over 30 min and stirred at this temperature for another 6 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL), and the resulting biphasic mixture was rapidly stirred until the precipitate became white in color. The mixture was further diluted with saturated aqueous $NaHCO_3$ (10 mL) and extracted with ethyl acetate (4 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo.* The crude product was purified by column chromatography on silica gel (40→60% EtOAc/hexane) to afford amino alcohol **46** as an orange oil (80.6 mg, 42%).

Data for (*E*)-4-(benzo[*d*][1,3]dioxol-5-yl)-5-(benzylamino)-5-phenylpent-3-en-1-ol (46): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.22 (m, 10H), 6.69 (d, *J* = 7.9 Hz, 1H), 6.37 (s, 1H), 6.35 (d, *J* = 8.4 Hz, 1H), 5.93 (s, 2H), 5.86 (t, *J* = 7.4 Hz, 1H), 4.45 (s, 1H), 3.80 (appd. q, *J* = 13.3 Hz, 2H), 3.64 (t, *J* = 6.6 Hz, 2H), 2.26 (dt, *J* = 7.4, 6.6 Hz, 2H), 1.58 (br, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.53, 146.75, 145.26, 142.27, 140.83, 132.90, 128.78, 128.58, 128.56, 128.13, 127.45, 127.33, 125.13, 122.85, 110.06, 108.27, 101.22, 68.96, 62.95, 52.09, 32.80; IR (thin film, NaCl) ν_{max} 3321 (br), 3062, 3027, 2886, 1602, 1487, 1453, 1436, 1331, 1237, 1040, 936, 732 cm^{-1}; HRMS (EI, H) *m/z* calc'd for $C_{25}H_{25}NO_3$ $[M + H]^+$ 388.1907, found 388.1907.



Synthesis of (*E*)-3-(6-benzyl-7-phenyl-6,7-dihydro-[1,3]dioxolo[4,5-*g*]isoquinolin-8(*5H*)-ylidene)propan-1-ol (17). To a solution of amino alcohol **46** (60.8 mg, 0.157 mmol) in EtOH (3 mL) was added 1,3,5-trioxane (212 mg, 2.35 mmol) and concentrated aqueous HCl (1.57 mmol). The reaction was heated at reflux for 20 h. After cooling down to room temperature, the solvent was removed *in vacuo*, then the residue was taken up in chloroform. The resulting solution was successively washed with saturated aqueous $NaHCO_3$, H_2O, and brine, then dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (15-20% EtOAc/hexane) to afford piperidine **17** as a pale yellow oil (49.8 mg, 79%).

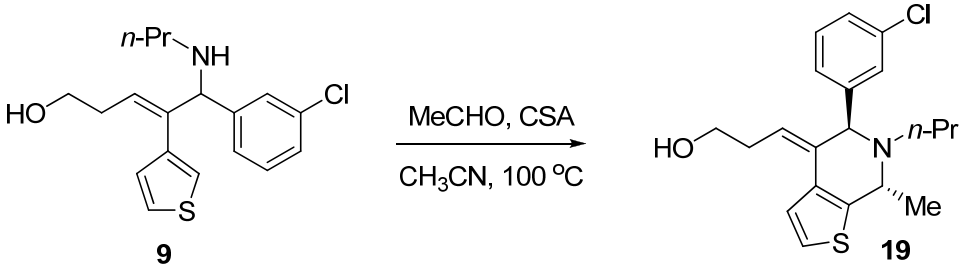
Data for (*E*)-3-(6-benzyl-7-phenyl-6,7-dihydro-[1,3]dioxolo[4,5-*g*]isoquinolin-8(*5H*)-ylidene)propan-1-ol (17): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45-7.18 (m, 10H), 7.10 (s, 1H), 6.43 (s, 1H), 5.95 (s, 2H), 5.44 (dd, *J* = 8.5, 5.6 Hz, 1H), 4.35 (s, 1H), 3.87-3.79 (m, 4H), 3.73 (d, *J* = 13.5 Hz, 1H), 3.75 (d, *J* = 13.5 Hz, 1H), 2.90-2.75 (m, 2H), 1.43 (br, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.27, 146.17, 142.14, 139.80, 133.88, 130.18, 129.22, 128.71, 128.44, 128.22, 127.42, 127.20, 126.56, 125.68, 108.54, 106.82, 101.24, 69.95, 63.35, 59.13, 50.93, 30.03; IR (thin film, NaCl) ν_{max} 3569, 3414 (br), 3083, 3064, 3027, 2886, 2246, 1601, 1502, 1482, 1451, 1315, 1240, 1039, 937, 734 cm^{-1}; HRMS (EI, H) *m/z* calc'd for $C_{26}H_{25}NO_3$ $[M + H]^+$ 400.1907, found 400.1909.



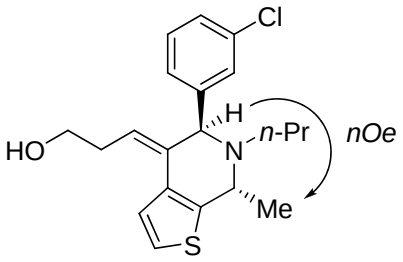
Synthesis of (*E*)-3-(5-(3-chlorophenyl)-6-propyl-6,7-dihydrothieno[2,3-*c*]pyridin-4(*5H*)-ylidene)propan-1-ol (18). To a solution of amino alcohol **9** (39.5 mg, 0.118 mmol) in CH_3CN (2.6 mL) was added 1,3,5-trioxane (212 mg, 2.35 mmol) and (1*S*)-(+)-

10-camphorsulfonic acid (41.1 mg, 0.117 mmol). The reaction was heated at reflux for 20 h. After cooling down to room temperature, the reaction was quenched with aqueous 1N NaOH (4 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo.* The crude product was purified by column chromatography on silica gel (20-30% EtOAc/hexane) to afford piperidine **18** as a pale yellow oil (29.0 mg, 71%).

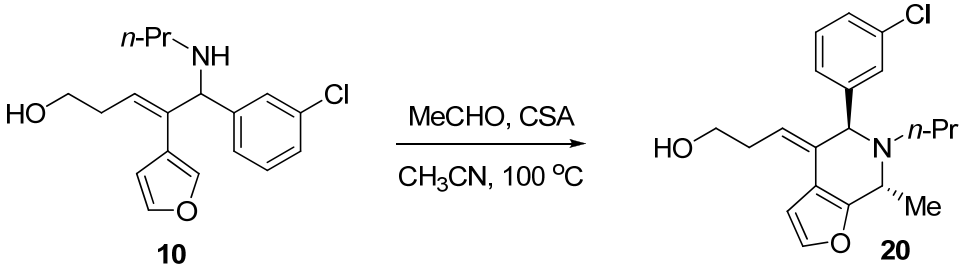
Data for (*E*)-3-(5-(3-chlorophenyl)-6-propyl-6,7-dihydrothieno[2,3-*c*]pyridin-4(5*H*)-ylidene)propan-1-ol (18): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 5.3 Hz, 1H), 7.26 (s, 1H), 7.10-7.06 (m, 4H), 5.32 (t, *J* = 7.1 Hz, 1H), 4.26 (s, 1H), 3.74 (t, *J* = 6.7 Hz, 2H), 3.69 (d, *J* = 3.8 Hz, 2H), 2.73 (dt, *J* = 6.7, 6.7 Hz, 2H), 2.49 (t, *J* = 7.2 Hz, 2H), 1.58-1.49 (m, 3H), 0.90 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.16, 136.45, 134.01, 132.41, 129.33, 129.26, 128.25, 127.07, 126.21, 126.10, 124.39, 122.63, 68.73, 62.55, 55.86, 46.56, 32.60, 30.10 (residual acetone peak), 21.39, 11.86; IR (thin film, NaCl) ν_{max} 3351 (br), 2958, 2930, 1726, 1594, 1571, 1470, 1422, 1378, 1319, 1187, 1047, 908, 779, 680 cm^{-1}; LRMS (EI, H) *m/z* calc'd for $C_{19}H_{22}ClNOS$ $[M + H]^+$ 348.1, found 348.5.



Synthesis of (*E*)-3-((5*R*,7*R*)-5-(3-chlorophenyl)-7-methyl-6-propyl-6,7-dihydrothieno [2,3-*c*]pyridin-4(5*H*)-ylidene)propan-1-ol (19). To a solution of amino alcohol **9** (32.6 mg, 0.097 mmol) in CH_3CN (2.1 mL) in a sealed tube was added acetaldehyde (27 μL, 0.049 mmol) and (1*S*)-(+)-10-camphorsulfonic acid (33.9 mg, 0.146 mmol). The reaction was heated in a 100 °C oil bath for 20 h. After cooling down to room temperature, the reaction was quenched with aqueous 1N NaOH (4 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo.* The crude product was purified by column chromatography on silica gel (25% EtOAc/hexane) to afford piperidine **19** as a pale yellow oil (single diastereomer, 24.2 mg, 69%). The relative stereochemistry was determined by ^{1}H NMR.

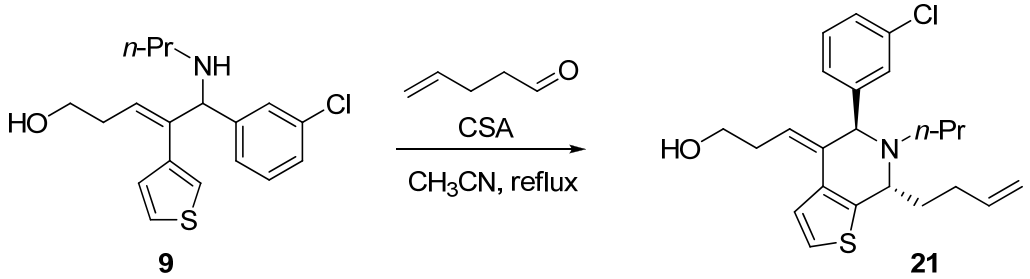


Data for (*E*)-3-((5*R*,7*R*)-5-(3-chlorophenyl)-7-methyl-6-propyl-6,7-dihydrothieno [2,3-*c*]pyridin-4(5*H*)-ylidene)propan-1-ol (19): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 5.3 Hz, 1H), 7.32 (s, 1H), 7.17-7.15 (m, 4H), 5.36 (t, *J* = 7.1 Hz, 1H), 4.51 (s, 1H), 3.90 (q, *J* = 7.1 Hz, 1H), 3.82 (t, *J* = 6.7 Hz, 2H), 2.81 (dt, *J* = 6.7, 6.7 Hz, 2H), 2.62-2.55 (m, 1H), 2.37-2.30 (m, 1H), 1.63-1.54 (m, 3H), 1.43 (d, *J* = 7.1 Hz, 3H), 0.97 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.03, 143.13, 133.98, 132.34, 129.25, 129.15, 128.41, 127.01, 126.44, 126.35, 124.22, 122.38, 67.96, 62.54, 50.23, 47.75, 32.52 21.86, 19.49, 11.95; IR (thin film, NaCl) ν_{max} 3350 (br), 2964, 2931, 2872, 1593, 1571, 1471, 1422, 1376, 1306, 1186, 1047, 909, 683 cm^{-1}; LRMS (EI, H) *m/z* calc'd for $C_{20}H_{24}ClNOS$ $[M + H]^+$ 362.1, found 362.6.



Synthesis of (*E*)-3-((5*R*,7*R*)-5-(3-chlorophenyl)-7-methyl-6-propyl-6,7-dihydrofuro [2,3-*c*]pyridin-4(5*H*)-ylidene)propan-1-ol (20). To a solution of amino alcohol **10** (54.6 mg, 0.170 mmol) in CH_3CN (4.1 mL) in a sealed tube was added acetaldehyde (52 μL, 0.927 mmol) and (1*S*)-(+)-10-camphorsulfonic acid (64.5 mg, 0.278 mmol). The reaction was heated in a 100 °C oil bath for 20 h. After cooling down to room temperature, the reaction was quenched with aqueous 1N NaOH (4 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (20% EtOAc/hexane) to afford piperidine **20** as a pale yellow oil (single diastereomer, 35.0 mg, 60%). The relative stereochemistry was assigned by analogy with compound **19**.

Data for (*E*)-3-((5*R*,7*R*)-5-(3-chlorophenyl)-7-methyl-6-propyl-6,7-dihydrofuro [2,3-*c*]pyridin-4(5*H*)-ylidene)propan-1-ol (20): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.24 (m, 1H), 7.21 (s, 1H), 7.10-7.07 (m, 3H), 6.64 (d, *J* = 2.0 Hz, 1H), 5.24 (t, *J* = 7.2 Hz, 1H), 4.39 (s, 1H), 3.71 (t, *J* = 6.7 Hz, 2H), 3.67 (q, *J* = 7.0 Hz, 2H), 2.64 (dt, *J* = 6.8 Hz, 2H), 2.48-2.41 (m, 1H), 2.30-2.23 (m, 1H), 1.54-1.45 (m, 3H), 1.30 (d, *J* = 7.0 Hz, 3H), 0.88 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.06, 143.38, 141.44, 133.96, 129.44, 129.26, 128.45, 127.08, 126.41, 122.77, 115.14, 108.80, 67.00, 62.42, 48.74, 48.23, 31.79, 21.94, 15.45, 11.95; IR (thin film, NaCl) ν_{max} 3350 (br), 3064, 2962, 2932, 2873, 1593, 1572, 1471, 1316, 1156, 1047, 892, 685 cm^{-1}; LRMS (EI, H) *m/z* calc'd for $C_{20}H_{24}ClNO_2$ $[M + H]^+$ 346.2, found 346.6.

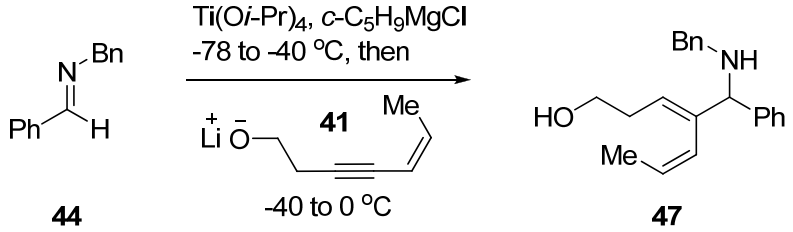


9 **21**

Synthesis of (*E*)-3-((5*R*,7*R*)-7-(but-3-enyl)-5-(3-chlorophenyl)-6-propyl-6,7-dihydrothieno[2,3-*c*]pyridin-4(5*H*)-ylidene)propan-1-ol (21). To a solution of amino alcohol **9** (38.5 mg, 0.115 mmol) in CH_3CN (2.5 mL) in a sealed tube was added 4-pentenal (90 μL, 0.917 mmol) and (1*S*)-(+)-10-camphorsulfonic acid (40.1 mg, 0.173 mmol). The reaction was heated at reflux for 20 h. After cooling down to room temperature, the reaction was quenched with aqueous 1N NaOH (4 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (10-20% EtOAc/hexane) to afford piperidine **21** as a pale yellow oil (single diastereomer, 25.6 mg, 56%). The relative stereochemistry was assigned by analogy with compound **19**.

Data for (*E*)-3-((5*R*,7*R*)-7-(but-3-enyl)-5-(3-chlorophenyl)-6-propyl-6,7-dihydrothieno[2,3-*c*]pyridin-4(5*H*)-ylidene)propan-1-ol (21): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 5.3 Hz, 1H), 7.27 (s, 1H), 7.13-7.07 (m, 4H), 5.76-5.66 (m, 1H), 5.29 (t, *J* = 7.0 Hz, 1H), 4.97 (d, *J* = 10.2 Hz, 1H), 4.87 (d, *J* = 10.2 Hz, 1H), 4.49 (s, 1H), 3.76 (t, *J* = 6.7 Hz, 2H), 3.69-3.66 (m, 1H), 2.78-2.73 (m, 2H), 2.47-2.39 (m, 1H), 2.26-

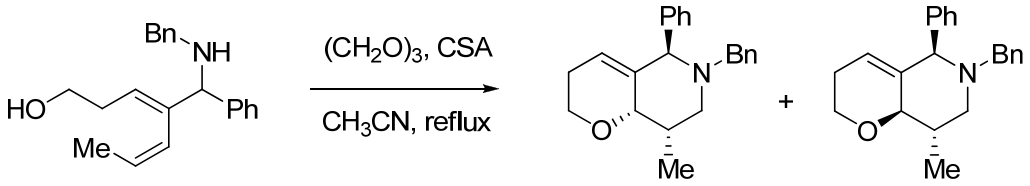
2.17 (m, 1H), 2.12-2.03 (m, 1H), 1.88-1.73 (m, 2H), 1.57-1.48 (m, 3H), 0.91 (t, J = 9.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.08, 142.14, 138.01, 133.93, 132.59, 129.17, 129.07, 128.47, 126.93, 126.62, 126.39, 124.35, 122.20, 115.17, 66.90, 62.60, 53.92, 46.60, 32.58, 31.49, 29.65, 21.12, 11.95; IR (thin film, NaCl) ν_{max} 3390 (br), 3077, 2960, 2931, 2872, 1715, 1641, 1594, 1572, 1471, 1417, 1171, 1045, 913, 684 cm^{-1}; LRMS (EI, H) *m/z* calc'd for $C_{23}H_{28}ClNOS$ $[M + H]^+$ 402.2, found 402.5.



Synthesis of (3*E*,5*Z*)-4-((benzylamino)(phenyl)methyl)hepta-3,5-dien-1-ol (47). To a solution of imine **44** (90 μL, 97.5 mg, 0.5 mmol) and Ti(O*i*-Pr)$_4$ (222 μL, 213 mg, 0.75 mmol) in diethyl ether (2.5 mL) at –78 °C was added dropwise *c*-C_5H_9MgCl (2.26 M in diethyl ether, 1.5 mmol) via a gas-tight syringe. The mixture was warmed to –40 °C over 30 min and stirred at this temperature for another 2 h. Then a solution of lithium alkoxide **41** in diethyl ether (1 mL), generated from deprotonation of the corresponding alcohol (86 μL, 82.5 mg, 0.75 mmol) with *n*-BuLi (2.55 M in hexane, 0.8 mmol) at –78 °C followed by warming to 0 °C over 20 min, was added dropwise to the brown solution of imine-Ti complex at –40 °C via cannula. The resulting mixture was warmed to 0 °C over 30 min and stirred at this temperature for another 6 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL), and the resulting biphasic mixture was rapidly stirred until the precipitate became white in color. The mixture was further diluted with saturated aqueous $NaHCO_3$ (10 mL) and extracted with ethyl acetate (4 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo.* The crude product was purified by column chromatography on silica gel (30% EtOAc/hexane) to afford amino alcohol **47** as a pale yellow oil (114 mg, 74%).

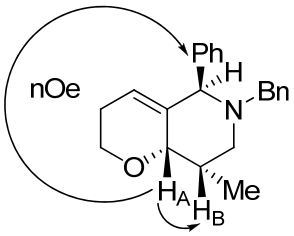
Data for (3*E*,5*Z*)-4-((benzylamino)(phenyl)methyl)hepta-3,5-dien-1-ol (47): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29-7.12 (m, 10H), 5.63-5.51 (m, 3H), 4.16 (s, 1H), 3.69-3.57 (m, 4H), 2.17 (dt, J = 6.7 Hz, 2H), 1.61 (br, 2H), 1.30 (d, J = 5.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.26, 140.59, 140.50, 128.93, 128.34, 128.16, 128.08, 127.30, 126.87,

126.84, 125.72, 123.74, 67.97, 62.39, 51.54, 32.69, 14.78; IR (thin film, NaCl) ν_{max} 3320 (br), 3084, 3061, 3025, 3007, 2911, 2877, 1602, 1494, 1472, 1453, 1051, 1029, 737, 700 cm^{-1}; HRMS (EI, H) *m/z* calc'd for $C_{21}H_{25}NO$ $[M + H]^+$ 308.2009, found 308.2001.

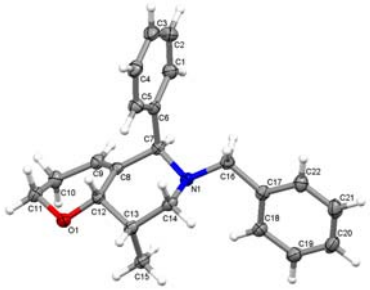


47 **22** **22a**

Synthesis of (5*R*,8*S*,8a*S*)-6-benzyl-8-methyl-5-phenyl-3,5,6,7,8,8a-hexahydro-*2H*-pyrano[3,2-*c*]pyridine (22). To a solution of amino alcohol **47** (42.4 mg, 0.138 mmol) in CH_3CN (3 mL) was added 1,3,5-trioxane (372 mg, 4.14 mmol) and (1*S*)-(+)-10-camphorsulfonic acid (32.0 mg, 0.138 mmol). The reaction was heated at reflux for 20 h. After cooling down to room temperature, the reaction was quenched with aqueous 1N NaOH (4 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo.* The crude product was purified by column chromatography on silica gel (3-5% EtOAc/hexane) to afford two pure diastereomers (**22**:**22a** = 12:1, 29.8 mg, 68%) as pale yellow oils. The relative stereochemistry was determined by ^{1}H NMR. An X-ray crystal structure was also obtained for **22**.

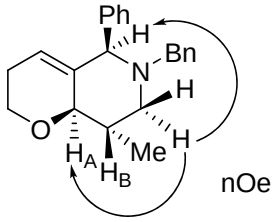


$J_{A,B}$ = 2.9 Hz



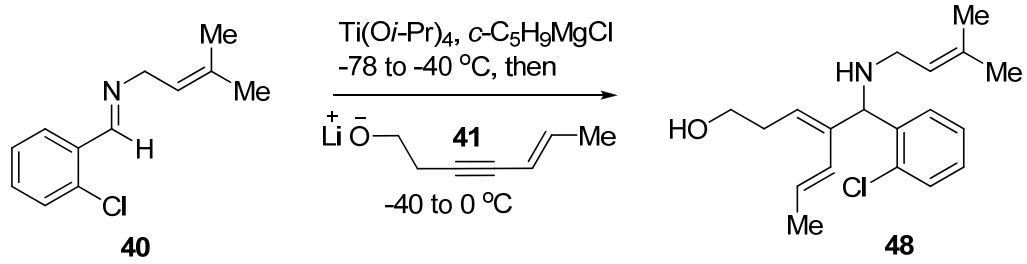
Data for (5*R*,8*S*,8a*S*)-6-benzyl-8-methyl-5-phenyl-3,5,6,7,8,8a-hexahydro-*2H*-pyrano[3,2-*c*]pyridine (22): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.48 (m, 2H), 7.39-7.22 (m, 8H), 5.90 (d, *J* = 5.7 Hz, 1H), 4.53 (d, *J* = 2.9 Hz, 1H), 4.27 (s, 1H), 4.02-3.98 (m, 1H), 3.76 (s, 2H), 3.60 (dt, *J* = 11.0, 3.1 Hz, 1H), 3.25 (dd, *J* = 13.2, 4.0 Hz, 1H), 2.56 (dd, *J* = 13.2, 4.0 Hz, 1H), 2.53-2.43 (m, 1H), 2.28-2.19 (m, 1H), 1.98-1.91 (m, 1H), 1.12 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.10, 140.24, 136.13, 128.24,

127.62, 126.65, 122.82, 73.92, 68.16, 63.55, 59.58, 52.90, 35.81, 25.17, 13.99; IR (thin film, NaCl) ν_{max} 3084, 3059, 3025, 3064, 2908, 2833, 1600, 1492, 1451, 1384, 1351, 1264, 1151, 1107, 1081, 699 cm^{-1}; LRMS (EI, H) *m/z* calc'd for $C_{22}H_{25}NO$ $[M + H]^+$ 320.2, found 320.6.



$J_{A,B}$ = 11.6 Hz

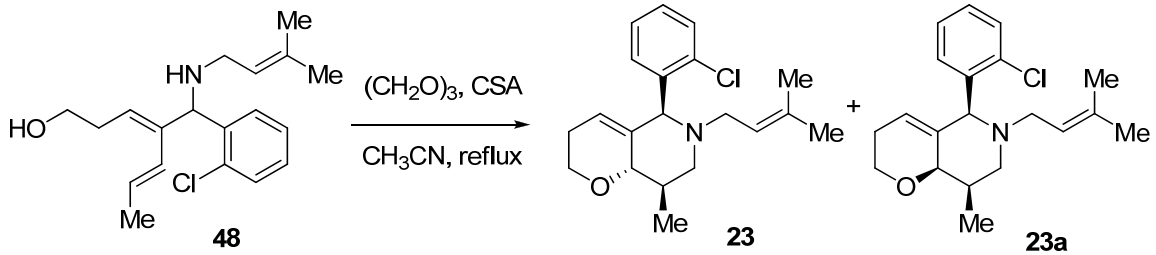
Data for (5*R*,8*S*,8a*R*)-6-benzyl-8-methyl-5-phenyl-3,5,6,7,8,8a-hexahydro-*2H*-pyrano[3,2-*c*]pyridine (22a): ^{1}H NMR (400 MHz, C_6D_6) δ 7.40 (d, *J* =7.5 Hz, 2H), 7.21 (d, *J* = 7.4 Hz, 2H), 7.14-6.95 (m, 8H), 4.77 (s, 1H), 3.78 (d, *J* = 13.6 Hz, 1H), 3.66-3.62 (m, 1H), 3.54 (s, 1H), 3.52 (d, *J* = 11.6 Hz, 1H), 3.19 (dt, *J* = 10.7, 3.6 Hz, 1H), 2.89 (dd, *J* = 11.7, 3.7 Hz, 1H), 2.60 (d, *J* = 13.6 Hz, 1H), 2.03-1.89 (m, 2H), 1.65 (dd, *J* = 11.6, 11.6 Hz, 1H), 1.31-1.26 (m, 1H), 0.87 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.63, 140.50, 139.35, 129.59, 128.76, 128.55, 128.45, 128.30, 128.17, 128.12, 127.39, 126.70, 121.21, 80.19, 71.45, 62.77, 60.07, 58.21, 36.77, 25.66, 15.89; IR (thin film, NaCl) ν_{max} 3061, 3027, 2954, 2923,2851, 2791, 1494, 1452, 1370, 1277, 1103, 1045, 736, 701 cm^{-1}; LRMS (EI, H) *m/z* calc'd for $C_{22}H_{25}NO$ $[M + H]^+$ 320.2, found 320.6.



Synthesis of (3*E*,5*E*)-4-((2-chlorophenyl)(3-methylbut-2-enylamino)methyl)hepta-3,5-dien-1-ol (48). To a solution of imine **40** (310 μL, 343 mg, 1.65 mmol) and Ti(O*i*-Pr)$_4$ (444 μL, 426 mg, 1.5 mmol) in diethyl ether (5 mL) at –78 °C was added dropwise *c*-C_5H_9MgCl (2.26 M in diethyl ether, 3.0 mmol) via a gas-tight syringe. The mixture was warmed to –40 °C over 30 min and stirred at this temperature for another 3 h. Then a solution of lithium alkoxide **41** in diethyl ether (1 mL), generated from deprotonation of the corresponding alcohol (57 μL, 55 mg, 0.5 mmol) with *n*-BuLi (2.55 M in hexane,

0.55 mmol) at –78 °C followed by warming to 0 °C over 20 min, was added dropwise to the brown solution of imine-Ti complex at –40 °C via cannula. The resulting mixture was warmed to 0 °C over 30 min and stirred at this temperature for another 6 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL), and the resulting biphasic mixture was rapidly stirred until the precipitate became white in color. The mixture was further diluted with saturated aqueous $NaHCO_3$ (10 mL) and extracted with ethyl acetate (4 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (30% EtOAc/hexane) to afford amino alcohol **48** as a pale yellow oil (112 mg, 70%).

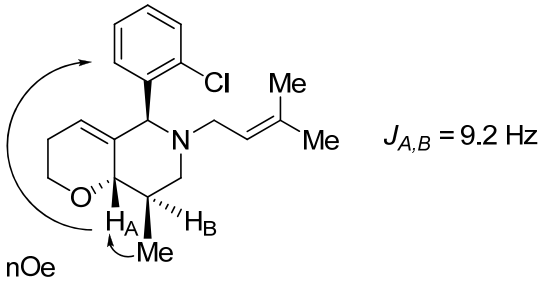
Data for (3*E*,5*E*)-4-((2-chlorophenyl)(3-methylbut-2-enylamino)methyl)hepta-3,5-dien-1-ol (48): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.7 Hz, 1H), 7.27 (d, *J* = 7.9 Hz, 1H), 7.19-7.09 (m, 2H), 6.23 (d, *J* = 15.8 Hz, 1H), 5.77-5.70 (m, 1H), 5.37 (t, *J* = 7.7 Hz, 1H), 5.21 (t, *J* = 8.4 Hz, 1H), 4.86 (s, 1H), 3.60-3.56 (m, 2H), 3.07 (dd, *J* = 6.4, 6.4 Hz, 2H), 2.44-2.38 (m, 2H), 1.69 (d, *J* = 6.6 Hz, 3H), 1.64 (s, 3H), 1.50 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.39, 139.41, 135.31, 134.37, 129.96, 129.26, 128.51, 127.24, 126.95, 126.90, 125.00, 123.05, 62.78, 60.39, 46.31, 31.57, 26.11, 19.37, 19.37, 18.15; IR (thin film, NaCl) ν_{max} 3345 (br), 3035, 2912, 2874, 1673, 1571, 1443, 1376, 1048, 962, 755, 699 cm^{-1}; HRMS (EI, H) *m/z* calc'd for $C_{19}H_{26}ClNO$ $[M + H]^+$ 320.1776, found 320.1771.



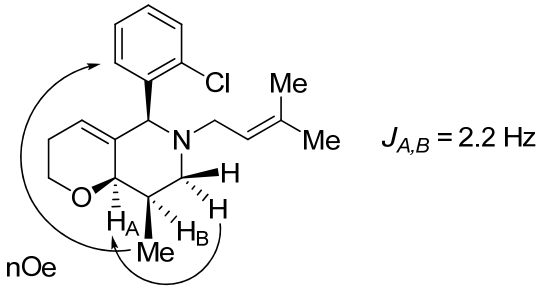
48 **23** **23a**

Synthesis of (5*R*,8*R*,8a*S*)-5-(2-chlorophenyl)-8-methyl-6-(3-methylbut-2-enyl)-3,5,6,7,8,8a-hexahydro-*2H*-pyrano[3,2-*c*]pyridine (23). To a solution of amino alcohol **48** (66.2 mg, 0.207 mmol) in CH_3CN (5 mL) was added 1,3,5-trioxane (159 mg, 1.76 mmol) and (1*S*)-(+)-10-camphorsulfonic acid (40.8 mg, 0.176 mmol). The reaction was heated at reflux for 20 h. After cooling down to room temperature, the reaction was quenched with aqueous 1N NaOH (4 mL) and extracted with dichloromethane (3 x 10 mL). The

combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo.* The crude product was purified by column chromatography on silica gel (5% EtOAc/hexane) to afford two pure diastereomers (**23**:**23a** = 1.6:1, 78.9 mg, 79%) as pale yellow oils. The relative stereochemistry was determined by ^{1}H NMR.

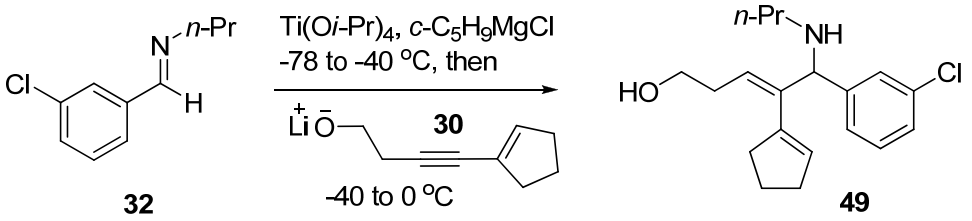


Data for (5*R*,8*R*,8a*S*)-5-(2-chlorophenyl)-8-methyl-6-(3-methylbut-2-enyl)-3,5,6,7,8, 8a-hexahydro-*2H*-pyrano[3,2-*c*]pyridine (23): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.36 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.22-7.13 (m, 2H), 5.90 (s, 1H), 5.24 (t, *J* = 6.4 Hz, 1H), 4.75 (s, 1H), 4.12 (d, *J* = 9.2 Hz, 1H), 3.97-3.94 (m, 1H), 3.59 (dt, *J* = 9.9, 3.8 Hz, 1H), 3.14-3.06 (m, 2H), 2.69 (dd, *J* = 13.3, 4.9 Hz, 1H), 2.57-2.53 (m, 1H), 2.40-2.33 (m, 1H), 2.00-1.90 (m, 2H), 1.70 (s, 3H), 1.52 (s, 3H), 1.08 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.91, 137.23, 135.26, 134.78, 130.79, 129.45, 128.23, 126.66, 122.44, 122.36, 78.43, 66.23, 63.51, 52.93, 51.83, 34.65, 26.29, 26.10, 18.25, 17.55; IR (thin film, NaCl) ν_{max} 3062, 2956, 2913, 2852, 1463, 1440, 1376, 1275, 1211, 1103, 1039, 855, 743 cm^{-1}; LRMS (EI, H) *m/z* calc'd for $C_{20}H_{26}ClNO$ $[M + H]^+$ 332.2, found 332.6.



Data for (5*R*,8*R*,8a*R*)-5-(2-chlorophenyl)-8-methyl-6-(3-methylbut-2-enyl)-3,5,6,7,8, 8a-hexahydro-*2H*-pyrano[3,2-*c*]pyridine (23a): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.28-7.19 (m, 2H), 7.13-7.10 (m, 1H), 5.06-5.04 (m, 1H), 4.63 (d, *J* = 5.7 Hz, 1H), 4.18 (s, 1H), 4.12 (s, 1H), 3.87-3.84 (m, 1H), 3.46 (dt, *J* = 11.2, 3.2 Hz, 1H), 2.94 (dd, *J* = 11.7, 3.2 Hz, 1H), 2.78 (dd, *J* = 13.9, 5.0 Hz, 1H), 2.58-2.54 (m,

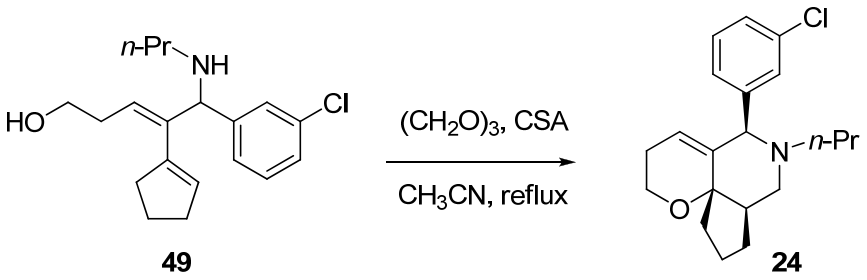
1H), 2.38 (dd, *J* = 11.7, 3.2 Hz, 1H), 2.18-2.09 (m, 2H), 1.69-1.62 (m, 1H), 1.61 (s, 3H), 1.36 (s, 3H), 1.01 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.96, 136.99, 135.12, 135.06, 131.68, 129.35, 128.42, 127.22, 122.26, 121.42, 77.60, 65.54, 63.57, 56.78, 53.22, 34.37, 26.29, 25.98, 18.21, 12.44; IR (thin film, NaCl) ν_{max} 3060, 2964, 2922, 2853, 2804, 1463, 1444, 1385, 1277, 1134, 1109, 1074, 1050, 756 cm^{-1}; LRMS (EI, H) *m/z* calc'd for $C_{20}H_{26}ClNO$ $[M + H]^+$ 332.2, found 332.6.



Synthesis of (*E*)-5-(3-chlorophenyl)-4-cyclopentenyl-5-(propylamino)pent-3-en-1-ol (49). To a solution of imine **32** (83 μL, 90.8 mg, 0.5 mmol) and Ti(O*i*-Pr)$_4$ (222 μL, 213 mg, 0.75 mmol) in diethyl ether 2.5 mL) at –78 °C was added dropwise *c*-C_5H_9MgCl (2.20 M in diethyl ether, 1.5 mmol) via a gas-tight syringe. The mixture was warmed to –40 °C over 30 min and stirred at this temperature for another 2 h. Then a solution of lithium alkoxide **30** in diethyl ether (1 mL), generated from deprotonation of the corresponding alcohol (102 μL, 102 mg, 0.75 mmol) with *n*-BuLi (2.55 M in hexane, 0.8 mmol) at –78 °C followed by warming to 0 °C over 20 min, was added dropwise to the brown solution of imine-Ti complex at –40 °C via cannula. The resulting mixture was warmed to 0 °C over 30 min and stirred at this temperature for another 6 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL), and the resulting biphasic mixture was rapidly stirred until the precipitate became white in color. The mixture was further diluted with saturated aqueous $NaHCO_3$ (10 mL) and extracted with ethyl acetate (4 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo.* The crude product was purified by column chromatography on silica gel (30% EtOAc/hexane) to afford amino alcohol **49** as a pale yellow oil (107 mg, 67%).

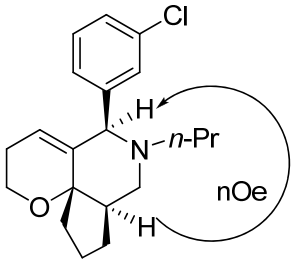
Data for (*E*)-5-(3-chlorophenyl)-4-cyclopentenyl-5-(propylamino)pent-3-en-1-ol (49): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (s, 1H), 7.15-7.09 (m, 3H), 5.44 (t, *J* = 7.3 Hz, 1H), 5.29 (s, 1H), 4.13 (s, 1H), 3.57 (t, *J* = 6.6 Hz, 2H), 2.49-2.43 (m, 1H), 2.39-2.23 (m, 5H), 2.12-1.98 (m, 2H), 1.74-1.68 (m, 2H), 1.47-1.34 (m, 4H), 0.83 (t, *J* = 7.4 Hz, 3H); ^{13}C

NMR (126 MHz, $CDCl_3$) δ 145.57, 142.68, 141.00, 134.36, 130.51, 129.62, 127.99, 127.29, 126.13, 124.08, 67.62, 63.07, 50.34, 36.96, 33.19, 32.97, 24.02, 23.69, 12.26; IR (thin film, NaCl) ν_{max} 3325 (br), 3060, 2957, 1595, 1573, 1473, 1379, 1317, 1293, 1193, 1076, 1050, 999, 785, 725 cm^{-1}; HRMS (EI, H) *m/z* calc'd for $C_{19}H_{26}ClNO$ $[M + H]^+$ 320.1776, found 320.1768.



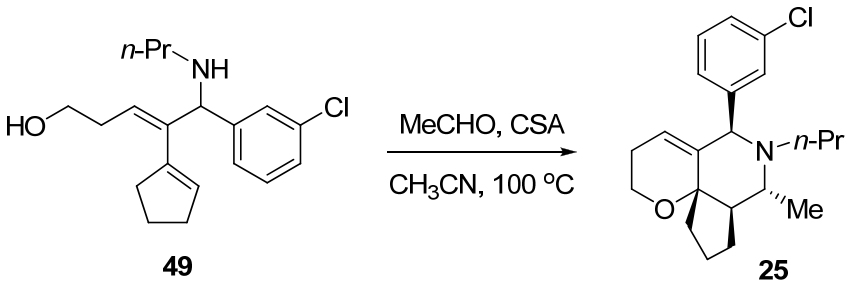
49 **24**

Synthesis of (5*S*,7a*R*,10[1]*S*)-5-(3-chlorophenyl)-6-propyl-3,5,6,7,7a,8,9,10-octahydro-*2H*-cyclopenta[*c*]pyrano[2,3-*d*]pyridine (24). To a solution of amino alcohol **49** (77.1 mg, 0.241 mmol) in CH_3CN (5 mL) was added 1,3,5-trioxane (217 mg, 2.41 mmol) and (1*S*)-(+)-10-camphorsulfonic acid (55.9 mg, 0.241 mmol). The reaction was heated at reflux for 20 h. After cooling down to room temperature, the reaction was quenched with aqueous 1N NaOH (4 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo.* The crude product was purified by column chromatography on silica gel (5% EtOAc/hexane) to afford piperidine **24** as a pale yellow oil (single diastereomer, 45.8 mg, 57%). The relative stereochemistry was determined by ^1H NMR.



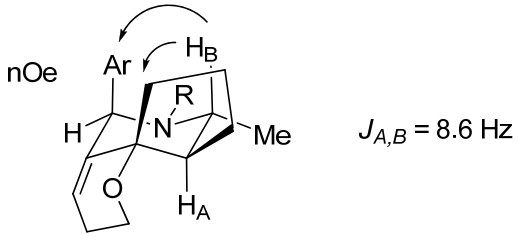
Data for (5*S*,7a*R*,10[1]*S*)-5-(3-chlorophenyl)-6-propyl-3,5,6,7,7a,8,9,10-octahydro-*2H*-cyclopenta[*c*]pyrano[2,3-*d*]pyridine (24): ^1H NMR (500 MHz, $CDCl_3$) δ 7.46 (s, 1H), 7.33 (d, *J* = 7.6 Hz, 1H), 7.17-7.10 (m, 2H), 5.76 (s, 1H), 4.02 (s, 1H), 3.76-3.65 (m, 2H), 2.56-2.38 (m, 5H), 2.15-2.10 (m, 1H), 1.94 (dt, *J* = 17.6, 4.3 Hz, 1H), 1.90-1.83 (m, 1H), 1.57-1.50 (m, 2H), 1.46-1.37 (m, 3H), 1.22-1.05 (m, 2H), 0.85 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.21, 137.01, 134.13, 129.22, 126.90, 126.48, 125.05,

124.67, 83.78, 68.94, 59.01, 55.47, 51.23, 44.30, 33.83, 27.89, 25.99, 22.34, 21.24, 11.82; IR (thin film, NaCl) ν_{max} 3328 (br), 3082, 3060, 3026, 2923, 2875, 1949, 1600, 1494, 1452, 1049, 750, 700 cm^{-1}; HRMS (EI, H) *m/z* calc'd for $C_{20}H_{26}ClNO$ $[M + H]^+$ 332.1776, found 332.1762.



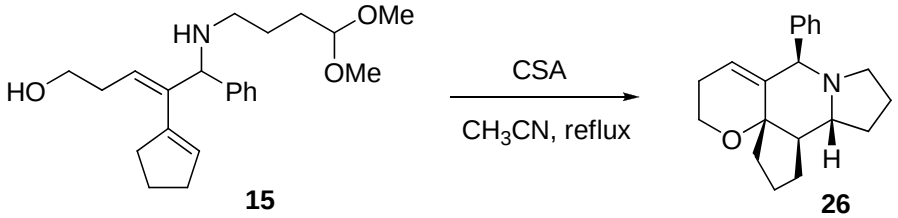
49 **25**

Synthesis of (*5S*,*7R*,7a*R*,10[1]*S*)-5-(3-chlorophenyl)-7-methyl-6-propyl-3,5,6,7,7a,8,9, 10-octahydro-*2H*-cyclopenta[*c*]pyrano[2,3-*d*]pyridine (25). To a solution of amino alcohol **49** (35.3 mg, 0.110 mmol) in CH_3CN (2.5 mL) in a sealed tube was added acetaldehyde (31 μL, 0.550 mmol) and (1*S*)-(+)-10-camphorsulfonic acid (38.3 mg, 0.165 mmol). The reaction was heated in a 100 °C oil bath for 20 h. After cooling down to room temperature, the reaction was quenched with aqueous 1N NaOH (4 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo.* The crude product was purified by column chromatography on silica gel (5% EtOAc/hexane) to afford piperidine **25** as a pale yellow oil (single diastereomer, 25.0 mg, 66%). The relative stereochemistry was determined by ^1H NMR.



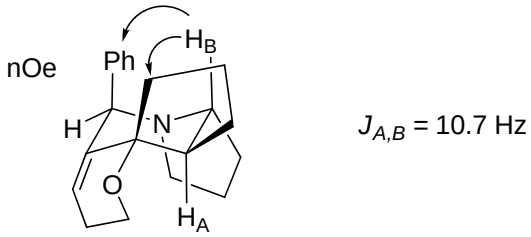
Data for (*5S*,*7R*,7a*R*,10[1]*S*)-5-(3-chlorophenyl)-7-methyl-6-propyl-3,5,6,7,7a,8,9, 10-octahydro-*2H*-cyclopenta[*c*]pyrano[2,3-*d*]pyridine (25): ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.34 (d, *J* = 6.3 Hz, 1H), 7.17-7.08 (m, 2H), 5.72 (dd, *J* = 4.7, 2.6 Hz, 1H), 4.14 (s, 1H), 3.74-3.71 (m, 2H), 2.60 (dq, *J* = 8.6, 6.7 Hz, 1H), 2.53-2.42 (m, 2H), 2.41-2.33 (m, 1H), 1.98-1.91 (m, 1H), 1.89-1.80 (m, 2H), 1.63-1.58 (m, 1H), 1.56-1.46 (m, 1H), 1.40-1.28 9m, 4H), 1.1201.06 (m, 1H), 1.03 (d, *J* = 6.8 Hz, 3H), 0.84 (t, *J* = 7.3 Hz,

3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.41, 136.54, 134.13, 129.23, 127.03, 126.46, 125.14, 124.72, 83.32, 67.57, 58.73, 52.26, 51.20, 47.59, 34.16, 27.62, 25.89, 22.24, 21.95, 16.11, 11.89; IR (thin film, NaCl) ν_{max} 3061, 2958, 2871, 2831, 2240, 1593, 1569, 1470, 1378, 1279, 1085, 906, 736, 706 cm^{-1}; LRMS (EI, H) *m/z* calc'd for $C_{21}H_{28}ClNO$ $[M + H]^+$ 346.2, found 346.6.



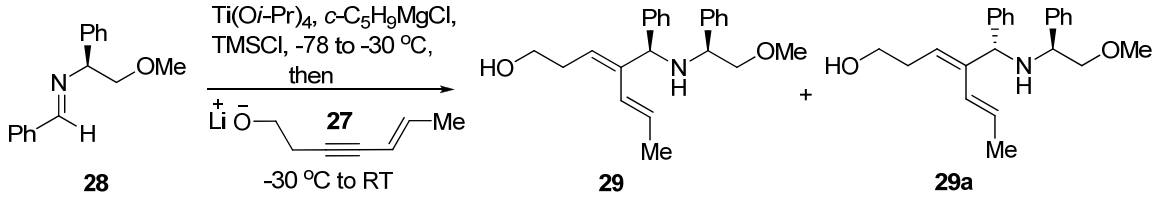
15 **26**

Synthesis of (3[1]*S*,8*R*,12a*R*,12b*R*)-8-phenyl-2,3,5,6,8,10,11,12,12a,12b-decahydro-*1H*-cyclopenta[*g*]pyrano[3,2-*f*]indolizine (26). To a solution of amino alcohol **15** (30.0 mg, 0.090 mmol) in CH_3CN (2.1 mL) was added (1*S*)-(+)-10-camphorsulfonic acid (62.6 mg, 0.270 mmol). The reaction was heated at reflux for 20 h. After cooling down to room temperature, the reaction was quenched with aqueous 1N NaOH (4 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo.* The crude product was purified by column chromatography on silica gel (10% EtOAc/hexane) to afford piperidine **26** as a pale yellow oil (single diastereomer, 13.4 mg, 52%). The relative stereochemistry was determined by ^{1}H NMR.



Data for (3[1]*S*,8*R*,12a*R*,12b*R*)-8-phenyl-2,3,5,6,8,10,11,12,12a,12b-decahydro-*1H*-cyclopenta[*g*]pyrano[3,2-*f*]indolizine (26): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.42 (m, 2H), 7.25-7.21 (m, 2H), 7.14-7.10 (m, 1H), 5.82 (dd, *J* = 4.8, 2.4 Hz, 1H), 4.39 (s, 1H), 3.78-3.67 (m, 2H), 3.01-2.90 (m, 2H), 2.80 (dd, *J* = 10.7, 6.4 Hz, 1H), 2.53-2.44 (m, 1H), 2.04-2.17 (m, 6H), 1.56-1.40 (m, 3H), 1.37-1.28 (m, 1H), 1.16-1.09 (m, 1H), 0.95-0.87 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.07, 128.04, 126.19, 125.06, 83.64, 65.21, 58.82, 57.70, 49.57, 48.06, 32.80, 29.60, 26.36, 26.24, 21.10, 21.06; IR (thin film, NaCl)

ν_{max} 3057, 3024, 2956, 2918, 2868, 2830, 1693, 1600, 1488, 1446, 1364, 1278, 1213, 1103, 1015, 927, 716 cm^{-1}; LRMS (EI, H) *m/z* calc'd for $C_{20}H_{25}NO$ $[M + H]^+$ 296.2, found 296.5.

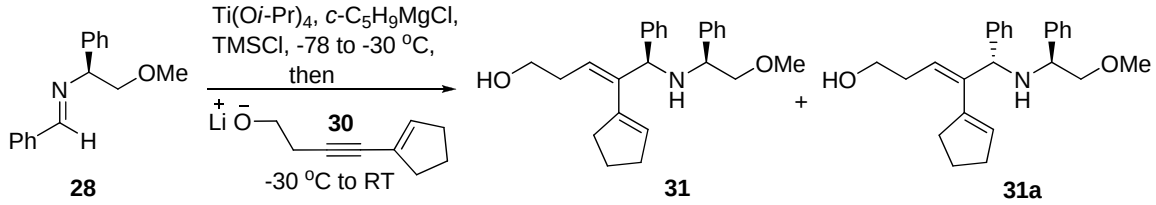


Synthesis of (3*E*,5*E*)-4-((*R*)-((*S*)-2-methoxy-1-phenylethylamino)(phenyl)methyl) hepta-3,5-dien-1-ol (29). To a solution of imine **28** (246 μL, 263 mg, 1.1 mmol), Ti(O*i*-Pr)$_4$ (296 μL, 284 mg, 1.0 mmol) and TMSCl (254 μL, 217mg, 2.0 mmol) in diethyl ether (3.2 mL) at –78 °C was added dropwise *c*-C_5H_9MgCl (1.85 M in diethyl ether, 2.0 mmol) via a gas-tight syringe. The mixture was warmed to –30 °C over 30 min and stirred at this temperature for another 2.5 h. Then a solution of lithium alkoxide **27** in diethyl ether (1 mL), generated from deprotonation of the corresponding alcohol (55 μL, 55 mg, 0.5 mmol) with *n*-BuLi (2.44 M in hexane, 0.55 mmol) at –78 °C followed by warming to 0 °C over 20 min, was added dropwise to the brown solution of imine-Ti complex at –30 °C via cannula. The resulting mixture was slowly warmed to room temperature over 24 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL), and the resulting biphasic mixture was rapidly stirred until the precipitate became white in color. The mixture was further diluted with saturated aqueous $NaHCO_3$ (10 mL) and extracted with ethyl acetate (4 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo.* The crude product was purified by column chromatography on silica gel (10→35% EtOAc/hexane) to afford two pure diastereomers[5] (**29**:**29a** = 85:15, 121 mg, 73%) as orange oils. The relative stereochemistry was assigned by analogy based on previously reported stereoselective coupling of imine **28** with alkynes.[6,7]

Data for (3*E*,5*E*)-4-((*R*)-((*S*)-2-methoxy-1-phenylethylamino)(phenyl)methyl) hepta-3,5-dien-1-ol (29): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.19 (m, 10H), 6.25 (d, *J* = 15.9 Hz, 1H), 5.61 (t, *J* = 7.4 Hz, 1H), 5.50 (qd, *J* = 15.9, 6.6 Hz, 1H), 4.30 (s, 1H), 4.01-3.96 (m, 1H), 3.78 (t, *J* = 6.6 Hz, 2H), 3.51-3.44 (m, 2H), 3.35 (s, 3H), 2.69-2.51 (m, 2H), 2.19 (br, 2H), 1.68 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.66, 140.97,

138.91, 128.39, 128.14, 127.87, 127.75, 127.44, 127.17, 126.60, 126.33, 125.17, 77.94, 62.72, 61.55, 59.69, 58.76, 31.27, 18.96; IR (thin film, NaCl) ν_{max} 3343 (br), 3084, 3061, 3027, 2926, 2879, 1668, 1601, 1492, 1454, 1377, 1108, 963, 700 cm^{-1}; LRMS (EI, H) *m/z* calc'd for $C_{23}H_{29}NO_2$ $[M + H]^+$ 352.2, found 352.6; $[\alpha]_D^{20}$ -37.5 (*c* 0.60, $CHCl_3$).

Data for (3*E*,5*E*)-4-((*S*)-((*S*)-2-methoxy-1-phenylethylamino)(phenyl)methyl) hepta-3,5-dien-1-ol (29a): ^1H NMR (400 MHz, $CDCl_3$) δ 7.25-7.12 (m, 10H), 6.05 (d, *J* = 16.9 Hz, 1H), 5.42-5.33 (m, 2H), 4.26 (s, 1H), 3.69-3.65 (m, 1H), 3.52 (t, *J* = 6.5 Hz, 2H), 3.40 (dd, *J* = 8.4, 8.4 Hz, 1H), 3.34-3.29 (m, 1H), 3.17 (s, 3H), 2.32 (dt, *J* = 6.9, 6.9 Hz, 2Hh), 1.55 (d, *J* = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.64, 141.39, 140.92, 128.32, 128.29, 127.97, 127.63, 127.47, 127.01, 126.76, 126.42, 124.16, 77.91, 62.39, 61.17, 59.61, 58.69, 31.25, 18.76; IR (thin film, NaCl) ν_{max} 3350 (br), 3026, 2925, 1601, 1492, 1454, 1377, 1103, 1048, 963, 760, 701 cm^{-1}; LRMS (EI, H) *m/z* calc'd for $C_{23}H_{29}NO_2$ $[M + H]^+$ 352.2, found 352.6; $[\alpha]_D^{20}$ +64.0 (*c* 0.35, $CHCl_3$).



Synthesis of (*R*,*E*)-4-cyclopentenyl-5-((*S*)-2-methoxy-1-phenylethylamino)-5-phenylpent-3-en-1-ol (31). To a solution of imine **28** (246 μL, 263 mg, 1.10 mmol), Ti(O*i*-Pr)$_4$ (296 μL, 284 mg, 1.0 mmol) and TMSCl (254 μL, 217mg, 2.0 mmol) in diethyl ether (3.2 mL) at –78 °C was added dropwise *c*-C_5H_9MgCl (1.85 M in diethyl ether, 2.0 mmol) via a gas-tight syringe. The mixture was warmed to –30 °C over 30 min and stirred at this temperature for another 2.5 h. Then a solution of lithium alkoxide **30** in diethyl ether (1 mL), generated from deprotonation of the corresponding alcohol (68 μL, 68 mg, 0.5 mmol) with *n*-BuLi (2.44 M in hexane, 0.55 mmol) at –78 °C followed by warming to 0 °C over 20 min, was added dropwise to the brown solution of imine-Ti complex at –30 °C via cannula. The resulting mixture was slowly warmed to room temperature over 43 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL), and the resulting biphasic mixture was rapidly stirred until the precipitate became white in color. The mixture was further diluted with saturated aqueous $NaHCO_3$ (10 mL) and extracted with ethyl acetate (4 x 20 mL). The combined organic extracts were

washed with brine, dried over $MgSO_4$, and concentrated *in vacuo.* The crude product was purified by column chromatography on silica gel (10→40% EtOAc/hexane) to afford two pure diastereomers[5] (**31**:**31a** = 75:25, 134 mg, 71%) as orange oils. The relative stereochemistry was assigned by analogy based on previously reported stereoselective coupling of imine **28** with alkynes.[6,7]

Data for (*R*,*E*)-4-cyclopentenyl-5-((*S*)-2-methoxy-1-phenylethylamino)-5-phenylpent-3-en-1-ol (31): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.18 (m, 10H), 5.49 (t, *J* = 7.3 Hz, 1H), 5.44 (t, *J* = 2.1 Hz, 1H), 4.12-4.09 (m, 2H), 3.74 (t, *J* = 6.3 Hz, 2H), 3.52-3.47 (m, 2H), 3.39 (s, 3H), 2.53-2.40 (m, 2H), 2.32-2.27 (m, 2H), 2.15-2.06 (m, 1H), 2.00-1.92 (m, 1H), 1.77-1.69 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.13, 140.94, 140.74, 140.71, 129.88, 127.90, 127.42, 127.17, 126.49, 124.60, 78.15, 63.77, 62.91, 59.74, 58.93, 36.66, 32.82, 32.62, 23.59; IR (thin film, NaCl) ν_{max} 3325 (br), 3061, 3027, 2925, 2889, 2847, 1601, 1493, 1454, 1194, 1106, 1028, 700 cm^{-1}; LRMS (EI, H) *m/z* calc'd for $C_{25}H_{31}NO_2$ $[M + H]^+$ 378.2, found 378.6; $[\alpha]_D^{20}$ -29.7 (*c* 1.67, $CHCl_3$).

Data for (*S*,*E*)-4-cyclopentenyl-5-((*S*)-2-methoxy-1-phenylethylamino)-5-phenylpent-3-en-1-ol (31a): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.10 (m, 10H), 5.30 (t, *J* = 7.4 Hz, 1H), 5.25 (s, 1H), 4.03 (s, 1H), 3.64 (dd, *J* = 8.3, 4.5 Hz, 1H), 3.50 (t, *J* = 6.6 Hz, 1H), 3.40 (dd, *J* = 9.5, 8.3 Hz, 1H), 3.31 (dd, *J* = 9.5, 4.5 Hz, 1H), 3.19 (s, 3H), 2.26-2.18 (m, 4H), 1.96-1.91 (m, 2H), 1.68-1.60 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.81, 142.29, 141.49, 141.17, 129.43, 128.29, 128.09, 127.88, 127.89, 127.35, 126.74, 122.66, 77.63, 63.47, 62.65, 59.28, 58.70, 36.32, 32.80, 32.58, 23.56; IR (thin film, NaCl) ν_{max} 3342 (br), 3060, 3026, 2925, 2890, 2847, 1601, 1493, 1454, 1380, 1194, 1105, 1048, 760, 701 cm^{-1}; LRMS (EI, H) *m/z* calc'd for $C_{31}H_{45}ClN_2OSi$ $[M + H]^+$ 525.3, found 525.8; $[\alpha]_D^{20}$ +61.7 (*c* 0.68, $CHCl_3$).

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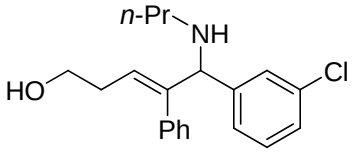

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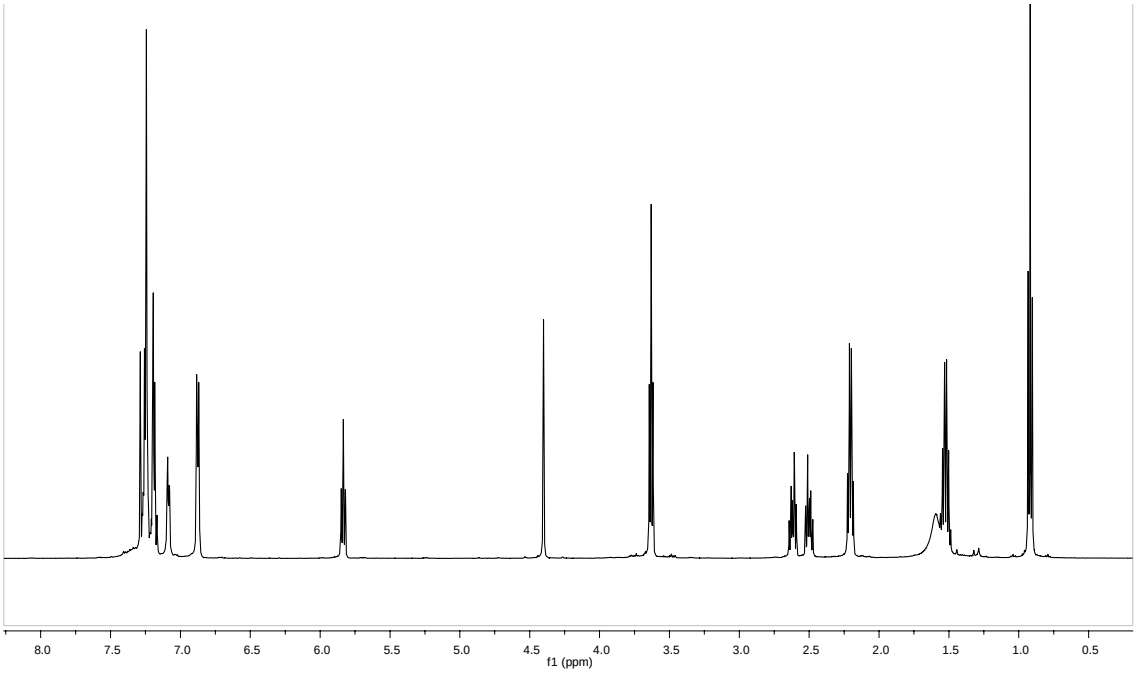
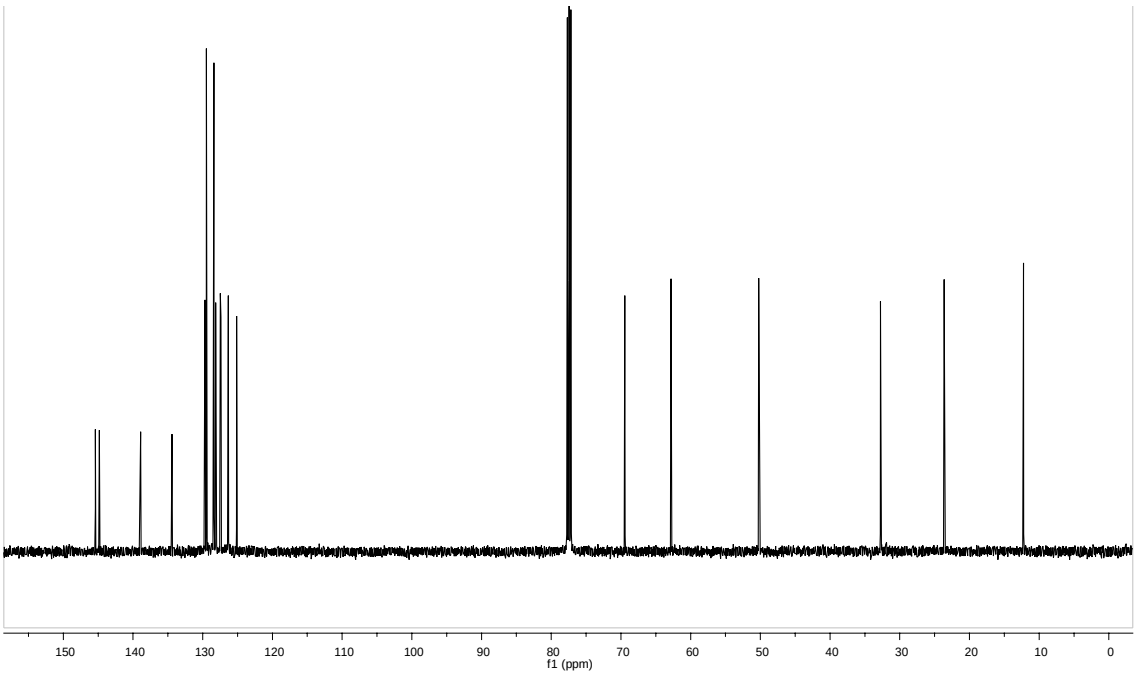
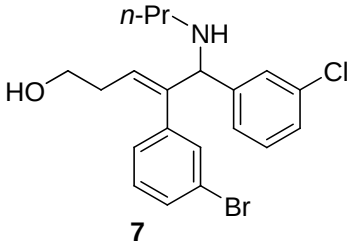
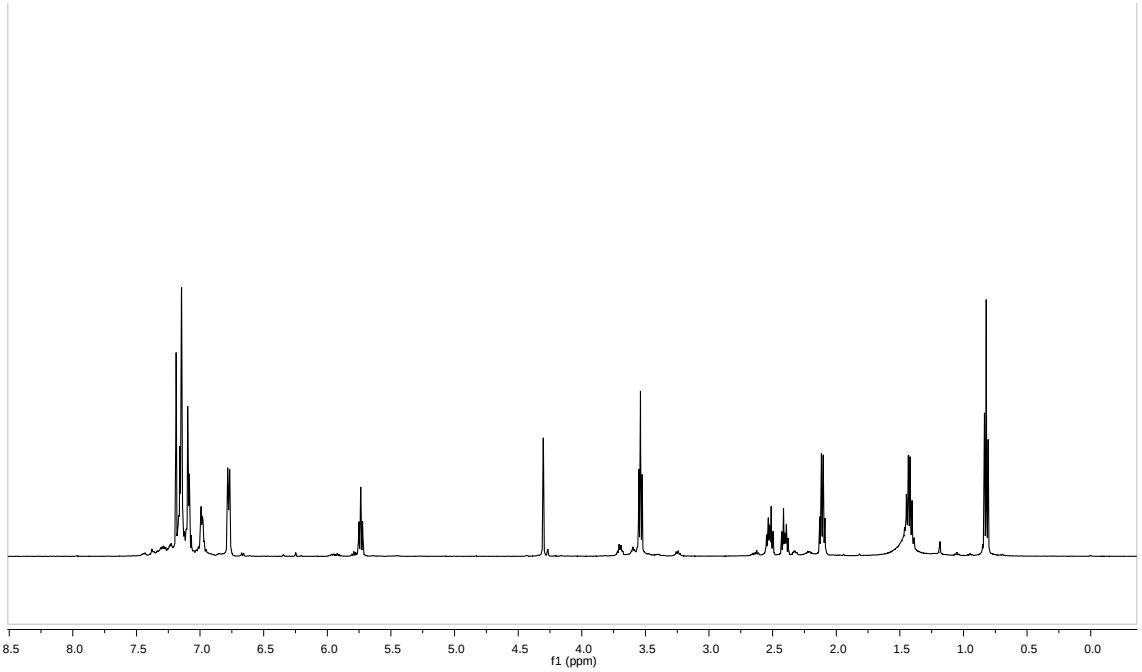


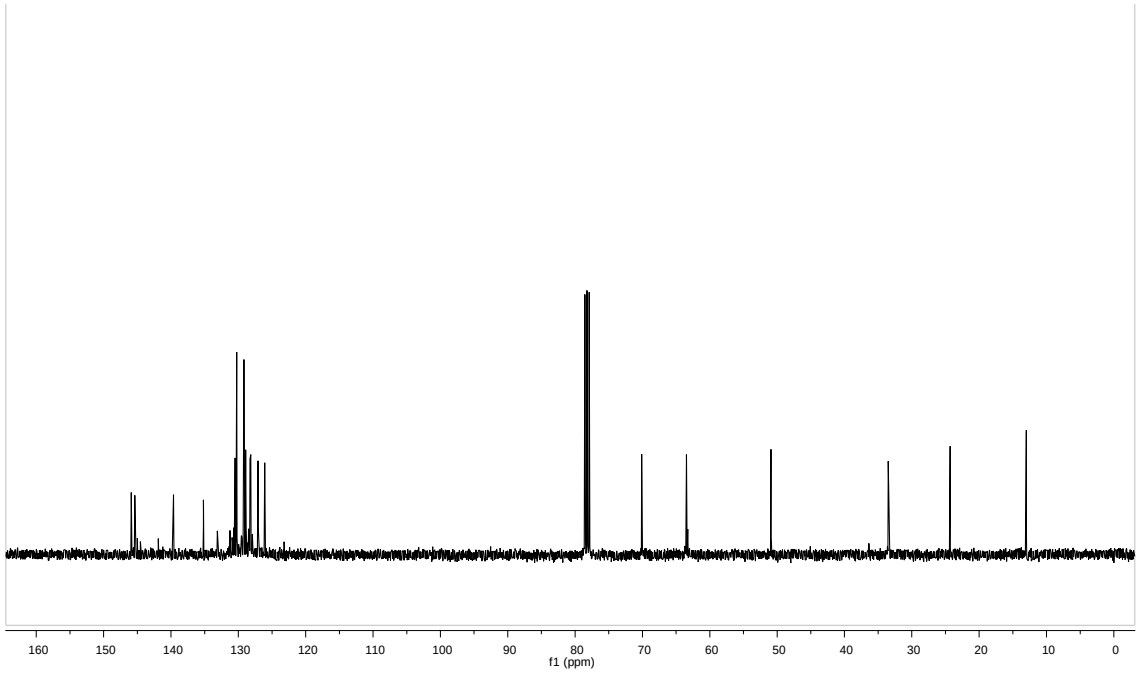


^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) of compound **6**.

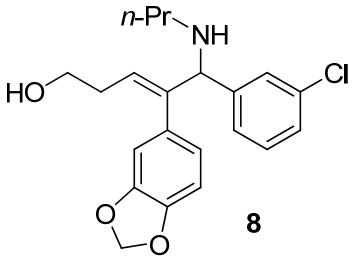


7





^{1}H NMR (500 MHz) and ^{13}C NMR (100 MHz) of compound **7**.



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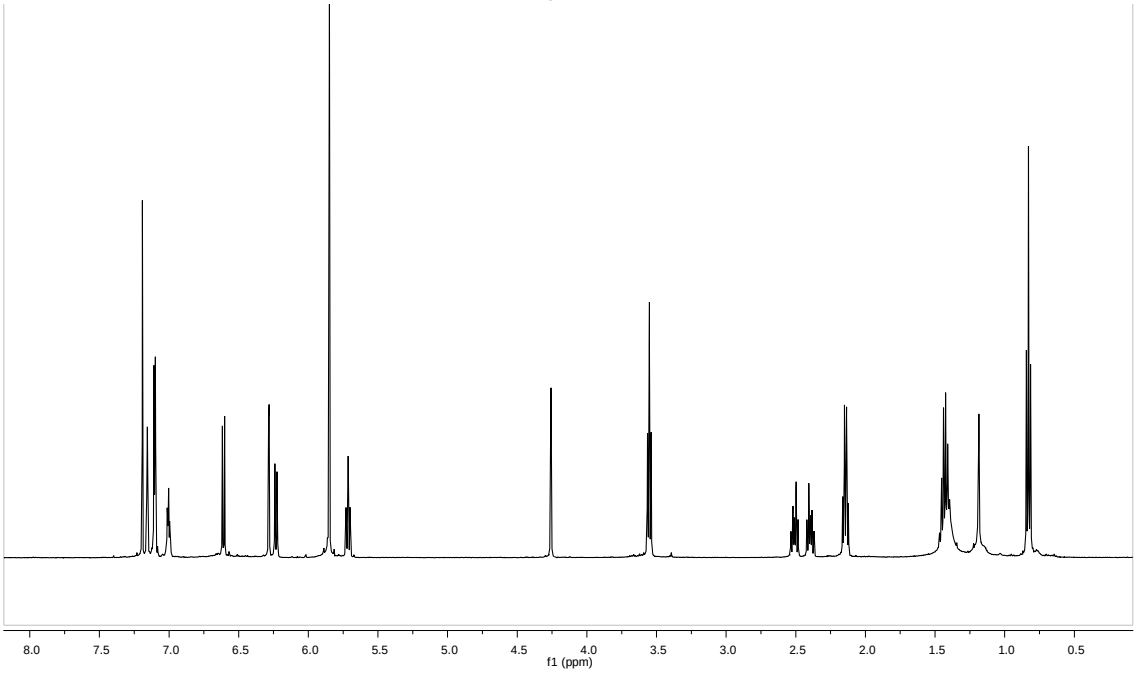
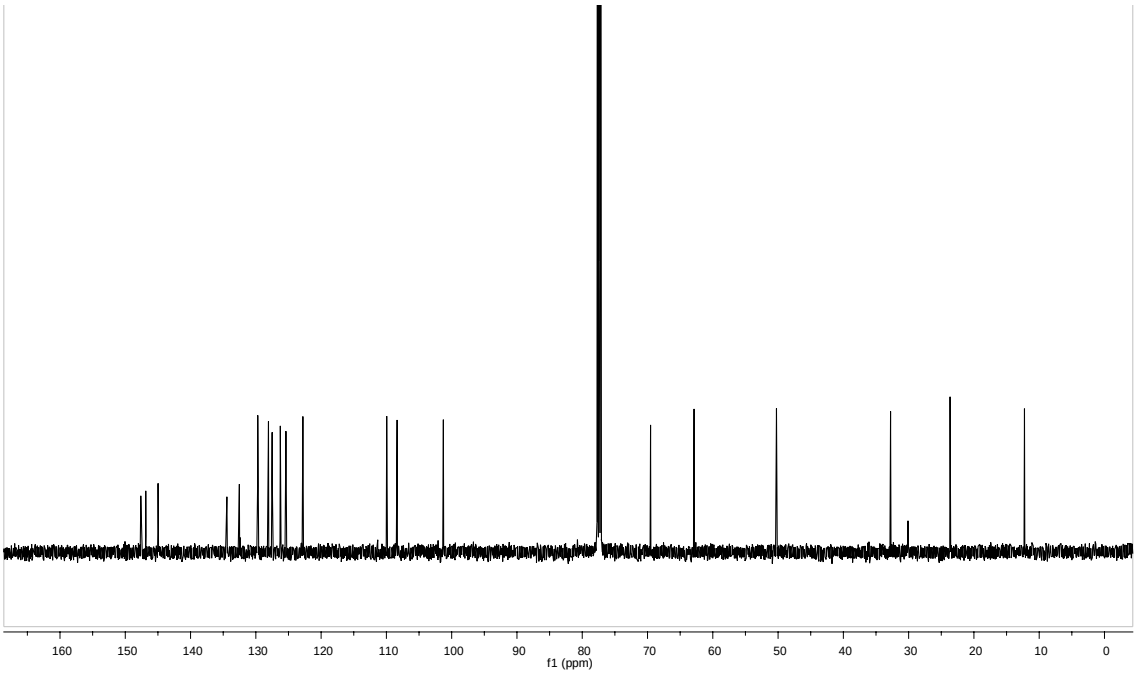
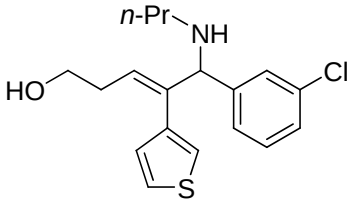




^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) of compound **8**.



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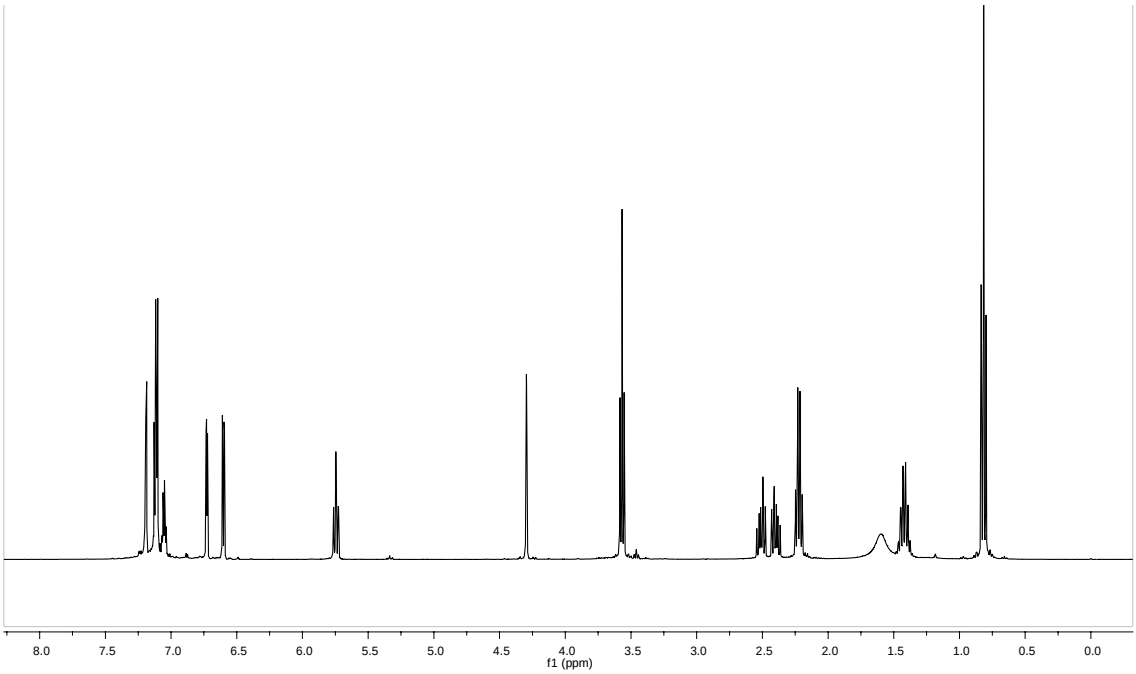
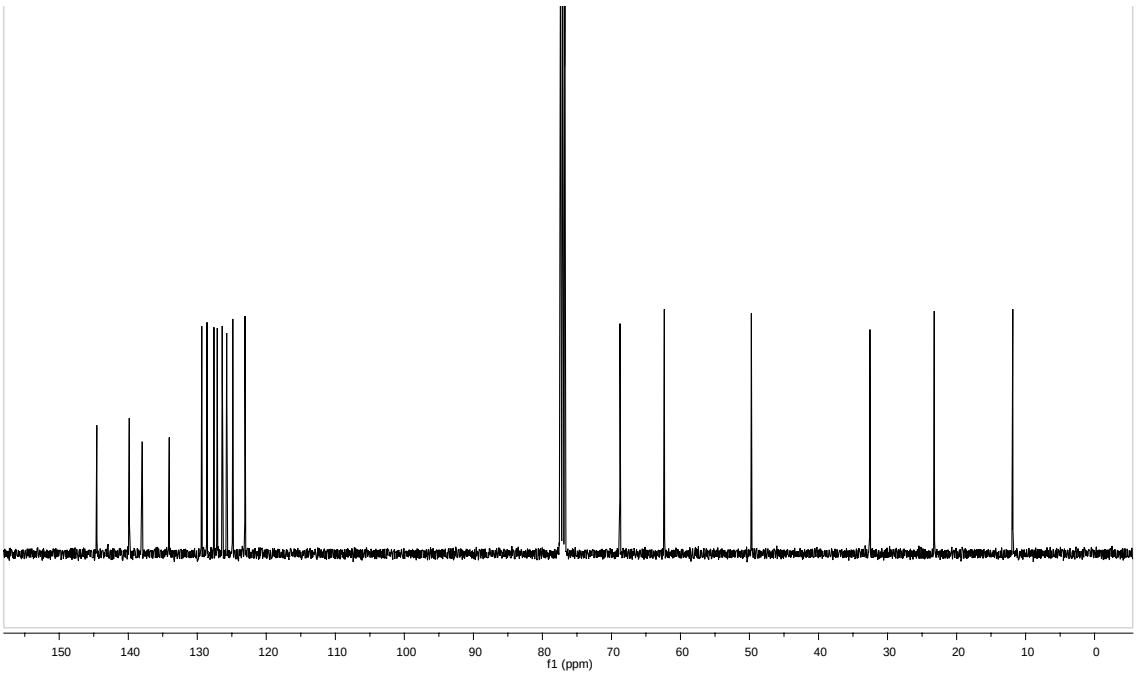
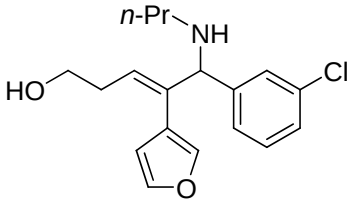




^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **9**.



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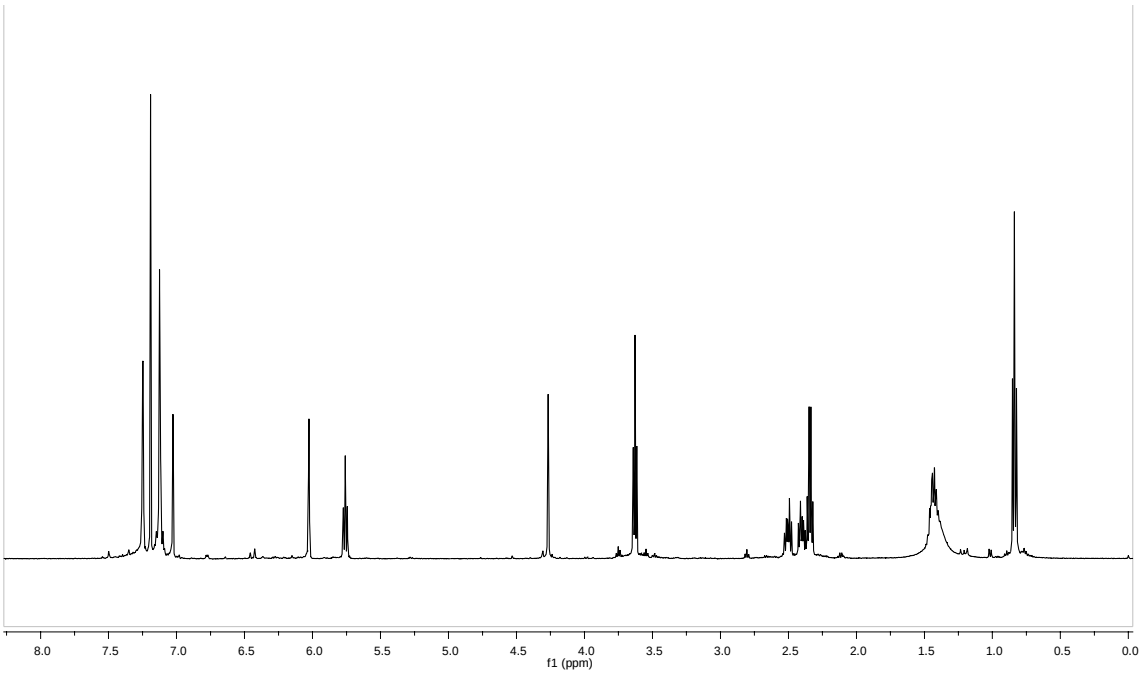
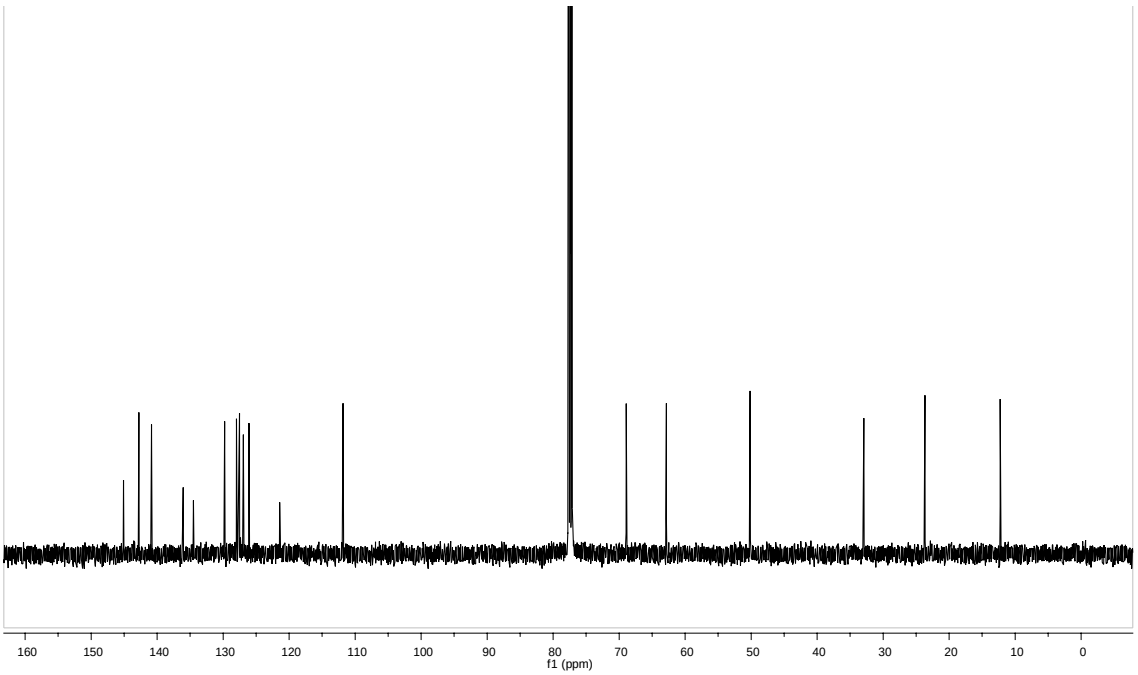
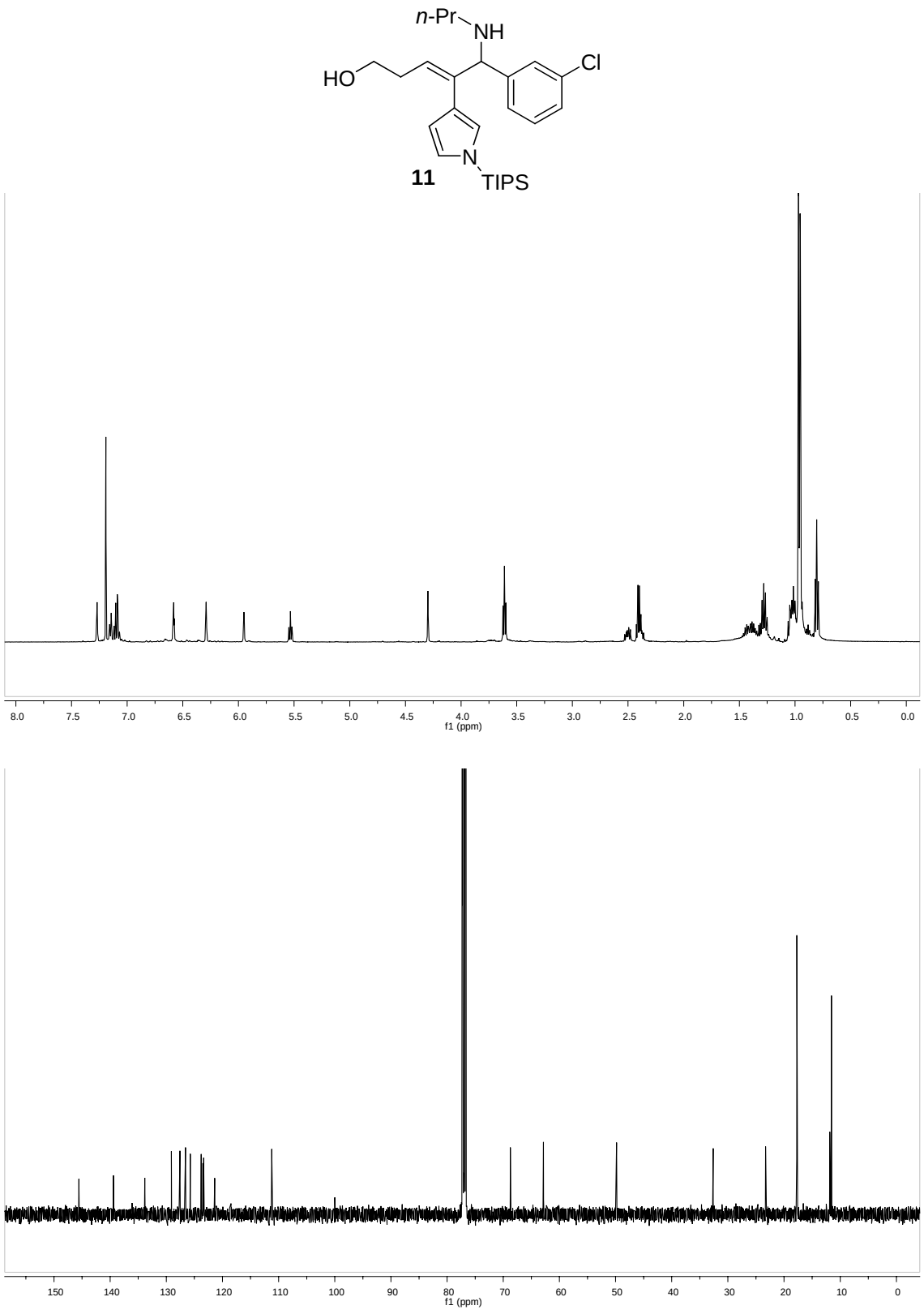
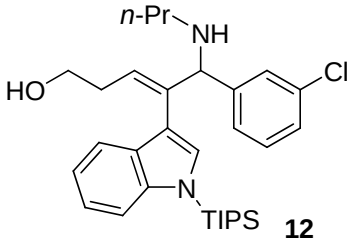




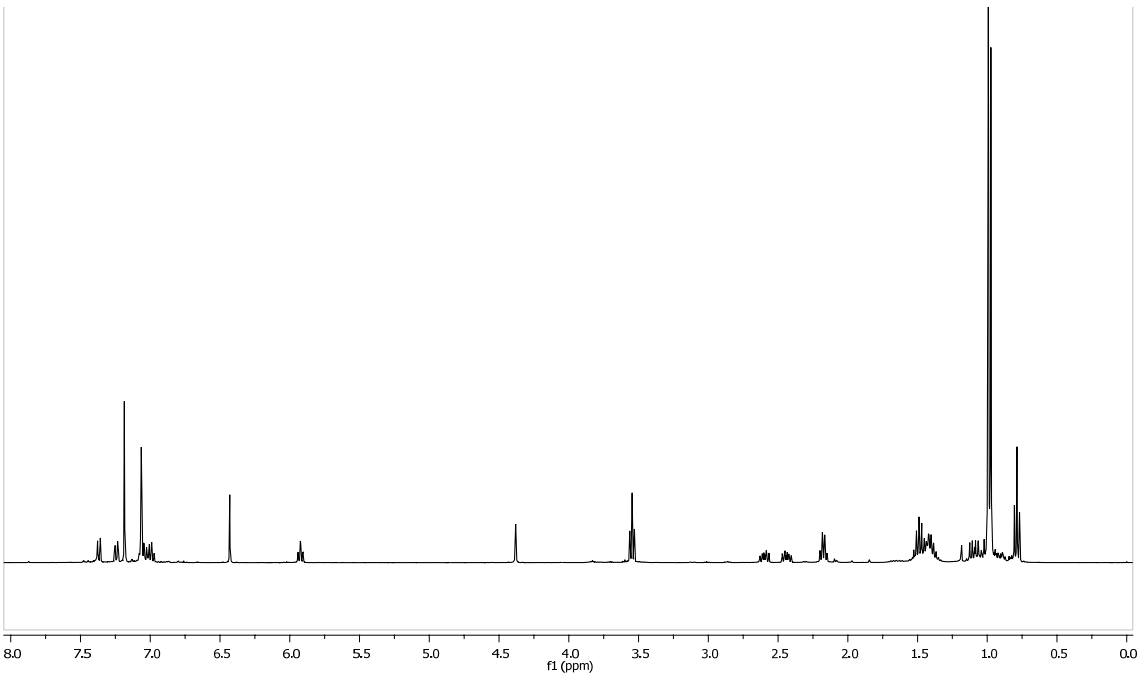
^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) of compound **10**.

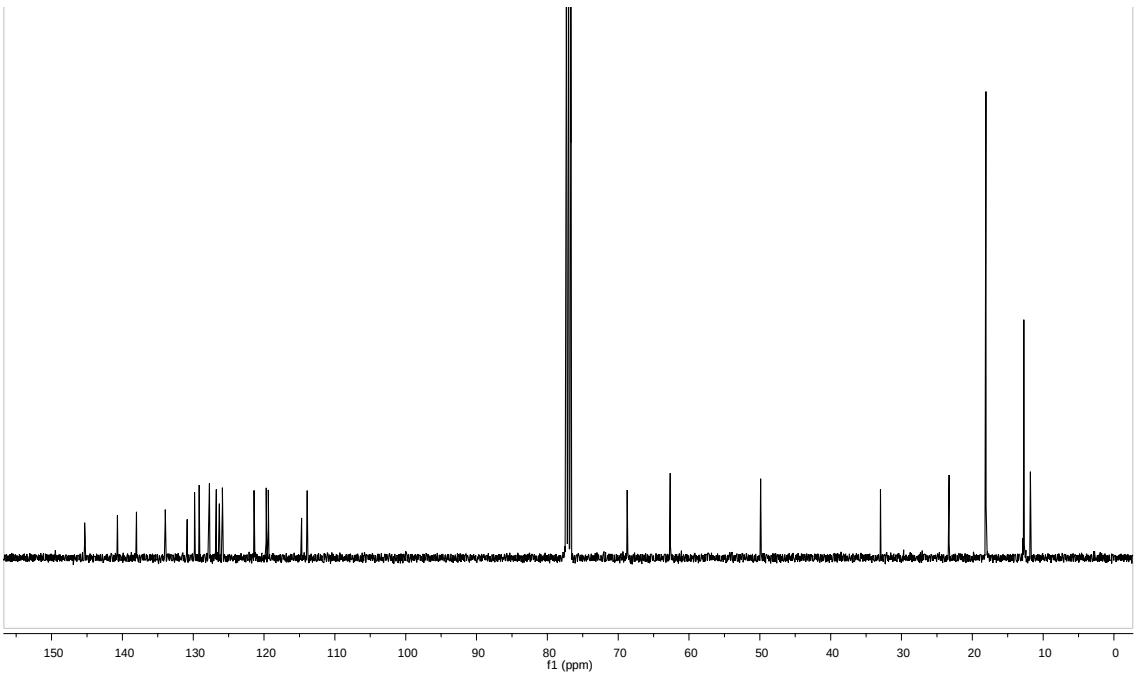


^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) of compound **11**.

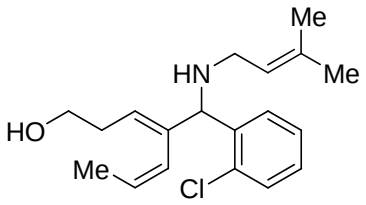


12

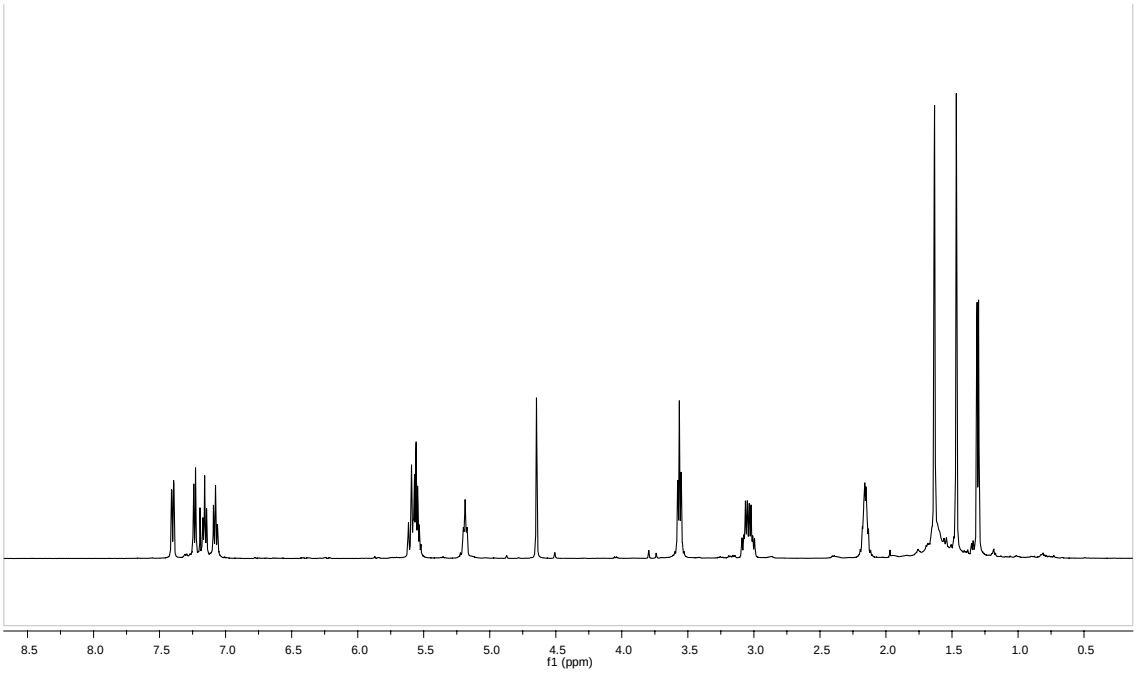


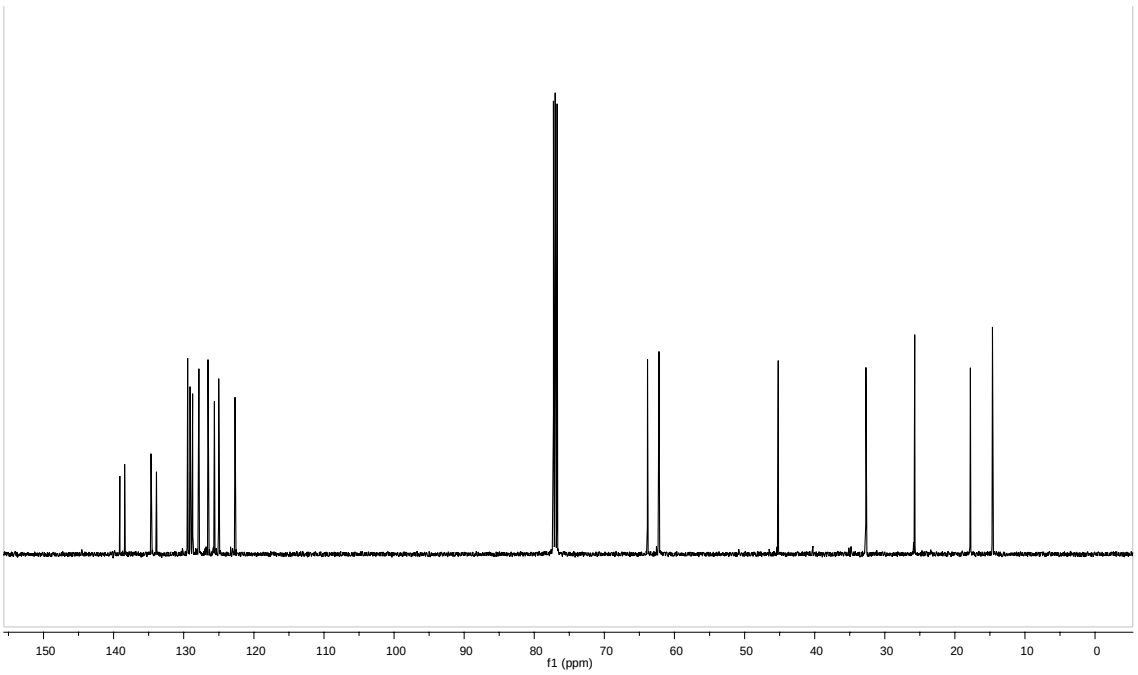


^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **12**.

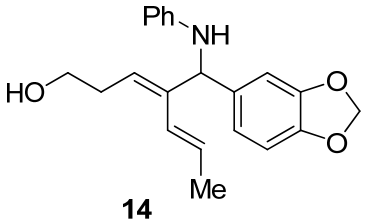


13





^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) of compound **13**.



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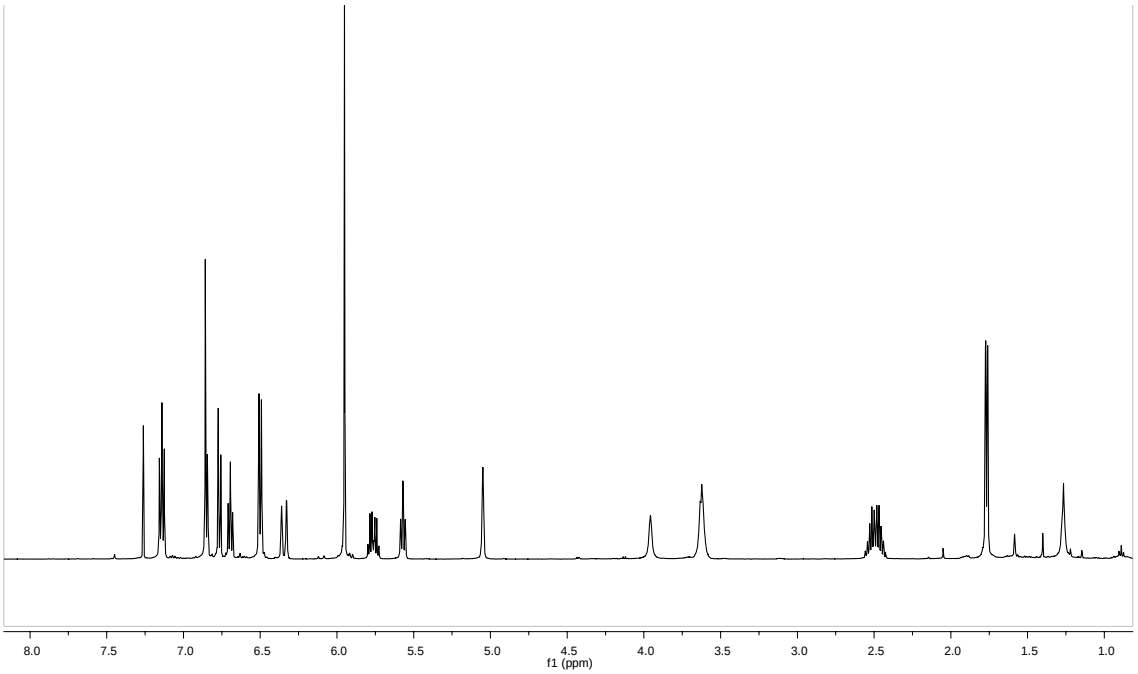
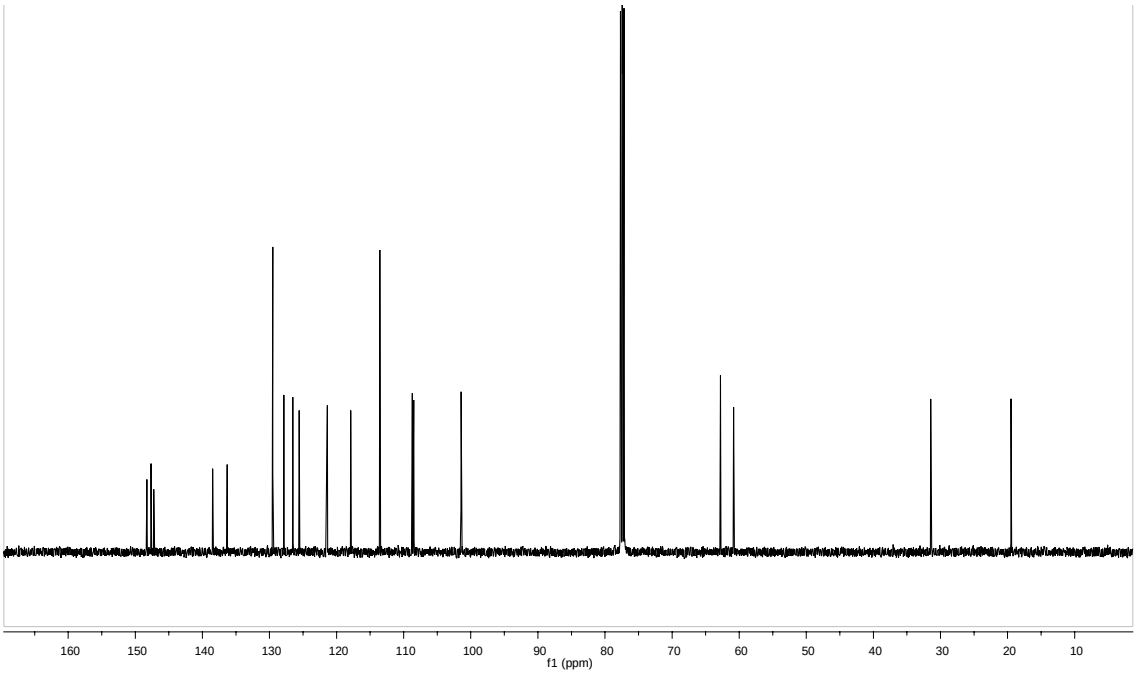
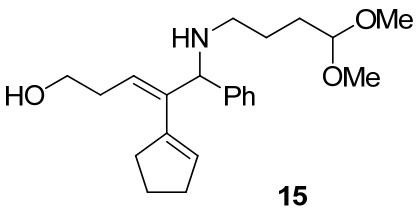
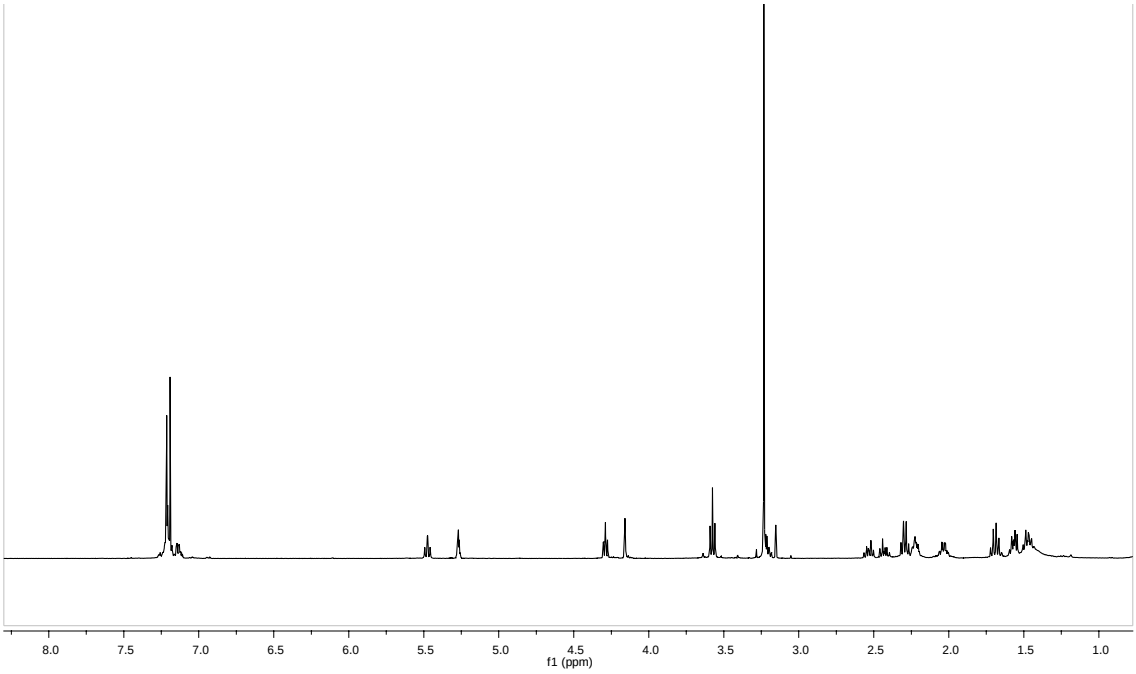


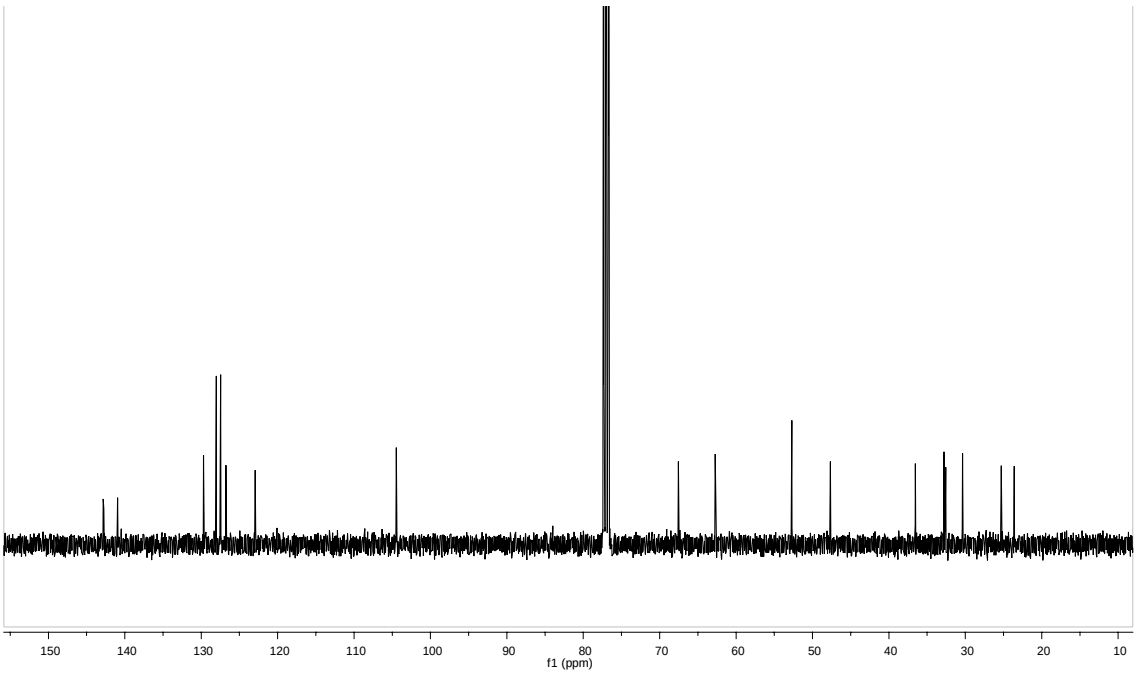


^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) of compound **14**.

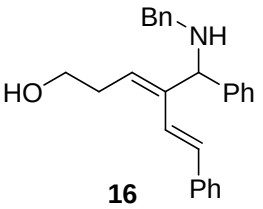


15

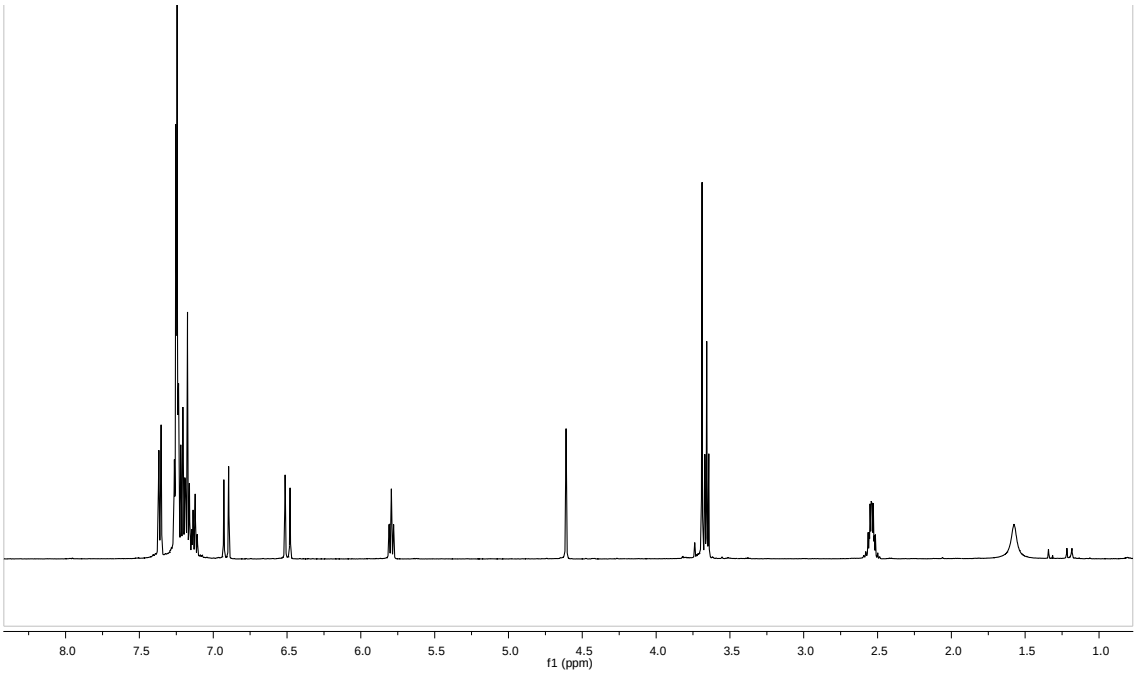


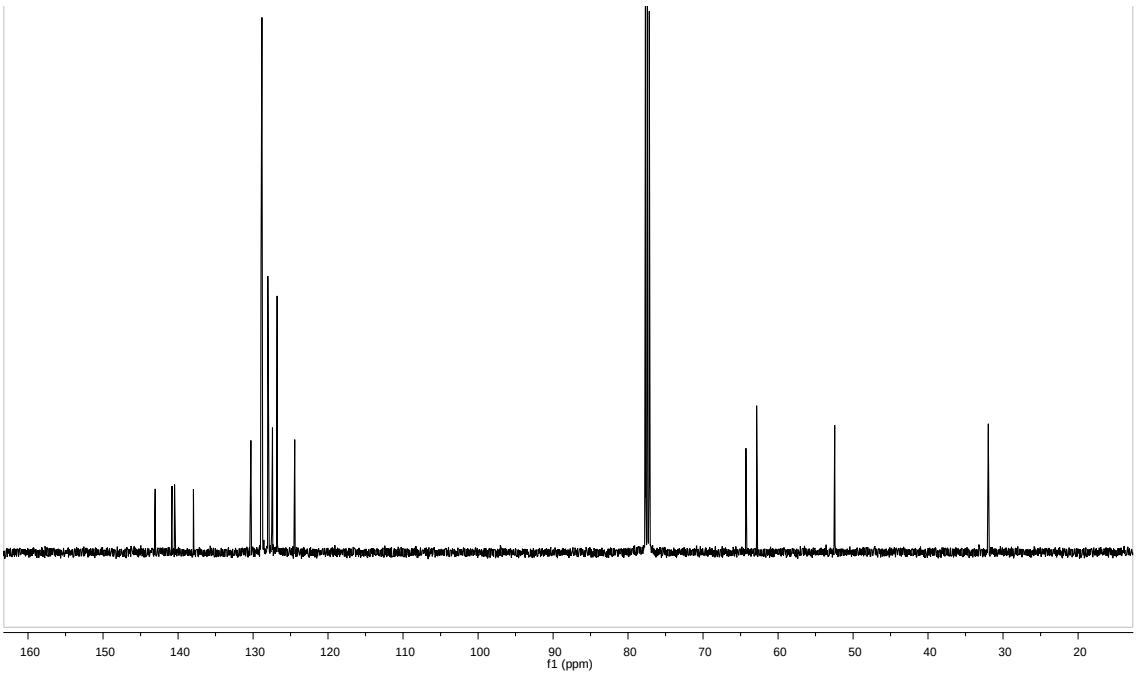


^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **15**.

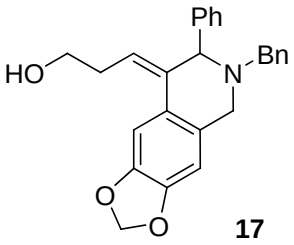


16





^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) of compound **16**.



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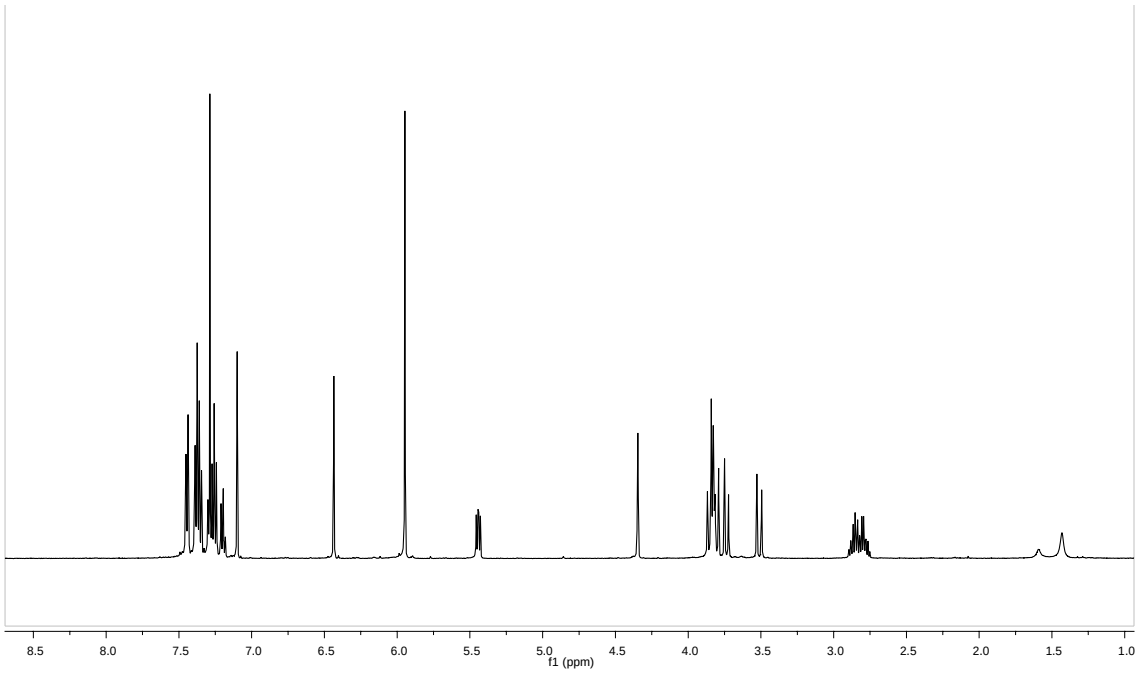
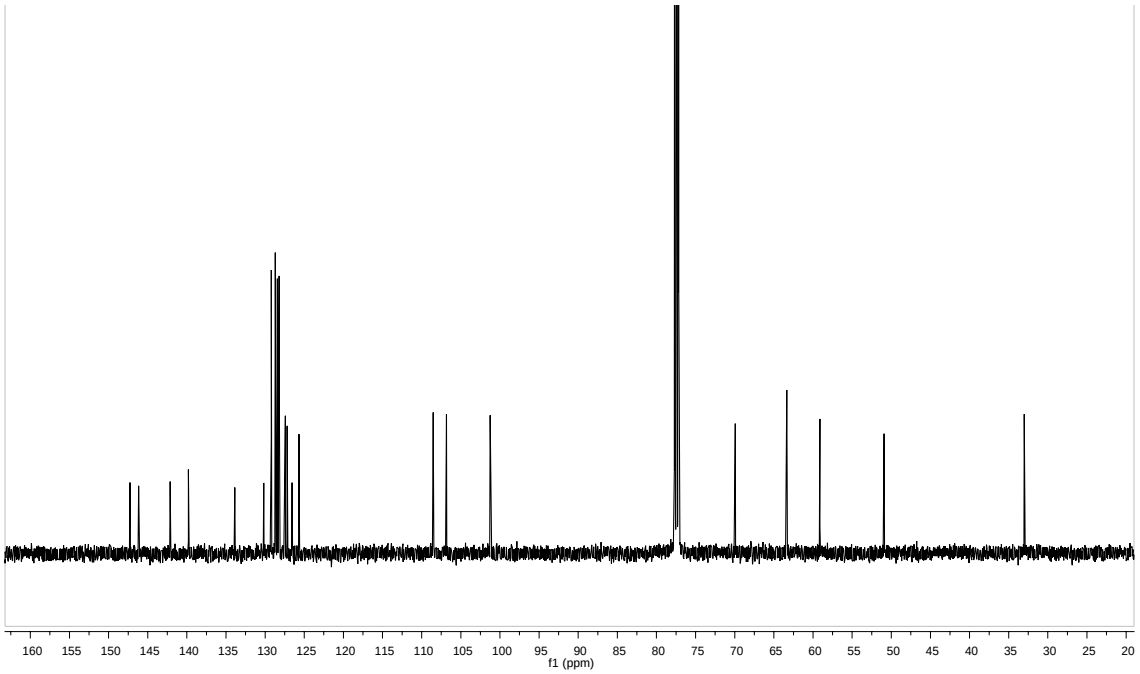
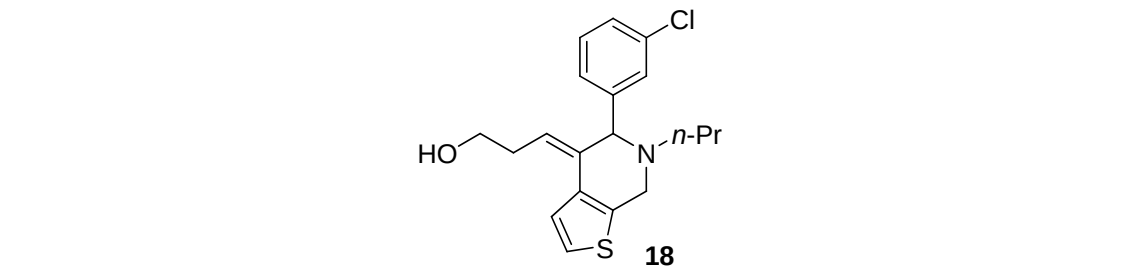




^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) of compound **17**.



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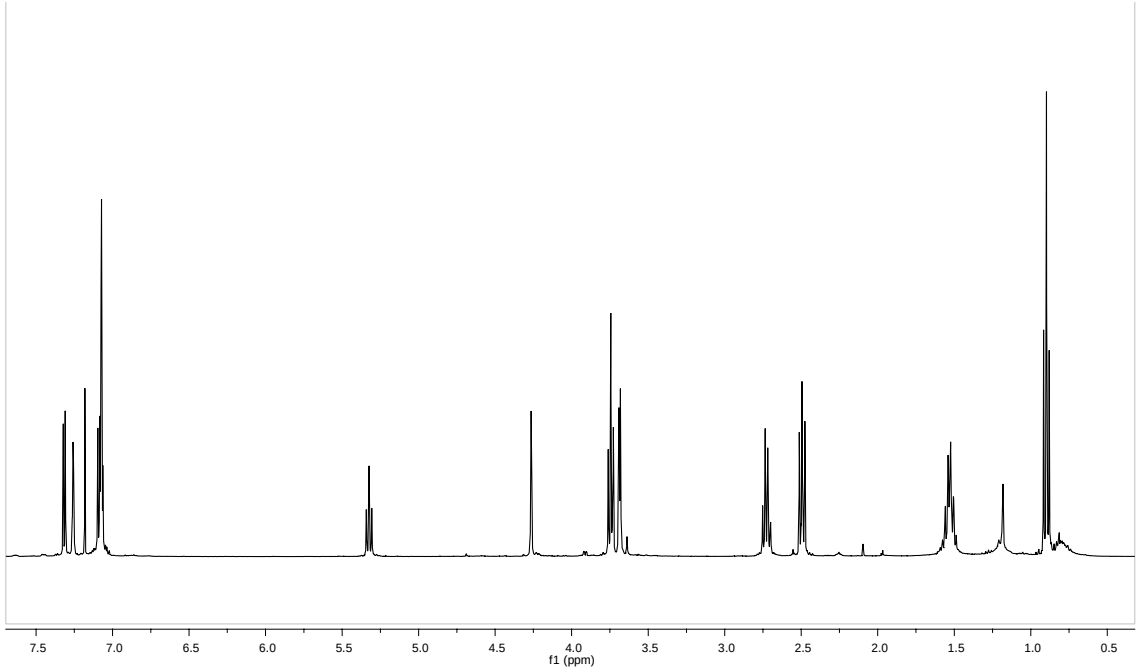
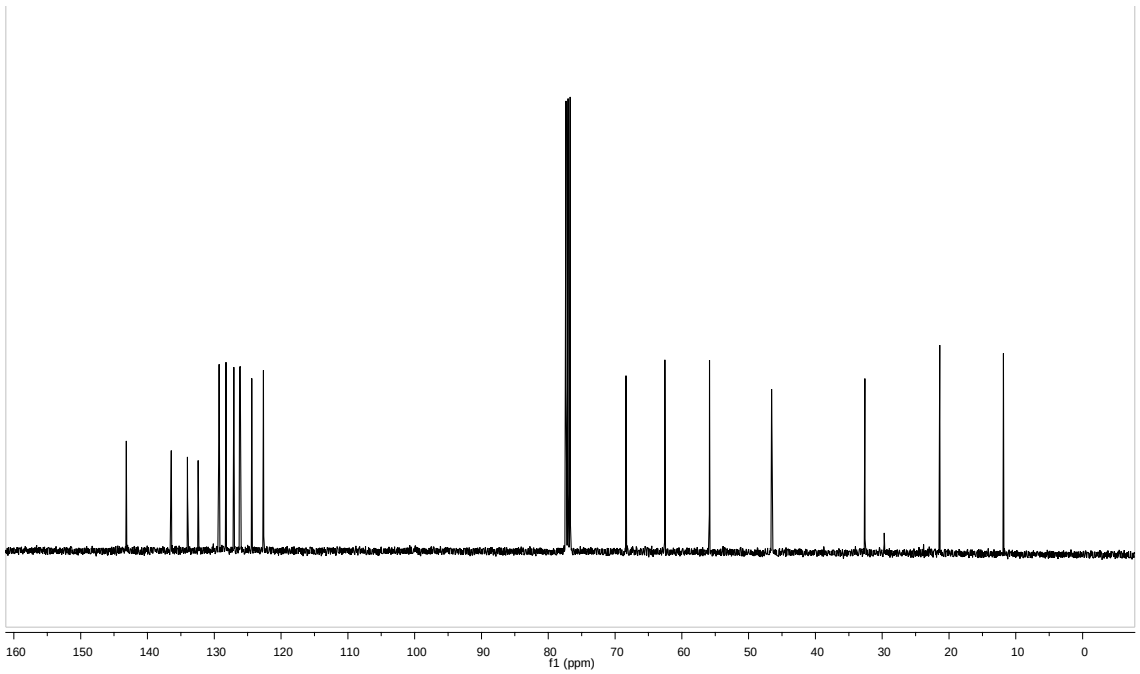
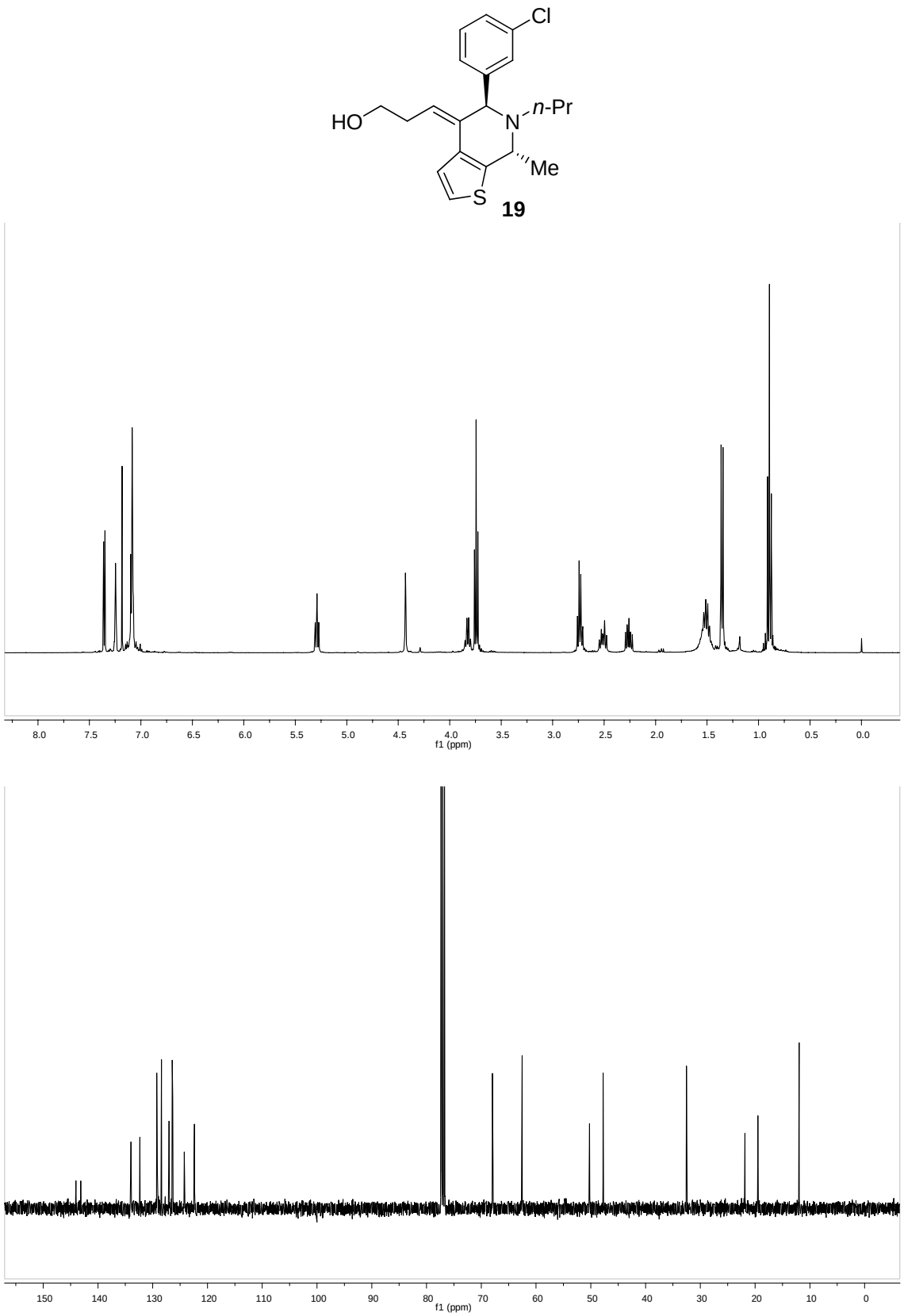
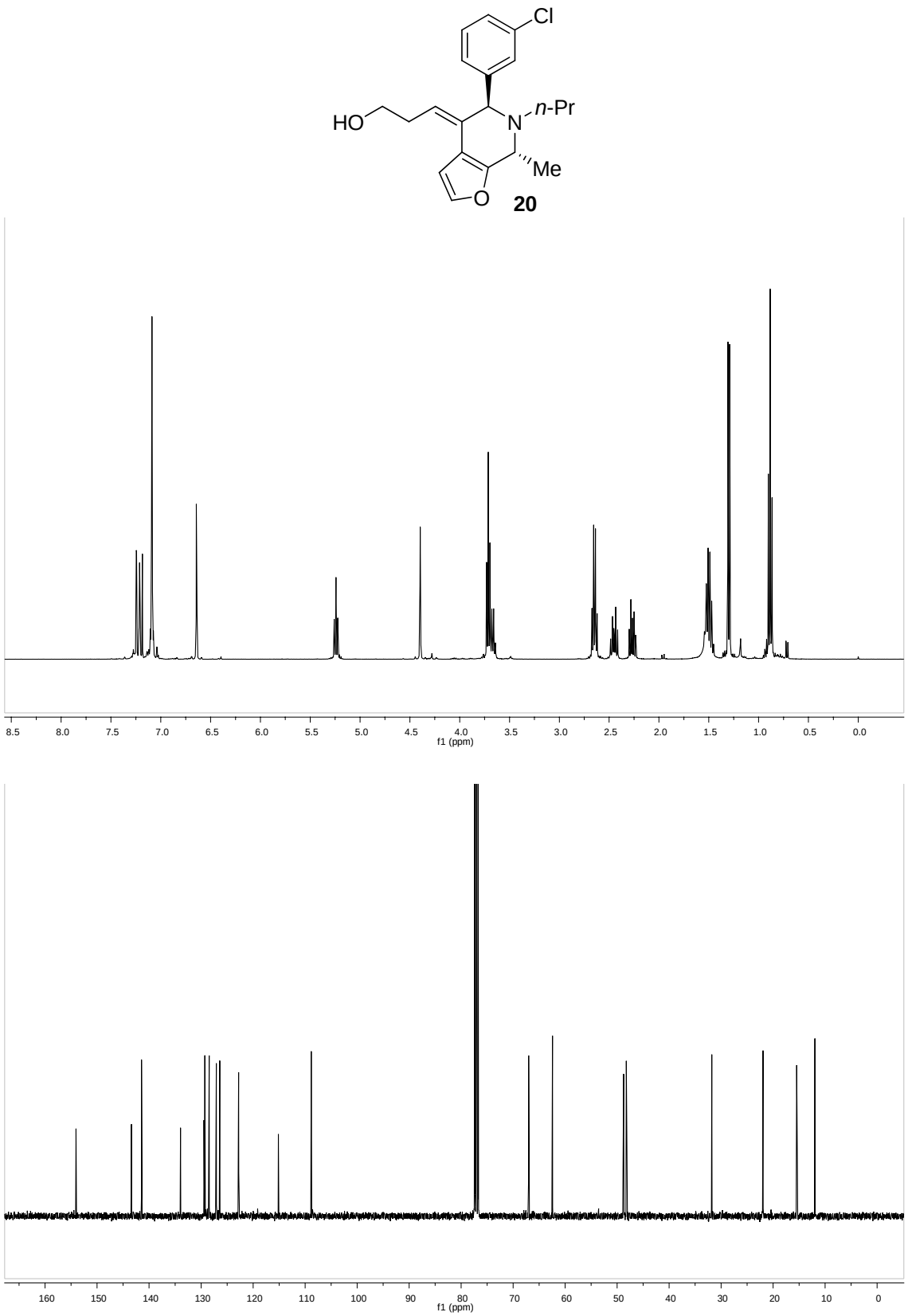




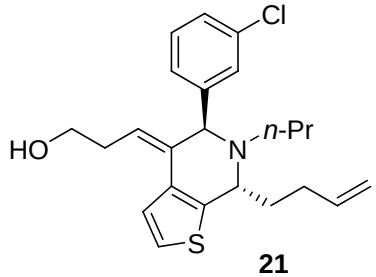
^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **18**.



^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **19**.



^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **20**.



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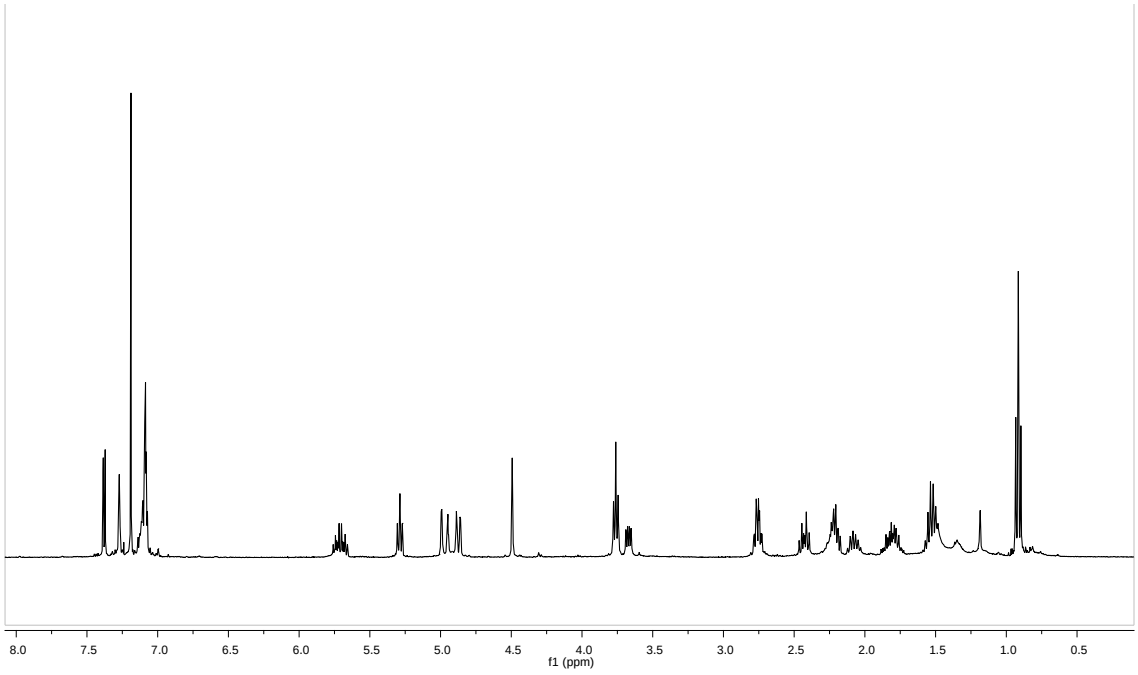
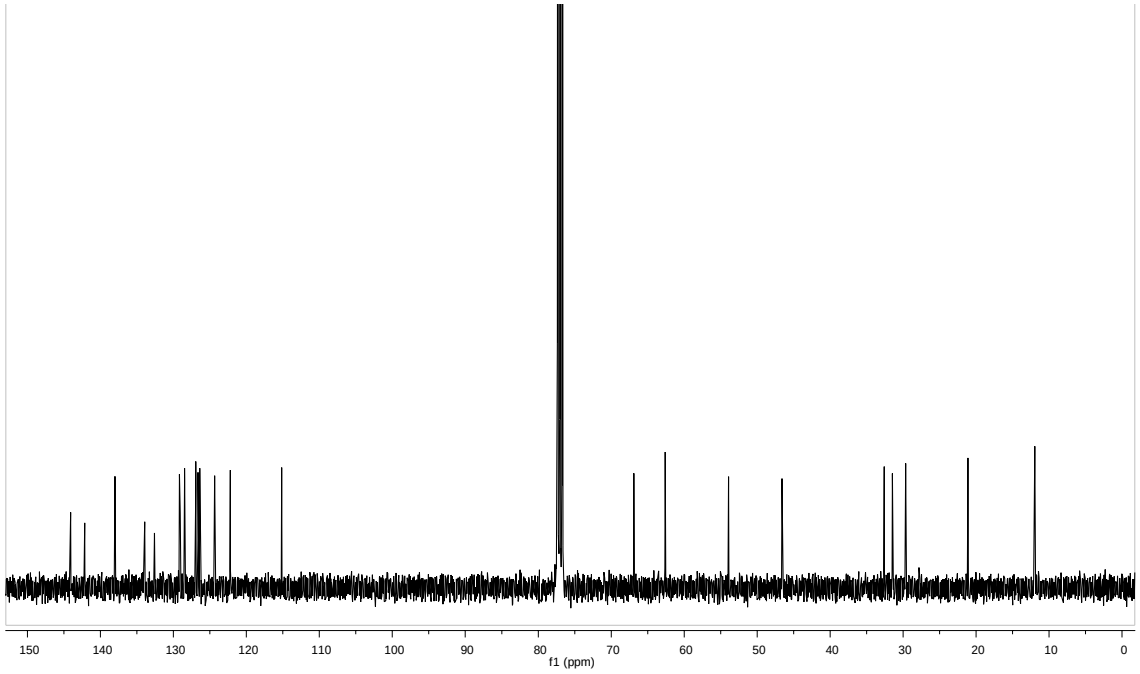
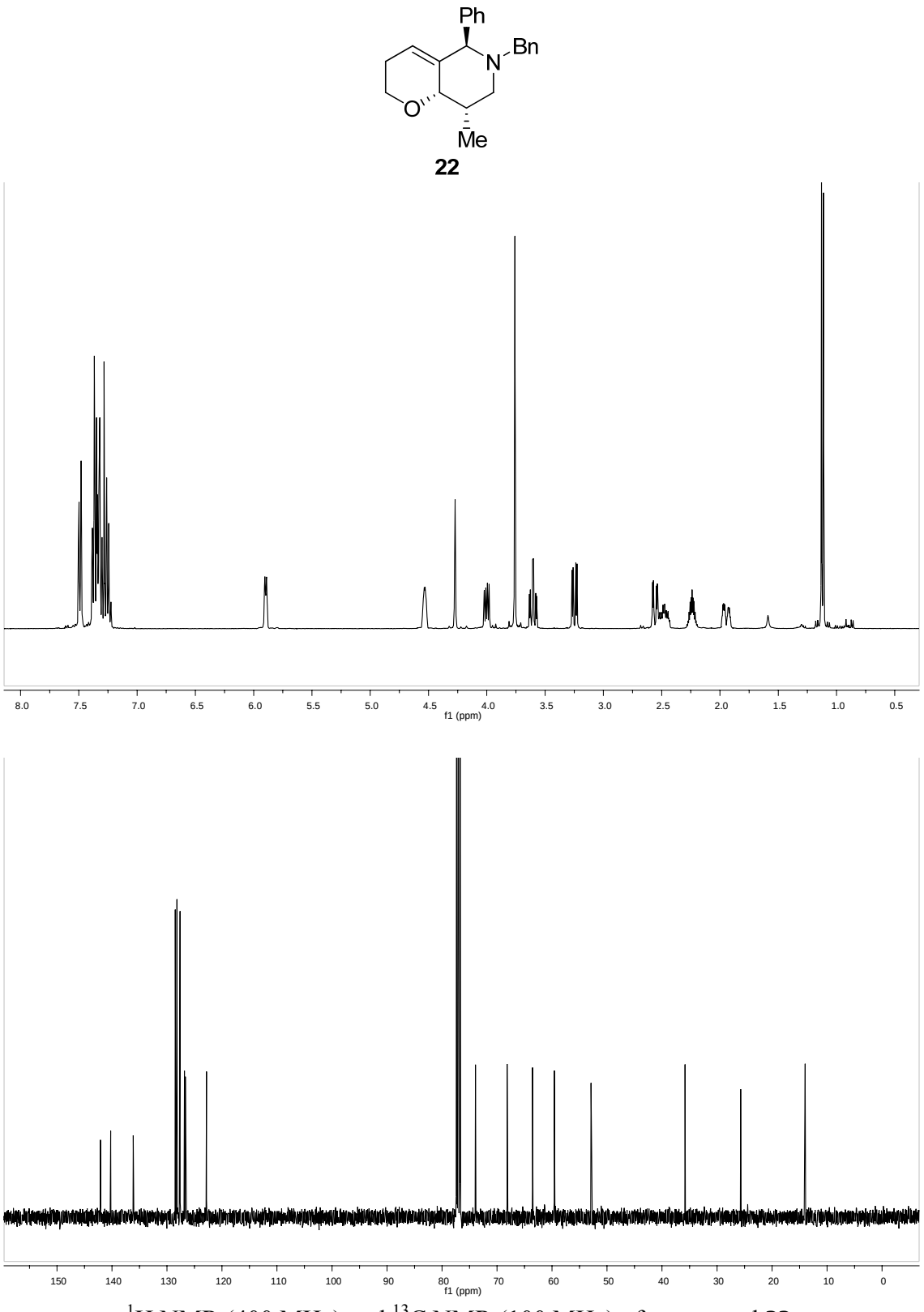


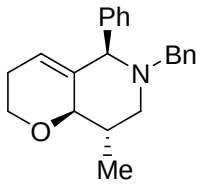


^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **21**.

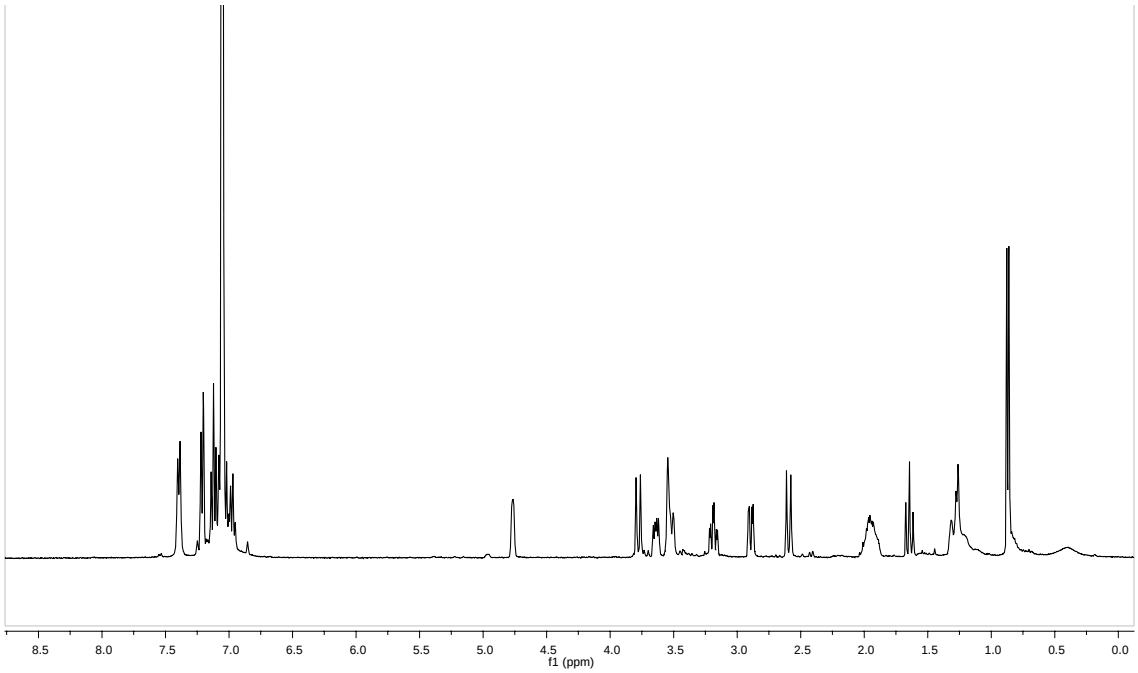


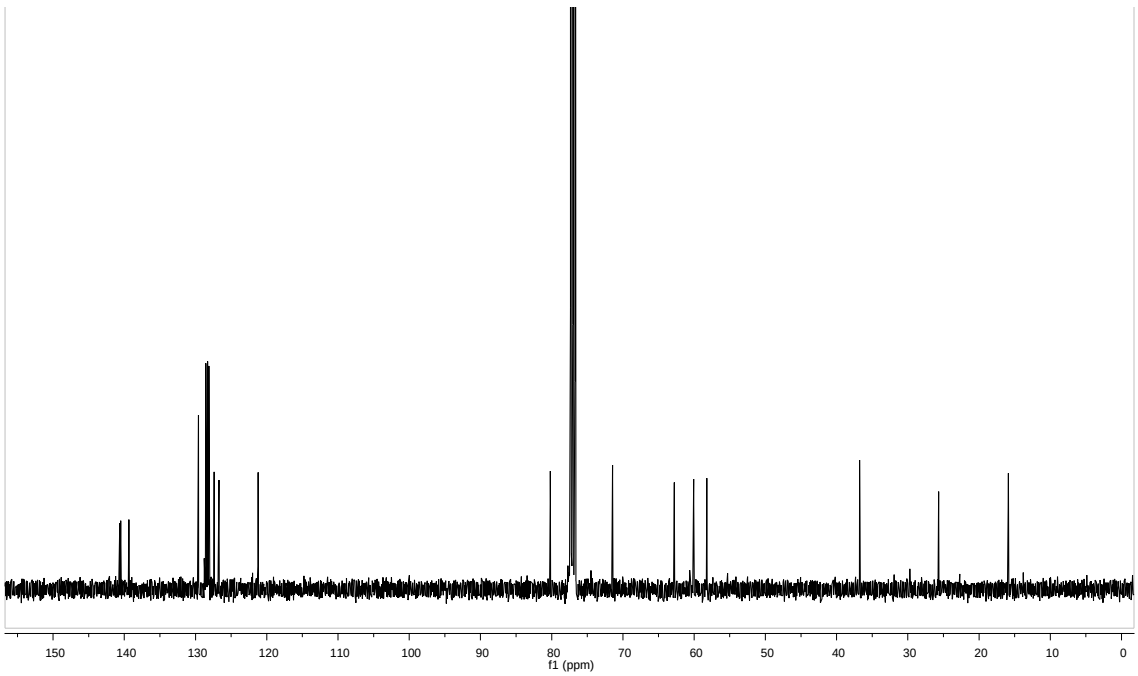
22

^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **22.**

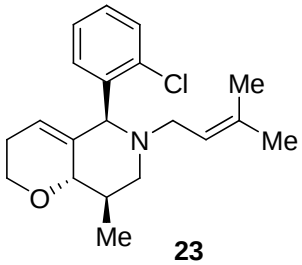


22a

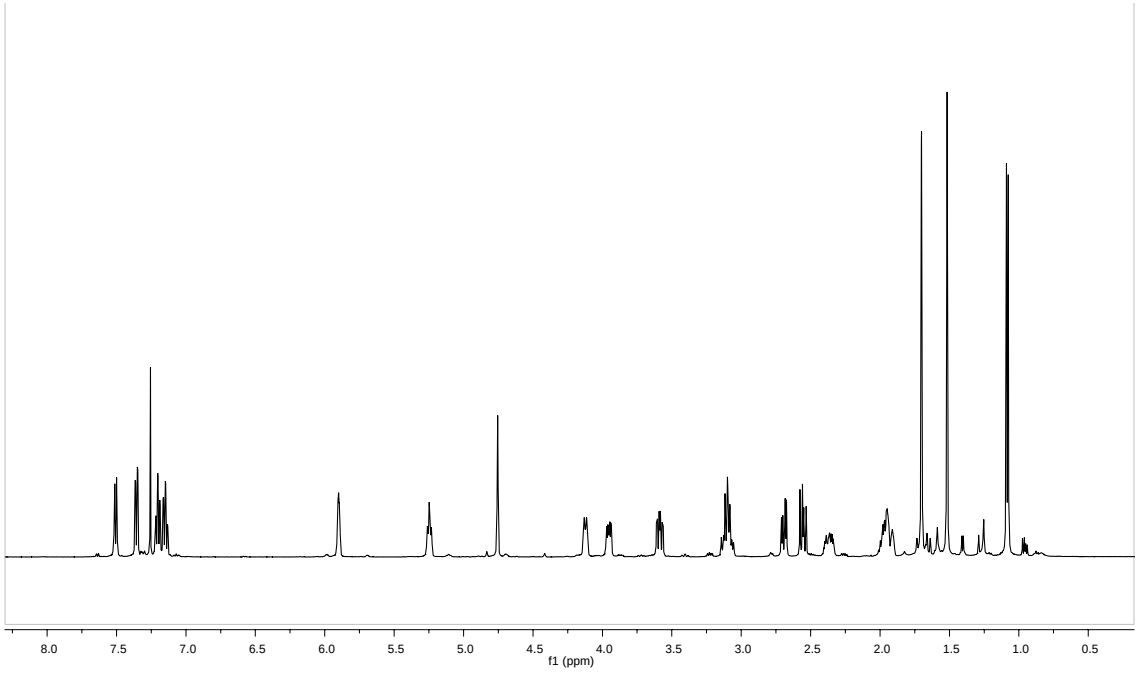


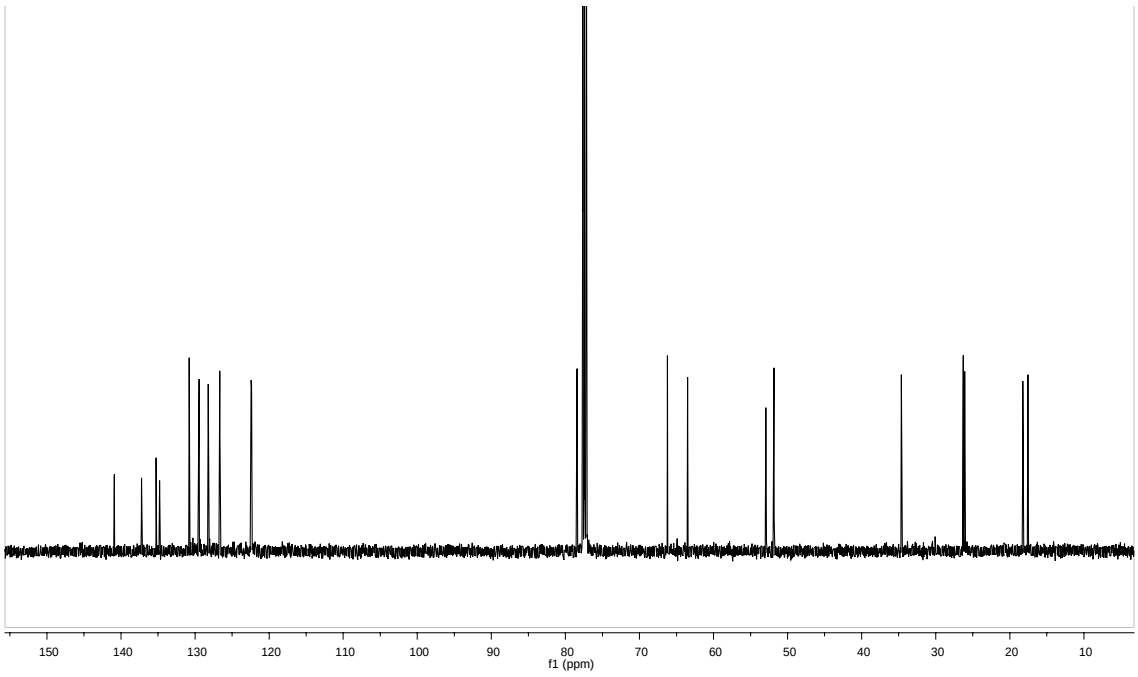


^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **22a**.

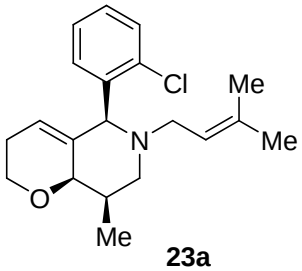


23

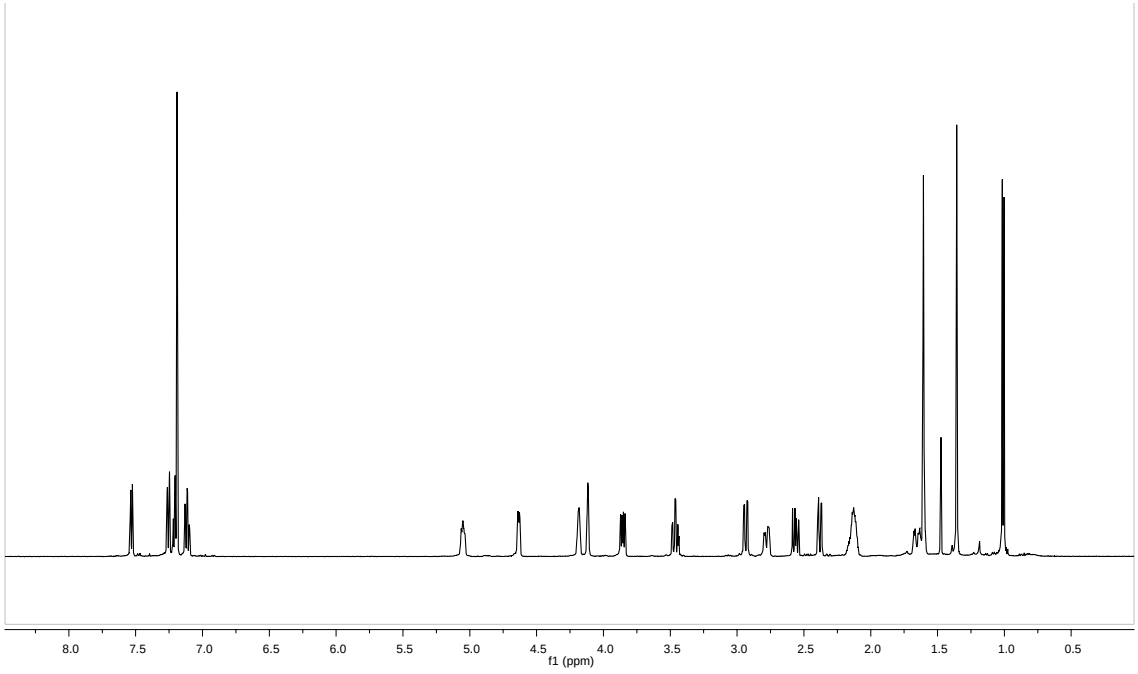


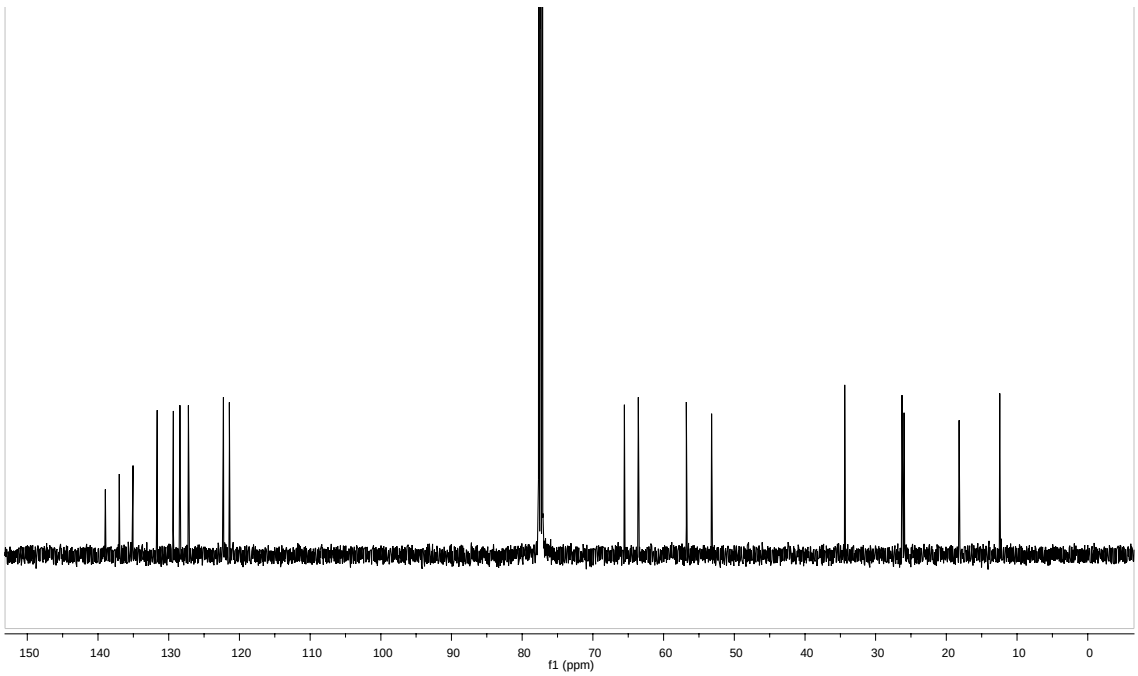


^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) of compound **23.**

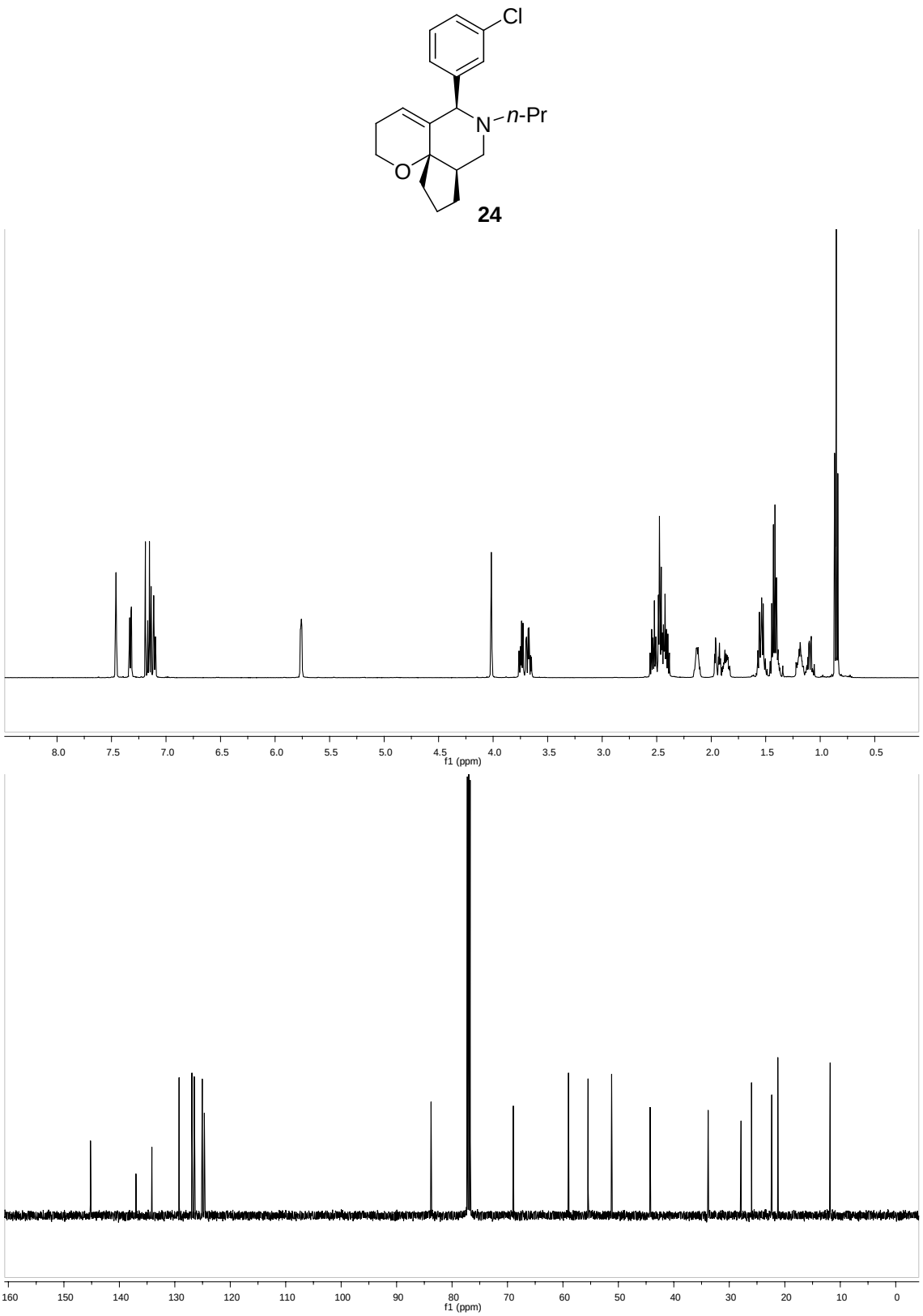


23a



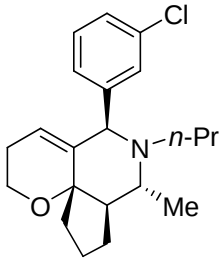


^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) of compound **23a.**

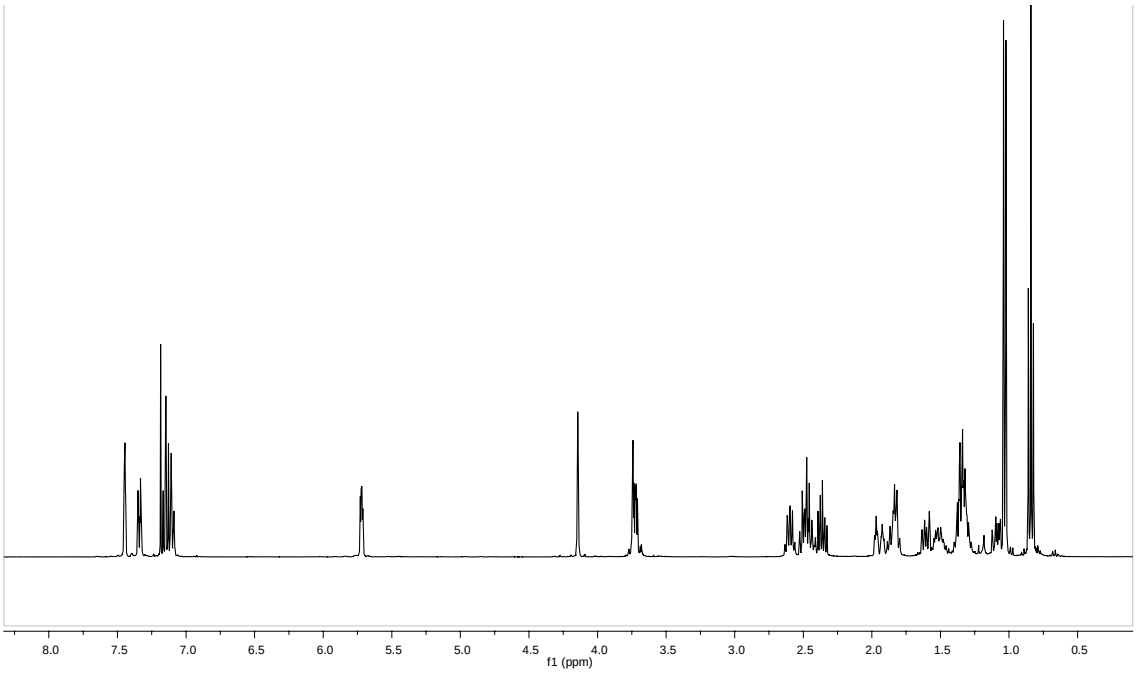


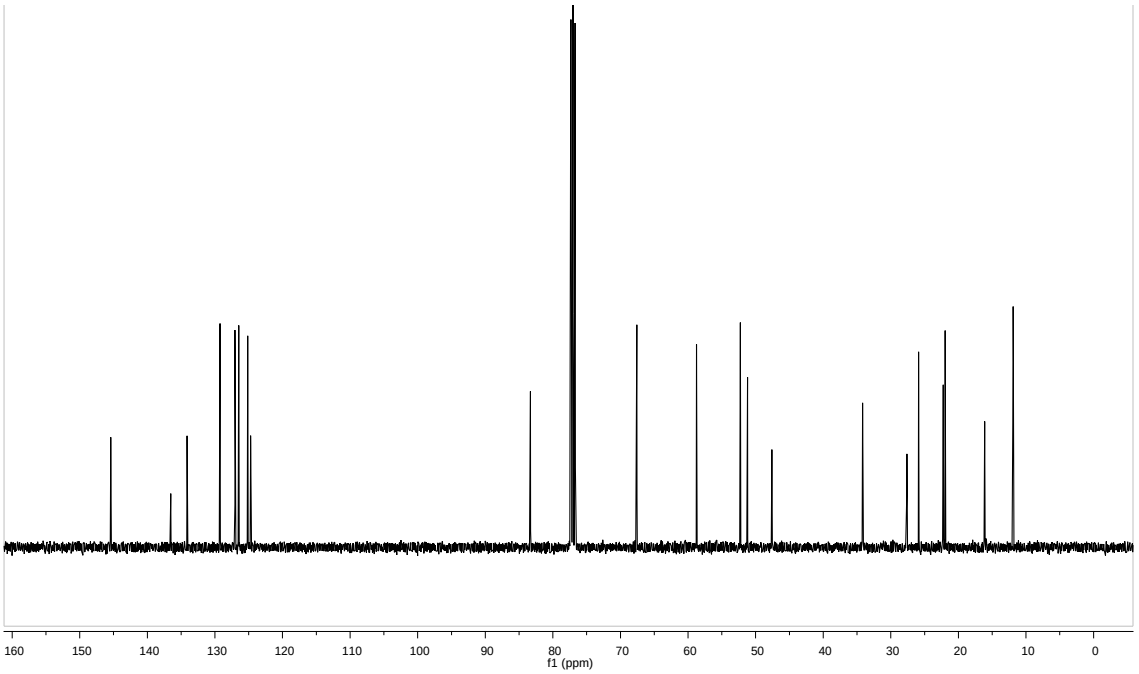
24

^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) of compound **24**.

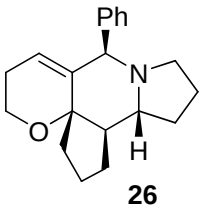


25

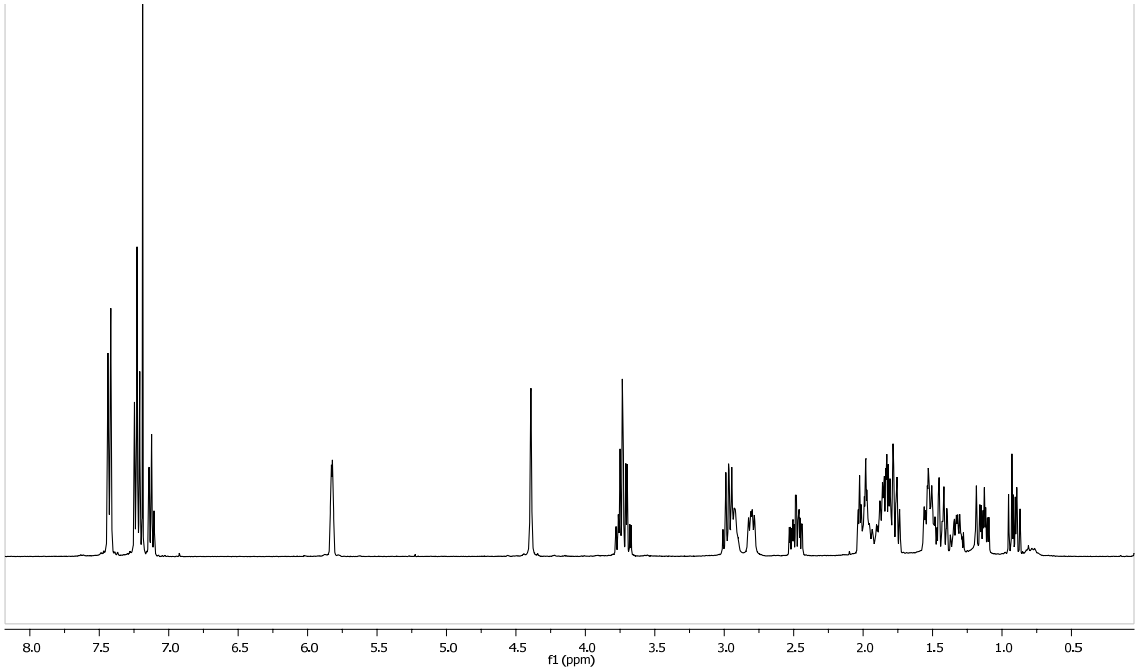


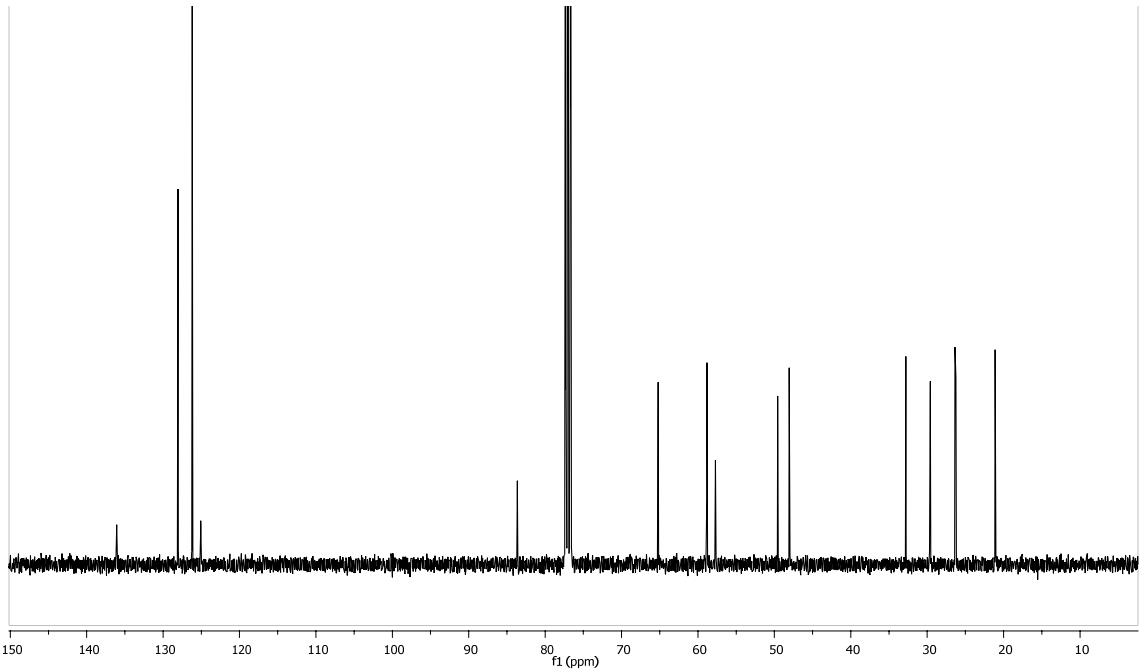


^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **25.**

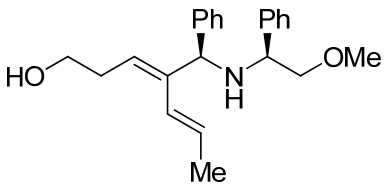


26





^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **26**.



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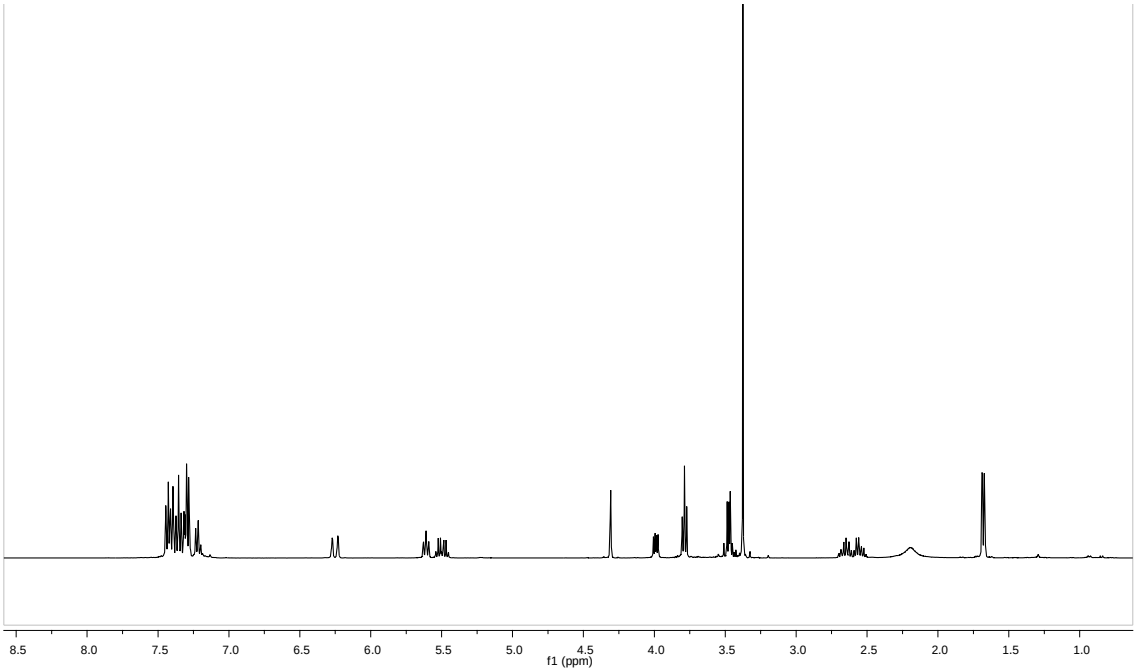
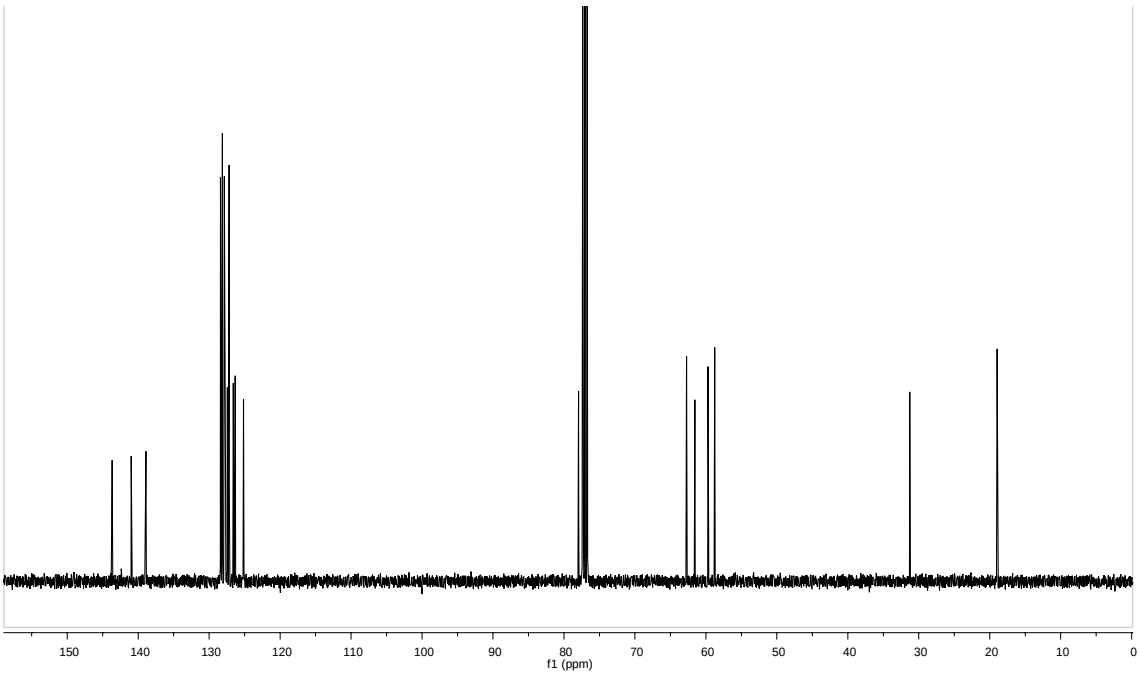
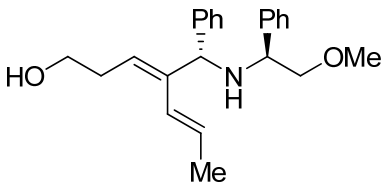
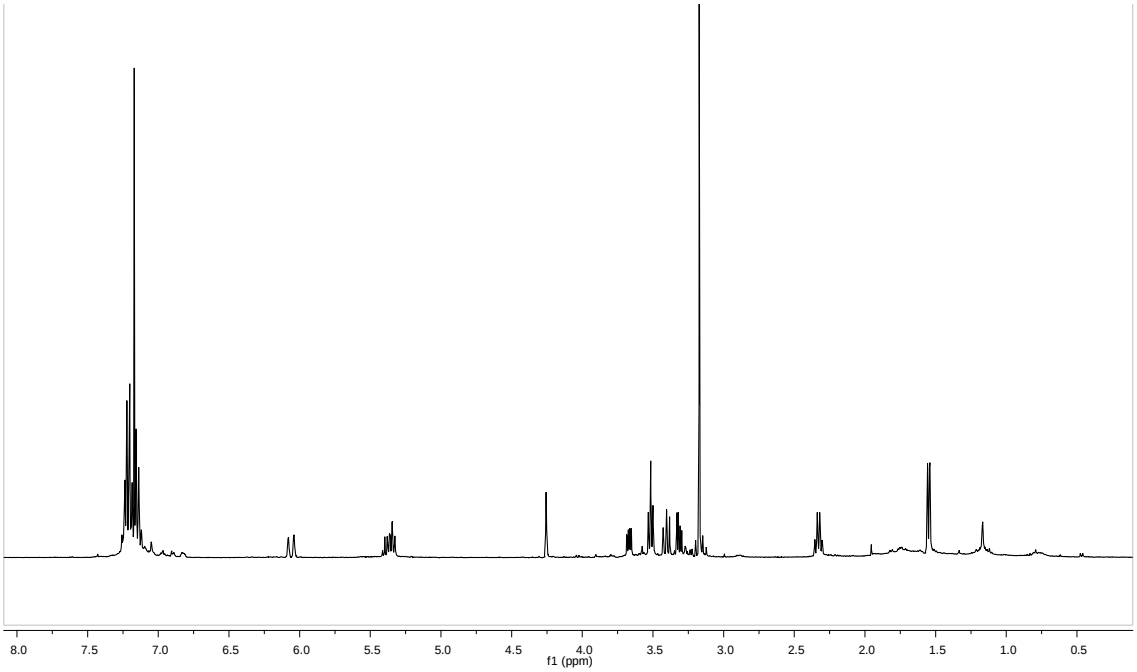


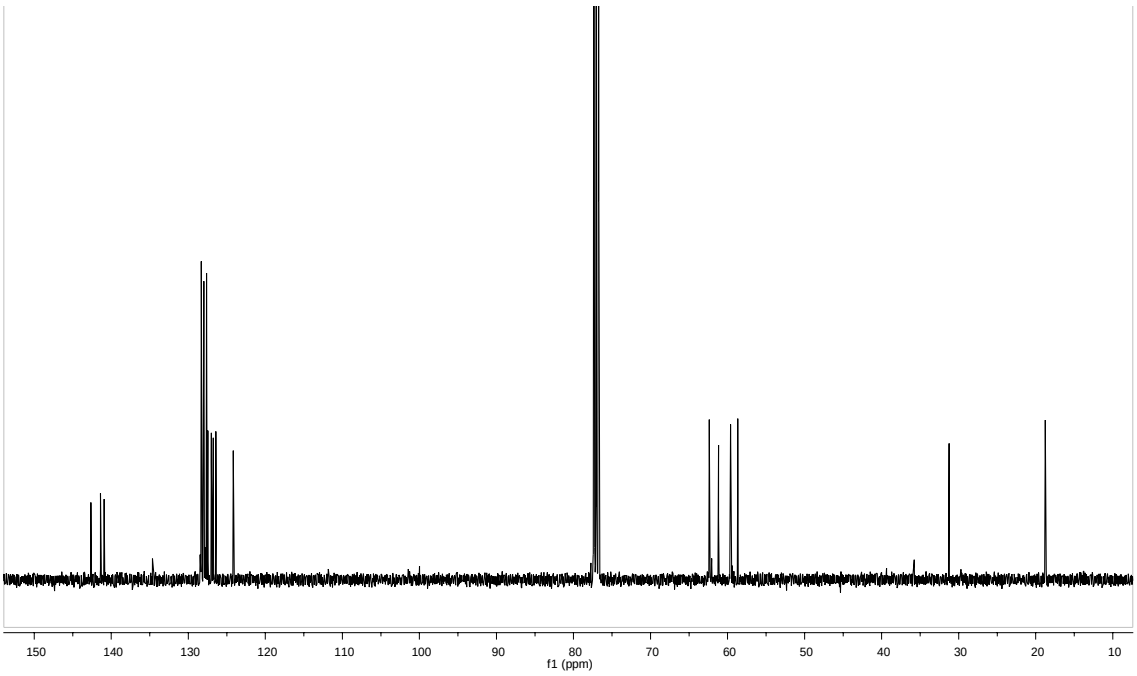


^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **29**.

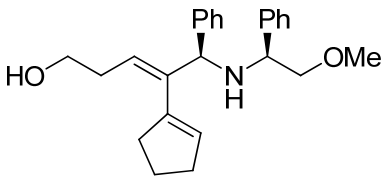


29a

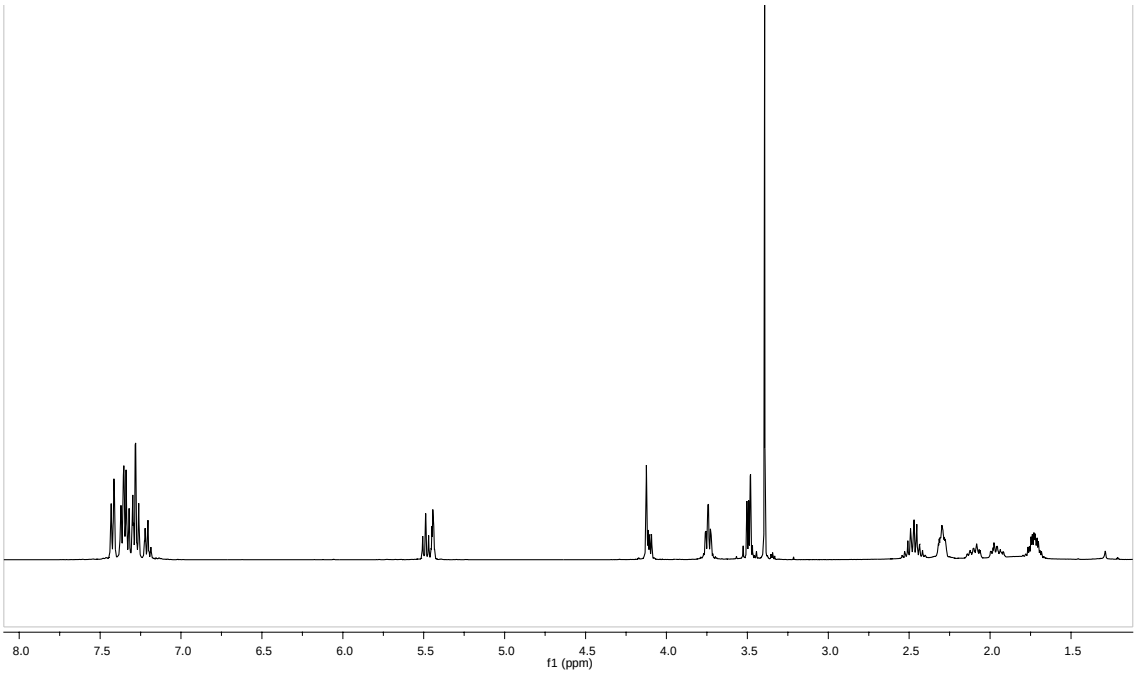


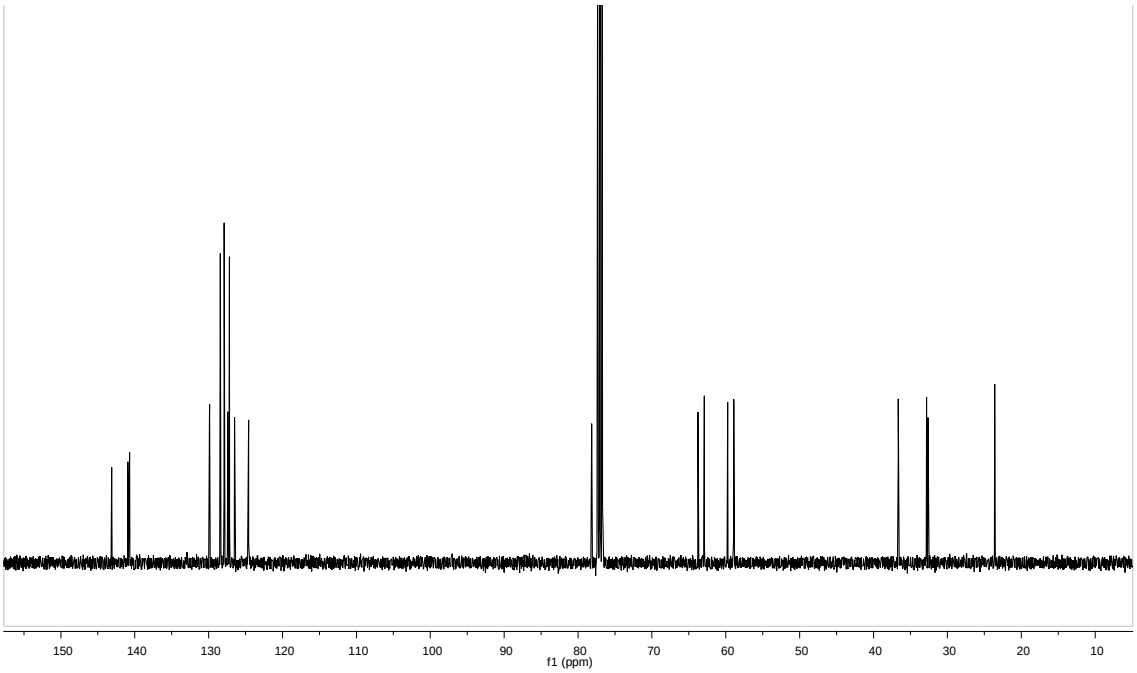


^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **29a**.

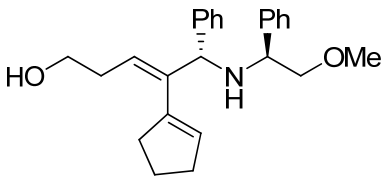


31

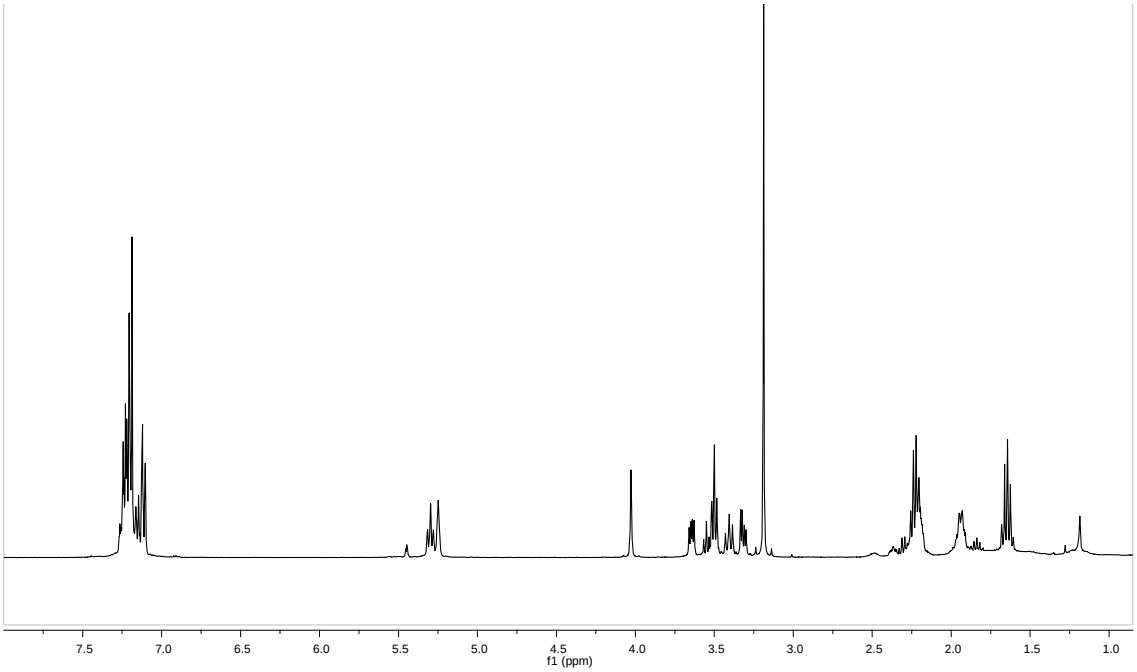


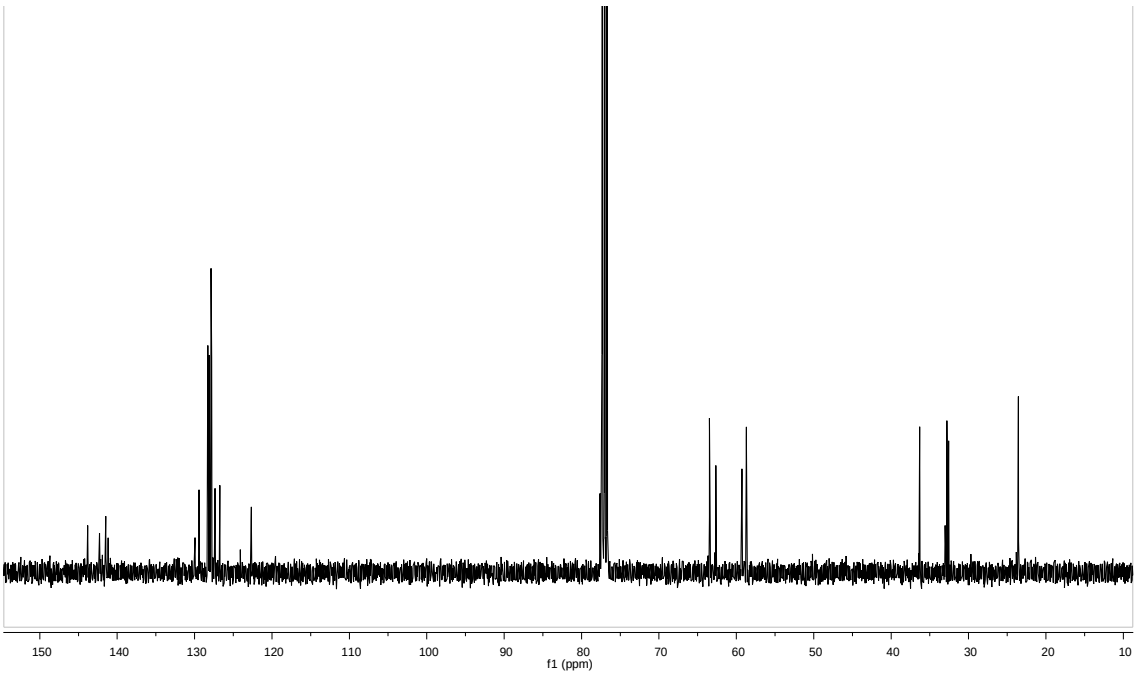


^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **31**.

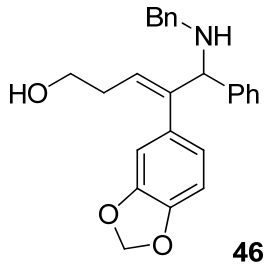


31a

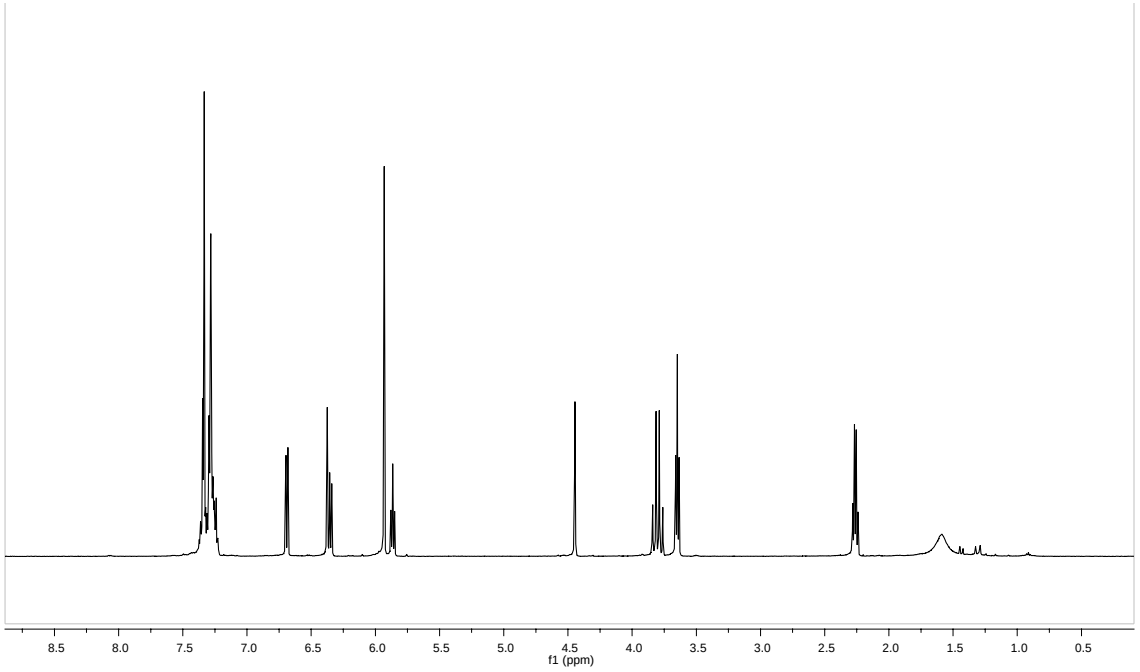


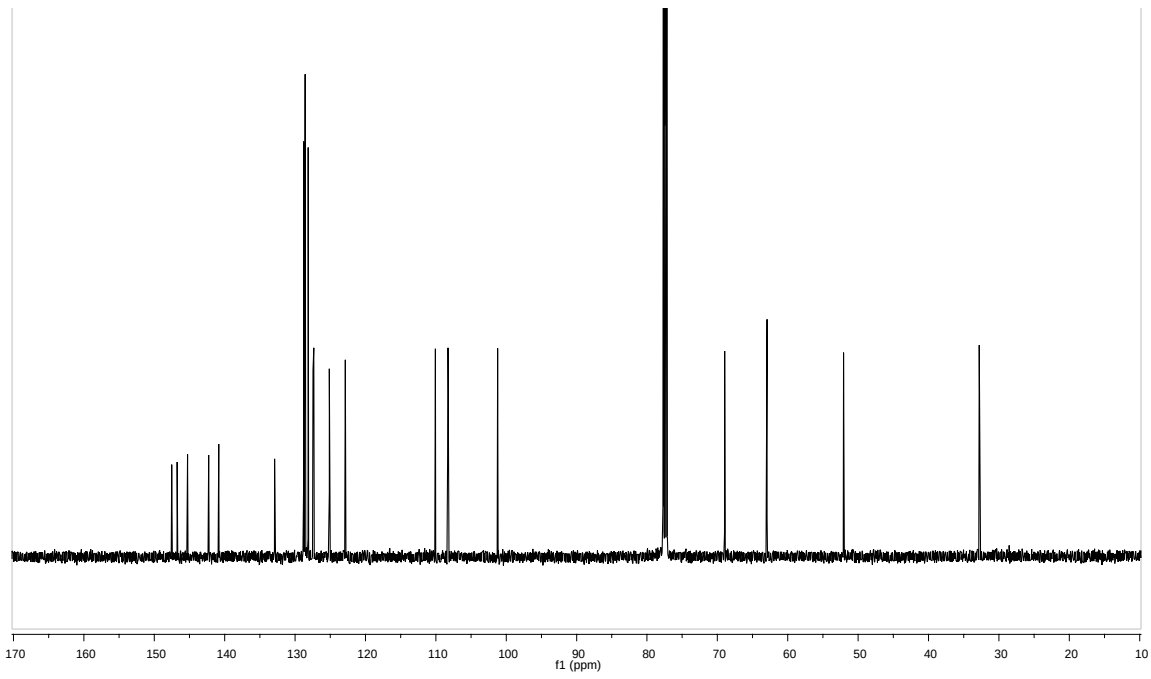


^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) of compound **31a**.

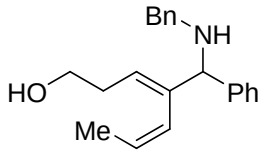


46

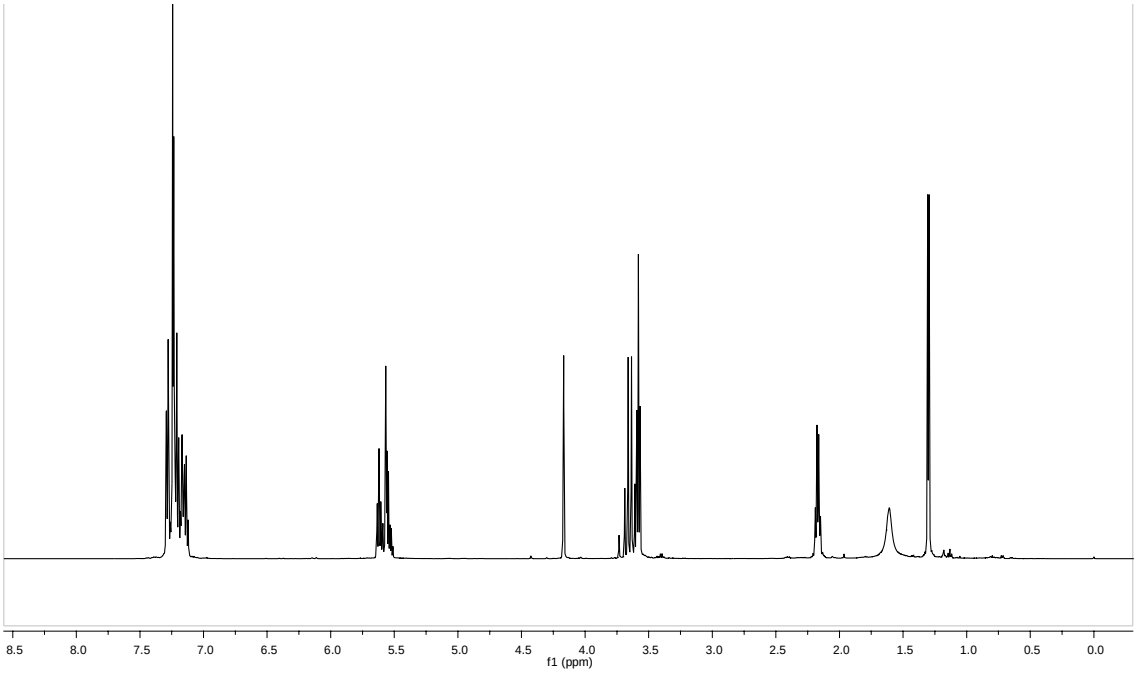


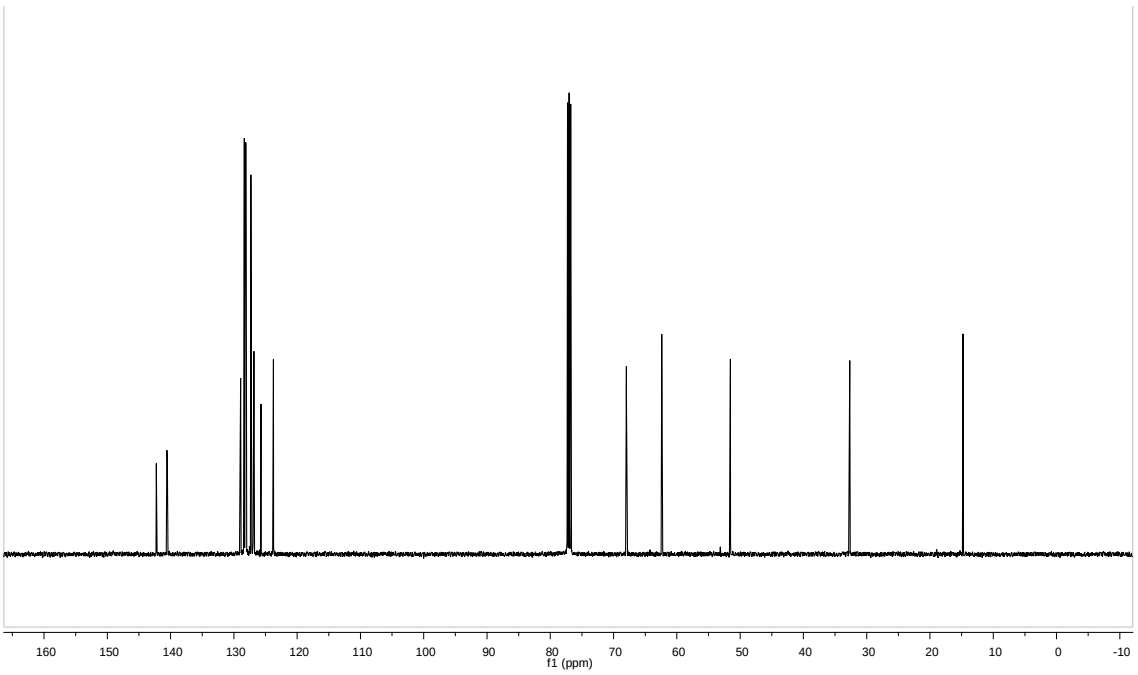


^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) of compound **46**.

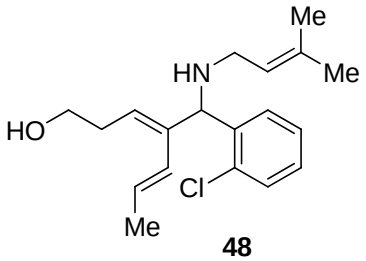


47

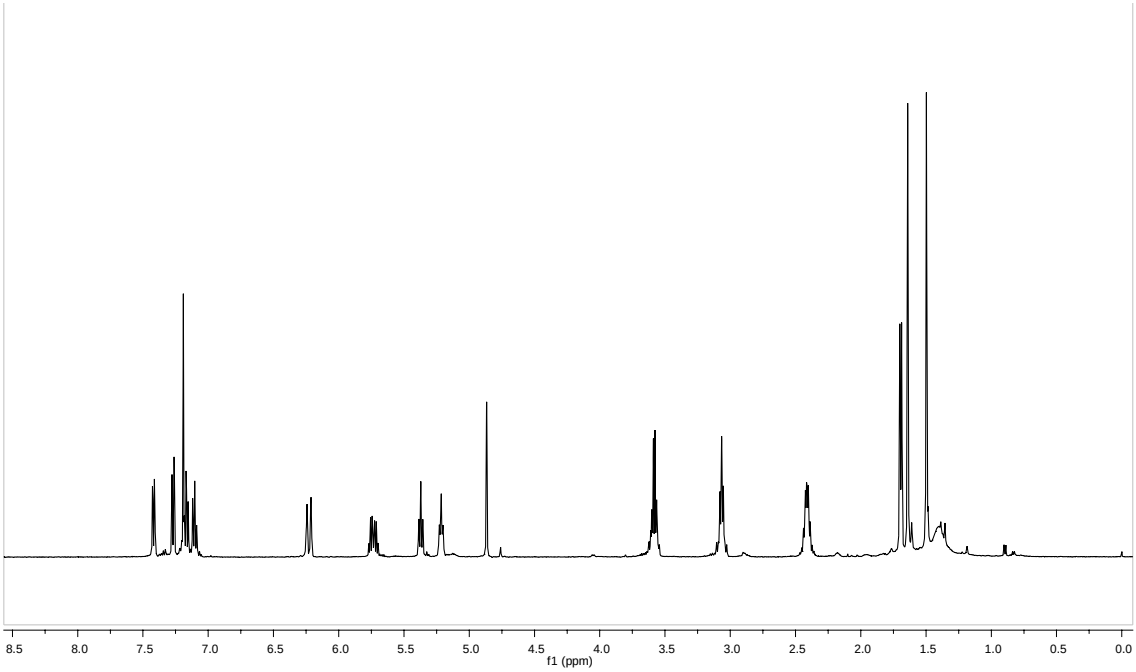


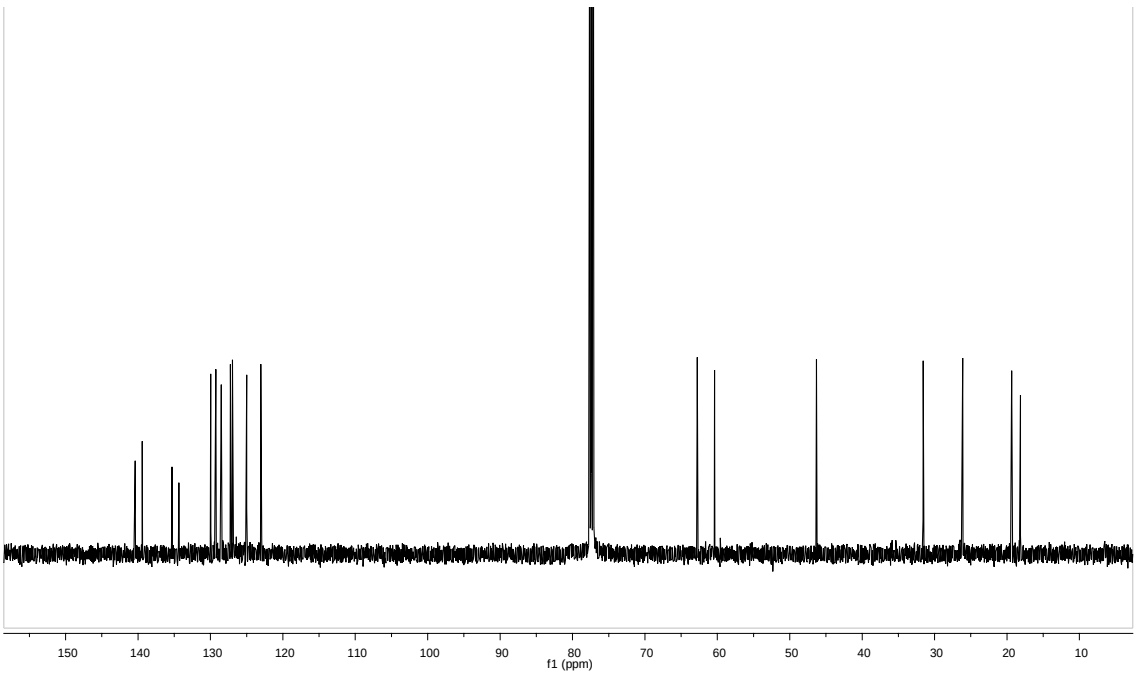


^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) of compound **47**.

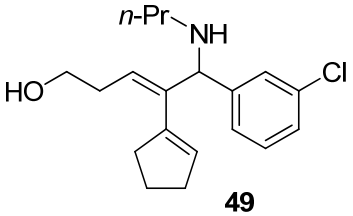


48

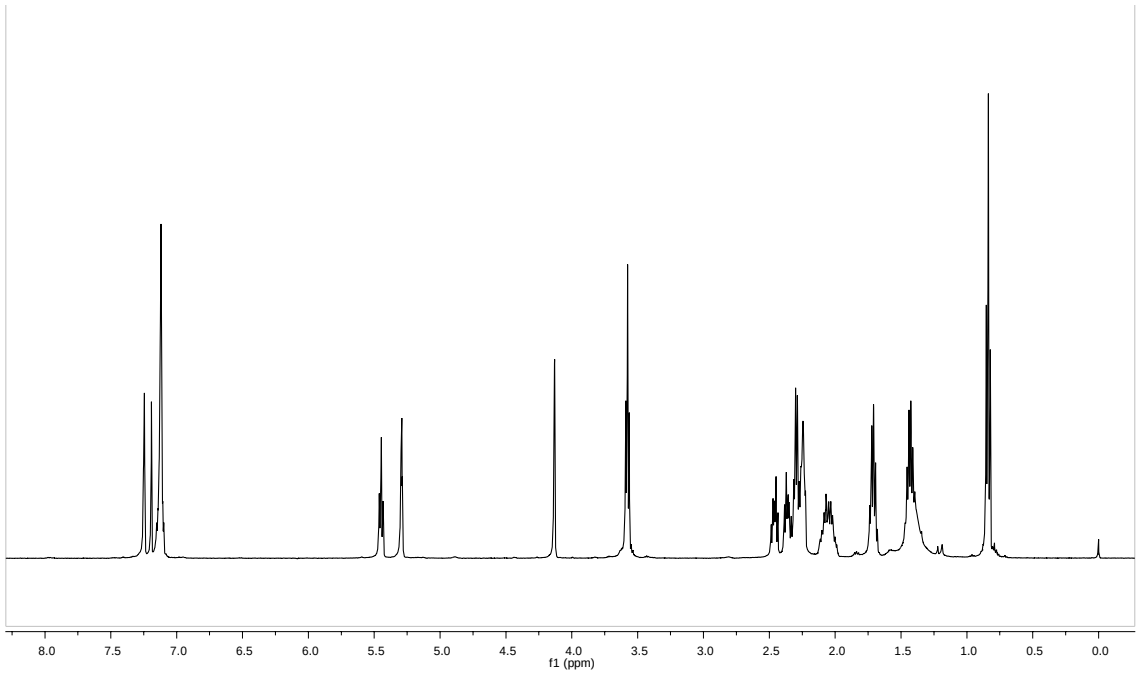


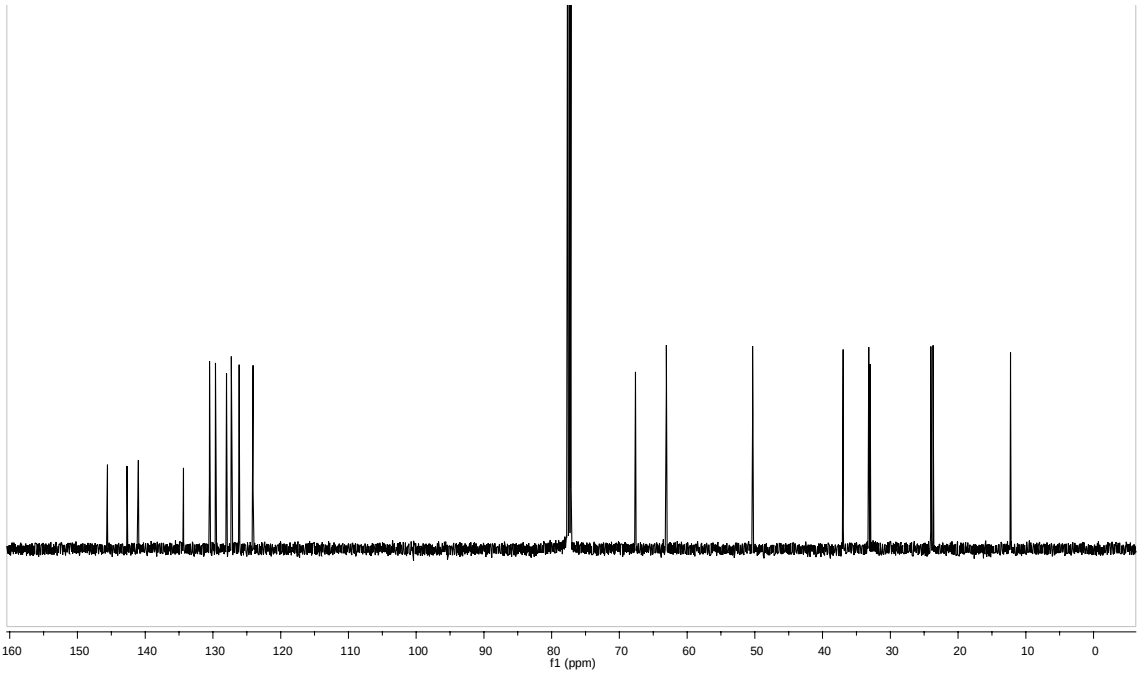


^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) of compound **48**.



49





^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) of compound **49**.